DISSERTATION

N-HETEROCYCLIC CARBENE CATALYSIS: APPLICATION TO THE TOTAL SYNTHESIS OF CEPHALIMYSIN A, AND DEVELOPMENT OF MULTICATALYTIC CASCADE REACTIONS

Submitted by

Stephen Lathrop

Department of Chemistry

In partial fulfillment of the requirements

For the Degree of Doctor of Philosophy

Colorado State University

Fort Collins, Colorado

Spring 2011

Doctoral Committee:

Advisor: Tomislav Rovis

John L. Wood
Debbie Crans
Matthew Shores
Shane Kanatous

ABSTRACT

N-HETEROCYCLIC CARBENE CATALYSIS: APPLICATION TO THE TOTAL SYNTHESIS OF CEPHALIMYSIN A, AND DEVELOPMENT OF MULTICATALYTIC CASCADE REACTIONS

Application of the *N*-Heterocyclic carbene catalyzed Stetter reaction to the total synthesis of 9-*epi*-cephalimysin A has been realized. The approach centers on the use of an asymmetric catalytic Stetter reaction to access the spirocyclic core of cephalimysin A. Specifically it was found that a photoisomerization/Stetter protocol allows rapid access to an intermediate readily amenable for further functionalization. This intermediate was further elaborated to three stereoisomers of the naturally occurring cephalimysin A.

During the investigation of cephalimysin A an interesting side product was observed that led to the development of several multicatalytic cascade reactions utilizing *N*-heterocyclic carbenes. Specifically the pairing of secondary-amine catalysts with *N*-heterocyclic carbenes allowed for the synthesis of densely functionalized cyclopentanones in a single step. Moreover, a synergistic relationship was observed between the two catalysts. This partnership allowed for the products to be achieved in higher selectivity than would have been possible if conducting the reactions in a stepwise fashion.

ACKNOWLEGMENTS

I first have to thank my advisor Tom Rovis for the opportunity to work in his lab. He has truly been a great mentor and advisor. Without his teaching and guidance I would not be half the chemist I am today. The time and effort he put in to my development as a scientist is truly appreciated.

I want to thank all the wonderful people I have had the opportunity to work with during my time in the Rovis group. I feel honored to not only call them colleagues but also friends. I first want to thank the great post-docs I have had the pleasure of working with: Art, Matt, Oleg, Jeff, Stéphane and Brian they have been great examples of what it takes to be a good chemist and were integral in my own learning. To those I have had the opportunity to share a lab with for the last five years: Big Jeff, Visor, Becky, the Bush, Cool Kid, and J-Dogg it was always a great work environment. To the rest of the Rovis group: Kerr, Naz, Hippie, Jav, T-Bone, Jenn, Qin, Big Mark, Becca, Kate, Dan, Oberg, Wheeler, Todd, Oz, Claire, Tim, and Garrett it has been great to get to know you and become friends we have had a lot of good times and good roof sessions together. I want to thank Harit and Heather Vora for being great friends for the last five years and I don't think I could have made it through this without them.

I also want to thank my family: Kent and Patty, Hollyn and Eric, Mark and Kelly and all of their wonderful children. They were always supportive and a true blessing in my life. I have to thank my Mom and Dad for always being there for me. I would not be the person I am without their love and support.

Last but not least I have to thank my amazing girlfriend Jennifer who I had the opportunity to meet in grad school. We have had some great times together in Colorado and I look forward to continuing those in the future wherever that may be.

TABLE OF CONTENTS

Chapter 1

N-Heterocyclic Carbene Catalysis and Cephalimysin A

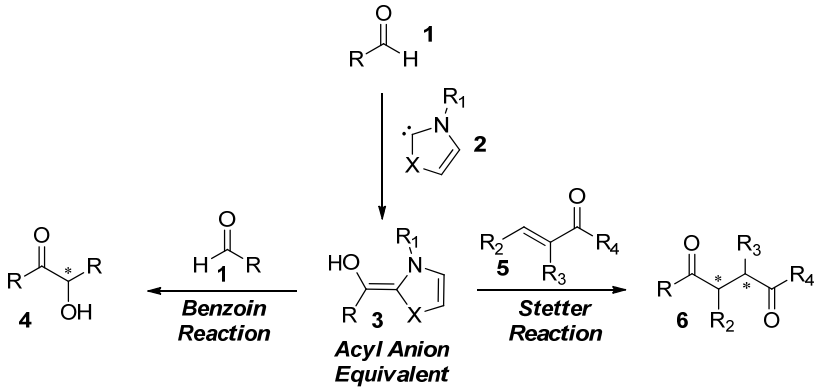
1.1 *N*-Heterocyclic Carbene Catalysis

1.1.1 Introduction

N-heterocyclic carbenes (NHC) have a rich history in the field of organic chemistry. Since the initial isolation of stable nucleophilic carbenes by Bertrand[1] and Arguendo[2], *N*-heterocyclic carbenes have been utilized as ligands in various metal-based catalytic reactions.[3] NHCs have also proven effective for the organocatalytic formation of C-C bonds.[4] NHCs in organocatalysis are typically employed to render aldehydes nucleophilic, thereby reversing their typical reactivity. This reversal is referred to as umpolung reactivity.[5]

The NHC-catalyzed benzoin and Stetter reactions are two manifolds in which the nucleophilic aldehyde, or more commonly termed acyl anion equivalent, has been used to form C-C bonds. The benzoin reaction involves the reaction of a catalytically generated acyl anion equivalent **3** with another equivalent of aldehyde to generate α-hydroxy ketones **4** (Scheme 1). Similary, the Stetter reaction utilizes the acyl anion equivalent this time in the addition to Michael acceptors to afford 1,4-difunctionalized products, typically 1,4-dicarbonyls (Scheme 1).

Scheme 1.



Both transformations have recently been rendered asymmetric by using enantioenriched thiazolium and triazolium salts as precatalysts *vide infra*. This recent development allows access to a variety of functionalized products in high enantioselectivity.

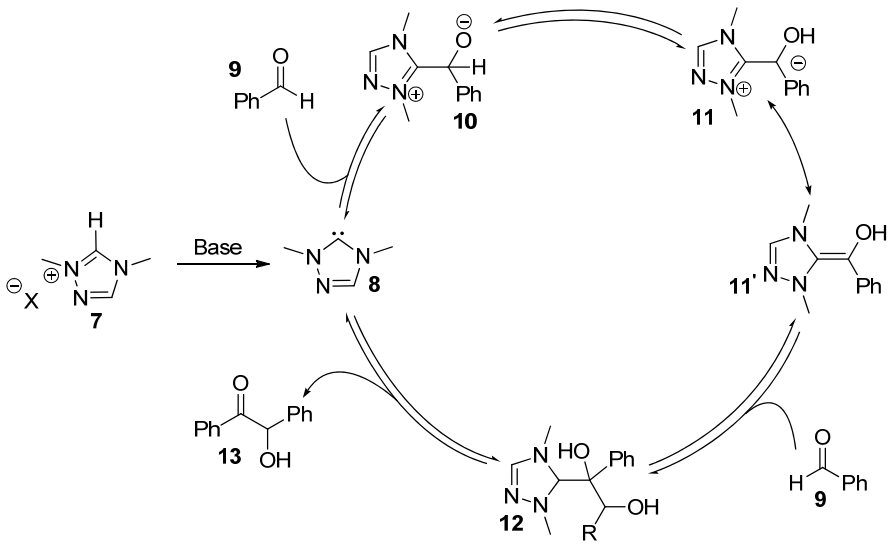
1.1.2 The Benzoin Reaction

The first example of a benzoin reaction dates back to 1832 when Liebig and Wöhler discovered that cyanide catalyzes the formation of α-hydroxy ketones from aldehydes.[6] In 1903 Lapworth reported the currently accepted mechanism for the cyanide catalyzed benzoin reaction.[7] 40 years later Ukai and co-workers reported that thiazolium salts in the presence of base also catalyze the benzoin reaction.[8] In 1958 Breslow elucidated the mechanism of the thiazolium catalyzed benzion reaction.[9] Breslow's proposed mechanism was in close agreement with Lapworth's mechanism for the cyanide catalyzed benzoin reaction.

Breslow proposed that base initiates the catalytic cycle by deprotonation of the azolium salt to generate the carbene **8**. Nucleophilic addition of the carbene into the electrophilic aldehyde generates tetrahedral intermediate **10**. Subsequent intermolecular

proton transfer results in formation of the acyl anion **11,** which is commonly known as the Breslow intermediate (**11'**). Nucleophilic addition of **11'** into a second aldehyde generates tetrahedral intermediate **12** and is the key C-C bond forming event. Collapse of the tetrahedral intermediate affords the α-hydroxy ketone product and regenerates the carbene catalyst. It has been shown that the benzoin catalytic cycle is completely reversible and therefore represents a significant challenge for the development of asymmetric variants due to racemization.

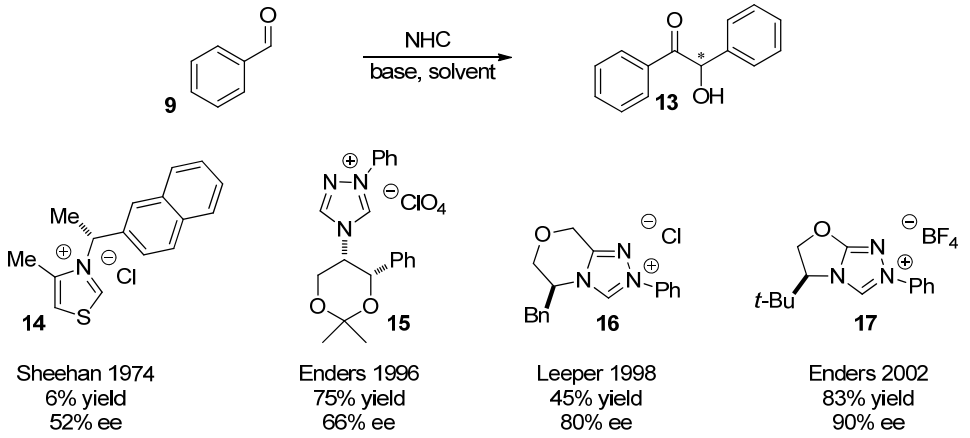
Scheme 2.



In 1966 Sheehan reported the first asymmetric example of a benzoin reaction with benzaldehyde forming the benzion product in 22% ee.[10] Subsequently, Sheehan reported that using thiazaolium salt **14** as the carbene precursor afforded the product in 52% ee albeit in only 6% yield (Scheme 3).[11] This result was the high water mark for the enantioselective benzoin reaction for over 20 years. In 1996, Enders and co-workers identified triazolium salt **15** as an efficient carbene precursor.[12] The desired benzoin product was obtained in good yield and 66% ee. Leeper and coworkers built upon this

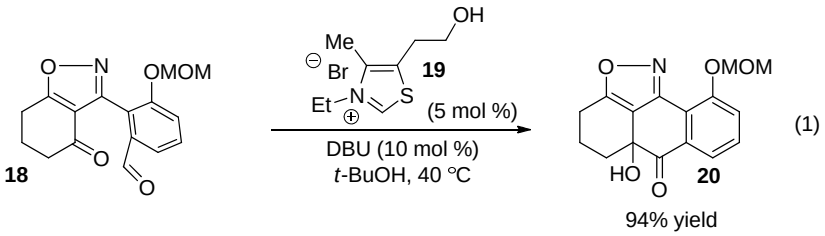
initial discovery by developing the fused bicylcic triazolium **16** to give the product in a vastly superior 80% ee.[13] Finally, Enders reported the more reactive triazolium salt **17**, which afforded the benzoin product in 90% ee.[14] This example represents the state of the art for the intermolecular benzoin reaction.

Scheme 3.



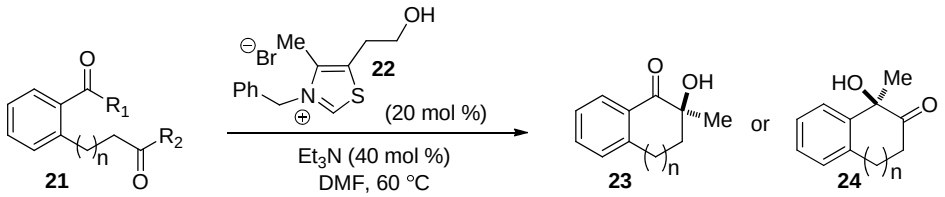
One of the major drawbacks of the benzoin reaction is that it is for the most part limited to the coupling of two equivalent aldehydes. Attempts to use two distinct aldehydes typically results in a thermodynamically driven mixture of products due to the reversible nature of the benzoin reaction.

More recently, intramolecular crossed aldehyde-ketone benzoin reactions have been realized. In 2003, Suzuki and co-workers described the first example of alehdye-ketone benzoin reaction in their syntheses of preanthraquinones.[15] They have shown that aldehyde **18** reacts intramolecularly with a ketone in the presence of thiazolium **19**, and DBU to afford the desired hydroxy-ketone **20** in excellent yield (eq 1).



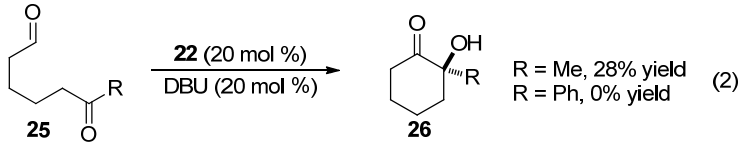
Soon after Suzuki's initial communication, Enders and co-workers reported a similar transformation, and they made three interesting observations.[16] First Enders and coworkers found that six-membered ring formation is significantly higher yielding than five-membered ring formation (Table 1, entries 1 and 2). Second, the reaction between aliphatic aldehydes and aromatic ketones is lower yielding than with aromatic aldehydes and aliphatic ketones (entries 2 and 3).

Table 1.



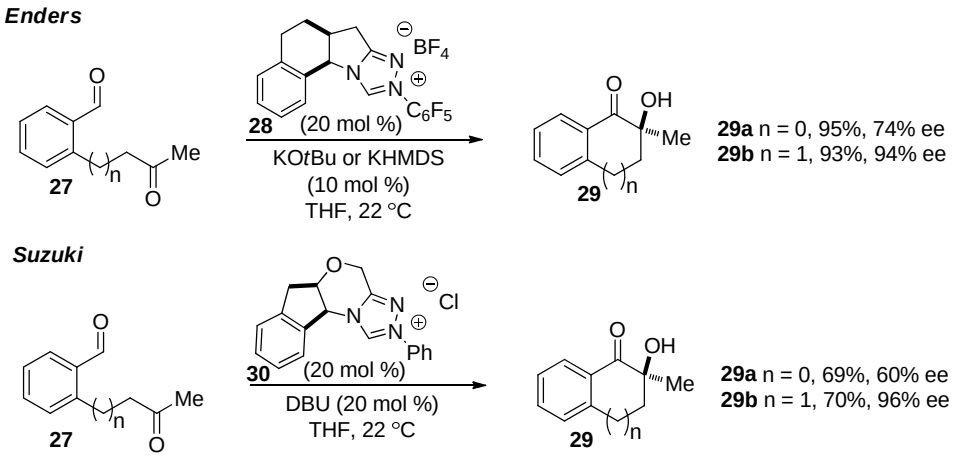
entry	n	R_1	R_2	yield	prdt
1	0	H	Me	18%	**23**
2	1	H	Me	69%	**23**
3	1	Ph	H	47%	**24**

Third, aliphatic tethered aldehyde-ketones give a further reduction in yield (eq 2). When phenyl ketone **25** is used in these aliphatic systems, no desired product is obtained and only aldehyde-aldehyde benzoin products are observed (eq 2).



Enders[17] and Suzuki[18] have both recently published an asymmetric variant of the intramolecular crossed benzoin reaction. Enders employs chiral lactam derived triazolium salt **28** while Suzuki uses the aminoindanol triazolium **30** developed by Rovis and co-workers. Notably, both Enders and Suzuki observe a marked decrease in enantioselectivity between the six-membered and the corresponding five-membered cyclization precursors (Scheme 4).

Scheme 4.



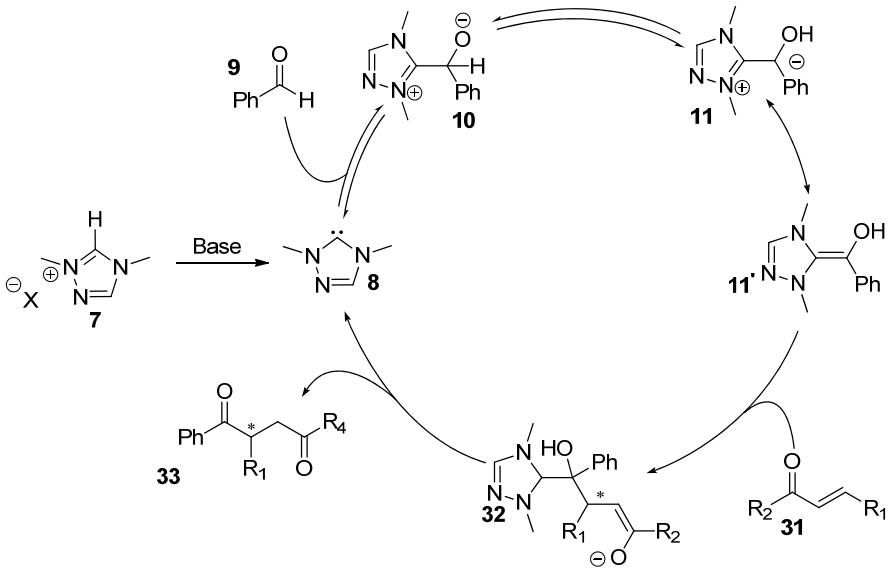
Although neither author discusses this disparity between the six and five-membered cyclization selectivity, it could be due to the 5-membered rings propensity to undergo a retrobenzoin process which allows for racemization.

1.1.3 The Stetter Reaction

In the 1970s Stetter described that cyanide catalyzes the intermolecular addition of aldehydes to Michael acceptors to afford 1,4-dicarbonyl compounds.[19] He later found that thiazolium salts in the presence of base also catalyze this transformation.[20] The mechanism of the Stetter reaction is analogous to the benzoin reaction (Scheme 5). Deprotonation of

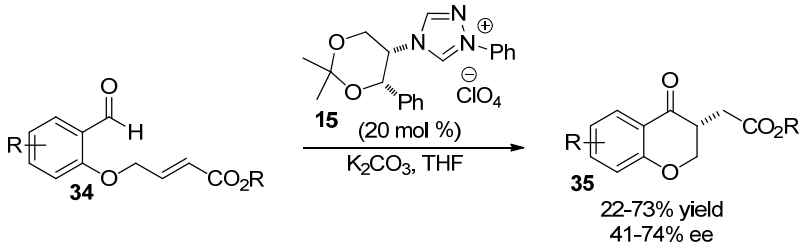
the azolium and addition of the newly formed carbene into an aldehyde generates the Breslow intermediate **11'**. In the presence of a Michael acceptor, a 1,4 addition occurs between acyl anion **11** and acceptor **31** to generate tetrahedral intermediate **32**. Tautomerization and collapse of the tetrahedral intermediate affords the 1,4 dicarbonyl product and regenerates the carbene catalyst.

Scheme 5.



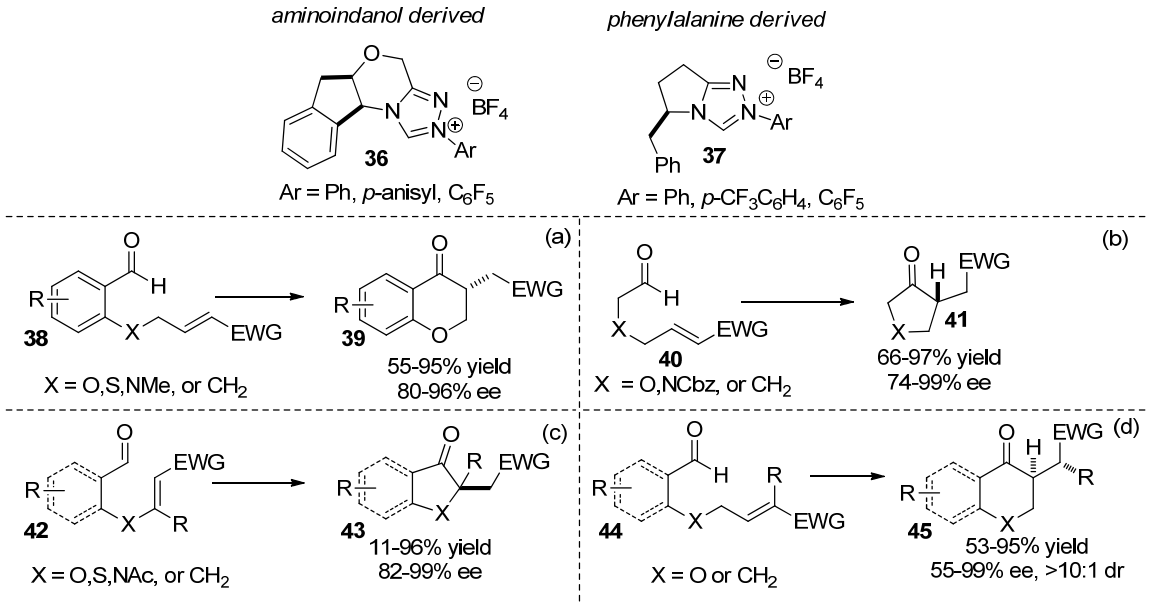
In 1995 Cignak and co-workers described the first detailed investigation of the intramolecular Stetter reaction using achiral triazolium salts.[21] A year later, Enders reported the first asymmetric example of the intramolecular Stetter reaction using triazolium **15** (Scheme 6).[22] The 4-chromanone products (**35**) are obtained in good yield and moderate enantioselectivity.

Scheme 6.



More recently Rovis and co-workers developed two new enantioenriched triazolium salt scaffolds, which have been found to be effective catalysts for the asymmetric Stetter reaction (Scheme 7). Aminoindanol derived triazolium **36** along with phenylalanine derived triazolium **32**[23] proved useful for a variety of intramolecular Stetter reactions to generate 4-chromanone products in good yield and high enantioselectivity (Scheme 7, eq a).

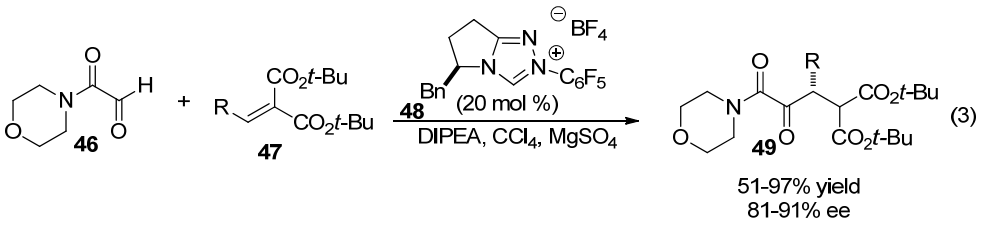
Scheme 7.



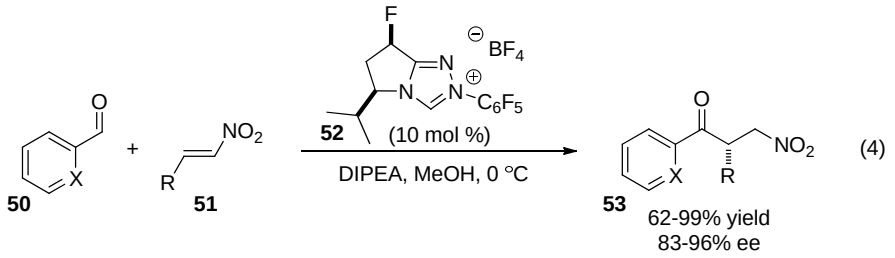
Rovis' carbene catalysts are also effective with aliphatic tethered Michael acceptors and generate cyclopentanone products in high yield and enantioselectivity (eq b). The scope

was expanded to include the formation of quaternary stereocenters (eq c). Finally substitution at the α position of the Michael acceptor allows for the formation of two stereocenters with high enantio- and diastereoselectivity (eq d).[24] Presently these catalysts represent the high-water mark for enantioselectivity in the intramolecular Stetter reaction.

Although multiple examples exist for the asymmetric intramolecular Stetter reaction, the corresponding asymmetric intermolecular reaction has been met with limited success. One of the reasons for the lack of success in the asymmetric intermolecular Stetter reaction is that β-substituted Michael acceptors give reduced yields in the reaction. However, In 2008 Rovis and co-workers described the first highly enantioselective intermolecular Stetter reaction using phenylalanine derived triazolium **48** (eq 3).[25] The reaction of glyoxamides with alkylidenemalonates affords 1,4-dicarbonyl products **49** in good yield and enantioselectivity.



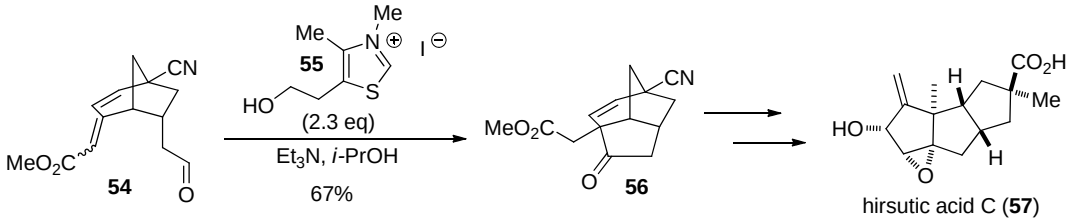
The enantioselective intermolecular Stetter reaction has been further expanded to include heteroaromatic aldehydes and nitroalkenes (eq 4).[26] It was found that *cis*-fluorinated triazolium **52** affords the β-nitroketones **53** in excellent yield and enantioselectivity.



1.1.4 Stetter Reaction in Total Synthesis

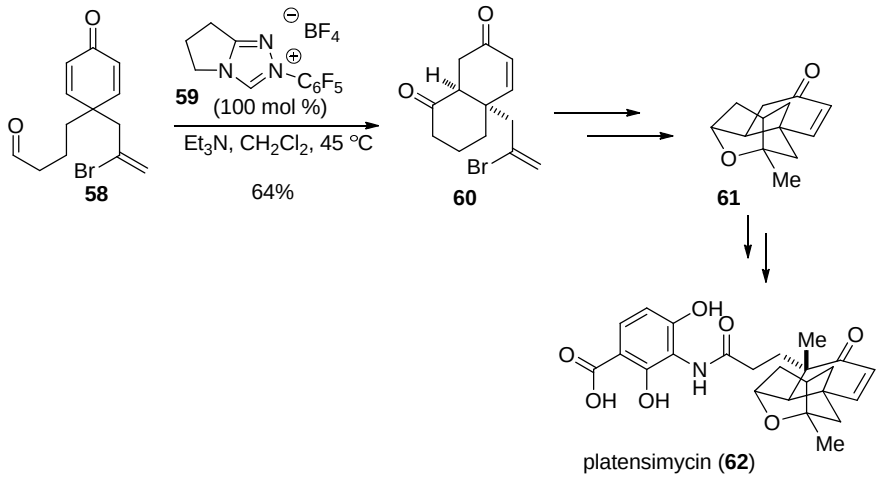
Although the Stetter reaction has been known since the 1970's there are relatively few examples of its use in natural product synthesis. Typically, in more complex systems it is necessary to use stoichiometric amounts of the carbene precursor. This is highlighted by both Trost's synthesis of hirsutic acid C and Nicolaou's formal synthesis of platensimycin. Trost and co-workers used a stoichiometric intramolecular Stetter reaction in their synthesis of hirsutic acid C (**57**).[27] Aldehyde **54** undergoes a thiazolidene mediated 5-*exo*-trig Stetter reaction to afford tricycle **56** (Scheme 8). The tricyclic compound was further elaborated to hirusutic acid C. Notably, 2.3 equivalents of triazolium salt were required in order to achieve good yields of the Stetter product **56**.

Scheme 8.



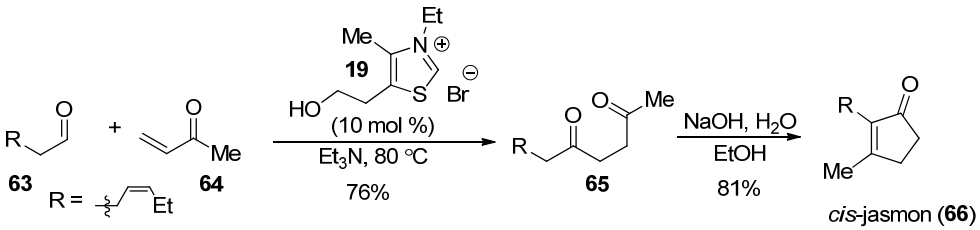
Nicolaou and co-workers have employed a stiochiometric triazolidene mediated intramolecular Stetter reaction in a formal total synthesis of platensimycin (**62**) (Scheme 9).[28] It was found that treatment of triazolium **59** with triethylamine in the presence of aldehyde **58** affords the desired bicycle **60** in moderate yield. This bicyclic product was further functionalized to intermediate **61,** which was previously utilized by Nicolaou and coworkers in their total synthesis of platensimycin.

Scheme 9.



Examples of utilizing a catalytic Stetter reaction in natural product synthesis have been shown. These reactions typically involve the intermolecular reaction between aldehydes and Michael acceptors lacking substitution at the β position. In 1975 Stetter and coworkers reported the thiazolidene carbene catalyzed intermolecular Stetter reaction in the total synthesis of *cis*-jasmon **66** (Scheme 10).[29] The Stetter reaction between methyl vinyl ketone and aldehyde **63** affords the 1,4-dicarbonyl compound **65**. Treatment of **65** with base forms *cis*-jasmone (**66**) in good yield.

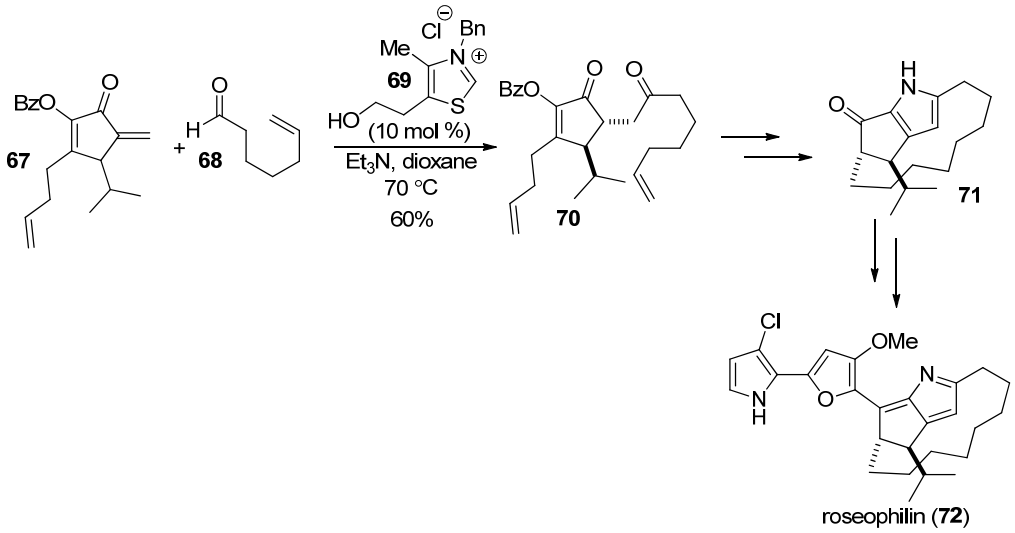
Scheme 10.



Tius and coworkers utilized a thiazolidene catalyzed intermolecular Stetter reaction between aldehyde **68** and cyclopentanone **67** in their formal total synthesis of roseophilin

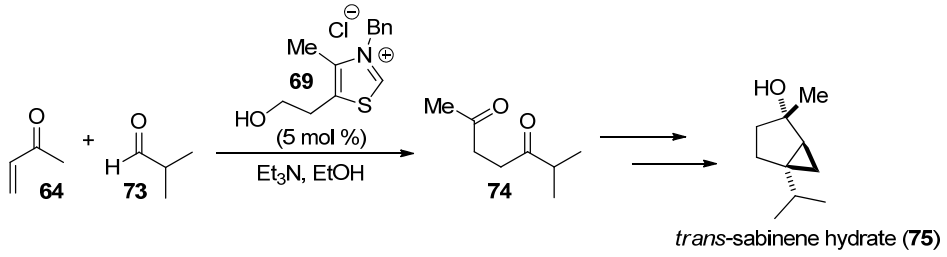
(**72**).[30] The Stetter reaction affords 1,4-dicarbonyl **70** which was further elaborated to macrocycle **71**. Macrocycle **71** is an intermediate in Fürstner's total synthesis of roseophilin **72**.[31]

Scheme 11.



Galopin employed an intermolecular Stetter reaction between isobutyraldehyde (**73**) and methyl vinyl ketone (**64**) to afford 1,4-dicarbonyl **74** (Scheme 12).[32] This 1,4-dicarbonyl was used as a precursor to *trans*-sabinene hydrate (**75**).

Scheme 12.



The previous examples highlight the power of the Stetter reaction through its application to total synthesis. However, the catalytic examples are limited to Michael acceptors without substitution at the β position and more complex substrates require a stoichiometric amount of the catalyst. Furthermore, there are no known examples of a catalytic, asymmetric Stetter reaction being used in natural product synthesis.

1.1.5 Summary

Over the last 67 years NHCs have been utilized as catalysts for a variety of transformations. Initially, thiazolium salts were used as precatalysts for the benzoin and Stetter reactions. The introduction of triazolium salts, by Enders and co-workers, as efficient precatalysts for the catalytic generation of nucleophilic aldehydes allowed for the development of new enantioselective catalysts. Of these newly developed catalysts, the aminoindanol and phenylalanine derived triazolium precatalysts introduced by Rovis and co-workers allowed for both the intra- and intermolecular Stetter reactions to be realized with excellent control of enantioselectivity. We were excited about the possibility of exploiting these highly effective catalysts in the enantioselective synthesis of complex natural products.

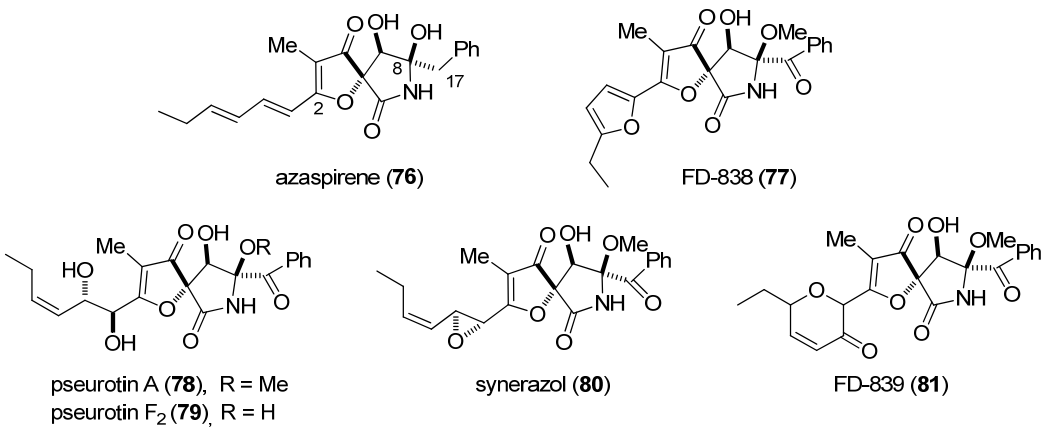
1.2 Cephalimysin A

1.2.1 Spirofuranone Lactam Containing Natural Products

Having previously shown the power of the Stetter reaction for the asymmetric formation of C-C bonds we aimed to highlight this recently developed methodology by

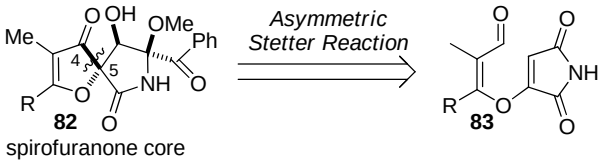
applying it to asymmetric natural product synthesis. Due to their interesting structure we were interested in a family of natural products containing a unique 1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione core skeleton (Scheme 13). These molecules are highlighted by their highly substituted spirocyclic core, in which each carbon of the spirocycle has at least one substitution. These spirofuranone containing natural products also contain three contiguous stereocenters, two of which are tertiary. The family of natural products differs in the nature and oxidation state of the pendant group at C-2 of the furanone ring. They also differ in the alkylation of the heminaminal oxygen at C-8 and the oxidation state of the benzyl group at C-17.

Scheme 13.



We believed that these spirocyclic natural products would allow us to showcase the power of the asymmetric Stetter reaction to rapidly access complex molecular architectures. Based on previous success utilizing the asymmetric Stetter reaction to access benzafuranones and dihydrofuranones containing tertiary stereocenters (Scheme 7, Sect 1.1.3), we hypothesized that these spirofuranone containing natural products could be rapidly accessed via an asymmetric Stetter reaction (Scheme 14).

Scheme 14.



Looking at the spirofuranone core, we saw the 1,4 relationship between the methoxy group and the ketone made for a reasonable bond disconnection for a Stetter reaction to occur between C-4 and C-5.

Along with their unique spicocylic core these molecules also display a range of interesting biological activities. Azaspirene (**76**) isolated from the fungus *Neosartorya* sp. has shown potent anti-angiogenic activity.[33] Specifically azaspirene was shown to inhibit the vascular endothelial growth factor (VEGF)-induced cell migration in human umbilical vein endothelial cells (ED_{100} = 27.1μM). FD-838 (**77**) isolated from *Aspergillus fumigatus fresenius* F-838 was reported to induce the differentiation of leukemia in cultures and to inhibit the growth of certain Gram-positive bacteria and fungi.[34] Pseurotins (**78** and **79**) were isolated from the culture broth of *Pseudeurotium ovalis.* Pseurotin A (**78**) was reported to inhibit chitin synthase as well as induce cell differentiation of PC12 cells.[35] Synerazol (**80**) isolated from the culture broth of *Aspergillus fumigatus* has shown both antibiotic and antifungal activity.[36]

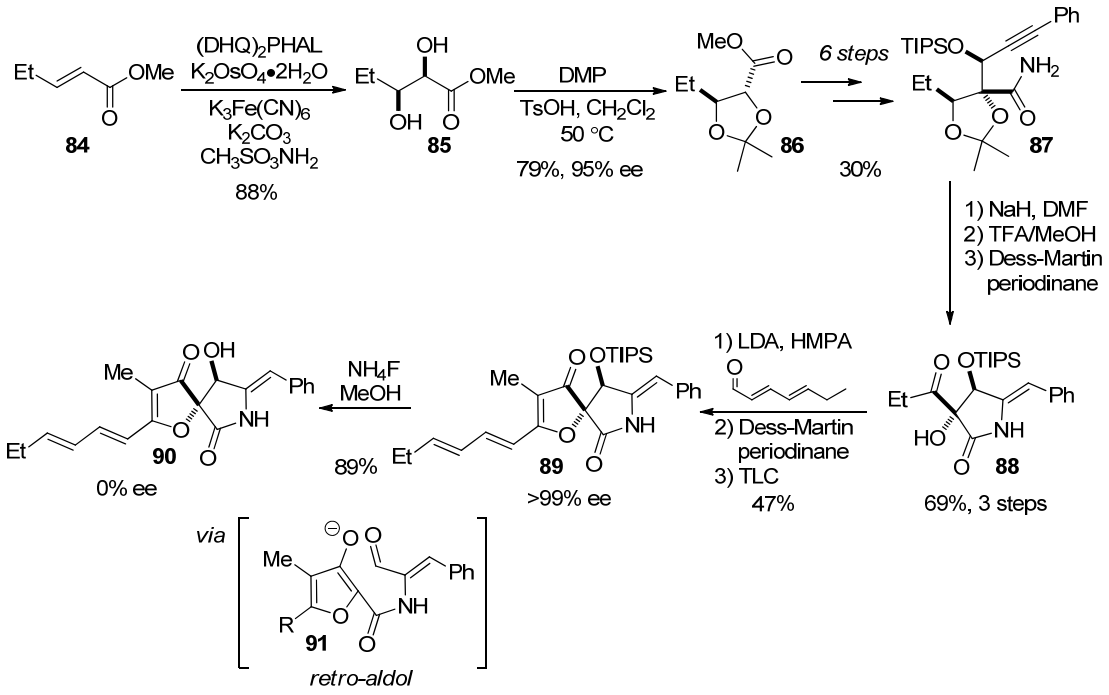
1.2.2 Previous Syntheses of Spirofuranone Lactam Containing Natrual Products

In 2002 Hayashi reported the total synthesis of (-)-azaspirene, which was the first total synthesis of these unique spirofuranone containing natural products.[37] Hayashi and

coworker's approach entered on a catalytic asymmetric dihydroxylation to access the enantioenriched lactam and a biosynthetically inspired aldol reaction to install the necessary hexadiene side chain.

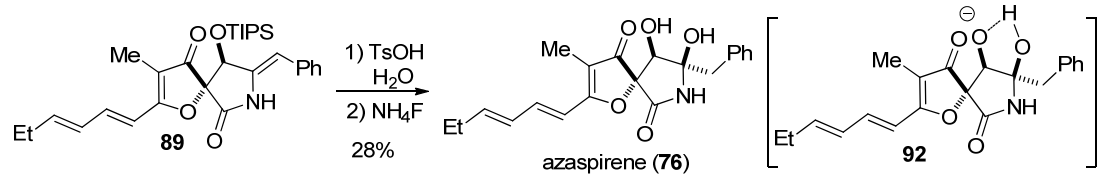
Their synthesis commenced with asymmetric dihydroxylation of α,β-unsaturated ester **84** followed by protection of the diol as the acetonide generates **86** in good yield and 95% ee (Scheme 15). A further six steps affords amide **87**. Treatment of the amide with sodium hydride forms the lactam, subsequent deprotection of the acetonide and oxidation of the secondary alcohol affords ketone **88** in good yield. Treatment of the ketone with LDA followed by addition of the aldehyde generates the aldol product, which upon oxidation and treatment with silca gel gives the spirofuranone **89**. It was found that deprotection of the secondary alcohol **89** affords the free alcohol **90** in excellent yield however with complete racemization. It is believed that under these slightly basic conditions that racemization occurs via a retro-aldol mechanism generating achiral intermediate **91**.

Scheme 15.



This racemization pathway was overcome by installing the aminal hydroxyl group first, followed by deprotection (Scheme 16). This protocol affords azaspirene (**76**) in 16 total steps in 99% ee. Hayashi suggests that the presence of the diol prevents the retro aldol form occurring during the deprotection of the secondary alcohol (**92**).

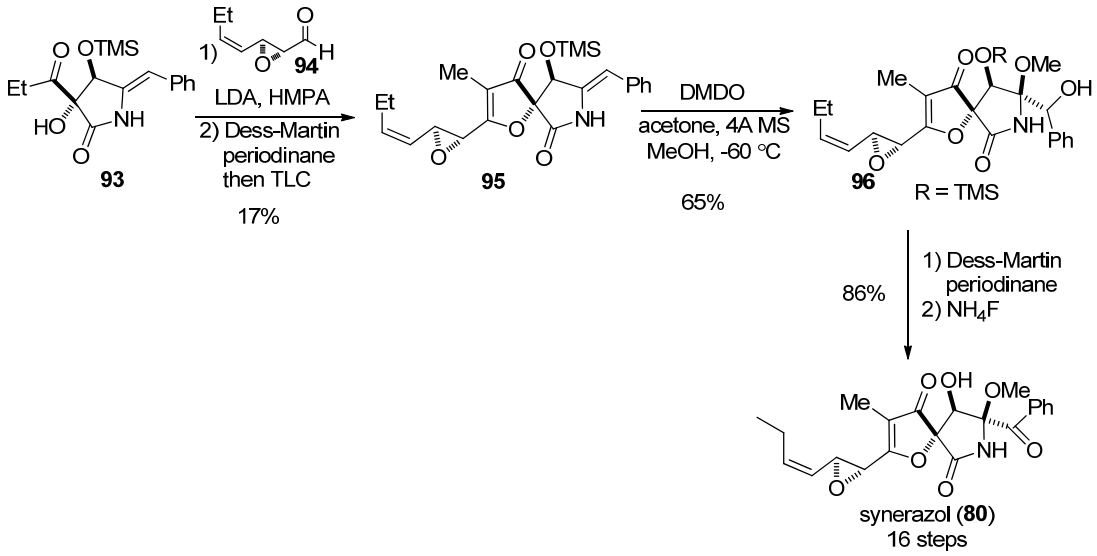
Scheme 16.



Hayashi and coworkers have also applied this general approach to the total synthesis of synerazol (**80**) (Scheme 17).[38] An aldol reaction between TMS protected γ-lactam **93** and epoxy aldehyde **94,** is followed by oxidation and exposure to silica gel to give the furanone **95**. Selective epoxidation of the enamide olefin followed by *in situ*

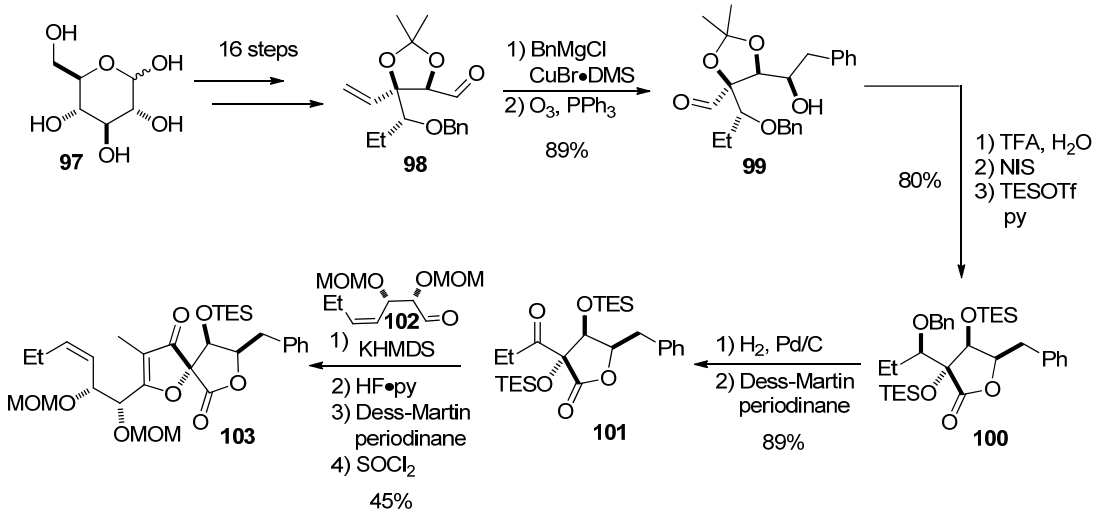
opening with methanol affords functionalized lactam **96**. Oxidation of the secondary alcohol followed by deprotection generates synerazol (**80**) in 17 steps. The same protocol has been used for the total synthesis of FD-838.[39]

Scheme 17.



Tadano and coworkers published total syntheses of azaspirene as well as pseurotins A and F_2.[40] Tandano's approach utilizes D-glucose as the starting material and also implements an aldol to install the desired side chains. In 16 linear steps from D-glucose Tando arrives at aldehyde **98** (Scheme 18). Addition of benzyl Grignard into aldehyde **98** followed by ozonolysis affords aldehyde **99**. Deprotection of the acetonide, oxidation of the lactol and protection of the secondary alcohol generates lactone **100**. Hydrogenolysis of the benzyl alcohol followed by oxidation yields ethyl ketone **101**, which is a similar intermediate **88** and **93** used by Hayashi and co-workers in their synthesis of azaspirene, synerazol and FD-838.

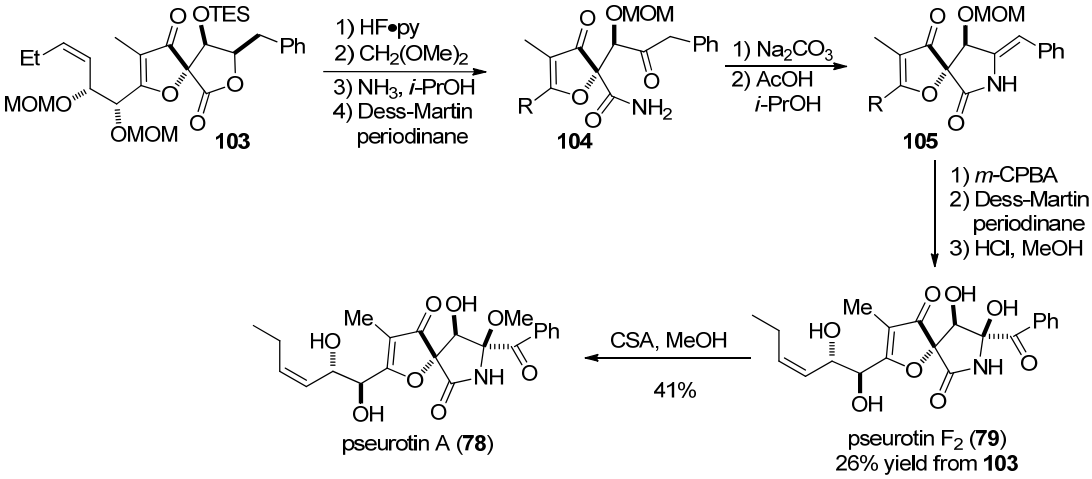
Scheme 18.



With lactone **103** in hand an Aldol reaction between ketone and aldehyde **102** followed by deprotection of the tertiary alcohol, oxidation and elimination generates spirofuranone **103**. This key intermediate allows access to the spirocyclic core of the pseurotins, A (**78**) and F_2 (**79**).

From spirocycle **103**, deprotection and reprotection of the secondary alcohol as the MOM ether followed by opening of the lactone with ammonia and oxidation of the resultant secondary alcohol affords amide **104** (Scheme 19).

Scheme 19.



Treatment of amide **104** with base initiates cyclization onto the ketone; acid mediated elimination generates benzylidene lactam **105**. Epoxidation of the enamide followed by *in situ* opening, and oxidation of the secondary alcohol then deprotection of the MOM ethers affords natural product pseurotin F_2 (**79**) in 36 linear steps. Pseurotin F_2 (**79**) can be converted to pseurotin A (**78**) by simple treatment with acidic methanol. Tanado and co-workers have used lactone **103** in a similar manner to complete a total synthesis of azaspirene (**76**).

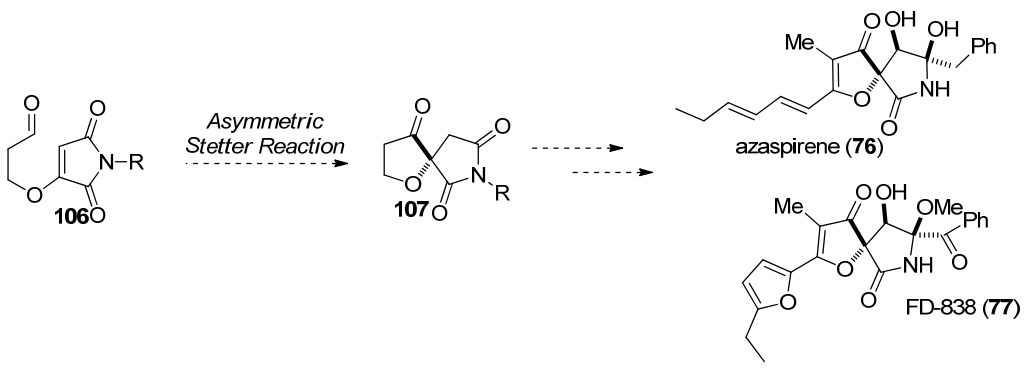
To date these two groups provide the only total syntheses of this family of natural products. Although Hayashi's synthesis succeeds in rapidly accessing the natural product, final steps for azaspirene are relatively low yielding. Similarly Hayashi's approach to synerazol suffers from a poor yielding aldol, oxidation and cyclization sequence (17%, 3 steps). Tanado's total synthesis of the pseurotins and azaspirene suffers from a rather high step count.

1.2.3 Previous Work Towards Azaspirene and FD-838 in the Rovis Group

Initial applications of the asymmetric Stetter reaction to the synthesis of spirofuranone lactam containing natural products were focused on azaspirene (**76**) and FD-838 (**81**). This work was carried out by post-doctoral fellow Arturo Orellana. A portion of this work has been published and this section will highlight the published work as well as relevant unpublished results.[41]

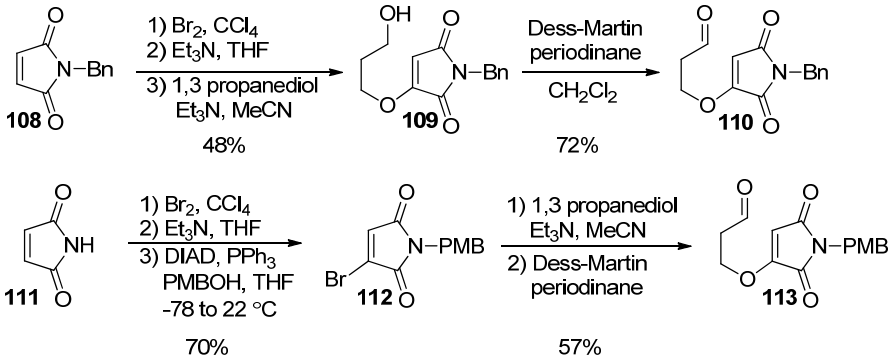
The approach centered on the application of the asymmetric Stetter reaction of aldehyde tethered maleimide **106** as a rapid entry to the spirocyclic core of both azaspirene (**76**) and FD-838 (**77**) (Scheme 20).

Scheme 20.



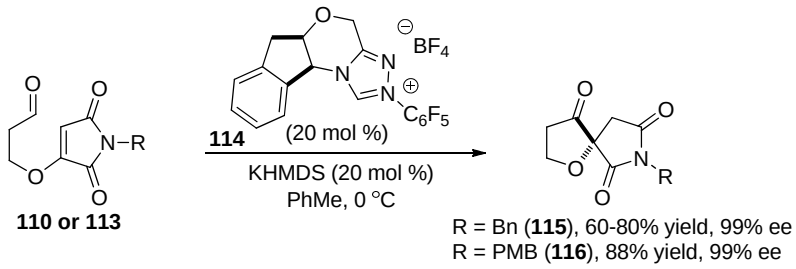
Synthesis of the aldehyde-tethered maleimide **106** was accomplished in four steps from commercially available *N*-benzyl maleimide (**108**) (Scheme 21). Bromination of maleimide **108** followed by elimination and conjugate addition-elimination of 1,3-propanediol affords alcohol **109**. Dess-Martin periodinane oxidation generates the desired aldehyde in good yield. A similar route was used to synthesize the *para*-methoxybenzyl protected maleimide **113**.

Scheme 21.



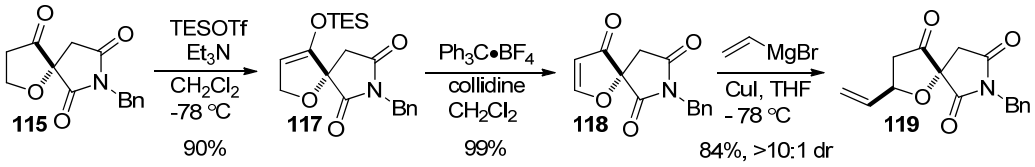
Treatment of aldehyde **110** or **113** with aminoindanol derived triazolium in the presence of KHMDS affords the desired spirocyclic product in good yield and excellent enantioselectivity (Scheme 22).

Scheme 22.



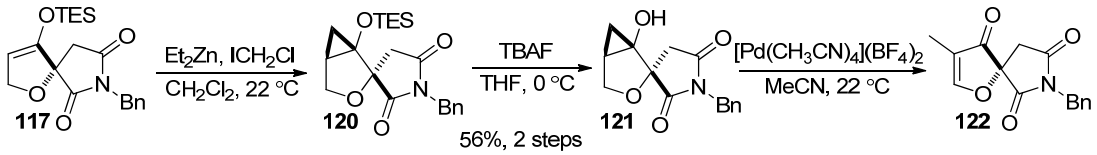
Having shown that the asymmetric Stetter reaction efficiently accesses the desired spirocycle, focus was turned to further elaboration of the core to azaspirene (**76**). Enolization or spirocycle **115** followed by and trapping with TESOTf affords the silylenolether **117** (Scheme 23). Subsequent oxidation via hydride abstraction generates the furanone **118**. Conjugate addition of vinyl Grignard takes place in the presence of copper (I) iodide to give **119**. This route showed potential for installing the necessary C-2 side chain for azaspirene.

Scheme 23.



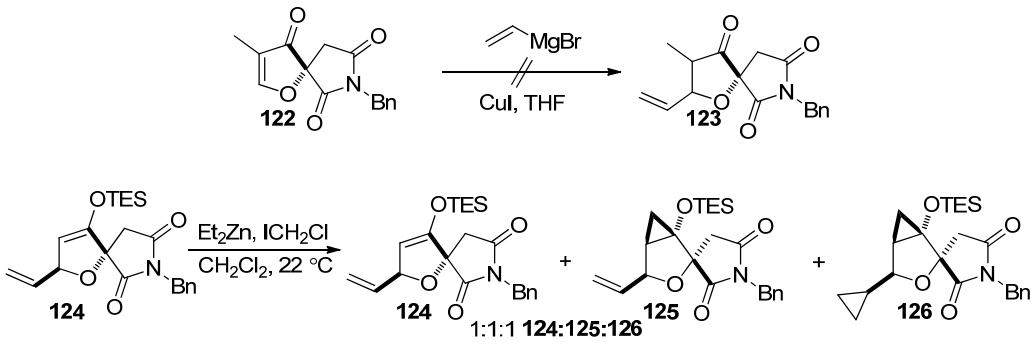
Installation of the methyl group is achieved via an oxidative cyclopropane ring opening (Scheme 24). Cyclopropanation of the silylenolether **117** followed by deprotection generates cyclopropanol **121**. Treatment of cyclopropane **121** with palladium affords furanone **122**, containing the desired methyl group.

Scheme 24.



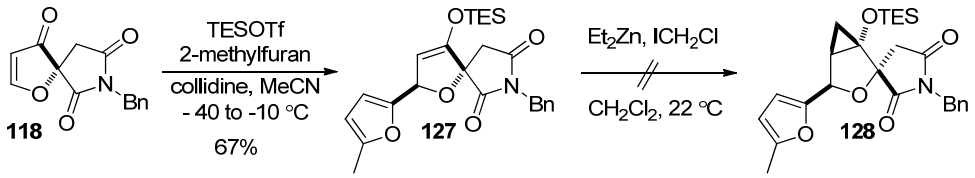
Unfortunately, attempts to further functionalize key intermediates **119** and **122** failed to yield the desired products. Conjugate addition of vinyl Grignard into the α-methyl furanone **122** failed to deliver the desired product (Scheme 25). Similarly, attempts to cyclopropanate the β-substituted siylenolether **124** gave a mixture of starting material, desired cyclopropane **125**, and over cyclopropanated product **126**.

Scheme 25.



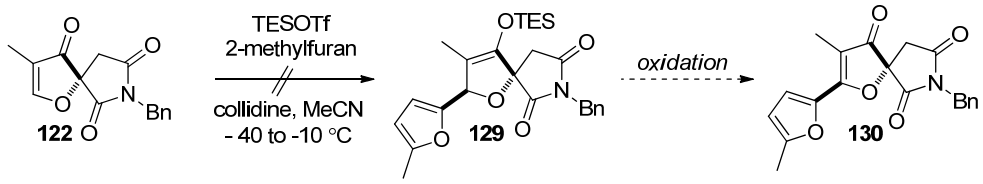
Having limited success accessing azaspirene via the spirocyclic succinimide **115** attention was turned towards FD-838 (**81**). It was found that Friedel-Crafts type conjugate addition of methyl furan to enone **118** generates the desired β-substituted enolether **127** (Scheme 26). However, attempted cyclopropanation of the enolether failed to afford the desired product presumably due to over cyclopropanation of the furan ring.

Scheme 26.



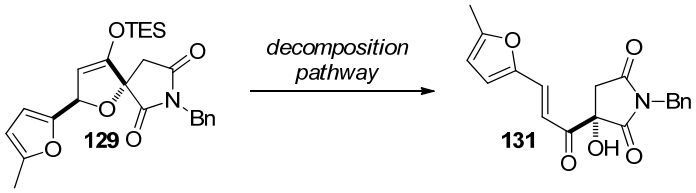
The inability to install the cyclopropane after installation of the furan ring forced a change in the order of events. However, the conjugate addition of methylfuran failed on the α-methyl furanone **122** (Scheme 27). These results are similar to those found while trying to access the azaspirene (**76**) framework.

Scheme 27.



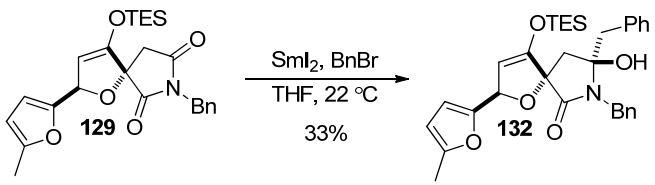
One of the complications observed when dealing with silylenolether **129** was its propensity to undergo ring-opening to afford enone **131** (Scheme 28). This decomposition pathway made scale up of this intermediate difficult and complicated further screening of reaction conditions.

Scheme 28.



However it was found that selective functionalization of the succinimide carbonyl could be achieved via Barbier type alkylation of siylenol ether **129** (Scheme 29). Treatment of enolether **129** with samarium diiodide and benzyl bromide affords the hemiaminal **132** in moderate yield. This reaction is complicated by the undesired ring opening of the spirocycle, generating a complex mixture of side products.

Scheme 29.

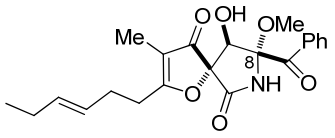


Although this study highlights the power of the Stetter reaction to rapidly access the spirocyclic framework desired for the synthesis of azaspirene and FD-838 further functionalization has proven difficult. Chemoselectivity and substrate decomposition are two of the major problems encountered in this approach.

1.2.4 Cephalimysin A

In 2007 the isolation and structural elucidation of cephalimysin A, a new member of the spirofuranone lactam containing natural products was reported in the literature (Scheme 30).[42] Cephalimysin A (**133)** was recovered from the culture broth of *Aspergillus fumigatus* initially isolated from the marine fish *Mugil cephalus*. This metabolite exhibited significant cytotoxic activity against the murine P388 leukemia cell line (IC_{50} = 15.0 nM) and the human HL-60 leukemia cell line (IC_{50} = 9.5 nM).

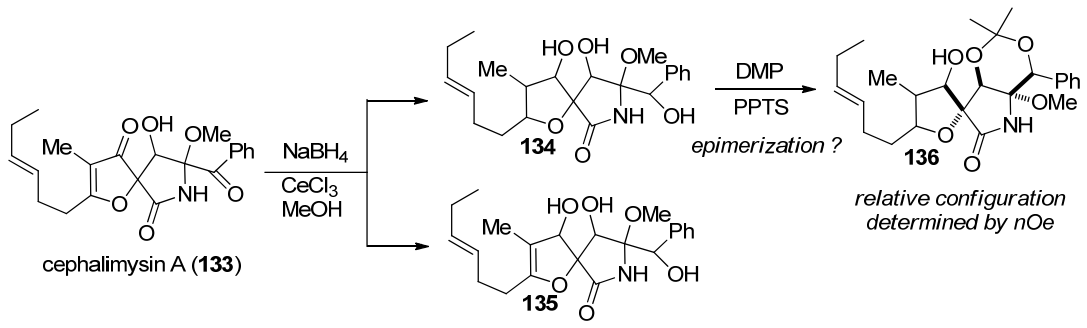
Scheme 30.



cephalimysin A (**133**)
initially proposed structure

Interestingly, the structure of cephalimysin A was proposed to be epimeric at C-8 when compared to all other members of the spirofuranone lactam containing natural products. The initial structure of cephalimysin A was determined by chemical modifications of the isolated natural product. Treatment of cephalimysin A (**133**) with sodium borohydride and cerium trichloride affords a mixture of triols **134** and **135** (Scheme 31).

Scheme 31.

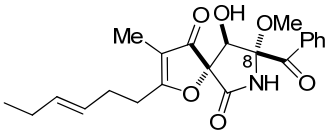


Subsequent treatment of triol **134** with dimethoxypropane (DMP) and pyridium *para*-toluene sulfonate (PPTS) generates acetonide **136**. The relative stereochemistry of this product was assigned by rigorous nOe analysis which established that the hydroxyl and methoxy groups are in a *trans* relationship to one another. We hypothesize that epimerization at C-8 takes place under the acidic conditions for acetonide formation, and therefore the reported structure is in error. The absolute stereochemistry was determined by the modified Mosher method and is consistent with all other members of this family of natural products.

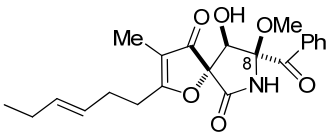
Interested in the disparity between the proposed structure of cephalimysin A and all other members of this family of natural products, we sought to pursue its total synthesis. The previous synthetic efforts towards azaspirene (**76**) and FD-838 (**81**) gave us valuable insight and shaped our plan for the synthesis of cephalimysin A.

In May 2010 Yamada and coworkers, the original isolation authors, reported a corrected structure of cephalimysin A in which the methoxy group at C-8 has been inverted and is consistent with the other spirocyclic natural products (Scheme 32).[43]

Scheme 32.



cephalimysin A (**133**)
initially proposed structure
July 2007



cephalimysin A (**137**)
revised structure
May 2010

1.2.5 Summary

Spirofuranone lactam-containing compounds represent a family of natural products with a unique spirocyclic core and diverse biological activity. Previous syntheses of these molecules suffer from low yields and high step counts. It has been found that the asymmetric Stetter reaction allows for rapid access to the spirocyclic core of these molecules, however further functionalization has proven difficult. In 2007 a new member of this family of natural products was identified (cephalimysin A) which was originally proposed to be epimeric at C-8. Intrigued by this disparity a program directed at employing the asymmetric Stetter reaction for the total synthesis of cephalimysin A was initiated.

1.3 References

[1] Igau, A.; Grutzmacher, H.; Baceiredo A.; Berand, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 6463.

[2] Arduengo, A. J.; Dias, R. L.; Harlow, R.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

[3] For reviews, see: (a) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 725. (b) Bourissou, D.; Guerret, O.; Gabbai, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39. (c) Herrman, W. A.. *Angew. Chem. Int. Ed.* **2002**, *41,* 1291.

[4] For reviews, see: (a) Read de Alaniz, J.; Rovis, T. *Synlett* **2009**, 1189. (b) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (c) Ender, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (d) Johnson, J. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1326.

[5] Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.

[6] Wöhler, F.; Liebig, J. *Ann. Pharm. (Lemgo, Ger.)* **1832**, *3*, 249.

[7] Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.

[8] Ukai, T.; Dokawa, T.; Tsubokawa, S. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296

[9] (a) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 2719. (b) Breslow, R.; Kim, R. *Tetrahedron Lett.* **1994**, *35*, 3719.

[10] Sheehan, J. C.; Hunnemann, D. H.; *J. Am. Chem. Soc.* **1966**, *88*, 3666.

[11] Sheehan, J. C.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196.

[12] Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta.* **1996**, *79*, 1217.

[13] Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891.

[14] Enders, D.; Kallfass, U. *Angew Chem. Int. Ed.* **2002**, *41*, 1743.

[15] Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432.

[16] Enders, D.; Niemeier, O. *Synlett* **2004**, 2111.

[17] Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 1463.

[18] Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 3492.

[19] Stetter, H.; Schreckenberg, M. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 81.

[20] Stetter, H.; Kuhlmann, H. *Chem. Ber.* **1976**, *109*, 2891.

[21] Ciganek, E. *Synthesis* **1995**, 1311.

[22] Enders, D.; Breuer K; Runsink, J.; Teles, J. H. *Helv. Chim. Acta.* **1996**, *79*, 1899.

[23] For synthesis of these triazolium salts see (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725. (b) Vora, H. U.; Lathrop, S. P.; Reynolds, N. T.; Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *Org. Synth.* **2010**, *87*, 350.

[24] (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (b) Kerr, M. S.; Rovis, T. *Synlett.* **2003**, 1934. (c) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (d) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284. (e) Moore, J. L.; Kerr, M. S.; Rovis, T. *Tetrahedron* **2006**, *62*, 11477. (f) Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73,* 2033.

[25] (a) Liu, Q.; Perrault, S.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130,* 14066. (b) Liu, Q.; Rovis, T. *Org. Lett.* **2009**, *11*, 2856.

[26] DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131*, 10872.

[27] Trost, B. H.; Shuey, C. D.; DiNinno, F.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1284.

[28] Nicolaou, K. C.; Tang, Y.; Wang, J. *Chem. Commun.* **2007**, 1922.

[29] Stetter, H.; Kuhlmann, H.; *Synthesis* **1975**, 379.

[30] Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649.

[31] Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817.

[32] Galopin, C. C. *Tetrahedron Lett.* **2001**, *42*, 5589.

[33] Asami, Y.; Kakeya, H.; Onose, R.; Yoshida, A.; Matsuzaki, H.; Osada, H. *Org. Lett.* **2002**, *4*, 2845.

[34] Mizoue, K.; Okazaki, T.; Hanada, K.; Amamoto, T.; Yamagishi, M.; Omura, S.; Eur. Pat. Appl. EP 216607, *J* P Appl. 205278.

[35] (a) Bloch, P.; Tamm, C.; Bollinger, P.; Petcher, T. J.; Weber, H. P. *Helv. Chim. Acta.* **1976**, *59*, 137. (b) Wenke, J.; Anke, H.; Sterner, O. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 961 (c) Komagata, D.; Fujita, S.; Yamashita, N.; Saito, S.; Morino, T. *J. Antibiot.* **1996**, *49*, 958.

[36] Ando, O.; Satake, H.; Nakajina, M.; Sato, A.; Nakamura, T.; Kinoshita, T.; Furuya, K.; Haneishi, T. *J. Antiiot.* **1991**, *44*, 382.

[37] Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 12078.

[38] (a) Hayashi, Y.; Shoji, M.; Mukaiyama, T.; Gotoh, H.; Yamaguchi, S.; Nakata, M.; Hideaki, K.; Osada, H. *J. Org. Chem.* **2005**, *70*, 5643. (b) Hayashi, Y.; Shoji, M.; Yamaguchi, S.; Mukaiyama, T.; Yamaguchi, J.; Kakeya, H.; Osada, H. *Org. Lett.* **2003**, *5*, 2287.

[39] Hayashi, Y.; Sankar, K.; Ishikawa, H.; Nozawa, Y.; Mizoue, K.; Kakey, H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3863.

[40] (a) Aoki, S.; Oi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1703. (b) Aoki, S.; Oi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Heterocycles* **2004**, *62*, 161.

[41] Orellana, A.; Rovis, T. *Chem. Commun.* **2008**, 730.

[42] Yamada, T.; Imai, E.; Nakatui, K.; Numata, A.; Tanaka, R. *Tetrahedron Lett.* **2007**, *48*, 6294.

[43] Yamada, T.; Kitada, H.; Kajimoto, T.; Numata, A.; Tanaka, R. *J. Org. Chem.* **2010**, *75*, 4146.

Chapter 2

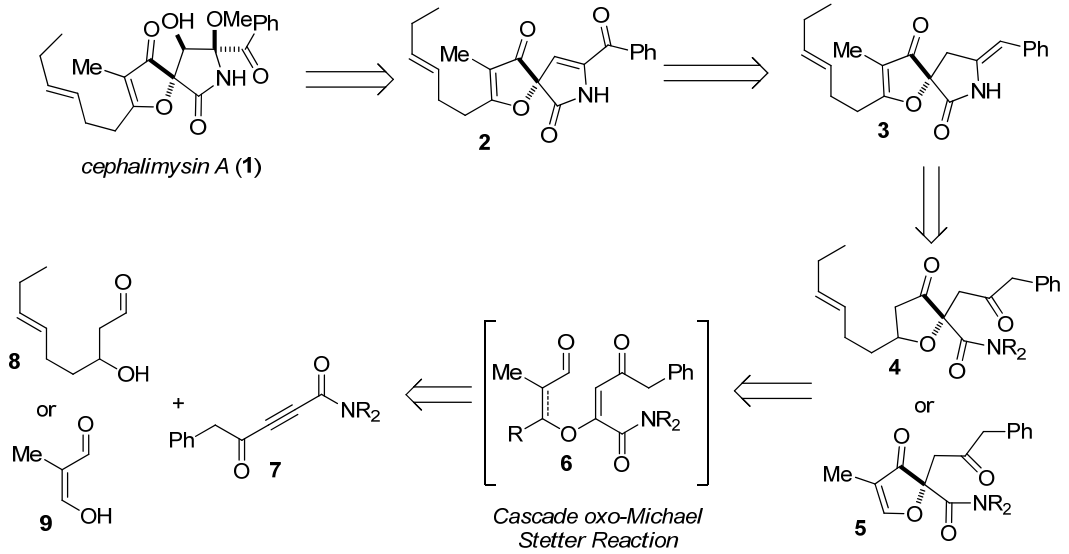
First Generation Approach Towards Cephalimysin A

2.1 Retrosynthetic Strategy

The previous approach towards azaspirene and FD-838 in the Rovis group highlighted the power of the Stetter reaction in enantioselectively accessing the spirocyclic core of these molecules. However, further functionalization of the molecule proved difficult (*vide supra*, Ch. 1, Sect.1.2.3). In our approach to cephalimysin A we sought to utilize a more convergent and efficient approach. We believed that employing a cascade process would allow us to quickly access the spirocyclic core of cephalimysin A (**1**) (Scheme 1).

Working back from the natural product **1**, we believed that late stage introduction of the hydroxy and methoxy group could be achieved via an epoxidation of enone **2** followed by epoxide opening with methanol. Enone **2** would be derived from selective oxidation of enamide **3** followed by oxidation to the ketone followed by elimination. The benzylidene lactam **3** could be derived either from the β-substituted dihydrofuranone **4** or α-methyl furanone **5**. These two cyclic products would arise from an oxa-Michael/Stetter cascade process. The β-hydroxy aldehydes **8** or **9** would undergo a base-catalyzed Michael addition to afford intermediate **6** that, in the presence of a carbene catalyst, would perform an asymmetric intramolecular Stetter reaction to generate **4** or **5**.

Scheme 1.

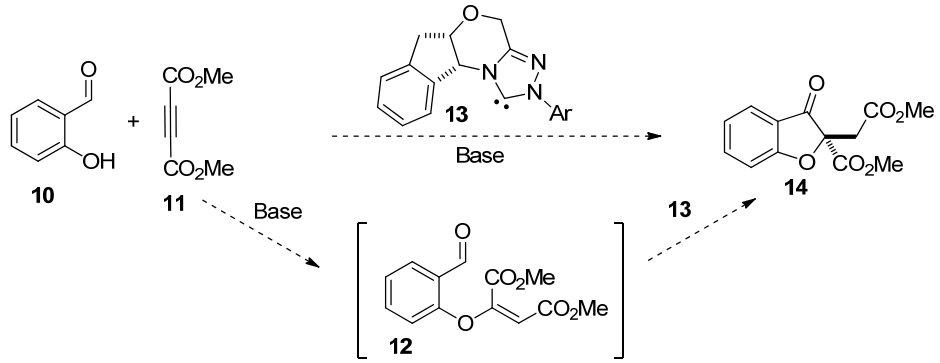


The advantage of this route is that the cascade process would allow for a very rapid and convergent entry to cephalimysin A. Aldehyde **8** would arrive at intermediate **4** with the alkenyl side chain already in place. Conversely, aldehyde **9** affords the product **5** with the previously difficult to install methyl group in place. It also gives the enone which is at the correct oxidation state for conjugate addition of the alkenyl side chain. Use of the activated phenylacetyl ynamide **7** would access the product containing the desired phenyl group. In order to investigate the feasibility of our approach to cephalimysin A, a model system was examined to test our proposed oxa-Michael cascade.

Section 2.2 Cascade Approach, Model System

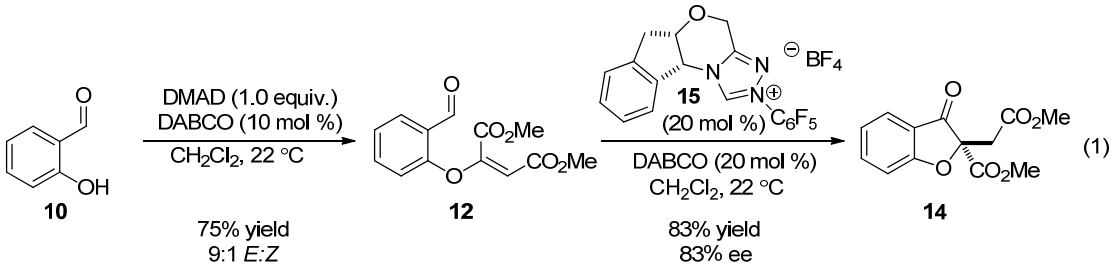
To investigate the proposed cascade process, we chose salicylaldehyde (**10**) as our β-hydroxy aldehyde and dimethyl acetylene dicarboxylate (DMAD) as the activated alkyne (Scheme 2).

Scheme 2.

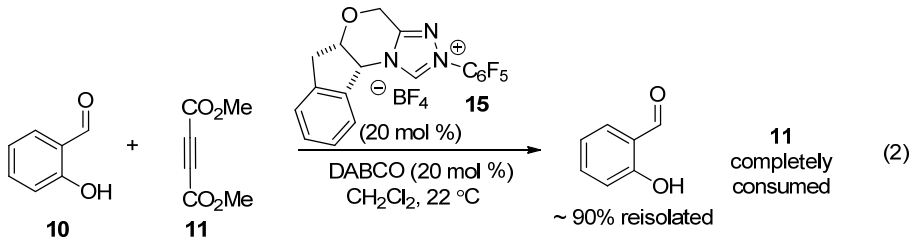


Phosphines[1], amines[2] and certain transition metals[3] are known to catalyze the conjugate addition of oxygen nucleophiles to activated alkynes. A recent report by Fan and co-workers showed that various alcohols undergo conjugate addition into DMAD in the presence of catalytic 1,4-diazobicyclo[2.2.2]octane (DABCO).[2a] These basic conditions seemed promising for our desired cascade process as they should generate active carbene catalyst *in situ* while also facilitating the conjugate addition.

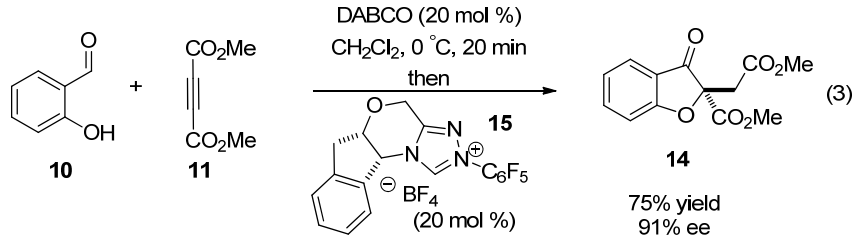
First, the reaction was conducted in a stepwise manner with isolation of aldehyde **12**. It was found that treatment of salicylaldehdye and DMAD with DABCO affords the desired aldehyde **12** in good yield and *E/Z* selectivity (eq 1). Treatment of the aldehyde with triazolium salt **15** in the presence of DABCO generates the desired benzofuranone **14** in good yield and enantioselectivity.



Having determined that the stepwise process was indeed possible, we turned our attention to conducting the reaction in a one-pot, cascade fashion (eq 2). Addition of all reagents followed by addition of DABCO led to decomposition of the alkyne and recovery of salicylaldehdye.

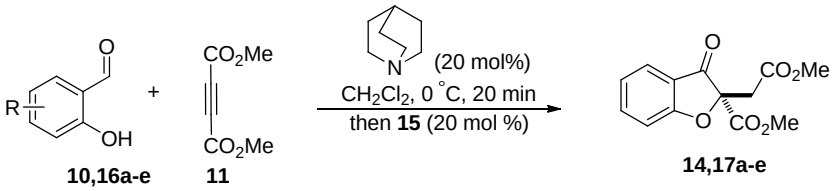


We presumed that the base-generated carbene catalyst was reacting with the alkyne, inhibiting the reaction. *N*-heterocyclic carbenes have been shown capable of nucleophilic addition into DMAD and other alkynes.[4] To prevent this carbene catalyzed decomposition of DMAD, the triazolium salt was added upon completion of the first step (typically < 20 min). Under these conditions the desired product was obtained in good yield and enantioselectivity (eq 3).

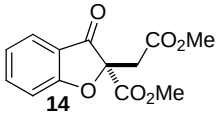
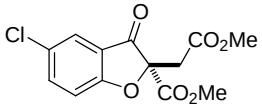
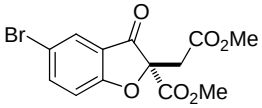
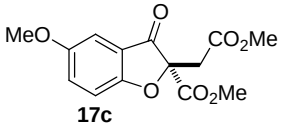
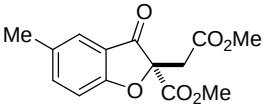
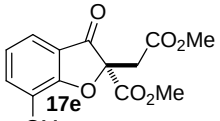


It was found that a variety of salicylaldehydes participate in the reaction in the presence of quinuclidene as the base to give the desired product in good yields and enantioselectivities (Table 1).

Table 1.

