Organocatalytic Michael Addition Reactions of Nitrostyrenes and Application in the Synthesis of Selected Indolizidine and Quinolizidine Alkaloids

By

© **Moorthy N. V. G.**

A thesis submitted to the School of Graduate Studies

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

Memorial University

St. John's, Newfoundland

October 2017

To my Family

ABSTRACT

The organocatalytic asymmetric conjugate addition of carbon nucleophiles and heteroatom nucleophiles to electron deficient nitroalkenes is an important tool for the synthesis of highly functionalized building blocks for applications in medicinal and synthetic organic chemistry. Although the enantioselective conjugate addition reactions of β-nitrostyrenes are well known, the corresponding conjugate addition reactions of α-nitrostyrenes are not reported. The present study examines the organocatalytic asymmetric, enamine-mediated conjugate addition reaction of aldehydes or cyclic ketones to α-nitrostyrenes that were generated *in situ* from the corresponding nitroacetates. The details of this study are described in Chapter 2 of this thesis.

The utility of the above methodology was demonstrated by application in the formal total synthesis of 4-aryl indolizidine alkaloids, (+)-lasubine II and (-)-subcosine II. The organocatalytic Michael addition of 1,4-cyclohexanedione monoethylene ketal to an appropriate α-nitrostyrene which were generated *in situ* from the corresponding nitroacetate gave the key γ-nitroketone which was used as the starting material in the alkaloid synthesis. The details of this study are described in Chapter 3.

Finally, an enantiomerically enriched γ-nitroketone obtained from the organocatalytic Michael addition of 1,4-cyclohexanedione monoethylene ketal to a β-nitrostyrene has been utilized in the synthesis of a recently isolated indolizidine alkaloid,

(+)-fistulopsine B, which is of interest due to its anticancer activity. Details of this investigation are described in Chapter 4.

Acknowledgements

I will be always grateful to my supervisor Prof. Sunil V. Pansare for creating a truly exciting and highly rewarding graduate experience. He has taught me a great amount about chemistry and science in general. I admire his creativity and desire for excellence, which have inspired me during my graduate career.

I express my gratitude to Prof. Graham Bodwell and Prof. Chris Flinn, my thesis committee members, for providing me their comments and valuable suggestions during the program. I would like to thank Prof. Yuming Zhao and Prof. Paris Georghiou for helpful discussions and encouragement during the program and graduate courses.

I am also thankful to have supporting colleagues working with me in the lab. My special thanks to Dr. Rajendar Dyapa, he was the senior member of the group when I started my program. He was very helpful and co-operative in the lab which helped me to adjust and adapt to the new environment in a very short time. I also would like to thank my other seniors in the lab, Dr. Eldho Paul, Dr. Kaivalya Kulkarni and Dr. Rakesh Thorat for their support and encouragement in the lab. I would like to thank my current group members, Mr. Amarender Manchoju, Mr. Gopinathan Muthuswamy, Mr. Ritesh Annadate and Ms. Seerat Virk, for their support in the lab. Support from my colleagues from other research groups at MUN is greatly appreciated.

I would like to thank Dr. Celine Schneider for the training and assistance with NMR spectroscopy. Ms. Linda Winsor for the training and support with mass spectrometry, and Mr. Nick Ryan for the support with IR spectroscopy.

I would like to thank Mr. Dave Murphy for his help with computer-related matters. I thank Ms. Mary Flinn, Ms. Rosalind Collins, Ms. Ebony Penny, Ms. Gina Jackson and Ms. Melissa Petten in the Chemistry department for their assistance with administrative matters. I thank Mr. Steve Ballard and Ms. Bonita Smith for providing store-room support. I would like to extend thanks to colleagues in the teaching labs, Mr. Patrick Hannon, Mr. Cliff McCarthy, Ms. Anne Sheppard and Mr. Dave Stirling, for their wonderful support.

I also wish to thank the Department of Chemistry, Memorial University of Newfoundland, Natural Sciences and Engineering Research Council of Canada, and Canada Foundation for Innovation for financial support.

Finally, I want to give my deepest thanks to my family, especially my mom and dad. I wish to thank my wife Nethra, for her love, patience, support and encouragement during the most difficult time of my graduate program. This thesis certainly would not have been possible without the love and encouragement from them. Last but not the least, I thank all my friends in St. John's who helped me in the beginning to settle down.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

Ac	acetyl
APCI	atmospheric pressure chemical ionization
aq.	aqueous
Boc	*tert*-butoxycarbonyl
Bn	benzyl
br	broad
BuLi	butyl lithium
cat.	catalytic
Cbz	benzyloxycarbonyl
CPME	cyclopentyl methyl ether
CSA	camphor sulfonic acid
CI	chemical ionization
DCC	1,3-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine

DMP	Dess-Martin periodinane
DME	1,2-dimethoxyethane
DMEAD	di-2-methoxyethyl azodicarboxylate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ds	diastereoselectivity
ee	enantiomeric excess
EI	electrospray ionization
eq.	equivalent(s)
er	enantiomeric ratio
Et	ethyl
EWG	electron withdrawing group
g	gram
h	hour
HCT 116	human colorectal carcinoma cell line
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
i-Bu	isobutyl
In	Indium
i-Pr	isopropyl
IR	infrared
J	coupling constant

LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
NaHMDS	sodium hexamethyldisilazide
M	molar
M^+	molecular ion
MCF7	Michigan Cancer Foundation-7
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram
min	minute
mL	milliliter
mmol	millimole
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
m/z	mass to charge ratio
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect
Ph	phenyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PNBA	*para*-nitrobenzoic acid
Pr	propyl
PTSA	*para*-toluenesulfonic acid

RaNi	Raney nickel
rt	room temperature
t-Bu	tertiary butyl
TBAF	tetrabutylammonium fluoride
TBPS	*tert*-butyl(chloro)diphenylsilane
TEA	triethylamine
TFA	trifluoroacetic acid
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	tetramethylsilyl
TMEDA	tetramethylethyldiamine
Ts	*p*-toluenesulfonyl
Zn	zinc

Chapter 1

Introduction

1.1 Organocatalytic conjugate addition reactions

The conjugate addition of nucleophiles to the β-position of α,β-unsaturated carbonyl compounds (Michael reaction) is an important method for making a carbon–carbon bond.[1] Due to the high demand for optically active compounds, much effort has been devoted to the development of asymmetric Michael reactions, since stereogenic centers can be constructed in the course of the Michael reaction.[1] Although asymmetric conjugate additions have, over the years, been dominated by using chiral catalysts containing metals, small organic molecules (organocatalysts) have been developed, over the past decade, as efficient catalysts for these reactions.[2]

Carbon nucleophiles with active methylene groups are extensively used in direct Michael additions, while simple carbonyl compounds need to be activated as enol ethers or enamines prior to addition to a Michael acceptor (Figure 1.1). In this case, direct addition of unmodified carbonyl compounds to Michael acceptors would avoid unwanted chemical transformations and also reduce the overall synthetic effort.

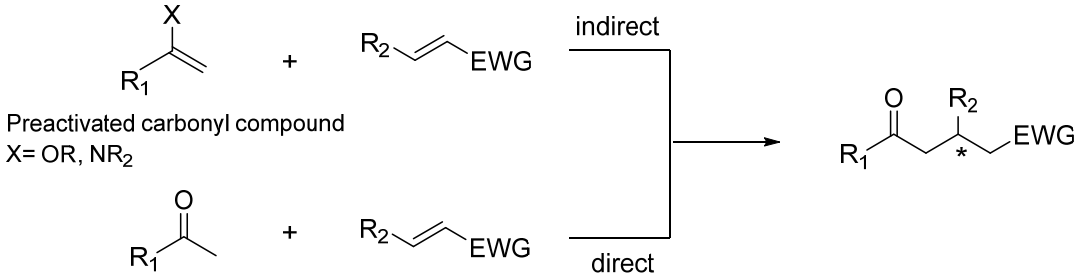


Figure 1.1 Direct and indirect Michael addition.

In this context, the concept of aminocatalysis[3] has received considerable attention in recent years. In the presence of a secondary amine, catalytic activation of an aldehyde or a ketone (the Michael donor) may take place through enamine formation (a synthetic equivalent of to an enolate) for the addition to a Michael acceptor (Figure 1.2, path a). Alternatively, Michael acceptors containing a carbonyl group can be activated by the formation of an iminium species (Figure 1.2, path b).

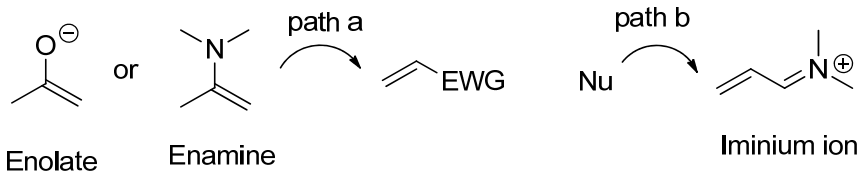


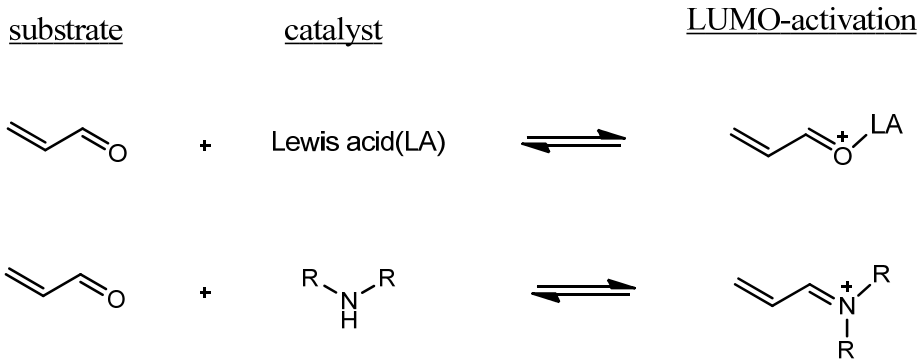
Figure 1.2 Activation of a Michael donor and Michael acceptor.

The following is a brief introduction to key developments in the areas of iminium ion- and enamine-mediated organocatalytic conjugate addition reactions. Since the main focus of the investigations described in this thesis is on enamine mediated conjugate addition reactions, a more detailed review is provided on this particular topic and iminium ion catalysis is only briefly discussed.

1.2 Organocatalytic conjugate addition reactions via iminium catalysis

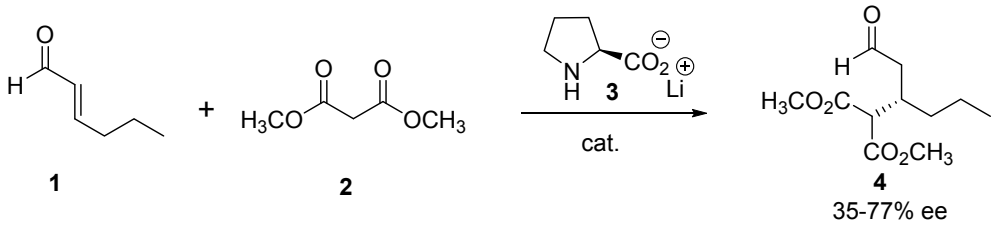
By its very nature, iminium ion catalysis requires the use of enones or enals as Michael acceptors. In 2000, MacMillan reported the activation of unsaturated aldehydes and ketones by reversible iminium ion formation with chiral amines as a highly generalized strategy for conjugate addition reactions.[4,5] The formation of the iminium ion lowers the LUMO energy of the carbonyl substrate to better match the HOMO of the

nucleophile. This activation effect is similar to that associated with reactions involving metal-based Lewis acids (Scheme 1.1).[1]



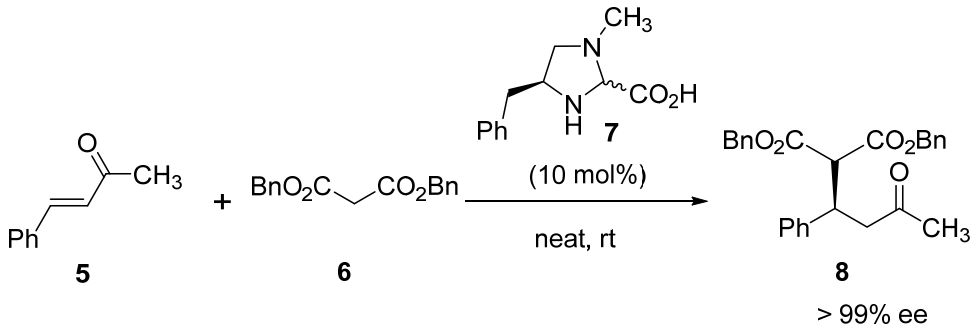
Scheme 1.1

Iminium catalysis forms the basis for several conjugate addition reactions of various Michael donors such as malonates,[7,8] nitroalkanes[9,10] and thiols[11] to enones as well as for Mukaiyama-Michael reactions of silyloxyfurans with enals.[5,6] The first iminium-catalyzed conjugate addition (malonate **2** to enone **1**) was reported by Yamaguchi and co-workers[12] in 1991 using the lithium salt of (*S*)-proline **3** to obtain moderate to good enantioselectivities (Scheme 1.2).



Scheme 1.2

In 2003, Jørgensen developed the highly enantioselective organocatalytic Michael addition[13] of malonates such as **6** to *α,β*-unsaturated enones such as **5** using an imidazolidine catalyst **7**, which was readily prepared from phenylalanine (Scheme 1.3).



Scheme 1.3

The following is a summary of the enamine-mediated organocatalytic Michael reactions of aldehydes and ketones with a variety of Michael acceptors.

1.3 Organocatalytic conjugate addition reactions via enamine catalysis

Chiral amines can catalyze the asymmetric conjugate addition of aldehydes and ketones to electron-deficient alkenes (Michael acceptors) such as nitroalkenes, enones, and vinyl sulfones by *in situ* formation of enamines from the starting aldehydes and ketones.[2] The enamine catalysis relies on the reversible formation of enamines from a catalytic amount of primary or secondary amine. The formation of an iminium ion is the first step of the catalytic cycle (Figure 1.3). This results in a significant increase in α-C-H acidity which facilitates enamine formation.[1e] Nucleophilic addition of the enamine to the Michael acceptor ultimately generates an iminium ion, which undergoes hydrolysis under the reaction conditions, to regenerate the amine catalyst.

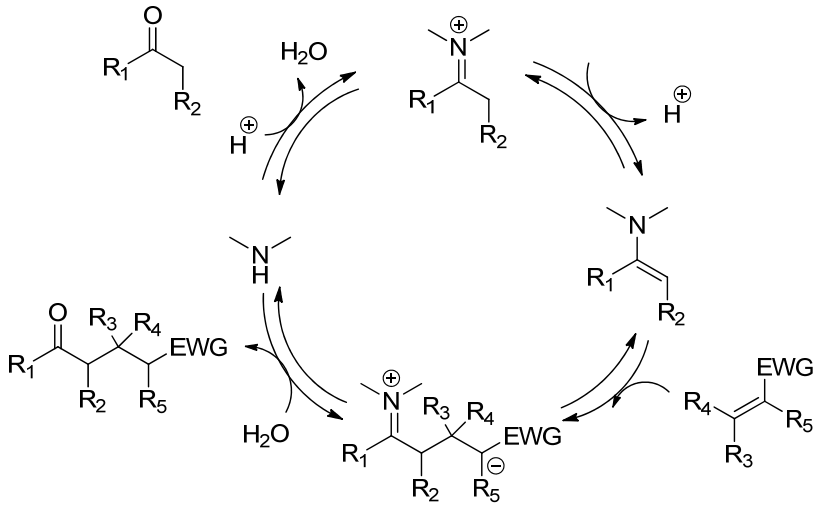
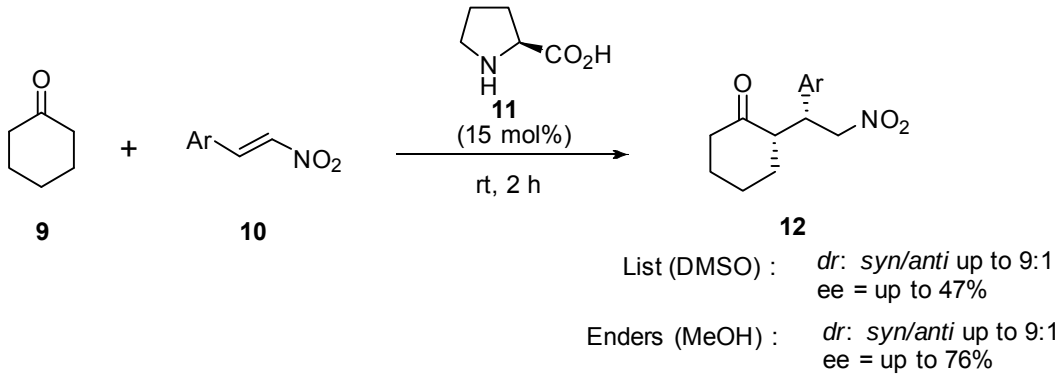


Figure 1.3 Enamine-catalyzed Michael reaction.[1e]

Although asymmetric conjugate additions have, over the years, been dominated by the application of chiral Lewis acids as catalysts, [14,15] more recently, organocatalysts have been added as efficient tools.[2] For the vast majority of these reactions, chiral secondary amines are used as catalysts. The following is a brief summary of organocatalytic conjugate addition of ketones to nitroalkenes using enamine catalysis.

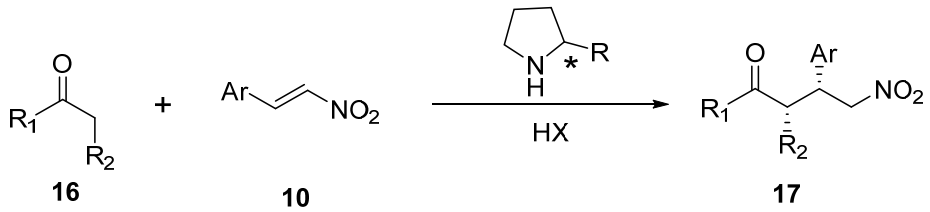
1.4 Functionalized pyrrolidines as organocatalysts for the ketone-nitroalkene conjugate addition reactions

List *et al.* developed the first enamine-catalyzed asymmetric Michael reaction of ketone **9** to nitroalkenes **10**.[16] The reaction was catalyzed by (*S*)-proline (**11**) in DMSO to afford the desired *γ*-nitroketones **12** in high yields and good diastereoselectivities, but only low enantioselectivities (Scheme 1.4). In a related study, Enders used methanol as the solvent to obtain better enantio- and diastereoselectivities.[17]



Scheme 1.4

Since the initial report by List, several chiral pyrrolidine-based catalysts having an *N*-containing side chain or heterocycle were developed (Figure 1.4), and either the free amine or the corresponding salts were shown to promote the highly *syn*-selective addition of cyclic and acyclic ketones **16** to nitroalkenes **10**[2e,g] (Scheme 1.5). Quite often the role of the acid co-catalyst (HX, Scheme 1.5) is to promote iminium ion formation, and consequently enamine formation, which results in an overall rate acceleration and increased conversion.



Scheme 1.5

Numerous secondary amine based catalysts[18-33] have been reported for these reactions. A selection of catalysts reported in the early days of the reactions (organocatalytic ketone-nitroalkene conjugate addition) are shown in Figure 1.4.

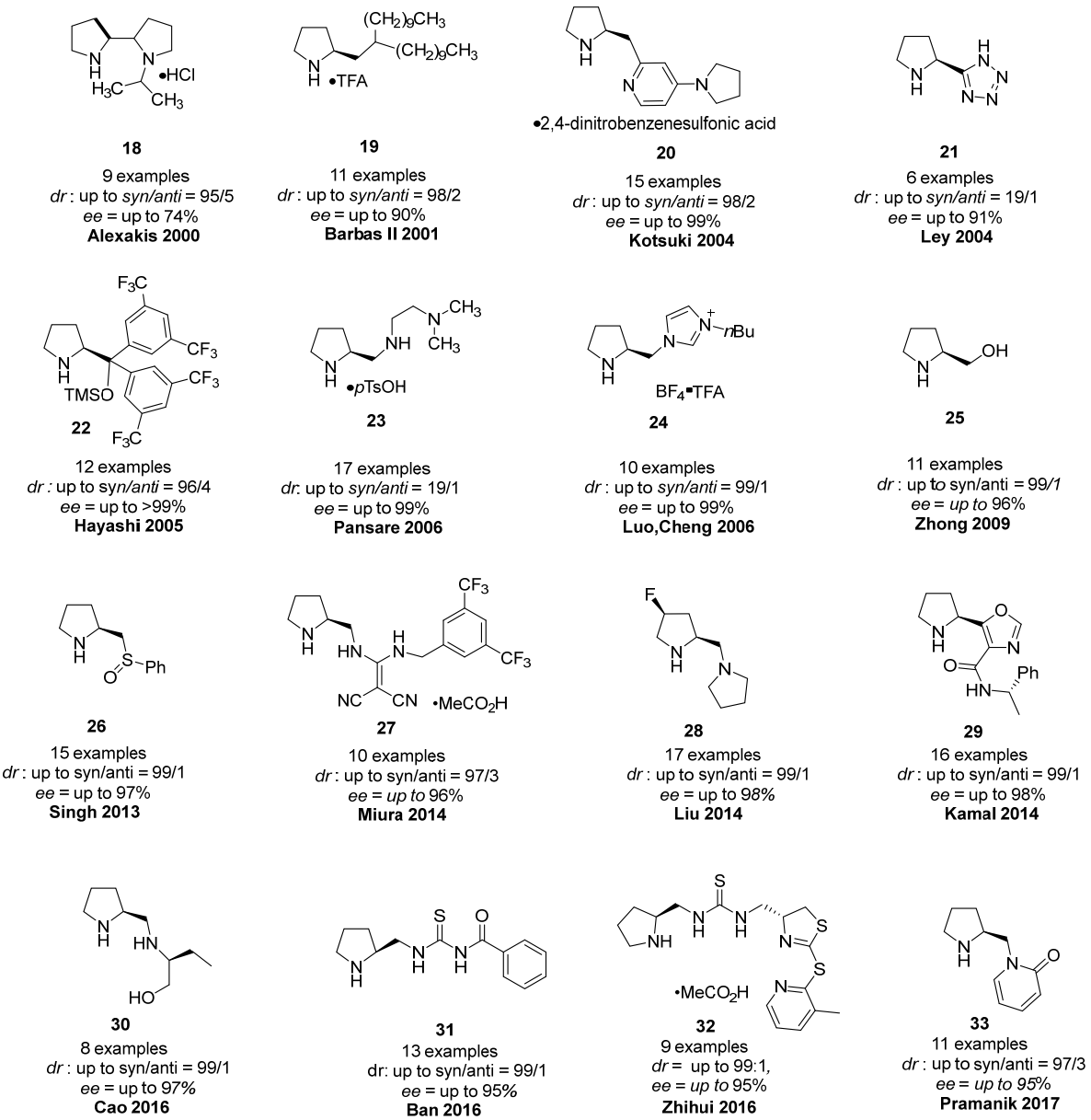
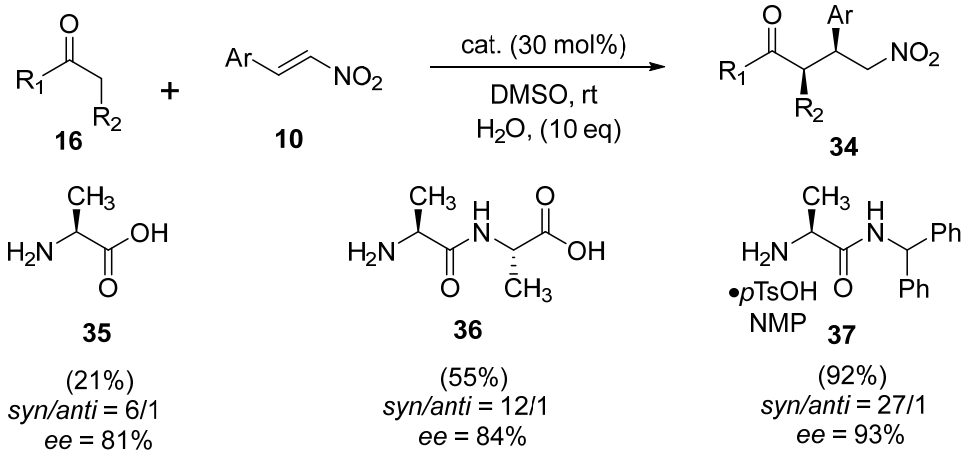


Figure 1.4 Selected organocatalysts for the ketone-nitroalkene conjugate addition.

1.5 Chiral, functionalized primary amines as organocatalysts for the ketone-nitroalkene conjugate addition reaction

1.5.1 Chiral peptides as organocatalysts for the ketone-nitroalkene conjugate addition reaction

Alanine **35** and alanine-containing small oligopeptides have also shown good stereoselectivities in the addition of ketones **16** to nitroalkenes **10**[34] (Scheme 1.6). The L-ala-L-ala dipeptide **36** is more selective than monomer **35**, while the alanine derivative **37** is a much better catalyst than **35** and **36**.[35]

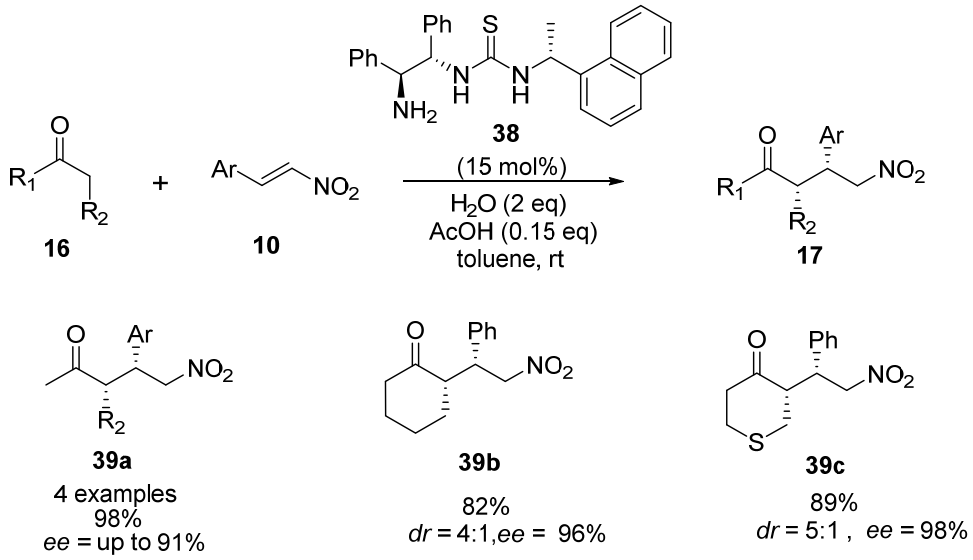


Scheme 1.6

1.52 Chiral amino-thioureas as organocatalysts for the ketone-nitroalkene conjugate addition reaction

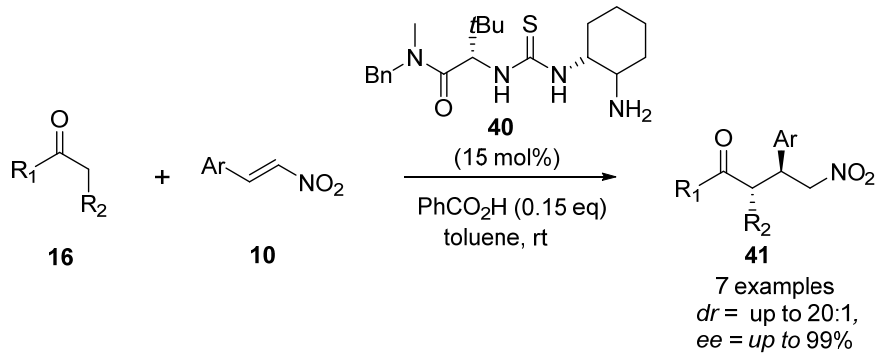
In 2006, Tsogoeva, Schmatz, and co-workers utilized primary amine derived chiral thiourea catalysts in the Michael reaction of ketones **16** to nitroalkenes **10**.[36,37] Thiourea **38**, bearing a primary amine, promoted the addition of ketones to nitroalkenes

(Scheme 1.7) with moderate diastereoselectivities (up to 6:1 *dr*) but excellent enantioselectivities (up to 99% *ee*). Water plays an important role in the regeneration of the catalyst and enamine formation is accelerated by acidic additives.



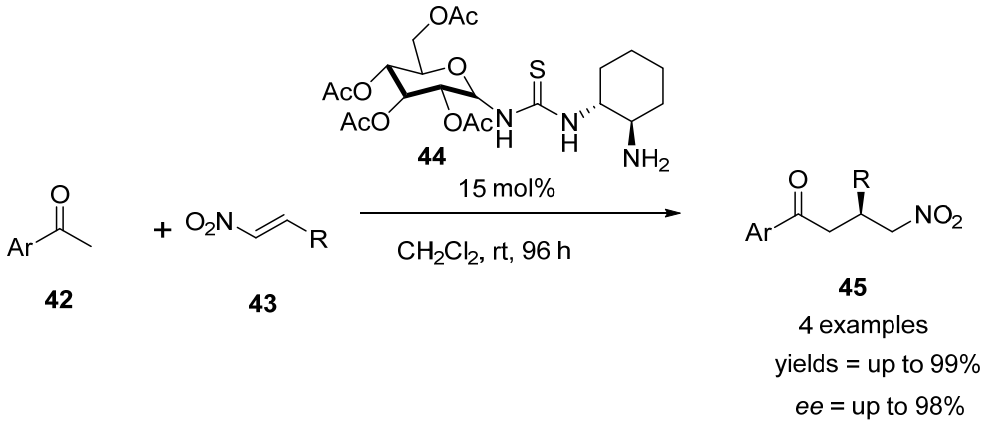
Scheme 1.7

In 2006, Huang and Jacobsen used a similar primary amine thiourea catalyst **40** for the conjugate addition of ketones **16** to nitroalkenes **10**.[38] While the reactions performed in polar and/or protic solvents proceeded slowly, nonpolar solvents and high concentrations turned out to be beneficial. Thiourea containing catalyst **40** furnished Michael adducts with excellent *anti*-selectivity (up to 20:1 *dr*) and enantioselectivities (up to 99%). A (*Z*)-enamine intermediate was proposed for the observed *anti*-diastereoselectivity (Scheme 1.8).



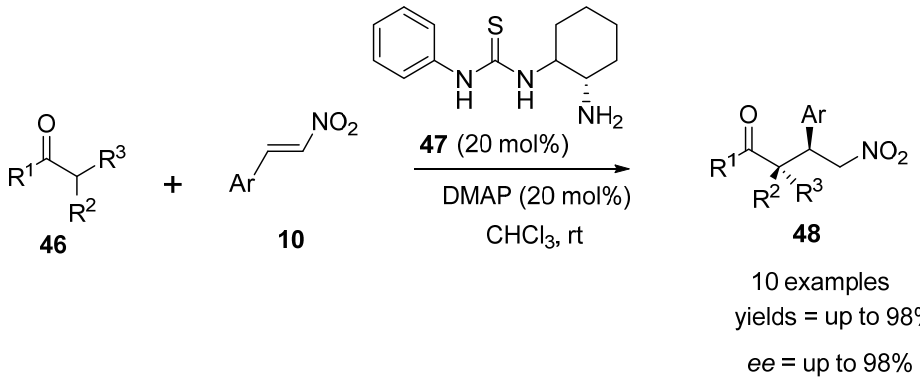
Scheme 1.8

In 2007, Ma and co-workers reported a new primary amine-thiourea[39] catalyst **44** for the Michael addition of aromatic ketones **42** to nitroalkenes **43** to provide Michael adducts **45** with excellent enantioselectivities and moderate to good yields (Scheme 1.9).



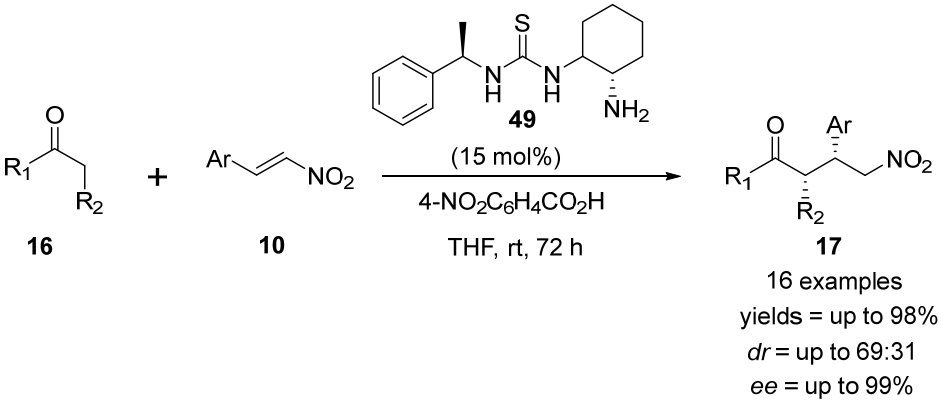
Scheme 1.9

In 2009, the Yan group developed a simple chiral thiourea[40] catalyst **47** derived from cyclohexane-1,2-diamine for the Michael addition of aldehydes **46** to nitroalkenes **10** to afford Michael adducts **48** (Scheme 1.10) with excellent enantioselectivities and yields. In the case of ketones, low enantioselectivities and yields were observed. The use of base additives is essential for good yields and excellent enantioselectivities.



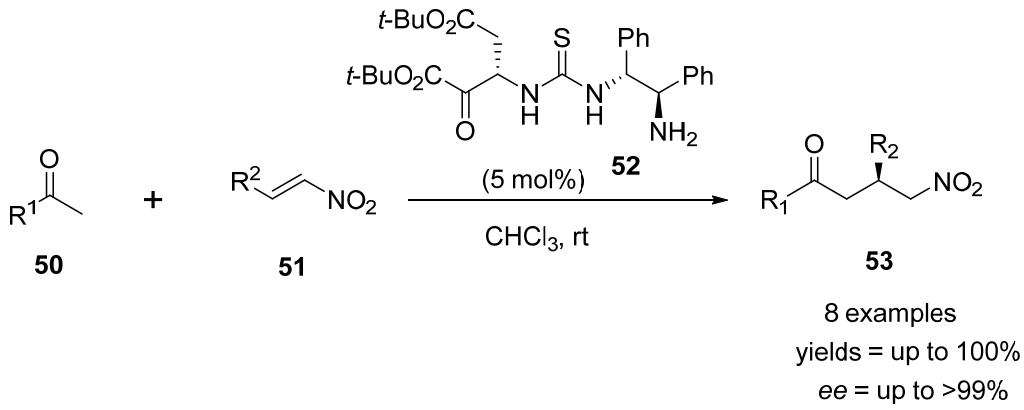
Scheme 1.10

In 2010, Xu and co-workers, applied a primary amine-thiourea[41] catalyst **49** developed by the Tsogeva group for the conjugate addition of ketones **16** to nitroalkenes **10** to provide Michael adducts **17** with excellent enantioselectivities and good to high yields (Scheme 1.11).



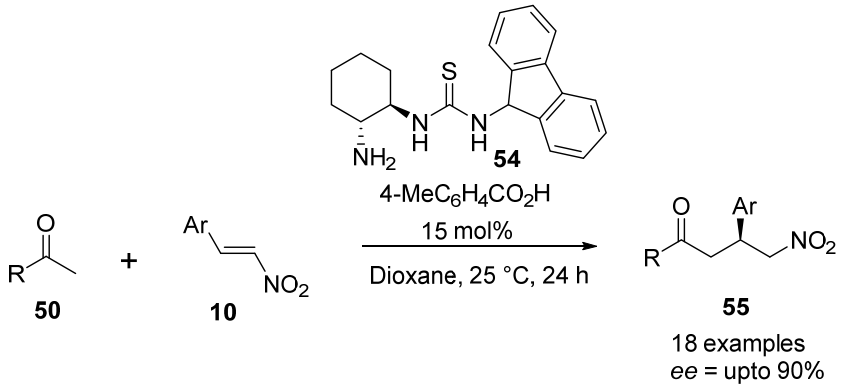
Scheme 1.11

In 2012, Kokotos and co-workers reported the Michael addition of aryl methyl ketones **50** to nitroalkenes **51** in the presence of di-*tert*-butyl aspirate[42]-derived catalyst **52** to afford Michael adducts **53** with excellent enantioselectivities and high yields (Scheme 1.12).



Scheme1.12

In 2014, Li and co-workers developed a new primary amine-thiourea[43] organocatalyst **54** derived from chiral 1,2-diaminocyclohexane. The chiral 1,2-diaminocyclohexane derived thiourea catalyst was able to catalyze the Michael addition of acetophenone derivatives **50** to *β*-nitrostyrenes **10**. The steric hindrance provided by the fluorenyl backbone in the catalyst allowed the formation of Michael adducts **55** with good enantioselectivities (Scheme 1.13).



Scheme 1.13

Numerous other primary amine-thiourea based catalysts have been reported for these reactions. A selection of catalysts reported for the organocatalytic ketone-nitroalkene conjugate addition reactions is shown in Figure 1.5.

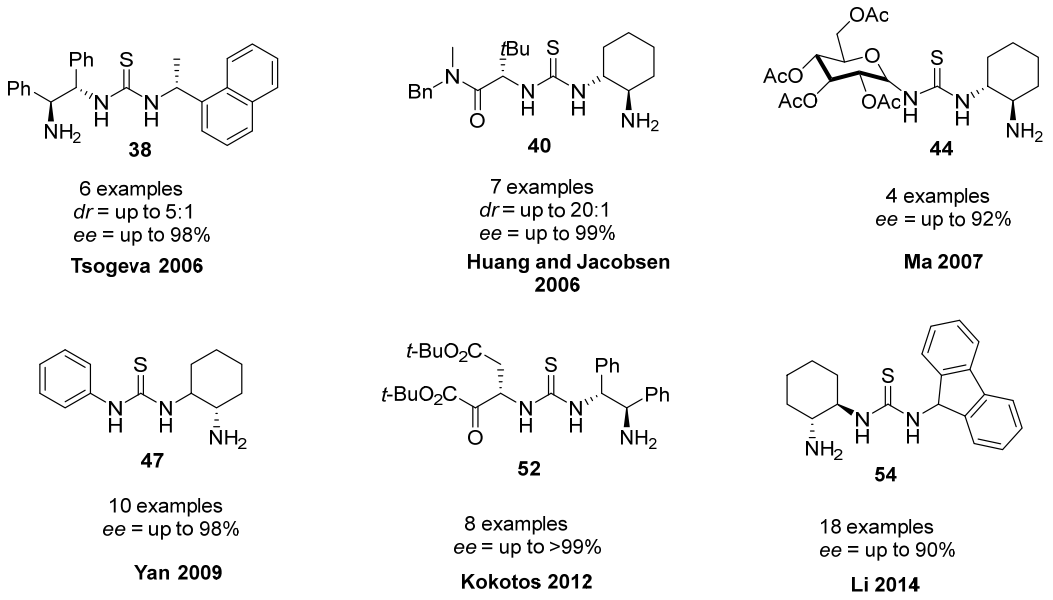
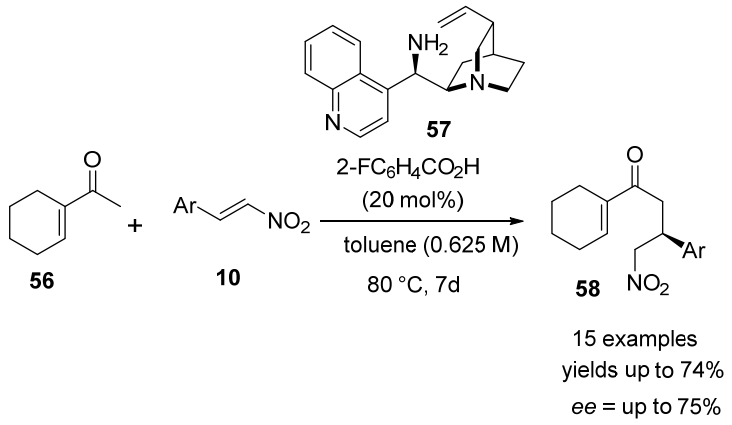


Figure 1.5 Selected organocatalysts for the ketone-nitroalkene conjugate addition.

1.53 Chiral triamines as organocatalysts for ketone-nitroalkene conjugate addition reactions

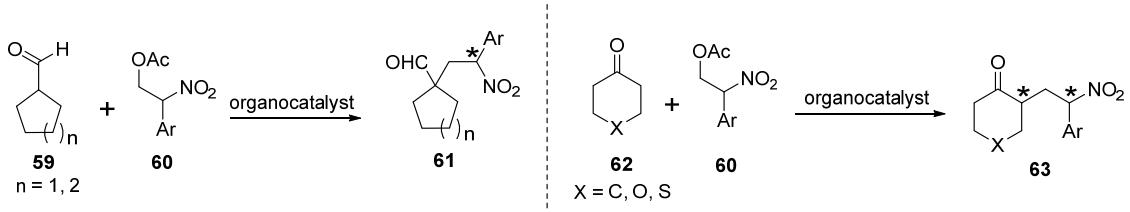
In 2015, Pan *et al.* developed the first enamine catalyzed asymmetric Michael reaction of α-branched cyclized enones **56** to nitroalkenes **10**.[44] The reaction was catalyzed by primary amine catalyst **57** in toluene to provide the desired nitroketone **58** with 55% yield. The enantioselectivities of the reactions are moderate (70-75%, Scheme 1.14).



Scheme 1.14

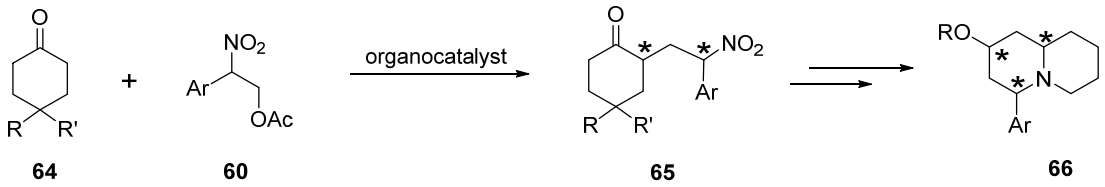
1.54 Research Objectives

Although the enantioselective organocatalytic conjugate addition of ketones to β-nitrostyrenes are well known, the corresponding reactions of α-nitrostyrenes are not reported. Hence the first objective of our study was to develop an organocatalyzed asymmetric conjugate addition of aldehydes **59** and ketones **62** to α-nitrostyrenes (Scheme 1.17).



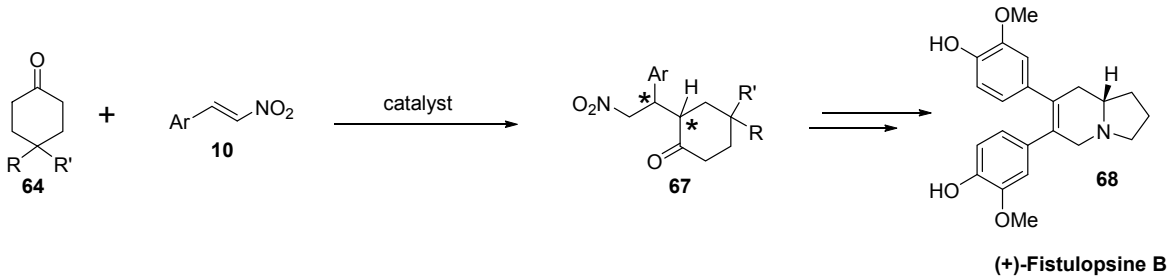
Scheme 1.17

The second objective was to utilize the γ-nitroketones **63** (Scheme 1.17) as key starting materials in the synthesis of selected 4-aryl quinolizine alkaloids (Scheme 1.18).



Scheme 1.18

The final objective was an application of the organocatalytic Michael addition of ketones to β-nitrostyrenes. This project constitutes an extension of the methodology for indolizidine synthesis that was previously developed[47] in the Pansare group. The general strategy, shown in Scheme 1.19, involves the organocatalytic synthesis of the γ-nitroketone **67** which is then converted to the target indolizidine. In the present investigation, this methodology was applied in the total synthesis of an indolizidine alkaloid, (+)-fistulopsine B (**68**) that was isolated in 2016.



Scheme 1.19

1.55 References

1) For selected reviews of asymmetric Michael additions, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *10,* 933. (c) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (d) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry*, **2010**, *21*, 2561. (e) Sulzer-Mosse, S.; Alexakis, A. *Chem. Commun.* **2007**, *30*, 3123. (f) Enders, D.; Seki, A. *Eur. J. Org. Chem.* **2002**, 1877. (g) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. For recent examples, see: (h) Chen, Q.; Qiao, Y.; Ni, B. *Synlett* **2013**, *24*, 839. (i) Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Zhang, F.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9124. (j) Wang. L.; Liu. J.; Miao. T.; Zhou. W.; Li. P.; Ren. K.; Zhang. X. *Adv. Synth. Catal.* **2010**, *352*, 2571. (k) Singh, K. N.; Singh, P.; Singh, P; Lal, N.; Sharma, S. K. *Bioorg. Med. Chem. Lett.* **2012**, *22,* 4225. (l) Sternativo, S.; Calandriello, A.; Costantino, F.; Testaferri, L.; Tiecco, M.; Marini, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 9382. (m) Alonso, D. A.; Baeza, A.; Chinchilla, R.; Gomez, C.; Guillena, G.; Pastor, I. M.; Ramon, D. J. *Molecules* **2017**, *22*, 895.

2) For selected reviews on asymmetric organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed*. **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed*. **2004**, *43*, 5138. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem.Rev.* **2007**, *107*, 5471. (d) Notz, W.; Tanaka, F.; Barbas, C.F. III *Acc. Chem. Res.* **2004**, *37*, 580. (e) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed*., **2008**, *47*, 4638. (f) Kotsuki, H.;

Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 757. (g) Johnston, J. N. *J. Am. Chem. Soc.* **2011**, *133*, 2330. Hansen, J.; Zeeshan, M. *Mini Rev. Org. Chem.* **2014**, *11*, 432.

3) List, B.; *Synlett*. **2001**, *11*, 1675.

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

5) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

6) Mekonnen, A.; Carlson, R. *Eur. J. Org. Chem.* **2006**, *8*, 2005.

7) Halland, N.; Aburel, P. S.; Jorgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 661.

8) Knudsen, K. R.; Mitchell, C. E. T.; Ley, S. V. *Chem. Commun.* **2006**, 66.

9) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975.

10) Mitchell, C. E. T.; Brenner, S. E.; Ley, S. V. *Chem. Commun.* **2005**, 5346.

11) Li, B. J.; Jiang, L.; Liu, M.; Chen, Y. C.; Ding, L. S.; Wu, Y. *Synlett.* **2005**, 603.

12) Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc. Chem. Commun.* **1991**, 1088.

13) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 661.

14) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, *2*, 171.

15) Guo, H.-C.; Ma, J.-A. *Angew. Chem. Int. Ed*. **2006**, *45*, 354.

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

17) Seki, A.; Enders, D. *Synlett* **2002**, *1*, 26.

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

29) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew.Chem. Int. Ed.* **2000**, *39*, 4093.

20) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, III, C. F. *J. Am. Chem. Soc*. **2001**, 5260.

21) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558.

22) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D.M.; Ley, S. V. *Chem. Commun.* **2004**, 1808.

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

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

25) Luo, S.; Mi, X. ; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093.

26) Chua, P. J.; Tan, B.; Zeng, X.; Zhong, G.; *Biorg. Med. Chem. Lett.* **2009**, *19*, 3915.

27) Singh, K. N.; Singh, P.; Kaur, A.; Singh, P.; Sharma, S. K.; Khullar, S.; Mandal, S. K. *Synthesis* **2013**, *45*, 1406.

28) Nakashima, K.; Hirashima, S. –I.; Kawada, M.; Koseki, Y.; Tada, N.; Itoh, A.; Miura, T. *Tetrahedron Lett*. **2014**, *55*, 2703.

29) Wang, Y.; Jiang, M.; Liu, J. –T. *Tetrahedron Asymmetry* **2014**, *25*, 212.

30) Kamal, A.; Sathish, M.; Srinivasulu, V.; Chetna, J.; Chandra Shekar, K.; Nekkanti, S.; Tangella, Y.; Shankaraiah, N. *Org. Biomol. Chem*. **2014**, *12*, 8008.

31) Yang, M.; Zhang, Y. C.; Zhao, J. Q.; Yang, Q. S.; Ma, Y.; Cao, X. H. Russ. *J. Gen. Chem.* **2016**, *86*, 1381.

32) Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901.

33) Mahato, C. K.; Kundu, M.; Pramanik, A. *Tetrahedron Asymmetry* **2017**, *28*, 511.

34) Olalla –R. A.; Retamosa, M. G.; Cossio, F. P. *J. Org. Chem.* **2015**, *80*, 5588.

35) Wang, Y.; Li, D.; Lin, J.; Wei, K.; *RSC Adv.,* **2015**, *5*, 5863.

36) Xu, Y.; Zou, W; Sunden, H.; Ibrahem, I.; Cordova, A. *Adv. Synth. Catal.* **2006**, *348*, 418.

37) Xu, Y.; Cordova, A. *Chem. Commun.* **2006**, 460.

38) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826.

39) Liu, K.; Cui, H. –F.; Nie, J.; Dong, K. –Y.; Li, X.-J.; Ma, J.-A. *Org. Lett*., **2007**, *9*, 923.

40) Zhang, X.-J.; Liu, S.-P.; Lao, J.-H.; Du, G.-J.; Yan, M.; Chan, A. S. C. *Tetrahedron: Asymmetry*, **2009**, *20*, 2818.

41) Li, B.-L.; Wang, Y.-F.; Luo, S.-P.; Zhong, A.-G.; Li, Z.-B.; Du, X.-H.; Xu, D.-Q. *Eur. J. Org. Chem*., **2010**, 656.

42) Tsakos, M.; Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.,* **2012**, *354*, 740.

43) Yu, L.; Li, P.; *Tetrahedron Lett.* **2014**, *55*, 3697.

44) Nath, U.; Banerjee, A.; Ghosh, B.; Pan, S. C.; *Org. Biomol. Chem*. **2015**, *13*, 7076.

45) Ban, S.-R.; Zhu, X.-X.; Zhang, Z.-P.; Xie, H.-Y.; Li, Q.-S. *Eur. J. Org. Chem*. **2013**, *2013*, 2977.

46) Wang, H.; Wang, Z.; Li, S.; Qiu, Y.; Liu, B.; Song, Z.; Liu, Z. *Chem. Res. Chin. Univ*. **2016**, *32*, 373.

47) Pansare, S. V.; Lingampally, R.; Dyapa, R.; *Eur. J. Org. Chem*. **2011**, 2235.

Chapter 2

Organocatalytic Michael Addition of Carbon Nucleophiles to *in situ* Generated α-Nitrostyrenes

2.1 Introduction

Organocatalytic asymmetric Michael addition reactions of symmetrical ketones and aldehydes to β-nitroalkenes, a reaction that generates two contiguous stereocenters, have been extensively investigated in recent years.[1] The synthetic utility of this reaction is also due to the nitro group, which can be utilized in numerous synthetic transformations.[2c] The use of β-nitroalkenes in these reactions generates γ-nitroketones with 1,2-stereocenters. This kind of 1,2-stereoinduction is now well established and has also been extensively investigated in other C-C bond forming reactions such as the aldol and Mannich reactions. In contrast, the construction of 1,3-stereocenters in a carbon-carbon bond forming reaction is not very common[2] (shown in Figure 2.1). Interestingly, the organocatalytic Michael addition of ketones or aldehydes to α-nitrostyrenes would generate γ-nitroketones with 1,3-stereocenters. This process, which complements the conjugate addition to β-nitrostyrenes, is not well studied and catalytic enantioselective versions of such a reaction had not been reported when our studies were initiated.

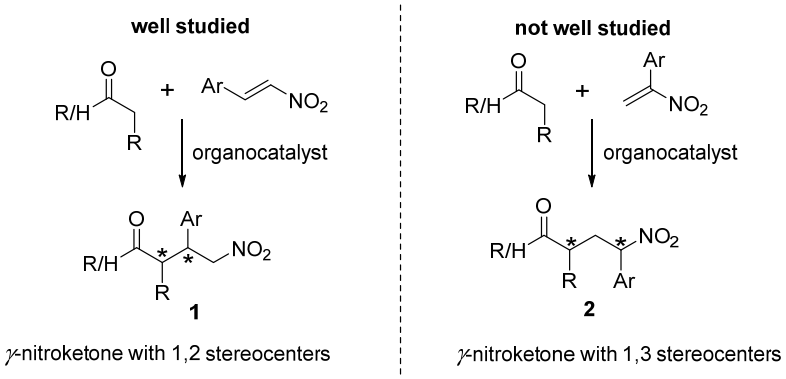


Figure 2.1 Asymmetric induction of adjacent 1,2 stereocenters and non-adjacent 1,3 stereocenters

This chapter describes the first enamine-mediated enantioselective organocatalytic Michael addition reaction of ketones and aldehydes to α-nitrostyrenes.

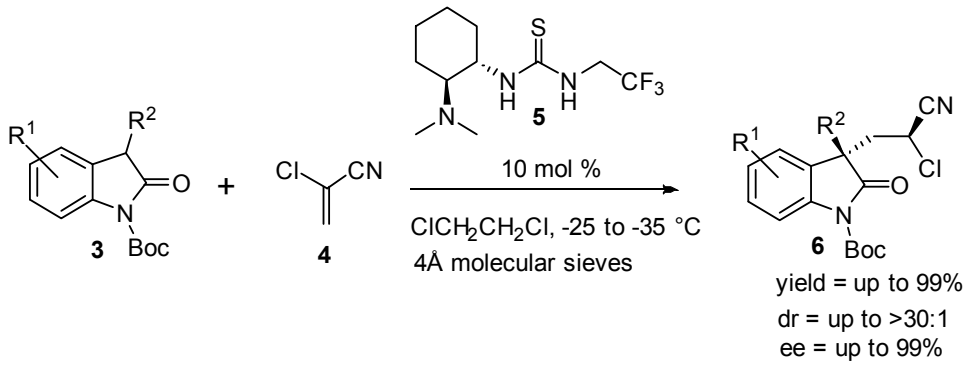
2.2 Objective

The main objective of our study was to utilize cyclic ketones and aldehydes as the Michael donors in catalytic enantioselective conjugate addition reactions with α-nitrostyrenes as the Michael acceptors. Nitroalkenes have been of special interest as excellent Michael acceptors due to the strong electron-withdrawing effect of the nitro group. In addition, conjugate addition of carbonyl compounds to the nitroalkene offers synthetically useful γ-nitrocarbonyl derivatives for the preparation of complex synthetic targets.[3] In addition, the nitro group itself is particularly versatile as it may be transformed into diverse functionalities.[2c]

2.3 Literature Survey

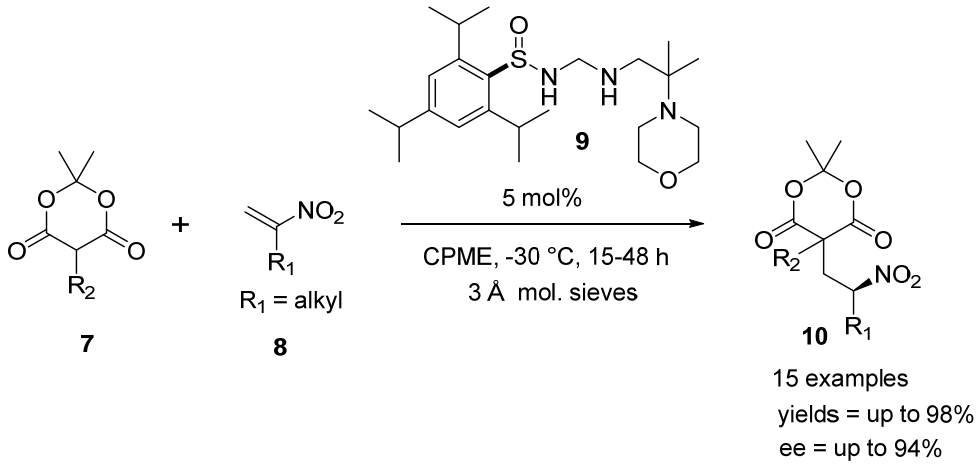
Although no studies on the catalytic enantioselective Michael addition of nucleophiles to α-nitrostyrenes had been reported at the time we started our investigations, a few reports describing the catalytic enantioselective construction of 1,3-stereocenters were available. The following is a brief summary of these methods.

In 2010, Cheng and co-workers reported the first catalytic conjugate addition reaction of 3-substituted oxindoles **3** to 2-chloroacrylonitriles **4** in the presence of a bifunctional tertiary amine thiourea catalyst[4] **5** to afford chiral oxindoles **6** with good yields and excellent diastereo- and enantioselectivity (Scheme 2.1).



Scheme 2.1

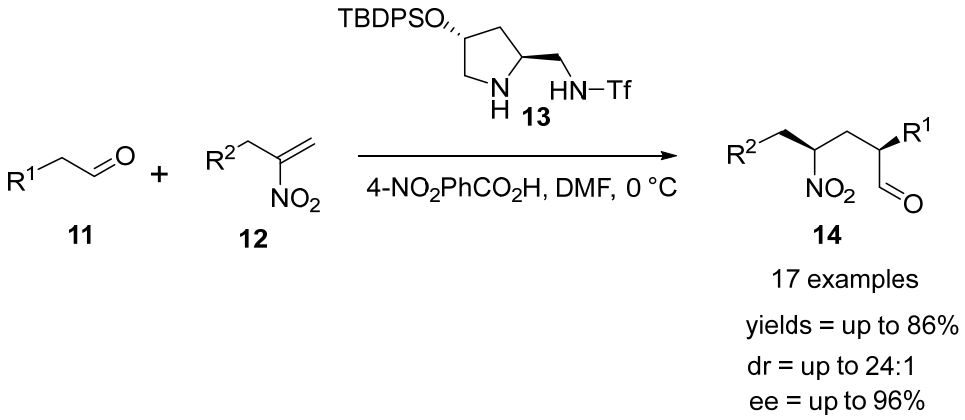
In 2012, Ellman and co-workers reported the first enantioselective catalytic nucleophilic addition of α-substituted Meldrum's acid[1a] **7** to α-alkyl nitroalkenes **8** followed by an enantioselective protonation to provide **10** with good yields and high enantioselectivity (up to 94%, Scheme 2.2). The catalyst of choice was an *N*-sulfinyl urea catalyst **9** which bears a chiral center at the sulfur atom.



Scheme 2.2

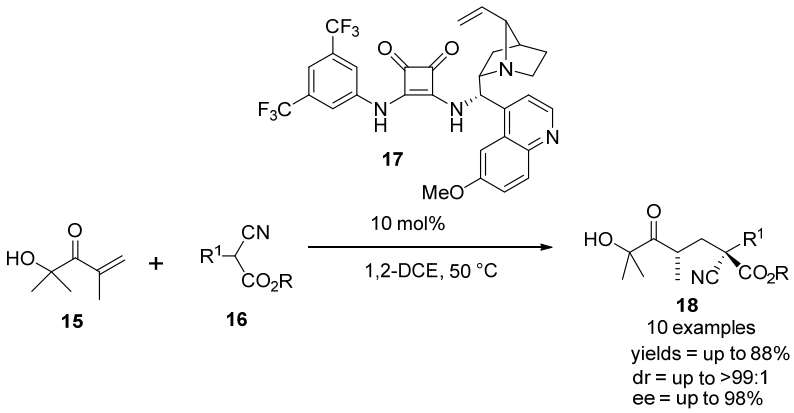
In 2013, Peng and co-workers reported the first organocatalytic asymmetric Michael addition of aldehydes[1b] **11** to α-alkyl nitroalkenes **12** by using the (*S*)-proline-

derived catalyst **13** (Scheme 2.3). The *γ*-nitro aldehydes **14** were formed with good yields and good diastereo- and enantioselectivity.



Scheme 2.3

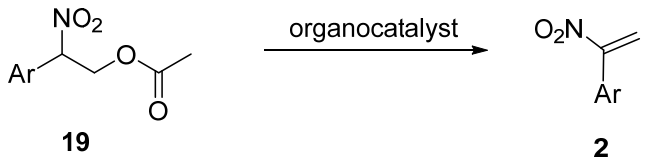
In 2016, Palomo and co-workers reported the asymmetric Michael addition/*α*-protonation of *α*'-hydroxy enone **15** with *α*-substituted cyanoacetates[5] **16** by using a bifunctional Brønsted base catalyst **17** (Scheme 2.4). This methodology provided the acyclic carbonyl adducts **18** in good yields and high diastereo- and enantioselectivity.



Scheme 2.4

2.4 Results and Discussion

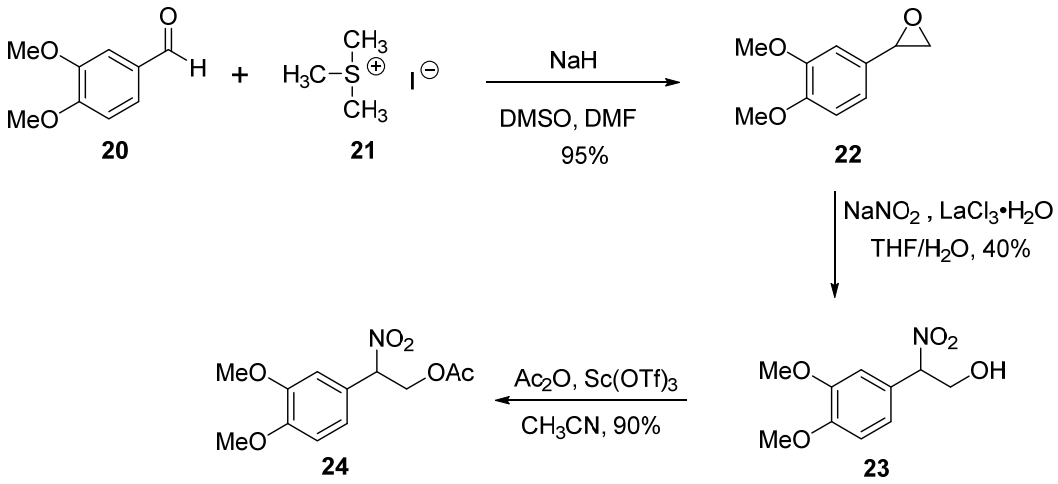
We initiated studies on the Michael addition of ketone **33** to a suitable α-nitrostyrene. In anticipation of the high reactivity of the α-nitrostyrene and the known tendency of such nitroalkenes to either polymerization[6] or rearrangement,[7] we chose to generate the required α-nitrostyrene **2** *in situ*[8] from the corresponding nitroacetate **19** (Fig. 2.2).



19 **2**

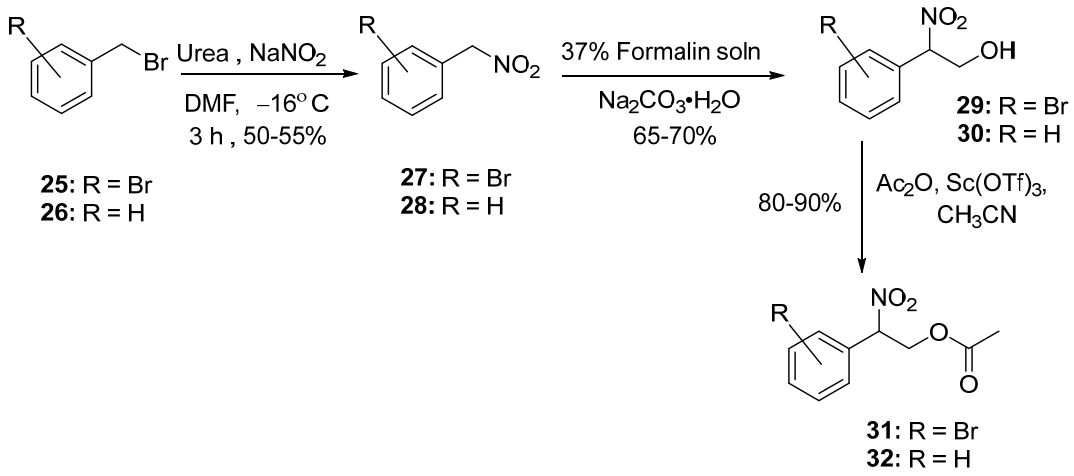
Fig 2.2 α-Nitrostyrene generated *in situ* from the corresponding nitroacetate 19**.**

The nitroacetates utilized in this study were synthesized from easily available starting materials by employing two different procedures. The first method relies on the regioselective ring opening of an epoxide with nitrite anion as the nucleophile (Scheme 2.5). The starting epoxide **22** was synthesized from the commercially available veratraldehyde **20** and salt **21** following the Corey-Chaykovsky protocol (Scheme 2.5). Ring opening of epoxide **22** in the presence of $NaNO_2$ and $LaCl_3 \cdot H_2O$[9] provided the nitroalcohol **23** (40%). Acetylation of **23** in the presence of scandium triflate afforded nitroacetate **24** in 90% yield.



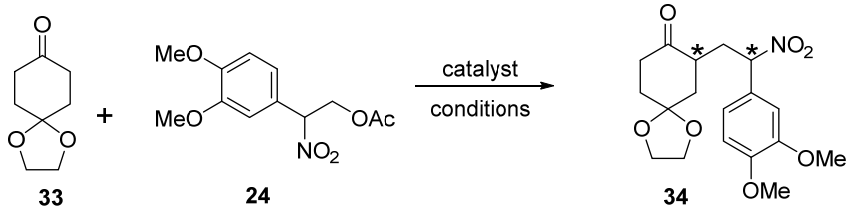
Scheme 2.5

An alternative method for the synthesis of other nitroacetates used in this study is shown in Scheme 2.6. This method uses benzyl bromides **25** or **26** as the starting materials. Displacement of the benzylic bromide with $NaNO_2$ provided the nitro compounds **27** and **28** from **25** and **26**, respectively. A Henry reaction of the nitro compounds **27** and **28** in the presence of Na_2CO_3 and a calculated amount of 37% formalin solution afforded the nitroalcohols **29** and **30** in 65-70% yield. Finally, **29** and **30** were subjected to acetylation with acetic anhydride in the presence of scandium triflate to afford the nitroacetates **31** and **32** in 80-90% yield.



Scheme 2.6

The Michael addition of ketone **33** to the α-nitrostyrene generated *in situ* from 3,4-dimethoxy phenyl nitroacetate **24** was selected as the model reaction for determining the optimum reaction conditions (Scheme 2.7).



Scheme 2.7

Initially, various proline derived primary and secondary amine catalysts were screened for their ability to induce the elimination of acetate from **24** as well as catalyze the Michael addition of ketone **33** to provide nitroketone **34**. The effect of various acid additives was also examined. DMF was used as the solvent for the screening of the acid additives, because previously the Pansare group, we reported the Michael addition of carbon nucleophiles to β-nitrostyrenes,[10] using DMF as the optimal solvent. The proline-

derived diamine and triamine catalysts and the acid co-catalysts examined in this study are shown in Figure 2.3.

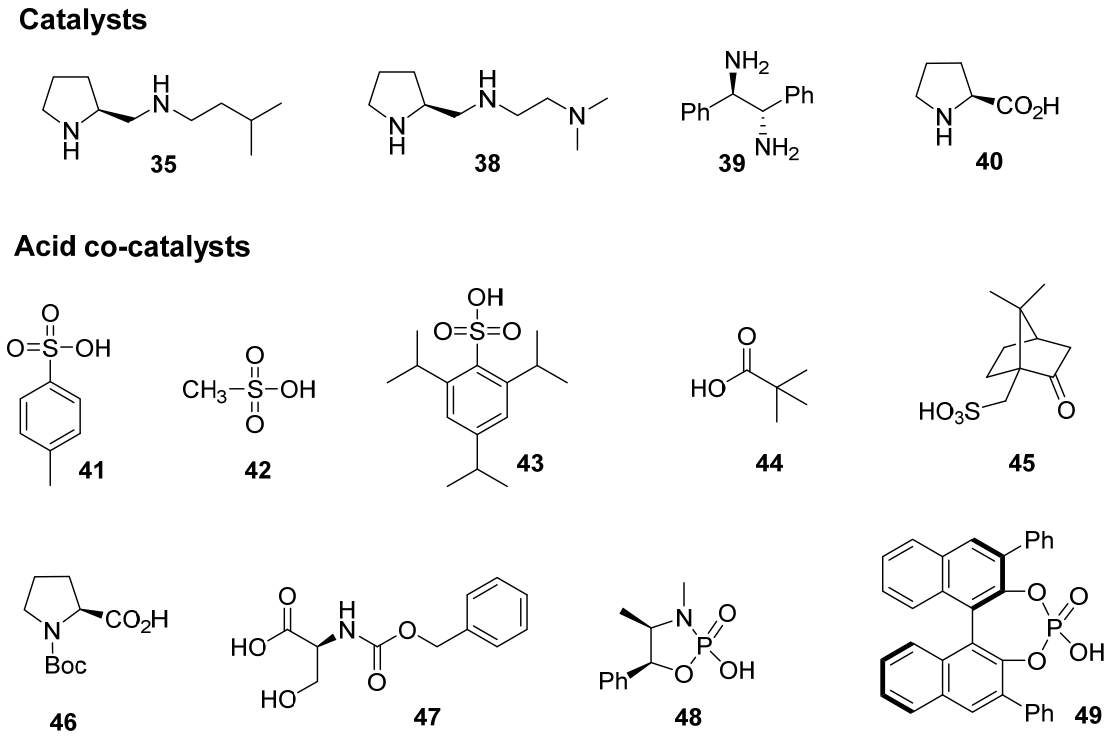
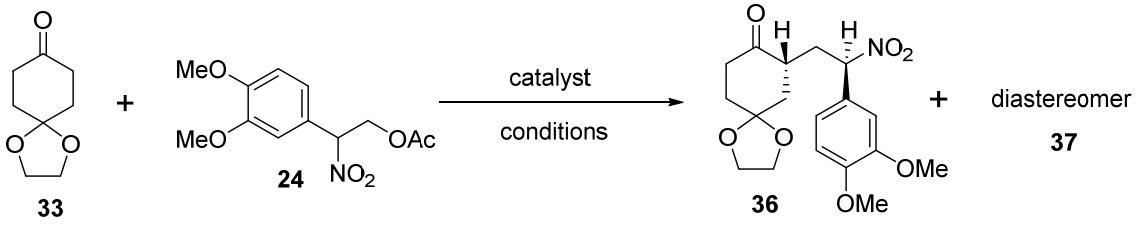


Fig 2.3 Catalysts and acid co-catalysts employed in the screening of the Michael addition of cyclic ketones to *in situ* generated α-nitrostyrenes.

In the absence of an acid co-catalyst, the yield of the Michael addition reaction as well as the enantiomeric excess of the products is significantly lower. The use of achiral acid catalysts results in an increase in yield and enantiomeric excess (as compared to the reaction without an acid co-catalyst) of the Michael adduct, but this increase is more pronounced when a chiral acid is used. The best result is obtained with the diamine catalyst **35** and (1*S*)-camphorsulfonic acid **45** at ambient temperature as shown in Table 2.1.

Table 2.1: Catalyst and additive screening for the organocatalytic Michael addition of ketone to *in situ* generated *α*-nitrostyrene



33 + 24 → 36 + **37**

(All reactions are done with 5 eq. of ketone, DMF solvent)

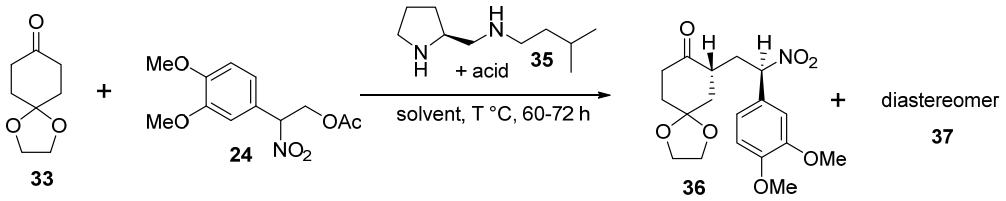
Entry	Catalyst	Acid additive	Yield[a] (%)	ee[b] (%)	
			(36+37)	36	37
1	38	**41**	-	-	-
2	35	**45**	-	-	-
3	35	**40**	12	12	nd
4	35	**46**	-	-	-
5	35	**47**	29	51	43
6	35	**48**	32	71	67
7	35	**49**	47	72	58
8	35	**44**	-	-	-
9	35	**42**	39	65	59
10	35	**41**	49	72	57
11	35	**43**	51	67	60
12	**35**	**45**	**56**	**75**	**60**
13	39	**45**	41	41	nd
14	40	**45**	57	12	nd

[a]Isolated yields. [b]Chiral HPLC analysis. [nd]not determined.

Next, we screened several solvents like DMF, dichloromethane, chloroform, ethyl acetate and acetonitrile as shown in Table 2.2. Initially, we examined the reactions at ambient temperature with various solvents. In all of the reactions, the required Michael

addition product was obtained, but always as a mixture of diastereomers. When methanesulfonic acid was used as the co-catalyst, DMF, dichloromethane and chloroform emerged as the most promising solvents. An improved reaction rate and better enantioselectivity were observed when (1*S*)-camphorsulfonic acid was used as the co-catalyst in DMF and acetonitrile. It appeared that DMF should be the solvent of choice for further optimization studies with diamine catalyst **35**. We also studied the organocatalytic Michael addition reaction at lowered temperature with the hope of increasing the yield and enantioselectivity of the reaction using DMF as the solvent. Reactions with (1*R*)-camphorsulfonic acid and (1*S*)-camphorsulfonic acid were both examined in DMF at 0 °C. Of these additives, (1*S*)-camphorsulfonic acid provided better yields and enantioselectivity (Table 2.2, entries 10 and 11).

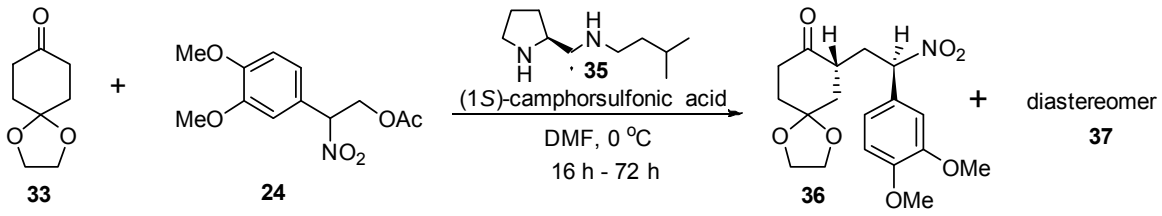
Table 2.2: Solvent survey for the organocatalytic Michael addition reaction of 33 to *in situ* generated α-nitrostyrene



Entry	Acid	Solvent	Temp.	Yield[a] (%)		ee[b] (%)	
				36	**37**	**36**	**37**
1	MsOH	DMF	rt	25	15	65	69
2		CH_2Cl_2	rt	32	13	67	57
3		$CHCl_3$	rt	-	-	-	-
4		EtOAc	rt	25	10	55	54
5	**1(*S*)-camphorsulfonic acid**	**DMF**	**rt**	**40**	**16**	**75**	**60**
6		CH_3CN	0 °C – rt	41	17	84	51
7		CH_2Cl_2	0 °C	-	-	-	-
8		$CHCl_3$	0 °C	-	-	-	-
9		EtOAc	0 °C	-	-	-	-
10	(1*R*)-camphorsulfonic acid	DMF	0 °C	25	23	88	58
11	**(1*S*)-camphorsulfonic acid**	**DMF**	**0 °C**	**51**	**23**	**92**	**52**

[a]Isolated yields. [b]Chiral HPLC analysis.

From this study, the diamine **35** (20 mol %) in the presence of (1*S*)-camphorsulfonic acid as the co-catalyst (20 mol %) in DMF emerged as the catalytic system of choice.



Scheme 2.8

The synthesis of nitroketone **36** constitutes the first example of the stereoselective Michael addition of a ketone to an *in situ* generated α-nitrostyrene. The diastereoselectivity of the process is low (~1.5:1 dr), but the diastereomers can be easily separated to provide the major diastereomer in synthetically useful yield (51-52%) and enantiomeric excess (82-92% ee). The enantiomeric excess of the minor diastereomers is typically low (50-55% ee). Treatment of pure **36** (92% ee) with catalyst **35** (20 mol %) in the presence of ketone **33** (5 equiv) did not result in any loss of enantiomeric excess of **36** under the conditions employed for the Michael addition. The minor diastereomer could not be detected in this reaction mixture. These observations suggest that the Michael adduct **36** does not revert back to **33** and the nitroalkene and also that the minor diastereomer is not obtained by the epimerization of the major diastereomer under the reaction conditions.

Although the mechanistic details for the formation of **36** are not established, a plausible mechanism is shown in Figure 2.4.

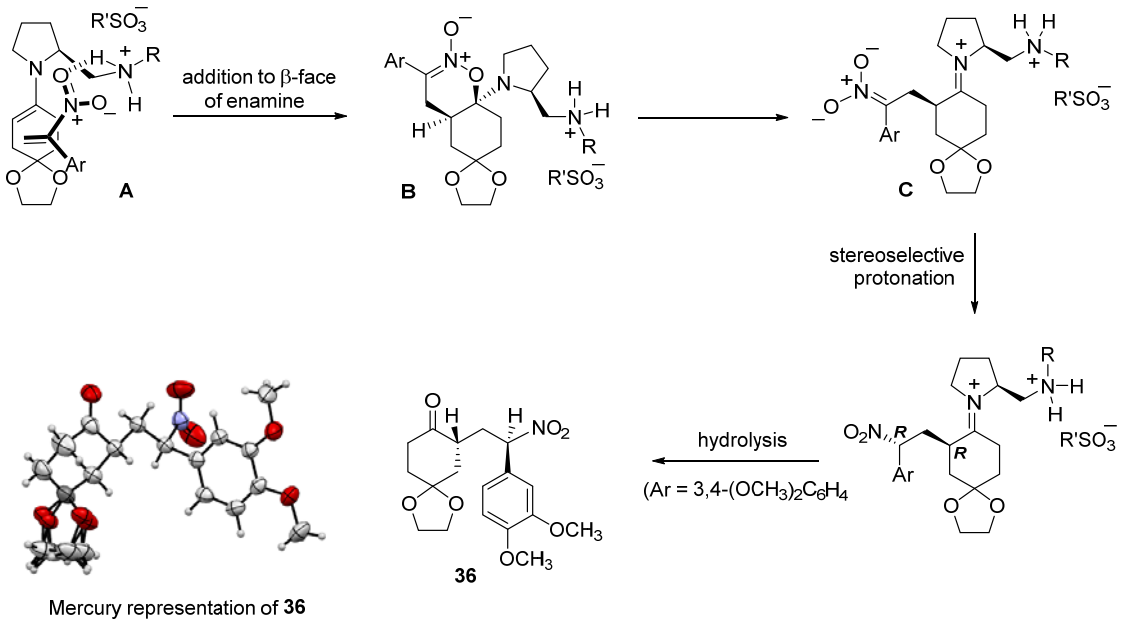


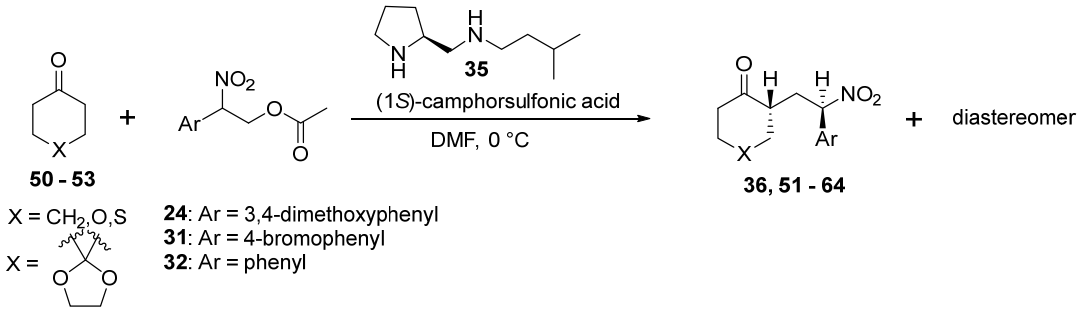
Figure 2.4 Formation of major diastereomer **36** and X-ray crystal structure of nitroketone **36**.

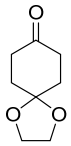
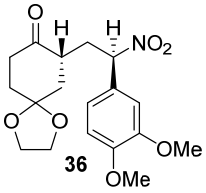
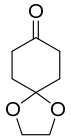
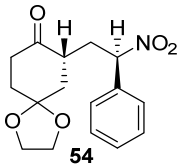
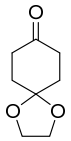
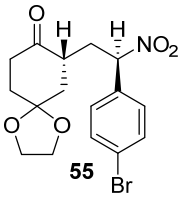
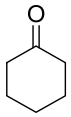
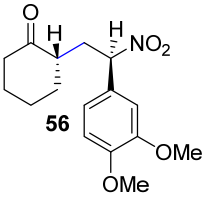
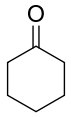
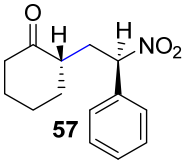
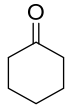
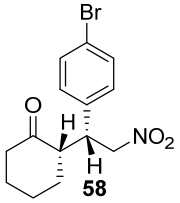
It is likely that the Michael addition of **33** with the *α*-nitrostyrene derived from **24** proceeds via a hydrogen-bonded[11] intermediate **A** (Figure 2.4) in which the nitroalkene is delivered to the *β*-face of the enamine derived from **33** and catalyst **35**. This step establishes the ring stereocenter in the major diastereomer **36**, and it could generate the 1,2-oxazine *N*-oxide intermediate **B**. Similar intermediates have previously been proposed[2e] in stoichometric reactions of 4-*tert*-butylcyclohexanone-derived enamines with *α*-nitrostyrene and two of the 1,2-oxazine *N*-oxide intermediates were isolated and characterized in these studies. Subsequent opening of the oxazine produces the nitronate **C**, which is protonated stereoselectively to generate the benzylic stereocenter in **36**. The origin of the stereoselectivity in the protonation step is not known at present. The low diastereoselectivity of the Michael addition may be due to the high reactivity of the *α*-

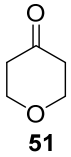
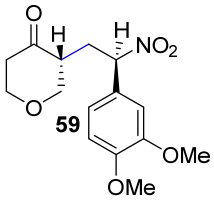
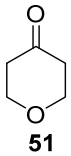
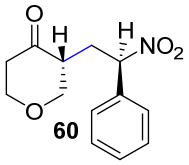
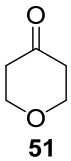
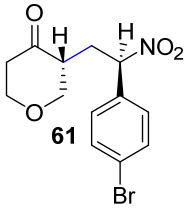
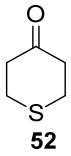
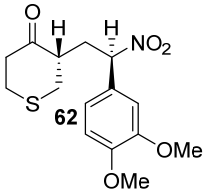
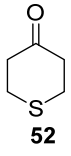
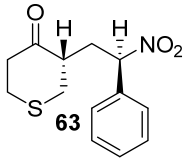
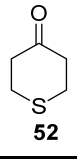
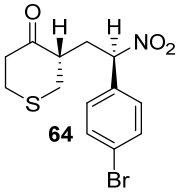
nitrostyrene, which enables a competing, non-hydrogen-bonded addition to the α-face of the enamine. The absolute configuration of **36** (*R*,*R*) was established by X-ray crystallographic analysis.[12]

Having established the optimized set of conditions for the conjugate addition reaction, the utility of diamine catalyst **35** was examined for Michael addition reactions of a variety of cyclic (6-membered) ketones to selected *in situ* generated α-nitrostyrenes. These reactions proceeded efficiently with moderate enantioselectivity and diastereoselectivity as shown in the Table 2.3.

Table 2.3: Results of organocatalytic Michael addition of a variety of cyclic ketones to *in situ* generated α-nitrostyrenes



Entry [a]	Starting material Ketone	Starting material Nitroacetate	Product	Yield[b] (%)	dr[c]	ee[d](%)
1	 **53**	**24**	 **36**	51	1.7:1	92
2	 **53**	**32**	 **54**	51	1.4:1	80
3	 **53**	**31**	 **55**	52	1.3:1	86
4	 **50**	**24**	 **56**	44	1.6:1	92
5	 **50**	**32**	 **57**	58	2.3:1	74
6	 **50**	**31**	 **58**	30	single diastereomer	97

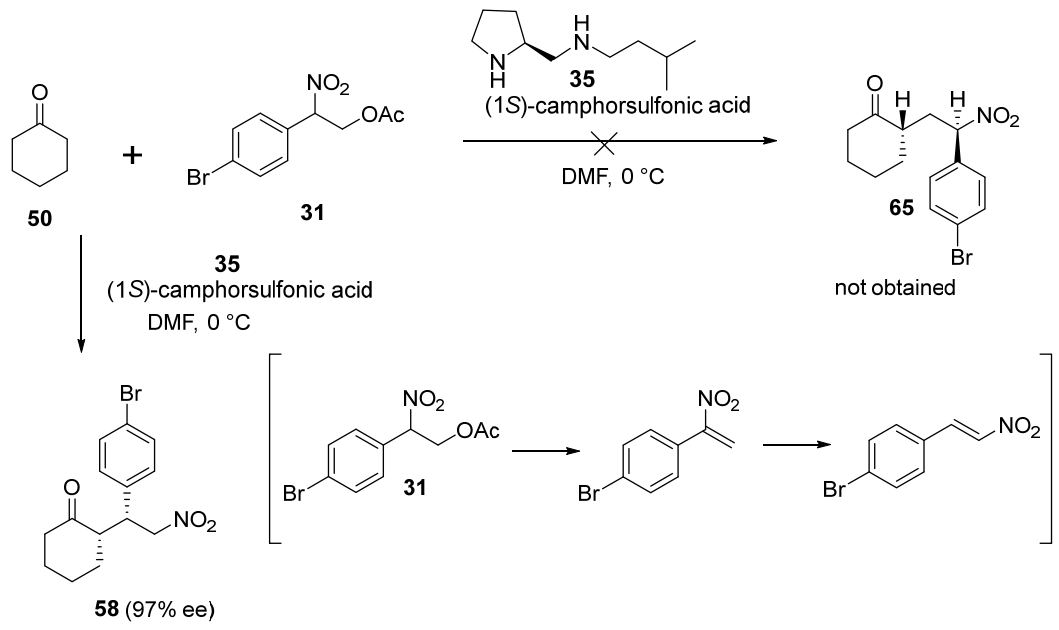
7	 **51**	**24**	 **59**	53	1.7:1	80
8	 **51**	**32**	 **60**	46	1.3:1	90
9	 **51**	**31**	 **61**	37	1.2:1	20
10	 **52**	**24**	 **62**	50	1.7:1	rac
11	 **52**	**32**	 **63**	24	1:1	60
12	 **52**	**31**	 **64**	37	1.1:1	79

[a]All reactions were done in DMF for 72 h at 0 °C, with 5eq. of ketone.
[b]Isolated yields. [c]Determined by ^{1}H NMR of crude product.
[d]Chiral HPLC analysis.

As seen from Table 2.3, a range of six-membered cyclic ketones, having various functionalities, could react with *in situ* generated α-nitrostyrenes to afford the corresponding γ-nitroketone products. As mentioned before, these were obtained as a

mixture of diastereomers (dr = 1-1.7:1) and, with the exception of ketones **61** and **62**, only the diastereomer which is obtained with good enantiomeric excess is shown. The stereochemical assignment for the nitroketones **54-64** is based on the similarity of their ^{1}H NMR spectra to that for nitroketone **36**, the stereochemistry of which was assigned by X-ray crystallography. Overall, the organocatalytic Michael addition of cyclic, six-membered ketones with *in situ* generated α-nitrostyrenes gave the required products with low diastereoselectivity but, in most instances, the enantiomeric excess of one of these diastereomers was good (80% to 92%). The reasons for the low enantiomeric excess of the ketones **61** and **62** are not known at this time. The low enantiomeric excess of **61** is particularly difficult to explain because ketones **59** and **60**, both obtained with tetrahydropyran-4-one as the Michael donor, are obtained with good enantiomeric excess (80% and 90% ee respectively).

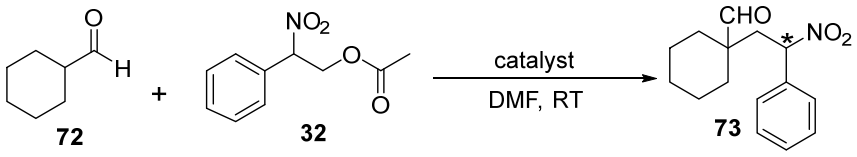
As mentioned previously, a potential problem with using α-nitrostyrenes is their facile rearrangement to the corresponding β-nitrostyrenes in the presence of a base. This rearrangement was not observed in the vast majority of the reactions that we have examined. The only exception is the reaction of cyclohexanone with 4-bromophenyl nitroacetate **31** which gave the Michael adduct **57** (97% ee) arising from the reaction of **50** with the β-nitrostyrene obtained from the rearrangement of the α-nitrostyrene obtained from **31** during the course of the reaction. The desired Michael adduct **65** was not obtained in this reaction (Scheme 2.10).



Scheme 2.10

Having established the feasibility of the Michael addition of cyclic ketones to *in situ* generated α-nitrostyrenes, we proceeded to examine this reaction with aldehydes as the Michael donors.

Initially, we examined the reaction of cyclohexane carboxaldehyde **72** and phenyl nitroacetate **32** (Scheme 2.11) with various proline-derived catalysts as shown in Figure 2.5.



Scheme 2.11

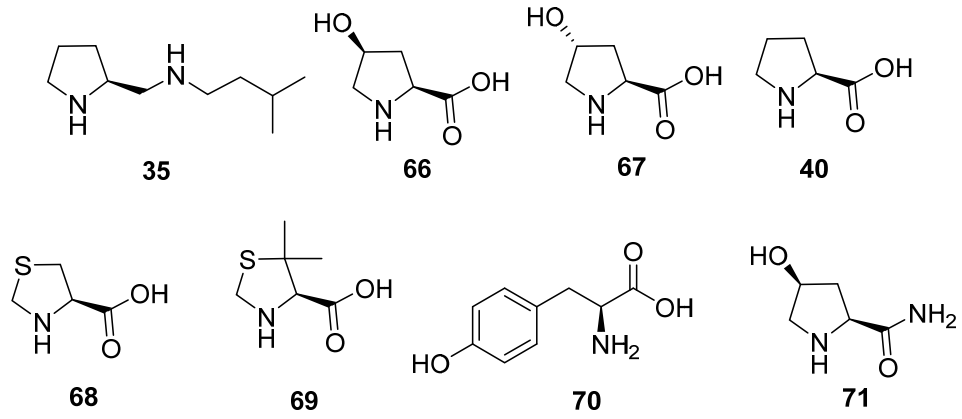
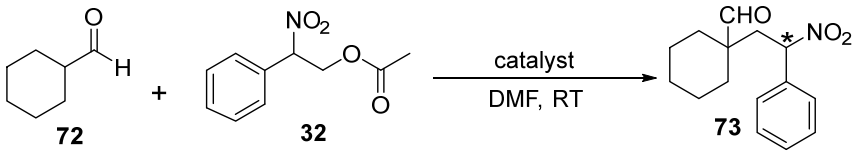


Fig: 2.5 Catalysts employed for the screening of the Michael addition of α-disubstituted aldehydes to α-nitrostyrenes

Table 2.4: Catalyst screening for the organocatalytic Michael addition of aldehydes to *in situ* generated α-nitrostyrenes



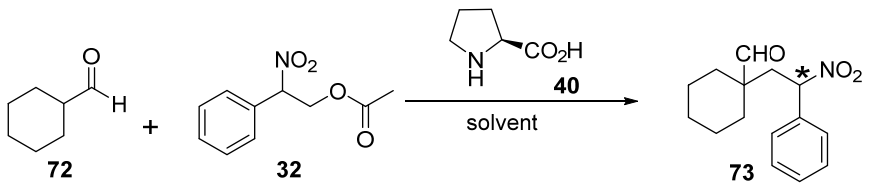
Entry	catalyst	Time	Yield[a] (%)	ee[b] (%)
1	35	3 d	-	-
2	66	2 d	45	60
3	67	3 d	32	50
4	**40**	**16 h**	**43**	**70**
5	68	8 d	-	-
6	69	21 h	33	racemic
7	70	8 d	25	84
8	71	8 d	-	-

[a]Isolated yields. [b]Chiral HPLC analysis.

It was immediately apparent that the optimized reaction conditions for the Michael addition of cyclic ketones to α-nitrostyrenes do not work well for cyclohexane carboxaldehyde. When the diamine catalyst **35**, which was the catalyst of choice in the ketone studies was employed, no product was observed with cyclohexane carboxaldehyde as the Michael donor. Only the β-nitrostyrene obtained from the rearrangement of the α-nitrostyrene was observed in cyclohexane carboxaldehyde, suggesting that either enamine formation from the aldehyde or reaction of the enamine with the α-nitrostyrene is an issue in these reactions. Studies with other catalysts were comparatively more fruitful. The use of *cis* 4-hydroxy-proline **66** and *trans* 4-hydroxy-proline **67** as catalysts gave us moderate yield and low enantioselectivity. However, in the case of proline amide **68** and (*S*)-4-thiazolidinecarboxylic acid **68**, no reaction was observed. The use of (*S*)-tyrosine as the catalyst gave the required product in low yield (25%), but good enantiomeric excess (84% ee). The use of (*S*)-proline as the catalyst gave us promising results with 43% yield and 70% ee as shown in Table 2.4.

A solvent optimization study was then conducted with (*S*)-proline as the catalyst and the results are summarized in Table 2.5. It was apparent that the reaction works well only with DMF and DMSO as solvents, giving the expected Michael adduct **73** with moderate yield and enantioselectivity.

Table 2.5: Solvent screening for the organocatalytic Michael addition of aldehydes to *in situ* generated *α*-nitrostyrenes

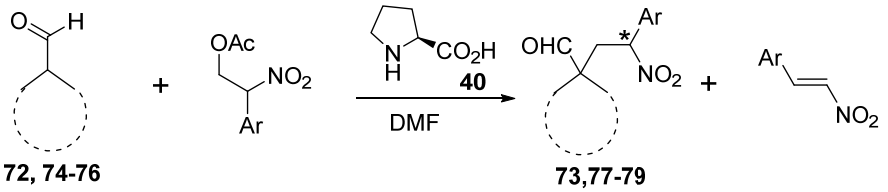


Entry	Solvent	Time	Yield[a] (%)	ee[b] (%)
1	EtOAc	6 d	-	-
2	CH_2Cl_2	6 d	-	-
3	Chloroform	6 d	-	-
4	CH_3CN	6 d	-	-
5	Toluene	6 d	-	-
6	DCE	6 d	-	-
7	MeOH	94 h	-	-
8	**DMF**	**16 h**	**43**	**70**
9	DMSO	16 h	33	67

[a]Isolated yields. [b]Chiral HPLC analysis.

In order to examine the scope of the reaction, the optimized conditions were then examined for the Michael addition of a variety of *α*-substituted aldehydes to *in situ* generated *α*-nitrostyrenes. The results are shown in Table 2.6.

Table 2.6: Results of Organocatalytic Michael addition of a variety of α-disubstituted aldehydes to *in situ* generated α-nitrostyrenes

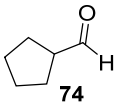
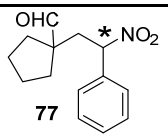
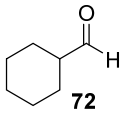
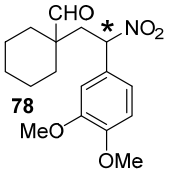
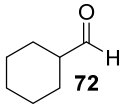
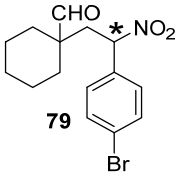
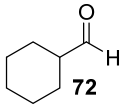
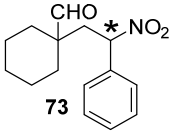
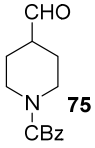


72, 74-76

24: Ar = 3,4-dimethoxyphenyl
31: Ar = 4-bromophenyl
32: Ar = phenyl

73,77-79

80: Ar = 3,4-dimethoxyphenyl
81: Ar = 4-bromophenyl
82: Ar = phenyl

Entry	Nucleophiles	Product	Catalyst	Yield[a] (%)	ee[b] (%)	Yield[c] of β-nitrostyrenes (%)
1	 **74**	 **77**	38	41	35	36
2	 **72**	 **78**	38	40	70	38
3	 **72**	 **79**	38	45	69	40
4	 **72**	 **73**	38	43	76	42
5	 **75**	Not obtained	-	-	-	55
6	 **76**	Not obtained	-	-	-	42

[a]Isolated yields. [b]Chiral HPLC analysis. [c]Isolated yields of rearranged β-nitrostyrenes.

