2011

TOWARDS THE TOTAL SYNTHESIS OF THE CAPURAMYCIN FAMILY OF NATURAL PRODUCTS

Jesse M. Jacobsen
University of Kentucky, jmjaco2@uky.edu

ABSTACT OF THESIS

TOWARDS THE TOTAL SYNTHESIS OF THE CAPURAMYCIN FAMILY OF NATURAL PRODUCTS.

Despite over a century of advancement, tuberculosis remains a grave threat to world health. In particular, third world countries continue to struggle with the crushing weight of the disease. Furthermore, the emergence of drug resistance in TB strains poses a significant threat to the first world where incidence and mortality is low. The dwindling efficacy of current drug regimens necessitates research into new small molecules capable of arresting the growth and spread of TB. The capuramycin family of nucleoside antibiotics shows strong potential to become part of this new generation of anti-TB small molecules. Indeed, their ability to inhibit Translocase I, a key enzyme in the biosynthesis of bacterial cell walls, makes them exciting targets for medicinal chemistry efforts.

The synthesis of the family focused on dividing the molecules into three congruent, synthetically separate parts: the variable amide linked tail, the hexauronic acid linker, and the uridine "head". Construction of the ubiquitous core structure comprised of the hexauronic acid and uridine would allow rapid diversification while the variable tail would allow SAR studies and development of novel new members of the family.

KEYWORDS: Tuberculosis, Translocase I, Capuramycin, Total Synthesis, Medicinal Chemistry

Jesse M. Jacobsen

June 3, 2011

TOWARDS THE TOTAL SYNTHESIS OF THE CAPURAMYCIN FAMILY OF NATURAL PRODUCTS.

By

Jesse M. Jacobsen

Dr. Steven G. VanLanen
Director of Thesis

Dr. Jurgen Rohr
Co-Director of Thesis

Dr. Jim Pauly
Director of Graduate Studies

June 3, 2011

RULES FOR THE USE OF THESES

Unpublished theses submitted for the Master's degree and deposited in the University of Kentucky Library are as a rule open for inspection, but are to be used only with due regard to the rights of the authors. Bibliographical references may be noted, but quotations or summaries of parts may be published only with the permission of the author, and with the usual scholarly acknowledgments.

Extensive copying or publication of the thesis in whole or in part also requires the consent of the Dean of the Graduate School of the University of Kentucky.

A library that borrows this thesis for use by its patrons is expected to secure the signature of each user.

Name Date

THESIS

Jesse M. Jacobsen

The Graduate School

University of Kentucky

2011

TOWARDS THE TOTAL SYNTHESIS OF THE CAPURAMYCIN FAMILY OF NATURAL PRODUCTS.

Thesis

A thesis submitted in partial fulfillment of the
requirements for the degree of Master of Science in the
College of Pharmaceutical Sciences
at the University of Kentucky

By

Jesse M. Jacobsen

Lexington, Kentucky

Director: Dr. Steven G. Van Lanen, Assistant Professor of Pharmaceutical Sciences.
Co-Director: Dr. Jurgen Rohr, Professor of Pharmaceutical Sciences

Lexington, Kentucky

2011

Acknowledgements

This thesis represents the culmination of an eminently bizarre and unexpected journey through the bowels of graduate research. I could not have envisioned three years ago upon graduation (or even a year ago) writing this thesis instead of continuing the epic slog towards a PhD. It has been a rollercoaster ride through some incredibly rough patches, but I feel I've learned a great deal about myself and the world--things that transcend merely the chemistry and academic experiences.

I guess I should actually acknowledge some people here instead of waxing philosophical. I'll start by thanking Dr. Van Lanen, my unwitting final advisor for this work. I am grateful for the chance to seek refuge in his lab following the fall and dissolution of the Elliott lab. I'm especially grateful that I was allowed the incredible amount of freedom to continue on this project under my own direction. I would also like to thank the remaining members of my committee--Drs. Jurgen Rohr and Kyung-Bo Kim for taking the time to oversee the completion of this thesis and my masters.

Above and beyond all I need to thank my family, particularly my mother. When the weight of everything threatened to grind me into an unsavory paste, you were there to back me up no matter where the world took me. I surely would have succumbed to the incredible stress of a dissolving lab without your love and guidance. I also need to thank my amazing girlfriend Lura for being my escape from the world. The many beers, conversations, and simple time we've shared have helped me overcome.

I need to thank all my friends and coworkers who have made life measurably more bearable. Thanks for the support, especially for my off the wall crazy ideas regarding the future. Finally, my cats, Ozymandias and Laurie, need thanks for being there when I get home every day from work. Their fuzzy aloofness and love have kept my insanity level relatively low.

Prost!

Table of Contents

Acknowledgements iii

List of Figures vi

List of Tables vii

List of Schemes viii

Chapter 1: Background 1

1.1 Tuberculosis Overview 1

1.2 Current Treatments for Tuberculosis 2

1.3 Translocase 1 Inhibitors: Nucleoside Antibiotics 3

1.4 Capuramycin 5

1.5 Synthetic Studies of Capuramycin 6

1.6 Our Retrosynthetic Methodology 11

Chapter 2: The Uridine Moiety 14

2.1 Background 14

2.2 Work Utilizing Cyclouridine 16

2.3 Bis-5'-3'-protection 19

2.4 Exploration of the Passerini Reaction 21

Chapter 3: The Hexauronic Linker 24

3.1 Background 24

3.2 Hetero-Diels–Alder Chemistry 25

3.3 Direct Mannose Approach 30

Chapter 4: The Amide Tails 34
4.1 Background 34
4.2 First Attempted Synthesis of A-500359A Lactam 34
4.3 Synthesis Utilizing Pyrolysis of Methionine Sulfoxide 36
4.4 Asymmetric Allylic Alkylation 38
4.5 Work Towards the Tail Segment of A-102395 47

Chapter 5: Conclusions 51

Appendix I: List of Abbreviations 53
Appendix II: Experimental 55
References 93
Vita 102

List of Figures

Figure 1.1: First Line Anti-TB Small Molecules 2
Figure 1.2: Nucleoside Translocase I Inhibitors 3
Figure 1.3: A Peptidoglycan Subunit 4
Figure 1.4: The Capuramycin Family of Nucleoside Antibiotics 5
Figure 1.5: Non-natural Analogs 7
Figure 4.1: Unusual Linear Tail of A-102395 47

List of Tables

Table 1.1: Anti-bacterial Activity of Capuramycin and Analogs 7
Table 2.1: Oxidative Passerini Reaction of 2',3'-isopropylidene Uridine 22
Table 4.1: Screening RCM Conditions on 101 41

List of Schemes

Scheme 1.1: Ester-Amide Exchange Catalyzed by CapW 6
Scheme 1.2: Knapp Synthesis of the Uridine Core..... 8
Scheme 1.3: Knapp Synthesis of the Mannuronic Acid Linker..... 8
Scheme 1.4: Finishing the Knapp Synthesis..... 9
Scheme 1.5: Kurosu's Synthetic Route 10
Scheme 1.6: Finishing the Synthesis 11
Scheme 1.7: Our Retrosynthetic Analysis 13
Scheme 2.1: Silylation of Uridine..... 15
Scheme 2.2: Synthesis of Cyclouridine 15
Scheme 2.3: Silylation of Cyclouridine 16
Scheme 2.4: Elaboration of the 3'-*O*-Methylether 17
Scheme 2.5: Attempted Cyclouridine Ring Opening 18
Scheme 2.6: Iodide Opening of 36 19
Scheme 2.7: *Bis*-3'-5'-protection of Uridine and Elaboration 20
Scheme 2.8: The Passerini Reaction..... 21
Scheme 3.1: Modified Knapp Route..... 24
Scheme 3.2: Hetero-Diels-Alder Synthesis of Carbohydrates..... 25
Scheme 3.3: Synthesis of Hetero-Dienes..... 26
Scheme 3.4: Synthesis of Benzyl Substituted Hetero-Diene 26
Scheme 3.5: Attempted Synthesis of 60 27
Scheme 3.6: Attempted Synthesis of *cis*-1-benzoyloxy-2-(trimethylsiloxy)ethene 28
Scheme 3.7: Synthesis of -OBn and -OTBS Dienophiles..... 28
Scheme 3.8: Synthesis of Sulfur Containing Dienophile..... 29
Scheme 3.9: Hetero-Diels-Alder Reaction 30
Scheme 3.10: Updated Direct Mannose Route 31
Scheme 3.11: Synthesis of Allyl-protected Mannuronic Acid 32
Scheme 3.12: Synthesis of Protected Amide and Ester 33
Scheme 4.1: Initial Retrosynthetic Analysis of the A-500359A Lactam..... 34
Scheme 4.2: Attempted Synthesis of 85 35

Scheme 4.3: Synthesis of Dipeptide for Olefination 36
Scheme 4.4: Pyrolysis of Methionine Sulfoxide..... 37
Scheme 4.5: AAA of Phthalimide and Butadiene Monoxide..... 38
Scheme 4.6: Elaboration Towards Ring Closure..... 39
Scheme 4.7: Olefin Metathesis Mechanism..... 40
Scheme 4.8: Previous Ring Closing of 7-membered Lactams 41
Scheme 4.9: Hydrogenation of 108a/b..... 42
Scheme 4.10: *N*-Cbz-protected Lactam and Manipulation..... 43
Scheme 4.11: Synthesis of Novel Imide for AAA Reaction 44
Scheme 4.12: AAA Reactions of 116..... 45
Scheme 4.13: Rearrangement following AAA 45
Scheme 4.14: Investigation of the Ring Closing Reaction 46
Scheme 4.15: Retrosynthetic Analysis of the A-102395 Tail..... 47
Scheme 4.16: Synthesis of Western Tail Fragment..... 48
Scheme 4.17: Initial Easter Segment Synthetic Efforts..... 49
Scheme 4.18: Synthesis of the Eastern Fragment..... 50
Scheme 4.19: Attempted Buchwald Amidation..... 50

Chapter 1: Background

1.1 Tuberculosis Overview

Tuberculosis (TB) is a disease that primarily targets the human respiratory tract caused by different strains of the mycobacterium family of infectious agents.[1] TB is an ancient disease[2] that is personified by a persistent cough that often brings up blood as well as fever, chills, pallor, fatigue, and weight loss. In 1882 it was found that an infectious agent caused TB[3] and shortly thereafter incidence and mortality began to decline. With the advent of a viable vaccine and the discovery of streptomycin in 1944[4], a more concentrated effort was made to fight the disease. By the 1980's, TB had been largely purged from the western world.

Standard TB infections, however, are still one of the leading causes of death in many developing nations particularly in Africa and Asia. Shockingly, it is estimated that nearly one third of the *entire* human population carries the most common *Mycobacterium tuberculosis* strain. The vast majority of cases remain in an asymptomatic latent state with only a 10% chance of the disease becoming active. However, once the infection becomes active, mortality can be as high as 50%. In 2009 alone 1.7 million people died from active TB infections making it the second leading cause of infectious mortality behind HIV.[1]

Drug resistant strains of TB have begun to emerge in all countries surveyed by the World Health Organization. Multi-Drug Resistant TB (MDR-TB) and eXtensively Drug Resistant TB (XDR-TB) have also been seen to emerge in recent years creating a serious threat to even first world countries where the incidence and mortality of TB has remained low. In former Soviet Bloc countries the incidence of drug resistant TB can be as high as 35% of all cases.[5]

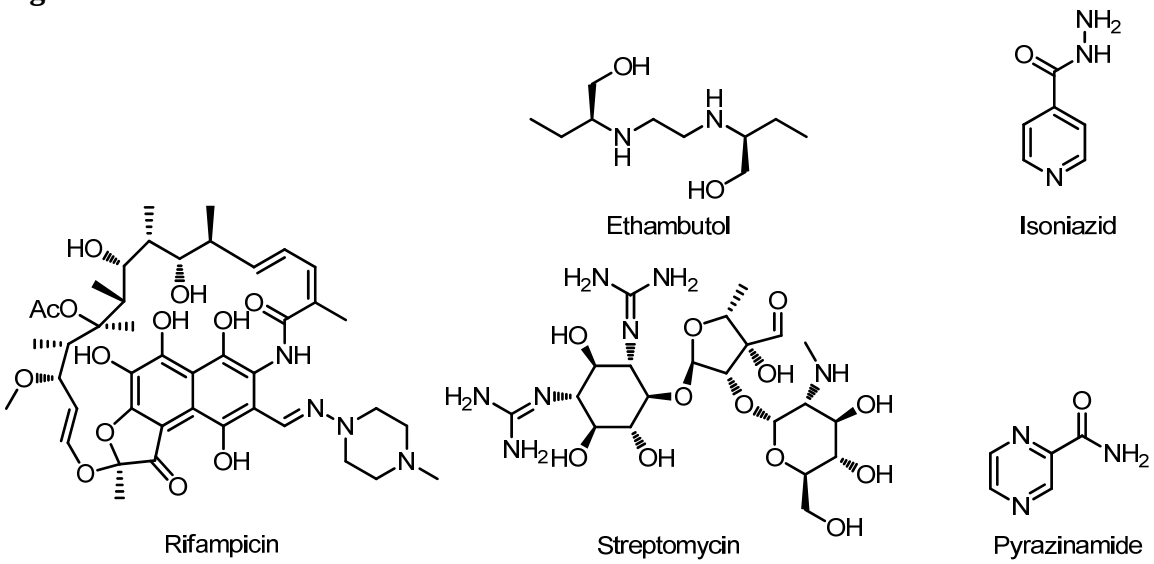
Patients with AIDS are also at extreme risk due to their immunocompromised state. Judicious choice of drug regimens for both disease must also be made to minimize the risk of serious side effects.[6] The prevalence (450 per 100,000) and mortality (33% of

total global mortality) in Africa can be strongly correlated to the AIDS epidemic currently ravishing the continent.[1]

1.2 Current Treatments for Tuberculosis

The antibiotics streptomycin, isoniazid, pyrazinamide, ethambutol, and rifampicin constitute the first line of defense against active and latent TB (**Figure 1.1**).[7] Standard treatment procedures call for a combination of these drugs to be taken daily for a time frame of 4-6 months. The use of such a drug cocktail and the long dosing regime is necessary to ensure complete eradication of the *Mycobacterium* as well as prevent the onset of resistance.

Figure 1.1: First Line Anti-TB Small Molecules



With such a long term and complicated treatment regime, patient compliance becomes a serious issue. Discontinuation of the medication prematurely can lead to relapse and the development of resistance, thus hampering further efforts. Furthermore, hepatotoxicity is a common side effect from several of the first line drugs and patients' liver functions need to be monitored during treatment.

Second line compounds such as fluorquinolines (e.g. ciprofloxacin) and cycloserine are available in the event of the first line failing, adverse side effects, and/or

drug resistance.[7] However, efficacy, cost, and their own side effects make second line drugs decidedly less than ideal.

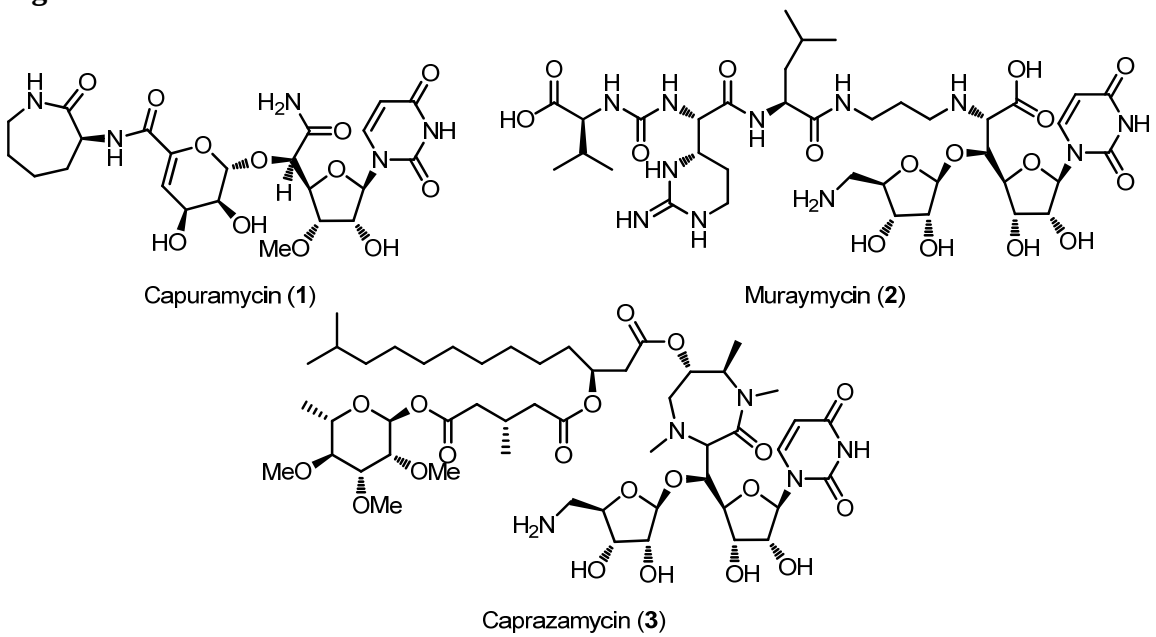
The emergence of MDR-TB and XDR-TB has created a serious dilemma in terms of treatment regimes. Successful treatment of these hardier strains requires extended dosing regimens of 18 months and longer as well as even more complicated drug cocktails.[8]

While the need for treatment remains, the last frontline drug added to the arsenal was rifampin over 40 years ago. Currently only a handful of drugs, however promising, fill the TB drug pipeline.[8, 9] This dearth of new treatments means the spread of MDR and XDR-TB remains a very serious risk to third and first world countries alike.

1.3 Translocase 1 Inhibitors: Nucleoside Antibiotics

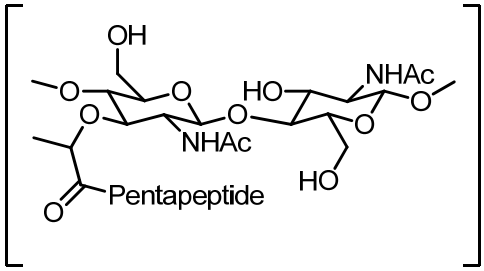
The issues associated with current drug regimes and drug resistance means that new compounds with novel modes of action are of great importance in the continued fight against TB. In the past two decades, nucleoside antibiotics of the capuramycin (**1**), muraymycin (**2**), and caprazamycin (**3**) families have shown potential in becoming a new generation of anti-TB medications (**Figure 1.2**)[10].

Figure 1.2: Nucleoside Translocase I Inhibitors



The novel mode of action possessed by these nucleoside antibiotics revolves around inhibition of peptidoglycan biosynthesis.[10] Peptidoglycan is the primary polymeric constituent of bacterial cell walls. The backbone of peptidoglycan is an alternating β-1, 4-linked glycan composed of *N*-acetylglucosamine (Glc*N*Ac) and *N*-acetylmuramic acid (Mur*N*Ac). To the 3-position of the Mur*N*Ac sugar is attached a short polypeptide (normally 5 amino acids) which allows cross linking between the 3-amino acid (lysine or d-aminopimelate) and between the 4/5 peptide bond of another unit (**Figure 1.3**). These cross-links provide structural rigidity which allows the cell wall to withstand the osmotic pressure of the cell's cytoplasm.

Figure 1.3: A Peptidoglycan Subunit



Peptidoglycan biosynthesis is a complex process that begins on they cytoplasmic side of the cell membrane. The process begins with the transformation of UDP-Glc*N*Ac into UDP-Mur*N*Ac. To the UDP-Mur*N*Ac is attached a series of amino acids providing the requisite polypeptide chain. The new UDP-Mur*N*Ac-pentapeptide is then used to provide phospho-Mur*N*Ac-pentapeptide which is transferred to a membrane bound undecaprenyl phosphate by the enzyme translocase I or MraY.

The Glc*N*Ac unit is then attached via translocase II from a UDP-Glc*N*Ac molecule. At this point the nascent peptidoglycan is flipped from the cytoplasmic to the extra-cellular face of the membrane. Afterwards, the peptidoglycan unit is joined to others and cross-linked to form the cell wall.

Targeting of cell wall biosynthesis is, by itself, a non-novel means of incurring antibiotic activity. For example, the β-lactam antibiotics (penicillin) and vancomycin both work by inhibiting different aspects of cell wall biosynthesis. The inhibition of translocase I as a means to antibiotic activity, however, suggests that such compounds

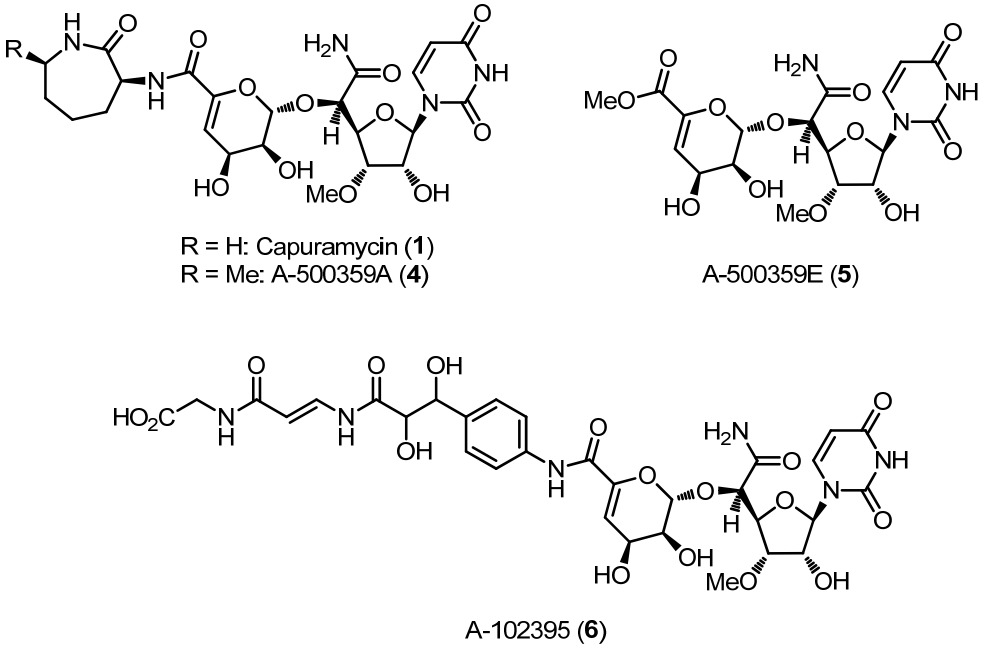
should be active against MDR and XDR-TB. Furthermore, the lack of translocase I homologs in mammals lowers the risk for potential side effects.

1.4 Capuramycin

Capuramycin itself was first isolated in 1985 from the culture broth of *Streptomyces griseus* and was shown to be a potent inhibitor of *E. coli* translocase I (IC_{50} = 0.01 μg/ml).[11] Furthermore, capuramycin was shown to be active against several strains of mycobacteria and presented low toxicity in mice. In 1988, the structure of capuramycin was solved via NMR, chemical, and X-ray methods.[12] It was found that the structure is comprised of a 3'-*O*-methyl-uridine moiety joined to an *l*-taluronamide via a glycosidic linkage. Finally, a peptide bond from the 5-position of the taluronamide joins a 2-(*S*)-aminocaprolactam to the structure.

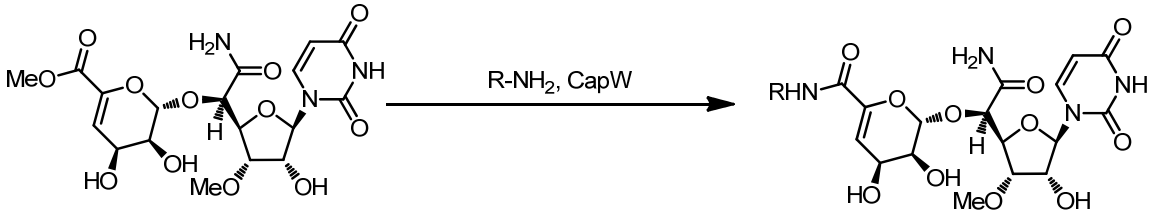
The core uridine/taluronamide moiety represents a common core motif in several related analogs in the capuramycin family.[13] As shown in **Figure 1.4**, the family varies largely in the makeup of the lactam tail.

Figure 1.4: The Capuramycin Family of Nucleoside Antibiotics



The simplest member of the family A-500359E (**5**) was recently shown to be the likely progenitor to the entire family. It was found that the enzyme dubbed CapW could affect a unique ester-amide exchange reaction thus appending on a large number of free amines (**Scheme 1.1**).[14] Thus, the synthesis of **5** and analogous compounds represents an excellent point for rapid diversification and SAR studies.

Scheme 1.1: Ester-Amide Exchange Catalyzed by CapW



A-500359E (**5**)

1.5 Synthetic Studies of Capuramycin

Hotoda and co-workers[15] at the Sankyo Co. conducted a large screen of synthetic analogues derived from **1**, **4**, and **5**. In the first paper, the role of the amide tail was explored via installation of numerous substituted phenyl, benzyl, and phenylethyl groups.[15a] Their second paper involved addition of lipophilic acyl groups onto the 2'-position of the uridine moiety.[15b] In both cases several potent analogs were discovered as exemplified in **Figure 1.5**. Their inhibitory activity against several strains of mycobacterium is displayed in **Table 1.1**.

While these studies have provided exciting results thus far, they are limited due to the nature of the chemical modifications. In all cases, bacterially synthesized **1**, **4**, and **5** make up the starting material, preventing modifications to the core skeleton. If such changes are to be made, the compounds will need to be synthesized from the ground up. Thus, total synthesis will theoretically provide analog compounds that cannot otherwise be accessed

Figure 1.5: Non-natural Analogs

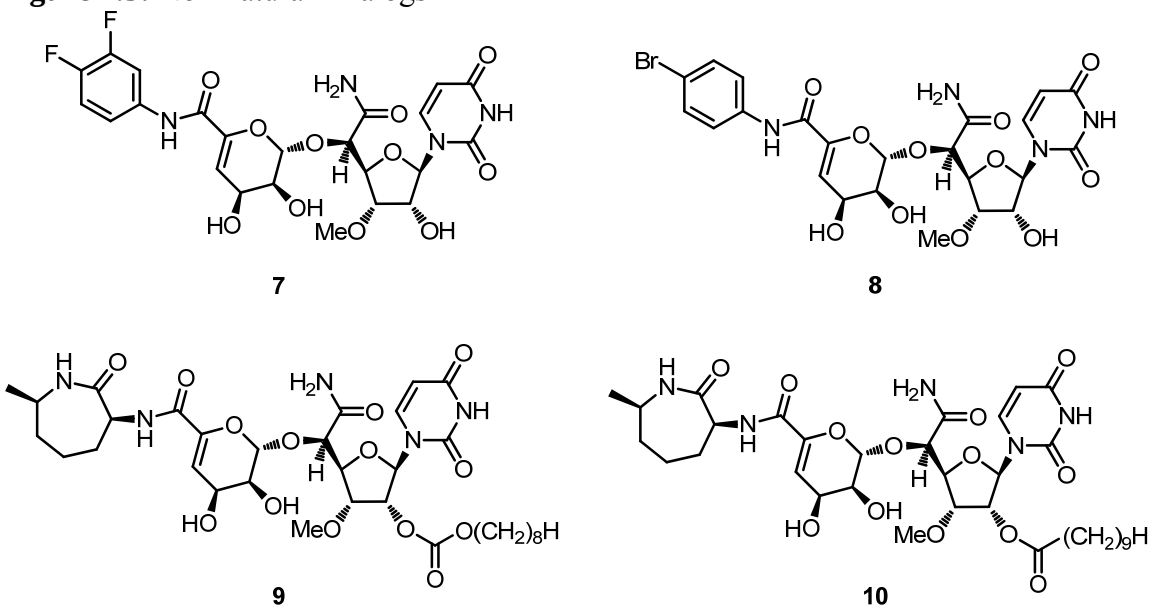


Table 1.1: Anti-bacterial Activity of Capuramycin and Analogs

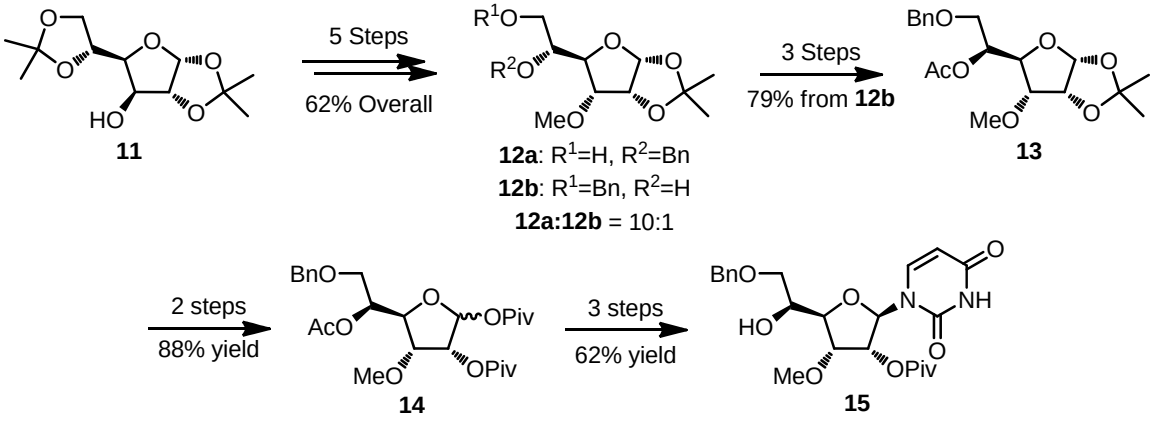
Compound	Translocase I IC_{50}[a)]	*M. Smegmantis* SANK 75075[b)]	*M. Avium* NIHJ1605[b)]	*M. intracellulare* ATCC1954 E-3[b)]
1	10	12.5	8	8
4	10	6.5	8	4
7	9	6.25	2	0.5
8	20	6.25	0.5	0.5
9	500	25	8	0.5
10	550	6.25	<0.063	<0.063

a) ng/mL b) MIC in μg/ml

Two total syntheses of capuramycin have been achieved thus far. The first was disclosed in 1994 by Knapp and Nandan.[16] This synthesis begins from commercially available diacetone glucose (**11**, **Scheme 1.2**). Mitsunobu inversion of the 3-position followed by methylation, selective deprotection, and stannylene acetal mediated mono-benzylation yielded **12a** and **12b** in good overall yield but with poor selectivity for the desired **12b**. The 5-hydroxyl was then inverted utilizing Mitsunobu chemistry using *p*-nitrobenzoic acid as the nucleophile. Cleavage of the nitrobenzoate and subsequent acetate formation provided **13** in good yield. The second isopropylidene was then opened

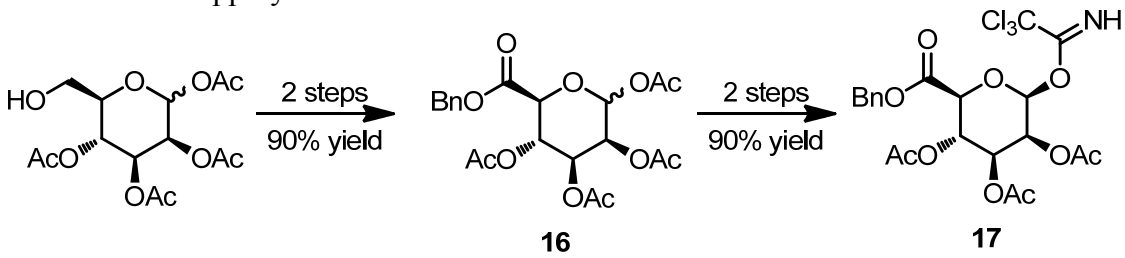
up using acetic acid and the hydroxyls protected as pivalates (**14**). The ribose unit was then activated by conversion to the phenylthio ether with TMS-OTf. Finally, the uracil nucleobase was installed using NIS and TfOH followed by acetate deprotection to achieve **15**.

Scheme 1.2: Knapp Synthesis of the Uridine Core



Construction of the hexuronic acid moiety started with the ruthenium catalyzed oxidation of 1, 2, 3, 4-tetra-*O*-acetyl-D-mannopyranose followed by benzyl ester formation (BnBr, $NaHCO_3$; **Scheme 1.3**) to provide **16**. The anomeric position was then selectively deprotected with 2-aminoethanol and converted into the activated trichloroacetamide **17**.

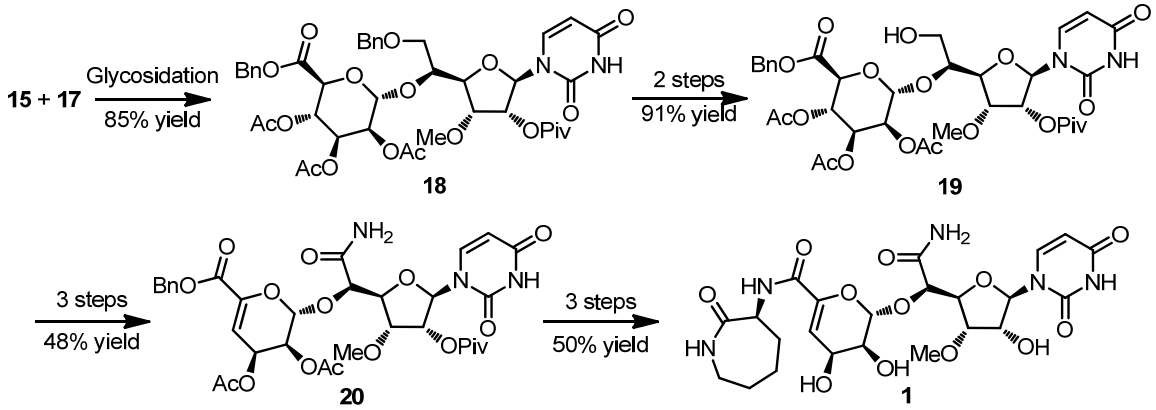
Scheme 1.3: Knapp Synthesis of the Mannuronic Acid Linker



Coupling of **15** and **17** was achieved with TMS-OTf to give the nearly completed core (**18**, **Scheme 1.4**) in 85% yield. Hydrogenation of the benzyl groups followed by reprotection of the benzyl ester provided the free 6'-position for elaboration (**19**). This was carried out via PDC oxidation to the acid followed by conversion to the primary

amide **20** in moderate yield. To complete the first synthesis of **1**, the 4''-acetate was eliminated with DBU, the ester deprotected, commercially available 2-(*S*)-aminocaprolactam was coupled on, and universal deprotection affected with methanolic sodium hydroxide.

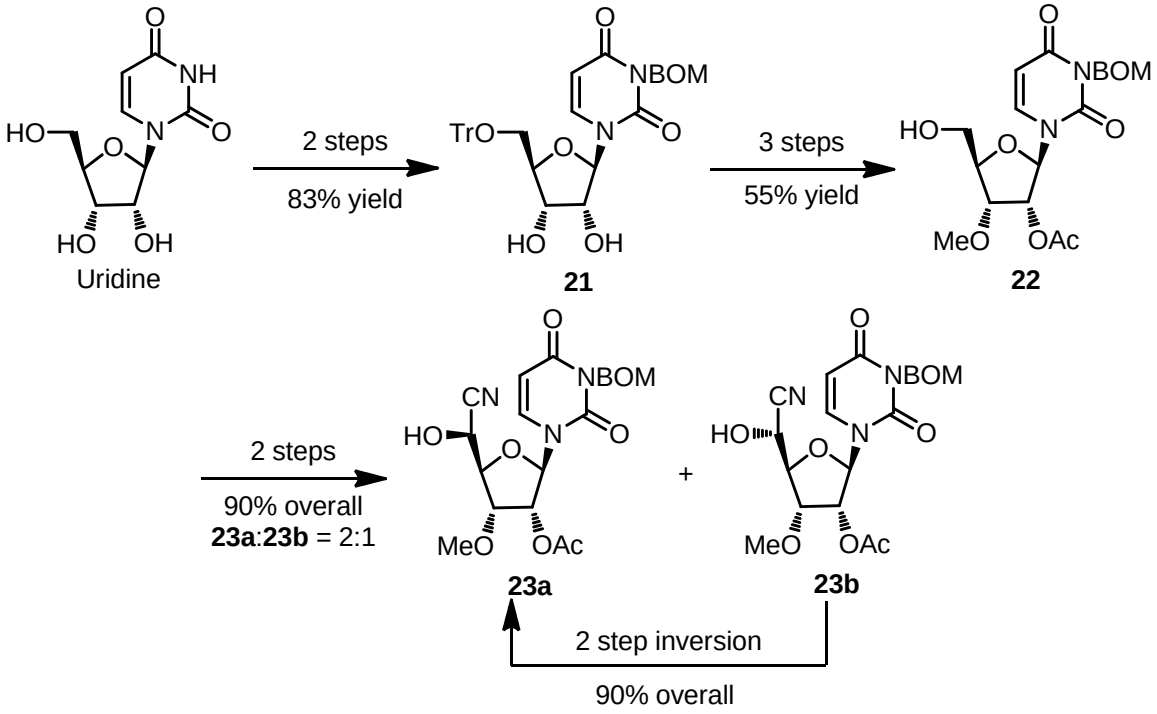
Scheme 1.4: Finishing the Knapp Synthesis



Overall the synthesis requires 22 steps (longest linear sequence) and is hampered by a myriad of functional and protecting group interconversions. Especially damming is the need for two Mitsunobu inversions and the poor selectivity from the stannylene acetal mediated benzylation. While the synthesis does provide ample opportunity for structural diversification, the route is too long and unwieldy to be of much use.