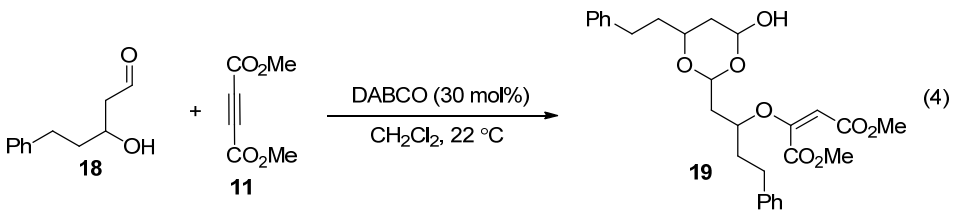


10,16a-e **11** **14,17a-e**

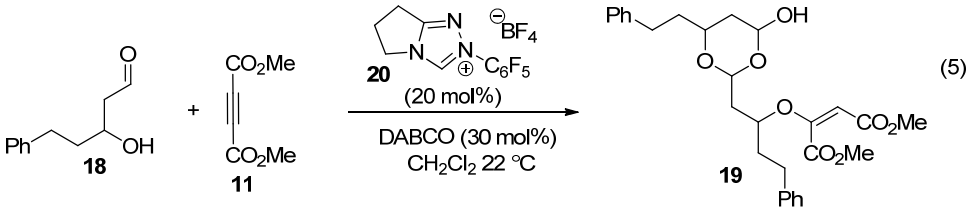
entry	product	yeild	ee
1	 **14**	75%	91%
2	 **17a**	73%	85%
3	 **17b**	80%	88%
4	 **17c**	68%	73%
5	 **17d**	80%	79%
6	 **17e**	75%	91%

The utility of this transformation has been further investigated by Claire Filloux and the findings were recently published.[5]

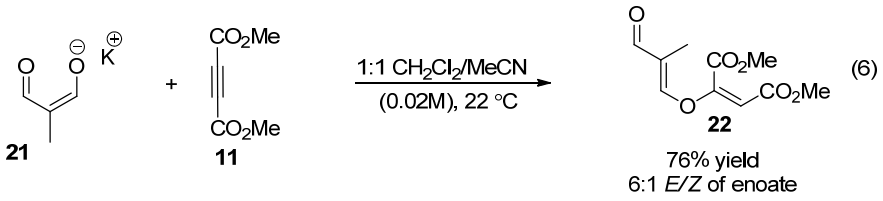
Having shown that the desired cascade is possible, we sought to apply this methodology to the synthesis of cephalimysin A. We first examined the use of alkyl β-hydoxy aldehydes in the desired cascade. Treatment of aldehyde **18** with DABCO in the presence of DMAD afforded only the acetal product **19** (eq. 4).



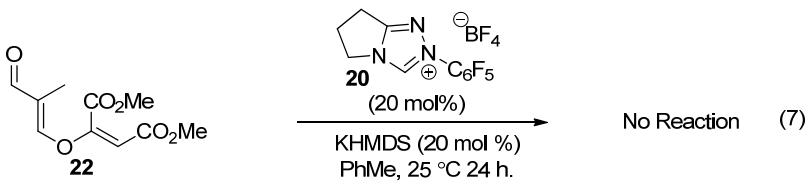
Although the acetal product formed quickly, we presumed that acetal formation would be reversible, and with this in mind the one-pot cascade reaction was examined. However, no desired Stetter product was observed (eq 5). All attempts to overcome the acetal formation failed to provide the desired product.



Next, we turned our attention to the use of methylmalondialdehyde **21** in the desired conjugate addition into DAMD. It was found that treatment of DMAD with methylmalondialdehyde in a DCM/MeCN mixture afforded the desired product in good yield (eq 5). However, the product was obtained as a single *E* olefin isomer of the enal.



In order for the Stetter reaction to proceed, an isomerization of the α,β-unsaturated aldehyde to the *Z* isomer is necessary. Although the wrong olefin isomer (*E*) was isolated, we thought the enal could isomerize under the Stetter reaction conditions. However, upon treatment of **22** with triazolium salt **20** and KHMDS only the starting material was observed (eq. 7).

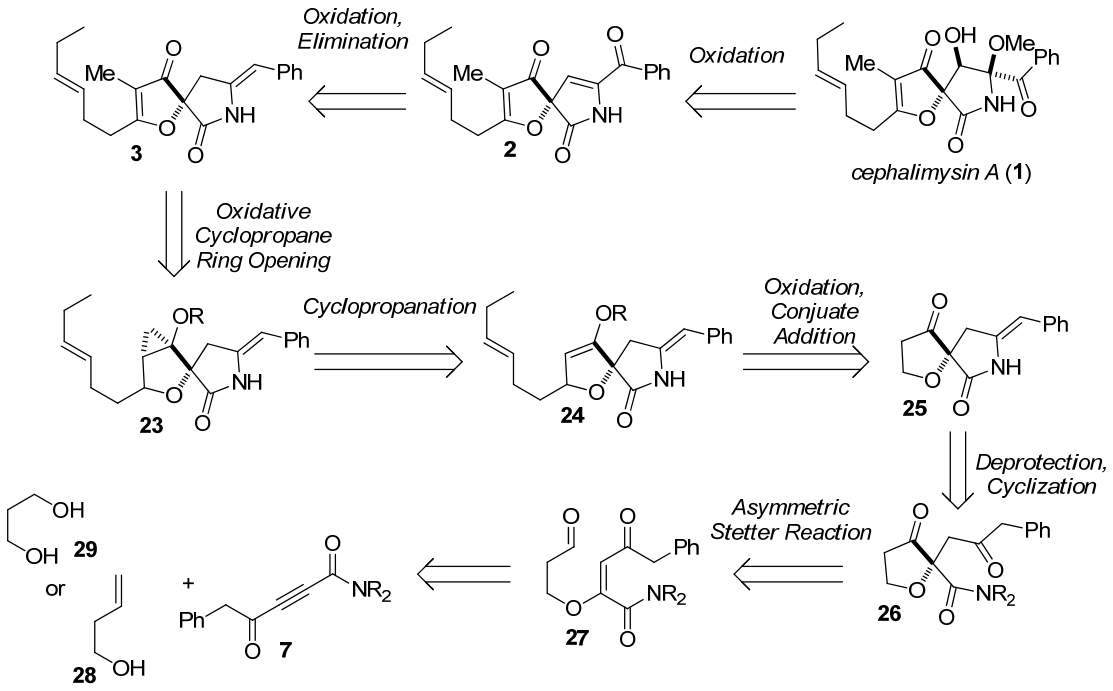


At this point, we concluded that this cascade would not be a feasible route to access the core of cephalimysin A, and an alternate approach was deemed necessary.

2.3 Alternate Approach to the Stetter Precursor

Although the cascade approach towards cephalimysin A failed, we believed that the conjugate addition of an alcohol into an alkyne was still a viable route to access the Stetter precursor in a convergent manner. The revised retrosynthetic approach is focused on the formation of benzylidene lactam **3** (Scheme 3).

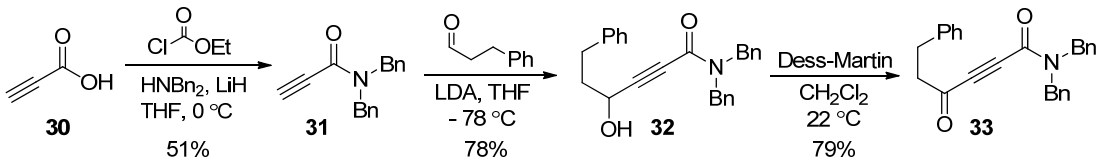
Scheme 3.



This intermediate (**3**) would arise from oxidative cyclopropane ring opening of **23**. The cyclopropane would come from the cyclopropanation of enol ether **24**. Enol ether **24** would be generated from oxidation of **25** to the enone followed by organocuprate conjugate addition and trapping. The spirocyclic core would arise from deprotection and cyclization of the dihydrofuranone **26**. The dihydrofuranone would be accessed from an asymmetric intramolecular Stetter reaction of aldehyde **27**. The aldehyde **27** would be generated from oxa-Michael of either allyl carbinol (**28**) or 1,3 propane diol (**29**) into activated alkyne **7**, followed by oxidation of the resulting alcohol or olefin.

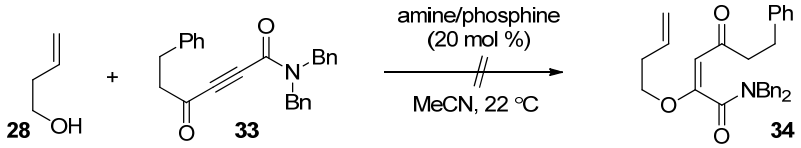
To investigate the viability of the proposed oxa-Michael reaction model alkyne **33** was synthesized (Scheme 4). Amidation of propiolic acid via the mixed anhydride affords the propynamide **31** in moderate yield.[6] Treatment of ynamide **31** with LDA followed by addition of hydrocinnamaldehyde generates propargyl alcohol **32**.[7] Dess-Martin oxidation[8] gives the desired activated alkyne **33** via a convenient three step procedure.

Scheme 4.



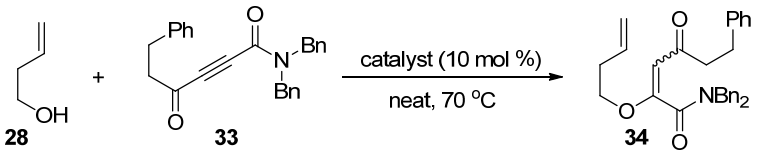
As mentioned previously amines and phosphines have been shown to catalyze the conjugate addition of alcohols to activated alkynes. A screen of various amines and phosphines in the desired conjugate addition with allyl carbinol failed to yield the desired product (Scheme 5). In most cases only starting material was observed, under more forcing conditions decomposition of the alkyne was observed.

Scheme 5.



A more thorough search of the literature revealed an example by Tani and co-workers in which silver triflate was used to catalyze the conjugate addition of various alcohols into DMAD.[3b] As a result of this example a number of transition metal catalysts were investigated in the desired conjugate addition (Table 2). To our delight a variety of metals facilitated the conjugate addition to afford terminal olefin **34**.

Table 2.

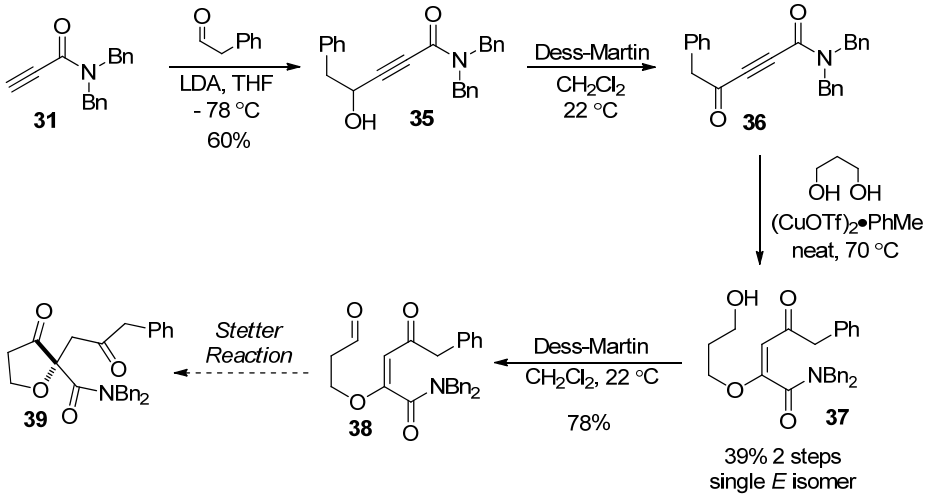


entry	catalyst	temp (°C)	yield	*E:Z*
1	$AuCl_3$	70	NR	-
2	$Pd(MeCN)_2Cl_2$	70	decomp	-
3	$Cu(OTf)_2$	70	36%	>20:1
4	AgOTf	70	43%	3:1
5	AuCl	70	trace	-
6	Ph_3PAuCl	70	trace	-
7	$(CuOTf)_2$•PhMe	70	44%	1.5:1
8	$(CuOTf)_2$•PhMe	50	61%	1:1.5
9	$(CuOTf)_2$•PhMe	25	45%	1:1.2
10	$PtCl_2$	70	decomp	-
11	$Cu(OTf)_2$	50	18%	>20:1

Of the metals screened, silver(I) triflate, copper(II) triflate, and copper(I) triflate toluene complex gave the best yields (entries 3, 4, and 8). Having conditions to facilitate the oxa-Michael reaction we sought to apply these for the synthesis of the Stetter precursor.

Synthesis of the desired activated alkyne **36** was carried out as previously shown, but phenylacetyl aldehyde was substituted as the electrophile. With alkyne **36** in hand the desired conjugate addition was carried out (Scheme 6). A switch to the 1,3 propanediol was utilized since the reaction was conducted in a large excess of alcohol. With this alcohol, copper(I) triflate toluene complex was found to be the optimal catalyst affording the primary alcohol **37** in good two step yield. More importantly the product was obtained as a single *E* olefin isomer as confirmed by nOe studies. This was advantageous because it has been shown that *Z* olefin Michael acceptors tend to give lower enantioselectivities in the intramolecular Stetter reaction.[9] From the alcohol **37** Dess-Martin oxidation affords the somewhat unstable aldehyde **38** in good yield.

Scheme 6.



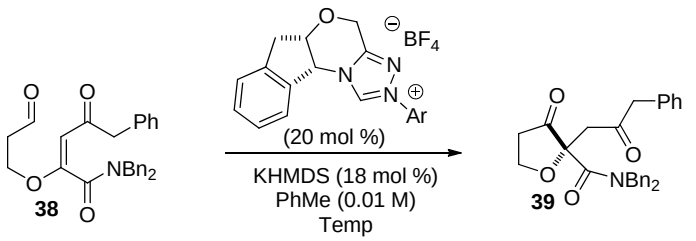
2.4 Stetter Reaction

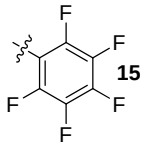
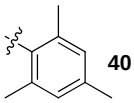
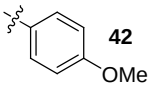
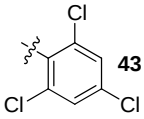
With the aldehyde in hand, we were ready to investigate the asymmetric intramolecular Stetter reaction to afford dihydrofuranone **39**. Initial screening revealed that

toluene as the solvent and KHMDS as the base were the optimal conditions at low concentration (0.01 M). The low concentration is necessary to prevent the intermolecular benzoin reaction.

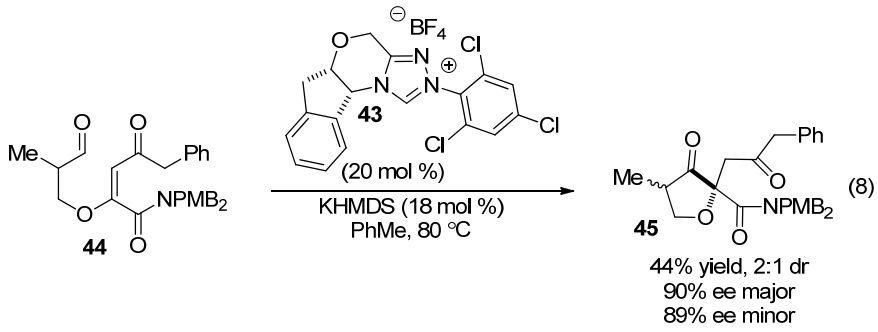
Having identified conditions that afford the desired product, a screen of chiral triazolium salts derived form aminoindanol was carried out (Table 3). Varying the aryl group on the triazolium salt revealed an interesting trend relating to both the electronic and steric nature of the aryl group. The pentafluorophenyl catalyst **15** gave the desired product in good yield, but moderate enantioselectivity (entries 1-3). The electron rich mesityl catalyst **40** affords the product with diminished yield and a fortunate 89% ee (entries 4 and 5). Other electron rich aryl groups afford low yields and moderate enantioselectivities (entries 6 and 7). We suspected that both high yields and enantioselectivity could be obtained by utilizing a sterically larger electron withdrawing group on the aryl ring. Indeed, trichlorophenyl catalyst **43** affords the product in both good yield and high enantioselectivity (entries 8 and 9).

Table 3.

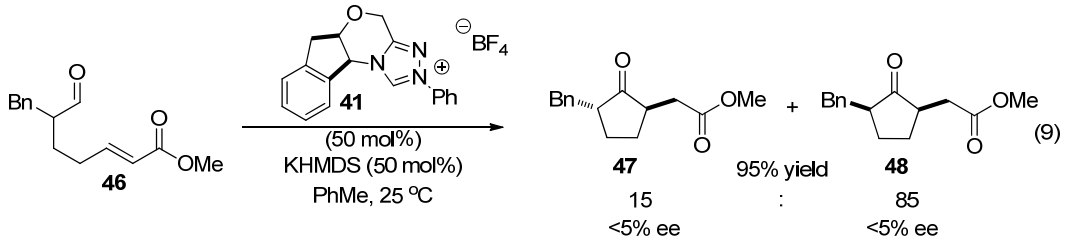


entry	Ar	temp (°C)	yield	ee
1	 **15**	22	30%	66%
2		60	41%	68%
3		80	53%	68%
4	 **40**	22	22%	87%
5		60	24%	89%
6	 **41**	60	19%	72%
7	 **42** OMe	60	18%	72%
8	 **43**	60	61%	89%
9		80	50%	90%

We also examined the Stetter reaction with α-methyl aldehyde **44**. This aldehyde was synthesized utilizing the same procedure as shown previously except the 1,3 propane diol has been substituted with 2-methyl 1,3 propanediol. Under the optimized conditions the α-methyl aldehyde afforded the desired product in 44% yield, 2:1 dr and 90% ee for the major diastereomer and 89% ee for the minor diastereomer (eq 8).



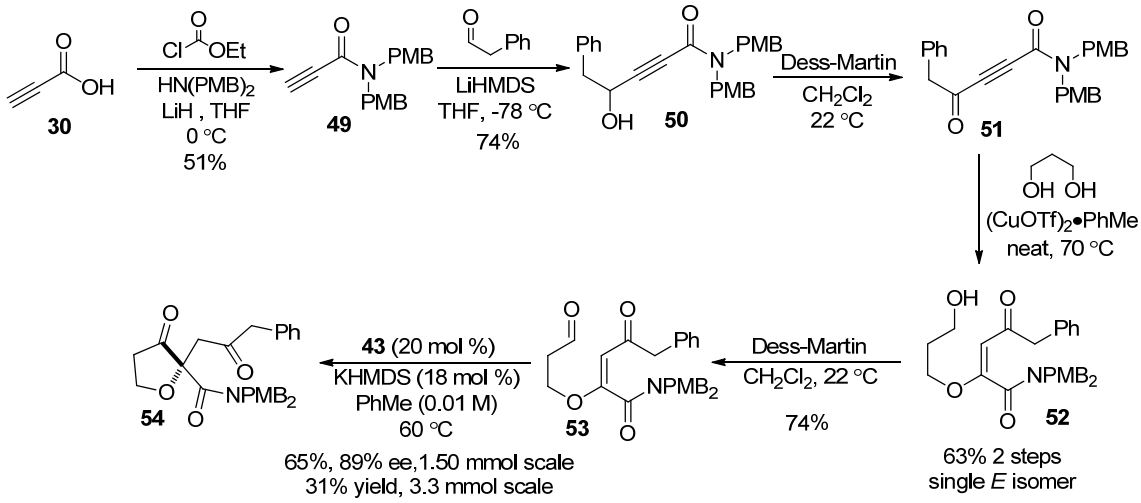
This result was unexpected as Rovis and co-workers have previously shown that α-stereocenters generally give the Stetter product in good diastereoselectivity but with no enantioinduction (eq 9).[10]



Although the yield was low, this unexpected result was encouraging as we believed it would allow us to install the desired methyl group early in the synthesis.

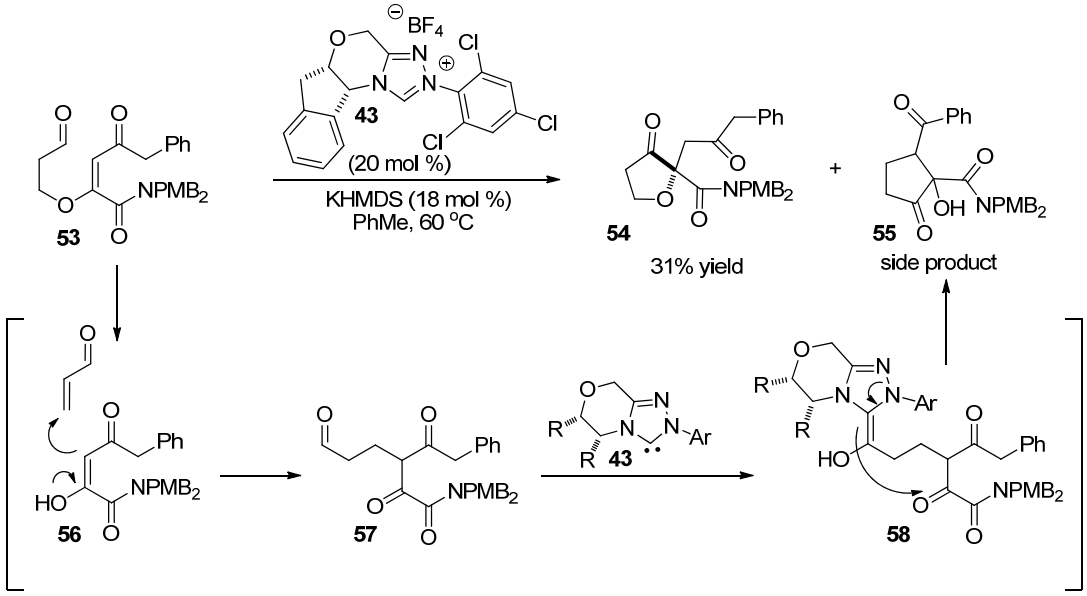
Having devised a route to the dihydrofurnanone **39** we sought to continue our synthesis of cephalimysin A. We decided to switch the nitrogen protecting group from benzyl to the *para*-methoxybenzyl group for easier deprotection. Furthmore, di-*para*-methoxybenzyl amide **51** could be synthesized in a similar manner to the dibenzyl and could be carried out on gram scale (Scheme 7).

Scheme 7.



When the Stetter reaction was scaled up to 3.3 mmol, a dramatic drop in the isolated yield of the dihydrofuranone **54** was observed. After careful investigation of the crude reaction mixture and isolation of by-products, it was found that cyclopentanone **55** was the major side product formed during the reaction (Scheme 8).

Scheme 8.

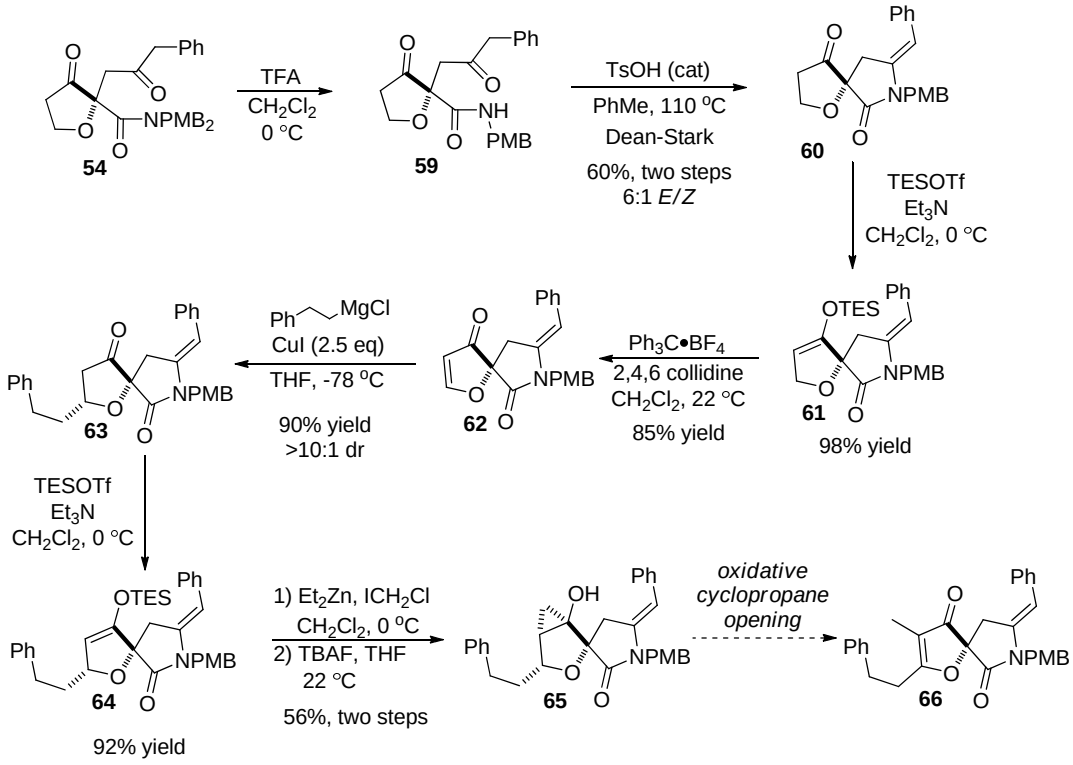


The unexpected product is believed to come from decomposition of the starting material into acrolein and tricarbonyl **56**. Under the basic conditions the tricarbonyl can add in a conjugate fashion to form aldehyde-tethered ketone **57**. The resultant aldehyde can then react with the carbene to afford Breslow intermediate **58**. This intermediate undergoes an intramolecuar benzoin reaction to afford hydroxy-ketone **55**. Although this side product was undesired in our synthesis of cephalimysin A, it presented unique reactivity and was further investigated (See Ch. 4, Sect 4.4.2).

2.5 Synthesis of Cyclopropanol

With the dihydrofuranone in hand we sought to form the spirocycle and functionalize the left hand side of the molecule. As described previously the oxidative cyclopropane ring opening is integral to the synthesis of fully substituted furanone **3** (Sect. 2.3 Scheme 3). Cyclopropanol **65** was made in eight, straight forward steps (Scheme 9). From dihydrofuranone **54** mono-deprotection followed by acid catalyzed cyclization and elimination affords benzylidene lactam **60**. Formation of silylenol ether **61** and oxidation via hydride abstraction[11] generates the desired enone **62**. Conjugate addition of phenethyl cuprate yields **63**, in this model system. A subsequent enolization and trapping affords enolether **64**. Silylenolether **64** was considerably more stable than the similar enol ether utilized by Dr. Orellena in his efforts towards FD-838 (Scheme 28, Ch. 1). Simmons-Smith cyclopropanation of the enol ether followed by deprotection of the siloxyether generates the desired cyclopropanol **65**.

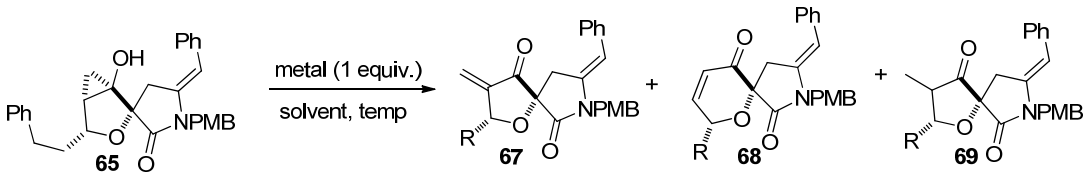
Scheme 9.



2.6 Cyclopropane Ring Opening

With cyclopropanol **65** in hand an investigation of the cyclopropane ring opening ensued. We were hopeful that the palladium-catalyzed oxidative ring opening utilized in the group's previous efforts towards azaspirene could be applied to this substrate (Scheme 24, Ch. 1).[12] A screen of various palladium catalysts afforded a mixture of exomethylene product **67**, ring-expanded product **68,** or starting material (Table 4, entries 1-4). However, Zeise's dimer generated the dihydrofuranone **69** in 40% yield (entry 5). This type of transformation has been previously reported by Jennings and coworkers.[13]

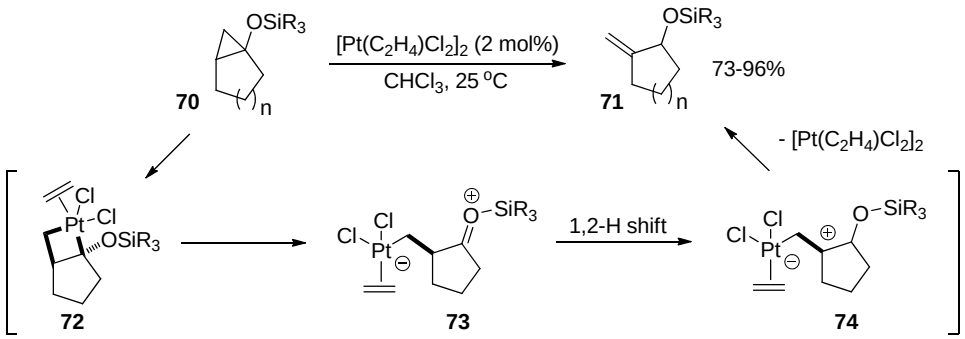
Table 4.



entry	Metal	Solvent	Temp	Products
1	$Pd(OAc)_2$	MeCN	60	**67** and **68**
2	$[Pd(MeCN)_4](BF_4)_2$	MeCN	25	**67** and **68**
3	$[Pd(MeCN)_4](BF_4)_2$	DCM	25	S.M.
4	$[Pd(PhCN)_2]Cl_2$	DCM	25	S.M
5	$[Pt(C_2H_4)Cl_2]_2$	DCM	25	**69** (40% yield)

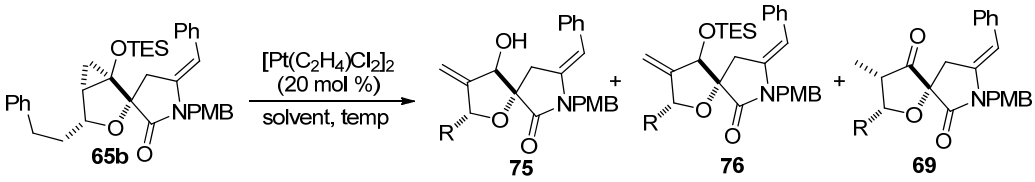
Encouraged by this result a more thorough literature search was carried out and revealed a similar example of platinum catalyzed cyclopropane ring opening by Sonada and co-workers.[14] They reported a Zeise's dimer catalyzed siloxycyclopropane ring opening reaction to afford protected allylic alcohols **71** (Scheme 9). The reaction is believed to proceed via insertion of the platinum into the cyclopropane to form platinacycle **72**. Heterolytic cleavage of the platinum siloxy carbon bond gives zwitterion **73** that undergoes a 1,2 hydrogen shift and elimination of the platinum to afford allyl silyl ether **71**. This example was promising as no ring expansion products were observed.

Scheme 9.



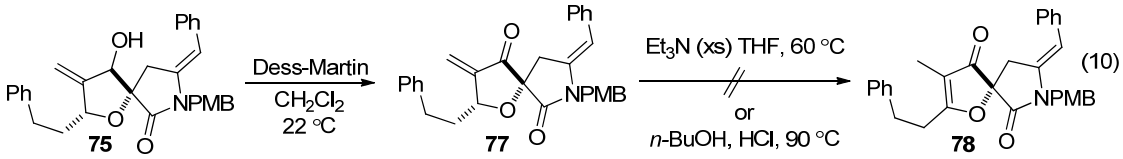
Upon investigating this platinum-catalyzed ring opening it was found that temperature has a marked effect on the yield of the desired product. At room temperature only starting material was observed (Table 5, entry 1). Interestingly, conducting the reaction at 50 °C results in cyclopropane ring opening followed by an unexpected *in situ* deprotection to afford allylic alcohol **75** in moderate yield (entry 2). Switching the solvent to THF delivered only ketone **69** (entry 3). Utilizing toluene as the solvent affords a mixture of alcohol **75** and silyl ether **76** in good yield (entry 4).

Table 5.



entry	solvent	temp (°C)	product	yield
1	$CHCl_3$	25	S.M.	-
2	$CHCl_3$	50	**75**	55%
3	THF	50	**69**	21%
4	PhMe	80	**75** and **76**	71%

Although generating the exo-cyclic olefin is less desirable, it was thought that isomerization to the tetrasubstituted enone would be feasible. With this in mind the allylic alcohol was oxidized with Dess-Martin periodinane to afford exo-cyclic enone **77**. Attempts to isomerize the olefin under both acidic and basic conditions failed to generate the desired furanone **78** (eq 10).

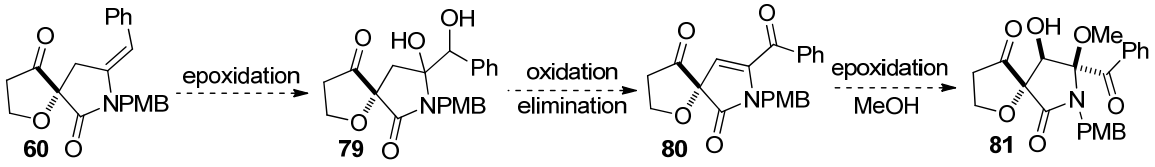


Although this isomerization failed under the few conditions attempted, we believe that further investigation into the isomerization would lead to the desired product. However, at this time we chose to focus on functionalizing the right hand portion of the molecule before moving forward with this route.

2.7 Benzylidene Lactam Oxidation

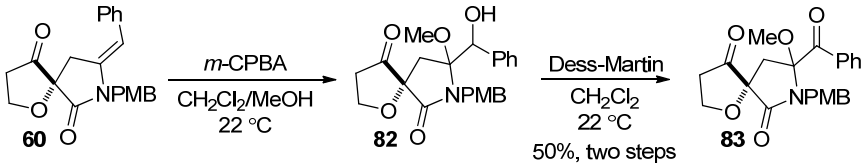
Since we had a route to the desired funtionalized furanone, we sought to investigate the functionalization of the lactam ring. From the benzylidene lactam **60,** we hoped to use conditions similar to Hayashi and co-workers (Scheme 17, Ch. 1) to afford the diol **79** (Scheme 10). Oxidation of diol **79** would afford the α-hydroxy ketone which would undergo subsequent elimination to afford the desired enone **80**. Epoxidation of the enone olefin followed by opening of the epoxide with methanol would give the fully functionalized lactam **81**.

Scheme 11.



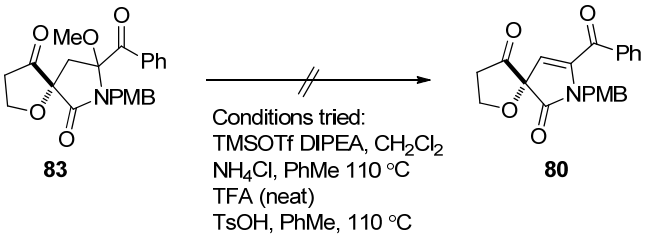
Epoxidiation of benzylidene lactam in the presence of *m*-CPBA in a DCM/MeOH afforded the hemiaminal **82** as a mixture of diastereomers.[15] Treatment of the crude material with Dess-Martin periodinane generates the desired α-methoxy ketone **83** (Scheme 12).

Scheme 12.



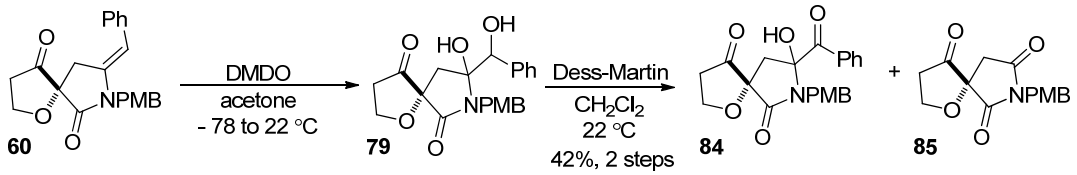
A variety of conditions were examined to facilitate the desired elimination of α-methoxy ketone **83** (Scheme 13).[16] However under protic and Lewis acidic conditions no desired product was obtained.

Scheme 13.



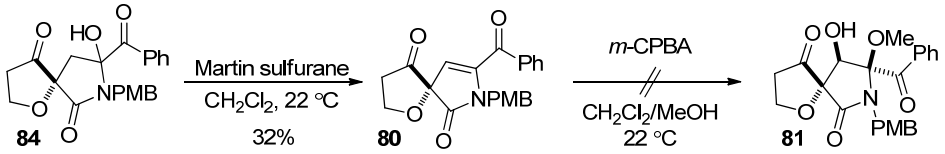
Although elimination failed to occur with the α-methoxy aldehyde, we wanted to examine the use of the α-hydroxy ketone. Synthesis of the α-hydroxy ketone was performed in a similar manner to that of **83** (Scheme 14). Epoxidation with DMDO followed by *in situ* opening of the epoxide with water gave diol **79**. Oxidation of the diol with Dess-Martin periodane resulted in the desired ketone **84** but in slightly lower yields than with hydroxy methylether **82**. The succinimide product **85** was formed as the major byproduct, which we believe occurs via an oxidative cleavage of the 1,2-diol. Although unexpected, the cleavage of 1,2-diols by Dess-Martin periodane has been reported in the literature.[17]

Scheme 14.



The desired elimination could be accomplished in the presence Martin-sulfurane[18] to yield enone **80** albeit in low yield (Scheme 15).

Scheme 15.



Attempts to carry out the desired epoxidation with subsequent methanol opening failed to deliver the desired product **81**. Although this epoxidation failed we still believed that functionalization of enamide **80** should allow access to the fully substituted lactam ring of cephalimysin A. However at this juncture we chose to evaluate our progress towards the natural product in hopes of developing a slightly more streamLined approach.

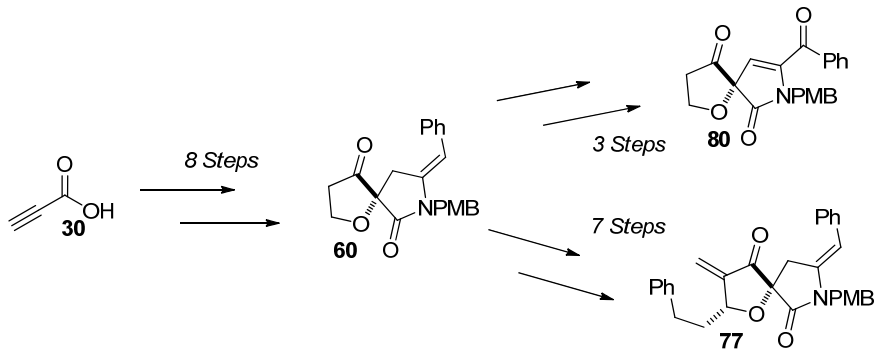
2.8 Summary of First Generation Approach

Our first generation approach to cephalimysin A is highlighted by three key synthetic steps. Synthesis of the Stetter precursor via a copper catalyzed conjugate addition to activiated alkyne **51**. Development of an asymmetric intramolecular Stetter reaction to deliver the dihydrofuranone **54** with high enantioselectivity and optimization of a platinum catalyzed cyclopropane ring opening to install the desired methyl group.

We were able to access the spirocyclic benzylidene lactam **60** enantioselectively in eight steps from commercially available propiolic acid via an asymmetric Stetter reaction

(Scheme 16). This spirocyclic intermediate could be elaborated in a further three steps to enone **80**. The same intermediate **60** was functionalized in seven steps to the exocyclic enone **77**.

Scheme 16.



Although a number of problems were overcome while pursuing this route and two functionalized intermediates were synthesized, the overall step count was less than desirable. We believed that we could utilize the Stetter reaction in a more convergent manner, which would allow for quicker synthesis of cephalimysin A. Thus we geared our efforts toward a second generation approach that will be discussed in the following chapter.

2.8 References

[1] (a) Painter, F. F.; Metz, M.; Bauschke, G.; *Synthesis* **2002**, 869. (b) Crisp, G. T.; Millan, M. J. *Tetrahedron* **1998**, *54*, 637. (c) Inanaga, J.; Baba, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 241.

[2] (a) Fan, M.-J. Li, G.-Q.; Liang, Y.-M. *Tetrahedron* **2006**, *62*, 6782. (b) Tae, J.; Kim, K.-O. *Tetrahdron Lett.* **2003**, *44*, 2125. (c) Ciganek, E. *Synthesis* **1995**, 1311.

[3] (a) Kuram, M. R.; Bhanuchandra, M.; Sahoo, A. K. *J. Org. Chem.* **2010**, *75*, 2247. (b) Kataoka, Y.; Matsumoto, O.; Tani, K. *Chem. Lett.* **1996**, 727. (c) Bertz, S. H.; Dabbagh, G.; Cotte, P. *J. Org. Chem.* **1982**, *47*, 2216.

[4] (a) Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297. (b) Nair, V.; Bindu, S.; Sreekumar, V.; Rath, N. P. *Org. Lett.* **2003**, *5,* 665.

[5] Filloux, C. M.; Lathrop, S. P.; Rovis, T. *Proc. Nat. Acad. Sci.* **2010**, Early view DOI/10.1073/pnas.1002830107.

[6] Coppola, G. M.; Damon, R. E. *Syn. Commun.* **1993**, *23*, 2003.

[7] (a) Coppola, G. M.; Damon, R. E. *J. Heterocyclic Chem.* **1995**, *32*, 1133. (b) Crimmins, M. T.; Nantermet, P. G.; Trotter, B. W.; Vallin, I. M.; Watson, P. S.; McKerlie, L. A.; Reinhold, T. L.; Cheung, A. W.; Stetson, K. A.; Dedopoulou, D.; Gray, J. L. *J. Org. Chem.* **1993**, *58*, 1038.

[8] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *4155.*

[9] Kerr, M. S.; Rovis, T. *Synlett* **2003**, 1934.

[10] Reynolds, N. T.; Rovis, T. *Tetrahedron* **2005**, *61*, 6368.

[11] (a) Jung, M. E.; Pan, Y.-G.; Rathke, M. W.; Sullivan, D. F.; Woodbury, R. P. *J. Org. Chem.* **1977**, *42*, 3961. (b) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.

[12] Example of palladium and copper catalyzed cyclopropane opening see: (a) Li, L.-Z.; Guo, X.-Q.; Xue, S. *Tetrahedron* **2006**, *62,* 7762 (b) Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629. (b) Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, 147.

[13] Hoberg, J. O.; Jennings, P. W. *Organometallics* **1996**, *15*, 3902**.**

[14] Ikura, K; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 1520.

[15] (a) Zhou, X.; Huang, P.-Q. *Synlett* **2006**, 1235. (b) Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron*, **2000**, *56*, 8855.

[16] (a) Peixoto de Silva, K.; Godoi, M. N.; Grorreia, C. R. D.; *Org. Lett.* **2007**, *9*, 2815. (b) Salański, P.; Ko, Y. K.; Lee, K.-I. *Mendeleev Commun.* **2006**, *16*, 46. (c) Rojas-Roussaeau, A.; Langlois, N. *Tetrahedron* **2001**, *57*, 3389. (d) Back, T.; Brummerhop, H. *J. Prakt. Chem.* **1999**, *341*, 312.

[17] (a) Moorthy, J. N.; Singhal, N.; Senapati, K. *Org. Biomol. Chem.* **2007**, *5*, 767. (b) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61***,** 9272.

[18] (a) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 2339, 2341 (b) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327. (c) Martin, J. C.; Arhart, R. J.; Franz, J. A.; Perozzi, E. F.; Kaplan, L. J. *Org. Synth.* **1977**, *57*, 22.

Chapter 3

Second Generation Approach Towards Cephalimysin A

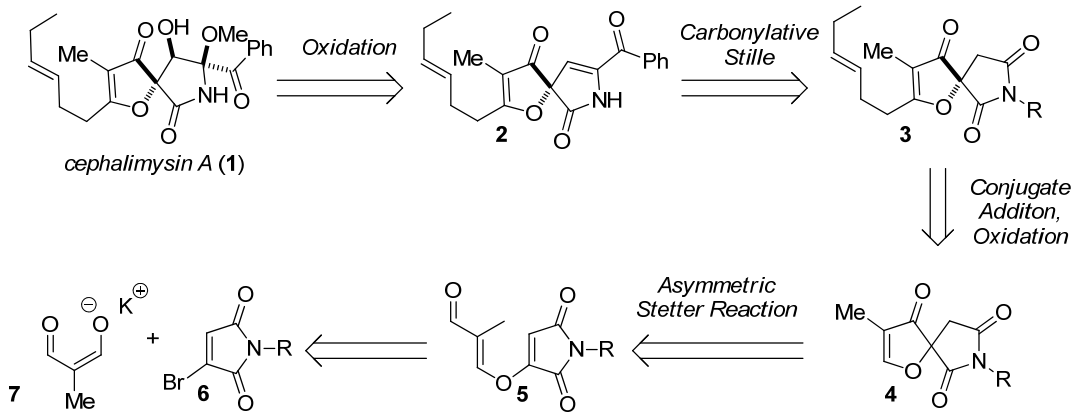
3.1 Retrosynthetic Strategy

Our previous approach towards cephalimysin A revealed that the Stetter reaction provides entry to the desired spirocyclic core. However, oxidation of the spirocyclic to the furanone and subsequent installation of the methyl group proved tedious. We believed effecting the Stetter reaction of an α-methyl enal would greatly increase the efficiency of our synthesis. With this in mind we hoped to take advantage of an earlier result in which the potassium salt of methyl malonyldialdehyde was found to add in a conjugate manner to DMAD (Ch. 2. eq. 6). Although we previously had shown that conjugate addition into activated alkynes provided entry to the desired Stetter precursor we decided revert back to the maleimide substrate utilized by Rovis and coworkers in their efforts towards azaspirene and FD-838 (Scheme 22, Ch. 1). We believed that utilizing the maleimide provided us with the most rapid entry to the desired spirocyclic core of cephalimysin A (**1)**.

As in our previous approach, we planned to access cephilymisin A by oxidation of enone **2** (Scheme 1). Enone **2** would be derived from furanone **3** via formation of the vinyl triflate followed by carbonylative Stille reaction and deprotection of the lactam nitrogen. The furanone **3** should be easily accessed from spirocycle **4** by conjugate addition into the spirocycle **4** followed by oxidation to back to furanone. The spirocycle **4** would arise from

an intramolecular asymmetric Stetter reaction of α,β-unsaturated aldehyde tethered-maleimide **5**. Conjugate addition of methyl malonyldialdehdye (**7**) to bromomaleimide **6** followed by elimination should easily access aldehyde-tethered maleimide **5**.

Scheme 1.



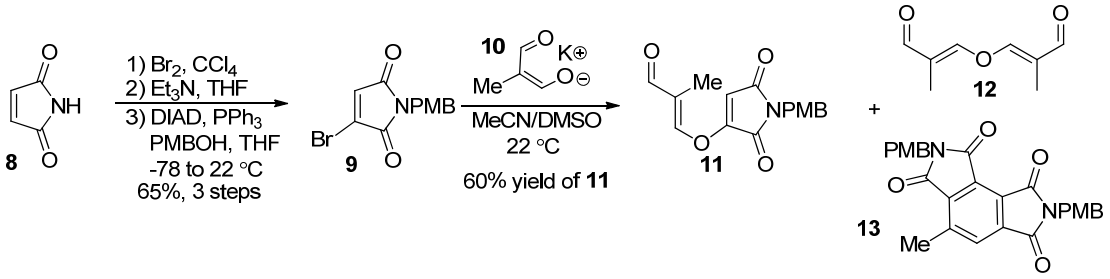
Central to this proposed route is a successful Stetter reaction of α-methyl enal **5**. We have previously shown that aldehydes containing α substitution are tolerated in the Stetter reaction (Ch. 2, eq. 8). However, in order for the Stetter reaction to proceed the *Z* olefin isomer of enal **5** must be accessible. Although it was unclear which olefin isomer we would obtain from the oxa-Michael reaction, we believed that if the undesired *E* isomer of the enal was generated it could be isomerized to the desired *Z* isomer prior to the Stetter reaction or *in situ*.

3.2 Isomerization and Stetter Reaction

The synthesis of the desired Stetter reaction precursor **11** was carried out in a straight forward manner in four steps from commercially available maleimide (**8**) (Scheme 2). Dibromination of maleimide, elimination and Mitsunobu protection of the nitrogen with *para*-methoxybenzyl alcohol affords bromomaleimide **9** in good yield over three

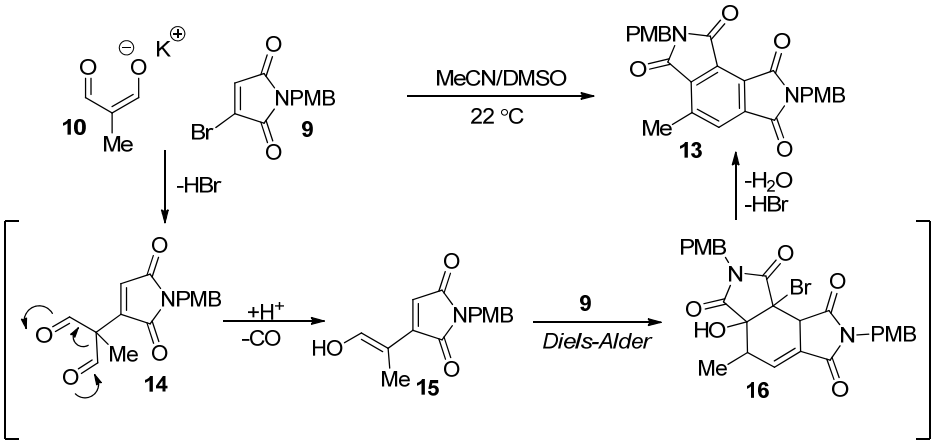
steps.[1] Treatment of maleimide **9** with the potassium salt of dialdehyde **10**[2] in a mixture of acetonitrile and dimethylsulfoxide affords the aldehyde-tethered maleimide in moderate yield as a single (*E*) isomer. Two byproducts, dialdehdye **12** and arene **13** were also isolated from the reaction mixture. Dialdehyde **12** presumably results from conjugate addition of the methylmalonylaldehdye to the product enal **11** followed by elimination of hydroxy-maleimide.

Scheme 2.



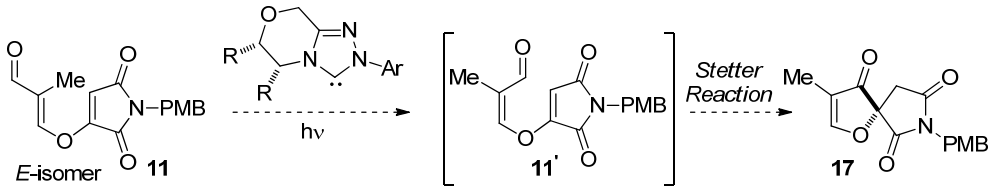
The proposed mechanism for the formation of **13** is outlined in Scheme 3. Michael addition of the carbon of **10** generates dialdehdye **14**. Decarbonylation forms the diene **15** which undergoes a Diels-Alder reaction with a second equivalent of maleimide **9** to form intermediate **16**. Subsequent aromatization generates the observed product **13**.

Scheme 3.



Having accessed enal **11** as the undesired (*E*) isomer we began exploring conditions that would allow for isomerizaiton of the enal. Olefins are known to isomerize upon ultra-violet radiation. For example, Alonso and co-workers have shown that α-nitro-α,β-unsatruated alehdyes undergo facile isomerization upon exposure to to UV radiation.[3] We believed that conducting the Stetter reaction under similar conditions would allow for an *in situ* isomerization to a mixture of (*E*) and (*Z*) isomers. Stetter reaction of the (*Z*) isomer would drive the photoismerization to the (*Z*) isomer as well as afford the desired spirocycle **17** (Scheme 4).

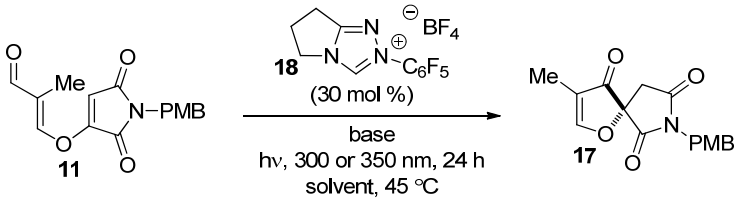
Scheme 4.



Indeed, an initial screen revealed that exposure of enal **11** to either 300 or 350 nm light in the presence of achiral triazolium salt **18** and base generates the desired spirocyclic product (Table 1). Conducting the reaction in toluene with KHMDS or Hunig's base

affords the desired product in low conversion (entries 1 and 2). Conducting the reaction in chloroform with Hunig's base results in almost complete conversion, however only a 10% isolated yield of the desired product is obtained (entry 3). Switching the base to sodium acetate affords the desired product in 41% isolated yield (entry 4). The use of cesium carbonate results in complete decomposition of the starting material (entry 5).

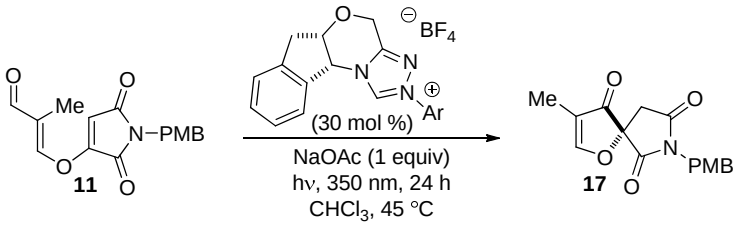
Table 1.

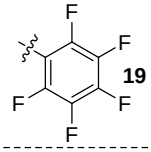
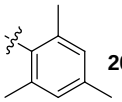
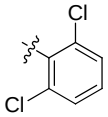
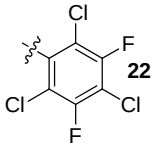
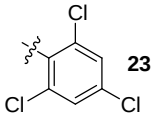
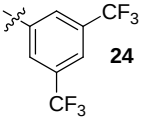


entry	solvent	base (equiv.)	conversion (% yield)
1	PhMe	KHMDS (0.3)	25%
2	PhMe	DIPEA (1.0)	35%
3	$CHCl_3$	DIPEA (1.0)	90% (10)
4	$CHCl_3$	NaOAc (1.0)	70% (41)
5	$CHCl_3$	Cs_2CO_3 (0.3)	decomp.

Having identified conditions to access the racemic spirocycle **17** via photoisomerization/Stetter reaction, we sought to explore the enantioselective variant of this reaction. Subjection of the aldehyde to a variety of enantioenriched aminoindanol derived triazolium salts affords the desired product (Table 2). Use of pentafluorophenyl catalyst **19** generates low yields of the product in surprisingly low enantioselectivity (entry 1). The more electron rich catalyst **20** also affords the product in low yield and enantioselectivity (entry 2). Chlorophenyl catalysts **21**, **22**, and **23**, give the product in slightly increased yields and enantioselectivities (entries 3-5). Surprisingly, the bis(trifluoromethyl)-phenyl catalyst **24** delivers the opposite enantiomer in moderate yield and good enantioselectivity (entry 6).

Table 2.

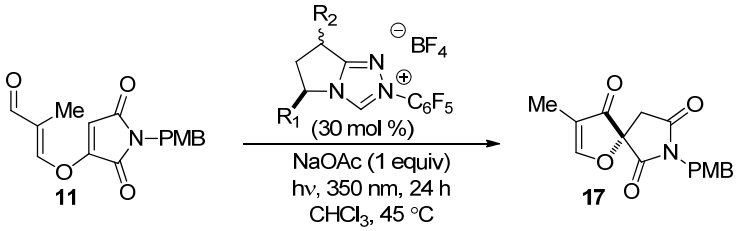


entry	Ar	yield	ee
1	 **19**	35%	28%
2	 **20**	22%	17%
3	 **21**	30%	50%
4	 **22**	57%	71%
5	 **23**	40%	60%
6	 **24**	47%	- 87%

A variety of amino-acid derived triazolium salts were also investigated in the intramolecular Stetter reaction (Table 3). It was found that increasing the steric bulk of the catalyst increases the ee from 50% ee for the benzyl catalyst to 74% ee for the *iso*-propyl catalyst (entries 1 and 2). The cyclohexyl catalyst affords the product with similar enantioselectivity to that of the *iso*-propyl catalyst (entry 3). Utilizing catalysts containing

fluorine substitution on the backbone increases the yields, however it has no significant effect on enantioselectivity (entries 4-6).

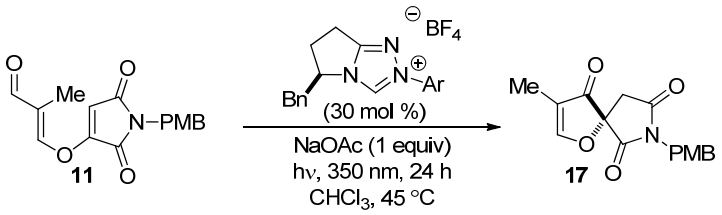
Table 3.

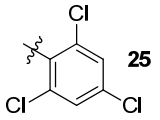
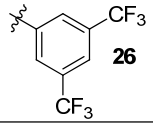


entry	R_1	R_2	yield	ee
1	Bn	H	37%	50%
2	*i*-Pr	H	17%	74%
3	Cy	H	26%	72%
4	*i*-Pr	(*cis*)-F	45%	70%
5	*t*-Bu	(*cis*)-F	trace	-
6	*i*-Pr	(*trans*)-F	30%	66%

Having obtained moderate enantioselectivity with the amino-acid derived catalysts the effect of the electronics of the aryl group was examined. Switching from the pentafluorphenyl catalyst to trichlorocatalyst **25** affords a significant increase in enantioselectivity (Table 4, entry 1). Interestingly, switching to the bis(trifluoromethyl)phenyl catalyst **26** results in a decrease in the observed enantioselectivity (entry 2). In this case unlike with catalyst **24** no inversion of the major enantiomer is observed.

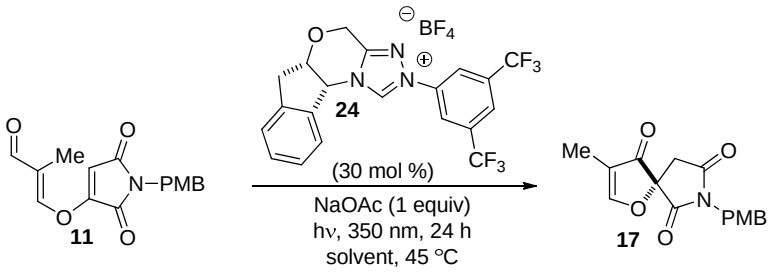
Table 4.



entry	Ar	yield	ee
1	 **25**	20%	72%
2	 **26**	32%	44%

Having found aminoindanol derived catalyst **24** affords the spirocyclic product in good enantioselectivity we sought to further increase the yield of the reaction. A screen of solvents reveals benzene to be the optimal solvent, generating the product in good yield and enantioselectivity (Table 5, entry 3). Conducting the reaction in more polar solvents such as THF, MeCN, and MeOH leads mainly to decomposition of the starting aldehyde (entries 4-6), while utilizing toluene or dichloroethane leads to reduced yield of the product (entries 1 and 2). One possibility for the increased yield observed in benzene is the ability of benzene to act as a photosensitizer and potentially facilitating the *E* to *Z* isomerization of the α,β-unsaturated aldehyde. However, addition of known photosensitizers benzophenone or diphenyl disulfide to the reaction does not further increase the yield.

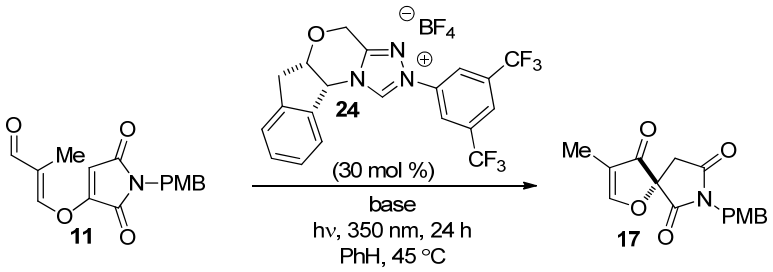
Table 5.



entry	solvent	yield	ee
1	DCE	40%	92%
2	PhMe	43%	94%
3	PhH	63%	94%
4	THF	decomp	-
5	MeCN	trace	-
6	*i*-PrOH	decomp	-

Examination of other inorganic bases under the optimized conditions gave no further increase in yield (Table 6). The use of potassium carbonate fails to deliver any of the desired product, while cesium carbonate and sodium benzoate result in diminished yield of the desired product (entries 1-3). Changing the amount of base employed also gives improvement of yield. Namely utilizing 0.5 equivalents of sodium acetate leads to a slower reaction and affords the product in 52% yield (entry 5). Similarly, increasing the amount of sodium acetate leads to a decrease in product yield (entry 6).

Table 6.



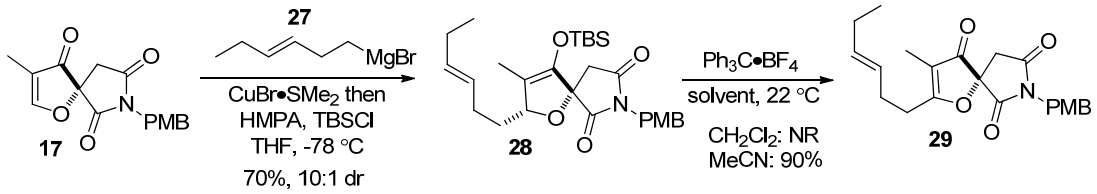
entry	base (equiv)	yield	ee
1	K_2CO_3 (1.0)	NR	-
2	Cs_2CO_3 (1.0)	27%	84%
3	NaOBz (1.0)	42%	91%
4	NaOAc (0.5)	52%	94%
5	NaOAc (2.0)	35%	94%

With an efficient, enantioselective route to the spirocyclic core of cephalimysin A, we begun investigating further functionalizaiton. We hoped to take advantage of a carbonylative Stille reaction as a key step to install the benzyol group.

3.3 Carbonylative Stille Reaction

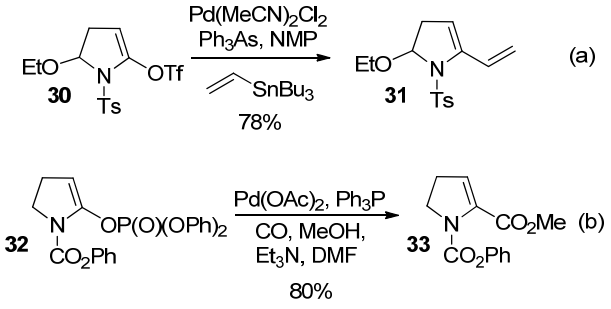
With spirocycle **17** in hand we sought to synthesize the fully functionalized furanone and then investigate the carbonylative Stille reaction. Treatment of spirocycle **17** with Grignard reagent **27** in the presence of copper bromide dimethylsulfide complex followed by addition of TBSCl generates the desired silylenolether **28** in good yield and diastereoselectivity (Scheme 5). With silylenolether in hand we sought to achieve oxidation to the enone in a similar manner as used in our previous approach (Ch. 2, Scheme 9). Treatment of silylenolether **28** with trityl cation in dichloromethane affords fails to deliver the desired product. However switching to acteonitrile as the solvent generates the desired furnanone **29** in excellent yield.

Scheme 5.



Arriving at the furanone is short order we began our investigation into a carbonylative Stille reaction to install the benzoyl group. Speckamp and co-workers have shown that pyrrolidinone derived vinyl triflates undergo Stille reaction with vinyl stannanes in good yield (Scheme 6, eq a).[4] Nicolaou and co-workers have demonstrated similar reactivity with pyrrolidinone-derived vinyl phosphonates (Scheme 6, eq b).[5] They have shown that the vinyl phosphonates **32** undergo palladium catalyzed carbonylation in good yields.

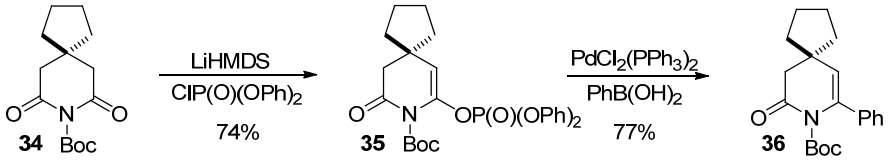
Scheme 6.



In these lactam systems the stability of the vinyl triflate or phosphonate is central to the success of the reaction. Vinyl phosphonates have been shown to be more stable than the corresponding vinyl triflates.[6] A number of examples using vinyl triflates or phosphonates derived from lactams have been demonstrated; however, the use of imides as precursors is less common. In one such example, Gillaizeau and co-workers have shown that vinyl

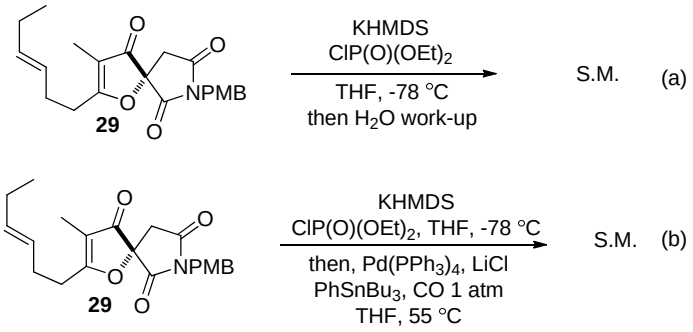
phosphonates can be generated from glutaramide **34** and subsequently utilized in a Suzuki cross coupling reaction (Scheme 7).[7]

Scheme 7.

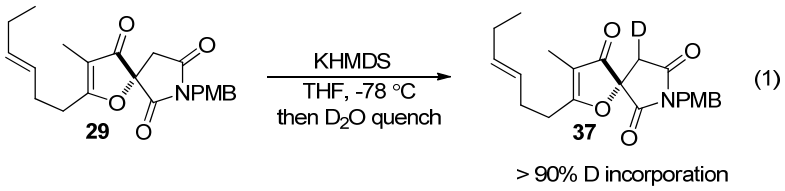


To the best of our knowledge, there are no examples of succinimide-derived phosphonates in the literature. Nonetheless, we chose to investigate the formation of vinyl phosphonate of succinimide **29**. Our initial focus was placed on formation of the vinyl phosphonte given their reported greater stability than the analogous vinyl triflates. Treatment of succinimide **29** with KHMDS followed by diethyl chlorophosphate generated a single new product as determined by TLC. We assumed this compound to be the desired vinyl phosphonate; however, only starting material was observed upon aqueous work-up of the reaction mixture (Scheme 8, eq a). We believed that the aqueous work up was responsible for the reversion of the product to starting material, and hoped to address this issue by conducting the desired Stille reaction in the same pot as the vinyl phosphonate. Unfortunately, this two-step one pot procedure afforded only starting material (Scheme 8, eq b).

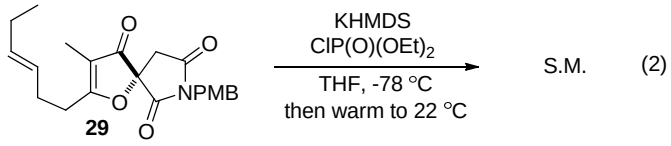
Scheme 8.



To gain further insight the spirocycle **29** was treated with KHMDS and quenched with D_2O after one hour. This resulted in almost complete deuterium incorporation, evidencing the formation of the desired enolate (eq 1). This observation also suggests that the vinyl phosphonate is formed under the reaction conditions and it is the aqueous work-up or warming that cause reversion back to starting material.



Careful monitoring of the reaction gave further evidence to the instability of the vinyl phosphonate. Addition of diethyl chlorophosphate to the preformed enolate at -78 °C resulted in disappearance of the starting material accompanied by formation of a new more polar spot. Upon allowing the reaction to simply warm to room temperature the new more polar spot disappears and the starting material is once again observed by TLC. Upon concentration of the reaction mixture only starting material is observed by ^{1}H nmr (eq 2).

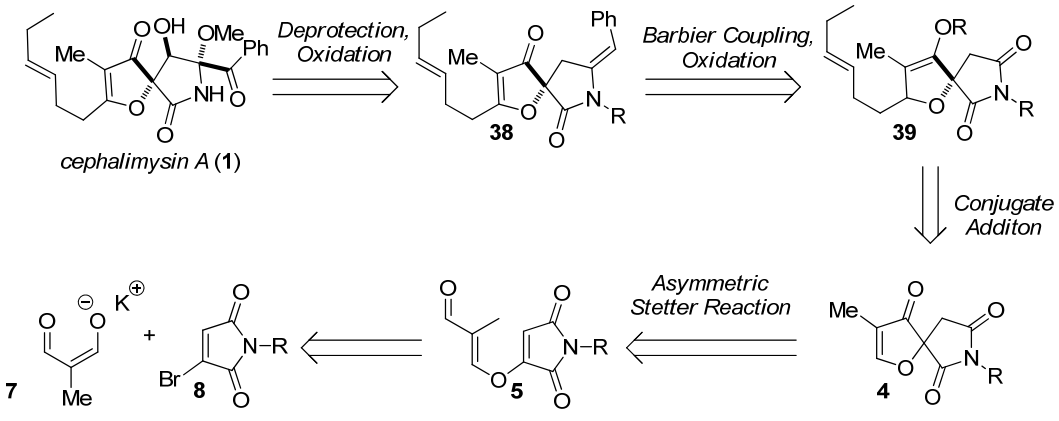


These control experiments indicate that the vinyl phosphonate is unstable at room temperature. Due to the instability of the vinyl phosphonate a new route to install the desired benzoyl group was examined.

3.4 Barbier Coupling

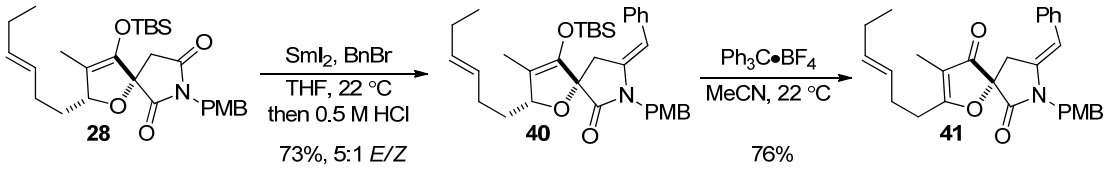
In revising our strategy for installing the benzoyl group, we were inspired by Rovis and coworkers' previous work towards azaspirene and FD-838. Specifically we believed we could utilize a similar Barbier type coupling as an entry to the functionalized lactam (Ch. 1, Scheme 29). With this in mind, we devised a new reterosynthetic approach in which oxidation of benzylidene lactam **38** would furnish cephalimysin A (Scheme 9). The benzylidene lactam **38** would arise from Barbier coupling of succinimide **39** with benzyl bromide followed by elimination upon acidic workup. Oxidation of the enol ether would generate the furanone **38**. We would access succinimide **39** by the previously identified route.

Scheme 9.



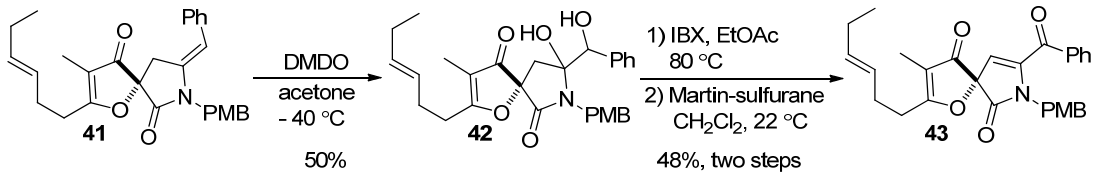
We began to examine our revised synthetic strategy by investigating the Barbier coupling between succinimide **28** and benzyl bromide (Scheme 10). Indeed, treatment of succinimide **28** with benzyl bromide and samarium diiodide at room temperature followed by acid work-up affords the desired benzylidene lactam **40** in good yield.[8] Subsequent oxidation delivers spirocyclic lactam **40** and completes the furanone portion of cephalimysin A.

Scheme 10.



With benzylidene lactam **41** in hand, we began exploring the final functionalizaiton of the lactam ring. Using conditions similar to those utilized by Hayashi and co-workers in their synthesis of synerazol, treatment of **41** with dimethyldioxirane (DMDO) affords the diol **42** in moderate yield (Scheme 11).[9] Oxidation of the secondary alcohol to the ketone with IBX followed by Martin-sulfurane mediated elimination generates the desired enone **43** in moderate yield.

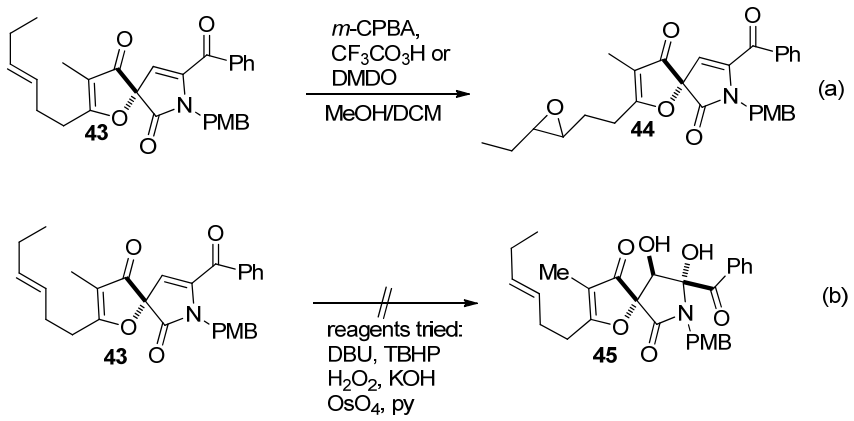
Scheme 11.



With spirocycle **43** in hand conditions to selectively oxidize the enamide olefin in the presence of the distal olefin were examined. Treatment of enamide **43** with a variety of electrophilic epoxidation reagents results in only epoxidation of the alkenyl side chain

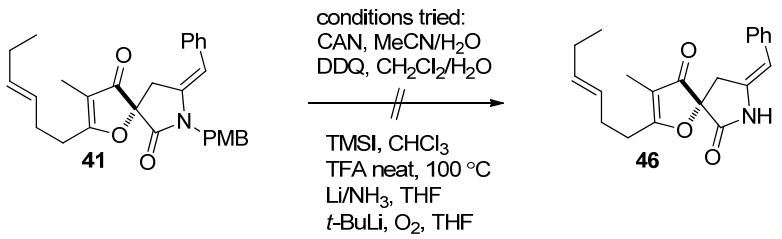
(Scheme 12, a). Treating spirocycle **43** with nucleophilic reagents typically results in decomposition of the starting material (Scheme 12, b).

Scheme 12.



Although these epoxidation methods failed to give the desired product we hypothesized that deprotection of the PMB group would make the enamide more nucleophilic and therefore be more likely to react with the electrophilic reagents used. However various attempts to remove the PMB group failed to yield the desired product (Scheme 13).

Scheme 13.



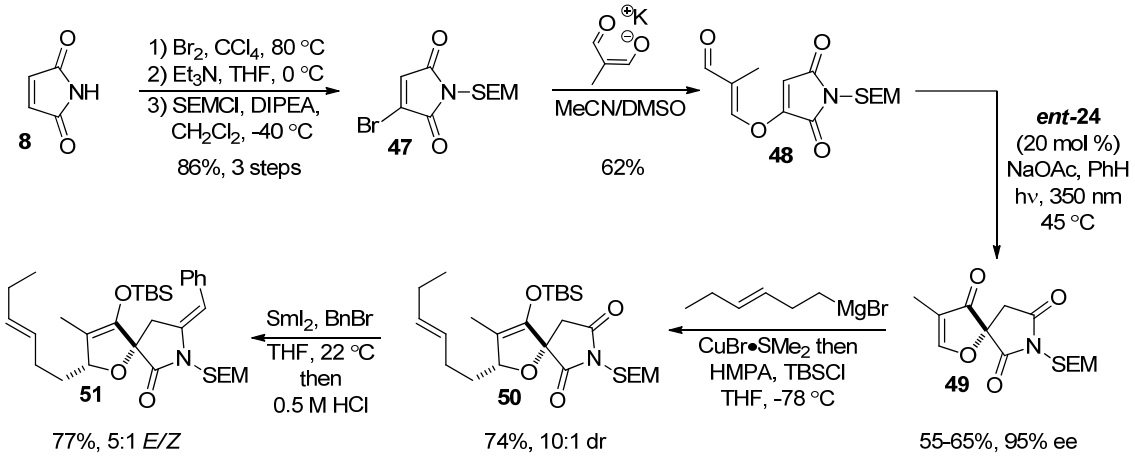
3.5 Protecting Group Strategy

With our lack of success in removing the PMB group from lactam **41** we sought to utilize a slightly more labile protecting group. One difficulty in choosing a better

protecting group is the limited amount of options for the initial protection of the maleimide. Typical protecting groups for maleimides such as phenyl, benzyl, or alkyl were not ideal for our synthesis due to the harsh reaction conditions necessary to remove them. Additionally, typical nitrogen protecting groups such as tosyl, Boc, or Ac are believed to be difficult to access with maleimides and few such examples exist in the literature. We were intrigued by an example by Coleman and coworkers involving a [2-(trimethylsilyl)ethoxy]methyl (SEM) protected maleimide in their total synthesis of lucilactaene.[10] We believed a SEM protecting group would allow for easier deprotection than our previously employed PMB protecting group. Therefore we chose to pursue synthesis of cephalimysin A utilizing a SEM protecting group.

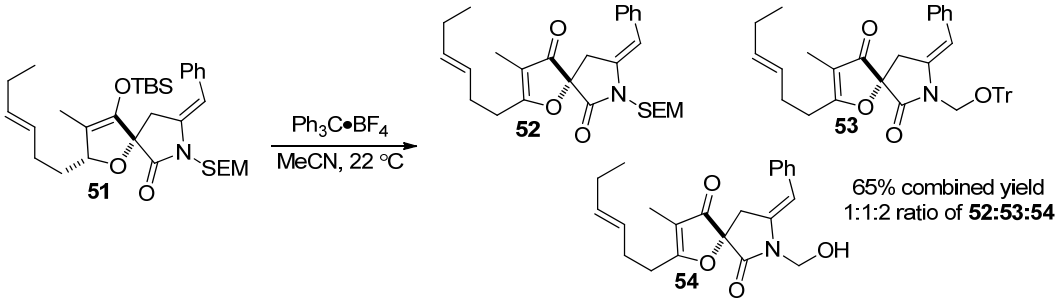
Synthesis of the desired SEM protected bromomaleimide **47** was achieved in three steps form maleimide (Scheme 14). Following the same four-step sequence used for the PMB protected analog affords the silylenolether **51**. Importantly, the Stetter reaction affords the SEM protected spirocycle **49** in similarly good yield and enantioselectivity.

Scheme 14.



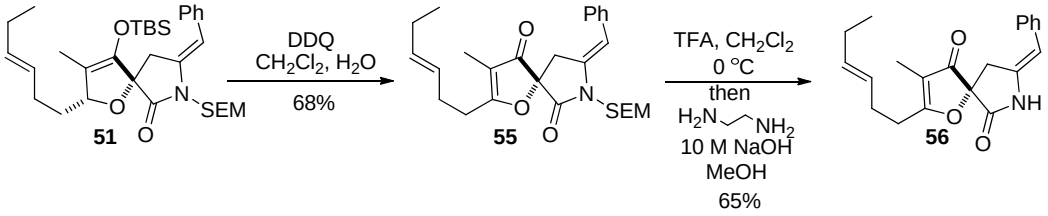
However, treatment of silylenolether **51** with trityl cation under the previously developed conditions affords a mixture of the desired furanone **52**, semi-deprotected aminal **54**, and trityl aminal **53** (Scheme 15).

Scheme 15.



Although these oxidation conditions afford a mixture of products it was found that treatment of siloxyenolether **51** with DDQ affords the desired furanone **55** in good yield (Scheme 16).[11] It was found that deprotection of the SEM group could be accomplished via a simple two step procedure. Treatment of **55** with TFA followed by exposure of the crude hemiaminal with ethylene diamine and sodium hydroxide in methanol generates the desired deprotected lactam **56**.

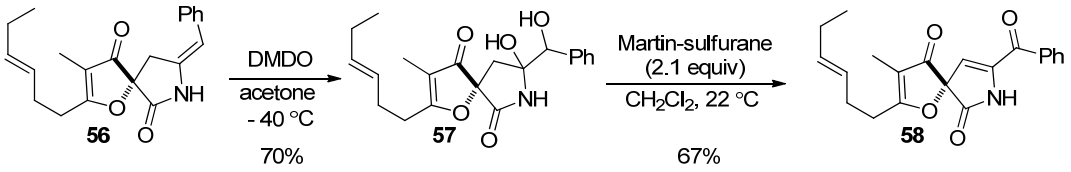
Scheme 16.



From here oxidation of the benzylidene lactam **56** with DMDO affords the diol in good yield (Scheme 16). It was serendipitously found that treatment of diol **57** with 2.1

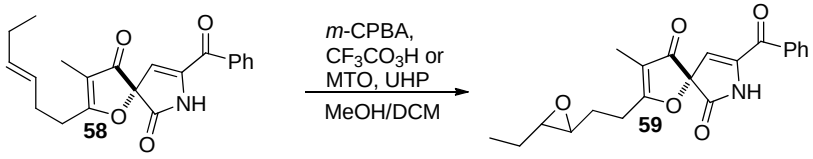
equivalents of Martin-sulfurane mediates both oxidation of the secondary alcohol to the ketone as well as elimination of the tertiary alcohol to generate the desired enone **58**. Although unexpected, oxidation of activated secondary alcohols by Martin-sulfurane has been described in the literature.[12]

Scheme 16.



Having accessed the desired deprotected enamide we sought to investigate the electrophilic epoxidation. Again attempts to epoxidize the enamide double bond failed and only epoxidiation of the distal olefin is observed (Scheme 17).

Scheme 17.

