12-2013

Towards the Total Synthesis of Antascomicin B. Efforts to Construct the C1-C21 Fragment

Juliette Rivero-Castro
University of Arkansas, Fayetteville

Towards the Total Synthesis of Antascomicin B. Efforts to Construct the C1-C21 Fragment

Towards the Total Synthesis of Antascomicin B. Efforts to Construct the C1-C21 Fragment

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in Chemistry

By

Juliette Rivero-Castro
Industrial University of Santander
Bachelor in Chemistry, 2000
University of Arkansas
Master of Science in Chemistry, 2009

December 2013
University of Arkansas

This dissertation is approved for recommendation to the Graduate Council.

_____
Dr. Matthias McIntosh
Dissertation Director

_____
Dr. Neil Allison
Committee Member

_____
Dr. Suresh K. Thallapuranam
Committee Member

_____
Dr. Wei Shi
Committee Member

ABSTRACT

Antascomicin B is a macrolide isolated from a strain of *Micromonospora*. It possesses structural similarities to FK506 and rapamycin and exhibits potent binding ability to FKBP12. Recent reports suggest that small molecule ligands of FKBP12 possess potent neuroprotective and neurodegenerative properties in mouse models of Parkinson's disease. Our approach to the C1-21 fragment of antascomicin B involves an asymmetric amino-Claisen rearrangement originally developed by Tsunoda et al.[35] report the scalability of the preparation and rearrangement of an allylic amide possessing a silyloxy group at the terminal position of the alkene. The Tsunoda-Claisen rearrangement uses inexpensive (*S*)-α-methylbenzylamine as the chiral auxiliary. The allylic amide underwent rearrangement to establish the C14 and C15 stereocenters in high yield and good diastereoselectivity. We found a surprisingly high yielding acid mediated lactonization that was employed to cleave the α-methylbenzyl amide. Details of these studies and further elaboration of the lactone are discussed. We also describe the progress toward the synthesis of the C1-21 fragment of the natural product.

ACKNOWLEDGEMENTS

I would like to thank my advisor, Dr. Matthias McIntosh, for his instruction, guidance, patience and intellectual and economical support throughout my graduate studies at the University of Arkansas. His encouragement, advice and his trust made it a pleasure to work in the McIntosh Group.

Additionally, I would like to thank the members of my dissertation committee, Drs. Robert Gawley, Neil Allison, T.K.S Kumar and Wei Shi for their support, advice and availability to discuss ideas every year during my committee meetings. I owe special thanks to Dr. Gawley for his encouragement and valuable suggestions during my writing.

I also want to thank both the old and the new members of the McIntosh group for their friendship and support. I owe special thanks to Silvana Dormi for all the chemistry discussions and her willingness to help me to solve problems. I want to thank John Hutchinson for his advice given throughout this project and his encouragement to work hard every day. Special thanks to David Clay for all the valuable talks about antascomicin B and for sharing his broad knowledge about beer stiles.

I would like to extend my gratitude to the Biochemistry and Chemistry department of the University of Arkansas who has financed the last two years of my graduate studies as well as everyone who has made contributions of time, skills, and energy to complete this work.

I would like to thanks COLCIENCIAS and LASPAU entities for their economic and legal support which allowed me to pursue graduate studies in the USA.

My deepest thanks go out to my family and good friends. My hard working parents Ramon A. Rivero and Damaris Castro who gave me the opportunity to pursue my college education. Thanks to my siblings, Ramon, Cesar, Jonathan, and, Paola for their encouragement to never give up. Thanks to Solanhz Ortiz and Catalina Ortega for their patience of being a good listeners in my chemical frustrated moments.

Last, but not least, I would like to thank my lovely boyfriend Brian Walker for his enormous support during my last year of studies in graduate school and for making my life much easier in Fayetteville.

TABLE OF CONTENTS

I. MODE OF ACTION OF FK506, RAPAMYCIN AND ANTASCOMICINS 1

A. Background and Significance 1

B. Isolation and Biological Properties of Antascomicins 5

II. TOWARD TO THE TOTAL SYNTHESIS OF ANTASCOMICIN B: EFFORTS TO CONSTRUCT THE C1-C21 FRAGMENT 6

A. Retrosynthetic Analysis of Antascomicin B 6

B. Initial Strategy to Prepare the C1-C21 Unit 7

C. 2nd Generation Approach to Construct the C10-C16 Fragment 15

D. Installation of the 1,2-*syn* (C14-C15) Stereorelationship *via* Amino-Claisen Rearrangement 16

1. Amino-Claisen Rearrangement of Amide Enolates 16

2. Asymmetric Amino-Claisen Rearrangement of Silyloxyallyl-propanamide **34** 25

E. Attempts to Build the 1,4-*anti* (C11-C14) Stereorelationship *via* Ring-Closing Olefin Metathesis 36

1. Efforts to construct the β,γ-Unsaturated Lactone **37** by Ring-Closing Metathesis 36

2. Ring Closing Metathesis of Allylester **36** in Presence of Diallylmalonate 42

F. Cross Metathesis Attempt to Introduce the 1,4-*anti*-configuration of the C10-C16 fragment 46

G. Efforts to Install the 1,4-*anti* (C11-C14) Stereorelationship through Allylic Diazene Rearrangement 47

1. Attempts to Prepare Silyloxybutanoic Acid **120** by Ozonolysis 49

2. Ozonolysis of Amide **35a** in Presence of Pyridine 55

3. Other Oxidation Efforts to Form Carboxylic Acid **127** and Aldehyde **137** 59

H. Third Generation Route to Construct the C10-C21 Fragment 60

1. Preparation of Silyloxypyranone **137** through Hydroboration/Oxidation 60

2. Efforts to Introduce the C17-C21 Hexadiene Arm *via* Grignard Addition 65

I. Asymmetric Suzuki Cross-Coupling Strategy to Construct the C1-C2 Fragment of Antascomicin B 68

1. Attempts to Synthesize the Vicinal Tricarbonyl Region of Antascomicin B *via* Amide Bond Formation 69

2. Efforts to build the Vicinal Tricarbonyl Region *via* Aminolysis 73

3. Attempts to Synthesize Borane-pentamide **176** *via* Iridium-Catalyzed Hydroboration 76

J. Future Work 78

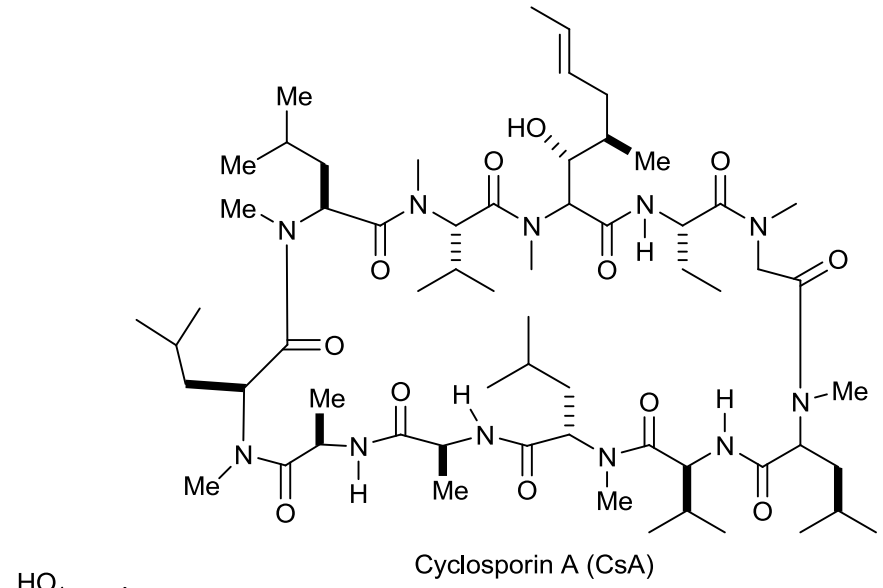
III. EXPERIMENTAL SECTION 79

IV. BIBLIOGRAPHIC REFERENCES 88

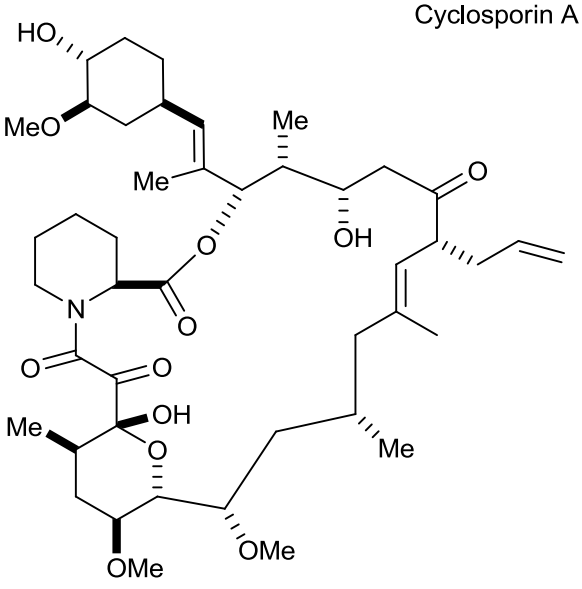
I. MODE OF ACTION OF FK506, RAPAMYCIN AND ANTASCOMICINS

A. Background and Significance

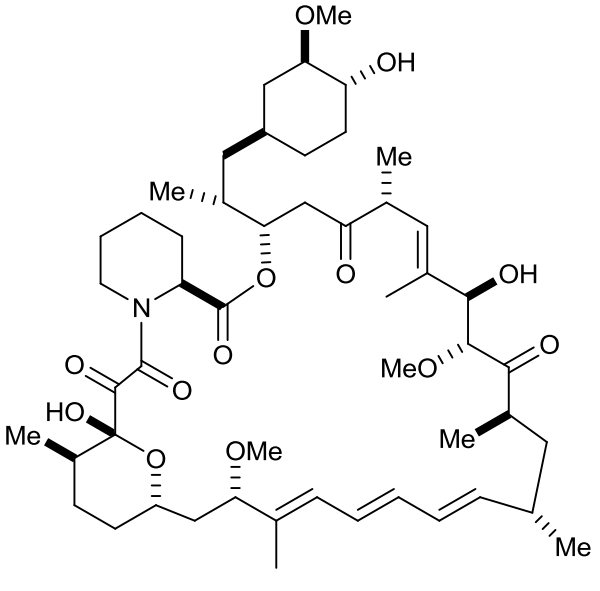
FK506 (tacrolimus),[1-3] a natural product of *Streptomyces tukubaensis*, and rapamycin (sirolimus),[4-6] produced by *Streptomyces hygroscopicus*, are potent immunosuppressive agents, which have a mode of action and toxicity profile similar to those of cyclosporine A (CsA), an immunosuppressive cyclic undecapeptide produced by *Tolypocladiuminflatum* (Scheme 1). These three natural products have been used clinically to prevent rejection of transplantation of kidney, heart, liver and bone marrow.[7]



Cyclosporin A (CsA)



FK506



Rapamycin

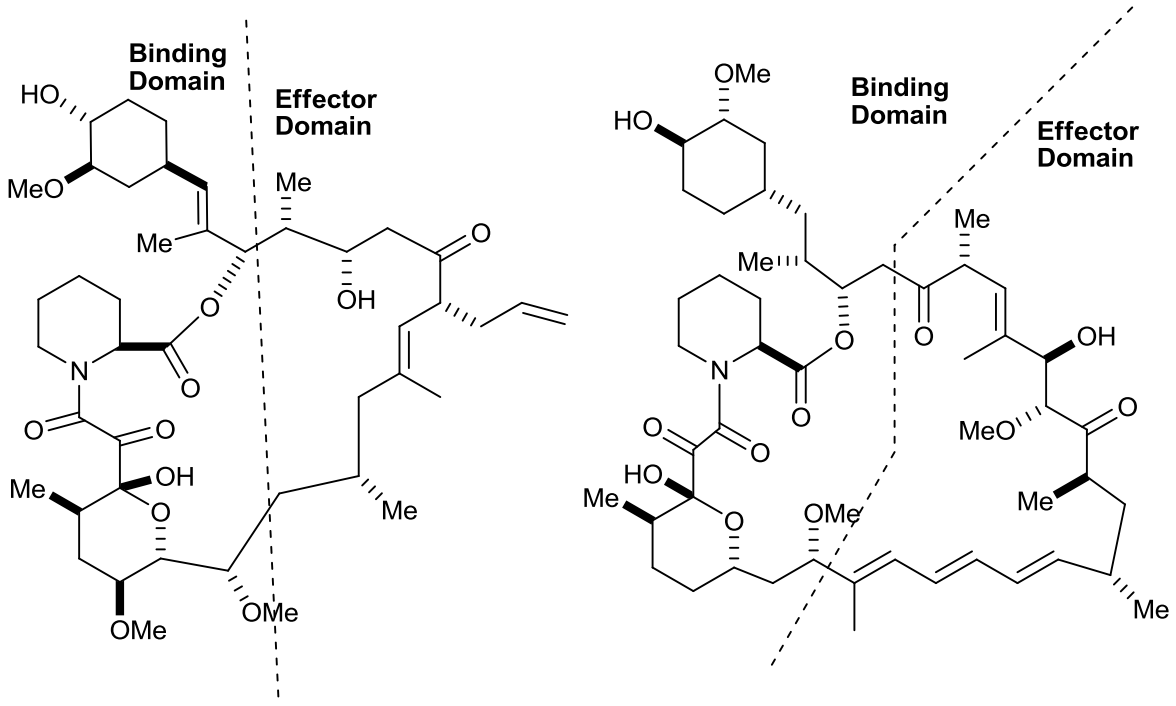
Scheme 1. Structures of Cyclosporin (CsA), FK506 and Rapamycin

The biological modes of action of these promising natural products have been extensively investigated over the past four decades.[7,8] FK506, cyclosporine A (CsA), and rapamycin belong to a family of macrocyclic immunosuppressants which share the same initial target at the cellular level. Biochemical and genetic studies have demonstrated all of the above macrocyclic compounds form active complexes with specific protein conjugates called immunophilins. CsA interacts with a series of cyclophilin proteins (CyP) that are prevalent in almost all cells. FK506 and rapamycin bind a class of structurally similar immunophilins named FK506 binding proteins (FKBPs). FKBP12 is the most important one for the immunosuppressive activity of rapamycin in the FKBP family.[9,10]

Initially, scientists proposed that rapamycin and FK506 induced the inhibition of peptidylprolyl *cis-trans*-isomerase (PPIase) activity of the immunophilins and that activity resulted in the immunosuppressive action of these natural products.[11,12] However, further studies made to several synthetic analogs of rapamycin and FK506 showed the PPIase binding affinity but did not show the immunosuppressive activity.[13,14] Therefore, this hypothesis was not enough to explain the action mechanism of these macrocyclic compounds.

It was later discovered that CsA-cyclophilin and FK506-FKBP12 form a ternary complex with calcineurin, a calcium calmodulin-dependent serine-threonine protein phosphatase.[15] This latter interaction blocks the calcineurins' ability to dephosphorylate the cytoplasmic subunit of nuclear factor of activated T cells (NF-ATC), preventing its translocation to the nucleus, and consequently the transcription of cytokine genes, in T lymphocytes.[16] Thus, the principal cause that induces the immunosuppressive effects of CsA and FK506 at the molecular level is attributed to the inhibition of the translocation of NF-ATC. Similarly, the rapamycin-FKBP12 complex was determined to be the mammalian target of rapamycin (mTOR), which inhibits the phosphorylation and activation of serine/threonine kinase, specifically P70 S6 kinase, a central regulator of translation and cell proliferation.[17,18]

X-ray crystallography studies of both calcineurin and mTOR *via* the FK506 or rapamycin-FKBP12 complexes has revealed that the strong binding of both FK506 and rapamycin to FKBP12 is through hydrophobic interactions using the tricarbonyl pipecolyl fragment of their structure.[19,20] The other portion of the molecule remains accessible to the solvent. Hence, FK506 and rapamycin are described as having a binding domain for their interaction with FKBP12, and an effector domain for imparting the cellular response (Scheme 2). Since FK506 and rapamycin possess nearly similar binding domains, it could explain why they share the same cellular target. Also, the different biological responses could be attributed to the effector domain regions where FK506 and rapamycin are quite different. To date, these interactions are considered the main reason for the differing biological activity of these natural products.

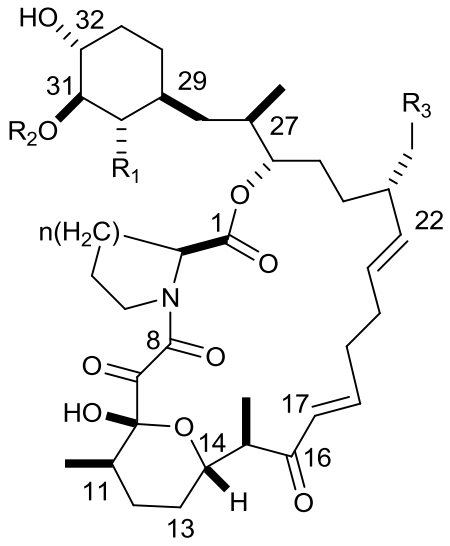


Scheme 2. FKBP12 ligand interactions

In addition to the immunosuppressive activities, it has been reported that FK506, rapamycin and its derivatives display neuroregenerative and neuroprotective activity, while CsA showed only neuroprotective activity.[7] Due to the fact that these substances easily cross the blood brain barrier, they could be used in the treatment of nerve injuries and neurological diseases. Even though the mode of action of the neural activity of FKBP has not yet been fully explained, it has been demonstrated that the neurotrophic properties of FKBP ligands do not depend on calcineurin-mediated effects. Moreover, FKBP ligands are now considered prominent targets for the development of new drugs for the treatment and cure of neurodegenerative diseases such as Alzheimer's and Parkinson's.[21]

B. Isolation and Biological Properties of Antascomicins

During the pursuit for novel substances that might exhibit similar bioactivity to FK506 and rapamycin, five new macrolides antascomicins A-E were discovered (Scheme 3).[22] The macrolides were produced in a fermentation process of a strain of the genus *Micromonospora*, isolated from the soil sample collected in China. The structures of these five compounds were elucidated by NMR spectroscopy and X-ray crystallographic analysis.[22] This novel family of compounds is structurally related to FK506, binds strongly to FKBP12 in the same range as do FK506 and rapamycin, but interestingly does not show immunosuppressive activity. It has been discovered that the levels of FKBP12 found in the brain are nearly 50 times higher than in the immune system,[23] making these FKBP12 ligands promising targets for probing the neurological system roles.[24]



Compound	R_1	R_2	R_3	n	FKBP12 binding IC_{50} (nM)
Antascomicin A	H	H	H	2	2.0
B	OH	H	H	2	0.7
C	OH	Me	H	2	1.0
D	H	H	H	1	5.2
E	H	H	OH	2	0.7
Rapamycin					0.6
FK506					1.1

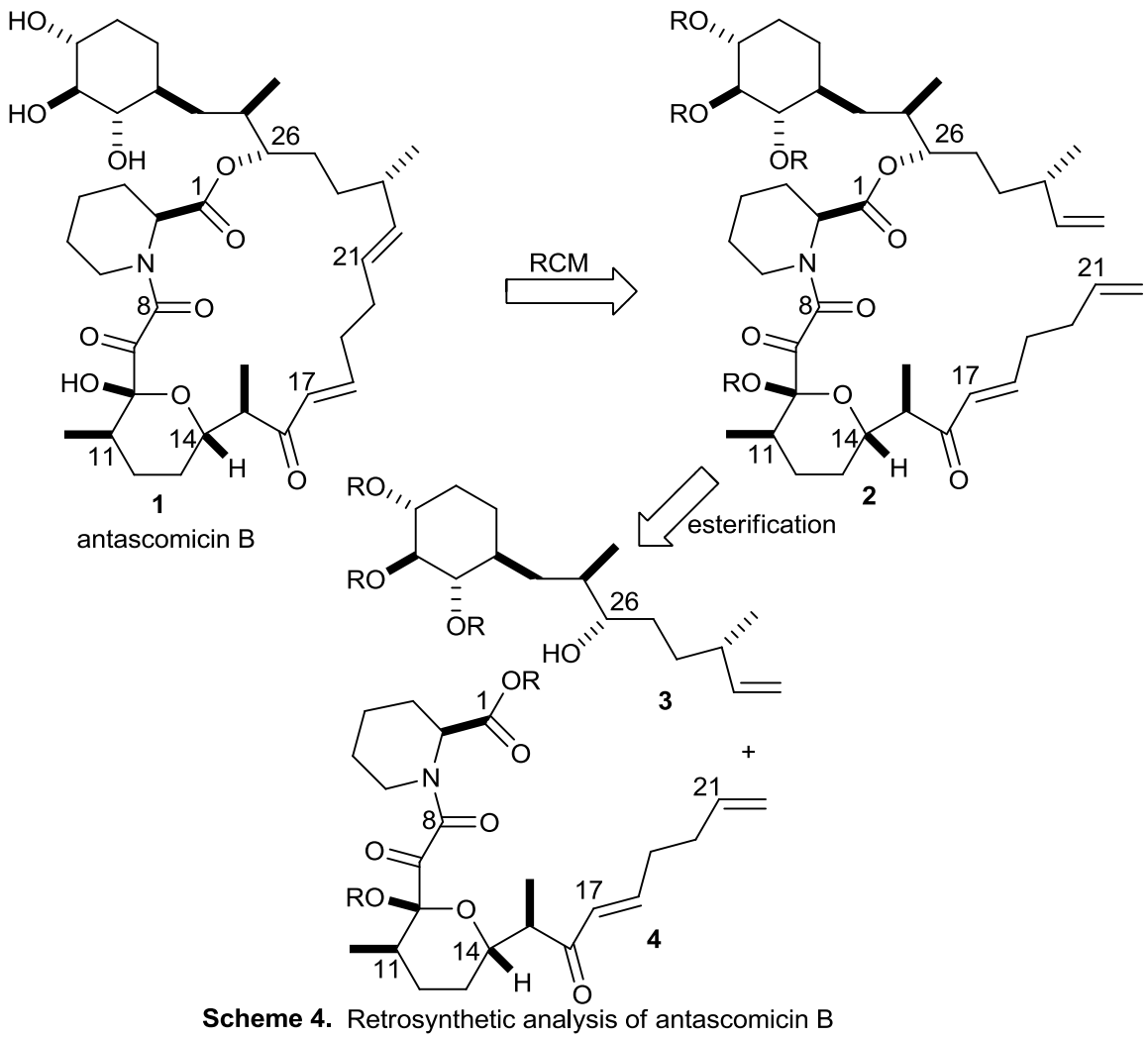
Scheme 3. Structures and FKBP12 binding assay of antascomicin family

The lack of immunosuppressive activity of antascomicin family has taken the attention of the biochemical community and has become very attractive for the synthetic organic chemist. Up to date, Ley's group has reported the first and only total synthesis of antascomicin B.[25] No other complete synthesis of the antascomicin family has been published. However, the stereoselective synthesis of the fragments C1-C21 and C22-C34 of antascomicin A has been reported by Chakraborty's group;[26,27] additionally, Fuwa et al. have described the synthesis of the C18-C34 fragment of antascomicin A.[28]

II. TOWARD THE TOTAL SYNTHESIS OF ANTASCOMICIN B: EFFORTS TO CONSTRUCT THE C1-C21 FRAGMENT

A. Retrosynthetic Analysis of Antascomicin B

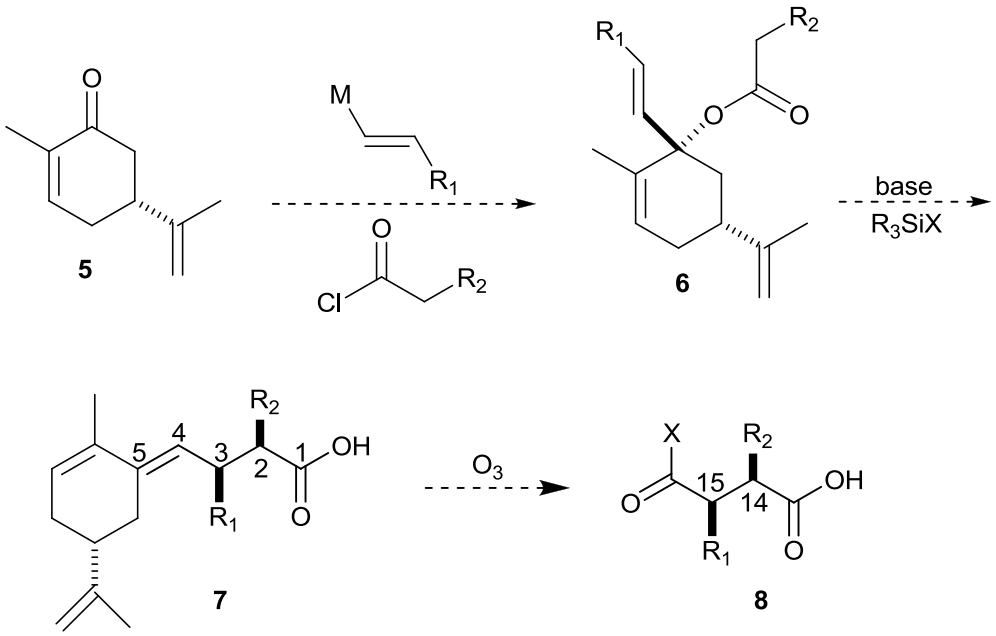
Both the potentially useful biological properties and the structural features of the antascomicin family stimulated us to initiate the total synthesis of antascomicin B (**1**) (Scheme 4). This polyketide target has potent FKBP12 binding ability, contains lactol, lactone, and lactam functionalities, a masked tricarbonyl moiety and twelve stereogenic centers. Our retrosynthetic plan involves a ring closing metathesis (RCM) to close the macrocyclic ring. The acyclic triene **2** will be accessed by assembling the C1-C21 and C22-C34 fragments *via* esterification (Scheme 4). In this report we describe the efforts to synthesize the fragment C1-C21 of the macrolide.



Scheme 4. Retrosynthetic analysis of antascomicin B

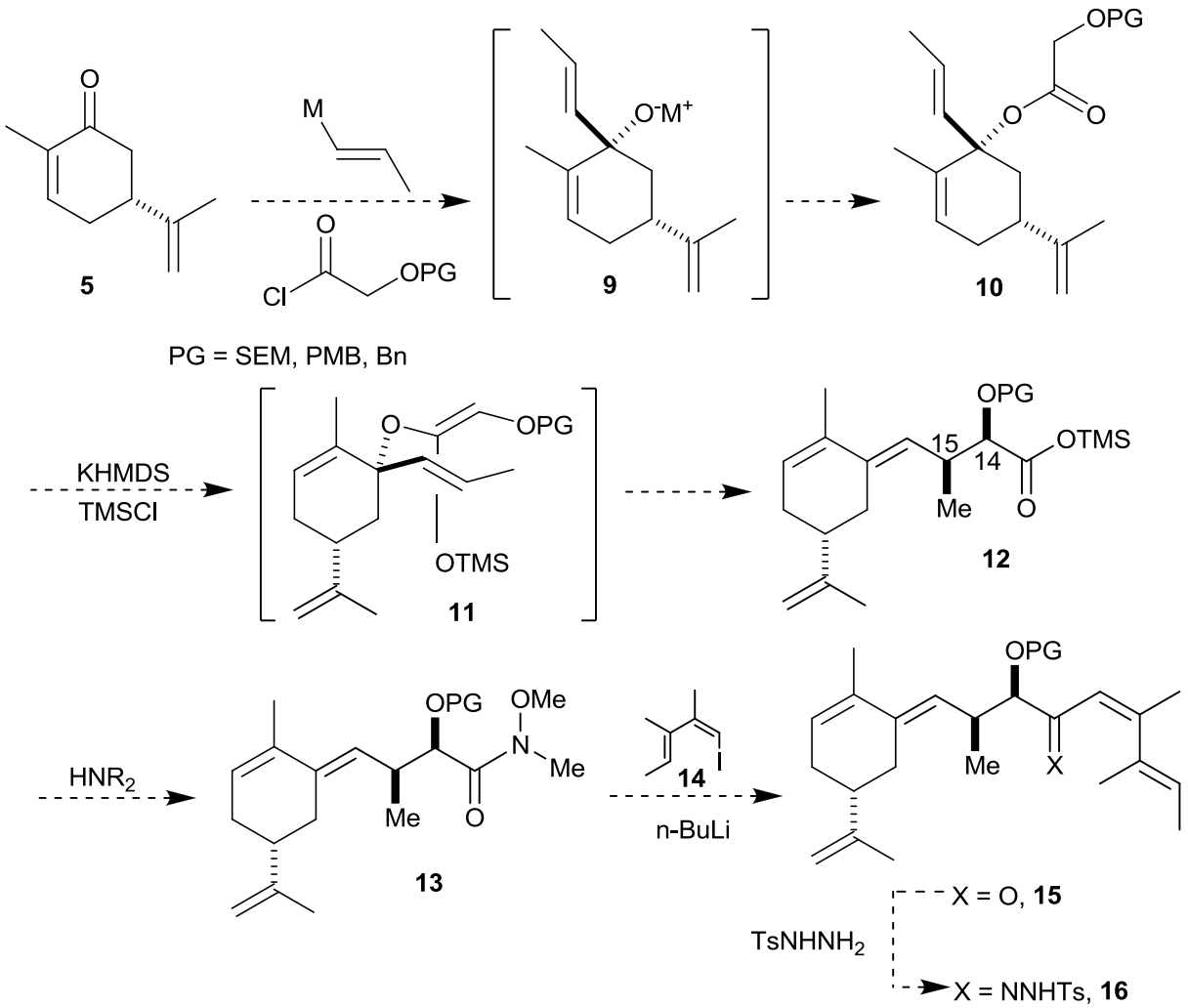
B. Initial Strategy to Prepare the C1-C21 Unit

Our initial approach to prepare the C1-C21 fragment **4** of antascomicin B began with the construction of the C10-C16 carbon framework, which possesses both 1,2-*syn* (C14-C16) and 1,4-*anti* (C11-C14) stereorelationships. Since extensive studies from our group have demonstrated that the Ireland-Claisen rearrangement of carvone-derived *bis*-allylic esters such as **6** occurs with good to high diastereoselectivity,[29,30] we planned to use this methodology to install the C14-C15 stereocenters. Additionally, the trisubstituted alkene that is formed at C4 and C5 of the pentenoic acid product **7** can serve as a latent carbonyl group (Scheme 5). Also, both enantiomers of carvone are commercially available and inexpensive.



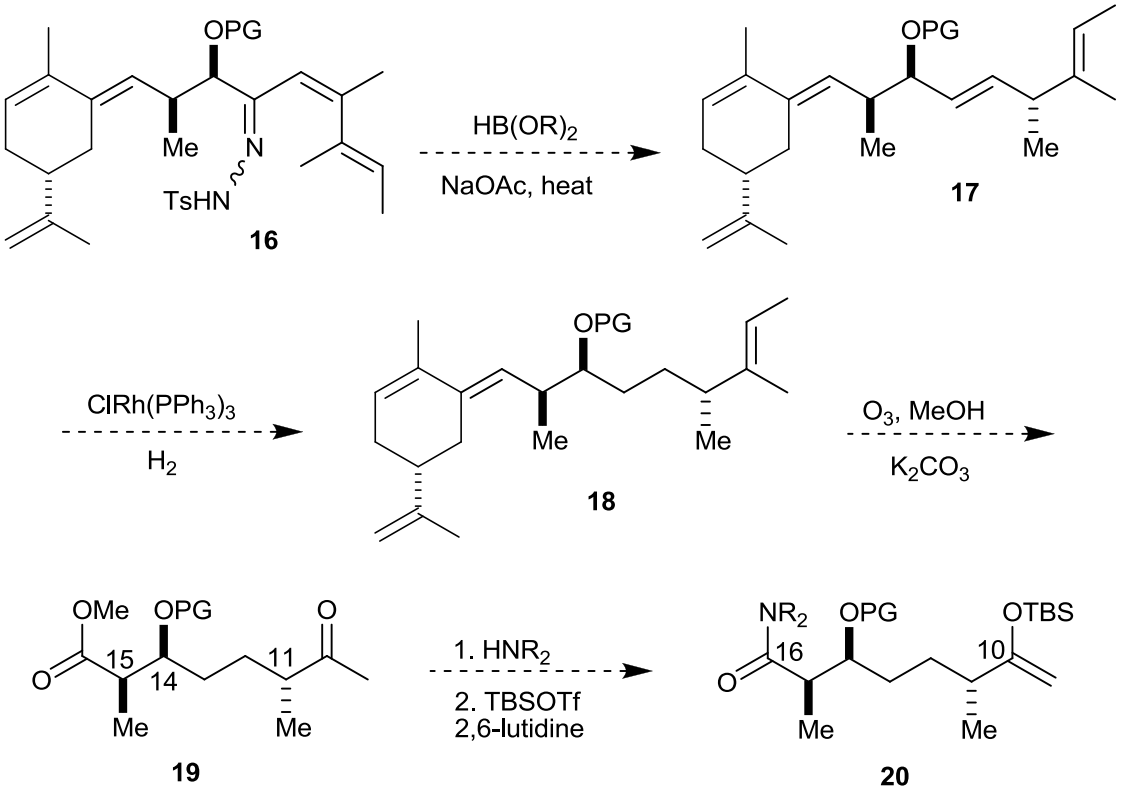
Scheme 5. Ireland-Claisen strategy to install C14-C15 stereocenters

Therefore, we would expect to obtain *bis*-allylic ester **10** through axially selective addition of *E*-propenyl Li to (*R*)-(-)-carvone (**5**) followed by acylation (Scheme 6). Then, *Z*-selective enolization of the ester, followed by silylation would provide silyl ketene acetal **11.** Rearrangement *via* the expected chair-like transition state would form the ketene acetal product **12** with the desired stereocenters, which would be converted in situ to Weinreb amide **13**. Addition of the vinyl Li species derived from iodide **14** will generate dienone **15**. Formation to tosylhydrazone **16** would follow standard protocols.