More recently Kurosu et al.[17] published an updated synthesis starting from uridine itself (**Scheme 1.5**). To start off, the imide nitrogen was BOM protected and then the 5'-hydroxyl tritylated. From here, stannylene acetal chemistry was again employed to methylate the 2' and 3'-positions with moderate selectivity. The isomers were separated and the desired 3'-*O*-methyl ether was converted into the 2'-*O*-acetate and then detritylated in fair yield (**22**). The primary hydroxyl was then oxidized to the unstable aldehyde via Moffatt conditions (DCC, dichloroacetic acid) and cyanide addition was carried out using $Ti(O^iPr)_4$ as a Lewis Acid catalyst. Only moderate selectivity for the desired diastereomer **23a** could be achieved despite attempts to screen a number of chiral ligands (BINOL). The undesired diastereomer **23b** could be converted into **23a** via Mitsunobu inversion.

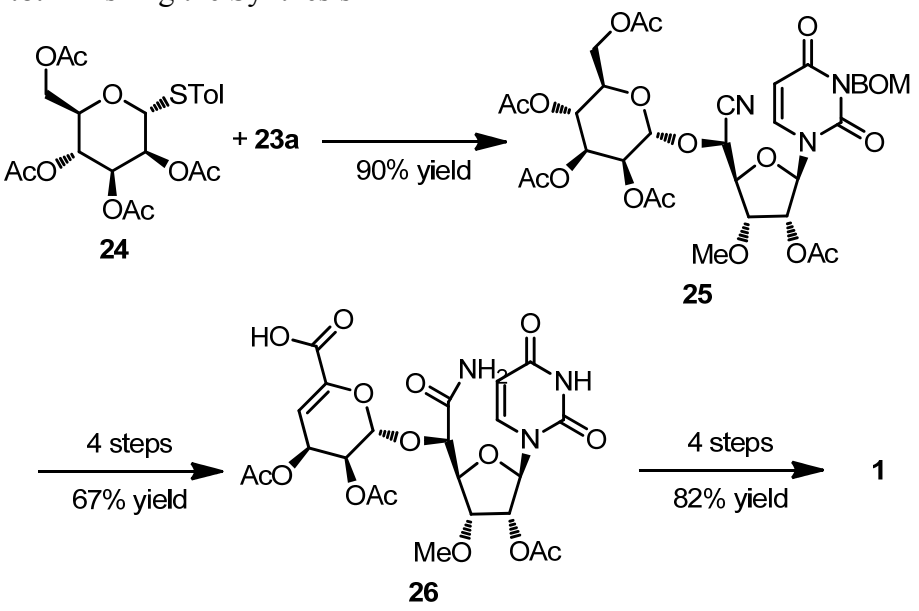
Scheme 1.5: Kurosu's Synthetic Route



From here an activated mannose derivative (**24**, prepared from per-acetylated mannose) was coupled on using NIS and $AgBF_4$ (**25**, **Scheme 6**). Conversion of the cyanide to the amide was then carried out utilizing a platinum complex and the 5''-OAc deprotected using tin. BOM deprotection followed by Parikh-Doering oxidation (SO_3•py) resulted in concurrent elimination of the 4''-acetate. The synthesis was rounded out with oxidation of the unsaturated aldehyde to the acid, coupling of 2-(*S*)-aminocaprolactam, and global deprotection.

As with the earlier synthesis, the majority of the synthetic effort revolved around elaboration of the uridine moiety. In both syntheses the need for numerous protection and deprotection steps as well as step intensive Mitsunobu inversions bogs down the overall synthetic methodology.

Scheme 1.6: Finishing the Synthesis



In light of this, we embarked on the synthesis of the capuramycin family of nucleoside antibiotics with the intention of providing a simple, scalable synthetic route that would allow rapid development of unique analogues for SAR studies. We sought out methods to avoid extensive use of protecting groups as well as providing ample opportunity to make critical changes to the overall carbon skeleton.

1.6 Our Retrosynthetic Methodology

We initially sought to complete a rapid synthesis of a core structure similar to **5** that would allow diversification as well as feeding experiments to the known enzymes. Our end target became the total synthesis of A-500359A (**4**) for two main reasons. First, no total synthesis of **4** had yet been reported due to the need to construct the aminocaprolactam from the ground up (unlike capuramycin where the lactam is commercially available). The need for ground up construction would also give use a valuable opportunity to modify the seven-membered lactam ring system; something that had not previously been tried. Second, while **1** and **4** showed similar overall activity profiles, non-natural analogs of **4** have been shown to be significantly more active than identical analogs of **1**.

Our initial retrosynthetic analysis is shown in **Scheme 1.7**. We aimed to break the molecule into three roughly equal portions and build each up independently before final couplings and deprotections. In this convergent manner, we'd cut down on the longest linear sequence and allow synthesis of more material than would be possible by a linear approach.

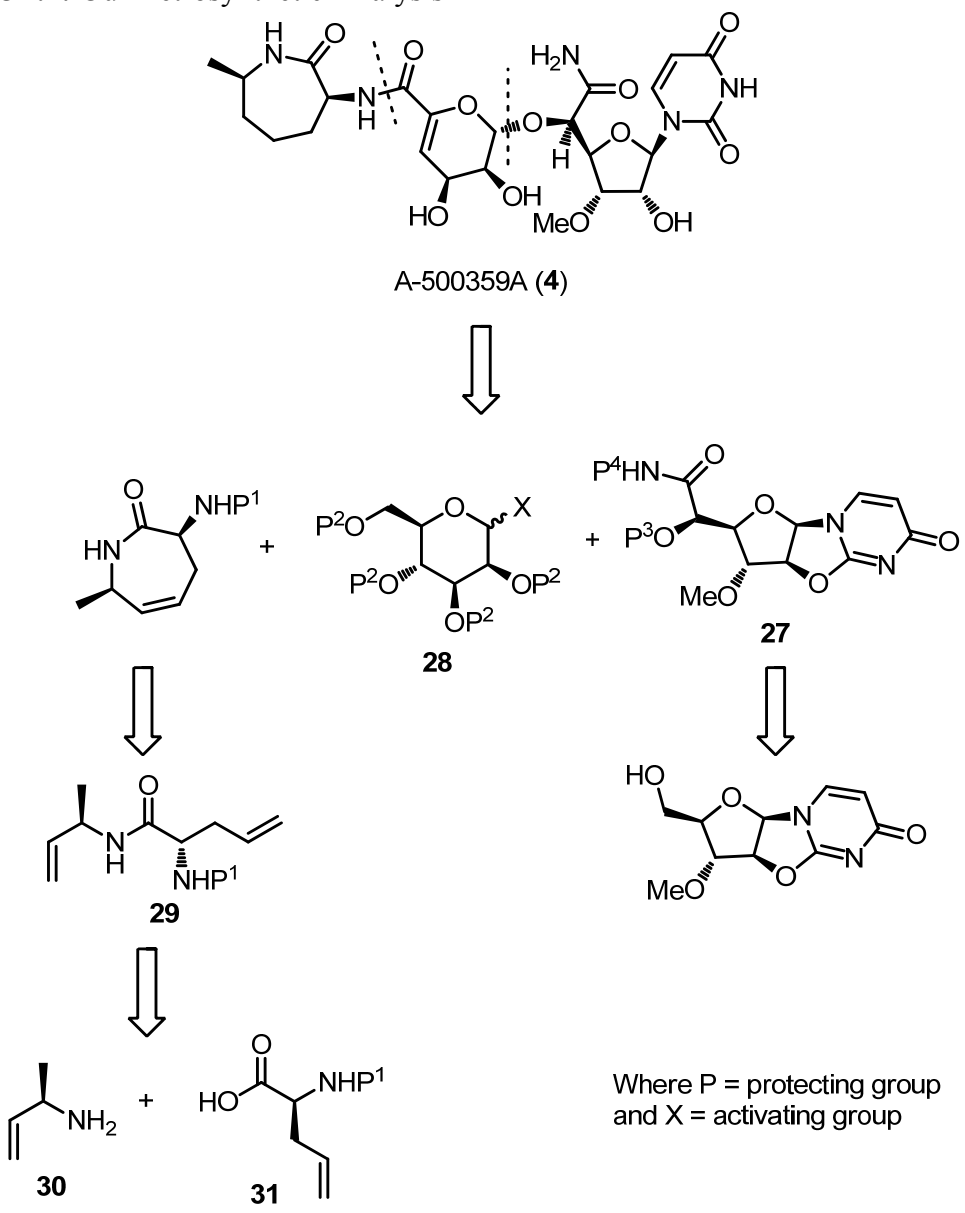
We envisioned the uridine portion arising from a cyclouridine type structure such as **27** derived from a 3'-*O*-methyl cyclouridine which would come from cyclouridine itself. The benefits, we rationalized, of this approach were: the commercial availability of cyclouridine, the elimination of one hydroxyl and the uracil amide from the reactivity, and the disparate reactivity between the remaining two hydroxyls.

Our initial thoughts for the middle uronic acid segment utilized the well-established chemistry seen in the Knapp synthesis with a few modifications. We envisioned using a suitably protected and activated mannose derivative (**28**) that could be readily prepared from cheap mannose.

For the synthesis of the aminocaprolactam, we would need to install functionality that could be burned off prior to coupling to the remainder of the molecule. An endo-cyclic double bond would allow for a ring closing reaction of a suitably protected linear amide such as **29**. This linear amide would then be derived from the coupling of a chiral 3-amino-propene unit (**30**) and an *N*-protected allylglycine (**31**).

We hypothesized that this route would provide a straightforward synthesis of the capuramycin family while providing ample opportunity for structural modifications. Furthermore, key intermediates could be fed to isolated enzymes in the biosynthetic pathway to help elucidate their function and substrate scope.

Scheme 1.7: Our Retrosynthetic Analysis



Chapter 2: The Uridine Moiety

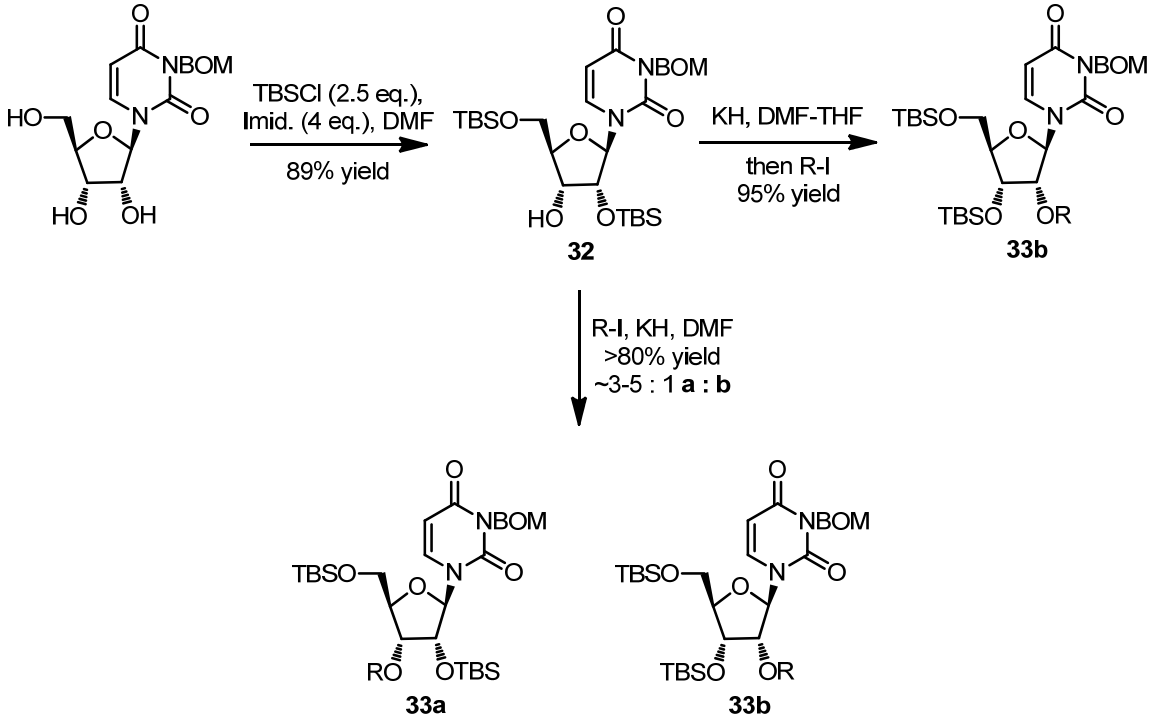
2.1 Background

As demonstrated in the previous chapter, the synthesis of the uridine unit of the capuramycin family remains a difficult synthetic venture. Selective methylation of the 3'-*O*-methyl ether normally requires numerous instances of protection and deprotection while setting the 5'-stereochemistry remains a challenge despite the implementation of chiral catalysis.

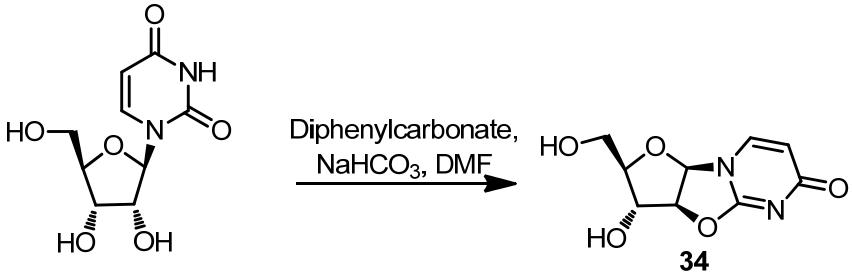
Another paper published by Kurosu and Li further demonstrates the issues with 3'-methylation.[18] During work to synthesize non-natural analogs, Kurosu synthesized a 2', 5'-bis-TBS uridine derivative **32** (**Scheme 2.1**). It was found that reacting **32** with alkyl iodides and KH in DMF provided a mixture of alkylated isomers at the 2' and 3'-positions with moderate selectivity for the 3'-*O*-methyl ether. Pre-treating **32** with KH in DMF-THF followed by alkyl iodide quench resulted in formation of only **33b** after TBS migration.. Thus, while selective protection of the 2' and 5'-positions is possible, any further elaborations would be hampered by the possibility of protecting group walking.

We hoped to overcome these issues by starting from commercially available cyclouridine **34** (TCI 9.10 $/g, **Scheme 2.2**). Cyclouridine is also readily synthesized by reacting uridine with diphenylcarbonate and catalytic base in hot DMF.[19] The cyclouridine precipitates out and is easily collected via filtration in pure form. Cyclouridine and other cyclonucleosides are well known and can be prepared from any of the hydroxyls around the ribose unit.[20] Furthermore, numerous biologically active cyclonucleosides are known, and thus cyclouridine represents an excellent opportunity for novel capuramycin analogs.

Scheme 2.1: Silylation of Uridine



Scheme 2.2: Synthesis of Cyclouridine



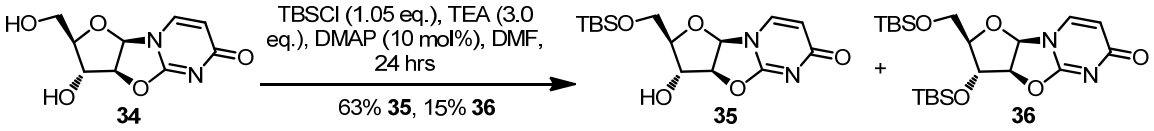
The use of cyclouridine eliminates both the 2'-hydroxyl as well as the uracil imide. Ideally, this would mean the need for only a single protecting group to be installed at the 5'-position, leaving the 3'-OH open for methylation. After deprotection, oxidation of the primary alcohol to the aldehyde would present a useable substrate for a Passerini type reaction to install the α-hydroxy amide linker for the remainder of the molecule.

2.2 Work Utilizing Cyclouridine

Our synthesis began with attempts to directly methylate the 3'-OH of cyclouridine. Initial attempts were made utilizing stannylene acetal chemistry similar to that seen in Kurosu's synthesis of capuramycin.[17, 21] While the stannylene acetal could be generated using standard dibutyltin oxide conditions, the resultant methylation yielded only complex mixtures from which no useable product could be isolated. Other attempts were made using Ag_2O[22] and phenylboronic acid[23] to affect this transformation to no avail.

From here we turned to standard protection of the 5'-hydroxyl group. Initial attempts with trityl chloride in refluxing pyridine did not yield any useable product. Standard silylation conditions (TBSCl 1.2 eq., Imid. 2.5 eq., DMF) resulted in only a 57% yield of the desired 5'-silyl ether (with a small amount of 3', 5'-bis-silyl product). The use of $AgNO_3$ did not yield any suitable product.[24] It was found, however, that the combination of TBSCl (1.05 eq.), TEA (3 eq.), and DMAP (10 mol%), in DMF[25] provided an improved 63% of **35** along with 15% of the bis-silyl ether **36** (yield relative to uridine, **Scheme 2.3**). Normally, these results would be unexpected since the conditions should be selective for the primary alcohol. Most likely, the poor solubility of cyclouridine is to blame. As the first silylation event takes place, the product is more soluble than the starting material, giving it more time to react further.

Scheme 2.3: Silylation of Cyclouridine



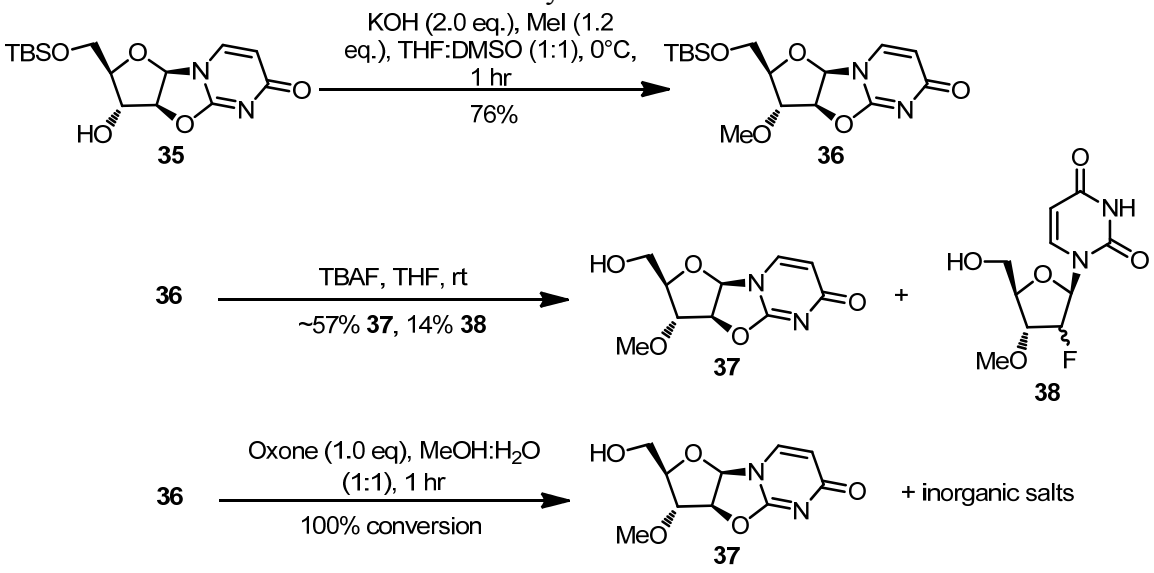
In any event, the desired mono-silyl ether could be prepared on gram scale using this methodology. From here we attempted to methylate the 3'-position. Standard procedures using strong bases such as NaH or KO*t*Bu proved to be untenable due to the instability of the cyclouridine framework. In the presence of such strong bases, abstraction of the 1'-hydrogren followed by elimination of the uracil ring yields the 1', 2'-unsaturated uridine product.

Purdie methylation (Ag_2O, MeI)[22] did appear to yield the desired product in low yield. Competing ring opening proved to be a major shortcoming for this methodology

and yielded undesired 2'-*O*-methyl arabino products. Attempts to utilize Meerwein's Salt ($Me_3O^+BF_4^-$)[26] and Proton Sponge or DBU and MeI resulted in complex mixtures and no reaction, respectively.

With some experimentation, it was found that reacting **35** with 2 eq. of powdered KOH, and 1.1 eq. MeI in 1:1 THF:DMSO at 0°C provided the desired methyl ether **36** in 76% yield with little to no side products (**Scheme 2.4**).[27] Extended reaction times or increased temperatures invariably led to the formation of side products, however.

Scheme 2.4: Elaboration of the 3'-*O*-Methylether



Deprotection of the 5'-*O*-TBS ether was then attempted using standard conditions (TBAF in THF).[28] The desired product **37** could be isolated, albeit in only 57% yield. Complicating the deprotection were several factors: 1) the desired product was very polar making column chromatography and separation from tetra-butylammonium salts difficult and 2) competing cyclouridine opening due to fluoride addition. Indeed, the 2'-fluorinated compound (**38**) was isolated in 14% yield.

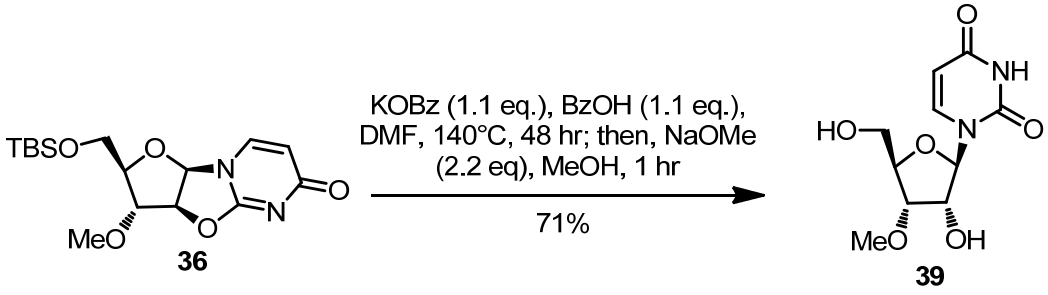
Removal of the TBS group with acid was deemed untenable due to the instability of the cyclouridine framework to acidic conditions. Instead **36** was treated with 1 eq. of Oxone in 1:1 MeOH:H_2O.[29] LC/MS of the reaction mixture showed complete conversion within an hour and formation of only a single new peak with mass matching the desired product (**37**). Isolation proved to be the stumbling point again, however. The extreme

polarity of **37** rendered extraction away from the spent Oxone impossible and normal phase column chromatography difficult. Reverse phase MPLC was attempted utilizing the Biotage Flash and C18 Snap Cartridges. However, decomposition of the product was observed and clean isolation from residual Oxone salts proved difficult. Furthermore, the deprotected cyclouridine in this impure state was found to not be a viable substrate for the following oxidation and Passerini reaction.

Changing tactics, opening of the cyclouridine tricycle at this point was attempted. If opening with an oxygen nucleophile that could then be deprotected was achievable, then it would be possible to avoid the extreme polarity of **37**. Searching the literature provided a bleak outlook, however.[30] Oxygen nucleophiles preferentially attack the tricycle at the 2-position (uracil numbering) providing the arabino product after ring opening. In only a few limited cases has the ribo product been achieved with an oxygen nucleophile.

Reacting **36** with KOBz (1.0 eq.) and BzOH (1.0 eq.) in refluxing DMF for 48 hours followed by addition of MeOH and NaOMe and chromatography provided an opened uridine with no 5'-O-TBS group in 71% yield (**39**, **Scheme 2.5**).[30] The coupling constants of the sugar unit suggested the correct ribo configuration.

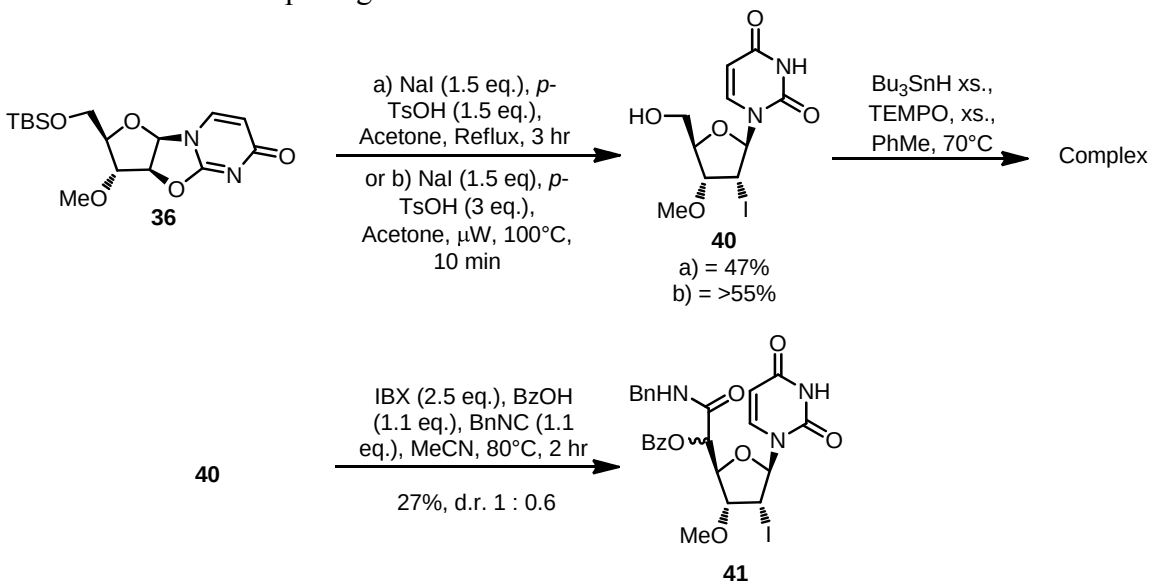
Scheme 2.5: Attempted Cyclouridine Ring Opening



Due to the need to distinguish between the two alcohols of this opened uridine, we next explored opening of the ring system with iodine. It is known that iodide attacks yielding the desired ribo product.[30] It was believed that exposing the iodide to a radical initiator and then trapping with TEMPO would provide a useful intermediate. The TEMPO would then be deprotected utilizing Zn in acid.[31] To this end, **36** was treated with NaI (1.5 eq.) and *p*-TsOH (1.5 eq.) in refluxing acetone for three hours (**Scheme**

2.6).[32] After workup and column it was found that the iodine had indeed added in along with concurrent TBS deprotection to afford **40** in 47% yield. Adding 3 eq. of *p*-TsOH and irradiating the mixture in the microwave gave a variable yield of **40** ranging from 50% to >80%. Subsequent attempts were made to exploit the iodine by treating with excess Bu_3SnH and excess TEMPO in 70°C PhMe which led to a complex mixture from which nothing could be isolated. Reaction of **40** under oxidative Passerini conditions (that is 2.5 eq. of IBX, 1.1 eq. of BzOH, and 1.1 eq. of BnNC in refluxing acetonitrile) yielded **41** in 29% yield as a 1 : 0.6 mixture of diastereomers.[33]

Scheme 2.6: Iodide Opening of **36**



The aggravation of the cyclouridine's inherent fragility and incorrigible reactivity profile led us to consider other means of constructing the uridine core of these molecules.

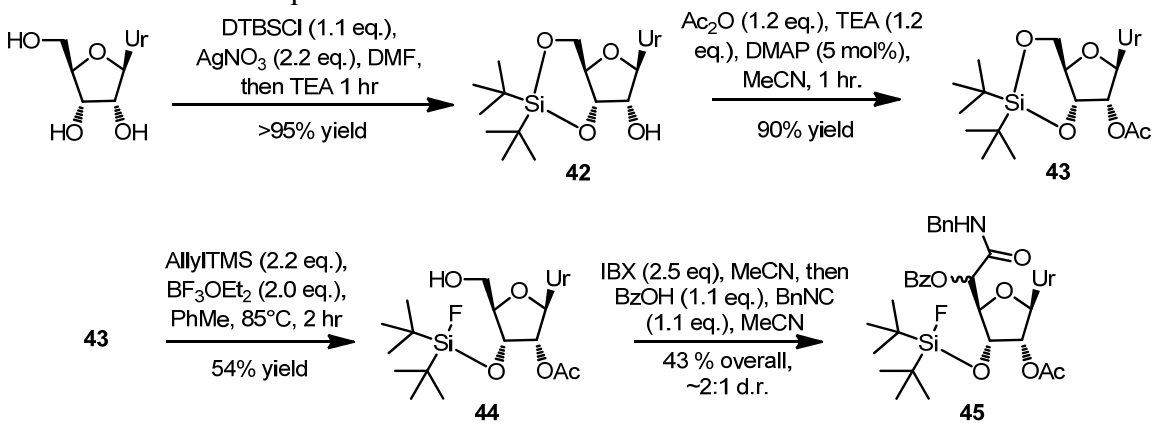
2.3 Bis-5'-3'-protection

After leaving behind the cyclouridine route, we began exploring 3', 5'-bis-protection as a means to juggle the hydroxyl groups of uridine. Indeed, such protection is known in the literature through a *tert*-butylsilylene moiety.[28] This protecting group also offers the ability to selectively deprotect at a single position. Theoretically, protection of the 3' and 5'-positions followed by orthogonal protection of the 2'-hydroxyl and finally

selective deprotection of the least hindered (5') alcohol would achieve a uridine unit suitable for elaboration.

To realize this, uridine was reacted with di-*tert*-butyldichlorosilane (1.1 eq.) and $AgNO_3$ (2.2 eq.) in DMF followed by addition of TEA (2.2 eq.).[34] The desired di-*tert*-butylsilylene uridine (**42**) was then isolated in >95% yield as a white solid (**Scheme 2.7**). The 2'-position of **42** was then protected as the acetate via standard conditions (Ac_2O, TEA, DMAP) in 90% yield.

Scheme 2.7: *Bis*-3'-5'-protection of Uridine and Elaboration



To effect selective unmasking, a fluoride source is used alongside a fluorine scavenger to moderate the overall reactivity and prevent complete deprotection. By treating **43** with BF_3•Et_2O (2.0 eq.) and allylTMS (2.2 eq.) in toluene (0.08 M, 85°C, 2 hrs)[35] the desired mono-deprotection could be induced. However, the free 5' product (**44**) could only be isolated in upwards of 54% after chromatography.

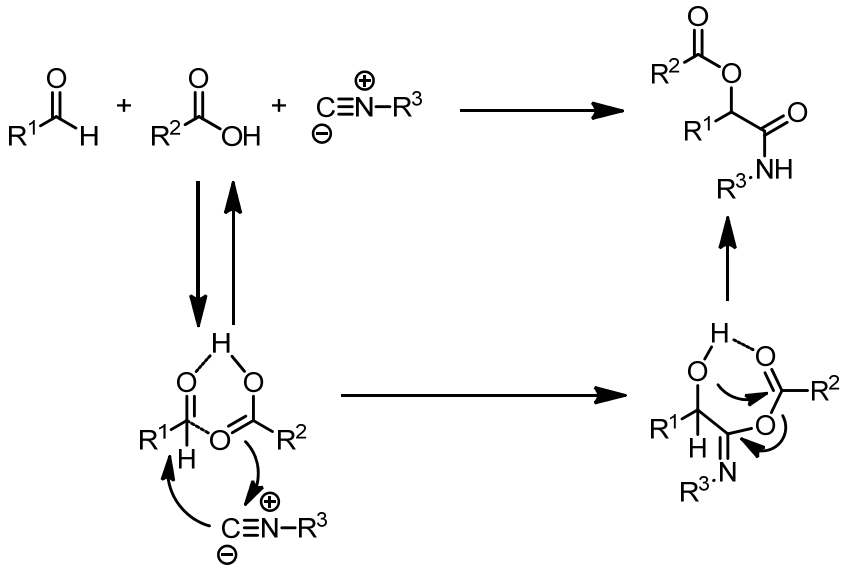
From here, oxidation of the free 5'-hydroxyl was effected using IBX (2.5 eq.) in gently refluxing acetonitrile (0.5 M).[36] After filtration to remove spent IBX, the residue was immediately subjected to a Passerini reaction with benzyl isocyanide (1.1 eq.) and benzoic acid (1.1 eq.) in acetonitrile (0.5 M). Following the reaction via LC/MS showed formation of two products with identical masses corresponding to the two possible diastereomers. After work-up, the diastereomers (**45**) could be separated via slow column chromatography in yields of 29% and 14%. No identification of the configurations was made due to the tiny amount of material recovered.

An attempt to deprotect the 3'-silyl ether was made using TBAF, however, no products could be isolated via PTLC.

2.4 Exploration of the Passerini Reaction

For elaboration of the 5'-glycosidic linkage and carboxamide, we envisioned utilization of the nearly century old Passerini reaction.[37] The Passerini reaction represents one of the first multi-component reactions to be explored. During the reaction, a ketone or aldehyde reacts with a carboxylic acid and isocyanide to yield an α-acyloxy amide as seen in **Scheme 2.8**.[38] The reaction mechanism is postulated to involve initial acidic activation of the aldehyde by the acid. The formally divalent isocyanide then inserts between the acid and aldehyde. Acyl migration occurs, forming the amide as well as the ester. The mild and flexible nature of the reaction has made it very popular for rapid library construction.

Scheme 2.8: The Passerini Reaction

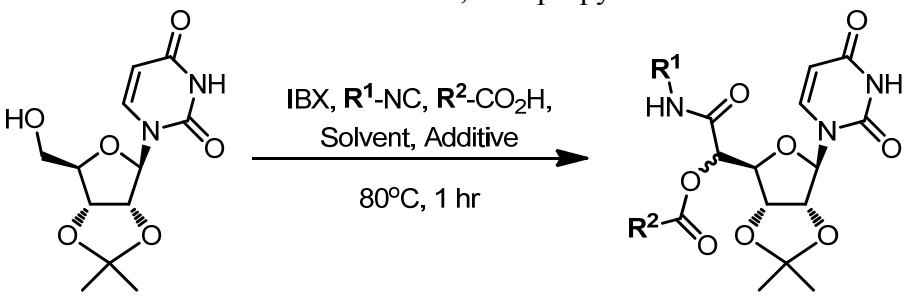


The major drawback for our purposes, however, was the lack of stereocontrol during the course of the reaction. Indeed, only a handful of examples utilizing chiral substrates[39] or ligands[40] have been demonstrated in the literature and usually with only

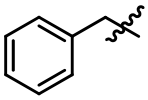
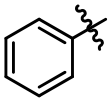
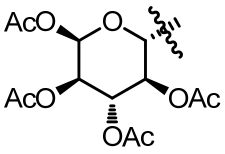
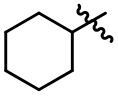
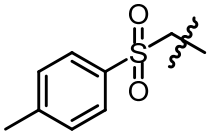
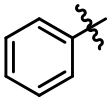
limited selectivity. We initially theorized that the chiral nature of the uridine substrate would provide some measure of induction during the course of the reaction.

To test this hypothesis we started by synthesizing 2', 3'-isopropylidene-uridine **46** from uridine and 2, 2-dimethoxypropane with catalytic *p*-toluenesulfonic acid.[28] Compound **46** was then subjected to an oxidative Passerini reaction utilizing IBX as the oxidant and a variety of isocyanides and acids to yield adducts **47** (**Table 2.1**).[33]

Table 2.1: Oxidative Passerini Reaction of 2',3'-isopropylidene Uridine



46 **47**

Entry	Solvent	R^1	R^2	Yield
1	Anhydr. MeCN			76%
2	MeCN			85%
3	MeCN:H_2O (1:1)			NR
4	MeCN			67%
5				56%
6				39%
7				0%

Our baseline reaction was **46** with benzoic acid and benzyl isocyanide in acetonitrile. It was found that under anhydrous conditions (entry 1) the product did form in moderate yield but with no selectivity. Acetonitrile directly out of the bottle (not dried) improved the yield to 85% (entry 2) but with no change in diastereoselectivity. Addition of water completely shut down the reaction pathway.

Acetic acid also proved to be a viable reaction partner (entry 4) albeit in depressed yield. The use of a chiral auxiliary acid (entry 5)[39a] resulted in moderate yield but no change in selectivity. Swapping for the more bulky cyclohexylisocyanide and the chiral auxiliary did yield a poor amount of product, but with no apparent change to the diastereoselectivity (entry 6). Finally, TOSMIC proved to be an unacceptable partner in the reaction (entry 7).

We postulated at this point that we could induce selectivity through the use of a chiral catalyst.[40] We envisioned a chiral phosphoric acid that would both activate the aldehyde for isocyanide attack and induce chirality in the product by guiding the isocyanide.[40, 41] We began work on a series of BINOL derived phosphoric acids for use in this project as well as for implementation into a general, enantioselective Passerini reaction. Due to Dr. Elliott's resignation, however, the project was terminated.

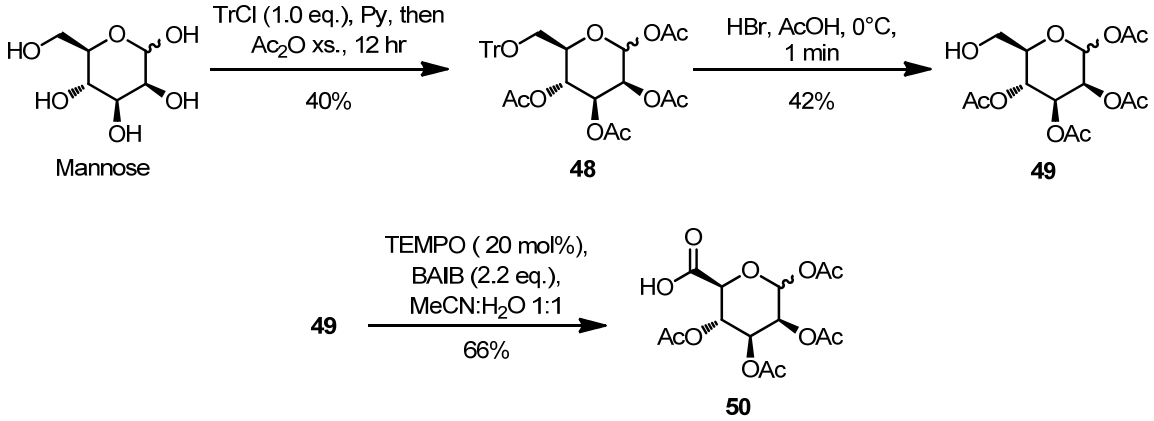
Chapter 3: The Hexauronic Linker

3.1 Background

As with the uridine core discussed in the previous chapter, synthesis of the hexauronic acid linker has several major issues involved. Foremost, is again, the need to juggle numerous reactive groups around the ring. The use of a substantial number of protection and deprotection steps is normally required to manipulate such carbohydrates and provide desired openings for elaboration. However, this mires the synthesis in added steps that detract from the overall yields and robustness of the route. A synthesis, minimizing the use of protecting groups would be highly desirable from a medicinal chemistry standpoint.

