Enantioenriched Oxazolidinones as Synthesis Scaffolds and Efforts towards the Total Synthesis of Marineosin A

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The utility of enantioenriched oxazolidinones in the preparation of small chiral building blocks has been investigated. Hard nucleophile induced ring opening reactions of oxazolidinones provided a series of enantioenriched α-hydroxy carbonyl compounds. Soft nucleophile induced ring opening reactions of oxazolidinones have been attempted. Aldol reactions and Mannich reactions of oxazolidinones afforded the addition products with good results. Additionally, the aldol addition products were able to be converted to enantioenriched α,β-dihydroxy carbonyl compounds with a quaternary chirality center at the α position. In addition, chiral diol was also obtained through the reductive ring opening reaction of oxazolidinone.

The synthesis of marineosin A, a structurally unique natural product exhibiting acute cytotoxicity, has been under investigation in our laboratory. The previously unreported spiroaminal structure consisting of tetrahydropyrrole ring and dihydropyran ring has been synthesized through a radical cyclization in model study. The 12-membered macrocyclic pyrrole core synthesis has been accomplished by Stetter reaction in model study. It is worth noting that this is the first time that Stetter reaction was used in macrocyclization reaction. Both the diene fragment and the dienophile fragment have been prepared successfully towards the synthesis of the densely functionalized tetrahydropyran ring in marineosin A.

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LIST OF ABBREVIATIONS

AAC	Acyl halide-aldehyde cyclocondensation
BHT	Butylated hydroxytoluene
Bn	Benzyl
Boc	*t*-Butyloxycarbonyl
Cbz	Carboxybenzyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIBAL	Diisobutylaluminium hydride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
e.e.	Enantiomeric excess
FMO	Frontier molecular orbital

LDA	Lithium diisopropylamide
m-CPBA	*meta*-Chloroperoxybenzoic acid
MTBE	methyl *tert*-butyl ether
NaHMDS	Sodium bis(trimethylsilyl)amide
NMP	*N*-Methyl-2-pyrrolidone
Ns	(Nitrophenyl)sulfonyl
PCC	Pyridinium chlorochromate
PMP	*p*-Methoxyphenyl
RT	Ambient temperature
TBAF	Tetrabutylammonium floride
TBS	*t*-Butyldimethylsilyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-Tetramethylethylenediamine
TMG	Tetramethylguanidine
TMS	Trimethylsilyl
TMSQd	*O*-Trimethylsilylquinidine
TMSQn	*O*-Trimethylsilylquinine
Tris	2,4,6-triisopropylbenzenesulfonyl
Ts	*p*-Toluenesulfonyl
TTMPP	Tris(2,4,6-trimethoxyphenyl)phosphine

1.0 ENANTIOENRICHED OXAZOLIDINONES AS SYNTHESIS SCAFFOLDS

1.1 INTRODUCTION

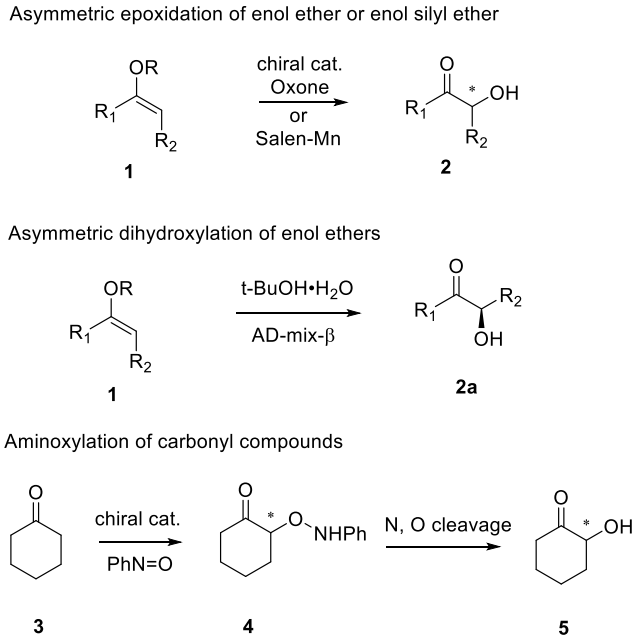
1.1.1 Introduction of chiral *α*-functionalized carbonyl compounds

Optically active *α*-functionalized carbonyl compounds, such as *α*-hydroxy acids and *α*-amino acids, are of great importance due to their application in "nearly all fields of organic chemistry".[1] For example, chiral *α*-functionalized carbonyl compounds are versatile building blocks and pivotal intermediates in organic synthesis. They also can be found in a number of natural compounds of biological importance. The significance of *α*-functionalized carbonyl compounds has led to an intensive effort in the development of new methodologies for the synthesis of these compounds by the application of asymmetric catalysis.[2] At present, it still remains a popular yet challenging research field.

1.1.1.1 Introduction of chiral α-hydroxyl carbonyl compounds The stereoselective synthesis of *α*-hydroxyl carbonyl compounds is of great importance in pharmaceutical industry due to the prevalence of the structural motif in many biologically active molecules. Compounds containing the unit are also useful synthons for the preparation of natural products such as antitumor agents, antibiotics, pheromones and sugars.[3] Consequently, numerous researchers have aimed for the

synthesis of enantiomerically pure α-hydroxyl carbonyl compounds employing a number of strategies. In particular, enantioselective oxidation of enolates received the most attention. The method can be divided into two categories: stoichiometric chiral reagent induced reactions and asymmetric catalytic reactions of prochiral enolates.[4] The latter, catalytic approach is more efficient and yet more challenging. Several general methods of this access have emerged during the past few decades including asymmetric epoxidation of enol ethers,[5] asymmetric dihydroxylation of enol ethers,[6] and aminoxylation of carbonyl compounds[7] (Scheme 1).

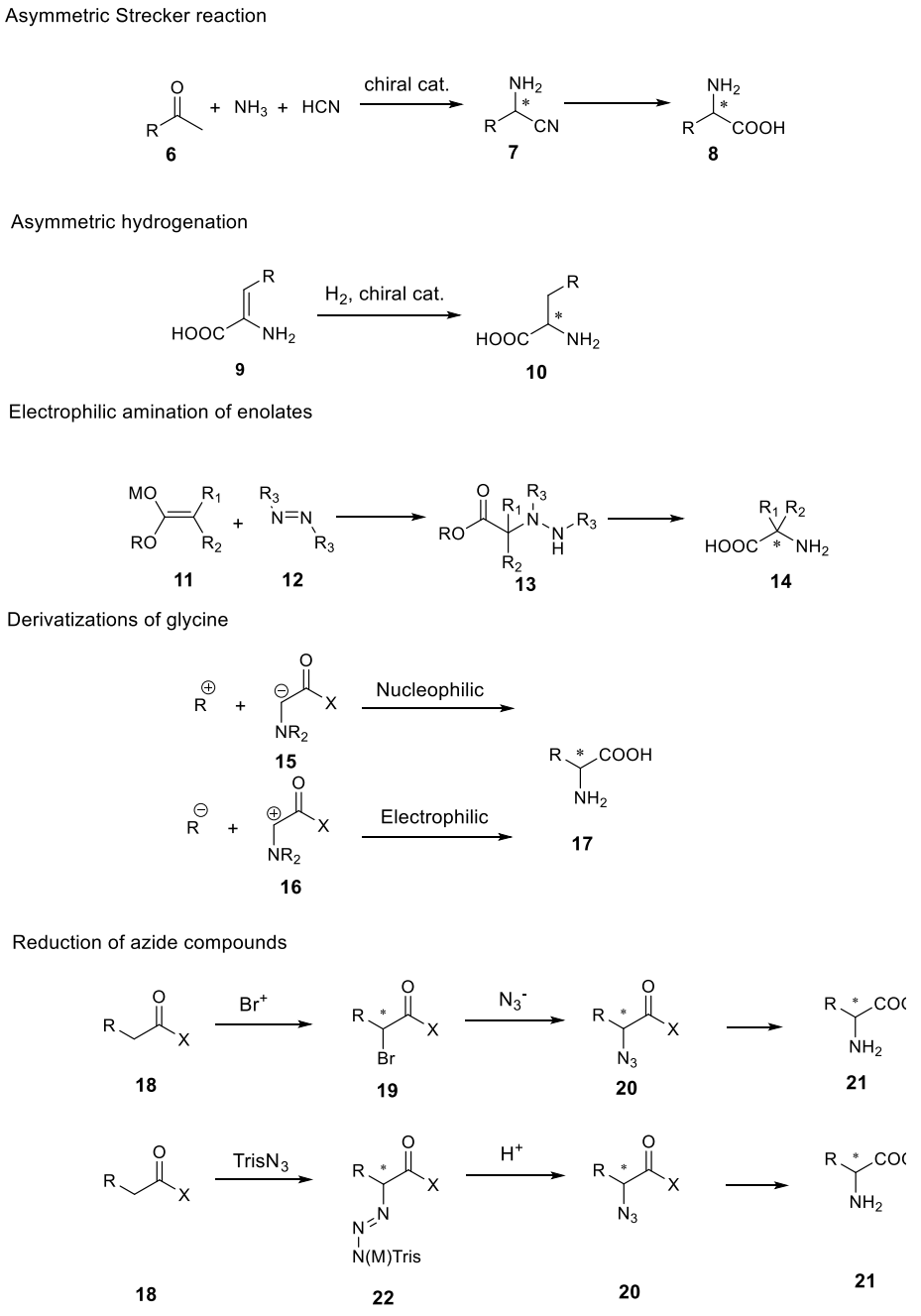
Scheme 1 General Methods of Preparation of α-Hydroxy Carbonyl Compounds



1.1.1.2 Introduction of chiral α-amino acids Chiral α-amino acids represent an important source of chiral α-amino carbonyl compounds. Such compounds exhibit diverse biological functions and can be modified into various chiral intermediates with broad applications in biology and pharmaceutical science.[8] Amino acids have many applications in the synthesis of enantioenriched heterocycles,[9] utility as chiral auxiliaries,[10] and as chiral catalysts in asymmetric transformations.[11]

The development of new reaction methodology to provide efficient routes to synthesize chiral α-amino acids has progressed rapidly over the last few decades and continues to be an active area of investigation.[8, 12] There are several main routes to obtain optically active α-amino acid including biotechnological methods, chemical synthesis using compounds from the chiral pool, resolution of a racemic mixture, and asymmetric synthesis. Among established methods, asymmetric synthesis is considered to be clearly advantageous over competing strategies. In the past decades, several general methods of chiral α-amino acids synthesis have been developed, such as the asymmetric Strecker reaction[13], asymmetric hydrogenation of dehydroamino acids[14], electrophilic amination of enolates[15], derivatizations of glycine,[8] and reduction of α-azido acids[16] (Scheme 2).

Scheme 2 General Methods of *α*-Amino Acids Synthesis



1.1.1.3 Introduction of α,β-dihydroxy carbonyl compounds A wide range of important compounds in organic chemistry contain *syn*-*α*,*β*-dihydroxy carbonyl functionalities with a quaternary chirality center at the *α*-position. The motif occurs in carbohydrates as well as many

natural products.[17] Meanwhile, the structure is thought as one kind of important synthon for the preparation of diol or glycerin frameworks in organic synthesis. For instance, the unique unit was found in TMC-95A **23**, a proteasome inhibitor[18] and fragenone A **24**[19] (Figure 1). In addition, the motif is a key intermediate in the synthesis of bioactive molecules, such as variabilin A **25,** an antibiotic from the marine sponge, *Ircinia variabilis*[20] and antifungal agent **27**[21] (Figure 2).

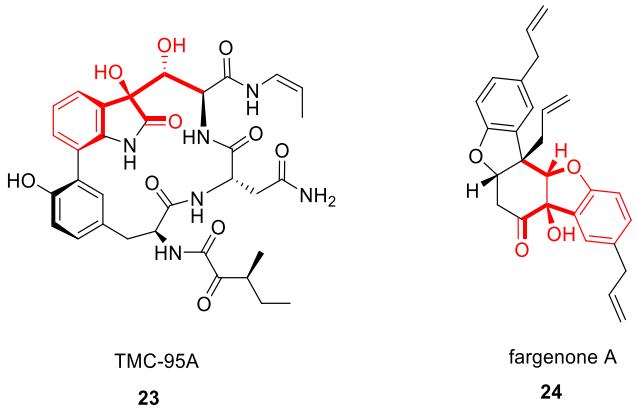


Figure 1 Selective Natural Product Containing *syn*-α,β-Dihydroxy Carbonyl Motif

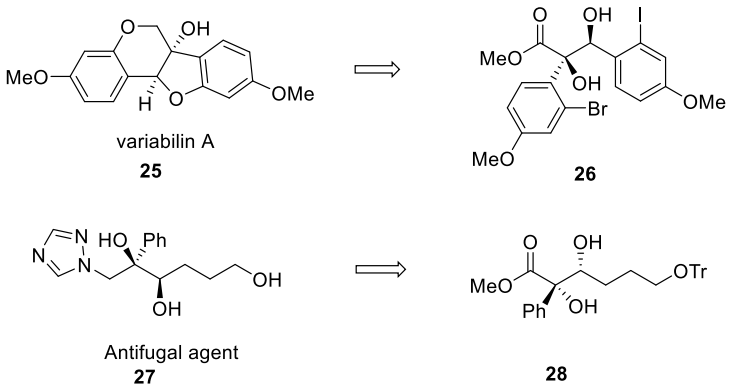
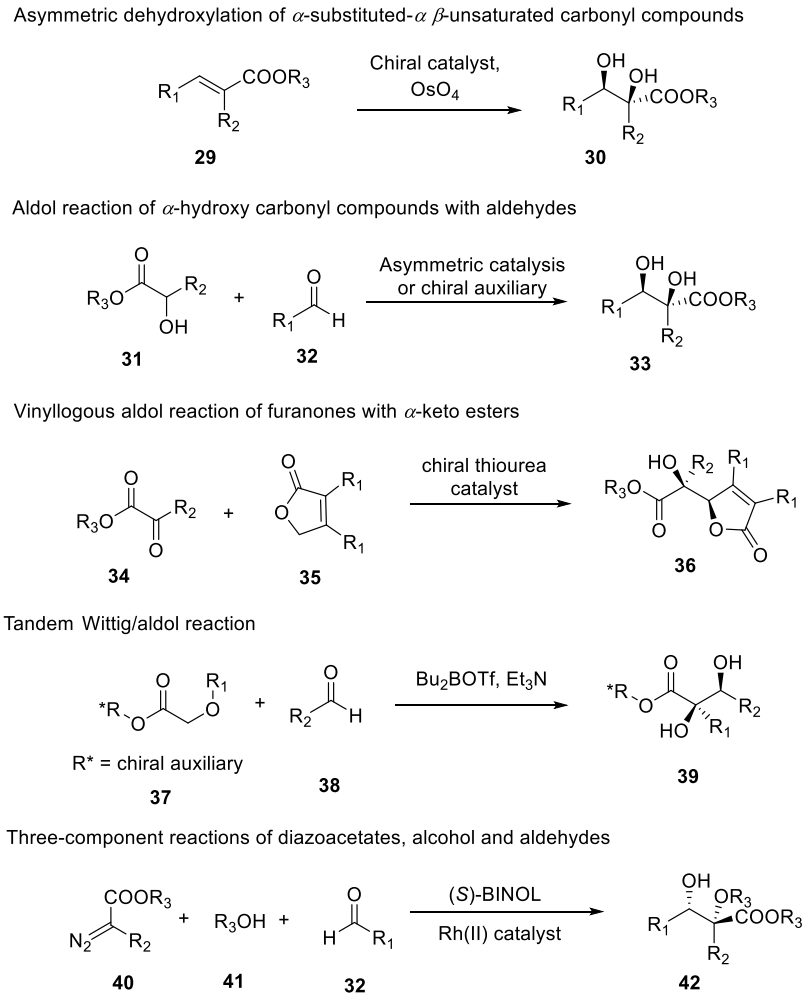


Figure 2 The Use of *syn*-α,β-Dihydroxy Carbonyl Compounds as Synthons in Total Synthesis

By reason of the great importance, there is a particular demand for the development of efficient methods for the stereoselective synthesis of various chiral *α,β*-dihydroxy carbonyl compounds with a quaternary chirality center at *α*-position. At present, several different methods have been reported. The methods include: asymmetric dihydroxylation of *α*-substituted-*α,β*-

unsaturated carbonyl compounds,[22] the asymmetric aldol reaction of α-hydroxy carbonyl compounds with aldehydes,[23] the asymmetric aldol reaction of furanones with α-keto esters,[21] the tandem Wittig/aldol reaction[24] and the three-component reaction of aryl diazoacetates, alcohol and aldehydes[25] (Scheme 3).

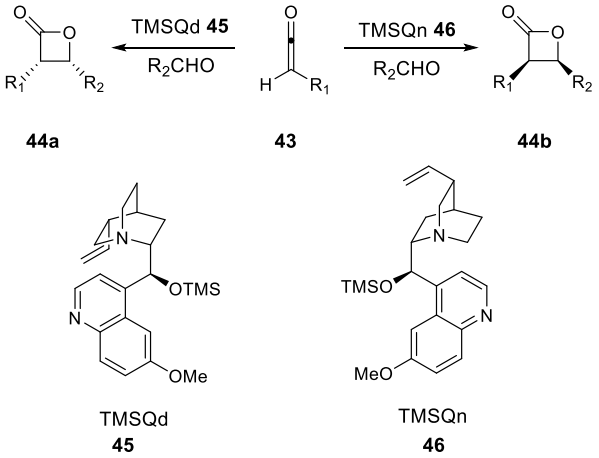
Scheme 3 General Methods for the Preparation of *syn*-α-β-Dihydroxy (2,3-dihydroxy) Carbonyl Functionalities with a-Quaternary Carbon



1.1.2 Previous work

One area of research in our group has focused on the rapid and economical preparation of optically active small molecule building blocks that relate directly to the complex stereochemical and structure motifs in natural products. Catalyzed enantioselective acyl halide-aldehyde cyclocondensation (AAC) reactions developed by our group provide convenient access to *β*-lactones with high enantioselectivities under both Lewis acid-catalyzed and Lewis base-catalyzed conditions (Scheme 4).[26] The versatility of the *β*-lactones derived from the AAC reaction is considerable. Enantioenriched lactones serve as templates for a diverse array of structures. When hard nucleophiles are used in the ring opening reaction of *β*-lactones, an addition-elimination reaction occurs at the carbonyl group, affording several kinds of chiral *β*-hydroxy compounds. For example, alkoxy anions provide *β*-hydroxy esters,[26] amines afford the *β*-hydroxy amides,[27] and enolates give *β*-hydroxy ketones.[28] Soft nucleophiles, such as azides or organocopper reagents, perform S_N2 reaction at the C-O bond to provide enantioenriched *β*-azido acids,[29] *β*-alkyl acids or conjugated allenic acids,[30] respectively (Figure 3).

Scheme 4 Previous AAC Reaction in Our Group



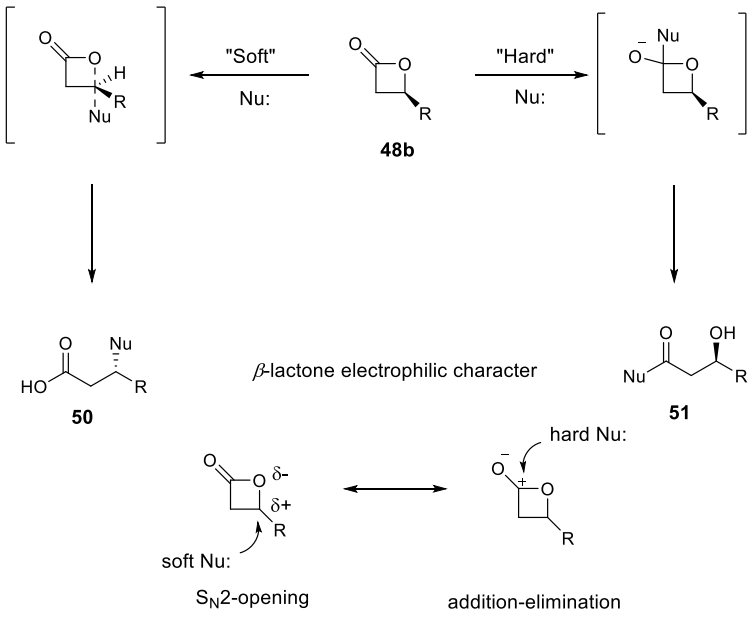
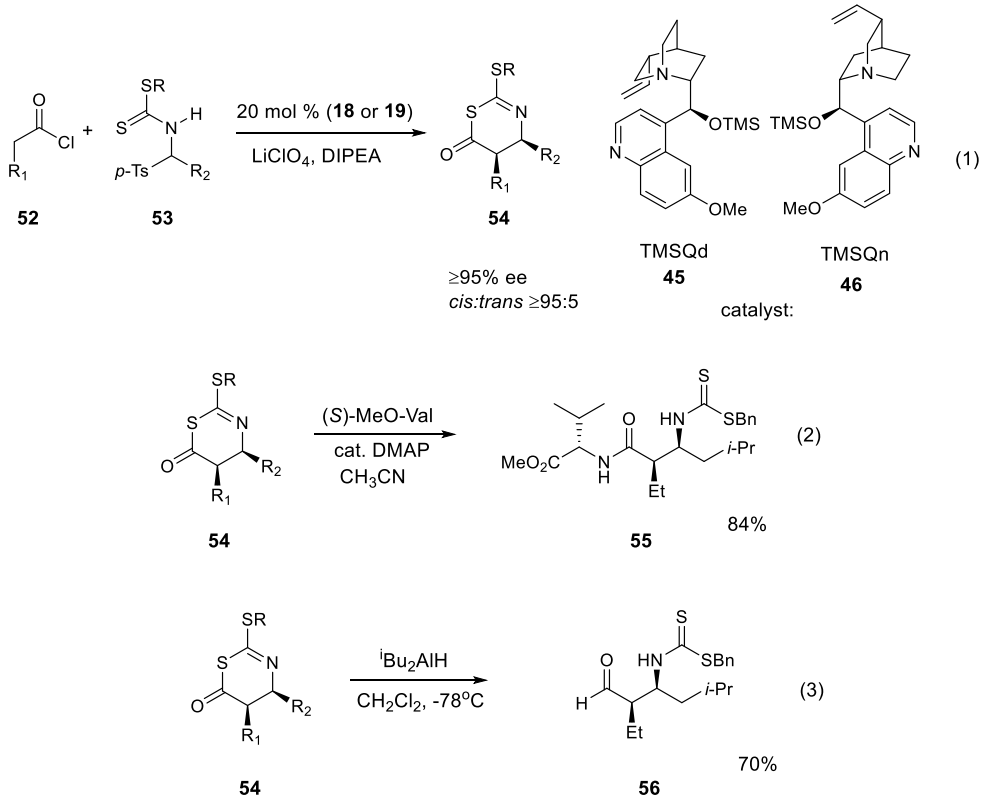


Figure 3 Ring opening of β-Lactone by Hard/soft Nucleophiles

Based on the success of the AAC reactions as surrogates for asymmetric catalyzed aldol reactions, our group endeavored to extend this reaction to other enantioselective cycloaddition reactions. In 2007, our group reported catalytic asymmetric [4+2] cyclocondensation reaction of ketenes and *N*-thioacyl imines, which afford the chiral 4,5-*cis*-disubstituted 1,3-thiazin-6-one derivatives **54** as an alternative to traditional Mannich reactions (Equation 1).[31] The utility of the enantioenriched [4+2] adducts was revealed through the ring opening process of thiazinone heterocycle **54**. Amine-mediated ring opening of thiazinone with valine methyl ester provided the *α,β*-dipeptide derivative **55** (Equation 2), while hydride-mediated thiazinone reduction led directly to the optically active *β*-amino aldehyde derivative **56** (Equation 3).



Encouraged by the success of previous cyclocondensation work, we investigated the cinchona alkaloid-catalyzed ketene-oxaziridine cyclocondensation as a surrogate for enolate-hydroxylation methodology (Equation 4). A series of chiral oxazolidinones with different substituents at the 5-position could be accessed with high yields and enantioselectivities. According to Evan's mechanistic study in the metal enolate-oxaziridine reaction,[32] we envision the reaction proceeding as outlined in Figure 4. First, chiral ketene enolate is generated by addition of cinchona alkaloids (TMSQn or TMSQd) to the *in situ* formed ketene, ensuring the facial selectivity towards electrophiles. Next, the oxaziridine undergoes nucleophilic attack by chiral ketene enolate and generates the intermediate. Cyclization onto the carbonyl gives enantioenriched oxazolidinone as well as the regenerated catalyst to finish the catalytic cycle.

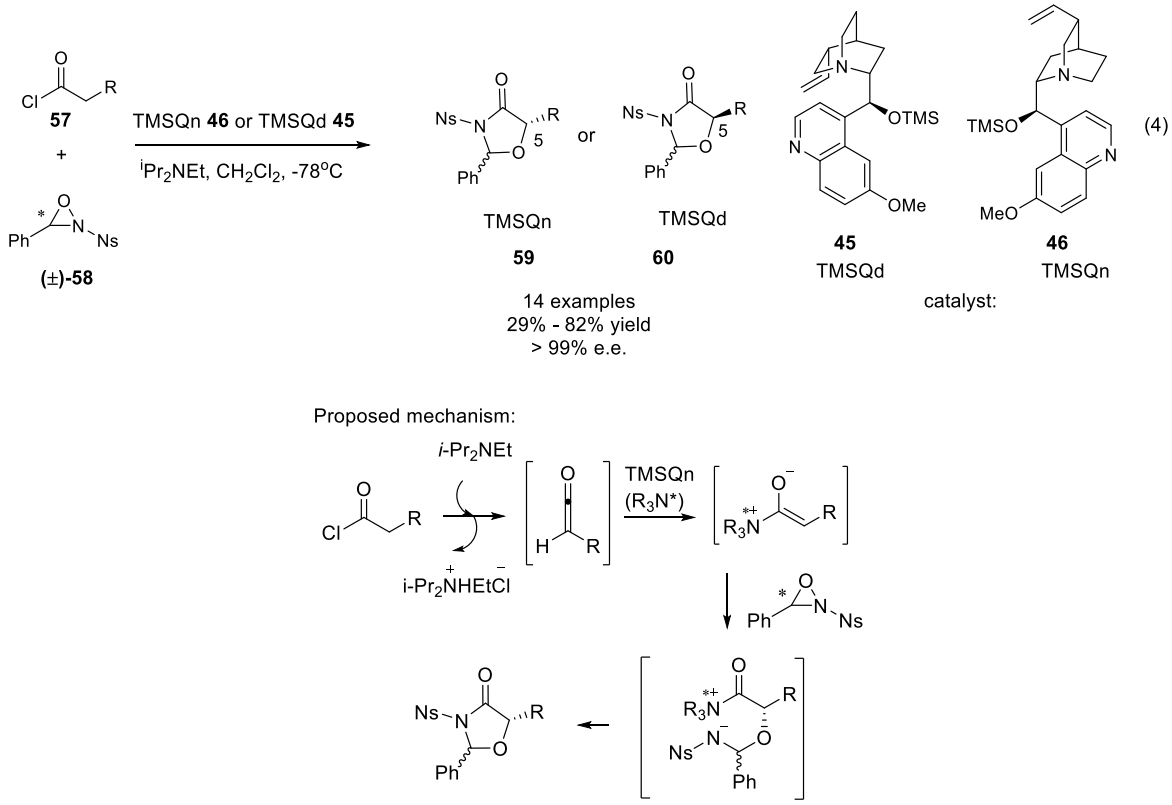


Figure 4 Proposed Mechanism of Acyl Chloride-Oxaziridine Cyclocondensations

1.1.3 Project design

Group precedent suggested that these enantioenriched oxazolidinones would be subject to chemoselective ring opening reaction either at the carbonyl group or the C-O bond, when using hard or soft nucleophiles respectively. In previous work, when hard nucleophiles were used with chiral *β*-lactones, such as sodium methoxide or morpholine, the nucleophile selectively attacked the carbonyl group through an addition-elimination pathway. While soft nucleophiles, such as azides, sulfonamide anions, or Gilman reagents were employed, the C-O bond was broken by direct S_N2 substitution (Figure 5).[26, 29, 33] We anticipated that enantioenriched oxazolidinones would exhibit similar reactivity patterns due to the ring strain associated with oxazolidinones

because of bond length compression of the C–N/C–O bonds. Furthermore, ring opening at C5 would liberate a highly stabilized anion very similarly to the intermediate derived from *β*-lactone opening. Therefore, by using hard nucleophiles in the ring opening process, we expected that the *α*-hydroxy carbonyl compounds would be obtained through the addition-elimination process. On the contrary, *α*-substituted acid or amide products would be anticipated from the direct S_N2 substitution pathway if soft nucleophiles were used in the ring opening reaction (Figure 6).

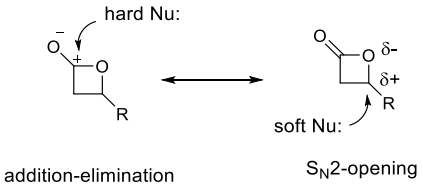


Figure 5 Nucleophile-dependent β-Lactone Ring Opening Pathways

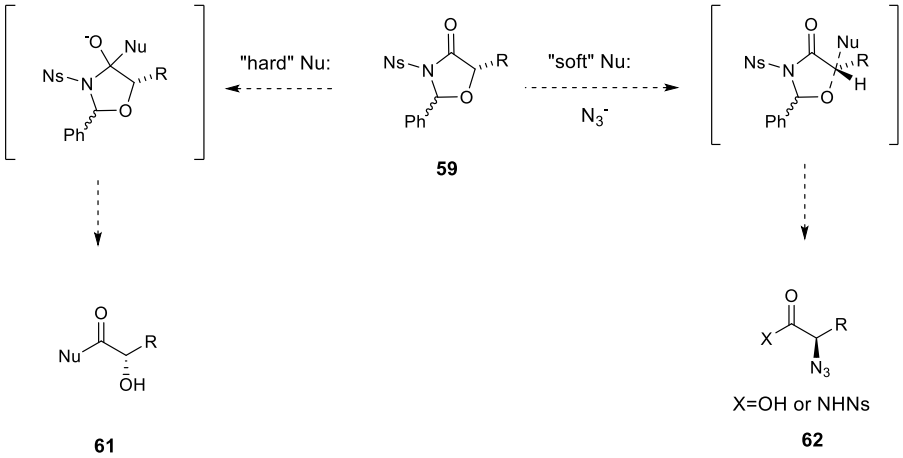
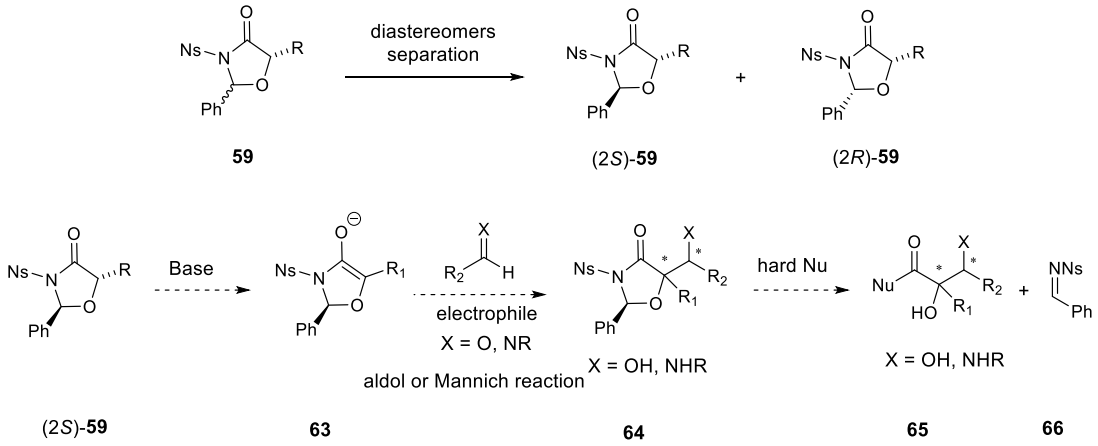


Figure 6 Proposed Reaction Route of Hard/soft Nucleophile Induced Ring Opening Reactions of Oxazolidinones

In addition to being an electrophile towards nucleophilic attack, the carbonyl moiety on oxazolidinone **59** may act as an enolate nucleophile in a series of transformations to construct useful structures. For instance, our oxazolidinones could be used as chiral nucleophiles to provide enantioenriched oxazolidinone derivatives through aldol or Mannich reactions. According to our

previous reaction design of hard nucleophile induced-ring opening reaction of our oxazolidinones, chiral *α,β*-dihydroxy carbonyl or *α*-hydroxy-*β*-amino carbonyl building blocks would be obtained after further hard nucleophile induced ring opening reaction of the aldol or Mannich addition products (Scheme 5).

Scheme 5 Proposed Preparation of *α,β*-Dihydroxy Carbonyl or *α*-Hydroxy-*β*-amino Carbonyl Compounds from Enantioenriched Oxazolidinones



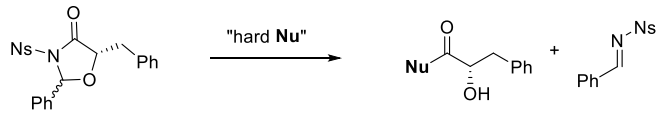
1.2 ENANTIOENRICHED OXAZOLIDINONES AS SYNTHESIS SCAFFOLDS

1.2.1 Hard nucleophile induced ring opening reactions of enantioenriched oxazolidinones

The first goal of the project was to develop a methodology for the preparation of enantioenriched *α*-hydroxy carbonyl compounds. In our research, the benzyl substituted enantioenriched oxazolidinones **67** provided an approach to various *α*-hydroxy carbonyl compounds through facile ring opening reactions by different hard nucleophiles. When catalytic sodium methoxide was used in methanol, the *α*-hydroxy ester **68** was obtained in 89% yield and 99% ee from the 1:1 diastereomeric mixture of oxazolidinone **67** (Table 1, entry 1). Ammonia in methanol provided the

α-hydroxy amide **69** in 94% yield (Table 1, entry 2). Since Weinreb amides provide access to functionalized ketones and aldehydes in organic synthesis, we also attempted using the *N*,*O*-dimethylhydroxyamine as the hard nucleophile in our reaction and *α*-hydroxy Weinreb amide **70** was obtained with satisfactory results (94% yield, 97% ee) (Table 1, entry 3). Reacting the oxazolidinone **67** with morpholine and catalytic amount of DMAP in THF afforded the *α*-hydroxy amide **71** in 85% yield and 97% ee. (Table 1, entry 4). Lithium hydroxide hydrolysis of oxazolidinone **67** resulted in *α*-hydroxy acid **72** in 79% yield and 98% ee. (Table 1, entry 5). In conclusion, we successfully developed a facile and efficient two-step method to obtain a collection of α-hydroxy carbonyl compounds with high yields and enantioselectivities.

Table 1 Hard Nucleophile Induced Ring Opening Reaction of Oxazolidinones



67 **68-72** **66**

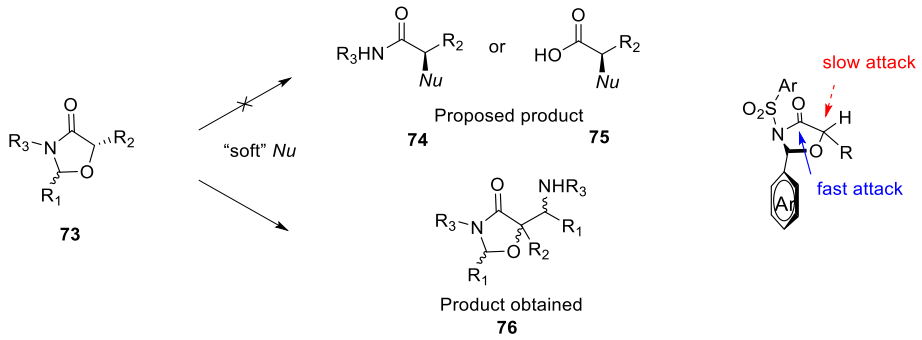
Entry	Conditions	**Nu**	Yield[a]	Ee[b]
1	MeONa, MeOH	MeO **68**	89%	99%
2	NH_4OH, MeOH	NH_2 **69**	94%	N.D.
3	Me_2AlCl, NHMe(OMe)•HCl, DCM	Me, N, OMe **70**	94%	97%
4	Morpholine, DMAP, THF	O, N **71**	85%	97%
5	LiOH, MeOH, THF, H_2O	OH **72**	79%	98%

[a] isolated yield [b] ee values was determined by HPLC or GC.

1.2.2 Soft nucleophile induced ring opening reaction of enantioenriched oxazolidinones

Soft nucleophiles, such as azide, proved especially successful in S_N2 ring opening reaction of β-lactones, are expected to offer the best chance for realizing analogous reactivity patterns in enantioenriched oxazolidinones to provide the α-azido carbonyl compounds as equivalents for α-amino acids. In this light, a multitude of reaction conditions and methods failed to facilitate breaking the C-O bond selectively through an S_N2 pathway. Attempted methods included using different types of soft nucleophiles, (e.g. sodium azide, sodium cyanide, sodium thiocyanate, potassium phthalimide, Gilman reagents etc.); using transition metal-azide complex nucleophiles instead of the high electron-density azide anion nucleophiles (such as $Ti(O\textit{i}\text{-}Pr)_2(N_3)_2$, $\textit{n}\text{-}Bu_3SnN_3$, $VO(O\textit{i}\text{-}Pr)(N_3)_2$, $Ti(\eta\text{-}C_5H_5)_2N_3Cl$, etc); activating azido-based soft nucleophiles (e.g. diphenylphosphoryl azid (DPPA)/4-dimethylaminopyridine (DMAP) system, tetramethylethylenediamine (TMEDA)/$TMSN_3$ system, tris(2,4,6-trimethoxypehnyl)phosphine (TTMPP)/$TMSN_3$ etc.); activating the aminal oxygen through protic acid or Lewis acid; and lastly, modifying the structure of oxazolidinones both electronically (increasing the electrophilicity of the C-O bond through inducing a strong electron withdrawing functional group on the 5-position) or sterically (increasing the steric hindrance of the substituent on the 2 position and the amide protecting group to shield the amide). However, under most of these reaction conditions, the nucleophiles attacked the carbonyl group instead of the C-O bond as a major reaction pathway, which meant the proposed S_N2 reaction route was exceedingly difficult to accomplish.