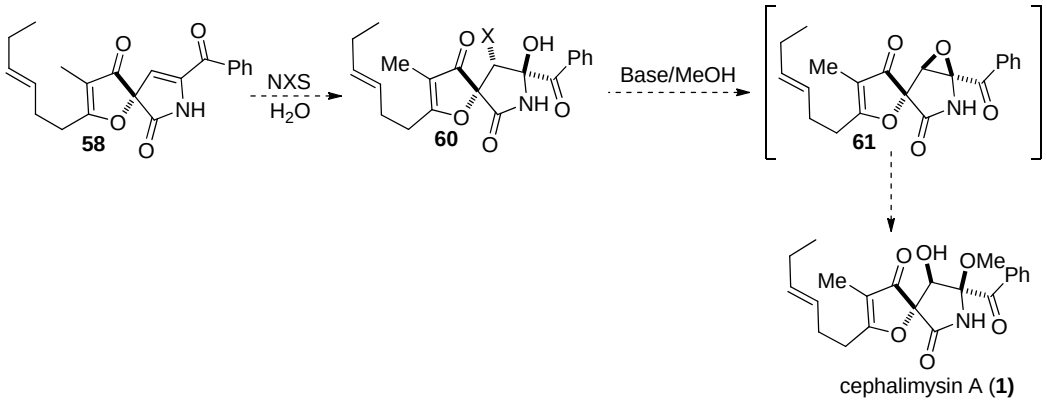


3.6 Haloetherification Strategy

Having found the selective electophilic epoxidation of the enamide double bond to be unfeasible we turned our attention to an alternate strategy to functionalize the lactam. It has been shown that treating enamides with a halogenating reagent in the presence of water generates the halohydrin.[13] He hoped to utilize this reactivity in our system to generate halohydrin **60** (Scheme 18). Exposure of the halohydrin to base should afford the transient

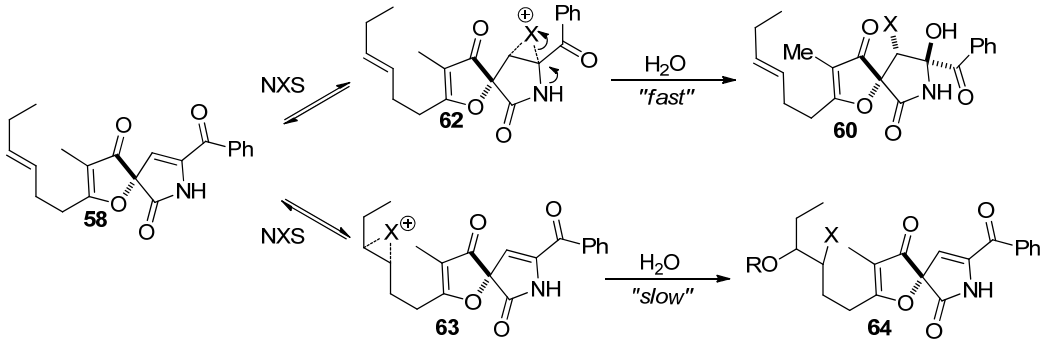
epoxide **61** which in the presence of methanol would open up to deliver the initially proposed structure of cephalimysin A.

Scheme 18.



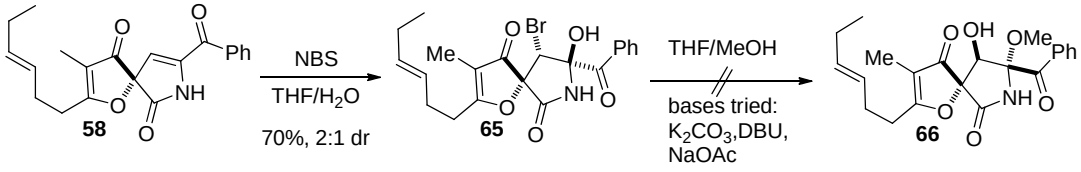
Although this route still requires the enamide double bond to react preferentially over the distal olefin, we believed that the reversibility of the halonium ion formation might allow for the desired chemoselectivity (Scheme 19). We based this hypothesis on the evidence that bromonium ions form reversibly and it is the opening of the bromonium ion that is rate limiting.[14] As such, treatment of **58** with a halogenating agent should form an equilibrium mixture of halonium ions **62** and **63**. Nucleophilic attack of H_2O would afford either the desired halohydrin **60** or the undesired **64**. We hypothesized that donation of the nitrogen lone pair into the σ^* orbital of the halonium ion would weaken the C-X bond and make it more prone to nucleophilic attack, favoring the desired product **60**.

Scheme 19.



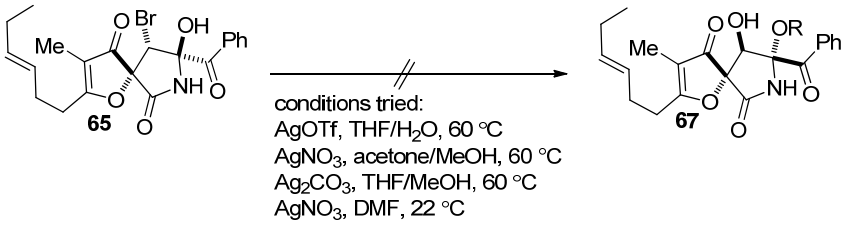
Indeed, treatment of enamide **58** with NBS in a mixture of THF/H_2O affords the desired halohydrin as 2:1 mixture of diastereomers (Scheme 20). However, exposure of halohydrin **65** to various bases in the presence of methanol results in rapid decomposition of the starting material and none of the desired product is obtained.

Scheme 20.



It is also know that silver salts can facilitate the same type of transformation via a strong coordination to halide.[15] However, treatment of bromohydrin with various silver salts also fails to deliver the desired product (Scheme 21). In most cases only starting material was observed, under more forcing conditions elimination of the hydroxyl group occurs to afford the vinyl bromide.

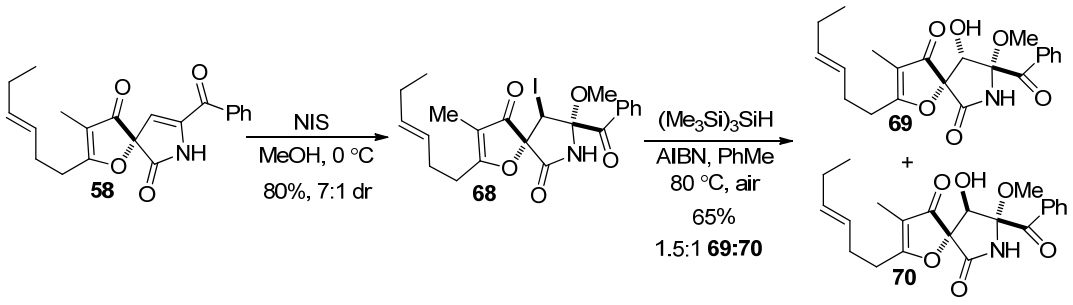
Scheme 21.



It is known that alkyl iodides can be utilized to generate an alkyl radical which can be trapped with either molecular oxygen[16] or TEMPO[17] to afford the oxygenated species. We hoped to utilize this approach to install the appropriate alcohol. Iodoetherification of enamide **58** generates the alkyl iodide **68** in 80% yield and 7:1 dr (Scheme 22). Treatment of the iodide with tristrimethylsilane and AIBN in the presence of air generates the desired alcohol as a 1.5:1 ratio of diastereomers (**69** and **70**).

However the ^{1}H nmr spectrum of the two products obtained did not match that of the reported ^{1}H nmr of the natural isolate. We sought to identify which diastereomers of cephalimysin A we had generated.

Scheme 22.

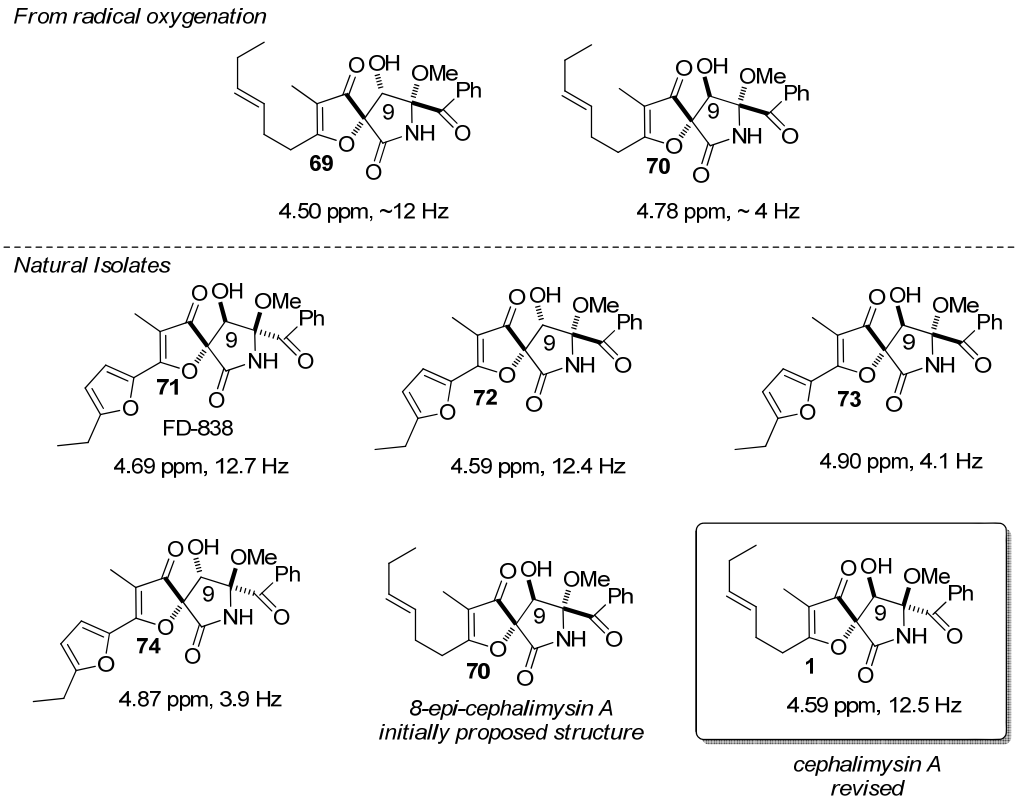


During the course of our investigation it was found in studies on related natural product FD-838 that the relative stereochemistry between the hydroxy and methyl ether can be determined by examination of the coupling constant of the proton at C-9 (Scheme 23).[18]

Specifically, if the hydroxyl group and methyl ether are *cis* to one another the coupling constant of the proton at C-9 is approximately 12 Hz due to the intramolecular hydrogen bond (Scheme 23, **71** and **72)**. However when the two groups are positioned *trans* to one another the coupling constant is approximately 4 Hz (**73** and **74)**. These observations led to the revision of the structure of cephalimysin A. The correct structure of cephalimysin A (**1**) was determined to posses a *cis* relationship between the hydroxy group and the methyl ether as evidenced by the 12.5 Hz coupling constant.

With this information, we know that our synthetic compound **69** possesses a *cis* relationship between the hydroxy group and the methyl ether based on the coupling constant of the proton at C-9 (~ 12 Hz). Since the chemical shifts do not match that of the

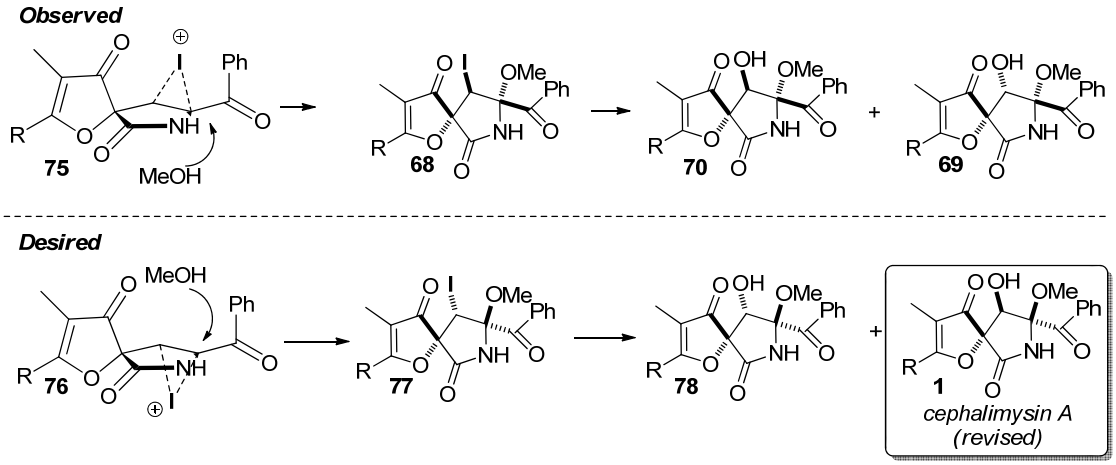
Scheme 23.



naturally occurring cephalimysin A (**1**) we conclude that the structure for **69** must be as shown in Scheme 23. The minor diastereomer **70** exhibits a *trans* relationship between the hydroxyl and methoxy group based on the smaller coupling constant at C-9 (~ 4Hz). The stereochemistry for the minor diastereomer (**70**) is determined to be as shown assuming that the configuration at C-8 (the hemiaminal position) must be the same in both diastereomers. This diastereomer matches the originally proposed structure of cephalimysin A;[19] the fact that our synthetic **70** does not match the ^{1}H nmr of the natural product reinforces the structurally assignment of cephalimysin A (**1**) is as shown in Scheme 23.

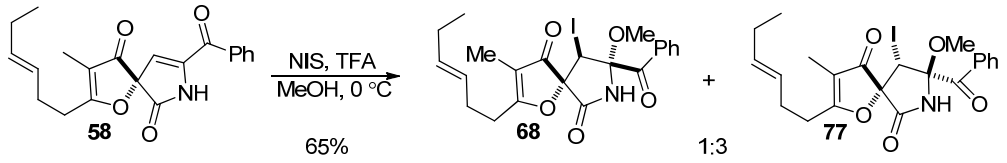
The stereochemistry at C-8 in products **69** and **70** is presumably determined during the haloetherification. This means in order to obtain the correct diastereomer of the natural product we need to invert the diastereoselectivity of the haloetherification reaction. Examination of the proposed transition state for the haloetherifcation reaction suggests a possible explanation for the observed diastereoselectivity (Scheme 24). To generate the observed diastereomer the iodonium ion must form on the same face as the furanone carbonyl (**75**). The proximity of the Lewis basic oxygen may be responsible for stabilizing this iodonium ion preferentially. We hypothesized that protonation of the ketone would disrupt this Lewis basic interaction and allow for formation of the other iodonium intermediate **76** and access to the desired diastereomer.

Scheme 24.



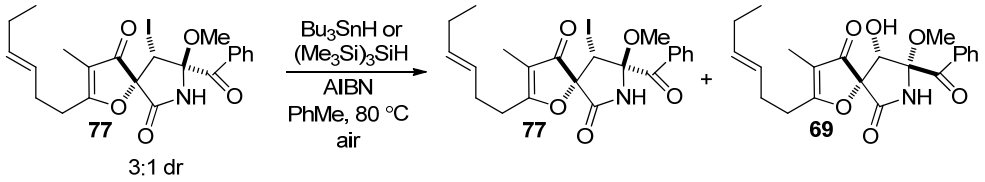
Indeed, the addition of trifluoacetic acid to our previously developed haloetherification conditions results in a reversal in diastereoselectivity to give the desired diastereomer **77** in a 3:1 ratio (Scheme 25).

Scheme 25.



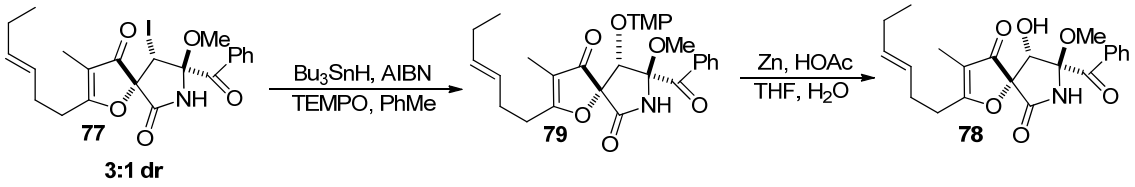
With the desired diastereomer of alkyl iodide **77** in hand we sought to utilize our radical oxygenation protocol to install the desired alcohol. Unfortunately treatment of the diastereomeric mixture of iodide **77** with either tris(trimethylsilyl)silane or tributyltinhydride in the presence of AIBN and air gives no oxygenation of the major diastereomer (Scheme 26). Only a small amount of the oxygenated product **69** derived from the minor diastereomer was observed.

Scheme 26.



As mentioned, TEMPO has also been shown to trap alkyl radicals and generate oxygenated product, upon reduction of the N-O bond. Treatment of iodide **77** with tributyl tinhydride in the presence of TEMPO followed by cleavage of the N-O bond generates the alcohol **78** as a single diastereomer (Scheme 27). After examination of the ^{1}H nmr spectrum it was found that the alcohol and methyl ether possess a *trans* relationship as determined by the 4 Hz coupling observed for the C-9 proton. At this point we have successfully accessed the three diastereomers of cephalimysin A. Work at utilizing this approach is still on going and should allow for the selective formation of natural cephalimysin A.

Scheme 27.



3.7 Conclusion

The development of a photoisomerization/Stetter reaction protocol has allowed for the rapid synthesis of the spirocyclic core of cephalimysin A. The spirocyclic core was further elaborated to arrive at three diastereomers of the naturally occurring cephalimysin

A. Although the naturally occurring diastereomer has yet to be achieved via this route, the ability to rapidly access late stage intermediates should allow for further investigation and eventually the first total synthesis of cephalimysin A (**1**).

3.8 References

[11] (a) Sahoo, M. K.; Mhaske, S. B.; Argade, N. P. *Synthesis* **2003**, 346. (b) Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352.

[2] O'Sullivan, P.T.; Buhr, W.; Fuhry, M. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194.

[3] Martínez-Bescos, P.; Gagide-Fagín, F.; Roa, L. F.; Ortiz-Lara, J. C.; Kierus, K.; Ozores-Viturro, L.; Fernández-González, M.; Alonso, R.; *J. Org. Chem.* **2008**, *73*, 3745.

[4] Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62,* 8131.

[5] Nicolaou, K. C.; Shi, G.-Q.; Namoto, K.; Bernal, F. *Chem. Commun.* **1998**, 1757.

[6] For a review see: Occhiato, E. G. *Mini-Reviews in Org. Chem.* **2004**, *1*, 149.

[7] Mousset, D.; Gillaizeau, I.; Sabatié, A.; Bouyssou, P.; Coudert, G. *J. Org. Chem.* **2006**, *71*, 5993.

[8] Farcas, S.; Namy, J.-L. *Tetrahedron Lett.* **2001**, *42*, 879.

[9] Hayashi, Y.; Shoji, M.; Mukaiyama, T.; Gotoh, H.; Yamaguchi, S.; Nakata, M.; Hideaki, K.; Osada, H. *J. Org. Chem.* **2005**, *70*, 5643.

[10] Coleman, R. S.; Walozak, M. C.; Campbell, E. L. *J. Am. Chem. Soc.* **2005**, *127*, 16038.

[11] For oxidation of silylenolethers with DDQ see: (a) Sha, C.-K.; Santhosh, K. C.; Lih, S.-H. *J. Org. Chem.* **1998**, *63*, 2699. (b) Kanazawa, A.; Delair, P.; Pourashraf, M.; Greene, A.

E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1911. (c) Fevig, T. L.; Elliott, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, 5064. (d) Flemming, I.; Paterson, I. *Synthesis* **1979**, 736.

[12] Wensley, A. M.; Hardy, A. O.; Gonsalves, K. M.; Koviach, J. L. *Tetrahedron Lett.* **2007**, *48*, 2431.

[13] (a) Levraud, C.; Calvet-Vitale, S.; Bertho, G.; Dhimane, H. *Eur. J. Org. Chem.* **2008**, 1901 (b) Bull, J. A.; Balskus, E. P.; Horan, R. A. J.; Langner, M.; Ley, S. V. *Chem. Eur. J.* **2007**, *13*, 5515.

[14] Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131.

[15] Rodrigues, J.; Dulcère J.-P. *Synthesis* **1993**, 1177.

[16] (a) Mayer, S.; Prandi, J. *Tetrahedron* **1998**, *54*, 8753. (b) Nakamura, E.; Sato, K.; Imanishi, Y. *Synlett* **1995**, 525. (c) Prandi, J.; Moutel, S. *Tetrahedron Lett.* **1994**, *35*, 8163 (d) Nakamura, E.; Inubushi T.; Aoki, S.; Machii, D. *J. Am. Chem. Soc.* **1991**, *113*, 8990.

[17] (a) Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271. (b) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Melcher, L. M. *J. Org. Chem.* **1990**, *55*, 5196.

[18] Yamada, T.; Kitada, H.; Kajimoto, T.; Numata, A.; Tanaka, R. *J. Org. Chem.* **2010**, *75*, 4146.

[19] Yamada, T.; Imai, E.; Nakatuji, K.; Numata, A.; Tanaka, R. *Tetrahedron Lett.* **2007**, *48*, 6294.

Chapter 4

Development of a Multicatalytic, Secondary Amine/*N*-Heterocyclic Carbene Cascade

4.1 Cascade Catalysis Background

4.1.1 Introduction

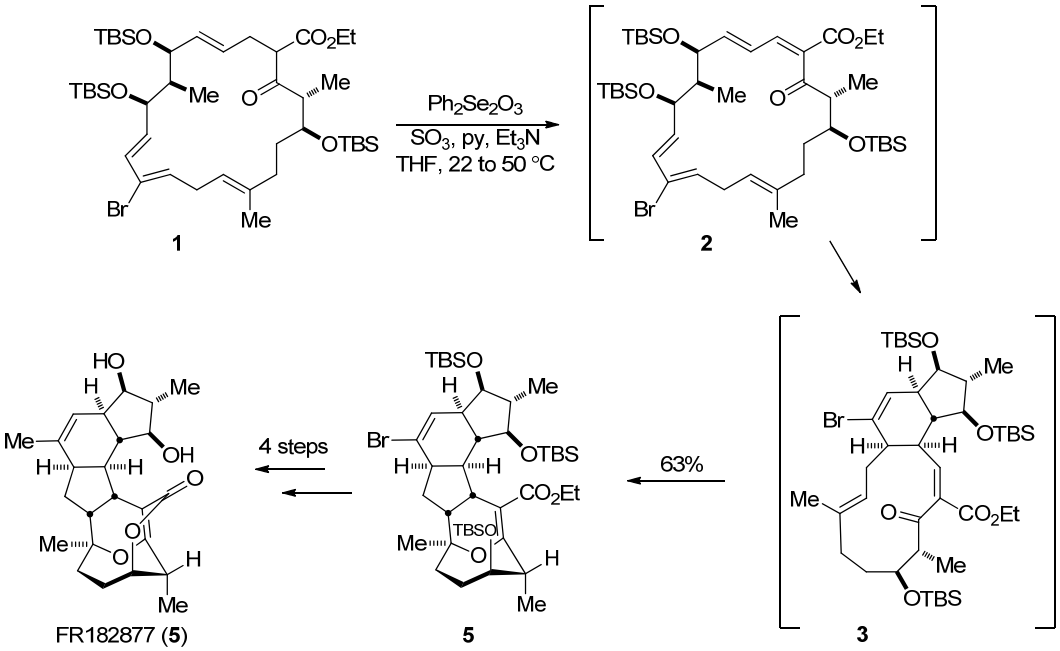
The ability to rapidly access complex molecular architectures from simple, readily available starting materials is of great importance to organic chemists. Nature utilizes a variety of enzymes to convert simple raw materials into a seemingly countless number of natural products. These natural products display a range of complexity and biological activity. For the last 200 years, organic chemists have sought methods for the synthesis of complex natural products in order to exploit their biological properties as well as to study their mode of action. Although many complex natural products have been synthesized—indeed, it is believed that chemical synthesis is now capable of building almost any known natural isolate in small quantities—the ability to synthesize these molecules efficiently on large scale still represents a significant challenge.

In contrast to traditional approaches to natural products that link together discrete bond-forming reactions separated by work-up and purification steps, another method for the rapid formation of complex molecules exploits the use of domino or cascade reactions. Tietze has defined cascade or domino reactions as "the transformation of two

or more bond-forming reactions under identical reaction conditions, in which the latter transformations take place at the functionalities obtained in the former-bond forming reactions".[1] In an ideal procedure, multiple transformations are accomplished without sequential addition of reagents or catalysts and without manipulation of reactions conditions over time. In ideal or sequential manifestation, cascade processes can greatly reduce the time and waste generated from work-up and purification after each transformation. Cascade reactions also boast the advantage of ushering potentially unstable intermediates directly to the next chemical transformation, obviating the need for a difficult isolation step.

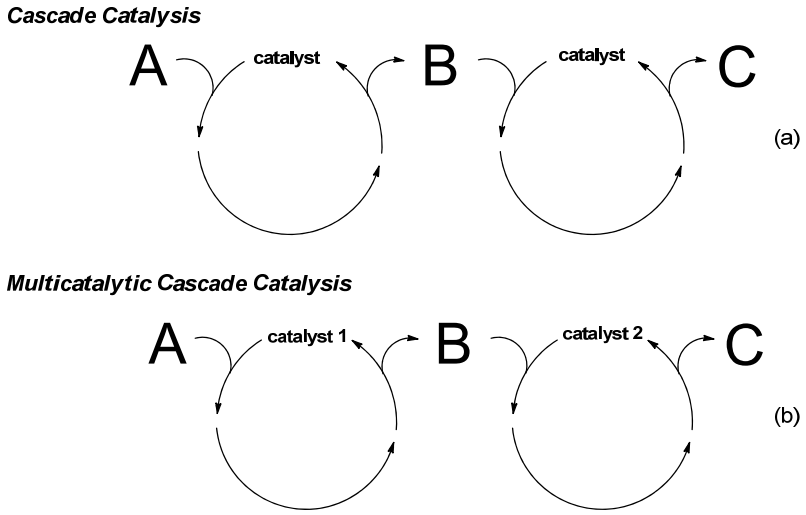
As testament to their utility, a number of examples of domino or cascade reactions exist for the synthesis of natural products.[1] above Evans' elegant syntheses of FR182877 (**5**) highlights the power of such transformations.[2] In the domino sequence, oxidation of **1** to enoate **2** spurs an intramolecular Diels-Alder reaction to generate tricycle **3** (Scheme 1). Tricycle **3** is then poised to participate in a subsequent, inverse demand hetero-Diels-Alder reaction to afford pentacycle **4** in 63% yield. The advanced intermediate is further elaborated in four steps to give the natural product FR182877 (**5**).

Scheme 1.



Although the described cascade achieves the goal of rapidly accessing molecular complexity, the starting cascade precursor itself is enantioenriched and takes 18 linear steps to generate. It would be more desirable to mimic Nature and start with simple, achiral starting materials and access complex molecules enantioselectivity in a single step. One method in which these demands can be achieved is asymmetric cascade catalysis.[3] In the simplest case, cascade catalysis involves the use of a single catalyst to facilitate two or more bond forming events. In such a cascade, the starting material A is converted to intermediate B by the catalyst in a first catalytic cycle. B then undergoes a subsequent catalytic process to afford the desired product (Figure 1, a). In theory, this type of process can be extended to allow for greater than two bond forming events. In practice, however, the number of possible transformations mediated by a single catalyst is limited by the catalyst's inherent reactivity.

Figure 1.



One potential method for overcoming these limitations is by using multiple catalysts in the same reaction. In a multicatalytic cascade sequence, starting material is converted to intermediate B by catalyst 1. B is then converted to product C in the presence of second catalyst (Figure 1, b). This type of multicatalytic manifold enables diverse bond forming events. In an ideal catalytic cascade process, simple starting materials can be used to access complex enantioenriched molecules in a single step. This process of using multiple catalysts to exert their control over multiple bond forming events in the same reaction mimics nature's use of multiple enzymes to generate complex products.

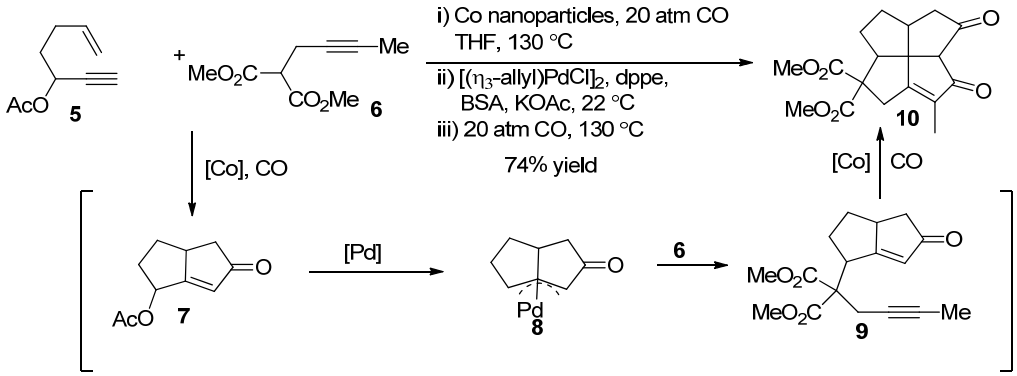
However desirable, multicatalytic cascade reactions have their associated difficulties. One major challenge in the development of multiple catalyst systems is that each catalyst present must be compatible with all reagents, intermediates, and other catalysts from the onset of the reaction. This limitation is sometimes overcome by the addition of catalysts or reagents in a stepwise manner (alternately, biphasic conditions can occasionally be used). Indeed, a number of examples of multicatalytic cascade

reactions exist in the literature,[4] and a few relevant examples highlighting the power and limitations of these transformations will be discussed in the following section.

4.1.2 Examples of Multicatalytic Cascade Reactions

The use of two different transition metals in multicatalytic cascade reactions has been recently accomplished. Chung and co-workers have utilized a cobalt/palladium multicatalytic cascade to synthesize fenestranes (Scheme 2).[5] Initial cobalt nanoparticale-catalyzed Pauson-Khand reaction generates bicyclopentenone **7**. Subsquent palladium-catalyzed allylic alkylation affords enyne **9**. This intermediate undergoes a second cobalt-catalyzed Phauson-Khand reaction to generate tetracycle **10**.

Scheme X.

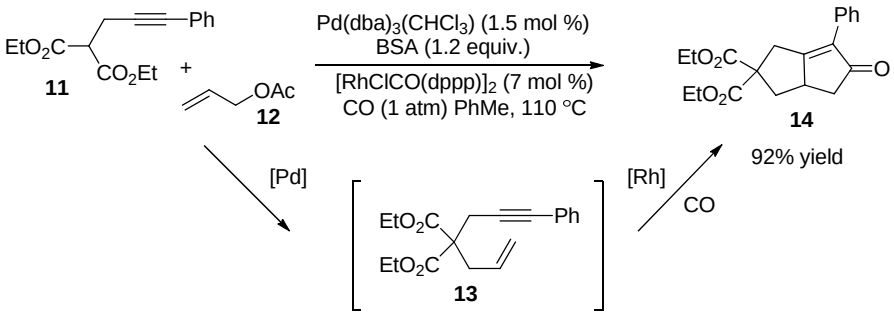


Although the reaction is accomplished in a single vessel, numerous operations are required at different stages to ensure reagent and catalyst compatibility at all times. For example, the palladium catalyst and nucleophile cannot be added until the first cyclization is complete and the system is purged with nitrogen. In order for the final cyclization to proceed, on the other hand, carbon monoxide must be reintroduced to the system. The removal of carbon dioxide prior to the second step is presumably due to

carbon monoxide's propensity to act as a ligand on palladium, therefore inhibiting the allylic alkylation. Although this example highlights the power of the cascade process in its ability to access complex tetracycle **10** from simple starting materials, it also emphasizes the difficulty in developing a reaction in which all catalysts and reagents can be introduced at the onset of the reaction.

However, it is possible to execute such a multicatalytic cascade with a single operation. Jeong and co-workers have utilized a similar palladium/rhodium multicatalytic cascade for the synthesis of bicyclopentenones (Scheme 3).[6] The first step proceeds via a palladium-catalyzed allylic alkylation to afford enyne intermediate **13**. This intermediate undergoes a subsequent rhodium-catalyzed Phauson-Khand type reaction to afford the desired bicyclopentenone **14**.

Scheme 3.

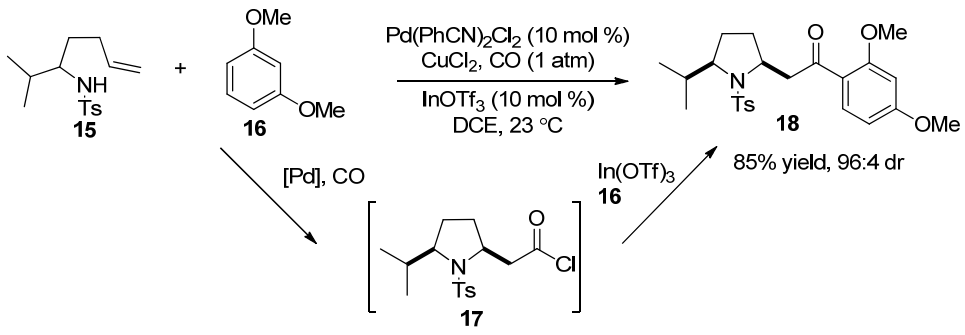


Notably, all catalysts and reagents are present from the onset of the reaction. When the reaction was monitored by GC analysis, it was found that intermediate **13** was formed quickly and then slowly transformed to final product **14**. The authors also note that the one pot reaction gives higher yields of product than those obtained in an analogous sequence in which the reactions are run sequentially with purification of intermediates. The authors state that this increase in yield of the one-pot process is presumably due to

suppression of unwanted side products through a rapidly driven equilibrium. This example of the synergistic effect of multiple catalysts highlights the ability of one-pot cascade process to actually outperform the stepwise process.

A recent example by Lambert and coworkers highlights yet another advantage of multi-catalytic cascade reactions: the ability to funnel somewhat unstable intermediates to more stable desired products without the need for isolation.[7] They have shown that amio carbonylation can be coupled with an *in situ* Friedel-Crafts reaction to afford substituted pyrrolidines in a single operation. The palladium catalyzed aminocarbonylation affords acid chloride **17** (Scheme 4).

Scheme 4.

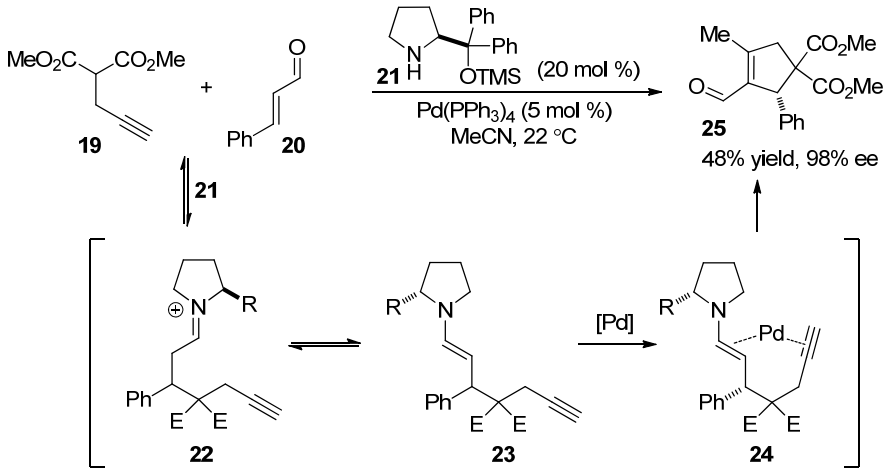


The acid chloride in the prescence of a nucleophilic arene and catalytic indium triflate proceeds to undergo a Friedel-Crafts reaction to afford the pyrrolidinyl ketone **18** in good yield and diastereoselectivity. In this reaction, like the bicyclopentanone sequence described in the previous paragraph, all reagents and catalysts are present from the onset of the reaction.

Not only can multicatalytic cascade reactions improve upon sequential transformations, but they can access reactivity that would not be accessible in a stepwise

case. An example that highlights this advantage is Córdova's recently published dynamic kinetic asymmetric transformation (DYKAT) utilizing a secondary amine and palladium-mediated multicatalytic process.[8] The reaction involves pyrrolidine **21**-catalyzed Michael addition of malonate **19** to α,β-unsaturated aldehyde **20** to generate intermediate **22** (Scheme 5). Tautomerization of the iminium to the enamine **23** followed by palladium-catalyzed cycloisomerzation affords the desired cyclopentene **25** in moderate yield and excellent enantioselectivity.

Scheme 5.

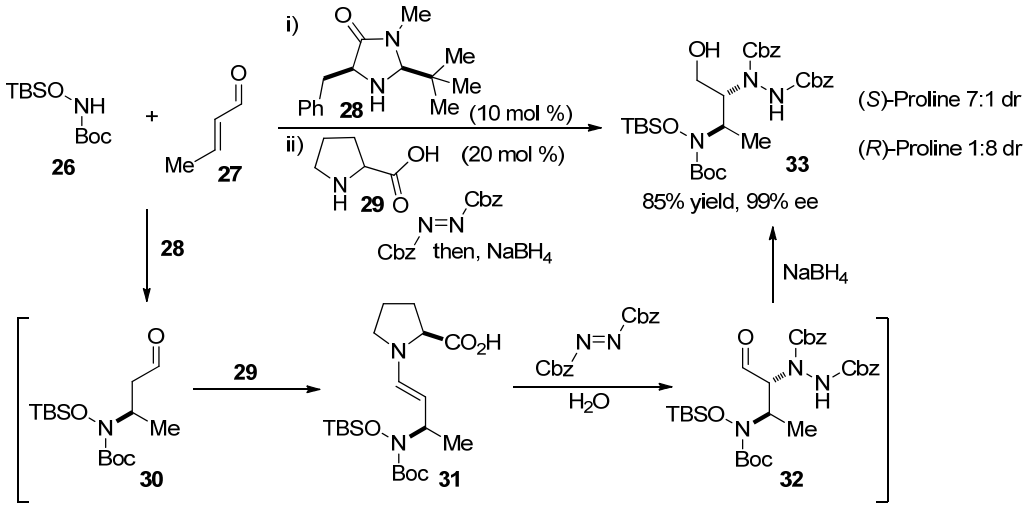


The authors propose that the iminium intermediate **22** undergoes a facile retro-Michael reaction, thereby establishing an epimerization pathway for enamine **23.** Preferential reaction of palladium catalyst with one diastereomer of **23** affords enantioenriched product **25** in high selectivity. In this way, reaction reversibility is capitalized on in a multicatalytic manifold to allow for high enantioselectivity of the final product.

Yet another advantage of multicatalyic cascades is their ability to access multiple stereochemical outcomes of distinct bond forming events. Specifically, substrate control can be exploited or overridden by proper catalyst choice. This type of control allows for

the selective formation of diastereomers with a simple change of the antipode of one or more of the catalysts. A recent account by MacMillian and co-workers emphasizes the power of this type of stereochemical control.[9] They were able to pair imidizaolidinone **28**-catalyzed enantioselective Michael addition of siloxycarbamate **26** to enal **27** to afford intermediate **30** (Scheme 6).

Scheme 6.

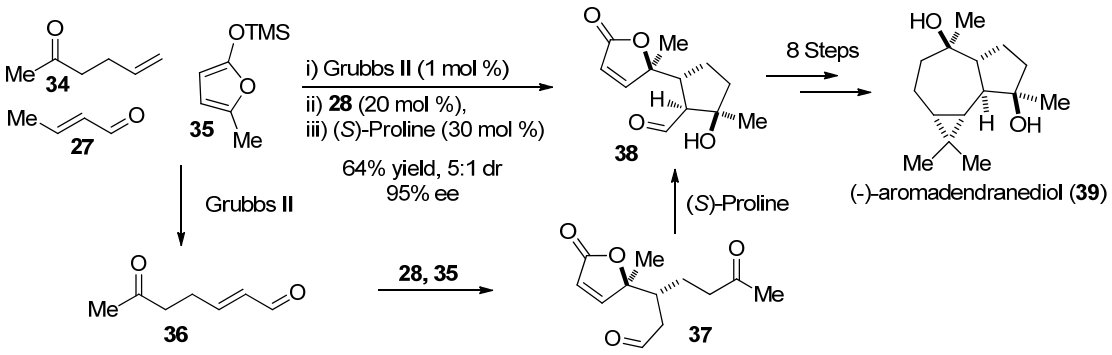


Subsequent addition of dibenzylazodicarboxyalte and proline catalyst **29** affords the diaminated product **33** in high yield with excellent diastero- and enantioselectivity. This general cascade could be utilized for a number of nucleophiles including indoles, silyloxyoxazoles, and siloxyfurans. In all cases, switching the enantiomer of proline catalyst results in formation of the opposite diastereomer of the product.

The cascade descibed has been expanded to include a third catalyst. A Grubbs cross metathesis can be utilized as the first reaction of the sequence to generate the desired α,β-unsaturated aldehyde for the secondary amine catalyzed Michael addition. This approach was used for the total synthesis of (-)-aromadendranediol (Scheme 7). Grubbs metathesis

affords enal **36,** which undergoes enantioselective Michael addition in the presence of catalyst **28** with siloxyfuran **35** as the nucleophile to afford intermediate **37**. Addition of proline to this intermediate promotes a diastereoselective enamine cyclization to generate the bicyclic product **38**. This intermediate was carried a further 8 steps to arrive at (-)-aromadendranediol (**39**). The ease with which complex intermediate **38**, which contains four stereocenters, is assembled from readily available starting materials highlights the power of the multicatalytic process.

Scheme 7.



Although the power of secondary amine mutlicatalysis in specific applications such as those described is irrefutable, its scope is somewhat limited by inherent catalyst reactivity. Intrigued by the possibility of utilizing our library of triazolylidene carbenes in a multicatalytic process, we initiated a program developed at achieving this goal. We envisioned that a number of catalysts could potentially be paired with our family of triazolylidene carbenes in a multicatalytic manner. We postulated that transition metals, phosphines, thioureas, quaternary ammonium salts, cinchonidines, and secondary amines might all be viable catalysts in our desired multicatalytic cascade. Moreover, because of the inherent basicity of both *N*-heterocyclic carbenes and secondary amines, we

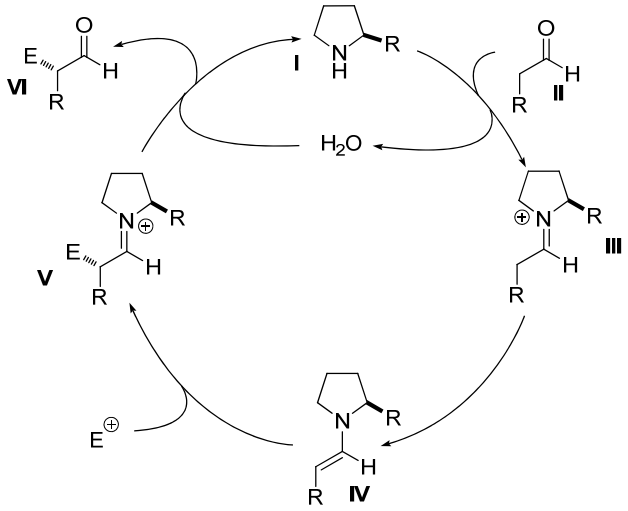
speculated these catalysts could coexist in a single flask and mediate complementary bond-forming events without mutual interference.

4.2 Secondary Amine Catalysis Background

4.2.1 Introduction

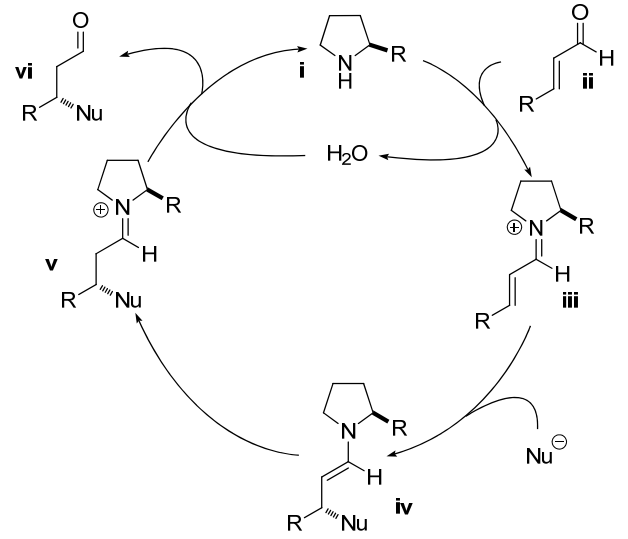
The use of amines to form both reactive imines (iminium) and enamines from suitable ketones or aldehydes has been known for over 150 years.[10] However, only recently have these intermediates been utilized in asymmetric, catalytic reactions. Of the amines utilized in catalytic asymmetric reactions, cyclic secondary amines have enjoyed the most success. Secondary amine activation of carbonyls can proceed via enamine or iminium activation. The enamine activation pathway proceeds through condensation of the amine onto aliphatic carbonyl **II** to form iminium ion **III** (Scheme 8).[11] The iminium ion can then tautomerize to the nucleophilic enamine **IV**. Stereoselective, electrophillic trapping of the enamine followed by hydrolyisis of the resulting iminium **V** provides α functionalized aldehyde **VI** and regenerates secondary amine catalyst **I**.

Scheme 8.



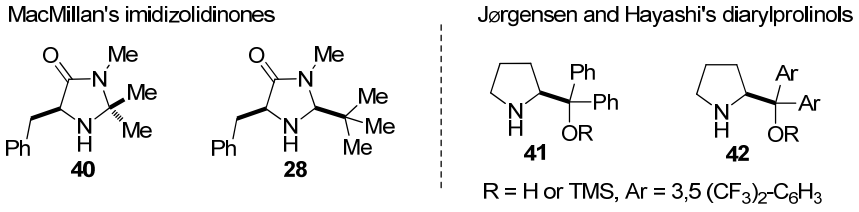
Iminium activiation proceeds via a similar pathway; this time, condensation of the amine onto the α,β-unsaturated carbonyl **ii** activates the β position for stereoselective, nucleophilic attack (Scheme 9). The resulting enamine **iv** tautomerizes to the iminum and hydrolyzes to form the desired product **vi** and regenerate catalyst.[12]

Scheme 9.



Of the secondary amines typically used for catalytic reactions, two architectures have dominated. First, MacMillian has developed a family of imidizolidinone catalysts that have proven useful for a wide range of transformations (scheme 10).[13] Additionally, Jørgensen[14] and Hayshi[15] are both credited with discovering the utility of diarylprolinol and diarylprolinol silyl ethers as efficient catalysts for both enamine and iminium activitation

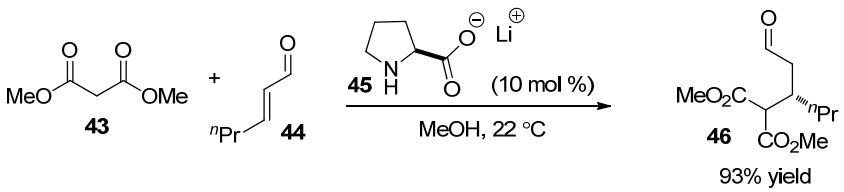
Scheme 10.



4.2.2 Iminium Catalysis

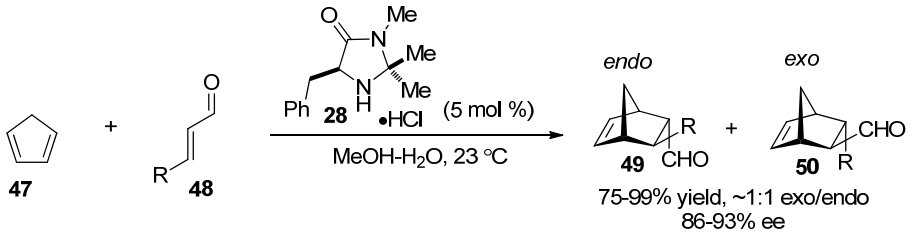
Yamaguchi is credited with the discovery of the asymmetric, iminium-catalyzed conjugate addition reaction.[16] Treatment of hexenal with a catalytic amount of the lithium salt of proline in the presence of dimethylmalonate affords the Michael addition product in good yield (Scheme 11). The authors do not report the enantioselectivity of the transformation.

Scheme 11.



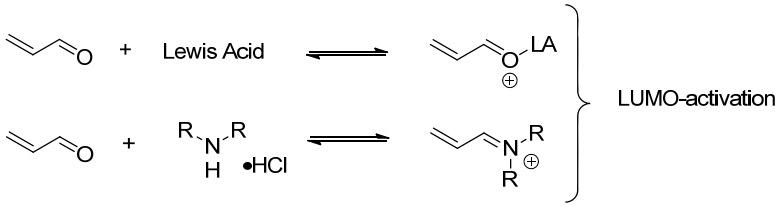
Although Yamaguchi's reaction provided proof of principle, it was only after another nine years that iminium catalysis became a synthetically useful tool for the enantioselective formation of carbon-carbon bonds. In 2000, MacMillan disclosed a Diels-Alder reaction between cyclopentadiene and various α,β-unsaturated aldehydes catalyzed by imidazolidinone **28** (Scheme 12).[13] The bicyclic product **49** was generated in good yield and enantioselectivity. This method was extended to various dienes which provided products in similarly good results.

Scheme 12.



MacMillan and co-workers were the first to explain how the iminium catalyst facilitated such reactions. Comparison of the LUMO-lowering abilities of Lewis acids to that of the catalytically-generated iminium ion led to the hypothesis that generation of the iminium ion lowers the LUMO of the unsaturated system, thereby accessing reactivity towards dienes otherwise inaccessible at ambient temperatures (Scheme 13).[17]

Scheme 13.



This concept is further supported by the downfield shift (~5-10 ppm) of the β carbon in α,β-unsaturated iminium ions compared to the corresponding aldehydes in the ^{13}C nmr.[18] This shift suggests that the β carbon of the iminium cation exhibits significantly higher electrophilicity at the beta carbon than does the parent aldehyde.

Since these seminal publications, numerous examples of iminium catalysis have been reported in the literature. A number of different nucleophiles have been shown to undergo enantioselective conjugate addition to α,β-unsaturated aldehydes and ketones in the presence of secondary amine catalysts. The reaction proceeds with a variety of carbon, hydrogen, oxygen, sulfur, and nitrogen nucleophiles. Similarly, a variety of both [4+2] and [3+2] cycloadditons have been described utilizing iminium catalysis.[12]

Asymmetric iminium catalysis has also been expanded to include an assortment of cascade reactions. Due to the sheer number of these transformations they cannot all be covered in this brief summary. A number of reviews have recently been published and the reader is directed to those references for further examples.[3c,e] Pertinent examples, however, will be highlighted in the following sections.

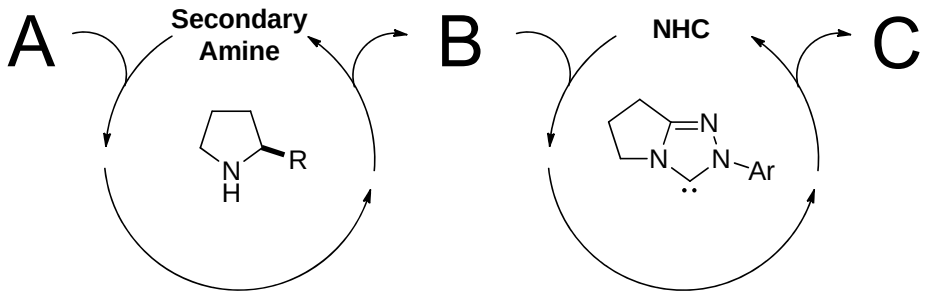
4.3 Development of Cascade Reactions Using *N*-heterocyclic Carbenes

4.3.1 Initial Investigations

Given our group's interest in utilizing *N*-heterocyclic carbenes as catalysts for C-C bond forming reactions and the ubiquity of secondary amines in asymmetric catalysis, we initiated a program directed at investigating these two catalyst archetypes in a multicatalytic cascade process. Moreover, because of the inherent basicity of both

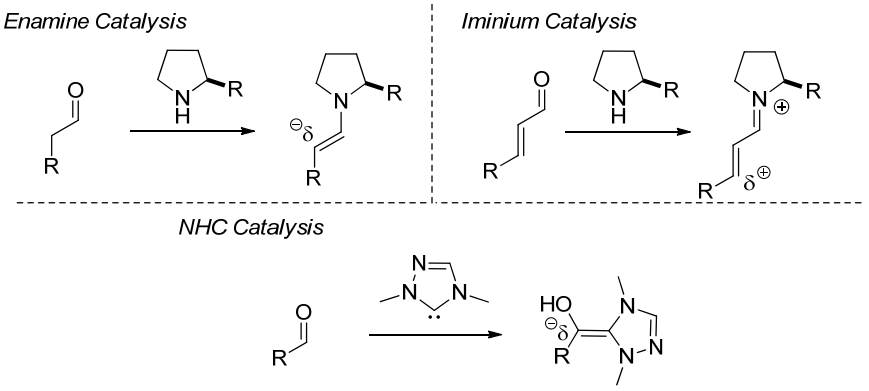
NHCs and secondary amines, we speculated these catalysts could coexist in a single flask and mediate complementary bond-forming events without mutual interference (Scheme 14).

Scheme 14.



Indeed, the expected complementary reactivity of NHCs and secondary amines was a primary factor motivating our study. As shown previously, secondary amines react with aldehydes to generate either enamines which are nucleophilic at the α position or iminium ions which are electrophilic at the β-postition (Scheme 15).

Scheme 15.

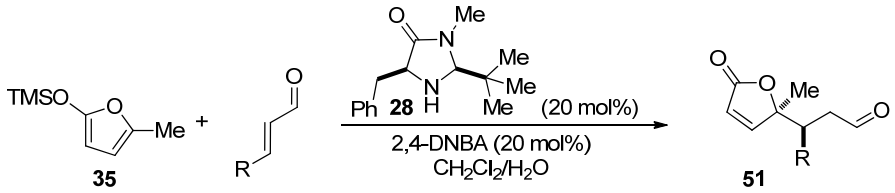


This reactivity is complementary to the nucleophilic acyl anion generated with aldehydes and NHCs. The combination of these catalysts in a single reaction should allow us to take

advantage of these unique reactivity patterns to access architectures not easily accessible with amine catalysis alone.

With this overall goal in mind, we became intrigued by an example reported by MacMillan and co-workers utilizing siloxyfurans as nucleophiles in a secondary amine-catalyzed Mukaiyama-Michael reaction to afford γ-butenolide products with high levels of diastero- and enantioselectivity (Table 1).[19]

Table 1.

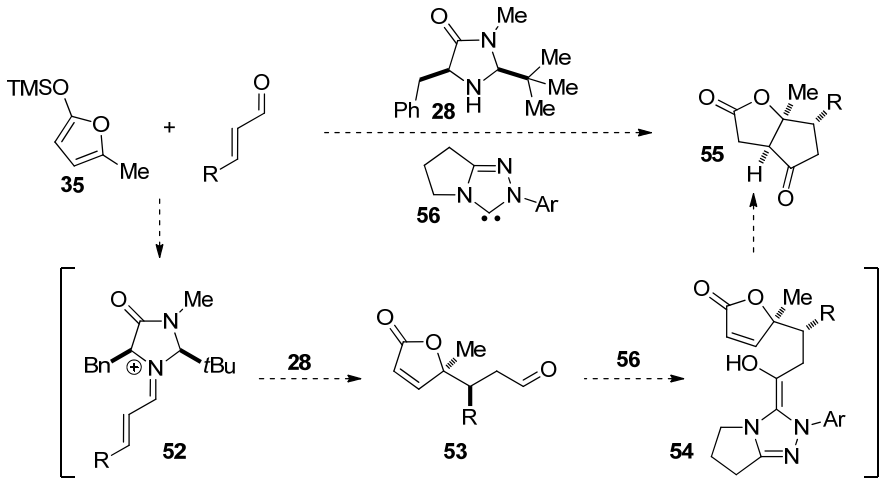


entry	R	temp (°C)	time (h)	% yield	dr	% ee
1	Me	-70	11	81	22:1	92
2	Pr	-50	20	87	31:1	84
3	*i*-Pr	-20	30	80	7:1	98
4	Ph	-40	30	77	1:6	99
5	CO_2Me	-60	22	84	11:1	99

We believed that the butenolide products, which contain an aldehyde-tethered Michael acceptor, would provide us with the perfect opportunity to investigate a secondary amine/*N*-heterocyclic carbene-catalyzed cascade reaction to access bicylic lactones containing three stereocenters in a single step from readily available starting materials. The proposed cascade is outlined below (Scheme 16). Secondary amine **28** would activate the α,β-unsaturated aldehyde to form iminium **52**. Conjugate addition of siloxy furan **35** to the activated aldehyde would form butenolide **53**. Finally, aldehyde **53** would undergo an intramolecular Stetter reaction in presence of carbene **56,** via Breslow

intermediate **54** to afford the bicyclic product **55** containing three new stereocenters (Scheme 16).

Scheme 16.



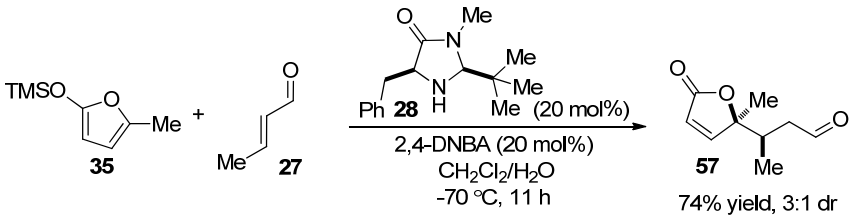
We were aware that this cascade would present a critical challenge. Development of this cascade would require reconciliation of seemingly incompatible acidic and basic conditions of the Mukaiyama-Michael reaction and the Stetter reaction, respectively. While the presence of an acid cocatalyst facilitates the Mukaiyama-Michael, it would presumably prohibit carbene formation since basic conditions are necessary in order to deprotonate the triazolium salt.

4.3.2 Development of a Mukiyama-Michael/Stetter Cascade

In order to test the feasibility of the Stetter reaction of substrate **57** , a sequential reaction was first attempted. In a sequential reaction, each catalytic transformation is conducted separately with isolation and purification of intermediates between. Synthesis of the butenolide **57** according to MacMillan's reported procedure was accomplished in

respectable yield but with significantly lower diastereoselectivity than that reported (Scheme 17).

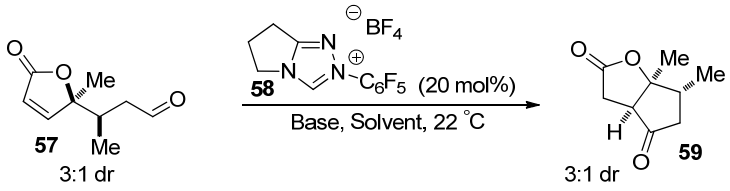
Scheme 17.



The lower observed diastereoselectivity likely results from variability in the temperature over the eleven hour period

With the desired aldehyde in hand, the Stetter reaction was then examined. A brief screen of conditions revealed that treatment of aldehyde **57** with either KHMDS or DIPEA in the presence of pentafluorophenyl triazolium salt **58** afforded the desired bicycle **59** in moderate yield and unchanged 3:1 dr (Table 2).

Table 2.

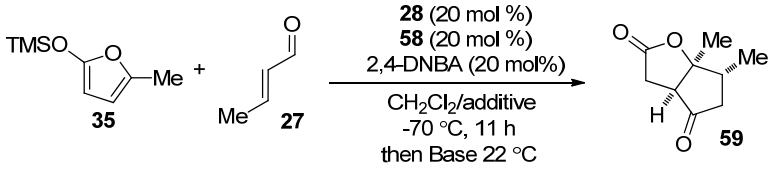


entry	base	equiv.	solvent	yield
1	KHMDS	0.2	PhMe	50%
2	KHMDS	0.2	CH_2Cl_2	47%
3	DIPEA	2	PhMe	17%
4	DIPEA	2	CH_2Cl_2	50%

Having determined that the desired Stetter reaction is possible, our attention turned to the development of a one-pot procedure to afford the bicyclic lactone. Due to the

cryogenic and acidic conditions necessary for the secondary amine-catalyzed Mukiyama-Michael process, which we knew to be unfavorable for carbene catalysis, the reaction was conducted in a one-pot, step-wise manner. All reagents including triazolium salt **58** but excluding base were added to the flask at -70 °C. Upon completion of the first step (as determined by TLC), base was added, and the reaction was allowed to warm to room temperature (Table 3).

Table 3.



entry	base (equiv.)	additive	yield	dr
1	KHMDS (0.4)	H_2O	trace	-
2	DIPEA (2.0)	H_2O	22%	3:1
3[a]	DIPEA (2.0)	H_2O	19%	3:1
4	DIPEA (2.0)	*i*-PrOH	37%	4:1

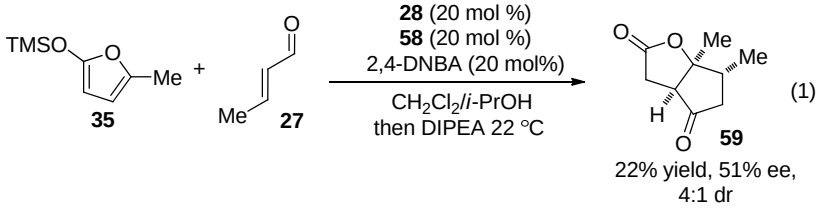
a) **58** (20 mol %) and DIPEA added after 11 hours.

In the event, secondary amine-catalyzed Mukiyama-Michael reaction takes place in the presence of the triazolium salt **58** under the acidic conditions. Moreover, addition of the triazolium salt with base upon completion of the conjugate addition does not increase the overall yield of the reaction indicating that the triazolium salt **58** does not interfere with iminium catalyzed conjugate addition (entry 3). A brief screen of conditions revealed DIPEA to be the optimal base for initiating the Stetter reaction (entry 2).

Because water is known to inhibit the Stetter reaction[20] we next explored the use of alcoholic additives in the reaction. It is believed that in the absence of water/alcohol additive the catalytic turnover is inhibited by formation of $(TMS)_2O$, which removes

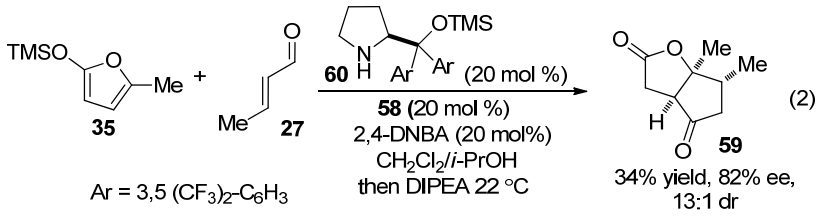
water from the catalytic cycle and prevents catalyst turnover. When isopropanol was utilized as the additive, the overall reaction yield increased to 37% with a slight increase in diastereoselectivity (Table 3, entry 4).

Because we hoped to eventually avoid the use of cryogenic conditions, the reaction was next conducted at room temp to investigate the effect on yield and selectivity. At room temperature, with imidazolidinone **28** as catalyst, the desired product was obtained in low yield and moderate diastereoselectivity and low enantioselectivity (eq 1).



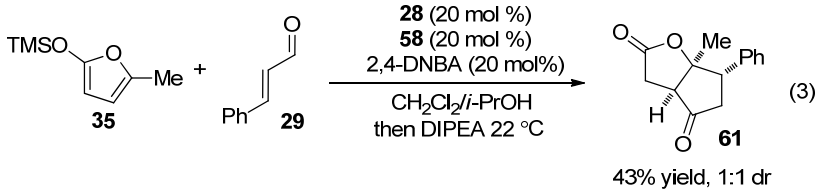
(1)

The reaction was also examined with proline-derived catalyst **60** at room temperature. In this case, the product was obtained in slightly better yields. More significantly, an increase in diastereoselectivity and enantioselectivity was observed (eq 2).



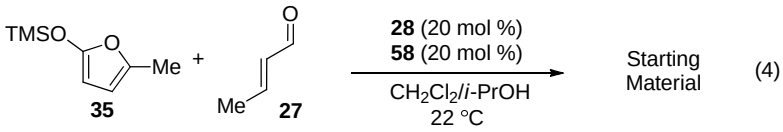
(2)

One potential reason for the low yields of the bicyclic lactone is the volatility of the isolated product. In order to test whether material might be lost during removal of solvent; the reaction was run with higher boiling *trans*-cinnamaldehyde. The one-pot reaction with *trans*-cinnamaldehyde afforded the bicyclic product **61** with a slight increase in yield as a 1:1 mixture of diastereomers (eq 3).



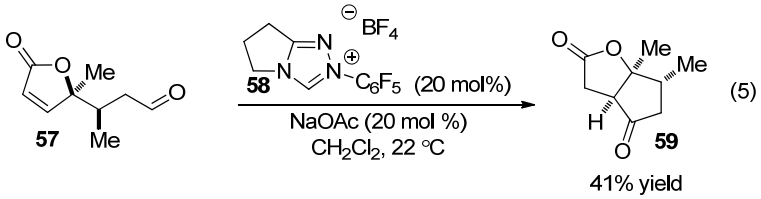
(3)

Although yields in our one-pot, two-step procedure were not ideal, we decided to investigate the possibility of carrying out the reaction in one-pot, one-step sequence wherein all reagents are present from the beginning of the reaction. Initially, it was thought that imidazolidinone catalyst **28** might be basic enough to deprotonate the triazolium salt and generate the active carbene. The deprotonation of the triazolium would also presumably facilitate iminium formation. To probe this possibility, the reaction was conducted in the absence of exogenous acid. This attempt led to only starting material (eq 4). Addition of DIPEA under the same conditions led only to decomposition, and no desired product was obtained.



(4)

This result suggests that acid is essential in order for the iminium-catalyzed cascade reaction to proceed. We wondered if it might be possible to identify a buffer system, the acid of which could participate in iminium activation and the conjugate base of which could deprotonate the carbene. To test this possibility, the Stetter reaction was examined using sodium acetate as the base. If this weak base could deprotonate the carbene (thereby facilitating the Stetter reaction) then acetic acid could potentially serve as an iminium cocatalyst. Reaction of aldehyde **27** in the presence of triazolium salt **58** and sodium acetate affords the product in 41% yield (eq 5).

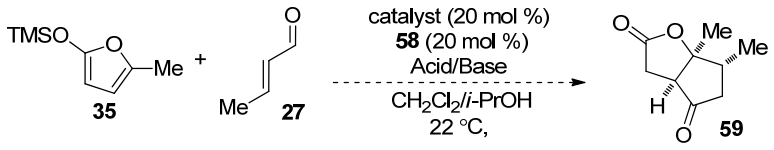


(5)

However, when the cascade process was examined using acetic acid, only intermediate aldehyde **57** was observed (Table 4, entry 1). Reaction with sodium acetate, on the other hand, afforded starting material (entry 2). Finally, a mixture of sodium acetate and acetic acid also afforded starting material (entry 3).

Despite these results with catalyst **28**, we were encouraged that favorable conditions could be eventually be identified: when catalyst **60** is used in the reaction under slightly basic conditions, for example, intermediate aldehyde **57** is observed (entry 4). This result shows that with catalyst **60,** no exogenous acid is necessary in order to facilitate the iminium-catalyzed Mukiyama-Michael reaction, and it gives promise for the development of a truly one-pot, one-step procedure for the synthesis of the bicyclic lactone **59**.

Table 4.



entry	catalyst	acid (mol %)	base (mol %)	result
1	**28**	HOAc (20)	-	aldehyde **57**
2	**28**	-	NaOAc (20)	NR
3	**28**	HOAc (20)	NaOAc (10)	NR
4	**60**	-	NaOAc (10)	aledhye **57**

Although a one-pot, one-step procedure has yet to be developed, a facile, two-step protocol leads to the desired product in moderate yields and diastereoselectivity.

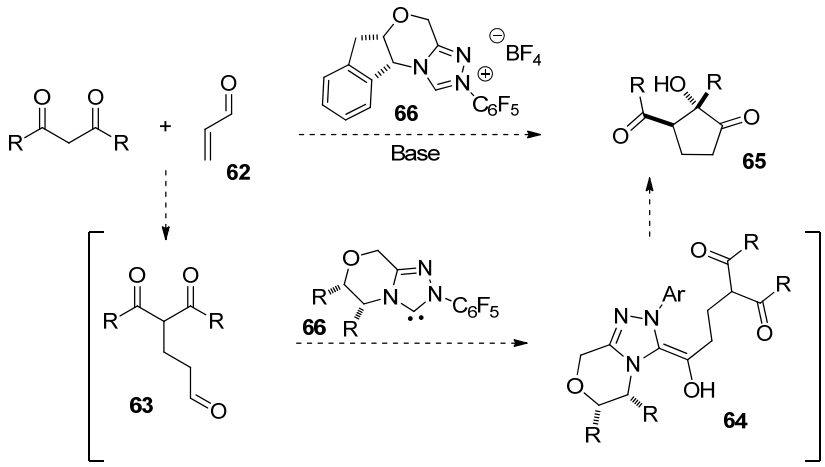
Research aimed at developing a truly one-pot protocol as well as at improving yield, enantio- and diastereoselectivity is currently being pursued in the Rovis group.

4.4 Development of a Michael/Benzoin Multicatalytic Cascade Sequence

4.4.1 Initial Discovery and Plan

Although the previously discussed Mukiyama-Michael/Stetter cascade reaction has yet to be fully developed, it encouraged us that secondary amine catalysis could work compatibly with *N*-heterocyclic carbene catalysis in a multicatalytic cascade sequence. In fact, an unexpected result was obtained in efforts towards cephalymsin A (Chapter 1) that shifted our focus to another potential cascade reaction. As previously discussed in Ch. 2, Sect. 2.4 the cyclopentanone byproduct observed while carrying out the desired Stetter reaction results from a "cascade" Michael addition followed by a benzoin reaction (Ch.2, Sect 2.4, Scheme 8). We wondered if we could harness this reactivity in a general cascade sequence (Scheme 18). Our proposed cascade would involve base-catalyzed conjugate addition of 1,3-dicarbonyls to α,β unsaturated aldehydes **62** to afford aldehyde tethered-ketones **63.** In the presence of a carbene catalyst, aldehydes **63** would then undergo an intramolecular, crossed benzion reaction to afford cyclopentanone products **65** via a formal [3+2] reaction.

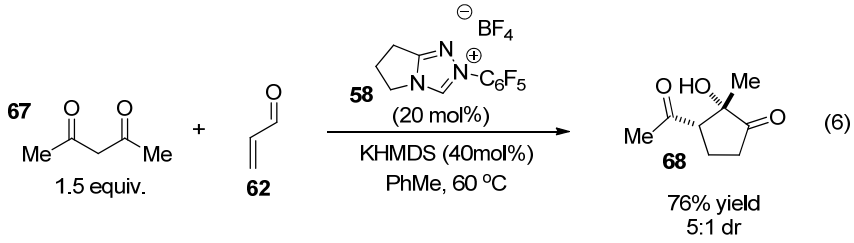
Scheme 18.



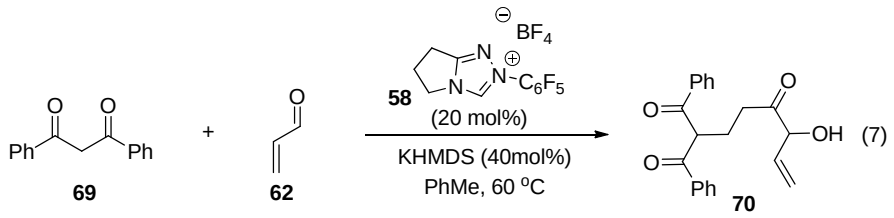
Based on the precedent of both base-catalyzed Michael addition of 1,3-dicarbonyls to α,β unsaturated aldehydes[21] as well as the recent development of the carbene-catalyzed crossed benzoin reaction (See Ch. 1, Sect 1.1.2) we were confidant that this cascade process could be achieved.

4.4.2 Investigation into Michael/Benzion Cascade

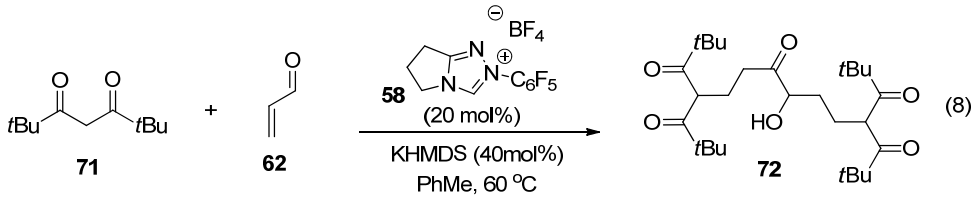
Initial investigations into the proposed Michael/benzoin cascade reaction centered on the use of acetylacetone as the 1,3 dicarbonyl nucleophile and acrolein as the electrophile. We found that treatment of acetylacetone **67** and acrolein **62** with traizolium salt **58** and KHMDS afforded the desired product in good yield and diastereoselectivity (eq 6). In order to prevent carbene-catalyzed decomposition of acrolein it was necessary to add acrolein slowly over 15 minutes.



Encouraged by this initial result, effort was made to investigate the scope of the racemic reaction. A variety of carbon nucleophiles were examined in the reaction. First, a screen of various 1,3 diketones yielded some interesting results. Specifically, exposure of dibenzoyl methane **69** to the optimized conditions did not afford any desired product. Instead, a crossed benzoin reaction between the intermediate aldehyde and acrolein was observed (eq 7).

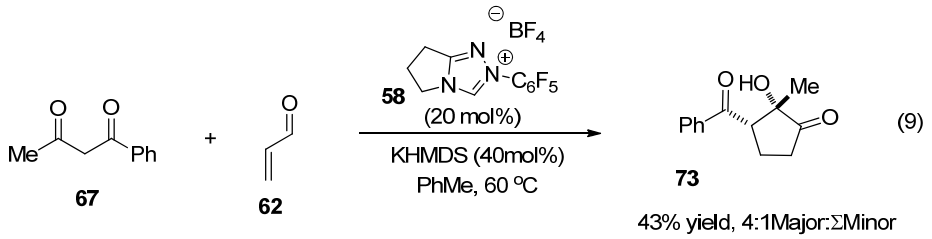


Moreover, di-*tert*butyl diketone afforded only crossed benzoin dimer **72** under the optimized conditions. In these cases, it seems that sterics surrounding the ketone prevent the desired intramolecular benzoin reaction from occurring (eq 8).



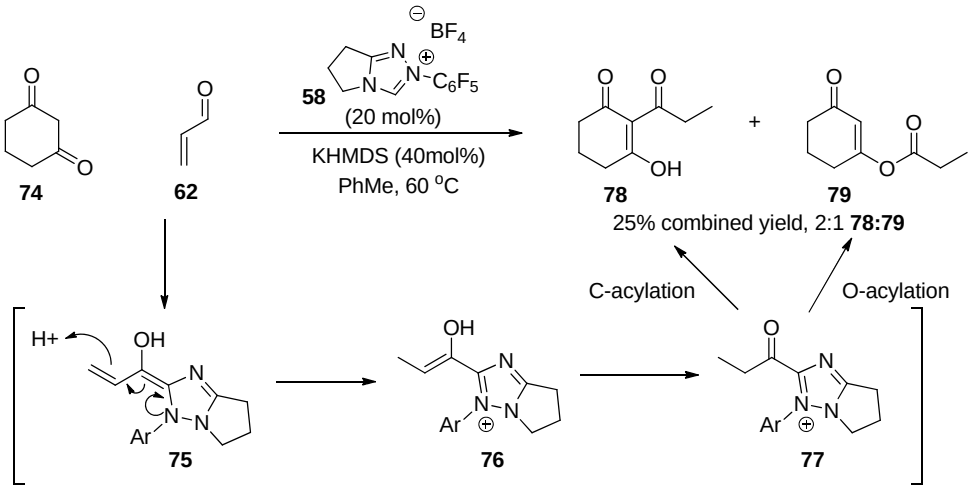
These results can be understood in light of the results obtained by Enders. As discussed previously (Ch. 1, Sect 1.1.2, eq 2), crossed benzoin reaction of phenyl ketone with aliphatic aldehyde tether provides no intramolecular benzoin product whereas the reaction with methyl ketone proceeds to give the cyclized product.

In an attempt to put the low reactivity of phenyl ketones in the benzoin reaction to our advantage, benzylidene acetone was examined in the reaction. Under the standard conditions, a single regioisomer of the desired product was indeed obtained in moderate yield (eq 9).



Another interesting result was obtained when 1,3-cyclohexadione (**74**) was subjected to the reaction. Instead of the expected bicyclic product, tricarbonyl **78** and ester **79** were isolated (Scheme 19).

Scheme 19.



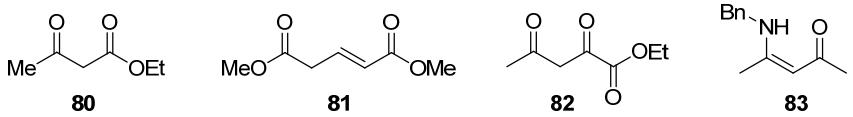
These products are believed to arrive from a *N*-hetereocyclic carbene-catalyzed redox process. In the proposed mechanism, carbene reacts with acrolein to afford Breslow intermediate **75**. However, instead of undergoing the previously-described benzoin or Stetter reactions, Breslow intermediate **75** undergoes a β-protonation event to afford enol **76**. This intermediate tautomerizes to yield acyl azolium **77**. The acyl azolium can then

react with either the carbon or oxygen nucleophile of **74** to yield **78** and **79**. Although these *N*-heterocyclic carbene-catalyzed redox processes are well known in the literature and represent efficient syntheses of esters, amides, and carboxylic acids, this is the first example, to our knowledge, of such a redox reaction that utilizes carbon nucleophiles to form ketone products.[22] This interesting transformation is currently being examined in the Rovis group.

In an effort to expand the scope of nucleophiles capable of participating in our Michael/benzoin cascade reaction, a series of potential partners were screened. In the event, β-ketoester **80**, dimethyl glutaconate **81**, tricarbonyl **82**, and enamine **83** proved unreactive under the optimal conditions (Scheme 20).

Scheme 20.

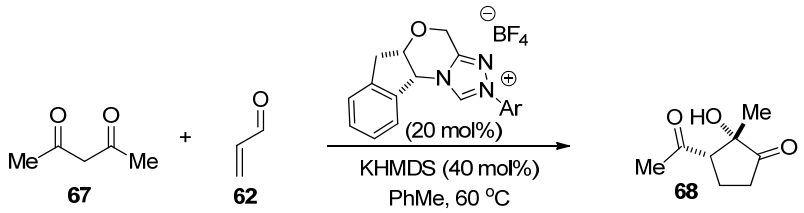
Unreactive Nucleophiles



80 **81** **82** **83**

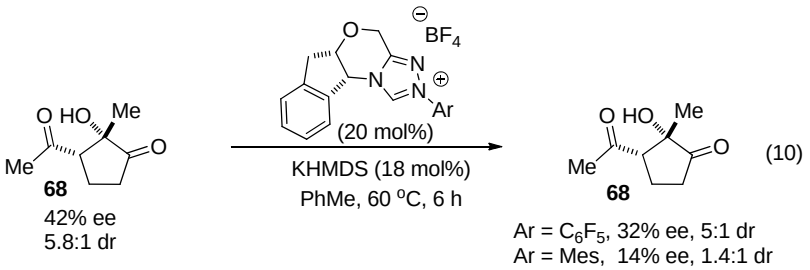
Although the scope of this transformation was somewhat limited we decided to investigate an asymmetric variant of this reaction. We found that a variety of chiral triazolylidenes catalyze the desired reaction (Table 5). Although enantioselectivities were uniformLy low, a clear trend was observed between the electronic nature of the triazolium and the yield, diastereoselectivity, and enantioselectivity. Specifically, increasing electron donating ability of the aryl group on the catalyst resulted in a decrease to all three.

Table 5.



entry	Ar	yield	ee	dr
1	C_6F_5	74%	41%	5.7:1
2	$C_6H_2Cl_3$	58%	23%	3.6:1
3	Ph	55%	18%	3.4:1
4	Mes	34%	0%	1.7:1
5	*p*-MeOPh	NR	-	-

A possible explanation for this trend is the presence of a competing retro-benzoin reaction catalyzed by more electron-rich catalysts. In order to investigate this possibility, enantioenriched product **68** was treated with both pentafluorophenyl triazolium and mesityl triazolium precatalyst in the presence of KHMDS (eq 10). It was found that after six hours, pentafluorophenyl triazolium-derived carbene caused only slight empimerization from 42% ee and 5.8:1 dr to 32% ee and 5:1 dr, while mesityl-desired carbene caused significant empimerization from 42% ee and 5.8:1 dr to 14% ee and 1.4:1 dr.

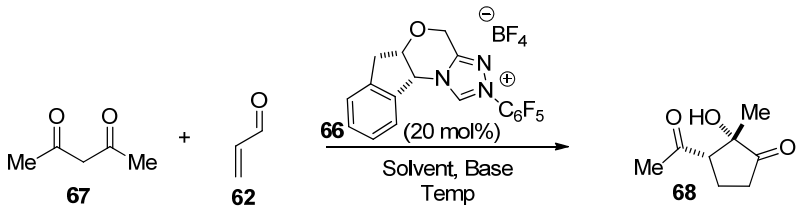


These results show that electron-rich catalysts indeed cause epimerization of the cyclopentanone product. However, it is not conclusive whether epimerization proceeds

via a retro benzoin pathway. It is also possible that a retro-aldol process could be promoted by more basic catalysts.

With the recognition that our reaction was susceptible to epimerization pathways, we performed a brief screen of solvents and bases in an effort to improve enantioselectivity (Table 6).

Table 6.



