DISSERTATION

THE PROGRESS TOWARDS THE TOTAL SYNTHESIS OF (*ent*)-MPC1001

Submitted by

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ABSTRACT

THE PROGRESS TOWARDS THE TOTAL SYNTHESIS OF (*ent*)-MPC1001

Herein are my efforts toward the total synthesis of (*ent*)-MPC1001, beginning with the development of a novel asymmetric [1-3]-dipolar cycloaddition utilizing a vinyl silane and a chiral lactone template. The mechanism of the cycloaddition was investigated and the cyclized product can be elaborated in 6 steps to the A-B-C ring system of the MPC family of natural products. However, the key ring-closing metathesis reaction provided irreproducible results. Therefore, a macrolactonization was utilized to synthesize an advanced lactone derivative. Current research is focused on the elaboration of the lactone to the oxepin ring.

Efforts were also focused on the development of a novel β-hydroxy-α-amino acid derivative to be used in the preparation of analogues of the natural product (*ent*)-MPC1001. The amino acid was efficiently prepared in six steps *via* a Mukaiyama aldol reaction by a chiral oxazinone and 3-bromo-4-methoxybenzaldehyde.

With the dipole product and the β-hydroxyl-α-amino acid derivative in hand, efforts were focused on the coupling of the two components to afford the DKP.

Research was also focused on the installation of the diaryl ether portion of (*ent*)-MPC1001 as well as an interesting dimerization reaction. The dimerization reaction can serve as a point of divergence to the aronotin family of natural products.

ACKNOWLEDGMENTS

First, I would like to thank Professor Robert M. Williams for his understanding, support, encouragement, and creative autonomy that allowed me to develop as an independent scientist. I am extremely grateful for the opportunity that he gave me and I feel forever indebted to him.

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A special thanks needs to be granted to the Chemistry main office secretaries as well as accountants. It is people like you that work behind the scenes that keep the chemistry department working as a well-oiled machine.

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ABBREVIATIONS

Ac_2O	acetic anhydride
$BF_3{\cdot}Et_2O$	boron trifluoride etherate
BHT	2,6-bis(1,1-dimethylethyl)-4-methylphenol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BrBzCl	*p*-bromobenzoyl chloride
Bu_4NF	tetrabutyl ammonium fluoride
Bu_4NI	tetrabutyl ammonium iodide
Cbz	benzyloxycarbonyl
CCl_4	carbon tetrachloride
CH_2Cl_2	dichloromethane
DBU	1,8-diazabicycloundec-7-ene
DEAD	dimethyl amino pyridiene
DEAD	diethyl azodicarboxylate
DKP	diketopiperazine
DMAP	4-dimthylamino)-pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide

EDCI	ethyl-dimethylaminopropylcarbodiimide
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
ETP	epipolythiodioxopiperazine
HOAt	1-hydroxyazabenzotriazole
HOBt	1-hydroxybenzotriazole
ImH	imadazole
$LiAlH_4$	lithium aluminum hydride
m-CPBA	*m*-chloroperbenzoic acid
MeCN	aceonitrile
MeOH	methanol
MOMCl	chloromethyl methyl ether
N_2H_2	hydrazine
$NaBH_4$	sodium borohydride
$NaBH_4$	sodium borohydride
$NaIO_4$	sodium periodate
n-BuLi	butylithium
NMO	4-methyl morpholine *N*-oxide
O_3	ozone
PCC	pyridinium chorochromate
$Pd(OAc)_4$	lead tetraacetate
Pd/C	palladium on carbon

Ph	phenyl
Ph_3P	triphenylphosphine
$PhCH_3$	toluene
PhSeCl	phenyl selenium chloride
Rbf	Round-bottomed flask
$SOCl_2$	thionyl chloride
TBDPS	*tert*-butyldiphenylsilyl
TBSCl	*Tetr*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyl dimethylsilyl trifluoromthansulfonate
t-BuLi	*tert*-butyllithium
TCC	trichloroisocyanuric acid
TEA, NEt_3	triethylamine
TEMPO	(2,2,6,6-tetramethyl-1-piperidinyloxy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TsOH, *p*-TsOH	p-toluenesulfonic acid

CHAPTER 1: Introduction and Overall Review

1.1 Background.

The initial interest in the epipolythiodioxopiperazines (ETP) compounds was due to the growth of molds on animal feed.[1] These fungal contaminates allow for the production of mycotoxins (i.e. MPC1001) which are hypothesized to be produced from a natural stimuli.[1] Once produced, these toxins pose a severe threat to animals and human health.[2] Since the first occurrences of *Trichoderma viride*, scientists have been interested in these invasive molds.[1]

A structurally related compound to MPC1001 (**3**) is gliotoxin (**2**), which is the most wildly investigated of the epipolythiodioxopiperazines since the 1930's (Figure 1.1). Both of these compounds contain a unique epidithiodioxopiperazine moiety in which the disulfide bridge is accountable for the potency of these compounds. For example, *in vitro* Gliotoxin (**2**) is known to inhibit transcription factor NF-κB by noncompetitive inhibition of the 20S proteosome preventing the degradation of IκBα in yeast.[3,4] The suppression of NF-κB causes apoptosis in various cell lines; however, the mechanism remains unclear.[5] Interestingly, Gliotoxin also has shown inhibition against the replication of (+) and (-) sense RNA in poliovirus and has been shown to reduce the reactivity of rabbit muscle creatine kinase by the formation of internal disulfide bonds.[6,7] Similarly, gliotoxin has shown to create mixed disulfide bonds which has also inhibit

platelet formation.[8] Qin and co-workers showed that gliotoxin diminished the amount of hepatic stellate cells, which play an important role with the regulation of stem cells. The diminished amount of hepatic stellate cell can result in sever liver damage.[9] Mixed disulfide bonds have also reacted with membrane thiols of the brain mitochondria that allows for a collapse of the membrane potential and the efflux of Ca^{2+} and Mg^{2+}.[10] Exposure to gliotoxin has played a critical role in the apoptosis by cyto C release and caspase-3 activation,[11] affecting dendritic cells[12] and T Cells.[12]

Gliotoxin demonstrated an increased allergic immune response by having a direct effect on the IL-12 secretion provided by oxidative stress.[13] Sheppard and co-workers showed that *Asperigullus fumigatus,* a gliotoxin producing fungus, is associated with lung disease by allowing for pulmonary mast cell degranulation.[14]

Gliotoxin has some positive biological usages. Gliotoxin exhibits antitrypanosomal activity[15], as well as exhibits NOX inhibitor effect that is responsible for oxidative damage-related disease like inflammation, vascular atherosclerosis, and fibrotic disorders.[16] Gliotoxin showed inhibition of osteoclasts, which are responsible for rheumatoid arthritis and periodontal disease.[17] Gliotoxin has also been shown to inhibit angiogenesis, which is a trigger for thrombosis, hypoxia, and pro-inflammatory cytokine release.[18] Mycoparasitic strains of *Trichoderma*, which are known to produce gliotoxin, are utilized as commercial biofungicides.[19] These *Trichoderma* products make up 60% of the biofungicide market.[20]

One of the neglected tropical diseases in Sub-Saharan Africa is African trypanosomiasis, also known as African sleeping sickness. This disease is produced by the parasite *Trypanosoma bruceli* which allows for the swelling of the brain and affects >

50,000 people annually in 36 countries of Africa.[21] Gliotoxin showed nanomolar activity against the parasite; however, the compounds mammalian toxicity precludes their therapeutic usage. [22]

One possible therapeutic use of gliotoxin would be to enhance radiosensitivity to ^{60}Co γ-irradiation in human hepatatoma cell lines by inhibiting the activation of the Gadd45a-p38-NFκB survival pathway that prevents radiation-induced cell death.[23] Blocking the inflammation pathway with gliotoxin and allowing for an enhancing irradiation-induced apoptosis is a promising therapy to increase tumor death.

On the other hand, the reduction of gliotoxin (**2**) to the bis(methylthio) derivative results in inactivation of these compounds.[2]

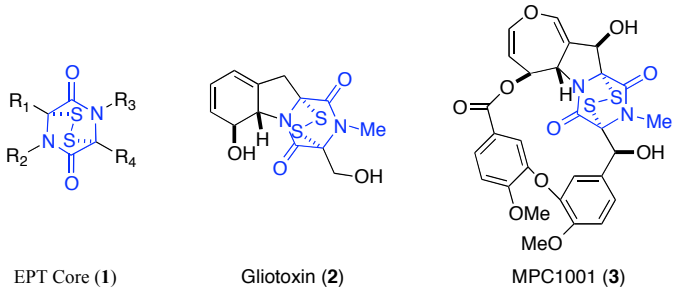


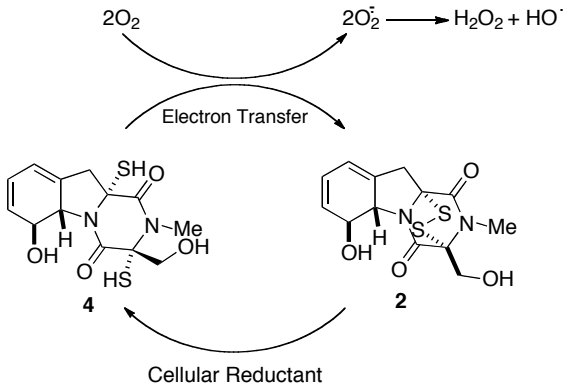
Figure 1.1. Blue core = epidithiodioxopiperazine moiety (ETP)

1.3 Cytotoxicity.

The mechanism for gliotoxin's activity involves a dithiol/disulfide seen in Scheme 1. A sequence of papers by Whitesides describes the formation of the bridged disulfide by an S_N2 displacement of a thiolate ion on the bridged disulfide.[24] Whitesides also has shown that the rate constant for this S_N2 displacement is larger in DMF and DMSO than water by a factor of 2300. [25] These data suggest that the thiolate-disulfide interchange might occur in an environment with a much lower dielectronic constant than water.[26] Indeed, a kinetic study on the disulfide-thiolate interchange in coenzyme A and

cysteine with glutathione was reported by Rabenstein and co-workers. The rate constants were determined by NMR suggesting that the mechanism of reduction of the disulfide is an S_N2 reaction.[27]

Another mode of reactivity, which also contributes to the cytotoxicity of these compounds, is the production of reactive O_2 species through redox cycling. The reactive oxygen species results from the reduction of the disulfide bridge shown in (Scheme 1.1). [28] The reduction of O_2 by the dithiol produces superoxide, which regenerates the disulfide bridge. The redox cycling continues until necrosis of the cell occurs.



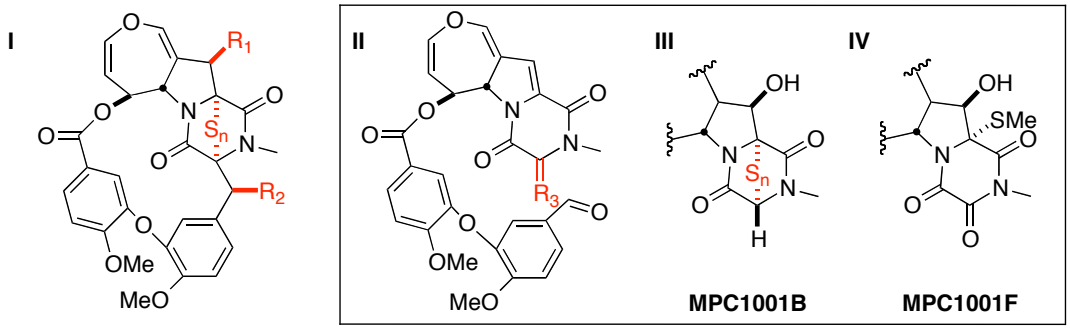
Scheme 1.1. Redox recycling.

Understanding the biological activity of gliotoxin (**2**) will further the understanding of MPC1001 (**3**). Two possibilities exist which may allow for the ETP compounds to function as therapeutic agents. One possibility would be to selectively inhibit NF-κB and induce apoptosis specifically in cancer cells. Another would be to impede the autoxidation of the dithiol compound and reduce necrosis in normal cells. In order to further explore the mechanism of action and the reduction potentials of MPC1001 (**3**), an efficient synthesis is needed.

1.4 Biological activity on the MPC1001 Family of Natural Products.

Since the isolation of gliotoxin (**2**) in 1973 by Weindling and co-workers,[1] there have been at least 14 subclasses of natural products that fall into this category.[29] One of these subcatorgies is the MPC1001 family of natural products. In 2004, MPC 1001 (**3**) and seven other analogues (**4** – **12**) were isolated from the mycelium of *Cladorrhinum sp*. by Hasegawa and coworkers[30]. (Table 1) Each compound, except for compound **8**, exhibits antiproliferative activity against the human prostate cancer cell line (DU145) (Table 1.1).[30] The substantial decrease in the IC_{50} values for compounds **7** (IC_{50} 83 nM), **9** (IC_{50} 350 nM), and **10** (IC_{50} 450 nM) may provide evidence that the disulfide bridge, as well as the 15 membered macrocycle, are crucial for the compounds' biological activity. However, no biological evidence has been achieved to support this claim.

Table 1.1. Antiproliferative activity of isolated compounds. Taken from Hasegawa, A.; Kanda, Y.; Nakai, R.; Ogawa, T.; Onodera, H.; Tsumagari, N.; *J. Org. Chem.* **2004**, *22*, 4101.

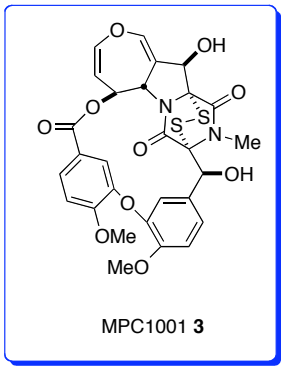


	Type	n	R_1	R_2	R_3	Amt. Iscol.*	IC_{50}*
MPC1001 3	I	2	OH	OH	-	260.2 mg	9.3 nM
MPC1001B 4	I	2	H	OH	-	7.7 mg	39.0 nM
MPC1001C 5	I	2	OH	H	-	1.7 mg	12.0 nM
MPC1001D 6	I	3	OH	OH	-	60.6 mg	16.0 nM
MPC1001E 7	III	-	-	-	-	58.9 mg	83.0 nM
MPC1001F 8	IV	-	-	-	-	6.1 mg	-
MPC1001G 9	II	-	-	-	S	12.0 mg	350.0 nM
MPC1001H 10	II	-	-	-	O	14.3 mg	450.0 nM

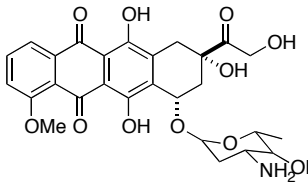
* Amount iscolated from 5 L of culture.
* Antiproliferative activites against DU145 human prostate cancer cell line. IC_{50} (nmol / L)

The antiproliferative activity of MPC1001 (**3**) was also compared to four known antitumor agents. As illustrated in table 1.2, MPC1001 (**3**) was shown to be more potent than adraimycin (**13**), etoposide (**14**), and mitomycin C (**15**). Even though the mechanism of action for MPC 1001 (**3**) is unknown, an efficient synthesis of MPC 1001 and its analogs are needed to explore the biological activity of this family of compounds. Understanding the biological activity may provide a therapeutic usage for these natural products.

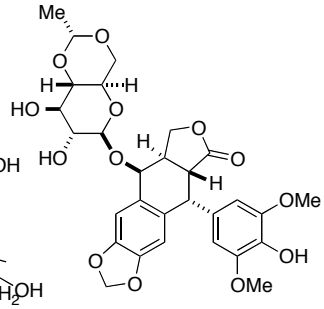
Table 1.2. Antiproliferative activity of antitumor agents.



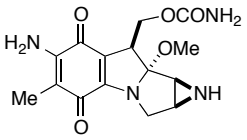
MPC1001 **3**



Adriamycin **13**



Etoposide **14**



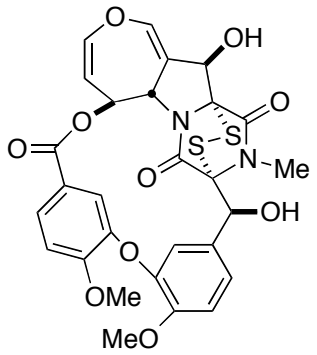
Mitomycin C **15**

	IC_{50} (nmol / L)*
MPC1001	9.3
Adriamycin	20
Mitomycin C	25
Etoposide	400

*Antiproliferative activites against DU145 human prostate cancer cell line

1.5 Structural Features.

MPC1001 (**3**) has interesting structural features that render this compound a relevant synthetic target. The core of the molecule is centered around a five membered pyrrolidine ring that contains four contiguous stereocenters. The pyrrolidine ring is fused to a seven membered 4,5-dihydrooxepin ring and a six membered diketopiperazine ring with a bridged disulfide that accounts for the ETP family of natural products' biological activity (Figure 1.2).[2] This tricyclic ring system is embedded in a fourteen membered macrocycle that contains a structurally interesting β-hydroxy-α-amino acid moiety.



MPC1001 **3**

Figure 1.2. MPC1001 (**3**).

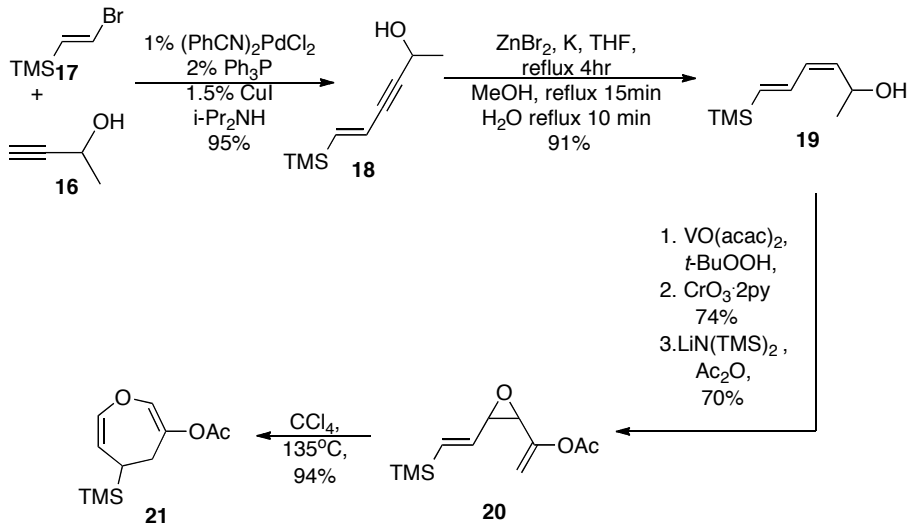
CHAPTER 2: Synthetic Approaches to MPC1001

2.1 Introduction.

Since the isolation of the aranotins in 1968[31], the oxepin ring has eluded the scientific community for over 40 years. Most synthetic approaches, like those from White, Snapper, and Kishi, afford the oxepin in a simple but concise model system. However, it was not until 2009 that the oxepin ring was made in a complex setting.

2.2 White's approach.

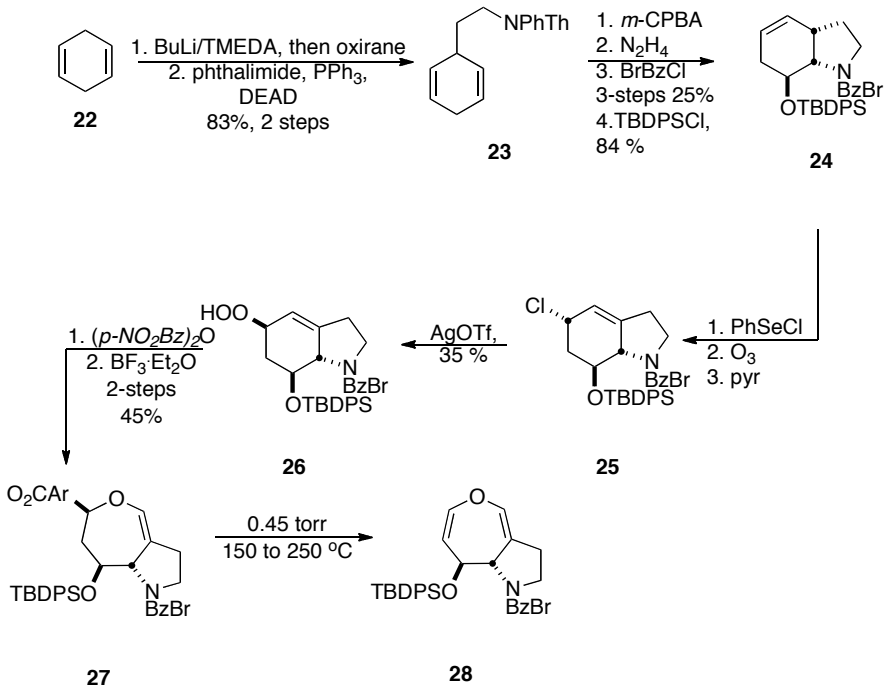
Most synthetic approaches to the oxepin ring are similar to White's approach[32] (Scheme 2.1). These approaches utilized a Cope rearrangement to afford the 4,5-dihydrooxepin ring. This efficient route utilizes a readily available enyol **16**, which underwent a Sonogashira coupling to afford the secondary alcohol **17**. The triple bond is reduced by a highly activated Rieke zinc reduction to the *cis*-double bond **19** in high yield. The allylic double bond was selectively epoxidized, oxidized to the ketone, and followed by formation of the allyic ester **20**. Compound **20** was heated in CCl_4 for 12 h, which induced a [3-3]-sigmatropic rearrangement, to give the 4,5-dihydeooxepin ring **21**.



Scheme 2.1. White's approach.

2.3 Kishi's approach.

Kishi and co-workers utilized a Criegee rearrangement for the synthesis of the oxepin ring **28** (Scheme 2.2).[33] Lithiation of 1,4-cyclohexadiene followed by trapping with oxirane gave the alcohol which was converted to the protected amine **23** with phthalimide, triphenylphosphine, and DEAD. The olefin **23** was expoxidized followed by closure of the ring and protection to give the fused ring **24**. Treatment of **24** with PhSeCl and O_3 formed the double bond which was followed by formation of the peroxide with silver triflate to give compound **26**. The peroxide **26** was subjected to $(p\text{-}NO_2bz)_2O$ and $BF_3{\cdot}Et_2O$-catalyzed rearrangement to afford the oxepin-carbamate **27** in 85% yield. Finally, vacuum pyrolysis provided the 7-5 model system **28**.

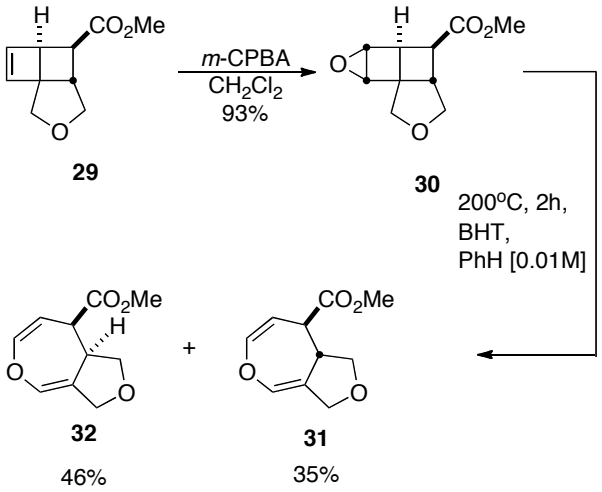


22 **23** **24** **25** **26** **27** **28**

Scheme 2.2. Kishi's approach.

2.4 Snapper's cycloaddition.

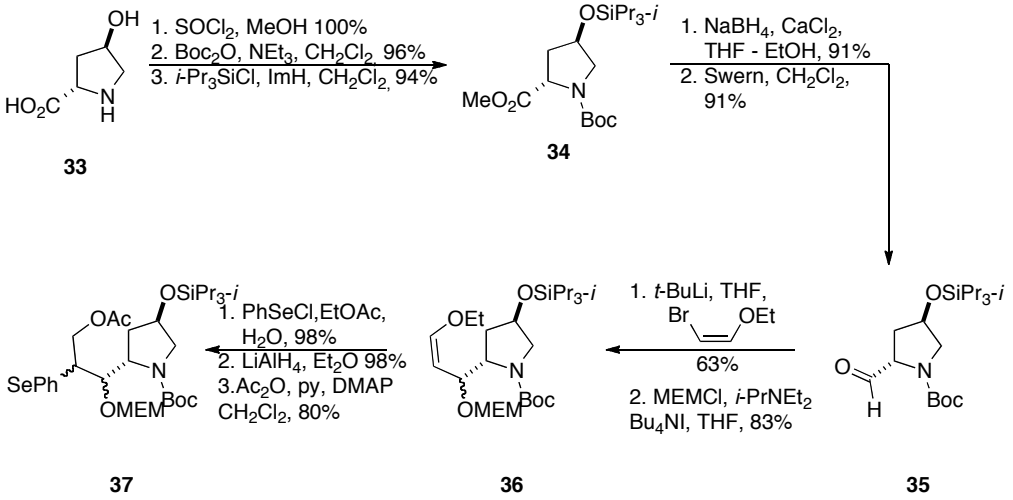
In 2004, Snapper and co-workers utilized a strained bicyclo- [5.3.0] ring **29** system to afford a 7-5-ring system (Scheme 2.3).[34] Compound **29** was readily available in three steps from cyclobutene.[15] The strained ring system **29** was epoxidized to give the cyclization precursor **30**.[35] Thermal fragmentation of compound **30** in BHT at 200 °C revealed the oxepin rings **31** and **32** in good yield.



Scheme 2.3. Snapper's approach.

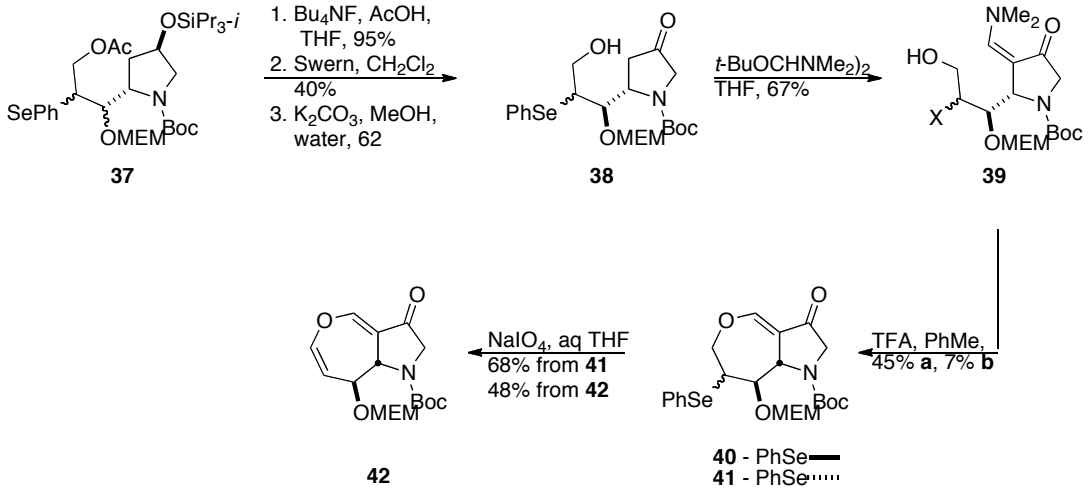
2.5 Clive's 1st approach.

The starting point for Clive's synthesis began with commercially available 4-hydroxy-L-proline (**33**), which was converted in three steps to the fully protected amine **34** (Scheme 2.4). [36] The ester **34** was reduced to the alcohol and reoxidized to the aldehyde **35**. Nucleophilic addition of (*Z*)-2-ethoxylvinyllithium gave the epimeric alcohols that were protected as their MEM ethers **36**. Treatment of compound **36** with PhSeCl gave the α-(phenylseleno) aldehydes, which were reduced and acetylated to give the ester **37**.



Scheme 2.4. Clive's 1st approach.

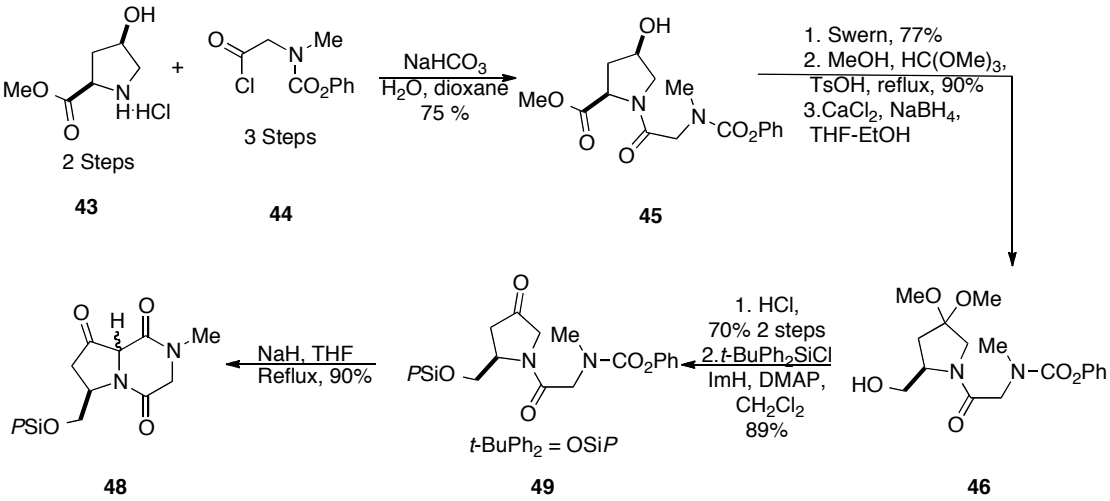
Removal of the silicion protecting group, Swern oxidation, and deacetylation gave the free alcohol **38** (Scheme 2.5). Treatment of compound **38** with Bredereck's reagent formed the vinylogous amide **39**, which was subject to an acid mediated addition-elimination sequence to give a 6.7:1 mixture of ethers **40** and **41** respectively. Finally, selenoxide elimination gave the 7-5 model system **42**.



Scheme 2.5. Clives' 1st approach.

2.6 Clives' 2nd approach.

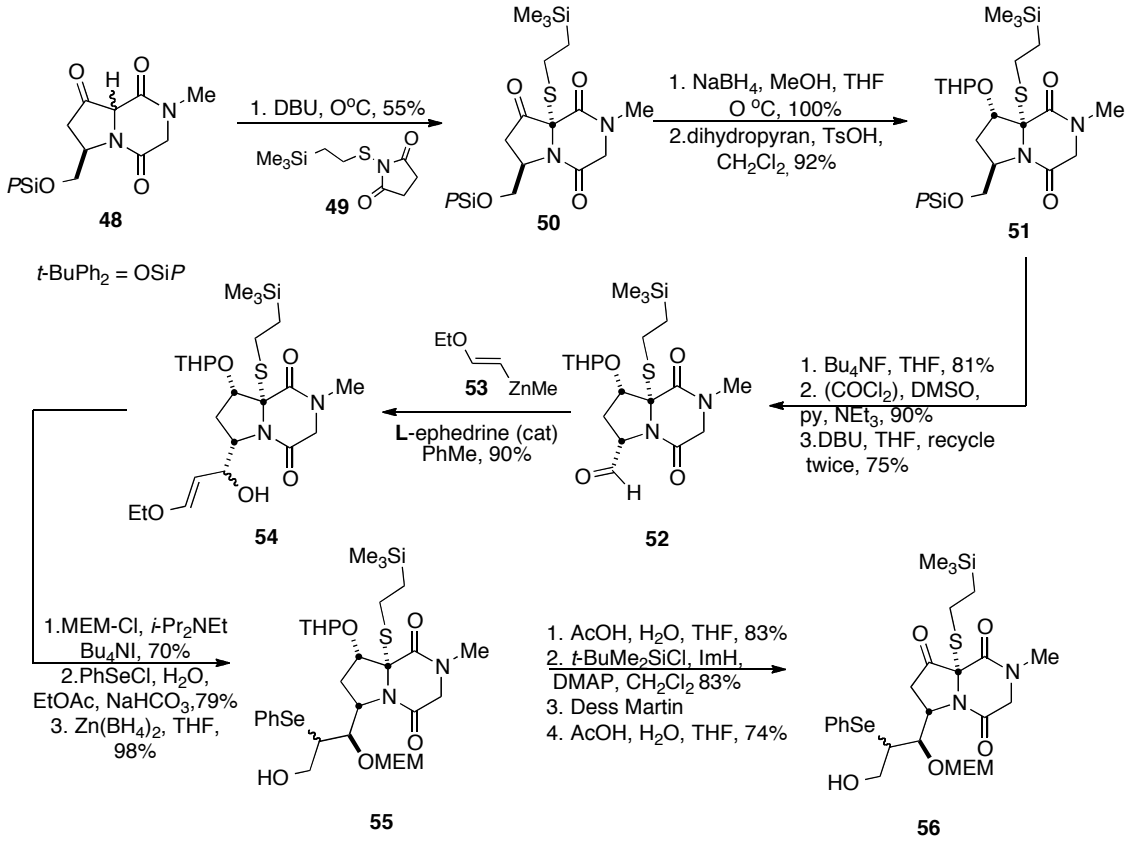
Clive and coworkers second-generation synthesis was sought to make the tricyclic model system (Scheme 2.6).[37] *Cis*-4-hydroxyl-D-proline hydrochloride (**43**) was prepared in 2 steps from commercially available 4-hydroxy-L-proline.[38] The other coupling component **44** was made in two steps from *N*-methylglycine. The nitrogen was acylated followed by a Swern oxidation, formation of the ketal, and reduction of the ester gave the alcohol **45**. The primary alcohol **46** was protected as the TBDPS ether followed by cleavage of the ketal and closure of the diketopiperazine, which gave the cyclic system **48**.



Scheme 2.6. Clive's 2nd approach.

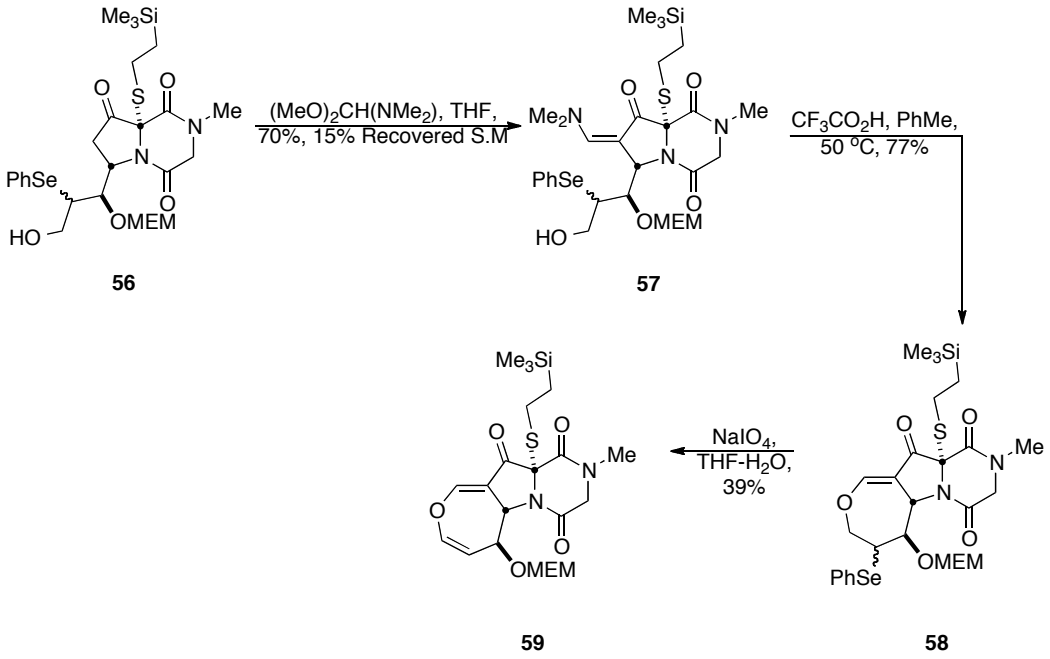
Treatment of DKP with DBU and sulfating reagent **49**[39] gave sulfide **50** (Scheme 2.7). Reduction of ketone **50** to the alcohol and protection gave compound **51**. Deprotection of the primary alcohol, Swern oxidation, and epimerization with DBU gave aldehyde **52**. Homologation of the aldehyde **52** with the (ethoxylvinyl) zinc reagent (**53)** in the presence of L-ephedrine gave the mixture of epimeric alcohols **54** that were protected as their MEM ethers. Treatment with PhSeCl and reduction with zinc

borohydride afforded the primary alcohols **55**. Next, A sequence of protection group manipulations over four steps gave the primary alcohol **56**.



Scheme 2.7. Clives' 2nd approach.

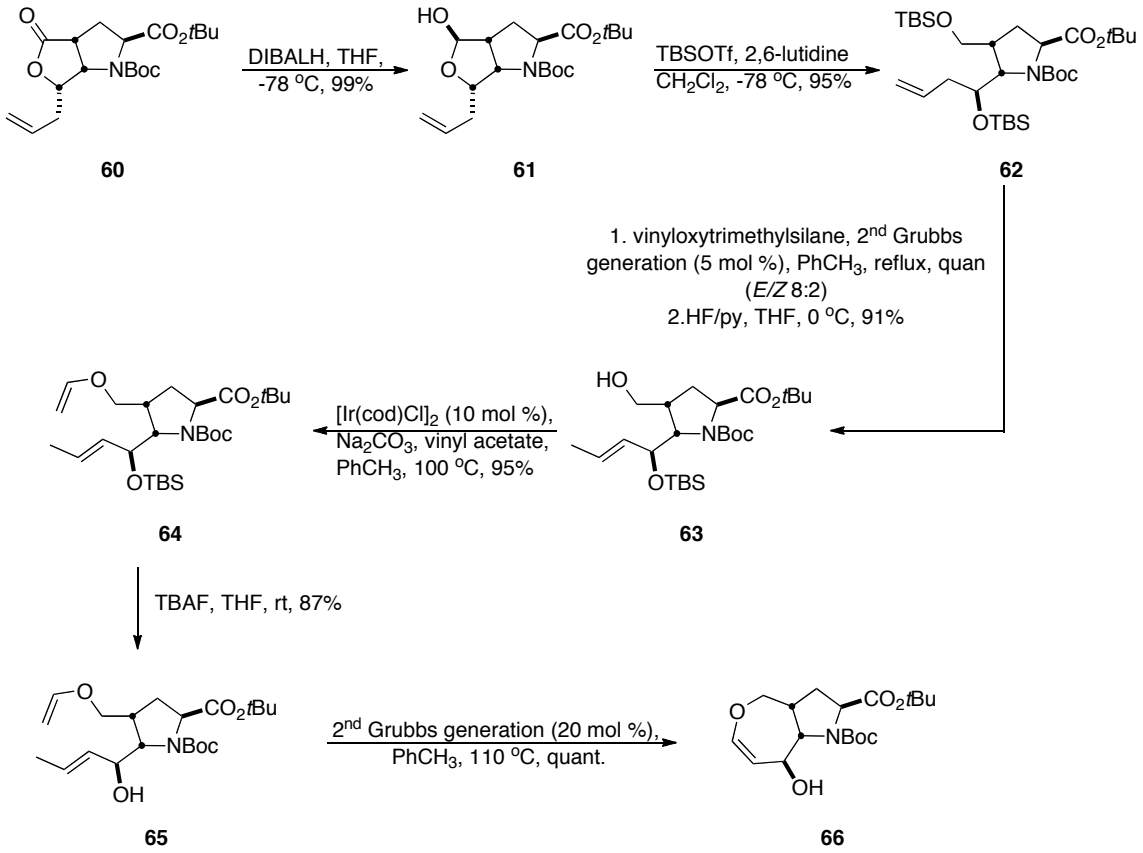
Formation of the vinylogous amide **57** with Brederreck's reagent afforded the cyclization precursor (Scheme 2.8). Amide **57** was treated with TFA followed by $NaIO_4$ to afford the 7-5-6 ring system **59**.



Scheme 2.8. Clives' 2nd approach.

2.7 Bräse's approach.

The most recent synthetic approach toward MPC1001 (**3**) was performed by Bräse and coworkers (Scheme 2.9).[40] Lactone **60,** which was prepared in 5 steps from L-pyro-glutamic acid[41], was reduced to the lactol **61** followed by TBS protection of the bisalcohols. Isomerization of the terminal double bond with Grubbs 2nd generation catalyst and selective deprotection of the secondary alcohol with HF/pyridine gave the primary alcohol **63**. Treatment of compound **63** with $[Ir(cod)Cl]_2$ afforded the vinyl ether **64,** and subsequent exposure to TBAF gave the free alcohol **65**. Finally, RCM of ether **65** afforded the oxepin ring **66**.



Scheme 2.9. Bräse's approach.

CHAPTER 3: Synthetic Research

3.1 Introduction.

The synthetic focus in this thesis is towards (*ent*)-MPC1001 (**67**). One of the first major synthetic challenges of this project was to construct a five membered pyrrolidine ring with four continuous stereocenters with the correct relative and absolute stereochemistry (Figure 3.1). Next, this five membered pyrrolidine needed to have synthetic handles (R_1 and R_2) that could be elaborated later into the six-membered diketopiperazine ring, as well as the synthetically challenging seven-membered oxepin ring.

Toward this end, one of the focal points of this project was to devise a stereocontrolled asymmetric approach to the pyrrolidine core. It has been shown that the [1-3]-dipolar cycloaddition has been useful for the synthesis of natural products as well as heterocyclic compounds.[42] Therefore, I rationalized that a [1-3]-dipolar cycloaddition may be useful for the synthesis of the pyrrolidine core of (*ent*)-MPC1001 (**67**). However, three problems had to be considered. The first was to get the reaction to work. Second, once the correct aldehyde is found, the azomethine ylide would need to be trapped with a dipolarophile that would useful in the synthesis of (*ent*)-MPC1001 (**67**). Next, this three component one pot reaction must afford the correct regio- as well as stereochemistry for the core pyrrolidine ring in (*ent*)-MPC1001 (**67**). Finally, the cycloaddition reaction must be scalable.

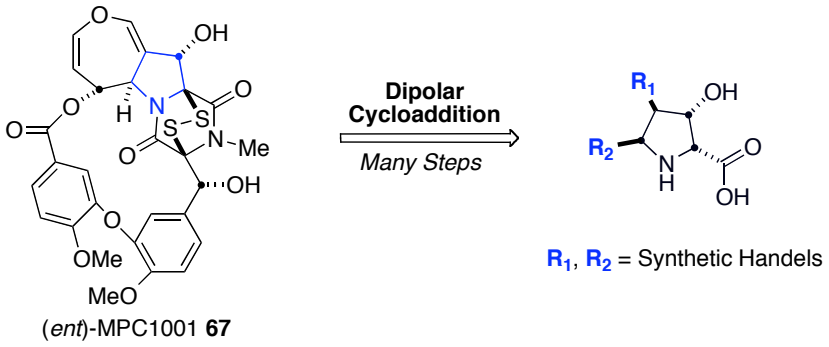
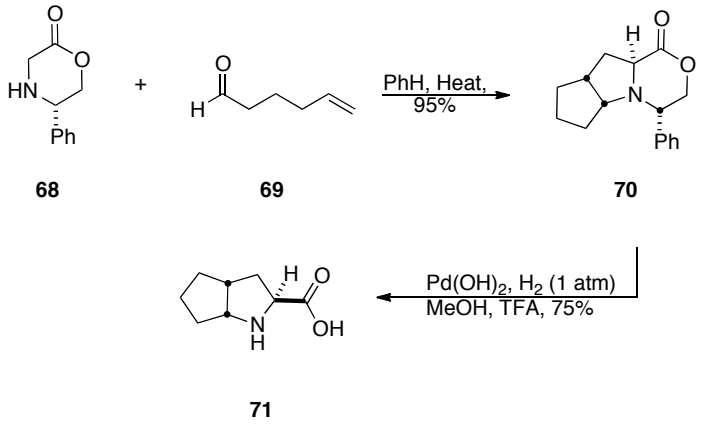


Figure 3.1. [1-3]-dipolar cycloaddition approach to MPC1001.

3.2. Expanded Williams' Methodology.

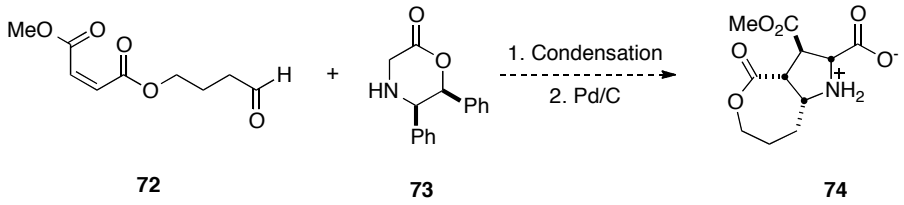
The first approach to (*ent*)-MPC1001 (**67**) was based upon an elaboration of a model system by Williams' and co-workers (Scheme 3.1).[43] Harwood utilized a chiral oxazinone template **68** in a highly diastereocontrolled [1-3]-dipolar cycloaddition with 5-hexenal (**69**) in refluxing toluene with molecular sieves to generate a azomethine ylide. The ylide was trapped by the terminal olefin in an intramolecular fashion to afford a chiral proline derivative **70**. The oxazinone template could be removed with palladium hydroxide under H_2 (1 atm) in methanol with a catalytic amount of TFA to reveal the unnatural amino acid **71** in 75% yield.



Scheme 3.1. Harwood's cycloaddition.

To expand upon Hardwoods results, a model system was attempted to make a seven membered ring with oxazinone **73** (Williams' lactone) and a terminal olefin (Scheme 3.2). The condensation of aldehyde **72** with Williams' lactone (**73**) followed by an intramolecular cyclization could set the four stereogenic centers and the seven membered ring needed for the synthesis of (*ent*)-MPC1001 (**67**). The chiral template could then be cleaved to afford the corresponding acid **74**. The chemistry developed on the simple model system could subsequently be applied to a more complex system toward the total synthesis of (*ent*)-MPC1001 (**67**).

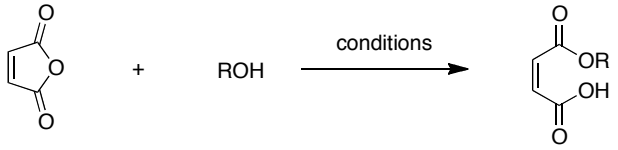
3.2.1 Application of the Williams' Approach.



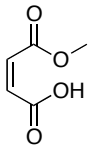
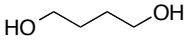
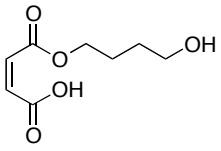
Scheme 3.2. Proposed Intermolecular cycloaddition model study.

The first attempt to synthesize precursor **72** was prepared by the addition of alcohols **78** and **79** to maleic anhydride (**75) (**Table 3.1).[44] Numerous attempts to synthesize precursor **77** resulted in a low yield or recovered starting material. However, switching the Lewis acid from zinc chloride to boron trifluoride dietherate afforded products **80** and **81**, but the yields were lower than expected (entry 2, 5).[45]

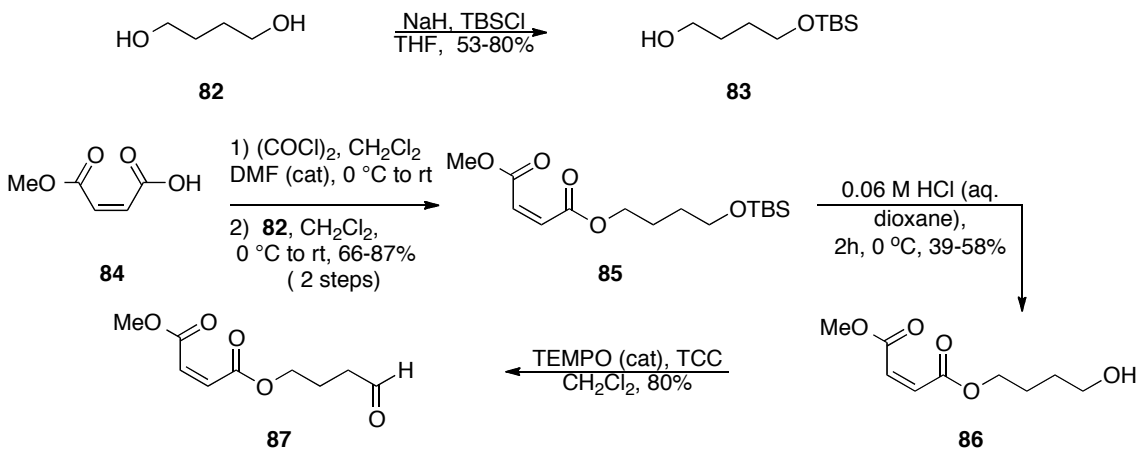
Table 3.1. Synthesis towards derivative **77**.



75 **76** **77**

Entry	*ROH*	*Conditions*	*Desired Product*	*Result*
1	MeOH **78**	3 mol% $ZnCl_2$,Et_3N, MeOH, CH_2Cl_2	 **80**	NR
2	**78**	BF_3•OEt_2, MeOH	**80**	31%
3	 **78**	3 mol% $ZnCl_2$, THF	 **81**	NR
4	**78**	NaH, THF	**81**	<10%
5	**78**	BF_3 •OEt_2, CH_2Cl_2	**81**	16%

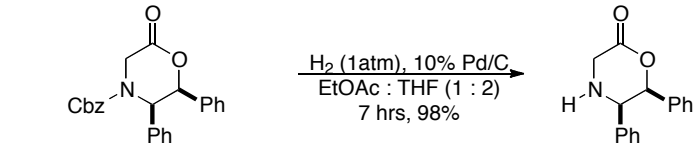
The second attempt to obtain the dipolarophile **72** was more successful (Scheme 3.3). The synthesis begins with the monoprotection of 1,4-butane diol (**82**)[46] followed by coupling with the acyl chloride, generated from compound **84**, to afford the diester **85** in 87% yield. The O-TBS was removed under acidic conditions to yield the free alcohol **86** in 39-58% yield.[6] The oxidation of alcohol **86** to the aldehyde **87** proceeded with TEMPO and trichloroisocyanuric acid and resulted in 80% yield.[47]



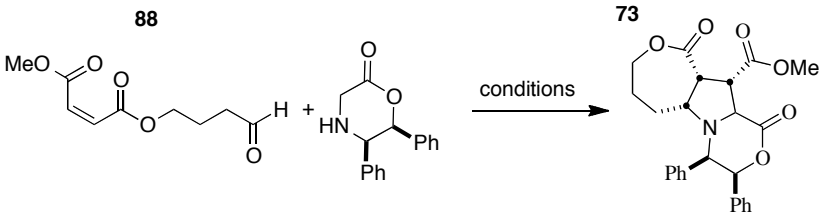
Scheme 3.3. Synthesis of ester aldehyde **29.**

Removal of the Cbz protecting group in the presence of H_2 (1 atm) and 10% Pd/C afforded the compound **27** in 98% yield (Table 3.2). With the secondary amine **33** and aldehyde **33** in hand, the [1-3]-dipolar cycloaddition was attempted as illustrated in Table 5. Each attempt was unsuccessful for creating the fused ring system. One problem may be the formation of the iminium; therefore, the Bronsted acid TsOH was used to activate the carbonyl and possibly accelerate the reaction. This reaction also resulted in recovered starting material. Therefore, a new precursor was synthesized.

Table 3.2. Two component intermolecular coupling.



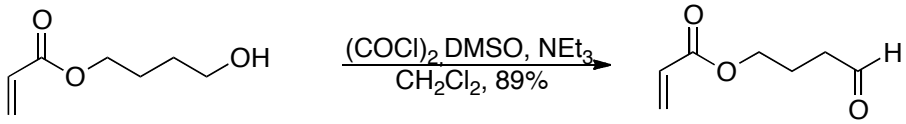
88



72 **73** **89**

Entry	*Conditions*	*Result*
1	PhH, 3ÅMS, Δ,12 hr	NR
2	$PhCH_3$, Δ, 12 hr	NR
3	TsOH, 3ÅMS, $PhCH_3$, Δ, 12 hr	NR

The synthesis of the new dipolarophile began with the oxidation of alcohol **90** under various conditions (Scheme 3.4). The following three types of conditions were attempted: TEMPO[6] Dess Martin[48] and Swern.[49] The Swern reaction proved to be the best to furnish aldehyde 91 consistently in 89% yield.



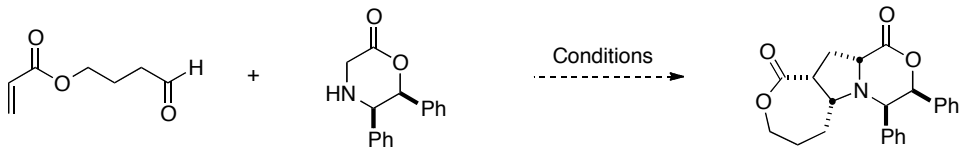
90 **91**

Scheme 3.4. Oxidation of Alcohol **90**.

For the subsequent dipolar cycloaddition with aldehyde **89** variables such as equivalents, temperatures, solvents, and additives were manipulated (Table 3.3).

However, the reactions resulted in an undesired product **91** and recovered starting material. The undesired product appears to result from a dimer of the starting material.

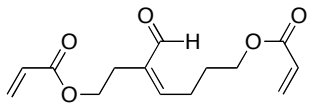
Table 3.3. Two component coupling.



91 **73** **92**

Entry	*Aldehyde (equivalents)*	*Temperature*	*Solvent*	*Additives*	*Product*
1	5	140 (Sealed Tube)	$PhCH_3$	3 ÅMS	Undesired
2	5	140 (Sealed Tube)	$PhCH_3$	$MgSO_4$	Undesired
3	1	148 (Sealed Tube)	Ph_3CH_3	3 ÅMS	Undesired
4	4	Reflux	PhH	3 ÅMS	Undesired
5	5	Reflux	$PhCH_3$	$MgSO_4$	Undesired
6	1	Reflux	$PhHCH_3$	3 ÅMS	Undesired

Undesired Product



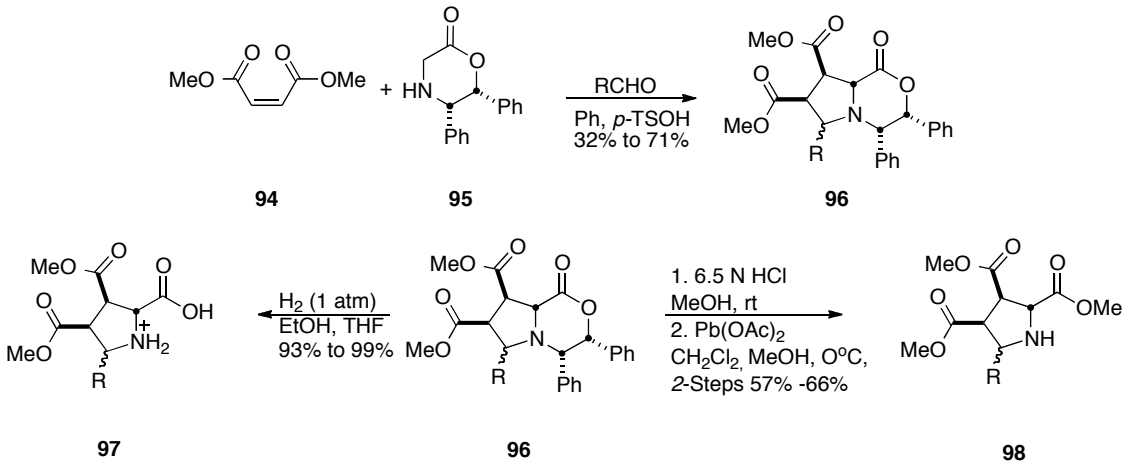
93

3.3 Williams' Methodology.

Concurrently, an intramolecular model system was attempted with amine **95**. It was believed that if a simple model system utilizing intermolecular cycloaddition was effective, then it could be applied to a more complex setting towards the total synthesis of (*ent*)-MPC1001 **67**.[50]

Williams and coworkers utilized amine **95** that can be treated with a variety of aldehydes in the presence of *p*-toluenesulfonic acid and benzene to afford the azomethine

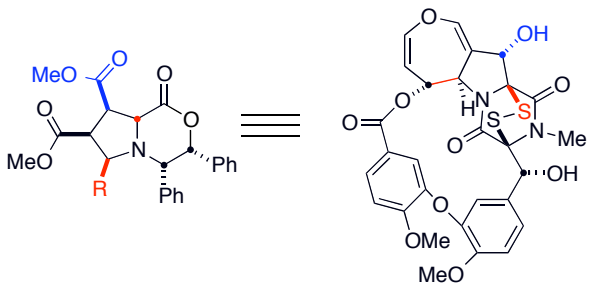
ylide.[30] (Scheme 3.5) The azomethine ylide was utilized in a cycloaddition with dimethyl maleate **(94)** to provide the complex heterocycles **96**. The template can removed with Pd/C and H_2 at 1 atm to afford the acid **97** or a stepwise cleavage of the template by 6.5 N HCl in MeOH at room temperature, followed by oxidative cleavage with lead $Pb(OAc)_4$ to give the methyl ester **98**.



94 **95** **96** **97** **96** **98**

Scheme 3.5. Williams' cycloaddition.

In all cases, the endo transition was observed as well as the dipolarophile approaches from the less-hindered face of the oxazinone. It was postulated that the success of Aldous' work would give the correct regiochemistry as well as stereochemistry around the core of pyrrolidine ring for (*ent*)-MPC1001 (**67**) (Figure 3.1).

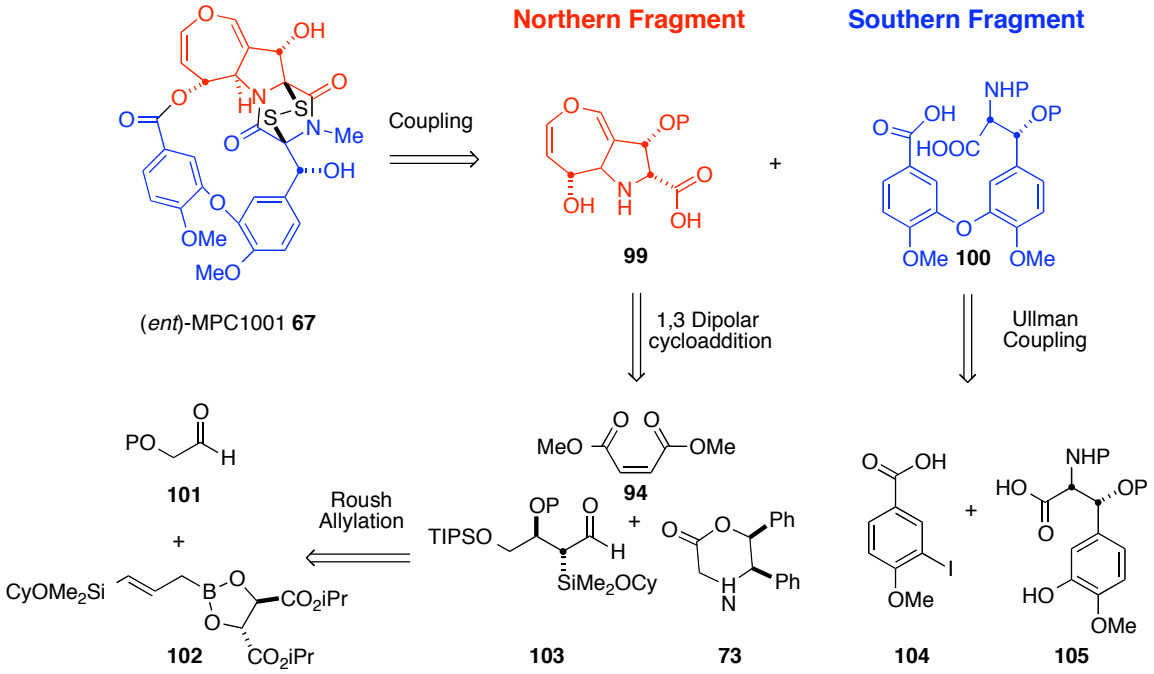


96 (*ent*)-MPC1001 **67**

Figure 3.1. Dipole Product compared to the core of (*ent*)-MPC1001 (**67**).

3.3.1 Application of the Williams' Methodology.

With the success of the Williams methodology, a basic retrosynthesis of (*ent*)-MPC1001 (**67**) was devised (Scheme 3.6). The synthesis of (*ent*)-MPC1001 (**67**) may occur from the coupling of the northern **99** and southern fragment **100,** followed by incorporation of the disulfide. The dihydrooxpin of the northern piece could be prepared via an intramolecular dipolar cycloaddition of aldehyde **103**, Williams' lactone (**73**), and dimethyl maleate (**94**). The aldehyde **103** could be prepared from a Roush allylation of the chiral boron reagent **102** and the protected alcohol **101**.[51] The southern portion **100** could originate from an Ullman coupling of the commercially available 3-Iodo-4-methoxy-benzoic acid **104** and the unnatural amino acid **105**.[52]

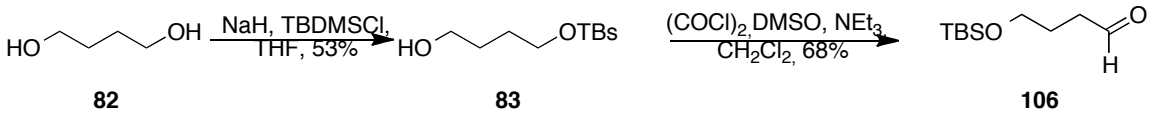


Scheme 3.6. First retrosynthetic approach towards (*ent*)-MPC1001 **67**.

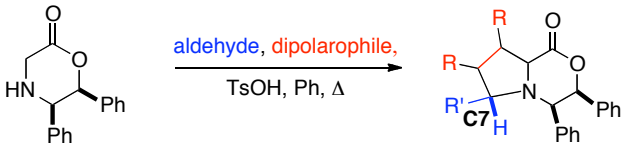
The possibility of utilizing the Williams group's chemistry to construct the dihydrooxpin core of (*ent*)-MPC1001 (**67**) seemed promising; however, the dipolar

cycloaddition was extremely problematic in the performed model study (Table 3.4). First the aldehyde **106** was constructed. The aldehyde **106** was furnished from the monoprotection of 1,4-butane diol (**82**) by TBDPSCl, followed by a Swern oxidation.[53,9] The dipolar cycloaddition was attempted with maleic anhydride (**108**) in the presence of TsOH. However, no desired product was observed. Changing the dipolarophile to dimethyl maleate provided the product **94** with a 1: 1 dr. seen in the crude NMR.

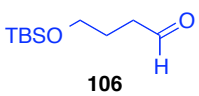
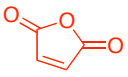
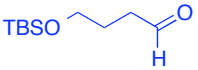
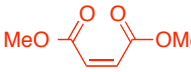
Table 3.4. Initial attempts for the intramolecular cycloaddition.



82 **83** **106**



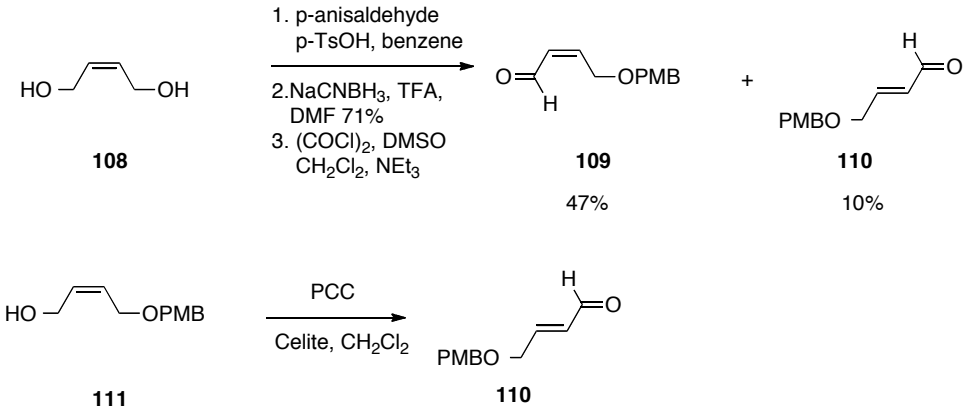
73 **107**

Entry	*Aldehyde*	*Dipolarophile*	*Result*
1	 **106**	 **108**	NR
2	 **106**	 **94**	(1 :1) dr

The mixture of diastereomers is believed to result from the formation of the *Z* and *E* ylides that reacted with dimethyl maleate (**94**) to afford the bicycloadducts **107**. Dr. Sebahar has previously shown that the diaselectivity at the C-7 position can vary considerably depending upon the bulkiness of the aldehyde.[54] Therefore, a more rigid

α,β unsaturated aldehyde **112** was synthesized that would be suitable for the total synthesis of (*ent*)-MPC1001 **67**.

The α,β unsaturated aldehyde **110** was synthesized from the cis diol **108** in three steps (Scheme 3.7). The Swern reaction yielded the desired cis double bond (aldehyde **109)** with a 47% yield, as well as the *trans* double bond (aldehyde **110**) in 10% yield. The aldehyde **109** proved to be unstable and slowly epimerized to the *trans* double bond even when stored at -78 °C. As a result of the slow epimerization, other oxidations as well as acid epimerization conditions were explored to convert aldehyde **109** to aldehyde **110**. The condition that worked the best was the PCC oxidation.[55] The oxidation of the *cis* alcohol **111** occurred within the first ten minutes of the reaction followed by a slow epimerization of the olefin over a two hour period to the *trans* double bond seen in compound **110**.



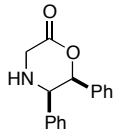
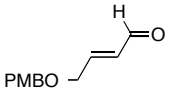
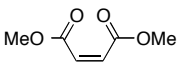
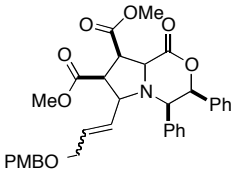
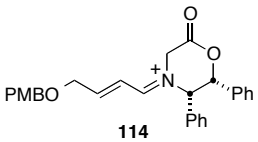
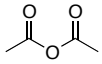
Scheme 3.7. Synthesis of olefin in aldehyde **112**.

The dipolar cycloaddition was attempted with aldehyde **110**, dimethyl maleate (**94),** and William's lactone (**73)** (Table 3.5). The reaction was carried out at room temperature and at reflux in the presence of benzene with catalytic TsOH. At room

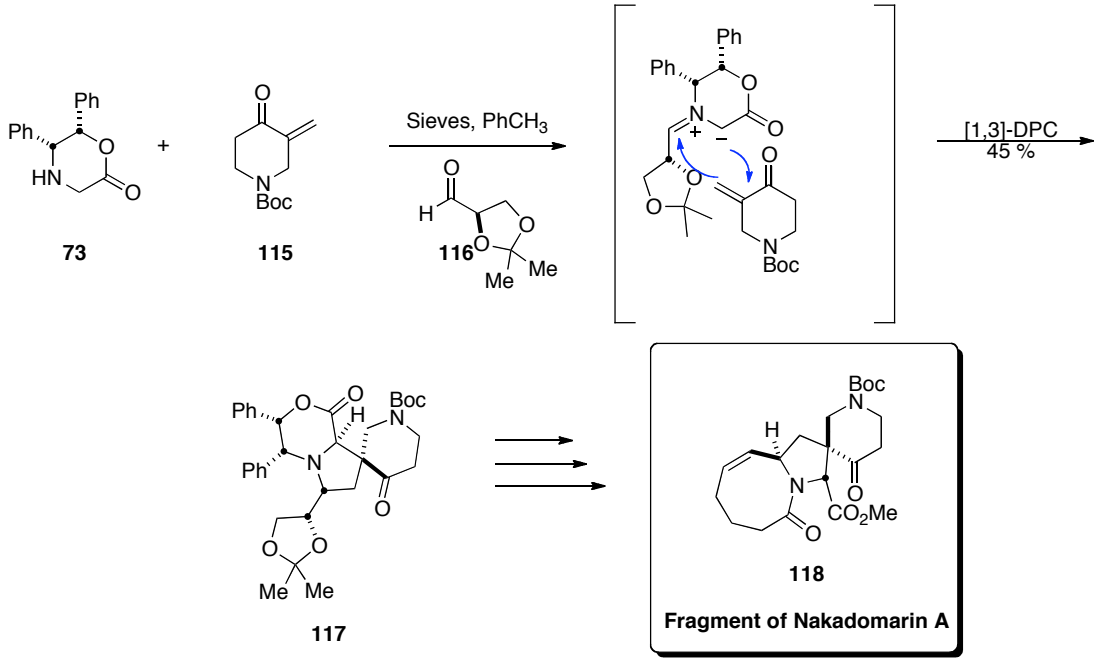
temperature, as seen in entry one, the reaction resulted in one compound by TLC that could not be identified. Addition of heat or exposure to column chromatography resulted in a complex mixture of products and complete recovery of dimethyl maleate (**94**). Inspection of the crude reaction by ^{1}H NMR revealed no lactone **73** or aldehyde **110** and no consumption of dimethyl maleate (**94**). Refluxing the reaction, seen in entry two, resulted in a complex mixture of compounds that were not isolated and identified.