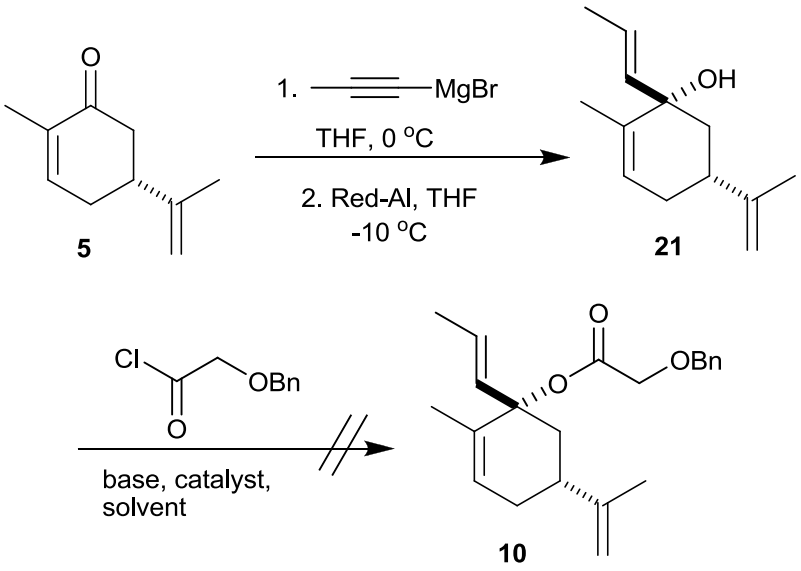
Scheme 6. Initial strategy to install C14-C15 stereocenters

The plan to generate the 1,4-*anti* (C11-C14) relative configuration was by diastereoselective reduction of the tosylhydrazone **16** and subsequent allylic diazene rearrangement (ADR) strain controlled to yield the E-*anti*-alkene **17** (Scheme 7). Our group lab has found that the isopropylidene alkene can be selective reduced by using Wilkinson's catalyst. Thus, it seems highly probable that the hydrogenation of the disubstituted *E*-alkenes would occur similarly to give tetraene **18**. Methyl ester **19** would be obtained by exhaustive ozonolysis of the triene and oxidative fragmentation of the intermediate ozonide under basic conditions. Weinreb amidation followed by regioselective enolization of the methyl ketone would afford the desire enol silane **20**.



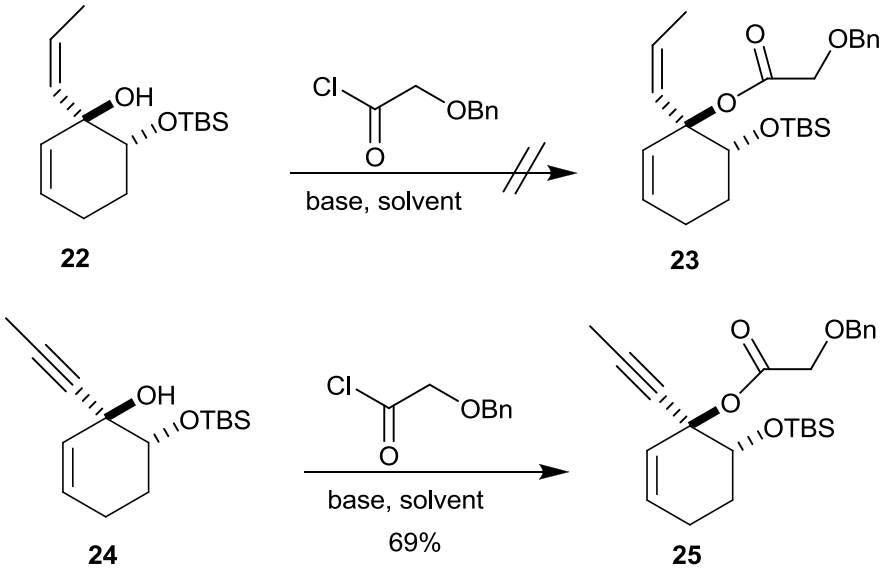
Scheme 7. Initial strategy to build the C10-C16 fragment

Several attempts to synthesize *bis*-allylic ester **10** by addition of propenyl MgBr or propenyl Li to (*R*)-(-)-carvone (**5**), followed by *in situ* acylation of the intermediate alkoxide **9** were unsuccessful. We always recovered some of the starting carvone and traces of the corresponding allylic alcohol. We also tried to acylate the previously prepared and isolated allylic alcohol **21** (Scheme 8). However, no acylation product was obtained using typical acylation conditions, and the *bis*-allylic alcohol was fully recovered. All the details and reaction conditions of the above mentioned reactions are published in a Master thesis.[31]



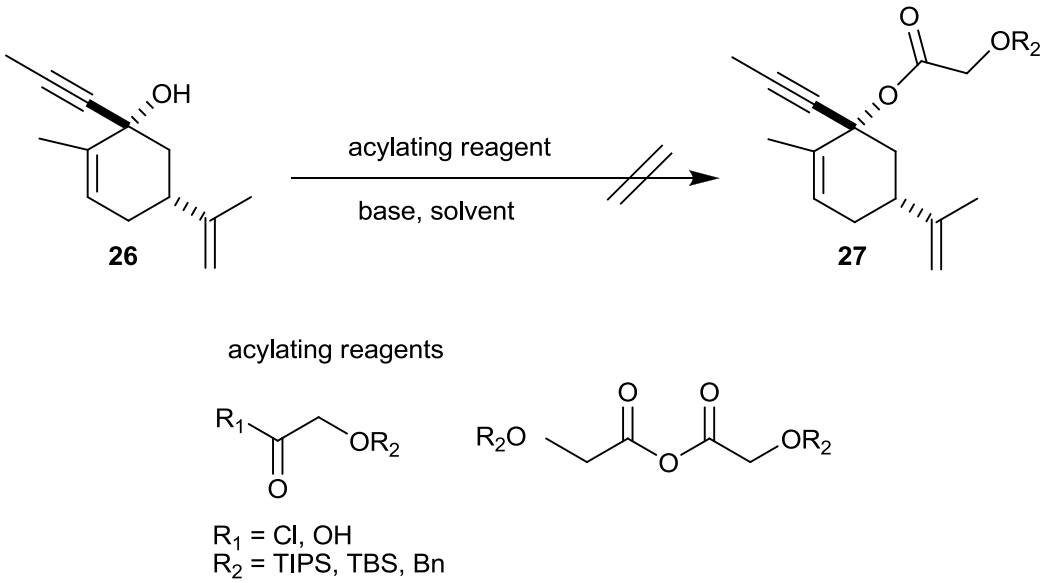
Scheme 8. Efforts to acylate allylic alcohol **21**

We considered both the steric hindrance of the tertiary allylic alcohol and the easy deprotonation of the corresponding glycolate esters by the intermediate alkoxides were likely causing the difficulty in the acylation. Also, previous studies in our lab demonstrated that acylation of allylic alcohol **22** did not occur. However, the acylation reaction of propargylic alcohol **24** proceeded in a good yield (Scheme 9).[32]



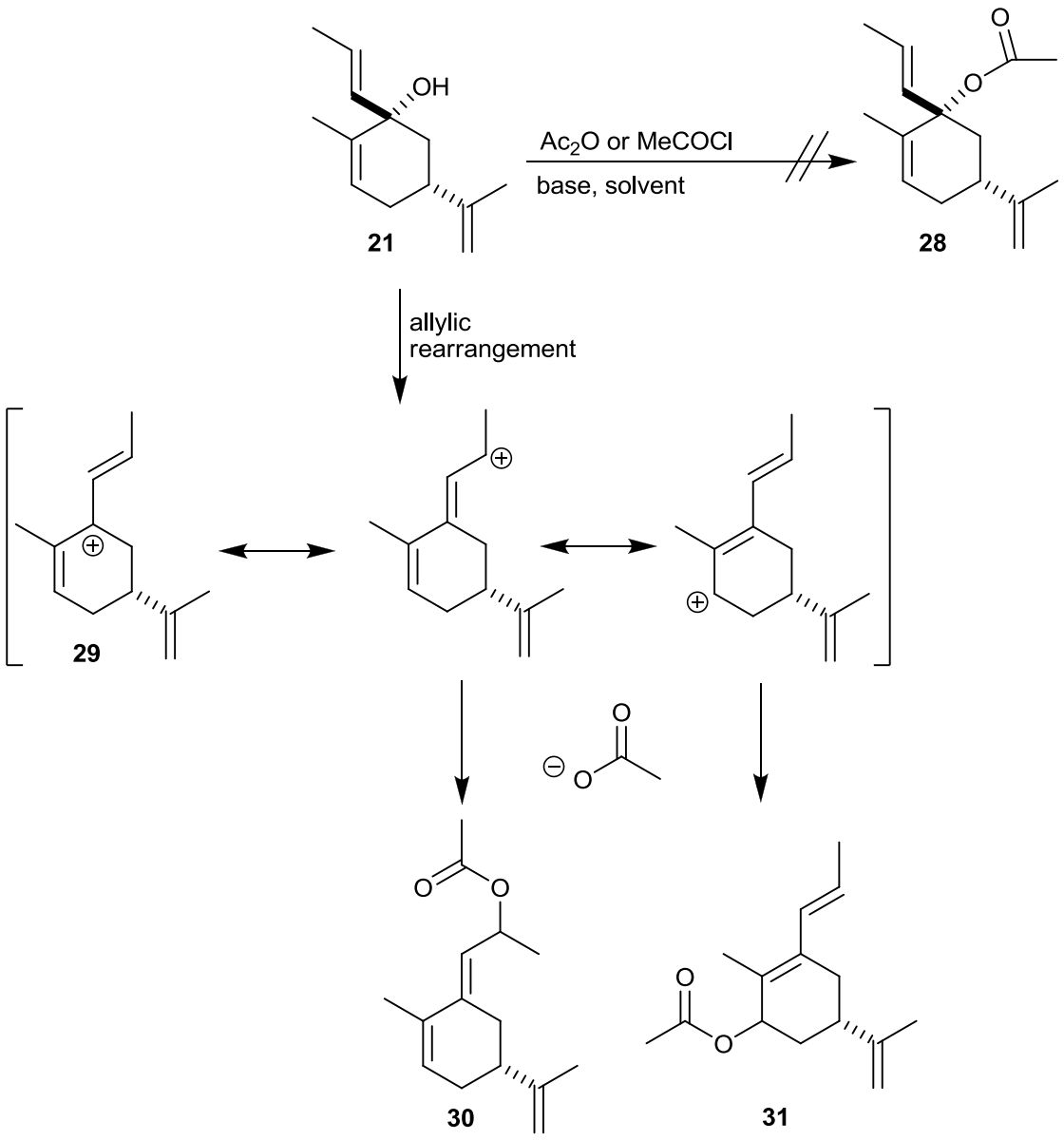
Scheme 9. Acylation studies reported by McIntosh group

Thus, we tried to acylate the less hindered propargylic alcohol **26**, but unfortunately, after examining a variety of conditions, no acylated product was formed (Scheme 10). Instead, most of the starting alcohol was recovered. Based on those results, we thought that steric interactions between the bulky protecting group of the acylating reagent and the hindered tertiary alkoxide did not allow for the acylation. Therefore, we attempted to make the acetate ester of allylic alcohol **21** (Scheme 11), but a complex mixture was obtained.



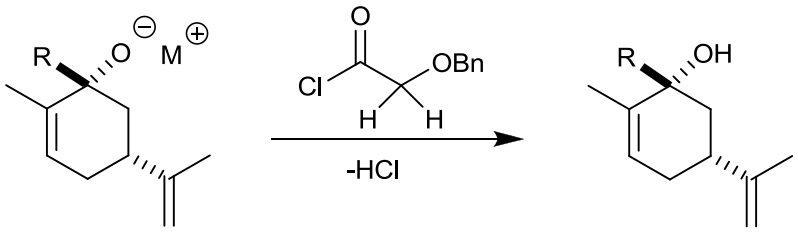
Scheme 10. Efforts to prepare propargylic ester **27**

Analyzing the ^{1}H-NMR data of the complex mixture, we hypothesized that one possible side reaction for the acetylation of the alcohol **21** is the formation of the pentadienyl cation **29**, which could lead to a number of allylic rearrangement and decomposition products including esters **30** and **31** (Scheme 11). This type of allylic rearrangements has been previously observed by both the McIntosh[29] and other groups.[33,34]



Scheme 11. Possible acetylation side products of alcohol **21**

As we mentioned above, another reasonable explanation why we were not be able to acylate either the allylic or the propargylic alcohol is because the corresponding hindered tertiary alkoxides are basic enough to deprotonate the acylating reagent, forming a ketene by elimination of the chloride apparently although no direct evidence for this was observed (Scheme 12).



9, R = propenyl
32, R = propynyl

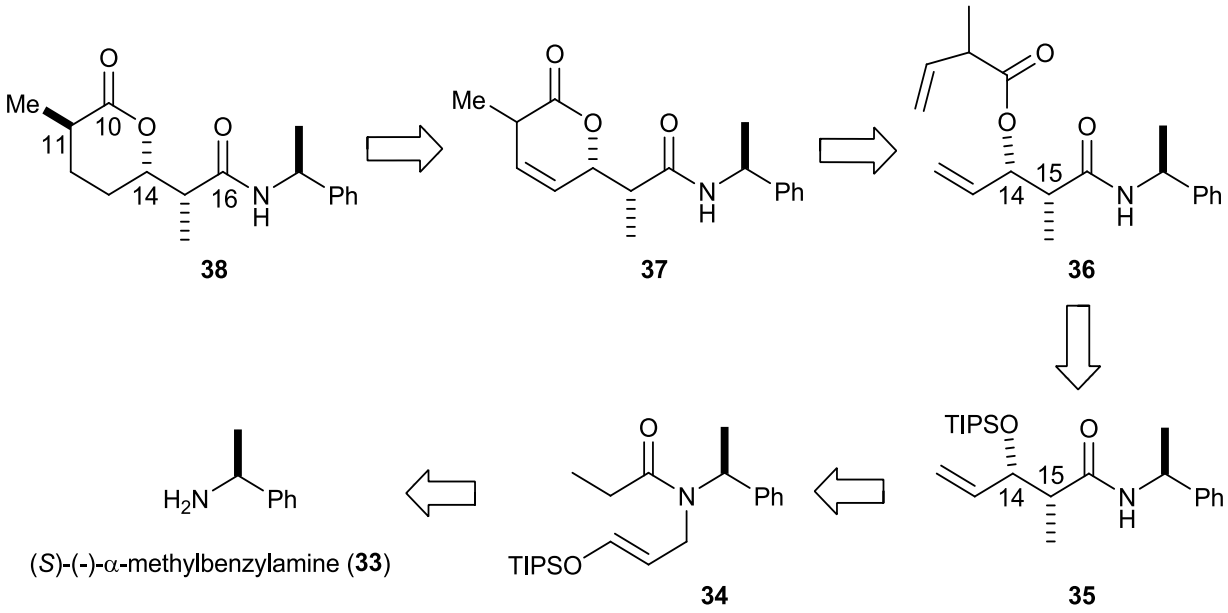
21, R = propenyl
26, R = propynyl

Scheme 12. Possible deprotonation of acylating reagent

C. 2nd Generation Approach to Construct the C10-C16 Fragment

Since all of the efforts toward the preparation of the desired *bis*-allylic ester derived from (*R*)-carvone (**5**) were unsatisfactory, we revised our synthetic route to construct the C10-C16 fragment (Scheme 13).

We reasoned that propionamide **38** could be synthesized by isomerization of the double bond of β,γ-unsaturated lactone **37** followed by amide-directed hydrogenation. Using Grubb's catalyst, target molecule **37** could be formed by RCM of allyl ester **36**, which could be obtained from amide **35**. Amide **35** is a product of the asymmetric amino-Claisen rearrangement of silyloxy amide **34**, which could be formed from (*S*)-*α*-methylbenzylamine (**33**).

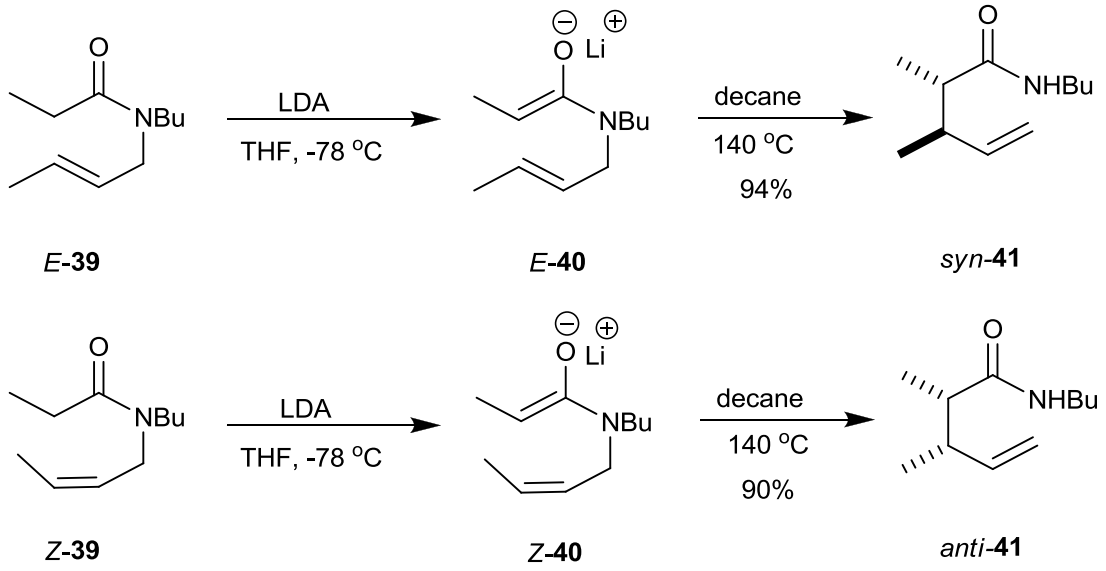


Scheme 13. Retrosynthetic strategy of the C10-C16 unit of antascomicin B

D. Installation of the 1,2-*syn* (C14-C15) Stereorelationship *via* Amino-Claisen Rearrangement

1. Amino-Claisen Rearrangement of Amide Enolates

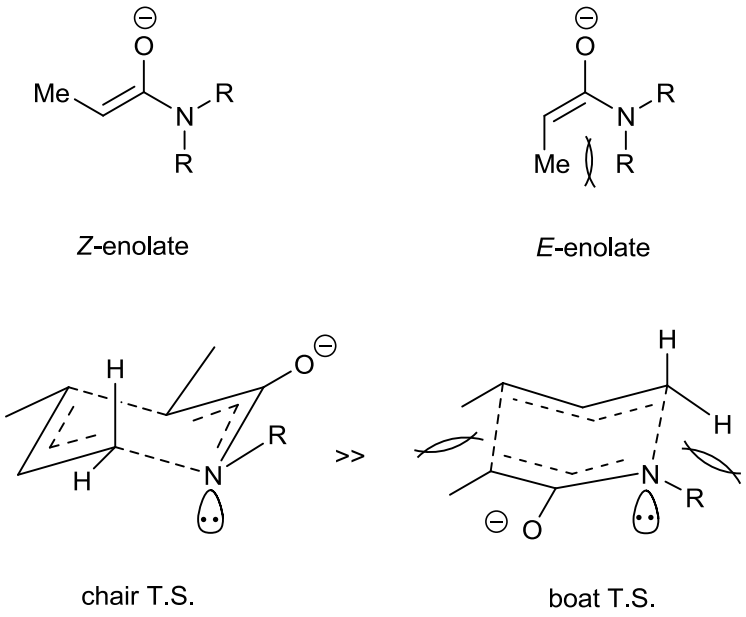
Studies of the amino-Claisen rearrangement of amide enolates by Tsunoda's group[35] have demonstrated that deprotonation of the *E*- and *Z*-N-2-butenyl-N-butylpropanamides **39** with LDA at -78 °C in THF generated the corresponding *Z*-enolates **40** (Scheme 14). The rearrangement was induced after removal of THF and heating the enolates at 140 °C in decane to generate *syn*- and *anti*-N-butyl-2,3-dimethyl-4-pentenamides **41**, respectively.



E-**39** into **41**: ratio *syn*-**41**:*anti*-**41**: 99.4:0.6
Z-**39** into **41**: ratio *syn*-**41**:*anti*-**41**: 37:63

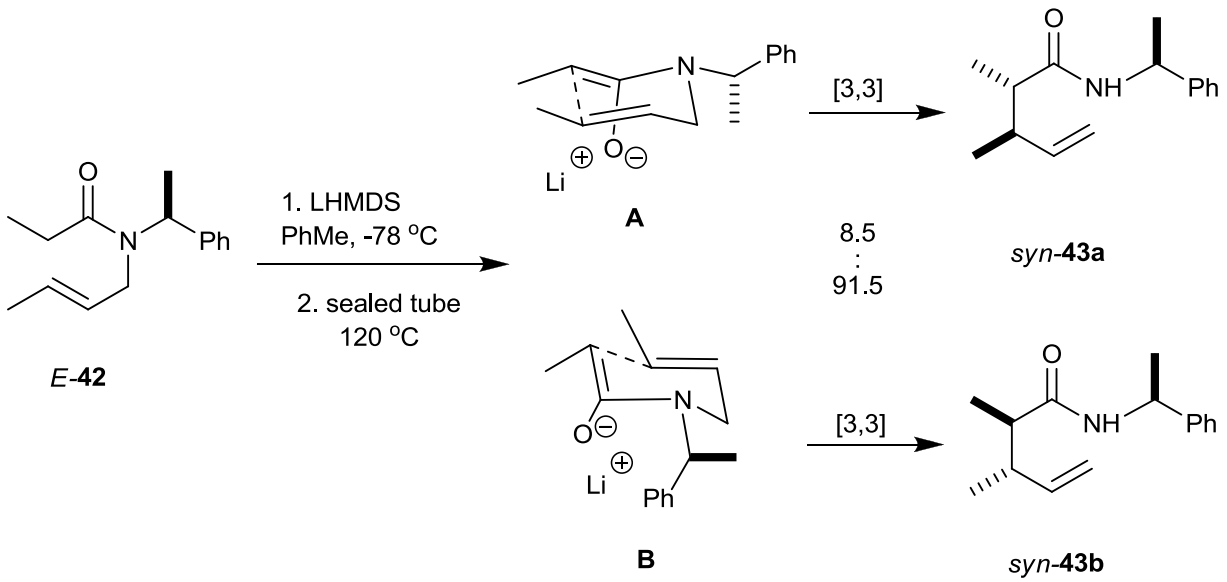
Scheme 14. Amino-Claisen rearrangement of amide enolates

The excellent diastereoselectivity achieved from allylic amide *E*-**39** is due to both the exclusive formation of the *Z*-enolate due to allylic strain[36] and the chair conformation of the transition state of the amino-Claisen rearrangement (Scheme 15). The preferred chair-like transition state may be attributed to eclipsing interactions present in any boat-like transition state.



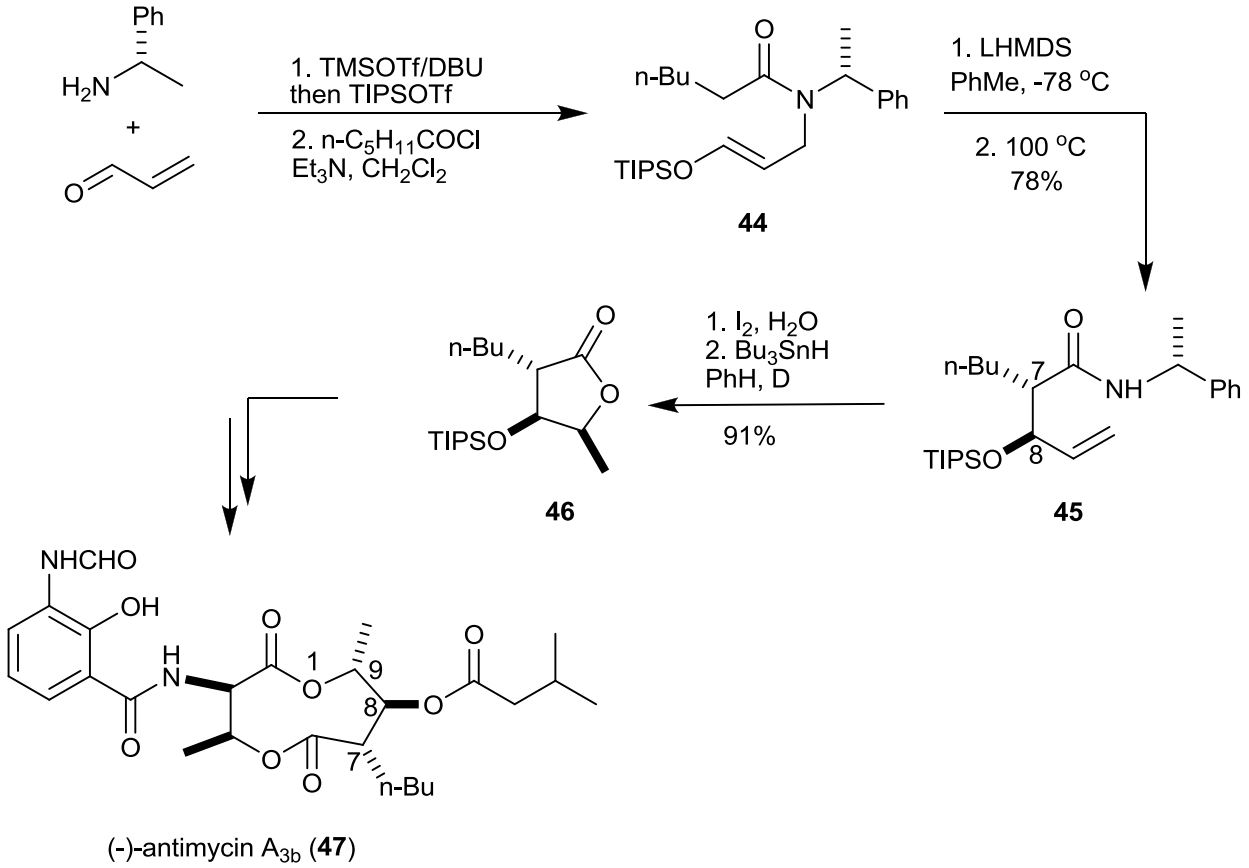
Scheme 15. Transition states of the amino-Claisen rearrangement of amide enolates

Based on the high internal asymmetric induction achieved for the reaction of the enolate derived from *E*-N-2-butenyl-N-butylpropamide *E*-**39**, and taking advantage of the trivalent nitrogen atom, Tsunoda extended the reaction to amide enolates containing chiral N-alkyl groups.[37] They found that the α-methyl benzyl amine moiety directed rearrangement of carboxamide *E*-enolate **42** to the corresponding *syn*-amides **43** in 85% yield (Scheme 16). The *anti*-amide isomers were not detected, showing that the reaction likely proceeded *via* a chair-like transition state. To date, the rationale for the relative diastereoselectivity preference for *syn*-amide **43b** over the *syn*-amide **43a** (91.5:8.5) is still unclear. Tsunoda also investigated the effect of other chiral auxiliaries attached to the carboxamide **42**.[38] In most of cases, *S*- configured auxiliaries generated the *syn*-amides in 66-90% yield and 70-84% de.



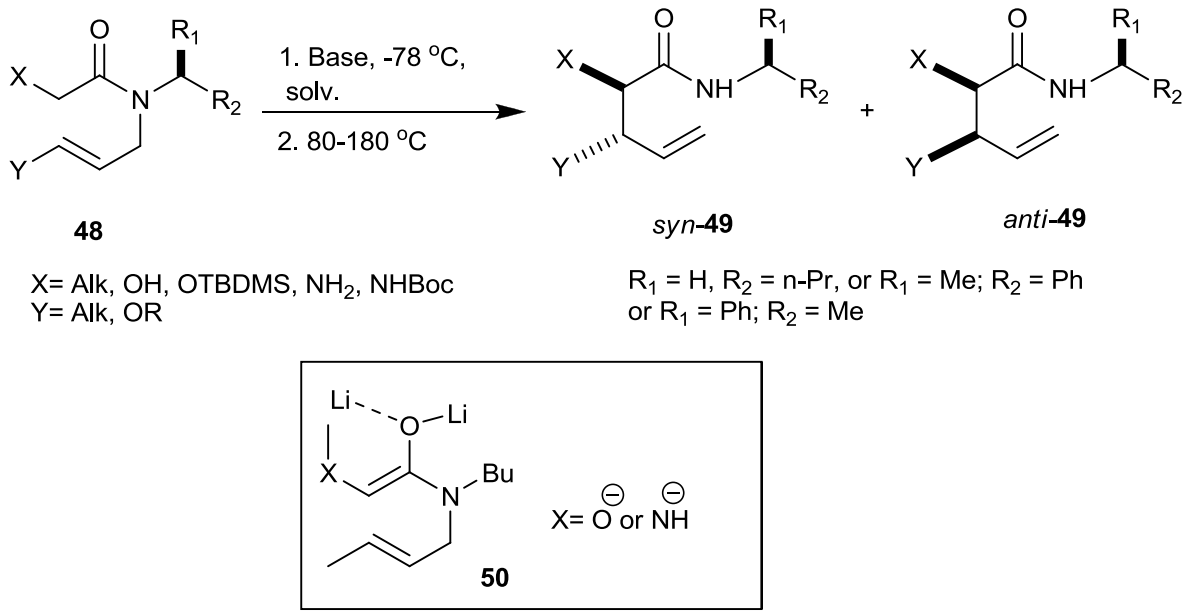
Scheme 16. Asymmetric induction of the carboxamide *E*-**42**

Tsunoda's group has applied the asymmetric amino-Claisen rearrangement of different types of carboxyamides for the synthesis of several natural products. Including antibiotic (-)-antimycin A_{3b}.[39] Amide **44** was made from from (*R*)-(+)-phenethylamine and acrolein *via* a condensation-acylation sequence (Scheme 17). Using standard conditions,[36] the rearrangement of amide **44** produced a mixture of four diastereomers, from which the major *syn* (7S,8R; 7R,8S)-isomers **45** were isolated by SiO_2 column chromatography as an inseparable 82:18 mixture. Iodolactonization and subsequent reductive removal of the iodide afforded lactone **46**, which constitutes the C5-C8 fragment of the natural product **47**.



Scheme 17. Synthesis of antibiotic (-)-antimycin A_{3b} (**47**)

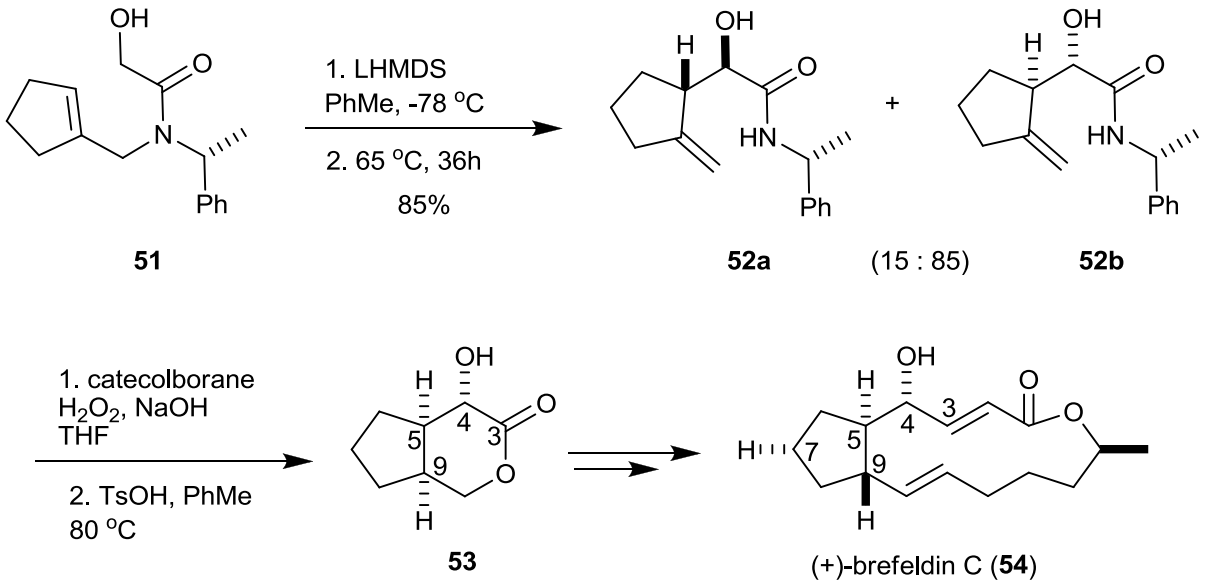
It has also been shown that this rearrangement reaction is highly facilitated by the presence of a hydroxy or an amino group at the α-position of the acyl group.[40] The [3,3]-sigmatropic rearrangement amide products **49** were formed through the rearrangement of the corresponding enolates generated by the treatment of carboxamides **48** with LDA or LHMDS in THF or toluene (Scheme 18).



Scheme 18. Amino-Claisen rearrangement of carboxamides **48**

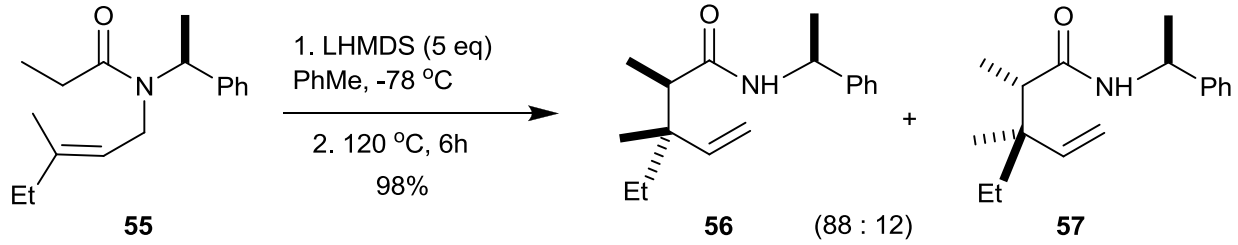
Excellent *syn* selectivity (98:2) was observed for nearly all cases. Placing the OH and NH_2 group at the α-position of acyl group facilitates the rearrangement. This was attributed to the possible lithium chelate formation species between the enolate oxygen and α-heteroatom, such as **50** (inset). When the OH or NH_2 group is blocked by other functionality decelerates the reaction, in fact, the NBoc protection did not give any rearrangement product. Also, trapping of enolates as TMS N,O-ketene acetals and subsequent thermal rearrangement resulted in lower yield and selectivity as in α-alkyl derivatives, contrary to the reaction of ester enolates where their silyl enolate trapping is usually necessary for good results.