The results in Table 2.6 indicate that this methodology has certain limitations. Firstly, rearrangement of the α-nitrostyrene to β-nitrostyrene during the course of the reaction cannot be prevented in reactions with cyclopentanecarboxaldehyde and cyclohexane carboxaldehyde. Secondly, a change in the cyclohexane carboxaldehyde structure at a site that is quite far from the aldehyde has a detrimental effect on the reaction as seen by the lack of reactivity of aldehyde **75** (Table 2.6, entry 5). In addition, an acyclic α-disubstituted aldehyde also failed to react. It should be mentioned that, in order to avoid the formation of diastereomeric products, only α-disubstituted aldehydes were examined in this study.

2.5 Conclusions

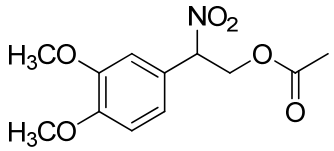
In summary, the organocatalytic Michael addition of aldehydes and cyclic ketones to α-nitrostyrenes was achieved. The reaction works well for cyclic ketones but the diastereoselectivity is low. The scope of the reaction with aldehydes is limited and the enantioselectivities are low to moderate. Since there is no literature precedent for the reaction of α-nitrostyrenes with aldehydes, determining the stereochemistry of the major enantiomer of the Michael addition products **73** and **77** to **79** is challenging. However, we have observed that the enantiomeric excess of **78** can be enhanced by repeated recrystallization,[13] and are therefore optimistic that a crystal structure of the Michael adduct **78** can be obtained to provide the required stereochemical information.

2.6 Experimental Section:

General procedure for the synthesis of nitroacetates

To a solution of the nitroalcohol in CH_3CN at 0 ^oC was added acetic anhydride followed by $Sc(OTf)_3$. The mixture was stirred for 30 min at 0 ^oC and then at ambient temperature for 2 h. The reaction mixture was cooled to 0 ^oC, water was added and the resulting mixture was diluted with ethyl acetate and washed with water. The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel.

2-(3,4-Dimethoxyphenyl)-2-nitroethyl acetate (24):



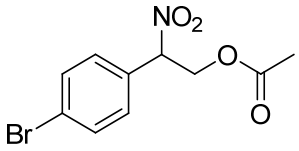
A mixture of 2-(3,4-dimethoxyphenyl)oxirane (4.00 g, 22.2 mmol), $NaNO_2$ (11.9 g, 173 mmol) and $LaCl_3 \cdot 7H_2O$ (10.9 g, 44.4 mmol) in THF: H_2O (1:1, 160 mL) was vigorously stirred at ambient temperature for 12 h. The mixture was then extracted with ether (4 × 25 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1:1) to provide 1.50 g (30%) of 2-(3,4-dimethoxyphenyl)-2-nitroethanol as a yellow foam.

Reaction of the above nitroalcohol (1.84 g, 8.1 mmol), acetic anhydride (1.14 mL, 12.1 mmol) and $Sc(OTf)_3$ (40 mg, 0.08 mmol) in CH_3CN (40 mL) at 0 ^oC according to

the general procedure gave, after purification of the crude product by flash chromatography on silica gel (hexanes/EtOAc, 7:3), 1.70 g (81%) of **24** as a yellow solid.

IR (neat): 1742, 1550, 1516, 1448, 1427, 1394, 1366, 1224, 1146, 1022 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 8.3, 2.0, Ar*H*), 6.95 (d, 1H, *J* = 2.0, Ar*H*), 6.88 (d, 1H, *J* = 8.3, Ar*H*), 5.67 (dd, 1H, *J* = 10.7, 3.4, C*H*NO_2), 4.95 (dd, 1H, *J* = 12.3, 10.7, C*H*$_2$OCOCH$_3$), 4.48 (dd, 1H, *J* = 12.3, 3.4, C*H*$_2$OCOCH$_3$), 3.90 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 2.09 (s, 3H, OCOC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (*C*=O), 150.8 (Ar*C*$_{ipso}$), 149.5 (Ar*C*$_{ipso}$), 122.9 (Ar*C*$_{ipso}$), 120.7 (Ar*C*), 111.3(Ar*C*), 110.2 (Ar*C*), 88.6 (*C*HNO_2), 63.9 (*C*H$_2$OCOCH$_3$), 56.06 (O*C*H$_3$), 55.98 (O*C*H$_3$), 20.6 (CO*C*H$_3$). MS (ESI, pos.): *m*/*z* 292.0 $(M+Na)^+$; HRMS (ESI, pos.): *m*/*z* 270.1015 (270.0978 calc. for ($C_{12}H_{16}NO_6$ $(M+H)^+$), 292.0794 (292.0797 calc. for ($C_{12}H_{15}NNaO_6$ $(M+Na)^+$).

2-(4-Bromophenyl)-2-nitroethyl acetate (31):



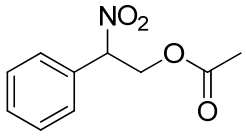
To a solution of (4-bromophenyl)-nitromethane (1.0 g, 4.6 mmol) in THF (5 mL) was added aqueous formaldehyde (37% w/v, 0.14 mL, 4.6 mmol) followed by sodium carbonate monohydrate (631 mg, 5.1 mmol) and the mixture was stirred at ambient temperature for 12 h. The THF was removed under reduced pressure and the residue obtained was dissolved in ethyl acetate (30 mL). The solution was washed with water (5 mL) and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure.

The residue obtained was purified by flash chromatography on silica gel (hexane/EtOAc, 8:2) to provide 0.7 g (70%) of 2-(4-bromophenyl)-2-nitroethanol as a white solid.

Reaction of the above nitroalcohol (600 mg, 2.4 mmol), acetic anhydride (0.34 mL, 3.7 mmol) and $Sc(OTf)_3$ (12 mg, 0.02 mmol) in CH_3CN (10 mL) at 0 ^oC according to the general procedure gave, after purification of the crude product by flash chromatography on silica gel (hexanes/EtOAc, 8:2), 645 mg (92%) of **31** as a white solid.

IR (neat): 1737, 1554, 1365, 1246, 1125, 1050, 1009, 927 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, 2H, *J* = 8.4, Ar*H*), 7.34 (d, 2H, *J* = 8.4, Ar*H*), 5.69 (dd, 1H, *J* = 10.4, 3.6, C*H*NO_2), 4.90 (dd, 1H, *J* = 12.3, 10.4, C*H*$_2$OCOCH$_3$), 4.50 (dd, 1H, *J* = 12.3, 3.6, C*H*$_2$OCOCH$_3$), 2.09 (s, 3H, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (*C*=O), 132.6 (2 × Ar*C*), 129.5 (Ar*C*$_{ipso}$), 129.3 (2 × Ar*C*), 125.1 (Ar*C*$_{ipso}$), 88.1 (*C*HNO_2), 63.5 (*C*H$_2$OCOCH$_3$), 20.6 (COC*H*$_3$).HRMS (ESI, pos.): *m*/*z* 286.9798 (286.9793 calc. for ($C_{10}H_{10}{}^{79}BrNO4)^+$), *m*/*z* 309.9694 (309.9691 calc. for [$C_{10}H_{10}{}^{79}BrNNaO_4$(M+Na)$^+$), *m*/*z* 311.9666 (311.9670 calc. for ($C_{10}H_{10}{}^{81}BrNNaO_4$(M+Na)$^+$).

2-Nitro-2-phenylethyl acetate (32):



To a solution of phenyl nitromethane (0.90 g, 6.6 mmol) in THF (5 mL) was added aqueous formaldehyde (37% w/v, 0.2 mL, 6.6 mmol) followed by sodium carbonate monohydrate (895 mg, 7.2 mmol) and the mixture was stirred at ambient temperature for 12 h. The THF was removed under reduced pressure and the residue was dissolved in ethyl

acetate and washed with water (5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue obtained was purified by flash chromatography on silica gel (hexanes/EtOAc, 8:2) to provide 450 mg (45%) of 2-nitro-2-phenyl ethanol as a white solid.

Reaction of the above nitroalcohol (0.5 g, 3 mmol), acetic anhydride (0.42 mL, 4.5 mmol) and $Sc(OTf)_3$ (15 mg, 0.03 mmol) in CH_3CN (8 mL) at 0 ºC according to the general procedure gave, after purification of the crude product by flash chromatography on silica gel (hexanes/EtOAc, 8:2), 565 mg (90%) of **32** as a dark orange liquid.

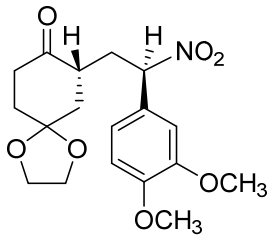
IR (neat): 1744, 1553, 1366, 1304, 1218, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.37-7.48 (m, 5H, Ar*H*), 5.73 (dd, 1H, *J* = 10.6, 3.4, C*H*NO_2), 4.95 (dd, 1H, *J* = 12.3, 10.6, C*H*$_2$OCOCH_3), 4.50 (dd, 1H, *J* = 12.3, 3.4, C*H*$_2$OCOCH_3), 2.08 (s, 3H, COC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.24 (*C*=O), 130.66 (ArC_{ipso}), 130.60 (Ar*C*), 129.3 (2 × Ar*C*), 127.6 (2 × Ar*C*), 88.8 (*C*HNO_2), 63.8 (*C*H$_2$OCOCH_3), 20.6 (*C*OCH_3); MS (ESI, pos.): *m/z* 232.0, $(M+Na)^+$; HRMS: *m*/*z* 209.0692 (209.0688 calc. for $C_{10}H_{11}NO_4)^+$, 232.0579 (232.0586 calc. for ($C_{10}H_{11}NNaO_4$ $(M+Na)^+$).

General experimental procedure for the Michael addition of ketones to nitroalkenes:

To a solution of the ketone, catalyst **35**, and (1*S*)-camphorsulfonic acid in DMF was added the nitroacetate and the resulting solution was stirred at 0 ºC for 72 h except when noted otherwise. Ethyl acetate (5 mL) was added and the solution was washed with water,

dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel.

(*R*)-7-((*R*)-2-(3,4-Dimethoxyphenyl)-2-nitroethyl)-1,4-dioxaspiro[4.5]decan-8-one (36):



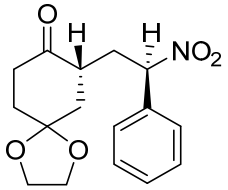
To a solution of 1,4-cyclohexanedione monoethylene ketal (**33**, 11.6 g, 74.3 mmol), (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (505 mg, 3.0 mmol), and (1*S*)-camphorsulfonic acid (690 mg, 3.0 mmol) in DMF (46 mL) was added 3,4-dimethoxyphenyl nitroacetate **24** (4 g, 14.8 mmol) and the resulting solution was stirred at 0 ^oC for 72 h. Ethyl acetate (100 mL) was added and the solution was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel to provide 2.45 g (45%) **36** with 92% ee as a white solid.

R_f = 0.25 (hexanes/EtOAc, 7:3); IR (neat): 2959, 2873, 1708, 1546, 1510, 1264, 1231, 1150, 1137, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 8.30, 2.1, Ar*H*), 6.96 (d, 1H, *J* = 2.1, Ar*H*), 6.86 (d, 1H, *J* = 8.3, Ar*H*), 5.63 (dd, 1H, *J* = 10.3, 4.4, C*H*NO_2), 4.03-4.01 (m, 4H, OCH_2CH_2O), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 2.75-2.63 (m, 2H, COC*H*, CH_2CHNO_2), 2.35-2.49 (m, 2H, CH_2CH_2CO, CH_2CHNO_2), 2.30 (dd, 1H, *J* = 10.3, 4.1, CH_2CH_2CO), 2.13-1.99 (m, 2H, COCH_2, COCHCH_2), 1.97 (dd, 1H, *J* = 13.6, 4.9, COCH_2) 1.78 (t, 1H, *J* = 13.3, COCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.4

(*C*O), 150.2 (Ar*C*$_{ipso}$), 149.2 (Ar*C*$_{ipso}$), 127.2 (Ar*C*$_{ipso}$), 120.3 (Ar*C*), 111.1 (Ar*C*$_{ipso}$), 110.2 (Ar*C*), 106.8 (O*C*O), 89.6 (*C*HNO$_2$), 64.9 (O*C*H$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 56.0 (O*C*H$_3$), 55.9 (O*C*H$_3$), 43.3 (CO*C*H), 41.4 (*C*H$_2$CHC(O)O), 38.3 (*C*H$_2$CHNO$_2$), 34.8 (*C*H$_2$CO), 34.0 (*C*H$_2$CH$_2$C(O)O); MS (ESI, neg.): 364.1 $(M-H)^-$; HRMS (ESI, neg.): *m/z* 365.1469 (365.1475 calc. for $C_{18}H_{23}NO_7(M^-)$); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 60/40, flow rate 1 mL min^{-1}, λ= 247 nm): t_{major} = 10.20 min., t_{minor} = 12.98 min., 92% ee.

Crystals suitable for X-ray analysis were obtained by dissolving **36** (10 mg) in isopropyl alcohol (0.4 mL) followed by addition of hexanes (0.6 mL) to this solution. The resulting clear solution was left at ambient temperature for gradual evaporation. The precipitated crystals were collected after 48 h, dried in vacuo and analyzed.

(*R*)-7-((*R*)-2-Nitro-2-phenylethyl)-1,4-dioxaspiro[4.5]decan-8-one (54):

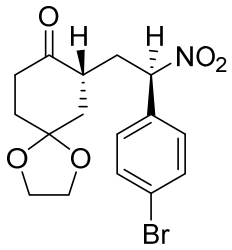


To a solution of cyclohexanedione monoethylene ketal (0.37 g, 2.4mmol), (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (16 mg, 0.1 mmol), and (1*S*)-camphor sulfonic acid (22 mg, 0.1mmol) in DMF (2 mL) was added phenyl nitroacetate **32** (100 mg, 0.47mmol) and the resulting solution was stirred at 0 ^oC for 36 h. Ethyl acetate (10 mL), was added and the solution was washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 80:20) to provide 73 mg (50%) of **54** with 80% ee as a white solid.

IR (neat):1712, 1548, 1362, 1305, 1124, 1089, 1055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ

7.50-7.42 (m, 2H, Ar*H*), 7.43-7.36 (m, 3H, Ar*H*), 5.70 (dd, 1H, *J* = 10.3, 4.3, C*H*NO_2), 4.06-3.96 (m, 4H, OCH_2CH_2O), 2.77-2.61 (m, 2H, NO_2CHCH_2), 2.55-2.45 (m, 1H, COC*H*), 2.45-2.25 (m, 2H, COCH_2), 2.15-1.90 (3H, CH_2CH_2, CHCH_2 (ring)), 1.77 (t, 1H, *J* = 13.0, CHCH_2 (ring)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.3 (*C*O), 134.9 (ArC_{ipso}), 129.8 (ArC_{ipso}), 129.0 (2 x Ar*C*), 127.4 (2 x Ar*C*), 106.8 (O*C*O), 89.8 (*C*HNO_2), 64.9 (O*C*H_2CH_2O), 64.7 (OCH_2*C*H_2O), 43.3 (*C*H_2C-O), 41.4 (*C*H_2C-O), 38.3 (*C*H_2CHNO_2), 34.8 (*C*H_2C=O), 34.2 (*C*HC=O); MS (ESI, pos.): *m*/*z* 328.1 $(M+Na)^+$; HRMS (ESI, pos.): *m*/*z* 328.1158 (328.1161 calc. for ($C_{16}H_{19}NNaO_5$ $(M+Na)^+$). HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, λ= 247 nm): t_{major} = 10.88 min., t_{minor} = 13.97 min., 80% ee.

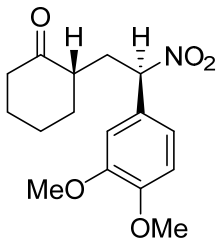
(*R*)-7-((*R*)-(4-Bromophenyl)-2-nitroethyl)-1,4-dioxaspiro[4.5]decan-8-one (55):



To a solution of cyclohexanedione monoethtylene ketal (0.40 g, 2.6 mmol), (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (18 mg, 0.1 mmol), and (1*S*)-camphorsulfonic acid (24 mg, 0.1 mmol) in DMF (2 mL) was added 4-bromophenyl nitroacetate **31** (150 mg, 0.5 mmol) and the resulting solution was stirred at 0 °C for 16 h. Ethyl acetate (10 mL) was added and the solution was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 75:25) to provide 0.1 g (50%) of **55** with 86% ee as a white gum.

IR (neat): 1713, 1550, 1489, 1361, 1124, 1056 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, 2H, *J* = 8.5, Ar*H*), 7.34 (d, 2H, *J* = 8.5, Ar*H*), 5.66 (dd, 1H, *J* = 10.2, 4.2, C*H*NO_2), 4.08-3.96 (m, 4H, OC*H*$_2$C*H*$_2$O), 2.75-2.62 (m, 2H, NO_2CHC*H*$_2$), 2.45-2.25 (m, 3H, COC*H*$_2$,COC*H*), 2.15-1.95 (m, 3H, CH_2C*H*$_2$, CHC*H*$_2$ (ring)), 1.77 (t, 1H, *J* = 13.0, CHC*H*$_2$ (ring)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.3 (*C*O), 133.8 (Ar*C*$_{ipso}$), 132.3 (2 x Ar*C*), 129.1 (2 x Ar*C*), 124.1 (Ar*C*$_{ipso}$), 106.8 (O*C*O), 89.1 (*C*HNO_2), 64.9 (O*C*H$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 43.2 (*C*H$_2$C-O), 41.6 (*C*H$_2$C-O), 38.3 (*C*H$_2$CHNO_2), 34.8 (*C*H$_2$C=O), 34.2 (*C*HC=O); HRMS (ESI, pos.): *m*/*z* 383.0363 (383.0638 calc. for $C_{16}H_{18}BrNO_5$ (M^+)), 384.0433 (384.0477 calc. for $C_{16}H_{19}BrNO_5$ $(M+H)^+$), 406.0255 (406.0266 calc. for ($C_{16}H_{18}{}^{79}BrNNaO_5$ $(M+Na)^+$), 408.0237 (408.0245 calc. for ($C_{16}H_{18}{}^{81}BrNNaO_5$ $(M+Na)^+$). HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min^{-1}, λ= 247 nm): t_{major} = 13.16 min., t_{minor} = 22.39 min., 86% ee.

(*S*)-2-((*R*)-2-(3,4-Dimethoxyphenyl)-2-nitroethyl)cyclohexanone (56):

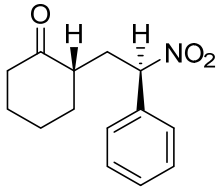


Reaction of cyclohexanone (96 μL, 0.92 mmol) and (1*S*)-Camphorsulfonic acid (9.0 mg, 0.037 mmol) in the presence of (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (6.0 mg, 0.037 mmol) was added nitroacetate (50 mg, 0.18 mmol) according to the general procedure gave, after the purification of the crude product by flash

column chromatography on silica gel (85/15 hexanes/ethyl acetate), 25 mg (44%) of **56** as a white foam.

IR (neat): 2935, 2853, 1703, 1547, 1514, 1364, 809, 564 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 8.3, 2.0, Ar*H*), 6.97 (d, 1H, *J* = 2.0, Ar*H*), 6.85 (d, 1H, *J* = 8.3, Ar*H*), 5.63 (dd, 1H, *J* = 10.2, 4.4, Ar*H*), 3.91 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 2.50-2.42 (m, 2H, C*H*$_2$CHNO$_2$), 2.37-2.25 (m, 3H, C*H*$_2$(CO), C*H*(CO)), 2.20-2.08 (m, 2H, C*H*$_2$), 1.91-1.88 (m, 1H, C*H*$_2$), 1.75-1.57(m, 2H, C*H*$_2$), 1.51-1.43 (m, 1H, C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 211.8 (*C*O), 150.2 (Ar*C*$_{ipso}$), 149.2 (Ar*C*$_{ipso}$), 127.3 (Ar*C*$_{ipso}$), 120.4 (Ar*C*), 111.0 (Ar*C*), 110.2 (Ar*C*), 89.8 (*C*HNO$_2$), 56.0 (O*C*H$_3$), 55.9 (O*C*H$_3$), 47.3 (*C*HNO$_2$), 42.3 (*C*H$_2$CO), 34.9 (*C*H$_2$), 34.4 (*C*H$_2$CHNO$_2$), 28.1 (*C*H$_2$), 25.2 (*C*H$_2$); HRMS (APPI, pos.): *m*/*z* 308.1469 (308.1500 calc. for ($C_{16}H_{22}NO_5$ $(M+H)^+$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 70/30, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 17.19 min., t_{minor} = 15.07 min., 92% ee.

(*S*)-2-((*R*)-2-Nitro-2-phenylethyl)cyclohexanone (57):

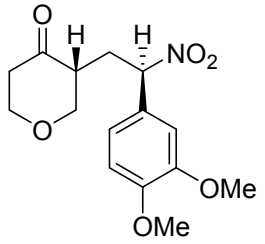


Reaction of cyclohexanone (0.12 mL, 1.2 mmol) and (1*S*)-Camphorsulfonic acid (11 mg, 0.047 mmol) in the presence of (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (8.0 mg, 0.047 mmol) was added nitroacetate (50 mg, 0.23 mmol) according to the general procedure gave, after the purification of the crude product by flash

column chromatography on silica gel (98/2 hexanes/ethyl acetate), 34 mg (58%) of **57** as a yellow gum.

IR (neat): 2937, 2859, 1704, 1545, 1448, 1364, 1296, 1070, 710, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.49-7.39 (m, 5H, Ar*H*), 5.72 (dd, 1H, *J* = 10.2, 4.3, C*H*NO_2), 2.49-2.28 (m, 5H, C*H*$_2$CO, C*H*$_2$CHNO_2, C*H*(CO), C*H*$_2$), 2.19-2.07 (m, 2H, CH_2C*H*, C*H*$_2$CH), 1.91-1.87 (m, 1H, C*H*$_2$CH), 1.72-1.56 (m, 2H, C*H*$_2$), 1.50-1.37 (m, 1H, C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 211.8 (*C*O), 134.9 (Ar*C*$_{ipso}$), 129.8 (Ar*C*), 129.0 (2 x Ar*C*), 127.5 (2 x Ar*C*), 90.0 (*C*HNO_2), 47.4 (*C*HCH_2), 42.3 (*C*H_2CO), 35.0 (*C*H_2CHNO_2), 34.5 (*C*H_2), 28.1 (*C*H_2), 25.3 (*C*H_2); HRMS (APPI, pos.): *m*/*z* 248.1278 (248.1300 calc. for ($C_{14}H_{18}NO_3$ $(M+H)^+$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 9.11 min., t_{minor} = 7.85 min., 74% ee.

(*R*)-Tetrahydro-3-((*R*)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)pyran-4-one (59):

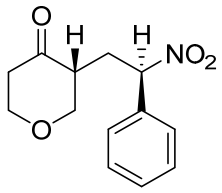


Reaction of tetrahydropyran-4-one (85 μL, 0.92 mmol) and (1*S*)-Camphorsulfonic acid (9.0 mg, 0.037 mmol) in the presence of (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (7.0 mg, 0.037 mmol) and 3,4-dimethoxyphenyl nitroacetate **24** (50 mg, 0.18 mmol) according to the general procedure gave, after the purification of the crude product by flash column chromatography on silica gel (75/25 hexanes/ethyl acetate), 30 mg (53%) of **59** as a yellow solid.

M. P. = 125-132˚C.

IR (neat): 2969, 2936, 2845, 1707, 1601, 1552, 1514, 1461, 1441, 1367, 1267, 1146, 1019, 763 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 8.3, 2.0, Ar*H*), 6.95 (d, 1H, *J* = 2.0, Ar*H*), 6.86 (d, 1H, *J* = 8.3, Ar*H*), 5.63 (dd, 1H, *J* = 10.1, 4.7, C*H*NO_2), 4.31-4.22 (m, 2H, OC*H*$_2$), 3.91 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 3.72-3.63 (ddd, 1H, OC*H*$_2$), 3.37 (t, 1H, *J* = 10.8, OC*H*$_2$), 2.73-2.52 (m, 2H, COC*H*CH_2, COC*H*$_2CH_2$), 2.48-2.38 (m, 2H, COCHC*H*$_2$), 2.27-2.18 (m, 1H, COC*H*$_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 207.0 (*C*O), 150.3 (Ar*C*$_{ipso}$), 149.3 (Ar*C*$_{ipso}$), 126.7 (Ar*C*$_{ipso}$), 120.4 (Ar*C*), 111.1 (Ar*C*), 110.0 (Ar*C*), 89.2 (*C*HNO_2), 72.6 (O*C*H$_2$CH), 68.8 (O*C*H$_2CH_2$), 56.0 (O*C*H$_3$), 55.9 (O*C*H$_3$), 48.1 (OCH$_2$*C*H), 42.7 (CO*C*H$_2$), 29.7 (COCH*C*H$_2$); HRMS (APPI, pos.): *m/z* 310.1281 (310.1300 calc. for $C_{15}H_{20}NO_6$ $[M+H]^+$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 42.31 min., t_{minor} = 36.85 min., 80% ee.

(*R*)-Tetrahydro-3-((*R*)-2-nitro-2-phenylethyl)pyran-4-one (60):

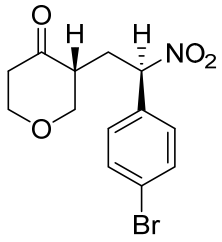


Reaction of tetrahydropyran-4-one (0.11 mL, 1.19 mmol) and (1*S*)-Camphorsulfonic acid (11 mg, 0.047 mmol) in the presence of (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (8.0 mg, 0.047 mmol) and phenylnitroacetate **32** (50 mg, 0.23 mmol) according to the general procedure gave, after the purification of the crude product by flash column chromatography on silica gel (95/5 hexanes/ethyl acetate), 27 mg (46%) of **60** as a white solid.

M. P. = 68.1-75.1 °C.

IR (neat): 2970, 2922, 2857, 1703, 1544, 1364, 1291, 1208, 1150, 1100, 1079, 1015, 964, 714, 694, 654 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.40 (m, 5H, Ar*H*), 5.70 (dd, 1H, *J* = 10.2, 4.3, C*H*NO_2), 4.32-4.23 (m, 2H, OC*H*$_2$), 3.71-3.64 (ddd, 1H, OC*H*$_2$), 3.36 (t, 1H, *J* = 10.9, OC*H*$_2$), 2.71-2.59 (m, 2H, C*H*$_2$(CO)), 2.44-2.36 (m, 2H, C*H*$_2$CHNO_2), 2.31-2.23 (m, 1H, C*H*(CO)); ^{13}C NMR (75 MHz, $CDCl_3$): 207.0 (*C*O), 134.5 (Ar*C*$_{ipso}$), 130.0 (Ar*C*), 129.2 (2 x Ar*C*), 127.4 (2 x Ar*C*), 89.4 (*C*HNO_2), 72.6 (OCH_2CH), 68.8 (OCH_2CH_2), 48.2 (CO*C*HCH_2), 42.8 (CO*C*H_2), 29.9 (*C*H_2CHNO_2); HRMS (APPI, pos.): *m/z* 272.1032 (272.0900 calc. for $C_{13}H_{15}NNaO_4$ $[M+Na]^+$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 28.01 min., t_{minor} = 12.75 min., 90% ee.

(*R*)-3-((*R*)-2-(4-Bromophenyl)-2-nitroethyl)-tetrahydropyran-4-one (61):

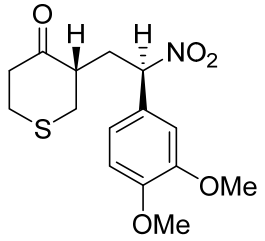


Reaction of tetrahydropyran-4-one (80 μL, 0.86 mmol) and (1*S*)-Camphorsulfonic acid (8.0 mg, 0.034 mmol) in the presence of (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (6.0 mg, 0.034 mmol) and 4-bromophenyl nitroacetate **31** (50 mg, 0.17 mmol) according to the general procedure gave, after the purification of the crude product by flash column chromatography on silica gel (80/20 hexanes/ethyl acetate), 21 mg (37%) of **61** as a white solid.

M. P. = 88.6-92 °C.

IR (neat): 2966, 2922, 2854, 1712, 1549, 1489, 1410, 1365, 1225, 1150, 1101, 1011, 970, 824, 749 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, 2H, *J* = 8.5, Ar*H*), 7.34 (d, 2H, *J* = 8.5, Ar*H*), 5.68 (dd, 1H, C*H*NO_2), 4.30-4.21 (m, 2H, OC*H*$_2$), 3.66 (ddd, 1H, OC*H*$_2$), 3.35 (t, 1H, *J* = 10.9, OC*H*$_2$), 2.80-2.50 (m, 2H, COC*H*CH_2, COC*H*$_2CH_2$), 2.44-2.22(m, 2H, COCHC*H*$_2$), 2.26-2.17 (m, 1H, COC*H*$_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 207 (*C*O), 133.4 (ArC_{ipso}), 132.4 (2 x Ar*C*), 129.1 (2 x Ar*C*), 124.4 (Ar*C*), 88.7 (*C*HNO_2), 72.6 (O*C*H_2CH), 68.8 (O*C*H_2CH_2), 48.1 (*C*HCH_2), 42.8 (CO*C*H_2), 29.8 (*C*H_2CHNO_2); HRMS (APPI, neg.): *m/z* 326.0022 (326.0000 calc. for $C_{13}H_{13}$ ^{79}$BrNO_4$ $[M-H]^-$), 328.0004 (328.0000 calc. for $C_{13}H_{13}^{81}BrNO_4$ $[M-H]^-$);HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 70/30, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 34.26 min., t_{minor} = 12.82 min., 20% ee.

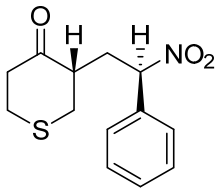
(*S*)-Tetrahydro-3-((*R*)-2-(3,4-dimethoxyphenyl)-2-nitroethyl)thiopyran-4-one (62):



Reaction of tetrahydrothiopyran-4-one (0.1 g, 0.92 mmol) and (1*S*)-Camphorsulfonic acid (9.0 mg, 0.036 mmol) in the presence of (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (7.0 mg, 0.036 mmol) and 3,4-dimethoxy phenyl nitroacetate **24** (50 mg, 0.18 mmol) according to the general procedure gave, after the purification of the crude product by flash column chromatography on silica gel (80/20 hexanes/ethyl acetate), 30 mg (50%) of **62** as a yellow gum.

IR (neat): 2958, 2919, 2837, 1704, 1601, 1550, 1514, 1427, 1359, 1240, 1142, 1114, 1020, 852, 808, 764, 700 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): (**major diastereomer**): δ 7.02 (dd, 1H, *J* = 8.3, 2.1, Ar*H*), 6.95 (d, 1H, *J* = 2.1, Ar*H*), 6.86 (d, 1H, *J* = 8.3, Ar*H*), 5.59 (dd, 1H, *J* = 10.2, 4.6, C*H*NO_2), 3.91 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.00-2.93 (m, 3H, SCH_2, COCH_2), 2.77-2.72 (m, 3H, SCH_2, COCH_2), 2.45-2.35 (m, 1H, CH_2C*H*NO_2); ^{13}C NMR (75 MHz, $CDCl_3$): (**major diastereomer**): 208.9 (*C*O), 150.3 (ArC_{ipso}), 149.5 (Ar*C*), 126.8 (Ar*C*), 120.5 (Ar*C*), 111.0 s(Ar*C*), 110.1 (Ar*C*), 89.3 (*C*HNO_2), 56.1 (OCH_3), 55.9 (OCH_3), 49.9 (CO*C*HCH_2), 44.6 (CO*C*H_2), 36.5 (*C*H_2), 34.2 (*C*H_2), 31.2 (*C*H_2CHNO_2); (**minor diastereomer**): 208.7 (*C*O), 150.4 (ArC_{ipso}), 149.5 (ArC_{ipso}), 126.1 (ArC_{ipso}), 120.5 (Ar*C*), 111.2 (Ar*C*), 110.3 (Ar*C*), 87.8 (*C*HNO_2), 56.1 (OCH_3), 49.6 (CO*C*HCH_2), 44.4 (CO*C*H_2), 36.2 (*C*H_2), 33.7 (*C*H_2), 30.1 (*C*H_2); HRMS (APPI, neg.): *m/z* 329.0911 (329.0900 calc. for $C_{15}H_{18}NO_5S$ $[M-H]^-$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 38.80 min., t_{minor} = 42.55 min., racemic.

(*S*)-Tetrahydro-3-((*R*)-2-nitro-2-phenylethyl)-thiopyran-4-one (63):



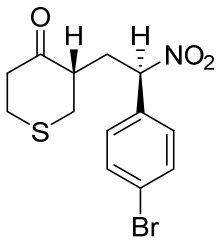
Reaction of tetrahydrothiopyran-4-one (140 mg, 0.047 mmol) and (1*S*)-Camphorsulfonic acid (11 mg, 0.047 mmol) in the presence of (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (8.0 mg, 0.047 mmol) and phenyl nitroacetate **32** (50 mg, 0.23 mmol) according to the general procedure gave, after the purification of the crude

product by flash column chromatography on silica gel (95/5 hexanes/ethyl acetate), 15 mg (24%) of **63** as a white solid.

M. P. = 120-121.8 °C.

IR (neat): 2986, 2902, 1701, 1541, 1417, 1294, 1110, 1089, 1013, 774, 717, 673 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.41 (m, 5H, Ar*H*), 5.62 (dd, 1H, *J* = 10.1, 4.4, C*H*NO_2), 2.98-2.95 (m, 3H, SC*H*$_2$, COC*H*$_2$), 2.77-2.72 (m, 4H, SC*H*$_2$, COC*H*$_2$, $COCH_2$C*H*CH_2), 2.56-2.38 (m, 1H, CH_2C*H*NO_2); ^{13}C NMR (75 MHz, $CDCl_3$): 208.8 (*C*O), 134.5 (ArC_{ipso}), 129.9 (Ar*C*), 129.1 (2 x Ar*C*), 127.4 (2 x Ar*C*), 89.5 (*C*HNO_2), 49.9 ($COCHCH_2$), 44.6 (COCH_2), 36.6 (*C*H_2), 34.4 (*C*H_2), 31.2 (*C*H_2CHNO_2); HRMS (APPI, neg.): *m/z* 264.0696 (264.0700 calc. for $C_{13}H_{14}NO_3S$ $[M-H]^-$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 80/20, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 32.51 min., t_{minor} = 12.57 min., 90% ee.

(*S*)-3-((*R*)-2-(4-Bromophenyl)-2-nitroethyl)-tetrahydrothiopyran-4-one (64):



Reaction of tetrahydrothiopyran-4-one (100 mg, 8.65 mmol) and (1*S*)-Camphorsulfonic acid (8 mg, 0.34 mmol) in the presence of (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine catalyst **35** (6.0 mg, 0.34 mmol) and 4-bromophenyl nitroacetate **31** (50 mg, 1.7 mmol) according to the general procedure gave, after the purification of the crude product

by flash column chromatography on silica gel (95/5 hexanes/ethyl acetate), 16 mg (24%) of **64** as a white solid.

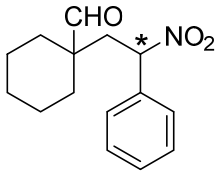
M. P. = 100-105 °C.

IR (neat): 2961, 2921, 2852, 1707, 1544, 1486, 1414, 1358, 1288, 1226, 1113, 1072, 1010, 967, 904, 858, 820, 744, 572 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, 1H, *J* = 8.5, Ar*H*), 7.34 (d, 1H, *J* = 8.5, Ar*H*), 5.58 (dd, 1H, *J* = 10.1, 4.4, C*H*NO_2), 3.00-2.95 (m, 3H, SC*H*$_2$, COC*H*$_2$), 2.78-2.72 (m, 4H, SC*H*$_2$, COC*H*$_2$, $COCH_2CHCH_2$), 2.52-2.34 (m, 1H, C*H*$_2$$CHNO_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 208.8 (*C*O), 133.5 (ArC_{ipso}), 132.4 (2 x Ar*C*), 129.1 (2 x Ar*C*), 124.3 (Ar*C*), 88.9 (*C*HNO_2), 49.9 ($COCHCH_2$), 44.7 (CO*C*H$_2$), 36.6 (*C*H$_2$), 34.4 (*C*H$_2$), 31.2 (*C*H_2CHNO_2); HRMS (ESI, neg.): *m/z* 341.9824 (341.9800 calc. for $C_{13}H_{13}{}^{79}BrNO_3S$ $[M-H]^-$); 343.9797 (343.9800 calc. for $C_{13}H_{13}{}^{81}BrNO_3S$ $[M-H]^-$); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 19.62 min., t_{minor} = 15.42 min., 79% ee.

General experimental procedure for the Michael addition of aldehydes to nitroalkenes:

To a solution of the aldehyde and catalyst **40** in DMF was added the nitroacetate and the resulting solution was stirred at ambient temperature for 72 h. After completion of the reaction (TLC), ethyl acetate (5 mL) was added and the resulting solution was washed with water (5 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel.

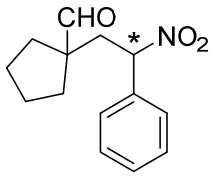
1-(2-Nitro-2-phenylethyl)cyclohexanecarbaldehyde (73):



Reaction of cyclohexane carboxaldehyde **72** (0.14 mL, 1.2 mmol) and phenyl nitroacetate **32** (50 mg, 0.24 mmol) in the presence of (*S*)-proline catalyst **40** (4.0 μL, 0.047 mmol) according to the general procedure gave, after the purification of the crude product by flash column chromatography on silica gel (95/5 hexanes/ethyl acetate), 27 mg (43%) of **73** as a white gum.

IR (neat): 2932, 2856, 1720, 1552, 1453, 1363, 719, 696 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.32 (s, 1H, C*H*O), 7.47-7.36 (m, 5H, Ar*H*), 5.48 (dd, 1H, *J* = 8.0, 5.0, CH_2NO_2), 2.89 (dd, 1H, *J* = 15.3, 8.0, CH_2CHNO_2), 2.21 (dd, 1H, *J* = 15.3, 5.0, CH_2CHNO_2), 1.96-1.84 (m, 2H, CH_2), 1.57-1.51 (m, 2H, CH_2), 1.38-1.26 (m, 6H, CH_2); ^{13}C NMR(75 MHz, $CDCl_3$): 204.7 (*C*HO), 135.3 (ArC_{ipso}), 130.0 (Ar*C*), 129.2 (2 x Ar*C*), 127.6 (2 x Ar*C*), 87.3 (*C*HNO_2), 49.0 (CHO-(*C*)-CH_2), 39.8 (*C*H_2CHNO_2), 31.4 (*C*H_2), 30.2 (*C*H_2), 25.3(*C*H_2), 22.1 (*C*H_2), 21.2 (*C*H_2); HRMS (APPI, pos.): *m/z* 262.1434 (262.1400 calc. for $C_{15}H_{20}NO_3[M+H]^+$), 284.1444 (284.1300 calc. for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 98/2, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 28.96 min., t_{minor} = 27.70 min., 76% ee.

1-(2-Nitro-2-phenylethyl)cyclopentanecarbaldehyde (77):

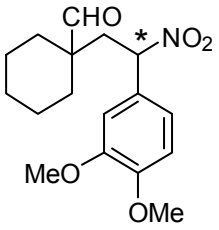


Reaction of cyclopentane carboxaldehyde **79** (0.13 mL, 1.19 mmol), phenyl nitroacetate (50 mg, 0.23 mmol) and (*S*)-proline catalyst **40** (5.5 mg, 0.047 mmol) according to the general procedure gave, after the purification of the crude product by flash column chromatography on silica gel (98/2 hexanes/ethyl acetate), 31 mg (52%) of **82** as a yellow solid.

M. P. = 86.4-89 °C.

IR (neat): 2962, 2879, 1689, 1546, 1454, 1365, 1281, 1225, 940, 911, 717, 692, 504 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 9.29 (s, 1H, C*H*O), 7.46-7.38 (m, 5H, Ar*H*), 5.49 (dd, 1H, *J* = 7.5, 5.6, C*H*NO_2), 2.86 (dd, 1H, *J* = 15.0, 7.5, C*H*$_2$CHNO_2), 2.46 (dd, 1H, *J* = 15.0, 5.6, C*H*$_2$CHNO_2), 2.05-1.86 (m, 2H, C*H*$_2$), 1.74-1.48 (m, 5H, C*H*$_2$), 1.42-1.33 (m, 1H, C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 182.3 (*C*HO), 135.2 (ArC_{ipso}), 129.8 (Ar*C*), 128.9 (2 x Ar*C*), 127.8 (2 x Ar*C*), 89.4 (*C*HNO_2), 52.6 (CHO-(*C*)-CH_2), 41.9 (*C*H$_2$CHNO_2), 37.4 (*C*H$_2$), 35.1 (C*H*$_2$), 24.7 (*C*H$_2$), 24.4 (*C*H$_2$). HRMS (APPI, neg.): *m/z* 246.1137 (246.113 calc. for $C_{14}H_{16}NO_3$ $[M-H]^-$); HPLC: Chiralpak AD-H (hexane/*i*-PrOH, 90/10, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 7.90 min., t_{minor} = 8.56 min., 35% ee.

1-(2-(3,4-Dimethoxyphenyl)-2-nitroethyl)cyclohexanecarbaldehyde (78):



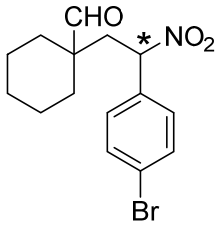
Reaction of cyclohexane carboxaldehyde **72** (0.11 mL, 0.92 mmol) and 3,4-dimethoxyphenyl nitroacetate **24** (50 mg, 0.18 mmol) in the presence of (*S*)-proline catalyst **40** (3.0 μL, 0.037 mmol) according to the general procedure gave, after the purification of the crude product by flash column chromatography on silica gel (1:1 hexane/ethyl acetate), 25 mg (41%) of **83** as a white solid.

M. P. = 77.6-83 °C.

IR (neat): 2934, 2854, 1721, 1594, 1551, 1517, 1453, 1365, 1266, 1145, 1025 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.31 (s, 1H, C*H*O), 6.98 (dd, 1H, *J* = 8.3, 2.1, Ar*H*), 6.92 (d, 1H, *J* = 2.1, Ar*H*), 6.83 (d, 1H, *J* = 8.3, Ar*H*), 5.41 (dd, 1H, *J* = 7.7, 5.5, C*H*NO_2), 3.90 (s, 3H, OC*H*$_3$), 3.88 (s, 3H, OC*H*$_3$), 2.78 (dd, 1H, *J* = 15.2, 7.7, C*H*$_2$CHNO_2), 2.24 (dd, 1H, *J* = 15.2, 5.5, C*H*$_2$CHNO_2), 1.96-1.84 (m, 1H, C*H*$_2$), 1.60-1.50 (m, 3H, C*H*$_2$), 1.41-1.26 (m, 5H, C*H*$_2$). ^{13}C NMR(75 MHz, $CDCl_3$): 204.7 (*C*HO), 150.4 (Ar*C*$_{ipso}$), 149.4 (Ar*C*$_{ipso}$), 127.5 (Ar*C*$_{ipso}$), 120.7 (Ar*C*), 111.1 (Ar*C*), 110.3 (Ar*C*), 87.1(*C*HNO_2), 56.1(O*C*H_3), 55.9(O*C*H_3), 48.9 (CHO-(*C*)-CH_2), 39.8 (*C*H_2CHNO_2), 31.5 (*C*H_2), 30.3 (*C*H_2), 25.3 (*C*H_2), 22.1 (*C*H_2), 20.0 (*C*H_2); HRMS (APPI, pos.): *m/z* 322.1638 (322.1654 calc. for $C_{17}H_{23}NO_5[M+H]^+$). HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 70/30, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 16.68 min., t_{minor} = 18.34 min., 83% ee.

1-(2-(4-Bromophenyl)-2-nitroethyl) cyclohexanecarbaldehyde (79):



Reaction of cyclohexane carboxaldehyde **72** (0.11 mL, 0.92 mmol) and 4-bromophenyl nitroacetate **31** (50 mg, 0.18 mmol) in the presence of (*S*)-proline catalyst **40** (3.0 μL, 0.037 mmol) according to the general procedure gave, after the purification of the crude product by flash column chromatography on silica gel (98/2 hexanes/ethyl acetate), 23 mg (40%) of **84** as a yellow gum.

IR (neat): 2930, 2845, 1720, 1553, 1489, 1451, 1363, 1073, 1011, 825, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.34 (s, 1H, C*H*O), 7.52 (d, 2H, *J* = 8.5, Ar*H*), 7.31 (d, 2H, *J* = 8.5, Ar*H*), 5.44 (dd, 1H, *J* = 7.9, 4.9, C*H*$_2$NO$_2$), 2.82 (dd, 1H, *J* = 15.3, 7.9, C*H*$_2$NO$_2$), 2.16 (dd, 1H, *J* = 15.3, 4.9, C*H*$_2$NO$_2$), 1.92-1.82 (m, 2H, C*H*$_2$), 1.59-1.53 (m, 2H, C*H*$_2$), 1.41-1.20 (m, 6H, C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 204.7 (*C*HO), 134.2 (Ar*C*$_{ipso}$), 132.4 (2 x Ar*C*), 129.2 (2 x Ar*C*), 124.4 (Ar*C*$_{ipso}$), 86.7 (*C*HNO$_2$), 49.0 (CHO-(*C*)-CH$_2$), 39.5 (*C*H$_2$NO$_2$), 31.4 (*C*H$_2$), 30.2 (*C*H$_2$), 25.3 (*C*H$_2$), 22.0 (*C*H$_2$), 21.9 (*C*H$_2$), 21.9 (*C*H$_2$); HRMS (ESI, neg.): *m/z* 338.0411 (338.0400 calc. for $C_{15}H_{17}{}^{79}BrNO_3$ [M-H]$^-$), 340.0392 (340.0400 calc. for $C_{15}H_{17}{}^{81}BrNO_3$ [M-H]$^-$); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 70/30, flow rate 1 mL min−1, λ= 254 nm): t_{major} = 22.11 min., t_{minor} = 13.24 min., 69% ee.

2.7 References:

1) For reviews, see: a) Dalko, P. L.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175. b) Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, 719-724.

2) Only three reports of enantioselective organocatalytic Michael additions to α-alkyl nitroalkenes are available a) Kimmel, K. L.; Weaver, J. D.; Lee, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 9058-9061; b) B. Zheng, H. Wang, Y. Han, C. Liu, Y. Peng, *Chem. Commun.* **2013**, *49*, 4561-4563; c) Han, Y.; Zheng, B.; Peng, Y. *Adv. Synth. Catal.* **2015**, *357*, 1136. For Stoichiometric reactions of preformed α-nitrostyrene with achiral enamines, see: (d) Bradamante, P.; Pitacco, G.; Risaliti, A.; Valentin, E. *Tetrahedron Lett.* **1982**, *23*, 2683. (e) Benedetti, F.; Drioli, S.; Nitti, P.; Pitacco, G.; Valentin, E. *ARKIVOC* **2001**, (*v*), 140. For classical examples of multistep approaches to α,γ-substituted carbonyl patterns en route to erythromycins, see: a) E. J. Corey, P. B. Hopkins, S. K. Sung-eun, Y. Krishnan, P. Nambiar, J. R. Falck, *J. Am. Chem. Soc.* **1979**, *101*, 7131-7134; b) R. B. Woodwar, E. Logusch, K. P. Nambiar, K. Sakan, D. E. Ward, B. W. Au-Yueng, P. Balram, L. J. Browne, P. J. Card, C. H. Chen, *J. Am. Chem. Soc.* **1981**, *103*, 3215-3217; c) G. Stork, D. R. Rychnovsky, *J. Am. Chem. Soc.* **1987**, *109*, 1565-1567; d) J. Mulzer, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1452-1454; *Angew. Chem.* **1991**, *103*, 1484-1486. e) R. Sturmer, K. Ritter, R. W. Hofmann, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 101-103; *Angew. Chem.* **1993,** *105*, 112-114. For a synthesis of a racemic α,γ-substituted carbonyl pattern with all carbon quaternary/tertiary non adjacent stereocenters, see: J.-H. Fan, W.-T. Wei, M.-B. Zhou, R.-J. Song, J.-H. Li, *Angew.*

Chem. Int. Ed. **2014**, *53*, 6650-6654; *Angew. Chem.* **2014**, *126*, 6768-6772.

3) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, 1992. (b) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171. (c) Berner, 0. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (d) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (e) Christoffers, J.; Baro, A. *Angew. Chem.* **2003**, *115*, 1726; *Angew. Chem., Int. Ed.* 2003, *42*, 1688.

4) Li, X.; Luo, S.; Cheng, J. –P. *Chem. Eur. J*. **2010**, *16*, 14290.

5) Iriarte, I. ; Vera, S.; Badiola, E.; Mielgo, A.; Oiarbide, M.; Garcia, J. M.; Odriozola, J. M.; Palomo, C.; *Chem. Eur. J.* **2016**, *22*, 13690.

6) Kunetsky, R. A.; Dilman, A. D.; Struchkova, M. I.; Tartakovsky, V. A.; Ioff, S. L. *Tetrahedron Lett*. **2005**, 46, 5203.

7) (*S*)-Proline and (1*R*,2*R*)-1,2-diphenylethylenediamine provided **35** in low yield and low ee. (1*R*,2*S*)-Ephedrine was not effective as a catalyst.

8) For application in the conjugate additions of thiols, see: Baricordi, N.; Benetti, S.; Bertolasi, V.; De Risi, C.; Pollini, G. P.; Zamberlan, F.; Zanirato, V. *Tetrahedron* **2012**, *68*, 208.

9) Borah, J. C.; Gogoi, S.; Boruwa, J.; Barua, N. C. *Synth. Commun.* **2005**, *35*, 873-878.

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

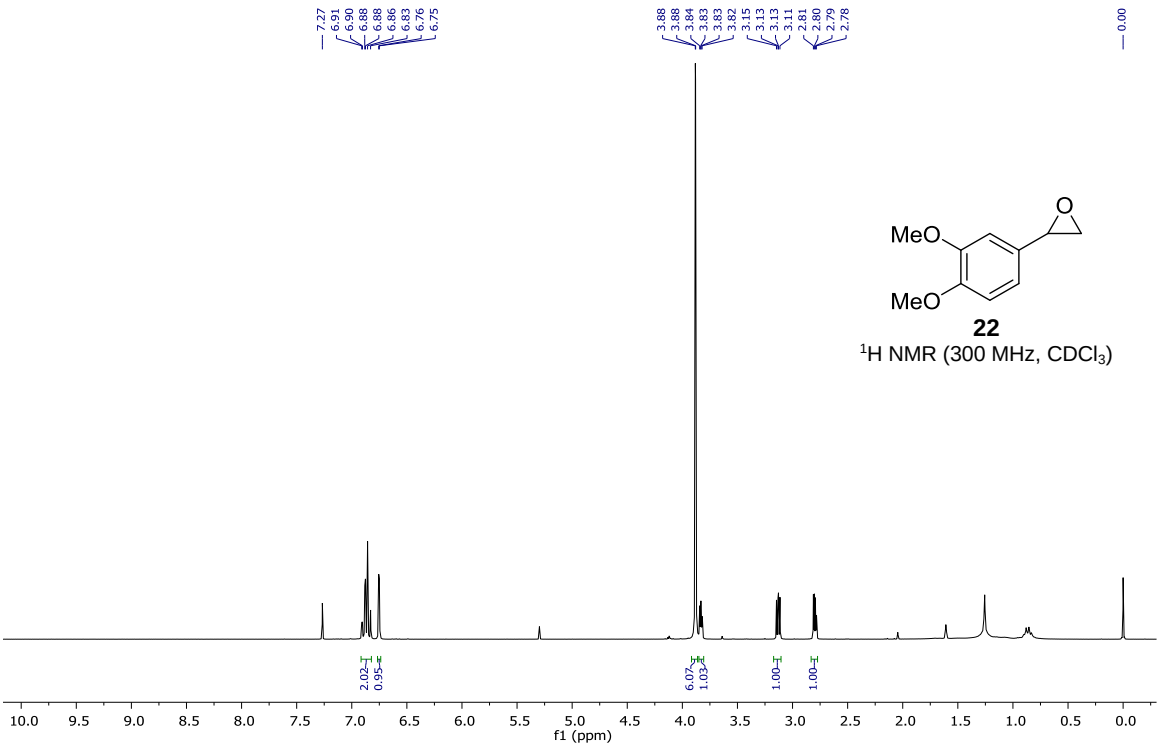
11) For a theoretical study of the role of hydrogen bonding in the Michael addition of enamines to nitroalkenes, see: Arno, M.; Zaragoza, R. J.; Domingo, L. R. *Tetrahedron Asymmetry* **2007**, *18*, 157.

12) The crystallographic data has been deposited with the Cambridge Crystallographic

Data Centre, reference no. CCDC 1423549.

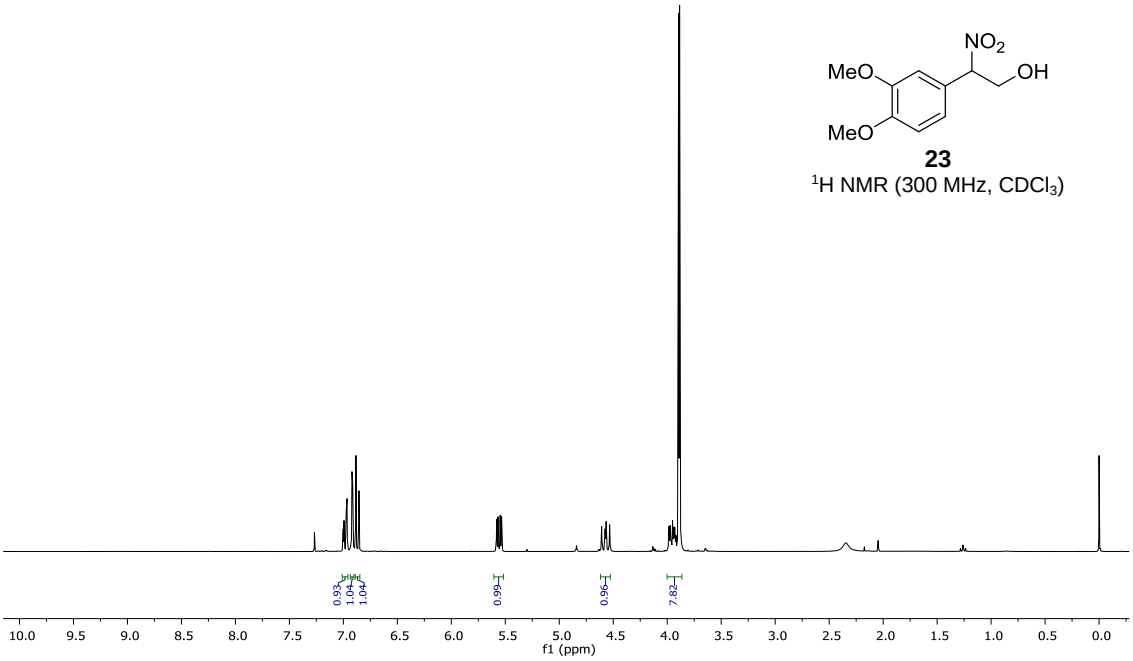
13) Ritesh A. Annadate, unpublished results from the Pansare group.

2.8 Selected ^{1}H NMR, ^{13}C NMR Spectra and Chiral HPLC Chromatograms.



22

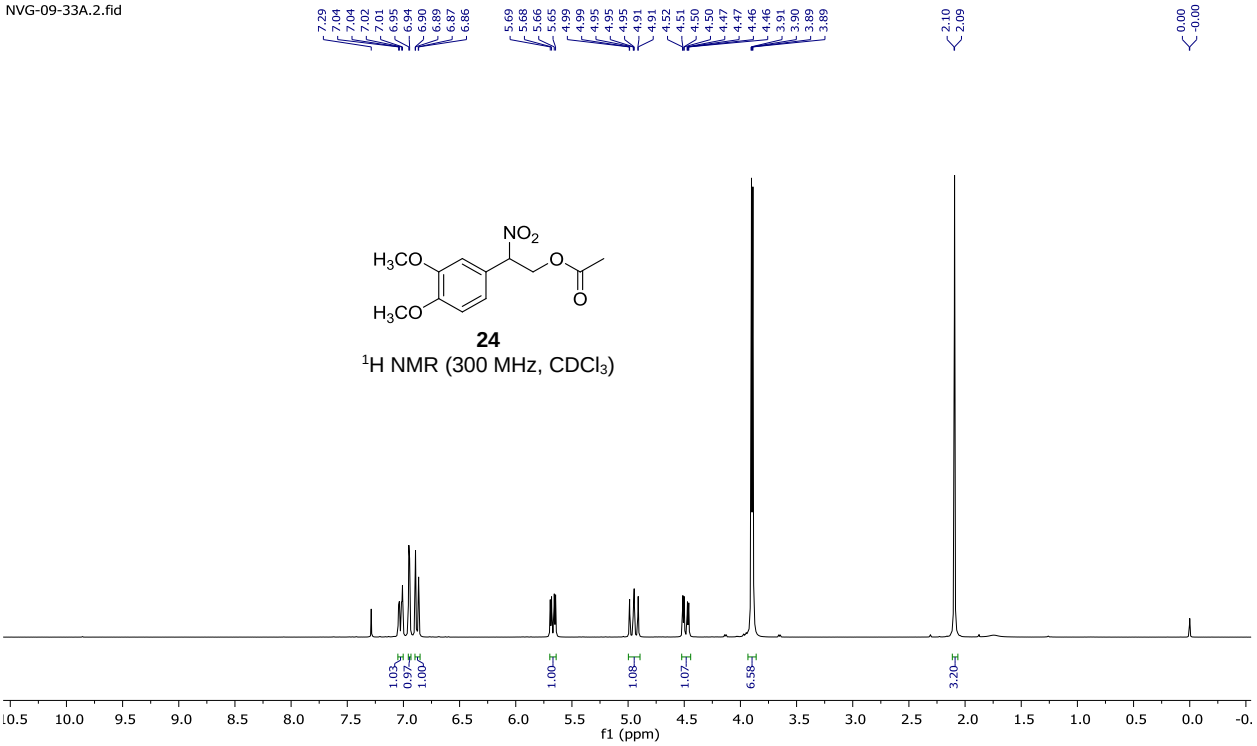
^{1}H NMR (300 MHz, $CDCl_3$)



23

^{1}H NMR (300 MHz, $CDCl_3$)

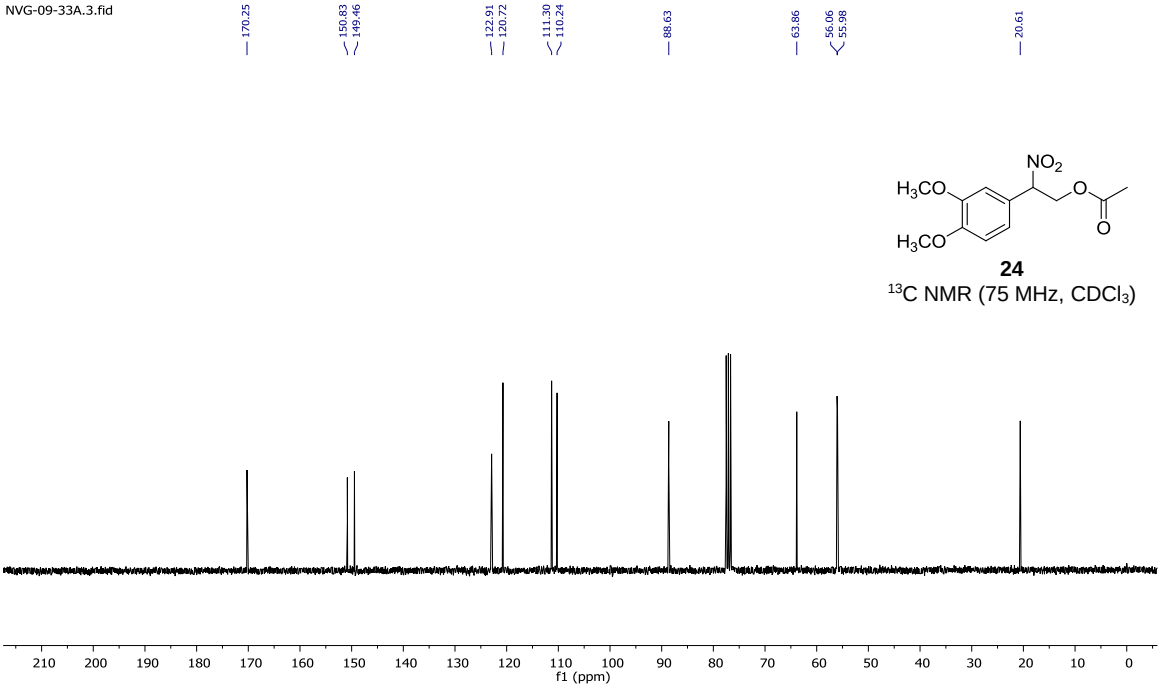
NVG-09-33A.2.fid



24

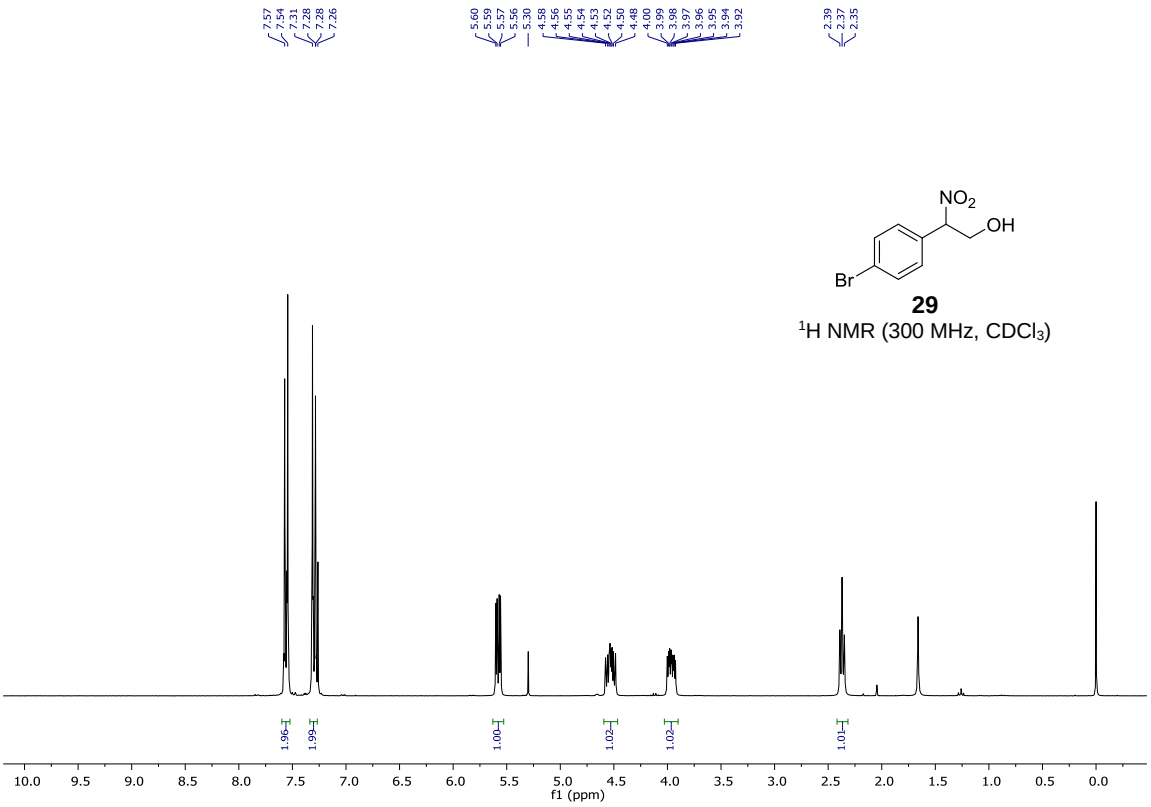
^{1}H NMR (300 MHz, $CDCl_3$)

NVG-09-33A.3.fid



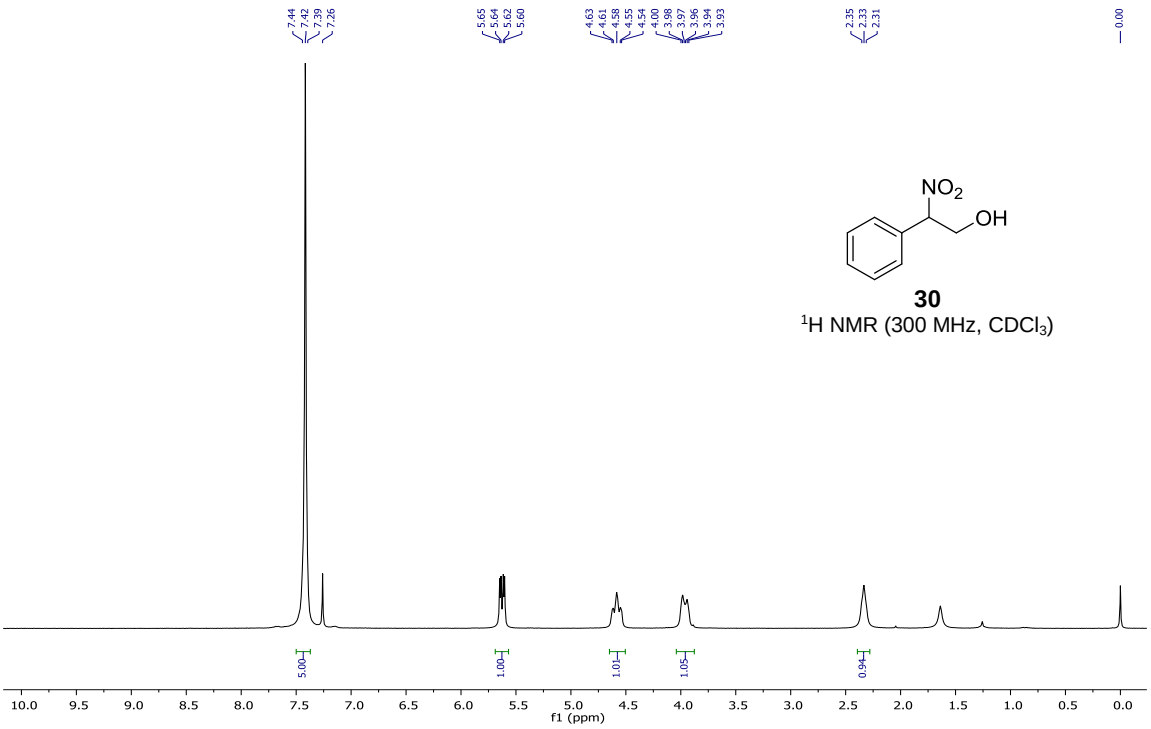
24

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



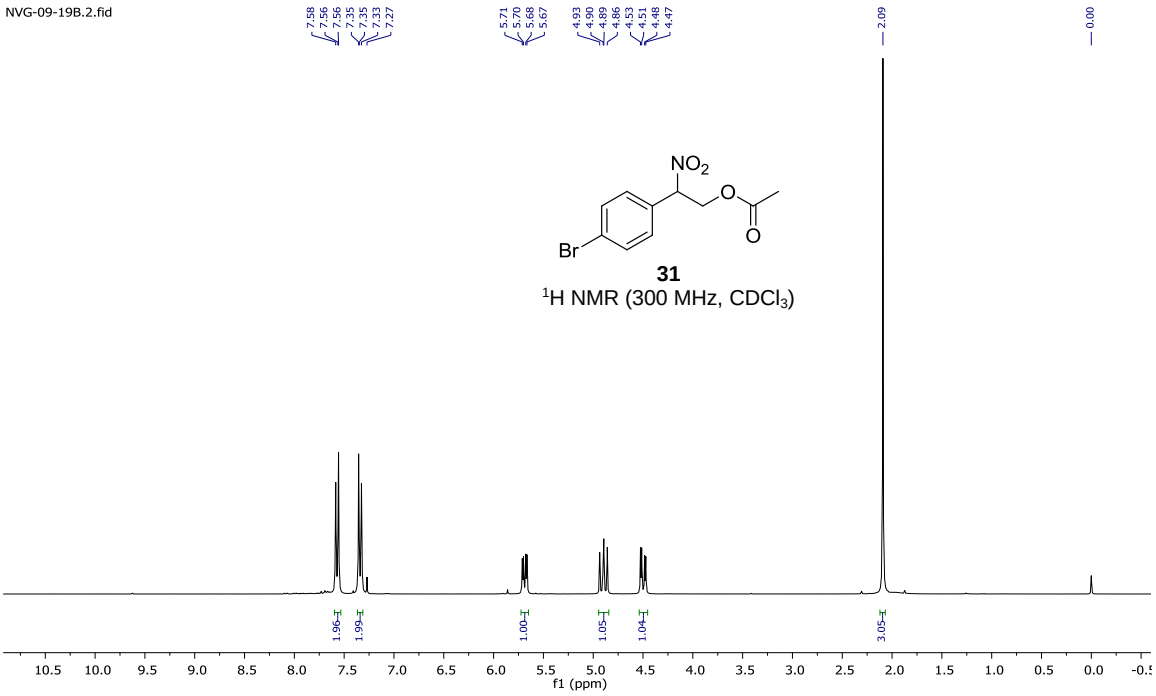
29

^{1}H NMR (300 MHz, $CDCl_3$)



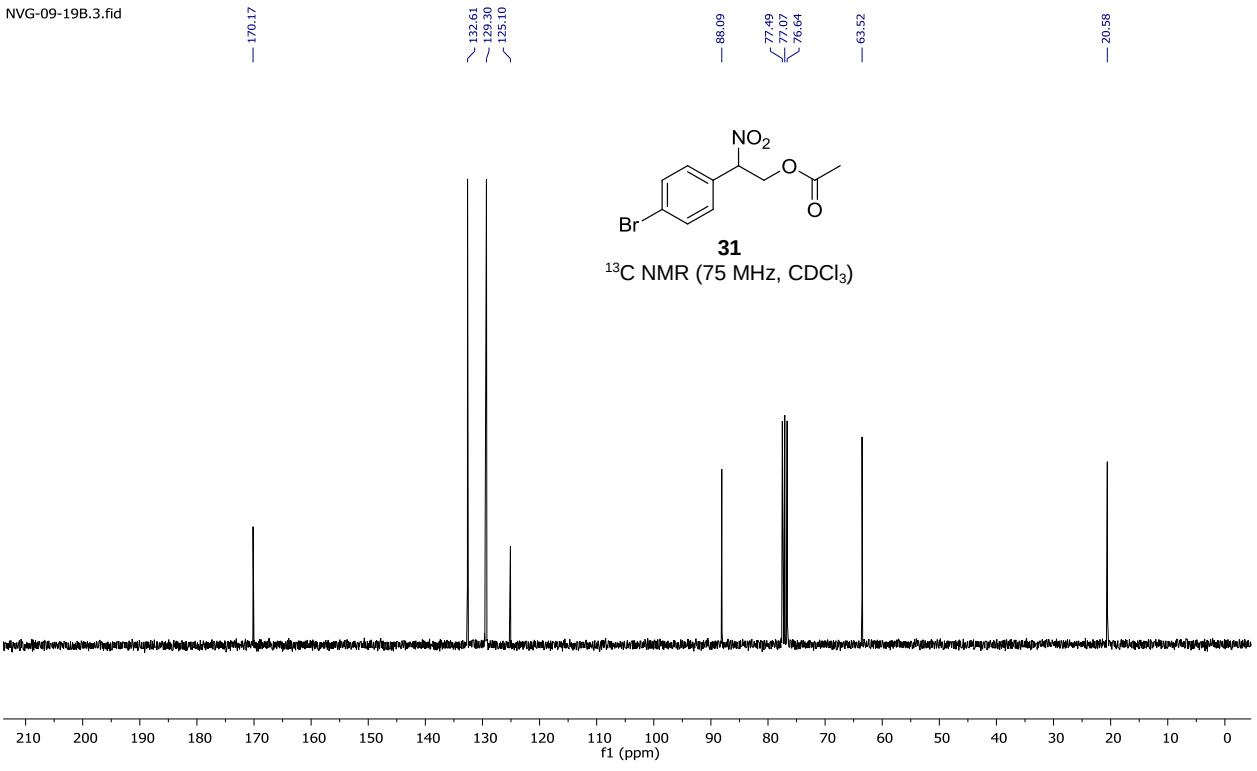
30

^{1}H NMR (300 MHz, $CDCl_3$)



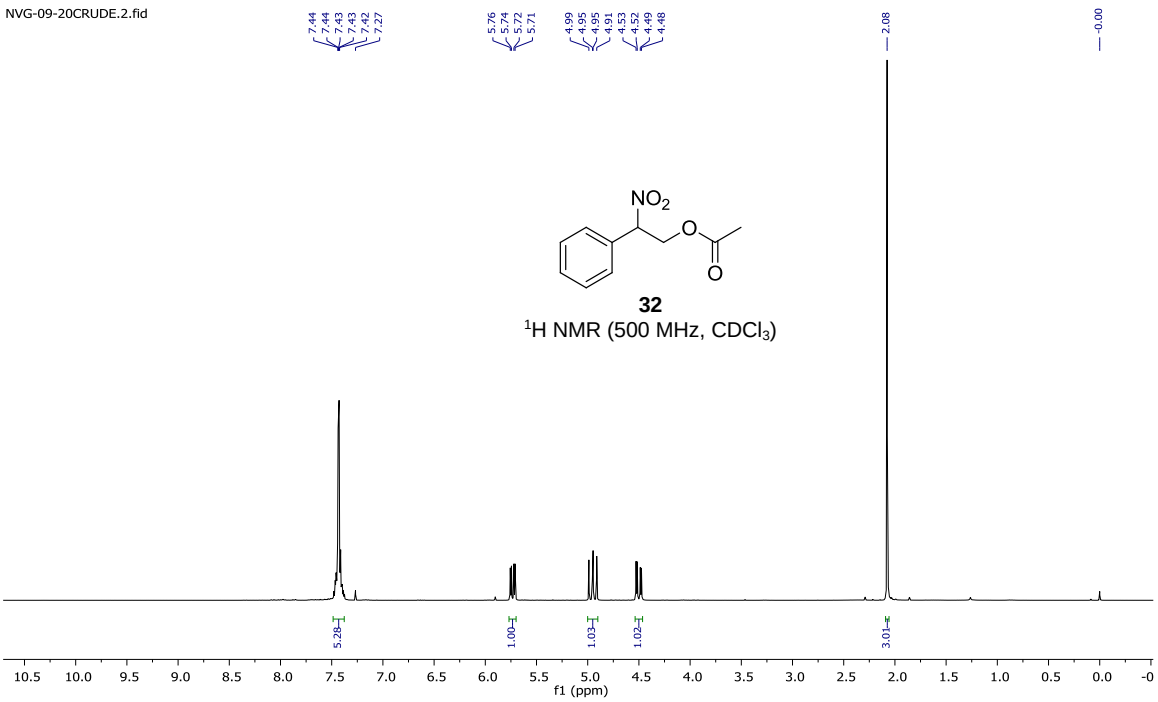
31

^{1}H NMR (300 MHz, $CDCl_3$)



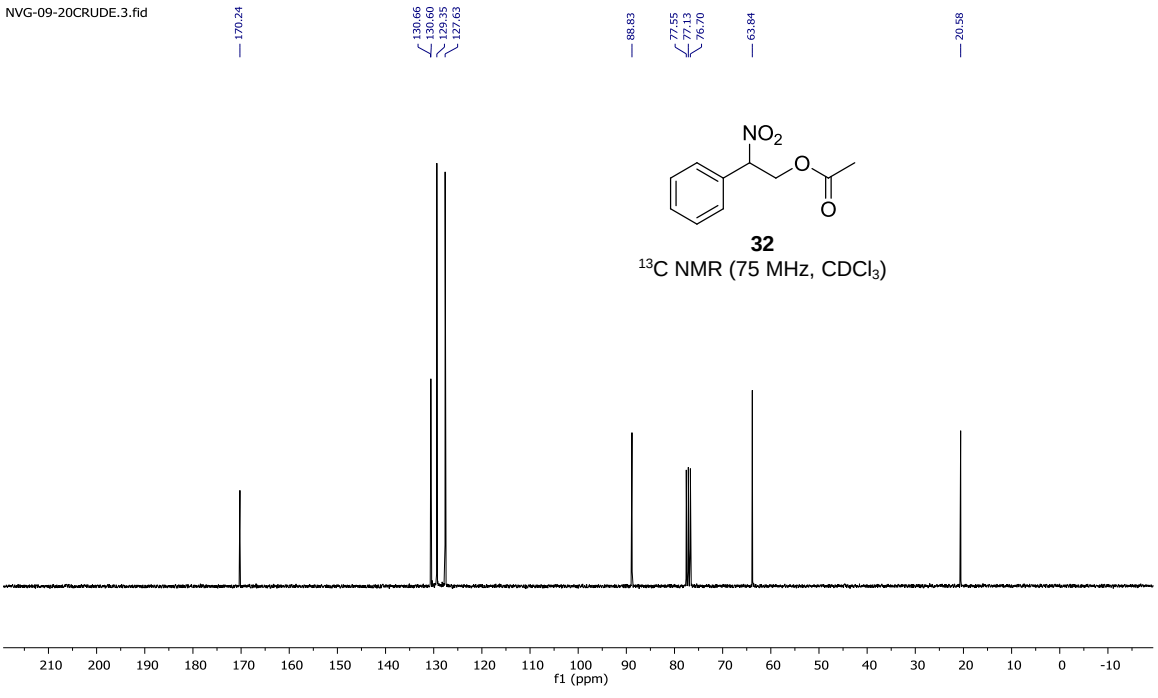
31

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



32

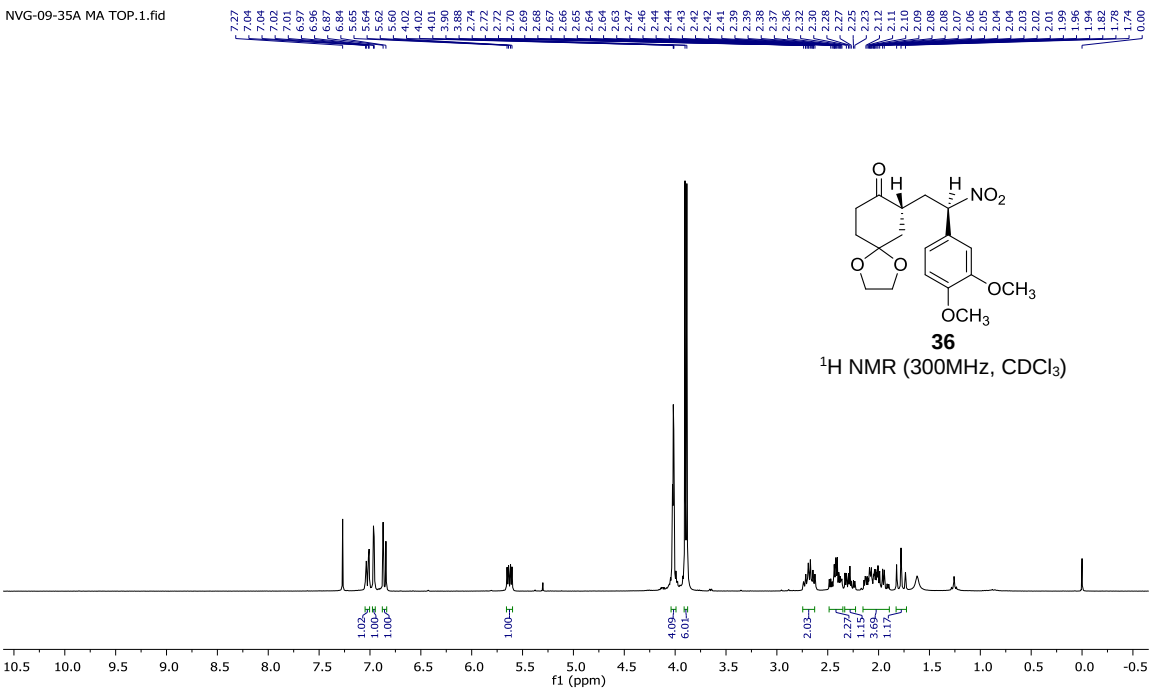
^{1}H NMR (500 MHz, $CDCl_3$)



32

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

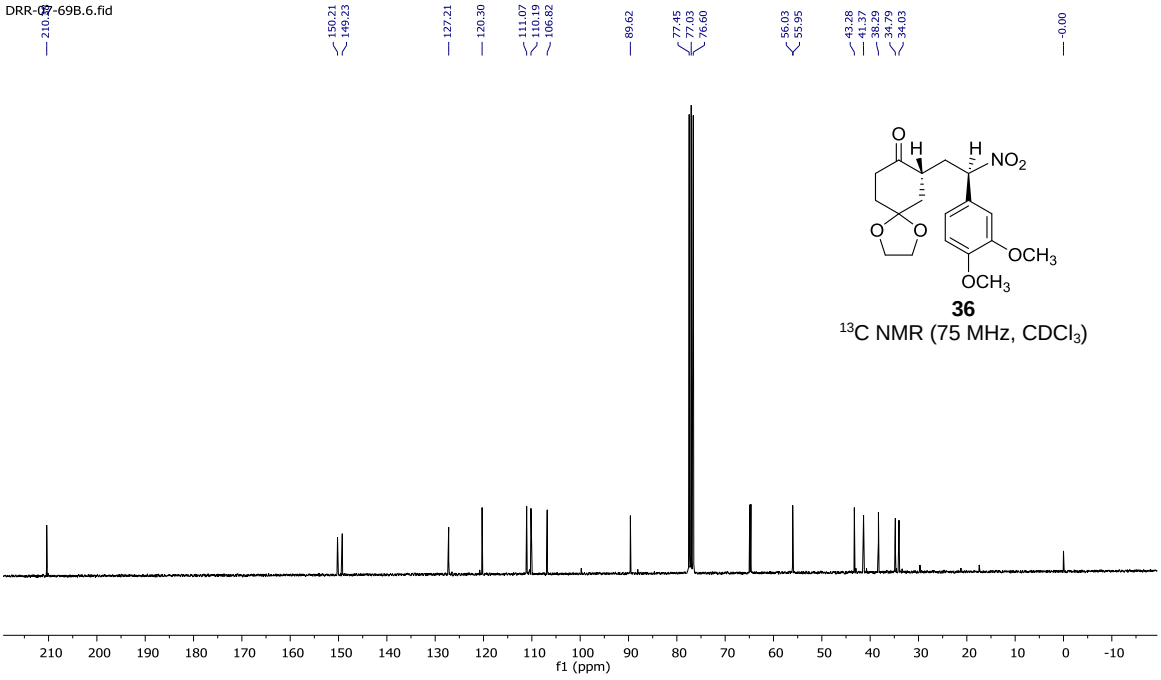
NVG-09-35A MA TOP.1.fid



36

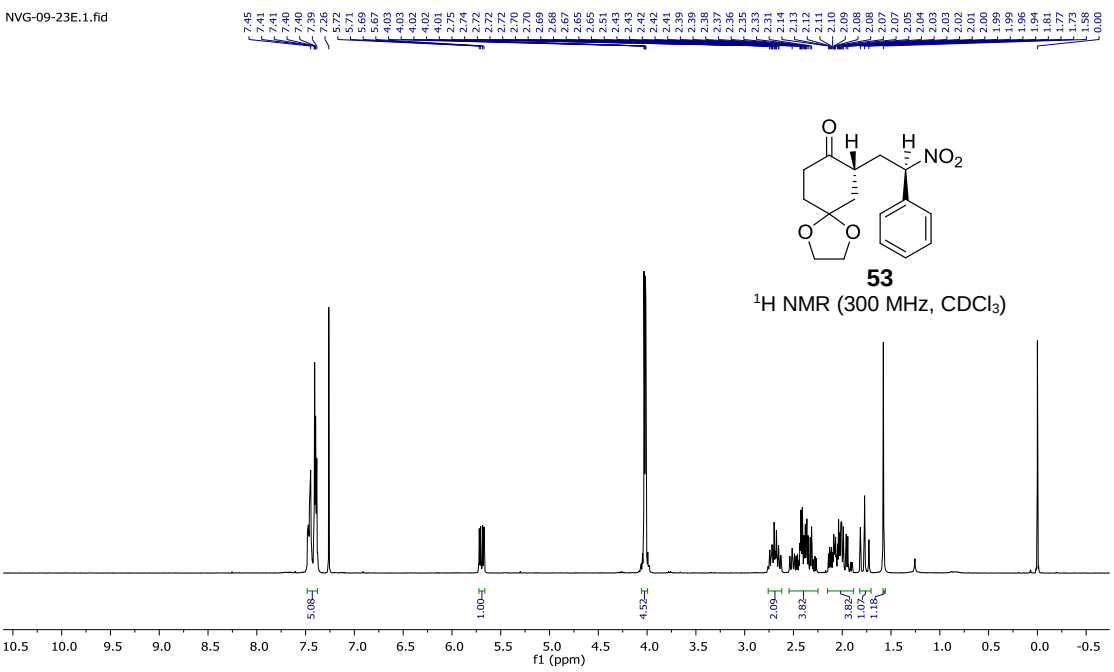
^{1}H NMR (300MHz, $CDCl_3$)

DRR-07-69B.6.fid



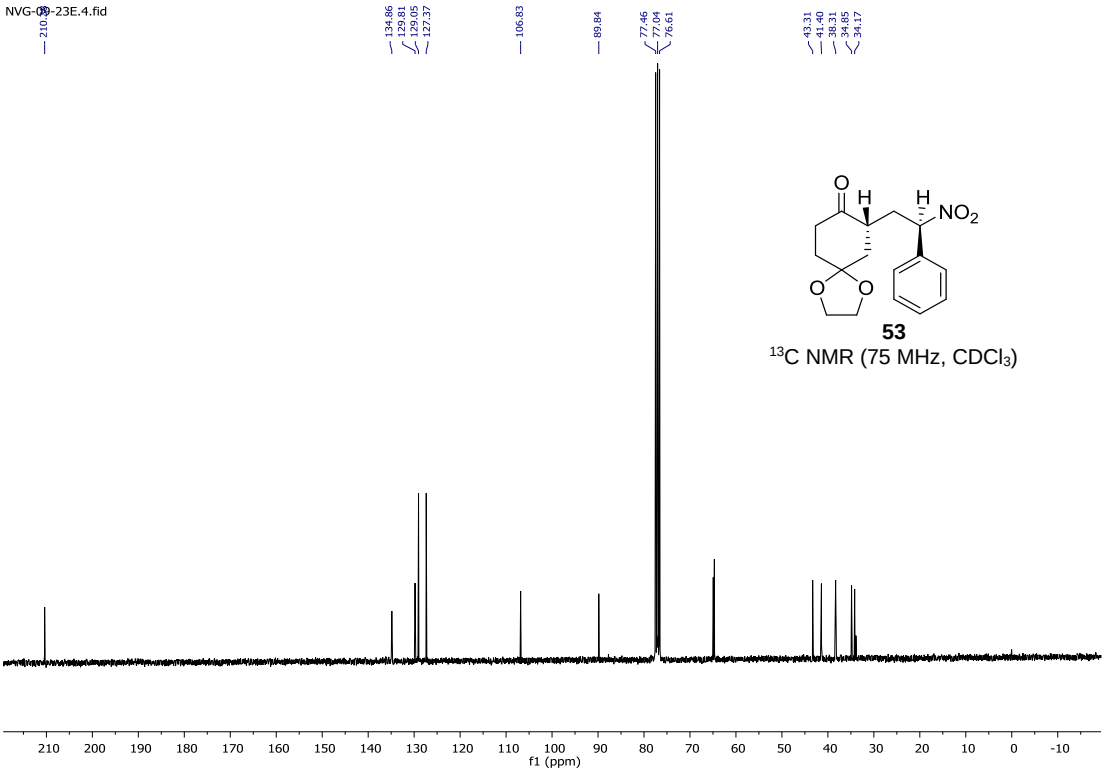
36

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



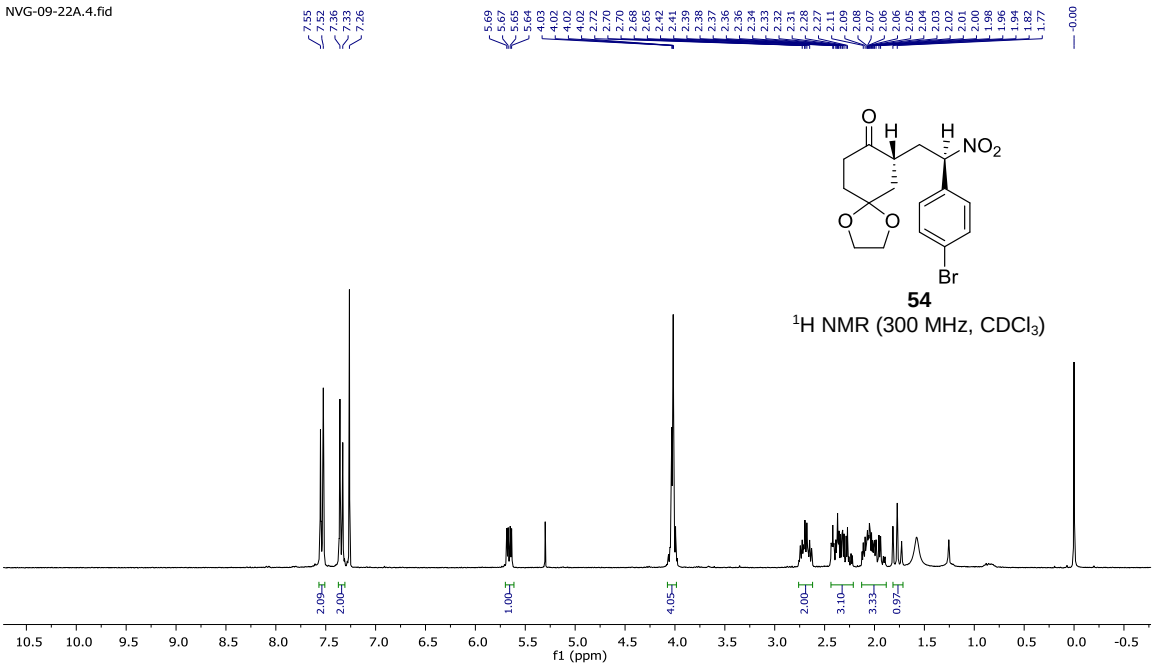
53

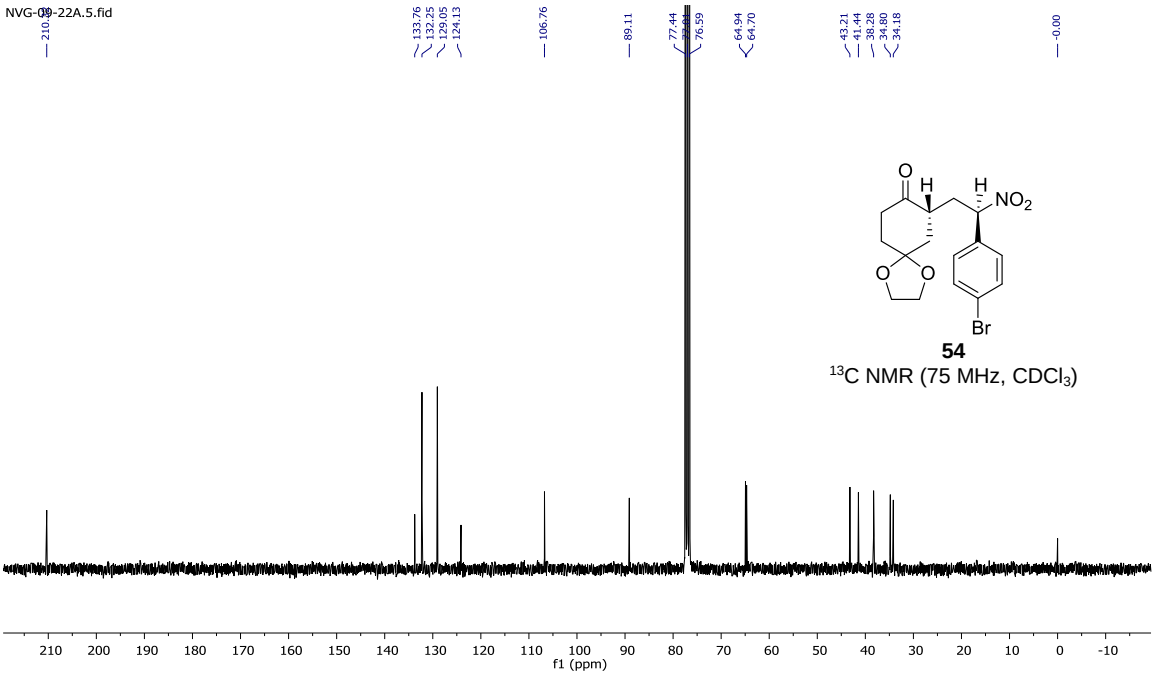
^{1}H NMR (300 MHz, $CDCl_3$)