As a final effort, the formation of the iminium ion was attempted with the lactone **73** and aldehyde **110** seen in entries 3 and 4, which proved to be difficult. Water was collected with a Dean Stark, seen in entry 5, which provides evidence of the formation of the iminium ion. Addition of dimethyl maleate (**94**) after 45 minutes of refluxing the lactone **73** and aldehyde **110** in anhydrous EtOAc resulted in a complex mixture of compounds that were not identified. However, many unsuccessful attempts to afford a cycloadduct or to identify the formation of the iminium ion prompted a new approach towards the pyrrolidine ring.

Table 3.5. Cycloaddition attempts with aldehyde **26**.

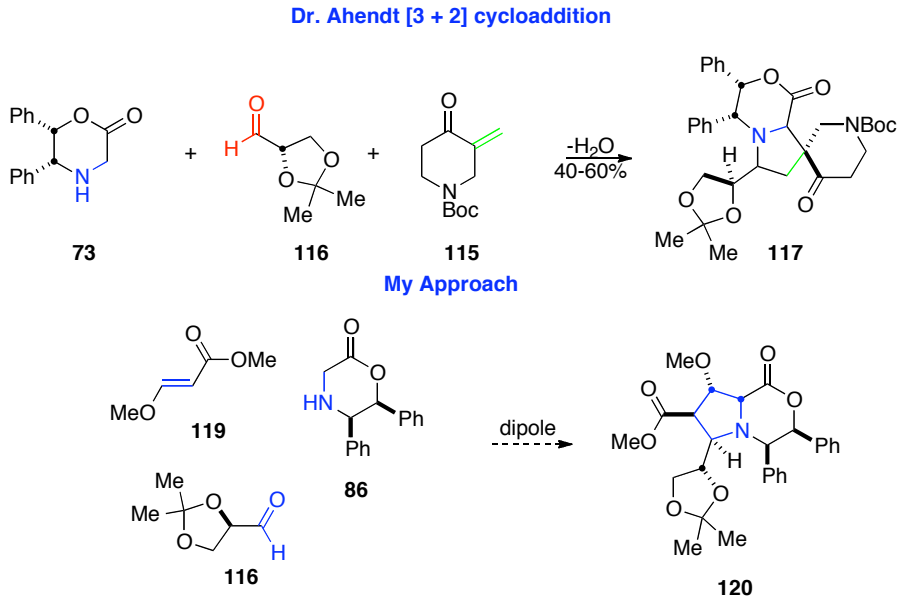
Entry	*Amine*	*Aldehyde*	*Dipolarophile*		*Result*
1	 **73**	 **110**	 **94**	TsOH, Benzene, r.t	 **112**
2	**73**	**110**	**94**	TsOH, Benzene, reflux	**112**
			Preforming Iminium ion		
3	**73**	**110**	Dean Stark trap	TsOH, Benzene	Collected small amount of water
4	**73**	**110**	**94**	D^6 Toluene 60 °C	 **114**
5	**73**	**110**	 **113** EtOAc 85 °C sealed tube	**94**	No iscolated Products

Noticing that the degree of unsaturation in α,β unsaturated aldehyde **110** was problematic, the attention turned towards utilizing an slightly more rigid aldehyde that could produce a cycloadduct. Previous experimentation by Kateri Ahendt utilized aldehyde **116** towards the total synthesis of Nakadomarin in a stereocontrolled asymmetric intermolecular 1,3-dipolar cycloaddition (Scheme 3.8).[56] Dr. Ahendt utilized secondary amine **73**, a mannose derived aldehyde **116** and a α,β-unsaturated ketone **115** to produce the pyrrolidene ring (**117**) in 45% yield.



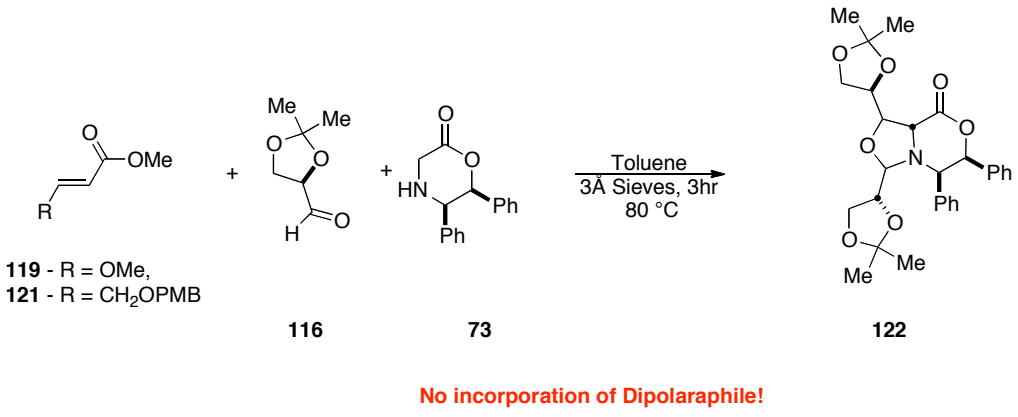
Scheme 3.8. Dr. Ahendt cycloaddition approach towards Nakadomarin A.

Dr. Ahendt's previous success with aldehyde **116** provided insight on the cycloaddition, which was explored in the total synthesis of (*ent*)-MPC1001 (**67**) (Scheme 3.9). It was hypothesized that amine **73** could condense on the mannose-derived aldehyde **116** to form the azomethine ylide followed by incorporation of the dipolarophile **119** which would give the cyclized product **120**.



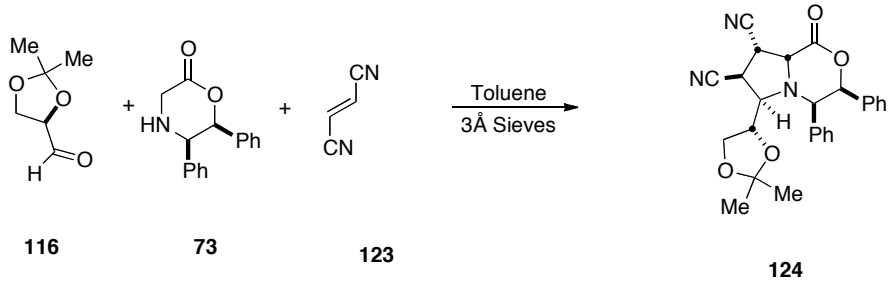
Scheme 3.9. Dipolar cycloaddition.

Initial experimentation with dipolarophile **119** and **121** with lactone **73** resulted in the unexpected product **122** and complete recovery of dipolarophiles **119** and **121** (Scheme 3.10). Even though the desired product was not obtained, the formation compound **122** reveals that the amine is nucleophilic enough to form the azomethine ylide.



Scheme 3.10. Unexpected Product **122**.

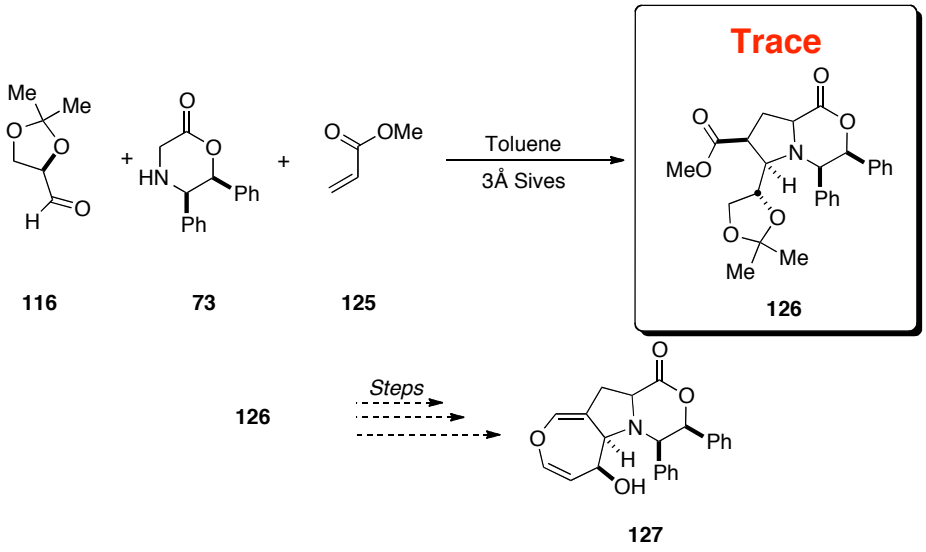
As a result of the unexpected product **122**, numerous dipolarophiles were examined to test the reactivity of the azomethine ylide (Scheme 2.11). First, fumeronitrile (**123**) was utilized and gave a very clean reaction to afford the cyclized product **124**. Obtaining the cycloadduct **124** is important because the desired product can be produced without the formation of the byproduct **122**.



116 **73** **123** **124**

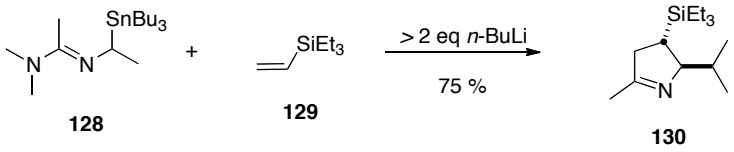
Scheme 3.11. [1-3]-dipolarcycloaddition with fumeronitrile (**123**).

Next with the success of fumeronitrile (**123**), methyl acrylate (**125**) was tested (Scheme 3.12). It was hypothesized that methyl acrylate (**125**) would be the ideal test substrate for this reaction. If the correct regioselectivity of the cycloaddition could be obtained, the ester could be further elaborated into the oxepin ring **127**. Unfortunately, the crude reaction revealed a complex mixture of compounds, but the desired compound **126** was obtained in trace amounts. Therefore, it was hypothesized as well as investigated next that a sterically bulky group could be introduced adjacent to the ester to affect the selectivity of the reaction.



Scheme 3.12. Cycloaddition with methyl acrylate (**125**).

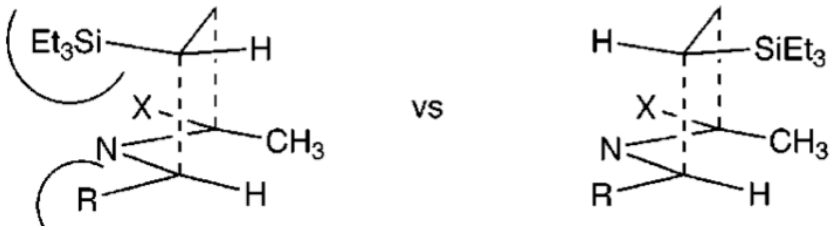
Peterson and coworkers utilized a transmethylation between lithium and tin to form an azaallyl anion, which can be trapped with various dipolarophiles to afford a wide array of pyrrolines.[57] One particular example imine **128** was subjected to 2.7 equivalents of *n*-BuLi in the presence of triethylvinylsilane **(129)** to produce cycloadduct **130** (Scheme 3.13). The success of this reaction prompted the use of a vinyl silane as a substrate for a dipolarophile.



Scheme 3.13. Peterson Cycloaddition.

Peterson describes the selectivity of the reaction to be consistent with allyl anions.[58] Assuming that once the tin is lost the imine takes an (E,E)-geometry, the endo/exo selectivity can be addressed. For the cycloaddition with vinyltriethylsilane

(**129**), the exo orientation **131** is favored over endo **132** based on steric affects between the methyl group and the silicon (Scheme 3.14).

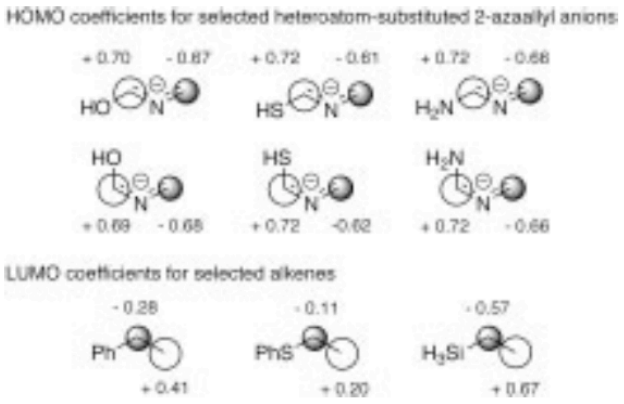


Endo **131** Exo **132**

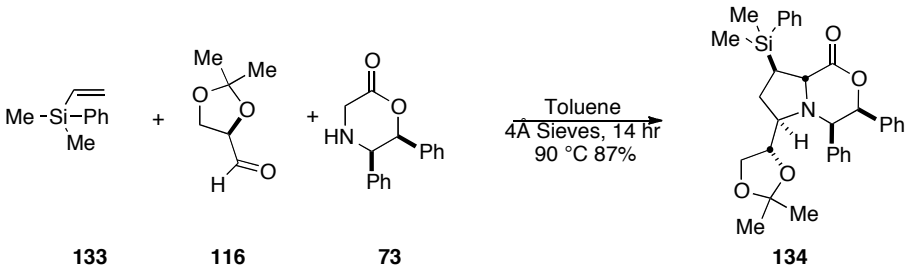
Scheme 3.14. Exo vs. Endo selectivity. Taken from Pearson H. W.; Stevens P. E.; *J. Org. Chem.* 1998, 63, 9812.

The regio selectivity is consistent with the semiempirical calculation conducted by Dewar and co-workers of the Homo of the 2-azaallyl anion and the LUMO of the alkene as illustrated in Table 3.6.

Table 3.6. Orbital Coefficients. Taken from Pearson H. W.; Stevens P. E.; *J. Org. Chem.* 1998, 63, 9812.



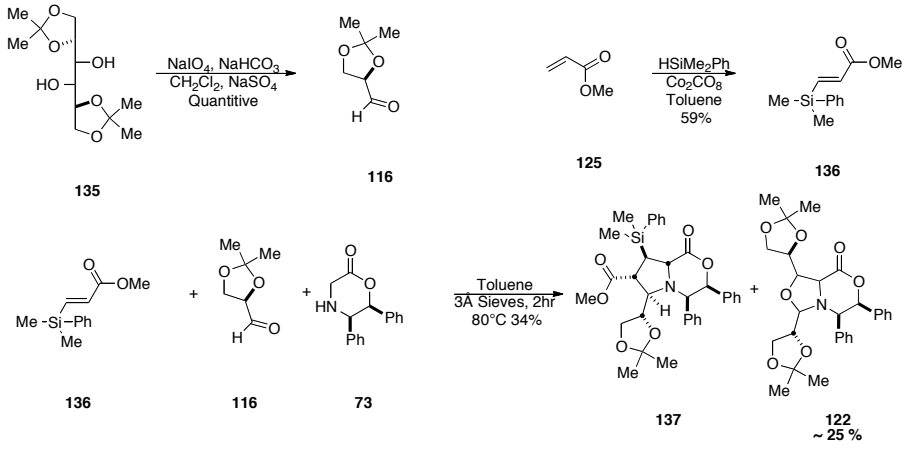
To test Peterson's results, a simple cycloaddition was attempted with silane **133**, amine **73**, and aldehyde **116**. The predicted product **134** was obtained in 86% yield with the optimized conditions described later (Scheme 3.15).



Scheme 3.15. Cycloaddition with silane **133**.

3.3 Novel [1-3]-Dipolar Cycloaddition.

Next, the cycloaddition was attempted on a more complex substrate. The aldehyde **116** was formed in quantitative yield by periodate oxidation of sugar **135**[59] (Scheme 3.16). The silicon compound **136** was synthesized in 63% yield from methyl acrylate (**125**).[60] The cycloaddition proceeded smoothly at 80 °C for 2 hours to give the product **137** in 33% yield and de of 93:7 and a 25% yield of the byproduct **122**. Product **137** was analyzed by ^{1}H NMR, ^{13}C NMR, HRMS, COSY, 1D and 2D NOE, HSQC, ^{29}Si NMR, and HMBC. These preliminary data provide evidence for the regiochemistry and stereochemistry seen in compound **137**.

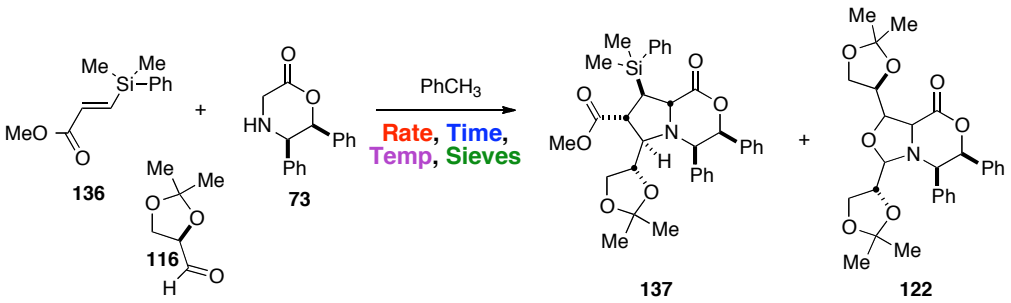


Scheme 3.16. Silicon cycloaddition.

3.3.1 Optimization.

With the correct regio as well as stereochemistry set, the reaction was optimized. All the reactions in entries 1 through 7 were done on a 50 mg scale with 1 equivalent of lactone **73**, except for entry 8, which was done with 1 g of lactone **73** (Table 3.7). Previous conditions, as seen in entry one, allowed for a 30 % isolated yield on average of the desired product **137** and a 22 % yield of the byproduct **122.** Extending the reaction time to 14 hrs (entry 2) and utilizing a pressure tube at 190 ºC for up to three days (entry 3) did not have a significant affect upon optimizing the yield of the desired product **137**. Changing from 3Å to 4Å molecular sieves allowed for 57% yield of compound **137** and 18% yield of byproduct **122** seen in entry 4. When the equivalents of the dipolarophile **136** (15 Eq) in entry 5 were increased, this allowed for an increased yield of the desired product **137** to 63%, and a reduced yield of the undesired byproduct **122** to less than 10%. Utilizing a syringe pump with the addition rate of 0.05ml/hr with a total reaction time of 14 hours increased the yield of the desired product **137** to 75% in entry 6, and lowered the yield of byproduct **122** significantly. Extending the total reaction time to 3 days with 15 equivalents of dipolarophile **136,** with an addition rate of 2 ml/hr resulted in a 78% yield of the desired compound **137** and provided trace amounts of the byproduct **122**. Finally, scaling the reaction up to 1 gram as seen in entry 8, allowed for a 85% with a 10 : 1 dr of the desired product **137** and trace amounts of compound **122**.

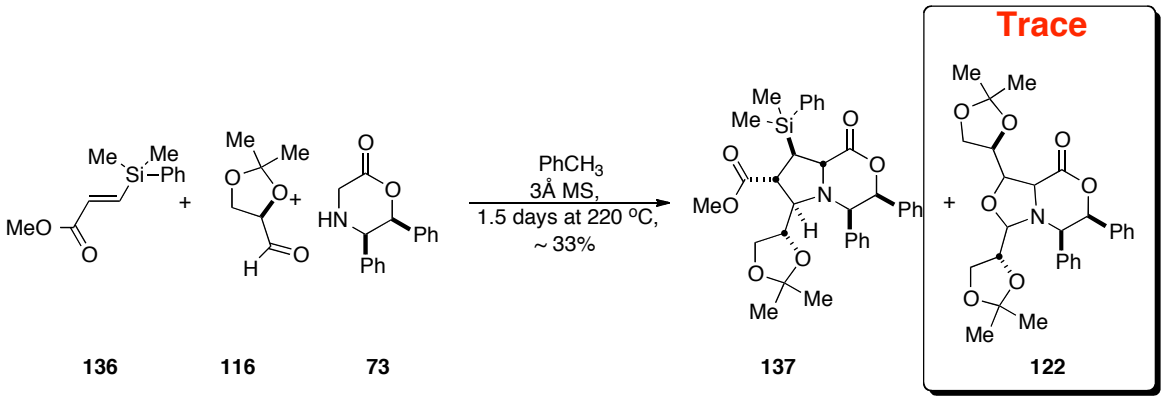
Table 3.7. Optimization of the cycloaddition.



Entry	Lactone	Aldehyde	Dipolarophile	Addition Rate	Total Time	Temp °C	Sieves	Product Yield 137	Byproduct Yield 122
1.	1 Eq (+)	1.25 Eq	3 Eq	NA	3 hrs	80°C	3Å MS	~ 30 %	~ 22 %
2.	1 Eq (+)	1.25 Eq	3 Eq	NA	14 hrs	80°C	3Å MS	30 % 10 : 1.4 dr	16 %
3.	1 Eq (+)	1.25 Eq	3 Eq	NA	3 Days	190°C Pressure tube	3Å MS	33 % 10 : 1.6 dr	didn't isolate
4.	1 Eq (+)	1.4 Eq	3 Eq	NA	14 hrs	1. 80°C 2. 90°C	4Å MS	1. 57% 2. 57%	1. 18% 2. NA
5.	1 Eq (+)	2 Eq	15 Eq	NA	14 hrs	90°C	4Å MS	63 % 10 : 1 dr	> ~10%
6.	1 Eq (+)	1.4 Eq	3 Eq	.05ml/hr	14 hrs	90°C	4Å MS	1. 61% 2. 75%	1. NA 2. ~10%
7.	1 Eq (+) 1g scale	4 Eq in 30 ml	15 Eq	2ml/hr	3 Days	90°C	4Å MS	78 % 10 : 1 dr	Trace
8.	**1 Eq (+) 1g scale**	**4 Eq in 30 ml**	**3 Eq**	**2ml/hr**	**24 hrs**	**90°C**	**4Å MS**	**85 % 10 : 1 dr**	**Trace**

Attention has also been focused on understanding the reactivity of the intermolecular dipolarcycloaddition with a vinyl silane **136** (Scheme 3.17). Elevating the temperature in a pressure tube for 3 days afforded the desired dipolar product **137** in approximately 33% yield. Even though the isolated product **137** was not pure by NMR, only a trace amount of dimerized byproduct **122** was isolated. Due to the isolation of only trace amounts of compound **122**, the reactivity of the byproduct **122** was investigated in more detail.

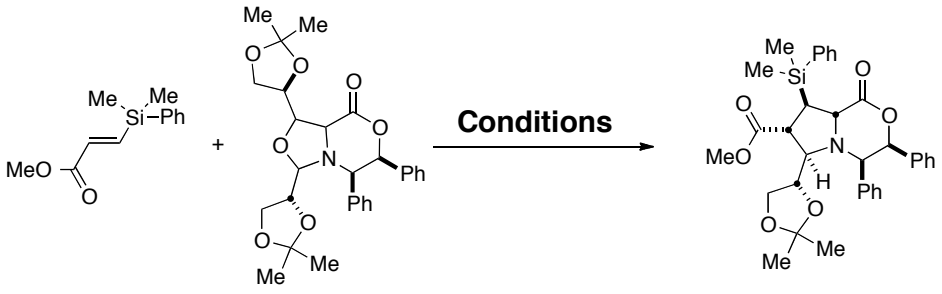
3.3.2 Mechanistic Studies.



Scheme 3.17. Dipolarcycloaddition in pressure tube.

The reactivity of compound **122** was explored under various temperatures in the presence of the dipolarophile **136** seen in Table 11. As the temperature increased to 160 °C and above, the desired dipolar product **137** can be seen in the crude NMR (Table 3.8). Allowing for the reaction to be heated in a pressure tube at 220 °C for 12 hours resulted in a 28% purity of the desired product **137** seen in entry 4. Therefore, as the temperature approaches 160 °C, an equilibrium may exist between the byproduct **122** and the desired dipolar product **137**.

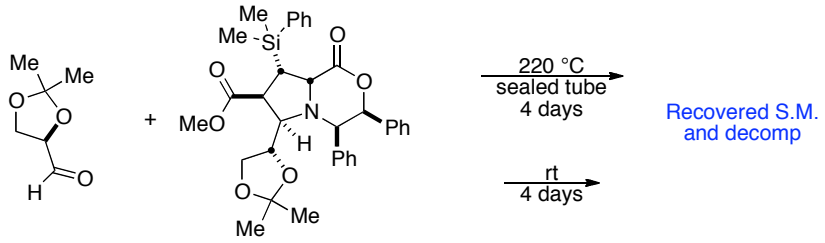
Table 3.8. Interesting reactivity of byproduct **122**.



136 **122** **137**

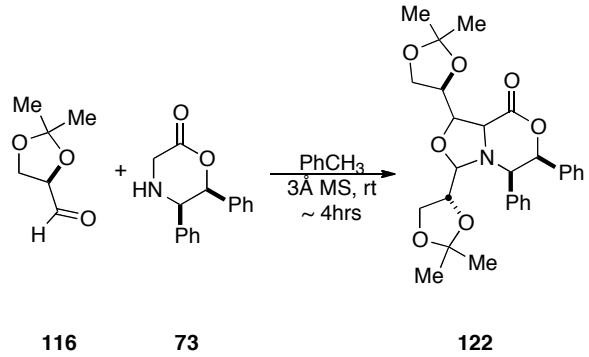
Entry	*Condtions*	*Result*
1	**136** + **122**, 90 °C sealed tube 1.5 days	S.M.
2	**136** + **122**, 160 °C sealed tube 12 hrs	**136** + **122** + trace **137**
3	**136** + **122**, 190 °C sealed tube 12 hrs	**136** + **137** 1 : 1
4	**136** + **122**, 220 °C sealed tube 12 hrs	**137** 28 %

One interesting question that still needs to be answered whether or not there can be an equilibrium between the dipolar product **137** and the byproduct **122**. Placing compound **137** in a sealed tube at 220 °C in the presence of the mannose-protected aldehyde **116** and rt for four days provided decomposition as well as recovered starting material, but no byproduct **122** could be isolated (Scheme 3.18). Therefore, in this case compound **137** is the thermodynamic product and it appears that no equilibrium exists between dipolar product **137** and byproduct **122**.



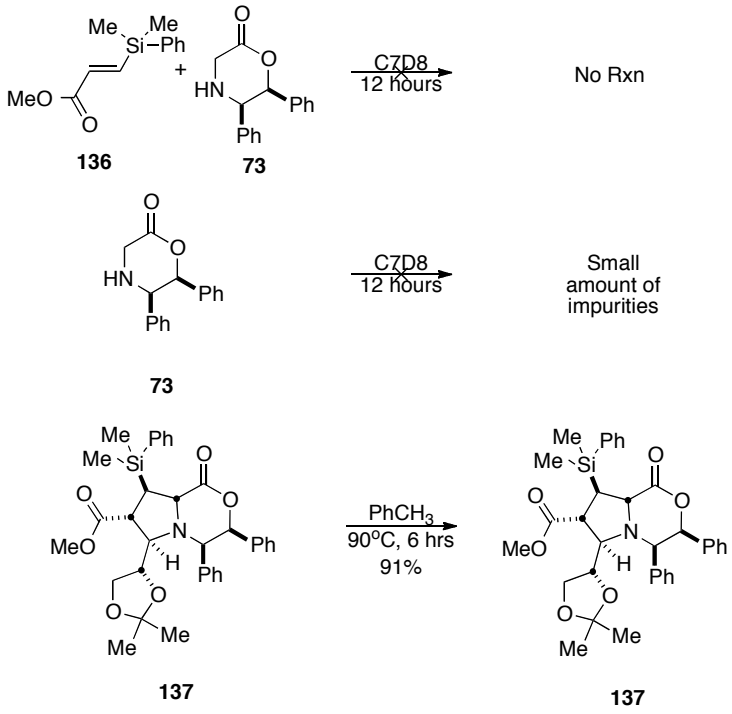
Scheme 3.18. No isolation of byproduct **122**.

The condensation between Williams' Lactone **73** and the mannose protected aldehyde **116** provided the dimerized or kinetic product **122** within 5 hrs at rt (Scheme 3.19). These experiments show that the byproduct is readily formed at room temperature.



Scheme 3.19. Formation of dimerized product **122** at rt.

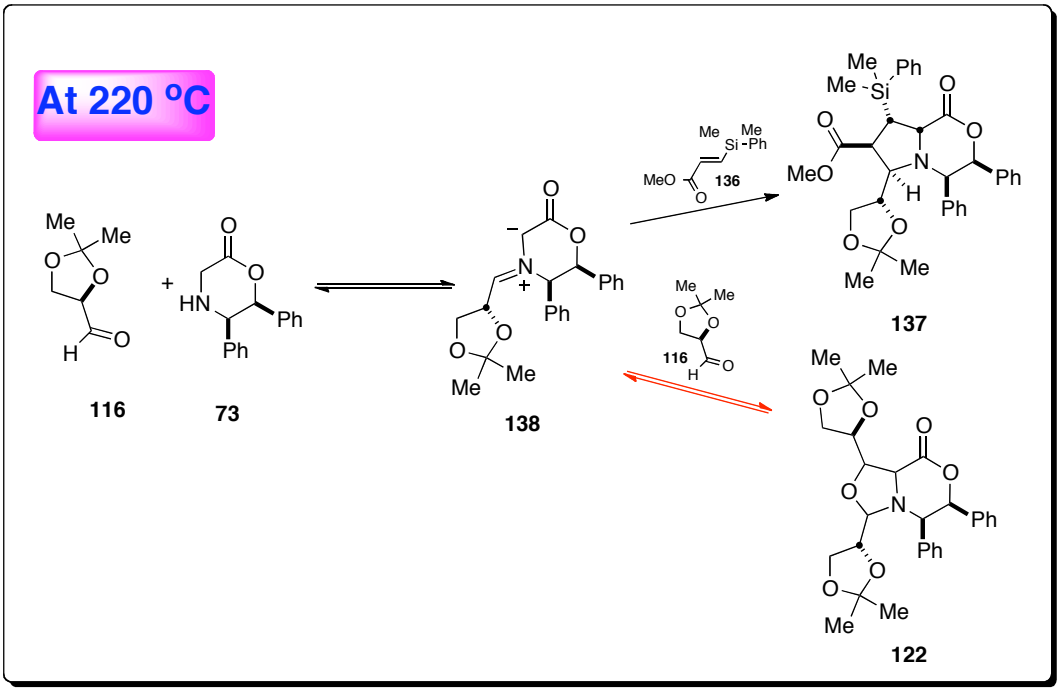
Next the stability of reagents was checked; heating the starting materials in D_8 toluene for 6 hours didn't result in any reaction and only slight decomposition was observed (Scheme 3.20). The secondary amine **73** was also streaked on TLC and some decomposition was observed by 2D TLC. Furthermore, heating the product **137** for 6 hours in toluene followed by column chromatography resulted in a 91% yield of recovered dipole product **137**. Therefore, there may be a slight loss of material due to decomposition, but it is not significant enough to effect the reaction.



Scheme 3.20. Stability of Reagents.

In conclusion, when the reaction is run at 90 °C, Williams' Lactone **73** condenses with the aldehyde **116** to form the 1,3 dipole intermediate **138**. The imine **138** can either react with the dipolarophile **136** to afford the thermodynamic product **137** or the imine **138** can condense with another equivalent of aldehyde **116** to form the kinetic product **122** (Scheme 3.21).

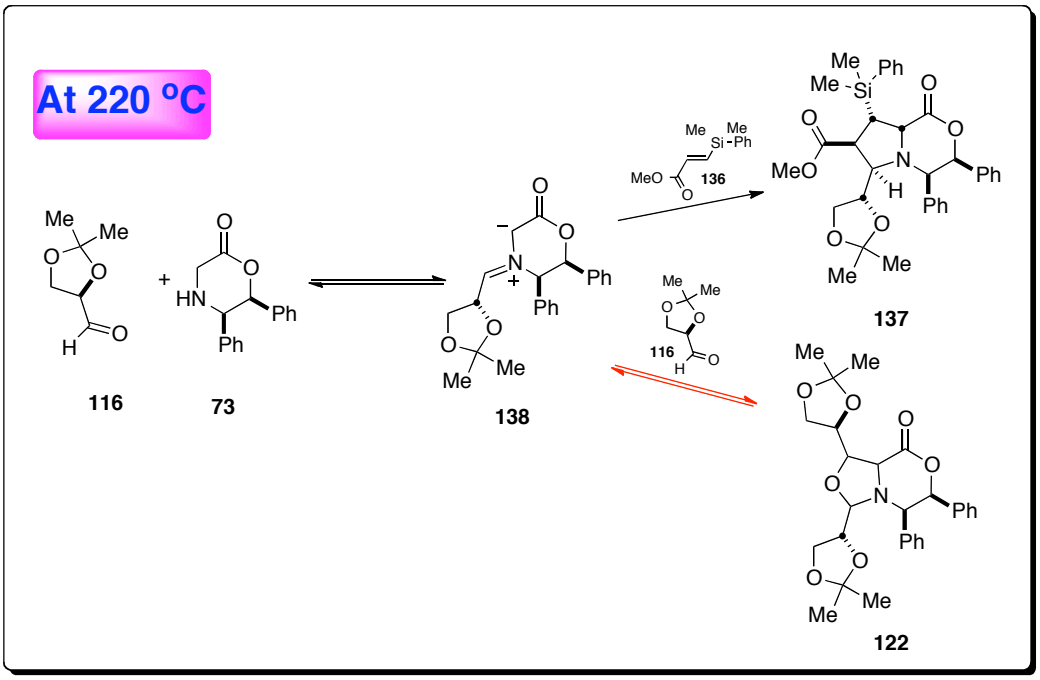
Proposed Mechanism



Scheme 3.21. Cycloaddition at 90 °C.

In contrast to the reaction run at 90 °C, and above 160 °C, William's Lactone **73** condenses with the aldehyde **116** to form the 1,3 dipole intermediate **138 (**Scheme 3.22). At elevated temperatures the imine **138** is in equilibrium with compound **122,** and can react with the dipolarophile **138** to form the desired product **137** in a 28% purity as seen in table 11, entry 4. The equilibrium that exists between the kinetic product **122** and the imine **138** may be used to convert the unwanted byproduct **122** to the desired dipolar product **137**.

Proposed Mechanism



Scheme 3.22. Cycloaddition at 220 °C.

3.3.3 Expanded Methodology.

With the dipolar cycloaddition optimized, attention was turned to expanding the methodology that has been previously developed for a more structurally complex aldehyde. The two aldehydes **139** and **140** that have been explored are seen in Figure 3.2. The two compounds are sugars **(150**, **151)** that can serve as masked aldehydes. These sugars are in equilibrium between the straight chain (open) and fructose (closed) form. If the equilibrium would shift toward the open form and reveal the aldehyde **139**, then Williams' Lactone **73** could condense onto one of these aldehydes and form a dipolar cycloaddition with the vinyl silane **136** to afford the desired product **154** (Scheme 3.23).

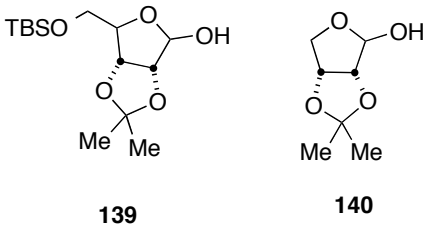
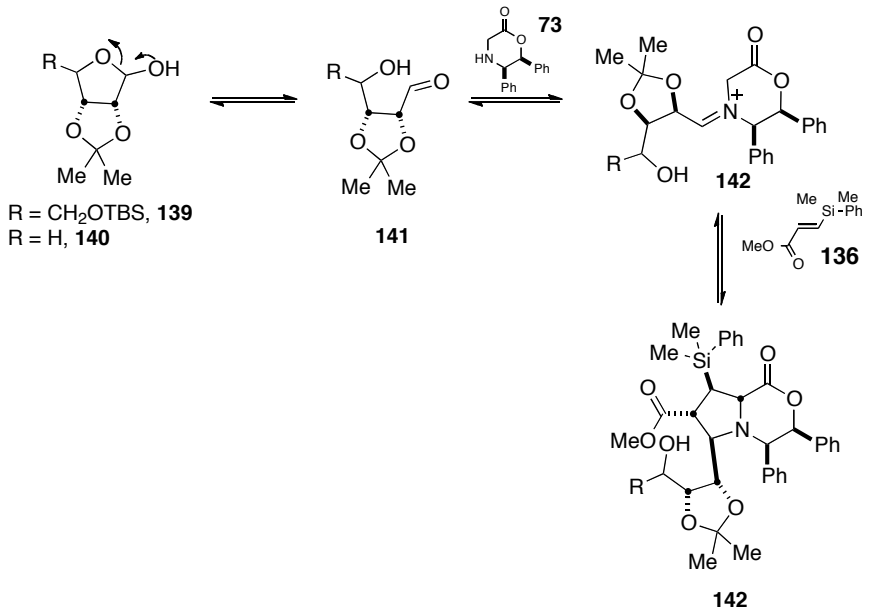


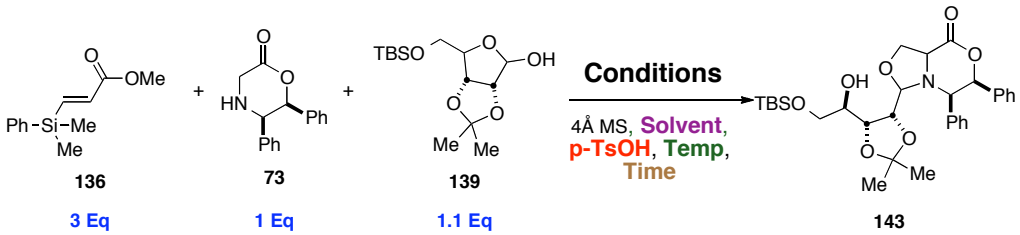
Figure 3.2. Masked aldehydes



Scheme 3.23. Possible cycloaddition with sugars **150** and **151**.

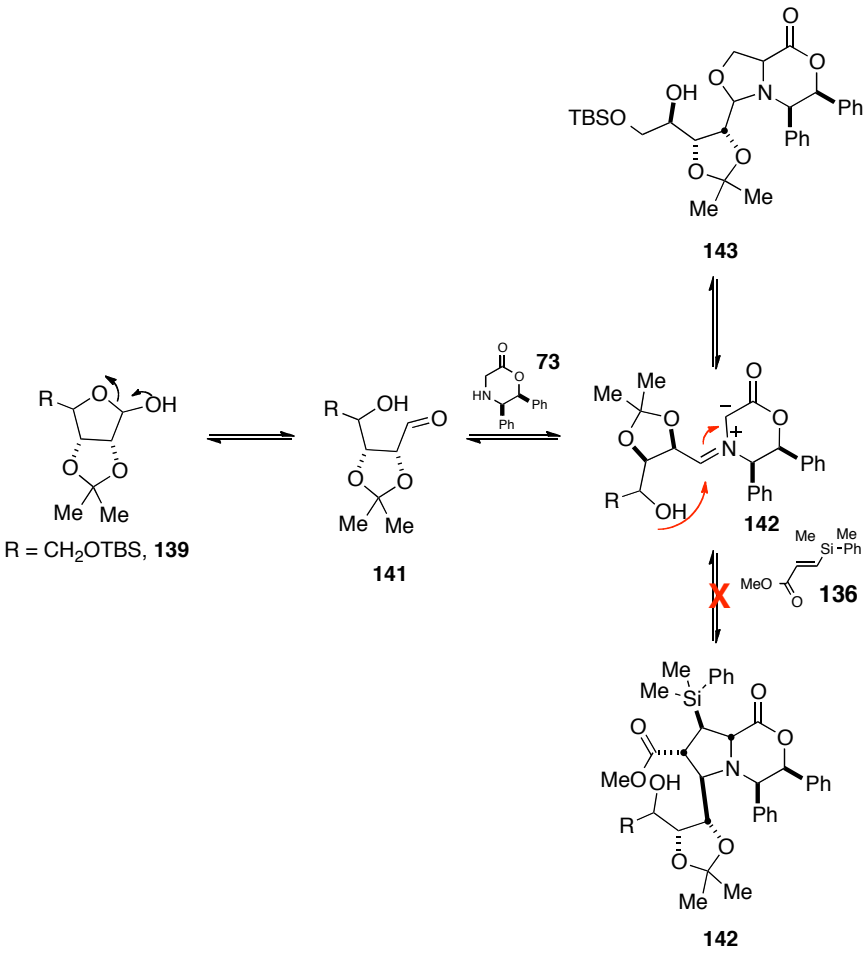
The TBS protected sugar **139** can be prepared in two steps from ribose.[61] Unfortunately, all attempts to form the desired product **142** was not successful Table 3.9**.** The reaction was extremely sluggish potentially due to the steric bulkiness of the primary TBS group. However, entry 7 showed the best results in an 8 hr period. The only isolated product was compound **143**. This compound was extremely difficult to separate from the TBS protected sugar **139**. However, after running a prep plate for 12 hours only **143** was isolated. The proton of compound **143** did contain some of the TBS protected sugar in it; however, the mass spectrometry showed 562.259 which represents compound **143**. The mass spectrometry did not show 844 for the dimmer or 305 for the protected sugar **142.**

Table 3.9. Attempted cycloaddition with sugar **36**.



Entry	*Solvent*	*p-TsOH*	*Temp*	*Time*	*Result*
1	$PhCH_3$	N/A	rt	8 hrs	No Rxn
2	$PhCH_3$	N/A	rt	24 hrs	No Rxn
3	$PhCH_3$	1 Eq	90°C	2.5 days	Complex Mixture
4	$PhCH_3$	N/A	90°C	8 hrs	No Rxn
5	$PhCH_3$	.1 Eq	75°C	8 hrs	sluggish
6	CH_3CN	N/A	rt	24 hrs	sluggish
7	**CH_3CN**	**.1 Eq**	**75°C**	**8 hrs**	**byproduct**

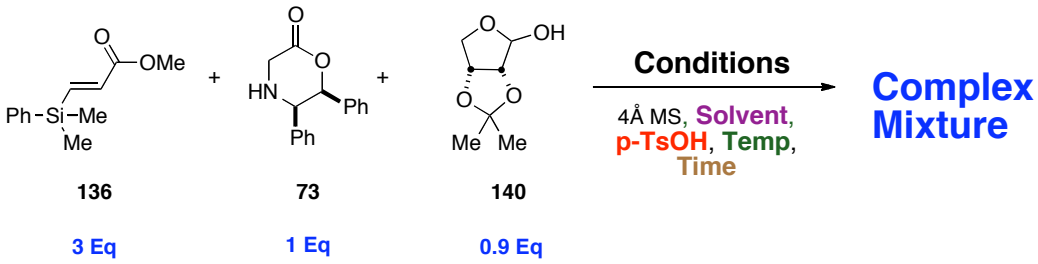
This result revealed some valuable information: 1. Amine **73** can condense onto the aldehyde **139** and form the iminium ion **142** (Scheme 3.24). 2. The closure of the resulting secondary alcohol onto the iminium ion **142** is faster to produce compound **143**, compared to trapping of the imine **142** by the dipolarophile **136**. Therefore, the alcohol may have to be protected to prevent byproduct **143** from forming.



Scheme 3.24. Proposed Mechanism.

Sugar **140** has also been recently investigated seen in Table 3.10. Just as in the case of the TBS protected sugar **139**, no desired product has been obtained. Each of the conditions revealed no more lactone by crude NMR and two new UV-active spots by TLC. However, all attempts to column or prep plate this crude mixture resulted in no identifiable material.

Table 3.10. Attempted cycloaddition with sugar **140**.



136 **73** **140**

3 Eq **1 Eq** **0.9 Eq**

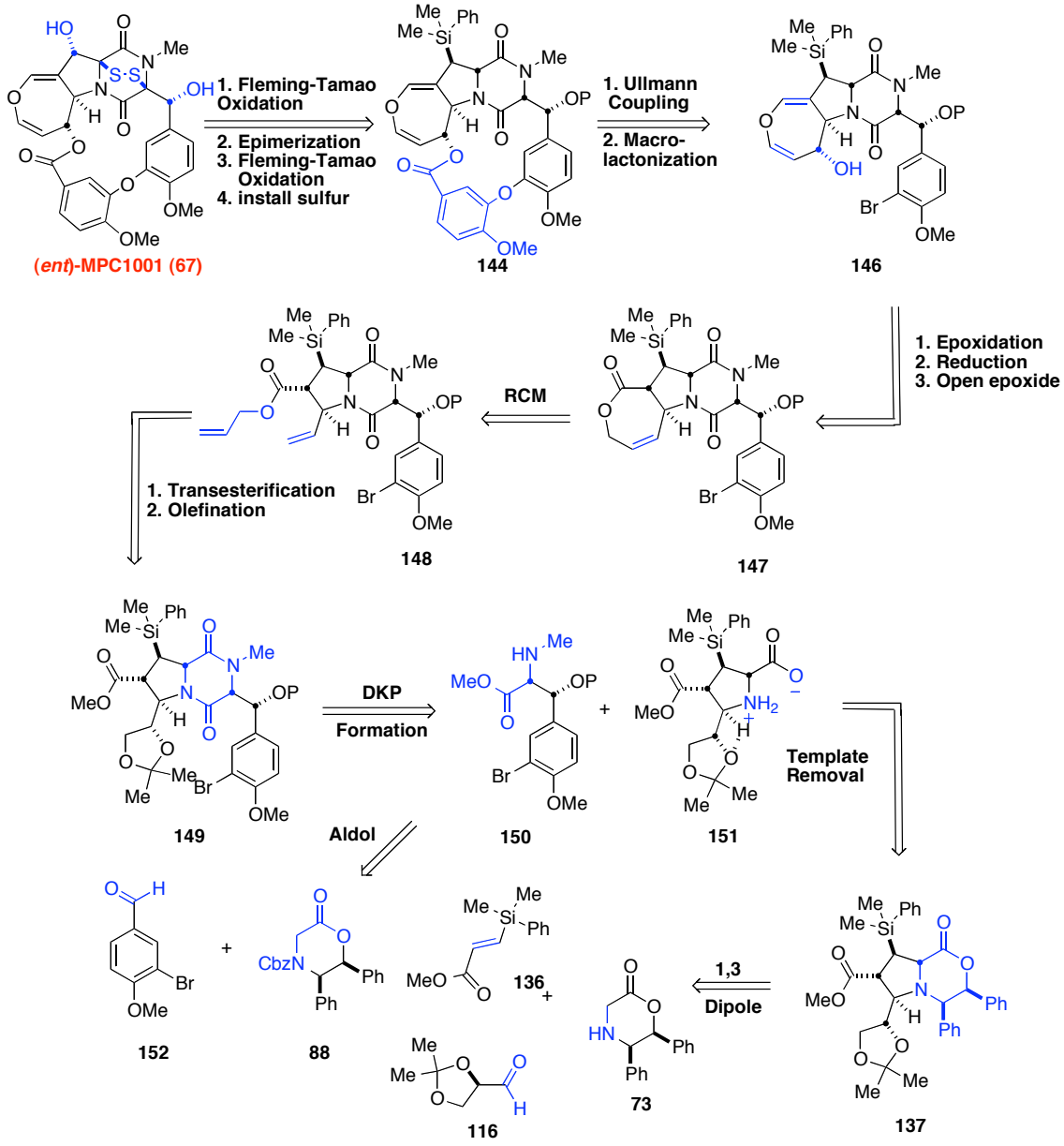
Entry	*Solvent*	*p-TsOH*	*Temp*	*Time*	*Result*
1	$PhCH_3$	1 Eq	90 °C	24 hrs	Complex Mixture
2	$PhCH_3$	1 Eq	280 °C	2 days	Complex Mixture
3	$PhCH_3$	0.1 Eq	75 °C	3 days	Complex Mixture
4	CH_3CN	0.1 Eq	75 °C	24 hrs	Complex Mixture

In conclusion, with lack of success of the masked aldehydes, focus was turned toward utilizing cycloadduct **137** for the total synthesis of (*ent*)-MPC1001 (**67**), as described in chapter 4.

CHAPTER 4: Synthetic progress toward (*ent*)-MPC1001 (67).

4.1 Overall retrosynthetic approach to (*ent*)-MPC1001 (67).

The overall retrosynthetic approach of (*ent*)-MPC1001 (**67**) was revised utilizing cycloadduct **137** (Scheme 4.1). The newly proposed retrosynthesis was envisioned from a late stage installation of the disulfide bridge, a Fleming-Tamao oxidation, as well as an epimerization of the silicon derivative **144** seen in Scheme 33. Compound **144** may arise from a modified Ullman Coupling with 3-hydroxyl-4-methoxy-benzoic acid, followed by a macrolactonization to form the 15-membered macrocycle. Reduction of the seven membered lactone followed by epoxidation of the *cis* double bond and subsequent Lewis acid ring opening of compound **147** could afford compound **146**. The cyclic lactone **147** could be prepared by metathesis of the terminal olefins of compound **148**. The double bonds may originate from the deprotection of the acetonide and elimination of the diol as well as transesterification of the methyl ester **149** with allyl alcohol. Formation of the diketopiperazine **149** could arise from the coupling of the β-hydroxyl amino acid **150** and tetrahydropyrrole **151**. The unnatural amino acid **130** could arise from an asymmetric aldol reaction of **152** and lactone **88**. A novel three-component asymmetric 1,3 dipolar cycloaddition may be utilized to construct the pyrrolidine ring **137**, which could be followed by the removal of the template to afford the tetrahydropyrrole derivative **151**.

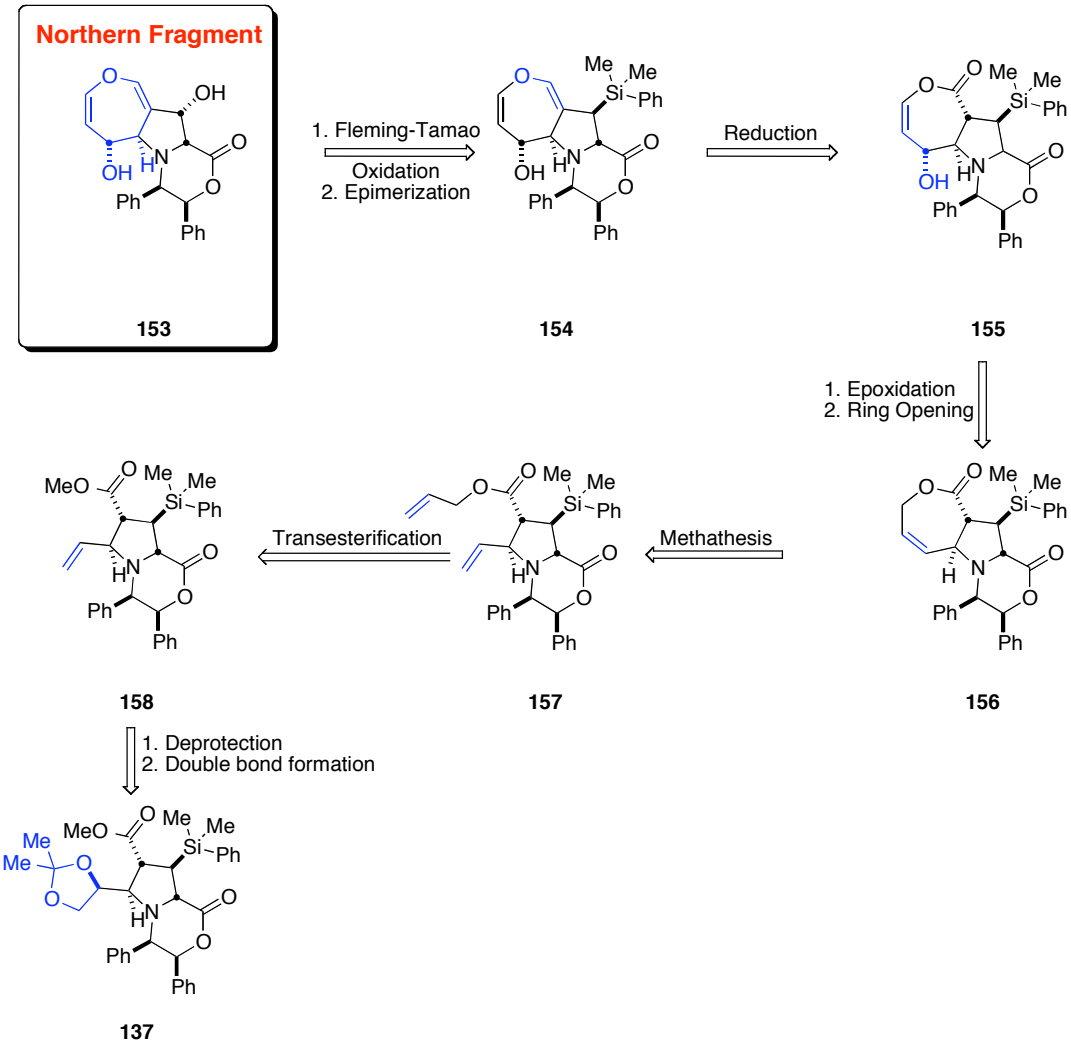


Scheme 4.1. Retrosynthetic approach to (*ent*)-MPC 1001 (**67**).

4.2 Synthetic Progress Toward the Oxepin Ring.

Before the synthesis of (*ent*)-MPC1001 (**67**) can occur, an efficient synthesis of the oxepin ring needs to be addressed. With the success of the production of cycloadduct **137**, emphasis was focused on the synthesis of the oxepin ring in a model system (Scheme 4.2). A retrosynthetic approach to compound **153** was proposed from a

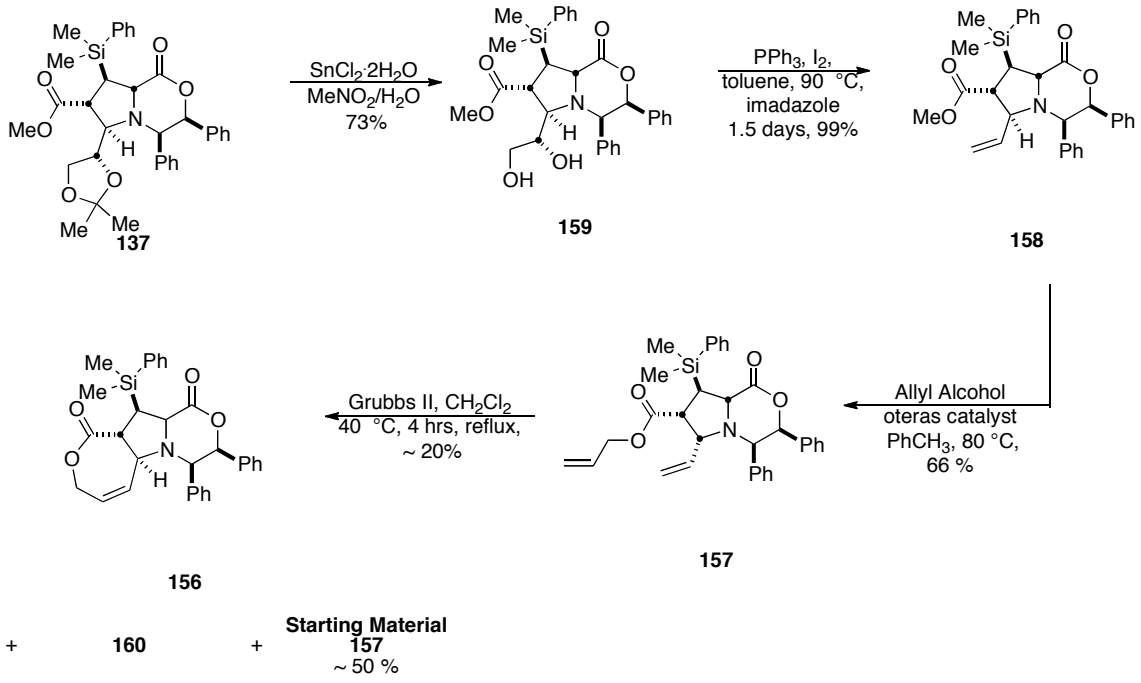
Fleming-Tamao oxidation and epimerization of the silicon derivative **154.** Reduction of the lactone **155** could afford the divinyl ether derivative **154**. Lactone **155** may result from the epoxidation of a double bond and subsequent Lewis acid ring opening of compound **156**. The cyclic lactone **156** could be prepared by metathesis of the terminal olefins located on compound **157**. Addition of the allyl group may originate from transesterification of compound **158** and allyl alcohol. Deprotection of the acetonide and elimination of the diol from compound **137** may prepare compound **158**.



Scheme 4.2. Retrosynthetic approach to oxepin ring.

4.2.1 Metathesis Approach.

Compound **158** was obtained in three steps (Scheme 4.3). Step one included deprotection of the acetonides in the presence of $SnCl_2 \cdot 2H_2O$ followed by formation of the terminal olefin **158** with I_2 and Tributylphosphine at 80 °C. Transesterification occurred with Otera's catalyst and allyl alcohol at 90 °C in a pressure tube which gave the metathesis precursor **157**. Compound **157** was subject to ring closing metathesis to give the desired product **156.**

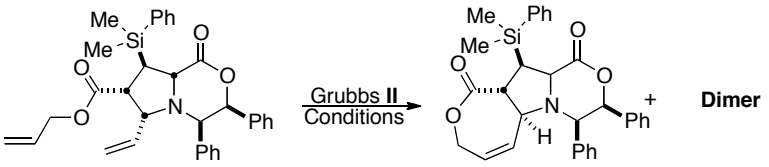


Scheme 4.3. Metathesis Approach.

Optimization of the ring closing metathesis has proven to be extremely challenging (Table 4.1). Initial experimentation with the Grubbs second-generation catalyst was focused on forcing the reaction to completion in the microwave as well as refluxing in CH_2Cl_2 (entry 1 and 3). Numerous reaction conditions were attempted and experimentation showed that concentrating the reaction greater than 0.09 M afforded a

mixture of compounds by TLC. However, 20% of the desired product **156** as well as 30% of the starting material **157** and a minimal amount of dimer was recovered. Furthermore, diluting the reaction more than 0.00055 M resulted in no reaction. Even though the reaction seemed to be irreproducible, focus was turned to the introduction of the DKP **161**.

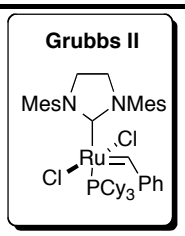
Table 4.1. Metathesis Attempts.



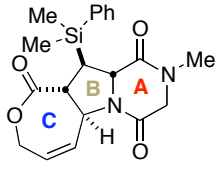
157 **156** **160**

Microwave

Entry	*Temp*	*Concentration*	*Time*	*Results*
1	40°C - 150°C	0.09M - 0.00055 M	5min - 8.5hr	Results vary
		Reflux		
2	40°C	0.0011M	4 days	**157** + **156** + **160**
3	98°C	0.00055 M	-	No Rxn



One possible explanation for this incomplete reaction could be due to the steric interactions of the diphenyl moieties located on the glycine template with the bulky Grubbs catalyst.



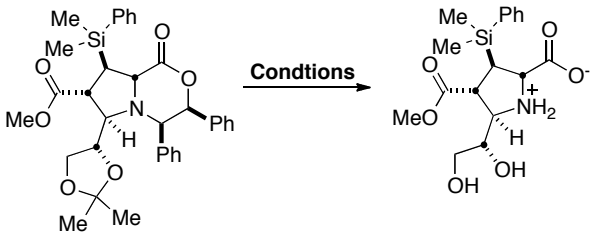
161

Figure 4.1

To test this hypothesis, the construction of the DKP **161** should occur before the metathesis reaction that affords the seven membered lactone ring labeled C (Figure 4.1).

The synthesis of the DKP **161** began with deprotection of the lactone template **137** Table 4.2. The reduction of the template in the presence of 10% Pd/C and $Pd(OH)_2$, entries 1 through 4, was sluggish and took approximately 1.5 days for the reaction to run to completion. Conversely, 0.8 eq of $PdCl_2$ in the presence of absolute ethanol and hydrogen at 1 atm provided the reduced product in 3 hours seen in entry 6. The reduced product was first taken on crude and the secondary amine was protected with FmocOsu and a saturated solution of aqueous sodium bicarbonate. The protection step proved to be quite sluggish as well and afforded only trace amounts of the protected amine seen in entry 6. The zwitterion **162** can be isolated in 82% yield seen in entry 7. Utilizing 2 equivalents of acetyl chloride seen in entry 8 also allowed for the reduction of the template in 3 hours. The *in situ* generation of 2 Eq of HCl is extremely important for this reaction to proceed in a timely manner. The yield of the reduction can be quite consistent if pure acetyl chloride is used. When a fresh bottle of acetyl chloride is utilized for the reaction the yield can be reported consistently at 75% yield seen in entry 8.

Table 4.2. Deprotection of Template.



137 **162**

Entry	***Condtions***	***Result***
1	10% Pd/C (45 % by weight)), H_2 80psi, 3 days	reduction more than 3 days
2	10% Pd/C, H_2 (1 atm) EtOH : EtOAc 1:1	1.5 days reduction
3	1.$Pd(OH)_2$, EtOH, H_2 (1 Atm)	1 week sluggish
4	$Pd(OH)_2$ EtOH, H_2 (1 atm) MeOH: EtOAc 1:1	1.5 days reduction
5	1. $PdCl_2$ (.5eq) 9hrs, EtOH, H_2 (1 atm) 2. FmocOsu, $NaHCO_3/CH_2Cl_2$, 12hrs	reduction 9hrs Protection Sluggish
6	1. $PdCl_2$ (.8eq) 3hrs, EtOH, H_2 (1 atm) 2. FmocOsu, $NaHCO_3/CH_2Cl_2$, 12hrs	reduction 3hrs Protection Sluggish
7	$PdCl_2$, H_2 (1 atm) EtOH	**82 %**
8	1. 10% Pd/C 10mg, 2 Eq Acetyl Chloride EtOH, H_2 (1 atm), 12 hrs	**75 %**

The crystal structure of the zwitterion **162** confirms that the dipolarophile **136** approaches the *E*-azomethine ylide in an *endo*-fashion from face opposite the phenyl moieties, also known as *beta.* (Figure 4.2**)** The crystal structure is further supported by g-

COSY, 1D and 2D NOE, H^1-NMR, Si^{29}-NMR, mass spectroscopy, HSQC, and HMBC experiments (seen in the experimental). In three steps from commercially available starting material the dihydropyrrole **162** of (*ent*)-MPC1001 (**67**) can be constructed with three of the four necessary stereocenters. However, in order to have both correct regio and stereochemistry of the (*ent*)-MPC1001 (**67**), the carbon labeled C_1 of compound **162** needs to be epimerized.

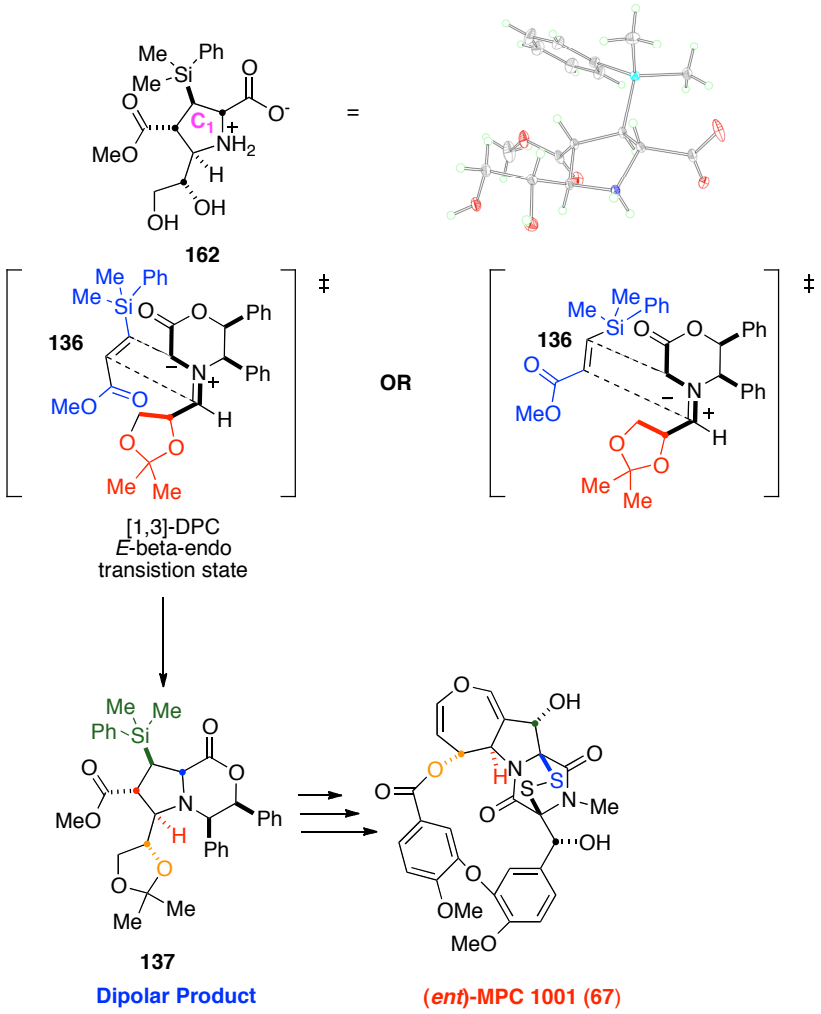
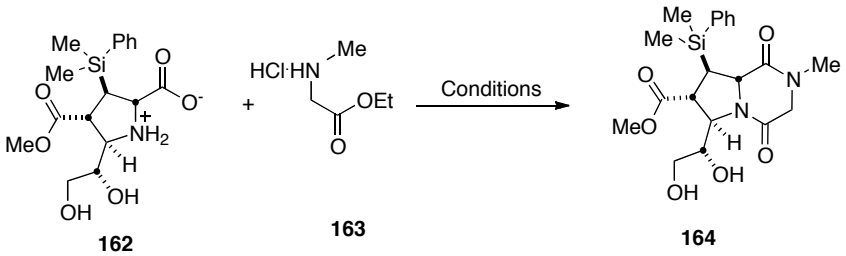


Figure 4.2. Explanation of stereochemistry.

With amino acid **162** in hand, the DKP was installed. Numerous coupling reagents were tested, but BOPCl was the only reagent that provided the desired compound **164** (Table 4.3).

Table 4.3. Deprotection of Template.

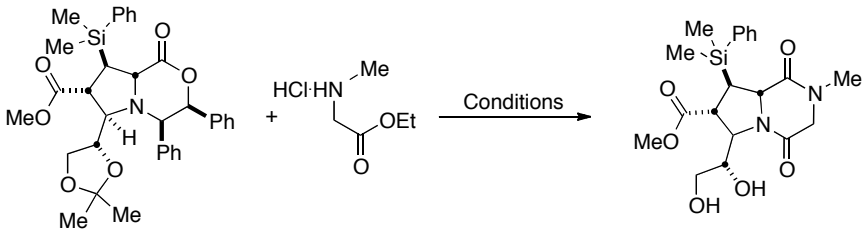


162 **163** **164**

Entry	*Condtions*	*Result*
1	BOPCl,NEt_3,CH_3CN,	60 %
2	EDC·HCl,HoBT, *i*-Pr_2NEt, CH_2Cl_2	No Rxn
3	HATU, *i*-Pr_2NEt, CH_2Cl_2	No RXN
4	HATU,HoBT, *i*-Pr_2NEt, CH_2Cl_2	No RXN

It was also observed that the dipole product **137** could be directly coupled with sarcosine ethyl ester hydrochloride **163** (Table 4.4). Compound **137** was first subjected to reduction of the lactone template with 0.8 eq of $PdCl_2$ in the presence of absolute ethanol and hydrogen under 1 atmosphere followed by a BOPCl amino acid coupling with sarcosine ethyl ester hydrochloride **163**. The reaction was stirred for 2 days and then was treated with 1 N HCl for one hour, which afforded the coupled product **164** in 40% yield. EDCI was also utilized as an amino acid coupling reagent, but the reaction was discarded due to a complex mixture of undesired compounds.

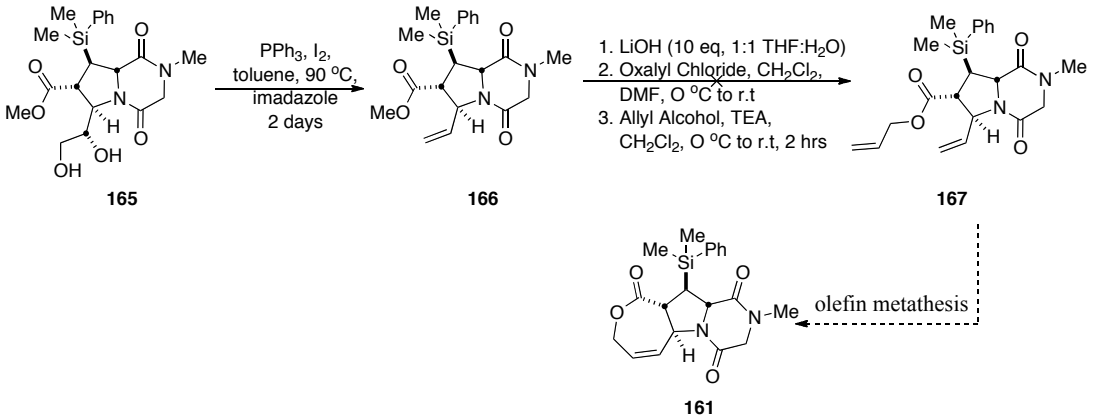
Table 4.4. One pot coupling.



