Catalytic Asymmetric Bond Constructions in Complex Molecule Synthesis. An Approach to the Synthesis of Spirolide C and the Development of Enantioselective Enolate Hydroxylation Reactions

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Catalytic Asymmetric Bond Constructions in Complex Molecule Synthesis. An Approach to the Synthesis of Spirolide C and the Development of Enantioselective Enolate Hydroxylation Reactions

Binbin Guo, PhD

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The asymmetric synthesis of spirolide C, a highly potent marine toxin, has been investigated in our laboratory. The construction of C_7-C_{28} bis-spiroketal was completed through a strategy utilizing an intermolecular Stetter reaction and a biomimetic ketalization process. Stereocenters were set in great diastereo- and enantioselectivity via asymmetric catalysis. The efficiency of the synthesis was demonstrated by its convergency and high yields.

A cinchona alkaloid catalyzed ketene-oxaziridine cyclocondensation has been developed to provide an access to enantioenriched α-hydroxy carbonyl compounds. The oxazolidinones arising from the cyclocondensation were converted to various α-hydroxy carbonyl compounds via nucleophilic ring openings. Greater than 98% *ee* was achieved in oxazolidinone formation and the subsequent ring openings proceeded with retention of the *ee* or minor epimerization.

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LIST OF ABBREVIATIONS

AAC……..Acyl halide-aldehyde cyclocondensation

AChBP…….……..Acetylcholine-binding protein

APCI……...…Atmospheric pressure chemical ionization

ASAP…….….Atmospheric solids analysis probe

BBN……..Borabicyclo[3.3.1]nonane

BINOL……1,1’-Bi-2-naphthol

CSA……...….Camphorsulfonic acid

DIBAL-H.....…...Diisobutylaluminium hydride

DIPEA…….....*N*,*N*-Diisopropylethylamine

DMAP……..4-Dimethylaminopyridine

DMF…….....*N*,*N*-Dimethylformamide

DMP……...Dess-Martin periodinane

DMSO……..Dimethylsulfoxide

dr…….....Diastereomeric ratio

ee…….....Enantiomeric excess

equiv……Equivalents

Grubbs II……Grubbs catalyst 2nd generation

Hoveyda-Grubbs II……Hoveyda-Grubbs catalyst 2nd generation

HRMS…….....High resolution mass spectrum

Ipc.....Isopinocampheyl

LDA…….Lithium diisopropylamide

NaHMDS…….....Sodium bis(trimethylsilyl)amide

NMO……..*N*-Methylmorpholine *N*-oxide

Ns……(Nitrophenyl)sulfonyl

PMB…….……..…*p*-Methoxybenzyl

PPTS……..……Pyridinium *p*-toluenesulfonate

pyr…….Pyridine

RT……...…….Ambient temperature

TBS……...*tert*-Butyldimethylsilyl

TBSOTf…….*tert*-Butyldimethylsilyl triflate

TEMPO…….(2,2,6,6,-Tetramethylpiperidin-1-yl)oxyl

TES…….....Triethylsilyl

THF….....Tetrahydrofuran

TLC……Thin-layer chromatography

TMS……Trimethylsilyl

TMSQd……...…….*O*-Trimethylsilylquinidine

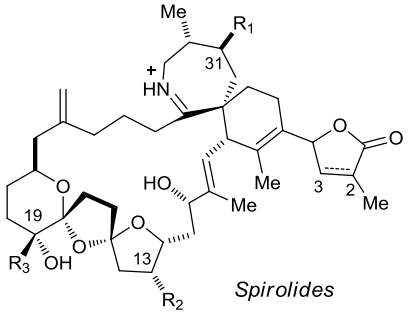
TMSQn……..…….*O*-Trimethylsilylquinine

Tf……...……..…Trifluoromethanesulfonate

1.0 INTRODUCTION

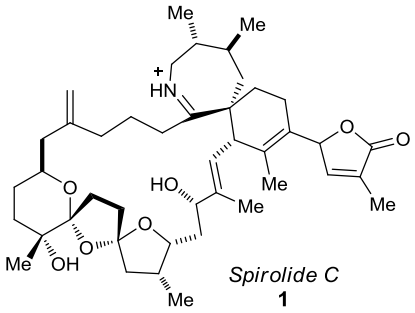
1.1 BIOLOGICAL ACTIVITIES AND STRUCTURE FEATURES

Cyclic imine phycotoxins are an emerging class of marine toxins characterized by their fast acting toxicity,[1] including spirolides **1** (Figure 1),[2] gymnodimines **2**,[3] pinnatoxins **3**,[4] pteriatoxins **4**,[5] and spiro-prorocentrimines **5** (Figure 2).[6] These natural products are macrocyclic compounds with imine and spiro-linked ether moieties, exhibiting similar toxicity in the intraperitoneal mouse assay.[1] The imine group functions as their common pharmacophore.[7] The major source of these toxins is unicellular algae. A specific example is the dinoflagellate *Alexandrium ostenfeldii* which produces spirolides.[2] These toxins pose a potential threat to human health, especially to people living in the coastal areas, as they can move up the food chain through shellfish and other seafood.[8] In order to enhance the safety of consumers, studies of the chemical structure, identity, and mechanism of action of these toxins are necessary.



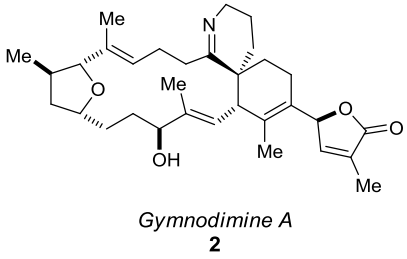
Spirolides

Spirolide	R_1	R_2	R_3	Δ
A	H	Me	Me	$\Delta^{2,3}$
B	H	Me	Me	
C	**Me**	**Me**	**Me**	$\Delta^{2,3}$
D	Me	Me	Me	

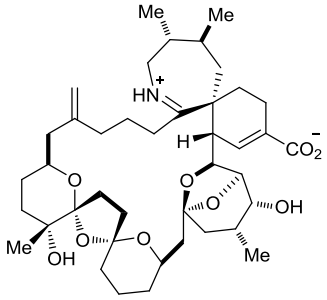


Spirolide C
1

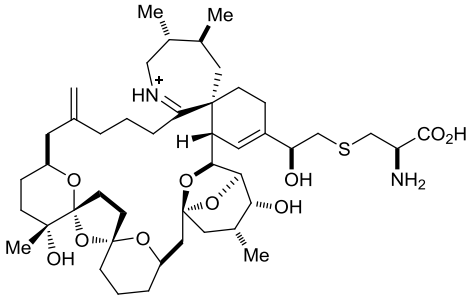
Figure 1. Structures of spirolides A-D



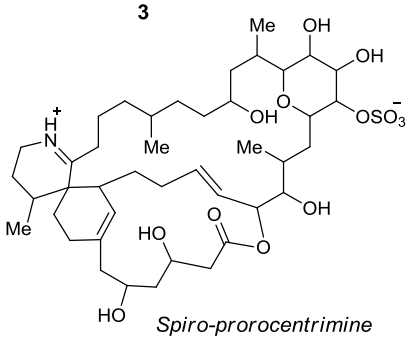
Gymnodimine A
2



Pinnatoxin A
3



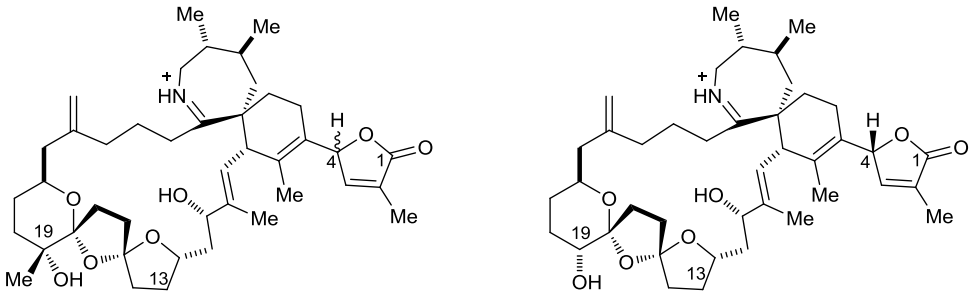
Pteriatoxin A
4



Spiro-prorocentrimine
5

Figure 2. Representative examples of other cyclic imine phycotoxins

Spirolides (A-D) (Figure 1) were first isolated in 1995 by Hu and co-workers from shellfish extracts harvested from the south-eastern coast of Nova Scotia in Canada.[9] There have been 14 members of spirolides reported to date. Spirolides contain an unusual 5,5,6 bis-spiroketal moiety embedded within a 23-membered all carbon macrocycle along with a 6,7-spirocyclic imine structure that is also present in related gymnodimines, pinnatoxins and pteriatoxins. Given the structural complexity, it has been extremely challenging to establish the total configuration based on spectroscopic data. The relative stereochemistry of 13-desmethyl spirolide C (**6**), except for the stereogenic center at C4, was elucidated in 2001 by means of NMR analysis and molecular modeling.[10] The relative stereochemistry of spirolides B and D were also determined by comparison of their NMR data with 13-desmethyl spirolide C. The relative stereochemistry at C4 remained unknown until 2009 when it was assigned in the 13,19-didesmethyl spirolide C (**7**) via computational studies.[11] Despite the extensive structural analysis, a stereoselctive synthesis of spirolides is still required to confirm the structure unambiguously. To date, the total synthesis of any member in the spirolide family has not been reported, but the syntheses of the 5,5,6 bis-spiroketal of spirolides B and D have been accomplished by Ishihara[12] and Brimble.[13] Studies on the 6,7-spiroimine moiety are ongoing in the Zakarian group.[14]



13-Desmethyl spirolide C
6

13,19-Didesmethyl spirolide C
7

Figure 3. Relative stereochemistry of 6 and 7

Spirolides are toxic to mice by intraperitoneal injection, with spirolide C having an LD_{50} value of 8.0 μg/kg.[15] The mechanism of action is believed to be interfering in the action of certain neurotransmitters based on two main characters of the toxic effects.[1] Rapid expression of neurological symptoms appears in a few minutes after intraperitoneal administration in mice. Death occurs within 20 min under the lethal dose, otherwise the mice experiencing full recovery.

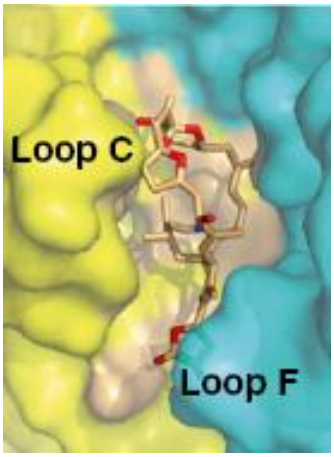


Figure 4. Structure of the spirolide-AChBP complex (graphic from Bourne, Y. et al. *Proc. Natl. Acd. Sci.* 2010, *107*, 6076-6081)

Further studies revealed that the neurotoxicity of spirolides is due to the inhibition of both the nicotinic and muscarinic acetylcholine receptors in the nervous system.[16] As the nicotinic acetylcholine receptor surrogates, spirolides exhibit picomolar affinity to acetylcholine-binding proteins (AChBP).[8] The diffusion-limited association with AChBP and slow dissociation thereof account for the irreversible binding mode of spirolides. Crystal structure (Figure 4) of 13-desmethyl spirolide C **6** bound to AChBP illustrated the molecule neatly imbedded within the pocket which accommodated acetylcholine under physiological conditions. Hydrogen bonding of the protonated imine group in spirolides with the carbonyl oxygen of loop C Trp147 placed the toxin in the center of the pocket. The complementarity of the bis-spiroketal moiety and the interface of the protein further contributed to the high affinity.[8] The importance of the spiroimine unit to the toxicity was further confirmed during the investigation of spirolide derivatives (Figure 5). When the imine moiety was reduced to secondary amine **8**, this compound showed very mild toxicity.[17] The keto-amine hydrolysis derivatives, spirolides E **9** and F **10**, were completely nontoxic.[17]

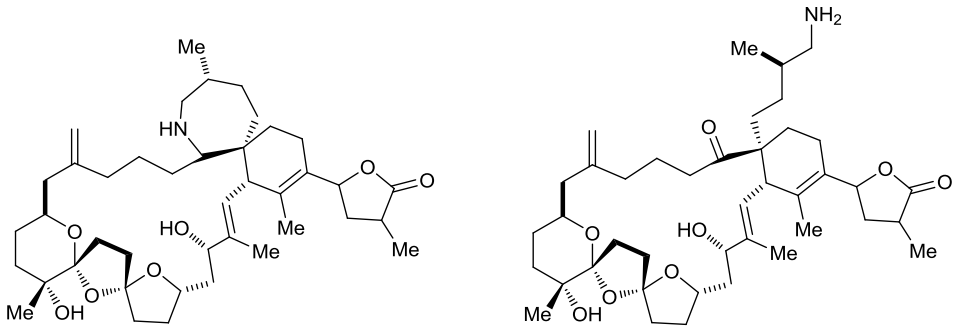


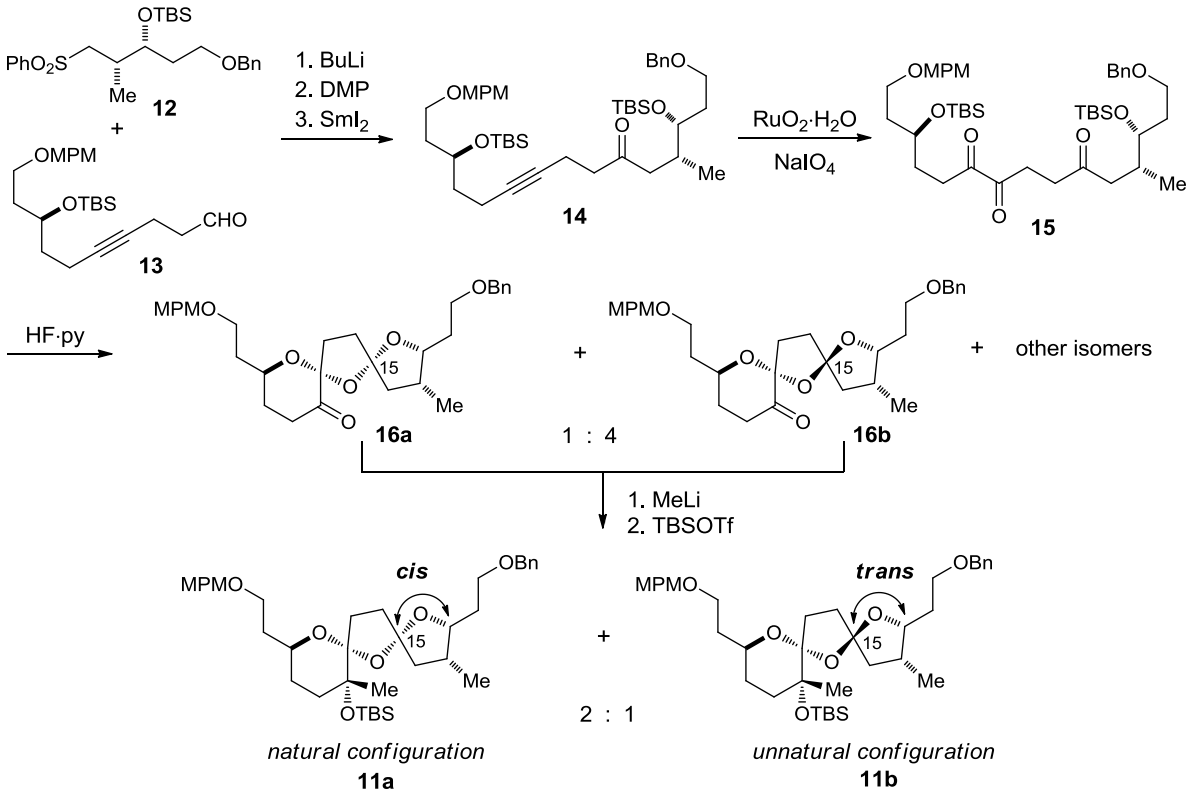
Figure 5. Spirolides lacking the imine moiety showed reduced toxicity

1.2 PREVIOUS STUDIES IN THE SYNTHESIS OF SPIROLIDE C

Previous studies in the synthesis of spirolide C (**1**) have been reported by Ishihara,[12] Brimble,[13] and Zakarian.[14] Ishihara and Brimble synthesized the 5,5,6 bis-spiroketal fragment, although via different strategies. Instead of targeting the bis-spiroketal, Zakarian's synthesis commenced with constructing the substituted cyclohexene with the stereocenters set by a diastereoselective Ireland-Claisen rearrangement. His approach was inspired by the success in the total synthesis of pinnatoxin A **3** (Figure 2),[18] which has a homologous structure to spirolide C (**1**). Despite continuing efforts towards the total synthesis for over a decade, there has been no complete synthesis of spirolide C reported to date or of other members in the spirolide family.

In 2004, Ishihara accomplished the synthesis of the bis-spiroketal moiety in spirolide C (Scheme 1). The tricyclic framework was constructed by a one-step ketalization of the acyclic triketone **15**. This triketone **15** was obtained by ruthenium oxide catalyzed oxidation of the alkyne precursor **14**. This alkyne could be accessed via a sequence of nucleophilic addition of α-sulfonyl anion **12**-Li to the aldehyde **13**, desulfurization and oxidation of the resultant secondary alcohol. Upon removal of the TBS ether with HF·pyridine, the ketalization took place under the same conditions to give the desired tricyclic compound **16a** and its C_{15} epimer **16b** as a 1:4 mixture. Interestingly, the subsequent methyl lithium addition and TBS protection of the intervening tertiary alcohol afforded the bis-spiroketals (**11a** and **11b**) of different diastereomeric ratio (2:1), favoring the desired configuration as in spirolide C. The author rationalized the shift of equilibrium was due to a change of ground state energy differences between these two silylated isomers as a result of breaking the hydrogen bonding interactions.[12]

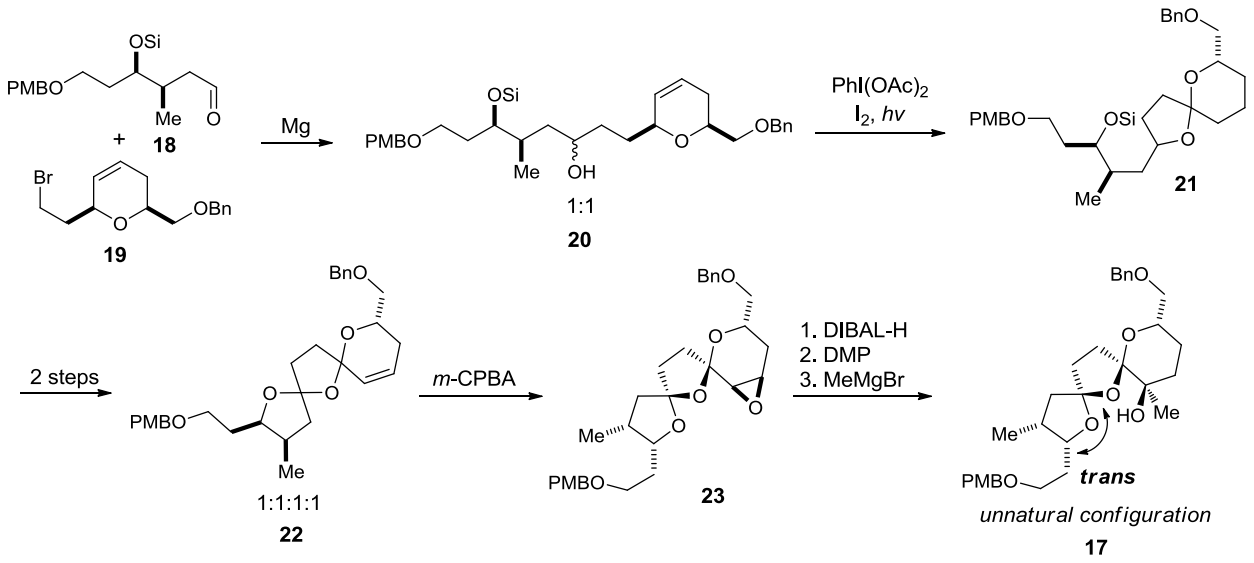
Scheme 1. Ishihara's synthesis of bis-spiroketal



The Brimble group exploited an oxidative radical cyclization methodology to build the bis-spiroketal fragment **17** towards the synthesis of spirolide C (Scheme 2).[13] The cyclization precursor **20** was obtained as a 1:1 mixture of diastereomers by a Barbier reaction of dihydropyran **19** with aldehyde **18**. Irradiation of **20** in the presence of iodobenzene diacetate and iodine gave spiroketal **21** which upon removal of the silyl ether was subjected to a second oxidative radical cyclization, providing the bis-spiroketal **22** as a 1:1:1:1 mixture of diastereomers. Treating this 1:1:1:1 mixture with *m*-CPBA, surprisingly, gave the epoxide **23** as a single diastereomer. The presence of *m*-chlorobenzoic acid and water in *m*-CPBA presumably facilitated the equilibration to the thermodynamically most favored isomer **23**. Epoxide **23** underwent regioselective ring opening with DIBAL-H, and the resultant alcohol was oxidized

upon exposure to Dess-Martin periodinane. Stereoselective axial addition of methylmagnesium bromide to the ketone afforded tertiary alcohol **17**, however, with the undesired configuration (*trans*). The *trans* stereochemistry of **17** was determined by nOe analysis.

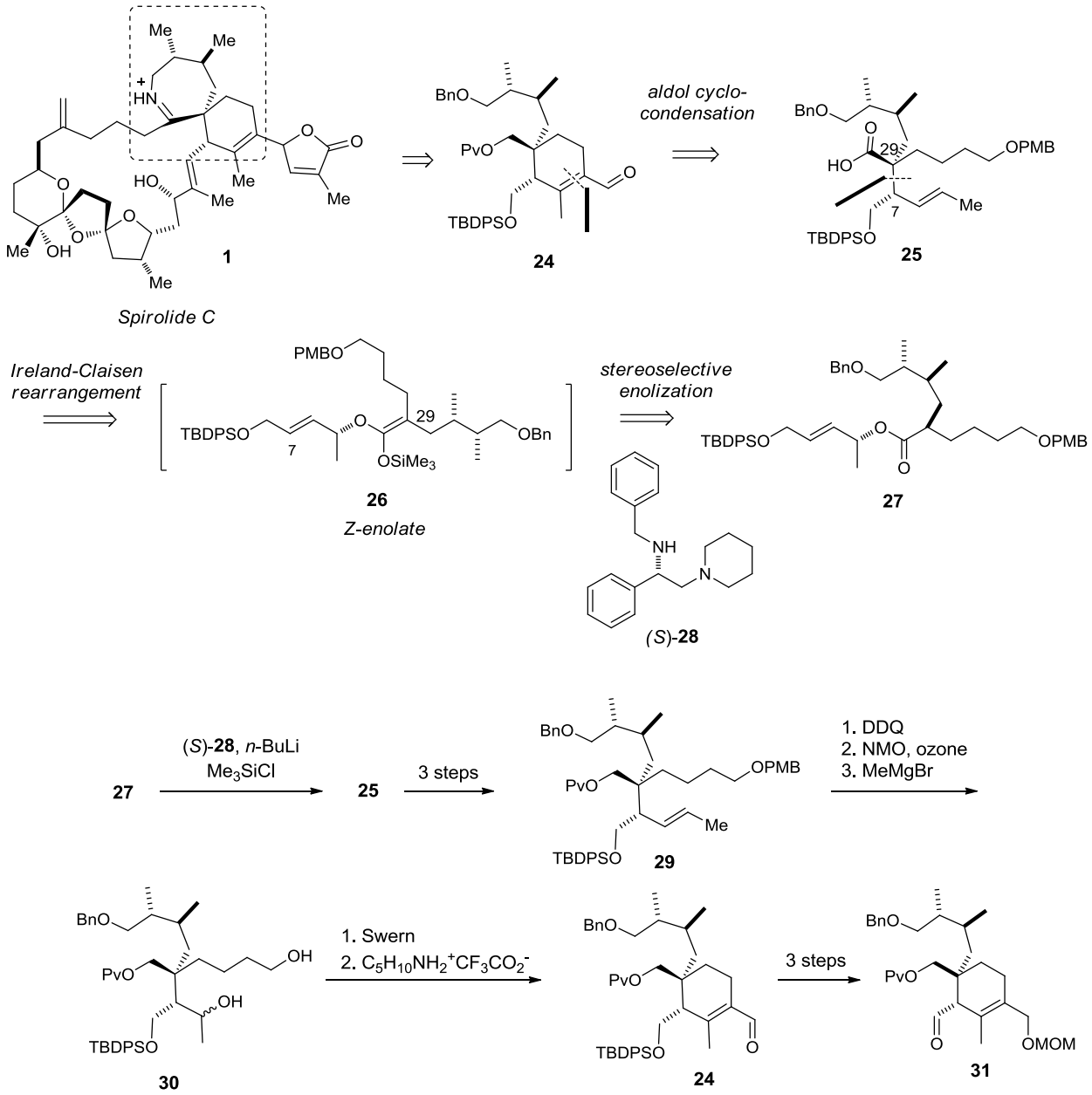
Scheme 2. Brimble's synthesis of bis-spiroketal 17



As stated before, Zakarian and his co-workers initiated the synthesis of spirolide C by constructing the substituted cyclohexene which would later become the spiroimine unit in the natural product (Scheme 3). Following the similar strategy as in the study of pinnatoxin A, where the author utilized an Ireland-Claisen rearrangement for the assembly of the spiroimine unit, they planned to employ the same transformation to set the vicinal stereocenters (C_7 and C_{29}) in spirolide C. In the forward sense, the rearrangement precursor **26** was generated in favor of the *E* enolate via stereoselective enolization of **27** using chiral lithium amide (*S*)-**28**-Li. The ensuing Ireland-Claisen rearrangement proceeded with great diastereoselectivity to give **25**. Upon converting the resultant carboxylic acid to the corresponding pivaloate **29**, the olefin functionality was transformed to the secondary alcohol **30** by ozonolysis and subsequent

metylmagnesium bromide addition. Double oxidation of the diol **30** to the keto aldehyde set the stage for an aldol cyclocondensation, which was accomplished in the presence of piperidinium trifluoroacetate, affording the cyclized compound **24** to complete the synthesis of the substituted cyclohexene **31**.[14a]

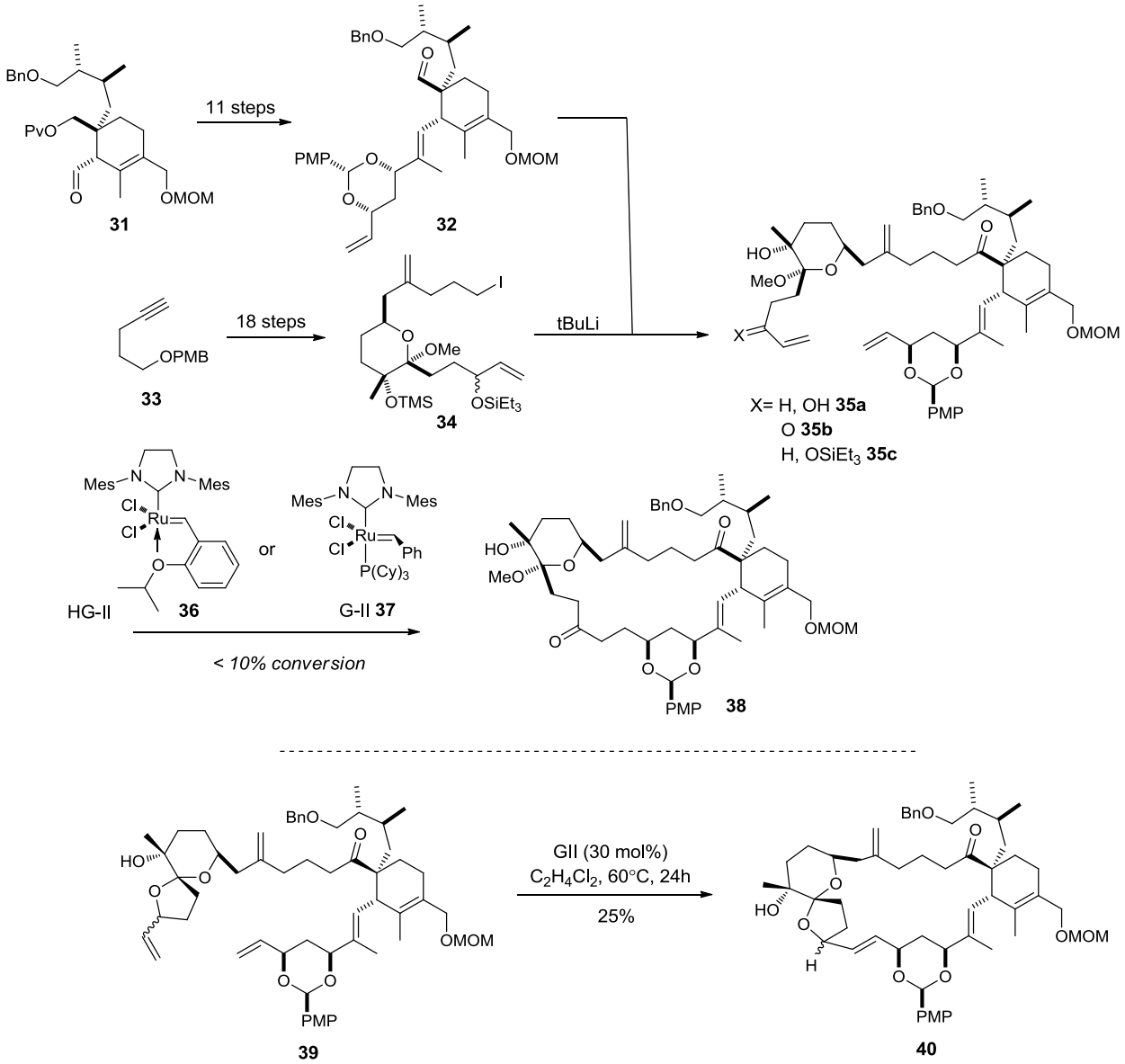
Scheme 3. Zarkarian's synthesis of the cyclohexene ring 31



Zakarian planned to utilize a ring-closing metathesis (RCM) to close the macrocycle prior to assembling the bis-spiroketal in spirolide C (Scheme 4).[14b] To this end, the aforementioned cyclohexene **31** was advanced to **32** in 15 steps. Iodide **34** was prepared from **33** in 18 steps. A direct addition of the alkyl lithium reagent **34**-Li, generated by lithium-iodine exchange from

iodide **34**, with aldehyde **32** afforded coupled product **35a** after Dess-Martin oxidation and desilylation. Extensive studies on the key RCM reaction were performed using compounds **35a**, **35b** and **35c** as the substrates and Hoveyda-Grubbs II **36** or Grubbs II **37** as the catalyst. In all cases, the RCM reaction proceeded very sluggish at 40 °C, leading to less than 10% conversion to the desired macrocycle **38**. Increasing the reaction temperature to 90 °C resulted in complete decomposition. The lack of reactivity of the substrates was presumably attributed to the steric bulk around the two terminal olefins. In response, spiroketal **39** was employed in the RCM reaction, under the hypothesis that a more compact substrate would grant greater reactivity. Indeed, subjecting **39** to the optimized conditions (Grubbs II 30 mol%, 1,2-dichloroethane, 60 °C, 24h) afforded macrocycle **40** in an improved yield (24%), however, still inadequate for continuing the synthesis of spirolide C.