This asymmetric amino-Claisen rearrangement has been successfully employed in the construction of the C4-C5 sterogenic centers in the total synthesis of the natural product (+)-brefeldin C (**54**).[41] Thus the rearrangement of 2-hydroxyacetamide **51** using 2.5 equivalents of LHMDS at -78 °C and then heating at 65 °C for 36 hours afforded a separable mixture of the amides **52a** and **52b** in 15:85 ratio, giving the desired amide **52b** as a major product. Hydroboration-oxidation of the isolated amide **52b** followed by acid catalyzed yielded the lactone **53**, which constituted C3-C10 fragment of the natural product **54** (Scheme 19).



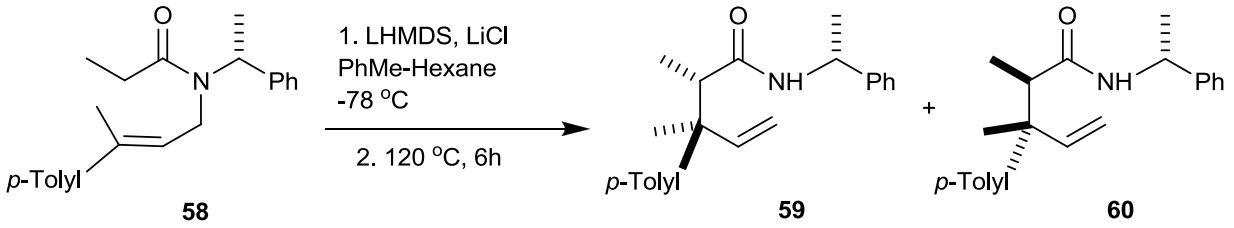
Scheme 19. Synthesis of (+)-brefeldin C using Amino-Claisen rearrangement

Another interesting application of the amino-Claisen rearrangement of amide-enolates was the asymmetric construction of the quaternary carbon center in the total synthesis of (+)-α-cuparenone.[42] Previous studies demonstrated that the enolate of N-(*E*)-crotyl-N-(*S*)-phenylethylpropanamide **55** needed excess LHMDS in order to undergo the rearrangement in high yield and stereoselectivity (Scheme 20).[43] By contrast, a complex mixture of products was obtained using 1.5 equivalents of LHMDS.



Scheme 20. Generating quaternary carbon *via* amino-Claisen rearrangement

Based on these results, the amino-Claisen rearrangement of *p*-tolylpropanamide **58** containing an (*R*)-phenylethyl moiety on the amide nitrogen was employed as a key step in the installation of one of the quaternary centers presents in (+)-α-cuparenone. Initially, a complex product mixture was obtained when the *p*-tolylpropanamide **58** was treated with 3 equivalents of the LHMDS. However, the addition of 20 equivalents of LHMDS afforded the desired rearrangement products with 83% yields and 88:12 stereoselectivity (Scheme 21, Table 1, entry 5).



58 **59** **60**

Scheme 21. Amino-Claisen rearrangement studies of crotylamide **58**

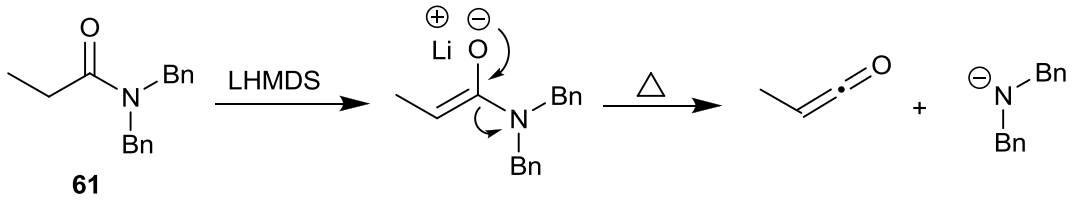
Table 1. Results of amino-Claisen rearrangement studies of crotylamide **58**

Entry	LHMDS (eq)	LiCl (eq)	Yield (%)	Ratio (2*S*/2*R*)
1	3	-[a]	-[b]	-[c]
2	5	-[a]	57	77/23
3	10	-[a]	68	87/13
4	15	-[a]	74	88/12
5	20	-[a]	83	88/12
6	10	5	77	90/10
7	10	10	83	88/12

[a] None, [b] complex mixture, [c] Not determined

The reason why the addition of excess base favored the rearrangement of this crotylpropanamides is unclear. Tsunoda's group suspected that one of the undesired reactions could be due to the decomposition of the enolates of the carboxamides *via* ketene formation. Thus, they made N,N-dibenzylpropanamide **61** as a model compound to study the decomposition pathways. Initially, they recovered 83% of **61** when it was treated with 1.5 equivalents of LHMDS at 80 °C for one hour, but when the reaction was conducted at 120 °C for the same time, only 46% of **61** was observed. On the other

hand, 86% of the propanamide **61** was recovered when the reaction was performed at 120 ^{o}C for an hour using five equivalents of LHMDS. These results indicated that the decomposition occurred at 120 ^{o}C, the same temperature at which the rearrangement took place. Excess LHMDS apparently stabilized the amide enolates and consequently prevented their decomposition to ketene and other undesired side reactions (Scheme 22).

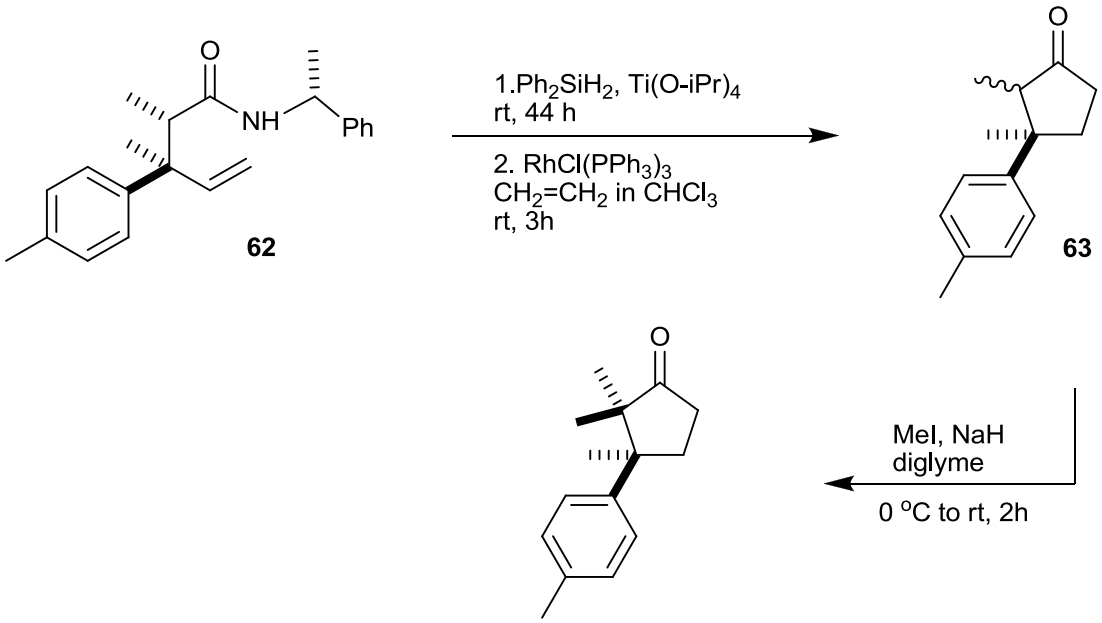


61

Scheme 22. Decomposition of the lithium enolate amide **61**

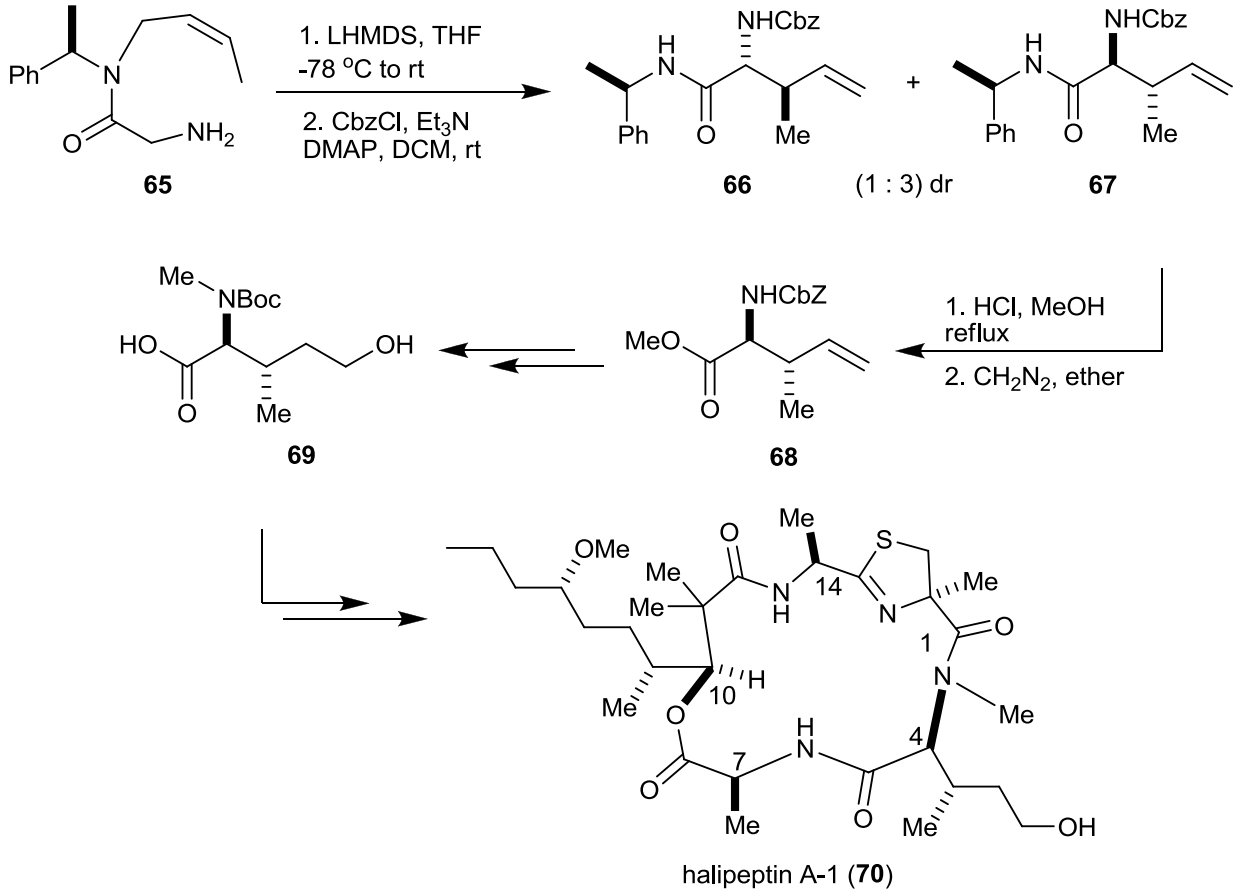
Studies of ketone alkylation reactions reported by Streitwieser et al.[44,45] suggested that the aggregate formed by the close proximity of two or more lithium cations to the enolate oxygen make the α-carbon of the lithium enolate electron deficient, thus making the enolate a poorer nucleophile. Therefore, Tsunoda's group suggested that the presence of large amounts of LHMDS delayed the decomposition of the amide enolate aggregates, thus favoring the amino-Claisen rearrangement. They also found that addition of lithium salts instead of LHMDS reduced the amount of base required for the rearrangement. After trying several different types of lithium salts, the best result was attained using 10 equivalents of LiCl with 10 equivalents of LHMDS (Table 1, entry 7).

Reduction of amide **62** with diphenylsilane-Ti(O-$_i$Pr)$_4$ followed by cyclization in presence of Wilkinson's catalyst afforded the cyclopentanone ring intermediate **63**. Alkylation of **63** with methyl iodide and NaH gave the cyclopentanoid natural product **64** (Scheme 23).



Scheme 23. Total synthesis of the (+)-α-cuparenone (**64**)

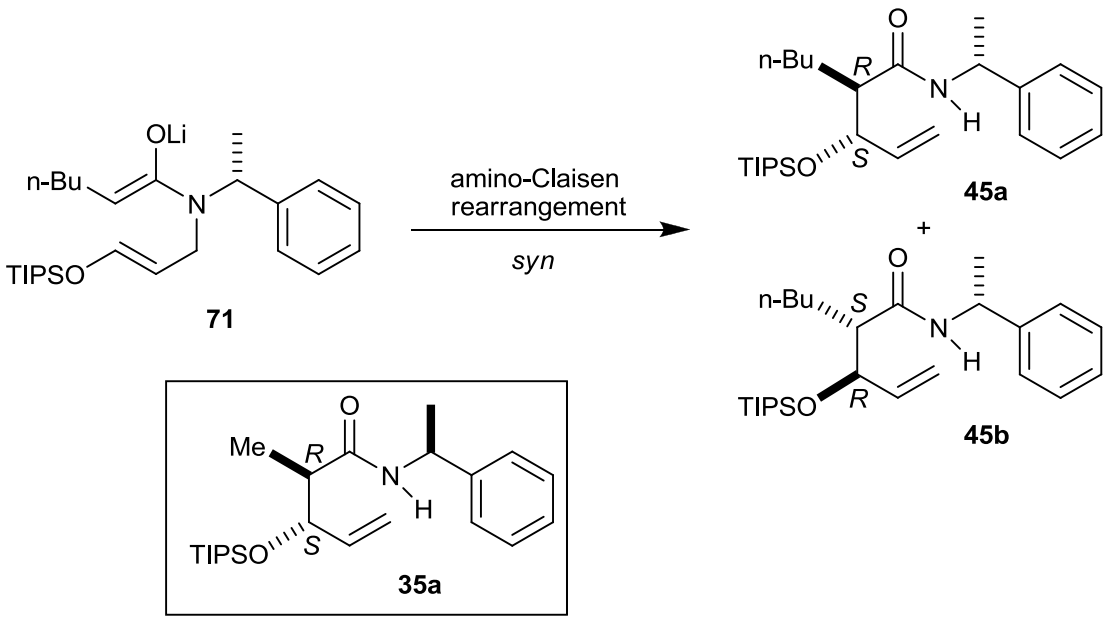
Another example of the amino-Claisen rearrangement of amide enolates was the preparation of the N-methyl-δ-hydroxyisoleucine amino acid **69** as a key intermediate in the total synthesis of marine cyclic depsipeptide halipeptin A-1(**70**).[46] A separable mixture of diastereomers was obtained after exposing (*Z*)-2-butenylpropanamide **65** to 2.4 equivalents of LHMDS. Moderate diastereoselectivity was observed (**66**/**67**=3:1), but 52% of the major isomer **67** was isolated by recrystallization. Cleaving the chiral auxiliary of **67** under acidic conditions and subsequently esterification with CH_2N_2 gave the methyl ester **68** (Scheme 24).



Scheme 24. Preparation of N-methyl amino acid **69** used in the total synthesis of **70**

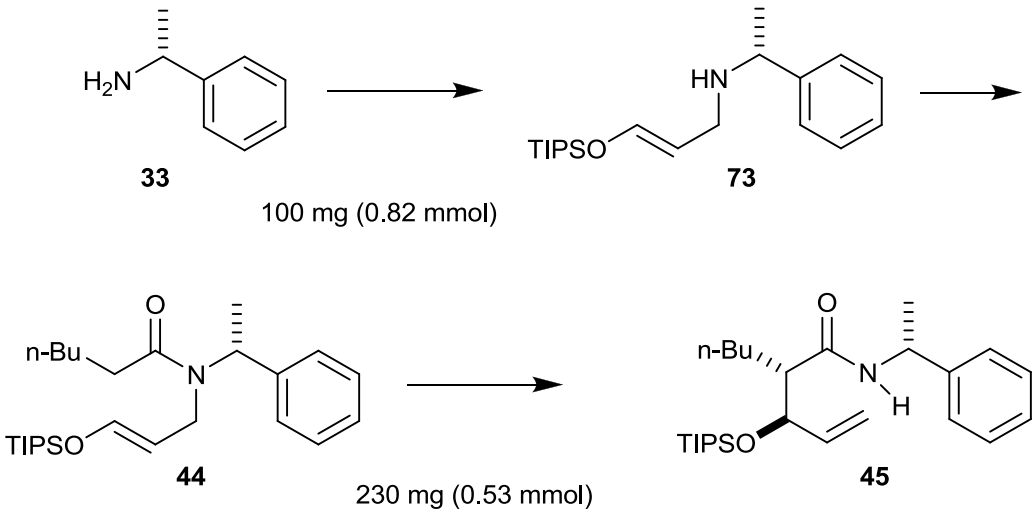
2. Asymmetric Amino-Claisen Rearrangement of Silyloxyallyl-propanamide 34

As we mentioned before, Tsunoda's group reported the [3,3] sigmatropic rearrangement of amide enolate **71** to generate 2,3-*syn* pent-4-enamides **45** (Scheme 25) to construct the (7S,8R)-stereogenic centers as a key step in the total synthesis of antimycin A_{3b}.



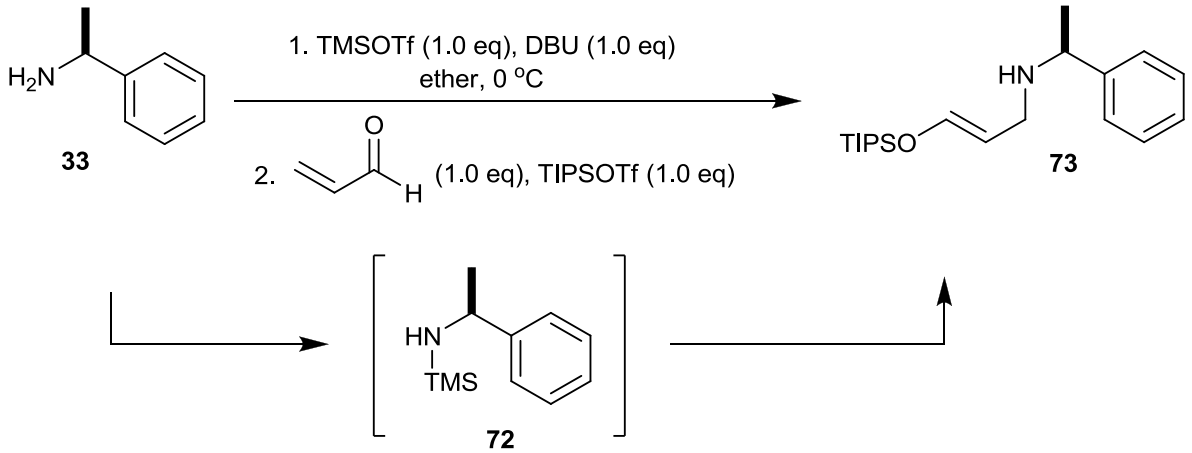
Scheme 25. Tsunoda's amino-Claisen rearrangement of enolates **71**

Due to the close structural similarity between Tsunoda's pentenamides **45** and our pentenamides **35** (Scheme 25, inset), we considered that this asymmetric strategy could be efficiently applied to prepare amide **35** with the (14S,15R)-configuration present in the antascomicin B (**1**) (cf. Scheme 13). Additionally, we sought explore the scalability of the amino-Claisen rearrangement. The longest scale that had been reported for the preparation of silyloxypropene amine **73** was 100 mg (0.82 mmol) and 230 mg (0.53 mmol) for the rearrangement of amide **44** (Scheme 26).



Scheme 26. The largest scale reactions reported by Tsunoda's group

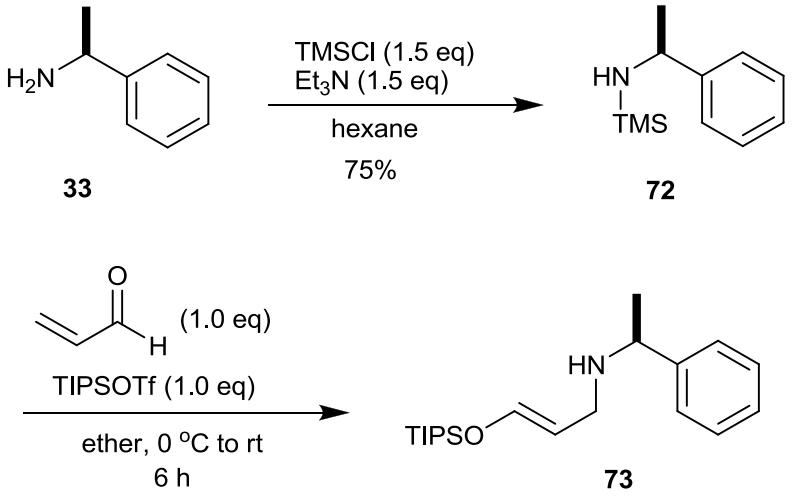
Our approach to install the desired stereocenters started with the preparation of the precursor to the amino-Claisen rearrangement, silyloxyallylpropanamide **34**. Following Tsunoda's protocol, the first step in the synthesis was the silylation of (*S*)-methylbenzylamine (**33**) with trimethylsilyltriflate (TMSOTf)/DBU at 0 °C in ether (Scheme 27).[38] Then, in situ addition of triisopropylsilyltriflate (TIPSOTf) and acrolein afforded the crude product **73**, which was isolated by silica gel flash chromatography. The *E*-configuration of the double bond in the amine product was verified by ^{1}H-NMR spectroscopy ($^{3}J_{\text{-trans}}$ = 14.9 Hz).



Scheme 27. In situ preparation of the silyloxypropene amine **73**

Table 2. Limitation in the preparation of silyloxypropene amine **73**		
Entry	Amine **33**, g (mmol)	Amine **73** % Yield
1	1.0 (8.25)	42 – 58
2	1.5 (12.3)	32 – 44
3	2.5 (20.6)	28 -36
4	3.5 (28.8)	15 – 32
5	4.0 (33.0)	5 – 10
6	5.0 (41.2)	5 – 8

Increasing the amount of amine **33** beyond 8.25 mmol resulted in a steady decrease in the yield (Table 2). Also, a complex mixture and formation of TIPSOH were observed each time the reaction was performed. Initially, we suspected that the lowered yield was due to an inefficient in situ silylation of amine **33**. Therefore, we purified silylamine **72** by vacuum distillation (Scheme 28).[47] Interestingly, using purified silylamine **72** gave lower yield than the in situ reaction (Table 3).

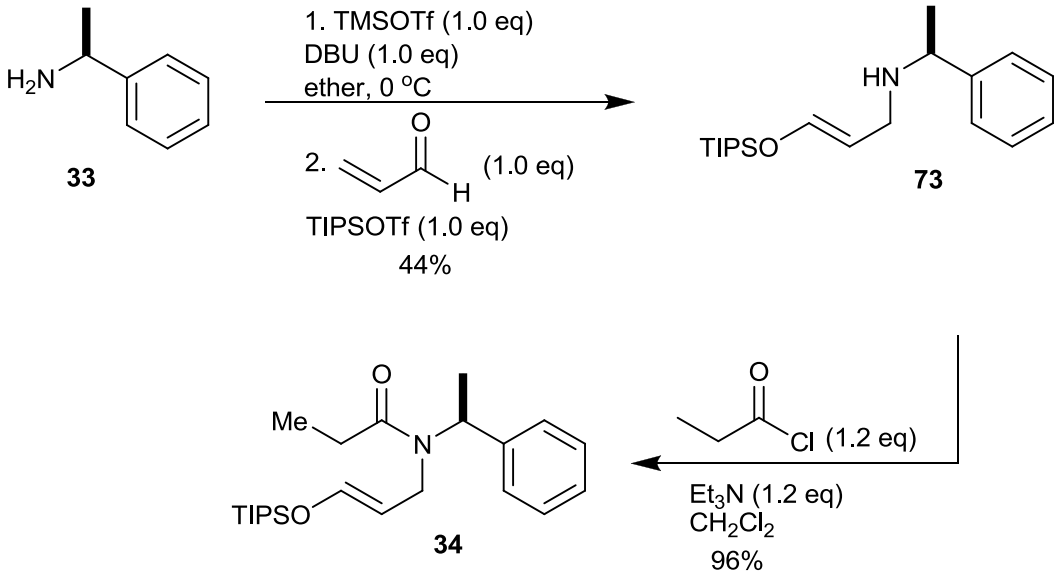


Scheme 28. Making silyloxy propene amine **73** from silylamine **72**

Table 3. Results of making amine **73** from silylamine **72**		
Entry	TMS-amine **72**, g (mmol)	Amine **73** % Yield
1	1.0 (5.2)	20 – 28
2	3.0 (15.1)	19
3	6.5 (33.6)	18

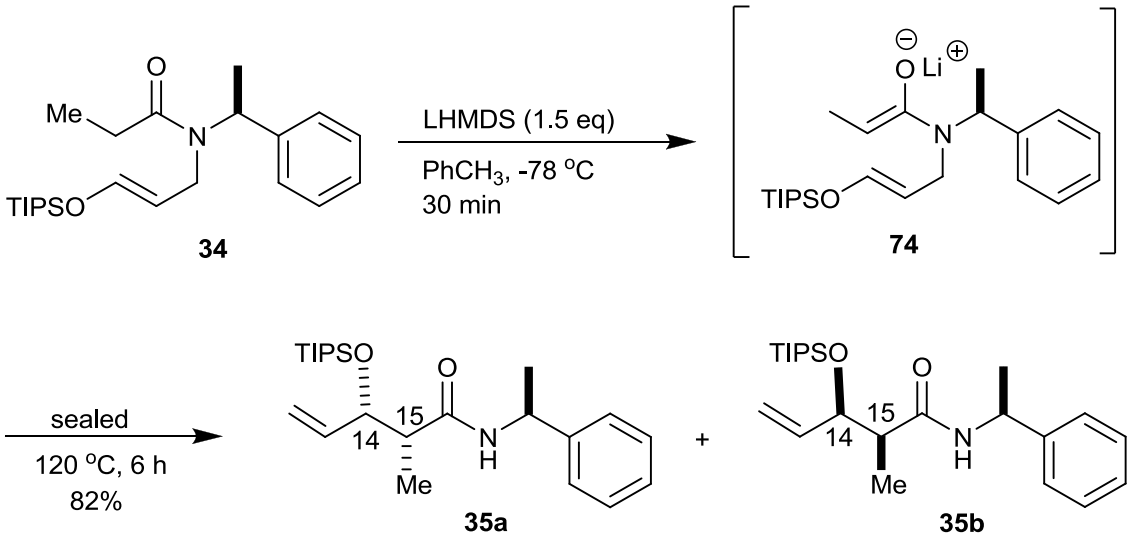
It is unclear why the conjugate addition of the in situ formed silylamine **72** provided much better yields than the pure silylamine **72** (Table 3). However, two different possibilities could explain these results. First, each time the reaction was performed large amounts of TIPSOH were isolated. Thus, the lower yields of the reaction could be caused by the fast quenching of the TIPSOTf to TIPSOH. Second, polymerization of acrolein could be also responsible for the lower efficiency of the conjugate addition reaction.

In order to produce multigram amounts of amide **34**, we performed multiple up to 1.5 g (12.3 mmol) parallel reactions (cf. Scheme 27, table 2, entry 2). After isolating the combined amine **73** by flash chromatography, acylation of **73** with propanoyl chloride in the presence of triethylamine in CH_2Cl_2 at 0 ^{o}C generated 96% of allyl propene amide **34** (Scheme 29). According to analysis of NMR data, amide **34** was sufficiently pure that further purification was not necessary. Similar results were obtained when we scaled the acylation reaction of **73** to 9.5 g (28.4 mmol).



Scheme 29. N-acylation of **73** to yield allyl amide **34**

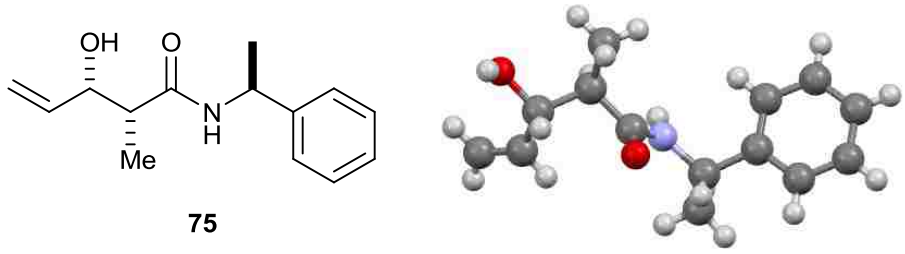
Having the desired precursor **34** in hand, we carried out the deprotonation with lithium hexamethyldisilazide (LHMDS) in toluene at -78 °C (Scheme 30). After 30 min, the reaction mixture was allowed to warm to rt, and sealed in a pressure vessel. Heating of sealed solution at 120 °C for 6 h afforded a mixture of the rearranged *β*-silyloxy amides **35** in 82 % yield.



Scheme 30. Amino-Claisen rearrangement of amide **34**

Two diastereomers were formed in a 4.2:1 ratio according to GC analysis of a crude sample of the reaction mixture. Based on Tsunoda's[34-38] precedent, we presumed that the *syn*-amides **35a** and **35b** were formed. However, in our hands no other isomer was observed.

Using silica gel column chromatography we were able to enrich the major diastereomer **35a** to 96:4 ratio according with GC analysis. Moreover, X-ray crystallographic analysis of the desilylated amide **75** confirmed the *syn* relative configuration of the rearrangement amides (Figure 1).

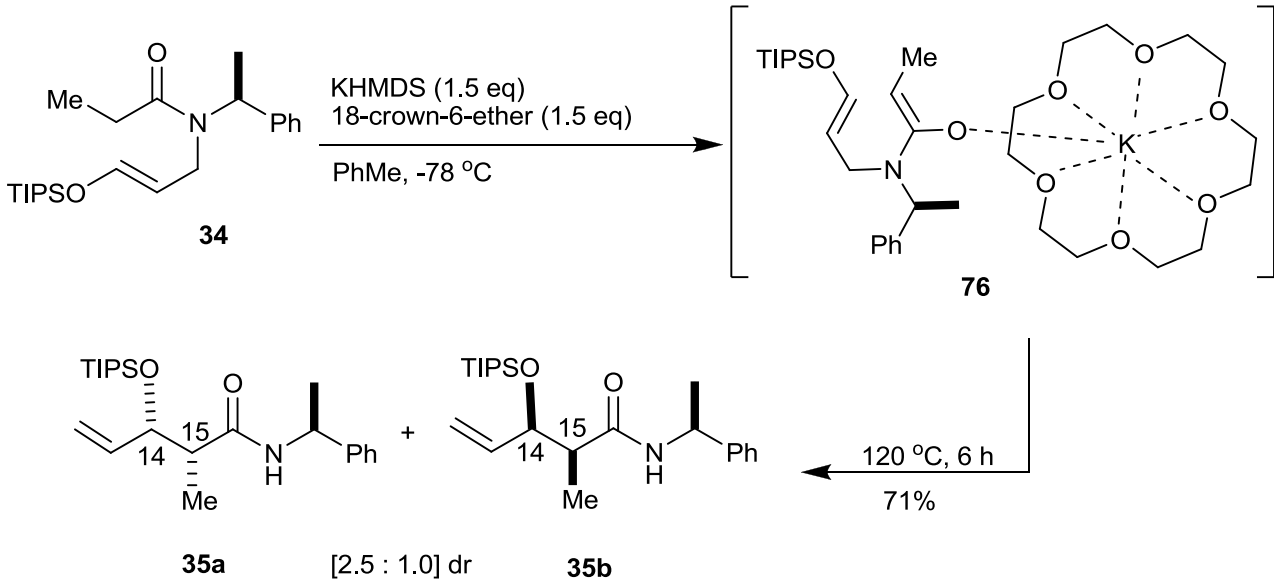


75

Figure 1. X-ray structure of desilylated amide **75**

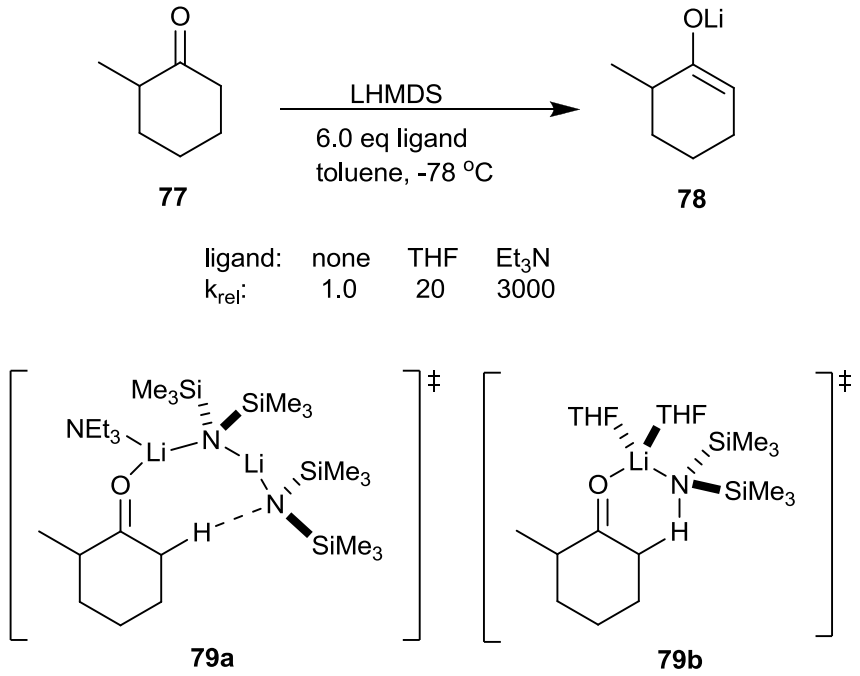
Although the above protocol provided good yield of the desired *β*-1,2-*syn* silyloxyamides **35**, the moderate diastereoselectivity in the amino-Claisen rearrangement step motivated us to try to improve it.