137 **163** **164**

Conditions	Result
1. $PdCl_2$ H_2 (1 atm) 2. BopCl,NEt_3,CH_3CN, then 1 M HCl	40%
1. $PdCl_2$, EtOH, H_2 (1atm) 2. EDCI, DMAP, *i*-Pr_2NEt, CH_3CN	No reaction

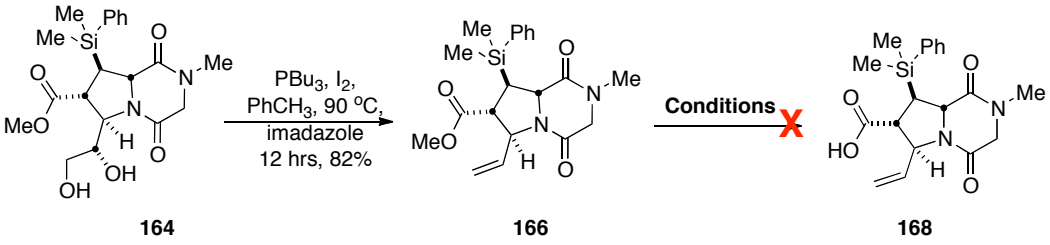
With compound **165** in hand, the modified Corey-Winter olefination occurred with a clean spot to spot conversion with the previously attempted condition (Scheme 4.4). However, one of the main problems of this reaction is the co-spotting of the triphenylphosine oxide with product **166**. Due to this problem, formation of the acid was attempted with refluxing 10 equiv. of LiOH in a 1:1 water : THF mixture for 12 hours, followed by formation of the acid chloride and the addition of allyl alcohol. Unfortunately, the newly formed ester **167** or any other identifiable compound was unable to be isolated.



Scheme 4.4. Attempted synthesis of compound **161**.

Changing from Ph_3P to Bu_3P allowed for the isolation of the pure product **166** in 82% yield (Table 4.5). Next, an attempt was made to isolate the free carboxylic acid **168** at room temperature, as well as at 40 °C in a 1:1 water : THF mixture in the presence of 10 equiv. of LiOH and was unsuccessful resulting in decomposition. Unfortunately, the isolation of the newly formed acid **168** or any other identifiable compound was unsuccessful.

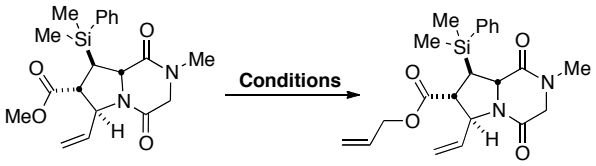
Table 4.5. Attempts to form acid **168**.



Entry	*Condtions*	*Result*
1.	LiOH (10 eq) 1:1 ($THF:H_2O$) rt	Decomp
2.	LiOH (10 eq) 1:1 ($THF:H_2O$) 40 °C	Decomp

Concurrently, The transformation of the methyl **166** to allyl ester **167** has proven to be difficult (Table 4.6.) First, a three step sequence was attempted to isolate the allyl ester **167**. Formation of the acid was attempted with refluxing 10 eq of LiOH in a 1:1 water:THF mixture for 12 hours, followed by formation of the acid chloride and the addition of allyl alcohol. Next, deprotonation of allyl alcohol with NaH (60% in mineral oil) at 0 °C followed by warming to room temperature and the addition of the methyl ester **166** resulted in decomposition. Utilizing 1eq of Otera's catalyst **169** in toluene at 80 °C after 4 days resulted in the formation of the allyl ester **167** in 95 % yield as seen in entry 4.

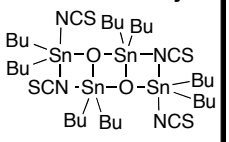
Table 4.6. Transesterification.



166 **167**

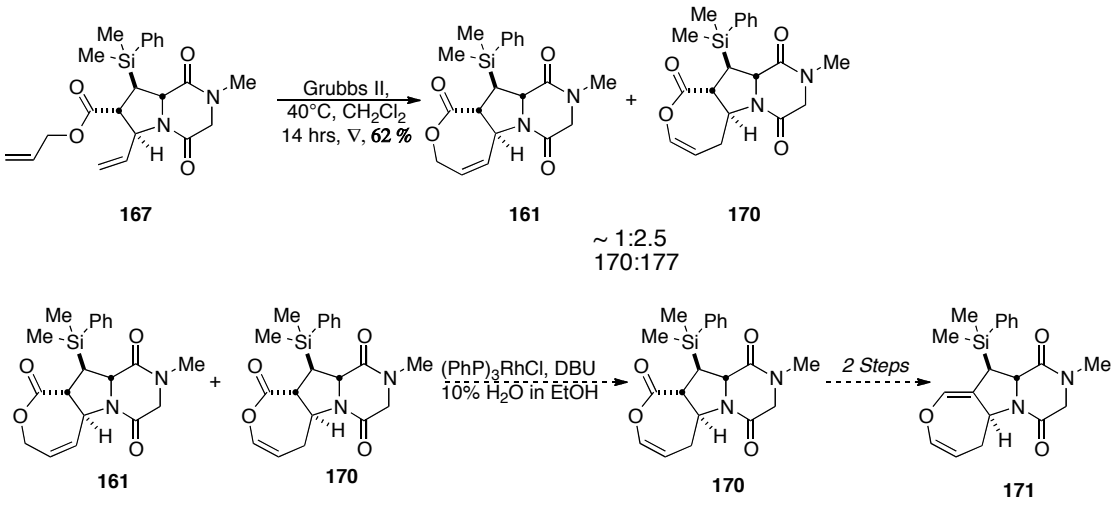
Entry	*Condtions*	*Result*
1	1. LiOH (10 eq, 1:1 THF:H_2O) 2. Oxalyl Chloride, CH_2Cl_2, DMF, 0 °C to r.t 3. Allyl Alcohol, TEA, CH_2Cl_2, 0 °C to r.t, 2 hrs	Decomp
2	Allyl Alcohol, NaH (60% Mineral oil) $NaSO_3$, THF, 0 °C	Decomp
3	Allyl Alcohol (5 eq), uteras catalyst (1 eq), $PhCH_3$, 80 °C, 3 days	S.M. and trace product
4	Allyl Alcohol (50 eq) uteras catalyst (1 eq) $PhCH_3$, 80 °C, 4 days	**> 95 %**

Otera's Catalyst



169

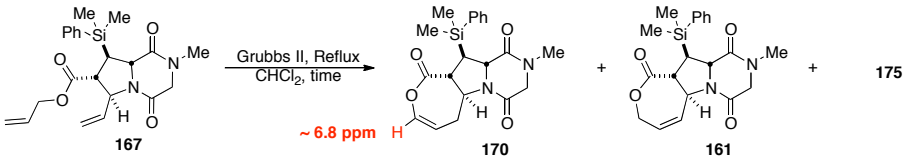
With compound **167** in hand, the first attempt at the olefin metathesis proceeded with trace products (**161** and **170**) and recovered starting material (Scheme 4.5). The reaction is irreproducible under any conditions or catalyst (Grubbs I , Grubbs II , and Hoveda-Grubbs 2nd generation catalyst) that have been attempted. *However, after a thorough degassing of CH_2Cl_2 with argon multiple times, the metathesis with 9 mol% of the Grubbs 2nd catalyst at reflux proceeded* ***ONCE*** *in a 62% yield with a 2.5:1 ratio of isomerizes* on a 1mg scale. The major isomer is believed to be the thermodynamic product **170** while the minor isomer **161** is believed to be the kinetic product. The remaining mixture of 0.3 mg was subjected to isomerization conditions with Wilkinson Catalyst in the presence of DBU, but due to the minimal amount of starting material, no identifiable compound was isolated.



Scheme 4.5. Synthesis of the 7-5-6 core

Table 4.7 illustrates my efforts toward optimizing the RCM of compound **167**. Varying the catalyst, concentration, time, solvent, or amount of catalyst loading resulted in an irreproducible reaction. However, freeze-pump-thaw-degas of the solvent allows for the reaction to be initiated, but the reaction has gone to completion only once.

Table 4.7. Efforts towards the optimizing the RCM of compound **167**.



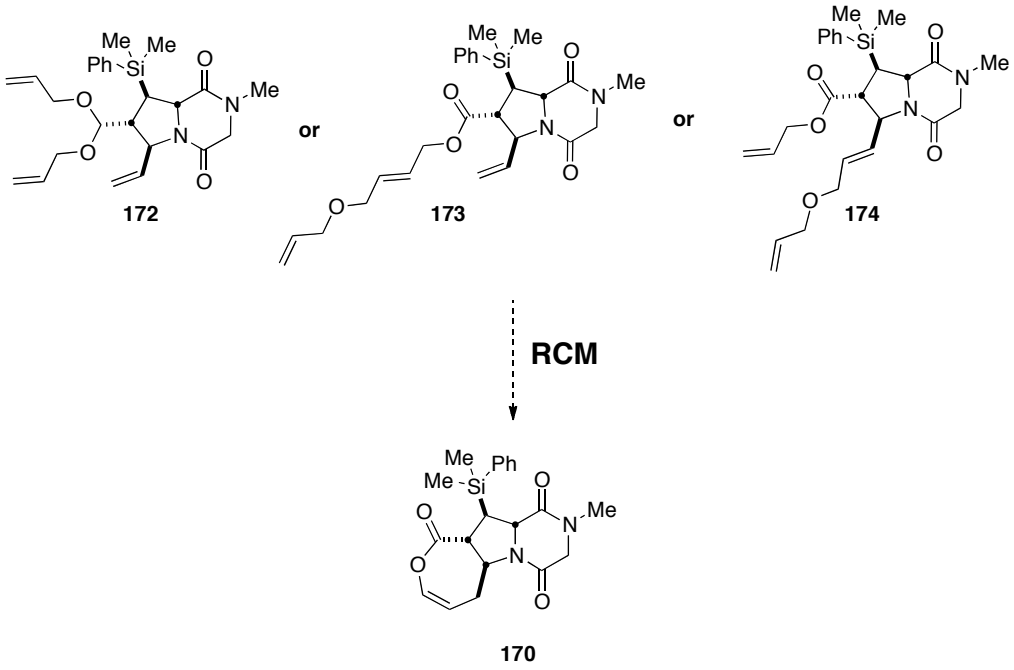
need to fully characterize 170 and 161 to confirm I have made them to move forward

Conditions

Scale	*Note*	*Catalyst*	*Concentration*	*Time*	*Mol % of Catalyst*	*Result*
4 mg	Na	My bottle Grubbs II	.0008*M*	24 hrs	10 Mol %	S.M.
10 mg	Freeze-pump-thaw-degass	My bottle Grubbs II	.04*M*	20 hrs	10 Mol %	S.M.
2.2 mg	added $Ti(O\text{-}i\text{-}Pr)_4$	My bottle Grubbs II	.0008*M*	overnite	30 Mol %	S.M.
5 mg	Na	Grubbs hoveyda second	.04*M*	24 hrs	20 Mol %	S.M.
4 mg	Na	Wood Group Grubbs II	.04*M*	24 hrs	10 Mol %	S.M.
2 mg	Freeze-pump-thaw-degass	Wood Group Grubbs II	.0008*M*	20 hrs	22 Mol %	1:1:0.3 **170**:**167**:**161** by nmr
10 mg	Freeze-pump-thaw-degass	Wood Group Grubbs II	.0008*M*	17 hrs	50 Mol %	Small amount of **170** Mostly **167**
5 mg	Freeze-pump-thaw-degass	Wood Group Brubbs II	.004*M*	overnite	50 Mol %	1:3 **170**:**167** by nmr

Starting material cospots with products A and B. So this makes charazation very very very hard. See doublet at 6.8ppm so I think 177 is the major product, but I cannot say for sure.

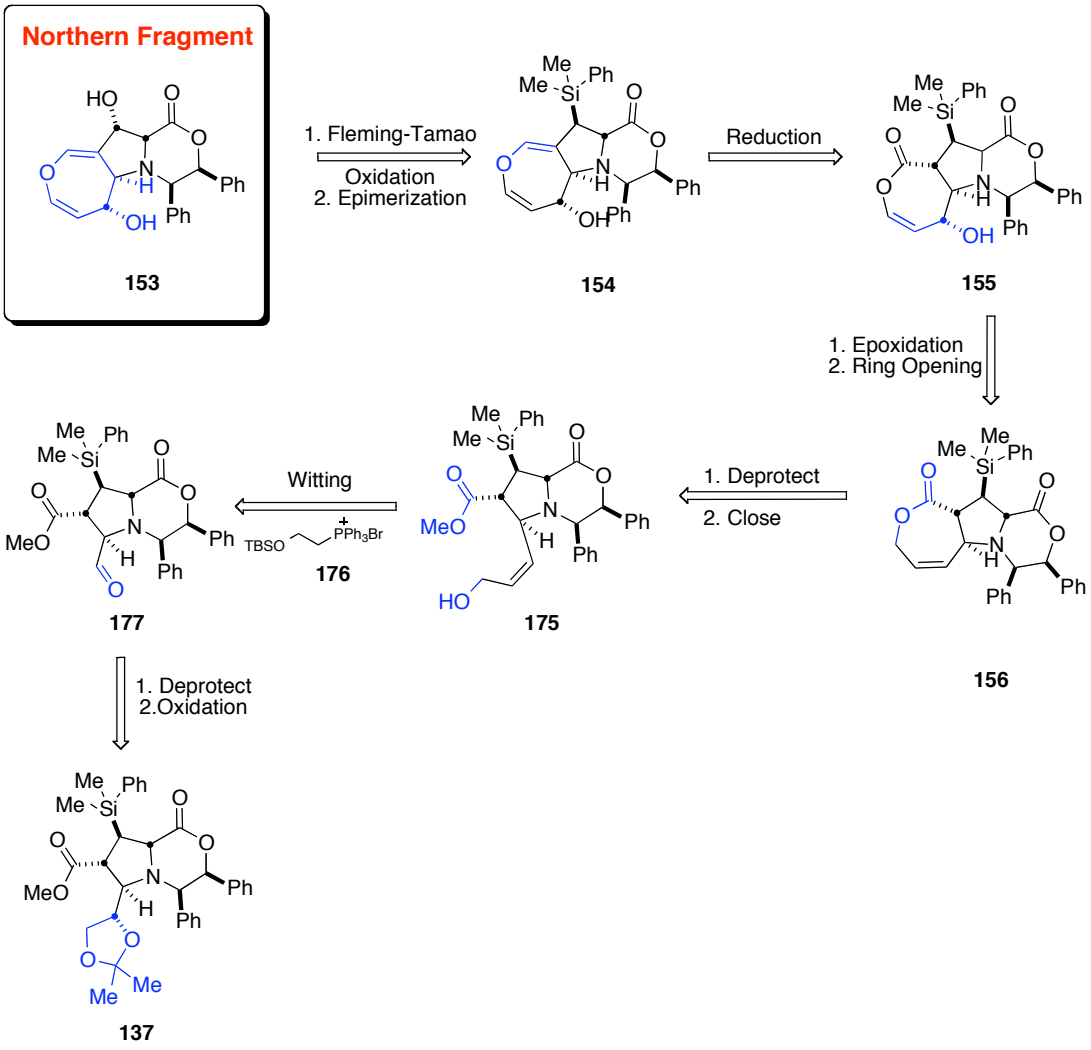
Future experimentation on this route could be focused on making the divinyl acetyl **172** which may allow for the RCM to occur (Scheme 4.6). Also, there is a possibility of utilizing a relay ring closing metathesis with compounds **173** or **174**.



Scheme 4.6. Future experimentation.

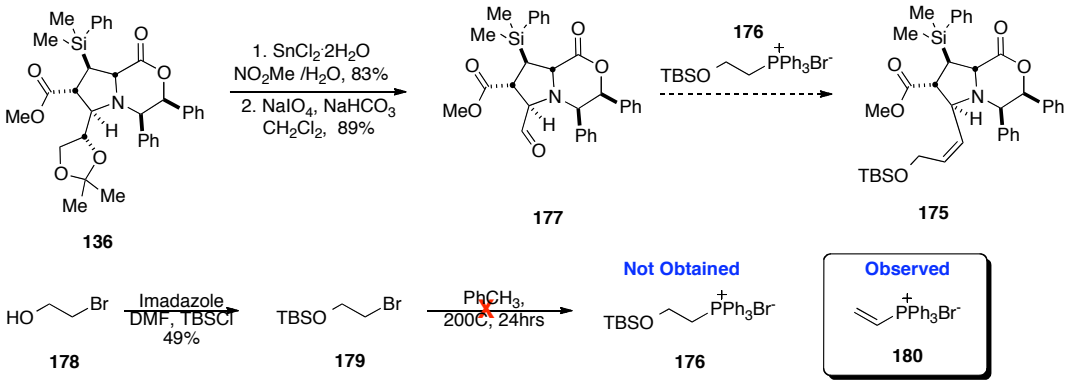
4.2.2 Yamaguchi Macrolactonization Approach.

Since the RCM proved problematic, a new approach was necessary to access the oxepin ring. The main focal point of this retrosynthesis was to access a compound that contains a terminal hydroxyl group that can be cyclized to give a seven membered lactone **156** (Scheme 4.7). The oxepin ring **153** can be accessed from a Fleming-Tamao oxidation and epimerization of the silicon derivative **154**. Reduction of the lactone **155** could afford the divinyl ether derivative **154**. Lactone **155** may result from the epoxidation of a double bond and subsequent Lewis acid ring opening of compound **156**. Compound **156** can result from closure of the primary alcohol onto the ester. A Witting reaction with the protected alcohol **176** could afford compound **156**. The aldehyde **177** can result from deprotection of the acetonide and oxidation of compound **137**.



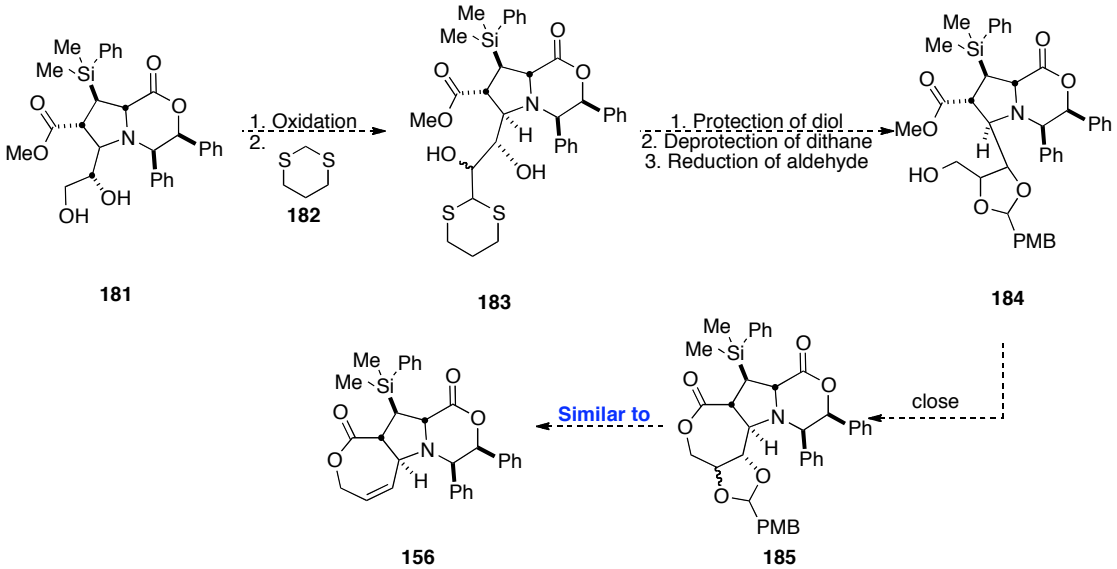
Scheme 4.7. Approach to Compound **153**.

Compound **177** was obtained in two steps. Step one included deprotection of the acetonides in the presence of $SnCl_2 \cdot 2H_2O$, followed by oxidation in the presence of $NaIO_4$ which gave the aldehyde **184** (Scheme 4.8). However, obtaining the Witting reagent **176** could not be realized. The primary hydroxyl group of compound **179** was protected and upon heating in a sealed tube the TBS group readily eliminated to give compound **180**.



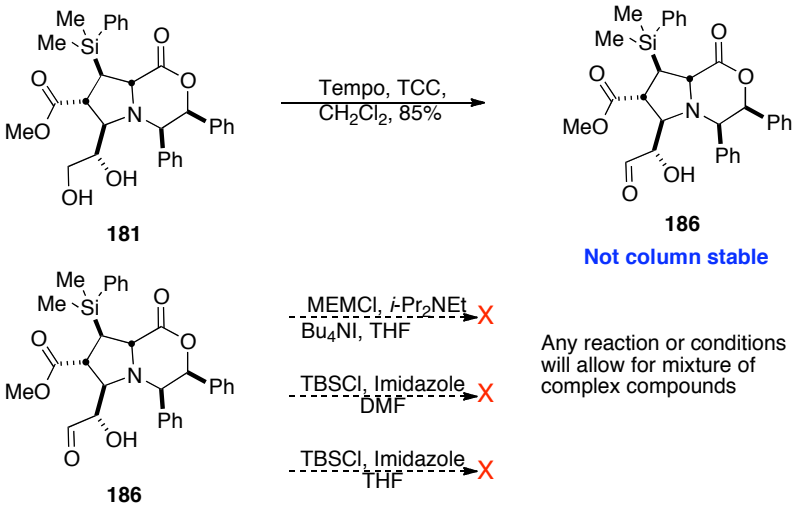
Scheme 4.8. Elimination of TBS Group.

With diol **181** in hand, it was believed that the primary hydroxyl group could be oxidized and reacted with dithiane (**182**) to give compound **183** (Scheme 4.9). Dithiane (**182**) would serve as a one carbon homologation unit. The two free alcohols can be protected, followed by deprotection of the dithiane and reduction which would reveal the primary alcohol **184**. Compound **184** could be closed to the seven membered lactone **185**. This would serve as an alternative route to a compound similar to **156.**



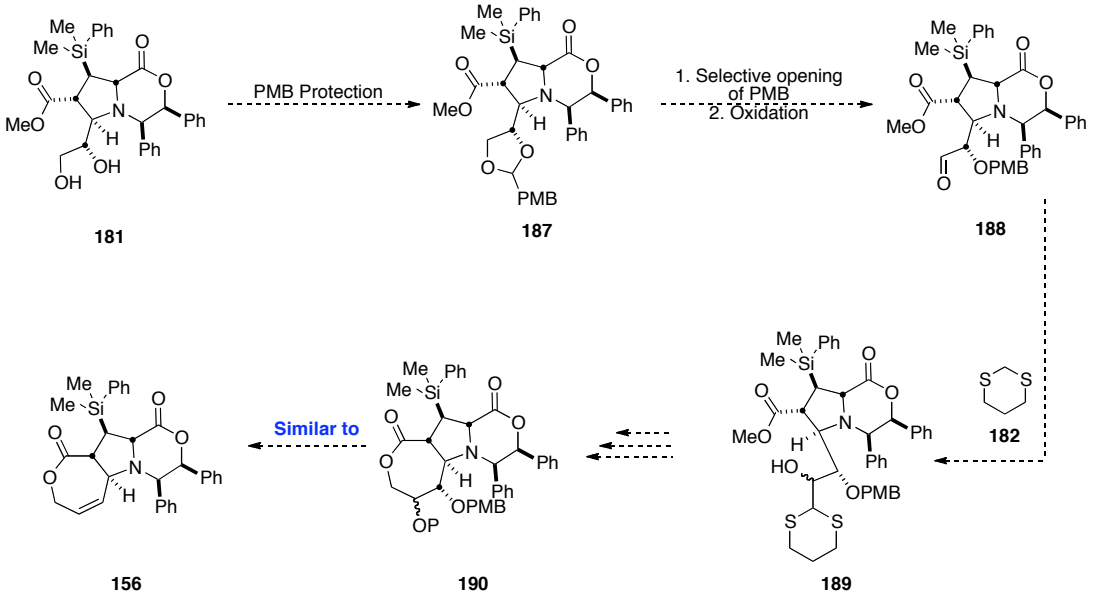
Scheme 4.9. Alternative route **156**.

The diol **181** was easily oxidized to the aldehyde **186** in the presence of TCC and TEMPO with 89% yield (Scheme 4.10). However, protection of the secondary alcohol proved very difficult. A MEM group, as well as a TBS group, were attempted as protecting groups for the secondary alcohol, but compound **186** proved particularly unstable. Any attempts to purify or protect the alcohol resulted in complex mixture of compounds.



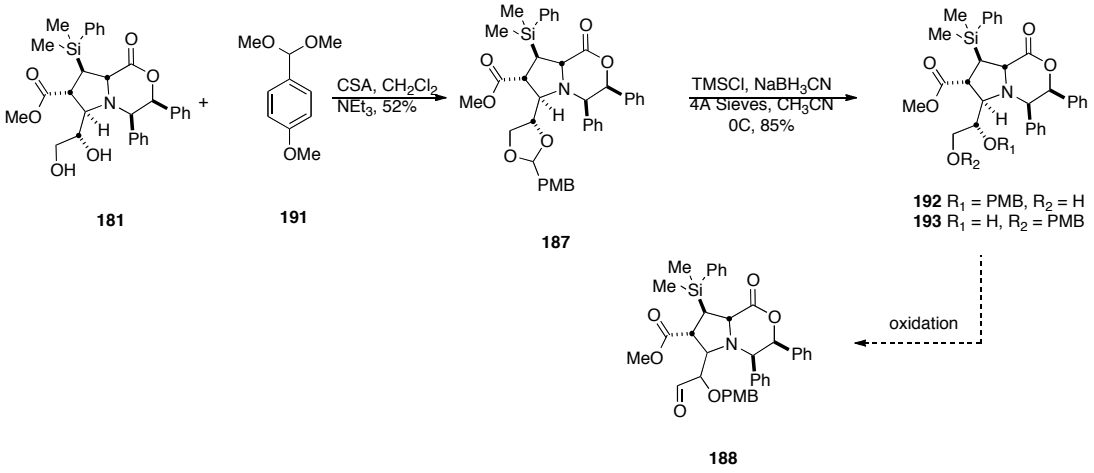
Scheme 4.10. Protection of secondary hydroxyl group.

In lieu of the instability of compound **186,** the diol **181** could be protected first, then oxidized to the aldehyde **188** Scheme 4.11. With the aldehyde **188**, it could be used quickly in the next step with a one carbon homologation with dithiane (**182)** to afford compound **189**.



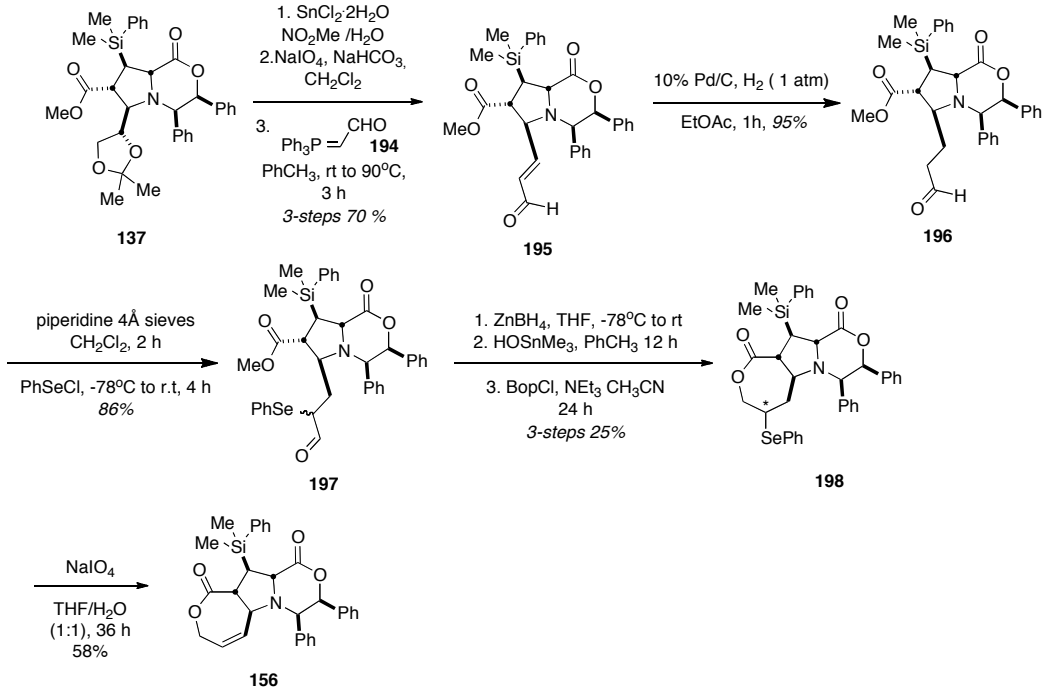
Scheme 4.11. Formation of PMB ether.

The diol **181** was first protected as the PMB ether in a 66 % yield with 13% recovered starting material (Scheme 4.12). The PMB group was then opened to the two protected alcohols with a 85% yield in the presence of TMSCl and sodium cyanoborohydride with a 1 : 1 regioselectivity of compounds **192** and **193.**



Scheme 4.12. Formation of PMB ether and reduction.

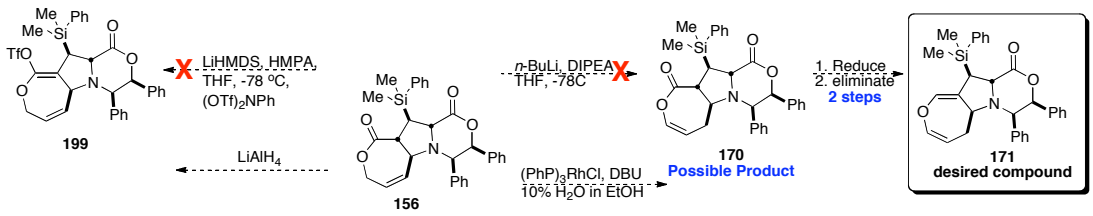
Finally, the lactone ring can be made in 9 steps from the dipole product **137**. Deprotection of the acetonides in the presence of $SnCl_2 \cdot 2H_2O$, followed by formation of the aldehyde by $NaIO_4$ and witting olefination with (triphenylphosphoranyidene) acetaldehyde (**194**) gave the α,β- unsaturated aldehyde **195** in 70% purity over the three steps (Scheme 4.13). Reduction of the double bond with 10% Pd/C at 1 atm of H_2 followed by formation of the imine and installation of selenium gave compound **196** in 85% purity. Aldehyde **196** can be reduced with $ZnBH_4$ at -78°C to give alcohol **197** followed by formation of the acid with Me_3SnOH. The alcohol was treated with BopCl and NEt_3 to give the lactone **198** in a 25% yield followed by elimination of the selenium with $NaIO_4$ to give the olefin **156.**



Scheme 4.13. Synthesis of lactone ring.

With the degree of unsaturation in place, it was thought that the double bond could be isomerized with *n*-BuLi followed by reduction of the lactone, and elimination

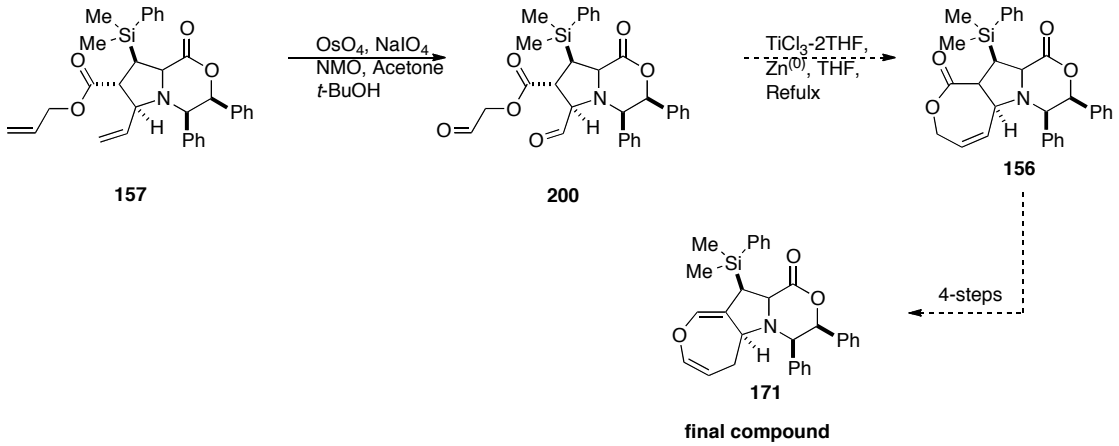
would give the oxepin ring **171** (Scheme 4.14). However, primary experimentation resulted in no reaction. Isomerization with *n*-BuLi as well as formation of the vinyl tiflate with N-Phenyl triflamide in the presence of LiHMDS resulted in no reaction and possible decomposition. Quenching the reaction with D_2O resulted in no incorporation of deuterium. Therefore, it is hypothesized that either the base is too bulky or the proton alpha to the ester is not antiperiplanar to the pie system of the carbonyl. Future experimentation will subject olefin **156** to isomerization conditions with Wilkinson's Catalyst in the presence of DBU as well as reduction of the lactone with $LiAlH_4$ to attempt to afford the lactone **171**.



Scheme 4.13. Late stage manipulations to oxepin ring.

4.3.3 McMurry Approach.

Another concurrent approach to the oxepin ring is via a McMurry cyclization (Scheme 4.14). Treatment with OsO_4 and $NaIO_4$ in the presence of NMO gave the dialdehyde **200**. With the dialdehyde **200** in hand, closure of the ring may be possible and in another 4 steps completion of the oxepin ring **171**. That remains to be accomplished.

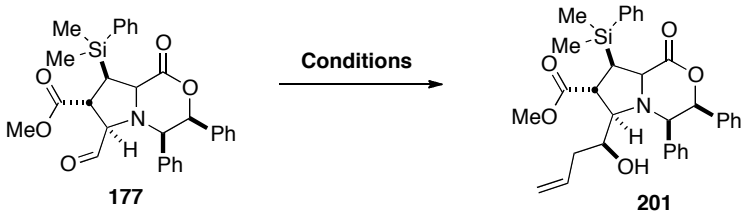


Scheme 4.14. McMurry Approach.

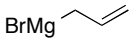
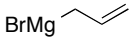
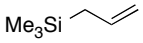
4.4 Installation of the Secondary Alcohol.

One problem that still needs to be addressed is the installation of the secondary OH group on the oxepin ring. In all the synthetic approaches, the secondary alcohol is brought in from the aldehyde **116** that is utilized in the cycloaddition. However, the functionality is destroyed and would have to be put in again at a later stage. Therefore, synthetic work has been done to allow for the installation of the secondary alcohol with aldehyde **177** (Table 4.8).

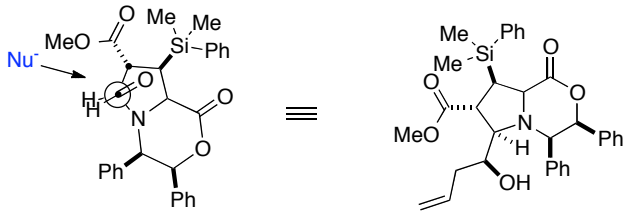
Table 4.8. Sakurali Allylation.



177 201

Nucelophile	Solvent	Lewis Acid	Temp	Result
 **202**	CH_2Cl_2	$Cu(OTf)_2$	rt	No RXN
 **203**	THF	N/a	-78 °C	No RXN
 + Zn	THF	N/a	-78 °C	No RXN
 **204**	CH_2Cl_2	$Bf_3{\cdot}OEt_2$	-78 °C to rt	79%

The selectivity has been described by the open transition state (Figure 6). The carbonyl is activated by the Lewis acid, followed by addition of the incoming electrophile. The possible explanation for the observed stereochemistry can be seen below.

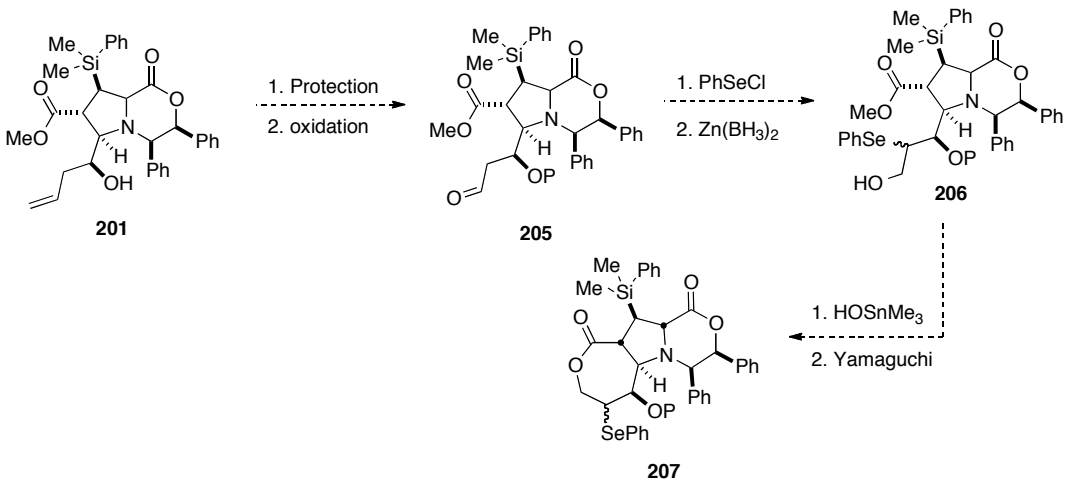


177 201

Figure 4.2. Transition state analysis.

Once the alcohol has been protected, the terminal olefin can be oxidized to the aldehyde **205** followed by the installation of selenium and reduction with $Zn(BH_4)$ to

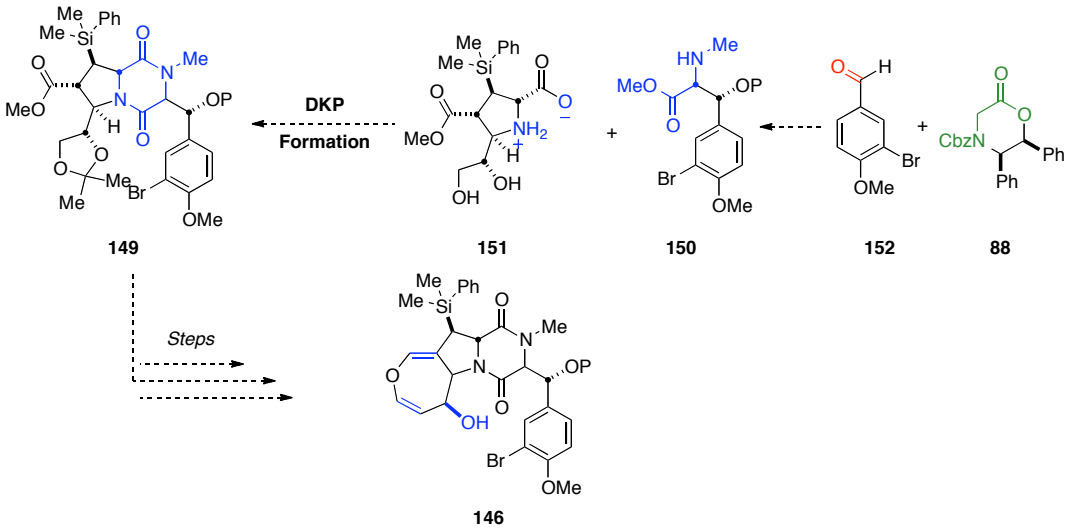
give the alcohol **206** (Scheme 4.15). The ester **206** can be hydrolyzed to the acid and cyclization can occur to give the lactone **207**. Compound **207** is now prepared for completion of the oxepin ring.



Scheme 4.15. Formation of Lactone **207**.

4.5 Synthetic Progress Toward the Diketopiperazine.

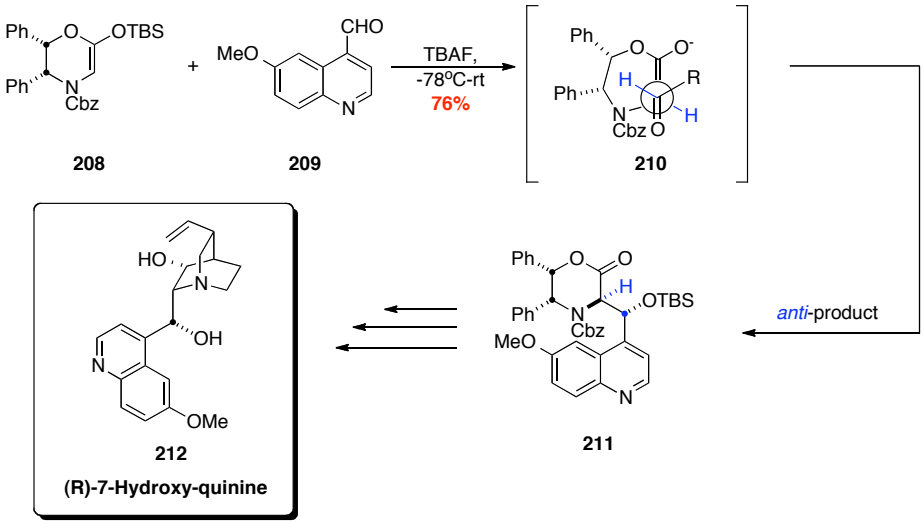
Chiral β-hydroxyl-α-amino acid **150** is another portion of MPC 1001 that was addressed. This amino acid should be coupled to zwitterions **151** and produce the DKP **149**. Once the DKP is formed, compound **149** can be elaborated into the oxepin ring **146** (Scheme 4.16).



Scheme 4.16. Formation of DKP.

4.5.1 Preparation of a Chiral β-hydroxyl-α-amino Acid Analogue.

Previously, in the Williams research group a TBAF-promoted asymmetric aldol reaction with silyl enol ether **208** was utilized to establish the C8 and C9 stereocenters (R)-7-Hydroxyl-quinine **212** (Scheme 4.17). The *anti*-product **211** was isolated in a 76% yield and an excellent diastereoselectivty (>30:1).[62]



Scheme 4.17. Previous work done in Williams group.

Once fluoride is introduced to the reaction mixture the OTBS group is removed. The removal of the TBS group then generates a carboxylate ion followed by addition into the aldehyde **209,** affording the product **211 (**Figure 4.3). This allows for two main contributing transition states that will dictate the outcome of the reaction. One transition state **213** has the carboxylate ion *anti* to the quinoline moiety, while the other transition state **214** puts the carboxylate ion *syn* to the quinoline group. The transition state **214** is unfavored due to steric interaction between the lactone ring and the quinine moiety; therefore, favoring the less sterically demanding transition state **213** between the carboxylate ion, and the quinoline moiety favoring the *anti*-product as seen above.

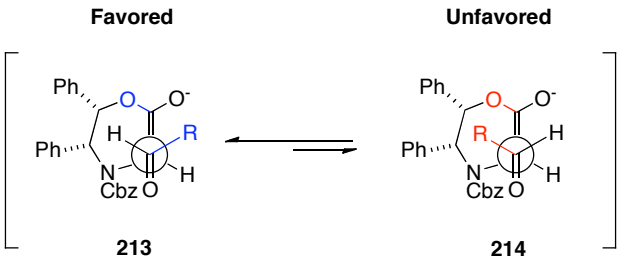
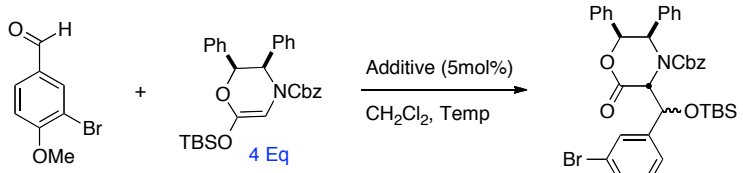


Figure 4.3. Transition state analyses.

The TBAF conditions were utilized as described above. Upon attempting the exact conditions with silyl enol ether **208** and aldehyde **152**, the silyl enol ether **208** was hydrolyzed. There are three possible reasons for this result: 1.) Hydrolysis of the silyl enol ether was much faster than the addition to the aldehyde 2.) It is quite possible that product could be formed, but the product could then be converted back to starting material by a retro-aldol reaction 3.) The bottle of 1 M TBAF in THF contains 5% H_2O resulting in the observed ether **208** hydrolysis. Eliminating one of these possibilities, the reaction was run under anhydrous conditions.

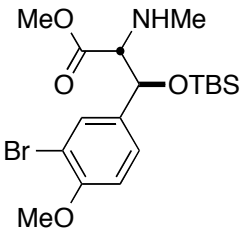
The Mukaiyama aldol with silane **208** and aldehyde **152** proved to be successful (Table 4.9). Entry two proved the best results to afford product **213** with a quantitative yield. The regioselecvity can be described by the previous argument seen in Figure 4.3 (Table 4.9).

Table 4.9. Mukaiyama aldol conditions.



152 **208** **213**

Entry	Temp	Eq Additive	Eq Aldehyde	Result
1	r.t and 0C	$Sc(Otf)_2$	1	30 minutes at r.t 56% 2 hrs at 0C 60%
2	r.t	$Cu(Otf)_2$	1	$Cu(Otf)_3$ 75 %
3	-78C to -30C to 0C	$Sc(Otf)_2$	1	$Sc(Otf)_3$ 60%

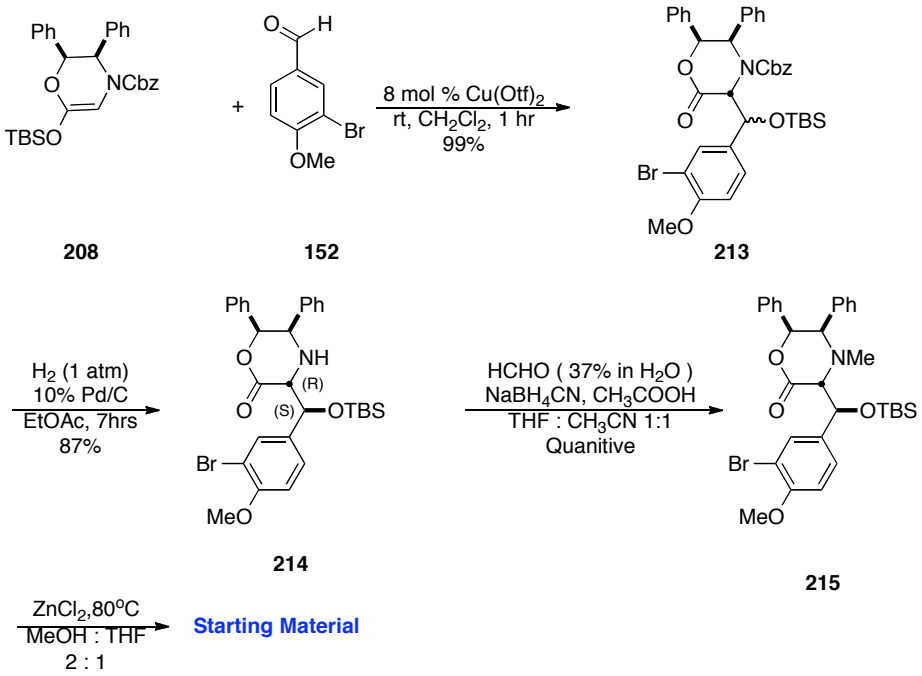


214

Figure 4.4

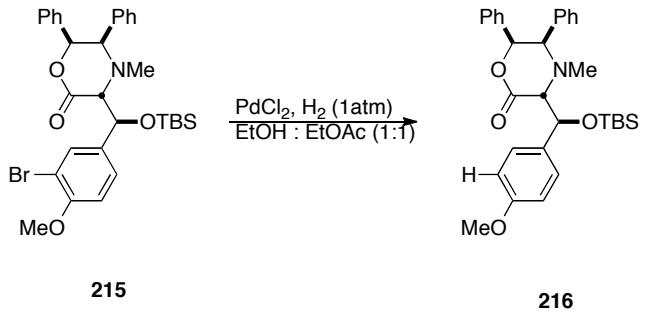
With the coupled product in hand, focus can now commence on the synthesis of the unnatural amino acid **214** seen in figure 9**.** After some experimentation, we found that dropwise addition of silylenol ether **208** to a mixture of aldehyde **152** and 8 mol % $Cu(OTf)_2$ in CH_2Cl_2 provided compound **213** in a 99% yield (Scheme 4.16). Removal of the Cbz protecting group in

the presence of H_2 (1atm) and 10% Pd/C afforded the secondary amine **214** in 87% yield. Reductive amination of compound **214** resulted in a clean conversion to the tertiary amine **215** in a quantitative yield. Unfortunately, opening of lactone **215** under $ZnCl_2$ and methanol THF mixture (2:1) resulted in recovered starting material over an extended period of time (one week) at 80°C.



Scheme 4.16. Progress toward unnatural amino acid **26**.

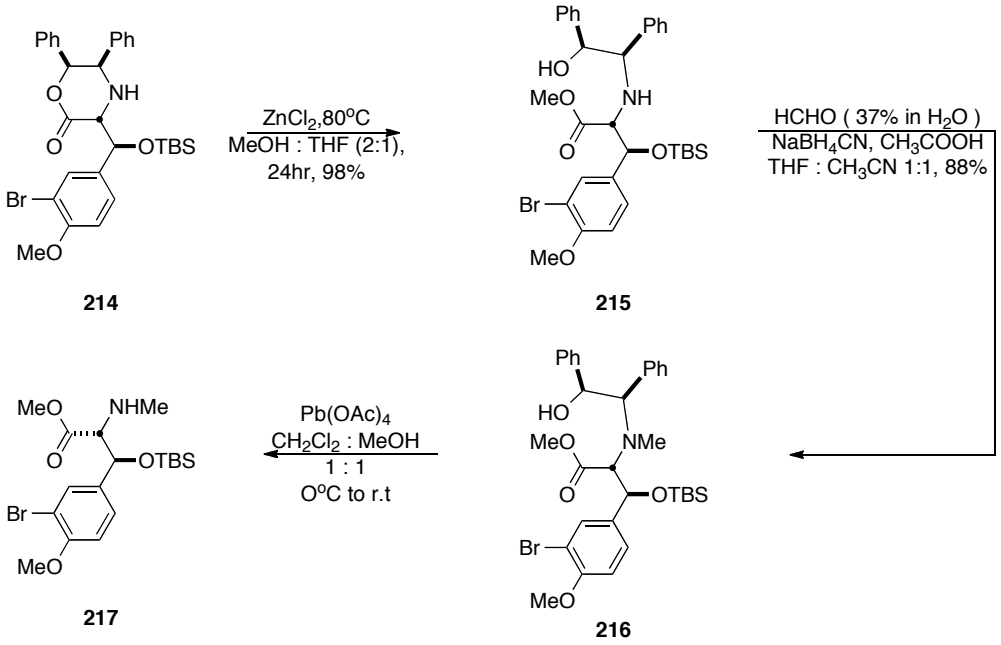
Catalytic hydrogenation was explored with $PdCl_2$ and H_2 at 1 atm. This proved to be unsuccessful due to the loss of the aromatic bromide seen in compound **216** (Scheme 4.17).



215 **216**

Scheme 4.17. Hydrogenation Attempt.

Finally, Lewis acid mediated ring opening of compound **214** in the presence of $ZnCl_2$ followed by reductive amination and template removal under $Pb(OAc)_4$ resulted in the unnatural amino acid **217** (Scheme 4.18**).**

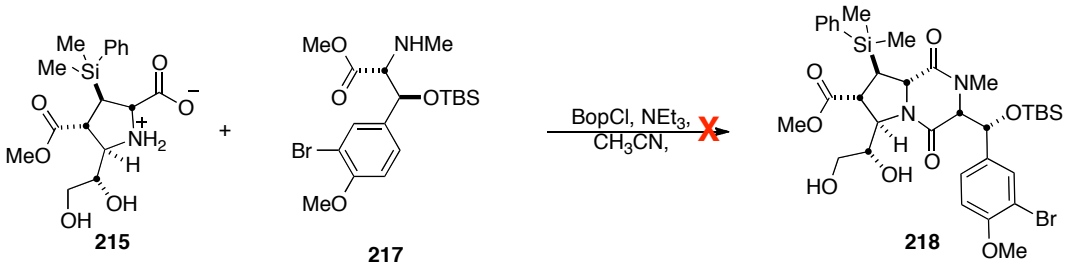


214 **215** **217** **216**

Scheme 4.18. Synthesis of Amino Acid **217**.

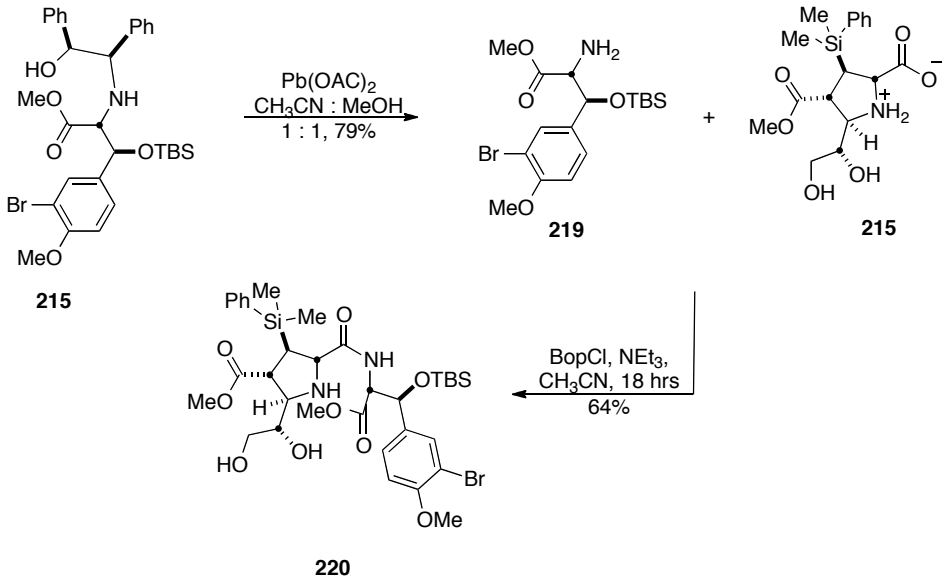
4.5.2 Synthetic Attempts to Form the DKP.

With the unnatural amino acid in hand, compound **217** was attempted to be coupled with the zwitterion **151** under previously optimized conditions with BOPCl and sarocine ethyl ester **163** (Scheme 4.19). Unfortunately, only starting material was observed and no reaction occurred.



Scheme 4.19. Formation of DKP.

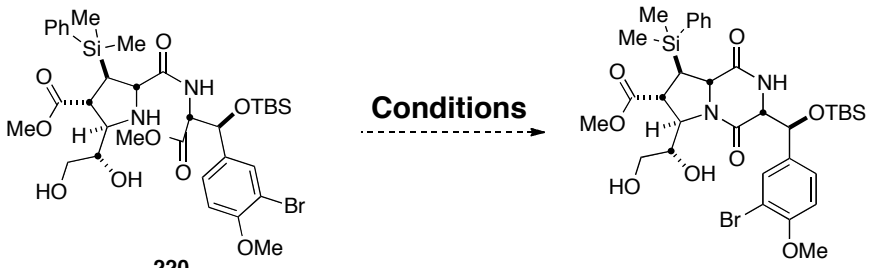
Next, the primary amine was synthesized from methyl ester **215 (**Scheme 4.20). The template was removed with $Pb(OAc)_4$ which provided unnatural amino acid **219**. Compound **219** was coupled with **215** with BOPCl in acetonitrile and NEt_3 to afford the amide **220** in 70% yield.



Scheme 4.20. Formation of peptide bond.

However, closure to the diketopiperazine did not occur (Table 4.10). Numerous conditions were attempted as illustrated in table 21, but only starting material was recovered.

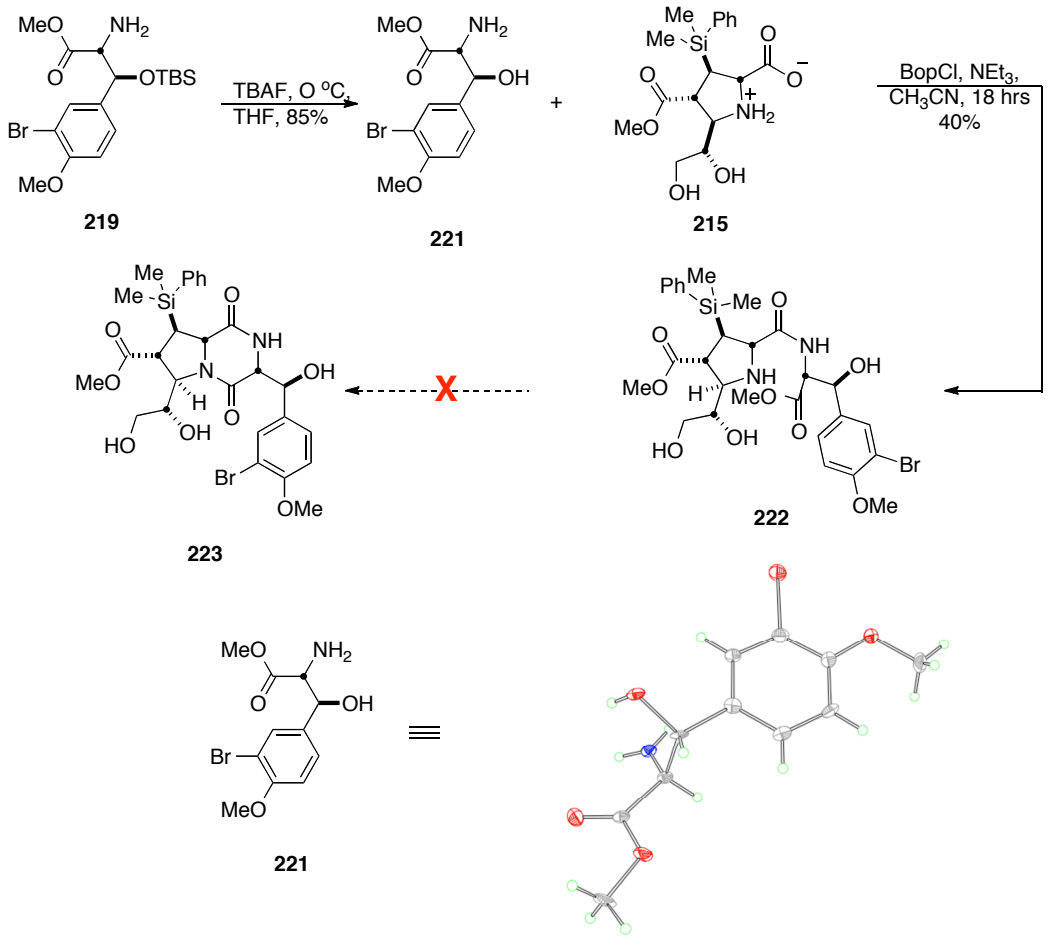
Table 4.10. Attempts towards closure of the DKP.



220 **221**

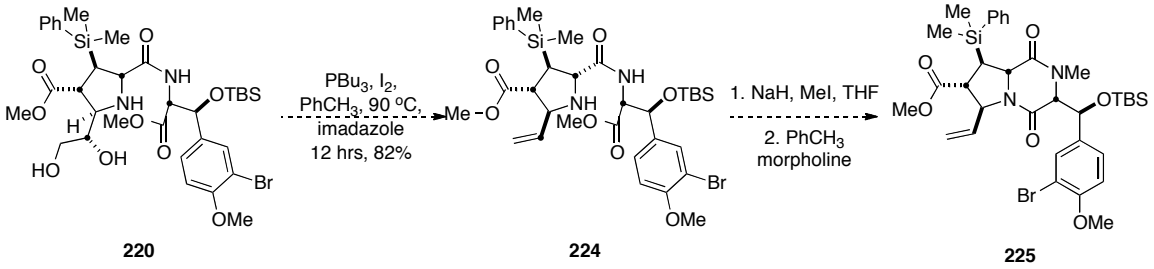
Entry	Temp	Time	Solvent	Additive	Result
1.	90 °C	9 hrs	$PhCH_3$	N/A	S.M.
2.	90 °C	3 days	$PhCH_3$	morpholine	S.M.
3.	90 °C	3 days	CH_3CN	morpholine	S.M.
4.	90 °C Microwave	20 min	$PhCH_3$	morpholine	S.M.
5.	90 °C	3 days	$PhCH_3$	2-hydroxypyridine	S.M.
6.	90 °C	3 days	CH_3CN	2-hydroxypyridine	S.M.
7.	90 °C Microwave	20 min	$PhCH_3$	2-hydroxypyridine	S.M.
8.	180 °C Pressure tube	17hrs	$PhCH_3$	Imidazole	Stil methyl ester possible epimerization
9.	75 °C	18 hrs	CH_3CN	N/A	S.M.
10.	130 °C Pressure tube	18 hrs	$PhCH_3$	N/A	S.M.

The TBS group was removed prior to the cyclization, and the amide bond was formed with BOPCl (Scheme 4.21). However, just as in the case with compound **220** the DKP was not able to be close. A crystal structure was able to be obtained of the secondary alcohol **221**. The crystal structure proves that the aldol reaction gave the *anti*-product.



Scheme 4.21. Production of Amino Acid **221** and crystal structure.

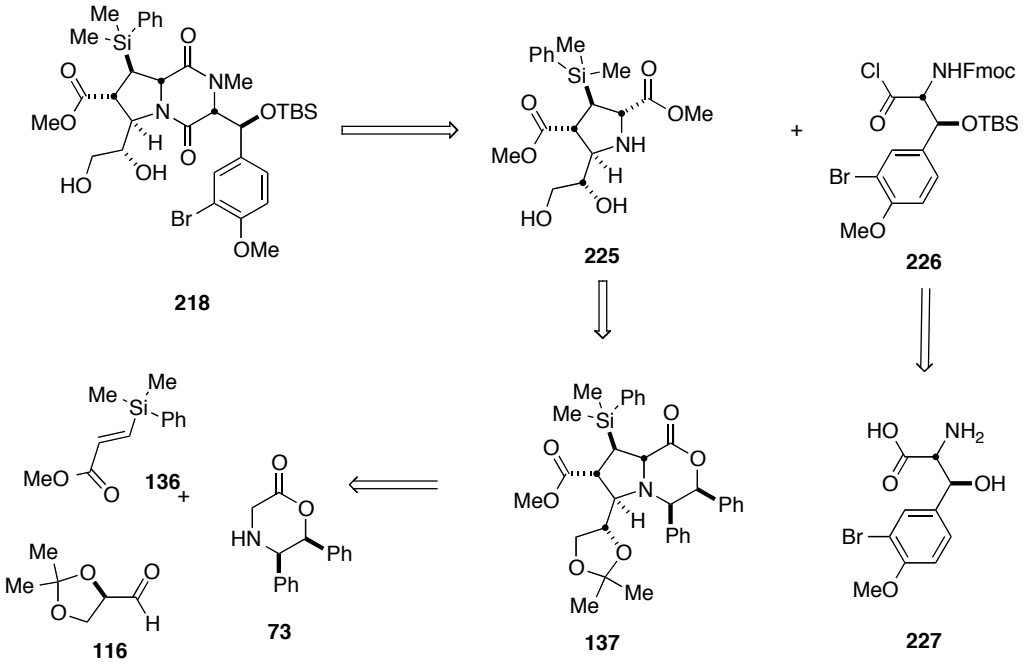
Due to the unfortunate attempts to close the DKP, the amide should be methylated to make the *N*-methyl amine **225**. Methylating the amine will allow for the amide to be in the *cis* conformation and should be poised for an easier closure of the DKP (Scheme 4.22).



Scheme 4.22. Future Experimentation.

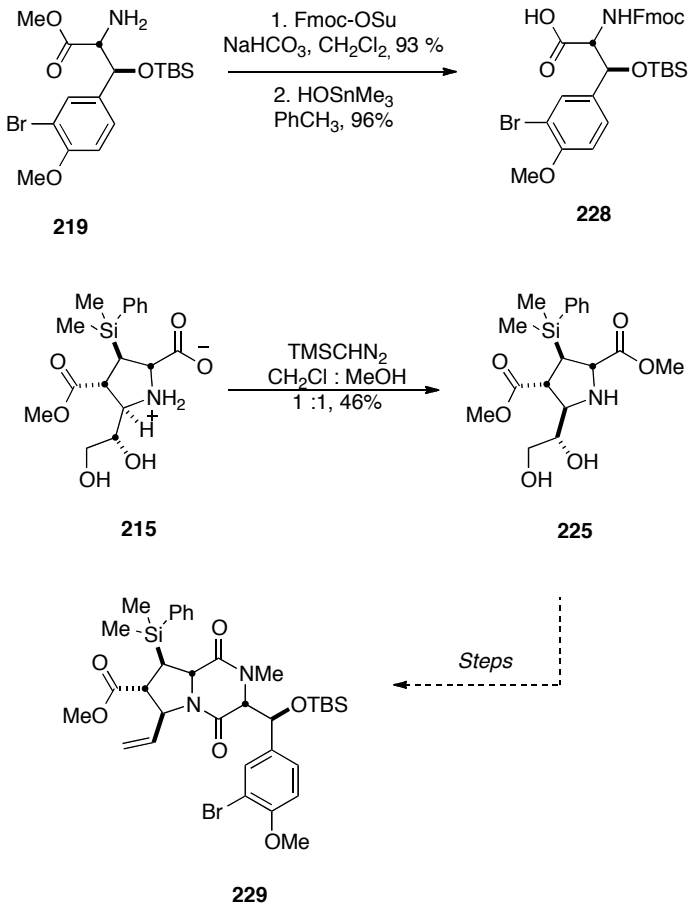
4.5.3 Acid Chloride Approach to DKP.

It is also possible to construct the DKP with an activated acid **226**. Williams and co-workers showed an acid chloride can be utilized to form a DKP in the total synthesis of (-)-Jorumycin.[63] Retrosynthetically, the acid chloride **226** can arise from compound **227** in two steps. The dipole template can be cleaved and coupled to the acid chloride **226** to from the DKP **218** (Scheme 4.23).



Scheme 4.23. Retrosynthetic approach to DKP **218**.

The primary amine **219** was Fmoc protected, followed by formation of the acid **228** in the presence of Trimethyltin hydroxide (Scheme 4.24**)**. The amino acid derivative **215** was methylated to give the ester **225**. With the two amino acid portion in hand, future experimentation should be focused on formation of the DKP **229**.

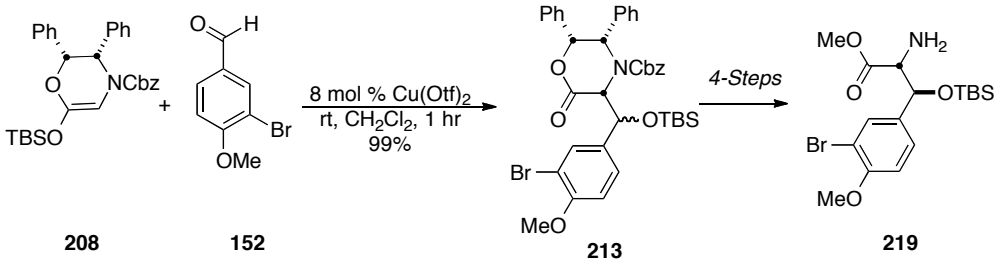


Scheme 4.24. Acid Chloride approach to DKP.

4.6 Synthetic Progress Toward the Biaryl Portion.

The final focal point of my thesis addresses the biaryl ether portion of (*ent*)-MPC1001 (**67**). As previously developed, a Lewis acid catalyzed Mukaiyama aldol

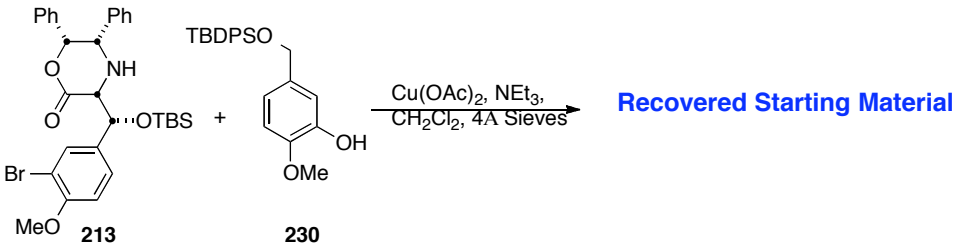
reaction with **208** and **152** gave the desired adduct **213** in good yield and 2:1 dr (Scheme 4.25). Compound **213** can be elaborated in 4 steps to the β-hydroxy-α-amino acid **219**.



208 **152** **213** **219**

Scheme 4.25. Synthesis of unnatural amino acid **45**.

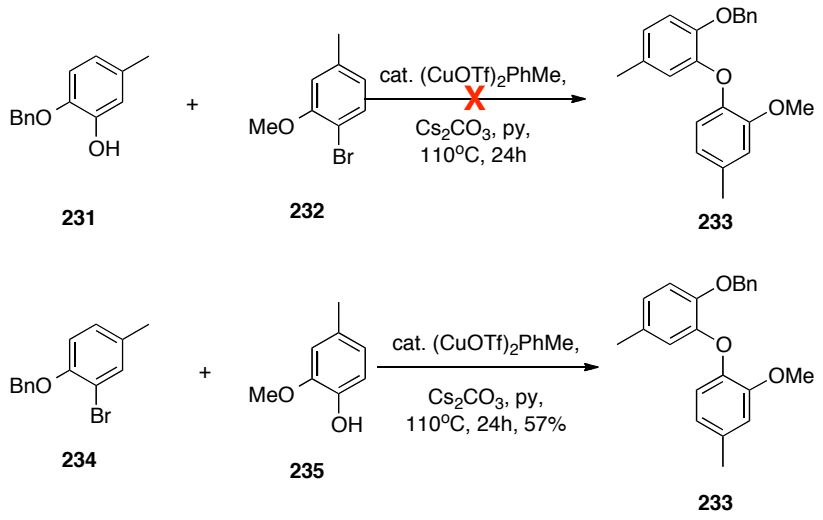
Preliminary experimentation utilizing the Chan-Evans-Lam conditions to form the biaryl ether portion of (*ent*)-MPC1001 (**67)** (Scheme 4.26) has been unsuccessful and resulted in recovery of starting material with phenol **230** and amine **213**. Even varying the copper salts among CuBr, $CuBr_2$, CuO, CuO_2 under these conditions resulted in recovery of starting material.