Scheme 4. Studies on RCM reactions to construct the macrocycle of spirolide C



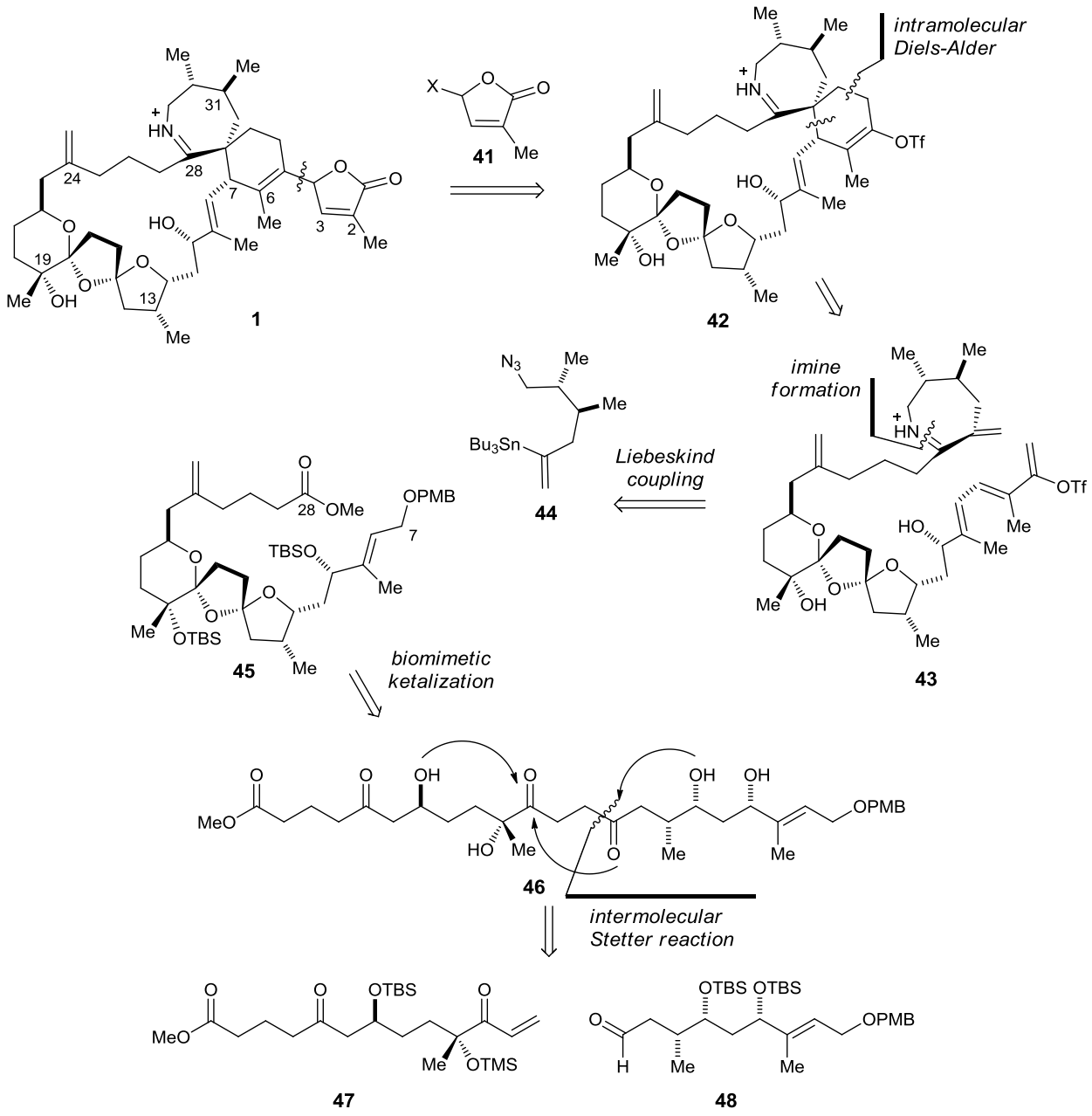
In conclusion, spirolides, isolated 15 years ago, still represent an active area of research in both synthetic chemistry and biology. The total synthesis of spirolides remains a challenge to date, despite impressive progress in these aforementioned partial syntheses. The low natural abundance of spirolides currently hampers efforts towards pharmacological evaluation, and

possible medicinal applications. Therefore, an efficient stereoselective synthesis of spirolide C is of great importance.

1.3 RETROSYNTHETIC ANALYSIS OF SPIROLIDE C

Our retrosynthesis of spirolide C **1** aims at high convergency and limited functional group manipulations to achieve atom economy and synthetic efficiency (Scheme 5). The butenolide subunit **41** will be installed at the last step through a metal-mediated coupling reaction after closing the macrocycle **42**. The macrocyle will be constructed via an intramolecular iminium ion Diels-Alder reaction between a conjugated triflic enolate and the dieneophile component located at the top half of the molecule **43**. Compound **43** can be further dissected via a Liebeskind coupling[19] into vinyl stannane **40** and densely functionalized bis-spiroketal **45**. We propose a biomimetic ketalization[20] to generate the bis-spiroketal **45** from acyclic precursor **46** under thermodynamic control. Compound **46** will be joined by two fragments (**47** and **48**) having comparable complexities through an intermolecular Stetter reaction. Utilizing an intermolecular Stetter reaction for fragment coupling is one of the key features of our synthesis, and such a transformation has not been implemented in the context of complex molecule synthesis. We reported herein the completion of bis-spiroketal **45**.

Scheme 5. Retrosynthesis of spirolide C



2.0 COMPLETION OF THE C7-C28 BIS-SPIROKETAL

2.1 SYNTHESIS OF THE ENONE FRAGMENT

Our investigation commenced with constructing enone fragment **47** as illustrated in Figure 6. Our primary goal was to generate an efficient route where the requisite stereocenters would be established via asymmetric catalysis from achiral starting materials. To this end, it was decided to set the C_{22} stereocenter by attaining the enantioenriched β-lactone **49** via the acyl halide-aldehyde cyclocondensation (AAC) from aldehyde **50** and acetyl bromide.[21] β-Lactones can undergo amine-based nucleophilic ring opening to deliver products that are the functional equivalent of amide aldol adducts.[22] Based on this reactivity pattern, we decided to convert β-lactone **49** to the requisite ketoester **47** via nucleophilic attack of organozinc reagent **51** to accomplish the C_{24}-C_{25} bond construction. In order to introduce the C_{19} stereocenter, we planned to utilize a Sharpless asymmetric dihydroxylation[23] on the C_{18}-C_{19} olefin.

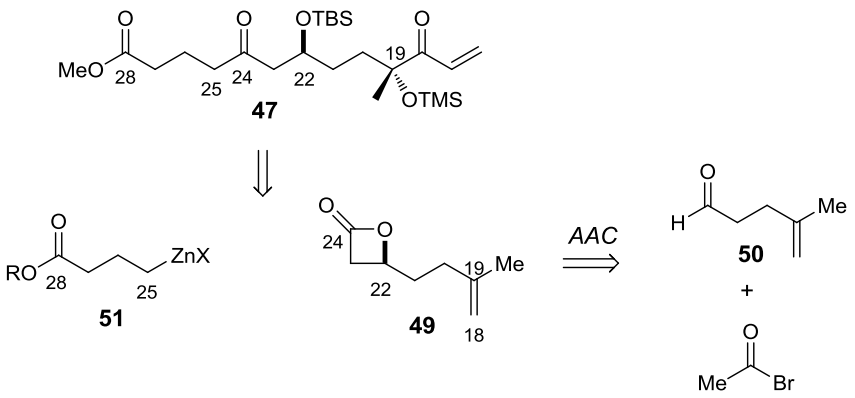
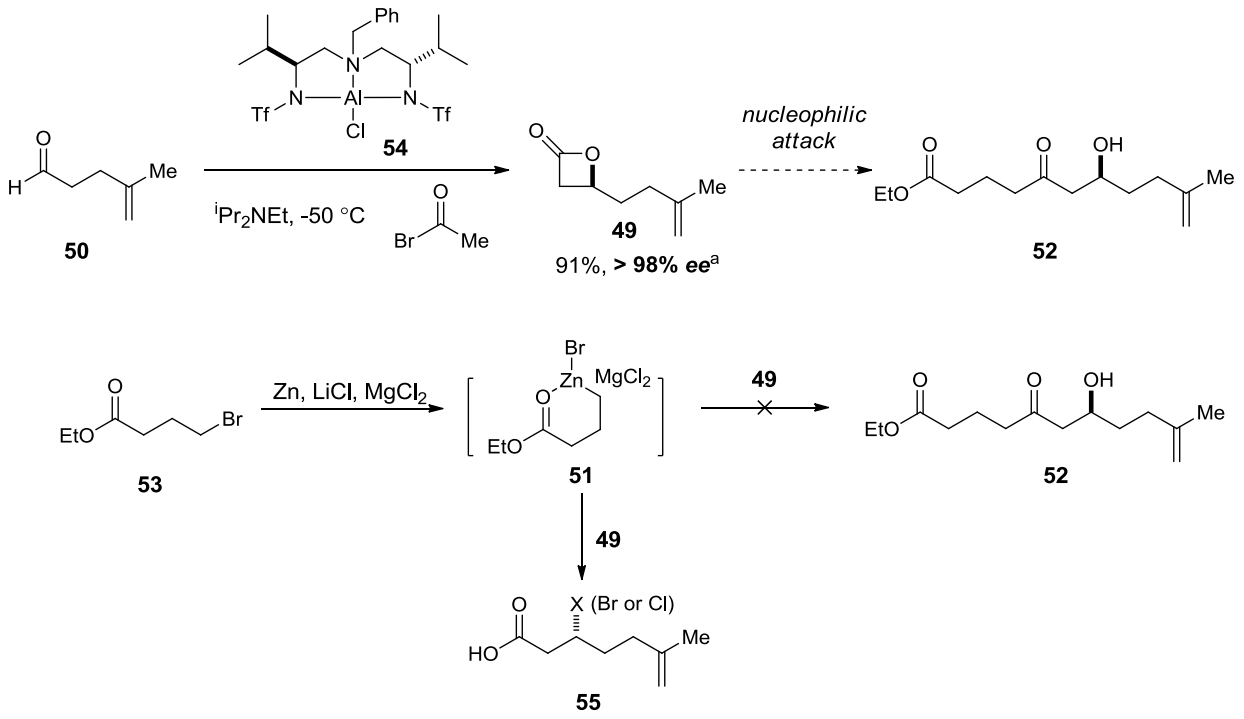


Figure 6. Retrosynthesis of the enone fragment 47

Following the retrosynthesis mentioned above, we initiated our investigation with a Lewis acid catalyzed AAC reaction between aldehyde **50** and acetyl bromide (Scheme 6). Utilizing Al(III)-triamine complex **54** as the catalyst, aldehyde **50** underwent cyclocondensation with the *in situ*-generated ketene arising from acetyl bromide to produce β-lactone **49** (91%, >98% *ee*). We planned to ring open the β-lactone with organozinc reagent **51** based on literature precedent. Knochel has demonstrated that functionalized organozinc reagents, such as **51**, can add to aromatic aldehydes and ketones effectively in the presence of $MgCl_2$.[24] Employing Knochel's protocol, ethyl 4-bromobutanoate **53** was reacted with magnesium powder in a THF solution of $ZnCl_2$ and LiCl at 25 °C for 1.5 h to generate **51**. Exposing β-lactone **49** to **51** at ambient temperature overnight, however, only provided halogenated carboxylic acid **55** in 52% yield but none of the desired ketoester. It was reasoned that the carbon nucleophile **51** was unreactive to add into the β-lactone while the halogen anion (Br^- or Cl^-) in the reaction system underwent nucleophilic ring opening to give **55**, a reactivity that has been observed with azide and sulfonamide anion nucleophiles.[22] Based on this result, we needed to identify a more reactive carbon nucleophile to accomplish the desired lactone-to-ketoester conversion.

Scheme 6. AAC reaction and initial attempts at converting the β-lactone to the ketoester



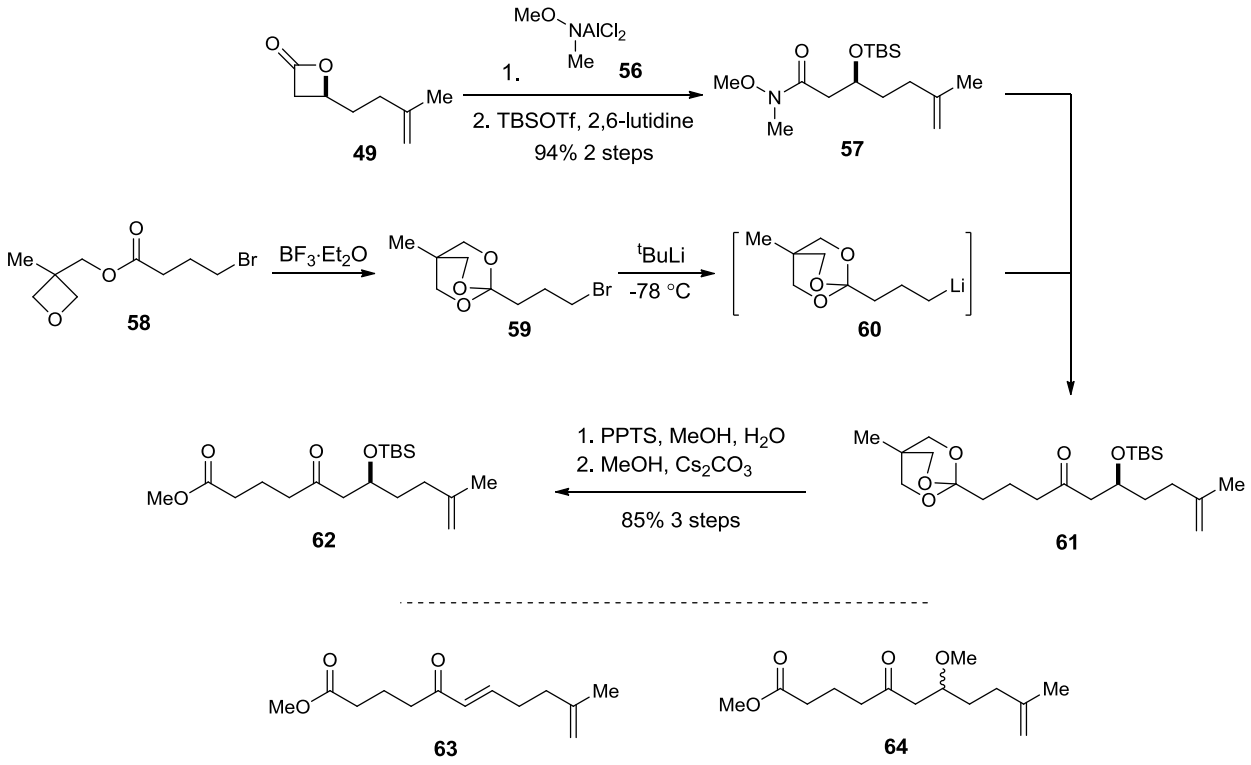
[a] The *ee* and the absolute stereochemistry were determined by Trost ester analysis of the ring opened product of **49** (See experimental section for details).

We then decided to employ a two-step approach to construct the ketoester utilizing a more reactive organolithium rea

gent as the nucleophile (Scheme 7). First step involved converting β-lactone **49** to Weinreb amide **57** which was accomplished though nucleophilic attack of $MeON(Me)AlCl_2$ **56** followed by silylation of the intervening secondary alcohol (94%, two steps). The requisite organolithium reagent **60** was prepared according to Corey's protocol.[25] An initial rearrangement of **58** to **59** took place in the presence of catalytic $BF_3{\cdot}OEt_2$ and the subsequent lithium-halogen exchange occurred upon treating **59** with ^{t}BuLi at −78 °C. This *in situ*-generated organolithium reagent **60** underwent nucleophilic attack at the carbonyl of **57** to produce the corresponding keto-orthoester **61** (−78 °C, 3h). Rapid hydrolysis of crude **61** was

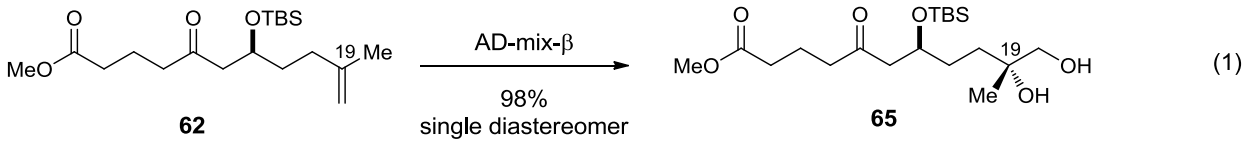
accomplished under acidic conditions (0.1 equiv of PPTS, MeOH:H_2O=32:1, ambient temperature) and the ensuing methanolysis was carried out in a one-pot fashion by introducing Cs_2CO_3 (2 equiv) in the reaction mixture to afford the desired ketoester **62** (85%, three steps). The nature of the base was critical to allow for clean transesterification, as switching to less expensive K_2CO_3 led to fast β-elimination of the TBS ether. This was proved by the isolation of both enone **63** and β-methoxy ketone **64** byproducts.

Scheme 7. Revised synthesis of the ketoester



Having accessed ketoester **62**, we set out to install the C_{19} tertiary alcohol via Sharpless asymmetric dihydroxylation (SAD).[23] Under the typical SAD conditions, treating **62** with AD-mix-β in 1:1 *t*-BuOH/H_2O provided diol **65** in 98% yield as a single diastereomer determined by ^{13}C NMR (Eq 1). The absolute configuration of C_{19} was assigned (*R*) according to the

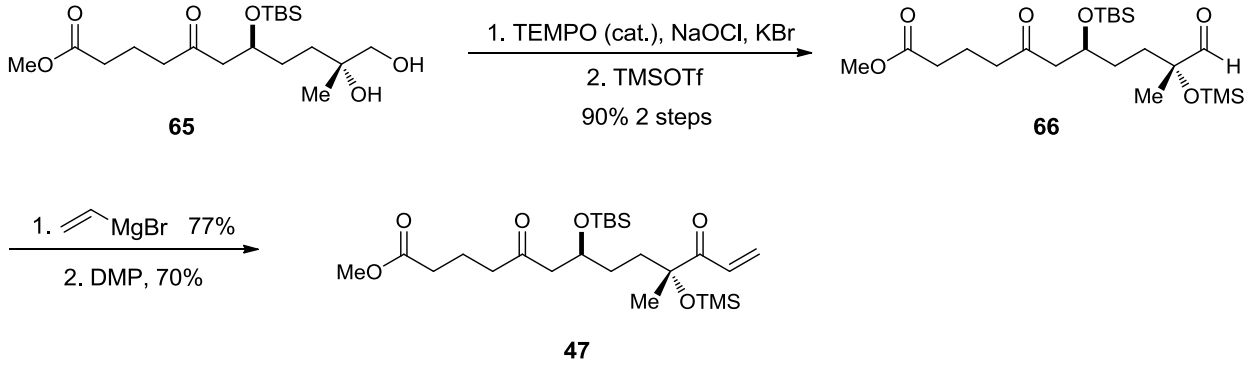
mnemonic device developed by Sharpless and co-workers.[23] The excellent diastereoselectivity of the dihydroxylation was surprising given that 1,1-disubstituted olefins typically show reduced selectivity due to lack of steric bias.[26]



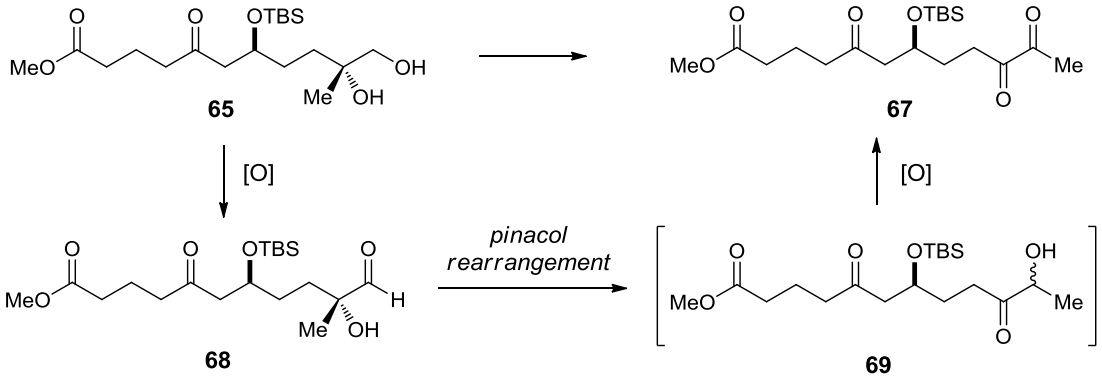
(1)

In order to complete the synthesis of fragment **47**, we utilized an oxo ammonium oxidation[27] to convert the primary alcohol in **66** to an aldehyde and then perform a Grignard addition and a Dess-Martin oxidation to finalize the enone (Scheme 8). In the event, treating **65** with catalytic 2,2,6,6-tetramethylpiperidine (TEMPO), KBr, and NaOCl solution afforded aldehyde **66** upon silylation of the tertiary alcohol with TMSOTf (90% yield, two steps). The exact stoichiometry of NaOCl (1.0 equiv) was crucial to avoid substantial over-oxidation of **65**. In the presence of excess oxidant, triketone **67** was isolated as a byproduct, presumably via pinacol rearrangement of **68** and oxidation of the resulting secondary alcohol **69**. Chemoselective Grignard addition of vinylmagnesium bromide took place at the aldehyde (77%) and the secondary alcohol thus obtained was treated with Dess-Martin periodinane to give the targeted enone fragment **47** (70%). This enone was stored in benzene at −25 °C with a crystal of 2,6-di-*tert*-butyl-4-methylphenol (BHT) to prevent polymerization.

Scheme 8. Complete the enone synthesis and possible over oxidation



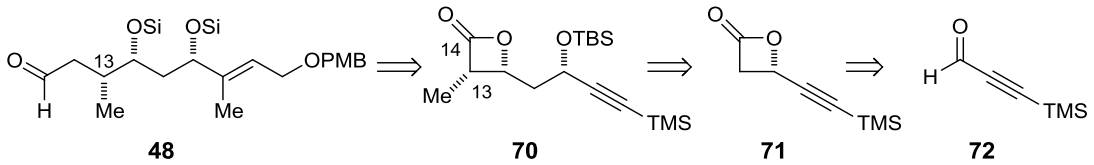
Over oxidation:



2.2 EXPLORATORY SYNTHESIS OF THE ALDEHYDE FRAGMENT

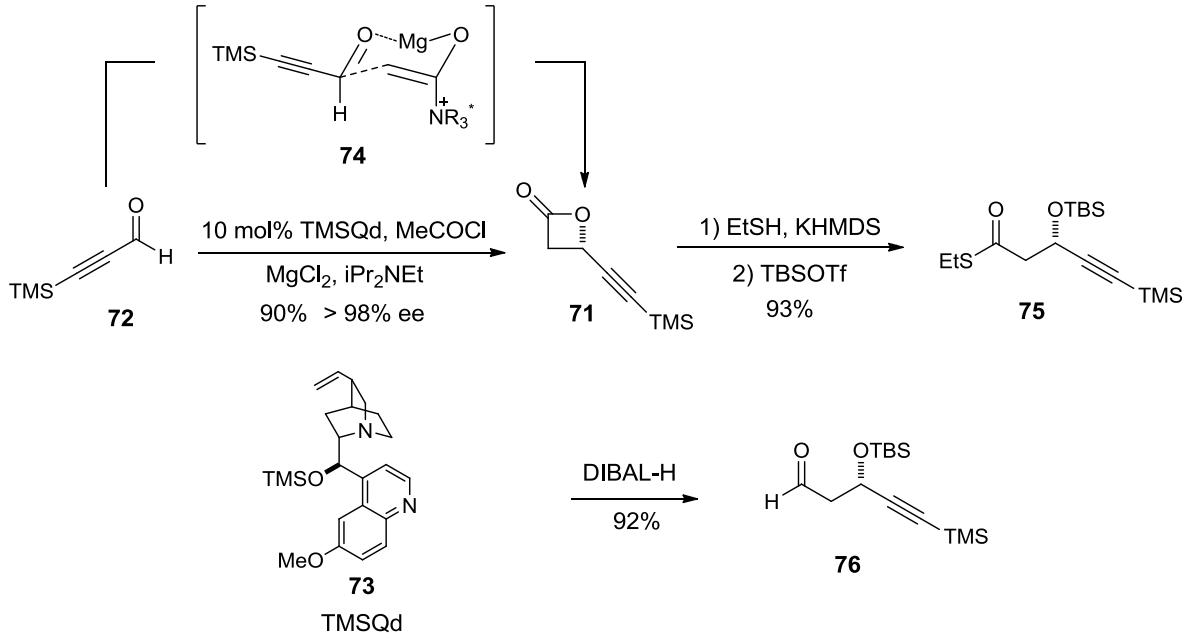
With the synthesis of enone fragment **47** completed, our next step was to access aldehyde **48** that would be joined with **47** to construct the carbon back bone of the bis-spiroketal in spirolide C. Our initial plan of introducing the three stereocenters in **48** was to prepare enantioenriched β-lactone **70** via two consecutive AAC reactions (Scheme 9).[21a] The following structure modifications of **70** would involve insertion of a methylene group between C_{13} and C_{14} and elaboration of the alkyne group to a trisubstituted olefin.

Scheme 9. Initial plan for the aldehyde fragment synthesis



Our synthesis began with a Lewis base-catalyzed AAC reaction to attain enantioenriched β-lactone **71** (Scheme 10). Utilizing TMSQd **73** (10 mol %) as the catalyst and $MgCl_2$ (1.0 equiv) as the Lewis acid, aldehyde **72** underwent cyclocondensation with acetyl chloride at −78 °C to afford β-lactone **71** (90%, >98% *ee*). The excellent enantioselectivity was achieved by going through the closed transition state **74**.[28] We then employed a one-pot procedure to ring open **71** and protect the resulting secondary alcohol. Nucleophilic attack of ethane thiol catalyzed by KHMDS (0.1 equiv) yielded the secondary alcohol that was trapped by *in situ* silylation with TBSOTf to give thioester **75** in 93% yield. Thioester **75** was then reduced to aldehyde **76** with DIBAL-H (92%), setting the stage for a second AAC reaction.

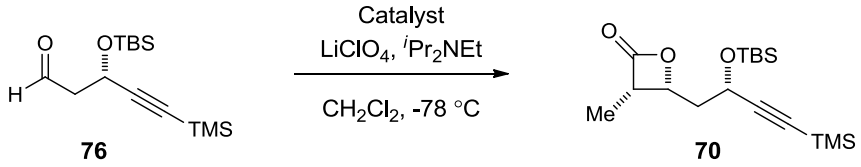
Scheme 10. Early stage of the aldehyde fragment synthesis



In comparison to the aforementioned AAC reaction of **72** (Scheme 10), the cyclocondensation of aldehyde **76** with propionyl chloride required more experimentation to reach a satisfactory result (Table 1). Compared to **72**, aldehyde **76** was anticipated to show diminished reactivity in the AAC reaction due to steric bulk imposed by the OTBS group. In response, we chose a stronger Lewis acid ($LiClO_4$) to facilitate the reaction by increasing the electrophilicity of **76**. When using two equivalents of $LiClO_4$ and 10 mol % of TMSQd, cyclocondensation between **76** and propionyl chloride only afforded a modest yield of 40% (Entry 1). The β-lactone product **70** was contaminated by inseparable impurities containing silyl groups (TBS and TMS) identified by ^{1}H NMR. The structure of the impurities remained elusive though. We attributed this impurity formation to a retro-aldol process of aldehyde **76** under the influence of excess Lewis acids. In order to suppress this unproductive retro-aldol without retarding the desired cyclocondensation, we decided to lower the stoichiometry of the Lewis acid

to 0.3 equivalent while increase the catalyst loading (TMSQd) to 20 mol %. As a result, the reaction became much cleaner but the conversion of the aldehyde dropped to 60%, resulting in a lower yield (32%) (Entry 2). Eventually, switching to a more reactive catalyst, *O*-methylquinidine (MeQd, 20 mol %),[28] in combination with $LiClO_4$ (0.5 equiv) gave β-lactone **70** in 65% yield as a 5.6:1 inseparable mixture of diastereomers. The moderate diastereoselectivity was attributed to the mismatched nature of the catalyst and substrate with respect to stereocontrol (Figure 7). Evans has shown that β-oxygenated aldehydes **77** inherently favored a 1,3-*anti*-relationship between the newly formed hydroxyl group and the pre-existing one (**79**).[29]

Table 1. Optimization of the AAC reaction of 76 to 70



Entry	Catalyst	Loading (mol%)	L.A. equiv	d.r.[a]	yield %[b]
1	TMSQd	10	2.0	4.2:1	40[c]
2	TMSQd	20	0.3	4.2:1	32[d]
3	MeQd	20	1.0	5.6:1	56[d]
4	MeQd	20	0.5	5.6:1	65[d]

[a] Determined by ^1H NMR. [b] Isolated yield of two diastereomers. [c] Products were contaminated by inseparable impurities. [d] Clean products

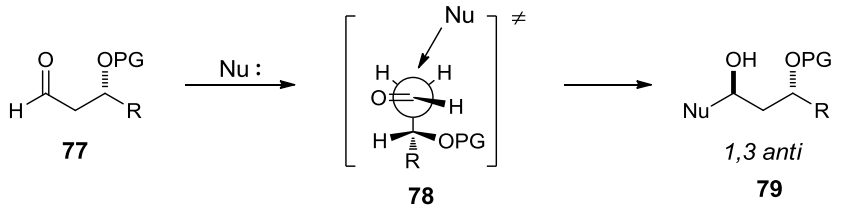
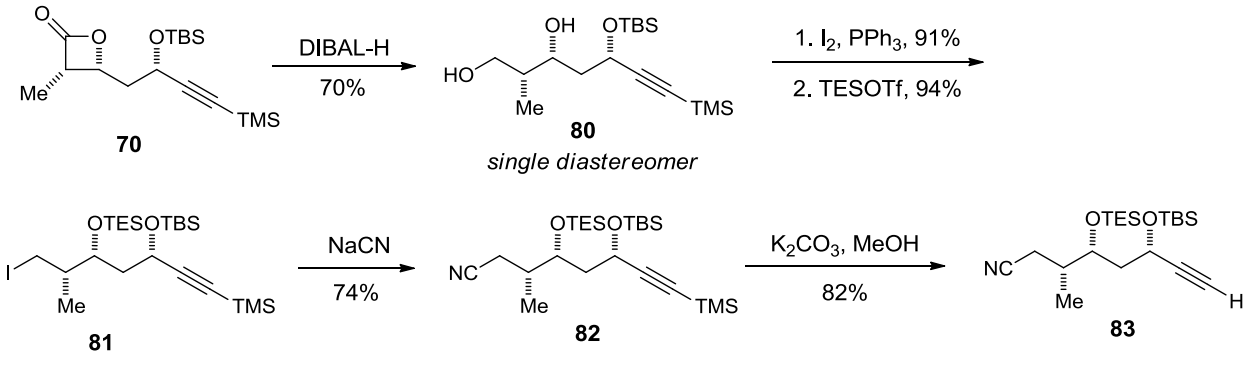


Figure 7. Evans' model for substrate-controlled 1,3-diastereoselectivity

To complete the fragment synthesis, we needed to convert the β-lactone functionality of **70** to a one carbon homologated aldehyde and also transform the TMS alkyne to a trisubstituted olefin. To achieve these goals, we treated **70** with DIBAL-H at −50 °C to afford reductive ring opening and isolated diol **80** as a single diastereomer after flash column chromatography. Iodination of the primary alcohol took place upon exposing **80** to I_2 and triphenylphosphine (91%). After silylation with TESOTf, iodide **81** was subjected to a S_N2 reaction with sodium cyanide (DMSO, 60 °C) to give **82** (74%). Selective deprotection of the TMS alkyne with K_2CO_3 in MeOH at ambient temperature gave **83** in 82% yield. It was initially planned to use the zirconium catalyzed carboalumination chemistry[30] to install the methyl group on the alkyne. However, a model study dismissed this strategy due to no reaction or decomposition occurring at extended reaction time (Figure 8). We attributed the observed lack of reactivity of **84** to the bulky TBS ether that interfered with the coordination of the triple bond to the zirconium metal center and such coordination is required for effective carbon-metal addition.[31]