Initially, we wished to follow a route similar to the one laid down by Knapp and Nandan.[16] Their starting point, however, requires several steps from commercially available mannose. First, the 5-OH is tritylated followed by per-acetylation to achieve **48** in fair yield after recrystallization (**Scheme 3.1**).[42] Deprotection of the trityl group using HBr in acetic acid proved simple (42% yield), however recrystallization of the resultant tetra-acetate **49** was troublesome. TEMPO oxidation went smoothly in a decent 66% yield to afford acid **50**.

Scheme 3.1: Modified Knapp Route

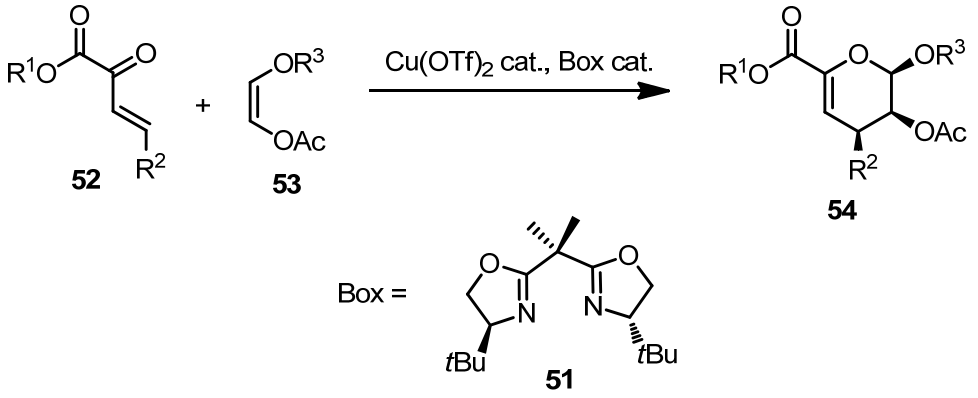


Upon further consideration, we found this route to be undesirable due to its use of numerous protecting groups as well as the overall inflexibility. Indeed, it would be very difficult to distinguish the 2, 3, and 4-hydroxyls around the mannose ring, preventing synthesis of analogues for SAR studies. We soon began contemplating a new approach that would allow for structural modifications without the need to resort to extensive and tedious protecting group interchanges.

3.2 Hetero-Diels–Alder Chemistry

There is extensive precedent for the synthesis of carbohydrate derivatives employing a hetero-Diels–Alder reaction to quickly construct the 6-member framework.[43] We were particularly intrigued by the work of Evans[43d] and Jørgensen[43e] where a copper catalyst employing box ligands (**51**, **Scheme 3.2**) was used to fuse a β, γ-unsaturated-α-keto esters (**52**) with a vinyl ether (**53**) to give a carbohydrate derivative **54**. We felt that this methodology would allow rapid construction of the hexauronic acid linker and provide ample flexibility to modify different positions around the ring system.

Scheme 3.2: Hetero-Diels–Alder Synthesis of Carbohydrates

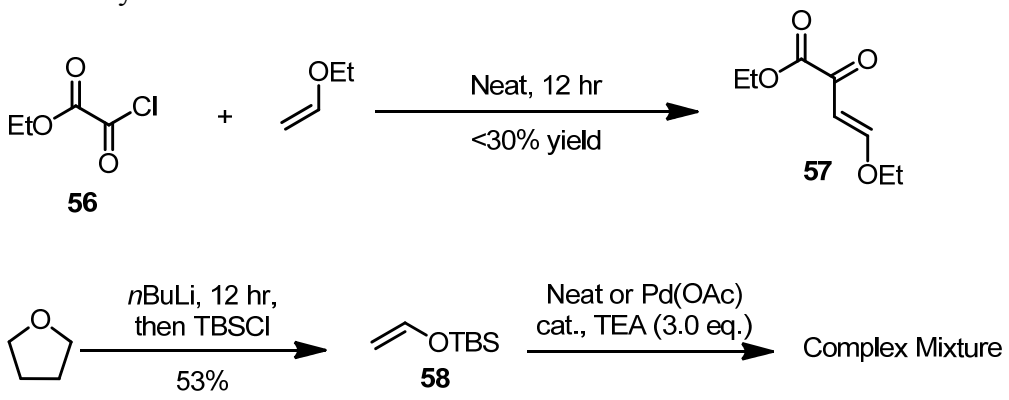


We began with the known synthesis of keto ester **55** from ethyl chloro(oxo)acetate (**56**) and ethyl vinyl ether (EVE) (**Scheme 3.3**).[44] Adding EVE to neat **56** at 0°C and allowing to warm overnight followed by distillation afforded the desired keto ester **57** in low yield.

Several other vinyl ethers were synthesized in an attempt to allow the simplest deprotection of the carbohydrate possible. TBS vinyl ether (**58**) was synthesized by

reaction of THF with *n*BuLi followed by quenching with TBSCl in 53% yield following distillation. Attempted coupling with **58** using the conditions listed above only produced a complex mixture. Fearing cleavage of the silyl group via formed HCl, TEA was added as an acid scavenger. No product could be isolated, however.

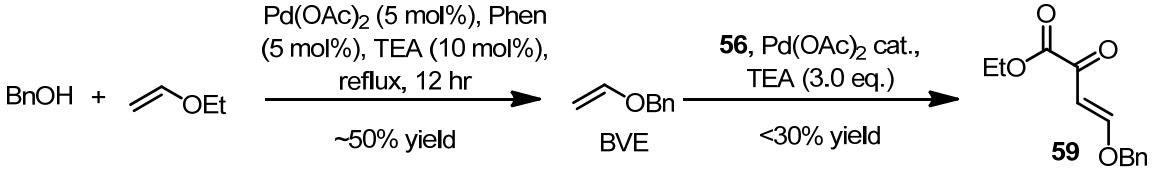
Scheme 3.3: Synthesis of Hetero-Dienes



From here we attempted to make a benzyl variant. Benzyl vinyl ether (BVE) is known to be accessible in moderate yield via a mercury promoted exchange between BnOH and EVE following tedious distillation.[45] In our hands the reaction proved to be untenable and the need for super-stoichiometric amounts of mercury further added to the need for a new method. Searching the literature revealed that the same transformation could be conducted utilizing palladium and a phenanthroline ligand.[46] Indeed, treatment of BnOH with EVE (20 eq.), $Pd(OAc)_4$ (5 mol%), phenanthroline (5 mol%), and TEA (10 mol%) provided pure BVE in >50% yield after filtration of the reaction through activated charcoal and evaporation of excess EVE (**Scheme 3.4**).

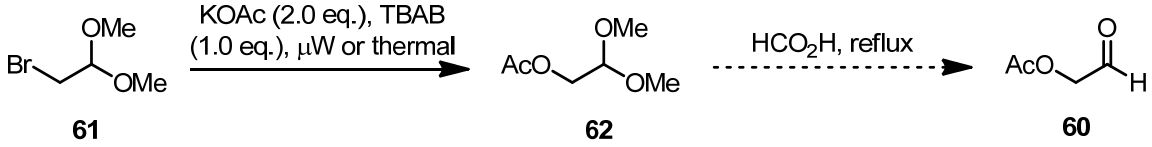
The collected BVE could be combined with **56** to provide the hetero-diene **59** in low yields. It was found that the product could only be isolated in reasonable amounts using extremely fast column chromatography due to **59**'s notable fragility.

Scheme 3.4: Synthesis of Benzyl Substituted Hetero-Diene



From here it was necessary to prepare the dienophiles to complete the hetero-Diels–Alder reaction. We sought compounds that would either provide a pre-activated carbohydrate post-cycloaddition or would allow for simple deprotection and activation. To this end we initially attempted to make acetoxy acetaldehyde (**60**, **Scheme 3.5**) which can then be converted into *cis*-1-acetoxy-2(trimethylsiloxy)ethene, providing a useable dienophile.[47] The microwave reaction of bromoacetaldehyde dimethyl acetal (**61**) with KOAc (2.0 eq) and TBAB (1.0 eq.) in acetonitrile provided acetoxyacetaldehyde dimethyl acetal (**62**) as a somewhat impure liquid after distillation. Decomposition of the dimethyl acetal was attempted in refluxing formic acid; however, no product was obtained.

Scheme 3.5: Attempted Synthesis of **60**

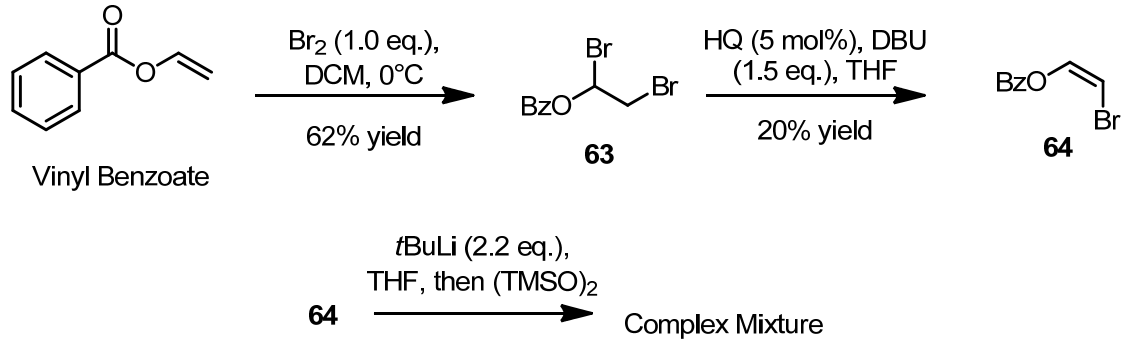


61 **62** **60**

We changed tact here by attempting to synthesize the benzoate analog of *cis*-1-acetoxy-2(trimethylsiloxy)ethene which we hypothesized would be easier to handle overall. Commercially available vinyl benzoate was reacted with 1 eq. of molecular bromine in DCM at 0°C to provide 1, 2-dibromoethyl benzoate **63** in 62% yield after column chromatography (**Scheme 3.6**).[48] **63** was then treated with hydroquinone (HQ, 5 mol%) and DBU (1.5 eq.) in THF to provide isomerically pure **64** in 20% yield. This was then subjected to lithium-halogen exchange using *t*BuLi and careful quench with trimethylsilyl peroxide. To our consternation, only a complex mixture resulted, presumably from attack of the anion on the benzoate moiety.

It is known that α-oxy aldehydes can be converted, with good geometric selectivity, into acetoxy ethenes analogous to the dienophiles we desired.[49] We designed a group of three such aldehydes with α-benzyloxy, α-silyloxy, and α-phenylthio groups that could then be transformed into the requisite dienophiles with either amenable protecting groups or activating groups at the anomeric position.

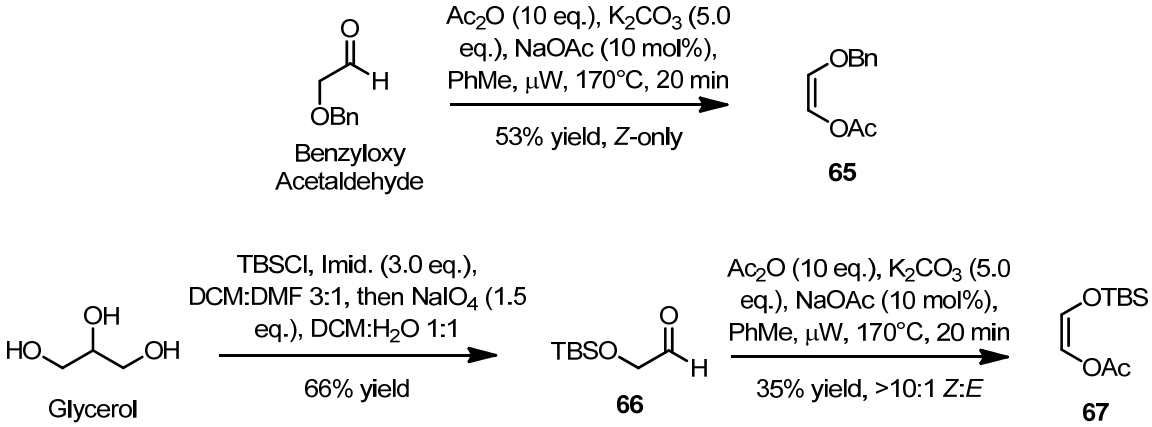
Scheme 3.6: Attempted Synthesis of *cis*-1-benzoyloxy-2-(trimethylsiloxy)ethene



We started with commercially available benzyloxy acetaldehyde and reacted it with Ac_2O (10 eq.), K_2CO_3 (5 eq.), and NaOAc (10 mol%) in PhMe in the microwave. After 20 minutes at 170°C and chromatography, the desired *Z*-alkene **65** was obtained in 53% yield and with no trace of the *E*-isomer (**Scheme 3.7**).

The *tert*-butyldimethylsiloxy acetaldehyde was synthesized in two steps from glycerol.[50] Mono-silylation of glycerol was obtained by treatment of TBSCl with excess glycerol and imidazole (3 eq.) in DCM:DMF (3:1). The crude extract was then treated with $NaIO_4$ (1.5 eq.) in a 1:1 mixture of DCM and H_2O to provide 66% of **66** after work-up. This aldehyde was then subjected to the previously mentioned conditions to afford **67** in only 35% yield with >10:1 geometric selectivity for the *Z*-isomer.

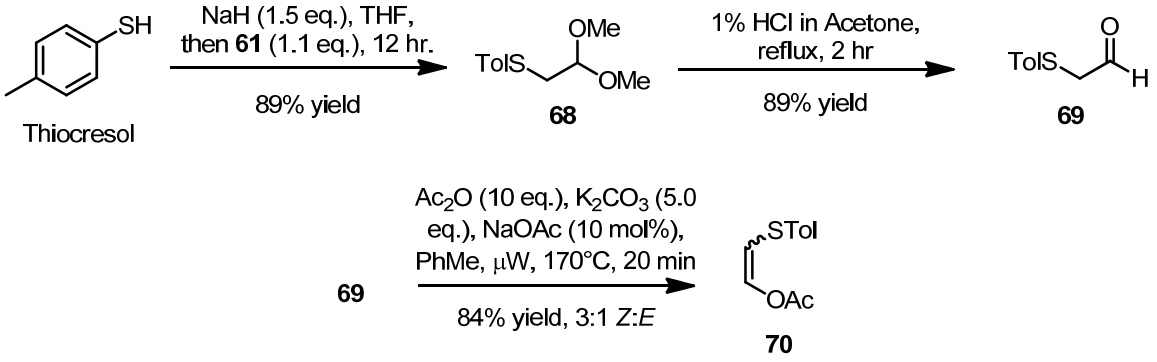
Scheme 3.7: Synthesis of -OBn and -OTBS Dienophiles



We had the most hope for the thioether derivative. After cycloaddition, this derivative would place an activating group on the anomeric position, leaving the product ready to couple with no further modifications.[51] To obtain the dienophile, thiocresol was

treated with NaH (1.5 eq.) in THF and then quenched with bromoacetaldehyde dimethyl acetal **61** (**Scheme 3.8**). Colum chromatography provided **68** in 89% yield which was then deprotected by refluxing in acetone with HCl followed by solvent evaporation to yield aldehyde **69** in 89% yield.[52] Subjecting **69** to the standard conditions provided **70** as a mixture of geometric isomers in 84% yield (*Z*:*E* = 3:1). While the desired Z isomer was favored by the reaction, the mixture proved to be virtually inseparable. Enrichment was possible via *very* slow column chromatography to ratios as high as 20:1.

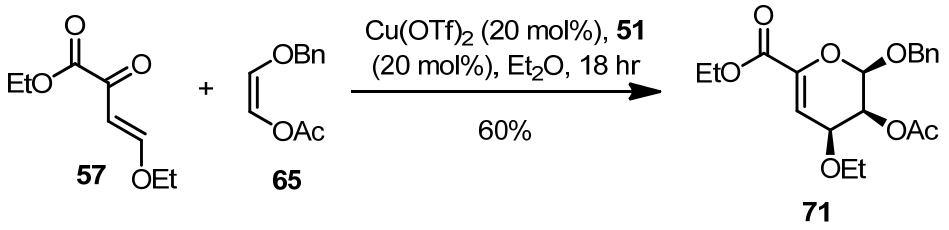
Scheme 3.8: Synthesis of Sulfur Containing Dienophile



Turning now to the actual hetero-Diels–Alder reaction, we hoped to first replicate results presented in previous papers.[43e] To this end, hetero-diene **57** was reacted with benzyl dienophile **65** (1.5 eq.), $Cu(OTf)_2$ (20 mol%), and box ligand **51** (20 mol%) in freshly distilled ether (**Scheme 3.9**). After stirring overnight, the product carbohydrate derivative was obtained in 60% yield via chromatography (literature yield: 61%, 66% ee). The carbohydrate **71** was then treated with BBr_3 in DCM. Analysis of the reaction mixture showed that the pyran ring was preferentially being cleaved to either the exocyclic benzyl or ethyl ether.

Bolstered by this initial result, we attempted to run the reaction utilizing **59** and benzyl dienophile **65**. However, only a minute amount of product was observed. In the case of the TBS (**67**) and thiopcresol (**70**) dienophiles no reaction was observed to take place.

Scheme 3.9: Hetero-Diels–Alder Reaction



Given the extreme fragility of the hetero-diene and the lack of positive results with the cycloaddition, it was decided to abandon this route in favor of a more direct approach from mannose.

3.3 Direct Mannose Approach

Turning back towards this more linear approach, we still desired an approach that would allow flexibility. That is, we wished to distinguish between the hydroxyl substituents on the mannose ring to allow tailoring and potential SAR studies. To that end, it was decided that commercially available methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside (**72**) would be a viable starting point.[53]

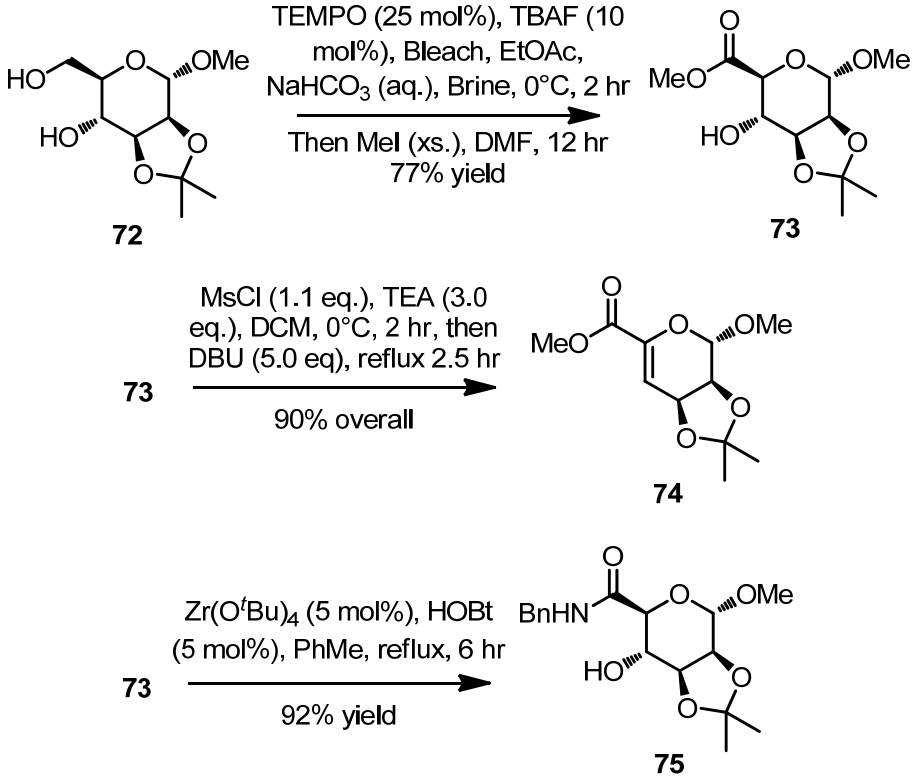
Reaction of **72** with TEMPO (25 mol%), TBAF (10 mol %), and household bleach in a buffered solution of EtOAc, $NaHCO_3$, and brine resulted in selective oxidation at the 5 position to the carboxylic acid (**Scheme 3.10**).[54] The crude acid was then subjected to methylation using MeI in DMF to yield 77% of methyl ester **73**. An attempt was made to couple 2-(*S*)-aminocaprolactam utilizing PyBOP to the crude acid, however, only a complex mixture resulted.

Conversion of the free hydroxyl to the mesylate was accomplished via treatment of **73** with MsCl (1.1 eq.) and TEA (3 eq.) in DCM at 0°C. Addition of 5 eq. DBU to the reaction mixture followed by a 2 hour reflux resulted in clean elimination of the mesylate to give the α-β-unsaturated ester **74** in 90% overall yield after chromatography.

Exploring all options, we wished to find out whether we could use Porco's ester–amide exchange chemistry to install various amide functionalities off of the mannuronic acid.[55] Heating methyl ester **73** with benzylamine (1.1 eq.), $Zr(O^tBu)_4$ (5 mol%), and HOBt (5 mol%) in PhMe resulted in smooth ester-amide exchange giving amide **75** in 92%

yield. Attempts to extend this methodology to the installation of the aminocaprolactam function did not result in any reaction. It was hypothesized that the HCl from the aminocaprolactam salt was inhibiting the reaction; however, addition of DIPEA as a scavenger did not yield any product.

Scheme 3.10: Updated Direct Mannose Route



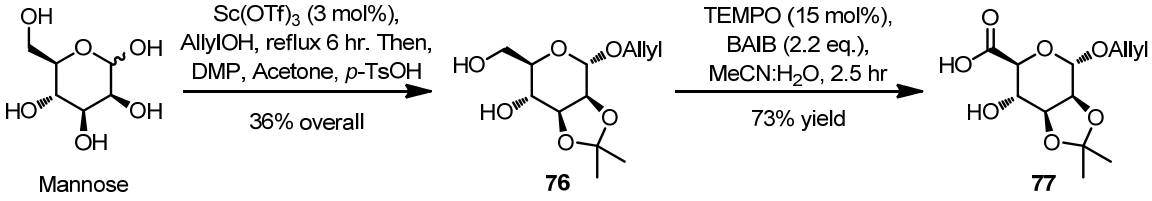
Carbohydrates **73**, **74**, and **75** were subjected to a variety of conditions in an attempt to convert the anomeric methyl ether into an activated thioether moiety. Reactions with TMSSPh and activators such as TMSOTf[51] and ZnI[56] resulted in decomposition of the product or merely silylation of the free hydroxyl of **73**/**75**.

From here, direct cleavage of the anomeric ether was attempted utilizing acidic conditions. In nearly all circumstances (TFA, HCl, AcOH) only isopropylidene deprotection could be observed. When stressed (heating, longer reaction times) these conditions gave intractable mixtures of products. It appeared that the anomeric ether was equivalent to the Rock of Gibraltar.

Due to the remarkable stability of the anomeric methyl ether, we considered switching it out for a more labile group. After consideration and literature searching, we opted to synthesize the allyl ether equivalent. Mannose was refluxed in excess allyl alcohol with $Sc(OTf)_3$ (3 mol%) for 6 hours (**Scheme 3.11**).[57] After evaporation of the excess allyl alcohol, the crude material was subjected to the protecting conditions described previously affording 36% (overall) of **76** along with a trace of the *bis*-isopropylidene.

The standard oxidation conditions used for the methyl-mannoside proved to be recalcitrant when applied to the allyl derivative. Instead BAIB (2.2 eq.) was used as the terminal oxidant with TEMPO (15 mol%) in aqueous acetonitrile.[58] Under these conditions the oxidation was complete in 2.5 hours and acid **77** could be extracted from the condensed solution in 73% yield.

Scheme 3.11: Synthesis of Allyl-protected Mannuronic Acid

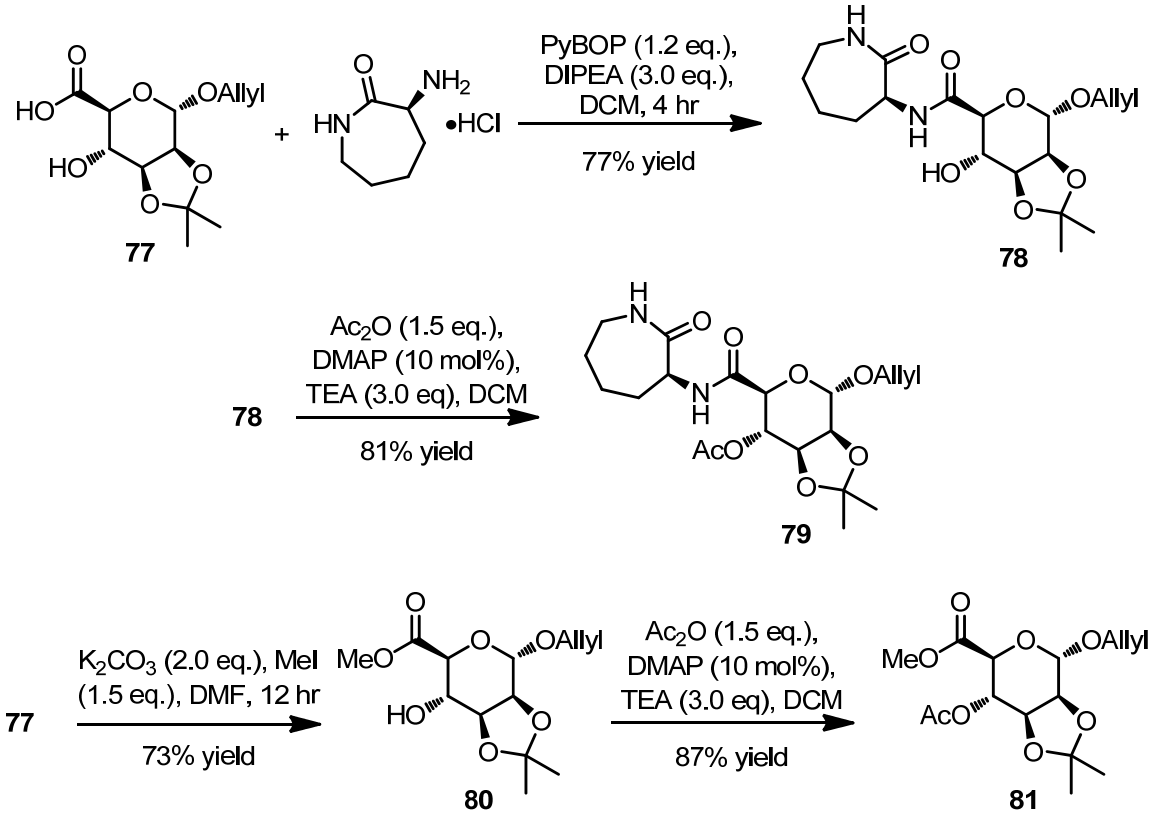


Coupling **77** with 2-(*S*)-aminocaprolactam could be accomplished by stirring with PyBOP (1.2 eq.) and DIPEA (3.0 eq.) in DCM for 4 hours (**Scheme 3.12**). The resultant amide **78** was recovered in 77% yield after column chromatography. The amide was then acetylated at the 4-position using 1.5 eq. Ac_2O along with 10 mol% DMAP and 3 eq. TEA in DCM to provide **79** in 81% yield.

Acid **77** could also be converted into the methyl ester via reaction with K_2CO_3 (2.0 eq.) and MeI (1.5 eq.) in DMF to provide **80** in 73% yield. Acetylation as above provided ester **81** in 87% yield after chromatography.

Deprotection of the allyl ether was attempted using a two-step methodology. First, the allyl group was isomerized using palladium on carbon in refluxing methanol followed by oxidative cleavage using *m*CPBA. In both the case of **79** and **81** the isomerization was found to work, however, the cleavage failed to yield anything other than complicated mixtures of products.

Scheme 3.12: Synthesis of Protected Amide and Ester



Chapter 4: The Amide Tails

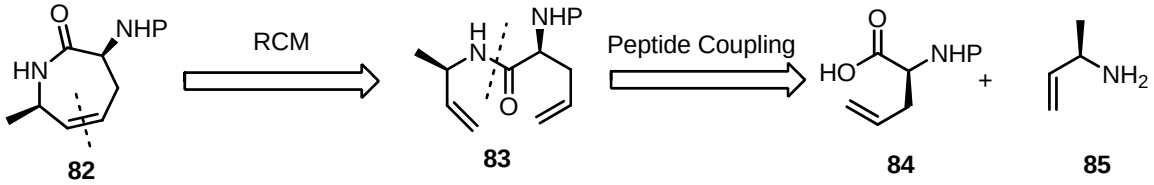
4.1 Background

The amide tail of the capuramycin family is the largest variance between members as well as a critical moiety for biological activity.[13, 15] Fortunately, the capuramycin tail segment, 2-(*S*)-aminocaprolactam, is commercially available in enantiomerically pure form. As such, the previous syntheses merely stapled this structure on at the end of the synthesis.[16, 17]

For our synthesis, we wished to explore other members of the family. Our primary target, A-500359A, has an added chiral methyl group on the lactam ring. While a fairly minute change from capuramycin, this renders a great deal of difficulty onto any synthesis. Notably the need to synthesize this unique tail from the ground up as it is not commercially available.

Our initial aim was to synthesize an intermediate 7-membered lactam possessing an endo-cyclic olefin (**82**, **Scheme 4.1**). This would allow fragmentation into linear fragment **83** that could then be sewn together via ring closing metathesis. The linear fragment would give rise from the coupling of a suitably protected allylglycine (**84**) and (*R*)-3-amino-butene (**85**). We viewed **85** as our initial point of entry into the route as its synthesis had previously been reported.

Scheme 4.1: Initial Retrosynthetic Analysis of the A-500359A Lactam



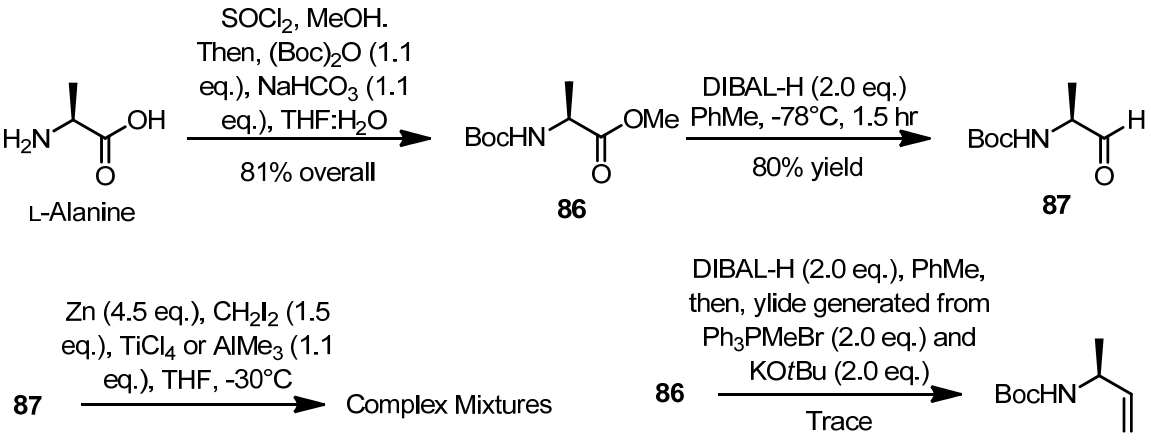
4.2 First Attempted Synthesis of A-500359A Lactam

Our synthesis commenced with the protection of L-alanine. Thionyl chloride in MeOH converted the free acid to its amino ester which was then protected with Boc_2O in

81% overall yield (**Scheme 4.2**). The ester moiety was then partially reduced via careful use of DIBAL-H to yield aldehyde **87** in 80% yield. The key step at this point was conversion of the aldehyde to a methylene unit. Normally, a Wittig olefination would be used; however, there is substantial precedent for the racemization of the chiral center under Wittig conditions.[60]

The Nozaki–Oshima reagent[61] had been used previously to avoid racemization of the chiral center.[59] We attempted to deploy this methodology by reacting **87** with zinc dust (4.5 eq.), diiodomethane (1.5 eq.), and trimethylaluminum (1.1 eq.) in THF. However, a complex mixture resulted from which only starting material was isolated. Activation of the zinc with HCl or switching to $TiCl_4$ did not yield any product either.

Scheme 4.2: Attempted Synthesis of **85**



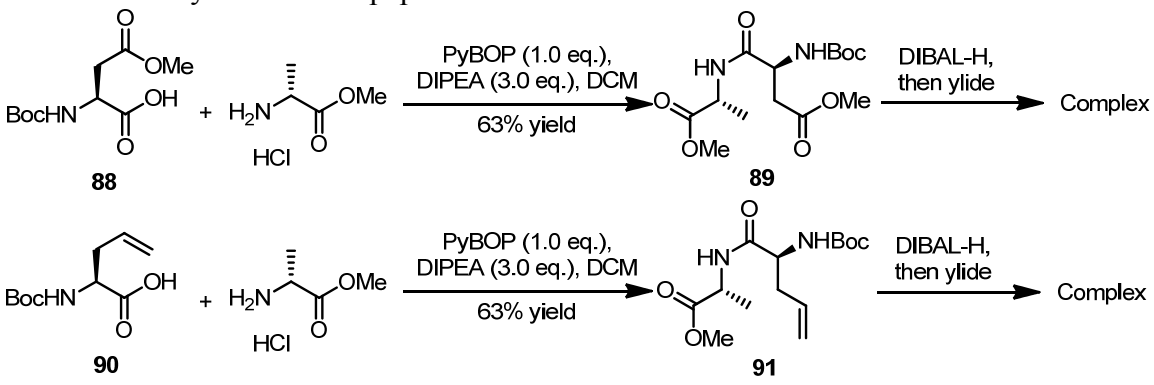
With this negative result we next pursued a modified, one-pot Wittig reaction which had previously been shown to prevent racemization of α-chiral aldehydes.[62] To this end, methyl ester **86** was reduced using 2.0 eq. of DIBAL-H in PhMe at -78°C. The ylide was pre-formed by reacting methyltriphenylphosphonium bromide with potassium *tert*-butoxide in THF. After one hour of reduction, the preformed ylide was cannulated into the first solution and the entire mixture refluxed overnight. Work-up provided an oil by which product could be detected via NMR but only a trace could be isolated.

From here, we investigated whether we could couple our two amino acids together and then install the olefin moieties (Scheme **4.3**). Protected aspartic acid derivative **88** (prepared in two steps, ref. 63) was coupled to D-alanine methylester hydrochloride (1.1 eq.)[64] utilizing PyBOP (1.0 eq.) and DIPEA (3.0 eq.) in DCM. The

dipeptide **89** was isolated in 63% yield following column chromatography (Scheme **4.3**). Attempted one-pot reduction/Wittig olefination only produced a trace amount of product under various conditions.

To help alleviate the need for the two reductions and two olefinations to happen in a single pot, **88** was replaced with *N*-Boc-allylglycine (**90**). Coupling of **90** to D-alanine methyl ester hydrochloride was affected as above to give dipeptide **91** in 63% yield. Attempts to install the single olefin moiety using the two step DIBAL reduction/Nozaki–Oshima olefination and the one step reduction/Wittig met with failure, however.

Scheme 4.3: Synthesis of Dipeptide for Olefination



4.3 Synthesis Utilizing Pyrolysis of Methionine Sulfoxide

We now began to look at alternative routes to the vinylglycine unit of the dipeptide. Our contemplation led us to consider adding additional functional handles to the structure that could then be removed at the appropriate time or provide access to simple analogue compounds. With the primary difficulty centered around installation of the chiral methyl unit, we considered instead having an alcohol moiety further extend the chain. Such a group could be removed by a variety of conditions and would be an exceptionally robust handle for analogue elaboration and SAR studies.