213 **230**

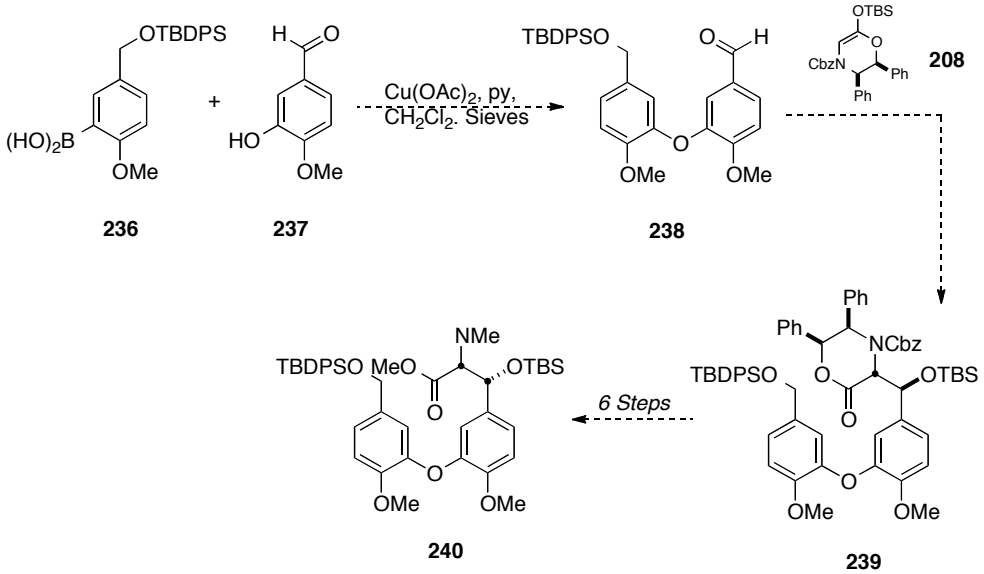
Scheme 4.26. Attempted Chan-Evan-Lam conditions.

Previous work by Cuny and co-workers on the coupling of two electron rich substituted aryl rings shows such couplings are highly difficult (Scheme 4.27). Those authors showed that depending on which aryl compound the boronic acid was attached to, the reaction either gave a 50 % yield or no reaction at all.



Scheme 4.27. Cuny's Results.

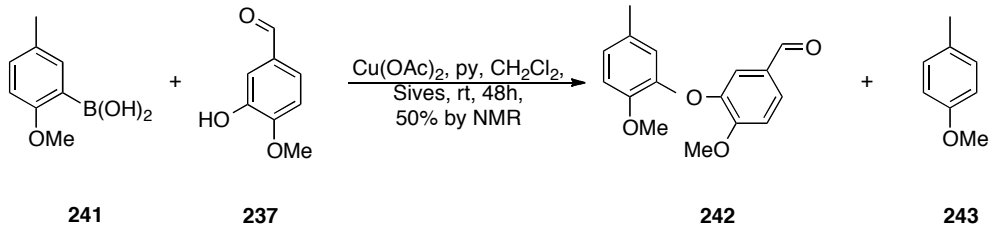
Given this disheartening result, it was postulated that the biaryl portion could be installed prior to the Lewis acid catalyzed Mukaiyama aldol reaction (Scheme 4.28).



Scheme 4.28. Installation of biaryl portion first

The coupling was attempted in a simple model system with the boronic acid **241** and aldehyde **237** in the presence of $Cu(OAc)_2$ and pyridine at room temperature to

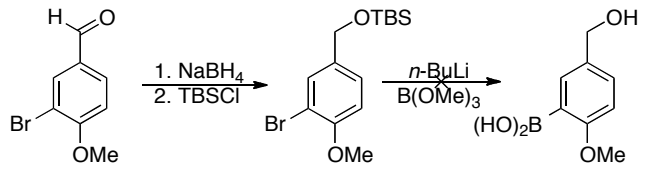
produce the coupled product **242** (Scheme 4.29). These conditions may be necessary to afford the biaryl ether portion seen in (*ent*)-MPC1001 (**67**).



241 **237** **242** **243**

Scheme 4.29. Chan-Evans-Lam Reaction.

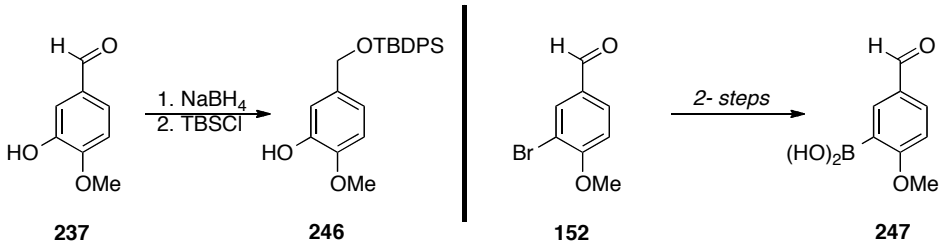
Reduction of aldehyde **152** afforded the alcohol followed by TBS protection, which reveals compound **244** (Scheme 4.30). However, conversion of the aryl bromide to the boronic acid **52** resulted in the loss of the TBS group. The free primary OH may affect the outcome of the Ullman reactions, so another method was explored to make the boronic acid.



152 **244** **245**

Scheme 4.30. Loss of TBS group.

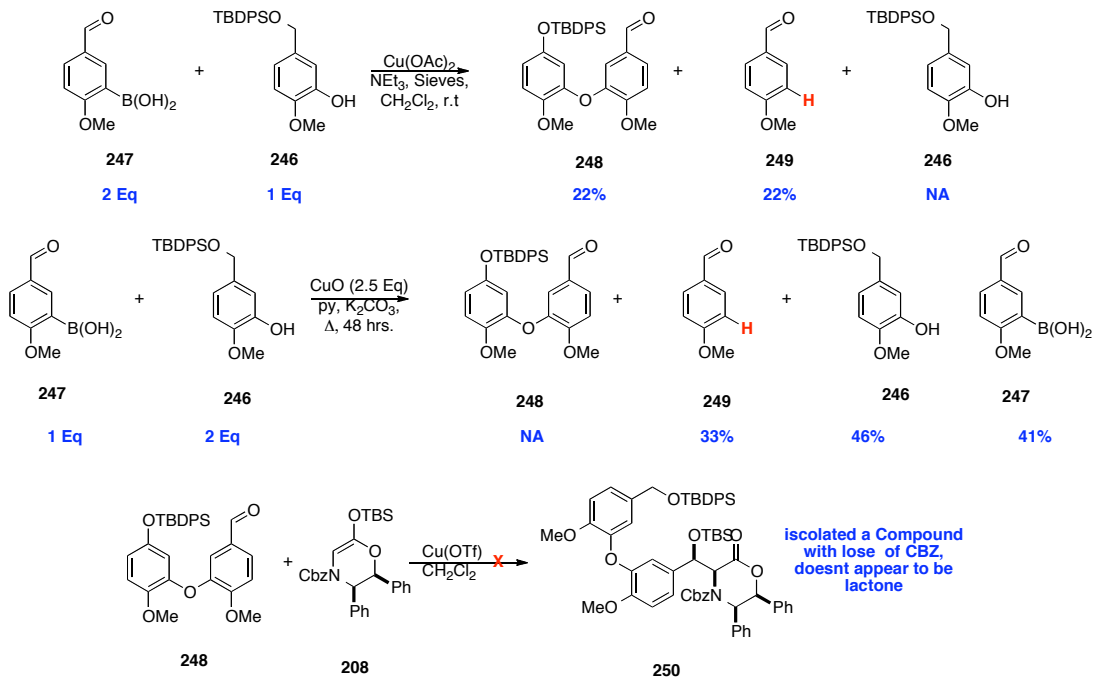
Since the TBS group was lost during the preparation of the boronic acid, vanillin (**237**) was converted to the more robust TBDPS protected alcohol **246** and boronic acid **247** can be made from in two steps from compound **152** (Scheme 4.31).



237 **246** **152** **247**

Scheme 4.32. Preparation of coupling partners.

Coupling of the boronic acid **247** in a 0.017M molar solution of phenol **246** in the presence of $Cu(OAc)_2$, NEt_3, and 4A powdered gave the desired coupled product **248** in a 22% yield and 21 mg of the protodeboronation byproduct **249** (Scheme 4.32). There was no recovery of the protected alcohol **246.** Changing the concentration of the phenol **246** to 0.038M in CH_2Cl_2 yielded no product, heating the reaction in $PhCH_3$ resulted in a complex mixture of compounds, and changing the order of addition had no effect upon increasing the yield of the reaction. In most cases protodeboronation was the major product. Utilizing CuO yielded 33% of the byproduct **249**, 41% recovery of the boronic acid **247,** and 46% of the protected alcohol **246**. Since the yield of the desired product is low, it is hypothesized that the protodeboronation is faster then the coupling due to the election-rich boronic acid. Nevertheless, the biaryl compound **248** can be obtained. Preliminary experimentation on the Lewis acid catalyzed Mukaiyama aldol under the optimized conditions yielded no product. The crude HNMR showed removal of the cbz protecting group on the lactone. More material will be needed to further address this problem.

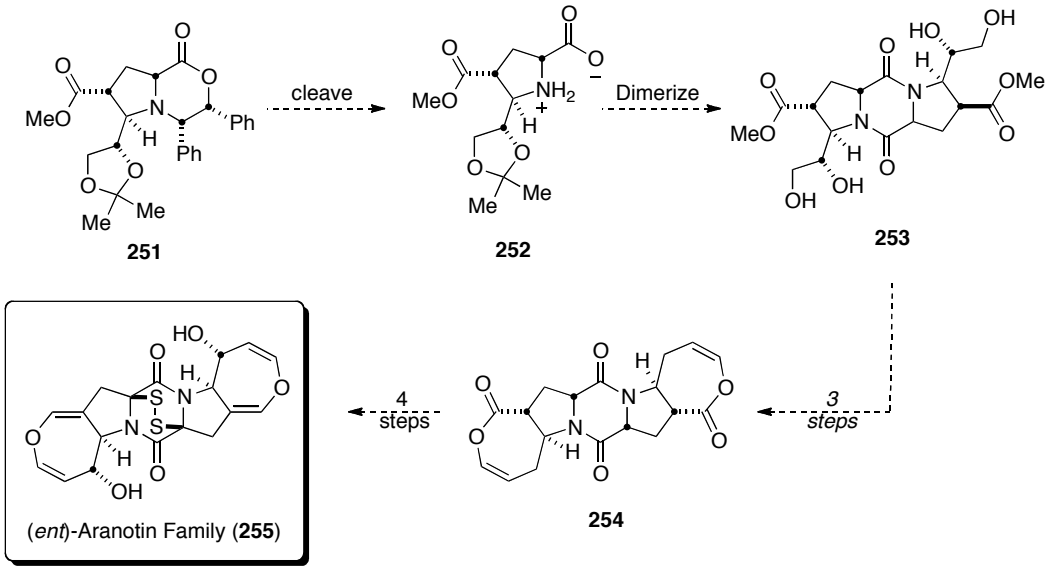


Scheme 4.32. Ullman coupling conditions.

4.7 Progress Toward the Aranotin Family of Natural Products.

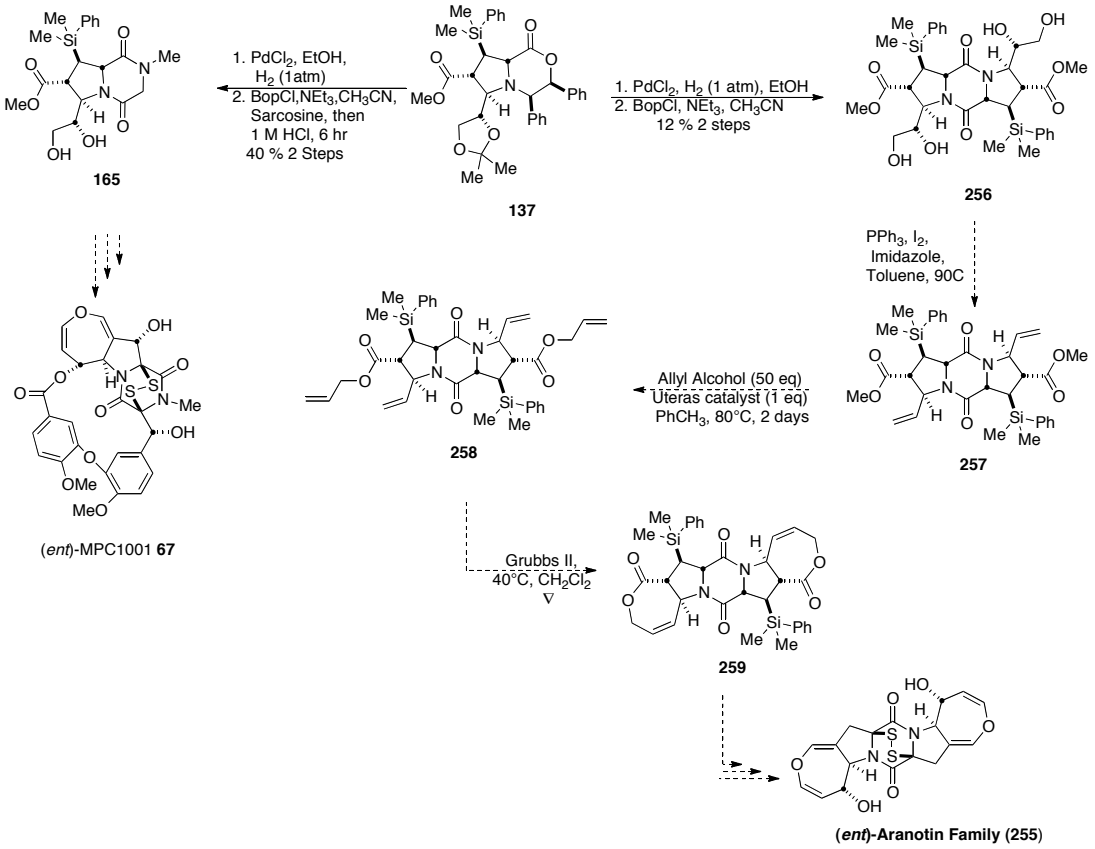
Since the aranotins and MPC1001 family of natural products have a similar core structure, it was believed that the dipole product could be a point of divergence to access both families of natural products (Scheme 4.34). Deprotection of lactone template **251** would afford the amino acid **252**. The amino acid **252** may be dimerized to form the DKP **253** and be further elaborated in a three-step sequence that has previously been developed to afford the vinyl ether **254**. Once compound **254** has been assessed, another

four steps would afford the Aranotin family of natural products.



Scheme 4.34. Proposed synthesis of the Aranotin family of natural products **10**.

Bräse has shown $MeOPCl_2$ has been utilized in the dimerization of amino acids to afford DKP derivatives.[64] However, utilizing $MeOPCl_2$ has failed to yield any desired product, but the reduction of compound **137** with $PdCl_2$ followed by dimerization with BOPCl resulted in a 12% yield of the desired compound **256** (Scheme 4.35). The dimerized product **256** could be elaborated to (*ent*)-aranotin (**225**). Cleavage of the template with $PdCl_2$ allows for the isolation of the amino acid **256** and possible access to two families of natural products.



Scheme 4.35. Dimerization to make DKP.

4.7.1 Removal of the Hydroxyl Group.

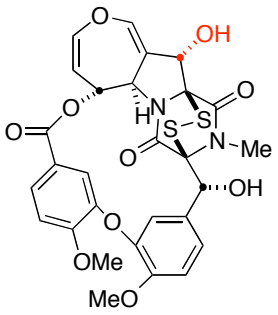
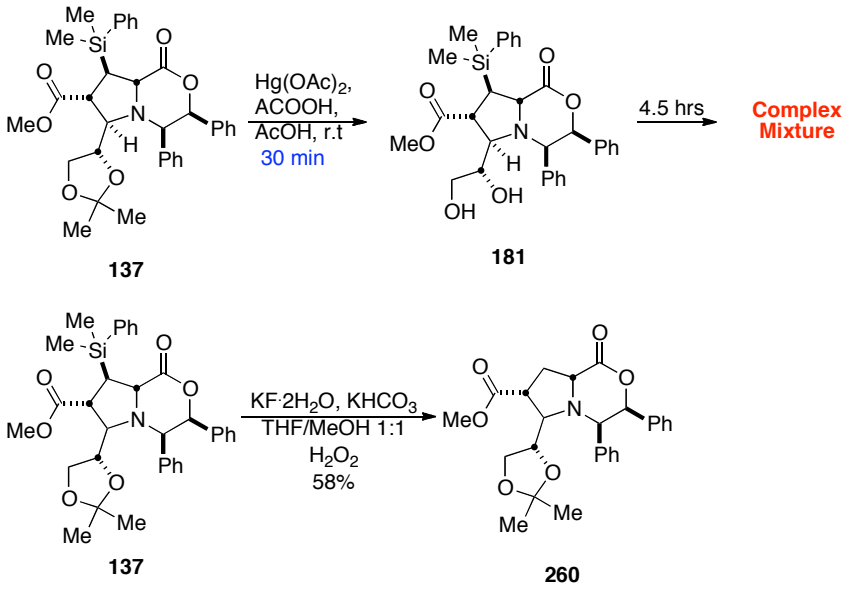


Figure 4.5

Preliminary experimentation has been focused on the oxidation of the carbon-bound silicon to the corresponding secondary alcohol. This oxidation is necessary for installation of a hydroxyl group on the pyrrolidene backbone of MPC1001 seen in red in Figure 4.5. Experimentation was focused on the oxidation of compound **137** with $Hg(OAc)_2$ in the presence of a peracetic acid solution that contained a 15% solution of acetic acid and 1% H_2SO_4 for 4.5 hours seen in Scheme 4.36. Within the first thirty minutes of the reaction, the acetonide was deprotected to reveal the diol **181**. Extending the reaction length past 30 minutes never revealed any

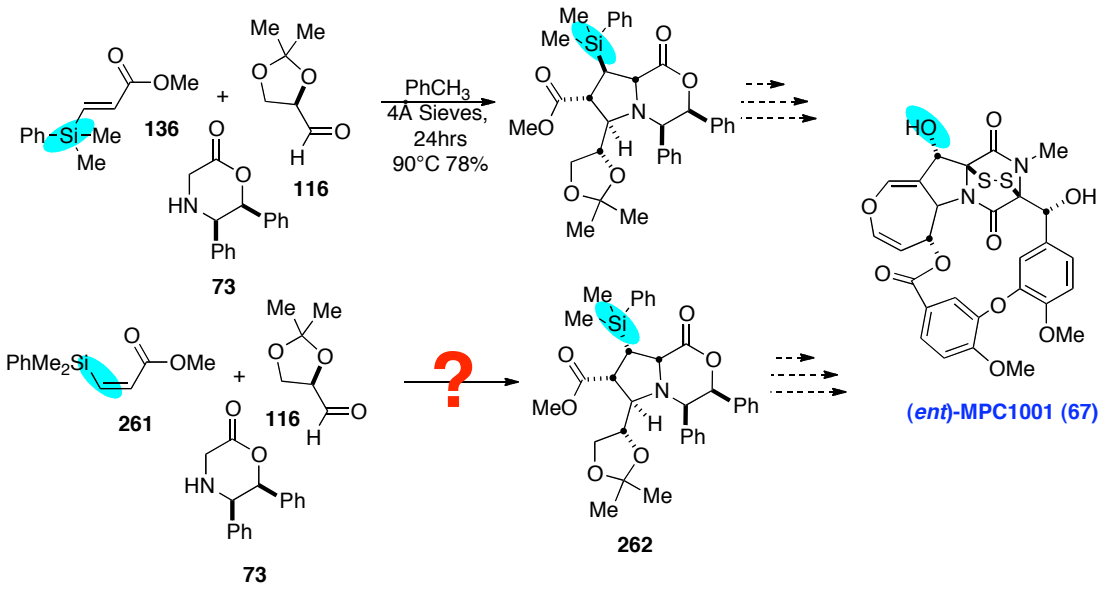
identifiable compound that could be isolated. Changing the conditions to aqueous fluoride and peroxide allowed for a protodesilylation pathway to occur and isolation of compound **260** in 58% yield.



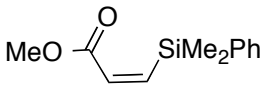
Scheme 4.36. Preliminary Experimentation with the Fleming-Tamao Oxidation.

Even though the protodesilylation pathway occurred upon exposure to milder oxidation conditions, it is believed that compound **260** may be useful in the total synthesis of the Aranotin family of natural products.

It is thought that a cycloaddition with the *cis* dipolarophile **261** (Figure 4.6) would afford the correct stereochemistry around the carbon backbone. (Scheme 4.37).



Scheme 4.37. Utilizing dipolarophile **261**.



261

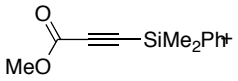
Figure 4.7

The synthesis commenced with the addition of methyl propiolate (**263)** to chloro(dimethyl)phenylsilane (**264)** to afford an array of several products seen in Table 4.11. Entry 3 showed that premixing *n*-BuLi with chloro(dimethyl)phenylsilane (**264)** at -78 °C resulted in the direct addition of *n*-BuLi to compound **263** affording compound **267**. Extending the reaction time to 6 hours at -78 °C allowed for dimerization of methyl propiolate (**263)** to produce compound **266**. Interestingly, changing the base to *t*-BuLi dramatically effected the result of the reaction. When *t*-BuLi was added to a stirring solution of 5eq of chloro(dimethyl)phenylsilane (**264**) and 1 eq of methyl propiolate (**263)** at -78 °C, followed by warming to room temperature, this resulted in 52% yield of the desired compound **265** as seen in entry 8.

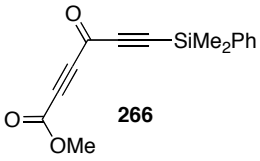
Table 4.11. Addition of methyl propiolate (**37**) to dimethylcholorphenylsilane (**38**).

263 **264**

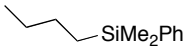
Products



265



266

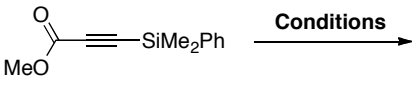


267

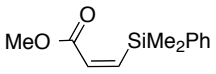
Conditions	Result
1. NaHMDS, -78 °C	trace **265**
2. NaH, 0 °C	Decomp
3. *n*-BuLi, -78 °C, then $ClSiMe_2Ph$, then ester	**267** Scene in crude, No **265,** or **266**
4. *n*-BuLi, -78 °C, 6hr.	**266,** trace **265**
5. *n*-BuLi, -78 °C, 2hr, MeOD Quench, -78C	Messy Dicarded
6. *n*-BuLi, -78 °C, 2hr, MeOD Quench, 0 °C	Messy Dicarded
7. **263** + **264** (5eq), cool to -78 °C , dropwise, *t*-BuLi, stir **15 min,** warm rt, stir 2 hours.	54 % **265,** trace
8. **263** + **264** (5eq), cool to -78 °C , dropwise, *t*-BuLi, stir **5 min**, warm rt, stir 2 hours.	52 % **265, NO 266**
9. **263** + **264** (1eq), cool to -78 °C , dropwise, *t*-BuLi, stir **10 min**, warm rt, stir 2 hours.	trace **265,** Trace **266** discarded due to being messy

With compound **265** in hand, the reduction with Lindlar's catalyst proceeded smoothly to produce the cis olefin **261** seen in table 4.12. The choice of solvent was crucial for this reaction. As seen in entry two, utilizing THF allowed for the reaction to take 3 days; on the other hand, using methanol as a solvent took about 1 hour (entry 2). The best results occurred with 16% Lindlar's catalyst by weight in the presence of methanol and hydrogen at 1 atm which afforded the product **261** in 78% yield.

Table 4.12. Reduction of compound **41**.

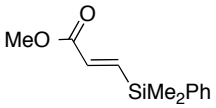


265

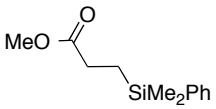


261

Conditions	Result
1. Lindlar 10% by weight, H_2 (1atm), MeOH	1 hr, product and S.M
2. Lindlar 10% by weight, H_2 (1atm), THF	3 days, very clean slugish
3. Lindlar 16% by weight, H_2 (1atm), MeOH, 31mg	7 hrs 78% **261**
4.$NaBH_4$, EtOH, $Ni(OAc)_2$ ethylenediamine, H_2 (1 atm)	complex mixture

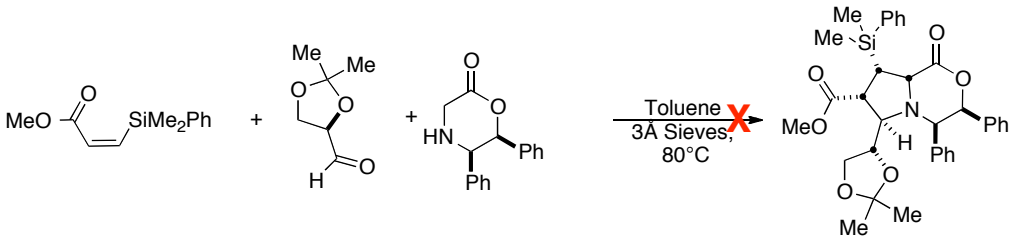


136



268

With the dipolarophile **261** in hand, the cycloaddition was attempted with the lactone **73** as well as the mannose derived aldehyde **116** with the unoptimized conditions. Unfortunately, the reaction resulted in a complex mixture of compounds (Scheme 68).



261 **116** **73** **262**

Scheme 4.37. Reduction of compound **41**

4.8 Conclusion.

Herein describes the progress towards the total synthesis of (*ent*)-MPC1001. The approach is based upon a novel asymmetric [1-3]-dipolar cycloaddition utilizing a vinyl silane (**136)** and a chiral lactone template (**73**). The template of the coupled product

(**137**) was able to be cleaved to give the amino acid **162**. A crystal structure of compound **162** was able to be obtained and confirms that the dipolarophile **136** approaches the *E*-azomethine ylide in an *endo*-fashion from face opposite the phenyl moieties. The amino acid **162** was coupled to sarcosine ethyl ester hydrochloride **163** to afford the diketopiperazine **164**. Compound **164** was elaborated in three steps to the metathesis precursor **167**. Exposure of compound **167** to Grubbs 1st and 2nd as well as Hoveyda-Grubbs 2nd generation catalyst provided irreproducible results. Therefore, a new approach to the oxepin ring was observed utilizing a Yamaguchi macrolactonization to afford lactone **156**. The double bond can be epoxidized, and subsequent Lewis acid ring opening would give the allyl alcohol. The lactone can be partially reduced and then eliminated to give the oxepin ring.

Amino acid **162** was also attempted to be incorporated into the diketopiperazine of (*ent*)-MPC1001. The coupling partner **217** was constructed from a Lewis acid catalyzed Mukaiyama aldol reaction with lactone **208** and aldehyde **152**. However, standard previously developed coupling conditions with BopCl did not give rise to the desired diketopiperazine **218**. In lieu of this, primary amine **219** was constructed and amino acid **219** was coupled to give rise to the peptide bond. However, the DKP could not be closed under numerous conditions. It is believed to solve this problem that amine **220** should be methylated first, then subjected to closure conditions to give the DKP **225** as seen in scheme 54

Another focal point of my thesis addresses the biaryl ether portion of (*ent*)-MPC1001 (**67**) Figure 8**.** Coupling of the boronic acid **247** in a 0.017M molar solution of

phenol **246** in the presence of $Cu(OAc)_2$, NEt_3, and 4A powdered gave the desired coupled product **248.**

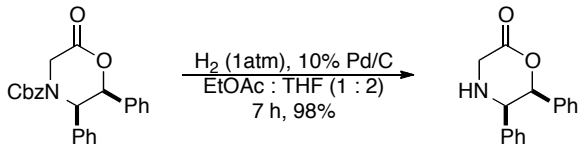
Since the aranotins and MPC1001 family of natural products have a similar core structure, it was believed that the dipole product (**137**) could be a point of divergence to access both families of natural products. Towards this end, the lactone template was removed with palladium chloride. The incipient amino acid was dimerized to afford dioxopiperazine **256**. Efforts are being directed at the further elaboration of this highly functionalized species towards the aranotins.

CHAPTER 5: Experimental Section

5.1 General Considerations.

All reactions requiring moisture sensitive conditions were carried out in flame-dried round bottom flasks equipped with magnetic stir bars. ACS grade solvents were purchased from Sigma Aldrich and used without further purification. ^{1}H and ^{13}C NMR spectra were obtained on either a Varian Mercury-Inova 300 or a Varian 400 spectrometer at ambient temperature. Mass spectra were recorded on a Fisons VG Quattro-SQ spectrometer. Reaction products were purified by flash chromatography using standard grade silica gel purchased from Sorbent Technologies. Reactions were monitored by thin layer chromatography (TLC) using glassbacked silica gel plates (60Å) purchased from Silicycle. TLC plates were visualized using UV irradiation. Optical rotations were taken on autopol III automatic polarimeter.

5.2 Experimental Procedures



88 **73**

(5*R*,6*S*)-5,6-diphenylmorpholin-2-one (73):

To a flame dried 500 mL rbf was added compound **88** (7.2g, 0.02 mol, 1 equiv.) and dissolved in EtOAc (86 mL) and THF (200 mL). The flask was heated under a heat gun until the solid was dissolved and the clear solution was hot gravity filtered. The reaction vessel was left to cool for 45 minutes to rt. The reaction was sparged with argon before adding 10 Mol % Pd/C (3.6g by weight). The reaction was stirred under an atmosphere of H_2 (1 atm) for 7 h at which time the compound was completely consumed as observed by TLC. The reaction was filtered through celite with EtOAc (100 mL). The combined filtrates were dried with Na_2SO_4, and concentrated to dryness to give pure product **73** (4.41g, 98 % yield) that was utilized without further purification. (ps-347-1, ps2-39-sm)

$[\alpha]^{25}_D$ = - 182.2 (*c* = 0.15 $CHCl_3$)

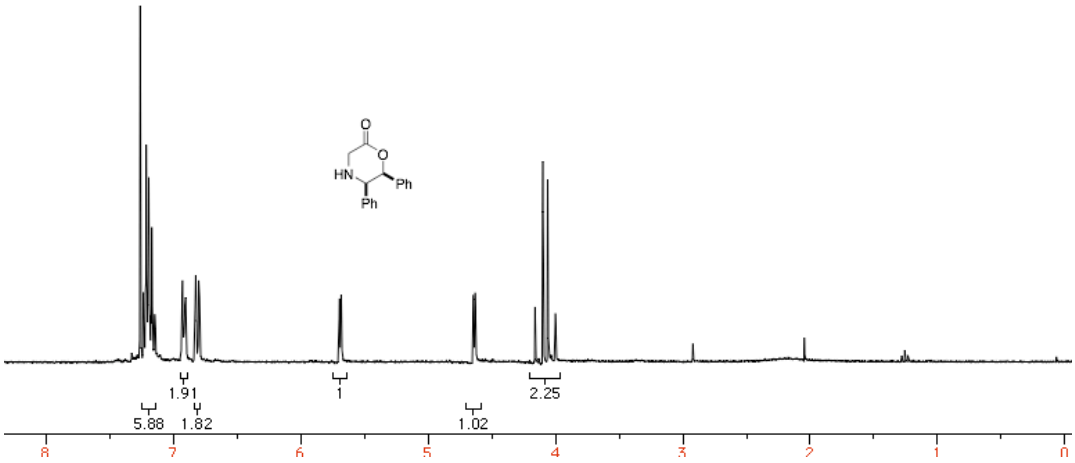
R_f= 0.16 (60:40 Hexane/EtOAC)

IR (neat) ν 1735, 1457, 1340, 1208 cm^{-1}

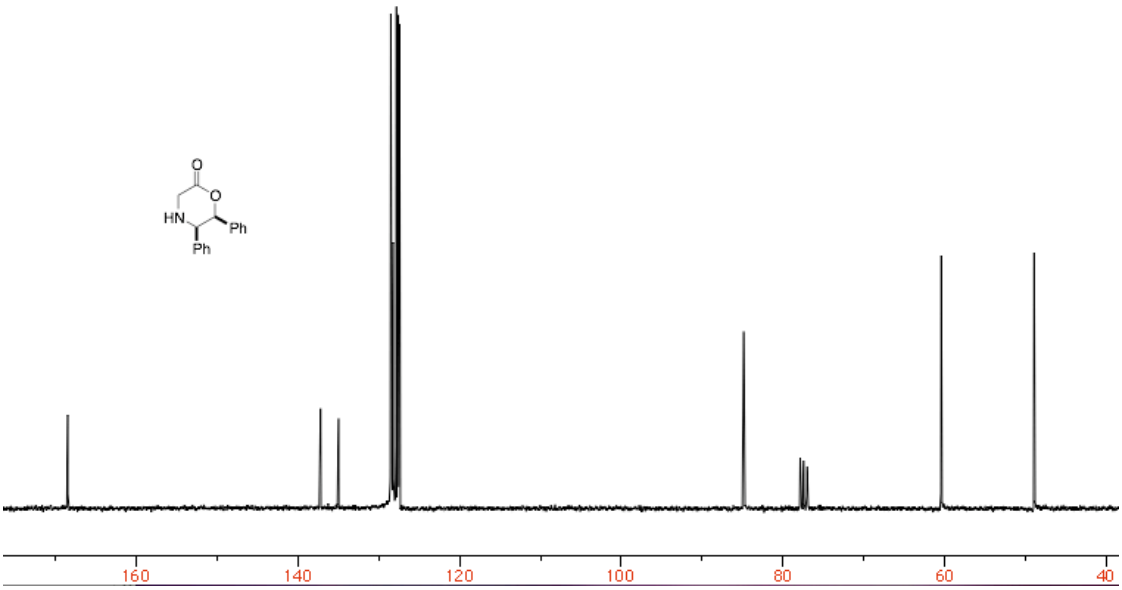
^1H NMR ($CDCl_3$ 300MHz) : δ 7.25 – 6.79 (m, 10H), 5.67 (d, *J* = 3.6, 1H), 4.63 (d, *J* = 3.9, 1H), 4.13 (d, *J* = 18.3, 1H), 4.03 (d, *J* = 18.6, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 168.45, 137.18, 134.96, 128.50, 128.41, 128.23, 127.82, 127.62, 127,43, 84.87, 60.44, 48.96.

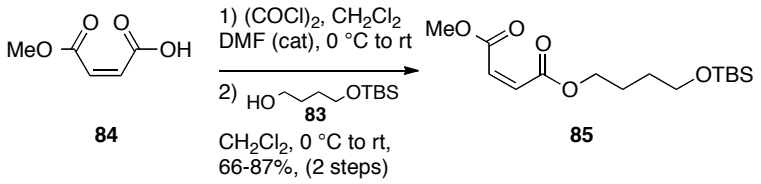
HRMS Calcd for $C_{16}H_{16}NO_2$ $[M+H]^+$ 254.11 Found 254.11$[M+H]^+$



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **73**



^{13}C NMR spectrum (300 MHz, $CDCl_3$) of compound **73**



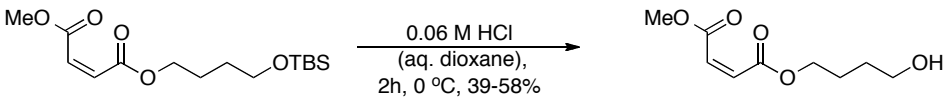
4-((tert-butyldimethylsilyl)oxy)butyl methyl maleate (85):

Oxalyl chloride (1.37 mL, 1.50 mmol, 2 equiv.) was added to the acid **84** (1 g, 7.68 mmol, 1 Eq) at 0 ^{0}C in CH_2Cl_2 (7 mL) under argon atmosphere. Following the addition of DMF (1 Drop) , the reaction was kept at 0 ^{0}C for ten minutes and warmed to rt and stirring continued for 1 h. The yellowish reaction mixture was then condensed under reduced pressure until a constant weight. The resulting residue was dissolved in CH_2Cl_2 (7 mL) and syringed into a stirred solution of TEA (2.5 mL, 19.0 mmol. 2.5 equiv.) and **82** (3.14 g, 15.0 mol, 2 equiv.) in CH_2Cl_2 (7 mL) at 0 ^{0}C. The reaction was warmed to rt and stirring continued for 2 h. Water was added to the reddish mixture and extracted with CH_2Cl_2 (3 x 25 mL) and finally combined organic layers were than dried over $MgSO_4$ to afford the coupled product **85** (87% yield) **(**ps-23-1, ps-26-1, ps-38-2)

^{1}H NMR ($CDCl_3$): δ 6.8 (s , 2 H), δ 4.2 (t , 2 H), δ 3.8 (s , 3 H), δ 3.6 (t, 2 H), δ 1.75 (m, 2H), δ 1.55 (m, 2H), δ 0.09 (s, 9H), δ 0.05 (s, 6H).

HRMS Calcd for $C_{15}H_{29}O_5Si$ $[M+H]^+$ 317.17 Found 317.20 $[M+H]^+$

^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **85**



85 **86**

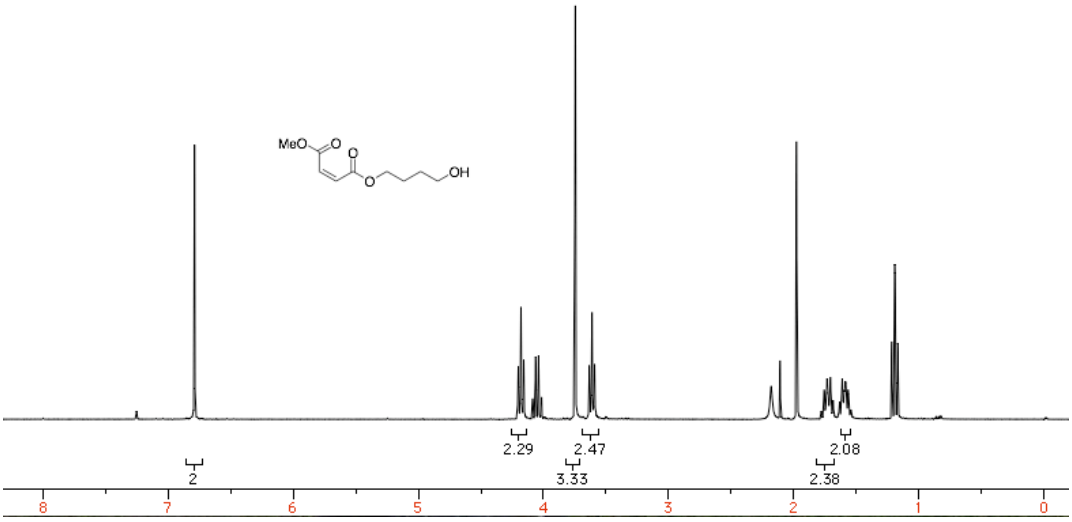
4-hydroxybutyl methyl maleate (86):

To a solution of **85** (3.89 g, 1.22 mmol, 1 equiv.) in dry THF (10 ml) was added 0.06M HCl in a 50% methanol solution. The reaction was stirred at 0 ^{0}C for 2 h. After cooling, the reaction was quenched by a saturated aqueous solution of $NaHCO_3$ (150 mL) followed by extraction with EtOAc (3 x 100 mL) . The combined organic layers were washed with a saturated aqueous solution of brine (100 mL) and dried over Na_2SO_4 which gave compound **86** (58% yield). (ps-10-3)

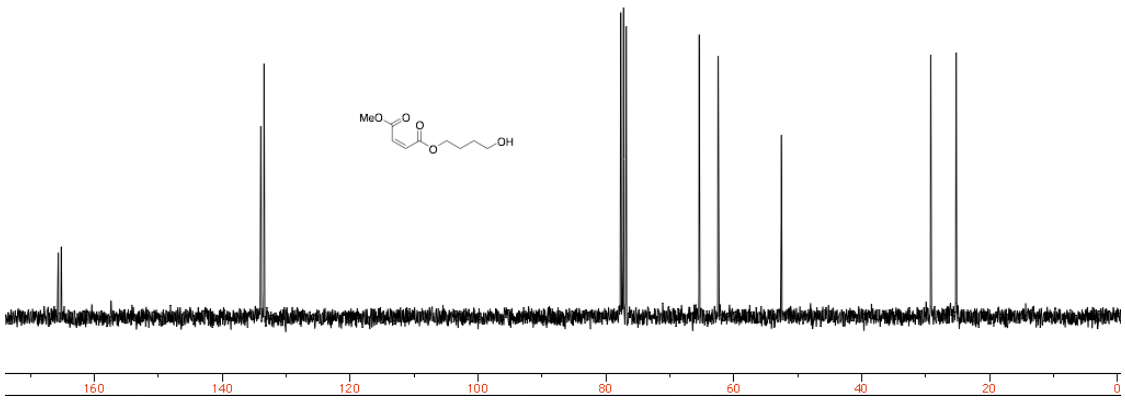
^{1}H NMR ($CDCl_3$): δ 6.8 (s, 2H), δ 4.2 (t, 2H), δ 3.8 (s, 3H), δ 3.6 (t, 3H), δ 1.8 (m, 3H), δ 1.6 (m, 2H).

^{13}C NMR ($CDCl_3$): δ 165.65, 165.19, 133.97, 133.48, 65.41, 62.44, 52.56, 29.19, 25.21.

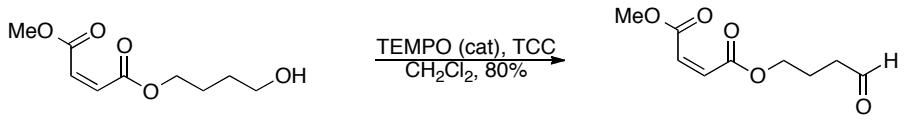
HRMS Calcd for $C_{15}H_{29}O_5Si$ $[M+H]^+$ 203.1 Found 303.08 $[M+H]^+$.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **86**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **86**

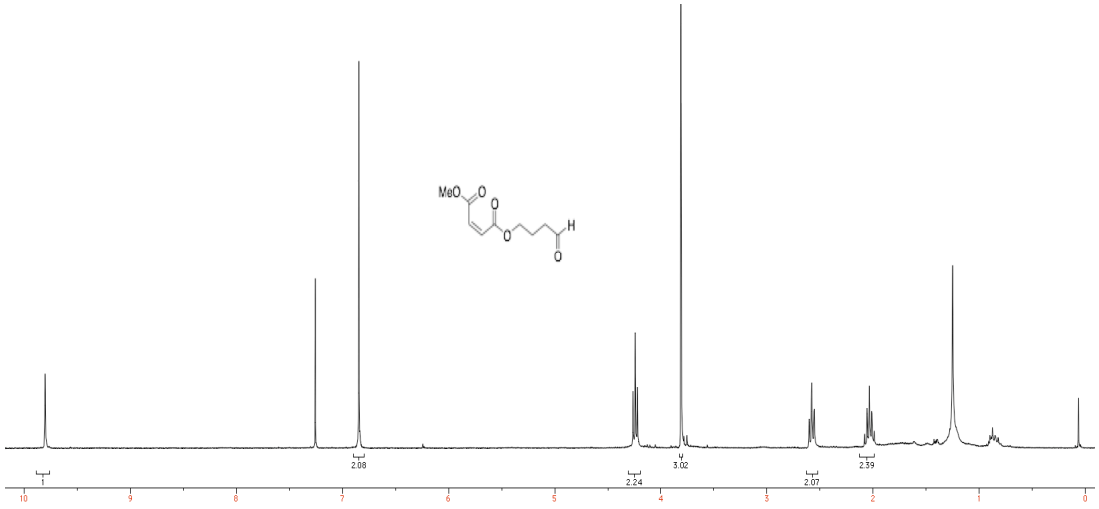


86 **87**

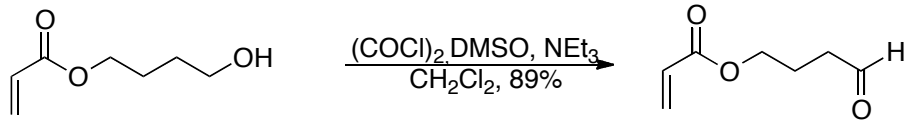
methyl (4-oxobutyl) maleate (87):

To a flame dried 25 mL rbf was added trichloroisocyanuric acid (30 mg, 0.013 mmol, 0.95 equiv.) to a solution of **86** (25 mg, 0.0124 mmol, 1 equiv.) in CH_2Cl_2 (2ml). The solution was stirred and maintained at 0 ^{0}C followed by the addition of TEMPO (1 crystal). The solution turned yellow then orange and was brought to rt and stirred for 15 minutes. The reaction was then filtered through Celite and the organic phase was washed with a saturated aqueous solutions of $NaHCO_3$ (20 mL), 1 N HCl (20 mL), and brine (20 mL) to afford the product **87** (80% yield). **(**ps-015-1)

^{1}H NMR ($CDCl_3$): δ 9.8 (t, J = 1, 1H), δ 6.9 (s, 2H), δ 4.3 (t, J = 6.6, 2H), δ 3.6 (s, 3H), δ 2.6 (m, 2H), δ 2.1 (m, 2H)



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **87**

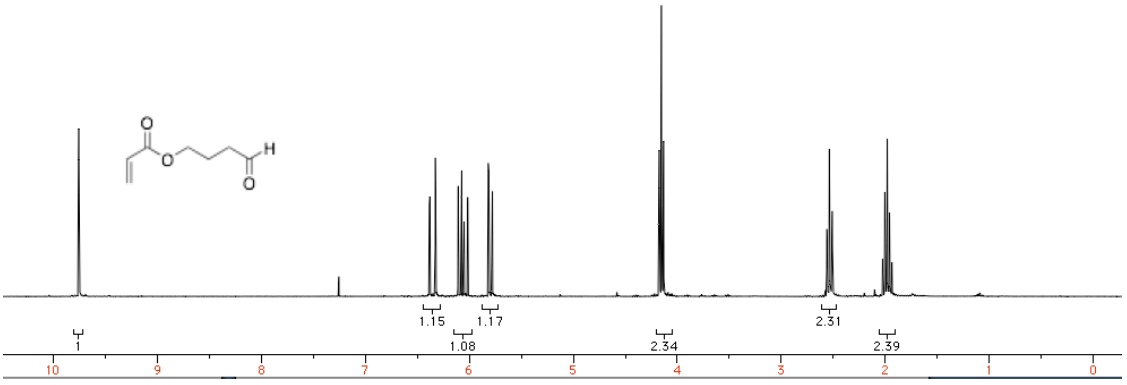


90 **91**

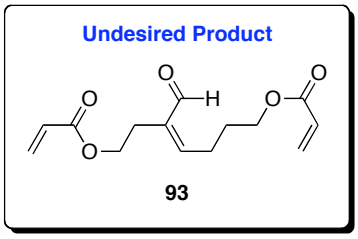
4-oxobutyl acrylate (91):

To a flame dried rbf equipped with a stir bar was added CH_2Cl_2 (54 mL). The flask was cooled to -78 °C and $(COCl)_2$ (2 mL, 2.28 mmol, 1.1 equiv.), and DMSO (3.24 mL, 4.57 mmol, 1.1 equiv.) was added over 5 minutes. Stirring was continued for 15 minutes at -78 °C then a solution of **90** (2.88 mL 2.08 mmol, 1.1 equiv.) in a mixture of CH_2Cl_2 (45 mL) and DMSO (11 mL) was added. The cloudy solution was stirred at -78 °C followed for another 20 minutes followed by the addition of Et_3N (16.26 mL, 12.4 mmol, 6 equiv.) and stirring continued for another 3 h. The organic layer was washed with water (100 mL), saturated aqueous solutions of NH_4Cl (100 mL), $NaHCO_3$ (100 mL), NaCl (100 mL) . The organic layer was dried over $MgSO_4$ and distilled at 65 °C to give aldehyde **91** (2.5 g, 89% yield). (ps-057-1)

^{1}H NMR ($CDCl_3$): δ 9.75 (t, J = 1.2, 1H), 6.35 (dd, J = 1.6, 17, 1H), 6.06 (dd, J = 10, 17, 1H), 5.79 (dd, J = 10, 1.6, 1H), 4.15 (t, J = 6.3), 2.53 (m, 2H), 2.00 (m, 2H).

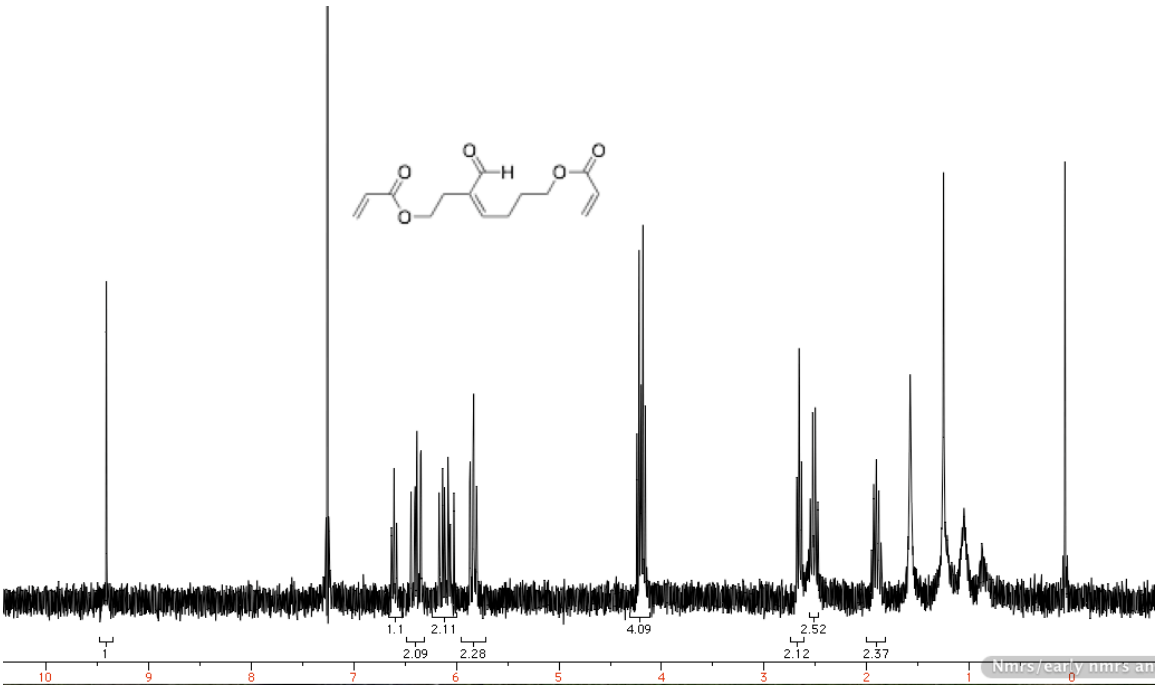


^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **91**

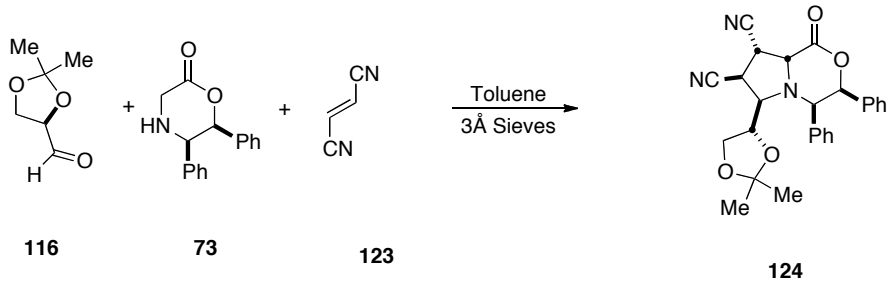


(Z)-3-formylhept-3-ene-1,7-diyl diacrylate (93):

^{1}H NMR ($CDCl_3$): δ 9.41 (s, 1H), 6.60 (t, 1H), 6.38 (m, 2H), 6.10(m, 2H), 5.83 (m, 2H), 4.21 (m, 4H), 2.66 (t, 2H), 2.52 (m, 2H), 1.97 (m, 2H). (ps-084-4)



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **93**



116 **73** **123** **124**

(3S,4R,6R,7S,8S,8aR)-6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxo-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7,8-dicarbonitrile (124):

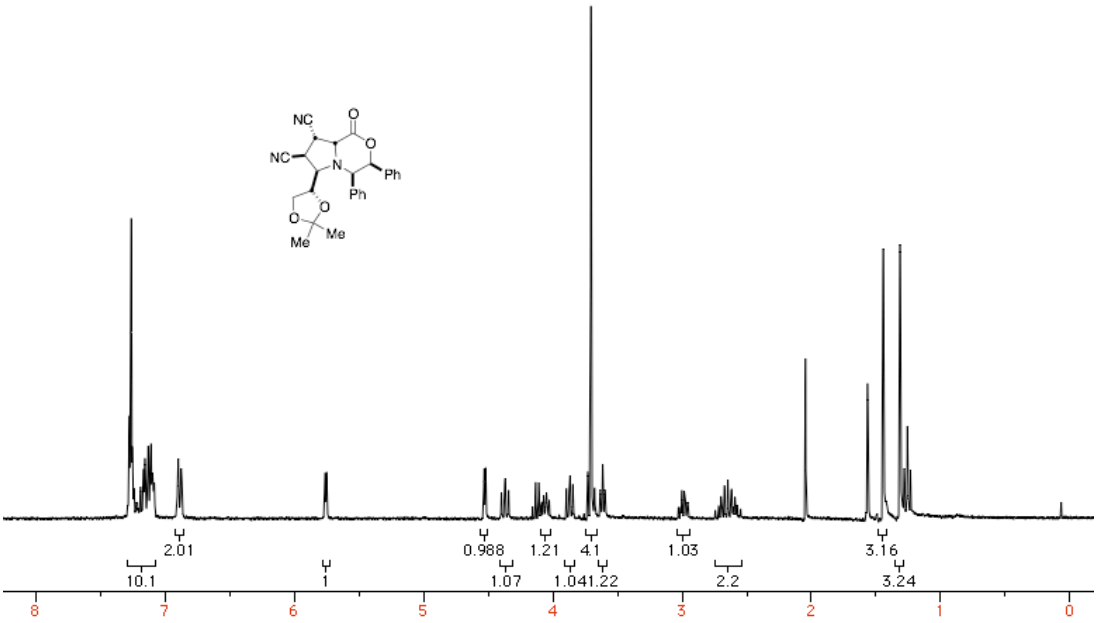
To a 10 mL rbf was added **73** (50 mg, 0.019, 1 equiv.), **123** (46 mg, 0.059, 3 equiv.) and **116** (32 mg, 0.024 mmol, 1.25 equiv.) and was heated to at 80 °C and stirred until no more lactone **73** was present by TLC. The reaction concentrated and purified by preparatory TLC to yield the desired product **124**. (ps-184-b)

R_f= 0.55 (70:30 Hexanes:EtOAc)

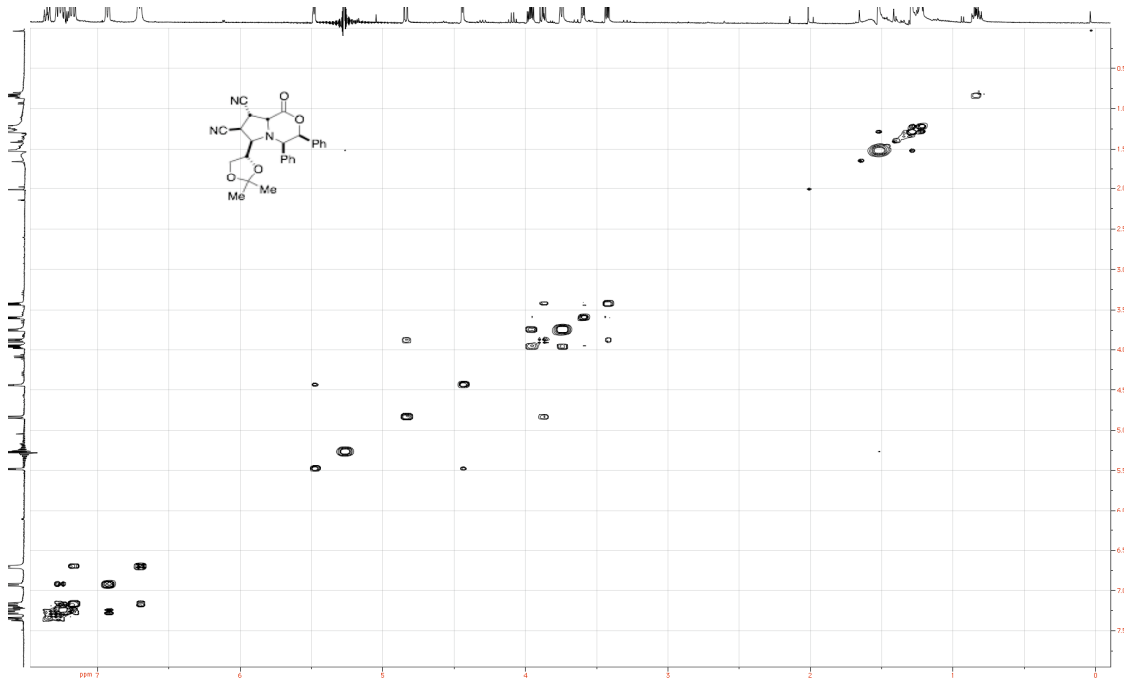
^{1}H NMR ($CDCl_3$): δ 7.37 – 6.68 (m, 10H), 5.47 (d, J = 2.7, 1H), 4.83 (d, *J* = 6.3, 1H), 4.44 (d, *J* = 2.7, 1H), 3.96 (ddd, 2.7, 5.1, 5.1, 1H), 3.88 (dd, *J* = 4.8, 6.3, 1H), 3.74 (m, 2H), 3.59 (dd, *J* = 3.0, 3.0, 1H), 3.43 (dd, *J* = 2.7, 4.8, 1H), 1.52 (s, 3H), 1.29 (s, 3H).

HRMS Calcd for $C_{26}H_{25}N_3O_5$ $[M+H]^+$ 444.18 Found 444.20 $[M+H]^+$.

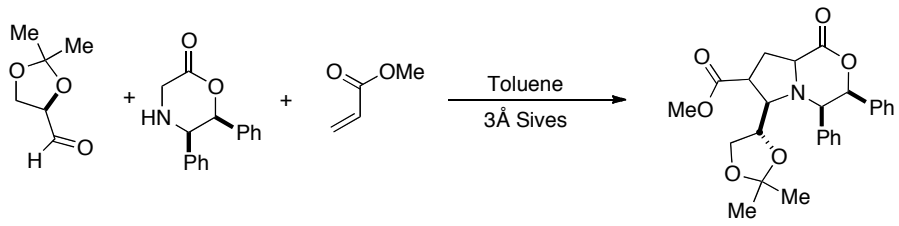
.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **44**



COSY spectrum (400 MHz, $CDCl_3$) of compound **44**



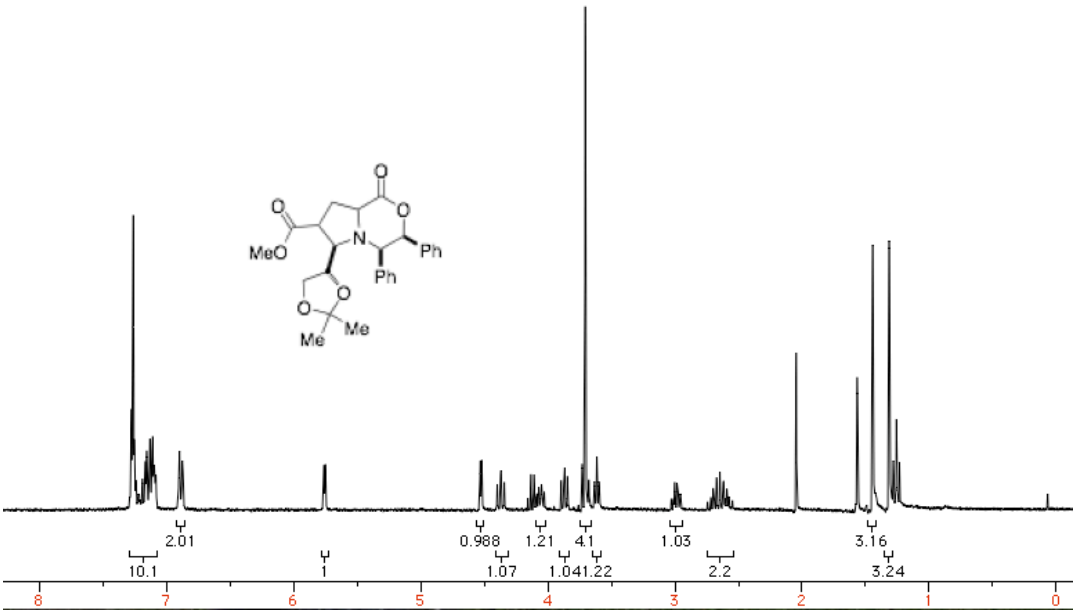
(3S,4R,6R)-methyl6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxo-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (126):

To a 10 mL rbf was added **73** (30 mg, 0.011 mmol, 1 equiv.), **125** (38 mg, 0.043 mmol, 3 equiv.) and **116** (19 mg, 0.14 mmol, 1.25 equiv.), and $PhCH_3$ (10 mL). The reaction was heated to at 80 °C and stirring continued until no more lactone **73** was present by TLC. The reaction concentrated and purified by preparatory TLC (80:20 Hexanes:EtOAc, Ran 3 times in the solvent mixture) to yield the desired product **126**. (ps-180-3)

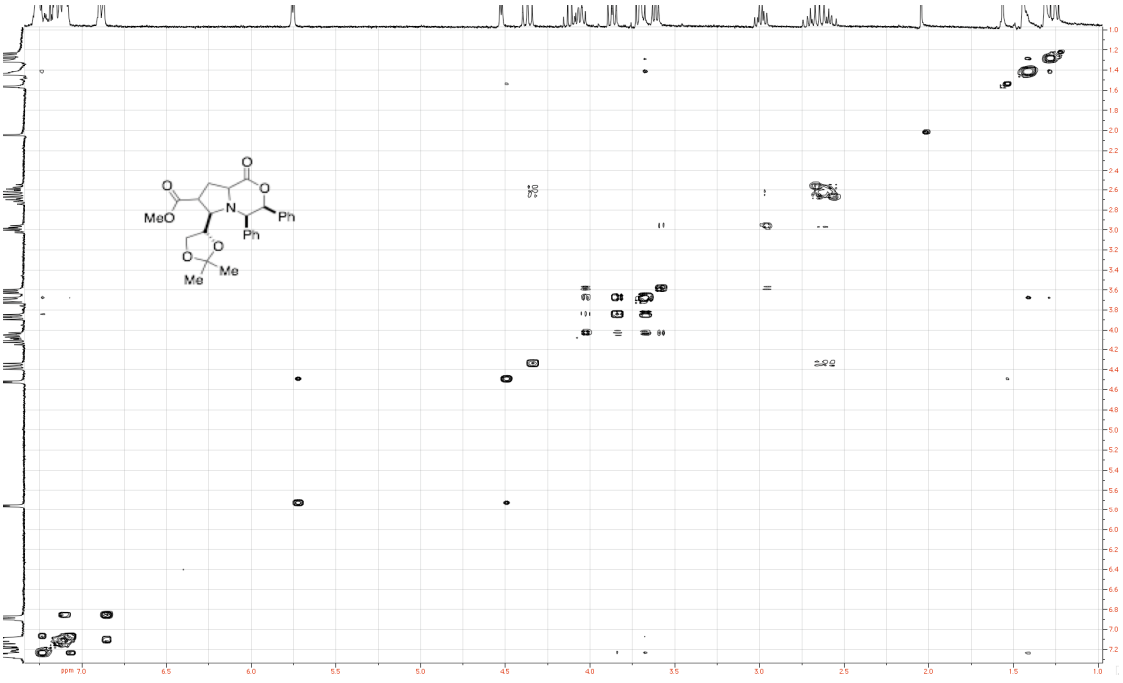
R_f=0.24 (80:20 Hexanes:EtOAc, Ran 3 times in solvent mixture)

^{1}H NMR ($CDCl_3$): δ 7.27 – 6.86 (m, 10H), 5.76 (d, J = 3.3, 1H), 4.52 (d, *J* = 3.3 1H), 4.36 (t, *J* = 8.7, 1H), 4.05 (dd, J = 4.2, 10.5, 1H), 3.85 (dd, *J* = 8.1, 6.3, 1H), 3.70 (m, 4H), 3.61 (t, *J* = 5.4, 1H), 3.00 (ddd, *J* = 5.1, 8.1, 8.1, 1H), 2.62 (m, 2H) 1.44 (s, 3H), 1.31 (s, 3H).

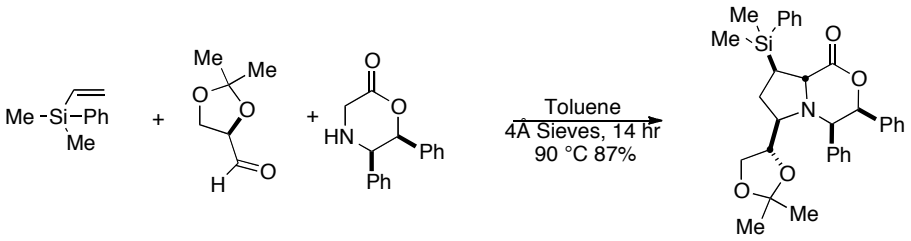
HRMS Calcd for $C_{26}H_{25}N_3O_5$. $[M+H]^+$ 452.20 Found 452.20 $[M+H]^+$.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **126**



COSY spectrum (400 MHz, $CDCl_3$) of compound **126**



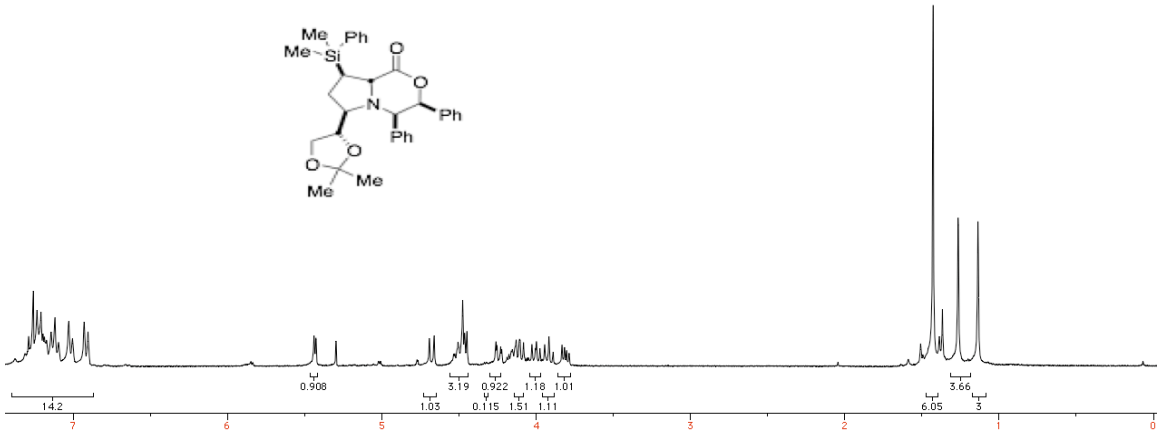
133 **116** **73** **134**

(3*S*,4*R*,6*R*,8*R*,8a*S*)-8-(dimethyl(phenyl)silyl)-6-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,4-diphenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (134):

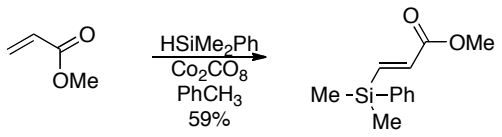
To a flame dried 100 mL rbf equipped with a stir bar was added amine **73** (50 mg, 0.019 mol, 1 equiv.), dipolarophile **133** (107 μL, 0.0592 mol, 3 equiv.), 4Å powdered molecular sieves and $PhCH_3$ (107 μL). The reaction was heated to 90°C and aldehyde **116** (103 mg, 0.078 mmol, 4 equiv.) was dissolved in $PhCH_3$ (1 mL) followed by syringe pump addition. The reaction was stirred for 14 h followed by filtration over celite, and concentrated to afford the crude material. The yellowish material was subjected to flash chromatography to afford the desired product **134** (90 mg, 87% yield) (ps2-77-5)

Note: the 4A molecular sieves were flame dried over a propane torch 3 times and purged with argon 3 times.