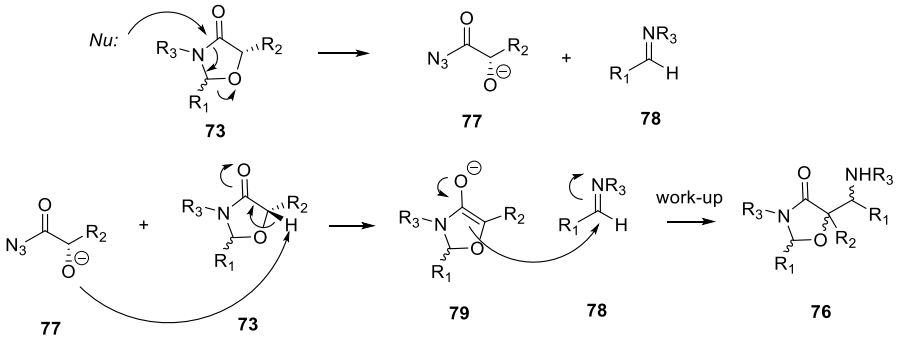
Scheme 6 Attempted Soft Nucleophile Induced Ring Opening Reaction of Oxazolidinones



Methods attempted:

1. Change soft nucleophiles
   e,g. NaCN, NaSCN, Potassium phthalimide, Gilman reagent etc.
2. Activate nucleophile
   e.g. DPPA/DMAP; $TMSN_3$/TMEDA; $TMSN_3$/TTMPP etc.
3. Lower the electron density of nucleophile
   e.g. $Ti(Oi\text{-}Pr)_2(N_3)_2$, $n\text{-}Bu_3SnN_3$, $VO(Oi\text{-}Pr)(N_3)_2$, $Ti(\eta\text{-}C_5H_5)_2N_3Cl$ etc.
4. Activate the oxygen by protic or Lewis acid
5. Increase the electrophilicity of C-O bond through changing R_2
   e.g. *para*-fluorophenyl, para-nitrophenyl
6. Block the carbonyl through increasing the sterics of R_1 and R_3

Reaction pathway and mechanism



1.2.3 Alkylation of chiral oxazolidinones

1.2.3.1 First attempts on the aldol reaction of oxazolidinones Our third goal was to develop a methodology for the synthesis of chiral *α*,*β*-dihydroxy carbonyl or *α*-hydroxy-*β*-amino carbonyl building blocks for complex natural product synthesis. In our previous attempts at soft nucleophile-induced ring opening reactions (Scheme 6), oxazolidinone deprotonation and subsequent enolate

functionalization emerged as a common reaction pathway for 5-aryl substituted substrates, giving precedent for this endeavor. Accordingly, we examined conditions for optimizing the transformations of fuctionalization of oxazolidinone eonlates (Scheme 7). First, the two diastereomers of our oxazolidinone prepared from our methodology were separated through column chromatography and following recrystallization, isolating only the *trans*, enantiomerically pure product **83** as starting material. This is because the chirality center at the 2-position of oxazolidinone **83** was envisioned to control the enantioselectivity of the enolate functionalization reaction while our methodology provided a pair of diastereoisomers at the 2-position. Benzaldehyde, a commonly used electrophile in the study of aldol reaction, was used as the electrophile in our aldol reaction of our oxazolidinone. During the initial attempts, treatment of oxazolidinone **83** with 1.1 equivalent lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78 ^{o}C followed by addition of benzaldehyde afforded the desired product **85** in only 18% isolated yield (Table 2, entry 1). Soft enolization conditions (Hünig's base, Bu_2BOTf) failed to provide any desired product probably because of the difficulty to form the boron enolates from the oxazolidinones due to the steric hindrance between substituents on 3, 5-position of oxazolidinone and boron moiety (Table 2, entry 2). Attempted enolate formation using Hünig's base and $TiCl_4$ gave the decomposition product likely owing to the incompatibility between the N, O-acetal and the strong Lewis acid (Table 2, entry 3). A detailed analysis of the product mixtures emerging from these reactions suggested that the retro-aldol reaction of our addition product may be the major factor for the poor yield under LDA conditions. Therefore, we planned further investigation into identifying whether the retro-aldol reaction of our addition product happen in our system.

Scheme 7 Proposed Reaction Pathway Using Oxazolidinones as Nucleophiles

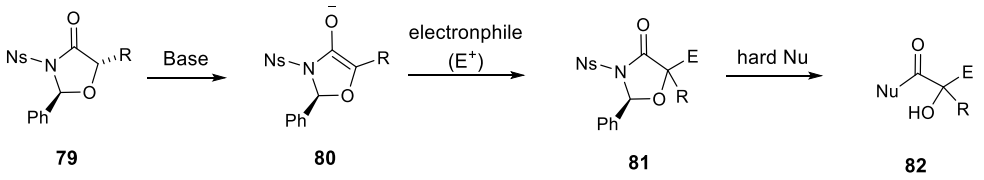
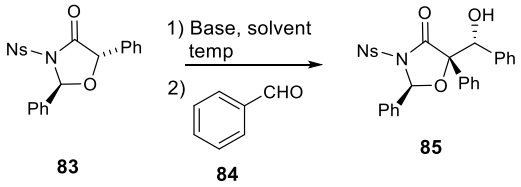


Table 2 First Attempts on the Aldol Reaction of Oxazolidinones



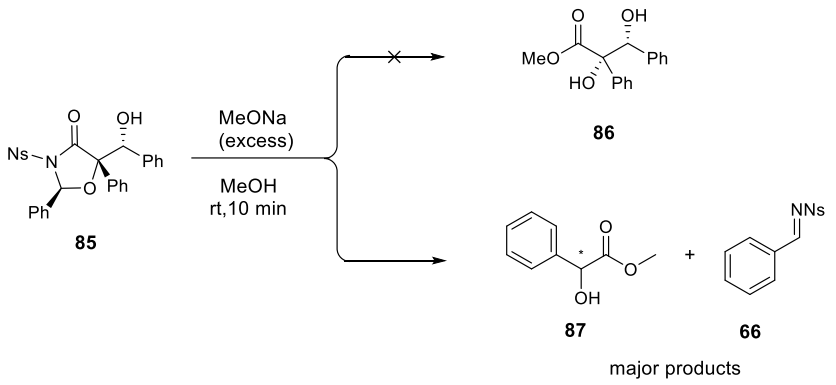
Entry	Condition	Solvent	Temp	Time	Yield[a]
1	LDA (1.1 equiv)	THF	-78 °C	1 h	18%
2	DIPEA, Bu_2BOTf	DCM	-78 °C	4 h	N.R.
3	DIPEA, $TiCl_4$	DCM	-78 °C	2 h	Decomposition

[a] combined yield of diastereoisomers

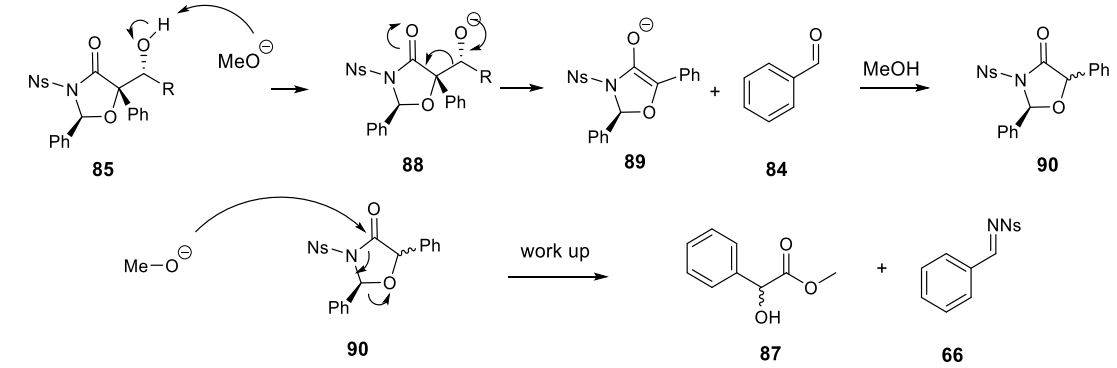
1.2.3.2 Retro-aldol study of addition products To test our assumption of the possible retro-aldol reaction, we planned to treat our aldol addition product **85** with excess sodium methoxide in methanol. The secondary alcohol was anticipated to be partially deprotonated by the excess sodium methoxide. If the retro-aldol reaction happened, the oxazolidinone **90** would be formed which would be further attacked by sodium methoxide to give α-hydroxy ester **87**. If there were no retro-aldol reaction, the sodium methoxide would directly attack the carbonyl and form the α,β-dihydroxy ester **86**. Thus, the various reaction products would allow us to deduce whether the retro-aldol reaction was playing a significant role in these reactions. In a model experiment of treating aldol addition product **85** with excess sodium methoxide, all starting material diminished

on TLC after 10 min. The major products were confirmed to be *α*-hydroxy ester **87** and imine **66,** indicating that the retro-aldol reaction happens easily in our system and almost certainly caused the low yield of the preceding reactions. A detailed mechanism based on the products obtained is proposed in scheme 8. The aldol addition product **85** was first partially deprotonated by the excess sodium methoxide to afford the anion **88**, which underwent the retro-aldol reaction and provided enolate **89** and benzaldehyde. The tautomerization of enolate **89** in methanol afforded oxazolidinone **90**. The oxazolidinone **90** was further attacked by sodium methoxide, which was proven in our previous hard nucleophile induced ring opening reaction of oxazolidinones, to afford α-hydroxy carbonyl compound **87**.

Scheme 8 Retroaldol Reaction Study



Proposed mechanism:



1.2.3.3 Reaction condition optimization The unexpected retro-aldol reaction necessitated finding another base instead of LDA in the aldol reaction of oxazolidinone with benzaldehyde because that the corresponding lithium aldolate was thought as the major reason for the retro-aldol reaction. The ideal base needed to possess sufficient basicity to deprotonate the α-position of carbonyl group while generating a conjugate acid that would protonate the aldolate alkoxide rapidly enough to prevent the retro-aldol reaction. Among common bases, DMAP attracted our attention due to observed epimerization of the 5-position of enantioenriched 2,5-diphenyloxazolidinone **83** in previous ring opening reactions attempts, indicating that DMAP can deprotonate our oxazolidinone and thus emerged as a potential alternative. Initial attempts using DMAP in THF at room temperature give product **85** in 78% yield after 96 h, although with poor selectivity (Table 3, entry 1). We attributed the low selectivity to the possibility of an open transition state of the aldol reaction due to the lack of chelating group for two-point binding to enolate and aldehyde.

With the aim of improving both efficiency and enantioselectivity, a metal-based Lewis acid was added with the anticipation of forming a closed transition state (Figure 7). Fortunately, lithium chloride improved both reaction activity and selectivity remarkably. This reaction finished in 24 h with 73% yield and the selectivity increased to 86:6:8 (major isomer : minor isomer : $\sum$ of other isomers) (Table 3, entry 2). Treatment with lithium hypochlorite and lithium bromide led to similar yields and selectivities (Table 3, entry 3 and 4). Lithium iodide, however, failed to yield desired aldol addition product under similar reaction conditions. Instead, lithium iodide led to the decomposition of oxazolidinone. (Table 3, entry 5). Application of lithium triflate afforded comparable yield and selectivity albeit with longer reaction times (Table 3, entry 6). Conversely. commonly used Lewis acid magnesium bromide ethyl etherate ($MgBr_2 \bullet OEt_2$) resulted in a significant decrease in both yield (29% yield) and selectivity (72:18:10) (Table 3, entry 7), which

may be caused by the moderate solubility of magnesium bromide ethyl etherate in THF. Cerium chloride only afforded trace product probably due to the bad solubility of $CeCl_3$ in THF (Table 3, entry 8). Trace product was obtained when using boron trifluoride ethyl etherate as Lewis acid. (Table 3, entry 9). No reaction took place with strong Lewis acid such as tin(IV) chloride and zinc bromide (Table 3, entry 10 and 11). This is most likely due to the formation of the unreactive adduct between DMAP and these strong Lewis acids as boron trifluoride ethyl etherate, tin (IV) chloride and zinc bromide. The yield improved to 85% by increasing the amount of Lewis catalyst to 3 equivalents however no increase in selectivity was observed (Table 3, entry 12).

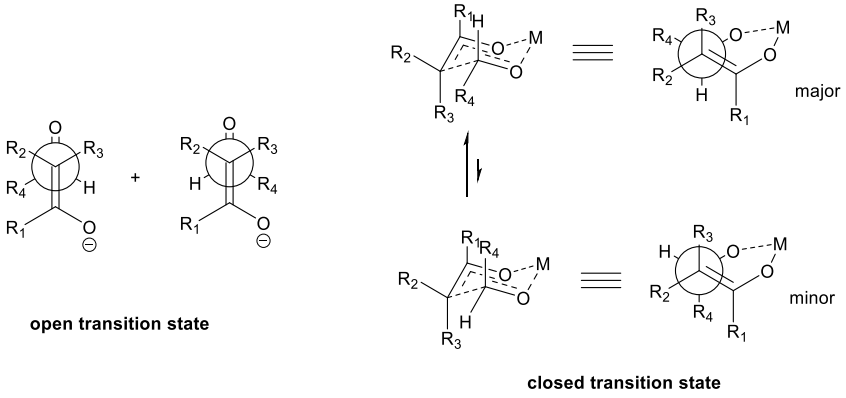
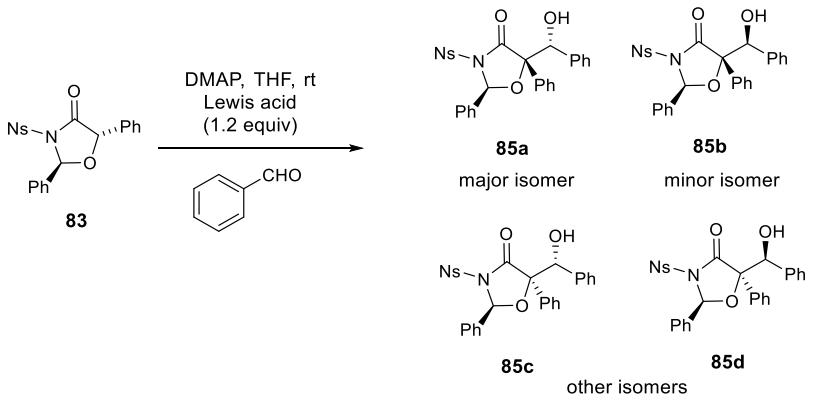


Figure 7 Open transition state vs. closed transition state of aldol reaction

Table 3 Screen of Lewis Acid



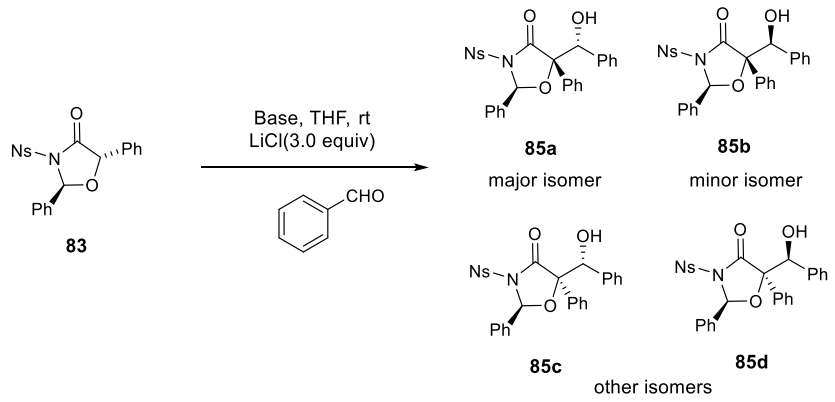
Entry	Lewis acid	Time	Yield[a]	A:B:other isomers[b]
1	None	96 h	78%	52:41:7
2	LiCl	24 h	73%	86:6:8
3	$LiClO_4$	24 h	65%	86:6:8
4	LiBr	24 h	67%	86:5:9
5	LiI	24 h	Decomposition	N.D.
6	LiOTf	48 h	75%	85:8:7
7	$MgBr_2•Et_2O$	96 h	29%	72:18:10
8	$CeCl_3$	96 h	Trace	N.D.
9	$BF_3•Et_2O$	96 h	Trace	N.D.
10	$SnCl_4$	48 h	N.R.	
11	$ZnBr_2$	48 h	N.R.	
12	LiCl (3.0 equiv)	24 h	85%	86:6:8

[a] combined yield of diastereoisomers [b] determined by ^1H NMR

Since the base played a decisive role in our aldol reaction, we next screened several commonly used organic bases in the aldol reaction of oxazolidinone **83** with benzaldehyde using

3.0 equivalent LiCl as Lewis acid in THF at room temperature to determine whether there were better alternatives to DMAP. *N*,*N*-diisopropylethylamine lowered the reaction efficiency and afforded only 23% yield of desired product **85** yet maintained selectivity comparable to the DMAP conditions (Table 4, entry 2). Treating oxazolidinone **83** with triethylamine led to similar results compared with DMAP, although a small decrease is observed in both yield (72%) and selectivity (83:5:12) (Table 4, entry 3). Both 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) and 1,1,3,3-tetramethylguanidine (TMG) resulted in a quick decomposition probably due to competing reactions stemming from their moderate nucleophilicity (Table 4, entry 4 and 5). No reaction happened when 2,6-lutidine was used in our reaction. This is probably because that the 2,6-lutidine is not basic enough to deprotonate oxazolidinones. (Table 4, entry 6). Compared with other bases for which the reaction usually took 24 h or more, 1,4-diazabicyclo[2,2,2]octane (DABCO) exhibited quite high activity and the reaction finished in 5 h. However, the yield dropped to 50% and the selectivity is somewhat inferior compared with DMAP (79:6:15) (Table 4, entry 7). Overall the experiments suggested that the suitable base for this reaction should have sufficient basicity to deprotonate the α-position of oxazolidinone while the conjugated acid of the base can be deprotonated by the aldolate alkoxide. Besides, the base should have poor nucleophilicity to avoid attacking on carbonyl and decreasing the yield. In all, DMAP was confirmed as the most suitable base in our system.

Table 4 Screen of Base



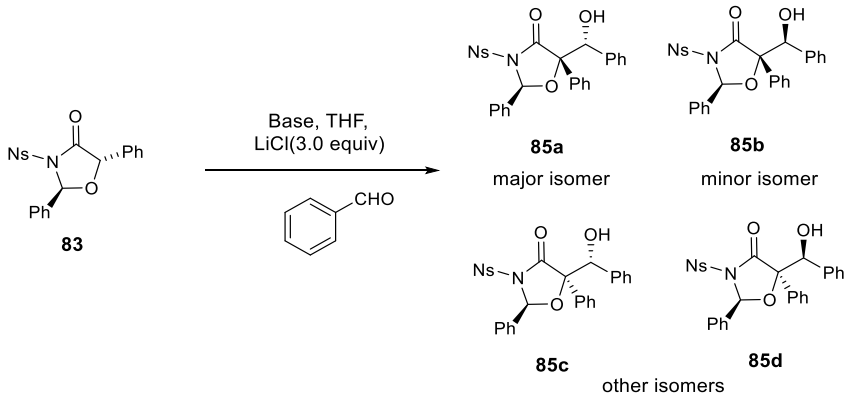
Entry	Base	Time	Yield[a]	A:B:other isomers[b]
1	DMAP	24 h	85%	86:6:8
2	DIPEA	96 h	23%	83:7:10
3	Et_3N	24 h	72%	83:5:12
4	DBU	1 h	Decomposition	N.D.
5	TMG	1 h	Decomposition	N.D.
6	2,6-lutidine	48 h	N.R.	
7	DABCO	5 h	50%	79:6:15

[a] combined yield of diastereoisomers [b] determined by ^1H NMR

The choice of solvent is often crucial for selectivity in asymmetric catalysis and solvent effects are rather unpredictable as they can perform multiple roles in a reaction (e.g. coordination, shuttles for reactive intermediates and hydrogen bond acceptor/donor)[34]. Therefore, a solvent screen will assist in determining optimum condition. Diethyl ether afforded 59% yield and 80:10:10 selectivity in 96 h and the low activity is probably due to the poor solubility of oxazolidinone **83** in diethyl ether (Table 5, entry 2). Use of DCM afforded poor yield (24%) and moderate selectivity (69:16:15) (Table 5, entry 3). Toluene led to good selectivity (82:11:7) but unsatisfactory yield (56%) (Table 5, entry 4). Replacing THF with 1,2-dimethoxyethane (DME)

or 1,4-dioxane led to a slight drop in both yield and selectivity (Table 5, entry 5 and 6). When methyl *tert*-butyl ether (MTBE) was used as solvent, the selectivity is good (83:12:5) though the reaction required longer time (48 h) and provided moderate yield (53%) (Table 5, entry 7). Consequently, THF was identified as the optimal solvent for the transformation. Increasing the temperature to 40 ^{o}C or 50 ^{o}C in THF gave no improvement in either the yield or the selectivity (Table 5, entry 8 and 9).

Table 5 Screen of Solvent and Temperature

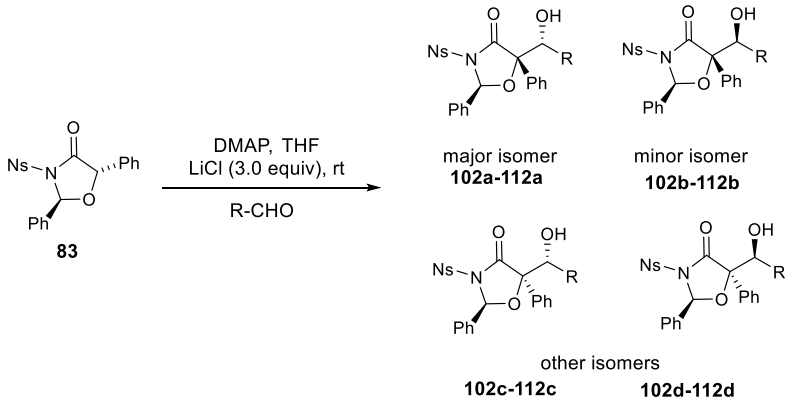


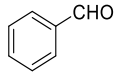
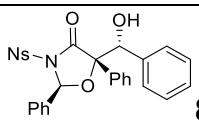
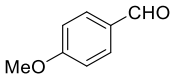
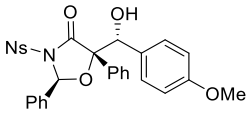
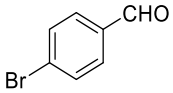
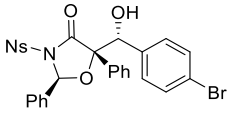
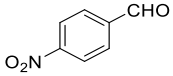
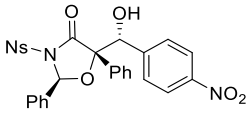
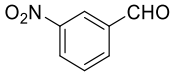
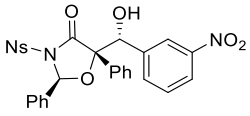
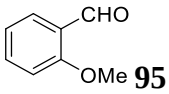
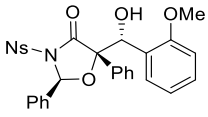
Entry	Solvent	Temp	Time	Yield[a]	A:B:other isomers[b]
1	THF	rt	24 h	85%	86:6:8
2	Et_2O	rt	96 h	59%	80:10:10
3	DCM	rt	96 h	24%	69:16:15
4	Toluene	rt	96 h	56%	82:11:7
5	DME	rt	24 h	72%	84:7:9
6	1,4-dioxane	rt	24 h	63%	80:14:6
7	MTBE	rt	48 h	53%	83:12:5
8	THF	40 ^{o}C	20 h	63%	84:8:8
9	THF	50 ^{o}C	20 h	38%	71:11:18

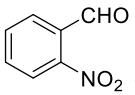
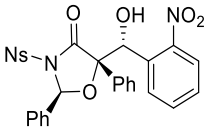
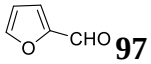
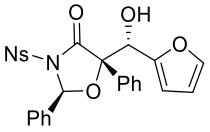
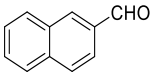
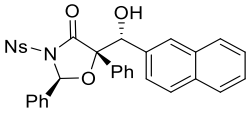
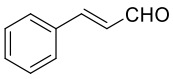
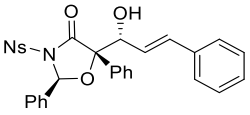
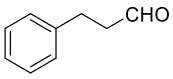
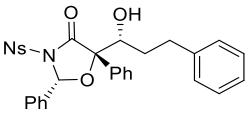
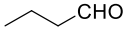
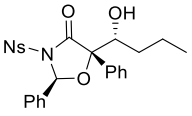
[a] combined yield of diastereoisomers [b] determined by ^{1}H NMR

1.2.3.4 Substrate scope The substrate scope of this reaction was explored and the results are summarized (Table 6). *para*-Methoxybenzaldehyde provided the aldol addition product **102** in 68% yield and 73:13:14 selectivity (Table 6, entry 2). When the electron donating ability of the substituent of benzaldehyde decreased, both the yield (71%) and the selectivity (85:7:8) increased (Table 6, entry 3). The benzaldehyde with the electron withdrawing nitro group at para position further improved the reaction activity (85%) and provided good enantioselectivity (84:5:11) (Table 6, entry 4). *meta*-Nitrobenzaldehyde afforded similar results (91% yield, 83:7:10 selectivity) compared with *para*-nitro substituted benzaldehyde (Table 6, entry 5). *ortho*-Methoxybenzaldehyde still afforded excellent selectivity (83:9:8) while the yield decreased to 64% (Table 6, entry 6). 2-Nitrobenzaldehyde gave good yield (78%) but the selectivity dropped (72:8:20) (Table 6, entry 7). Other aromatic aldehydes such as 2-furylaldehyde and 2-naphthaldehyde are also applicable in the reaction with good results. (90% yield, 85:8:7 selectivity and 71% yield, 78:8:14 selectivity respectively) (Table 6, entry 8-9). Aldol addition product **110** was obtained with good regioselectivity (1,2-addition, exclusively) and enantioselectivity (82:10:8) when cinnamaldehyde was used (Table 6, entry 10). In addition, the reaction is not only limited to aryl or alkenyl aldehyde but can also be applied to alkyl aldehyde such as hydrocinnamaldehyde and butyraldehyde though the selectivity significantly decreased (Table 6, entry 11-12).

Table 6 Substrate Scope



Entry	Aldehyde	Major Product	Time	Yield[a]	A:B:other isomers[b]
1	 **84**	 **85a**	24h	85%	86:6:8
2	 **91**	 **102a**	48h	68%	73:13:14
3	 **92**	 **103a**	30h	71%	85:7:8
4	 **93**	 **104a**	18h	85%	84:5:11
5	 **94**	 **105a**	18h	91%	83:7:10
6	 **95**	 **106a**	48h	64%	83:9:8

7	 **96**	 **107a**	24h	78%	72:8:20
8	 **97**	 **108a**	16h	90%	85:8:7
9	 **98**	 **109a**	48h	71%	78:8:14
10	 **99**	 **110a**	24h	65%	82:10:8
11	 **100**	 **111a**	48h	69%	48:31:21
12	 **101** (10 equiv)	 **112a**	24h	77%	51:34:15

[a] combined yield of diastereoisomers [b] determined by ^{1}H NMR

1.2.3.5 Identification of chirality The stereochemistry of the major diastereomeric product from our aldol reaction of enantioenriched oxazolidinones was unambiguously confirmed by X-ray crystallography. The major isomer **104a** was isolated from the mixture of isomers through column chromatography and the single crystal of **104a** was obtained through vapor diffusion using a dichloromethane and hexane system. Figure 8 clearly illustrates that the two oxygen atoms at the

α and β positions of the carbonyl adopt the *syn* configuration whereupon the absolute configuration of α-position of carbonyl is *S*-configuration while β-position of carbonyl is *R*-configuration.

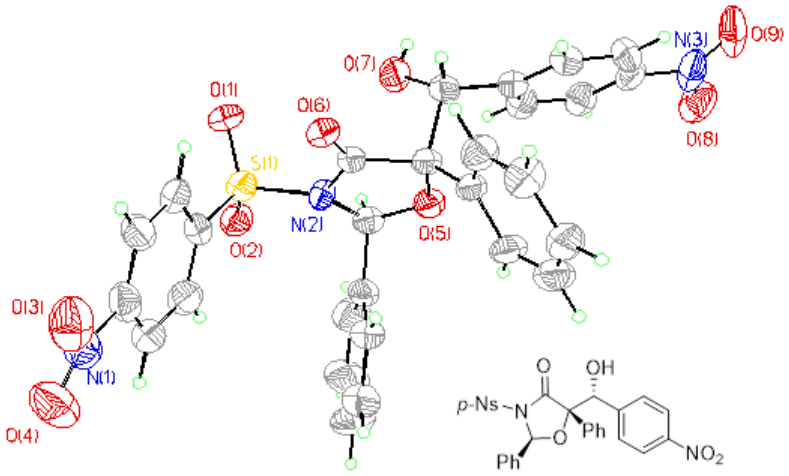
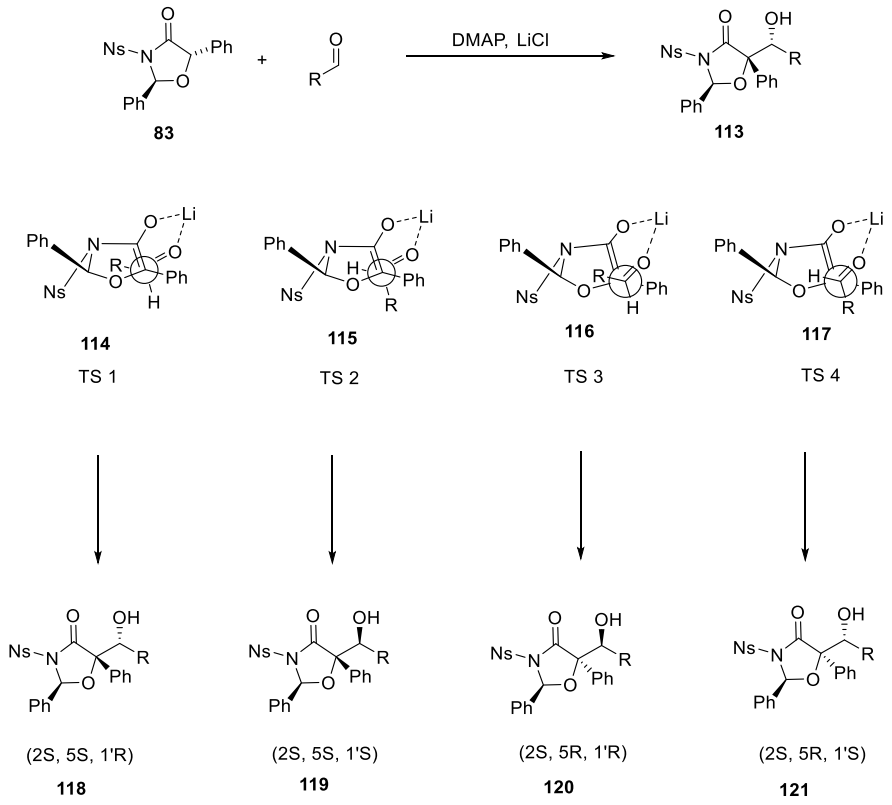


Figure 8 Structure and ORTEP Illustration of 104a with Thermal Ellipsoids Drawn at the 50% Probability Level (Hydrogen Atoms have been Omitted for Clarity)

A rationalization for the stereochemical outcome of the aldol reaction of enantioenriched oxazolidinones to aldehydes is detailed in Scheme 9. Among all the four possible transition states, transition states **TS1** and **TS2** are kinetically favored compared with **TS3** and **TS4** for reason that the aldehyde approaches the enolate through the less hindered *Si* face. In the first two transition states, **TS1** is more favored than **TS2** due to the steric interactions between the R on the aldehyde and the phenyl group at the C5 position in TS2.

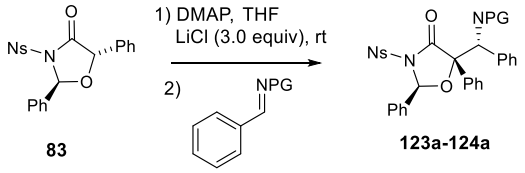
Scheme 9 Stereochemical Outcome of the Aldol Reaction of Oxazolidinones to Aldehydes Affording Diastereoisomeric Mixture of Products

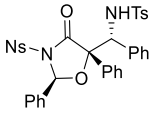
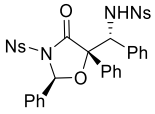


1.2.3.6 Attempts on Mannich reaction of oxazolidinones Based on the success of the aldol methodology, we pursued closely related Mannich additions as a potential route to α-hydroxy-β-amino carbonyl compounds. A reaction employing *N*-tosyl imine **122** with 3.0 equiv LiCl in THF at room temperature afforded the Mannich addition product **123** in 78% yield and 65:26:9 selectivity (Table 7, entry 1). *N*-Nosyl imine **66** gave similar results under the same reaction condition (82% yield, 65:22:13 selectivity) (Table 7, entry 2). Compared with aldol reactions, the decrease of the selectivity may be caused by the loose closed transition state due to the bulky group on the imine nitrogen. Limitations, however, were encountered in the Mannich reaction with *in situ* formed alkyl imines. This can be attributed to the quick imine-enamine tautomerization rate

compared with the Mannich reaction rate, which led to side reactions. In all, we successfully developed the Mannich reaction of our oxazolidinone with aromatic imines to afford α-hydroxy-β-amino carbonyl compounds with moderate outcome.

Table 7 Mannich Reaction of Oxazolidinones

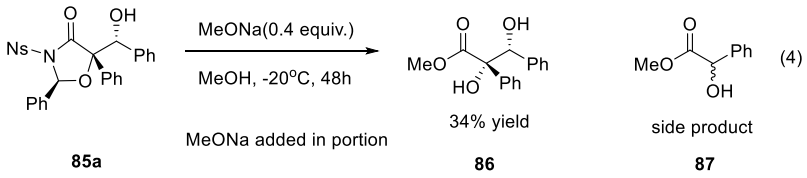


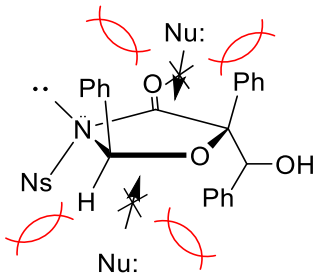
Entry	Imine	Product	Time	Yield[a]	A:B:other isomers[b]
1	 **122**	 **123a**	24h	78%	65:26:9
2	 **66**	 **124a**	18h	82%	65:22:13

[a] combined yield of diastereoisomers [b] determined by ^{1}H NMR

1.2.3.7 Ring Opening Reaction of Aldol Product Hard nucleophiles induced ring opening reactions of enantioenriched oxazolidinones have already been proved to be successful. Herein, we anticipated that enantioenriched aldol products should provide a direct route to the preparation of chiral *syn*-*α*,*β*-dihydroxy carbonyl compounds through the same hard nucleophile induced ring opening reaction. We planned to use a series of hard nucleophiles including sodium methoxide, ammonium hydroxide, Weinreb amide and morpholine in the ring opening reaction of **85a**, which gave excellent outcome in the hard nucleophile induced ring opening reaction of enantioenriched oxazolidinone **67**. Nonetheless, problems were encountered during the exploratory reactions. Among these hard nucleophiles induced ring opening reaction of **85a,** only the sodium methoxide

gave the desired ring opening product **86** and the best yield (34% yield) was obtained when 0.4 equivalent sodium methoxide in MeOH solution was added in 2 portions at -20 ^{o}C in MeOH over 48 hours. (Equation 4) The major byproduct was **87**, which was formed by retro-aldol reaction of **85a** followed by sodium methoxide induced ring opening reaction of the forming oxazolidinone. All other hard nucleophiles including ammonium hydroxide, morpholine, and dimethylhydroxylamine failed to provide the desired ring opening product. Instead, retro-aldol reactions of **85a** followed by ring opening reaction of the retro-aldol products were the major reaction pathway in these reactions. The failure of these hard nucleophiles in the ring opening reaction of **85a** can be attributed to two reasons. First, the basicity of some hard nucleophiles caused the retro-aldol reaction by deprotonating the hydroxyl group on **85a**. Second, the phenyl rings on the 2, 5-positions of oxazolidinone **85a** shielded the *Si*-face of the amide while the alkyl group on the 5-position and the nosyl group shielded the *Re*-face of the amide group, which made the nucleophile hard to approach the amide group (Figure 9).