Scheme 11. Structural modification of β-lactone 70



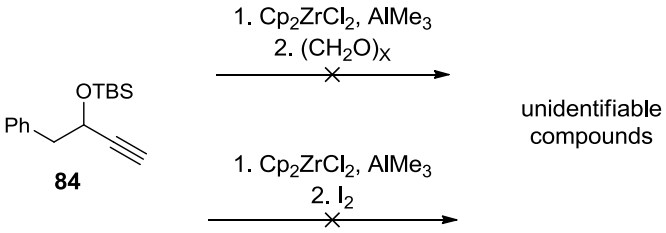
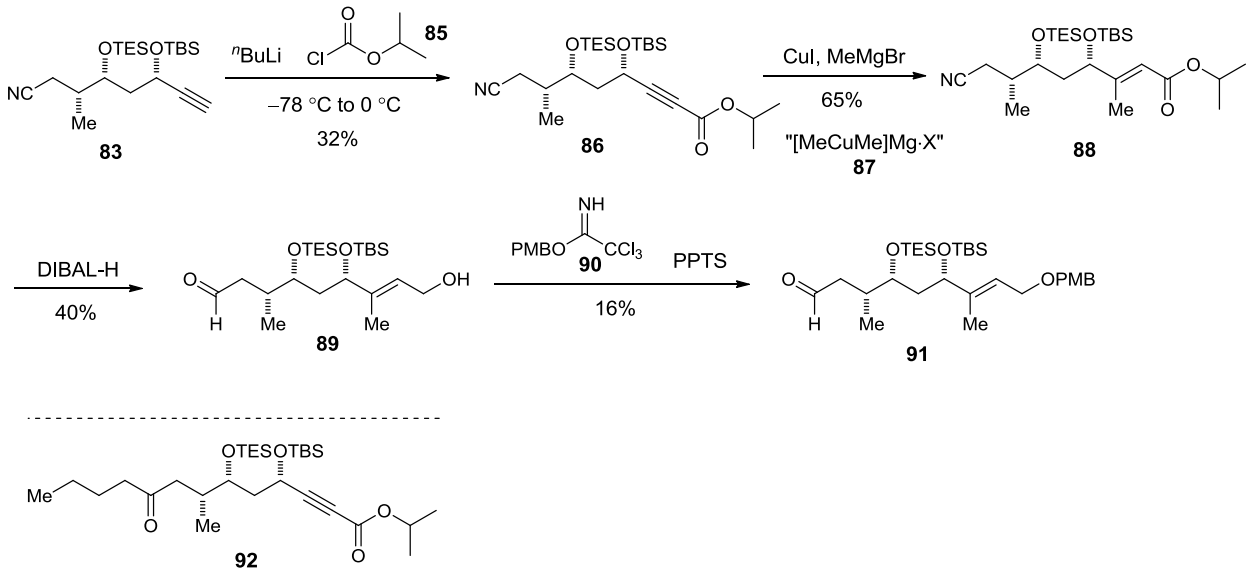


Figure 8. Attempted model studies on the carboalumination

We next pursued an alternate method, copper-mediated conjugated addition, to covert alkyne **83** to a trisubstituted olefin.[32] This time we focused on utilizing the activated alkyne **86** as the substrate (Scheme 12). Alkyne **86** was prepared by deprotonating **83** with ^{n}BuLi (−78 °C) followed by *in situ* acylation with isopropyl chloroformate **85** (32%). The modest yield was attributed to unproductive addition of ^{n}BuLi to the nitrile group in **86**, evidenced by the isolation of **92** (22%) after hydrolysis. The following conjugated addition proceeded smoothly upon exposing **86** to the *in situ*-generated cupric reagent **87** from MeMgBr and CuI (2:1) to yield **88** (65%). Double reduction of the nitrile and the ester groups in **88** was achieved by employing 3.0 equivalents of DIBAL-H at −50 °C, albeit in modest yield (40%). We then decided to protect the primary alcohol **88** as PMB ether. Considering the aldehyde functionality is sensitive to strong

base conditions, we chose mild acid-catalyzed conditions to form the PMB ether. Exposing **89** to PMB-acetimidate **90** and pyridinium *p*-toluenesulfonate (PPTS) overnight provided **91** as the major product (crude ^{1}H NMR), however, only led to 16% isolated yield after flash column chromatography. We assumed that aldehyde **91** was sensitive to silica gel and prone to decomposition during the course of separation. Overall, it took 14 steps to synthesize aldehyde fragment **91** in 0.23% yield from commercially available starting materials. The lack of efficiency of this route prompted us to pursue an alternative one to **91**.

Scheme 12. Complete the synthesis of the aldehyde fragment via AAC approach



2.3 FINALIZED ROUTE TO THE ALDEHYDE FRAGMENT

The previous synthesis of the aldehyde fragment displayed the efficacy of our AAC chemistry to construct stereocenters, however, modest yields were encountered in the conversion of an alkyne

to a trisubstituted olefin as well as the PMB protection in the last step. If we could integrate the trisubstituted olefin and the PMB group in the starting material **93** (Figure 9), we would be able to avoid these low-yielding structural modifications and ultimately increase the overall synthetic yield. Following the literature procedure, aldehyde **93** was prepared in decagram quantity (78%, four steps).[33] Unfortunately, attempted AAC reactions of **93** under Lewis acid- or Lewis base-catalyzed conditions proved futile with only recovery of **93** (Figure 9). Instead, we decided to use a Keck-type allylation reaction[34] followed by an asymmetric Brown crotylation[35] to set the requisite stereocenters (Scheme 13). The resulting terminal olefin in **96** could be converted to an aldehyde by a hydroboration-oxidation sequence.

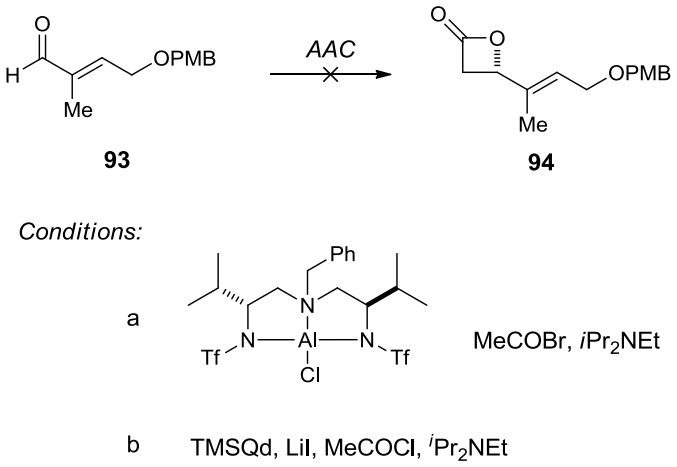
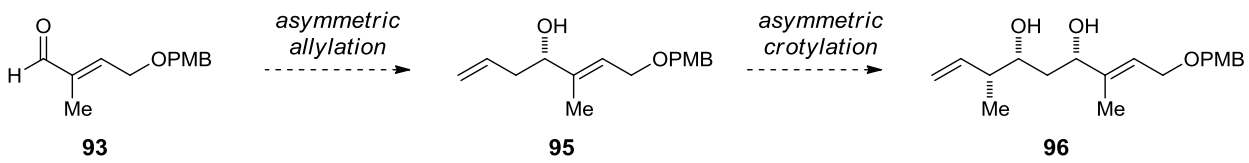


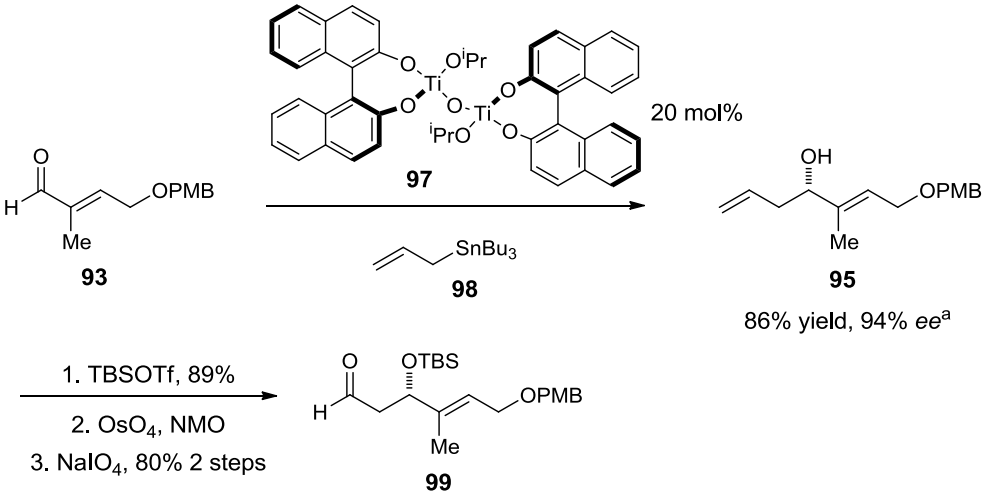
Figure 9. Modified starting material and attempted AAC reactions

Scheme 13. New strategy to establish stereocenters in the aldehyde fragment



The asymmetric allylation of aldehyde **93** was executed by following Maruoka's procedure (Scheme 14).[34] Maruoka and co-workers disclosed a Keck-type enantioselective allylation catalyzed by Ti(IV)-BINOL complex **97**. In the presence of **97** (20 mol %), aldehyde **93** was reacted with allyltributylstannane **98** at 0 °C to produce chiral carbinol **95** (86%, 94% *ee*). Upon silylation of **95** with TBSOTf (89%), we employed a dihydroxylation-oxidative cleavage sequence to access aldehyde **99** (80%, two steps).[36] Chemoselective dihydroxylation at the terminal olefin was achieved by utilizing 1.0 equivalent of NMO and keeping the reaction temperature at 0 °C, as the internal olefin is deactivated to the dihydroxylation by the steric hindrance.

Scheme 14. Keck-type asymmetric allylation catalyzed by Ti(IV)-BINOL complex 97

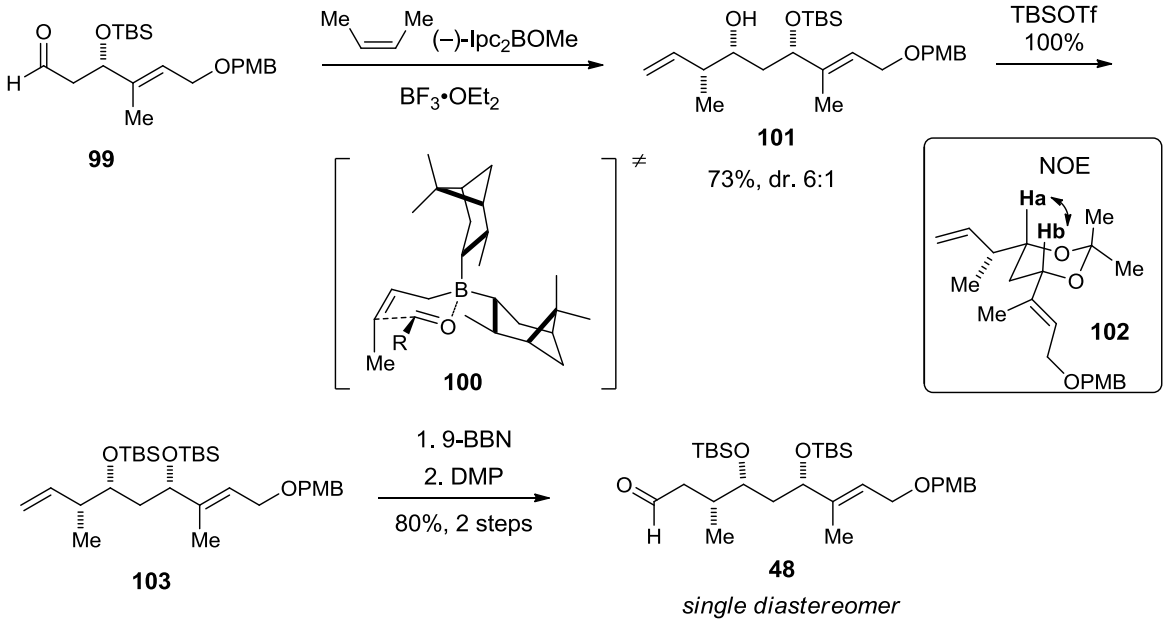


[a] The *ee* was determined by Mosher ester analysis (see experimental section).

To complete the fragment synthesis, an asymmetric Brown crotylation was utilized to set the other two stereocenters required in aldehyde fragment **48** (Scheme 15).[35] Treating **99** with the *in situ*-generated crotyl-(−)-Ipc-borane afforded **101** after 3h at −78 °C as a 6:1 mixture of

diastereomers (73%). The major diastereomer was confirmed to have the desired stereochemistry by nOe analysis after converting **101** to the acetonide derivative **102**.[37] We observed a strong signal between the **Ha** and **Hb** in the NOESY spectrum, indicating a *syn* relationship between the alkoxy groups. It is noteworthy that the diastereoselectivity (6:1) in the crotylation reaction is comparable to the previous AAC approach (5.6:1). Upon silylation of this diastereomer mixture with TBSOTf (100%), chemoselective hydroboration (9-BBN) of the terminal olefin in **103** and the subsequent Dess-Martin oxidation of the intervening alcohol delivered aldehyde fragment **48** which was isolated as a single diastereomer after flash column chromatography (80%, two steps). This optimized route only required eight steps, leading to an enhanced overall yield of 36%.

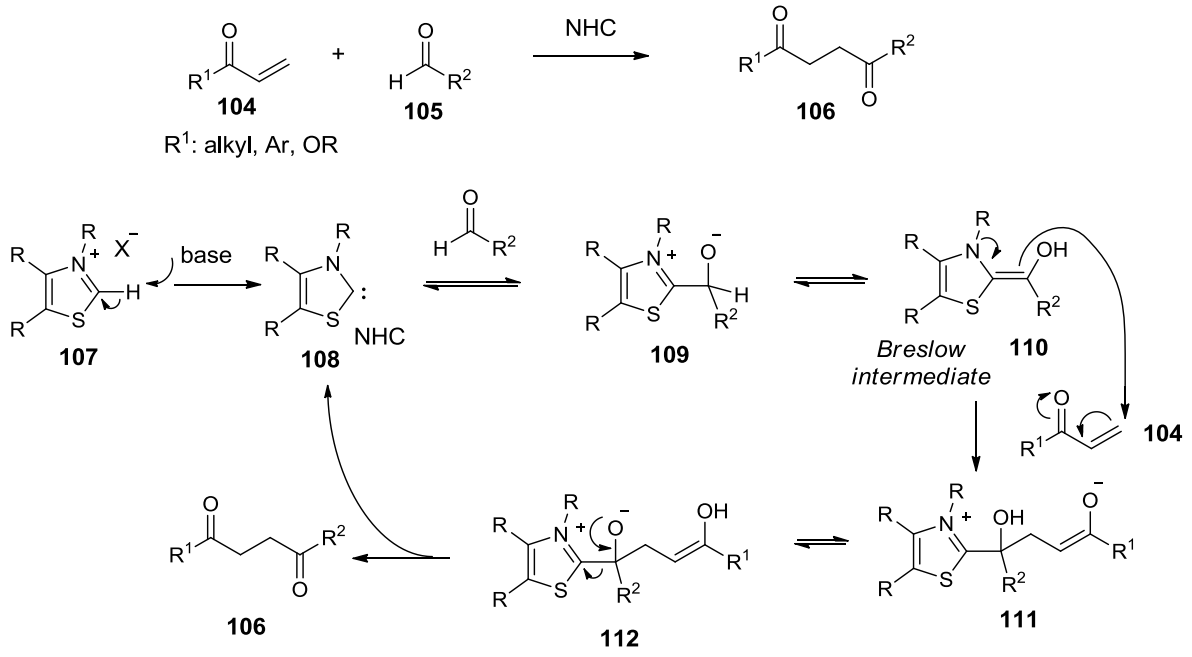
Scheme 15 Asymmetric Brown crotylation and completion of the fragment synthesis



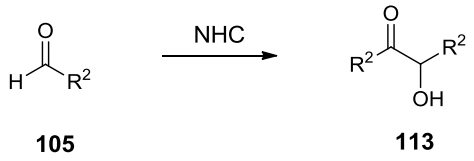
2.4 COUPLING THE ENONE AND THE ALDEHYDE FRAGMENTS

Constructing the carbon back bone of the bis-spiroketal moiety in spirolide C required joining the enone and the aldehyde fragments by attaining a 1,4-dicarbonyl connectivity. The Stetter reaction rose as a proper strategy. Since the seminal work of Stetter in 1973, the *N*-heterocyclic carbene (NHC)-catalyzed addition of aldehydes to Michael acceptors, the Stetter reaction, has been widely used as a catalytic method for the synthesis of 1,4-dicarbonyl and related compounds.[38,39] The significance of this transformation lies in the capacity of generating an "unnatural" functional group distance, which is difficult to accomplish using traditional methods. In the catalytic cycle, aldehyde **105** is activated by carbene **108** under generation of the Breslow intermediate **110** (Scheme 16).[40] This acyl anion equivalent **110** undergoes nucleophilic attack to the Michael acceptor **104** that is followed by regeneration of catalyst **108** to produce the 1,4-dicarbonyl product **106**.

Scheme 16. The Stetter reaction and its mechanism



Despite extensive studies in this area, the intermolecular Stetter reaction has been rarely utilized on complex molecules in a natural product synthesis. There are several limitations that restrain its synthetic utility. The competing side reaction, benzoin condensation,[40] is inevitable and excess aldehyde is typically required to achieve an appreciable yield of the Stetter product (Figure 10). In the case of late-stage fragment coupling, superstoichiometry of one coupling partner will drastically diminish the efficiency of the entire synthesis. Further, when using unreactive aliphatic aldehyde, reactions require forcing conditions, such as prolonged time, elevated temperature and excess bases, which are not compatible with diverse functional groups. Despite these disadvantages, the Stetter reaction possesses compelling features for us since it allows for direct access to the 1,4-dicarbonyl connectivity and after the next acid-mediated ketalization step, we can establish the required bis-spiroketal scaffold in a total of two steps from the enone and the aldehyde fragments.

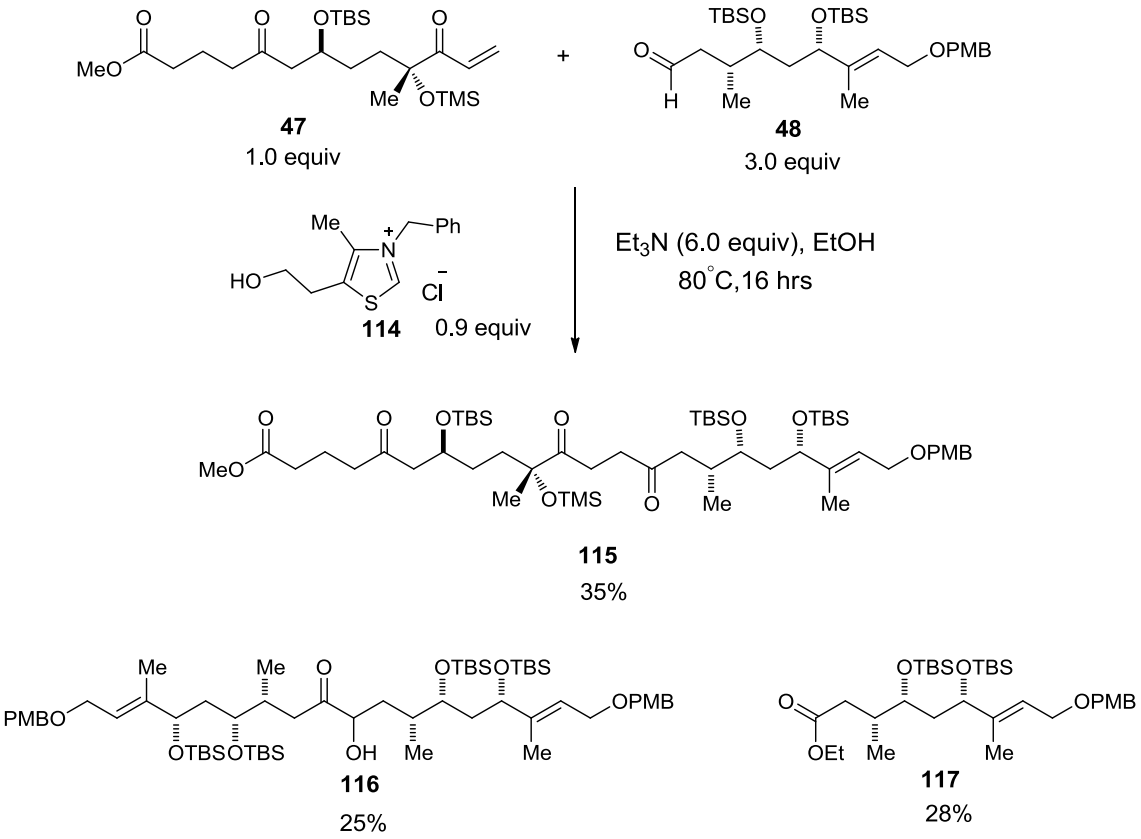


105 **113**

Figure 10. Benzoin condensation

To initiate the study of the fragment coupling, we started with the thiazolium-based NHC catalyst **114** due to its rich history in the Stetter transformation (Scheme 17).[38] Refluxing a mixture of catalyst **114** (0.9 equiv), enone **47** (1.0 equiv), aldehyde **48** (3.0 equiv), and Et_3N (6.0 equiv) in EtOH for 16h afforded the coupled product **115** in 35% yield. Along with **115**, we also isolated the benzoin condensation product **116** (25%) as well as byproduct **117** (28%) arising from air oxidation of **48** catalyzed by **114**.[41] Despite the modest conversion, enone **47** was consumed completely according to the crude ^1H NMR, indicating its limited stability under the reaction conditions. Such instability of **47** was further confirmed by its rapid polymerization even at low temperature, forming an opaque white plastic. Seemingly, if the desired Stetter reaction proceeded at a slow rate, the polymerization of the enone would deplete the active monomer and as a result, aldehyde **48** would be consumed by either benzoin condensation or air oxidation. Therefore, in order to improve the yield, we needed to identify a more reactive and selective catalyst for the Stetter reaction.

Scheme 17. Initial attempts at the Stetter reaction utilizing thiazolium-based catalyst 114



Our next choice of catalyst was Rovis catalyst **118**[42] (Figure 11), based on its efficacy demonstrated in Nicolaou's synthesis of Lomaiviticin aglycon. Nicolaou and co-workers identified **118** as an active catalyst for a late stage ring construction by way of a benzoin-type transformation.[43] Although this reaction benefits from the intramolecular setting, the observed efficiency (70%) indicates great reactivity of the catalyst, considering the steric bulk of the substrate. This time we employed a full equivalent of the catalyst **118** in combination with enone **47** (1.0 equiv), aldehyde **48** (2.0 equiv) and Et_3N (10 equiv) for the Stetter reaction. After refluxing the mixture for 16h in CH_2Cl_2, the coupled product **115** was only isolated in 24% yield. In the course of the reaction, substantial amount of "rubber" material precipitated out of the solution, implying polymerization of enone **47**.

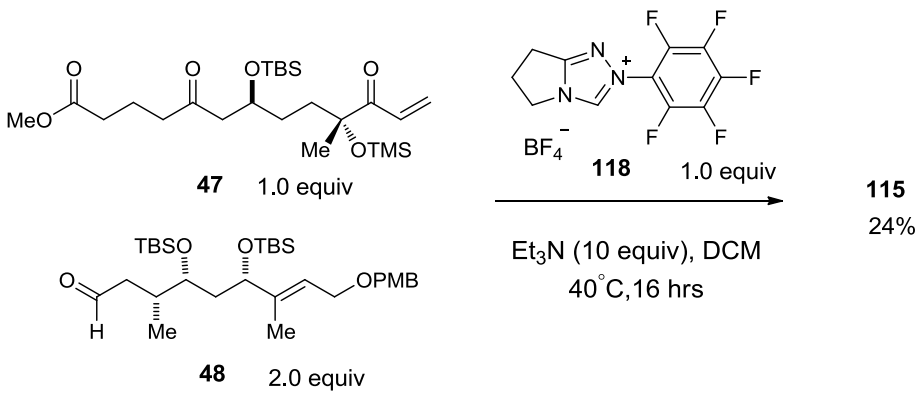
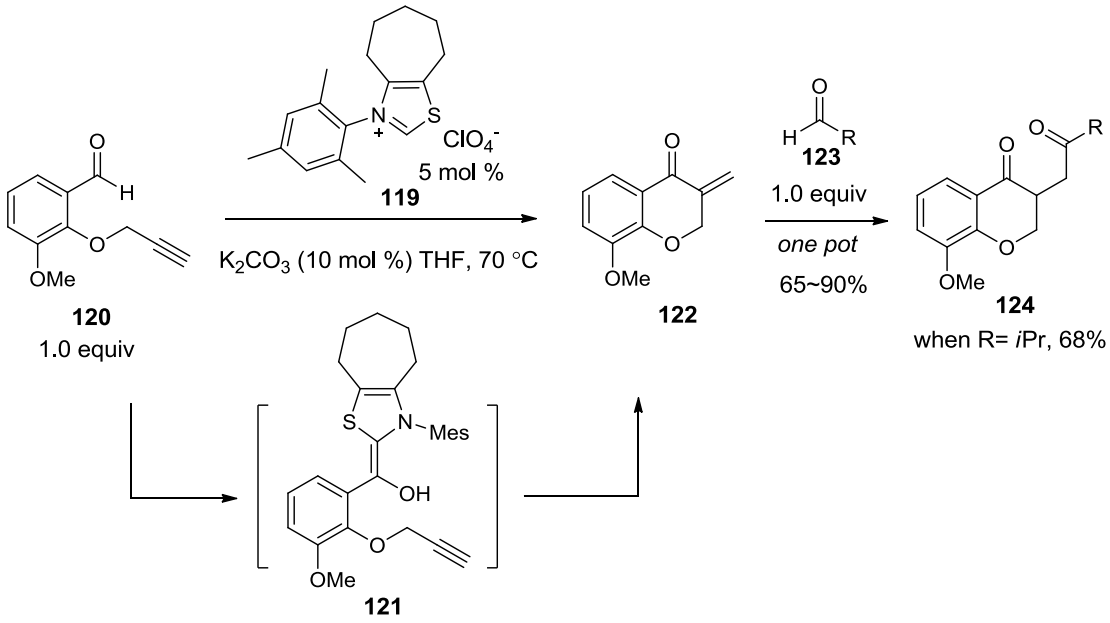


Figure 11. Utilize the Rovis catalyst for the Stetter reaction

In the search for a proper catalyst for our coupling reaction, a thiazolium-based NHC catalyst **119** caught our attention (Scheme 18). This catalyst exhibited great reactivity in a hydroacylation-Stetter cascade reaction disclosed by Glorius in 2010.[44] The *in situ*-generated NHC catalyst derived from deprotonation of **119** activated aldehyde **120** to form the corresponding Breslow intermediate **121** that added to the tethered alkyne functionality. The resulting enone product **122**, under the influence of the same NHC catalyst, participated in a Stetter reaction with external aldehydes **123** to give 1,4-diketone products **124** in yields ranging from 65% to 90%. Of great interest to us is the ability of incorporating unreactive aldehyde, such as isobutyraldehyde **123** (R= ^{i}Pr) as the coupling partner. In comparison to aromatic aldehydes, isobutyraldehyde is usually much less reactive due to greater steric hindrance. However, the comparably high yield obtained utilizing isobutyraldehyde encouraged us to explore the reactivity of **119** in our coupling reaction.

Scheme 18. Hydroacylation-Stetter cascade reaction



Following Glorius's protocol,[45] we synthesized the thiazolium salt **119** to probe its reactivity in coupling **47** and **48** (Figure 12). The catalyst precursor **119** (20 mol %) and K_2CO_3 (40 mol %) were weighed in the glove box and added in the reaction vial equipped with aldehyde **48** (1.0 equiv) and enone **47** (1.5 euqiv). Anhydrous THF was introduced in the reaction mixture under N_2 atmosphere. This THF solution was refluxed for 3 h with exclusion of air to afford the coupled product **115** in quantitative yield with no observed benzoin condensation. This unparalleled efficacy of **115** is rather difficult to analyze without thorough mechanistic studies. It is well known that the performance of an NHC catalyst not only relies on its σ-donating property and thus the nucleophilicity of the free NHC, but also on the π-donating character relevant to the nucleophilicity of the Breslow intermediate.[45] Based on our results, a highly unsymmetrical environment of the carbene catalyst with bulky substitution (Mes) on the nitrogen atom and no substitution on the sulfur atom may be responsible for this particular reactivity.

Nevertheless, the great efficiency of our coupling reaction highlights the potential of utilizing the intermolecular Stetter reaction for complex molecule synthesis.

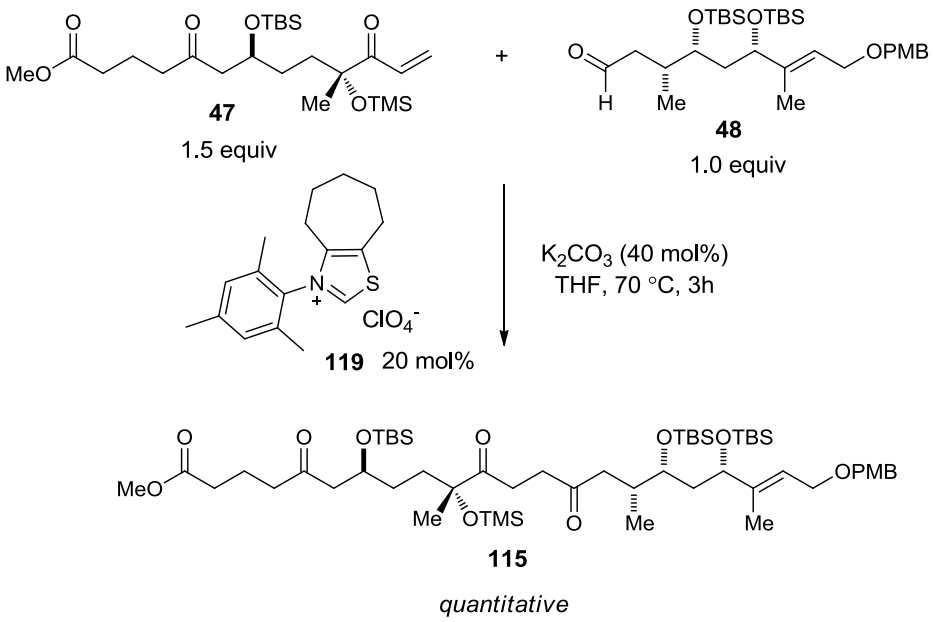


Figure 12. Optimized conditions for the Stetter reaction

2.5 BIS-SPIROKETAL SYNTHESIS

The success of the coupling reaction propelled us to investigate the proposed biomimetic ketalization of acyclic **115** to construct the bis-spiroketal in spirolide C (Figure 13). To simplify the synthesis, we planned to use acidic conditions to remove the silyl groups and also facilitate the cyclization.[46] Treating **115** with camphorsulfonic acid (0.5 equiv) in MeOH provided the bis-spiroketals *trans*-**125** and *cis*-**125** in 72% yield after 16 h. The diastereoselectivity was 6:1 favoring the unnatural *trans* isomer which is parallel to the results observed in other groups.[12,13]

Attempts to shift the equilibrium towards the desired epimer proved unfruitful, including increasing reaction temperature which caused complete decomposition and switching to non-polar solvent such as cyclohexane which shut down the ketalization due to lack of solubility. We believe that the unnatural epimer *trans*-**125** adopts a conformation that accommodates optimal hydrogen bonding interaction between free hydroxyl groups and the ether linkage in the tricycle. Nonetheless, the equilibration to the desired epimer is envisaged to occur when closing the macrocycle, since the natural epimer places the two "arms" of the bis-spiroketal in proximity which will become the future diene and dienophile components for the Diels-Alder reaction.