Our first attempt to achieve this goal was to use potassium hexamethyldisilazide (KHMDS) instead of LHMDS, in the presence of 18-crown-6. We reasoned that a more reactive anion ($^{-}$HMDS) could facilitate the formation of the intermediate enolate **76** and consequently generate better diastereoselectivity of amides **35a,b** (Scheme 31). However, GC analysis showed the dr of **35a,b** decreased drastically to 2.5:1.



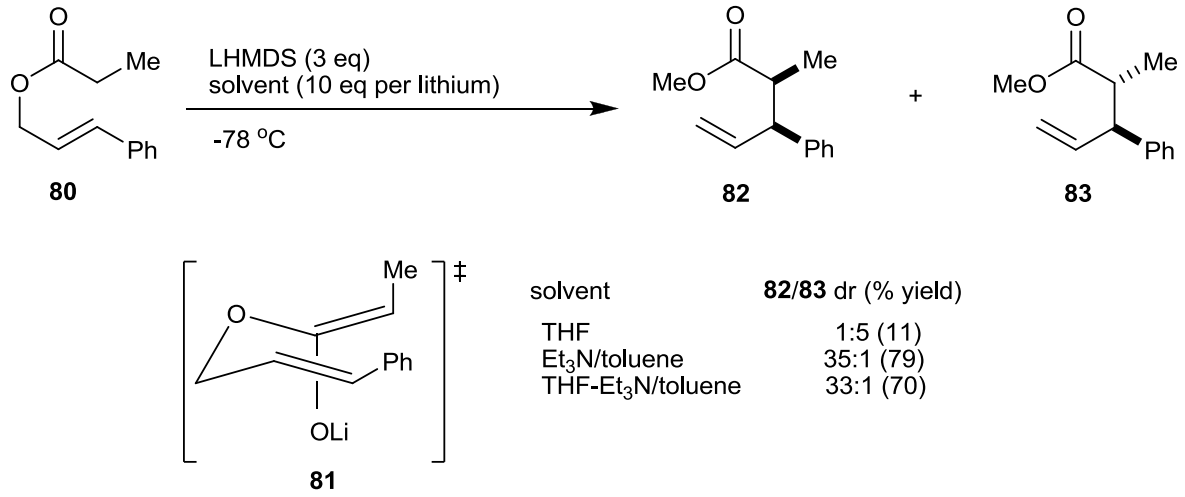
Scheme 31. Attempt to improve diasterioselectivity of rearranged amides **35a,b**

Collum et al. have investigated solvent dependence of LHMDS structure in the enolization of ketones and esters.[48, 49] They found that, in the presence of triethylamine (Et_3N/toluene), the enolization of 2-methylcyclohexanone is > 100 times faster than the same enolization made in neat THF (Scheme 32).[50] Mechanistic studies also revealed that the Et_3N-mediated rate acceleration resulted from severe steric effects affiliated with solvation in the reactant that are relieved in the transition state structure **79a**. By contrast, the LHMDS/THF-mediated enolizations proceed through a conventional monosolvated-dimer based transition structure **79b**.



Scheme 32. Influence of Et_3N on the LHMDS-mediated enolization of **77**

Collum has also reported the selectivities and reactivities of THF and Et_3N-solvated lithium enolates in the Ireland-Claisen rearrangement (Scheme 33).[51] They found that enolization of ester **80** using LHMDS/Et_3N (1/10 ratio) in toluene generated *E*-**81** faster than using LHMDS/THF (1/10 ratio) in Et_3N/toluene. Qualitative rate studies showed that Et_3N-solvated enolates rearranged approximately 20 times faster than with added THF.

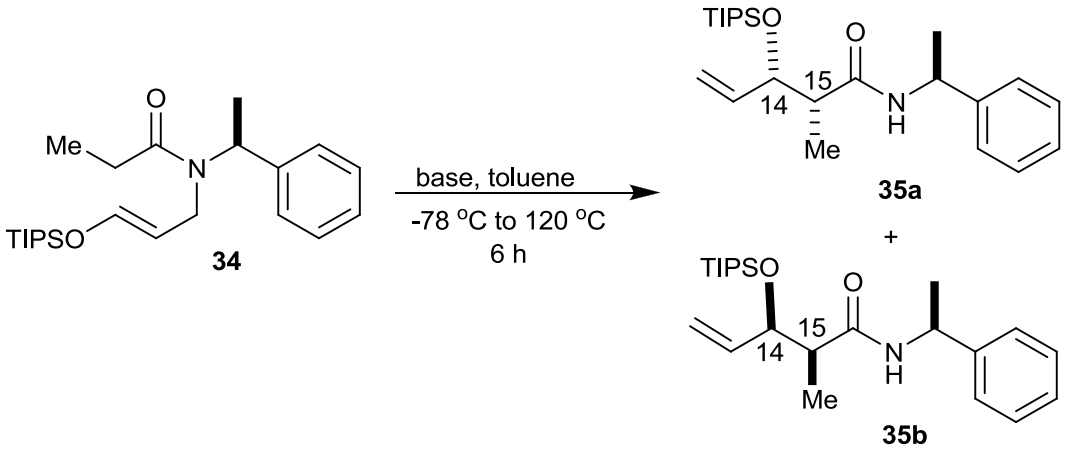


Scheme 33. THF and Et_3N lithium enolate reactivity in the Ireland-Claisen rearrangement

Professor David Collum suggested that the diastereoselectivity of the amino-Claisen rearrangement of amide **34** would possibly be improved by generating the amide enolate **74** in presence of excess of Et_3N (personal communication).

Enolization of amide **34** with 2 eq of LHMDS and 5 eq of Et_3N in toluene at -78 °C showed no improvement of the diastereoselectivity (Table 4, entry 2). However, use of 10 eq of Et_3N afforded a 7.7:1 dr of **35a** and **35b** in 86% isolated yield. Use of 1.5 eq of LHMDS and 10 eq of Et_3N provided the same dr as when the rearrangement was carried out in the absence of Et_3N. Two equivalents of the LHMDS were required to provide 7.7:1 dr.

Table 4. Diastereoselectivity optimization of the amino-Claisen rearrangement



Entry	Base (eq)/additive (eq)	% Yield	*syn*-dr ratio
1	LHMDS (1.5)	78	4.2 : 1.0
2	LHMDS (2.0)/Et_3N (5.0)	82	4.0 : 1.0
3	LHMDS (2.0)/Et_3N (10.0)	86	7.7 : 1.0
4	LHMDS (2.0)/Et_3N (15.0)	84	7.7 : 1.0
5	LHMDS (2.0)/Et_3N (20.0)	85	7.7 : 1.0
6	LHMDS (1.5)/Et_3N (10.0)	80	4.0 : 1.0

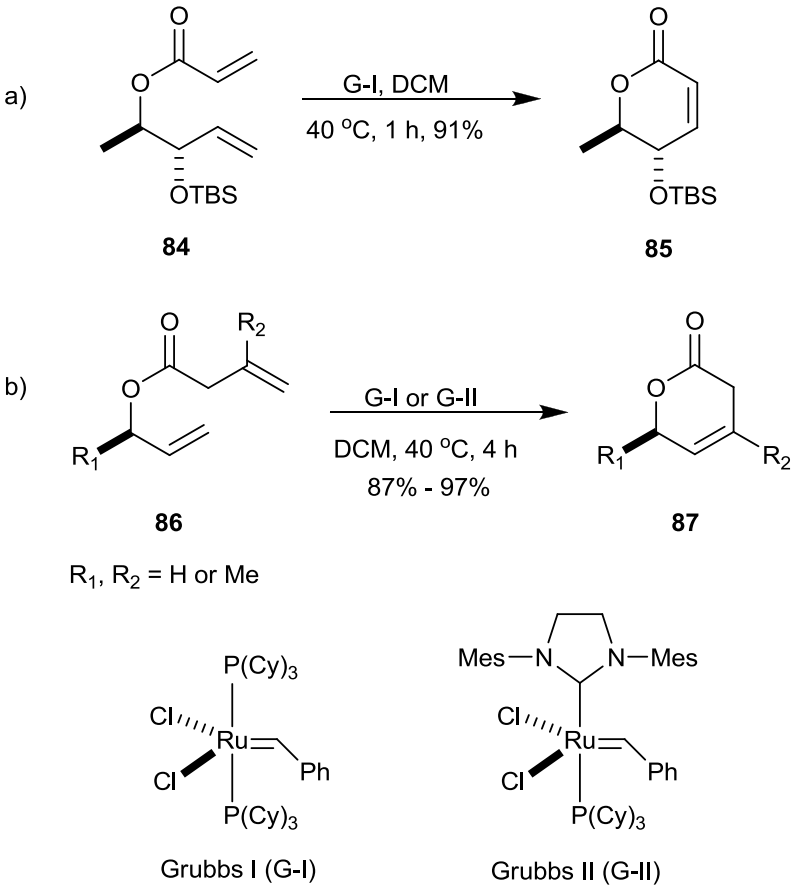
Using the optimized reaction conditions (Table 4, entry 3), we were able to scale the reaction to 9.6 g (24.6 mmol) of amide without decreasing the diastereoselectivity. The major diastereomer **35a** was isolated by column chromatography.

Our next objective was to install the C11/C14 relative configuration for the C10-C16 fragment of antascomicin B. In order to achieve this goal, we proposed to use ring-closing metathesis methodology to establish the 1,4-*anti* stereorelationship.

E. Attempts to Build the 1,4-*anti* (C11-C14) Stereorelationship *via* Ring-Closing Olefin Metathesis

1. Efforts to Construct the β,γ-Unsaturated Lactone 37 by Ring-Closing Metathesis

Ring-closing metathesis (RCM) of unsaturated esters has been successfully used to obtain unsaturated δ-lactones as key intermediates in the total synthesis of bioactive natural products.[51-54] For example, the Nicolaou group's asymmetric synthesis of the **B** and **C** pyran rings of the antibiotic everninomicin used ring-closing olefin metathesis of acrylate **84** to provide α,β-unsaturated δ-lactone **85** (Scheme 34, eq a).[52]

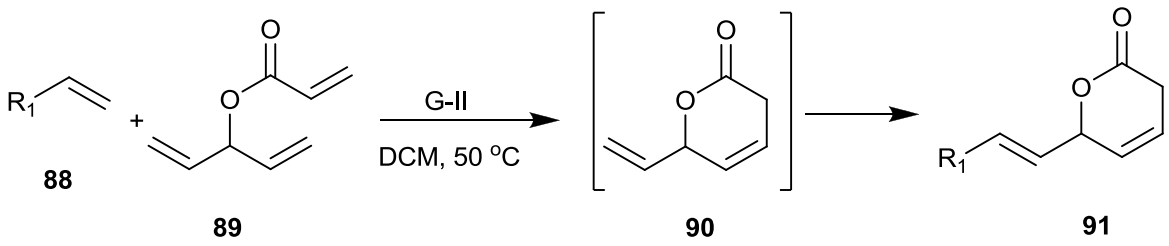


Scheme 34. Synthesis of methyl-substituted δ-lactones via RCM

Grubb's first (G-I) and second generation (G-II) catalyst complexes have been also effectively utilized by Wang et al. in the formation of β,γ-unsaturated methyl-substituted δ-lactones **87** (Scheme 34 eq b).[53, 54] Most of the RCM products of the stereo-defined allyl esters **86** were produced in high yields using either catalyst GI or GII. The main difference between the two reactions was the catalyst loading (G-I=5 % mol;

G-II=1 % mol). To prevent the formation of cross-metathesis byproducts, the concentration of the RCM reactions was approximately 0.01 M.

The synthesis of (*E*)-δ-alkenyl-β,γ-unsaturated δ-lactones *via* tandem ring-closing/cross-metathesis (RCM/CCM) in the presence of Grubbs type II catalyst has been investigated by Piva's group (Scheme 35).[55] They found that the RCM/CCM of pentadienyl ester **89** with olefins **88** using 5% of the catalyst in DCM at 50 ^{o}C for 4 h had to be conducted in highly dilute solutions (10^{-2} M); otherwise, complex mixtures were observed.

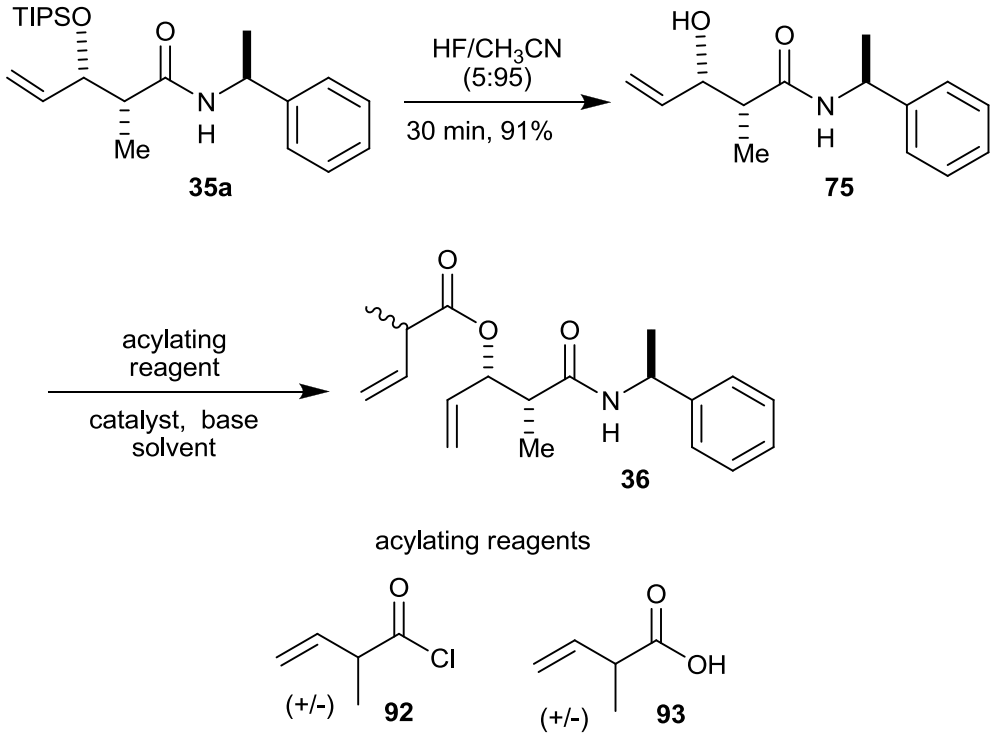


88 **89** **90** **91**

R_1 = $C_{11}H_{23}$, $C_{13}H_{27}$, C_5H_{11}, CH_2Br

Scheme 35. The acces to (*E*)-alkenyl δ-lactones by RCM/CCM process

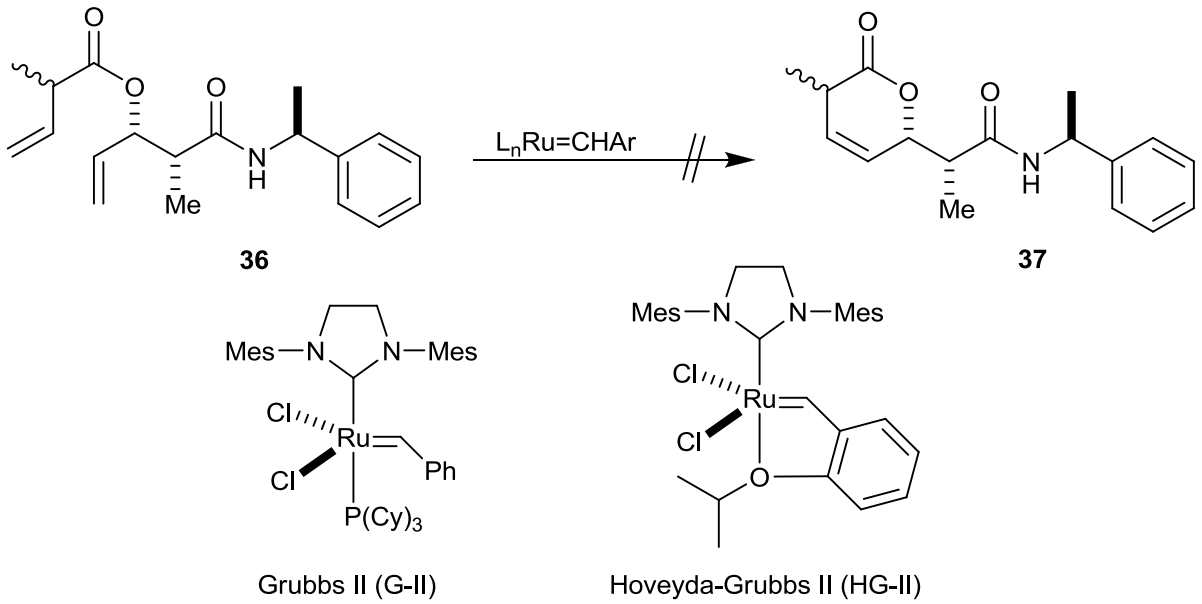
The few examples described above suggest that the RCM could be a convenient route to unsaturated δ-lactones. Thus, our first step in the synthesis was the preparation of RCM precursor **36**, which commenced with desilylation of TIPS ether with a 5:95 solution of hydrofluoric acid and acetonitrile to afford allyl alcohol **75** (Scheme 36). The best yield of the desired allylester **36** was obtained by treatment of alcohol **75** with 2-methyl-3-butenoic acid and dicyclohexylcarbodiimide (DCC) in the presence of base and catalyst (Scheme 36, Table 5, entry 2).



Scheme 36. Preparation of allylic ester **36**

Table 5. Acylation reaction of allyl alcohol **75**					
Entry	Acylating reagent (eq)/catalyst (eq)	Base (eq)	Reaction Conditions	%Yield	SM recovered (%)
1	**92** (1.5)/no catalyst	n-BuLi (1.1)	-78 ^{o}C to rt 10 h	38	0
2	**93** (1.0)/DMAP (0.5)	DCC (1.1)	0 ^{o}C to rt 72 h	57	18
3	**93** (1.1)/DMAP (3.5)	DCC (2.5)	0 ^{o}C to rt 20 h	40	21
4	**92** (1.2)/no catalyst	TEA (1.2)	0 ^{o}C to rt 24 h	52	19

Unfortunately, under standard RCM reaction conditions the allyl ester **36** was found to be unreactive (Scheme 37). Increasing the loading of catalyst and varying the concentration of the reaction mixture gave only recovered starting material and a complex mixture.

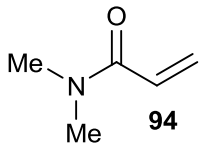
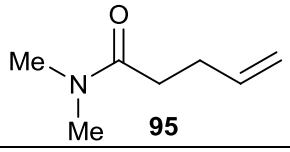
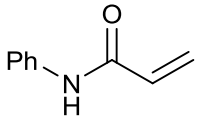
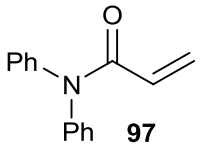


Scheme 37. RCM attempts to afford δ-lactone **37**

Similar results were obtained when the reaction mixture was heated under reflux in DCM for 19 h (Table 6, entries 1-5). When the reaction was performed in toluene using 16% of Grubbs' II catalyst, and heated at 80 ^{o}C for 24 h, less than 5% of the cyclized product was observed, accompanied by a complex unidentifiable mixture (Table 6, entry 8). If the reaction mixture was maintained at rt for 24 h in presence of 15% of G-II 60 % of the starting allyl ester **36** was recovered (Table 6, entry 9).

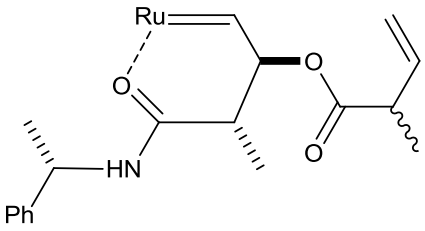
Table 6. RCM reaction conditions of the allyl ester **36**				
Entry	L_nRu=CHPh (%)	Solvent	Reaction conditions	Result
1	HG-II (0.9)	DCM	rt, 24 h	SM + complex mixture
2	HG-II (3.0)	DCM	rt, 24 h	SM + complex mixture
3	HG-II (5.0)	DCM	50 ^{o}C, 19 h	SM + complex mixture
4	HG-II (7.0)	DCM	50 ^{o}C, 19 h	SM + complex mixture
5	HG-II (7.0)/Ti(O*i*Pr)$_4$ (0.3)	DCM	50 ^{o}C, 19 h	SM + complex mixture
6	G-II (6.0)	PhMe	80 ^{o}C, 24 h	complex mixture
7	G-II (8.0)	PhMe	80 ^{o}C, 24 h	**37** (<< 2 %) + complex mixture
8	G-II (16.0)	PhMe	80 ^{o}C, 24 h	**37** (<< 5 %) + complex mixture
9	G-II (15.0)	DCM	rt, 24 h	60 % recovery of SM

We do not have an explanation why the RCM process of the allyl ester **36** failed. The RCM may fail when alkenes are either sterically hindered or electronically similar. Grubbs has reported that the efficiency of cross metathesis of α,β-unsaturated amides with terminal olefins is affected by the substituents on the amide nitrogen.[56] For example, the cross-coupling reaction of dimethylacrylamides **94** and **95** with styrene resulted in lower yields (Table 7, entry 1-2). In contrast, higher yields of cross products were obtained when phenylacrylamides **96** and **97** were used (Table 7, entry 3-4). They suggested that the amide carbonyl group may chelate to the Ru center, and more electron-rich amides have a higher propensity for chelation (Scheme 38, eq a). We speculate that the amide carbonyl group in our substrate might trap the catalyst by forming the six member chelated complex, and consequently stop the metathesis process (Scheme 38, eq b).

Table 7. Cross metathesis reaction of α,β-unsaturated amides		
Entry	Acrylamide	% yield of CM with styrene
1	 **94**	25
2	 **95**	33
3	 **96**	69
4	 **97**	87
All reactions were made using 5 % of G-II catalyst and 1.9 eq of styrene (0.2 M in DCM).		

a)

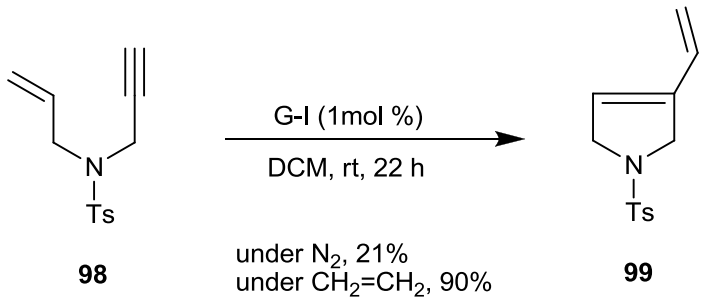
b)



Scheme 38. Proposed Ru chelates

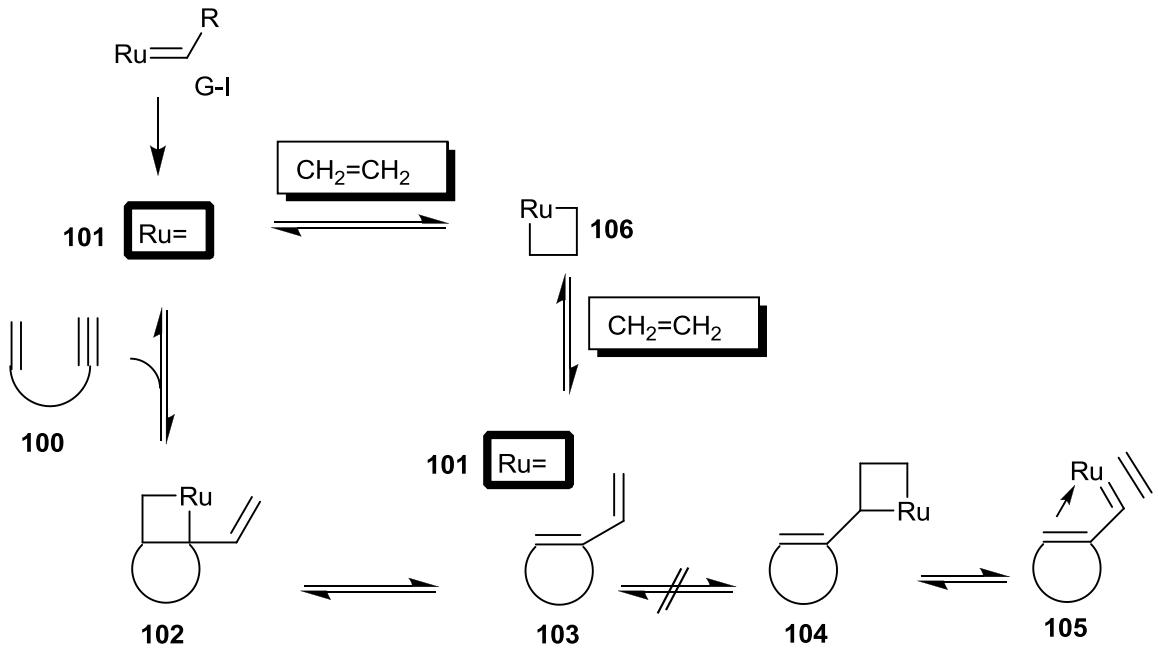
2. Ring Closing Metathesis of Allylester 36 in Presence of Diallylmalonate

The problem of unreactive alkenes has been overcome in some cases by the generation of a more reactive methylidene carbene. For example, in 1998, Mori et al.[57] reported that the treatment of enyne **98**, having no substituent on the alkyne, with G-I at room temperature yield only 21 % of diene **99** (Scheme 39). However, when the reaction was carried out under an atmosphere of ethylene gas, the reaction generated 90 % yield of diene **99**.



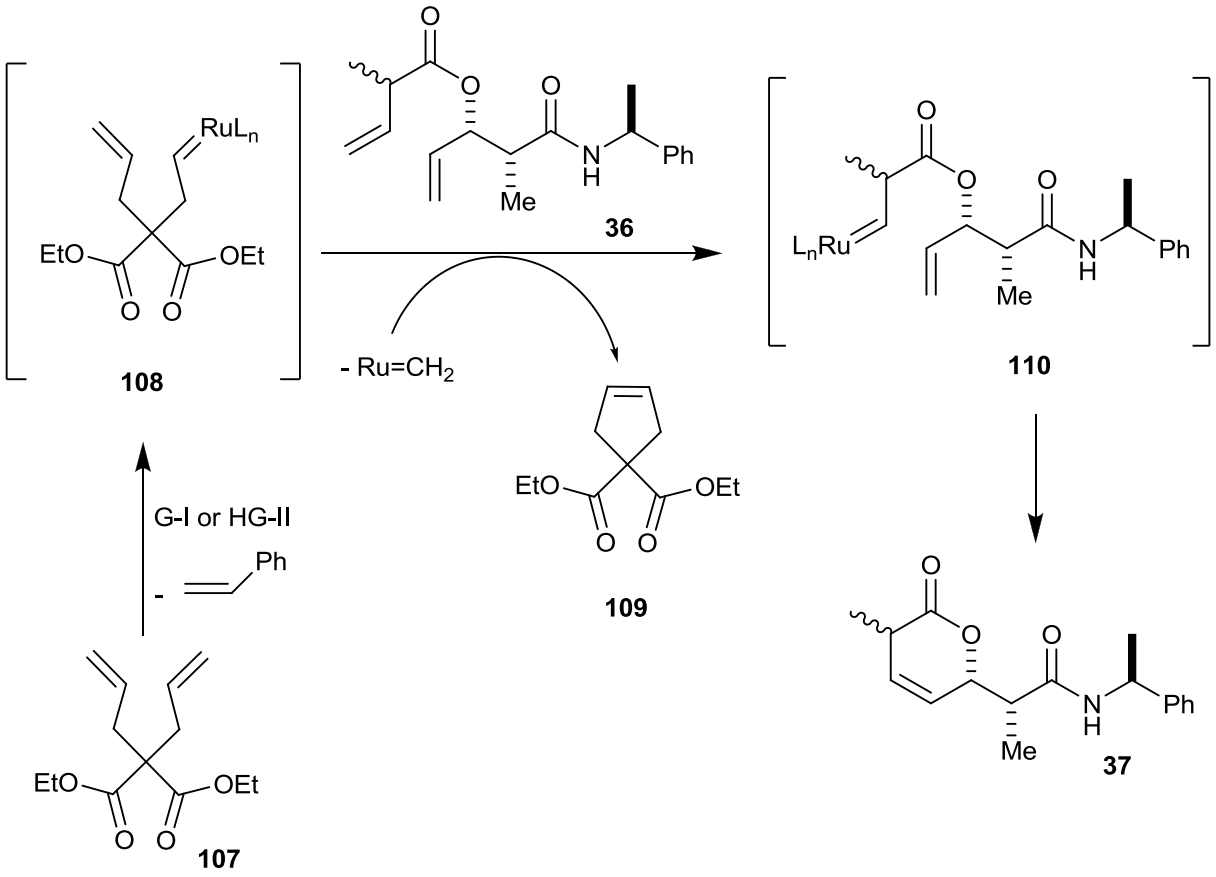
Scheme 39. Mori's conditions on the enyne RCM

This remarkable effect of the ethylene on the yield of Ru-catalyzed enyne RCM reactions was mechanistically explained by a continual reactivation of the ruthenium catalyst keeping it an active through generation of ruthenacyclobutane **106** which is in a state of equilibrium with methylidene ruthenium complex **101** and ethylene gas (Scheme 40). Thus, keeping the equilibrium towards intermediate **106** the active catalyst can readily react with the corresponding starting material **100**. In the absence of ethylene, the methylidene complex **101** can react with diene **103** to generate a less active species such as **104** and **105**.



Scheme 40. Enyne RCM in the presence of ethylene

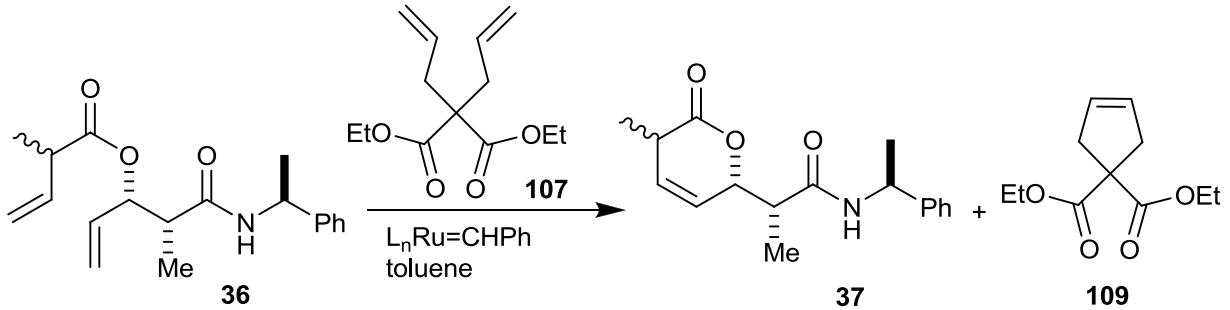
In our case, we applied the same concept by using diallylmalonate **107** which can react quickly with both G-II and HG-II catalysts[58] and consequentially deliver the ruthenium to the olefin **36** to generate the ruthenium olefin intermediate **110** through ejection of the by-product cyclopentene carboxylate **109** (Scheme 41). Then, cyclization of the active olefin **110** will afford the desired δ-lactone **37**.



Scheme 41. Applying RCM to form δ-lactone **37**

The diallylmalonate substrate **107** was prepared from diethyl malonate following standard conditions.[59] When the mixture of **107** and the corresponding ester **36** were treated with 12 mol % of either G-II or HG-II catalyst (0.0032 M in toluene, sealed pressure vessel, 80 ^{o}C) the cyclized product **37** was obtained in 73% and 77% yield, respectively (Table 8, entries 1-2). Unfortunately the efficiency of the RCM process depends on the concentration of the reaction mixture, which has to be very dilute. When we performed the reaction at higher concentrations, the major product observed was the RCM product of the diallylmalonate **107**, and also some starting material was recovered (Table 8, entries 3-5). This is a very limiting factor because we would need very large amounts of solvent to scale up the reaction. For example, the largest scale setting on this RCM process was 100 mg and 110 mL of solvent was needed to obtain cyclic product **37**. Thus, we considered this methodology was not viable in our case.

Table 8. Efforts to improve the RCM process to get δ-lactone **37**

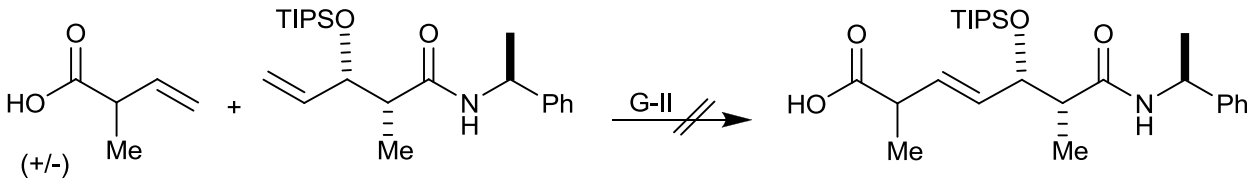


36 **37** **109**

Entry	L_nRu=CHPh (%)	Concentration (M)	Reaction Conditions	Result
1	G-II (12.0)	0.0032	80 °C, 2 h	**37** (73 %)
2	HG-II (12.0)	0.0032	80 °C, 2 h	**37** (77 %)
3	G-II (12.0)	0.0063	80 °C, 2 h	**36** + **109** + complex mixture
4	HG-II (5.0)	0.0079	80 °C, 6 h	**37** (<< 5%) + complex mixture
5	G-II (5.0)	0.0079	80 °C, 6 h	complex mixture
6	G-II (12.0)	0.0079	80 °C, 2 h	**109**

F. Cross Metathesis Attempt to Install the 1,4-*anti*-Configuration of the C10-C16 Fragment

We also examined cross metathesis (CM) between the amino-Claisen product **35a** and carboxylic acid **93** as an alternative to RCM. Unfortunately, no reaction was observed in any of the attempts using Grubbs' type II (Scheme 42).