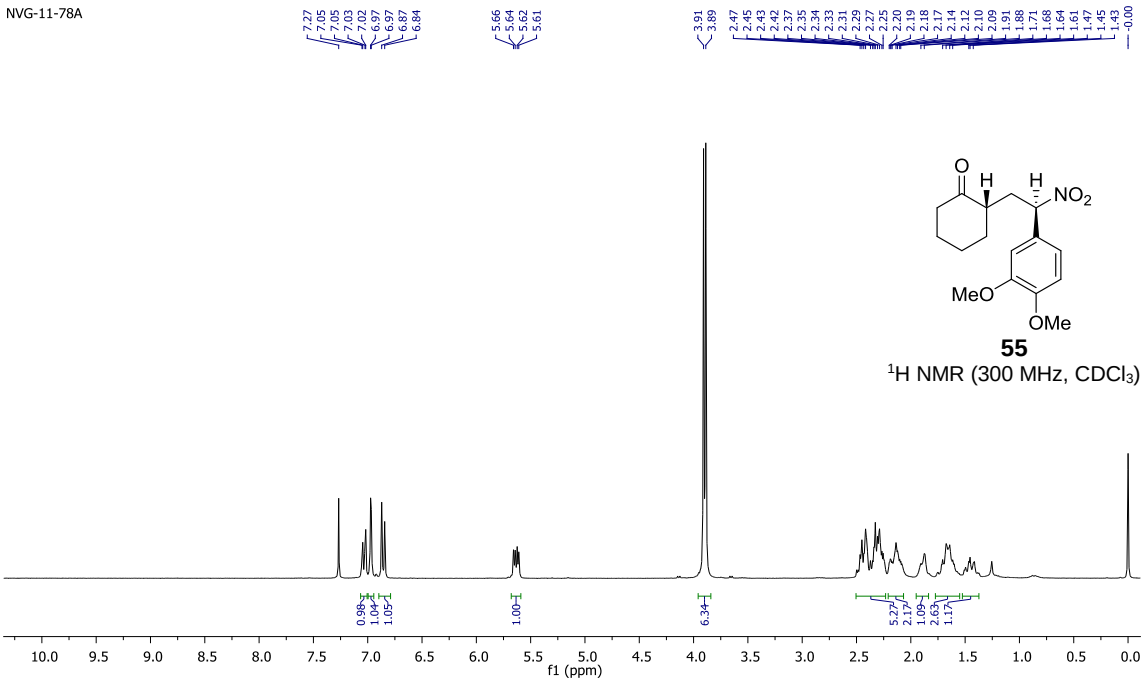


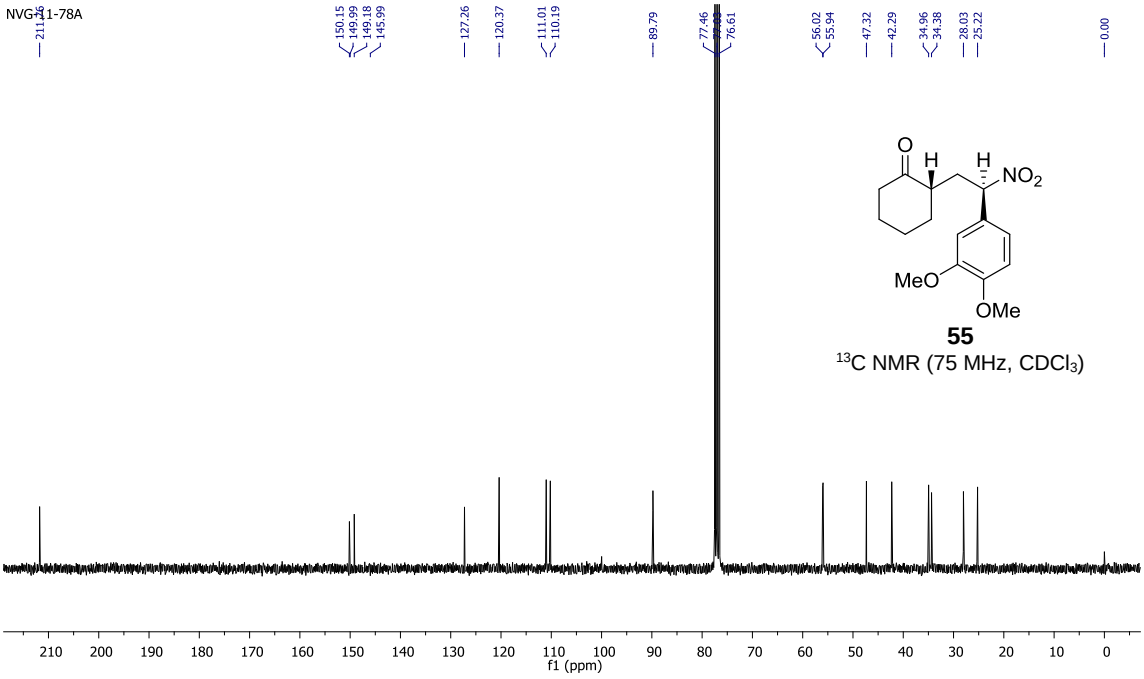
53

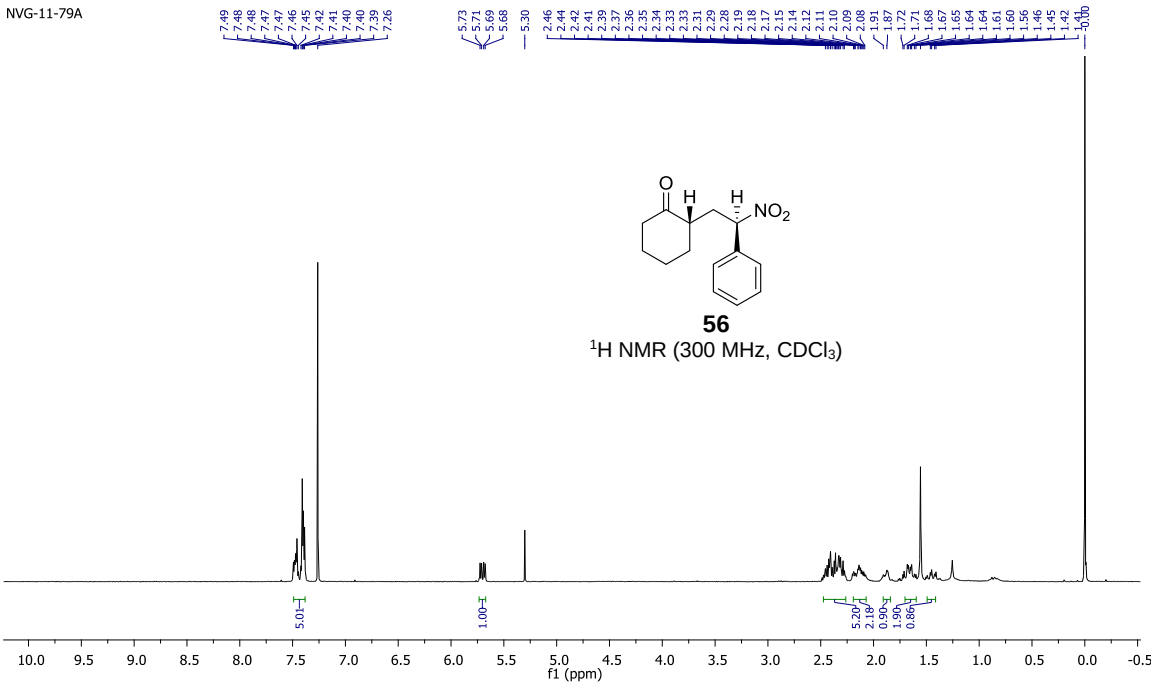
^{13}C NMR (75 MHz, $CDCl_3$)

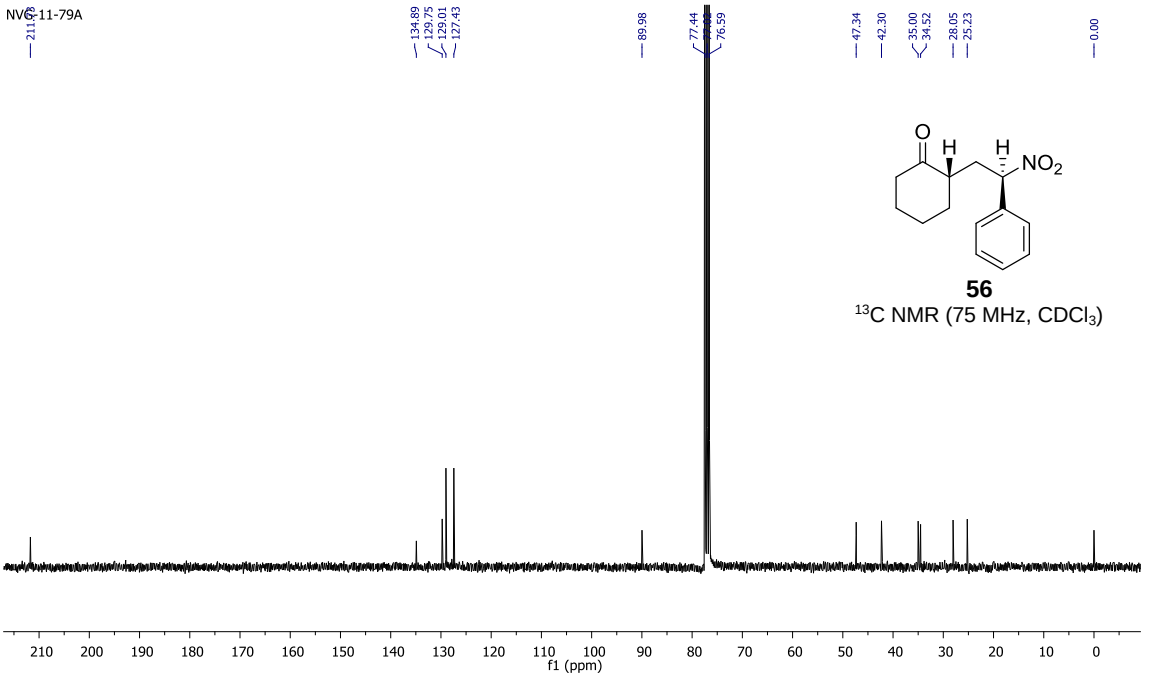

NVG-09-22A.4.fid
7.55
7.52
7.36
7.33
7.26
5.69
5.67
5.65
5.64
4.03
4.02
4.02
2.72
2.70
2.70
2.68
2.65
2.42
2.41
2.39
2.38
2.37
2.36
2.36
2.34
2.33
2.32
2.31
2.28
2.27
2.11
2.09
2.08
2.07
2.06
2.06
2.05
2.04
2.03
2.02
2.01
2.00
1.98
1.96
1.94
1.82
1.77
0.00
O
H
H
NO2
O
O
Br
54
1H NMR (300 MHz, CDCl3)
2.09
2.00
1.00
4.05
2.00
3.10
3.33
0.97
10.5 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 -0.5
f1 (ppm)


NVG-09-22A.5.fid
210.09
133.76
132.25
129.05
124.13
106.76
89.11
77.44
76.59
64.94
64.70
43.21
41.44
38.28
34.80
34.18
-0.00
O
H
H
NO2
O
O
Br
54
13C NMR (75 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

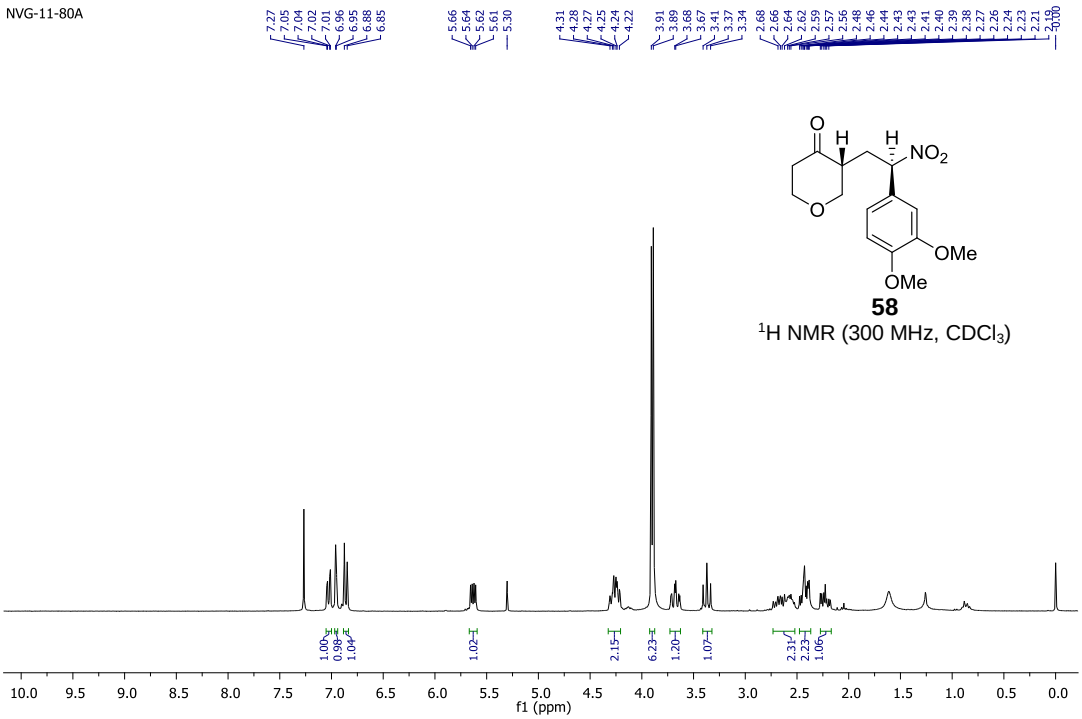

NVG-11-78A
7.27
7.05
7.05
7.03
7.02
6.97
6.97
6.87
6.84
5.66
5.64
5.62
5.61
3.91
3.89
2.47
2.45
2.43
2.42
2.37
2.35
2.34
2.33
2.31
2.29
2.27
2.25
2.20
2.19
2.18
2.17
2.14
2.12
2.10
2.09
1.91
1.88
1.71
1.68
1.64
1.61
1.47
1.45
1.43
-0.00
O
H
H
NO2
MeO
OMe
55
1H NMR (300 MHz, CDCl3)
0.98
1.04
1.05
1.00
6.34
5.27
2.17
1.09
2.63
1.17
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)


NVG-11-78A
211.14
150.15
149.99
149.18
145.99
127.26
120.37
111.01
110.19
89.79
77.46
77.03
76.61
56.02
55.94
47.32
42.29
34.96
34.38
28.03
25.22
0.00
O
H
H
NO2
MeO
OMe
55
13C NMR (75 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


NVG-11-79A
O
H
H
NO2
56
1H NMR (300 MHz, CDCl3)
f1 (ppm)

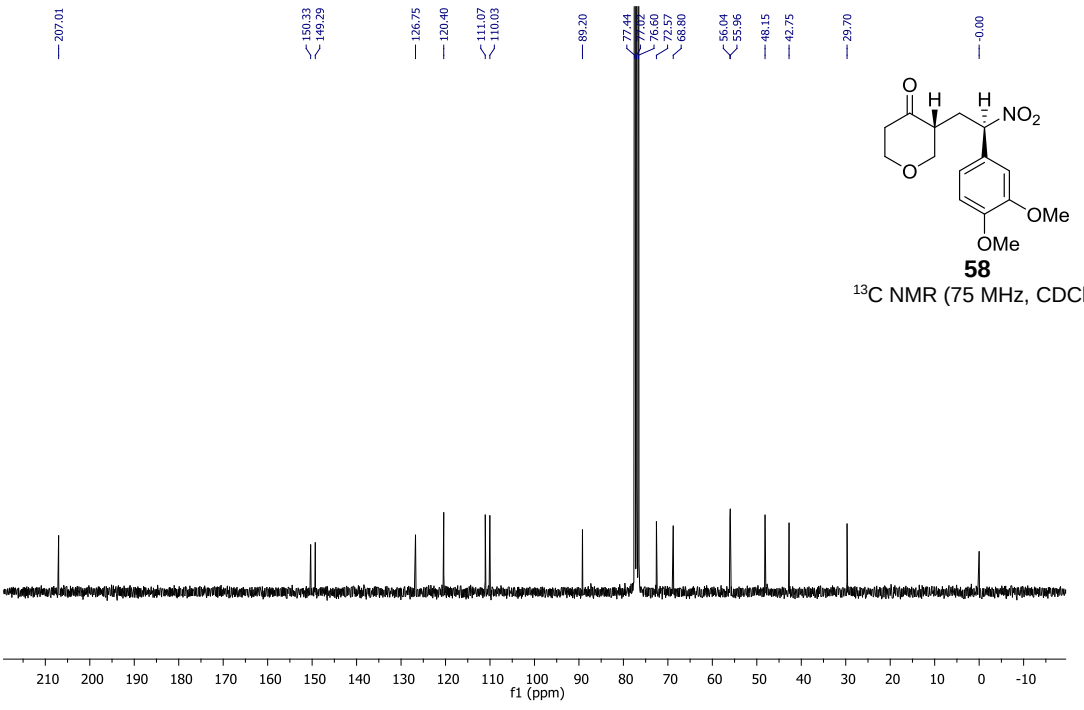

NVG-11-79A
O
H
H
NO2
56
13C NMR (75 MHz, CDCl3)
f1 (ppm)

NVG-11-80A



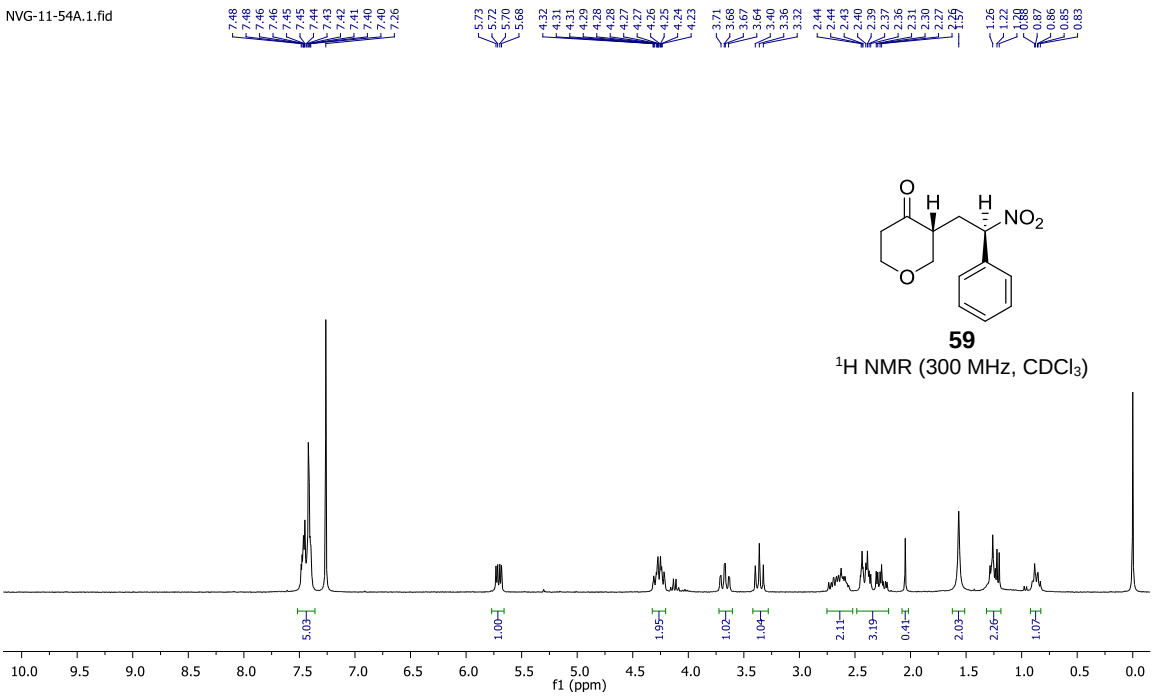
58

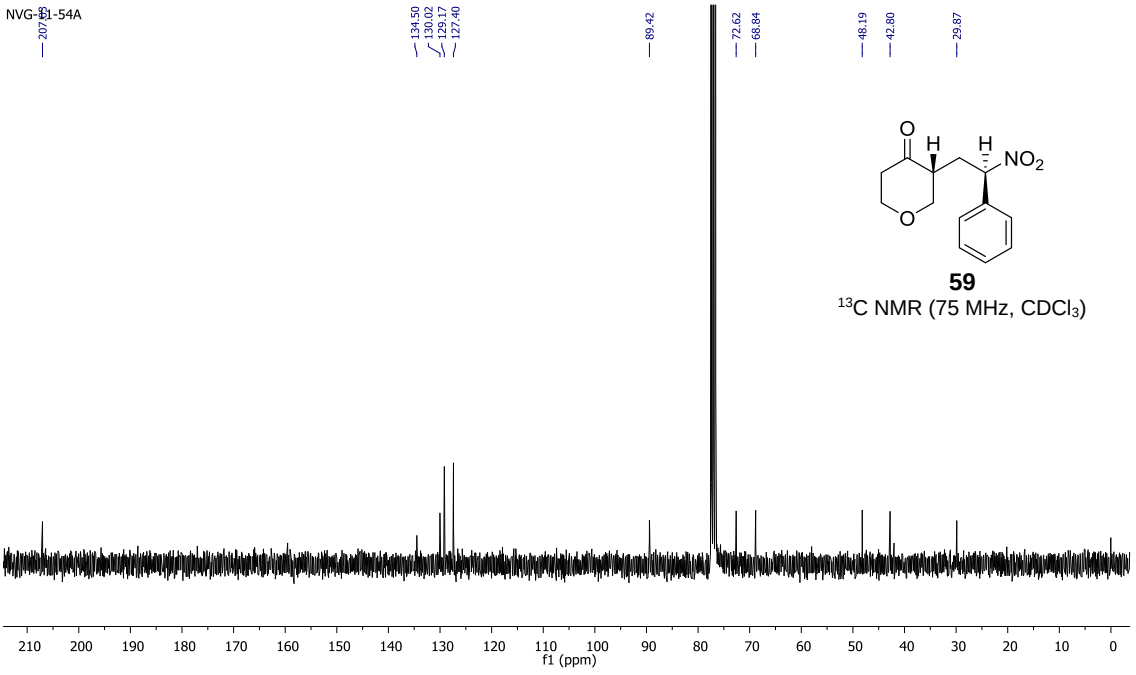
^{1}H NMR (300 MHz, $CDCl_3$)

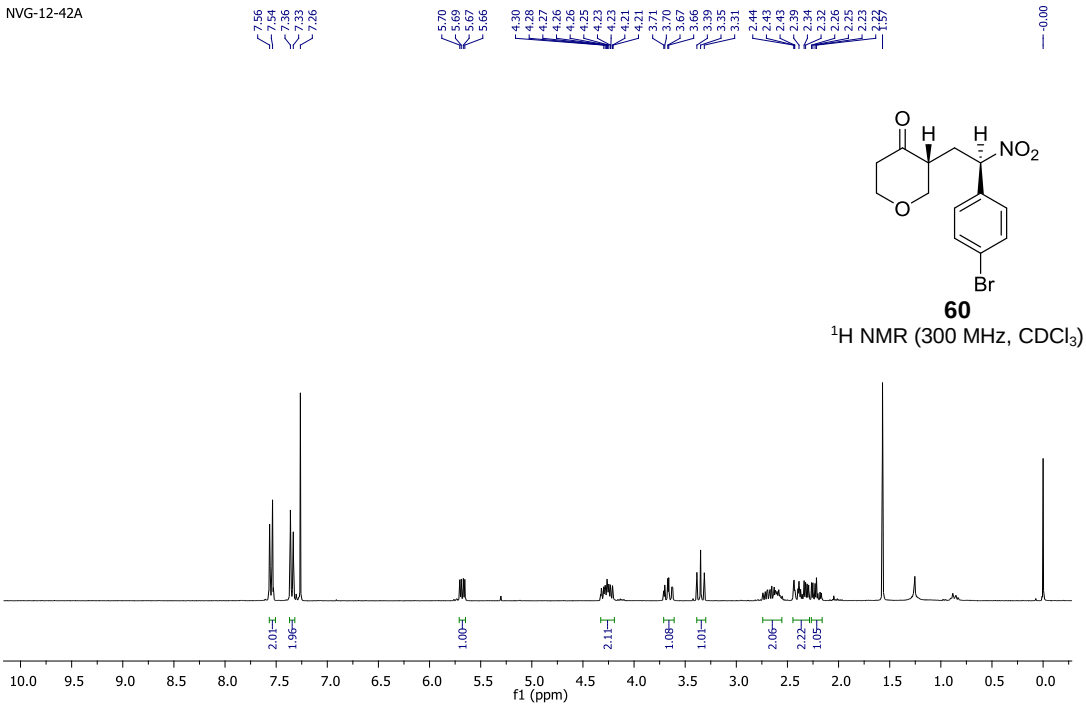


58

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

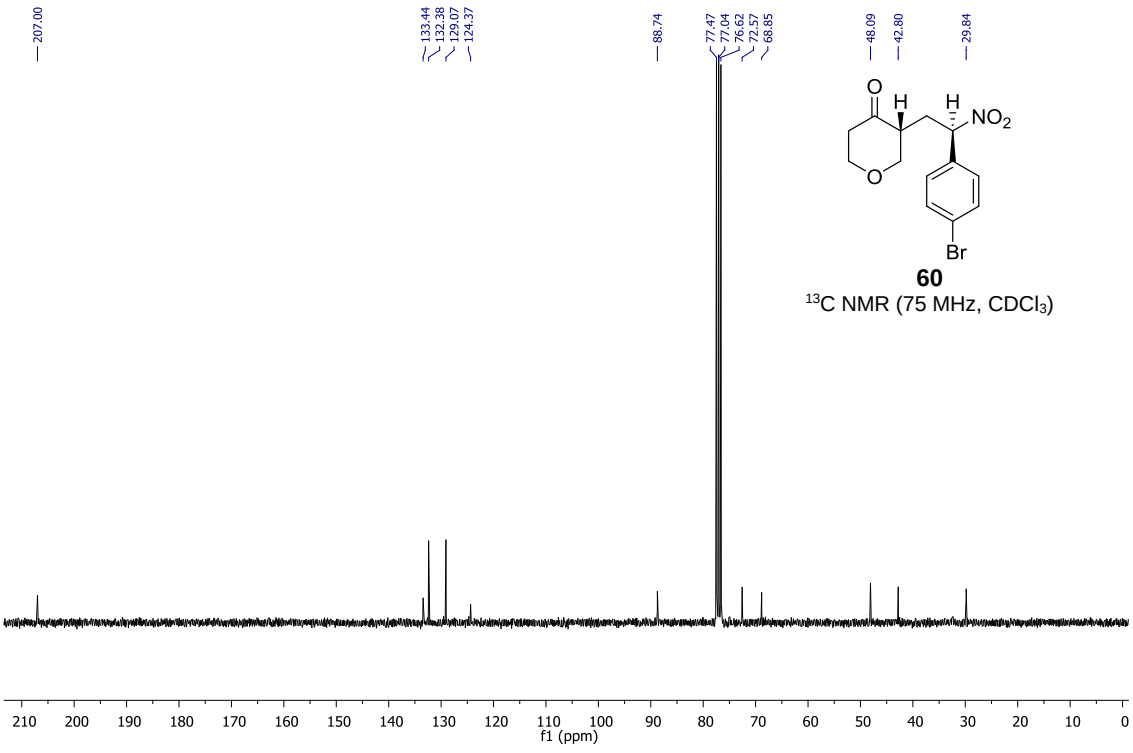

NVG-11-54A.1.fid
7.48 7.48 7.46 7.46 7.45 7.45 7.44 7.43 7.42 7.41 7.40 7.40 7.26
5.73 5.72 5.70 5.68
4.32 4.31 4.31 4.29 4.28 4.28 4.27 4.27 4.26 4.25 4.24 4.23
3.71 3.68 3.67 3.64 3.40 3.36 3.32
2.44 2.44 2.43 2.40 2.39 2.37 2.36 2.31 2.30 2.27 2.25 1.97
1.26 1.22 0.88 0.87 0.86 0.85 0.83
O
H
H
NO2
O
59
1H NMR (300 MHz, CDCl3)
5.03 1.00 1.95 1.02 1.04 2.11 3.19 0.41 2.03 2.26 1.07
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)


NVG-11-54A
207.21
134.50
130.02
129.17
127.40
89.42
72.62
68.84
48.19
42.80
29.87
O
H
H
NO2
O
59
13C NMR (75 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



60

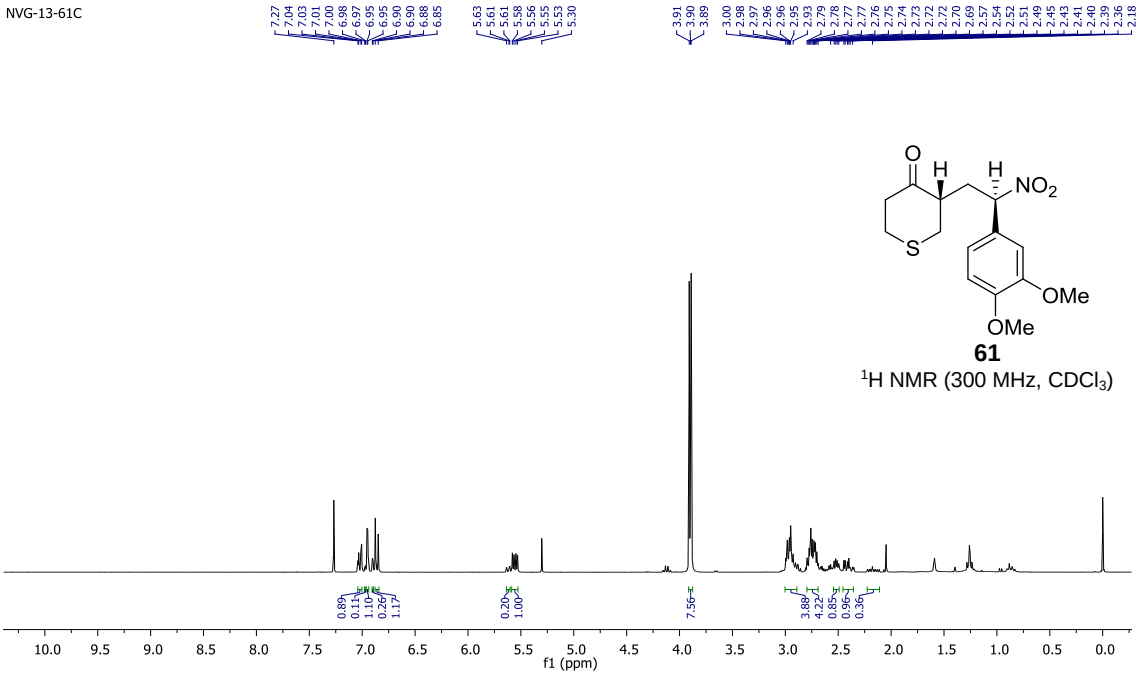
^{1}H NMR (300 MHz, $CDCl_3$)



60

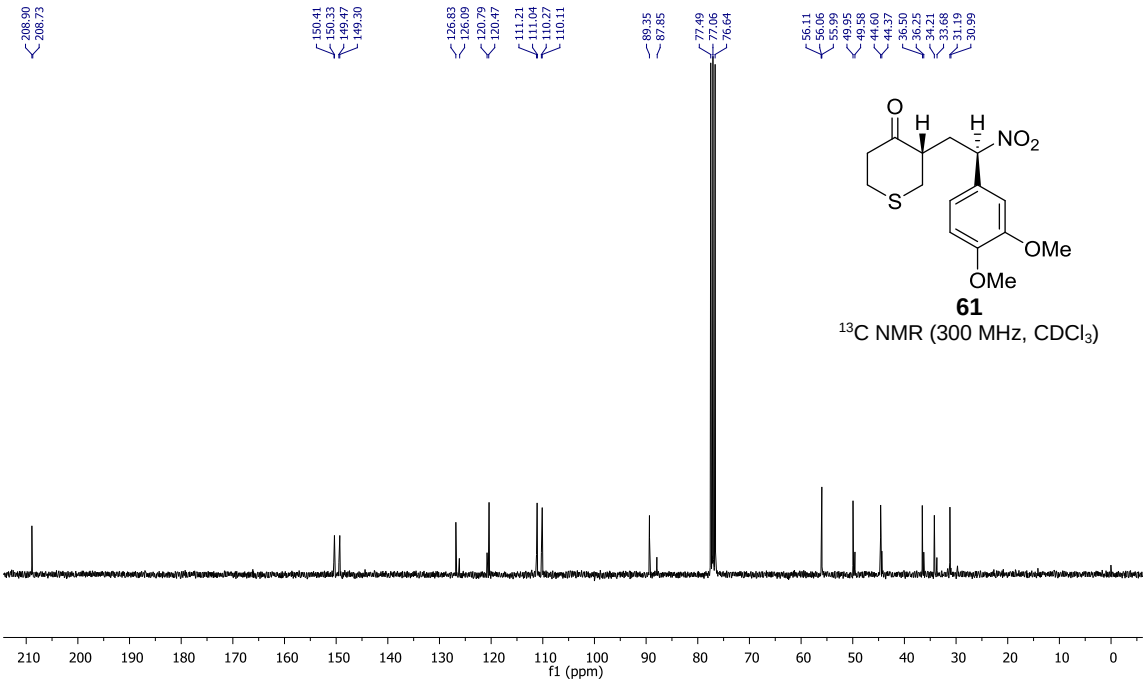
^{13}C NMR (75 MHz, $CDCl_3$)

NVG-13-61C



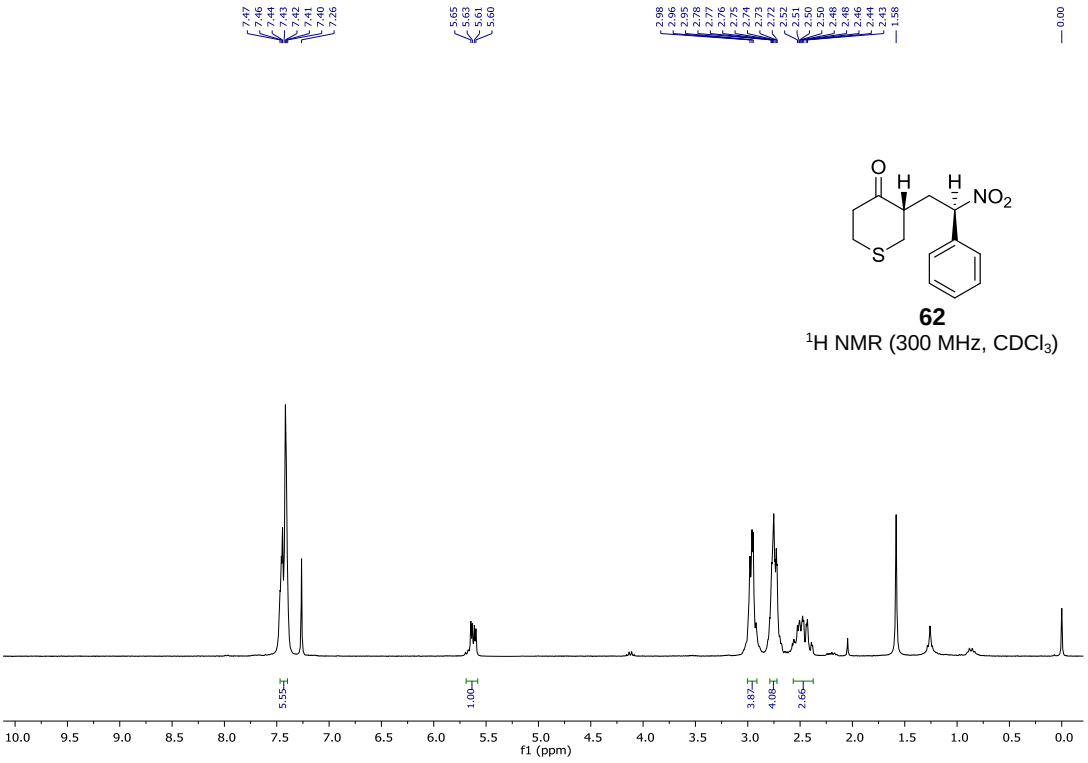
61

^{1}H NMR (300 MHz, $CDCl_3$)



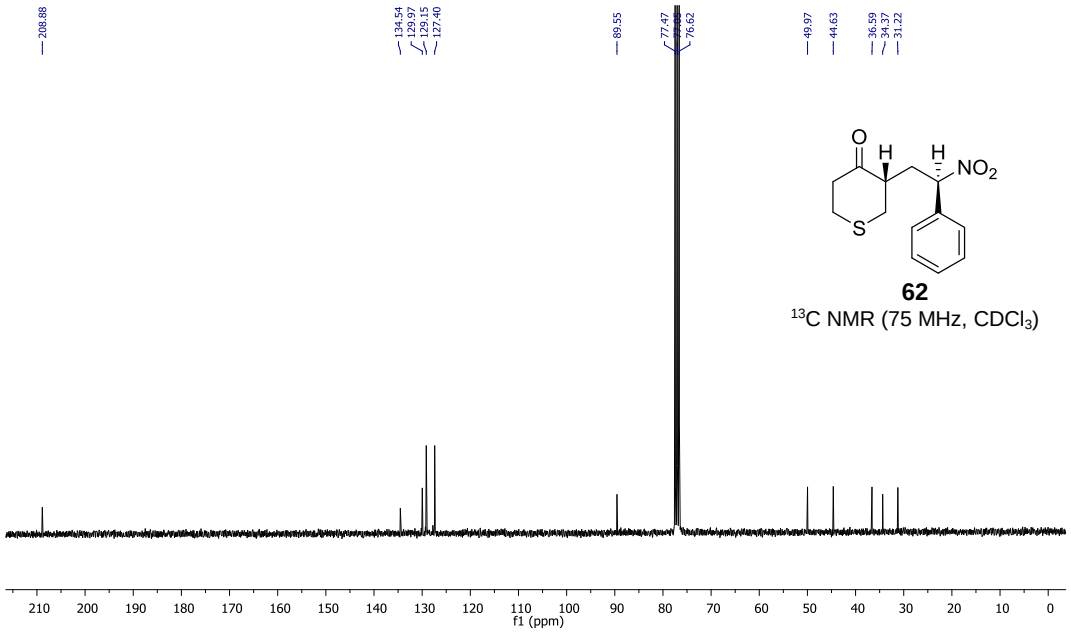
61

^{13}C NMR (300 MHz, $CDCl_3$)



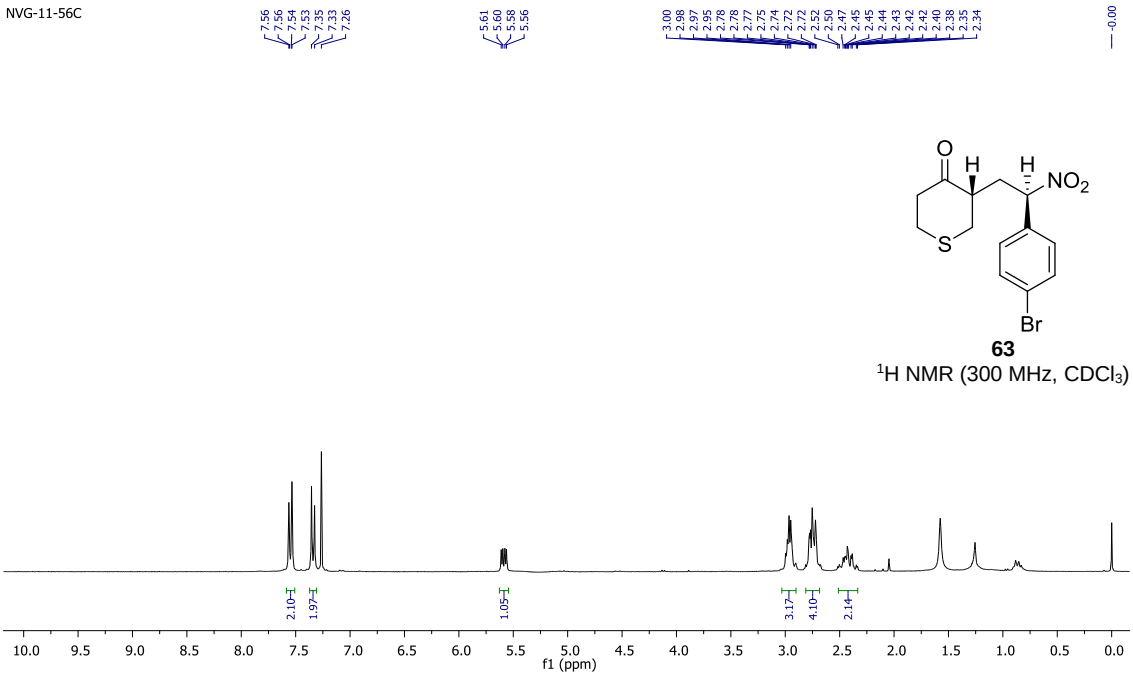
62

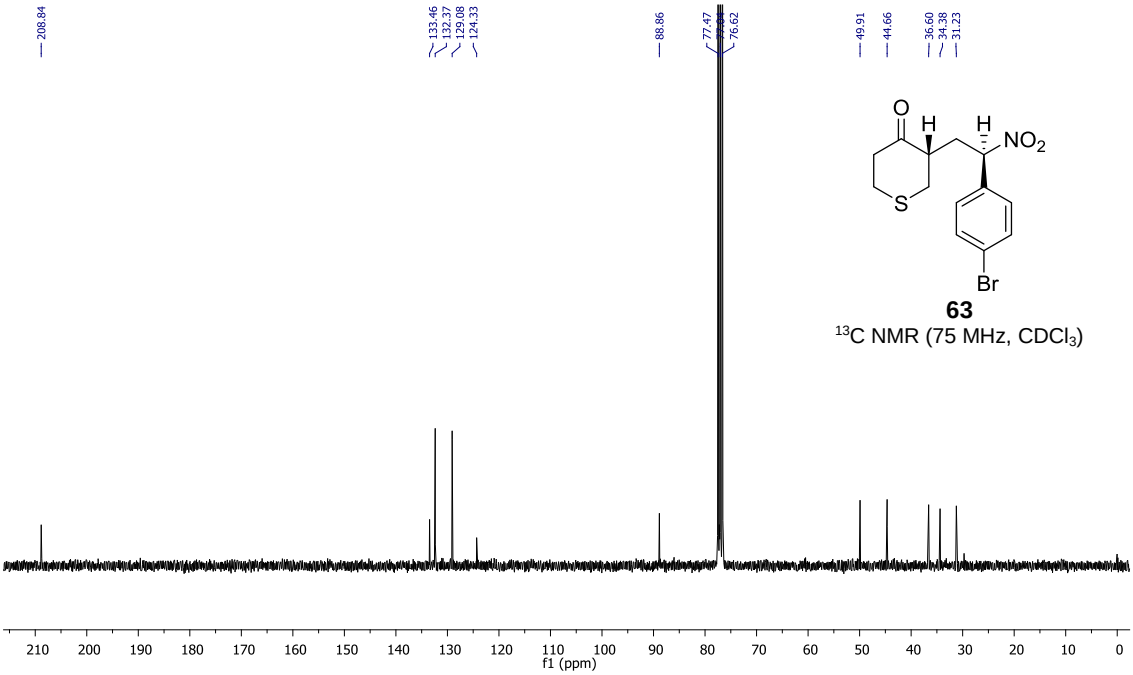
^{1}H NMR (300 MHz, $CDCl_3$)

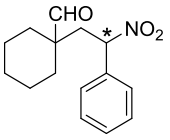


62

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

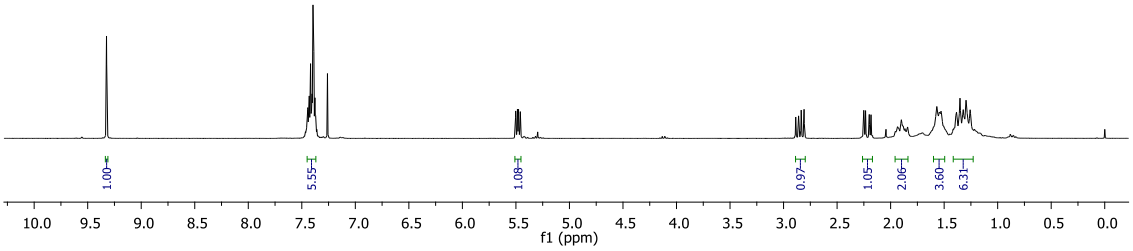

NVG-11-56C
7.56
7.56
7.54
7.53
7.35
7.33
7.26
5.61
5.60
5.58
5.56
3.00
2.98
2.97
2.95
2.78
2.78
2.77
2.75
2.74
2.72
2.72
2.52
2.50
2.47
2.45
2.45
2.44
2.43
2.42
2.42
2.40
2.38
2.35
2.34
-0.00
O
H
H
NO2
S
Br
63
1H NMR (300 MHz, CDCl3)
2.10
1.97
1.05
3.17
4.10
2.14
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
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)

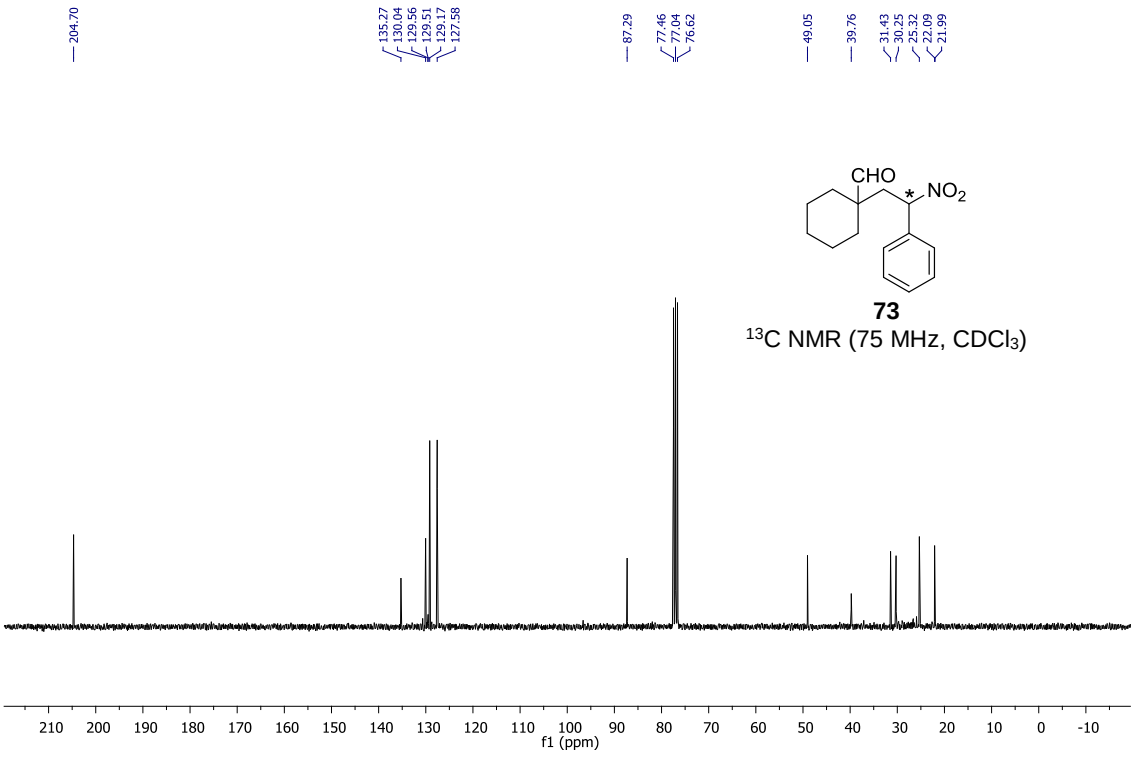

208.84
133.46
132.37
129.08
124.33
88.86
77.47
77.04
76.62
49.91
44.66
36.60
34.38
31.23
O
H
H
NO2
S
Br
63
13C NMR (75 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



73

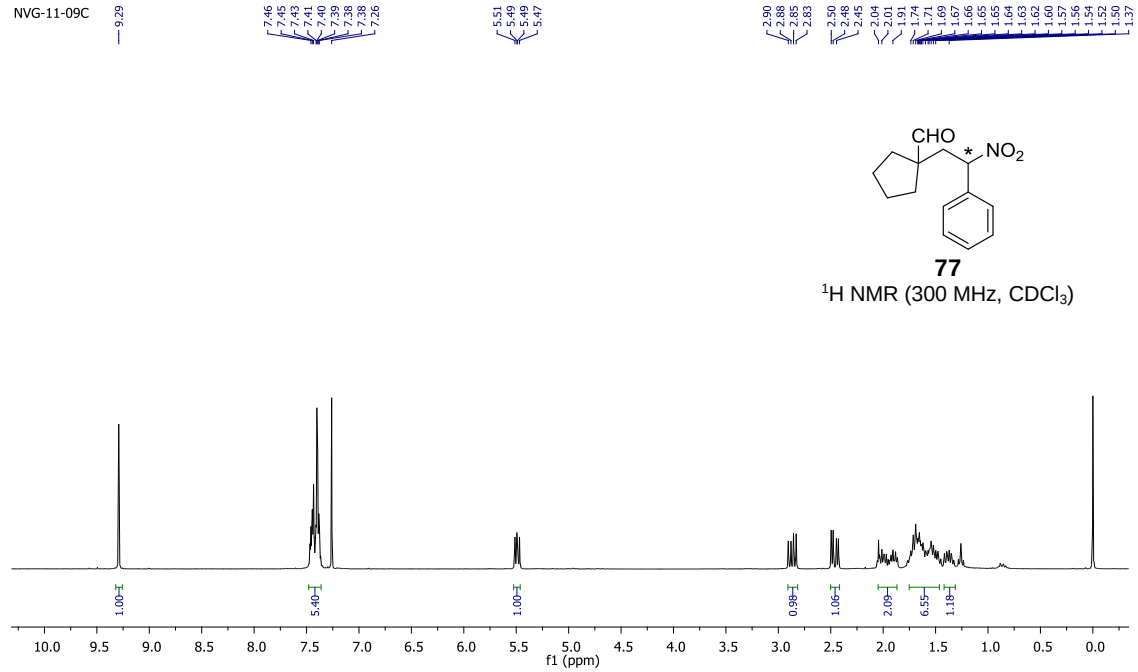
^{1}H NMR (300 MHz, $CDCl_3$)

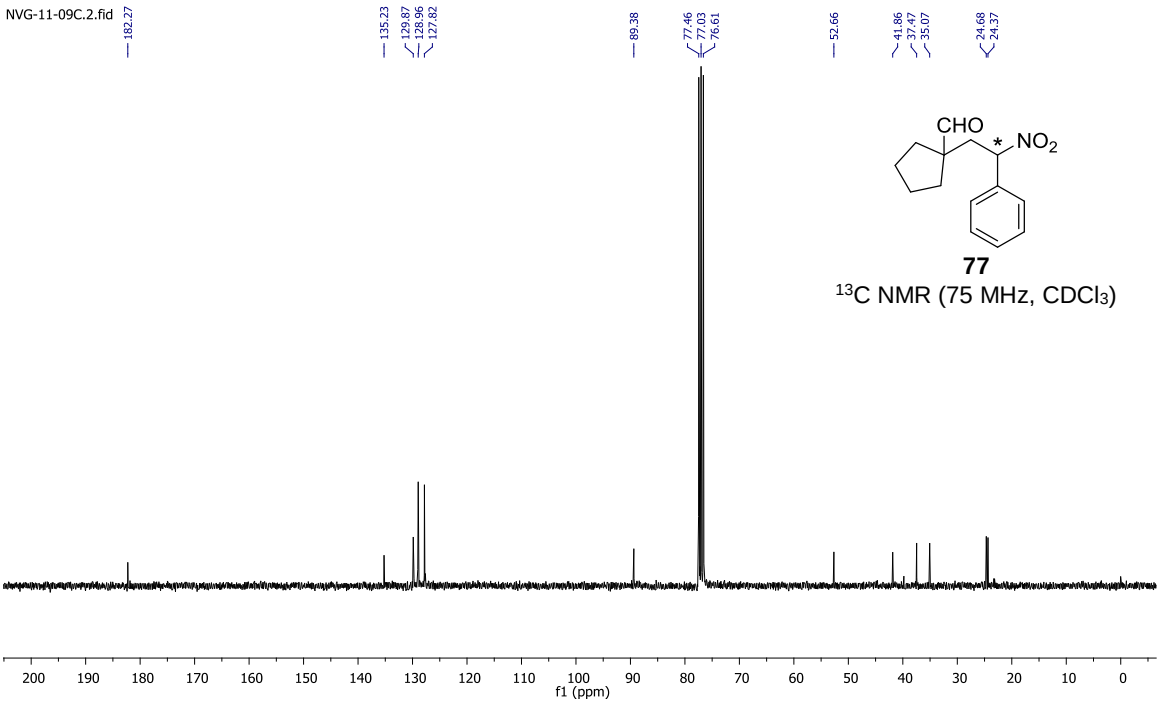


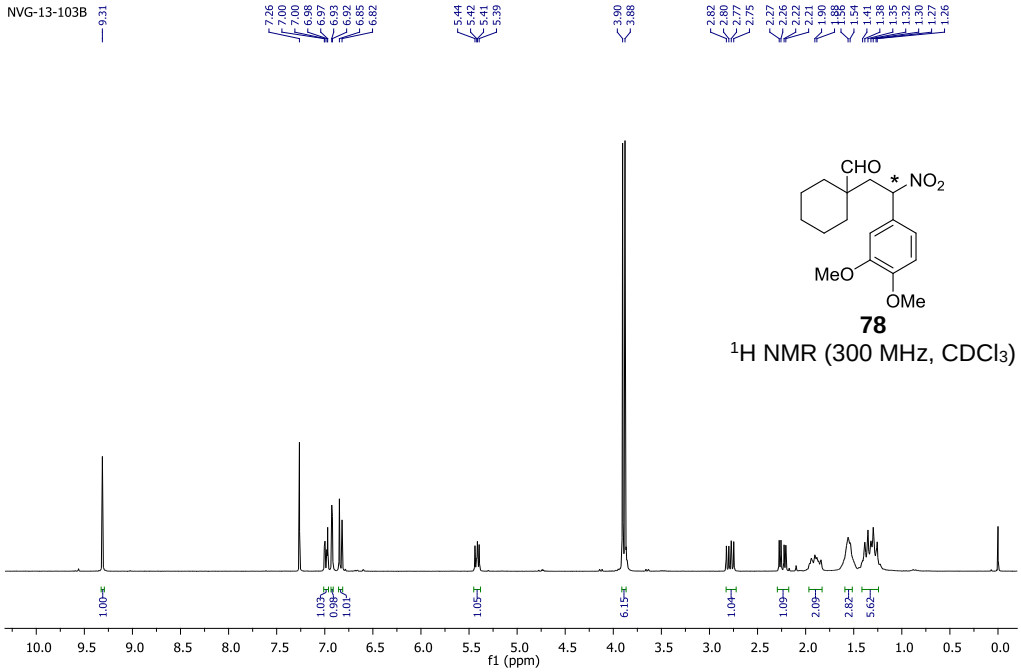


73

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

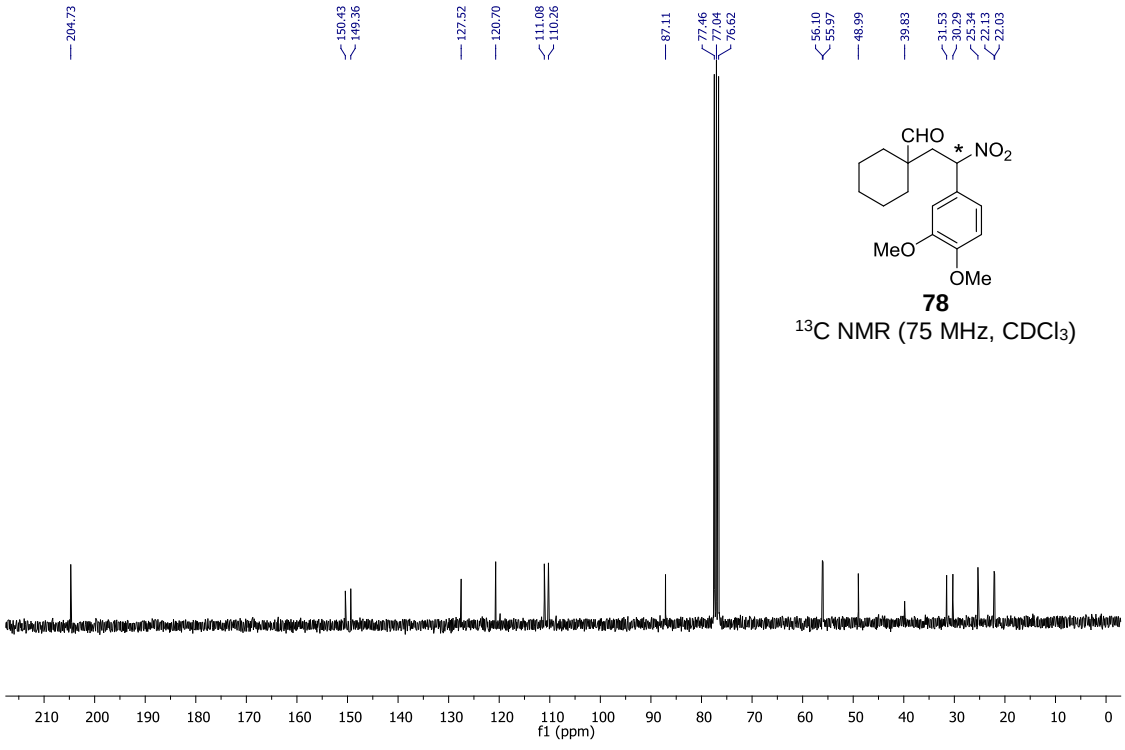

NVG-11-09C
9.29
7.46
7.45
7.43
7.41
7.40
7.39
7.38
7.38
7.26
5.51
5.49
5.49
5.47
2.90
2.88
2.85
2.83
2.50
2.48
2.45
2.04
2.01
1.91
1.74
1.71
1.69
1.67
1.66
1.65
1.65
1.64
1.63
1.62
1.60
1.57
1.56
1.54
1.52
1.50
1.37
CHO
NO2
*
77
1H NMR (300 MHz, CDCl3)
1.00
5.40
1.00
0.98
1.06
2.09
6.55
1.18
10.0
9.5
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)


NVG-11-09C.2.fid
182.27
135.23
129.87
128.96
127.82
89.38
77.46
77.03
76.61
52.66
41.86
37.47
35.07
24.68
24.37
CHO
NO2
*
77
13C NMR (75 MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



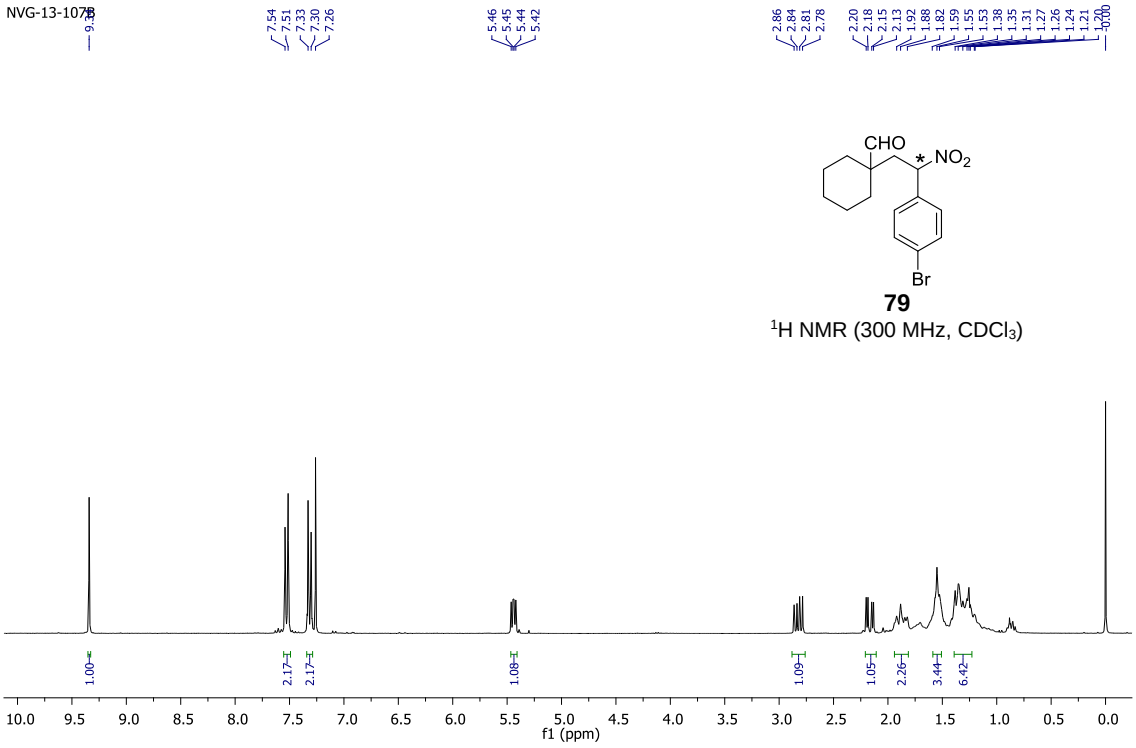
78

^{1}H NMR (300 MHz, $CDCl_3$)



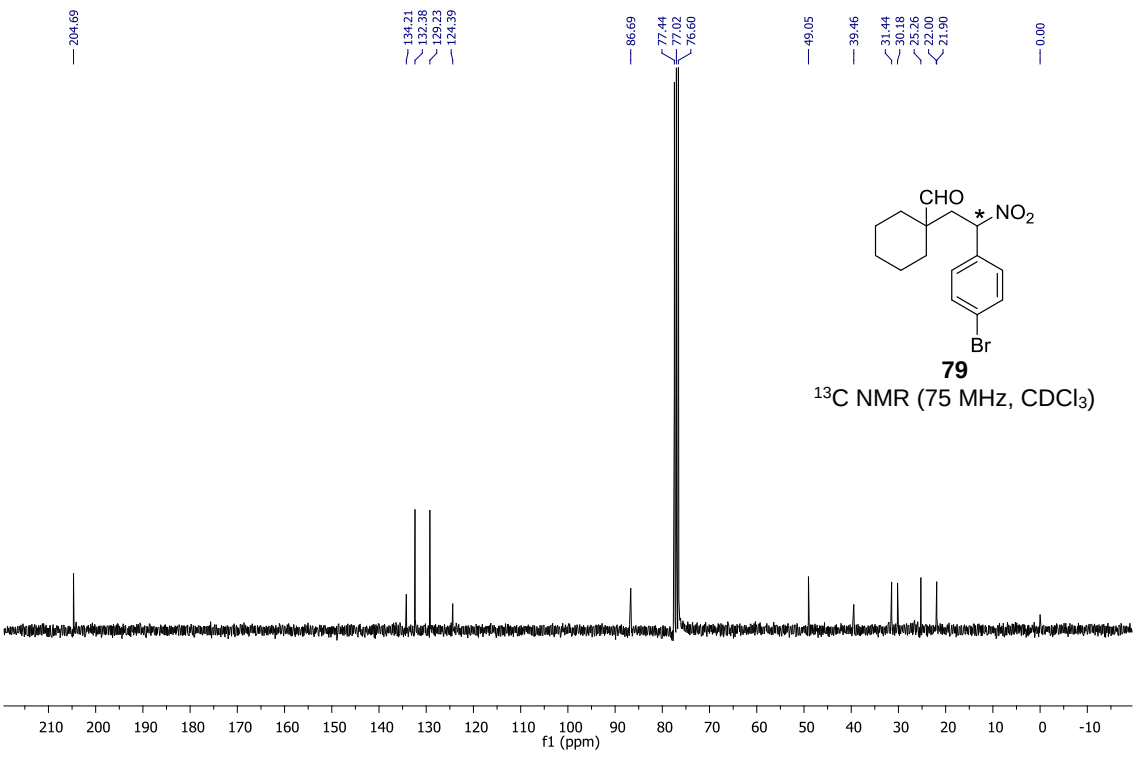
78

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



79

^{1}H NMR (300 MHz, $CDCl_3$)



79

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

Memorial University

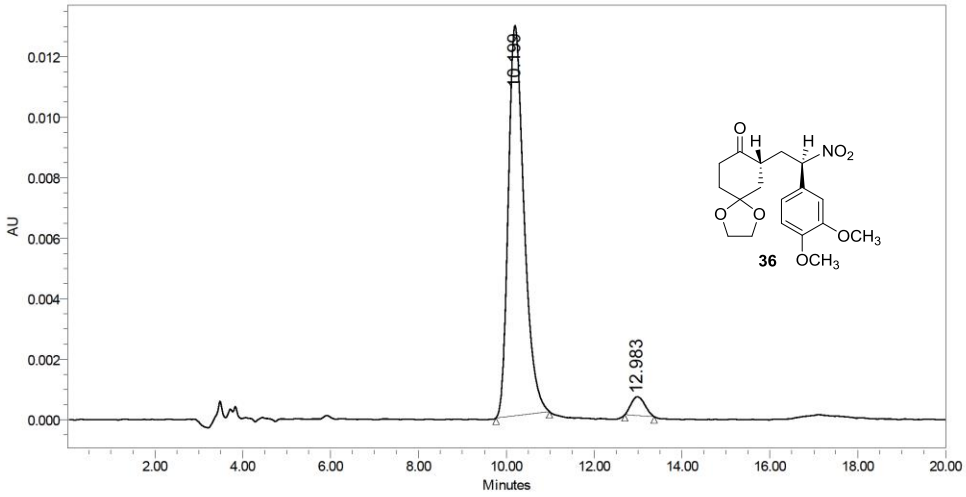
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-08-44A MICHAEL TOP	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	17/08/2015 7:50:16 PM NDT
Vial:	1	Acq. Method:	ASH 60%HEX 40%IPA
Injection #:	1	Date Processed:	17/08/2015 8:16:27 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	20.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	10.199	322486	96.00	12907	95.41
2	12.983	13435	4.00	622	4.59

Report Method: Individual Control Report

Page: 1 of 1

Printed: 19/08/2015 5:35:25 PM Canada/Newfoundland

Memorial University

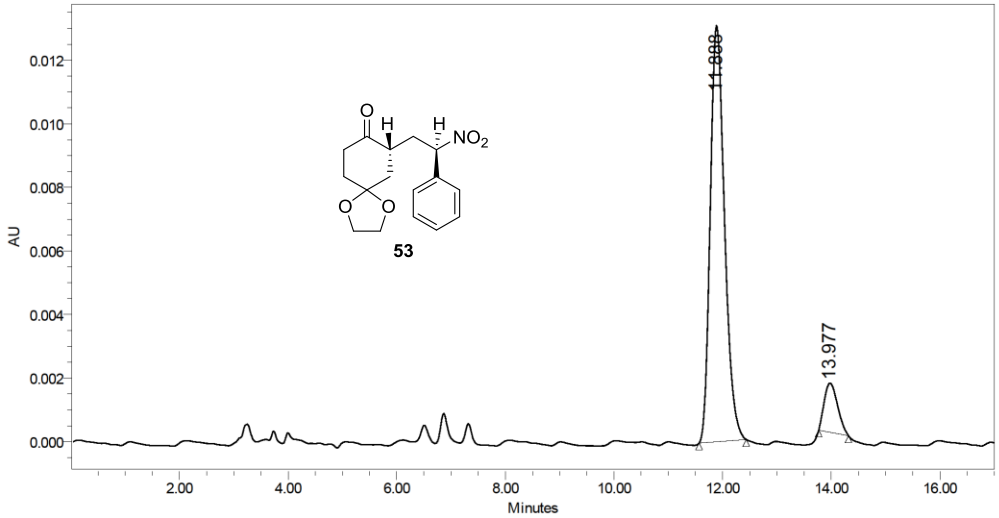
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-09-23E MICHAEL TOP	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	19/08/2015 5:02:33 PM NDT
Vial:	1	Acq. Method:	AS_H 90Hex10IPA
Injection #:	1	Date Processed:	19/08/2015 5:25:27 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	17.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



53

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	11.888	239056	90.07	13108	89.43
2	13.977	26347	9.93	1550	10.57

Report Method: Individual Control Report

Page: 1 of 1

Printed: 19/08/2015 5:34:01 PM Canada/Newfoundland

Memorial University

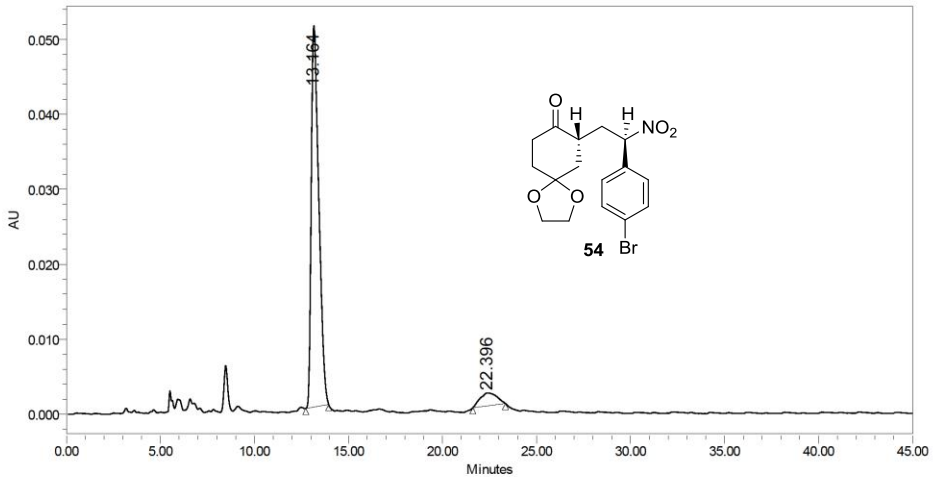
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-09-22B TOPSPOT	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	12/08/2015 7:31:40 PM NDT
Vial:	1	Acq. Method:	AS_H 90Hex10IPA
Injection #:	1	Date Processed:	12/08/2015 8:17:48 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	45.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.164	1414468	93.06	50883	96.76
2	22.396	105546	6.94	1705	3.24

Report Method: Individual Control Report

Page: 1 of 1

Printed: 19/08/2015

5:36:21 PM Canada/Newfoundland

Memorial University

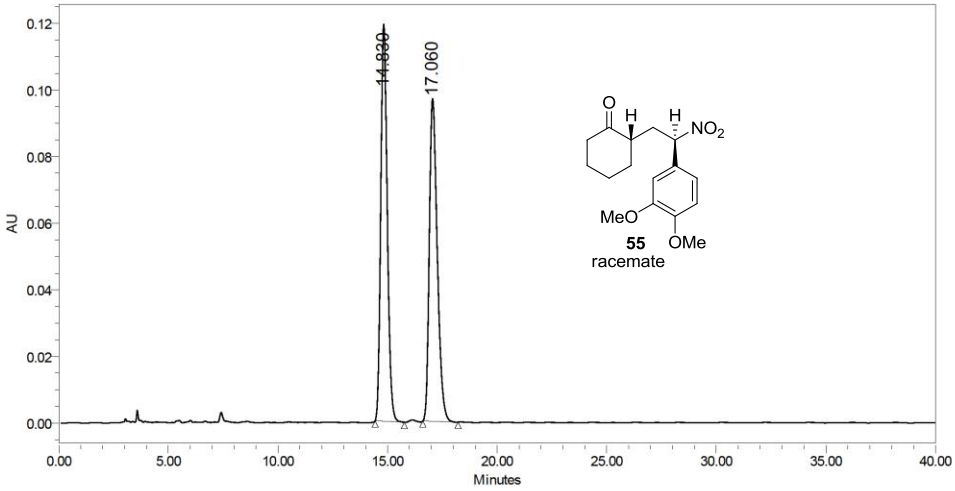
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-78A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	22/06/2016 11:41:44 AM NDT
Vial:	27	Acq. Method:	AD_H 90Hex10IPA
Injection #:	1	Date Processed:	22/06/2016 1:30:32 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	14.830	2444967	50.06	119194	55.15
2	17.060	2438716	49.94	96914	44.85

Memorial University

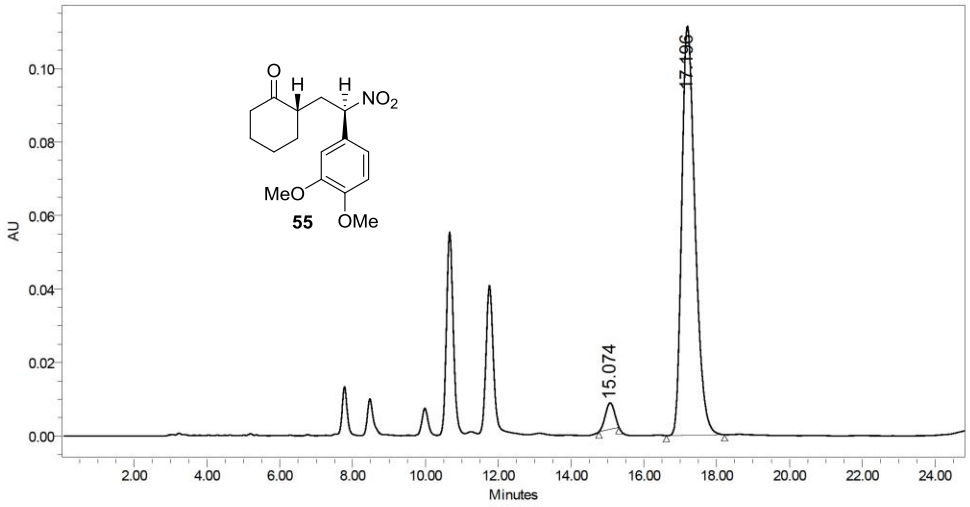
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-10-57B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	14/04/2016 4:13:01 PM NDT
Vial:	1	Acq. Method:	AD_H 90Hex10IPA
Injection #:	1	Date Processed:	14/04/2016 4:38:44 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.074	123038	4.15	7189	6.06
2	17.196	2841331	95.85	111438	93.94

Memorial University

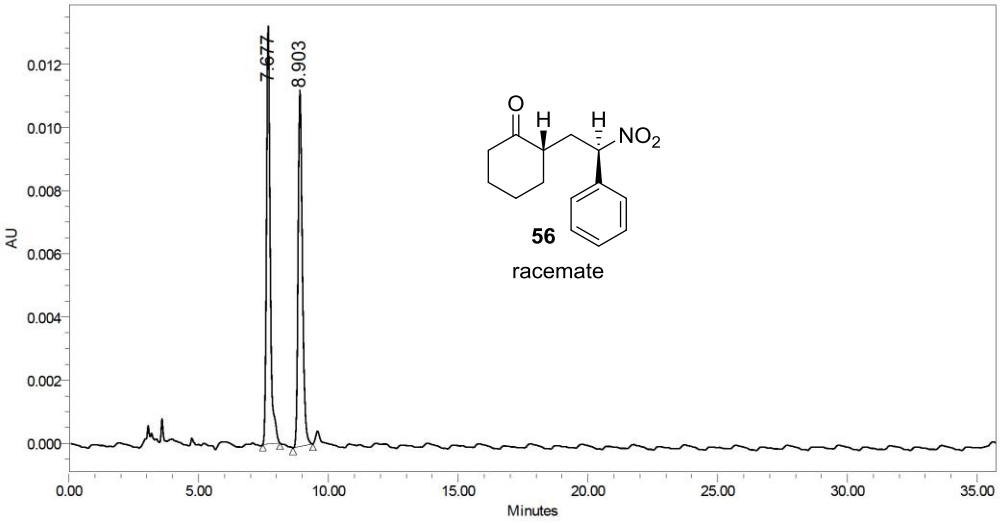
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-79A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	25/06/2016 1:03:13 PM NDT
Vial:	31	Acq. Method:	AD_H 90Hex10IPA
Injection #:	1	Date Processed:	25/06/2016 1:39:13 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



56

racemate

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.677	133272	50.59	13269	54.04
2	8.903	130186	49.41	11285	45.96

Memorial University

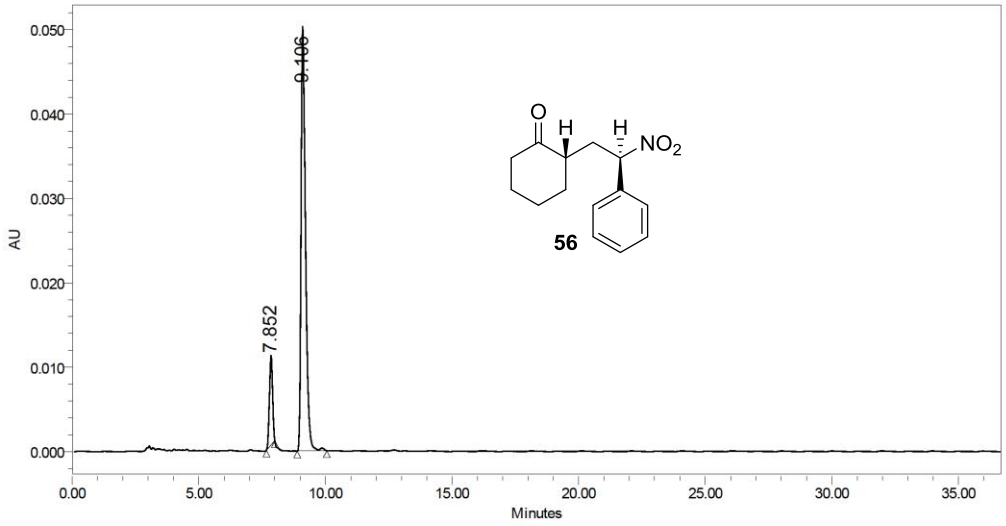
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-10-58b	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	23/05/2016 2:23:35 PM NDT
Vial:	1	Acq. Method:	AD_H 90Hex10IPA
Injection #:	1	Date Processed:	23/05/2016 3:13:49 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	50.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.852	91775	12.98	10562	17.32
2	9.106	615256	87.02	50427	82.68

Report Method: Individual Control Report

Page: 1 of 1

Printed: 23/05/2016

3:14:13 PM Canada/Newfoundland

Memorial University

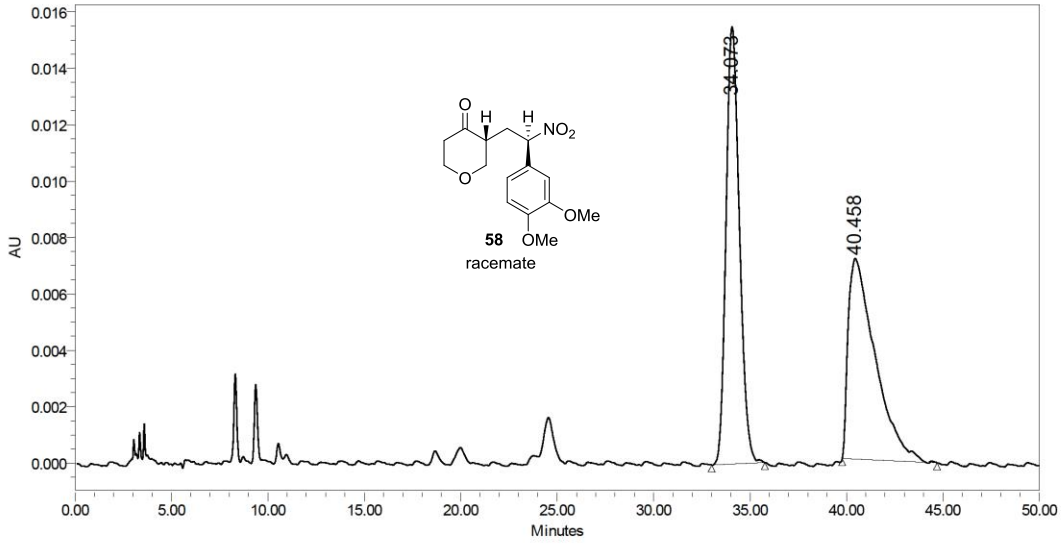
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-80A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	23/06/2016 5:15:45 PM NDT
Vial:	30	Acq. Method:	AD_H 90Hex10IPA_1
Injection #:	1	Date Processed:	23/06/2016 6:06:05 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	50.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	34.073	748895	51.91	15505	68.55
2	40.458	693715	48.09	7113	31.45

Report Method: Individual Control Report

Page: 1 of 1

Printed: 23/06/2016 6:06:36 PM Canada/Newfoundland

Memorial University

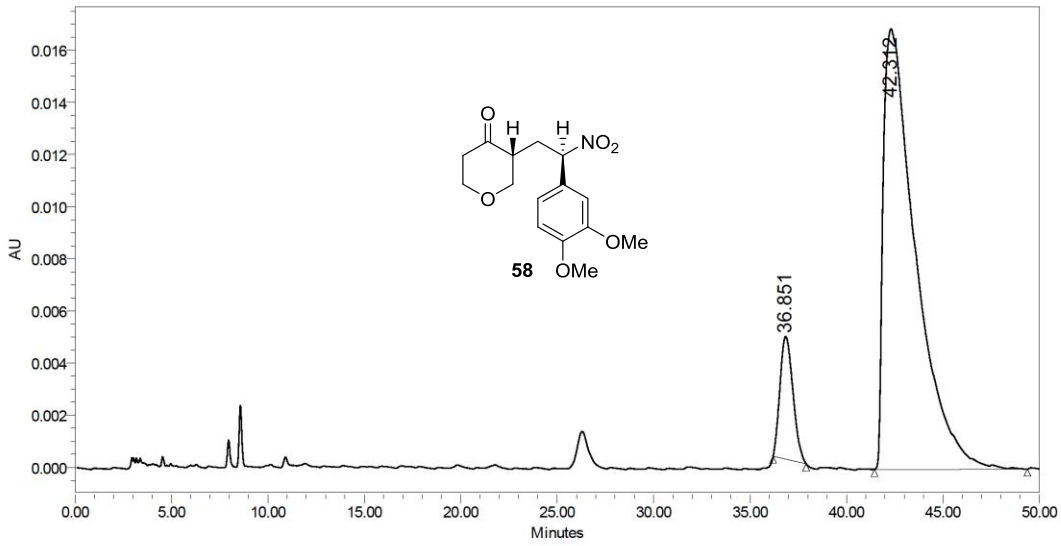
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-45b	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	21/05/2016 3:38:50 PM NDT
Vial:	1	Acq. Method:	AD_H 90Hex10IPA
Injection #:	1	Date Processed:	21/05/2016 4:44:35 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	50.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	36.851	220846	10.10	4701	21.76
2	42.312	1966671	89.90	16904	78.24

Report Method: Individual Control Report

Page: 1 of 1

Printed: 21/05/2016

4:45:15 PM Canada/Newfoundland

Memorial University

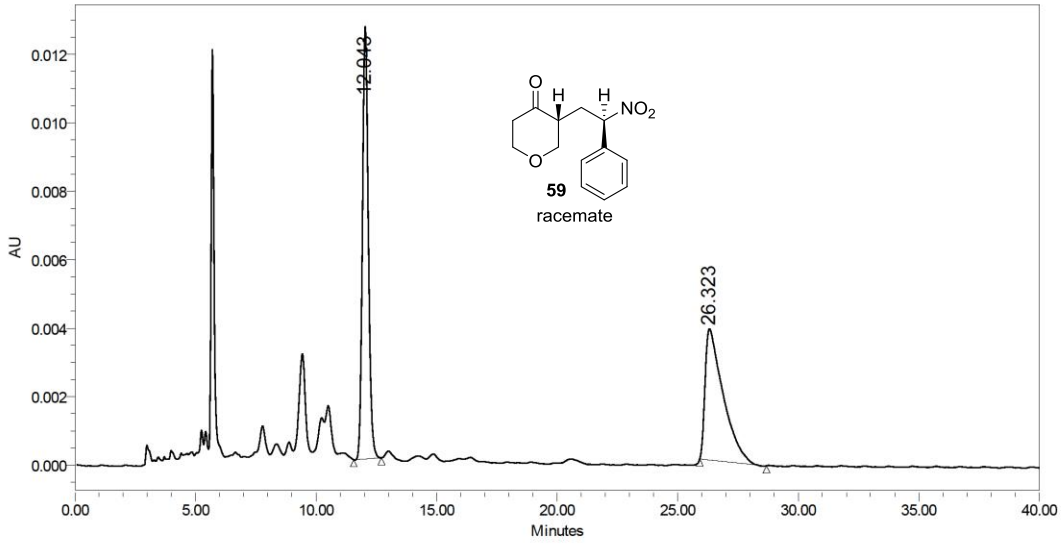
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-12-50B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	03/02/2017 10:24:32 AM NST
Vial:	142	Acq. Method:	AD_H 80%HEX 20%IPA
Injection #:	1	Date Processed:	03/02/2017 11:05:12 AM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.043	215736	51.99	12647	76.74
2	26.323	199182	48.01	3832	23.26

Memorial University

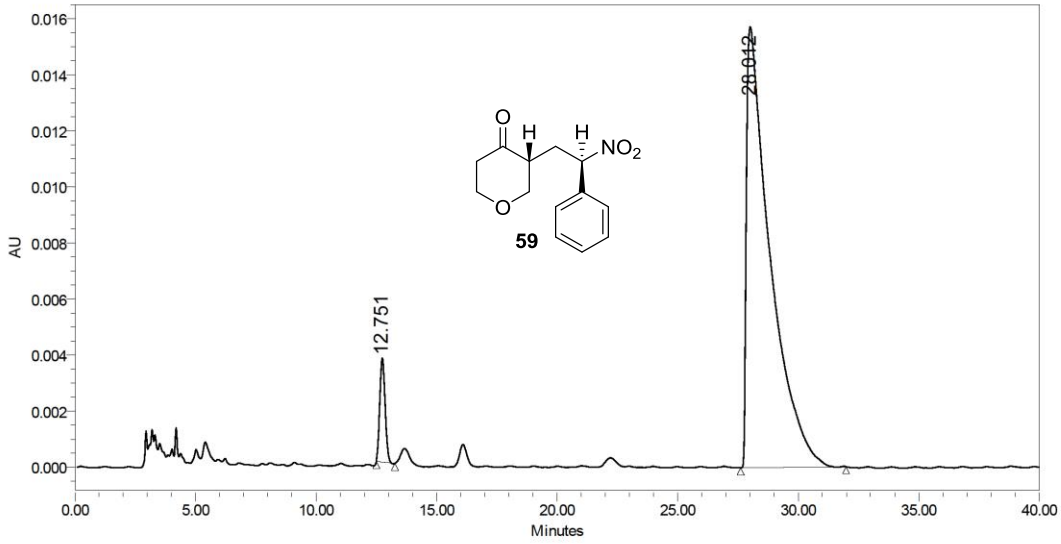
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-54A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	01/06/2016 5:34:30 PM NDT
Vial:	7	Acq. Method:	AD_H 80%HEX 20%IPA
Injection #:	1	Date Processed:	06/10/2016 10:11:47 AM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.751	57844	5.14	3714	19.10
2	28.012	1066886	94.86	15731	80.90

Memorial University

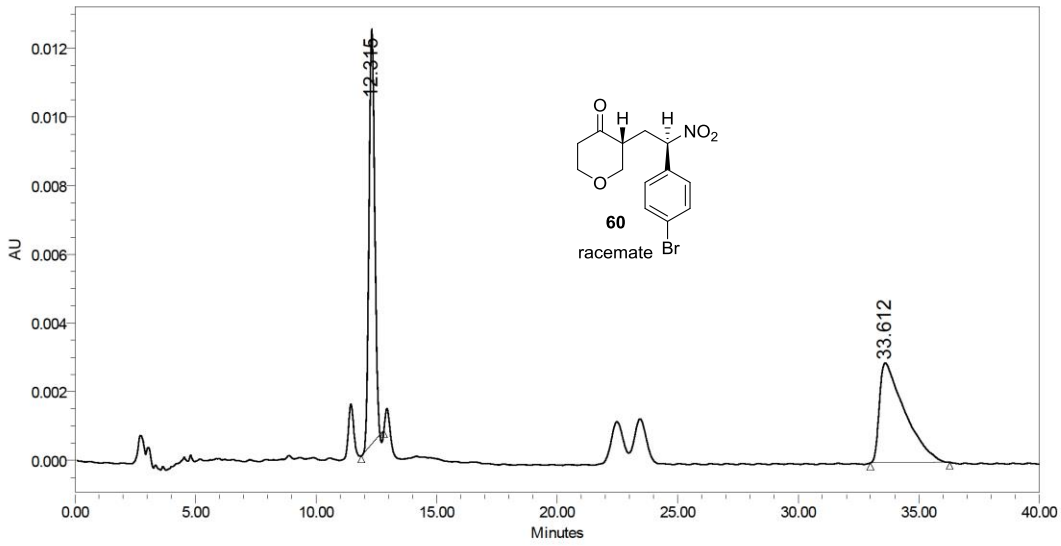
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-12-42A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	01/02/2017 3:39:30 PM NST
Vial:	133	Acq. Method:	AD_H 70%HEX 30%IPA
Injection #:	1	Date Processed:	01/02/2017 4:54:32 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.315	200999	48.69	12090	80.61
2	33.612	211804	51.31	2908	19.39

Memorial University

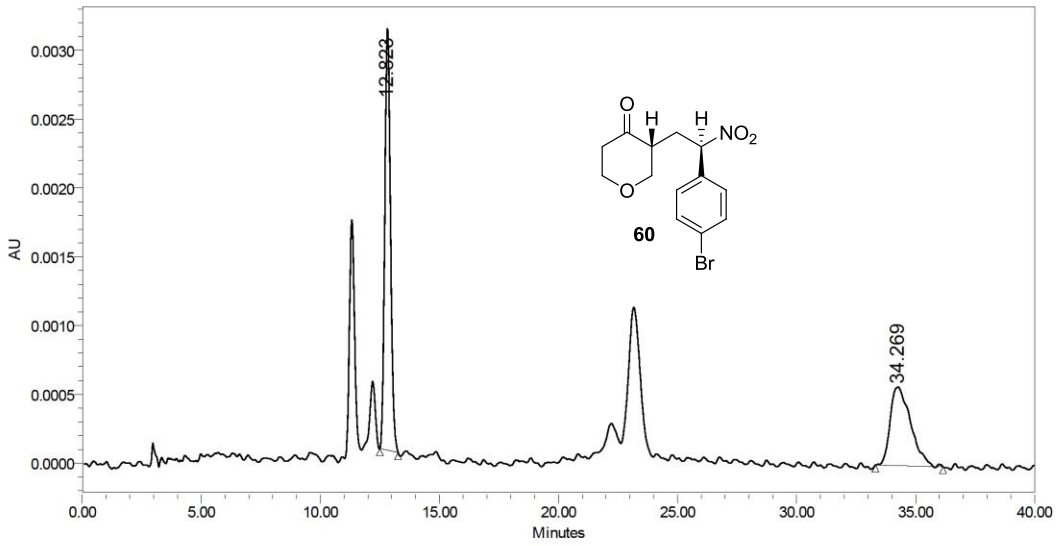
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-52b	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	01/02/2017 7:10:38 PM NST
Vial:	136	Acq. Method:	AD_H 70%HEX 30%IPA
Injection #:	1	Date Processed:	20/07/2017 7:51:20 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.823	51190	59.92	3066	84.29
2	34.269	34246	40.08	571	15.71

Memorial University

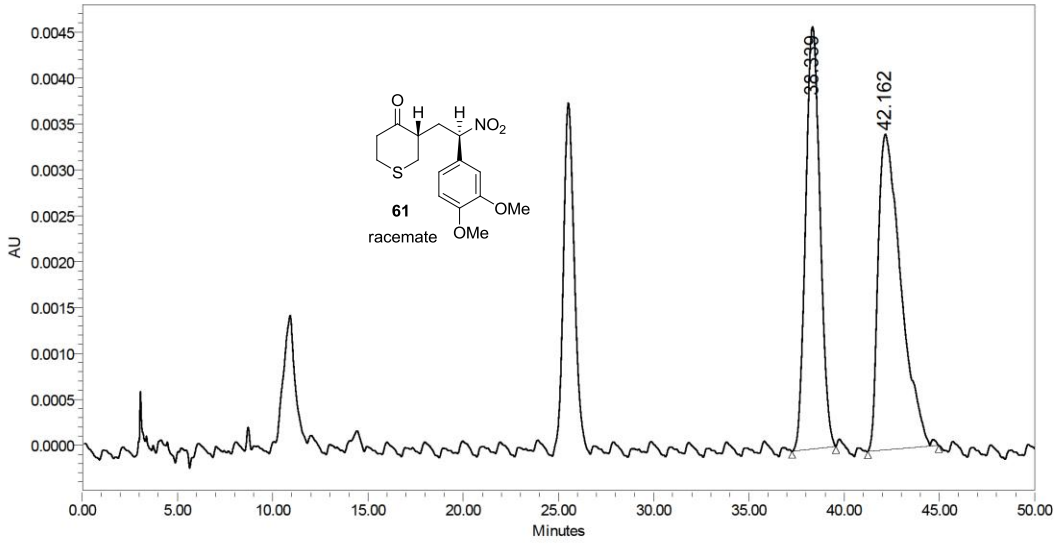
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-32B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	07/08/2016 1:07:24 PM NDT
Vial:	81	Acq. Method:	AD_H 90%HEX 10%IPA_254NM
Injection #:	1	Date Processed:	07/08/2016 2:01:52 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	50.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	38.339	242052	45.78	4599	57.22
2	42.162	286728	54.22	3438	42.78

Memorial University

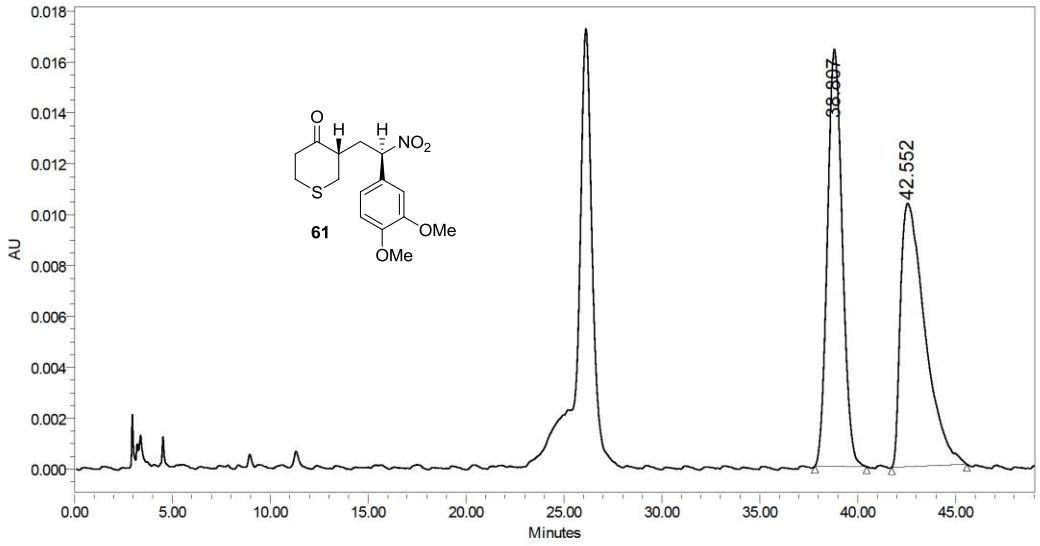
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-46B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	19/07/2016 5:58:52 PM NDT
Vial:	70	Acq. Method:	AD_H 90%HEX 10%IPA_254NM
Injection #:	1	Date Processed:	20/07/2017 9:55:01 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	50.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	38.807	864558	49.03	16379	61.29
2	42.552	898763	50.97	10346	38.71

Report Method: Individual Control Report

Page: 1 of 1

Printed: 20/07/2017

9:55:49 PM Canada/Newfoundland

Memorial University

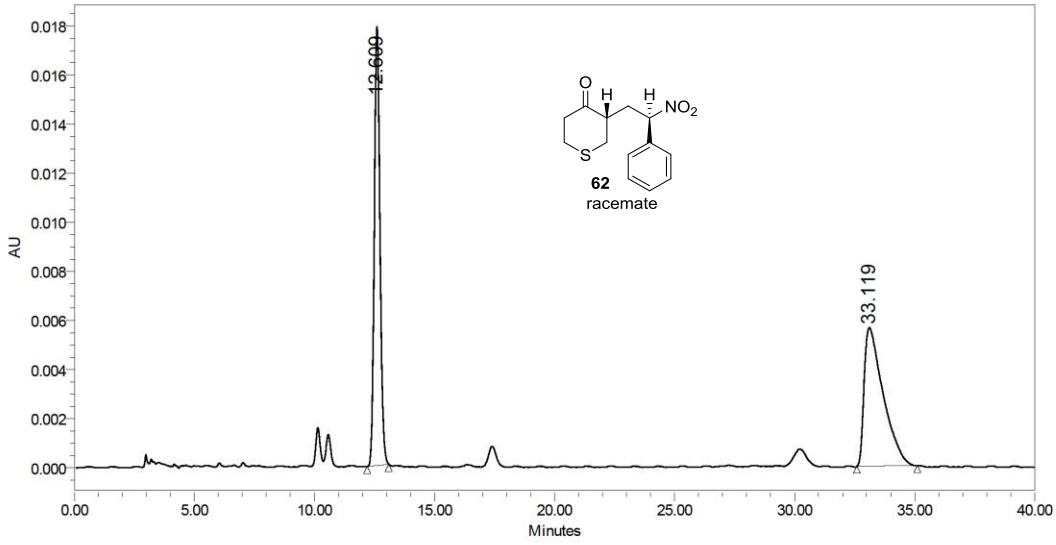
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-66B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	18/07/2016 5:32:29 PM NDT
Vial:	65	Acq. Method:	AD_H 80%HEX 20%IPA
Injection #:	1	Date Processed:	20/07/2017 8:24:23 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.609	292046	48.50	17915	76.06
2	33.119	310171	51.50	5640	23.94

Report Method: Individual Control Report

Page: 1 of 1

Printed: 20/07/2017

8:24:49 PM Canada/Newfoundland

Memorial University

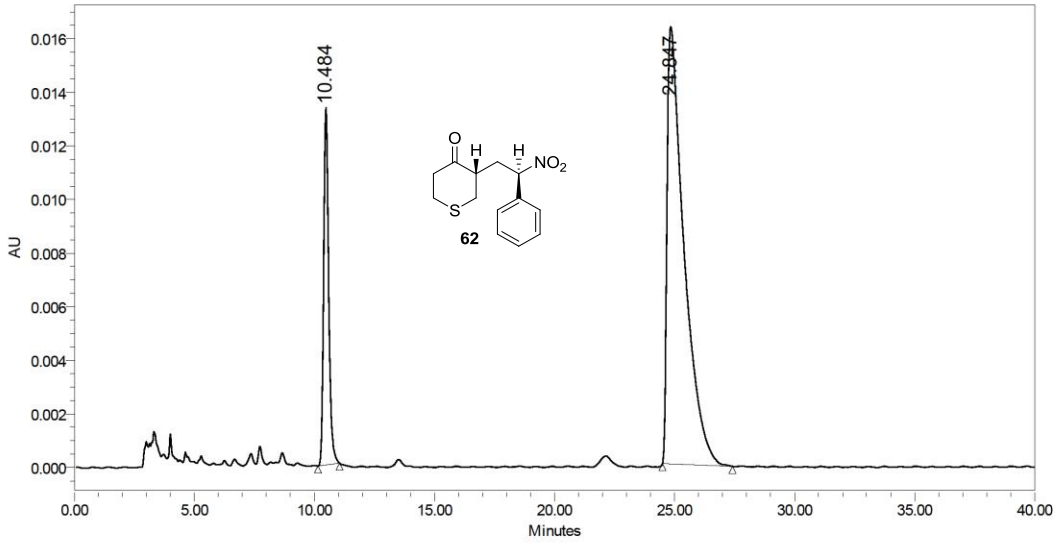
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-55B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	18/07/2016 8:22:59 PM NDT
Vial:	67	Acq. Method:	AD_H 70%HEX 30%IPA
Injection #:	1	Date Processed:	20/07/2017 8:32:26 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	10.484	193049	19.44	13335	44.98
2	24.847	800032	80.56	16314	55.02