^{1}H NMR ($CDCl_3$): δ 7.28 – 6.90 (m, 15H), 5.43 (d, J = 3.6, 1H), 4.67 (d, J = 9.0, 1H), 4.67 (m, 3H), 4.24 (dd, J = 2.1, 9.0, 1H), 4.10 (m, 1H), 4.00 (dd, J = 6.9, 8.7, 1H), 3.91 (t, J = 8.1, 1H), 3.80 (dd, J = 4.8, 9.0, 1H), 1.42 (s, 6H), 1.26 (s, 3H), 1.13 (s, 3H)



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **134**



125 **136**

(E)-methyl 3-(dimethyl(phenyl)silyl)acrylate (136):

To a 250 mL rbf was added triphenylsilane (9.13 mL, 5.80 mol, 25 equiv.), methyl acrylate (**125**) (26 mL, 29.0 mol, 125 equiv.) and $PhCH_3$ (58 ml). The flask was purged with argon three times and cooled to 0 °C. Dicobalt octacarbonyl (793 mg, 0.23 mmol, 1 equiv.) was slowly added over a 30 min period followed by slowly warming to rt. Stirring continued for 3 h. The black crude reaction was concentrated to dryness and then dissolved in 95:5 Hexane:EtOAc solution containing silica gel. The slurry was evaporated to dryness and purified by flash chromatography (gradient elution, 99:1 to 95:5 hexane:EtOAc) to give silane **136** (7.6 g, 59% yield). ps-410-2

Caution ! The reaction is extremely exothermic at rt should be handled with care.

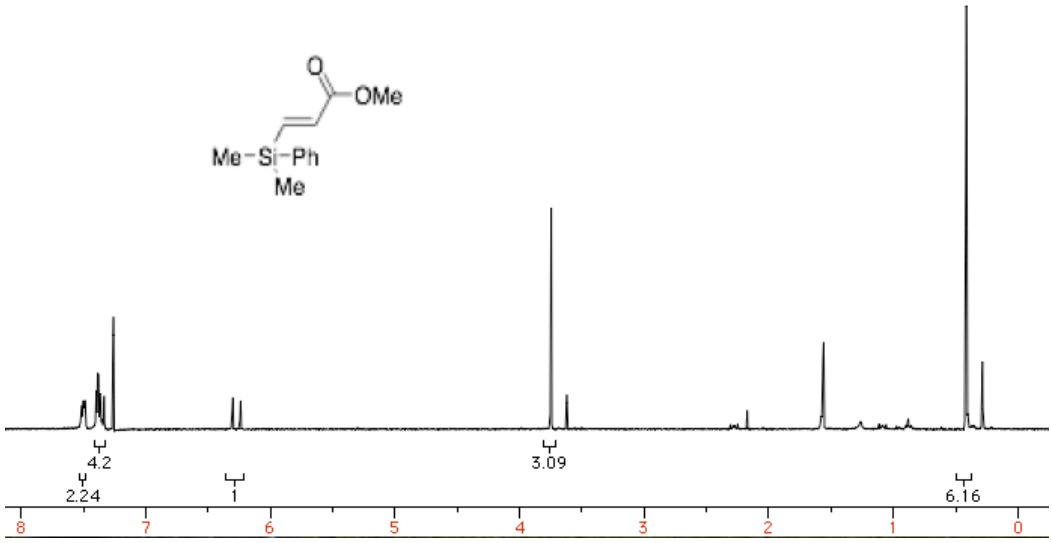
R_f=0.37 (95:5 Hexanes:EtOAc)

^{1}H NMR ($CDCl_3$): δ 7.51 – 7.33 (m, 6H), 6.26 (d, J = 17.7, 1H), 3.74 (s, 3H), 0.41 (s, 6H).

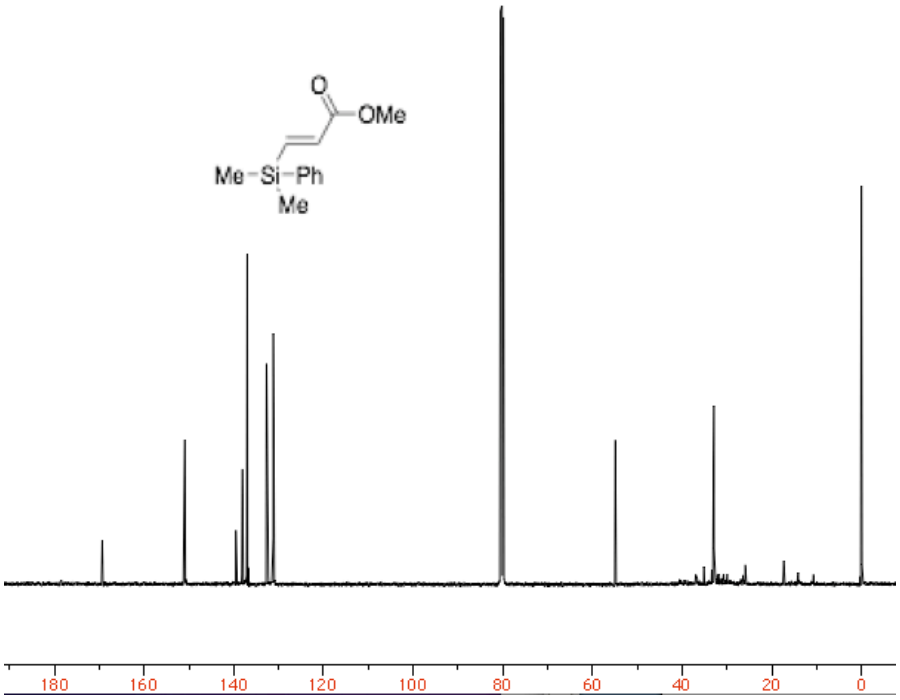
IR (neat) ν 2926, 1731, 1430, 1227, 1167, 1115, cm^{-1}

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.36, 150.95, 139.53, 138.09, 137.029, 132.71, 131.20, 54.89, 32.90, -0.005

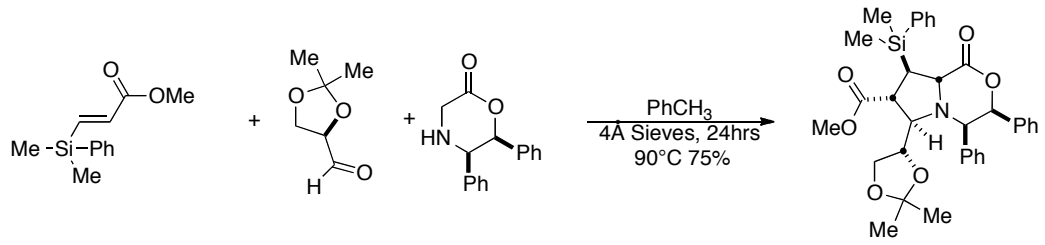
HRMS Calcd for $C_{26}H_{25}N_3O_5$. $[M+H]^+$ 443.2 Found 443.18 $[M+H]^+$.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **136**



^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **136**



136 **116** **73** **137**

(3S,4R,6R,7R,8R,8aS)-methyl 8-(dimethyl(phenyl)silyl)-6-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxo-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (137):

To a flame dried 100ml rbf equipped with a stir bar was added amine **73** (1.0 g, 0.00394 mol, 1 equiv.), dipolarophile **136** (13.0 g, 0.0592 mol, 4 equiv.), 4Å powdered molecular sieves (3 or spatula full) and $PhCH_3$ (2.36 mL). The reaction was heated to 90 °C and aldehyde **116** (2.05 g, 0.157 mol, 4 equiv.) was dissolved in $PhCH_3$ (30 ml) followed by syringe pump addition at 2 mL/hr. The reaction was stirred for 24 h followed by filtration over celite, and concentrated to afford the crude material. The yellowish material was subjected to flash chromatography (gradient elution, 95:5 Hexane/EtOAc to 90:10 Hexane/EtOAc) to afford 1.8 grams of the desired product **137** (1.8 g, 75% yield) (ps2-87-4) (NMR matches ps-204-2)

Note: the 4A molecular sieves were flame dried over a propane torch 3 times and purged with argon 3 times.

$[\alpha]^{25}_D$ = - 14.6 (*c* = 0.3, $CHCl_3$)

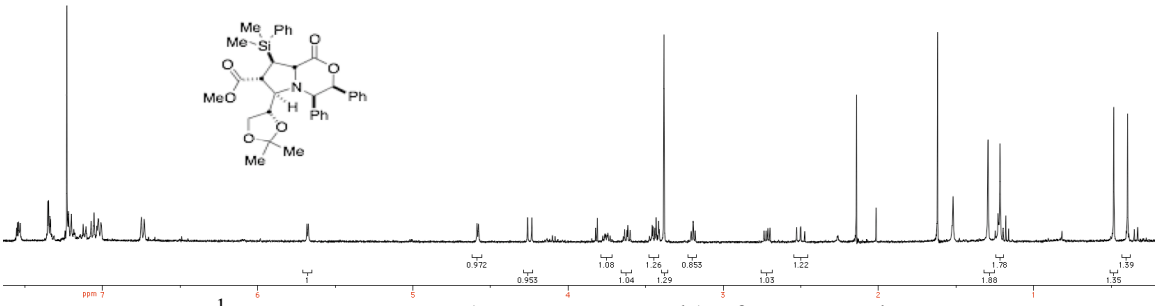
R_f=0.32 (80:20 Hexanes:EtOAc)

IR (neat) ν 2924, 2854, 1736, 1638, 1458, 1377, 1259 1159, 1073, cm^{-1}

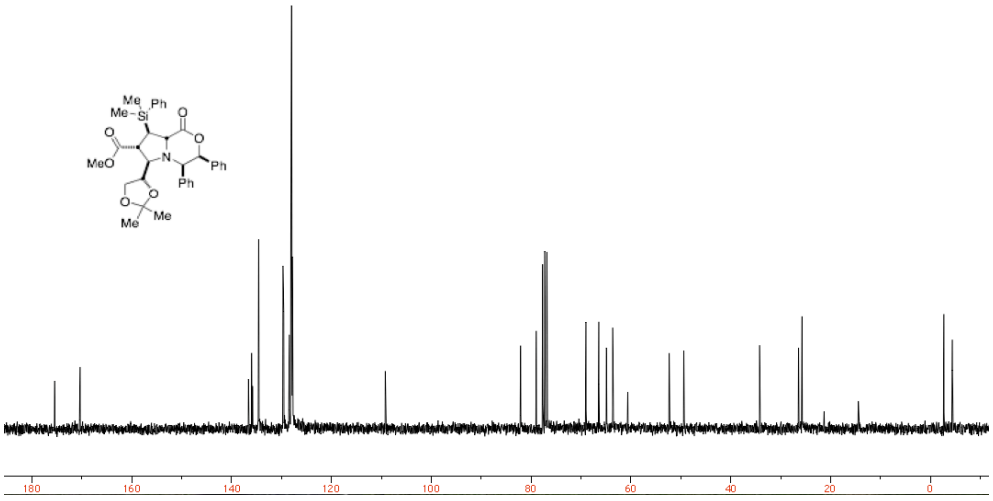
^{1}H NMR ($CDCl_3$ 300MHz) : δ 7.58 – 6.74 (m, 15H), 5.69 (d, J = 3.3, 1H), 4.61, (d, J = 3.6, 1H), 4.28 (d, J = 6.9, 11.1H), 3.76 (m, 1H), 3.63 (dd, J = 6.0, 8.1, 1H), 3.45 (dd, J = 8.1, 15.0, 1H), 3.28 (t, J = 5.1, 5.1, 1H), 2.75 (dd, J = 4.5, 9.3, 1H), 2.53 (dd, J = 9.9, 10.2, 1H), 1.32 (s, 1H), 1.24 (s, 1H), 0.51 (s, 1H), 0.42 (s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$) 175.47, 170.36, 136.63, 136.00, 135.80, 134.59, 129.71, 12956, 128.43, 128.10, 128.00, 127.91, 127.83, 109.21, 82.10, 78.97, 69.01, 66.43, 64.90, 63.65, 52.33, 49.40, 34.21, 26.42, 25.72, -2.70, -4.39.

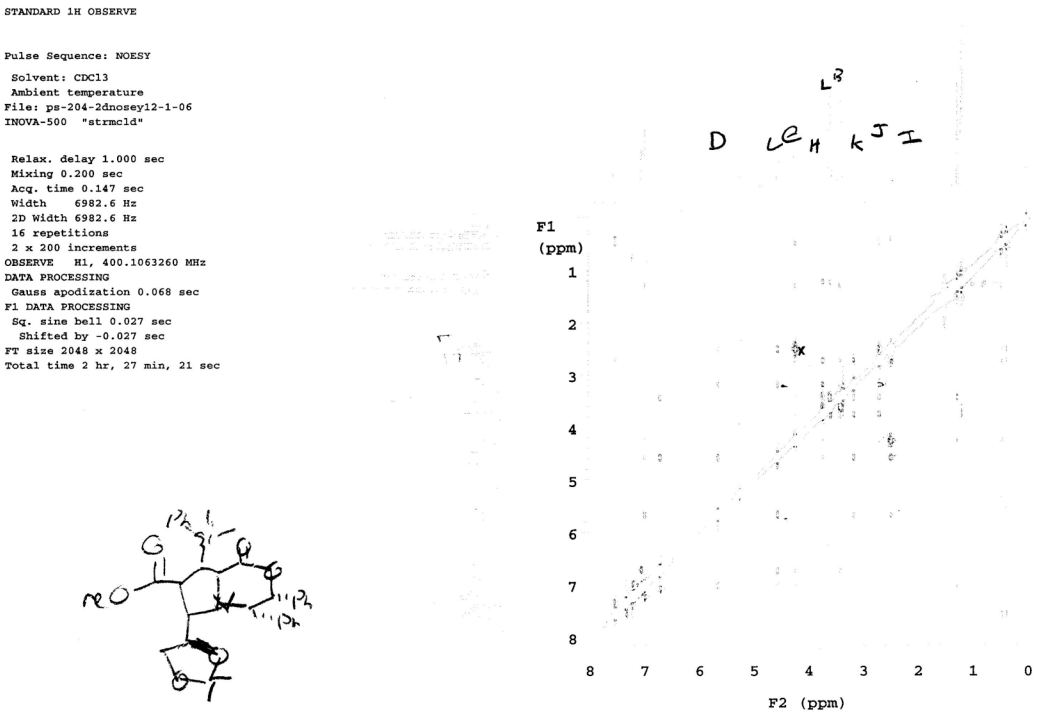
HRMS Calcd for $C_{34}H_{39}NO_6Si$. $[M+H]^+$ 586.26 Found 586.30 $[M+H]^+$.



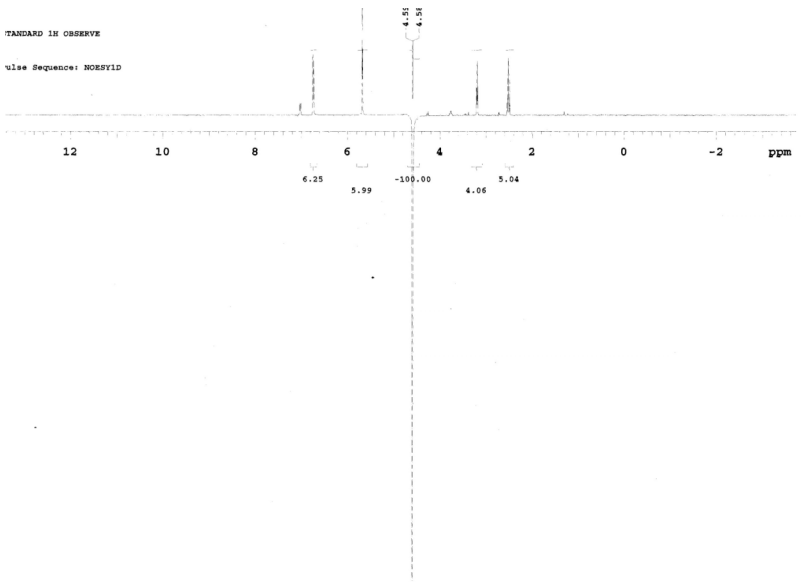
^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **137**



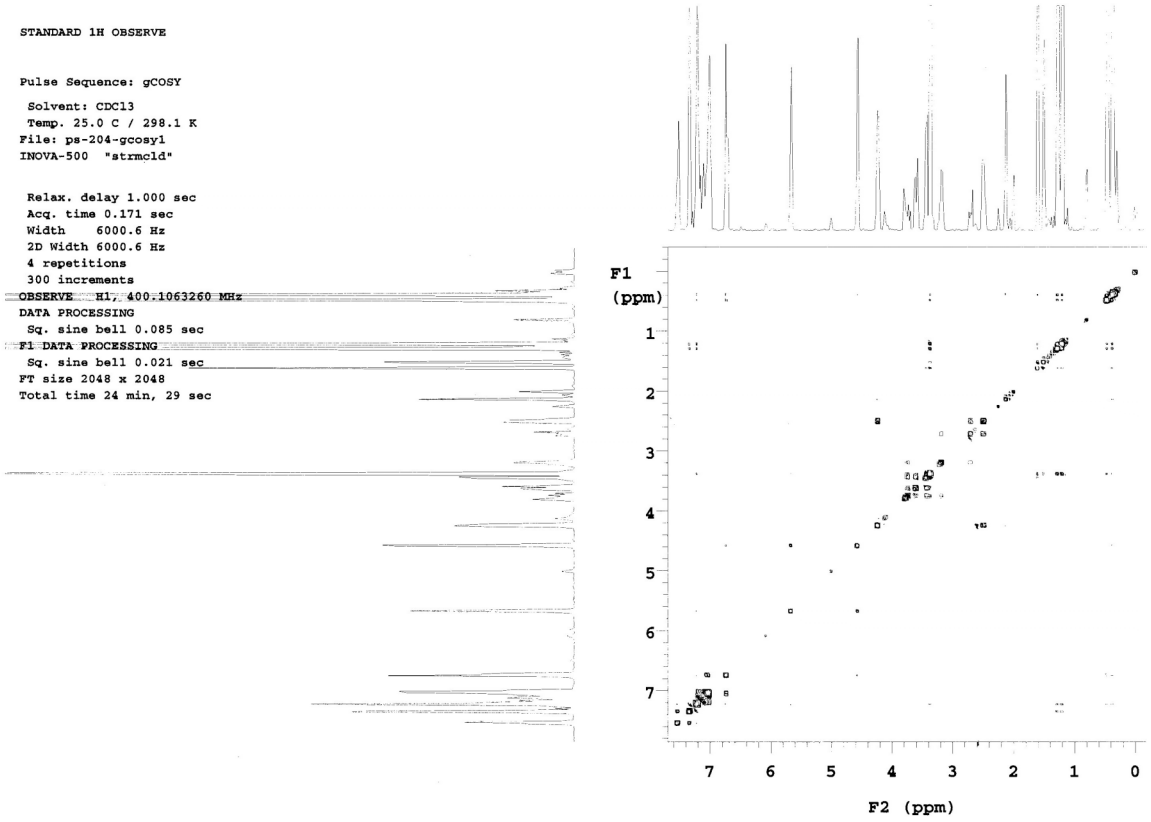
^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **137**



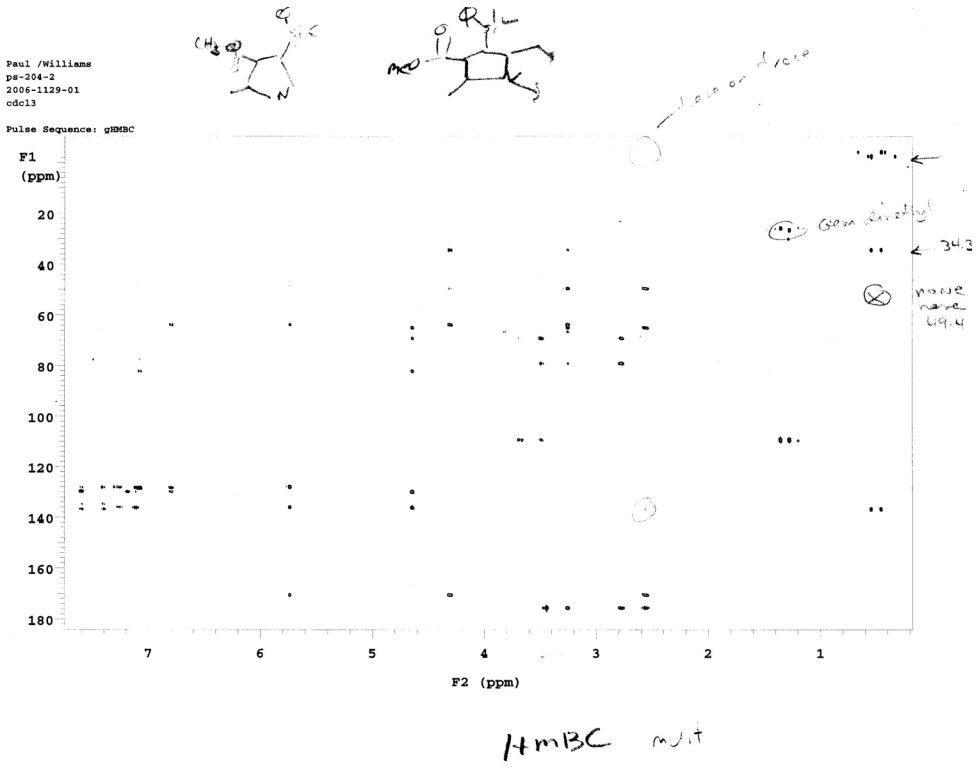
NOSEY spectrum (400 MHz, $CDCl_3$) of compound **137**



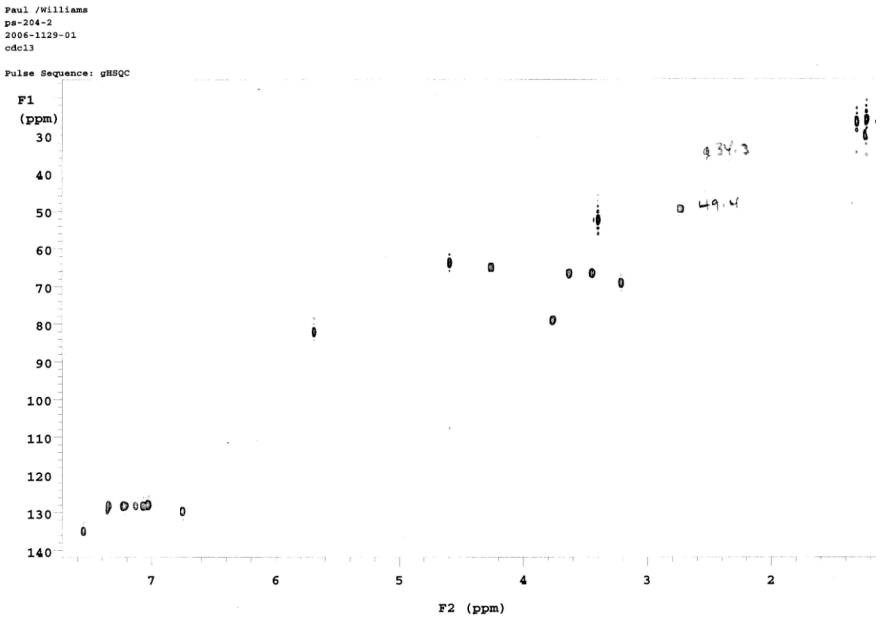
nOe spectrum (300 MHz, $CDCl_3$) of compound **137**



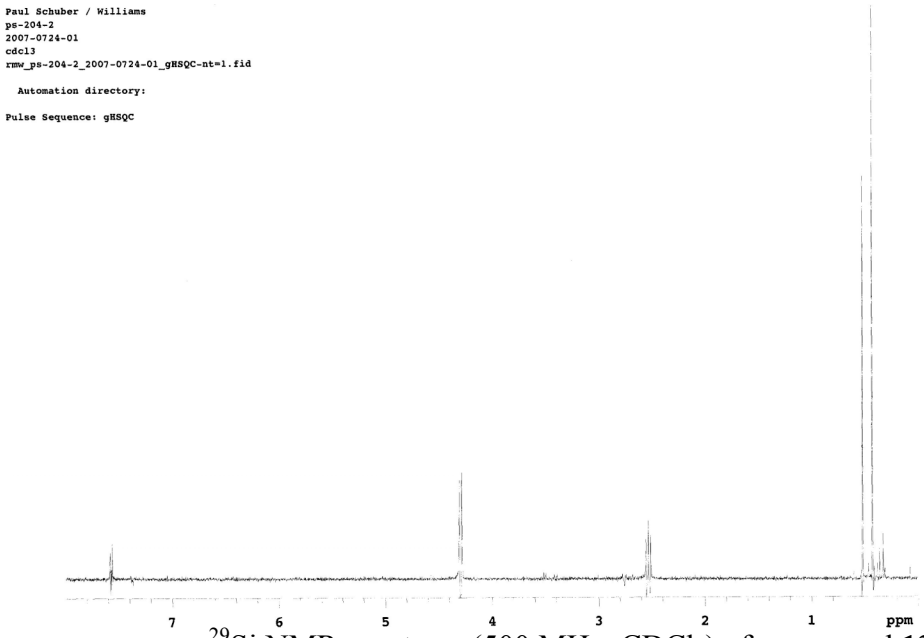
COSEY spectrum (400 MHz, $CDCl_3$) of compound **137**



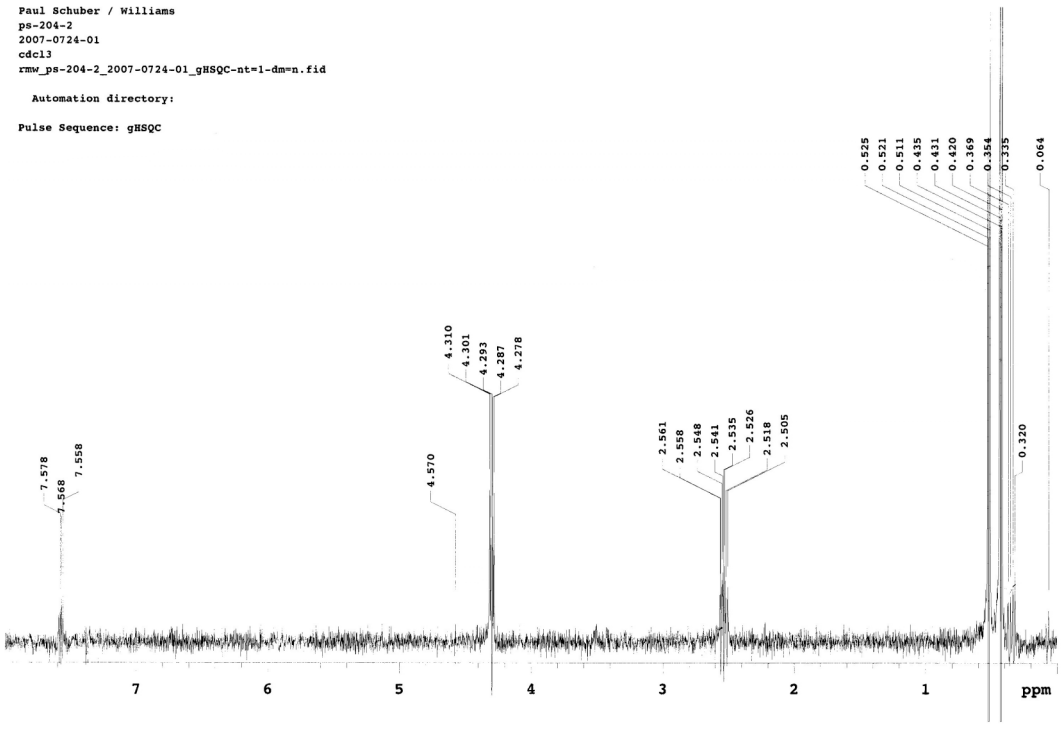
HMBC spectrum (500 MHz, $CDCl_3$) of compound **137**



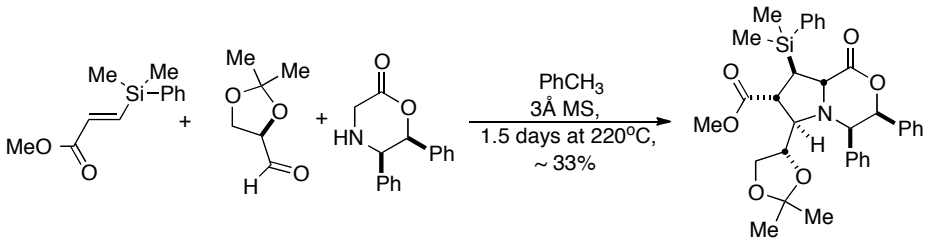
HSQC spectrum (500 MHz, $CDCl_3$) of compound **137**



^{29}Si NMR spectrum (500 MHz, $CDCl_3$) of compound **137**



^{29}Si NMR spectrum (500 MHz, $CDCl_3$) of compound **137**



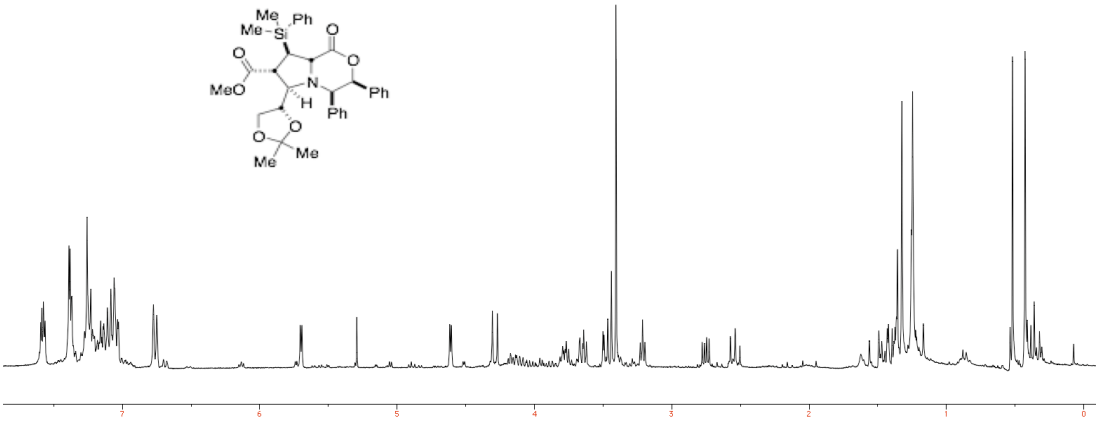
136 **116** **73** **137**

(3S,4R,6R,7R,8R,8aS)-methyl 8-(dimethyl(phenyl)silyl)-6-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxo-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (137):

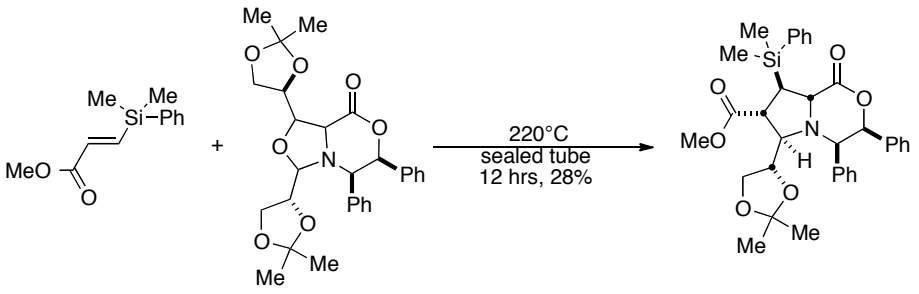
To a flame dried 25 mL pressure tube was added a stir bar, 3 Å molecular sieves, Williams' Lactone **73** (100 mg, 0.395mmol, 1equiv.), dipolarophile **136** (226 mg, 1.18 mmol, 3 equiv.), and aldehyde **116** (64 mg, 0.493 mmol, 1.25 equiv.). The reaction was slowly heated to 220 °C for 1.5 days followed by being filtered over celite and concentrated to yield the crude material. The crude material was columned in 95:5 Hexanes/EtOAc to afford the pure material **137** (7 mg 33% yield). (ps-476-1)

R_f=0.32 (80:20 Hexanes:EtOAc)

^{1}H NMR ($CDCl_3$ 300MHz) : δ 7.59 – 6.75 (m, 17 H), 6.69 (d, J = 3.6, 1H), 4.60 (d, J = 3.6, 1H), 4.29 (d, J = 10.8, 1H), 3.77 (m, 1H), 3.64 (m, 1H), 3.44 (m, 1H), 3.21 (t, J = 5.1, 5.1, 1H), 2.75 (dd, J = 5.4, 9.9, 1H), 2.53 (dd, J = 10.5, 10.5, 1H), 1.32 (s, 3H), 1.24 (s,3H), 0.51 (s, 3H), 0.42 (s, 3H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **137**



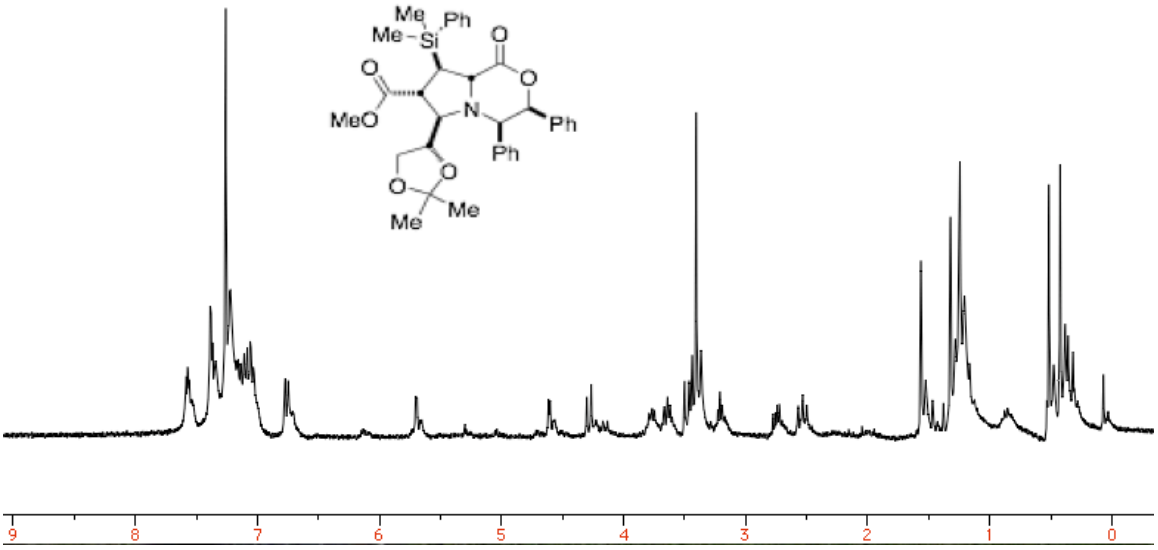
136 **122** **137**

3S,4R,6R,7R,8R,8aS)-methyl 8-(dimethyl(phenyl)silyl)-6-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxo-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (137):

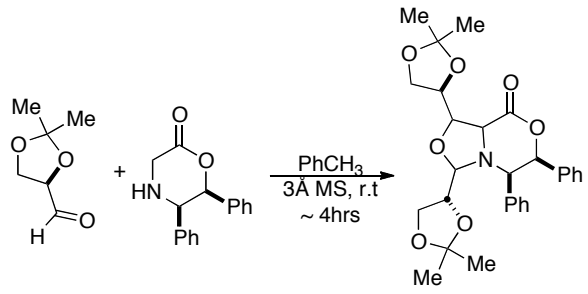
To a flame dried 25 mL pressure tube was added a stir bar, 3 Å molecular sieves, byproduct **122** (30 mg, 0.060 mmol, 1 equiv.), and dipolarophile **136** (30 mg, 0.18 mmol, 3 equiv.). The reaction was slowly heated to 220°C for 12 h followed by being filter and concentrated to yield the crude material. The crude material was columned in 90:10 Hexanes/EtOAc to afford compound **137** (10mg , 28% yield). (ps-472-d2)

R_f=0.32 (80:20 Hexanes:EtOAc)

^{1}H NMR ($CDCl_3$ 300MHz) : δ 7.59 – 6.75 (m, 17 H), 6.69 (d, J = 3.6, 1H), 4.60 (d, J = 3.6, 1H), 4.29 (d, J = 10.8, 1H), 3.77 (m, 1H), 3.64 (m, 1H), 3.44 (m, 1H), 3.21 (t, J = 5.1, 5.1, 1H), 2.75 (dd, J = 5.4, 9.9, 1H), 2.53 (dd, J = 10.5, 10.5, 1H), 1.32 (s, 3H), 1.24 (s,3H), 0.51 (s, 3H), 0.42 (s, 3H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **137**



116 **73** **122**

(5R,6S)-1,3-bis((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-5,6-diphenyltetrahydrooxazolo[4,3-c][1,4]oxazin-8(3H)-one (122):

To a 10 mL vial equipped with a stir bar in $PhCH_3$ (250 μl) was added Williams' lactone **73** (25 mg, 0.098 mmol, 1 equiv.), 3 Å molecular sieves, and aldehyde **116** (79 mg, 0.464 mmol, 5 equiv.). The reaction was stirred at rt until the reaction was complete by TLC and then columned in an EtOAc hexane mixture to afford compound **122** (30 mg, 53% yield). (ps-472-sm)

$[\alpha]^{25}_D$ = - 106.6 (*c* = 0.42, $CHCl_3$)

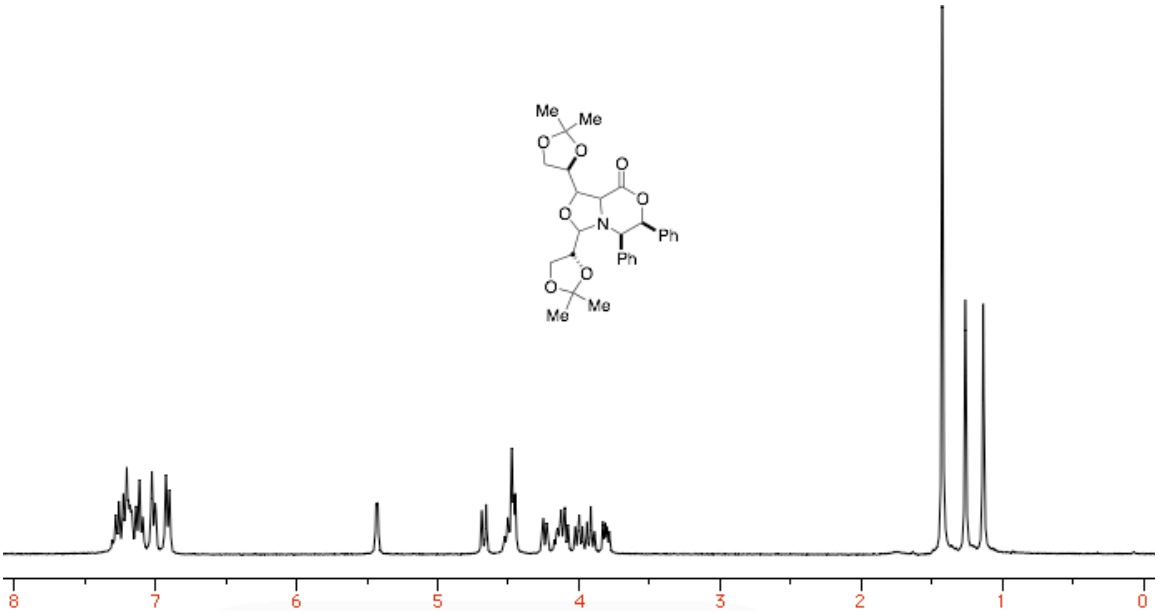
R_f=0.55 (70:30 Hexanes:EtOAc)

IR (neat) ν 3925, 1736, 1457, 1370, 1220, 1142, 1069

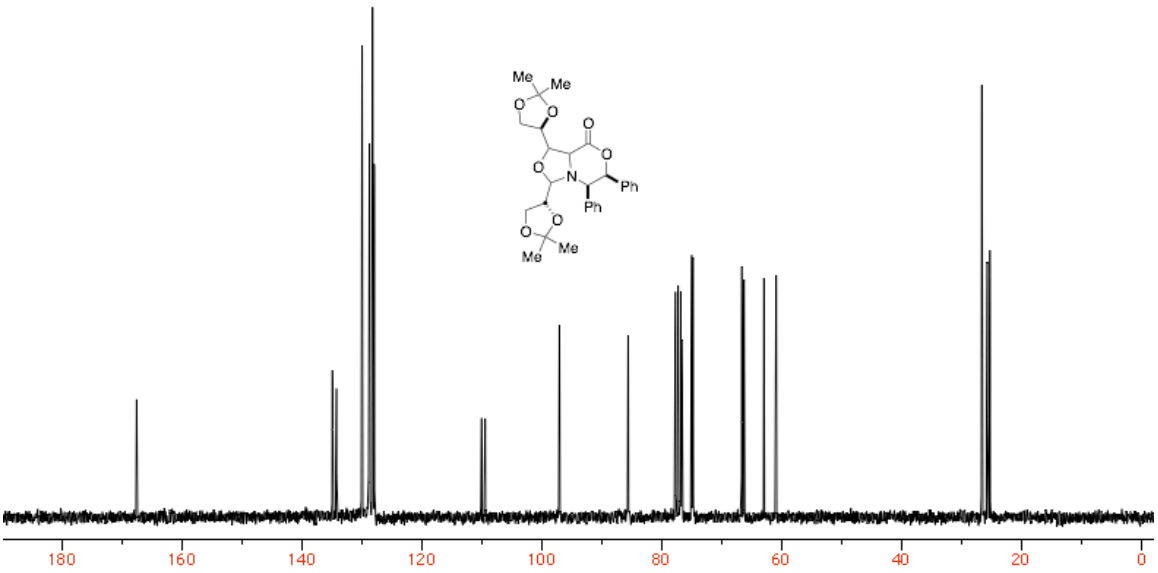
^{1}H NMR ($CDCl_3$ 300MHz) : δ 7.30 – 6.90 (m, 10 H), 5.43 (d, J = 3.6, 1H), 4.67 (d, J = 9.3, 1H), 4.53 – 4.44 (m, 3H), 4.24 (dd, J = 3.0, 9.3, 1H), 4.17 – 4.07 (m, 2H), 3.99 (dd J = 15.9, 8.7, 1H), 3.91 (dd, J = 7.8, 7.8, 1H), 3.80 (dd, J = 4.8, 9.0, 1H), 1.42 (s, 6H), 1.26 (s,3H), 1.13 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 177.54, 134.90, 134.22, 129.95, 128.80, 128.72, 128.65, 128.21, 127.92, 110.04, 109.43,97.048, 85.59, 76.64, 74.98, 74.76, 66.64, 66.26, 62.26, 60.91, 26.62, 25.70, 25.26

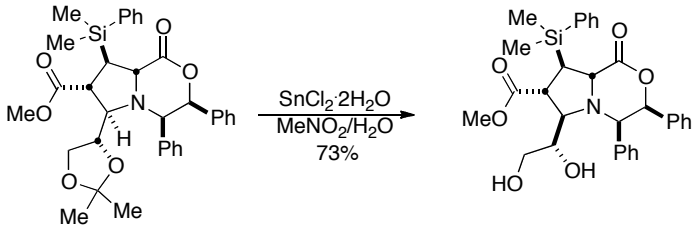
HRMS Calcd for $C_{29}H_{34}NO_7$ $[M+H]^+$ 496.2, Found 496.2 $[M+H]^+$.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **122**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **18**



137 159

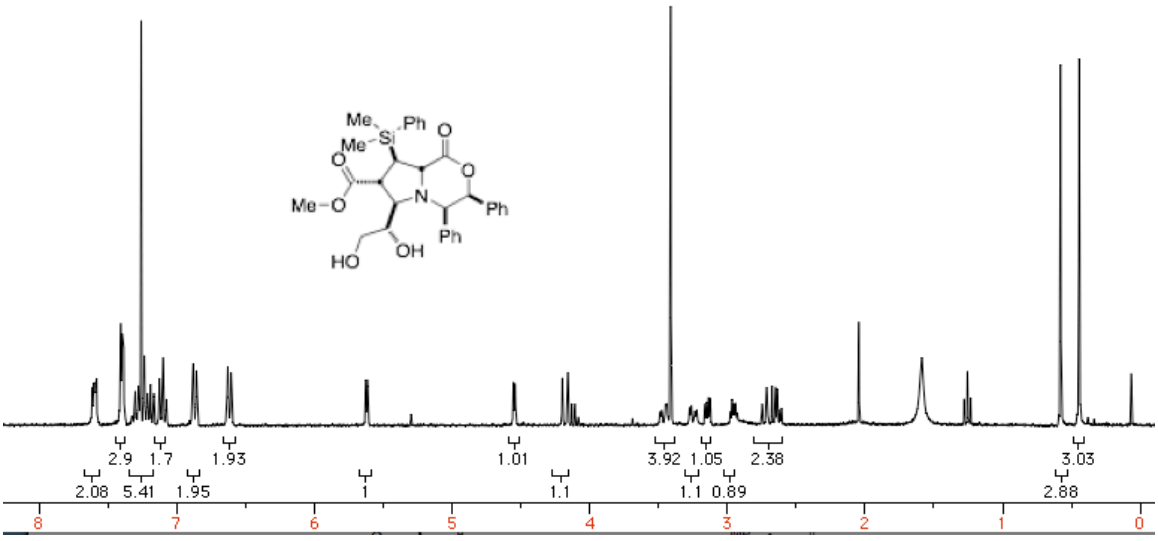
(3*S*,4*R*,6*R*,7*R*,8*R*,8a*S*)-methyl 6-(1,2-dihydroxyethyl)-8-(dimethyl(phenyl)silyl)-1-oxo-3,4-diphenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-7-carboxylate (159):

To a 50 mL rbf equipped with a stir bar was added compound **137** (800 mg, 1.36 mmol, 1 equiv), in NO_2Me saturated with H_2O (20 mL). $SnCl_2 \cdot 2H_2O$ (921 mg, 4.08 mmol, 3 equiv.) was added to the reaction mixture in small portions. The reaction was stirred for 2 h and saturated aqueous solution of $NaHCO_3$ (15 ml) was added followed by the addition of EtOAc (20 mL) The crude reaction mixture was filtered over celite, separated, and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers was washed with H_2O (3 x 10 mL), dried, filtered, and concentrated to afford 622 mg of crude material. The crude material was then purified by flash chromatography (gradient elution, 70:30 to 50:50 Hexane/EtOAc) to give the pure material **159** (73% yield). (ps2-292-2)

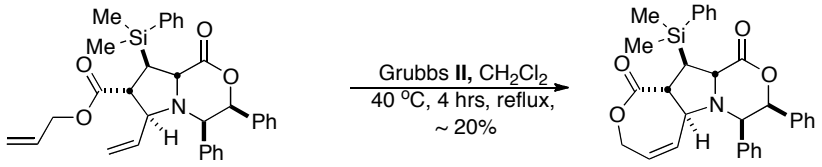
R_f= 0.55 (50:50 EA/Hex)

^{1}H NMR ($CDCl_3$ 300MHz) : δ. 7.61 – 6.62 (m, 15H), 5.61 (d, J = 3.3, 1H), 4.53 (d, J = 3.6, 1H), 4.17 (d, J = 12, 1H), 3.45 (dd, J = 3.6, 12, 1H), 3.41 (s, 3H), 3.25 (dd, J = 3.9, 11.7, 1H), 3.14 (J = 3.0, 7.2, 1H) 2.95(m, J= 3.6,3.6,7.2,1H) 0.58 (s, 3H), 0.44 (s,3H).

HRMS Calcd for $C_{33}H_{38}NO_4Si$ $[M+H]^+$ 572.24 Found 572.24 $[M+H]^+$.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **159**

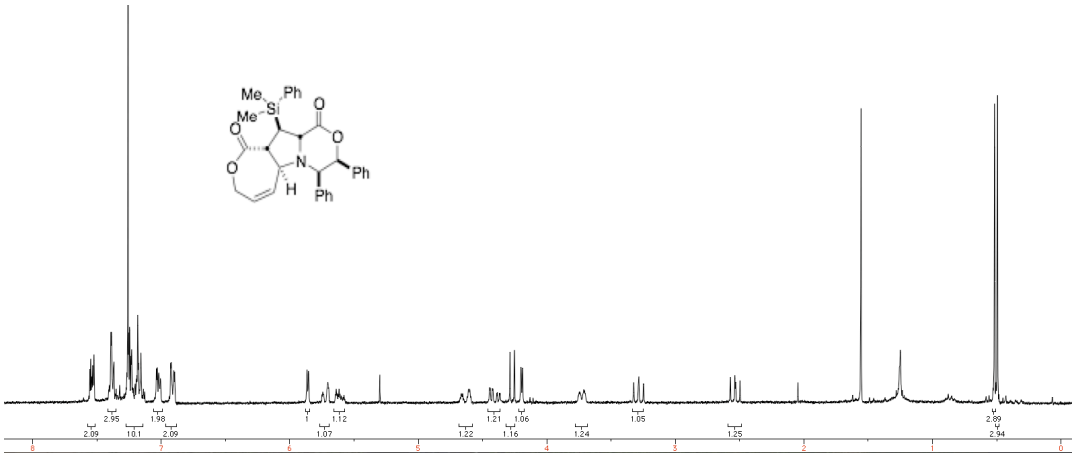


157 156

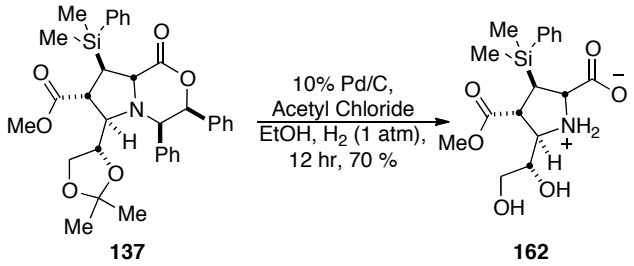
(3S,4R,5aS,10aR,11R,11aS)-11-(dimethyl(phenyl)silyl)-3,4-diphenyl-3,4,8,10a,11,11a-hexahydro-1H-oxepino[3',4':4,5]pyrrolo[2,1-c][1,4]oxazine-1,10(5aH)-dione (156):

To a flame dried 100 mL rbf was added compound **157** (25 mg, 0.046 mmol, 1 equiv.) in CH_2Cl_2 (42 mL). To the light brown reaction mixture was added a solution of Grubb's second generation catalyst (4 mg, 0.0047 mmol, 0.1 equiv.) in CH_2Cl_2 (5 mL) The reaction was sparged with argon before refluxing for 4 h. The reaction was cooled to rt and the solvent was removed *in vacuo*. The crude material was then purified by flash chromatography (gradient elution from 80:20 to 50:50 Hexane:EtOAc) to afford compound **156** (20% yield). (ps-383-4, ps2-454-3)

^{1}H NMR ($CDCl_3$, 300MHz) : δ 7.55 – 6.89 (m, 15H), 5.85 (d, J = 3.3, 1H), 5.72 (m, 1H), 5.63 – 5.59 (m, 1H), 4.62 (m, 1H), 4.40(m, 1H), 4.26 (d, J = 10.5, 1H), 4.20 (d, J = 3.3, 1H), 3.72 (m, 1H), 3.28 (dd, J = 11.4, 11.4, 1H), 2.53 (dd, J = 12.0, 11.4, 1H), 0.51 (s, 3H), 0.49 (s, 3H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **156**



137 **162**

(2S,3R,4R,5R)-5-(1,2-dihydroxyethyl)-3-(dimethyl(phenyl)silyl)-4-(methoxycarbonyl)pyrrolidin-1-ium-2-carboxylate (162):

To a 100 mL rbf was added compound **137** (500 mg, 0.835 mmol, 1 equiv.) in absolute ethanol (5 mL). The reaction was sparged with argon and 10% Pd on carbon (250 mg by weight) was added followed by equipment of the round bottom with a stir bar and a balloon of H_2. Acetyl chloride (181 μl, 2.55 mmol, 3 equiv.) was added to the reaction mixture and stirring continued overnight and monitored by TLC until all starting material was consumed. The reaction was filtered over celite, and concentrated to reveal a white foam. The foam was dissolved in CH_2Cl_2 (20 mL) and was purified by flash chromatography with C18 reverse phase silica gel 90:10 CH_3CN/H_2O to provide pure product **162** (240 mg, 70 % yield) that is slightly soluble in water. (ps2-284-2) (ps-435-2)

R_f = 0.50 (60:40 CH_3CN/H_2O.)

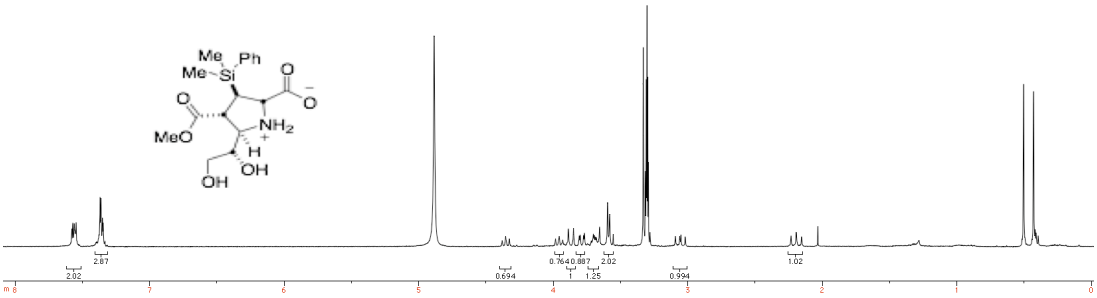
$[\alpha]^{25}_D$ = -10.3 (*c* = 1.05, $CHCl_3$)

IR (neat) ν 3333, 2955 2349, 1737, 1629, 1428, 1368, 1200, 1052, 778 cm^{-1}

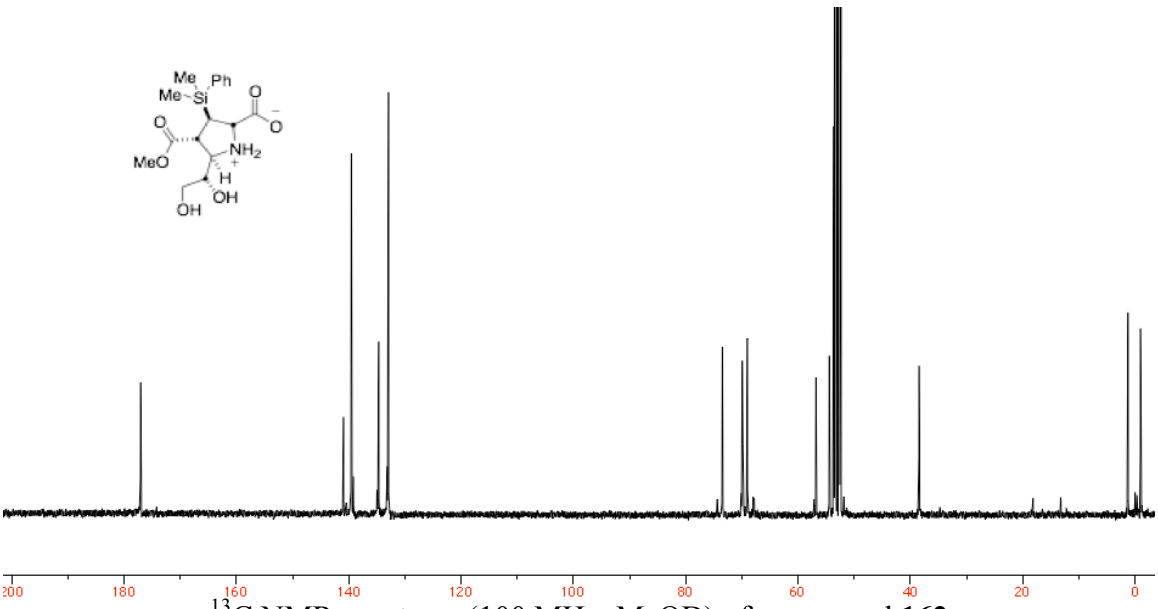
^1H NMR (CD_3OD_3, 300MHz) (ps-435-2) : δ 7.57 – 7.64 (m, 2H), 7.39 – 7.33 (m, 2H), 4.35 (t, J = 18, 1H), 3.95 (t, J = 15, 1H), 3.86 (d, J = 9, 1H), 3.79 (dd, J = 2.1, 9.6, 1 H), 3.70 (m, 1H) 3.33 (s, 3H), 3.06 (dd, J = 9.6, 12.3, 1H) 2.19 (dd, J = 8.4, 9.0, 1H) 0.50 (s, 3H), -0.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 177.04, 140.92, 139.53, 139.18, 134.65, 133.13, 132.92, 73.47, 69.93, 69.82, 69.04, 56.81, 54,.45, 38.46, 1.26, -0.95.

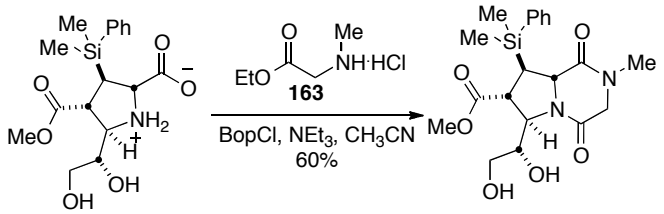
HRMS Calcd for $C_{17}H_{25}NO_6Si[M+H]^+$ 367.1 Found 368.1 (M+H).



^{1}H NMR spectrum (300 MHz, MeOD) of compound **162**



^{13}C NMR spectrum (100 MHz, MeOD) of compound **162**



(6R,7R,8R,8aS)-methyl 6-(1,2-dihydroxyethyl)-8-(dimethyl(phenyl)silyl)-2-methyl-1,4-dioxooctahydropyrrolo[1,2-a]pyrazine-7-carboxylate (164):

To a 100 mL rbf was added **162** (281 mg, 0.76 mmol, 1 equiv.), CH_3CN (10 mL), sarcosine ethyl ester hydrochloride **163** (163 mg, 1.07 mmol, 1.4 equiv.), TEA (692 μl, 4.97 mmol, 6.5 equiv.) and the reaction was stirred for 30 minutes followed by the addition of BopCl (272 mg. 1.07 mmol, 1.4 equiv). The reaction was stirred for 2 days and evaporated to dryness. EtOAc (5 mL) and 1NHCl (5 mL) was added and stirring continued for 1 h. The aqueous layer was extracted with EtOAc (2 x 10 mL) and washed with a saturated solution of $NaHCO_3$ (2 x 10 ml), H_2O (2 x 10 mL) and NaCl (2 x 10mL). The light yellow material was dried over $NaSO_4$ and concentrated. The crude reaction mixture was purified by flash chromatography (gradient elution 98.75:1.25 to 93:7 DCM/MeOH) to afford 217 mg of compound **164** (60% yield).

R_f = 0.41 (95:5 DCM/MeOH.)

$[\alpha]^{25}_D$ = 18.5 (*c* = 1.78, $CHCl_3$)

IR (neat) ν 3406, 2953, 1736, 1652, 1468, 1406, 1340, 1300, 1255, 1212, 1111,

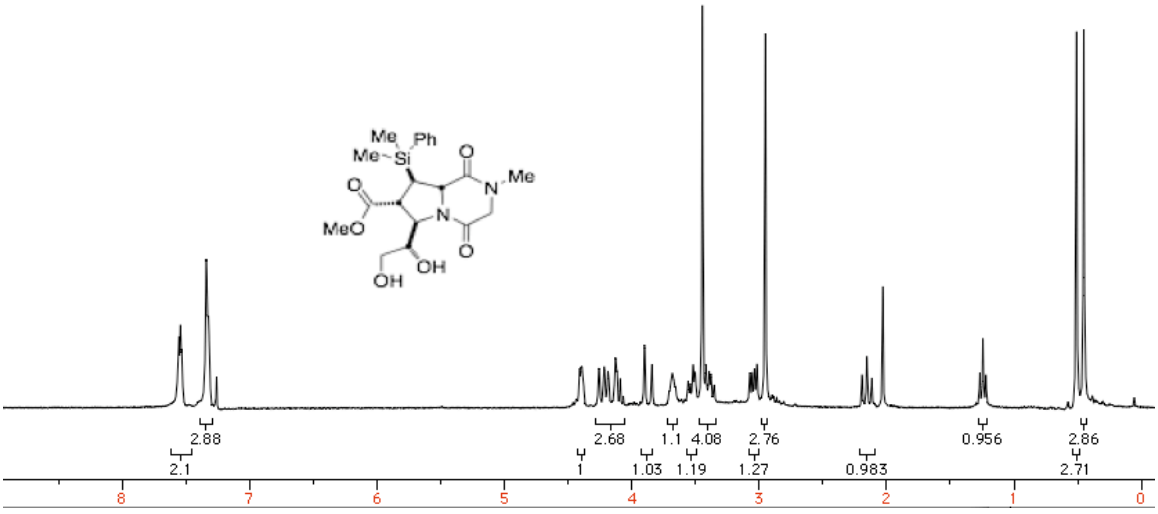
1044 cm^{-1};

^1H NMR ($CDCl_3$, 400MHz, ps-115-2) : δ 7.54 – 7.52 (m, 2H), 7.33 – 7.31 (m, 3H), 4.38 (dd, J = 2.7, 4.2, 1H), 4.20 (d, J = 9.3, 1H), 4.14 (dd, 1H), 3.87 (dd, 1H), 3.68 – 3.86 (m, 1H), 3.56 – 3.50 (m, 1H), 3.44 (s, 3H), 3.39 (dd, J = 5.1, 14.4, 1H), 3.00, (dd, J = 3.0, 8.4,

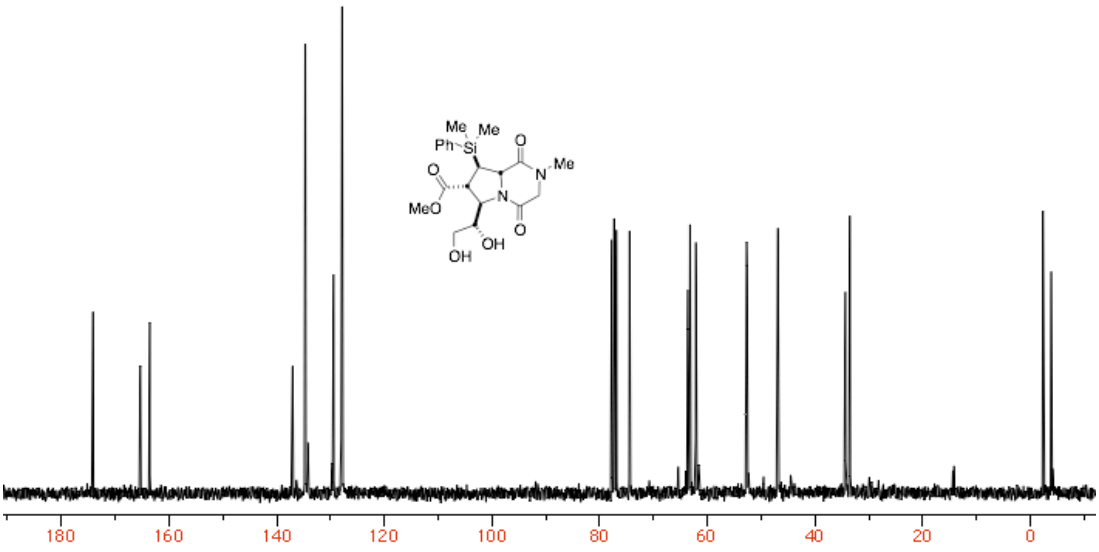
1H), 2.95 (s, 3H), 2.15 (dd, J = 8.4, 9.0, 1H), 1.21 (t, J = 4.8, 1H) 0.50 (s, 3H), 0.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 174.13, 165.34, 163.57, 137,03, 134.70, 129.44, 127.84, 74.44, 63.61, 63.20, 62.13,

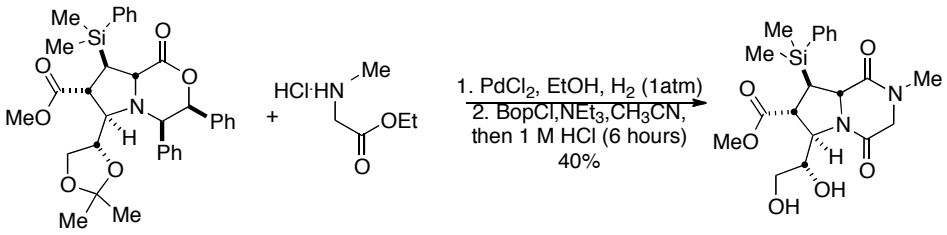
HRMS Calcd for $C_{20}H_{28}BrN_2O_6SiNa$ $[M+H]^+$ 443.1 Found 443.1 (M+H and sodium).



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **164**



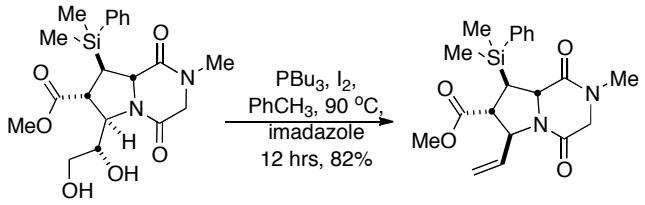
^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **164**



137 **163** **164**

(6R,7R,8R,8aS)-methyl 6-(1,2-dihydroxyethyl)-8-(dimethyl(phenyl)silyl)-2-methyl-1,4-dioxooctahydropyrrolo[1,2-a]pyrazine-7-carboxylate (164):

To a flame dried 5 mL rbf was added compound **137** (102 mg, 0.17 mmol, 1 equiv.) in absolute ethanol (1.5mL). The reaction was sparged with argon before adding $PdCl_2$ (25 mg, 0.01 mmol, 0.8 equiv.) to the reaction mixture followed by equipment of the round bottom with a stir bar and a balloon of H_2 (1 atm). The reaction was stirred overnight, filtered over celite, and concentrated under reduced pressure to afford 87 mg of crude product. The bold yellow compound was then left on the pump for 2 h. The crude free amino acids was redissolved in CH_3CN (1.5 mL) followed by the addition of sarcosine ethyl ester hydrochloride (126 mg, 0.495mmol, 2.95 equiv.), and BopCl (60 mg. 0.576 mmol, 2.2 equiv.). The reaction vessel was vented with argon (3 x) followed by the addition of NEt_3 (104 μl, 0.746 mmol, 4.3 equiv.). The reaction was stirred for 2 days. 1 N HCl (10 mL) and EtOAc (10 mL) was added and stirring continued for another h. The two layers were separated and the aqueous layer was extracted EtOAc (3 x 10 mL. The combined organics were dried over Na_2SO_4 and concentrated. The crude reaction mixture was purified by flash chromatography (gradient elution, 98.75:1.25 to 95:5 DCM/MeOH) to give compound **164** (30 mg, 40% yield.) (ps-437-1-18)



164 **166**

(6*S*,7*R*,8*R*,8a*S*)-methyl 8-(dimethyl(phenyl)silyl)-2-methyl-1,4-dioxo-6-vinyloctahydropyrrolo[1,2-*a*]pyrazine-7-carboxylate (166):

To a 50 mL rbf equipped with a stir bar was added compound **164** (202 mg, 0.483 mmol, 1 equiv.) tributylphosphine (408 μl, 1.92 mmol, 4 equiv), imidazole (131 mg, 1.92 mmol, 4 equiv) in $PhCH_3$ (10 mL). The reaction was heated to 90 °C upon addition of I_2 (731 mg, 2.88 mmol, 6 equiv.) in small portions the reaction was stirred for 24 h. The red was diluted with EtOAc (25 mL) and the organic layer was washed with 10% aqueous solution of $NaSO_4$ (20 mL), H_2O (2 x 20 mL) and a saturated solution of NaCl (2 x 20 mL). The reaction was dried, concentrated and purified by flash chromatography in 98.25:1.75 DCM/MeOH to afford pure compound **166** (153 mg, 82% yield)

NOTE: A long column is needed to get rid of the excess Bu_3P or purification with a second column) ps2-159-3

R_f = 0.44 (97:3 DCM/MeOH).