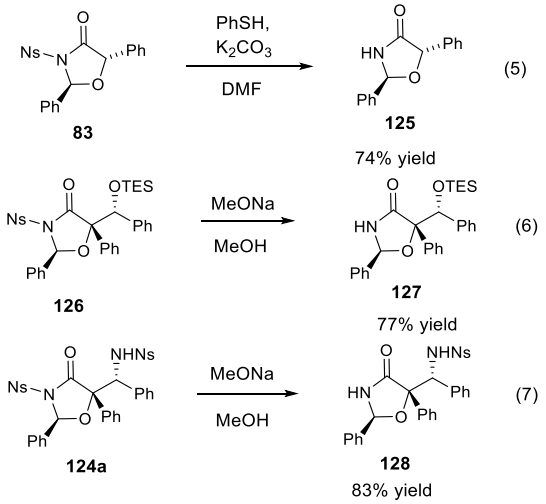


Nu is hard to approach carbonyl through either *Si* face or *Re* face

Figure 9 The Shielded Carbonyl of Oxazolidinone 85a

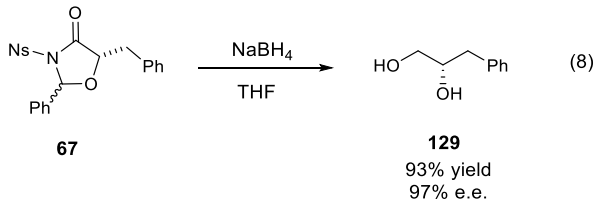
1.2.4 Other Derivations of Chiral Oxazolidinones

4-Oxazolidinone heterocycles have garnered considerable interest due to the existence of this structural motif in many natural products displaying promising antimicrobial activity.[35] Indeed, our methodology can access this important family of heterocycles by deprotecting the nitrogen functionality. According to the reported nosyl deprotection method[36], removing the nosyl protecting group of the oxazolidinone **83** was accomplished by using thiophenol and sodium carbonate in dimethylformamide at room temperature with 74% yield, which gave a forthright method to provide unprotected, optically active 4-oxazolidinones (Equation 5). In addition, for some oxazolidinone derivatives such as **126** and **124a,** in which the amide was shielded by the nosyl group and substituents on the 2 and 5 positions of oxazolidinones, simple sodium methoxide in methanol provided the unprotected oxazolidinone compounds with 77% and 83% yields respectively (Equation 6 and 7). In all, this methodology represents an efficient two-step method for accessing enantioenriched unprotected oxazolidinones.



Chiral 1,2-diols are found in a vast assortment of natural, biologically active molecules and thus the pursuit of new synthetic methods to prepare enantioenriched 1,2-diols remains an interesting topic. Generally, enantioenriched 1,2-diols are prepared by the following routes: ring

opening reactions of chiral epoxides,[37] asymmetric dihydroxylation of olefins,[38] hydrogenation of α-hydroxy carbonyls,[39] enzymatic reactions[40] and the reduction of α-keto-esters.[41] In consideration of the high activity of the carbonyl group in our oxazolidinone, we speculated that the compounds may serve as precursors to prepare chiral 1,2-diols as a useful synthon in organic synthesis through a reductive ring opening reaction. Sodium borohydride reduction of oxazolidinone **67** confirmed our assumption and afforded the 1,2-diol **129** with 93% yield and 97% ee (Equation 8)



67 **129**
93% yield
97% e.e.

(8)

1.3 CONCLUSION

In all, our group has successfully developed a new methodology for synthesizing chiral oxazolidinones through the cinchona-alkaloid catalyzed cyclocondensation reaction of acyl chlorides and oxaziridines with excellent yields and enantioselectivities, which afforded an access to a wide variety of useful structures and synthons. Reacting oxazolidinone **67** with hard nucleophiles effected addition-elimination to form a series of α-hydroxy carbonyl compounds. The proposed S_N2 substitution route was proven to be exceedingly difficult to accomplish. Aldol reaction and Mannich reaction of our oxazolidinones provided the addition product with good results. Additionally, the aldol addition products can be converted into enantioenriched α,β-dihydroxy carbonyl compounds with a quaternary chirality center at the α position as useful

synthons in natural product synthesis. The unprotected chiral oxazolidinones can be easily obtained by removing the nosyl protection group. Furthermore, chiral diol building blocks can also be obtained through the reductive ring opening reaction of our oxazolidinones.

2.0 EFFORTS TOWARDS THE TOTAL SYNTHEISI OF MARINEOSIN A

2.1 INTRODUCTION

2.1.1 Marineosin

Marine actinomycetes are among the most fertile sources of structurally unique secondary metabolites. Some of the known compounds have potent biological activities and broad applications in the field of pharmaceutical drug development.[42] Streptomyces, a diverse group of soil bacteria highly prolific in the production of microbially-derived antibiotics, belongs to the antinomycete family.[43] A family of compounds known as prodigiosins display various structural substitutions of a common pyrrolylpyrromethene core (Figure 10). Of particular interest, marineosins A **136** and B **137**, related to the prodigiosin class of polypyrrole bacterial pigments,[44] were isolated from a marine-derived streptomyces-related actinomycete collected by Fenical and coworkers in 2008 (Figure 11).[45] Due to previously unreported unique structure and acute structure-dependent cytotoxiticy, marineosins are attractive targets both in medicinal and synthetic chemistry.

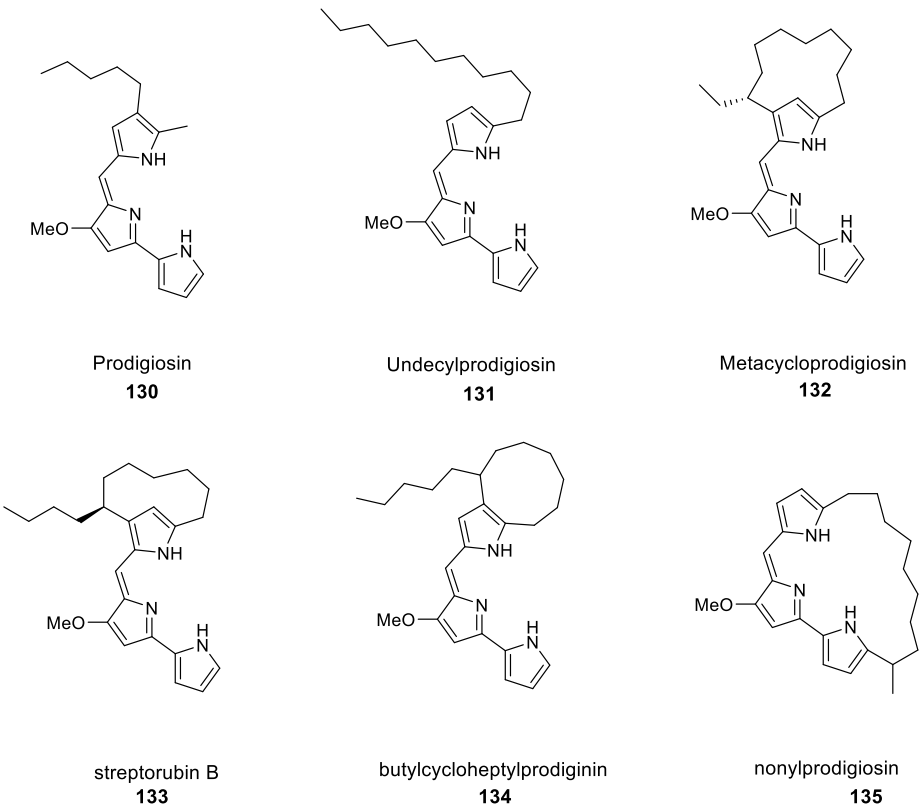


Figure 10 Representative Members of the Prodigiosin Family

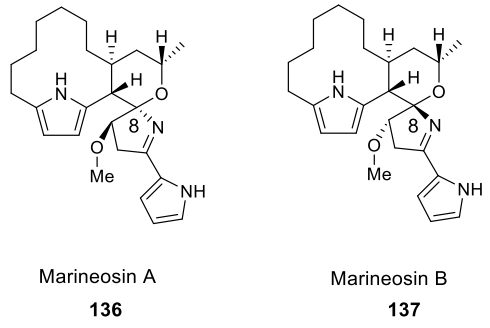


Figure 11 Marineosin A and Marineosin B

Marineosin A and B exhibit several unique structural features. Spiroaminals, also called oxa-aza spirobicyclic frameworks, spiroaminoketals or spiro-*N*,*O*-ketals, are substructures existing in many biologically active compounds.[46] The marineosins, which have a poly-pyrrole structure, possess 4-methoxy-2-pyrrolylazacyclopentene chromophores in addition to a previously

unknown spiroaminal constellation formed by adjacent tetrahydropyran and dihydropyrrole rings.[47] The two different configurations adopted by the spiro-tetrahydropyran-dihydropyrrole aminals in marineosin A and B can be rationalized through stability effects. A plausible explanation of why marineosin A is more favorable than marineosin B invokes the stabilizing anomeric effect available to marineosin A.[48]

Marineosin A displays human colon carcinoma HCT-116 inhibition with an IC_{50} of 0.5 μM. Testing in the NCI 60 cell line panel demonstrated considerable selectivity against melanoma and leukemia cell lines. Marineosin A and marineosin B possess opposite configurations at the C_7 and C_8 stereocenters and, as a result, marineosin B exhibits substantially decreased activity in all of the assays.[45]

2.1.2 Previous work on the total synthesis of marineosin A

2.1.2.1 Lindsley's synthesis In 2010 Lindsley reported the first synthetic efforts towards marineosin A **136** and marineosin B **137**, which were described by evaluation of the proposed biosynthesis (Figure 12).[49] The biosynthetic route proposed by the Fenical group was investigated, which featured an inverse-electron-demand hetero-Diels-Alder reaction as the key step to form the tetrahydropyran ring and the chiral spiroaminal structure in one single step. However, the proposed inverse-electron-demand hetero-Diels-Alder reaction from poly-pyrrole **139** could not be accomplished despite of various reaction conditions including thermal, microwave, photochemical,

Lewis acid catalysis and mineral acid catalysis. Herein, it was concluded that the proposed biosynthetic route was not viable under laboratory conditions.

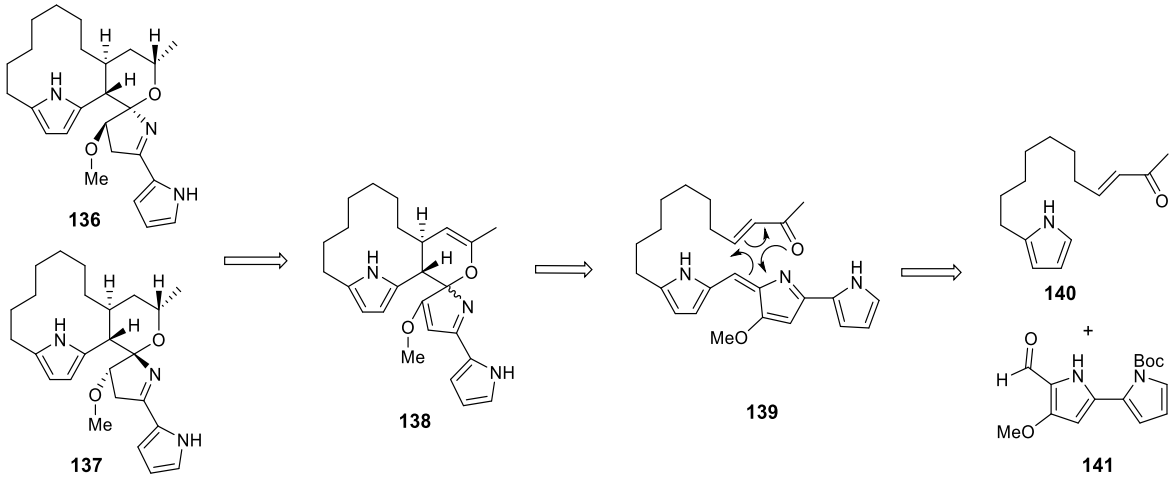
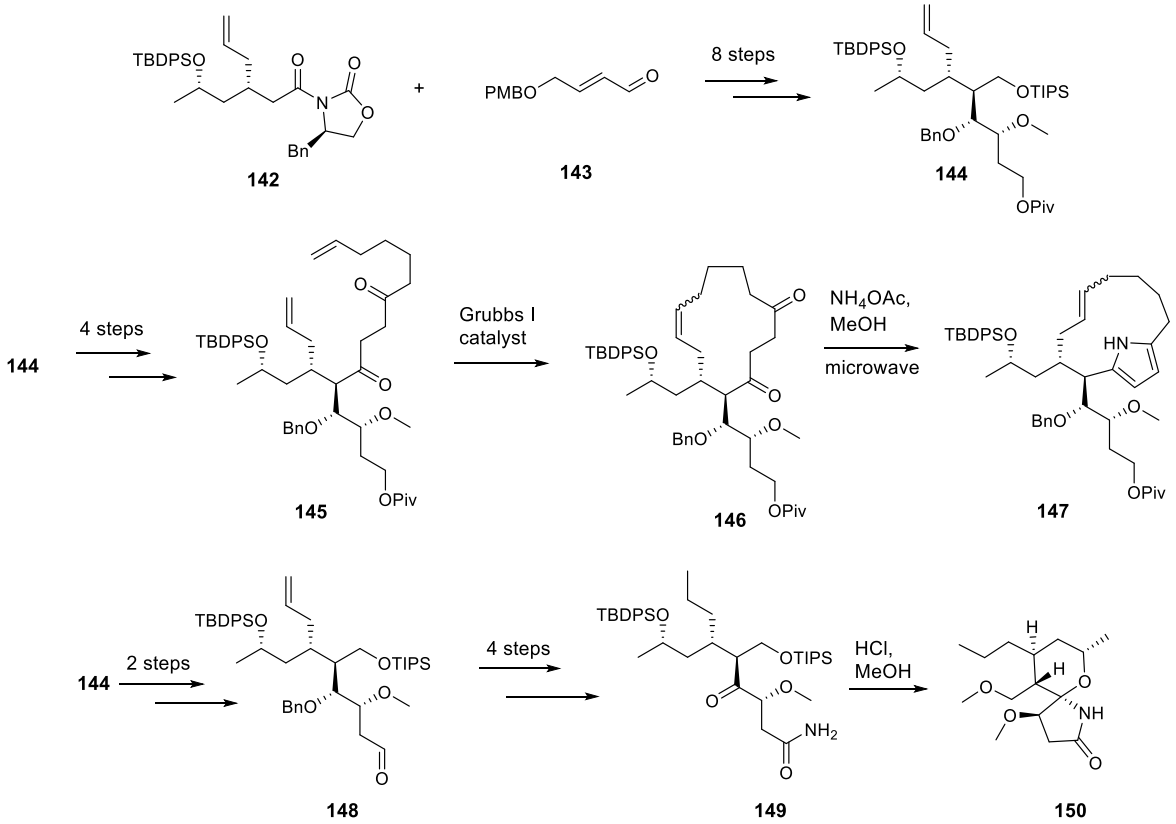


Figure 12 Retrosyntic Analysis of Marineosin A by the Lindsley Group

In 2013, the Lindsley group also described the enantioselective construction of the 12-membered macrocyclic pyrrole core **147** and spiroaminal structure **150** from the identical starting material **144**, originally prepared from chiral oxazolidinone **142** and aldehyde **143** after several steps (Scheme 10).[50] The alkene **145** was synthesized from **144** through a series of transformations. After a ring-closing metathesis reaction and Paal-Knorr pyrrole synthesis reaction, the desired macrocyclic pyrrole **147** was achieved from **145,** with an overall 5.1% yield from the beginning starting material in 20 steps. Furthermore, the chiral spiroaminal moiety **150** was assembled in 38% yield from the same structure **144** through an acid-mediated cyclization strategy after a series of transformations.

Scheme 10 Lindsley's Synthesis of Macrocyclic Pyrrole and Functionalized Spiroaminal Model



Meanwhile, the Lindsley group illustrated another enantioselective route to the spiroaminal structure in 9% overall yield (Figure 13).[51] Grignard addition of **155** to chiral pyrrolidin-2,5-dione **154** followed by the treatment with *p*-toluenesulfonic acid generated the iminium salt **157**, which was further attacked by the hydroxy group leading to the construction of spiroaminal **153**. Removal of the 4-methoxybenzyl (PMB) protecting group using ceric ammonium nitrate resulted in the desired spiroaminal structure **151**.

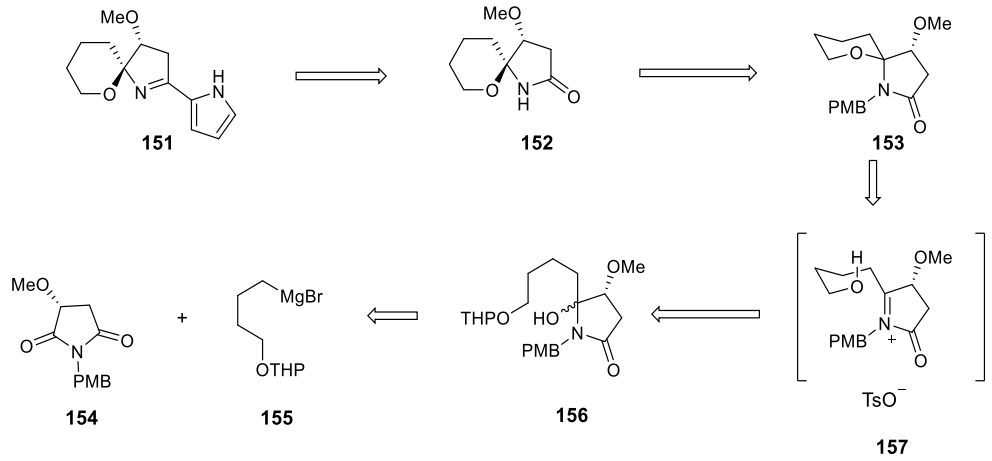


Figure 13 Lindsley's Synthesis of Spiroaminal Moiety

2.1.2.2 Snider's synthesis Since the spiroaminal moiety of the marineosins consisting of tetrahydropyran and dihydropyrrole rings appeared to be unprecedented, Snider's work focused on the synthetic route of the spiroaminal substructure **158** (Figure 14).[47] The model enone **162**, lacking the macrocyclic ring, was used as the starting material for the synthesis of the spiroaminal moiety. The alcohol protection and *N*-oxide cycloaddition afforded isoxazolinyl ketone **161**, which underwent hydrogenolysis to afford the hemi-iminal **160**. Methylation of **160** gave methyl ether iminal **159**. Treatment of **159** with aqueous hydrochloric acid hydrolyzed the protecting group and effected the loss of methanol to give the desired spiroaminal **158** as a mixture of diastereoisomers.

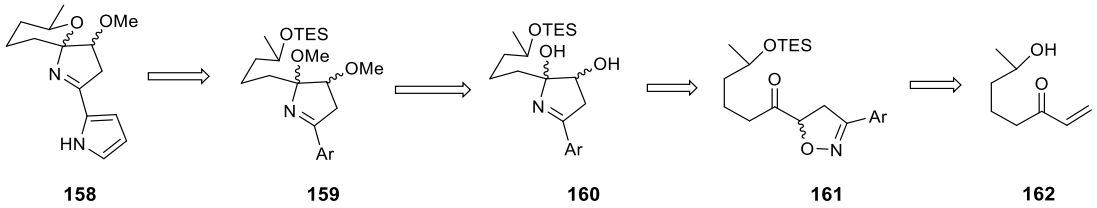
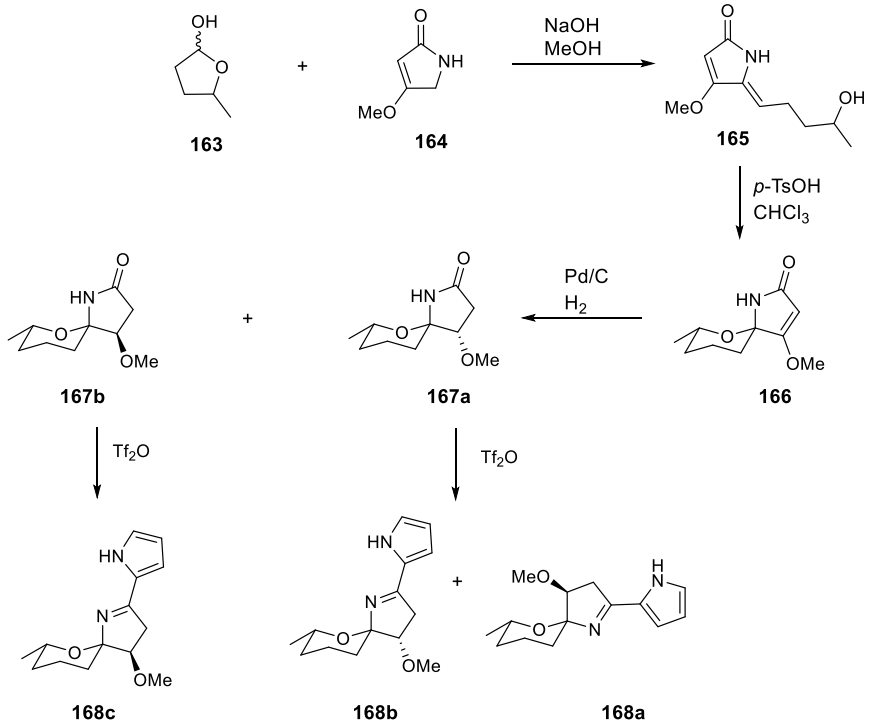


Figure 14 Retrosynthetic Analysis of Spiroaminal Moiety of Marineosin A by the Snider Group

2.1.2.3 Shi's work In 2013, the Shi group developed a new strategy to construct the spiroaminal fragment of marineosins A and B (Scheme 11).[52] Treatment of 5-methyltetrahydrofuran-2-ol **163** with **164** afforded the dihydropyrrol-2-one **165**. *N*-acyliminium ion cyclization of **165** under acidic condition provided **166**. A Pd/C reduction then provided isomers **167a** and **167b** with 64% and 27% yield, respectively. The Tf_2O mediated Vilsmeier-Haack type reaction with pyrrole provided the final product spiroaminal as a series of isomers. The anomeric effect and electronic repulsion between the two oxygen atoms of **168** was assumed to result in the formation of the undesired isomer. On the contrary, in the case of marineosin A or B, the fused macrocyclic ring will probably push the methoxy group away from it to form a more stable configuration.

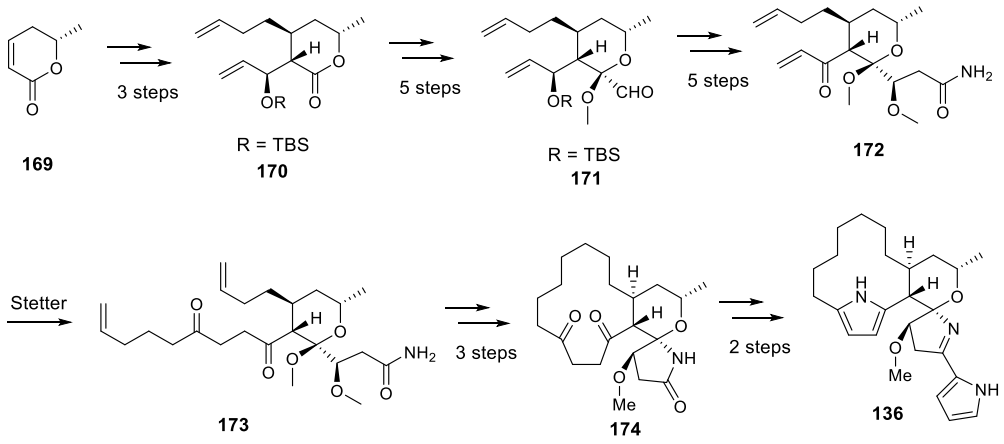
Scheme 11 Shi's Work on the Formation of Spiroaminal Moiety



The Shi group further reported the first total synthesis of marineosin A with 1.6% overall yield in 2016 (Scheme 12).[53] Beginning from chiral pyranone **169**, conjugated addition of Gilman reagent, aldol reaction and TBS protection afforded lactone **170**. Ring opening reaction of **170** by

lithium thiazole, ketal formation and a three steps conversion from thiazole to aldehyde provided aldehyde **171**. Reacting aldehyde **171** with (cyanomethyl)lithium, followed by the methylation of alcohol, nitrile reduction, alcohol deprotection and oxidation to ketone yielded amide **172**, which was advanced to 1,4-diketone **173** via the Stetter reaction. Spirocyclization of **173** was accomplished using boron trifluoride ethyl etherate and the ring-closing metathesis followed by hydrogenation of alkene provided macrocycle structure **174**. Conversion of **174** to the pyrrole with a microwave-assisted Paal-Knorr process followed by Vilsmeier-Haack type reaction gave the final product marineosin A **136**.

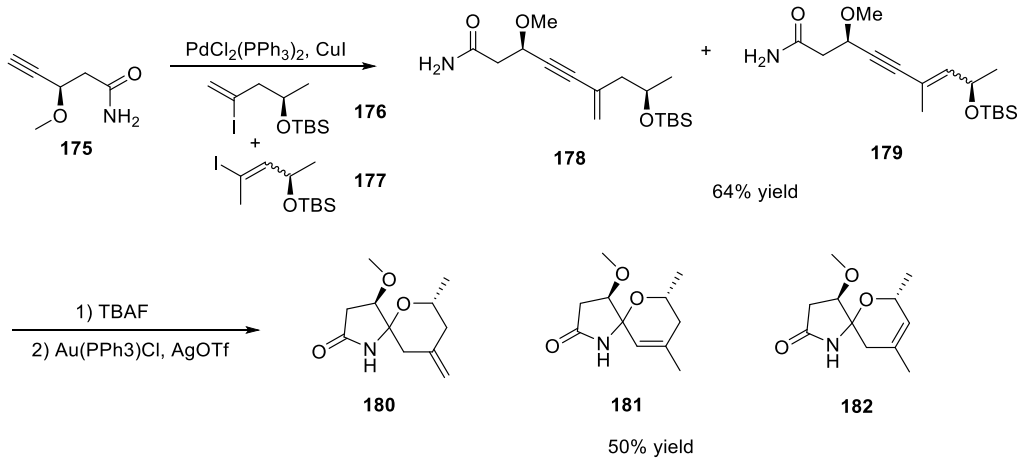
Scheme 12 The First Total Synthesis of Marineosin A by the Shi Group



2.1.2.4 Sarli's work The Sarli research group investigated the gold-catalyzed spiroamidoketalization of alkynyl amidoalcohols and provided an efficient method for the synthesis of spiro-aminol analogue of marineosin A (Scheme 13).[54] Sonogashira cross-coupling reaction of amide **175** with an inseparable mixture of volatile alkenyl iodide **176** and **177** afforded alkynylamides **178** and **179** in a total of 64% yield. TBS deprotection and gold catalyzed

cyclization provided a mixture of spiroaminal structures **180**, **181** and **182** in a total of 50% yield. The major isomer **181** was isolated and identified (more than 65% of the total spiroaminals).

Scheme 13 Sarli's Spiroaminal Synthesis



2.2 EFFORTS TOWARDS THE TOTAL SYNTHESIS OF MARINEOSIN A

2.2.1 Retrosynthesis of marineosin A

The molecule of marineosin A contains three challenging sites including the pyrrole-containing 12-membered macrocycle ring, densely functionalized tetrahydropyran ring and previously unreported spiroaminal structure consisting of tetrahydropyran ring and dihydropyrrole ring. (Figure 15) Considering the molecule's chemical sensitivity and recognizing its three challenging sites, the retrosynthetic analysis outlined in Figure 16 was chosen. Given the high sensitivity of the pyrrole units, we expected the pyrrole ring on the spiroaminal could be introduced by Vilsmeier-Haack reaction and the macrocyclic pyrrole could be synthesized by Paal-Knorr

reaction at a later stage, revealing intermediate **183** as a potential precursor. Inspired by the structural feature of **183** containing the 1,4-diketone motif, we decided to access the macrocycle through a Stetter reaction from enone **184**, which has never been used in a macrocyclization reaction before. Considering the activity of hydrogen at the 2-position of tetrahedropyran ring, our approach towards the preparation of spiral aminal **184** would involve either a radical cyclization or a nitrene insertion and manipulation of protected alcohol from ester **186**. An *exo*-selective asymmetric hetero-Diels-Alder reaction was expected to afford the chiral dihydro-*2H*-pyran ring **186** between diene **187** and dienophile **188** followed by substrate-directed asymmetric hydrogenation of the olefin and methylation through oxocarbenium ion ensuring the correct configuration of stereocenter and methyl group.

Construction of diene **187** was realized to come from the coupling reaction from *trans*-vinyl triflate **189**, which could be prepared using *N*-phenyltriflimide from *β*-keto ester **190** followed DIBAL-H reduction and primary alcohol protection. The *β*-keto ester **190** would be prepared from diol **191** straightforwardly. The dienophile **188** would be set from **192** through the methylation and ozonolysis of the double bond. The oxidation of deoxyribose **194**, a widely used chiral starting material, followed by the bromination with simultaneous acylation and zinc mediated elimination was anticipated to afford the desired allyl alcohol **192**.

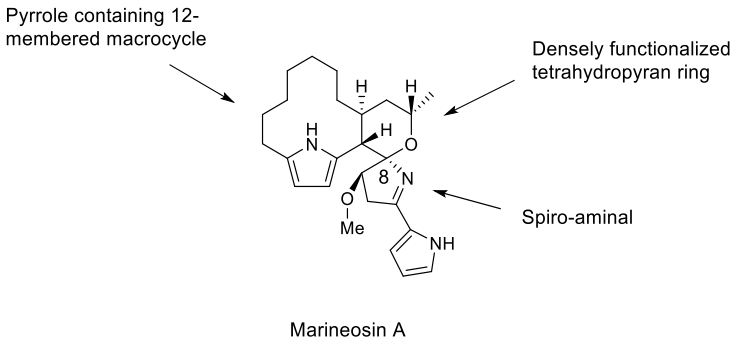


Figure 15 Structural Analysis of Marineosin A

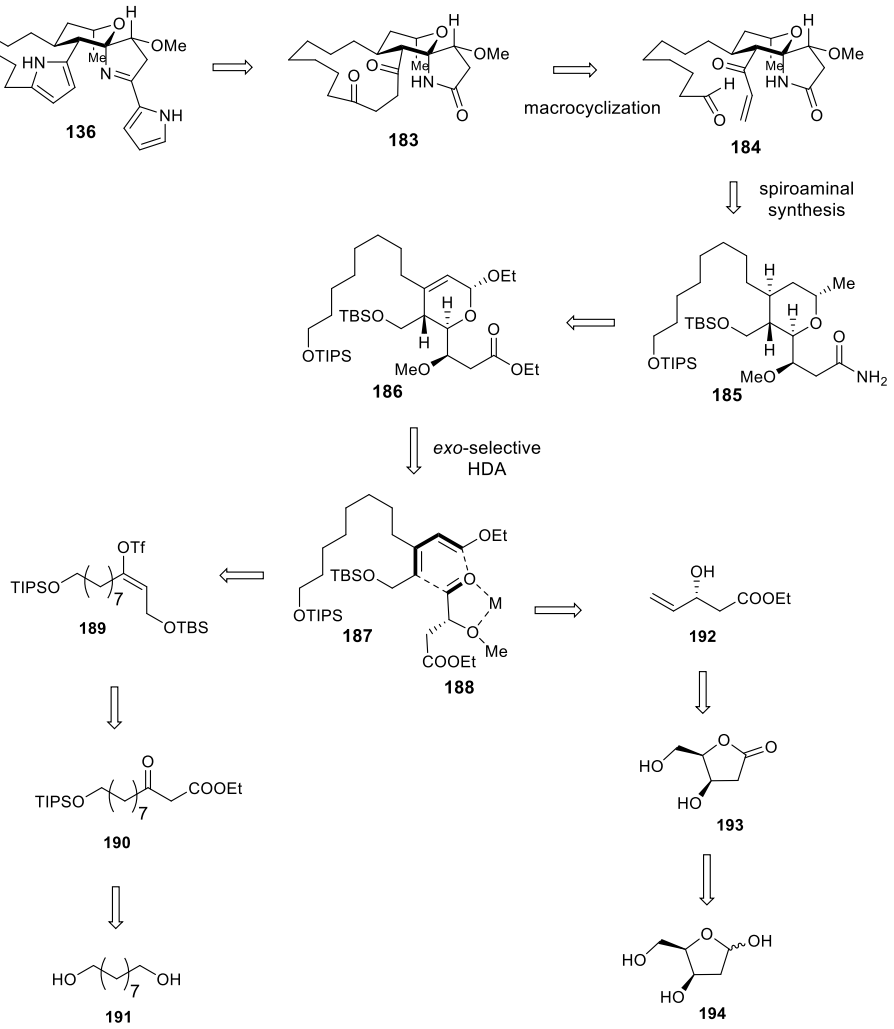


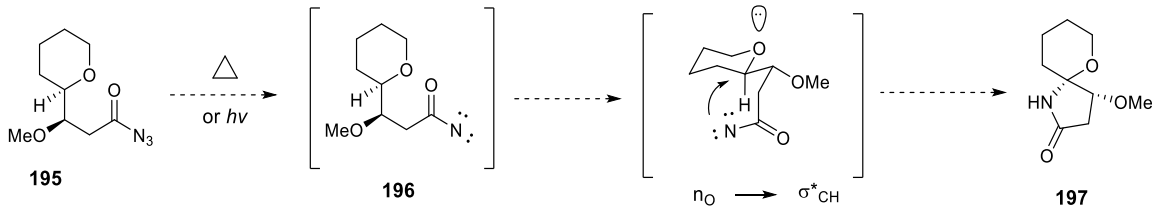
Figure 16 Retrosynthetic Analysis of Marineosin A

2.2.2 Model Study of spiroaminal structure of marineosin A

2.2.2.1 Model Study of spiroaminal structure of marineosin A through nitrene insertion As depicted in Figure 16, both the macrocyclization and the spiro-aminal construction are both at a late stage in our synthesis. Herein, to determine the feasibility of the spiroaminal formation, a model study was carried out prior to the total synthesis. Towards this goal, we envisioned that the

acyl nitrene would potentially provide access to the structure at the beginning. As outlined in the model study (Scheme 14), the approach to the chiral spiroaminal relies upon the thermal or photolytic breakdown of the acyl azide **195** to deliver the corresponding acyl nitrene followed by the ideally positioned insertion across the C-H bond. While the use of nitrene insertion in natural products synthesis has already been reported,[55] acyl nitrene insertion is relatively uncommon.[56] It was proven that under some circumstances, the proximity of the two reacting sites would significantly accelerates the reaction by lowering the activation energy.[57] Similarly, in our structure, the proximity of acyl nitrene and C_{sp3}-H bond would strongly favor the insertion process. Additionally, the favorable entropy associated with 5-membered ring formation and the labilization of the axial C_1-H bond resulting from the antiperiplanar alignment of the oxygen non-bonding electron pair and $\sigma^*_{C\text{-}H}$ should effectively enforce the desired regioselective C-H insertion. We were aware, however, that competing Curtius rearrangement could be problematic.

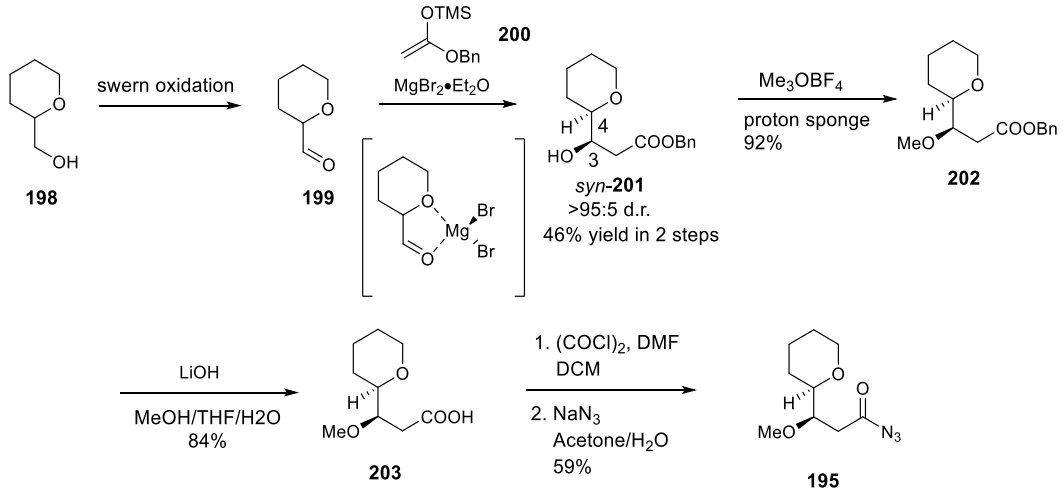
Scheme 14 Proposed Nitrene Insertion Route to Construct Chiral Spiroaminal Structure



Synthesis of a pyran derivative **195** possessing the relevant stereochemical relationships necessary to test the nitrene insertion was achieved by Swern oxidation of hydroxymethylenepyran **198** to afford aldehyde **199**. (Scheme 15) Chelation controlled addition of freshly prepared benzyl 1-[(trimethylsilyl)oxy]vinyl ether **200** to aldehyde **199** provided *β*-hydroxy ester **201** possessing the correct C_3-C_4 *syn* stereochemistry in 46% yield after 2 steps. The Mukaiyama aldol product **201** underwent the methylation by trimethyloxonium tetrafluoroborate and proton sponge to form the *O*-methylation product **202** in 92% yield. A three-step sequence of benzyl ester hydrolysis by

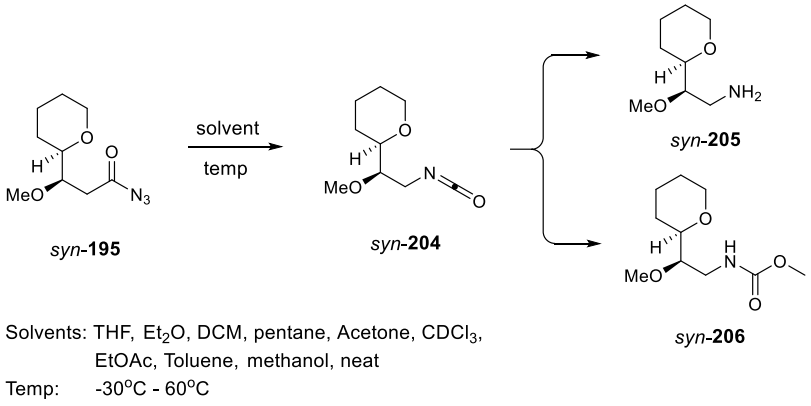
lithium hydroxide, acid to acyl chloride conversion by oxalyl chloride with DMF and sodium azide addition in acetone provided the desired acyl azide **195** in 50% yield.