Memorial University

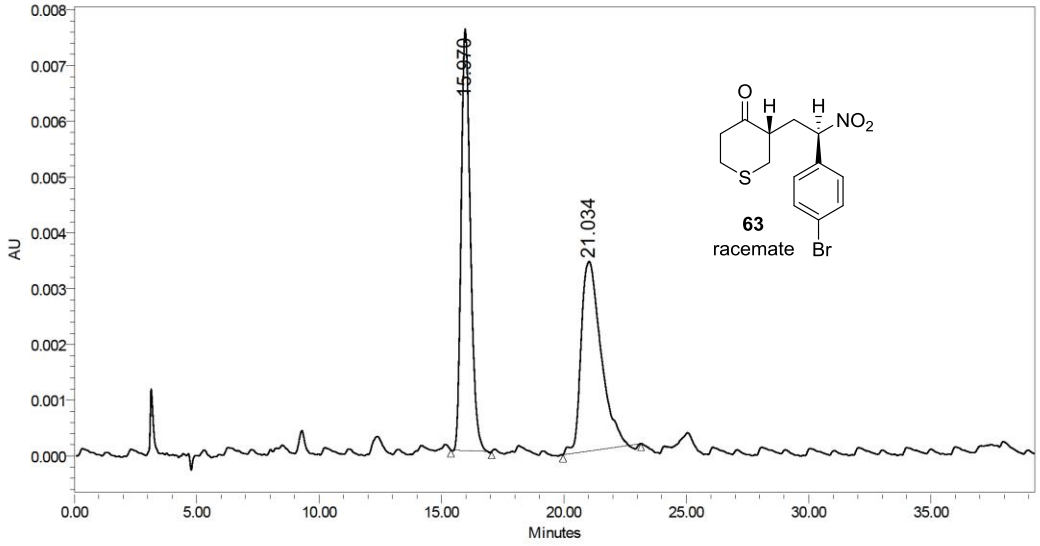
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-87B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	02/07/2016 4:25:18 PM NDT
Vial:	42	Acq. Method:	AS_H 90Hex10IPA
Injection #:	1	Date Processed:	02/07/2016 5:05:00 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.970	197990	50.46	7563	68.99
2	21.034	194414	49.54	3399	31.01

Report Method: Individual Control Report

Page: 1 of 1

Printed: 02/07/2016

5:05:28 PM Canada/Newfoundland

Memorial University

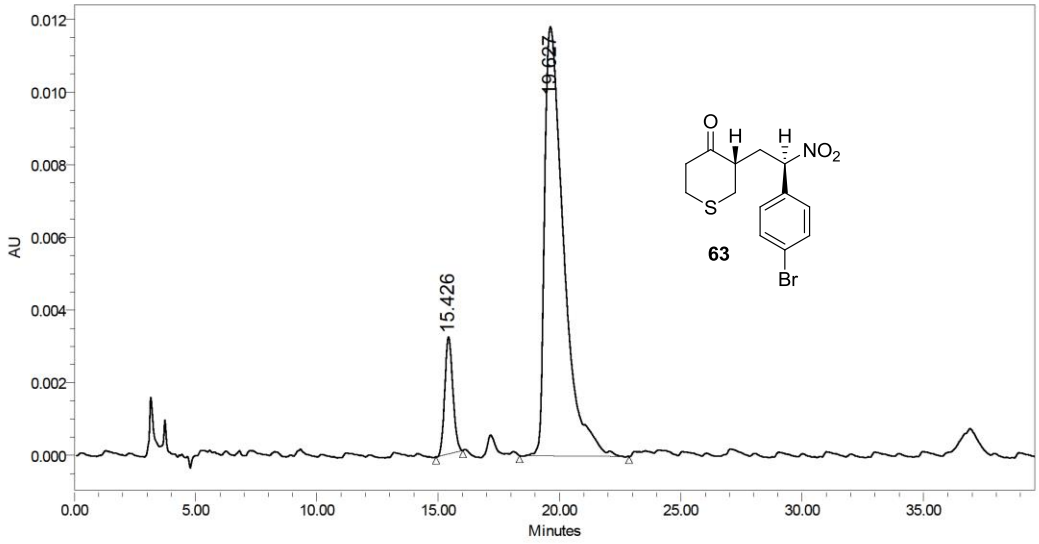
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-56C	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	29/06/2016 6:30:00 PM NDT
Vial:	38	Acq. Method:	AS_H 90Hex10IPA
Injection #:	1	Date Processed:	29/06/2016 7:10:24 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	15.426	74607	10.34	3229	21.46
2	19.627	646824	89.66	11815	78.54

Memorial University

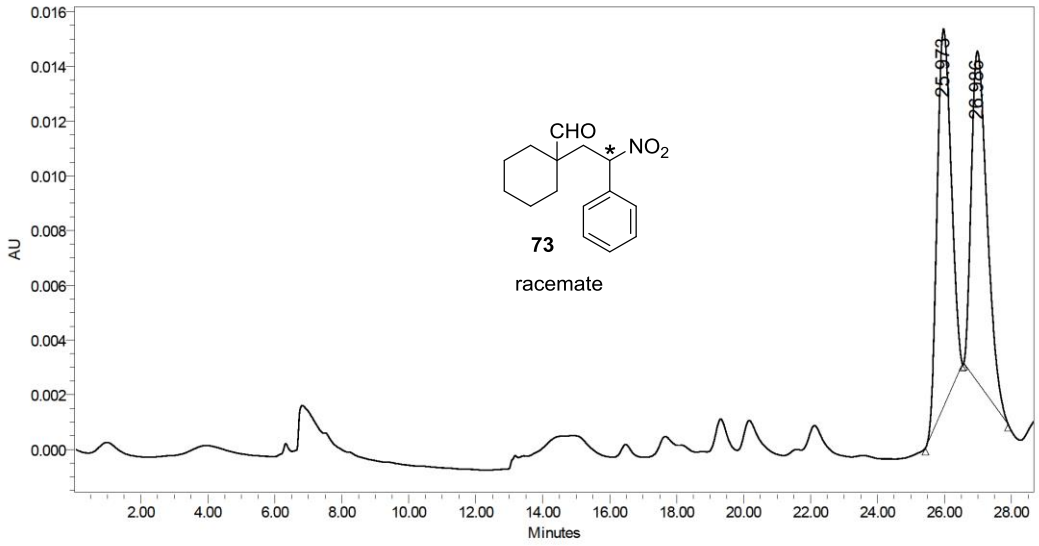
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-13-99B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	25/01/2017 2:27:54 PM NST
Vial:	109	Acq. Method:	AS_H 98%HEX 2%IPA 1
Injection #:	1	Date Processed:	20/07/2017 9:23:23 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	30.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	25.973	400664	50.32	13826	53.35
2	26.986	395593	49.68	12088	46.65

Memorial University

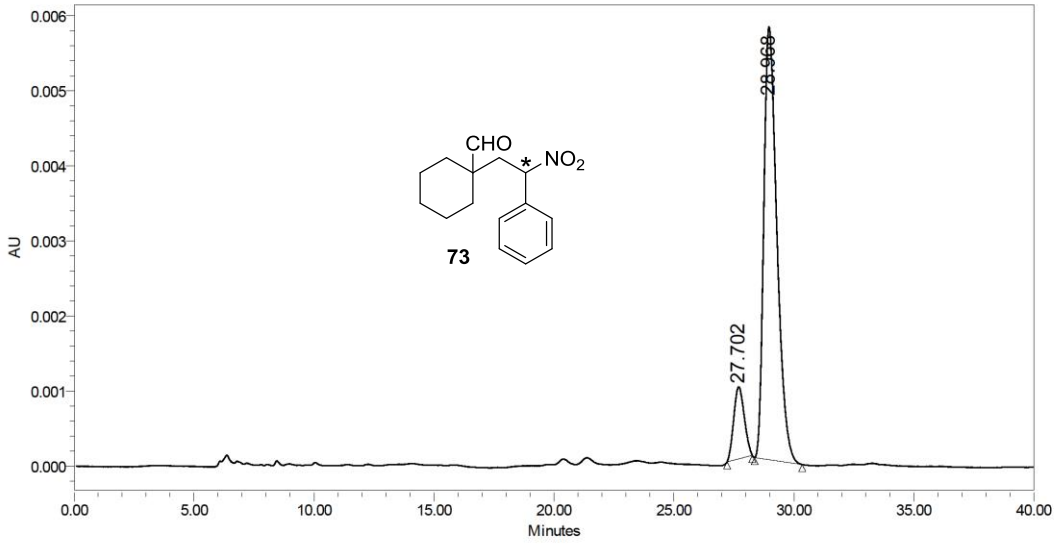
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-10-72C	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	11/03/2016 11:06:14 AM NST
Vial:	1	Acq. Method:	AS_H 98%HEX 2%IPA 1
Injection #:	1	Date Processed:	11/03/2016 11:58:43 AM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	27.702	29228	11.80	959	14.26
2	28.968	218567	88.20	5767	85.74

Report Method: Individual Control Report

Page: 1 of 1

Printed: 11/03/2016

11:59:34 AM Canada/Newfoundlanc

Memorial University

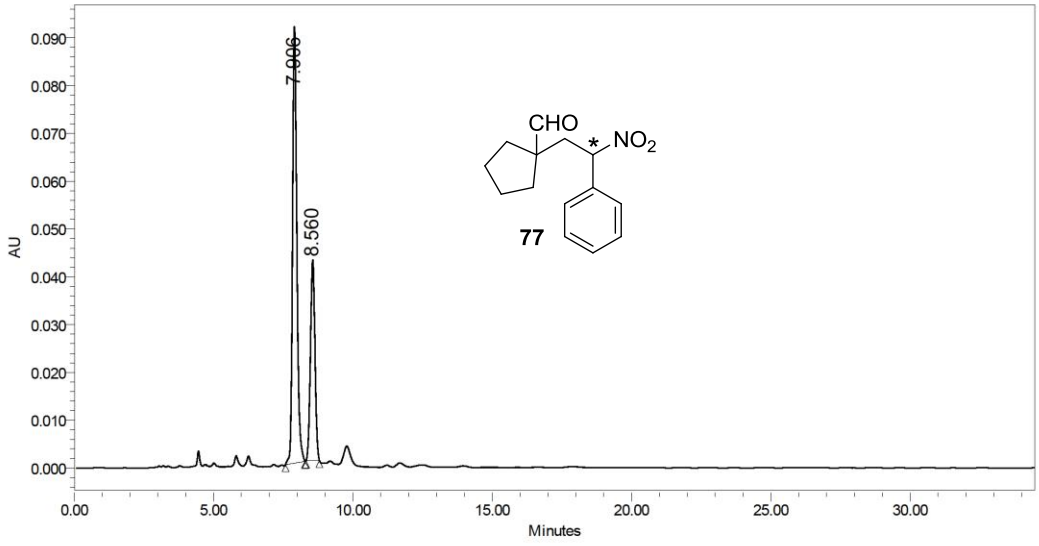
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-09B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	01/04/2016 3:19:40 PM NDT
Vial:	1	Acq. Method:	AD_H 90Hex10IPA
Injection #:	1	Date Processed:	01/04/2016 3:56:10 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	7.906	977057	67.50	91493	68.48
2	8.560	470364	32.50	42117	31.52

Report Method: Individual Control Report

Page: 1 of 1

Printed: 01/04/2016

3:57:08 PM Canada/Newfoundland

Memorial University

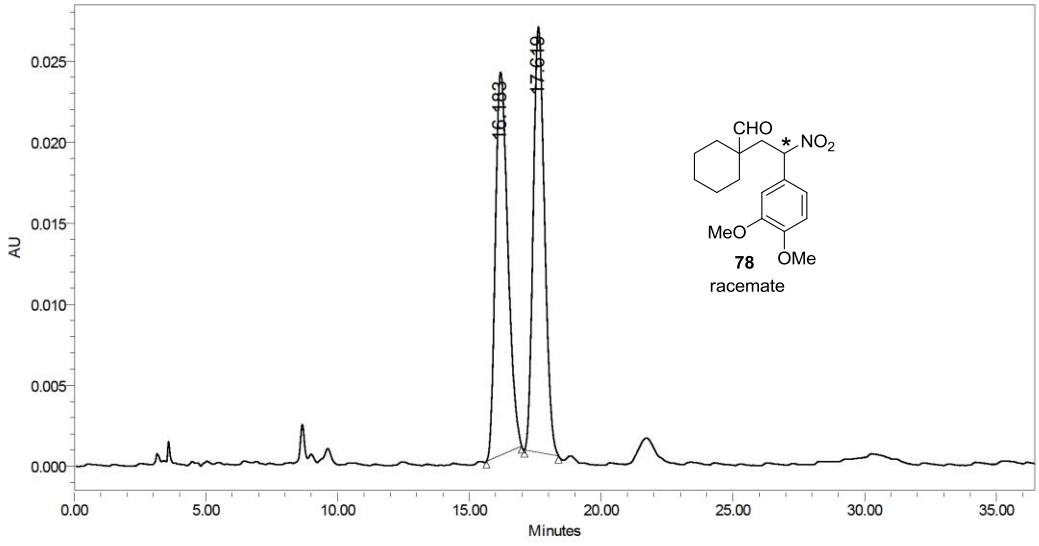
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-11-75B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	16/06/2016 4:13:12 PM NDT
Vial:	23	Acq. Method:	AS_H 90Hex10IPA
Injection #:	1	Date Processed:	16/06/2016 4:50:40 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.183	777564	49.80	23618	47.36
2	17.619	783764	50.20	26255	52.64

Memorial University

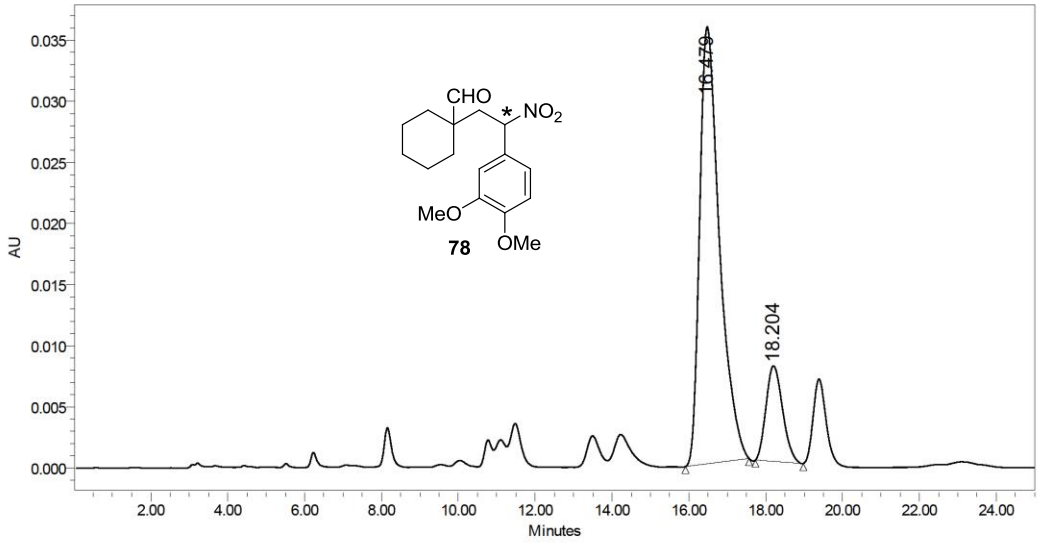
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-10-67A	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	29/02/2016 9:07:44 PM NST
Vial:	1	Acq. Method:	AS_H 90Hex10IPA
Injection #:	1	Date Processed:	20/07/2017 8:58:49 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	25.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	16.479	1282530	84.54	35754	82.07
2	18.204	234463	15.46	7809	17.93

Report Method: Individual Control Report

Page: 1 of 1

Printed: 20/07/2017

8:59:25 PM Canada/Newfoundland

Memorial University

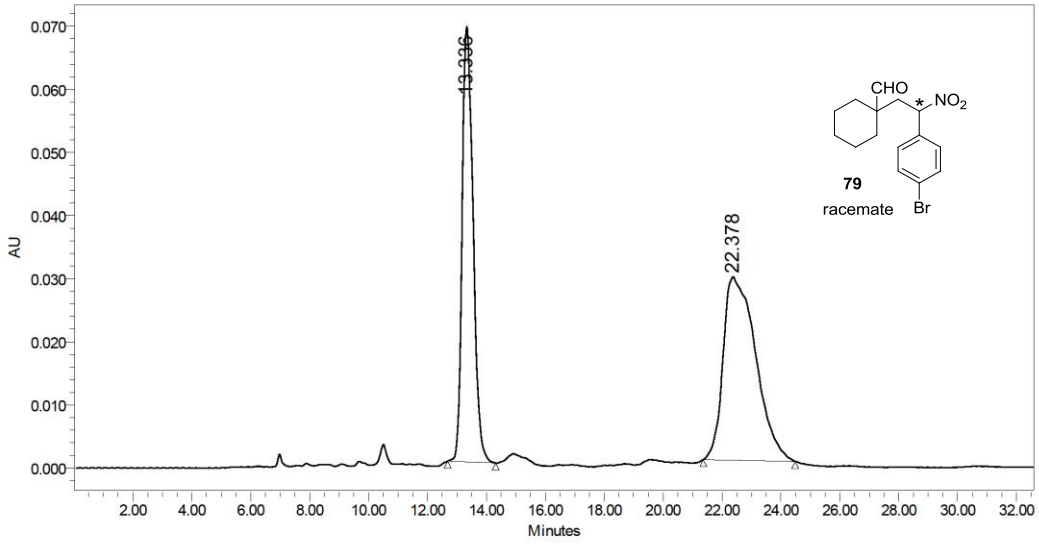
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-13-107b	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	25/01/2017 4:56:25 PM NST
Vial:	111	Acq. Method:	AD_H 90Hex10IPA
Injection #:	1	Date Processed:	25/01/2017 5:29:48 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.336	1780733	44.38	68947	70.35
2	22.378	2231407	55.62	29060	29.65

Memorial University

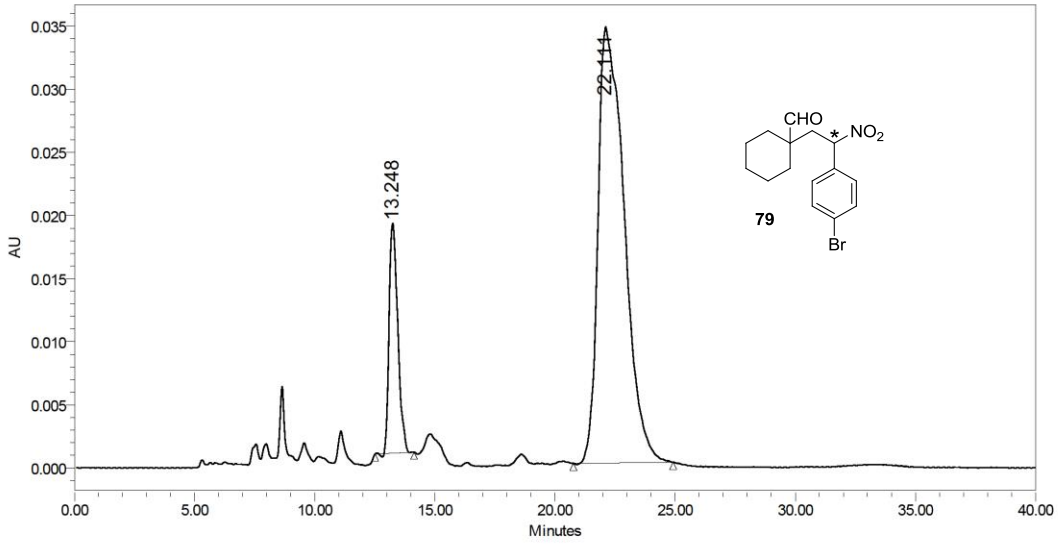
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-13-111B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	26/01/2017 4:32:47 PM NST
Vial:	117	Acq. Method:	AD_H 90Hex10IPA
Injection #:	1	Date Processed:	20/07/2017 9:11:51 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	13.248	459886	14.92	18213	34.51
2	22.111	2623039	85.08	34569	65.49

2.9 X-Ray Crystallographic Data for γ-Nitroketone 36

Acknowledgement:

We thank Dr. Hilary A. Jenkins, McMaster University, for the X-ray crystallography of γ-nitro ketone **36**.

Experimental

A colorless rod-shaped specimen of $C_{18}H_{23}NO_7$, approximate dimensions 0.220 mm x 0.246 mm x 0.448 mm, was used for the X-ray crystallographic analysis. X-ray data were measured using rotating anode-generated Cu radiation (λ = 1.34 Å) and a Bruker 6K SMART CCD detector, at room temperature. Unit cell parameters were initially established from reflections in the first 100 frames in three orientations.

The integration of the data using a hexagonal unit cell yielded a total of 21010 reflections to a maximum θ angle of 70.06° (0.82 Å resolution), of which 3170 were independent (average redundancy 6.628, completeness = 99.0%, R_{int} = 3.95%, R_{sig} = 2.18%) and 3097 (97.70%) were greater than $2\sigma(F^2)$. The final cell constants of a = 10.20930(10) Å, b = 10.20930(10) Å, c = 30.4222(3) Å, volume = 2746.08(6) $Å^3$, are based upon the refinement of the XYZ-centroids of reflections above 20 σ(I). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.7529 and 0.8772.

The structure was solved and refined using the Bruker SHELXTL Software Package (v.2014/6), using the space group P 65, with Z = 6 for the formula unit, $C_{18}H_{23}NO_7$. The final anisotropic full-matrix least-squares refinement on F^2 with 281 variables converged at R1 = 3.14%, for the observed data and wR2 = 9.29% for all data. The goodness-of-fit was 1.075. The largest peak in the final difference electron density synthesis was 0.120 $e^-/Å^3$ and the largest hole was -0.115 $e^-/Å^3$ with an RMS deviation of 0.026 $e^-/Å^3$. On the basis of the final model, the calculated density was 1.326 g/cm^3 and F(000), 1164 e^-.

Table 1. Crystal data and structure refinement for nitroketone 36

Identification code	P65	
Empirical formula	C18 H23 N O7	
Formula weight	365.37	
Temperature	295(2) K	
Wavelength	1.54178 Å	
Crystal system	Hexagonal	
Space group	$P6_5$	
Unit cell dimensions	a = 10.20930(10) Å	α= 90°.
	b = 10.20930(10) Å	β= 90°.
	c = 30.4222(3) Å	γ = 120°.
Volume	2746.08(6) $Å^3$	
Z	6	

Density (calculated)	1.326 g/cm^3
Absorption coefficient	0.860 mm^{-1}
F(000)	1164
Crystal size	0.448 x 0.246 x 0.220 mm^3
Theta range for data collection	5.002 to 70.063°.
Index ranges	-11<=h<=12, -12<=k<=12, -35<=l<=32
Reflections collected	21010
Independent reflections	3170 [R(int) = 0.0395]
Completeness to theta = 67.679°	99.1 %
Absorption correction	Numerical
Max. and min. transmission	0.8772 and 0.7529
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3170 / 1 / 281
Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0314, wR2 = 0.0911
R indices (all data)	R1 = 0.0321, wR2 = 0.0929
Absolute structure parameter	0.11(9)
Extinction coefficient	n/a
Largest diff. peak and hole	0.120 and -0.115 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for P65. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(11)	-2491(2)	4824(2)	1166(1)	64(1)
O(12)	5110(2)	9304(3)	1827(1)	68(1)
O(14)	6998(2)	8816(2)	1404(1)	58(1)
O(17)	1323(3)	9835(2)	743(1)	90(1)
O(18)	2796(4)	10193(2)	214(1)	93(1)
N(16)	1935(2)	9399(2)	494(1)	49(1)
C(1")	3025(2)	7935(2)	779(1)	41(1)
C(1')	119(2)	6800(2)	746(1)	43(1)
C(2")	3349(2)	8486(3)	1210(1)	45(1)
C(2')	1663(2)	7786(2)	539(1)	41(1)
C(5)	-1411(3)	2825(3)	200(1)	52(1)
O(1)	-1766(16)	2390(20)	-241(7)	58(2)
C(2)	-798(11)	1784(10)	-383(3)	71(2)
C(3)	-342(8)	1346(8)	50(2)	71(1)
O(4)	-534(18)	2260(20)	383(6)	61(2)
C(5A)	-1411(3)	2825(3)	200(1)	52(1)
O(1A)	-1460(30)	2460(50)	-267(14)	58(2)
C(2A)	-1240(20)	1238(18)	-283(6)	71(2)
C(3A)	244(16)	2115(15)	-36(4)	71(1)
O(4A)	-230(40)	2440(40)	319(12)	61(2)
C(3")	4673(3)	8762(3)	1413(1)	47(1)
C(4")	5704(2)	8471(2)	1182(1)	45(1)
C(5")	5349(3)	7877(3)	765(1)	50(1)
C(6")	4018(3)	7619(3)	563(1)	47(1)
C(6)	-644(3)	4535(3)	240(1)	47(1)
C(7)	-426(3)	5109(2)	714(1)	44(1)
C(8)	-1922(3)	4227(3)	962(1)	53(1)
C(9)	-2680(5)	2532(3)	924(1)	80(1)
C(10)	-2903(4)	2051(3)	443(1)	71(1)

C(13)	4150(4)	9661(5)	2072(1)	78(1)
C(15)	8073(3)	8581(4)	1174(1)	71(1)

Table 3. Bond lengths [Å] and angles [°] for P65.

O(11)-C(8)	1.204(3)
O(12)-C(3")	1.358(3)
O(12)-C(13)	1.417(4)
O(14)-C(4")	1.363(3)
O(14)-C(15)	1.419(3)
O(17)-N(16)	1.199(3)
O(18)-N(16)	1.202(3)
N(16)-C(2')	1.533(3)
C(1")-C(6")	1.376(3)
C(1")-C(2")	1.399(3)
C(1")-C(2')	1.510(3)
C(1')-C(2')	1.520(3)
C(1')-C(7)	1.530(3)
C(1')-H(1'B)	0.98(3)
C(1')-H(1'A)	1.03(3)
C(2")-C(3")	1.381(3)
C(2")-H(2")	0.93(3)
C(2')-H(2'A)	0.99(3)
C(5)-O(4)	1.40(2)
C(5)-O(1)	1.40(2)
C(5)-C(10)	1.513(4)
C(5)-C(6)	1.520(3)
O(1)-C(2)	1.469(17)
C(2)-C(3)	1.536(11)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
C(3)-O(4)	1.456(19)

C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700
C(5A)-O(1A)	1.46(4)
C(5A)-O(4A)	1.49(4)
C(5A)-C(10)	1.513(4)
C(5A)-C(6)	1.520(3)
O(1A)-C(2A)	1.37(4)
C(2A)-C(3A)	1.52(2)
C(2A)-H(2AA)	0.9700
C(2A)-H(2AB)	0.9700
C(3A)-O(4A)	1.29(4)
C(3A)-H(3AA)	0.9700
C(3A)-H(3AB)	0.9700
C(3")-C(4")	1.415(3)
C(4")-C(5")	1.376(4)
C(5")-C(6")	1.392(4)
C(5")-H(5")	0.99(3)
C(6")-H(6")	1.04(4)
C(6)-C(7)	1.531(3)
C(6)-H(6B)	0.99(3)
C(6)-H(6A)	0.98(3)
C(7)-C(8)	1.528(3)
C(7)-H(7A)	0.98(3)
C(8)-C(9)	1.506(4)
C(9)-C(10)	1.522(5)
C(9)-H(9B)	0.90(5)
C(9)-H(9A)	1.02(5)
C(10)-H(10B)	0.9700
C(10)-H(10A)	0.9700
C(13)-H(13C)	0.9600
C(13)-H(13B)	0.9600
C(13)-H(13A)	0.9600
C(15)-H(15C)	0.9600
C(15)-H(15B)	0.9600

C(15)-H(15A)	0.9600

C(3")-O(12)-C(13)	117.7(2)
C(4")-O(14)-C(15)	116.4(2)
O(17)-N(16)-O(18)	122.5(2)
O(17)-N(16)-C(2')	119.7(2)
O(18)-N(16)-C(2')	117.7(2)
C(6")-C(1")-C(2")	119.3(2)
C(6")-C(1")-C(2')	119.6(2)
C(2")-C(1")-C(2')	121.0(2)
C(2')-C(1')-C(7)	113.09(18)
C(2')-C(1')-H(1'B)	106.2(17)
C(7)-C(1')-H(1'B)	108.2(17)
C(2')-C(1')-H(1'A)	107.9(16)
C(7)-C(1')-H(1'A)	112.5(16)
H(1'B)-C(1')-H(1'A)	109(2)
C(3")-C(2")-C(1")	120.8(2)
C(3")-C(2")-H(2")	119(2)
C(1")-C(2")-H(2")	120(2)
C(1")-C(2')-C(1')	117.64(19)
C(1")-C(2')-N(16)	105.74(17)
C(1')-C(2')-N(16)	108.54(18)
C(1")-C(2')-H(2'A)	107.8(17)
C(1')-C(2')-H(2'A)	113.6(16)
N(16)-C(2')-H(2'A)	102.2(18)
O(4)-C(5)-O(1)	111.6(11)
O(4)-C(5)-C(10)	105.9(6)
O(1)-C(5)-C(10)	105.6(6)
O(4)-C(5)-C(6)	111.9(8)
O(1)-C(5)-C(6)	110.1(9)
C(10)-C(5)-C(6)	111.5(2)
C(5)-O(1)-C(2)	107.1(12)
O(1)-C(2)-C(3)	103.6(11)
O(1)-C(2)-H(2A)	111.0

C(3)-C(2)-H(2A)	111.0
O(1)-C(2)-H(2B)	111.0
C(3)-C(2)-H(2B)	111.0
H(2A)-C(2)-H(2B)	109.0
O(4)-C(3)-C(2)	104.7(9)
O(4)-C(3)-H(3A)	110.8
C(2)-C(3)-H(3A)	110.8
O(4)-C(3)-H(3B)	110.8
C(2)-C(3)-H(3B)	110.8
H(3A)-C(3)-H(3B)	108.9
C(5)-O(4)-C(3)	107.8(14)
O(1A)-C(5A)-O(4A)	95.4(19)
O(1A)-C(5A)-C(10)	116.5(12)
O(4A)-C(5A)-C(10)	118.8(12)
O(1A)-C(5A)-C(6)	107.7(17)
O(4A)-C(5A)-C(6)	105.3(14)
C(10)-C(5A)-C(6)	111.5(2)
C(2A)-O(1A)-C(5A)	106(3)
O(1A)-C(2A)-C(3A)	90.8(19)
O(1A)-C(2A)-H(2AA)	113.5
C(3A)-C(2A)-H(2AA)	113.5
O(1A)-C(2A)-H(2AB)	113.5
C(3A)-C(2A)-H(2AB)	113.5
H(2AA)-C(2A)-H(2AB)	110.8
O(4A)-C(3A)-C(2A)	100(2)
O(4A)-C(3A)-H(3AA)	111.7
C(2A)-C(3A)-H(3AA)	111.7
O(4A)-C(3A)-H(3AB)	111.7
C(2A)-C(3A)-H(3AB)	111.7
H(3AA)-C(3A)-H(3AB)	109.5
C(3A)-O(4A)-C(5A)	109(3)
O(12)-C(3")-C(2")	125.9(2)
O(12)-C(3")-C(4")	114.8(2)
C(2")-C(3")-C(4")	119.3(2)

O(14)-C(4")-C(5")	125.3(2)
O(14)-C(4")-C(3")	115.3(2)
C(5")-C(4")-C(3")	119.4(2)
C(4")-C(5")-C(6")	120.5(2)
C(4")-C(5")-H(5")	121.2(19)
C(6")-C(5")-H(5")	118.3(19)
C(1")-C(6")-C(5")	120.6(2)
C(1")-C(6")-H(6")	120.0(17)
C(5")-C(6")-H(6")	119.4(17)
C(5A)-C(6)-C(7)	114.0(2)
C(5)-C(6)-C(7)	114.0(2)
C(5A)-C(6)-H(6B)	108.8(18)
C(5)-C(6)-H(6B)	108.8(18)
C(7)-C(6)-H(6B)	109.1(19)
C(5A)-C(6)-H(6A)	106.2(18)
C(5)-C(6)-H(6A)	106.2(18)
C(7)-C(6)-H(6A)	108.4(19)
H(6B)-C(6)-H(6A)	110(3)
C(8)-C(7)-C(1')	109.03(19)
C(8)-C(7)-C(6)	109.18(19)
C(1')-C(7)-C(6)	113.2(2)
C(8)-C(7)-H(7A)	104.8(19)
C(1')-C(7)-H(7A)	111.0(18)
C(6)-C(7)-H(7A)	109.3(18)
O(11)-C(8)-C(9)	121.4(3)
O(11)-C(8)-C(7)	123.3(2)
C(9)-C(8)-C(7)	115.3(2)
C(8)-C(9)-C(10)	110.6(3)
C(8)-C(9)-H(9B)	106(3)
C(10)-C(9)-H(9B)	117(3)
C(8)-C(9)-H(9A)	103(3)
C(10)-C(9)-H(9A)	107(3)
H(9B)-C(9)-H(9A)	112(4)
C(5A)-C(10)-C(9)	110.6(3)

C(5)-C(10)-C(9)	110.6(3)
C(5)-C(10)-H(10B)	109.5
C(9)-C(10)-H(10B)	109.5
C(5)-C(10)-H(10A)	109.5
C(9)-C(10)-H(10A)	109.5
H(10B)-C(10)-H(10A)	108.1
O(12)-C(13)-H(13C)	109.5
O(12)-C(13)-H(13B)	109.5
H(13C)-C(13)-H(13B)	109.5
O(12)-C(13)-H(13A)	109.5
H(13C)-C(13)-H(13A)	109.5
H(13B)-C(13)-H(13A)	109.5
O(14)-C(15)-H(15C)	109.5
O(14)-C(15)-H(15B)	109.5
H(15C)-C(15)-H(15B)	109.5
O(14)-C(15)-H(15A)	109.5
H(15C)-C(15)-H(15A)	109.5
H(15B)-C(15)-H(15A)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for P65. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(11)	64(1)	60(1)	56(1)	-5(1)	17(1)	22(1)
O(12)	52(1)	100(2)	53(1)	-22(1)	-10(1)	39(1)
O(14)	43(1)	67(1)	68(1)	3(1)	-1(1)	30(1)
O(17)	97(2)	57(1)	130(2)	10(1)	39(2)	48(1)
O(18)	130(2)	49(1)	75(2)	18(1)	31(2)	26(1)
N(16)	51(1)	41(1)	52(1)	1(1)	-6(1)	20(1)
C(1")	42(1)	36(1)	43(1)	2(1)	3(1)	18(1)
C(1')	43(1)	41(1)	45(1)	-4(1)	2(1)	21(1)
C(2")	40(1)	48(1)	47(1)	-4(1)	3(1)	22(1)
C(2')	46(1)	38(1)	40(1)	-2(1)	0(1)	20(1)
C(5)	67(1)	48(1)	48(1)	-8(1)	-10(1)	34(1)
O(1)	71(6)	71(2)	52(3)	-19(2)	-18(5)	49(5)
C(2)	106(6)	83(6)	48(4)	-8(3)	-2(3)	65(5)
C(3)	99(4)	67(3)	72(3)	-7(3)	-11(3)	61(3)
O(4)	87(7)	70(5)	49(6)	-10(3)	-14(4)	56(5)
C(5A)	67(1)	48(1)	48(1)	-8(1)	-10(1)	34(1)
O(1A)	71(6)	71(2)	52(3)	-19(2)	-18(5)	49(5)
C(2A)	106(6)	83(6)	48(4)	-8(3)	-2(3)	65(5)
C(3A)	99(4)	67(3)	72(3)	-7(3)	-11(3)	61(3)
O(4A)	87(7)	70(5)	49(6)	-10(3)	-14(4)	56(5)
C(3")	43(1)	50(1)	45(1)	-1(1)	2(1)	22(1)
C(4")	38(1)	41(1)	55(2)	9(1)	5(1)	20(1)
C(5")	49(1)	50(1)	57(2)	5(1)	11(1)	30(1)
C(6")	53(1)	47(1)	42(1)	-1(1)	6(1)	25(1)
C(6)	55(1)	44(1)	43(1)	0(1)	2(1)	25(1)
C(7)	47(1)	41(1)	43(1)	-2(1)	-2(1)	22(1)
C(8)	61(1)	48(1)	42(1)	-2(1)	3(1)	21(1)
C(9)	94(2)	47(2)	76(2)	11(1)	30(2)	19(2)
C(10)	72(2)	40(1)	83(2)	-10(1)	3(2)	15(1)

C(13)	61(2)	113(3)	61(2)	-36(2)	-9(1)	43(2)
C(15)	48(1)	87(2)	91(2)	6(2)	4(1)	43(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for P65.

	x	y	z	U(eq)
H(1'B)	-590(40)	7000(30)	583(10)	52
H(1'A)	170(30)	7150(30)	1066(10)	52
H(2")	2660(30)	8660(30)	1364(11)	54
H(2'A)	1730(30)	7520(30)	229(11)	50
H(2A)	84	2544	-539	86
H(2B)	-1350	909	-571	86
H(3A)	-989	277	111	85
H(3B)	700	1572	39	85
H(2AA)	-1123	959	-579	86
H(2AB)	-2000	365	-123	86
H(3AA)	699	1497	23	85
H(3AB)	958	3018	-194	85
H(5")	6040(40)	7650(40)	598(11)	59
H(6")	3790(30)	7220(30)	241(12)	56
H(6B)	350(40)	4990(40)	93(11)	57
H(6A)	-1300(40)	4830(30)	88(11)	57
H(7A)	270(40)	4860(30)	865(10)	52
H(9B)	-3510(50)	2150(50)	1093(17)	96
H(9A)	-1880(50)	2310(50)	1046(17)	96
H(10B)	-3338	963	425	85
H(10A)	-3602	2311	307	85
H(13C)	4583	10030	2357	118
H(13B)	4039	10425	1921	118

H(13A)	3176	8771	2106	118
H(15C)	8934	8858	1359	107
H(15B)	7624	7534	1094	107
H(15A)	8389	9192	913	107

Table 6. Torsion angles [°] for P65.

C(6")-C(1")-C(2")-C(3")	2.2(3)
C(2')-C(1")-C(2")-C(3")	-173.6(2)
C(6")-C(1")-C(2')-C(1')	126.3(2)
C(2")-C(1")-C(2')-C(1')	-57.9(3)
C(6")-C(1")-C(2')-N(16)	-112.3(2)
C(2")-C(1")-C(2')-N(16)	63.4(3)
C(7)-C(1')-C(2')-C(1")	-72.9(3)
C(7)-C(1')-C(2')-N(16)	167.2(2)
O(17)-N(16)-C(2')-C(1")	-100.1(3)
O(18)-N(16)-C(2')-C(1")	78.0(3)
O(17)-N(16)-C(2')-C(1')	27.0(3)
O(18)-N(16)-C(2')-C(1')	-154.9(3)
O(4)-C(5)-O(1)-C(2)	-12.8(16)
C(10)-C(5)-O(1)-C(2)	-127.4(10)
C(6)-C(5)-O(1)-C(2)	112.1(12)
C(5)-O(1)-C(2)-C(3)	21.4(15)
O(1)-C(2)-C(3)-O(4)	-22.5(13)
O(1)-C(5)-O(4)-C(3)	-2.3(14)
C(10)-C(5)-O(4)-C(3)	112.1(8)
C(6)-C(5)-O(4)-C(3)	-126.1(9)
C(2)-C(3)-O(4)-C(5)	15.6(11)
O(4A)-C(5A)-O(1A)-C(2A)	36(2)
C(10)-C(5A)-O(1A)-C(2A)	-90.1(18)
C(6)-C(5A)-O(1A)-C(2A)	143.8(17)
C(5A)-O(1A)-C(2A)-C(3A)	-56.7(19)

O(1A)-C(2A)-C(3A)-O(4A)	59(3)
C(2A)-C(3A)-O(4A)-C(5A)	-39(2)
O(1A)-C(5A)-O(4A)-C(3A)	5(3)
C(10)-C(5A)-O(4A)-C(3A)	129.5(17)
C(6)-C(5A)-O(4A)-C(3A)	-105(2)
C(13)-O(12)-C(3")-C(2")	-1.8(4)
C(13)-O(12)-C(3")-C(4")	178.2(3)
C(1")-C(2")-C(3")-O(12)	179.5(2)
C(1")-C(2")-C(3")-C(4")	-0.4(3)
C(15)-O(14)-C(4")-C(5")	2.2(3)
C(15)-O(14)-C(4")-C(3")	-178.0(2)
O(12)-C(3")-C(4")-O(14)	-1.7(3)
C(2")-C(3")-C(4")-O(14)	178.2(2)
O(12)-C(3")-C(4")-C(5")	178.1(2)
C(2")-C(3")-C(4")-C(5")	-2.0(3)
O(14)-C(4")-C(5")-C(6")	-177.6(2)
C(3")-C(4")-C(5")-C(6")	2.7(3)
C(2")-C(1")-C(6")-C(5")	-1.5(3)
C(2')-C(1")-C(6")-C(5")	174.3(2)
C(4")-C(5")-C(6")-C(1")	-0.9(3)
O(1A)-C(5A)-C(6)-C(7)	-176.7(11)
O(4A)-C(5A)-C(6)-C(7)	-75.8(13)
C(10)-C(5A)-C(6)-C(7)	54.3(3)
O(4)-C(5)-C(6)-C(7)	-64.1(7)
O(1)-C(5)-C(6)-C(7)	171.2(5)
C(10)-C(5)-C(6)-C(7)	54.3(3)
C(2')-C(1')-C(7)-C(8)	175.6(2)
C(2')-C(1')-C(7)-C(6)	-62.7(3)
C(5A)-C(6)-C(7)-C(8)	-49.4(3)
C(5)-C(6)-C(7)-C(8)	-49.4(3)
C(5A)-C(6)-C(7)-C(1')	-171.1(2)
C(5)-C(6)-C(7)-C(1')	-171.1(2)
C(1')-C(7)-C(8)-O(11)	-3.9(4)
C(6)-C(7)-C(8)-O(11)	-128.0(3)

C(1')-C(7)-C(8)-C(9)	174.4(3)
C(6)-C(7)-C(8)-C(9)	50.3(3)
O(11)-C(8)-C(9)-C(10)	123.8(3)
C(7)-C(8)-C(9)-C(10)	-54.6(4)
O(1A)-C(5A)-C(10)-C(9)	179.6(18)
O(4A)-C(5A)-C(10)-C(9)	66.5(18)
C(6)-C(5A)-C(10)-C(9)	-56.2(3)
O(4)-C(5)-C(10)-C(9)	65.8(9)
O(1)-C(5)-C(10)-C(9)	-175.8(9)
C(6)-C(5)-C(10)-C(9)	-56.2(3)
C(8)-C(9)-C(10)-C(5A)	55.9(4)
C(8)-C(9)-C(10)-C(5)	55.9(4)

Symmetry transformations used to generate equivalent atoms:

Chapter 3

Formal Synthesis of (+)-Lasubine II and (−)-Subcosine II via Organocatalytic Michael Addition of a Ketone to an α-Nitrostyrene

A portion of this work has been published in Organic Letters:

Moorthy, N. V. G.; Dyapa, R.; Pansare, S. V.; *Org. Lett.* **2015**, *17*, 5312.

Mr. N. V. G. Moorthy has carried out all of the experimental work described in this publication and in this Chapter. Dr. R. Dyapa conducted the initial experiments on the optimization of the organocatalytic Michael addition reaction for the synthesis of the starting γ-nitroketone for the synthesis of Lasubine II.

3.1 Introduction

The principal objective of the work described in this chapter was to explore the possibility of utilizing the organocatalytic asymmetric Michael addition reaction of *in situ* generated α-nitrostyrenes (Chapter 2 of this thesis) as a key reaction in a target oriented synthetic investigation. To this effect, we decided to explore the use of the product γ-nitroketones obtained from ketone/α-nitrostyrene Michael addition reactions in the synthesis of selected alkaloids that contain the quinolizidine framework. The 4-arylquinolizidine motif was chosen as the synthetic target for this purpose.

The 4-arylquinolizidine motif is found in several lythraceae alkaloids of which (−)-lasubine I (1) and (−)-lasubine II (**2**) are prominent examples (Figure 3.1).[1] From a structural perspective, the lasubine framework is incorporated in other members of the lythraceous alkaloids such as subcosines I (4) and II[1](**5**) and the macrocyclic lactones (+)-lythrine[2](**3**) and (+)-vertine[2](**4**). Hence, a synthetic strategy for the lasubines also provides a potential route to the macrocyclic members of the lythraceae family.

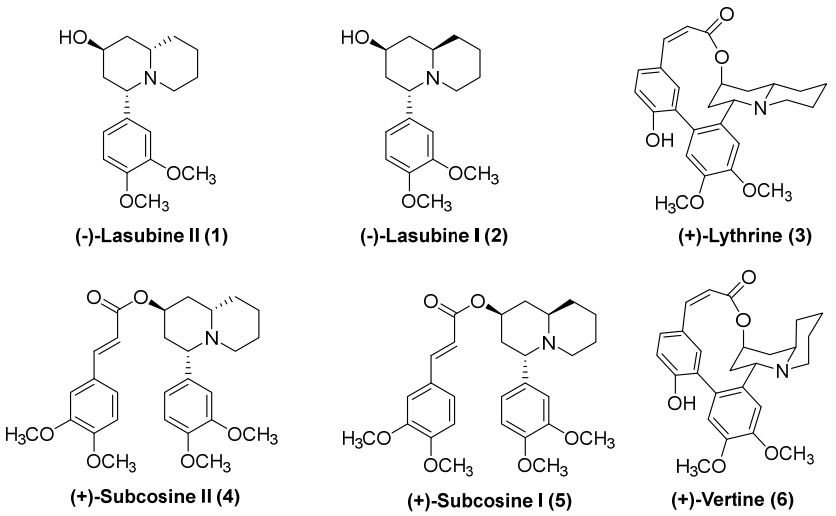
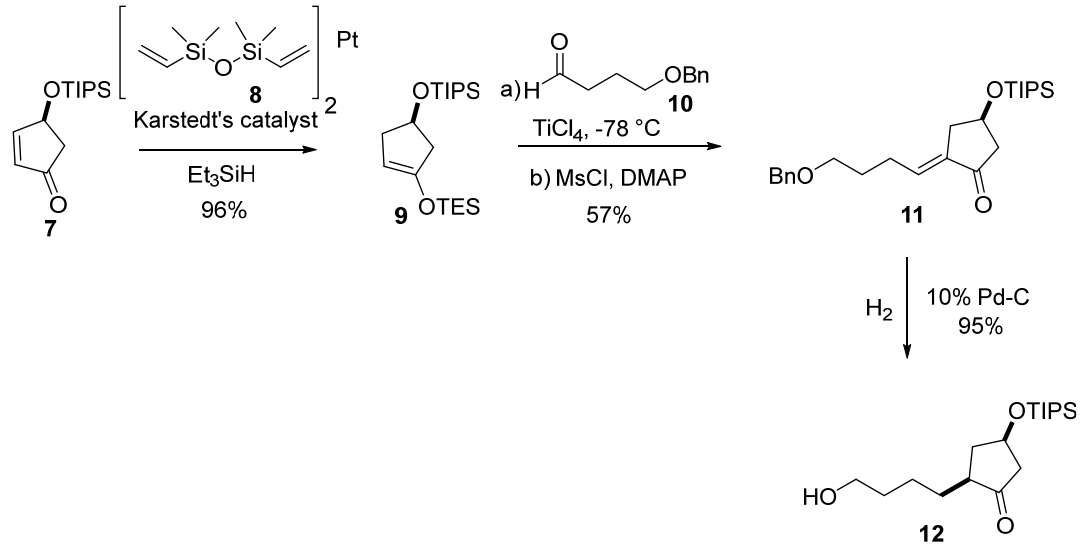


Figure 3.1: Selected alkaloids having a 4-arylquinozilidine motif.

Several enantioselective syntheses of lasubine II have therefore been investigated,[3] and only three enantioselective syntheses of subcosine II are documented.[3] The following section provides a summary of the enantioselective syntheses of lasubine II that have been reported since 2010.

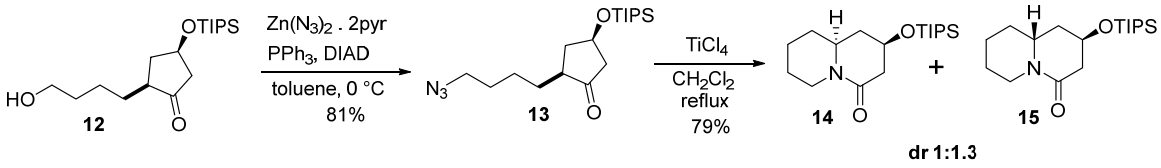
3.2 Synthetic routes to lasubine II reported since 2000

In 2003, Aube and co-workers reported the enantioselective formal synthesis of (−)-lasubine II.[3j] Enol ether **9** was synthesized from the TIPS protected 4-(*S*)-(-)-hydroxy-2-cyclopentenone **7** using Karstedt's catalyst **8** (Scheme 3.1). Next, enol ether **9** was subjected to a Mukaiyama aldol reaction with aldehyde **10** followed by dehydration to provide the enone **11**. Debenzylation and catalytic hydrogenation of **11** with 10% Pd/C in ethanol afforded the alcohol **12** as a single stereoisomer.



Scheme 3.1

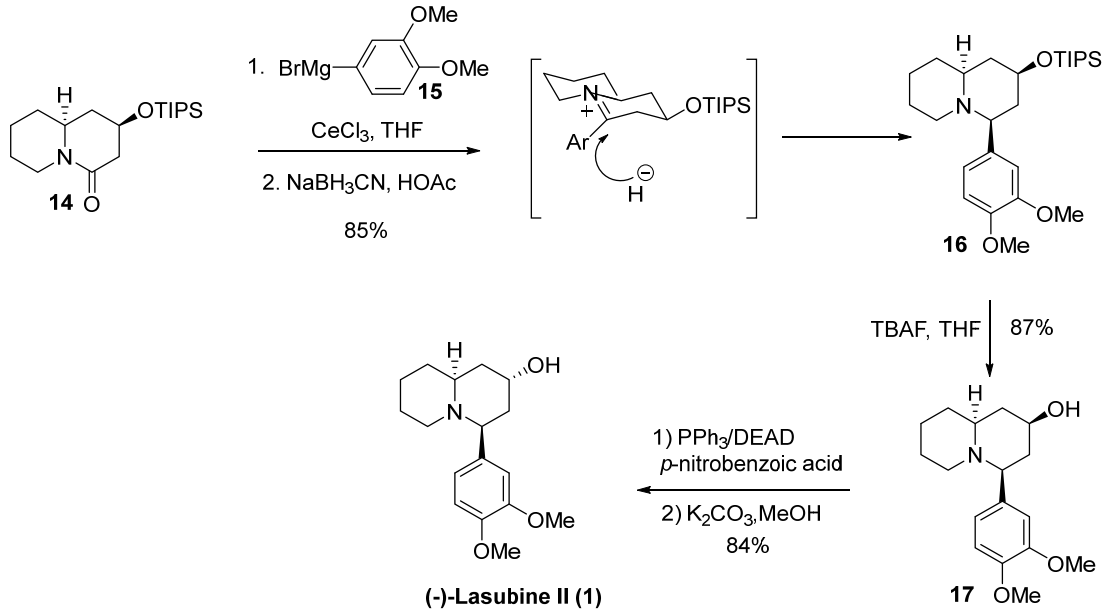
Azide **13** was prepared from the alcohol **12** by using a modified Mitsunobu reaction. Subsequent treatment of azide **13** with $TiCl_4$ provided the lactams **14** and **15** (Scheme 3.2) via a Schmidt rearrangement.



Scheme 3.2

Lactam **14** was subjected to a Grignard reaction, with the reagent derived from 4-bromoveratrole (**15**), in the presence of anhydrous $CeCl_3$. The resulting alkoxide was directly treated with $NaBH_3CN$ in the presence of acetic acid to provide the quinolizidine **16** as a single diastereomer in 85% yield. Presumably, the hemiaminal that is formed after

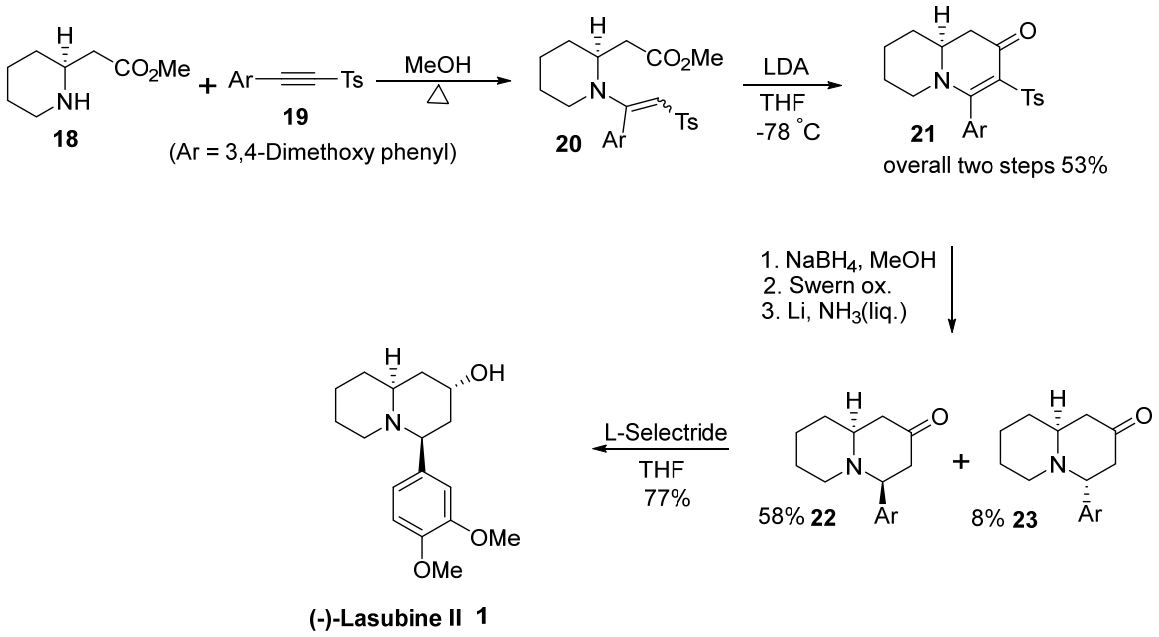
protonating the alkoxide with acetic acid, generates an iminium ion which is stereoselectively reduced by $NaBH_3CN$. Removal of the TIPS protecting group with TBAF in THF afforded (−)-2-*epi*-lasubine II (**17**) in 87% yield (Scheme 3.3). The conversion of **17** to (−)-lasubine II (**1**) by a Mitsunobu inversion of the secondary alcohol is known.[3k]



Scheme 3.3

In 2005, Back and co-workers reported the total synthesis of (−)-lasubine II by the conjugate addition and intramolecular acylation of an amino ester with an acetylenic sulfone (Scheme 3.4).[3h] Conjugate addition of aminoester (*S*)-**18** to acetylenic sulfone **19** was effectively carried out in refluxing methanol for 4 h. The resultant adduct **20** was cyclized by deprotonation of the vinyl sulfone with LDA to afford enaminone **21**. Treatment of the enaminone **21** with $NaBH_4$ resulted in the reduction of the enamine and the ketone to provide an inseparable mixture of diastereomers of the secondary alcohol. Swern oxidation of this mixture followed by desulfonylation with Li/NH_3 (liq.) provided

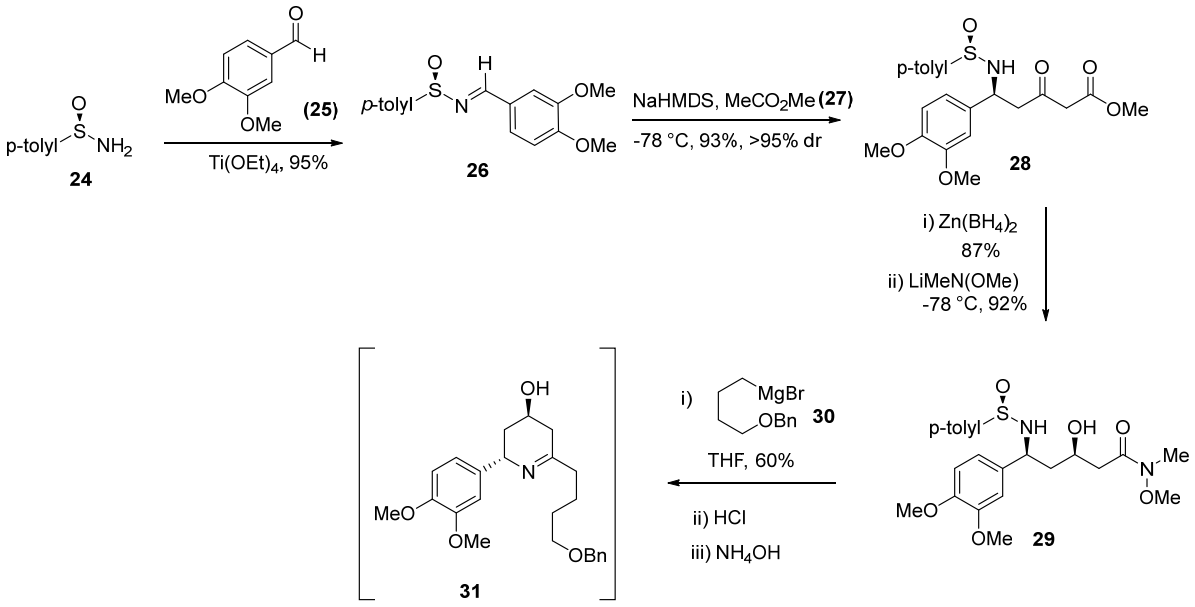
the easily separable ketones **22** and **23** in 58% and 8% overall yields respectively (Scheme 3.4). Finally, the stereoselective reduction of ketone **22** with L-selectride afforded (−)-lasubine II (**1**).



Scheme 3.4

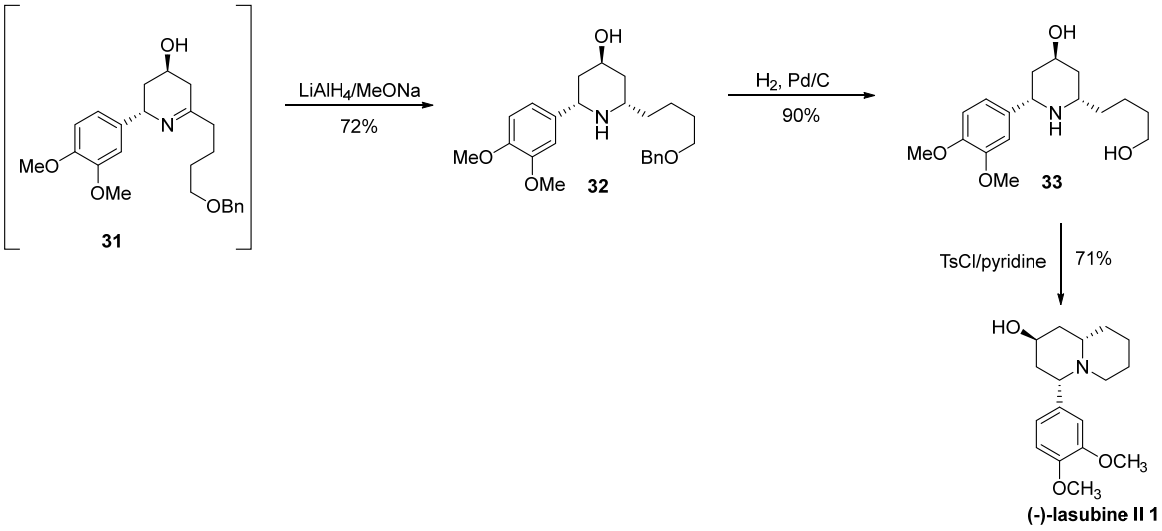
Davis and co-workers reported the highly stereoselective synthesis of (−)-lasubine II from a suitably functionalized *δ*-amino-*β*-hydroxyketone.[31] Condensation of sulfonamide **24** with aldehyde **25** provided the corresponding sulfinimine **26** in 95% yield. Treatment of **26** with the enolate of methyl acetate (**27**) provided the *β*-ketoester **28**. This was subjected to a highly diastereoselective reduction with zinc borohydride, followed by reaction with the lithium salt of *N*,*O*-dimethylhydroxylamine to afford the Weinreb amide **29** (Scheme 3.5). Reaction of **29** with the Grignard reagent **30**, cleavage of the sulfonamide

under acidic conditions (4 M HCl) and neutralization with conc. NH_4OH gave the cyclic imine **31**.



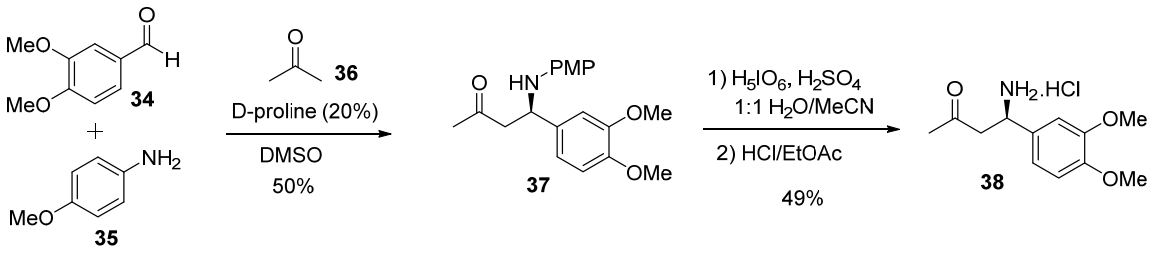
Scheme 3.5

The crude imine **31** was not isolated, but was reduced with $LiAlH_4$/MeONa to give the *cis*-hydroxypiperidine **32**. Removal of the benzyl group by hydrogenolysis gave a 90% yield of alcohol **33**. Finally, activation of the alcohol in **33** as the tosylate (TsCl/pyridine) proceeded with concomitant cyclization to provide (−)-lasubine II (**1**) (Scheme 3.6) in 71% yield.



Scheme 3.6

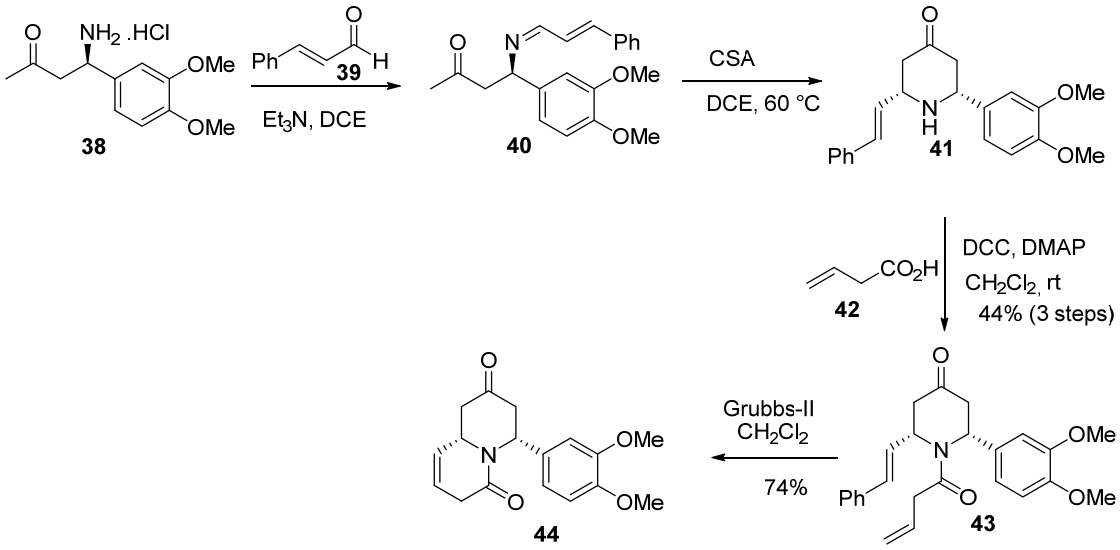
In 2009, Rutjes and co-workers reported the enantioselective synthesis of both enantiomers of lasubine II[3e] by a proline-catalyzed asymmetric Mannich reaction. The *R*-aminoketone **37** was obtained from veratraldehyde **34** and *p*-anisidine **35** by a proline catalyzed asymmetric Mannich reaction. Deprotection of *N*-PMP amine **37** under H_5IO_6 acidic conditions followed by treatment with HCl provided the amine salt **38**.



Scheme 3.7

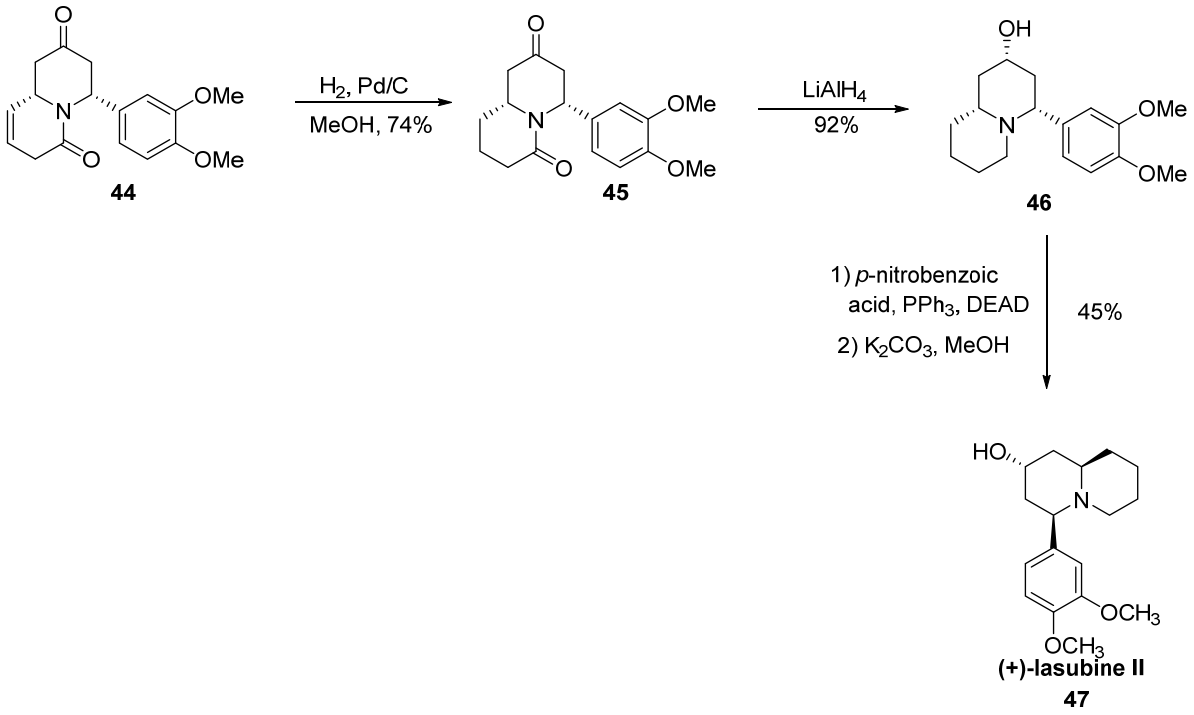
The conversion of ketone **38** to imine **40** was achieved by the treatment of ketone **38** with cinnamaldehyde (**39**) in the presence of Et_3N in dichloroethane. The imine **40** was

then cyclized in the presence of camphorsulfonic acid to provide the piperidine **41**, presumably via an intramolecular Mannich reaction (Scheme 3.8). Acylation of **41** with vinyl acetic acid followed by a ring closing metathesis in the presence of the Grubbs second-generation catalyst provided the unsaturated lactam **44**.



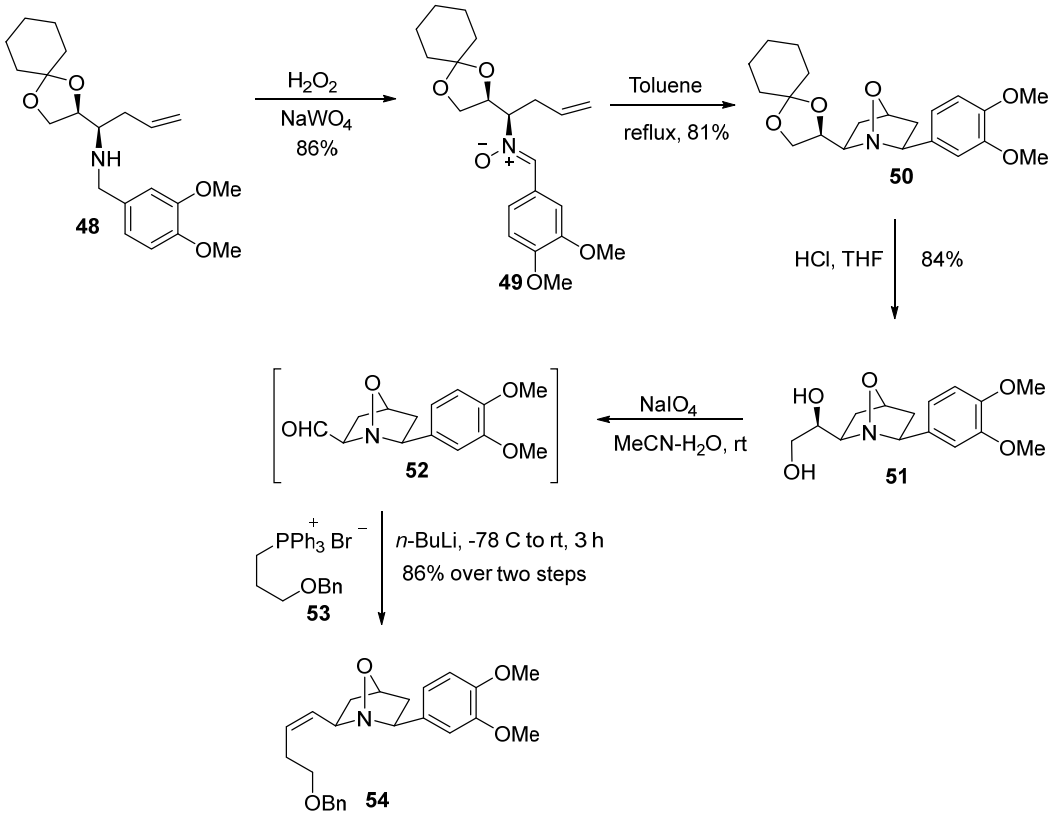
Scheme 3.8

Hydrogenation of the unsaturated lactam **44** provided the ketolactam **45**. Reduction of **45** with LAH provided the (+)-2-*epi*-lasubine II (**46**). A Mitsunobu reaction of **46** provided (+)-lasubine II **47** (Scheme 3.9).



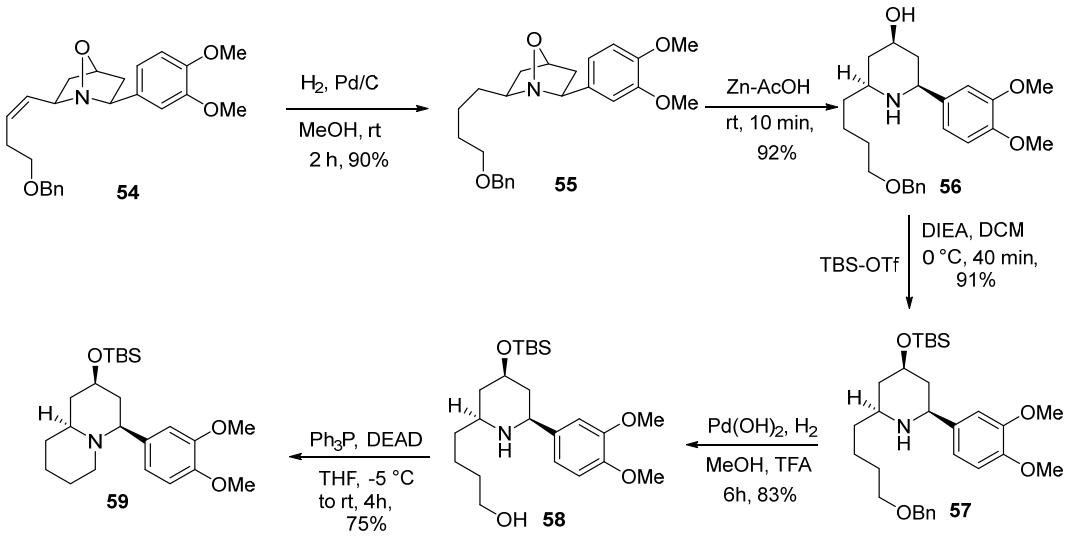
Scheme 3.9

Chattopadhyay and co-workers reported the enantiodivergent synthesis of both enantiomers of lasubine II.[3a] The nitrone **49** was obtained from the *syn* amine **48** on treatment with hydrogen peroxide-sodium tungstate reagent. The nitrone was subjected to intramolecular cycloaddition in toluene to provide **50**. Next, the diol functionality in **50** was liberated by acid hydrolysis of the ketal to provide **51**. Oxidative cleavage of diol **51** provided the aldehyde **52**. A three-carbon Wittig homologation of **52** provided the *cis* olefin **54**.



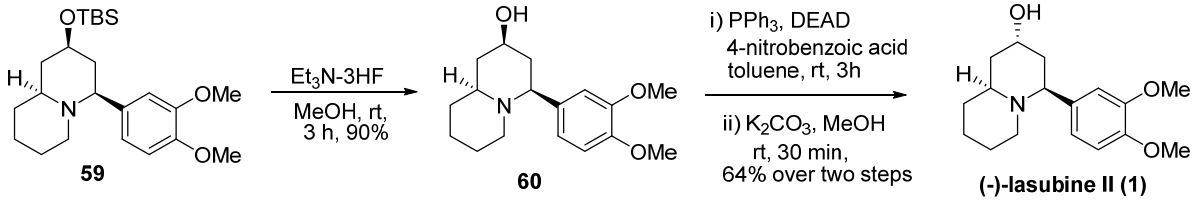
Scheme 3.10

Hydrogenation of **54** provided **55**, which upon reduction with Zn/AcOH afforded 4-hydroxy piperidine **56** (Scheme 3.11) by cleavage of the *N-O* bond. Protection of the alcohol in **56** as a TBS ether gave **57**. Debenzylation of **57** (H_2, $Pd(OH)_2$) provided the alcohol **58**, which underwent cyclization under Mitsunobu conditions to provide the quinolizidine **59**.



Scheme 3.11

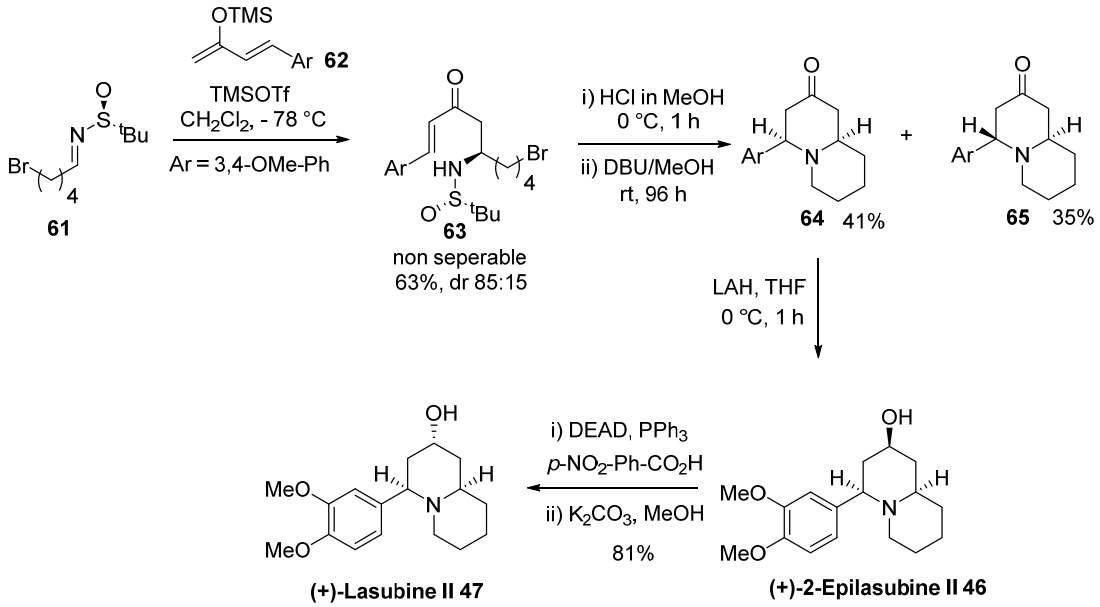
Finally, removal of the TBS protecting group in **59** to give **60**, and subsequent Mitsunobu reaction[3k] of **60** afforded (−)-lasubine II (**1**, Scheme 3.12).



Scheme 3.12

In 2016, Prasad and co-workers reported the total synthesis of (+)-lasubine II (**47**) starting from *N*-sulfinylimine **61**.[4] Treatment of **61** with silyl enol ether **62** afforded product **63** in 63% yield with 85:15 diastereomeric ratio. Removal of the sulfinyl group in the major diastereomer **63** followed by treatment with DBU furnished *cis* and *trans*-

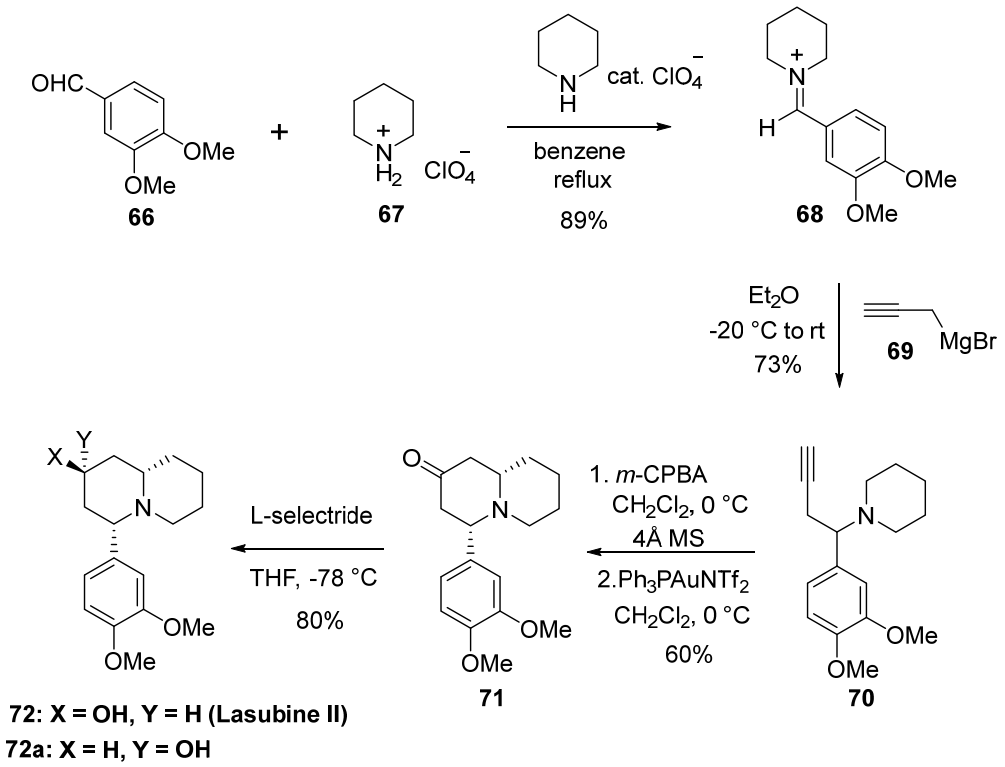
quinolizidines **64** and **65**, in 41% and 35% yield respectively, involving an *in situ* tandem Michael addition/displacement of bromine. Reduction of the ketone in **64** with LAH furnished 2-*epi*-lasubine II (**46)**, which on Mitsunobu inversion provided (+)-lasubine II (**47)** in 81% yield (Scheme 3.13).



Scheme 3.13

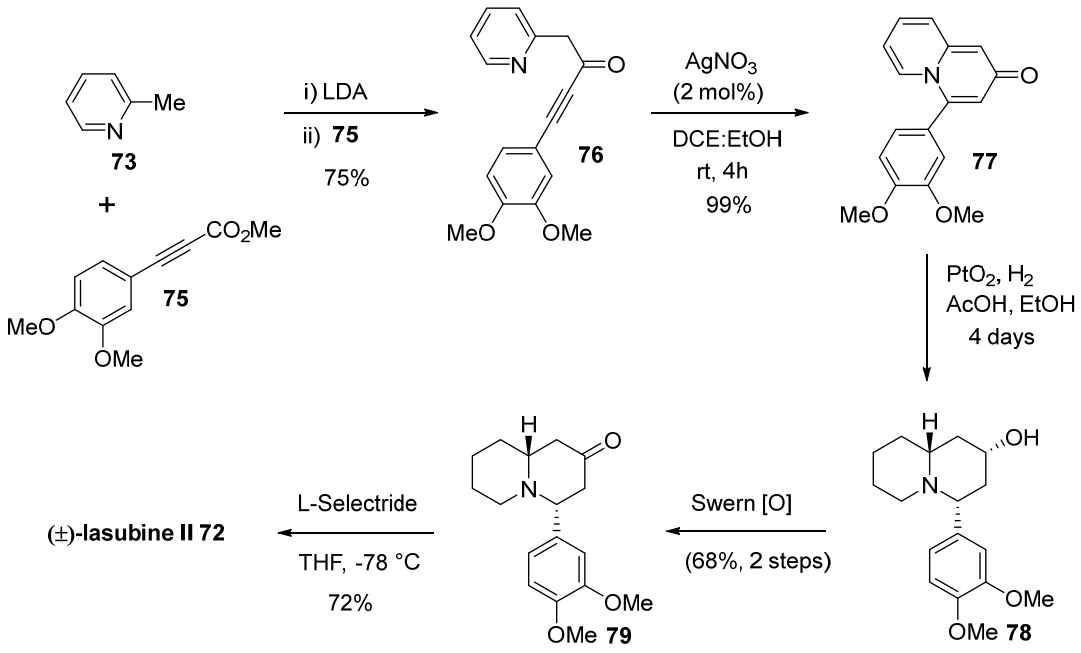
In addition to the enantioselective syntheses described above, syntheses of racemic lasubine II were also reported since 2010. In 2012, Yang and co-workers reported the racemic total synthesis of lasubine II.[5] This synthesis starts with aldehyde **66** which on treatment with piperidine perchlorate **67** provided iminium salt **68**. Next, the iminium salt **68** was subjected to a Grignard reaction with **69** to afford tertiary benzylic amine **70**. Cyclization of **70** to **71** was effected by treatment with *m*-CPBA followed by $Ph_3PAuNTf_2$

(Scheme 3.14). Finally, the reduction of ketone **71** with L-Selectride provided (±)-lasubine II (**72**) in 66% yield along with the diastereomeric (±)-2-*epi*-lasubine I (**72a)** in 14% yield.



Scheme 3.14

In 2016, William and co-workers reported the five-step racemic total synthesis of lasubine II.[6] Deprotonation of 2-picoline **73** (Scheme 3.3) with LDA followed by acylation with **75** afforded **76**. Next, **76** was subjected to silver (I) catalyzed cyclization to provide **77**. Hydrogenation of **77** afforded quinolizidine **78**, which was then subjected to the Swern oxidation to afford ketone **79** (Scheme 3.15). Finally, **79** was reduced with L-selectride to provide (±)-lasubine II **72** in 36% overall yield.



Scheme 3.15

3.3 Results and Discussion

In developing a synthetic route to the quinolizidine framework in lasubine II (Figure 3.2), we noted that the relative stereochemistry of the secondary alcohol and the benzylic stereocenter could be established regardless of the stereochemistry in a bicylic precursor, as either of these stereocenters can be inverted at a later stage if necessary.[7] The retrosynthetic strategy for the synthesis of (+)-lasubine II and (−)-subcosine II is provided in Figure 3.2.

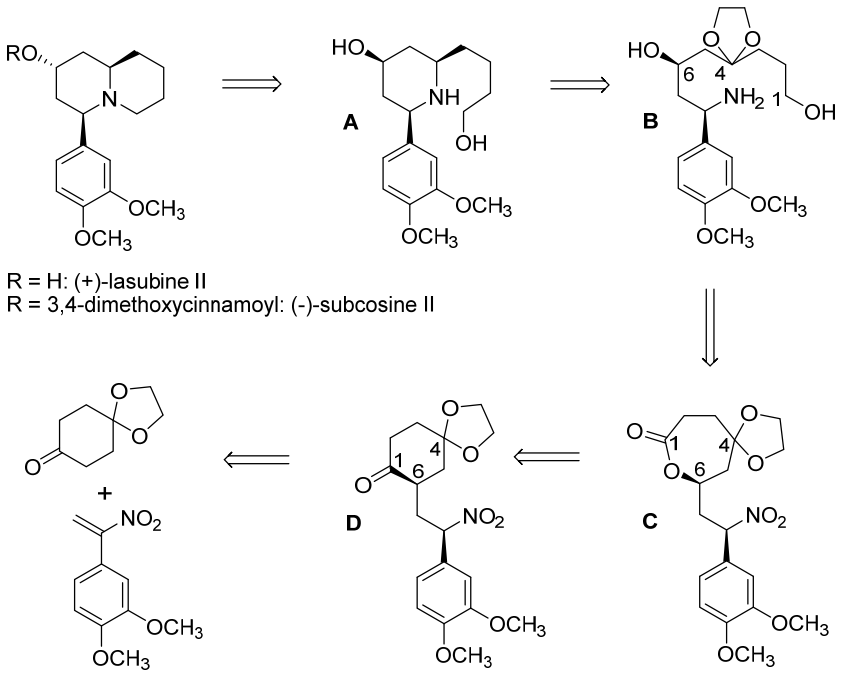
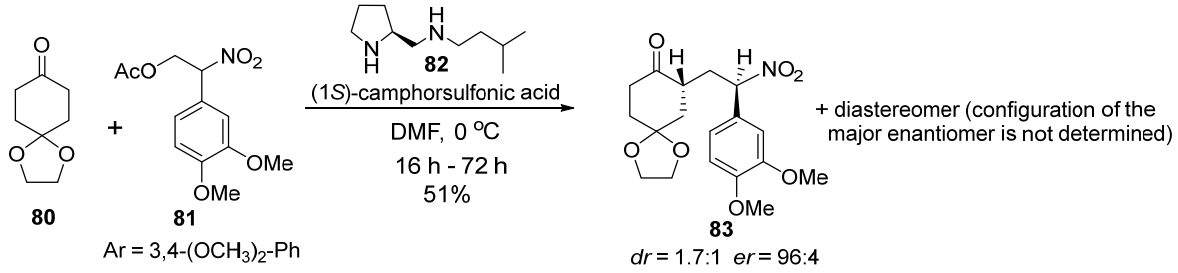


Figure 3.2 Retrosynthesis of (+)-lasubine II and (−)-subcosine II.

The required quinolizidine framework could be obtained by cyclization of a trisubstituted piperidine **A**. Construction of **A** was planned from a diastereomerically pure acyclic precursor **B** by homologation of the alcohol, deprotection of the acetal, and piperidine ring formation by intramolecular reductive amination. We anticipated that 1,3-induction during the formation of the piperidine ring[8] would assist in setting the new stereocenter in the product (diequatorial disposition of Ar and side chain in **A**). Compound **B** derives from the nitrolactone **C** by reductive ring opening of the lactone. The nitrolactone ultimately leads to the *γ*-aryl-*γ*-nitroketone **D** as the key starting material. From a methodology development perspective, *γ*-aryl-*γ*-nitroketones like **D** are appealing starting materials for 2,6-disubstituted 3-hydroxypiperidines such as **B**, many of which have interesting biological profiles and are also valuable synthetic intermediates.[9] We therefore

chose to address the stereoselective synthesis of the γ-nitroketone **D** by employing the organocatalytic Michael addition of a monoprotected cyclohexanedione to an α-nitrostyrene as the pivotal step.

The organocatalytic Michael addition of ketone **80** with nitroacetate **81** in presence of the proline-derived diamine catalyst **82** provided the nitroketone **83** (Scheme 3.16). The details of this synthesis are discussed in Chapter 2 of this thesis.

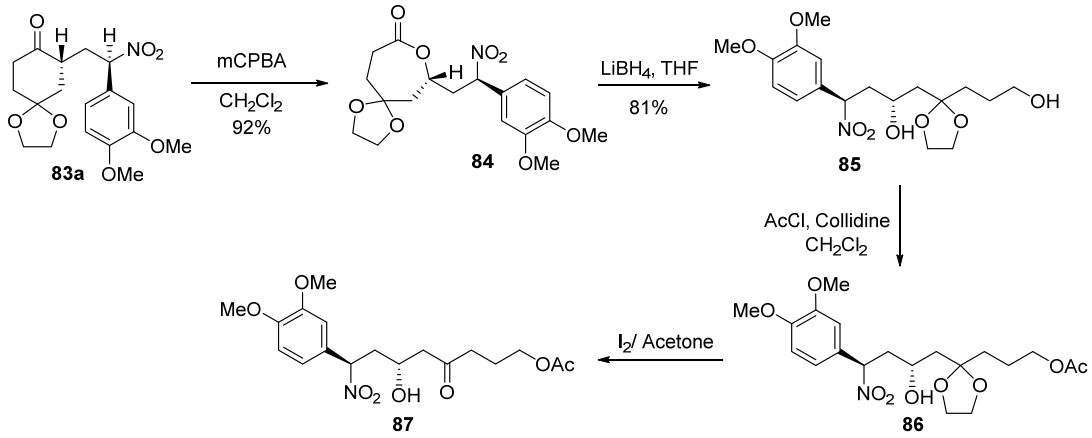


Scheme 3.16

The diastereoselectivity of the process is low (~1.5:1 dr), but the diastereomers can be easily separated to provide the major diastereomer in synthetically useful yield (51-52%) and enantiomeric excess (82-92% er).[10] Employing the optimized reaction conditions, gram quantities of **83** could be synthesized routinely. The absolute configuration of **83** (*R*,*R*) was established by X-ray crystallographic analysis as shown in Chapter 2 (page 33) of this thesis.

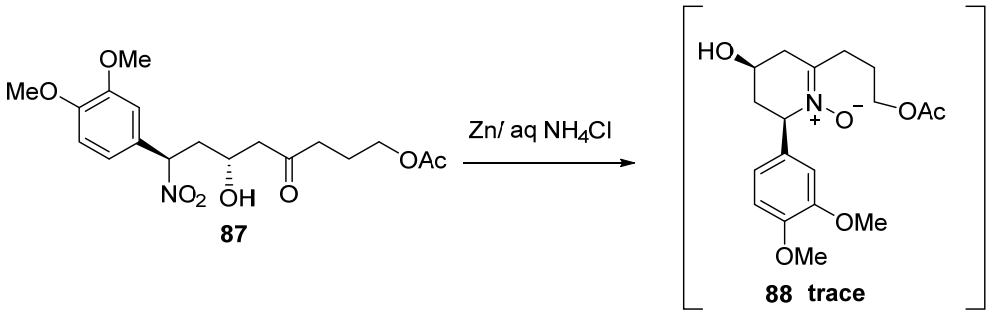
With **83** in hand, the synthesis of the lasubine was initiated. Treatment of **83** with *m*CPBA provided the Baeyer-Villiger oxidation product **84**, which was reduced to the

nitrodiol **85**. In order to prevent potentially competing reactions involving the primary alcohol in **85** (hemiacetal formation and its reduction to a tetrahydrofuran[11] in subsequent transformations), it was converted to the primary acetate **86** prior to the hydrolysis of acetal. This provided *δ*-nitroketone **87** (Scheme 3.17) which was examined as a precursor to the functionalized piperidine ring in lasubine.



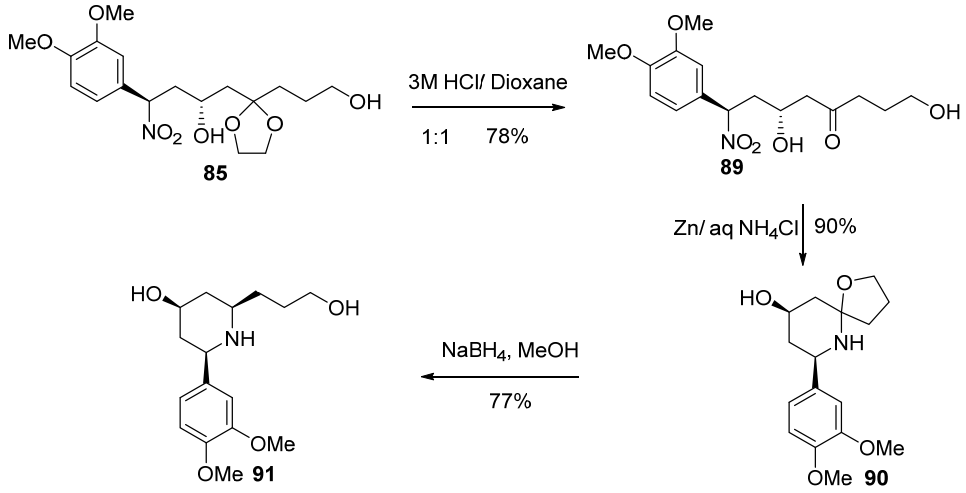
Scheme 3.17

Initial studies with **87** were focused on converting nitroketone **87** to cyclic nitrone **88** (Scheme 3.18), which could potentially be reduced stereoselectively to establish the third stereocenter in the piperidine ring. However, only a trace amount of nitrone **88** could be detected in the complex mixture of products obtained from the attempted reduction of **87** (Zn/aq, NH_4Cl). It is plausible that **88** is unstable and it undergoes unwanted side reactions such as dehydration and/or isomerization[12] to the conjugated nitrone.



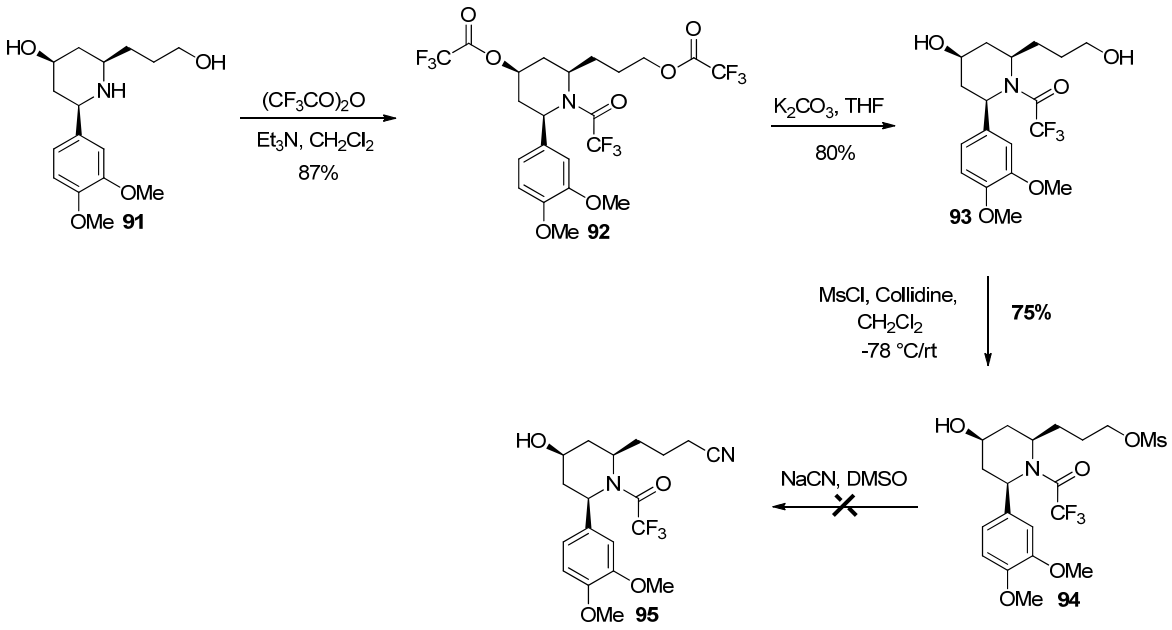
Scheme 3.18

In an alternative approach, and having diol **85** in hand, the ketal in **85** was hydrolyzed (3M HCl/dioxane 1:1) to give ketodiol **89.** Reductive cyclization of **89** by treatment with Zn/aq. NH_4Cl afforded spiropiperidine **90**. Notably, the anticipated nitrone, corresponding to **88**, was not detected in this reaction. Presumably, cyclization of the pendant primary alcohol onto the nitrone directly leads to **90**. The stereochemistry of the spiro ring junction in **90** was not determined in this study. Reduction of **90** with $NaBH_4$/MeOH provided amino alcohol **91**.