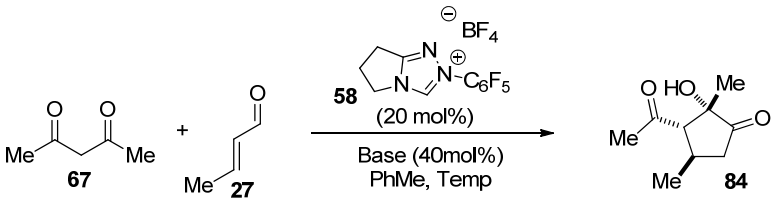
solvent	base	temp (°C)	yield	ee	dr
PhMe	*t*-BuOK	60	21%	27%	4.2:1
PhMe	DBU	60	18%	29%	3.2:1
PhMe	DIPEA	60	NR	-	-
PhMe	*t*-BuOK	25	21%	28%	3.5:1
THF	KHMDS	25	NR	-	-
THF	*t*-BuOK	25	29%	38%	5.5:1
THF	DBU	25	18%	37%	2.8:1

Unfortunately, change of base and solvent proved unsuccessful in increasing the enantioselectivity appreciably. Rather, any deviation from the previously described conditions led to a decrease in yield and selectivity.

Although the enantioselectivities obtained in the cascade sequence remained only fair, we sought to expand the scope by utilizing β-substituted enals as electrophiles. In this situation, the enantioselectivity of the initial Michael addition is not controlled by the carbene catalyst. However, the possibility of expanding the scope to access more

complex products was intriguing. Initial reaction with crontanaldehyde **27** under the optimized conditions did not yield the desired product (Table 7, entry 1). Presumably, aldehyde activation would be necessary to encourage reaction of the more-hindered β-substituted substrates. We hypothesized that a secondary amine might function not only as a base to deprotonate the triazolium salt but woud also serve as a catalyst to activate aldehydes toward Michael addition via iminium activation. To our delight, the use of pyrrolidine as the base affords the desired product in fair yield and in good diastereoselectivity (Table 7, entry 2).

Table 7.



entry	base	temp (°C)	yield	dr
1	KHMDS	60	NR	-
2	pyrrolidine	22	25%	6:1 dr

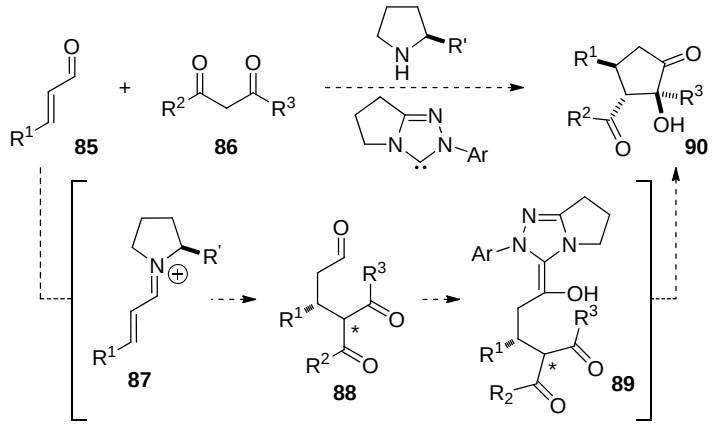
Although the desired product was obtained in low yield, we were encouraged by this result. If pyrrolidine were facilitating the reaction via iminium activation, we presumed that a chiral secondary amine could be utilized to control the stereocenter formed in the Michael addition, thereby providing products enantioselectivity. Investigation into the use of chiral secondary amines in a Michael/benzoin cascade will be discussed in the next section.

4.5 Secondary Amine/*N*-Heterocyclic Carbene Multicatalytic Cascade

4.5.1 Concept and Background

Supposing that pyrrolidine catalyzes the desired Michael/benzoin casade reaction between crotonaldehyde and acetylacetone via iminium activation, we sought to develop an asymmetric variant of this reaction. We postulated that reaction between an α,β-unsaturated aldehyde **85** and 1,3-dicarbonyl **86** in the presence of a chiral secondary amine would generate aldehyde tethered ketone **88** enantioselectively (Scheme 21). This intermediate should undergo a crossed benzoin reaction in the presence of the carbene as showcased in the previous section. This process would lead to the enantioselective synthesis of densely functionalized cyclopentanones via a formal [3+2] sequence.

Scheme 21.

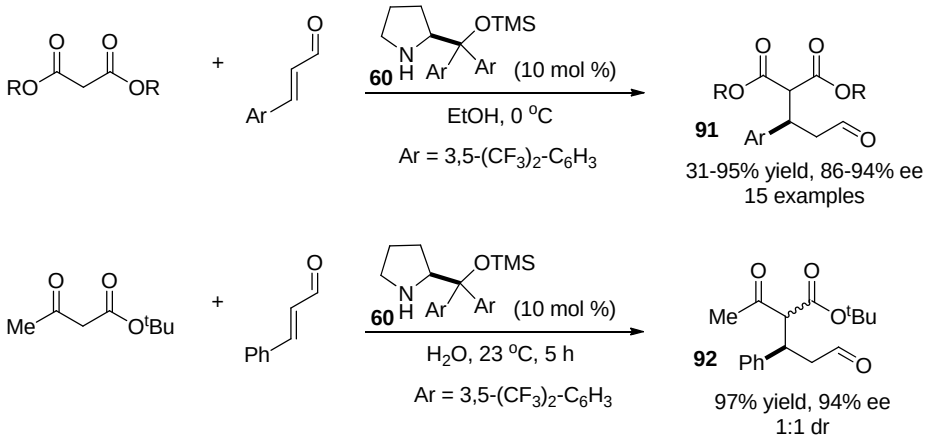


In this proposed cascade the secondary amine would be responsible for the enantiodetermining step (the conjugate addition), and the benzoin reaction would presumably be substrate controlled. This potentially would allow access to cyclopentanones with high enantioselectivity without relying on a chiral carbene catalyst.

However, it is also possible that a chiral carbene could override the inherent substrate direction and allow access to the opposite diastereomer.

A brief search of the literature revealed that the enantioselective Michael addition of 1,3-dicarbonyls into α,β-unsaturated aldehydes utilizing secondary amines has been widely studied. It has been shown that a variety of 1,3 diketones, β-keteoesters, β-ketoamides, and malonates participate in the reaction with high enantioselectivity.[23] Most relevant to the proposed reaction is Jørgensen's work utilizing malonates and β-ketoesters in a secondary amine-catalyzed Micheal addition.[23a,d] Specifically, Jørgensen has shown that 3,5 bistrifluomethyl diphenyl prolinol TMS ether catalyst **60** affords aldehyde products **91** in good yield and excellent enantioselectivity (Scheme 22). When β-ketoesters are used, the product is obtained as 1:1 mixture of diastereomers.

Scheme 22.



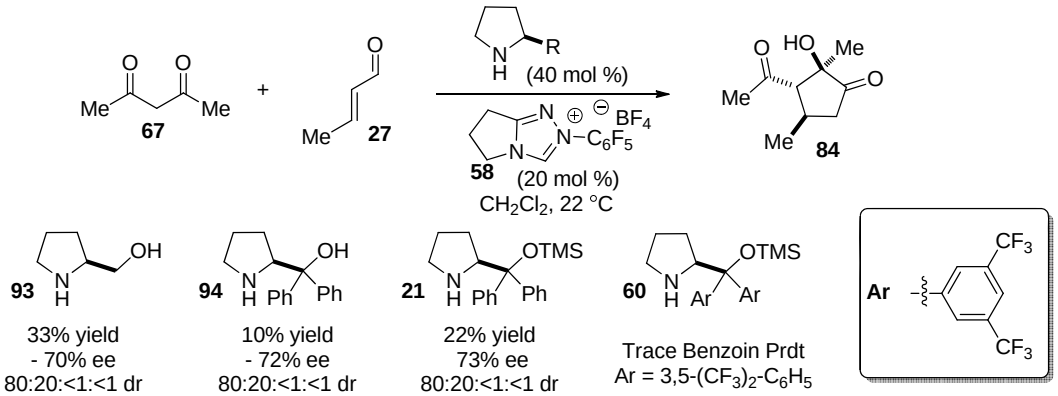
Upon inspection of the conditions used in the previous examples, we were cautiously optimistic that our proposed cascade could be carried out in a one-pot fashion. Unlike the majority of iminium catalysis, the conjugate addition of 1,3-dicarbonyls has been shown to proceed in the absence of an acid cocatalyst. Typically, acid co-catalysts are necessary

in secondary amine catalysis to help facilitate iminium/enamine formation. In the case of 1,3 dicarbonyls, the C-H methylene proton is presumably acidic enough (pKa = ~13)[24] to behave as a mild acid for iminium formation. We believed the absence of strong acid might allow the secondary amine and carbene to be present in the same reaction mixture simultaneously.

4.5.2. Initial Optimization

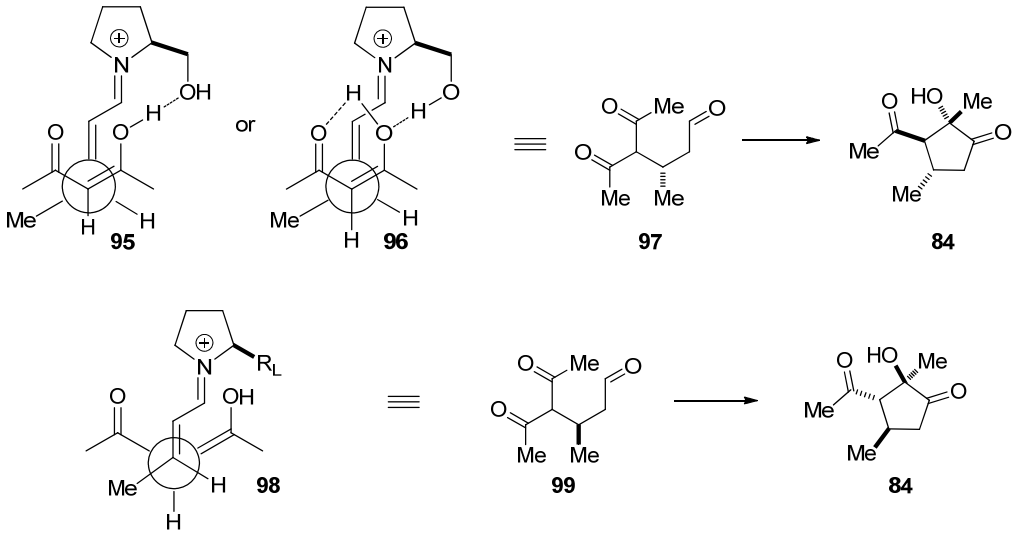
Initially, we wanted to limit the number of variables in the reaction by utilizing the secondary amine catalyst as both iminium catalyst as well as the base used for carbene generation. We were delighted to find that a variety of secondary amine catalysts promoted formation of the desired product in high enantioselectivity, albeit in low yield. Interestingly, prolinol catalysts **93** and **94** afford the opposite enantiomer of product relative to that provided by diphenyl prolinol catalyst **21** (Scheme 23). This inversion of selectivity has been previously documented for similar 1,3-dicarbonyl compounds.[23e]

Scheme 23.



The enantiomer observed with catalyst **21** is rationalized to form through a transition state in which the front face of the iminium is shielded by the large diphenyl TMS alcohol, forcing the nucleophile to attack from the opposite face **98** (Scheme 24). Although the origin of the observed enantioinversion with catalysts **93** and **94** is not fully elucidated, we speculate that it arises from the free alcohol's ability to direct the nucleophile to its same face via hydrogen bonding. This may occur either via hydrogen bonding between the enol tautomer of **67** to the Lewis basic oxygen of the catalyst **95** or by hydrogen bond donation of catalyst to the enol oxygen **96** (Scheme 24). Given that the opposite enantiomer of product is obtained when the hydrogen of the catalyst is replaced by a TMS group, hydrogen bond donation from catalyst to enol oxygen seems more likely to account for enantioselectivity reversal.

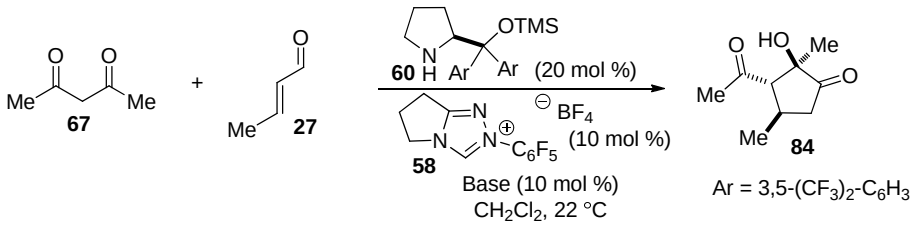
Scheme 24.



Although we were able to obtain the desired product in good enantioselectivity under the described initial conditions, we sought to improve the overall yield of the reaction. We hypothesized that the low yields observed for the test reaction arose from slow

formation of carbene. To alleviate this problem, catalytic triethylamine was added to the reaction. As we surmised, the expected product was obtained in better (33%) yield and 84% ee in the presence of the previously unreactive bistrifluomethyl diphenyl catalyst **60** (Table 8, entry 1). The use of sodium acetate as the base further improved the yield to 55%, and the product was obtained in 86% ee and 4:1 diastereoselectivity (Table 8, entry 2). It is worth noting that in all cases; only two of the possible four diastereomers were observed by GC/MS analysis.

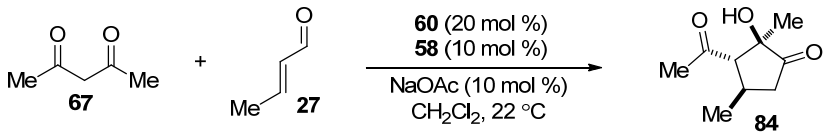
Table 8.



entry	base	yield	ee	dr
1	Et_3N	33%	84%	80:20:<1:<1
2	NaOAc	55%	86%	80:20:<1:<1

While addition of base had increased reaction efficiency slightly, we were not satisfied, and we aimed at further improving the overall yield of the reaction. It was found that increasing the concentration of the reaction enables isolation of product in 74% yield (Table 9, entry 3). Moreover, doubling the equivalents of diketone results in a further boost in yield to 93% while maintaining high levels of selectivity (Table 9, entry 4).

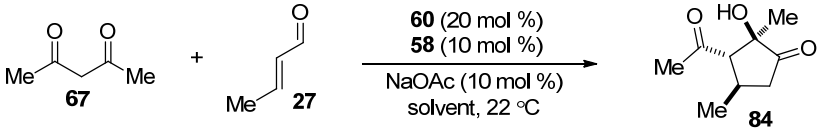
Table 9.



entry	equiv. **67**	equiv. **27**	concentration	yield	ee	dr
1	1	2	0.06 M	53%	85%	80:20:<1:<1
2	2	1	0.06 M	74%	85%	80:20:<1:<1
3	1	1	0.1 M	74%	86%	80:20:<1:<1
4	2	1	0.1 M	93%	86%	80:20:<1:<1

A solvent screen revealed that polar, protic solvents result in a significant loss of yield and enantioselectivity (Table 10, entries 5 and 6) while halogenated solvents give the highest levels of enantioselectivity (Table 10, entries 1 and 2). Moreover, it was found that chloroform increases the diastereoselectivity from 4:1 to 5:1.

Table 10.



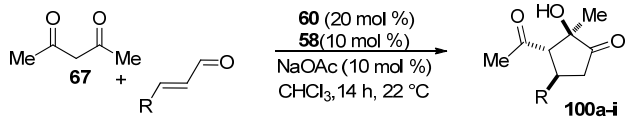
entry	solvent	yield[a]	ee	dr
1	DCE	67%	86%	80:20:<1:<1
2	$CHCl_3$	82%	86%	85:15:<1:<1
3	THF	NR	-	-
4	PhMe	87%	84%	80:20:<1:<1
5	EtOH	trace	70%	80:20:<1:<1
6	*i*-PrOH	29%	70%	80:20:<1:<1

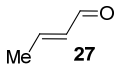
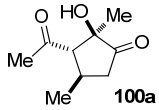
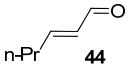
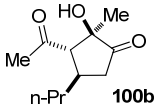
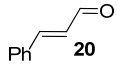
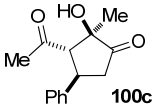
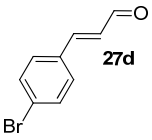
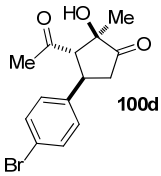
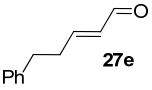
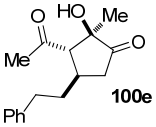
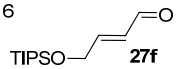
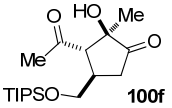
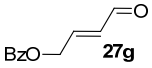
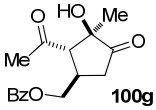
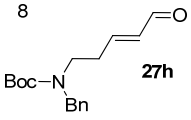
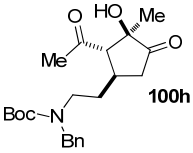
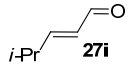
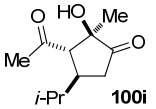
a) reaction carried out with 1 equiv. of **67** and **27**.

With optimal conditions in hand for accessing the desired cyclopentanone product, we sought to investigate the scope of this multicatalytic cascade process.

4.5.3. Scope and Limitations

Table 11.



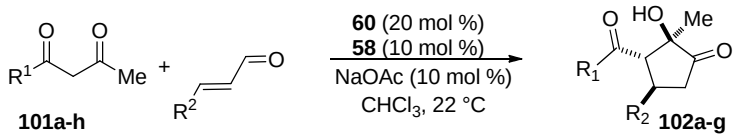
Entry	Aldehyde	Product	Yield (%) (dr)	ee (%)
1	 **27**	 **100a**	93 (85:15:<1<1)	86
2	 **44**	 **100b**	77 (85:15:<1<1)	93
3	 **20**	 **100c**	60 (80:20:<1:<1)	85
4	 **27d**	 **100d**	70 (85:15:<1<1)	80
5	 **27e**	 **100e**	59 (80:20:<1:<1)	95
6	 **27f**	 **100f**	71 (75:25:<1:<1)	92
7	 **27g**	 **100g**	72 (80:20:<1:<1)	95
8	 **27h**	 **100h**	60 (85:15:<1:<1)	90
9	 **27i**	 **100i**	32 (67:33:<1:<1)	82

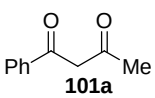
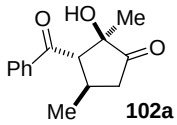
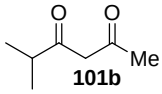
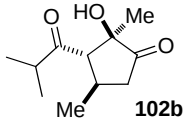
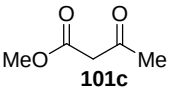
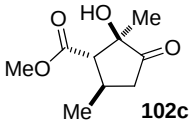
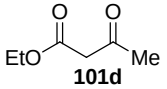
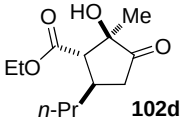
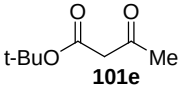
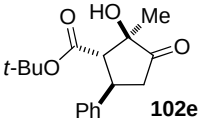
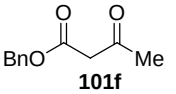
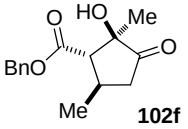
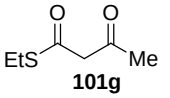
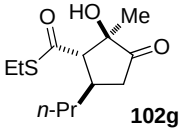
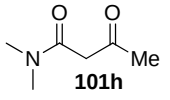
A series of α,β-unsaturated aldehydes were examined under the optimized reactions conditions. Both alkyl and aromatic enals deliver the desired products in good yields and enantioselectivities (Table 11). α,β-unsaturated aryl aldehydes tend to give slightly lower enantioselecitivities than their alkyl counterparts. Protected alcohols and amines also participate in the reaction to afford products amenable to further functionalization in good yield and selectivity (entries 6-8). One limitation to the described reaction is that sterically large enals show diminished reactivity under the standard conditions. However, these substrates still react with good levels of enantioselectivity (entry 9).

Having explored the scope of our Michael/benzoin cascade with respect to α,β-unsaturated aldehydes, we sought to investigate the use of unsymmetrical 1,3-dicarbonyls (Table 12). We found that unsymmetrical diketones **101a** and **101b** undergo the desired reaction chemoselectively to afford cyclopentanone products **102a** and **102b** (entries 1 and 2). In a fashion analogous to that reported by Enders (Ch.1, eq 2), methyl ketone of **101a** reacts preferentially over the phenyl ketone to give a product ratio of 4:1 (major: the sum of all other potential regioisomers and diastereomers). Similarly, the methyl ketone reacts preferentially over the isopropyl ketone to give **102b** in good yield.

β-Ketoesters also serve as competent nucleophiles in the cascade reaction. Methyl, ethyl, *tert*-butyl, and benzyl acetoacetate provide the desired products with both alkyl and aromatic enals providing products in good yields and high levels of enantioselectivity (entries 3-6). β-ketothioester **101g** can also be utilized, affording the desired product with good selectivity. However, unlike the symmetrical 1,3-diketones, the β-ketoesters afford of all four possible diastereomers with moderate selectivity.

Table 12.



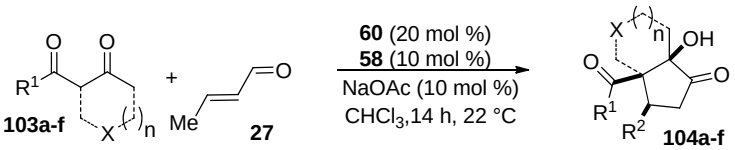
entry	R^2	1,3-dicarbonyl	product	yield (%) (dr)	ee (%)[a]
1	Me **27**	 **101a**	 **102a**	74 (4:1)[b]	87
2	Me **27**	 **101b**	 **102b**	68 (4:1)[b]	78
3	Me **27**	 **101c**	 **102c**	90 (64:33:3:<1)	91
4	*n*-Pr **44**	 **101d**	 **102d**	80 (60:30:8:2)	93
5	Ph **20**	 **101e**	 **102e**	86 (60:35:5:<1)	97
6	Me **27**	 **101f**	 **102f**	90 (58:39:2:<1)	82
7	*n*-Pr **44**	 **101g**	 **102g**	56 (69:22:6:3)	81
8	Me **27**	 **101h**	NR	-	-

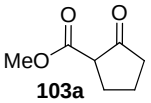
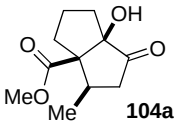
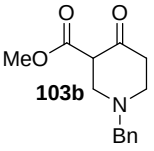
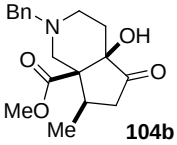
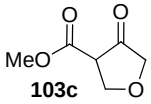
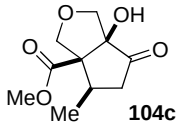
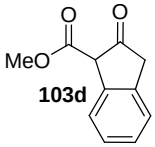
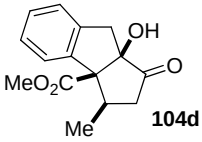
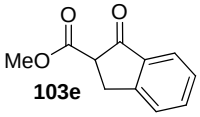
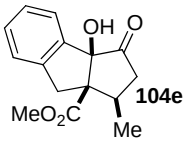
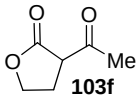
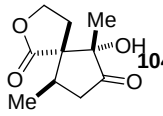
a) ee of major diastereomer
b) ratio refers to major isomer:Σ of all other isomers

We envisioned that application of this multicatalytic cascade reaction for the formation of bicyclic products could significantly boost the synthetic utility of this process. Indeed, cyclic β-ketoesters react under the optimized conditions to give both

[3.3.0] and [4.3.0] bicyclic systems (Table 13, entries 1-4) in good yield, enantioselectivity and diastereoselectivity. Both oxygen and protected nitrogen functionalities are tolerated in the cyclic β-ketoester backbone to afford highly functionalized bicyclic structures. Interestingly, indene-derived β-ketoester affords product in good yield; however, it does so in greatly diminished enantioselectivity (Table 13, entry 4). Not surprisingly, regioisomeric compound **104e** affords only trace product, presumably due to the steric constraints of the ketone. This result can be compared to the result obtained with benzylidene acetone (**101a**), in which the methyl ketone reacts preferentially over the phenyl ketone (Table 12, entry 1). These results show once again that phenyl ketones are slow to cyclize under the described reaction conditions. Lastly, acetylbutyrolactone **103f** undergoes the desired reaction to form the densely functionalized spirocyclic product **104f** in good yield and enantioselectivity.

Table 13.



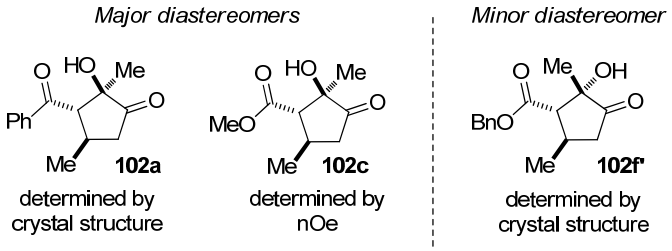
Entry	β-Ketoester	Product	Yield (%) (dr)	ee (%)
1	 **103a**	 **104a**	79 (80:20:<1:<1)	94
2	 **103b**	 **104b**	76 (85:15:<1:<1)	90
3	 **103c**	 **104c**	90 (66:33:<1:<1)	79
4	 **103d**	 **104d**	59 (50:50:<1:<1)	13
5	 **103e**	 **104e**	< 20% (-)	-
6	 **103f**	 **104f**	72 (73:18:9:<1)	77

The described reaction has been shown to be a versatile method for the enantioselective formation of densely functionalized products. The cascade process is amenable to a wide variety of α,β-unsaturated aldehydes and 1,3 dicarbonyls.

4.5.4 Efforts Aimed at Improving Diastereoselectivity

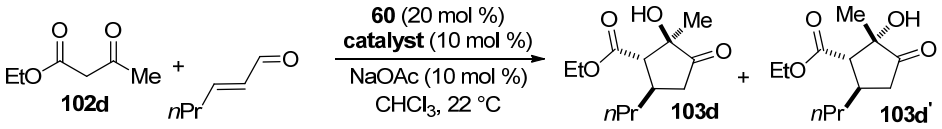
Intrigued by the lack of diastereoselectivity of the β-ketoester substrates, we sought to identify the two major diastereomers that were being formed in this reaction. Determination of the relative stereochemistry of the major diastereomer was accomplished via crystal structure of **102a** (Scheme 25). nOe studies of the major diastereomer of **102c** revealed the same relative configuration to that of **102a**. Interestingly, the crystal structure of the minor diastereomer of **102f** showed the product to be epimeric at the tertiary alcohol. This data suggests that the benzoin reaction is responsible for the lower diastereoselectivity observed for the β-ketoester substrates.

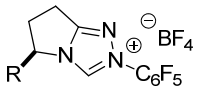
Scheme 25.



In an effort to improve the diastereoselectivity of the benzoin cyclization, a number of chiral triazolium salts were screened in the reaction between hexenal and ethyl acetoacetate (**102d**) (Table 14). No significant improvement in diastereoselectivity was observed when both phenylalanine- and aminoindanol-derived triazolium precatalysts were screened. Moreover, electron-rich catalysts shut down reactivity entirely. Even more vexing was the apparent lack of correlation between selectivity and catalyst.

Table 14.

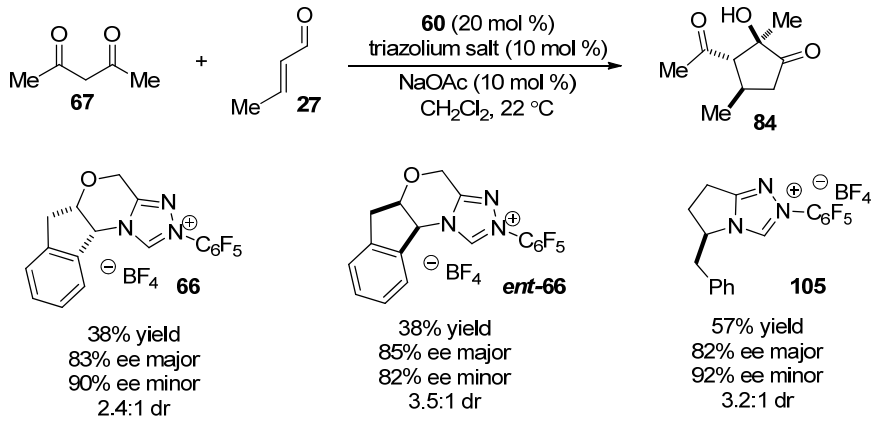


entry	catalyst	yield	dr	ee (**103d**)	ee(**103d'**)
					
1	R = H	80%	60:30:8:2	93%	92%
2	R = Bn	69%	55:35:6:4	83%	93%
3	R = *i*Pr	69%	51:42:5:2	82%	95%
4	R = Cy	77%	65:16:18:1	87%	62%
5	R = *i*Bu	75%	52:40:4:4	96%	82%
6	R = *t*Bu	53%	40:45:6:9	82%	87%
7	**66**	75%	38:38:17:7	81%	94%
8	*ent*-**66**	86%	43:20:28:9	87%	74%

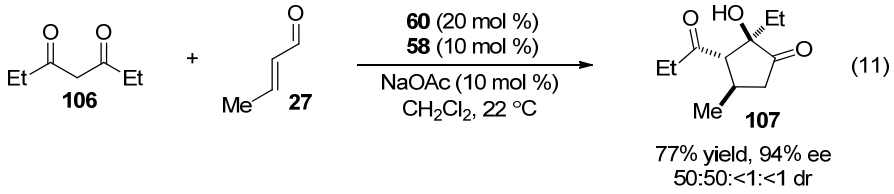
Although chiral carbene catalysts failed to improve the diastereoslectvity of the cascade process with β-ketoesters, we wanted to investigate the use of chiral carbenes in conjunction with symmetrical 1,3-diketones. We hoped that by utilizing a chiral carbene of the correct antipode, we could override the inherent diastereoselectivity of the reaction to obtain the opposite product diastereomer. This type of approach relates to MacMillan's use of different antipodes of proline to selectively generate each desired diastereomer of his desired product (Scheme 6, Sect. 4.1.2).

In the reaction of acteylacetone and crotonaldehyde, the use of a variety of chiral triazolium salts resulted only in a small change in magnitude but not in direction of diastereoselectivity (Scheme 26).

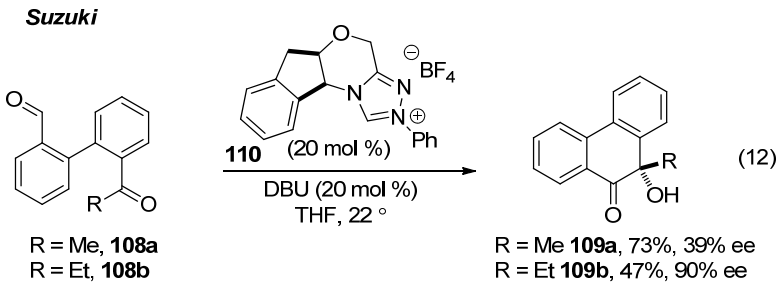
Scheme 26.



On the other hand, we imaged that a substrate giving near 1:1 dr under the established conditions would be superior for investigating the effect of chiral carbenes in the reaction since its diastereoselectivity might be more susceptible to catalyst influence. During the course of our 1,3-diketone scope, we found that 3,5 heptanedione provides product in good yield and excellent enantioselectivity but in 1:1 dr (eq 11).



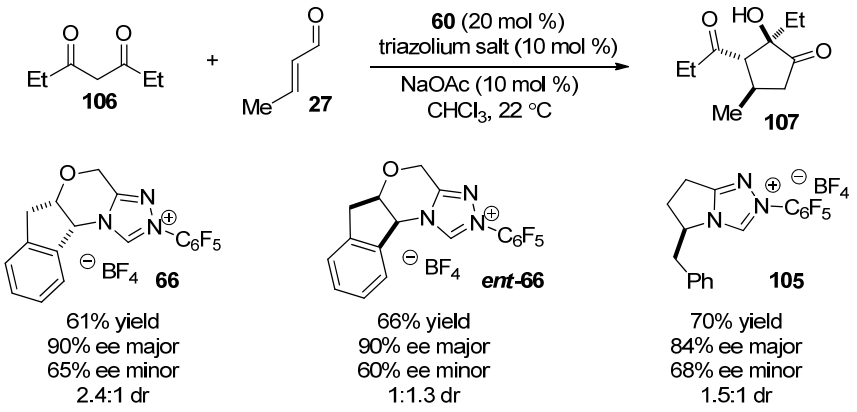
This result was unexpected considering the relatively small difference in size between methyl and ethyl groups of **67** and **106**, respectively. Although this difference cannot be completely explained, Suzuki and co-workers have reported a similar result (eq 12).[25]



Specifically, it was observed that intramolecular aldehyde ketone benzoin with methyl ketone **108a** gives product in 39% ee (~2:1 er) and the ethyl ketone **108b** affords the product in 90% ee (19:1 er). This example highlights the effect subtle changes in the ketone can have on the intramolecular benzoin reaction.

With substrate **106** in hand, we screened a number of chiral carbenes on this system (Scheme 26). Indeed, a small effect on diastereoselectivity was observed. Catalyst **66** affords the product in 2.4:1 dr while the antipode ***ent*-66** inverts the diastereoselectivity (1:1.5 dr). Both catalysts lower enantioselectivity of the minor diastereomer significantly.

Scheme 26.

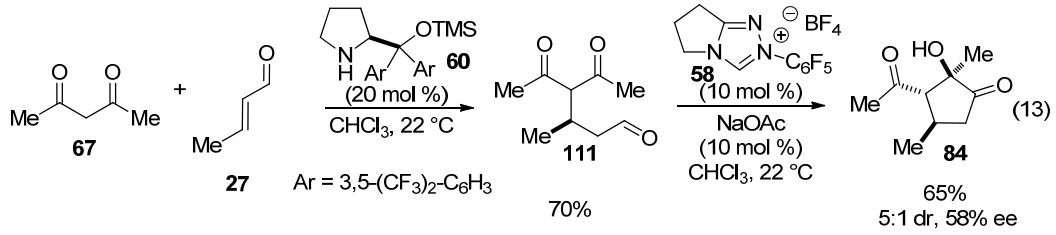


Although the use of chiral carbenes in our cascade sequence failed to significantly impact the diastereoselectivity of the reaction, the slight change observed with diketone **106** provides hope that a system could be developed to afford each diastereomer selectively.

4.5.5 Mechanistic Investigations

Having examined the scope of the reaction with respect to both aldehyde and nucleophile, we sought to better understand mechanistic aspects of the dual catalytic

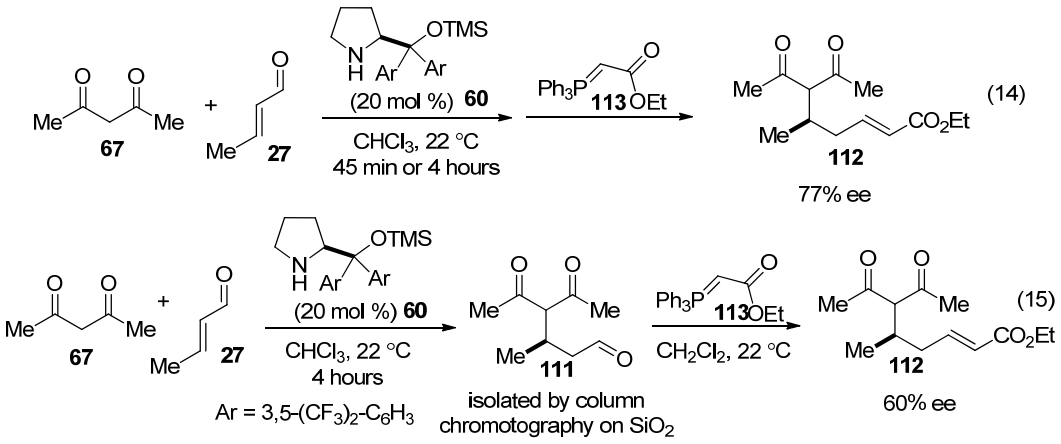
cycle. To elucidate this process, we performed the reaction in a stepwise manner. Acetylacetone and crotonaldehdye were treated with catalyst **58** in the absence of base or triazolium salt to afford, after isolation, the intermediate aldehyde **111** in 70% yield. This intermediate was then treated with triazolium salt **58** and sodium acetate. Surprisingly, the cyclopentanone product was obtained in much lower (58%) ee and diminished yield (eq 13).



We postulated that the disparity in enantioselectivity obtained between the one pot reaction (93% yield, 86% ee) and the sequential reaction (46% yield, 58% ee) might arise from a competitive retro-Michael process in the iminium-catalyzed conjugate addition step. The retro-Michael would result in erosion of ee by generating a thermodynamic equilibrium between starting materials and product. As asymmetric catalysis is only accomplished in a kinetic manifold, this equilibrium results in necessary racemization of the initially formed product.

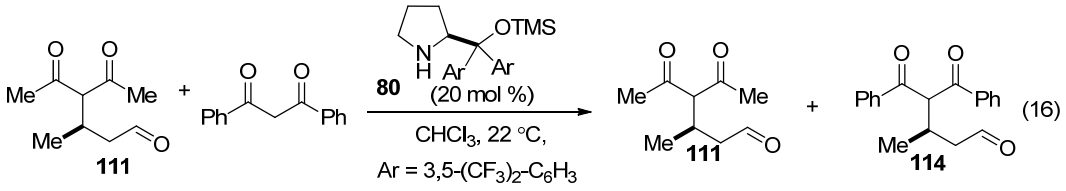
In order to examine the role of a retro-Michael reaction in ee erosion, a number of control experiments were conducted. In order to perform the control experiments, it was necessary to determine the enantioselectivity of the intermediate aldehyde. Due to the instability of the aldehyde and the difficulty associated with separating the enantiomers on chiral GC, we decided to convert the aldehyde to the more stable and more easily separated enoate **112** via Wittig reaction prior to isolation and analysis.

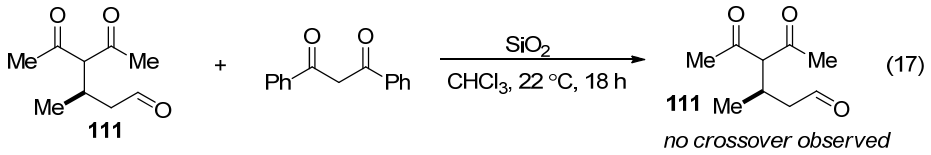
To determine the ee of the intermediate aldehyde formed under conjugate addition conditions, crotonaldehyde **27** and diketone **67** were treated with secondary amine catalyst **60** followed by *in situ* trapping with Wittig reagent. Enoate **112** is isolated in 76% ee (eq 14). This result differs both from the previously observed 58% ee of cyclopentanone **84** when the reaction is carried out in a step-wise fashion with isolation of the aldehyde as well as with the 86% ee observed in the one-pot sequence. We believed that silica gel could potentially facilitate epimerization of the intermediate aldehyde upon purification. Indeed, when intermediate aldehyde **111** was isolated by column chromatography and then subjected to the Wittig reaction, enoate **112** was obtained in 60% ee. This erosion suggests that silica gel is indeed promoting epimerization (eq 15).



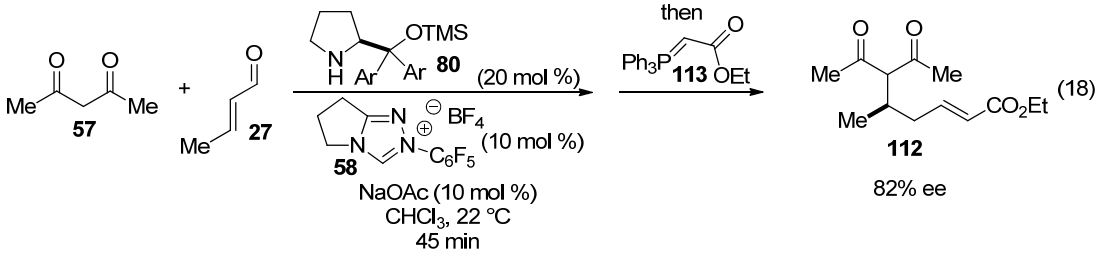
Further evidence for a retro-Michael induced epimerization emerged from a crossover experiment. Treatment of aldehyde **111** with prolinol **60** in the presence of dibenzoylmethane leads to generation of the crossover product in about 20% (eq 16). This crossover is exacerbated by silica gel (eq 16). However, no crossover is observed when the aldehyde is treated with only silca gel under identical conditions (eq 17). These reactions strongly suggest that a prolinol-mediated retro-Michael reaction is responsible

for the degradation of enantioselectivity in the two step reaction. This erosion is intensified by silica gel, explaining the significant drop in enantioselectivity of the final product obtained from an intermediate aldehyde that has been isolated and purified.





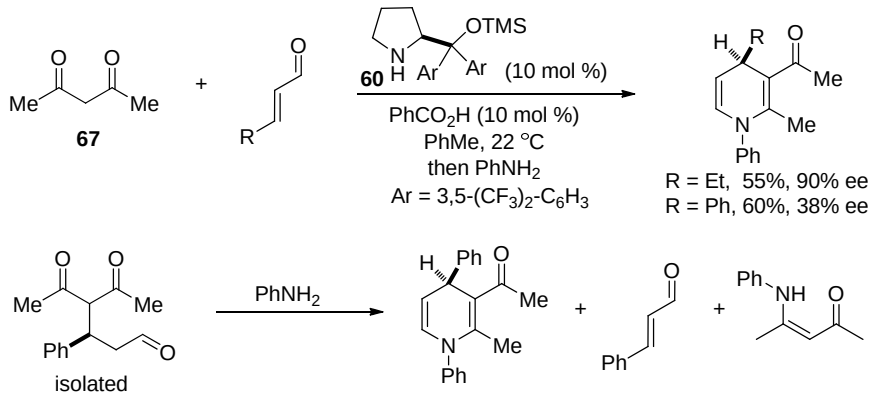
Finally, we were interested in determining the ee of the intermediate aldehyde in the one pot reaction. To this end, crotonaldehyde and diketone were stirred with amine, azolium and base for 45 minutes followed by addition of Wittig reagent **113.** Enoate **112** was isolated in 82% ee (eq 18) which matches closely with the 86% ee observed for cyclopentanone **84** in the one-pot reaction.



Based on the observation that intermediate aldehyde **111** is susceptible to a retro-Michael reaction under amine catalysis, we speculate that the carbene catalyst prevents this amine-catalyzed epimerization event by rapidly shuttling intermediate aldehyde **111** to product.

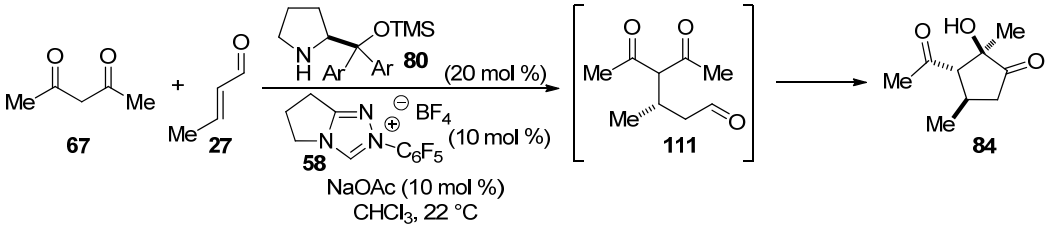
A competitive retro-Michael epimerization pathway may explain the lower enantioselectivities observed with certain substrates, aromatic enals with 1,3-diketons tend to generate the product with lower enantioslectivies than their alkyl counterparts. Indeed, Jorgensen has recently reported a similar retro-Michael-promoted empimerization of enals and 1,3-diketones (Scheme 27).[26] Notably, it was observed that aromatic aldehydes participate with much lower selectivity than alkyl aldehydes due to this retro-Michael process.

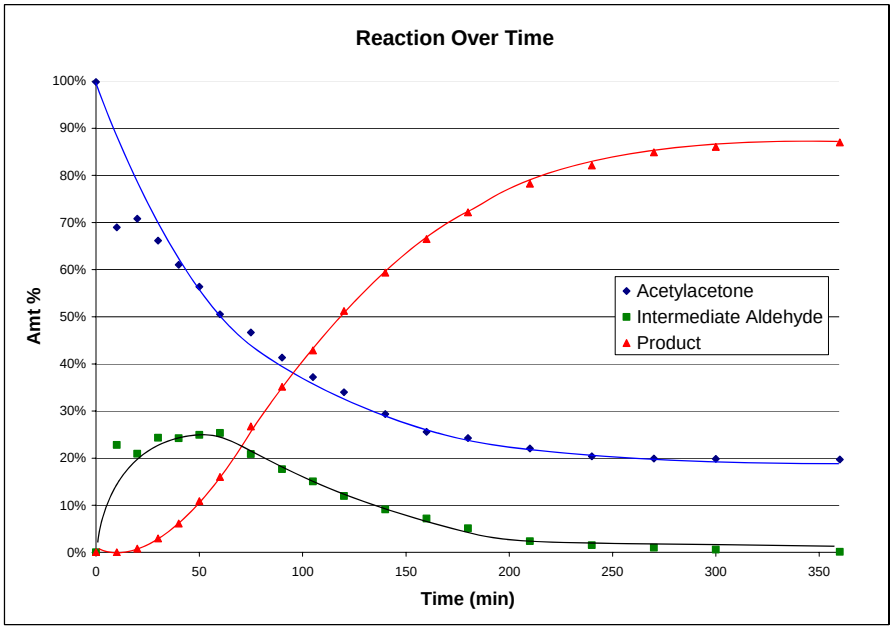
Scheme 27.



To lend final credence to the hypothesis that the intermediate aldehyde is shuttled rapidly to product in the one pot reaction, we monitored the reaction between aceytlacetone and crontonaldehdye by GC by withdrawing aliquots at regular intervals (Scheme 28). The GC data reveals only moderate build-up of intermediate aldehyde **111** is obtained with continuous formation of cyclopentanone **84**. This data suggests that both catalytic cycles are operating concurrently in the reaction flask.

Scheme 28.





The lower enantioselectivity observed for cyclopentanone **84** obtained from the stepwise process (58% vs 86% in the one-step process) highlights the power of this cascade process. Specifically, the presence of carbene catalyst **58** during the conjugate addition step facilitates formation of the desired product in high enantioselectivity by shuttling the retro-Michael prone aldehyde to product before significant epimerization can occur. In this way, cascade catalysis can enable reactivity that is not easily obtained in the stepwise process. The previously described cascade Michael/benzoin reaction has been recently published.[27]

4. 6 Conclusion

In summary, we have discovered that *N*-heterocyclic carbenes can be paired with secondary amine catalysts to rapidly afford functionalized products from simple, readily-available starting materials in multicatalytic cascade sequences. The described cascades have been utilized to afford both bicyclic lactone products and densely functionalized cyclopentanone products with good selectivity. Moreover, we have found that cascade sequence for the formation of cyclopentanones actually outperforms the stepwise process with respect to both yield and selectivity, and we have demonstrated that amine and carbene catalysts work concurrently to afford products with high enantioselectivity. These initial discoveries should allow for further studies aimed at utilizing *N*-hetereocyclic carbenes in multicatalytic cascade reactions.

4.7 References

[1] Tietze, L. F.; Brasche, G.; Gericke, K. M.; *Domino Reactions in Organic Synthesis* Wiley-VCH: Verlag GMbH and Co. KGaA: Weinheim Germany **2006**.

[2] Evans, D. A.; Starr, J. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787.

[3] For reviews see: (a) Ajamian, A.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 3754. (b) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (d) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, *46*, 1570. (e) Xinhong, Y.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.

[4] For review see: (a) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.

[5] Son, S. U.; Park, K. H.; Chung, Y. K. *J. Am. Chem. Soc.* **2002**, *124,* 6838.

[6] Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220.

[7] Cernak, T. A.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 3124.

[8] Zhao, G.-L.; Ullah, F.; Deiana, L.; Lin, S.; Zhang, Q.; Sun, J.; Ibrahem, I.; Dziedzic, P.; Cordova, A. *Chem. Eur. J.* **2010**, *16*, 1585.

[9] Simmons, B.; Walji, A.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4349.

[10] Schiff, H. *Liebigs Ann.* **1864**, *131*, 118.

[11] For a recent review of enamine catalysis see: Mukerjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

[12] For a recent review of iminium catalysis see: Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5471.

[13] Ahrendt, K. A.; Broth, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

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

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

[16] Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* **1991**, 1088.

[17] Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

[18] (a) Childs, R. F.; Dickie, B. D. *J. Am. Chem. Soc.* **1983**, *105*, 5041. (b) Pankratz, M; Childs, R. F. *J. Org. Chem.* **1985**, *50*, 4553. (c) Childs, R. F.; shaw, G. S.; Lock, C. J. L. *J. Am. Chem. Soc.* **1989**, *111,* 5424.

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

[20] Read de Alaniz, J.; Kerr, M. S.; Moore, J. L.; Rovis, T. *J. Org. Chem.* **2008**, *73*, 2033.

[21] Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Organic Reactions* **1959**, *10*, 179.

[22] (a) Reynolds, N. T.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126,* 9518. (b) Reynolds, N. T.; Rovis T. *J. Am. Chem. Soc.* **2005**, *127,* 16406. (c) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796. (d) Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 2860.

[23] (a) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2006**, *45*, 4305. (b) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Org. Chem*. **2006**, *12*8, 5475. (c) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2007**, *46*, 1101. (d) Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun*. **2006**, 4928. (e) Hayashi, Y.; Toyoshima, M.; Gotoh, H.; Ishikawa, H. *Org. Lett*. **2009**, *11*, 45. (f) Rueping, M.; Sugiono, E.; Merino, E. *Chem. Eur. J*. **2008**. *14*, 6329. (g) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 3699.

[24] Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

[25] Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 2713.

[26] Franke, P. T.; Johansen, R. L.; Bertelsen, S.; Jørgensen, K. A. *Chem. Asian J.* **2008**, *3*, 216.

[27] Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2009**, *131,* 13628.

Chapter 2 Experimental

First Generation Approach Towards Cephalimysin A

General Methods.

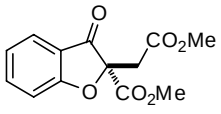
All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring unless otherwise stated. Reaction solvents including dichloromethane (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), toluene (PhMe), benzene, (PhH), Acetonitrile (MeCN), and Methanol (MeOH) were degassed with argon and passed through two columns of neutral alumina. HPLC grade Chloroform preserved with pentane was purchased from Fisher Scientific. ACS grade dimethyl sulfoxide (DMSO) was purchased from EDI chemical Inc. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light, cerium ammonium molybdenate, $KMnO_4$, or anisaldehyde stains followed by heating.

^1H nmr spectra were recorded on Varian 300 or 400 MHz spectrometers at ambient temperature unless otherwise stated. Data is reported as follows: chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm), toluene-d_8 (7.09, 7.0, 6.98, 2.09 ppm) or benzene-d_6 (7.16 ppm) multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). ^{13}C NMR was recorded on Varian 300 or 400 MHz spectrometers (at 75 or 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.2 ppm) or toluene-d_8 (137.86 (1), 129.4 (3), 128.33 (3), 125.49 (3), 20.4 (5) ppm). Infrared spectra were obtained on a Nicolet Avatar

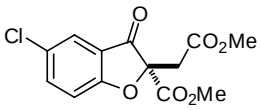
320 FT-IR spectrometer or Bruker Tensor 27 FT-IR spectrometer. Mass spectra were obtained on a Fisions VG Autospec.

General procedure for One-Pot, Two-Step oxa-Michael/Stetter Reaction.

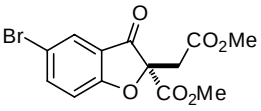
A 10 mL round bottom flask was equipped with a magnetic stir bar under argon and charged sequentially with DMAD (**11**) (33 μl, 0.268 mmol) and salicylaldehdye (**10**) (26 μL, 0.268 mmol). DCM (2.5 mL) was added and the mixture was cooled to 0 °C. Quinuclidene (6 mg, 0.054 mmol) was added and the reaction was monitored by TLC until consumption of **12** was observed (typically <30 min). Triazolium salt **15** (25 mg, 0.054 mmol) was added at this time. Upon completion of the reaction as determined by TLC analysis the mixture was filtered through a plug of silica and eluted with ~20 mL of Et_2O and concentrated *in vacuo*. The resulting crude product was purified via flash chromatography.



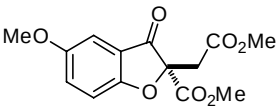
(*R*)-methyl 2-(2-methoxy-2-oxoethyl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (14). Isolated 53 mg, 75% yield; HPLC analysis-Chiracel IC column, 60:40 hexanes/*i*-PrOH, 0.7mL/min, major enantiomer: 14.9 min, minor enantiomer: 27.0 min, 91% ee; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.66 (m, 2H), 7.22 (d, 1H, J = 8.4 Hz), 7.14 (t, 1H, J = 7.5 Hz) 3.76 (s, 3H), 3.64 (s, 3H), 3.47 (d, 1H, J = 17.5 Hz), 3.10 (d, 1H, J = 17.5 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 194.6, 172.3, 169.0, 165.6, 138.7, 125.1, 123.1, 119.5, 113.7, 88.0, 53.8, 52.4, 38.5; IR (thin film/NaCl) 2950, 1747, 1614, 1465, 1214 cm^{-1}; HRMS $[C_{13}H_{13}O_6]^+$ cald 265.0707, found 265.0710.



(*R*)-methyl 5-chloro-2-(2-methoxy-2-oxoethyl)-3-oxo-2,3 dihydro-benzofuran-2-carboxylate (17a). Isolated 58 mg, 73% yield; HPLC analysis-Chiracel IC column, 50:50 hexanes/*i*-PrOH, 0.7mL/min, major enantiomer: 13.7 min, minor enantiomer: 20.7 min, 85% ee; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.65 (d, 1H, *J* = 2.3 Hz), 7.17 (d, 1H, *J* = 2.3 Hz), 7.60 (dd, 1H, *J* = 8.8, 2.3 Hz), 7.17 (d, 1H, *J* = 17.6 Hz), 3.77 (s, 1H), 3.65 (s, 1H), 3.45 (d, 1H, *J* = 17.6 Hz) 3.21 (d, 1H, *J* = 17.6 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 193.6, 170.7, 168.8, 165.2, 138.4, 128.7, 124.4, 121.0, 115.0, 88.9, 53.9, 52.5, 38.4; IR (thin film/NaCl) 2956, 1756, 1606, 1463, 1212 cm^{-1}; HRMS $[C_{13}H_{11}ClNaO_6]^+$ cald 321.0136, found 321.0137.

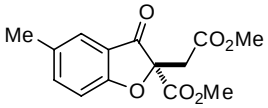


(*R*)-methyl 5-bromo-2-(2-methoxy-2-oxoethyl)-3-oxo-2,3 di-hydrobenzofuran-2-carboxylate (17b). Isolated 73 mg, 80% yield; HPLC analysis-Chiracel IC column, 50:50 hexanes/*i*-PrOH, 0.7mL/min, major enantiomer: 14.2 min, minor enantiomer: 20.5 min, 88% ee; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.79 (d, 1H, *J* = 8.7 Hz), 7.72 (dd, 1H, *J* = 8.8, 1.6 Hz), 7.12 (d, 1H, *J* = 8.8 Hz) 3.75 (s, 1H), 3.63 (s, 1H) 3.42 (d, 1H, *J* = 17.6 Hz), 3.20 (d, 1H, *J* = 17.6 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 193.4, 171.0, 168.8, 165.2, 141.1, 127.5, 121.5, 115.6, 88.7, 53.9, 52.5, 38.4 ; IR (thin film/NaCl) 2950, 1757, 1737, 1609, 1460, 1440, 1214 cm^{-1}; HRMS $[C_{13}H_{11}BrNaO_6]^+$ cald 364.9631, found 364.9637.

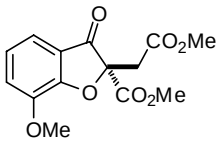


(*R*)-methyl 5-methoxy-2-(2-methoxy-2-oxoethyl)-3-oxo-2,3-di-hydrobenzofuran-2-carboxylate (17c). Isolated 54 mg, 68% yield; HPLC analysis-Chiracel IC column, 50:50 hexanes/*i*-PrOH, 1.0 mL/min, major enantiomer: 40.7 min, minor enantiomer: 24.5 min, 73% ee; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 8.6 Hz), 6.68 (m, 2H), 3.88 (s, 3H), 3.77 (s, 3H), 3.67 (s, 3H), 3.48 (d,

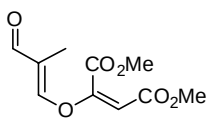
1H, J = 17.4 Hz) 3.00 (d, 1H, J = 17.4 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 192.0, 175.0, 169.2, 169.0, 165.9, 126.2, 112.9, 112.2, 96.6, 88.9, 56.1, 53.7, 52.4, 38.5 ; IR (thin film/NaCl) 2950, 1747, 1711, 1614, 1440, 1286 cm^{-1}; HRMS $[C_{14}H_{15}O_7]^+$ cald 295.0812, found 295.0812.



(*R*)-methyl 2-(2-methoxy-2-oxoethyl)-5-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (17d). Isolated 60 mg, 80% yield; HPLC analysis-Chiracel IC column, 60:40 hexanes/*i*-PrOH, 0.7 mL/min, major enantiomer: 15.6 min, minor enantiomer: 19.7 min, 79% ee; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.47 (m,2H), 7.12 (m, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 3.46 (d, 1H, J = 17.4 Hz), 3.09 (d, 1H, J = 17.4 Hz), 2.35 (s, 3H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 194.7, 170.9, 169.0, 165.8, 140.0, 132.8, 124.5, 119.4, 113.3, 88.3, 53.7, 52.4, 38.6, 20.7 ; IR (thin film/NaCl) 2953, 1747, 1721, 1619, 1490, 1209 cm^{-1}; HRMS $[C_{14}H_{14}O_6]^+$ cald 279.0863, found 279.0865.

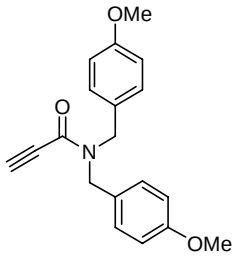


(*R*)-methyl 7-methoxy-2-(2-methoxy-2-oxoethyl)-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (17d). Isolated 59 mg, 75% yield; HPLC analysis-Chiracel IC column, 60:40 hexanes/*i*-PrOH, 0.7 mL/min, major enantiomer: 19.9 min, minor enantiomer: 33.5 min, 91% ee; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.28 (dd, 1H, J = 7.7, 1.2 Hz), 7.16 (dd, 1H, J = 7.7, 1.2 Hz), 7.09 (t, 1H, J = 7.8 Hz) 3.96 (s, 3H), 3.75 (s, 3H), 3.63 (s, 3H), 3.46, (d, 1H, J = 17.6 Hz), 3.30 (d, 1H, J = 17.6 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 195.0, 168.8, 165.6, 162.4, 146.5, 123.6, 121.1, 119.3, 116.0, 88.3, 56.4, 53.9, 52.4, 38.4, ; IR (thin film/NaCl) 2956, 1723, 1617, 1504, 1438, 1206 cm^{-1}; HRMS $[C_{14}H_{14}NaO_7]^+$ cald 317.0632, found 317.0637.



dimethyl 2-(((*E*)-2-methyl-3-oxoprop-1-en-1-yl)oxy)maleate (22)

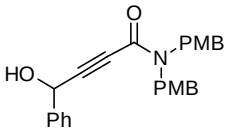
To a solution of **21**[1] (20 mg, 0.16 mmol) in 8 mL of a 1:1 mixture of DCM/MeCN was added DMAD (**11**) (40 μL, 0.32 mmol) dropwise over 5 min. The reaction was allowed to stir 12 h. Upon completion the reaction was quenched with sat NH_4Cl and diluted with Et_2O. The organics were separated and the aqueous layer was washed with Et_2O. The organics were combined and washed with H_2O and brine dried with $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by column chromatography 3:1 hexanes/EtOAc (R_f = 0.3, 3:1, hexanes/EtOAc) affords 28mg, 76% yield of **22** as a 6:1 mixture of *E* to *Z* isomers. ^{1}H nmr (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.15 (q, 1H, *J* = 1.3, 2.6 Hz) 5.73, (s, 1H), 3.93 (s, 3H), 3.77 (s, 3H) 1.79 (d, 3H, *J* = 1.3 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 159.6, 159.4, 153.7, 130.1, 129.2, 128.2, 127.8, 114.4, 114.3, 79.6, 77.6, 77.3, 77.0, 76.2, 55.5, 55.4, 50.7, 45.5; IR (thin film/NaCl) 2957, 1726, 1685, 1638, 1438, 1369, 1154, cm^{-1}; HRMS $[C_{10}H_{10}O_6]^+$ calcd 229.0707, found 299.0701.



_N,N_-bis(4-methoxybenzyl)propiolamide (49)

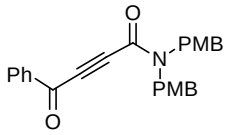
To a solution of propiolic acid (**30**) (4 mL, 64.6 mmol) in 55 mL of THF was added LiH (568 mg, 67.1 mmol) portion wise with periodic cooling in an ice bath to keep the reaction at room temperature. After addition was complete, the mixture was stirred at room temperature for 18 h then cooled to – 10 °C (ice/brine bath). A solution of ethyl chloroformate (6 mL, 62.7 mmol) in 10 mL of THF was added dropwise over ~ 20 min. After addition the reaction was allowed to warm to room temperature and stirred a further 45 min. The mixture is then cooled to 0 °C and a solution of di-*para*-methoxybenzyl amine in 20 mL of THF is added dropwise over 30 min. The reaction was then allowed to stir 4 h and then concentrated *in vacuo*. The thick residue was dissolved in DCM and washed sequentially with 10% $NaHCO_3$, 1M HCl, H_2O, brine,

dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification via column chromatography 3:1 hexanes/EtOAc (R_f = 0.3, hexanes/EtOAc) affords 12.0 g, 62% yield of **49** as a yellow oil which solidifies into a waxy solid upon solid upon standing. ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.14 (d, 2H, *J* = 8.7 Hz), 7.11 (d, 2H, *J* = 8.7 Hz) 6.87 (d, 2H, *J* = 8.7 Hz) 6.83 (d, 2H, *J* = 8.7 Hz), 4.57 (s, 2H), 4.38 (s, 2H) 3.78 (s, 3H), 3.76, (s, 3H), 3.16 (s, 1H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 159.6, 159.4, 153.7, 130.1, 129.2, 128.2, 127.8, 114.4, 114.3, 79.6, 77.6, 77.3, 77.0, 76.2, 55.5, 55.4, 50.7, 45.5 ; IR (thin film/NaCl) cm^{-1}; HRMS $[C_{19}H_{19}O_3]^+$ calcd 309.13515, found 309.13649.



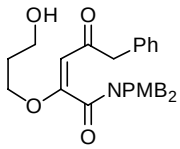
4-hydroxy-*N,N*-bis(4-methoxybenzyl)-4-phenylbut-2-ynamide (50). To a solution of LiHMDS (6.0 g, 35.9 mmol) in 250 mL of THF at -78 °C was added a solution of ynamide **49** (10.0 g, 32.3 mmol) in 40 mL of THF over 30 min via syringe pump. After an additional 30 min of stirring a solution of freshly distilled phenylacetyl aldehyde (4.3 mL, 38.8 mmol) was added via syringe over 5 min. After an additional 30 min of stirring the reaction was quenched with sat NH_4Cl and allowed to warm to room temperature. The reaction was dilluted with Et_2O and the organic layer was seperated and washed with H_2O and brine and dried over $MgSO_4$. Solvent was removed *in vacuo*. Purification via column chromotography 2:1 hexanes/EtOAc (R_f = 0.3, 1:1 hexanes/EtOAc) yields 10.4 g, 74% yield of **50** as a yellow oil. ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.18 (m, 5H), 7.08 (m, 4H), 6.86 (m, 4H), 4.77 (t, 1H, *J* = 7.3), 4.38 (s, 2H), 4.37 (s, 2H), 3.82 (s, 3H), 3.80, (s, 3H), 3.08 (dd, 1H, *J* = 6.4, 13.5 Hz), 3.03 (dd, 1H, *J* = 7.1, 13.5 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 159.5, 159.4, 154.6, 136.3, 130.1, 130.0, 129.3, 128.7, 128.3, 128.0, 127.6, 114.4, 114.3, 92.8, 78.3, 63.4, 55.6, 55.5, 50.7, 45.5, 43.6, ; IR (thin

film/NaCl) 3375 br, 2932, 2235, 1611, 1512, 1456, 1249, 1034 cm^{-1}; HRMS $[C_{27}H_{27}NO_4]^+$ calcd 429.19401, found 429.19239.



***N,N*-bis(4-methoxybenzyl)-4-oxo-4-phenylbut-2-ynamide (51)**

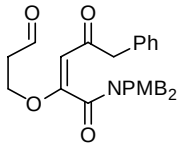
To a solution of alcohol **50** (10.4 g, 24.1 mmol) in 250 mL of DCM was added Dess-Martin periodane (15.3 g, 36.2 mmol). Upon consumption of starting material as determined by TLC analysis (~ 1 h) the reaction was quenched with a 1:1 mixture of sat. $NaHCO_3$/sat. $Na_2S_2O_3$ (250 mL) and allowed to stir till the organic layer becomes clear. The mixture is then diluted with Et_2O and the organic layer was separated and washed with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford 10.2 g, 99% yield of a yellow oil. Yamide **51** is used in the next reaction without further purification. ^1H nmr (400 MHz, $CDCl_3$) δ 7.25 (m, 3H), 7.10 (d, 2H, *J* = 8.8 Hz), 7.02 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 6.85 (d, 2H, *J* = 8.8 Hz), 4.38 (s, 2H), 4.33 (s, 2H), 3.89 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 193.4, 183.4, 159.5, 159.3, 131.7, 129.9, 129.7, 129.0, 128.9, 127.7, 127.5, 126.9, 114.3, 114.1, 98.5, 85.7, 81.5, 55.3, 55.2, 51.9, 50.4.



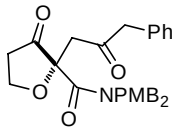
(*E*)-2-(3-hydroxypropoxy)-*N,N*-bis(4-methoxybenzyl)-4-oxo-5-phenylpent-2-enamide (52).

50 mL of 1,3 propane diol was added to yamide **51** (7.0 g, 16.4 mmol) followed by CuOTf•PhMe (847 mg, 1.64 mmol). The mixture was heated to 70 °C and allowed to stir 15 h. Upon completion the reaction was diluted with EtOAc and filtered through a plug of silica gel and eluted with EtOAc. The organics were combined and washed with H_2O 2Xs and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude material via column chromatography 1:4 hexanes/EtOAc (R_f = 0.2, 1:1

hexanes/EtOAc) afforded 5.3 g, 64% yield of **52** as a brown oil. ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.24 (m, 7H) 7.01 (d, 2H, *J* = 8.8 Hz), 6.84 (d, 2H, *J* = 8.8 Hz), 6.80 (d, 2H, *J* = 8.8), 5.59 (s, 1H), 4.47 (s, 2H), 4.11 (s, 2H), 3.88 (t, 2H, *J* = 6.2 Hz), 3.78 (s, 3H), 3.77 (s, 3H), 3.70 (s, 2H) 3.63 (t, 2H, *J* = 5.9 Hz), 1.85 (q, 2H, *J* = 6.0, 12.0 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 194.9, 165.6, 164.1, 159.1, 158.9, 134.7, 130.1, 129.5, 129.3, 128.7, 127.9, 127.4, 126.4, 113.9, 113.8, 99.8, 66.8, 58.5, 55.2, 50.7, 49.7, 45.3, 31.3; IR (thin film/NaCl) 3423 br, 2934, 2836, 1681, 1646, 1612, 1513, 1420, 1248, 1110 cm^{-1}; HRMS $[C_{30}H_{33}NO_6]^+$ calcd 504.2381, found 504.2381.

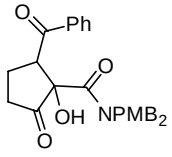


(*E*)-*N*,*N*-bis(4-methoxybenzyl)-4-oxo-2-(3-oxopropoxy)-5-phenylpent-2-enamide (53). To a solution of alcohol **52** (5.3 g, 10.5 mmol) in 105 mL of DCM was added Dess-Martin periodane (6.7 g, 15.8 mmol) Upon consumption of starting material as determined by TLC (~ 1h) hexanes was added and the resulting white solid was removed via filtration add washed with Et_2O. The filtrate was washed with 1 M HCl, sat $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography 2:1 hexanes/EtOAc containing 0.5% AcOH. The collected fractions were combined and washed with sat. $NaHCO_3$, H_2O, brine and dried over $MgSO_4$ and concentrated *in vacuo* to yield 3.9 g, 74% yield of **53** as a yellow oil. The product was found to be highly unstable and used in the next reaction immediately. ^{1}H nmr (400 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.27 (m, 7H), 7.00 (d, 2H, *J* = 8.6 Hz), 6.85 (d, 2H, 8.7 Hz) 6.82 (d, 2H, *J* = 8.7 Hz), 5.59 (s, 1H), 4.48 (s, 2H), 4.08 (s, 2H), 4.06 (t, 2H, *J* = 6.1 Hz), 3.80 (s, 6H), 3.74 (s, 2H), 2.80 (t, 2H, *J* = 6.0 Hz) ;



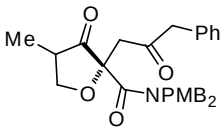
(*S*)-*N*,*N*-bis(4-methoxybenzyl)-3-oxo-2-(2-oxo-3-phenylpropyl)-tetrahydrofuran-2-carboxamide (54)

Triazolium salt **43** (151 mg, 0.32 mmol) was added to a flame dried round bottom flask under argon. 160 mL of toluene was added to flask and argon was bubbled through the mixture for 5 min followed by addition of KHMDS (57 mg, 0.30 mmol) as solution in 10 mL of toluene. The reaction is allowed to stir for 10 min at ambient temperature and then placed in a 60 °C oil bath and allowed to stir for 5 min. To the mixture was added aldehyde **54** (791 mg, 1.6 mmol) in 10 mL of toluene over 10 min. The reaction was allowed to stir a further 12 h, upon completion the mixture was allowed to cool to room temperature and filtered through a pad of silica and eluted with EtOAc. The organics were combined and concentrated *in vacuo*. The crude product was purified via column chromatography 3:1 hexanes/EtOAc (R_f = 0.5, 1:1 hexanes/EtOAc) to afford 515 mg, 65 % yield of a yellow oil. HPLC-analysis Chiracel AD-H column, 70:30 hexanes/*i*-PrOH, 1.0 mL/min: major enantiomer 18.2 min, minor enantiomer 33.0 min, 89% ee. ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.22 (m, 4H), 7.02 (m, 5H), 6.87 (m, 4H), 4.62 (d, 1H, *J* = 15.7 Hz) 4.46 (d, 1H, 16.9 Hz), 4.37 (s, 2H), 4.21 (ddd, *J* = 6.2, 8.9, 8.9 Hz) 4.07 (ddd, 1H, *J* = 6.5, 8.9, 8.9 Hz), 3.81 (s, 3H), 3.79 (s, 3H), 3.60 (s, 2H), 3.29 (d, 1H, *J* = 17.8 Hz), 3.20 (d, 1H, *J* = 17.8 Hz), 2.78 (ddd, 1H, *J* = 6.5, 8.8, 18.2 Hz), 2.55 (ddd, 1H, *J* = 6.2, 8.9, 18.2 Hz) ; ^{13}C nmr (100 MHz, $CDCl_3$) δ 208.0, 203.2, 167.6, 159.0, 133.1, 129.7, 129.4, 128.7, 128.0, 127.2, 114.2, 114.0, 83.8, 64.4, 55.3, 50.2, 48.6, 47.9, 46.4, 35.0 ; IR (thin film/NaCl) 2928, 2837, 2251, 1770, 1720, 1634, 1612, 1585, 1302, cm^{-1}; HRMS $[C_{30}H_{32}NO_6]^+$ calcd 502.2224, found 502.2234.



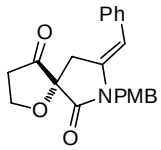
2-benzoyl-1-hydroxy-N,N-bis(4-methoxybenzyl)-5-oxocyclopentane-carboxamide (55). ^{1}H nmr (400 MHz, C_6D_6) δ 7.03 (m, 8H), 6.77, (d, 4H, *J* = 8.6 Hz), 4.96 (s, 1H), 4.68 (d, 1H, *J* = 15.7), 4.60 (d, 1H, *J* = 14.6 Hz),

4.49 (d, 1H, *J* = 14.6 Hz), 4.42 (d, 1H, *J* = 15.7 Hz), 3.68 (t, 1H, *J* = 6.9 Hz), 3.54 (d, 1H, *J* = 15.6 Hz), 3.47 (d, 1H, *J* = 15.6 Hz), 3.33 (s, 3H), 3.28 (s, 3H), 2.30 (ddd, 1H, *J* = 5.9, 9.5, 19.1 Hz), 2.15 (ddd, 1H, *J* = 6.2, 9.7, 19.1 Hz), 1.82 (m, 1H), 1.65 (m, 1H); ^{13}C nmr (100MHz,C_6D_6)δ 210.0, 208.6, 170.0, 159.8, 159.7, 133.5, 130.1, 130.0, 129.3, 129.1, 128.9, 128.7, 128.2, 127.9, 127.4, 114.6, 114.5, 83.97, 54.9, 54.8, 53.12, 49.7, 47.5, 34.1, 21.9; IR (thin film/NaCl) 3420 br, 1759, 1709, 1612, 1512, 1302, cm^{-1}; HRMS $[C_{30}H_{32}NO_6]^+$ calcd 502.2224, found 502.2228.



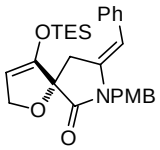
(2*S*)-*N*,*N*-bis(4-methoxybenzyl)-4-methyl-3-oxo-2-(2-oxo-3-phenylpropyl)tetrahydrofuran-2-carboxamide (45). Triazolium salt **43** (4.0 mg, 0.008 mmol) was added to a flame dried round bottom flask under argon. 3 mL of toluene was added to the flask and argon was bubbled through the mixture for 5 min followed by addition of KHMDS (1.4 mg, 0.007 mmol) as a solution in 0.5 mL of toluene. The reaction is allowed to stir for 10 min at ambient temperature and then placed in an 80 °C oil bath and allowed to stir for 5 min. To the mixture was added aldehyde **44** (20 mg, 0.40 mmol) in 0.5 mL of toluene dropwise via syringe. The reaction was allowed to stir a further 12 h, upon completion the mixture was allowed to cool to room temperature and then filtered through a pad of silica and eluted with EtOAc. The organics were combined and concentrated *in vacuo*. The crude product was purified via column chromatography 1:1 hexanes/EtOAc (R_f = 0.1 3:1 hexanes/EtOAc) to afford 9 mg, 44% yield of **45** as a 3:1 mixture of diastereomers. HPLC-analysis Chiracel AD-H column, 70:30 hexanes/*i*-PrOH, 1.0 mL/min: Major diastereomer: major enantiomer 17.8 min, minor enantiomer 23.6 min, 89% ee. Minor diastereomer: major enantiomer 35.9 min, minor enantiomer 19.1 min. ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.17 (m, 5H), 6.99 (m, 4H), 6.80 (m, 4H), 4.65 (d, 1H, *J* = 15.7

Hz), 4.42 (d, 1H, *J* = 14.2 Hz), 4.39 (t, 1H, *J* = 9.0 Hz) 4.34 (d, 1H, *J* = 15.7 Hz), 4.20 (dd, 1H, *J* = 8.2, 9.7 Hz), 4.14 (d, 1H, *J* = 15.7 Hz), 3.76 (s, 3H), 3.73 (s, 3H), 3.54 (s, 2H), 3.30 (d, 1H, *J* = 17.9 Hz), 3.12 (d, 1H, *J* =17.9 Hz), 2.60 (m, 1H), 1.20 (d, 3H, *J* = 6.9 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 208.9, 203.2, 168.1, 159.0, 133.2, 129.7, 129.4, 128.8, 128.0, 127.2, 114.2, 114.0, 83.9, 71.5, 55.3, 55.4, 50.2, 48.7, 47.8, 46.8, 40.1, 11.2; IR (thin film/NaCl) 2932, 2361, 1770, 1718, 1635, 1612, 1511, 1301 cm^{-1}; HRMS $[C_{30}H_{32}NO_6]^+$ calcd 516.2381, found 516.2370.

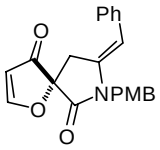


(*S,E*)-8-benzylidene-7-(4-methoxybenzyl)-1-oxa-7-azaspiro[4.4]nonane-4,6-dione (60). Dihydrofuranone **54** (2.0 g, 4.0 mmol) was dissolved in DCM (20 mL) and cooled to 0 °C. TFA (20 mL) was then added and the reaction was allowed to stir at 0 °C. Upon consumption of starting material as determined by TLC analysis the DCM and TFA were removed under reduced pressure. The resulting crude material was dissolved in toluene (40 mL) and *para*-toluenesulfonic acid (15 mg, 0.08 mmol) was added. The reaction flask was equipped with a Dean-Stark condenser and heated to reflux. Upon completion of the reaction as determined by TLC analysis the reaction was allowed to cool to room temperature and the solvent was removed *in vacuo*. The resulting crude material was purified via column chromatography 2:1 hexanes/EtOAc (R_f = 0.3, 2:1 hexanes/EtOAc) to afford 888 mg, 61% yield of **60** as yellow oil in a 6:1 mixture of *E/Z* olefin isomers. ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.25 (t, 2H, *J* = 7.3), 7.19 (d, 2H, *J* = 8.7 Hz), 7.13 (t, 3H, *J* = 8.2), 6.86 (d, 2H, *J* = 8.7 Hz), 5.86 (t, 1H, *J* = 2.1 Hz), 4.73 (d, 1H, *J* = 15.5 Hz), 4.65 (q, 1H, *J* = 9.0 Hz), 4.64 (d, 1H, *J* = 15.5 Hz), 4.33 (dt, 1H, *J* = 4.6, 9.0 Hz), 3.79 (s, 3H), 3.20 (dd, 1H, *J* = 2.1, 16.8 Hz), 2.96 (dd, 1H, *J* = 2.1, 16.8 Hz), 2.75 (ddd, 1H, *J* = 4.6, 7.9, 18.4 Hz), 2.59 (dt, 1H, *J* = 8.6, 18.4 Hz); ^{13}C nmr (100

MHz, $CDCl_3$) δ 211.7, 171.0, 159.0, 136.1, 135.7, 128.5, 128.2, 127.9, 127.0, 126.1, 114.2, 106.0, 83.0, 65.2, 55.2, 43.7, 35.9, 34.3; IR (thin film/NaCl) 2360, 1759, 1716, 1654, 1513, 1305, cm^{-1}; HRMS $[C_{22}H_{22}NO_4]^+$ calcd 364.1543, found 364.1545.

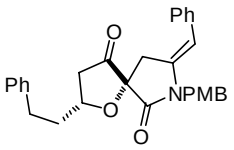


(*S*,*E*)-8-benzylidene-7-(4-methoxybenzyl)-4-((triethylsilyl)oxy)-1-oxa-7-azaspiro[4.4]non-3-en-6-one (61). To spirocycle **60** (125 mg, 0.34 mmol) in DCM (4 mL) at 0 °C was added sequentially triethylamine (96 μL, 0.69 mmol) and TESOTf (117 μL, 0.52 mmol). Upon consumption of starting material as determined by TLC analysis, the reaction was diluted with Et_2O and washed sequentially with sat. $NaHCO_3$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude material by column chromatography affords 161 mg (98% yield) of **61** as a colorless oil.

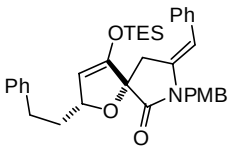


(*S*,*E*)-8-benzylidene-7-(4-methoxybenzyl)-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (62). To a solution of enol ether **61** (124 mg, 0.26 mmol) in DCM (6.5 mL) at room temperature was added 2,4,6 collidine (100 μL, 0.75 mmol), and triphenylcarbenium tetrafluoroborate (343 mg, 1.04 mmol). Upon completion of the reaction as determined by TLC analysis the mixture was diluted with Et_2O and washed with H_2O and brine, died over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by column chromatography 2:1 hexanes/EtOAc (R_f = 0.4, 1:1 hexanes/EtOAc) affords 80 mg (85% yield) of **62** as a yellow oil. ^1H nmr (400 MHz, $CDCl_3$) δ 8.41 (d, 1H, *J* = 2.6 Hz), 7.25 (m, 4H), 7.14 (m, 3H), 6.88 (d, 2H, *J* = 8.6), 5.96 (t, 1H, *J* = 2.1 Hz), 5.78 (d, 1H, *J* = 2.6 Hz), 4.88, (d, 1H, *J* = 15.6 Hz), 4.78 (d, 1H, *J* = 15.6 Hz), 3.80 (s, 3H), 3.47 (dd, 1H, *J* = 2.1, 16.9), 3.28 (dd, 1H, *J* = 2.1, 16.9); ^{13}C nmr (100 MHz, $CDCl_3$) δ 200.4, 178.8, 159.1, 153.3, 135.0, 128.5, 128.3, 127.9, 126.7, 126.3, 114.3, 106.8, 106.5, 87.2,

55.2, 44.4, 33.2 cm^{-1}; IR (thin film/NaCl) 2926, 2853, 1729, 1704, 1660, 1612, 1562, 1305 cm^{-1}; HRMS $[C_{22}H_{20}NO_4]^+$ calcd 362.1387, found 362.1375.