$[\alpha]^{25}_D$ = 28.0 (*c* = 0.891, $CHCl_3$)

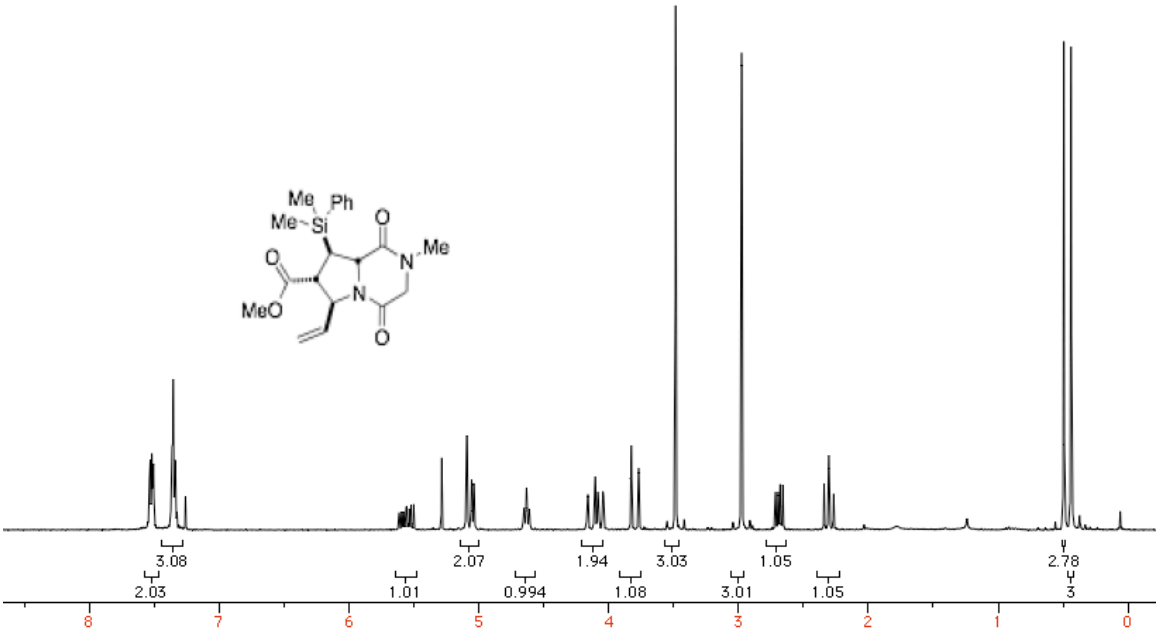
IR (neat) ν 2954, 1736, 1671, 1435, 1256, 1111, 843, 779, 739, 703 cm^{-1}

^1H NMR ($CDCl_3$, 300MHz): δ 7.70 – 7.43 (m, 45H), 5.62 – 5.50 (m, 1H), 5.10 – 5.04 (m, 2H), 4.64 (t, J = 3.9, 3.9, 1H), 4.17 - 4.04 (m, 2H), 3.80 (dd, 1H), 3.49 (s, 3H), 2.98 (s,

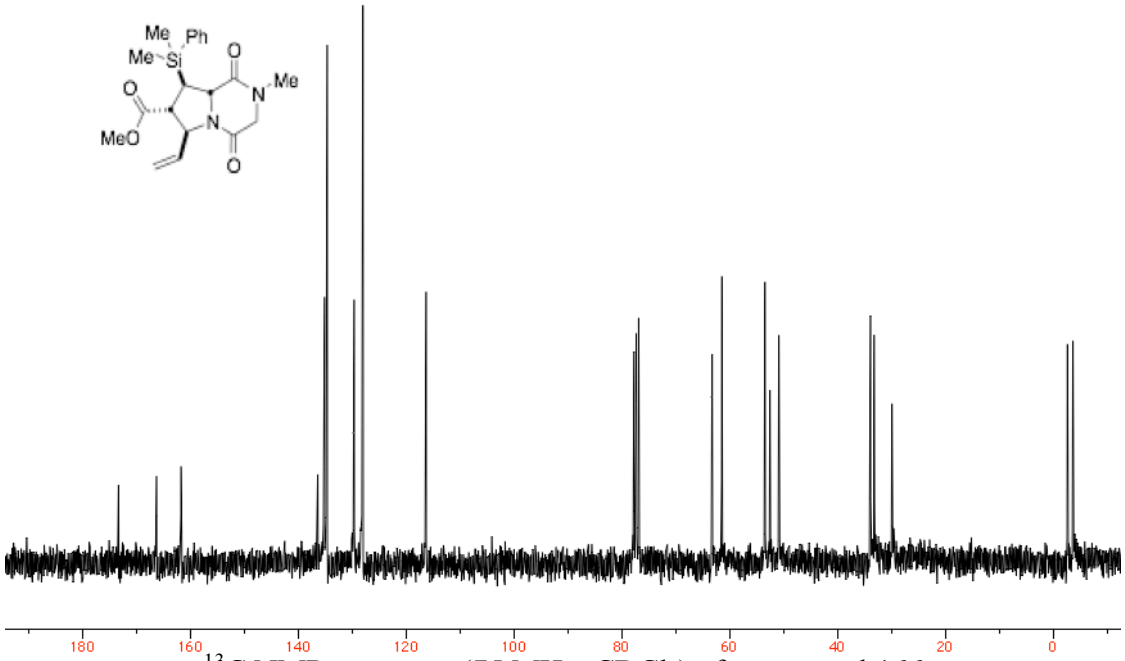
3H), 2.69 (dd, J = 6.0, 11.4, 1H), 2.31 (dd, J = 11.1, 10.5, 1H), -0.50 (s, 3H), 0.44 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 173.33, 166.28, 161.74, 136.39, 135.13, 134.65, 129.64, 128.15, 128.02, 116.30, 63.27, 61.46, 53.47, 52.53, 50.88, 33.90, 33.21, 29.91, -2.60, -3.63

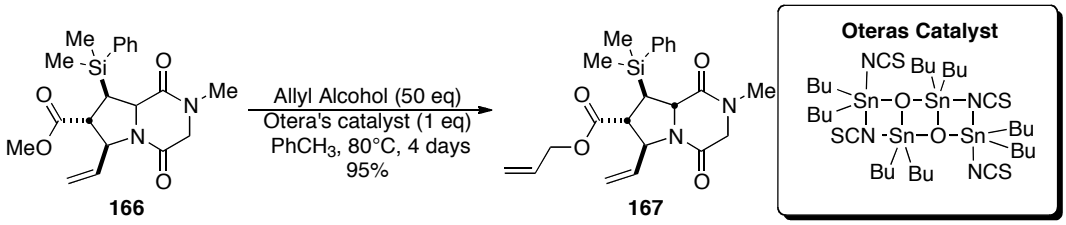
HRMS Calcd for $C_{20}H_{26}N_2NaO_4Si$ $[M+H]^+$ 409.1 Found 409.1 (M+H and sodium).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **166**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **166**



(6*S*,7*R*,8*R*,8a*S*)-allyl 8-(dimethyl(phenyl)silyl)-2-methyl-1,4-dioxo-6-vinyloctahydropyrrolo[1,2-*a*]pyrazine-7-carboxylate (167):

To a 10 mL pressure vessel equipped with a stir bar was added compound **166** (72 mg, 0.186 mmol, 1 equiv.), allyl alcohol (633 μl, 9.31 mmol, 50 equiv.) and Otera's catalyst (222 mg, 0.186 mmol, 1 equiv.) in $PhCH_3$ (2 mL). The reaction was heated at 80 °C for 4 days and filtered over a pad of silica, and put on a vacuum pump overnight. The crude residue was purified by flash chromatography (gradient elution, 98.75:1.25 to 97:3 DCM/MeOH to afford **167** (69 mg, 90% yield). (ps2-144-2)

R_f = 0.40 (97:3 DCMMeOH)

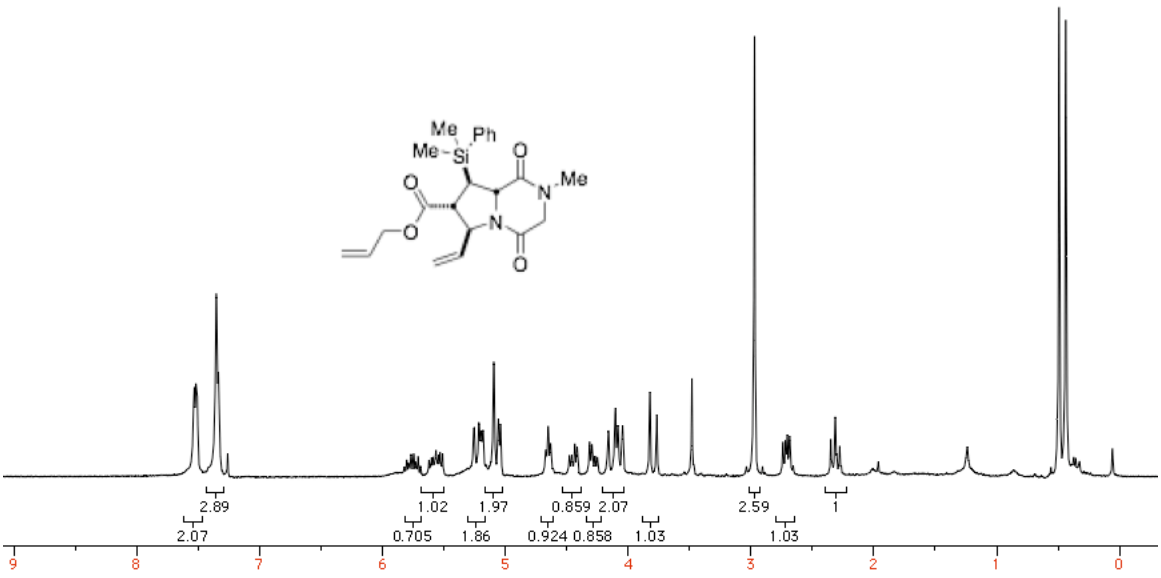
$[\alpha]^{25}_D$ = 26.4 (*c* = 0.56, $CHCl_3$)

IR (neat) ν 29.25, 2854, 1735, 1670, 1453, 1299, 1257, 1157, 1111 cm^{-1}

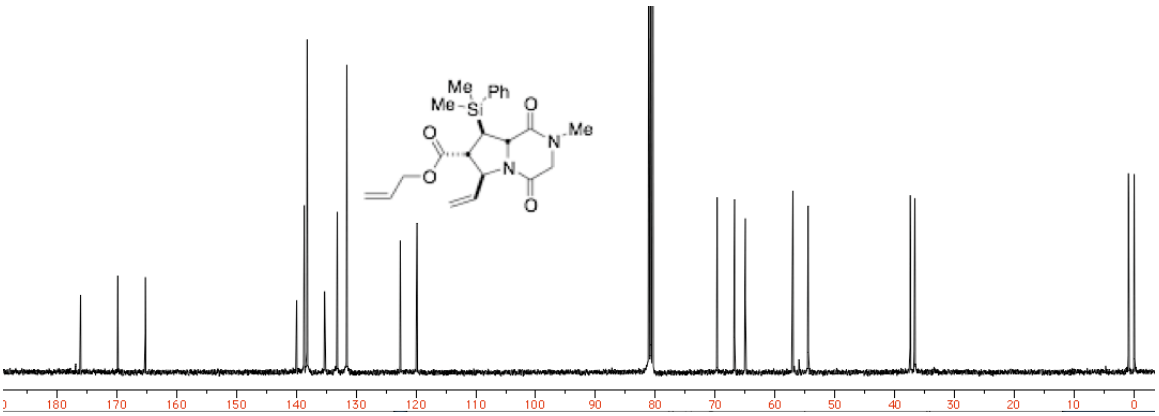
^{1}H-NMR ($CDCl_3$ 300MHz) : δ 7.57 - 7.51 (m, 2H), 7.36 – 7.34 (m, 3H), 5.70, (ddd, 1H), 6.52 (m, J = , 1H), 5.27 – 5.16 (m, J = , 2H), 5.107 – 5.05 (m, J = , 2H), 4.66 (t, J = 8.13, 1H), 4.49 – 4.26 (m, 1H), 4.33 – 4.26 (m,1H), 4.10 (dd, J = 17.1, 24.0, 2H), 3.83 (d, J =, 1H), 2.98 (s, 3H), 2.72 (dd, J = 6.0, 10.8, 1H), 2.32 (t, J = 11.1, 1H), 0.50 (s, 3H), 0.44 (s, 3H),

^{13}C NMR (75 MHz, $CDCl_3$) 176.04, 169.83, 165.21, 139.93, 138.66, 138.18, 135.26, 133.15, 131.55, 122.62, 119.83, 69.66, 66.76, 64.97, 57.01, 54.447, 37.42, 37.42, 36.64, 0.09, -.00

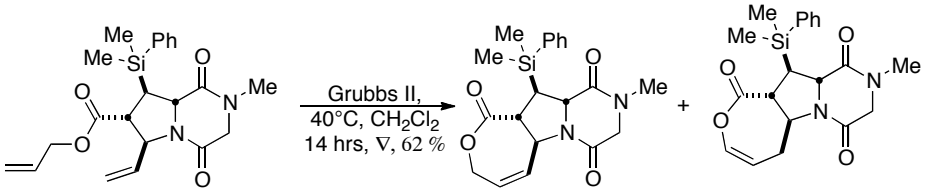
HRMS Calcd for $C_{20}H_{26}N_2NaO_4Si$ $[M+H]^+$ 435.1 Found 435.1 (M+H and sodium).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **167**



^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **167**



167 **161** **170**

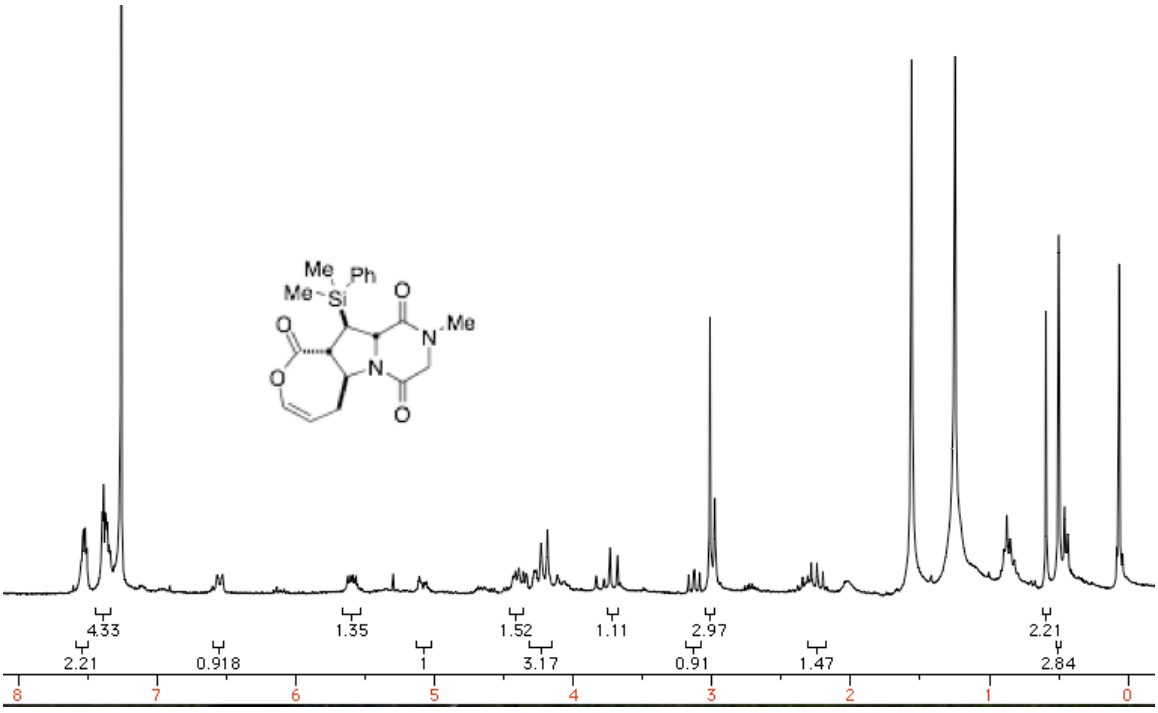
~ 1:2.5
170:177

(5a*S*,10a*R*,11*R*,11a*S*)-11-(dimethyl(phenyl)silyl)-2-methyl-2,3,5a,6,11,11a-hexahydrooxepino[3',4':4,5]pyrrolo[1,2-*a*]pyrazine-1,4,10(10a*H*)-trione (170):

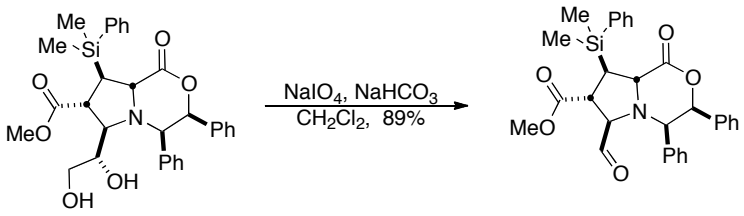
To a flame dried 10 mL rbf equipped with a stir bar was added **167** (7 mg, 0.0168 mmol, 1 equiv.) and CH_2Cl_2 (20 mL). The reaction was sparged with argon. A reflux condenser was added to the round bottom and the reaction vessel was sparged with argon for 10 minutes. Another 10 mL flask was flame dried and CH_2Cl_2 (2 mL) was added followed by sparging with argon. Grubbs Second Generation catalyst (2 mg, 0.00153 mmol, 0.09 equiv.) was added and the reaction was quickly taken up in a syringe and added to the flask that contained compound **26**. The reaction was taken to 40 °C and was refluxed for 14 hours. Upon completion, the reaction was evaporated and prepplated to give compound **161** and compound **170** (ps-473-4)

^{1}H NMR ($CDCl_3$ 300MHz) : δ 7.54 – 7.33 (m, 5H), 6.54 (d, J = 12.0, 1H). 5.60 (m, 1H), 5.10 (m, 1H), 4.36 (dd, J = 7.5, 16.8), 4.27 (m, 1H), 4.20 (d, J = 13.2, 1H). 3.71 (d, J = 14.7), 3.13, (dd, J = 11.1, 12.9, 1 H), 3.01 (s, 3H), 2.24 (dd, J = 12.0, 13.2), 0.59 (s, 3H), 0.50 (s, 3H).

HRMS Calcd for $C_{20}H_{24}N_2O_4SiNa$ $[M+H]^+$ 407.1 Found 407.1



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **170**



181 **177**

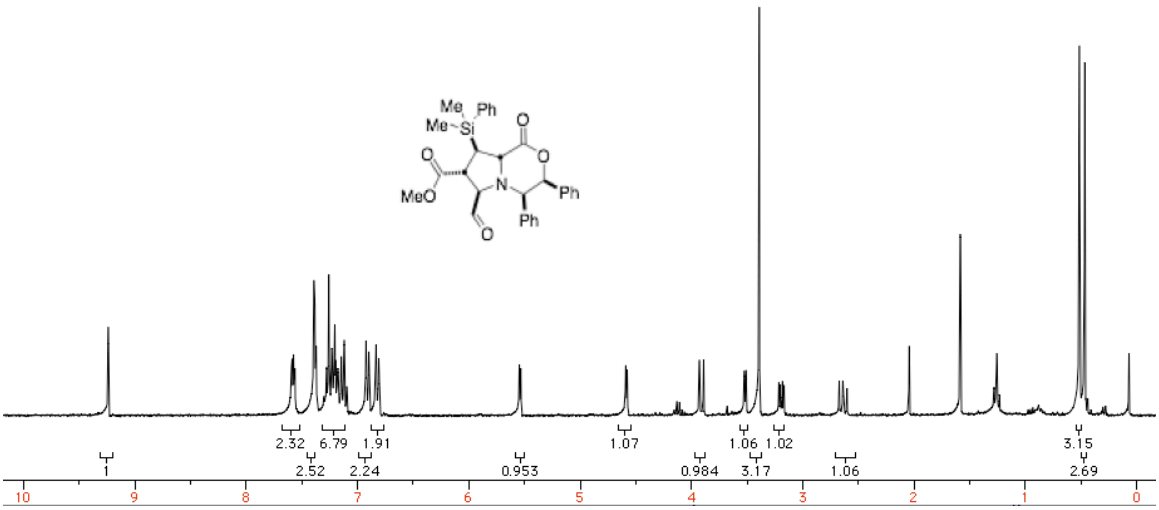
(3S,4R,6R,7R,8R,8aS)-methyl 8-(dimethyl(phenyl)silyl)-6-formyl-1-oxo-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (181):

To a 100 mL rbf was added **181** (495 mg, 0.91 mmol, 1 equiv.) and dissolved in a mixture of CH_2Cl_2 (5 mL) and $NaHCO_3$ (250 μl). $NaIO_4$ (292 mg, 0.17 mmol, 1.5 equiv) was added in portions over a 30 minute period. After 24 h of vigorously stirring $NaSO_4$ was added and stirring continued for another 30 minutes. The crude reaction mixture was then filtered and concentrated to give 413 mg of crude material. The material was then purified by flash chromatography (gradient elution, 70:30 to 50:50 Hexanes/EtOAc) to afford compound **177** (350 mg, 89 % yield). (ps2-293-3, p2-293-4)

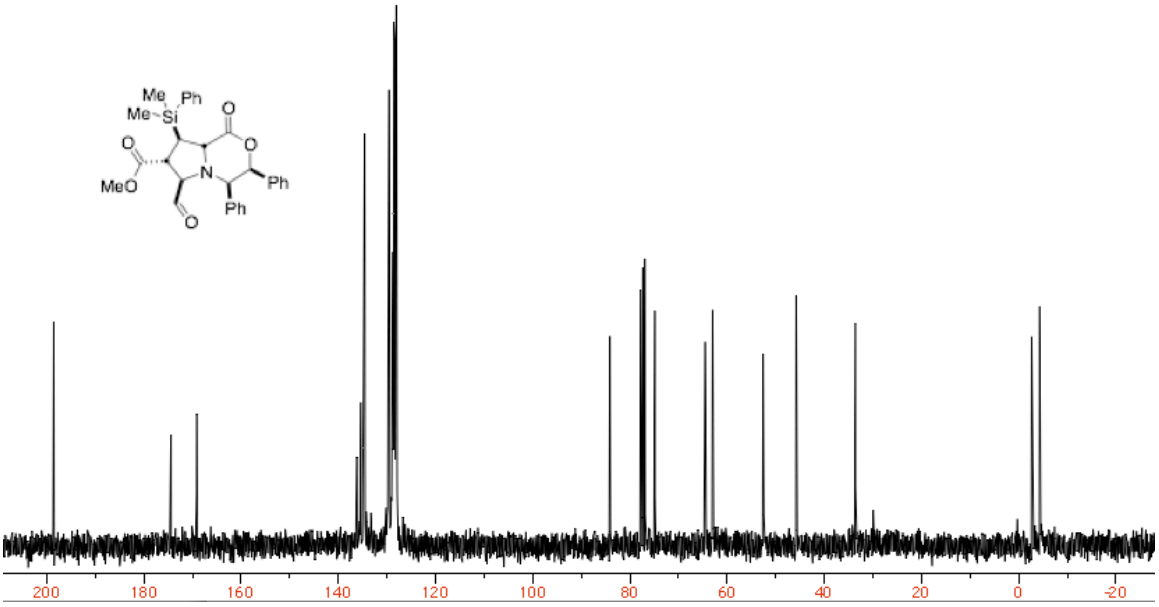
R_f = 0.74 (50:50 Hexanes/EtOAc),

^{1}H NMR ($CDCl_3$ 300MHz) : δ. 9.23 (s,1H) 7.59 – 6.80 (m, 15H), 5.54 (d, J = 3.0, 1H), 4.58 (d, J = 3.9, 1H), 3.91 (d, J = 11.4, 1H), 3.52 (d, J = 4.5, 1H), 3.31 (s, 3H), 3.19 (dd, J = 4.5, 9.3, 1H), 2.64 (J = 9.6, 11.4, 1H), 0.51 (s, 3H), 0.46 (s,3H).

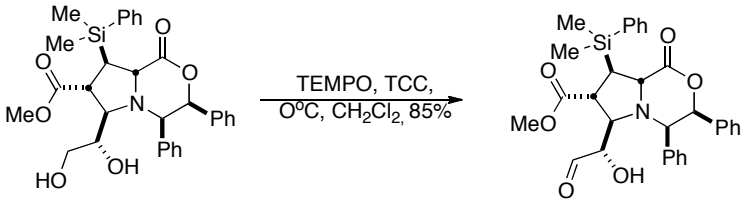
^{13}C NMR (75 MHz, $CDCl_3$) 198.57. 174.44, 169.14, 136.19, 135.39, 134.86, 134.61, 129.71, 129.58, 128.78, 128.71, 128.56, 128.36. 128.09, 127.95, 84.13, 74.87, 64.53, 62.98, 52.59, 45.76, 33.60, -2.66, -4.29.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **177**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **177**

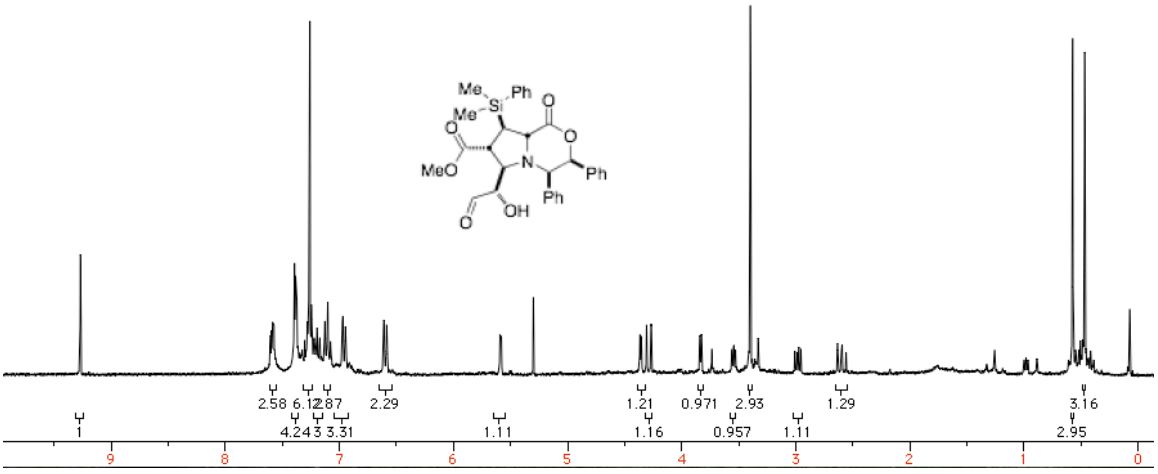


181 **186**

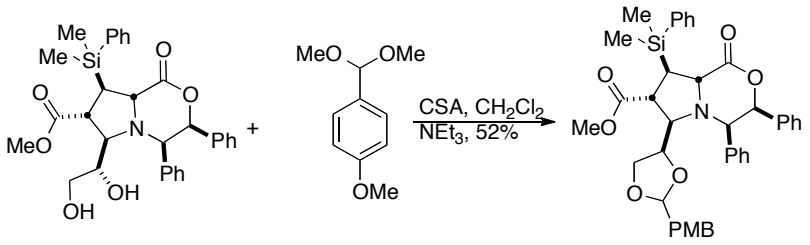
To a 10 mL rbf was added TCC (9 mg, 0.036 mmol, 1.05 equiv.) to a solution of **181** (20 mg, 0.036 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at O °C. Tempo (1 crystal) was added to the reaction and stirring continued for 45 minutes. A saturated aqueous solution of Na_2CO_3 was added and the organic layer was washed with 1N HCl (1 mL) and NaCl (1 mL) The organic layer was then dried over Na_2SO_4, concentrated to compound (17mg, 85% yield) that was used directly in the next . (ps2-321-1)

R_f = 0.33 (60:40 Hexanes:EtOAc)

^{1}H NMR ($CDCl_3$ 300MHz) : δ. 9.28 (s, 1H) 7.60 – 6.58 (m, ~15H), 5.59 (d, J = 3.3, 1H), 4.35 (d, J = 3.3, 1H), 4.28 (d, J = 12.0, 1H), 3.83 (d, J = 3.9, 1H), 3.54 (dd, J= 4.2, 5.4, 1H), 3.39 (s, 3H), 2.98 (dd, J = 5.4, 10.5, 1H), 2.59 (dd, J = 12.0, 10.5, 1H) 0.53 (s, 3H), 0.46 (s,3H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **44**

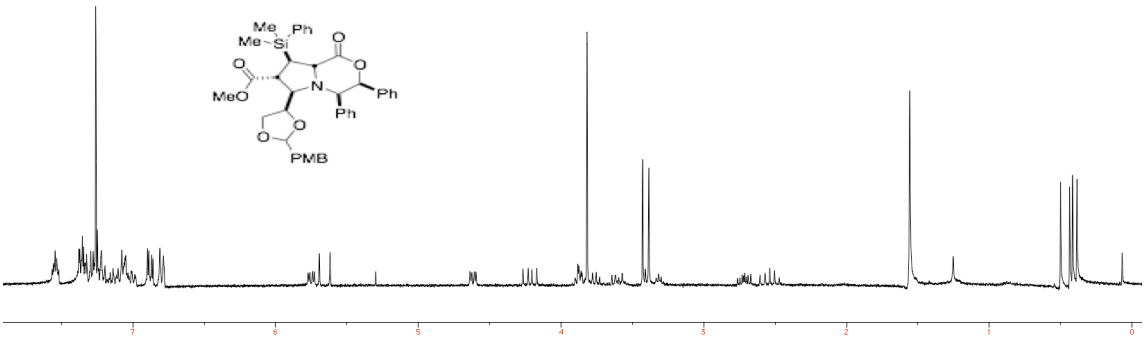


181 **191** **187**

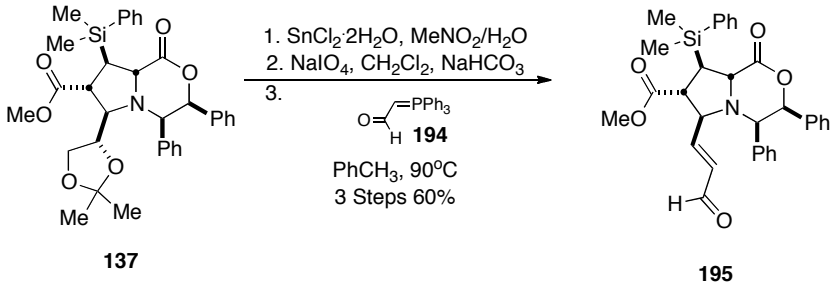
To a solution of diol **181** (158 mg, 0.028 mmol, 1 equiv.) in CH_2Cl_2 (3 mL) was added **191** (132 mg, 0.07 mmol, 2.5 equiv.) and CSA (7mg, 0.003 mmol, 0.1 equiv.). The reaction was stirred at rt for 6 h followed by the addition of NEt_3 (40 μL, 0.028 mmol, 1 equiv.) and $PhCH_3$ (10 mL). The reaction was refluxed for 12 h and concentrated under reduced pressure to give the crude material that was purified by flash chromatography (gradient elution, 10:90 to 20:80 Hexanes:EtOAc) to give compound **187** (127 mg, 66%) (ps2-370-2, ps2-251-2)

^{1}H NMR ($CDCl_3$ 300MHz) : δ - 7.56 – 6.78 (m, ~44H) Intergration off, 5.77 (d, J = 3.0, 1H), 5.73(d, J = 3.6, 1H), 5.69 (s, 1H), 5.62 (s, 1H), 4.63 (d, J = 3.0, 1H), 4.60 (d, J = 3.0, 1H), 4.25 (d, J = 9.0, 1H), 4.19 (J = 10.2, 1H), 3.88 (m, 2 H), 3.81 (s, 6H), 3.75 (m, 2H), 3.61 (m, 2H), 3.42 (s, 3H), 3.38 (s, 3H), 2.71 (m, 2H), 2.53 (m, 2H), 0.50 (s, 3H), 0.43 (s, 3H), 0.41 (s, 3H), 0.38 (s, 3H)

HRMS Calcd for $C_{39}H_{41}NO_7Si$ $[M+H]^+$ 664.27 Found 664.27.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **187**



(3S,4R,6S,7R,8R,8aS)-methyl 8-(dimethyl(phenyl)silyl)-1-oxo-6-((E)-3-oxoprop-1-en-1-yl)-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (195)

To a 250 mL rbf equipped with a stir bar was added compound **137** (1.41g , 2.30 mmol, 1 equiv.), in NO_2Me (20 mL) saturated with H_2O. $SnCl_2{\cdot}2H_2O$ (1.65 g, 7.10 mmol, 3 equiv.) was added to the reaction mixture in small portions. The reaction was stirred for 2 h and saturated aqueous solution of $NaHCO_3$ (15 mL) was added followed by the addition EtOAc (20 mL) The crude reaction mixture was filtered over celite, separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers was washed with H_2O (3 x 10 mL), dried, filtered, and concentrated to afford 1.37 g of pure material that was transferred to a 100 ml rbf. The diol (1.37 g, 2.50 mmol, 1 Eq) was dissolved in a CH_2Cl_2 (20 mL) followed by the addition of a saturated aqueous solution of $NaHCO_3$ (250 μl). $NaIO_4$ (850 mg, 3.76 mmol, 1.5 equiv.) was added in portions over a 30 minute period. After 48 h of vigorously stirring $NaSO_4$ was added and stirring continued for another 30 minutes. The reaction mixture was filtered with fritted funnel, and concentrated to give 1.07 g of pure material. (Note- If the reaction is slow, more $NaIO_4$ can be added to speed the reaction up). The aldehyde (1.07 g, 2.08 mmol, 1 equiv.) was added to a 100 mL rbf and azeotroped with $PhCH_3$ (20 mL). Then (triphenylphosphoranyidene) acetaldehyde (760 mg, 2.50 mmol, 1.2 equiv.) was

added and the reaction was slowly warmed from rt to 90 °C and stirring continued for 3 h. The reaction was concentrated and purified by flash chromatography 80:20 HexanesEtOAc afford compound **195** (750 mg, 70 % yield)

R_f = 0.41 (70:30 Hexane/EtOAc)

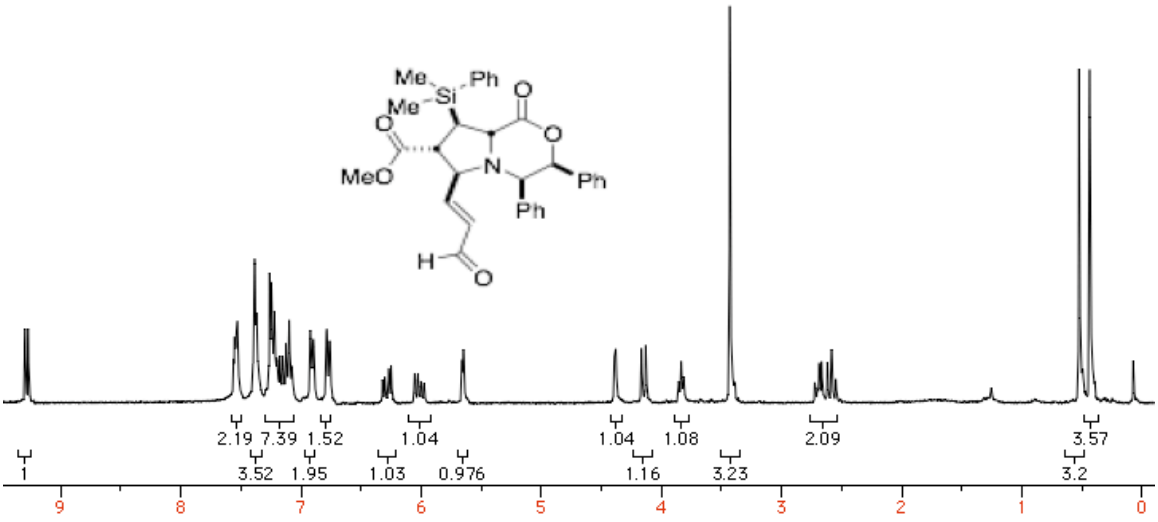
$[\alpha]^{25}_D$ = -63.1 (*c* = 0.63, $CHCl_3$)

IR (neat) ν 2924, 2853, 1738, 1691, 1497, 1454, 1428, 1347, 1231, 1172, 1113 cm^{-1}

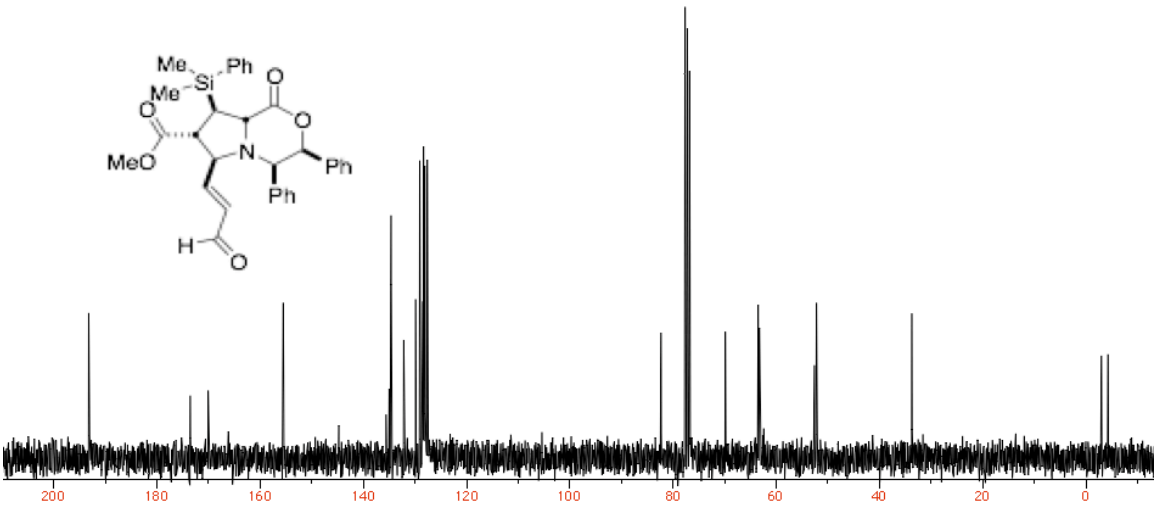
^1H NMR ($CDCl_3$ 400MHz) : δ. 9.28 (d, J=7.80, 1H) 7.56 – 6.74 (m, 15H), 6.28 (dd, J = 6.0, 15.6, 1H), 5.66 (d, J = 3.9, 1H), 4.38 (d, J = 3.6, 1H), 4.15 (d, J = 10.5 1H), 3.83 (t, J= 12.3, 1H), 3.43 (s, 3H), 2.72 – 2.54 (m, 2H) 0.52 (s, 3H), 0.43 (s,3H)

^{13}C NMR (100 MHz, $CDCl_3$) 193.21, 173.53, 170.06, 155.527, 135.70, 135.59, 134.99, 134.62, 132.17, 129.87, 129.08, 128.60, 128.48, 128.33, 128.17, 128.10, 127.61, 82.32, 69.867, 63.50, 63.268, 52.59, 52.20, 33.73, -2.99, -4.26.

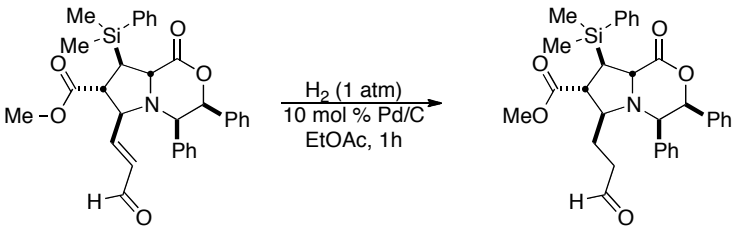
HRMS Calcd for $C_{32}H_{33}NO_5Si$ $[M+H]^+$ 540.2 Found 540.2



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **195**



^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **195**



195 **195**

(3S,4R,6S,7R,8R,8aS)-methyl 8-(dimethyl(phenyl)silyl)-1-oxo-6-(3-oxopropyl)-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (195A)

To a flame-dried 10 mL rbf was added compound **195** (310 mg, 0.57 mmol, 1.0 equiv.) in EtOAc (5 mL). The reaction was sparged with argon before adding 10 mol % Pd/C (150mg , 0.24 equiv.) The reaction was stirred under an atmosphere of H_2 (1 atm) for 1 h at which time compound **195** was completely consumed as observed by TLC. The reaction was filtered through celite with EtOAc (100 mL). The combined filtrates were dried with Na_2SO_4, and concentrated to dryness to give compound **195** (300 mg, 96% yield). The crude reaction mixture was directly used in the next reaction without purification. (ps3-438-1)

R_f = 0.36 (70:30 Hexane/EtOAc)

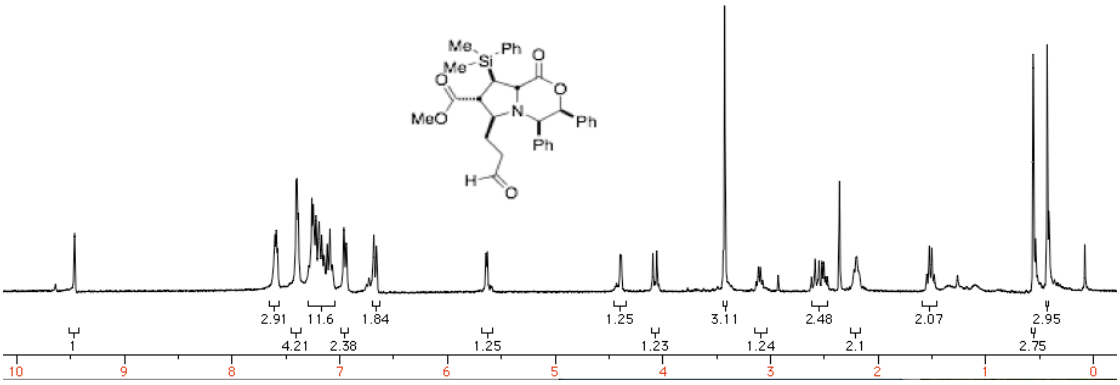
$[\alpha]^{25}_D$ = -51.3 (*c* = 0.33, $CHCl_3$)

IR (neat) ν 2925, 2854, 1734, 1455, 1259, 701 cm^{-1}

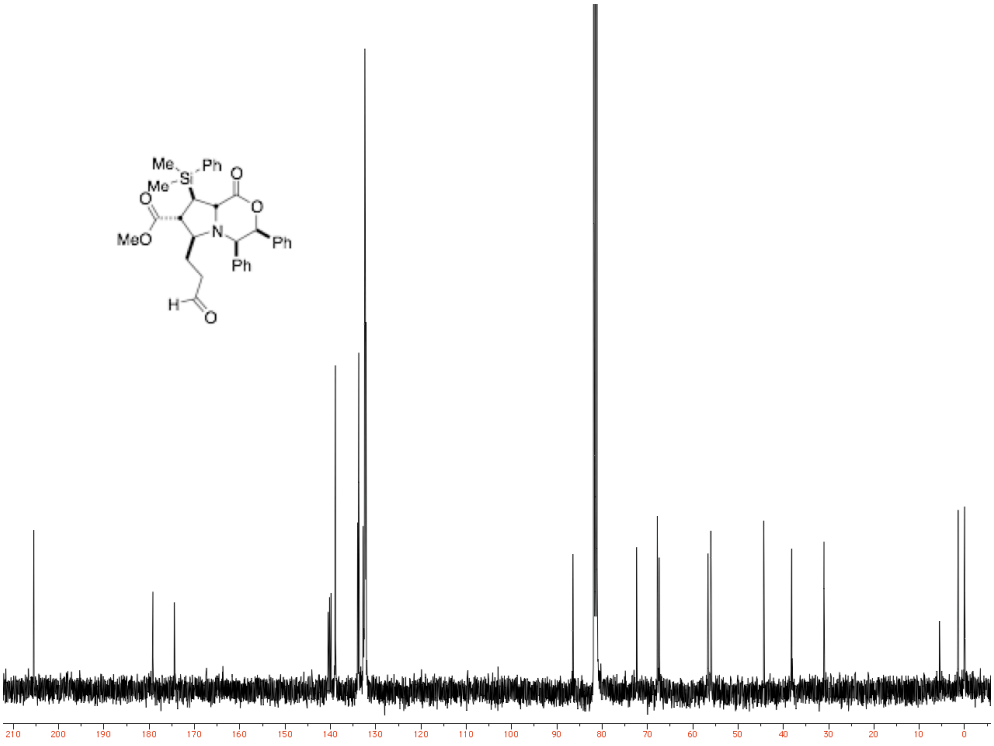
^1H NMR ($CDCl_3$ 300MHz) : δ. 9.46 (s, 1H), 7.61 – 6.66 (m – 15H)

5.64 (d, J = 2.7, 1H), 4.34 (d, J = 3.6, 1H), 4.07 (d, J = 10.8, 1H), 3.42 (s, 3H), 3.10 (dd, J = 5.4, 11.7, 1H), 2.54 m, 2H), 2.19 (m, 2H), 1.51 (dd, J = 6, 11.4, 2H), 0.56 (s, 3H), 0.43 (s, 3H).

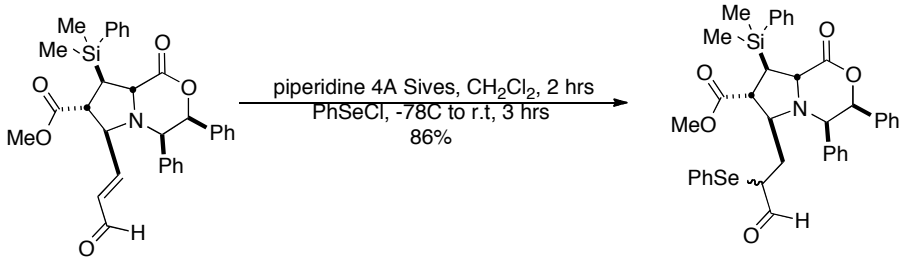
^{13}C NMR (100 MHz, $CDCl_3$) 205.49, 179.19, 174.45, 140.47, 140.19, 139.86, 138.95, 138.91, 134.00, 133.74, 132.76, 132.46, 132.40, 132.30, 132.24, 132.15, 132.12, 86.45, 72.40, 67.83, 67.42, 56.64, 56.02, 44.34, 38.18, 31.03, 5.53, 1.41, -0.00



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **195**



^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **195**



195 **196**

(3S,4R,6S,7R,8R,8aS)-methyl 8-(dimethyl(phenyl)silyl)-1-oxo-6-(3-oxo-2-(phenylselanyl)propyl)-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (196)

To a flame dried 100 mL recovery flask was added 4 Å powered molecular sieves, compound **195** (298 mg, 0.058 mmol, 1 equiv.), CH_2Cl_2 (10 mL) and piperdine (73 μL, 0.07 mmol, 1.25 equiv.). The reaction was stirred for 3 h and concentrated redissolved in THF (10 mL) and evaporated down in THF (3 x 10 mL) and put on a vacuum pump for 1 hr. THF (5 mL) was added and the reaction was collected to -78 °C. A solution of PhSeCl (167 mg, 0.08 mmol, 1.5 equiv.) was added in THF (2 mL) to the reaction and stirring continued for 1 h at -78 °C. The reaction was warmed to rt and stirring continued for 3 h. The reaction was filtered over celiete with EtOAc (20 mL), dried over Na_2SO_4 followed by purification purified by flash chromatography (gradient elution, 95:5 to 70:30 Hexane/EtOAc) to afford compound **196** (350 mg, 86% yield)

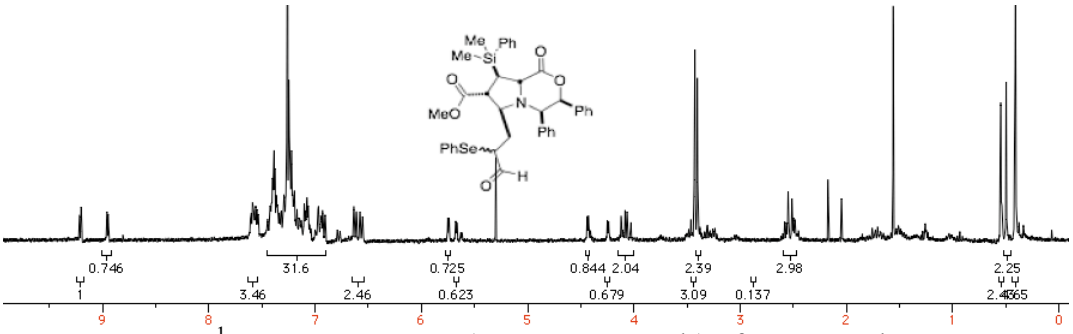
R_f = 0.58 (70:30 Hexane/EtOAc)

$[\alpha]^{25}_D$ = -48.8 (*c* = 0.23, $CHCl_3$)

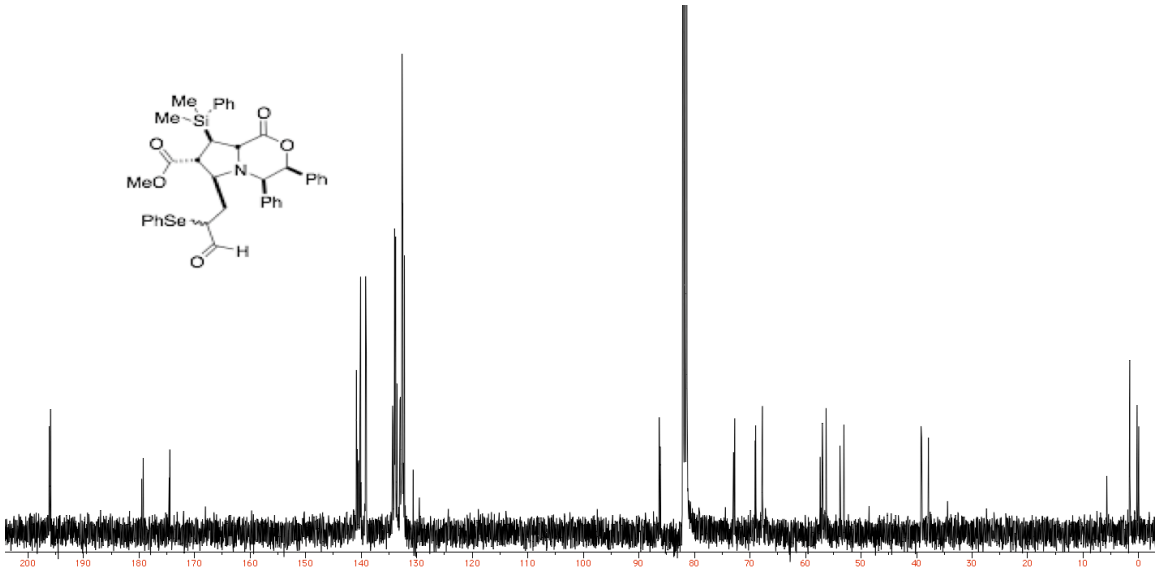
IR (neat) ν 2925, 2854, 1736, 1455, 1259, 1112 cm^{-1}

^{1}H NMR ($CDCl_3$ 300MHz) : δ. 9.20 (d, J = 1.8, 1H), 8.95 (d, J = 3.0, 1H), 7.60 – 6.55 (m, 40H), 5.75 (d, J = 3.3, 1H), 5.67 (d, J = 3, 1H), 4.44 (d, J = 6.0, 1H), 4.24 (d, J = 3.6, 1H), 4.07 (dd, J = 11.1, 16.8, 2H), 3.42(s, 3H), 3.40(s, 3H), 2.53 (m, 3H), 0.54 (s, 3H), 0.49 (s, 3H), 0.41 (s, 6H).

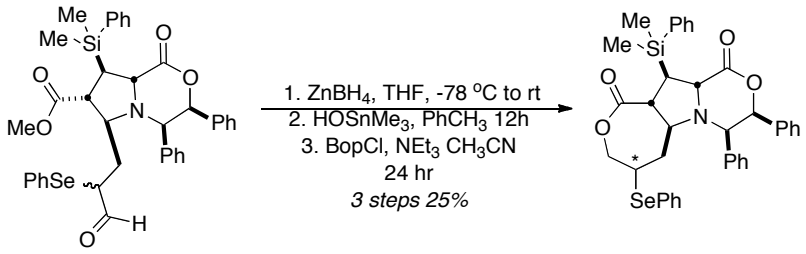
^{13}C NMR (100 MHz, $CDCl_3$) 196.15, 195.93, 179.49, 179.25, 174.55, 174.46, 140.86, 140.69. 140.56, 140.46, 140.24, 140.16, 140.11, 140.02, 139.19, 139.12, 139.08, 86.33, 86.14, 72.95, 72.40, 69.06, 68.97, 67.78, 67.75, 57.36, 56.96, 56.88, 56.29, 53.79, 53.08, 39.19, 39.10, 37.92, 37.86 , 5.75, 1.65, 1.16, 0.29, -0.00



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **196**



^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **196**



196 197

(3S,4R,6S,7R,8R,8aS)-8-(dimethyl(phenyl)silyl)-6-(4-hydroxy-2-(phenylselanyl)butyl)-1-oxo-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylic acid (197):

To a flame dried 10 mL rbf was added **196** (114 mg, 0.0163 mmol, 1 equiv.) and THF (3 mL). The reaction was cooled to -78 °C and warmed to rt while a 0.083M solution of $Zn(BH_4)$ in THF was added dropwise until the reaction was complete by TLC. The organic layer was washed with a saturated aqueous NH_4Cl solution (3 mL, and H_2O (2 mL) and dried with Na_2SO_4, and concentrated to dryness to give 93 mg of pure product that was used directly in the next reaction. [ps3-90-1, R_f= 0.46 (70:30 Hexane/EtOAc)] The crude reaction mixture was dissolved in $PhCH_3$ (5 mL) and Trimethyltin hydroxide (240 mg, 0.13 mmol, 10 equiv.) was added. The reaction was heated at 90 °C and let stir for 24 h. The reaction was evaporated to give 73 mg of crude material that was purified by plug of silica gel with 97:3 DCM/MeOH to give 73 mg of crude material that was used directly in the next reaction. (ps3-93-1, R_f= 0.51 (93:7 DCM/MeOH)]. To a 10 mL rbf was added the acid (73 mg, 0.01g mmol, 1 equiv.), CH_3CN (3 mL), TEA (82 μl, 0.06 mmol, 6 equiv.) and BopCl (54 mg. 0.021 mmol, 2.0 equiv.). The reaction was stirred for 24 h and was evaporated to dryness. EtOAc (2 mL) and 1N HCl (2 mL) was added and stirring continued for 15 minutes. The organic layer was washed with 1N HCl (2 x 2 mL), water (2 x 2 mL) and a saturated aqueous solution of NaCl (2 mL). The crude material

was dried over Na_2SO_4 and concentrated. The light yellow material was purified by flash chromatography (gradient elution, 95:5 to 70:30 Hexanes:EtOAc) to give **197** (27 mg, 25% yield). (ps3-94-2)

R_f = 0.30 (80:20 Hexane/EtOAc)

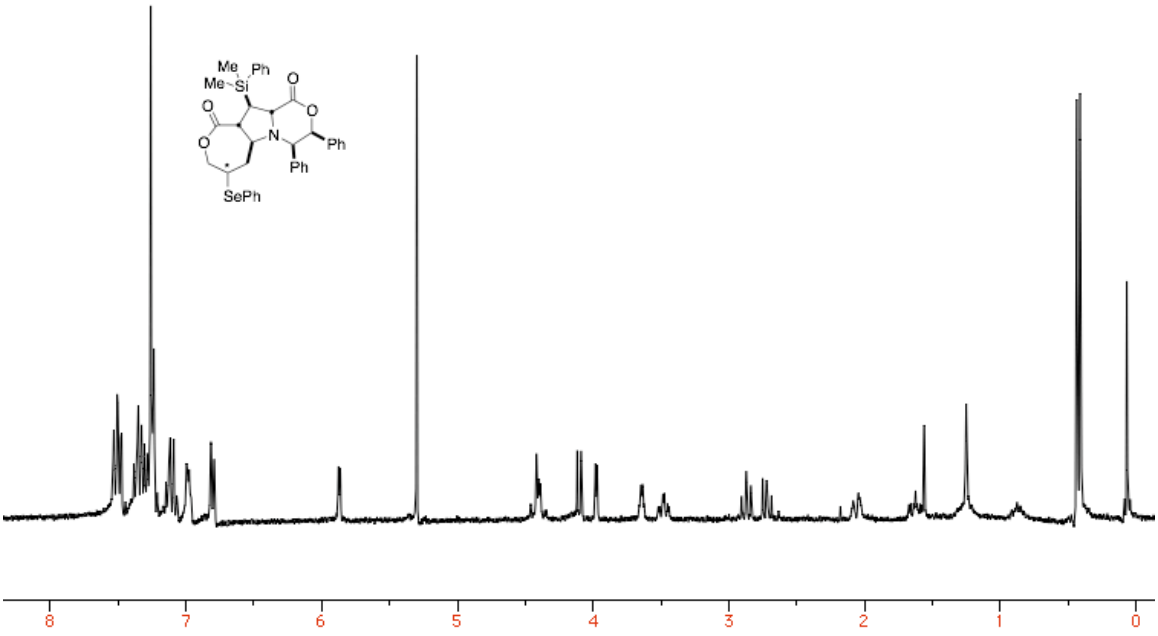
$[\alpha]^{25}_D$ = +21.6 (*c* = 0.16, $CHCl_3$)

IR (neat) ν 2925, 2854, 1742, 1579, 1463, 1378, 1260, 1111, cm^{-1}

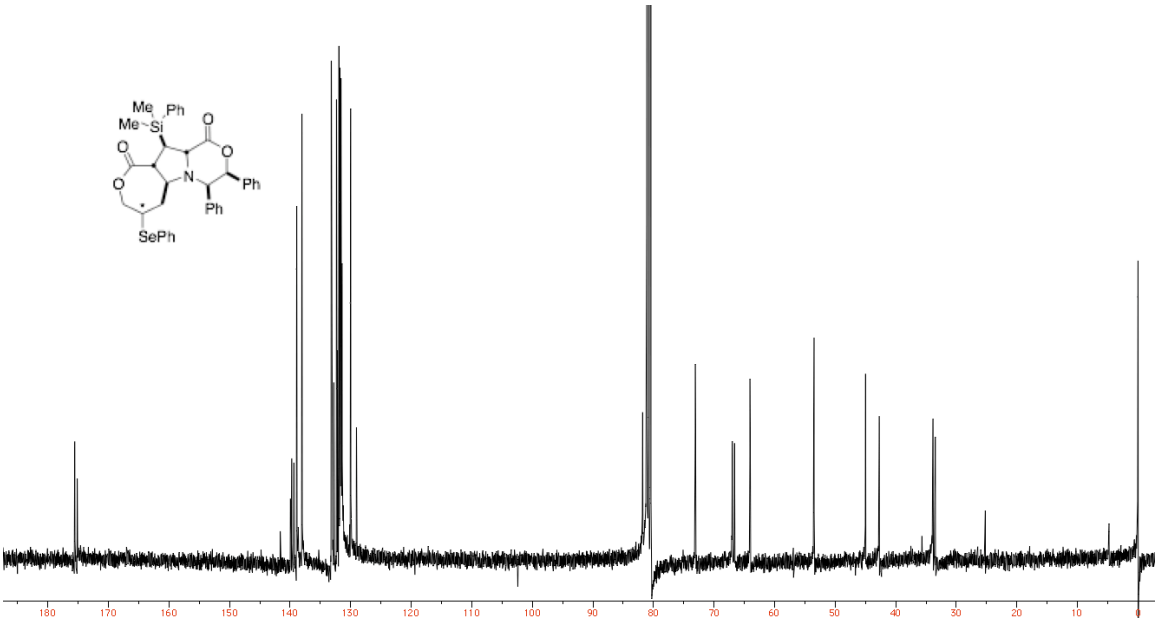
H NMR ($CDCl_3$ 300MHz) : δ. 7.53 – 6.79 (m, 20H), 5.87 (d, J = 3.9, 1H), 4.01 (m, 2H), 4.09 (d, 8.7, 1H), 3.97 (d, J = 5.4, 1H), 3.64 (m,1H), 2.87 (t, J = 10.5, 1H), 2.71 (dd, J = 8.7, 10.8, 1H), 2.04 (m, 1H), 1.61 (m, 1H), 0.43 (s, 3H), 0.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) 175.54, 175.14, 141.62, 139.95, 139.72, 139.38, 138.81, 138.87, 138.40, 133.21, 132.78, 132.34, 132.18, 131.97, 131.94, 131.89, 131.78, 131.73, 131.59, 131.54, 131.42, 130.00, 129.04, 81.08, 73.10, 66.98, 66.63, 64.07, 53.49, 44.99, 42.73, 33.86 33.47, 25.22, 0.00, -0.03.

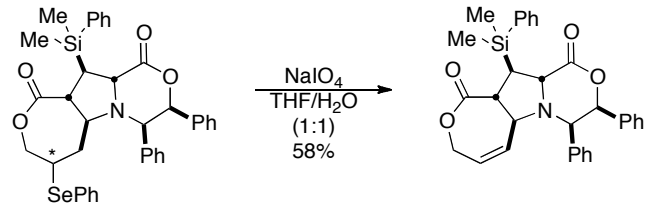
HRMS Calcd for $C_{37}H_{37}NO_4SeSi$ $[M+H]^+$ 668.1 Found 668.1



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **198**



^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **198**



(3S,4R,5aS,10aR,11R,11aS)-11-(dimethyl(phenyl)silyl)-3,4-diphenyl-3,4,8,10a,11,11a-hexahydro-1H-oxepino[3',4':4,5]pyrrolo[2,1-c][1,4]oxazine-1,10(5aH)-dione (156)

To a 10 mL recovery flask was added **198** (9 mg, 0.0013 mmol, 1 equiv.) and dissolved in a 4:1 THF/H_2O (1 mL). $NaIO_4$ (56mg, 0.0269 mmol, 20 equiv.) was added over 30 minutes and let stir for 31 h at rt. Na_2SO_4 was added and the reaction was filtered over celite, concentrated, to give 11 mg of crude material that was purified by flash chromatography (gradient elution 95:5 to 70:30 Hexanes/EtOAc) to give compound **156** (4 mg, 58 % yield). (ps3-4-2)

R_f = 0.33 (60:40 Hexanes:EtOAc)

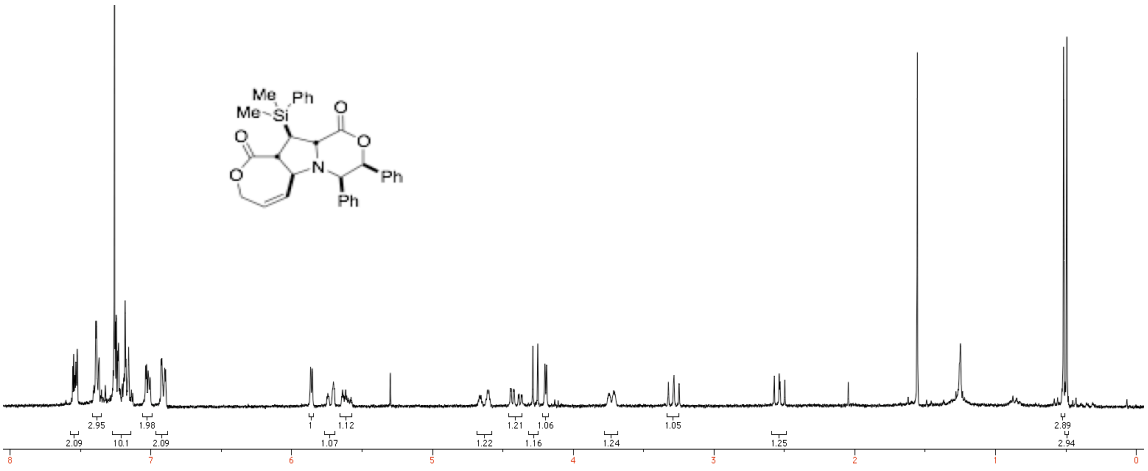
$[\alpha]^{25}_D$ = +17.5 (*c* = 0.43, $CHCl_3$)

IR (neat) ν 2924, 2853, 1744, 1497, 1455, 1427, 1402, 1262, 1158 cm^{-1}

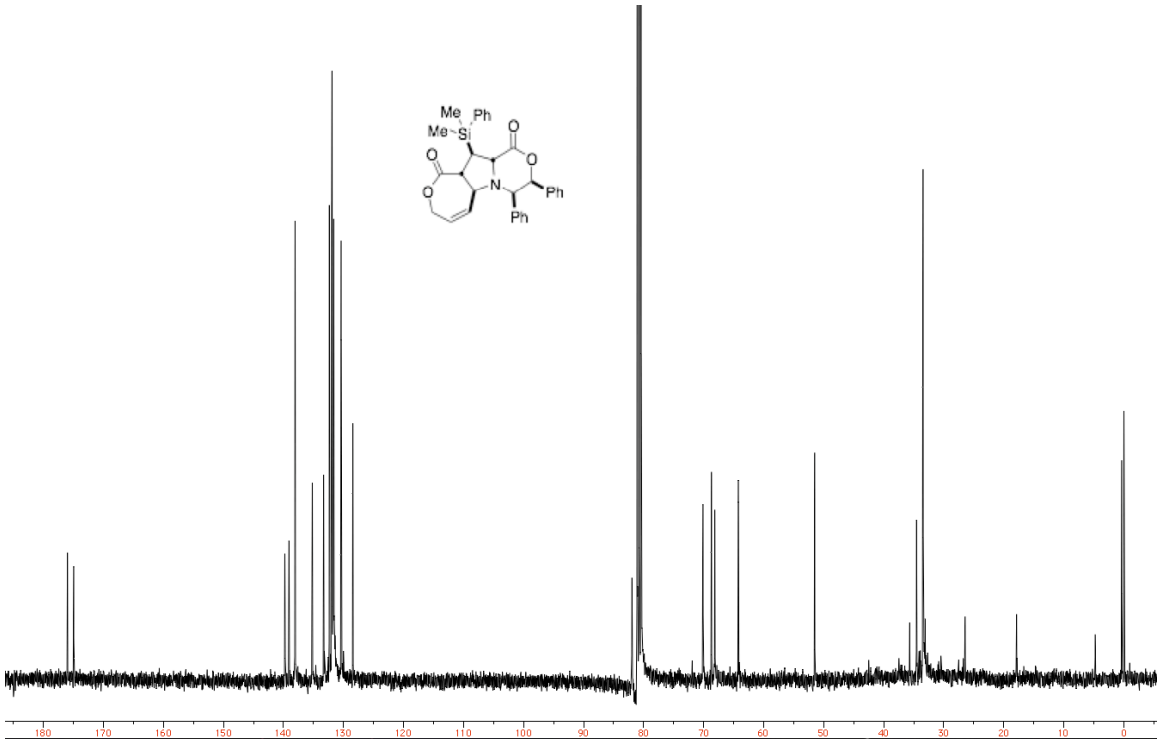
^1H NMR ($CDCl_3$, 300MHz) : δ 7.55 – 6.89 (m, 15H), 5.85 (d, J = 3.3, 1H), 5.72 (m, 1H), 5.63 – 5.59 (m, 1H), 4.62 (m, 1H), 4.40(m, 1H), 4.26 (d, J = 10.5, 1H), 4.20 (d, J = 3.3, 1H), 3.72 (m, 1H), 3.28 (dd, J = 11.4, 11.4, 1H), 2.53 (dd, J = 12.0, 11.4, 1H), 0.51 (s, 3H), 0.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) 175.98, 174.94, 139.77, 139.72, 139.08, 135.19, 133.31, 132.37, 131.97 131.92, 131.65, 131.63, 130.39, 128.44, 81.95, 70.11, 68.70, 68.14, 64.22, 51.51, 35.68, 34.54, 33.25, 0.35, -0.00.