Scheme 3.19

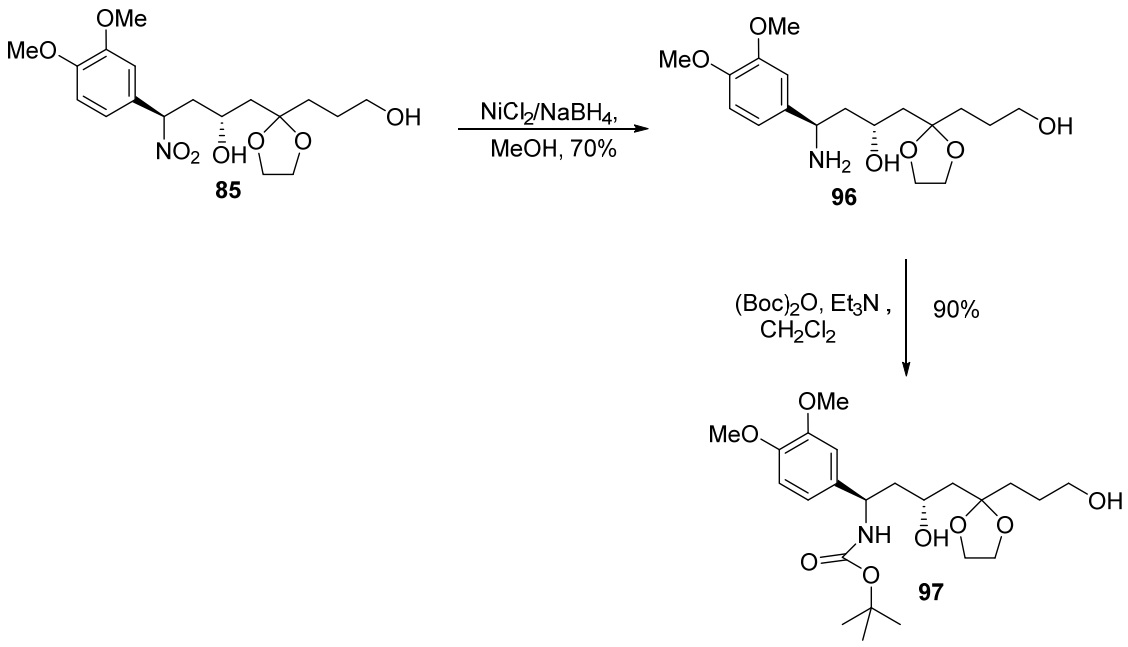
Treatment of **91** with trifluoroacetic anhydride provided the tris-trifluoroacetyl derivative **92**. Selective hydrolysis of the trifluoroacetyl esters in **92** afforded trifluoroacetamide **93**. Unfortunately, attempted homologation of **93** by conversion to the mesylate and subsequent treatment with NaCN afforded a complex mixture of undesired products (Scheme 3.20).



Scheme 3.20

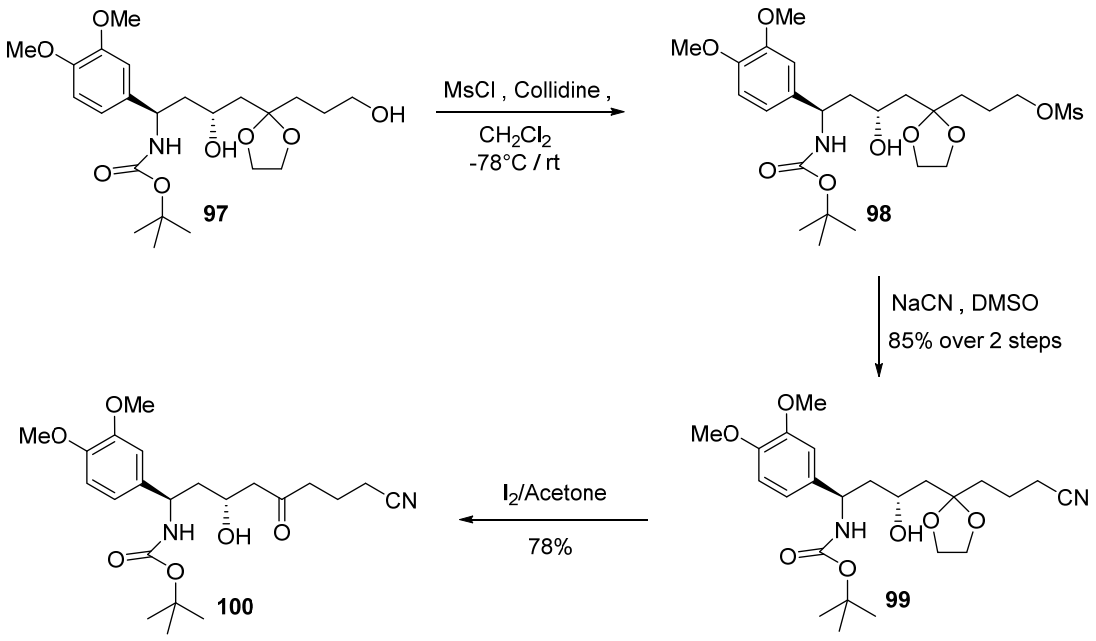
In our continued search for a synthetic protocol that would ultimately lead to the required trisubstituted piperidine intermediate (A, Figure 3.2), an alternative strategy that involved the initial complete reduction of the nitro group in **71** to a primary amine was envisaged. Thus, the reduction of nitrodiol **85** with $NiCl_2/NaBH_4$ in MeOH afforded the

aminodiol **96** in 70% yield. Protection of the free amine in **96** with Boc anhydride provided the *N*-Boc compound **97** in 90% yield (Scheme 3.21).



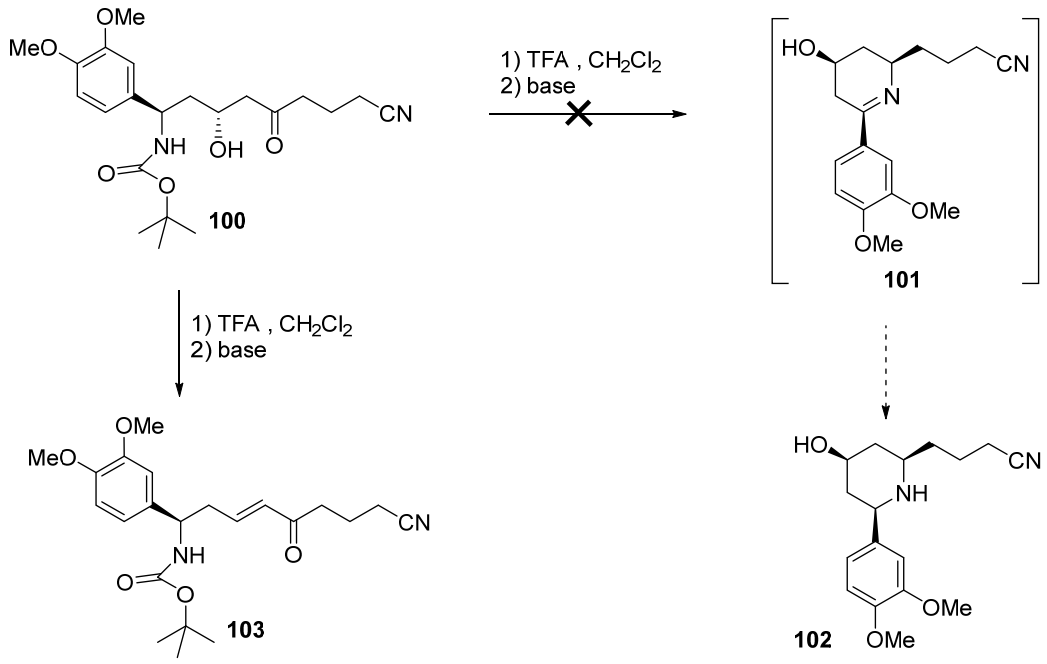
Scheme 3.21

In contrast to the previously unsuccessful homologation attempt with **97**, treatment of **97** with mesyl chloride and subsequent cyanation in the presence of NaCN smoothly provided the required nitrile **99** in 85% yield (overall in 2 steps Scheme 3.22). Removal of the acetal in **99**, by treatment with iodine in acetone, provided ketone **100** in 78% yield.



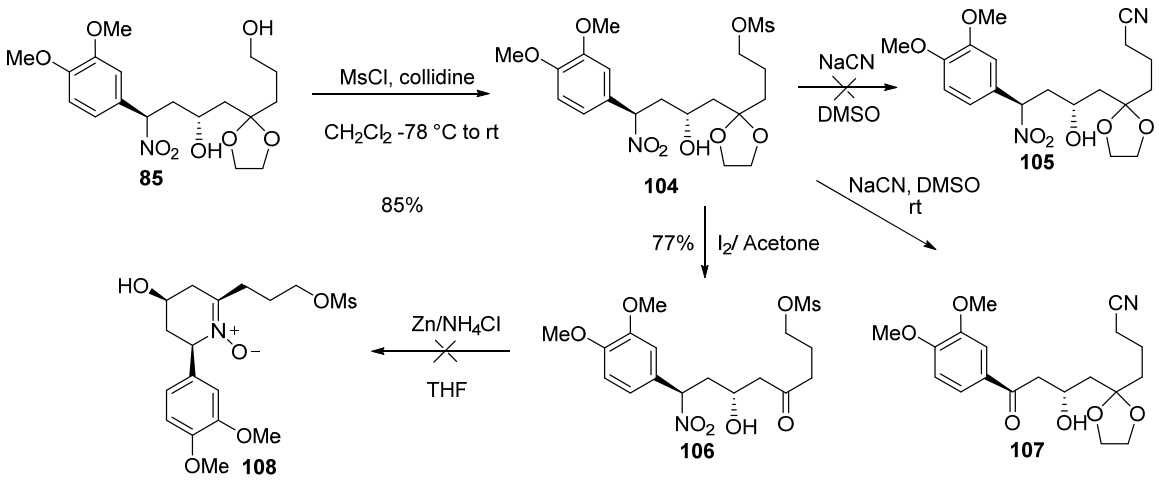
Scheme 3.22

According to our synthetic plan, the next step involved deprotection of the amine in **100** followed by an intramolecular amination of the ketone in **100**. Unfortunately, treatment of **100** with TFA followed by neutralization and subsequent treatment with $NaBH_3CN$ did not provide any of the expected piperidine **102**. Small amounts of undesired enone **103** could be detected in the crude product from the proton NMR spectrum (Scheme 3.23).



Scheme 3.23

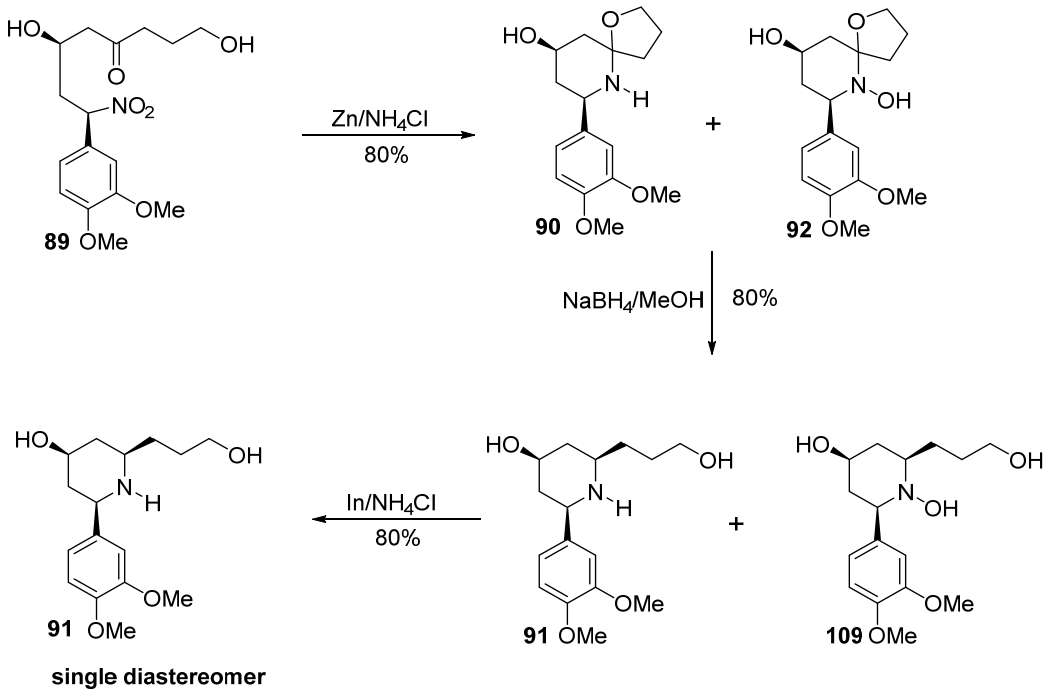
In another approach, the mesylation of nitrodiol **85** afforded the mesylated product **101**. However, treatment of **104** with NaCN in DMSO afforded only ketone **107**, the product of a Nef reaction of **104** (Scheme 3.24). Furthermore, attempted conversion of **104** to the nitrone **108** via the ketone **106** was also unsuccessful. Although deprotection of **104** provided **106**, the conversion of **106** to **108** was unsuccessful and resulted in a complex mixture of undesired products.



Scheme 3.24

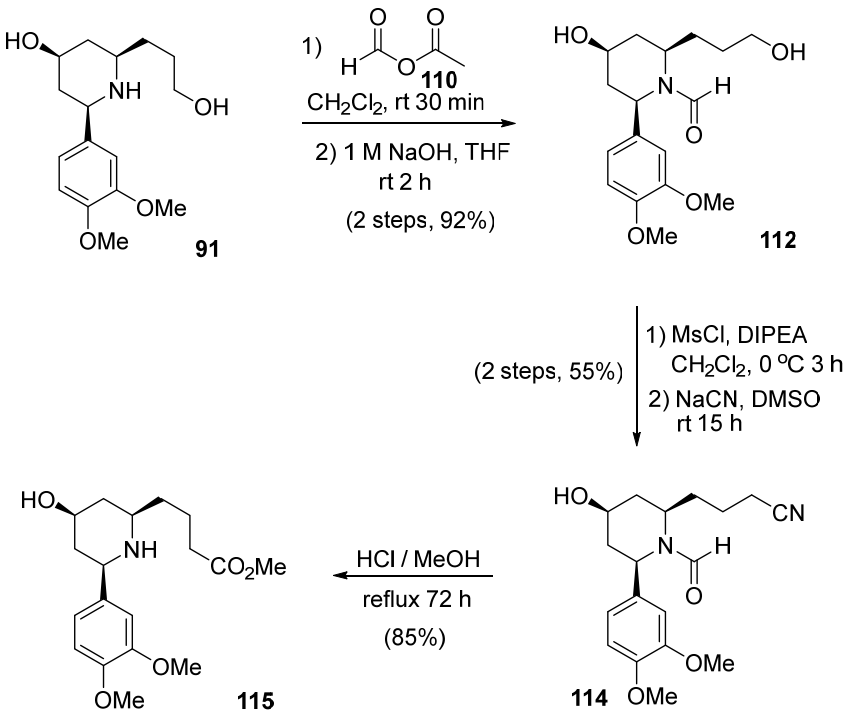
Given the lack of success in strategies that did not involve a cyclic nitrone as the key intermediate, we chose to re-examine our initial synthetic attempts described in Scheme 3.9. Although, in previous studies, we had converted **89** to **90** (Scheme 3.9), repeated reduction of the nitroketone **89** with Zn/aq. NH_4Cl provided an inseparable mixture of the piperidine **90** and the *N*-hydroxypiperidine **92** (Scheme 3.25). Attempts to convert the hydroxylamine to the amine by varying the amounts of zinc used for the reduction were unsuccessful. The precise reasons for the partial reduction of **89** are not known at present. However, the mixture of **90** and **92** could be used further. This mixture was first reduced with $NaBH_4$ to provide a mixture of the trisubstituted piperidine **91** and the corresponding *N*-hydroxypiperidine **109**. Subsequent reduction of this mixture with indium metal provided **91** as a single diastereomer. The newly formed stereocenter in **91** was assigned the *R* configuration on the assumption that the 2,6-*cis* (diequatorial) isomer

would be favored[8] in the reduction of the imine or nitrone that is transiently formed from **91** and **109** (Scheme 3.25).



Scheme 3.25

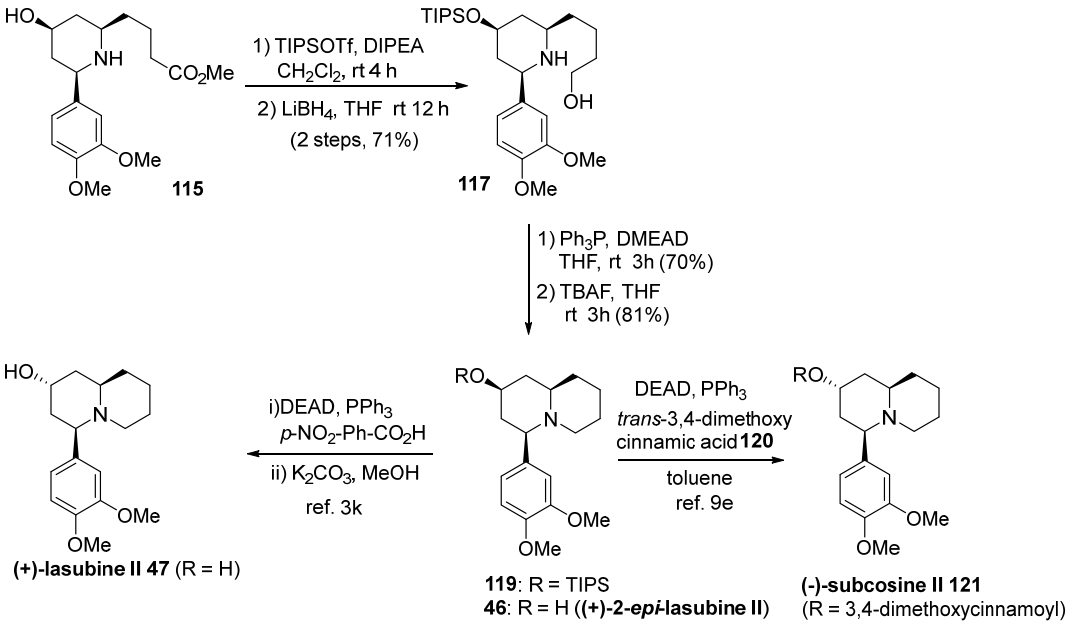
The conversion of **91** into the quinolizidine framework required a homologation of the hydroxypropyl side chain at C6. This was achieved by transitory protection of the nitrogen by formylation (treatment with excess formic acetic anhydride, followed by basic hydrolysis of the concurrently formed formate ester) to provide **112** (Scheme 3.26) followed by activation of the primary alcohol as the mesylate and subsequent cyanation to provide **114**. Simultaneous methanolysis of the nitrile as well as the formamide in **114** provided the amino ester **115**.



Scheme 3.26

Reduction of the ester in **115** and cyclization of the resulting aminodiol could potentially provide 2-*epi*-lasubine II. However, the observation[3a] that this aminodiol, prepared by an unrelated approach, has poor solubility in conventional solvents suggested the need for an alternative strategy. Hence, the secondary alcohol in **115** was first protected as a TIPS ether. Subsequent reduction of the ester provided **117** (Scheme 3.27), which was cyclized to **119** employing a Mitsunobu-type reaction (Ph_3P, di-2-methoxyethyl azodicarboxylate (DMEAD)[13]). Deprotection of **119** provided (+)-2-*epi*-lasubine II **46** (Scheme 3.27). The enantiomer of **46** has previously been converted into (−)-lasubine II by Mitsunobu reaction of the secondary alcohol,[3k] and a Mitsunobu reaction of *ent*-**7** with

3,4-dimethoxycinnamic acid provided (+)-subcosine II.[9e] Thus, the present synthesis of **46** constitutes a formal synthesis of (+)-lasubine II **47** and (−)-subcosine II **121**.



Scheme 3.27

3.4 Conclusion

In conclusion, the first examples of organocatalytic enantioselective Michael additions of a ketone to *in situ* generated *α*-nitrostyrenes have been developed. The methodology has been applied to a formal synthesis of (+)-lasubine II and (−)-subcosine II. We are currently investigating the scope of the Michael addition reaction and the application of this methodology in the stereoselective synthesis of various trisubstituted piperidines.

A comparison of the overall yields and the number of steps involved in the enantioselective synthesis of lasubine II reported since 2000 as shown in the Table 3.1.

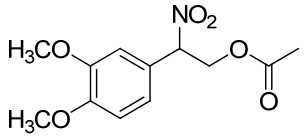
Table 3.1: Comparsion of number of steps and overall yields for the enantioselective syntheses of lasubine II.

Authors	Year	# of steps	% overall yield
Davis *et. al*	2000	9	3
Aube *et. al*	2002	11	21
Back *et. al*	2002	6	2
Rutjes *et. al*	2009	10	3
Chattopadhyay *et. al*	2011	17	2
Pansare *et. al*	2015	21	3
Prasad *et. al*	2016	8	14

As compared to other enantioselective syntheses of lasubine II, ours syntheses involved a longer linear sequence. However, the novelty of our synthesis is the use of organocatalysis as an important tool for the enantioselective synthesis of a key starting material.

3.5 Experimental section

2-(3,4-Dimethoxyphenyl)-2-nitroethyl acetate (81):



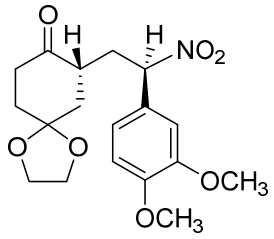
A mixture of 2-(3,4-dimethoxyphenyl)oxirane (4.00 g, 22.2 mmol), $NaNO_2$ (11.90 g, 172.5 mmol) and $LaCl_3 \cdot 7H_2O$ (10.9 g, 44.4 mmol) in THF: H_2O (1:1, 160 mL) was vigorously stirred at ambient temperature for 12 h. The mixture was then extracted with ether (4 × 25 mL) and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes/EtOAc, 1:1) to provide 1.5 g (30%) of 2-(3,4-dimethoxyphenyl)-2-nitroethanol as a yellow foam.

Reaction of the above nitroalcohol (1.84 g, 8.1 mmol), acetic anhydride (1.14 mL, 12.1 mmol) and $Sc(OTf)_3$ (40 mg, 0.08 mmol) in CH_3CN (40 mL) at 0 ^oC, after purification of the crude product by flash chromatography on silica gel (hexanes/EtOAc, 7:3), 1.7 g (81%) of **81** as a yellow solid.

R_f = 0.3 (hexanes/EtOAc, 7:3). IR (neat): 1742, 1550, 1516, 1448, 1427, 1394, 1366, 1224, 1146, 1022cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 8.3, 2.0, Ar*H*), 6.95 (d, 1H, *J* = 2.0, Ar*H*), 6.88 (d, 1H, *J* = 8.3, Ar*H*), 5.67 (dd, 1H, *J* = 10.7, 3.4, C*H*NO_2), 4.95 (dd, 1H, *J* = 12.3, 10.7, C*H*$_2$OCOCH$_3$), 4.48 (dd, 1H, *J* = 12.3, 3.4, C*H*$_2$OCOCH$_3$), 3.90 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 2.09 (s, 3H, OCOC*H*$_3$).^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (*C*=O), 150.8 (Ar*C*$_{ipso}$), 149.5 (Ar*C*$_{ipso}$), 122.9 (Ar*C*$_{ipso}$), 120.7 (Ar*C*), 111.3(

Ar*C*), 110.2 (Ar*C*), 88.6 (*C*HNO$_2$), 63.9 (*C*H$_2$OCOCH$_3$), 56.06 (O*C*H$_3$),55.98 (O*C*H$_3$), 20.6 (CO*C*H$_3$).MS (ESI, pos.): *m*/*z* 292.0 $(M+Na)^+$ HRMS (ESI, pos.): *m*/*z* 270.1015 (270.0978 calc. for ($C_{12}H_{16}NO_6$ $(M+H)^+$), 292.0794 (292.0797 calc. for ($C_{12}H_{15}NNaO_6$ $(M+Na)^+$).

(*R*) -7-((*R*)-2-(3,4-Dimethoxyphenyl)-2-nitroethyl)-1,4-dioxaspiro[4.5]decan-8-one (83):

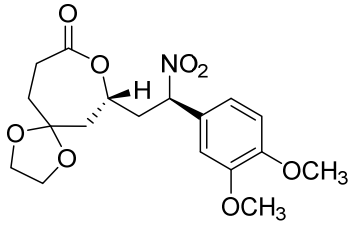


To a solution of 1,4-cyclohexanedione monoethylene ketal (**80**, 11.6 g, 74.3 mmol), (*S*)-2-methyl-*N*-(pyrrolidin-2-ylmethyl)propan-1-amine (**82**)[1] (505 mg, 3.0 mmol), and (1*S*)-Camphor sulfonic acid (690 mg, 3.0 mmol) in DMF (46 mL) was added **81** (4.00 g, 14.8 mmol) and the resulting solution was stirred at 0 ^oC for 72 h. Ethyl acetate (100 mL) was added and the solution was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel to provide 2.45 g (45%) **83** with 92% ee as a white solid. R_f = 0.25 (hexanes/EtOAc, 7:3); $[\alpha]_D^{20}$ = +18.2 (*c* 1, CH_2Cl_2) ; IR (neat): 2959, 2873, 1708, 1546, 1510, 1264, 1231, 1150, 1137, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 8.3, 2.1, Ar*H*), 6.96 (d, 1H, *J* = 2.1, Ar*H*), 6.86 (d, 1H, *J* = 8.3, Ar*H*) 5.63 (dd, 1H, *J* = 10.3, 4.4, C*H*NO$_2$), 4.03-4.01 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.90 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 2.75-2.63 (m, 2H, COC*H*, C*H*$_2$CHNO$_2$), 2.35-2.49 (m, 2H, C*H*$_2$CH$_2$CO), 2.30 (dd, 1H, *J* = 10.3, 4.1, C*H*$_2$CH$_2$CO),

2.13-1.99 (m, 2H, COC*H*$_2$, COCHC*H*$_2$), 1.97 (dd, 1H, *J* = 13.6, 4.9, COC*H*$_2$) 1.78 (t, 1H, *J* = 13.3, COCHC*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.4 (*C*O), 150.2 (Ar*C*$_{ipso}$), 149.2 (Ar*C*$_{ipso}$), 127.2 (Ar*C*$_{ipso}$), 120.3 (Ar*C*), 111.1 (Ar*C*$_{ipso}$), 110.2 (Ar*C*), 106.8 (O*C*O), 89.6 (*C*HNO$_2$), 64.9 (O*C*H$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 56.0 (O*C*H$_3$), 55.9 (O*C*H$_3$), 43.3 (CO*C*H), 41.4 (*C*H$_2$CHC(O)O),38.3 (*C*H$_2$CHNO$_2$), 34.8 (*C*H$_2$CO), 34.0 (*C*H$_2$CH$_2$C(O)O); MS (ESI, neg.): 364.1 $(M-H)^-$; HRMS (ESI, neg.): *m/z* 365.1469 (365.1475 calc. for $C_{18}H_{23}NO_7(M^-)$); HPLC: Chiralpak AS-H (hexane/*i*-PrOH, 60/40, flow rate 1 mL min^{-1}, λ= 247 nm): t_{major} = 10.20 min., t_{minor} = 12.98 min., 92% ee.

Crystals suitable for X-ray analysis were obtained by dissolving **83** (10 mg) in isopropyl alcohol (0.4 mL) followed by addition of hexanes (0.6 mL) to this solution. The resulting clear solution was left at ambient temperature for gradual evaporation. The precipitated crystals were collected after 48 h, dried in vacuo and analyzed.

(*R*)-7-((*R*)-2-(3,4-Dimethoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro[4.6]undecan-9-one (84):

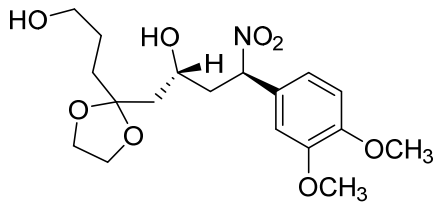


To a solution of the nitroketone **83** (2.45 g, 6.71 mmol) in anhydrous dichloromethane (70 mL) at ambient temperature, was added solid sodium phosphate heptahydrate (2.34 g, 8.73 mmol) followed by *m*-chloroperoxybenzoic acid (3.59 g, 20.8 mmol). The resulting white slurry was stirred vigorously at ambient temperature for 16 h.

Dichloromethane (70 mL) was added and the resulting solution was washed with saturated aqueous sodium bicarbonate (3 x 15 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a white, solid foam. Purification of the crude product by flash chromatography on silica gel (hexanes/EtOAc, 40:60) provided 2.35 g (92%) of **84** as a yellow foam.

R_f = 0.4 (hexanes/EtOAc, 40:60);$[\alpha]_D^{20}$ = +30.0 (*c* 1, CH_2Cl_2); IR (neat): 1732, 1552, 1514, 1252, 1238, 1153, 1098, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, *J* = 2.1, 8.3, Ar*H*), 6.96 (d, 1H, *J* = 2.1, Ar*H*), 6.86 (d, 1H, *J* = 8.3, Ar*H*), 5.77 (dd, 1H, *J* = 2.6, 11.5, C*H*NO_2), 4.54-4.47 (m, 1H, C*H*-O), 4.05-3.95 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.90 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 2.87-2.74 (m, 2H, C*H*$_2$C(O)O), 2.63-2.56 (ddd, 1H, *J* = 2.0, 6.4, 8.4), 2.27-2.17 (ddd, 1H, *J* = 2.7, 10.8, 13.5), 2.05-1.80 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ174.0 (*C*O), 150.4 (Ar*C*), 149.3 (Ar*C*), 126.6 (Ar*C*), 120.3 (Ar*C*), 111.2 (O*C*O), 110.4 (Ar*C*), 107.3 (Ar*C*), 86.9 (*C*HNO_2), 71.7 (*C*H-O-C(O)), 65.2 (OCH$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 56.04 (O*C*H$_3$), 55.98 (O*C*H$_3$), 44.9 (CO*C*H), 40.3 (*C*H$_2$CHC(O)O), 32.7 (*C*H$_2$CHNO_2), 29.2 (*C*H$_2$CH$_2$C(O)O); MS (APCI, neg.): 380.0 $(M-1)^-$; HRMS (EI, pos.): *m*/*z* 381.1423 (381.1424 calc. for $C_{18}H_{23}NO_8$ (M^+)).

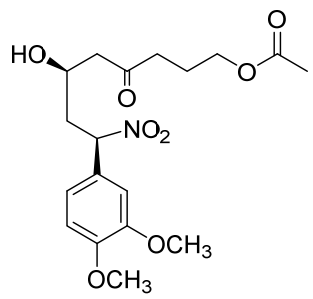
(2*R*,4*R*)-4-(3,4-Dimethoxyphenyl)-1-(2-(3-hydroxypropyl)-1,3-dioxolan-2-yl)-4-nitrobutan-2-ol (85):



To a solution of the lactone **84** (2.35 g, 6.16 mmol) in THF (60 mL) at 0 °C (ice/salt bath), was added lithium borohydride (188 mg, 8.63 mmol). The mixture was stirred at 0 °C for 30 min. and then at ambient temperature for 3 h. It was then cooled to 0 °C and 2 mL of cold water was added to give a mixture containing a white precipitate. The THF was removed under reduced pressure and the residue was dissolved in ethyl acetate (60 mL) and the aqueous layer was separated. The organic layer was dried (Na_2SO_4) and concentrated to provide 1.91 g (81%) of the nitroketal **85** as a pale yellow gum. This material was pure by ^{1}H NMR and was used in the step without purification. An analytical sample was obtained by flash chromatography on silica gel (EtOAc).

R_f = 0.25 (EtOAc); $[\alpha]_D^{20}$ = –21.7 (*c* 1, $CHCl_3$); IR (neat): 3498 (br), 1547, 1517, 1422, 1365, 1264, 1247, 1142, 1056, 1024, 949 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.04 (dd, 1H, *J* = 8.3, 2.1, Ar*H*), 6.98 (d, 1H, *J* = 2.1, Ar*H*), 6.86 (d, 1H, *J* = 8.3, Ar*H*), 5.84 (dd, 1H, *J* =11.3, 2.9, C*H*NO_2), 4.01 (br s, 4H, OC*H*$_2$C*H*$_2$O), 3.90 (br s, 4H, OC*H*$_3$, C*H*OH), 3.88 (s, 3H, OC*H*$_3$), 3.74 (br s, 1H,), 3.64 (br t, 2H, C*H*$_2$OH), 2.70-2.65 (ddd, 1H, *J* = 14.5, 11.3, 2.0), 1.93-1.72 (m, 7H), 1.70-1.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ150.1 (Ar*C*), 149.2 (Ar*C*), 127.6 (Ar*C*), 120.3 (Ar*C*), 111.6 (O*C*O), 111.1 (Ar*C*), 110.4 (Ar*C*), 87.3 (*C*HNO_2), 64.9 (O*C*H$_2$CH$_2$O), 64.7 (OCH$_2$*C*H$_2$O), 64.3 (*C*HOH), 62.7 (*C*H$_2$OH), 56.01 (O*C*H$_3$), 56.00 (O*C*H$_3$), 42.9 (*C*H$_2$), 41.5 (*C*H$_2$), 33.7 (*C*H$_2$), 27.0 (*C*H$_2$). MS (ESI, neg.): 384.1 $(M–1)^-$; HRMS (EI, pos.): *m*/*z* 385.1730 (385.1737 calc. for $C_{18}H_{27}NO_8$ (M^+)).

(6*R*, 8*R*)-8-(3,4-Dimethoxyphenyl)-6-hydroxy-8-nitro-4-oxooctyl acetate (87):



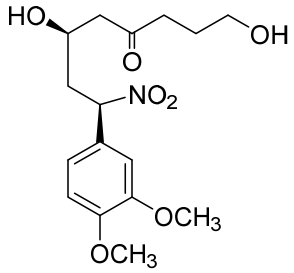
A solution of the diol **85** (100 mg, 0.26 mmol) in dry dichloromethane (3 mL) was cooled to –78 °C and acetyl chloride (22 μL, 0.3 mmol) and collidine (69 μL, 0.5 mmol) were added. The solution was stirred at –78 °C for 2 h and then at ambient temperature for 2 h. Dichloromethane (3 mL) was added and the resulting solution was washed with aq. HCl (0.5 M, 5 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 78 mg (70%) of the acetate **86** as a pale yellow gum. This was used in the next step without purification.

To a solution of the above ketal (60 mg, 0.14 mmol) in acetone (0.5 mL) was added iodine (1.7 mg, 14 mmol) and the solution was stirred at ambient temperature for 30 min. The acetone was removed under reduced pressure and the residue was diluted with dichloromethane (5 mL). The resulting solution was washed successively with aqueous $Na_2S_2O_3$ (5% w/v, 2 mL) and brine (2 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide 44 mg (82%) of the nitro ketone **87** as a yellow solid. This material was pure by ^{1}H NMR and was directly used in the next step.

R_f = 0.3 (hexanes/EtOAc, 60:40); IR (neat): 3509 (br), 1710, 1548, 1516, 1462, 1421, 1364, 1238, 1145, 1106, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03 (dd, 1H, J = 8.3,

2.2, Ar*H*), 6.96 (d, 1H, *J* = 2.2, Ar*H*), 6.85 (d, 1H, *J* = 8.3, Ar*H*), 5.83 (dd, 1H, *J* = 11.3, 2.8, C*H*NO_2), 4.08 (t, 2H, *J* = 6.3, CH_2OCOCH_3), 4.11-4.14 (m, 1H, C*H*OH), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.41 (brs, 1H, CHO*H*), 2.65-2.73 (m, 2H, NO_2CHCH_2), 2.46-2.63 (m, 4H, CH_2C(O)CH_2), 2.04 (s, 3H, COCH_3), 1.88-1.98 (m, 2H, C$H_2$$CH_2$OCOC$H_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0 (*C*=O), 171.1 (O*C*(O)CH_3), 150.2 (Ar*C*), 149.2 (Ar*C*), 127.3 (Ar*C*),120.3 (Ar*C*),111.1 (Ar*C*), 110.4 (Ar*C*), 87.2 (*C*HNO_2), 64.2 (*C*HOH), 63.4 (*C*H_2OCOCH_3), 56.03 (O*C*H_3), 55.97 (O*C*H_3), 48.8 (*C*H_2CO), 40.2 (CO*C*H_2), 39.7 (NO_2CH*C*H_2), 22.5 (*C*$H_2$$CH_2$CO), 20.9 (OCO*C*$H_3$); MS (ESI, pos.): *m*/*z* 406.1 $(M+Na)^+$ HRMS (EI, pos.): *m*/*z* 383.1583 (383.1580 calc. for $(C_{18}H_{25}NO_8)^+$), 406.1474 (406.1478 calc. for $(C_{18}H_{25}NNaO_8$ $(M+Na)^+$).

(6*R*,8*R*)-8-(3,4-Dimethoxyphenyl)-1,6-dihydroxy-8-nitrooctan-4-one (89):

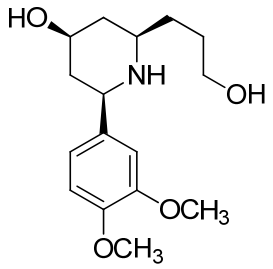


A solution of the ketal **85** (1.91 g, 4.96 mmol) in a mixture of 3M aqueous HCl and dioxane (1:1, 24 mL) was stirred at 0 ºC for 30 min. and then at ambient temperature for 1 h. The solution was neutralized with saturated aqueous sodium bicarbonate and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow gum. Purification of

the crude product by flash chromatography on silica gel (hexanes/EtOAc, 20:80) provided 1.33 g (78%) of **89** as a white foam.

R_f = 0.25 (hexanes/EtOAc, 20:80); $[\alpha]_D^{20}$= +6.5 (*c* 1, $CHCl_3$); IR (neat): 3519 (br), 1706, 1550, 1512, 1461, 1419, 1364, 1261, 1146, 1020 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 7.04 (dd, 1H, *J* = 8.3, 2.1, Ar*H*), 6.98 (d, 1H, *J* = 2.1, Ar*H*), 6.86 (d, 1H, *J* = 8.3, Ar*H*), 5.77 (dd, 1H, *J* = 11.3, 2.7, C*H*NO_2), 4.09-4.00 (m, 1H,), 3.90 (s, 3H, OC*H*$_3$), 3.88 (s, 3H, OC*H*$_3$), 4.00-3.75 (m (overlaps with OCH_3 singlets), 2H), 3.66 (m, 2H), 3.56 (s, 1H), 2.75-2.52 (m, 6H), 2.05-1.90 (m, 2H), 1.90-1.75 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 150.2 (Ar*C*), 149.2 (Ar*C*), 127.4 (Ar*C*), 120.3 (Ar*C*), 111.1 (Ar*C*), 110.4 (Ar*C*), 87.3 (*C*HNO_2), 64.3 (*C*HOH), 62.0 (*C*H_2OH), 56.03 (O*C*H_3), 56.00 (O*C*H_3), 49.1, 40.3, 40.2, 26.2. MS (ESI, neg.): 340.1 $(M-1)^-$; HRMS (EI, pos.): *m*/*z* 341.1472 (341.1475 calc. for $C_{16}H_{23}NO_7$ (M^+)).

(2*R*, 4*S*, 6*R*)-2-(3,4-Dimethoxyphenyl)-6-(3-hydroxypropyl)piperidin-4-ol (91):



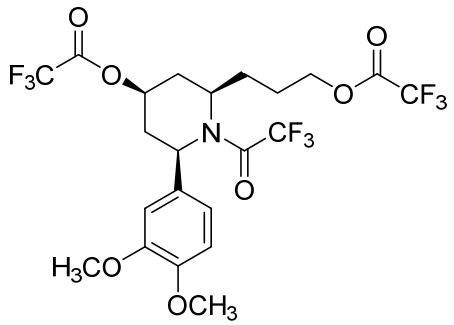
To the solution of nitroketone **89** (1.33 g, 3.9 mmol) in THF (25 mL) was added a solution of NH_4Cl (208 mg, 3.9 mmol) in water (3.6 mL) followed by activated Zn powder (2.53 g, 39.0 mmol). The mixture was stirred vigorously at ambient temperature under nitrogen for 3 h. The mixture was then filtered through a pad of celite, the residue was washed with THF, and the combined filtrates were concentrated under reduced pressure to

provide 1.04 g of **90** piperidine as a pale yellow foam. This was used in the next step without purification.

To a solution of **90** (1.04 g) in MeOH (18 mL) at 0 ºC was added sodium borohydride (0.53 g, 14.2 mmol). The mixture was stirred at 0ºC for 30 min. and then at ambient temperature for 2 h. Aqueous HCl (2 M, 15 mL) was added and the mixture was concentrated under reduced pressure to remove MeOH. The resulting aqueous mixture was basified (pH~ 10) with solid NaOH and then extracted with ethyl acetate (25 x 3 mL). The combined extracts were dried (Na_2SO_4) and concentrated to provide 0.89 g of piperidine **91** as a white gum.

IR (neat): 3342 (br), 2936, 2840, 1517, 1453, 1421, 1263, 1163, 1143, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.93-6.81 (m, 3H, Ar*H*), 3.89 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.90-3.80 (m (overlaps with OCH_3 singlets), 1H, C*H*OH), 3.69 (dd, 1H, *J* =11.7, 2.4, ArC*H*), 3.60-3.55 (m, 2H, C*H*$_2$OH), 2.90-2.80 (m, 1H, C*H*$_2$CHNH), 2.25-2.15 (m, 1H, NC*H*), 2.05-1.96 (m, 2H, C*H*$_2$CHOH), 2.15-1.95 (br, 1H, N*H*), 1.70-1.60 (m, 5H, CH_2C*H*$_2$OH), 1.52 (m, 1H, *J* = 11.6, C*H*$_2$$CH_2CH_2OH$), 1.35 (m, 1H, *J* = 11.6, C*H*$_2$$CH_2CH_2OH$).$^{13}C$ NMR (75 MHz, $CDCl_3$): δ 149.0 (Ar*C*$_{ipso}$), 148.3 (Ar*C*$_{ipso}$), 135.6(Ar*C*$_{ipso}$), 118.6 (Ar*C*), 111.1 (Ar*C*), 110.1 (Ar*C*), 69.3 (*C*HOH), 62.7 (*C*H_2OH), 59.1 (Ar*C*H), 55.9 (2 x O*C*H_3), 54.8 (*C*HNH), 42.8, (ArCH*C*H_2), 40.7 (*C*H_2CHOH), 35.1 (*C*H_2CH_2OH), 29.4 (*C*$H_2(CH_2)_2OH$). MS (APCI, pos.): 296.2 $(M+1)^+$; HRMS (EI, pos.): *m*/*z* 295.1774 (295.1784 calc. for $C_{16}H_{25}NO_4$ (M^+)).

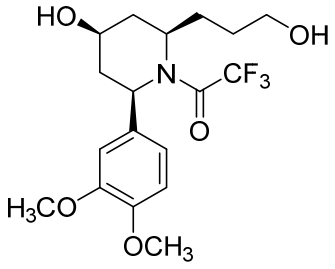
3-((2*R*,4*S*,6*R*)-6-(3,4-Dimethoxyphenyl)-4-(2,2,2-trifluoroacetoxy)-1-(2,2,2-trifluoroacetyl)piperidin-2-yl)propyl 2,2,2-trifluoroacetate (92):



To an ice cold solution of amino alcohol **91** (90 mg, 0.30 mmol) in dichloromethane (2 ml) containing pyridine (86 μL, 1.06 mmol) and 4-(dimethylamino)pyridine (2 mg, 0.01 mmol) was added trifluoroacetic anhydride (0.15 mL, 1.06 mmol). The solution was stirred at ambient temperature for 12 h, water was added and the solution was extracted with dichloromethane and the combined extracts were dried (Na_2SO_4), and concentrated in vacuum to provide 0.136 g (80%) of **92** as a brown gum. This crude material was taken for the next step without further purification.

IR (neat): 2964, 2927, 2845, 1783, 1679, 1517, 1456, 1353, 1137, 1023 cm^{-1}.

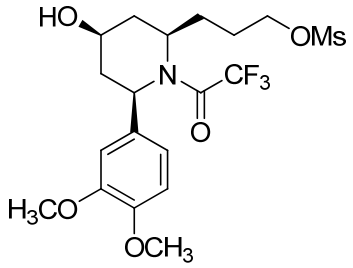
1-((2*R*, 4*S*, 6*R*)-2-(3,4-Dimethoxyphenyl)-4-hydroxy-6-(3-hydroxypropyl)piperidin-1-yl)-2, 2, 2-trifluoroethanone (93):



The residue **92** (136 mg, 0.23 mmol) was dissolved in THF (7 mL), K_2CO_3 (71 mg, 0.51 mmol) was added and the mixture was stirred at the ambient temperature for 24 h. Water was added and the mixture was extracted with dichloromethane (5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated in vacuum. The crude **93** was obtained as a brown gum.

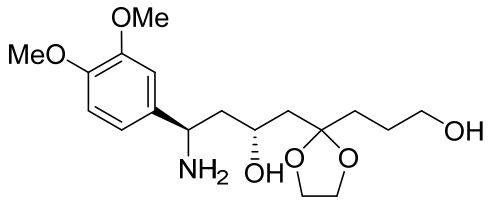
IR (neat): 3398, 2924, 2853, 1677, 1518, 1456, 1418, 1256, 1200, 1142, 1026 cm^{-1}.

3-((2*R*,4*S*,6*R*)-6-(3,4-Dimethoxyphenyl)-4-hydroxy-1-(2,2,2 trifluoroacetyl)piperidin-2-yl)propyl methanesulfonate (94):



To a stirred solution of **93** (70 mg, 0.178 mmol) in dichloromethane (2 mL), at -78 ^oC, was added DIPEA (31μL) followed by methanesulfonyl chloride (14 μL, 0.178 mmol) in dichloromethane (2 mL) over 15 min at -78 ^oC. The reaction mixture was warm up to ambient temperature. Cold water (3 mL) was added and the organic layer was separated, washed with water (5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated to provide 65 mg (77%) as a brown gum of the crude mesylate **94** as a yellow gum. This crude material was immediately used in the next step.

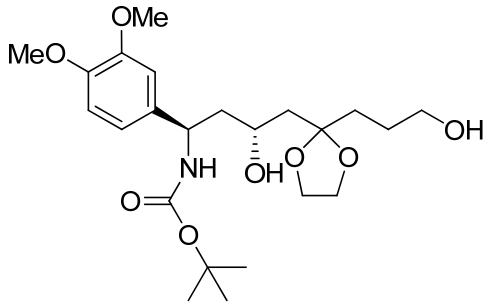
(2*R*, 4*R*)-4-Amino-4-(3, 4-dimethoxyphenyl)-1-(2-(3-hydroxypropyl)-1, 3-dioxolan-2-yl)butan-2-ol (96):



To a solution of **85** (550 mg, 1.42 mmol) methanol was added $NiCl_2$ (370 mg, 2.85 mmol) at -20 °C followed by $NaBH_4$ (540 mg, 14.2 mmol) in portions over the period of 1h. The reaction mixture was stirred at -20 °C for 1 h and at ambient temperature for 2 h. Then the reaction mixture was concentrated to remove methanol and 3 M NaOH (10 ml) was added to the residue followed by ether (15 ml). The resulting suspension was filtered and the organic layer was separated, washed with brine and dried (Na_2SO_4). It was then concentrated under vacuum, provided **96** of 70% as a yellow gum and the crude was used in the next step without further purification.

IR (neat): 3500, 2930, 2365, 2329, 1672, 1594, 1305, 1260, 1143, 1094, 905, 833, 730 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89-6.83 (m, 3H, ArH), 4.21 (br s, C*H*OH), 4.11-3.94 (m, 5H, C*H*NH_2, OC*H*$_2$C*H*$_2$O), 3.89 (s, 3H, OC*H*$_3$), 3.88 (s, 3H, OC*H*$_3$), 3.63 (t, 2H, *J* = 6.1, C*H*$_2$OH), 1.82-1.60 (m, 8H, C*H*$_2$CH$_2$CH$_2$OH, C*H*$_2$CH$_2$OH, C*H*$_2$CHOH, C*H*$_2$C(OCH$_2$CH$_2$O)). MS (ESI, pos.): *m/z* 356.2 (356.44 calc. for $C_{18}H_{30}NO_6$ $[M+H]^+$).

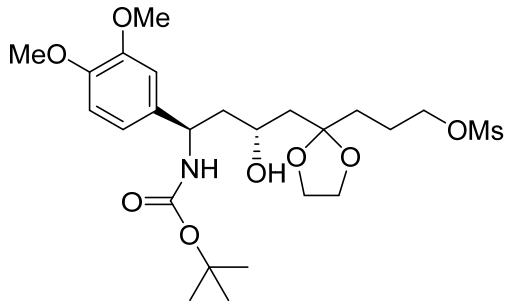
***tert*-Butyl (1*R*,3*R*)-1-(3, 4-dimethoxyphenyl)-3-hydroxy-4-(2-(3-hydroxypropyl)-1,3-dioxolan-2-yl)butylcarbamate (97):**



To a solution of **96** (0.350g, 0.98 mmol) in dichloromethane (12 mL), Et_3N (0.13ml, 0.98 mmol) followed by boc anhydride (230 mg, 1.08 mmol) was added in an ice bath. The reaction was warmed up to ambient temperature and allowed to stir for 12 h in ambient temperature. The reaction mixture was diluted with dichloromethane and washed with water. The organic layer was separated and dried (Na_2SO_4). It was then concentrated through vacuum to provide 400 mg of **97** (90%) as a yellow gum. This material was taken further without purification.

IR (neat): 3450, 2980, 2926, 2365, 2328, 1808, 1763, 1689, 1513, 1459, 1367, 1314, 1119, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.86-6.80 (m, 3H, ArH), 4.00-3.93 (m, 4H, OCH_2CH_2O), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87-3.86 (br s, CHOH), 3.62 (m, 2H, CH_2OH), 1.93-1.57 (m, 8H, $CH_2CH_2CH_2OH$, CH_2CH_2OH, CH_2CHOH, $CH_2C(OCH_2CH_2O)$) 1.47-1.36 (m, 9H, $(CH_3)_3C$).

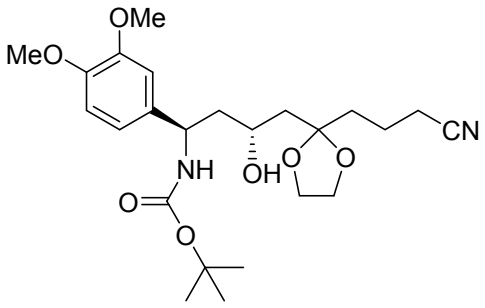
3-(2-((2*R*,4*R*)-4-(*tert*-Butoxycarbonylamino)-4-(3, 4-dimethoxyphenyl)-2-hydroxybutyl)-1, 3-dioxolan-2-yl)propyl methanesulfonate (98):



To a stirred solution of **97** (75 mg, 0.16 mmol) in dichloromethane (2 mL), at -78 ^{o}C, was added collidine (44 μL) followed by methanesulfonyl chloride (13.0 μL, 0.164 mmol) in dichloromethane (10 mL) over 15 min at -78 ^{o}C. The reaction mixture was warm up to ambient temperature. Cold water (3 mL) was added and the organic layer was separated, washed with water (5 mL), brine (5 mL), dried (Na_2SO_4) and concentrated to provide 80 mg as a brown gum of the crude mesylate **98** as a yellow gum. This was immediately used in the next step.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87-6.78 (m, 3H, Ar*H*), 5.60-5.57 (br s, N*H*, rotamer), 4.85 (br s, C*H*NH, rotamer), 4.22 (t, 2H, *J* = 6.0, CH_2CH_2OH), 3.99-3.94 (m, 4H, OCH_2CH_2O), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.87 (br s, C*H*OH), 3.00 (s, 3H, OSO_2CH_3),1.93-1.62 (m, 8H, $CH_2CH_2CH_2OH$,CH_2CH_2OH, CH_2CHOH, $CH_2C(OCH_2CH_2O)$), 1.49-1.33 (br m, 9H, $(CH_3)_3C$).

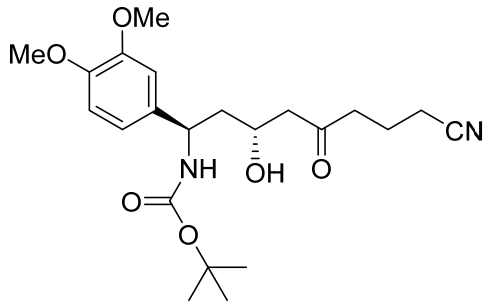
***tert*-Butyl (1*R*,3*R*)-4-(2-(3-cyanopropyl)-1,3-dioxolan-2-yl)-1-(3,4-dimethoxyphenyl)-3-hydroxybutylcarbamate (99):**



To a solution of the mesylate **98** (80 mg, 0.15 mmol) in anhydrous DMSO (2 mL) at ambient temperature was added NaCN (15 mg, 0.3 mmol). The mixture was stirred at ambient temperature for 15 h. Ethyl acetate was added to the reaction mixture and the solution was washed with water (5 mL), brine (3 mL) and then dried (Na_2SO_4). It was then concentrated to provide 59 mg (85%) of **99** as a dark red gum.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.84-6.82 (m, 3H, Ar*H*), 5.54 (br s, 1H, N*H*), 4.84 (br s, 1H, C*H*NH), 3.98-3.96 (m, 4H, OCH_2CH_2O), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.88-3.86 (br s, C*H*OH), 2.36 (t, 2H, CH_2CN), 1.92-1.62 (m, 8H, CH_2CH$_2$OH, CH_2CHOH, CH_2C(OCH$_2$CH$_2$O)) 1.49-1.34 (br m, 9H, (CH_3)$_3$C).

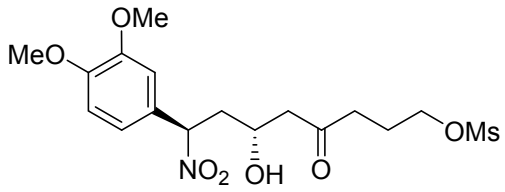
***tert*-Butyl(1*R*,3*R*)-8-cyano-1-(3,4-dimethoxyphenyl)-3-hydroxy-5-oxooctylcarbamate (100):**



To a solution of **99** (34 mg, 0.07 mmol) in acetone (0.5 mL) was added iodine (1.0 mg, 0.007 mmol) and the solution was stirred at ambient temperature for 2 h. The acetone was removed under reduced pressure and the residue was diluted with dichloromethane (5 mL). The resulting solution was washed successively with aqueous $Na_2S_2O_3$ (5% w/v, 2 mL) and brine (2 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide 27 mg (90%) of **100** as a brown gum. This material was pure by ^1H NMR and was directly used in the next step.

IR (neat): 2973, 2364, 2328, 2254, 1699, 1599, 1508, 1257, 1169, 907, 728 cm^{-1}.

(6*R*,8*R*)-8-(3,4-Dimethoxyphenyl)-6-hydroxy-8-nitro-4-oxooctylmethanesulfonate (106):

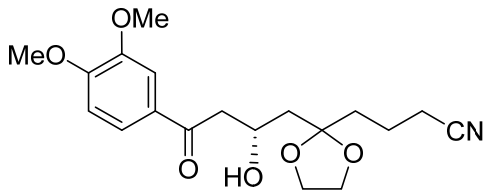


To a stirred solution of **85** (50 mg, 0.129 mmol) in dichloromethane (1 mL), at -78 ^{o}C, was added collidine (35μL) followed by methanesulfonyl chloride (10μL, 0.164 mmol) in dichloromethane (1 mL) over 15 min at -78 ^{o}C. The reaction mixture was warmed up to ambient temperature. Cold water (3 mL) was added and the organic layer was separated, washed with water (3 mL), brine (3 mL), dried (Na_2SO_4) and concentrated to provide 40 mg (67%) of the crude mesylate **104** as a yellow gum. This was immediately used in the next step

To a solution of **104** (145 mg, 0.31 mmol) in acetone (2 mL) was added iodine (4.0 mg, 0.014 mmol) and the solution was stirred at ambient temperature for 2 h. The acetone was removed under reduced pressure and the residue was diluted with dichloromethane (5 mL). The resulting solution was washed successively with aqueous $Na_2S_2O_3$ (5% w/v, 2 mL) and brine (2 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to provide 100 mg (77%) of the **106** as a yellow liquid. This material was pure by ^{1}H NMR and was directly used in the next step.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (dd, 1H, *J* = 8.3, 2.2, Ar*H*), 6.97 (d, 1H, *J* = 2.1, Ar*H*), 6.85 (d, 1H, *J* = 8.3, Ar*H*), 5.83 (dd, 1H, C*H*NO_2), 4.27 (t, 2H, *J* = 6.1, C*H*$_2$OMs), 4.14-4.06 (m, 1H), 3.91 (s, 3H, OC*H*$_3$), 3.89 (s, 3H, OC*H*$_3$), 3.01 (s, 3H, OSO_2CH_3), 2.74-2.55 (m, 4H, C*H*$_2$CHOH, C*H*$_2$COCH_2), 2.09-1.93 (m, 4H, C*H*$_2$CH_2CH_2OMs, C*H*$_2$CH_2OMs).

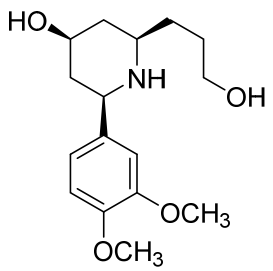
(*R*)-3-(2-(4-(3,4-Dimethoxyphenyl)-2-hydroxy-4-oxobutyl)-1,3-dioxolan-2-yl)propyl methanesulfonate (107):



To a solution of mesylate **104** (13 mg, 0.02 mmol) in DMSO (0.25 mL) was added sodium cyanide (3 mg, 0.05 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature for one hour. Then the reaction mixture was washed with 0.5 mL of water and extracted with (2 x 3 mL) of ethyl acetate. The organic layer was separated and dried (Na_2SO_4). It was then concentrated under reduced pressure and the crude **107** was obtained as a yellow gum.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, 1H, *J* = 8.4, Ar*H*), 7.56 (s, 1H, Ar*H*), 6.92 (d, 1H, *J* = 8.4, Ar*H*), 4.30 (t, 2H, *J* = 6.0, C*H*$_2$OMs), 4.05-4.01 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.98 (s, 3H, OC*H*$_3$), 3.96 (s, 3H, OC*H*$_3$), 3.66 (s, 1H, C*H*OH), 3.22 (dd, 1H, *J* = 16.8, 6.2, COC*H*$_2$), 3.07 (dd, 1H, *J* = 16.8, 6.2, COC*H*$_2$), 3.04 (s, 3H, OSO$_2$C*H*$_3$), 1.99-1.88 (m, 6H, C*H*$_2$(C)CH$_2$, C*H*$_2$CH$_2$CH$_2$OMs, CH$_2$C*H*$_2$CH$_2$OMs).

(2*R*,4*S*,6*R*)-2-(3,4-Dimethoxyphenyl)-6-(3-hydroxypropyl)piperidin-4-ol (91):



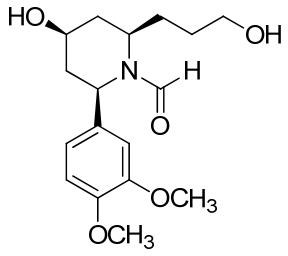
To the solution of nitroketone **89** (1.33 g, 3.9 mmol) in THF (25 mL) was added a solution of NH_4Cl (208 mg, 3.9 mmol) in water (3.6 mL) followed by activated Zn powder (2.53 g, 39.0 mmol). The mixture was stirred vigorously at ambient temperature under nitrogen for 3 h. The mixture was then filtered through a pad of celite, the residue was washed with THF, and the combined filtrates were concentrated under reduced pressure to provide 1.04 g of an inseparable mixture of **90** (piperidine) and **92** (*N*-hydroxy piperidine) as a pale yellow foam. This was used in the next step without purification.

To a solution of **90+92** (1.04 g) in MeOH (18 mL) at 0 ºC was added sodium borohydride (530 mg, 14.2 mmol). The mixture was stirred at 0ºC for 30 min. and then at ambient temperature for 2 h. Aqueous HCl (2 M, 15 mL) was added and the mixture was concentrated under reduced pressure to remove MeOH. The resulting aqueous mixture was basified (pH~10) with solid NaOH and then extracted with ethyl acetate (3 x 25 mL). The combined extracts were dried (Na_2SO_4) and concentrated to provide 0.89 g of a mixture of **91** and the corresponding *N*-hydroxy piperidine **109** as a white gum. This was dissolved in a mixture of EtOH (15 mL) and saturated aqueous NH_4Cl (7 mL). Indium powder (0.65 g, 5.7 mmol) was added and mixture was heated at 85 ºC for 4h. The mixture was then cooled, filtered through a pad of celite, and concentrated. Saturated aqueous Na_2CO_3 (5 x 3 mL)

was added to the residue and the mixture was extracted with ethyl acetate (2 x 15 mL). The combined extracts were dried over (Na_2SO_4) and concentrated to provide 0.81 g (70%) of the amine **91** as a colorless gum. This was pure by ^{1}H NMR and was used in the next step without purification.

R_f = 0.25 (CH_2Cl_2/MeOH, 95:5); $[\alpha]_D^{20}$ = +12.4 (*c* 1, $CHCl_3$); IR (neat): 3342 (br), 2936, 2840, 1517, 1453, 1421, 1263, 1163, 1143, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93-6.81 (m, 3H, Ar*H*), 3.89 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.90-3.80 (m (overlaps with OCH_3 singlets), 1H, C*H*OH), 3.69 (dd, 1H, *J* =11.7, 2.4, ArC*H*), 3.60-3.55 (m, 2H), 2.90-2.80 (m, 1H), 2.25-2.15 (m, 1H), 2.05-1.96 (m, 2H), 2.15-1.95 (br, 1H, N*H*), 1.70-1.60 (m, 5H, CH_2CH_2OH), 1.52 (m, 1H, *J* = 11.6, $CH_2CH_2CH_2OH$), 1.35 (m, 1H, *J* = 11.6, $CH_2CH_2CH_2OH$);^{13}C NMR (75 MHz, $CDCl_3$): δ149.0 (Ar*C*$_{ipso}$), 148.3 (Ar*C*$_{ipso}$), 135.6(Ar*C*$_{ipso}$), 118.6 (Ar*C*), 111.1 (Ar*C*), 110.1 (Ar*C*), 69.3 (*C*HOH), 62.7 (*C*H_2OH), 59.1 (Ar*C*H), 55.9 (2 x O*C*H_3), 54.8 (*C*HNH), 42.8, (ArCH*C*H_2), 40.7 (*C*H_2CHOH), 35.1 (*C*H_2CH_2OH), 29.4 (*C*$H_2(CH_2)_2$OH). MS (APCI, pos.): 296.2 $(M+1)^+$; HRMS (EI, pos.): *m*/*z* 295.1774 (295.1784 calc. for $C_{16}H_{25}NO_4(M^+)$).

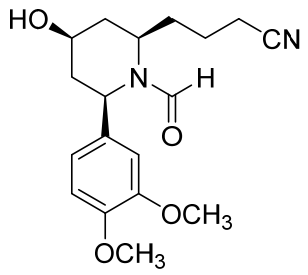
(2*R*,4*S*,6*R*)-2-(3,4-Dimethoxyphenyl)-4-hydroxy-6-(3-hydroxypropyl)piperidine-1-carbaldehyde (112):



To a cooled (0 ºC) solution of the amino diol **91** (0.76 g, 2.6 mmol) in dichloromethane (18 mL) was added acetic formic anhydride (0.46 mL, 5.1 mmol). The solution was stirred at ambient temperature for 15 min. and then concentrated under reduced pressure to provide 0.88 g of the formamido diformate derivative of **110** as a yellow gum. This was dissolved in THF (15 mL), 1M NaOH (15 mL) was added and the mixture was stirred at ambient temperature for 2 h. The THF was removed under reduced pressure, the residue was dissolved in dichloromethane (30 mL) and the solution was washed with water (2 ×5 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to provide 745 mg (92%) of **112** as a colorless gum.

R_f = 0.30 (CH_2Cl_2/MeOH, 95:5); $[\alpha]_D^{20}$ = +42.0 (c 1, $CHCl_3$); IR (neat): 3379 (br), 2937, 2872, 1642, 1515, 1462, 1418, 1254, 1142, 1063, 1023, 911 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.16 (br s, 1H, C*H*O), 7.20-6.75 (br m, 3H, Ar*H*), 4.75-4.60 (br, 0.5H), 4.35-4.30 (br, 0.5H), 4.17-4.08 (m, 1H), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.70-3.40 (br, 2H), 2.45-2.15 (br, 4H), 2.05-1.96 (m, 2H), 1.95-1.80 (br, 1H), 1.75-1.65 (m, 1H), 1.65-1.25 (br, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ164.0-163.0 (br), 149.0-147.5 (br), 134.0-133.0 (br), 119.2, 112.0-110.0 (br), 64.7, 61.9 (br), 56.7-56.0 (br), 55.96, 55.92, 49.8 (br), 37.3 (br), 35.4 (br), 34.2-33.0 (br), 32.8 (br), 29.3 (br). MS (CI, pos.): 324.2 $(M+1)^+$; HRMS (APPI, pos.): *m*/*z* 323.1737 (323.1733 calc. for $C_{17}H_{25}NO_5$ (M^+)).

4-((2*R*,4*S*,6*R*)-6-(3,4-Dimethoxyphenyl)-1-formyl-4-hydroxypiperidin-2-yl)butanenitrile (114):



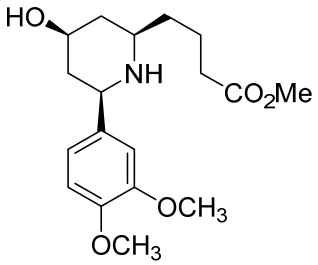
To a stirred solution of **112** (745 mg, 2.30 mmol) in dichloromethane (15 mL), at 0 ^{o}C, was added DIPEA (0.4 mL) followed by methanesulfonyl chloride (0.18 mL, 2.30 mmol) in dichloromethane (10 mL) over 15 min. Stirring was continued at 0 ^{o}C for 3 h. Cold water (7 mL) was added and the organic layer was separated, washed with water (3 x 15 mL), brine (1 x 15 mL), dried (Na_2SO_4) and concentrated to provide 0.76 g of the crude mesylate **113** as a yellow gum. This was immediately used in the next step.

To a solution of the mesylate **113** (0.76 g, 1.9 mmol) in anhydrous DMSO (15 mL) at ambient temperature was added NaCN (0.93 g, 18.9 mmol). The mixture was stirred at ambient temperature for 15 h. Ethyl acetate was added to the reaction mixture and the solution was washed with water (3 x 30 mL), brine (30 mL) and then dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc) to provide 349 mg (55%) of **114** as a colourless gum.

R_f = 0.20 (EtOAc); $[\alpha]_D^{20}$ = +8.0 (*c* 0.7, $CHCl_3$); IR (neat): 3407 (br), 2938 (br), 2247, 1643, 1515, 1459, 1419, 1256, 1143, 1077, 1024, 916 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.20 (br s, 1H, C*H*O), 7.25-6.75 (br m, 3H, Ar*H*), 4.80-4.70 (br, 0.5H), 4.30-4.25 (br, 0.5H), 4.22-4.18 (m, 1H), 3.88 (s, 3H, OC*H*$_3$), 3.87 (s, 3H, OC*H*$_3$), 2.50-1.75 (br, 7H),

1.75-1.50 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.1 (br), 163.2 (br), 149.9-147.5 (br), 133.4 (br), 120.0-119.5 (br), 119.3, 64.9, 56.01, 55.96, 48.7 (br), 36.8-36.3 (br), 36.1-35.7(br), 35.7-35.4 (br), 35.4-35.0 (br), 33.0-32.0 (br), 22.59, 16.8. MS (APCI, pos.): 333.2 $(M+1)^+$; HRMS (APPI, pos.): *m*/*z* 332.1733 (332.1736 calc. for $C_{18}H_{24}N_2O_4(M^+)$).

Methyl-4-((2*R*,4*S*,6*R*)-6-(3,4-dimethoxyphenyl)-4-hydroxypiperidin-2-yl)butanoate (115):

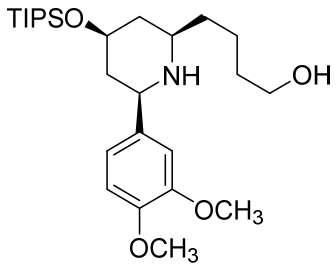


A solution of nitrile **114** (0.349 g, 1.0 mmol) in methanolic HCl (3 M, 14 mL) was heated to reflux for 72 h. The methanol was removed under reduced pressure and the residue was neutralized with saturated aqueous sodium bicarbonate (2 × 10 mL). The resulting mixture was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to provide 285 mg (80%) of **115** as a colorless gum. In repeated preparations, the crude product was of sufficient purity to be directly used in the next step.

R_f = 0.25 (CH_2Cl_2/MeOH, 95:5); $[\alpha]_D^{20}$ = + 29.8 (*c* 0.5, $CHCl_3$); IR (neat): 3377 (br), 2929, 2847, 1733, 1515, 1452, 1368, 1308, 1259, 1157, 1029 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94 (d, 1H, *J* = 2.0, ArH), 6.89 (dd, 1H, *J* = 8.2, 2.0, ArH), 6.82 (d, 1H, *J* = 8.2, Ar*H*),

3.90 (s, 3H, OC*H*$_3$), 3.87 (s, 3H, OC*H*$_3$), 3.82-3.75 (m, 1H, C*H*OH), 3.66 (s, 3H, CO_2CH_3), 3.61 (dd, 1H, *J* = 11.5, 2.4, ArC*H*), 2.74-2.71 (m, 1H, C*H*NH), 2.33 (t, 2H, *J* = 7.4, $CH_2CO_2CH_3$), 2.11-2.08 (m, 1H), 2.05-2.02 (m, 1H), 1.75-1.65 (m, 2H), 1.55-1.70 (br, N*H*), 1.54-1.48 (m, 2H, CH_2CH_2COOMe), 1.46 (q (overlaps with m), 1H, *J* = 11.3, $CH_2CH_2CH_2COOMe$), 1.15 (q, 1H, *J* = 11.3, $CH_2CH_2CH_2COOMe$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9 (*C*O), 149.0 (Ar*C*$_{ipso}$), 148.3 (Ar*C*$_{ipso}$), 136.6 (Ar*C*$_{ipso}$), 118.8 (Ar*C*), 111.0 (Ar*C*), 110.0 (Ar*C*), 69.7 (*C*HOH), 59.4 (Ar*C*H), 55.95 (O*C*H$_3$), 55.93 (O*C*H$_3$), 55.0 (CO_2CH_3), 51.6 (N*C*H), 43.7 (CH*C*H$_2$), 41.3 (CH*C*H$_2$), 36.1 (NCH*C*H$_2$CH$_2$), 34.0 (NCHCH$_2$*C*H$_2$), 21.4 (*C*H$_2$CO$_2$CH$_3$). MS (APCI, pos.): 338.2 $(M+1)^+$; HRMS (APPI, pos.): *m*/*z* 337.1881 (337.1889 calc. for $C_{18}H_{27}NO_5(M^+)$).

4-((2*R*,4*S*,6*R*)-6-(3,4-Dimethoxyphenyl)-4-((triisopropylsilyl)oxy)piperidin-2-yl)butan-1-ol (117):

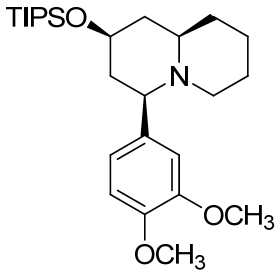


To a solution of the aminoester **115** (285 mg, 0.84 mmol) in dichloromethane (12 mL) at 0 ºC was added DIPEA (0.15 mL, 0.85 mmol) followed by TIPSOTf (0.25 mL, 0.93 mmol) and the mixture was stirred at ambient temperature for 4 h. Dichloromethane (15 mL) was added and the solution was washed with water (10 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 375 mg of the crude TIPS ether of **116**. This was used immediately in the next step without purification.

To a solution of the TIPS ether **116** (375 mg, 0.76 mmol) in dry THF (6 mL) at 0 ºC was added $LiBH_4$ (33 mg, 1.5 mmol) and the mixture was stirred at ambient temperature for 12 h. Aqueous HCl (0.1 M, 6 mL) was added, the mixture was stirred for 15 mins. and then neutralized with aqueous NaOH (6 M). The resulting mixture was extracted with ethyl acetate (2 x 15) and the combined extracts were dried (Na_2SO_4) and concentrated to provide 0.25 g (71%) of **117** as an oil. This was pure by ^1H NMR and was used in the next step without purification.

R_f = 0.25 (CH_2Cl_2/MeOH, 95:5); $[\alpha]_D^{20}$ = +5.0 (c 1, $CHCl_3$); IR (neat): 3318 (br), 2939, 2864, 1516, 1463, 1379, 1264, 1231, 1140, 1108, 1065, 1029, 996 cm^{-1};^1H NMR (300 MHz, $CDCl_3$): δ 6.98 (br s, 1H, Ar*H*), 6.89 (dd, 1H, *J* = 8.2, 1.9,Ar*H*), 6.81 (d, 1H, *J* = 8.2, ArH), 3.91 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.80-3.87 (m, 1H, C*H*OH), 3.64-3.52 (m, 3H), 2.75-2.50 (m, 1H), 2.10-1.90 (m, 1H), 1.87-1.35 (m, 12H, Ar*H*), 1.30-1.20 (m, 1H), 1.06 (br s, 18H, CH(C*H*$_3$)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0 (2 x Ar*C*$_{ipso}$), 148.4 (Ar*C*$_{ipso}$), 119.2 (Ar*C*), 111.0 (Ar*C*), 110.4 (Ar*C*), 70.00, 70.02 (*C*HOSi), 62.6 (*C*H_2OH), 59.8 (Ar*C*H), 56.01 (O*C*H_3), 55.96 (O*C*H_3), 55.5 (*C*HNH), 43.8 (SiOCH*C*H_2), 41.9 (SiOCH*C*H_2), 36.2 (*C*$H_2CH_2CH_2CH_2OH$, or CH_2CH_2*C*H_2CH_2OH), 32.5(*C*$H_2CH_2CH_2CH_2OH$, or CH_2CH_2*C*H_2CH_2OH), 22.2(CH_2*C*$H_2CH_2CH_2OH$), 18.13 (CH(*C*H_3)$_2$), 12.4 (*C*H(CH_3)$_2$). MS (APCI, pos.): *m*/*z* 466.3 $(M+1)^+$; HRMS (APPI, pos.): *m*/*z* 465.3263 (465.3274 calc. for $C_{26}H_{47}NO_4Si(M^+)$).

(2*S*,4*R*,9a*R*)-4-(3,4-Dimethoxyphenyl)-2-(triisopropylsilyloxy)octahydro-1H-quinolizine (119)[3j]:

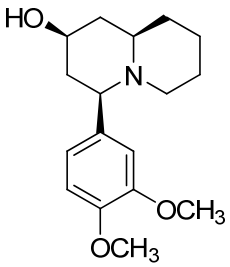


To a solution of the aminoalcohol **117** (250 mg, 0.53 mmol) in dry THF (5 mL), at –5 ºC under nitrogen, was added Ph_3P (282 mg, 1.07 mmol) followed by DMEAD (252 mg, 1.07 mmol). The mixture was stirred at ambient temperature for 3 h and concentrated. The residue was dissolved in ethyl acetate (5 mL) and the solution was washed with water (7 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 80:20) to give 166 mg (70%) of **119** as a colorless gum.

R_f = 0.25 (hexanes/EtOAc, 80:20); $[\alpha]_D^{23}$= +53.3 (*c* 0.3, $CHCl_3$, lit.[1] $[\alpha]_D^{23}$= – 48.6 (c 0.15, $CHCl_3$) for the enantiomer); IR (neat): 2936, 2864, 1510, 1463, 1382, 1263, 1230, 1110, 1070, 1031, 910, 882, 815 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10-6.75 (br m, 3H, Ar*H*), 3.89 (s, 3H, OC*H*$_3$), 3.86 (s, 3H, OC*H*$_3$), 3.81-3.75 (m, 1H), 2.85 (dd, 1H, *J* =11.8, 2.7), 2.68-2.63 (apparent br d, 1H, *J* = 11.5), 1.97-1.82 (m, 3H), 1.71-1.55 (m, 6H), 1.55-1.35 (m, 5H), 1.27-1.19 (m,1H), 1.04 (br s, 18H, CH(C*H*$_3$)$_2$). Spectrum matches Aube's. Integration listing in aliphatic region does not match Aube's, but his listing also does not match his actual spectrum.^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9 (Ar*C*), 137.3 (Ar*C*), 120.0-119.0 (br, Ar*C*), 111.0-110.0 (br, Ar*C*), 69.1, 68.4, 61.1 (Ar*C*H), 56.0(O*C*H$_3$), 55.9

(OCH_3), 53.1 (*C*HNH), 45.8, 43.7, 33.8, 26.2, 24.7, 18.1 ($CH(CH_3)_2$), 12.4 ($CH(CH_3)_2$). Agrees with Aube, also looks like Aube's spectrum which also has broad peaks, but lists 4 peaks that are not seen in the actual spectrum. MS (APCI, pos.): 448.3 $(M+1)^+$. HRMS (APPI, pos.): *m/z* 447.3169 (447.3169 calc. for $C_{26}H_{45}NO_3Si(M^+)$).

(2*S*,4*R*,9a*R*)-4-(3,4-Dimethoxyphenyl)octahydro-1H-quinolizin-2-ol(2-*epi*-lasubine II, 46):



To the solution of **119** (162 mg, 0.36 mmol) in anhydrous THF (5 mL), at 0 ºC, was added a solution of tetrabutylammonium fluoride in THF (0.36 mL of a 1.0 M solution, 0.36 mmol). The mixture was stirred at ambient temperature for 3 h and then concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 95:5) to provide 85 mg (81%) of **46** as clear colorless oil.

R_f = 0.25 (CH_2Cl_2/MeOH, 95:5)$[\alpha]_D^{20}$ = +47.9 (c 0.6, $CHCl_3$, lit.[3b] $[\alpha]_D^{20}$ = +43.4 (c 1.0, $CHCl_3$));IR (neat): 3363 (br), 2929, 2852, 2790, 1512, 1454, 1382, 1363, 1263, 1230, 1137, 1059, 1030 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10-6.75 (br m, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 3.75 (m, 1H), 2.92 (br d, 1H, *J* = 11.0), 2.70 (br d, 1H, *J* = 11.0), 2.05-1.90 (brm, 3H), 1.75-1.35 (br m, 9H), 1.25 (m, 1H); agrees well with Ma[3k], Rovis.[3b] ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9(ArC_{ipso}), 136.4 (ArC_{ipso}), 120.0-119.4 (br, 2 x Ar*C*), 111.0 110.5

(br, 2 x Ar*C*), 68.5, 68.2, 61.0 (Ar*C*H), 55.99 (O*C*H$_3$), 55.86 (O*C*H$_3$), 52.9 (*C*HNH), 45.2, 42.8 (OCH*C*H$_2$), 33.6, 26.0, 24.6. agrees well with Rutjes, Chattopadhyay. MS (APCI, pos.): 292.1 $(M+1)^+$; HRMS (APPI, pos.): *m*/*z* 291.1842 (291.1834 calc. for $C_{17}H_{25}NO_3(M^+)$).

3.6 References:

1) a) Isolation and structure determination: Fuji, K.; Yamada, T.; Fujita, E.; Murota, H. Chem. Pharm. Bull. **1978**, 26, 2515.

2) a) Rumalla, C. S.; Jadhav, A.N.; Smillie, T.; Fronczek, F. R.; Khan, I. A. *Phytochemistry* **2008**, *69*, 1756. b) Ferris, J. P.; Boyce, C. B.; Briner, R. C. *J. Am. Chem. Soc.* **1971**, *93*, 2942.

3) a) Saha, N.; Biswas, T.; Chattopadhyay, S. K. *Org. Lett.* **2011**, *13*, 5128. b) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370. c) Cheng, G.; Wang, X.; Su, D.; Liu, F.; Hu, Y. *J. Org.Chem.* **2010**, *75*, 1911. d) Chandrasekhar, S.; Murali, R. V. N. S.; Reddy, Ch. R. *Tetrahedron Lett.* **2009**, *50*, 5686. e) Verkade, J. M. M.; van der Pijl, F.; Willems, M. M. J. H. P.; Quaedflieg, P. J. L. M.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2009**, *74*, 3207. f)Weymann, M.; Kunz, H. Z. *Naturforschung B. Chem. Sci.* **2008**, *63*, 425. g) Lim, J.; Kim, G. *Tetrahedron Lett.* **2008**, *49*, 88. h) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 967. i) Zaja, M.; Blechert, S. *Tetrahedron* **2004**, *60*, 9629. j) Gracias, V.; Zeng, Y.; Desai, P.; Aube, J. *Org. Lett.* **2003**, *5*, 4999. k) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927. l) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623. m) Ukaji, Y.; Imai, M.; Yamada, T.; Inomata, K. *Heterocycles* **2000**, *52*, 563. n) Charlard, P.; Remuson, R.; Gelas-Mialhe, Y; Gramain, J. –C. *Tetrahedron*: *Asymmetry* **1998**, *9*, 4361. Formal enantioselective syntheses of Lasubine II: o) Shi, S. –L; Wei, X, -F, *J. Am. Chem. Soc.* **2010**, *132*, 12216. p) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216. q) Coldham, I.; Leonori, D.; *J. Org.Chem.* **2010**, *75*, 4069.

4) Reddy, A. A.; Reddy, P. O.; Prasad, K. R. *J. Org. Chem.* **2016**, *81*, 11363.

5) Shan, Z. –H.; Liu, J.; Xu, L, -M.; Tang, Y. –F.; Chen, J. –H.; Yang, Z. *Org. Lett.* **2012**, *14*, 3712.

6) James, M. J.; Niall D. G.; O'Brien, P.; Taylor, J. K.; Unsworth, W. P. *Org. Lett.* **2016**, *18*, 6256.

7) Epimerisation of the C4 stereocenter: Pilli, R. A.; Dias, L. C.; Maldaner, A.O. *J. Org. Chem.* **1995**, *60*, 717. For inversion of the C2 stereocenter, see ref 3k.

8) For the stereoselective reduction of 2,6-disubstituted, 2,3,4,5-tetrahydropyridines to *cis* 2,6-disubstituted piperidines, see Ryckman, D. M.; Stevens, R. V. *J. Org. Chem.* **1987**, *52*, 4274.

9) Selected recent reports: a) Martin, T. J.; Rovis, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 5368. b) Shi, S, -L.; Wei, X. –F.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2012**, *134*, 17019. c) Daly, M.; Cant, A. A.; Fowler, L. S.; Simpson, G. L.; Senn, H. M.; Sutherland, A. *J. Org.Chem.* **2012**, *77*, 10001. d) Marca, E.; Delso, I.; Tejero, T.; Merino, P. *Tetrahedron* **2012**, *68*, 6674. e) Cui, L.; Li, C.; Zhang, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9178. F) Leflemme, N.; Freret, T.; Boulouard, M.; Dallemagne, P.; Rault, S. *J. Enzym. Inhib. Med. Chem.* **2005**, *20*, 551.

10) The enantiomeric excess of the minor diastereomers is typically low (50-55% ee). Treatment of pure **83** (92% ee) with catalyst **82** (20 mol%) in the presence of ketone **80** (5 equiv) did not result in any loss of enantiomeric excess of **83** under the conditions employed for the Michael addition. The minor diastereomer could not be detected in this reaction mixture. These observations suggest that the Michael adduct

83 does not revert back to **80** and the nitroalkene and also that the minor diastereomer is not obtained by the epimerization of the major diastereomer under the reaction conditions.

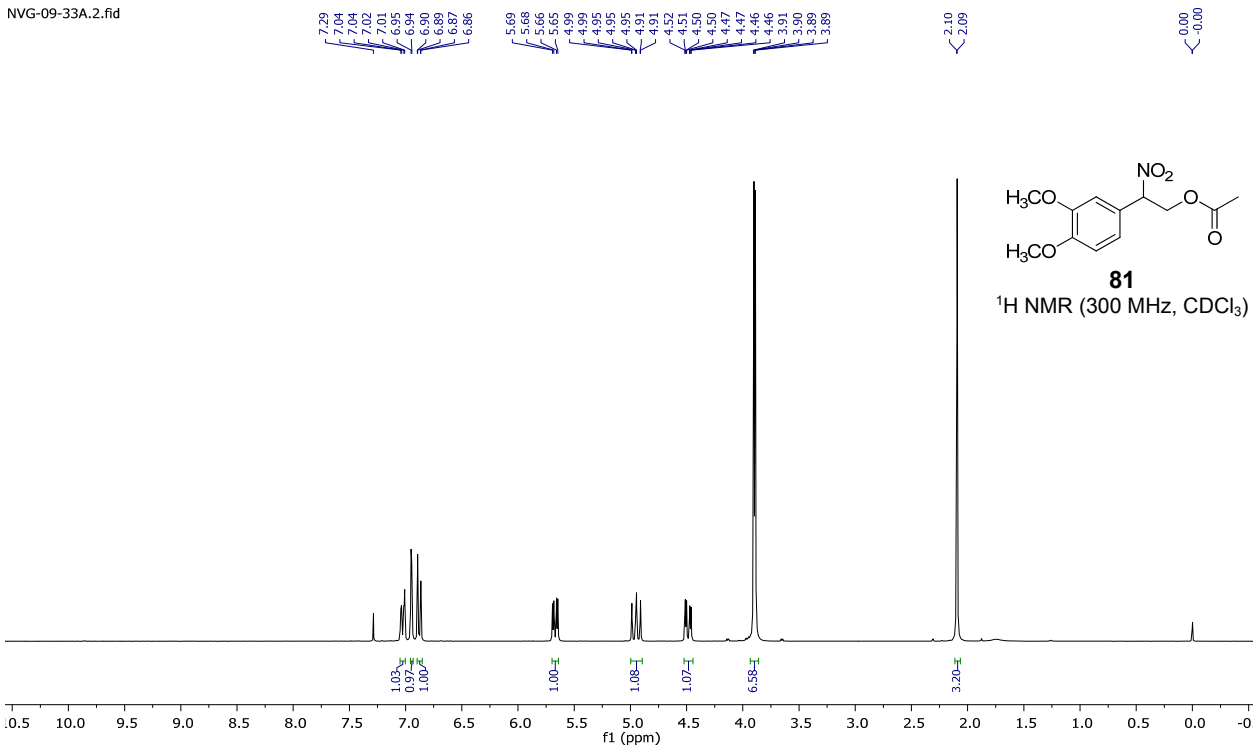
11) Gellert, B. A.; Kahlke, N.; Feurer, M.; Roth, S. *Chem. –Eur. J.* **2011**, *17*, 12203.

12) Ali, S. A.; Hashmi, S. M. A.; Siddiqui, M. N.; Wazeer, M. I. M. *Tetrahedron* **1996**, *52*, 14917.

13) DMEAD is reduced to a water –soluble hydrazine dicarboxylate, thereby simplifying the purification of **103**. a) Sugimura, T.; Hagiya, K. *Chem. Lett.* **2007**, *36*, 566. b) Hagiya, K.; Muramoto, N.; Misaki, T.; Sugimura, T. *Tetrahedron* **2009**, *65*, 6109. DMEAD is commercially available.