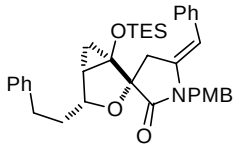


(2*S*,5*S*,*E*)-8-benzylidene-7-(4-methoxybenzyl)-2-phenethyl-1-oxa-7-azaspiro[4.4]nonane-4,6-dione (63). A solution of enone **62** (40 mg, 0.11 mmol) and copper(I) iodide (53 mg, 0.28 mmol) in THF (3.5 mL) was cooled to -78 °C. To the cold mixture was added phenethyl magnesium chloride (277 μL of a 1.0 M soln in THF), 0.28 mmol) drop wise via syringe. Upon completion of the reaction as determined by TLC analysis sat NH_4Cl was added and the mixture was diluted with Et_2O. The aqueous layer was separated and the organics were washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by column chromatography 6:1 hexanes/EtOAc (R_f = 0.5, 2:1 hexanes/EtOAc) affords 47 mg (90% yield) of a clear oil as a single diastereomer. ^1H nmr (300 MHz, $CDCl_3$) δ 7.23 (m, 12H), 6.88 (2, 2H, *J* = 9.0 Hz) 5.87 (t, 1H, *J* = 1.8 Hz), 4.97 (m, 1H), 4.83 (d, 1H, *J* = 15.9 Hz), 6.72 (d, 1H, *J* = 15.9), 3.79 (s, 3H), 3.30 (dd, 1H, *J* = 1.8, 16.8 Hz), 3.09 (dd, 1H, *J* = 1.8, 16.8 Hz), 2.86 (dd, 1H, *J* = 6.6, 18.3), 2.80 (m, 2H), 2.29 (dd, 1H, *J* = 9.0, 18.3 Hz), 2.04 (m, 2H).

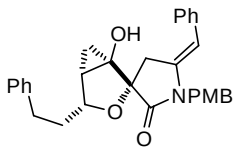


(2*S*,5*S*,*E)*-8-benzylidene-7-(4-methoxybenzyl)-2-phenethyl-4-((triethylsilyl)oxy)-1-oxa-7-azaspiro[4.4]non-3-en-6-one (64). To spirocycle **63** (47 mg, 0.10 mmol) in DCM (1.5 mL) at 0 °C was added sequentially triethylamine (35 μL, 0.25 mmol) and TESOTf (46 μL, 0.20 mmol). Upon consumption of starting material as determined by TLC analysis, the reaction was diluted with Et_2O and washed sequentially with sat. $NaHCO_3$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude material by column chromatography 9:1

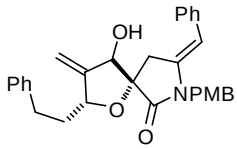
hexanes/EtOAc (R_f = 0.4, 3:1 hexanes/EtOAc) affords 54 mg (92% yield) of **64** as a colorless oil. ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.20 (m, 12H), 6.82 (d, 2H, *J* = 8.7 Hz), 5.78 (t, 1H, *J* = 1.8 Hz), 5.16 (dt, 1H, *J* = 1.2, 4.8 Hz), 4.93 (d, 1H, *J* = 15.3), 4.81 (d, 1H, *J* = 1.2 Hz), 4.66 (d, 1H, *J* = 15.3 Hz), 3.28 (dd, 1H, *J* = 1.8, 16.5 Hz), 3.04 (dd, 1H, *J* = 1.8, 16.5 Hz), 2.18 (m, 2H), 1.90 (m, 2H), 0.88 (t, 9H, *J* = 12 Hz), 0.67 (q, 6H, *J* = 12 Hz).



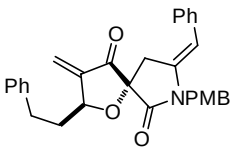
(*1R,2S,4S,5S,E*)-5'-benzylidene-1'-(4-methoxybenzyl)-4-phenethyl-1-((triethylsilyl)oxy)-3-oxaspiro[bicyclo[3.1.0]hexane-2,3'-pyrrolidin]-2'-one (65b). To a solution of enol ether **64** (182 mg, 0.31 mmol) in DCM (4 mL) at 0 °C was added diethylzinc (123 μL, 52% wt, 0.63 mmol) dropwise and the mixture was allowed to stir for 5 min. Chloroiodomethane (91 μL, 1.25 mmol) was added dropwise and the reaction was allowed to warm to room temperature. The reaction was allowed to stir 2 h further (monitoring the reaction by TLC was not possible since starting material and product have the same R_f) and then cooled to 0 °C and quenched with sat. NH_4Cl and diluted with Et_2O. The organic phase is washed with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude product which could be utilized in the deprotection without further purification. However analytically pure material could be obtained by purification via column chromatography 9:1 hexanes/EtOAc (R_f = 0.4, 3:1 hexanes, EtOAc) to afford 129 mg (69% yield) of **65b** as a colorless oil. ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.28 (m, 12H), 6.86 (d, 2H, *J* = 8.4 Hz), 5.87 (t, 1H, *J* = 1.8 Hz), 5.03 (d, 1H, *J* = 15 Hz), 5.58 (d, 1H, *J* = 15 Hz), 3.97 (dd, 1H, *J* = 5.1, 8.4 Hz), 3.80 (dd, 1H, *J* = 1.8, 16.2 Hz), 3.79 (s, 3H), 2.90 (dd, 1H, *J* = 1.8, 16.2 Hz), 2.80 (m, 2H), 1.92 (m, 2H), 1.72 (t, 1H, *J* = 5.4 Hz), 1.53 (dd, 1H, *J* = 5.1, 9.3 Hz), 1.15 (dd, 1H, *J* = 6.3 Hz, 9.3 Hz), 0.78 (t, 9H, *J* = 8.1 Hz), 0.45 (q, 6H, *J* = 7.2 Hz).



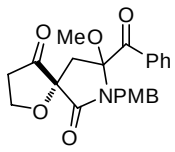
(*1R,2S,4S,5S,E*)-5'-benzylidene-1-hydroxy-1'-(4-methoxybenzyl)-4-phenethyl-3-oxaspiro[bicyclo[3.1.0]hexane-2,3'-pyrrolidin]-2'-one (65). To crude siloxycyclopropane **65b** (76 mg, 0.13 mmol) in THF (1.5 mL) at 0 °C was added TBAF (130 μL of a 1.0 M soln in THF, 0.13 mmol). Upon completion of the reaction as determined by TLC analysis (< 30 min) the mixture is diluted with EtOAc and washed with H_2O, brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification of the crude product by column chromatography affords 34 mg (55% yield over the two steps) of cyclopropanol **65** as a colorless oil. ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.26 (m, 12H), 6.85 (d, 2H, *J* = 9.0 Hz), 5.86 (t, 1H, *J* = 2.1 Hz), 4.85 (d, 1H, *J* = 15.3 Hz), 4.75 (d, 1H, *J* = 15.3 Hz), 3.96 (dd, 1H, *J* = 5.4, 8.4 Hz), 3.78 (dd, 1H, *J* = 2.1, 15.9 Hz), 3.77 (s, 3H), 2.95 (dd, 1H, *J* = 2.1, 15.9 Hz), 2.76 (m, 2H), 1.72 (m, 2H), 1.14 (dd, 1H, *J* = 5.1 Hz, 8.4 Hz).



(*2S,4R,5S,E*)-8-benzylidene-4-hydroxy-7-(4-methoxybenzyl)-3-methylene-2-phenethyl-1-oxa-7-azaspiro[4.4]nonan-6-one (75). A solution of siloxycyclopropane **65b** (10 mg, 0.017 mmol) in $CHCl_3$ (1 mL) was added to Zeise's dimer (1 mg, 0.0017) and heated to 50 °C. After 12 h. the reaction was allowed to cool to room temperature, filtered through a plug of silica gel and eluted with Et_2O. Concentration of the organics and purification of the crude product by column chromatography affords 4.5 mg (55% yield) of allylic alcohol **75**. ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.22 (m, 12H), 6.86 (d, 2H, *J* = 8.7 Hz), 5.86 (t, 1H, *J* = 1.7 Hz), 5.35 (t, 1H, *J* = 2.4 Hz), 5.16 (t, 1H, *J* = 2.4 Hz), 5.02 (m, 1H), 4.83 (d, 1H, *J* = 15.4 Hz), 4.73 (d, 1H, *J* = 15.4 Hz), 4.55 (m, 1H), 4.42 (d, 1H, *J* = 5.7 Hz), 3.79 (s, 3H), 3.35 (dd, 1H, *J* = 1.7, 17.0 Hz), 3.21 (dd, 1H, *J* = 1.7, 17.0 Hz), 2.70 (m, 2H), 2.02 (m, 1H), 1.87 (m, 1H).

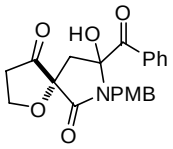


(*2S,5S,E*)-8-benzylidene-7-(4-methoxybenzyl)-3-methylene-2-phenethyl-1-oxa-7-azaspiro[4.4]nonane-4,6-dione (77). To a solution of alcohol **75** (6 mg, 0.0125 mmol) in 1 mL of DCM was added Dess-Martin periodane (8 mg, 0.019 mmol). Upon consumption of starting material as determined by TLC analysis (~ 1 h) the reaction was quenched with a 1:1 mixture of sat. $NaHCO_3$/sat. $Na_2S_2O_3$ (1 mL) and allowed to stir till the organic layer becomes clear. The mixture is then diluted with Et_2O and the organic layer was separated and washed with H_2O and brine dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by column chromatography affords 5 mg, (83% yield) of **77.** ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.22 (m, 12H), 6.88 (d, 2H, *J* = 8.7 Hz), 6.29 (d, 1H, *J* = 2.7 Hz), 5.88 (t, 1H, *J* = 2.1 Hz), 5.52 (d, 1H, *J* = 2.1 Hz), 5.38 (dd, 1H, *J* = 3.0, 7.9 Hz), 4.84 (d, 1H, *J* = 15.5 Hz), 4.73 (d, 1H, *J* = 15.5 Hz), 3.79 (s, 3H), 3.39 (dd, 1H, *J* = 2.7, 17.0 Hz), 3.07 (dd, 1H, *J* = 2.7, 17.0 Hz), 2.83 (m, 2H), 2.20 (m, 1H), 2.00 (m, 1H).



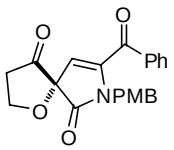
(5S)-8-benzoyl-8-methoxy-7-(4-methoxybenzyl)-1-oxa-7-azaspiro[4.4]nonane-4,6-dione (83). To a solution of benzylidene lactam **60** (30 mg, 0.083 mmol) in a 1:1 mixture of DCM/MeOH (3 mL) was added *m*-CPBA (20 mg, 0.116 mmol). Upon consumption of starting material as determined by TLC analysis, the reaction is dilluted with DCM and washed with sat. $NaHCO_3$, H_2O and brine. Concentration of the organics affords alcohol **82** as a mixture of diastereomers. The crude alcohol **82** was then disolved in 1 mL of DCM and Dess-Martin periodane (67 mg, 0.16 mmol) is added and allowed to stir for 1 h, then the reaction is quenched with a 1:1 mixture of sat. $NaHCO_3$/sat. $Na_2S_2O_3$ (1 mL) and allowed to stir till the organic layer becomes clear. The mixture is then diluted with Et_2O and the organic layer is separated and washed

with H_2O and brine dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by column chromatography 2:1 hexanes/EtOAc (R_f = 0.4, 1:1 hexanes/EtOAc) affords 24 mg (71% yield) of **83** as a 4:1 mixture of diastereoemers. Major Diastereomer: ^{1}H nmr (300 MHz, $CDCl_3$) δ 8.02 (d, 2H, *J* = 7.2 Hz), 7.60 (t, 1H, *J* = 7.2 Hz), 7.45 (t, 2H, *J* = 7.2 Hz), 7.33 (d, 2H, *J* = 8.4 Hz), 6.80 (d, 2H, *J* = 8.4 Hz), 4.82 (d, 1H, *J* = 15.0 Hz), 4.74 (q, 1H, *J* = 8.7 Hz), 4.34 (dt, 1H, *J* = 4.5, 8.7 Hz), 4.11 (d, 1H, *J* = 15.0 Hz), 3.77 (s, 3H), 2.98 (s, 3H), 2.84 (ddd, 1H, *J* = 4.8, 8.4, 18.3 Hz), 2.65 (d, 1H, *J* = 15.6 Hz), 2.57 (dt, 1H, *J* = 7.8, 17.4), 2.41 (d, 1H, *J* = 15.6 Hz).

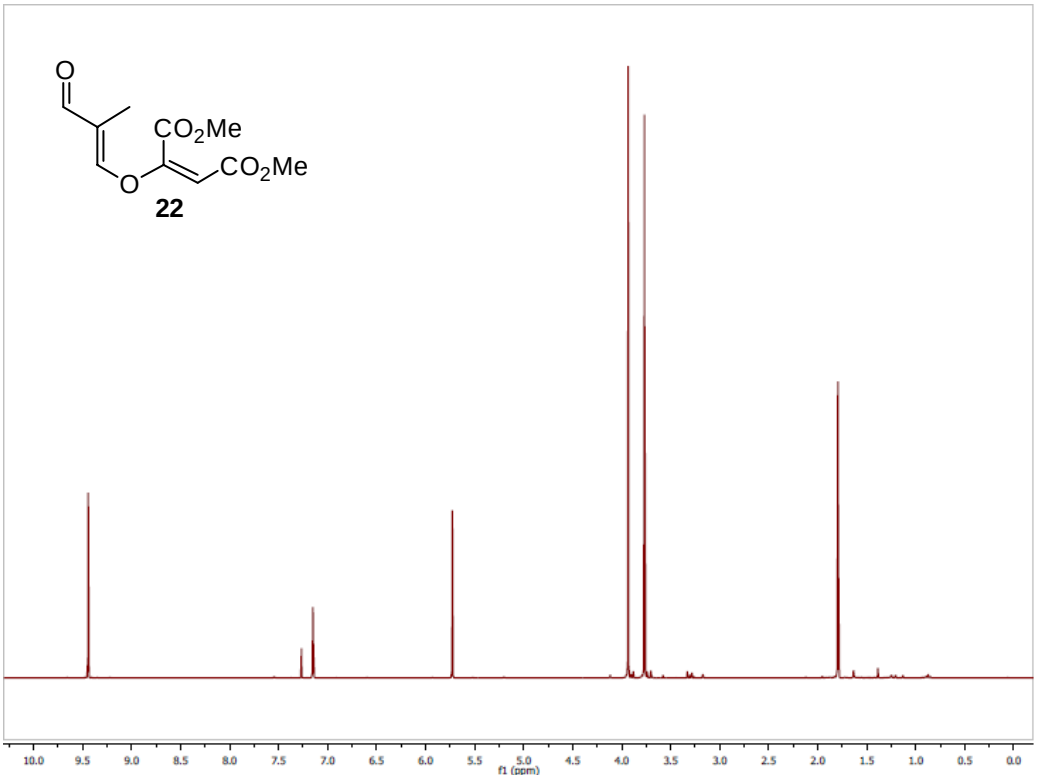


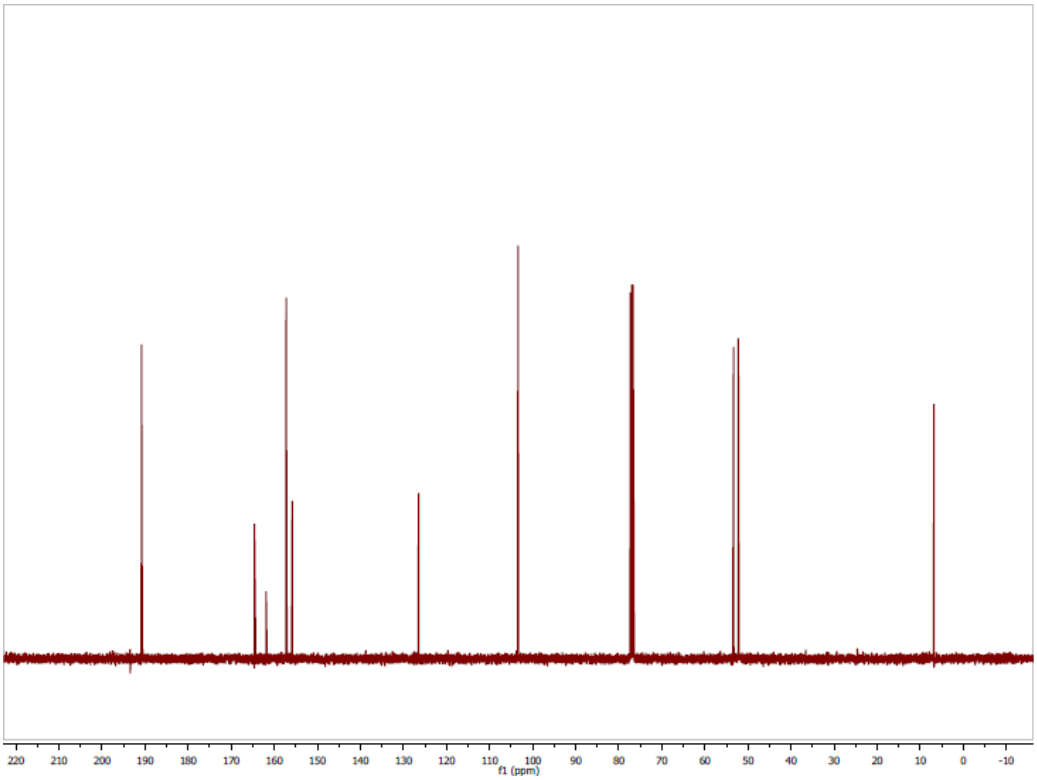
(5S)-8-benzoyl-8-hydroxy-7-(4-methoxybenzyl)-1-oxa-7-azaspiro-[4.4]nonane-4,6-dione (84). A solution of benzylidene lactam **60** (25 mg, 0.069 mmol) in DCM (2 mL) is cooled to -78 °C and DMDO (2.75 mL of a 0.05 M soln. in acetone, 0.138) is added dropwise. The reaction is allowed to warm to room temperature over 4 h. Upon warming to room temperature DMS (~ 200 μl) is added and the solvent is removed *in vacuo* to afford the crude diol **79**. The crude diol is dissolved in DCM (1 mL) and Dess-Martin periodane (35 mg, 0.083 mmol) is added and allowed to stir for 1 h. then the reaction is quenched with a 1:1 mixture of sat. $NaHCO_3$/sat. $Na_2S_2O_3$ (1 mL) and allowed to stir till the organic layer becomes clear. The mixture is then diluted with Et_2O and the organic layer is separated and washed with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by column chromatography affords 11 mg, (42% yield) of hydroxy ketone **84** as a 1.5:1 mixture of diastereomers. Major diastereomer: ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.82 (d, 2H, *J* = 7.4 Hz), 7.51 (t, 1H, *J* = 7.4 Hz), 7.33 (t, 2H, *J* = 8.0 Hz), 6.95 (d, 2H, *J* = 8.6 Hz), 6.50 (d, 2H, *J* = 8.6 Hz), 5.49 (s, 1H), 4.73 (q, 1H, *J* = 8.6 Hz), 4.47 (d, 1H, *J* = 14.2 Hz), 4.44 (m, 1H), 4.15 (d, 1H, *J* =

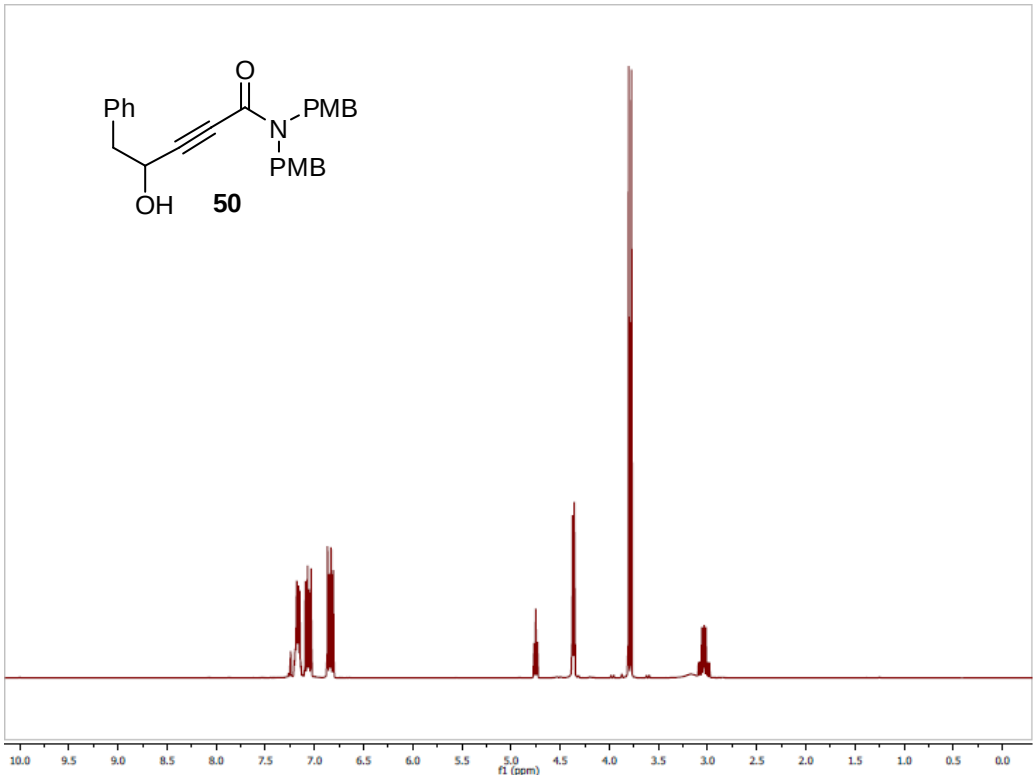
14.2), 3.64 (s, 3H), 3.09 (d, 1H, *J* = 15.1 Hz), 2.89 (ddd, 1H, *J* = 4.2, 7.7, 18.6 Hz), 2.67 (m, 1H), 2.20 (d, 1H, *J* = 15.1 Hz).

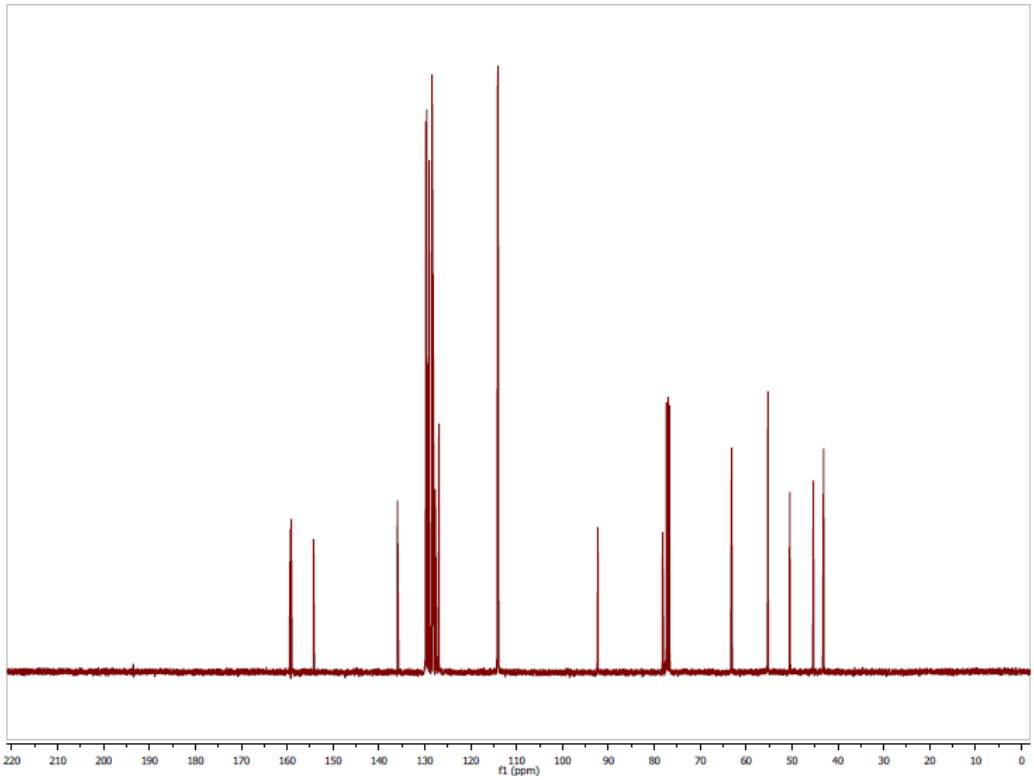


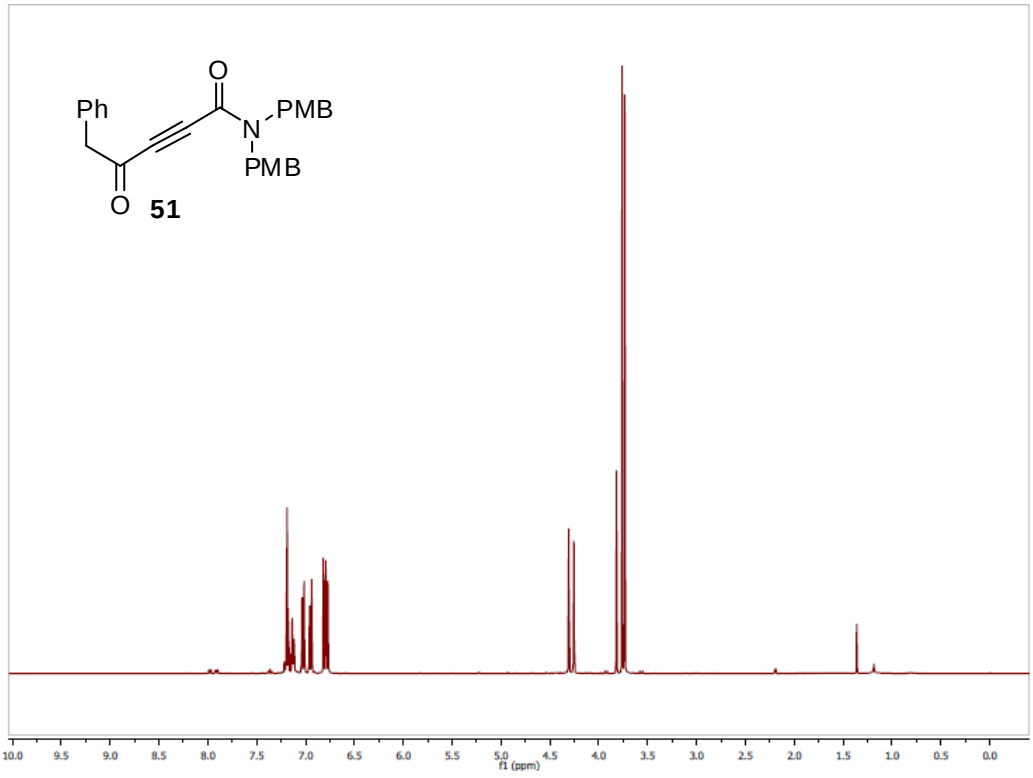
(*S*)-8-benzoyl-7-(4-methoxybenzyl)-1-oxa-7-azaspiro[4.4]non-8-ene-4,6-dione (80). To a solution of hydroxyketone **84** (20 mg, 0.051 mmol) in DCM (1.5 mL) was added Martin-sulfurane (170 mg, 0.253 mmol) as a solution in DCM (1 mL). The reaction is stirred for 30 min followed by filtration through a plug of silica and concentration *in vacuo*. Purification of the crude product via column chromatography affords 6 mg (32% yield) of **80**. ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.63 (d, 2H, *J* = 7.5), 7.59 (t, 1H, *J* = 7.5 Hz), 7.40 (t, 2H, *J* = 7.6 Hz), 7.03 (d, 2H, *J* = 8.7 Hz), 6.69 (d, 2H, *J* = 8.7 Hz), 5.58 (s, 1H), 5.05 (ddd, 1H, *J* = 6.4 Hz, 8.7 Hz, 15.1 Hz), 4.99 (d, 1H, *J* = 14.8 Hz), 4.10 (ddd, 1H, *J* = 4.4, 6.2, 10.9 Hz), 3.68 (s, 3H), 2.94 (m, 2H).

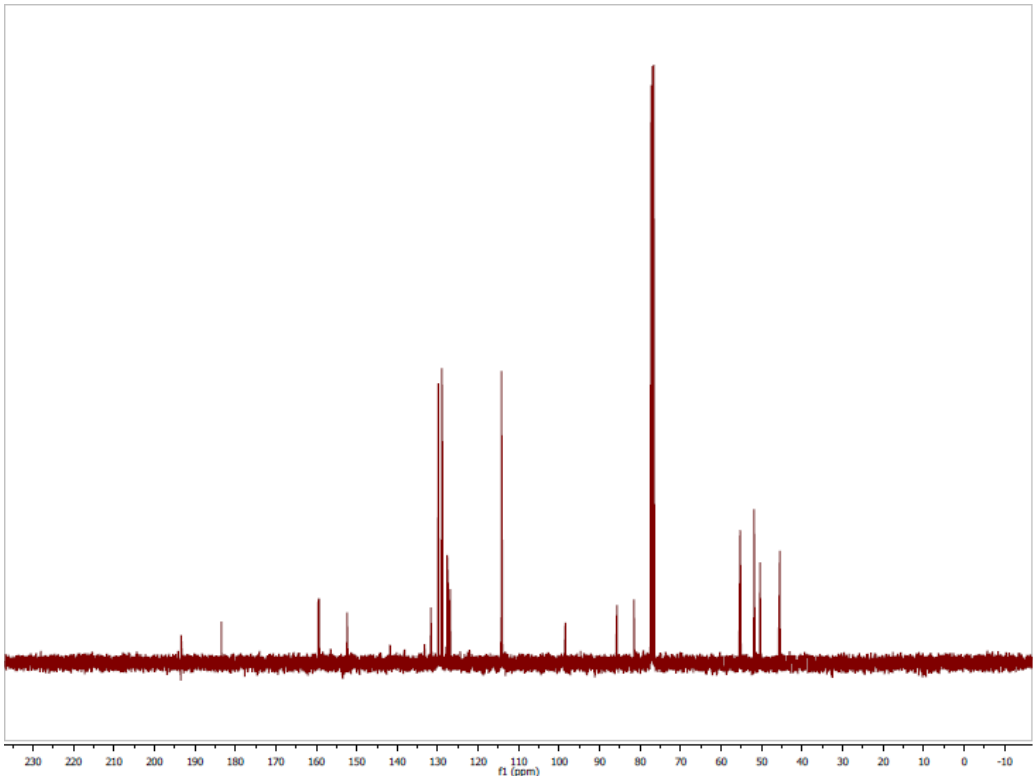

O
CO2Me
CO2Me
O
22
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

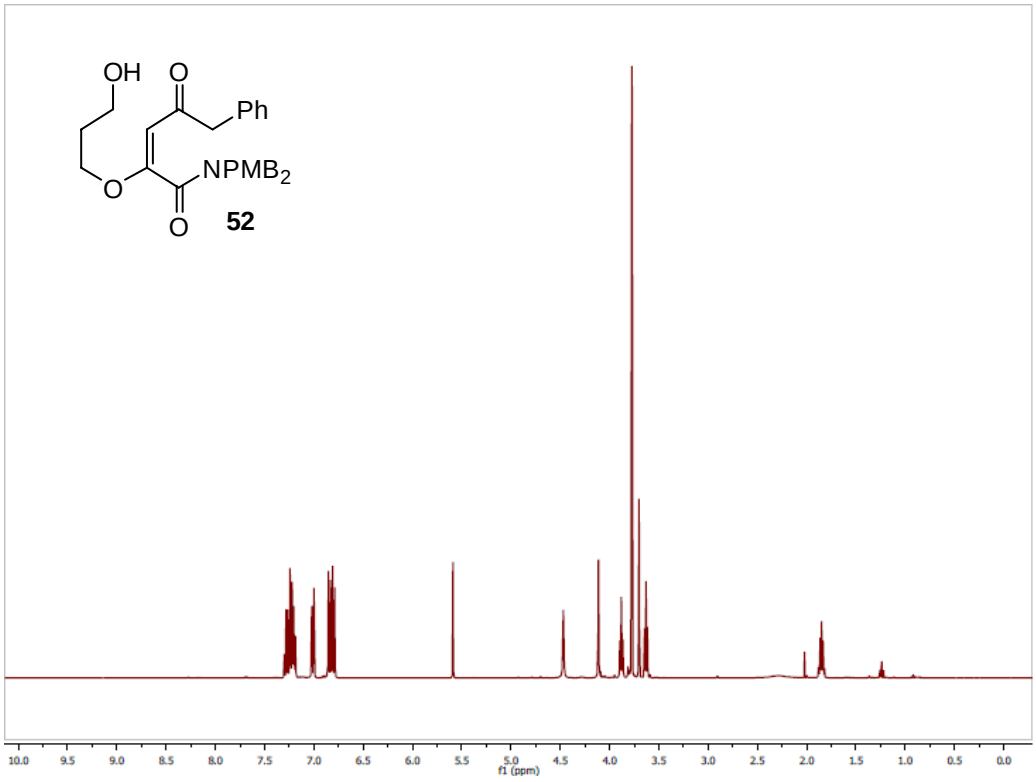

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

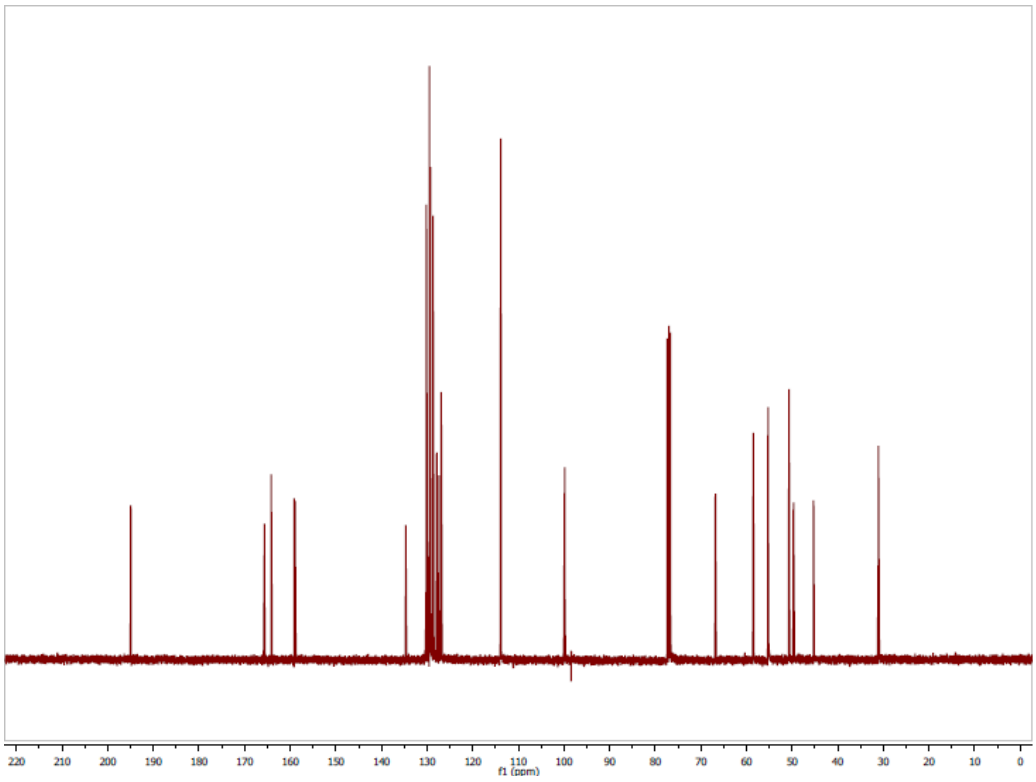

O
Ph
PMB
N
PMB
OH
50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

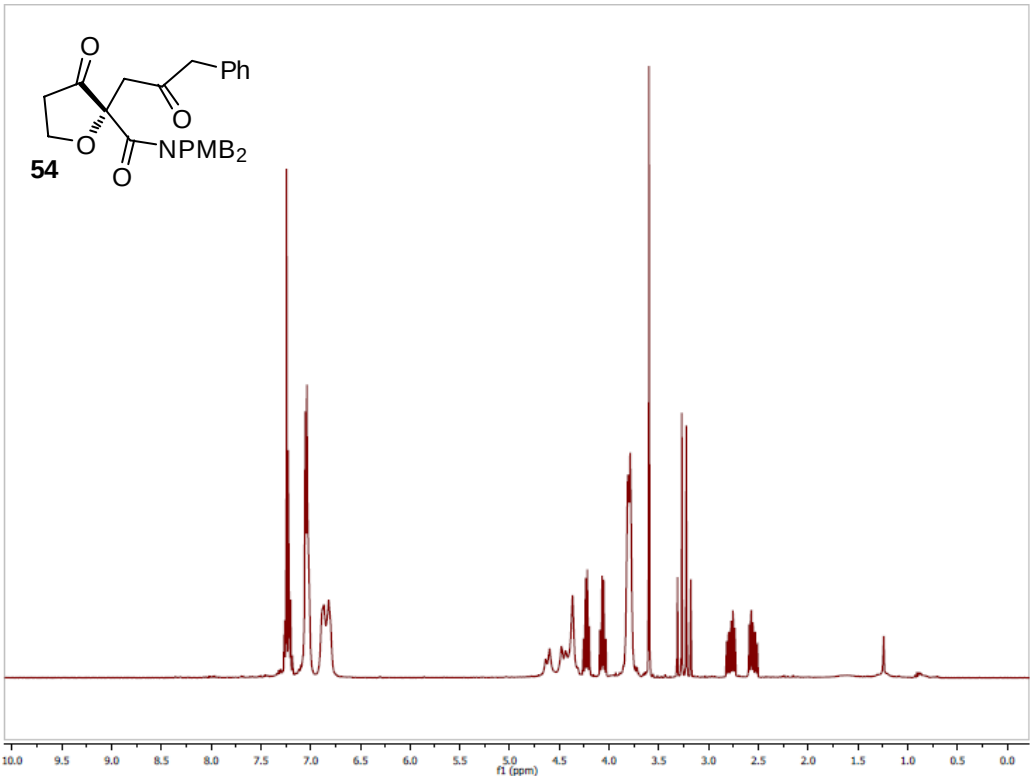

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

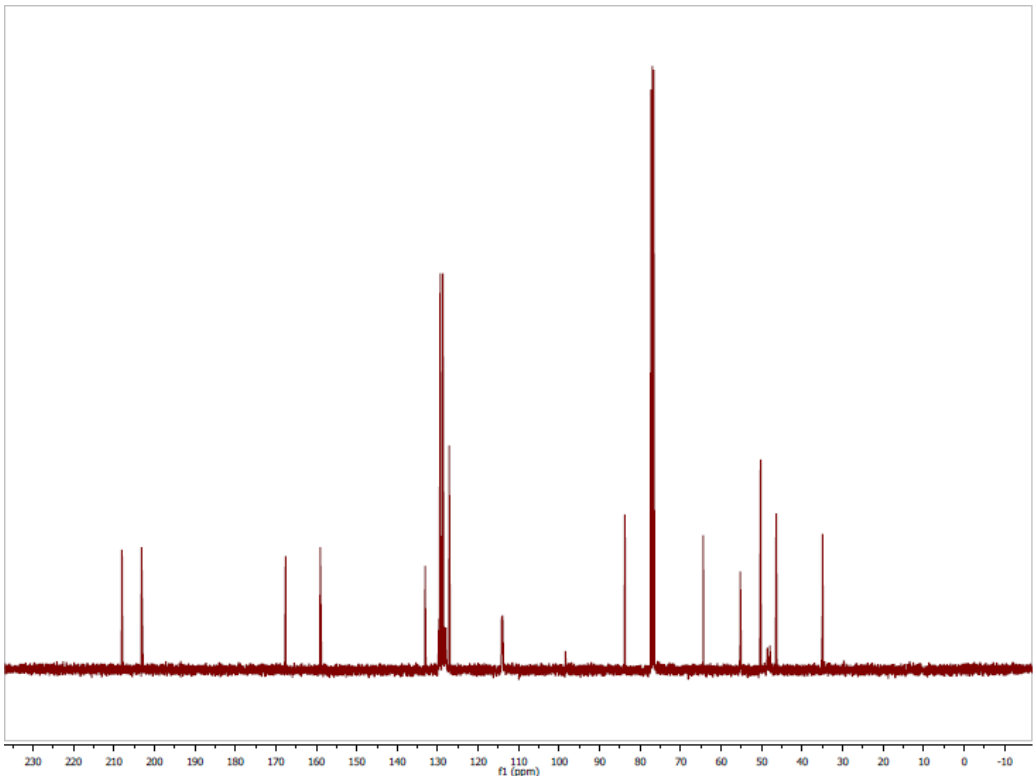

Ph
O
N
PMB
PMB
O
51
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

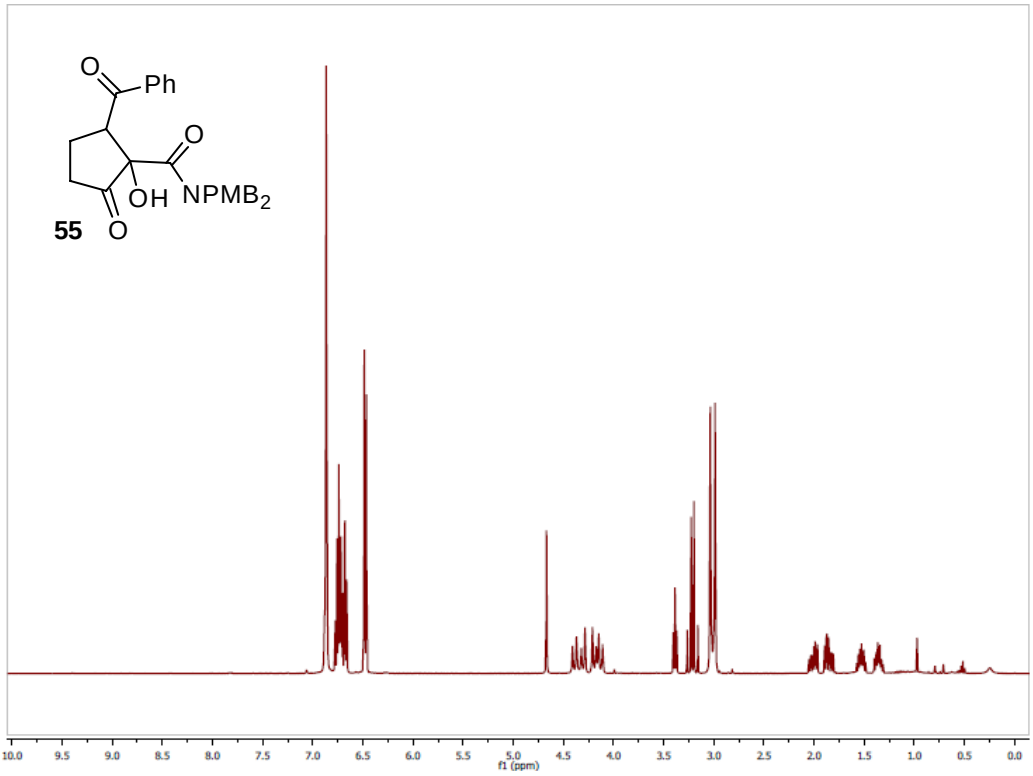

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

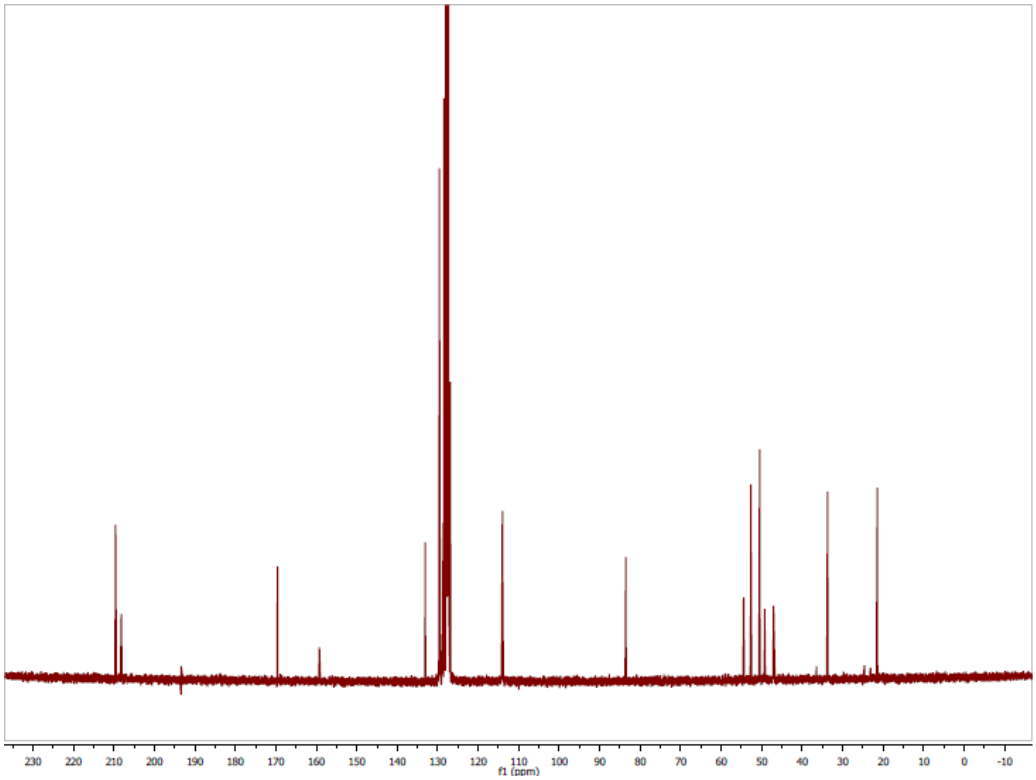

OH
O
Ph
NPMB2
O
O
52
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

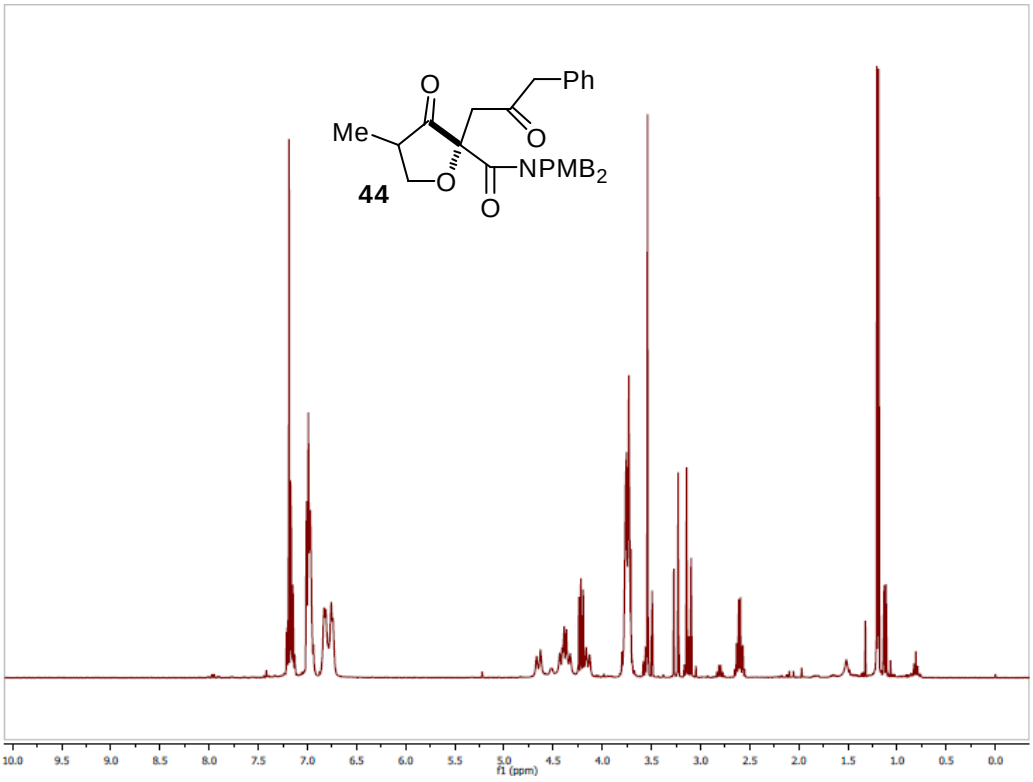

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

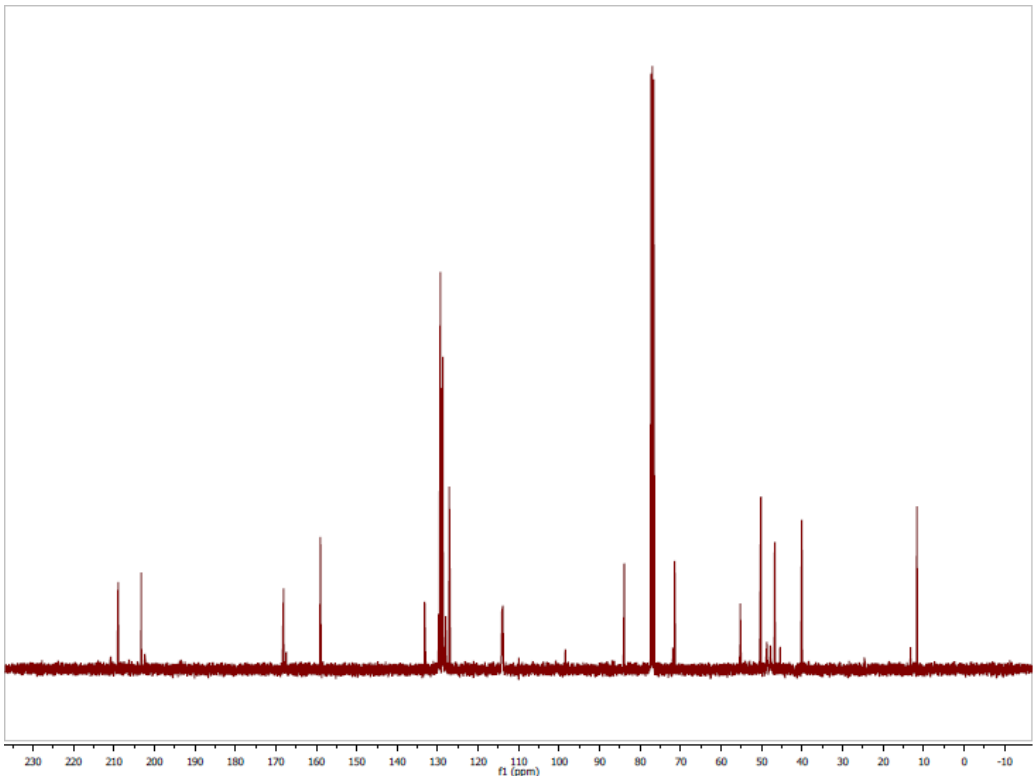

O
Ph
O
O
NPMB2
O
54
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

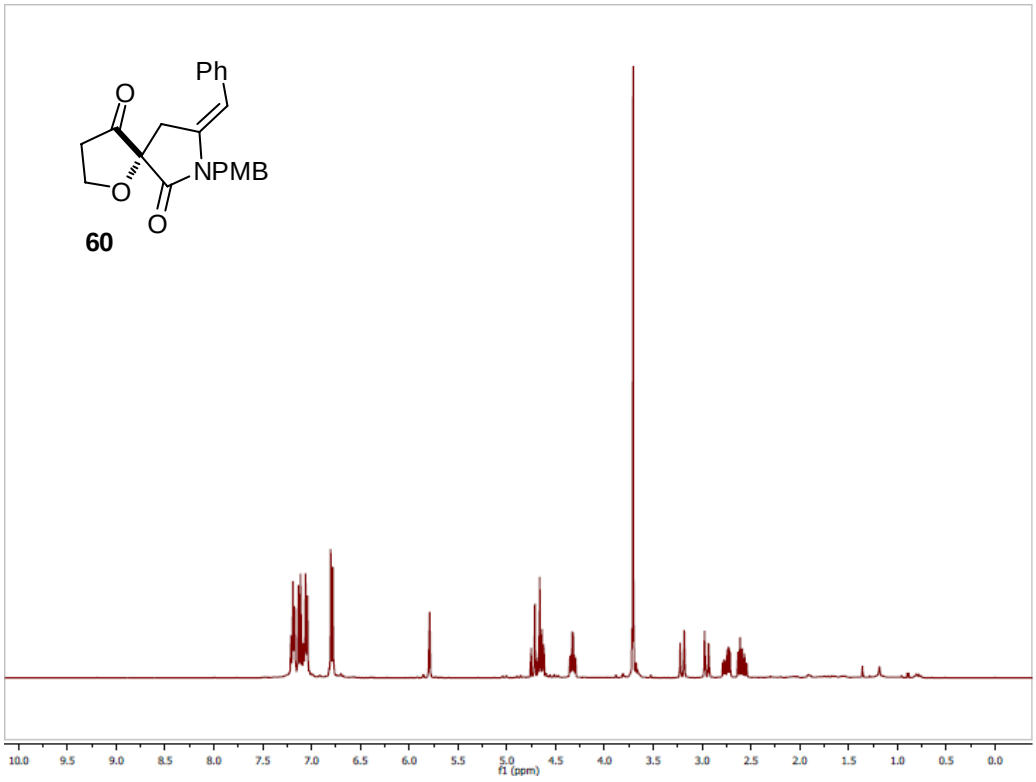

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

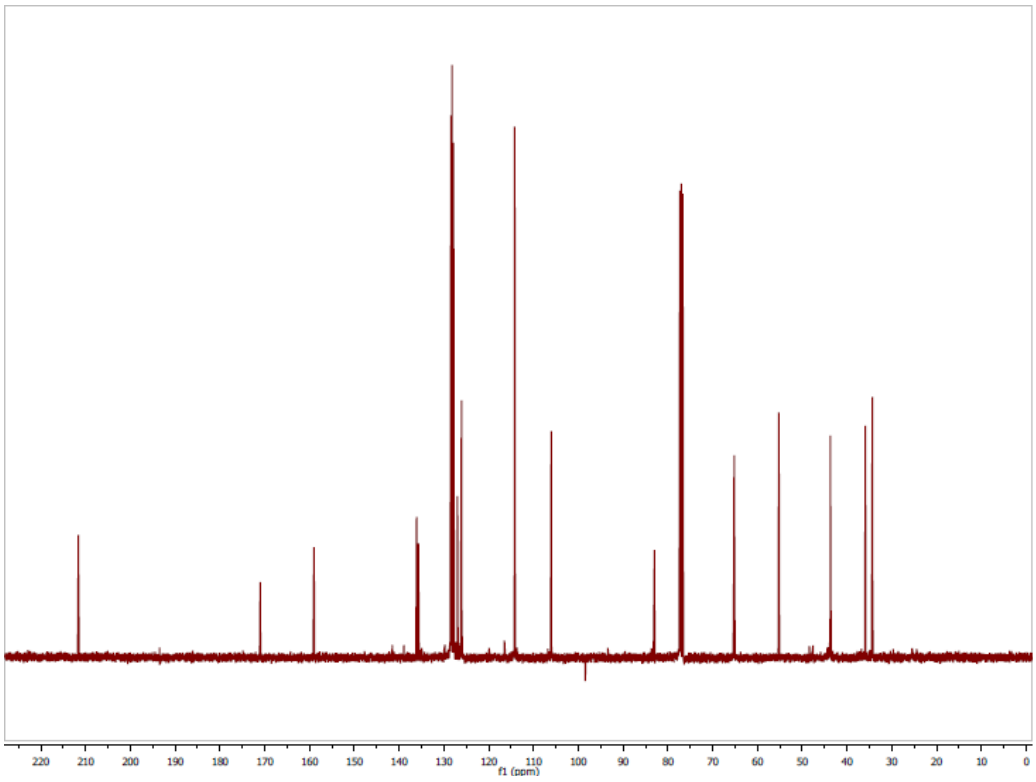

O
Ph
O
OH
NPMB2
55
O
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

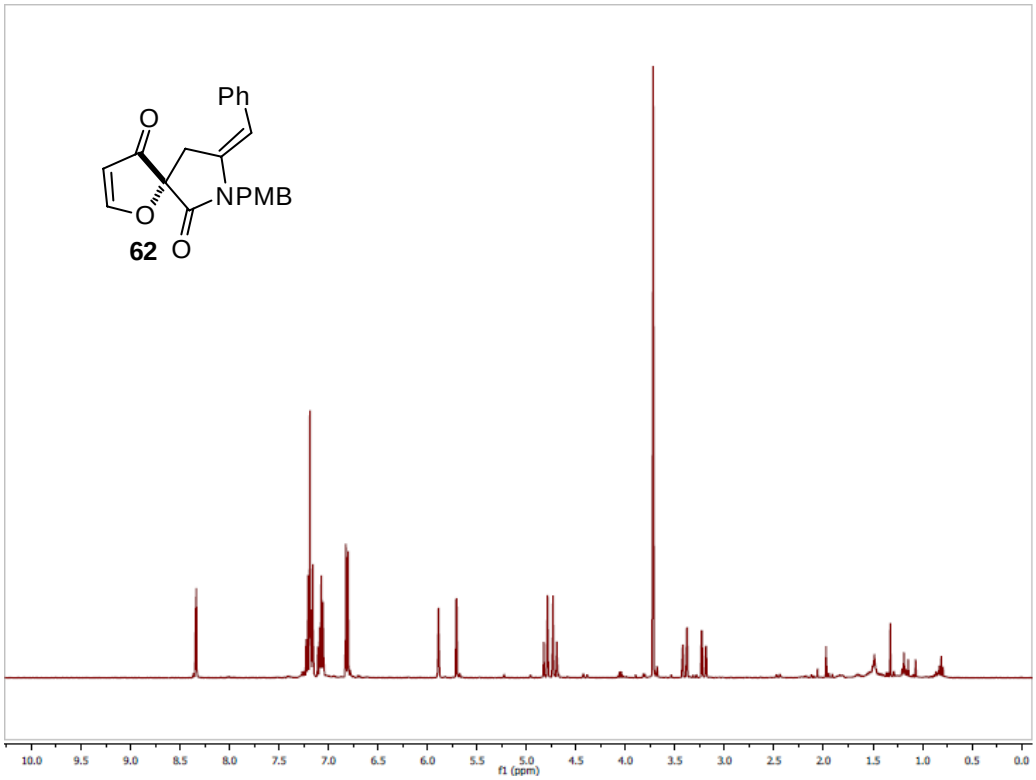

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

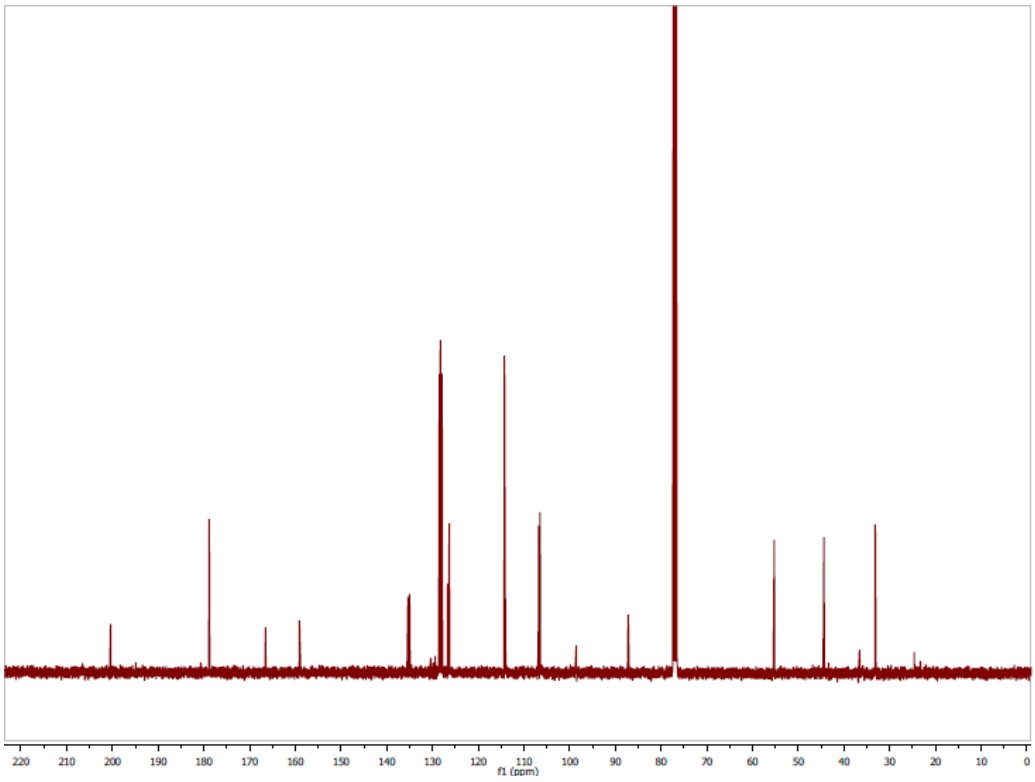

O
Ph
Me
O
NPMB2
O
O
44
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

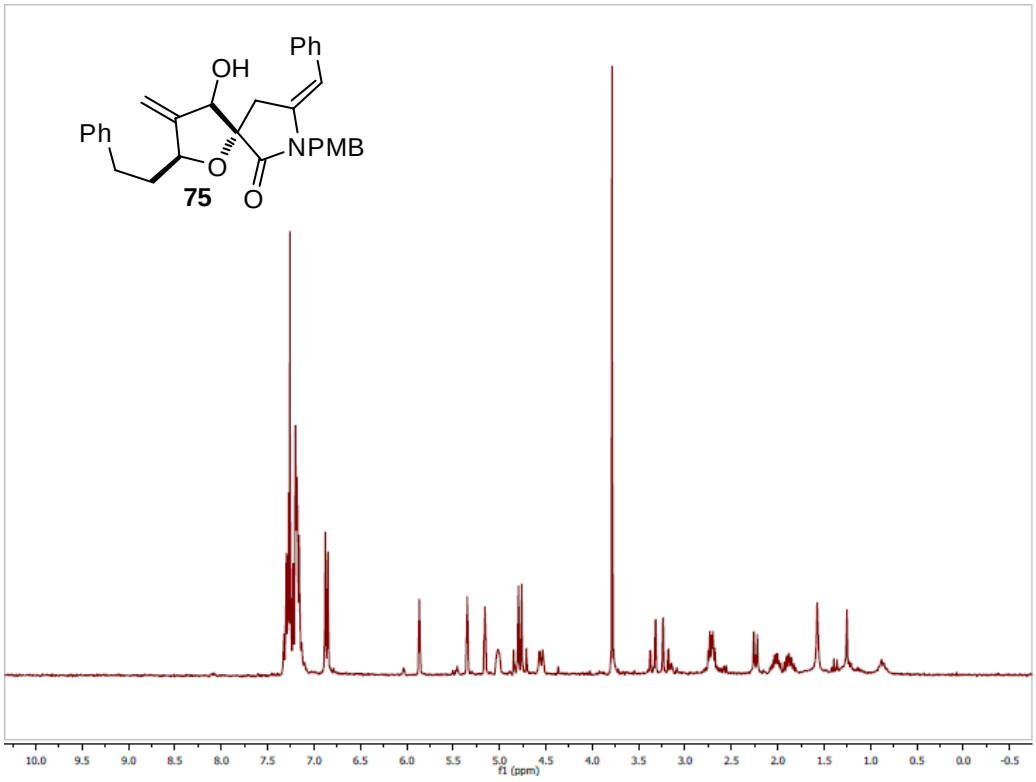

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

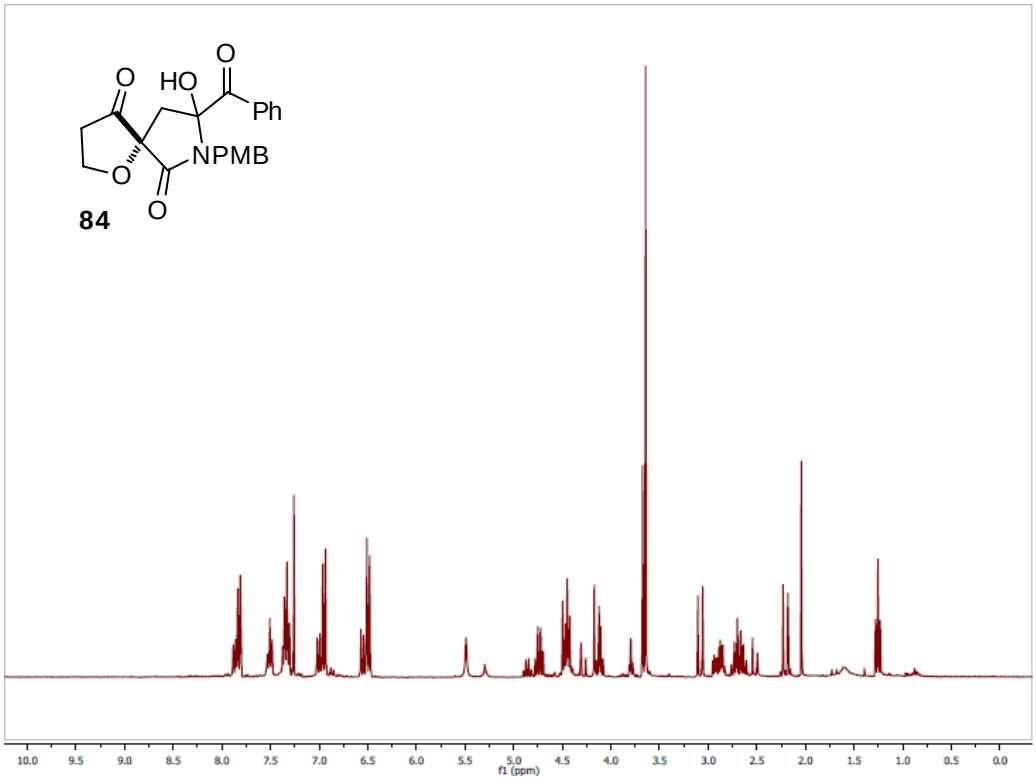

Ph
O
NPMB
O
O
60
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

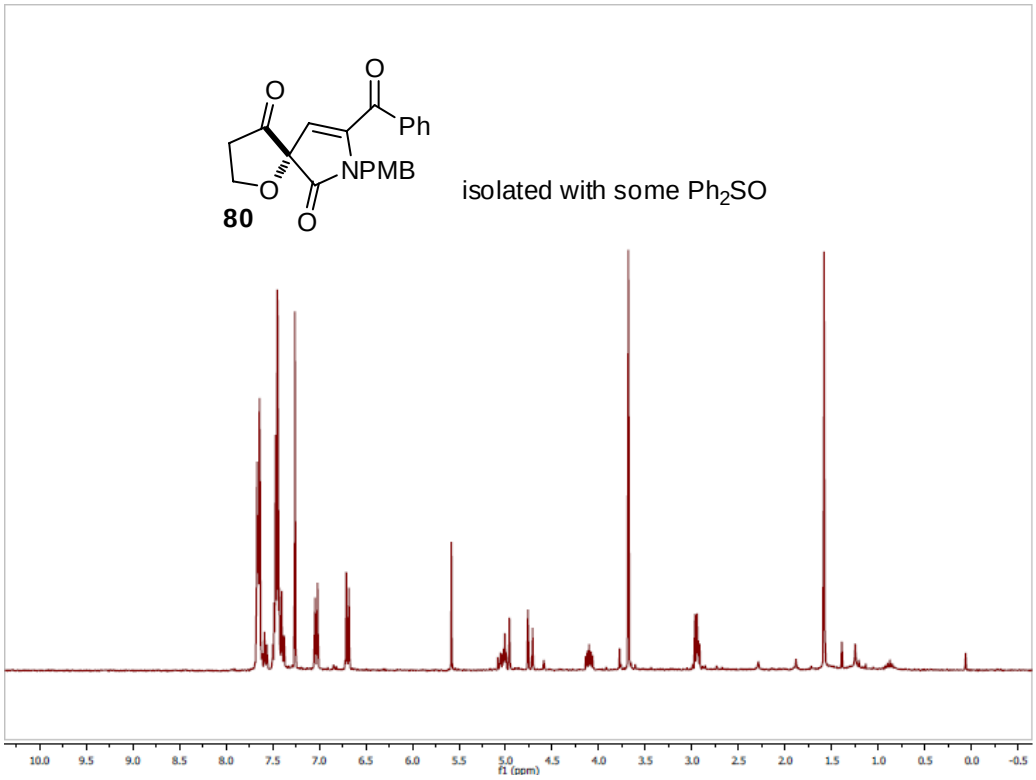

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
O
NPMB
O
O
62
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)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
OH
Ph
NPMB
O
O
75
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)


O
HO
O
Ph
NPMB
O
O
84
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)



References

[1] O'Sullivan, P.T.; Buhr, W.; Fuhry, M. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194.

Chapter 3 Experimental

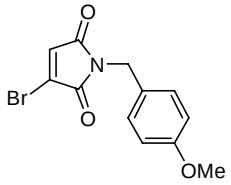
Second Generation Approach Towards Cephalimysin A

General Methods.

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring unless otherwise stated. Reaction solvents including dichloromethane (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), toluene (PhMe), benzene, (PhH), Acetonitrile (MeCN), and Methanol (MeOH) were degassed with argon and passed through two columns of neutral alumina. HPLC grade Chloroform preserved with pentane was purchased from Fisher Scientific. ACS grade dimethyl sulfoxide (DMSO) was purchased from EDI chemical Inc. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light, cerium ammonium molybdenate, $KMnO_4$, or anisaldehyde stains followed by heating.

^1H nmr spectra were recorded on Varian 300 or 400 MHz spectrometers at ambient temperature unless otherwise stated. Data is reported as follows: chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm), toluene-d_8 (7.09, 7.0, 6.98, 2.09 ppm) or benzene-d_6 (7.16 ppm) multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). ^{13}C NMR was recorded on Varian 300 or 400 MHz spectrometers (at 75 or 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.2 ppm) or toluene-d_8 (137.86 (1), 129.4 (3), 128.33 (3), 125.49 (3), 20.4 (5) ppm). Infrared spectra were obtained on a Nicolet Avatar

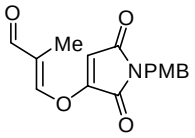
320 FT-IR spectrometer or Bruker Tensor 27 FT-IR spectrometer. Mass spectra were obtained on a Fisions VG Autospec.



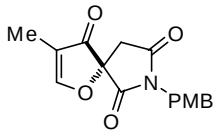
3-bromo-1-(4-methoxybenzyl)-1*H*-pyrrole-2,5-dione (9). Prepared according to the general procedures.[1,2] To a solution of maleimide (20.5 g, 212 mmol) dissolved in 300 mL of CCl_4 was added Br_2 (12 mL, 232 mmol) in 200 mL of CCl_4 dropwise over 45 min via addition funnel. The reaction was fitted with a reflux condenser and heated to 80 °C for 1 h. The reaction was allowed to cool to room temperature and the resulting precipitate was filtered and washed 2X's with CCl_4 to afford the dibromide as a slightly orange solid (52.8 g). The dibromide (52.8 g, 206 mmol) was dissolved in 700 mL of THF and cooled to 0 °C. To the mixture was added triethylamine (31.5 mL, 226 mmol) as a solution in THF (100 mL) over 30 min via addition funnel. After addition the reaction was allowed to stir at 0 °C for a further 2 h. The reaction was allowed to warm to room temperature and the organics were removed *in vacuo*. The residue was dissolved in EtOAc (800 mL) and washed 2X's H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford 35.4 g of N-H bromomaleimide as a light brown solid which was used in the following step without further purification.

Triphenylphosphine (22.4 g, 85.2 mmol) was dissolved in THF (580 mL), the resulting solution was cooled to -78 °C. DIAD (16.5 mL, 85.2 mmol) was added over 5 min and the reaction was allowed to stir for 5 min after which *para*-methoxybenzyl alcohol (11.7 mL, 93.76 mmol) was added in one portion and the reaction was allowed to stir another 5 min. Neopentyl alcohol (4.13 g, 46.9 mmol) and N-H bromomaleimide (15.0 g, 85.2 mmol) were added sequentially as solids and the resulting suspension was allowed to stir 5 min at -78 °C before being allowed to warm to room temperature. The reaction was

allowed to stir ~12 h at room temperature at which time TLC analysis indicated complete consumption of the starting material. The mixture was concentrated *in vacuo* and purified via column chromatography 4:1 hexanes/EtOAc to afford 17.0 g (68% yield) of PMB-protected maleimide **9**. ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.29 (d, 2H, *J* = 8.6 Hz), 6.85 (s, 1H), 6.83 (d, 2H, *J* = 8.6 Hz), 4.64 (s, 2H), 3.78 (s, 3H); All other spectral properties matched those previously reported.[3]

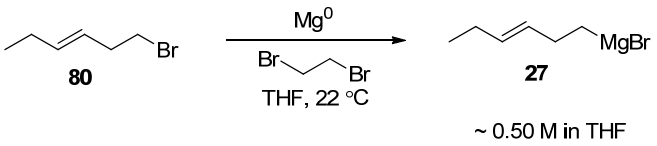


(*E*)-3-((1-(4-methoxybenzyl)-2,5-dioxo-2,5-dihydro-1H-pyrrol-3-yl)oxy)-2-methylacrylaldehyde (11). To a solution PMB-maleimide **9** (4.3 g, 14.7 mmol) in MeCN (30 mL) was added **10**[4] (1.4 g, 11.3 mmol) as a solution in DMSO (60 mL) over 30 min via addition funnel. The reaction was allowed to stir 1 h at ambient temperature and then quenched with sat NH_4Cl and diluted with EtOAc. The aqueous layer was washed twice more with EtOAc and organic were combined and washed 2Xs H_2O, 2Xs brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product via column chromatography 12:1 PhMe/EtOAc (R_f = 0.4, 6:1 PhMe/EtOAc) affords 2.04 g (60% yield) of aldehyde **11** as a light brown oil which solidifies upon standing. The aldehyde was found to decompose if left on the bench top over the course of a couple days. However storage as a solution in DCM at 0 °C allows for safe keeping for ~ 2 weeks without appreciable decomposition. ^{1}H nmr (300 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.41 (q, 1H, *J* = 1.3 Hz), 7.30 (d, 2H, *J* = 8.7 Hz), 6.84 (d, 2H, *J* = 8.7 Hz), 5.83 (s, 1H), 4.63 (s, 2H), 3.78 (s, 3H), 1.87 (d, 3H, *J* = 1.3 Hz). Full characterization has been carried out for similar aldehyde **48** *vida infra.*

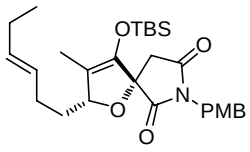


(*S*)-7-(4-methoxybenzyl)-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6,8-trione (17). Triazolium salt **24** (425 mg, 0.82 mmol) was added to an oven dried sealed tube under argon (sealed tube typically gives higher yields of the product) followed by benzene (80 mL) followed by argon bubbling through the solution for 5 min. To the homogenous solution was added NaOAc (225 mg, 2.74 mmol) and the mixture was allowed to stir for 15 min. Aldehyde **11** (825 mg, 2.74 mmol) was added to the reaction as a solution in benzene (10 mL, in some cases DCM was also added to help solubilize the aldehyde) and the reaction was sealed and placed in a Rayonet photochemical reactor equipped with 350 nm UV lamps. The reaction was irradiated for 36-48 h (upon irradiation the internal temperature rose to ~45 °C over the first 1 h). The resulting dark brown mixture was filtered through a plug of silica gel and concentrated *in vacuo*. Purification of the crude product via column chromatography 9:1 PhMe/EtOAc (R_f = 0.4, 6:1 PhMe/EtOAc, the product is slightly less polar than the starting aldehyde) affords 480 mg (58% yield) of spirocylce **17** as a brown oil. HPLC analysis-Chiracel IA column, 93:7 hexanes/*i*-PrOH, 1.0 mL/min, major enantiomer: 32.9 min, minor enantiomer: 44.3 min, 94% ee; $[\alpha]_D^{21}$ = -103.3 (c = 0.010 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 8.15 (q, 1H, *J* = 1.2 Hz), 7.27 (d, 2H, *J* = 8.8 Hz), 6.82 (d, 2H, *J* = 8.8 Hz), 4.62 (s, 2H), 3.75 (s, 3H), 3.07 (d, 1H, *J* = 18.1 Hz), 2.93 (d, 1H, *J* = 18.1 Hz), 1.73 (d, 3H, *J* = 1.2 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 199.5, 175.0, 171.8, 169.2, 159.4, 130.0, 126.8, 115.0, 114.1, 85.2, 55.2, 42.8, 37.0, 5.3; IR (thin film/NaCl) 1791, 1719, 1616, 1514, 1433, cm^{-1}; HRMS $[C_{16}H_{16}NO_5]^+$ calcd 302.1023, found 302.1028.

(*E*)-hex-3-en-1-ylmagnesium bromide (27).

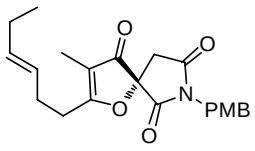


To a mixture of magnesium turnings (1.34 g, 55.2 mmol in THF (10 mL) was added the alkyl bromide **80**[5] (3.0 g, 18.4 mmol) in THF (10 mL) over 1 h via syringe pump. Upon addition of ~ 2 mL of the alkyl bromide solution, dibromoethane (~ 200 μl) was added to the reaction mixture (a rapid exotherm is observed). After full addition of the alkyl bromide solution the mixture is allowed to stir for 30 min and is used in the next step immediately. The reaction typically generates a 0.50 – 0.60 M solution of the Grignard in THF as determined via titration with menthol and 1,10 phenanthroline as the indicator.

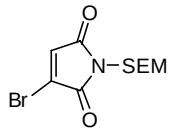


(2*R*,5*S*)-4-((tert-butyldimethylsilyl)oxy)-2-((E)-hex-3-en-1-yl)-7-(4-methoxybenzyl)-3-methyl-1-oxa-7-azaspiro[4.4]non-3-ene-6,8-dione (28). To a solution of spirocycle **17** (771 mg, 2.56 mmol) and CuBr•SMe_2 (790 mg, 3.84 mmol) in THF (20 mL) at -78 °C was added Grignard **27** (8 mL, 3.84 mmol, 0.5 M soln in THF) over 10 min and allowed to stir 45 min. A solution of TBSCl (810 mg, 5.38 mmol) and HMPA (7.2 mL, 41.5 mmol) in THF (7 mL) was added dropwise and the reaction was allowed to stir 30 min followed by warming to 0 °C over 1 h. The reaction was quenched with pH 7 phosphate buffer and allowed to warm to room temperature. The resulting mixture was diluted with Et_2O and the organic layer separated. The aqueous layer was washed once more with Et_2O and the combined organics were washed 2Xs H_2O, 2Xs brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product via column chromatography 30:1 hexanes/EtOAc affords 912 mg (70% yield) of **28** as a 10:1 mixture of diastereomers. ^{1}H nmr (300 MHz, $CDCl_3$) δ 7.34 (d, 2H, *J*

= 8.6 Hz), 6.80 (d, 2H, *J* = 8.6 Hz), 5.43 (m, 2H), 4.91 (m, 1H), 4.57 (s, 2H), 3.76 (s, 3H), 2.93 (d, 1H, *J* = 18.4), 2.67 (d, 1H, *J* = 18.4 Hz), 1.97 (m, 4H), 1.70 (m, 1H), 1.60 (s, 3H), 1.44 (m, 1H), 0.94 (t, 3H, *J* = 7.4 Hz), 0.77 (s, 9H), 0.15 (s, 3H), 0.00 (s, 3H).

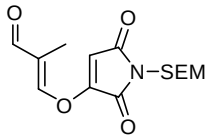


(*S*,*E*)-2-(hex-3-en-1-yl)-7-(4-methoxybenzyl)-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6,8-trione (29). To a solution triphenylcarbeneium tetrafluoroborate (660 mg, 2.0 mmol) in MeCN (8 mL) at 0 °C was added collidine (132 μL, 1.0 mmol) followed by enol ether **28** (192 mg, 0.50 mmol) in MeCN (2 mL). The reaction was allowed to warm to room temperature and stirred there for 2 h. Upon completion the solution was diluted with ether and washed with H_2O 2Xs, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product by column chromatography 6:1 to 3:1 hexanes/EtOAc (R_f = 0.4, 6:1 hexanes/EtOAc) affords 171 mg (90% yield) of enone **29** as a yellow oil. $[\alpha]_D^{21}$ = -45.9 (c = 0.010 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.29 (d, 2H, *J* = 8.8 Hz), 6.88 (d, 2H, *J* = 8.8 Hz), 5.52 (dtt, 1H, *J* =1.2, 6.3, 12.6, 15.1) 5.40 (dtt, 1H, *J* = 1.5, 6.8, 13.6, 15.1) 4.64 (d, 1H, *J* = 14.3) 4.63 (d, 1H, *J* = 4.63), 3.77 (s, 3H) 3.07 (d, 1H, *J* = 18.0 Hz), 2.89 (d, 1H, *J* = 18.0 Hz), 2.61 (m, 2H), 2.36 (m, 2H), 1.99 (m, 2H), 1.70 (s, 3H), 0.95 (t, *J* = 7.4 Hz) ; ^{13}C nmr (100 MHz, $CDCl_3$) δ 199.0, 189.7, 172.1, 169.7, 159.4, 134.5, 130.0, 127.0, 125.9, 114.1, 110.4, 85.0, 55.2, 42.7, 37.1, 29.2, 29.0, 25.4, 13.7, 5.76; IR (thin film/NaCl) 2962, 2873, 1792, 1720, 1628, 1515, 1434, cm^{-1}; HRMS $[C_{22}H_{26}NO_5]^+$ calcd 384.1805, found 384.1813.