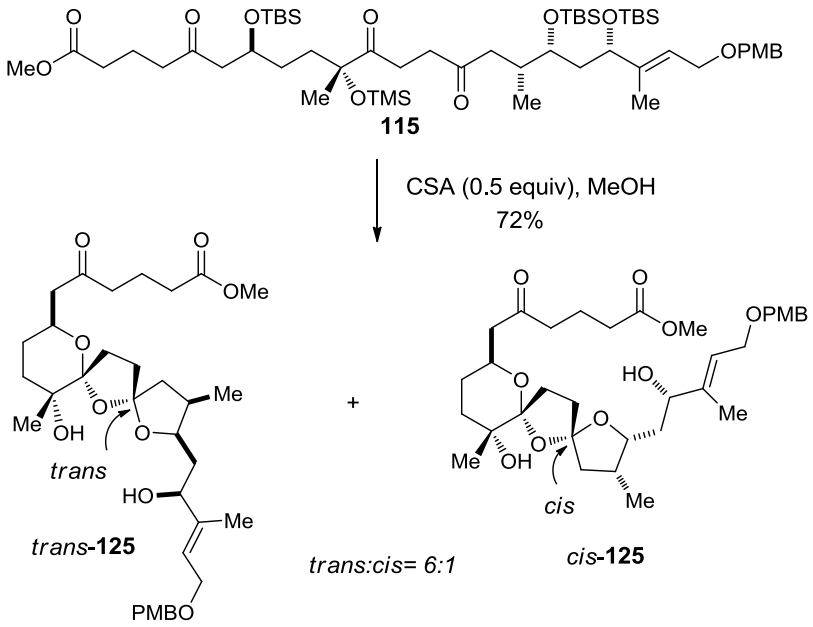
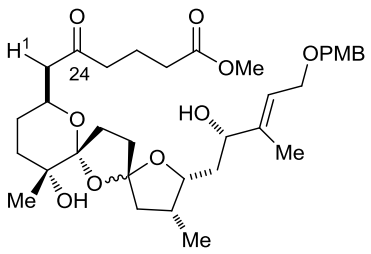


Figure 13. Acid-mediated silyl group removal and concomitant cyclization

In comparison to spirolide C, bis-spiroketals (*trans*-**125** and *cis*-**125**) possessed a ketone instead of an exo methylene group at C_{24} (Eq 2). A methylenation of this ketone unit was warranted to continue the synthesis of spirolide C. Considering most methylenation conditions are not compatible with free hydroxyl groups, protecting the diol seemed necessary prior to the

olefination. Surprisingly, treating **125** with TBSOTf and 2,6-lutidine at 0 °C led to complete decomposition within 1h (Eq 2). We assumed the unanticipated complication was due to the inductive effect of the β-alkoxy group that increased the acidity of the α proton (H^1) next to the ketone, resulting in the formation of a silyl enol ether. This hypothesized silyl enol ether intermediate could lead to side products via ring opening the six-membered ring and/or nucleophilic addition to carbonyls in an intermolecular or intramolecular fashion. In response, we needed to search for an appropriate olefination method to install the methylene in the presence of free hydroxyl groups and the acidic α proton.



125

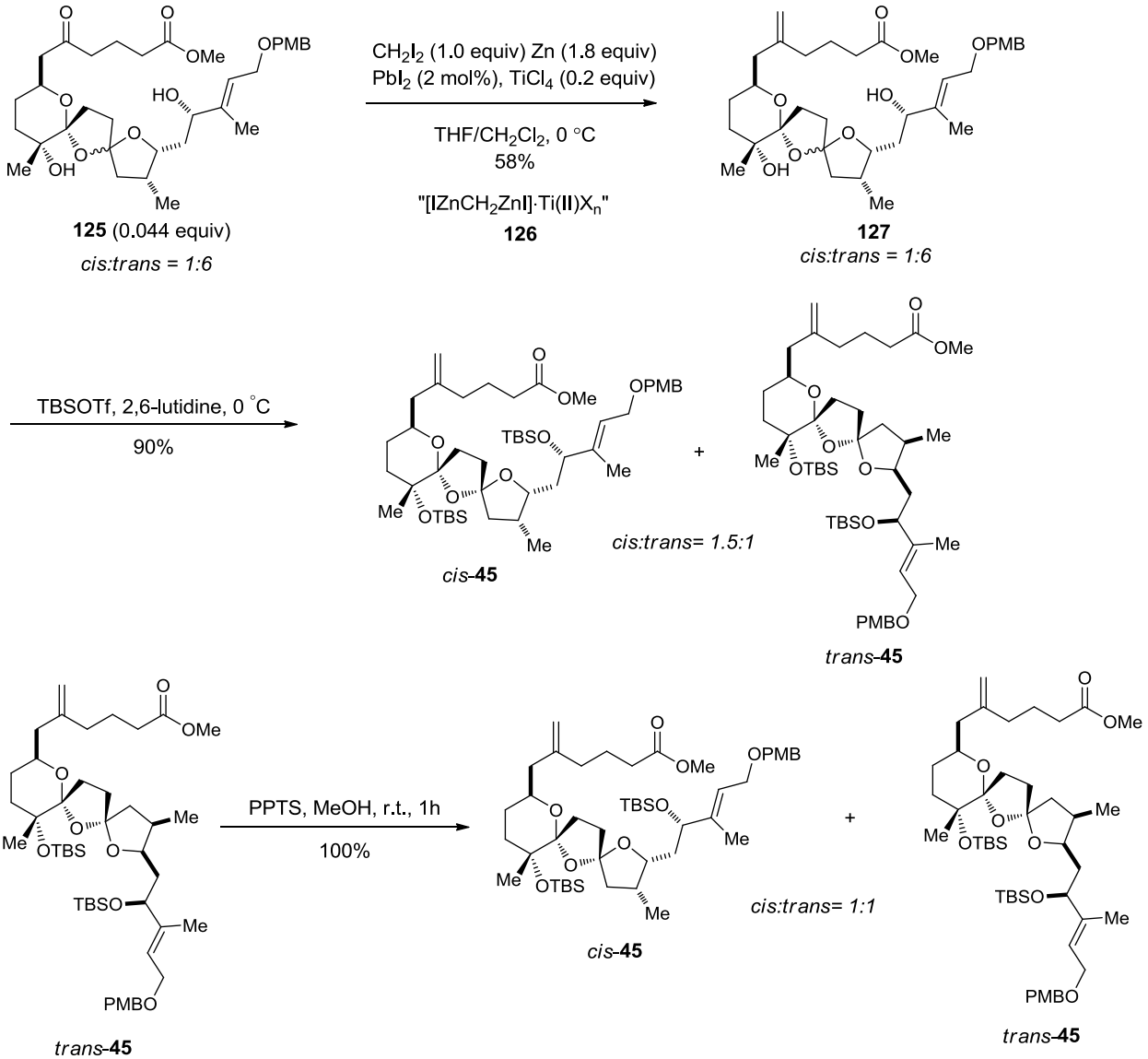
dr 1:6

TBSOTf, 2,6-lutidine, 0 °C → *decomposition* (2)

Methylenation of the sensitive and sterically hindered ketone **125** was achieved through a Takai olefination (Scheme 19).[47] The active methylenation reagent **126** was generated by mixing CH_2I_2, Zn dust, and catalytic PbI_2 in THF that was followed by addition of $TiCl_4$. The identity of the reagent was suggested as a germinal dizinc-Ti(II) complex **126**.[48] Exposing **125** to **126** produced **127** in 58% yield after stirring at 0 °C for 3h. The diastereomeric ratio was unchanged at this stage. The subsequent TBS silylation of the diol **127** proceeded smoothly with TBSOTf and 2,6-lutidine, providing the protected bis-spiroketals (*cis*-**45** and *trans*-**45**) in a combined 90% yield (Scheme 19). Interestingly, the diastereomeric ratio changed from 1:6 to 1.5:1, favoring the desired epimer (*cis*-**45**). It was assumed that by breaking the hydrogen bonding, the ground

state energy gap between these two epimers changed accordingly. Further, these epimers were separable by flash column chromatography. In order to enrich the desired epimer, the isolated *trans*-**45** was equilibrated in MeOH with excess PPTS, affording a 1:1 ratio of *cis*-**45** to *trans*-**45** after 1 h (Scheme 19). Therefore, by one cycle of separation and re-equilibration, we can access *cis*-**45** in a synthetically useful yield (60~70%).

Scheme 19. Finalize the synthesis of bis-spiroketal *cis*-45



In conclusion, we completed the stereoselective synthesis of bis-spiroketal *cis*-**45**. The route we developed highlighted the unprecedented implementation of an intermolecular Stetter reaction in fragment coupling. The ensuing acid-facilitated desilylation and ketalization provided an efficient access to the bis-spiroketal structure which upon functional group manipulations delivered *cis*-**45** with the desired configuration. This convergent approach should also be appropriate for the synthesis of other members in the spirolide family, and amenable to the generation of a range of non-natural spiroketal analogs for further structure and biological studies.

3.0 INTRODUCTION

The availability of efficient syntheses of enantioenriched α-hydroxy carbonyl compounds [(*R*)-**128** and (*S*)-**128**] is of great importance in the synthetic community due to their prevalence in many biologically active molecules. Compounds possessing this unit are useful synthons for asymmetric synthesis of natural products, including antitumor agents, antibiotics, pheromones, and sugars.[49] Many methods have been developed to prepare these compounds [(*R*)-**128** and (*S*)-**128**], among which the enantioselective oxidation of enolates has been used most frequently (Figure 14). Variants of this method fall into two categories: using stoichiometric chiral inducing agents or employing asymmetric catalysis on the prochiral enolates. The latter approach is more efficient and challenging and is the focus of the work in this document.

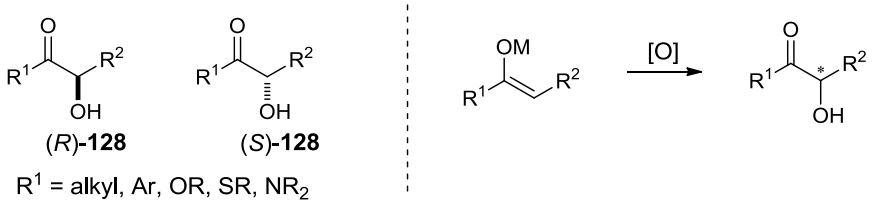
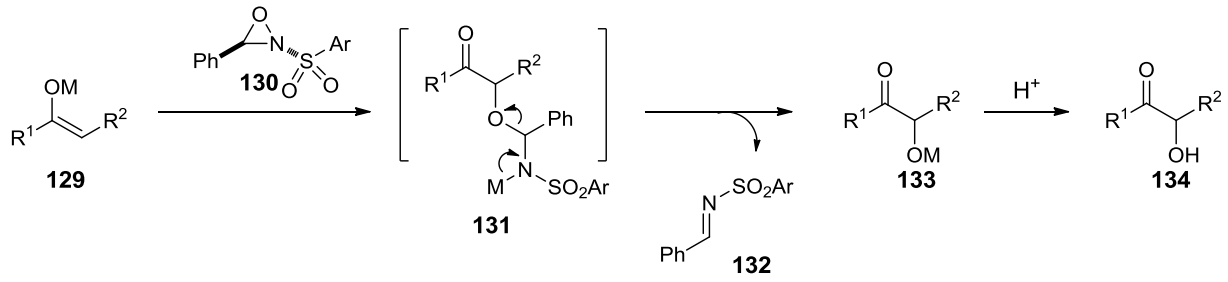


Figure 14. Chiral α-hydroxy carbonyl compounds and enantioselective enolate oxidation methods

N-Sulfonyl oxaziridine **130** has emerged as one of the most widely used electrophilic oxidants to allow for direct enolate oxidation (Scheme 20).[49] Such reactivity lies in the weak N-O bond as well as the strong electron withdrawing character of the sulfonyl group. The

hydroxylation is thought to proceed through a nucleophilic attack of enolate carboanion **129** at the electrophilic oxygen atom in **130**, generating the transient sulfonamide anion **131**. This intermediate will collapse and liberate the α-hydroxy carbonyl compound **133**, along with *N*-sulfonyl imine byproduct **132**.[50] Precedent of utilizing oxaziridine **130** to accomplish the enantioselective enolate α-hydroxylation will be discussed in the following chapter.

Scheme 20. General mechanism of enolate oxidation with *N*-sulfonyl oxaziridine



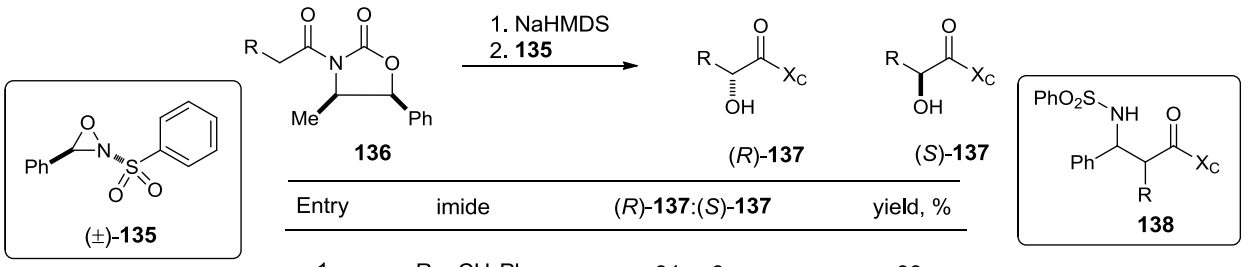
3.1 ASYMMETRIC ENOLATE ALPHA-HYDROXYLATION WITH STOICHIOMETRIC CHIRAL INDUCING AGENTS

The conventional methods for asymmetric enolate α-hydroxylation with *N*-sulfonyl oxaziridines involve either stoichiometric chiral auxiliaries or chiral oxidizing reagents. When using chiral auxiliaries, the stereo outcome is controlled by the covalently bonded chiral subunit which is removed after the oxidation.

Evans disclosed an asymmetric oxygenation of chiral imide enolates with racemic *N*-benzenesulfonyl oxaziridine (±)-**135** (Davis' reagent).[51] Treating the sodium enolate of **136** with a slight excess of (±)-**135** gave (*R*)-**137** and (*S*)-**137** in a ratio from 90:10 to 99:1 (Table 2). The

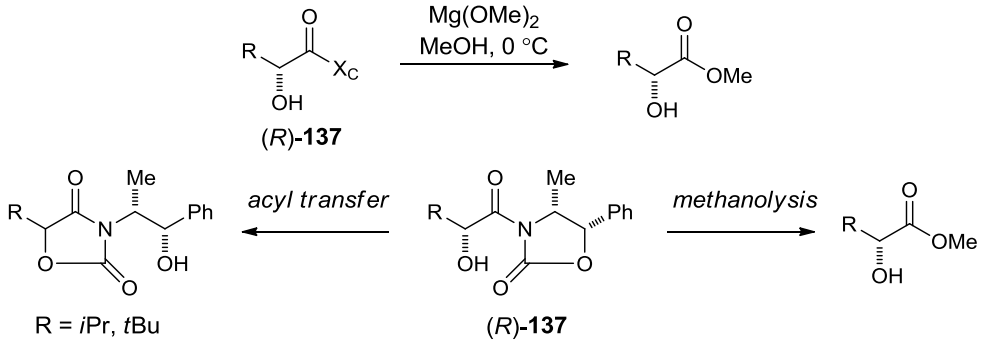
author also noticed a counter-ion dependent phenomenon in product distribution. The sodium enolate of **136** gave predominately α-hydroxy products **137**, while the lithium counterpart led to 54% of **137** as well as 44% of the aldol adduct **138**. The carboximide auxiliary was removed without substantial racemization by transesterification using $Mg(OMe)_2$ in MeOH at 0 °C. In most cases, methanolysis proceeded in yields ranging from 80% to 90%. However, the base-catalyzed intramolecular acyl transfer became prevalent with the hindered substrates (R=*i*Pr, *t*Bu, etc) (Scheme 21).

Table 2. Asymmetric α-hydroxylation of chiral carboximide enolates



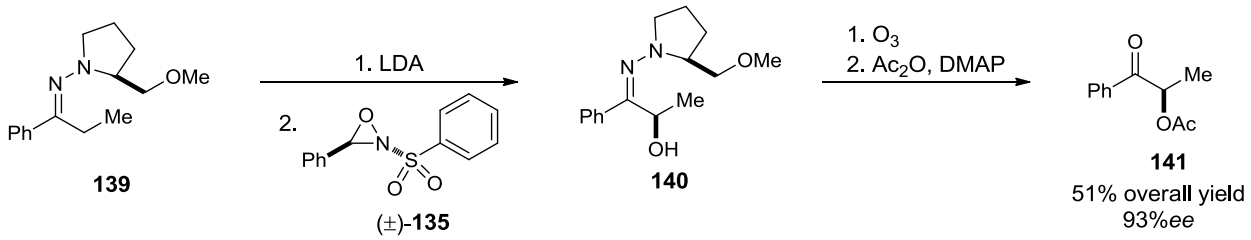
Entry	imide	(*R*)-**137**:(*S*)-**137**	yield, %
1	R = CH_2Ph	94 : 6	86
2	R = Ph	90 : 10	77
3	R = *t*Bu	99 : 1	94

Scheme 21. Possible acyl transfer in the methanolysis step



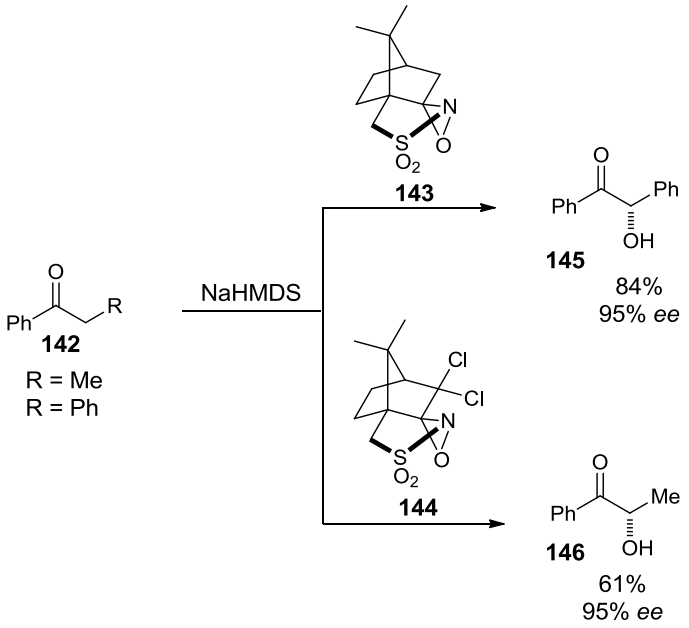
Another example of auxiliary induced α-hydroxylation was demonstrated by Enders and Bhushan in the study of chiral hydrazones (Scheme 22).[52] The azaenolate derived from (*S*)-amino-2-(methoxymethyl)pyrrolidine hydrazone **139** was reacted with (±)-**135**, affording the α-hydroxy hydrazone **140**. The subsequent ozonolysis removed the auxiliary, providing the chiral hydroxyl ketone that was isolated after acylation in excellent enantioselectivity (93% *ee*).

Scheme 22. Chiral hydrazone based enantioselective α-hydroxylation



Despite that chiral auxiliary induced asymmetric enolate hydroxylation often provides high levels of enantioselectivities, an inherent disadvantage of any chiral auxiliary based asymmetric synthesis is the necessity for preparing and eventually removing the auxiliary. This problem can be avoided by using chiral oxaziridines to accomplish stereocontrol. The most frequently used chiral oxaziridines are camphorsulfonyl oxaziridine **143**[53] and its derivatives (such as **144**).[54] Yields and enantioselectivities highly depended upon the nature of the substrates, counterions of the enolates, the solvent, reaction temperature, and the chiral oxaziridines. The influence of these variables, however, was often case-specific.[49] Although great enantioselectivity could be achieved by careful choice of the chiral oxaziridine (Scheme 23), in many cases, the stereo induction was only moderate.

Scheme 23. Chiral oxaziridine induced enantioselective α-hydroxylation

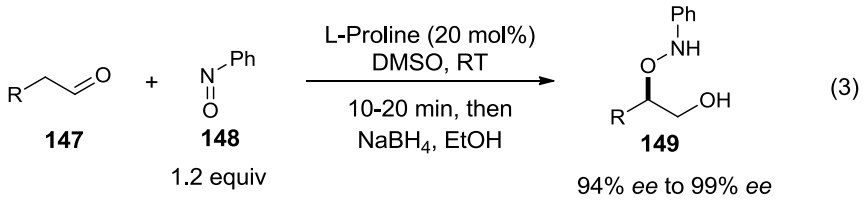


3.2 CATALYTIC ASYMMETRIC ENOLATE ALPHA-HYDROXYLATION

In comparison to auxiliary-controlled enantioselective enolate α-hydroxylation, methods based on asymmetric catalysis have significant advantages including atom economy and limited functional group manipulations (such as removal of the auxiliary). The indirect catalytic approach has been disclosed for over two decades, including the asymmetric dihydroxylation of enol ethers developed by Sharpless,[55] the asymmetric epoxidation of silyl enol ethers with a chiral dioxirane,[56] and the asymmetric epoxidation of enol ethers with a chiral Mn-salen catalyst.[57] One common feature of these methods is that they all require converting the carbonyl substrates to isolable enol ethers prior to the oxidation step. As a result, the enantioselectivity of the reaction depends on the *Z,E* purity of the prochiral enol ether and exclusive *Z* or *E* enol ether

formation is not usually trivial. Therefore, this type of methods has not received wide applications in organic synthesis.

The development of direct α-oxygenation of carbonyl compounds in a catalytic, asymmetric fashion has not been accomplished until very recently.[58] MacMillan[58b] and Zhong[58a] simultaneously developed enantioselective α-oxygenation of aldehydes utilizing proline as the organocatalyst and nitrosobenzene **148** as the oxidant (Eq 3). Oxidation of the aldehyde was facile at ambient temperature, providing excellent enantioselectivity (94% *ee* to 99% *ee*). The α-oxyaldehyde products were oligomeric in solution and thus were isolated after being reduced to the corresponding primary alcohols **149**.

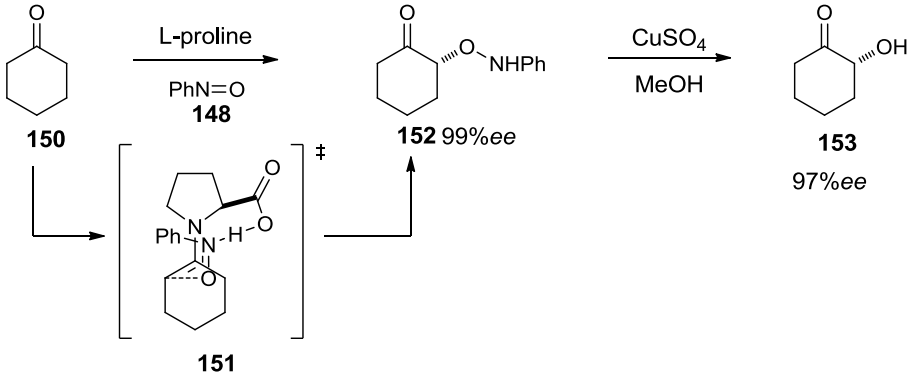


(3)

Shortly after, Hayashi and co-workers reported an analogous proline-catalyzed enantioselective α-oxygenation of ketones.[58f] As illustrated in Scheme 24, reacting cyclohexanone **150** with nitrosobenzene **148** catalyzed by proline (10 mol%) in DMF gave the α-aminoxy compound **152** (77% yield, >99% *ee*) after 24h. Hydrogen bonding between the carboxylic acid group of proline and the nitrogen atom of nitrosobenzene was critical for enantioselctivity by securing a closed transition state **151**. The N-O bond cleavage was accomplished by exposing **152** to $CuSO_4$ (0.3 equiv) in MeOH to deliver the chiral α-hydroxy compound **153** with negligible epimerization (97% *ee*). This methodology, however, only

applies to simple cyclic ketone substrates. When using acyclic ketones, reaction produced a mixture of α-oxygenated and aminated products.

Scheme 24. Proline catalyzed α-oxygenation of cyclic ketones



Despite the progress in relevant organocatalysis, chiral auxiliary assisted enolate α-hydroxylation still remains the method of choice when preparing optically active α-hydroxy carbonyl compounds due to broader substrate scope and better reaction consistency. An asymmetric catalysis that embraces wide substrate scope and operational simplicity has not been discovered. Such an unmet challenge prompted us to explore the prospect of utilizing the ketene-oxaziridine cyclocondensation as a surrogate to accomplish the enantioselective enolate α-hydroxylation.

4.0 DEVELOPMENT OF CATALYTIC ASYMMETRIC ENOLATE ALPHA-HYDROXYLATION VIA ACID CHLORIDE-OXAZIRIDINE CYCLOCONDENSATION

4.1 REACTION DESIGN

Our goal was to develop a catalytic asymmetric methodology to prepare enantioenriched α-hydroxy carbonyl compounds with broad substrate scope using easily accessible catalysts. Encouraged by the success of cinchona alkaloid catalyzed ketene aldehyde cyclocondensation developed in our group,[21] we were interested in investigating the potential of the ketene-oxaziridine cyclocondensation as a surrogate for enolate α-hydroxylation methodologies (Figure 15). Specifically, the cyclocondensation of the *in situ*-generated ketene and racemic *N*-sulfonyl oxaziridines (±)-**130** would gave enantioenriched oxazolidinone heterocycles, [(*S*)-**155** or (*R*)-**155**] which upon ring opening with nucleophiles, generate an array of chiral α-hydroxy carbonyl compounds [(*S*)-**156** or (*R*)-**156**].

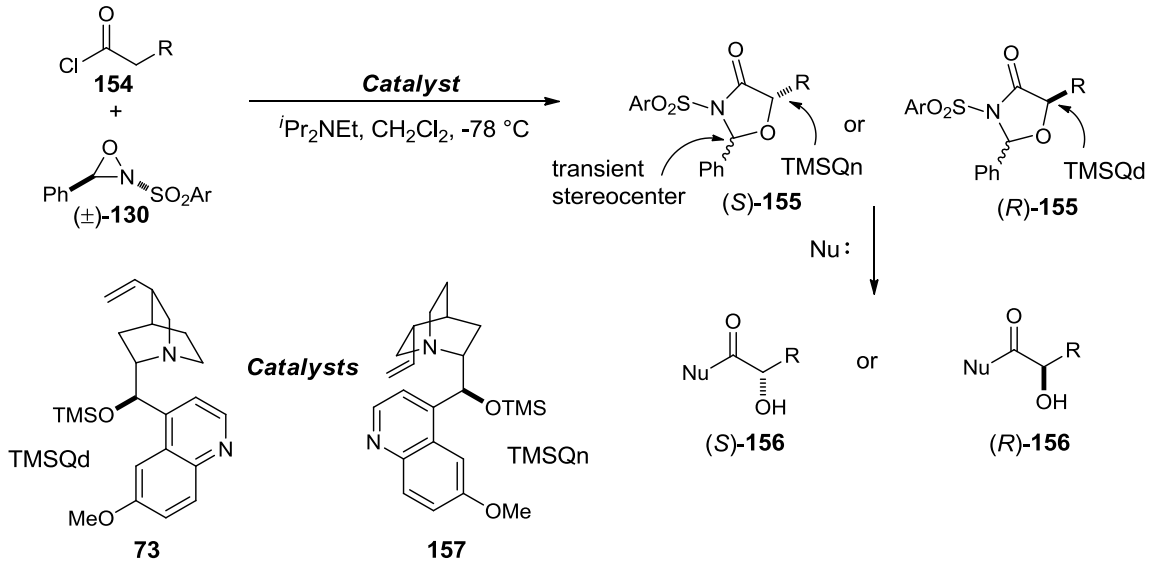
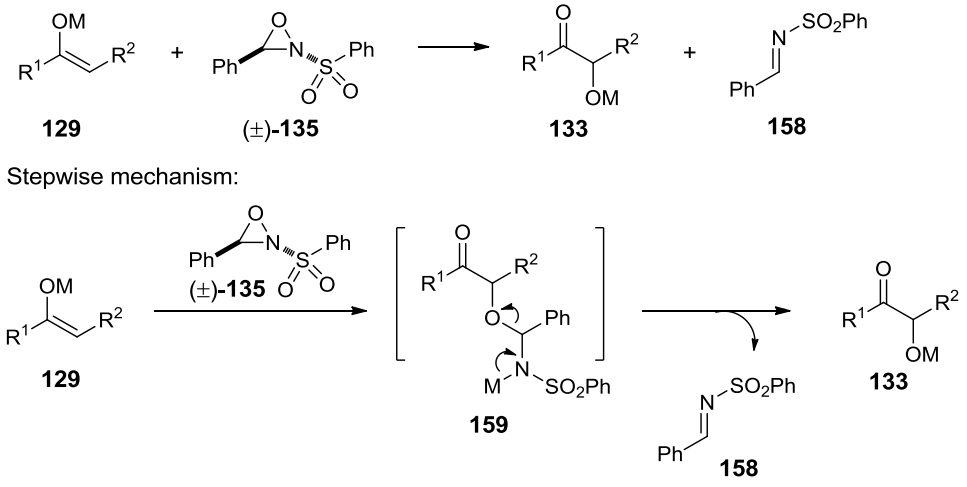


Figure 15. Catalytic synthesis of chiral oxazolidinones as the surrogate for enolate α-hydroxylation

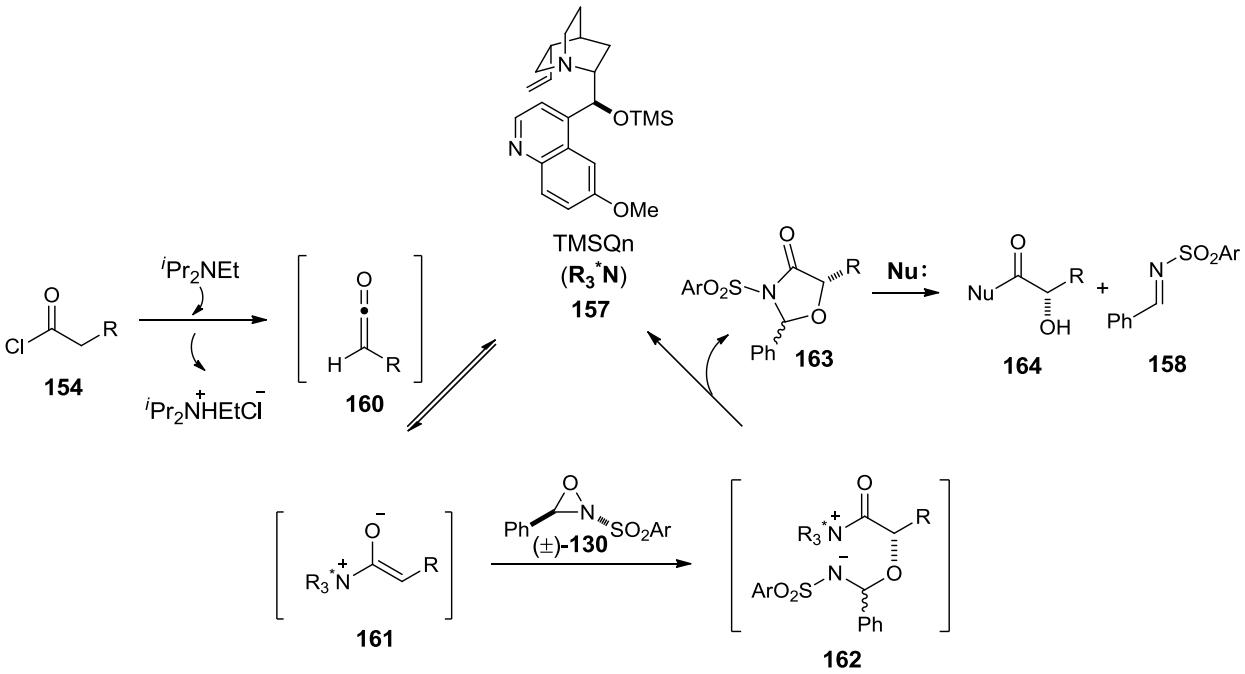
Our reaction design was guided by previous studies in our laboratory which determined that chiral ketene enolates, generated by addition of cinchona alkaloids (TMSQn or TMSQd) to ketenes, exerted excellent facial selectivity and reactivity toward electrophiles such as aldehydes and imines.[21,59] Considering *N*-sulfonyl oxaziridines were highly electrophilic, we attempted to investigate their reactivity towards the chiral ketene-derived enolates. Precedent has shown that the reaction of metal enolates and *N*-sulfonyl oxaziridines directly led to α-hydroxyl carbonyl compounds (Scheme 25). However, Evans noticed that the formation of α-hydroxy carbonyl compounds (**133**) and the imine byproduct (**158**) was not a concerted process, suggesting a stepwise mechanism where a short-lived sulfonamide intermediate **159** was involved in the reaction.[51] This sulfonamide intermediate is the key to our proposed catalytic ketene-oxaziridine cyclocondensation described in Scheme 26. When the ketene enolate **161** underwent nucleophilic attack at oxaziridine (±)-**130**, sulfonamide intermediate **162** thus generated would cyclize onto the carbonyl to give enantioenriched oxazolidinone **163** along with regeneration of

the catalyst **157**. Oxazolidinones **163** could be converted to α-hydroxy carbonyl compounds through nucleophilic ring openings.