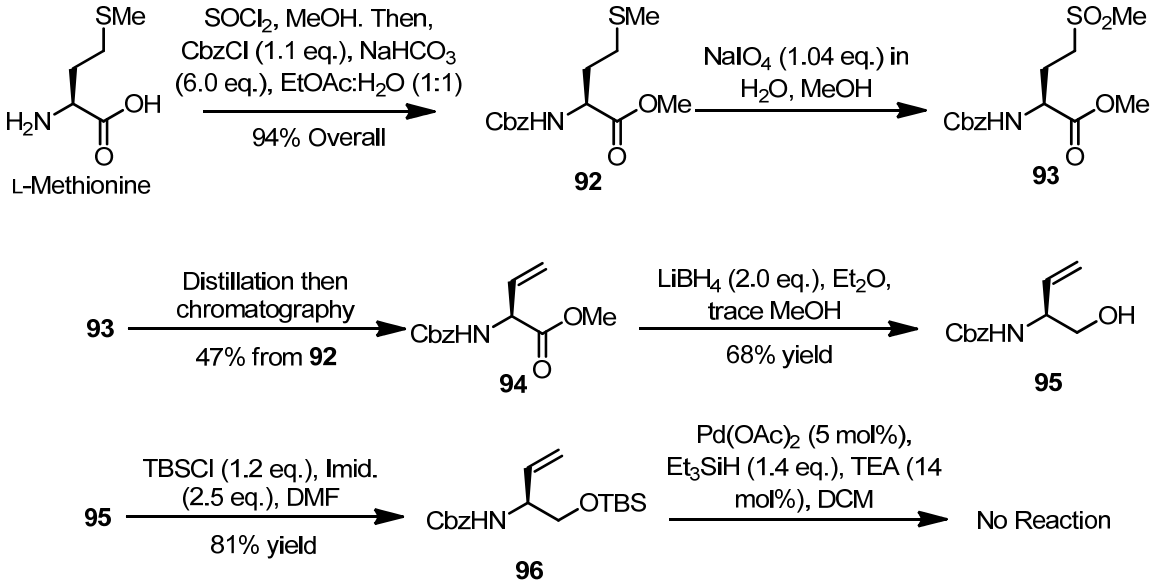
A literature search showed that it was possible to arrive at the desired unit via pyrolysis of a methionine sulfoxide.[65] L-Methionine was first transformed into its methyl ester followed by *N*-protection as a Cbz carbamate ($NaHCO_3$ [6.0 eq.] CbzCl [1.1 eq.], H_2O:EtOAc [1:1]) in 94% yield for the two steps (**92**, **Scheme 4.4**). Oxidation of the

sulfide to the sulfoxide was accomplished using $NaIO_4$ (1.04 eq.) in methanol at 0°C. The clear oil obtained upon work-up was found to be pure sulfoxide **93**. This sulfoxide was then subjected to pyrolysis via distillation on a Kugelrohr to yield a yellow distillate. Chromatography of this distillate afforded the desired vinylglycine **94** in 47% yield.

Complete reduction of the methyl ester was accomplished using $LiBH_4$ (2.0 eq) in Et_2O with trace MeOH.[66] The resultant alcohol **95** was isolated in 68% yield and then subjected to silylation by TBSCl (1.2 eq.) and imidazole (2.5 eq.) in DMF to provide protected olefin **96** in 81% yield.

To deprotect the CBZ amine, we reacted **96** with 5 mol% of $Pd(OAc)_2$, 1.4 eq. of Et_3SiH, and 14 mol% of TEA in DCM.[67] However, only starting material was found upon work-up.

Scheme 4.4: Pyrolysis of Methionine Sulfoxide



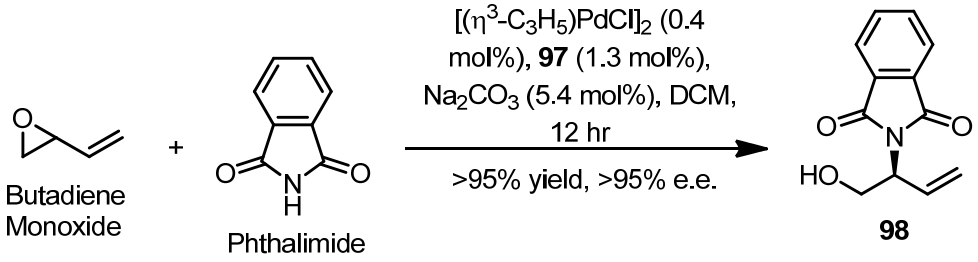
Reassessing this route, we found a number of troubling features. Notably the sheer number of steps needed to synthesize such a small subunit of the lactam. If SAR studies were to be carried out on the A-500359A lactam, then the route would have to be as short and as concise as possible. Furthermore, the need to selectively cleave off the CBZ group in the presence of the reducible olefin proved more problematic than originally thought.

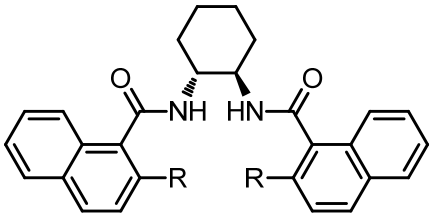
4.4 Asymmetric Allylic Alkylation

Asymmetric allylic alkylation (AAA) and the Tsuji–Trost reaction are powerful, robust methodologies for the metal catalyzed addition of a nucleophile onto an allyl (or longer) skeleton.[38, 68] It has previously been reported that phthalimide can add into butadiene monoxide under AAA conditions to give an enantiomerically pure, amine protected olefin similar to **95** in excellent yield.[69]

In our hands this reaction could be replicated beautifully. Butadiene monoxide was reacted with phthalimide (1.1 eq.), $NaCO_3$ (5.4 mol%), Trost Ligand **97** (1.3 mol%), and $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.4 mol%) in DCM to give **98** in greater than 95% yield (**Scheme 4.5**).

Scheme 4.5: AAA of Phthalimide and Butadiene Monoxide





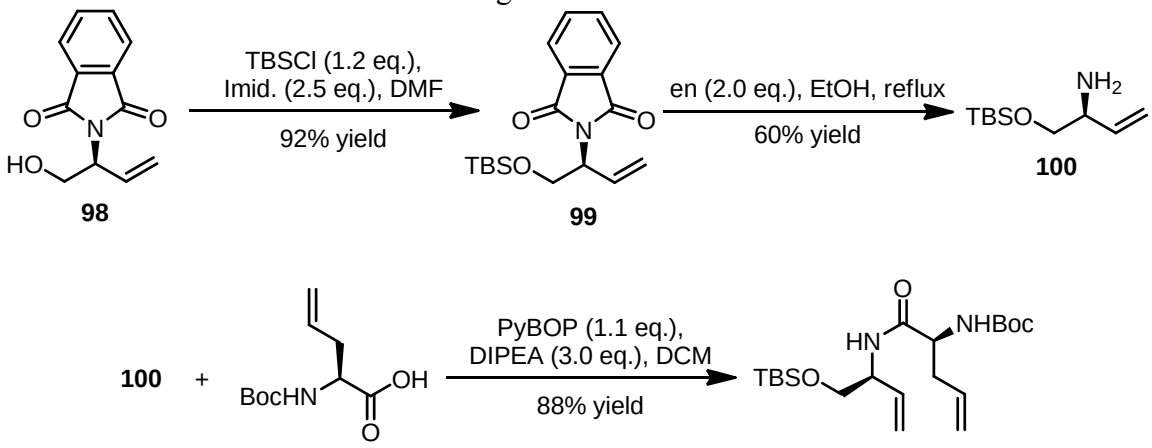
97, R = PPh_3

Protection of the alcohol was readily affected under standard conditions to give TBS ether **99** in 92% yield (**Scheme 4.6**). Deprotection of the phthalimide group proved to be somewhat problematic. Standard deprotection using methylhydrazine only gave poor yields (<30%) or mixtures of partially de-protected products.[70] Two-step deprotection utilizing $NaBH_4$ in aqueous isopropanol followed by acidic cleavage also gave poor yields.[71] It was found that refluxing **99** in ethanol with 2.0 eq. of

ethylenediamine (en) resulted in complete conversion in about 3 hours and the deprotected allyl amine **100** could be isolated in upwards of 69% yield.

Next, **100** was coupled to *N*-Boc-allylglycine utilizing EDCI (1.1 eq.) and DIPEA (3.0 eq.) in DCM. Diene **101** was then isolated in only 23% yield post-workup. Switching to PyBOP (1.1 eq.), **101** was isolated in 88% yield after chromatography.

Scheme 4.6: Elaboration Towards Ring Closure

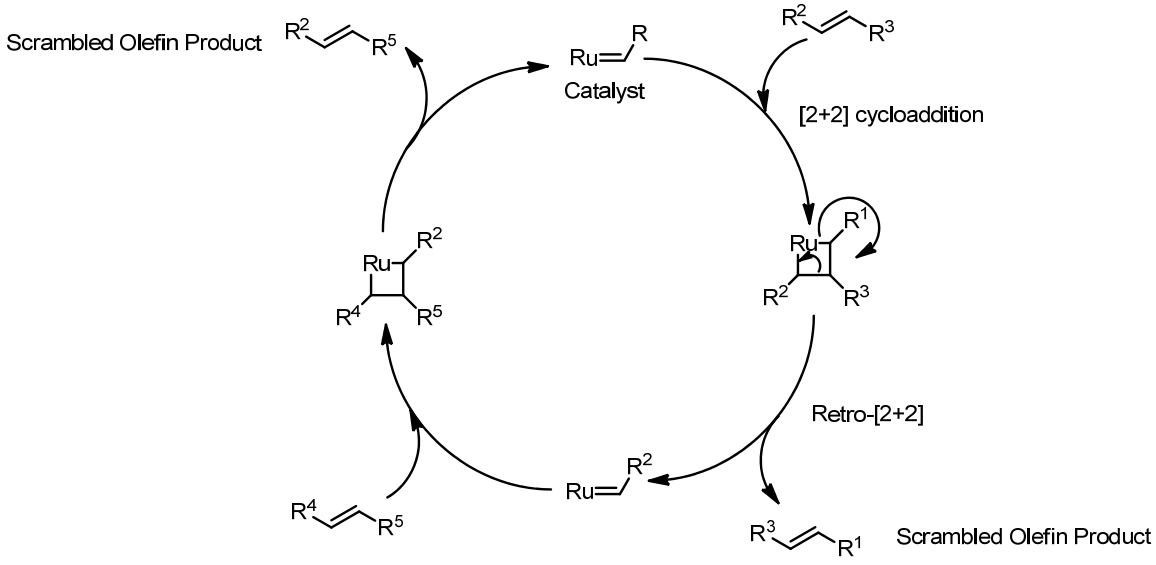


With the critical diene structure in hand, it was now possible to explore the ring closing metathesis (RCM) reaction that would stitch the 7-membered lactam together. RCM is a subcategory of the incredibly powerful olefin metathesis reaction pioneered by Nobel Prize winners Grubbs, Schrock, and Chauvin. During the course of the reaction reactive olefins are scrambled via ruthenium (Grubbs) or molybdenum (Schrock) catalysts. The reaction has become one of the staples of modern organic chemistry in everything from total synthesis,[72] to on scale-drug synthesis,[73] to commodity chemicals[74] due to its gentle conditions, functional group tolerance, and overall robustness.

Mechanistically a ruthenium carbene undergoes reversible [2+2] cyclization with a reacting alkene (**Scheme 4.7**). The resultant metallocyclobutane can then either collapse via retro-[2+2] to give the original reactants or collapse to yield a new metal carbene and a new olefin. By carefully adjusting reaction conditions, this scrambling effect can be controlled to yield useful products. For example, if the reacting olefin undergoes ring opening and relief of strain during the reaction, it is unfavorable for the ring to reform

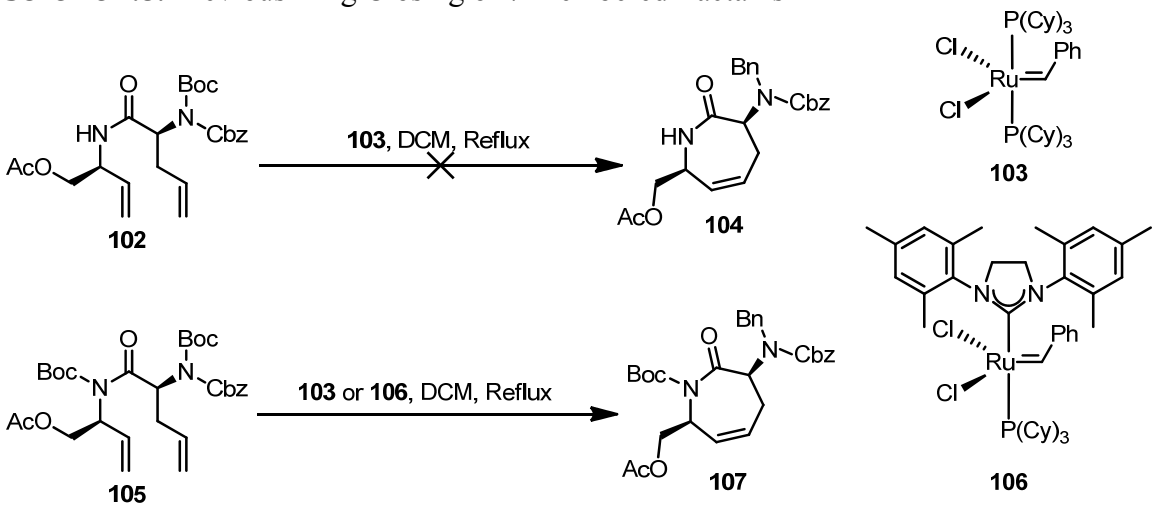
due to the high activation barrier of the reverse reaction. The expulsion of gaseous products, such as ethylene, can also drive the reaction in the forward, controlled direction.

Scheme 4.7: Olefin Metathesis Mechanism



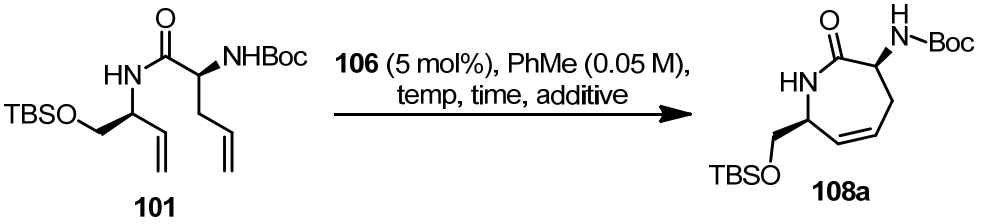
It had previously been shown that the diene **102** could not be closed via direct ring closing metathesis utilizing Grubb's first generation catalyst **103** (**Scheme 4.8**).[75] The authors postulated that the linear dipeptide lacked the conformational bias to position the olefins in close enough proximity for fusion. Indeed, ring closing was only possible after Boc protection of the amide (**105**) using the Grubbs' second generation catalyst (**106**) to yield lactam **107**. The Boc substitution presumably led to an unlocking of the amide conformation, allowing the olefins to come within proper closing distance.

Scheme 4.8: Previous Ring Closing of 7-membered Lactams



With our substrate **101** we decided to press ahead and attempt ring closure using the 2nd-generation Grubbs catalyst **106**. Refluxing **101** and 5 mol% of **106** in toluene for 24 hours did, to our surprise, yield the desired 7-membered lactam **108a** in about 45% yield and as a mixture with the starting diene (**Table 4.1**). It was found that both the starting diene and the closed product eluted at the same time via TLC making reaction monitoring difficult.

Table 4.1: Screening RCM Conditions on **101**

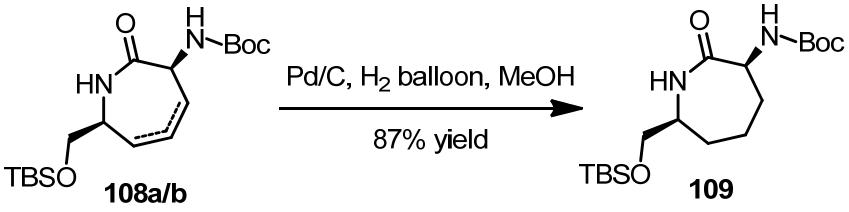


Entry	Temp (°C)	Time	Additive	Yield
1	80[a)]	24 hr	None	45%[c)]
2	160[b)]	5 min		88%[d)]
3	140[b)]	20 min		80%[d)]
4	160[b)]	5 min	Benzoquinone (10 mol%)	92%

a) Run in an oil bath. b) Run in microwave reactor. c) Isolated as 4:1 mix of **101** and **108a**; yield is calculated of **108a**. d) Isolated as a mix of **108a** and isomer **108b**

From here we moved towards the microwave reactor in an attempt to force complete conversion. Heating to 160°C for 5 min resulted in complete consumption of starting material (by NMR) and formation of a mixture of products in 88% yield (combined). NMR analysis after chromatography showed that the mixture was likely the result of olefin migration post-ring closing. Indeed, hydrogenation of this mixture with Pd/C under a balloon of H_2 produced a single product saturated lactam **109** in 87% yield (**Scheme 4.9**). Since the hydrogenation produced a single product with no detectable diastereomers, we believe that the olefin migration occurs to the east, providing another di-substituted alkene. Indeed, this would be the favored course since migration towards the silyl ether would involve severe steric restraints.

Scheme 4.9: Hydrogenation of **108a/b**



Searching the literature revealed that such olefin migration was a common feature of high temperature metathesis reactions where degradation of the original catalyst to reactive ruthenium hydrides occurred.[76] Following this precedent we found that addition of 10 mol% benzoquinone led to a complete suppression of the olefin isomerization while boosting the yield to 92% (**Table 4.1**, entry 4).

From here it was merely necessary to burn off the excess oxygen, reduce the double bond, and deprotect the exocyclic nitrogen. As stated previously, the olefin was readily reduced under standard hydrogenation conditions to give saturated lactam **109** in good yield. We wanted, however, to minimize the number of steps for the entire synthesis so thought it prudent to explore ways to eliminate as many of the unnecessary functionalities at once.

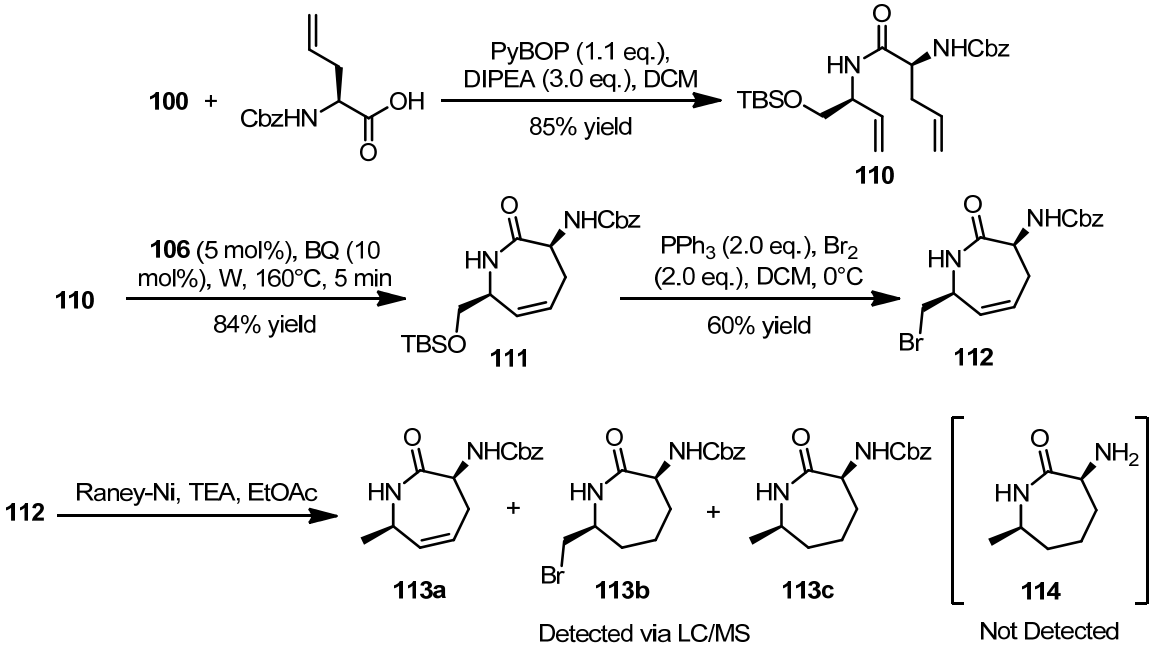
To eliminate the extraneous oxygen it would be necessary to convert from the TBS ether to an activated unit capable of being burned away. Our initial inquest provided a reference to the one-pot conversion of TBS ethers into *p*-toluenesulfonates via action of

*p*TsF and DBU.[77] Reacting **108** with *p*TsF (1.0 eq.) and DBU (20 mol%) in refluxing acetonitrile did not, however, consume the starting material.

At this point we began to consider our entire endgame strategy. The most desirable outcome would be the concurrent hydrogenation of the olefin, deprotection of the amine, and removal of the oxygen moiety (or its activated congener). As such we first decided to switch the Boc amine protection for a Cbz protecting group rationalizing the reductive lability would mesh well with the need to hydrogenate the double bond. Conversion of the oxygen to a bromide would also aid in this endeavor as it could be hydrogenated off with the other groups.

To this end **100** was coupled with *N*-Cbz-allylglycine using standard conditions in 85% yield (**Scheme 4.10**). Diene **110** was then closed in 89% yield to provide lactam **111**. From here we were able to perform a one-step conversion of the TBS ether into a bromide. Lactam **111** was reacted with triphenylphosphine dibromide pre-generated from 2.0 eq. of PPh_3 and 2.0 eq. of elemental bromine to provide bromide **112** in 60% yield.[78]

Scheme 4.10: *N*-Cbz-protected Lactam and Manipulation



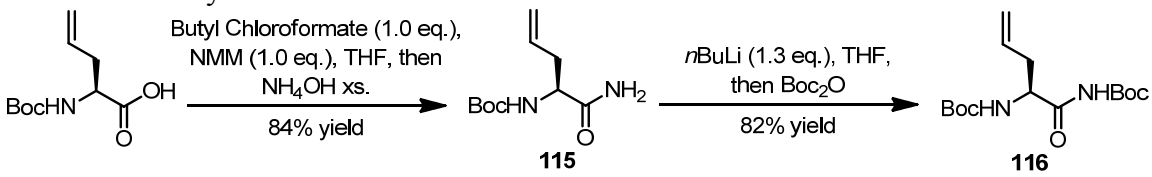
Now came the final stage of the synthesis; **112** was treated with Raney–Nickel (activated with 5M NaOH) and the reaction monitored by LC/MS. To our delight, we could detect lactams **113a-c** in various states of hydrogenation; however, the CBZ group

remained stubbornly in place even after extended reaction times (24 hrs). Indeed the desired mass of **114** was never detected.

During the course of this work, we began to contemplate if we could shorten the route by avoiding the tenacious phthalimide group entirely. By converting an allylglycine into an amide and then appending a carbamate group onto the amide, a suitably nucleophilic nitrogen moiety could be constructed. This nucleophile would then be used in a AAA reaction to directly achieve the desired skeleton without the need for the infuriating phthalimide deprotection and subsequent peptide coupling.

To this end, *N*-Boc-allylglycine was reacted with butyl chloroformate (1.0 eq.) and *N*-methylmorpholine (1.0 eq.) in THF to generate the mixed anhydride which was then decomposed with an excess of ammonium hydroxide (**Scheme 4.11**). The amide **115** was obtained in 84% yield after simple acid-base workup. Deprotonation of **115** was carried out using 1.3 eq. of *n*BuLi in THF; subsequent addition of Boc_2O led to the formation of imide **116** in 82% yield post-chromatgraphy.

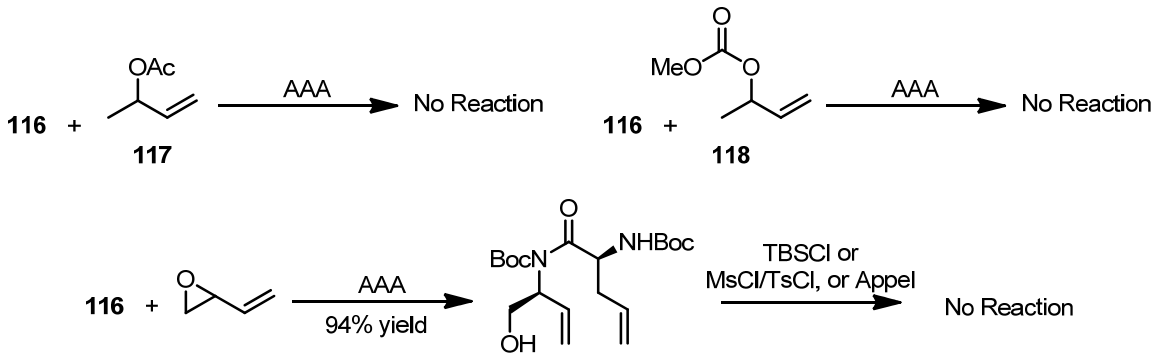
Scheme 4.11: Synthesis of Novel Imide for AAA Reaction



We attempted to first add **116** into allylic acetate **117** using standard AAA conditions to no avail. Swapping the acetate for the more reactive carbonate also led to no reaction. Addition to butadiene monoxide did, however, yield a white, solid product whose NMR spectrum and mass were consistent with the desired product **119a** in ca. 78% yield (**Scheme 4.12**).

From here we attempted to functionalize the free alcohol to prepare for ring closure. Conversion to the tosylate (TsCl, TEA/TsCl, DABCO), mesylate (MsCl, TEA) or to the TBS ether (TBSCl, Imid) all resulted in only recovered starting material. Similarly, an Appel reaction (CBr_4, PPh_3) yielded only starting material.

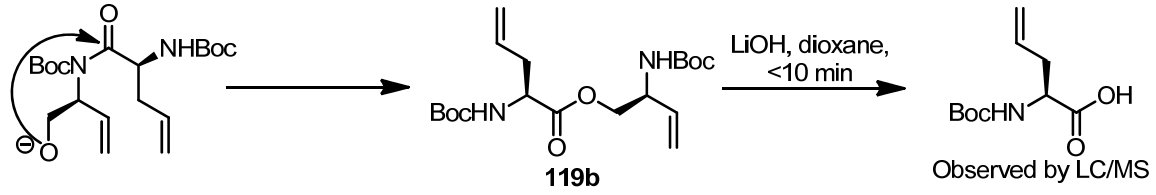
Scheme 4.12: AAA Reactions of **116**



Perplexed by this apparently unreactive, primary alcohol we turned to the literature. We found that the opening of aziridines or epoxides utilizing *N*-Boc-amides similar to **116** under our AAA conditions resulted in facile migration of the acyl group onto the amine or alcohol following ring opening. If our reaction was following a similar trajectory, then the product we were actually isolating was arising from either migration of the Boc group or the entire allylglycine unit.

To test which side was migrating, we reacted **119** with LiOH in dioxane. In less than ten minutes, all starting material was consumed by TLC. Analysis of the reaction mixture via LC/MS clearly showed formation of *N*-Boc-allylglycine with no other major peaks observed. This disheartening result demonstrated that, indeed, the allylglycine had migrated to give the more labile ester **119b** which was then easily cleaved upon exposure to hydroxide (**Scheme 4.13**). This effectively ended this route of exploration.

Scheme 4.13: Rearrangement following AAA



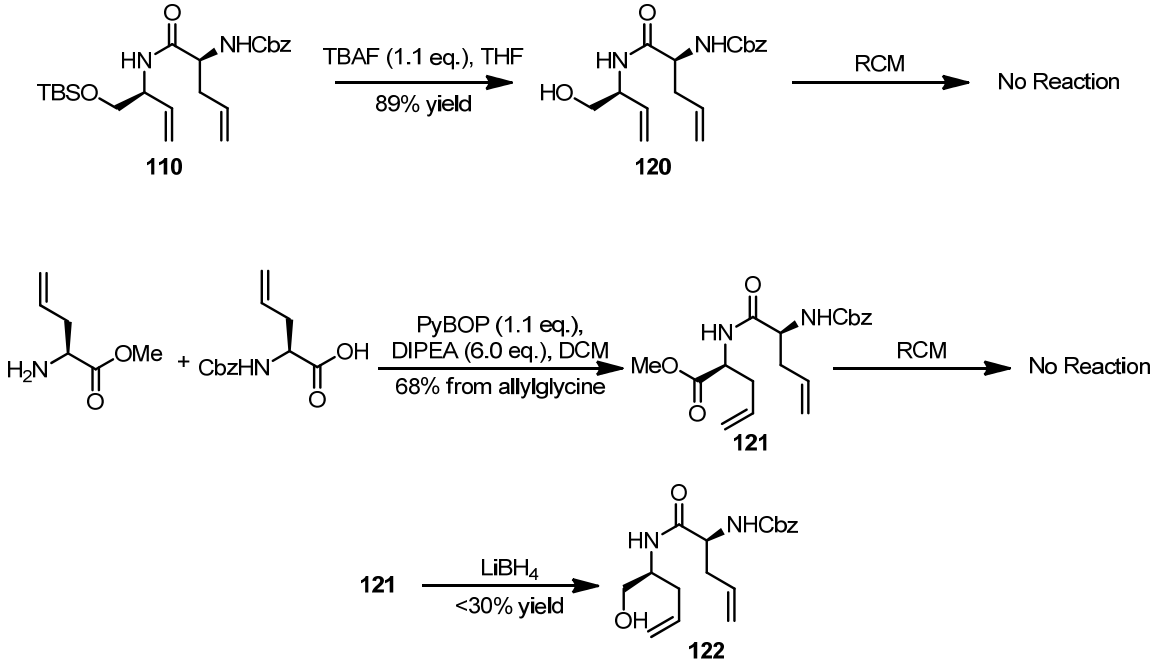
We also wished to explore the nature of the ring closing metathesis reaction. We found it quite interesting that in our case **101** and **110** undergo ring closure under thermal conditions even though previous work had shown such molecules to have unfavorable conformations.[75] We postulated that there might be a silyl–nitrogen interaction taking

place that allowed the olefins to come close enough together for ring closing to be attainable.

To probe this we first removed the silyl group from **110** (TBAF 1.1 eq., THF) in 89% yield (**Scheme 4.14**). Subjecting the diene **120** to our ring closing conditions did not yield any isolable, cyclized product. Instead, **120** was recovered with what is believed to be polymeric material.

From here we constructed an 8-membered ring precursor via the sequential esterification of allylglycine ($SOCl_2$, MeOH) and coupling to *N*-Cbz-allylglycine (1.1 eq. PyBOP, 6.0 eq. DIPEA, DCM) to yield diene **121** in 68% yield over the two steps. Ring closing of this ester yielded only starting material. Selective reduction of the methyl ester was attempted utilizing $LiBH_4$, however, the desired alcohol could only be isolated in low (<30% yield). Our end goal would have been varying the alcohol protecting group to determine if the facile ring required a silicon atom to be present in close proximity to the carboxamide.

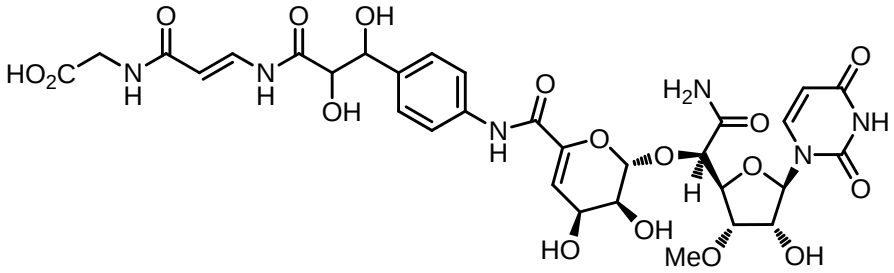
Scheme 4.14: Investigation of the Ring Closing Reaction



4.5 Work Towards the Tail Segment of A-102395

Unlike capuramycin and A-500359A, the tail amide of A-102395 is a linear construct consisting of a *p*-aniline attached to a diol unit. This diol is linked through an ene-amide to a capping glycine unit as shown in **Figure 4.1**.

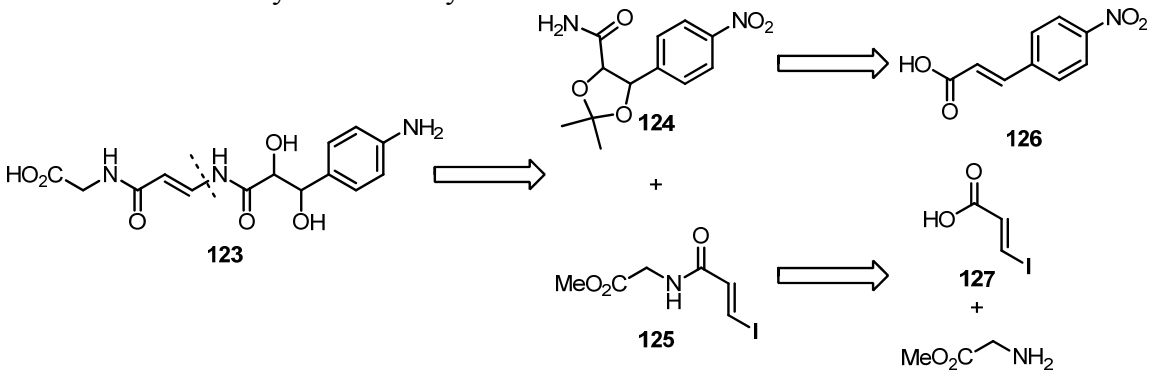
Figure 4.1: Unusual Linear Tail of A-102395



A-102395 (**6**)

Retrosynthetically we believed that the synthesis could be achieved via joining of a vinyl halide (**125**) to an amide (**124**) which would stitch the entire tail together (**Scheme 4.15**). The vinyl halide would be synthesized from the coupling of a protected glycine to *E*-iodoacrylic acid (**127**). The amide portion would arise from *p*-nitro-cinnamic acid which would be esterified, subjected to dihydroxylation, and then an ester-amide exchange before coupling.

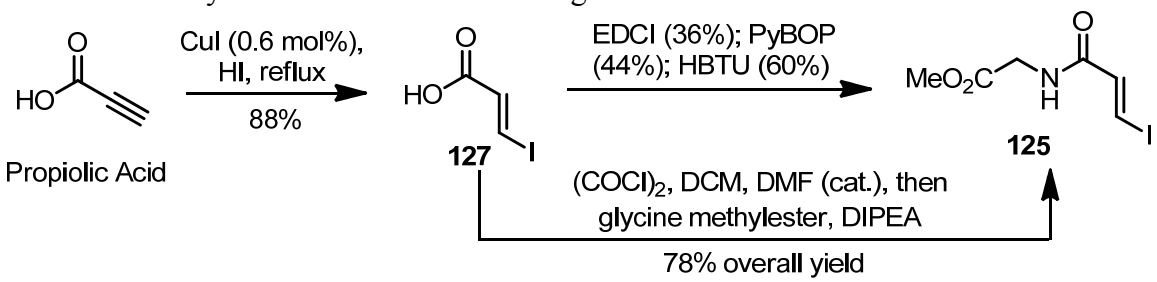
Scheme 4.15: Retrosynthetic Analysis of the A-102395 Tail



In the forward direction, propiolic acid was heated with CuI (0.6 mol%) in HI to provide *E*-iodoacrylic acid **127** in 88% yield after separation of the precipitated product via filtration (**Scheme 4.16**).[80] Coupling this acid and glycine methyl ester hydrochloride

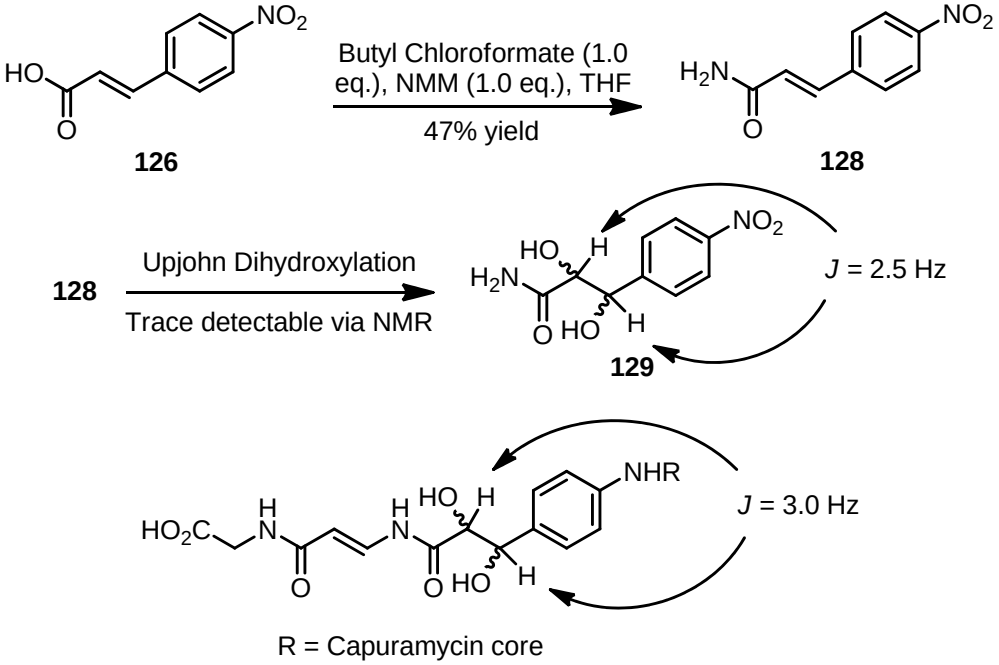
with EDCI (1.5 eq.) and DIPEA (4.0 eq.) yielded only 36% of the desired vinyl iodide **125**. PyBOP provided 44% of **125** while the use of HBTU (1.1 eq.) resulted in an improved yield of 60%. It was found, however, that simply generating the acyl chloride of *E*-iodoacrylic acid followed by addition of glycine methylester hydrochloride and DIPEA provided **125** in upwards of 78% yield.