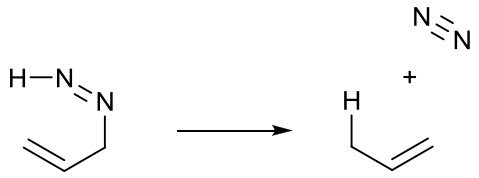


Scheme 42. Attempts to obtain heptanoic acid **111** via CM

Table 9. Results of the CM of amide **35a** with olefin **93**				
Entry	L_nRu=CHPh (%)	Solvent	Reaction Conditions	Result
1	G-II (5.0)	DCM	50 ^oC, 12 h	Recovered SM
2	G-II (7.0)	DCM	50 ^oC, 24 h	Recovered SM
3	G-II (7.0)	DCM	50 ^oC, 72 h	Recovered SM
4	G-II (12.0)	PhMe	80 ^oC, 3 h	Recovered SM
5	G-II (12.0)	PhMe	100 ^oC, 9 h	Recovered SM

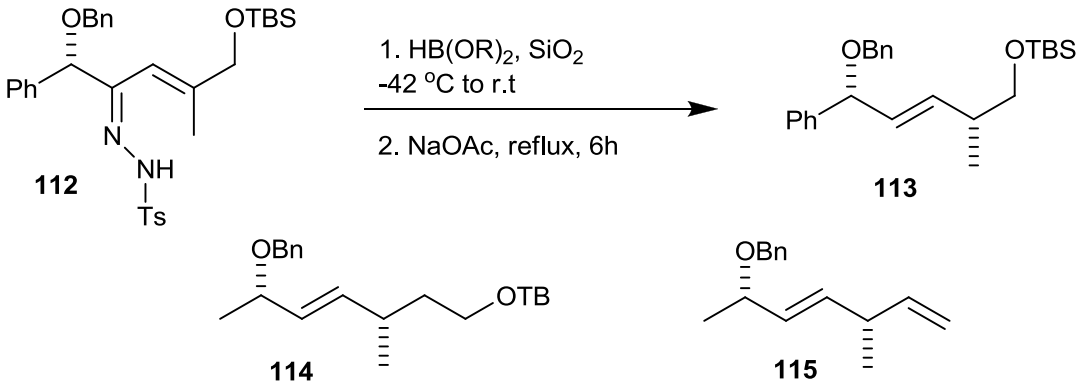
G. Efforts to Introduce the 1,4-*anti* (C11-C14) Stereorelationship through Allylic Diazene Rearrangement

The ene reaction, originally defined by Alder et al,[60] involves the addition of an alkene possessing an allylic hydrogen (ene) to a compound having electron-deficient multiple bonds (enophile), following in most cases a thermal concerted [2πs + 2πs + 2σs] pathway. The retro-ene reaction that involves the elimination of molecular nitrogen from 1-diazo-2-propene to obtain propene is called the allylic diazene rearrangement (ADR) (Scheme 43).



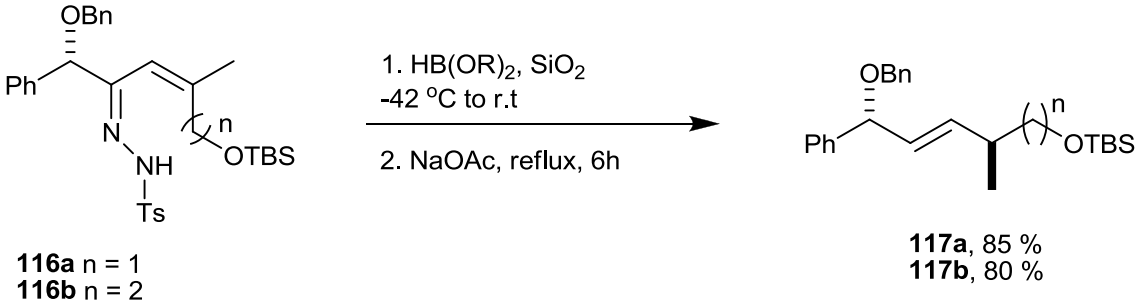
Scheme 43. The ADR general reaction

The ADR has been employed to install sp^3 stereocenters in a variety of cyclic systems.[61, 62] However, there were no examples in acyclic systems prior to the reports from our group.[63] We demonstrated that 1,4-*syn*- or 1,4-*anti* acyclic stereorelationships can be generated in high yield and diastereoselectivity by one pot reduction/allylic diazene rearrangement of α,β-unsaturated tosyl hydrazones. For example, the treatment of tosyl hydrazone **112** with catecolborane and silica gel at low temperature for 2 h, followed by addition of NaOAc and heating the reaction mixture for 6 h, afforded 1,4-*syn*-*E*-2 alkenyl product **113** in 92 % yield and ≥ 20:1 *dr*. The 1,4-*syn*- products **114** and **115** were obtained in the similar fashion (Scheme 44).



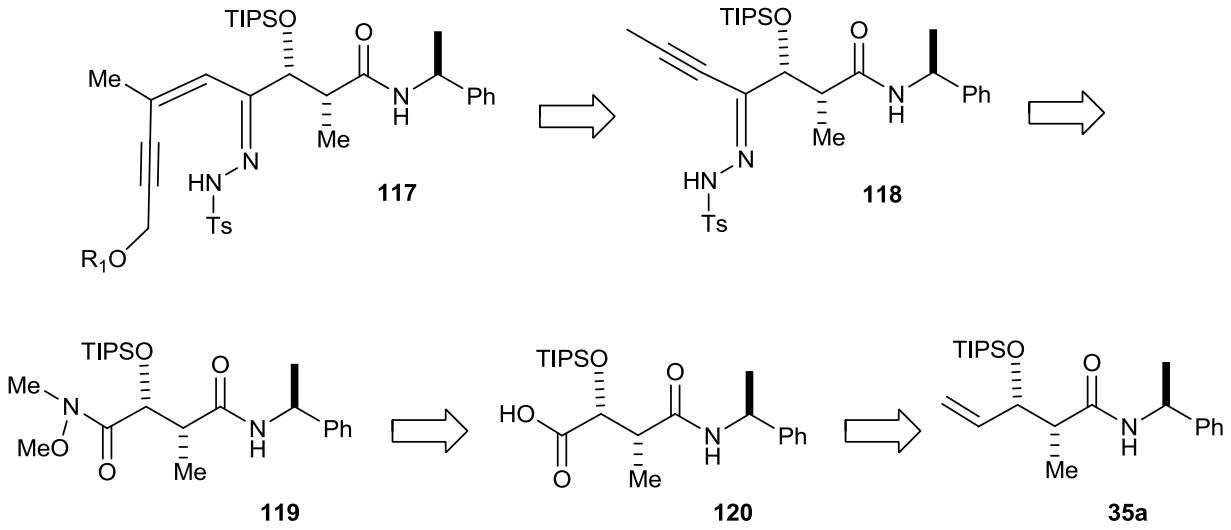
Scheme 44. Reductive tranposition of tosyl hydrazone **112**

We also reported examples of the formation of 1,4-*anti* alkenes **117** in good yield and ≥ 20:1 *dr*, from *Z*-alkene α,β-unsaturated tosyl hydrazones **118** (Scheme 45).



Scheme 45. Generation of 1,4-*anti* alkenes **117**

Therefore, we recognized that we could use the ADR to install the C11/C14 relative configuration for the C10-C16 fragment. Retrosynthetically hydrazone *Z*-**118** could be constructed from alkyne **119** by Pd catalyzed cross coupling addition of acetylenes.[64] This target molecule **119** could be formed by acylation of Weinreb amide **120** with propynyllithium, following by addition of tosyl hydrazide.[68] The amide **120** could be derived from carboxylic acid **120** which could be obtained by oxidative cleavage of the terminal olefin of the amino-Claisen product **35a** (Scheme 46).

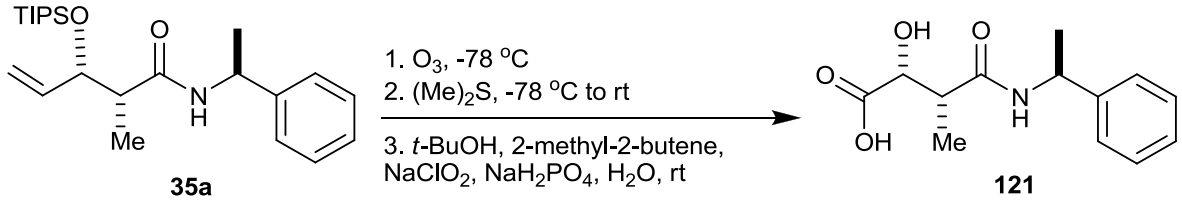


Scheme 46. Retrosynthetic plan to form *Z*-tosylhydrazone **117**

1. Attempts to Prepare the Silyloxybutanoic Acid 120 by Ozonolysis

The first step to obtain carboxylic acid **120** involved the oxidation cleavage of the terminal olefin of the amino-Claisen product **35a** with a stream of ozone in methanol followed by direct reduction-oxidation protocols.[65] However, the expected acid **120** was not formed and 53 % of the starting olefin was recovered (Table 10, entry 1). Surprisingly, in all attempts where the alkene was exposed for longer periods of time to ozone, or using a mixture of MeOH-DCM solvents, we recovered starting material in 41-53 % yield. Furthermore, the TIPS group was also cleaved and 16-20 % of the hydroxy acid **121** was generated (Table 10, entries 2-6).

Table 10. Attempts to prepare butanoic acid **120** *via* ozonolysis

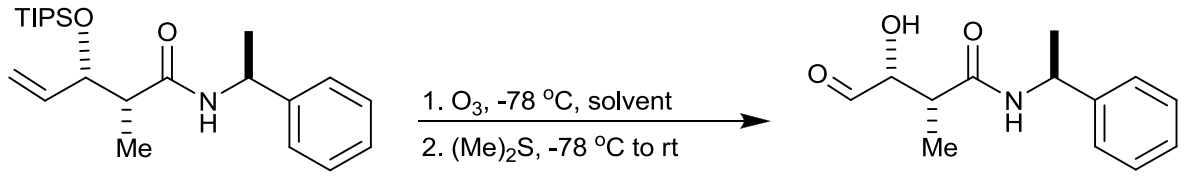


35a **121**

Entry	O_3 (min)	Solvent	$(Me)_2S$ (eq)	SM (%)	Hydroxy acid **121** (%)
1	20	MeOH	6.0	53	---
2	45	MeOH	6.0	41	18
3	60	MeOH	6.0	43	16
4	90	MeOH	6.0	46	19
5	45	MeOH-DCM (1:1)	6.0	41	16
6	45	MeOH-DCM (1:1)	50.0	44	19

In order to better understand what was occurring in the reaction, we simplified the ozonolysis of alkene **35a** by not performing the final oxidation step. Ozonolysis of a methanolic solution of the alkene **35a** followed by reduction with dimethyl sulfide (DMS) resulted in low yield (≤ 16 %) of hydroxyaldehyde **122** and ≤ 42 % yield of recovered starting material (Table 11, entries 1-3). Neither use of a large excess of DMS nor use of a MeOH-DCM solvent mixture improved the results (Table 11, entries 4-5).

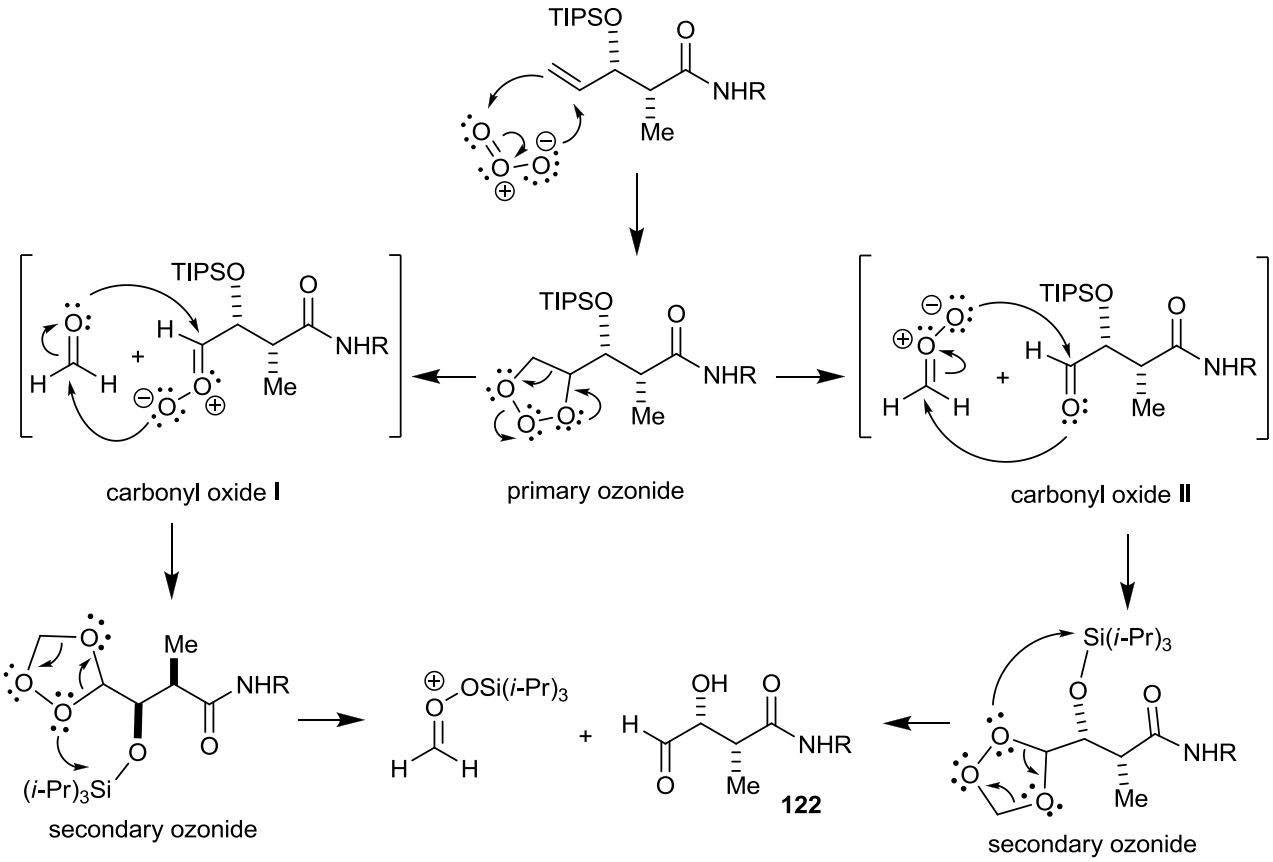
Table 11. Reductive ozonolysis results of the olefin **35a**



35a **122**

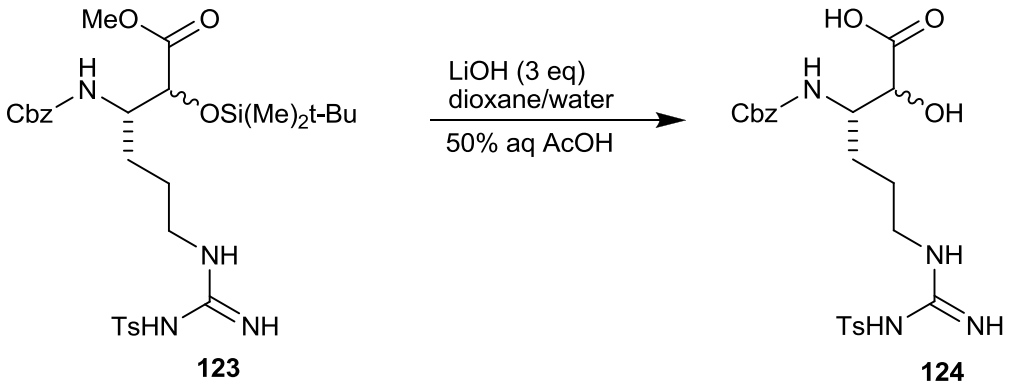
Entry	O_3 (min)	Solvent	$(Me)_2S$ (eq)	Results: **35a** (%), **122** (%)
1	45	MeOH	6.0	**35a** (42), **122** (14)
2	60	MeOH	12.0	**35a** (38), **122** (16)
3	60	MeOH	36.0	**35a** (41), **122** (14)
4	60	MeOH-DCM (1:1)	6.0	**35a** (44), **122** (15)
5	60	MeOH-DCM (1:1)	36.0	**35a** (41), **122** (14)

These results suggest that the cleavage of the TIPS group occurred subsequent to reaction of the alkene with ozone. Based on these observations and the Criegee mechanism for the ozonolysis,[66-68] we speculate two different reasons that could explain this results. First, the removal of the TIPS group probably happened in the reduction step of the secondary ozonide. Maybe it is the silyl group which induced the reduction to get the hydroxyaldehyde **122** (Scheme 47). The last could be a reason why using 6.0 eq or 36.0 eq of the DMS did not represent any important difference in the results.



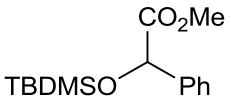
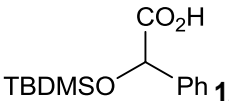
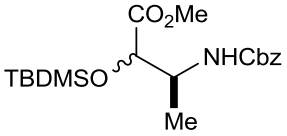
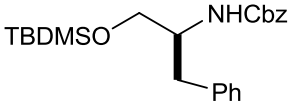
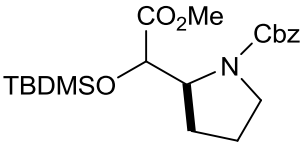
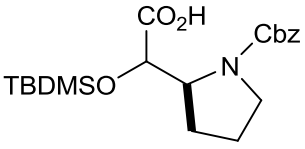
Scheme 47. Suggested cleavage pathway for TIPS ether group

The second speculation is based on a Greco et al. report.[69] They found that standard saponification conditions and mild acidification of α-silyloxy homo-arginine derivative **123** generated the unexpected desilylated amino acid **124** (Scheme 48). In order to explain this unusual desilylation reaction they undertook systematic studies by exposing related substrates to the saponification/acidification procedure (Table 12).

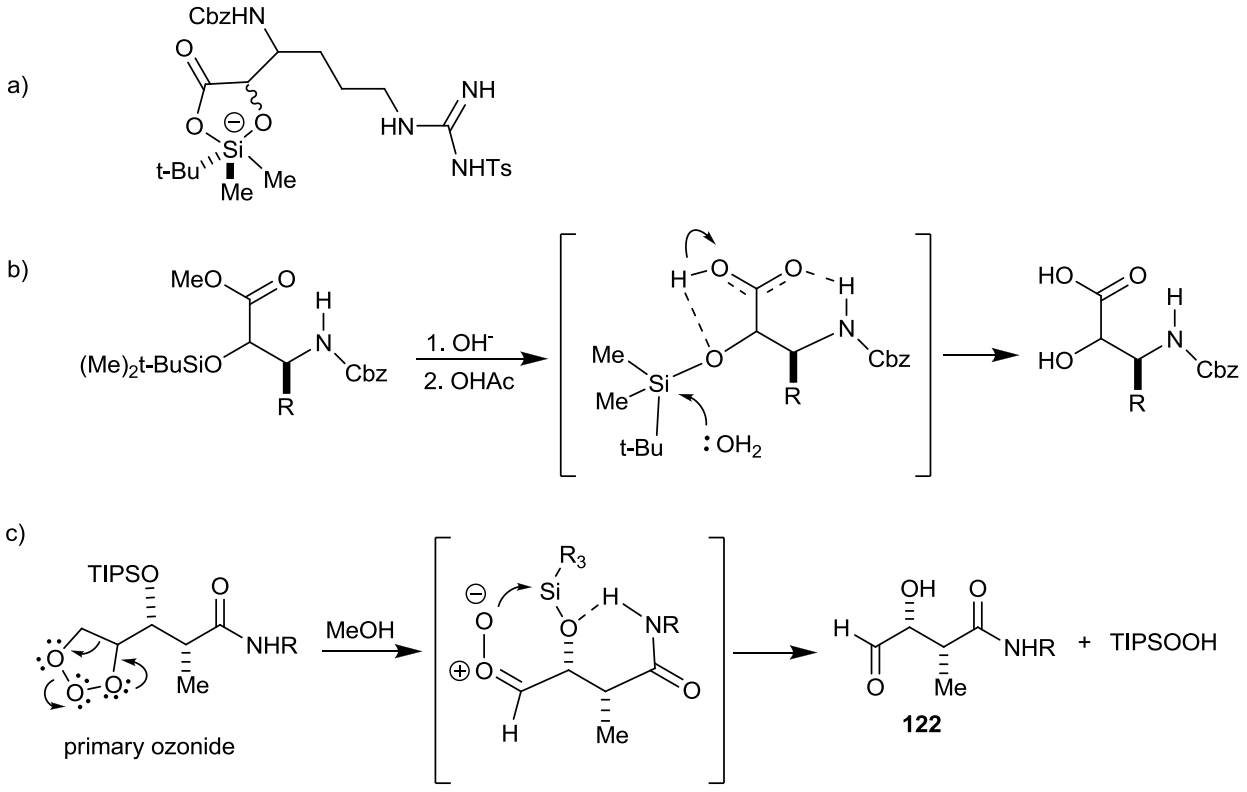


Scheme 48. Unsual lability of α-silyloxy β-amino carboxylic acid **123**

Table 12. Saponification process of amino acid derivatives **125-128**

Entry	Substrates	products
1	 **125**	 **125a**
2	 **126**	 **126a** + **126b**
3	 **127**	no reaction
4	 **128**	 **128a**
Reaction conditions: LiOH (3 eq), dioxane:water (9:1) and 50% aq solution of AcOH		

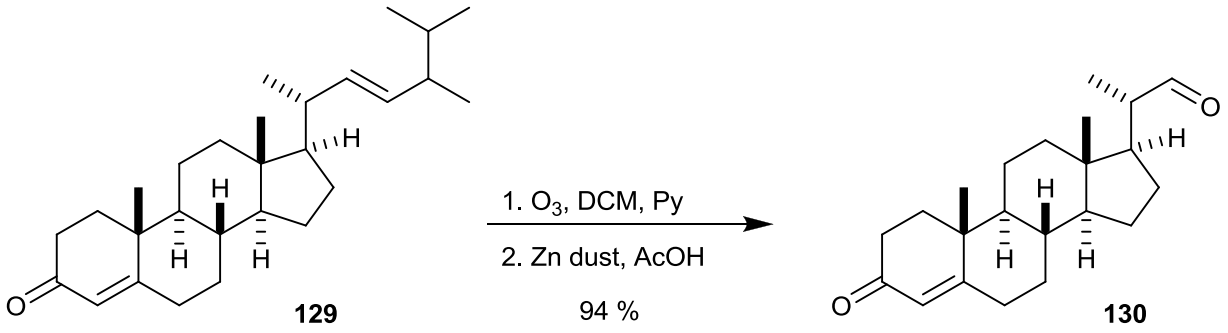
According with their results, they considered that intramolecular hypervalent silicon species (Scheme 50, eq a) was not formed since saponification of ester **125** yielded silyl-protected acid **125a** (Table 12, entry 1). The desilylation process appears to be unrelated to the amino acid side chain, because the major product of saponification of alanine derivative **126** gave desilylated acid **126a** (Table 12, entry 2). Thus, they suggested that hydrogen bonding between the α-amino hydrogen and the carbonyl oxygen is crucial to facilitate protondesilylation (Scheme 49, eq b). Thus, saponification of proline **128**, which cannot experience this hydrogen bond, generated silylated acid **128a** (Table 12, entry 4). Based on these findings, in our case, we speculate that the secondary ozonide was not formed and the loss of the TIPS group probably happened in the reduction step of the primary ozonide. Hydrogen bonding between the NH proton and the silyl ether oxygen may promote the desilylation of the TIPS-protected amide (Scheme 49, eq c).



Scheme 49. Suggested desilylation pathway of TIPS group based on Greco's studies

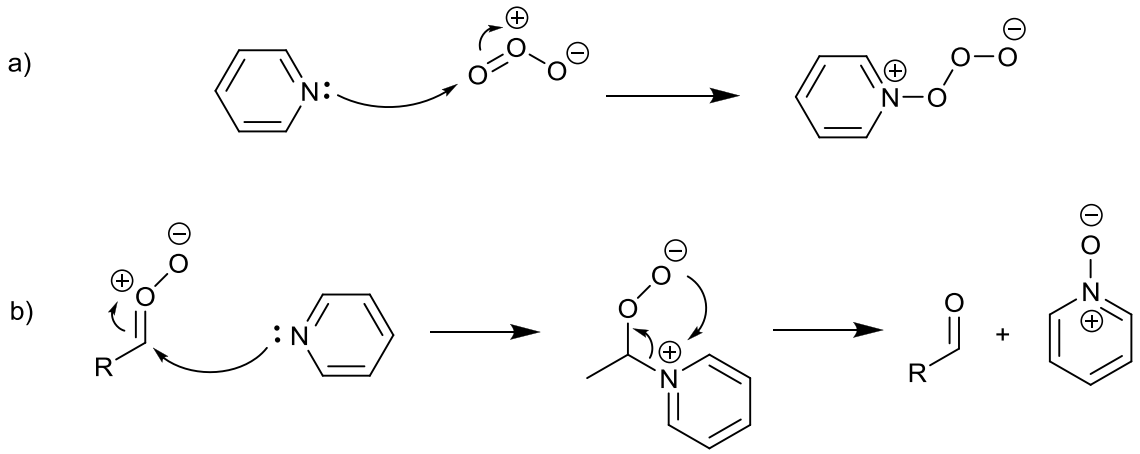
2. Ozonolysis of Amide 35a in Presence of Pyridine

There are several reports performing the ozonolysis of alkenes in presence of pyridine to direct the formation of ketones or aldehydes.[70-72] For example, it was found that the selective cleaving of the least substituted alkene in the ozonolysis reaction of 4,22-stigmastadien-3-one **129** in presence of pyridine lead the resulting aldehyde **130** in high yield upon reduction (Scheme 50).[73] Performing the reaction in absence of pyridine generated a mixture of cleavage products.



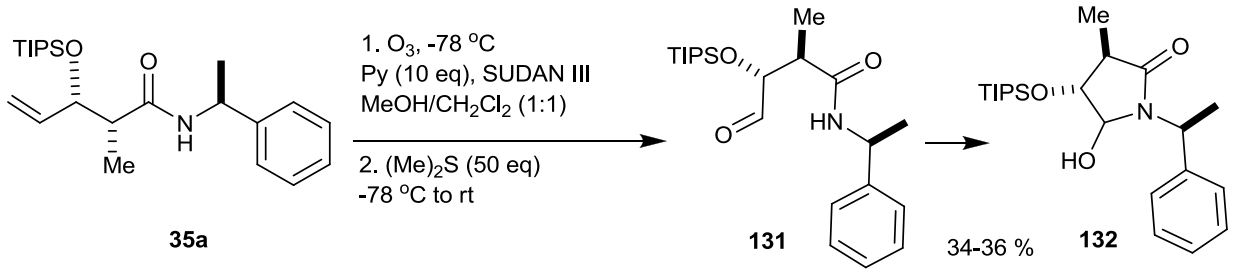
Scheme 50. Selective oxonolysis reaction of **129** in presence of pyridine

Although there is not clear explanation what is the role of the pyridine in the ozonolysis reaction, the authors postulated two possible explanations. First, the nucleophilic pyridine could react with ozone to form a less electrophilic pyridine-ozone species. This adduct would be a weak oxidant and consequently enhance the chemoselectivity (Scheme 51, eq a). Second, the nucleophilic pyridine could directly attack the electrophilic carbon of the carbonyl oxide and following rearrangement generate the aldehyde and pyridine N-oxide (Scheme 51 eq b). However, monitoring the ozonized tetramethylethylene reaction in the presence of stoichiometric amounts of pyridine by NMR spectroscopy did not show the formation of pyridine oxide. Instead, most of the pyridine remained unchanged during the cleavage reaction.[74]

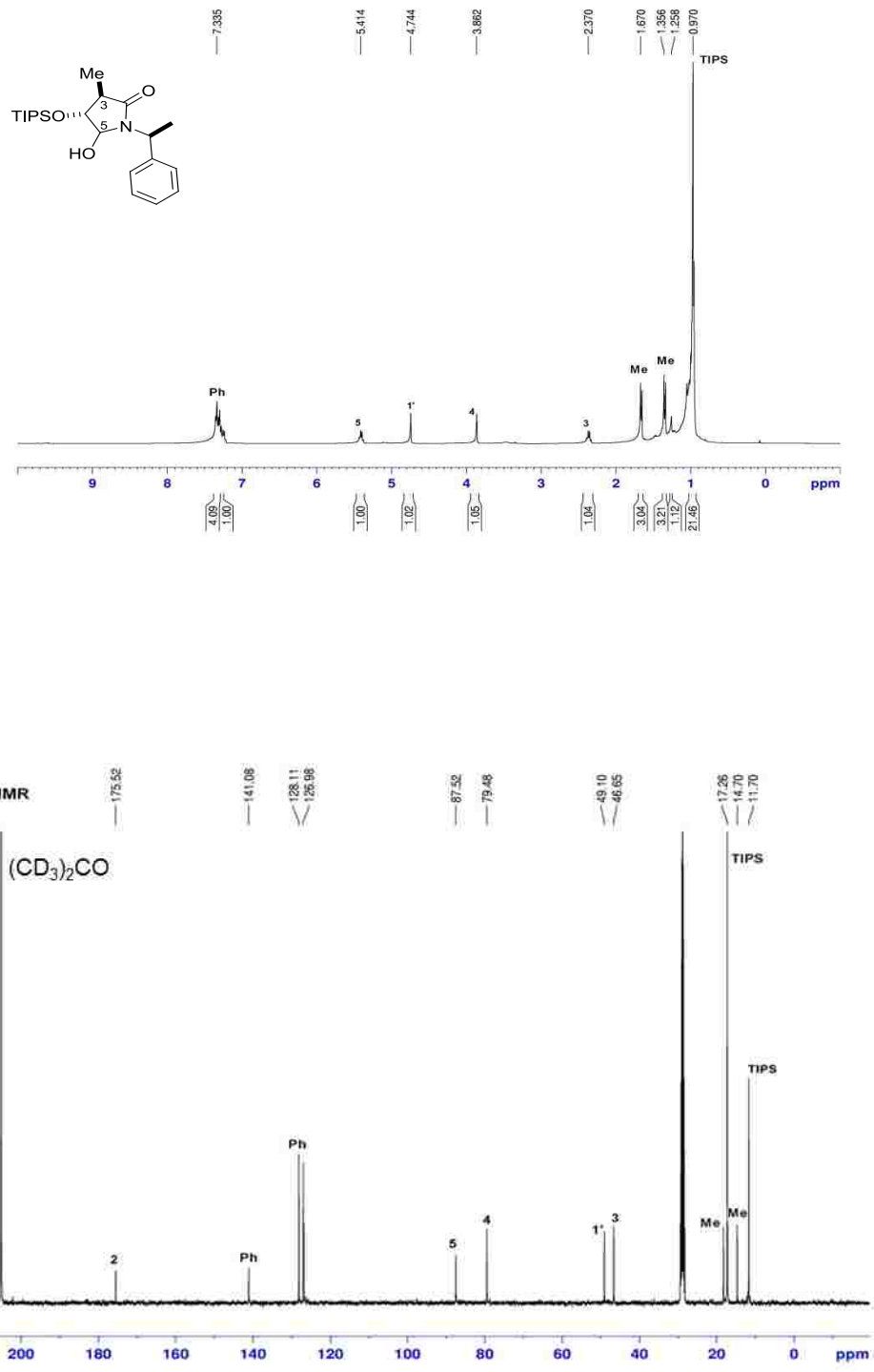


Scheme 51. Postulated role of of pyridine in the ozonolysis of alkenes

Appling these ozonolysis reaction conditions to olefin **35a** (Scheme 52), we found that in all cases ~ 35 % yield of the silyloxyaldehyde **132** was obtained and ~ 20 % yield of the starting material was recovered. Spectroscopic analysis of the ^{1}H and ^{13}C NMR spectra showed clearly that the silyloxyaldehyde **131** exist exclusively in its tautomeric σ-hydroxy lactam form **132** (Scheme 53).

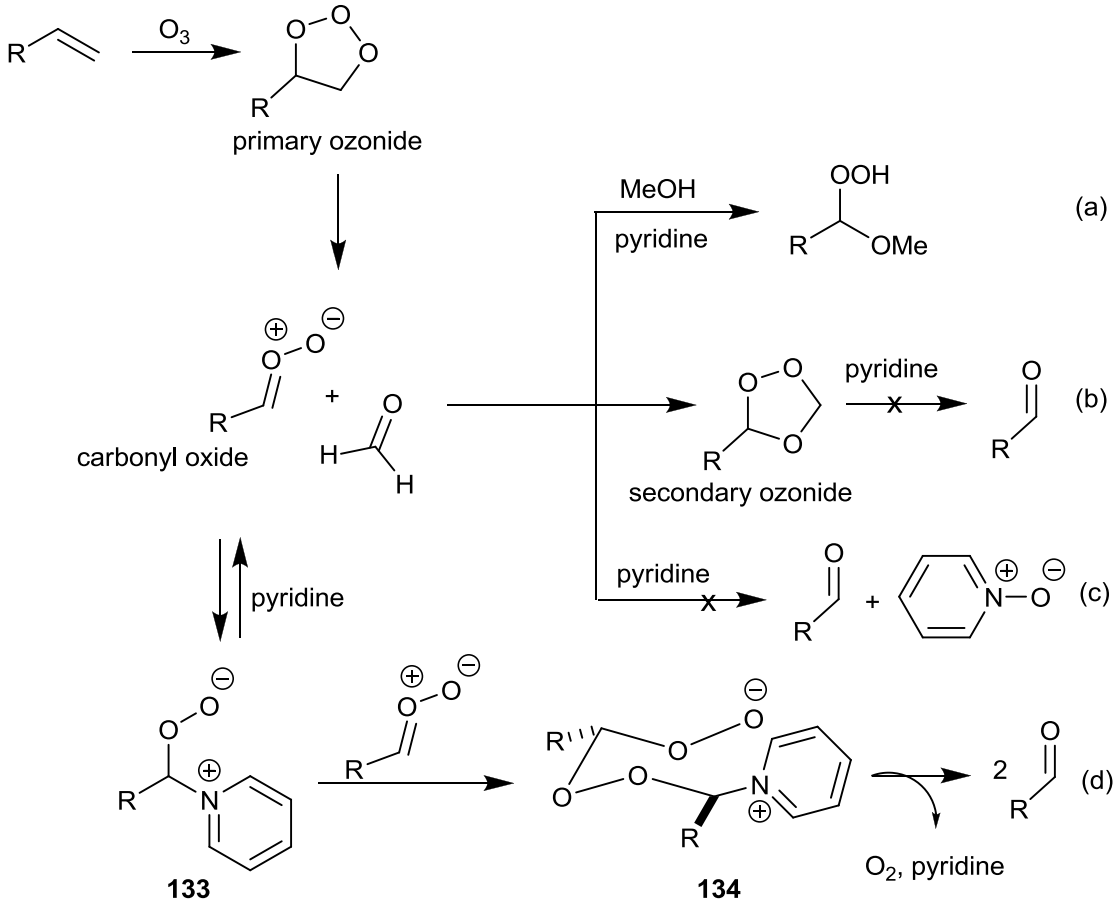


Scheme 52. Reductive ozonolysis of the olefin **35a** in presence of pyridine



Scheme 53. ^{1}H and ^{13}C-NMR spectra of the σ-hydroxy lactam **132**

These experiments suggest that the pyridine plays a critical role, not only in the formation of the σ-hydroxy lactam product, but also in the stability of the TIPS ether. Recently, Dussault et al. proposed that pyridine acts as a catalyst in the ozonolysis reaction.[75] They observed that: 1) the reaction of different olefins in the presence of pyridine and methanol always yielded hydroxyperoxyacetals (Scheme 54 path a), 2) isolated 2° ozonides did not react with pyridine to produce carbonyl products (Scheme 54, path b), and 3) pyridine did not reduce the carbonyl oxide intermediate to produce aldehyde and pyridine oxide (Scheme 54, path c). They concluded that a feasible mechanism would involve the nucleophilic addition of pyridine to the carbonyl oxide to generate zwitteron **133**. Reaction of this zwitteron with another molecule of the carbonyl oxide would result in the formation of the zwitterionic peroxyacetal **134**, which could fragment to a molecule of O_2, two carbonyl groups, and pyridine (Scheme 54, path d).