Scheme 15 Preparation of Acyl Azide in Model Study of Spiroaminal Synthesis



Having access to nitrene precursor acyl azide **195**, we next examined the reaction conditions of the acyl nitrene insertion. Different solvent may benefit to different conformation due to the solvent effect.[58] Therefore, the direct nitrene insertion reaction was screened in different solvents in the anticipation that some solvents would strongly favor the conformation of **195** beneficial to the C-H insertion reaction. Several common solvents were screened and in all cases, the Curtius rearrangement product was the only product. That is, the acyl azide decomposed into acyl nitrene, which underwent rearrangement to afford the isocyanate **204**. The isocyanate **204** can be further attacked by the nucleophile as water or methanol to afford more stable products as amine **205** and carbamate **206** for characterization (Scheme 16). This reaction was also screened under different temperature and solvent-free conditions. Nevertheless, only the Curtius rearrangement products were observed in all cases, which meant the direct nitrene insertion of our structure was hard to be accomplished under laboratory conditions.

Scheme 16 Study of Acyl Nitrene Insertion Reaction

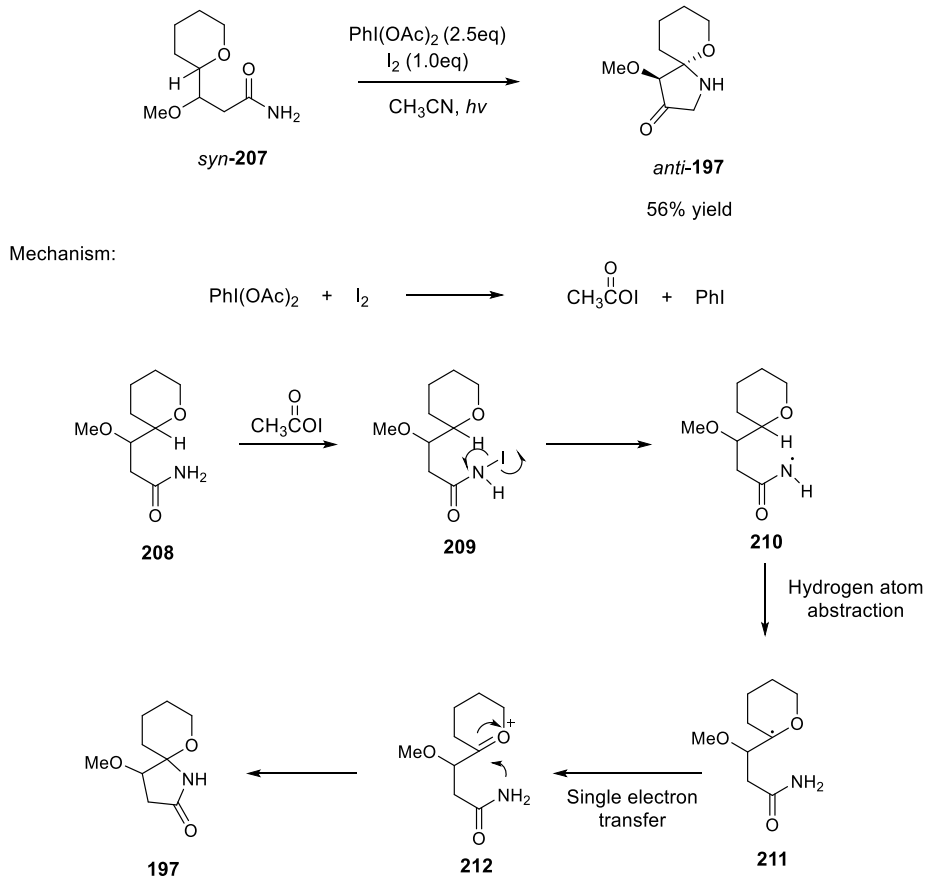


2.2.2.2 Model Study of spiroaminal structure of marineosin A through radical cyclization

Since direct nitrene C-H insertion did not afford the direct insertion products, another route based on the radical cyclization illustrated by the Suárez group[59] was proposed. In this event, treating amide **207**, which was prepared directly from acid **203**, with (diacetoxyiodo)benzene and iodine in acetonitrile under visible light afforded the *anti*-spiroaminal **197** as the only isomer in 56% yield. Comparing the spectrum of our product with the spectrum reported by the Lindsley group[51], the configuration of **197** was conformed with the methoxy group of **197** adopting an *anti*-orientation relative to the ether oxygen (scheme 17). The mechanism was proposed as follows: first the reaction of (diacetoxyiodo)benzene with iodide provides the acetyl hypoiodite. Next the acetyl hypoiodite converts the amide **208** into the corresponding hypoiodite **209**. Then the nitrogen radical **210** is formed through the homolytic cleavage of N-I bond. After the tandem hydrogen abstraction and single electron transfer, the oxocarbenium ion **212** produced is further attacked by intramolecular nucleophilic addition of amide to afford the spiroaminal structure **197**. Similar to the trend in natural spiroketals prevalently possessing the optimal thermodynamically stable configuration,[60] the configuration of **197** could be attributed to electronic repulsion between the

two oxygen atoms, rendering the *anti*-isomer as the lower energy isomer compared with the *syn* isomer (Figure 17). However, in the natural product marineosin A structure, the interaction between the fused macrocycle ring and the methoxy group will likely make the methoxy group stay away to ensure a more stable configuration (Figure 17). In view of this, we believe the radical cyclization in the model reaction should provide the desired configuration of the spiroaminal moiety in our total synthesis.

Scheme 17 Synthesis of Spiroaminal 197 Through Radical Route and Proposed Mechanism



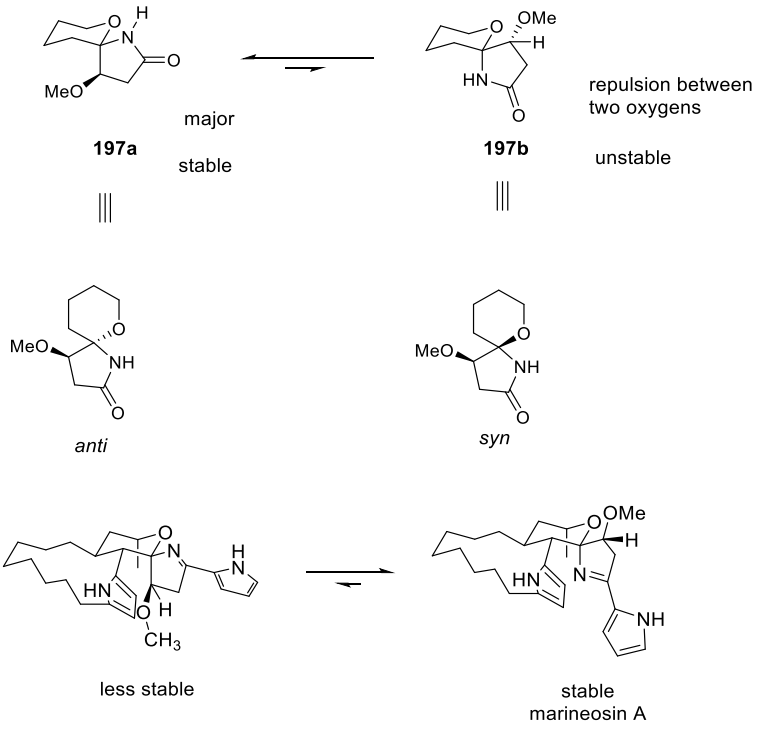


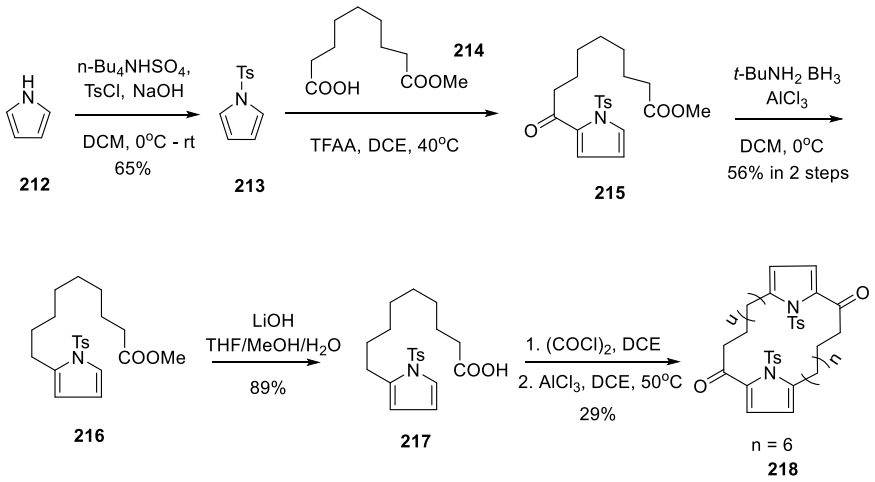
Figure 17 Configuration Analysis of Spiromainal Structure

2.2.3 Model study of the macrocyclization

2.2.3.1 Model study of the macrocyclization through intramolecular acylation With the success of our spiroaminal moiety synthesis, we simultaneously pursued an investigation into the macrocyclization of the highly strained, 12-membered ring that would occur later in our synthesis. In addressing the synthetic objective, previously published intramolecular acylation macrocyclization influenced our initial efforts to construct the pyrrole-containing macrocycle.[61] To validate whether the proposed method was applicable in our structure, the pyrrolyl acid **217** was prepared as displayed in Scheme 18. Pyrrole **212** was first protected with 4-tolunesulfonyl chloride in 65% yield. The Friedel-Crafts acylation of 1-tosylpyrrole **213** with monomethyl azelate

214 and trifluoroacetic anhydride (TFAA) followed by a selective reduction of carbonyl to methylene by using borane *tert*-butylamine and aluminum chloride afforded pyrrolyl ester **216** in 56% yield. Hydrolysis of the resulting ester **216** afforded the desired acid **217** in 89% yield. At this point, we were ready to explore the key Friedel-Crafts macrocyclization. After several attempts, only the acid to acyl chloride conversion followed by the aluminum chloride mediated macrocyclization provided the ring-closing product **218**. However, HR-MS analysis revealed that the ring-closed product was actually the dimer rather than desired macrocycle.

Scheme 18 Preparation of Macrocycle Through Intramolecular Acylation Reaction



The formation of the undesired macrocycle product **218** was attributed to the steric hindrance of the tosyl protecting group on pyrrole, which greatly increased the energy of the 12-member ring and made it extremely hard for the acyl chloride to approach the 5-position of pyrrole by rounding the tosyl group (Figure 18). Therefore, the tosyl pyrrole was deprotected to diminish the impact of the steric hindrance of the protecting group in the anticipation of obtaining the desired macrocycle. Deprotection of **217** was accomplished with 5 N sodium hydroxide solution and methanol under reflux condition, providing the unprotected pyrrolyl acid **219** in 55% yield (Equation 9) Due to the significant nucleophilicity of the unprotected pyrrole, we used TFAA instead of the oxalyl chloride for the reaction. Unfortunately, pyrrolyl acid **217** directly reacted

with TFAA to afford product **220** rather than the desired macrocycle, which compelled us to explore alternatives for the macrocyclization. (Equation 10)

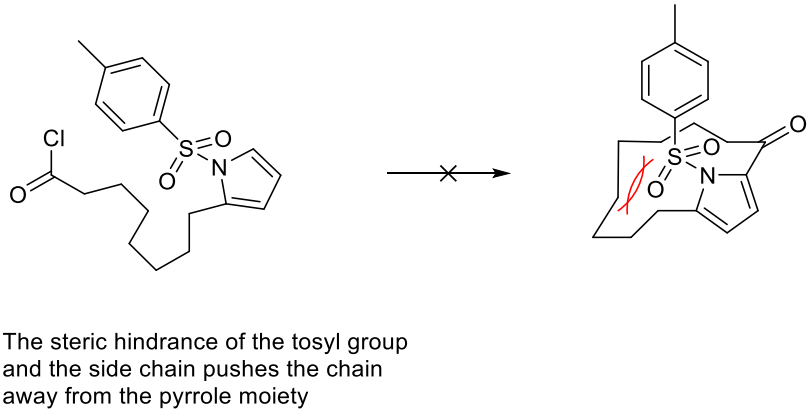
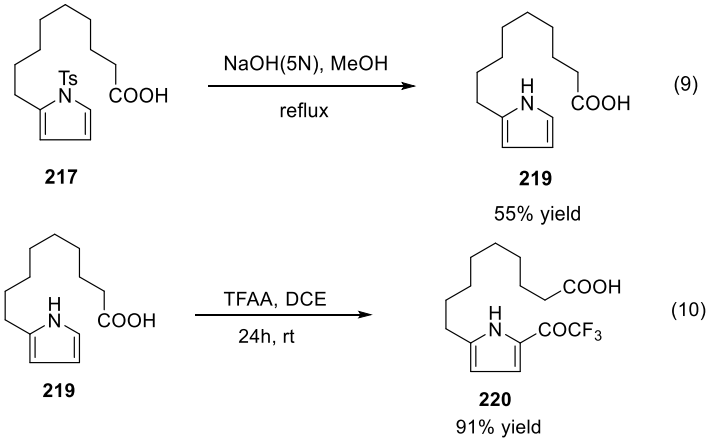


Figure 18 Analysis of steric hindrance of the macrocyclization



2.2.3.2 Model study of the macrocyclization through Stetter reaction Based on the instability exhibited by the pyrrole heterocycle in attempted macrocyclizations and the failure in our previous synthetic route with substrates containing pyrrole, we anticipated to prepare the macrocycle ring first without pyrrole followed by the microwave assisted Paar-Knorr reaction to assemble the desired pyrrole structure. Targeting a 1,4-diketone as a precursor to the requisite pyrrole allowed us to consider a Stetter reaction for the construction of the macrocycle. To the best of our

knowledge, the Stetter reaction had never been used as a macrocyclization reaction before. Since the pioneering work of Stetter in 1973, the *N*-heterocyclic carbene (NHC) -catalyzed addition of aldehydes to Michael acceptors, have enjoyed extensive utility in the synthesis of 1,4-dicarbonyl compounds that would ordinarily require multistep operations for their synthesis.[62] These umpolung conjugate additions are accepted to proceed by the activation of aldehyde **225** with the *in situ* formed carbene catalyst to generate the nucleophilic Breslow intermediate **230**. The Breslow intermediate undergoes an irreversible addition to the Michael acceptor, followed by the proton transfer and regeneration of the catalyst to produce the 1,4-dicarbonyl compound **226** (Figure 20).

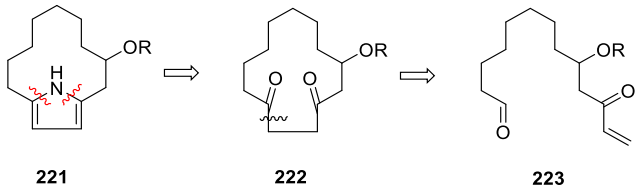


Figure 19 Retrosynthetic Analysis of the Model Macrocycle Through Stetter Reaction

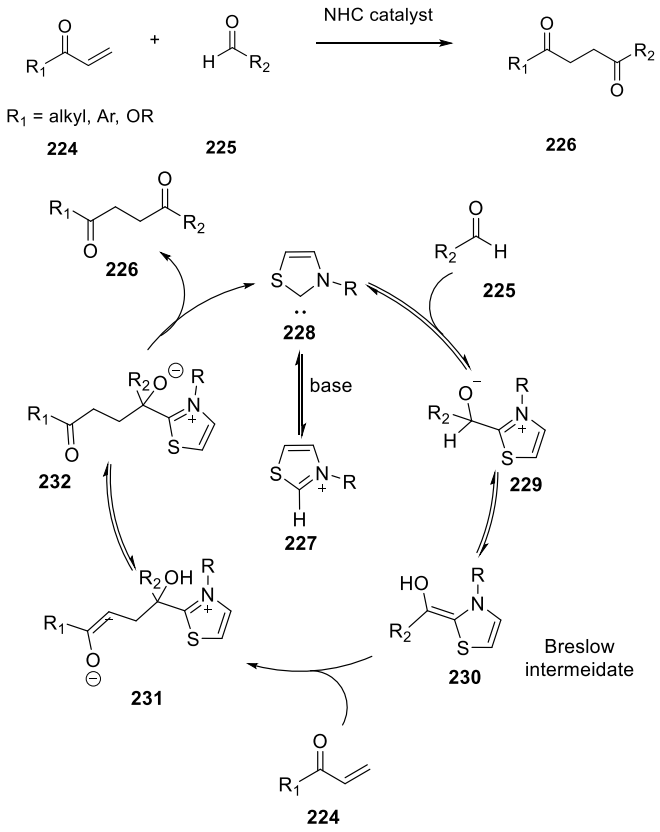
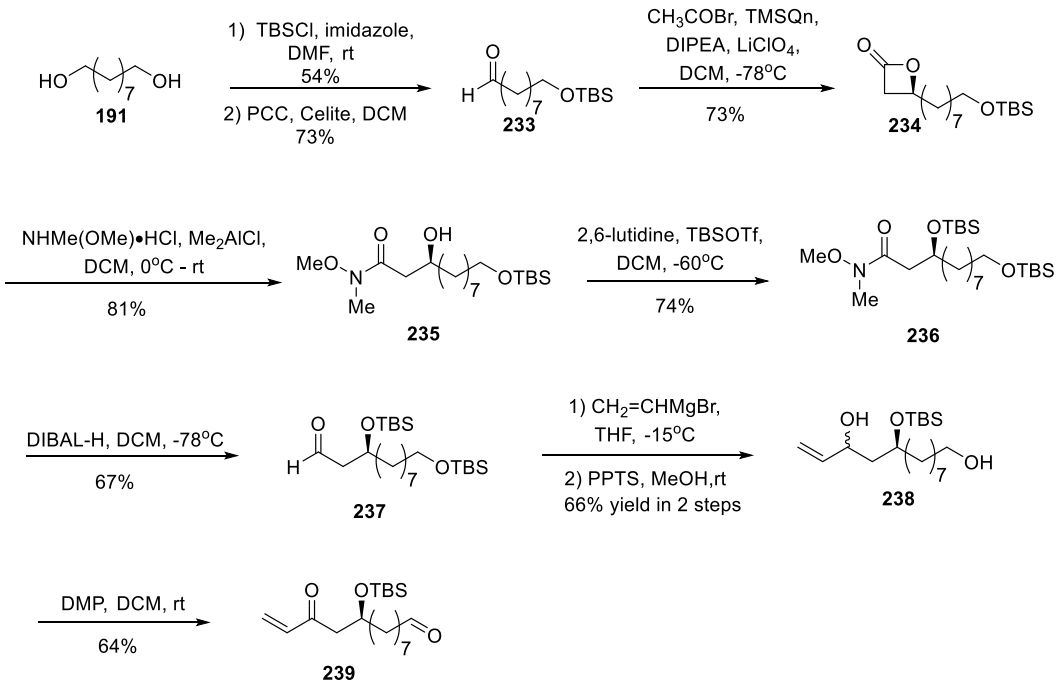


Figure 20 Stetter Reaction and Mechanism

To evaluate the Stetter-based macrocycle synthesis, the requisite aldehyde-enone **239** was prepared as outlined in Scheme 19. The protection of 1,9-nonanediol **191** at one end with TBS protecting group followed by PCC oxidation of the unprotected hydroxy group provided aldehyde **233** in 39% yield. Alkaloid-catalyzed ketene-aldehyde cycloaddition of **233** afforded the *β*-lactone **234** in 73% yield. [26, 33, 63] Ensuing lactone ring opening with *N*,*O*-dimethylhydroxylamine afforded *β*-hydroxy amide **235** in 81% yield, whereupon the hydroxy group was protected using *tert*-butyldimethylsilyl triflate at low temperature to give **236** in 74% yield. Reacting Weinreb amide **236** with DIBAL-H provided aldehyde **237** in 67% yield. Grignard addition reaction to **237** followed by the selective deprotection of the terminal hydroxy group using pyridinium *p*-toluenesulfonate (PPTS) gave the diol **238** as a mixture of two diastereoisomers in 66% yield after

two steps. At last, Dess-Martin Periodinane (DMP) oxidation of diol **238** provided the Stetter precursor **239** in 64% yield (Scheme 19).

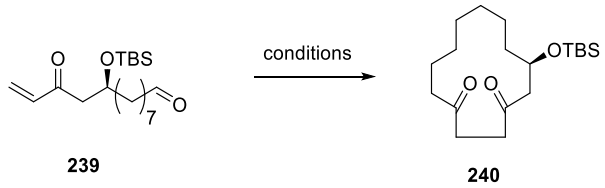
Scheme 19 The Synthesis of Enone 239



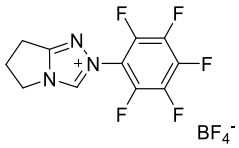
With enone **239** prepared, we began to screen our proposed Stetter macrocyclization conditions. Based on the efficacy demonstrated in several total synthesis,[64] Rovis catalyst **241** was screened first in our reaction. However, only trace product was obtained at 60 °C when triethylamine was used as base and toluene was used as solvent (Table 8, entry 1). The increase of temperature to 100 °C led to little improvement (Table 8, entry 2). The thizaolium-based catalyst **242**, which exhibited great activity in the intermolecular Stetter reaction in the synthesis of spirolide C attracted our attention.[65] The previously reported reaction conditions in the synthesis of spirolide C[65] (catalyst **242** and K_2CO_3 in THF) showed no reaction activity. This is probably due to the bad solubility of potassium carbonate in THF and trace butylated hydroxytoluene (BHT) in THF, especially at a very low concentration (1.0 mmol/L) (Table 8, entry 3). Increasing the temperature and using Hünig's base instead of the inorganic base did not afford any desired

product either. (Table 8, entry 4). Finally, changing the base into DBU, a more basic base than Hünig's base, led to the desired macrocyclization product **240** in 35% yield (Table 8, entry 5). Despite the modest conversion, **239** was consumed completely according to the crude ^{1}H NMR. One explanation for this moderate yield is the intrinsic polymerization characteristic of sterically unhindered enones.[66] Indeed, scattered opaque white plastic was observed left in the syringe when a solution of **239** was added to the solution of catalyst **242** and base via a syringe pump in the macrocyclization. It is worth noting that the reaction successfully generated a 12-membered macrocycle from a precursor that was devoid any preorganization or hindered rotational degrees of freedom. At last, the microwave assisted Paal-Knorr pyrrole synthesis delivered the desired macrocycle **243** in 72% yield (Equation 11), which proved our proposed macrocyclization is useful and promising.

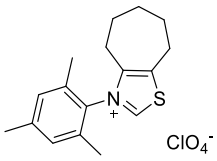
Table 8 Investigation into the Stetter Macrocyclization Reaction



239 240



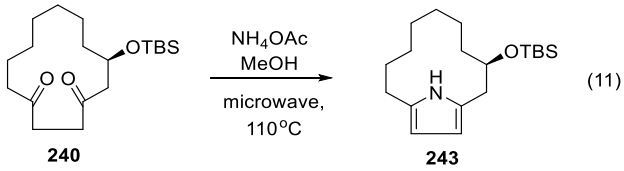
Catalyst **241**



Catalyst **242**

Entry	Catalyst	Condition	Temp	Time	Yield
1	**241**	Et_3N, toluene, 1.0 mmol/L	60 °C	24h	trace
2	**241**	Et_3N, toluene, 1.0 mmol/L	100 °C	24h	SM:Prod = 15:1[a]
3	**242**	K_2CO_3, THF, 1.0 mmol/L	60 °C	24h	N.R.
4	**242**	DIPEA, toluene, 0.85mmol/L	80 °C	24h	N.R.
5	**242**	DBU, toluene, 1.0 mmol/L	100 °C	24h	35%

[a] The ratio is determined by the crude ^1H NMR. [b] isolated yield



240 243 (11)

2.2.4 Metal-chelated exo-selective hetero-Diels-Alder reaction

With the success of our model reactions for the challenging spiroaminal structure and macrocycle preparation, we began our total synthesis towards marineosin A. Four stereocenters on the

tetrahydropyran ring posed a special challenge to construct stereospecifically. The hetero-Diels-Alder (HDA) reaction, which provides a highly effective route in preparation of six-membered ring such as dihydropyrans and dihydropyrones,[67] emerged as a prosperous strategy. However, the inverse-electron-demand hetero-Diels-Alder reaction was not applicable in the synthesis of marineosin A according to Lindsley's work.[49] Additionally, traditional Lewis acid catalyzed hetero-Diels-Alder reactions result in the formation of the *endo* product as the major isomer by reason of secondary orbital bonding interactions between the diene and dienophile.[68] A chiral phosphoric acid catalyzed *exo*-selective HDA reaction[69] failed to provide the chiral dihydropyran ring in our previous attempts. Inspired by the work of Danishefsky in chelation-controlled *exo*-selective hetero-Diels-Alder reactions of chiral alkoxy aldehydes, we have been interested in constructing the tetrahydropyran ring through a similar *exo*-selective HDA reaction followed by substrate-directed hydrogenation and methylation (Figure 21). The *exo* selectivity is the result of approach of the diene on the less hindered face of the metal-chelated optically active aldehyde.

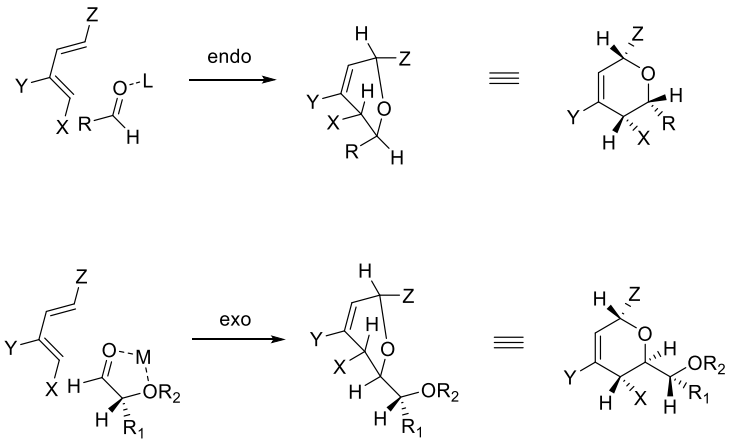
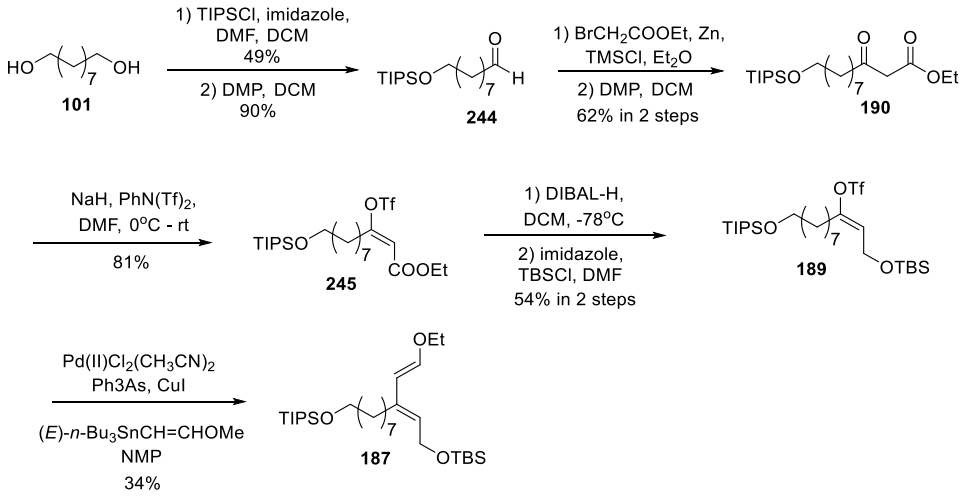


Figure 21 Exo-selective Hetero-Diels-Alder Reaction

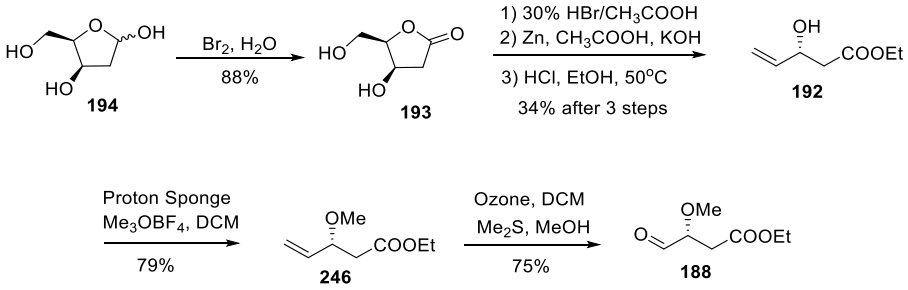
In order to explore the proposed HDA reaction, the diene synthesis began with mono-TIPS protection of 1,9-nonanediol **101** followed by DMP oxidation to afford the aldehyde **244** in 44% yield. Reformatsky reaction of aldehyde **244** and ethyl bromoacetate followed by the DMP

oxidation of the resulting alcohol led to the beta-keto ester **190** in 62% yield. The *trans* isomer of the vinyl triflate **245** was prepared from **244** using *N*-phenyltriflimide and sodium hydride in DMF with 81% yield. Reducing the unsaturated ester **245** and TBS protection of the resulting allyl alcohol [(1) DIBAL-(H), THF; (2) TBSCl, imidazole] provided vinyl triflate **189** in 54% yield after two steps. Finally, Stille coupling of vinyl triflate **189** and freshly prepared organotin reagent gave the desired diene for the proposed HDA reaction (34% yield) (Scheme 20).

Scheme 20 The Preparation of Diene 187



Scheme 21 The Preparation of Dienophile 192



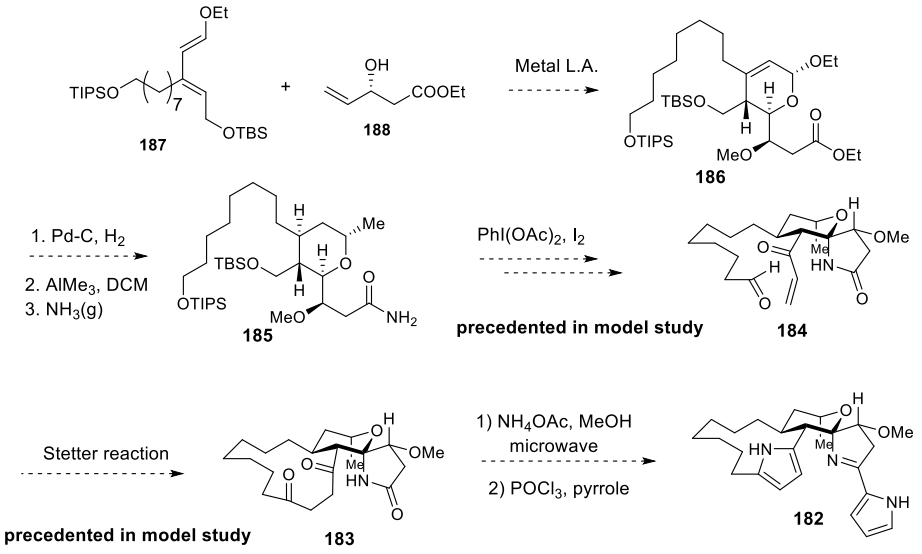
The chiral dienophile **189** was readily obtained from the commercially available 2-deoxy-*L*-ribose **194**. Treatment of **194** with bromine in water gave 2-deoxy-L-ribonolactone **193** in 88%

yield. Bromination of the 5-position in acetic acid with simultaneous acylation of the other hydroxy groups followed by zinc mediated elimination, which further underwent basic hydrolysis process to remove the acyl group and subsequent esterification of the terminal acid in ethanol gave the chiral allyl alcohol **192** in 34% yield.[70] Methylation of alcohol by proton sponge and trimethyloxonium tetrafluoroborate provided allyl ether **246** in 79% yield. Ultimately, the ozonolysis of the alkene afforded the desired aldehyde **188** as the dienophile in 75% yield (Scheme 21).

2.3 FUTURE WORK

Since both the diene **187** and the dienophile **188** had already been prepared, we planned to screen the metal-chelated *exo*-selective hetero-Diels-Alder reaction to optimize the outcome for the preparation of chiral dihydropyran ring **186** in the next step. The dihydropyran **186** will then undergo the substrate-directed hydrogenation and methylation through oxocarbenium ion to provide the desired core structure tetrahydropyran **185**. Next, we will have the opportunity to apply our previous successful model reactions – the radical cyclization and the Stetter macrocyclization in the synthesis to prepare the spiroaminal structure and the macrocycle followed by the Vilsmeier-Haack reaction to afford the final marineosin A structure (Scheme 22).

Scheme 22 Future Work towards the Total Synthesis of Marineosin A



2.4 SUMMARY

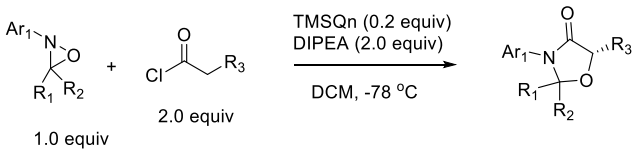
In summary, in consideration of the challenging structural features of marineosin A, as well as the late-stage preparation of the challenging structures in our retrosynthetic analysis, we studied the model reactions to prepare the spiroaminal structure and the macrocycle structure. In the model system, the spiroaminal structure was obtained through a radical cyclization and the configuration analysis increased our confidence to obtain the isomer observed in marineosin A structure. A Stetter reaction gave us surprising results during the macrocyclization study. To the best of our knowledge, this is the first time that Stetter reaction was used in a macrocyclization reaction. In the total synthesis of marineosin A, both the diene and the dienophile has already been synthesized towards the preparation of dihydropyran ring through the proposed *exo*-selective HDA reaction.

3.0 EXPERIMENTAL FOR ENANTIOENRICHED OXAZOLIDINONES AS SYNTHESIS SCAFFOLDS

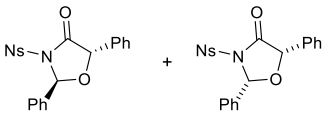
General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$(c = g/100 mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance (^{1}H: 300MHz; ^{13}C: 75MHz), a Bruker Avance (^{1}H: 400MHz, ^{13}C: 100MHz) or a Bruker Avance (^{1}H: 500MHz, ^{13}C: 125MHz) spectrometer with chemical shifts reported relative to residual $CHCl_3$ (7.26 ppm) for ^{1}H and $CDCl_3$ (77.0 ppm) for ^{13}C NMR spectra. Mass spectra were obtained on a VG-7070 or Fisons Autospec high resolution magnetic sector mass spectrometer.

Unless otherwise stated, all reactions were carried out in dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous solvent (CH_2Cl_2, THF, DMF, diethyl ether and toluene) were obtained by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. *N*, *N*-diisopropylethylamine, triethylamine, pyridine, acetonitrile and diisopropylamine were distilled under nitrogen from calcium hydride. Benzaldehyde, 2-furaldehyde, cinnamaldehyde, butyraldehyde, hydrocinnamaldehyde, *p*-anisaldehyde and acetyl bromide were distilled before use. All the commercial chemicals are purchased from Aldrich Chemical Co or

Fisher Scientific Co. Flash chromatography was performed on EM silica gel 60 (230-240 mesh) unless noted otherwise.

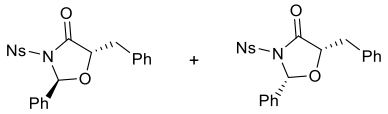


General Procedure A: Catalytic asymmetric ketene-oxaziridine cycloaddition: To a solution of *O*-trimethylsilylquinine (TMSQn) (0.2 equiv) in DCM was added *N*,*N*-diisopropylethylamine (2.0 equiv, 0.5 M). The resulting solution was cooled to −78 °C and stirred. The oxaziridine (1.0 equiv) and the acyl chloride (2.0 equiv) were combined and dissolved in CH_2Cl_2 (0.3 M for the oxaziridine) in a separate flask and the resulting homogeneous mixture was then transferred into the previously made −78 °C solution via a syringe pump over 2h. Full consumption of the oxaziridine would be observed by TLC once the addition was complete. The reaction was stirred for another 0.5 h and quenched at the same temperature by adding Et_2O and slurry usually formed. The heterogeneous mixture was then filtered through a short pad of celite, eluting with Et_2O. The filtrate was concentrated and the crude material was purified by flash column chromatography.