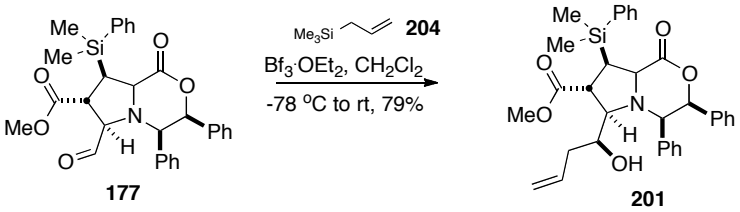
HRMS Calcd for $C_{31}H_{31}NO_4Si$ $[M+H]^+$ 510.20 Found 510.20.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **156**



^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **156**



(3*S*,4*R*,6*R*,7*R*,8*R*)-methyl 8-(dimethyl(phenyl)silyl)-6-((*S*)-1-hydroxybut-3-en-1-yl)-1-oxo-3,4-diphenylhexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-7-carboxylate (201):

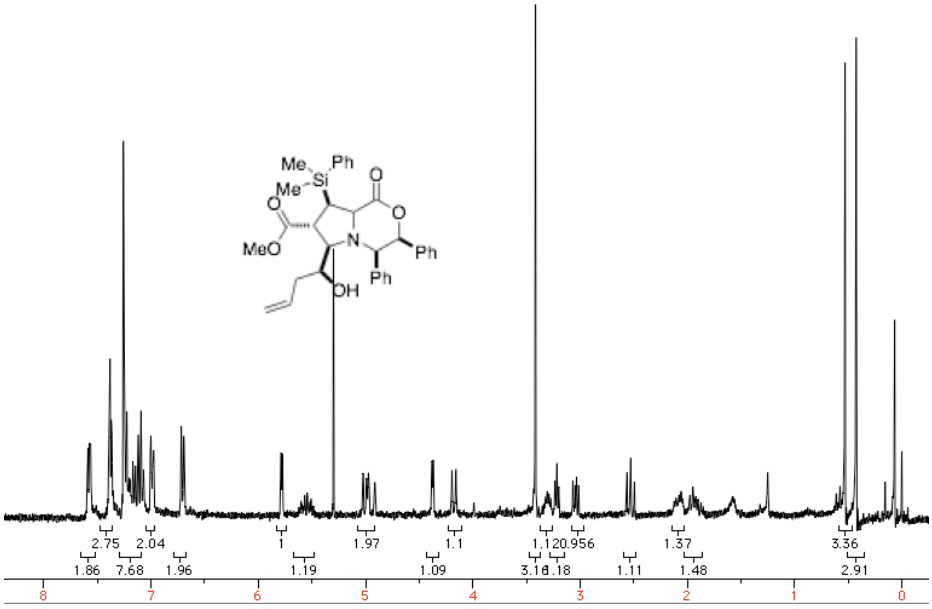
To a flame dried 5 mL rbf was added **177** (14 mg, 0.002 mmol, 1 equiv.), silane **204** (5 μL, 0.003 mmol, 1.1 equiv.), and CH_2Cl_2 (1 mL). The reaction was cooled to -78 °C and $BF_3{\cdot}OEt_2$ (5 μL, 0.003 mmol, 1.1 equiv.) was added and stirring continued for 15 minutes followed by warming to rt. The reaction was stirred for another 30 minutes followed by the addition of H_2O (2 mL). The organic layer was separated from the aqueous and washed with H_2O (2 x 5 mL) and $NaCl_{aq}$ (2 x 5 mL), dried over Na_2SO_4, and concentrated to give 12 mg of pure product **201** that was used directly in the next reaction. (ps3-54-2)

R_f = 0.48 (70:30 Hexanes:EtOAc)

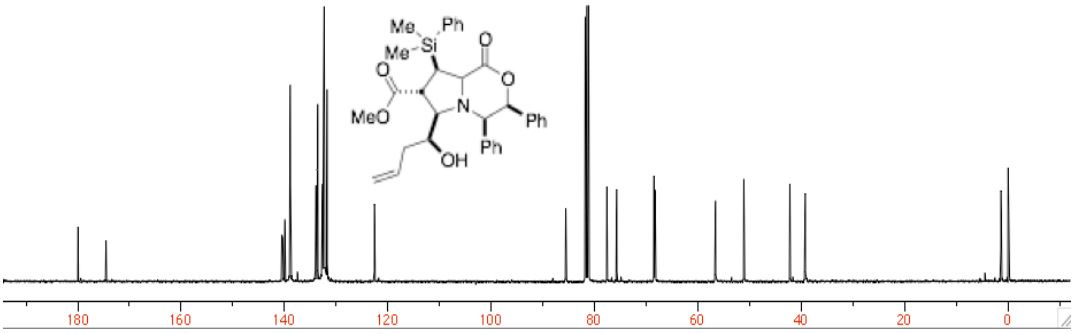
^{1}H NMR ($CDCl_3$, 300MHz) : δ 7.59 – 6.69 (m, 15H), 5.78 (d, J = 3.6, 1H), 5.54 (m, 1H), 4.89 (dd, J = 9.0,14.4, 2H), 4.37 (1, J = 3.6, 1H), 3.41 (s, 3H), 3.30 (m, 1H), 3.21 (t, J = 4.2, 1H), 3.03 (dd, J = 6.3, 10.2, 1H), 2.52 (t, J = 10.2, 1H) , 2.07 (m, 1H), 1.92 (m, 1H), 0.53 (s, 3H), 0.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 179.95, 274.52, 140.52, 140.34, 139.93, 138.89, 138.83, 133.92, 133.57, 132.65, 132.43, 132.32, 132.30, 131.76, 122.59, 85.58, 77.63, 75.72, 68.52, 68.29, 56.60, 51.12, 42.22, 39.24, 1.38, -0.00.

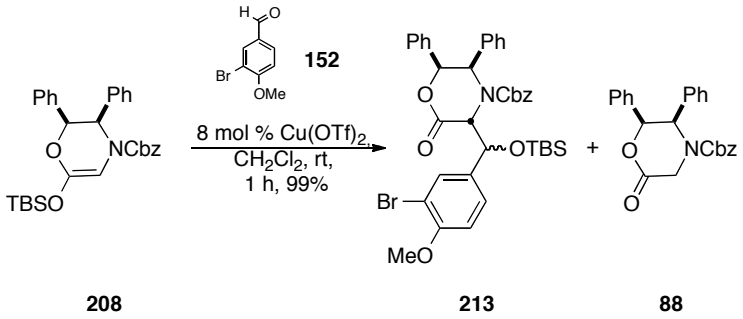
HRMS Calcd for $C_{33}H_{37}NO_5Si$ $[M+H]^+$ 556.24 Found 556.25



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **201**



^{1}H NMR spectrum (100 MHz, $CDCl_3$) of compound **201**



(3*R*,5*S*,6*R*)-benzyl3-((3-bromo-4-methoxyphenyl)((*tert*-butyldimethylsilyl) oxy)methyl)-2-oxo-5,6-diphenylmorpholine-4-carboxylate compound (213):

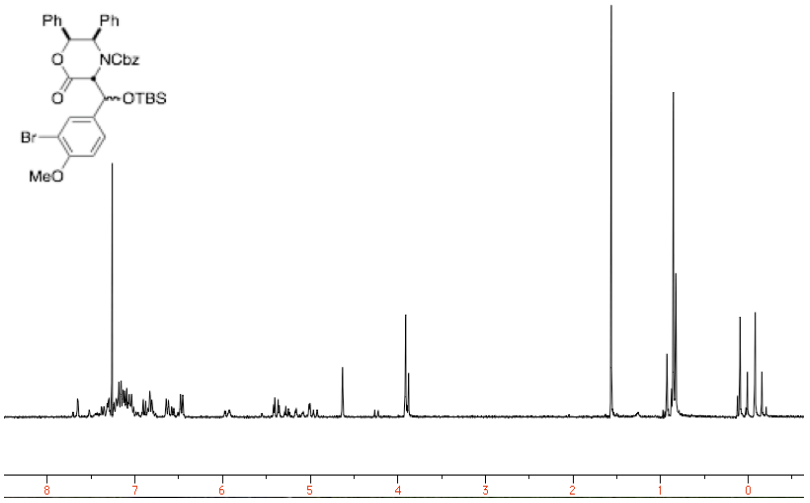
To a flame-dried 200 mL round bottomed flask (rbf) was added compound **152** (1.28 g, 5.95 mmol, 1.0 equiv.) and $Cu(OTf)_2$ (127 mg, 0.04 mmol, 8 mol%) in CH_2Cl_2 (50 mL). Compound **208** (5.98 g, 1.19 mmol, 2 equiv.) in CH_2Cl_2 (20 mL) as added via syringe over 1 h. The reaction was stirred for another 1 h at which time aldehyde **152** was completely consumed as observed by TLC. The purple solution was concentrated to dryness and then dissolved in a 93:5:1 hexane:EtOAc:triethylamine (TEA) solution containing silica gel. The slurry was evaporated to dryness and added to a column of silica gel pretreated with 93:5:1 hexane:EtOAc:TEA. The crude mixture was subjected to flash chromatography (gradient elution, 90:10:1 to 50:50:1 hexane:EtOAc:TEA) to afford **213** (4.24 g, 99% yield) as an inseparable mixture of diastereomers. Compound **208** (1.40 g) and **88** (634 mg) were recovered and recycled. (ps2-299-4)

R_f= 0.44 (80:20 hexane/EtOAc)

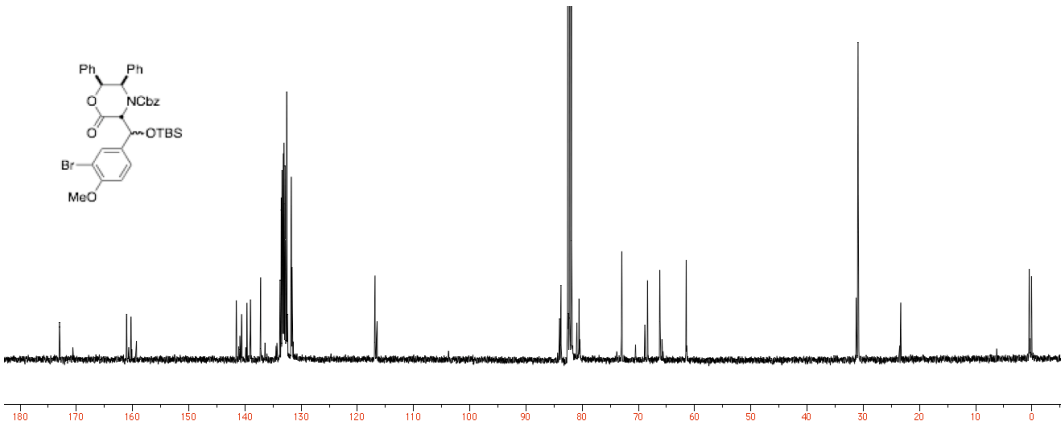
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.70 – 6.45 (m, 36H), 5.41 (d (major), *J* = 3.9 Hz, 1H), 5.36 (d (major), *J* = 4.2 Hz, 1H), 5.29 (d, (minor), J = 4.2 Hz, 1H), 5.24 (d (minor), *J* = 3.90 Hz, 1H), 5.16 (d (major), *J* = 3.30 Hz, 1H), 5.00 (d (major), *J* = 3.30, 1H), 4.94 (d

(minor), J = 12.00 Hz, 1H), 4.63 (s (major), 2 H) 4.25, (d (minor), J = 12.00 Hz, 1H), 3.91 (s (major), 3H), 3.88 (s (minor), 3H), 0.09 (s (major), 3H), 0.01 (s (minor), 3H), -0.07 (s (major), 3H), -0.155 (s (minor), 3H).

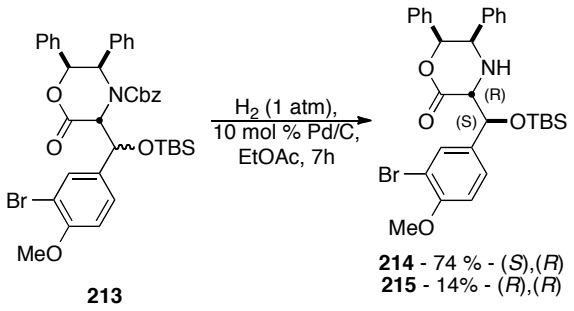
^{13}C NMR (100 MHz, $CDCl_3$) 172.98, 172.96, 170.62, 161.07, 160.67, 160.27, 160.11, 159.30, 141.53, 141.09, 140.90, 140.64, 140.60, 139.85, 139.64, 139.05, 139.02, 137.26, 137.20, 136.43, 134.46, 134.30, 133.75, 133.60, 133.54, 133.40, 133.34, 133.28, 133.24, 133.17, 133.05, 133.02, 132.96, 132.89, 132.86, 132.81, 132.73, 132.64, 132.57, 132.45, 131.67, 131.63, 131.55, 131.41, 116.95, 116.86, 116.67, 116.62, 116.58, 116.48, 84.06, 84.03, 83.77, 82.45, 80.94, 80.57, 80.44, 73.01, 72.95, 70.51, 68.85, 68.38, 66.20, 66.13, 65.80, 61.53, 61.49, 61.42, 31.22, 31.15, 30.92, 30.88, 23.50, 23.32. 23.30, 0.52, 0.46, 0.43, 0.28, 0.06, -0.00.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **213**

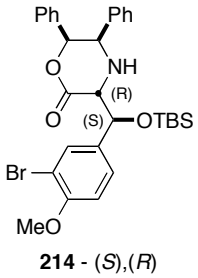


^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **213**



(3R,5S,6R)-3-((S)-(3-bromo-4-methoxyphenyl)((tert-butyldimethylsilyl)oxy)methyl)-5,6-diphenylmorpholin-2-one (214):

To a flame-dried 250 mL rbf was added compound **213** (11.18 g, 0.01 mol, 1.0 equiv.) in EtOAc (75 mL). The reaction was sparged with argon before adding 10 mol % Pd/C (5.0 g by weight). The reaction was stirred under an atmosphere of H_2 (1 atm) for 7 h at which time compound **18** was completely consumed as observed by TLC. The reaction was filtered through celite with EtOAc (100 mL). The combined filtrates were dried with Na_2SO_4, and concentrated to dryness. The crude reaction mixture was purified by flash chromatography (gradient elution 95:5 to 80:20 Hexane:EtOAc) to afford **214** (6.63 g, 71% yield) and **215** (1.46 g, 16% yield).



214 - (*S*),(*R*)

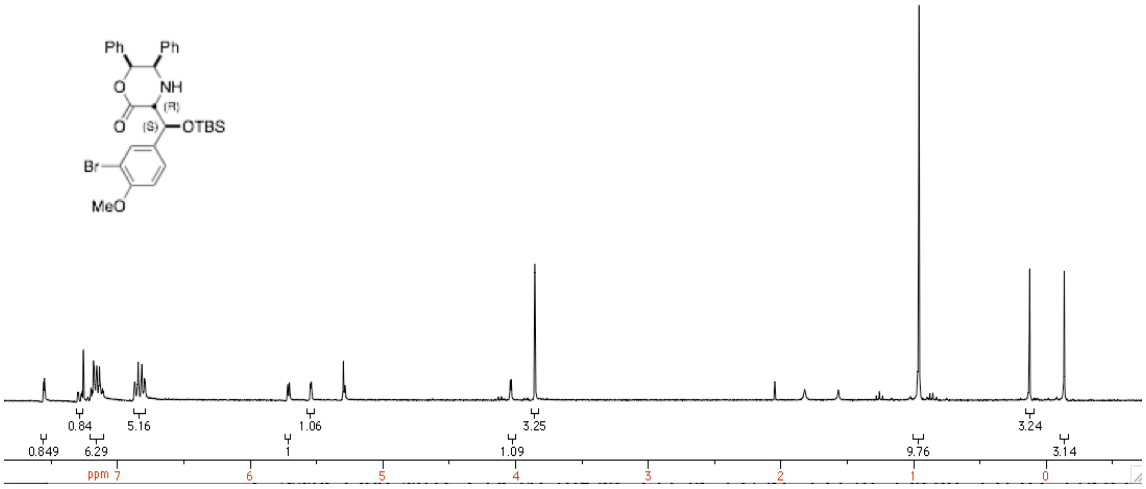
R_f = 0.626 (80:20 Hexane/EtOAc)

$[\alpha]^{25}_D$ = +8.8 (*c* = 0.90, $CHCl_3$).

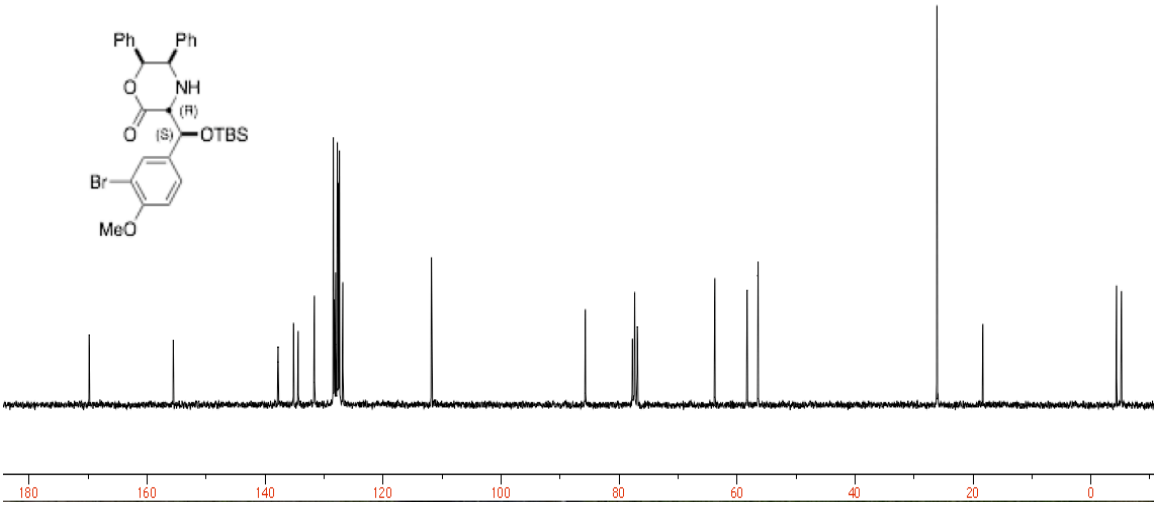
^{1}H NMR ($CDCl_3$, 300MHz, major) : δ 7.59 (d, *J* = 2.1, 1H), 7.30 – 7.11 (m, 7H), 6.85 (m, 5H), 5.71 (d, *J* = 3.9, 1H), 5.47 (d, *J* = 2.1, 1H), 5.29 (d, *J* = 3.6, 1H), 4.03 (d, *J* = 2.4, 1H), 3.85 (s, 3H), 0.96 (s, 9H), 0.12 (s, 3H), 0.13 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 169.84, 155.58, 137.81, 135.20, 134.40, 131.65, 128.45, 128.27, 128.04, 127.76, 127.58, 127.41, 126.84, 111.82, 85.71, 63.76, 58.296, 56.43, 26.11, 18.32, -4.33, -5.17.

HRMS Calcd for $C_{30}H_{36}BrNO_4Si$ $[M+H]^+$ 582.16 Found 582.00 (M+H).

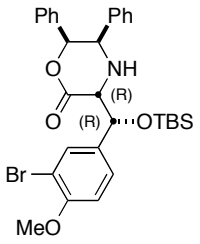


^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **214**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **214**

(3R,5S,6R)-3-((R)-(3-bromo-4-methoxyphenyl)((tert-butyldimethylsilyl)oxy)methyl)-5,6-diphenylmorpholin-2-one (20)



215 - (*R*),(*R*)

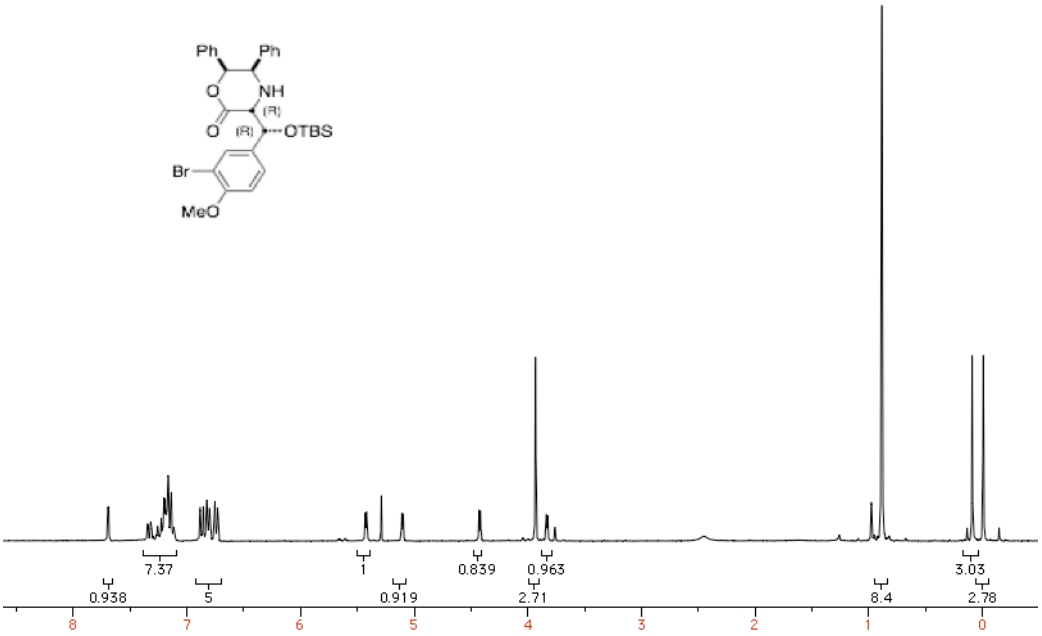
R_f = 0.775 (80:20 Hexane/EtOAc)

$[\alpha]^{25}_D$ = - 81.8 (*c* = 0.23, $CHCl_3$)

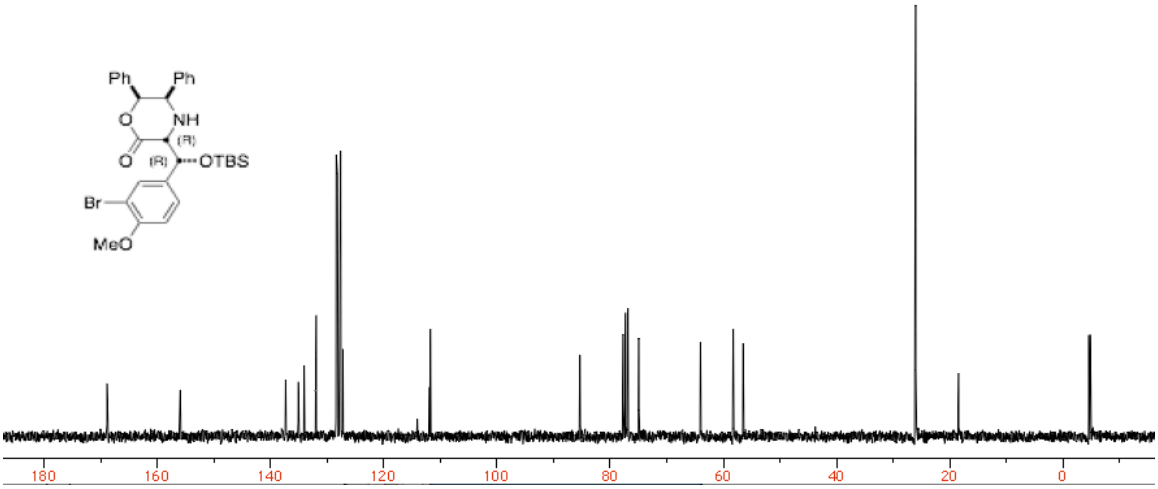
^{1}H NMR ($CDCl_3$, 300MHz, minor) : δ 7.71 (d, *J* = 2.1, 1H), 7.36 – 7.10 (m, 7H), 6.89 – 6.73 (m, 5H), 5.40 (d, *J* = 3.6, 1H), 5.11 (d, *J* = 3.6, 1H), 4.44 (d, *J* = 3.5, 1H), 3.92 (s, 3H), 3.84 (d, *J* = 3.6, 1H), 0.898 (s, 9H), 0.104 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 168.82, 155.90. 137.31, 135.07, 131.92, 128.37, 128.32, 128.29, 127.74, 127.61, 127.21, 111.92, 111.74, 85.32, 74.94, 64.04, 58.25, 56.50, 26.04, 18.45, -4.54, -4.80.

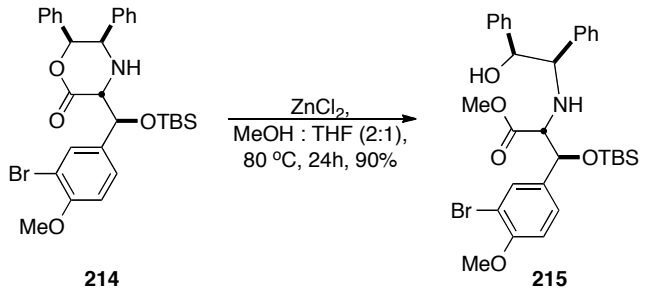
Calcd for $C_{30}H_{36}BrNO_4Si$ $[M+H]^+$ 582.16 Found 582.00 (M+H).



^{1}HNMR spectrum (300 MHz, $CDCl_3$) of compound **215**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **215**



214 **215**

(2R,3S)-methyl 3-(3-bromo-4-methoxyphenyl)-3-((tert-butyldimethylsilyl)oxy)-2-(((1S,2R)-2-hydroxy-1,2-diphenylethyl)amino)propanoate (215):

Compound **214** (1.56 g, 2.75 mol, 1.0 equiv.) was added to a 350 mL pressure flask and dissolved in absolute MeOH (44 mL) and THF (22 mL) under argon atmosphere. Anhydrous $ZnCl_2$ (14 mL, 1.37 mol, 5 equiv., 1 M in Et_2O) was added and heated to 80 °C and stirring proceeded for a 24 h. The reaction was cooled to room temperature and diluted with EtOAc (50 mL) and a saturated aqueous solution. Na_2CO_4 (50 mL). Stirring continued for 30 minutes. The reaction was filtered through celite, dried over Na_2SO_4, and concentrated. The crude mixture was purified by flash chromatography (gradient elution, 90:10 to 80:20 hexane/EtOAc) to give pure product **215** (1.47 g, 90% yield). (ps2-301-2)

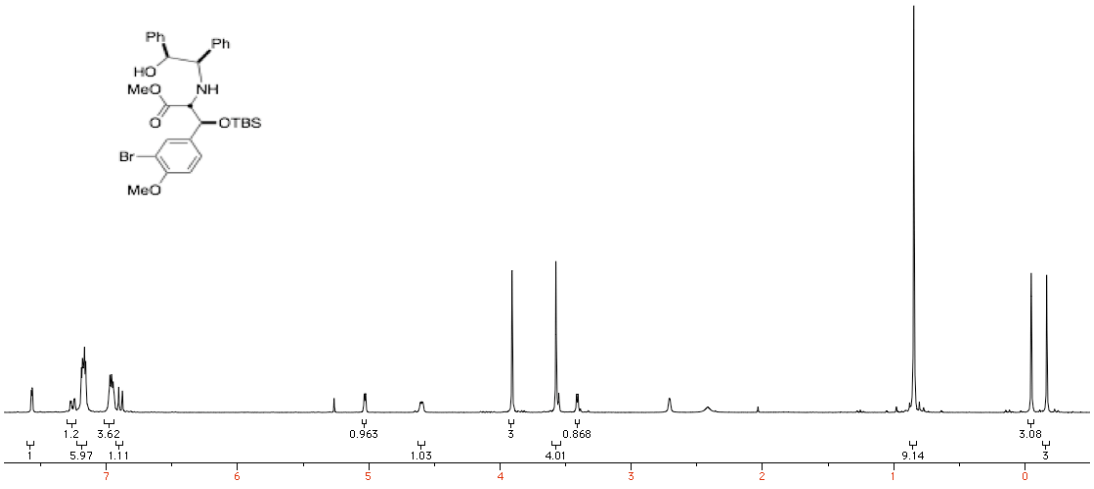
R_f = 0.350 (80:20 Hexane/EtOAc)

$[\alpha]^{25}_D$ = + 56.2 (*c* = 0.26, $CHCl_3$)

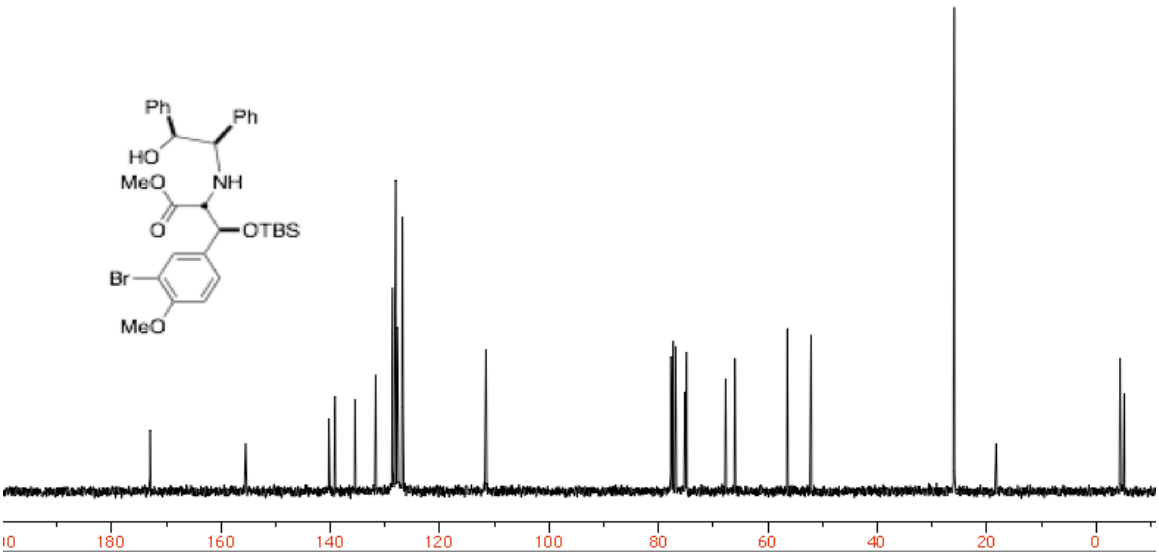
^{1}H NMR ($CDCl_3$, 300MHz) : δ 7.52 (d, *J* = 1.5, 1H), 7.20 – 7.18 (m, 7H), 6.98 – 6.91 (m, 5H), 5.02 (d, *J* = 2.7, 1H), 4.59 (d, *J* = 5.1, 1H), 3.92 (s, 3H), 3.57 (s, 3H), 3.48 (d, *J* = 5.1, 1H), 3.38 (d, *J* = 3, 1H), 0.82 (s, 9H), -0.07 (s, 3H), -0.183 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 172.94, 155.49, 140.26, 139.13, 135.48, 131.70, 128.63, 128.04, 127.76, 127.56, 126.81, 126.70, 111.53, 111.44, 75.14, 74.87, 67.70, 66.00, 54.44, 52.10, 25.91, 18.26, -4.41, -5.16.

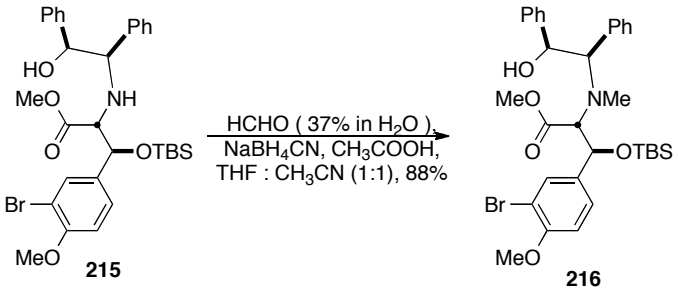
HRMS Calcd for $C_{31}H_{40}BrNO_5Si$ $[M+H]^+$ 614.19 Found 614.1 (M+H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **215**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **215**



(2*R*,3*S*)-methyl-3-(3-bromo-4-methoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy) -2-(((1*S*,2*R*)-2-hydroxv 1,2diphenylethyl)(methyl)amino)propanoate (216):

To a 250 mL rbf was added compound **215** (1.43 g, 2.23 mmol, 1.0 equiv.) and dissolved in THF (10 mL) and CH_3CN (10 mL). $NaBH_4CN$ (289 mg, 0.44 mmol, 2.0 equiv.) was added, followed by dropwise addition of acetic acid (390 μl, 4.46 mmol, 2.1 equiv., 12 M) and HCHO (900 μl, 1.1 mmol, 5 equiv., 37% in H_2O). Stirring continued for 6 h and then the reaction was diluted with EtOAc (50 mL). The two layers were separated and the organic layer was washed with a saturated aqueous solutions of $NHCl_4$ (2 × 50 mL), $NaHCO_3$ (50 mL), and $NaCl_{aq}$ (50 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude reaction was purified by flash chromatography (gradient elution, 90:10 Hexane:EtOAc to 85:15 Hexane:EtOAc) to afford compound **216** (1.23 g, 88% yield). **(**ps2-246-2)

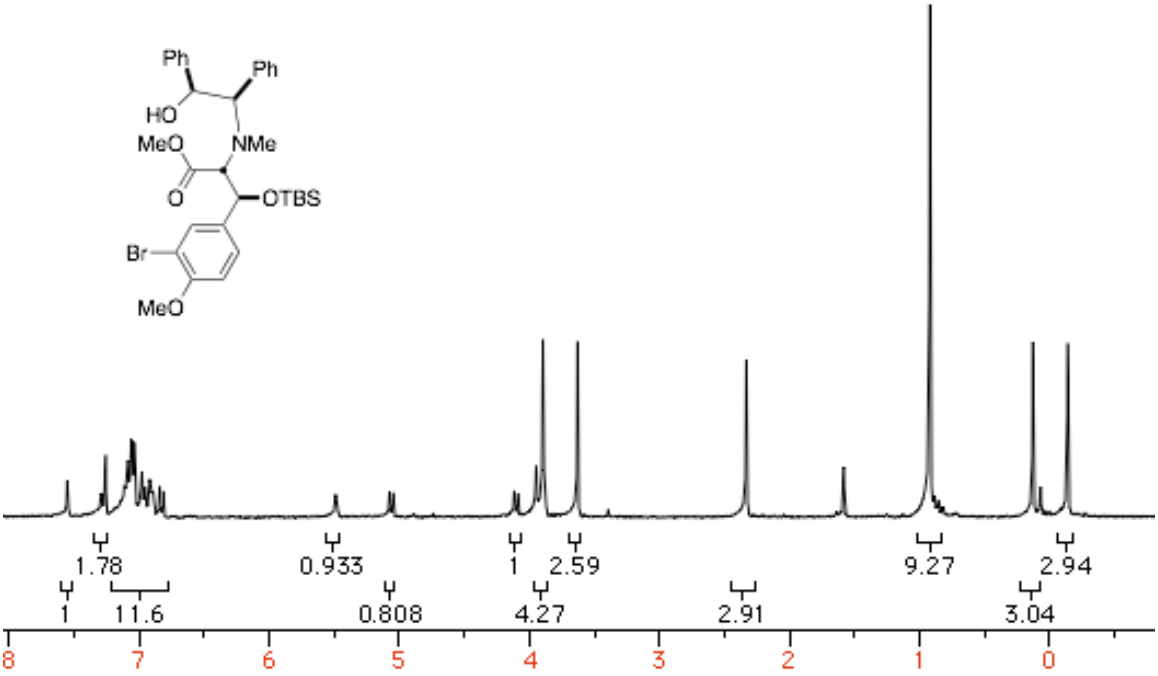
R_f = 0.48 (80:20 Hexanes:EtOAc)

$[\alpha]^{25}_D$ = + 97.5 (*c* = 0.8, $CHCl_3$).

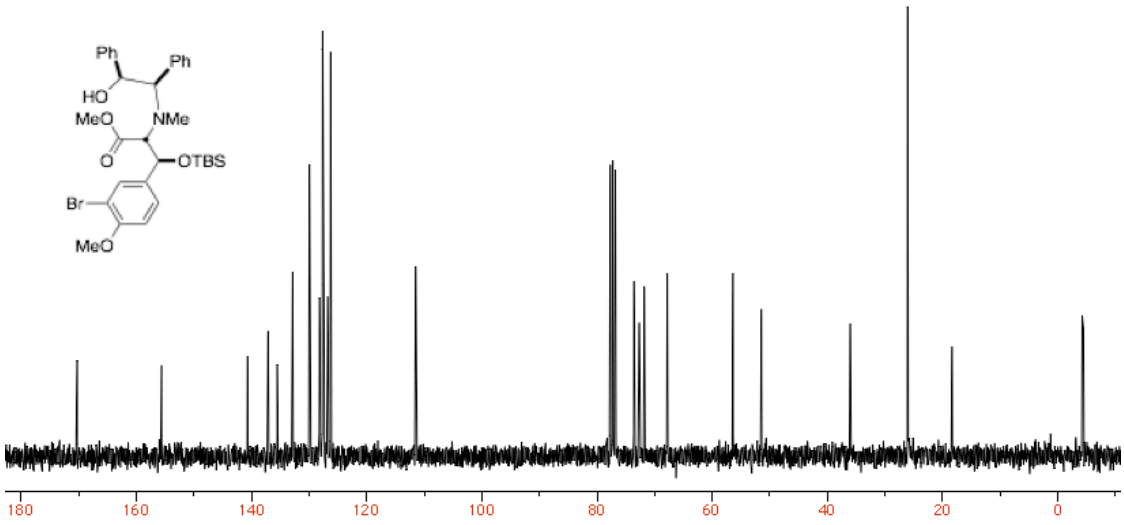
^{1}H NMR ($CDCl_3$, 300MHz) δ 7.55 (d, *J* = 2.1, 1H), 7.34 – 7.26 (m, 1H), 7.11 – 6.81 (m, 11H), 5.48, (d, *J* = 3.3, 1H), 5.06 (d, *J* = 8.7,1H), 4.11 (d, *J* = 8.7, 1H), 3.89 (s, 3H), 3.89 (d, *J* = 3.3, 1H), 3.63 (s, 3H), 2.33 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), -0.13 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 170.25, 155.60, 140.67, 137.11, 135.51, 132.85, 132.85, 129.93, 128.16, 127.63, 127.54, 127.41, 126.76, 126.24, 111.48, 111.33, 73.59, 72.67, 71.79, 67.80, 56.40, 51.47, 36.04, 26.08, 18.36, -4.22, -4.45.

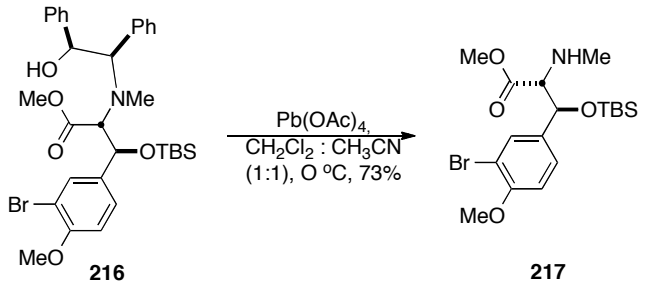
HRMS Calcd for $C_{32}H_{42}BrNO_5Si$ $[M+H]^+$ 628.20 Found 628.21 (M+H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **216**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **216**



(2R,3S)-methyl 3-(3-bromo-4-methoxyphenyl)-3-((tert-butyldimethylsilyl)oxy)-2-(methylamino)propanoate (217):

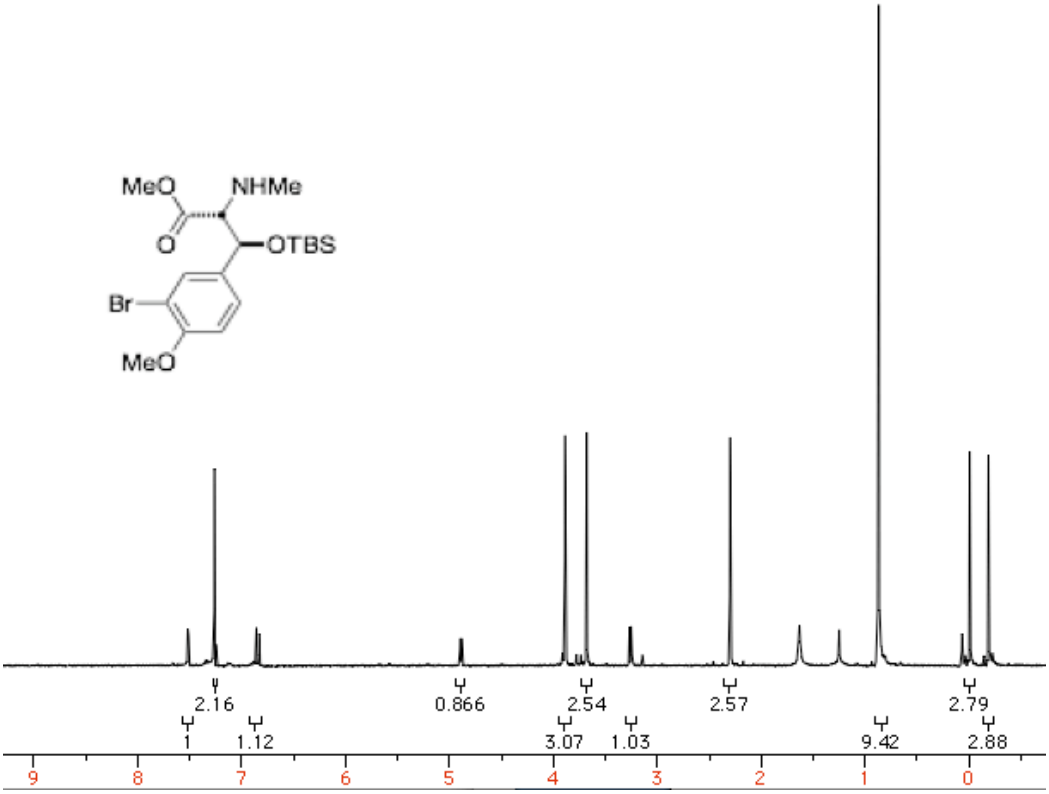
Compound **216** (1.14 g, 1.81 mmol, 1.0 equiv.) was azeotroped with $PhCH_3$ (2 × 40 mL). Compound **216** was redissolved in CH_2Cl_2 (10 mL) and CH_3CN (10 mL) under an argon atmosphere and then cooled to 0 °C and stirred for 15 minutes. $Pb(OAc)_4$ (1.80 g, 3.63 mmol, 2.0 equiv.) was added and stirring continued for 30 minutes. The reaction was then 0 °C by the addition of a saturated aqueous solution of $NaHCO_3$ (20 mL) and EtOAc (20 mL) was added to the reaction mixture at 0 °C and the layers were separated. The organic layer was washed with water (40 mL), and saturated aqueous solution of $NaHCO_3$ (40 mL), $NaCl_{aq}$ (40 mL), dried over Na_2SO_4, and concentrated to afford the crude material. The crude mixture was purified by flash chromatography (gradient elution, 90:10 to 70:30 Hexanes:EtOAc) to give compound **217** (570 mg, 73% yield). (ps-312-1)

R_f = 0.39 (70:30 Hexanes:EtOAc)

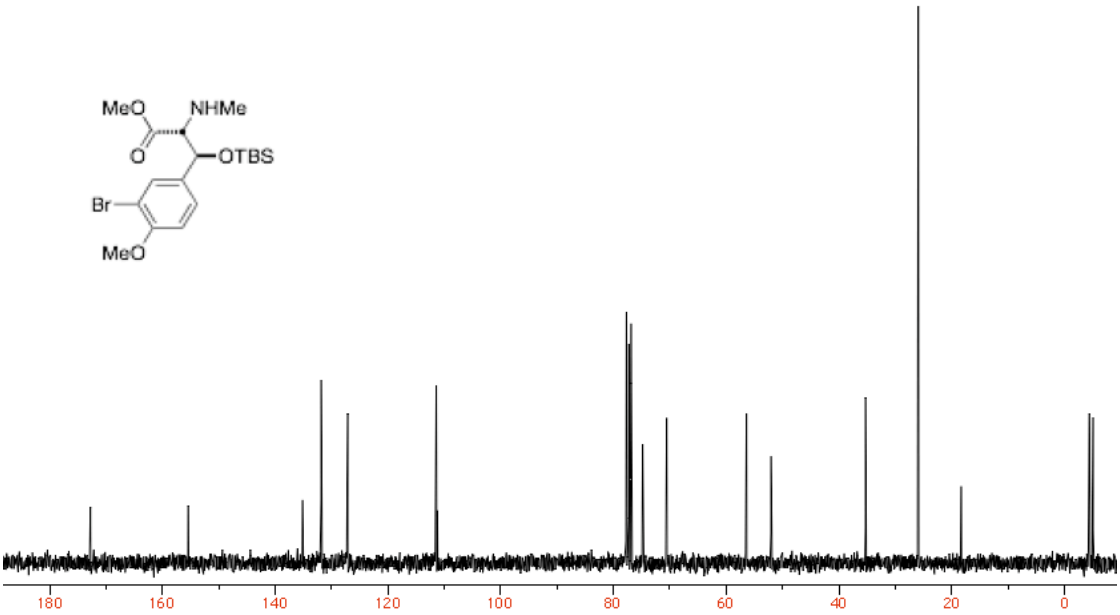
$[\alpha]^{25}_D$ = + 30.0 (*c* = 0.16, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 300 MHz,) δ 7.52 (d, J = 2.1, 1H) 7.26 (s, 1H), 6.89 (d, J = 8.7, 1H), 5.10 (d, J = 2.7, 1H), 3.89 (s, 3H), 3.73 (s, 3H), 3.48 (d, 2.7, 1H), 0.88 (s, 9H), -0.012 (s,3H), -0.15 (s, 3H).

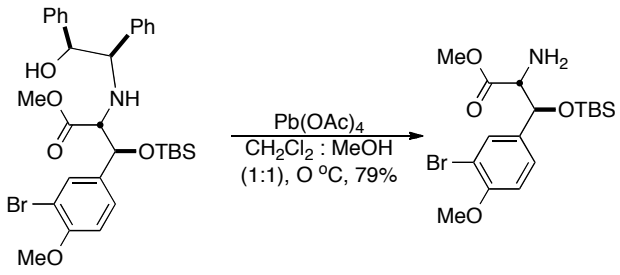
^{13}C NMR (75 MHz, $CDCl_3$) 172.76, 155.41, 135.13, 131.82, 127.12, 111.40, 111.20, 74.79, 70.53, 56.38, 52.02, 35.25, 25.91, 18.29, -4.42, -5.09. HRMS Calcd for $C_{18}H_{30}BrNO_5Si$ 432.11 $[M+H]^+$ Found 432.08 (M+H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **217**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **217**



215 **219**

(2*R*,3*S*)-methyl 2-amino-3-(3-bromo-4-methoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)propanoate (219):

Compound **215** (1.90 g, 3.09 mmol, 1.0 equiv.) was azeotroped with $PhCH_3$ (2 × 40 mL) and redissolved in CH_2Cl_2 (20 mL) and CH_3CN (20 mL) under argon atmosphere The reaction was cooled to 0 °C and let to stir for 15 minutes. $Pb(OAc)_4$ (3.05 g, 6.18 mmol, 2 equiv.) was added, and stirring continued for 30 minutes. The reaction was quenched at 0 °C by the addition of a saturated aqueous solution of $NaHCO_3$ (30 mL) and EtOAc (30 mL). The layers were separated. The organic layer was washed with water (50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL), $NaCl_{aq}$ (50 mL), dried over Na_2SO_4, and concentrated to afford the crude material. The crude mixture was purified by flash chromatography (gradient elution, 1.25:98.75 to 3:97 MeOH:DCM) to give **219** (1.03 g, 79% yield). (ps2-307-4)

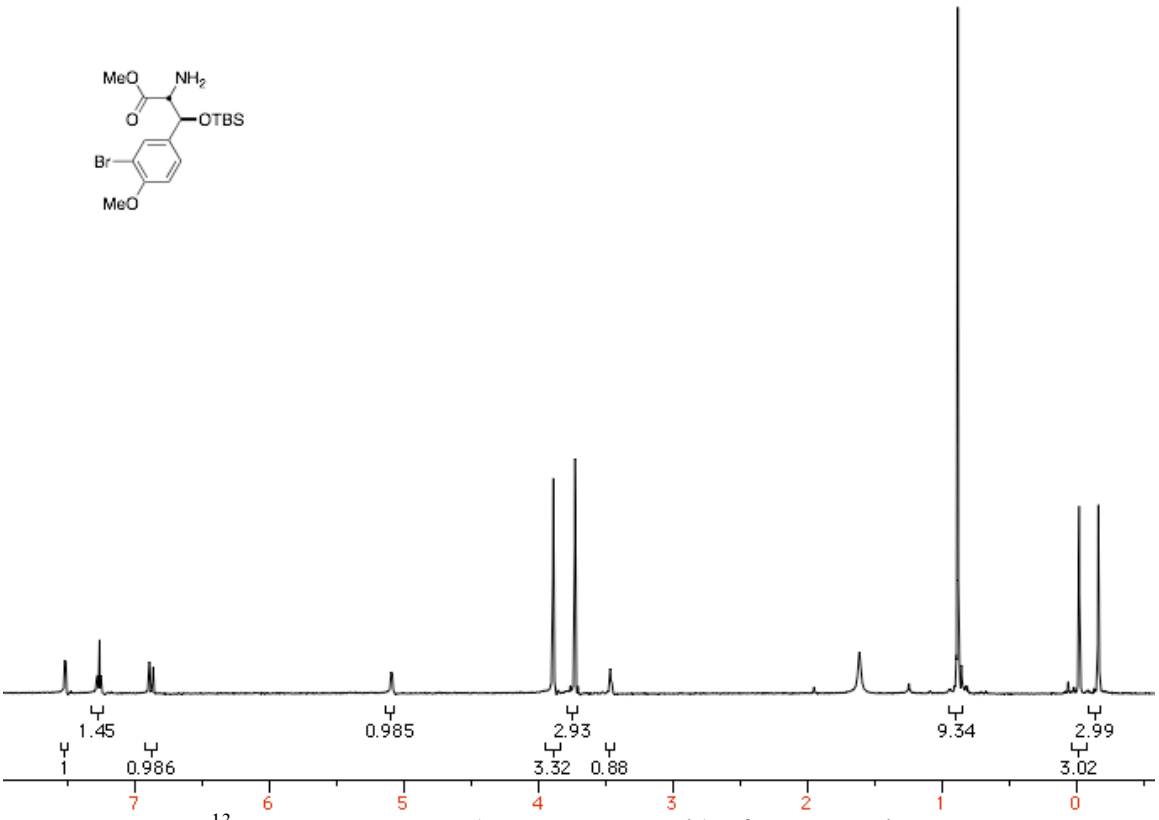
R_f = 0.36 (97:3 DCM:MeOH)

$[\alpha]^{25}_D$ = + 23.7 (*c* = 0.80, $CHCl_3$)

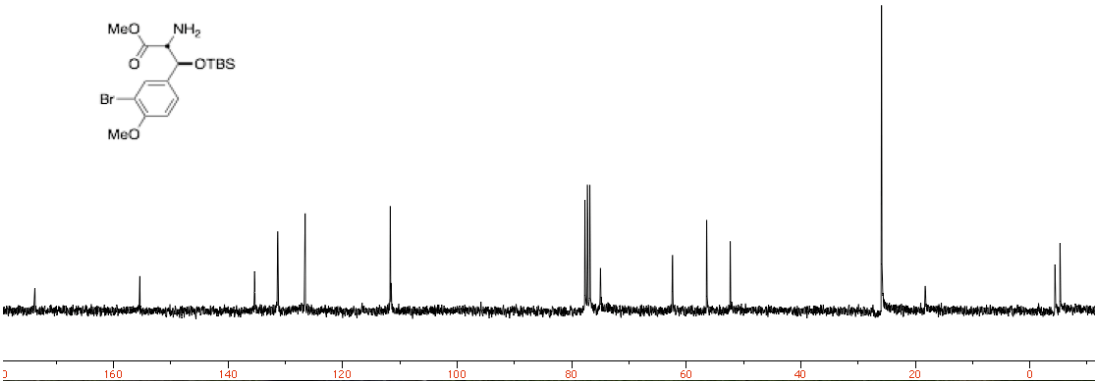
^{1}H NMR ($CDCl_3$ 300MHz) : δ. 7.51 (d, *J* = 2.1, 1H) 7.6 (dd, *J* = 2.1, 8.4, 1H), 6.87 (d, *J* = 8.7, 1H), 5.09 (d, *J* = 2.7, 1H), 3.88 (s, 3H), 3.72 (s, 3H), 3.48 (d, *J* = 3.0, 1H), 0.88 (s, 9H), 0.01 (s, 3H), -0.16 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) 155.51, 135.39, 131.33, 126.54, 111.68, 111.54, 74.99, 62.38, 56.43, 52.31, 25.31, 25.89, 18.20, -4.36, -5.26.

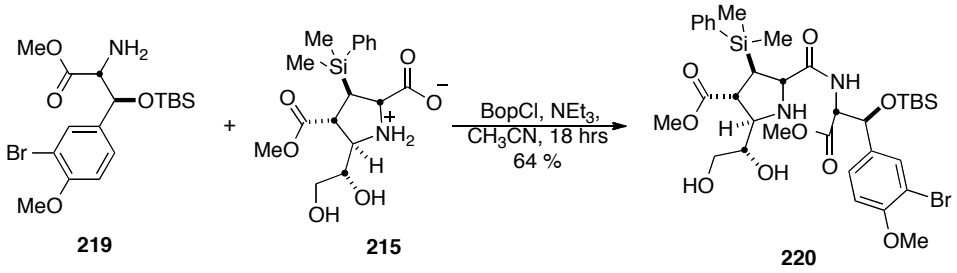
HRMS Calcd for $C_{17}H_{28}BrNO_5Si$ 418.10 $[M+H]^+$ Found 418.10 (M+H)



^{13}H NMR spectrum (300 MHz, $CDCl_3$) of compound **219**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **119**



(2R,3R,4R,5S)-methyl5-(((1R,2R)-1-(3-bromo-4-methoxyphenyl)-1-((tert-butyldimethylsilyl)oxy)-3-methoxy-3-oxopropan-2-yl)carbamoyl)-2-((S)-1,2-dihydroxyethyl)-4-(dimethyl(phenyl)silyl)pyrrolidine-3-carboxylate (220)

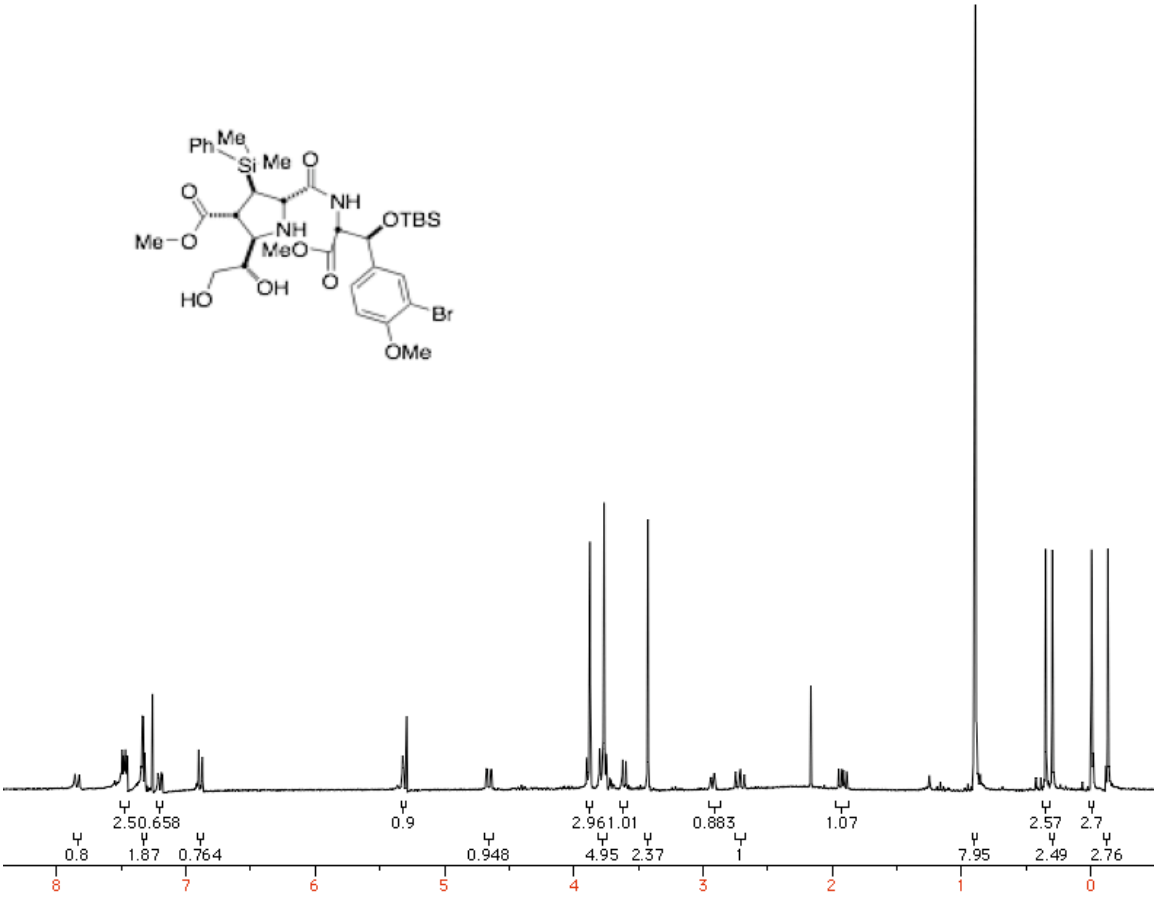
To a 10 mL rbf was added **219** (88 mg, 0.239 mmol, 1 equiv.), CH_3CN (1 mL), Amino Acid **215** (82 mg, 0.215 mmol, 0.8 equiv.), and TEA (145 μl, 1.43 mmol, 6 equiv.). The reaction was stirred for 30 minutes followed by the addition of BopCl (70 mg. 0.262 mmol, 1.1 equiv.). The reaction was stirred for 18.5 h and was evaporated to dryness. EtOAc and 1 NHCl was added and stirring continued for 15 minutes. The organic layer was washed with saturated aqueous solution of $NaHCO_3$, water and a saturated aqueous solution of NaCl. The crude material was dried over Na_2SO_4 and concentrated. The light yellow material was purified by flash chromatography (gradient elution, 1.25:98.75 to 5:95 MeOH:DCM) to give **23** (90 mg, 64% yield). (ps2-307-4, ps2-327-3)

^{1}H NMR ($CDCl_3$, 300MHz) δ. 7.91 (d, J = 11.4, 1H) 7.48 – 7.45 (m, 3H), 7.32 – 7.30 (m, 2H), 7.20 (dd, J = 2.1, 8.7, 1H), 6.89 (d, J = 8.4, 1H), 5.32 (d, J = 1.50, 1H), 4.64 (dd, J= 1.8, 9.9, 1H), 3.86 (s, 3H), 3.79 – 3.59 (m, 7H), 3.60 (d, J = 7.5, 1H), 3.41 (s, 1H), 2.91 (dd, J = 1.5, 9.3, 1H), 2.71 (dd, J= 9.3, 10.8, 1H),1.89 (dd, J= 7.5, 10.8, 1H), 0.89 (s, 9H), 0.33 (s, 3H), 0.28 (s,3H).

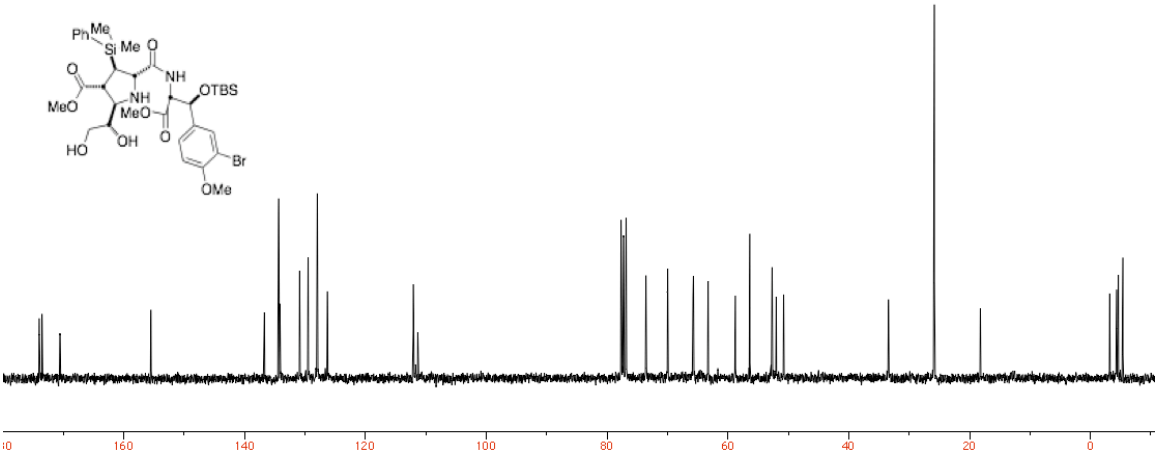
^{13}C NMR (75 MHz, $CDCl_3$) 173.99, 173.53, 170.56, 155.51, 136.72, 134.37, 134.16, 130.90, 129.492, 127.96, 126.30, 112.07, 111.33, 73.57, 69.97, 65.79, 65.71, 63.28, 58.78, 56.38, 52.69, 50.13, 50.78, 33.42, 25.84, 18.12g

-3.19, -4.33, -4.61, -5.37.

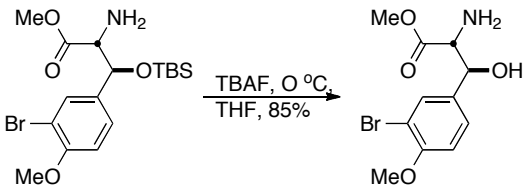
HRMS Calcd for $C_{34}H_{51}BrN_2O_9Si_2$ 767.23 $[M+H]^+$ Found 767.23 (M+H)



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **220**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **220**



219 **221**

(2R,3S)-methyl 2-amino-3-(3-bromo-4-methoxyphenyl)-3-hydroxypropanoate (221):

To a 10 mL rbf was added **219** (183 mg, 0.42 mmol, 1.0 equiv.) and THF (1 mL). The reaction was cooled to 0 °C and was stirred for 10 minutes. TBAF (366 mg, 0.46 mmol, 3.0 equiv.) was added, and stirring continued for 45 minutes, at which point EtOAc (5 mL) and saturated NH_4Cl was added to the reaction at 0 °C. The organic layer was washed with saturated $NaHCO_3$ (5 mL), H_2O (5 mL), and $NaCl_{aq}$ (2 × 5 mL). The organic layer was dried over $NaSO_4$ and concentrated. The crude mixture was purified by flash chromatography (gradient elution, 1.25:98.75 to 7:93 MeOH:DCM) to give **221** (100 mg, 85% yield). (ps2-318-10)

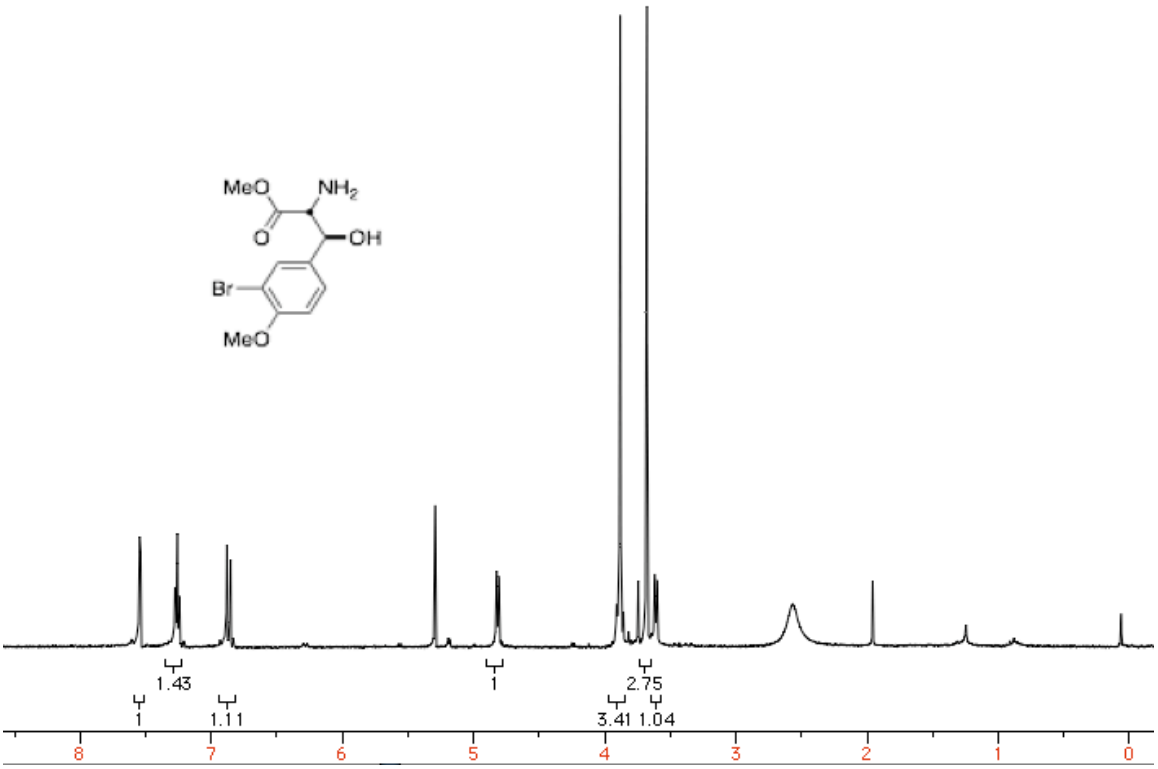
R_f = 0.33 (93:7 DCM:MeOH)

$[\alpha]^{25}_D$ = - 12.8 (*c* = 0.46, $CHCl_3$)

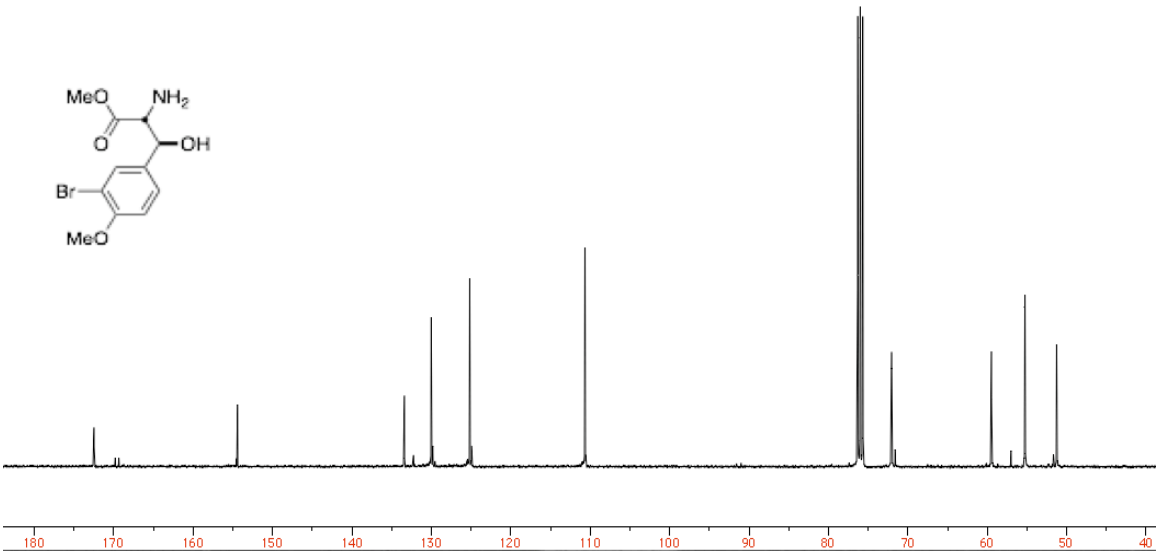
^{1}H NMR ($CDCl_3$ 300MHz) : δ. 7.53 (d, *J* = 2.1, 1H) 7.27 – 7.24 (m, 1H), 6.86 (d, *J* = 8.7, 1H), 4.81 (d, *J* = 5.1, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.60 (d, *J* = 5.1, 1H), 2.57 – 2.53 (bs, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) 172.49, 154.41, 133.40, 130.02, 129.82, 125.18, 124.94, 110.66, 72.04, 59.47, 55.25, 51.27

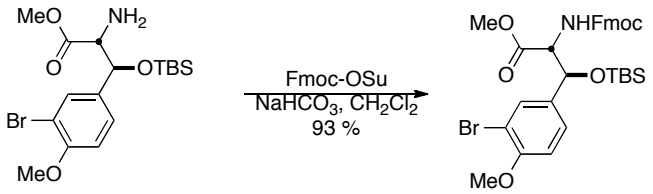
Calcd for $C_{11}H_{14}BrNO_4$ 303.01 $[M+H]^+$ Found 403.01(M+H)



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **221**



^{13}C NMR spectrum (100 MHz, $CDCl_3$) of compound **221**



219 **220**

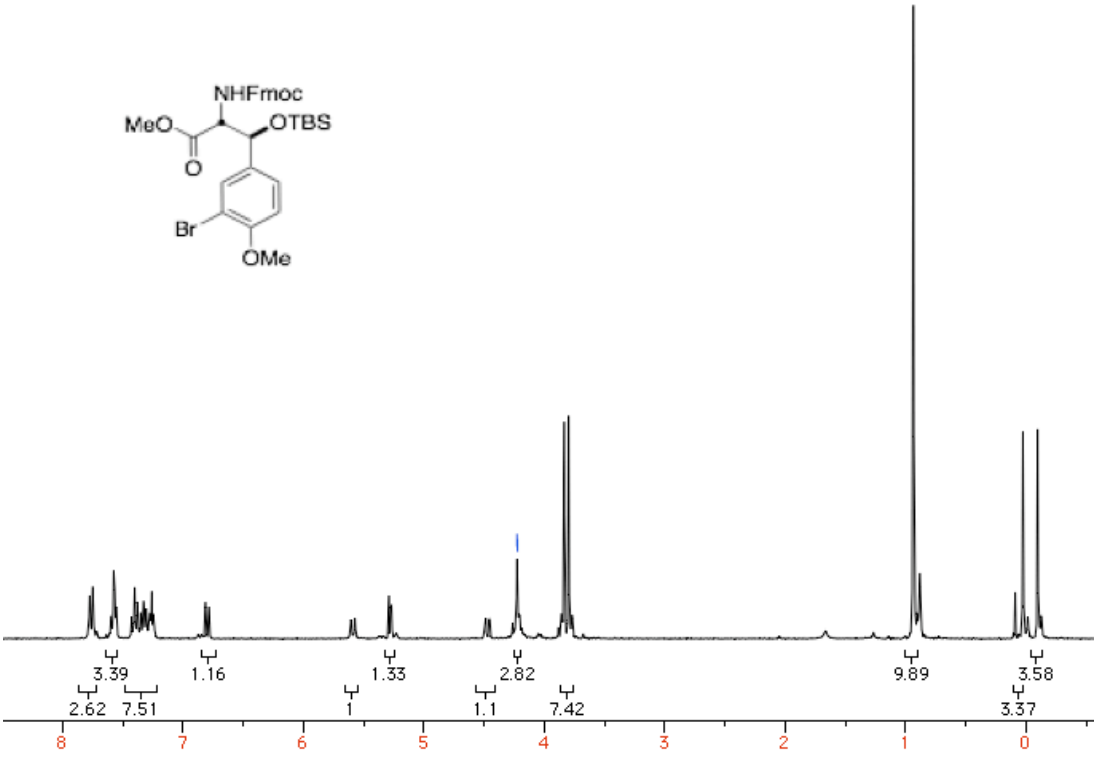
(2*R*,3*S*)-methyl2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(3-bromo-4-methoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)propanoate (220):

To a 10 mL recovery flask that contained **219** (97 mg, 0.229 mmol, 1 equiv.) and dissolved CH_2Cl_2 (2 mL) and a saturated solution $NaHCO_3$ (250µl) was added Fmoc-OSu (114 mg, 0.337 mmol, 1.5 equiv.) at rt. The reaction was stirred for 6 h and diluted with CH_2Cl_2 (5 mL) and H_2O (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 ml). The organic extracts were combined, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude material. The crude reaction mixture was purified by flash chromatography (gradient elution, 95:5 hexanes:EtOAc to 85:15 hexanes/EtOAc) to give compound **220** (134mg, 93% yield) (ps2-356-3)

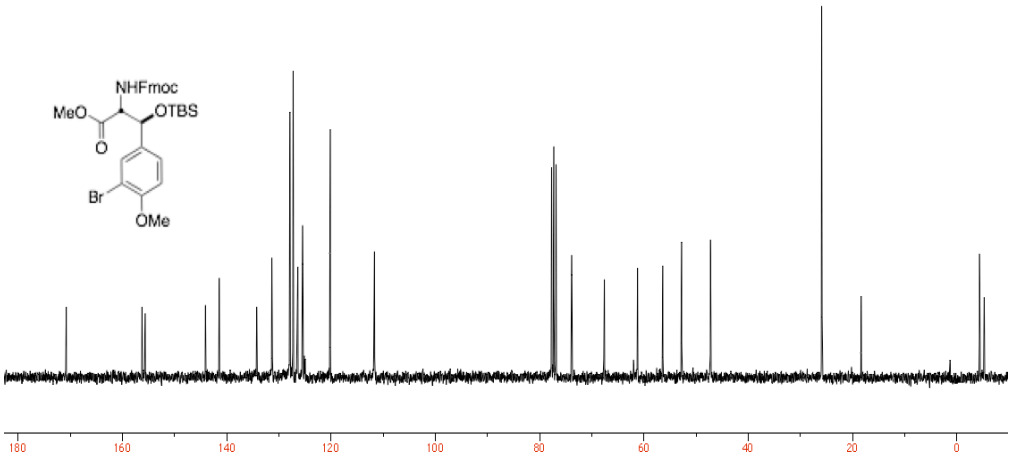
R_f = 0.41 (80:20 Hexanes/EtOAc)

($CDCl_3$ 300MHz) : δ. 7.77 – 7.23 (m, ~13H) 6.79 (d, J = 6.9, 1H), 5.58 (d, J = 9.6 , 1H), 5.27 (d, J = 2.1, 1H), 4.48 (dd, J = 2.1, 9.9, 1H), 4.22 (m, 2H) 3.83 (s, 3H), 3.79, 0.93 (s, 9H), 0.02 (s, 3H), -0.09 (s, 3H).