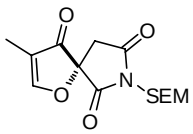
3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrrole-2,5-dione (47). To a solution of N-H bromomaleimide (10.0 g, 56.8 mmol) in DCM (500 mL) at -40 °C (MeCN/dry ice) was added diisopropylethylamine (15.8 mL, 90.9 mmol)

followed by SEMCl (11.0 mL, 62.5 mmol). The reaction was allowed to stir 1.5 h and then quenched with sat. NH_4Cl and allowed to warm to room temperature. After separation of the organic layer the aqueous layer was washed once more with DCM. The combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford dark brown oil. Purification of the crude product by column chromatography 15:1 to 10:1 hexanes/EtOAc (R_f = 0.4, 6:1 hexanes/EtOAc) affords 14.8 g (86% yield) of **47** as a yellow oil. ^{1}H nmr (400 MHz, $CDCl_3$) δ 6.93 (s, 1H), 4.93 (s, 2H), 3.56 (t, 2H, *J* = 8.3), 0.90 (t, 2H, *J* = 8.4 Hz), 0.03 (s, 9H) ; ^{13}C nmr (100 MHz, $CDCl_3$) δ 168.2, 165.1, 132.3, 132.0, 67.4, 67.3, 17.9, 1.4; IR (thin film/NaCl) 2954 2896, 1783, 1730, 1589, 1414, 1390, cm^{-1};



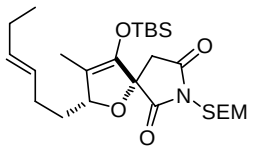
(*E*)-3-((2,5-dioxo-1-((2-(trimethylsilyl)ethoxy)methyl)-2,5-dihydro-1H-pyrrol-3-yl)oxy)-2-methylacrylaldehyde (48). To a solution SEM-maleimide **47** (10.0 g, 32.7 mmol) in MeCN (75 mL) was added **10**[6] (3.40 g, 27.2 mmol) as a solution in DMSO (125 mL) over 30 min via addition funnel. The reaction was allowed to stir 1 h at ambient temperature and then quenched with sat. NH_4Cl and diluted with Et_2O. The aqueous layer was washed twice more with Et_2O and organic were combined and washed 2Xs H_2O, 2Xs brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product via column chromatography 12:1 to 6:1 PhMe/EtOAc (R_f = 0.4, 6:1 PhMe/EtOAc) affords 5.25 g (62% yield) of aldehyde **48** as a yellow oil which solidifies upon standing. The aldehyde was found to decompose if left on the bench top over the course of a couple days. However storage as a solution in DCM at 0 °C allows for safe keeping for ~ 2 weeks without appreciable decomposition. ^{1}H nmr (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.44 (s, 1H), 5.92 (s, 1H), 4.92 (s, 2H), 3.56 (t, 2H, *J* = 8.2 Hz), 0.90 (t, 2H, *J* = 8.2 Hz), 0.04 (s, 9H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 190.8, 168.2, 164.3, 156.7, 155.7,

127.8, 102.8, 67.5, 66.8, 18.1, 7.3, 1.3. IR (thin film/NaCl) 2962, 2873, 1792, 1720, 1628, 1515, 1434, cm^{-1};



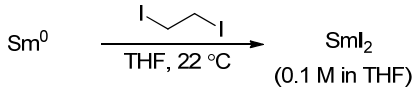
(S)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-1-oxa-7-azaspiro-[4.4]non-2-ene-4,6,8-trione (49). Triazolium salt **24** (827 mg, 1.60 mmol) was added to an oven dried sealed tube under argon (sealed tube typically gives higher yields of the product) followed by benzene (150 mL) followed by argon bubbling through the solution for 5 min. To the homogenous solution was added NaOAc (658 mg, 8.02 mmol) and the mixture was allowed to stir for 15 min. Aldehyde **48** (2.50 g, 8.02 mmol) was added to the reaction as a solution in benzene (20 mL, in some cases DCM was also added to help solubilize the aldehyde) and the reaction was sealed and placed in a Rayonet photochemical reactor equipped with 350 nm UV lamps. The reaction was irradiated for 36-48 h (upon irradiation the internal temperature rose to ~45 °C over the first 1 h). The resulting dark brown mixture was filtered through a plug of silica gel and concentrated *in vacuo*. Purification of the crude product via column chromatography 12:1 to 9:1 PhMe/EtOAc (R_f = 0.5, 6:1 PhMe/EtOAc, the product is slightly less polar than the starting aldehyde) affords 1.55 g (62% yield) of spirocylce **49** as a brown oil. HPLC analysis-Chiracel IA column, 95:5 hexanes/*i*-PrOH, 1.0 mL/min, major enantiomer: 22.8 min, minor enantiomer: 17.2 min, 95% ee; $[\alpha]_D^{21}$ = 85.5 (c = 0.010 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 4.94 (d, 1H, *J* = 10.4 Hz), 4.92 (d, 1H, *J* = 10.4 Hz), 3.56 (t, 2H, *J* = 8.4 Hz), 3.09 (d, 1H, *J* = 18.2 Hz), 2.98 (d, 1H, *J* = 18.2 Hz), 1.73 (s, 3H) 0.89 (t, 2H, *J* = 8.4 Hz), -.0.04 (s, 9H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 199.6, 175.3, 172.0, 169.4, 115.2, 85.4, 68.5, 67.9, 37.1, 18.0, 5.5, 1.3; IR (thin film/NaCl) 3096, 2954, 2896,

1798, 1730, 1619, 1447, 1339, cm^{-1}; HRMS $[C_{14}H_{25}NO_5SiNH_4]^+$ calcd 329.1527, found 329.1540.

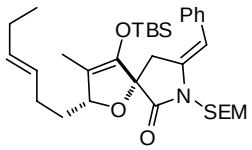


(*2R*,5*S*)-4-((tert-butyldimethylsilyl)oxy)-2-((*E*)-hex-3-en-1-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-1-oxa-7-azaspiro-[4.4]non-3-ene-6,8-dione (50). To a solution of spirocycle **49** (3.40 g, 10.9 mmol) and $CuBr•SMe_2$ (3.37 g, 16.4 mmol) in THF (80 mL) at -78 °C was added Grignard **27** (30 mL, 16.4 mmol, 0.55 M soln in THF) over 20 min and allowed to stir 45 min. A solution of TBSCl (3.46 g, 22.9 mmol) and HMPA (31 mL, 177.0 mmol) in THF (30 mL) was then added dropwise and the reaction was allowed to stir 30 min and then allowed to warm to 0 °C over 1 h. The reaction was quenched with pH 7 phosphate buffer and allowed to warm to room temperature. The resulting mixture was diluted with Et_2O and the organic layer separated. The aqueous layer was washed once more with Et_2O and the combined organics were washed 2Xs H_2O, 2Xs brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product via column chromatography 30:1 hexanes/EtOAc affords 4.05 g (74% yield) of **50** as a 10:1 mixture of diastereomers. $[\alpha]_D^{21}$ = -24.7 (c = 0.013 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 5.44 (ddt, 2H, *J* = 5.9, 11.5, 26.8 Hz), 4.93(d, 1H, *J* = 10.3 Hz), 4.92 (m, 1H), 4.88 (d, 1H, *J* = 10.3 Hz), 3.60 (t, 2H, *J* = 8.7 Hz), 3.00 (d, 1H, *J* = 18.5 Hz), 2.70 (d, 1H, *J* = 18.5 Hz), 1.99 (m, 4H), 1.75 (m, 1H), 1.62 (s, 3H), 1.46 (m, 1H), 0.96 (t, 3H, *J* = 7.4 Hz), 0.86 (s, 9H), 0.22 (s, 3H), 0.09 (s, 3H), 0.01 (s, 9H). ^{13}C nmr (100 MHz, $CDCl_3$) δ 180.7, 178.2, 144.8, 136.5, 132.3, 117.6, 90.0, 89.9, 71.7, 71.5, 43.4, 38.2, 31.0, 29.5, 22.0, 21.9, 17.8, 13.4, 2.5, 0.06, 0.01; IR (thin film/NaCl) 2956, 2932, 2860, 1793, 1727, 1703, 1389, 1342, 1235, 1088 cm^{-1}; HRMS $[C_{26}H_{47}NO_5Si_2Na]^+$ calcd 532.2885, found 532.2892.

Samarium Diiodide

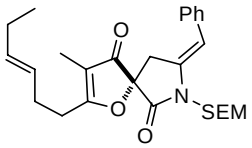


To a flame dried flask under argon was added samarium (7.52 g, 25.0 mmol) and THF (200 mL). To the resulting mixture a solution of 1,2-diiodoethane (3.52 g, 12.5 mmol) in THF (50 mL) was added dropwise over 30 min. The reaction was allowed to stir for 2 h at which time a deep blue solution of SmI_2 (0.1 M in THF) was obtained and used in the next reaction.

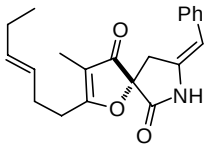


***2R,5S,E*)-8-benzylidene-4-((*tert*-butyldimethylsilyl)oxy)-2-((*E*)-hex-3-en-1-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-1-oxa-7-azaspiro[4.4]non-3-en-6-one (51).** To a solution of enol ether **50** (3.2 g, 6.28 mmol) and benzyl bromide (1.5 mL, 12.6 mmol) in 60 mL of THF at room temperature was added a freshly prepared solution of samarium diiodide (250 mL of a 0.1 M in THF, 25.0 mmol) via filter tip cannula over 30 min. The reaction was allowed to stir for 1 h, then cooled to 0 °C and quenched with 0.05 M HCl and allowed to warm to room temperature for 1 h. The mixture was extracted 2Xs with Et_2O and the combined organics were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product via column chromatography 30:1 to 15:1 hexanes/EtOAc (R_f = 0.6, 6:1 hexanes/EtOAc) affords 2.8 g (77 % yield) of **51** as a 5:1 mixture of *E:Z* oflefin isomers. $[\alpha]_D^{21}$ = -9.0 (c = 0.010 g/mL, CH_2Cl_2)*E* isomer; ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.27 (m, 4H), 7.16 (t, 1H, *J* = 7.2 Hz), 6.16 (t, 1H, *J* = 2.0 Hz), 5.43 (ddt, 2H, *J* = 5.7, 10.9, 26.5 Hz), 5.14 (d, 1H, *J* = 10.8 Hz), 4.98 (d, 1H, *J* = 10.8 Hz), 4.89 (m, 1H), 3.61 (t, 2H, *J* = 7.9 Hz), 3.27 (dd, 1H, *J* = 2.0, 17.1 Hz), 2.97 (dd, 1H, *J* = 2.0, 17.1 Hz), 1.96 (m, 4H), 1.73 (dtd, 1H, *J* = 3.3, 7.7, 19.6 Hz), 1.60 (s, 3H), 1.43 (dq, 1H, *J* = 6.75, 13.8 Hz) 0.92 (t, 3H, *J*

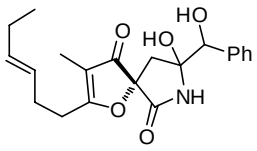
= 7.4 Hz), 0.83 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H), 0.01 (s, 9H). ^{13}C nmr (100 MHz, $CDCl_3$) δ 178.1, 146.2, 141.2, 140.6, 136.2, 132.7, 132.4, 131.9, 129.7, 117.0, 109.4, 90.7, 89.3, 74.2, 70.3, 39.7, 31.1, 29.5, 22.1, 21.8, 17.9, 13.4, 2.6, 0.09, 0.0; IR (thin film/NaCl) 2956, 2931, 2858, 1731, 1702, 1657, 1448, 1332, 1257, 1083 cm^{-1}; HRMS $[C_{33}H_{54}NO_4Si_2]^+$ calcd 584.3586, found 584.3586.



(*S*,*E*)-8-benzylidene-2-((*E*)-hex-3-en-1-yl)-3-methyl-7-((2-(trimethylsilyl)ethoxy)methyl)-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (55). To a solution of enol ether **51** (3.6 g, 6.2 mmol) in DCM (80 mL) and H_2O (8 mL) was added DDQ (4.2 g, 18.5 mmol) and the reaction was vigorously stirred for 2-3 h. The reaction was carefully quenched with sat $NaHCO_3$ and diluted with Et_2O. The aqueous layer was separated and washed once more with Et_2O and the organics were combined and washed with sat $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product via column chromatography 15:1 hexanes/EtOAc (R_f = 0.3, 6:1 hexanes/EtOAc) affords 1.96 g (68% yield) of **55**. $[\alpha]_D^{21}$ = 37.8 (c = 0.0127 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 6.30 (t, 1H, *J* = 1.9 Hz), 5.52 (dtt, 1H, *J* = 1.2, 6.3, 11.2, 16.4 Hz), 5.37 (dtt, 1H, *J* = 1.2, 6.3, 11.2, 16.4), 5.14 (d, 1H, *J* = 11.0 Hz), 5.07 (d, 1H, *J* = 11.0 Hz), 3.56 (m, 2H), 3.42 (dd, 1H, *J* = 1.9, 16.8 Hz), 3.16 (dd, 1H, *J* = 1.9, 16.8 Hz), 2.61 (m, 2H), 2.35 (m, 2H), 1.97 (m, 2H), 1.66 (s, 3H), 0.93 (t, 3H, *J* = 3.7 Hz), 0.01 (s, 9H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 201.9, 190.2, 169.3, 137.2, 136.3, 135.6, 129.9, 129.4, 127.6, 111.7, 108.3, 88.1, 71.8, 67.6, 34.8, 30.6, 30.4, 26.8, 19.1, 15.1, 7.2, 0.00; IR (thin film/NaCl) 3028, 2958, 2359, 2342, 1738, 1705, 1661, 1633, 1448, 1398, cm^{-1}; HRMS $[C_{27}H_{37}NO_4SiNa]^+$ calcd 490.2384, found 490.2388.

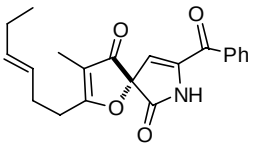


(*S*,*E*)-8-benzylidene-2-((*E*)-hex-3-en-1-yl)-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (56). To a solution of enone **55** (1.2 g, 2.6 mmol) in DCM (125 mL) at 0 °C was added trifluoroacetic acid (14 mL) dropwise over 10 min. The reaction was allowed to warm to room temperature and stir for 3 h. The reaction was then cooled to 0 °C and carefully quenched with sat $NaHCO_3$. The organic layer was separated and the aqueous layer was washed 2Xs with DCM. The organics were combined and washed with sat $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude hemiaminal was dissolved in MeOH (25 mL) and ethylene diamine (186 μL, 2.6 mmol) and 10 M NaOH (565 μl, 5.7 mmol) were added and the reaction was allowed to stir 30 min. The majority of the MeOH was removed *in vacuo* and the resulting residue was dissolved in EtOAc and washed with H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the crude product via column chromatography 2:1 hexanes/EtOAc affords 564 mg (65% yield) of **56**. $[\alpha]_D^{21}$ = 34.8 (c = 0.010 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.30 (t, 2H, *J* = 7.8 Hz), 7.18 (m, 3H), 6.04 (t, 1H, *J* = 2.0 Hz), 5.55 (dtt, 1H, *J* = 1.2, 6.3, 12.3, 15.0), 5.41 (dtt, 1H, *J* = 1.2, 6.3, 12.3, 15.0), 3.48 (dd, 1H, *J* = 2.0, 17.1), 3.22 (dd, 1H, *J* = 2.0, 17.1 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 200.5, 189.0, 168.4, 135.5, 134.2, 133.2, 128.5, 127.6, 126.2, 110.4, 106.5, 87.0, 34.4, 29.2, 29.0, 25.4, 13.7, 5.8; IR (thin film/NaCl) 2962, 2928, 1735, 1677, 1619, 1496, 1452, 1405 cm^{-1}; HRMS $[C_{21}H_{24}NO_3]^+$ calcd 338.1751, found 338.1755.



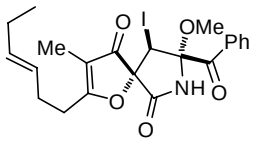
(5*S*)-2-((*E*)-hex-3-en-1-yl)-8-hydroxy-8-(hydroxy(phenyl)methyl)-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (57). To a solution of lactam **56** (207 mg, 0.61 mmol) in acetone (6 mL) at -78 °C was added DMDO[7] (9 mL of a 0.09 M soln in acetone, 0.80 mmol). The reaction was

then placed in a cold bath at -40 °C and allowed to stir for 10 h. The reaction was then re-cooled to -78 °C and quenched with dimethylsulfide (~200 μl) and allowed to warm to room temperature. The organics were then removed under reduced pressure to afford the crude diol. Purification of the crude product via column chromatography 2:1 hexanes/EtOAc (R_f = 0.4, 1:1 hexanes/EtOAc) affords 160 mg (70% yield) of diol **57** as a 3:1 mixture of diastereomers. Major diastereomer: ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.53 (m, 5H), 7.01 (s, 1H), 6.03 (s, 1H), 5.50 (dtt, 1H, *J* = 1.5, 6.8, 15.2, 15.4 Hz) 5.35 (dtt, 1H, *J* = 1.5, 6.8, 15.2, 15.4 Hz), 4.83 (s, 1H), 3.47 (s, 1H), 2.68 (d, 1H, *J* = 13.3 Hz), 2.65 (m, 2H), 2.34 (m, 2H), 2.13 (d, 1H, *J* = 13.3 Hz), 1.97 (m, 2H), 1.65 (s, 3H), 0.93 (t, 3H, *J* = 7.4 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 202.9, 194.0, 167.5, 138.0, 134.5, 128.6, 128.4, 127.8, 126.2, 110.2, 89.4, 86.8, 86.2, 76.7, 38.4, 29.6, 29.2, 25.6, 13.8, 5.8; IR (thin film/NaCl) 3355 br, 2962, 2928, 1726, 1682 1609, 1453, 1408 cm^{-1}; HRMS $[C_{21}H_{26}NO_5]^+$ calcd 372.1805, found 372.1802.

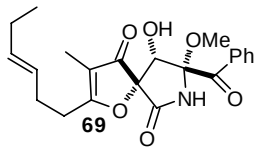


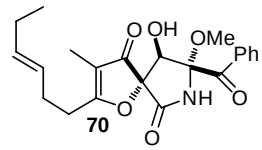
(*S*,*E*)-8-benzoyl-2-(hex-3-en-1-yl)-3-methyl-1-oxa-7-azaspiro[4.4]nona-2,8-diene-4,6-dione (58). To a solution of diol **57** (70 mg, 0.20 mmol) in DCM (8 mL) was added a solution of Martin-sulfurane (295 mg, 0.44 mmol) in DCM (8 mL) via syringe pump over 30 min at room temperature. After addition the reaction was allowed to stir 10 min and then quenched with *i*-PrOH and filtered through a plug of silica, eluted with Et_2O and the filtrate was concentrated *in vacuo*. Purification of the crude product via column chromatography 8:1 hexanes/acetone (R_f = 0.4, 2:1 hexanes/EtOAc) affords 47 mg (67% yield) of **58** as a yellow oil. $[\alpha]_D^{21}$ = 90.8 (c = 0.010 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.86 (d, 2H, *J* = 8.0 Hz), 7.63 (t, 1H, *J* = 7.5 Hz), 7.57 (bs, 1H), 7.49 (t, 2H, *J* = 8.0 Hz), 5.80 (d, 1H, *J* = 1.8 Hz), 5.56

(dtt, 1H, *J* = 1.4, 6.8, 13.6, 15.0 Hz), 5.41 (dtt, 1H, *J* = 1.4, 6.8, 13.6, 15.0 Hz), 2.68 (m, 2H), 2.40 (m, 2H), 1.99 (m, 2H), 1.73 (s, 3H), 0.94 (t, 3H, *J* = 7.5 Hz) ^{13}C nmr (100 MHz, $CDCl_3$) δ 195.7, 189.6, 185.4, 169.4, 143.5, 135.4, 134.4, 133.6, 129.0, 128.7, 126.0, 124.8, 115.3, 111.3, 90.8, 29.2, 29.0, 25.4, 13.7, 6.2 ; IR (thin film/NaCl) 2960, 1743, 1702, 1628, 1446, 1395, 1370 cm^{-1}; HRMS $[C_{21}H_{22}NO_4]^+$ calcd 352.1543, found 352.1544.

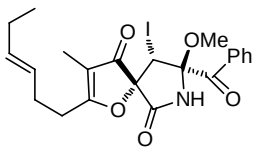


(*5S,8S,9R*)-8-benzoyl-2-((*E*)-hex-3-en-1-yl)-9-iodo-8-methoxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (68). To a solution of spirocycle **58** (5 mg, 0.014 mmol) in MeOH (0.5 mL) at 0 °C was added a solution of *N*-iodosuccinimide (3.2 mg, 0.014 mmol) in MeOH (0.3 mL) and the reaction was allowed to stir for 20 min. The crude mixture was filtered through a plug of silica and the filtrate was concentrated *in vacuo*. Purification of the crude product via column chromatography 6:1 to 3:1 hexanes/EtOAc (R_f = 0.4, 2:1 hexanes/EtOAc) affords 6 mg (80% yield) of **68** as a 7:1 mixture of diastereomers. $[\alpha]_D^{21}$ = 42.7 (c = 0.0085 g/mL, CH_2Cl_2) Major diastereomer: ^{1}H nmr (300 MHz, $CDCl_3$) δ 8.16 (d, 2H, *J* = 7.4 Hz), 7.62 (t, 1H, *J* = 7.5 Hz), 7.48 (t, 2H, *J* =7.9 Hz), 7.24 (bs, 1H), 5.52 (m, 2H), 5.12 (s, 1H), 3.52 (s, 3H), 2.70 (m, 2H), 2.44 (m, 2H), 2.01 (m, 2H), 1.70 (s, 3H), 0.96 (t, 3H, *J* = 7.4 Hz) ^{13}C nmr (100 MHz, $CDCl_3$) δ 197.8, 191.6, 189.0, 163.3, 134.3, 134.1, 133.2, 130.7, 128.6, 126.3, 112.2, 91.7, 85.8, 51.6, 29.4, 29.3, 25.9, 25.5, 13.6, 5.9; IR (thin film/NaCl) 3253 br, 2960, 1735, 1700, 1626, 1447, 1401, 1373 cm^{-1}; HRMS $[C_{22}H_{24}INO_5]^+$ calcd 510.0774, found 510.0771.





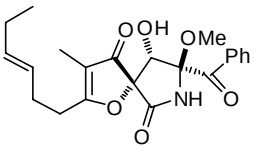
8,9 *epi*-cephalimysin A (69) and 8-*epi*-cephalimysin A (70). To a solution of iodide **68** (5 mg, 0.01 mmol) in toluene (2 mL) at 80 °C



was added a mixture of tristrimehtylsilane (0.03 mmol) and AIBN (0.015 mmol) in toluene (1 mL) over a 2 h period via syringe pump. During the addition air was bubbled through the reaction mixture via syringe needle. After addition the reaction was allowed to stir 1 h further at 80 °C. Upon cooling to room temperature the reaction is filtered through a plug of silica and the filtrate is concentrated *in vacuo*. Purification of the crude reaction via colum chromatography 3:1 to 2:1 hexanes/EtOAc affords 1.5 mg of **69** (R_f = 0.2, 2:1 hexanes/EtOAc) and 1.0 mg of **70** (R_f = 0.3, 2:1 hexanes/EtOAc) (67% combined yield). **69** $[\alpha]_D^{21}$ = 74.1 (c = 0.0022 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 8.30 (d, 2H, *J* = 8.6 Hz), 7.64 (t, 1H, *J* = 7.4 Hz), 7.48 (t, 2H, *J* = 8.0 Hz), 5.60 (m, 1H), 5.48 (m, 1H), 4.50 (d, 1H, *J* = 12.6 Hz), 3.33 (s, 3H), 3.20 (d, 1H, *J* = 12.6 Hz), 2.72 (m, 2H), 2.43 (m, 2H), 2.05 (m, 2H), 1.69 (s, 3H), 1.00 (t, 3H, *J* = 7.5 Hz) ^{13}C nmr (100 MHz, $CDCl_3$) δ 199.5, 193.8, 188.7, 166.8, 134.5, 134.4, 132.9, 130.6, 128.6, 126.5, 112.5, 92.3, 86.6, 73.1, 51.5, 29.3, 29.0, 25.4, 13.5, 5.7; IR (thin film/NaCl) 3320 br, 2927, 1734, 1685, 1624, 1559, 1507 cm^{-1}; HRMS $[C_{22}H_{25}NO_6]^+$ calcd 400.1755, found 400.1759. **70** $[\alpha]_D^{21}$ = 87.6 (c = 0.0030 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 8.21 (d, 2H, *J* = 8.5 Hz), 7.63 (t, 1H, *J* = 7.4 Hz), 7.50 (t, 2H, *J* = 8.3 Hz), 5.60 (m, 1H), 5.44 (m, 1H), 5.20 (d, 1H *J* = 4.1 Hz), 4.78 (d, 1H, *J* = 4.10), 3.27 (s, 3H), 2.71 (m, 2H), 2.43 (m, 2H), 2.03 (m, 2H), 1.71 (s, 3H), 0.99 (t, 3H, *J* = 7.4 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 201.2, 192.3, 191.3, 167.7, 134.5, 134.0, 133.8, 129.3, 128.7, 125.9, 112.6, 96.5, 85.6, 79.0, 51.4, 29.3, 29.0, 25.4, 13.6, 5.5; HRMS $[C_{22}H_{25}NO_6]^+$ calcd 400.1755, found 400.1757

(*5S,8R,9S*)-8-benzoyl-2-((*E*)-hex-3-en-1-yl)-9-iodo-8-methoxy-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6-dione (77). To a solution of spirocycle **58** (10 mg, 0.028) in

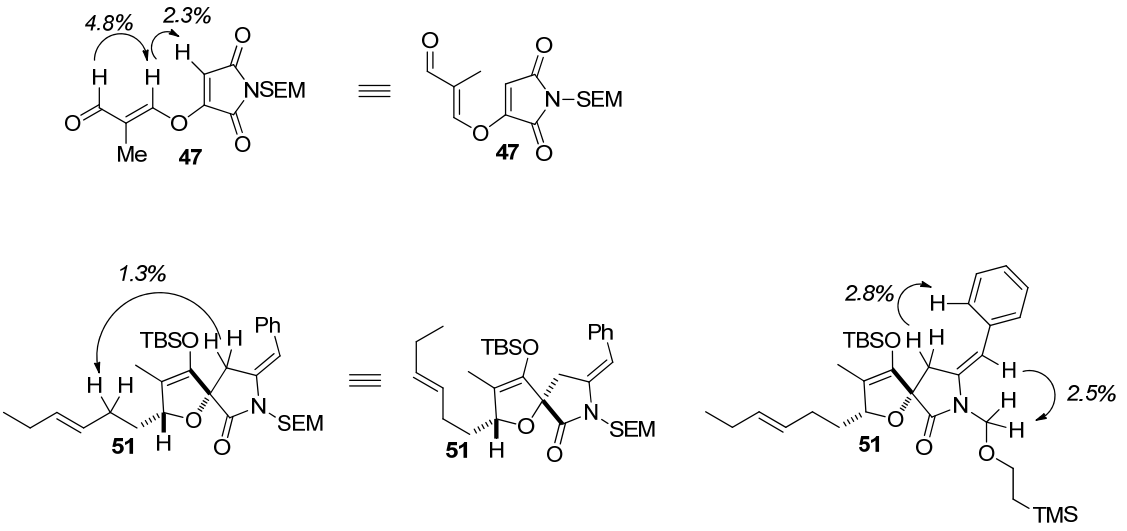
MeOH (1.5 mL) at 0 °C was added trifluroacetic acid (5 drops) followed by a solution of *N*-iodosuccinimide (6.4 mg, 0.028 mmol) in MeOH (0.5 mL). The reaction was allowed to stir for 15 min and then filtered through a plug of silica gel, eluted with Et_2O and the filtrate was concentrated *in vacuo*. Purification of the crude product via column chromatography 4:1 hexanes/EtOAc (R_f = 0.3, 2:1 hexanes/EtOAc) affords 10 mg (71% yield) of **77** as a 4:1 mixture of diastereomers. $[\alpha]_D^{21}$ = -65.0 (c = 0.0070 g/mL, CH_2Cl_2) Major diastereomer: ^{1}H nmr (300 MHz, $CDCl_3$) δ 8.21 (d, 2H, *J* = 8.6 Hz), 7.62 (t, 1H, *J* = 7.4 Hz), 7.48 (t, 2H, *J* = 7.5 Hz), 7.27 (bs, 1H), 5.49 (m, 2H), 4.94 (s, 1H), 3.34 (s, 3H), 2.66 (m, 2H), 2.40 (m, 2H), 1.98 (m, 2H), 1.68 (s, 3H), 0.94 (t, 3H, *J* = 7.3); ^{13}C nmr (100 MHz, $CDCl_3$) δ 195.2, 192.1, 188.2, 166.8, 134.2, 133.9, 132.5, 130.1, 128.6, 126.2, 110.8, 94.4, 87.0, 52.1, 29.1, 20.0, 27.6, 13.6, 5.9; IR (thin film/NaCl) 3267 br, 2926, 2359, 1737, 1705, 1629, 1447, 1398, 1069 cm^{-1}; HRMS $[C_{22}H_{24}INO_5Na]^+$ calcd 532.0591, found 532.0578.

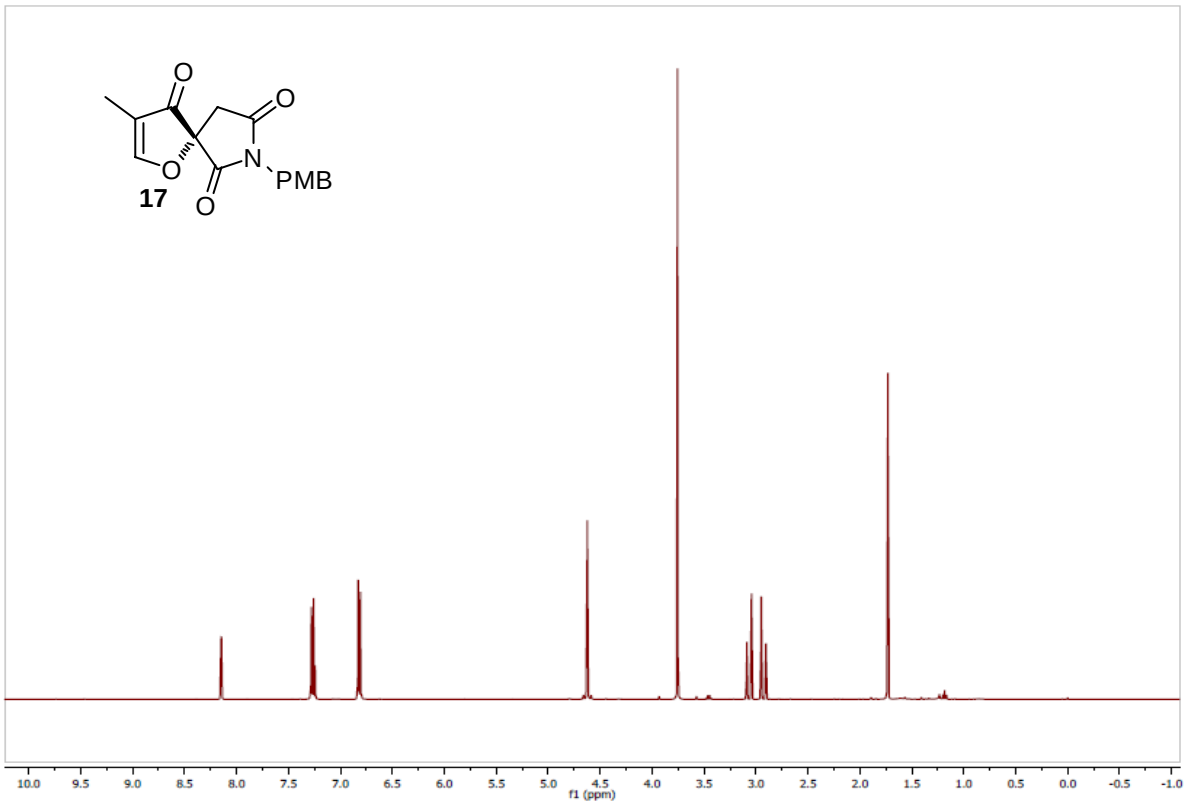


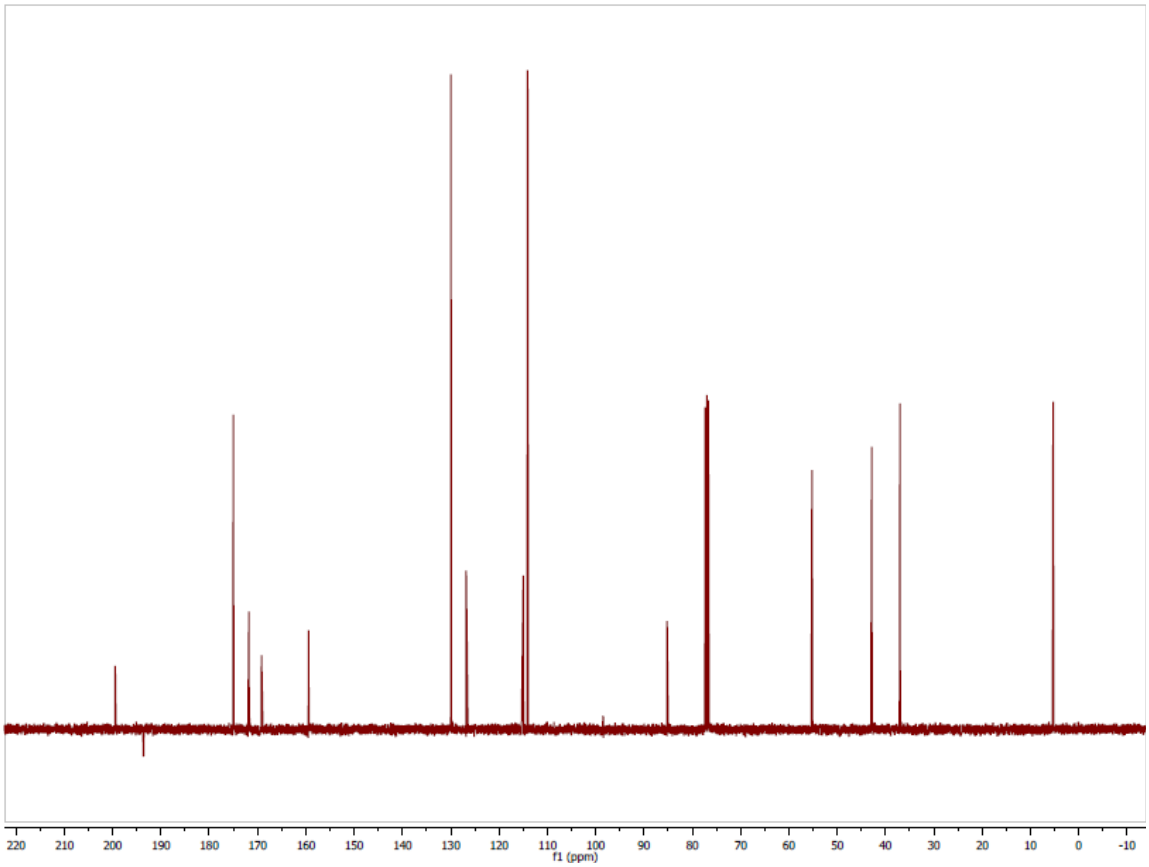
9-*epi*-cephalimysin A (78). To a solution of iodide **77** (1 mg, 0.0020 mmol) in toluene was added TEMPO (1.6 mg, 0.010 mmol) and tributyltin hydride (0.0020 mmol). The reaction was heated to 70 °C and during the next 30 min tributyltin hydride (0.0020 mmol) was added twice more. The reaction was allowed to stir 30 min more and then cooled to room temperature and filtered through a plug of silica, eluted with Et_2O and the filtrate was concentrated *in vacuo*. The crude material was used in the next step without further purification. To a solution of the crude product in acetic acid (0.6 mL), THF (0.2 mL) and H_2O (0.2 mL) was added Zinc dust (1.6 mg, 0.024) and the mixture was heated to 70 °C. After 2 h, the reaction mixture was

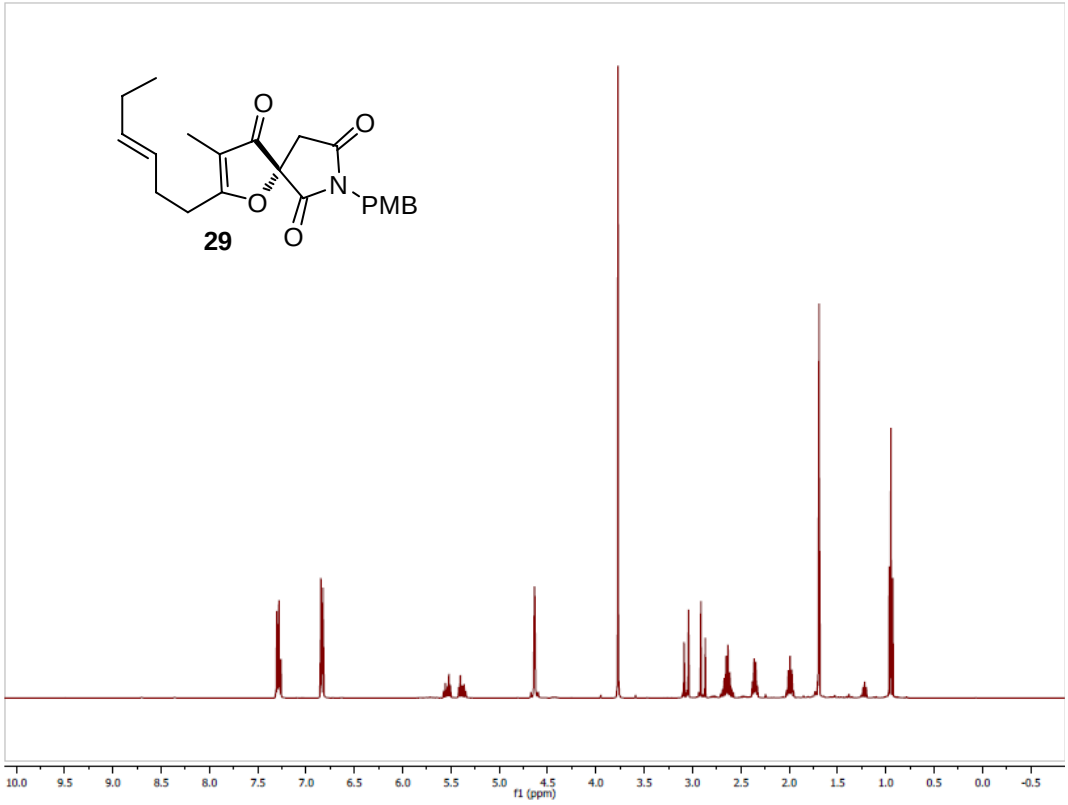
allowed to cool to room temperature and the zinc was removed via filtration. The filtrate was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc and filtered once more. The filtrate was concentrated *in vacuo* to afford the crude product. Purification of crude mixture via column chromatography affords **78**. ^{1}H nmr (400 MHz, $CDCl_3$) δ 8.23 (d, 2H, *J* = 7.2 Hz), 7.62 (t, 1H, *J* = 7.9 Hz), 7.48 (t, 2H, *J* = 7.9 Hz), 5.45 (m, 2H), 4.79 (d, 1H, *J* = 3.6 Hz), 3.32 (s, 3H), 2.55 (d, 1H, *J* = 3.6 Hz), 2.36 (m, 2H), 2.02 (m, 2H), 1.96 (m, 2H), 1.70 (s, 3H), 0.88 (t, 1H, *J* = 7.4 Hz).

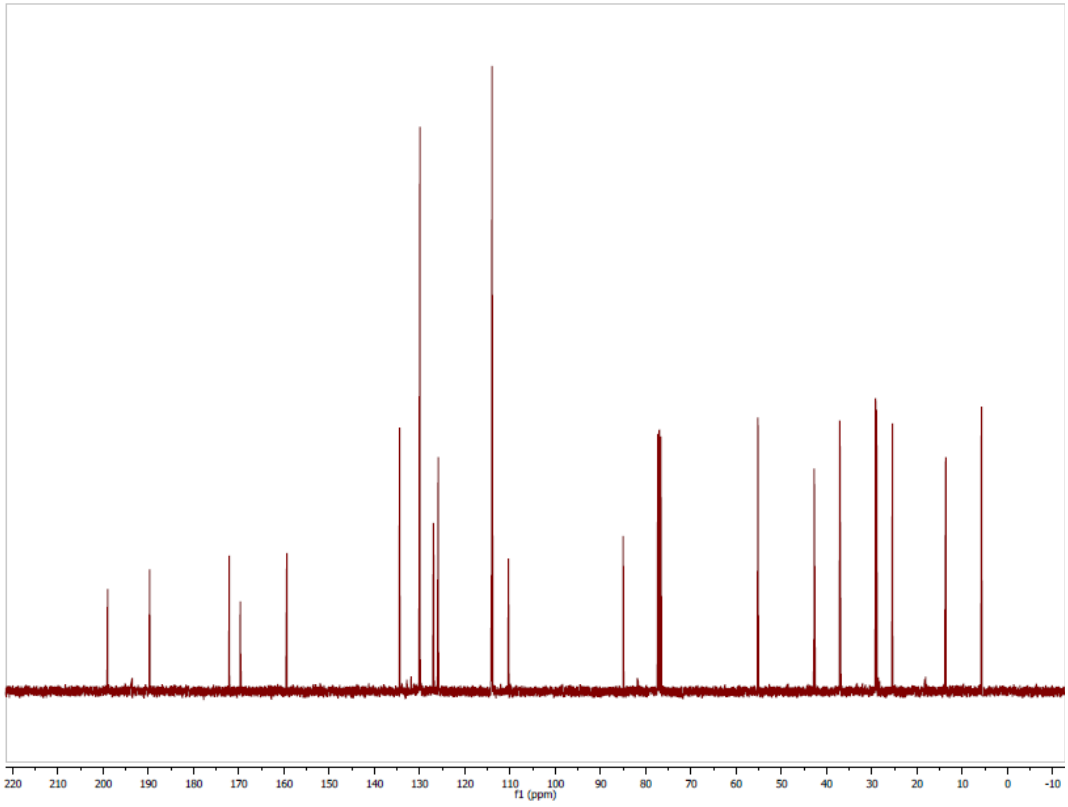
Stereochemical Asignment (nOe experiments)

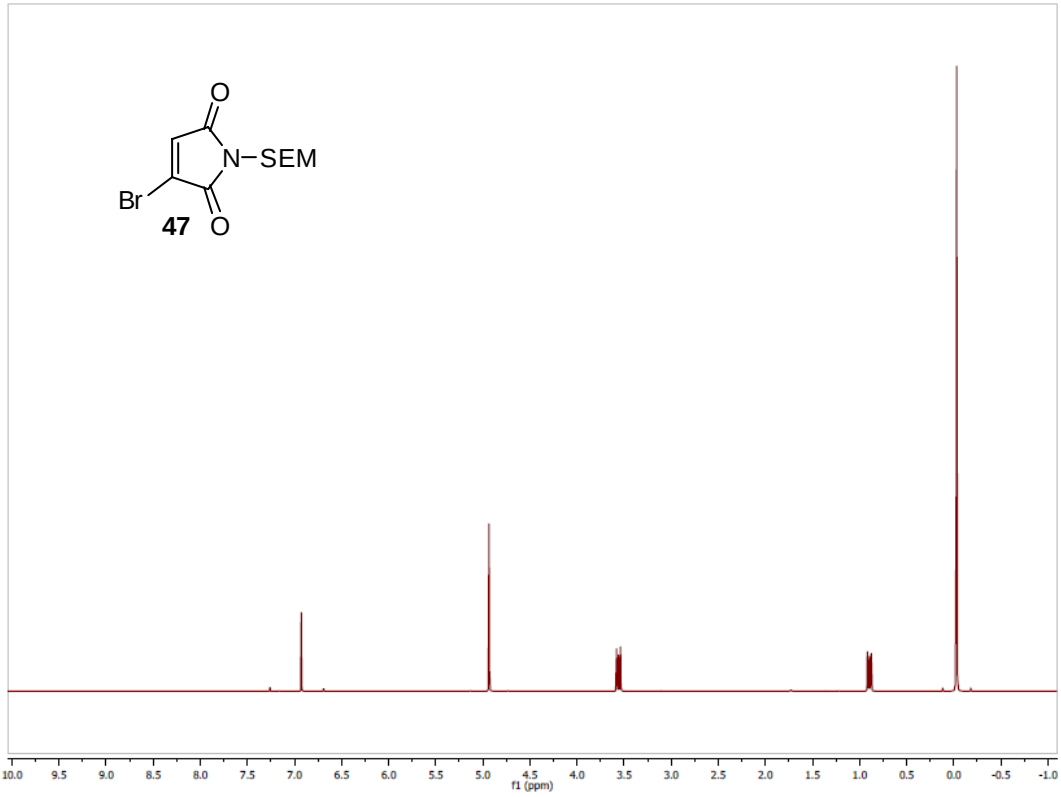


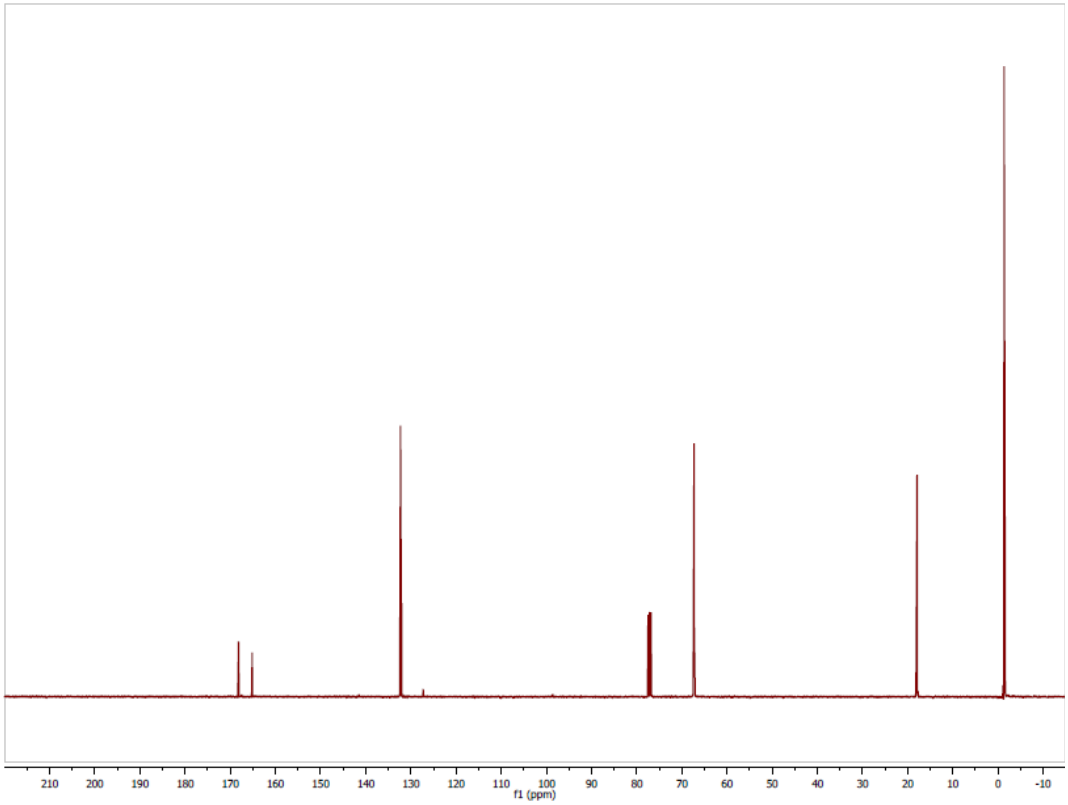

O
O
O
N
PMB
O
17
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

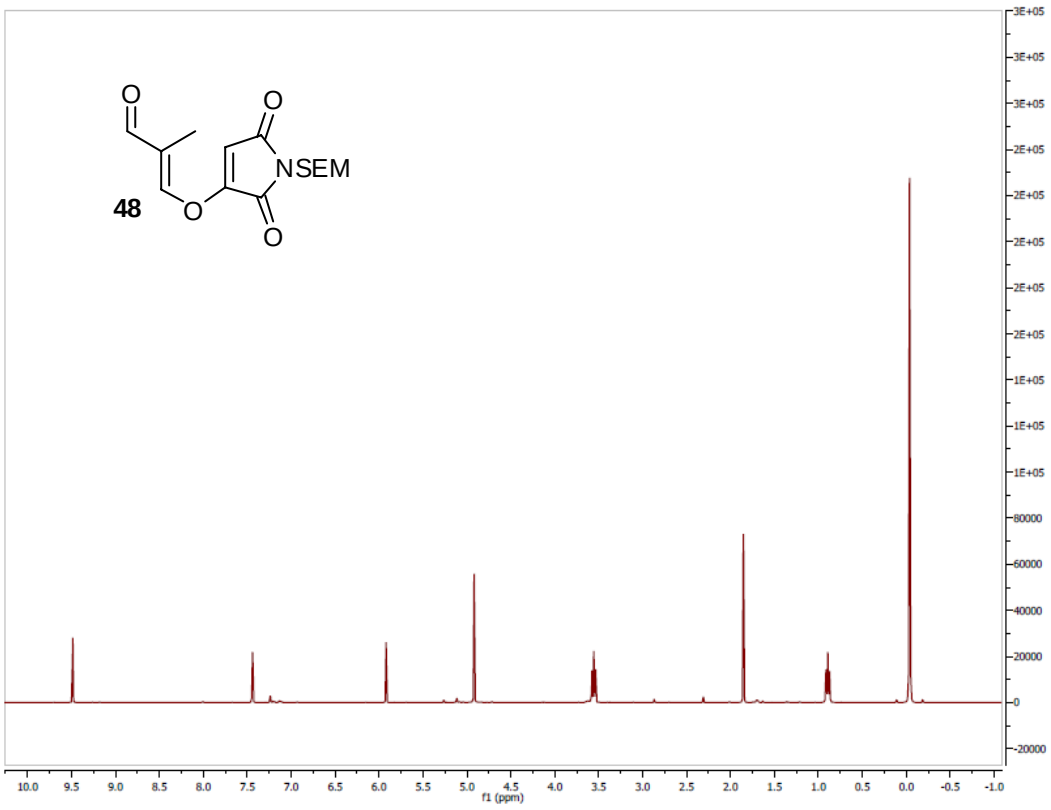

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

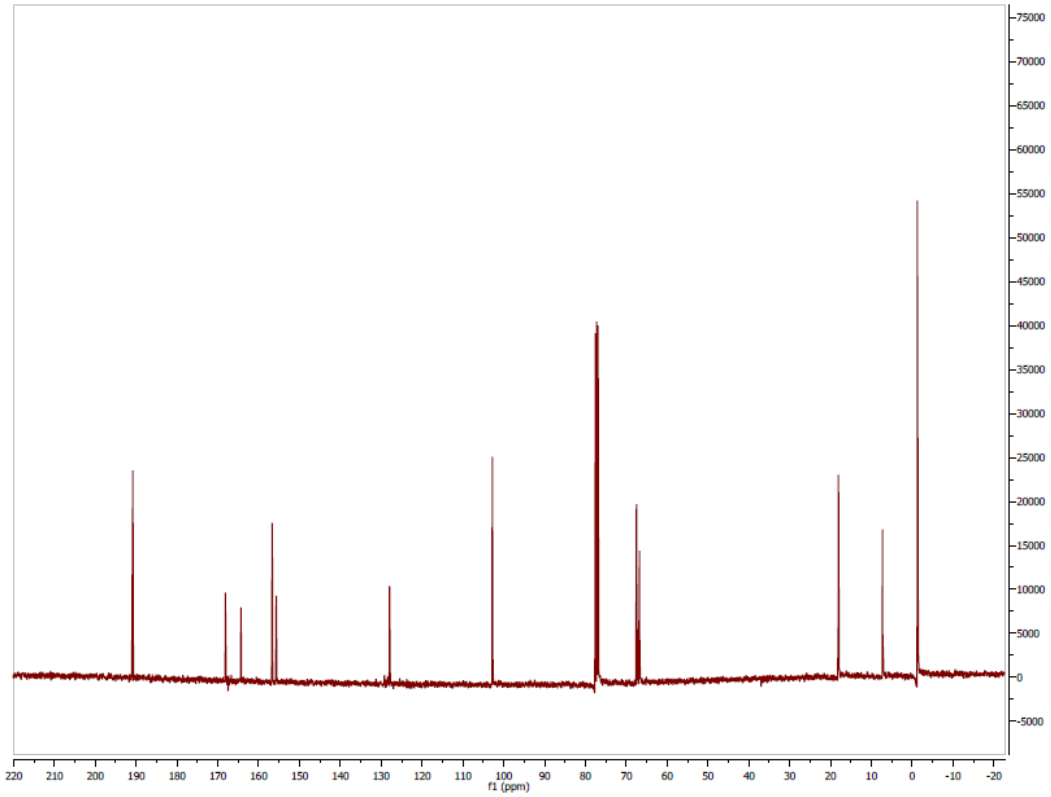

O
O
N
PMB
O
O
29
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

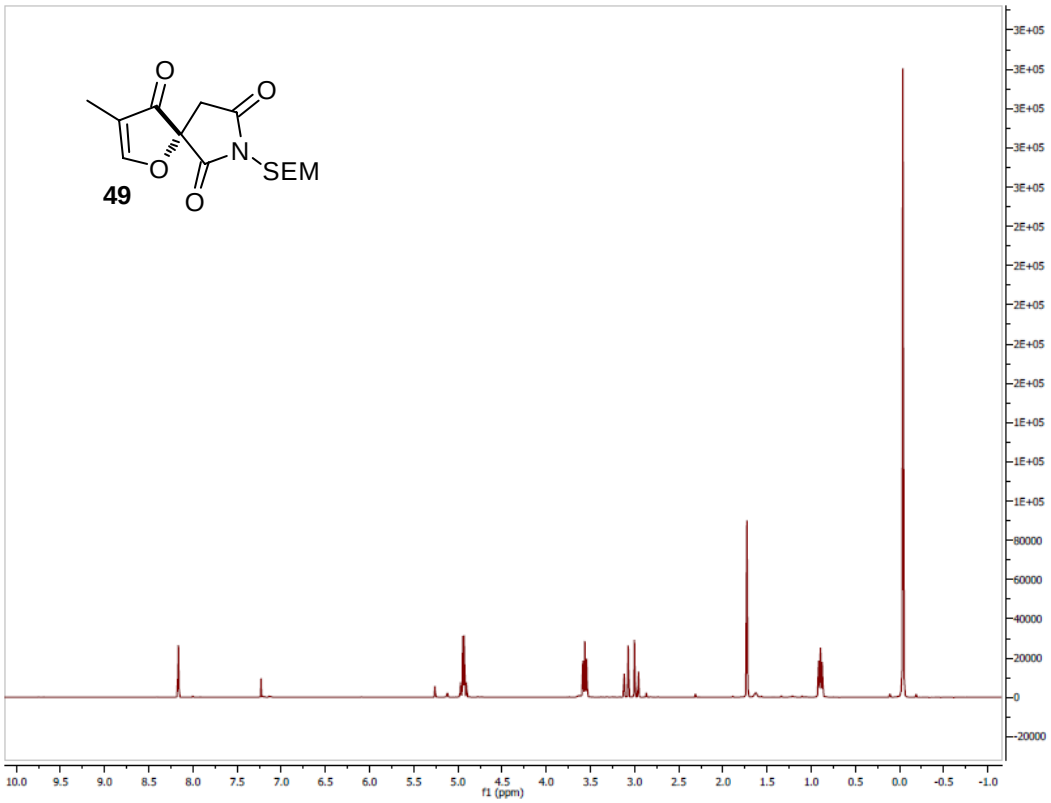

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

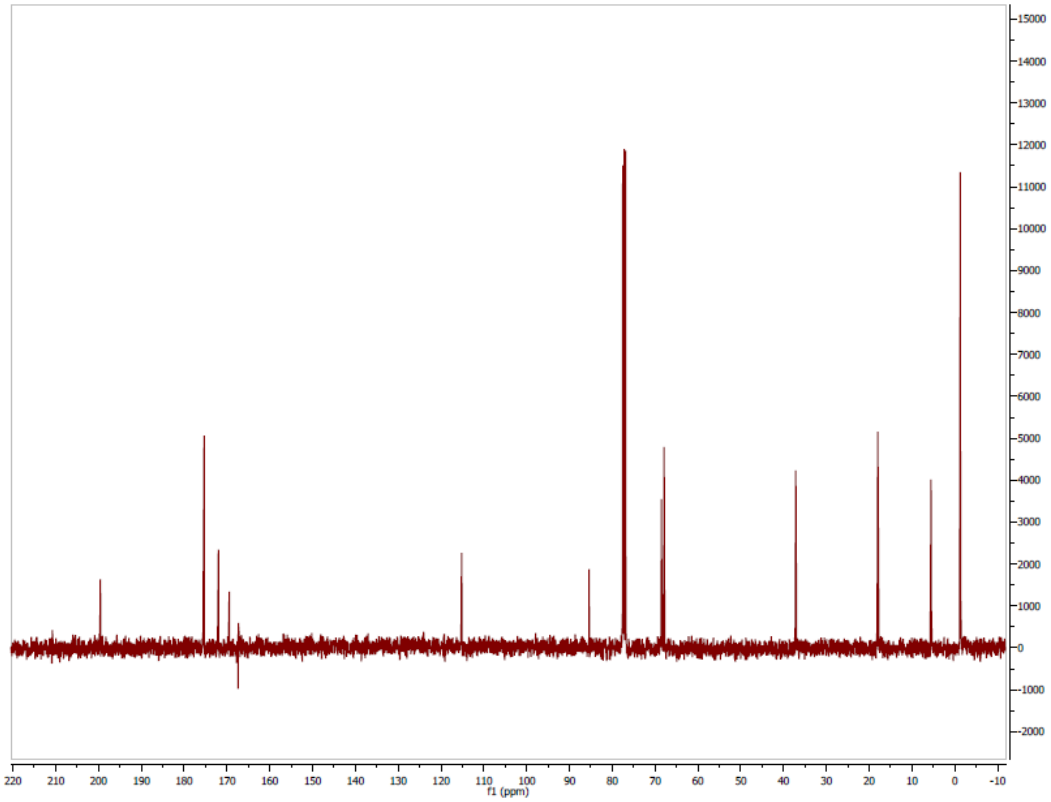

O
N−SEM
Br
O
47
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

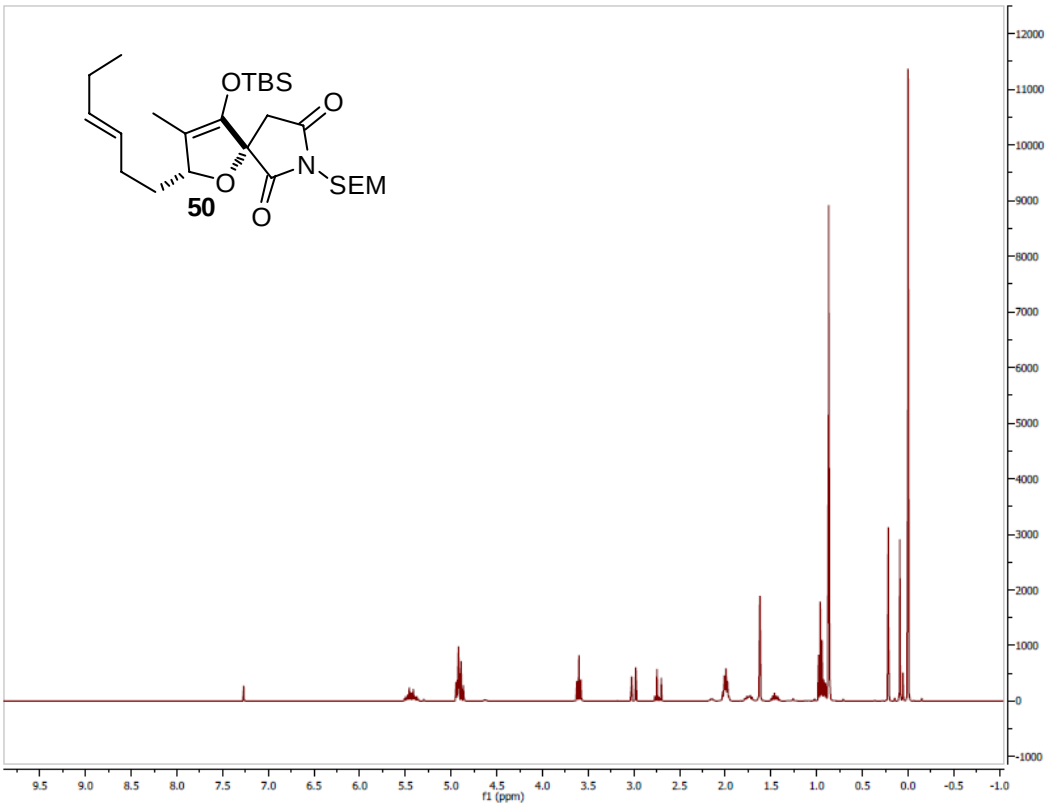

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

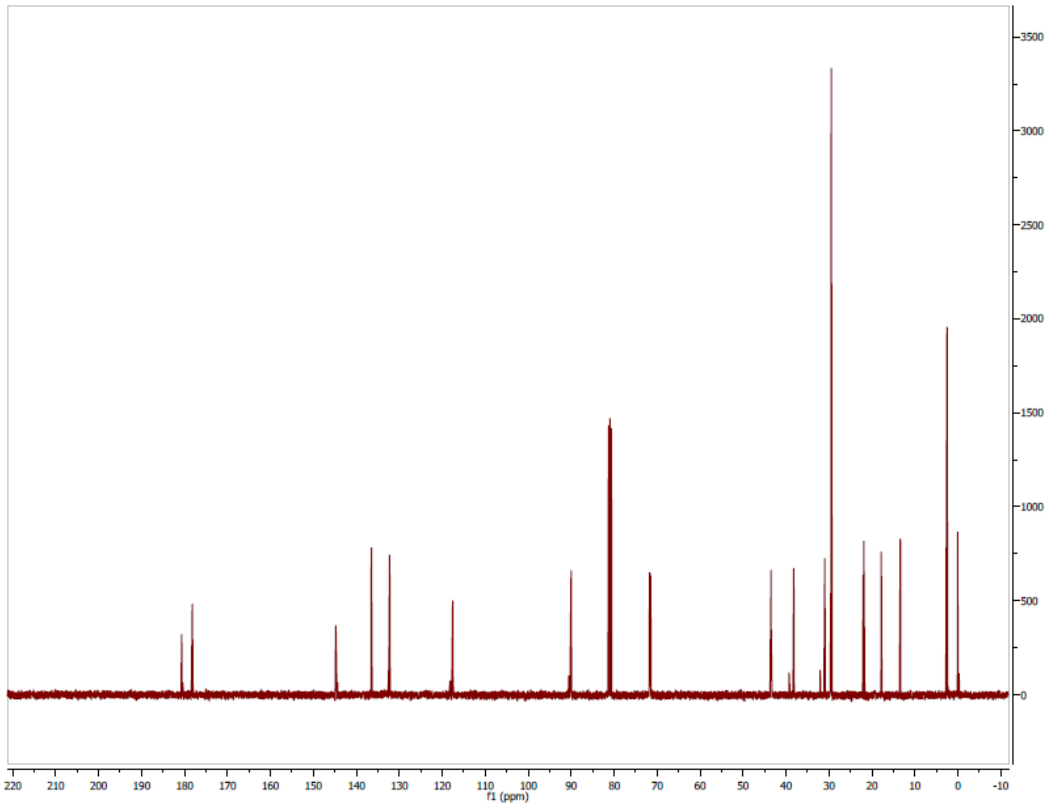

O
O
NSEM
O
O
48
3E+05
2E+05
1E+05
80000
60000
40000
20000
0
-20000
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

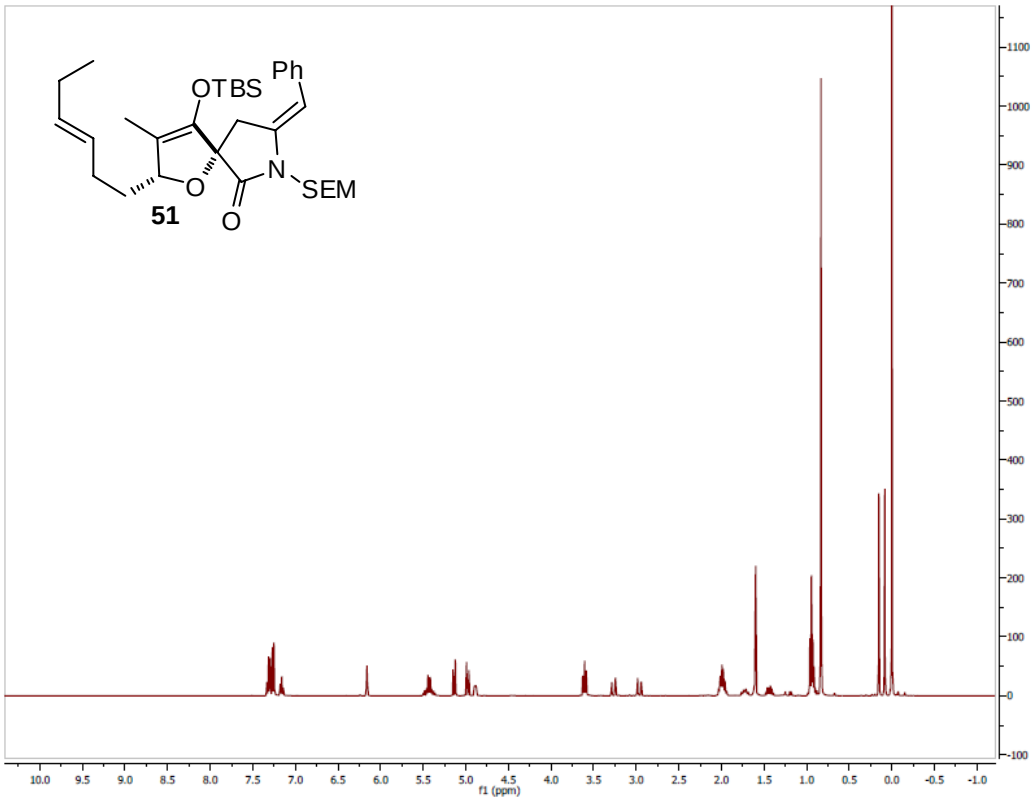

75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

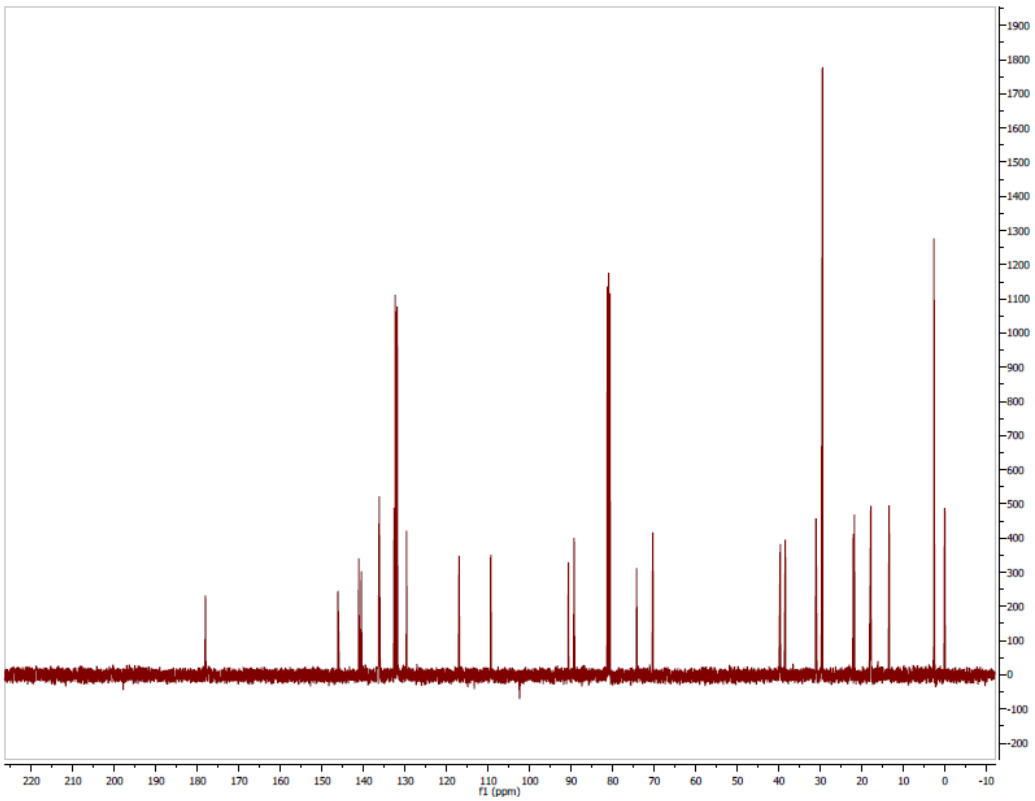

O
O
O
N
SEM
O
49
3E+05
2E+05
1E+05
80000
60000
40000
20000
0
-20000
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

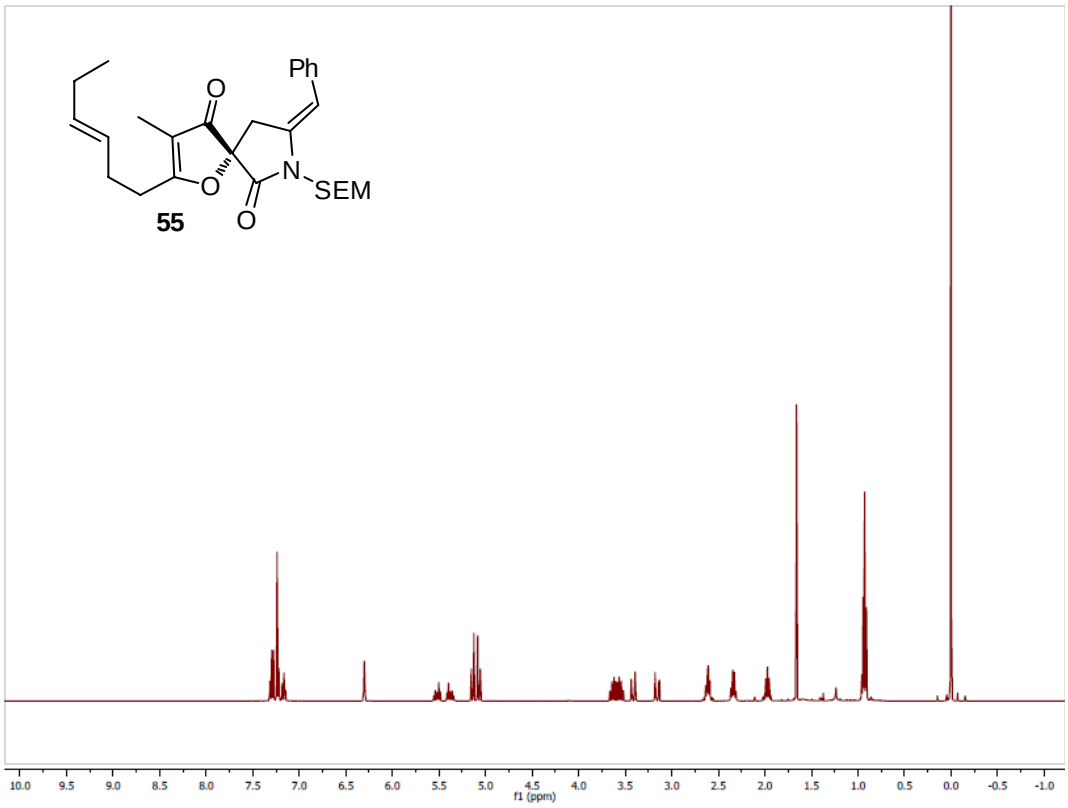

15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

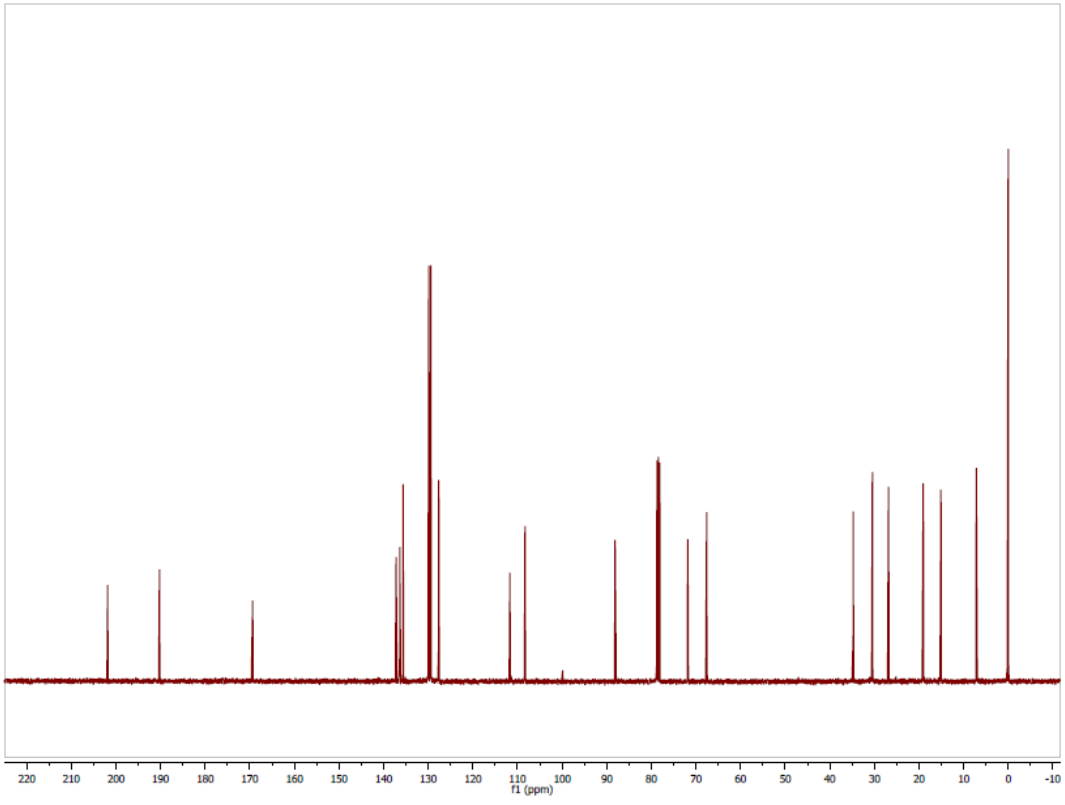

OTBS
O
N
SEM
O
O
50
f1 (ppm)

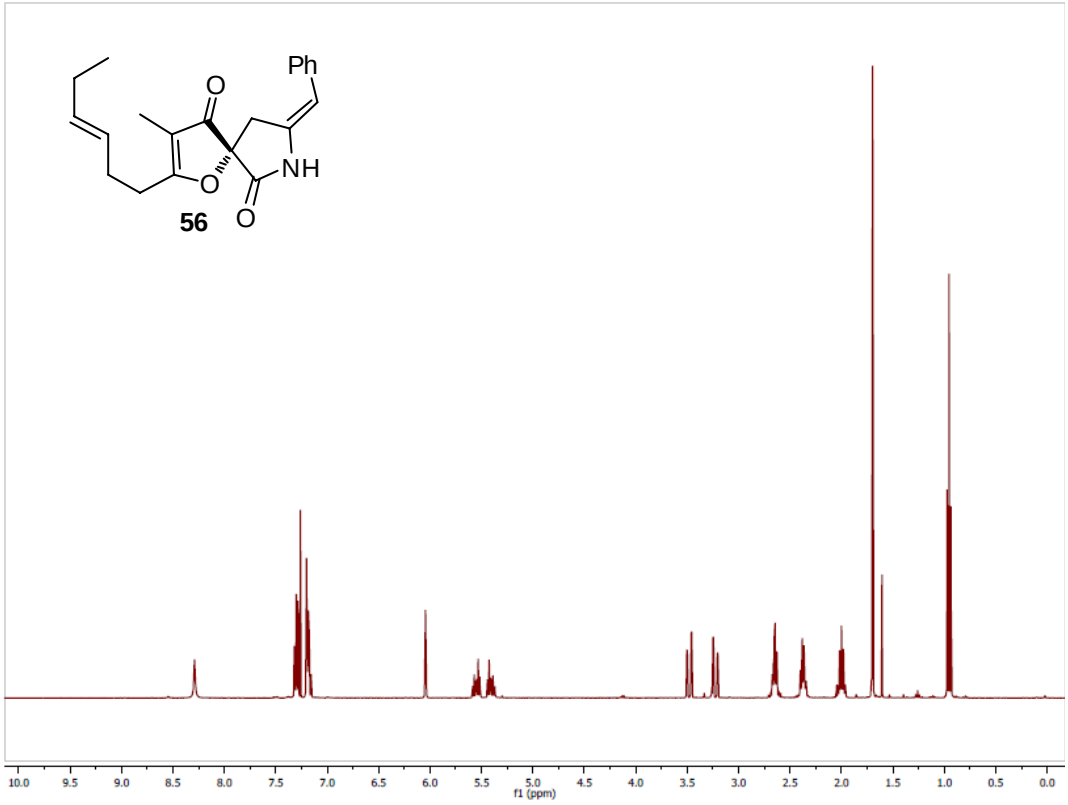

f1 (ppm)


OTBS
Ph
N
SEM
O
O
51
f1 (ppm)

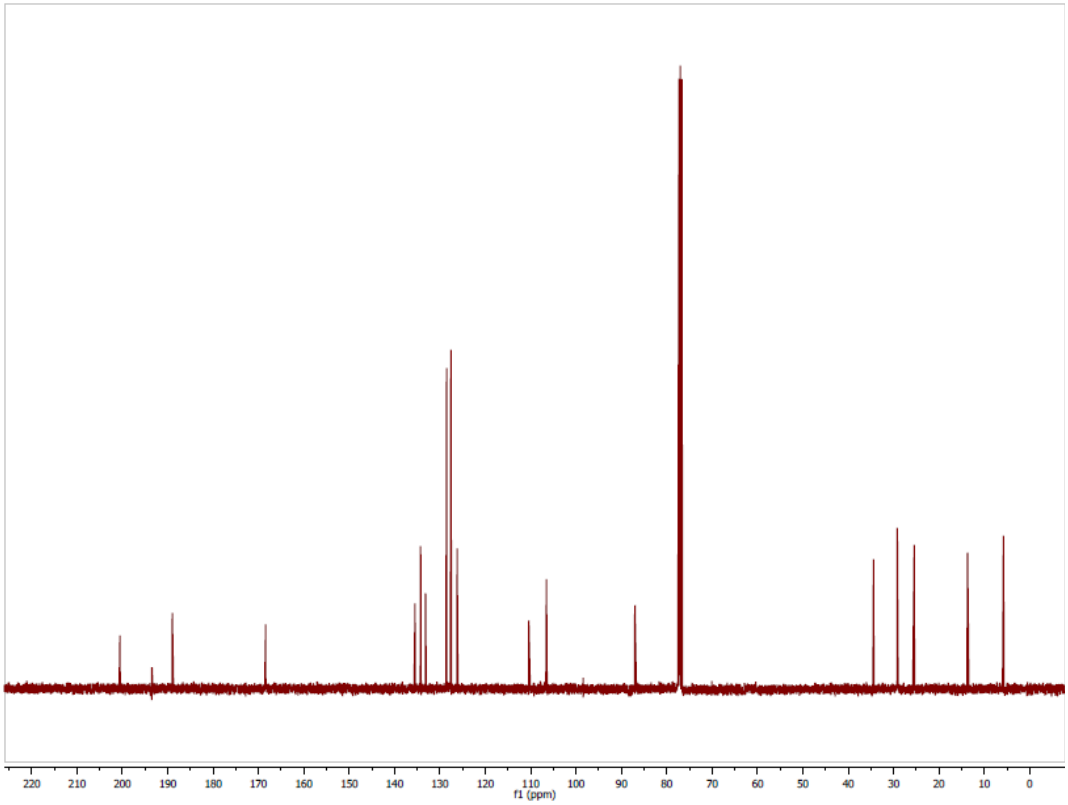

f1 (ppm)