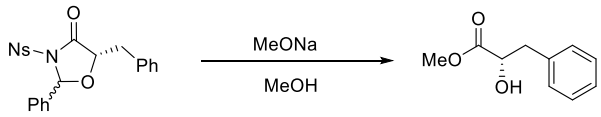
(5*S*)-3-[(4-Nitrophenyl)sulfonyl)]-2,5-diphenyloxazolidin-4-one (83): General Procedure A was followed by employing 3.1 g of *N*-nosyl oxaziridine **±58** (10 mmol, 1.0 equiv), 0.8 g of TMSQn (2 mmol, 0.2 equiv), 3.5 mL of *N*, *N*-diisopropylethylamine (20 mmol, 2.0 equiv) and 2.6 mL of phenylacetyl chloride (20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 5% ethyl acetate in hexane) to yield 3.3 g (78% yield) of the product as a mixture of two diastereomers. The two diastereomers were further separated by column

chromatography followed by recrystallization in hexane/ethyl acetate. Characterization of *anti* product: $[\alpha]_D^{20}$ -87.8, (c = 0.60, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) 8.18 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 7.49 (t, J = 6.8 Hz, 1H), 7.42-7.36 (m, 9H), 6.72 (s, 1H), 5.51 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 168.6, 150.8, 142.9, 135.9, 133.7, 130.6, 129.5, 129.4, 129.0, 128.9, 127.6, 126.1, 123.9, 91.3, 78.7 ppm. Characterization of *syn* product: $[\alpha]_D^{20}$ 28.4, (c = 0.94, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) 8.16 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.47 (t, J = 6.8Hz, 1H), 7.41-7.36 (m, 9H), 6.24 (s, 1H), 5.49 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 168.4, 150.7, 143.3, 135.4, 133.2, 130.8, 129.3, 129.1, 128.7, 128.6, 128.5, 126.2, 124.0, 90.7, 78.8 ppm. These compounds' characterization data matched the data provided in the following literature: Guo, B. PhD dissertation, University of Pittsburgh, 2012.



(5*S*)-5-Benzyl-3-[(4-nitrophenyl)sulfonyl]-2-phenyloxazolidin-4-one (67): General Procedure A was followed by employing 2.6 g of *N*-nosyl oxaziridine **±58** (8.33 mmol, 1.0 equiv), 0.7 g of TMSQn (1.67 mmol, 0.2 equiv), 2.9 mL of *N*, *N*-diisopropylethylamine (16.7 mmol, 2.0 equiv) and 2.5 mL of 3-phenylpropanoyl chloride (16.7 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 5% ethyl acetate in hexane) followed to yield 2.4 g (66% yield) of the product as a mixture of two diastereomers. The two diastereomers were further purified by column chromatography followed by recrystallization in hexane/ethyl acetate for characterization. Characterization of *anti* product: $[\alpha]_D^{20}$ -80.2, (c = 1.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 8.13 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.21-7.14 (m, 7H), 6.75 (d, J = 8.4 Hz, 2H), 6.36 (s, 1H), 4.75 (t, J = 4.4 Hz, 1H),

3.21-3.19 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 169.3, 150.6, 143.6, 135.2, 134.8, 130.5, 130.1, 128.9, 128.6, 128.4, 128.2, 127.1, 123.8, 90.8, 78.4, 36.8 ppm; HRMS (ES+) *m/z* calculated for $[M+H]^+$ $C_{22}H_{19}N_2O_6S$: 439.0964; found: 439.0977. Characterization of *syn* product: $[\alpha]_D^{20}$ 25.8, (c = 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 8.15 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.8 Hz, 2H), 7.43 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.27-7.20 (m, 7H), 6.20 (d, J = 1.2 Hz, 1H), 4.81 (td, J = 4.8, 1.2 Hz, 1H), 3.19 (dd, J = 14.4, 3.6 Hz, 1H), 3.09 (dd, J = 14.4, 5.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 169.6, 150.8, 143.0, 136.5, 134.5, 130.4, 129.9, 129.3, 128.8, 128.5, 127.3, 127.2, 123.9, 91.4, 78.0, 37.6 ppm; HRMS (ES+) *m/z* calculated for $[M+H]^+$ $C_{22}H_{19}N_2O_6S$: 439.0958; found: 439.0974.



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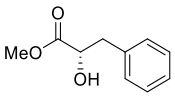
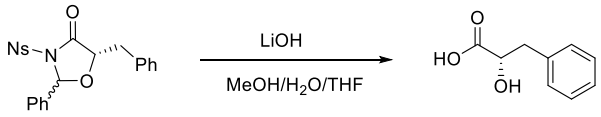


Methyl (*S*)-2-hydroxy-3-phenylpropanoate (68): To a stirred solution of oxazolidinone **67** (87.7 mg, 0.2 mmol, 1.0 equiv) in 4 mL of MeOH was added 25% MeONa in MeOH solution (17µL, 0.08 mmol, 0.4 equiv) at 0 ºC. The resulting mixture was stirred at this temperature for 2 hours and then warm up to ambient temperature and stirred overnight. After all the oxazolidinone **67** diminished on TLC, 2 mL of HCl in MeOH (5%) was added into the reaction to hydrolysis the imine byproduct. The resulting mixture was stirred for 10 min at ambient temperature and diluted with ethyl acetate and washed with water. The organic layer was separated and the aqueous layer was extracted ethyl acetate and the combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was further purified by flash column chromatography (SiO_2, 15% ethyl acetate in Hexane) to yield 32.2 mg (89% yield) of the title

compound as colorless oil. $[\alpha]_D^{20}$ -8.0, (c = 0.83, $CHCl_3$), ^{1}H NMR (300MHz, $CDCl_3$) 7.25-7.12 (m, 5H), 4.41-4.35 (m, 1H), 3.69 (s, 3H), 3.05 (dd, J = 13.8, 4.2 Hz, 1H), 2.89 (dd, J = 13.8, 6.6 Hz, 1H), 2.61 (d, J = 5.7Hz, 1H) ppm, ^{13}C NMR (100MHz, CDCl3) 174.6, 136.3, 129.5, 128.4, 126.9, 71.3, 52.5, 40.6 ppm. Separating the enantiomers by GC [flow rate 1.0 mL/min, method: 105 ^{o}C for 10 min, ramp @ 0.7 ^{o}C/min to 220 ^{o}C, hold for 10 min; T_r: 46.7 min (*R*), 48.4 min (*S*)] provided the enantiomer ratio *S*:*R* = 0.4 : 99.6 (99% *e.e.*).



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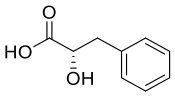
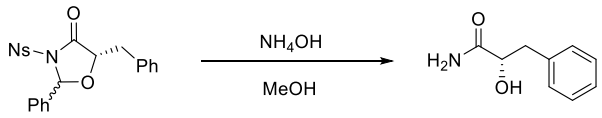


(*S*)-2-Hydroxy-3-phenylpropanoic acid (72): Lithium hydroxide monohydrate (16.8 mg, 0.4 mmol, 2.0 equiv) was suspended in H_2O/MeOH/THF = 0.4 mL/0.4 mL/1.2 mL and oxazolidinone **67** (87.7 mg, 0.2 mmol, 1.0 equiv) was added to the solution. The resulting solution was then stirred overnight at room temperature. After removal of the solvent under *vacuo*, the residue was then taken up in 5 mL of 1 M HCl and extracted with chloroform. The aqueous layer was extracted with chloroform (5 mL x 3). The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue was further purified by column chromatography (SiO_2, 30% ethyl acetate in hexane) to afford 26.1 mg (0.16 mmol, 79% yield) of the desired product as a white solid. $[\alpha]_D^{20}$ -23.2, (c = 1.37, acetone), ^{1}H NMR (500MHz, d_6-acetone) 7.31-7.20 (m, 5H), 4.38 (dd, J = 8.0, 4.0 Hz, 1H), 3.12 (dd, J = 14.0, 4.0 Hz, 1H), 2.91 (dd, J = 14.0, 7.5Hz, 1H), 2.08 (s, 1H) ppm; ^{13}C NMR (125MHz, d6-acetone) 175.3, 138.9, 130.5, 129.0, 127.3, 72.1, 41.3 ppm. E.e. 98%. The e.e. value was determined by converting it into the corresponding methyl ester then using GLC.



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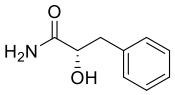
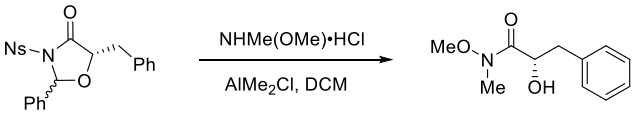


(*S*)-2-Hydroxy-3-phenylpropanamide (69): To a stirred solution of oxazolidinone **67** (87.7 mg, 0.2 mmol, 1.0 equiv) in 4 mL of MeOH was added 0.5 mL of ammonium hydroxide (28% - 30% NH_3 in water) and the resulting mixture was kept stirring at room temperature for 10 min. The mixture was concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2, MeOH/DCM = 10:90) to provide 31.0 mg (94% yield) of the product as a white solid. $[\alpha]_D^{20}$ -73.6, (c = 0.72, $CHCl_3$), ^{1}H NMR (400 MHz, CDCl3) 7.37-7.33 (m, 2H), 7.30-7.26 (m, 3H), 6.36 (br, 1H), 5.43 (br, 1H), 4.34 (td, J = 8.4, 4.4 Hz, 1H), 3.26 (dd, J = 14.0, 4.0 Hz, 1H), 2.93 (dd, J = 14.0, 8.4 Hz, 1H), 2.38 (d, J = 4.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl3) 175.0, 136.6, 129.5, 128.9, 127.2, 72.8, 40.8 ppm.



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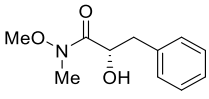
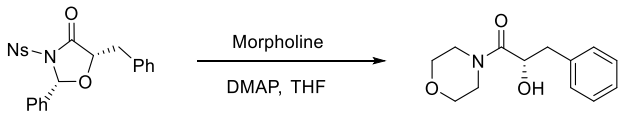


(*S*)-2-Hydroxy-*N*-methoxy-*N*-methyl-3-phenylpropanamide (70): To a 0 °C solution of 39.0 mg of *N,O*-dimethylhydroxylamine hydrochloride (0.4 mmol, 4.0 equiv) in 1.0 mL of CH_2Cl_2 was added 0.4 mL of dimethylaluminum chloride (0.4 mmol of 1M hexanes solution, 4.0 equiv). Once addition was complete, the reaction was removed from the ice bath and warmed to ambient temperature where it was stirred for 0.5h. The resulting solution was cooled to 0 °C

whereupon 43.9 mg of oxazolidinone **67** (0.1 mmol, 1.0 equiv) was added. The resulting solution was cooled to 0 ^{o}C and allowed to warm slowly to ambient temperature. All starting material diminished on TLC overnight. The reaction was quenched with 1M HCl (1 mL) and diluted with 10 mL of H_2O and 10 mL of CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The crude product was further purified by column chromatography (hexane/ethyl acetate = 70:30) to afford 19.8 mg (94% yield) of desired product as a white solid. $[\alpha]_D^{20}$ -47.1, (c = 0.89, $CHCl_3$), ^{1}H NMR (500MHz, $CDCl_3$) 7.31-7.28 (m, 2H), 7.24-7.22 (m, 3H), 4.63 (br, 1H), 3.73 (s, 3H), 3.28-3.25 (m, 4H), 3.07 (dd, J = 13.5, 3.0 Hz, 1H), 2.85 (dd, J = 13.5, 7.5 Hz, 1H) ppm, ^{13}C NMR (125MHz, CDCl3) 174.2, 137.3, 129.5, 128.3, 126.7, 69.7, 61.4, 41.0, 32.5 ppm. E.e. 97% HPLC (Daicel Chiralpak OD, hexanes/*i*-PrOH = 96:4, flow rate 1.0 mL/min, λ= 220 nm); major isomer: t_R = 23.8 min, minor isomer: t_R = 21.1 min



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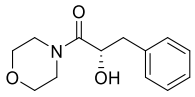
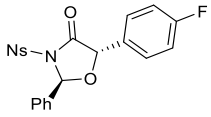
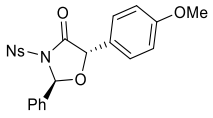


(*S*)-2-Hydroxy-1-morpholino-3-phenylpropan-1-one (71): To a stirred solution of 87.7 mg of oxazolidinone **67** (0.2 mmol, 1.0 equiv) and 12.2 mg of DMAP (0.1 mmol, 0.5 equiv) in 2 mL of THF was added 0.17 mL of morpholine (2.0 mmol, 10.0 equiv) dropwise at ambient temperature. The reaction was stirred at ambient temperature and monitored by TLC. After 24 hours, all the starting material diminished on TLC and the reaction was diluted with 5 mL of DCM and quenched with 5 mL of saturated NH_4Cl aqueous solution. The organic layer was separated and the aqueous layer was extracted with DCM (5 mL X 3). The combined organic layer was dried

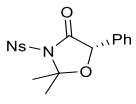
over sodium sulfate and concentrated. The crude product was purified by flash column chromatography (hexane/ethyl acetate = 30:70 – 50:50) to afford 39.8 mg (85% yield) of desired product as a colorless oil. $[\alpha]_D^{20}$ +24.7, (c = 0.81, $CHCl_3$), ^{1}H NMR (500MHz, $CDCl_3$) 7.32-7.29 (m, 2H), 7.25-7.21 (m, 3H), 4.58 (t, J = 6.5Hz, 1H), 3.68-3.51 (m, 5H), 3.31-3.26 (m, 2H), 3.10-3.03 (m, 1H), 2.95 (dd, J = 14.0, 7.0 Hz, 1H), 2.90 (dd, J = 14.0, 6.5 Hz, 1H) ppm; ^{13}C NMR (125MHz, $CDCl_3$) 172.5, 136.4, 129.4, 128.6, 127.0, 68.6, 66.6, 66.0, 45.4, 43.6, 42.4 ppm. E.e. 97% HPLC (Daicel Chiralpak OD, hexanes/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ= 220 nm); major isomer: t_R = 50.4 min, minor isomer: t_R = 62.0 min



(2*R*,5*S*)-5-(4-Fluorophenyl)-3-[(4-nitrophenyl)sulfonyl]-2-phenyloxazolidin-4-one: General Procedure A was followed by employing 4.3 g of *N*-nosyl oxaziridine **±58** (14 mmol, 1.0 equiv), 1.1 g of TMSQn (2.8 mmol, 0.2 equiv), 4.9 mL of *N*,*N*-diisopropylethylamine (28 mmol, 2.0 equiv) and 3.8 mL of 2-(4-fluorophenyl)acetyl chloride (28 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 5% ethyl acetate in hexane) followed by recrystallization in hexane and ethyl acetate to yield 0.71 g (23% yield) *cis*-product as a white solid. $[\alpha]_D^{20}$ -26.1, (c = 1.42, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) 8.19 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 9.0 Hz, 2H), 7.50-7.33 (m, 7H), 7.12 (t, J = 8.4 Hz, 2H), 6.72 (s, 1H), 5.49 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 168.4, 163.3 (d, J = 247 Hz), 150.9, 142.8, 135.7, 130.7, 129.5, 128.9, 128.1, 128.0, 127.5, 123.9, 116.1 (d, J = 21 Hz), 91.3, 78.1 ppm. This compound's characterization data matched the data provided in the following literuature: Guo, B. PhD dissertation, University of Pittsburgh, 2012.

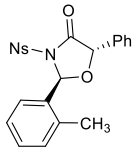


(2S,5*S*)-5-(4-Methoxyphenyl)-3-[(4-nitrophenyl)sulfonyl]-2-phenyloxazolidin-4-one: General Procedure A was followed by employing 2.1 g of *N*-nosyl oxaziridine **±58** (6.9 mmol, 1.0 equiv), 0.5 g of TMSQn (1.37 mmol, 0.2 equiv), 2.4 mL of *N*,*N*-diisopropylethylamine (13.7 mmol, 2.0 equiv) and 2.1 mL of 2-(4-methoxyphenyl)acetyl chloride (13.7 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 5% ethyl acetate in hexane) followed by recrystallization in hexane and ethyl acetate to yield 0.53g (34% yield) *trans*-product as a light yellow solid. $[\alpha]_D^{20}$ 75.4, (c = 0.59, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) 8.17 (d, J = 9.0 Hz, 2H), 7.67 (d, J = 9.0 Hz, 2H), 7.49 (t, J = 3.0 Hz, 1H), 7.38-7.36 (m, 4H), 7.32 (d, J = 8.7 Hz, 2H) 6.90 (d, J = 8.7 Hz, 2H), 6.59 (d, J = 1.2 Hz, 1H), 5.43 (s, 1H), 3.79 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 168.7, 160.3, 150.8, 143.4, 135.5, 130.8, 129.3, 128.6, 128.5, 127.9, 125.3, 124.0, 114.2, 90.6, 78.9, 55.3 ppm. This compound's characterization data matched the data provided in the following literuature: Guo, B. PhD dissertation, University of Pittsburgh, 2012.

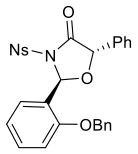


(*S*)-2,2-Dimethyl-3-[(4-nitrophenyl)sulfonyl]-5-phenyloxazolidin-4-one: General Procedure A was followed by employing 258 mg of 3,3-dimethyl-2-[(4-nitrophenyl)sulfonyl]-1,2-oxaziridine (1.0 mmol, 1.0 equiv), 80 mg of TMSQn (0.2 mmol, 0.2 equiv), 0.35 mL of *N*,*N*-diisopropylethylamine (2.0 mmol, 2.0 equiv) and 0.26 mL of phenylacetyl chloride (2.0 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 10% ethyl acetate in hexane) followed by recrystallization in hexane and ethyl acetate to yield 222 mg (59% yield) of desired

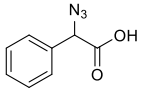
product as a white solid. IR (thin film): 3109, 2980, 1754, 1607, 1534, 1497, 1373, 1087, 856, 739, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 8.38 (d, J = 9.2 Hz, 2H), 8.29 (d, J = 8.8 Hz, 2H), 7.35-7.34 (m, 5H), 5.26 (s, 1H), 1.99 (s, 3H), 1.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 169.3, 151.0, 143.6, 133.9, 130.2, 129.1, 128.7, 126.3, 124.2, 98.4, 28.7, 27.3 ppm; HRMS (ES+) *m/z* calculated for $[M+H]^+$ $C_{17}H_{17}N_2O_6S$: 377.0807; found: 377.0817.



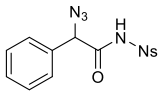
(2*R*,5*S*)-2-[2-(Methyl)phenyl]-3-[(4-nitrophenyl)sulfonyl]-5-phenyloxazolidin-4-one: General Procedure A was followed by employing 1.6 g of 2-[(4-nitrophenyl)sulfonyl]-3-(o-tolyl)-1,2-oxaziridine (5.0 mmol, 1.0 equiv), 0.4 g of TMSQn (1.0 mmol, 0.2 equiv), 1.8 mL of *N*,*N*-diisopropylethylamine (10.0 mmol, 2.0 equiv) and 1.3 mL of phenylacetyl chloride (10.0 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 5% ethyl acetate in hexane) and further recrystallization in hexane and ethyl acetate to yield 0.21 g (19% yield) *cis*-product as a white solid. $[\alpha]_D^{20}$ -29.6, (c = 1.14, $CHCl_3$); IR (thin film): 3106, 3067, 2981, 1759, 1607, 1533, 1495, 1350, 1228, 855, 740, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 8.22 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.8 Hz, 2H), 7.42 (s, 5H), 7.38-7.34 (m, 2H), 7.13-7.06 (m, 2H), 6.98 (s, 1H), 5.41 (s, 1H), 2.46 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 168.9, 150.9, 142.8, 137.6, 133.6, 133.4, 131.5, 130.4, 129.6, 129.4, 129.0, 126.9, 126.2, 126.2, 124.0, 88.8, 78.3, 18.8 ppm; HRMS (ES+) *m/z* calculated for $[M+Na]^+$ $C_{22}H_{18}N_2O_6NaS$: 461.0783; found: 461.0775.



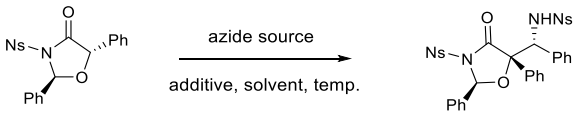
(2*R*,5*S*)-2-[2-(Benzyloxy)phenyl]-3-[(4-nitrophenyl)sulfonyl]-5-phenyloxazolidin-4-one: General Procedure A was followed by employing 6.8 g of 3-(2-[benzyloxy)phenyl]-2-[(4-nitrophenyl)sulfonyl]-1,2-oxaziridine (6.8 mmol, 1.0 equiv), 0.5 g of TMSQn (1.36 mmol, 0.2 equiv), 2.4 mL of *N*,*N*-diisopropylethylamine (13.6 mmol, 2.0 equiv) and 1.8 mL of phenylacetyl chloride (13.6 mmol, 2.0 equiv). The product was purified by a quick flash chromatography (30% ethyl acetate in hexane) followed by recrystallization in ethyl acetate and hexane to yield 0.18 g (10% yield) *cis*-product as a light yellow solid. $[\alpha]_D^{20}$ -17.2, (c = 2.40, $CHCl_3$); IR (thin film): 3110, 3032, 2925, 1708, 1601, 1531, 1496, 1349, 1229, 1088, 854, 740, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.11 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 9.0 Hz, 2H), 7.44-7.30 (m, 11H), 7.23 (s, 1H), 7.05-6.96 (m, 3H), 5.38 (s, 1H), 4.98 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 168.9, 157.6, 150.8, 143.2, 136.1, 133.4, 132.0, 129.6, 128.9, 128.6, 128.6, 128.2, 127.6, 126.4, 123.9, 120.9, 112.7, 78.7, 70.6 ppm; HRMS (ES+) *m/z* calculated for $[M+H]^+$ $C_{28}H_{23}N_2O_7S$: 531.1226; found: 531.1236.



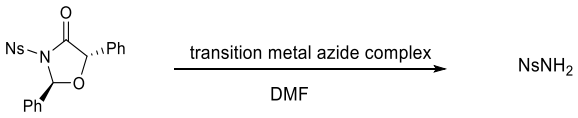
2-Azido-2-phenylacetic acid: 2-Bromo-2-phenylacetic acid (118 mg, 0.55 mmol, 1.0 equiv) and sodium azide (54 mg, 0.83 mmol, 1.5 equiv) were mixed in 2 mL of dry DMF and stirred at room temperature. The reaction was stopped after 24 h by removing the DMF in *vacuo*. The crude product was purified by flash column chromatography (10% MeOH in DCM) to yield 41 mg (42% yield) of 2-azido-2-phenylacetic acid as a white solid. ^1H NMR (300 MHz, $CDCl_3$): 7.42 (app, s, 5H), 5.03 (s, 1H) ppm. 3.90-3.20 (br, 1H) ppm.[71]



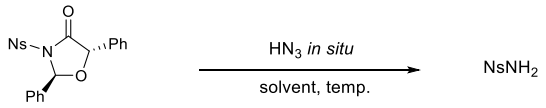
2-Azido-*N*-[(4-nitrophenyl)sulfonyl]-2-phenylacetamide: DMAP (293 mg, 2.4 mmol, 2.4 equiv) was added to a suspension of EDCI·HCl (249 mg, 1.3 mmol, 1.3 equiv) in 2.5 mL of DCM. The mixture was stirred at room temperature until all the solids dissolved and then was cooled to 0 ^{o}C. 2-azido-2-phenylacetic acid (177 mg, 1.0 mmol, 1.0 equiv) was added followed by *p*-$NsNH_2$ (243 mg, 1.2 mmol, 1.2 equiv) and the reaction was stirred at room temp for 20 h. Diethyl ether (5 mL) was added and the organic mixture was washed with 2N HCl (8 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude product was further purified by flash column chromatography (SiO_2, 10% methanol in DCM) to afford 195 mg (54% yield) of 2-azide-*N*-[(4-nitrophenyl)sulfonyl]-2-phenylacetamide as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) 8.88 (br, 1H), 8.36 (d, J = 9.0 Hz, 2H), 8.25 (d, J = 9.0 Hz, 2H), 7.42 (m, 3H), 7.26-7.24 (m, 2H), 5.06 (s, 1H) ppm; HRMS (ES+) *m/z* calculated for $[M+Na]^+$ $C_{17}H_{11}N_5O_5SNa$: 384.0379; found: 384.0383.



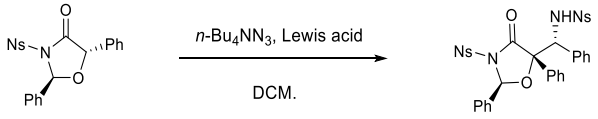
General Procedure B: Direct azide induced ring opening reaction of oxazolindinone: To a solution of azide source compound (1.1 – 5.0 equiv) in solvent was added a solution of oxazolidinone (1.0 equiv) in solvent. The resulting solution was kept stirring at different temperature and monitored by TLC. After all the starting material diminished on TLC, the mixture was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over sodium sulfate and concentrated. The crude mixture was further purified by flash column chromatography.



General Procedure C: Transition metal azide complex induced ring opening reaction of oxazolidinone: To a solution of freshly prepared transition metal azide complex (1.2 equiv) in solvent was added a solution of oxazolidinone (1.0 equiv) in solvent. The resulting solution was kept stirring at different temperature and monitored by TLC. The mixture was quenched with saturated $NaHCO_3$, extracted with EtOAc and the combined organic layer was dried over sodium sulfate and concentrated. The crude mixture was further purified by flash column chromatography.

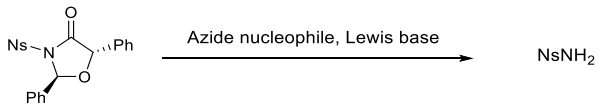


General Procedure D: Hydrazoic acid induced ring opening reaction of oxazolidinone: To a solution of oxazolidinone (1.0 equiv) in dry solvent was added $TMSN_3$ (2.0 equiv) and MeOH. The mixture was warmed up and monitored by TLC. After all the starting material diminished on TLC, the mixture was quenched with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over sodium sulfate and concentrated. The crude product was further purified by flash column chromatography.

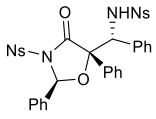


General Procedure E: Lewis acid catalyzed azide induced ring opening reaction of oxazolidinone: To a dry solution of Lewis acid (1.5 equiv) in solvent was added a solution of oxazolidinone (1.0 equiv) followed by tetrabutylammonium azide (1.5 equiv). The mixture was

kept stirring at room temperature and monitored by TLC. After all the starting material diminished on TLC, the mixture was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over sodium sulfate and concentrated. The crude product was further purified by flash column chromatography.

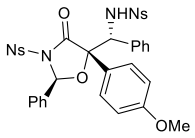


General Procedure F: Lewis base activated azide induced ring opening reaction of oxazolidinone: To a solution of azide nucleophile (1.5 equiv) was added Lewis base (1.5 equiv) and the mixture was kept stirring at room temp for 10min, then a solution of oxazolidinone (1.0 equiv) was added. The mixture was kept stirring at different temperature and monitored by TLC. After all the starting material diminished on TLC, the mixture was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc and the combined organic layer was dried over sodium sulfate and concentrated. The crude product was further purified by flash column chromatography.

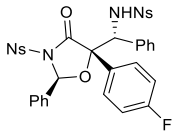


4-Nitro-*N*-({(2*R*)-3-[(4-nitrophenyl)sulfonyl]-4-oxo-2,5-diphenyloxazolidin-5-yl}(phenyl)methyl)benzenesulfonamide (124a): $[\alpha]_D^{20}$ -14.6, (c = 1.50, $CHCl_3$), IR (thin film): 3311, 3108, 2923, 1754, 1532, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.30 (d, J = 9.0 Hz, 2H), 7.94 (t, J = 8.7 Hz, 4H), 7.60 (d, J = 9.0 Hz, 2H), 7.37-7.30 (m, 2H), 7.22-7.18 (m, 4H), 7.04 (t, J = 7.5 Hz, 5H), 6.91 (t, J = 6.9 Hz, 2H), 6.79 (d, J = 7.5 Hz, 2H), 6.38 (s, 1H), 6.18 (d, J = 10.2 Hz, 1H), 4.78 (d, J = 10.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, CDCl3) 168.9, 151.2, 149.6, 145.1,

142.2, 136.0, 135.0, 134.1, 130.4, 129.7, 128.7, 128.5, 128.4, 128.3, 128.1, 128.1, 127.7, 127.5, 125.3, 124.4, 123.7, 91.7, 86.8, 64.6 ppm. HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{34}H_{27}N_4O_{10}S_2$: 715.1163; found: 715.1148.

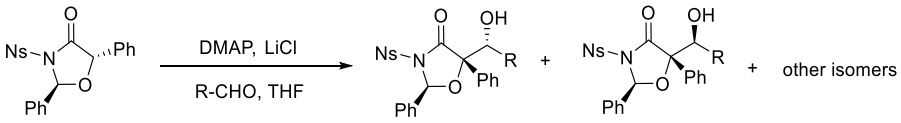


***N*-({(2*S*)-5-(4-Methoxyphenyl)-3-[(4-nitrophenyl)sulfonyl]-4-oxo-2-phenyloxazolidin-5-yl}(phenyl)methyl)-4-nitrobenzenesulfonamide**: $[\alpha]_D^{20}$ -3.0, (c = 1.21, $CHCl_3$), IR (thin film): 3120, 3025, 2932, 1711, 1609, 1535, 1512, 1380, 1250, 1107, 1034, 856, 736, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.27 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 9.0 Hz, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.8 Hz, 2H), 7.12-7.06 (m, 3H), 7.01-6.96 (m, 4H), 6.85 (d, J = 7.5 Hz, 2H), 6.54 (d, J = 9.0 Hz, 2H), 6.27 (s, 1H), 5.85 (d, J = 10.5 Hz, 1H), 4.75 (d, J = 10.5 Hz, 1H), 3.68 (s, 3H) ppm; ^{13}C NMR (125 MHz, CDCl3) 169.1, 159.7, 151.2, 149.6, 145.3, 142.3, 136.0, 134.4, 130.4, 129.7, 128.5, 128.5, 128.3, 128.2, 127.7, 127.6, 127.0, 126.7, 124.4, 123.7, 113.4, 91.7, 86.4, 64.7, 55.1 ppm. HRMS (ES+) *m/z* calculated for $[M+H]^+$ $C_{35}H_{28}N_4O_{11}S_2Na$: 767.1094; found: 767.1119.

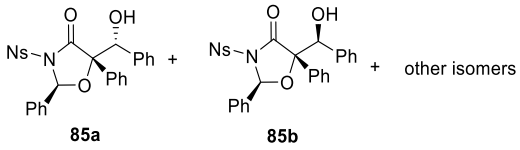


***N*-({(2*R*)-5-(4-Fluorophenyl)-3-[(4-nitrophenyl)sulfonyl]-4-oxo-2-phenyloxazolidin-5-yl}(phenyl)methyl)-4-nitrobenzenesulfonamide (54)**: $[\alpha]_D^{20}$ 6.3, (c = 0.75, $CHCl_3$), IR (thin film): 3308, 3108, 2928, 1606, 1537, 1508, 1351, 855, 837, 738, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 8.32 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 8.0 Hz, 2H), 7.16-7.13 (m, 2H), 7.04-7.00 (m, 3H), 6.90 (t, J = 7.6 Hz, 2H), 6.73-6.69 (m, 4H), 6.48 (s, 1H), 5.85 (d, J = 10.4 Hz,

1H), 4.74 (d, J = 10.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CDCl3) 168.9, 162.7 (d, J = 247 Hz), 151.3, 149.7, 145.0, 142.1, 135.9, 133.8, 130.8 (d, J = 3 Hz), 130.6, 129.8, 128.6, 128.5, 128.3, 128.2, 127.6, 127.4, 127.3, 124.5, 123.8, 115.1 (d, J = 22 Hz), 91.7, 86.6, 64.6 ppm; HRMS (ESI) *m/z* calculated for $[M-H]^-$ $C_{34}H_{24}N_4O_{10}FS_2$: 731.0923; found: 731.0922.

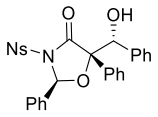


General Procedure G: **Aldol reaction of oxazolidinone:** To a flame dried 2 dram vial was added oxazolidinone (0.1 mmol, 1.0 equiv), DMAP (0.12 mmol, 1.2 equiv) and lithium chloride (0.3 mmol, 3.0 equiv), then 2 mL of solvent was added through a syringe followed by aldehyde (0.2 mmol, 2.0 equiv). The mixture was kept stirring at room temperature and monitored by TLC. After all the starting material diminished on TLC, 10 mL of NH_4Cl solution (aq) was added to quench the reaction and aqueous layer was extracted with EtOAc (10 mL X 3). The combined organic layer was dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography to afford the desired product.

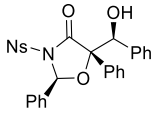


General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 20 µL of benzaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, hexane/ethyl acetate = 85:15) to yield 45.3 mg (85% yield) of product as a mixture of diastereomers. (major isomer/minor isomer/∑ of other isomers =

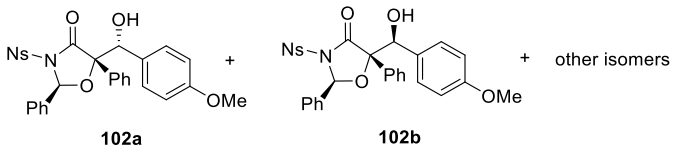
86:6:8). The major isomer and the minor isomer were further separated by column chromatography for characterization.



(2*S*,5*S*)-5-[(*R*)-Hydroxy(phenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (85a): $[\alpha]_D^{20}$ -26.6, (c = 0.95, $CHCl_3$), ^{1}H NMR (500MHz, $CDCl_3$) 8.19 (d, J = 9.0 Hz, 2H), 7.80 (d, J = 9.0 Hz, 2H), 7.45-7.38 (m, 3H), 7.34-7.29 (m, 4H), 7.22-7.14 (m, 4H), 7.10 (t, J = 7.5 Hz, 2H), 7.02 (d, J = 7.5 Hz, 2H), 6.89 (s, 1H), 5.27 (d, J = 3.5 Hz, 1H), 2.31 (d, J = 3.5 Hz, 1H) ppm; ^{13}C NMR (125MHz, CDCl3) 170.7, 150.8, 143.2, 137.0, 136.9, 135.4, 130.4, 129.7, 128.5, 128.4(2C), 128.3, 128.0, 127.8, 127.7, 125.4, 123.9, 92.3, 87.2, 80.9 ppm. HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{28}H_{23}N_2O_7S$: 531.1220; found: 531.1226.

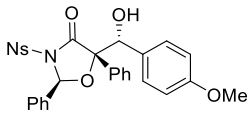


(2*S*,5*S*)-5-[(*S*)-Hydroxy(phenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (85b): $[\alpha]_D^{20}$ -1.2, (c = 0.31, $CHCl_3$), ^{1}H NMR (500MHz, $CDCl_3$) 8.11 (d, J = 9.0 Hz, 2H), 7.66-7.64 (m, 2H), 7.56 (d, J = 9.0 Hz, 2H), 7.48-7.37 (m, 9H), 7.27-7.23 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 7.0 Hz, 2H), 5.92 (s, 1H), 5.20 (d, J = 4.0 Hz, 1H), 2.09 (d, J = 4.0 Hz, 1H) ppm; ^{13}C NMR (125MHz, CDCl3) 168.6, 150.7, 142.8, 136.6, 136.3, 135.6, 130.4, 129.4, 129.0, 128.9, 128.8, 128.5 (2C), 128.1, 127.8, 125.7, 123.9 ppm. HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{28}H_{23}N_2O_7S$: 531.1220; found: 531.1209.

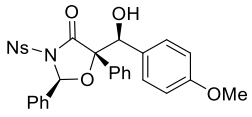


102a 102b

General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 24 µL of *p*-anisaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 38.1 mg (68% yield) of product as a mixture of diastereomers. (major isomer/minor isomer/∑ of other isomers = 73:13:14). The major isomer and the minor isomer were further separated by column chromatography for characterization.

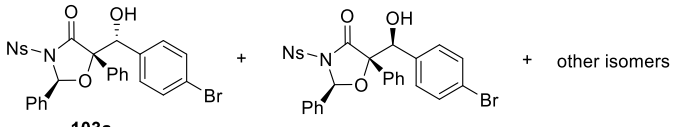


(2*S*,5*S*)-5-[(*R*)-Hydroxy(4-methoxyphenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (102a): $[\alpha]_D^{20}$ -41.5, (c = 0.53, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 8.19 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 9.0 Hz, 2H), 7.40-7.32 (m, 8H), 7.21-7.20 (m, 2H), 6.95 (d, J = 8.5 Hz, 2H), 6.88 (s, 1H), 6.63 (d, J = 8.5 Hz, 2H), 5.22 (d, J = 3.0 Hz, 1H), 3.69 (s, 3H), 2.25 (d, J = 3.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 170.8, 150.8, 143.2, 136.9, 135.5, 130.4, 129.7, 129.2, 129.0, 128.5(2C), 128.4, 128.2, 128.0, 125.3, 123.8, 113.2, 92.3, 87.2, 80.5, 55.1 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ $C_{29}H_{24}N_2O_8NaS$: 583.1146; found: 583.1131.