3.7 Selected ^{1}H NMR and ^{13}C NMR Spectra

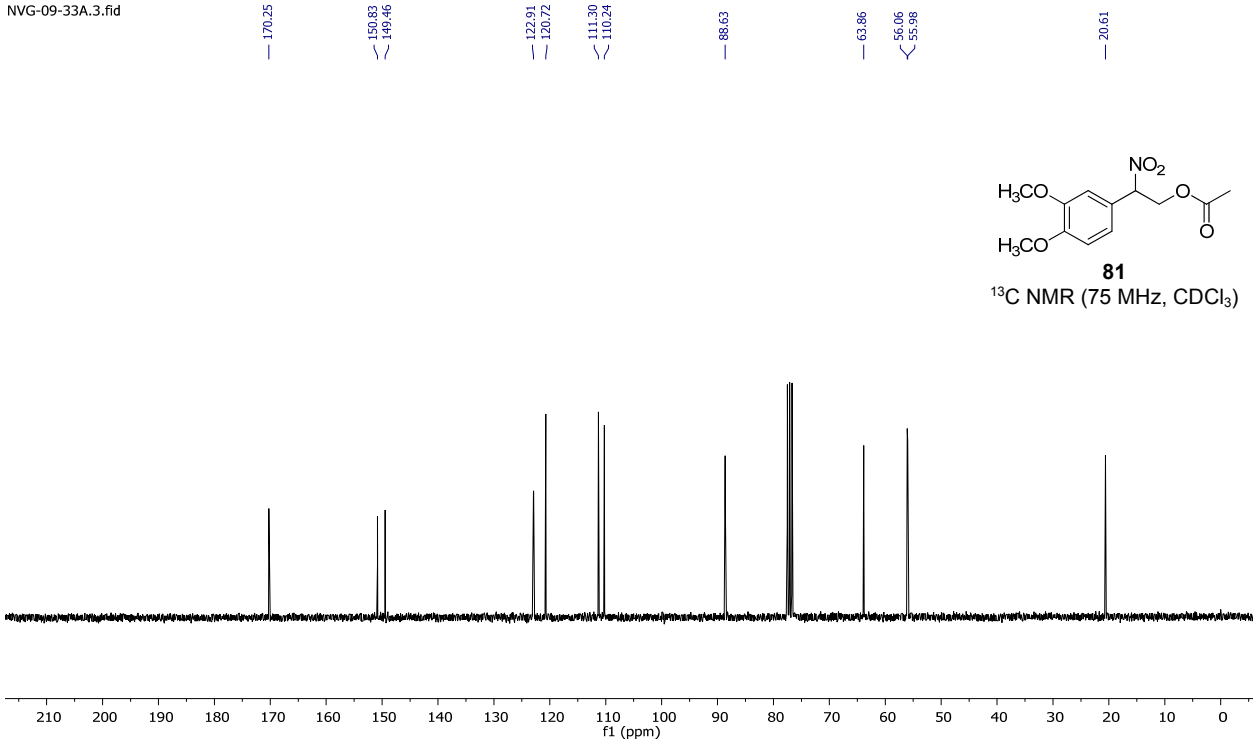
NVG-09-33A.2.fid



81

^{1}H NMR (300 MHz, $CDCl_3$)

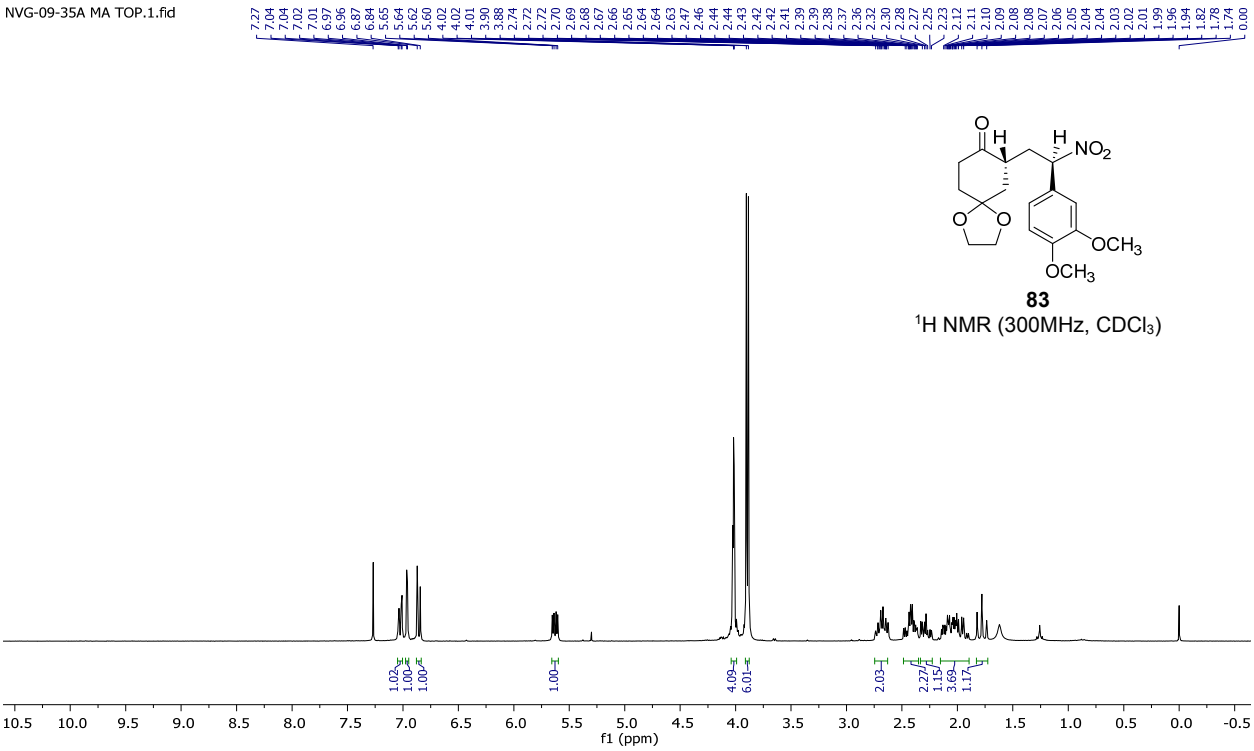
NVG-09-33A.3.fid



81

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

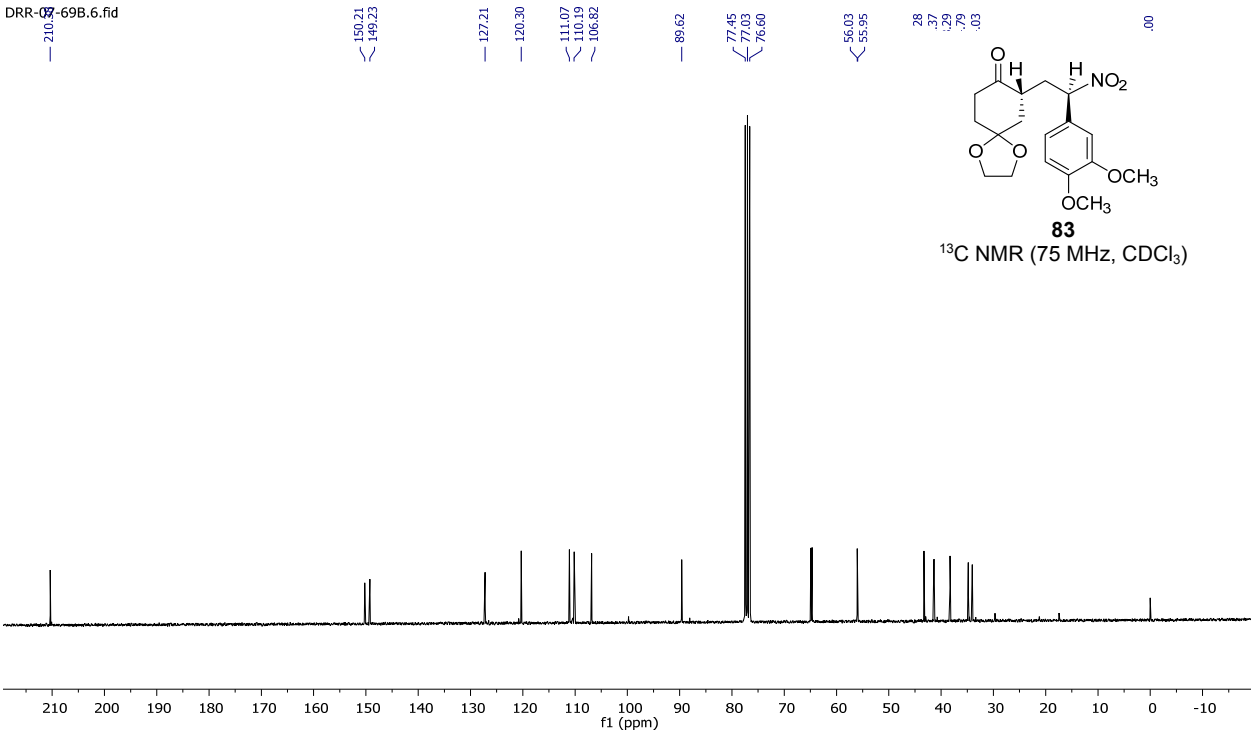
NVG-09-35A MA TOP.1.fid



83

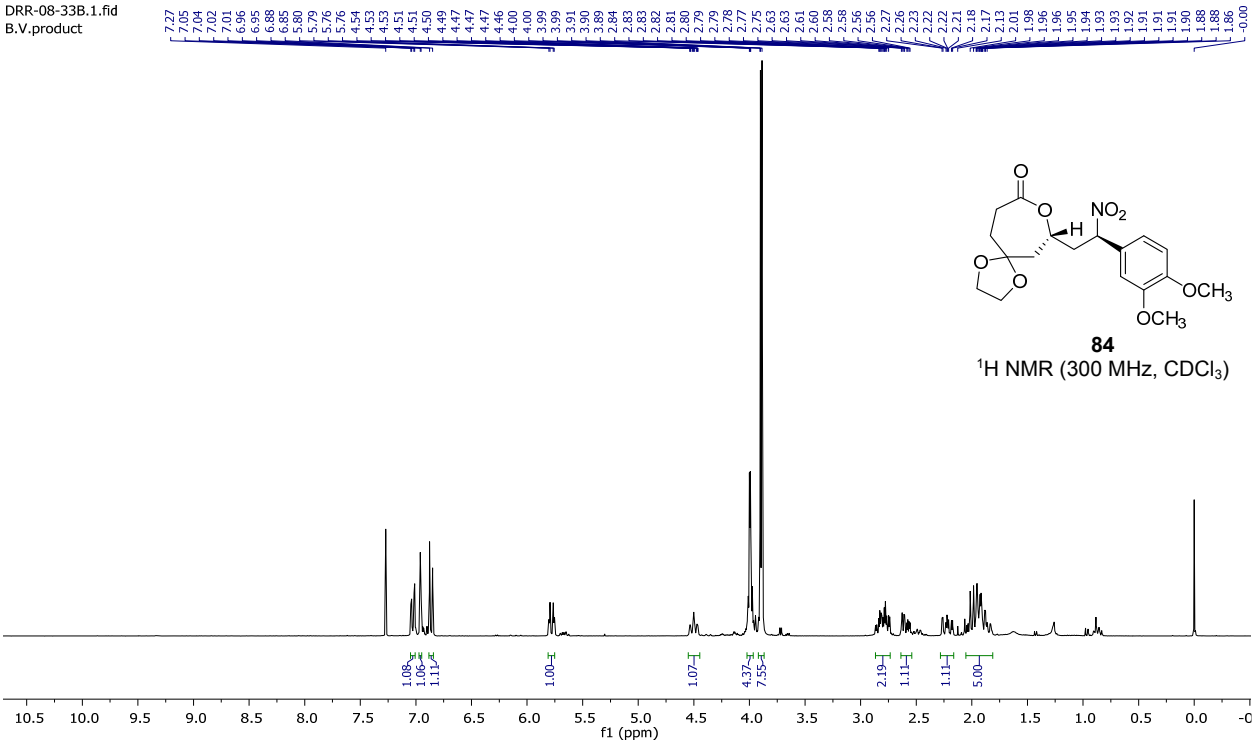
^{1}H NMR (300MHz, $CDCl_3$)

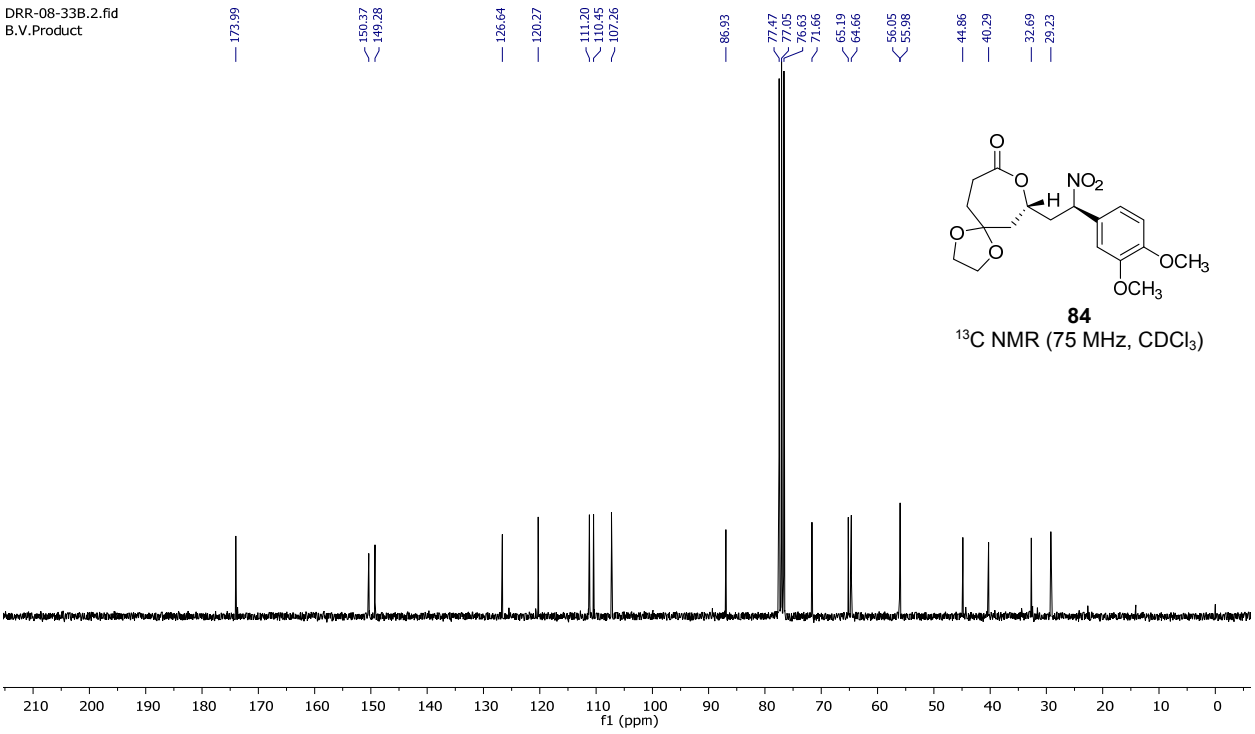
DRR-07-69B.6.fid



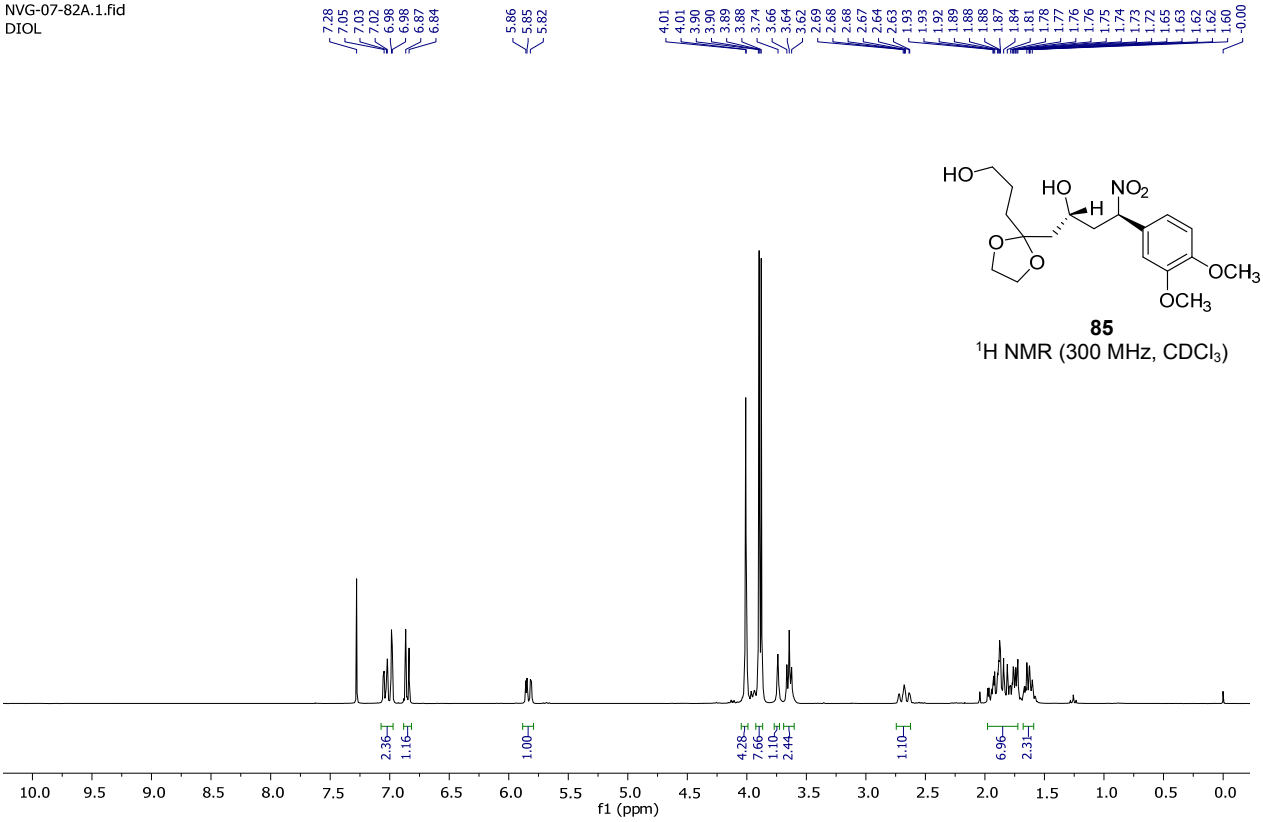
83

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


DRR-08-33B.1.fid
B.V.product
84
^{1}H NMR (300 MHz, CDCl$_3$)
f1 (ppm)


DRR-08-33B.2.fid
B.V.Product
84
^{13}C NMR (75 MHz, CDCl$_3$)
f1 (ppm)

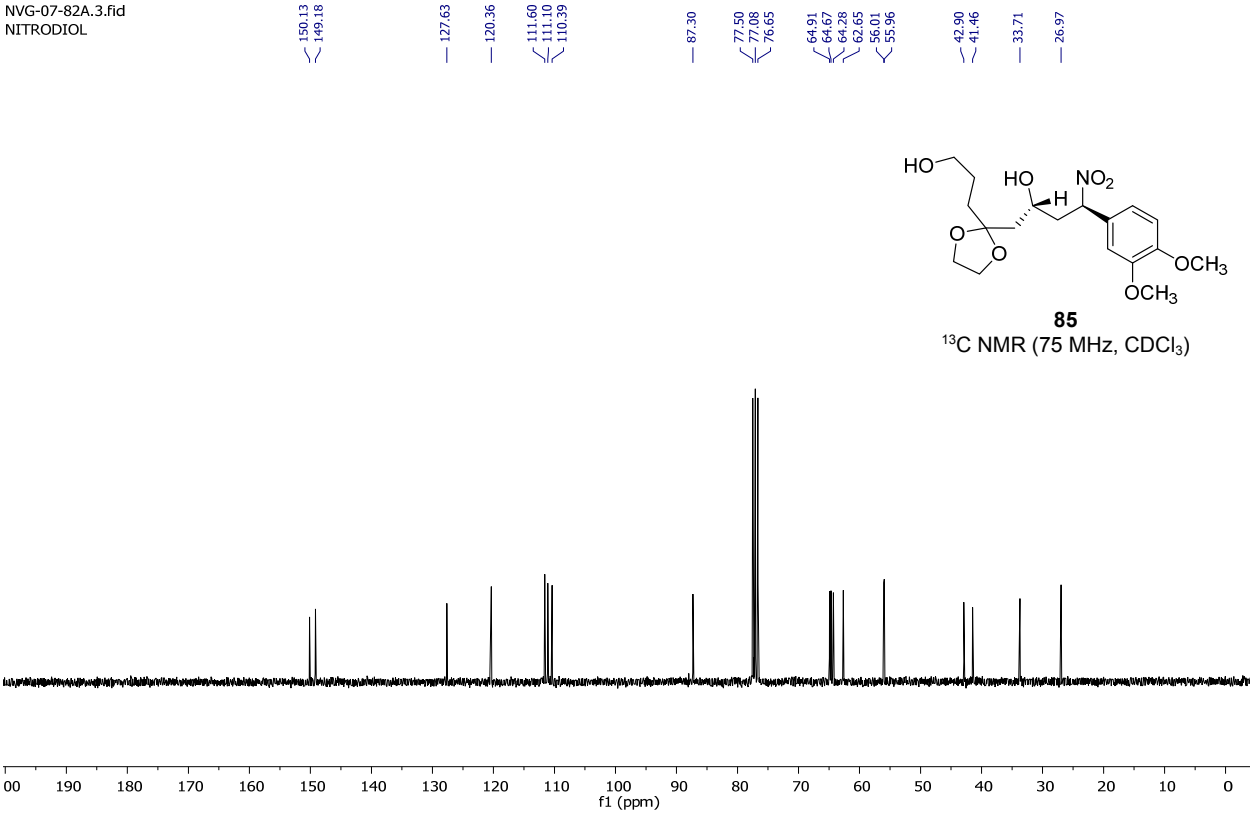
NVG-07-82A.1.fid
DIOL



85

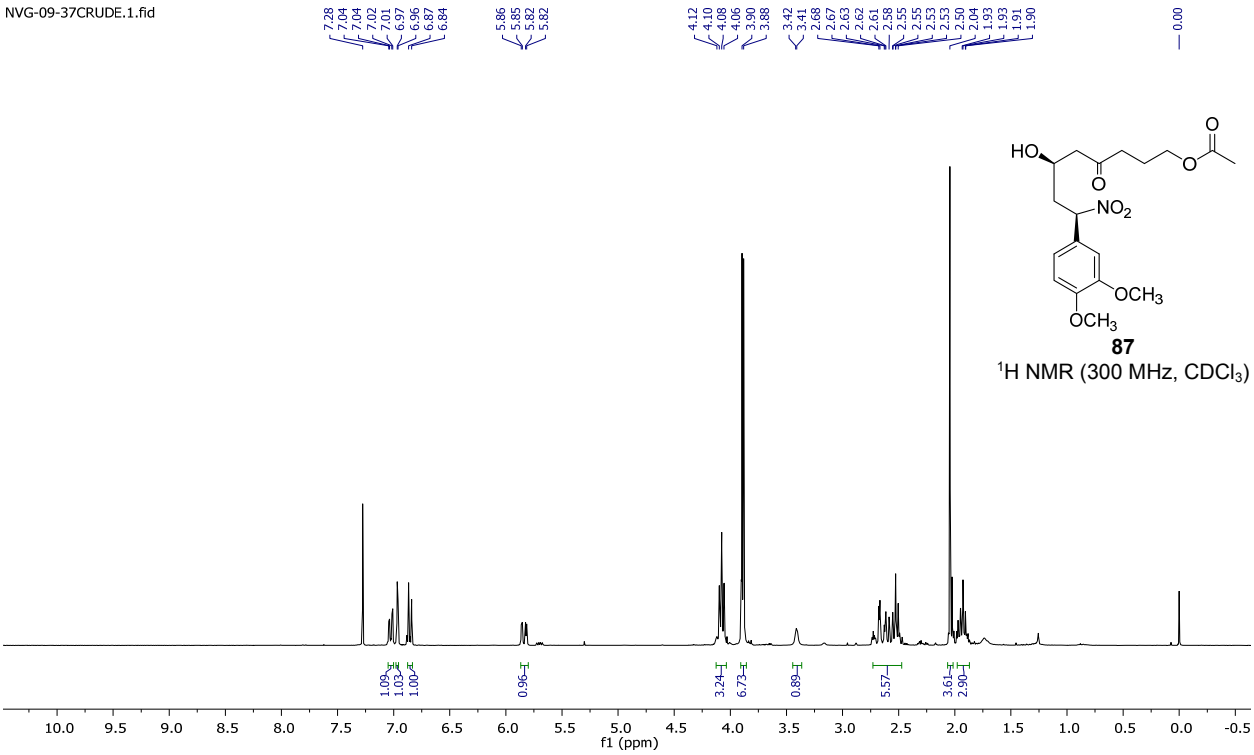
^{1}H NMR (300 MHz, $CDCl_3$)

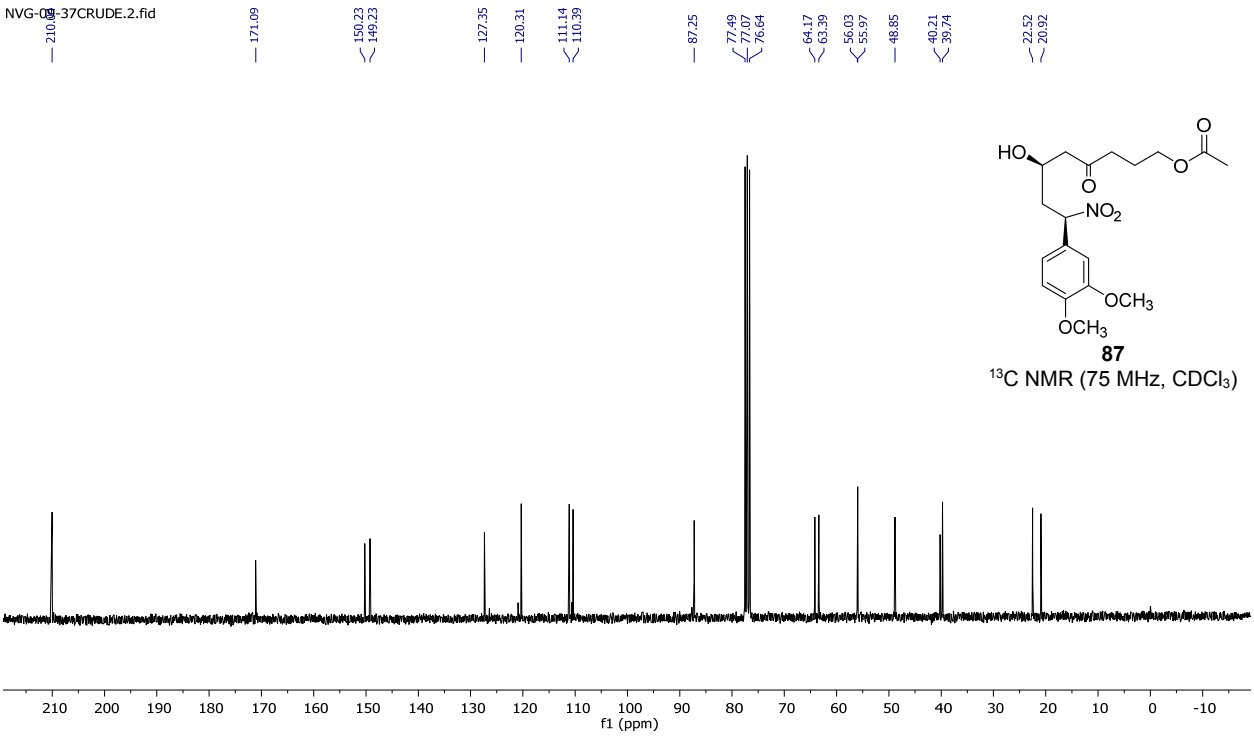
NVG-07-82A.3.fid
NITRODIOL

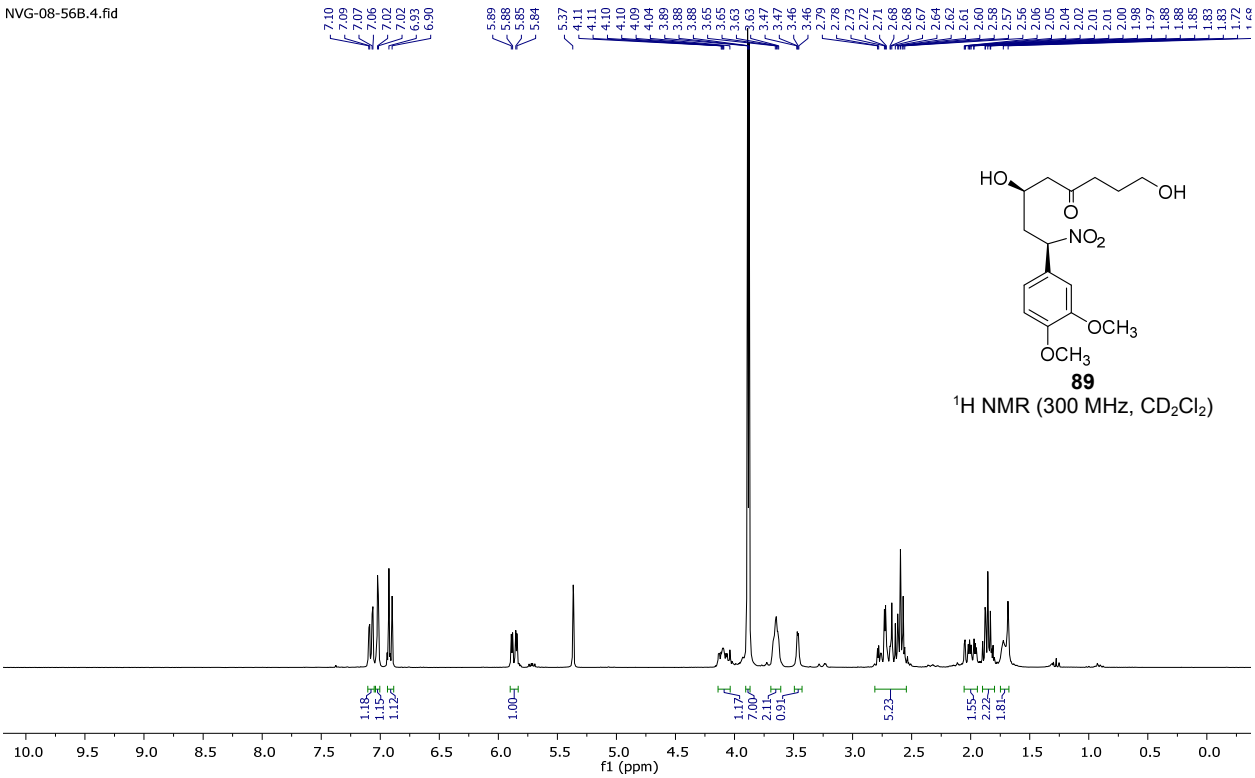


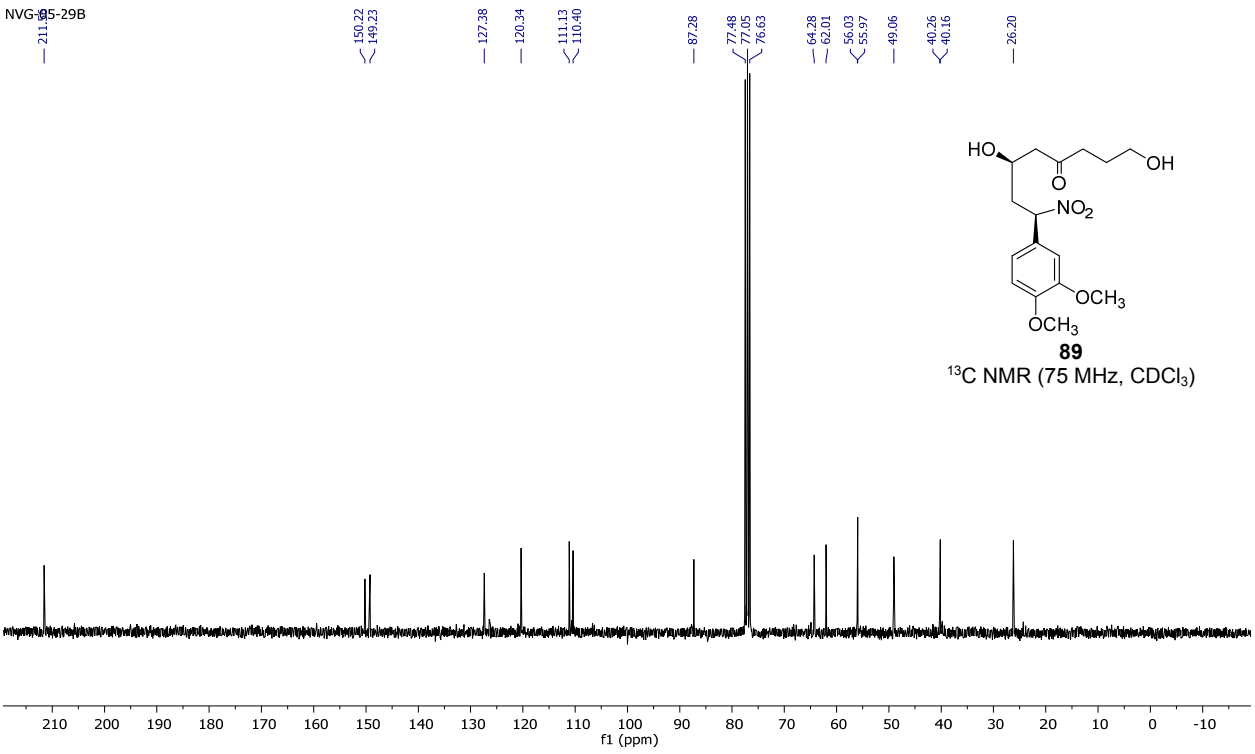
85

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

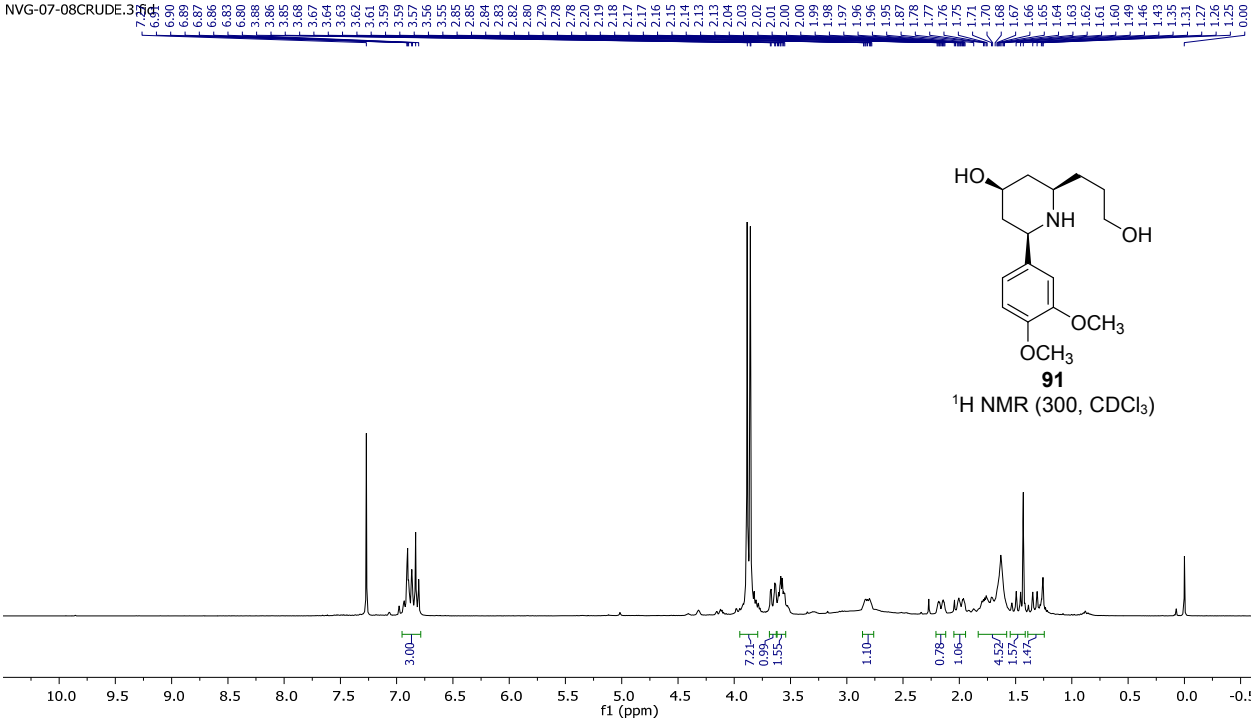

NVG-09-37CRUDE.1.fid
7.28
7.04
7.04
7.02
7.01
6.97
6.96
6.87
6.84
5.86
5.85
5.82
5.82
4.12
4.10
4.08
4.06
3.90
3.88
3.42
3.41
2.68
2.67
2.63
2.62
2.61
2.58
2.55
2.55
2.53
2.53
2.50
2.04
1.93
1.93
1.91
1.90
0.00
HO
O
O
O
NO2
OCH3
OCH3
87
1H NMR (300 MHz, CDCl3)
1.09
1.03
1.00
0.96
3.24
6.73
0.89
5.57
3.61
2.90
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 -0.5
f1 (ppm)


NVG-09-37CRUDE.2.fid
210.04
171.09
150.23
149.23
127.35
120.31
111.14
110.39
87.25
77.49
77.07
76.64
64.17
63.39
56.03
55.97
48.85
40.21
39.74
22.52
20.92
HO
O
O
O
NO2
OCH3
OCH3
87
13C NMR (75 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


NVG-08-56B.4.fid
HO
OH
O
NO2
OCH3
OCH3
89
1H NMR (300 MHz, CD2Cl2)
f1 (ppm)


NVG-05-29B
HO
OH
O
NO2
OCH3
OCH3
89
13C NMR (75 MHz, CDCl3)
f1 (ppm)

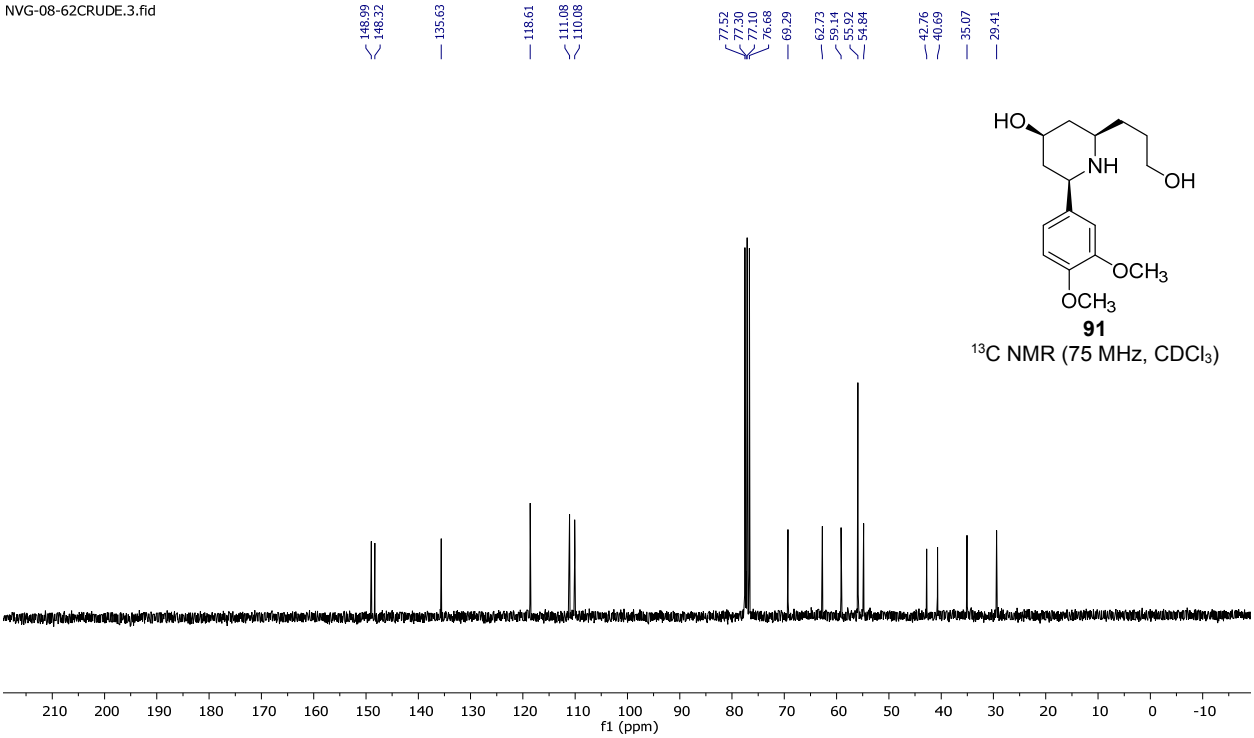
NVG-07-08CRUDE.3.fid



91

^{1}H NMR (300, $CDCl_3$)

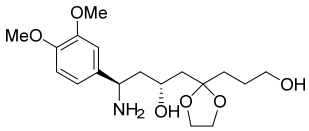
NVG-08-62CRUDE.3.fid



91

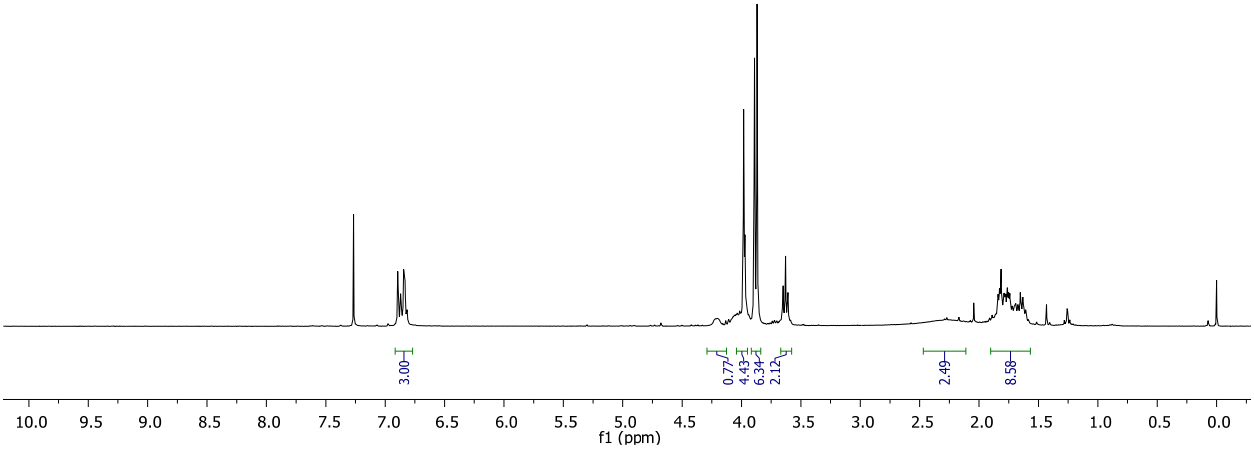
^{13}C NMR (75 MHz, $CDCl_3$)

NVG-05-85CRUDE
REDUCTION

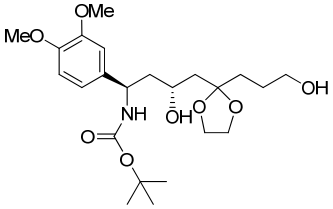


96

^{1}H NMR (300 MHz, $CDCl_3$)

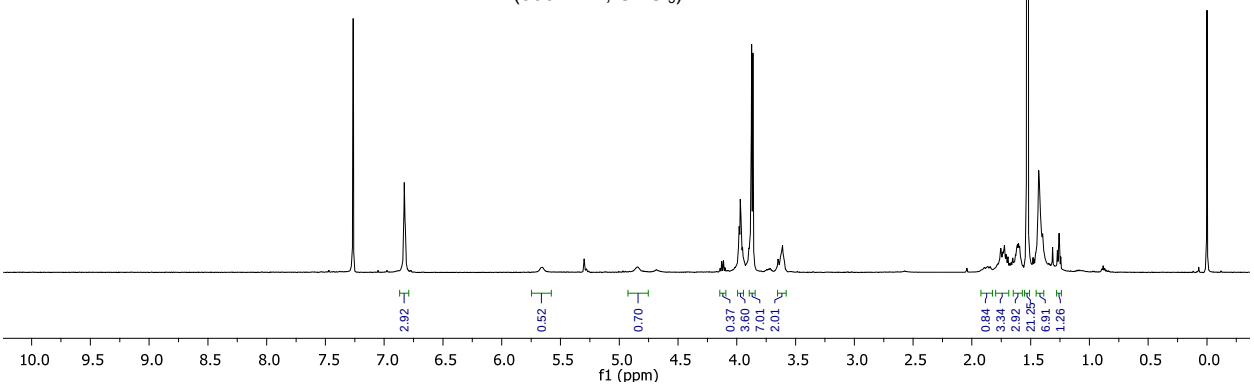


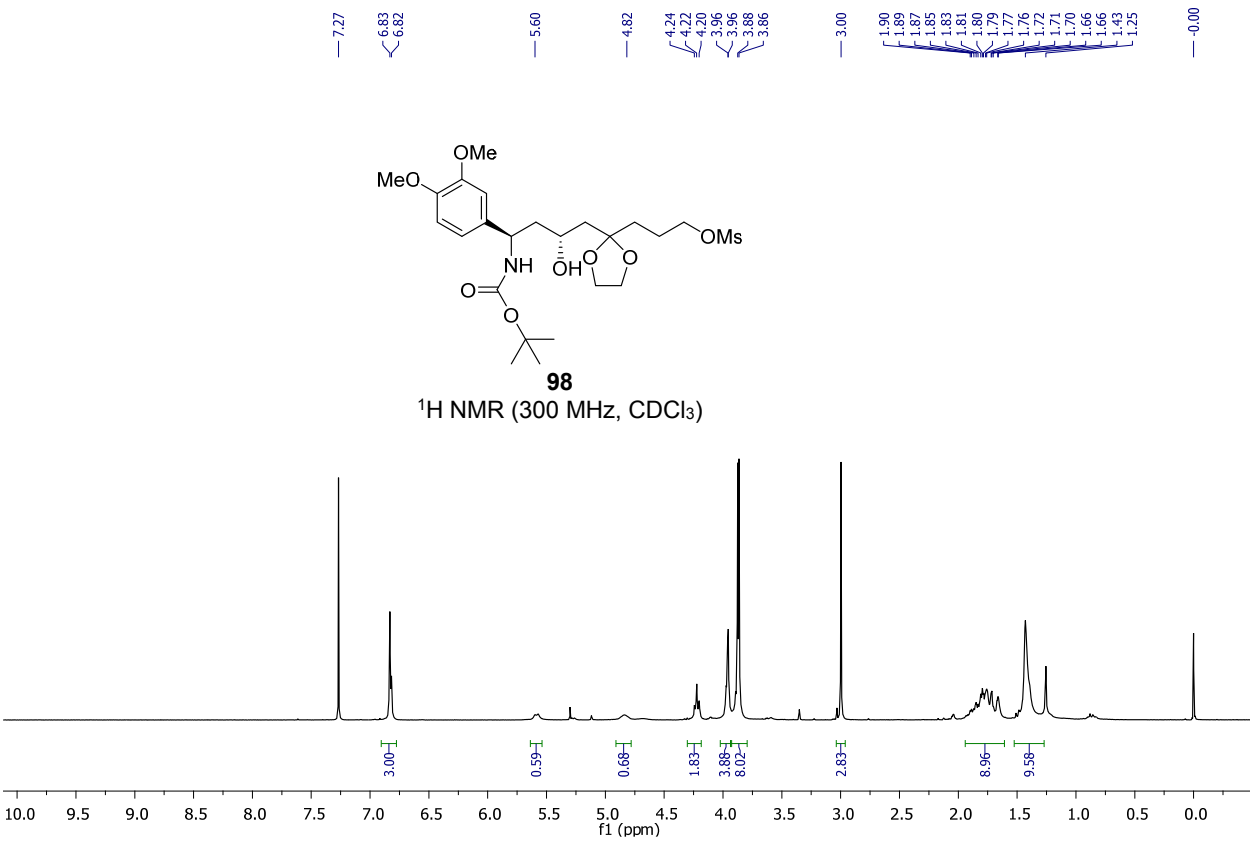
NVG4835/1
NVG-05-91 BOC PROTECTION



97

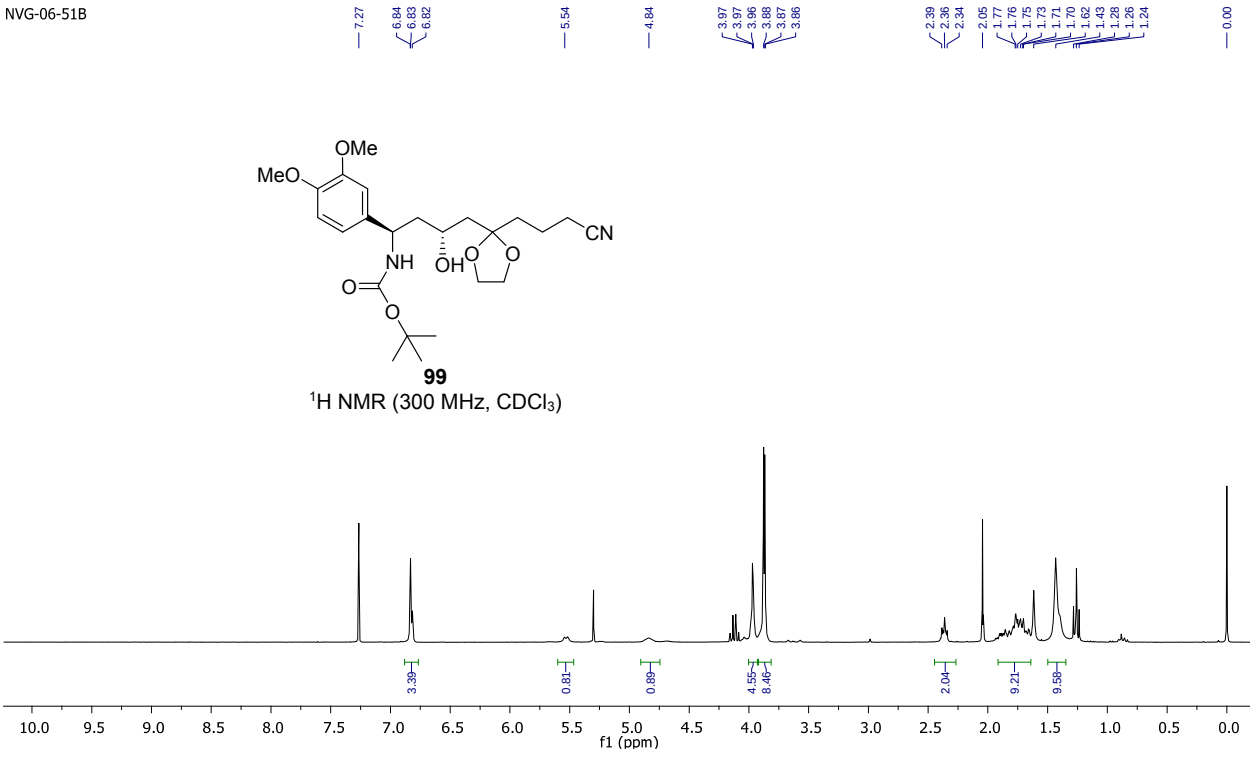
^{1}H NMR (300 MHz, $CDCl_3$)





98

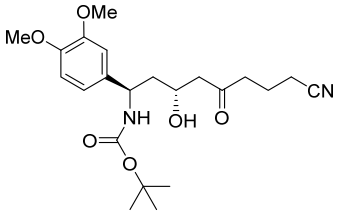
^{1}H NMR (300 MHz, $CDCl_3$)



99

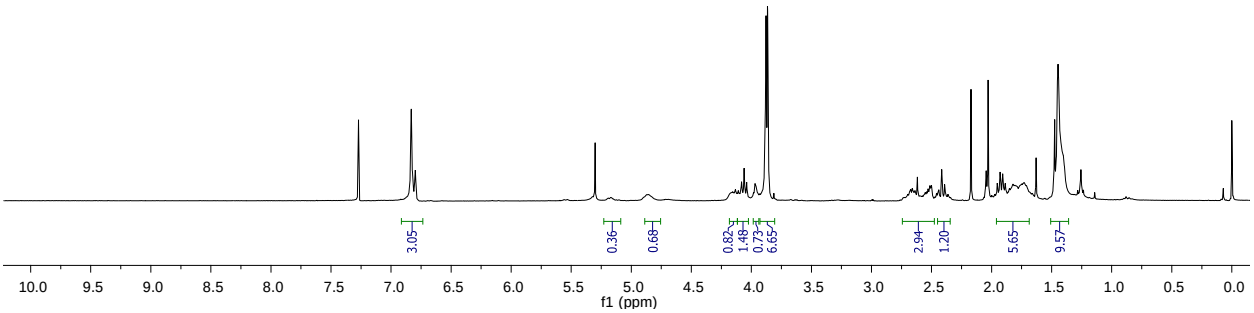
^{1}H NMR (300 MHz, $CDCl_3$)

NVG-06-57 CRUDE
DEPROTECTION

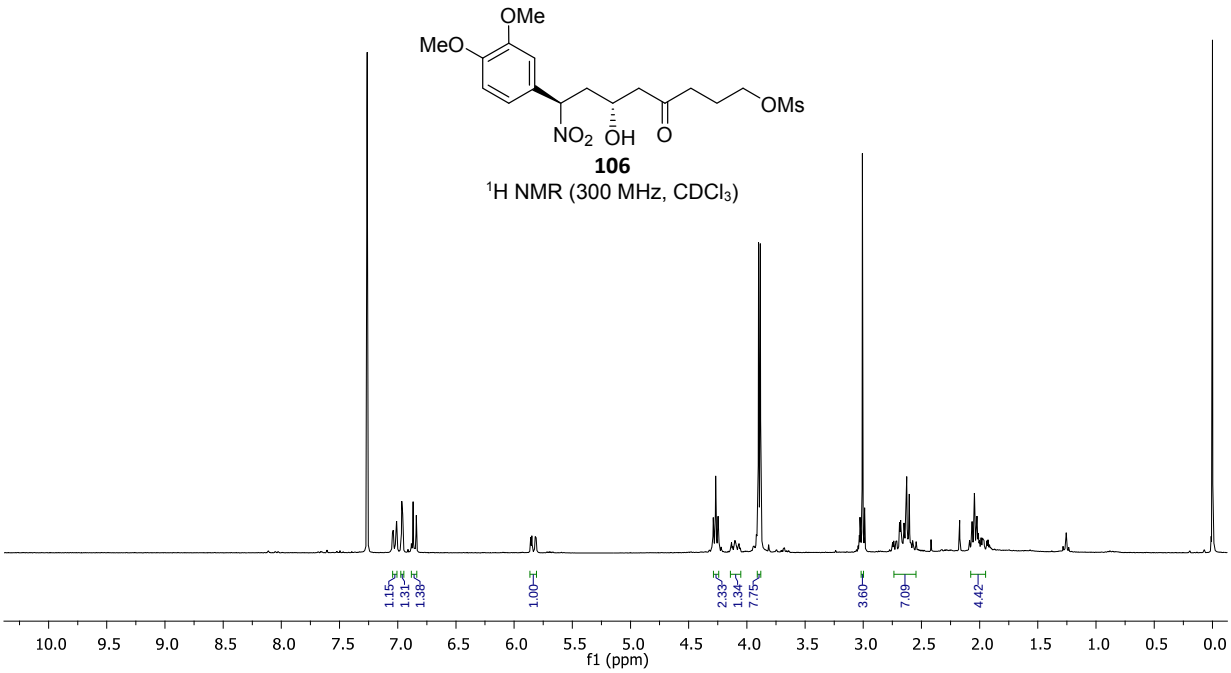


100

^{1}H NMR (300 MHz, $CDCl_3$)

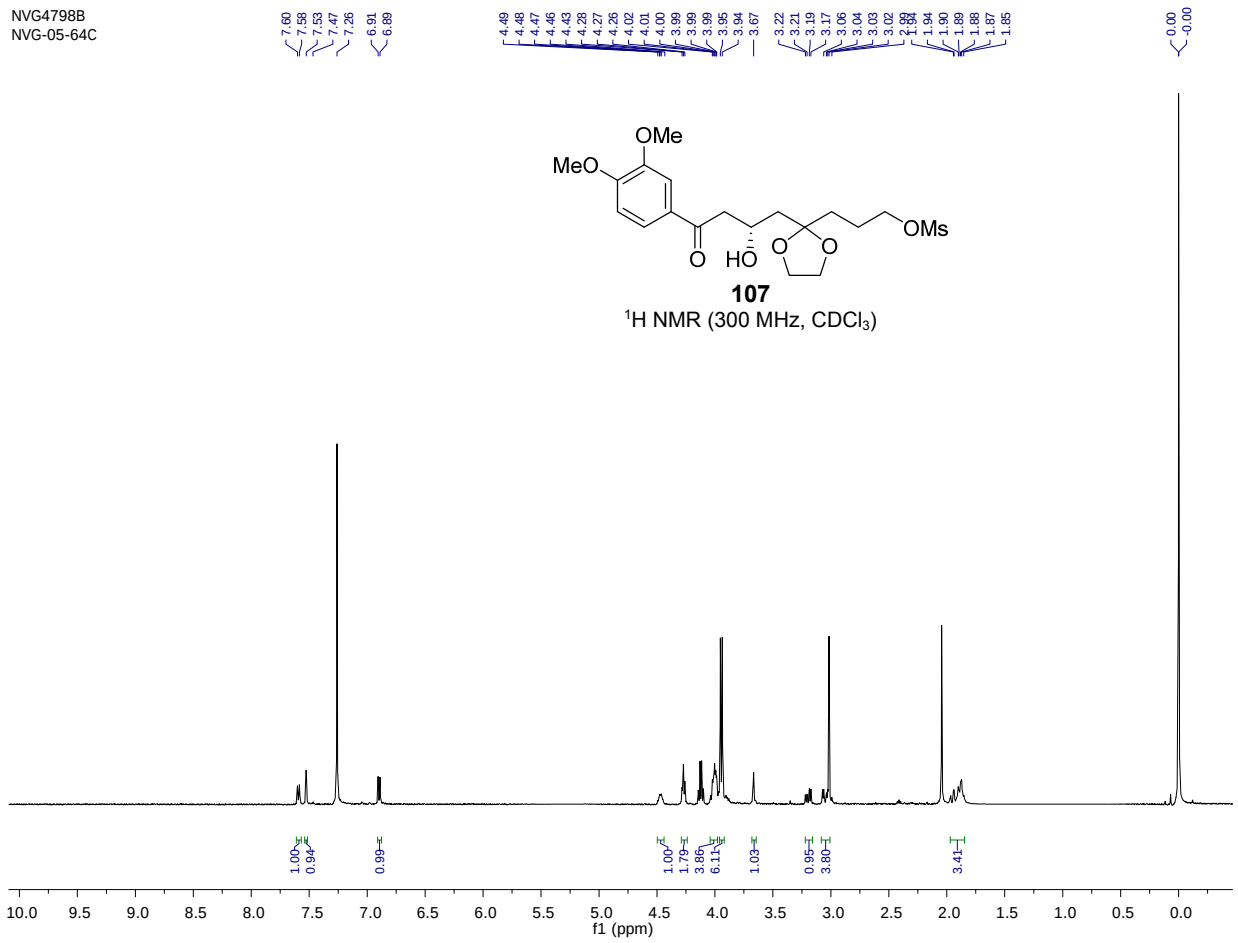


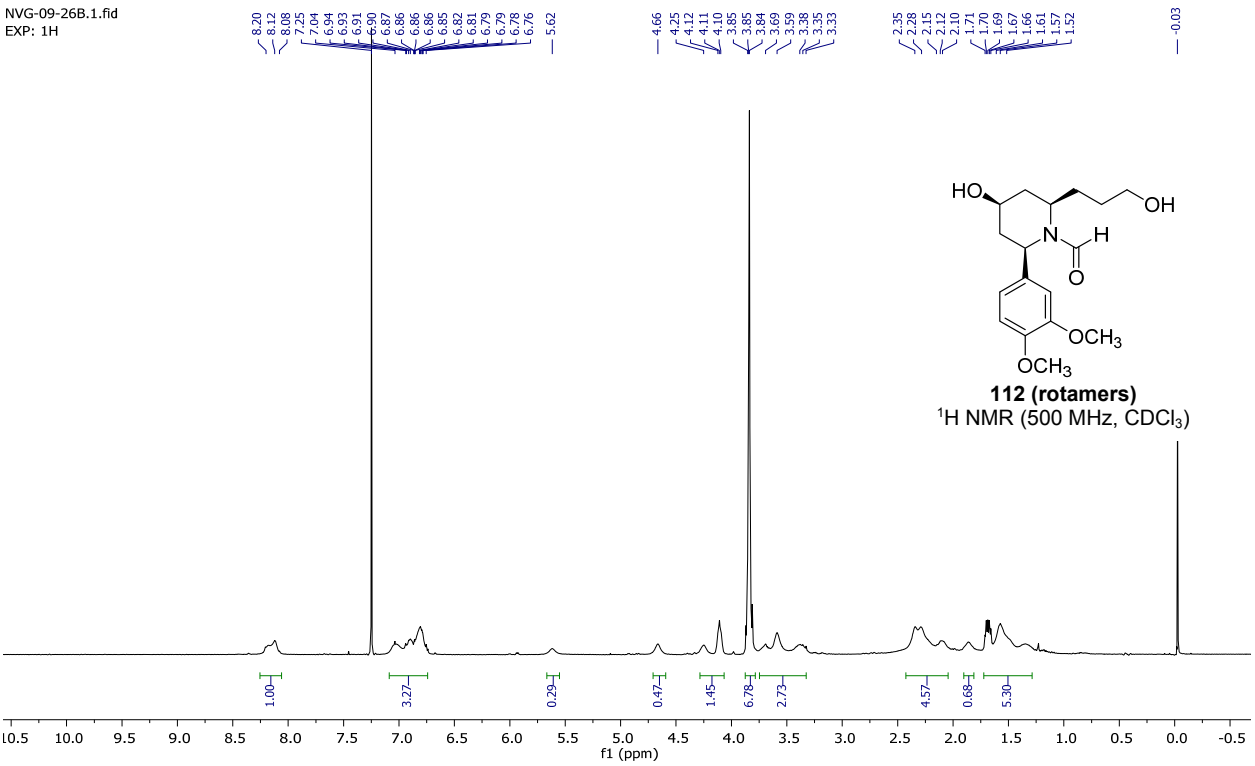
NVG-06-96CRUDE

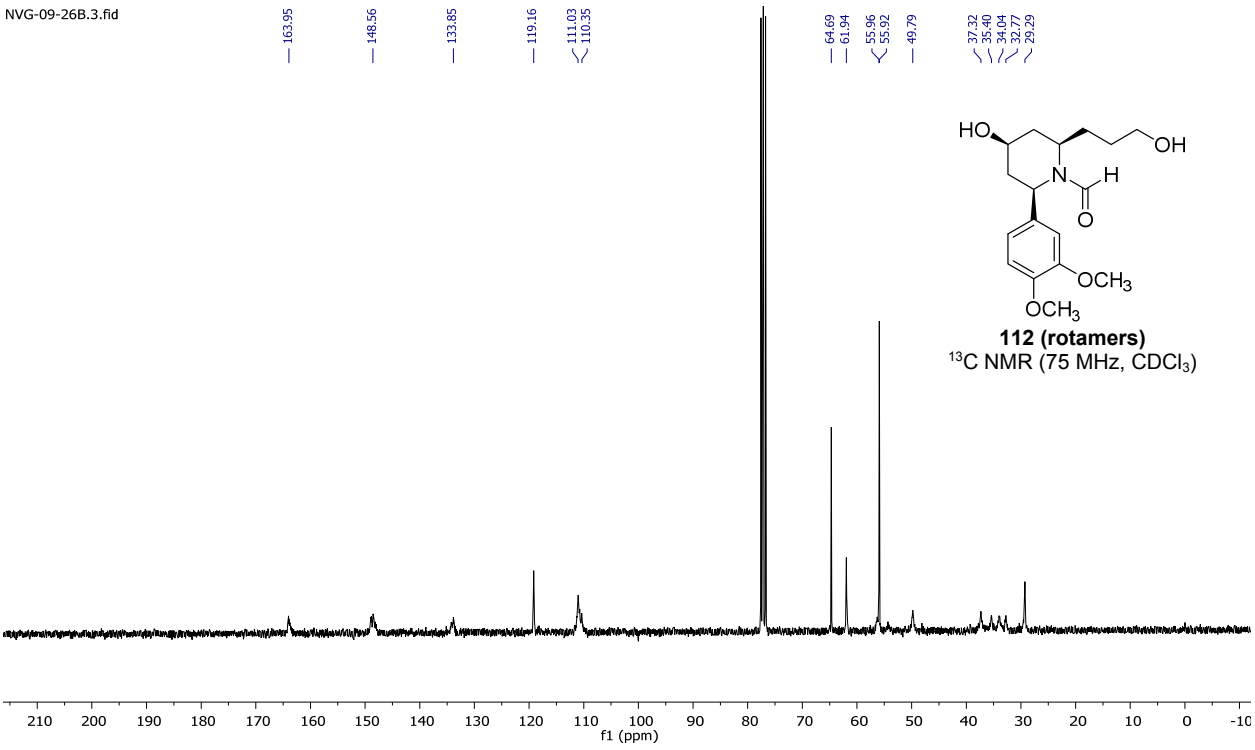


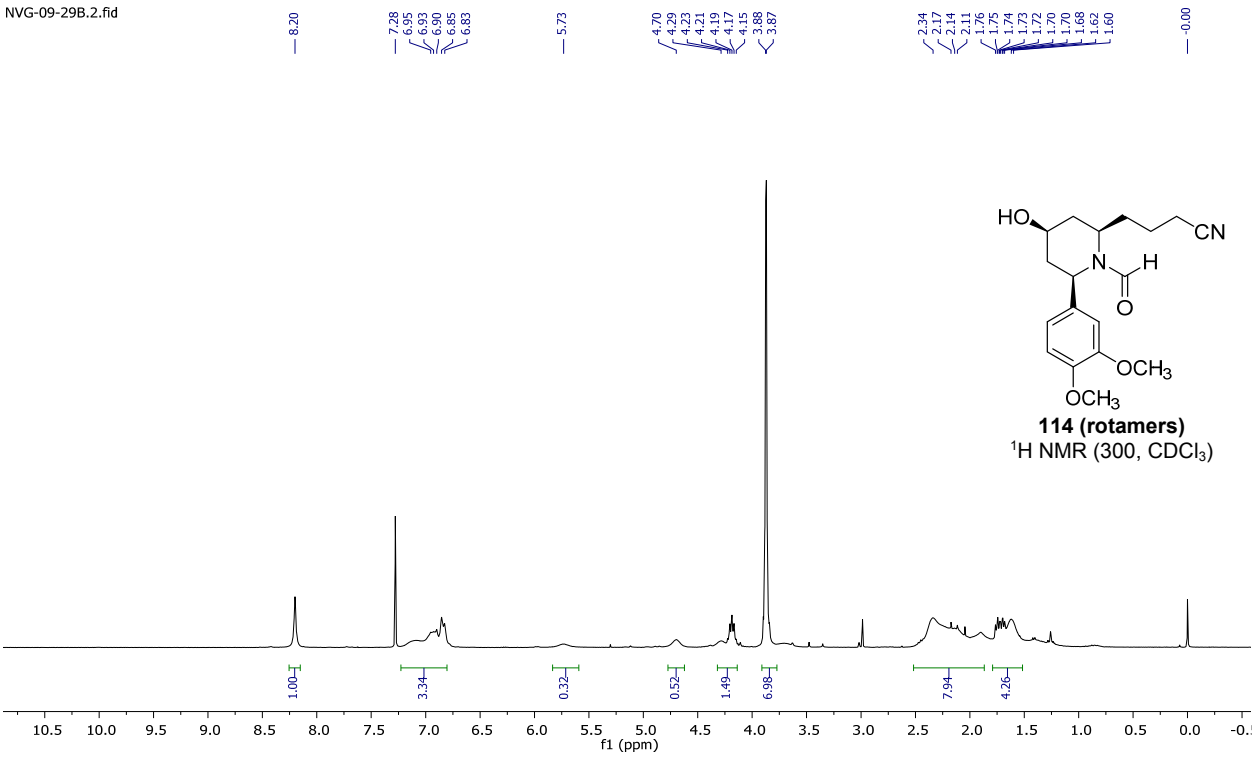
106

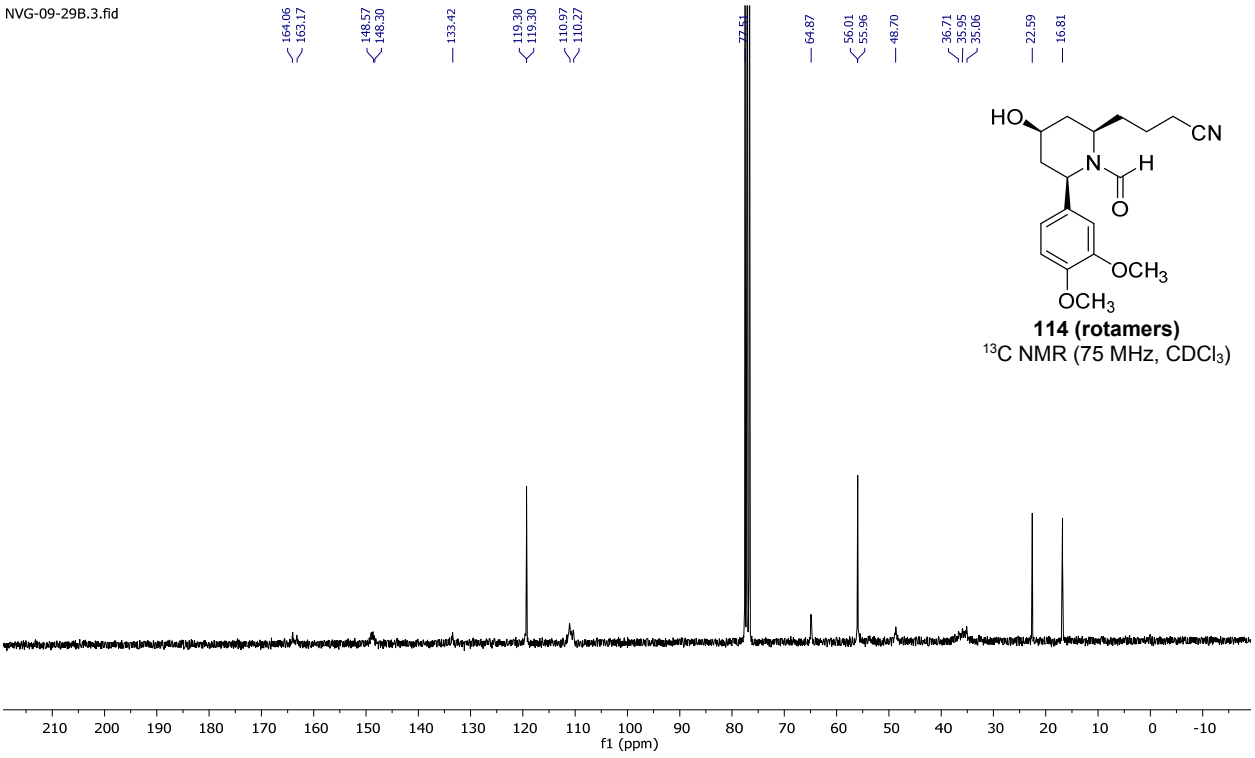
^{1}H NMR (300 MHz, $CDCl_3$)


NVG4798B
NVG-05-64C
OMe
MeO
OMs
O
HO
O
O
107
1H NMR (300 MHz, CDCl3)
f1 (ppm)

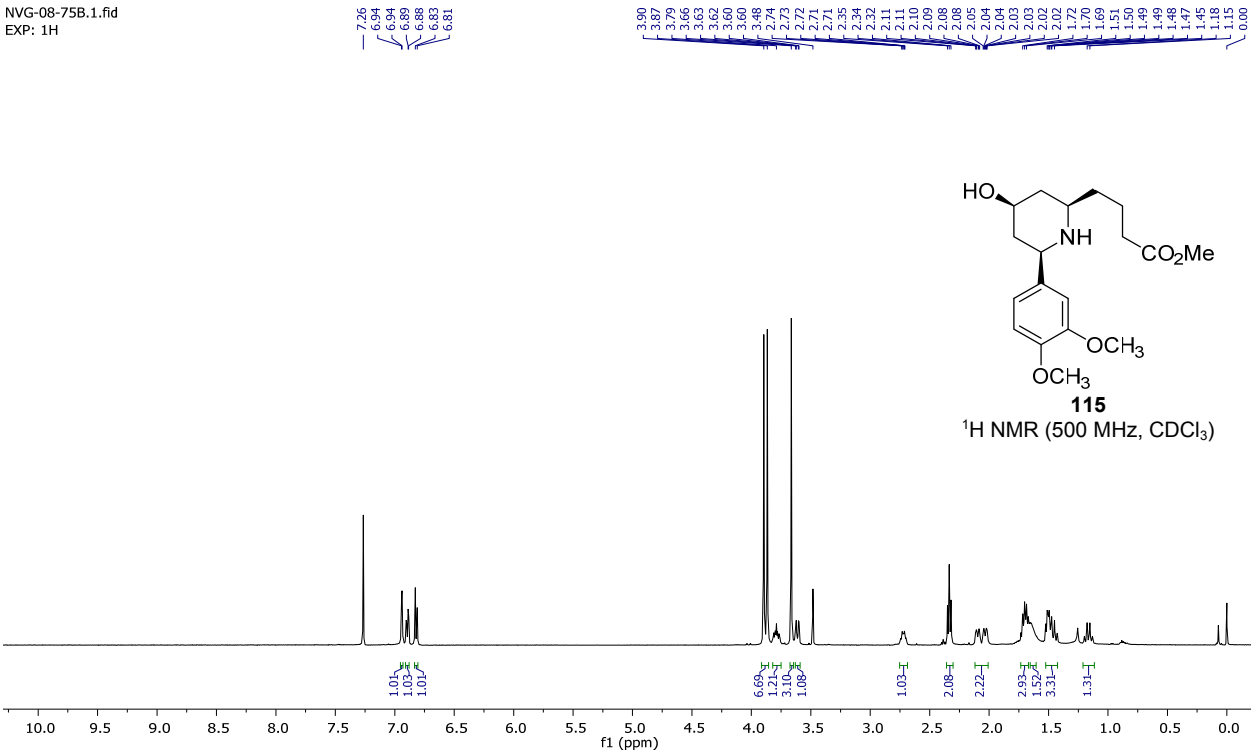

NVG-09-26B.1.fid
EXP: 1H
HO
OH
N
H
O
OCH3
OCH3
112 (rotamers)
1H NMR (500 MHz, CDCl3)
f1 (ppm)


NVG-09-26B.3.fid
HO
OH
N
H
O
OCH3
OCH3
112 (rotamers)
13C NMR (75 MHz, CDCl3)
f1 (ppm)


NVG-09-29B.2.fid
8.20
7.28
6.95
6.93
6.90
6.85
6.83
5.73
4.70
4.29
4.23
4.21
4.19
4.17
4.15
3.88
3.87
2.34
2.17
2.14
2.11
1.76
1.75
1.74
1.73
1.72
1.70
1.70
1.68
1.62
1.60
-0.00
HO
CN
N
H
O
OCH3
OCH3
114 (rotamers)
1H NMR (300, CDCl3)
1.00
3.34
0.32
0.52
1.49
6.98
7.94
4.26
f1 (ppm)


NVG-09-29B.3.fid
164.06
163.17
148.57
148.30
133.42
119.30
119.30
110.97
110.27
77.51
64.87
56.01
55.96
48.70
36.71
35.95
35.06
22.59
16.81
HO
CN
N
H
O
OCH3
OCH3
114 (rotamers)
13C NMR (75 MHz, CDCl3)
f1 (ppm)

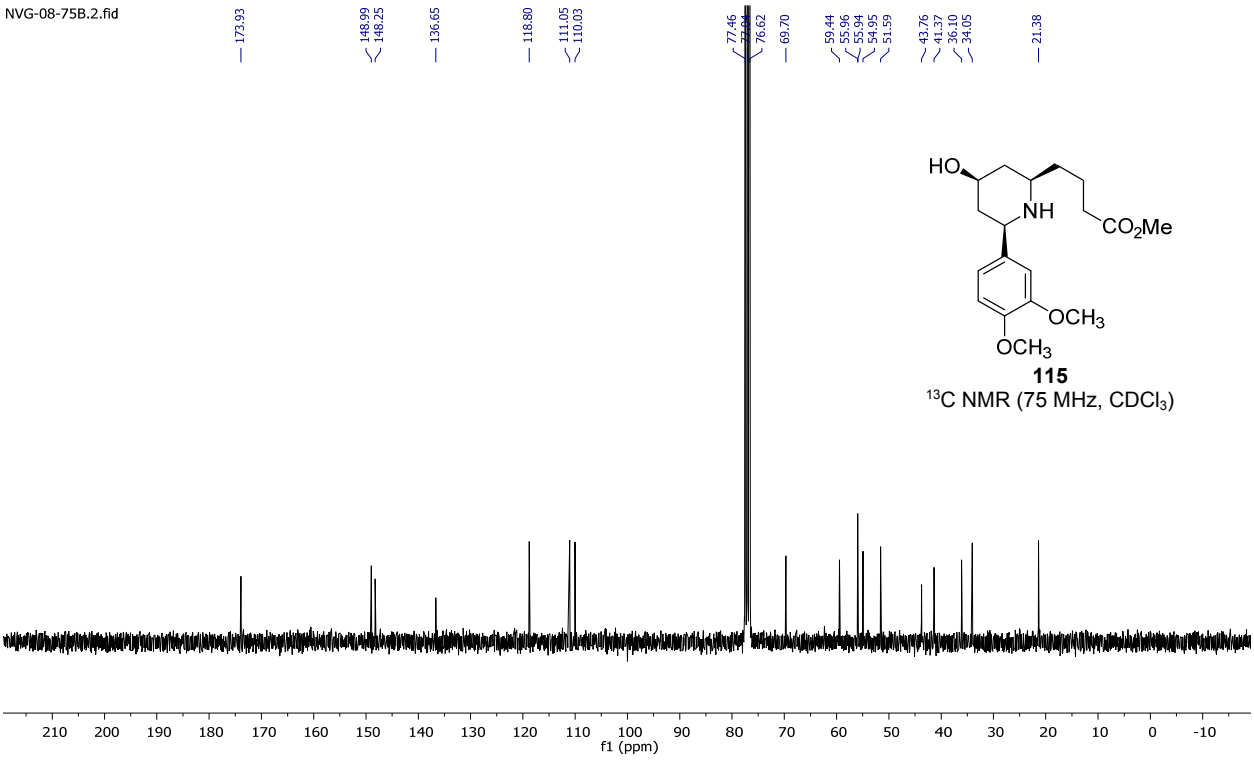
NVG-08-75B.1.fid
EXP: 1H



115

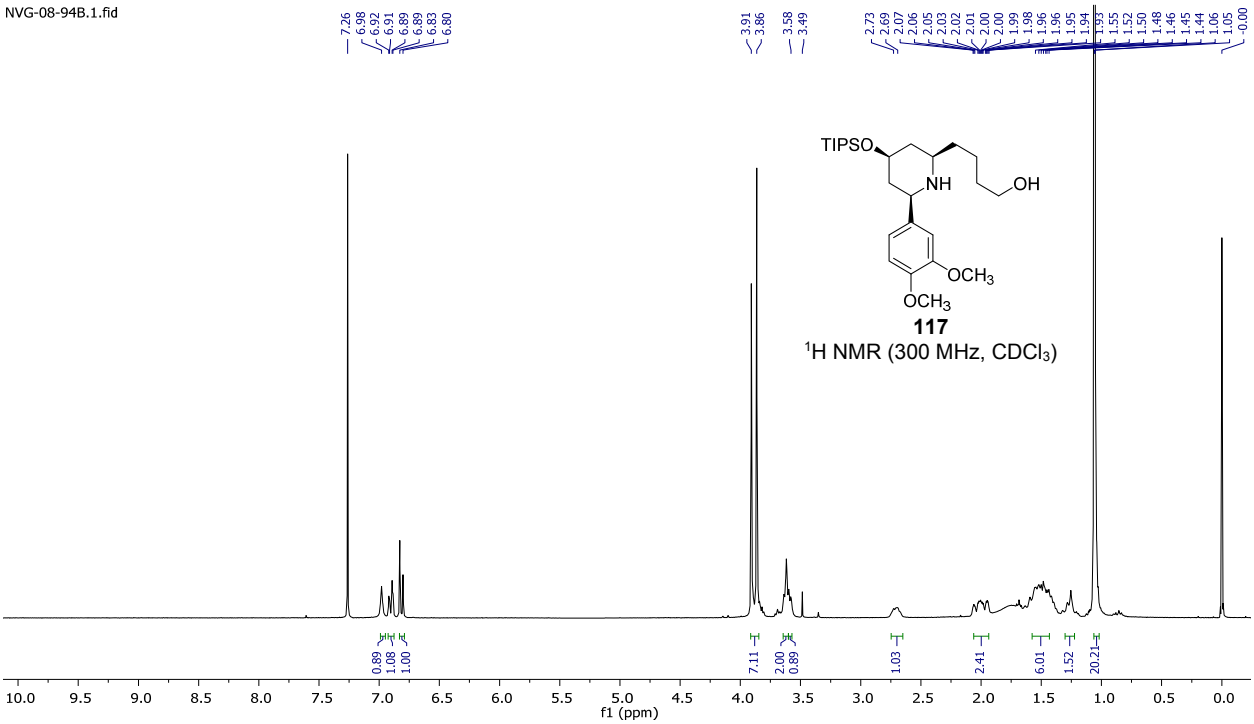
^{1}H NMR (500 MHz, $CDCl_3$)

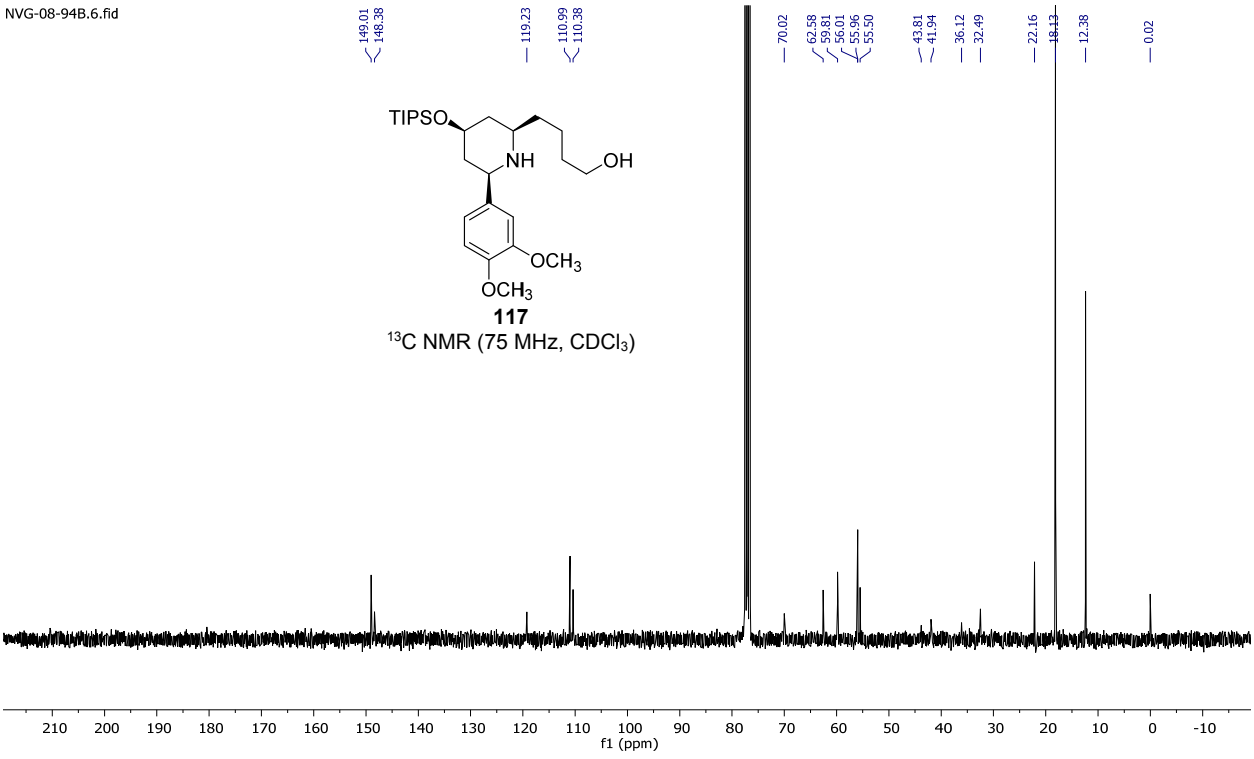
NVG-08-75B.2.fid

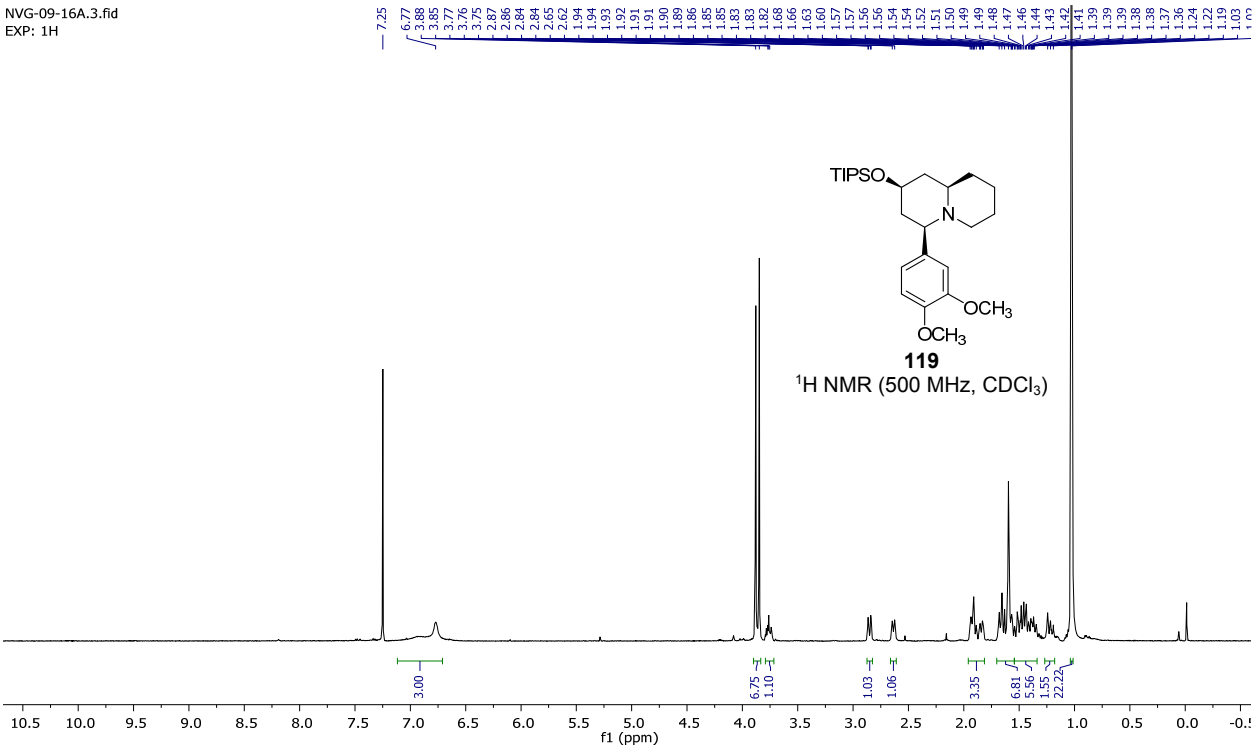


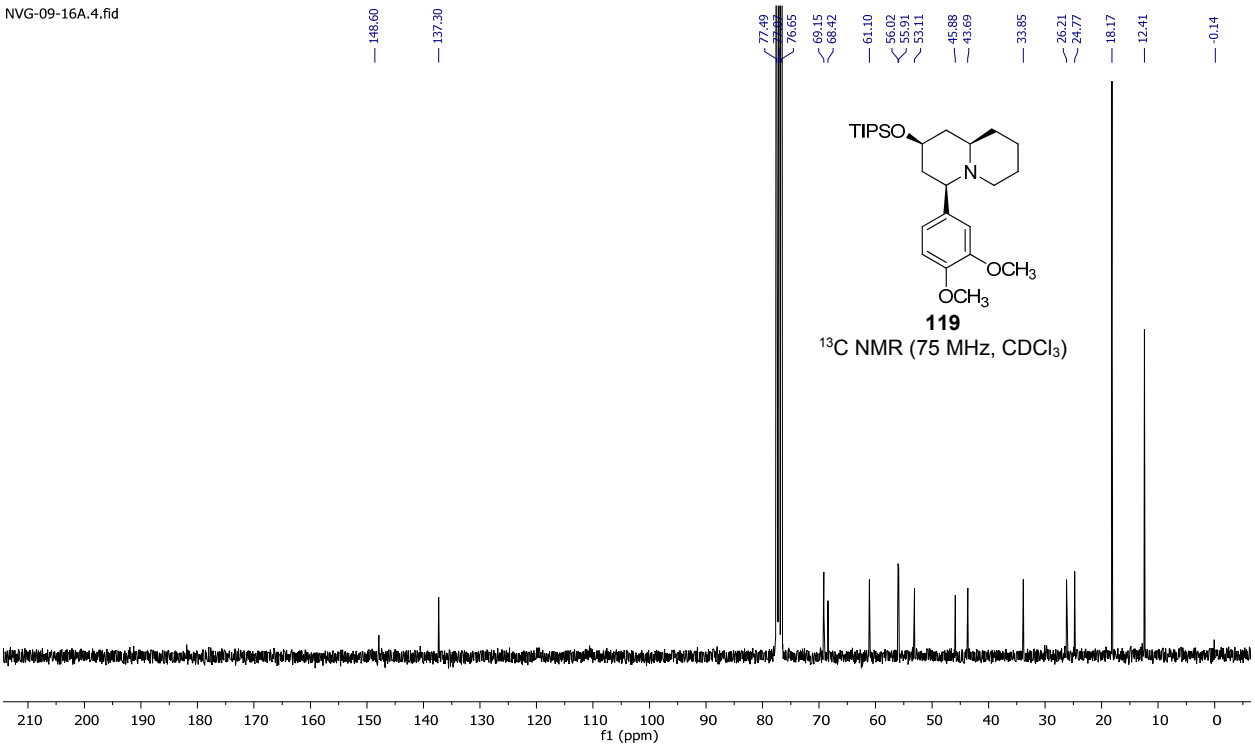
115

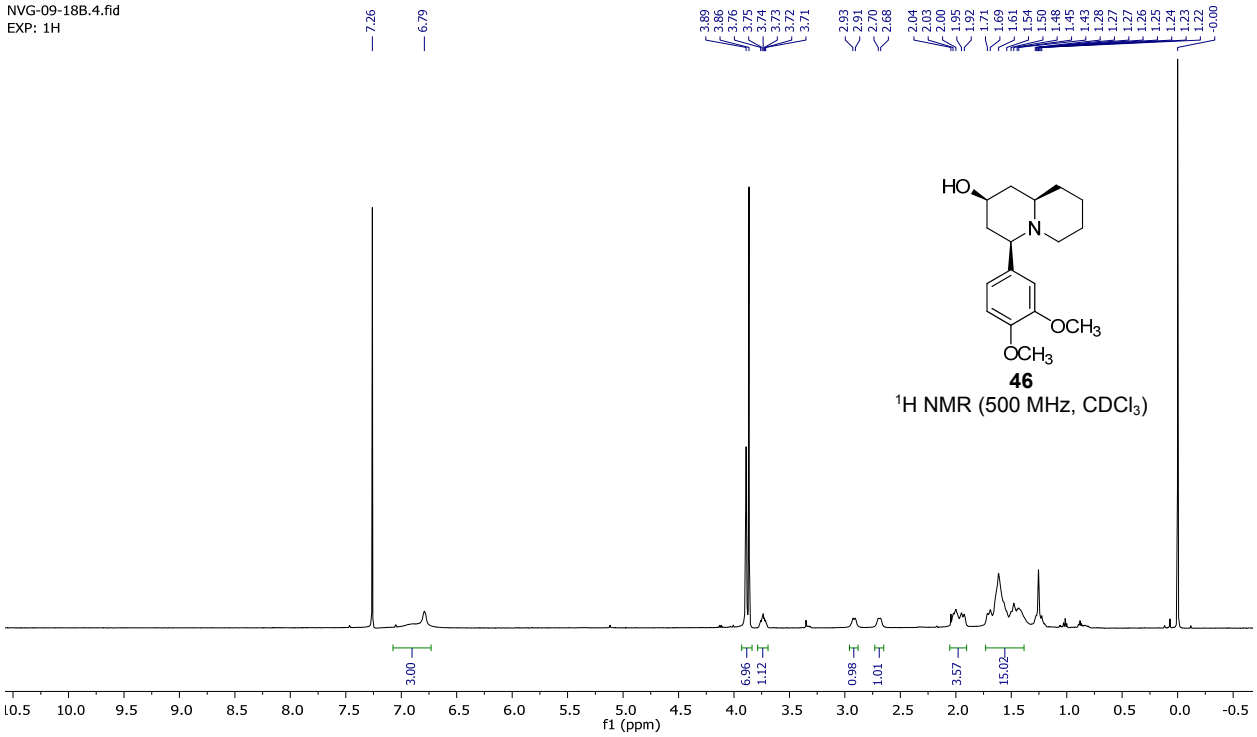
^{13}C NMR (75 MHz, $CDCl_3$)

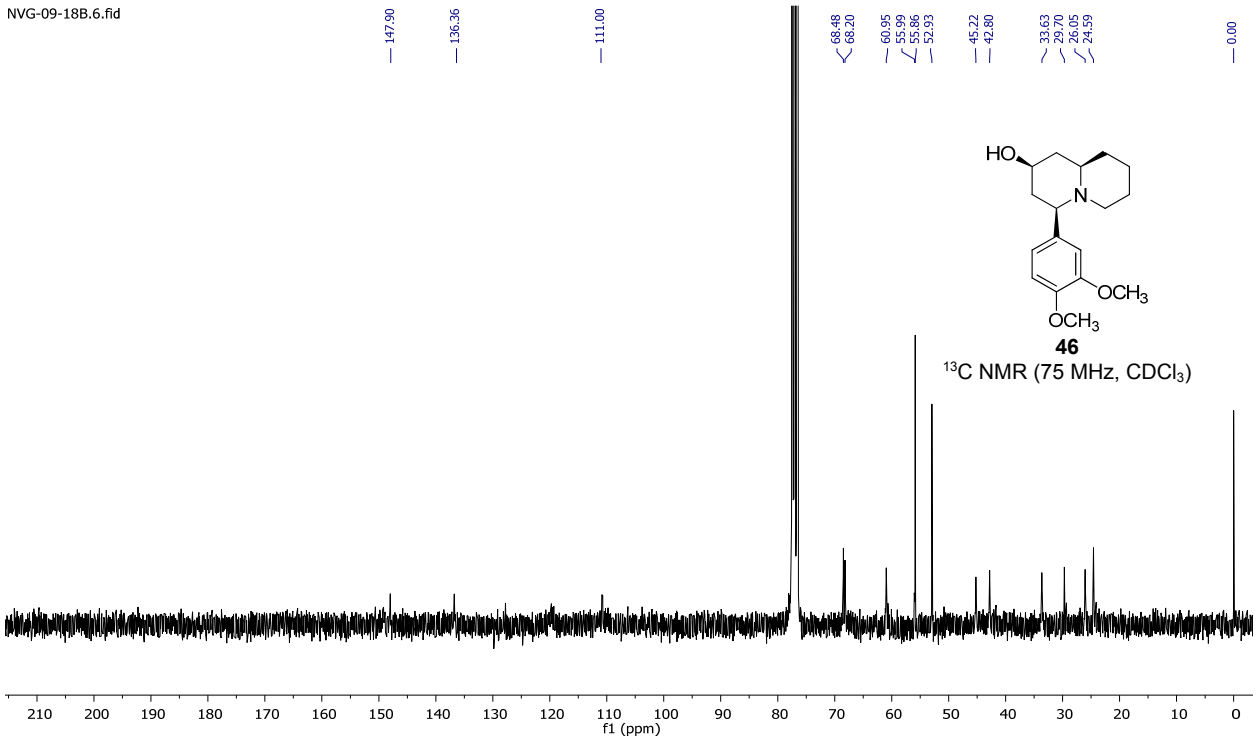

NVG-08-94B.1.fid
TIPSO
NH
OH
OCH3
OCH3
117
1H NMR (300 MHz, CDCl3)
f1 (ppm)


NVG-08-94B.6.fid
TIPSO
NH
OH
OCH3
OCH3
117
13C NMR (75 MHz, CDCl3)
f1 (ppm)


NVG-09-16A.3.fid
EXP: 1H
TIPSO
N
OCH3
OCH3
119
1H NMR (500 MHz, CDCl3)
f1 (ppm)


NVG-09-16A.4.fid
TIPSO
N
OCH3
OCH3
119
13C NMR (75 MHz, CDCl3)
f1 (ppm)


NVG-09-18B.4.fid
EXP: 1H
HO
N
OCH3
OCH3
46
1H NMR (500 MHz, CDCl3)
f1 (ppm)


NVG-09-18B.6.fid
HO
N
OCH3
OCH3
46
13C NMR (75 MHz, CDCl3)
f1 (ppm)

Memorial University

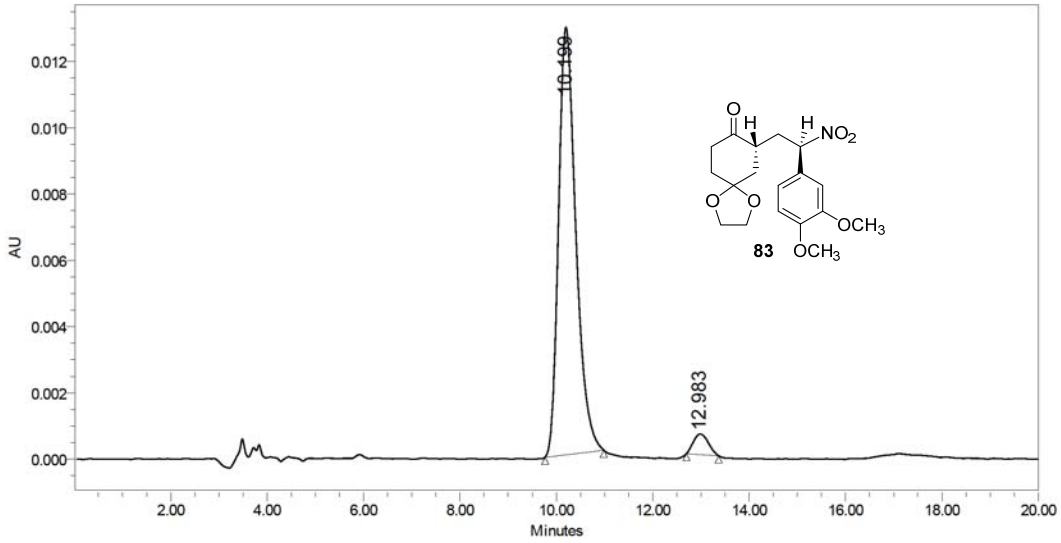
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-08-44A MICHAEL TOP	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	17/08/2015 7:50:16 PM NDT
Vial:	1	Acq. Method:	ASH 60%HEX 40%IPA
Injection #:	1	Date Processed:	17/08/2015 8:16:27 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	20.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



83

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	10.199	322486	96.00	12907	95.41
2	12.983	13435	4.00	622	4.59

Chapter 4

Synthesis of Fistulopsine B: Application of an Organocatalytic Michael Addition Reaction

4.1 Introduction

The indolizidine motif is a prominent structural unit in numerous alkaloids[1] and also constitutes a major class of glycosidase inhibitors.[2] In addition, several indolizidines have an interesting biological profile which includes antibacterial, antiviral, antitumor and antidiabetic properties.[3] Aryl-substituted indolizidines are also of interest; either as bioactive natural products[4] or as peptidomimetics.[5] Accordingly, the synthesis of arylindolizidines continues to be intensely investigated and general synthetic strategies toward aryl-fused[6] or aryl-substituted indolizidines[7] as well as other functionalized[8] indolizidines have been reported.[9] Recently, two arylindolizidine alkaloids (−)-fistulopsine A (**1**, Figure 4.1) and (+)-fistulopsine B (**2**), which are structurally similar to the arylindolizidine alkaloid (+)-septicine (**3**), were isolated from the bark and the leaves of *Ficus fistulosa*.[10] Fistulopsine A and B have potent *in vitro* antiproliferative activity against breast (MCF7) and colon (HCT 116) carcinoma cell lines.[11]

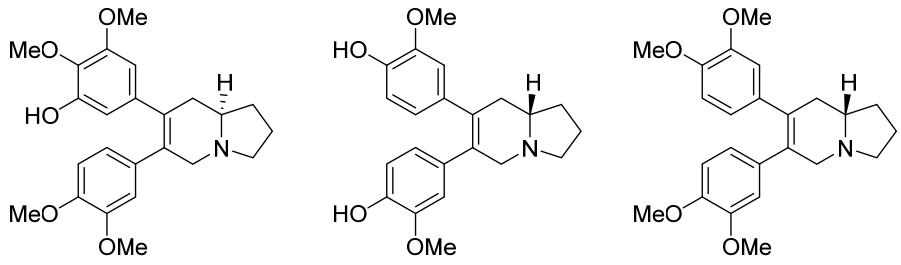
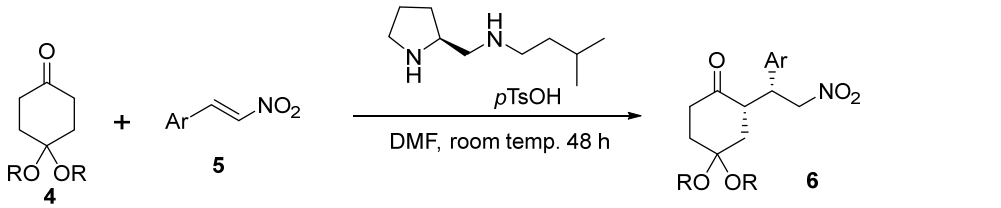


Figure 4.1: **Structures of (-)-fistulopsine A, (+)-fistulopsine B and (+)-septicine**.

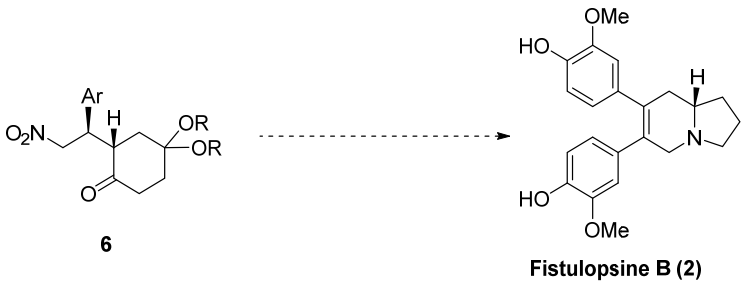
4.2 Objective

Our interest in indolizidines stems from our studies on the organocatalytic synthesis of *γ*-nitroketones from cyclic ketones and 2-nitrovinylarenes via an enamine-based Michael addition reaction as shown in Scheme 4.1.[12] This Michael addition reaction has been extensively studied and the development of new catalysts for the process continues at a remarkable pace.[13]



Scheme 4.1

Undoubtedly, the full potential of organocatalytic ketone-nitroalkene will be realized only when the *γ*-nitroketone products are utilized in target-oriented synthesis, but this has been relatively unexplored.[14] We therefore chose to examine the application of a suitably functionalized *γ*-nitroketone **6** (Scheme 4.2) in the synthesis of (+)-fistulopsine B. At the time of writing this thesis, the synthesis of (+)-fistulopsine B had not been reported.



Scheme 4.2

4.3 Results and Discussion

The strategy for the synthesis of fistulopsine B follows our previously reported synthesis of the diarylindolizidine alkaloids (+)-ipalbidine and (+)-antofine.[15] A retrosynthetic analysis is provided in Figure 4.2.