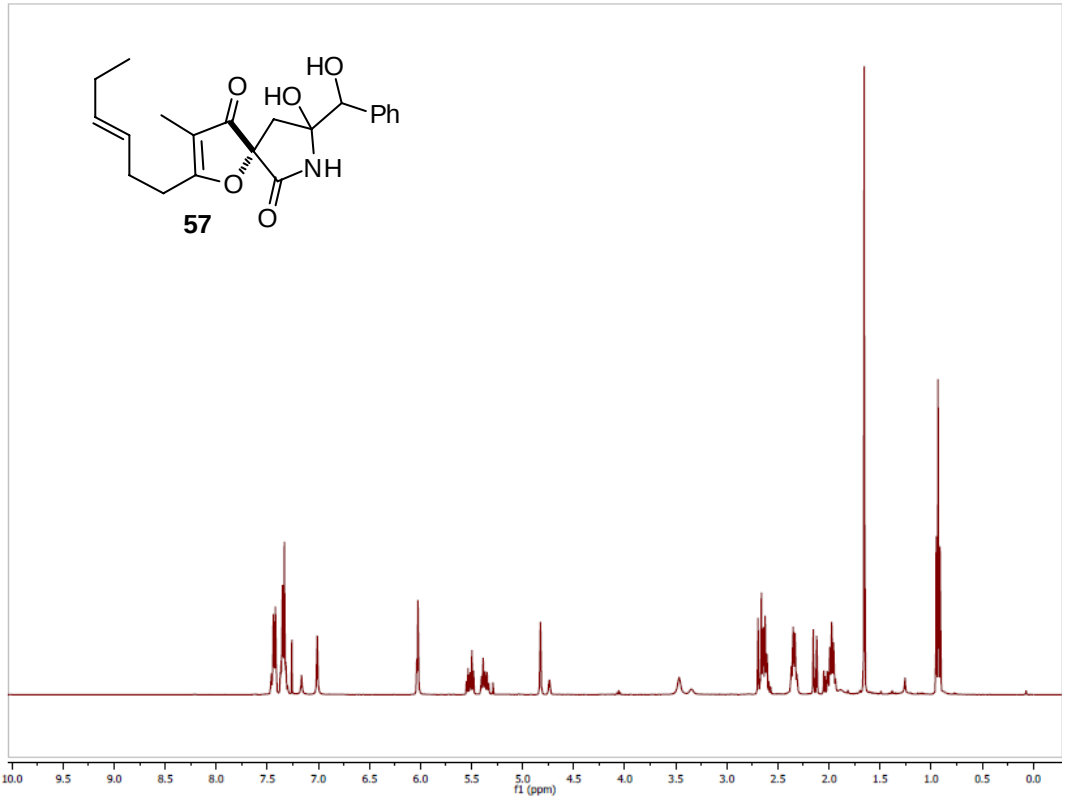

Ph
O
O
N
SEM
O
55
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

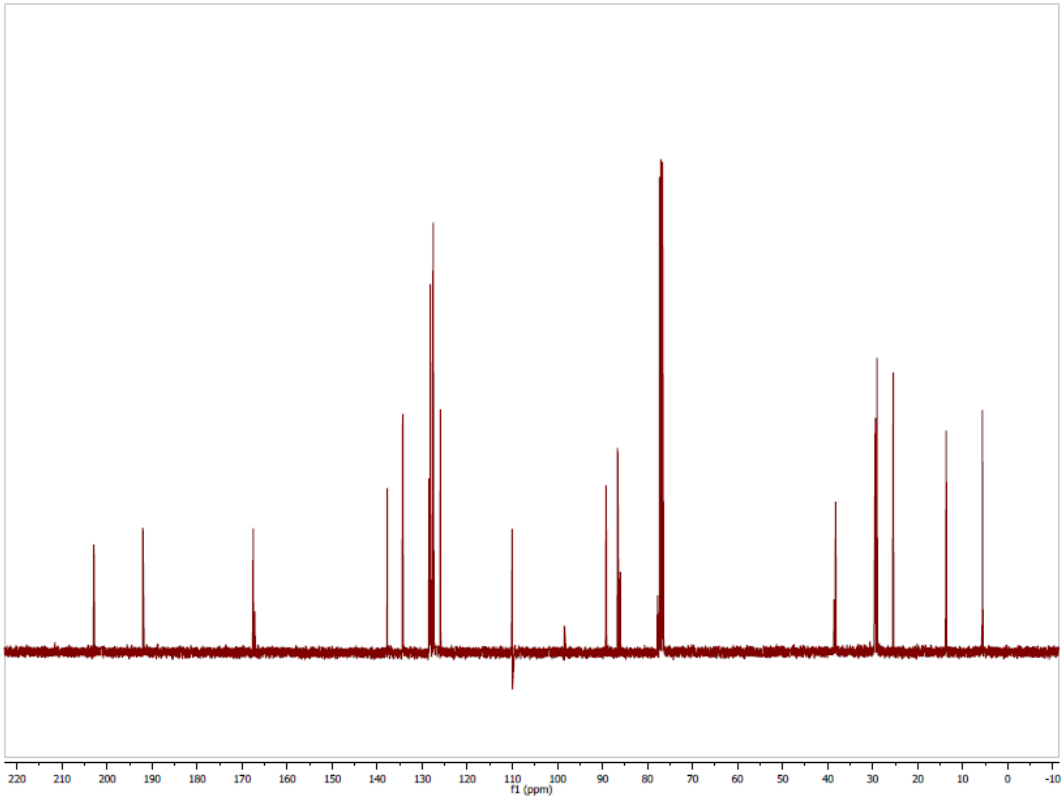

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

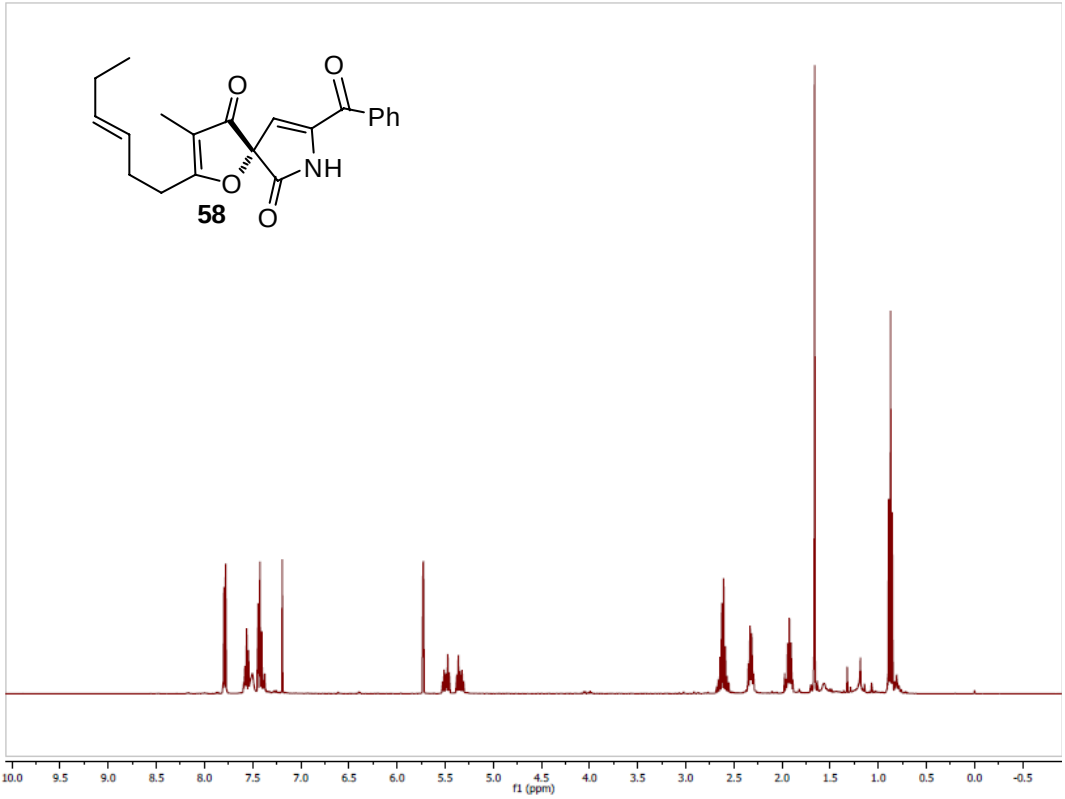

Ph
O
NH
O
O
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

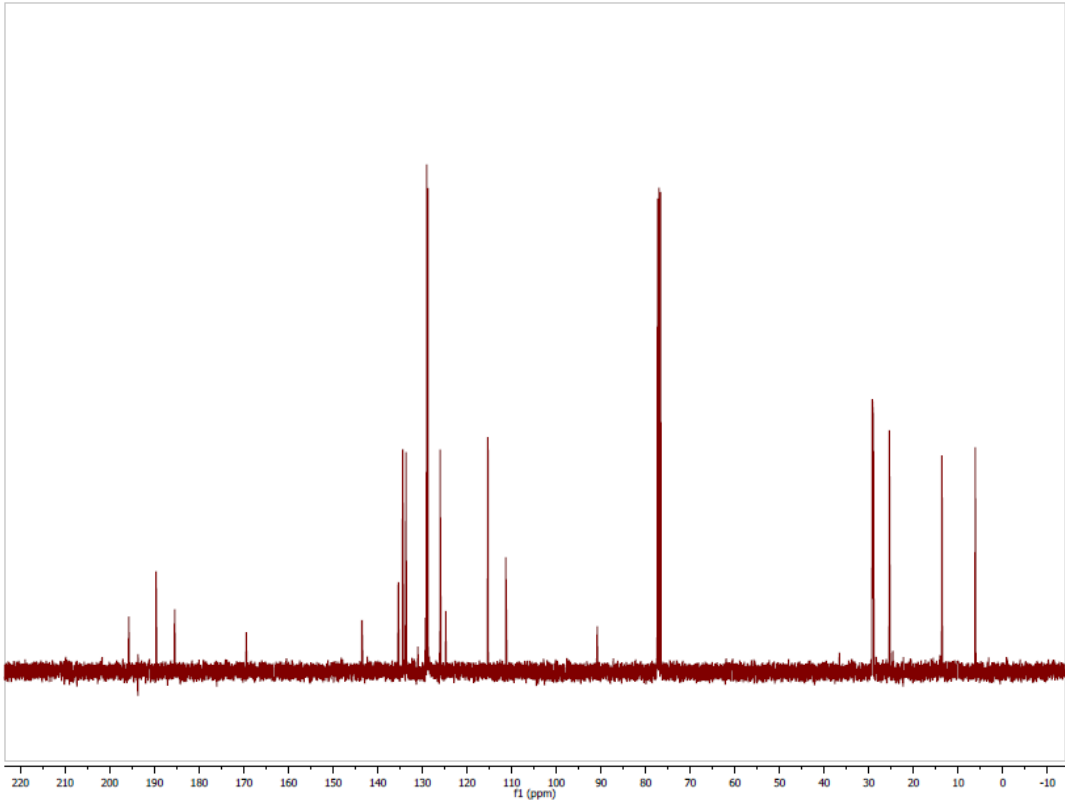
56

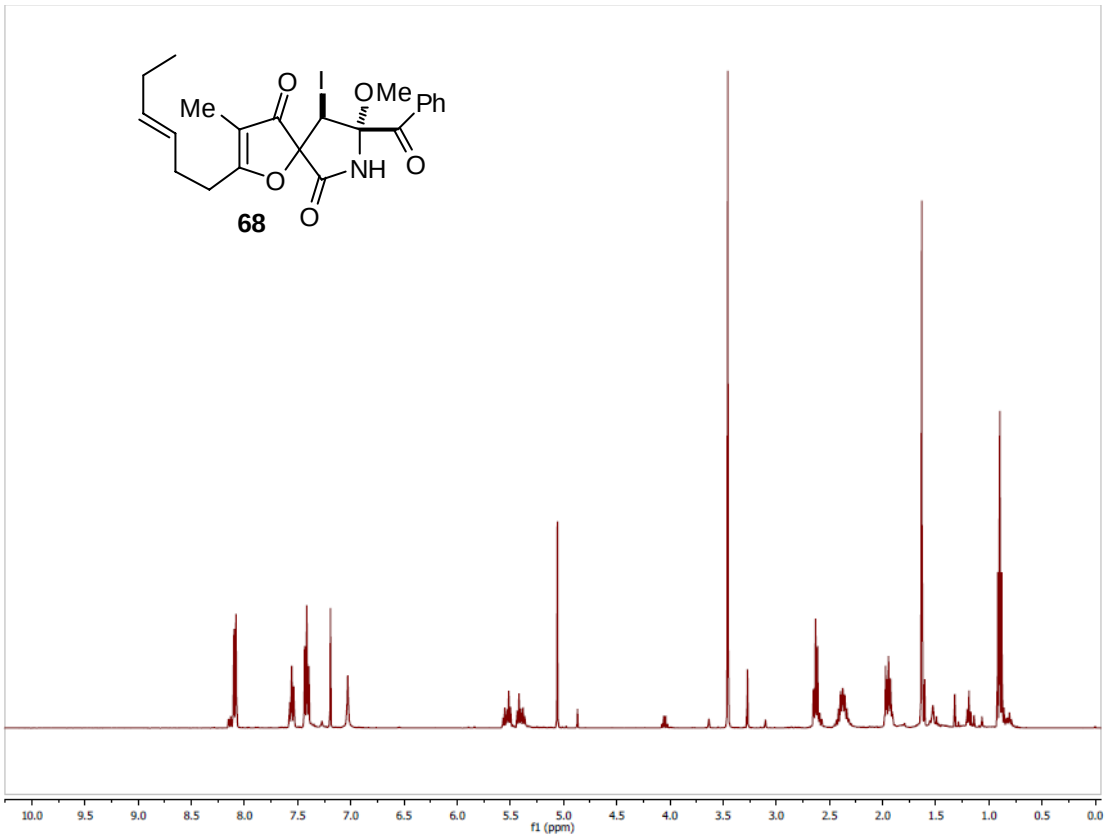

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

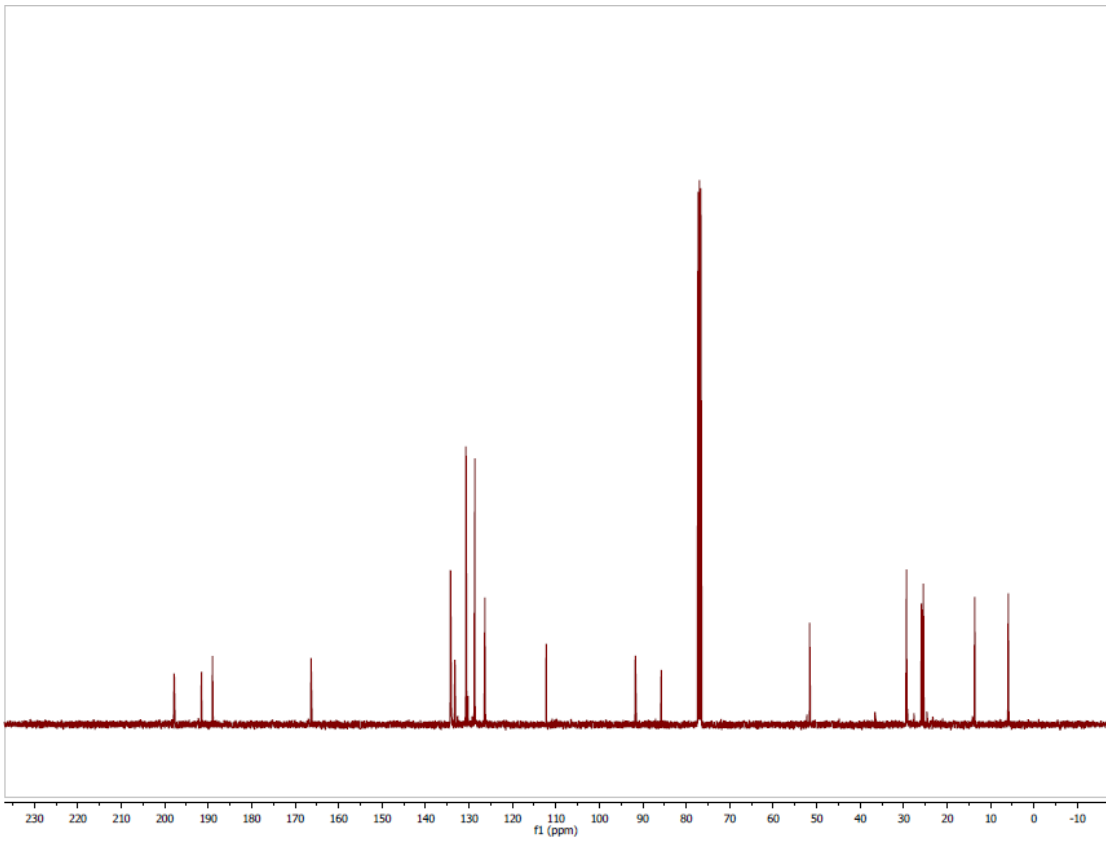

HO
O
HO
Ph
NH
O
O
57
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

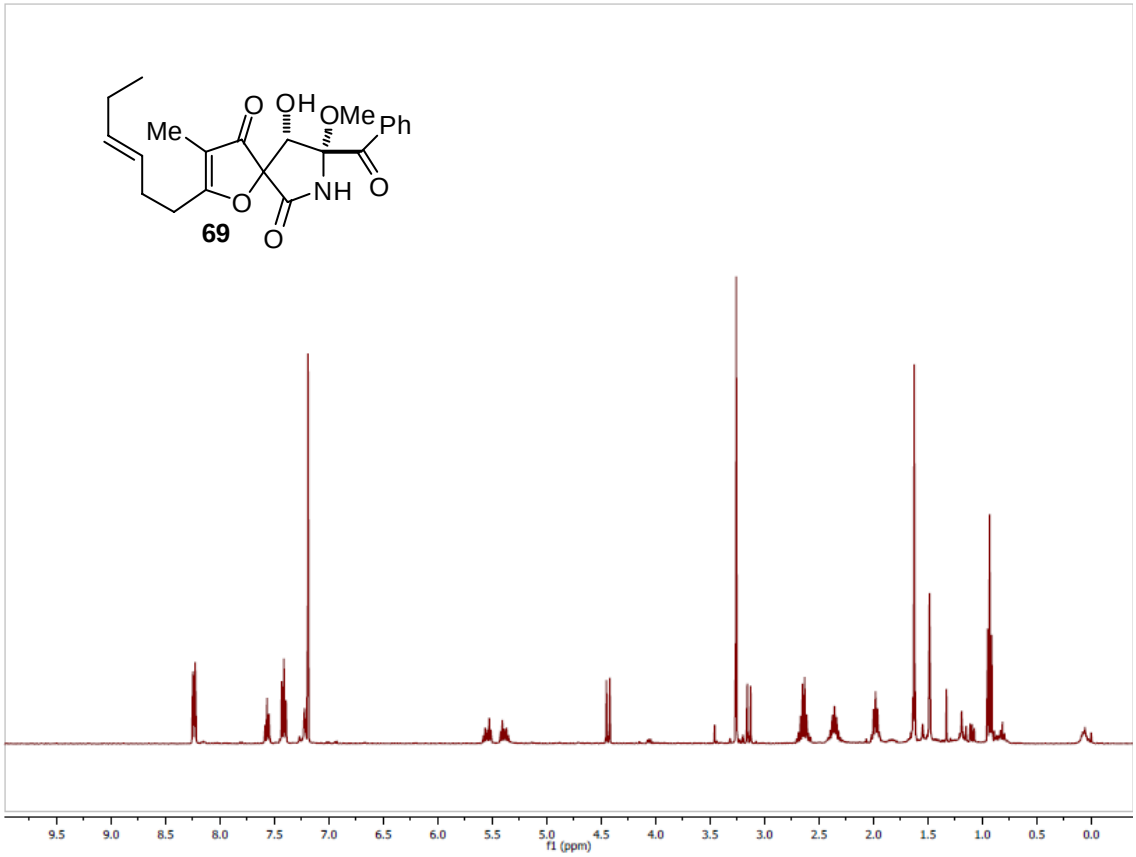

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

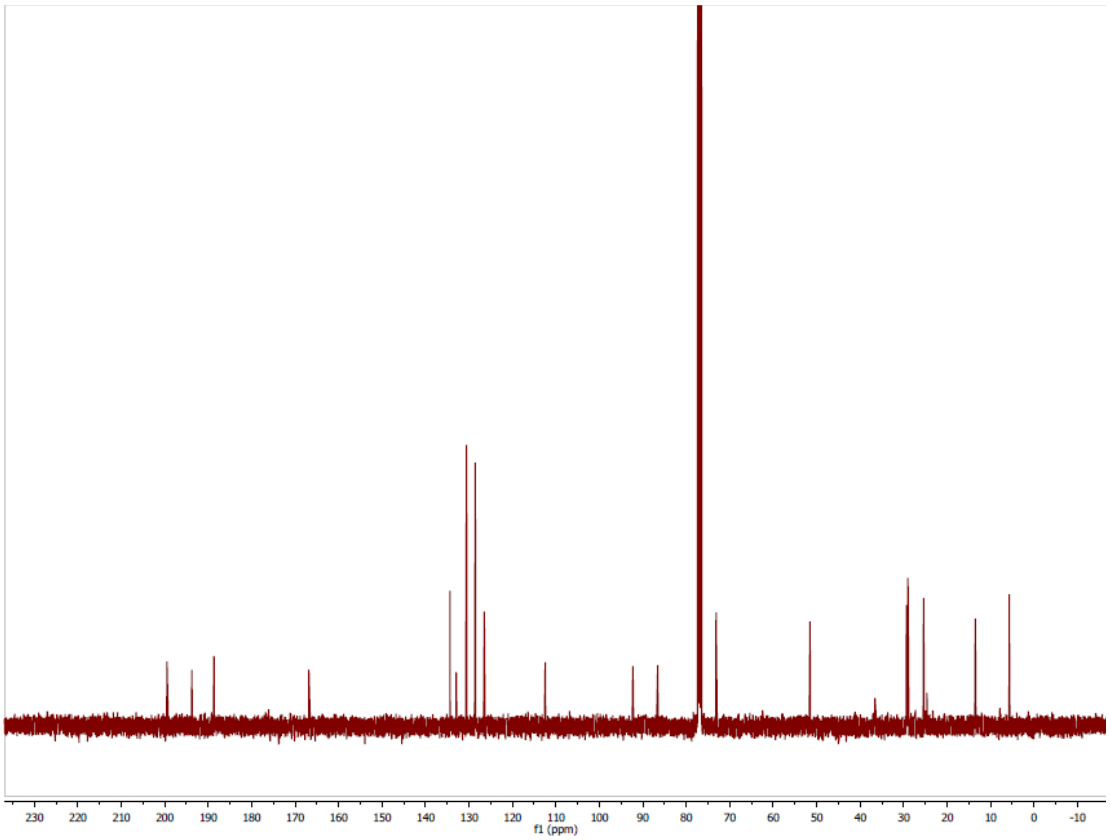

O
O
Ph
NH
O
O
58
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

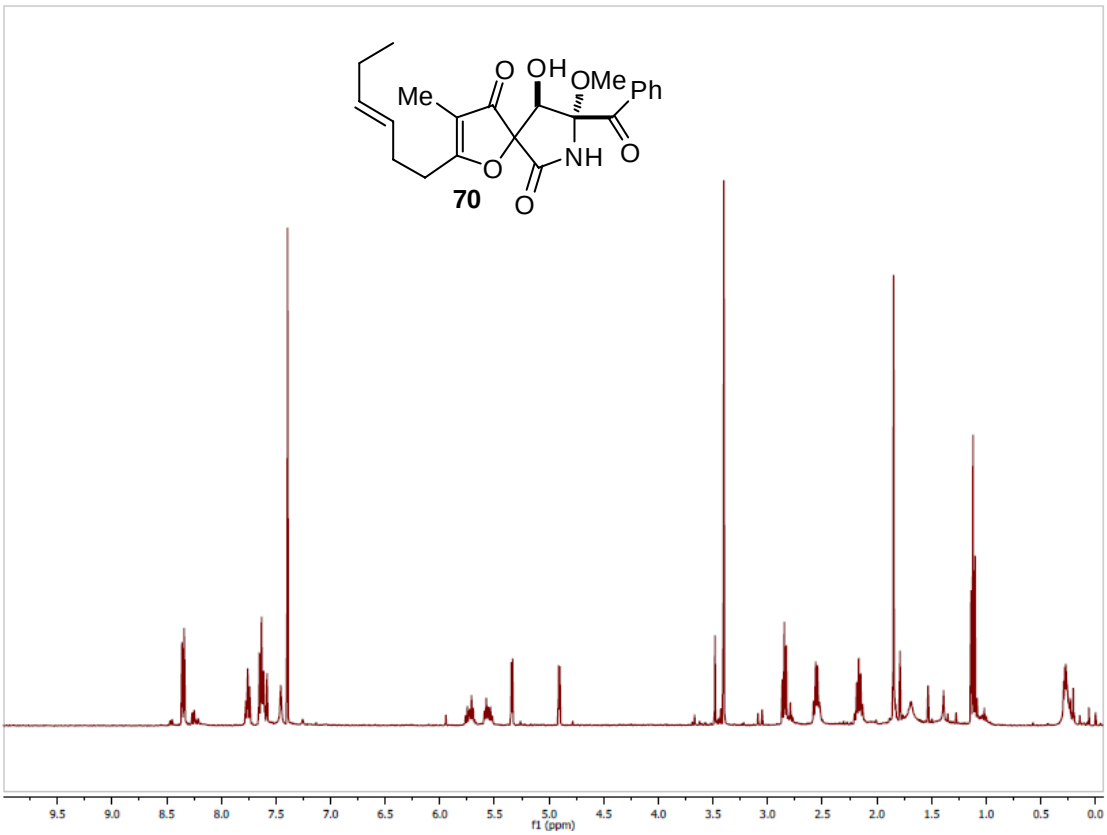

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

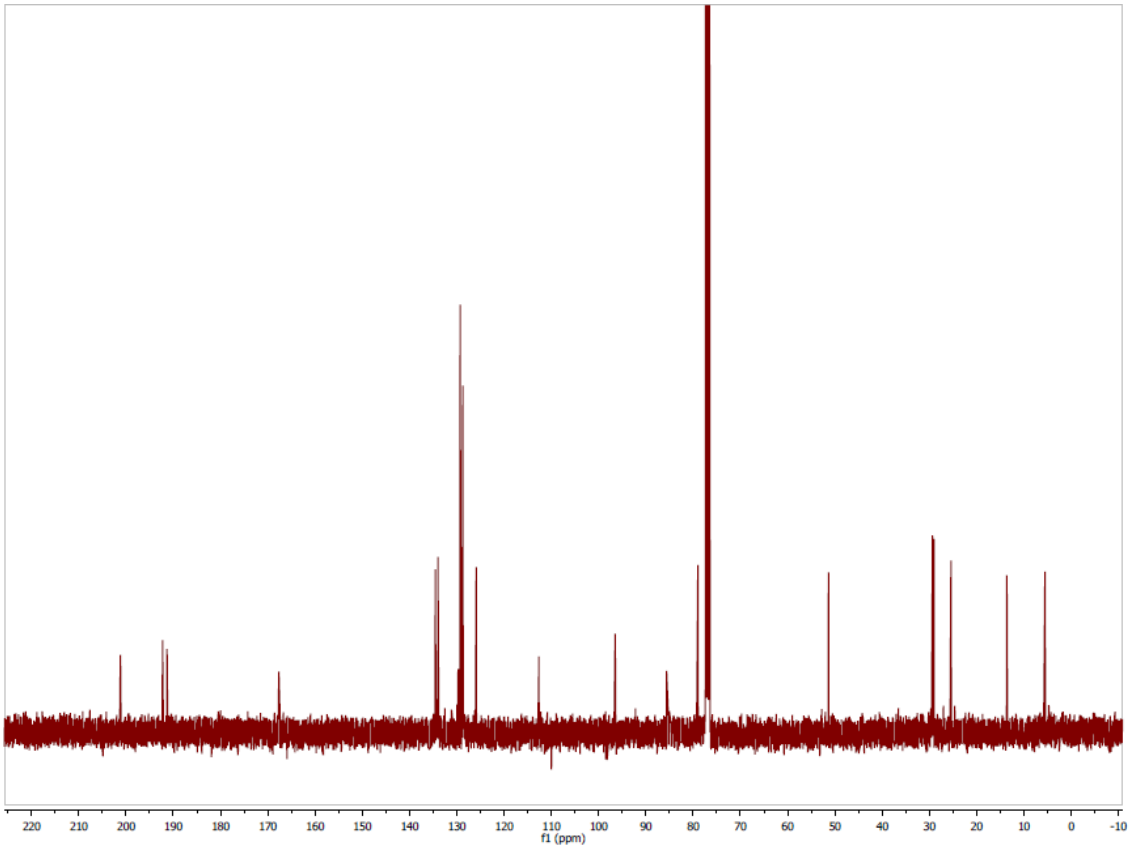

Me
O
I
OMe
Ph
O
NH
O
O
68
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

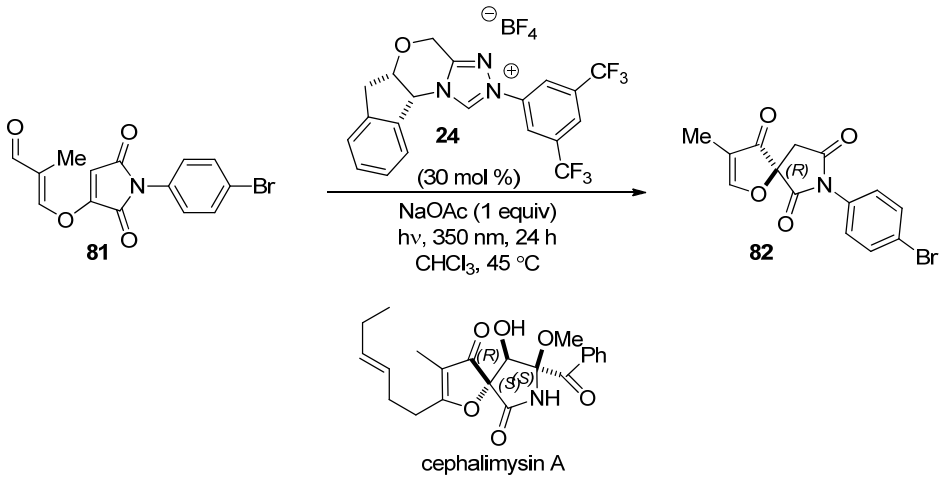

Me
O
OH
OMe
Ph
O
NH
O
O
69
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
O
OH
OMe
Ph
O
O
NH
O
O
70
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)


220
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)

Determination of Absolute Configuration of Stetter Product



The absolute configuration was determined by the crystal structure of the spirocycle shown **82**. This revealed that catalyst **24** yields the wrong enantiomer. Therefore when change was made to the SEM protecting group the ***ent*-24** catalyst was used to ensure the correct absolute stereochemistry.

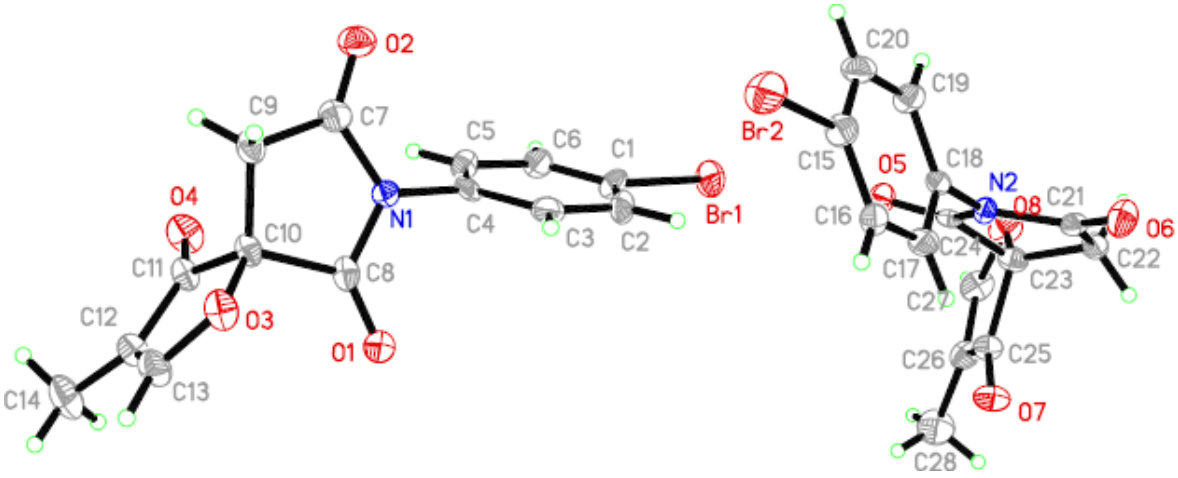


Table 1. Crystal data and structure refinement for **82**.

Identification code	**82**
Empirical formula	$C_{14}H_{10}BrNO_4$
Formula weight	336.14
Temperature	120 K
Wavelength	0.71073 Å

Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.8419(3) Å	α= 90°
	b = 6.55680(10) Å	β= 102.8190(10)°
	c = 20.7441(4) Å	γ = 90°
Volume	1570.53(6) Å^3	
Z	4	
Density (calculated)	1.422 Mg/m^3	
Absorption coefficient	2.628 mm^{-1}	
F(000)	672	
Crystal size	0.21 x 0.16 x 0.09 mm^3	
Theta range for data collection	1.76 to 31.62°.	
Index ranges	-17<=h<=17, -9<=k<=9, -30<=l<=30	
Reflections collected	37895	
Independent reflections	10026 [R(int) = 0.0540]	
Completeness to theta = 31.62°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8017 and 0.6136	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10026 / 1 / 364	
Goodness-of-fit on F^2	0.972	
Final R indices [I>2sigma(I)]	R1 = 0.0497, wR2 = 0.1177	
R indices (all data)	R1 = 0.0750, wR2 = 0.1254	
Absolute structure parameter	0.051(8)	
Largest diff. peak and hole	1.013 and -0.583 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **82**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	5687(1)	3090(1)	7814(1)	33(1)
Br(2)	8395(1)	9184(1)	7089(1)	37(1)
C(1)	5026(3)	4598(5)	7036(2)	21(1)
C(2)	5347(3)	6630(6)	7000(2)	24(1)
C(3)	4886(3)	7719(6)	6438(2)	24(1)
C(4)	4125(3)	6756(6)	5923(2)	18(1)
C(5)	3823(3)	4729(5)	5957(2)	20(1)
C(6)	4283(3)	3639(5)	6526(2)	23(1)
C(7)	3924(3)	7603(6)	4715(2)	25(1)
C(8)	2792(3)	9400(6)	5319(2)	19(1)
C(9)	3251(3)	9101(6)	4236(2)	23(1)
C(10)	2336(3)	9928(5)	4587(2)	19(1)
C(11)	1146(3)	8904(5)	4354(2)	19(1)
C(12)	330(3)	10537(6)	4246(2)	25(1)
C(13)	935(4)	12266(6)	4347(2)	26(1)
C(14)	-963(4)	10270(8)	4034(2)	39(1)
C(15)	8420(3)	7729(6)	7886(2)	26(1)
C(16)	8025(3)	8725(5)	8392(2)	21(1)
C(17)	8035(3)	7663(6)	8957(2)	23(1)
C(18)	8399(3)	5648(6)	9024(2)	18(1)
C(19)	8812(3)	4692(5)	8525(2)	23(1)
C(20)	8814(3)	5727(6)	7937(2)	26(1)
C(21)	9146(3)	4947(5)	10235(2)	19(1)
C(22)	8869(3)	3439(6)	10735(2)	21(1)
C(23)	7733(3)	2546(5)	10392(2)	21(1)
C(24)	7623(3)	2973(6)	9666(2)	18(1)
C(25)	6667(3)	3494(5)	10592(2)	19(1)
C(26)	5991(4)	1807(6)	10739(2)	25(1)
C(27)	6586(4)	114(6)	10670(2)	26(1)
C(28)	4861(4)	2066(8)	10934(2)	38(1)
N(1)	3607(2)	7875(4)	5337(1)	17(1)

N(2)	8359(3)	4578(4)	9627(1)	16(1)
O(1)	2477(2)	10088(4)	5786(1)	26(1)
O(2)	4595(3)	6320(4)	4624(1)	29(1)
O(3)	2113(2)	12060(4)	4527(1)	24(1)
O(4)	1011(3)	7050(4)	4289(2)	30(1)
O(5)	6986(2)	2131(4)	9203(1)	22(1)
O(6)	9885(3)	6230(5)	10312(1)	29(1)
O(7)	6523(3)	5329(4)	10621(1)	27(1)
O(8)	7598(3)	376(4)	10490(1)	27(1)

Table 3. Bond lengths [Å] and angles [°] for **82**.

Br(1)-C(1)	1.907(3)
Br(2)-C(15)	1.903(3)
C(1)-C(6)	1.370(5)
C(1)-C(2)	1.392(5)
C(2)-C(3)	1.372(5)
C(3)-C(4)	1.388(5)
C(4)-C(5)	1.382(5)
C(4)-N(1)	1.436(4)
C(5)-C(6)	1.384(5)
C(7)-O(2)	1.200(5)
C(7)-N(1)	1.433(4)
C(7)-C(9)	1.495(5)
C(8)-O(1)	1.200(4)
C(8)-N(1)	1.385(5)
C(8)-C(10)	1.535(5)
C(9)-C(10)	1.532(5)
C(10)-O(3)	1.423(4)
C(10)-C(11)	1.538(5)
C(11)-O(4)	1.230(4)
C(11)-C(12)	1.426(5)
C(12)-C(13)	1.333(6)
C(12)-C(14)	1.506(6)
C(13)-O(3)	1.368(5)
C(15)-C(20)	1.389(6)

C(15)-C(16)	1.403(5)
C(16)-C(17)	1.361(5)
C(17)-C(18)	1.387(5)
C(18)-C(19)	1.388(5)
C(18)-N(2)	1.444(4)
C(19)-C(20)	1.397(5)
C(21)-O(6)	1.199(5)
C(21)-N(2)	1.412(4)
C(21)-C(22)	1.521(5)
C(22)-C(23)	1.496(5)
C(23)-O(8)	1.451(4)
C(23)-C(24)	1.507(5)
C(23)-C(25)	1.545(5)
C(24)-O(5)	1.214(4)
C(24)-N(2)	1.380(5)
C(25)-O(7)	1.218(4)
C(25)-C(26)	1.437(5)
C(26)-C(27)	1.340(6)
C(26)-C(28)	1.491(6)
C(27)-O(8)	1.344(5)

C(6)-C(1)-C(2)	122.3(3)
C(6)-C(1)-Br(1)	119.2(3)
C(2)-C(1)-Br(1)	118.4(3)
C(3)-C(2)-C(1)	118.8(3)
C(2)-C(3)-C(4)	119.0(3)
C(5)-C(4)-C(3)	121.9(3)
C(5)-C(4)-N(1)	118.0(3)
C(3)-C(4)-N(1)	120.1(3)
C(4)-C(5)-C(6)	118.9(3)
C(1)-C(6)-C(5)	119.0(3)
O(2)-C(7)-N(1)	122.9(3)
O(2)-C(7)-C(9)	129.1(3)
N(1)-C(7)-C(9)	108.0(3)
O(1)-C(8)-N(1)	126.1(3)
O(1)-C(8)-C(10)	127.6(3)

N(1)-C(8)-C(10)	106.2(3)
C(7)-C(9)-C(10)	104.3(3)
O(3)-C(10)-C(9)	116.3(3)
O(3)-C(10)-C(8)	109.0(3)
C(9)-C(10)-C(8)	105.1(3)
O(3)-C(10)-C(11)	105.2(3)
C(9)-C(10)-C(11)	113.0(3)
C(8)-C(10)-C(11)	108.0(3)
O(4)-C(11)-C(12)	131.1(4)
O(4)-C(11)-C(10)	123.6(3)
C(12)-C(11)-C(10)	105.3(3)
C(13)-C(12)-C(11)	107.0(3)
C(13)-C(12)-C(14)	128.4(4)
C(11)-C(12)-C(14)	124.6(4)
C(12)-C(13)-O(3)	116.0(3)
C(20)-C(15)-C(16)	123.0(3)
C(20)-C(15)-Br(2)	118.7(3)
C(16)-C(15)-Br(2)	118.3(3)
C(17)-C(16)-C(15)	117.8(3)
C(16)-C(17)-C(18)	121.1(3)
C(17)-C(18)-C(19)	120.6(3)
C(17)-C(18)-N(2)	118.7(3)
C(19)-C(18)-N(2)	120.8(3)
C(18)-C(19)-C(20)	120.1(3)
C(15)-C(20)-C(19)	117.4(3)
O(6)-C(21)-N(2)	123.8(3)
O(6)-C(21)-C(22)	128.8(3)
N(2)-C(21)-C(22)	107.4(3)
C(23)-C(22)-C(21)	103.7(3)
O(8)-C(23)-C(22)	115.6(3)
O(8)-C(23)-C(24)	109.6(3)
C(22)-C(23)-C(24)	105.8(3)
O(8)-C(23)-C(25)	103.6(3)
C(22)-C(23)-C(25)	114.6(3)
C(24)-C(23)-C(25)	107.4(3)
O(5)-C(24)-N(2)	126.1(3)

O(5)-C(24)-C(23)	127.3(3)
N(2)-C(24)-C(23)	106.5(3)
O(7)-C(25)-C(26)	131.2(4)
O(7)-C(25)-C(23)	122.8(3)
C(26)-C(25)-C(23)	105.9(3)
C(27)-C(26)-C(25)	106.5(3)
C(27)-C(26)-C(28)	130.4(4)
C(25)-C(26)-C(28)	123.1(4)
C(26)-C(27)-O(8)	116.5(3)
C(8)-N(1)-C(7)	112.8(3)
C(8)-N(1)-C(4)	123.8(3)
C(7)-N(1)-C(4)	123.4(3)
C(24)-N(2)-C(21)	112.2(3)
C(24)-N(2)-C(18)	124.3(3)
C(21)-N(2)-C(18)	123.2(3)
C(13)-O(3)-C(10)	106.2(3)
C(27)-O(8)-C(23)	107.3(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for **82**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	37(1)	36(1)	23(1)	7(1)	-1(1)	11(1)
Br(2)	46(1)	45(1)	23(1)	12(1)	13(1)	7(1)
C(1)	29(2)	20(2)	13(1)	0(1)	6(1)	-1(1)
C(2)	21(2)	27(2)	22(2)	-6(1)	-4(1)	-2(2)
C(3)	20(2)	24(2)	30(2)	-7(1)	8(1)	2(2)
C(4)	8(2)	24(2)	21(2)	1(1)	3(1)	2(1)
C(5)	18(2)	24(2)	19(1)	-2(1)	4(1)	-7(1)
C(6)	28(2)	18(2)	21(2)	1(1)	4(1)	3(1)
C(7)	20(2)	32(2)	24(2)	5(1)	9(1)	-1(2)
C(8)	17(2)	22(2)	18(1)	6(1)	2(1)	-4(1)
C(9)	20(2)	29(2)	20(1)	9(2)	4(1)	1(2)

C(10)	15(2)	21(2)	21(2)	5(1)	2(1)	-1(1)
C(11)	14(2)	18(2)	23(2)	6(1)	2(1)	-2(1)
C(12)	23(2)	25(2)	26(2)	2(2)	3(2)	4(2)
C(13)	29(2)	17(2)	31(2)	6(2)	2(2)	6(2)
C(14)	22(2)	42(3)	46(3)	4(2)	-5(2)	3(2)
C(15)	25(2)	33(2)	20(2)	4(1)	7(1)	0(2)
C(16)	21(2)	22(2)	20(1)	0(1)	2(1)	0(1)
C(17)	16(2)	29(2)	24(2)	-4(1)	9(1)	-4(1)
C(18)	10(2)	26(2)	18(1)	-3(1)	5(1)	-2(1)
C(19)	30(2)	15(2)	23(2)	-1(1)	5(1)	3(1)
C(20)	23(2)	30(2)	26(2)	0(2)	12(2)	3(2)
C(21)	19(2)	24(2)	17(1)	-1(1)	7(1)	3(1)
C(22)	19(2)	28(2)	17(1)	2(1)	5(1)	2(1)
C(23)	22(2)	15(2)	25(2)	3(1)	7(1)	4(1)
C(24)	15(2)	18(2)	22(1)	-4(1)	5(1)	7(2)
C(25)	23(2)	13(2)	24(2)	2(1)	8(1)	0(1)
C(26)	29(2)	25(2)	21(2)	0(1)	9(2)	-4(2)
C(27)	34(2)	18(2)	28(2)	2(1)	13(2)	-7(2)
C(28)	33(3)	46(3)	40(2)	4(2)	17(2)	-7(2)
N(1)	17(2)	19(1)	17(1)	0(1)	4(1)	0(1)
N(2)	18(2)	15(1)	15(1)	-1(1)	2(1)	0(1)
O(1)	26(2)	28(1)	22(1)	-2(1)	3(1)	4(1)
O(2)	32(2)	32(2)	28(1)	5(1)	14(1)	8(1)
O(3)	26(2)	14(1)	29(1)	5(1)	1(1)	-5(1)
O(4)	29(2)	17(1)	41(2)	-1(1)	2(1)	-4(1)
O(5)	25(2)	22(1)	19(1)	0(1)	4(1)	-4(1)
O(6)	30(2)	36(2)	22(1)	-2(1)	6(1)	-10(1)
O(7)	28(2)	21(1)	35(2)	-1(1)	14(1)	4(1)
O(8)	38(2)	17(1)	28(1)	2(1)	9(1)	4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **82**.

	x	y	z	U(eq)
H(2)	5863	7239	7350	29
H(3)	5081	9082	6403	29
H(5)	3319	4108	5604	24
H(6)	4090	2275	6562	27
H(9A)	2889	8437	3824	28
H(9B)	3747	10189	4144	28
H(13)	578	13537	4299	32
H(14A)	-1145	9487	3633	58
H(14B)	-1326	11584	3959	58
H(14C)	-1241	9569	4375	58
H(16)	7765	10066	8344	25
H(17)	7793	8299	9304	27
H(19)	9088	3361	8583	28
H(20)	9069	5101	7593	31
H(22A)	9461	2393	10840	25
H(22B)	8805	4125	11140	25
H(27)	6312	-1176	10743	31
H(28A)	4460	784	10894	58
H(28B)	4399	3052	10649	58
H(28C)	4996	2530	11383	58

References

[1] For N-H bromomalemide: Sahoo, M. K.; Mhaske, S. B.; Argade, N. P. *Synthesis* **2003**, 346.

[2] For benzyl protection of Malemides: Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352.

[3] Martinez, A.; Alonso, M.; Castro, A.; Dorronsoro, I.; Gelpí, J. L.; Luque, F. J.; Pérez, C.; Moreno, F. J.; *J. Med. Chem.* **2005**, *48*, 7103.

[4] O'Sullivan, P.T.; Buhr, W.; Fuhry, M. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194.

[5] Molander, G. A.; Figueroa, R.; *Org Lett.* **2006**, *8*, 75.

[6] O'Sullivan, P.T.; Buhr, W.; Fuhry, M. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc.* **2004**, *126*, 2194.

[7] Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91.

Chapter 4 Experimental

Development of a Multicatalytic, Secondary Amine/*N*-Heterocyclic Carbene Cascade

General Methods.

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring unless otherwise stated. Reaction solvents including dichloromethane (DCM), diethyl ether (Et_2O), tetrahydrofuran (THF), toluene (PhMe), benzene, (PhH), Acetonitrile (MeCN), and Methanol (MeOH) were degassed with argon and passed through two columns of neutral alumina. HPLC grade Chloroform preserved with pentane was purchased from Fisher Scientific. ACS grade dimethyl sulfoxide (DMSO) was purchased from EDI chemical Inc. Column chromatography was performed on SiliCycle®Silica*Flash*® P60, 40-63μm 60A. Thin layer chromatography was performed on SiliCycle® 250μm 60A plates. Visualization was accomplished with UV light, cerium ammonium molybdenate, $KMnO_4$, or anisaldehyde stains followed by heating.

^1H nmr spectra were recorded on Varian 300 or 400 MHz spectrometers at ambient temperature unless otherwise stated. Data is reported as follows: chemical shift in parts per million (δ, ppm) from $CDCl_3$ (7.26 ppm), toluene-d_8 (7.09, 7.0, 6.98, 2.09 ppm) or benzene-d_6 (7.16 ppm) multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz). ^{13}C NMR was recorded on Varian 300 or 400 MHz spectrometers (at 75 or 100 MHz) at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ (77.2 ppm) or toluene-d_8 (137.86 (1), 129.4 (3), 128.33 (3), 125.49 (3), 20.4 (5) ppm). Infrared spectra were obtained on a Nicolet Avatar

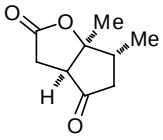
320 FT-IR spectrometer or Bruker Tensor 27 FT-IR spectrometer. Mass spectra were obtained on a Fisions VG Autospec.

α,β-Aldehydes and 1,3 dicarbonyls were either purchased from Aldrich or Acros or prepared via literature procedures (**27d**,[1] **27e**,[2] **27f**,[3] **27g**,[4] **27h**,[5] and **101g**[6]). *β*-ketoester **103b** was purchased form Aldrich as the HCl salt. The free base was generated by stirring in saturated $NaHCO_3$ and extraction with ethyl acetate. 3,5-bistrifluoromethyl diphenyl prolinol TMS **60** ether catalyst was prepared according to literature procedure.[7] All triazolium catalysts were prepared according to literature procedure.[8]

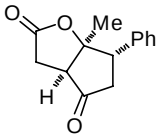
General Procedure for the Mukiyama Micheal/Stetter Reaction.

A 1-dram vial was equipped with a magnetic stir bar and placed under an argon atmosphere. To the vial was added secondary amine catalyst **28** or **60** (0.070 mmol, 0.2 equiv.), triazolium salt **3** (25 mg, 0.070 mmol, 0.2 equiv.) 2,4-dinitrobenzoic acid (15 mg, 0.070 mmol, 0.2 eq) and 1.5 mL of DCM. Crotonaldehyde **2** (88 μL, 1.06 mmol, 3.0 equiv.) was then added and the reaction was allowed to stir at ambient temperature for ~10 min. After 10 min the reaction was cooled to the appropriate temperature. Siloxyfurnan **35** (60 mg, 0.352 mmol, 1.0 equiv.) was dissolved in 0.5 mL of DCM and added to the reaction dropwise via syringe. The reaction was allowed to stir for 4-5 at room temperature or 10 hours at -70 °C at which point TLC indicated formation of intermediate aldehyde (R_f = 0.2, 2:1 hexanes/EtOAc, aldehyde shows up as a blue spot upon staining with anisaldehdye). DIPEA (123 μL, 0.704 mmol, 2.0 equiv.) is then added and the reaction is allowed to stir for 1 hour at which point complete conversion of the intermediate aldehyde and formation of product bicyclic lactone **59** was observed by TLC (R_f = 0.25, 2:1

hexanes/EtOAc, product **59** shows up as a brown spot upon staining with anisaldehdye). The reaction mixture was then filtered through a pad of silca (~ 1 in) and eluted with 10 mL of diethyl ether. Concentration and purification by silca gel chromatography (3:1 to 2:1 hexanes/EtOAc) affords the desired product. (Caution the bicyclic product is believed to be somewhat volatile and care should be taken when concentrating the crude mixture and the purified product.)



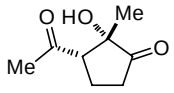
(*3aS,6R,6aS*)-6,6a-dimethyltetrahydro-2H-cyclopenta[b]furan-2,4(5H)-dione (59). According to the general procedure at room temperature utilizing catalyst **28** affords 20 mg (34% yield) of **59**. GC analysis-Chiraldex BDM-1 column at 140 °C at 1 mL/min; major enantiomer 21.5 min, minor enantiomer 22.0 min 52% ee; $[\alpha]_D^{21}$ = 72.5 (c = 0.012 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 2.84 (dd, 1H, *J* = 10.6, 18.6 Hz), 2.62 (m, 4H), 2.10 (ddd, 1H, *J* = 1.7, 2.6, 18.6 Hz), 1.45 (s, 3H), 1.02 (d, 3H, *J* = 7.5 Hz); ^{13}C nmr (100 MHz, $CDCl_3$) δ 215.8, 174.1, 93.0, 50.9, 45.2, 37.6, 32.5, 20.9, 16.8; IR (thin film/NaCl) 2971, 2937, 2360, 1778, 1747, 1588, cm^{-1}; HRMS $[C_9H_{12}O_3NH_4]^+$ calcd 186.1125, found 186.112.



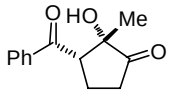
(*3aS,6S,6aS*)-6a-methyl-6-phenyltetrahydro-2*H*-cyclopenta[b]furan-2,4(5*H*)-dione (61). According to the general procedure at room temperature affords **61** in 43% yield. ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 3.40 (dd 1H, *J* = 8.9, 12.6 Hz), 2.92 (dd, 1H, *J* = 9.7, 18.2 Hz), 2.81 (dd, 1H, *J* = 6.0, 18.2 Hz , 2.79 (m, 3H), 1.47 (s, 3H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 214.5, 173.9, 135.0, 129.1, 128.5, 127.9, 91.2, 54.0, 50.5, 42.9, 32.3, 22.3; IR (thin film/NaCl) 2924, 1774, 1745, 1498, 1284, cm^{-1}; HRMS $[C_{14}H_{14}O_3NH_4]^+$ calcd 248.1281, found 248.1277.

General Procedure for the Michael/Benzion reaction with Acrolein.

To a flame dried flask under argon was added triazolium salt **58** (18 mg, 0.049) followed by toluene (3 mL). To the heterogenous mixture was added KHMDS (18 mg, 0.098 mmol) in toluene (1 mL) via syringe and the reaction was allowed to stir for 10 min at room temperature. The reaction was then heated to 60 °C and appropriate diketone (0.363 mmol) was added followed by acrolein (16 μL, 0.242 mmol) in toluene (1 mL) over 15 min. Upon completion of the reaction as determined by TLC analysis the reaction was allowed to cool to room temperature and the mixture was filtered through a plug of silica gel and concentrated *in vacuo*. Purification of the crude product via column chromatography affords the desired product.



3-acetyl-2-hydroxy-2-methylcyclopentanone (68). According to the general procedure affords 29 mg (76% yield) of **68** as a 5:1 mixture of diastereomers. Major Diastereomer: ^{1}H nmr (400 MHz, $CDCl_3$) δ 3.03 (dd, 1H, *J* = 7.2, 11.7 Hz), 2.46 (m, 1H), 2.25 (s, 3H), 2.10 (m, 2H), 1.88 (m, 1H), 0.99 (s, 1H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 217.8, 207.3, 78.5, 58.0, 32.2, 30.7, 19.4, 17.7; IR (thin film/NaCl) 3447 br, 2924, 2360, 1749, 1702, 1366 cm^{-1}; HRMS $[C_8H_{12}O_3NH_4]^+$ calcd 174.1125, found 174.1118.



3-benzoyl-2-hydroxy-2-methylcyclopentanone (73). According to the general procedure affords 23 mg (43% yield) of **73** as a 4:1 mixture of the major prodcut to the sum of all other isomers. Major Diastereomer: ^{1}H nmr (400 MHz, $CDCl_3$) δ 8.13 (d, 2H, *J* = 6.3 Hz), 7.58 (t, 1H, *J* = 7.4 Hz), 7.47 (t, 2H, *J* = 7.9), 4.04 (dd, 1H, *J* = 7.1, 10.5 Hz), 2.79 (s, 1H), 2.61 (m, 1H), 2.45 (m, 2H), 2.07 (m, 1H), 1.08 (s, 3H);

^{13}C nmr (100 MHz, $CDCl_3$) δ 218.0, 199.2, 137.2, 133.5, 129.2, 128.5, 79.1, 52.8, 32.7, 19.9, 19.5; IR (thin film/NaCl) 3429 br, 2359, 1747, 1733, 1671, 1447, 1298 cm^{-1}; HRMS $[C_{13}H_{14}O_3NH_4]^+$ calcd 236.1281, found 236.1274.

General Procedure for Multicatalytic Cascade Michael/Benzoin Reaction:

A 1 dram vial was equipped with a magnetic stir bar under argon and charged with 8.0 mg (0.022 mmol) of triazolium salt **58**. $CHCl_3$ (1 mL), 1,3 dicarbonyl (0.448 mmol), and enal (0.224 mmol) were added sequentially followed by 26.3 mg (0.044 mmol) of siloxy prolinol **60** and 1.8 mg (0.022 mmol) of sodium acetate in one portion. After stirring at ambient temperature for 12 h the reaction was filtered through a 1in plug of silica, eluted with Et_2O (~10 mL) and concentrated *in vacuo*. The resulting crude product was purified by flash silica gel chromatography.

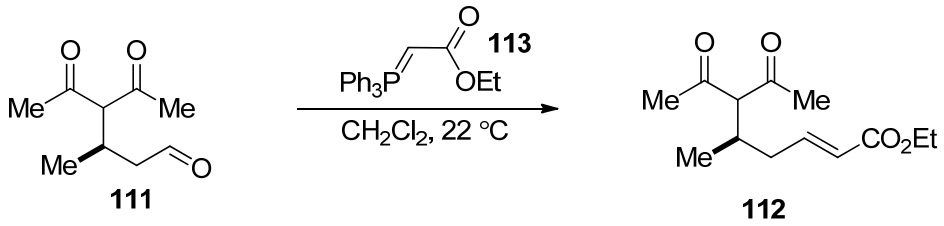
Procedure for preparation of 102c on 2.4 mmol Scale

A 10 mL round bottom flask was equipped with a magnetic stir bar under argon and charged with 44.0 mg (0.12 mmol) of triazolium salt **58**. $CHCl_3$ (5 mL), methyl acetoacetate 520 μL (4.82 mmol), and crotonaldehyde 200 μL (2.41 mmol) were added sequentially followed by 144 mg (0.241 mmol) of siloxy prolinol **60** and 10.0 mg (0.12 mmol) of sodium acetate in one portion. After stirring at ambient temperature for 12 h the reaction was pre-absorbed on silca gel and purified by flash silica gel chromatography (4:1 hexanes/EtOAc, R_f = 0.3 2:1 hexanes/EtOAc). 404 mg of the desired product **102c** was isolated as a separable mixture of diatereomers (90% yield). 64:33:3:<1 dr, 91% ee (major diastereomer).

Procedure for Preparation of Aldehyde 111:

A 1 dram vial was equipped with a magnetic stir bar and placed under an argon atomosphere. $CHCl_3$ (1 mL), acetylacetone 48 μL (0.448 mmol), and crotonaldehdye 19 μL (0.224 mmol) were added sequentially followed by 26.3 mg (0.044 mmol) of siloxy prolinol **60.** After stirring at ambient temperature for 12 h the reaction was filtered through a 1 in plug of silica, eluted with Et_2O (~10 mL) and concentrated *in vacuo*. The resulting crude product was submitted to flash silica gel chromatography (2:1 hexanes/EtOAc, R_f = 0.2, 2:1 hexanes/EtOAc) to afford 27 mg of semi-pure material (~80% pure) in 70% yield. For complete characterization and determination of ee the resultant aldehyde **111** was converted to the α,β-unsaturated ethyl ester via wittig reaction (*vida infra)*.

Procedure for Preparation of α,β-unsaturated Ethyl Ester 112.

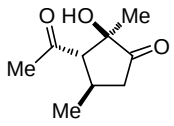


Aldehyde **111**, 20 mg (0.118 mmol) was dissolved in CH_2Cl_2 (1 mL) and added to a 1 dram vial equipped with magnetic stir bar. (Carbethoxymethylene)-triphenylphosphorane (**113**) 41 mg (0.118 mmol) was added and the reaction was allowed to stir at ambient temperature. After stirring for 30 minutes the reaction was filtered through a 1 in plug of silica, eluted with Et_2O (~10 mL) and concentrated *in vacuo*. The resulting crude product was purified by flash silica gel chromatography (4:1 hexanes/EtOAc, R_f = 0.4, 2:1 hexanes/EtOAc). 21 mg of desired product **112** was isolated as a separable mixture of

olefin isomers (75% yield) 5:1 *E/Z*, 60% ee (*E* isomer). Chiracel A-DH column 97:3 hexanes/*iso*-propanol, 1.0 mL/min, peaks appear at 11.85 (minor) and 13.00 (major).

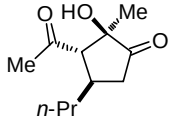
Procedure for Preparation of Cyclopentanone 84 from Aldehyde 111

A 1 dram vial was equipped with a magnetic stir bar under argon and charged with 4.3 mg (0.012 mmol) of triazolium salt **58**. $CHCl_3$ (1 mL), aldehyde **111** 20mg (0.118 mmol), were added sequentially followed by sodium acetate 1 mg (0.012 mmol). After stirring at ambient temperature for 12 h the reaction was filtered through a 1in plug of silica, eluted with Et_2O (~10 mL) and concentrated *in vacuo*. The resulting crude product was purified by flash silica gel chromatography (2:1 hexanes/EtOAc, R_f = 0.3 2:1 hexanes/EtOAc). 13 mg of the desired product **7** was isolated as an inseparable mixture of diatereomers (65% yield). 85:15 :<1:<1 dr, 58% ee (major diastereomer). Chiraldex BDM-2 column at 140 °C at 1 mL/min; peaks appear at 8.55 minutes (major) and 8.88 minutes (minor).

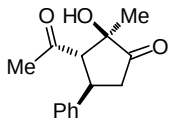


(2*R*,3*S*,4*R*)-3-acetyl-2-hydroxy-2,4-dimethylcyclo-pentanone (84). According to the general procedure affords 35 mg (93% yield) of **84** as 85:1:<1:<1 mixture of diastereomers. GC analysis Chiraldex BDM-2 column at 140 °C at 1 mL/min; peaks appear at 8.55 minutes (major) and 8.88 minutes (minor), 86% ee $[\alpha]_D^{21}$ = -32.8 (c = 0.010 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 2.95 (bs, 1H), 2.75 (d, *J* = 11.0 Hz, 1H), 2.66 (dd, *J* = 19.4, 9.2, 1H), 2.55 (m, 1H), 2.26 (s, 1H), 1.90 (dd, *J* = 19.6, 10.0, 1H) 1.03 (d, *J* = 6.2, 3H), 1.01 (s, 3H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 217.8, 207.4, 80.2, 66.0, 41.3, 32.0, 26.5, 20.3, 19.8; IR (thin film/NaCl) 3447 (br), 2966, 2925, 2873,

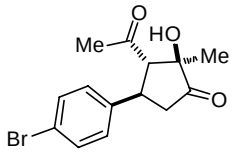
1767, 1711, 1362, 1271, 1168, 1132, cm^{-1}; HRMS: (ESI-) calculated for $C_9H_{14}O_3$, 170.0943. Found 170.0941.



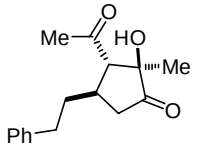
(2*R*,3*S*,4*R*)-3-acetyl-2-hydroxy-2-methyl-4-propylcyclopentanone (100b). According to the general procedure affords 34.0 mg, 77%, 93% ee (Major) 85:15:<1:<1 dr of **100b**. GC analysis Chiraldex Chiraldex BDM-2 column at 140 °C at 1 mL/min; peaks appear at 17.07 minutes (major) and 17.96 minutes (minor). $[\alpha]_D^{21}$ = -42.2 (c = 0.010 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 2.97 (bs, 1H), 2.83 (d, *J* = 11.0 Hz, 1H), 2.69 (dd, *J* = 9.5, 19.4 Hz, 1H), 2.55 (m, 1H), 2.29 (s, 1H), 1.93 (dd, *J* = 9.7, 19.6 Hz, 1H), 1.48 (m, 1H), 1.28 (m, 2H), 1.13 (m, 1H), 1.04 (s, 3H) 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C nmr (100 MHz, $CDCl_3$) δ 217.7, 207.5, 80.0, 64.6, 39.4, 37.8, 32.1, 31.4, 21.3, 20.5, 14.3; IR (thin film/NaCl) 3457 (br), 2960, 2919, 2863, 1757, 1706, 1373, 1275, 1183, 1137, cm^{-1}; HRMS: (ESI+) Calculated for $C_{11}H_{18}O_3$, 198.1256. Found 198.1258.



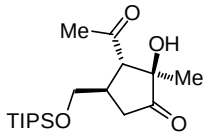
(2*R*,3*S*,4*R*)-3-acetyl-2-hydroxy-2-methyl-4-phenylcyclopentanone (100c). According to the general procedure affords 31.0 mg, 60%, 85% ee (Major) 80:20:<1:<1 dr . GC analysis Chiraldex BDM-1 column at 170 °C at 2 mL/min; peaks appear at 14.47 minutes (major) and 14.95 minutes (minor). $[\alpha]_D^{21}$ = +4.5 (c = 0.010 g/mL, CH_2Cl_2) ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 3.75 (ddd, *J* = 20.0, 11.5, 9.3 Hz, 1H), 3.38 (d, *J* = 11.5 Hz, 1H), 2.98 (dd, *J* = 20.1, 9.5 Hz, 1H), 2.48 (dd, *J* = 20.1, 10.6 Hz, 1H), 2.20 (s, 3H), 1.17 (s, 3H ; ^{13}C nmr (100 MHz, $CDCl_3$) δ 216.6, 206.3, 141.6, 129.0, 127.6, 127.3, 80.3, 65.6, 41.6, 37.2, 32.0, 20.5; IR (thin film/NaCl) 3226 (br), 3021, 2914, 2848, 1751, 1711, 1367, 1270, 1168, cm^{-1}; HRMS: (ESI+) Calculated for $C_{14}H_{16}O_3$, 232.1099. Found 232.11.



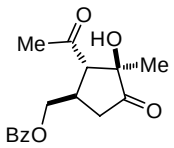
(2*R*,3*S*,4*R*)-3-acetyl-4-(4-bromophenyl)-2-hydroxy-2-methylcyclopentanone (100d) Yield: 49.0 mg, 70%, 80% ee (Major) 85:15:<1:<1 (Isolated as an inseparable mixture of two diastereomers) Physical State: white solid, mp = 128-130 °C (from CH_2Cl_2) R_f: 0.3 (2:1 hex/EtOAc), Purified 3:1 hex/EtOAc $[\alpha]_D^{21}$ = -5.9 (c = 0.010 g/mL, CH_2Cl_2) HPLC Analysis: Chiracel O-DH column 90:10 hexanes/*iso*-propanol, 1.0 mL/min; peaks appear at 10.25 minutes (minor) and 15.98 minutes (major). IR: (NaCl, neat) 3442 (br), 2960, 2924, 2863, 1751, 1701, 1491, 1368, 1178, 1137 cm^{-1} ^1H NMR: (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H) 3.64 (ddd, *J* = 10.4, 10.4, 10.4 Hz, 1H), 3.23 (d, *J* = 11.7 Hz, 1H), 2.88 (dd, *J* = 20.0, 9.6 Hz, 1H) 2.35 (dd, *J* = 20.2, 10.6 Hz, 1H) 2.12 (s, 3H), 1.07 (s, 3H) ^{13}C NMR: (100 MHz, $CDCl_3$): δ 216.1, 206.0, 140.7, 132.2, 129.4, 121.2, 80.2, 65.7, 41.4, 36.7, 31.9, 20.5 HRMS: (ESI-) Calculated for $C_{14}H_{15}BrO_3$, 370.0416. Found 370.0423.



(2*R*,3*S*,4*R*)-3-acetyl-2-hydroxy-2-methyl-4-phenethylcyclopentanone (100e) Yield: 34.0 mg, 59%, 95% ee 80:20:<1:<1 dr (Major) (Isolated as an inseparable mixture of two diastereomers) Physical State: colorless oil R_f: 0.3 (2:1 hex/EtOAc), Purified 4:1 hex/EtOAc $[\alpha]_D^{21}$ = -14.2 (c = 0.010 g/mL, CH_2Cl_2) GC Analysis: Chiraldex BDM-1 column at 170 °C at 2 mL/min; peaks appear at 34.26 minutes (major) and 36.08 minutes (minor). IR: (NaCl, neat) 3431 (br), 3057, 3016, 2929, 2853, 1757, 1706, 1460, 1362 cm^{-1} ^1H NMR: (400 MHz, $CDCl_3$) δ 7.20 (m, 5H), 2.84 (d, *J* = 11.0 Hz, 1H), 2.69 (dd, *J* = 19.4, 9.2 Hz, 1H), 2.59 (m, 3H), 2.26 (s, 3H), 1.97 (dd, *J* = 19.6, 9.6 Hz, 1H), 1.88, (1H, m), 1.43 (1H, m) ^{13}C NMR: (100 MHz, $CDCl_3$): δ 217.1, 207.2, 141.5, 128.7, 128.4, 126.3, 79.8, 64.5, 39.3, 37.1, 34.4, 31.9, 31.4, 20.4 HRMS: (ESI-) Calculated for $C_{16}H_{20}O_3$, 260.14124. Found 260.14119.

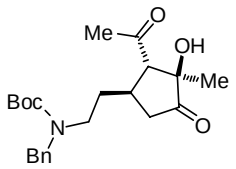


(2*R*,3*S*,4*R*)-3-acetyl-2-hydroxy-2-methyl-4-((triisopropylsilyloxy)-methyl)cyclopentanone (102c) Yield: 48.0 mg, 63%, 92% ee 75:25:<1:<1 dr (Major) (Isolated as an inseparable mixture of two diastereomers) Physical State: colorless oil R_f: 0.4 (3:1 hex/EtOAc), Purified 6:1 hex/EtOAc $[\alpha]_D^{21}$ = -8.2 (c = 0.010 g/mL, CH_2Cl_2) HPLC Analysis: Chiracel O-DH column 98:2 hexanes/*iso*-propanol, 1.0 mL/min; peaks appear at 7.94 minutes (minor) and 9.90 minutes (major). IR: (NaCl, neat) 3421 (br), 2934, 2920, 2863, 1757, 1711, 1450, 1383, 1122, 1096 cm^{-1} ^1H NMR: (400 MHz, $CDCl_3$) δ 3.66 (ddd, *J* = 17.0, 10.2, 3.8 Hz, 2H), 3.17 (d, *J* = 10.7 Hz, 1H), 2.7 (m, 1H), 2.52 (dd, *J* = 19.6, 9.2 Hz, 1H), 2.38 (dd, *J* = 19.8, 9.8 Hz, 1H), 2.27 (s, 3H), 1.05 (s, 1H), 1.0 (m, 21H) ^{13}C NMR: (100 MHz, $CDCl_3$): δ 217.2, 207.5, 80.1, 63.1, 59.5, 35.3, 33.9, 31.6, 20.5, 18.1, 12.0 HRMS: (ESI+) Calculated for $C_{18}H_{34}O_4Si$, 342.2229. Found 342.2227.

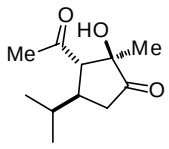


((1*R*,2*S*,3*R*)-2-acetyl-3-hydroxy-3-methyl-4-oxocyclopentyl)methyl Benzoate (100g) Yield: 47.0 mg, 72%, 95% ee (Major) 80:20:<1:<1 (Isolated as an inseparable mixture of two diastereomers) Physical State: off white solid mp = 119-121 °C (from CH_2Cl_2) R_f: 0.2 (2:1 hex/EtOAc), Purified 2:1 hex/EtOAc $[\alpha]_D^{21}$ = -9.2 (c = 0.010 g/mL, CH_2Cl_2) HPLC Analysis: Chiracel O-DH column 90:10 hexanes/*iso*-propanol, 1.0 mL/min; peaks appear at 14.39 minutes (minor) and 15.82 minutes (major). IR: (NaCl, neat) 3457 (br), 3058, 2955, 2924, 2899, 1752, 1701, 1372, 1291, 1127 cm^{-1} ^1H NMR: (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8.1 Hz, 1H), 4.35 (dd, *J* = 11.1, 4.7 Hz, 1H), 4.25 (dd, *J* = 11.1, 4.5 Hz, 1H) 3.06 (m, 1H), 3.05 (d, *J* = 6.6 Hz, 1H), 2.72 (dd, *J* = 19.8, 8.5 Hz, 1H), 2.29 (s, 3H), 2.27 (dd, *J* = 19.8, 8.0 Hz, 1H), 1.08 (s, 3H) ^{13}C NMR: (100 MHz, $CDCl_3$): δ 215.9,

206.5, 166.6, 133.5, 129.8, 128.7, 79.9, 65.6, 60.5, 35.9, 31.1, 20.4 HRMS: (ESI+) Calculated for $C_{16}H_{18}O_5$, 290.1154. Found 290.1157.



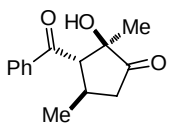
***tert*-butyl 2-((1*R*,2*S*,3*R*)-2-acetyl-3-hydroxy-3-methyl-4-oxocyclopentyl)ethyl(benzyl)carbamate (100h)** Yield: 52.0 mg, 60%, 90% ee (Major) 85:15:<1:<1 (Isolated as an inseparable mixture of two diastereomers) Physical State: yellow oil R_f: 0.2 (2:1 hex/EtOAc), Purified 2:1 hex/EtOAc $[\alpha]_D^{21}$ = -26.7 (c = 0.010 g/mL, CH_2Cl_2) HPLC Analysis: Chiracel OD-H column 95:5 hexanes/*iso*-propanol, 1.0 mL/min; peaks appear at 14.96 minutes (minor) and 19.80 minutes (major). IR: (NaCl, neat) 3441 (br), 2960, 2924, 2863, 1751, 1701, 1491, 1367, 1280, 1178 cm^{-1} ^1H NMR: (300 MHz, 95 °C, toluene-d_8) δ 7.10 (m, 5H), 4.30 (q, *J* = 23.8, 15.5 Hz, 2H) 3.03 (m, 2H) 2.43 (d, *J* = 10.6 Hz, 1H) 2.29 (dd, *J* = 18.5, 9.2, 1H) 2.28 (m, 1H) 2.0 (s, 3H) 1.59 (dd, *J* = 19.0, 9.0 Hz, 1H) 1.58 (m, 1H) 1.40 (s, 9H), 1.08 (m, 1H) 0.77 (s, 3H) ^{13}C NMR: (75 MHz, 95 °C, toluene-d_8): δ 214.8 204.8, 155.4, 139.0, 128.3, 128.4, 127.1, 79.2, 79.1, 64.3, 50.6, 45.1, 38.8, 33.5, 30.6, 29.2, 28.2, 22.9 HRMS: (ESI+) Calculated for $C_{22}H_{31}NO_5$, 389.2202. Found 389.2208.



(2*R*,3*S*,4*S*)-3-acetyl-2-hydroxy-4-isopropyl-2-methylcyclopentanone (100i)

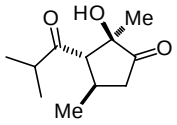
Yield: 14.0 mg, 32%, 82% ee (Major) 67:33:<1:<1 dr (Isolated as an inseparable mixture of two diastereomers) Physical State: colorless oil R_f: 0.35 (2:1 hex/EtOAc), Purified 3:1 hex/EtOAc. $[\alpha]_D^{21}$ = -22.8 (c = 0.010 g/mL, CH_2Cl_2) GC Analysis: Chiraldex BDM-2 column at 140 °C at 1 mL/min; peaks appear at 15.36 minutes (major) and 15.93 minutes (minor). IR: (NaCl, neat) 3442 (br), 2966, 2925, 2873, 1757, 1706, 1372, 1280, 1250, 1193 cm^{-1} ^1H NMR: (400 MHz, $CDCl_3$) δ 2.93 (d, *J* = 11.1 Hz,

1H), 2.57 (dd, *J* =19.6, 9.8 Hz, 1H), 2.47 (m, 1H), 2.27 (s, 3H), 2.00 (dd, *J* = 19.6, 9.2 Hz, 1H), 1.55 (m, 1H), 1.01 (s, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H) ^{13}C NMR: (100 MHz, $CDCl_3$): δ 217.5, 207.7, 80.5, 62.0, 38.1, 36.3, 32.0, 23.6, 21.6, 20.8, 19.0 HRMS: (ESI+) Calculated for $C_{11}H_{18}O_3$, 198.1256. Found 198.1259.



(2*S*,3*R*,4*S*)-3-benzoyl-2-hydroxy-2,4-dimethylcyclopentanone (102a)

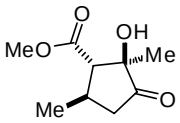
Yield: 39.0 mg, 74%, 87% ee (Major) 4:1 Major:Σ Minor (Major diastereomer is separable from other regio- and diastereomers). Physical State: white solid, mp = 87-90 °C (from CH_2Cl_2) R_f: 0.5 (2:1 hex/EtOAc), Purified 5:1 hex/EtOAc $[\alpha]_D^{21}$ = -62.0 (c = 0.010 g/mL, CH_2Cl_2) GC Analysis: Chiraldex BDM-2 column at 170 °C at 2 mL/min; peaks appear at 19.37 minutes (major) and 20.06 minutes (minor). IR: (NaCl, neat) 3471 (br), 2961, 2929, 2869, 1751, 1672, 1451, 1368, 1213 cm^{-1} ^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.2 Hz, 2H) 7.57 (t, *J* = 7.6 Hz, 1H) 7.46 (t, *J* = 7.6 Hz, 2H) 3.66 (*d*, *J* = 10.7 Hz, 1H) 2.84 (m, 1H) 2.76 (dd, *J* = 19.0, 8.7 Hz, 1H) 2.06 (dd, *J* = 19.2, 10.2 Hz, 1H) 1.06 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 3H) ^{13}C NMR: (100 MHz, $CDCl_3$): δ 217.9, 199.2, 138.0 133.7, 129.4, 128.7, 80.8, 61.0, 41.6, 28.2, 20.7, 19.7; HRMS: (ESI+) Calculated for $C_{14}H_{16}O_3$, 232.1099. Found 232.1096.



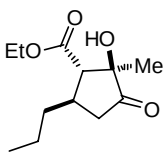
(2*R*,3*S*,4*R*)-2-hydroxy-3-isobutyryl-2,4-dimethylcyclopentanone (102b).

Yield 30 mg, 68%, 78% ee, 4:1 Major:Σ Minor (Major diastereomer is separable from other regio- and diastereomers). Physical State clear oil; R_f: 0.3 (3:1 hex/EtOAc), Purified 6:1 hex/EtOAc GC Analysis: Chiraldex BDM-1column at 140 °C at 1 mL/min; peaks appear at 12.5 minutes (major) and 13.1 minutes (minor). IR: (NaCl, neat) 3447, 2968, 1748, 1704, 1458, 1370 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 3.14 (d, 1H, *J* = 11.1 Hz), 3.05 (hept, 1H, *J* = 7.1 Hz), 2.86 (dd, 1H, *J* = 9.0, 19.4, Hz), 2.75 (m,

1H), 2.12 (dd, 1H, *J* = 10.1, 19.4 Hz), 1.29 (d, 3H, *J* = 7.2 Hz), 1.25 (d, 3H, *J* = 6.6 Hz) 1.19 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 217.7, 213.1, 80.4, 63.3, 41.2, 41.1, 26.8, 20.5, 19.3, 18.5, 16.5; HRMS: (ESI+) Calculated for $C_{11}H_{18}O_3NH_4$, 216.1594. Found 216.1589.

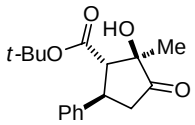


(1*S*,2*R*,5*R*)-methyl 2-hydroxy-2,5-dimethyl-3-oxocyclopentane-carboxylate (102c). Yield: 38.0 mg, 90% yield, 91% ee (Major) 64:33:3:<1 dr (Major diastereomer is separable from other diastereomers). Physical State: white solid, mp = 79-81 °C (from CH_2Cl_2); R_f: 0.3 (2:1 hex/EtOAc), Purified 4:1 hex/EtOAc; $[\alpha]_D^{21}$ = -51.1 (c = 0.010 g/mL, CH_2Cl_2); GC Analysis: Chiraldex BDM-2 column at 140 °C at 2 mL/min; peaks appear at 21.55 minutes (major) and 22.48 minutes (minor). IR: (NaCl, neat) 3431 (br), 2971, 2909, 1746, 1716, 1440, 1363, 1244, 1209, 1163 cm^{-1}; ^{1}H NMR: (400 MHz, benzene-d_6) δ 3.21 (s, 3H), 2.59 (bs, 1H), 2.36 (d, *J* = 11.1 Hz, 1H), 2.03 (m, 1H) 1.91 (dd, *J* = 19.8, 8.7 Hz, 1H), 1.25 (dd, *J* = 19.2, 10.4 Hz, 1H), 0.92 (s, 1H) 0.61 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 216.8, 172.0, 80.1, 59.4, 52.3, 41.6, 28.4, 20.6, 19.7. HRMS: (ESI-) Calculated for $C_9H_{14}O_4$, 186.0892. Found 186.0892.

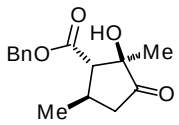


(1*S*,2*R*,5*R*)-ethyl 2-hydroxy-2-methyl-3-oxo-5-propylcyclopentane-carboxylate (102d). Yield: 41.0 mg, 80%, 93% ee (Major) 60:30:8:2 dr (Major diastereomer is separable from other diastereomers); Physical State: colorless oil; R_f: 0.3 (2:1 hex/EtOAc) Purified 4:1 hex/EtOAc. $[\alpha]_D^{21}$ = -55.2 (c = 0.010 g/mL, CH_2Cl_2); GC Analysis: Chiraldex BDM-2 column at 140 °C at 2 mL/min; peaks appear at 21.55 minutes (major) and 22.48 minutes (minor). IR: (NaCl, neat) 3421 (br), 2955, 2934, 2873, 1751, 1726, 1654, 1383, 1270, 1188 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 4.23 (q, *J* = 14.1, 6.4 Hz, 2H) 2.68 (dd, *J* = 19.6, 8.7 Hz, 1H) 2.64 (d, *J* = 11.5 Hz 1H)

2.43 (m, 1H) 1.94 (dd, *J* = 19.6, 10.0 Hz, 1H) 1.58 (m, 1H) 1.4-1.2 (m, 3H) 1.29 (t, *J* = 7.0 Hz, 3H) 1.16 (s, 3H) 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 216.7, 171.6, 79.9, 61.2, 58.1, 39.6, 37.6, 33.1, 21.0, 20.7, 14.6, 14.2; HRMS: (ESI+) Calculated for $C_{12}H_{20}O_4$, 228.1362. Found 228.1358.