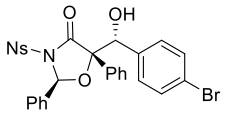
(2*S*,5*S*)-5-[(*S*)-Hydroxy(4-methoxyphenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (102b): $[\alpha]_D^{20}$ -17.8, (c = 0.28, $CHCl_3$), ^{1}H NMR (500 MHz, CD_2Cl_2) 8.14 (d, J = 9.0 Hz, 2H), 7.62 (d, J = 9.0 Hz, 2H), 7.56-7.54 (m, 2H),

7.42 (t, J = 7.0 Hz, 1H), 7.33-7.25 (m, 7H), 7.14 (d, J = 7.5 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 6.08 (s, 1H), 5.09 (s, 1H), 3.83 (s, 3H), 2.18 (br, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 168.7, 160.1, 150.7, 142.8, 136.5, 135.7, 130.4, 129.4, 129.0, 128.8, 128.6, 128.5 (2C), 128.0, 125.7, 123.8, 113.8, 91.3, 87.8, 79.5, 55.4 ppm. HRMS (ESI) *m/z* calculated for $[M-H]^-$ $C_{29}H_{23}N_2O_8S$: 559.1170; found: 559.1190.



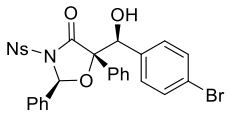
103a 103b

General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 37.0 mg of *p*-bromobenzaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 43.4 mg (71% yield) of product as a mixture of diastereomers. (major isomer/minor isomer/$\sum$ of other isomers = 85:7:8). The major isomer and the minor isomer were further separated by column chromatography for characterization.

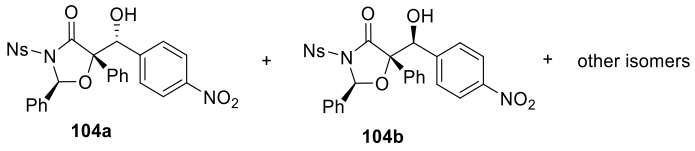


(2*S*,5*S*)-5-[(*R*)-(4-Bromophenyl)(hydroxy)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (103a): $[\alpha]_D^{20}$ -25.2, (c = 0.85, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 8.19 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.45-7.42 (m, 1H), 7.38-7.36 (m, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.31-7.29 (m, 2H), 7.23-7.21 (m, 5H), 6.88 (s, 1H), 6.87 (d, J = 8.0 Hz, 2H), 5.25 (d, J = 4.0 Hz, 1H), 2.48 (d, J = 4.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 170.5, 150.8, 143.1, 136.7, 136.0, 135.1, 130.8, 130.4, 129.6, 129.4, 128.5(2C),

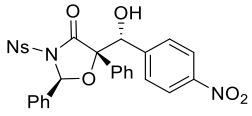
128.3, 128.2, 125.3, 123.9, 122.5, 92.3, 87.0, 80.2 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{28}H_{22}BrN_2O_7S$: 609.0326; found: 609.0299.



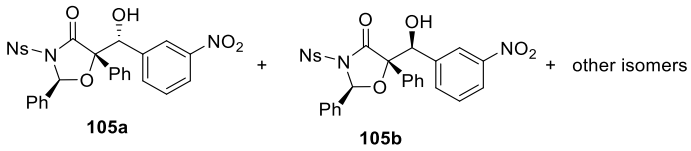
(2*S*,5*S*)-5-[(*S*)-(4-Bromophenyl)(hydroxy)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (103b): $[\alpha]_D^{20}$ -5.3, (c = 0.19, $CHCl_3$), ^1H NMR (500 MHz, acetone-d6) 8.42 (d, J = 9.0 Hz, 2H), 7.97 (d, J = 9.0 Hz, 2H), 7.44-7.42 (m, 3H), 7.35 (t, J = 7.5 Hz, 2H), 7.31-7.24 (m, 7H), 7.02 (d, J = 8.5 Hz, 2H), 6.58 (s, 1H), 5.15 (d, J = 5.0 Hz, 1H), 5.10 (d, J = 5.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 168.5, 150.8, 142.6, 136.3, 135.5, 135.1, 131.4, 130.4, 129.5, 129.0, 128.5, 127.9, 125.7, 123.9, 123.0, 91.4, 87.4, 79.3 ppm; HRMS (ESI) *m/z* calculated for $[M-H]^-$ $C_{28}H_{20}BrN_2O_7S$: 607.0169; found: 607.0167.



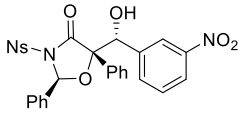
General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 30.2 mg of *p*-nitrobenzaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 48.9 mg (85% yield) of product as a mixture of diastereomers. (major isomer/minor isomer/$\sum$ of other isomers = 84:5:11). The major isomer was further separated by column chromatography for characterization.



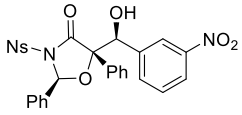
(2*S*,5*S*)-5-[(*R*)-Hydroxy(4-nitrophenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (104a): $[\alpha]_D^{20}$ -37.2, (c = 0.83, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) 8.19 (d, J = 9.0 Hz, 2H), 7.94 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.5 Hz, 2H), 7.47-7.43 (m, 1H), 7.37-7.35 (m, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.29-7.21 (m, 5H), 7.14 (d, J = 8.5 Hz, 2H), 6.92 (s, 1H), 5.41 (d, J = 4.0 Hz, 1H), 2.65 (d, J = 4.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 170.0, 150.9, 147.8, 144.0, 143.0, 136.4, 134.7, 130.6, 129.6, 128.9, 128.6(2C), 128.4, 128.3, 125.3, 123.9, 122.7, 92.4, 87.1, 79.8 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{28}H_{22}N_3O_9S$: 576.1071; found: 576.1050.



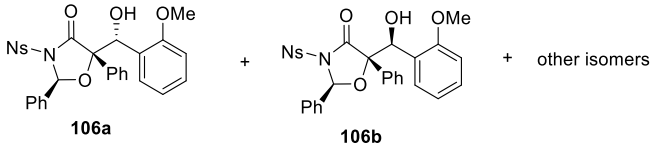
General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 30.2 mg of *m*-nitrobenzaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 52.1 mg (91% yield) of product as a mixture of diastereomers. (major isomer/minor isomer/$\sum$ of other isomers = 83:7:10). The major isomer and the minor isomer were further separated by column chromatography for characterization.



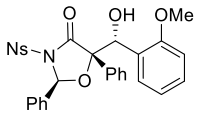
(2*S*,5*S*)-5-[(*R*)-Hydroxy(3-nitrophenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (105a): $[\alpha]_D^{20}$ -29.9, (c = 1.02, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) 8.20 (d, J = 9.0 Hz, 2H), 8.01 (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 7.78 (d, J = 9.0 Hz, 2H), 7.44 (t, J = 7.0 Hz, 1H), 7.36 (d, J = 7.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.36-8-7.23 (m, 5H), 7.16 (d, J = 8.0 Hz, 1H), 6.94 (s, 1H), 5.42 (d, J = 4.0 Hz, 1H), 2.66 (d, J = 4.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 170.1, 150.9, 147.7, 143.0, 139.0, 136.4, 134.7, 133.6, 130.5, 129.6, 128.9, 128.6, 128.4, 128.3, 125.3, 123.9, 123.2, 122.8, 92.4, 87.0, 79.7 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{28}H_{22}N_3O_9S$: 576.1071; found: 576.1046.



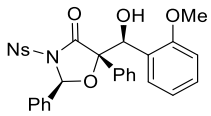
(2*S*,5*S*)-5-[(*S*)-Hydroxy(3-nitrophenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (105b): $[\alpha]_D^{20}$ +5.3, (c = 0.19, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) 8.24 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 8.20 (t, J = 2.0 Hz, 1H), 8.12 (d, J = 9.0 Hz, 2H), 7.66 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.5 Hz, 1H), 7.51 (dd, J = 8.0, 2.0 Hz, 2H), 7.41-7.32 (m, 4H) 7.22 (t, J = 8.0 Hz, 2H), 7.01 (d, J = 7.0 Hz, 2H), 6.13 (s, 1H), 5.27 (d, J = 3.5 Hz, 1H), 2.42 (d, J = 3.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 168.3, 150.9, 148.0, 142.5, 138.5, 135.8, 134.5, 133.9, 130.5, 129.5, 129.2, 129.1, 128.6, 128.5, 127.9, 125.8, 123.9, 123.8, 123.0, 91.4, 87.0, 79.1 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{28}H_{22}N_3O_9S$: 576.1071; found: 576.1076.



General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 27.2 mg of *o*-anisaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 35.8 mg (64% yield) of desired product as a mixture of diastereomers. (major isomer/minor isomer/$\sum$ of other isomers = 83:9:8). The major isomer and the minor isomer were further separated by column chromatography for characterization.

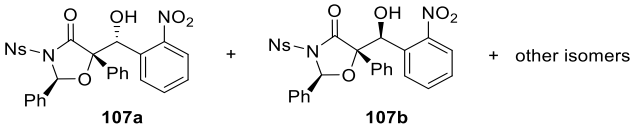


(2*S*,5*S*)-5-[(*R*)-Hydroxy(2-methoxyphenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (106a): $[\alpha]_D^{20}$ -22.0, (c = 0.86, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) 8.20 (d, J = 9.2 Hz, 2H), 7.82 (d, J = 9.2 Hz, 2H), 7.43-7.40 (m, 3H), 7.35-7.28 (m, 3H), 7.33-7.28 (m, 5H), 7.17-7.10 (m, 4H), 6.85 (s, 1H), 6.79 (t, J = 7.2 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 5.73 (d, J = 5.2 Hz, 1H), 3.45 (s, 3H), 2.94 (d, J = 5.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 170.7, 156.6, 150.7, 143.2, 137.0, 135.2, 130.3, 129.6, 129.4, 128.5, 128.3, 128.0, 127.5, 125.6, 125.2, 123.8, 120.2, 110.2, 92.2, 87.6, 75.0, 55.0 ppm; HRMS (ESI) *m/z* calculated for $[M+NH_4]^+$ $C_{29}H_{28}N_3O_8S$: 578.1592; found: 578.1570.



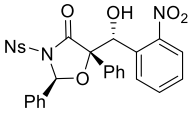
(2*S*,5*S*)-5-[(*S*)-Hydroxy(2-methoxyphenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (106b): $[\alpha]_D^{20}$ -7.0, (c = 0.63, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) 8.05 (d, J = 9.0 Hz, 2H), 7.56-7.54 (m, 2H), 7.50 (d, J = 9.0 Hz, 2H),

7.42-7.35 (m, 8H), 7.11 (dd, J = 8.0, 1.0 Hz, 2H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.25 (s, 1H), 5.53 (d, J = 6.5 Hz, 1H), 3.76 (s, 3H), 3.10 (d, J = 6.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 168.1, 157.2, 150.5, 143.2, 136.4, 136.0, 130.3, 130.0, 129.4, 129.3, 128.4(2C), 128.3, 127.9, 125.9, 124.7, 123.7, 120.6, 110.7, 91.2, 87.6, 76.4, 55.3 ppm; HRMS (ESI) *m/z* calculated for $[M+NH_4]^+$ $C_{29}H_{25}N_2O_8S$: 561.1326; found: 561.1308.



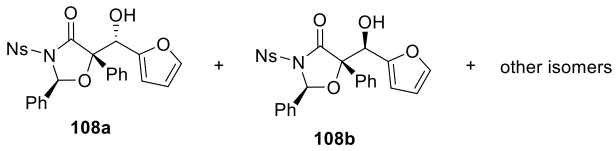
107a **107b**

General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 30.2 mg of *o*-nitrobenzaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 45.1 mg (78% yield) of product as a mixture of diastereomers. (major isomer/minor isomer/$\sum$ of other isomers = 72:8:20). The major isomer was further separated by column chromatography for characterization.



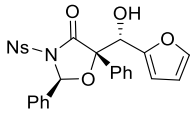
(2*S*,5*S*)-5-[(*R*)-Hydroxy(2-nitrophenyl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (107a): $[\alpha]_D^{20}$ -20.3, (c = 0.83, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 8.20 (d, J = 9.0 Hz, 2H), 7.88 (dd, J = 8.0, 1.0 Hz, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.53-7.48 (m 2H), 7.44 (t, J = 7.0 Hz, 1H), 7.34-7.21 (m, 8H), 7.15 (t, J = 7.5 Hz, 2H), 6.84 (s, 1H), 6.18 (d, J = 5.5 Hz, 1H), 3.16 (d, J = 5.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 169.8, 150.9, 149.1, 142.9, 136.6, 134.1, 132.4, 131.2, 130.9, 130.5, 129.7, 129.1, 128.7, 128.6, 128.3, 128.2, 125.1,

123.9, 92.1, 87.1, 74.2 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{28}H_{22}N_3O_9S$: 576.1071; found: 576.1074.

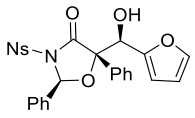


108a **108b**

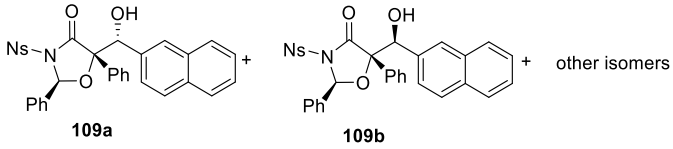
General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 17 µL of 2-furaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 10% ethyl acetate in hexane) to yield 41.7 mg (90% yield) of product as a mixture of diastereomers. (major isomer/minor isomer/$\sum$ of other isomers = 85:8:7). The major isomer and the minor isomer were further separated by column chromatography for characterization.



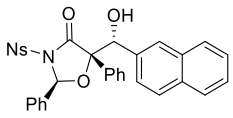
(2*S*,5*S*)-5-[(*R*)-Furan-2-yl(hydroxy)methyl]-3-[(4-nitrophenyl)sulfonyl)]-2,5-diphenyloxazolidin-4-one (108a): $[\alpha]_D^{20}$ -5.8, (c = 0.48, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 8.21 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H), 7.46-7.43 (m, 3H), 7.34 (t, J = 8.0 Hz, 2H), 7.29 (d, J = 7.0 Hz, 2H), 7.25-7.23 (m, 3H), 7.21 (d, J = 1.0 Hz, 1H), 6.82 (s, 1H), 6.15 (dd, J = 3.0, 1.5Hz, 1H), 6.03 (d, J = 3.0 Hz, 1H), 5.3 (s, 1H), 2.6 (br, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 169.9, 150.9, 150.1, 143.0, 142.5, 136.8, 134.9, 130.4, 129.7, 128.6, 128.5, 128.2(2C), 125.2, 123.9, 110.3, 109.3, 92.3, 86.8, 74.5 ppm. HRMS (ESI) *m/z* calculated for $[M+NH_4]^+$ $C_{26}H_{24}N_3O_8S$: 538.1279; found: 538.1292.



(2*S*,5*S*)-5-[(*S*)-Furan-2-yl(hydroxy)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (108b): $[\alpha]_D^{20}$ -1.1, (c = 0.38, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) 8.11 (d, J = 9.0 Hz, 2H), 7.62-7.58 (m, 5H), 7.54 (d, J = 1.0 Hz, 1H), 7.44 (t, J = 1.5 Hz, 2H), 7.36-7.34 (m, 3H), 7.29-7.27 (m, 1H), 7.12 (d, J = 8.0 Hz, 2H), 6.47 (dd, J = 6.0, 1.5 Hz, 1H), 6.45 (d, J = 3.0 Hz, 1H), 6.22 (s, 1H), 5.22 (d, J = 6.5 Hz, 1H), 2.36 (d, J = 6.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 168.0, 150.7, 150.2, 143.0, 142.9, 136.1, 135.2, 130.5, 129.4, 128.8, 128.5(2C), 128.2, 125.5, 123.8, 111.0, 109.5, 91.1, 87.0, 74.2 ppm. HRMS (ESI) *m/z* calculated for $[M+K]^+$ $C_{26}H_{20}N_2O_8KS$: 559.0599; found: 599.0589.

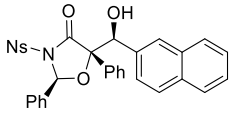


General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 31.2 mg of 2-naphthaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 41.0 mg (71% yield) of desired product as a mixture of diastereomers. (major isomer/minor isomer/$\sum$ of other isomers = 78:8:14). The major isomer and the minor isomer were further separated by column chromatography for characterization.

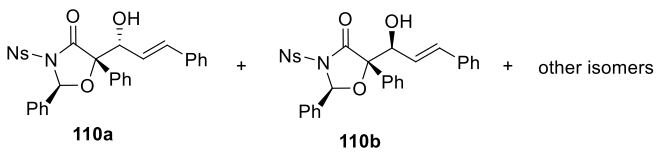


(2S,5*S*)-5-[(*R*)-Hydroxy(naphthalen-2-yl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (109a): $[\alpha]_D^{20}$ -16.3, (c = 0.98, $CHCl_3$), ^1H

NMR (400 MHz, $CDCl_3$) 8.18 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 8.8 Hz, 2H), 7.71-7.69 (m, 1H), 7.65-7.63 (m, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.50 (s, 1H), 7.42-7.38 (m, 5H), 7.32-7.31 (m, 4H), 7.21-7.16 (m, 3H), 7.12 (dd, J = 8.8, 1.6 Hz, 1H), 6.95 (s, 1H), 5.43 (d, J = 4.0 Hz, 1H), 2.49 (d, J = 4.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 170.7, 150.8, 143.1, 136.9, 135.4, 134.6, 133.1, 132.6, 130.4, 129.6, 128.5, 128.4, 128.3, 128.1(2C), 127.5, 127.3, 127.2, 126.3, 126.0, 125.4, 125.3, 123.8, 92.3, 87.3, 80.9 ppm. HRMS (ESI) *m/z* calculated for $[M+NH_4]^+$ $C_{32}H_{28}N_3O_7S$: 598.1642; found: 598.1621.



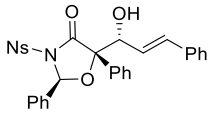
(2*S*,5*S*)-5-[(*S*)-Hydroxy(naphthalen-2-yl)methyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (109b): $[\alpha]_D^{20}$ +10.7, (c = 0.28, $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) 7.83 (d, J = 9.0 Hz, 2H), 7.81 (d, J = 8.5 Hz, 1H), 7.73 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.64-7.62 (m, 3H), 7.54 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.52 (d, J = 9.0 Hz, 2H), 7.48-7.46 (m, 1H), 7.42-7.38 (m, 1H), 7.37-7.35 (m, 3H), 7.29 (t, J = 8.0 Hz, 2H), 7.16 (d, J = 7.0 Hz, 2H), 6.07 (s, 1H), 5.28 (s, 1H), 2.13 (br, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 168.6, 150.5, 142.1, 136.8, 135.7, 134.1, 133.3, 132.6, 130.3, 129.2, 128.9, 128.6, 128.1(2C), 127.7, 127.6, 127.0, 126.5, 125.7, 125.0, 123.5, 91.4, 87.8, 79.9 ppm; HRMS (ESI) *m/z* calculated for $[M-H]^-$ $C_{32}H_{23}N_2O_7S$: 579.1220; found: 579.1214.



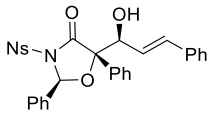
110a **110b**

General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol,

1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 25 μL of cinnamaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 37.5 mg (65% yield) of desired product as a mixture of diastereomers. (major isomer/minor isomer/$\sum$ of other isomers = 82:10:8). The major isomer and the minor isomer were further separated by column chromatography.

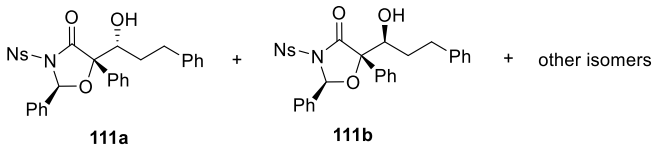


(2*S*,5*S*)-5-[(*R*,*E*)-1-Hydroxy-3-phenylallyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (110a): $[\alpha]_D^{20}$ -32.7, (c = 1.42, $CHCl_3$), ^{1}H NMR (500MHz, $CDCl_3$) 8.20 (d, J = 9.0 Hz, 2H), 7.84 (d, J = 9.0 Hz, 2H), 7.54 (dd, J = 8.0, 2.0 Hz, 2H), 7.46-7.44 (m, 1H), 7.36-7.28 (m, 7H), 7.21-7.16 (m, 5H), 6.85 (s, 1H), 6.38 (d, J = 15.5 Hz, 1H), 6.02 (dd, J = 15.5, 6.0 Hz, 1H), 4.88 (dd, J = 6.0, 3.5 Hz, 1H), 2.32 (d, J = 3.5 Hz, 1H) ppm; ^{13}C NMR (125MHz, $CDCl_3$) 170.5, 150.8, 143.1, 136.9, 135.6, 135.2, 134.6, 130.4, 129.7, 128.6, 128.5, 128.4, 128.2, 128.1, 126.6, 125.2, 124.3, 123.9, 92.3, 87.3, 79.5 ppm. HRMS (ESI) *m/z* calculated for $[M+NH_4]^+$ $C_{30}H_{28}N_3O_7S$: 574.1642; found: 574.1675.



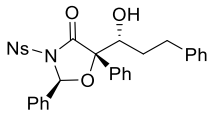
(2*S*,5*S*)-5-[(*S*,*E*)-1-Hydroxy-3-phenylallyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (110b): $[\alpha]_D^{20}$ -2.2, (c = 0.28, $CHCl_3$), ^{1}H NMR (500MHz, $CDCl_3$) 8.04 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.57-7.56 (m, 2H), 7.42-7.41 (m, 2H), 7.33-7.30 (m, 9H), 7.20 (d, J = 7.0 Hz, 2H), 6.69 (s, 1H), 6.62 (d, J = 16.0 Hz, 1H), 6.31 (dd, J = 16.0, 7.0 Hz, 1H), 4.69 (dd, J = 7.0, 4.0 Hz, 1H), 1.98 (d, J = 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.9, 150.8, 142.8, 136.7, 135.7, 135.3, 135.1, 130.4, 129.6, 128.8, 128.7, 128.6, 128.4, 127.9,

126.7, 125.7, 123.9(2C), 91.8, 87.3, 79.6 ppm. HRMS (ESI) *m/z* calculated for $[M+NH_4]^+$ $C_{30}H_{28}N_3O_7S$: 574.1642; found: 574.1672.



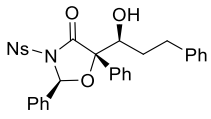
111a **111b**

General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 26 µL of hydrocinnamaldehyde (0.20 mmol, 2.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 37.5 mg (69% yield) of desired product as a mixture of diastereomers. (major isomer/minor isomer/∑ of other isomers = 48:31:21). The major isomer and the minor isomer were further separated by column chromatography for characterization.

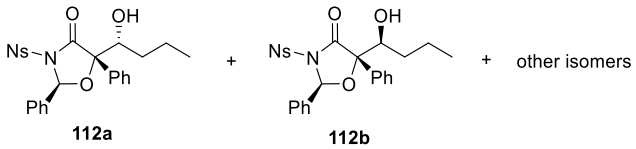


(2*S*,5*S*)-5-[(*R*)-1-Hydroxy-3-phenylpropyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (111a): $[\alpha]_D^{20}$ -33.3, (c = 0.21, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 8.19 (d, J = 9.0 Hz, 2H), 7.78 (d, J = 9.0 Hz, 2H), 7.45-7.42 (m, 2H), 7.36 (t, J = 8.0 Hz, 2H), 7.30-7.28 (m, 5H), 7.22-7.19 (m, 3H), 7.18-7.15 (m, 1H), 6.98 (d, J = 7.0 Hz, 2H), 6.78 (s, 1H), 4.20 (ddd, J = 10.0, 5.5, 2.0 Hz, 1H), 2.71 (ddd, J = 14.0, 9.5, 5.5 Hz, 1H), 2.48 (dt, J = 14.0, 8.0 Hz, 1H), 2.02 (d, J = 6.0 Hz, 1H), 1.84-1.77 (m, 1H), 1.44-1.38 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 171.0, 150.8, 143.0, 140.7, 136.8, 135.3, 130.4, 129.6, 128.6, 128.5, 128.4(2C), 128.2(2C),

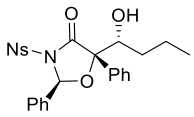
126.1, 125.1, 123.9, 92.0, 88.2, 77.7, 31.7, 31.0 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{30}H_7N_2O_7S$: 559.1534; found: 559.1473.



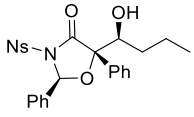
(2*S*,5*S*)-5-[(*S*)-1-Hydroxy-3-phenylpropyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (111b): $[\alpha]_D^{20}$ -2.1, (c = 0.64., $CHCl_3$), ^1H NMR (500 MHz, $CDCl_3$) 8.14 (d, J = 9.0 Hz, 2H), 7.76 (d, J = 9.0 Hz, 2H), 7.48-7.47 (m, 2H), 7.39 (t, J = 7.0 Hz, 1H), 7.29-7.27 (m, 5H), 7.24-7.21 (m, 3H), 7.10-7.08 (m, 4H), 6.67 (s, 1H), 3.99 (ddd, J = 10.5, 5.0, 2.0Hz, 1H), 2.86 (ddd, J = 14.0, 9.0, 5.0 Hz, 1H), 2.58 (ddd, J = 14.0, 9.0, 7.0 Hz, 1H), 1.94 (d, J = 4.5 Hz, 1H), 1.93-1.88 (m, 1H), 1.70-1.64 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 169.2, 150.9, 142.7, 141.0, 136.4, 135.4, 130.3, 129.6, 128.7, 128.5, 128.4, 127.8, 126.2, 125.6, 123.9, 91.5, 87.0, 77.6, 32.2, 32.0 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{30}H_7N_2O_7S$: 559.1534; found: 559.1482.



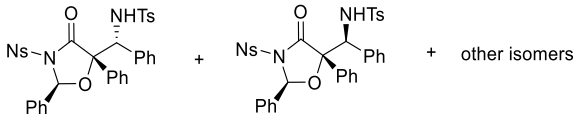
General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 80 µL of butyraldehyde (1.0 mmol, 10.0 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 38.2 mg (85% yield) of desired product as a mixture of diastereomers. (major isomer/minor isomer/$\sum$ of other isomers = 51:34:15). The major isomer and the minor isomer were further separated by column chromatography.



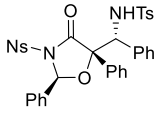
(2*S*,5*S*)-5-[(*R*)-1-Hydroxybutyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (112a): $[\alpha]_D^{20}$ -17.9, (c = 0.83, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 8.24 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H), 7.53-7.49 (m, 3H), 7.38 (t, J = 8.0 Hz, 2H), 7.34-7.33 (m, 5H), 6.79 (s, 1H), 4.23 (ddd, J = 10.5, 6.0, 2.5 Hz, 1H), 2.01 (d, J = 6.0 Hz, 1H), 0.98-0.94 (m, 4H), 0.79 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 171.2, 150.8, 143.1, 137.0, 135.5, 130.4, 129.7, 129.0, 128.6, 128.4, 128.1, 125.1, 123.9, 92.1, 88.1, 78.0, 31.6, 18.6, 13.6 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{25}H_{25}N_2O_7S$: 497.1382; found: 497.1352.



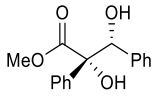
(2*S*,5*S*)-5-[(*S*)-1-Hydroxybutyl]-3-[(4-nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (112b): $[\alpha]_D^{20}$ -6.9, (c = 0.41, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 8.18 (d, J = 9.0 Hz, 2H), 7.73 (d, J = 9.0 Hz, 2H), 7.53-7.51 (m, 2H), 7.39 (t, J = 8.5 Hz, 1H), 7.30-7.23 (m, 5H), 7.09 (dd, J = 8.0, 1.0 Hz, 2H), 6.72 (s, 1H), 4.00 (ddd, J = 10.5, 5.0, 2.0 Hz, 1H), 1.86 (d, J = 5.0 Hz, 1H), 1.68-1.59 (m, 2H), 1.37-1.28 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 169.3, 150.9, 142.8, 136.4, 135.8, 130.3, 129.6, 128.6, 128.5, 128.3, 128.0, 125.7, 123.9, 91.5, 87.2, 78.2, 32.7, 19.2, 13.8 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{25}H_{25}N_2O_7S$: 497.1382; found: 497.1352.



General Procedure G was followed by employing 42.4 mg of oxazolidinone **83** (0.10 mmol, 1.0 equiv), 14.7 mg of DMAP (0.12 mmol, 1.2 equiv), 12.7 mg of LiCl (0.30 mmol, 3.0 equiv) and 28.5 mg of (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (0.11 mmol, 1.1 equiv). The product was purified by flash chromatography (SiO_2, 15% ethyl acetate in hexane) to yield 53.1 mg (78% yield) of product as a mixture of diastereomers. (major isomer/minor isomer/∑ of other isomers = 48:31:21). The major isomer was further separated by column chromatography for characterization.

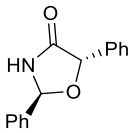


4-Methyl-*N*-((*R*)-{(2*S*,5*S*)-3-[(4-nitrophenyl)sulfonyl]-4-oxo-2,5-diphenyloxazolidin-5-yl}(phenyl)methyl)benzenesulfonamide (123a): $[\alpha]_D^{20}$ +12.6, (c = 0.70, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 8.37 (d, J = 9.0 Hz, 2H), 8.08 (d, J = 9.0 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.26-7.15 (m, 7H), 7.09 (t, J = 6.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 2H), 6.95 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 2H), 6.83 (t, J = 7.5 Hz, 2H), 6.66 (d, J = 7.5 Hz, 2H), 6.48 (s, 1H), 5.35 (d, J = 10.5 Hz, 1H), 4.69 (d, J = 10.5 Hz, 1H), 2.22 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 169.1, 151.3, 143.2, 142.3, 136.7, 136.3, 135.2, 134.6, 130.3, 130.0, 129.1, 128.6, 128.4, 127.9, 127.8, 127.7, 127.6, 127.5, 127.0, 125.4, 124.5, 91.9, 87.2, 64.4, 21.3 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{35}H_{30}N_3O_8S_2$: 684.1469; found: 684.1476.

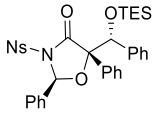


Methyl (2*S*,3*R*)-2,3-dihydroxy-2,3-diphenylpropanoate (86): To a -20 °C solution of oxazolidinone **85a** (35.6 mg, 0.067 mmol) in 2 mL of MeOH was added 3.1 µL of MeONa in

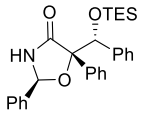
MeOH solution (25% w/w, 0.0134 mmol, 0.2 equiv) and the resulting mixture was kept stirring at this temperature for 24 hours. Then another 3.1 µL of MeONa in MeOH solution (25% w/w, 0.0134 mmol, 0.2 equiv) was added again to this solution and the mixture was kept stirring at this temperature for another 24 hours. The reaction was quenched with 20 µL of saturated NH_4Cl solution and the mixture was run through a plug of celite and concentrated. The product was purified by flash chromatography (SiO_2, 20% ethyl acetate in hexane) to yield 6.2 mg (34% yield) of product as a white solid. $[\alpha]_D^{20}$ -11.9, (c = 0.67, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) 7.49-7.47 (m, 2H), 7.23-7.21 (m, 3H), 7.15-7.09 (m, 5H), 5.42 (d, J = 8.1Hz, 1H), 3.98 (s, 1H), 3.92 (s, 3H), 2.86 (d, J = 8.1Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 174.6, 138.0, 137.8, 128.1, 128.0, 127.8(2), 127.6, 125.8, 82.0, 78.2, 53.8 ppm.[23]



(2*S*,5*S*)-2,5-Diphenyloxazolidin-4-one (125): To a solution of oxazolidinone **83** (246 mg, 0.58 mmol) in 4 mL of DMF was added potassium carbonate (241 mg, 1.74 mmol), followed by 77 µL of thiophenol (0.75 mmol) via a syringe. The resulting mixture was stirred at room temperature for 2 hours. The reaction was quenched by adding 10 mL of saturated $NaHCO_3$ solution and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated. The crude product was further purified by flash column chromatography (neutral alumina, 20% EtOAc in hexane) to afford the title product (103 mg, 74% yield) as a white solid. $[\alpha]_D^{20}$ 66.3, (c = 1.14, $CHCl_3$), ^{1}H NMR (500MHz, $CDCl_3$) 7.48-7.35 (m, 10H), 7.28 (br, 1H), 6.32 (d, J = 2.0 Hz, 1H), 5.43 (d, J = 2.0 Hz, 1H) ppm; ^{13}C NMR (125MHz, CDCl3) 173.2, 138.3, 136.0, 130.0, 129.0, 128.8, 128.7, 126.5, 126.3, 87.7, 78.4 ppm.

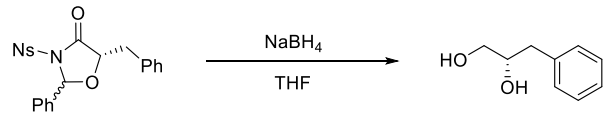


(2*S*,5*S*)-3-[(4-Nitrophenyl)sulfonyl]-2,5-diphenyl-5-{(*R*)-phenyl[(triethylsilyl)oxy]methyl}oxazolidin-4-one (126): To a -60 ^{o}C solution of oxazolidinone **83** (25.0 mg, 0.047 mmol) in 2 mL of DCM was added 27 µL of 2,6-lutidine (0.235 mmol, 5.0 equiv.) followed by 17 µL of TESOTf (0.094 mmol, 2.0 euqiv.) through a syringe. The resulting solution was kept stirring at this temp for 3 hours. The reaction mixture was quenched with saturated Na_2CO_3 solution. The mixture was extracted with EtOAc and the combined organic layer was washed with saturated NH_4Cl solution and dried over sodium sulfate. The crude product was further purified by column chromatography (SiO_2, 10% EtOAc in hexane) to afford 28.9 mg of desired product (0.045 mmol, 95% yield) as a white solid. $[\alpha]_D^{20}$ -18.7, (c = 1.13, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 8.05 (d, J = 9.0 Hz, 2H), 7.51 (d, J = 9.0 Hz, 2H), 7.41-7.38 (m, 3H), 7.27-7.26 (m, 2H), 7.21-7.18 (m, 5H), 7.12-7.09 (m, 1H), 7.04 (t, J = 7.5 Hz, 2H), 6.96 (d, J = 7.5 Hz, 2H), 6.88 (s, 1H), 5.27 (s, 1H), 0.95 (t, J = 8.0 Hz, 9H), 0.66-0.57 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 170.2, 150.5, 143.8, 137.5, 136.4, 135.8, 130.3, 129.0, 128.8, 128.3, 128.1(2C), 127.9(2C), 127.1, 125.5, 123.8, 92.1, 88.2, 81.8, 6.8, 4.6 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{34}H_{37}N_2O_7SSi$: 645.2085; found: 645.2085.

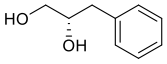


(2*S*,5*S*)-2,5-Diphenyl-5-{(*R*)-phenyl[(triethylsilyl)oxy]methyl}oxazolidin-4-one (127): To a solution of **126** (22.9 mg, 0.036 mmol) in 2 mL of MeOH was added 20 µL of MeONa solution in MeOH (25% w/w, 2.5 equiv.) via a syringe. The mixture was kept stirring at room temperature and monitored by TLC. All starting material diminished on TLC after 1 hour. Saturated NH_4Cl solution was added to quench the reaction. The reaction was extracted with

EtOAc and the combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography to afford 12.6 mg of unprotected product (0.027 mmol, 76% yield) as a white solid. $[\alpha]_D^{20}$ -45.5, (c = 0.11, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) 7.50-7.48 (m, 2H), 7.42-7.36 (m, 5H), 7.19-7.18 (m, 3H), 7.08-7.03 (m, 5H), 6.46 (s, 1H), 6.13 (s, 1H), 5.27 (s, 1H), 0.93-0.89 (m, 9H), 0.59-0.55 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 173.7, 138.7, 138.5, 137.5, 129.9, 128.6, 128.2, 127.6, 127.4(2C), 127.0, 125.5, 88.2, 87.4, 80.9, 6.7, 4.8 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{28}H_{34}NO_3Si$: 460.2302; found: 460.2315.

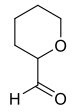


67 129

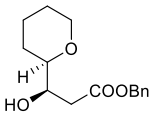


(*S*)-3-Phenylpropane-1,2-diol (129): To a stirred solution of oxazolidinone **67** (87.7 mg, 0.2 mmol, 1.0 equiv) in 2mL of THF was added 15.1 mg of $NaBH_4$ (0.4 mmol, 2.0 equiv) at ambient temperature. The reaction was stirred at ambient temperature and monitored by TLC. All the starting material diminished on TLC after 1 hour. The reaction was quenched with 1M HCl solution. The mixture was concentrated and purified by column chromatography (SiO_2, 60% EtOAc in Hexane) to yield 28.2 mg (93% yield) of the title compound as white solid. $[\alpha]_D^{20}$ -27.2, (c = 1.17, $CHCl_3$), ^{1}H NMR (300 MHz, CDCl3) 7.32-7.30 (m, 2H), 7.24-7.21 (m, 3H), 3.95-3.93 (m, 1H), 3.69 (dd, J = 11.1, 2.7 Hz, 1H), 3.52 (dd, J = 11.1, 6.9 Hz, 1H), 2.79-2.75 (m, 2H), 2.21 (br, 1H), 1.68 (br, 1H) ppm; ^{13}C NMR (100MHz, CDCl3) 137.6, 129.3, 128.7, 126.7, 73.0, 66.1, 39.8 ppm. E.e. 97% HPLC (Daicel Chiralpak OD, hexanes/*i*-PrOH = 97:3, flow rate 1.0 mL/min, λ= 220 nm); major isomer: t_R = 38.4 min, minor isomer: t_R = 35.6 min.