Scheme 4.16: Synthesis of Western Tail Fragment



In our initial attempts to synthesize the eastern half of the molecule, we tried to directly convert *p*-nitro-*trans*-cinnamic acid (**126**) into its amide. It was found that reacting **126** with 1.0 eq. butyl chloroformate and 1.0 eq. *N*-methylmorpholine resulted in an intractable precipitate from which some of the desired amide could be isolated (**Scheme 4.17**). The low solubility of the amide made isolation and manipulation very burdensome; however, Upjohn dihydroxylation did yield a detectable amount of the diol. The crude NMR showed that the coupling constant between the methines to be ~2.5 Hz which was in good agreement with the reported values for the natural product (3.0 Hz) suggesting the hydroxyls are in a *syn* arrangement.[13c]

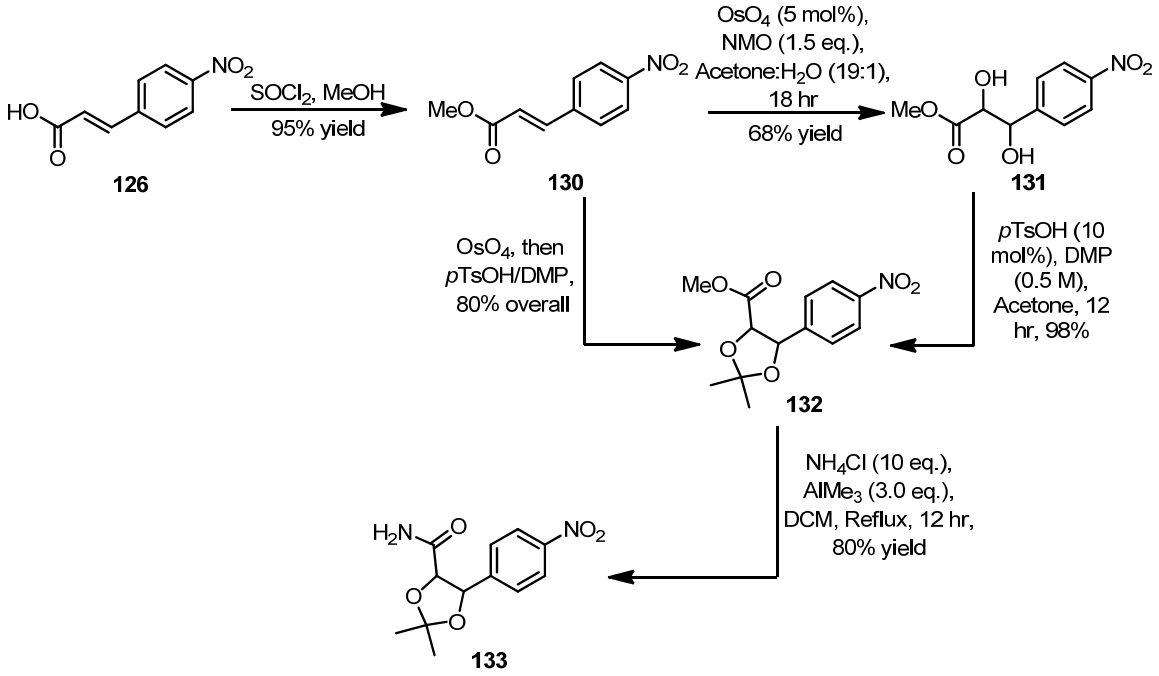
Scheme 4.17: Initial Easter Segment Synthetic Efforts



Due to the difficulty in working with the amide a new route was sought. Thus, the methyl ester of **130** was prepared utilizing $SOCl_2$ in methanol (**Scheme 4.18**). The methyl ester was then subjected to OsO_4 catalyzed dihydroxylation using 5 mol% osmium and 1.5 eq. of NMO as a terminal oxidant in aqueous acetone.[81] After workup, the desired diol **131** was isolated in 69% yield. From here, the diol could be protected as the isopropylidene (10 mol% *p*TsOH, 0.5 M 2, 2-dimethoxypropane, 0.5 M acetone) to yield **132** in 98% yield. It was also found that the crude diol post-dihydroxylation could be directly protected to give **132** in 80% yield over the two steps.

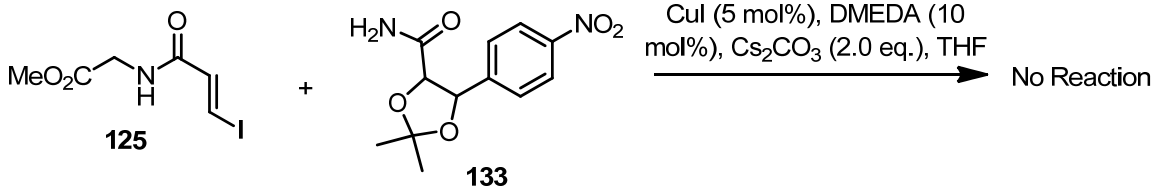
Installation of the amide onto **132** was done using $AlMe_3$ and NH_4Cl to generate an aminoaluminum reagent. After some experimentation, it was found reacting 10 eq. of NH_4Cl with 3.0 eq. $AlMe_3$ in DCM to pre-generate the desired reagent followed by addition of **132** and overnight reflux gave the desired amide **133** in 80% yield after column chromatography.

Scheme 4.18: Synthesis of the Eastern Fragment



From here we attempted to unify the tail segments via a Buchwald type coupling.[82] Vinyl halide **125** and amide **133** were reacted with CuI (5 mol%), DMEDA (10 mol%), and Cs_2CO_3 (2.0 eq.) in THF (**Scheme 4.19**). Neither thermal (reflux, 24 hr.) nor microwave irradiation (110°C, 10 min) yielded any detectable product. Running the reaction for longer resulted in the same—recovered starting materials via TLC analysis. Sadly, no conditions have yet been found to successfully knit **125** and **133** together.

Scheme 4.19: Attempted Buchwald Amidation



Chapter 5: Conclusions

Our aim in this project was to devise a concise and operationally straightforward synthesis of the capuramycin family of nucleoside antibiotics. Our primary goal was the synthesis of naturally occurring analog A-500359A. Along the way, we envisioned the development of a short route to the core of the family as well as a novel rout to non-commercially available tail lactam.

Our efforts were divided into three sections that corresponded to the three major moieties found in the molecule. Our initial synthetic efforts on the uridine head unit centered around the use of cyclouridine as a novel starting material. While we could successfully install the 3'-*O*-methyl ether in short order, elaboration of this intermediate to the required uridine aldehyde proved to be an insurmountable task. The fragility of the cyclouridine framework greatly limited the type of reactions that could be employed and made isolations difficult at best. We then switched to a *bis*-protection scheme utilizing uridine itself. Unfortunately, this route was also hampered with the abundant, unwanted reactivity of the parent uridine as well as numerous extraneous steps that greatly hindered route development.

We originally envisioned a hetero-Diels–Alder reaction to quickly and stereospecifically provide the hexauronic acid linker portion of the molecule. While there had been precedent set for such a route to provide the desired carbohydrate with the necessary stereochemistry, we failed to successfully deploy the method in the synthesis of a useful carbohydrate intermediate. Abandoning this route, we instead developed a direct route from a commercially available α-methyl-mannopyranoside. This route, however, was mired with the incredible stability of the anomeric methyl ether; indeed, the necessary intermediates could not be deprotected without complete decomposition.

An anomeric allyl ether derivative was successfully synthesized as a work-around. However, the deprotection of the allyl ether also proved difficult and could not be successfully completed as of the completion of this work.

The greatest bulk of our efforts concentrated on the synthesis of the A-500359A lactam tail. Our two initial routes proved to be mired in an exorbitant number of steps or simply chemistry that could not be forced to work. Deployment of an asymmetric allylic alkylation reaction did, however, provide a useful starting material allowing

stereospecific synthesis of the entire lactam skeleton in only 5 steps from commercially available material. Elaboration of this skeleton to the desired lactam was hoped to only require two steps. Unfortunately, the final, all important deprotection and hydrogenation proved only partially successful.

During the course of our work on this lactam we observed an interestingly facile medium ring synthesis via ring closing metathesis. Intrigued by this reaction, we had hoped to investigate why our particular substrate succeeded where others had totally failed. However, this part of the project was not elaborated upon following the departure of Dr. Greg Elliott.

Finally, we attempted to synthesize the novel, linear tail portion of A-102395. The two fragments of the tail could readily be synthesized, however, the desired amide coupling could not be realized under literature conditions.

In summary, the overall goals of this project were only partially met. The difficulty in juggling the reactivity of the numerous functional groups found in the core as well as the skeletons' inherent reactivity proved to be too difficult to overcome. The most successful part of the project was the synthesis of the tail segments. However, both areas again developed significant problems that, to date, have not been overcome.

Appendix I: List of Abbreviations

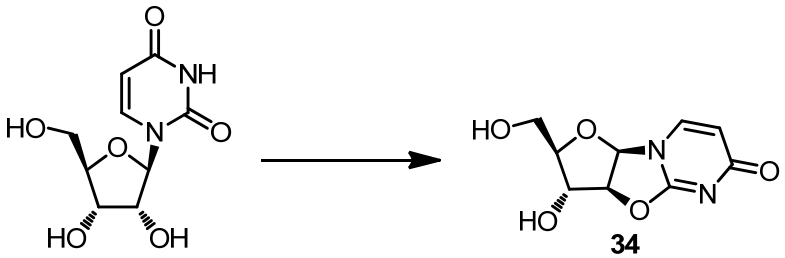
BAIB	*bis*-(Acetoxy)iodobenzene
Boc	*tert*-Butoxycarbonyl
Cbz	Carboxybenzyl
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMEDA	*N*,*N*'-Dimethylethylenediamine
DMF	*N*,*N*-Dimethylformamide
DMP	2,2-Dimethoxypropane
DMSO	Dimethylsulfoxide
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
EDCI	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
EtOAc	Ethyl Acetate
HBTU	*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HOBt	Hydroxybenzotriazole
Hz	Hertz
IBX	2-Iodoxybenzoic Acid
Imid	Imidazole
LC/MS	Liquid Chromatography/Mass Spectrometry
MeCN	Acetonitrile
Mp	Melting Point
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholin-*N*-oxide
NMR	Nuclear Magnetic Resonance Spectroscopy
p-TsOH	*para*-Toluenesulfonic Acid
PTLC	Preparative Thin Layer Chromatograph
Py	Pyridinde
PyBOP	(Benzotriazol-1-yl-oxy)tripyrrolidinophosphonium hexafluorophosphate
RCM	Ring Closing Metathesis
Rbf	Round Bottom Flask

TBAB	Tetra-*N*-butylammonium Bromide
TBAF	Tetra-*N*-butylammonium Fluoride
TBAI	Tetra-*N*-butylammonium Iodide
TBS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethylpiperdine-1-oxyl
Tf	Trifluoromethansulfonate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TOSMIC	Tosylmethyl Isocyanide
Tr	Trityl (Triphenylmethyl)

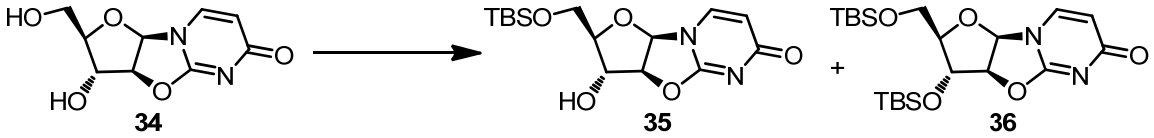
Appendix II: Experimental

General

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen unless otherwise noted. All liquid transfers were conducted using standard syringe or cannula techniques. DMF, DCM, toluene, and THF were purified via Innovative Technologies Pure-solv system. Et_2O was distilled from sodium/benzophenone immediately prior to use. MeCN and TEA were distilled from CaH_2 when needed. Phthalimide was recrystallized from hot EtOH immediately prior to use. All other reagents were used as received. $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and Trost Ligand **97** were obtained from Strem Chemicals. $(TMSO)_2$ was obtained from Gelest. Allylglycine was obtained from BetaPharma. $CDCl_3$, MeOD-D4, Acetone-D6, and DMSO-D6 were obtained from Cambridge Isotope Labs. All other reagents were obtained from either Acros or Aldrich. TLC plates were Dynamic Adsorbent aluminum backed silica gel with F-254 indicator. Plates were visualized via UV lamp and iodine or via staining with vanillin, $KMnO_4$, or ninhydrin followed by heating with a heat gun. Flash column chromatography was conducted with Dynamic Adsorbents 32-63 μm flash silica gel. MPLC was conducted with a Biotage® SP™ Flash system utilizing either HP-Sil (normal phase) or KP-C_{18}-HS (reverse phase) cartridges. Reactions utilizing microwave irradiation were run in a Biotage® initiator system. LC/MS was run on an Agilent 6120 Quadropole LC/MS system with an Eclipse XDB-C_{18} column. NMR spectra were recorded on either a Varian 500 (500 MHz ^1H and 126 MHz ^{13}C) or a Varian 300 (300 MHz ^1H and 25 MHz ^{13}C). Spectra were referenced to either TMS or residual solvent. Splitting patterns are abbreviated as such: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened resonance.

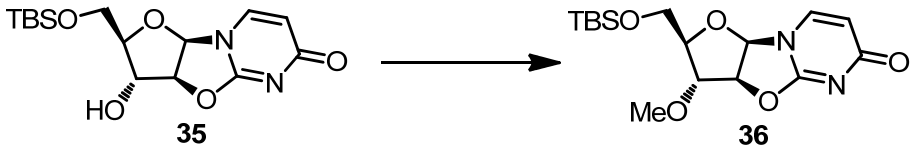


Cyclouridine (**34**) was prepared according to ref. 19. Uridine (3.0 g, 12.3 mmol) and diphenylcarbonate (2.89 g, 1.1 eq.) were suspended in dry DMF (4.0 M) and heated in a 100°C oil bath. Sodium bicarbonate (20.6 mg, 2 mol%) was added and the solution stirred vigorously for 2.5 hours The solids quickly went into solution and a precipitate began to form. After 2.5 hours, the reaction mixture was cooled in ice and the solid collected via filtration. The solid was dried on high vacuum to yield 2.2888g (10.1 mmol, 82%) of pure cyclouridine **34**. The NMR data for this solid were in good agreement with the literature values.

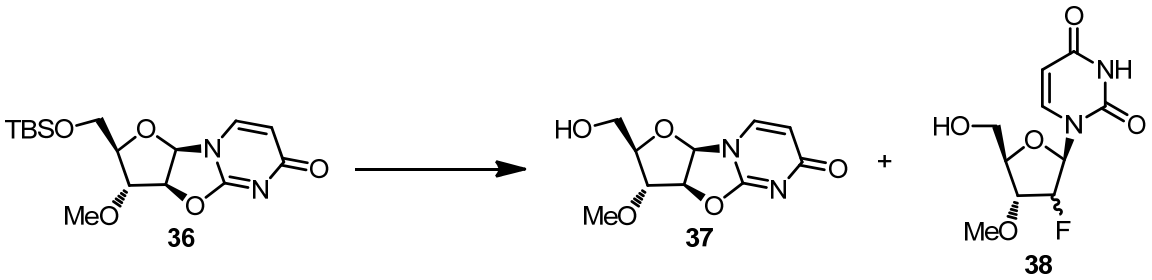


To **34** (3.0 g, 13.3 mmol) dissolved in DMF (0.7 M) was added DMAP (162 mg, 10 mol%) and TBSCl (2.105 g, 1.05 eq.). The solution was cooled in ice for ten minutes and then TEA (5.56 ml, 3.0 eq.) freshly distilled was added. The ice bath removed and the solution was stirred at rt for 24 hours. Water was added to the reaction and the solution extracted twice with EtOAc and twice with DCM. The combined organic layers were dried over $MgSO_4$ and condensed into a viscous oil. The oil was loaded onto a column and eluted with a 0%→20% gradient of MeOH in $CHCl_3$ to provide 2.844 g (8.36 mmol, 63%) of mono-protected **35a** and 907.1 mg (1.99 mmol, 15%) of bis-protected **35b** as white solids. **35a**: Mp = 140-142°C; ^{1}H NMR (500 MHz, DMSO-D6) δ: 7.869 (d, *J* = 7.5 Hz, 1H), 6.288 (d, *J* = 5.5 Hz, 1H), 5.950 (d, *J* = 4.5 Hz, 1H, -OH), 5.856 (d, *J* = 7.0 Hz, 1 H), 5.222 (d, *J* = 5.5 Hz, 1H), 4.338 (br s, 1H), 4.069 (ddd, *J* = 5.5, 5.0, 2.5 Hz, 1H), 3.455 (overlapping dd, 2H), 0.798 (s, 9H), -0.035 (s, 3H), -0.060 (s, 3H); ^{13}C (126 MHz, DMSO-D6) δ: 170.93, 159.50, 136.83, 108.73, 89.64, 88.65, 87.92, 74.08, 62.17, 25.71, 17.97, -5.50; MS m/z (%): 341 (100, M^+ + H).

35b: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.305 (d, *J* = 7.5 Hz, 1H), 6.122 (m, 1H), 6.015 (m, 1H), 5.082 (d, *J* = 3.0 Hz, 1H), 4.588 (s, 1H), 4.106 (m, 1H), 3.528 (m, 1H), 3.357 (m, 1H), 0.876 (s, 9H), 0.805 (s, 9H), 0.124 (m, 6H), -0.030 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.58, 159.47, 134.41, 110.52, 89.68, 89.11, 76.08, 61.77, 25.68, 18.26, 17.90, -4.92, -5.50.

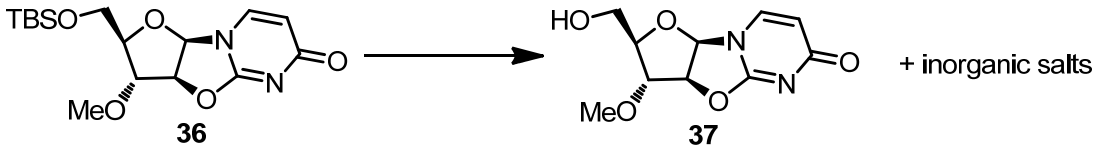


KOH pellets were powdered with an oven dried mortar and pestle and then added (989.6 mg, 2.0 eq.) to a dry rbf. THF and DMSO (1:1, 0.5 M, not pre-dried) were added and the suspension stirred in an ice bath for 10 minutes. **35** (3.0 g, 8.82 mmol) was added followed immediately by MeI (0.6 ml, 1.1 eq.). The solution was maintained at 0°C for 1 hour before being decanted into a separatory funnel and the remaining KOH rinsed with EtOAc. Water was added to the solution and three EtOAc extractions were executed. The combined organic extracts were washed with fresh water and brine before being dried over Na_2SO_4 and condensed. Pure **36** was obtained as a white solid after chromatography utilizing a 0%→10% gradient of MeOH in $CHCl_3$. MP = 138-140°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.314 (d, *J* = 7.5 Hz, 1H), 6.212 (d, *J* = 6.0 Hz, 1H), 5.852 (d, *J* = 7.5 Hz, 1H), 5.236 (d, *J* = 5.5 Hz, 1H), 4.141 (m, 1H), 4.038 (d, *J* = 2.5 Hz, 1H), 3.469 (dd, *J* = 11, 5.0 Hz, 1H), 3.347 (s, 3 H), 3.292 (dd, *J* = 11, 7.0 Hz, 1H), 0.723 (s, 9 H), -0.105 (s, 3 H), -0.124 (s, 3H); ^{13}C (25 MHz, $CDCl_3$) δ: 171.72, 159.56, 134.70, 110.57, 90.34, 86.59, 86.53, 84.69, 62.43, 58.18, 26.03, 18.53, -5.14; MS m/z (%): 355 (100, M^+ + H)

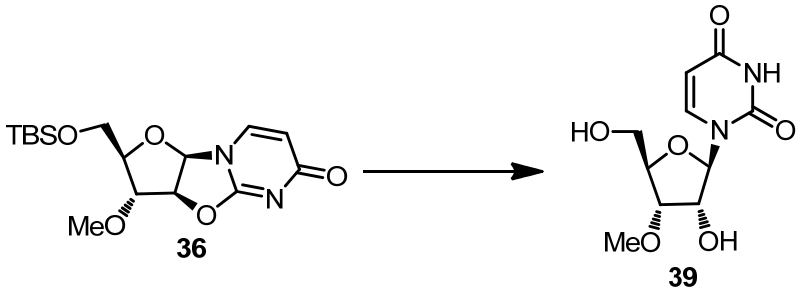


Silyl protected cyclouridine **36** (196.6 mg, 0.55 mmol) was dissolved in dry THF (0.3 M) and stirred in an ice bath. TBAF (1.0 eq.) was added and the colorless solution turned

amber. After 30 minutes, water was added and the solution extracted 3x with EtOAc. LC/MS analysis showed product in both organic and aqueous layers so the layers were combined and condensed into an orange oil. The oil was purified via Biotage using a 0%→45% gradient of MeOH in $CHCl_3$ to provide impure, deprotected cyclouridine **37** (~82.2 mg, 57%) and pure fluorinated uridine derivative **38** (19.3 mg, 14%). Analysis of **37** showed the major impurity to be tetra-butyl ammonium salts. **37**: ^{1}H NMR (500 MHz, MeOD-D4) δ: 7.816 (d, *J* = 7.5 Hz, 1H), 6.360 (d, *J* = 5.5 Hz, 1H), 6.052 (d, *J* = 7.5 Hz, 1H), 5.435 (d, *J* = 5.5 Hz, 1H), 4.329 (m, 1H), 4.222 (d, *J* = 2.0 Hz), 3.524 (dd, *J* = 12, 4.0 Hz, 1H), 3.481 (overlapping signals, 4H); MS m/z (%): 241 (100, M^+)
38: ^{1}H NMR (500 MHz, MeOD-D4) δ: 7.818 (d, *J* = 8.0 Hz, 1H), 6.016 (d, *J* = 4 Hz, 1H), 5.657 (d, *J* = 8.0 Hz, 1H), 4.271 (dd, *J* = 4.0, 1.0 Hz, 1H), 3.978 (m, 1H), 3.779 (overlapping m, 2H), 3.449 (s, 3H). MS m/z (%): 260 (5, M^+ + H), 259 (50, M^+), 113 (100).

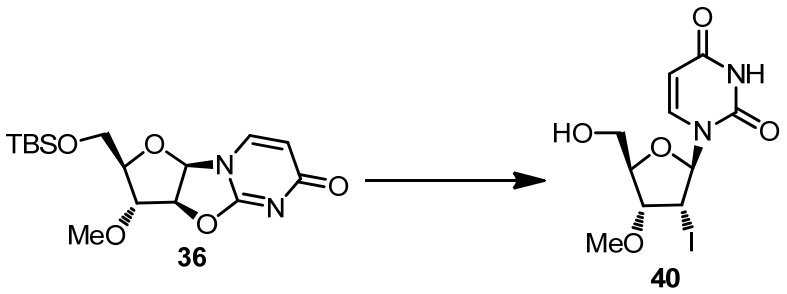


Silyl protected cyclouridine **36** (150 mg, 0.42 mmol) was dissolved in MeOH : H_2O (1 : 1, 0.12 M). Oxone (258.2 mg, 1.0 eq.) was added and the solution stirred at rt for 1 hour. LC/MS analysis showed complete conversion of **36** into **37**. Attempted isolation of **37** using normal and reverse phase chromatography led to impure mixtures (presumably of the desired product and spent Oxone salts) or decomposition of the product.



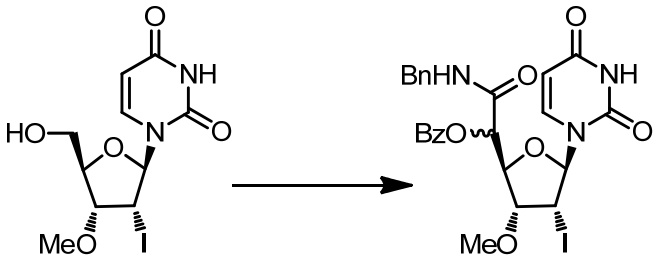
Silyl protected cyclouridine **36** (100 mg, 0.282 mmol) was added to a microwave vial along with DMF (0.2 M), benzoic acid (34.4 mg, 1.0 eq.), and potassium benzoate (45

mg, 1.0 eq). The vial was capped and heated in a 140°C oil bath for 48 hrs. The golden solution was transferred to an rbf and condensed before being dissolved in MeOH (0.2 M). Sodium methoxide (33.5 mg, 2.2 eq.) was added and the solution stirred for 30 min. Following concentration and chromatography, deprotected uridine derivative **39** was isolated (51.8 mg, 0.2 mmol, 71%). ^{1}H NMR (500 MHz, MeOD-D4) δ: 7.829 (d, *J* = 8.5 Hz, 1H), 6.018 (d, *J* = 4 Hz, 1H), 5.660 (d, *J* = 8.0 Hz, 1H), 4.272 (dd, *J* = 4.0, 2.5 Hz, 1H), 3.982 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.789 (overlapping m, 2H), 3.445 (s, 3H)



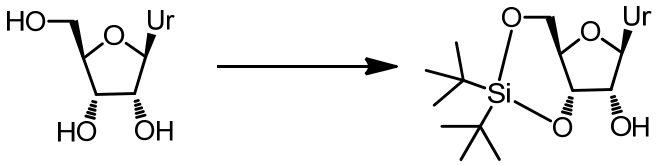
Silyl protected cyclouridine **36** (500 mg, 1.41 mmol) was dissolved in acetone (0.1 M). NaI (319.2 mg, 1.5 eq.) and *p*-TsOH (405.2 mg, 1.5 eq.) were added and the solution heated to 50°C. After 3 hrs. the solution was cooled and filtered. The filtrate was treated with 1 M $Na_2S_2O_3$ to dissipate the color. A white solid crashed out of solution and was removed via filtration. The filtrate was evaporated into a yellow gum and then partitioned between water and EtOAc. The phases were separated and the aqueous layer extracted twice more. The organic layer was dried over $MgSO_4$ and evaporated. The yellow solid was purified via a column chromatography using a 20:1 → 15:1 gradient of MeOH in $CHCl_3$ to give iodouridine **40** as a white solid (242.6 mg, 0.66 mmol, 47%). Alternatively, the reaction could be carried out in the microwave reactor using 3.0 eq. of *p*-TsOH and heating to 100°C for 10 min. Workup as above and column provided **40** in a variable yield of 55%-94%. ^{1}H NMR (500 MHz, MeOD-D4) δ: 8.067 (d, *J* = 8.5 Hz, 1H), 6.291 (d, *J* = 3.0 Hz, 1H), 5.696 (d, *J* = 8.5 Hz), 4.669 (t, *J* = 5.5 Hz, 1H), 4.147 (m, 1H), 3.853 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.723 (dd, *J* = 12.5, 3.0 Hz, 1H), 3.455 (m, 1H), 3.396 (s, 3H).

Iodouridine **40** (100 mg, 0.27 mmol) was dissolved in PhMe (0.03 M) along with TEMPO (211 mg, 5.0 eq.). The solution was placed in a 70°C oil bath and Bu_3SnH (0.73 ml, 10 eq.) was added slowly. After 2 hrs, the reaction was condensed and isolation attempted. Unfortunately, the desired product could not be purified away from the copious amount of residual tin.



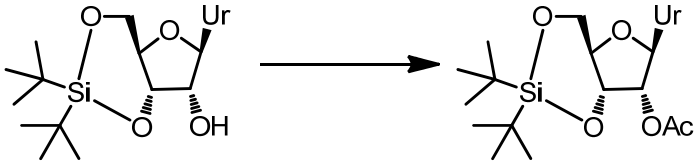
40 **41**

Iodouridine **40** (100 mg, 0.27 mmol), IBX (189 mg, 2.5 eq.), benzoic acid (36.3 mg, 1.1 eq.), and benzyl isocyanide (36 µL, 1.1 eq.) were heated to 80°C in acetonitrile. After 2 hrs, the solids were removed by filtration through Celite and the filtrate condensed. The residue was partitioned between DCM and water and the aqueous layer extracted twice more. The combined organic layers were washed with brine and dried over $MgSO_4$. Note that this is the standard procedure for the oxidative Passerini reaction. Careful chromatography was performed using a 100:0 → 10:1 → 5:1 → 2:1 → 1:1 → 0:100 gradient of EtOAc in hexanes. The Passerini adduct **41** was isolated in 29% yield as an inseparable mixture of diastereomers (1.7:1, 47.3 mg, 0.078 mmol). ^1H (500 MHz, $CDCl_3$) δ: 8.076 (d, *J* = 7.5 Hz, 1H, major) 8.050 (d, *J* = 8.5 Hz, 1H minor), 7.599 (m, 1H, major/minor overlap), 7.454 (m, 2H, major/minor overlap), 7.383 (d, *J* = 8.0 Hz, 1H, major), 7.100 (d, *J* = 8.0 Hz, 1H, minor), 5.990 (m, 1H, major/minor overlap), 5.774 (d, *J* = 4.0 Hz, 1H, major), 5.669 (dd, *J* = 8.0, 2.0 Hz, 1H, major), 5.586 (d, *J* = 5.5 Hz, 1H, minor), 5.554 (dd, *J* = 8.0, 2.0 Hz, 1H, minor), 4.763 (m, 2H, major/minor overlap), 4.643 (m, 2H, major/minor overlap), 4.303 (m, 1H, major/minor overlap), 3.954 (dd, *J* = 5.5, 2.0 Hz, 1H, minor), 3.653 (dd, *J* = 5.5, 4.0 Hz, major), 3.505 (s, 3 H, minor), 3.413 (s, 3 H, major).



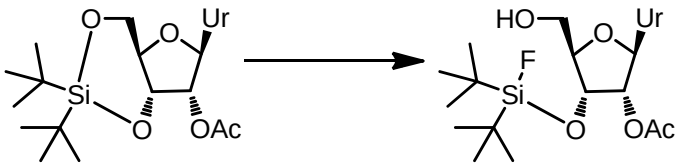
42

Uridine (1.0 g, 4.1 mmol) and $AgNO_3$ (1.53 g, 2.2 eq.) were suspended in DMF (0.34 M) and stirred in an ice bath. Di-*tert*-butyldichlorosilane (0.96 ml, 1.1 eq.) was added slowly. After complete addition, the reaction was stirred at room temperature for 15 min. TEA (1.3 ml, 2.2 eq.) was then added and the reaction condensed after 5 minutes. The maroon residue was taken up in EtOAc and passed through Celite. The filtrate was partitioned with water and the aqueous layer extracted 2x with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$ before being condensed into a white solid. This mostly pure material was completely purified by passing through a column utilizing a 2:1 → 1:1 → 0:100 gradient of EtOAc in hexanes. Bis-protected uridine **42** was collected in 88% yield (1.3866 g, 3.61 mmol) as a white solid. The spectral and MS data for the solid matched that reported in ref. 34.



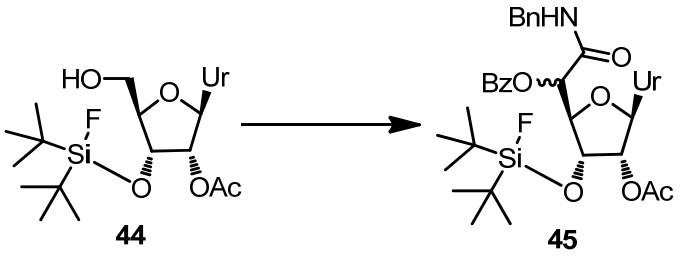
42 **43**

Uridine derivative **42** (3.61 mmol) from above was dissolved in acetonitrile (0.2 M) and treated with DMAP (22 mg, 5 mol%), Ac_2O (0.41 ml, 1.2 eq), and TEA (0.6 ml, 1.2 eq.). The solution was stirred for 1 hr before $CHCl_3$ and water were added. The phases were separated and the aqueous layer extracted 2x with $CHCl_3$. The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent and column (5:1 → 1:1 EtOAc in Hex) provided acetate **43** in 90% yield (1.3931 g, 3.27 mmol) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.829 (br s, 1H), 7.210 (d, J = 8.5 Hz, 1H), 5.786 (d, J = 8.0 Hz, 1H), 5.736 (d, J = 1.0 Hz, 1H), 5.480 (dd, J = 5.5, 1.0 Hz, 1H), 4.459 (dd, J = 8.5, 4.5 Hz, 1H), 4.234 (dd, J = 9.0, 5.5 Hz, 1H), 3.978 (m, 2H), 2.162 (s, 3H), 1.056 (s, 9H), 1.010 (s, 9H); ^{13}C (25 MHz, $CDCl_3$) δ: 169.10, 163.06, 149.56, 140.34, 103.00, 91.21, 74.94, 74.77, 74.130.



43 **44**

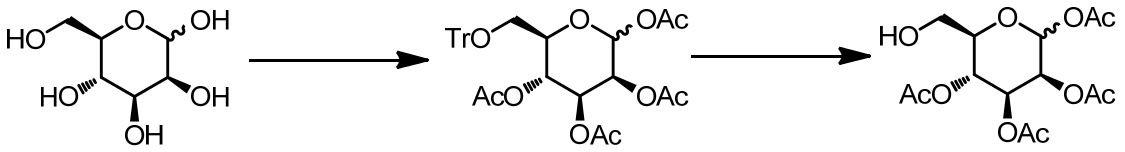
Acetate **43** (1.0 g, 2.34 mmol) was dissolved in PhMe (0.08 M) and treated with AllylTMS (0.79 ml, 2.2 eq.) and BF_3•OEt_2 (0.53 ml, 2.0 eq.). The solution was placed in an 85°C oil bath and stirred for 2 hours. The reaction was cooled to rt and quenched with 3% Na_2CO_3 turning the solution gold. The layers were separated and the organic layer was washed with water twice and brine before being dried over $MgSO_4$ and condensed into a white solid. Mono-deprotected uridine **44** was isolated in 54% yield (567.3 mg, 1.27 mmol) after column chromatography (2:1 → 1:1 → 1:5 → 0:100 EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.434 (br s, 1H), 7.650 (d, *J* = 14 Hz, 1H), 5.955 (d, *J* = 10.5 Hz, 1H), 5.758 (dd, *J* = 14, 3.0 Hz, 1H), 5.406 (dd [apparent t], *J* = 4.5 Hz, 1H), 4.177 (m, 1H), 3.978 (m, 1H), 3.854 (ddd, *J* = 18.5, 10, 3.5 Hz), 2.123 (s, 3H), 1.074 (s, 9H), 1.053 (s, 9H); ^{13}C NMR (25 MHz, $CDCl_3$) δ: 170.08, 163.90, 150.34, 141.44, 102.43, 89.23, 85.04, 75.43, 69.40, 60.58, 27.40, 27.29, 24.95, 20.88, 20.20; MS m/z (%): 447 (100, M^+), 335 (100).



44 **45**

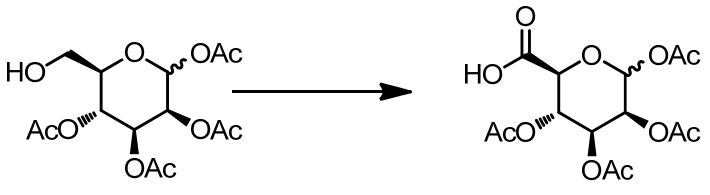
Uridine derivative **44** (100 mg, 0.215 mmol) was dissolved in MeCN (0.5 M). IBX (156 mg, 2.5 eq.) was added and the suspension refluxed. Monitoring by LC/MS showed slow conversion to the aldehyde. When complete (~ 20 hrs), the mixture was diluted with MeCN and the insoluble material removed via Celite filtration. The filtrate was condensed and taken up in MeCN (0.5 M) to which benzoic acid (29 mg, 1.1 eq.) and benzyl isocyanide (29 μL, 1.1 eq.) were added. The solution was stirred for 4 hours and then diluted with water and DCM. The phases were separated and the aqueous layer

extracted 2x with DCM. The combined organic layers were washed with brine and dried over $MgSO_4$ before the solvent was removed. Column chromatography (2:1 → 1:1 → 1:2 EtOAc in hexanes) yielded two fractions which proved to be diastereomers via NMR. The major isomer was collected in 29% yield (42.4 mg, 0.063 mmol) and the minor in 14% yield (20.6 mg, 0.030 mmol). **Major**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.762 (s, 1H), 8.105 (m, 2H), 7.622 (m, 1H), 7.466 (m, 4H), 7.239 (m, 4H, overlapping with residual $CHCl_3$), 6.595 (m, 1H), 5.716 (m, 3H), 5.535 (t, J = 8.5 Hz, 1H), 5.008 (t, J = 9.0 Hz, 1H), 4.662 (m, 2H), 4.356 (dd, J = 25, 8.5 Hz, 1H), 2.113 (s, 3H), 1.018 (s, 18H).



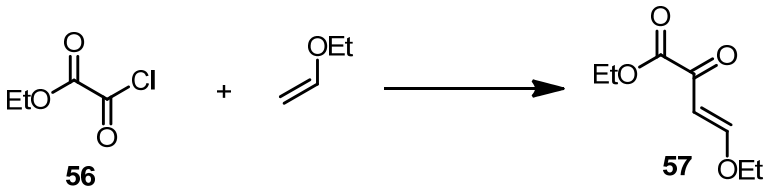
48 **49**

The synthesis of **49** was adapted from ref. 42. Mannose (2.0 g, 11.1 mmol) and TrCl (3.22 g, 1.0 eq) were added to a rbf which was then placed in a 50°C water bath. Pyridine was added and the mixture was stirred for two hours over which time all solids went into solution. To the golden solution was added Ac_2O (6 ml, 5.8 eq.) and the resultant solution stirred overnight. In the morning, the entire reaction was poured into ice water and the white precipitate collected. The solid was dissolved in hot EtOH and allowed to crystallize to yield two crops of **48** (2.701 g, 4.59 mmol total) for a combined yield of 40%. 2.351 g (4 mmol) of **48** was dissolved in AcOH (0.4 M) before being chilled in an ice bath. HBr (0.92 ml, 33% in AcOH) was added and the reaction stirred 1 minute before being filtered. The filtrate was run into cold water and extracted 2x with $CHCl_3$. The organic extracts were washed with cold water and dried over $MgSO_4$. The solvent was removed to provide a clear, sticky oil which proved recalcitrant to crystallization (579.9 mg, 1.66 mmol, 42%).



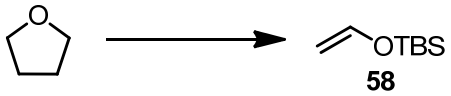
49 **50**

Protected mannose **49** (100 mg, 0.287 mmol) was dissolved in a 1:1 mixture of acetonitrile and water (0.5M). TEMPO (9 mg, 20 mol%) and BAIB (203.4 mg, 2.2 eq.) were added and the reaction stirred for 4 hours. The solvent was evaporated and the orange residue suspended in Et_2O. Upon standing, white circles of material precipitated out. Collection of these circles showed the desired carboxylic acid **50** in 66% yield (68.4 mg, 0.189 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.938 (d, *J* = 1.0 Hz, 1H), 5.468 (m, 2H), 5.178 (m, 1H), 4.203 (d, *J* = 9.0 Hz, 1H), 2.176 (s, 3H), 2.085 (s, 3H), 2.062 (s, 3H), 2.009 (s, 3H).