Scheme 25. Evans' mechanistic study in the metal enolate-oxaziridine reaction



Scheme 26. Proposed mechanism of the ketene-oxaziridine cyclocondensation



4.2 PROOF-OF-CONCEPT EXPERIMENTS

The proof-of-concept experiment was carried out using propionyl chloride as the ketene precursor, racemic *N*-benzenesulfonyl oxaziridine (±)-**135** as the oxidant, and TMSQd as the catalyst. The role of the Lewis acid ($LiClO_4$), similar as in the AAC chemistry, was believed to activate the oxaziridine by coordination to its oxygen atom. Following the typical AAC protocol,[21] slow adding propionyl chloride (2.0 equiv) into a −78 °C solution of oxaziridine (±)-**135** (1.0 equiv), diisopropylethylamine (2.0 equiv), TMSQd (20 mol %) and $LiClO_4$ (1.0 equiv) gave oxazolidinones **166a** and **166b** as a 3:1 inseparable mixture of diastereomers (43%) [See the experimental section (Chapter **6.0**) for the relative stereochemistry assignments of oxazolidinone products]. The slow addition was performed via a syringe pump to avoid substantial ketene dimerization.[60] Oxaziridine (±)-**135** was consumed completely at the end of the acid chloride addition. The reaction mixture was then quenched by addition of excess diethyl ether at −78 °C and warmed to ambient temperature followed by filtration through a silica gel plug. Besides the desired product (**166a** and **166b**), a substantial amount of *N*-sulfonyl imine **158** and benzaldehyde derived from hydrolysis of **158** were also obtained. Imine **158** co-eluted with the oxazolidinones, therefore, hydrolysis of the imine using 5% HCl in MeOH was necessary prior to flash column chromatography. As anticipated, the enantioselectivities of both diastereomers were excellent (>98% *ee*). The lack of diastereoselectivity of this reaction was inconsequential, as the aminal stereocenter would be removed in the ring-opening reaction.

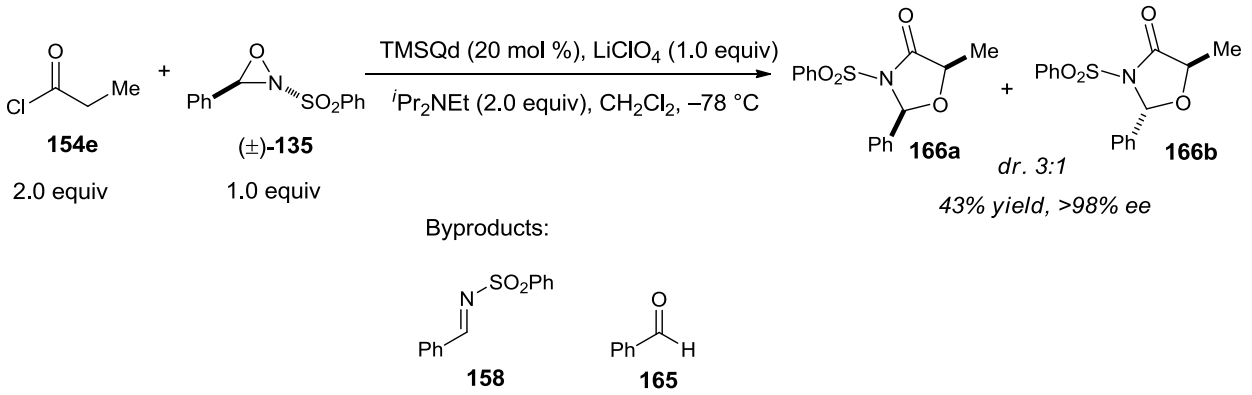


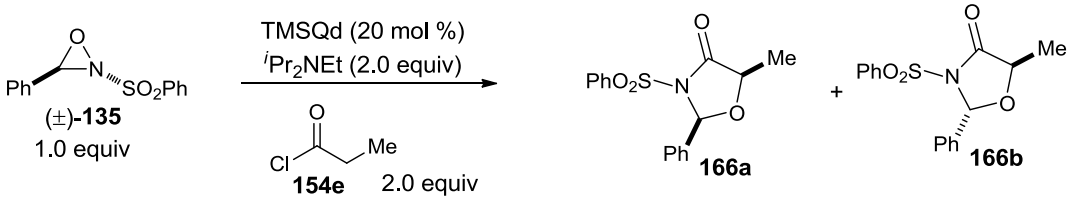
Figure 16. Proof-of-concept experiment for the ketene-oxaziridine cyclocondensation

4.3 PROBING THE EFFECTS OF LEWIS ACIDS ON THE CYCLOCONDENSATION

Encouraged by the success of the proof-of-concept experiment, we set out to optimize the reaction conditions to improve the yields. Since the Lewis acid would increase the electrophilicity of the oxaziridine by binding to the oxygen atom, the reaction optimization was initiated with a Lewis acid screen. The choice of Lewis acids was strictly limited, as the catalyst (TMSQn or TMSQd) we employed in the cyclocondensation is a Lewis base and will potentially form irreversible complexes with strong Lewis acids. We eliminated strong Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ and focused on oxophilic Lewis acids with moderate strength (Table 3). Reactions were performed by employing TMSQd as the catalyst (20 mol %), oxaziridine (±)-**135** (1.0 equiv) and two fold excess of methyl ketene which was generated *in situ* from propionyl chloride at −78 °C. Except in the cases using boron-based Lewis acids (Entries 8 and 9), small amounts of ether were utilized to assist solvating the Lewis acids. The diastereoselectivity was a

consistent 1:1 except when using $LiClO_4$ (Entry 1). Lewis acids such as $MgCl_2$, $MgBr_2 \cdot Et_2O$, $Sc(OTf)_3$, $In(OTf)_3$ and $B(OPh)_3$ (Entries 2, 3, 6, 7, and 8) showed no advantages over $LiClO_4$ in terms of yields. $ZnCl_2$ and $Zn(OTf)_2$ (Entries 4 and 5) increased the yield by about 10%. The best yield (70%) was attained when utilizing catalytic $B(OMe)_3$ (Entry 9).

Table 3. Investigation into the Lewis acids to promote the acid chloride-oxaziridine cyclocondensation



Entry	L.A.	equiv	**166a : 166b**[a]	yield %[b]
1	$LiClO_4$	1.0	3 : 1	43
2	$MgBr_2 \cdot Et_2O$	1.0	1 : 1	40
3	$MgCl_2$	1.0	1 : 1	40
4	$ZnCl_2$	1.0	1 : 1	53
5	$Zn(OTf)_2$	1.0	1 : 1	56
6	$Sc(OTf)_3$	0.3	1 : 1	42
7	$In(OTf)_3$	0.3	1 : 1	45
8	$B(OPh)_3$	0.3	1 : 1	42
9	$B(OMe)_3$	0.3	1 : 1	70

[a] Determined by ^1H NMR. [b] Combined yields of diastereomers

With $B(OMe)_3$ deemed as the appropriate Lewis acid, we were eager to test the reaction against other ketene substrates. Unfortunately, we observed a drastic decrease in yields as the

steric bulk of the ketene increased. For example, reactions employing pentanoyl chloride **154g** and phenylacetyl chloride **154a** provided the corresponding oxazolidinones in 54% and 24% yields respectively (Figure 17). Oxaziridine (±)-**135** was not completely consumed at the end of the reactions while full consumption was observed after 2h when using methyl ketene. Prolonging the reaction time, however, did not increase the reaction conversion, implying that the catalyst turnover was shut down after certain time.

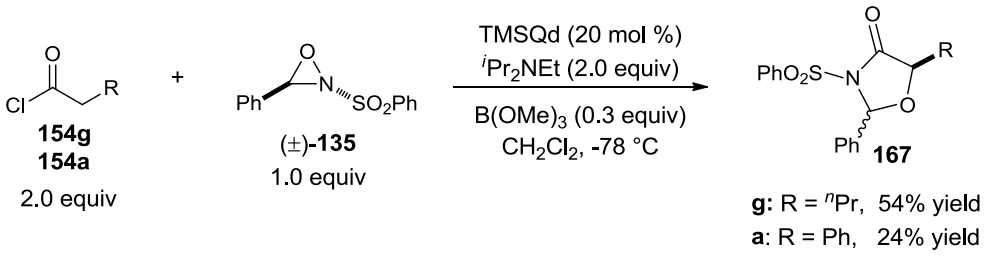
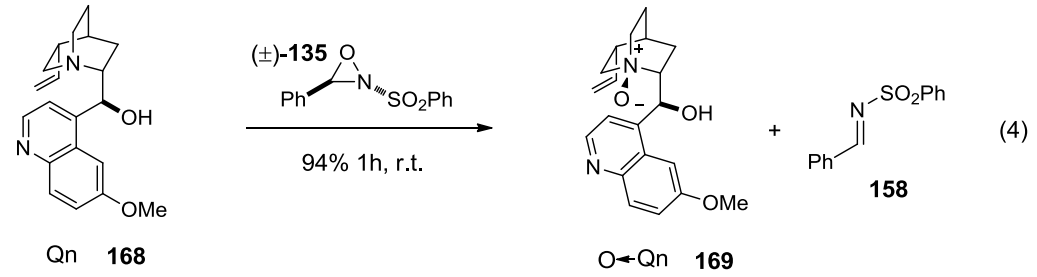


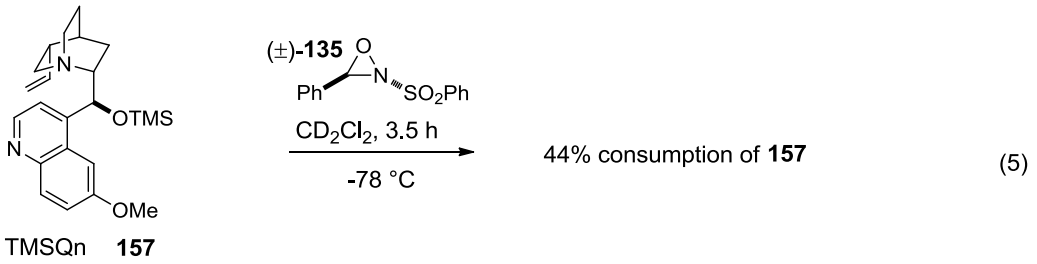
Figure 17. Cyclocondensations incorporating ketenes other than methyl ketene

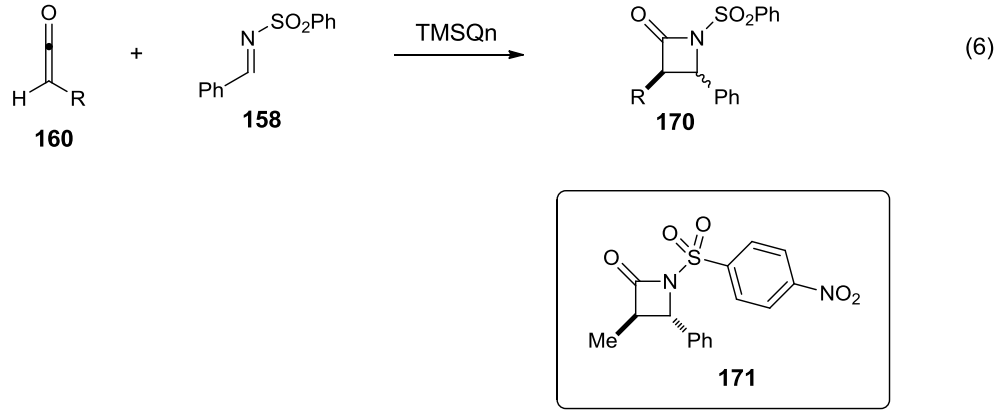
4.4 COMPETING SIDE REACTIONS

As mentioned above, we noticed that the catalyst (TMSQn or TMSQd) was deactivated after certain time in the phenylacetyl chloride-oxaziridine cyclocondensation. We assumed the catalyst was consumed or sequestered by competing side reactions. One plausible assumption was oxidation of the catalyst by the oxaziridine, based on the precedent that *N*-sulfonyl oxaziridines (±)-**135** could rapidly oxidize quinine **168** at ambient temperature to afford the corresponding *N*-oxide **169** (Eq 4).[61] In order to probe the extend of this oxidation in our reaction system, we performed a control experiment utilizing oxaziridine (±)-**135** (1.0 equiv),

TMSQn (20 mol %) and CD_2Cl_2 as the solvent (Eq 5). After 3.5h at −78 °C, excess triethylamine was added to quench the unreacted oxaziridine. Crude ^1H NMR of this reaction mixture showed 44% consumption of TMSQn, confirming that even at −78 °C, the oxaziridine could oxidize the catalyst to the *N*-oxide. This *N*-oxide was, however, inactive to catalyze the cyclization due to lack of electron lone pair on the quinuclidine nitrogen atom. Further, the byproduct of this unproductive oxidation was *N*-sulfonyl imine **158** that could undergo cyclocondensation with the ketene under the influence of the same catalyst to give β-lactam **170** (Eq 6). This reaction path was confirmed by X-ray crystal structure of **171** isolated as a byproduct when reacting propionyl chloride with *N*-*p*-nosyl oxaziridine. In conclusion, when the cyclocondensation between the ketene and the oxaziridine was slow, the oxaziridine would deactivate the catalyst through *N*-oxidation and thus terminate the catalytic cycle. Therefore, we needed to find an oxaziridine that could react more rapidly with the ketene than with the catalyst.





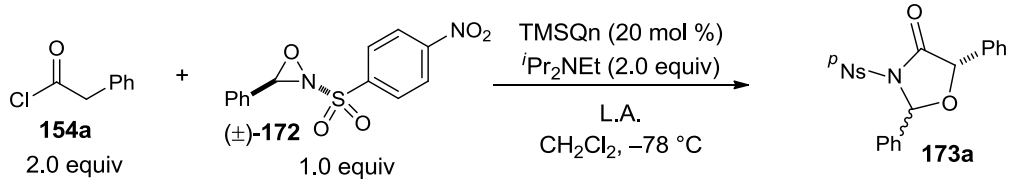


4.5 *N-P*-NOSYL OXAZIRIDINE AS THE NEW OXIDANT

In order to make the desired cyclocondensation more facile than the competing side reactions, we shifted our focus to using the more electrophilic oxaziridine, racemic *N-p*-nosyl oxaziridine (±)-**172**.[62] Due to the strong electron-withdrawing nature of the nitro group, (±)-**172** is much more reactive than the parent Davis' reagent. Indeed, in the reaction with phenylacetyl chloride,

full consumption of (±)-**172** was observed after 2h at −78 °C. However, only about 80% of oxaziridine (±)-**172** was transformed to oxazolidinones **173a** (Table 4), indicating the competing side reactions were not completely suppressed. It is noteworthy that the reaction proceeded with equal efficiency in the absence of the Lewis acid (Entry 1). For the operational convenience, the following investigations were conducted without incorporating Lewis acids.

Table 4. Investigation into the reactivity of *N*-*p*-nosyl oxaziridine in the acid chloride-oxaziridine cyclocondensation



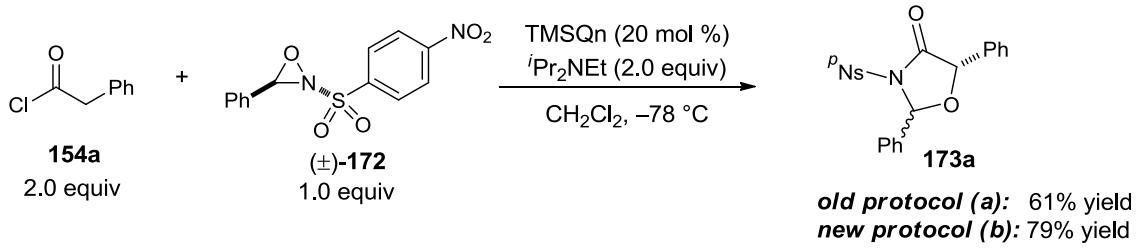
Entry	L.A.	equiv	conversion of **172** to **173a**, %[a]
1	none	-	73
2	$B(OMe)_3$	0.3	79
3	$B(OMe)_3$	1.0	79
4	$B(O^iPr)_3$	0.3	78
5	BPh_3	0.3	77

[a] Determined by crude ^1H NMR

The more electrophilic oxaziridine (±)-**172** did not require Lewis acid activation for the ketene-oxaziridine cyclocondensation, however, the selectivity of (±)-**172** needed to be further improved. Despite its full consumption in the reaction with phenyl acetyl chloride, we only isolated 61% yield of the corresponding oxazolidinone products (Scheme 27). The byproducts of this particular cyclocondensation were unfortunately unidentifiable. However, analogous reactions utilizing propionyl chloride as the ketene precursor led to *cis* and *trans* β-lactams (**171**

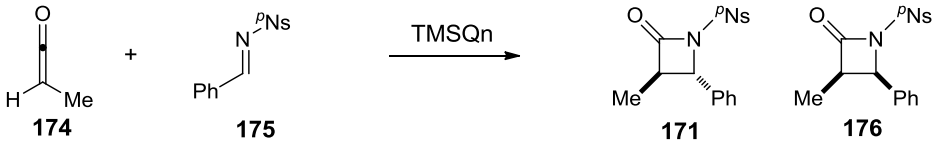
and **176**) besides the desired oxazolidinones. As mentioned before, the *N*-sulfonyl imine **175** that led to the β-lactam formation was arising from *N*-oxidation of the catalyst by the oxaziridine. Therefore, if we could limit the exposure of oxaziridine (±)-**172** to the catalyst prior to the cyclocondensation, we could potentially suppress the β-lactam formation and increase the yield of oxazolidinones. To this end, we devised the reaction protocol by slow adding oxaziridine (±)-**172** into the reaction. This was achieved by adding a mixture of **154a** and (±)-**172** into a −78 °C solution of TMSQn and $^{i}Pr_2NEt$ over a course of 2 h. As a result, the yield of **173a** was increased to 79% (Scheme 27).

Scheme 27. Revised protocol for the acid chloride-oxaziridine cyclocondensation



(a): A CH_2Cl_2 solution of **154a** was added to a –78 °C solution of TMSQn, $^{i}Pr_2NEt$ and (±)-**172** over 2h.
(b): A mixture of **154a** and (±)-**172** in CH_2Cl_2 was added to a –78 °C solution of TMSQn and $^{i}Pr_2NEt$ over 2h.

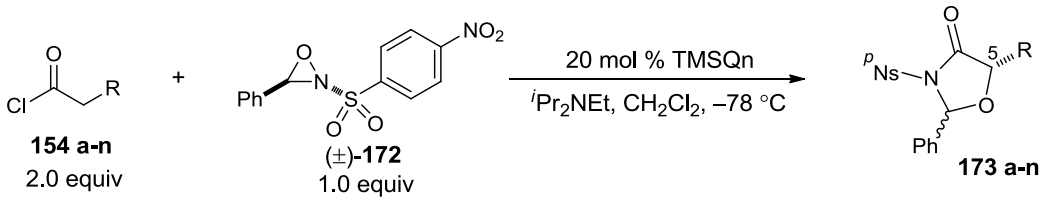
Side reactions and identified byproducts when using propionyl chloride:

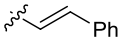
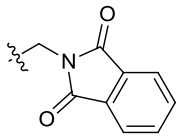


4.6 SUBSTRATE SCOPE OF THE ACID CHLORIDE-OXAZIRIDINE CYCLOCONDENSATION

Having formulated the optimized conditions for the acid chloride-oxaziridine cyclocondensation, we decided to probe the reaction scope with an array of structurally diverse ketenes. Slow adding the mixture of (±)-**172** (1.0 equiv) and **154a-n** (1.0 equiv) into a CH_2Cl_2 solution of TMSQn (20 mol %) and $^{i}Pr_2NEt$ (2.0 equiv) at −78 °C over the course of 2h gave oxazolidinones **173a-n** in good yields (59~82%) and excellent enantioselectivities (> 98% *ee*) (Table 5). Acid chlorides producing straight chain and β-branched alkyl ketenes provided the corresponding oxazolidinone in great yield (71~75%) and excellent enantioselectivity (>98% *ee*) (Entries e-h). Aryl-substituted acid chlorides participated in the cyclocondensation to produce the oxazolidinones with equal enantioselectivity (>98% *ee*) despite the greater tendency to epimerization (Entries a-d). In addition, acid chlorides possessing various heterocyclic or common heteroatom functionalities also participated in efficient condensation with (±)-**172** (Entries j, k, and m). Acid chlorides producing α-branched alkyl ketenes, however, afforded varied yields depending on the bulk of the ketene (Entries i and n). For example, cyclopropylacetyl chloride **154i** provided oxazolidinones in comparable yield (70%), while cyclohexylacetyl chloride **154n** only delivered a modest yield (29%). The steric hindrance of the cyclohexane ring presumably impeded the cyclocondensation to the degree that the competing side reactions became dominant.

Table 5. Investigation into the substrate scope of the acid chloride-oxaziridine cyclocondensation



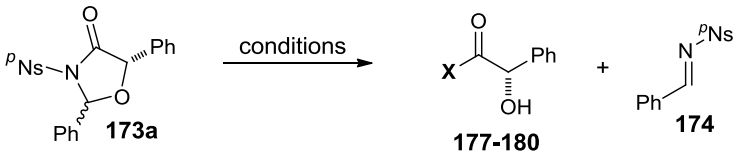
entry	Acid chloride **154 a-n**	% yield **173 a-n**[a] (*cis*:*trans*)	(5*S*)-**173** : (5*R*)-**173**[b]
a	R = Ph	79 (1:1)	>99:1
b	R = 4-MeOC$_6$H$_4$	79 (1:1)	>99:1
c	R = 4-FC$_6$H$_4$	76 (1:1)	>99:1
d	R = 1-Naphthyl	80 (1:1)	>99:1
e	R = Me	74 (1:1)	>99:1
f	R = Et	71 (1:1)	>99:1
g	R = ^{n}Pr	75 (1:1)	>99.1
h	R = CH$_2{}^c$C$_6$H$_{11}$	75 (1:1)	>99:1
i	R = ^{c}C$_3$H$_5$	70 (1:1)	>99:1
j	R = CH$_2$OC$_6$H$_5$	82 (1:1)	>99:1
k	R = 	70 (1:1)	>99:1
l	R = 	64 (1:1)	>99:1
m	R = 	59 (1:1)	>99:1
n	R = ^{c}C$_6$H$_{11}$	29 (1:1)	>99:1

[a] Combined yields of diastereomers; The diastereomeric ratio was determined by ^{1}H NMR.
[b] Determined by chiral HPLC

4.7 ACCESS TO ENANTIOENRICHED ALPHA-HYDROXY CARBONYL COMPOUNDS

The enantioenriched oxazolidinones provided an access to various α-hydroxy carbonyl compounds through facile ring openings achieved using diverse nucleophiles. Reacting the 1:1 diastereomeric mixture of 5-phenyl oxazolidinone **173a** (> 98% ee) with catalytic NaOMe (0.1 equiv) in MeOH afforded (*S*)-methyl mandelate **177** with limited epimerization (80%, 93% *ee*) (Entry 1). Attempts to use neutral conditions utilizing substoichiometric amount of DMAP in MeOH was unsuccessful, resulting in greater epimerization and lower yields. Likewise, reacting **173a** with ethyl thiolate (EtSK) in THF at 0 °C provided the α-hydroxy thioester **178** with no erosion in enantiomeric purity (72%, >98% *ee*) (Entry 2). Amine-mediated ring opening, exemplified by NH_3, proceeded smoothly in the ammonia saturated methanol solution to afford the α-hydroxy amide **179** (83%, >98% ee) (Entry 3). Attempts at ring opening the oxazolidinone with morpholine catalyzed by DMAP resulted in a great yield (90%) of the amide product **180**, however, it was accompanied by significant epimerization (Entry 4). Under neutral conditions (amine or alcohol coupled with catalytic DMAP), the ring opening reaction proceeded very slow and usually required overnight time to complete, leading to a greater degree of epimerization. Thus, to access enantioenriched α-hydroxy carbonyl compounds, careful choice of nucleophile is warranted and anion-based nucleophiles tend to shorten the reaction time and reduce the epimerization.

Table 6. Ring openings of oxazolidinones



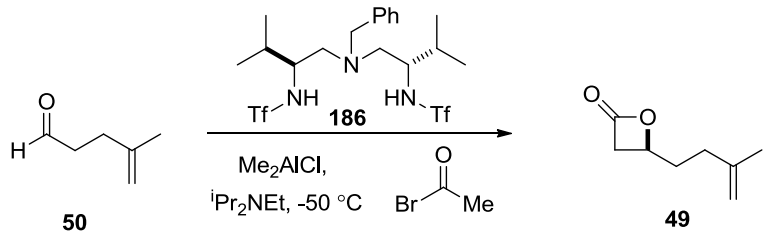
Entry	Conditions	X		% *ee* (% yield)
1	MeONa, MeOH	MeO	**177**	92[a] (80)
2	EtSK, THF	EtS	**178**	>98[b] (72)
3	NH_3, MeOH	NH_2	**179**	>98[c] (83)
4	morpholine, DMAP, CH_2Cl_2		**180**	5[d] (90)

[a] Determined by chiral GC. [b] Determined by chiral HPLC. [c] Determined by α_D comparison to the literature value.[70] [d] Determined by Trost ester analysis.[65]

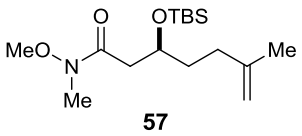
In conclusion, cinchona alkaloid catalyzed ketene-oxaziridine cyclocondensations provide a catalytic asymmetric alternative to tranditional enolate α-oxidation reactions. Using readily obtained acid chloride ketene precursors and an easily prepared oxaziridine oxidant, highly enantioenriched oxazolidinones are prepared in good yields that afford access to a wide variety of chiral α-hydroxy carbonyl compounds.

5.0 EXPERIMENTAL FOR SPIROLIDE C SYNTHESIS

General Information: Unless otherwise indicated, all reactions were performed in dry glassware under an atmosphere of oxygen-free nitrogen using standard inert atmosphere techniques for the manipulation of both solvents and reagents. Anhydrous solvents were obtained by passage through successive alumina- and Q5-packed columns on a solvent purification system. 2,6-Lutidine, *N*,*N*-diisopropylethylamine were purified by distillation over CaH_2. (2*S*,6*S*)-4-Benzyl-1,7-bis(trifluoromethylsulfonyl)-2,6-diisopropyl-1,4,7-triazaheptane **186** was prepared according to the literature procedure.[63] 3-Mesityl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*d*]thiazol-3-ium perchlorate **119** was synthesized by following Glorius' procedure.[45] Commercially available acetyl bromide was distilled under nitrogen. NMR spectra were recorded at the indicated magnetic field strengths with chemical shifts reported relative to residual $C\underline{\mathbf{H}}Cl_3$ (7.27 ppm) for ^1H and $\underline{\mathbf{C}}DCl_3$ (77.0 ppm) for ^{13}C spectra. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed over silica gel (230-240 mesh). Analytical gas chromatography (GC) was performed using a flame ionization detector and split mode capillary injection system using Varian Chirasil-Dex CB WCOT fused silica 25 m x 0.25 mm column (CP 7502). The concentration of the solution for optical rotations was in the unit of g 100 mL^{-1}.



(*S*)-4-(3-Methylbut-3-en-1-yl)oxetan-2-one (**49**): To a stirred solution of (2*S*,6*S*)-4-benzyl-1,7-bis(trifluoromethylsulfonyl)-2,6-diisopropyl-1,4,7-triazaheptane **186** (1.6 mmol, 0.1 equiv) in 110 mL of CH_2Cl_2 at 0 °C was added Me_2AlCl (1.6 mL, 1.0 M solution in hexane). This homogeneous solution was removed from the ice bath and stirred at ambient temperature for 1h before being cooled to −50 °C. To this −50 °C solution was added 4.74 mL of *N*,*N*-diisopropylethylamine (27.2 mmol, 1.7 equiv) followed by dropwise addition of 2.25 mL of acetyl bromide (30.4 mmol, 1.9 equiv) over a period of 60 s. The resulting yellow solution was stirred for 120 s whereupon a solution of 1.58 g of aldehyde **50**[64] (16.0 mmol, 1.0 equiv) in 5 mL of CH_2Cl_2 was added dropwise. The reaction was stirred at −50 °C for 16 h. Saturated aqueous NH_4Cl (100 mL) was added and mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The resulting crude residue was purified by flash chromatography on silica gel (15% Et_2O in hexanes) to afford 2.04 g (91%) of the title compound as a clear oil. $[\alpha]_D^{18}$ −0.91 (*c*, 1.6, $CHCl_3$); IR (thin film): 1827, 1134, 1113, 888, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.78 (s, 1H), 4.72 (s, 1H), 4.55-4.50 (m, 1H), 3.52 (dd, *J*= 16.5, 6.0 Hz, 1H), 3.09 (dd, *J*= 16.5, 4.0 Hz, 1H), 2.20-2.08 (m, 2H), 2.05-1.98 (m, 1H), 1.94-1.87 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 143.6, 111.1, 70.8, 42.8, 32.9, 32.6, 22.3; HRMS (ES+) *m/z* calcd for $C_8H_{13}O_2$ $[(M+H)^+]$: 141.0916; found: 141.0926.