4.0 EXPERIMENTAL FOR MARINEOSIN A SYNTHESIS

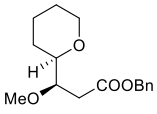


Tetrahydro-2*H*-pyran-2-carbaldehyde (199): To a -78 ^{o}C solution of oxalyl chloride (7.3 mL, 86.0 mmol) in 100 mL of DCM, DMSO (12.2 mL, 172.0 mmol) in 20 mL of DCM was added dropwise through a syringe pump. The mixture was kept stirring for 20 min at -78 ^{o}C and then a solution of tetrahydropyran-2-methanol (5.0 g, 43.0 mmol) in 30 mL of DCM was added dropwise. The mixture was kept stirring at this temperature for 30 min and then triethylamine (24.0 ml, 172 mmol) was slowly added. The reaction was warmed up to room temperature, stirred for 1 h and water was added. When the mixture became clear, it was extracted with DCM. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was run a quick column (SiO_2, 10% ethyl acetate in hexane) and used directly in next step without further purification.



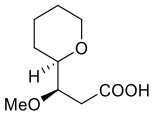
***syn*-Benzyl 3-hydroxy-3-(tetrahydro-2*H*-pyran-2-yl)propanoate (201)**: To the solution of freshly prepared tetrahydro-2*H*-pyran-2-carbaldehyde (43.0 mmol) and magnesium bromide ethyl etherate (12.2 g, 47.3 mmol) in 100 mL of DCM at -78 ^{o}C, {[1-(benzyloxy)vinyl]oxy}trimethylsilane (15.0 mL, 64.5 mmol) was added slowly via a syringe pump over 30 min. The reaction mixture was kept stirring at this temperature after 1 h, then warmed up

to 40 ^{o}C and kept stirring for 3 h. The mixture was quenched with buffer solution (pH=7) and the aqueous layer was extracted with DCM (100 mL x 3). The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by column chromatography (SiO_2, 20% ethyl acetate in hexane) to afford 5.2 g (19.7 mmol, 46% yield in two steps) of the product as yellow liquid. IR (thin film): 3461, 3045, 2939, 2853, 1733, 1089, 745, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.37-7.32 (m, 5H), 5.16 (s, 2H), 4.00 (dt, J = 11.0, 2.0 Hz, 1H), 3.94 (dt, J1 = 12.5 Hz, J2 = 5.0 Hz, 1H), 3.41 (td, J = 11.5, 2.5 Hz, 1H), 3.22 (ddd, J = 10.5, 5.0, 2.0 Hz, 1H), 2.59 (dd, J = 15.5, 7.5 Hz, 1H), 2.56 (dd, J = 15.0, 5.0 Hz, 1H), 1.86-1.85 (m, 1H), 1.55-1.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 171.9, 135.8, 128.5, 128.2, 128.1, 79.4, 70.8, 68.5, 66.4, 38.1, 27.2, 25.8, 23.0 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ $C_{16}H_{17}NO_3Na$: 287.1259; found: 287.1268.

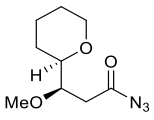


***syn*-Benzyl 3-methoxy-3-(tetrahydro-2*H*-pyran-2-yl)propanoate (202)**: To a solution of *syn*-benzyl 3-hydroxy-3-(tetrahydro-2*H*-pyran-2-yl)propanoate **201** (33 mg, 0.12 mmol) in 4 mL of DCM at room temperature was added proton sponge (160 mg, 0.75 mmol) followed by trimethyloxonium tetrafluoroborate (110 mg, 0.75 mmol). The reaction mixture was kept stirring at room temperature and monitored by TLC. The reaction mixture was quenched with saturated ammonium chloride solution and separated. The aqueous layer was extracted with DCM (10 mL x 3). The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by column chromatography (SiO_2, 5% ethyl acetate in hexane) to afford 32 mg (0.11 mmol, 92% yield) of product as yellow oil. IR (thin film): 2937, 1737, 1099, 742, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.35-7.33 (m, 5H), 5.16 (d, J = 12.3 Hz,

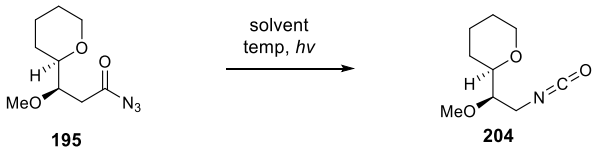
1H), 5.13 (d, J = 12.3 Hz, 1H), 3.99 (dt, J = 7.2, 1.8 Hz, 1H), 3.65 (dt, J = 7.2, 4.5 Hz, 1H), 3.41-3.34 (m, 5H), 2.66 (dd, J = 15.9, 5.1 Hz, 1H), 2.56 (dd, J = 15.9, 7.5 Hz, 1H), 1.87-1.85 (m, 1H), 1.60-1.41 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 171.8, 136.0, 128.5, 128.2, 128.1, 79.7, 78.3, 68.8, 66.2, 58.7, 35.6, 26.6, 26.0, 23.2 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ $C_{16}H_{17}NO_3Na$: 301.1416; found: 301.1427.



***syn*-3-Methoxy-3-(tetrahydro-2*H*-pyran-2-yl)propanoic acid (203)**: Lithium hydroxide monohydrate (9 mg, 0.22 mmol) was suspended in H_2O/MeOH/THF solution (0.4 mL/0.4 mL/1.2 mL) and *syn*-benzyl 3-methoxy-3-(tetrahydro-2*H*-pyran-2-yl)propanoate (31 mg, 0.11 mmol) was added to the solution. The resulting solution was then stirred overnight at room temp. After removal the solvent under *vacuo*, the residue was then taken up in 10 mL of 1 M HCl and extracted with chloroform. The aqueous layer was extracted with chloroform (10 mL x 3). The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by column chromatography (SiO_2, 30% ethyl acetate in hexane) to afford 19 mg (0.10 mmol, 89% yield) of the desired product as yellowish liquid. IR (thin film): 3225, 2936, 1735, 1096 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 10.96 (br, 1H), 4.03 (dt, J = 11.5, 2.0 Hz, 1H), 3.62 (dt, J = 7.5, 4.5 Hz, 1H), 3.45 (s, 3H), 3.44-3.40 (m, 2H), 2.71 (dd, J = 16.5, 10.0 Hz, 1H), 2.57 (dd, J = 16.0, 7.0 Hz, 1H), 1.89-1.88 (m, 1H), 1.57-1.45 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 176.6, 79.3, 78.4, 68.9, 58.8, 35.5, 26.6, 25.9, 23.1 ppm; HRMS (ES+) *m/z* calculated for $[M-OH]^+$ $C_9H_{15}O_3$: 171.1021; found: 171.1022.

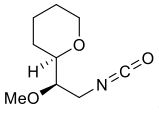


***syn*-3-Methoxy-3-(tetrahydro-2*H*-pyran-2-yl)propanoyl azide (195)**: Oxalyl chloride (128 μL, 1.50 mmol) was added to a stirred solution of *syn*-3-methoxy-3-(tetrahydro-2*H*-pyran-2-yl)propanoic acid **203** (95 mg, 0.50 mmol) and 5 μL of DMF in 5 ml of DCM in an ice bath. After a period of 1.5 h the solution was concentrated to oil and dissolved in a mixture of 4 mL of acetone and 1 mL of water and sodium azide was added. After stirring for 2 h, another 10 mL of water and ethyl acetate was added. The layers were separated and the aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue was further purified by column chromatography (SiO_2, 10% ethyl acetate in hexane) to afford 63 mg (0.30 mmol, 59% yield) of the desired product as light yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) 10.96 (br, 1H), 4.01 (dt, J = 11.2, 2.0 Hz, 1H), 3.65 (ddd, J = 8.4, 4.4, 4.0 Hz, 1H), 3.45 (s, 3H), 3.44-3.40 (m, 2H), 2.64 (dd, J = 16.0, 10.0 Hz, 1H), 2.54 (dd, J = 16.0, 8.0 Hz, 1H), 1.89-1.88 (m, 1H), 1.57-1.45 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 176.6, 79.3, 78.4, 68.9, 58.8, 35.5, 26.6, 25.9, 23.1 ppm.

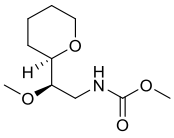


195 **204**

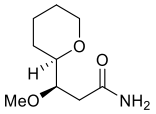
General Procedure H: Direct nitrene insertion of 195: To a 2 dram vial *syn*-3-methoxy-3-(tetrahydro-2H-pyran-2-yl)propanoyl azide **195** was added under nitrogen, then solvent was added through a syringe. The mixture was kept stirring at different temperature under nitrogen. After all the starting material diminished on TLC, the solvent was removed on rotary evaporator and the product was confirmed directly through crude ^{1}H NMR and ^{13}C NMR.



***syn*-2-(2-Isocyanato-1-methoxyethyl)tetrahydro-2H-pyran (204):** ^{1}H NMR (300 MHz, $CDCl_3$) 4.00 (dt, J = 11.1, 1.8 Hz, 1H), 3.51 (s, 3H), 3.45-3.36 (m, 4H), 3.21 (dt, J = 9.0, 4.5 Hz, 1H), 1.89-1.86 (m, 1H), 1.50-1.47 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 124.6, 82.5, 68.9, 59.3, 42.7, 26.9, 25.9, 23.2 ppm.

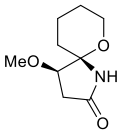


***syn*-Methyl [2-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)ethyl]carbamate (206)**: To a solution of isocyanate **204** in 2 mL of solvent, 2 mL of methanol was added and the mixture was kept stirring overnight. The solvent was removed through the rotary evaporator to provide the *syn*-methyl [2-methoxy-2-(tetrahydro-2*H*-pyran-2-yl)ethyl]carbamate as a colorless oil. IR (thin film): 3342, 2938, 1727, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 5.18 (br, 1H), 4.02 (dt, J = 11.4, 2.1 Hz, 1H), 3.66 (s, 3H), 3.56-3.51 (m, 1H), 3.44 (s, 3H), 3.42-3.36 (m, 2H), 3.28-316 (m, 2H), 1.89-1.86 (m, 1H), 1.61-1.46 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 157.2, 81.3, 78.9, 68.9, 58.8, 52.0, 40.8, 27.2, 25.9, 23.2 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_4H_{20}NO_4$: 218.1392; found: 218.1390.



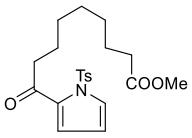
***syn*-3-Methoxy-3-(tetrahydro-2*H*-pyran-2-yl)propanamide (207)**: Oxalyl chloride (60 μL, 0.70 mmol, 1.2 equiv) was added to a stirred solution of *syn*-3-methoxy-3-(tetrahydro-2*H*-pyran-2-yl) propanoic acid **203** (110 mg, 0.58 mmol, 1.0 equiv) and 1 drop of DMF in 5 mL of DCM in ice bath. The reaction mixture was removed from ice-bath after 15 min and allowed to warm to room temperature. After stirring for 2 h, ammonia gas was induced for 5 min,

then 5 mL of H_2O was added and the layers were separated. The aqueous layer was extracted with DCM (10 mL x 3), washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (SiO_2, 40% ethyl acetate in hexane) to afford 77 mg (0.41 mmol, 71% yield) of the desired product as white solid. IR (thin film): 3397, 3210, 2937, 2851, 1681, 1097, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.03 (br, 1H), 5.27 (br, 1H), 4.04-4.01 (m, 1H), 3.54 (dt, J = 6.8, 4.8 Hz, 1H), 3.47 (s, 3H), 3.45-3.39 (m, 2H), 2.54 (dd, J = 14.8, 5.2 Hz, 1H), 2.45 (dd, J = 14.8, 6.8 Hz, 1H), 1.88-1.87 (m, 1H), 1.56-1.48 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) 173.8, 80.3, 78.6, 68.8, 58.8, 37.0, 27.0, 25.8, 23.1 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_9H_{18}NO_3$: 188.1287; found: 188.1269.



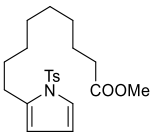
***anti*-4-Methoxy-6-oxa-1-azaspiro[4.5]decan-2-one (197)**: A solution of 87 mg of 3-methoxy-3-(tetrahydro-2H-pyran-2-yl)propanamide (0.47 mmol, 1.0 equiv) in 8 mL of acetonitrile containing 381.0 mg of (diacetoxyiodo)benzene (1.19 mmol, 2.5 equiv) and 119 mg of iodine (0.47 mmol, 1.0 equiv) was stirred under light at room temp and the reaction was monitored by TLC. 24 h later, the reaction mixture was poured into 20 mL of sodium thiosulfate solution and extracted with DCM. The organic layer was combined, washed with brine, dried over sodium sulfate and concentrated. The crude product was further purified by flash column chromatography (hexane/ethyl acetate = 1:1 to 1:2) to afford 46 mg of desired product as a colorless oil. ^1H NMR (400MHz, $CDCl_3$) 6.48 (br, 1H), 3.76-3.65 (m, 3H), 3.36 (s, 3H), 2.70 (dd, J = 17.2, 5.6 Hz, 1H), 2.31 (dd, J = 17.2, 1.2 Hz, 1H), 1.89-1.78 (m, 3H), 1.60-1.58 (m, 3H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 176.3, 91.3, 82.1, 62.8, 57.3, 35.4, 29.3, 25.1, 19.8 ppm. [51]

1-Tosyl-1*H*-pyrrole (213): A mixture of 10.0 mL of pyrrole (144 mmol, 1.0 equiv), 100 mL of DCM, 4.89 g of *n*-Bu_4NHSO_4 (14.4 mmol, 0.1 equiv) and 50 mL of NaOH solution (50% w/w) was made in a 500-mL round bottom flask. The stirred mixture was cooled in ice bath and 41.2g of TsCl (216 mmol, 1.5 equiv) was added. The mixture was kept stirring at room temp for 20 hours. The inorganic precipitate was collected on celite pad by vacuum filtration. The celite pad was washed by DCM till all the product was removed from celite pad. The solution was diluted with 50 mL of water and separated. The aqueous layer was extracted with DCM and the combined organic layer was washed with water and brine, dried over sodium sulfate and concentrated. Hexane was added to form the crystal. The crude crystals were filtered and further recrystallized from MeOH to afford 20.7 g desired product (93 mmol, 65% yield) as a white solid ^{1}H NMR (300MHz, $CDCl_3$) 7.74 (d, J = 8.4Hz, 2H), 7.28 (d, J = 8.4Hz, 2H), 7.15 (t, J = 2.1Hz, 2H), 6.28 (t, J = 2.1 Hz, 2H), 2.40 (s, 3H) ppm; ^{13}C NMR (125MHz, $CDCl_3$) 144.9, 136.2, 130.0, 126.8, 120.7, 113.5, 21.6 ppm.

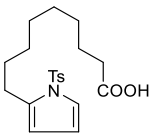


Methyl 9-oxo-9-(1-tosyl-1*H*-pyrrol-2-yl)nonanoate (215): To a solution of 0.69 g of 1-tosyl-1*H*-pyrrole (3.12 mmol, 1.0 equiv) in 20 mL of DCE were added 1.85 g of 9-methoxy-9-oxononanoic acid (85% w/w, 7.8 mmol, 2.5 equiv) and 1.76 mL of trifluoroacetic anhydride (12.47 mmol, 4.0 equiv). The resulting mixture was stirred at 40 ^{o}C overnight. Water was added until there is no bubbling observed. The mixture was washed successively with water, $NaHCO_3$ (aq) and brine. The organic layer was dried over sodium sulfate and concentrated. The crude

product was further purified by a quick flash column chromatography (hexane/ethyl acetate = 9:1) and used in next step directly.

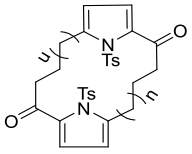


Methyl 9-(1-tosyl-1*H*-pyrrol-2-yl)nonanoate (216): A mixture of 52.2 mg of borane-*tert*-butylamine complex (0.60 mmol, 2.3 equiv) and 48.0 mg of $AlCl_3$ (0.36 mmol, 1.4 equiv) in 10 mL of dry DCM was stirred at room temp for 30 mins before cooled to 0 ^oC. A solution of freshly prepared **215** in 5 mL of DCM was added dropwise. After addition, the resulting solution was stirred for further 10 mins and then quenched with 5 mL of ice water. HCl (1 M, 10 mL) was added to help separating the two layers. The aqueous layer was extracted with DCM (10 mL X 3). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, hexane/ethyl acetate = 9:1) to afford 56.4 mg of product (0.144 mmol, 56% yield in two steps) as a white solid. ^1H NMR (400MHz, $CDCl_3$) 7.63 (d, J = 8.4 Hz, 2H), 7.29-7.26 (m, 3H), 6.19 (t, J = 3.2 Hz, 1H), 5.97 (d, J = 1.2 Hz, 1H), 3.67 (s, 3H), 2.63 (t, J = 7.6 Hz, 2H), 2.40 (s, 3H), 2.30 (t, J = 7.6 Hz, 2H), 1.62-1.50 (m, 4H), 1.30-1.26 (m, 10H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 174.3, 144.6, 136.6, 135.9, 129.9, 126.7, 122.2, 111.7, 111.2, 51.4, 34.1, 29.2 (2C), 29.1 (2C), 28.6, 27.1, 24.9, 21.6 ppm.



9-(1-Tosyl-1*H*-pyrrol-2-yl)nonanoic acid (217): Lithium hydroxide monohydrate (13.8 mg, 0.33 mmol, 3.0 equiv) was suspended in H_2O/MeOH/THF (1 mL/1 mL/3 mL) and 43.0 mg of methyl ester **216** (0.11 mmol, 1.0 equiv) was added to the solution. The resulting solution was then stirred overnight at ambient temperature overnight. After removal the solvent under

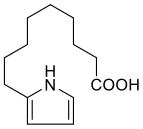
vacuo, the residue was then taken up in 10 mL of 1 M HCl and extracted with chloroform (10 mL x 3). The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude residue was further purified by column chromatography (SiO_2, 40% ethyl acetate in hexane) to afford 37.1 mg of the desired product (0.098 mmol, 89% yield) as a white solid. IR (thin film): 3146, 2927, 2858, 1719, 1597, 1459, 813 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) 7.63 (d, J = 8.4 Hz, 2H), 7.29-7.26 (m, 3H), 6.19 (t, J = 3.2 Hz, 1H), 5.97 (d, J = 1.6 Hz, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.40 (s, 3H), 2.35 (t, J = 7.6 Hz, 2H), 1.64-1.51 (m, 4H), 1.30-1.27 (m, 10H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 178.4, 144.6, 136.6, 135.9, 129.9, 126.7, 122.2, 111.7, 111.2, 33.7, 29.2, 29.1(2C), 29.0, 28.6, 27.1, 24.6, 21.6 ppm. HRMS (ESI) *m/z* calculated for $[M-H]^-$ $C_9H_{18}NO_3$: 376.1577; found: 376.1581.



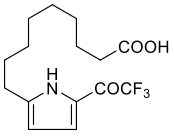
1^1,6^1-Ditosyl-1^1*H*,6^1*H*-1,6(2,5)-dipyrrolacycloicosaphane-2,7-dione (218):

To a solution of 76.3 mg of acid **217** (0.20 mmol) in 50 mL of DCE at room temperature was added 52 µL of oxalyl chloride (0.60 mmol) and the mixture was kept stirring at room temperature for 0.5 h. The resulting solution was added to a 200 mL of DCE solution containing 13.4 mg of aluminum chloride (0.1 mmol) at 40 ^oC via a syringe pump over 4 hours. After the addition was completed, the mixture was further kept stirring at 40 ^oC for 0.5 h. 20 mL of water was added to quench the aluminum chloride. The two layers were separated and the aqueous layer was extracted with DCE (20 mL X 3). The combined organic layer was concentrated to ~40 mL, dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 10% ethyl acetate in hexane) to afford 21.1 mg of macrocyclization

product (0.029 mmol, 29% yield) as a white solid. ^{1}H NMR (300MHz, $CDCl_3$) 7.68 (d, J = 8.4 Hz, 4H), 7.31 (d, J = 8.4 Hz, 4H), 7.27 (d, J = 3.3 Hz, 2H), 6.54 (d, J = 3.3 Hz, 2H), 3.07-3.02 (m, 2H), 2.82-2.74 (m, 2H), 2.69-2.63 (m, 4H), 2.42 (s, 6H), 1.64-1.53 (m, 4H), 1.28-1.20 (m, 20H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 197.9, 145.5, 140.7, 136.0, 130.2, 127.0, 125.0, 121.0, 111.3, 41.2, 30.0, 28.9(2C), 28.8, 28.6, 25.5, 24.1, 21.6 ppm; HRMS (ES+) *m/z* calculated for $[M+H]^+$ $C_{40}H_{51}N_2O_6S_2$: 719.3189; found: 719.3173.

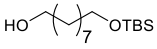


9-(1*H*-Pyrrol-2-yl)nonanoic acid (219): To a stirred solution of 124 mg of 9-(1-Tosyl-1*H*-pyrrol-2-yl)nonanoic acid **217** (0.33 mmol) in 10 mL of MeOH was added 2 mL of 5 N NaOH solution. The mixture was kept stirring under reflux for 48 hours. The solution was acidified with 10 mL of 1 N HCl and extracted with chloroform. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 2% MeOH in DCM) to afford 40.3 mg of desired product (0.18 mmol, 55% yield) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) 10.03 (br, 1H), 7.90 (br, 1H), 6.66 (dd, J = 4.0, 2.4 Hz, 1H), 6.13 (dd, J = 5.6, 2.4 Hz, 1H) 5.91 (s, 1H), 2.59 (t, J = 8.0 Hz, 2H), 2.35 (t, J = 7.6 Hz, 2H), 1.65-1.60 (m, 4H), 1.35-1.26 (m, 10H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 176.6, 132.8, 116.0, 108.3, 104.9, 33.8, 29.6, 29.2 (2C), 29.1, 29.0, 27.7, 24.6 ppm.

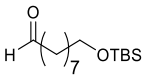


9-[5-(2,2,2-Trifluoroacetyl)-1H-pyrrol-2-yl]nonanoic acid (220): To a solution of 8.6 mg of 9-(1*H*-Pyrrol-2-yl)nonanoic acid **219** (0.038 mmol) in 150 mL of DCE was added 55 µL of trifluoroacetic anhydride (0.038 mmol). The resulting mixture was stirred at 60 ^{o}C for 24

hours. Water (10 mL) was added to the mixture. The organic layer was separated and concentrated to ~50 mL. The mixture was washed successively with water, $NaHCO_3$(aq) and brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 2% MeOH in DCM) to afford 11.1 mg of product (0.035 mmol, 91% yield) as a white solid. ^{1}H NMR (300MHz, d_4-MeOD) 7.10 (dd, J = 3.9, 1.8 Hz, 1H), 6.16 (d, J = 3.9 Hz, 1H), 2.68 (t, J = 7.5 Hz, 2H), 2.27 (t, J = 7.2 Hz, 2H), 1.70-1.57 (m, 4H), 1.42-1.31 (m, 8H) ppm; ^{13}C NMR (125MHz, d_4-MeOD) 177.7, 169.4 (q, J = 35 Hz), 148.6, 126.0, 123.8 (q, J = 3.75 Hz), 118.9 (q, J = 287.5 Hz), 111.8, 34.9, 30.3 (2C), 30.2 (2C), 28.6, 26.0 ppm.

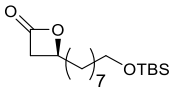


9-[(*tert*-Butyldimethylsilyl)oxy]nonan-1-ol: A solution of 15.8 g of nonane-1,9-diol (99 mmol, 1.0 equiv)) in 200 mL of THF was treated with 13.4 g of imidazole (198 mmol, 2.0 equiv) and 14.9 g of *tert*-butyldimethylsilyl chloride (99 mmol, 1.0 equiv). The resulting mixture was stirred at ambient temperature overnight, then quenched with 100 mL of saturated $NaHCO_3$ solution and extracted with Et_2O (100mL X 3). The combined organic layer was dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, EtOAc/hexane = 15: 85) to afford 17.6 g of mono-protected product (54 mmol, 54% yield) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) 3.64 (t, J = 6.8 Hz, 2H), 3.59 (t, J = 6.8 Hz, 2H), 1.58-1.49 (m, 4H), 1.30-1.26 (m, 10H), 0.89 (s, 9H), 0.04 (s, 6H) ppm.



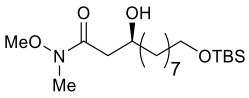
9-[(*tert*-Butyldimethylsilyl)oxy]nonanal (233): A round bottom flask was charged with 0.90 g of pyridinium chlorochromate (4.2 mmol, 1.5 equiv), 0.90 g of Celite (1:1 mass ratio to pyridinium chlorochromate) and 20 mL of DCM. Mono TBS-protected alcohol (0.76

g, 2.8 mmol, 1.0 equiv) was added to the stirred suspension at room temperature. All the starting material diminished on TLC after 2 hours. The solution was filtered through a pad of Celite and the pad of Celite was washed by DCM thoroughly. The combined solution was concentrated and the crude product was further purified by column chromatography (SiO_2, ethyl acetate/hexane = 5: 95) to afford 0.56 g of desired product (2.04 mmol, 73% yield) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) 9.76 (t, J = 2.0 Hz, 1H), 3.59 (t, J = 6.4 Hz, 2H), 2.42 (td, J = 7.6, 2.0 Hz, 2H), 1.64-1.61 (m, 2H), 1.52-1.48 (m, 2H), 1.32-1.30 (m, 10H), 0.89 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 202.9, 63.3, 43.9, 32.8, 29.3, 29.2, 29.1, 26.0, 25.7, 22.1, 18.4, -5.3 ppm.

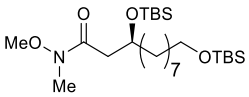


(*S*)-4-{8-[(*tert*-Butyldimethylsilyl)oxy]octyl}oxetan-2-one (234): To a stirred solution of 0.96 g of TMSQn (2.42 mmol, 0.1 equiv.) and 2.58 g of lithium perchlorate (24.2 mmol, 1.0 equiv) in 30 mL of diethyl ehter was added 30 mL of DCM and the resulting solution was cooled to -78 ^{o}C. To the cooled solution was added 10.5 mL of diisopropylethylamine (60.5 mmol, 2.5 equiv.) and a solution of 6.6 g of aldehyde **233** (24.2 mmol, 1.0 equiv.) in 10 mL of DCM. A solution of 3.6 mL of acetyl bromide (48.4 mmol, 2.0 equiv.) in 10 mL of DCM was added through a syringe pump over 1 hour and the mixture was kept stirring overnight at -78 ^{o}C. The mixture was quenched at -78 ^{o}C by adding 100 mL of diethyl ether. The resulting mixture was filtered through a pad of SiO_2 eluting with diethyl ether. The solution was concentrated and the crude product was further purified by column chromatography (SiO_2, 5% ethyl acetate in hexane) to afford 5.5 g of desired product (17.6 mmol, 73% yield) as a white solid. ^{1}H NMR (400MHz, $CDCl_3$) 4.53-4.47 (m, 1H), 3.60 (t, J = 6.4 Hz, 2H), 3.50 (dd, J = 16.4, 5.6 Hz, 1H), 3.05 (dd, J = 16.4, 4.4 Hz, 1H), 1.89-1.82 (m, 1H), 1.78-1.70 (m, 1H), 1.53-1.30 (m, 12H), 0.91 (s, 9H), 0.03 (s, 6H) ppm; ^{13}C

NMR (100MHz, $CDCl_3$) 168.3, 71.3, 63.2, 42.9, 34.7, 32.8, 29.4, 29.2, 29.1, 26.0, 25.7, 24.9, 18.4, -5.3 ppm. HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{17}H_{35}O_3Si$: 315.2350; found: 315.2368.

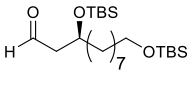


(*S*)-11-[(*tert*-Butyldimethylsilyl)oxy]-3-hydroxy-*N*-methoxy-*N*-methylundecanamide (235): To a 3 mL of DCM solution of 53.7 mg of N, O-dimethylhydroxylamine hydrochloride (0.56 mmol, 2.0 equiv) was added 0.56 mL of dimethylaluminum chloride solution (1.0 M in hexanes, 0.56 mmol, 2.0 equiv). The resulting solution was cooled to -40 °C and a 1 mL of DCM solution of 86.0 mg of β-lactone **234** (0.28 mmol, 1.0 equiv) was added. The reaction was kept stirring at -40 °C overnight. Saturated Rochelle salt solution (5 mL) and water (5 mL) was added and the reaction was warmed up to ambient temperature and stirred for extra 2 hours. The layers were separated and the aqueous layer was extracted with DCM (10 mL x 3). The combined organic layer was dried over sodium sulfate and concentrated. The crude product was used in next step without further purification.

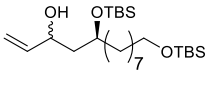


(*S*)-3,12-Bis[(*tert*-butyldimethylsilyl)oxy]-*N*-methoxy-*N*-methyldodecanamide (236): To a -60 °C solution of Weinreb amide **235** (0.28 mmol) from last step in 10 mL of DCM was added 48 µL of 2,6-lutidine (0.42 mmol, 1.5 equiv) followed by 97 µL of TBSOTf (0.42 mmol, 1.5 equiv). The resulting solution was kept stirring at -60 °C for 3 hours. Saturated $NaHCO_3$ (10 mL) was added and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was washed with 1M $NaHSO_4$ solution, dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 5% ethyl acetate in hexane) to afford 101 mg of desired product (74% yield in two steps) as a colorless oil.

^{1}H NMR (300MHz, CDCl3) 4.22 (td, J = 11.1, 5.7 Hz, 1H), 3.69 (s, 3H), 3.59 (t, J = 6.6 Hz, 2H), 3.17 (s, 3H), 2.71 (dd, J = 14.4, 6.9 Hz, 1H), 2.38 (dd, J = 14.7, 5.4 Hz, 1H), 1.52-1.46 (m, 4H), 1.37-1.28 (m, 10H), 0.89 (s, 9H), 0.86 (s, 9H), 0.06-0.03 (m, 12H) ppm; ^{13}C NMR (125MHz, $CDCl_3$) 172.6, 69.5, 63.3, 61.3, 39.6, 37.9,, 32.9, 31.9, 29.7, 29.6, 29.4, 26.0, 25.9, 25.8, 25.1, 18.4, 18.0, -4.6, -4.7, -5.3 ppm. HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{25}H_{56}NO_4Si_2$: 490.3742; found: 490.3740.

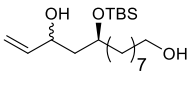


(*S*)-3,11-Bis[(*tert*-butyldimethylsilyl)oxy]undecanal (237): To a -78 ^{o}C solution of 101 mg of Weinreb amide **236** (0.21 mmol, 1.0 equiv) in 10 mL of dry DCM was added 0.25 mL of DIBAL solution (0.25 mmol, 1.0 M in hexanes, 1.2 equiv) dropwise. The resulting solution was kept stirring at -78 ^{o}C for 3 hours. Methanol (0.3 mL) was added and the mixture was warmed up to room temperature. The solution was filtered through a pad of celite and concentrated. The crude product was further purified by column chromatography (SiO_2, 10% ethyl acetate in hexane) to afford 60 mg of product (0.14 mmol, 67% yield) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) 9.81 (t, J = 2.4 Hz, 1H), 4.17(t, J = 6.0 Hz, 1H), 3.59 (t, J = 6.4 Hz, 2H), 2.51 (dd, J = 5.6, 2.4 Hz, 2H), 1.52-1.49 (m, 4H), 1.31-1.27 (m, 10H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07-0.05 (m, 12H) ppm.

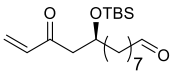


(5*S*)-5,13-Bis[(*tert*-butyldimethylsilyl)oxy]tridec-1-en-3-ol: To a stirred solution of 60 mg of aldehyde **237** (0.14 mmol, 1.0 equiv) in 10 mL of dry THF was added 0.28 mL of vinylmagnesium bromide (1.0 M in THF solution, 0.28 mmol, 2.0 equiv) slowly. The solution was stirred at this temperature for 1.5 h. The reaction was quenched by slow addition of 0.1 mL of acetic acid followed by 10 mL of aqueous NH_4Cl solution. The mixture was warmed to

room temperature and the organic phase was separated. The aqueous phase was extracted with Et_2O and the combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was used in next step without further purification.

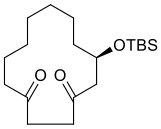


(9*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]tridec-12-ene-1,11-diol (238): To a solution of allyl alcohol from last step in 5 mL of MeOH was added 105.6 mg of pyridinium p-toluenesulfonate (0.42 mmol, 3.0 equiv). The reaction was stirred at room temperature overnight and then saturated $NaHCO_3$ was added to quench this reaction. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic extracts were dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 20% ethyl acetate in hexane) to afford 31.8 mg of product (66% yield in two steps, mixture of *cis:trans* isomers) as a light yellow oil. ^{1}H NMR *mixture of cis:trans isomers* (~3:2) ($CDCl_3$, 400MHz) 5.80-5.72 (m, 1H), 5.19-5.13 (m, 1H), 5.00-4.96 (m, 1H), 4.33 (br, 0.6H) 4.17 (br, 0.4H), 3.87-3.82 (m, 1H), 3.54 (t, J = 6.4 Hz, 2H), 3.19 (br, 0.4H), 3.08 (br, 0.6H), 1.57-1.40 (m, 4H), 1.28-1.12 (m, 12H), 0.80-0.78 (m, 9H), 0.02- -0.05(m, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100MHz) 141.3, 140.9, 114.0, 113.8, 72.8, 72.2, 71.2, 69.6, 63.1, 43.0, 38.0, 32.8, 29.7, 29.6, 29.5(2C), 29.3, 25.8, 25.7, 25.5, 24.6, 18.0, -4.0, -4.7 ppm.



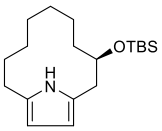
(*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-11-oxotridec-12-enal (239): DMP (148 mg, 0.35 mmol, 3.0 equiv) was added to a solution of 40 mg of alcohol **238** (0.12 mmol, 1.0 equiv) in 5 mL of DCM. The reaction was kept stirring at room temperature and monitored by TLC. All the starting diminished on TLC after 2 hours. Saturated $NaHCO_3$ (2 mL) and $Na_2S_2O_3$ (2 mL) was

added to this mixture. After all solids were dissolved, the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography. (SiO_2, 15% ethyl acetate in hexane) to afford 25.4 mg of product (64 % yield) as a light yellow oil. The purified product was used in next step immediately after purification due to the intrinsic polymerization characteristic of the unhindered enone. ^{1}H NMR (400MHz, $CDCl_3$) 9.76 (t, J = 1.6 Hz, 1H) 6.36 (dd, J = 17.6, 10.4 Hz, 1H), 6.21 (dd, J = 17.6, 1.2 Hz, 1H), 5.84 (dd, J = 10.8, 1.2 Hz, 1H), 4.22-4.16 (m, 1H), 2.80 (dd, J = 14.8, 6.8 Hz, 1H), 2.58 (dd, J = 14.8, 5.2 Hz, 1H), 2.42 (td, J = 7.2, 2.0 Hz, 2H), 1.64-1.61 (m, 2H), 1.48-1.43 (m, 2H), 1.31-1.26 (m, 8H), 0.83 (s, 9H), 0.08 (s, 3H), -0.01 (s, 3H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 202.9, 199.9, 137.5, 128.5, 69.2, 47.0, 43.9, 37.8, 29.4, 29.3, 29.1, 25.8, 25.0, 22.0, 18.0, -4.6, -4.7 ppm.

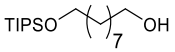


(*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]cyclotridecane-1,4-dione (240): To a solution of 42.8 mg of catalyst **242** (0.115 mmol, 1.5 equiv) and 35 µL of DBU (0.231 mmol, 3.0 equiv) in 50 mL of toluene at 100 ^{o}C was added a solution of 25.4 mg of freshly prepared enone **239** (0.077 mmol, 1.0 equiv) in 24 mL of toluene dropwise through a syringe pump over 8 hours. The resulting mixture was stirred at this temperature for another 16 hours then cooled to room temperature. The resulting mixture was concentrated and directly loaded on a silica gel column and purified (10% ethyl acetate in hexane) to afford 9.2 mg of product (35% yield) as a light yellow oil. ^{1}H NMR (300MHz, $CDCl_3$) 4.13-4.06 (m, 1H), 2.84-2.73 (m, 2H), 2.63 (dd, J = 15.3, 9.3 Hz, 1H), 2.55-2.42 (m, 4H), 2.32-2.28 (m, 1H), 1.59-1.53 (m, 2H), 1.40-1.02 (m, 10H), 0.80 (s, 9H), 0.01 (s, 6H) ppm; ^{13}C NMR (125MHz, $CDCl_3$) 209.5, 208.0, 67.6, 51.8, 41.9, 37.8,36.6, 34.5, 26.2, 26.1, 25.6,

25.1, 21.8, 21.5, 18.2, -4.5(2C) ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{19}H_{37}O_3Si$: 341.2506; found: 341.2470.