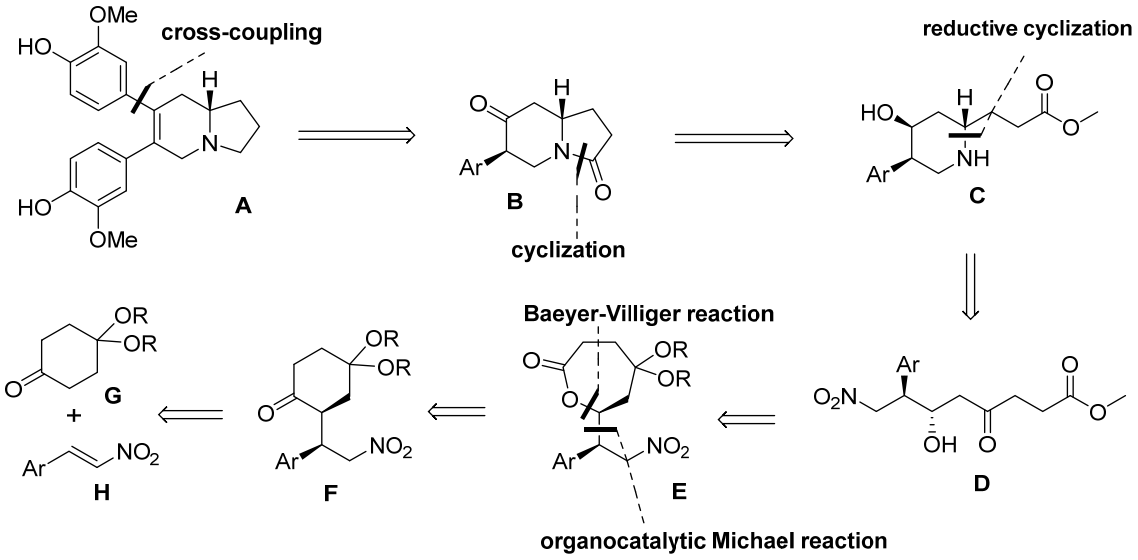
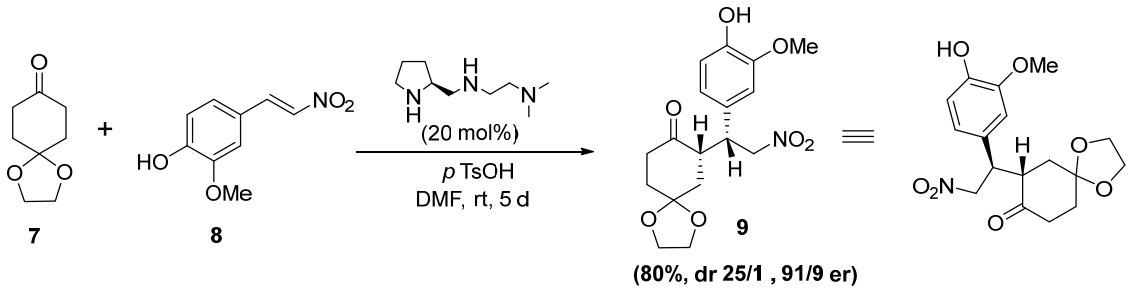


Figure 4.2 Retrosynthetic analysis for fistulopsine B.

According to our synthetic plan, fistulopsine B (the target alkaloid **A**) could be obtained from the ketone **B** by conversion to an enol triflate and cross-coupling with an aryl partner. Compound **B** could be constructed from the trisubstituted piperidine **C** by the cyclization of a suitable side chain, followed by oxidation of the alcohol. Compound **C** could be obtained from a diastereomerically pure acyclic precursor **D** by reductive cyclization involving the nitro group and the ketone. Compound **D** derives from lactone **E** by reductive ring opening followed by methanolysis and deprotection of the ketal. Finally, lactone **E** derives from a Baeyer-Villiger oxidation of the *γ*-nitroketone **F** which, in turn,

could be obtained from the organocatalytic Michael addition of a monoprotected 1,4-cyclohexanedione **G** to a β-nitrostyrene **H** (Figure 4.2).

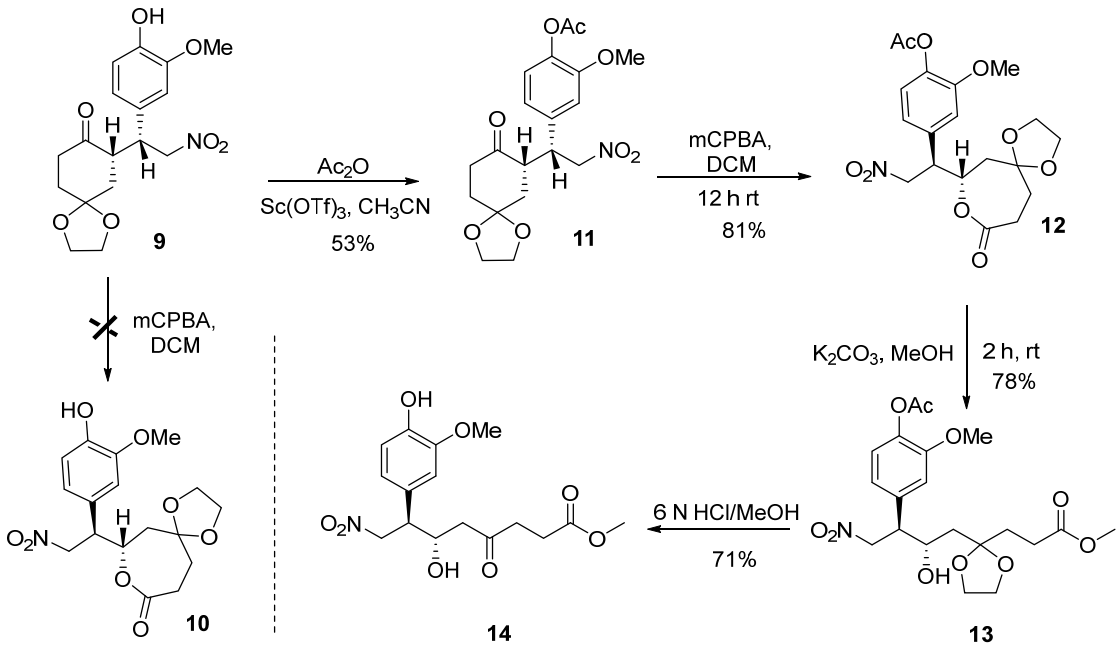
Our studies thus began with the synthesis of an appropriate γ-nitroketone starting material for fistulopsine B. Accordingly, the organocatalytic Michael addition of cyclohexane-1,4-dione monoethylene ketal (**7**) and 4-hydroxy-3-methoxy-β-nitrostyrene[16] (**8**), employing the triamine catalyzed protocol[13] developed in the Pansare group, provided nitroketone **9** in good yield and stereoselectivity (*er* = 91/9, *dr* > 19/1).



Scheme 4.3

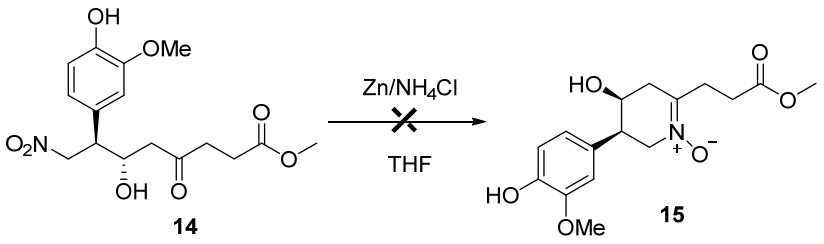
Somewhat unexpectedly, the Baeyer-Villiger oxidation of nitroketone **9** was unsuccessful (Scheme 4.4). Instead, complete decomposition of **9** was observed and the anticipated lactone **10** could not be detected in the crude reaction mixture. Although the precise reasons for the decomposition of **9** are not known, it is possible that the phenol functionality in **9** is incompatible with the peracid used in the reaction. Some support for this hypothesis was provided by the observation that conversion of **9** to the corresponding acetate **11** (53%), by reaction with acetic anhydride in the presence of $Sc(OTf)_3$ in acetonitrile, was beneficial. Thus, the Baeyer-Villiger oxidation of **11** provided the lactone

12 in good yield (81%). Methanolysis of **12** resulted in lactone ring opening to provide the nitroester **13** (78%). Subsequent hydrolysis of the ketal and concomitant deacetylation in **13** generated the highly functionalized octanoate **14** (Scheme 4.4, 55% over two steps) that has all the required carbon atoms for the indolizidine framework of fistulopsine B.



Scheme 4.4

With the functionalized octanoate **14** in hand, its conversion to the key trisubstituted piperidine intermediate B (see retrosynthetic Figure 4.2) was investigated next. Toward this goal, and as in our previous studies,[16] we attempted a reductive cyclization involving the nitro group and the ketone in **14**. Unfortunately, the attempted reduction of nitroketone **14** with zinc in aqueous ammonium chloride resulted in decomposition of **14** and the expected nitrone **15** was not obtained (Scheme 4.5).

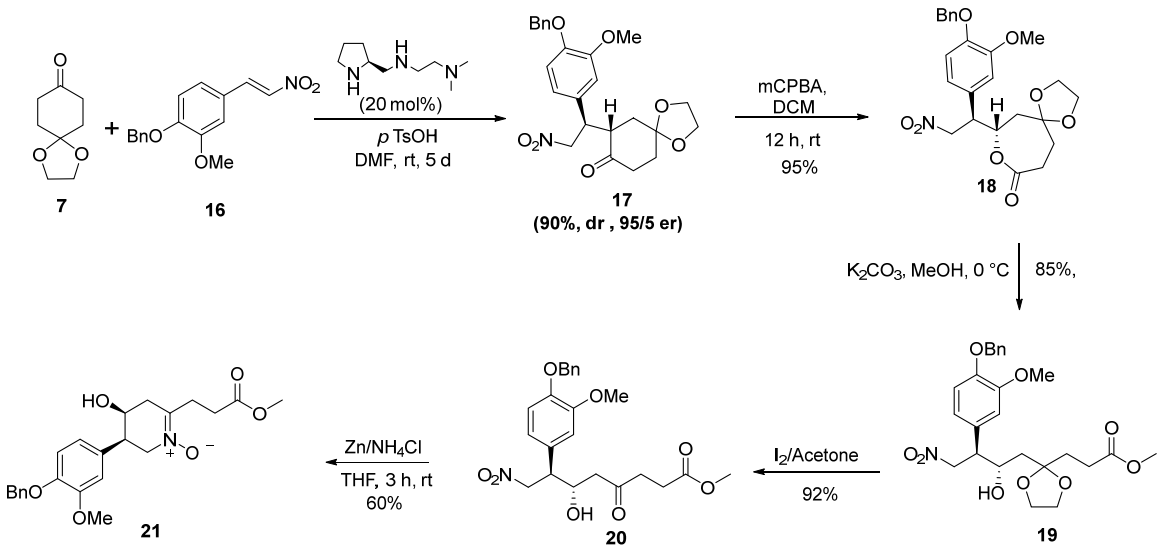


Scheme 4.5

Since the only difference between **14** and some of our previously, successfully, studied substrates for the reductive cyclization in the presence of the free phenolic functionality, it was reasonable to assume that an *O*-protected version of **14** would be more suitable for our purposes. Also, as the *O*-acetyl derivative **13** was deacetylated during hydrolysis of ketal, and since the phenyl acetate functionality was considered to be generally unsuitable, due to its reactivity, for subsequent transformations, we decided to employ a more robust protecting group for the phenol. Accordingly, the nitrostyrene **16** (4-benzyloxy-3-methoxy-*β*-nitrostyrene,[17] Scheme 4.6), in which the problematic phenolic functionality is protected as a benzyl ether, was chosen as the starting material for our modified synthetic approach.

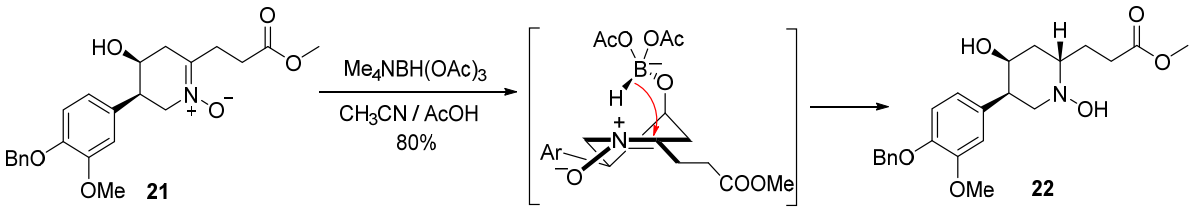
As expected, the organocatalytic Michael addition of **7** to **16** employing our triamine catalyzed protocol,[13] provided nitroketone **17** in good yield and stereoselectivity (*er* = 94/6, *dr*> 19/1, Scheme 4.6). Baeyer-Villiger oxidation of **17** provided lactone **18** in excellent yield (95%). Methanolysis of **18** and subsequent hydrolysis of the ketal generated the highly functionalized octanoate **20** (Scheme 4.6, 90% over two steps) that has all the required carbon atoms for the indolizidine framework. Gratifyingly, reductive cyclization

of nitroketone **20**, with zinc in aq. ammonium chloride, was successful and provided nitrone **21** in 60% yield (Scheme 4.6).



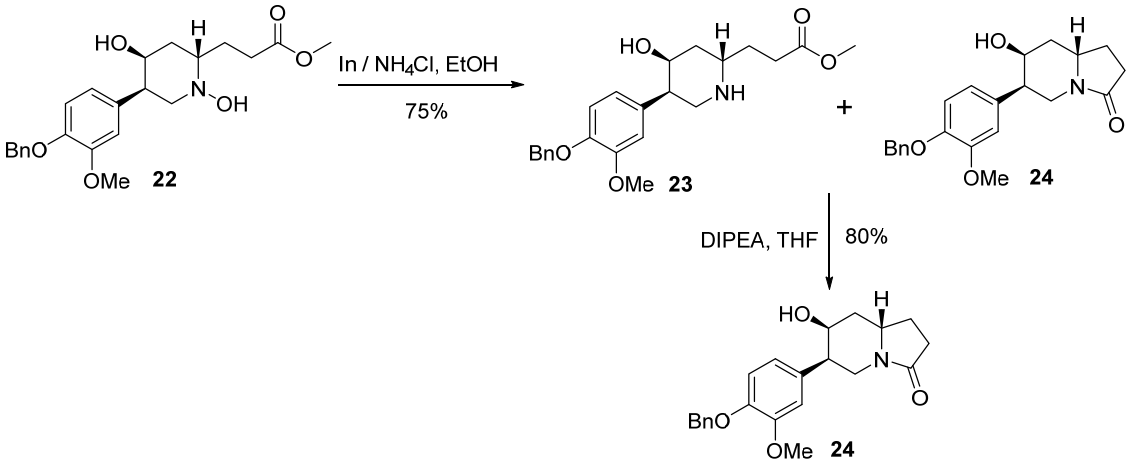
Scheme 4.6

In the next crucial, and stereochemistry defining step, nitrone **21** was anticipated to undergo a stereoselective reduction due to its 1,3 disposition with the secondary alcohol stereocenter. Thus, treatment of **21** with $Me_4NBH(OAc)_3$ provided hydroxyl amine **22** (80%) as a single diastereomer, presumably via a hydroxyl-directed reduction[18] (Scheme 4.7). At this stage, **22** was assigned the shown stereochemistry which was assumed to derive from an intramolecular hydroxyl-directed reduction of **21**. Notably, this reduction sets a stereocenter that would be ultimately retained in the target fistulopsine B.



Scheme 4.7

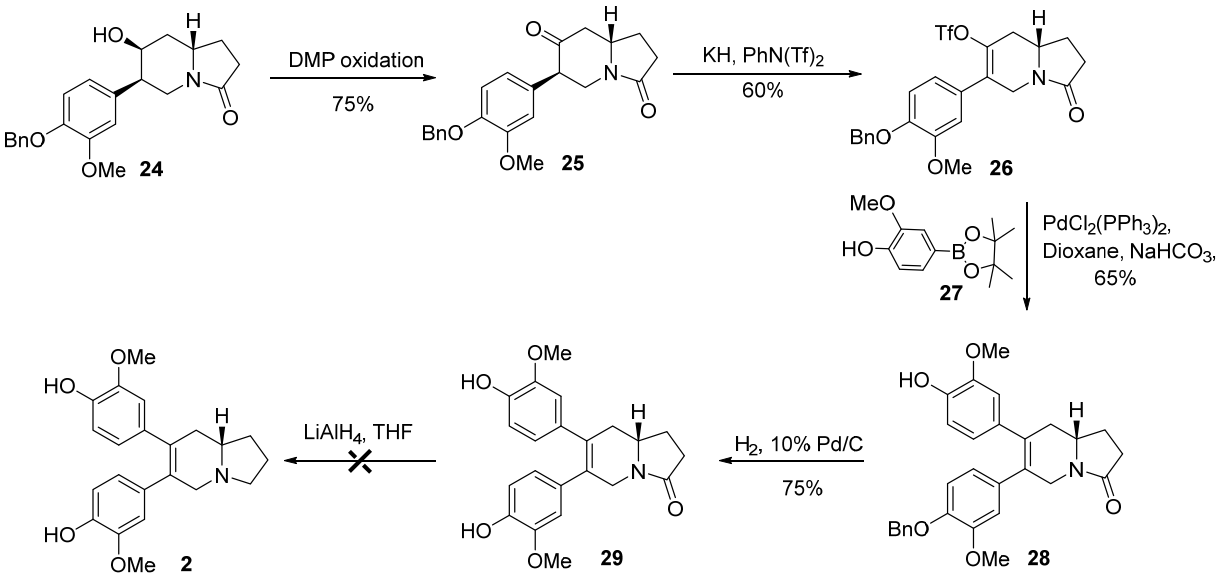
With the key piperidine **22** in hand, its conversion to the indolizidine framework was examined next. Reduction of the N-O bond in **22** was achieved with indium metal to provide a mixture of the amino ester **23** and the corresponding indolizidine **24** resulting from cyclization of the amino ester. This product mixture was treated with DIPEA in refluxing THF to complete the lactamization and provide **24** (Scheme 4.8).



Scheme 4.8

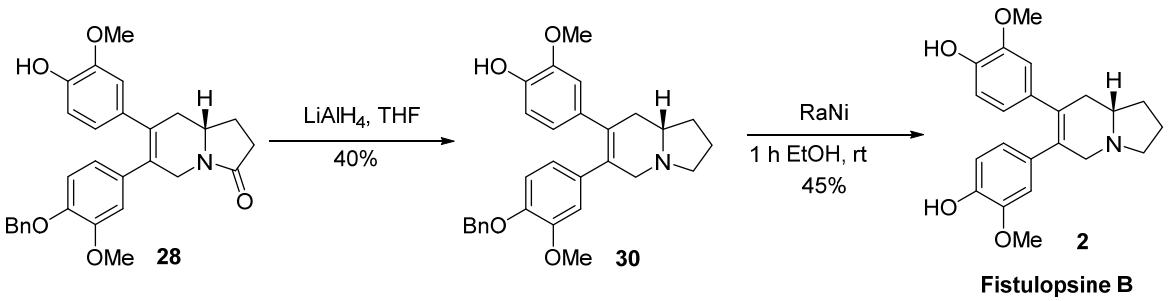
Oxidation of **24** (Dess-Martin periodinane) provided ketolactam **25** (80%). Conversion of **25** to enol triflate **26** followed by a Suzuki-Miyaura coupling[19] of **26** with

4-hydroxy-3-methoxyphenylboronic acid pinacolate[20] **27** furnished lactam **28**. Debenzylation of **28** with H_2, 10% Pd/C provided lactam **29** which is an amido analogue of fistulopsine B. Unfortunately, attempted reduction of amide **29** led to a complex mixture of products which did not contain any of the desired product Fistulopsine B (Scheme 4.9).



Scheme 4.9

In an alternative approach, amide **28** was first reduced to *O*-benzyl Fistulopsine B **(30)** in 40% yield. Debenzylation of **30** with Raney Nickel[21] in ethanol provided the target molecule, (+)-fistulopsine B, **2**, in 45% yield. Spectroscopic data for the synthetic sample is in agreement with reported[12] data for (+)-fistulopsine B isolated from the natural source.



Scheme 4.10

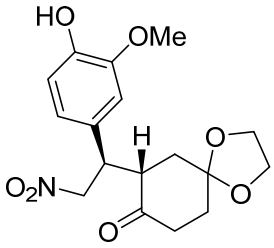
The fistulopsine B obtained from this synthesis has a small amount of an impurity that is seen only in the ^{13}C NMR (peak at δ 29.7, see Section **4.7**). This impurity could not be easily removed. Since the amount of fistulopsine available to us was the limiting factor, the synthesis is currently being repeated to obtain fistulopsine B in amounts that are sufficient for a more rigorous purification. It may be noted that similar difficulties have been encountered during the synthesis of other, highly polar, tertiary amine-containing alkaloids.[22]

4.4 Conclusion

In conclusion, an organocatalytic Michael addition based, first enantioselective total synthesis of the recently isolated indolizidine alkaloid (+)-Fistulopsine B was accomplished (13 steps, 1% overall yield). This approach has potential applications in the synthesis of analogs of Fistulopsine B by changing the aryl cross-coupling partner.

4.5 Experimental section

(*S*)-7-((*R*)-1-(4-(Hydroxy)-3-methoxyphenyl)-2-nitroethyl)-1,4-dioxaspiro[4.5]decan-8-one (9):

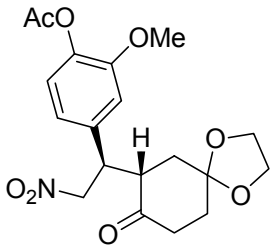


To a solution of 1,4-cyclohexanedione monoethylene ketal (2.00 g, 12.8 mmol), N^1,N^1-dimethyl-N^2-(((*S*)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine (88.0 mg, 0.512 mmol) and *p*-toluene sulfonic acid monohydrate (97 mg, 0.512 mmol) was added a solution of 4-hydroxy-3-methoxy-*β*-nitrostyrene **8** (0.500 mg, 2.56 mmol) in DMF (5 mL) and the resulting solution was stirred at ambient temperature for 5 d. Ethyl acetate (25 mL) was added and the solution washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (55/45 hexanes/EtOAc) to provide 0.720 g (80%) of nitroketone **9** as a white foam with 91% ee.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (d, 1H, *J* = 8.6, Ar*H*), 6.66-6.63 (m, 2H, Ar*H*), 5.63 (s, 1H, O*H*), 4.91 (dd, 1H, *J* = 12.3, 4.7, C*H*$_2$NO$_2$), 4.56 (dd, 1H, *J* = 12.3, 9.8, C*H*$_2$NO$_2$), 3.98-3.86 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.86 (s, 3H, OC*H*$_3$), 3.74 (dt, 1H, *J* = 9.8, 4.7, ArC*H*), 3.06-2.96 (m, 1H, COC*H*), 2.75-2.64 (m, 1H, COC*H*$_2$), 2.49-2.41 (m, 1H, COC*H*$_2$), 2.05-1.94 (m, 2H, CHC*H*$_2$), 1.76-1.69 (m, 1H, CH$_2$C*H*$_2$), 1.55 (t, 1H, *J* = 13.1, CH$_2$C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.5 (*C*O), 146.7 (Ar*C*$_{ipso}$), 145.1 (Ar*C*$_{ipso}$), 129.0 (Ar*C*$_{ipso}$), 120.4 (Ar*C*H), 114.9 (Ar*C*H), 111.2 (Ar*C*H), 107.1 (O*C*O), 79.1 (*C*H$_2$NO$_2$), 64.8

(O*C*H_2CH_2O), 64.6 (OCH_2*C*H_2O), 55.9 (O*C*H_3), 48.3 (CO*C*H), 43.2 (*C*HC$H_2$$NO_2$), 39.3 (CO*C*$H_2$), 38.7 (*C*$H_2$), 35.1 (*C*$H_2$); HRMS (APPI): *m/z* 351.1326 (351.1318 calc. for $C_{17}H_{21}NO_7$ $[M]^+$), 352.1392 (352.1396 calc. for $C_{17}H_{22}NO_7$ $[M+H]^+$). HPLC (Chiralpak AS-H, hexanes/2-propanol: 60/40, flow rate 1.0 mL/min, 254 nm): t_{minor} = 10.61 min, t_{major} = 14.30 min, ee = 91 %, dr = 20:1 (average value from multiple reactions).

(*S*)-7-((*R*)-1-(4-(Acetoxy)-3-methoxyphenyl)-2-nitroethyl)-1, 4-dioxaspiro [4.5] decan-8-one (11):

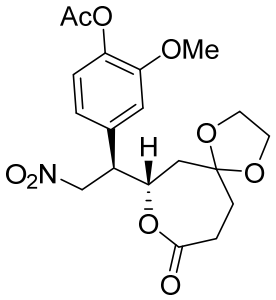


To the solution of nitroketone **9 (**100 mg, 0.280 mmol) in CH_3CN at 0 °C was added acetic anhydride (40.0 μL, 0.42 mmol) followed by $Sc(OTf)_3$ (1.4 mg, 0.0028 mmol). The mixture was stirred for 30 min at 0 °C and then at ambient temperature for 2 h. The reaction mixture was cooled to 0 °C, water was added followed by ethyl acetate (15 mL). The resulting mixture was washed with water (10 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (60/40 hexanes/Ethyl acetate) to provide 72 mg (65%) of acetate **11** as yellow foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (d, 1H, *J* = 8.1, Ar*H*), 6.78 (d, 1H, *J* = 1.9, Ar*H*), 6.73 (dd, 1H, *J* = 8.1, 2.0, Ar*H*), 4.90 (dd, 1H, *J* = 12.7, 4.8, C*H*$_2$$NO_2$), 4.62 (dd, 1H, *J* = 12.7, 9.6, C*H*$_2$$NO_2$), 3.99-3.86 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.81 (s, 3H, OC*H*$_3$), 3.81-3.79 (m, 1H,

CH_2CH_2), 3.10-3.01 (m, 1H, ArC*H*), 2.75-2.64 (dt, 1H, *J* = 13.3, 6.6, COC*H*), 2.48-2.42 (m, 1H, COCH_2), 2.30 (s, 3H, OCOCH_3), 2.05-1.94 (m, 2H, COC*H*, CH_2), 1.78-1.71 (m, 1H, CHCH_2), 1.59 (t, 1H, *J* = 13.1, CH_2CH_2).

(*S*)-7-((*R*)-1-(4-(Acetoxy)-3-methoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro[4.6]undecan-9-one (12):

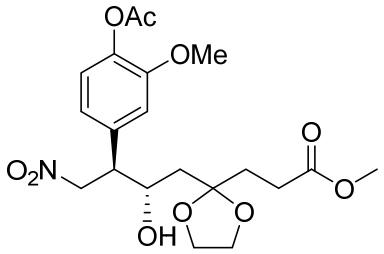


To a solution of acetate **11** (50.0 mg, 0.12 mmol) in anhydrous dichloromethane (3 mL) at ambient temperature was added solid sodium phosphate (44.0 mg, 0.16 mmol) followed by *m*-chloroperbenzoic acid (~77%, 68.0 mg, 0.39 mmol). The resulting white slurry was stirred vigorously at ambient temperature for 16 h. Dichloromethane (3 mL) was added and the mixture was washed with aq. $NaHCO_3$ (2 x 5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1:1 hexanes/EtOAc) to provide 42.0 mg (81%) of **12** as a yellow foam.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (dd, 1H, *J* = 7.4, 1.0, ArC*H*), 6.84-6.81 (m, 2H, ArC*H*), 4.95 (dd, 1H, *J* = 13.0, 4.7, CH_2NO_2), 4.76 (dd, 1H, *J* = 13.0, 9.1, CH_2NO_2), 4.80-4.72 (m, 1H, (CO)OC*H*), 3.89-3.79 (m, 3H, OCH_2CH_2O), 3.84 (s, 3H, OCH_3), 3.68-3.54 (m, 2H,

ArC*H*, OCH_2CH_2O), 2.88-2.78 (m, 1H, CH_2CO), 2.66-2.58 (m, 1H, CH_2CO), 2.30 (s, 3H, OCH_3), 1.94-1.90 (m, 2H, $COCH_2(C)CH_2$, 1.87-1.85 (m, 2H, $CH_2(C)CH_2$).

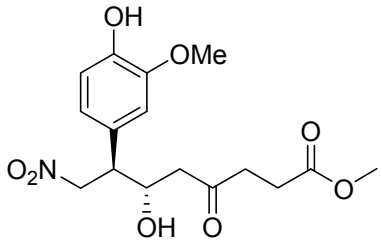
Methyl 3-(2-((2*S*, 3*R*)-3-(4-(acetoxy)-3-methoxyphenyl)-2-hydroxy-4-nitrobutyl)-1,3-dioxolan-2-yl)propanoate (13):



A solution of the lactone **12** (42 mg, 0.10 mmol) in methanol (1 mL) was cooled to 0 °C and potassium carbonate (28 mg, 0.20 mmol) was added. The mixture was stirred at ambient temperature for 2 h. The mixture was cooled to 0 °C, neutralized with aq. HCl (0.5 M) and the solution was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 35 mg, (78%) of nitroketal **13** as a light brown gum. This material was pure by ^{1}H NMR and was directly used further.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.86 (d, 1H, *J* = 7.9, ArC*H*), 6.69-6.65 (m, 2H, ArC*H*), 5.65 (br s, 1H, O*H*), 5.03 (dd, 1H, *J* = 12.6, 5.2, CH_2NO_2), 4.58 (dd, 1H, *J* = 12.6, 9.6, CH_2NO_2), 3.99 -3.96 (m, 4H, OCH_2CH_2O), 3.89-3.86 (s, 1H, C*H*OH),m 3.86 (s, 3H, OCH_3), 3.64 (s, 3H, CO_2CH_3), 3.39-3.33 (m, 1H, ArC*H*), 2.27-2.17 (m, 1H, $COCH_2$), 2.17 (s, 3H, $C(O)CH_3$), 2.07-1.97 (m, 2H, $CH_2(C)CH_2$), 1.88-1.81 (m, 1H, $CH_2(C)CH_2$), 1.66-1.64 (m, 2H, $CH_2(C)CH_2$).

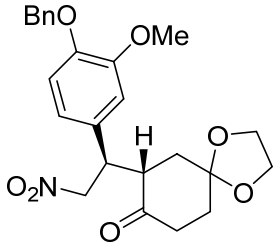
(6*S*, 7*R*)-Methyl 7-(4-(hydroxy)-3-methoxyphenyl)-6-hydroxy-8-nitro-4-oxooctanoate (14):



To a solution of nitroketal **13** (35 mg, 0.070 mmol) in methanol (0.5 mL) was added 6 M HCl (0.4 mL) and the solution was stirred at the ambient temperature for 24 h. The methanol was removed under reduced pressure and the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to provide 20 mg, (71%) of nitroketone **14** as a brown gum. The material was pure by ^{1}H NMR and was directly used in the next step.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 (d, 1H, ArC*H*), 6.70-6.65 (m, 2H, ArC*H*), 5.59 (s, 1H, O*H*), 5.08 (dd, 1H, *J* = 12.8, 5.1, C*H*$_2$NO$_2$), 4.63 (dd, 1H, *J* = 12.8, 9.7, C*H*$_2$NO$_2$), 4.25-4.15 (m, 1H, ArC*H*), 3.90 (s, 3H, ArOC*H*$_3$), 3.67 (s, 3H, CO$_2$C*H*$_3$), 3.58 (br d, 1H, CHO*H*), 3.48-3.41 (m, 1H, C*H*OH), 2.65-2.56 (m, 4H, C*H*$_2$COC*H*$_2$), 2.50-2.48 (m, 2H, C*H*$_2$CO$_2$CH$_3$);

(*S*)-7-((*R*)-1-(4-(Benzyloxy)-3-methoxyphenyl)-2-nitroethyl)-1,4-dioxaspiro[4.5]decan-8-one (17):

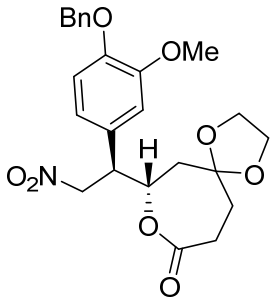


To a solution of 1,4-cyclohexanedione monoethylene ketal (16.4 g, 105 mmol), N^1,N^1- dimethyl-N^2-(((*S*)-pyrrolidin-2-yl)methyl)ethane-1,2-diamine (720 mg, 4.2 mmol) and *p*-toluene sulfonic acid monohydrate (800 mg, 4.2 mmol) was added a solution of 4-benzyloxy-3-methoxy-*β*-nitrostyrene **16** (6.0 g, 21 mmol) in DMF (60 mL) and the resulting solution was stirred at ambient temperature for 5 d. Ethyl acetate (200 mL) was added and the resulting solution washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The residue obtained was purified by flash column chromatography on silica gel (70/30 hexanes/EtOAc) to provide 8.3 g (89%) of **17** as a white foam with 95% ee.

IR (neat): 2925, 1709, 1548, 1510, 1257, 1232, 1139, 1117, 1011, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.29 (m, 5H, Ar*H*), δ 6.82 (d, 1H, *J* = 8.2, Ar*H*), 6.68 (d, 1H, *J* = 2.1, Ar*H*), 6.64 (d, 2H, *J* = 8.2, 2.1, Ar*H*), 5.11 (s, 2H, OCH_2Ph), 4.90 (dd, 1H, *J* = 12.4, 4.7, CH_2NO_2), 4.60 (dd, 1H, *J* = 12.4, 9.8, CH_2NO_2), 4.00-3.83 (m, 4H, OCH_2CH_2O), 3.86 (s, 3H, OCH_3), 3.79-3.7 (dt, 1H, *J* = 13.4, 6.6, ArC*H*), 3.07-2.93 (m, 1H, COC*H*), 2.76-2.62 (dt, 1H, *J* = 13.8, 6.6, COCH_2), 2.50-2.39 (m, 1H, COCH_2), 2.09-1.86 (m, 2H, CHCH_2), 1.74-1.64 (m, 1H, CH_2CH_2), 1.54 (t, 1H, *J* = 13.0, CH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$):

δ 210.5 (*C*O), 149.8 (Ar*C*$_{ipso}$), 147.8 (Ar*C*$_{ipso}$), 137.0 (Ar*C*$_{ipso}$), 130.2 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.4 (2 x Ar*C*), 120.2 (Ar*C*), 114.2 (Ar*C*), 112.0 (Ar*C*), 107.1 (O*C*O), 79.0 (*C*H$_2$NO$_2$), 71.1 (*C*H$_2$OPh), 64.8 (O*C*H$_2$CH$_2$O), 64.6 (OCH$_2$*C*H$_2$O), 56.1 (O*C*H$_3$), 48.3 (CO*C*H), 43.1 (*C*HCH$_2$NO$_2$), 39.3 (CO*C*H$_2$), 38.7 (*C*H$_2$), 35.1 (*C*H$_2$); HRMS (APPI, pos.) *m/z* 441.1801 (441.1788 calc. for $C_{24}H_{27}NO_7$ $[M]^+$); HPLC (Chiralpak AS-H, hexanes/2-propanol, 90/10, flow rate 1.0 mL/min, 254 nm): t_{minor} = 12.55 min, t_{major} = 17.54 min, ee = 95%, dr = 20:1 (average value from multiple reactions).

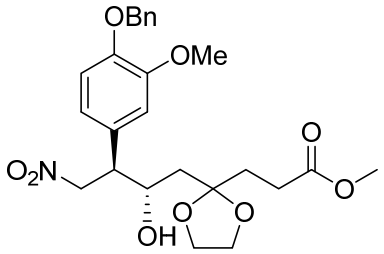
(*S*)-7-((*R*)-1-(4-(Benzyloxy)-3-methoxyphenyl)-2-nitroethyl)-1,4,8-trioxaspiro[4.6]undecan-9-one (18):



To a solution of nitroketone **17** (3.0 g, 6.8 mmol) in anhydrous dichloromethane (50 mL) at ambient temperature was added solid sodium phosphate (2.36 g, 8.80 mmol) followed by *m*-chloroperoxybenzoic acid (~77%, 3.63 g, 21 mmol). The resulting white slurry was stirred vigorously for 16 h at ambient temperature. Dichloromethane (100 mL) was added and the mixture was washed with aq. $NaHCO_3$ (2 x 60 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue obtained was purified by flash column chromatography on silica gel (60/40 EtOAc/hexanes) to provide 2.9 g (93%) of **18** as a yellow foam.

IR (neat): 2936, 2887, 1734, 1551, 1513, 1378, 1327, 1260, 1232, 1144, 1099, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ 7.44-7.31 (m, 5H, Ar*H*), 6.85 (d, 1H, *J* = 8.2, Ar*H*), 6.73 (d, 1H, *J* = 2.1, Ar*H*), 6.70 (dd, 1H, *J* = 8.2, 2.1, Ar*H*), 5.13 (s, 2H, OC*H*$_2$Ph), 4.93 (dd, 1H, *J* = 12.7, 4.7, C*H*$_2$NO$_2$), 4.72 (dd, 1H, *J* = 12.7, 9.3, C*H*$_2$NO$_2$), 4.74-4.63 (m, 1H (CO)OC*H*), 3.89 (s, 3H, OC*H*$_3$), 3.87-3.73 (m, 3H, OC*H*$_2$C*H*$_2$O), 3.56 (dt, 1H, *J* = 9.3, 4.7, ArC*H*), 3.47-3.41 (m, 1H, OCH$_2$C*H*$_2$O), 2.88-2.80 (m, 1H, C*H*$_2$CO), 2.66-2.56 (m, 1H, C*H*$_2$CO), 1.93-1.87 (m, 2H, C*H*$_2$(C)CH$_2$), 1.82-1.80 (m, 2H, CH$_2$(C)C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6 (*C*O), 150.0 (Ar*C*$_{ipso}$), 148.1 (Ar*C*$_{ipso}$), 136.8 (Ar*C*$_{ipso}$), 128.9 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 128.0 (Ar*C*), 127.4 (2 x Ar*C*), 120.5 (Ar*C*), 114.3 (Ar*C*), 111.8 (Ar*C*), 107.2 (O*C*O), 77.8 (*C*H$_2$NO$_2$), 75.8 (*C*OC(O)), 70.9 (O*C*H$_2$Ph), 65.0 (O*C*H$_2$CH$_2$O), 64.3 (OCH$_2$*C*H$_2$O), 56.1 (O*C*H$_3$), 48.5 (OCH*C*H$_2$), 41.4 (*C*HCH$_2$NO$_2$), 33.1 (*C*H$_2$(C)CH$_2$), 29.4 (CH$_2$(C)*C*H$_2$); HRMS (APPI, pos.): *m/z* 457.1749 (457.1737 calc. for $C_{24}H_{27}NO_8$ [M^+]), *m/z* 475.2086 (475.2080 calc. for $C_{24}H_{31}N_2O_8$ [$M+NH_4]^+$).

Methyl 3-(2-((2*S*, 3*R*)-3-(4-(benzyloxy)-3-methoxyphenyl)-2-hydroxy-4-nitrobutyl)-1,3-dioxolan-2-yl)propanoate (19):

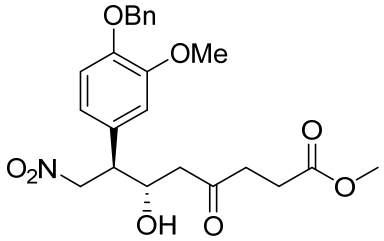


A solution of the lactone **18** (3.3 g, 7.2 mmol) in methanol (70 mL) was cooled to 0 °C and potassium carbonate (2.00 g, 14.4 mmol) was added. The mixture was stirred at

ambient temperature for 2 h. The mixture was then cooled to 0 °C, neutralized with aq. HCl (0.5 M) and the resulting solution was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 3.0 g, (85%) of the nitroketal **19** as a light brown gum. This material was pure by ^{1}H NMR and was directly used further.

IR (neat): 3499, 2953, 1732, 1549, 1515, 1453, 1436, 1379, 1261, 1233, 1141, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.44-7.29 (m, 5H, Ar*H*), 6.83 (d, 1H, *J* = 8.2, Ar*H*), 6.70 (d, 1H, *J* = 2.1, Ar*H*), 6.65 (dd, 1H, *J* = 8.2, 2.1, Ar*H*), 5.12 (s, 2H, OC*H*$_2$Ph), 5.02 (dd, 1H, *J* = 12.9, 5.3, C*H*$_2$NO$_2$), 4.59 (dd, 1H, *J* = 12.9, 9.5, C*H*$_2$NO$_2$), 4.08-3.98 (m, 1H, ArC*H*), 3.98-3.90 (m, 4H, OC*H*$_2$C*H*$_2$O), 3.86 (s, 3H, ArOC*H*$_3$), 3.63 (s, 3H, CO_2C*H*$_3$), 3.37 (dt, 1H, *J* = 9.3, 5.3, C*H*OH), 2.25-2.17 (m, 2H, CO_2C*H*$_2$), 2.05-1.95 (m, 1H, C*H*$_2$(C)CH_2), 1.87-1.77 (m, 1H, C*H*$_2$(C)CH_2), 1.66-1.62 (m, 2H, CH_2(C)C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6 (*C*O_2CH_3), 149.9 (Ar*C*$_{ipso}$), 147.9 (Ar*C*$_{ipso}$), 137.0 (Ar*C*$_{ipso}$), 130.3 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.3 (2 x Ar*C*), 120.1 (Ar*C*), 114.3 (Ar*C*), 111.8 (Ar*C*), 110.9 (O*C*O), 78.4 (*C*H_2NO_2), 71.0 (O*C*H_2Ph), 70.0 (*C*HOH), 65.1 (O*C*H_2*C*H_2O), 64.6 (O*C*H_2*C*H_2O), 56.1 (ArO*C*H_3), 51.7 (CO_2*C*H_3), 50.6 (HO-C*C*H_2), 40.5 (Ar*C*H), 31.8 (*C*$H_2CH_2COOCH_3$), 28.5 (*C*$H_2CO_2CH_3$); HRMS (APPI, pos.): *m/z* 489.2016 (489.1999 calc. for $C_{25}H_{31}NO_9$[M^+]), *m/z* 507.2317 (507.2343 calc. for $C_{25}H_{35}N_2O_9$ [$M+NH_4^+$])).

(6*S*,7*R*)-Methyl 7-(4-(benzyloxy)-3-methoxyphenyl)-6-hydroxy-8-nitro-4-oxooctanoate (20):

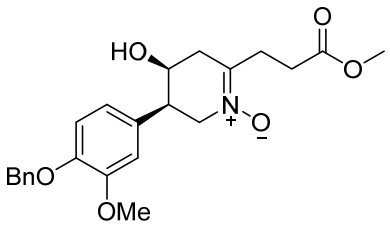


To a solution of nitroketal **19** (2.9 g, 5.9 mmol) in acetone (55 mL) was added iodine (150 mg, 0.6 mmol) and the solution was stirred at ambient temperature for 1 h. The acetone was removed under reduced pressure and the residue was diluted with dichloromethane (2 x 50 mL). The resulting solution was washed with aqueous $Na_2S_2O_3$ (5% w/v, 2 x 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. This procedure was repeated one more time with the same amount of materials to finally provide 2.4 g (92%) of nitroketone **20** as a white, fluffy solid. This material was pure by ^{1}H NMR and was directly used in the next step.

IR (neat): 3441, 2939, 2900, 1732, 1711, 1549, 1519, 1379, 1366, 1262, 1205, 1139, 1105, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) : δ 7.44-7.29 (m, 5H, Ar*H*), 6.83 (d, 1H, *J* = 8.2, Ar*H*), 6.71 (d, 1H, *J* = 2.1, Ar*H*), 6.65 (dd, 1H, *J* = 8.2, 2.1, Ar*H*), 5.11 (s, 2H, OC*H*$_2$Ph), 5.05 (dd, 1H, *J* = 12.8, 5.0, C*H*$_2$NO$_2$), 4.6 (dd, 1H, *J* = 12.8, 9.7, C*H*$_2$NO$_2$), 4.24-4.18 (m, 1H, Ar-C*H*), 3.87 (s, 3H, OC*H*$_3$), 3.65 (s, 3H, CO$_2$C*H*$_3$), 3.65 (s, 1H, CHO*H*), 3.50-3.42 (dt, 1H, *J* = 9.9, 5.2, C*H*OH), 2.61-2.55 (m, 4H, C*H*$_2$COC*H*$_2$), 2.54-2.45 (m, 2H, C*H*$_2$CO$_2$CH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): 209.8 (*C*O), 173.2 (*C*O$_2$CH$_3$), 150.0 (Ar*C*$_{ipso}$), 148.1 (Ar*C*$_{ipso}$), 136.9 (Ar*C*$_{ipso}$), 129.8 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 128.0 (Ar*C*), 127.4 (2 x

Ar*C*), 120.1 (Ar*C*), 114.3 (Ar*C*), 111.7 (Ar*C*), 78.4 (*C*H_2NO_2), 71.0 (*C*H_2OPh), 69.9 (*C*HOH), 56.1 (O*C*H_3), 52.0 ($CO_2C H_3$), 49.6 (HOC-*C*H_2CO), 47.1 (Ar*C*H), 37.8 (CO*C*H_2), 27.5 (*C*$H_2CO_2CH_3$); HRMS (APPI, pos.): *m/z* 445.1754 (445.1737 calc. for $C_{23}H_{27}NO_8$ [M^+]), *m/z* 463.2087 (463.2080 calc. for $C_{23}H_{31}N_2O_8$ [$M+NH_4$]$^+$).

(3*R*, 4*S*)-3-(4-(Benzyloxy)-3-methoxyphenyl)-4-hydroxy-6-(3-methoxy-3-oxopropyl)-2,3,4,5-tetrahydropyridine-1-oxide (21):

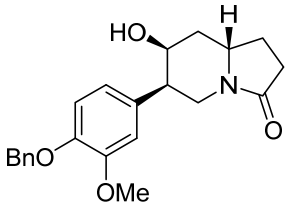


A solution of NH_4Cl (252 mg, 4.70 mmol) in water (11.5 mL) was added to a solution of the nitroketone **20** (2.1 g, 4.7 mmol) in THF (32 mL). Activated Zn powder (3.10 g, 47.1 mmol) was added and the mixture was stirred vigorously at room temperature under nitrogen for 3 h. The mixture was filtered (Celite), the filter cake was washed with THF, and the combined filtrates were concentrated under reduced pressure. Dichloromethane (50 mL) was added to the residue and the resulting mixture was washed with water (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (98/2 Dichloromethane/MeOH) to provide 1.2 g (63%) of the nitrone **21** as a purple foam.

IR (neat): 2948, 1735, 1511, 1453, 1435, 1265, 12124, 1196, 1173, 1133, 1070, 1007 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.30 (m, 5H, Ar*H*), 6.87-6.85 (m, 2H, Ar*H*), 6.75 (dd, 1H, *J* = 8.4, 2.0, Ar*H*), 5.15 (s, 2H, OC*H*$_2$Ph), 4.29 (br t, 1H, *J* = 13.6, ArC*H*), 4.19

(br s, 1H, C*H*OH), 3.92 (dd, 1H, *J* = 13.6, 5.7, C*H*$_2$N), 3.88 (s, 3H, OC*H*$_3$), 3.66 (s, 3H, CO_2CH_3), 3.21 (dd, 1H, *J* = 13.6, 5.7, C*H*$_2$N), 2.91-2.66 (m, 6H, C*H*$_2$C=N, $COCH_2CH_2$, $COCH_2$), 2.36 (br s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) : 173.7 (*C*O), 149.7 (ArC_{ipso}), 147.6 (ArC_{ipso}), 145.4 (*C*=NO), 137.03 (ArC_{ipso}), 130.9 (ArC_{ipso}), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.3 (2 x Ar*C*), 119.8 (Ar*C*), 114.0 (Ar*C*), 111.8 (Ar*C*), 71.0 (*C*H_2OPh), 64.9 (*C*H_2NO), 57.7 (Ar*C*H), 56.0 (O*C*H_3), 51.9 (CO_2CH_3), 44.0 (*C*HOH), 38.8 ($CH_2CO_2CH_3$), 28.3 (N=C*C*H_2), 27.4 (N=C*C*H_2); HRMS (APPI): *m/z* 413.1828 (413.1838 calc. for $C_{23}H_{27}NO_6$ [M^+]), *m/z* 414.1901 (414.1917 calc. for $C_{23}H_{28}NO_6$ [M+H]$^+$).

(6*R*,7*S*, 8a*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-7-hydroxyhexahydroindolizin-3(5*H*)-one (24):



To a solution of tetramethylammonium triacetoxyborohydride (891 mg, 3.39 mmol) in acetonitrile (4 mL) was added glacial acetic acid (2.26 mL). The mixture was stirred at 0 °C for 5 min and a solution of nitrone **21** (700 mg, 1.69 mmol) in acetonitrile (6 mL) was added. The mixture was stirred at 0 °C for 1 h and the pH of the solution was adjusted (pH 7 to 8) with aqueous NaOH (5% solution). The resulting mixture was extracted with dichloromethane (50 mL) and the combined extracts were dried (Na_2SO_4) and concentrated to give 630 mg (90%) of **22** as a purple foam. This crude material was used further.

^{1}H NMR (300 MHz, $CDCl_3$): 7.45-7.29 (m, 5H, ArC*H*), 6.84 (d, 1H, *J* = 8.2, ArC*H*), (m, 1H, ArC*H*), 6.70-6.64 (m, 2H, ArC*H*), 5.13 (s, 2H, OC*H*$_2$Ph), 3.92 (br s, 1H, ArC*H*), 3.87 (s, OCH_3), 3.67 (s, OCH_3), 3.46 (m, 1H, C*H*OH), 3.27-3.21 (m, 1H, ArC*H*CH_2), 2.99-2.87 (m, 1H, ArC*H*CH_2), 2.50-2.41 (m, 2H, COC*H*$_2$), 2.17-2.04 (m, 1H, NC*H*), 1.93-1.87 (m, 1H, OHCHC*H*$_2$), 1.71-1.62 (m, 1H, OHCHC*H*$_2$), 1.54-1.50 (m, 2H, NCHC*H*$_2$); HRMS (APPI, pos.): *m/z* 415.1982 (415.2000 calc. for $C_{23}H_{29}NO_6$ $[M]^+$) *m/z* 416.2055 (416.2100 calc. for $C_{23}H_{30}NO_6$ $[M+H]^+$);

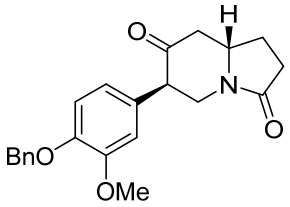
The hydroxylamine **22** (720 mg, 1.73 mmol) was dissolved in a mixture of ethanol (15 mL) and saturated aqueous NH_4Cl (3.6 mL). Indium powder (378 mg, 3.30 mmol) was added and the mixture was heated to reflux for 4 h. The mixture was cooled, filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Dichloromethane (25 mL) was added to the residue and the aqueous layer was separated. The organic layer was washed with saturated aqueous $NaHCO_3$ solution (2 × 10 mL), dried (Na_2SO_4) and concentrated to give 630 mg of a yellow gum. This material is a mixture of the amino ester **23** and the cyclization product (lactam **24**, ~30%) (^{1}H NMR analysis). The crude mixture was directly converted to the lactam as follows.

To a solution of crude aminoester and lactam mixture (280 mg) in THF (7 mL) was added diisopropylethylamine (24μL, 0.14 mmol) and the solution was heated to reflux for 5 h. The THF was removed under reduced pressure, the residue was dissolved in dichloromethane (15 mL) and the resulting solution was washed with aqueous HCl (0.5 M, 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to provide 200 mg (78%)

of lactam **24** as a pale yellow foam. This material was pure by ^{1}H NMR and was directly used further.

IR (neat): 3341, 2961, 2931, 1654, 1512, 1454, 1419, 1259, 1220, 1140, 1019 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, 1H, *J* = 7.4, Ar*H*), 7.36 (t, 2H, *J* = 7.4, ArH), 7.29-7.22 (m, 1H, *J* = 7.4, Ar*H*), 6.80 (d, 1H, *J* = 8.3, Ar*H*), 6.75 (d, 1H, *J* = 2.1, Ar*H*), 6.66 (dd, 1H, *J* = 8.3, 2.1, ArC*H*), 5.1 (s, 2H, OCH_2Ph), 4.11 (br s, 1H, NC*H*), 4.05 (dd, 1H, *J* = 12.7, 4.8 , NCH_2), 3.94-3.88 (m, 1H, ArC*H*), 3.85 (s, 3H, OCH_3), 3.31 (t, 1H, *J* = 12.7, NCH_2), 2.73-2.70 (ddd, 1H, *J* = 12.5, 4.8, 2.0, C*H*OH), 2.36 (br t, 2H, *J* = 7.0, COCH_2), 2.30 (br s, 1H, CH_2CHOH), 2.24-2.17 (m, 1H, CH_2CHOH), 2.16-2.12 (m, 1H, CH_2CH$_2$C(O)), 1.60-1.54 (m, 1H, CHCH_2CH), 1.45 (dt, 1H, *J* = 11.0, 2.1, NCHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 173.7 (N*C*O), 149.7 (ArC_{ipso}), 147.3 (ArC_{ipso}), 137.1 (ArC_{ipso}), 133.0 (ArC_{ipso}), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.3 (2 x Ar*C*), 119.6 (Ar*C*), 114.1 (Ar*C*), 111.7 (Ar*C*), 71.0 (O*C*H$_2$Ph), 68.8 (*C*HOH), 56.0 (O*C*H$_3$), 50.9 (N*C*H), 45.2 (N*C*H$_2$), 39.8 (Ar*C*H), 38.3 (HOCH*C*H$_2$), 30.6 (NCO*C*H$_2$), 24.7 (NCH*C*H$_2$); HRMS (APPI, pos.): *m/z* 367.1779 (367.1784 calc. for $C_{22}H_{25}NO_4$ [M$^+$]), *m/z* 368.1851 (368.1862 calc. for ($C_{22}H_{26}NO_4$ [M+H]$^+$).

(6*R*, 8a*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl) hexahydroindolizine-3,7-dione (25):

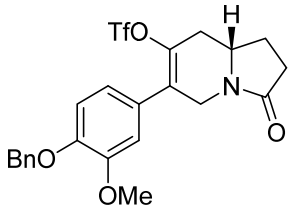


To a stirred solution of amidoalcohol **24** (200 mg, 0.540 mmol) in dichloromethane (4 mL) was added Dess-Martin periodinane (462 mg, 1.08 mmol) and the mixture was

stirred at ambient temperature for 3 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, the organic layer was separated and the aqueous layer was extracted with dichloromethane (15 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (Ethyl acetate) to provide 164 mg (83%) of **25** as a white solid.

IR (neat): 2934, 1680, 1514, 1454, 1419, 1262, 1220, 1142, 1029, 912 cm^{-1}; ^1H NMR (300 MHz,$CDCl_3$): δ 7.45-7.29 (m, 5H, Ar*H*), 6.86 (d, 1H, *J* = 8.2, Ar*H*), 6.66 (d, 1H, *J* = 2.1, Ar*H*), 6.62 (dd, 1H, *J* = 8.2, 2.1, Ar*H*), 5.14 (s, 2H, OCH_2Ph), 4.6 (dd, 1H, *J* = 12.5, 6.9, ArCC*H*), 4.03-3.94 (m, 1H, NC*H*), 3.86 (s, 3H, OCH_3), 3.60 (dd, 1H, *J* = 12.5, 6.9, NCH_2), 3.09 (t, 1H, *J* = 12.5, NCH_2), 2.73 (dd, 1H, *J* = 13.6, 3.9, COCH_2), 2.58-2.51 (m, 2H, COCH_2, NCOCH_2), 2.48-2.33 (m, 2H, NCOCH_2, $NCOCH_2CH_2$), 1.86-1.74 (m, 1H, $NCOCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.5 (*C*O), 173.6 (N*C*O), 149.6 (ArC_{ipso}), 147.8 (ArC_{ipso}), 137.1 (ArC_{ipso}), 128.6 (2 x Ar*C*), 127.9 (Ar*C*), 127.4 (Ar*C*), 127.3 (2 x Ar*C*), 121.1 (Ar*C*), 113.9 (Ar*C*), 112.8 (Ar*C*), 71.0 (O*C*H_2Ph), 57.1 (N*C*H), 56.1 (O*C*H_3), 55.3 (ArC*C*H), 48.6 (*C*H_2N), 45.1 (*C*H_2CO), 29.7 (*C*H_2CH_2CO), 24.7 (*C*H_2CO); HRMS (ESI, pos.) *m/z* 365.1639 (365.1627 calc. for $C_{22}H_{23}NO_4$ [M^+]), *m/z* 366.1709 (366.1705 calc. for $C_{22}H_{24}NO_4$ $[M+H]^+$).

(*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-3-oxo-1,2,3,5,8,8a-hexahydroindolizin-7-yl trifluoromethanesulfonate (26):

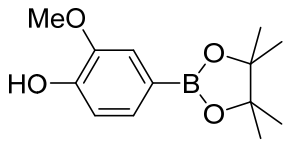


To a suspension of KH (73 mg, 0.54 mmol) in THF (2 mL) was added ketone **25** (100 mg, 0.27 mmol) at 0 °C. The mixture was stirred at 0 °C for 45 mins and then warmed to room temperature for 1 h and *N*-phenyl-bis(trifluoromethanesulfonimide) (105 mg, 0.29 mmol) was added in one portion and the mixture was stirred for 1 h at ambient temperature. Water (2 mL) was added and the mixture was extracted with EtOAc (5 mL). The combined layers were dried (Na_2SO_4) and concentrated to provide 121 mg (89%) of triflate **26** as a yellow foam. This was used further without purification. An analytical sample was obtained by flash column chromatography on silica gel (Ethyl acetate).

IR (neat): 2940, 2843, 1694, 1514, 1413, 1263, 1243, 1206, 1139, 1035, 947 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.30 (m, 5H, Ar*H*), 6.91-6.78 (m, 3H, Ar*H*), 5.16 (s, 2H, OC*H*$_2$Ph), 4.75 (br d, 1H, *J* = 18.1, NC*H*$_2$), 3.88 (s, 3H, OC*H*$_3$), 3.93-3.88 (m, 1H, NC*H*), 3.71 (br d, 1H, *J* = 18.1, NC*H*$_2$), 2.67-2.39 (m, 5H, COC*H*$_2$, C=CC*H*$_2$, COCH$_2$C*H*$_2$), 1.87-1.80 (m, 1H, COCH$_2$C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 173.8 (*C*O), 155.1 (TfO*C*=C), 149.5 (Ar*C*$_{ipso}$), 148.7 (Ar*C*$_{ipso}$), 139.6 (Ar*C*$_{ipso}$), 136.7 (Ar*C*$_{ipso}$), 128.6 (2 x Ar*C*), 127.9 (2 x Ar*C*), 127.3 (2 x Ar*C*), 125.5 (TfOC=*C*), 120.8 (Ar*C*), 115.2 (q, *J* = 109.4, *C*F$_3$), 113.7 (Ar*C*), 111.9 (Ar*C*), 70.9 (O*C*H$_2$Ph), 56.1 (O*C*H$_3$), 53.3 (N*C*H), 42.9 (N*C*H$_2$), 35.4

(C=C*C*H$_2$CH), 29.6 (COCH$_2$*C*H$_2$), 24.2 (CO*C*H$_2$); HRMS (APPI): *m/z* 497.1106 (497.1120 calc. for $C_{23}H_{23}F_3NO_6S$ $[M]^+$).

2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (27)[21]:

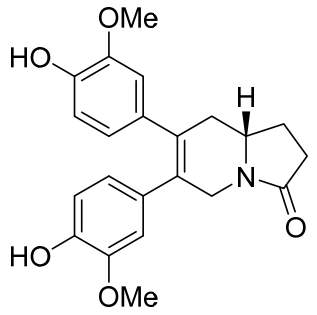


A mixture of 4-hydroxy-3-methoxyphenyl bromide (500 mg, 2.46 mmol), potassium acetate (725 mg, 7.38 mmol) and $PdCl_2$.dppf (140 mg, 0.025 mmol) in dry dioxane (10 mL) was stirred at 80 °C for 2 h. Bis(pinacolato)diboron (687 mg, 2.70 mmol) in dry dioxane (5 mL) was added and the mixture was stirred at 80 °C for 1 h. The solvent was removed under reduced pressure and the residue was suspended in ethyl acetate (15 mL). The mixture was filtered through a pad of celite and the pad washed with ethyl acetate (20 mL). The combined filtrates were washed with saturated aqueous ammonium chloride (10 mL), water (10 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (95/5 hexanes/Ethyl acetate) to provide 403 mg (65%) of 4-hydroxy-3-methoxy phenyl pinacolate **27** as a white solid.

IR (neat): 3486, 3361 (br), 2975, 2938, 1763, 1603, 1590, 1413, 1341, 1309, 1266, 1219, 1169, 1140, 1121, 1085, 1029, 962 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (dd, 1H, *J* = 7.8, 1.3, ArC*H*), 7.28 (d, 1H, *J* = 1.3, ArC*H*), 6.92 (d, 1H, *J* = 7.8, ArC*H*), 5.86 (s, 1H, O*H*), 3.92 (s, 3H, OC*H*$_3$), 1.33 (s, 12H, (C*H*$_3$)$_2$C-C(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 148.6 (Ar*C*$_{ipso}$), 146.1 (Ar*C*$_{ipso}$), 129.1 (Ar*C*$_{ipso}$, Ar*C*), 116.2 (Ar*C*), 114.1 (Ar*C*), 83.7

$(CH_3)_2C$-C$(CH_3)_2$), 83.5 $(CH_3)_2$C-$C(CH_3)_2$), 56.0 (OCH_3), 25.1 (($CH_3)_2$C-C$(CH_3)_2$), 24.9 (($CH_3)_2$C-C$(CH_3)_2$); HRMS (ESI): *m/z*: 249.1311 (249.1298 calc. for $C_{13}H_{18}BO_4$ $[M-H]^-$);

(*S*)-6,7-Bis (4-hydroxy-3-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5*H*)-one (29):



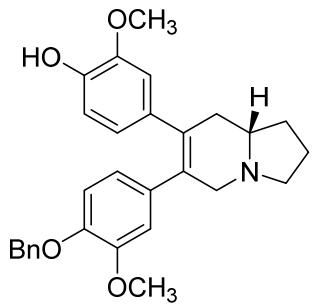
To a mixture of triflate **26** (70 mg, 0.14 mmol), 4-hydroxy-3-methoxy phenyl pinacolate ester **27** (42 mg, 0.17 mmol), and $PdCl_2{\cdot}(PPh_3)_2$ (20 mg, 0.030 mmol) in THF (1 mL) was added a saturated aqueous solution of $NaHCO_3$ (2.8 mL) and the resulting mixture was heated to reflux. After 15 min, the resulting solution was cooled to room temperature, diluted with cold water (5 mL) and then extracted with ethyl acetate (2 x 10 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo to provide 34 mg (51%) of **28** as a yellow gum. This was used further without purification.

The coupled product **28** (38 mg, 0.080 mmol) was dissolved in methanol (0.5 mL) and Pd/C (10%, 8 mg, 8 mmol) was added to the solution. The mixture was stirred under an atmosphere of hydrogen (balloon) for 5 h and then filtered through a pad of celite. The residue was washed with methanol (5 mL) and the combined filtrates were concentrated in

vacuo. The residue was purified by flash column chromatography (98/2 Dichloromethane/Methanol) to provide 21 mg (68%) of **29** as a yellow gum.

IR (neat): 3291 (br), 2927, 2853, 1660, 1595, 1515, 1461, 1423, 1372, 1269, 1206, 1166, 1033 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77 (d, 1H, *J* = 7.5, Ar*H*), 6.74 (d, 1H, *J* = 7.5, ArH), 6.62 (dt, 2H, *J* = 8.2, 1.9, Ar*H*), 6.46 (d, 1H, *J* = 1.9, Ar*H*), 6.37 (d, 1H, *J* = 1.9, Ar*H*), 5.6 (s, 1H, O*H*), 5.5 (s,1H, O*H*), 4.73 (dd, 1H, *J* = 18.5, 2.7, NCH_2), 3.94-3.87 (m, 1H, NC*H*), 3.79-3.73 (br d, 1H, *J* = 18.5, NCH_2), 3.61 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 2.74 (dd, 1H, *J* = 16.7, 4.4, COCH_2), 2.54-2.38 (m, 4H, COCH_2, C=CCH_2, COCH_2CH_2), 1.86-1.75 (m, 1H, COCH_2CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): 174.0 (*C*O), 146.0 (ArC_{ipso}), 145.9 (ArC_{ipso}), 144.6 (ArC_{ipso}), 144.3 (ArC_{ipso}), 133.8 (ArC_{ipso}), 131.8 (ArC=*C*CH$_2$CH), 131.4 (C=*C*CH$_2$N), 130.6 (ArC_{ipso}), 121.8 (Ar*C*), 121.3 (Ar*C*), 114.0 (Ar*C*), 113.9 (Ar*C*), 112.4 (Ar*C*), 112.3 (Ar*C*), 55.84 (O*C*H$_3$), 55.76 (O*C*H$_3$), 53.4 (N*C*H), 44.3 (N*C*H$_2$), 38.8 (C=C*C*H$_2$CH), 30.1 (COCH$_2$*C*H$_2$), 24.9 (CO*C*H$_2$); HRMS (APPI, pos.): *m/z* 381.1588 (381.1576 calc. for $C_{22}H_{23}NO_5$ [M^+]), *m/z* 382.1654 (382.1654 calc. for $C_{22}H_{24}NO_5$ $[M+H]^+$), *m/z* 404.1399 (404.1474 calc. for ($C_{22}H_{23}NNaO_5$) $[M+Na]^+$)).

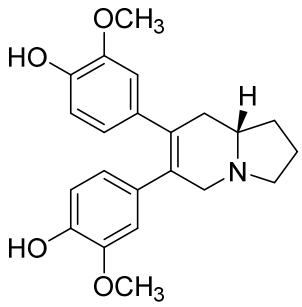
4-((*S*)-6-(4-(Benzyloxy)-3-methoxyphenyl)-1,2,3,5,8,8a-hexahydroindolizin-7-yl)-2-methoxyphenol (30):



To a suspension of $LiAH_4$ (17 mg, 0.44 mmol) in dry THF (1 mL) at 0 °C was slowly added a solution of the lactam **28** (50 mg, 0.10 mmol) in THF (1 mL). After stirring for 1 h at 0 °C, the mixture was stirred at ambient temperature for 24 h. It was then cooled to 0 °C and water (8 μL), 1M NaOH (18 μL), water (24 μL) were added sequentially with vigorous stirring. The precipitated inorganic salts were filtered and the residue washed with dichloromethane. The combined filtrates were dried (Na_2SO_4) and concentrated to provide 20 mg (40%) of **30** as a pale yellow gum.

IR (neat): 2933, 1599, 1509, 1461, 1416, 1383, 1263, 1208, 1169, 1141, 1032, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, 2H, *J* = 7.5, ArC*H*), 7.36 (t, 2H, *J* = 7.5, ArC*H*), 7.30-7.25 (m, 1H, ArC*H*), 6.74 (d, 1H, *J* = 8.1, ArC*H*), 6.70 (d, 1H, *J* = 8.3, ArC*H*), 6.65 (dd, 1H, *J* = 8.5, 2.0, ArC*H*), 6.61 (dd, 1H, *J* = 8.5, 2.0, ArC*H*), 6.52 (br d, 1H, *J* = 1.3, ArC*H*), 6.41 (br d, 1H, *J* = 1.6, ArC*H*), 5.08 (s, 2H, OCH_2Ph), 3.91 (br d, 1H, *J* = 15.5, NCH_2), 3.59 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.35-3.12 (br m, 1H, NC*H*), 2.75 (br d, 1H, *J* = 15.5, NCH_2), 2.47-2.30 (br m, 2H, NCH_2CH_2), 2.14-1.87 (m, 4H, NCHCH_2, NCHCH_2CH_2), 1.66-1.56 (m, 2H, $NCHCH_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 149.0 (ArC_{ipso}), 146.7 (ArC_{ipso}), 145.7 (ArC_{ipso}), 144.1 (ArC_{ipso}), 137.2 (2 x ArC_{ipso}), 133.1 (2 x ArC_{ipso}), 128.5 (2 x Ar*C*), 127.8 (Ar*C*), 127.2 (2 x Ar*C*), 121.2 (Ar*C*), 120.9 (Ar*C*), 113.76 (Ar*C*), 113.71 (Ar*C*), 113.5 (Ar*C*), 112.5 (Ar*C*), 70.9 (OCH_2Ph), 60.5 (N*C*H), 59.1 (NCH_2), 55.8 (OCH_3), 55.7 (OCH_3), 54.2 (NCH_2CH_2), 30.7 ($NCH_2CH_2CH_2$), 29.7 (NCHCH_2), 21.5 (NCH_2CH_2). HRMS (APPI): *m/z* 457.2233 (457.2253 calc. for $C_{29}H_{31}NO_4$ $[M]^+$), 458.2304 (458.2331 calc. for $C_{29}H_{32}NO_4$ $[M+H]^+$), *m/z* 480.2122 (480.2151 calc. for $C_{29}H_{31}NNaO_4$ $[M+Na]^+$); $[\alpha]^{23}_D$ = +36 (*c* = 0.5, CH_2Cl_2).

4-((*S*)-6-(4-(Hydroxy)-3-methoxyphenyl)-1,2,3,5,8,8a-hexahydroindolizin-7-yl)-2-methoxyphenol ((+)-fistulopsine B, 2):

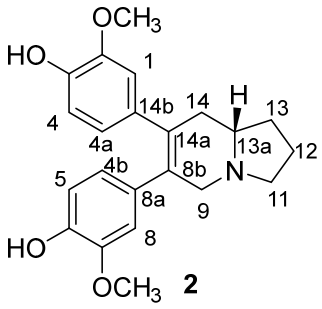


To a suspension of excess RaNi in ethanol (50% slurry in H_2O, 1 mL) was slowly added a solution of **30** (0.030 g, 6.56 mmol). The mixture was stirred at ambient temperature for 1 h and filtered through a pad of celite. The residue was washed with ethanol and the combined filtrates were concentrated in vacuo. The residue obtained was purified by preparative TLC (neutral alumina) to provide 10 mg (45%) of (+)-fistulopsine B (**2**) as a white solid.

IR (neat): 3315 (br), 2955, 2935, 1593, 1513, 1462, 1419, 1270 (br), 1208, 1168, 1124, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.71 (d, 2H, *J* = 8.1), 6.62 (dd, 2H, *J* = 8.1, 1.7), 6.44 (d, 1H, *J* = 1.3), 6.41 (d, 1H, *J* = 1.6), 3.87 (d, 1H, *J* = 16), 3.56 (s, 3H), 3.53 (s, 3H), 3.29 (br t, 1H, *J* = 7.3), 3.08 (d, 1H, *J* = 17.1), 2.73-2.69 (m, 1H), 2.41-2.39 (m, 2H), 2.26-2.24 (m, 1H), 2.15-1.95 (m, 1H), 1.96-1.92 (m, 1H), 1.85-1.79 (m, 1H), 1.61-1.55, (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 145.9, 145.7, 144.1, 143.9, 134.6, 132.8, 132.9, 132.5, 121.5, 121.2, 113.8, 113.7, 112.7, 112.5, 60.5, 57.6, 55.74, 55.68, 54.2, 38.5, 30.7, 21.3; HRMS (APPI): *m/z* 367.1766 (367.1784 calc. for $C_{22}H_{25}NO_4$ [M^+]), *m/z* 368.1838

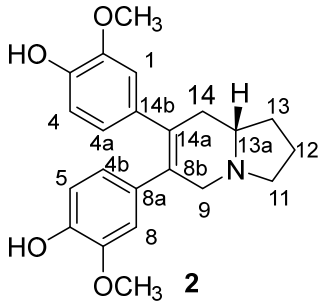
(368.1862 calc. for $C_{22}H_{26}NO_4$ $[M+H]^+$); $[\alpha]^{23}_D$ = +23.9 (*c* = 0.23, MeOH; lit.[12] $[\alpha]^{25}_D$ = +18 (*c* = 0.32, MeOH for the *S* enantiomer)).

Comparison of observed NMR data for compound 2 with reported[12] data



2

Position	**^{1}H NMR (500 MHz, $CDCl_3$)** Observed for **2**	**^{1}H NMR (600 MHz, $CDCl_3$)** Reported[12] for **2**
5, 4	6.71 (d, 2H, *J* = 8.1 Hz)	6.71 (d, 1H, *J* = 8.0 Hz), 6.70 (d, 1H, *J* = 8.0 Hz)
4a, 4b	6.62 (dd, 2H, *J* = 8.1, 1.7 Hz)	6.62 (dd, 2H, *J* = 8.0, 1.6 Hz)
8	6.44 (d, 1H, *J* = 1.3 Hz)	6.45 (d, 1H, *J* = 1.6 Hz)
1	6.41 (d, 1H, *J* = 1.6 Hz)	6.44 (d, 1H, *J* = 1.6 Hz)
9β	3.87 (d, 1H, *J* = 16.0 Hz)	3.86 (d, 1H, *J* = 16.0 Hz)
7-OMe	3.56 (s, 3H)	3.57 (s, 3H)
2-OMe	3.53 (s, 3H)	3.55 (s, 3H)
11β	3.29 (br t, 1H, *J* = 7.3 Hz)	3.29 (t, 1H, *J* = 9.0 Hz)
9α	3.08 (d, 1H, *J* = 17.1 Hz)	3.09 (d, 1H, *J* = 16.0 Hz)
14β	2.73-2.69 (m, 1H)	2.73 (d, 1H, *J* = 16.0 Hz)
13a, 14α	2.41-2.39 (m, 2H)	2.45 (m, 1H), 2.42 (m, 1H)
11α	2.26-2.24 (m, 1H)	2.28 (q, 1H)
13α	2.15-1.95 (m, 1H)	2.11 (m, 1H)
12b	1.96-1.92 (m, 1H)	1.94 (m, 1H)
12a	1.85-1.79 (m, 1H)	1.86 (m, 1H)
13β	1.61-1.55 (m, 1H)	1.57 (m, 1H)



2

Position	**^{13}C NMR (75 MHz, $CDCl_3$)** Observed for **2**	**^{13}C NMR (150 MHz, $CDCl_3$)** Reported[12] for **2**
7	145.9	146.62
2	145.7	146.43
6	144.1	144.53
3	143.9	144.32
14a	134.6	134.31
14b	133.1	132.86
8a	132.9	132.82
8b	132.5	132.26
4b	121.5	121.51
4a	121.2	121.30
5	113.8	114.44
4	113.7	114.33
8	112.7	113.24
1	112.5	113.00
13a	60.5	60.71
9	57.6	57.57
7-OMe	55.7	55.79
2-OMe	55.7	55.74
11	54.2	54.19
14α	38.5	38.02
13	30.7	30.58
12a	21.3	21.40

4.6 References:

1) (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. and previous reviews on indolizidine and quinolizidine alkaloids in the series; (b) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.

2) (a) Asano, N.; Nash, R. J.; Molyneux R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645. (b) *Iminosugars as Glycosidase Inhibitors* (Ed. A. E. Stütz) Wiley-VCH, Weinheim, 1999. (c) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.

3) a) Wong, C.–H.; Halcomb, R. L.; Ichibaka, Y.; Kajimoto, T. *Angew. Chem.* **1995**, *107*, 569. (b) Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541.

4) Chemler, S. R. *Curr. Bioact. Compd.* **2009**, *5*, 2.

5) Cluzeau, J.; Lubell, W. D.; *J. Org. Chem.* **2004**, *69*, 1504.

6) Reviews on phenanthroindolizidine alkaloids: (a) Li, Z.; Jin, Z.; Huang, R. *Synthesis* **2001**, 2365. (b) Bick, I.; Ralph, C.; Sinchai, W. *Alkaloids* **1981**, *19*, 193. (c) Govindachari, T. R.; Vishwanathan, N. *Heterocycles* **1978**, *11*, 587. Selected recent reports: (d) Banwell, M. G.; Sydnes, M. O. *Aust. J. Chem.* **2004**, *57*, 537. (e) Sharma, V. M.; AdiSeshu, K. V.; Krishna, C. V.; Prasanna, P.; Shekhar, V. C.; Venkateswarlu, A.; Rajagopal, S.; Ajaykumar, R.; Deevi, D. S.; Mamidi, N. V. S. R.; Rajagopalan, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1679. (f) Zhu, W.; Cai, G.; Ma, D. *Org. Lett.* **2005**, *7*, 5545. (g) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2782. (h) Boto, A.; De, L.; Yolanda, G.; Juan, A.; Hernandez, R. *Eur. J. Org. Chem.* **2005**, 3461.

7) Reviews: (a) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Eur.*

J. **2009**, *15*, 7808. (b) Perreault, S.; Rovis, T. *Chem. Soc. Rev.* **2009**, *38*, 3149. (c) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (d) *Beilstein J. Org. Chem.* **2007**, *3*, No. 27, thematic series on indolizidines and quinolizidines. (e) Jefford, C. W. *Curr. Org. Chem.* **2000**, *4*, 205. (f) Rajeswari, S.; Chandrasekharan, S.; Govindachari, T. R. *Heterocycles* **1987**, *25*, 659. Selected recent reports: (g) Iza, A.; Carrillo, L.; Vicario, J. L.; Badia, D.; Reyes, E.; Martinez, J. *Org. Biomol.Chem.* **2010**, *8*, 2238. (h) Sirisha, N.; Raghunathan, R. *Tetrahedron Lett.* **2010**, *51*, 2515. (i) Yang, D.; Micalizio, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 17548. (j) Affani, R.; Comesse, S.; Daich, A.; Hamon, L.; Kadouri-Puchot, C. *Heterocycles* **2009**, *78*, 2193. (k) Barbe, G.; Pelletier, G.; Charette, A. B. *Org. Lett.* **2009**, *11*, 3398. (l) Katoh, M.; Mizutani, H.; Honda, T. *Heterocycles* **2006**, *69*, 193.

8) (a) Min, H.-Y.; Chung, H.-J.; Kim, E.-H.; Kim, S.; Park, E.-J.; Lee, S. K.; *Biochem. Pharmacol.* **2010**, *80*, 1356. (b) Gao, W.; Chen, A. P. C.; Leung, C. H.; Gullen, E. A.; Furstner, A.; Shi, Q.; Wei, L.; Lee, K. H.; Cheng, Y. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 704.

9) Baumgartner, B. J.; Erdelmeier, C. A.; Wright, A. D.; Rali, T.; Sticher, O. *Phytochemistry* **1990**, *29*, 3330.

10) Tuyen, N. V.; Kim, D. S. H. L.; Fong, H. S.; Soejarto, D. D.; Khanh, T. C.; Tri, M. V.; Xuan, L. T. *Phytochemistry* **1999**, *50*, 467.

11) Yap, V. A.; Qazzaz, M. E.; Raja, V. J.; Bradshaw, T. D.; Loh, H. –S.; Sim, K. –S.; Yong, K. –T.; Low, Y. –Y.; Lim, K.–H. *Phytochemistry* **2016**, *15*, 136-141.

12) (a) Pansare, S.V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624. (b) Pansare, S.V.,

Kirby R.L. *Tetrahedron* **2009**, *65*, 4557.

13) Reviews: (a) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*,757 (b) Sulzer- Mosse, S.; Alexakis, A. *Chem. Commun*. **2007**, *30*, 3123. (c) Enders, D.; Seki, A. *Eur. J. Org. Chem*. **2002**, 1877. (d) Review on enamine catalysis : Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B.; *Chem. Rev.* **2007**, *107*, 5471. Selected recent reports: (e) Ni, B.; Zhang, Q.; Dhungana, K.; Headley, A. D. *Org. Lett.* **2009**, *11*, 1041. (f) Mandal, T.; Zhao, C.-G. *Angew. Chem. Int. Ed*. **2008**, *47*, 7714. (g) Almasi, D.; Alonso, D. A.; Gomez-Benoga, E.; Nagel, Y.; Najera, C. *Eur. J. Org. Chem.* **2007**, 2328.

14) Reports on the application of organocatalytic Michael addition products in total synthesis: (a) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 4656. (b) Ishikawa, H. Suzuki, T.; Hayashi, Y. *Angew. Chem. Int. Ed*. **2009**, *48*, 1304. (c) Pavol, J.; Cockfield, D. M.; Dixon. D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632. (d) Elsner, P.; Jiang, H.; Nielson, J. B.; Pasi, F.; Jørgenson, K. A. *Chem. Commun.* **2008**, 5827. (e) Andrey, O.; Vidonne, A.; Alexakis, A, *Tetrahedron Lett.* **2003**, *44*, 7901. (f) Hynes, P. S.; Stupple, P. A.; Dixon, D. J. *Org. Lett*. **2008**, *10*, 1389. (g) Hong, B.-C.; Kotame, P.; Tsai, C- W.; Liao, J. –H. *Org. Lett.* **2010**, *12*, 776. (h) Pansare, S. V.; Lingampally, R.; Kirby, R. L. *Org. Lett*.**2010**, *12*, 556. (i) Hong, B.–C.; Nimje, R. Y.; Wu, M.–F.; Sadani, A. *Eur. J. Org. Chem.* **2008**, 1149.

15) Pansare, S. V.; Lingampally, R.; Dyapa, R. *Eur. J. Org. Chem.* **2011**, *12*, 2235-2238.

16) Milhazes, N.; Calheiros, R.; Marques, M. P.; Garrido, J.; Cordeiro, M. N. D. S.; Rodrigues, C.; Quinteira, S.; Novais, C.; Peixe, L.; Borges, F. *Biorg. Med. Chem.*

2006, *14*, 4078-4088.

17) Sun, H.; Zhu, L.; Yang, H.; Qian, W.; Guo, L.; Zhou, S.; Gao, B.; Li, Z.; Zhou, Y.; Jiang, H.; Chen, K.; Zhen, X. *Biorg. Med. Chem.* **2013**, *21*, 856-868.

18) Evans, D. A.; Chapman, K. T.; Carriera, E. A. *J. Am. Chem. Soc*. **1988**, *110*, 3560.

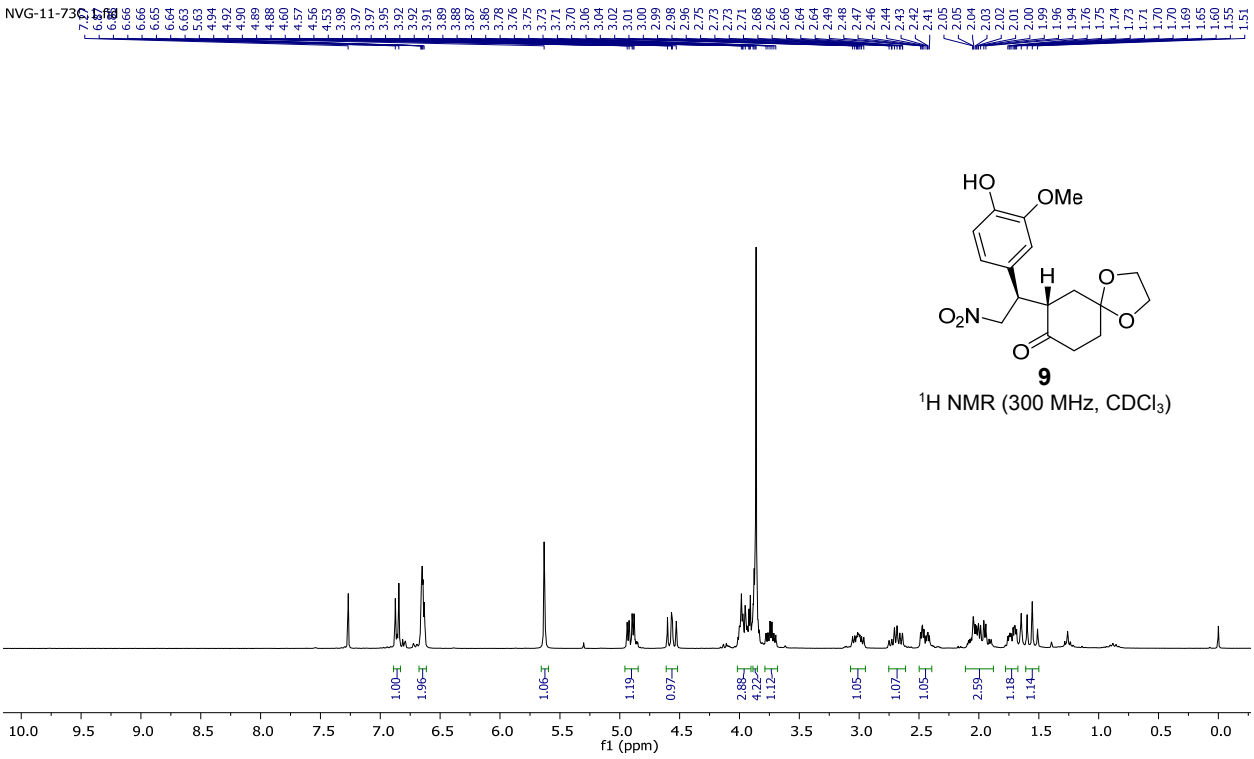
19) (a) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201. (b) Miyaura, N. Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

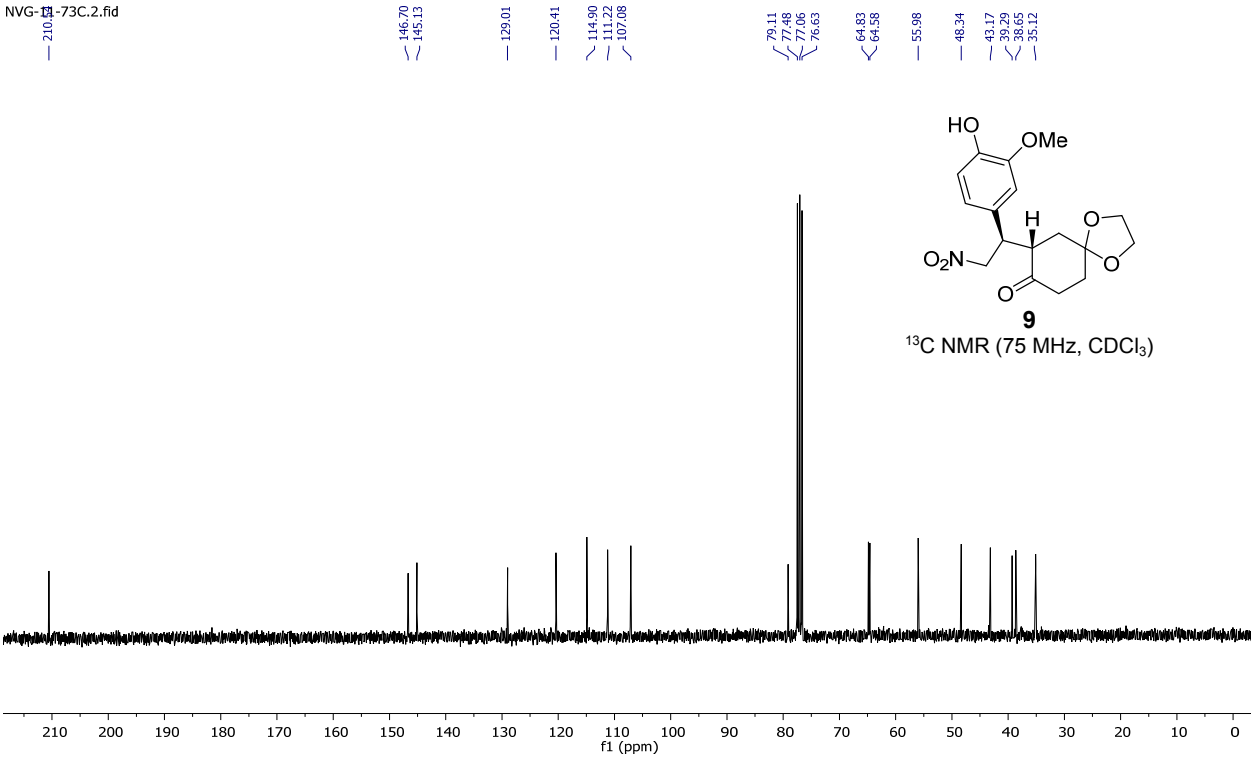
20) Weiser, P. T.; Chang, C.–Y.; McDonnell, D. P.; Hanson, R. N. *Biorg. Med. Chem.* **2014**, *22*, 917-926.

21) Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5397-5400.

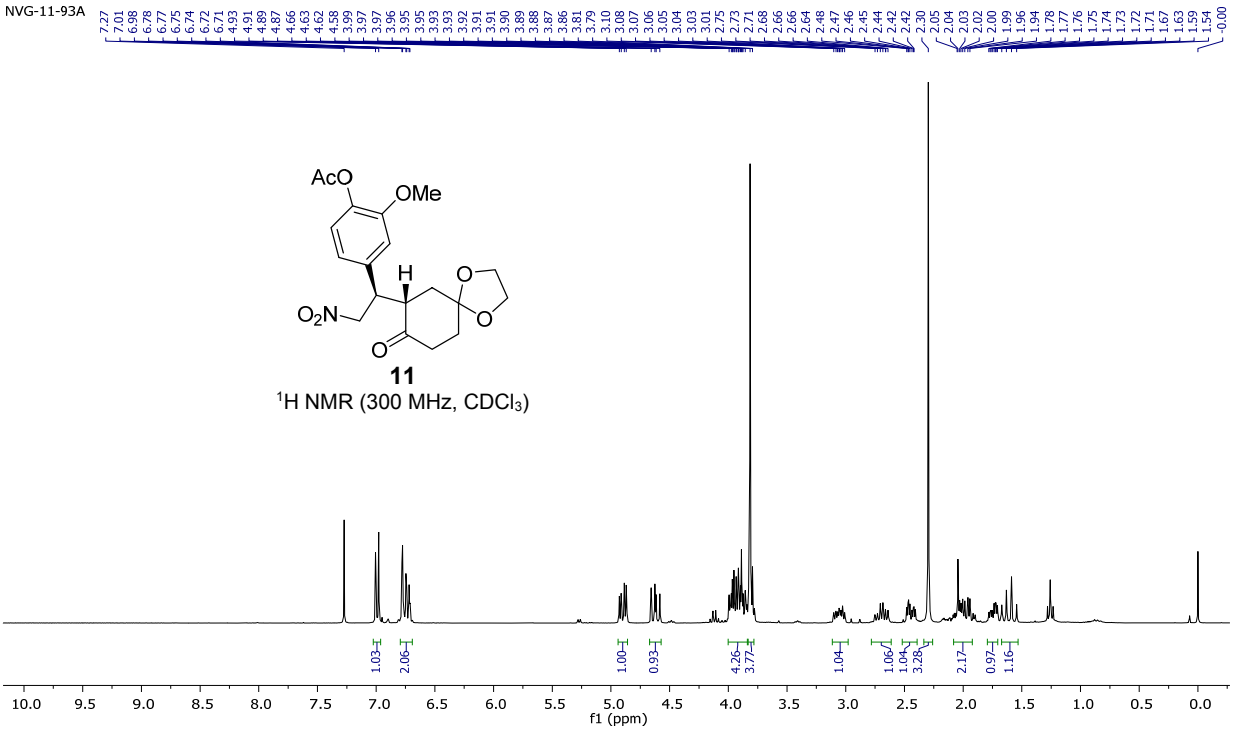
22) Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J .Org. Chem*. **1995**, *60*, 3574.