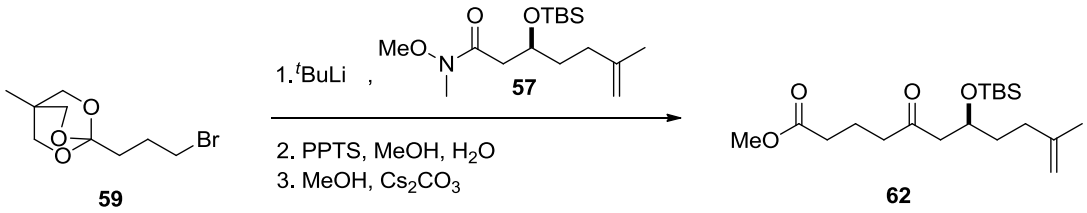


57

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,6-dimethylhept-6-enamide (**57**): To a suspension of 1.52 g of *N*,*O*-dimethylhydroxylamine hydrochloride (15.6 mmol, 2.0 equiv) in 18 mL of CH_2Cl_2 at 0 °C was slowly added 15.6 mL of dimethylaluminum chloride (15.6 mmol, 2.0 equiv, 1M hexanes solution). Once the addition was complete, the reaction was removed from the ice bath and stirred at ambient temperature for 1h. The reaction was cooled to −30 °C and a solution of 1.09 g (7.80 mmol, 1.0 equiv) of β-lactone **49** in 4 mL of CH_2Cl_2 was added over the course of 30 min via a syringe pump. The reaction was stirred for additional 45 min at this temperature and quenched with 40 mL of saturated Rochelle's salts solution (Caution: gas evolution). The mixture was then warmed to ambient temperature and stirred until two homogenous phases resulted. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was used without further purification.

To a stirred solution of crude product obtained above in 25 mL of CH_2Cl_2 at −50 °C was added 1.4 mL of 2,6-lutidine (12 mmol, 1.5 equiv) followed by 2.1 mL of TBSOTf (9.4 mmol, 1.2 equiv) dropwise. The reaction was stirred at this temperature for 1h and then quenched by 30 mL of saturated $NaHCO_3$ aqueous solution. The mixture was warmed to ambient temperature and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography on silica gel (10% EtOAc in hexanes) to afford 2.31 g (94% over two steps) of the titled compound as a clear oil. $[\alpha]_D^{21}$+1.6 (*c* 2.3, $CHCl_3$); IR (thin film): 2954, 2932, 2857, 1740, 1666, 1463, 1443, 1385, 1254, 1178, 1090, 1033, 1004, 886, 836, 812, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.703-4.701 (m, 1H), 4.689-4.688 (m, 1H), 4.29-4.23 (m, 1H), 3.70 (s, 1H), 3.18 (s, 1H), 2.75

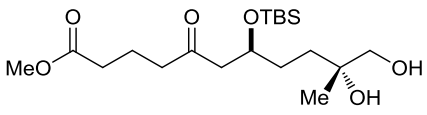
(dd, *J*= 14.4, 7.2 Hz, 1H), 2.42 (dd, *J*= 14.4, 5.2 Hz, 1H), 2.15-2.01 (m, 2H), 1.73 (s, 3H), 1.72-1.57 (m, 2H), 0.88 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 145.8, 109.8, 69.2, 61.3, 39.5, 35.9, 33.2, 32.0, 25.9, 22.6, 18.1, -4.6, -4.7; HRMS (ES+) *m*/*z* calcd for $C_{16}H_{33}NO_3SiNa$ [$(M + Na)^+$]: 338.2127; found: 338.2137.



(*S*)-Methyl 7-(*tert*-butyldimethylsilyloxy)-10-methyl-5-oxoundec-10-enoate (**62**): To a stirred solution of 6.23 g of alkyl bromide (**59**)[25] (24.8 mmol, 1.0 equiv) in 80 mL of Et_2O at −78 °C was added 29.0 mL of ^{t}BuLi (49.6 mmol, 2.0 equiv, 1.7 M solution in pentane) slowly. The resulting solution was stirred at this temperature for 1.5 h, whereupon 4.70 g of Weinreb amide **57** (15.0 mmol, 0.6 equiv) in 6 mL of Et_2O was added over 40 min via a syringe pump. The reaction was stirred at −78°C for additional 3 h. The reaction was quenched by 70 mL of saturated NH_4Cl aqueous solution and the mixture was warmed to ambient temperature. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 X 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was used without further purification.

To a stirred solution of the crude product obtained above in 70 mL of MeOH at ambient temperature was added 2.2 mL of H_2O followed by 0.377 g of pyridinium *p*-toluenesulfonate (1.50 mmol, 0.1 equiv to the Weinreb amide) in one portion. The reaction was stirred for 1h and cooled to 0 °C whereupon 9.98 g of Cs_2CO_3 (30.0 mmol, 2 equiv) was added in one portion. The

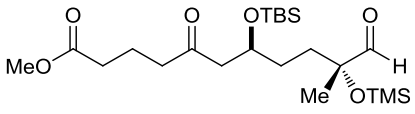
reaction was stirred at 0 °C for 2h and then filtered through a plug of silica gel, eluting with 20% of EtOAc in hexanes. The filtrate was concentrated under vacuum and the residue obtained was further purified via flash column chromatography on silica gel (2 L of 7% EtOAc in hexanes followed by 1 L of 15% EtOAc in hexanes) to afford 4.13 g (85% over 3 steps) of titled compound **62** as a clear oil, along with 0.42 g of unreacted Weinreb amide **57** recovered. $[\alpha]_D^{20}$+1.9 (*c* 1.3, $CHCl_3$); IR (thin film): 2953, 2932, 2857, 1741, 1716, 1439, 1374, 1254, 1196, 1089, 1041, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.67 (d, *J*= 16.5 Hz, 1H), 4.17 (pent, *J*= 5.5 Hz, 1H), 3.65 (s, 3H), 2.59 (dd, *J*= 15.0, 7.0 Hz, 1H), 2.49 (dt, *J*= 7.0, 4.5 Hz, 2H), 2.44 (dd, *J*= 15.0, 5.0 Hz, 1H), 2.33 (t, *J*= 7.0 Hz, 2H), 2.01 (t, *J*= 7.5 Hz, 2H), 1.91-1.82 (m, 2H), 1.70 (s, 3H), 1.62-1.52 (m, 2H), 0.85 (s, 9H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.9, 173.6, 145.5, 109.9, 68.7, 51.5, 49.9, 43.4, 35.7, 33.1, 33.0, 25.8, 22.6, 18.6, 18.0, -4.6, -4.7; HRMS (ES+) *m/z* calcd for $C_{19}H_{36}O_4SiNa$ [$(M + Na)^+$]: 379.2281; found: 379.2280.



65

(7*S*,10*R*)-Methyl-7-(*tert*-butyldimethylsilyloxy)-10,11-dihydroxy-10-methyl-5 oxoundecanoate (**65**): 1.4 g of commercially available AD-mix-β was dissolved in 5 mL of H_2O and 5 mL of ^{t}BuOH. The heterogeneous mixture was stirred at ambient temperature and produced two clear phases with the bottom phase appearing bright yellow. The mixture was cooled to 0 °C and 0.34 g of olefin **62** (1.0 mmol) dissolved in minimum amount of ^{t}BuOH was added dropwise. The mixture was stirred vigorously at 0 °C for 16h. The reaction was quenched with 2 g of solid Na_2SO_3 and the

mixture was warmed to ambient temperature and stirred for 0.5 h. The mixture was extracted with EtOAc (3 X 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified via flash column chromatography on silica gel (150 mL of 50% EtOAc in hexanes then 250 mL of 100% EtOAc) to afford 0.35 g of titled compound **65** (95%) as a clear oil, along with 30 mg of unreacted olefin **62**. $[\alpha]_D^{21}$+1.2 (*c* 1.1, $CHCl_3$); IR (thin film): 3409, 2954, 2932, 2857, 1738, 1716, 1462, 1439, 1409, 1375, 1254, 1203, 1175, 1050, 836, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.21 (pent, *J*= 5.0 Hz, 1H), 3.67 (s, 3H), 3.42 (t, *J*= 5.0 Hz, 2H), 2.62 (dd, *J*= 15.5, 6.5 Hz, 1H), 2.54-2.47 (m, 4H), 2.34 (t, *J*= 7.0 Hz, 2H), 2.21 (t, *J*= 6.0 Hz, 1H), 1.92-1.83 (m, 2H), 1.64-1.46 (m, 4H), 1.14 (s, 3H), 0.86 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.0, 173.7, 72.4, 70.0, 68.9, 51.6, 49.4, 43.3, 33.2, 33.0, 31.0, 25.8, 23.2, 18.6, 18.0, -4.6, -4.8; HRMS (ES+) *m*/*z* calcd for $C_{19}H_{38}O_6SiNa$ [$(M + Na)^+$]: 413.2335; found 413.2327.

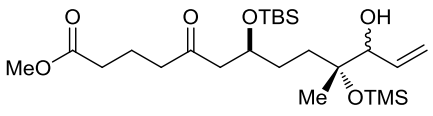


66

(7*S*,10*R*)-Methyl-7-(*tert*-butyldimethylsilyloxy)-10-methyl-5,11-dioxo-10 [(trimethylsilyl)oxy]undecanoate (**66**): A stirred biphasic mixture of diol **65** (1.68 g, 4.30 mmol, 1.0 equiv) and KBr (0.512 g, 4.30 mmol, 1.0 equiv) in 40 mL of CH_2Cl_2 and 20 mL of saturated $NaHCO_3$ aqueous solution was cooled to 0 °C. A few crystals of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were added in the reaction whereupon 5.8 mL of bleach (about 6% of NaOCl in H_2O) was added portionwise. The reaction turned orangey red and the color faded in 0.5 h. Another 0.7 mL of bleach was added and the reaction was stirred for additional 0.5 h.

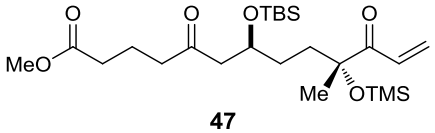
The reaction was then quenched with 20 mL of saturated $Na_2S_2O_3$ aqueous solution. After separating the organic phase, the aqueous phase was extracted with CH_2Cl_2 (2 X 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was used without further purification.

To a stirred solution of aldehyde obtained above in 22 mL of CH_2Cl_2 at −78 °C was added 0.9 mL of 2,6-lutidine (7.7 mmol, 1.8 equiv) followed by 1.2 mL of TMSOTf (6.4 mmol, 1.5 equiv) dropwise. The reaction was stirred at this temperature for 1h and quenched by adding 20 mL of saturated $NaHCO_3$ aqueous solution. The mixture was warmed to ambient temperature and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash column chromatography on silica gel (1 L of 14% EtOAc in hexanes) to afford 1.78 g of the titled compound **66** (90% over 2 steps) as a clear oil. $[\alpha]_D^{20}$+3.42 (*c* 3.19, $CHCl_3$); IR (thin film): 2955, 2896, 2857, 1740, 1438, 1410, 1375, 1253, 1196, 1142, 1082, 1021, 840, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 4.18-4.13 (m, 1H), 3.66 (s, 3H), 2.58 (dd, *J*= 15.5, 7.5 Hz, 1H), 2.49 (dt, *J*= 7.0, 3.0 Hz, 2H), 2.38 (dd, *J*= 15.5, 5.0 Hz, 1H), 2.33 (t, *J*= 7.0 Hz, 2H), 1.92-1.82 (m, 2H), 1.67-1.61 (m, 1H), 1.56-1.48 (m, 2H), 1.44-1.37 (m, 1H), 1.27 (s, 3H), 0.85 (s, 9H), 0.15 (s, 9H), 0.021(d, *J*= 26.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 204.6, 173.6, 80.4, 68.7, 51.6, 49.7, 43.4, 34.0, 33.0, 31.0, 25.8, 22.8, 18.6, 18.0, 2.3, -4.6, -4.8; HRMS (ES+) *m*/*z* calcd for $C_{22}H_{44}O_6Si_2Na$ $[(M + Na)^+]$: 483.2574; found: 483.2577.



(7*S*,10*R*)-Methyl-7-(*tert*-butyldimethylsilyloxy)-11-hydroxy-10-methyl-5-oxo-10 (trimethylsilyloxy)tridec-12-

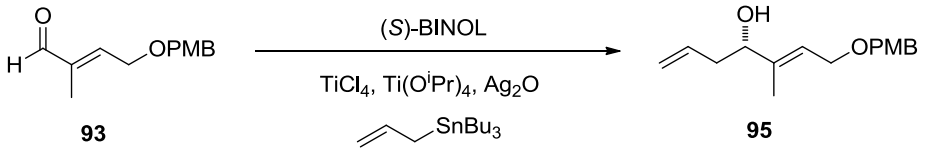
enoate : To a stirred solution of 1.73 g of aldehyde **66** (3.80 mmol, 1.0 equiv) in 40 mL of THF at −78°C was added 10.0 mL of vinylmagnesium bromide (7.22 mmol, 1.9 equiv, 0.74 M solution in THF) dropwise. The reaction was stirred at this temperature for 1.5h. The reaction was then quenched by slow addition of 0.5 mL of glacial acetic acid followed by 40 mL of saturated NH_4Cl aqueous solution. The mixture was warmed to ambient temperature and the organic phase was separated. The aqueous phase was extracted with EtOAc (3 X 30 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The material was purified via flash column chromatography on silica gel (200 mL of 15% EtOAc in hexanes then 600 mL 20% EtOAc in hexanes) to afford 1.48 g of the titled compound (80%) in a form of inconsequential diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (ddd, *J*= 17.5, 10.5, 6.5 Hz, 1H), 5.31 (dt, *J*= 17.0, 1.5 Hz, 1H), 5.19 (dt, *J*= 10.5, 1.5 Hz, 1H), 4.16-4.10 (m, 1H), 3.87-3.84 (m, 1H), 3.67 (s, 3H), 2.61-2.56 (m, 2H), 2.51 (dt, *J*= 7.5, 5.0 Hz, 2H), 2.41 (dd, *J*= 15.0, 4.5 Hz, 1H), 2.34 (t, *J*= 7.5 Hz, 2H), 1.91-1.84 (m, 2H), 1.63-1.42 (m, 4H), 1.33 (dt, *J*= 13.0, 4.0 Hz, 1H), 1.22 (s, 3H), 0.86 (s, 9H), 0.15 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.1, 173.6, 136.4, 117.0, 79.4, 78.4, 69.3, 51.6, 49.9, 43.5, 33.0, 31.4, 25.8, 23.8, 18.6, 18.0, 2.7, 2.5, -4.5, -4.8.



47

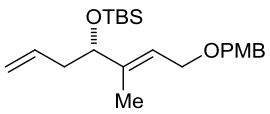
(7*S*,10*R*)-Methyl-7-(*tert*-butyldimethylsilyloxy)-10-methyl-5,11-dioxo-10 (trimethylsilyloxy)tridec-12-enoate (**47**): To a stirred solution of 0.276 g of the allylic alcohol (0.565 mmol, 1.0 equiv) in 6 mL of CH_2Cl_2 at ambient temperature was added 0.360 g of Dess-Martin periodinane (0.850 mmol, 1.5

equiv) in one portion. The resulting heterogeneous mixture was stirred for 1.5 h and quenched by 20 mL of 1:1 mixture of saturated $NaHCO_3$ aqueous solution and saturated NaS_2O_3 aqueous solution. The mixture was extracted with CH_2Cl_2 (3 X 20 mL) and combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash column chromatography on silica gel (100 mL of 7% EtOAc in hexanes then 300 mL 15% EtOAc in hexanes) to afford 0.197 g of titled compound **47** (71%) as a clear oil. $[\alpha]_D^{19}$+3.90 (*c* 2.36, $CHCl_3$); IR (thin film): 2955, 2897, 2857, 1740, 1710, 1438, 1401, 1373, 1253, 1199, 1162, 1082, 1049, 840, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.97 (dd, *J*= 17.5, 10.5 Hz, 1H), 6.35 (dd, *J*= 17.5, 2.0 Hz, 1H), 5.70 (dd, *J*= 10.5, 2.0 Hz, 1H), 4.16-4.12 (m, 1H), 3.66 (s, 3H), 2.56 (dd, *J*= 15.0, 7.5 Hz, 1H), 2.47 (dt, *J*= 7.0, 3.0 Hz, 2H), 2.35 (dd, *J*= 15.0, 4.5 Hz, 1H), 2.32 (t, *J*= 7.0 Hz, 2H), 1.91-1.83 (m, 2H), 1.72 (dt, *J*= 13.0, 5.0 Hz, 1H), 1.54 (dt, *J*= 13.0, 4.5 Hz, 1H), 1.47-1.36 (m, 2H), 1.35 (s, 3H), 0.84 (s, 9H), 0.13 (s, 9H), 0.04 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.6, 202.6, 173.5, 130.7, 129.0, 81.4, 68.8, 51.5, 49.7, 43.4, 35.9, 33.0, 31.5, 25.8, 24.4, 18.6, 17.9, 2.2, -4.6, -4.8; HRMS (ES+) *m/z* calcd for $C_{24}H_{46}O_6Si_2Na$ [(M + $Na)^+$]: 509.2731; found: 509.2696.



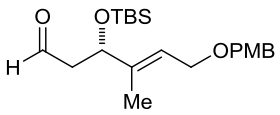
(*S*,*E*)-7-(4-Methoxybenzyloxy)-5-methylhepta-1,5-dien-4-ol (**95**): To a stirred solution of 1.15 mL of $TiCl_4$ (1.15 mmol, 0.05 equiv, 1.0 M solution in CH_2Cl_2) in 23 mL of CH_2Cl_2 at 0°C was added $Ti(O^iPr)_4$ (1.0 mL, 3.5 mmol, 0.15 equiv) dropwise. The resulting solution was allowed to warm to ambient temperature and stirred for 1h. 0.533 g of Ag_2O (2.30 mmol, 0.1 equiv) was

added into the reaction and the suspension was vigorously stirred overnight with exclusion of light. The mixture was then diluted with 46 mL of CH_2Cl_2 and 1.32 g of (*S*)-BINOL (4.60 mmol, 0.2 equiv) was added into the reaction in one portion. The reaction was stirred at ambient temperature for 2h before being cooled to −15 °C. The reaction was then treated sequentially with 4.63 g of aldehyde **93**[33] (21.0 mmol, 1.0 equiv) and 11.0 mL of allyltributylstannane (35.0 mmol, 1.7 equiv). The reaction was then allowed to warm to 0 °C and stirred for 6h. The reaction was quenched with 70 mL of saturated $NaHCO_3$ aqueous solution and the organic phase was separated. The aqueous phase was extracted with Et_2O (2 X 60 mL) and the combined organic extracts were filtered through a short pad of celite. After concentrating the filtrate under reduced pressure, the crude residue thus obtained was purified via flash chromatography on silica gel (1 L of 15% EtOAc in hexanes then 1 L of 25% EtOAc in hexanes) to afford 4.0 g of the titled compound **95** (86%) as a clear oil. $[\alpha]_D^{20}$−0.93 (*c* 4.1, $CHCl_3$); IR (thin film): 3416, 3000, 2934, 2858, 1612, 1513, 1462, 1365, 1302, 1248, 1175, 1035, 915, 820 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J*= 8.8 Hz, 2H), 6.89 (d, *J*= 8.8 Hz, 2H), 5.80 (ddt, *J*= 17.2, 10.0, 7.2 Hz, 1H), 5.66 (t, *J*= 6.8 Hz, 1H), 5.17-5.11 (m, 2H), 4.46 (s, 2H), 4.11-4.09 (m, 1H), 4.06 (d, *J*= 6.8 Hz, 2H), 3.82 (s, 3H), 2.40-2.27 (m, 2H), 1.79 (br s, 1H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 140.7, 134.6, 130.4, 129.4, 122.6, 117.9, 113.8, 75.8, 71.9, 66.0, 55.3, 39.8, 12.3; HRMS (ES+) *m*/*z* calcd for $C_{16}H_{22}O_3Na$ [$(M + Na)^+$]: 285.1467; found: 285.1476.



(*S*,*E*)-*tert*-Butyl{[7-(4-methoxybenzyloxy)-5-methylhepta-1,5-dien-4-yl]oxy}dimethylsilane: To a stirred solution of 4.16 g of alcohol **95** (16.0

mmol, 1.0 euqiv) in 60 mL of CH_2Cl_2 at −50 °C was added 2.8 mL of 2,6-lutidine (24 mmol, 1.5 equiv) followed by 4.4 mL of TBSOTf (19 mmol, 1.2 equiv) slowly. The reaction was stirred at this temperature for 1h and quenched by adding 50 mL of saturated $NaHCO_3$ aqueous solution. After separating the organic phase, the aqueous phase was extracted with CH_2Cl_2 (2 X 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash column chromatography on silica gel (5% EtOAc in hexanes) to afford 5.37 g of the titled compound (89%) as a clear oil. $[\alpha]_D^{20}$−0.430 (*c* 1.87, $CHCl_3$); IR (thin film): 2954, 2931, 2856, 1613, 1513, 1465, 1250, 1173, 1074, 1038, 1004, 914, 835, 776 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.28 (d, *J*= 8.8 Hz, 2H), 6.90 (d, *J*= 8.8 Hz, 2H), 5.77 (ddt, *J*= 17.2, 10.4, 6.8 Hz, 1H), 5.56 (t, *J*= 6.8 Hz, 1H), 5.08-5.00 (m, 2H), 4.44 (s, 2H), 4.09-4.06 (m, 3H), 3.82 (s, 3H), 2.35-2.21 (m, 2H), 1.62 (s, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.03 (3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 141.3, 135.4, 130.7, 129.3, 122.2, 116.4, 113.8, 77.8, 71.4, 65.9, 55.3, 41.2, 25.8, 18.2, 11.7, -4.6, -4.9; HRMS (ASAP) *m*/*z* calcd for $C_{22}H_{35}O_3Si$ $[(M-H)^+]$: 375.2362; found: 375.2355.

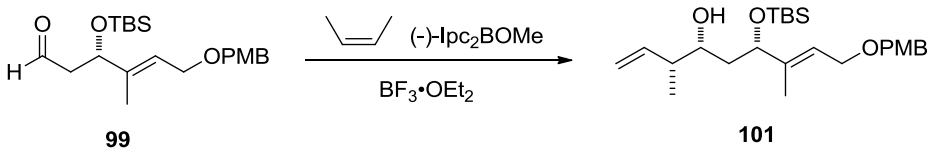


99

(*S*,*E*)-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)-4-methylhex-4-enal (**99**): To a 0 °C solution of 3.0 g of the diene (8.0 mmol, 1.0 equiv) in a mixed solvent of ^{t}BtOH/acetone/H_2O (16 mL/16 mL/4 mL, 4:4:1) were added 0.937 g of 4-methylmorpholine *N*-oxide (8.00 mmol, 1.0 equiv) and a few crystals of osmium tetroxide sequentially. The mixture was stirred at this temperature for 4h and quenched with 40 mL of saturated Na_2SO_3 aqueous solution. The mixture was extracted

with EtOAc (3 X 30 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was used without further purification.

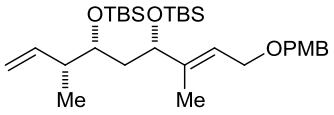
The crude diol obtained above was dissolved in a 1:1 mixture of THF and H_2O (16 mL, 16 mL). 3.42 G of sodium periodate (16.0 mmol, 2.0 equiv) was added in one portion. The reaction was stirred at ambient temperature for 2h and then filtered through a short pad of celite. The solid cake was rinsed repeatedly with Et_2O and H_2O. The filtrate was transferred to a separatory funnel and the aqueous phase was separated. The organic phase was washed sequentially with H_2O and brine and then dried over $MgSO_4$, filtered and concentrated. The crude material was purified via flash column chromatography on silica gel (8% EtOAc in hexanes then 13% EtOAc in hexanes) to afford 2.48 g of titled compound **99** (82% in 2 steps) as a clear oil. $[\alpha]_D^{21}$ −1.00 (*c* 16.0, $CHCl_3$); IR (thin film): 2954, 2931, 2895, 2856, 1726, 1613, 1513, 1465, 1250, 1174, 1085, 1038, 1004, 837, 778 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.77 (dd, *J*= 3.0, 2.5 Hz, 1H), 7.28 (d, *J*= 8.5 Hz, 2H), 6.90 (d, *J*= 9.0 Hz, 2H), 5.69 (t, *J*= 6.5 Hz, 1H), 4.60 (dd, *J*= 8.0, 4.0 Hz, 1H), 4.44 (s, 2H), 4.05 (d, *J*= 6.5 Hz, 2H), 3.82 (s, 3H), 2.69 (ddd, *J*= 15.5, 8.0, 3.0 Hz, 1H), 2.45 (ddd, *J*= 15.5, 4.0, 2.0 Hz, 1H), 1.64 (d, *J*= 1.0 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.6, 159.2, 139.9, 130.4, 129.4, 123.1, 113.8, 73.3, 71.8, 65.8, 55.3, 50.0, 25.7, 18.1, 11.9, -4.6, -5.2; HRMS (ES+) calcd for $C_{21}H_{34}O_4SiNa$ [$(M + Na)^+$]: 401.2124; found: 401.2114.



99 **101**

(3*R*,4*R*,6*S*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-3,7-dimethylnona-1,7-dien-4-ol (**101**): To a −78°C solution of 0.404 g of freshly sublimed ^{t}BuOK (3.60 mmol, 1.2 equiv) in 25 mL of THF was cannulated 0.85 mL of (*Z*)-2-butene (9.0 mmol, 3.0 equiv, 0.094 mL/mol, condensed at −78 °C) followed by adding 2.25 mL of ^{n}BuLi (3.6 mmol, 1.2 equiv) via syringe. The bright yellow suspension was stirred at −78 °C for 5 min, −45 °C for 10 min and then −78 °C for 15 min. A solution of 1.33 g of (−)-Ipc_2BOMe (4.20 mmol, 1.4 equiv) in 3 mL of Et_2O was cannulated into the reaction. The colorless solution was stirred for 30 min whereupon 0.56 mL of $BF_3{\cdot}Et_2O$ (4.5 mmol, 1.5 equiv) was added immediately followed by a solution of 1.1 g of aldehyde **99** (3.0 mmol, 1.0 equiv) in 4 mL of THF. The reaction was stirred at −78 °C for 3 h and then quenched by adding 8 mL of 3 N NaOH aqueous solution. 4 mL of H_2O_2 30% aqueous solution was carefully added dropwise (Caution: gas evolution). The mixture was then allowed to warm to ambient temperature and stirred for 12h. The mixture was then diluted with 60 mL of EtOAc and washed sequentially with 30 mL of H_2O and 30 mL of brine. The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude material was purified via flash column chromatography on silica gel (8% EtOAc in hexanes then 13% EtOAc in hexanes) to afford 0.95 g of the titled compound (73%) in a form of two diastereomers which could be separated at later stage. The characterization of the major diastereomer **101** is: $[\alpha]_D^{20}$−0.640 (*c* 5.30, $CHCl_3$); IR (thin film): 3466, 2954, 2930, 2857, 1612, 1513, 1463, 1363, 1302, 1251, 1173, 1073, 1005, 920, 836, 778 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J*= 9.0 Hz, 2H), 6.89 (d, *J*= 9.0 Hz, 2H), 5.80 (ddd, *J*= 18.0, 10.5, 7.5 Hz, 1H), 5.59 (t, *J*= 6.0 Hz, 1H), 5.09-5.02 (m, 2H), 4.44 (d, *J*= 2.0 Hz, 2H), 4.28 (dd, *J*= 8.5, 5.0 Hz, 1H), 4.03 (d, *J*= 6.5 Hz, 2H), 3.82 (s, 3H), 3.62 (ddd, *J*= 8.5, 5.5, 3.0 Hz, 1H), 2.28-2.22 (m, 1H), 1.03 (d, *J*= 6.5 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 141.1, 141.0,

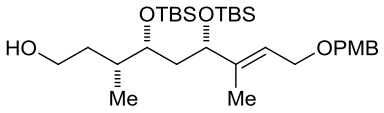
130.4, 129.3, 123.0, 114.9, 113.8, 79.4, 74.4, 71.9, 66.0, 55.3, 43.8, 39.5, 25.8, 18.0, 15.1, 11.6, -4.3, -5.1; HRMS (ES+) *m*/*z* calcd for $C_{25}H_{42}O_4SiNa$ [$(M + Na)^+$]: 457.2750; found: 457.2759.



103

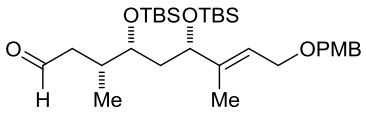
(5*R*,7*S*)-5-[(*R*)-But-3-en-2-yl]-7-[(*E*)-4-(4-methoxybenzyloxy)but-2-en-2-yl]-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (**103**): To a stirred −50 °C solution of 0.506 g of alcohol **101** (1.20 mmol, 1.0 euqiv) in 6 mL of CH_2Cl_2 was added 0.21 mL of 2,6-lutidine (1.8 mmol, 1.5 equiv) followed by 0.33 mL of TBSOTf (1.4 mmol, 1.2 equiv) dropwise. The reaction was stirred at this temperature for 1h and quenched by adding 6 mL of saturated $NaHCO_3$ aqueous solution. After separating the organic phase, the aqueous phase was extracted with CH_2Cl_2 (2 X 6 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash column chromatography on silica gel (5% Et_2O in hexanes) to afford 0.67 g of titled compound **103** (100%) as a clear oil. $[\alpha]_D^{21}$ 0 (*c* 1.23, $CHCl_3$); IR (thin film): 2955, 2931, 2890, 2857, 1513, 1463, 1362, 1250, 1078, 1039, 1005, 835, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J*= 8.5 Hz, 2H), 6.90 (d, *J*= 9.0 Hz, 2H), 5.95-5.88 (m, 1H), 5.56 (t, *J*= 6.0 Hz, 1H), 5.06-4.99 (m, 2H), 4.45 (s, 2H), 4.14 (t, *J*= 6.5 Hz, 1H), 4.06 (dd, *J*= 6.0, 3.0 Hz, 2H), 3.82 (s, 3H), 3.69 (dt, *J*= 6.0, 3.0 Hz, 1H), 2.38-2.34 (m, 1H), 1.64 (t, *J*= 6.5 Hz, 2H), 1.60 (s, 3H), 0.95 (d, *J*= 7.0 Hz, 3H), 0.913 (s, 9H), 0.906 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 141.9, 141.4, 130.6, 129.2, 122.8, 113.8, 113.7, 75.5, 72.5, 71.6, 66.0, 55.3, 41.7, 40.8, 26.0, 25.9, 18.1,

13.3, 11.3, -4.2, -4.3, -4.5, -4.9; HMRS (ES+) *m/z* calcd for $C_{31}H_{56}O_4NaSi_2$ [$(M+Na)^+$]: 571.3615; found: 571.3636.