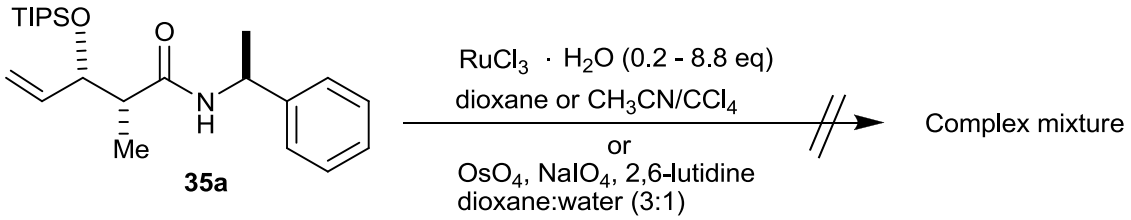


Scheme 54. Dussault mechanistic possibilities for the ozonolysis in presence of pyridine

Although Dussault's suggested mechanism is consistent with our speculation that the TIPS group cleavage would occur in the reduction step of the secondary ozonide (cf. Scheme 47). It seems unlikely that the 2° ozonide would prefer to react with a hindered silyl ether if it would not react with a much more nucleophilic pyridine.

3. Other Oxidation Efforts to Form Carboxylic Acid 127 and Aldehyde 137

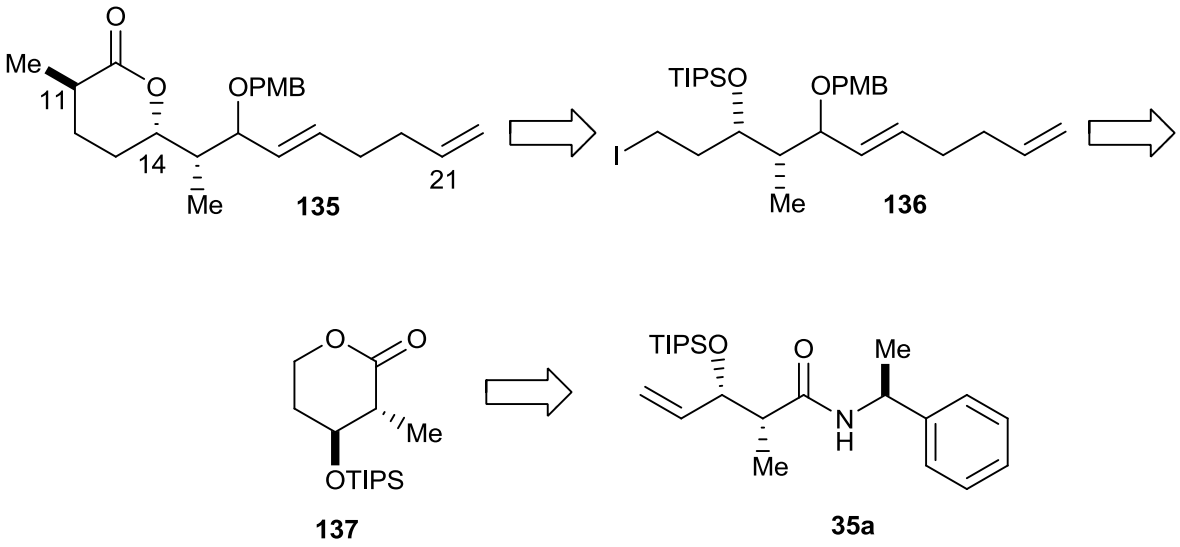
One of the most frequently employed procedures to obtain carboxylic acids from alkenes is the $RuCl_3$-$NaIO_4$ oxidation in the CCl_4-CH_3CN solvent system reported by Sharpless et al.[76, 77] Applying this protocol to alkene **35a** using several reaction conditions only produced unidentified complex mixtures. Similarly, treatment of olefin **35a** with OsO_4-$NaIO_4$ in the presence of 2,6-lutidine in dioxane-water[78] likewise led only complex mixtures (Scheme 55).



Scheme 55. Other oxidation efforts of alkene **35a**

H. Third Generation Route to Construct the C10-C21 Fragment of Antascomicin B

Due to the low reactivity of the terminal olefin of the amino-Claisen product **35a** in the oxidations, we sought another strategy to the C10-C21 fragment. The plan was to establish the desired C11 configuration using an Evan's alkylation reaction with iodo undecadiene **136**, which could be generated from pyranone **135** using standard protocols. Pyranone **137** can be obtained by acid hydrolysis of the hydroboration/oxidation product of the rearranged amide **35a** (Scheme 56).



Scheme 56. Proposed retrosynthetic route to build C10-C21 unit

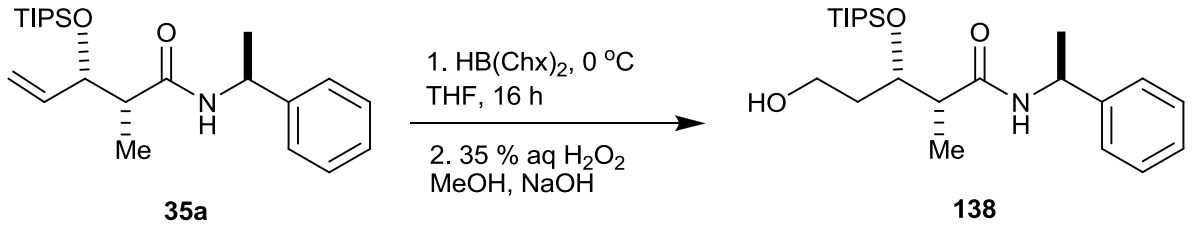
1. Preparation of Silyloxypyranone 137 through Hydroboration/Oxidation

One of the most useful methods to convert an alkene into an alcohol is hydroboration/oxidation.[79-81] One feature of this reaction is the regioselective addition of borane reagents such as dicyclohexyl borane to provide anti-Markovnikov alcohols.

The hydroboration oxidation of our substrate started with the in situ preparation of $(Chx)_2BH$, which precipitates as white crystals when 2.0 eq of cyclohexene is treated with 1.0 eq of $BH_3 \cdot SMe_2$ in ether at 0 ^oC.[82] Addition of a THF solution of olefin **35a** to the $(Chx)_2BH$ suspension followed by oxidation produced

the desired alcohol **138**. Initially, we only obtained 30 % of the product, while 57 % of the starting olefin was recovered (Table 13, entry 1).

Table 13. Hydroboration/oxidation of olefin **35a**

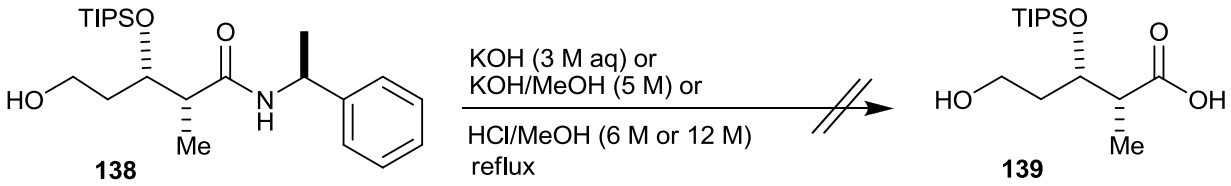


35a **138**

Entry	**35a** g (mmol)	$HB(Chx)_2$ (eq)	% yield of **138**
1	0.5 (1.28)	1.0	30
2	1.0 (2.56)	2.0	52
3	1.0 (2.56)	3.0	78
4	1.0 (2.56)	4.0	76
5	4.0 (10.3)	3.0	72

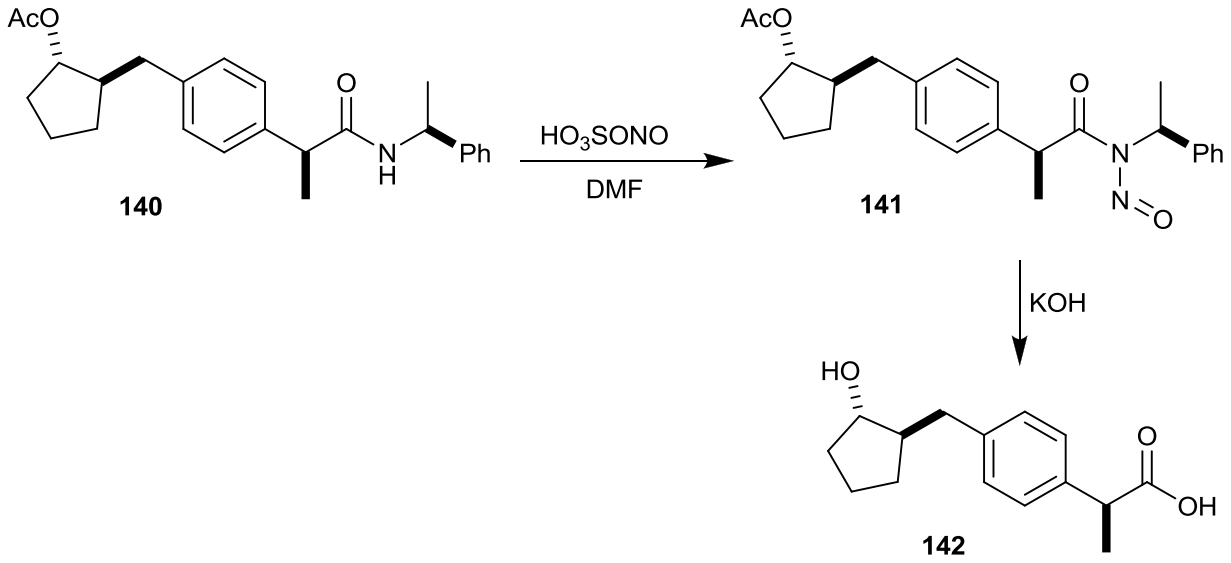
The addition of 3.0 eq of borane to **35a** furnished 78 % of alcohol **138**, which was the highest yield. Addition of 4 eq did not improve the yield (Table 13, entries 3-4). We were able to scale this process to 4.0 g (10.3 mmol) and obtained 72% yield of alcohol. However, we have been unable to reproduce these results every time the reaction was performed. Using exactly same reaction conditions, we sometimes obtain ~ 10 % of the desired alcohol and ~ 70 % of an unknown compound.

Our next objective was cleavage of the amide functionality of **138** to a lactone, carboxylic acid, or ester. Typical acidic or basic hydrolysis returned only starting material (Scheme 57).



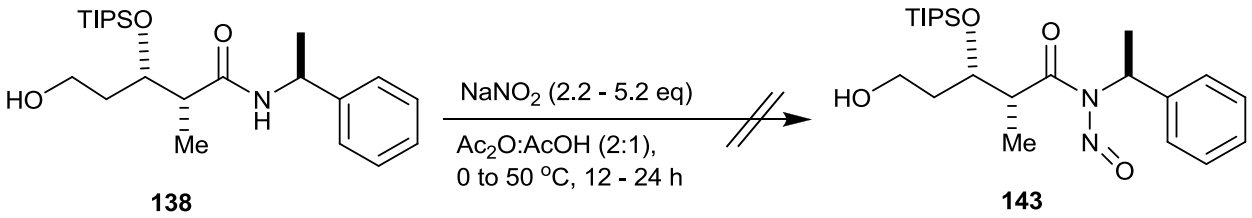
Scheme 57. Hydrolysis attemps to get carboxylic acid **139**

Multiple reports has shown that derivatization of secondary amides to N-nitrosoamides is a mild procedure to cleave amide bonds.[83-86] For example, in the final step of the synthesis of propionic acid **142**, the amide linkage was cleaved without racemization *via* nitrosoamide intermediate **141**, upon alkaline hydrolysis resulted in 70 % yield of **142** (Scheme 58).



Scheme 58. Synthetic application of nitrosation/hydrolysis strategy

In our case, hydroxyamide **138** was resistant to treatment with $NaNO_2$ in presence of acetic acid and acetic anhydride, returning only unreacted starting material (Scheme 59). Amide **35a** behaved similarly.

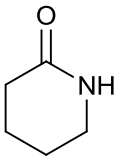
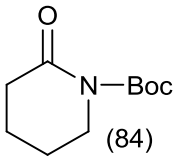


138 **143**

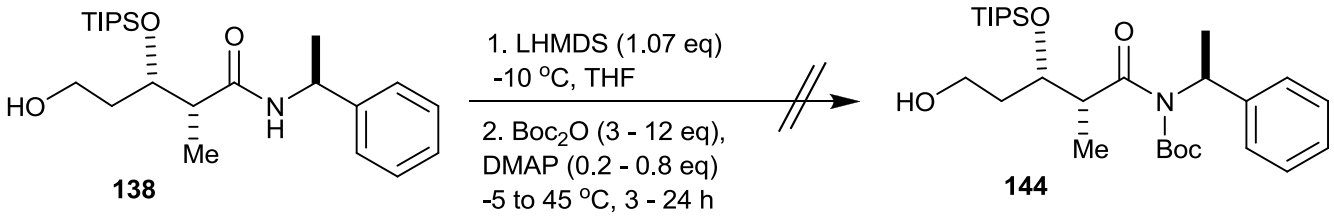
Scheme 59. Attempts to generate nitrosoamide **143**

Grieco et al.[87] reported that N-Boc derivatives of lactams and secondary amides undergo regioselective hydrolysis using LiOH or methanolysis to yield amino acids or esters respectively (table 14).

Table 14. Hydrolysis of N-Boc derivatives of lactam and secondary amides

Entry	Amide	N-Boc amide, (% yield)	Cleaved product, (% yield)
1		 (84)	$HOOC(CH_2)_3NHBoc$ (90)
2	$PhCH_2CONHCH_2Ph$	$PhCH_2CONCH_2Ph$ | Boc (87)	$PhCH_2COOH$ (91)
3	$t\text{-}C_6H_{13}CH{=}CHCONHC_4H_9$	$t\text{-}C_6H_{13}CH{=}CHCONC_4H_9$ | Boc (78)	$t\text{-}C_6H_{13}CH{=}CHCOOH$ (80)

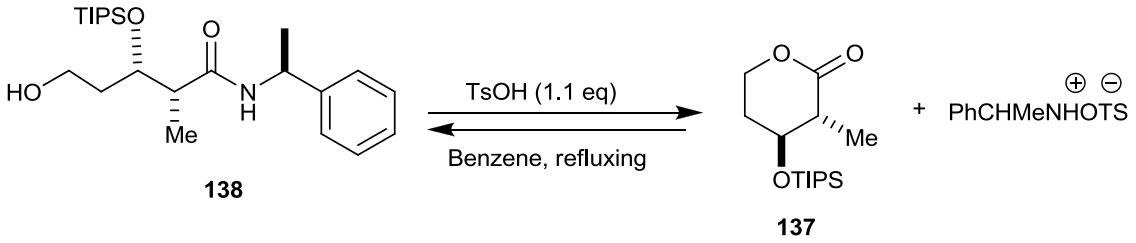
Unfortunately in our case, it was not possible to convert hydroxyamide **138** into its N-Boc derivative **144** efficiently. According with the crude ^{1}H-NMR data, we always observed less than 10% of the N-Boc amide product after treating **138** with LHMDS, Boc anhydride (Boc_2O) and DMAP in THF. Moreover, when we tried to purify the N-Boc derivative **144** from the crude mixture by column chromatography, we were able to recover the starting amide, but we never isolated **144**. The same result was obtained after several attempts using different reaction conditions (Scheme 60). Amide **35a** was also unreactive using same reaction conditions.



Scheme 60. Trying to make N-Boc amide **144**

Our next approach to amide cleavage was to perform a cyclization in acid medium to generate the corresponding lactone. Although the hydroxyamide **138** could be susceptible to β-elimination reactions, heating **138** in presence of 1.1 equivalent of tosic acid (PTSA) in refluxing benzene for 15 min furnished 48 % yield of the desired silyloxypyranone **138**. Additionally, 38 % of the starting amide was recovered and no elimination product was observed. It is important to mention that heating the reaction mixture longer than 15 min did not improve the yield (Table 15, entry 2-3). When scaled to 2.5 g (6.10 mmol), 46 % yield of the lactone product was obtained and 40 % of the hydroxyamide was recovered.

Table 15. Acid mediated cyclization of hydroxyamide **138**



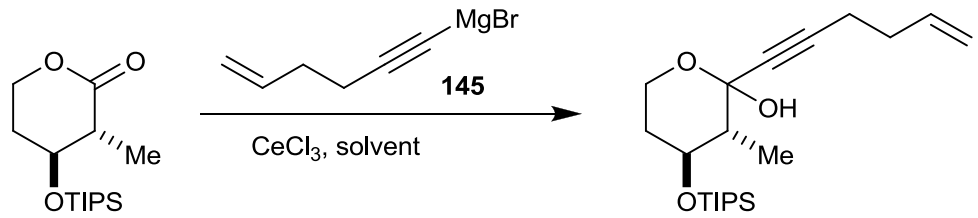
Entry	Reaction time (min)	**137** % yield	% Yield brsm
1	15	48	86
2	30	45	85
3	120	47	86

2. Efforts to Introduce the C17-C21 Hexadiene Arm *via* Grignard Addition

Having the silyloxypyranone **137** in hands, our next goal was to focus in installing the hexadiene fragment (C17-C21) of antascomicin B. To accomplish this, we expected that the addition of the known acetylide Grignard reagent **145** to the silyloxypyranone **137** and subsequent reduction would produce the corresponding diene.

The Grignard reaction began with addition of the pyranone **137** to an ether solution of hexenyl magnesium bromide (2 eq) at 0 ^{o}C, which was previously formed in situ by the treatment of allylmagnesium bromide with propagyl chloride.[88] After allowing the reaction mixture warming up to rt and then stirring for 14 h at 50 ^{o}C no desired product was obtained. Instead, most of the starting pyranone was recovered (Table 16, entry 1-2). Treating pyranone **137** with 4.0 eq of the Grignard reagent gave a mixture of products. Purification by silica gel column chromatography allowed recovery some of starting material, and *ca* 27 % yield of impure hexenyl pyranol **146** (Table 16, entry 3 - 4). Use of $CeCl_3$ did not improve the results (Table 16, entry 6-7).[89, 90]

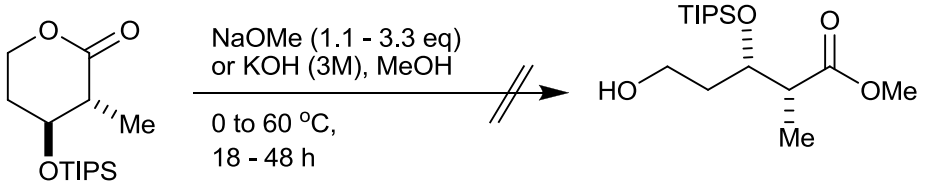
Table 16. Organometallic addition reaction of pyranone **137**



137 **146**

Entry	**145** (eq)	$CeCl_3$ (eq)	Solvent	Temp ^oC	Time	Results
1	2.0	--	THF-Ether	-10 to r.t	14 h	**137** recovered
2	2.0	--	THF-Ether	-10 to 50	24 h	**137** recovered
3	4.0	--	THF-Ether	-10 to r.t	14 h	**146** (27 %) + **137** (18%)
4	5.0	--	THF-Ether	-10 to 50	14 h	**146** (23 %) + **137** (19%)
5	6.0	--	THF-Ether	-10 to 85	12 h	complex mixture
6	3.0	3.0	THF	0 to r.t	6 h	complex mixture
7	6.0	6.0	THF	0 to r.t	6 h	complex mixture

We also tried saponification of the lactone to the corresponding hydroxyester **147**, but the silyloxypyranone **137** was extremely stable toward alkali conditions. Treatment of **137** with either methanolic sodium methoxide or methanolic potassium hydroxide returned only starting material (Scheme 61).

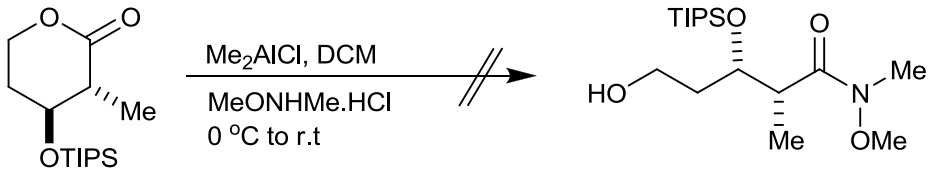


137 **147**

Scheme 61. Saponification efforts to form ester **147**

We next sought to install the C17-C21 hexadiene through the corresponding Weinreb amide. Most direct conversions of lactones or esters into the corresponding *N*-methoxy–*N*-methyl amides have employed trimethylaluminum-*N*,*O*-dimethylhydroxylamine hydrochloride (Me_3AlCl-MeONHMe·HCl).[91-93] However, this procedure has been found not efficient for bulky lactones.[94] Thus, an alternative methodology was reported by Nakata research group.[94] They found that sterically hindered lactones react smoothly with dimethylaluminum chloride and N,O-dimethylhydroxylamine hydrochloride (Me_2AlCl-MeONHMe·HCl) to furnish the desired Weinreb amides in excellent yield.

Lamentably in our case, the aminolysis reaction of silyloxypyranone **137** with Me_2AlCl (3 eq) and MeONHMe·HCl (3 eq) in DCM resulted only in recovered starting material. Leaving the reaction mixture for up to 24 h or up to 6 eq of dimethylhydroxylamine hydrochloride did not make any difference (Scheme 62).

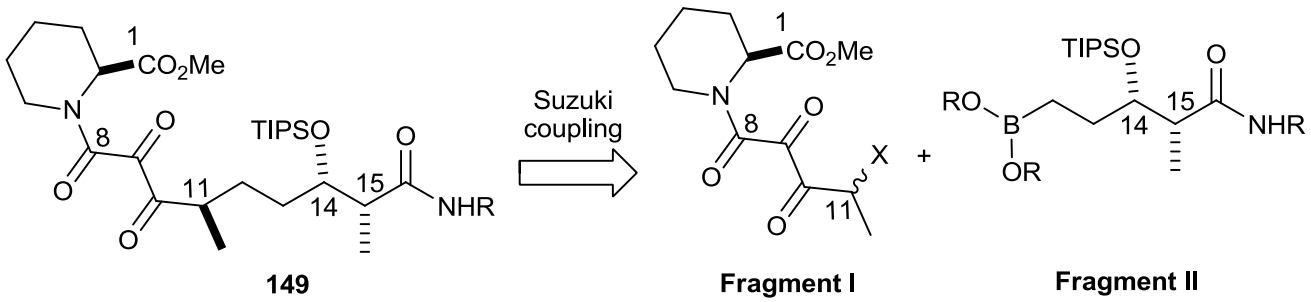


137 **148**

Scheme 62. Attempts to generate Weinreb amide **148**

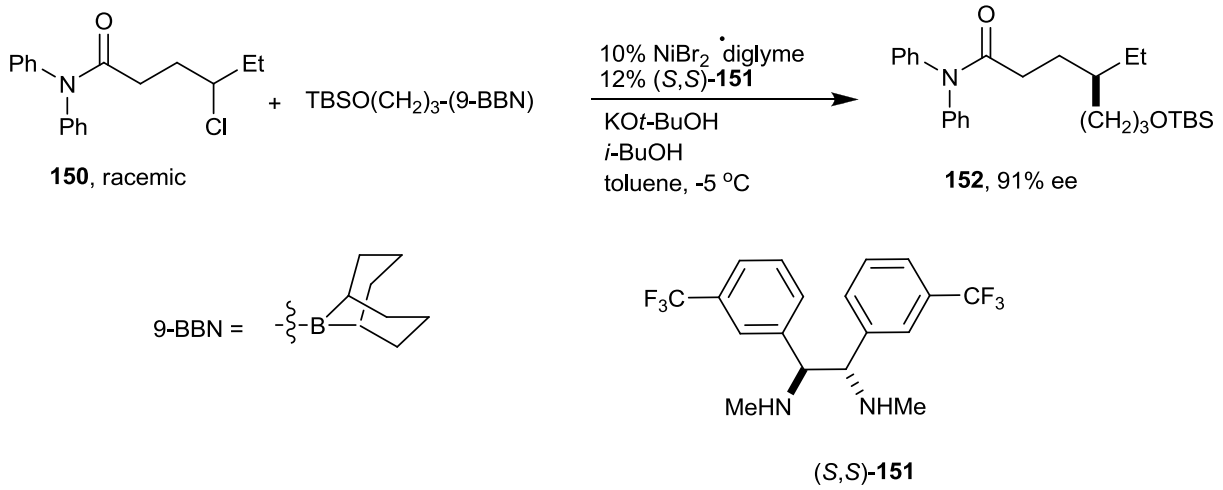
I. Asymmetric Suzuki Cross-Coupling Strategy to Construct the C1-C21 Fragment of Antascomicin B

Because of the aforementioned difficulties, we started to consider a fourth generation approach to the C1-C21 fragment of the macrolide. We proposed that the C1-C16 fragment could be assembled from tricarbonyl pipecolic carboxylate fragment **I** and boronate pentamide derivative fragment **II** by asymmetric Suzuki cross-coupling methodology (Scheme 63).



Scheme 63. Alternative synthesis to build C1-C16 fragment of antascomicin B

This idea was based on studies by Fu et al. of a nickel-catalyzed enantioselective Suzuki alkylation of racemic α-haloamides.[95] They established that $NiBr_2$·diglyme and (*S*,*S*)-diamine ligand **151** could catalyze cross-coupling of an γ-chloroamide **150** with $TBSO(CH_2)_3$-(9-BBN) to afford tertiary γ-alkylcarbonyl compound **152** with good enantioselectivity and yield (Scheme 64). Using the appropriate chiral catalyst we could potentially join the fragments, and install the C11-C14 *anti* stereorelationship. Fu's asymmetric Suzuki reaction has been applied to structurally simple molecules. It would represent a significant advance if we could apply Fu's strategy to the coupling of more complex compounds such fragments **I** and **II**.



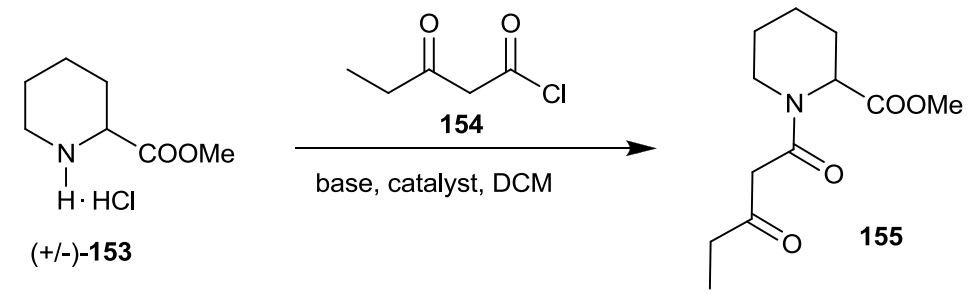
Scheme 64. Asymmetric Suzuki alkylation of γ-chloroamide **150**

1. Attempts to Synthesize the Vicinal Tricarbonyl Region of Antascomicin B *via* Amide Bond Formation

In order to establish the best reaction conditions to synthesize the vicinal diketo amide **155**, we started the synthesis using methyl ester **153** of the racemic mixture of the DL-pipecolic acid hydrochloride, which was prepared quantitatively from DL-pipecolic acid hydrochloride under standard conditions.[96] Then, acylation reaction of **153** with the corresponding oxopentanoyl chloride **154** in presence of base and catalyst was performed (Table 17).

The acylation reaction proved to be more problematic than we anticipated. First, standard acylation reaction conditions gave moderate yield of the desired diketo amide **155** (Table 17, entry 1-2). Second, silica gel flash chromatography was not an efficient technique to purify amide **155**. Proton NMR analysis always showed the presence of unidentifiable impurities. Furthermore, we were unable to scale the reaction even to 3.5 mmol. Attempting different reaction conditions, with or without catalyst, we recovered methyl ester **153** (Table 17, entry 3-5). Employing excess base, 2.0 eq of the acylating reagent, or heating the reaction mixture for long period of time did not make any difference (Table 17, entry 7). Treatment of **153** with 10 eq of dimethylformamide (DMF) and 3 eq of the Et_3N gave no reaction.[97] Heating the reaction mixture at 100 °C for two days gave the same result (Table 17, entry 8-9).

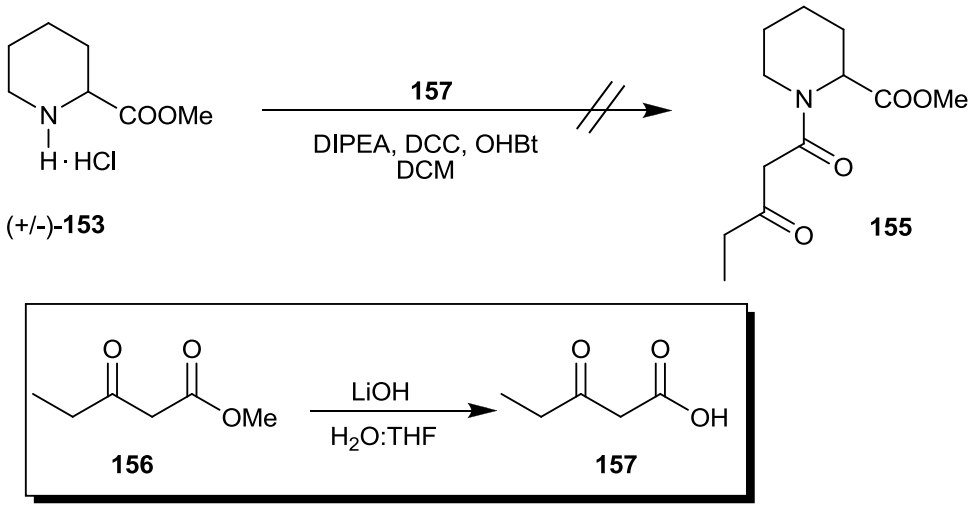
Table 17. Results of the acylation reaction of **153**



Entry	mmol	**154** (eq) / catalyst (eq)	Base (eq)	Conditions	Results
1	0.7	1.2 / no catalyst	TEA (1.2)	0 °C to r.t, 24 h	**155** (32 %), **153** (9 %)
2	0.7	1.2 / DMAP (1.1)	TEA (1.2)	0 °C to r.t, 24 h	**155** (35 %), **153** (12 %)
3	3.5	1.2 / no catalyst	TEA (1.2)	0 °C to r.t, 24 h	**153** (40 %)
4	3.5	1.5 / no catalyst	TEA (1.2)	0 °C to 70 °C, 36 h	**153** (52 %)
5	3.5	1.2 / DMAP (1.1)	TEA or DIPEA (1.2)	0 °C to 70 °C, 36 h	**153** recovered
6	0.7	1.2 / no catalyst	DIPEA (1.2)	0 °C to 70 °C, 36 h	**155** (< 5 %), **153** (52 %)
7	3.5	2.0 / no catalyst	TEA or DIPEA (4.0)	0 °C to 70 °C, 72 h	**153** recovered
8	0.7	1.0 / DMF (10.0)	TEA (3.0)	0 °C to r.t, 72 h	**153** recovered
9	0.7	1.0 / DMF (10.0)	TEA (3.0)	100 °C, 48 h	**155** (< 1%), **153** recovered

Looking forward to get better yield of the desired diketo amide **155**, we applied another typical process to form amide bonds, which is from the coupling of carboxylic acids and amines in presence of base and activating reagents, such as dicyclohexylcarbodiimide (DCC) and hydroxyl benzotriazole (HOBt).[6,26,98] Oxopentanoic acid **157** was prepared from the commercially available oxopentanoic ester **156**. Basic hydrolysis of **156** gave 82 % of the acid (Scheme 65, inset).

Unfortunately all the efforts to reach the desired oxoamide derivative **155** using this coupling protocol resulted in the formation of byproducts and the recovery of some of the starting amine **153** (Table 18, 1-5).