56 **57**

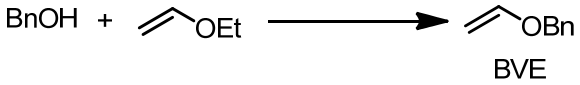
Typically, ethyl chloro(oxo)acetate was added slowly to vigorously stirred ethyl vinyl ether at 0°C and then allowed to warm overnight. The resultant sludge was then partitioned between DCM and H_2O. The aqueous layer was extracted twice more with DCM and the combined organic layers washed with sat. NH_4Cl followed by sat. $NaHCO_3$ before being dried over $MgSO_4$. Removal of the solvent yielded a red oil which could be purified via rapid column chromatography (5 : 1, EtOAc in hexanes) to yield mostly pure **57** as an orange oil in varying yield (< 30%). ^{1}H NMR (500 MHz, MeOD-D4) δ: 5.990 (d, *J* = 1.5 Hz, 1H), 5.422 (dd, *J* = 8.5, 1.5 Hz, 1H), 5.331 (t, *J* = 9.0 Hz, 1H), 5.262 (dd, *J* = 9.5, 8.0 Hz, 1H), 4.236 (d, *J* = 9.0 Hz, 1H), 2.113 (s, 1H), 2.019 (s, 3H), 1.984 (s, 3H), 1.934 (s, 3H).



58

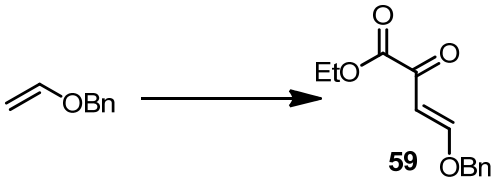
*n*BuLi (1.6 M, 16.3 ml, 26.08 mmol) was slowly added to 50 ml of vigorously stirred THF at rt. The solution was stirred for 24 hours during which time it turned grey. A solution of TBSCl (3.014 g, 20 mmol) in THF was added slowly at 0°C and the reaction stirred a further 3 hours at rt. Excess THF was removed via rotary evaporation and the residue partitioned between Et_2O and water. The aqueous layer was extracted 2x and the

combined organic layers were washed with brine and dried over $MgSO_4$ before the solvent was evaporated. The resultant oil was carefully distilled via Kugelrohr to provide 1.668 g (10.5 mmol, 53%) of TBS vinyl ether **58** as clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.411 (dd, *J* = 13, 6.0 Hz, 1H), 4.414 (dd, *J* = 13.5, 0.5 Hz, 1H), 4.088 (dd *J* = 6.0, 0.5 Hz, 1H), 0.905 (s, 9H), 0.130 (s, 6H).



BVE

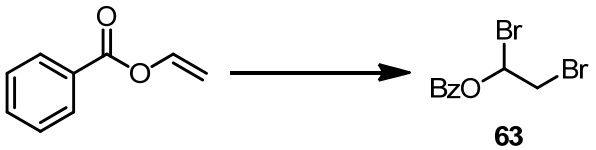
Ethyl vinyl ether (80 ml) was charged with $Pd(OAc)_2$ (449 mg, 2 mmol, 5 mol %) and phenanthroline (360.4 mg, 4 mmol, 10 mol%) causing the solution to turn cloudy yellow. Benzyl alcohol (4.16 ml, 40 mmol, 1.0 eq.) was added, which caused the solution to become transparent, followed by TEA (0.56 ml, 4 mmol, 10 mol%). The solution was gently refluxed which caused a color change to olive green. After 24 hrs, the entire solution was filtered through activated charcoal and the excess EVE evaporated. NMR and TLC showed that the residue was largely product contaminated with unreacted benzyl alcohol. The desired product was purified by loading onto a 100 g silica column and eluting on a Biotage Flash using a gradient of 7% → 60% DCM in hexanes. The collected clear liquid was found to be pure benzyl vinyl ether (2.602 g, 19.5 mmol, 49%). For characterization information, see ref. 45.



59

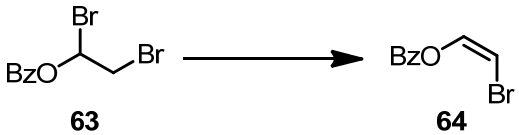
Benzyl vinyl ether (2.684 g, 20 mmol, 2.0 eq.) was added to ethyl chloro(oxo)acetate (1.12 ml, 10 mmol) at 0°C. $Pd(OAc)_2$ (22.5 mg, 1 mol%) and TEA (2 ml, 1.4 eq.) were added and the orange solution allowed to warm overnight. The reaction was then diluted with DCM and washed successively with water, sat. NH_4Cl, and sat. $NaHCO_3$. The solution was dried over Na_2SO_4 and condensed on a rotary evaporator. The residue was purified by very rapid column chromatography (5 : 1 EtOAc in hexanes) to yield a yellow orange oil containing predominately **59** (403.4 mg, 1.722 mmol, 17%). Benzyl vinyl

ether was recovered in 39% yield. The reaction provided a very variable yield from run to run. For characterization information, see ref. 43e.



63

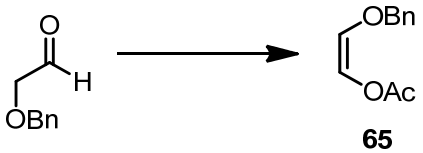
To an oven dried, 3 neck rbf was affixed a nitrogen bubbler line and a dropping funnel. The remaining neck was sealed with a rubber septum. Vinyl benzoate (2.77 ml, 20 mmol) was added followed by DCM (20 mol, 1 M). The stirred solution was chilled in a dry ice/acetone bath and allowed to equilibrate. The dropping funnel was charged with molecular bromine (1.0 ml, 20 mmol) and DCM (10 ml) before being slowly added to the reaction mixture. The reaction was then removed from the bath and allowed to warm to rt. After 1 hour, TLC indicated complete consumption of the starting material and the solvent was evaporated. The residue was purified via column chromatography using a gradient of pure hexanes → 10 : 1 EtOAc in hexanes. Dibromo **63** was collected as a clear oil (4.5802 g, 14.87 mmol, 74%) that solidified on standing. Scaling the reaction 2x caused a drop in overall yield to 62%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.101 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.642 (tt, *J* = 8.5, 1.0 Hz, 1H), 7.497 (m, 2H), 6.970 (dd, *J* = 10.0, 8.0 Hz, 1H), 4.096 (dd, *J* = 6.0, 4.5 Hz, 1H), 3.981 (dd, *J* = 6.0 Hz, 2.5 Hz, 1H).



63 **64**

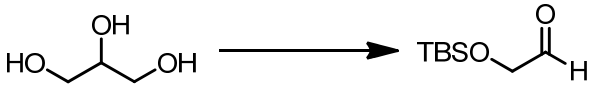
A solution of **63** (4.5802 g, 24.7 mmol) and THF (123.5 ml, 0.2 M) was chilled in a dry ice/acetone bath. DBU (5.5 ml, 1.5 eq.) and hydroquinone (136 mg, 5 mol%) were added and stirring continued in the cooling bath. After 1 hour, a precipitate could be seen in the reaction flask. Since the starting material and product had an identical Rf via TLC, NMR was used to follow the reaction. After 3.5 hours the spectrum showed near complete conversion so the reaction mixture was quickly filtered. As the solution warmed it became increasingly gummy and difficult to work with. The collected yellow filtrate was condensed and the residue purified on a Biotage Flash using a gradient of 0% → 11%

EtOAc in hexanes to provide **64** as a clear oil (1.124 g, 4.95 mmol, 20%) which solidified on standing. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.184 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.965 (d, *J* = 4.5 Hz, 1H), 7.642 (m, 1H), 7.507 (m, 2H), 5.790 (d, *J* = 4.5 Hz, 1H).



65

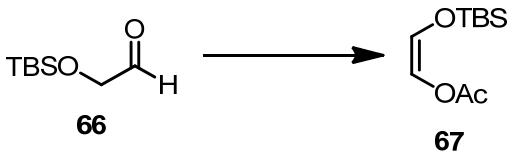
K_2CO_3 (1.38 g, 5.0 eq.) and NaOAc (20 mg, 10 mol%) were added to a suitable microwave vial with stir bar and capped. To the vial was added PhMe (6.7 ml, 0.3 M), benzyloxy acetaldehyde (0.28 ml, 2.0 mmol), and Ac_2O (1.9 ml, 10 eq.). The vial was placed in a Biotage Initiator and heated to 170°C for 20 minutes. CAUTION: The reaction evolves gas and pressure in the vial can get quite high. It is necessary to carefully vent the vial in a hood before removing the cap. The solution was filtered through a pad of Celite and rinsed with DCM. The filtrate was then condensed and the orange residue purified on a flash column using a gradient of hexanes → 5 : 1 EtOAc in hexanes. The alkene **65** was isolated as a yellow oil (201.2 mg, 1.05 mmol, 53%) that was found to be solely the *Z* isomer via proton NMR. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 (m, 5H), 6.513 (dd, *J* = 4.0, 1.0 Hz, 1H), 5.699 (dd, *J* = 4.0, 1.0 Hz, 1H), 4.85 (s, 2H), 2.19 (s, 3H).



66

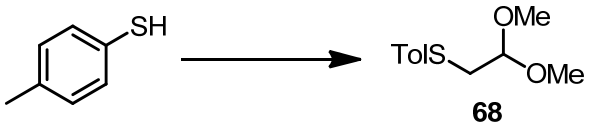
Glycerol (9.4 mL) was suspended in DCM (20 mL) and DMF (8 mL). Imidazole (1.35 g, 3.0 eq.) was added and the mixture chilled in an ice bath. TBSCl (1.0 g, 6.6 mmol) in DCM (5 mL) was added and the solution warmed to room temperature. After 1 hour, water was added and the mixture was extracted 3x with DCM and condensed into a clear oil. NMR of this crude showed the desired mono-silyl product as well as copious amounts of DMF so the oil was placed under high vacuum overnight. In the morning the oil was partitioned between DCM (12 mL) and H_2O (12 mL) and treated with $NaIO_4$ (2.14 g). After 3 hours, the phases were separated and the organic phase washed with

water and brine. The DCM solution was dried over Na_2SO_4 and condensed to achieve aldehyde **66** as a slightly yellow oil (755.5 mg, 4.33 mmol, 66%) that was of sufficient purity. The NMR spectrum of **66** was consistent with that reported in ref. 50.



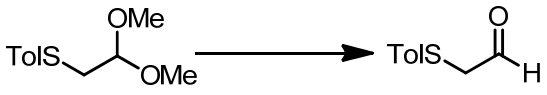
66 **67**

The synthesis of silyl enol ether **67** was accomplished using the same procedure as that employed in the synthesis of **65**. Amounts used are as follows: **66** (2.26 mmol), Ac_2O (2.15 mL), K_2CO_3 (1.561 g), NaOAc (19 mg), PhMe (32 mL). After Biotage separation (gradient 0% → 5% EtOAc in hexanes), **67** was isolated as a clear oil (170.6 mg, 0.788 mmol, 35%) with better than 10 : 1 isomeric selectivity (*Z* favored). **67**: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.086 (d, *J* = 10.5 Hz, 0.08H, *E*), 6.671 (d, *J* = 10.5 Hz, 0.08H, *E*), 6.499 (d, *J* = 3.5 Hz, 1H, *Z*), 5.788 (d, *J* = 3.5 Hz, 1H, *Z*), 2.128 (s, 3H, overlapping *Z*/*E*), 0.915 (s, 9H, overlapping *Z*/*E*), 0.146 (s, 6H, overlapping *Z*/*E*).



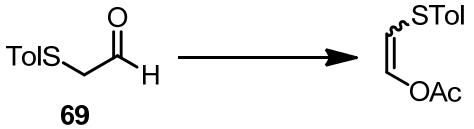
68

Thiocresol (1.0 g, 8.05 mmol) was dissolved in THF and chilled to 0°C. NaH (60% dispersion, 483 mg, 1.5 eq) was added and vigorous bubbling was noted. The white suspension was stirred at 0°C for 20 minutes and then **61** (1.05 ml, 1.1 eq.) was added. The reaction was warmed to room temperature and stirred overnight. In the morning, TLC showed complete consumption of thiocresol so the mixture was again chilled to 0°C and water carefully added. The mixture was then extracted 3x with EtOAc and the combined organic extracts washed with brine and dried over Na_2SO_4. After removal of the solvent, the product was purified via Biotage using a 0% → 10% gradient of EtOAc in hexanes to provide **68** as a yellow oil (1.5217 g, 7.17 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.301 (d, *J* = 8.0 Hz, 2H), 7.098 (dd, *J* = 8.0, 0.5 Hz, 2H), 4.499 (m, 1H), 3.350 (s, 6H), 3.070 (m, 2H), 2.317 (s, 3H).



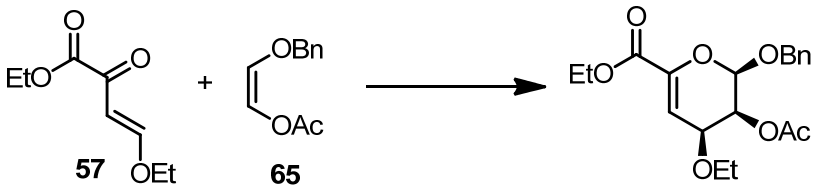
68 **69**

Sulfide **68** (4.81 mmol) was dissolved in acetone (4.81 ml, 1 M) and 1% aqueous HCl (4.81 ml) was added. The solution was heated to 80°C for 2 hours before the excess acetone was evaporated. The residue was taken up in EtOAc and washed successively with sat. $NaHCO_3$, water, and brine before being dried over Na_2SO_4. Filtration and rotary evaporation yielded aldehyde **69** as a pure yellow oil (711.1 mg, 4.28 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.541 (m, 1H), 7.270 (d, *J* = 8.0 Hz, 2H), 7.111 (dd, *J* = 8.0, 0.5 Hz, 2H), 3.543 (dd, *J* = 8.5, 1.0 Hz, 1H), 2.316 (s, 3H).

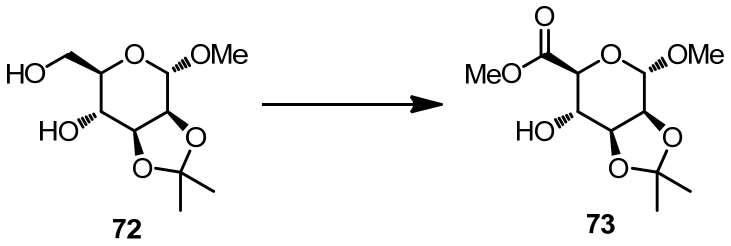


69 **70**

Aldehyde **69** (1.71 mmol) was dissolved in PhMe (24.4 ml, 0.07 M). To this was added Ac_2O (1.62 mL, 10 eq.), K_2CO_3 (1.181 g, 5 eq.), and NaOAc (14 mg, 10 mol%). The mixture was then placed in a 125°C oil bath and heated overnight. In the morning an aliquot (0.5 ml) was pulled and condensed. NMR showed consumption of starting material so the reaction was cooled to rt and filtered through a pad of Celite. The filtrate was condensed into an orange oil which was purified via Biotage utilizing a 0 % → 10% gradient of EtOAc in hexanes to provide a mixture of isomers **70** as a clear, slightly yellow oil (299.7 mg, 1.44 mmol, 84%). Proton NMR showed that the desired *Z* isomer was favored 3 : 1. Enrichment to >20 : 1 was possible via slow column chromatography using 20 : 1 diethyl ether in petroleum ether. ^{1}H NMR (500 MHz, $CDCl_3$, isomeric mixture) δ: 7.534 (d, *J* = 12 Hz, 1H, *E*), 7.303 (overlapping m, 3H, *Z*), 7.214 (d, *J* = 8.5 Hz, 2H, *E*), 7.131 (d, *J* = 8.5, 2H, *Z*), 7.109 (d, *J* = 8.5 Hz, 2H, *E*), 6.144 (d, *J* = 12 Hz, 1H, *E*), 5.689 (d, *J* = 5.5 Hz, 1H), 2.333 (s, 3H, *Z*), 2.319 (s, 3H, *E*), 2.2055 (s, 3H, *Z*), 2.163 (s, 3H, *E*).

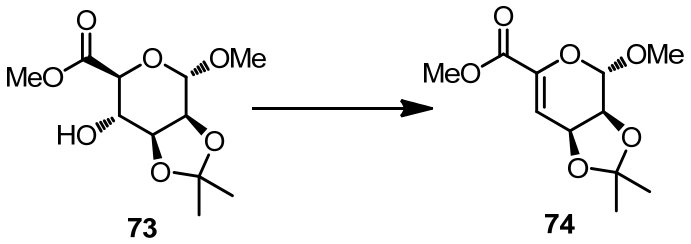


Box ligand **51** (47 mg, 20 mol%) and $Cu(OTf)_2$ (58 mg, 20 mol%) were added to a rbf followed by Et_2O (2.1 mL) and the blue mixture stirred for 30 minutes until green. Heterodiene **57** (137.7 mg, 0.8 mmol) and **65** (1.5 eq.) were added along with Et_2O (1.1 mL) and stirred overnight. The green solution was then loaded directly onto a Biotage SNAP cartridge and eluted using a 0% → 20% gradient of EtOAc in hexanes. The product **71** was isolated as a yellow oil (173.8 mg, 0.477 mmol, 60%). The spectral data for **71** matched those values reported in ref. 43e.



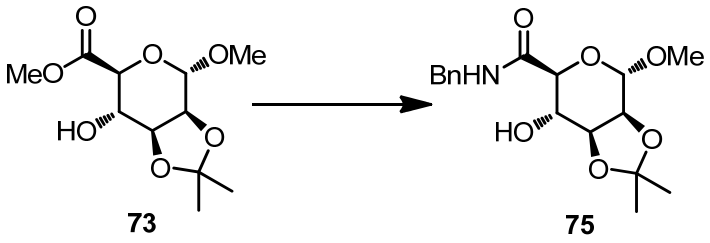
2,3-*O*-isopropylidene-α-D-mannopyranoside (**72**, 20 mmol) was dissolved in EtOAc (100 mL, 0.2 M). Saturated $NaHCO_3$ (59 mL, 0.35 M) was added alongside TBAF (15 mol%), and TEMPO (812.5 mg, 26 mol%). The orange solution was place in an ice bath and stirred vigorously. In a dropping funnel was combined household bleach (105 mL, 0.19 M), brine (105 mL, 0.19 M), and sat. $NaHCO_3$ (50 mL, 0.4 M). The bleach solution was slowly added to the chilled solution of **72** and then stirred for an additional 2 hours. All excess solvents were evaporated off with a rotary evaporator and the sludge filtered through a pad of silica gel eluting with methanol. The collected filtrate was evaporated and taken up in DMF (33.3 mL, 0.6 M). Iodomethane (4.5 mL, 4.4 M) was added and the reaction stirred overnight. In the morning, the thick orange paste was suspended in water and extracted 3x with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue purified via column chromatography using 50% EtOAc in hexanes. Methylester **73** was isolated as a white

solid in 73% yield (3.7949 g, 14.5 mmol). The spectroscopic data for **73** was found to be in good agreement with that reported in ref. 54.



73 **74**

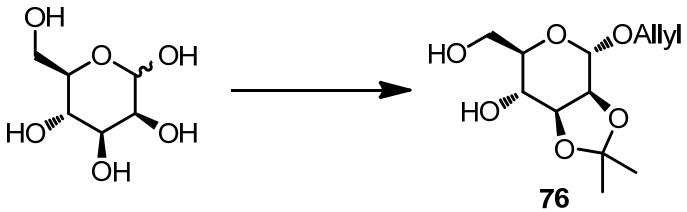
Methylester **73** (1.0 g, 3.81 mmol) was dissolved in DCM (38.2 mL, 1.0 M) and chilled in an ice bath. Methanesulfonyl chloride (0.32 mL, 1.1 eq.) was added followed by TEA (1.6 mL, 3.0 eq.). The reaction was stirred for 2 hours at 0°C at which time TLC indicated complete consumption of the starting material. DBU (4.2 mL, 5.0 eq.) was added and the reaction brought to a gentle reflux. After 2.5 hours, TLC again indicated consumption of the intermediate sulfonate. The reaction was cooled to rt and quenched with 1N $KHSO_4$. The phases were separated and the aqueous layer extracted twice more with DCM. The combined organic phases were washed with brine and dried over $MgSO_4$. Removal of the solvent provided unsaturated ester **74** as a pure, clear oil (832.3 mg, 3.41 mmol, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.196 (dd, *J* = 5.5, 1.0 Hz, 1H), 4.868 (d, *J* = 7.0 Hz, 1H), 4.695 (dd, *J* = 10, 6.5 Hz, 1H), 4.120 (dd, *J* = 10, 7.5 Hz, 1H), 3.830 (s, 3H), 3.575 (s, 3H), 1.454 (s, 3H), 1.391 (s, 3H).



73 **75**

Methylester **73** (100 mg, 0.38 mmol) was placed into an appropriate microwave vial alongside a stir bar. The vial was then charged with HOBt (2.6 mg, 5 mol%) and sealed. To the sealed vial were added PhMe (0.38 mL, 1.0 M), benzylamine (46 μL, 1.1 eq.), and $Zr(O^tBu)_4$ (7.6 μL, 5 mol%). The vial was placed into a 100°C oil bath and stirred vigorously for 6 hours. At this time, TLC indicated the complete consumption of **73** and the reaction was cooled. MeOH (1 mL) and DCM (1 mL) were added to the mixture and

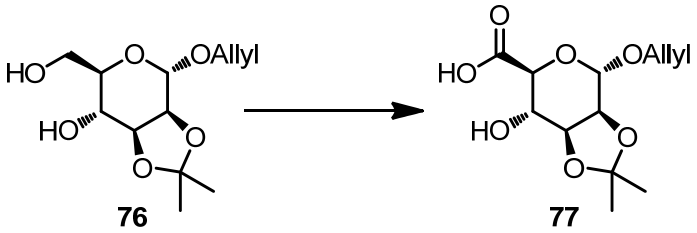
the entire solution filtered through a pad of silica gel. The filtrate was condensed into an orange oil which was purified via column chromatography using a 2:1 → 1:1 gradient of EtOAc in hexanes. Amide **75** was collected as a yellow oil (118.4 mg, 0.35 mmol, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.853 (d, *J* = 10 Hz, 1H), 6.721 (t, *J* = 10 Hz, 1H), 5.855 (m, 1H), 5.275 (overlapping m, 3H), 5.077 (m, 1H), 4.481 (dd, *J* = 18, 10.5 Hz, 1H), 4.331 (m, 1H), 4.153 (overlapping m, 2H), 4.028 (m, 2H), 3.257 (s, 2H), 2.116 (s, 3H), 2.001 (overlapping m, 2H), 1.821 (m, 2H), 1.545 (s, 3H), 1.357 (s, 3H), 1.260 (m, 1H); ^{13}C (25 MHz, $CDCl_3$) δ: 170.85, 137.07, 128.57, 127.54, 127.51, 109.56, 98.34, 76.96, 74.37, 70.4 67.77, 55.59, 42.88, 27.66, 25.92.



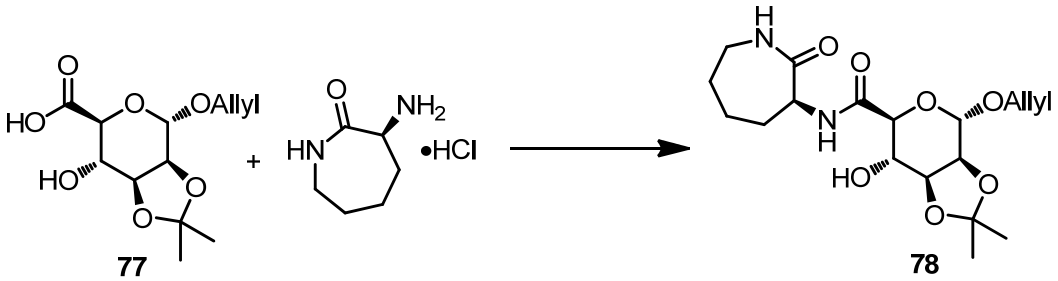
76

Mannose (10 g, 55.5 mmol) was suspended in allyl alcohol (37 mL) and $Sc(OTf)_3$ was added. The reaction was placed in a 100°C oil bath and stirred for 6 hours. At this point, the translucent mixture was cooled and the excess allyl alcohol removed on a rotary evaporator. The clear brown oily residue was taken up in acetone (111 mL, 0.5 M) and DMP (111 mL, 0.5 M) to which *p*TsOH (2.112 g, 20 mol%) was added. The mixture was stirred for 1 hour before water (224 mL, 0.2 M) was added. The emulsion was stirred for 4 hours before being quenched by the addition of sat. $NaHCO_3$. The volume was reduced on a rotary evaporator and the resultant aqueous suspension was extracted 3x with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and removal of the solvent left a crude material that was purified via column chromatography using a 5:1 → 1:1 → EtOAc gradient. Allyl mannopyranoside **76** was isolated as a clear oil (6.345 g, 24.4 mmol, 44%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.949 (m, 1H), 5.322 (ddd, *J* = 17.5, 3.0, 1.5 Hz, 1H), 5.245 (ddd, *J* = 10, 2.5, 1.5 Hz, 1H), 4.854 (d, *J* = 2.5 Hz, 1H), 4.414 (ddt, *J* = 13, 5.0, 1.5 Hz, 1H), 4.268 (dd, *J* = 6.0, 2.5 Hz, 1H), 4.209 (ddt, *J* = 13, 6.5, 1.0 Hz, 1H), 4.123 (dd, apparent t, *J* = 6.5 Hz, 1H), 3.905 (m, 2H), 3.841 (ddd, *J* = 12, 7.5, 5.0 Hz, 1H), 3.343 (ddd, *J* = 10, 4.5, 4.0 Hz, 1H), 2.576 (d, *J* = 4.0 Hz, 1H), 2.134 (dd, *J* = 7.5, 5.5 Hz, 1H), 1.568 (s, 3H), 1.399 (s, 3H); ^{13}C (25 MHz,

$CDCl_3$) δ: 133.23, 117.74, 109.38, 96.21, 78.41, 75.54, 69.61, 68.88, 68.00, 61.75, 27.95, 26.14.

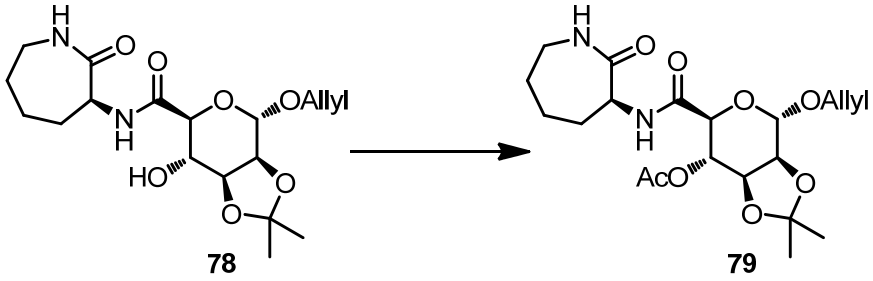


Pyranoside **76** (2.80 mmol) was dissolved in MeCN:H_2O (1:1, 5.6 mL, 0.5 M). TEMPO (66 mg, 15 mol%), and BAIB (1.984 g, 2.2 eq.) were added and the solution stirred for 2.5 hours. Excess solvents were evaporated and the residue was suspended in water. Saturated $NaHCO_3$ was added until the pH was raised above 8 and then the solution was extracted 2x with EtOAc. The aqueous layer was then acidified to pH ~2 using 10% HCl and extracted three more times with EtOAc. The second organic extracts were dried over $MgSO_4$ and condensed into a viscous oil which was acid **77** (557.4 mg, 2.03 mmol, 73%) of sufficient purity to carry forward. ^{1}H NMR (300 MHz, Acetone-D6) δ: 5.959 (m, 1H), 5.333 (ddd, *J* = 17.4, 3.3, 1.8 Hz, 1H), 5.193 (ddd, *J* = 10.4, 3.0, 1.5 Hz, 1H), 5.087 (s, 1H), 4.266 (ddt, *J* = 13.2, 5.1, 1.8 Hz, 1H), 4.095 (m, 4H), 3.900 (m, 1H), 1.434 (s, 3H), 1.315 (s, 3H); ^{13}C (25 MHz, Acetone-D6) δ: 171.54, 135.50, 118.05, 110.38, 98.31, 79.47, 76.64, 71.858, 71.08, 69.57, 28.82, 27.06.

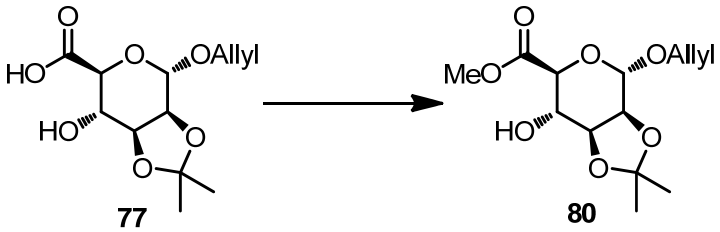


Acid **77** (100 mg, 0.365 mmol), 2-(*S*)-aminocaprolactam (66 mg, 1.1 eq.), and PyBOP (228 mg, 1.2 eq.) were suspended in DCM (1.2 mL, 0.3 M) and chilled in an ice bath. DIPEA (0.19 mL, 3.0 eq.) and DMAP (2.0 mg, 4 mol%) were added and the reaction allowed to warm to room temperature. After 4 hours, water was added and the phases separated. The aqueous phase was extracted 2x with DCM and the combined organic

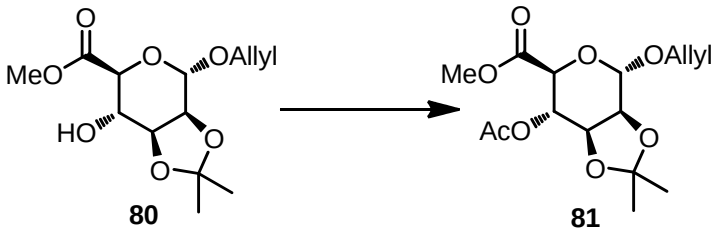
layers were washed with 1N $KHSO_4$, sat. $NaHCO_3$, and brine before being dried over $MgSO_4$. Removal of the solvent and purification on a column using 2:1 → 1:1 → 1:2 → EtOAc gradient provided amide **78** (107.6 mg, 0.28 mmol, 77%) as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.995 (d, *J* =5.7 Hz, 1H), 6.122 (br t, 1H), 5.890 (m, 1H), 5.355 (ddd, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.257 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.191 (s, 1H), 4.645 (d, *J* = 1.8 Hz, 1H), 4.537 (m, 1H), 4.217 (m, 3H), 4.066 (m, 2H), 3.841 (ddd, *J* = 9.3, 6.6, 1.8 Hz, 1H), 3.280 (m, 2H), 2.059 (m, 2H), 1.854 (m, 2H), 1.529 (s, 3H), 1.426 (m, 1H), 1.361 (s, 3H); ^{13}C NMR (25 MHz, $CDCl_3$) δ: 132.64, 118.70, 109.73, 96.35, 76.58, 74.82, 70.56, 68.80, 67.88, 51.89, 42.20, 31.52, 28.93, 27.98, 27.86, 26.06, 21.14, 21.14, 14.28.



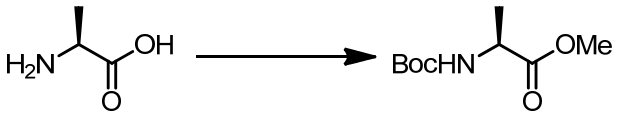
Amide **78** (0.18 mmol) was dissolved in DCM (0.6 mL, 0.3 M). Ac_2O (25 µL, 1.5 eq.), DMAP (2 mg, 10 mol%), and TEA (75 µL, 3.0 eq) were added and the reaction stirred for 1 hour. At this time water was added and the aqueous layer extracted 3x with DCM. The combined organic layers were washed with brine and dried over $MgSO_4$. Purification was completed on a silica gel column using a 1:1 → 1:3 → EtOAc gradient to provide **79** as a clear oil (62 mg, 0.146 mmol, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.853 (d, *J* = 3.0 Hz, 1H), 6.721 (t, *J* = 5.7 Hz, 1H), 5.855 (m, 1H), 5.275 (overlapping m, 3H), 5.105 (m, 1H), 4.481 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.331 (m, 1H), 4.165 (m, 2H), 4.028 (m, 2H), 3.257 (m, 2H), 2.116 (s, 3H), 2.020 (m, 2H), 1.821 (m, 2H), 1.545 (m, 3H), 1.472 (m, 1H), 1.357 (s, 3H), 1.260 (ddd, apparent td, *J* = 7.2, 7.2, 1.8 Hz, 1H); ^{13}C (25 MHz, $CDCl_3$) δ: 175.08, 169.93, 166.54, 132.68, 118.22, 109.89, 96.19, 75.26, 75.07, 70.39, 68.52, 67.60, 51.61, 42.02, 30.88, 28.90, 27.95, 27.66, 26.19, 21.04.



Acid **77** (2.03 mmol) was dissolved in DMF (6.8 mL, 0.3 M). K_2CO_3 (561 mg, 2.0 eq.) and iodomethane (0.19 mL, 1.5 eq.) were added and the reaction stirred for 3 hours. The solvent was decanted off and the remaining carbonate base was washed with EtOAc. The combined organic material was washed with water and brine and dried over $MgSO_4$. Column chromatography utilizing a 5:1 → 2:1 gradient of EtOAc in hexanes provided methylester **80** as a light orange oil (426.4 mg, 1.48 mmol, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.912 (m, 1H), 5.329 (ddd, *J* = 17.1, 3.3, 1.5 Hz, 1H), 5.254 (dd, *J* = 10.5, 1.2 Hz, 1H), 5.126 (s, 1H), 4.232 (overlapping m, 4H), 4.079 (overlapping m, 2H), 3.829 (s, 3H), 3.433 (d, *J* = 5.1 Hz, 1H), 1.510 (s, 3H), 1.350 (s, 3H); ^{13}C (25 MHz, $CDCl_3$) δ: 163.59, 132.73, 118.40, 109.86, 96.68, 76.09, 74.42, 70.334, 69.30, 68.73, 52.66, 27.24, 25.69.

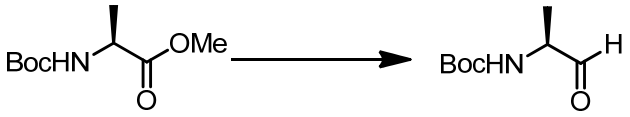


Methylester **80** was converted into acetate **81** utilizing the same basic method as the synthesis of **79**. Methylester (1.48 mmol), Ac_2O (0.21 mL, 1.5 eq.), DMAP (18 mg, 10 mol%), TEA (0.62 mL, 3 eq.), DCM (5 mL, 0.3 M). The product ester was isolated as a clear oil using a 5:1 → 2:1 gradient of EtOAc in hexanes (425.5 mg, 1.29 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.894 (m, 1H), 5.327 (ddd, *J* = 17.3, 3.0, 1.5 Hz, 1H), 5.211 (m, 3H), 4.246 (m, 3H), 4.077 (m, 2H), 3.757 (s, 3H), 2.094 (s, 3H), 1.539 (s, 3H), 1.354 (s, 3H); ^{13}C (25 MHz, $CDCl_3$) δ: 169.52, 168.19, 132.83, 117.99, 110.02, 96.37, 75.02, 74.85, 69.87, 68.70, 67.76, 52.54, 27.49, 26.15, 20.71.



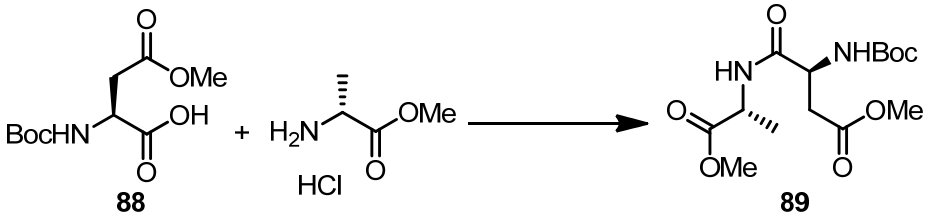
86

L-alanine (1.0g, 11.2 mmol) was suspended in MeOH (16.4 mL, 0.68 M) and chilled in an ice bath. $SOCl_2$ (1.8 mL, 2.2 eq.) was added slowly. After complete addition, the mixture was heated to 40°C for 3.5 hours. At this time, the solvent was carefully removed via rotary evaporation to provide a white solid which was further dried under high vacuum overnight. The crude solid was dissolved in THF/water (1:1, 37.3 mL, 0.3 M) and treated with $NaHCO_3$ (1.034 g, 1.1 eq.) and Boc_2O (2.8 mL, 1.1 eq.). After stirring for 8 hours, the mixture was extracted with Et_2O. The organic extract was dried over $MgSO_4$ and condensed into a light yellow oil. Colum chromatography (4:1 Hex:EtOAc) yielded the desired protected alanine **86** (1.8466 g, 9.08 mmol, 81%).