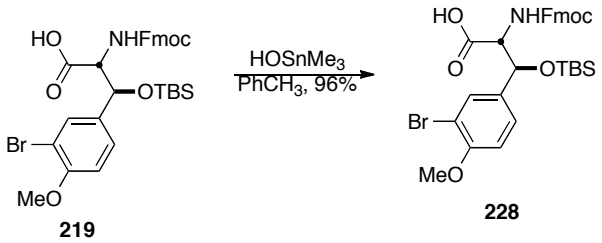
^{13}C NMR (75 MHz, $CDCl_3$) 170.79, 156.27, 155.61, 144.10, 144.031, 141.451, 134.25, 131.36, 127.28, 126.38, 125.46, 120.17, 73.84, 6759, 61.22, 56.37, 52.76, 47.23, 25.90, 18.32, -4.35, -5.52.



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **220**



^{13}C NMR spectrum (75 MHz, $CDCl_3$) of compound **220**



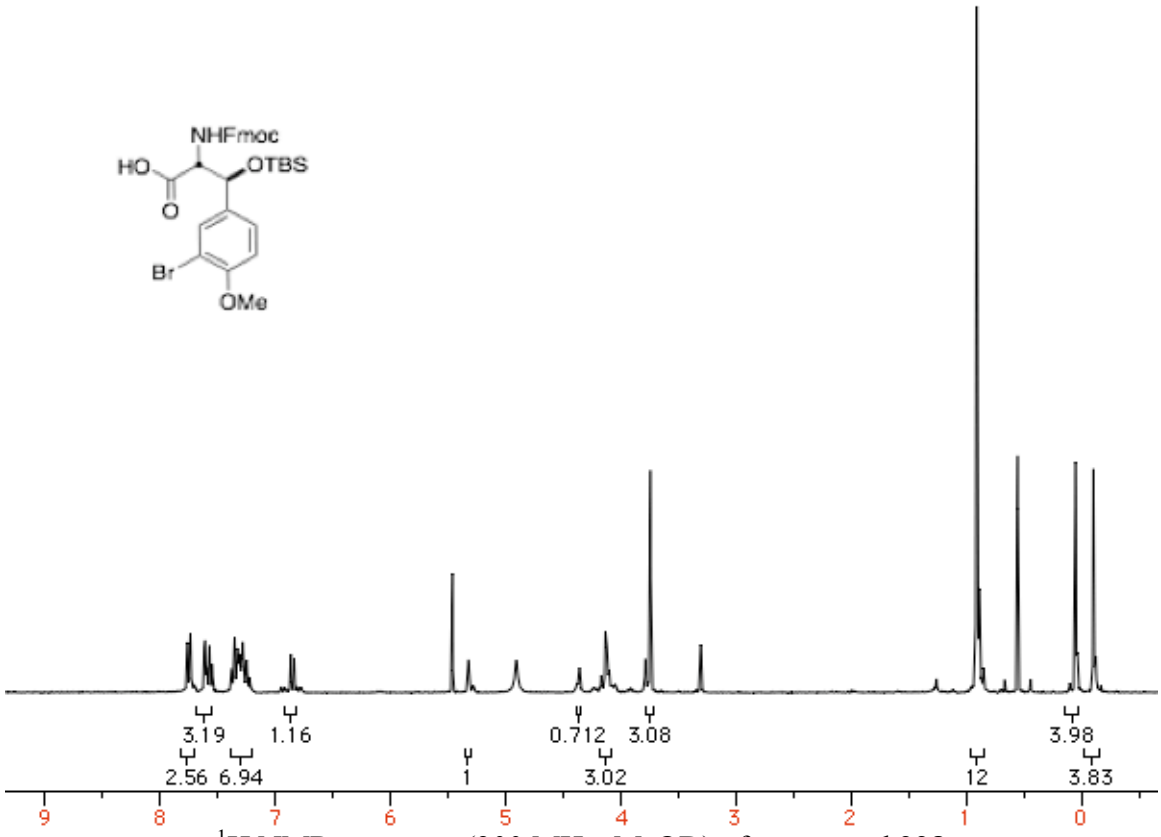
(2*R*,3*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-3-(3-bromo-4-methoxyphenyl)-3-((*tert*-butyldimethylsilyl)oxy)propanoic acid (228):

To a 10 mL recovery flask was added **219** (126 mg, 0.196 mmol, 1 equiv.), Trimethyltin hydroxide (355 mg, 1.96 mmol, 10 equiv.) and $PhCH_3$ (2 mL). The reaction was heated at 90 °C and let stir for 3 h and diluted with EtOAc (3 mL). The organic layer was washed with 1NHCl, and a saturated aqueous solution of NaCl followed by being dried over Na_2SO_4, and concentrated under reduced pressure to afford 254 mg of crude material. The crude reaction mixture was purified by flash chromatography (gradient elution, 97:3 DCM/MeOH to 93:7) to give compound **228** (118 mg, 96% yield). (ps2-357-2)

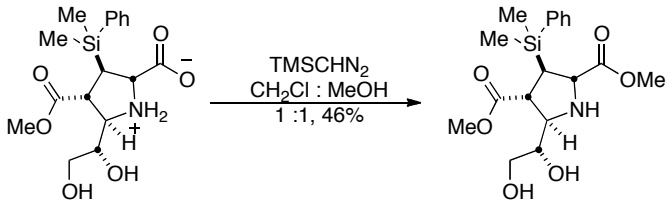
R_f= 0.41, (93:7 DCM/MeOH)

^{1}H NMR (MeOD 300MHz) : δ. 7.76 – 7.22 (m, ~13H) 6.85 (d, J = 9.0, 1H), 5.31 (d, J = 3.0 , 1H), 4.35 (d, J = 2.7, 1H), 4.13 – 4.09 (m, 3H), 3.74 (s, 3H), 0.91 (s, 9H), 0.05 (s, 3H), -0.10 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.18, 157.14, 155.77, 155.65, 143.99, 141.27, 135.00, 134.83, 131.40, 131.33, 127.74, 127.59, 127.01, 126.73, 125.14, 124.85, 124.67, 119.73, 111.73, 111.55, 110.93, 74.18, 74.01, 67.51, 67.21, 61.28, 55.54, 55.47, 25.15, 17.93, -5.54, -6.20



^{1}H NMR spectrum (300 MHz, MeOD) of compound **228**



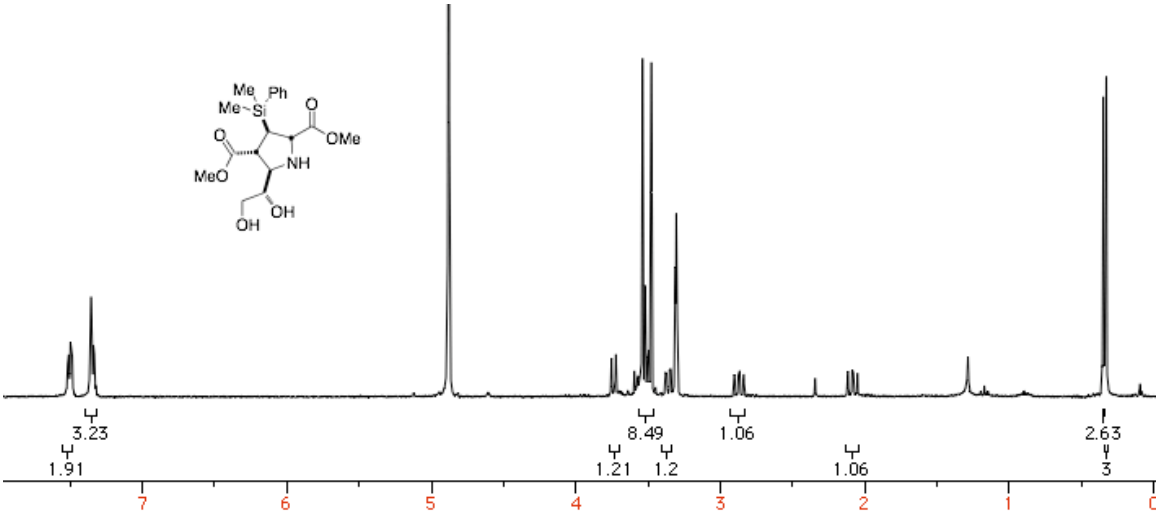
215 **225**

(2*S*,3*R*,4*R*,5*R*)-dimethyl5-(1,2-dihydroxyethyl)-3-(dimethyl(phenyl)silyl)pyrrolidine-2,4-dicarboxylate (225)

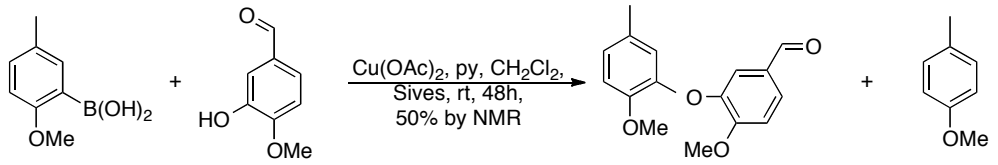
To a 5 mL rbf was added **215** (21mg, 0.05mmol, 1 Eq) and dissolved in of CH_2Cl_2 (250 μl) and MeOH (250 μl). $TMSCHN_2$ (approx 9 μl) was added until the solution remained yellow. The reaction was stirred for another 20 minutes and concentrated under reduced pressure to afford 20 mg of crude material. The crude material was purified by flash chromatography (gradient elution, 98.75:1.25 DCM/MeOH to 93:7) to give compound **225**. (10 mg, 46% yield) (ps2-359-7)

R_f = 0.50 (93:7 DCM:MeOH)

^{1}H NMR ($MeOD_3$ 300MHz) : δ. 7.51 – 7.33 (m, 5H) 7.27 – 7.24 (m, 1H), 3.74 (d, J = 9.0, 1H), 3.59 – 3.47 (m, 9H), 3.36 (dd, J= 2.4, 8.4, 1H), 2.85 (dd, J = 9.9, 11.1, 1H), 2.08 (dd, J= 8.7, 11.1, 1H), 0.34 (s, 3H), 0.32 (s,3H).



^{1}H NMR (300MHz, MeOD) of compound **225**.

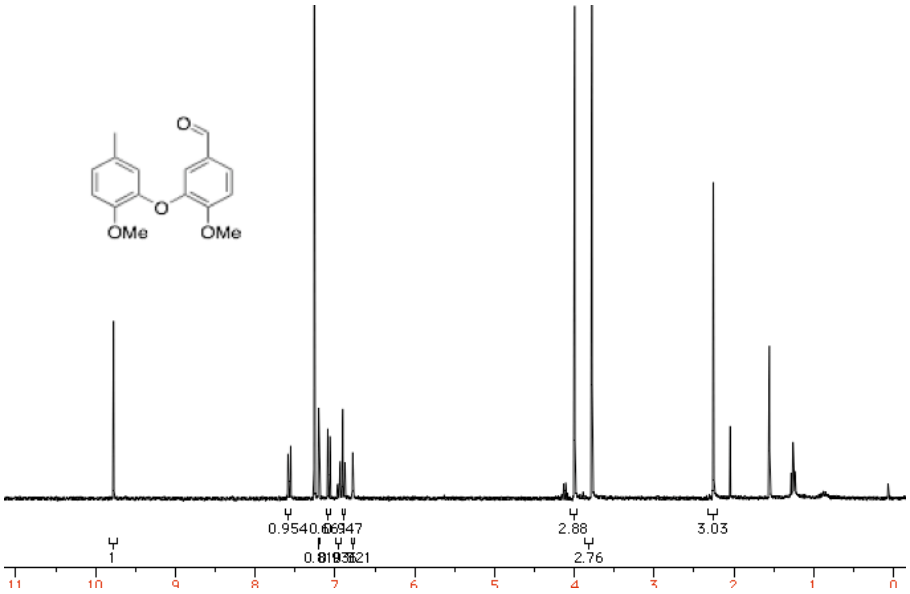


241 **237** **242** **243**

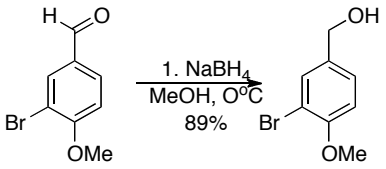
compound 242:

To a flame dried 5 mL rbf was added **241** and **237** and was cooled under argon was added 3 Å molecular sieves $Cu(OAc)_2$ (12 mg, 0.06 mmol, 1 equiv.), CH_2Cl_2 (602 μL) and pyridine (24 μL, 0.03mmol, 5 equiv). The reaction was stirred for 3 h at rt and then filtered over celite. The crude reaction mixture was then prep plated in 90:20 Hexane:EtOAc to afford the desired compound **242**. (ps-367-3)

^{1}H NMR ($CDCl_3$, 300MHz,) δ 9.77 (s,1H), 7.57 (dd, J = 1.8, 8.1, 1H), 7.20 (d, J = 2.1, 1H), 7.07 (d, J = 8.4, 1H), 6.94 – 6.87 (m, 2H), 6.77 (d, J = 2.1, 1H), 3.99 (s, 3H), 3.77 (s, 3H), 2.25 (s, 3H).



^{1}H NMR (300MHz, MeOD) of compound **242**

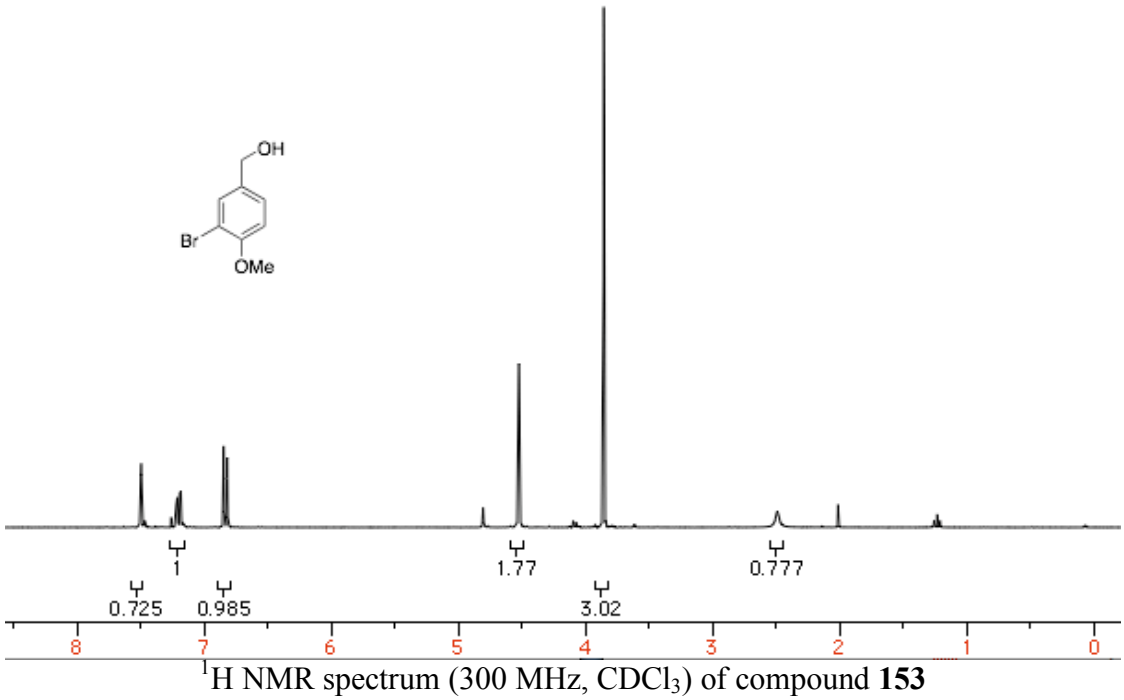


152 **153**

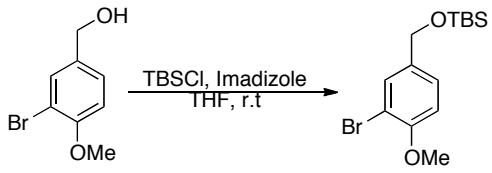
(3-bromo-4-methoxyphenyl)methanol (153):

To a 50 mL rbf was added **152** (540 mg, 2.51 mmol, 1 equiv.) in MeOH (5 mL) then $NaBH_4$ (263 mg, 6.97 mmol, 3 equiv.) was added. The reaction was stirred for 5 minutes and then 1N HCl was added and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The crude mixture dried over Na_2SO_4, and concentrated under reduced pressure to afford pure product **33** (448 mg, 89 % yield) (ps2-188-1, ps2-185-1)

^{1}H NMR ($CDCl_3$, 300MHz, ps2-185-1) δ 7.5 (d, J = 1.9, 1H), 7.20 (dd, J = 2.1, 8.4, 1H), 6.82 (d, J = 8.4, 1H), 4.52 (s, 2H), 3.87 (s, 3H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **153**

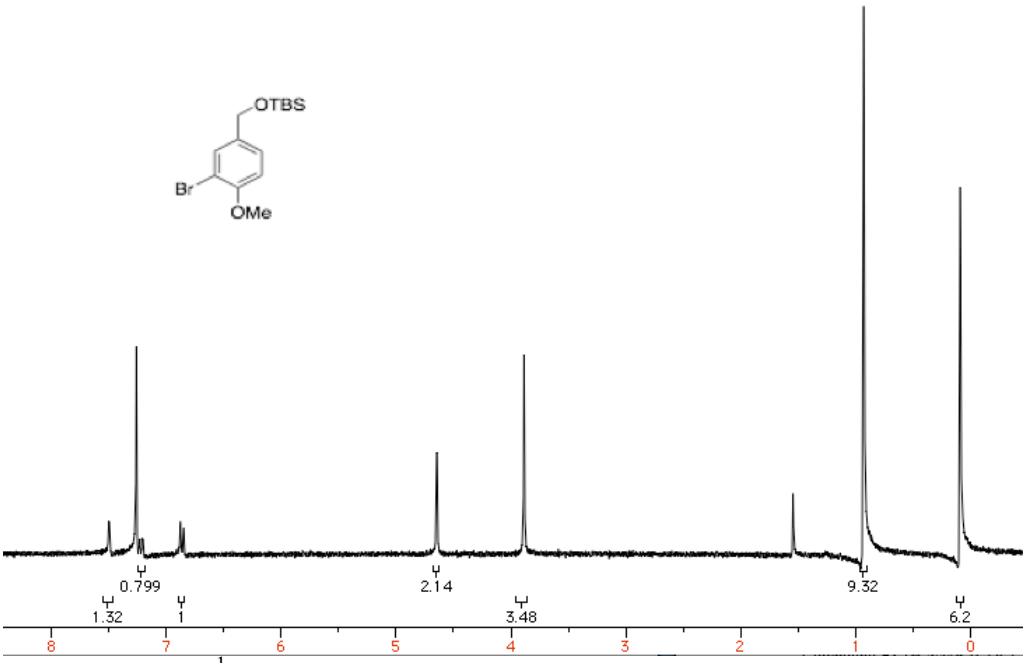


153 **245**

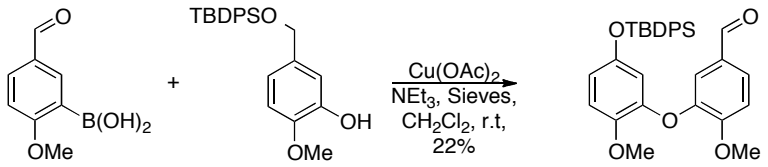
((3-bromo-4-methoxybenzyl)oxy)(tert-butyl)dimethylsilane (245):

To a 50 mL rbf was added **153** (420 mg, 1.95 mmol, 1 equiv.), TBSCl (442 mg, 2.93 mmol, 1.5 equiv.), Imidazole (200 mg, 2.93 mmol, 1.5 equiv.) in THF (10 mL). The reaction was stirred for 1 h and then diluted with a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The reaction was dried over Na_2SO_4, and concentrated under reduced pressure to afford the 850mg of crude material that was then purified by flash chromatography to reveal **245** (678 mg, 99 % yield) ps2-189-3

^{1}H NMR ($CDCl_3$, 300MHz, ps2-185-1) δ 7.49 (s, J = 1H), 7.20 (d, J = 3, 1H), 6.86 (d, J = 8.7, 1H), 4.64 (s, 2H), 3.86 (s, 3H) 0.93 (s, 9H), 0.09 (s, 3H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **245**

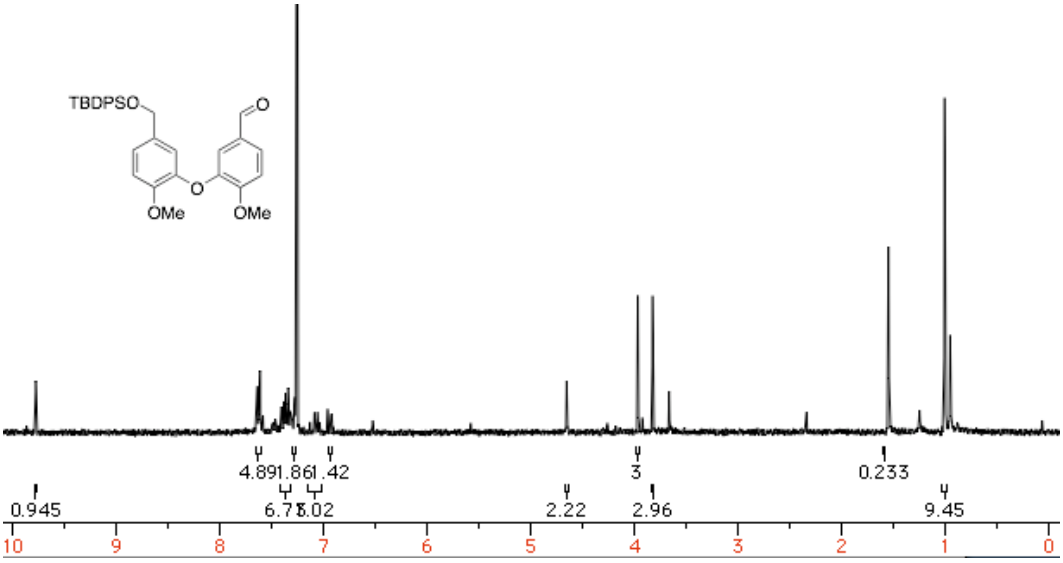


247 **246** **248**

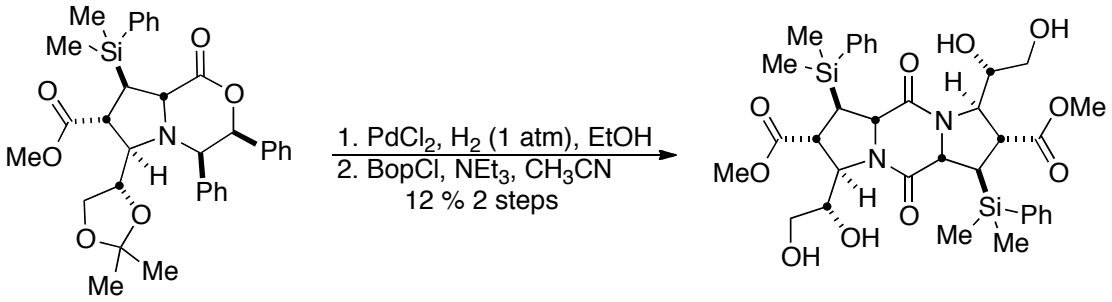
3-(5-((*tert*-butyldiphenylsilyl)oxy)-2-methoxyphenoxy)-4-methoxybenzaldehyde (248):

To a 50ml flask was added the phenol **246** (69 mg, 0.177 mmol, 1 equiv.) $Cu(OAc)_2$ (32 mg, 0.177 mmol, 1 equiv.), and the boronic acid **247** (63 mg, 0.355 mmol, 2 equiv.) and 4 Å molecular sieves. The reaction was dissolved in CH_2Cl_2 (10 mL) to make the concentration of the reaction 0.017*M* by phenol. The reaction was then stirred for 24h and filtered over celiete to produce the crude material. The crude reaction mixture was purified by flash chromatography (gradient elution, 80:20 to 60:40 Hexanes:EtOAc) afford compound **33** (22cmg, 22%) (ps2-204-15)

^{1}H NMR ($CDCl_3$, 300MHz, ps2-185-1) δ 9.71 (s 1H), 7.48 – 6.92 (m, _H), 4.65 (s, 2H), 3.96 (s, 3H), 3.92 (s, 3H), 1.01 (s, 9H).



^{1}H NMR spectrum (300 MHz, $CDCl_3$) of compound **248**



137 **256**

(1*R*,2*R*,3*R*,5a*S*,6*R*,7*R*,8*R*,10a*S*)-dimethyl 3,8-bis(1,2-dihydroxyethyl)-1,6-bis(dimethyl(phenyl)silyl)-5,10-dioxodecahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-2,7-dicarboxylate (256):

To a flame dried 10 mL rbf was added compound **137** (253 mg, 0.431 mmol, 1equiv.) in absolute ethanol (5 mL). The reaction was purged with Argon and $PdCl_2$ (61 mg, 0.03mmol, 0.8 equiv.) was added to the reaction mixture followed by equipment of the round bottom with a stir bar and a balloon of H_2 (1 atm). The reaction was stirred overnight, filtered over celite, and concentrated under reduced pressure to afford the crude product. The reaction was azeotroped with $PhCH_3$ (3 x 20 mL) and put on the pump for 1 h. BOPCl (138 mg, 0.10 mmol, 2.1 equiv.) was then added and the reaction vessel was then purged with argon for 5 minutes. The two compounds were dissolved in CH_3CN (5 mL) followed by cooling to -78 °C and dropwise addition of NEt_3 (342 μl, 2.64 mol, 6.1 equiv.). The reaction vessel was warmed to rt and stirred for 7 h followed by concentration and dilution by EtOAc (10 mL) and 1 N HCl (10 mL). The organic layers were separated and the aqueous layer was extracted EtOAc (3 x 10 mL) The reaction was purified by flash chromatography (gradient eluction, 98.75:1.25 to 95:5 DCM/MeOH) to afford compound **256** (18 mg, 12 % yield). (ps2-33-88, ps3-dimer)

$[\alpha]^{25}_{D}$ = - 129.4 (*c* = 0.68, $CHCl_3$)

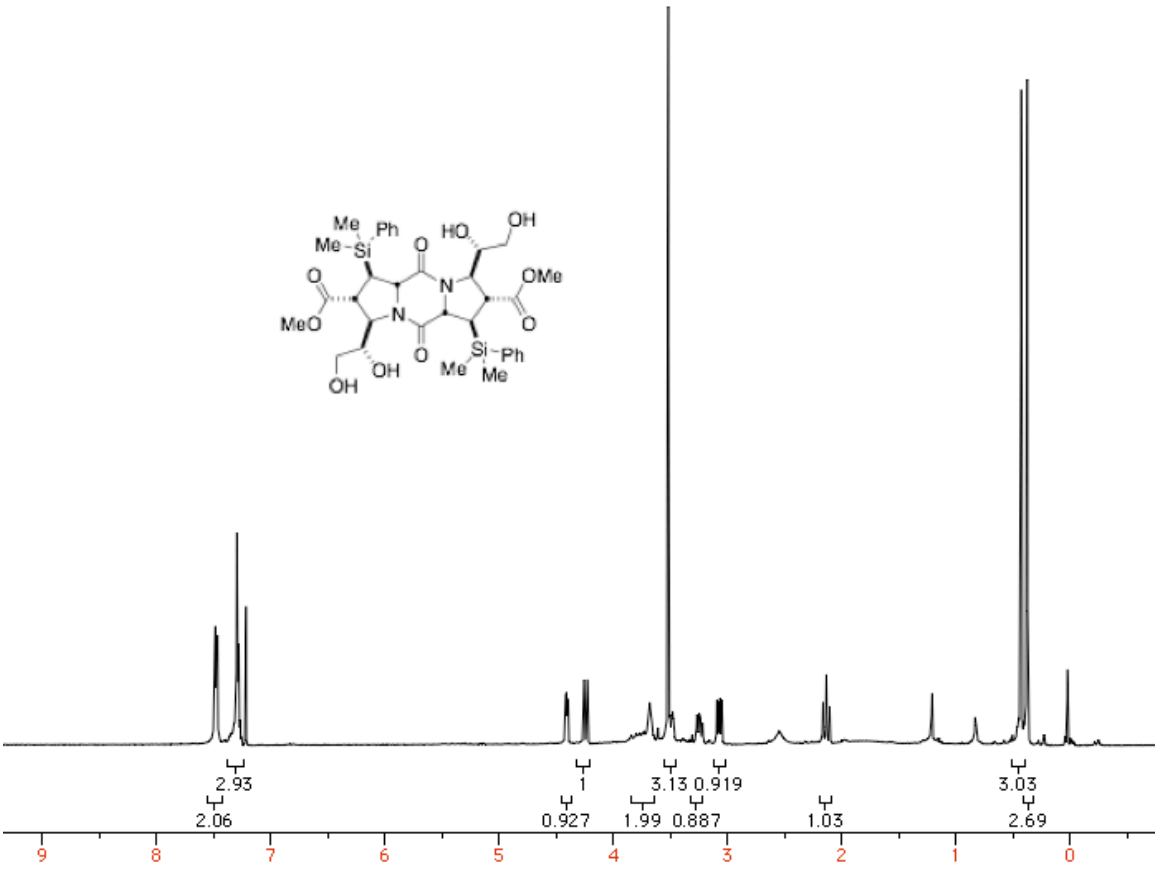
R_f = 0.39 (97:3 DCM:MeOH)

IR (neat) ν 3424, 2925, 1737, 1642, 1429, 1256, 1209, 1111, 1038 cm^{-1}

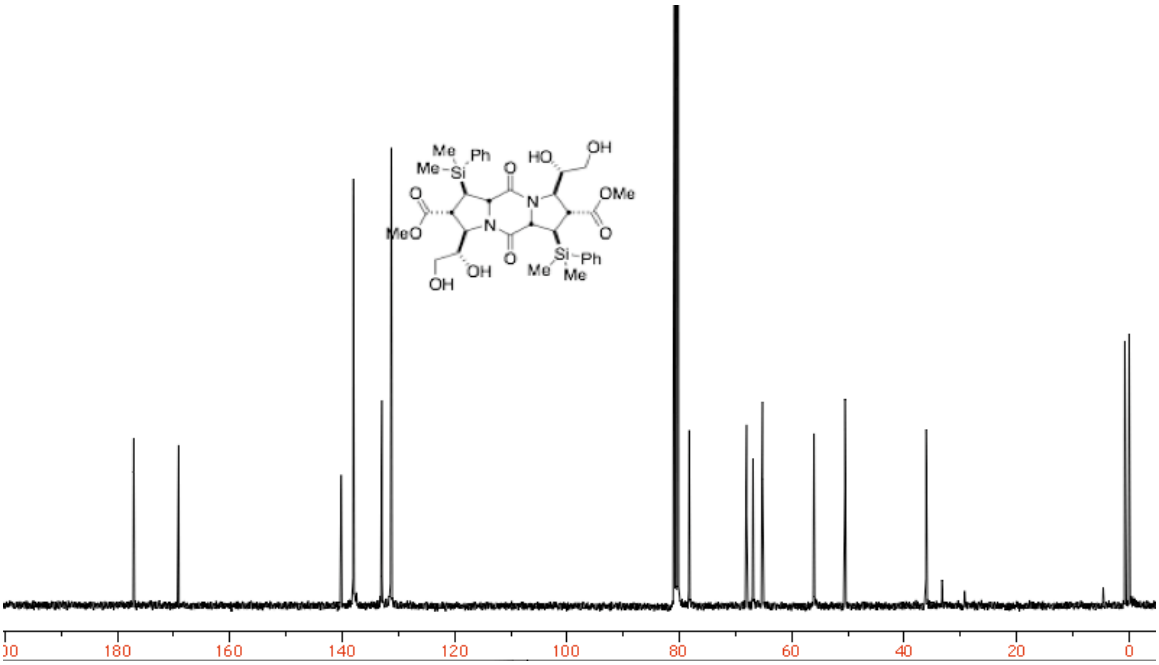
^1H NMR ($CDCl_3$ 300MHz) : δ 7.25 (m, 2H), 7.34 (m, 3H), 4.53 (dd, J = 3, 6, 1H) 4.27 (d, J = 12, 1H), 3.37 (m, 1H), 3.36 (m, 4H), 3.28 (dd, J = 7.5, 10.8, 1H), 3.11 (dd, J = 6, 11.4, 1H), 0.47 (s, 3H), 0.41 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.09, 169.09, 14018, 138.01, 132.93, 131.26, 78.2, 68.05, 65.22, 56.06, 50.53, 36.10, 0.77, -0.00

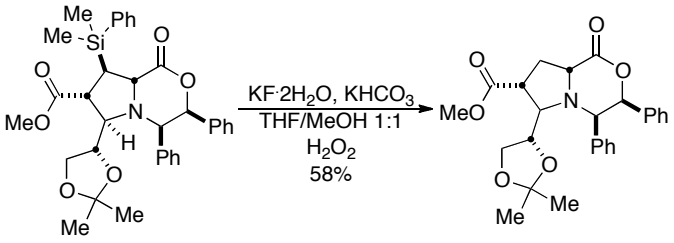
HRMS Calcd for $C_{34}H_{46}N_2BrO_{10}Si_2Na$: 721.2 Found 721.2 (M+H).



^1H NMR spectrum (400 MHz, $CDCl_3$) of compound **256**



^{13}C NMR spectrum (75 MHz, MeOD) of compound **256**

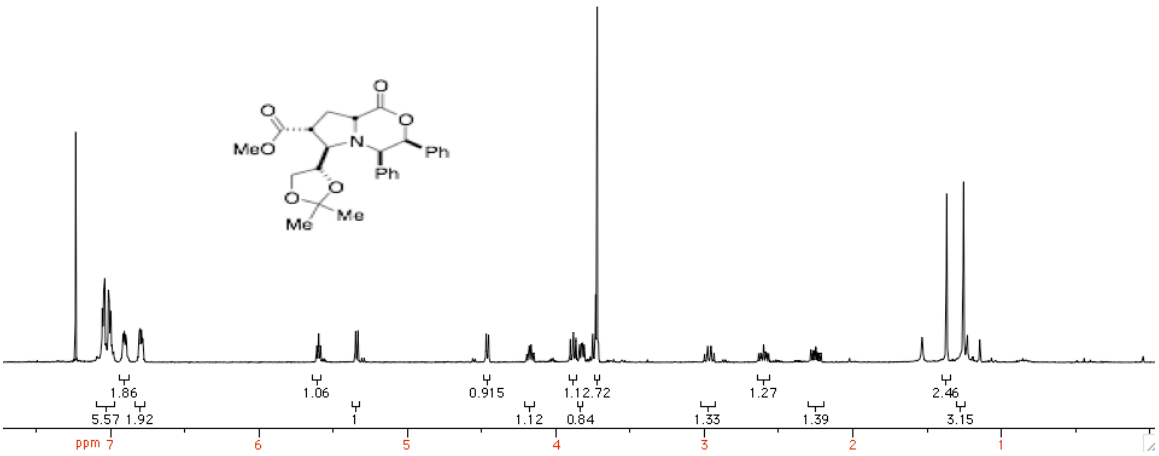


137 **260**

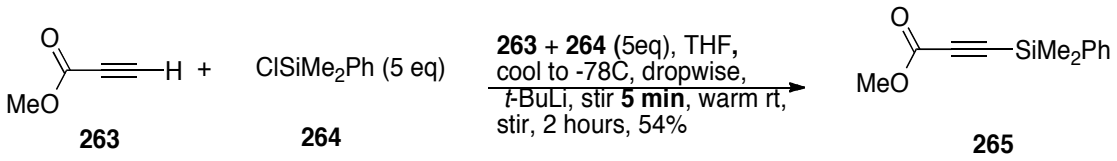
(3S,4R,6R,7R,8aR)-methyl 6-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxo-3,4-diphenylhexahydro-1H-pyrrolo[2,1-c][1,4]oxazine-7-carboxylate (260):

To a 10 mL flask with a stir bar was added $KF{\cdot}H_2O$ (10 mg, 0.110 mmol, 2.05 equiv.) and $KHCO_3$ (11 mg, 0.106 mmol, 2.08 equiv.) to a solution of **137** (30 mg, 0.051 mmol, 1 equiv.) in CH_3OH (500 μl) and THF (500 μl). The reaction was cooled to 0 °C and 70% peroxide in H_2O was added. The reaction was stirred for 9 h and filtered over celite and concentrated to afford the crude material. The reaction was purified by flash chromatography in 90:10 Hexane/EtOAc to afford compound **260** (14 mg, 58% yield). (ps2-17-400mhz)

^{1}H NMR ($CDCl_3$ 300MHz) : δ 7.07 – 6.80 (m, 5 H), 5.62 (t, J = 3.9, 3.9, 1H), 5.34 (d, J = 4.5, 1H), 4.46 (d, J = 4.5, 1H), 4.17 (ddd, J = 5.1, 5.1, 3.6, 1H), 3.90 (dd, J = 4.8, 6.3, 1H), 3.85 (dd, J = 3.6, 5.7, 1H), 3.77 – 3.73 (m, 4H) 2.98 (dd, J = 6.6, 6.6, 1H), 2.62 (ddd, J = 4.2, 6.3, 10.2, 1H), 2.27 (ddd, J = 3.3, 6.3, 9.9, 1H), 1.39 (s, 3H), 1.27 (s,3H).



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **260**



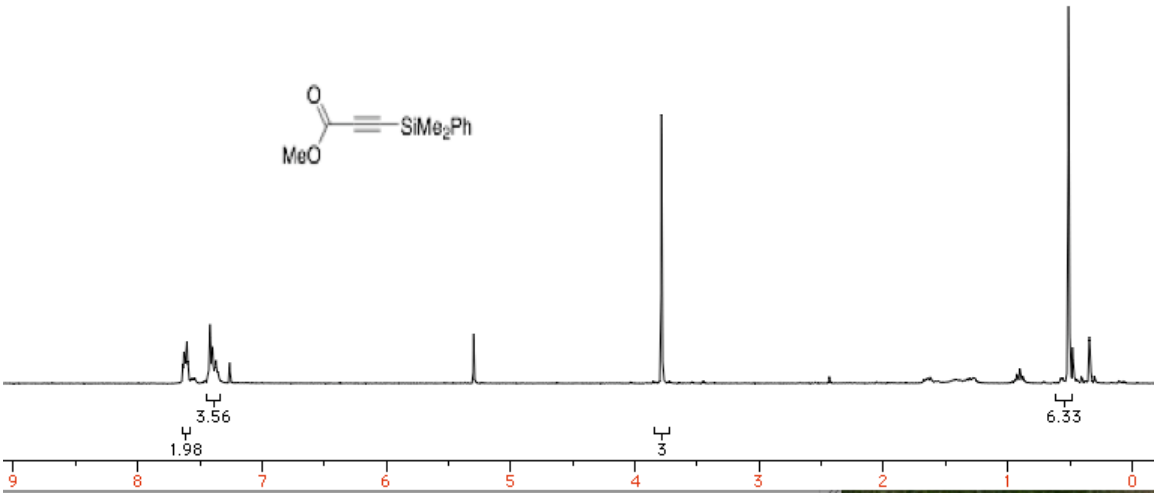
263 **264** **265**

methyl 3-(dimethyl(phenyl)silyl)propiolate (265):

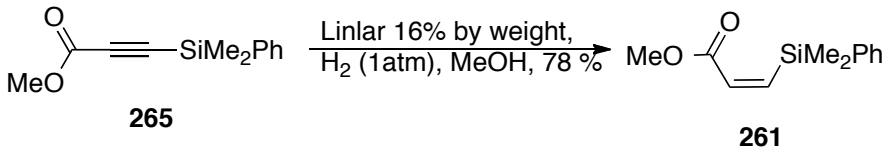
To a flame dried 10 mL rbf was added THF (1.75 mL), dimethylcholorphenylsilane **264** (401 mg, 3.96 mol, 5 equiv.), and methyl propiolate **263** (47 μL, 0.59 mmol, 1 equiv). The reaction was then cooled to -78 °C followed by a dropwise addition of *t*-BuLi (546 μL, 0.71 mmol, 1.2 equiv.) over a 15 minute period. Stirring continued for 5 minutes. The reaction was warmed to ambient temperature and stirring continued for another h. Saturated aqueous solution of NH_4Cl (1.5ml) was added and the aqueous layer was washed with EtOAc (2 x 5 ml). The organic layer was separated, dried and concentrated. was purified by flash chromatography to give the desired compound **265** (54 %) ps-390-3.

R_f=0.63 (90:10 Hexanes:EtOAc)

^{1}H NMR ($CDCl_3$, 300MHz) δ 7.63 – 7.37 (m, 5H), 3.78 (s, 3H), 0.50 (s, 6H).



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **265**



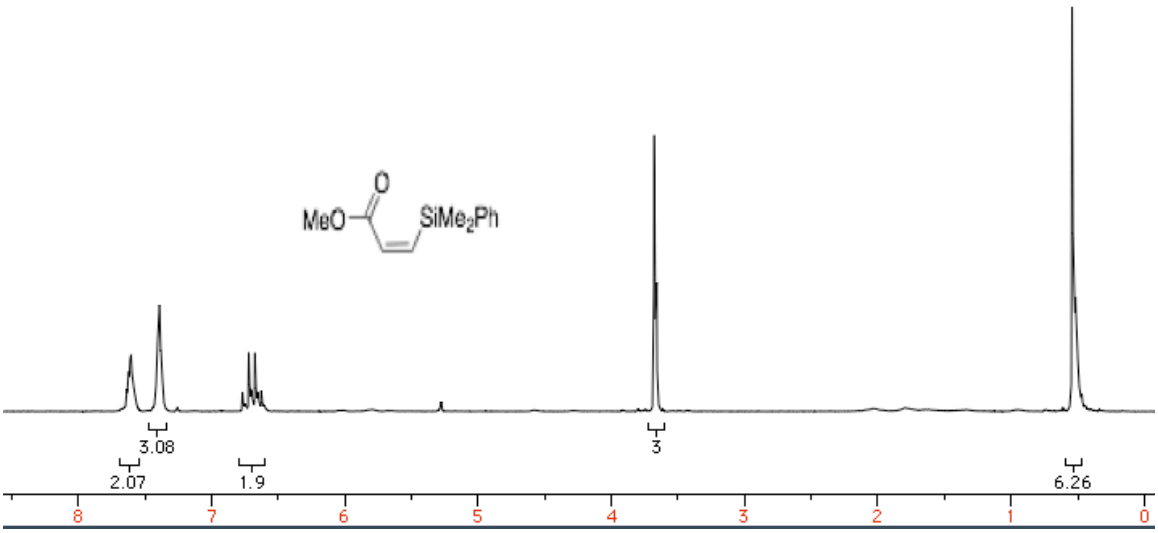
265 **261**

(*Z*)-methyl 3-(dimethyl(phenyl)silyl)acrylate (261):

To a flame dried rbf was added **265** (1.46 g, 0.00668 mol, 1 equiv.) in cyclohexane (30 mL). The reaction was purged with argon for 10 minutes followed by the addition of Lindlar's catalyst (204 mg, 14% by weight). The flask was purged with a balloon filled with H_2 (3x) and let stir for 7. The reaction was filter over celite to reveal the crude mixture that was purified by flash chromatography in 98.5:1.5 Hexane/EtOAc to give compound **261** (700 mg, 78 % yield) (ps-460-5)

R_f=0.61 (90:10 Hexanes:EtOAc)

^{1}H NMR ($CDCl_3$, 300MHz, ps-460-5) δ 7.63 – 7.35 (m, 5H), 6.75 (d, J = 14.4, 3H), 6.68 (d, J = 14.4, 1H), 3.67 (s, 3H), 0.54 (s, 3H).



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of compound **261**

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Appendix A X-ray Data for Compound 137.

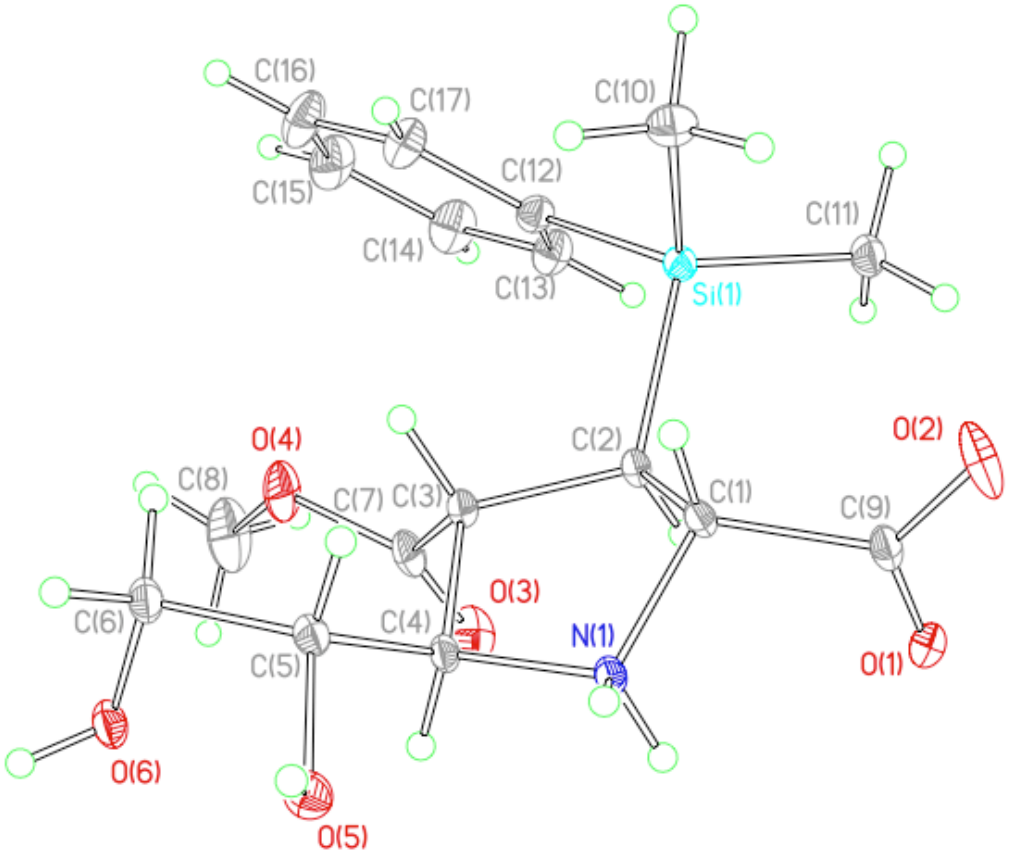

Table A.1. Crystal data and structure refinement for **137**.

Identification code	rw113	
Empirical formula	C17 H25 N O6 Si	
Formula weight	367.47	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.8891(3) Å	α= 90°.
	b = 6.1201(2) Å	β= 92.315(2)°.
	c = 15.7185(6) Å	γ = 90°.
Volume	950.54(6) $Å^3$	
Z	2	
Density (calculated)	1.284 Mg/m^3	
Absorption coefficient	0.155 mm^{-1}	
F(000)	392	
Crystal size	0.48 x 0.13 x 0.10 mm^3	
Theta range for data collection	2.39 to 33.83°.	
Index ranges	-15<=h<=15, -9<=k<=7, -24<=l<=24	
Reflections collected	27529	
Independent reflections	6440 [R(int) = 0.0328]	
Completeness to theta = 33.83°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9842 and 0.9295	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6440 / 1 / 231	
Goodness-of-fit on F^2	0.821	
Final R indices [I>2sigma(I)]	R1 = 0.0327, wR2 = 0.0965	
R indices (all data)	R1 = 0.0411, wR2 = 0.1055	
Absolute structure parameter	-0.03(8)	
Largest diff. peak and hole	0.408 and -0.206 e.$Å^{-3}$	

Table A.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for rw113. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4404(1)	7425(2)	1046(1)	12(1)
C(2)	4072(1)	8459(2)	1898(1)	12(1)
C(3)	2519(1)	8190(2)	1918(1)	12(1)
C(4)	2002(1)	8211(2)	969(1)	12(1)
C(5)	1101(1)	6274(2)	715(1)	14(1)
C(6)	-148(1)	6129(2)	1251(1)	16(1)
C(7)	1862(1)	10049(2)	2383(1)	17(1)
C(8)	188(2)	11004(4)	3330(1)	38(1)
C(9)	5770(1)	8223(2)	725(1)	15(1)
C(10)	5315(1)	4287(2)	2673(1)	21(1)
C(11)	6749(1)	8625(2)	2971(1)	18(1)
C(12)	4025(1)	7697(2)	3805(1)	16(1)
C(13)	4076(1)	9657(3)	4261(1)	21(1)
C(14)	3234(2)	10035(3)	4934(1)	28(1)
C(15)	2321(2)	8425(3)	5167(1)	30(1)
C(16)	2260(2)	6472(3)	4729(1)	31(1)
C(17)	3104(1)	6099(3)	4054(1)	23(1)
N(1)	3262(1)	8157(2)	460(1)	12(1)
O(1)	5887(1)	10225(2)	640(1)	24(1)
O(2)	6657(1)	6786(2)	613(1)	27(1)
O(3)	2118(1)	11955(2)	2283(1)	27(1)
O(4)	927(1)	9326(2)	2907(1)	25(1)
O(5)	733(1)	6612(2)	-157(1)	18(1)
O(6)	-912(1)	8101(2)	1187(1)	18(1)
Si(1)	5069(1)	7258(1)	2847(1)	13(1)

Table A.3. Bond lengths [Å] and angles [°] for rw113.

C(1)-N(1)	1.4974(14)
C(1)-C(2)	1.5293(15)
C(1)-C(9)	1.5401(15)
C(2)-C(3)	1.5462(14)

C(2)-Si(1)	1.9015(12)
C(3)-C(7)	1.5132(17)
C(3)-C(4)	1.5572(16)
C(4)-N(1)	1.5081(13)
C(4)-C(5)	1.5258(17)
C(5)-O(5)	1.4198(15)
C(5)-C(6)	1.5262(15)
C(6)-O(6)	1.4255(16)
C(7)-O(3)	1.2053(19)
C(7)-O(4)	1.3379(15)
C(8)-O(4)	1.439(2)
C(9)-O(1)	1.2385(18)
C(9)-O(2)	1.2591(16)
C(10)-Si(1)	1.8565(16)
C(11)-Si(1)	1.8631(12)
C(12)-C(13)	1.397(2)
C(12)-C(17)	1.4028(19)
C(12)-Si(1)	1.8793(12)
C(13)-C(14)	1.3927(19)
C(14)-C(15)	1.395(2)
C(15)-C(16)	1.379(3)
C(16)-C(17)	1.396(2)

N(1)-C(1)-C(2)	103.38(8)
N(1)-C(1)-C(9)	110.72(9)
C(2)-C(1)-C(9)	112.24(9)
C(1)-C(2)-C(3)	102.85(8)
C(1)-C(2)-Si(1)	113.81(8)
C(3)-C(2)-Si(1)	115.31(8)
C(7)-C(3)-C(2)	112.07(10)
C(7)-C(3)-C(4)	109.02(10)
C(2)-C(3)-C(4)	105.55(8)
N(1)-C(4)-C(5)	109.26(9)
N(1)-C(4)-C(3)	105.16(8)
C(5)-C(4)-C(3)	114.16(10)

O(5)-C(5)-C(4)	105.29(10)
O(5)-C(5)-C(6)	111.08(9)
C(4)-C(5)-C(6)	112.20(10)
O(6)-C(6)-C(5)	110.50(10)
O(3)-C(7)-O(4)	123.66(12)
O(3)-C(7)-C(3)	124.62(11)
O(4)-C(7)-C(3)	111.70(12)
O(1)-C(9)-O(2)	127.38(12)
O(1)-C(9)-C(1)	115.86(11)
O(2)-C(9)-C(1)	116.68(13)
C(13)-C(12)-C(17)	117.77(12)
C(13)-C(12)-Si(1)	121.61(10)
C(17)-C(12)-Si(1)	120.52(10)
C(14)-C(13)-C(12)	121.49(13)
C(13)-C(14)-C(15)	119.68(15)
C(16)-C(15)-C(14)	119.81(13)
C(15)-C(16)-C(17)	120.37(14)
C(16)-C(17)-C(12)	120.88(15)
C(1)-N(1)-C(4)	107.44(8)
C(7)-O(4)-C(8)	115.15(14)
C(10)-Si(1)-C(11)	109.51(6)
C(10)-Si(1)-C(12)	109.72(6)
C(11)-Si(1)-C(12)	111.59(6)
C(10)-Si(1)-C(2)	109.25(6)
C(11)-Si(1)-C(2)	109.93(6)
C(12)-Si(1)-C(2)	106.77(5)

Symmetry transformations used to generate equivalent atoms:

Table A.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for rw113. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	8(1)	16(1)	12(1)	-1(1)	0(1)	1(1)

C(2)	8(1)	15(1)	13(1)	-2(1)	1(1)	0(1)
C(3)	9(1)	15(1)	12(1)	-1(1)	1(1)	0(1)
C(4)	8(1)	15(1)	13(1)	0(1)	1(1)	0(1)
C(5)	11(1)	15(1)	16(1)	0(1)	-1(1)	-1(1)
C(6)	11(1)	17(1)	20(1)	0(1)	1(1)	-2(1)
C(7)	10(1)	25(1)	17(1)	-6(1)	2(1)	2(1)
C(8)	22(1)	52(1)	40(1)	-22(1)	16(1)	1(1)
C(9)	9(1)	27(1)	10(1)	-3(1)	0(1)	0(1)
C(10)	25(1)	17(1)	22(1)	2(1)	0(1)	2(1)
C(11)	13(1)	24(1)	18(1)	1(1)	0(1)	-2(1)
C(12)	17(1)	19(1)	12(1)	1(1)	0(1)	-2(1)
C(13)	23(1)	25(1)	16(1)	-2(1)	3(1)	-5(1)
C(14)	33(1)	33(1)	19(1)	-8(1)	6(1)	-4(1)
C(15)	31(1)	42(1)	19(1)	-2(1)	11(1)	-3(1)
C(16)	31(1)	38(1)	25(1)	4(1)	12(1)	-10(1)
C(17)	25(1)	24(1)	22(1)	0(1)	6(1)	-6(1)
N(1)	8(1)	15(1)	12(1)	0(1)	0(1)	0(1)
O(1)	15(1)	30(1)	28(1)	12(1)	4(1)	-2(1)
O(2)	9(1)	34(1)	40(1)	-19(1)	0(1)	2(1)
O(3)	23(1)	21(1)	36(1)	-8(1)	7(1)	3(1)
O(4)	16(1)	38(1)	24(1)	-9(1)	10(1)	-2(1)
O(5)	19(1)	20(1)	16(1)	-2(1)	-2(1)	-2(1)
O(6)	10(1)	22(1)	23(1)	0(1)	1(1)	0(1)
Si(1)	11(1)	15(1)	12(1)	1(1)	0(1)	-1(1)

Table A.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^{-3}) for rw113.

	x	y	z	U(eq)
H(1)	4405	5829	1095	14
H(2)	4276	10023	1870	14
H(3)	2295	6792	2182	14
H(4)	1510	9574	850	14

H(5)	1624	4919	777	17
H(6A)	-707	4911	1057	19
H(6B)	128	5869	1842	19
H(8A)	810	11933	3644	57
H(8B)	-424	10342	3713	57
H(8C)	-317	11856	2914	57
H(10A)	5886	4071	2200	32
H(10B)	4453	3607	2552	32
H(10C)	5732	3646	3175	32
H(11A)	7291	7888	3403	27
H(11B)	6625	10121	3134	27
H(11C)	7196	8570	2441	27
H(13)	4687	10733	4111	26
H(14)	3279	11355	5227	34
H(15)	1756	8668	5616	37
H(16)	1652	5398	4885	37
H(17)	3056	4773	3765	28
H(1A)	3153	7222	21	14
H(1B)	3434	9493	252	14
H(5A)	744	5440	-410	27
H(6)	-1692	7820	1026	28

Appendix B X-ray Data for Compound 221.

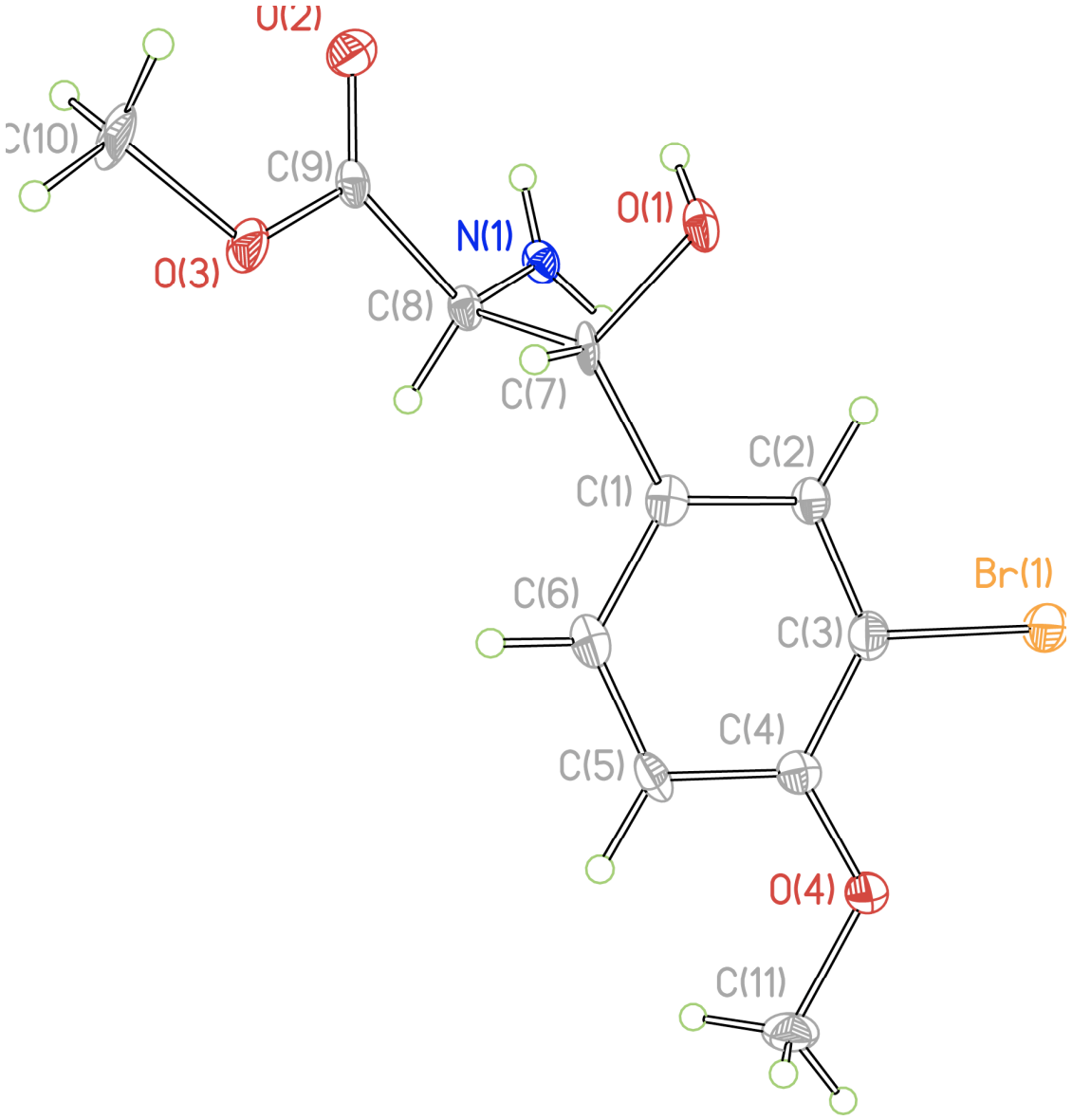

Table B.1. Crystal data and structure refinement for **221**.

Identification code	rw117	
Empirical formula	C11 H14 Br N O4	
Formula weight	304.14	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 4.60660(10) Å	α= 90°.
	b = 7.7265(2) Å	β= 90°.
	c = 34.1884(10) Å	γ = 90°.
Volume	1216.86(5) $Å^3$	
Z	4	
Density (calculated)	1.660 Mg/m^3	
Absorption coefficient	3.381 mm^{-1}	
F(000)	616	
Crystal size	0.098 x 0.166 x 0.176 mm^3	
Theta range for data collection	2.70 to 28.28°.	
Index ranges	-6<=h<=6, -10<=k<=10, -45<=l<=44	
Reflections collected	25423	
Independent reflections	2996 [R(int) = 0.0436]	
Completeness to theta = 28.28°	99.8 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2996 / 0 / 158	
Goodness-of-fit on F^2	1.246	
Final R indices [I>2sigma(I)]	R1 = 0.0545, wR2 = 0.1139	
R indices (all data)	R1 = 0.0601, wR2 = 0.1155	
Absolute structure parameter	0.94(2)	
Largest diff. peak and hole	0.841 and -1.452 $e.Å^{-3}$	

Table B.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for rw117. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x			
C(1)	2426(11)	7101(6)	8652(2)	18(1)
C(2)	3383(12)	5385(6)	8654(1)	16(1)
C(3)	5214(12)	4824(6)	8360(2)	22(1)
C(4)	6113(11)	5860(7)	8056(2)	18(1)
C(5)	5122(11)	7616(8)	8055(1)	21(1)
C(6)	3321(13)	8179(6)	8351(2)	22(1)
C(7)	552(11)	7828(5)	8978(2)	15(1)
C(8)	2371(11)	8941(6)	9261(2)	16(1)
C(9)	374(11)	10071(6)	9511(2)	16(1)
C(10)	-2479(13)	12623(9)	9495(2)	31(1)
C(11)	8867(15)	6283(9)	7476(2)	32(2)
N(1)	4162(9)	7827(5)	9499(1)	17(1)
O(1)	-777(8)	6452(5)	9185(1)	19(1)
O(2)	-125(9)	9858(5)	9849(1)	25(1)
O(3)	-662(10)	11368(5)	9294(1)	28(1)
O(4)	7852(10)	5170(5)	7779(1)	25(1)
Br(1)	6613(1)	2515(1)	8385(1)	28(1)

Table B.3. Bond lengths [Å] and angles [°] for rw117.

C(1)-C(6)	1.387(7)
C(1)-C(2)	1.397(7)
C(1)-C(7)	1.517(7)
C(2)-C(3)	1.382(8)
C(3)-C(4)	1.375(7)
C(3)-Br(1)	1.899(5)
C(4)-O(4)	1.352(6)
C(4)-C(5)	1.431(8)
C(5)-C(6)	1.380(7)

C(7)-O(1)	1.417(6)
C(7)-C(8)	1.543(7)
C(8)-N(1)	1.443(6)
C(8)-C(9)	1.528(7)
C(9)-O(2)	1.191(6)
C(9)-O(3)	1.336(6)
C(10)-O(3)	1.455(7)
C(11)-O(4)	1.426(7)

C(6)-C(1)-C(2)	118.7(5)
C(6)-C(1)-C(7)	119.5(4)
C(2)-C(1)-C(7)	121.8(4)
C(3)-C(2)-C(1)	119.1(5)
C(4)-C(3)-C(2)	123.4(5)
C(4)-C(3)-Br(1)	118.5(4)
C(2)-C(3)-Br(1)	118.0(4)
O(4)-C(4)-C(3)	118.7(5)
O(4)-C(4)-C(5)	124.0(5)
C(3)-C(4)-C(5)	117.3(5)
C(6)-C(5)-C(4)	119.2(5)
C(5)-C(6)-C(1)	122.3(5)
O(1)-C(7)-C(1)	109.6(4)
O(1)-C(7)-C(8)	109.8(4)
C(1)-C(7)-C(8)	111.0(4)
N(1)-C(8)-C(9)	111.8(4)
N(1)-C(8)-C(7)	109.4(4)
C(9)-C(8)-C(7)	110.0(4)
O(2)-C(9)-O(3)	125.1(5)
O(2)-C(9)-C(8)	125.4(5)
O(3)-C(9)-C(8)	109.5(4)
C(9)-O(3)-C(10)	116.2(4)
C(4)-O(4)-C(11)	117.9(5)

Symmetry transformations used to generate equivalent atoms:

Table B.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for rw117. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	10(2)	18(3)	24(2)	-2(2)	-3(2)	1(2)
C(2)	15(2)	14(2)	20(2)	1(2)	-2(2)	3(2)
C(3)	25(3)	17(2)	22(2)	-1(2)	-2(2)	-2(2)
C(4)	12(3)	22(2)	19(2)	-1(2)	-1(2)	-3(2)
C(5)	25(3)	13(2)	26(2)	5(2)	-1(2)	-6(3)
C(6)	22(3)	14(2)	28(3)	2(2)	-1(3)	-1(2)
C(7)	15(2)	4(2)	27(2)	0(2)	-3(2)	2(2)
C(8)	12(2)	11(2)	23(2)	0(2)	0(2)	0(2)
C(9)	12(2)	11(2)	23(2)	-1(2)	-3(2)	-2(2)
C(10)	37(3)	18(3)	39(3)	-7(3)	3(2)	19(3)
C(11)	36(4)	39(3)	20(3)	-1(2)	10(3)	-15(3)
N(1)	14(2)	13(2)	24(2)	3(2)	2(2)	3(2)
O(1)	11(2)	10(2)	37(2)	0(2)	5(2)	0(1)
O(2)	28(2)	25(2)	23(2)	-1(2)	4(2)	4(2)
O(3)	44(3)	16(2)	24(2)	2(2)	4(2)	14(2)
O(4)	34(3)	19(2)	23(2)	-1(2)	12(2)	-1(2)
Br(1)	38(1)	19(1)	28(1)	1(1)	7(1)	8(1)

Table B.5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^{\ 3}$) for rw117.

	x	y	z	U(eq)
H(2)	2796	4631	8851	20
H(5)	5685	8368	7856	25
H(6)	2686	9321	8349	26
H(7)	-968	8554	8862	18
H(8)	3639	9697	9107	19
H(10A)	-1435	13094	9714	47

H(10B)	-4213	12065	9587	47
H(10C)	-2989	13539	9318	47
H(11A)	9749	7290	7589	47
H(11B)	7264	6628	7314	47
H(11C)	10272	5680	7319	47
H(1A)	4017	7858	9750	20
H(1B)	5374	7131	9390	20
H(1)	-369	6526	9418	29