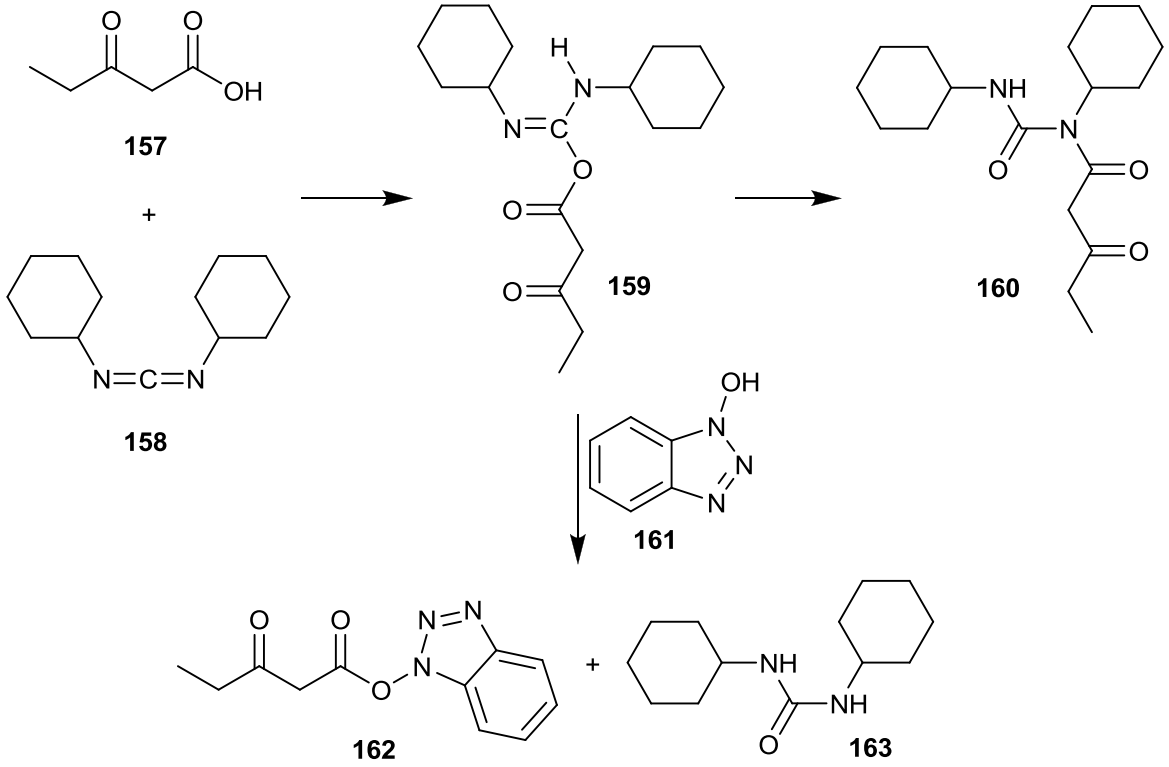


Scheme 65. Other efforts to prepare amide **155**

Table 18. Results of the acylation reaction attempts of amine **153** using activating reagents

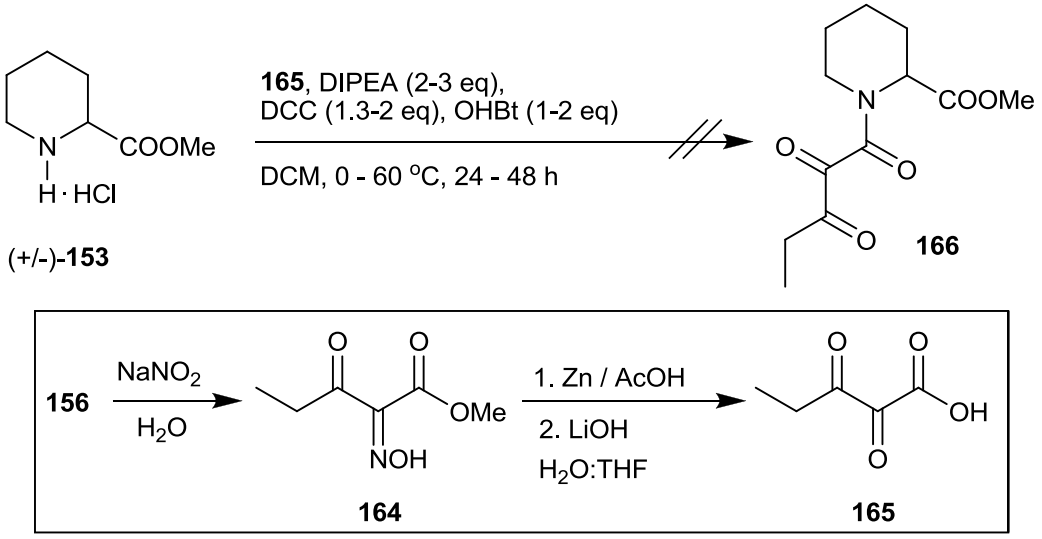
Entry	**157** (eq) / DCC (eq) / OHBt (eq)	mmol	DIPEA (eq)	Conditions	Results
1	1.0 / 1.3 / 1.0	0.7	2.0	0 °C to r.t, 24 h	**160** + **162** + **163** + **153** + complex mixture
2	1.5 / 1.5 / 1.5	0.7	3.0	0 °C to r.t, 24 h	**160** + **162** + **163** + **153** + complex mixture
3	1.0 / 1.3 / 1.0	0.7	2.0	60 °C, 48 h	**160** + **162** + **163** + **153** + complex mixture
4	1.5 / 1.5 / 1.5	0.35	2.0	0 °C to r.t, 72 h	**160** + **162** + **163** + **153** + complex mixture
5	3.0 / 3.0 / 3.0	0.7	6.0	r.t to 60 °C, 48 h	**160** + **162** + **163** + **153** + complex mixture

Although thin layer chromatography (TLC) of the crude reaction mixture showed many different spots, we were able to separate the more prominent spots by silica gel column chromatography. As a result, we obtained three fractions, and according with the ^{1}H-NMR data the first one corresponded to the mixture of dicyclohexylurea (DCU) **162** and N-acylurea **160**. The second fraction was a mixture of some DCU, N-acylurea and OBt ester **163** (Scheme 66) while the third fraction belongs to the not clean starting amine **153**. It is important to point out that the exactly same behavior of this acylation methodology was observed by varying the conditions and heating reaction at 60 ^{o}C for long periods of time (Table 18, entry 1-5).



Scheme 66. Generated products by coupling of DCC with acid **157**

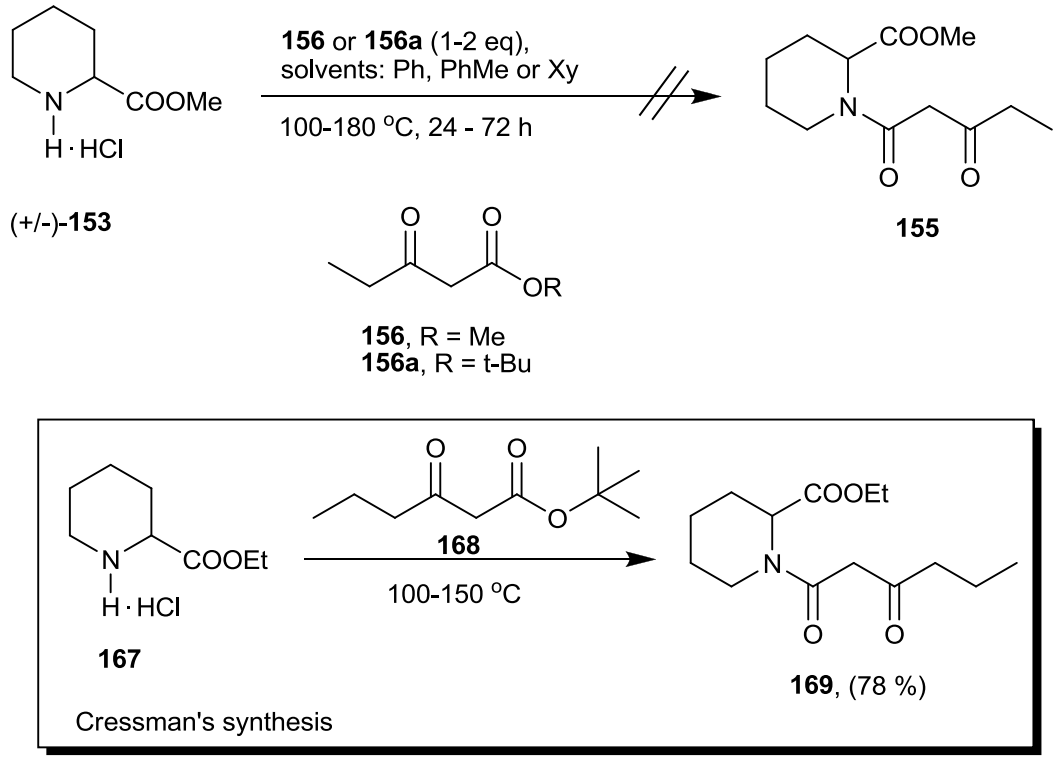
We also tried this method to couple amine **153** with the more electrophilic dioxopentanoic acid **165**. This acylating reagent was prepared from oxopentanoic ester **156**, which was oxidated with $NaNO_2$ to afford the oxime **164**. Subsequent deoximation employing Zn/AcOH, followed by basic hydrolysis afforded 85 % yield of the desired dioxo acid **165** (Scheme 67, inset). After attempting different several reaction conditions the desired dioxyamide **166** was not observed. Instead DCU and the corresponding N-acylurea byproducts were observed in the ^{1}H-NMR spectrum of the crude mixture.



Scheme 67. Efforts to make dioxoamide **166**

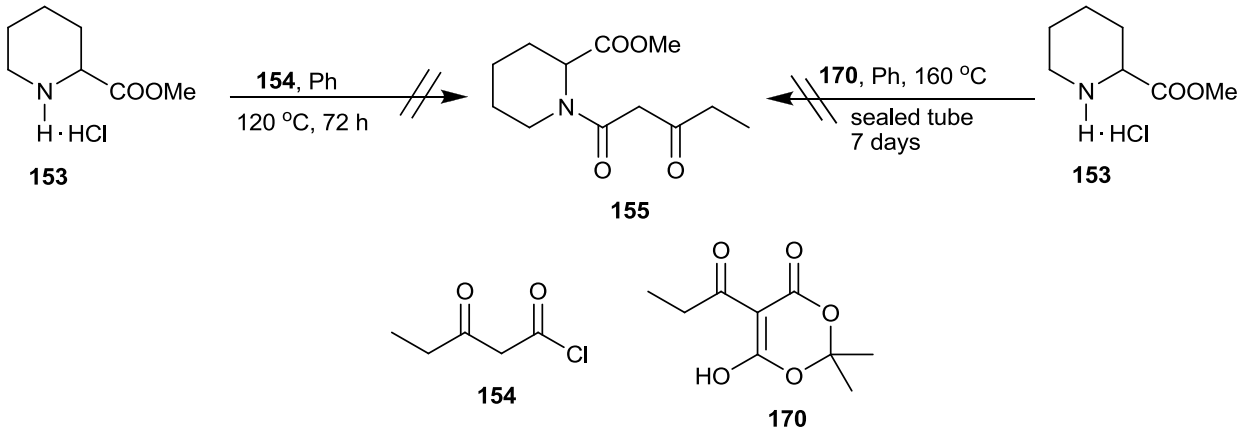
2. Efforts to build the Vicinal Tricarbonyl Region *via* Aminolysis

It has been demonstrated that the heating of a mixture of an amine with carboxylic acids or esters, respectively, is another method for the preparation of amides.[99] For example, Cressman synthesized β-keto amide derivative **169** by the pyrolysis reaction of β-keto ester **168** and ethylpipecolinate **167** (Scheme 68, inset).[100] Thus, we were expected that aminolysis of either oxopentanoic ester **156** or **156a** with amino ester **153** would furnish the corresponding wanted oxoamide **155** (Scheme 68). However, the amino ester was inert to the aminolysis process. Heating the reaction mixture in presence of high boiling point solvents for 72 h returned only starting amine **153**.



Scheme 68. Other efforts to prepare amide **155**

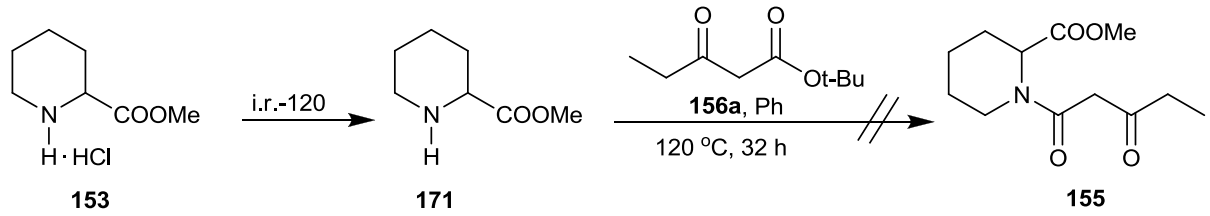
In addition, setting the pyrolysis of **153** with oxopentanoic acid chloride **154** for 3 days at 120 °C or with propionyl dioxinone **170** in a sealed tube for 7 days at 160 °C did not produce the desired **155** amide. In both cases **153** was completely recovered (Scheme 69).



Scheme 69. Other aminolysis attempts to get amide **155**

Due to the close similarities between Crossman's pyrolysis and ours, it is important to mention that most of the aminolysis experiments described above were repeated several times, and in our hands the formation of the product was never observed; instead we always recovered the starting amine **153**. These unsuccessful results might be attributed to the lack of nucleophilicity of **153** which is a methyl pipecolinate hydrochloride salt derivative.

In order to make free amino ester acid **171**, the hydrochloric amino ester salt **153** was dissolved in water and passed through a column of amberlite i.r.-120.[101] The residue obtained after rotatory evaporation of the water was crystallized from methanol-ether (90:10) to give 70 % of **171**. Pyrolysis of **171** with oxopentanoic ester **156a** for 32 h at 120 ^{o}C did not produce the expected oxoamide **155**, and only the starting amino ester **171** was recovered (Scheme 70).



153 **171** **155**

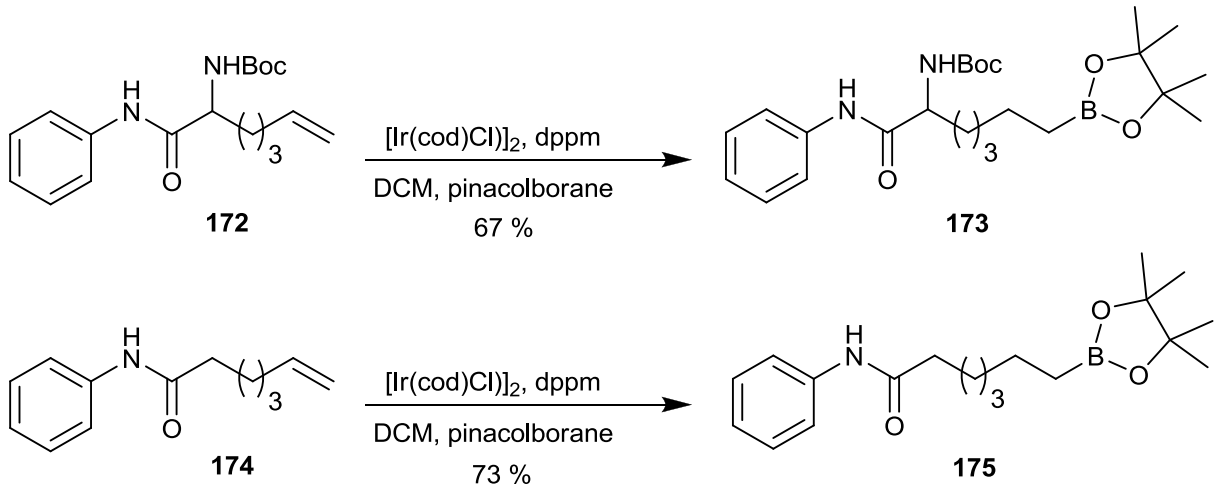
Scheme 70. Pyrolysis attempt of free amino ester **171** to get amide **155**

Although the acylation reaction of **153** generated the desired oxopiperidine derivative **155** in modest yield (35 %) (cf. Table 18, entry 2), we decided to stay with it and continue with the synthesis of fragment **II**, the pinacolborane complex **176**, and therefore try the Suzuki coupling strategy to construct the desired fragment of the natural product.

3. Attempts to Synthesize Borane-pentamide 176 *via* Iridium-Catalyzed Hydroboration

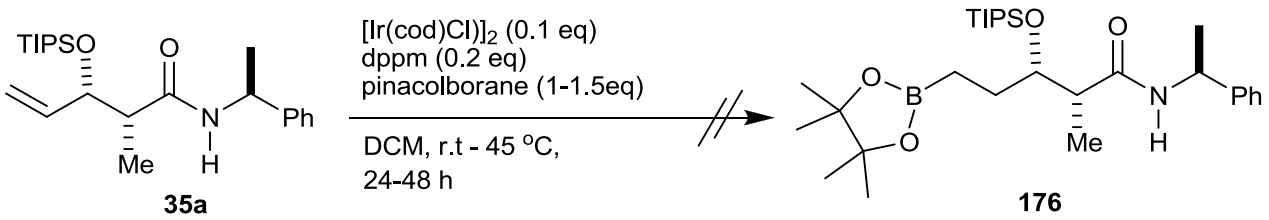
The addition of H-B reagents to alkenes and alkynes in the absence of catalysis requires high temperatures and long reaction times. On the other hand, catalyzed hydroboration can be carried out at room temperature and can also enhance the chemo-, regio- and stereoselectivities of the process.[102]

Miyaura et al.[103] has demonstrated that $[Ir(cod)Cl]_2$/dppm and $[Ir(cod)Cl]_2$/dppe complexes are extraordinary catalysts for hydroboration of terminal and internal olefins containing an aliphatic or aromatic substituent on the vinylic carbon with pinacolborane. This iridium-catalyzed hydroboration with pinacolborane methodology was applied to different alkenyl amides to prepare the corresponding boronic esters in good yields (Scheme 71).[104]



Scheme 71. Iridium-catalyzed hydroboration reported by Miyata et al.

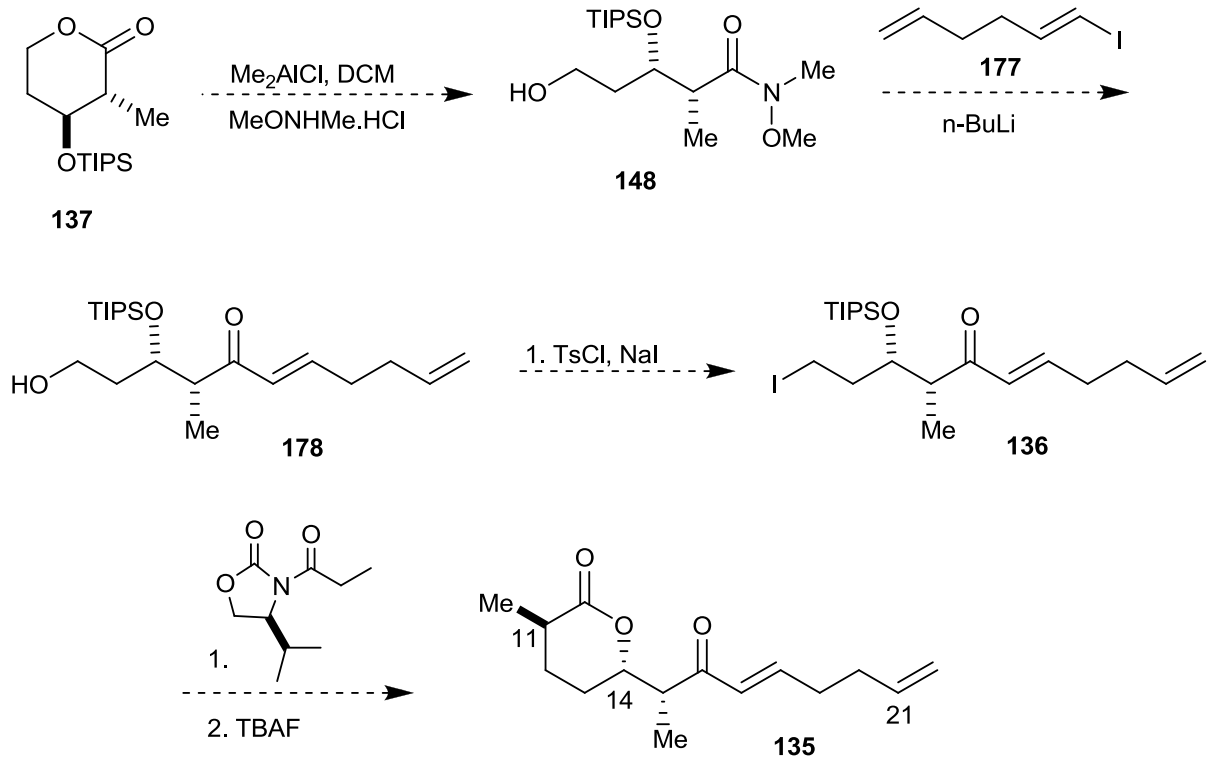
Thus, we applied this hydroboration protocol to our substrate, the pentenamide **35a**. The reaction was carried out at room temperature employing 1.5 eq of pinacolborane, 0.1 eq of $[Ir(cod)Cl]_2$ and 0.2 eq of dppm as a ligand (Scheme 72). Unfortunately, this process did not work for our amide substrate. All the efforts to get the desired alkylborane **176** ended in the recovering of ~ 12 % of pinacolborane, ~ 32 % of impure starting material and some decomposition products.



Scheme 72. Attempts to get amide **176** *via* iridium catalyzed hydroboration

J. Future Work

Due to the unsatisfactory results making fragments **I** and **II**, we propose other alternatives to construct the C10-C21 unit of the natural product. First, there are multiple reports that show the ring-opening Weinreb amide formation of lactones that are structurally similar to our lactone **137**.[96,104, 105] Thus, we would like to explore more this reaction and we also believe that it is possible to generate a reactive amide **148**. Second, we plan to set the C17-C21 hexadiene unit by nucleophilic addition of the lithium anion derived from iodide **177** to Weinreb amide **148**. Iodide **177** can be obtained in 4 steps from 1,5-pentanediol. Following standard protocols we expected to generate the iodo undecadiene **136**. Third, apply Evan's alkylation reaction to **136** to install the desired C11 stereorelationship (Scheme 73).



Scheme 73. Proposed synthetic route to construct C10-C21 fragment of antascomicin B

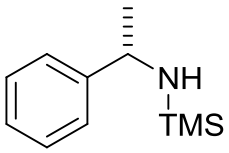
III. EXPERIMENTAL SECTION

General Information

All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques. All commercially available compounds were purchased from Alfa Aesar Organics, Acros Organics and Oakwood Products and used as received unless otherwise specified. Diethyl ether (Et_2O), tetrahydrofurane (THF) and dichloromethane (DCM) were purified over alumina using Solv-Tek ST-002 solvent purification system. Toluene and benzene were purified under CaH_2, and methanol was drying using molecular sieves (3 Å). Compound purification was performed by flash chromatography with the indicated solvents using 230x400 mesh, 60 Å porosity purchased from Sorbent Technologies, and by recrystallization from indicated solvents. Melting points were acquired on Fisher-Johns 352 melting point apparatus. All ^{1}H and ^{13}C NMR spectra were obtained on a 400 MHz Bruker Avance spectrometer. X-ray crystallography was carried out on a Bruker SMART X2S.

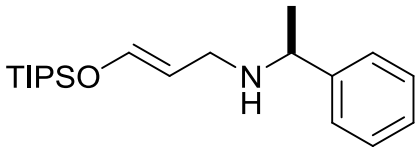
Extractive work-up is defined as extraction of the reaction mixture and the indicated aqueous solution three times with Et_2O or DCM and washing of the combined organic extracts with saturated NaCl solution. The extracts are drying over anhydrous MgSO4 and concentrated in vacuo.

Trimethylsilylamine 72



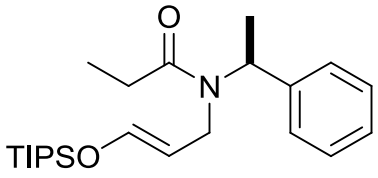
To a hexane solution of (*S*)-α-methylbenzylamine (**33**) (6.0 g, 50.0 mmol) was added TEA (10.5 mL, 74.3 mmol). The reaction mixture was heated under reflux for 15 min and then freshly distillated TMSCl (9.50 mL, 74.3 mmol) was added. After the mixture cooled to rt, stirring was continued for 24 h. The precipitated triethylammonium chloride was removed by filtration and washed with hexane. The solution was concentrated in vacuo. The residual colorless liquid was distilled in vacuo (bp.75 ^{o}C, 0.9 mm Hg) to give 6.7 g (28.9 mmol, 70 %) of silylamine **72**. ^{1}H NMR (400 MHz, CDCl3) δ 0.41 (s, 9H), 0.83 (br. s, 1H), 1.39 (d, J = 6.6 Hz, 3H), 4.06 (q, J = 6.6 Hz, 1H), 7.29-7.32 (m, 5H).

Silyloxyamine 73



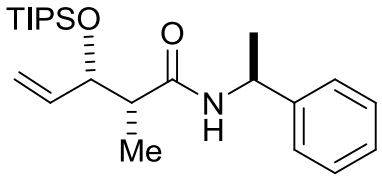
To a solution of (*S*)-α-methylbenzylamine **33** (1.5 g, 12.3 mmol) and TMSOTf (2.24 mL, 12.3 mmol) in ether (30 mL) at 0 ^{o}C was added DBU (1.84 mL, 12.3 mmol) dropwise. After stirring for 1 h, a solution of acrolein (1.38 mL, 12.3 mmol) and TIPSOTf (3.33 mL, 12.3 mmol) in ether (15 mL) was added and stirred for 1 h at 0 ^{o}C. The mixture was allowed to warm to rt and stirred for 6 h. The crude product was isolated by extractive work-up with Et_2O and purified by flash chromatography with 15/85 ethyl acetate/hexane to give the silyloxyamine **73** as clear yellow oil (1.82 g, 44 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 21H), 1.35 (dd, J= 6.55, J= 2.98, 3H), 3.81-3.88 (m, 1H), 5.08-5.18 (m, 1H), 6.39 (d, J= 14.87 Hz, 1H), 7.28-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.00, 17.75, 24.29, 44.84, 56.98, 108.67, 126.66, 128.42, 143.01, 145.45.

Silyloxyallyl-propanamide 34



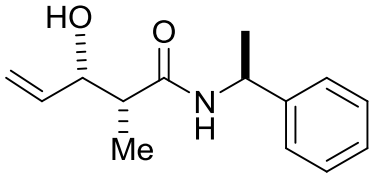
To a solution of amine **73** (6.0 g, 17.96 mmol) in DCM (30 mL) at 0 ^{o}C was added the Et_3N (3.00 mL, 21.55 mmol) and propanoyl chloride (1.87 mL, 21.55 mmol) dropwise. The mixture was allowed to warm to rt and stirred for 30 min. The crude product was isolated by extractive work-up with DCM, and purified by flash chromatography with 2/98 ethyl acetate/hexane to give propanamide **34** as colorless oil (6.7 g, 96 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19-1.04 (m, 24H), 1.53 (d, J = 7.03 Hz, 3H), 2.41 (q, J = 4.78 Hz, 2H), 3.46 (dd, J = 6.65, J = 16.73, 1H), 4.76 (m, 1H), 6.06 (dd, J = 13.99, 1H), 6.27 (d, J =11.92, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.52, 11.92, 16.89, 17.66, 26.99, 41.63, 51.00, 107.73, 122.20, 127.54, 128.36, 128.61, 141.30, 143.46, 174.20. Elemental Analysis: calcd for $C_{23}H_{39}NO_2Si$: C 70.90, H 10.09, N 3.59, found C 70.15, H 9.92, N 3.53

***β*-silyloxy amide 35a**



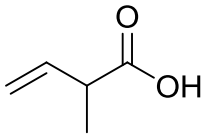
Amide **34** (9.6 g, 24.6 mmol) was treated with LHMDS (54.6 mL, 0.9 M solution in hexane, 49.12 mmol) in toluene (200 mL) at -78 ^{o}C. After stirring 30 min the reaction mixture was allowed to warm to rt, sealed in a pressure tube and heated at 120 ^{o}C for 6 h. The crude product was isolated by extractive work-up with Et_2O to give 82 % of the diastereomeric amide mixture **35**. The major diastereomer **35a** was separated by flash column chromatography with 2/98 ethyl acetate/hexane as a white solid (7.80 g, 7.7:1.0 dr, mp. 87 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11-1.05 (m, 24H), 1.47 (d, J = 6.90, 3H), 2.63 (m, 1H), 4.27 (m, 1H), 5.13 (m, 1H), 5.23 (m, 2H), 5.86 (m, 1H), 7.26-7.04 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.16, 12.91, 18.02, 21.83, 45.95, 48.45, 77.05, 117.20, 126.26, 127.10, 128.50, 136.20, 171.80. Elemental Analysis: calcd for $C_{23}H_{39}NO_2Si$: C 70.90, H 10.09, N 3.59, found C 70.92, H 10.15, N 3.59

Hydroxy pentenamide 75



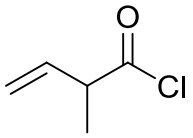
β-Silyloxy amide **35a** (1.8 g, 4.61 mmol) was treated with 36 mL of a 5:95 solution of hydrofluoric acid and acetonitrile. The reaction mixture was stirred for 30 min, and then 2 mL of 1M HCl was added. The crude product was isolated by extractive work-up with Et_2O. The hydroxy pentenamide **75** was formed as a white solid. (0.97 g, 91 %, mp. 144 ^oC). ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, J = 6.44 Hz, 3H),1.49 (d, J = 6.48 Hz, 3H), 2.43 (m, 1H), 3.61 (br. s, OH), 4.43 (t, J = 6.88 Hz, 1H), 5.14 (t, J = 6.88 Hz, 1H), 5.21 (app. d, J = 10.44 Hz, 1H), 5.32 (app. d, J = 17.20 Hz, 1H), 5.82 (m, 1H), 7.29-7.33 (m, 5H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.59, 21.97, 44.70, 48.65, 73.38, 116.42, 126.01, 127.35, 128.69, 137.25, 174.78. Elemental Analysis: calcd for $C_{14}H_{19}NO_2$: C 72.07, H 8.21, N 6.00, found C 71.56, H 8.21, N 5.97

(+/-) - Butenoic acid 93



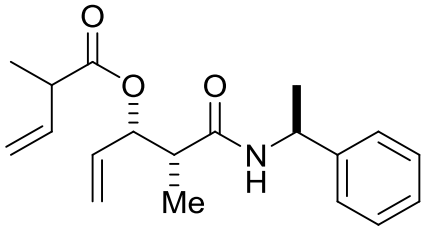
n-Butyllithium (35.9 mL, 2.87 M in hexane, 104.88 mmol) was added to a solution of diisopropylamine (15 mL, 109.87 mmol) in THF at -78 ^oC. A pale yellow solution was obtained after the stirred the mixture for 20 min under N_2 atmosphere. Then, a solution of tiglic acid (5.0 g, 49.9 mmol) in 30 mL of THF was added over a period of 30 min. The bath temperature was keeping between -40 ^oC to – 20 ^oC during the addition. The resulting yellow mixture was stirred at rt for 1h and then poured into stirred ice-cold solution of 3 M HCl (120 mL). The organic layer was separated, and the aqueous layer was saturated with solid NaCl and extracted with ethyl acetate. The yellow crude oil was purified by reduced pressure distillation to generate the pure acid as colorless oil (3.8 g, 80 %, bp. 85 ^oC). ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 7.08 Hz, 3H), 3.19 (q, J = 7.16 Hz, 1H), 5.17 (app. tdt, J = 1.25, 1.13, 11.29 Hz, 2H), 5.94 (tt, J = 7.2, 10.08 Hz, 1H), 11.67 (br. s, OH), ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.45, 43.47, 116.47, 136.40, 181.14.

(+/-) – Butenoyl chloride 92



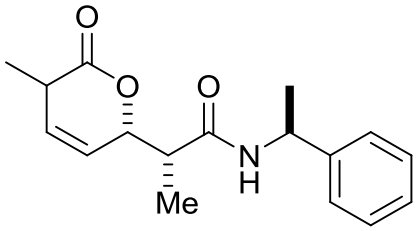
The butenoic acid **93** (2.0 g, 19.98 mmol) was placed in a dry flask under N_2 atmosphere and cooled at 0 ^{o}C. Then, freshly distilled oxalyl chloride (1.9 mL, 23.97 mmol) was added and the mixture was stirred overnight, allowing the ice bath to warm up to r.t. The acid chloride **92** was formed as pale yellow oil (1.7 g, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, J = 7.20 Hz, 3H), 3.56 (q, J = 7.20 Hz, 1H), 5.31 (m, 2H), 5.91 (tt, J = 7.2, 10.0 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.45, 48.47, 115.57, 137.40, 173.04.

Allyl ester 36



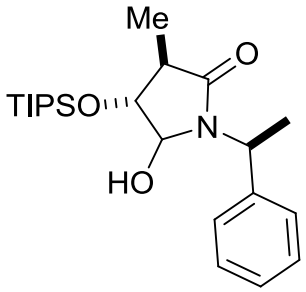
To a solution of butenoic acid **93** (45 mg, 0.45 mmol) in DCM (10 mL) at 0 ^{o}C was added DMAP (27.5 mg, 0.22 mmol), the hydroxyl pentenamide **75** (0.11 mg, 0.49 mmol) and DCC (0.10 g, 0.49 mmol). The mixture was allowed to warm to rt and stirred for 72 h. The resulting mixture was filtered and washed with 1M HCl. The crude product was isolated by extractive work-up with Et_2O. The crude was purified by flash chromatography with 10/90 ethyl acetate/hexane to give allyl ester **36** as a white solid (80 mg, 57 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (d, J = 7.0 Hz, 3H), 1.28 (d, J = 7.0 Hz, 3H), 1.49 (d, J = 6.88 Hz, 3H), 2.51 (quint, J = 6.96, 13.30 Hz, 1H), 3.16 (quint, J = 7.18, 14.12 Hz, 1H), 5.08 (m, 1H), 5.15 (m, 1H), 5.27 (m, 2H), 5.38 (m, 1H), 5.83 (m, 1H), 5.87 (m, 1H), 5.91 (m, 1H), 7.31-7.37 (m, 5H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.24, 16.53, 21.52, 43.93, 44.87, 48.64, 76.12, 116.47, 118.66, 126.21, 128.70, 128.61, 133.12, 136.87, 142.97, 171.19, 172.92.