86 **87**

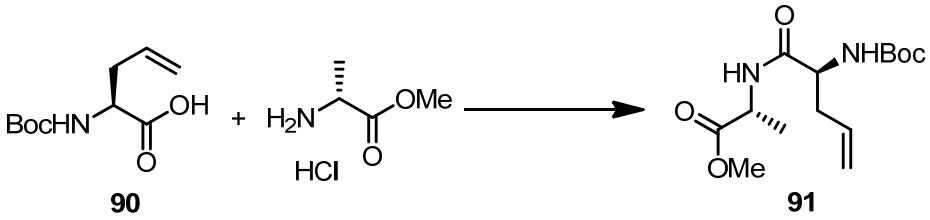
Protected alanine **86** (1.8466 g, 9.08 mmol) was dissolved in PhMe and cooled in a dry ice/acetone bath. After 20 minutes, DIBAL-H (2.0 eq.) was added slowly. After stirring for 1.5 hours, the reaction was quenched by the slow addition of EtOAc (2.0 mL) and MeOH (2.0 mL) then warmed to room temperature. The mixture was run into 10% aq. tartaric acid and extracted with a 1:1 mix of hexanes and EtOAc. The extracts were dried over $MgSO_4$ and the solvent removed to provide suitably pure aldehyde **87** (1.3664 g, 7.3 mmol, 80%). Spectroscopic data matched that found in ref. 59.



88 **89**

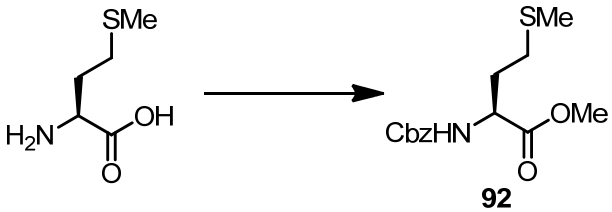
D-Alanine methylester hydrochloride (153.5 mg, 1.1 eq.) and PyBOP (520.4 mg, 1.0 eq.) were added to a rbf along with a stir bar. Aspartic acid derivative **88** (1.0 mmol) was

added as a solution in DCM (3.3 mL) and the entire reaction mixture was stirred in an ice bath for 10 minutes. DIPEA (0.52 mL, 3.0 eq.) was added and the solution warmed to room temperature. After 1 hr, water was added and the layers separated. The aqueous layer was extracted 2x with DCM and the combined organic layers were washed sequentially with 1N $KHSO_4$, sat. $NaHCO_3$, and brine before being dried over $MgSO_4$. Evaporation of the solvent and elution on a column (EtOAc) yielded dipeptide **89** (228.9 mg, 0.689 mmol, 69%). ^{1}H NMR (500 MHz, $CDCl_3$) δ:7.078 (d, J = 6.5 Hz, 1H), 5.744 (d, J = 8.0 Hz, 1H), 4.470 (ddd, J = 14, 7.0, 7.0 Hz, 2H), 3.666 (s, 3H), 3.622 (s, 3H), 2.846 (dd, J = 16, 3.5, Hz, 1H), 2.669 (dd, J = 16, 5.0 Hz, 1H), 1.390 (s, 9H), 1.331 (d, J = 7.5 Hz, 3H).



90 **91**

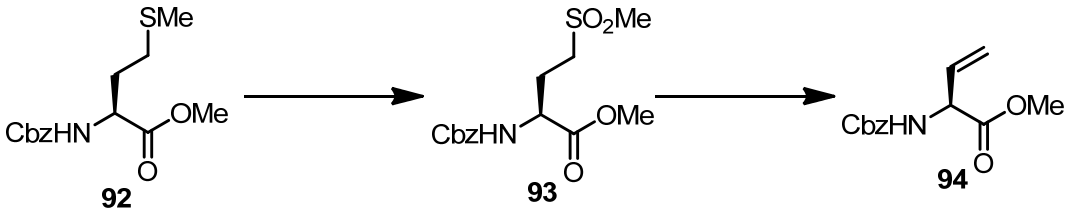
Dipeptide **91** was synthesized using the previous conditions. D-alanine methylester hydrochloride (304 mg, 1.1 eq.), *N*-Boc-allylglycine (1.98 mmol), PyBOP (1.133 g, 1.1 eq.), DIPEA (1.38 mL, 4.0 eq.), DCM (7 mL, 0.3 M). Reaction time was 2 hours. Dipeptide **91** was isolated as a clear oil using a 1:1 EtOAc:hexanes gradient (394.3 mg, 1.25 mmol, 63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.326 (d, J = 24 Hz, 1H), 5.688 (m, 1H), 5.585 (dd, J = 14.5, 8.0 Hz, 1H), 5.021 (overlapping, 2H), 4.502 (m, 1H), 4.237 (br s, 1H), 3.645 (s, 3H), 2.467 (m, 1H), 1.360 (s, 9H), 1.316 (dd, J = 7.5, 2.0 Hz, 3H).



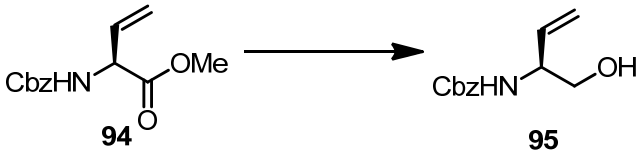
92

L-Methionine (5.0 g, 33.5 mmol) was suspended in MeOH (112 mL, 0.3 M) and chilled in an ice bath. $SOCl_2$ (5.35 mL, 2.2 eq.) was added slowly. After complete addition, the mixture was warmed to room temperature and stirred overnight. In the morning, the methanol was evaporated and the residue taken up in EtOAc (166 mL, 0.2 M) and water

(166 mL, 0.2 M). $NaHCO_3$ (16.4 g, 6.0 eq.) was carefully added and the mixture chilled in an ice bath. CbzCl (5.26 mL, 1.1 eq.) was added portionwise over 40 minutes. Following complete addition, the reaction was stirred for 6 hours in the melting ice bath and then the phases were separated. The organic layer was washed with sat. NH_4Cl and brine and then dried over $MgSO_4$. Filtration and removal of the solvent provided protected methionine **92** as a yellow oil of sufficient purity for the next step (9.39 g, 31.6 mmol, 94%). Spectroscopic data for isolated **92** matched that reported in ref. 65.

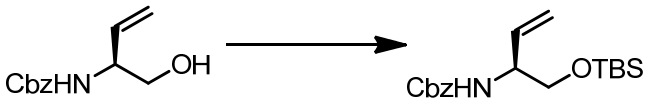


Protected methionine **92** (7.96 mmol) was dissolved in MeOH (26.5 mL, 0.3 M) and placed in an ice bath with vigorous stirring. A solution of $NaIO_4$ (1.771 g, 1.04 eq.) in water (9.63 mL) was placed in a dropping funnel and then slowly added to the solution of **92**. The milky white reaction was stirred for 3 hours during which time it began to thicken and become difficult to stir. The slurry was filtered and the filtrate was partially condensed until the clear solution became cloudy. At this point the solution was extracted 3x with DCM and the combined organic extracts washed with brine and dried over $MgSO_4$. Removal of the solvent provided the intermediate sulfoxide **93** of sufficient purity. Crude **93** was placed in a distillation bulb and carefully distilled via Kugelrohr (150°C, ~1 mmHg). The resultant yellow distillate was then run through a column eluting with a gradient of 10:1 → 4:1 EtOAc in hexanes. Vinyl glycine derivative **94** was obtained as a yellow oil (924 mg, 3.71 mmol, 47%). The protected vinyl glycine had matching spectroscopic data to that reported in ref. 65.



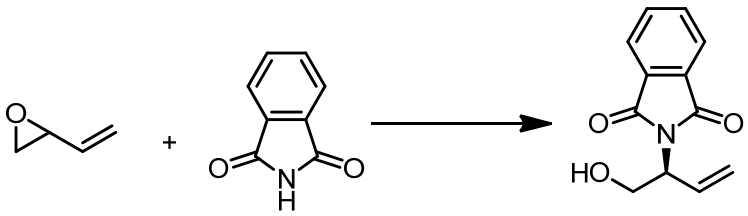
$LiBH_4$ (2.0 M in Et_2O, 3.15 mL, 1.0 eq.) was diluted with Et_2O (12.6 mL, not pre-dried) and stirred. In a vial vinyl glycine **94** (3.024 mmol) was dissolved in Et_2O (9.3 mL) and

MeOH was added (0.24 mL). The solution of **94** was carefully added to the $LiBH_4$ solution and vigorous bubbling was noted. The reaction was stirred for 3 hours before water was carefully added to quench. The solution was extracted 3x with EtOAc and the combined organic layers washed with brine and dried over $MgSO_4$. The solvents were removed and the crude oil purified via column chromatography using a 5:1 → 2:1 → 1:1 gradient of EtOAc in hexanes. Vinyl glycinol **95** was isolated as a clear oil which solidified upon standing (456.7 mg, 2.064 mmol, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.345 (m, 4H), 7.326 (m, 1H), 5.816 (ddd, *J* = 16.5, 11.5, 5.5 Hz, 1H), 5.259 (overlapping, 2H), 5.184 (s, 1H), 5.116(s, 2H), 4.328 (br s, 1H), 3.687 (m, 2H); ^{13}C (126 MHz) δ: 156.34, 136.24, 135.03, 128.51, 128.15, 128.11, 116.80, 66.94, 64.85, 54.95; MS m/z (%): 244 (40, M^+, + Na), 222 (34, M^+), 178 (100).



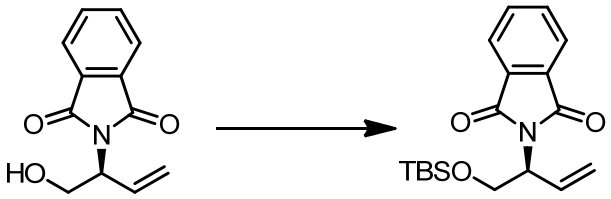
95 **96**

Vinyl glycinol **95** (2.064 mmol) was dissolved in DMF (3.2 mL, 0.65 M) and TBSCl (373.3 mg, 1.2 eq.) was added in one portion. The reaction was stirred in an ice bath for 10 minutes before imidazole (351.2 mg, 2.5 eq.) was added. The reaction was then removed from the ice bath and stirred overnight. The solution was dilute with EtOAc and washed with sat. $NaHCO_3$. The organic layer was then dried over $MgSO_4$ and condensed. The residue was then flashed through a column eluting with 10:1 EtOAc in hexanes. TBS ether **96** was collected as a white solid (562.5 mg, 1.676 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.337 (m, 5H), 5.853 (ddd, *J* = 17, 11, 5.5, Hz, 1H), 5.249 (d, *J* = 17 Hz, 1H), 5.174 (d, *J* = 10.5 Hz, 1H), 5.125 (s, 2H), 4.279 (s, 1H), 3.675 (m, 2H), 0.903 (s, 9H), 0.059 (s, 6H).



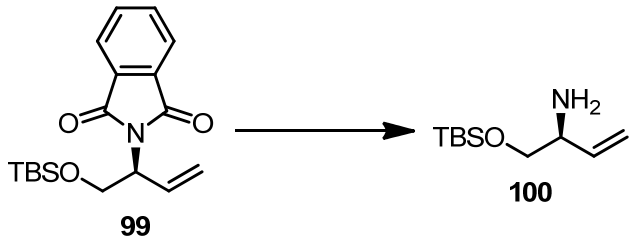
98

A 3-neck rbf was fitted with two septa and a nitrogen bubbler. Na_2CO_3 (85.8 mg, 5.4 mol%) was added with a stir bar and the flask evacuated while heating with a heat gun. Freshly recrystallized phthalimide (2.428 g, 5.4 mol%), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (22 mg, 0.4 mol%), and Trost ligand **97** (154.2 mg, 1.3 mol%) were added and the flask evacuated and refilled with nitrogen 3 times. DCM (150 mL, 0.1 M, degassed via nitrogen bubbling for 30 minutes) was added and the lemonade colored solution stirred vigorously. Butadiene monoxide (1.2 mL, 15 mmol) was added in one portion and the reaction stirred at room temperature for 12 hours. The solution was then condensed and the orange oil purified via column chromatography using 2:3 petroleum ether:Et_2O. Adduct **98** was obtained as a white solid (3.09g, 14.2 mmol, 95%). For spectroscopic data, see ref. 69.



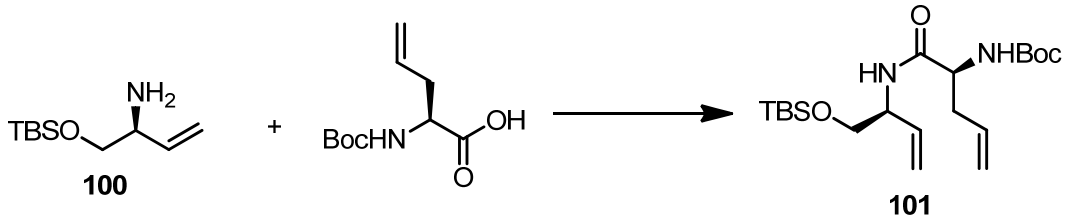
98 **99**

Vinyl glycinol **98** (3.0 g, 13.8 mmol) was dissolved in DMF (19.7 mL, 0.7 M) and TBSCl (2.91 g, 1.4 eq.) was added in one portion. The reaction mixture was stirred for 10 minutes in ice before imidazole (2.63 g, 2.8 eq.) was added. The reaction was then removed from the ice bath and stirred overnight. In the morning, the reaction was diluted with water and then extracted 3x with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The oil obtained after solvent evaporation was purified on a Biotage Flash using a 0% → 10% gradient of EtOAc in hexanes. Silyl ether **99** was isolated as a white solid (4.185 g, 12.63 mmol, 92%). ^1H (500 MHz, $CDCl_3$) δ: 7.857 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.737 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.154 (ddd, *J* = 17.5, 10.5, 7.25 Hz, 1H), 5.280 (dt, *J* = 17.5, 1.0 Hz, 1H), 5.229 (dt, *J* = 10.5, 1.0 Hz, 1H), 4.886 (m, 1H), 4.130 (dd, *J* = 10, 10 Hz, 1H), 3.836 (dd, *J* = 10, 6.5 Hz, 1H), 0.721 (s, 9H), -0.024 (s, 3H), -0.095 (s, 3H); ^{13}C (126 MHz, $CDCl_3$) δ: 168.20, 133.87, 132.30, 131.94, 123.08, 118.91, 62.15, 55.87, 25.56, 17.91, -5.56



99 **100**

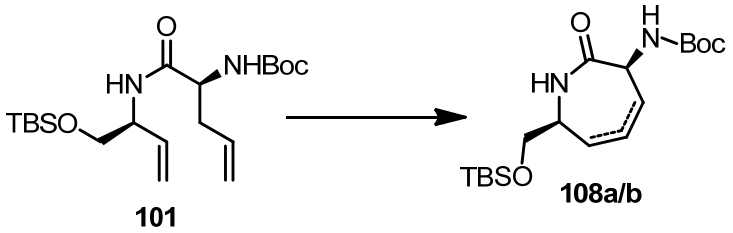
TBS ether **99** (2.5 g, 7.5 mmol) was dissolved in EtOH (25 mL, 0.3 M) and ethylenediamine (1.0 mL, 1.0 eq.) was added in one portion. The reaction was refluxed for 4 hours before the insoluble material was filtered off. The filtrate was condensed and product purified by passing through a TEA deactivated silica gel column eluted with Et_2O to provide free amine **100** as an oil (893 mg, 4.43 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.776 (dddd, *J* = 17, 10.5, 6.0, 1.0 Hz, 1H), 5.188 (ddd, *J* = 17, 2.0, 1.5 Hz, 1H), 5.060 (ddd, *J* = 10.5, 2.0, 1.0 Hz, 1H), 3.581 (ddd, *J* = 9.0, 4.0, 1.0 Hz, 1H), 3.404 (m, 1H), 3.353 (m, 1H), 1.396 (br s, 2H), 0.869 (s, 9H), 0.028 (s, 6H); ^{13}C (125 MHz, $CDCl_3$) δ: 139.14, 114.94, 67.76, 55.72, 25.76, 18.17, -5.495; MS m/z (%): 203 (16, M^+ + H), 202 (100, M^+), 185 (9).



100 **101**

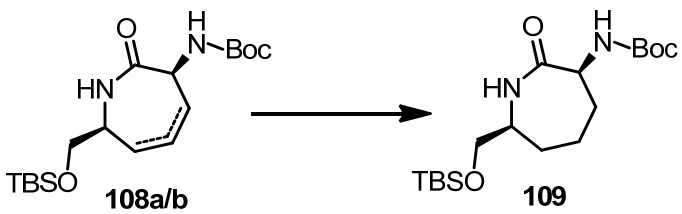
Free amine **100** (1.42 mmol, 1.1 eq.), *N*-Boc-allylglycine (279.8 mg, 1.3 mmol), and PyBOP (744 mg, 1.1 eq.) were dissolved in DCM (4.33 mL, 0.3 M) and chilled in an ice bath. DIPEA (0.68 mL, 3.0 eq.) was added and the reaction stirred for 1 hour in the bath and 6 hours at room temperature. At this time sat. NH_4Cl was added and the phases separated. The organic phase was then washed with sat. Na_2CO_3 and brine and dried over $MgSO_4$. The solvent was removed and the crude material purified on a column eluting with 10:1 MeOH in $CHCl_3$ to provide diene **101** as a white solid (453.9 mg, 1.14 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.479 (d, *J* = 8.0 Hz, 1H), 5.749 (overlapping m, 2H), 5.099 (overlapping m, 5H), 4.455 (m, 1H), 4.150 (m, 1H), 3.621 (d, *J* = 8.0 Hz, 2H), 2.471 (m, 2H), 1.396 (s, 9H), 0.848 (s, 9H), 0.008 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:

170.60, 155.53, 135.64, 133.17, 118.79, 115.96, 79.99, 64.85, 53.81, 52.68, 36.76, 28.21, 25.77, 18.19, -5.51, -5.55.



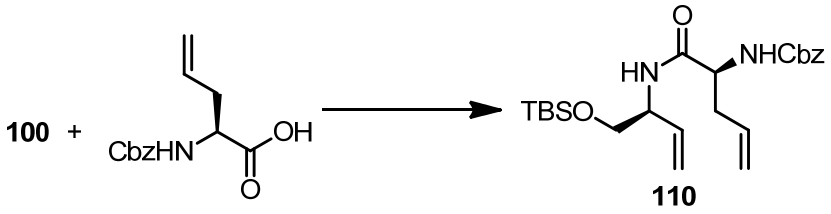
For the thermal ring closure catalyst **106** (14.7 mg, 5 mol%) and diene **101** (0.346 mmol) were added to a rbf and dissolved in PhMe (7 mL, 0.05 M). The reaction was then refluxed for 24 hours before the solvent was removed. Passing through a column eluted with 10:1 → 2:1 EtOAc in hexanes yielded a brownish oil containing the desired lactone **108** and **101** in a 4:1 mixture (85.5 mg total, 0.155 mmol **108**, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.250 (s, 1H), 5.766 (d, *J* = 6.5 Hz, 1H), 5.704 (m, 1H), 5.347 (m, 2H), 4.692 (m, 1H), 4.246 (m, 1H), 3.697 (m, 1H), 3.487 (dd, *J* = 10, 7.5 Hz, 1H), 2.616 (m, 1H), 2.178 (m, 1H), 1.382 (s, 9H), 0.837 (s, 9H), 0.027 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 173.53, 154.98, 129.51, 126.29, 79.43, 64.70, 51.43, 50.23, 32.53, 28.25, 25.69, 18.12, -5.57.

For the microwave accelerate ring closure catalyst **106** (5 mol%), benzoquinone (10 mol% if added), and **101** were added to a suitably sized microwave vial and capped. PhMe (0.05 M) was added and the reaction irradiated as per the Table **4.1**. After cooling to room temperature, the mixture was transferred to a rbf and the solvent evaporated. Chromatography as above provided the material as per Table **4.1**.

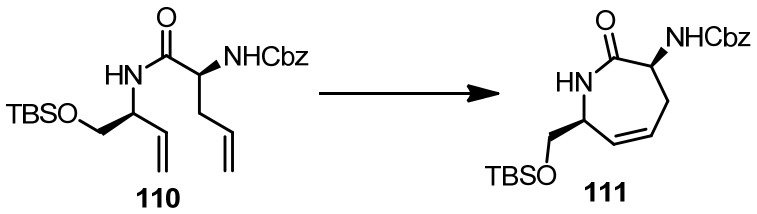


A mixture of dienes **108a/b** (154.9 mg, 0.418 mmol) was dissolved in MeOH (2.09 mL, 0.2 M) and 10% Pd/C (154.9 mg) was added. Hydrogen gas was bubbled through the

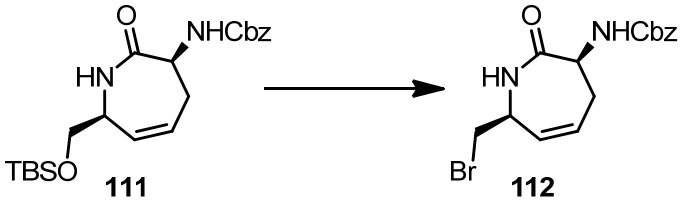
reaction mixture as it was stirred for 1.5 hours. At this time, the mixture was filtered through Celite and the solvent removed to provide saturated lactam **109** as a single compound with no detectable diastereomer formation (134.7 mg, 0.362 mmol, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.019 (s, 1H), 5.907 (d, *J* = 5.5 Hz, 1H), 4.210 (m, 1H), 3.664 (dd, *J* = 10, 3.5 Hz, 1H), 3.486 (dd, *J* = 10, 6.0 Hz, 1H), 3.395 (m, 1H), 2.059 (d, *J* = 14 Hz, 1H), 1.968 (m, 1H), 1.776 (m, 1H), 1.639 (dt, *J* = 11, 3.5 Hz, 1H), 1.491 (m, 1 H), 1.406 (s, 9H), 1.326 (m, 1H), 0.854 (s, 9H), 0.029 (s, 6H); ^{13}C (126 MHz, $CDCl_3$) δ: 174.50, 155.13, 79.32, 65.60, 54.37, 53.48, 32.14, 31.70, 28.34, 27.16, 25.75, 18.19, -5.54.



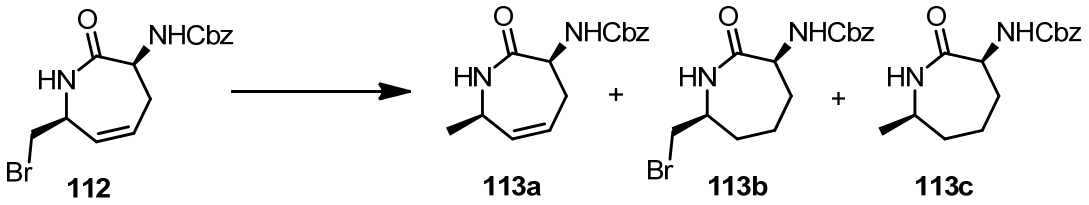
The Cbz protected diene **110** was synthesized using the same general procedure employed in the synthesis of **101**. Free amine **100** (881 mg, 4.3 mmol), *N*-Cbz-allylglycine (1.18 g, 1.1 eq.), PyBOP (2.46 g, 1.1 eq.), DIPEA (2.25 mL, 3.0 eq.), DCM (14.3 mL, 0.3 M). The reaction was stirred for 6 hours and then worked up as above. Isolation was accomplished using the Biotage Flash and a 0% → 40% gradient of EtOAc in hexanes to provide diene **110** as a white solid (1.573 g, 3.64 mmol, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.326 (m, 5H), 6.329 (d, *J* = 8.0 Hz, 1H, -NH), 5.751 (overlapping m, 2H), 5.289 (br s, 1H), 5.115 (overlapping m, 6H), 4.473 (m, 1H), 4.227 (m, 1H), 3.638 (s, 2H), 2.516 (t, *J* = 7 Hz, 2 H), 0.864 (s, 9H), 0.026 (s, 6 H); ^{13}C (126 MHz, $CDCl_3$) δ: 170.13, 156.00, 136.07, 135.60, 132.79, 128.42, 128.16, 119.23, 116.19, 67.09, 64.83, 54.29, 52.81, 37.02, 25.76, 18.21, -5.51.



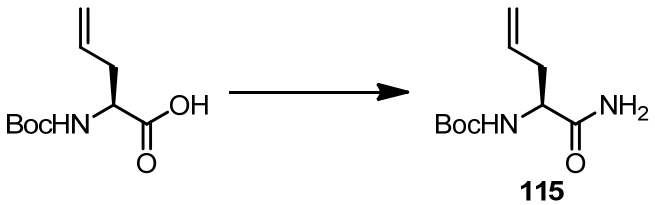
The ring closure of **110** proceeded as described above. Diene (100 mg, 0.23 mmol), **106** (10 mg, 5 mol%), benzoquinone (2 mg, 10 mol%), and PhMe (4.6 mL, 0.05 M). The product was purified via Biotage using a 0% → 40% gradient to provide **111** as a brown oil (77.8 mg, 0.19 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.355 (m, 4 H), 7.318 (m, 1H), 6.148 (s, 1 H), 6.076 (d, *J* = 6.5 Hz), 5.773 (m, 1H), 5.400 (m, 1H), 5.111 (d, *J* = 3.0 Hz, 2H), 4.794 (m, 1H), 4.305 (br s, 1H), 3.756 (dd, *J* = 10, 4.5 Hz, 1H), 3.535 (dd, *J* = 10, 8.0 Hz, 1H), 2.729 (m, 1H), 2.277 (m, 1H), 0.898 (s, 9H), 0.088 (s, 6H); ^{13}C (126 MHz, $CDCl_3$) δ: 173.04, 155.31, 136.32, 129.16, 128.30, 127.86, 126.39, 66.51, 64.60, 51.33, 50.58, 32.47, 25.63, 18.06, -5.59.



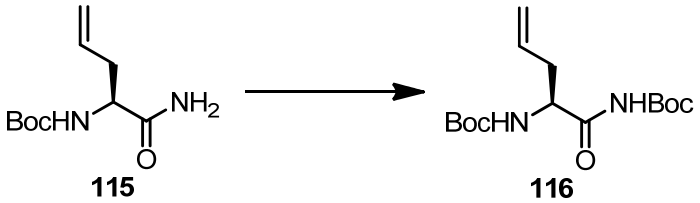
Triphenylphosphine (136.2 mg, 2.0 eq.) was dissolved in DCM (1.3 mL, 0.2 M) and stirred in an ice bath. Br_2 (27 μL, 2.0 eq) was added and the yellow solution stirred for 10 minutes. Lactam **111** (0.26 mmol) dissolved in DCM (0.4 mL) was added to the preformed triphenylphosphine bromide and the ice bath removed. After 2.5 hours, the reaction was diluted with water and extracted 2x with DCM. The organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvent the product was purified via Biotage eluting with a 7% → 60% gradient of EtOAc in hexanes. Bromolactam **112** was isolated as a solid with a small amount of triphenylphosphine garbage (55.2 mg, 0.156 mmol, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.324 (m, 4 H), 7.290 (m, 1H), 6.643 (d, *J* = 3.0 Hz, 1H), 6.107 (d, *J* = 6.5 Hz, 1H), 5.769 (m, 1H), 5.518 (dd, *J* = 11.5, 1.5 Hz, 1 H), 5.084 (s, 1 H), 4.831 (m, 1H), 4.606 (s, 1H), 3.513 (dd, *J* = 11, 4.0 Hz, 1H), 3.450 (dd, *J* = 11, 6.0 Hz, 1H), 2.684 (m, 1H), 2.224 (m, 1H); MS m/z (%): 356 (12, M^+ + H), 355 (83, M^+), 354 (13, M^+ + H), 353 (100, M^+), 311 (38), 310 (7), 309 (36).



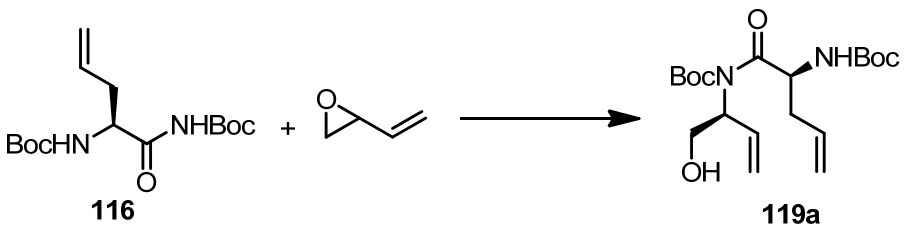
Aluminum-nickel powder was activated via sequential washing with 5N NaOH 3 times and then EtOAc twice. Bromolactam **112** (0.156 mmol) was dissolved in EtOAc (5 mL, 0.03 M) and was then treated with TEA (44 μL, 2.0 eq.) and an aliquot of the activated nickel. The reaction was stirred overnight and monitored via LC/MS. Three primary masses were observed (260, 341, and 262) corresponding to **113a**, **b**, and **c** respectively. The desired lactam **114** was never observed.



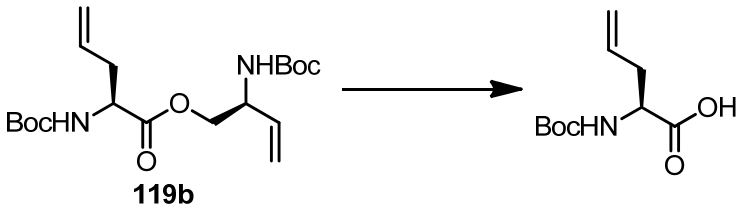
N-Boc-allylglycine (26.4 mmol) was dissolved in THF (53 mL, 0.5 M) and chilled in an ice bath. Butyl chloroformate (3.36 mL, 1.0 eq.) and *N*-methylmorpholine (2.9 mL, 1.0 eq.) were added sequentially and the reaction stirred for 15 minutes. At this time NH_4OH (15 mL, 10 eq.) was added to the milky yellow reaction which immediately became transparent. The ice bath was removed and the reaction stirred for a further 2 hours. At this time, the solvents were evaporated and the residue suspended in water before being acidified to pH ~2 with 1N $KHSO_4$. The mixture was extracted 3x with EtOAc and the combined organic extracts were washed with sat. $NaHCO_3$ and brine before being dried over $MgSO_4$. Filtration and removal of the solvents provided amide **115** as a pure, white solid (4.5699 g, 21.3 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.310 (br s, 1H), 5.879 (br s, 1H), 5.764 (m, 1H), 5.138 (overlapping, 3H), 4.196 (s, 1H), 2.507 (overlapping, 2H), 1.430 (s, 9H).



Amide **115** (714.5 mg, 3.33 mmol) was dissolved in THF (11.1 mL, 0.3 M) and placed in dry ice/acetone bath. *n*BuLi (1.3 eq.) was added slowly over the course of 10 minutes. The reaction was then stirred a further 30 minutes at -78°C before the addition of Boc_2O (2.3 mL, 3.0 eq.). The cooling bath was removed and the reaction allowed to stir at room temperature for 2 hours. At this time, the reaction was chilled in an ice bath and quenched by the slow addition of water followed by sat. NH_4Cl. The mixture was then extracted 3x with EtOAc and the combined organic extracts washed with brine and dried over $MgSO_4$. Removal of the solvent and purification via column chromatography (2:1 EtOAc in hexanes) provided imide **116** as a white solid (860.4 mg, 2.74 mmol, 82%). On scale-up to 21.3 mmol of **115** the reaction yield dropped to 54%. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.504 (br s, 1H), 5.664 (m, 1H), 5.240 (d, J = 7.0 Hz, 1H, amide rotamer), 5.036 (overlapping, 2H), 4.593 (br s, 1H, amide rotamer), 2.465 (m, 1H), 2.312 (m, 1H), 1.381 (s, 9H), 1.336 (s, 9H).

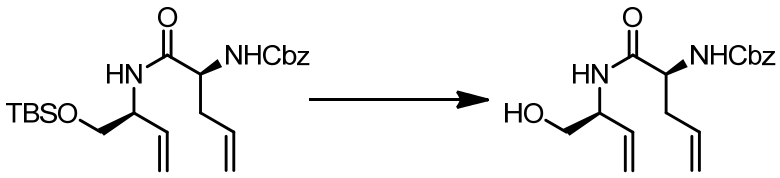


Diene **119** was synthesized utilizing the AAA protocol used in the synthesis of **98**. Butadiene monoxide (50 µL, 0.60 mmol), **116** (1.1 eq.), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (~1 mg, 0.4 mol%), Trost ligand **97** (6.4 mg, 1.3 mol%), DCM (6.2 mL, 0.1M). After 12 hours, **119** was isolated via column chromatography utilizing 5:1 EtOAc in hexanes (223.7 mg, 0.582 mmol, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.789 (ddd, J = 17.5, 11, 5.0 Hz, 1H), 5.696 (m, 1H), 5.41 (overlapping, 2H), 5.127 (overlapping, 3H), 4.927 (br s, 1H), 4.466 (s, 1H), 4.357 (m, 1H), 4.256 (dd, J = 11, 5.5 Hz, 1H), 4.193 (m, 1H), 2.503 (m, 2H), 1.449 (s, 9H), 1.442 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 171.95, 155.12, 155.05, 134.65, 132.23, 119.12, 116.66, 79.84, 79.66, 66.28, 52.83, 51.63, 36.47, 28.29, 28.16.



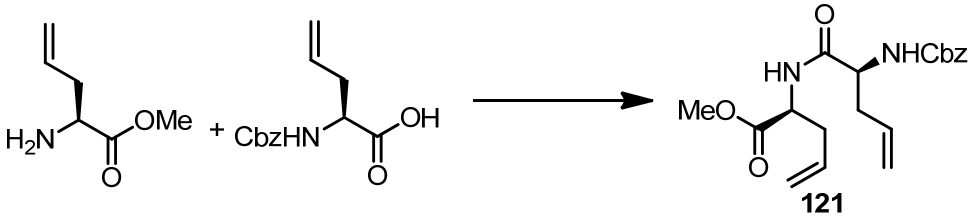
119b

Degradation of **119** was achieved by stirring the diene (50 mg, 0.13 mmol) in dioxane (0.5 mL, 0.26 M) and adding 1M LiOH (0.5 mL). After 10 minutes, TLC indicated complete consumption of **119** and LC/MS showed a single peak with mass of 214 which corresponds to *N*-Boc-allylglycine.



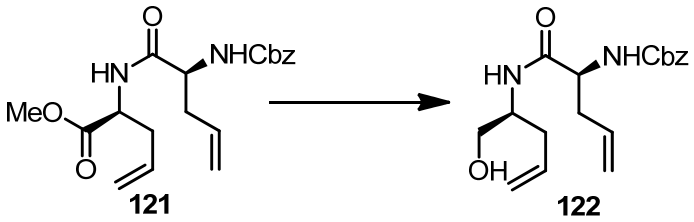
110 **120**

Diene **110** (200 mg, 0.46 mmol) was dissolved in THF (1.5 mL, 0.3 M) and chilled in an ice bath. TBAF (0.5 mL, 1.1 eq.) was added slowly and the reaction stirred for 2 hours as the ice melted. At this time, water was added and the reaction extracted 3x with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$. Purification of the crude mixture was achieved via Biotage using an 8% → 80% gradient of EtOAc in hexanes to provide deprotected alcohol **120** as a white solid (130 mg, 0.41 mmol, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.337 (m, 5H), 6.639 (s, 1H), 5.773 (m, 1H), 5.495 (d, J = 7.0 Hz), 5.161 (overlapping m, 6H), 4.535 (s, 1H), 4.264 (d, J = 5.5 Hz, 1H), 3.676 (m, 1H), 3.615 (m, 1H), 2.683 (s, 1H), 2.525 (m, 2H), ^{13}C (126 MHz, $CDCl_3$) δ: 171.17, 156.25, 135.96, 134.50, 132.75, 128.54, 128.18, 127.98, 119.29, 116.96, 67.21, 64.60, 54.44, 53.58, 36.83; MS m/z (%): 341 (5, M^+ + Na), 319 (100 M^+), 275 (18).

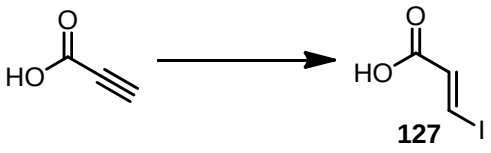


121

Allylglycine (1.0 g, 8.69 mmol) was dissolved in MeOH (13 mL, 0.68 M) and cooled in an ice bath. $SOCl_2$ (1.4 mL, 2.2 eq.) was added carefully and the reaction stirred at room temperature overnight. After careful evaporation of the solvent, the crude was taken up in DCM (30 mL, 0.3 M) and *N*-Cbz-allylglycine (2.38 g, 1.1 eq.), and PyBOP (5.0 g, 1.1 eq.) were added. The reaction mixture was stirred in an ice bath and then DIPEA (9.0 mL, 6.0 eq.) was added. The reaction was stirred for 6 hours before being worked up in the normal way. Isolation of the crude via Biotage was accomplished using a 4% → 40% gradient of EtOAc in hexanes to provide diene **121** as a white solid (2.1416 g, 5.94 mmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.349 (m, 5H), 6.544 (s, 1H), 5.744 (m, 1H), 5.631 (m, 1H), 5.295 (br s, 1H), 5.113 (overlapping m, 6 H), 4.649 (m, 1H), 4.258 (br s, 1H), 3.741 (s, 3H), 2.525 (overlapping m, 4H); MS m/z (%): 362 (23, M^+ + 2H), 361 (100, M^+ + H), 317 (12).