4.7 Selected ^{1}H NMR and ^{13}C NMR Spectra


HO
OMe
H
O
O
O_2N
O
9
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)


HO
OMe
H
O
O
O_2N
O
9
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

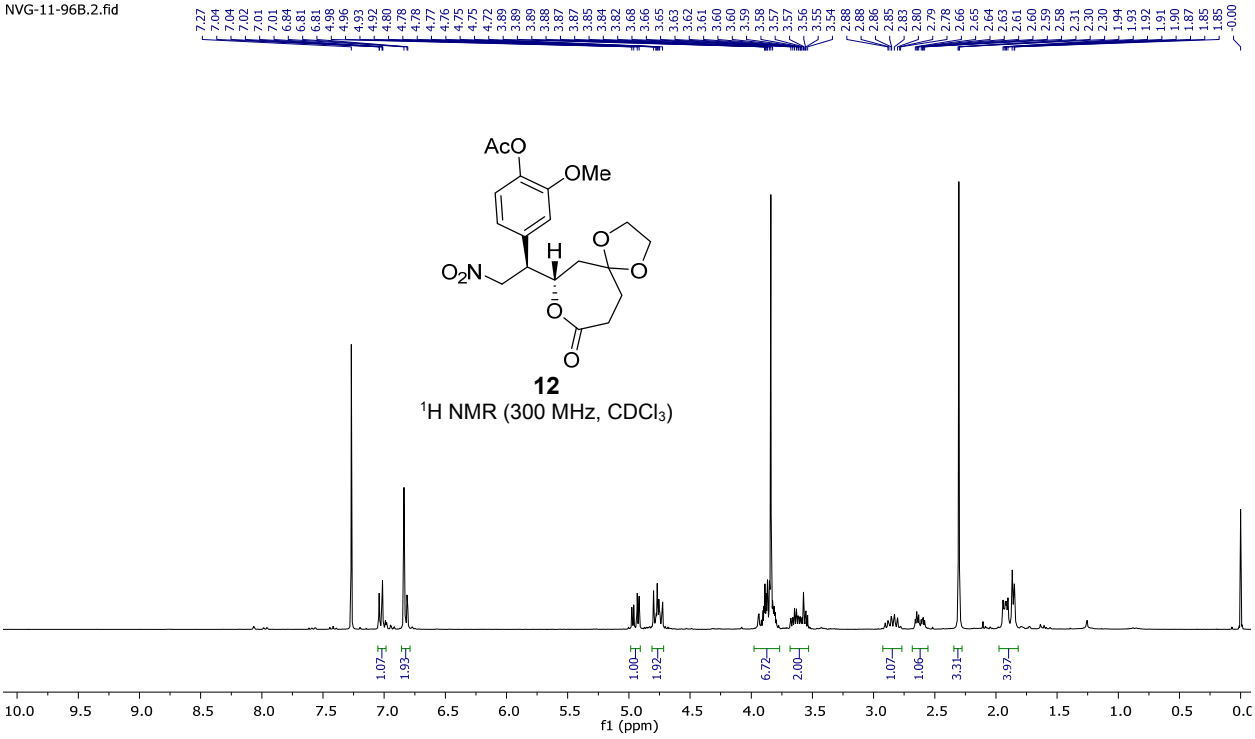
NVG-11-93A



11

^{1}H NMR (300 MHz, $CDCl_3$)

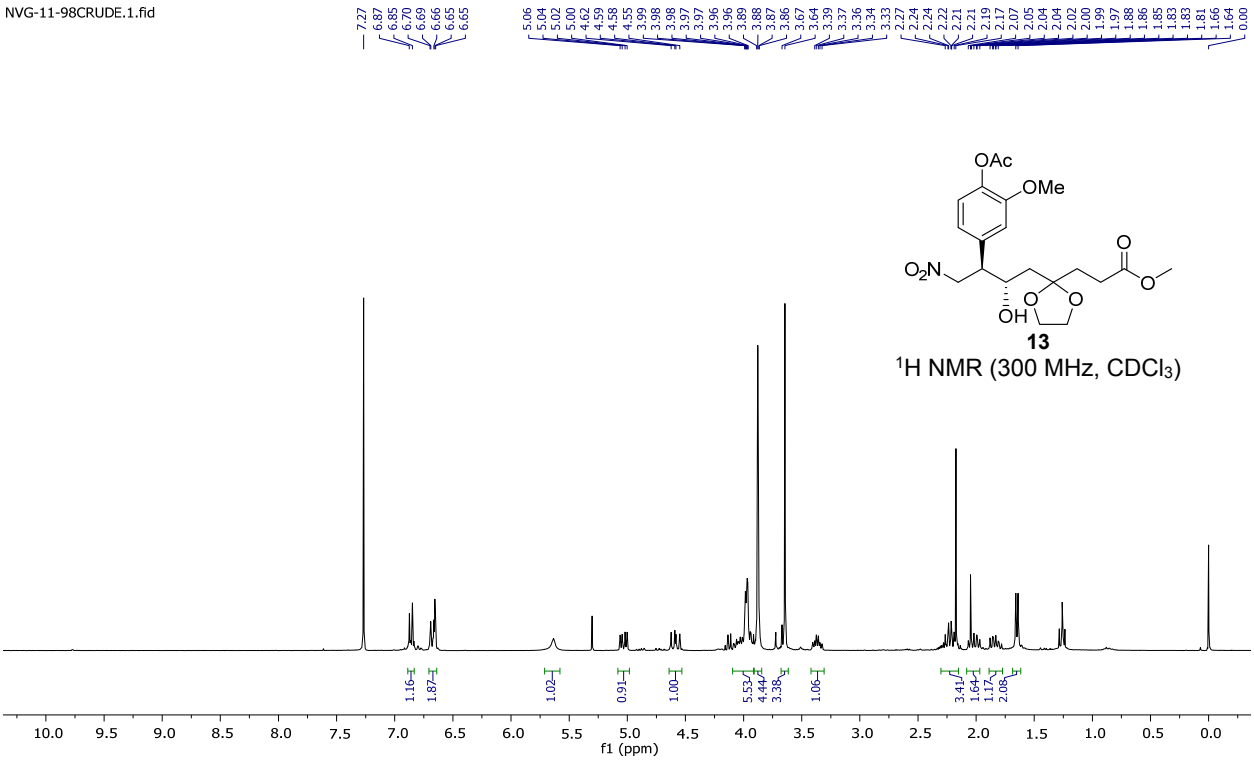
NVG-11-96B.2.fid



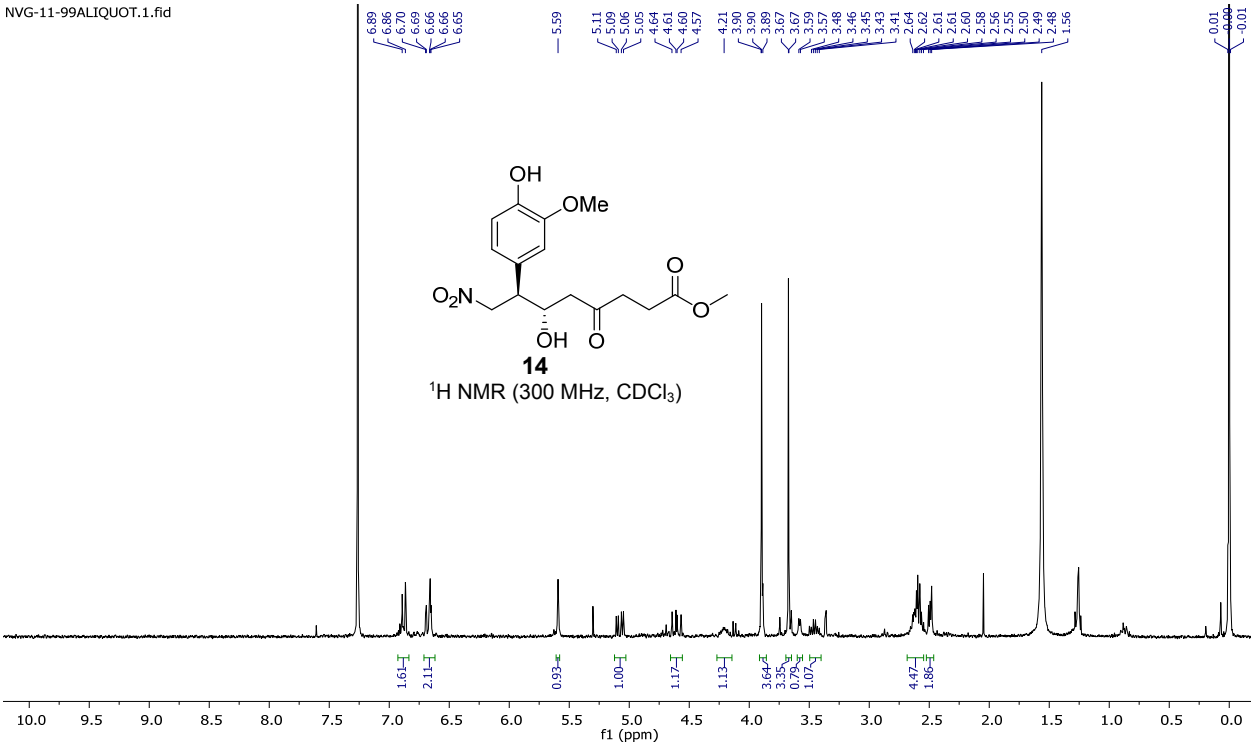
12

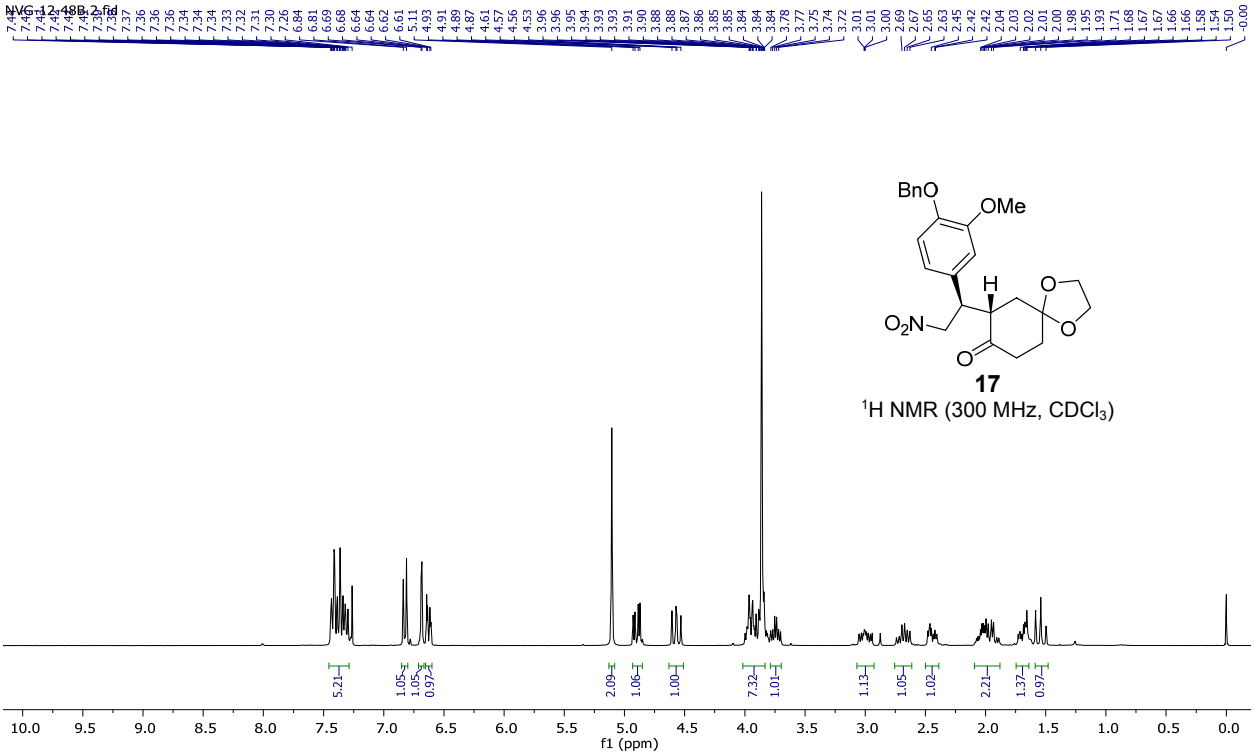
^{1}H NMR (300 MHz, $CDCl_3$)

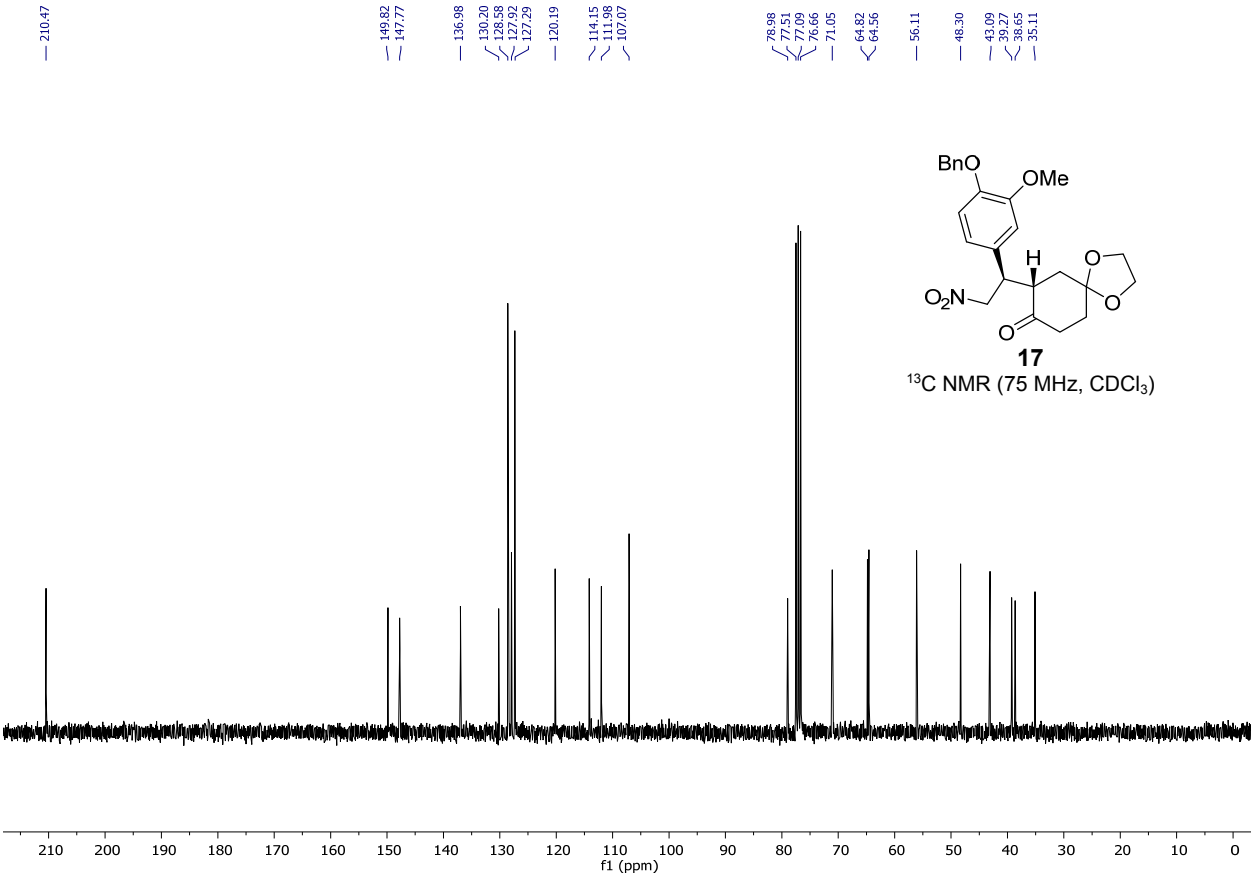
NVG-11-98CRUDE.1.fid

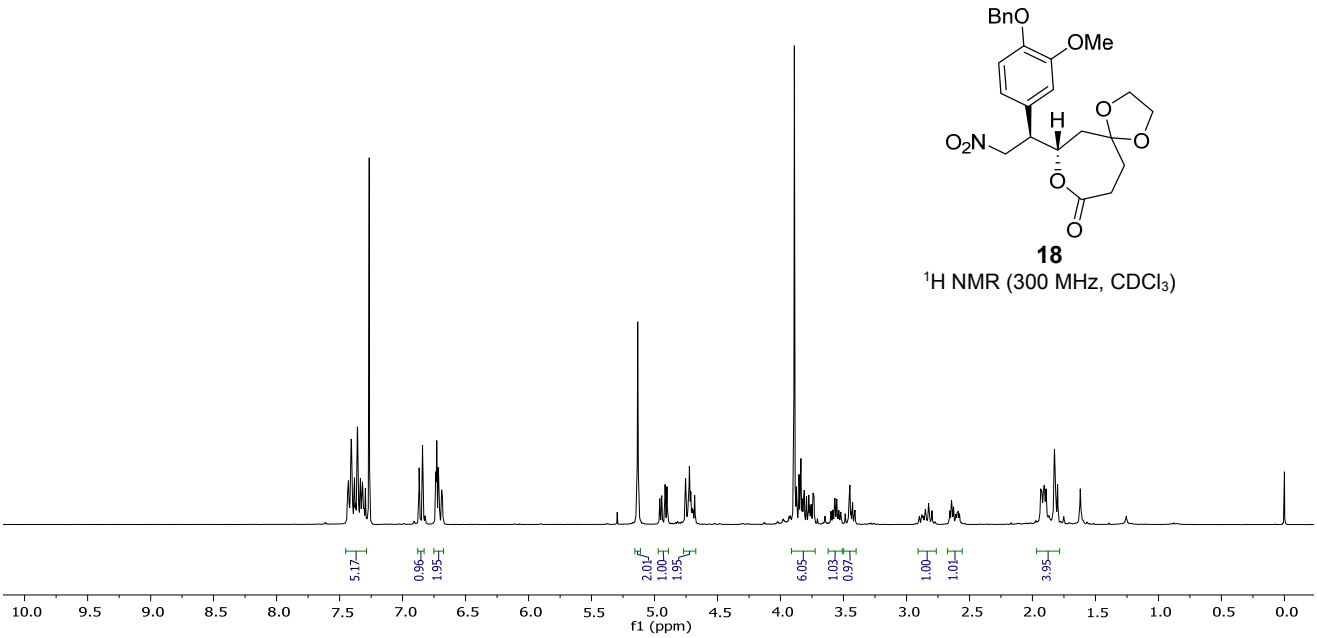


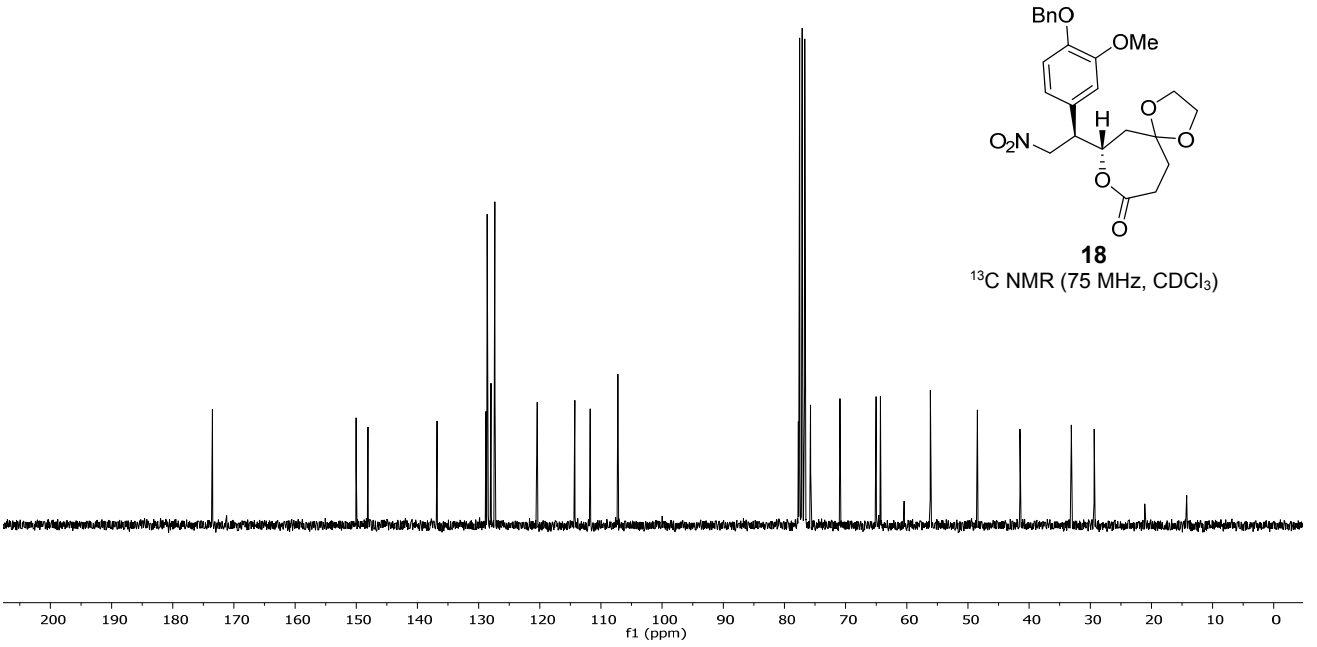
NVG-11-99ALIQUOT.1.fid

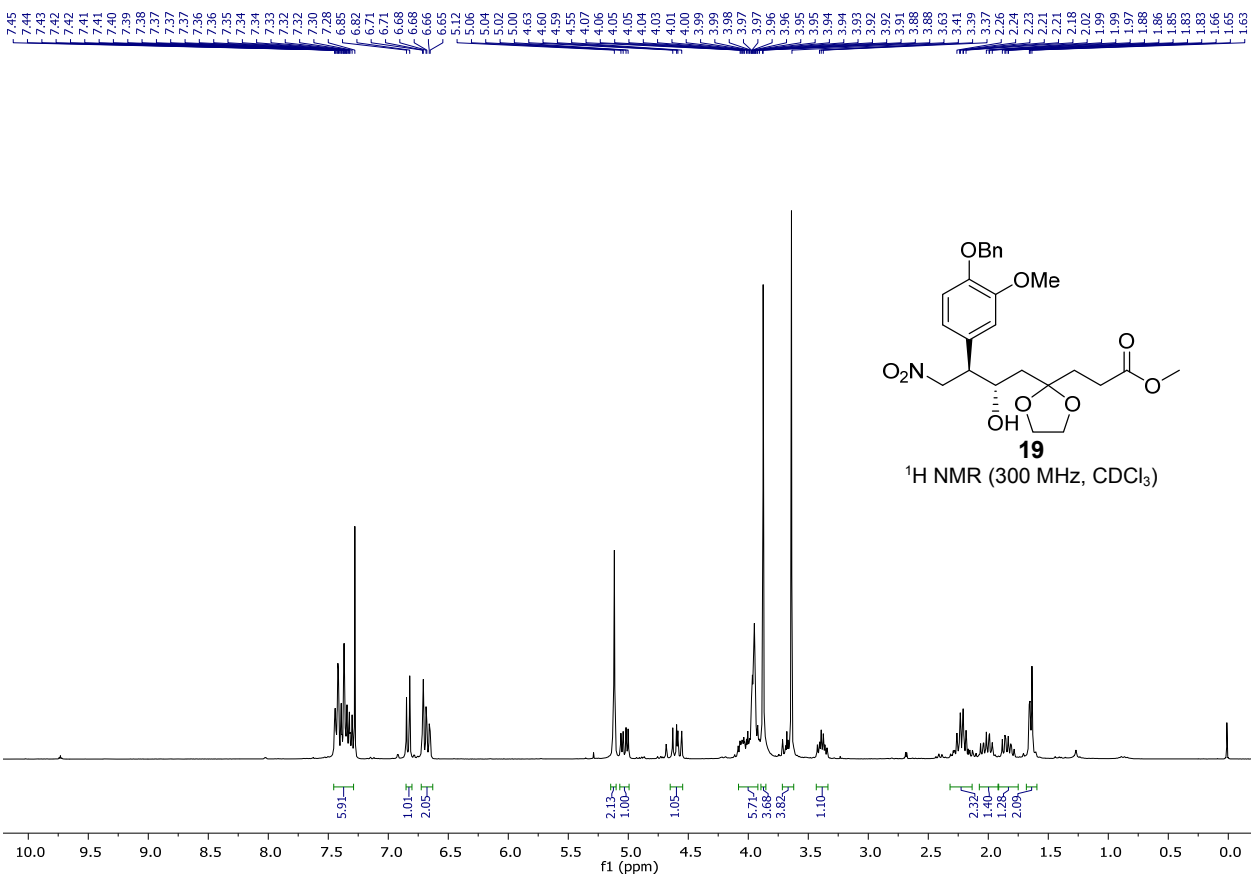


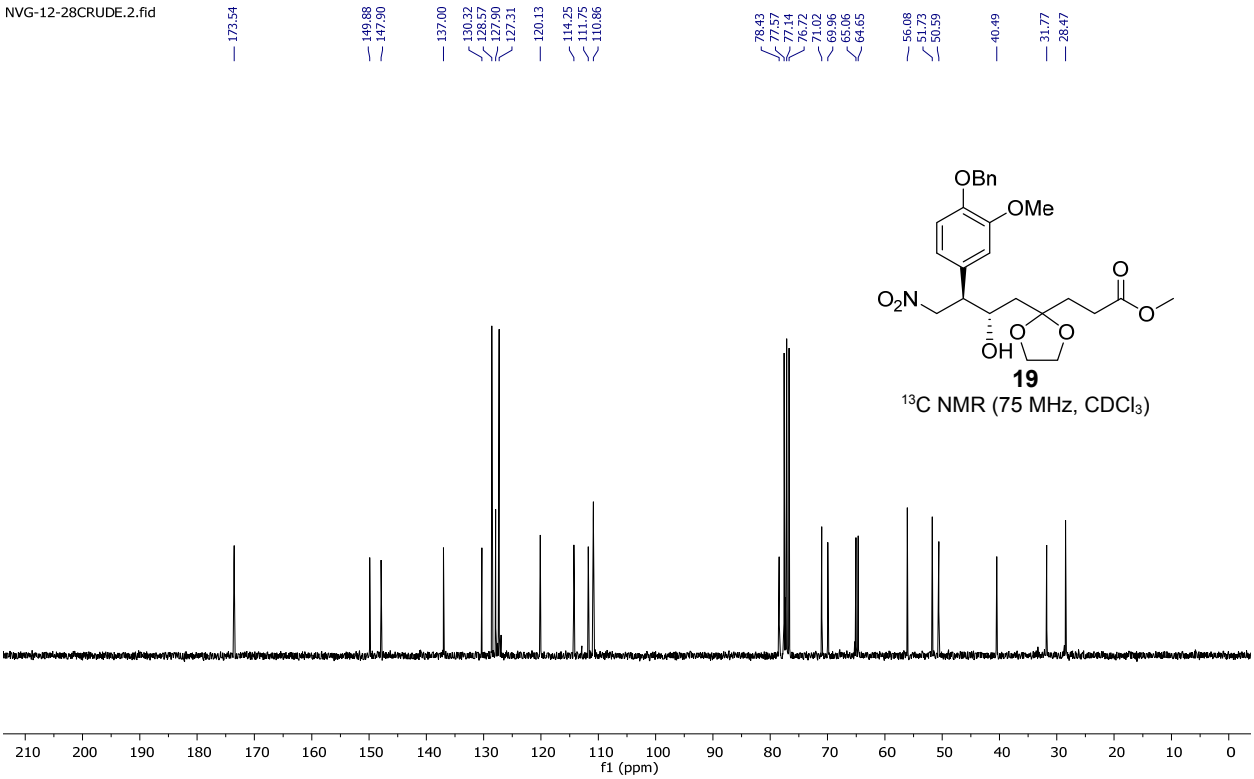

NVG-12-48B-2.fid
BnO
OMe
H
O
O
O_2N
O
17
^{1}H NMR (300 MHz, $CDCl_3$)
f1 (ppm)

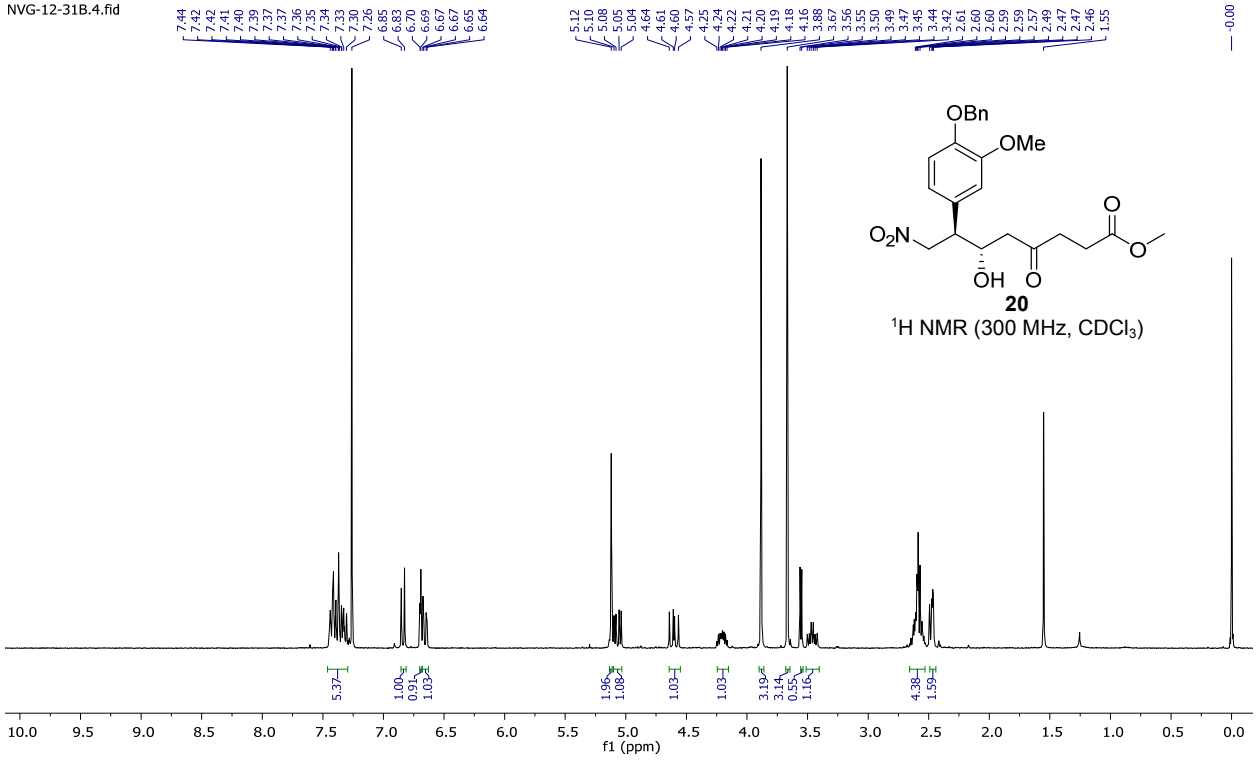

BnO
OMe
H
O
O
O_2N
O
17
^{13}C NMR (75 MHz, $CDCl_3$)
f1 (ppm)

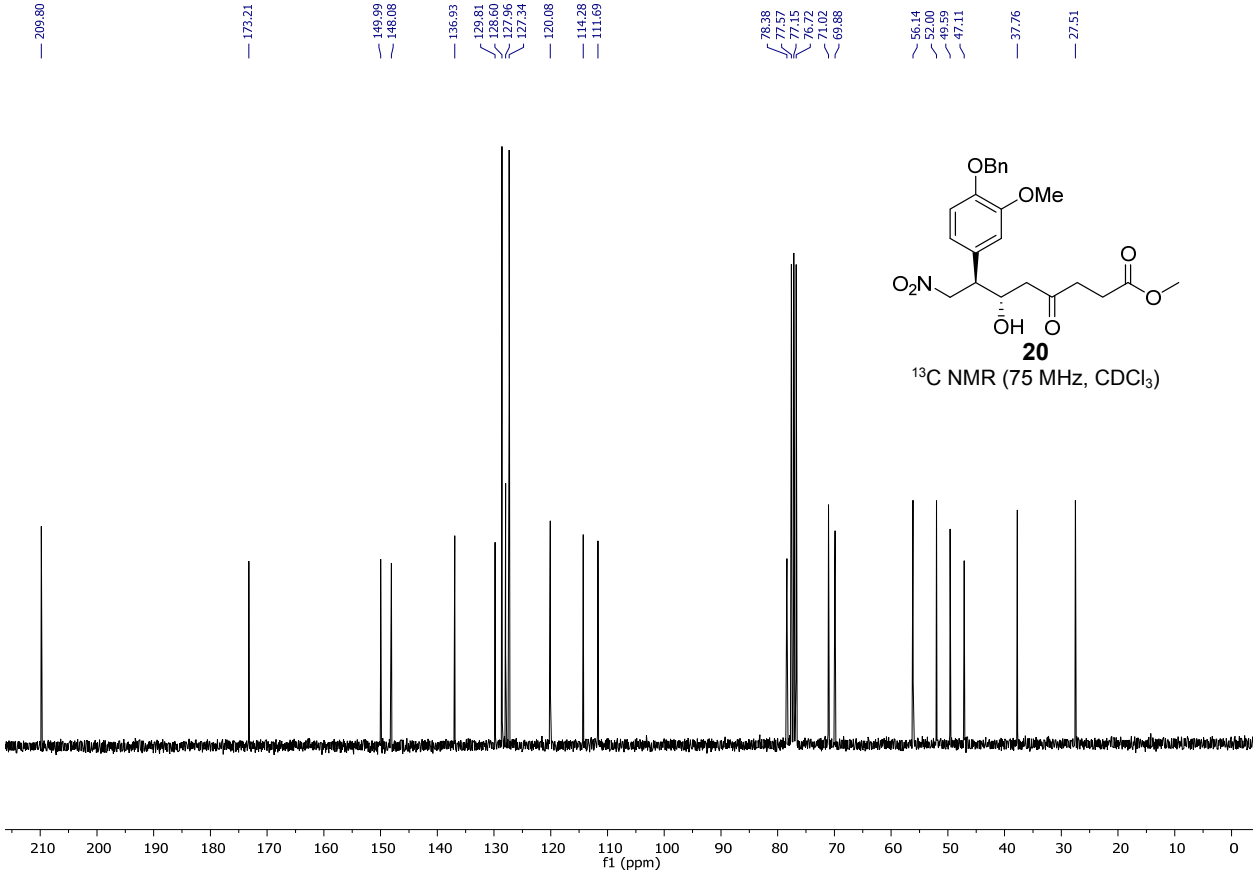

BnO
OMe
H
O2N
O
O
O
O
18
1H NMR (300 MHz, CDCl3)
5.17
0.96
1.95
2.01
1.00
1.95
6.05
1.03
0.97
1.00
1.01
3.95
f1 (ppm)

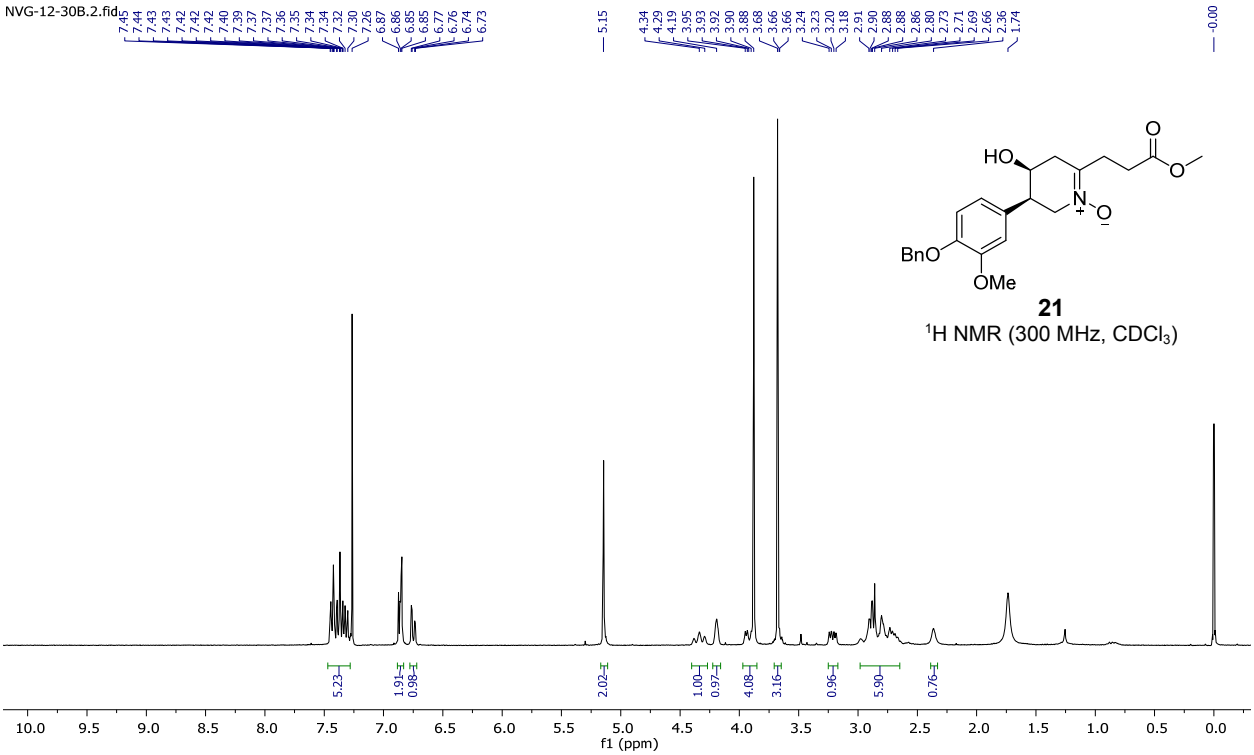

BnO
OMe
H
O2N
O
O
O
O
18
13C NMR (75 MHz, CDCl3)
f1 (ppm)

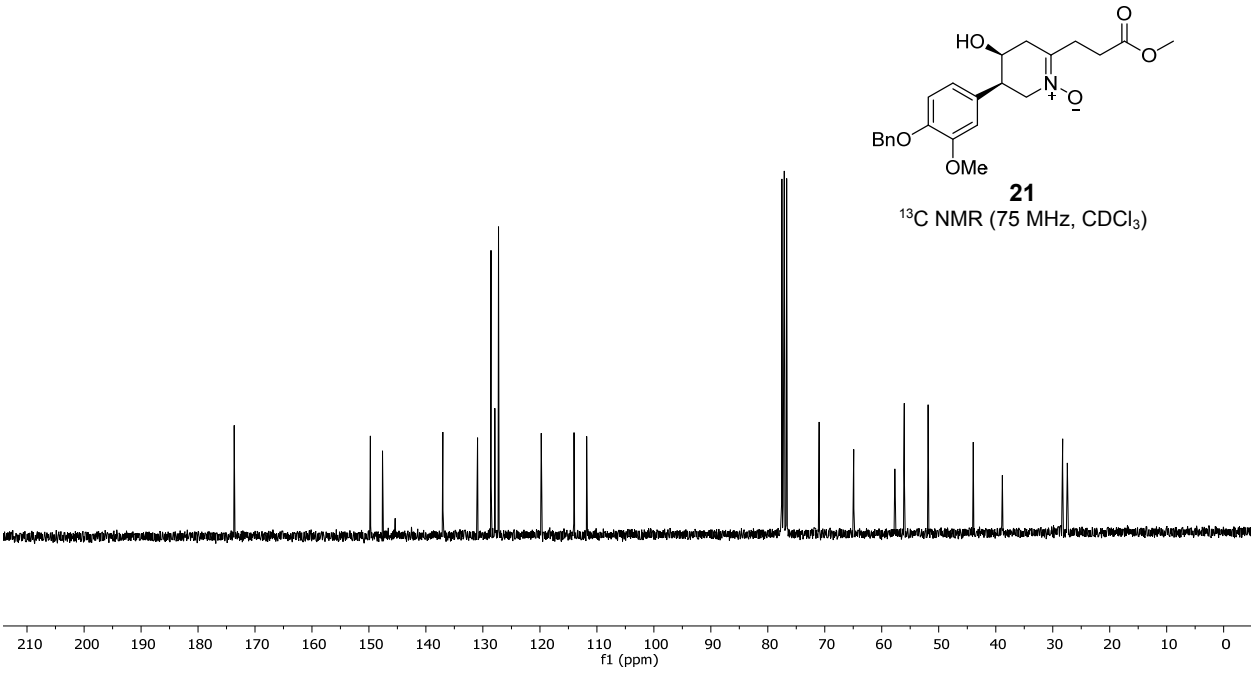

OBn
OMe
O2N
O
O
O
OH
19
1H NMR (300 MHz, CDCl3)
f1 (ppm)

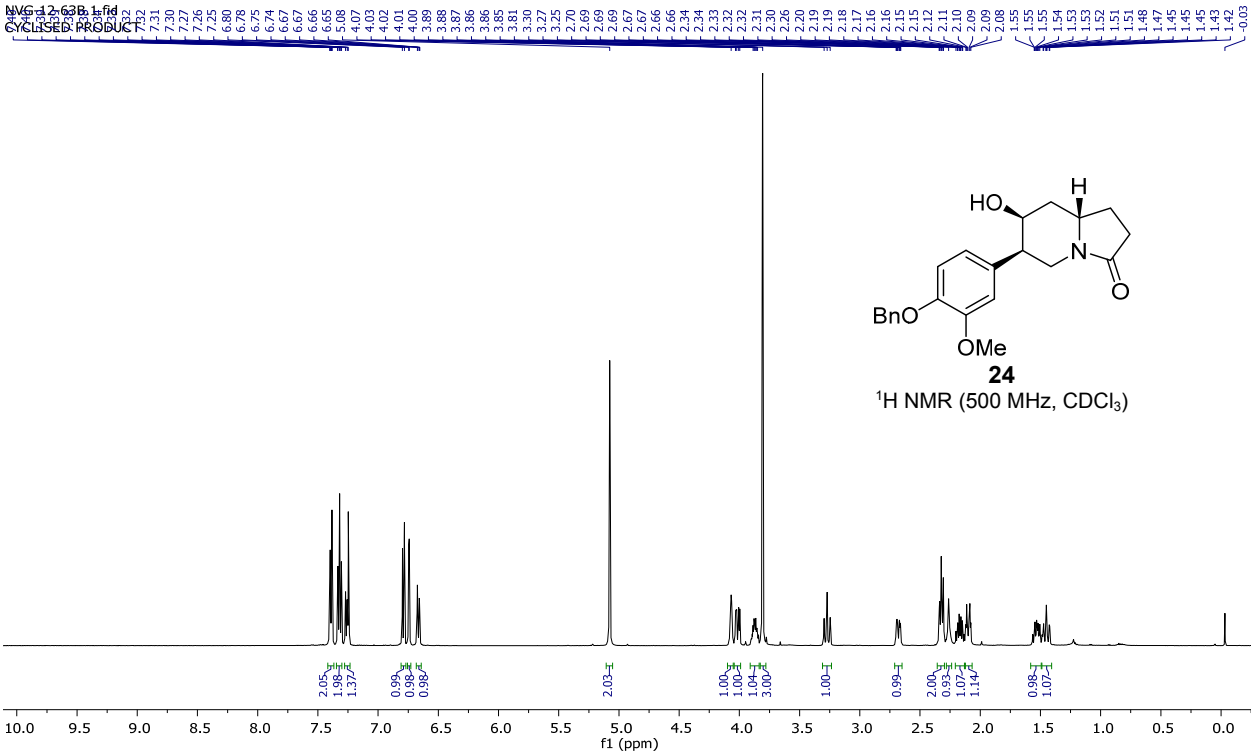

NVG-12-28CRUDE.2.fid
OBn
OMe
O2N
O
O
O
OH
19
13C NMR (75 MHz, CDCl3)
f1 (ppm)

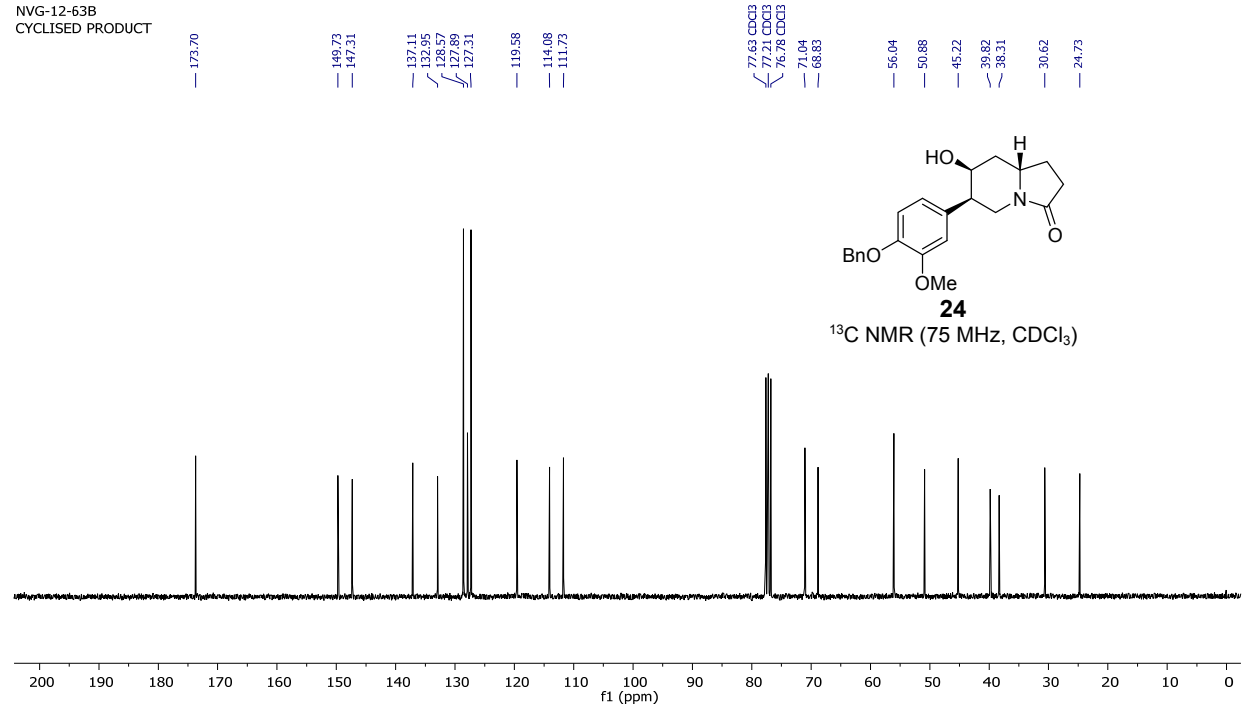

NVG-12-31B.4.fid
OBn
OMe
O2N
OH
O
20
1H NMR (300 MHz, CDCl3)
f1 (ppm)

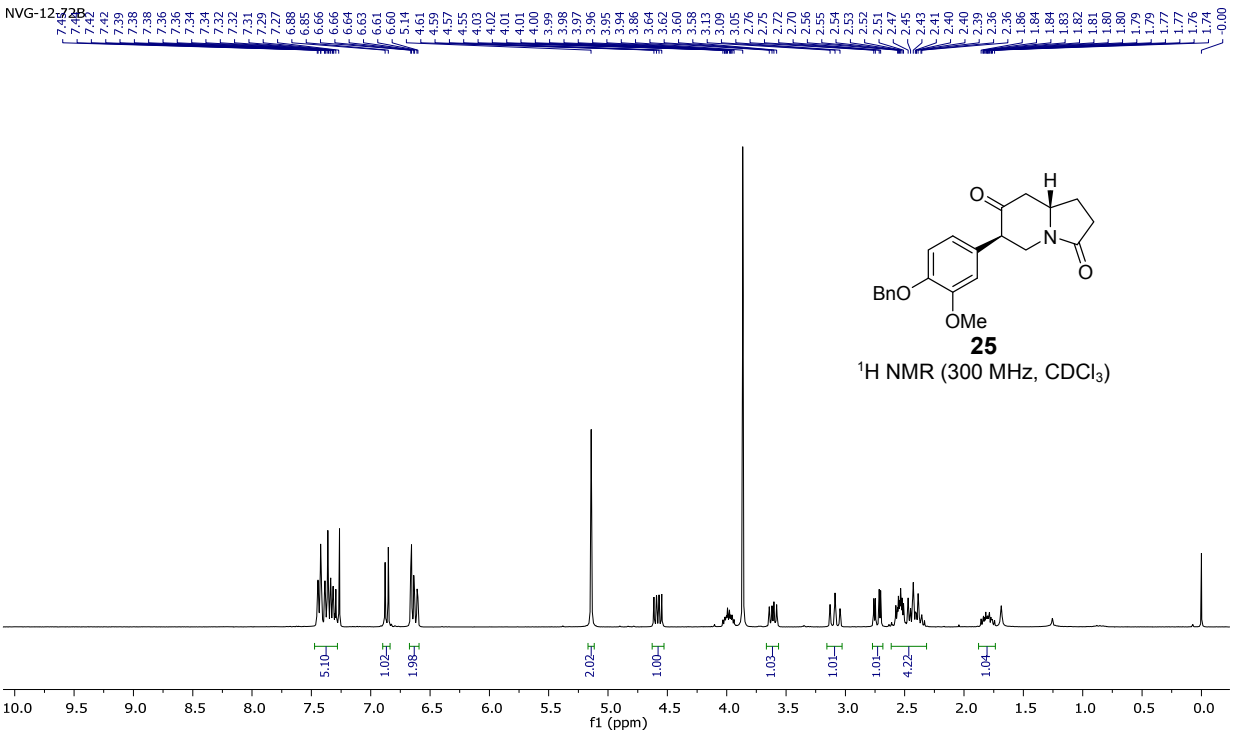

OBn
OMe
O2N
OH
O
20
13C NMR (75 MHz, CDCl3)
f1 (ppm)

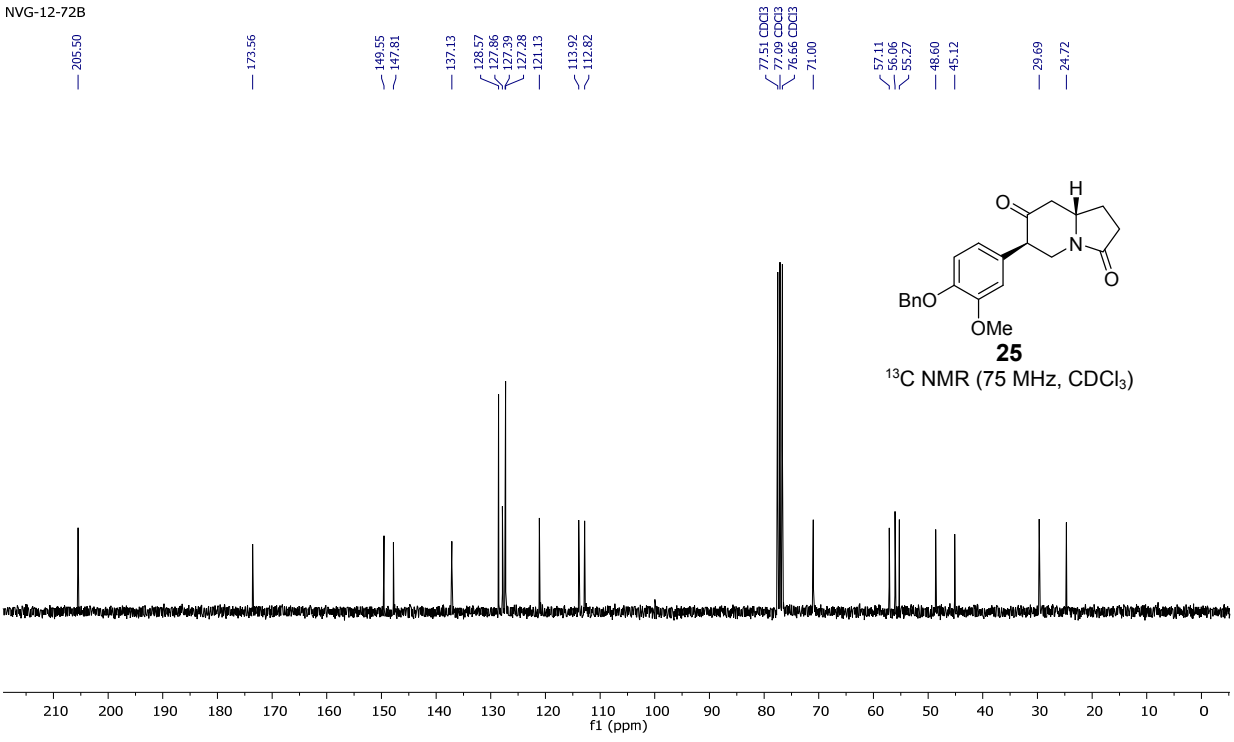

NVG-12-30B.2.fid
HO
O
O
N
O
BnO
OMe
21
1H NMR (300 MHz, CDCl3)
f1 (ppm)


HO
O
O
N
O
BnO
OMe
21
13C NMR (75 MHz, CDCl3)
f1 (ppm)

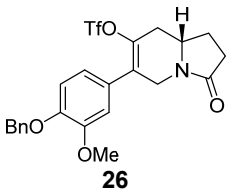

NVG-12-63B 1.fid
CYCLISED PRODUCT
HO
H
N
O
BnO
OMe
24
1H NMR (500 MHz, CDCl3)
f1 (ppm)


NVG-12-63B
CYCLISED PRODUCT
HO
H
N
O
BnO
OMe
24
13C NMR (75 MHz, CDCl3)
f1 (ppm)


NVG-12-72B
BnO
OMe
25
1H NMR (300 MHz, CDCl3)
f1 (ppm)

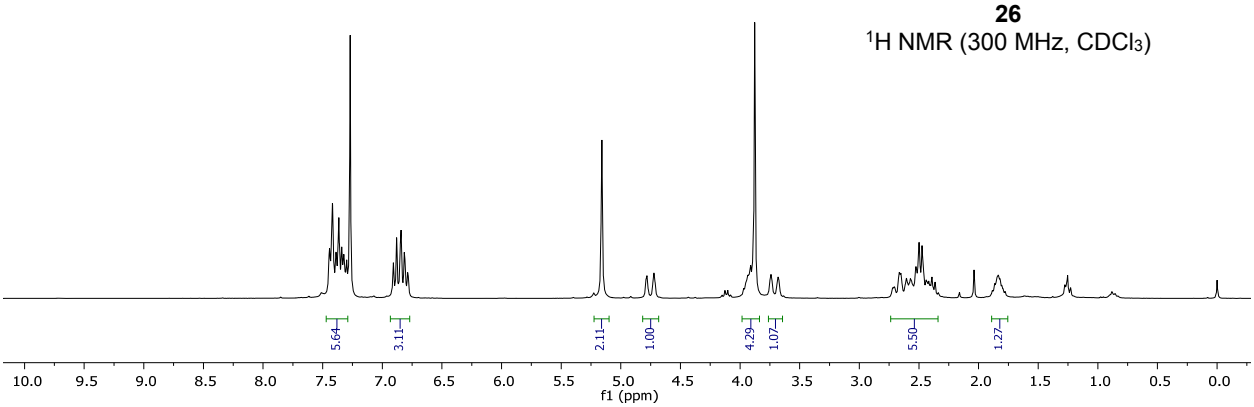

NVG-12-72B
BnO
OMe
25
13C NMR (75 MHz, CDCl3)
f1 (ppm)

NVG-12-86B.2.fid

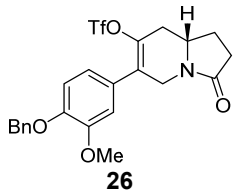


26

^{1}H NMR (300 MHz, $CDCl_3$)

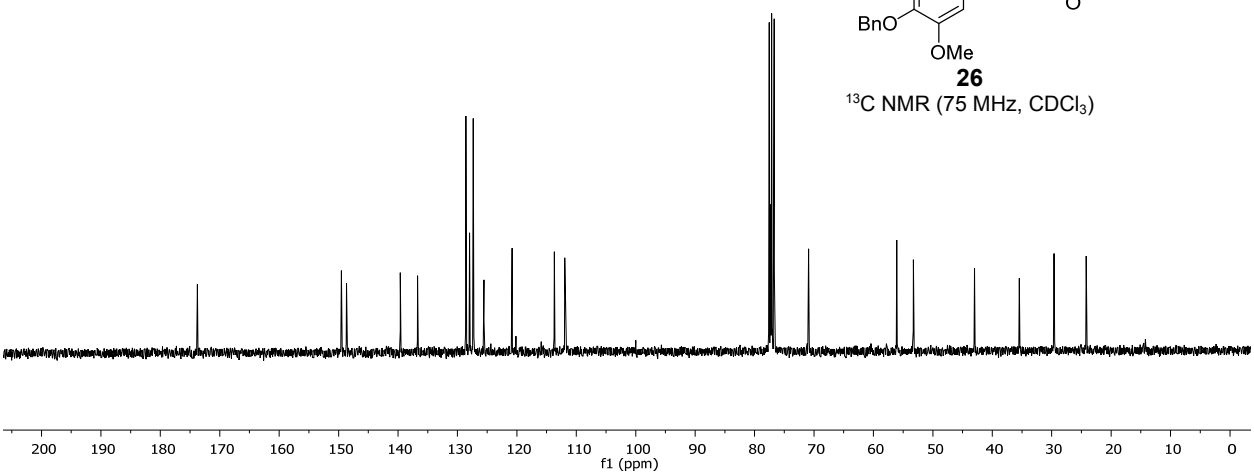


NVG-12-86B.4.fid

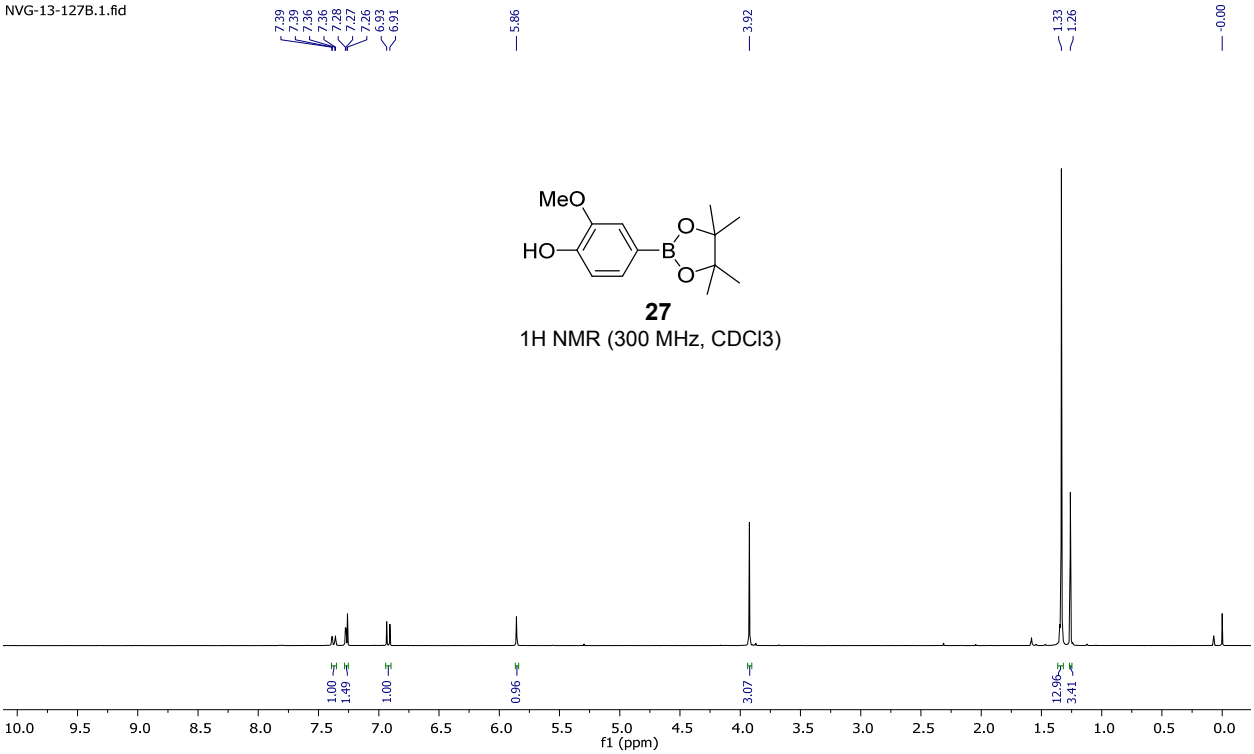


26

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

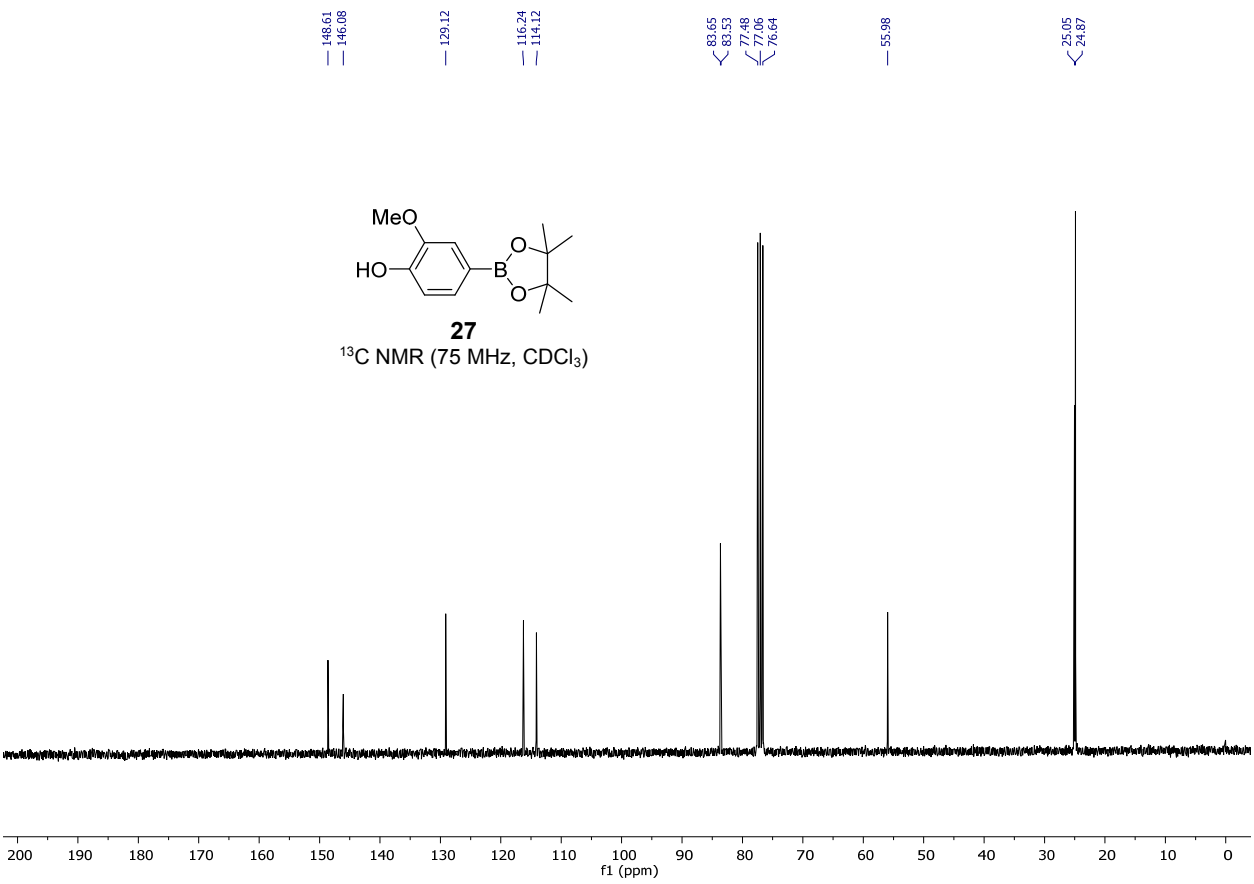


NVG-13-127B.1.fid



27

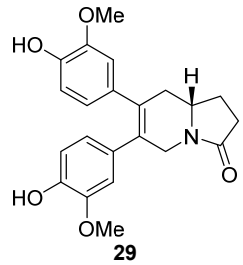
1H NMR (300 MHz, CDCl3)



27

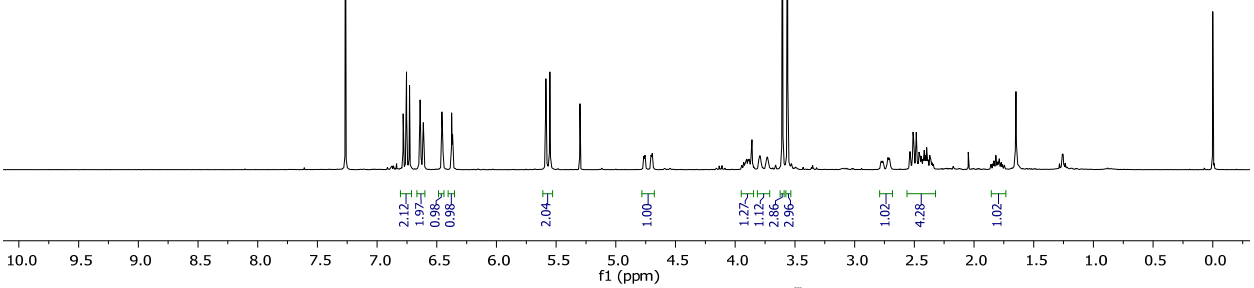
^{13}C NMR (75 MHz, $CDCl_3$)

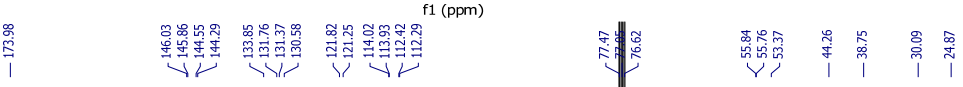
NVG-12-91B.1.fid

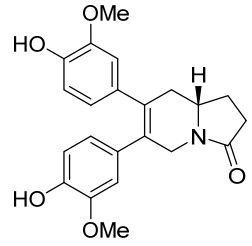


29

^{1}H NMR (300 MHz, $CDCl_3$)



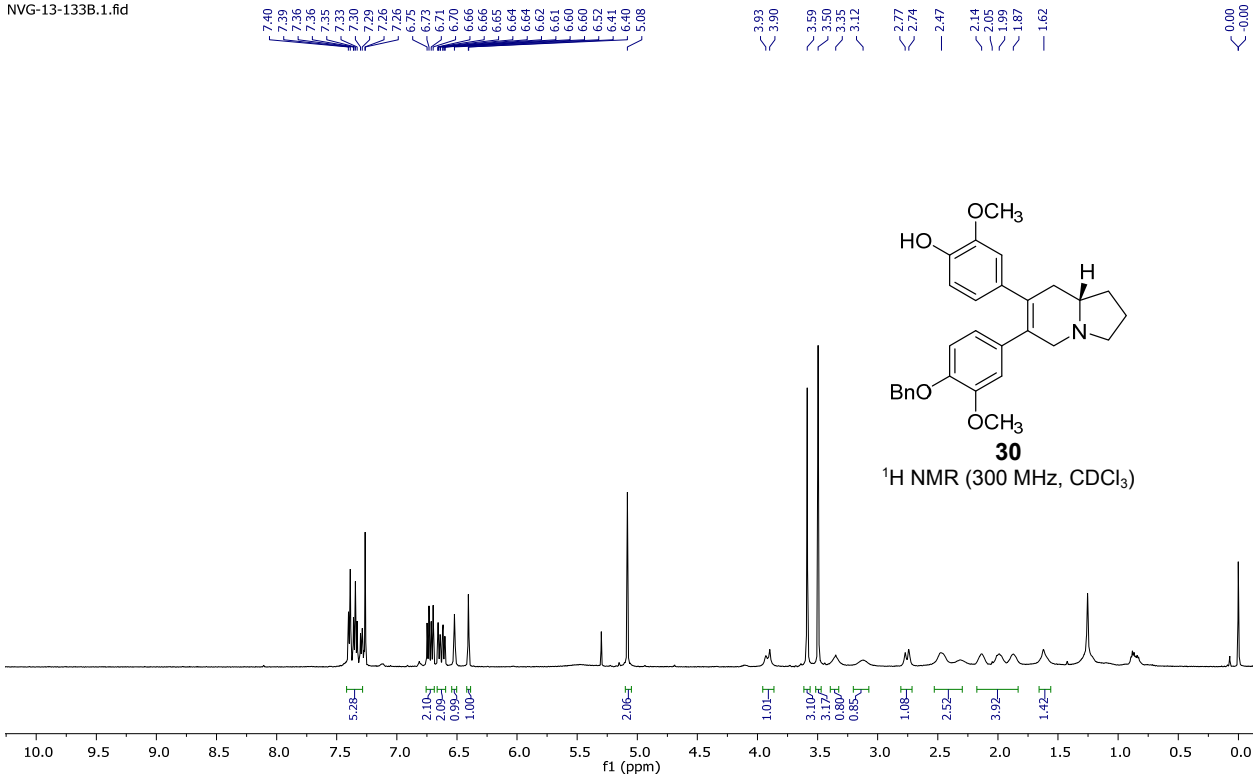


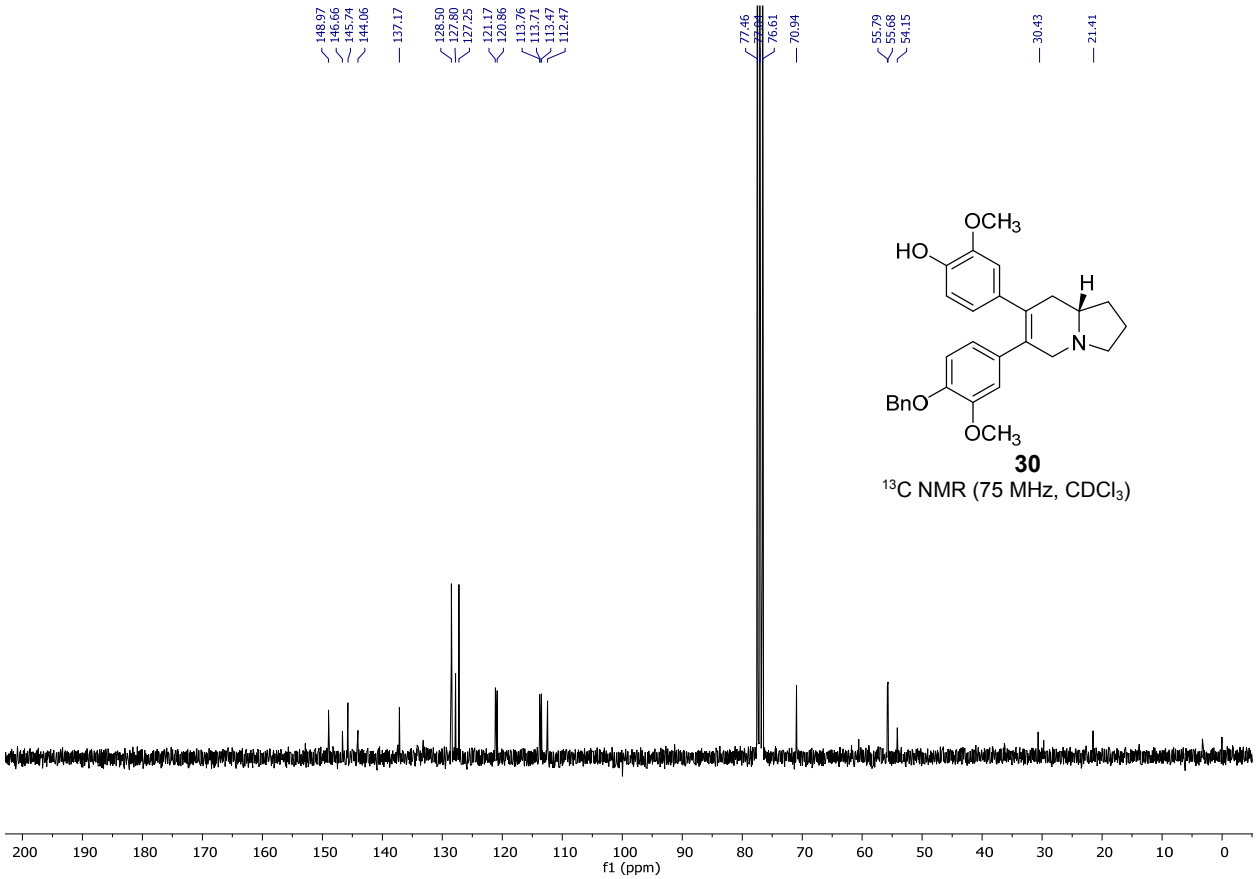


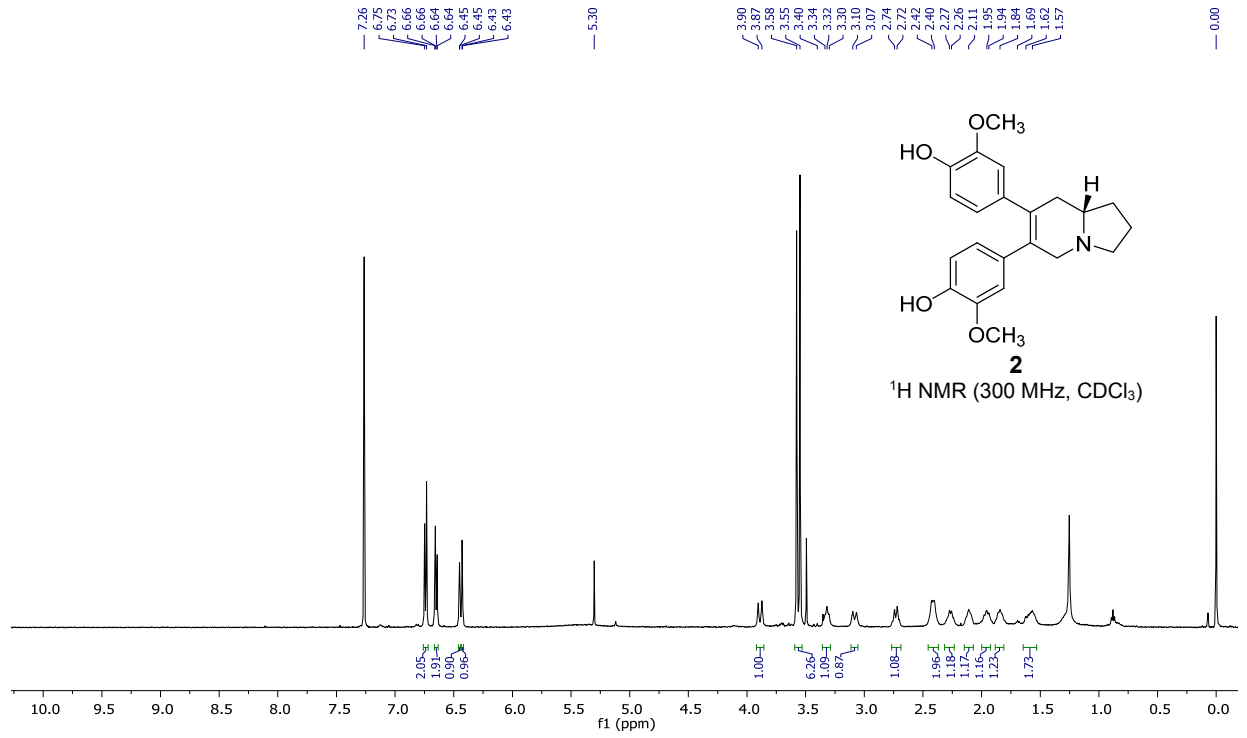
29

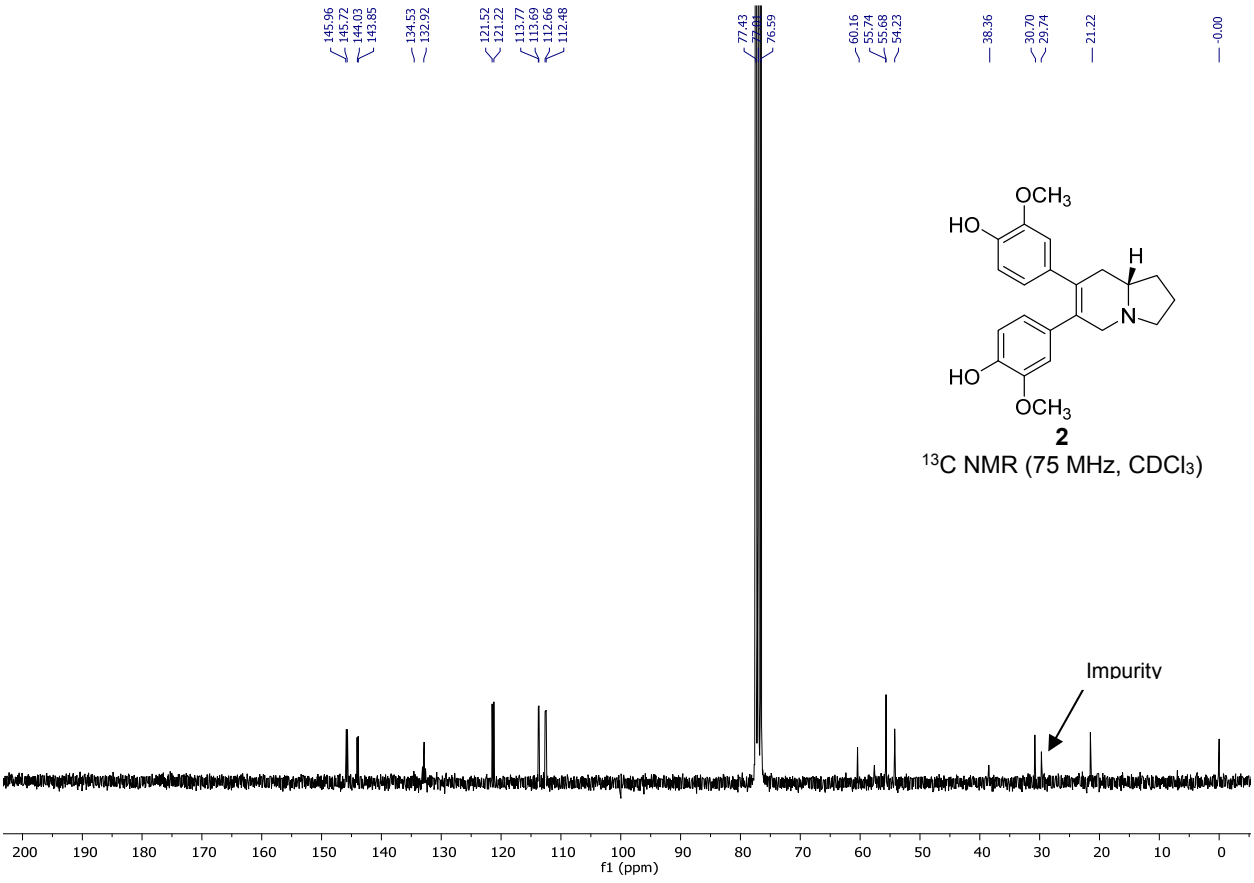
^{13}C NMR (75 MHz, $CDCl_3$)

NVG-13-133B.1.fid






OCH3
HO
H
N
HO
OCH3
2
1H NMR (300 MHz, CDCl3)
f1 (ppm)


OCH3
HO
H
N
HO
OCH3
2
13C NMR (75 MHz, CDCl3)
Impurity
f1 (ppm)

Memorial University

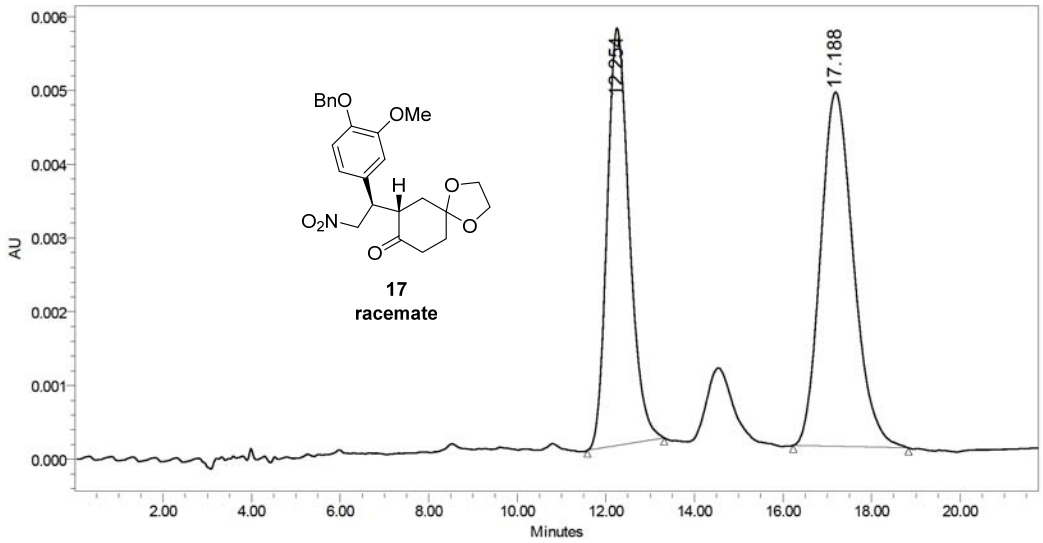
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-13-67B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	09/12/2016 12:15:26 PM NST
Vial:	104	Acq. Method:	ASH 60%HEX 40%IPA
Injection #:	1	Date Processed:	09/12/2016 12:38:27 PM NST
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



17
racemate

	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.254	196985	44.35	5661	54.11
2	17.188	247182	55.65	4801	45.89

Report Method: Individual Control Report

Page: 1 of 1

Printed: 09/12/2016

12:39:06 PM Canada/Newfoundland

Memorial University

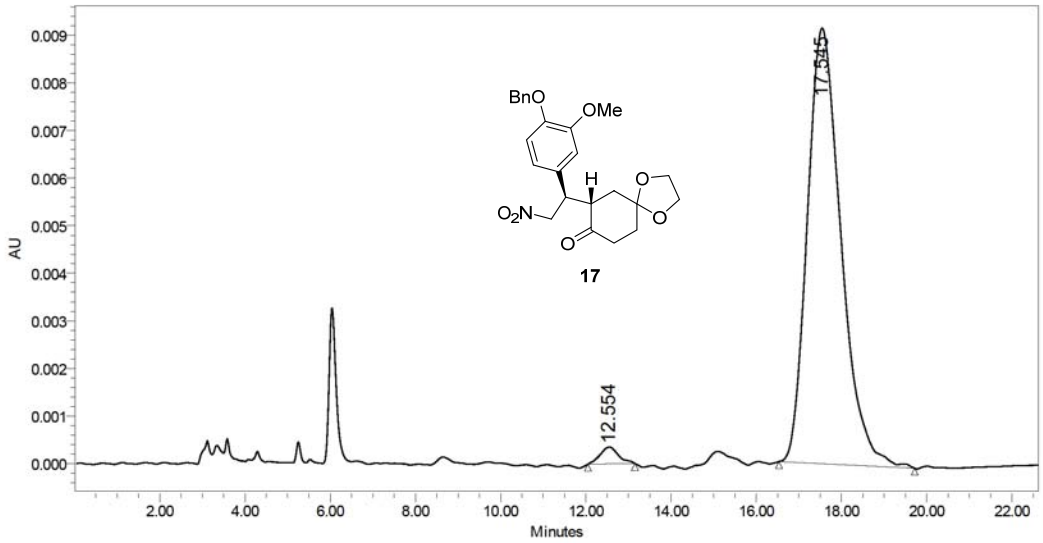
Project Name Moorthy

Reported by User: Breeze user (Breeze)

Breeze 2 HPLC System

SAMPLE INFORMATION

Sample Name:	NVG-12-52B	Acquired By:	Breeze
Sample Type:	Unknown	Date Acquired:	06/12/2016 6:54:25 PM NST
Vial:	103	Acq. Method:	ASH 60%HEX 40%IPA
Injection #:	1	Date Processed:	14/07/2017 5:38:30 PM NDT
Injection Volume:	10.00 ul	Channel Name:	2487Channel 1
Run Time:	40.00 Minutes	Channel Desc.:	
Column Type:		Sample Set Name	



	RT (min)	Area (µV*sec)	% Area	Height (µV)	% Height
1	12.554	10558	2.06	354	3.72
2	17.545	501752	97.94	9159	96.28

Report Method: Individual Control Report

Page: 1 of 1

Printed: 14/07/2017

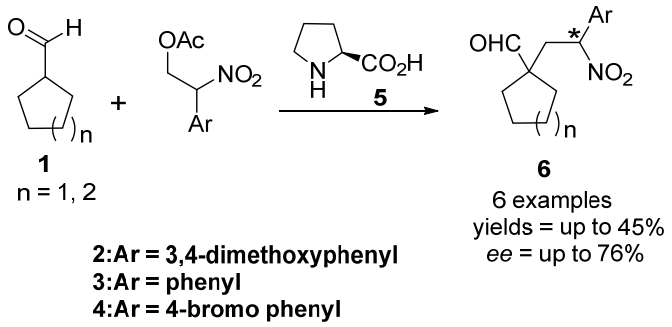
5:40:15 PM Canada/Newfoundland

Chapter 5 - Summary of the thesis

Conclusions

5.1 Organocatalytic conjugate addition reactions of aldehydes/ketones to *in situ* generated *α*-nitrostyrenes.

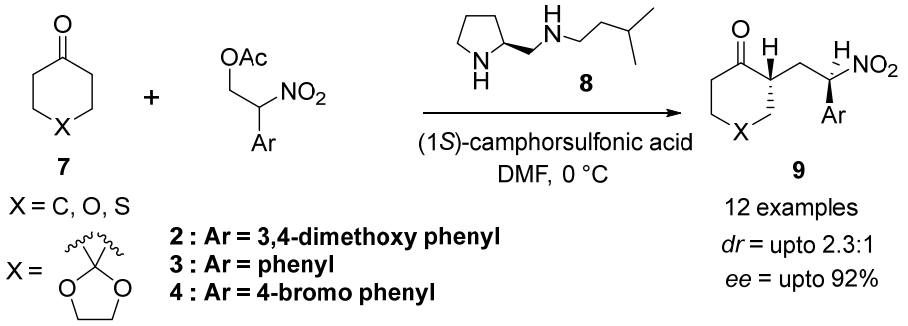
The organocatalytic, enamine mediated conjugate addition of aldehydes **1** to *α*-nitrostyrenes generated *in situ* from the corresponding nitroacetates was developed. A catalyst survey was carried out to find the optimal catalyst. Among the various catalysts examined, (*S*)-proline (**5**) gave the best result. The optimized conditions were employed in the study of the scope of the reaction with a variety of aldehydes. Overall, moderate yields (up to 45%) and enantioselectivities (up to 76%) were obtained.



Scheme 5.1

The organocatalytic, enamine mediated conjugate addition of cyclic ketones **7** to *α*-nitrostyrenes generated *in situ* from the corresponding nitroacetates (**2**-**4**) was also examined. In this case, a (*S*)-proline derived diamine was found to be the optimal catalyst. The optimized conditions were employed in the study of the scope of the

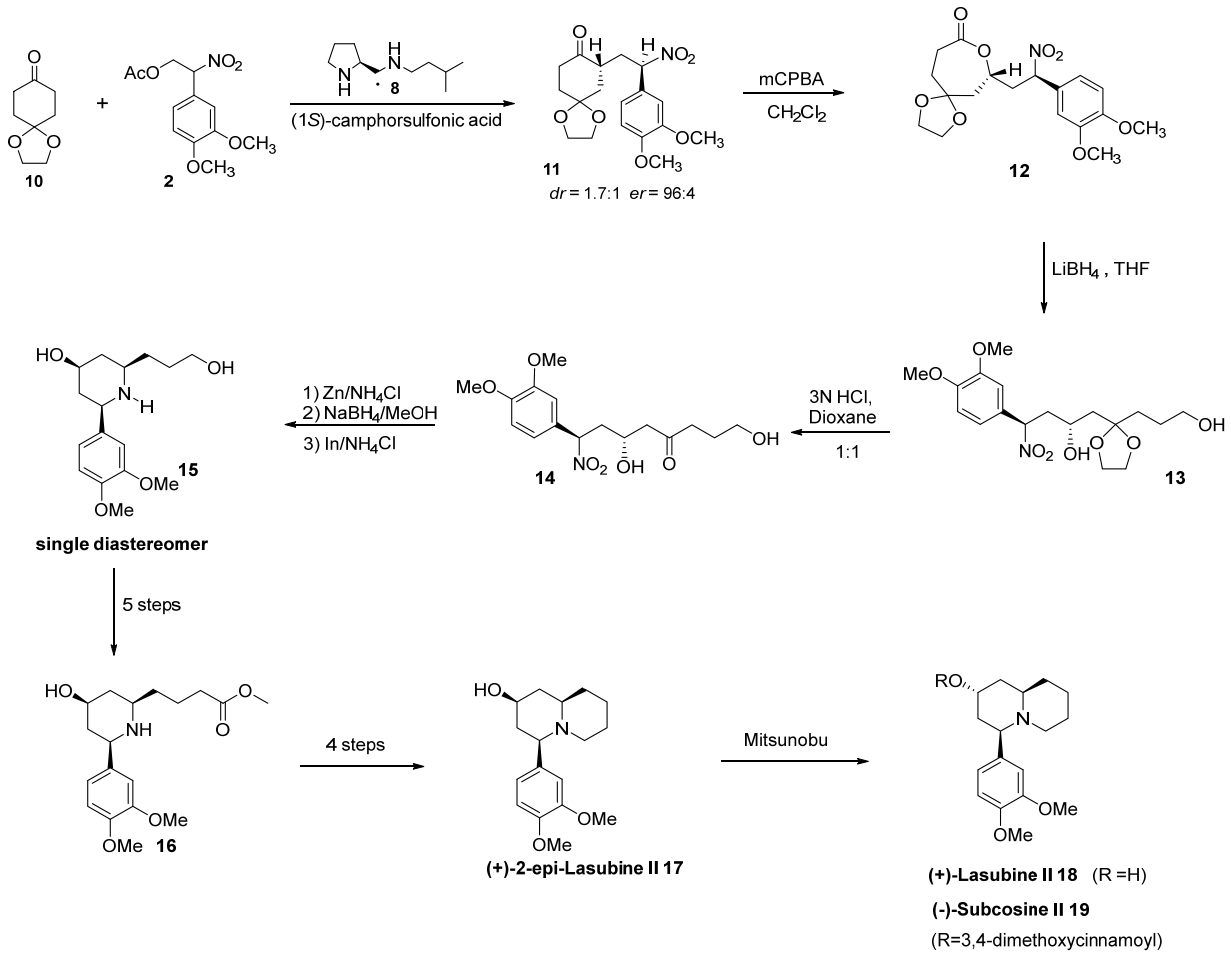
reaction with a variety of cyclic ketones. The Michael adducts **9** were obtained with moderate diastereoselectivities (up to 2.3:1) and moderate to good enantioselectivities (up to 92%).



Scheme 5.2

5.2 Formal Synthesis of (+)-Lasubine II and (-)-Subcosine II via Organocatalytic Michael Addition Reactions of a Ketone to *in situ* Generated *α*-Nitrostyrene

The above methodology was used as the key step in a synthesis of enantiomers of the naturally occurring quinolizidine alkaloids (+)-lasubine II (**18**) and (-)-subcosine II (**19**). The organocatalytic Michael addition of 1,4-cyclohexanedione monoethylene ketal **10** to the *α*-nitrostyrene generated *in situ* from the nitroacetate **2** gave the enantiomerically enriched *γ*-nitroketone **11**. Oxidative ring expansion of the ketone **11** and subsequent reduction provided a nitrodiol **13**. This is stereoselectively transformed to the key, functionalized piperidine intermediate which is readily converted to (+)-2-epilasubine II **17** which is the precursor for the formal total synthesis of (+)-lasubine II **18** and (-)-subcosine II **19** (Scheme 5.3).

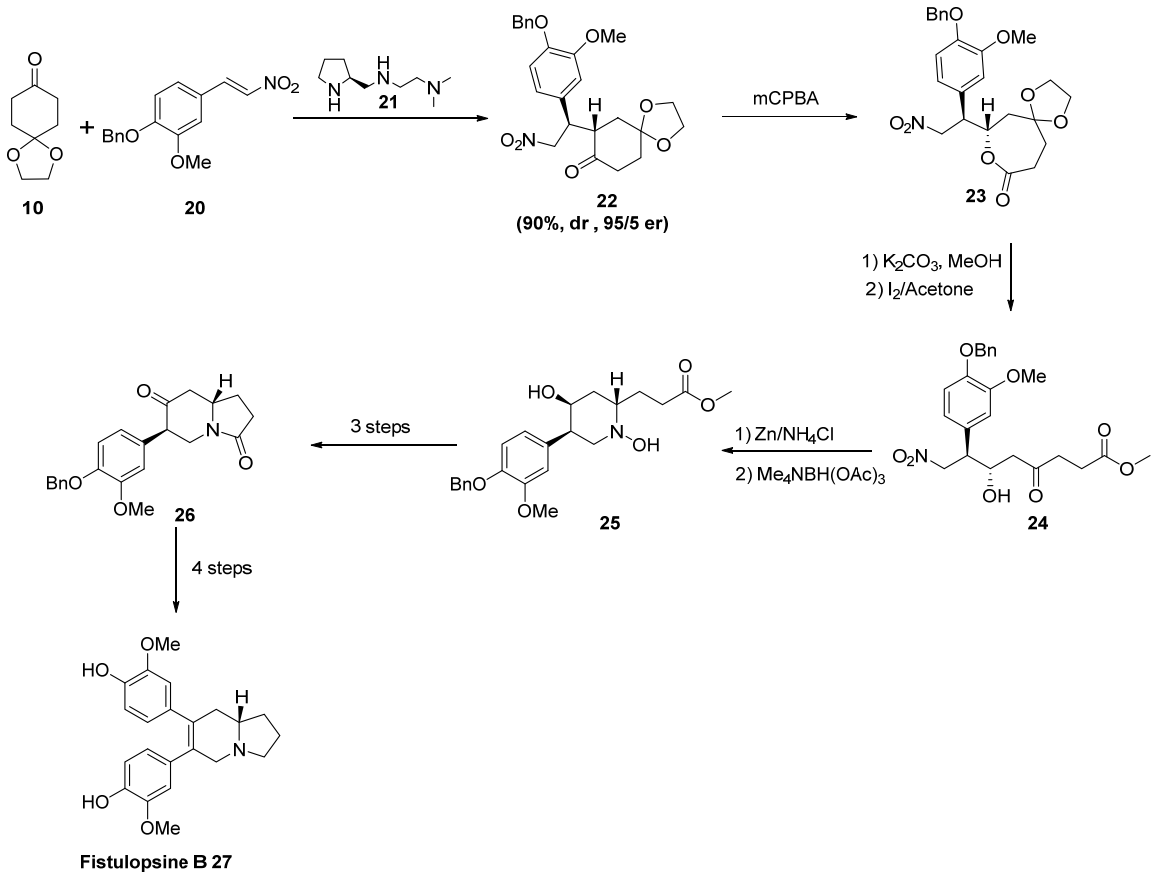


Scheme 5.3

5.3 Synthesis of Fistulopsine B: An Application of an Organocatalytic Michael Addition Reaction

In another organocatalysis-based investigation, an enantiomerically enriched *γ*-nitroketone was employed as the key starting material in the first total synthesis of the diarylindolizidine alkaloid (+)-fistulopsine B isolated[1] in 2016. Organocatalytic Michael addition of 1,4-cyclohexanedione monoethylene ketal **10** to *β*-nitrostyrene **20** in the presence of the (*S*)-proline-derived triamine catalyst **21** gave enantiomerically enriched *γ*-

nitroketone **23**. Oxidative ring expansion of the nitroketone **22**, followed by the methanolysis and deprotection provided the nitro ketoester **24**. This is stereoselectively converted to the functionalized piperidine **25** which was converted to (+)-fistulopsine B (**27**) in 7 steps.



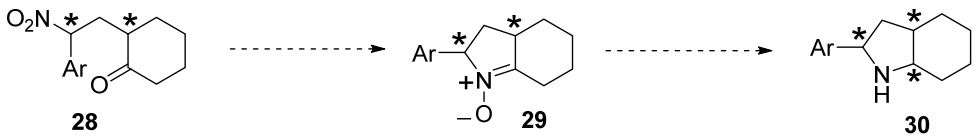
Scheme 5.4

In summary, an efficient synthesis of functionalized indolizidines and quinolizidines was developed from enantiomerically enriched *γ*-nitroketone starting materials which are readily available from the organocatalytic ketone-nitroalkene Michael addition reaction. This methodology was applied in the formal total synthesis of

quinolizidine alkaloids (+)-lasubine II (**18**) and (-)-subcosine II (**19**) and the first total synthesis of recently isolated indolizidine alkaloid (+)-fistulopsine B (**27**).

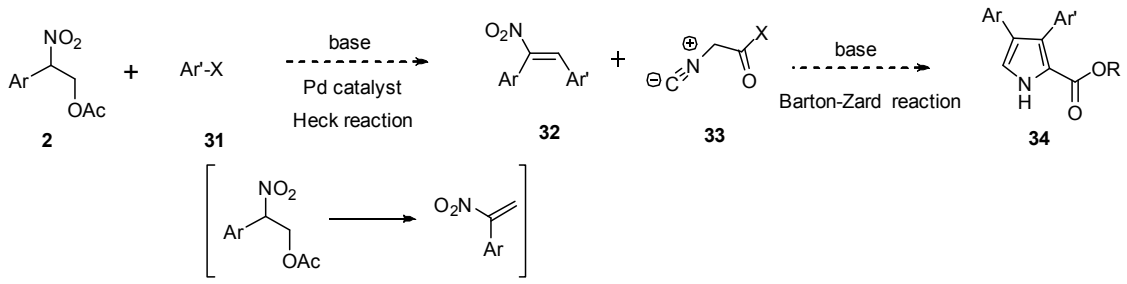
5.4 Future Work

The γ-nitroketones **28** obtained from the organocatalytic Michael addition of ketones to α-nitrostyrenes can be converted to nitrones **29** which could be useful in the stereoselective synthesis of 2-aryl octahydroindoles **30** (Scheme 5.5). These octahydroindoles may have applications in diversity oriented synthesis[2] and medicinal chemistry.[3]



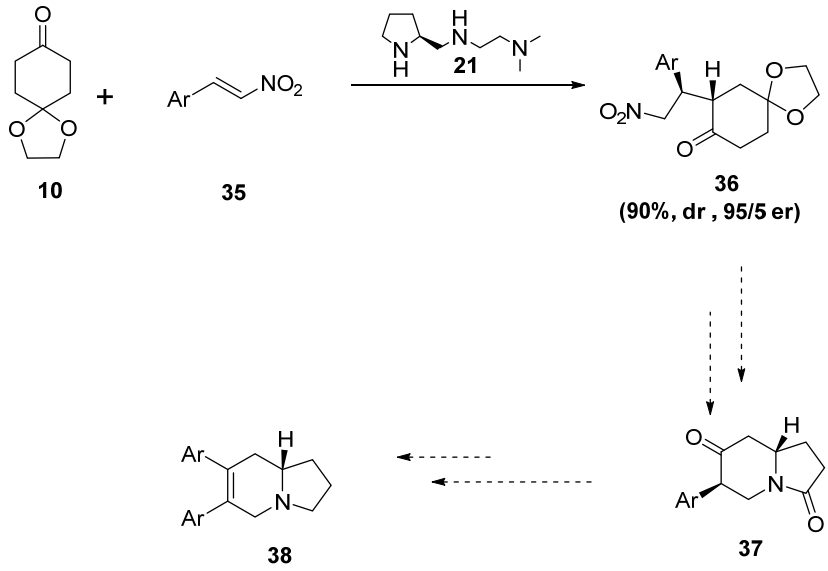
Scheme 5.5

Conjugate addition reactions of α-nitrostryrenes with other carbon nucleophiles can also be examined. For example, the palladium[4] catalyzed (Heck reaction) C-C coupling between aryl halides **31** and α-nitrostyrenes could provide diaryl nitroalkenes **32**. Subsequent Barton-Zard pyrrole cyclocondensation of isocyanoacetate with **33** should provide functionalized pyrroles such as **34** which have numerous applications in medicinal chemistry. If successful, this methodology may have wide application in the synthesis of functionalized pyrroles.[5]



Scheme 5.6

The synthetic approach to fistulopsine B has potential application in the syntheses of analogues of indolizidine alkaloids[6] by variation in the nitrostyrenes and the aryl-cross coupling partners. Organocatalytic Michael addition of 1,4-cyclohexanedione mono ethylene ketal **10** to a variety of *β*-nitrostyrenes **35** in presence of triamine catalyst **21** provides Michael adduct **36** which on several steps could provide ketone **37** followed by cross-coupling with different aryl groups and reduction could afford **38**.



Scheme 5.7

5.5 References:

1) Yap, V. A.; Qazzaz, M. E.; Raja, V. J.; Bradshaw, T. D.; Loh, H. –S.; Sim, K. –S.; Yong, K. –T.; Low, Y. –Y.; Lim, K.–H. *Phytochemistry* **2016**, *15*, 136-141.

2) (a) Hanessian, S.; Del Valle, J. R.; Xue, Y.; Blomberg, N. *J. Am. Chem. Soc.* **2006**, *128*, 10491. b) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064.

3) a) Hurst. M.; Javis, B. *Drugs* **2001**, *61*, 867. b) Monteagudo, E. S.; Calvani, F.; Catrambone, F.; Fincham, C. I.; Madami, A.; Meini,S.; Terracciano, R. J. *Pept. Sci.* **2001**, 270. c) Gass, J.; Khosla, C. *Cell. Mol. Life Sci.* **2007**, *64*, 345.

4) Kantam, M. L.; Srinivas, P.; Yadav, J.; Likhar, P. R.; Bhargava, S. *J. Org. Chem*. **2009**, *74*, 4882.

5) Yoon-Miller, J. P. S.; Bechtold, N. R.; Flewelling, S. A.; Macdonald, J. P.; Downey, C. R.; Cohen, E. A.; Pelkey, E. T. *J. Org. Chem.* **2011**, *76*, 8203.

6) a) Michael, J. P.; *Nat. Prod. Rep.* **2008**, *25*, 139. b) Daly, J. W.; Spande, T. F.; Garraffo, J. *Nat. Prod.* **2005**, *68*, 1556.