δ-Lactone 37



In a pressure vessel was mixed allyl ester **36** (0.1 g, 0.3174 mmol), diallyl malonate **107**, and 12 % mol of Grubbs' II in toluene (100 mL). The reaction mixture was sealed and heated for 2 h at 80 ^{o}C, then cooled to room temperature. The solvent was removed and the residue was purified by flash chromatography with 10/90 ethyl acetate/hexane to yield the cyclized product **37** (68 mg, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, J = 6.80 Hz, 3H), 1.24 (m, 1H), 1.35 (d, J = 7.20 Hz, 3H), 1.42 (d, J = 6.80 Hz, 3H), 2.61 (m, 1H), 5.07 (m, 1H), 5.79 (m, 1H), 5.87 (m, 1H), 6.44 (m, 1H), 7.10 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.85, 17.16, 21.98, 29.68, 45.32, 48.90, 80.19, 124.14, 126.07, 127.31, 128.65, 129.76, 143.01, 171.15, 172.26.

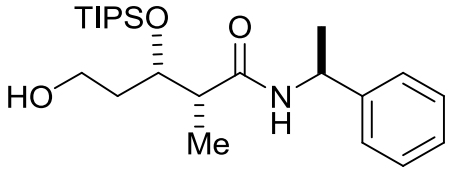
Hydroxy lactam 132



The β-silyloxy amide **35a** (0.26 g, 0.67 mmol) was taken up in 8 mL of DCM:MeOH (1:1) followed by the addition of pyridine (0.53 g, 6.67 mmol) and SUDAN III (indicator, 1 mg) at rt. The solution was cooled to -78 ^{o}C and exposed to a stream O_3 until a light yellow color persisted. The reaction mixture was stirred until the SM was totally consumed based on TLC analysis. The flask was flushed with N_2, and Me_2S (2.07 g, 33.36 mmol) was slowly added and allowed to warm up to rt over a 4 h period. After stirring for 1 h at rt, Et_2O (20 mL) was added and the mixture extracted with a saturated solution of $CuSO_4$ and then brine. The organic layer was concentrated and the crude product was purified by silica gel column chromatography (10/90 EtOAc/hexane). The lactam **132** was isolated as light yellow oil (0.18 g, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (m, 18H), 1.24 (m, 3H), 1.33 (d, J =

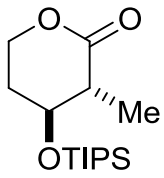
7.60 Hz, 3H), 1.65 (d, J = 7.20 Hz, 3H), 2.37 (q, J = 7.41 Hz, 1H), 3.86 (app. s, 1H), 4.74 (app. s, 1H), 5.39 (q, J = 7.08 Hz, 1H), 7.29–7.35 (m, 5H); ^{13}C NMR (100 MHz, CD_6CO) δ 11.70, 14.70, 17.26, 18.27, 46.65, 49.10, 79.48, 87.52, 126.98, 128.11, 141.08, 175.52.

Hydroxyamide 138



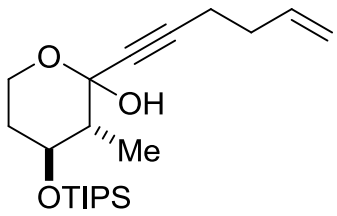
To a stirred solution of cyclohexene (6.56 g, 79.97 mmol) in ether (40 mL) at 0 ^{o}C was added $BH_3.SMe_2$ (4.0 mL, 10 M in THF, 45.01 mmol) through an addition funnel. The mixture was stirred for 3 h at 0 ^{o}C, during which white crystals precipitated. A THF solution of the *β*-silyloxy amide **35a** (4.0 g, 10.26 mmol) was added to the mixture and stirred until a clear solution was observed. A 3 M solution of NaOH (10.24 mL, 30.79 mmol) was added slowly, followed by the addition of MeOH (4 mL) and the slow addition of H_2O_2 (1.04 mL, 35 % wt in water, 12.32 mmol). The reaction mixture was stirred at rt for 3 h and then heated under reflux for 1 h at 40 ^{o}C. Extractive work-up with Et_2O yielded a white oil which was purified by silica gel flash chromatography using MeOH/DCM (5 / 95). The purified hydroxyamide **138** was a colorless viscous oil (3.01 g, 72 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (m, 18H), 1.07 (m, 3H), 1.12 (d, J = 7.20 Hz, 3H), 1.45 (d, J = 6.80 Hz, 3H), 1.83 (m, 2H), 2.64 (m, 1H), 3.79 (m, 2H), 4.12 (m, 1H), 5.11 (quint, J = 7.2 Hz, 1H), 7.29–7.32 (m, 5H), ^{13}C NMR (100 MHz, CD_6CO) δ 12.64, 13.26, 18.14, 21.66, 35.97, 45.92, 48.68, 59.31, 72.97, 126.27, 127.22, 128.54, 143.36, 172.89. Elemental Analysis: calcd for $C_{23}H_{41}NO_3Si$: C 67.76, H 10.14, N 3.44, found C 66.99, H 10.07, N 3.22

Silyloxypyranone 137



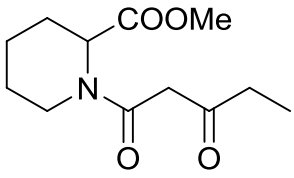
A mixture of hydroxyamide **138** (2.50 g, 6.13 mmol) and p-TsOH (1.28 g, 6.74 mmol) in benzene was heated under reflux for 15 min. After concentration in vacuo, silica gel column chromatography (EtOAc/hexane 5/95) of the residue provided product **137** as dense colorless oil (0.84 g, 48 %) and recovered **138** (0.29 g, 32 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (m, 18H), 1.08 (m, 3H), 1.34 (d, J = 7.40 Hz, 3H), 1.84 (m, 1H), 2.13 (m, 1H), 2.65 (m, 1H), 4.01 (dd, J = 4.89, 8.53, 1H), 4.29 (dt, J = 4.71, 4.71, 11.17, 1H), 4.59 (td, J = 3.70, 10.73, 10.92 Hz, 1H), 7.29–7.32 (m, 5H), ^{13}C NMR (100 MHz, CD_6CO) δ 12.29, 15.72, 18.00, 29.68, 44.93, 64.82, 70.19, 173.89. Elemental Analysis: calcd for $C_{15}H_{30}O_3Si$: C 62.89, H 10.59, found C 62.93, H 10.54

Pyranol 146



Allyl magnesium bromide (1M in Et_2O, 41.88 mL, 40 mmol) was cooled to –10 ^{o}C and propargyl chloride (9.3 M in toluene, 2.25 mL, 20 mmol) was added dropwise. The solution was stirred for 5 h at rt, during which time it became heterogeneous. The mixture was cooled to 0 ^{o}C and silyloxypyranone **137** (150 mg, 0.52 mmol) was added dropwise. The mixture was allowed to stir at rt for 14 h and the crude product was isolated by extractive work-up with Et_2O. The concentrated residue was partially purified by silica gel column chromatography using (EtOAc/hexanes, 10/90), (51 mg, 27 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (m, 18H), 1.08 (m, 3H), 1.25 (d, J = 7.10 Hz, 3H), 1.54 (m, 1H), 1.71 (m, 1H), 1.99 (m, 1H), 2.30 (m, 2H), 2.32 (m, 2H), 3.73 (m, 1H), 4.03 (m, 1H), 4.29 (m, 1H), 5.04 (m, 2H), 5.85 (m, 1H), ^{13}C NMR (100 MHz, CD_6CO) δ 1.00, 12.18, 13.36, 17.98, 29.69, 32.53, 44.57, 57.07, 72.10, 79.71, 84.47, 95.28, 115.67, 136.78. δ 1.14 (t, J = 7.20, 3H), 1.84 (s, N-OH), 2.83 (q, J = 7.20, 2H), 3.91 (s, 3H), ^{13}C NMR (400 MHz, CD_6CO) δ 12.94, 31.54, 51.26, 137.74, 144.63, 161.67.

Oxopentanoyl amide 161



A mixture of piperidine ester **153** (100 mg, 0.70 mmol), oxopentanoyl chloride **154** (112 mg, 0.84 mmol) and NEt_3 (0.12 mL, 0.84 mmol) in DCM (15 mL) was heated under reflux for 24 h. The concentrated residue was purified by silica gel column chromatography (EtOAc/hexanes, 25/75) to give a colorless oil of amide **155** (54 mg, 32 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, J = 7.22 Hz, 3H), 1.30 (m, 1H), 1.46 (ddd, J = 3.83, 7.40, 11.29 Hz, 1H), 1.61 (m, 1H), 1.65 (m, 1H), 1.72 (m, 1H), 2.37 (m, 1H), 2.60 (qd, J = 2.26, 7.28, 7.28, 7.28 Hz, 2H), 3.22 (td, J = 2.89, 13.05, 13.05 Hz, 2H), 3.58 (s, 2H), 3.75 (s, 3H), 5.36 (d, J = 5.52 Hz, 1H), ^{13}C NMR (100 MHz, CD_6CO) δ 7.55, 20.77, 25.13, 27.11, 35.94, 44.30, 49.38, 52.05, 52.27, 166.20, 171.44, 205.08.

IV BIBLIOGRAPHIC REFERENCES

1. Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T., Structure of FK506, a novel immunosuppressant isolated from Streptomyces. *J. Am. Chem. Soc.* **1987,** *109*, 5031-3.

2. Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G., Chemistry of tricarbonyl hemiketals and application of Evans technology to the total synthesis of the immunosuppressant (-)-FK-506. *J. Am. Chem. Soc.* **1990,** *112*, 2998-3017.

3. Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K., A Total Synthesis of FK-506. *J. Org. Chem.* **1996,** *61*, 6856-6872.

4. Vezina, C.; Kudelski, A.; Sehgal, S. N., Rapamycin (AY-22,989), a new antifungal antibiotic. I. Taxonomy of the producing streptomycete and isolation of the active principle. *J. Antibiot.* **1975,** *28*, 721-6.

5. Sehgal, S. N.; Baker, H.; Vezina, C., Rapamycin (AY-22,989), a new antifungal antibiotic. II. Fermentation, isolation and characterization. *J Antibiot (Tokyo)* **1975,** *28*, 727-32.

6. Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K., Total synthesis of rapamycin. *Chem.--Eur. J.* **1995,** *1*, 318-33.

7. Takahashi, N. In *Mode of action of FK506 and rapamycin*2002 Academic Press; pp 577-621.

8. Hamilton, G. S.; Steiner, J. P., Immunophilins: Beyond Immunosuppression. *J. Med. Chem.* **1998,** *41*, 5119-5143.

9. Van, D. G. D.; Standaert, R. F.; Schreiber, S. L.; Clardy, J., Atomic structure of the rapamycin human immunophilin FKBP-12 complex. *J. Am. Chem. Soc.* **1991,** *113*, 7433-4.

10. Harding, M. W.; Galat, A.; Uehling, D. E.; Schreiber, S. L., A receptor for the immunosuppressant FK506 is a cis-trans peptidyl-prolyl isomerase. *Nature (London)* **1989,** *341*, 758-60.

11. Fretz, H.; Albers, M. W.; Galat, A.; Standaert, R. F.; Lane, W. S.; Burakoff, S. J.; Bierer, B. E.; Schreiber, S. L., Rapamycin and FK506 binding proteins (immunophilins). *J. Am. Chem. Soc.* **1991,** *113*, 1409-11.

12. Sehgal, S. N.; Molnar-Kimber, K.; Ocain, T. D.; Weichman, B. M., Rapamycin: a novel immunosuppressive macrolide. *Med. Res. Rev.* **1994,** *14*, 1-22.

13. Liu, J.; Farmer, J. D., Jr.; Lane, W. S.; Friedman, J.; Weissman, I.; Schreiber, S. L., Calcineurin is a common target of cyclophilin-cyclosporin A and FKBP-FK506 complexes. *Cell (Cambridge, Mass.)* **1991,** *66*, 807-15.

14. Takahashi, N.; Hayano, T.; Suzuki, M., Peptidyl-prolyl cis-trans isomerase is the cyclosporin A-binding protein cyclophilin. *Nature* **1989,** *337*, 473-5.

15. Schreiber, S. L.; Crabtree, G. R., The mechanism of action of cyclosporin A and FK506. *Immunol. Today* **1992,** *13*, 136-42.

16. Schreiber, S. L., Chemistry and biology of the immunophilins and their immunosuppressive ligands. *Science (Washington, D. C., 1883-)* **1991,** *251*, 283-7.

17. Brown, E. J.; Albers, M. W.; Shin, T. B.; Ichikawa, K.; Keith, C. T.; Lane, W. S.; Schreiber, S. L., A mammalian protein targeted by G1-arresting rapamycin-receptor complex. *Nature* **1994,** *369*, 756-8.

18. Sabers, C. J.; Martin, M. M.; Brunn, G. J.; Williams, J. M.; Dumont, F. J.; Wiederrecht, G.; Abraham, R. T., Isolation of a protein target of the FKBP12-rapamycin complex in mammalian cells. *J. Biol. Chem.* **1995,** *270*, 815-22.

19. Bierer, B. E.; Somers, P. K.; Wandless, T. J.; Burakoff, S. J.; Schreiber, S. L., Probing immunosuppressant action with a nonnatural immunophilin ligand. *Science (Washington, D. C., 1883-)* **1990,** *250*, 556-9.

20. Choi, J.; Chen, J.; Schreiber, S. L.; Clardy, J., Structure of the FKBP12-rapamycin complex interacting with the binding domain of human FRAP. *Science (Washington, D. C.)* **1996,** *273*, 239-242.

21. Maddess, M. L.; Tackett, M. N.; Ley, S. V., Total synthesis studies on macrocyclic pipecolic acid natural products: FK506, the antascomicins and rapamycin. *Prog Drug Res* **2008,** *66*, 13, 15-186.

22. Fehr, T.; Sanglier, J.-J.; Schuler, W.; Gschwind, L.; Ponelle, M.; Schilling, W.; Wioland, C., Novel FKBP12 binding compounds from a Micromonospora strain. *J. Antibiot.* **1996,** *49*, 230-3.

23. Steiner, J. P.; Dawson, T. M.; Fotuhi, M.; Glatt, C. E.; Snowman, A. M.; Cohen, N.; Snyder, S. H., High brain densities of the immunophilin FKBP colocalized with calcineurin. *Nature* **1992,** *358*, 584-7.

24. Hamilton, G. S.; Wu, Y.-Q.; Limburg, D. C.; Wilkinson, D. E.; Vaal, M. J.; Li, J.-H.; Thomas, C.; Huang, W.; Sauer, H.; Ross, D. T.; Soni, R.; Chen, Y.; Guo, H.; Howorth, P.; Valentine, H.; Liang, S.; Spicer, D.; Fuller, M.; Steiner, J. P., Synthesis of N-Glyoxyl Prolyl and Pipecolyl Amides and Thioesters and Evaluation of Their In Vitro and In Vivo Nerve Regenerative Effects. *J. Med. Chem.* **2002,** *45*, 3549-3557.

25. Brittain, D. E. A.; Griffiths-Jones, C. M.; Linder, M. R.; Smith, M. D.; McCusker, C.; Barlow, J. S.; Akiyama, R.; Yasuda, K.; Ley, S. V., Total synthesis of antascomicin B. *Angew. Chem., Int. Ed.* **2005,** *44*, 2732-2737.

26. Chakraborty, T. K.; Mohan, B. K., Studies directed towards the synthesis of antascomicin A: stereoselective synthesis of the C1-C21 fragment of the molecule. *Tetrahedron Lett.* **2006,** *47*, 4999-5002.

27. Chakraborty, T. K.; Mohan, B. K.; Sreekanth, M., Studies directed towards the synthesis of antascomicin A: stereoselective synthesis of the C22-C34 fragment of the molecule. *Tetrahedron Lett.* **2006,** *47*, 5003-5005.

28. Fuwa, H.; Okamura, Y.; Natsugari, H., Synthetic studies on antascomicin A: construction of the C18-C34 fragment. *Tetrahedron* **2004,** *60*, 5341-5352.

29. Hong, S.-P.; Lindsay, H. A.; Yaramasu, T.; Zhang, X.; McIntosh, M. C., Intramolecularly Competitive Ireland-Claisen Rearrangements: Scope and Potential Applications to Natural Product Synthesis. *J. Org. Chem.* **2002,** *67*, 2042-2055.

30. Chai, Y.; Hong, S.-p.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C., New aspects of the Ireland and related Claisen rearrangements. *Tetrahedron* **2002,** *58*, 2905-2928.

31. Rivero-Castro, J. Installation of the C14-C15 stereocenters of the C10-C-16 fragment of antascomicin B via [3,3]-sigmatropic rearrangements. M s, University of Arkansas, Fayetteville2009.

32. Qi, W.; McIntosh, M. C., Toward the synthesis of antascomicin B. Synthesis of a model of the C22–C34 fragment via Ireland–Claisen and allylic diazene rearrangements. *Tetrahedron* **2008,** *64*, 7021-7025.

33. Zegarski, J.; Howard, B. M., Syntheses of marine ochtodane antifeedants via hydrolytic dehalogenation. *Tetrahedron Lett.* **1985,** *26*, 1363-6.

34. Miyaoka, H.; Kajiwara, Y.; Hara, Y.; Yamada, Y., Total Synthesis of Natural Dysidiolide. *J. Org. Chem.* **2001,** *66*, 1429-1435.

35. Ito, S.; Tsunoda, T., A few new methods for asymmetric synthesis. *Pure Appl. Chem.* **1990,** *62*, 1405-8.

36. Tsunoda, T.; Sasaki, O.; Ito, S., Aza-Claisen rearrangement of amide enolates. Stereoselective synthesis of 2,3-disubstituted carboxamides. *Tetrahedron Lett.* **1990,** *31*, 727-30.

37. Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y.; Ito, S., Asymmetric induction in aza-Claisen rearrangement of carboxamide enolates. Effect of chiral auxiliary on nitrogen. *Tetrahedron Lett.* **1992,** *33*, 1651-4.

38. Ito, S.; Tsunoda, T., A few new methods toward asymmetric synthesis. *J. Chin. Chem. Soc. (Taipei)* **1992,** *39*, 205-8.

39. Tsunoda, T.; Nishii, T.; Yoshizuka, M.; Yamasaki, C.; Suzuki, T.; Ito, S., A total synthesis of (-)-antimycin A3b. *Tetrahedron Lett.* **2000,** *41*, 7667-7671.

40. Tsunoda, T.; Tatsuki, S.; Shiraishi, Y.; Akasaka, M.; Ito, S., Asymmetric aza-Claisen rearrangement of glycolamide and glycinamide enolates. Synthesis of optically active α-hydroxy and α-amino acids. *Tetrahedron Lett.* **1993,** *34*, 3297-3000.

41. Inai, M.; Nishii, T.; Mukoujima, S.; Esumi, T.; Kaku, H.; Tominaga, K.; Abe, H.; Horikawa, M.; Tsunoda, T., Total synthesis of (+)-brefeldin C utilizing aza-Claisen rearrangement. *Synlett* **2011**, 1459-1461.

42. Nishii, T.; Miyamae, F.; Yoshizuka, M.; Kaku, H.; Horikawa, M.; Inai, M.; Tsunoda, T., Construction of an asymmetric quaternary carbon via an asymmetric aza-Claisen rearrangement and its application in the total synthesis of (+)-α-cuparenone. *Tetrahedron: Asymmetry* **2012,** *23*, 739-741.

43. Yoshizuka, M.; Nishii, T.; Sasaki, H.; Kitakado, J.; Ishigaki, N.; Okugawa, S.; Kaku, H.; Horikawa, M.; Inai, M.; Tsunoda, T., Promotion of asymmetric aza-Claisen rearrangement of N-allylic carboxamides using excess base. *Synlett* **2011**, 2967-2970.

44. Abu-Hasanayn, F.; Stratakis, M.; Streitwieser, A., Aggregation and Alkylation Kinetics of the Lithium Enolate of p-(Phenylsulfonyl)isobutyrophenone. *J. Org. Chem.* **1995,** *60*, 4688-9.

45. Streitwieser, A.; Wang, D. Z.-R., Aggregation and Reactivity of the Lithium Enolate of 2-Biphenylylcyclohexanone in Tetrahydrofuran. *J. Am. Chem. Soc.* **1999,** *121*, 6213-6219.

46. Yu, S.; Pan, X.; Ma, D., Asymmetric total syntheses of marine cyclic depsipeptide halipeptins A-D. *Chem.--Eur. J.* **2006,** *12*, 6572-6584.

47. Sewald, N.; Hiller, K. D.; Koerner, M.; Findeisen, M., Tandem protocol for the stereoselective synthesis of different polyfunctional β-amino acids and 3-amino-substituted carbohydrates. *J. Org. Chem.* **1998,** *63*, 7263-7274.

48. Zhao, P.; Collum, D. B., Ketone Enolization by Lithium Hexamethyldisilazide: Structural and Rate Studies of the Accelerating Effects of Trialkylamines. *J. Am. Chem. Soc.* **2003,** *125*, 14411-14424.

49. Zhao, P.; Condo, A.; Keresztes, I.; Collum, D. B., Reaction of Ketones with Lithium Hexamethyldisilazide: Competitive Enolizations and 1,2-Additions. *J. Am. Chem. Soc.* **2004,** *126*, 3113-3118.

50. Zhao, P.; Collum, D. B., Lithium Hexamethyldisilazide/Triethylamine-Mediated Ketone Enolization: Remarkable Rate Accelerations Stemming from a Dimer-Based Mechanism. *J. Am. Chem. Soc.* **2003,** *125*, 4008-4009.

51. Godenschwager, P. F.; Collum, D. B., Lithium Hexamethyldisilazide-Mediated Enolizations: Influence of Triethylamine on E/Z Selectivities and Enolate Reactivities. *J. Am. Chem. Soc.* **2008,** *130*, 8726-8732.

52. Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; Van, D. F. L., Stereocontrolled synthesis of the everninomicin A1B(A)C ring framework. *Angew. Chem., Int. Ed.* **1998,** *37*, 1874-1876.

53. Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G., Synthesis of 2,6-Dideoxy Sugars via Ring-Closing Olefinic Metathesis. *Org. Lett.* **2002,** *4*, 3875-3878.

54. Zhu, L.; Kedenburg, J. P.; Xian, M.; Wang, P. G., A systematic strategy for preparation of uncommon sugars through enzymatic resolution and ring-closing metathesis. *Tetrahedron Lett.* **2005,** *46*, 811-813.

55. Virolleaud, M.-A.; Bressy, C.; Piva, O., A straightforward synthesis of (E)-δ-alkenyl-β,γ-unsaturated δ-lactones by a tandem ring-closing/cross-coupling metathesis process. *Tetrahedron Lett.* **2003,** *44*, 8081-8084.

56. Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H., Synthesis of α,β-unsaturated amides by olefin cross-metathesis. *Angew. Chem., Int. Ed.* **2001,** *40*, 1277-1279.

57. Mori, M.; Sakakibara, N.; Kinoshita, A., Remarkable effect of ethylene gas in the intramolecular enyne metathesis of terminal alkynes. *J. Org. Chem.* **1998,** *63*, 6082-6083.

58. Hoye, T. R.; Jeon, J.; Tennakoon, M. A., Allylmalonate as an activator subunit for the initiation of relay ring-closing metathesis reactions. *Angew. Chem., Int. Ed.* **2011,** *50*, 2141-2143, S2141/1-S2141/54.

59. Kim, A.; Hong, J. H., Synthesis and anti-HCMV activity of novel 5'-nor-carbocyclic nucleosides. *Arch. Pharm. (Weinheim, Ger.)* **2005,** *338*, 522-527.

60. Alder, K.; Pascher, F.; Schmitz, A., Substituting additions. I. Addition of maleic anhydride and azodicarboxylic esters to singly unsaturated hydrocarbons. Substitution processes in the allyl position. *Ber. Dtsch. Chem. Ges. B* **1943,** *76B*, 27-53.

61. Hutchison, J. M.; Lindsay, H. A.; Dormi, S. S.; Jones, G. D.; Vicic, D. A.; McIntosh, M. C., Approach to the Synthesis of Cladiell-11-ene-3,6,7-triol. *Org. Lett.* **2006,** *8*, 3663-3665.

62. Movassaghi, M.; Ahmad, O. K., N-Isopropylidene-N'-2-nitrobenzenesulfonyl Hydrazine, a Reagent for Reduction of Alcohols via the Corresponding Monoalkyl Diazenes. *J. Org. Chem.* **2007,** *72*, 1838-1841.

63. Qi, W.; McIntosh, M. C., Acyclic 1,4-Stereocontrol via Reductive 1,3-Transpositions. *Org. Lett.* **2008,** *10*, 357-359.

64. Trost, B. M.; Chan, C.; Ruhter, G., Metal-mediated approach to enynes. *J. Am. Chem. Soc.* **1987,** *109*, 3486-7.

65. Koch, G.; Kottirsch, G.; Wietfeld, B.; Kuesters, E., Process Development of a Dual MMP/TNF Inhibitor (SDZ 242-484). *Org. Process Res. Dev.* **2002,** *6*, 652-659.

66. Criegee, R., Mechanism of ozonolysis. *Angew. Chem.* **1975,** *87*, 765-71.

67. Bunnelle, W. H., Preparation, properties, and reactions of carbonyl oxides. *Chem. Rev.* **1991,** *91*, 335-62.

68. Kuczkowski, R. L., The structure and mechanism of formation of ozonides. *Chem. Soc. Rev.* **1992,** *21*, 79-83.

69. Greco, M. N.; Zhong, H. M.; Maryanoff, B. E., Unusual lability of α-silyloxy β-amino carboxylic acid derivatives. *Tetrahedron Lett.* **1998,** *39*, 4959-4962.

70. Molander, G. A.; Cooper, D. J., Ozonolysis of Unsaturated Organotrifluoroborates. *J. Org. Chem.* **2007,** *72*, 3558-3560.

71. Trost, B. M.; Machacek, M. R.; Tsui, H. C., Development of Aliphatic Alcohols as Nucleophiles for Palladium-Catalyzed DYKAT Reactions: Total Synthesis of (+)-Hippospongic Acid A. *J. Am. Chem. Soc.* **2005,** *127*, 7014-7024.

72. Whitehead, A.; Waetzig, J. D.; Thomas, C. D.; Hanson, P. R., A Multifaceted Phosphate Tether: Application to the C15-C30 Subunit of Dolabelides A-D. *Org. Lett.* **2008,** *10*, 1421-1424.

73. Slomp, G., Jr.; Johnson, J. L., Ozonolysis. II. The effect of pyridine on the ozonolysis of 4,22-stigmastadien-3-one. *J. Am. Chem. Soc.* **1958,** *80*, 915-21.

74. Griesbaum, K., Role of pyridine in the ozonolysis of olefins-evidence against the pyridine oxide route. *Chem. Commun.* **1966**, 920-1.

75. Willand-Charnley, R.; Fisher, T. J.; Johnson, B. M.; Dussault, P. H., Pyridine Is an Organocatalyst for the Reductive Ozonolysis of Alkenes. *Org. Lett.* **2012,** *14*, 2242-2245.

76. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B., A greatly improved procedure for ruthenium tetroxide catalyzed oxidations of organic compounds. *J. Org. Chem.* **1981,** *46*, 3936-8.

77. Yang, D.; Zhang, C., Ruthenium-Catalyzed Oxidative Cleavage of Olefins to Aldehydes. *J. Org. Chem.* **2001,** *66*, 4814-4818.

78. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z., Improved Procedure for the Oxidative Cleavage of Olefins by OsO4-NaIO4. *Org. Lett.* **2004,** *6*, 3217-3219.

79. Zweifel, G.; Brown, H. C., Hydroboration of olefins. (+)-Isopinocampheol. *Org. Syn.* **1972,** *52*, 59-62.

80. Brown, H. C.; Pfaffenberger, C. D., Hydroboration of terpenes. VIII. Cyclic hydroboration of D-(+)-limonene. Stereoselective synthesis of D-(-)-(1R, 2R, 4R)-limonene-2,9-diol and D-(-)-(1R, 2R, 4R)-carvomenthol. *Tetrahedron* **1975,** *31*, 925-8.

81. Carlson, B. A.; Brown, H. C., Base-induced reaction of borinic acid esters with α,α-dichloromethyl methyl ether. New route to ketones via hydroboration. *J. Amer. Chem. Soc.* **1973,** *95*, 6876-7.

82. Arase, A.; Hoshi, M., A new synthesis of 2-alkyl-1,3-butadienes from internal alkenes and 1,4-dichloro-2-butyne via dialkyl(1,4-dichloro-2-buten-2-yl)boranes. *J. Chem. Soc., Chem. Commun.* **1987**, 531-2.

83. White, E. H., N-Alkyl-N-nitrosoamides. I. Methods of preparation. *J. Am. Chem. Soc.* **1955,** *77*, 6008-10.

84. White, E. H., N-Alkyl-N-nitrosoamides. II. A new method for the deamination of aliphatic amines. *J. Am. Chem. Soc.* **1955,** *77*, 6011-14.

85. White, E. H., N-Alkyl-N-nitrosoamides. III. Mechanism of the nitrogen-elimination reaction. *J. Am. Chem. Soc.* **1955,** *77*, 6014-22.

86. Mandai, T.; Yamakawa, T., An efficient synthesis of (2S)-2-{4-[(1R,2S)-2-hydroxycyclopentylmethyl]phenyl}propionic acid. *Synlett* **2000**, 862-864.

87. Flynn, D. L.; Zelle, R. E.; Grieco, P. A., A mild two-step method for the hydrolysis of lactams and secondary amides. *J. Org. Chem.* **1983,** *48*, 2424-6.

88. Priebe, H.; Hopf, H., Alkynes and cumulenes. Part 16. One-pot method for the synthesis of 1-alken-5-yne derivatives. *Angew. Chem.* **1982,** *94*, 299.

89. Liu, H.-J.; Shia, K.-S.; Shang, X.; Zhu, B.-Y., Organocerium compounds in synthesis. *Tetrahedron* **1999,** *55*, 3803-3830.

90. Denmark, S. E.; Edwards, J. P.; Nicaise, O., Organocerium additions to hydrazones: effects of reagent stoichiometry on efficiency and selectivity. *J. Org. Chem.* **1993,** *58*, 569-78.

91. Nahm, S.; Weinreb, S. M., N-Methoxy-N-methylamides as effective acylating agents. *Tetrahedron Lett.* **1981,** *22*, 3815-18.

92. Nakamura, S.; Shibasaki, M., Synthetic studies on tautomycin. Stereoselective construction of the C1-C26 region. *Tetrahedron Lett.* **1994,** *35*, 4145-8.

93. D'Aniello, F.; Mann, A.; Taddei, M., 1,3-Stereocontrol with Bromoallenes. Synthesis of N-Boc-ADDA, the Unique Amino Acid Present in Several Inhibitors of Serine/Threonine Phosphatases. *J. Org. Chem.* **1996,** *61*, 4870-4871.

94. Shimizu, T.; Osako, K.; Nakata, T., Efficient method for preparation of N-methoxy-N-methyl amides by reaction of lactones or esters with Me2AlCl-MeONHMe·HCl. *Tetrahedron Lett.* **1997,** *38*, 2685-2688.

95. Lundin, P. M.; Fu, G. C., Asymmetric Suzuki Cross-Couplings of Activated Secondary Alkyl Electrophiles: Arylations of Racemic α-Chloroamides. *J. Am. Chem. Soc.* **2010,** *132*, 11027-11029.

96. Confalone, P. N.; Huie, E. M.; Ko, S. S.; Cole, G. M., Design and synthesis of potential DNA cross-linking reagents based on the anthramycin class of minor groove binding compounds. *J. Org. Chem.* **1988,** *53*, 482-7.

97. Juli, C.; Sippel, M.; Jaeger, J.; Thiele, A.; Weiwad, M.; Schweimer, K.; Roesch, P.; Steinert, M.; Sotriffer, C. A.; Holzgrabe, U., Pipecolic Acid Derivatives As Small-Molecule Inhibitors of the Legionella MIP Protein. *J. Med. Chem.* **2011,** *54*, 277-283.

98. Hoveyda, H. R.; Karunaratne, V.; Orvig, C., Design and synthesis of multidentate 2-(2'-hydroxyphenyl)-2-thiazolines for biomedical application. *Tetrahedron* **1992,** *48*, 5219-26.

99. Jursic, B. S.; Zdravkovski, Z., A simple preparation of amides from acids and amines by heating of their mixture. *Synth. Commun.* **1993,** *23*, 2761-70.

100. Cressman, E. N. K., Synthesis of an indolizidinedione oxime inhibitor of acetyl-coenzyme a carboxylase (ACCase). *Bioorganic & Medicinal Chemistry Letters* **1994,** *4*, 1983-1984.

101. Overberger, C. G.; Shalati, M. D., Synthesis and resolution of substituted pipecolic acids. *Eur. Polym. J.* **1983,** *19*, 1055-65.

102. Burgess, K.; Ohlmeyer, M. J., Transition-metal promoted hydroborations of alkenes, emerging methodology for organic transformations. *Chem. Rev.* **1991,** *91*, 1179-91.

103. Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N., Iridium-catalyzed hydroboration of alkenes with pinacolborane. *Tetrahedron* **2004,** *60*, 10695-10700.

104. Dias, L. C.; Salles, A. G., Studies on the total synthesis of sanglifehrin A: stereoselective synthesis of the C(29)-C(39) fragment. *Tetrahedron Lett.* **2006,** *47*, 2213-2216.

105. Day, B. W.; Kangani, C. O.; Avor, K. S., Convenient syntheses of (2R,3S,4R)-3-(tert-butyldimethylsilanyloxy)-2,4-dimethyl-5-oxopentanoic acid methoxymethylamide from methacrolein. Preparation of C1-C7 and C17-C24 fragments of (+)-discodermolide. *Tetrahedron: Asymmetry* **2002,** *13*, 1161-1165.