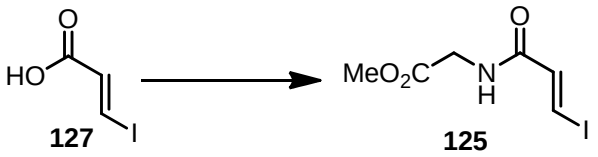


Diene **121** (750 mg, 2.08 mmol) was suspended in freshly distilled Et_2O (7 mL, 0.3 M) and chilled in an ice bath for ten minutes. $LiBH_4$ (90.6 mg, 2.0 eq.) was added in one portion and the ice bath removed. The white starting material slowly began to dissolve and after 5 hours, the reaction was warmed to a gentle reflux. After refluxing overnight, the reaction was cooled in an ice bath and carefully quenched with water. The mixture was extracted 3x with EtOAc and the combined organic extracts washed with brine and dried over $MgSO_4$. Filtration and evaporation of the solvent produced alcohol **122** (232.7 mg, 0.7 mmol, 34%).



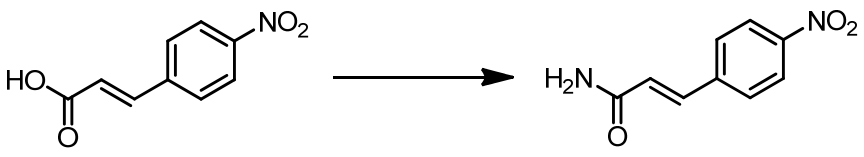
Copper (I) Iodide (50 mg, 0.6 mol%) and 57% HI (10 mL, 4.0 M) were added to a 2-neck rbf equipped with water condenser. Propiolic acid (2.5 mL, 40.5 mmol) was added slowly

and the rbf placed in a 130°C oil bath. After 30 minutes a large amount of solid precipitate can be seen in the reaction mixture. At this point, the reaction was removed from the oil bath and stirred in ice for 30 minutes. *E*-iodo acrylic acid **127** (7.0563 g, 35.6 mmol, 88%) was collected as fluffy white crystals via filtration, rinsing with water, and drying overnight under high vacuum. Spectroscopic data matched that provided in ref. 80.



127 **125**

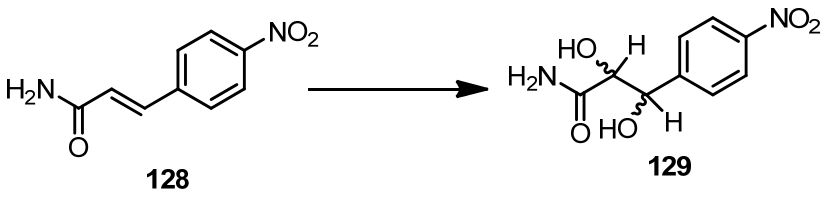
Vinyl iodide **127** (1.0 g, 5.05 mmol) was dissolved in DCM (17 mL, 0.3 M) and DMF (40 μL) was added. The mixture was stirred vigorously as $(COCl)_2$ (0.5 mL, ~1.1 eq.) was added. After the bubbling had ceased completely (approx. 2 hours), the yellow reaction mixture was cooled in an ice bath. Glycine methylester hydrochloride (1.27 g, 2.0 eq.) and DIPEA (4.4 mL, 5.0 eq.) were added and the entire mixture stirred for 30 minutes in the ice bath. At this time the reaction was quenched by the addition of sat. $NaHCO_3$ and the mixture extracted 3x with DCM. The combined organic extracts were washed with 1N $KHSO_4$, brine, and dried over $MgSO_4$. Removal of the solvent resulted in a brown solid that was purified via column chromatography (2:1 → 1:1 EtOAc in hexanes) to provide vinyl iodide **125** as a white solid (1.026 g, 3.8 mmol, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.770 (d, *J* = 14.5 Hz, 1H), 6.930 (d, *J* = 14.5 Hz, 1H), 6.344 (br s, 1H), 4.104 (d, *J* = 5.5 Hz, 2H), 3.785 (s, 3H); MS m/z (%): 270 (100, M^+ + H), 238 (25), 210 (6), 181 (7).



126 **128**

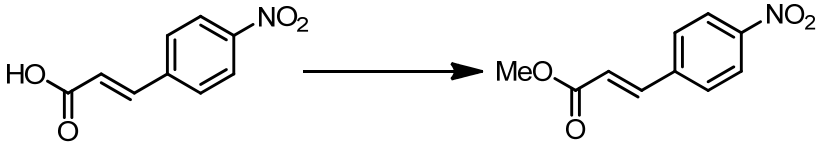
p-Nitro-trans-cinnamic acid (1.0 g, 5.2 mmol) was suspended in THF (17.3 mL, 0.3 M) and cooled in an ice bath. Butyl chloroformate (0.74 mL, 1.1 eq.) and NMM (0.63 mL, 1.1 eq.) were added and the reaction stirred for 1 hour. At this time, NH_4OH (2.9 mL, 10 eq.) was added and the reaction vigorously stirred for another 3 hours. The resultant

precipitate was collected via filtration and found to be desired amide **128** (468.1 mg, 2.44 mmol, 47%). ^{1}H NMR (300 MHz, Acetone-D6) δ: 8.279 (dd, *J* = 6.9, 2.1 Hz, 2H), 7.873 (dd, *J* = 6.9, 1.8 Hz, 2H), 7.629 (d, *J* = 15.9 Hz, 1H), 7.142 (br s, 1H), 6.926 (d, *J* = 15.6 Hz, 1H), 6.602 (br s, 1H); MS m/z (%): 193 (100, M^+ + H).



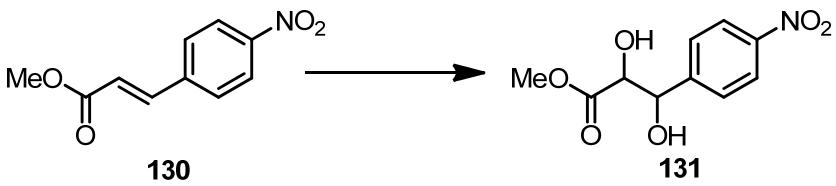
128 **129**

Amide **128** (100 mg, 0.52 mmol) was suspended in 10:1 acetone:water (5.2 mL, 0.1 M). To this was added *N*-methylmorpholine-*N*-oxide (91.4 mg, 1.5 eq.) and 4% aqueous OsO_4 (33 μL, 1 mol%). The reaction was stirred for 24 hours at which point it was diluted with Et_2O and a material was seen to oil out. Collection of the ethereal layer and condensation provided a mix of largely **128** and NMO. It was found that **128** could be removed by selective crystallization upon dilution with MeOH. The soluble portion was found to contain largely NMO by NMR, however, a quantity of the desired product could be observed to allow coupling constant calculations.



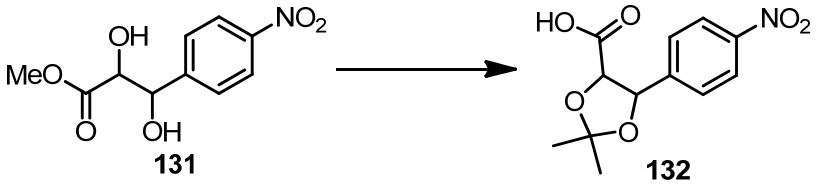
126 **130**

p-Nitro-trans-cinnamic acid (2.0 g, 10.35 mmol) was converted into its methyl ester via the standard conditions used previously. The methylester **130** was collected as a solid (2.040 g, 9.85 mmol, 95%). ^{1}H NMR (500 MHz, MeOD-D4) δ: 8.252 (dd, *J* = 9.0, 2.0 Hz, 2H), 8.035 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.788 (d, *J* = 16 Hz, 1H), 6.890 (d, *J* = 16.5 Hz, 1H), 3.762 (s, 3H).

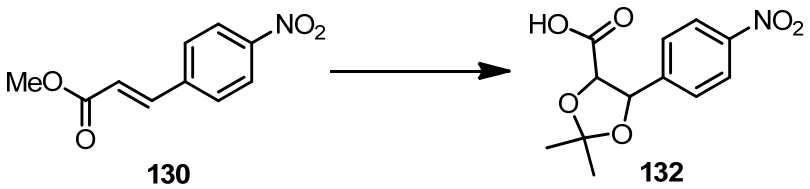


130 **131**

Methylester **130** (207.2 mg, 1 mmol) was suspended in 10:1 acetone:water (9 mL, 0.1 M) and NMO (175.7 mg, 1.5 eq.) was added along with 4% OsO_4 (0.32 mL, 5 mol%). The yellow suspension was stirred at room temperature for 30 hours turning black in the process. After this time, the solvent was carefully removed in the hood and the sludge subjected to column chromatography (1:1 → EtOAc) to yield the desired diol **131** (166.1 mg, 0.689 mmol, 69%). The reaction was scaled up to 1 g of starting material with a 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.220 (ddd, aparent dt, J = 9.0, 2.0, 2.0 Hz, 2H), 7.759 (dd, J = 9.0 Hz, 2.0 Hz, 2H), 5.217 (d, J = 1.5 Hz, 1H), 5.008 (br s, 1H), 4.400 (s, 1H), 4.305 (br s, 1H), 3.736 (s, 3H).

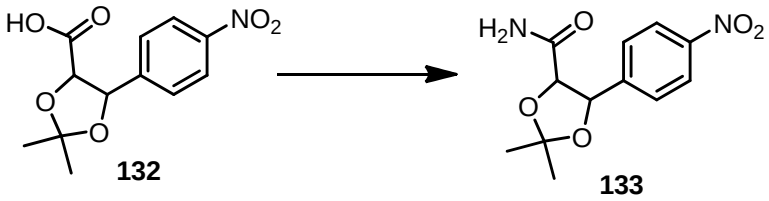


Diol **131** (558.3 mg, 2.31 mmol) was dissolved in acetone (4.6 mL, 0.5 M) and DMP (4.6 mL, 0.5 M). *p*TsOH (44 mg, 10 mol%) was added and the reaction mixture was stirred overnight. The solvent was removed and the resultant purple oil was purified via Biotage (0% → 30% gradient of EtOAc in hexanes) to provide isopropylidene **132** as a yellow oil which solidified on standing (638.8 mg, 2.2 mmol, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.247 (ddd, apparent dt, J = 8.5, 2.0, 2.0 Hz, 2H), 7.637 (d, J = 8.5 Hz, 2H), 5.283 (d, J = 7.5 Hz, 1H), 4.325 (d, J = 7.5 Hz, 1H), 3.840 (s, 3H), 1.629 (s, 3H), 1.570 (s, 3H).



Isopropylidene **132** can also be synthesized without isolation of the intermediate diol. Methylester **130** (689.1 mg, 3.33 mmol) was dissolved in 10:1 acetone:water (33.3 mL, 0.1 M). NMO (585 mg, 1.5 eq.) and 4% aqueous OsO_4 (1.06 mL, 5 mol%) were added and the reaction stirred for 24 hours. At this time the mixture was diluted with DCM and chilled in an ice bath. Sodium thiosulfate was added in portions and the solid became thick and difficult to stir. After 1 hour, sodium sulfate was added and the mixture stirred

overnight. In the morning the sludge was filtered and rinsed thoroughly with acetone. The filtrate was condensed and partitioned between EtOAc and water. The phases were separated and the aqueous layer was extracted twice more with EtOAc. The combined organic extracts were washed with water twice and dried over $MgSO_4$. After filtration and solvent evaporation, the crude diol was subject to the protecting conditions exactly as before. Chromatography provided **132** in 80% yield over the two steps (748.3 mg, 2.66 mmol).



NH_4Cl (1.42 g, 10 eq.) was heated in a rbf under high vacuum for two hours. DCM (26.6 mL, 0.1 M) was added and the reaction chilled in an ice bath for 20 minutes. 2.0 M $AlMe_3$ (4.0 mL, 3.0 eq.) was added and the mixture stirred for 30 minutes. Ester **132** (748.3 mg, 2.66 mmol) was added in DCM and the reaction brought to a gentle reflux. After approx. 44 hours the reaction was cooled in an ice bath. The reaction was diluted with EtOAc and then quenched by the careful addition of 10% HCl. The phases were separated and the aqueous layer was extracted 2x with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and condensed. Amide **133** was isolated via column chromatography utilizing a 2:1 → 1:1 → EtOAc gradient as an off white solid (563.3 mg, 2.115 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.236 (ddd, apparent dt, J = 9.0, 2.0 Hz, 2H), 7.753 (d, J = 9.0 Hz, 2H), 6.957 (br s, 1H), 5.618 (br s, 1H), 5.247 (d, J = 8.0 Hz, 1H), 4.267 (d, J = 7.5 Hz, 1H), 1.591 (s, 3H), 1.583 (s, 3H).

References

1. World Health Organization. Tuberculosis Fact Sheet. April 5, 2011. http://www.who.int/mediacentre/factsheets/fs104/en/index.html
2. Hershkovitz, I.; Donoghue, H. D.; Minnikin, D. E.; Besra, G. S.; Lee, O, Y-C.; Gernaey, A. M.; Galili, E.; Eshed, V.; Greenblatt, C. L.; Lemma, E.; et al. Detection and Molecular Characterization of 9000-Year-Old *Mycobacterium tuberculosis* from a Neolithic Settlement in the Eastern Mediterranean. *PLoS One* **2008**, *3*, e3426.
3. Nobel Foundation. The Nobel Prize in Physiology or Medicine 1905. April 5, 2011. http://nobelprize.org/nobel_prizes/medicine/laureates/1905/
4. Comroe, J. H., Jr. Pay Dirt: The Story of Streptomycin. Part 1. From Waksman to Waksman. *Am. Rev. Respir. Dis*., **1978**, 117, 773-781.
5. The World Health Organization. Anti-Tuberculosis Drug Resistance in the World. Report no. 4. **2008**.
6. Havlir, D. V.; Getahum, H.; Sanne, I.; Nunn, P. *JAMA*, **2008**, 300, 423-430.
7. Center for Disease Control. Treatment of Tuberculosis. April 5, 2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm
8. Ma, Z.; Lienhardt, C.; McIlleron, H.; Nunn, A. J.; Wang, X. Global Tuberculosis Drug Development Pipeline: the Need and the Reality, *The Lancet*, **2010**, 375, 2100-2109.
9. Check, E. After Decades of Drought, New Possibilities Flood TB Pipeline. *Nat. Med.*, **2007**, 13, 266.
10. Kimura, K.; Bugg, T. D. H. Recent Advances in Antimicrobial Nucleoside Antibiotics Targeting Cell Wall Biosynthesis. *Nat. Prod. Rep.*, **2003**, 20, 252-273.
11. Yamaguchi, H.; Sato, S.; Yoshida, S.; Takada, K.; Shitori, Y.; Seto, H.; Otake, N.; Capuramycin, a New Nucleoside Antibiotic. Taxonomy, Fermentation, Isolation, and Characterization. *J. Antibiot.*, **1986**, 39, 1047.
12. Seto, H.; Otake, N.; Sato, S.; Yamaguchi, H.; Takada, K.; Itoh, M.; Lu, H. S. M.; Clardy, J. The Structure of a New Nucleoside Antibiotic, Capuramycin. *Tetrahedron Lett.*, **1988**, 29, 2343-2346.

13. (a) Muramatsu, Y.; Maramatsu, A.; Ohnuki, T.; Ishii, M. M.; Kizuka, M.; Enokita, R.; Tsutsumi, S.; Arai, M.; Ogawa, Y.; Suzuki, T.; et al. Studies on Novel Translocase I Inhibitors, A-500359s I. Taxonomy, Fermentation, Isolation, Physio-chemical Properties, and Structure Elucidation of A-500359 A, C, D, and G. *J. Antibiot.*, **2003**, 56, 243-252. (b) Muramatsu, Y.; Miyakoshi, S.; Ogawa, Y.; Ohnuki, T.; Ishii, M. M.; Arai, M.; Takatsu, T.; Inukai, M. Studies on Novel Translocase I Inhibitors, A-500359s III. Deaminocaprolactam Derivatives of Capuramycin: A-500359E, F, H, M-1, and M-2. *J. Antibiot.*, **2003**, 56, 259-267. (c) Murakami, R.; Fujita, Y.; Kizuka, M.; Kagawa, T.; Muramatsu, Y.; Miyakoshi, S.; Takatsu, T.; Inukai, M. A-102395, A New Inhibitor of Bacterial Translocase I, Produced by *Amycolatopsis* sp. SANK 60206. *J. Antibiot.*, **2007**, 60, 690-695.

14. Funbashi, M.; Yang, Z.; Nonaka, K.; Hosobuchi, M.; Fujita, Y.; Shibata, T.; Chi, X.; Van Lanen, S. G. An ATP-Independent Strategy for Amide Bond Formation in Antibiotic Biosynthesis. *Nat. Chem. Bio.*, **2010**, 6, 581-586.

15. (a) Hotoda, H.; Furukwa, M.; Daigo, M.; Murayama, K.; Kaneko, M.; Muramatsu, Y.; Ishii, M. M.; Miyakoshi, S.; Takatsu, T.; Inukai, M.; et al. Synthesis and Antimycobacterial Activity of Capuramycin Analogues. Part 1: Substitution of the Azepan-2-one Moiety of Capuramycin. *Bioorg. Med. Chem. Lett.*, **2003**, 13, 2829-2832. (b) Hotoda, H.; Daigo, M.; Furukawa, M.; Murayama, K.; Hasegawa, C. A.; Kaneko, M.; Muramatsu, Y.; Ishii, M. M.; Miyakoshi, S.; Takatsu, T.; et al. Synthesis and Antimycobacterial Activity of Capuramycin Analogues. Part 2: Acylated Derivatives of Capuramycin-Related Compounds. *Bioorg. Med. Chem. Lett.*, **2003**, 13, 2833-2836.

16. Knapp, S.; Nandan, S. R. Synthesis of Capuramycin. *J. Org. Chem.*, **1994**, 59, 281-283.

17. Kurosu, M.; Li, K.; Crick, D. C. Concise Synthesis of Capuramycin. *Org. Lett.*, **2009**, 11, 2393-2396.

18. Kurosu, M.; Li, K. Synthetic Studies Towards the Identification of Novel Capuramycin Analogs with Mycobacterial Activity. *Heterocycles*, **2009**, 77, 217-225.

19. Roy, S. K.; Tang, J. Efficient Large Scale Synthesis of 2'-*O*-alkyl Pyrimidine Ribonucleosides. *Org. Process Res. Dev.*, **2000**, 4, 170-171.
20. Mieczkowski, A.; Roy, V.; Agrofoglio, L. A. Preparation of Cyclonucleosides. *Chem. Rev.*, **2010**, 110, 1828-1856.
21. David. S.; Hanessian, S. Regioselective Manipulation of Hydroxyl Groups via Organotin Derivatives. *Tetrahedron*, **1985**, 41, 643-663.
22. Greene, A. E.; Drian, C. L.; Crabbe. P. An Efficient Total Synthesis of ±-Brefeldin-A. *J. Am. Chem. Soc.*, **1980**, 102, 7583-7584.
23. Oshima, K.; Kitazono, E.-i.; Aoyama, Y. Complexation-Induced Activation of Sugar OH Groups. Regioselective Alkylation of Methyl Fucopyranoside via Cyclic Phenylboronate in the Presence of Amine. *Tetrahedron Lett.*, **1997**, 38, 5001-5004.
24. Hakimelahi, G. H.; Proba, Z. A.; Ogilvie, K. K. High Yield Selective 3'-Silylation of Ribonucleosides. *Tetrahedron Lett.*, **1981**, 22, 5243-5246.
25. Chaudhary, S. K.; Hernandes, O. 4-Dimethylaminopyridine: An Efficient and Selective Catalyst for the Silylation of Alcohols. *Tetrahedron Lett.*, **1979**, 20, 99-102.
26. Perst, H.; Seapy, D. G. Triethyloxonium Tetrafluoroborate. *e-Eros Ency. Reagents Org. Synth.* [Online] March 14, 2008. DOI: 10.1002/047084289X.rt223.pub2 (accessed April 6, 2011).
27. Johnston, R. A. W.; Rose, M. E. A Rapid, Mild, and Simple Procedure for Alkylation of Phenols, Alcohols, Amides, and Acids. *Tetrahedron*, **1979**, 35, 2169-2173.
28. Greene, T. H.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.
29. Sabitha, G.; Symala, M.; Yadav, J. S. A Mild, Efficient, Inexpensive, and Selective Cleavage of Primary *tert*-Butyldimethylsilyl Ethers by Oxone in Aqueous Methanol. *Org. Lett.*, **1999**, 1, 1701-1703.
30. Dai, Q.; Fredriksen, J. K.; Anderson, V. E.; Harris, M. E.; Piccrilli, J. A. Efficient Synthesis of [2'-^{18}O]Uridine and Its Incorporation into Oligonucleotides: A New

Tool for Mechanistic Study of Nucleotidyl Transfer Reactions by Isotope Effect Analysis. *J. Org. Chem.*, **2008**, 73, 309-311 and references therein.

31. Boger, D. L.; McKie, J. A. An Efficient Synthesis of 1,2,9,9a-Tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (CBI): An Enhanced and Simplified Analog of the CC-1065 and Duocarmycin Alkylation Subunits. *J. Org. Chem.*, **1995**, 60, 1271-1275.
32. Sukeda, M.; Shuto, S.; Sugimoto, I.; Ichikawa, S.; Matsuda, A. Synthesis of Pyrimidine 2'-Deoxy Ribonucleosides Branched at the 2'-Position via Radical Atom-Transfer Cyclization Reaction with a Vinylsilyl Group as a Radical-Acceptor Tether. *J. Org. Chem.*, **2000**, 65, 8988-8996.
33. Ngouansavanh, T.; Zhu, J. Alcohols in Isonitrile-Based Multicomponent Reaction: Passerini Reaction of Alcohols in the Presence of *O*-Iodoxybenzoic Acid. *Angew. Chem. Int. Ed.*, **2006**, 45, 3495-3497.
34. Dai, Q.; Piccirilli, J. A. Synthesis of 2'-*C*-β-Fluoromethyluridine. *Org. Lett.*, **2003**, 5, 807-810.
35. Yu, M.; Lynch, V.; Pagenkopf, B. L. Intramolecular Cyclopropanation of Glycals: Studies toward the Synthesis of Canadensolide, Sporothriolide, and Xylobovide. *Org. Lett.*, **2001**, 3, 2563-2566.
36. More, J. D.; Finney, N. S. A Simple and Advantageous Protocol for the Oxidation of Alcohols with *o*-Iodoxybenzoic Acid (IBX). *Org. Lett.*, **2002**, 4, 3001-3003.
37. Passerini, M. Isonitriles. II. Compounds with Aldehydes or with Ketones and Monobasic Organic Acids. *Gazz. Chim. Ital.*, **1921**, 51, 181-189.
38. Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*. Elsevier Academic Press: Burlington, 2005.
39. (a) Frey, R.; Galbraith, S. G.; Guelfi, S.; Lamberth, C.; Zeller, M. First Examples of a Highly Stereoselective Passerini Reaction: A New Access to Enantiopure Mandelamides. *Synlett*, **2003**, 10, 1536-1538. (b) Krishna, P. R.; Lopinti, K. Diastereoselective Passerini Reaction of Chiral 2, 3-Epoxy Aldehydes with TosMIC. *Synlett*, **2007**, 83-86. (c) Berlozecki, S.; Szymanski, W.; Ostaszewski, R. α-Amino Acids as Acid Components in the Passerini Reaction: Influence of N-Protection on the Yield and Stereoselectivity. *Tetrahedron*, **2008**, 64, 9780-9783.

(d) Krishna, P. R.; Dayaker, G.; Reddy, P. V. N. Diastereoselective Passerini Reactions using *p*-Toluenesulfonylmethyl Isocyanide (TosMIC) as the Isonitrile Component. *Tetrahedron Lett.*, **2006**, 47, 5977-5980.

40. (a) Kusebauch, U.; Beck, B.; Messer, K.; Herdtweck, E.; Dömling, A. Massive Parallel Catalyst Screening: Toward Asymmetric MCRs. *Org. Lett.*, **2003**, 5, 4021-4024. (b) Andreana, P. R.; Liu, C. C.; Schreiber, S. L. Stereochemical Control of the Passerini Reaction. *Org. Lett.*, **2004**, 6, 4231-4233. (c) Denmark, S. E.; Fan, Y. Catalytic, Enantioselective α-Additions of Isocyanides: Lewis Base Catalyzed Passerini-Type Reactions. *J. Org. Chem.*, **2005**, 70, 9667-9676. (d) Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. Catalytic Enantioselective Passerini Three-Component Reaction. *Angew. Chem. Int. Ed.*, **2008**, 47, 388-391. (e) Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. Brønsted Acid Catalyzed Enantioselective Three-Component Reaction Involving the α-Addition of Isocyanides to Imines. *Angew. Chem. Int. Ed.*, **2009**, 48, 6717-6721.

41. Yue, T.; Wang, M.-X.; Wang, D.-X.; Masson, G.; Zhu, J. Catalytic Asymmetric Passerini-Type Reaction: Chiral Aluminum-Organophophate-Catalyzed Enantioselective α-Addition of Isocyanides to Aldehydes. *J. Org. Chem.*, **2009**, 74, 8396-8399.

42. Reynolds, D. D.; Evans, W. L. The Synthesis of Certain Oligosaccharides Acetates in the Mannose Series. *J. Am. Chem. Soc.*, **1940**, 62, 66-69.

43. (a) Boger, D. L.; Robarge, K. D. A Divergent de Novo Synthesis of Carbohydrates Based on an Accelerated Inverse Electron Demand Diels-Alder Reaction of 1-Oxa-1,3-butadienes. *J. Org. Chem.*, **1988**, 53, 5793-5796. (b)Tietze, L. F.; Hartfiel, U. Hetero-Diels-Alder Reaction of Substituted 1-Oxabutadienes and 2-Ethoxyvinylacetate: An Entry to Various Natural Occurring Carbohydrates. *Tetrahedron Lett.*, **1990**, 31, 1697-1700. (c) Tietze, L. F. Stereodivergent Hetero-Diels-Alder Reactions of Chiral 1-Oxa-1,3-butadienes Through a Conformations Switch Induced by Lewis Acids. *Chem. Eur. J.*, **1996**, 2, 139-148. (d) Evans, D. A.; Johnson, J. S.; Olhava, E. J. Enantioselective Synthesis of Dihydropyrans. Catalysis of Hetereo-Diels-Alder Reactions by Bis(oxazoline) Copper (II) Complexes. *J. Am. Chem. Soc.*, **2000**, 122, 1635-1649. (e) Audrain, H.;

Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. A Novel Catalytic and Highly Enantioselective Approach for the Synthesis of Optically Active Carbohydrate Derivatives. *J. Org. Chem.*, **200**, 65, 4487-4497. (f) Gademann, K.; Chaves, D. E.; Jacobsen, E. N. Highly Enantioselective Inverse-Electron-Demand Hetero-Diels-Alder Reactions of α,β-Unsaturated Aldehydes. *Angew. Chem. Int. Ed.*, **2002**, 41, 3059-3061.

44. Tietze, L. F.; Meier, H.; Voβ, E. Highly Efficient Syntheses of Alkyl 3,3-Dialkoxypropanoates, Alkyl 4-Ethoxy-2-oxo-3-butenoates, and Monoprotected Malonaldehydes. *Synthesis*, **1988**, 274-277.

45. Nielsen, T. E.; Quement, S. L.; Juhl, M.; Tanner, D. Cu-mediated Stille Reactions of Sterically Congested Fragments: Towards the Total Synthesis of Zoanthamine. *Tetrahedron*, **2005**, 61, 8013-8024.

46. (a) McKeon, J. E.; Fitton, P. The palladium (II) Catalyzed Vinyl Interchange Reaction—II. *Tetrahedron*, **28**, 233-238. (b) Bosch, M.; Shlaf, M. Synthesis of Allyl and Alkyl Vinyl Ethers Using an in Situ Prepared Air-Stable Palladium Catalyst. Efficient Transfer Vinylation of Primary, Secondary, and Tertiary Alcohols. *J. Org. Chem.*, **2003**, 68, 5225-5227.

47. Rothermel, R.; Hanack, M. Synthesis of cis-Configurated Bis(trifluoromethyl)pyrethroids. *Liebigs Annalen der Chemie*, **1991**, 1013-1020.

48. (a) Stowel, J. K.; Widlanski, T. S. Halo Enol Phosphates: Regioselective Synthesis of Phosphatase Inactivators via a Complex-Induced Proximity Effect. *J. Am. Chem. Soc.*, **1994**, 116, 789-790. (b) He, R.; Deng, M.-Z. A Novel Method for the Construction of (*Z*,*E*) or (*Z*,*Z*)-Conjugated Alkadienyl Carboxylates. *Org. Lett.*, **2002**, 4, 2759-2762.

49. Denmark, S. E.; Schnute, M. E. Nitroalkene [4 + 2] Cycloadditions with 2-(Acyloxy)vinyl Ethers. Stereoselective Synthesis of 3-Hydroxy-4-substituted-pyrrolidines. *J. Org. Chem.*, **1994**, 59, 4576-4595.

50. Paterson, I.; Delgado, O.; Florence, G.; Lyothier, I.; O'Brien, M.; Scott, J. P.; Sereinig, N. A Second-Generation Total Synthesis of (+)-Discodermolide: The Development of a Practical Route Using Solely Substrate-Based Stereocontrol. *J. Org. Chem.*, **2005**, 70, 150-160.

51. Nicolaou, K. C.; Seitz, S. P.; Papahatjiz, D. P. A Mild and General Method for the Synthesis of *O*-Glycosides. *J. Am. Chem. Soc.*, **1983**, 105, 2430-2434.

52. Peng, H.; Cheng, Y.; Ni, N.; Li, M.; Chouhary, G.; Chou, H. T.; Lu, C.-D.; Tai, P. C.; Wang, B. Synthesis and Evaluation of New Antagonists of Bacterial Quorum Sensing in *Vibrio harveyi*. *Chemmedchem*, **2009**, 4, 1457-1468.

53. **72** can also be synthesized in one pot via sequential complete protection and then selective deprotection of the 4,6-isopropylidene. See: Evans, M. E.; Parrish, F. W. Monomolar Acetalations of Methyl α-D-Mannosides—Synthesis of Methyl α-D-Talopyranosides. *Carbohydrate Res.*, **1977**, 54, 105-114.

54. Becher, J.; Seidel, I.; Plass, W.; Klemm, D. Synthesis Pathway to Carbohydrate-Derived Salicylidenes Hydrazides as Ligands for Oxovanadium Complexes. *Tetrahedron*, **2006**, 62, 5675-5681.

55. Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. Catalytic Ester-Amide Exchange Using Group (IV) Metal Alkoxide-Activator Complexes. *J. Am. Chem. Soc.*, **2005**, 127, 10039-10044.

56. Paterson, I.; Paquet, T. Total Synthesis and Configurational Validation of (+)-Phorbaside A. *Org. Lett.*, **2010**, 12, 2158-2161.

57. Hsu, M. C.; Lee, J.; Kisihi, Y. Synthetic 3-O-Methylmannose-Containing Polysaccharides (sMMPs): Design and Synthesis. *J. Org. Chem.*, **2007**, 72, 1931-1940.

58. Epp, J. B.; Widlanski, T. S. Facile Preparation of Nucleoside-5'-carboxylic Acids. *J. Org. Chem.*, **1999**, 64, 293-295.

59. Moriwake, T.; Hamano, S.-I.; Saito, S.; Torii, S.; Kashino, S.; Synthesis of the Chiral (8*S*)-7-Aza-1,3(*E*),9-decatriene System from the Natural α-Amino Acids and Its Intramolecular Diels-Alder Reaction Directed Toward Chiral *tran*-Hydroisoquinolines. *J. Org. Chem.*, **1989**, 54, 4114-4120.

60. Please see the references cited in ref. 59.

61. Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. Effective methods of carbonyl methylenation using CH_2I_2-Zn-Me_3Al and CH_2Br_2-Zn-$TiCl_4$ system. *Tetrahedron Lett.*, **1978**, 2417-2420.

62. Wei, Z.-Y.; Knaus, E. E. Improved Synthesis of Chiral *N*-Protected Allylic Amines. *Synthesis*, **1994**, 1466-1463.

63. Schwarz, H.; Bumpus, F. M.; Page, I. H. Synthesis of a Biologically Active Octapeptide Similar to Natural Isoleucine Angiotonin Octapeptide. *J. Am. Chem. Soc.*, **1957**, 79, 5697-5703.

64. We switched from L to D-alanine due to the stereochemistry around the lactam's methyl substituent. L-alanine would have given us the incorrect stereoisomer.

65. Afzali-Ardakani, A.; Rapoport, H. L-Vinylglycine. *J. Org. Chem.*, **1980**, 45, 4817-4820.

66. Dewi-Wülfing, P. ; Blechert, S. Enantiospecific Synthesis of (+)-Hyacinthacine A_2. *Eur. JOC.*, **2006**, 1852-1856.

67. Coleman, R. S.; Shah, J. A. Chemoselective Cleavage of Benzyl Ethers, Esters, and Carbamates in the Presence of Other Easily Reducible Groups. *Synthesis*, **1999**, 1399-1400.

68. Trost, B. M.; Crawley, M. L. Asymmetric Transition-Metal-Catalyzed Allylic alkylations: Applications in Total Synthesis. *Chem. Rev.*, **2003**, 103, 2921-2943.

69. Trost, B. M.; Bunt, R. C. On Ligand Design for Catalytic Outer Sphere Reactions: A Simple Asymmetric Synthesis of Vinylglycinol. *Angew. Chem. Int. Ed.*, **1996**, 35, 99-102.

70. Roach, S. L.; Sen, S. E. A convenient Two-Step Procedure for the Synthesis of Substituted Allylic Amines from Allylic Alcohols. *Synthesis*, **1995**, 756-758.

71. Osby, J. O.; Martin, M. G.; Ganem, B. An Exceptionally Mild Deprotection of Phthalimides. *Tetrahedron Lett.*, **1984**, 25, 2093-2099.

72. Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Metathesis Reactions in Total Synthesis. *Angew. Chem. Int. Ed.*, **2005**, 44, 4490-4527.

73. Tsantrizos, Y. S.; Ferland, J.-M.; McClory, A.; Poirier, M.; Fariwa, V.; Yee, N. K.; Wang X.-J.; Haddad, N.; Wei, X.; Xu, J. Olefin Ring-Closing Metathesis as a Powerful Tool in Drug Discovery and Development – Potent Macrocyclic Inhibitors of the Hepatitis C Virus NS3 Protease. *J. Organomet. Chem.*, **2006**, 691, 5163-5171.

74. Rouhi, A. M. Olefin Metathesis: A Big Deal Reaction. *C&E News*, **2002**, 80, 29-33.

75. Del Valle, J. R.; Goodman, M. An Efficient RCM-Based Synthesis of Orthogonally Protected *meso*-DAP and FK565. *J. Org. Chem.*, **2004**, 69, 8946-8948.

76. Hong, S.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. Prevention of Undesirable Isomerization During Olefin Metathesis. *J. Am. Chem. Soc.*, **2005**, 127, 17160-17161.

77. Gembus, V.; Marsais, F.; Levacher, V. An Efficient Organocatalyzed Interconversion of Silyl Ethers to Tosylates Using DBU and *p*-Toluenesulfonyl Fluoride. *Synlett*, **2008**, 1463-1466.

78. Aizpurua, J. M.; Cassio, F. P. ; Palomo, C. Reagents and Synthetic Methods. 61. Reaction of Hindered Trialkylsilyl Esters and Trialkylsilyl Ethers with Triphenylphosphine Dibromide: Preparation of Carboxylic Acid Bromides and Alkyl Bromides Under Mild Neutral Conditions. *J. Org. Chem.*, **1986**, 51, 4941-4943.

79. Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T.; Dynamic Kinetic Asymmetric Allylic Amination and acyl Migration of Vinyl Aziridines with Imido Carboxylates. *Angew. Chem. In. Ed.*, **2007**, 46, 6123-6125.

80. Dixon, D. J.; Ley, S. V.; Longbottom, D. A. Copper(I)-Catalyzed Preparation of (E)-3-Iodoprop-2-enoic Acid. *Org. Syn.*, **2009** Coll. Vol. 11, 662.

81. Schröder, M. Osmium Tetraoxide *cis*-Hydroxylation of Unsaturated Substrates. *Chem. Rev.*, **1980**, 80, 187-213.

82. Jiang, L.; Job, G. E.; Klapers, A.; Buchwald, S. L. Copper-Catalyzed Coupling of Amides and Carbamates with Vinyl Halides. *Org. Lett.*, **2003**, 5, 3667-3669.

Vita

Personal Information

Name:	Jesse Jacobsen
Date of birth:	February 3, 1986
Place of birth:	Floral Park, NY

Education

July 2009-August 2011

College of Pharmaceutical Sciences

University of Kentucky

Lexington, KY

August 2004-May 2008

BS Chemistry, minor philosophy

University of Louisville

Louisville, KY

Honors

NSF Pre-doctoral Fellowship (2008)

Graduated *summa cum laude* (2008)

Recognized at Louisville ACS chapter meeting (2008)

ACS Award for graduating chemistry senior (2008)

Co-winner best overall undergraduate thesis (2008)

3rd prize, McKnight Prize in undergraduate chemistry poster competition (2007)

Publications

Arimitsu, S,; **Jacobsen, J. M**.; Hammond, G. B. "Synthesis of 2,4,5-Trisubstituted 3-Fluorofurans via Sequential Iodocyclization and Cross-Coupling of *gem*-Difluorohomopropargyl Alcohols."

Jacobsen, J. M.; Arimitsu, S.; Hammond, G. B.; Mashuta, M. S. "3-Fluoro-2,4,5-triphenylfuran." *Acta Cryst. E.*, **2007**, *E63*, o4337.

Arimitsu, S.; **Jacobsen, J. M**.; Hammond, G. B. "*gem*-Difluoropropargylation of Aldehydes Using Cat. In/Zn in Aqueous Media." *Tetrahedron Letters*, **2007**, *48*, 1625.