(3*R*,4*R*,6*S*,*E*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-3,7-dimethylnon-7-en-1-ol : To a stirred 0 °C solution of 0.61 g of diene **103** (1.1 mmol, 1.0 equiv) in 10 mL of Et_2O was added 0.256 g of 9-BBN dimer (1.05 mmol, 0.94 equiv) in one portion. The reaction was warmed to ambient temperature and stirred for 5h. The reaction was cooled to 0 °C and 12 mL of 1 N NaOH aqueous solution was added followed by careful addition of 12 mL of H_2O_2 30% aqueous solution. The resulting mixture was warmed to ambient temperature and stirred for 15 min and then poured into a separatory funnel equipped with 30 mL of saturated $NaHCO_3$ aqueous solution and 30 mL of CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 X 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash column chromatography on silica gel (5% EtOAc in hexanes then 15% EtOAc in hexanes) to afford 0.58 g of the titled compound (91%) as a clear oil. $[\alpha]_D^{20}$−0.0300 (*c* 3.39, $CHCl_3$); IR (thin film): 3426, 2954, 2931, 2886, 2857, 1613, 1514, 1464, 1385, 1362, 1302, 1251, 1174, 1059, 1007, 940, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J*= 8.8 Hz, 2H), 6.89 (d, *J*= 8.4 Hz, 2H), 5.55 (t, *J*= 6.0 Hz, 1H), 4.44 (s, 2H), 4.12 (t, *J*= 6.4 Hz, 1H), 4.04 (d, *J*= 6.4 Hz, 2H), 3.82 (s, 3H), 3.73-3.68 (m, 1H), 3.65-3.59 (m, 1H), 1.87 (br s, 1H), 1.79-1.71 (m, 2H), 1.67 (dt, *J*= 6.4, 2.8 Hz, 2H), 1.58 (s, 3H), 1.48-1.39 (m, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.84 (d, *J*= 6.4 Hz, 3H), 0.09 (s, 3H),

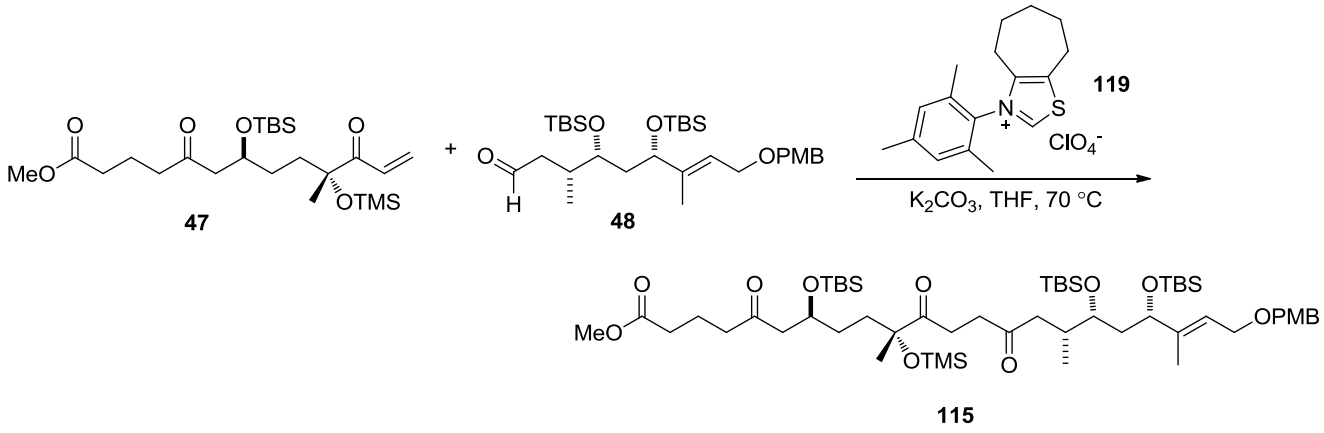
0.06 (s, 3H), 0.05 (s, 3H), 0.00 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 141.2, 130.5, 129.2, 123.0, 113.8, 75.6, 72.9, 71.6, 65.9, 61.6, 55.3, 39.8, 36.2, 34.8, 25.9, 25.8, 18.13, 18.10, 14.7, 11.2, -4.1, -4.2, -4.5, -4.9; HRMS (ES+) *m*/*z* calcd for $C_{31}H_{58}O_5Si_2Na$ [(M + Na)$^+$]: 589.3721; found: 589.3727.



48

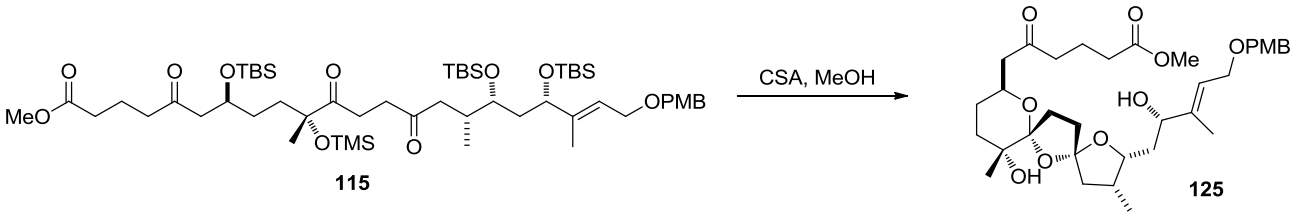
(3*R*,4*R*,6*S*,*E*)-4,6-Bis(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-3,7-dimethylnon-7-enal (**48**): To a stirred solution of 113 mg of the alcohol (0.200 mmol, 1.0 equiv) in 2 mL of CH_2Cl_2 was added 0.21 mL of 2,6-lutidine (1.8 mmol, 9.0 equiv) followed by 127 mg of Dess-Martin periodinane (0.300 mmol, 1.5 equiv) in one portion. The heterogeneous mixture was stirred vigorously at ambient temperature for 0.5 h and quenched by a 1:1 mixture of saturated $NaHCO_3$ and $Na_2S_2O_3$ aqueous solution (9 mL, 9 mL). The mixture was extracted with CH_2Cl_2 (3 X 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude material was purified via flash chromatography on silica gel (6% EtOAc in hexanes) to afford 100 mg of titled compound **48** (88%) as a clear oil. $[\alpha]_D^{19}$ −0.910 (*c* 1.32, $CHCl_3$); IR (thin film): 2955, 2931, 2887, 2856, 1727, 1613, 1513, 1464, 1385, 1362, 1250, 1173, 1080, 1039, 1007, 938, 836, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.79-9.78 (m, 1H), 7.27 (d, *J*= 9.0 Hz, 2H), 6.89 (d, *J*= 8.5 Hz, 2H), 5.55 (t, *J*= 6.0 Hz, 1H), 4.44 (d, *J*= 2 Hz, 2H), 4.12 (t, *J*= 7.0 Hz, 1H), 4.05 (dd, *J*= 6.0, 2.5 Hz, 2H), 3.82 (s, 3H), 3.65 (dt, *J*= 6.0, 2.0 Hz, 1H), 2.57-2.54 (m, 1H), 2.33-2.24 (m, 2H), 1.67-1.55 (m, 2H), 1.58 (s, 3H), 0.90 (s, 9 H), 0.89 (s, 9H), 0.87 (d, *J*= 7.0 Hz, 3H), 0.076 (s, 3H), 0.053 (s, 3H), 0.039 (s, 3H), 0.006 (s, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 202.6, 159.2, 141.0, 130.5, 129.2, 123.3, 113.8, 75.4, 72.1, 71.6, 66.0, 55.3, 47.5, 39.7, 32.2, 25.9, 25.8, 18.1, 18.0, 14.0, 11.2, -4.2, -4.3, -4.5, -5.0; HRMS (ES+) *m/z* calcd for $C_{31}H_{56}O_5Si_2Na$ [$(M+Na)^+$]: 587.3564; found: 587.3600.



(7*S*,10*R*,16*R*,17*R*,19*S*,*E*)-Methyl-7,17,19-tris(*tert*-butyldimethylsilyloxy)-22-(4 methoxybenzyloxy)-10,16,20-trimethyl-5,11,14-trioxo-10-(trimethylsilyloxy)docos-20-enoate (**115**): Into a vial with a Teflon cap and a magnetic stirring bar were charged 91.4 mg of aldehyde **48** (0.160 mmol, 1.0 equiv) and 120 mg of enone **47** (0.240 mmol, 1.5 equiv). The vial was transferred to the glove box, where 12 mg of thiozolium salt **119** (0.032 mmol, 0.2 equiv) and 9.0 mg of anhydrous K_2CO_3 (0.064 mmol, 0.4 equiv) were weighed out. The vial was removed from the glove box and 0.4 mL of THF was added. The suspension was stirred in a pre-heated oil bath at 70 °C for 3h (The solid went into solution and the reaction turned red after 10 min). The reaction mixture was directly loaded on a silica gel column and purified (100 mL of 7% EtOAc in hexanes, 200 mL of 13% EtOAc in hexanes and then 100 mL of 18% EtOAc in hexanes) to afford 172 mg of titled compound **115** (100%) as a light yellow oil. $[\alpha]_D^{19}$+1.50 (*c*

1.23, $CHCl_3$); IR (thin film): 2955, 2931, 2895, 2856, 1740, 1715, 1251, 1080, 1007, 837, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J*= 9.0 Hz, 2H), 6.88 (d, *J*= 9.0 Hz, 2H), 5.54 (t, *J*= 6.0 Hz, 1H), 4.43 (d, *J*= 1.5 Hz, 2H), 4.14-4.11 (m, 2H), 4.04 (t, *J*= 6.0 Hz, 2H), 3.81 (s, 3H), 3.67 (s, 3H), 3.58 (dt, *J*= 6.0, 2.5 Hz, 1H), 2.92 (ddd, *J*= 19.0, 7.0, 5.5 Hz, 1H), 2.81 (ddd, *J*= 19.0, 7.0, 5.5 Hz, 1H), 2.66 (ddd, *J*= 18.0, 7.5, 5.5 Hz, 1H), 2.61-2.53 (m, 3H), 2.49 (dt, *J*= 7.0, 3.5 Hz, 2H), 2.39-2.34 (m, 2H), 2.33 (t, *J*= 7.5 Hz, 2H), 2.24-2.19 (m, 1H), 1.87 (d qent, *J*= 7.5, 3.5 Hz, 2H), 1.79-1.73 (m, 1H), 1.66-1.61 (m, 1H), 1.59-1.49 (m, 3H), 1.57 (s, 3H), 1.33 (s, 3H), 1.28-1.24 (m, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.85 (s, 9H), 0.79 (d, *J*= 7.0 Hz, 3H), 0.17 (s, 9H), 0.065 (s, 3H), 0.054 (s, 3H), 0.053 (s, 3H), 0.035 (s, 3H), 0.003 (s, 3H), -0.004 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.2, 209.0, 208.8, 173.6, 159.1, 141.1, 130.6, 129.2, 123.2, 113.8, 82.6, 75.5, 72.5, 71.5, 68.9, 65.9, 55.3, 51.5, 49.8, 45.9, 43.5, 39.8, 36.6, 36.3, 33.3, 33.0, 31.7, 31.6, 26.0, 25.9, 25.8, 18.6, 18.14, 18.07, 18.0, 13.9, 11.0, 2.4, -4.2, -4.3, -4.47, -4.52, -4.8, -5.0; HRMS (TOF ES+) *m/z* calcd for $C_{55}H_{102}O_{11}Si_4Na$ $[(M + Na)^+]$: 1073.6397; found: 1073.6397.

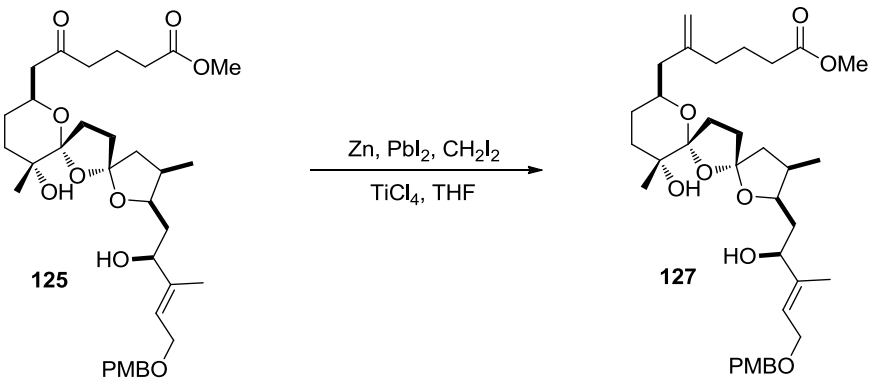


115 **125**

natural configuration: trans configuration = 1:6

Bis-spiroketal (**125**): To a stirred solution of 136 mg of ketone **115** (0.130 mmol, 1.0 equiv) in 3 mL of MeOH was added 15 mg of (1*R*)-(−)-10-camphorsulfonic acid (0.065 mmol, 0.5 equiv) in one portion. The reaction was stirred at ambient temperature for 16 h. The solvent was removed under reduced pressure and the residue was purified via flash column chromatography on silica

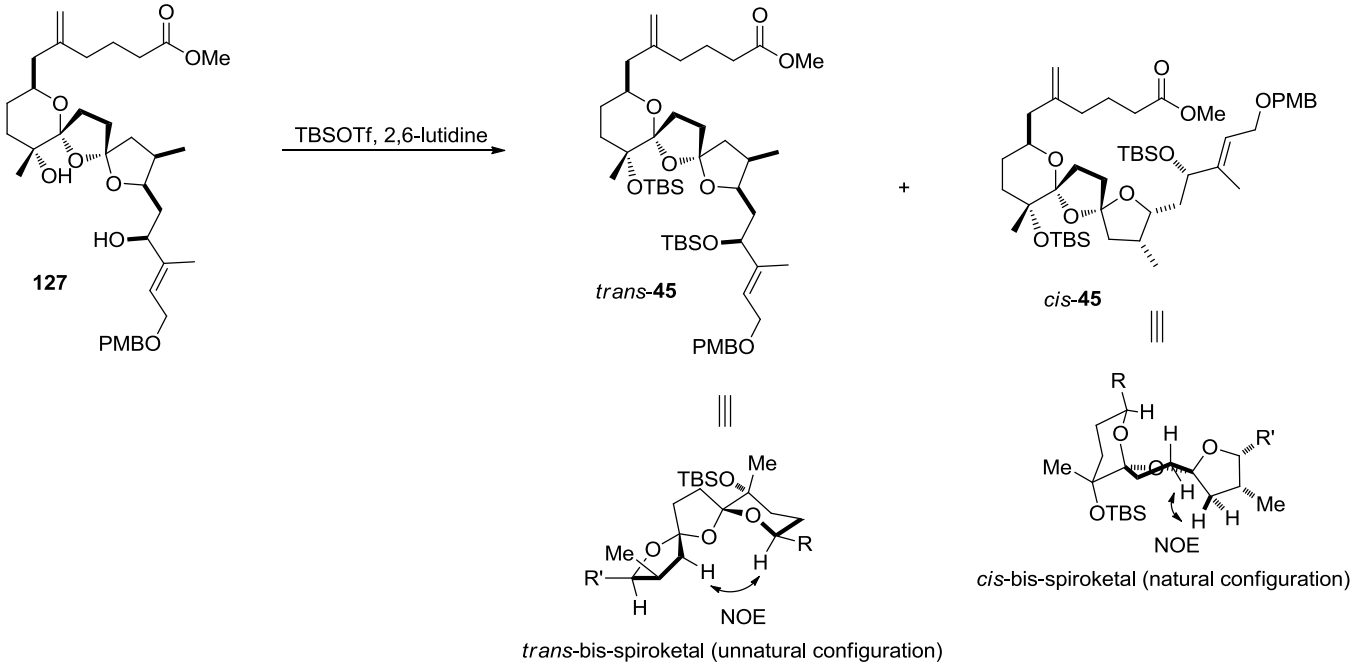
gel (150 mL of 50% EtOAc in hexanes then 300 mL of 70% EtOAc in hexanes) to afford 57.7 mg of titled compound **125** (72%) as a light yellow oil. The characterization of the major diastereomer *trans*-**125** is: $[\alpha]_D^{19}$+ 2.8 (*c* 0.74, $CHCl_3$); IR (thin film): 3468, 2944, 1737, 1714, 1612, 1513, 1442, 1379, 1301, 1249, 1207, 1174, 1073, 1033, 1003, 975, 930, 867, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J*= 8.5 Hz, 2H), 6.88 (d, *J*= 8.5 Hz, 2H), 5.68 (t, *J*= 6.5 Hz, 1H), 4.45 (s, 2H), 4.30-4.22 (m, 2H), 4.20 (dd, *J*= 8.5, 4.0 Hz, 1H), 4.05 (d, *J*= 6.5 Hz), 3.81 (s, 3H), 3.67 (s, 3H), 3.23 (brs, 1H), 2.58 (dd, *J*= 15.0, 9.0 Hz, 2H), 2.50 (q, *J*= 7.5 Hz, 2H), 2.45 (brs, 1H), 2.39-2.30 (m, 5H), 2.13 (dt, *J*= 12.5, 7.5 Hz, 1H), 1.97 (dd, *J*= 12.5, 7.5 Hz, 1H), 1.89 (t, *J*= 7.5 Hz, 2H), 1.87-1.81 (m, 1H), 1.76 (dd, *J*= 13.0, 8.5 Hz, 1H), 1.68-1.63 (m, 6H), 1.62-1.55 (m, 2H), 1.50-1.40 (m, 1H), 1.22 (s, 3H), 0.96 (d, *J*= 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.4, 173.6, 159.2, 140.9, 130.5, 129.4, 122.3, 115.3, 113.8, 110.7, 81.8, 76.5, 71.9, 68.5, 67.1, 66.0, 55.3, 51.6, 48.4, 43.5, 42.7, 35.7, 35.4, 35.2, 35.1, 33.0, 30.6, 30.1, 21.1, 18.6, 14.3, 12.4; HRMS (TOF ES+) *m/z* calcd for $C_{34}H_{50}O_{10}Na$ [$(M+Na)^+$]: 641.3302; found: 641.3309.



Bis-spiroketal (*trans*-**127**): Generating the methylenation reagent: A flame-dried 2 dram vial were charged with 59 mg of activated zinc (0.90 mmol, 1.8 equiv) and 4.1 mg of PbI_2 (0.0089 mmol, 0.018 equiv) under N_2 atmosphere. 1mL of THF was added and the resulting suspension

was stirred vigorously at ambient temperature whereupon one drop of distilled TMSCl was added. The mixture was stirred for 15 min before being cooled to 0 °C. 40 µL of CH_2I_2 (0.50 mmol, 1.0 equiv) was added dropwise and the black suspension thus generated was stirred vigorously for 2h at 0 °C. 0.1 mL of $TiCl_4$ (0.1 mmol, 0.2 equiv, 1.0 M solution in CH_2Cl_2) was added into the reaction and the greenish brown mixture was allowed to warm to ambient temperature and stirred for 30 min to afford the methylenation reagent. 13.9 mg of **125** (0.022 mmol, 0.22 equiv to $TiCl_4$) was added into the vial containing the methylenation reagent at 0 °C as a solution of THF (0.5 mL). The reaction was stirred at 0 °C for 3h and quenched by saturated Rochelle's salts aqueous solution and diluted with EtOAc. The mixture was allowed to warm to ambient temperature and stirred until two homogenous layers resulted (~1h). The organic phase was separated and the aqueous phase was extracted three times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified via flash chromatography on a pipet silica gel column, eluting with 5 mL of 30% EtOAc in hexanes followed by 10 mL of 50% EtOAc in hexanes and 10 mL of 70% EtOAc in hexanes to afford 8.0 mg of titled compound **127** (58%) as clear oil. The characterization of the major diastereomer *trans*-**127** is: $[\alpha]_D^{19}$+2.20 (*c* 1.64, $CHCl_3$); IR (thin film): 3459, 2938, 1737, 1612, 1513, 1441, 1377, 1337, 1301, 1248, 1173, 1071, 1035, 1002, 979, 932, 868, 822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 (d, *J*= 8.0 Hz, 2H), 6.88 (d, *J*= 8.0 Hz, 2H), 5.69 (t, *J*= 6.5 Hz, 1H), 4.80 (s, 1H), 4.79 (s, 1H), 4.45 (s, 2H), 4.27 (ddd, *J*= 10.0, 7.0, 3.0 Hz, 1H), 4.20 (dd, *J*= 8.5, 4.0 Hz, 1H), 4.05 (d, *J*= 6.5 Hz, 2H), 3.94-3.89 (m, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 2.54 (heptet, *J*= 7.0 Hz, 1H), 2.38 (dd, *J*= 12.5, 7.5 Hz, 1H), 2.32 (t, *J*= 7.5 Hz, 2H), 2.29-2.27 (m, 1H), 2.21 (dd, *J*= 12.5, 7.5 Hz, 1H), 2.16 (dd, *J*= 15.0, 8.0 Hz, 1H), 2.07-2.04 (m, 3H), 1.99 (dd, *J*= 12.5, 7.5 Hz, 1H), 1.85-1.81 (m, 1H), 1.79-1.75 (m, 3H), 1.71 (dd, *J*= 12.5,

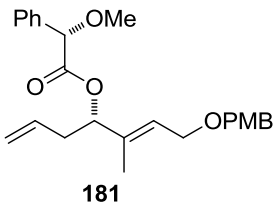
7.5 Hz, 1H), 1.66-1.64 (m, 4H), 1.62-1.55 (m, 3H), 1.42 (dq, *J*= 13.0, 4.0 Hz, 1H), 1.23 (s, 3H), 0.95 (d, *J*= 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 159.2, 145.7, 140.9, 130.6, 129.4, 122.3, 115.1, 113.8, 111.4, 110.8, 81.5, 76.5, 71.9, 68.9, 68.8, 66.0, 55.3, 51.5, 43.6, 41.7, 35.8, 35.7, 35.6, 35.4, 35.3, 33.5, 30.8, 30.3, 22.7, 21.2, 14.4, 12.4; HRMS (TOF ES+) *m/z* calcd for $C_{35}H_{52}O_9Na$ [$(M+Na)^+$]: 639.3509; found: 639.3508.



Bis-spiroketals (*trans*-**45**) and (*cis*-**45**): To a stirred solution of **127** (8.0 mg, 0.013 mmol, 1.0 equiv) and 2,6-lutidine (18 µL, 0.16 mmol, 12.0 equiv) in 0.5 mL of CH_2Cl_2 at 0 °C was added TBSOTf (18 µL, 0.078 mmol, 6.0 equiv) dropwise. The reaction was stirred for 1.5h until full consumption of the starting material was observed. The reaction was quenched by saturated $NaHCO_3$ aqueous solution and warmed to ambient temperature. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic

extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The ^{1}H NMR of the crude products showed 1.5:1 ratio of *cis*-**45** to *trans*-**45**. The crude material was purified via flash chromatography on pipet silica gel column, eluting with 5 mL of 5% EtOAc in hexanes followed by 10 mL of 10% EtOAc in hexanes and 10 mL of 15% EtOAc in hexanes to afford 4.5 mg of compound *trans*-**45** (41%) and 4.3 mg of compound *cis*-**45** (39%). Full characterization for compound *trans*-**45**: $[\alpha]_D^{19}$ +3.7 (*c* 0.62, benzene); IR (thin film): 2953, 2931, 2855, 1742, 1513, 1463, 1442, 1250, 1162, 1075, 1040, 965, 867, 836, 774 cm^{-1}; ^{1}H NMR (600 MHz, C_6D_6): δ 7.29 (d, *J*= 9.0 Hz, 2H), 6.82 (d, *J*= 9.0 Hz, 2H), 5.88 (t, *J*= 6.0 Hz, 1H), 4.87 (s, 1H), 4.83 (d, *J*= 1.2 Hz, 1H), 4.45-4.39 (m, 3H), 4.23 (dt, *J*= 8.4, 5.4 Hz, 1H), 4.05 (d, *J*= 6.6 Hz, 2H), 3.95 (dddd, *J*= 11.4, 8.4, 4.8, 3.6 Hz, 1H), 3.35 (s, 3H), 3.30 (s, 3H), 2.52-2.48 (m, 1H), 2.44 (dt, *J*= 12.0, 8.4 Hz, 1H), 2.32 (dd, *J*= 13.2, 7.2 Hz, 1H), 2.25 (dt, *J*= 12.0, 7.8 Hz, 1H), 2.23-2.15 (m, 2H), 2.15 (t, *J*= 7.8 Hz, 2H), 2.07 (ddd, *J*= 12.6, 9.0, 1.8 Hz, 1H), 2.03 (t, *J*= 7.8 Hz, 2H), 1.99 (dd, *J*= 14.4, 4.8 Hz, 1H), 1.83 (ddd, *J*= 13.8, 8.4, 5.4 Hz, 1H), 1.76 (pent, *J*= 7.8 Hz, 2H), 1.70 (ddd, *J*= 7.8, 3.6, 1.8 Hz, 1H), 1.69-1.67 (m, 1H), 1.66 (s, 3H), 1.64 (dd, *J*= 13.2, 8.4 Hz, 1H), 1.54 (ddd, *J*= 12.0, 4.2, 3.0 Hz, 1H), 1.37-1.34 (m, 1H), 1.32 (s, 3H), 1.32-1.29 (m, 1H), 1.15 (s, 9H), 1.03 (s, 9H), 0.82 (d, *J*= 7.2 Hz, 3H), 0.34 (s, 3H), 0.23 (s, 3H), 0.16 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 173.2, 159.7, 146.5, 140.6, 131.3, 129.4, 124.4, 115.1, 114.1, 111.8, 110.0, 78.2, 76.3, 73.0, 72.0, 68.8, 66.3, 54.7, 50.9, 46.4, 42.4, 37.6, 36.2, 36.0, 34.8, 34.7, 33.5, 30.9, 30.8, 26.5, 26.2, 25.2, 23.1, 18.6, 18.4, 14.4, 11.1, -1.6, -1.7, -4.3, -4.7; HRMS (TOF ES+) *m/z* calcd for $C_{47}H_{80}O_9Si_2Na$ [$(M+Na)^+$]: 867.5239; found: 867.5237. Full characterization for compound *cis*-**45**: $[\alpha]_D^{19}$ +2.8 (*c* 0.54, benzene); IR (thin film): 2952, 2931, 2856, 1741, 1513, 1462, 1250, 1171, 1135, 1039, 1010, 876, 835, 774; ^{1}H NMR (600 MHz, C_6D_6): δ 7.30 (d, *J*= 8.4 Hz, 2H), 6.83 (d, *J*= 9.0 Hz, 2H), 5.92 (app t, *J*= 6.0 Hz, 1H), 5.24 (s, 1H), 5.04 (s, 1H), 4.52 (dd,

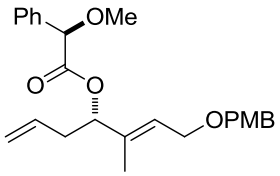
J= 7.8, 6.0 Hz, 1H), 4.42 (d, *J*= 4.2 Hz, 2H), 4.36 (dq, *J*= 7.2, 3.6 Hz, 1H), 4.07 (dd, *J*= 6.0, 4.2 Hz, 2H), 3.98 (dt, *J*= 10.2, 4.8 Hz, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 2.40 (ddd, *J*= 12.0, 10.8, 7.8 Hz, 1H), 2.33 (dd, *J*= 15.0, 7.8 Hz, 1H), 2.30-2.24 (m, 2H), 2.25 (t, *J*= 7.2 Hz, 2H), 2.20 (q, *J*= 7.2 Hz, 1H), 2.13 (dd, *J*= 15.0, 3.6 Hz, 1H), 2.10-2.00 (m, 4H), 1.90 (pent, *J*= 7.2 Hz, 2H), 1.88-1.87 (m, 1H), 1.79-1.73 (m, 2H), 1.71 (ddd, *J*= 11.4, 8.4, 2.4 Hz, 1H), 1.68 (s, 3H), 1.55 (ddd, *J*= 12.0, 4.2, 2.4 Hz, 1H), 1.50 (dddd, *J*= 13.2, 4.8, 2.4, 2.4 Hz, 1H), 1.44-1.36 (m, 1H), 1.30 (s, 3H), 1.03 (s, 9H), 0.99 (d, *J*= 6.6 Hz, 3H), 0.99 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), 0.167 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 173.1, 159.4, 145.9, 140.0, 131.0, 129.1, 124.3, 116.3, 113.7, 111.8, 109.5, 78.9, 76.3, 73.2, 71.6, 68.2, 65.9, 54.4, 50.5, 45.5, 42.1, 37.0, 36.9, 36.1, 35.5, 34.4, 33.3, 30.7, 30.6, 25.9, 25.8, 24.1, 22.9, 18.1, 13.9, 10.8, -1.9, -2.1, -4.6, -4.9; HRMS (TOF ES+) *m/z* calcd for $C_{47}H_{80}O_9Si_2Na$ [$(M+Na)^+$]: 867.5239; found: 867.5228. The relative stereochemistry of both *trans*-**45** and *cis*-**45** was established by NOESY.



181

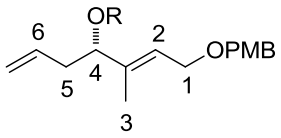
(*S*)-(*S,E*)-7-(4-Methoxybenzyloxy)-5-methylhepta-1,5-dien-4-yl 2-methoxy-2-phenylacetate (**181**): To a stirred solution of secondary alcohol **95** (26.3 mg, 0.100 mmol, 1.0 equiv), (*S*)-(+)-α-methoxypenylacetic acid (25.0 mg, 0.150 mmol, 1.5 equiv), and DMAP (12.2 mg, 0.100 mmol, 1.0 equiv) in 1.0 mL of CH_2Cl_2 at ambient temperature was added 31.0 mg of *N,N'*-dicyclohexylcarbodiimide (0.150 mmol, 1.5 equiv) in one portion. The reaction was stirred overnight. After evaporating the solvent, the crude material was purified via flash chromatography on silica gel (12% EtOAc in hexanes) to afford 40.5 mg of the titled compound (99%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.42 (m, 2H), 7.35-7.28 (m, 3H), 7.21 (d, *J*= 8.0 Hz, 2H), 6.88 (d, *J*= 8.5 Hz, 2H), 5.68 (ddt, *J*= 7.0, 10.5, 17.5 Hz, 1H), 5.44 (t, *J*= 6.5

Hz, 1H), 5.26 (t, *J*= 7.0 Hz, 1H), 5.09-5.03 (m, 2H), 4.76 (s, 1H), 4.30 (s, 2H), 3.90 (t, *J*= 6.5 Hz, 2H), 3.81 (s, 3H), 3.42 (s, 3H), 2.45-2.35 (m, 2H), 1.38 (s, 3H).



182

(*R*)-(*S*,*E*)-7-(4-Methoxybenzyloxy)-5-methylhepta-1,5-dien-4-yl 2-methoxy-2-phenylacetate (**182**): To a stirred solution of secondary alcohol **95** (26.3 mg, 0.100 mmol, 1.0 equiv), (*R*)-(−)-α-methoxypenylacetic acid (25.0 mg, 0.150 mmol, 1.5 equiv), and DMAP (12.2 mg, 0.100 mmol, 1.0 equiv) in 1.0 mL of CH_2Cl_2 at ambient temperature was added 31.0 mg of *N,N'*-dicyclohexylcarbodiimide (0.150 mmol, 1.5 equiv) in one portion. The reaction was stirred overnight. After evaporating the solvent, the crude material was purified via flash chromatography on silica gel (12% EtOAc in hexanes) to afford 35.8 mg of the titled compound (87%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.43 (m, 2H), 7.37-7.30 (m, 3H), 7.25 (d, *J*= 8.5 Hz, 2H), 6.89 (d, *J*= 9.0 Hz, 2H), 5.64 (t, *J*= 6.0 Hz, 1H), 5.44 (dddd, *J*= 19.0, 12.5, 9.5, 7.0 Hz, 1H), 5.24 (t, *J*= 6.5 Hz, 1H), 4.86-4.83 (m, 2H), 4.76 (s, 1H), 4.40 (s, 2H), 4.02 (d, *J*= 6.0 Hz, 2H), 3.81 (s, 3H), 3.42 (s, 3H), 2.33-2.23 (m, 2H), 1.60 (s, 3H).