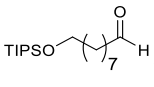


(*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-11*H*-1(2,5)-pyrrolacyclodecaphane (243): To a solution of 8.0 mg of macrocyclic 1,4-diketone **240** (0.024 mmol, 1.0 equiv) in 2 mL of MeOH in a microwave vial was added 92 mg of NH_4OAc (1.2 mmol, 5.0 equiv) and the vial was sealed and heated in a microwave reactor at 120 ^oC for 30 mins. The solution was cooled to room temperature, quenched with water and extracted with DCM. The combined organic layer was washed with saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 5% EtOAc in hexane) to afford 5.6 mg of desired product (0.017 mmol, 70% yield) as a light red oil. ^1H NMR (500 MHz, $CDCl_3$) 8.23 (br, 1H), 5.79 (t, J = 2.5 Hz, 1H), 5.76 (t, J = 2.5 Hz, 1H), 4.00-3.96 (m, 1H), 2.82 (dd, J = 14.5, 3.5 Hz, 1H), 2.73 (dd, J = 14.5, 8.0 Hz, 1H), 2.70-2.62 (m, 1H), 2.50 (ddd, J = 14.5, 10.5, 4.0 Hz, 1H), 1.53-1.49 (m, 6H), 1.33-1.14 (m, 4H), 1.01-0.98 (m, 2H), 0.94 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) 130.8, 128.8, 107.1, 106.2, 72.1, 36.4, 36.0, 27.2, 26.0(2C), 24.7, 22.9, 22.3, 18.1, 17.7, -4.7, -4.8 ppm. HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{19}H_{36}NOSi$: 322.2561; found: 322.2564.

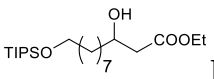


9-[(Triisopropylsilyl)oxy]nonan-1-ol: To a solution of 2.0 g of nonane-1,9-diol (12.5 mmol, 1.0 equiv.) in 20 mL of DCM and 2 mL of DMF were added 1.3 g of imidazole (18.7 mmol, 1.5 equiv.) followed by 2.7 mL of TIPSCl (13.8 mmol, 1.1 equiv.). The mixture was kept stirring at room temp overnight and quenched by adding 20 mL of brine. The organic phase was

separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over magnesium sulfate. The solvent was evaporated and the crude product was further purified by column chromatography (SiO_2, 20% ethyl acetate in hexane) to afford 1.93 g of product (6.2 mmol, 49% yield) as a light yellow liquid. ^{1}H NMR (300MHz, $CDCl_3$) 3.68-3.62 (m, 4H), 1.59-1.51 (m, 4H), 1.38-1.31 (m, 10H), 1.19 (t, J = 5.4 Hz, 1H), 1.10-0.98 (m, 21H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 63.2, 63.1, 33.0, 32.8, 29.6, 29.4, 29.3, 25.8, 25.7, 18.0, 12.2 ppm.

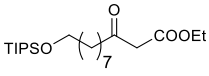


9-[(Triisopropylsilyl)oxy]nonanal (244): To a solution of 4.5 g of alcohol from last step (14.2 mmol, 1.0 equiv) in 100 mL of DCM was added 7.8 g of DMP (18.4 mmol, 1.3 equiv.). The resulting mixture was stirred at room temperature for 1.5 h. Saturated $NaHCO_3$ (20 mL) and saturated $Na_2S_2O_3$ solutions (20 mL) were added to this mixture. After all the solids were dissolved, the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude mixture was further purified by column chromarography (SiO2, 5% ethyl acetate in hexane) to afford 4.0 g of product (12.7 mmol, 90% yield) as a light yellow oil. ^{1}H NMR (300MHz, $CDCl_3$) 9.76 (t, J = 1.8 Hz, 1H), 3.67 (t, J = 6.3 Hz, 2H), 2.42 (td, J = 7.2, 1.8 Hz, 2H), 1.65-1.60 (m, 2H), 1.54-1.51 (m, 2H), 1.36-1.31 (m, 10H), 1.07-1.05 (m, 21H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 202.9, 63.4, 43.9, 33.0, 29.3, 29.2, 29.1, 25.7, 22.1, 18.0, 12.0 ppm.

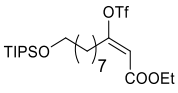


Ethyl 3-hydroxy-11-[(triisopropylsilyl)oxy]undecanoate: To a suspension of 203 mg of zinc dust (3.1 mmol, 1,6 equiv.) in 30 mL of diethyl ether was added 292 µL of TMSCl and the mixture was kept stirring at room temperature for 15 min. Aldehyde **244** (600 mg, 1.9

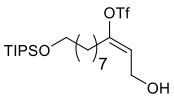
mmol, 1.0 equiv) and ethyl bromoacetate (384 mg, 2.3 mmol, 1.2 mmol) were added to this suspension. The mixture was kept stirring at reflux for 3 hours. A solution of 2 M HCl (2 mL) was added to this mixture and the solution was kept stirring for 20 mins. The layers were separated and the aqueous layer was extracted with ethyl ether. The combined organic layer was washed with $NaHCO_3$ solution, brine, dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 5% ethyl acetate in hexane) to afford 494 mg of desired alcohol (1.24 mmol, 65% yield) as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) 4.17 (q, J = 7.2 Hz, 2H), 3.99 (br, 1H), 3.65 (t, J = 6.8 Hz, 2H), 2.92 (d, J = 4.0Hz, 1H), 2.50 (dd, J = 16.4, 3.2 Hz, 1H), 2.39 (dd, J = 16.4, 8.8 Hz, 1H), 1.53-1.50 (m, 2H), 1.44-1.43 (m, 2H), 1.30-1.26 (m, 13H), 1.07 (d, J = 6.0 Hz, 18H) ppm; ^{13}C NMR(100MHz, $CDCl_3$) 173.2, 68.0, 63.5, 60.7, 41.3, 36.5, 33.0, 29.5 (2C), 29.4, 25.8, 25.5, 18.0, 14.2, 12.0 ppm.



Ethyl 3-oxo-11-[(triisopropylsilyl)oxy]undecanoate (190): To a solution of 329 mg of alcohol from last step (0.82 mmol, 1.0 mmol) in 10 mL of DCM was added 451 mg of DMP (1.06 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature for 1 h. Saturated $NaHCO_3$ (5 mL) and saturated $Na_2S_2O_3$ solutions (5 mL) were added to this mixture. After all the solids were dissolved, the mixture was extracted with DCM. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude mixture was further purified by column chromatography (SiO_2, 5% ethyl acetate in hexane) to afford 314 mg of desired product (0.78 mmol, 95% yield) as alight yellow oil. ^{1}H NMR (300MHz, $CDCl_3$) 4.20 (q, J = 7.2 Hz, 2H), 3.66 (t, J = 6.6 Hz, 2H), 3.42 (s, 2H), 2.53 (t, J = 7.2 Hz, 2H), 1.61-1.50 (m, 4H), 1.30-1.26 (m, 12H), 1.09-1.01 (m, 22H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 203.0, 167.3, 63.4, 61.3, 49.3, 43.0, 33.0, 29.3, 29.3, 29.0, 25.8, 23.4, 18.0, 14.1, 12.0 ppm.

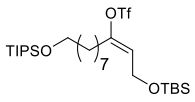


Ethyl (*E*)-3-{[(trifluoromethyl)sulfonyl]oxy}-11-[(triisopropylsilyl)oxy]undec-2-enoate (245): A solution of 64.8 mg of ketone **244** (0.162 mmol, 1.0 equiv) in 1 mL of DMF was added dropwise to a mixture of 7.1 mg of sodium hydride (60% w/w, 0.178 mmol, 1.1 equiv) in 1 mL of DMF. The reaction was stirred for 10 minutes at room temperature and the solution turned clear. Then 63.6 mg of *N*-phenyltrifluoromethanesulfonimide (0.178 mmol, 1.1 equiv) was added and the solution was stirred at room temperature for additional 3 hours. The crude mixture was diluted with diethyl ether, and the organic layer was washed with saturated NH_4Cl (aq), H_2O and brine. The combined organic layer was dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 5% ethyl acetate in hexane) to afford 69.6 mg of desired product (0.131 mmol, 81% yield) as a colorless oil. ^{1}H NMR (300M Hz, $CDCl_3$) 5.93 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.66 (t, J = 6.6 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 1.64-1.51 (m, 4H), 1.33-1.28 (m, 13H), 1.07-1.01 (m, 21H) ppm; ^{13}C NMR (100MHz, $CDCl_3$) 165.8, 164.1, 112.5, 63.4, 61.1, 33.0, 31.4, 29.2, 29.1, 28.8, 26.3, 25.7, 18.0, 14.1, 12.0 ppm.

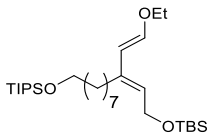


(*E*)-1-Hydroxy-11-[(triisopropylsilyl)oxy]undec-2-en-3-yl trifluoromethanesulfonate: To a solution of 517 mg of vinyl triflate **245** (1.0 mmol, 1.0 equiv) in 15 mL of DCM at -60 ^{o}C was added 4.0 mL of DIBAL-(H) (1.0 M in hexanes) and the mixture was kept stirring at this temperature for 1.5 hours. The reaction was quenched by adding 2 mL of MeOH and warmed up to room temperature. Saturated Rochelle salt solution was added and the solution was kept stirring at room temperature for 2 hours. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layer was dried over sodium

sulfate and concentrated. The crude product was directly used in next step without any further purification.

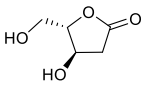


(*E*)-17,17-Diisopropyl-2,2,3,3,18-pentamethyl-4,16-dioxa-3,17-disilanonadec-6-en-7-yl trifluoromethanesulfonate (189): To a solution of allylic alcohol from last step (1.0 mmol, 1.0 equiv) from last step in 10 mL of DMF was added 136 mg of imidazole (2.0 mmol, 2.0 equiv) and 301 mg of TBSCl (2.0 mmol, 2.0 equiv). The resulting mixture was kept stirring at room temperature for 2 hours. Saturated $NaHCO_3$ was added to the solution followed by ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 3% ethyl acetate in hexane) to afford 327 mg of desired product (0.54 mmol, 54% yield in 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) 5.66 (t, J = 7.0 Hz, 1H), 4.22 (d, J = 7.0 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 2.38 (t, J = 7.5 Hz, 2H), 1.56-1.50 (m, 4H), 1.65-1.30 (m, 10H), 1.08-1.04 (m, 21H), 0.90 (s, 9H), 0.08 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 151.5, 121.2, 118.5 (q, J = 318 Hz), 63.4, 58.3, 33.0, 30.4, 29.3, 29.2, 28.8, 26.2, 25.8, 18.0, 12.0, -5.3 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{27}H_{56}O_5F_3SSi_2$: 605.3315; found: 605.3334.



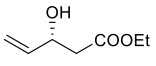
(*E*)-7-[(*E*)-2-Ethoxyvinyl]-17,17-diisopropyl-2,2,3,3,18-pentamethyl-4,16-dioxa-3,17-disilanonadec-6-ene (187): To a solution of 30.0 mg of vinyl triflate (0.050 mmol, 1.0 equiv) in 2 ml of 1-methyl-2-pyrrolidinone was added 1.3 mg of

bis(acetonitrile)dichloropalladium(II) (0.005 mmol, 0.1 equiv), 1.9 mg of copper(I) iodide (0.010 mmol, 0.2 equiv) and 3.1 mg of triphenylarsine (0.010 mmol, 0.2 equiv). A solution of 21.7 mg of (*E*)-tributyl(2-ethoxyvinyl)stannane (0.060 mmol, 1.2 equiv) in 1 ml of 1-methyl-2-pyrrolidinone was added and the reaction stirred for 24 h at room temperature under an atmosphere of nitrogen in dark. The reaction was diluted with ethyl acetate and the product was washed with aqueous KF solution. The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The product was purified by chromatography (SiO_2, 5% ethyl acetate in hexane) to afford 9.0 mg of product (34% yield) as light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 6.52 (d, J = 13.0 Hz, 1H), 5.46 (d, J = 13.0 Hz, 1H), 5.34 (t, J = 6.5 Hz, 1H), 4.24 (d, J = 6.5 Hz, 2H), 3.79 (q, J = 7.0 Hz, 2H), 3.66 (t, J = 7.0 Hz, 2H), 2.11 (t, J = 8.0 Hz, 2H), 1.54-1.52 (m, 2H), 1.30-1.27 (m, 11H), 1.08-1.04 (m, 21H), 0.90 (s, 9H), 0.07 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 146.6, 137.2, 125.5, 109.4, 65.2, 63.5, 59.9, 33.0, 29.8, 29.5 (2C), 29.3, 27.8, 26.0, 25.8, 18.4, 18.0, 14.8, 12.0, -5.0 ppm. HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_{30}H_{63}O_3Si_2$: 527.4316; found: 527.4359.

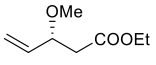


(4*R*,5*R*)-4-Hydroxy-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (193): To a solution of 0.51 g of 2-deoxy-*L*-ribose **194** (3.8 mmol, 1.0 equiv) in 10 mL of water was added 0.6 mL of bromine (11.4 mmol, 3.0 equiv) and the resulting solution was kept stirring at ambient temperature in the dark for 24 hours. Sodium sulfite and sodium carbonate were added until red color diminished and pH = 7. The mixture was filtered through a pad of celite and concentrated. The concentrated solution was further filtered through a pad of celite. The crude product was further purified by column chromatography (SiO_2, 10% MeOH in DCM) to afford 0.45 g of desired product (88% yield) as a light yellow solid. $[\alpha]_D^{20}$ 4.7 (c = 1.21, MeOH); ^{1}H NMR(400 MHz, D_2O) 4.66-4.62 (m, 2H), 3.95 (dd, J = 12.8, 2.4 Hz, 1H), 3.85 (dd, J = 12.8, 4.4 Hz, 1H), 3.14 (dd, J =

16.8, 6.8 Hz, 1H), 2.66 (dd, J = 16.8, 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, D_2O) 179.5, 88.9, 68.2, 61.0, 37.8 ppm.

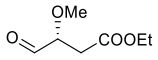


Ethyl (*R*)-3-hydroxypent-4-enoate (192): Lactone **193** (4.9 g, 37 mmol, 1.0 equiv) was stirred with 25 mL of HBr in acetic acid (33% w/w) at room temperature overnight. Excess acid was evaporated on a rotary evaporator and the resulting syrup was dissolved in 15 mL of 50% acetic acid solution (v/v). Zinc dust (15 g, 231 mmol, 6.0 equiv) was added in portions and the mixture was stirred at room temperature for 3 hours. To remove zinc salt and deacetylate the 3-position OH, the residue was dissolved in water and pH was adjusted to 10 using KOH. A white precipitate of $Zn(OH)_2$ was formed and removed by filtration. The filtrate was concentrated and the syrup was dissolved in ethanol and acidified with HCl. The KCl salt was removed by filtration. The mixture was kept stirring at 50 ^{o}C overnight and concentrated. The crude product was further purified by column chromatography (SiO_2, 30% ethyl acetate in hexane) to afford 1.5 g of product (34% yield) as a colorless oil. $[\alpha]_D^{20}$ 5.9, (c = 0.87, $CHCl_3$); ^{1}H NMR(500 MHz, $CDCl_3$) 5.89 (ddd, J = 17.5, 10.5, 5.5 Hz, 1H), 5.32 (dt, J = 17.5, 1.5 Hz, 1H), 5.16 (dt, J = 10.5, 1.5 Hz, 1H), 4.54 (ddd, J = 9.5, 5.5, 4.0 Hz, 1H), 4.18 (q, J = 7.0 Hz, 2H), 2.59 (dd, J = 16.0, 4.0 Hz, 1H), 2.52 (dd, J = 16.0, 8.5 Hz, 1H), 1.28 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR(125 MHz, $CDCl_3$) 172.3, 138.8, 115.4, 68.9, 60.8, 41.1, 14.2 ppm.



Ethyl (*R*)-3-methoxypent-4-enoate (246): To a solution of 1.20 g of alcohol **193** (8.3 mmol, 1.0 equiv) in 50 mL of DCM at 0 ^{o}C was added 5.42 g of proton sponge (24.9 mmol, 3.0 equiv) followed by 3.73 g of trimethyloxonium tetrafluoroborate (24.9 mmol, 3.0 equiv). The resulting solution was stirred at room temperature for 3 hours. The reaction was quenched by

addition of 20 mL of saturated $NaHCO_3$(aq). The phases were separated and the aqueous layer was extracted with DCM. The combined organic layer was washed with citric acid solution (10% w/w) andbrine, dried over sodium sulfate and concentrated. The crude product was further purified by column chromatography (SiO_2, 20% ethyl acetate in hexane) to provide 1.04 g of ethyl (*R*)-3-methoxypent-4-enoate (79% yield) as a colorless liquid. $[\alpha]_D^{20}$ 11.2, (c = 1.31, $CHCl_3$); ^1H NMR(400 MHz, $CDCl_3$) 5.70 (ddd, J = 17.6, 10.4, 7.6 Hz, 1H), 5.29 (d, J = 17.2 Hz, 1H), 5.24 (d, J = 10.4 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 4.03 (td, J = 7.6, 5.6 Hz, 2H), 3.29 (s, 3H), 2.60 (dd, J = 15.2, 8.4 Hz, 1H) 2.45 (dd, J = 15.2, 5.2 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) 170.9, 137.0, 118.0, 79.1, 60.5, 56.5, 41.0, 14.2 ppm.



Ethyl (*R*)-3-methoxy-4-oxobutanoate (188): To a -78 ºC solution of 220 mg of ethyl (*R*)-3-methoxypent-4-enoate (1.39 mmol, 1.0 equiv) in 20 mL of DCM/EtOH (9:1) was bubbled with ozone for 10 min, then 0.3 mL of Me_2S was added at this temperature and the mixture was allowed to warm up to ambient temperature and kept stirring at ambient temperature for another 2 hours. The solvent was removed under rotary evaporator. The crude mixture was further purified by column chromatography (SiO_2, 20% ethyl acetate in hexane) to provide 167 mg of α-methoxy aldehyde (75% yield) as a colorless liquid. $[\alpha]_D^{20}$ 11.2, (c = 1.31, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): 9.78 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.97 (dd, J = 6.8, 4.8 Hz, 1H), 3.51 (s, 1H), 2.77 (dd, J = 16.4, 4.8 Hz, 1H), 2.67 (dd, J = 16.4, 6.8 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (125MHz, $CDCl_3$) 202.2, 170.0, 81.8, 61.1, 58.7, 35.7, 14.1 ppm; HRMS (ESI) *m/z* calculated for $[M+H]^+$ $C_7H_{13}O_4$: 161.0808; found: 161.0814.

APPENDIX

X-RAY STRUCTURE OF **104a**

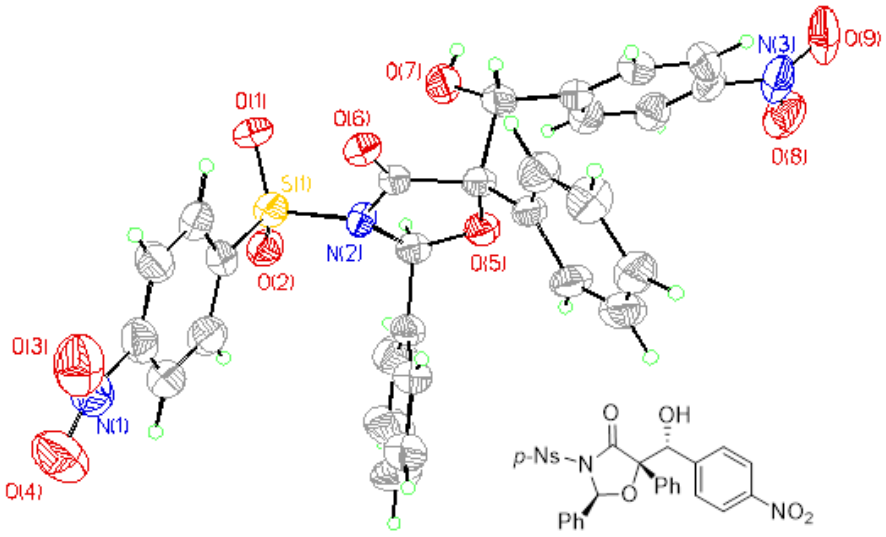


Figure 22 X-Ray Structure of 104a

ORTEP structure of **104a**. The molecular structure is drawn with 50% probability displacement ellipsoids; hydrogen atoms are drawn with an artificial radius.

Table 9 CIF Information for Compound 104a

Identification code	feng6080	
Chemical formula	$C_{28}H_{21}N_3O_9S$	
Formula weight	575.54 g/mol	
Temperature	230(2) K	
Wavelength	1.54178 Å	
Crystal size	0.020 x 0.020 x 0.180 mm	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.3390(5) Å	α = 90°
	b = 14.9243(9) Å	β = 90°
	c = 24.6171(13) Å	γ = 90°
Volume	2696.3(3) $Å^3$	
Z	4	
Density (calculated)	1.418 g/cm^3	
Absorption coefficient	1.596 mm^{-1}	
F(000)	1192	
Diffractometer	Bruker Apex II CCD	
Radiation source	IMuS micro-focus source, Cu	
Theta range for data collection	3.46 to 68.59°	
Index ranges	-8<=h<=8, -17<=k<=17, -28<=l<=29	
Reflections collected	21453	
Independent reflections	4941 [R(int) = 0.2124]	
Absorption correction	multi-scan	
Max. and min. transmission	0.9700 and 0.7600	
Structure solution technique	direct methods	
Structure solution program	SHELXS-97 (Sheldrick, 2008)	
Refinement method	Full-matrix least-squares on F2	

Refinement program	SHELXL-97 (Sheldrick, 2008)	
Function minimized	Σ w(Fo2 - Fc2)2	
Data / restraints / parameters	4941 / 0 / 371	
Goodness-of-fit on F2	0.980	
Δ/σmax	0.003	
Final R indices	2518 data; I>2σ(I)	R1 = 0.1074, wR2 = 0.2321
	all data	R1 = 0.1834, wR2 = 0.2909
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.1204P)^2]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	-0.0(1)	
Extinction coefficient	0.0085(16)	
Largest diff. peak and hole	0.555 and -0.891 eÅ^{-3}	
R.M.S. deviation from mean	0.138 eÅ^{-3}	

Table 10 Atomic Coordinates and Equivalent Isotropic Atomic Displacement Parameters (Å2) for 104a.

	x/a	y/b	z/c	U(eq)
S1	0.1358(4)	0.4945(2)	0.51824(10)	0.0650(9)
O1	0.1908(11)	0.4539(5)	0.4680(3)	0.075(2)
O2	0.9533(10)	0.5249(5)	0.5259(3)	0.072(2)
O3	0.8204(16)	0.7690(7)	0.5691(4)	0.110(3)
O4	0.5965(16)	0.8522(8)	0.5938(5)	0.128(4)
O5	0.0914(9)	0.3065(5)	0.6255(3)	0.063(2)
O6	0.4624(10)	0.3781(5)	0.5475(3)	0.0610(19)
O7	0.1467(11)	0.2329(5)	0.5242(3)	0.079(2)
O8	0.8376(19)	0.8901(8)	0.6918(4)	0.115(4)
O9	0.0907(18)	0.8208(8)	0.6718(5)	0.122(4)
N1	0.656(2)	0.7816(8)	0.5766(5)	0.094(3)
N2	0.1693(12)	0.4176(5)	0.5680(3)	0.057(2)

	x/a	y/b	z/c	U(eq)
N3	0.992(2)	0.8876(9)	0.6723(5)	0.092(4)
C1	0.4639(17)	0.5772(8)	0.5150(5)	0.070(3)
C2	0.5868(15)	0.6426(7)	0.5289(5)	0.070(3)
C3	0.5313(18)	0.7095(8)	0.5612(5)	0.074(3)
C4	0.354(2)	0.7159(8)	0.5826(5)	0.083(4)
C5	0.2313(17)	0.6490(8)	0.5688(5)	0.076(3)
C6	0.2889(16)	0.5793(7)	0.5348(5)	0.063(3)
C7	0.0167(14)	0.3839(7)	0.6008(4)	0.059(3)
C8	0.2695(14)	0.2852(7)	0.6059(4)	0.055(2)
C9	0.3199(14)	0.3643(6)	0.5695(4)	0.050(2)
C10	0.079(2)	0.4865(8)	0.6788(5)	0.080(4)
C11	0.023(3)	0.5495(11)	0.7170(6)	0.106(5)
C12	0.849(3)	0.5733(13)	0.7204(7)	0.132(7)
C13	0.720(3)	0.5400(12)	0.6842(9)	0.134(7)
C14	0.7743(18)	0.4775(10)	0.6443(6)	0.092(4)
C15	0.9552(16)	0.4507(8)	0.6441(5)	0.065(3)
C16	0.3443(16)	0.2817(8)	0.7061(4)	0.068(3)
C17	0.4666(19)	0.2669(9)	0.7482(6)	0.088(4)
C18	0.6398(18)	0.2430(9)	0.7384(5)	0.081(3)
C19	0.7030(16)	0.2360(10)	0.6842(5)	0.079(3)
C20	0.5794(14)	0.2484(8)	0.6427(5)	0.070(3)
C21	0.4033(13)	0.2713(7)	0.6515(4)	0.054(2)
C22	0.2622(15)	0.2027(7)	0.5673(4)	0.061(3)
C23	0.3055(18)	0.0545(8)	0.6139(5)	0.073(3)
C24	0.2413(19)	0.9792(7)	0.6381(5)	0.077(3)
C25	0.0639(18)	0.9695(8)	0.6454(4)	0.069(3)
C26	0.9402(17)	0.0318(8)	0.6291(5)	0.071(3)
C27	0.0019(15)	0.1074(8)	0.6021(4)	0.070(3)
C28	0.1887(15)	0.1197(7)	0.5955(4)	0.059(3)

Table 11 Bond Lengths (Å) for 104a.

S1-O2	1.427(8)	S1-O1	1.434(7)
S1-N2	1.697(8)	S1-C6	1.741(12)
O3-N1	1.232(16)	O4-N1	1.218(15)
O5-C7	1.416(12)	O5-C8	1.430(11)
O6-C9	1.196(11)	O7-C22	1.431(12)
O7-H7B	0.83	O8-N3	1.233(15)
O9-N3	1.230(16)	N1-C3	1.465(17)
N2-C9	1.362(13)	N2-C7	1.469(12)
N3-C25	1.486(16)	C1-C6	1.374(15)
C1-C2	1.372(16)	C1-H1A	0.94
C2-C3	1.340(16)	C2-H2A	0.94
C3-C4	1.405(18)	C4-C5	1.388(17)
C4-H4A	0.94	C5-C6	1.400(16)
C5-H5A	0.94	C7-C15	1.528(15)
C7-H7A	0.99	C8-C21	1.506(14)
C8-C9	1.527(14)	C8-C22	1.555(13)
C10-C15	1.357(17)	C10-C11	1.392(19)
C10-H10A	0.94	C11-C12	1.33(2)
C11-H11A	0.94	C12-C13	1.39(3)
C12-H12A	0.94	C13-C14	1.41(2)
C13-H13A	0.94	C14-C15	1.387(16)
C14-H14A	0.94	C16-C17	1.390(16)
C16-C21	1.421(13)	C16-H16A	0.94
C17-C18	1.342(16)	C17-H17A	0.94
C18-C19	1.416(17)	C18-H18A	0.94
C19-C20	1.379(15)	C19-H19A	0.94
C20-C21	1.354(14)	C20-H20A	0.94
C22-C28	1.520(15)	C22-H22A	0.99
C23-C24	1.356(16)	C23-C28	1.373(16)
C23-H23A	0.94	C24-C25	1.323(16)
C24-H24A	0.94	C25-C26	1.360(17)
C26-C27	1.386(15)	C26-H26A	0.94
C27-C28	1.392(15)	C27-H27A	0.94

Table 12 Bond Angles (°) for 104a.

O2-S1-O1	120.9(5)	O2-S1-N2	104.8(5)
O1-S1-N2	107.2(5)	O2-S1-C6	110.1(5)
O1-S1-C6	109.1(5)	N2-S1-C6	103.2(5)
C7-O5-C8	112.9(8)	C22-O7-H7B	109.5
O4-N1-O3	122.5(14)	O4-N1-C3	119.9(15)
O3-N1-C3	117.5(13)	C9-N2-C7	113.8(8)
C9-N2-S1	122.1(7)	C7-N2-S1	121.2(7)
O8-N3-O9	124.7(13)	O8-N3-C25	118.3(14)
O9-N3-C25	117.0(13)	C6-C1-C2	120.6(12)
C6-C1-H1A	119.7	C2-C1-H1A	119.7
C3-C2-C1	118.6(12)	C3-C2-H2A	120.7
C1-C2-H2A	120.7	C2-C3-C4	123.7(12)
C2-C3-N1	120.7(13)	C4-C3-N1	115.7(12)
C5-C4-C3	117.4(11)	C5-C4-H4A	121.3
C3-C4-H4A	121.3	C4-C5-C6	119.0(12)
C4-C5-H5A	120.5	C6-C5-H5A	120.5
C1-C6-C5	120.7(12)	C1-C6-S1	120.2(9)
C5-C6-S1	119.0(9)	O5-C7-N2	102.8(7)
O5-C7-C15	110.2(8)	N2-C7-C15	112.6(9)
O5-C7-H7A	110.3	N2-C7-H7A	110.3
C15-C7-H7A	110.3	O5-C8-C21	112.0(8)
O5-C8-C9	104.4(8)	C21-C8-C9	112.7(8)
O5-C8-C22	110.6(8)	C21-C8-C22	111.6(8)
C9-C8-C22	105.2(8)	O6-C9-N2	126.7(9)
O6-C9-C8	127.6(9)	N2-C9-C8	105.7(8)
C15-C10-C11	119.7(13)	C15-C10-H10A	120.2
C11-C10-H10A	120.2	C12-C11-C10	120.3(16)
C12-C11-H11A	119.8	C10-C11-H11A	119.8
C11-C12-C13	121.3(16)	C11-C12-H12A	119.4
C13-C12-H12A	119.4	C12-C13-C14	119.1(17)
C12-C13-H13A	120.4	C14-C13-H13A	120.4
C15-C14-C13	117.8(15)	C15-C14-H14A	121.1

C13-C14-H14A	121.1	C10-C15-C14	121.6(12)
C10-C15-C7	119.9(11)	C14-C15-C7	118.3(11)
C17-C16-C21	119.5(11)	C17-C16-H16A	120.2
C21-C16-H16A	120.2	C18-C17-C16	121.3(12)
C18-C17-H17A	119.4	C16-C17-H17A	119.4
C17-C18-C19	119.9(11)	C17-C18-H18A	120.0
C19-C18-H18A	120.0	C20-C19-C18	118.2(11)
C20-C19-H19A	120.9	C18-C19-H19A	120.9
C21-C20-C19	122.9(11)	C21-C20-H20A	118.5
C19-C20-H20A	118.5	C20-C21-C16	118.0(10)
C20-C21-C8	122.6(9)	C16-C21-C8	119.4(9)
O7-C22-C28	112.6(9)	O7-C22-C8	102.9(8)
C28-C22-C8	112.3(8)	O7-C22-H22A	109.6
C28-C22-H22A	109.6	C8-C22-H22A	109.6
C24-C23-C28	121.0(12)	C24-C23-H23A	119.5
C28-C23-H23A	119.5	C25-C24-C23	119.5(12)
C25-C24-H24A	120.3	C23-C24-H24A	120.3
C24-C25-C26	122.8(12)	C24-C25-N3	119.9(12)
C26-C25-N3	117.3(12)	C25-C26-C27	118.8(11)
C25-C26-H26A	120.6	C27-C26-H26A	120.6
C26-C27-C28	119.0(11)	C26-C27-H27A	120.5
C28-C27-H27A	120.5	C23-C28-C27	118.9(11)
C23-C28-C22	120.4(10)	C27-C28-C22	120.7(10)

Table 13 Anisotropic Atomic Displacement Parameters (Å2) for 104a.

The anisotropic atomic displacement factor exponent takes the form: -2π2[h2 a*2 U11 + ... + 2 h k a* b* U12]

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	0.0763(18)	0.0650(17)	0.0537(15)	0.0032(14)	-0.0001(13)	0.0061(14)
O1	0.096(5)	0.080(5)	0.050(4)	-0.011(4)	0.017(4)	0.008(4)
O2	0.076(5)	0.079(5)	0.062(4)	0.006(4)	0.000(4)	0.007(4)
O3	0.109(8)	0.112(8)	0.110(8)	0.022(6)	-0.027(7)	-0.018(6)
O4	0.149(10)	0.087(7)	0.148(10)	-0.024(8)	-0.004(8)	-0.024(7)
O5	0.070(5)	0.062(4)	0.057(4)	-0.004(4)	0.010(3)	-0.003(3)
O6	0.068(5)	0.066(5)	0.049(4)	-0.003(3)	0.011(4)	0.004(4)
O7	0.120(6)	0.062(5)	0.056(4)	0.000(4)	-0.026(5)	-0.010(4)
O8	0.140(9)	0.119(9)	0.085(7)	0.017(6)	0.016(7)	-0.041(7)
O9	0.159(10)	0.086(7)	0.122(8)	0.054(7)	-0.031(7)	-0.015(7)
N1	0.129(10)	0.074(8)	0.080(7)	0.007(6)	-0.024(8)	-0.005(8)
N2	0.070(5)	0.056(5)	0.044(5)	0.010(4)	0.001(4)	-0.002(4)
N3	0.121(11)	0.087(9)	0.067(7)	0.025(6)	-0.025(7)	-0.028(8)
C1	0.088(8)	0.066(7)	0.055(7)	0.011(6)	0.010(6)	0.006(6)
C2	0.080(8)	0.057(7)	0.073(8)	0.000(6)	-0.005(6)	-0.002(6)
C3	0.089(9)	0.061(8)	0.072(8)	0.011(6)	-0.018(7)	-0.006(6)
C4	0.120(11)	0.067(8)	0.061(7)	0.001(6)	-0.001(8)	0.002(8)
C5	0.082(8)	0.079(8)	0.067(8)	0.002(7)	0.004(6)	0.006(7)
C6	0.081(8)	0.047(6)	0.063(7)	0.006(5)	0.009(6)	0.004(5)
C7	0.061(6)	0.063(7)	0.054(6)	-0.007(5)	-0.002(5)	0.003(5)
C8	0.065(6)	0.050(6)	0.049(6)	-0.009(5)	0.006(5)	-0.001(5)
C9	0.062(6)	0.046(5)	0.043(5)	-0.003(4)	-0.001(5)	0.004(5)
C10	0.110(10)	0.067(8)	0.064(7)	-0.010(7)	0.002(7)	0.007(7)
C11	0.154(15)	0.081(10)	0.084(10)	-0.015(9)	-0.009(10)	0.001(10)
C12	0.19(2)	0.120(15)	0.088(12)	-0.032(11)	0.050(14)	0.025(15)
C13	0.149(18)	0.101(13)	0.152(17)	-0.026(12)	0.062(14)	0.031(12)
C14	0.085(9)	0.109(12)	0.082(9)	-0.003(8)	0.018(7)	0.021(8)
C15	0.076(8)	0.056(6)	0.063(7)	-0.007(6)	0.018(6)	-0.001(6)
C16	0.071(7)	0.081(8)	0.051(6)	-0.014(6)	0.004(6)	0.014(6)

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C17	0.111(10)	0.087(9)	0.066(7)	-0.022(7)	-0.016(8)	0.020(8)
C18	0.095(9)	0.086(9)	0.062(7)	-0.002(7)	-0.013(7)	0.010(7)
C19	0.063(7)	0.096(9)	0.078(9)	0.005(7)	-0.002(6)	0.002(6)
C20	0.063(7)	0.083(8)	0.063(7)	0.001(6)	0.003(6)	0.004(6)
C21	0.067(7)	0.051(5)	0.044(5)	-0.007(5)	0.007(4)	-0.007(5)
C22	0.078(7)	0.052(6)	0.054(6)	-0.010(5)	-0.007(5)	0.000(5)
C23	0.090(9)	0.063(7)	0.065(7)	-0.007(6)	0.001(6)	0.005(6)
C24	0.104(10)	0.049(7)	0.079(9)	0.004(6)	-0.001(7)	0.002(6)
C25	0.090(9)	0.070(8)	0.046(6)	0.004(6)	0.010(6)	-0.017(6)
C26	0.073(7)	0.078(8)	0.063(7)	0.001(6)	-0.009(6)	-0.011(6)
C27	0.074(8)	0.068(7)	0.067(7)	-0.001(6)	-0.006(6)	-0.014(6)
C28	0.072(7)	0.053(6)	0.051(6)	-0.008(5)	0.001(5)	0.000(5)

Table 14 Hydrogen Atomic Coordinates and Isotropic Atomic Displacement Parameters (Å2) for 104a.

	x/a	y/b	z/c	U(eq)
H7B	0.1055	0.1889	0.5076	0.119
H1A	0.4998	0.5305	0.4917	0.084
H2A	0.7073	0.6406	0.5160	0.084
H4A	0.3204	0.7637	0.6053	0.099
H5A	0.1112	0.6505	0.5821	0.091
H7A	-0.0869	0.3673	0.5770	0.071
H10A	0.2018	0.4688	0.6771	0.096
H11A	0.1092	0.5754	0.7406	0.128
H12A	-0.1882	0.6134	0.7477	0.159
H13A	-0.4025	0.5589	0.6863	0.161
H14A	-0.3091	0.4549	0.6188	0.11
H16A	0.2235	0.2985	0.7136	0.081
H17A	0.4273	0.2738	0.7843	0.106
H18A	0.7191	0.2308	0.7675	0.097
H19A	0.8259	0.2232	0.6768	0.095
H20A	0.6191	0.2406	0.6067	0.083
H22A	0.3856	0.1903	0.5529	0.073
H23A	0.4318	0.0622	0.6097	0.087
H24A	0.3224	-0.0658	0.6495	0.093
H26A	-0.1847	0.0236	0.6359	0.086
H27A	-0.0811	0.1498	0.5885	0.084

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