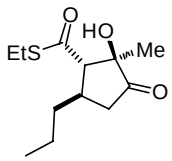


(1*S*,2*R*,5*R*)-tert-butyl 2-hydroxy-2-methyl-3-oxo-5-phenylcyclopentanecarboxylate (102e). Yield: 56.0 mg, 86%, 97% ee (Major) 60:35:5:<1 dr (Major diastereomer is separable from other diastereomers). Physical State: white solid, mp = 103-105 °C (from CH_2Cl_2) R_f: 0.6 (2:1 hex/EtOAc), Purified 5:1 hex/EtOAc; $[\alpha]_D^{21}$ = -112 (c = 0.010 g/mL, CH_2Cl_2); GC Analysis: Chiraldex BDM-1 column at 170 °C at 3 mL/min; peaks appear at 27.62 minutes (major) and 27.62 minutes (minor). IR: (NaCl, neat) 3439 (br), 3059, 3021, 3005, 2980, 2929, 1751, 1726, 1388, 1210 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 3.84 (ddd, *J* = 11.5, 11.5, 8.2 Hz, 1H) 3.76 (s, 1H), 3.01 (dd, *J* = 19.2, 8.4 Hz, 1H), 2.81 (d, *J* = 11.5 Hz, 1H), 2.43 (dd, *J* = 19.2, 11.3 Hz, 1H), 1.43 (s, 3H), 1.31 (s, 9H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 211.8, 171.6, 140.9, 128.9, 127.5, 127.6, 82.6, 59.2, 43.5, 41.7, 28.2, 21.7; HRMS: (ESI+) Calculated for $C_{17}H_{22}O_4$, 290.1518. Found 290.1516.

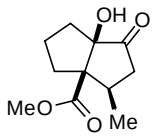


(1S,2R,5R)-benzyl 2-hydroxy-2,5-dimethyl-3-oxocyclopentanecarboxylate (102f). Yield: 53.0 mg, 90% yield, 82% ee (Major) 58:39:2:<1 dr (Major diastereomer is separable from other diastereomers). Physical State: white solid, mp = 49-51 °C (from CH_2Cl_2); R_f: 0.3 (2:1 hex/EtOAc), Purified 3:1 hex/EtOAc; $[\alpha]_D^{21}$ = -39.5 (c = 0.010 g/mL, CH_2Cl_2); GC Analysis: Chiraldex BDM-2 column at 180 °C at 3 mL/min; peaks appear at 19.50 minutes (minor) and 20.10 minutes (major). IR: (NaCl, neat) 3459 (br), 2961, 2931, 1752, 1731, 1456, 1383, 1190, 1156, 1084 cm^{-1}; ^{1}H NMR:

(400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.22 (dd, *J* = 15.6, 12.4 Hz, 2H), 2.67 (dd, *J* = 19.6, 8.7 Hz, 1H) 2.66 (d, *J* = 11.3 Hz, 1H), 2.49 (m, 1H), 1.94 (dd, *J* = 19.6, 10.4 Hz, 1H) 1.14 (d, *J* = 6.4 Hz, 3H), 1.10 (s, 1H). ^{13}C NMR: (75 MHz, $CDCl_3$): δ 216.5, 171.3, 135.9, 128.8, 128.5, 128.4, 80.2, 66.9, 59.5, 41.5, 28.4, 20.5, 19.7.

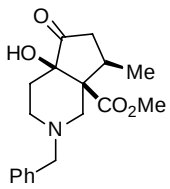


(1*S*,2*R*,5*R*)-tert-butyl 2-hydroxy-2-methyl-3-oxo-5-phenylcyclopentane-carboxylate (102g). Yield: 31.0 mg, 56%, 81% ee (Major) 69:22:6:3 dr (Major diastereomer is separable from other diastereomers). Physical State: yellow oil; R_f: 0.5 (2:1 hex/EtOAc), Purified 8:1 hex/EtOAc; $[\alpha]_D^{21}$ = -112 (c = 0.010 g/mL, CH_2Cl_2); GC Analysis: Chiraldex BDM-2 column at 140 °C at 3 mL/min; peaks appear at 37.19 minutes (major) and 39.13 minutes (minor). IR: (NaCl, neat) 3462(br), 2955, 2928, 2866, 1752, 1679, 1454, 1365, 1128, 1074 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 2.93 (q, *J* = 7.7 Hz, 2H) 2.87 (d, *J* = 11.1 Hz, 1H) 2.68 (dd, *J* = 19.6, 9.2 Hz, 1H) 2.57 (m, 1H) 1.94 (dd, *J* = 19.6, 10.0 Hz, 1H) 1.52 (m, 1H) 1.28 (m, 3H) 1.27 (t, *J* = 7.5 Hz, 3H) 1.13 (s, 3H) 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 216.6, 197.9, 80.2, 66.2, 39.7, 37.4, 33.1, 23.9, 21.1, 20.4, 14.8, 14.2; HRMS: (ESI+) Calculated for $C_{12}H_{20}O_3S$, 244.1133. Found 244.1136.

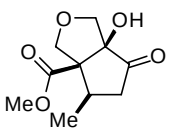


(3*R*,3a*R*,6a*R*)-methyl 6a-hydroxy-3-methyl-1-oxooctahydropentalene-3a-carboxylate (104a). Yield: 38.0 mg, 79%, 94% ee (Major) 4:1 dr (Major diastereomer is separable from other diastereomers). Physical State: colorless oil; R_f: 0.2 (2:1 hex/EtOAc), Purified 2:1 hex/EtOAc; $[\alpha]_D^{21}$ = -18.4 (c = 0.010 g/mL, CH_2Cl_2); GC Analysis: Chiraldex BDM-2 column at 140 °C at 3 mL/min; peaks appear at 12.61 minutes (minor) and 13.11 minutes (major). IR: (NaCl, neat) 3468 (br), 2965, 2873, 1739, 1710, 1448, 1258, 1156, 1042 cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 2.64 (s, 3H) 2.63

(dd, *J* = 18.9, 8.7 Hz, 1H) 2.38 (m, 1H) 2.19 (dd, *J* = 19, 10.9 Hz, 1H) 2.11-1.7 (m, 6H) 1.00 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 216.0, 173.0, 91.3, 67.9, 51.9, 40.9, 36.2, 34.4, 30.8, 22.6, 15.4 ;HRMS: (ESI+) Calculated for $C_{11}H_{16}O_4$, 212.1049. Found 212.1048.

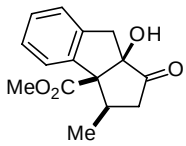


(4a*R*,7*R*,7a*S*)-methyl 2-benzyl-4a-hydroxy-7-methyl-5-oxooctahydro-1H-cyclopenta[c]pyridine-7a-carboxylate (104b). Yield: 54.0 mg, 76%, 90% ee (Major) 5:1 (Major diastereomer is separable from other diastereomers). Physical State: colorless oil; R_f: 0.3 (2:1 hex/EtOAc), Purified 3:1 hex/EtOAc ; $[\alpha]_D^{21}$ = -10.8 (c = 0.010 g/mL, CH_2Cl_2); HPLC Analysis: Chiracel O-DH column 95:5 hexanes/*iso*-propanol, 1.0 mL/min; peaks appear at 16.66 minutes (major) and 20.35 minutes (major). IR: (NaCl, neat) 3252 (br), 3021, 2961, 2815, 2768, 1758, 1736, 1451, 1258, 1229 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.28 (m, 5H), 3.61 (s, 3H) 3.56 (dd, *J* = 18.1, 13.2 Hz, 2H) 3.07 (ddq, *J* = 7.3, 6.2, 7.0, 10.2, 6.8 Hz, 1H) 2.96 (d, *J* = 12.4 Hz, 1H) 2.69 (ddd, *J* = 9.6, 2.6, 2.6 Hz, 1H) 2.65 (dd, *J* = 19.4, 9.8 Hz, 1H) 2.38 (d, *J* = 12.4, 1H) 2.43 (ddd, *J* = 11.9, 11.9, 2.8 Hz, 1H) 2.15 (dd, *J* = 19.4, 9.8 Hz, 1H) 1.84 (ddd, *J* = 12.8, 12.8, 4.9 Hz, 1H) 1.43 (ddd, *J* = 14.1, 14.1, 2.6 Hz, 1H) 0.90 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 215.8, 173.1, 138.7, 128.8, 128.5, 127.3, 79.2, 62.7, 57.7, 51.7, 50.7, 48.4, 39.3, 31.9, 29.3, 15.4; HRMS: (ESI+) Calculated for$C_{18}H_{23}NO_4$, 317.1627. Found 317.1625.

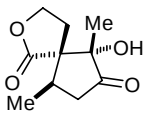


(3a*S*,4*R*,6a*S*)-methyl 6a-hydroxy-4-methyl-6-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate (104c). Yield 43 mg, 90%, 71% ee, 2:1 dr Physical State: colorless oil; R_f: 0.2 (1:1 hex/EtOAc), Purified 2:1 hex/EtOAc; GC Analysis: Chiraldex BDM-1 column at 140 °C at 3 mL/min; peaks appear at 12.3 minutes

(major) and 12.6 minutes (minor). IR: (NaCl, neat) 3422 (br), 1741, 1639, 1438, 1364, 1263 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) δ 4.20 (d, 1H, *J* = 9.0), 4.14 (d, 1H, *J* = 10.8 Hz), 4.06, (d, 1H, *J* = 9.0 Hz), 3.88 (d, 1H, *J* = 10.8 Hz), 3.73 (s, 3H), 3.13 (s, 1H), 2.75 (dd, 1H, *J* = 7.9, 18.1 Hz), 2.41 (m, 1H), 2.38 (dd, 1H, *J* = 11.4, 18.1 Hz), 1.12 (d, 3H, *J* = 6.8 Hz) ^{13}C NMR: (100 MHz, $CDCl_3$): δ 213.4, 169.9, 89.4, 71.4, 67.4, 51.9, 41.3, 32.2, 15.4; HRMS: (ESI+) Calculated for $C_{10}H_{14}O_5NH_4$, 232.1179. Found 232.1175.

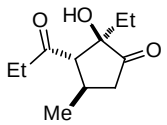


(3*R*,3a*S*,8a*R*)-methyl 8a-hydroxy-3-methyl-1-oxo-1,2,3,3a,8,8a-hexahydrocyclopenta[a]indene-3a-carboxylate (104d). Yield = 34 mg, 59%, 13% ee, 1:1 dr;. Physical State: colorless oil; R_f: 0.2 (1:1 hex/EtOAc), Purified 1:1 hex/EtOAc ; $[\alpha]_D^{21}$ = -15.2 (c = 0.0085 g/mL, CH_2Cl_2); HPLC Analysis: Chiracel A-SH column 90:10 hexanes/*iso*-propanol, 1.0 mL/min; peaks appear at 18.6 minutes (major) and 34.6 minutes (minor). IR: (NaCl, neat) 3263 (br), 2338, 1745, 1476, 1434, 1226 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) δ 7.40 (m, 4H), 3.87 (s, 3H), 3.48 (d, 1H, *J* = 16.4), 3.30 (d, 1H, *J* = 16.4), 3.28 (m, 1H), 2.73 (dd, 1H, *J* = 7.4, 18.0 Hz), 2.00 (dd, 1H, *J* = 12.6, 18.0 Hz); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 215.4, 172.3, 141.3, 138.1, 128.6, 127.0, 125.2, 125.0, 87.9, 67.0, 52.5, 43.3, 42.4, 41.7, 37.3, 34.8, 16.5; HRMS: (ESI+) Calculated for$C_{15}H_{16}O_4NH_4$, 278.1387. Found 278.1379.

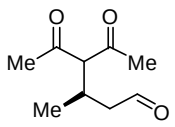


(5*S*,6*S*,9*R*)-6-hydroxy-6,9-dimethyl-2-oxaspiro[4.4]nonane-1,7-dione (104f). Yield = 32 mg, 72%, 77% ee, Physical State: white solid mp = 102-104 °C (from CH_2Cl_2); R_f: 0.2 (1:1 hex/EtOAc), Purified 1:1 hex/EtOAc ; $[\alpha]_D^{21}$ = -69.5 (c = 0.0070 g/mL, CH_2Cl_2); GC Analysis: BDM-1 column at 110 °C at 3 mL/min; peaks appear at 30.9 minutes (major) and 32.5 minutes (minor). IR: (NaCl, neat) 3448 (br), 2357, 1747, 1446, 1376 cm^{-1}; ^1H NMR: (400 MHz, $CDCl_3$) δ 4.35 (m, 2H), 2.77 (m 2H), 2.19

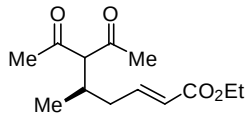
(m, 2H), 1.89 (m, 1H), 1.34, (s, 3H), 1.09 (d, 3H, J = 6.5 Hz); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 216.1, 83.3, 67.1, 56.0, 39.7, 31.4, 23.9, 21.2, 15.4; HRMS: (ESI+) Calculated for$C_{10}H_{14}O_4NH_4$, 216.1230. Found 216.1224.



(2*R*,3*S*,4*R*)-2-ethyl-2-hydroxy-4-methyl-3-propionylcyclopentanone (106). Yield = 34 mg, 77%, 94% ee; Physical State: clear oil R_f: 0.4 (3:1 hex/EtOAc), Purified 6:1 hex/EtOAc ; $[\alpha]_D^{21}$ = -37.8 (c = 0.0180 g/mL, CH_2Cl_2); GC Analysis: BDM-1 column at 140 °C at 1 mL/min; peaks appear at 13.7 minutes (major) and 14.9 minutes (minor). IR: (NaCl, neat) 3475 (br), 2970, 2939, 2881, 2360, 1749, 107, 1460, 1376 cm^{-1}; Due to co-elution of the two diastereomers deconvolution of the ^{1}H nmr and ^{13}C nmr proved difficult therefore these are not reported HRMS: (ESI+) Calculated for$C_{10}H_{18}O_3NH_4$, 216.1594. Found 216.1591.



(*R*)-4-acetyl-3-methyl-5-oxohexanal (111). Yield: 27.0 mg, 70%, 60% ee as determined by conversion to 11b *vida infra* Physical State: colorless oil R_f: 0.2 (2:1 hex/EtOAc), Purified 2:1 hex/EtOAc; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 3.66 (d, J = 9.2 Hz, 1H), 2.88 (m, 1H), 2.38 (m, 1H), 2.26 (m, 1H), 2.17 (s, 6H), 0.94 (d, J = 5.1 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$): δ 204.0, 203.7, 201.0, 74.0, 48.2, 30.4, 29.8, 28.3, 18.2.



(*R*,*E*)-ethyl 6-acetyl-5-methyl-7-oxooct-2-enoate (112). Yield: 21.0 mg, 75%, 60% ee (Major olefin isomer). Physical State: colorless oil R_f: 0.4 (2:1 hex/EtOAc), Purified 4:1 hex/EtOAc $[\alpha]_D^{21}$ = -41.3 (c = 0.010 g/mL, CH_2Cl_2) HPLC Analysis: Chiracel A-DH column 97:3 hexanes/*iso*-propanol, 1.0 mL/min; peaks appear at 11.85 minutes (minor) and 13.00 minutes (minor). IR: (NaCl, neat) 2977, 2936, 1716, 1698, 1651, 1360, 1268, 1179, 1044 cm^{-1}; ^{1}H NMR: (400 MHz, $CDCl_3$) δ 6.81 (ddd,

J = 15.3, 8.5, 6.6 Hz, 1H), 5.77 (ddd, *J* = 15.6, 1.3, 1.3 Hz, 1H) 4.14 (q, *J* = 14.3, 7.0 Hz, 2H), 3.50, (d, *J* = 10.2 Hz, 1H), 2.53 (m, 1H) 2.16 (m, 1H) 2.13 (s, 3H), 2.12 (s, 1H), 1.97 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.8 Hz). ^{13}C NMR: (100 MHz, $CDCl_3$): δ 204.0, 203.8, 166.3, 145.5, 124.1, 75.3, 60.5, 37.0, 32.0, 30.1, 29.7, 17.3, 14.4; HRMS: (ESI+) Calculated for $C_{13}H_{21}O_4$ 240.1362, Found 240.1363,

Reference

[1] Avery, T. A.; Caiazza, D.; Culbert, J. A.; Taylor, D. K.; Tienkink, E. R. T. *J. Org. Chem.* **2005**, *70*, 8334.

[2] Kang, J.; Lim, G. J.; Yoon, S. K.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564.

[3] Boone, M. A.; McDonald, F. E.; Lichter, J.; Lutz, S.; Cao, R.; Hardcastle, K. I. *Org. Lett.* **2009**, *11*, 851.

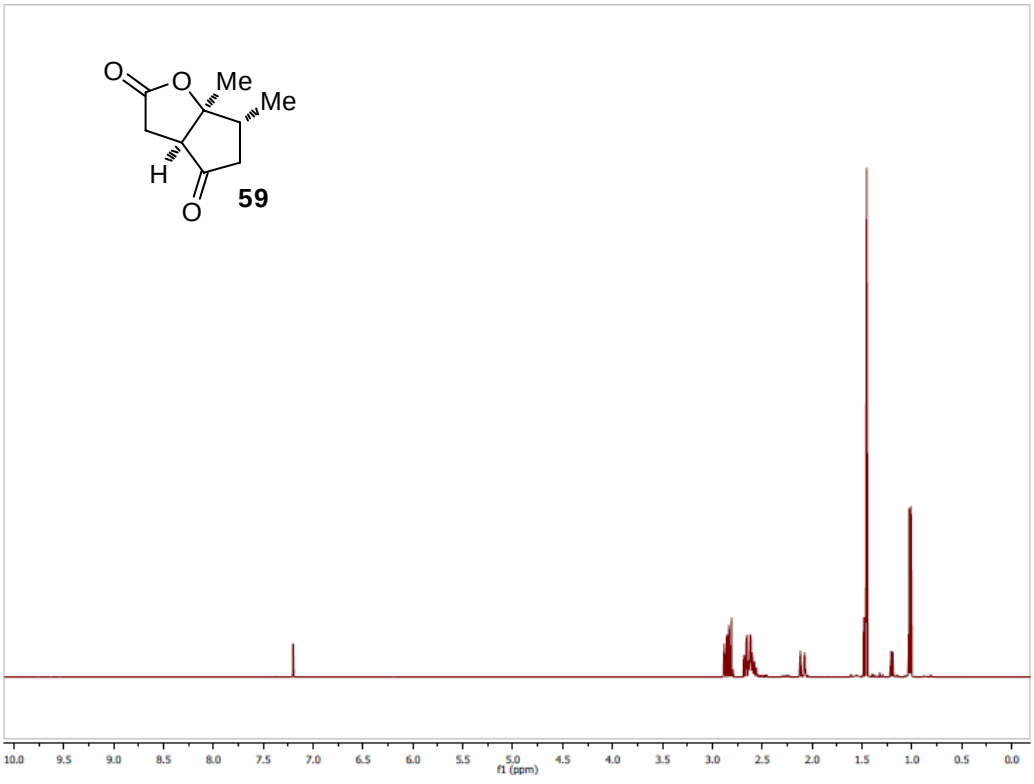
[4] Xie, X.; Lu, X.; Xu, W. *J. Org. Chem.* **2001**, *66*, 6545.

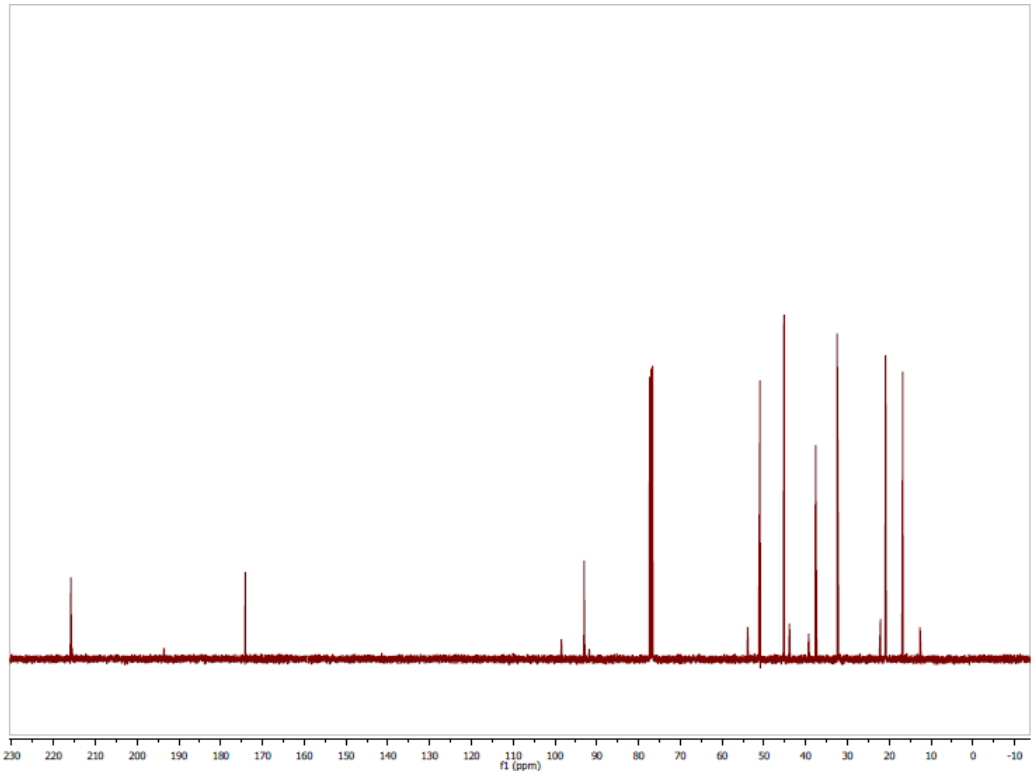
[5] Lutz, C.; Lutz, V.; Knochel, P. *Tetrahedron* **1998**, *54*, 6385.

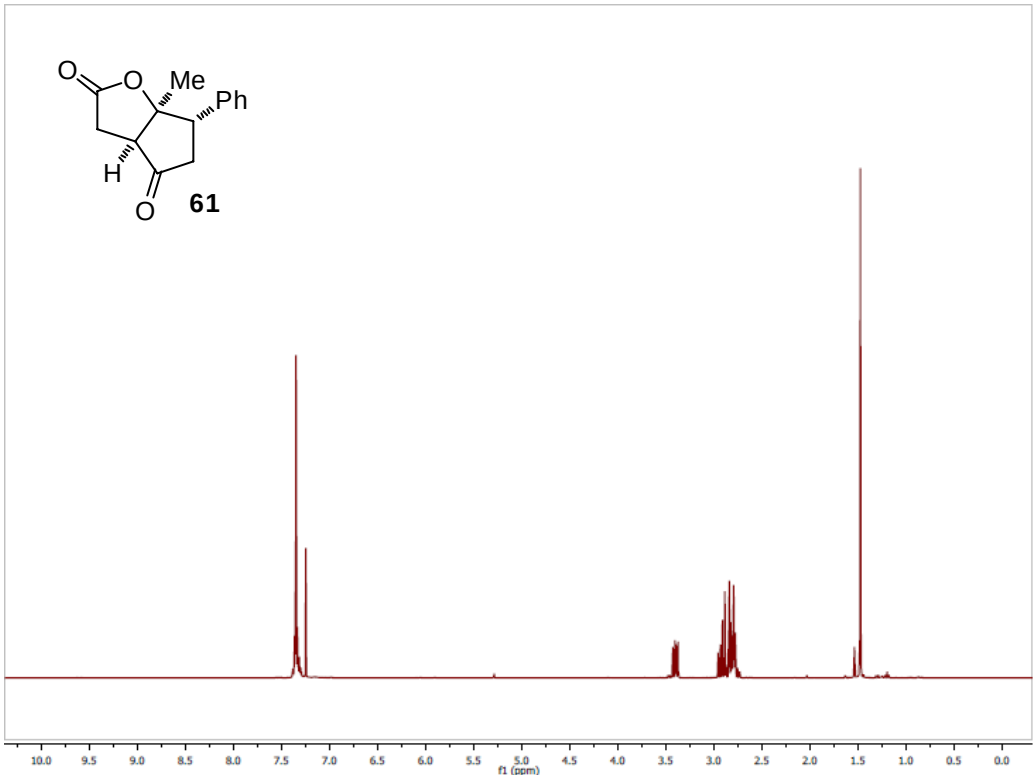
[6] Li, A. –H.; Moro, S.; Melman, N.; Ji, X.; Jacobson, K. A. *J. Med. Chem.* **1998**, *41*, 3186.

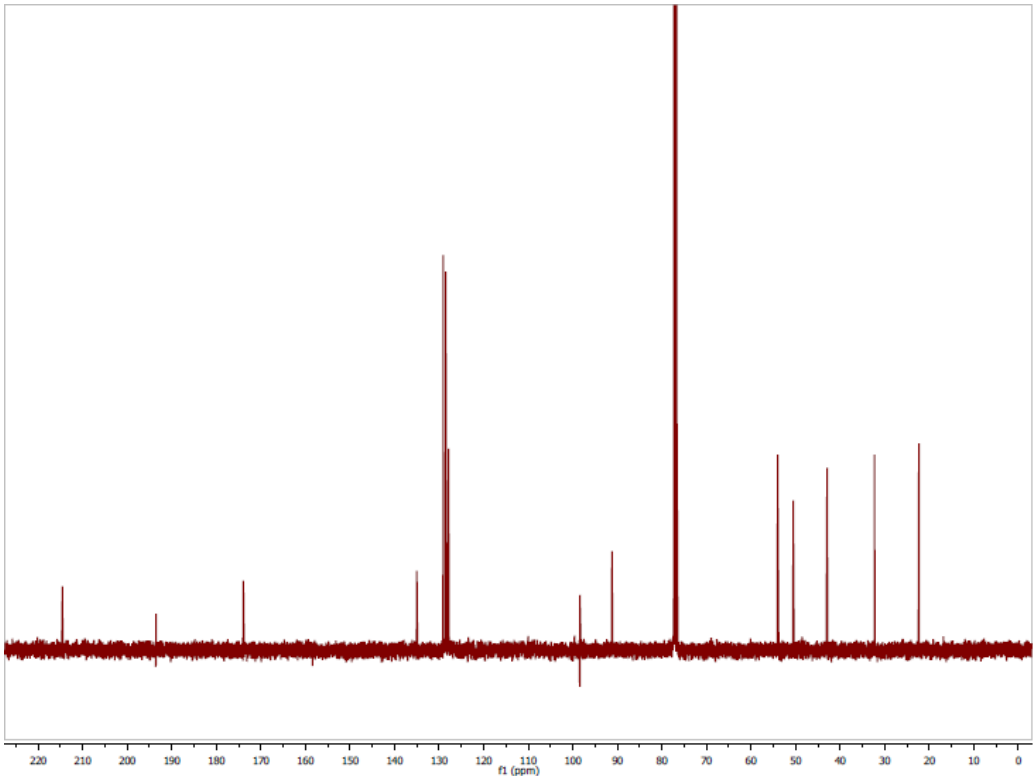
[7] (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794. (b) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8431.

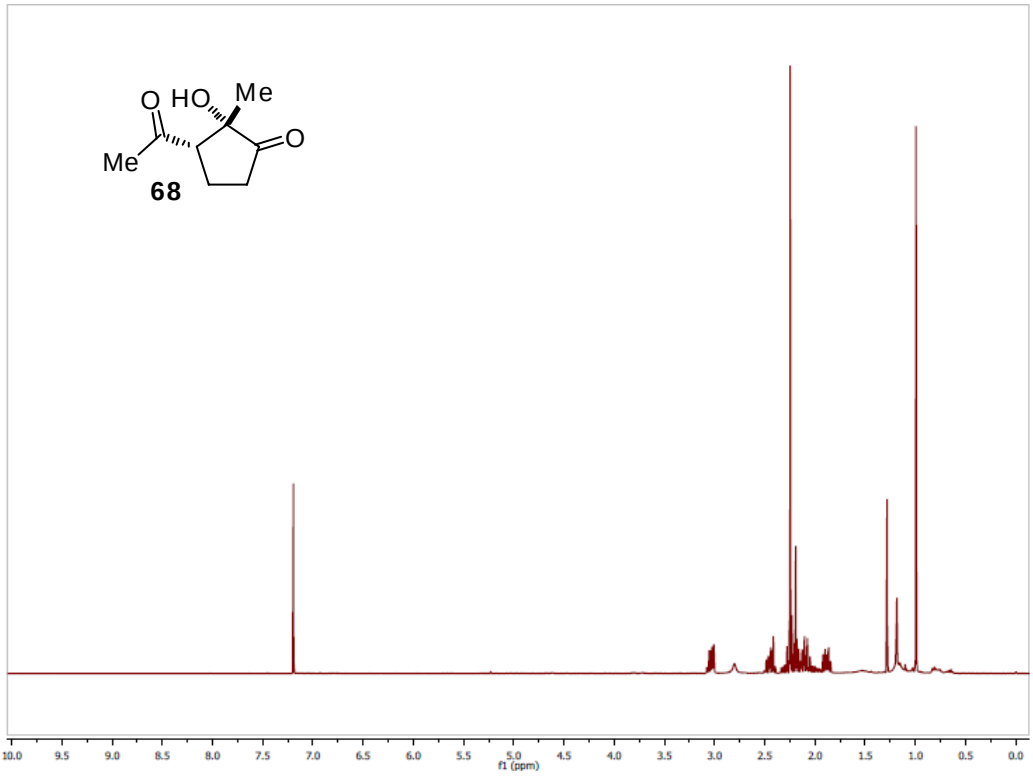
[8] (a) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725. (b) Vora, H. U.; Lathrop, S. P.; Reynolds, N. T.; Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *Org. Synth.* **2010**, *87*, 350.

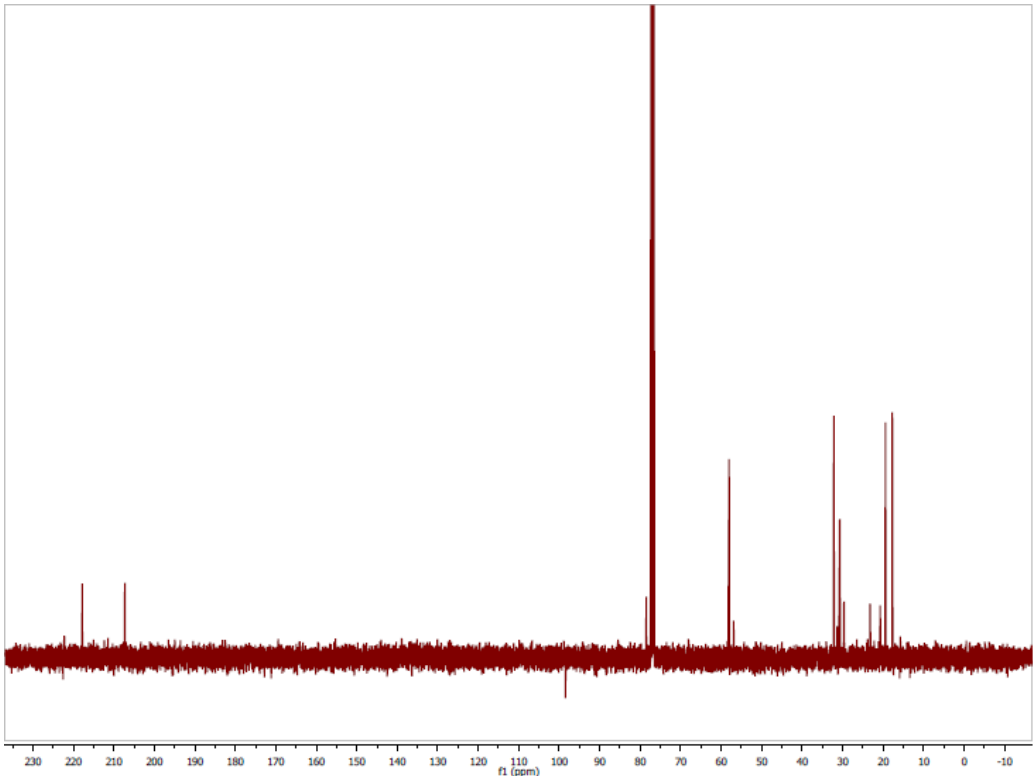

O
O
Me
Me
H
O
59
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

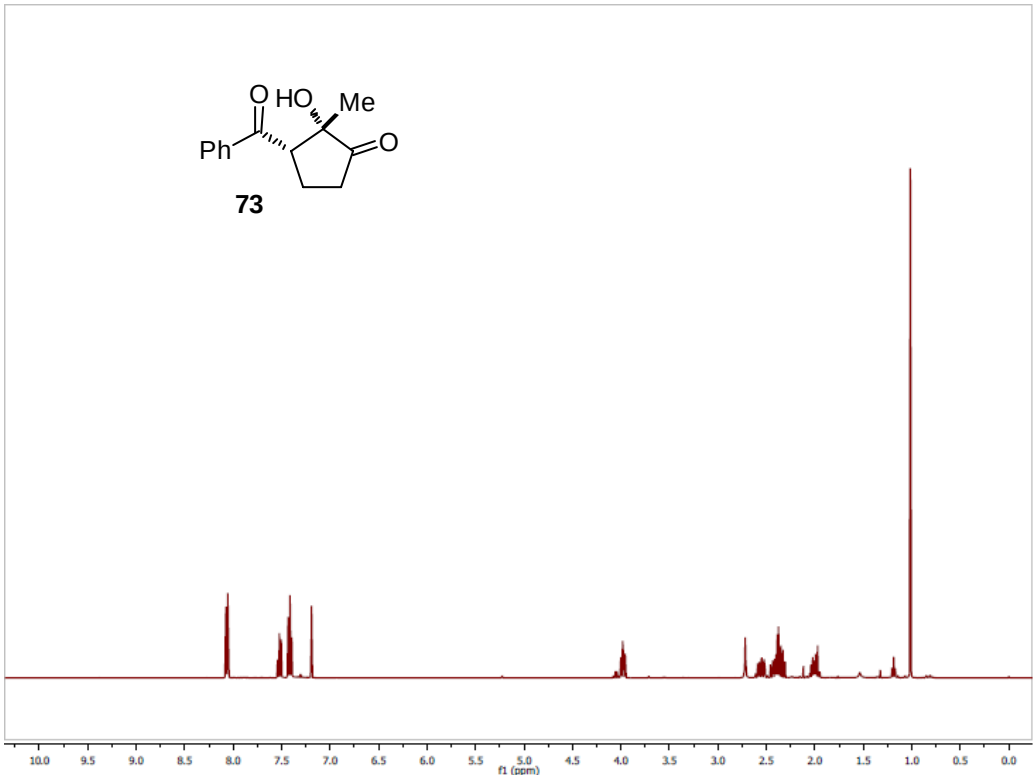

230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

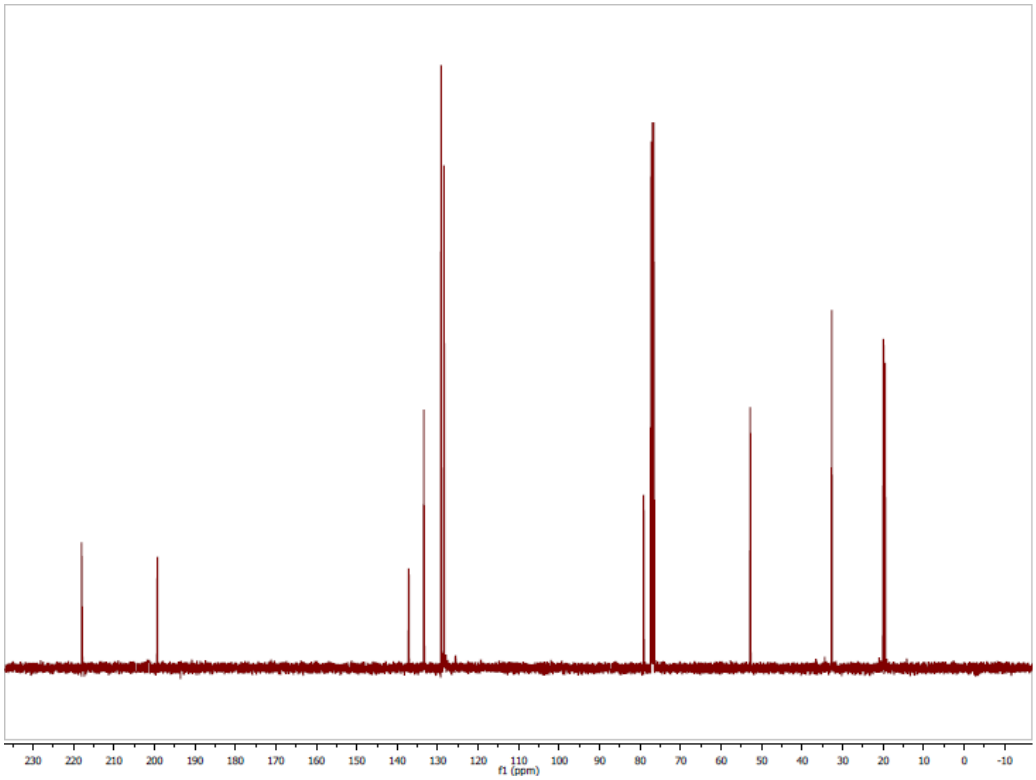

O
O
Me
Ph
H
O
61
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

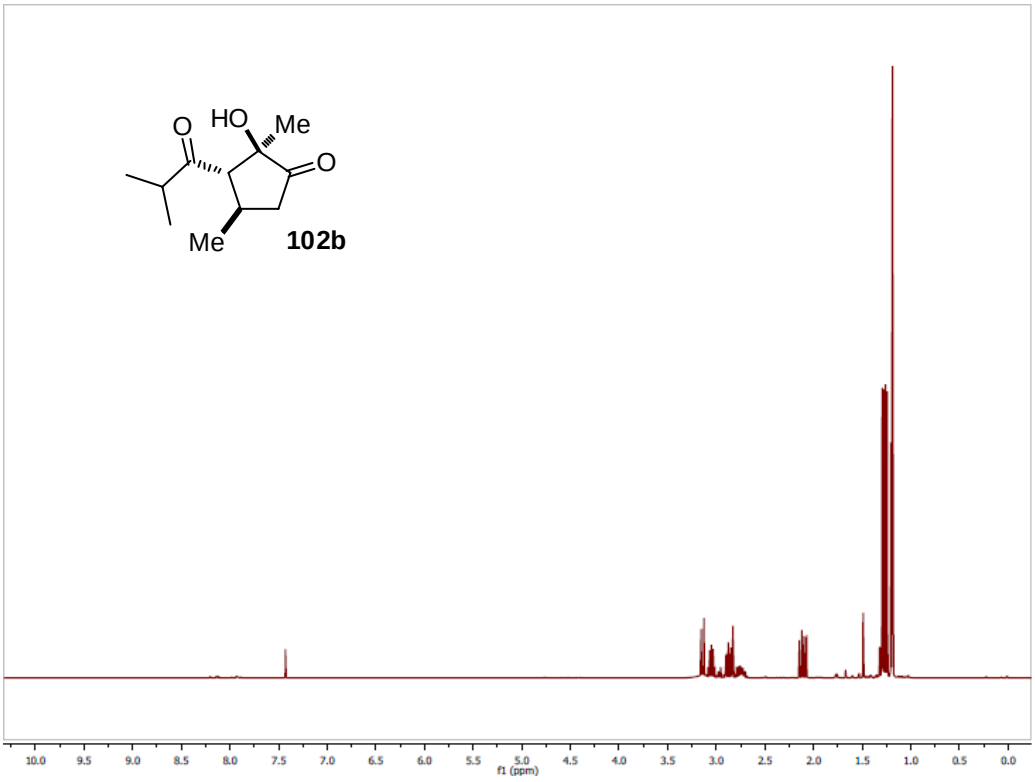

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
HO
Me
Me
O
68
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)

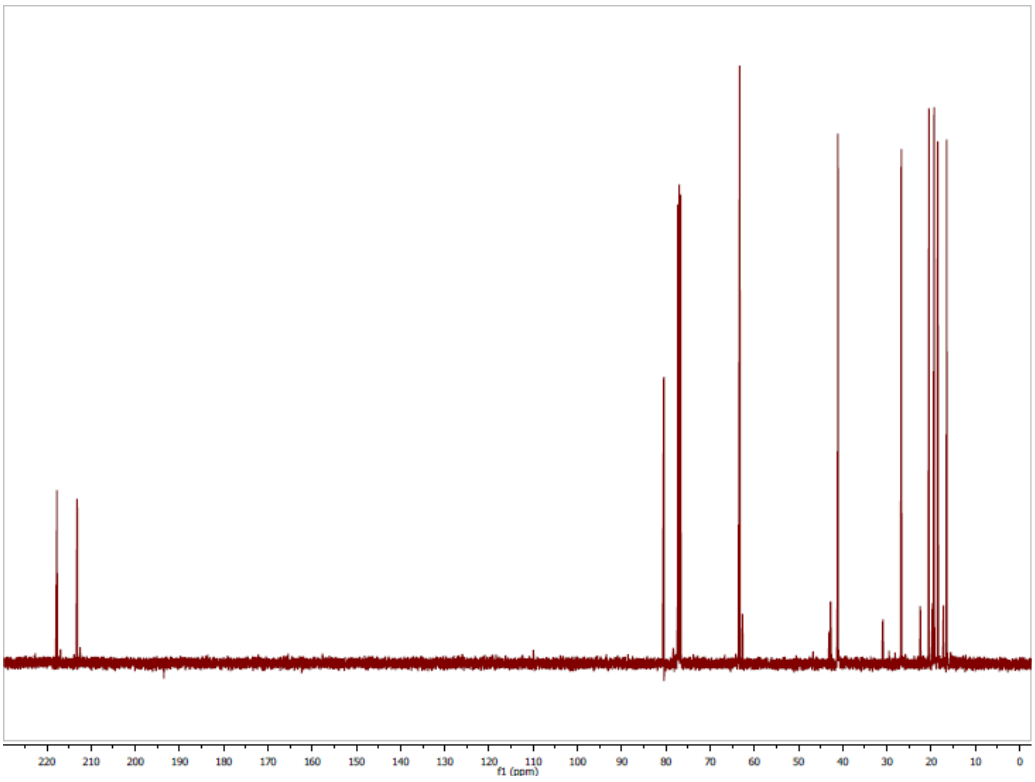

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

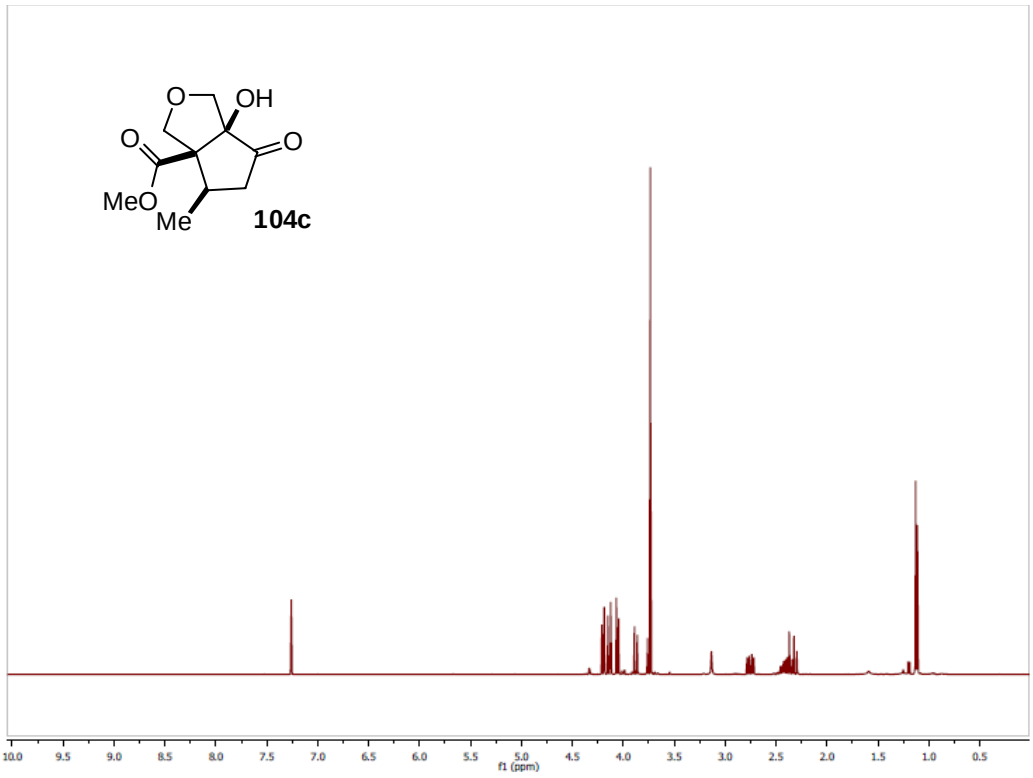

O
HO
Me
Ph
O
73
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

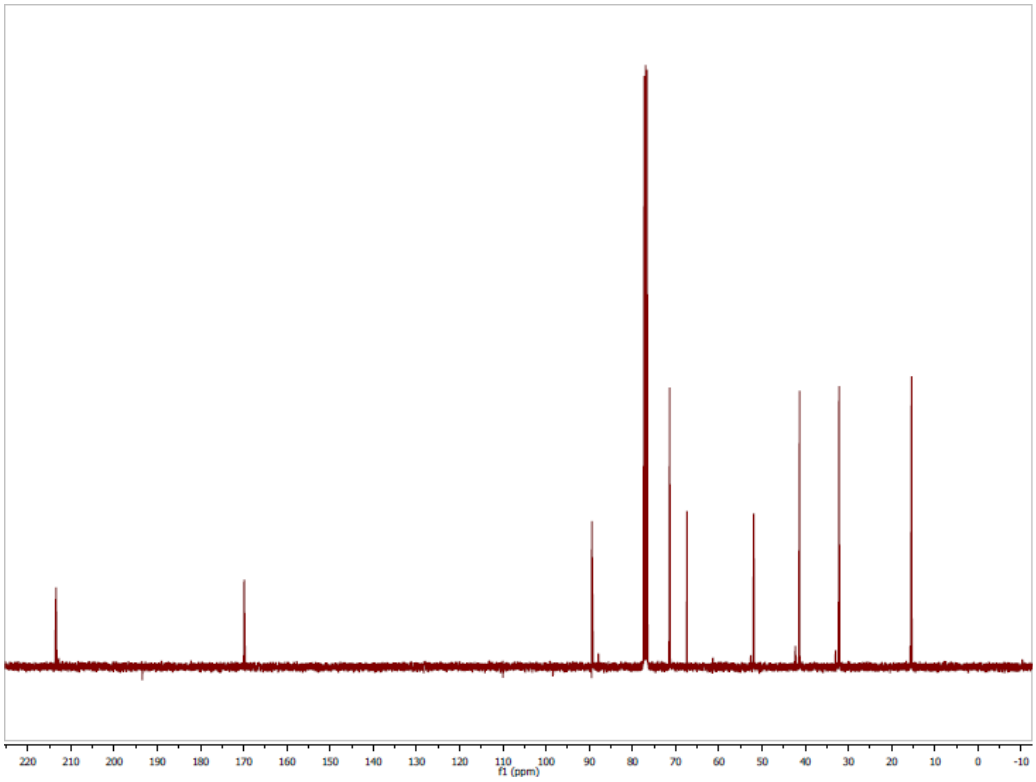

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

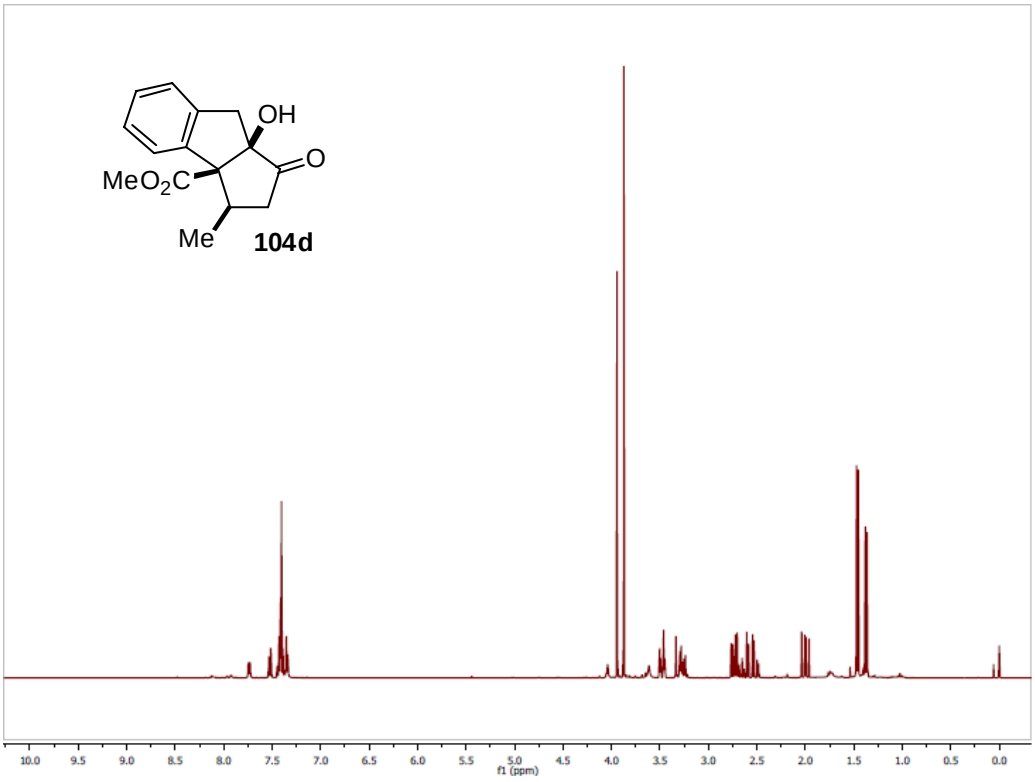

O
HO
Me
O
Me
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

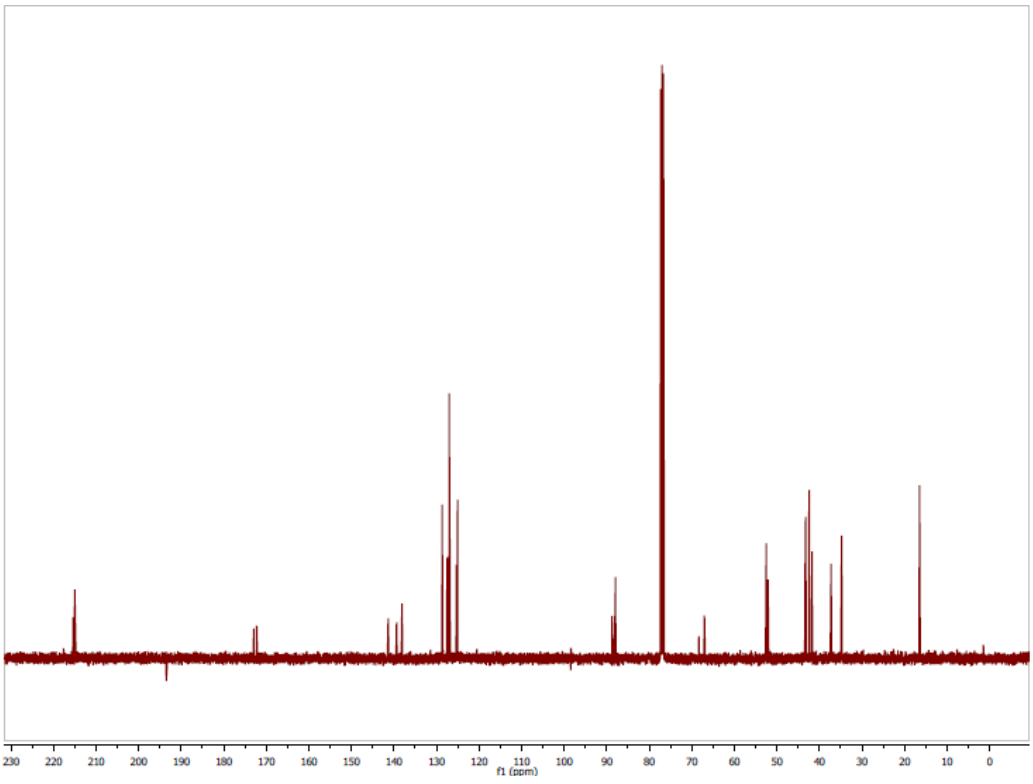
102b

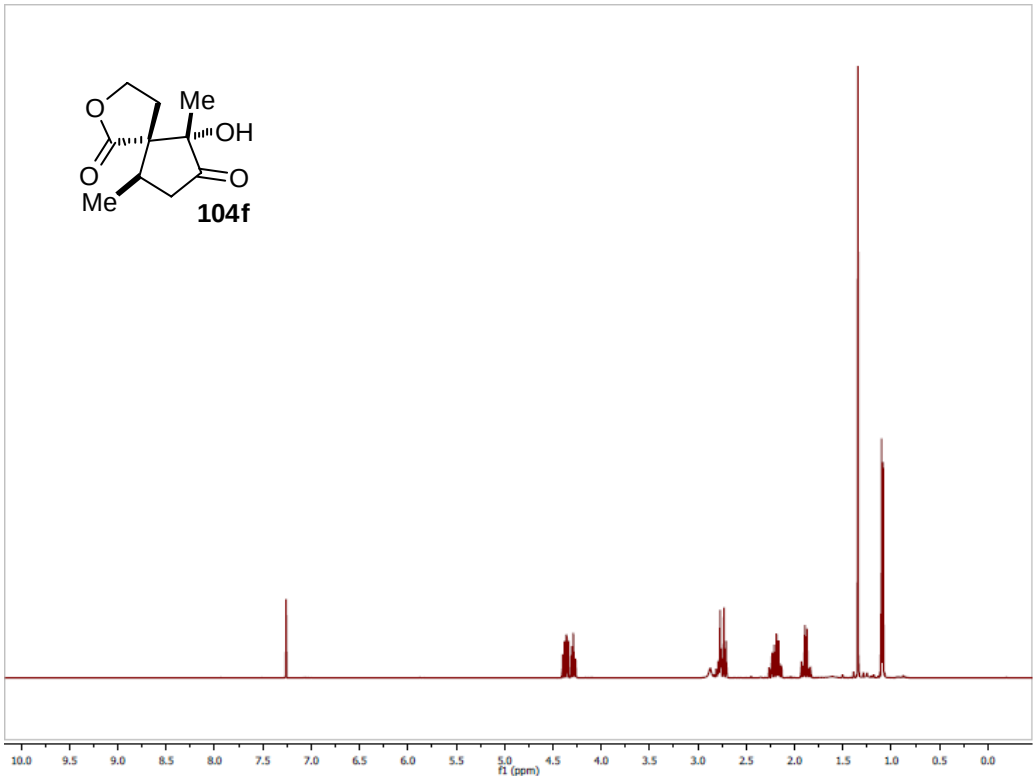

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

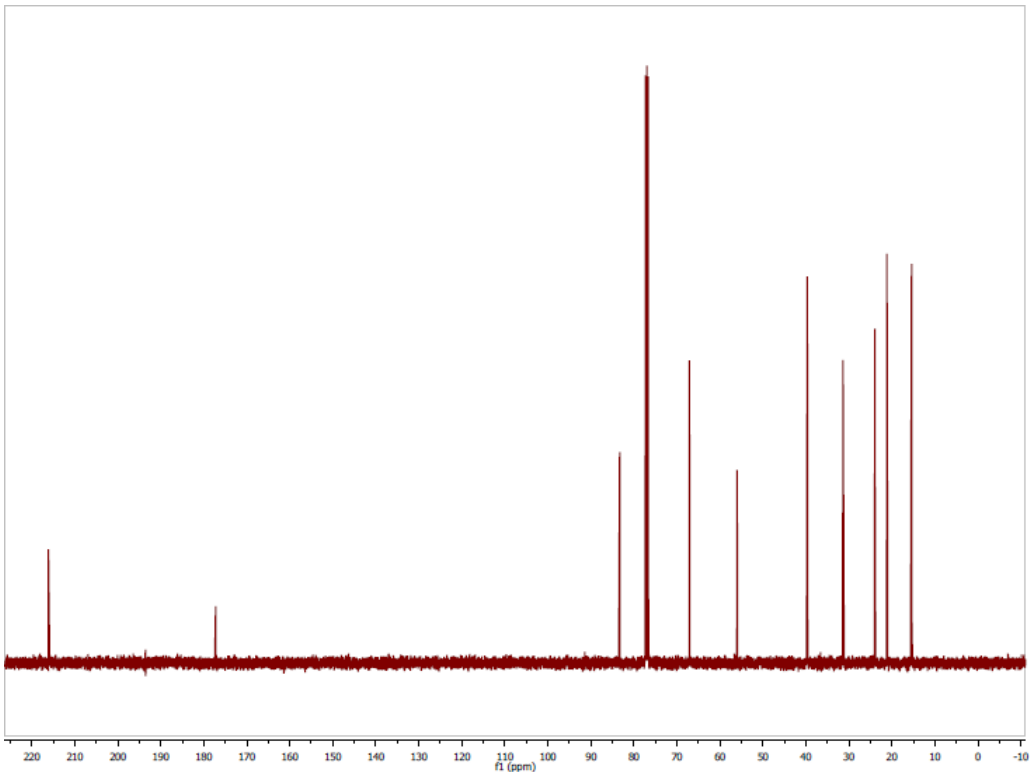

O
OH
O
O
MeO
Me
104c
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


220
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)

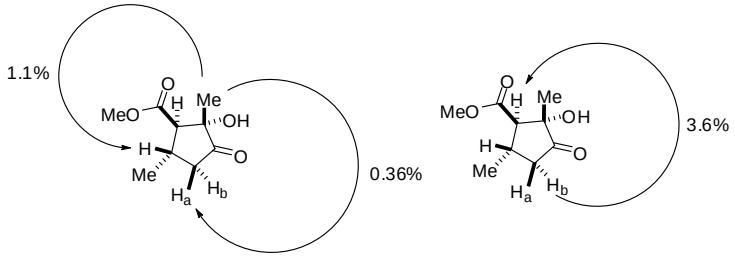

OH
O
MeO2C
Me
104d
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

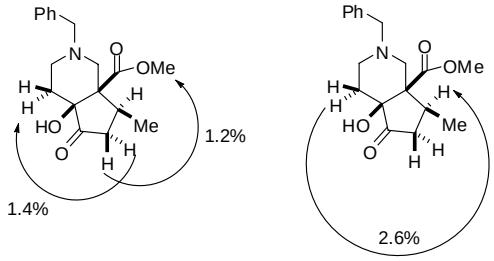

Me
OH
O
O
O
Me
104f
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

nOe For Compound 102c, Major Diastereomer



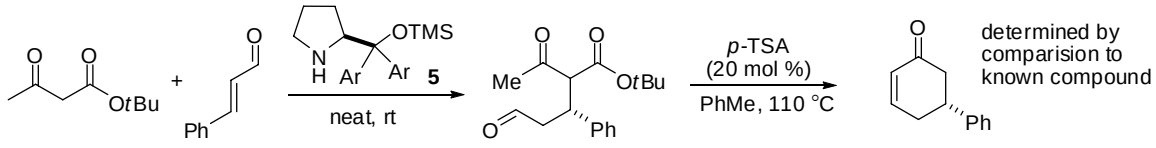
nOe For Compound 104b, Major Diastereomer



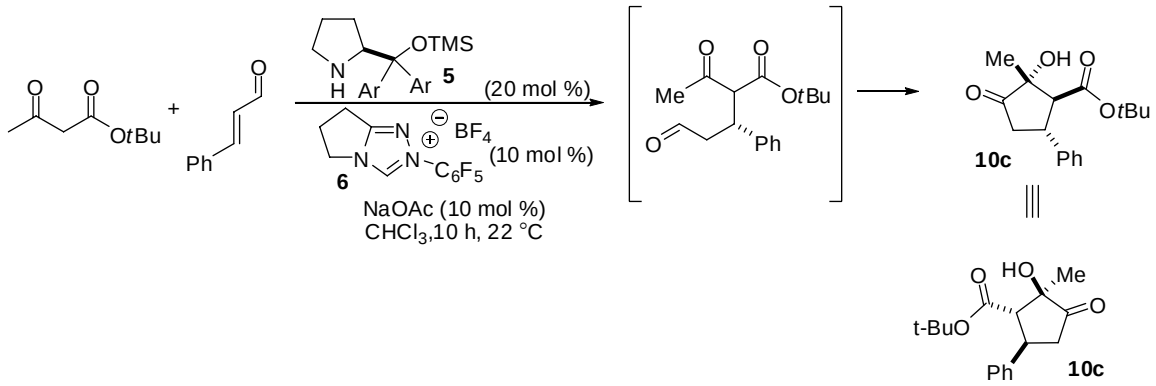
Determination of Absolute Configuration

Absolute configuration was assigned based on analogy to work done by Jørgensen and co-workers (Carlone, A.; Marigo, M.; North, C.; Landa, A.; Jørgensen, K. A. *Chem. Commun.* **2006**, 4928.)

Jørgensen



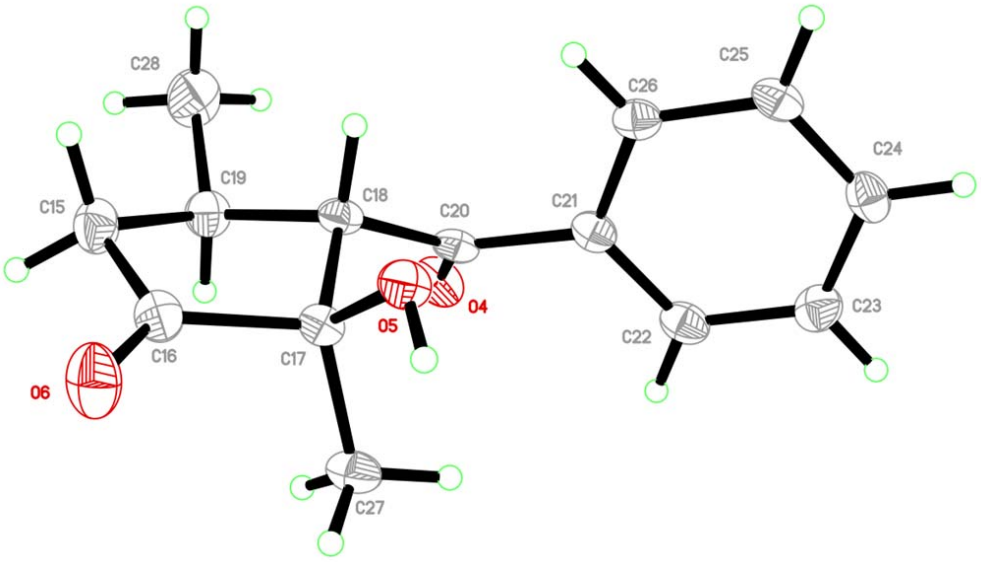
This Work

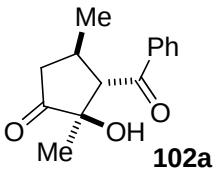


All cyclopentanone products described in this paper are based on this analogy.

Crystal Structure for Compound 102a

(Major Diastereomer)





102a

Table 1. Crystal data and structure refinement for compound **102a** (major diastereomer).

Identification code	**102a**
Empirical formula	$C_{14}H_{16}O_3$
Formula weight	232.27
Temperature	120 K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.7342(5) Å a= 90°.
	b = 15.4013(12) Å b= 93.861(3)°.
	c = 13.9378(10) Å g = 90°.
Volume	1228.11(17) Å^3
Z	4
Density (calculated)	1.256 Mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	496
Crystal size	0.35 x 0.13 x 0.09 mm^3
Theta range for data collection	1.97 to 28.29°.
Index ranges	-7<=h<=7, -20<=k<=20, -18<=l<=17
Reflections collected	21792
Independent reflections	5896 [R(int) = 0.0346]
Completeness to theta = 28.29°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9924 and 0.9700
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5896 / 1 / 313
Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0385, wR2 = 0.0867

R indices (all data) R1 = 0.0481, wR2 = 0.0911

Absolute structure parameter 0.2(7)

Largest diff. peak and hole 0.203 and -0.219 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **102a.** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3951(3)	3915(1)	1346(1)	19(1)
C(2)	4423(3)	2985(1)	1619(1)	22(1)
C(3)	2915(3)	2812(1)	2471(1)	19(1)
C(4)	2779(3)	3710(1)	2962(1)	17(1)
C(5)	2579(3)	4367(1)	2113(1)	19(1)
C(6)	786(3)	3771(1)	3624(1)	22(1)
C(7)	954(3)	4369(1)	4469(1)	21(1)
C(8)	2799(3)	4957(1)	4625(1)	23(1)
C(9)	2880(3)	5505(1)	5419(1)	29(1)
C(10)	1140(3)	5471(1)	6061(1)	31(1)
C(11)	-695(3)	4888(1)	5915(1)	31(1)
C(12)	-792(3)	4344(1)	5120(1)	26(1)
C(13)	3897(3)	2109(1)	3154(1)	26(1)
C(14)	97(3)	4490(1)	1677(1)	28(1)
C(15)	4225(3)	3155(1)	6605(1)	26(1)
C(16)	4523(3)	3672(1)	7519(1)	22(1)
C(17)	3307(3)	3202(1)	8333(1)	17(1)
C(18)	2662(3)	2307(1)	7868(1)	18(1)
C(19)	2304(3)	2487(1)	6779(1)	23(1)
C(20)	629(3)	1884(1)	8308(1)	19(1)
C(21)	922(3)	1565(1)	9324(1)	18(1)
C(22)	-929(3)	1669(1)	9918(1)	22(1)
C(23)	-770(3)	1325(1)	10840(1)	24(1)
C(24)	1193(3)	853(1)	11167(1)	22(1)
C(25)	3026(3)	743(1)	10577(1)	21(1)
C(26)	2917(3)	1110(1)	9662(1)	19(1)

C(27)	1196(3)	3739(1)	8576(1)	24(1)
C(28)	2385(4)	1674(1)	6161(1)	36(1)
O(1)	4510(2)	4285(1)	623(1)	27(1)
O(2)	3674(2)	5167(1)	2388(1)	23(1)
O(3)	-982(2)	3329(1)	3460(1)	36(1)
O(4)	-1284(2)	1813(1)	7861(1)	26(1)
O(5)	4897(2)	3074(1)	9143(1)	22(1)
O(6)	5538(2)	4355(1)	7641(1)	33(1)

Table 3. Bond lengths [Å] and angles [°] for **102a**.

C(1)-O(1)	1.2185(18)	C(18)-C(20)	1.502(2)
C(1)-C(2)	1.502(2)	C(18)-C(19)	1.543(2)
C(1)-C(5)	1.536(2)	C(19)-C(28)	1.522(3)
C(2)-C(3)	1.539(2)	C(20)-O(4)	1.2290(18)
C(3)-C(13)	1.524(2)	C(20)-C(21)	1.498(2)
C(3)-C(4)	1.546(2)	C(21)-C(26)	1.396(2)
C(4)-C(6)	1.520(2)	C(21)-C(22)	1.399(2)
C(4)-C(5)	1.555(2)	C(22)-C(23)	1.387(2)
C(5)-O(2)	1.4238(18)	C(23)-C(24)	1.391(2)
C(5)-C(14)	1.521(2)	C(24)-C(25)	1.388(2)
C(6)-O(3)	1.2295(18)	C(25)-C(26)	1.392(2)
C(6)-C(7)	1.492(2)		
C(7)-C(12)	1.397(2)	O(1)-C(1)-C(2)	127.00(14)
C(7)-C(8)	1.399(2)	O(1)-C(1)-C(5)	122.66(14)
C(8)-C(9)	1.390(2)	C(2)-C(1)-C(5)	110.34(12)
C(9)-C(10)	1.386(2)	C(1)-C(2)-C(3)	105.05(13)
C(10)-C(11)	1.388(3)	C(13)-C(3)-C(2)	113.72(13)
C(11)-C(12)	1.388(3)	C(13)-C(3)-C(4)	112.72(12)
C(15)-C(16)	1.503(2)	C(2)-C(3)-C(4)	103.55(12)
C(15)-C(19)	1.538(2)	C(6)-C(4)-C(3)	112.76(13)
C(16)-O(6)	1.209(2)	C(6)-C(4)-C(5)	113.69(13)
C(16)-C(17)	1.551(2)	C(3)-C(4)-C(5)	104.42(12)
C(17)-O(5)	1.4164(18)	O(2)-C(5)-C(14)	112.56(12)
C(17)-C(27)	1.523(2)	O(2)-C(5)-C(1)	110.03(12)
C(17)-C(18)	1.557(2)	C(14)-C(5)-C(1)	106.68(12)

O(2)-C(5)-C(4)	110.50(12)	O(5)-C(17)-C(18)	109.36(12)
C(14)-C(5)-C(4)	113.82(13)	C(27)-C(17)-C(18)	113.78(12)
C(1)-C(5)-C(4)	102.67(12)	C(16)-C(17)-C(18)	102.40(12)
O(3)-C(6)-C(7)	119.81(14)	C(20)-C(18)-C(19)	115.12(13)
O(3)-C(6)-C(4)	119.76(14)	C(20)-C(18)-C(17)	112.50(12)
C(7)-C(6)-C(4)	120.43(13)	C(19)-C(18)-C(17)	105.21(12)
C(12)-C(7)-C(8)	119.01(15)	C(28)-C(19)-C(15)	114.26(14)
C(12)-C(7)-C(6)	118.98(14)	C(28)-C(19)-C(18)	113.66(14)
C(8)-C(7)-C(6)	122.01(14)	C(15)-C(19)-C(18)	103.11(12)
C(9)-C(8)-C(7)	120.09(15)	O(4)-C(20)-C(21)	119.31(14)
C(10)-C(9)-C(8)	120.30(17)	O(4)-C(20)-C(18)	121.48(14)
C(9)-C(10)-C(11)	120.14(16)	C(21)-C(20)-C(18)	119.18(13)
C(10)-C(11)-C(12)	119.80(15)	C(26)-C(21)-C(22)	119.71(14)
C(11)-C(12)-C(7)	120.67(16)	C(26)-C(21)-C(20)	121.41(13)
C(16)-C(15)-C(19)	105.18(13)	C(22)-C(21)-C(20)	118.69(13)
O(6)-C(16)-C(15)	127.35(15)	C(23)-C(22)-C(21)	119.96(14)
O(6)-C(16)-C(17)	122.67(14)	C(22)-C(23)-C(24)	120.27(15)
C(15)-C(16)-C(17)	109.99(13)	C(25)-C(24)-C(23)	119.87(14)
O(5)-C(17)-C(27)	112.13(12)	C(24)-C(25)-C(26)	120.30(14)
O(5)-C(17)-C(16)	110.55(12)	C(25)-C(26)-C(21)	119.84(14)
C(27)-C(17)-C(16)	108.19(12)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **102a**. The anisotropic displacement factor exponent takes the form: $-2p^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}		U^{21}
C(1)	19(1)	C(8)	23(1)
C(2)	26(1)	C(9)	31(1)
C(3)	20(1)	C(10)	35(1)
C(4)	16(1)	C(11)	28(1)
C(5)	20(1)	C(12)	19(1)
C(6)	20(1)	C(13)	29(1)
C(7)	20(1)	C(14)	21(1)

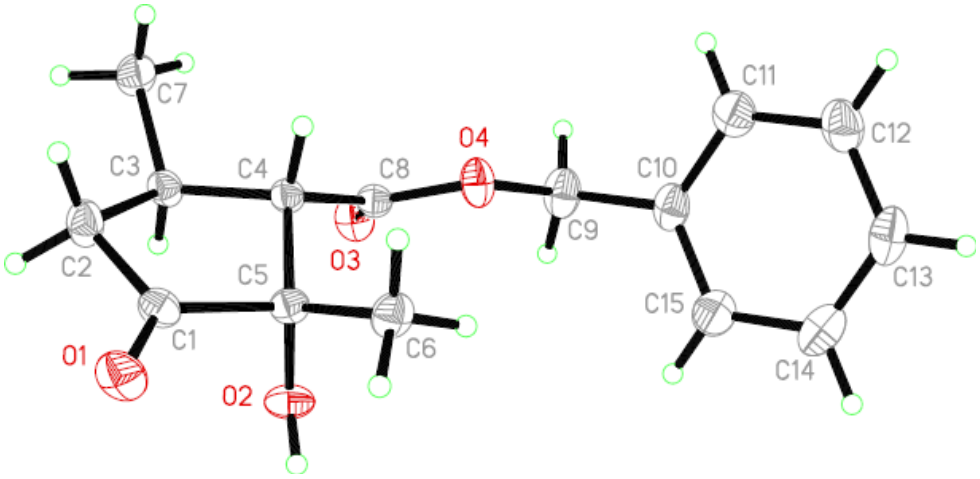
C(15)	27(1)	C(26)	18(1)
C(16)	16(1)	C(27)	20(1)
C(17)	17(1)	C(28)	50(1)
C(18)	19(1)	O(1)	40(1)
C(19)	23(1)	O(2)	26(1)
C(20)	21(1)	O(3)	26(1)
C(21)	18(1)	O(4)	21(1)
C(22)	18(1)	O(5)	25(1)
C(23)	22(1)	O(6)	34(1)
C(24)	26(1)		
C(25)	21(1)		

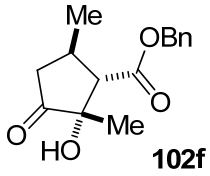
Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **102a**.

	x	y	z	U(eq)		x	y	z	U(eq)
H(2A)	6066	2899	1807	26	H(14C)	130	4819	1093	42
H(2B)	3981	2601	1086	26	H(15A)	5672	2865	6474	31
H(3)	1343	2642	2221	23	H(15B)	3755	3528	6065	31
H(4)	4254	3815	3341	21	H(18)	4018	1923	7973	22
H(8)	3973	4982	4197	27	H(19)	779	2766	6650	27
H(9)	4108	5896	5519	35	H(22)	-2266	1968	9695	26
H(10)	1202	5840	6590	38	H(23)	-1981	1411	11241	29
H(11)	-1855	4862	6350	38	H(24)	1278	611	11779	26
H(12)	-2033	3958	5020	31	H(25)	4332	423	10793	25
H(13A)	4006	1572	2810	39	H(26)	4171	1052	9277	23
H(13B)	2880	2035	3668	39	H(27A)	409	3455	9076	36
H(13C)	5422	2278	3415	39	H(27B)	144	3796	8014	36
H(14A)	-807	4796	2123	42	H(27C)	1704	4304	8792	36
H(14B)	-598	3933	1540	42	H(28A)	2182	1832	5495	55

H(28B)	1155	1286	6317	55	H(2)	2862	5573	2180	34
H(28C)	3867	1392	6283	55	H(5)	4834	3490	9508	33

X-Ray Crystal Structure for Compound 102f (Minor Diastereomer)





102f

Table 6. Crystal data and structure refinement for **102f** (minor diastereomer).

Identification code	**102f** (minor diastereomer).	
Empirical formula	$C_{15}H_{18}O_4$	
Formula weight	262.29	
Temperature	120 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 11.8387(6) Å	α = 90°.
	b = 4.9870(3) Å	β = 107.049(3)°.
	c = 12.2899(6) Å	γ = 90°.
Volume	693.70(6) Å^3	
Z	2	

Density (calculated)	1.256 Mg/m^3
Absorption coefficient	0.090 mm^{-1}
F(000)	280
Crystal size	0.33 x 0.32 x 0.28 mm^3
Theta range for data collection	1.73 to 32.59°.
Index ranges	-17<=h<=17, -7<=k<=7, -17<=l<=18
Reflections collected	17342
Independent reflections	4947 [R(int) = 0.0342]
Completeness to theta = 32.59°	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9753 and 0.9710
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4947 / 1 / 175
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0434, wR2 = 0.1091
R indices (all data)	R1 = 0.0526, wR2 = 0.1158
Absolute structure parameter	-0.3(7)
Largest diff. peak and hole	0.363 and -0.281 $e.Å^{-3}$

Table 7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **102f.** U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	6745(1)	9272(2)	239(1)	21(1)
C(2)	7958(1)	9599(3)	99(1)	25(1)
C(3)	8812(1)	8255(2)	1141(1)	20(1)
C(4)	8168(1)	8575(2)	2054(1)	17(1)
C(5)	6853(1)	8108(2)	1427(1)	18(1)
C(6)	5981(1)	9235(3)	1995(1)	24(1)
C(7)	10047(1)	9467(3)	1470(1)	26(1)
C(8)	8618(1)	6737(2)	3067(1)	19(1)
C(9)	8510(1)	5804(3)	4935(1)	29(1)
C(10)	7658(1)	6491(3)	5590(1)	25(1)
C(11)	7885(1)	8629(3)	6352(1)	30(1)
C(12)	7089(1)	9287(3)	6939(1)	32(1)
C(13)	6067(1)	7795(3)	6785(1)	34(1)
C(14)	5832(1)	5674(3)	6027(1)	38(1)
C(15)	6623(1)	5037(3)	5428(1)	32(1)
O(1)	5814(1)	9740(2)	-476(1)	28(1)
O(2)	6701(1)	5267(2)	1229(1)	24(1)
O(3)	9249(1)	4817(2)	3111(1)	27(1)
O(4)	8208(1)	7518(2)	3925(1)	25(1)

Table 8. Bond lengths [Å] and angles [°] for **102f**.

C(1)-O(1)	1.2141(13)	C(7)-C(3)-C(2)	113.23(10)
C(1)-C(2)	1.5051(16)	C(7)-C(3)-C(4)	114.07(9)
C(1)-C(5)	1.5416(16)	C(2)-C(3)-C(4)	102.56(9)
C(2)-C(3)	1.5338(16)	C(8)-C(4)-C(3)	114.03(9)
C(3)-C(7)	1.5228(16)	C(8)-C(4)-C(5)	112.40(9)
C(3)-C(4)	1.5389(15)	C(3)-C(4)-C(5)	105.32(9)
C(4)-C(8)	1.5110(15)	O(2)-C(5)-C(6)	112.05(9)
C(4)-C(5)	1.5390(15)	O(2)-C(5)-C(4)	106.95(9)
C(5)-O(2)	1.4399(14)	C(6)-C(5)-C(4)	116.11(9)
C(5)-C(6)	1.5134(16)	O(2)-C(5)-C(1)	103.77(9)
C(8)-O(3)	1.2057(14)	C(6)-C(5)-C(1)	114.71(9)
C(8)-O(4)	1.3415(14)	C(4)-C(5)-C(1)	102.01(9)
C(9)-O(4)	1.4622(15)	O(3)-C(8)-O(4)	123.86(11)
C(9)-C(10)	1.5025(18)	O(3)-C(8)-C(4)	125.65(11)
C(10)-C(15)	1.3870(18)	O(4)-C(8)-C(4)	110.49(9)
C(10)-C(11)	1.3927(19)	O(4)-C(9)-C(10)	106.64(9)
C(11)-C(12)	1.384(2)	C(15)-C(10)-C(11)	119.00(12)
C(12)-C(13)	1.385(2)	C(15)-C(10)-C(9)	120.50(12)
C(13)-C(14)	1.383(2)	C(11)-C(10)-C(9)	120.49(12)
C(14)-C(15)	1.387(2)	C(12)-C(11)-C(10)	120.36(13)
		C(11)-C(12)-C(13)	120.18(14)
O(1)-C(1)-C(2)	126.21(11)	C(14)-C(13)-C(12)	119.86(13)
O(1)-C(1)-C(5)	124.33(10)	C(13)-C(14)-C(15)	119.95(14)
C(2)-C(1)-C(5)	109.41(9)	C(14)-C(15)-C(10)	120.64(14)
C(1)-C(2)-C(3)	105.94(9)	C(8)-O(4)-C(9)	116.31(9)

Symmetry transformations used to generate equivalent atoms:

Table 9. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **102f**. 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}
C(1)	18(1)	22(1)	19(1)	-1(1)	1(1)	2(1)
C(2)	20(1)	36(1)	19(1)	4(1)	5(1)	2(1)
C(3)	15(1)	26(1)	17(1)	-2(1)	4(1)	1(1)
C(4)	15(1)	21(1)	16(1)	-1(1)	4(1)	-1(1)
C(5)	14(1)	20(1)	19(1)	1(1)	3(1)	1(1)
C(6)	18(1)	28(1)	27(1)	1(1)	9(1)	3(1)
C(7)	16(1)	38(1)	25(1)	1(1)	6(1)	-2(1)
C(8)	14(1)	24(1)	18(1)	-1(1)	2(1)	-2(1)
C(9)	26(1)	38(1)	22(1)	10(1)	7(1)	8(1)
C(10)	22(1)	35(1)	17(1)	8(1)	4(1)	5(1)
C(11)	23(1)	42(1)	21(1)	3(1)	1(1)	-1(1)
C(12)	33(1)	42(1)	20(1)	3(1)	5(1)	4(1)
C(13)	34(1)	45(1)	29(1)	9(1)	17(1)	6(1)
C(14)	31(1)	42(1)	45(1)	5(1)	19(1)	-4(1)
C(15)	31(1)	34(1)	31(1)	1(1)	11(1)	-2(1)
O(1)	19(1)	35(1)	24(1)	2(1)	-2(1)	5(1)
O(2)	16(1)	20(1)	30(1)	-1(1)	0(1)	-1(1)
O(3)	23(1)	32(1)	24(1)	4(1)	5(1)	7(1)
O(4)	28(1)	31(1)	18(1)	5(1)	8(1)	7(1)

Table 10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **102f**.

	x	y	z	U(eq)
H(2A)	8150	11483	69	30
H(2B)	8001	8740	-596	30
H(3)	8868	6342	981	24
H(4)	8265	10432	2327	21
H(6A)	6022	8221	2669	35
H(6B)	5196	9123	1479	35
H(6C)	6171	11076	2195	35
H(7A)	10543	8533	2117	40
H(7B)	10004	11327	1656	40
H(7C)	10372	9306	843	40
H(9A)	9315	6136	5395	34
H(9B)	8436	3929	4716	34
H(11)	8576	9619	6468	35
H(12)	7240	10735	7437	38
H(13)	5540	8218	7191	41
H(14)	5145	4675	5919	45
H(15)	6457	3622	4913	38
H(2)	5997	4932	948	35