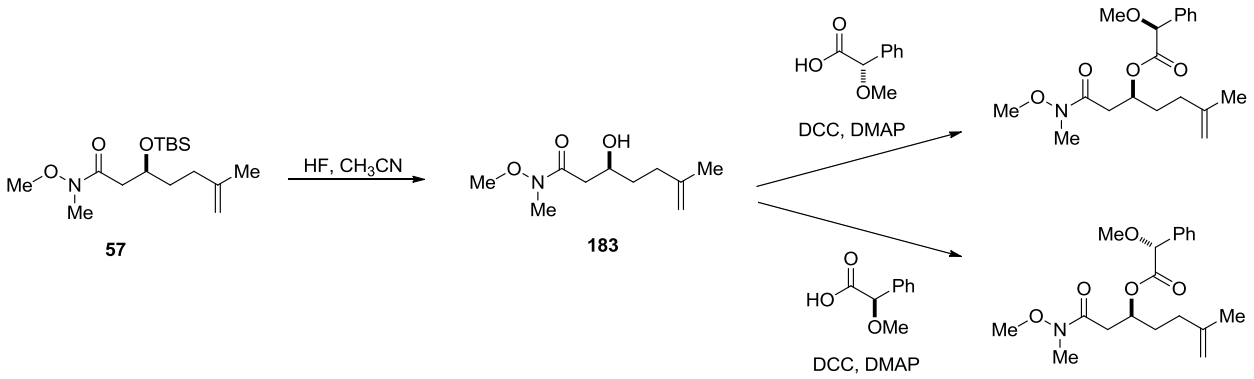
Proton numbering for *O*-methylmandelate esters

Table 7: Chemical Shifts of Protons in *O*-Methylmandelate Esters **181** and **182** and Application of the Trost method ($\delta_S-\delta_R$).[65]

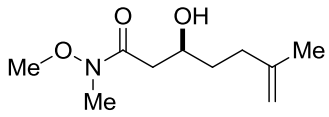
H#	δ (*S*)-ester **181**	δ (*R*)-ester **182**	$\Delta\delta= \delta_S-\delta_R$
1	3.895	4.016	−0.121
2	5.435	5.644	−0.209

3	1.380	1.596	−0.216
5	2.451 2.352	2.334 2.231	+0.117 +0.121
6	5.678	5.438	+0.240

The differences in chemical shifts indicate the absolute configuration of *S* at the C-4.

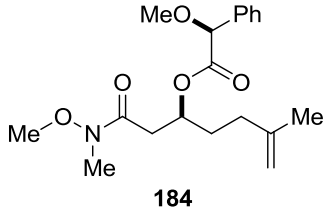


57 183



183

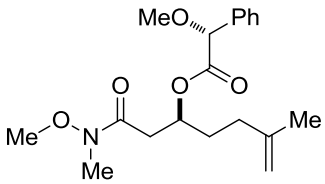
(*S*)-3-Hydroxy-*N*-methoxy-*N*,6-dimethylhept-6-enamide (**183**): To a stirred solution of compound **57** (188 mg, 0.600 mmol, 1.0 equiv) in 2 mL of CH_3CN at 0 °C was added 0.1 mL of HF acid (48 wt. % in water) dropwise. The reaction was stirred at this temperature for 2.5h and quenched by saturated $NaHCO_3$ aqueous solution. The organic phase was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude material was carried in the next step without further purification.



184

(*S*)-(*S*)-1-[Methoxy(methyl)amino]-6-methyl-1-oxohept-6-en-3-yl 2-methoxy-2-phenylacetate (**184**): To a stirred solution of the

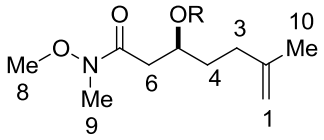
crude secondary alcohol (48.7 mg, 0.240 mmol, 1.0 equiv) in 2 mL of CH_2Cl_2 were added 60 mg of (*S*)-(+)-α-methoxypenylacetic acid (0.36 mmol, 1.5 equiv), 10 mg of DMAP (0.080 mmol, 0.33 equiv) and 74 mg of *N,N'*-dicyclohexylcarbodiimide (0.36 mmol, 1.5 equiv) sequentially. The resulting mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure and the crude product was purified via flash chromatography on silica gel, eluting with 100 mL of 20% of EtOAc in hexanes followed by 200 mL of 30% of EtOAc in hexanes and 200 mL of 40% EtOAc in hexanes, to afford 66 mg of the titled compound (78% over two steps) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (dd, *J*= 8.0, 1.5 Hz, 2H), 7.37-7.30 (m, 3H), 5.34 (pent, *J*= 6.4 Hz, 1H), 4.75 (s, 1H), 4.69 (s, 1H), 4.60 (d, *J*= 1.0 Hz, 1H), 3.55 (s, 3H), 3.42 (s, 3H), 3.04 (s, 3H), 2.72 (dd, *J*= 15.0, 6.5 Hz, 1H), 2.50 (dd, *J*= 15.5, 6.0 Hz, 1H), 1.97 (t, *J*= 8.0 Hz, 2H), 1.87-1.75 (m, 2H), 1.68 (s, 3H). The *ee* value of the compound **183** can be established as ≥ 95%, since only one diastereomer of **184** was observed in the spectrum.



185

(*R*)-(*S*)-1-[Methoxy(methyl)amino]-6-methyl-1-oxohept-6-en-3-yl 2-methoxy-2-phenylacetate (**185**): To a stirred solution of the crude secondary alcohol (67.7 mg, 0.340 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2 were added 85 mg of (*R*)-(−)-α-methoxypenylacetic acid (0.51 mmol, 1.5 equiv), 10 mg of DMAP (0.080 mmol, 0.24 equiv) and 105 mg of *N,N'*-dicyclohexylcarbodiimide (0.510 mmol, 1.5 equiv) sequentially. The resulting mixture was stirred at ambient temperature overnight. The solvent was removed under reduced pressure and the crude product was purified via flash chromatography on silica gel, eluting with 100 mL of 20% of EtOAc in hexanes followed by 200 mL of 30% of EtOAc in hexanes and 200 mL of 40% EtOAC in hexanes, to afford 98.3 mg of the titled compound (84% over two steps) as a clear oil. ^{1}H NMR (500 MHz,

$CDCl_3$): δ 7.44 (dd, *J*= 8.0, 1.5 Hz, 2H), 7.38-7.31 (m, 3H), 5.28-5.26 (m, 1H), 4.74 (s, 1H), 4.59 (s, 1H), 4.38 (d, *J*= 1.0 Hz, 1H), 3.68 (s, 3H), 3.43 (s, 3H), 3.16 (s, 3H), 2.77 (dd, *J*= 15.0, 6.5 Hz, 1H), 2.65 (dd, *J*= 15.0, 5.5 Hz, 1H), 1.78-1.59 (m, 4H), 1.54 (s, 3H).

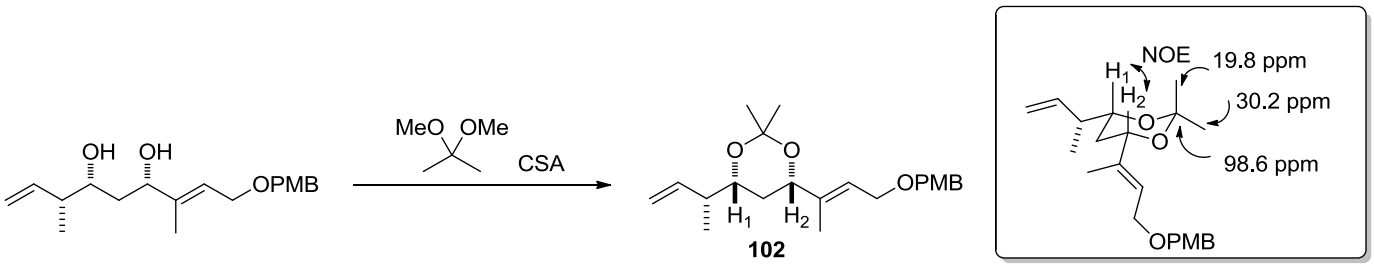


Proton numbering for *O*-methylmandelate esters

Table 8: Chemical Shifts of Protons in *O*-Methylmandelate Esters **184** and **185** and Application of the Trost method ($\delta_S - \delta_R$).

H#	δ (*S*)-ester **184**	δ (*R*)-ester **185**	$\Delta\delta = \delta_S - \delta_R$
1	4.686 4.596	4.585 4.385	+0.101 +0.211
6	2.721 2.496	2.775 2.649	−0.054 −0.153
8	3.548	3.678	−0.130
9	3.040	3.156	−0.116
10	1.676	1.543	+0.133

The differences in chemical shifts indicate the absolute configuration of *S* at the C-5 carbinol.

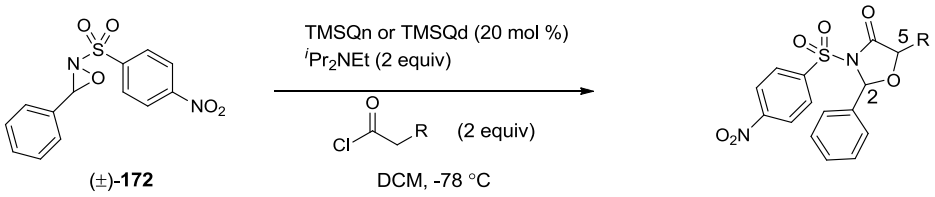


(4*R*,6*S*)-4-[(*R*)-But-3-en-2-yl]-6-[(*E*)-4-(4-methoxybenzyloxy)but-2-en-2-yl]-2,2-dimethyl-1,3-dioxane (**102**): To a stirred solution of the diol (24.8 mg, 0.0770 mmol, 1.0 equiv) in 1 mL of CH_2Cl_2 was added 0.10 mL of 2,2-dimethoxypropane (0.77 mmol, 10.0 equiv) followed by 17.9 mg of (1*R*)-(−)-10-camphorsulfonic acid (0.0770 mmol, 1.0 equiv). The reaction was stirred at ambient temperature for 24h. The reaction was quenched by saturated $NaHCO_3$ aqueous solution and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified via flash chromatography on silica gel eluting with 7% EtOAc in hexanes to afford 15.1 mg of the title compound (54%) as clear oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J*= 8.5 Hz, 2H), 6.88 (d, *J*= 8.5 Hz, 2H), 5.73 (ddd, *J*= 18.0, 10.5, 8.0 Hz, 1H), 5.68 (t, *J*= 6.5 Hz, 1H), 5.05 (d, *J*= 17.5 Hz, 1H), 5.02 (d, *J*= 10.5 Hz, 1H), 4.45 (s, 2H), 4.20 (**H$_2$**) (dd, *J*= 11.5, 1.5 Hz, 1H), 4.05 (d, *J*= 6.0 Hz, 2H), 3.81 (s, 3H), 3.62 (**H$_1$**) (ddd, *J*= 11.0, 7.0, 2.0 Hz, 1H), 2.20 (sextet, *J*= 7.0 Hz, 1H), 1.65 (s, 3H), 1.53 (dt, *J*= 12.5, 2.0 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.30 (q, *J*= 12.0 Hz, 1H), 1.05 (d, *J*= 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 140.1, 139.2, 130.5, 129.4, 122.5, 115.1, 113.8, 98.6, 73.8, 72.4, 72.1, 66.3, 55.3, 43.4, 33.1, 30.2, 19.8, 15.8, 12.8. NOESY spectrum of **102** showed a strong signal between **H$_1$** and **H$_2$**, therefore the stereochemistry of the diol is *syn*. In addition, based on Rychnovsky's ^{13}C NMR analysis, chemical shifts of **102** are consistent with the pattern characterized by *syn* diol compounds.[71a,b]

6.0 EXPERIMENTAL FOR KETENE ENOLATE ALPHA-HYDROXYLATION

General Information: Unless otherwise indicated, all reactions were performed in flame-dired glassware under an atmosphere of oxygen-free nitrogen using standard inert atmosphere techniques for the manipulation of both solvents and reagents. Anhydrous solvents (CH_2Cl_2, THF, diethyl ether) were obtained by passage through successive alumina- and Q5-packed columns on a solvent purification system. *N*,*N*-Diisopropylethylamine was distilled under nitrogen from CaH_2. *O*-Trimethylsilylquinidine (TMS-Qd) and *O*-trimethylsilylquinine (TMS-Qn) were prepared according to the literature procedure.[66] Commercially available propionyl chloride, butyryl chloride, valeryl chloride, and phenylacetyl chloride were distilled under N_2. Commercially available 4-methoxyphenylacetyl chloride, 1-naphthaleneacetyl chloride, 2-thiopheneacetyl chloride and 4-fluorophenylacetyl chloride were directly used without purification. Other acid chlorides were made from the corresponding acid and purified before use. Racemic *N*-*p*-nosyl oxaziridine was prepared according to the literature procedure.[62] NMR Spectra were recorded at the indicated magnetic field strengths with chemical shifts reported relative to residual $C\underline{\mathbf{H}}Cl_3$ (7.27 ppm) for ^1H and $\underline{\mathbf{C}}DCl_3$ (77.0 ppm) for ^{13}C spectra or residual $C\underline{\mathbf{H}}_2Cl_2$ (5.32 ppm) for ^1H and $\underline{\mathbf{C}}D_2Cl_2$ (53.8 ppm) for ^{13}C. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60-F plates. Flash chromatography was performed over silica gel (230-240 mesh). Analytical gas chromatography (GC) was performed using a flame ionization detector and split mode capillary injection system using Varian Chirasil-Dex

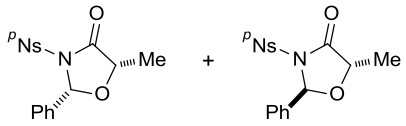
CB WCOT fused silica 25 m x 0.25 mm column (CP 7502). Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm) using a Daicel ChiracelTM OD-H column (250 x 4.6 mm) (Daicel Inc). The concentration of the solution for optical rotations was in the unit of g 100 mL^{-1}.



General Procedure A. Catalytic Asymmetric Ketene-Oxaziridine Cyclocondensation: To a solution of *O*-trimethylsilylquinine (TMSQn) or *O*-trimethylsilylquinidine (TMSQd) in CH_2Cl_2 was added *N*,*N*-diisopropylethylamine (2 equiv, 0.5 M). The resulting solution was cooled to −78 °C and stirred. The oxaziridine (1 equiv) and the acid chloride (2 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 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 10 mL of Et_2O and slurry usually formed. The heterogeneous mixture was then filtered through a short pad of silica, eluting with 40 mL of Et_2O. The filtrate was concentrated and the crude material was purified by flash column chromatography.

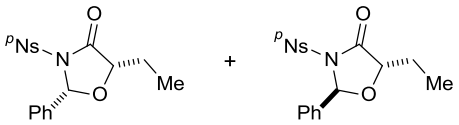
Enantiomeric excess determination: The enantiomeric excess was determined by chiral HPLC. The racemic samples were prepared by mixing products generated from utilizing TMSQn or TMSQd as the catalysts for the cyclocondensation. In some cases when four isomers (two enantiomers of each diastereomer) were not completely separated on HPLC, employing single diastereomers to determine the *ee* was necessary.

Stereochemistry assignment: The absolute stereochemistry at C5 of the oxazolidinones was assigned by comparison of the optical rotation of the ring opened compound [(*S*)-methyl mandelate **177**] to the literature value.[67] As for the relative stereochemistry of C2 and C5, we tentatively assigned the *syn* diastereomers as the ones that eluted first on column chromatography and the *anti* compounds as the ones that eluted last. 2D-NOESY analysis of **173a** further confirmed this assignment, as the *syn* isomer of **173a** showed a strong signal between the C2 proton and the C5 proton. The chemical shifts of the *syn* compounds were more down field in ^{1}H NMR among all the oxazolidinones. Further, all *syn* isomers have a negative optical rotation and *anti* ones have a positive optical rotation.



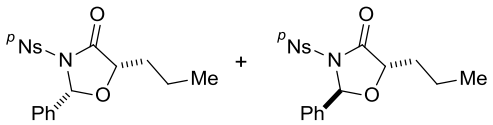
(5*S*)-5-Methyl-3-[(4-nitrophenyl)sulfonyl]-2-phenyloxazolidin-4-one (173e): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N,N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 52.1 μL of propionyl chloride (0.600 mmol, 2 equiv). The crude products were purified via flash chromatography (6% to 13% EtOAc in hexanes) to yield 81 mg (74%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved

by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −43.3 (*c* 2.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J*= 9.2 Hz, 2H), 7.79 (d, *J*= 8.8 Hz, 2H), 7.46 (t, *J*= 7.2, Hz, 1H), 7.39-7.34 (m, 2H), 7.29-7.27 (m, 2H), 6.57 (d, *J*= 0.8 Hz, 1H), 4.62 (dq, *J* = 0.8, 6.8 Hz, 1H), 1.50 (d, *J*= 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 150.8, 143.0, 136.1, 130.4, 129.5, 128.8, 127.2, 123.9, 90.7, 73.8, 17.0; IR ν_{max} cm^{-1}:2959, 2925, 2854, 1756, 1534, 1460, 1380, 1350, 1315, 1232, 1181, 1109, 1087, 1059, 760, 741; HRMS (ES+) *m/z* calcd for $C_{16}H_{14}N_2O_6NaS$ $(M+Na)^+$: 385.0470; found: 385.0474. Full characterization of the *anti* compound: $[\alpha]_D^{19}$ +49.5 (*c* 1.90, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*= 8.8 Hz, 2H), 7.62 (d, *J*= 8.8 Hz, 2H), 7.48 (t, *J*= 7.2 Hz, 1H), 7.38-7.29 (m, 4H), 6.45 (d, *J*= 0.8 Hz, 1H), 4.58 (dq, *J*= 0.8, 6.8 Hz, 1H), 1.52 (d, *J*= 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 150.7, 143.5, 135.3, 130.7, 129.1, 128.5, 128.4, 123.9, 90.6, 74.3, 16.8; ; IR ν_{max} cm^{-1}: 1747, 1533, 1384, 1351, 1315, 1292, 1219, 1202, 1181, 1089, 1056, 856, 741; HRMS (ES+) *m/z* calcd for $C_{16}H_{14}N_2O_6NaS$ $(M+Na)^+$: 385.0470; found: 385.0439. The *ee* (>98%) was determined by chiral HPLC employing the *syn* diastereomers. Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 15% ^{i}PrOH/85% hexanes, T_r: 17.3 min (2*R*, 5*S*), 23.0 min (2*S*, 5*R*).



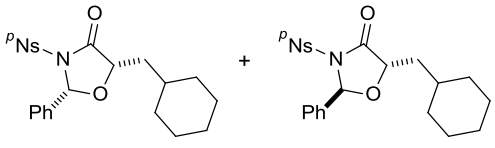
(5*S*)-5-Ethyl-3-[(4-nitrophenyl)sulfonyl]-2-phenyloxazolidin-4-one (173f): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 62.3 μL of butyryl chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 12% EtOAc in hexanes) to yield 80 mg (71%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved

by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −69.0 (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*= 8.8 Hz, 2H), 7.77 (d, *J*= 9.2 Hz, 2H), 7.46 (t, *J*= 7.2 Hz, 1H), 7.38-7.34 (m, 2H), 7.30-7.27 (m, 2H), 6.57 (d, *J*= 1.2 Hz, 1H), 4.51 (ddd, *J*= 1.2, 4.8, 6.4 Hz, 1H), 1.99-1.78 (m, 2H), 1.02 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 150.8, 143.1, 136.4, 130.4, 129.4, 128.8, 127.2, 123.9, 91.2, 78.4, 25.1, 8.6; IR ν_{max} cm^{-1}: 1756, 1534, 1382, 1351, 1316, 1230, 1181, 1089, 856, 742; HRMS (ES+) *m/z* calcd for $C_{17}H_{16}N_2O_6NaS$ $(M+Na)^+$: 399.0627; found: 399.0661. Full characterization of the *anti* compound: $[\alpha]_D^{19}$ +35.8 (*c* 1.09, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J*= 9.2 Hz, 2H), 7.65 (d, *J*= 9.2 Hz, 2H), 7.48 (t, *J*= 7.2 Hz, 1H), 7.38-7.30 (m, 4H), 6.43 (d, J= 1.2Hz, 1H), 4.42 (ddd, *J* = 1.2, 4.4, 6.8 Hz, 1H), 2.05-1.94 (m, 1H), 1.82 (dquintet, *J*= 14.4, 7.2 Hz, 1H), 1.04 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 150.7, 143.7, 135.4, 130.7, 129.1, 128.5, 128.4, 123.9, 90.6, 78.7, 24.4, 9.2; IR ν_{max}: 1757, 1534, 1373, 1355, 1312, 1218, 1177, 1110, 1089, 741; HRMS (ES+) *m/z* calcd for $C_{17}H_{16}N_2O_6NaS$ $(M + Na)^+$: 399.0627; found: 399.0647. The *ee* (>98%) was determined by chiral HPLC employing the the mixture of *syn* and *anti* diastereomers. Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 7% EtOH/93% hexanes, T_r: 15.6 min (2*R*, 5*S*), 19.2 min (2*S*, 5*R*), 25.0 min (2*S*, 5*S*), 27.3 min (2*R*, 5*R*).



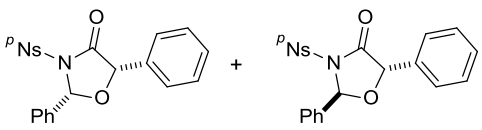
(5*S*)-3-[(4-Nitrophenyl)sulfonyl]-2-phenyl-5-propyloxazolidin-4-one (173g): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 72.7 μL of valeryl chloride (0.60 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 9% EtOAc in hexanes)

to yield 88 mg (75%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −69.9 (*c* 1.03, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*= 8.8 Hz, 2H), 7.75 (d, *J*= 9.2 Hz, 2H), 7.46 (t, *J*= 7.6 Hz, 1H), 7.38-7.34 (m, 2H), 7.29-7.26 (m, 2H), 6.56 (d, *J*= 1.2 Hz, 1H), 4.55 (ddd, *J*= 1.2, 4.4, 7.2 Hz, 1H), 1.90-1.73 (m, 2H), 1.54-1.40 (m, 2H), 0.95 (t, *J*= 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 150.8, 143.1, 136.3, 130.4, 129.4, 128.8, 127.3, 123.9, 91.1, 77.3, 33.6, 17.8, 13.6; IR ν_{max} cm^{-1}: 1756, 1534, 1383, 1350, 1314, 1181, 1108, 1088, 740; HRMS (ASAP) *m/z* calcd for $C_{18}H_{17}N_2O_6S$ $(M-H)^-$: 389.0809; found: 389.0815; Full characterization of the *anti* compound: $[\alpha]_D^{19}$ +34.9 (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*= 8.8 Hz, 2H), 7.64 (d, *J*= 9.2 Hz, 2H), 7.48 (t, *J*= 7.2 Hz, 1H), 7.38-7.29 (m, 4H), 6.43 (d, *J*= 1.2 Hz, 1H), 4.47 (ddd, *J*= 1.2, 4.0, 7.6 Hz, 1H), 1.96-1.89 (m, 1H), 1.79-1.70 (m, 1H), 1.53-1.44 (m, 2H), 0.94 (t, *J*= 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 150.7, 143.6, 135.4, 130.7, 129.1, 128.5, 128.4, 123.9, 90.7, 77.6, 33.2, 18.2, 13.6; IR ν_{max} cm^{-1}: 1757, 1534, 1383, 1350, 1313, 1217, 1182, 1089, 740; HRMS (ES+) *m/z* calcd for $C_{18}H_{18}N_2O_6NaS$ $(M+Na)^+$: 413.0783; found: 413.0811. The *ee* (>98%) was determined by chiral HPLC employing the *syn* diastereomers. Daicel Chiracel^{TM} OD-H column, flow rate 1.0 mL/min, 7% EtOH/93% hexanes, T_r: 12.4 min (2*R*, 5*S*), 14.3 min (2*S*, 5*R*).

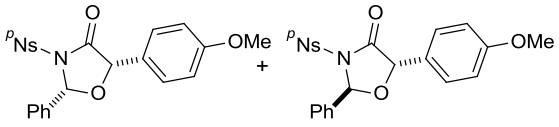


(5*S*)-5-(Cyclohexylmethyl)-3-[(4-nitrophenyl)sulfonyl]-2-phenyloxazolidin-4-one (173h): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol%), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 105 mg of 3-

cyclohexylpropanoyl chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 9% EtOAc in hexanes) to yield 100 mg (75%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{18}$ −63.9 (*c* 2.85, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*= 9.2 Hz, 2H), 7.76 (d, *J*= 8.8 Hz, 2H), 7.46 (t, *J*= 7.2 Hz, 1H), 7.38-7.34 (m, 2H), 7.29-7.27 (m, 2H), 6.55 (d, *J*= 0.8 Hz, 1H), 4.60 (ddd, *J*= 0.8, 4.4, 8.8 Hz, 1H), 1.77-1.62 (m, 7H), 1.57-1.50 (m, 1H), 1.27-1.11 (m, 3H), 1.01-0.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 150.8, 143.1, 136.3, 130.4, 129.4, 128.8, 127.3, 123.9, 90.8, 75.8, 38.9, 33.8, 33.6, 32.3, 26.2, 26.1, 25.9; IR ν_{max} cm^{-1}: 2925, 2851, 1756, 1534, 1383, 1350, 1317, 1230, 1181, 1108, 1089, 856, 758, 742; HRMS (ES+) *m/z* calcd for $C_{22}H_{24}N_2O_6NaS$ $(M+Na)^+$: 467.1253; found: 467.1263. Full characterization of the *anti* compound: $[\alpha]_D^{19}$ 0 (*c* 1.06, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*= 8.8 Hz, 2H), 7.63 (d, *J*= 8.8 Hz, 2H), 7.48 (t, *J*= 7.2 Hz, 1H), 7.38-7.30 (m, 4H), 6.43 (d, *J*= 1.2 Hz), 4.53 (ddd, *J*= 1.2, 3.6, 9.6 Hz), 1.86-1.80 (m, 1H), 1.79-1.76 (m, 1H), 1.71-1.60 (m, 6H), 1.26-1.08 (m, 3H), 1.00-0.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 150.7, 143.6, 135.4, 130.6, 129.1, 128.5, 123.9, 90.7, 76.0, 39.0, 33.9, 33.7, 32.2, 26.2, 26.0, 25.9; IR ν_{max} cm^{-1}: 2925, 2851, 1756, 1533, 1383, 1350, 1316, 1220, 1182, 1089, 741; HRMS (ES+) *m/z* calcd for $C_{22}H_{24}N_2O_6NaS$ $(M + Na)^+$: 467.1253; found: 467.1253. The *ee* (>98%) was determined by chiral HPLC employing the the mixture of *syn* and *anti* diastereomers. Daicel Chiracel™ OD-H column, flow rate 1.0 ml/min, 5% EtOH/95% hexanes, T_r: 11.7 min (2*R*, 5*S*), 14.1 min (2*S*, 5*R*), 19.2 min (2*R*, 5*R*), 22.3 min (2*S*, 5*S*).

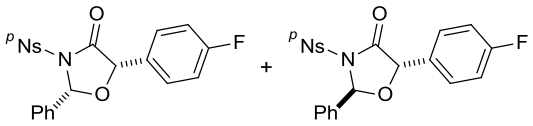


(5*S*)-3-[(4-Nitrophenyl)sulfonyl]-2,5-diphenyloxazolidin-4-one (173a): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 79.5 μL of phenylacetyl chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 13% EtOAc in hexanes) to yield 100 mg (79%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −96.4 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J*= 9.2 Hz, 2H), 7.75 (d, *J*= 9.2 Hz, 2H), 7.50 (t, *J*= 6.8 Hz, 1H), 7.46-7.36 (m, 9H), 6.73 (d, *J*= 1.2 Hz, 1H), 5.52 (d, *J*= 0.8 Hz, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 150.8, 142.9, 135.9, 133.7, 130.7, 129.5, 129.4, 129.0, 128.9, 127.6, 126.1, 123.9, 91.3, 78.7; IR ν_{max} cm^{-1}: 1757, 1533, 1384, 1350, 1230, 1181, 756, 741; HRMS (ES+) *m/z* calcd for $C_{21}H_{16}N_2O_6NaS$ $(M + Na)^+$: 447.0627; found: 447.0625. Full characterization of the *anti* compound: $[\alpha]_D^{19}$ +78.2 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J*= 9.2 Hz, 2H), 7.67 (d, *J*= 9.2 Hz, 2H), 7.54-7.49 (m, 1H), 7.44-7.35 (m, 9H), 6.64 (d, *J*= 1.2 Hz, 1H), 5.50 (d, *J*= 0.8 Hz, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 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; IR ν_{max} cm^{-1}: 1760, 1533, 1384, 1350, 1318, 1219, 1182, 1088, 742; HRMS (ES+) *m/z* calcd for $C_{21}H_{16}N_2O_6NaS$ $(M+Na)^+$: 447.0627; found: 447.0585. The *ee* (>98%) was determined by chiral HPLC employing the *syn* diastereomers. Daicel Chiracel™ OD-H column, flow rate 1.0 ml/min, 25% ^{i}PrOH/975% hexanes, T_r: 21.2 min (2*S*, 5*R*), 50.1 min (2*R*, 5*S*).



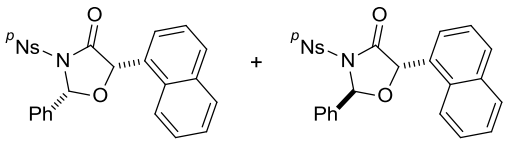
(5*S*)-5-(4-Methoxyphenyl)-3-[(4-nitrophenyl)sulfonyl]-2-phenyloxazolidin-4-one (173b): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 91.8 μL of 4-methoxyphenylacetyl chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 15% EtOAc in hexanes) to yield 107 mg (79%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −82.9 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*= 9.2 Hz, 2H), 7.76 (d, *J*= 9.2 Hz, 2H), 7.49 (t, *J*= 6.8 Hz, 1H), 7.42-7.31 (m, 6H), 6.94 (d, *J*= 8.8 Hz, 2H), 6.70 (d, *J*= 1.2 Hz, 1H), 5.46 (s, 1H), 3.83 (s, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 160.5, 150.8, 143.0, 135.9, 130.6, 129.5, 128.9, 127.8, 127.5, 125.7, 123.9, 114.5. 91.1, 78.6, 55.4; IR ν_{max} cm^{-1}: 1757, 1610, 1534, 1514, 1383, 1350, 1316, 1230, 1179, 1113, 1087, 741; HRMS (ES+) *m/z* calcd for $C_{22}H_{18}N_2O_7NaS$ $(M+Na)^+$: 477.0732; found: 477.0782; Full characterization of the *anti* compound: $[\alpha]_D^{17}$ +91.5 (*c* 1.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J*= 8.8 Hz, 2H), 7.67 (d, *J*= 9.2 Hz, 2H), 7.50 (t, *J*= 6.4 Hz, 1H), 7.40-7.31 (m, 6H), 6.91 (d, *J*= 8.8 Hz, 2H), 6.60 (d, *J*= 1.6 Hz, 1H), 5.44 (s, 1H), 3.80 (s, 3H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 160.3, 150.7, 143.4, 135.4, 130.8, 129.3, 128.6, 128.5, 127.9, 125.3, 124.0, 114.2, 90.5, 78.9, 55.3; IR ν_{max} cm^{-1}: 1758, 1611, 1534, 1516, 1461, 1383, 1350, 1317, 1252, 1219, 1180, 1088, 1029, 856, 742; HRMS (ES+) *m/z* calcd for $C_{22}H_{18}N_2O_7NaS$ $(M+Na)^+$: 477.0732; found: 477.0762. The *ee* (>98%) was determined by chiral HPLC employing the *syn* diastereomers.

Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 20% ^{i}PrOH/80% hexanes, T_r: 38.7 min (2*S*, 5*R*), 89.7 min (2*R*, 5*S*).



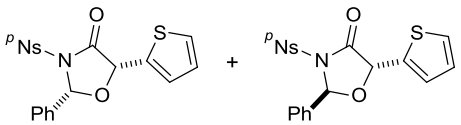
(5*S*)-5-(4-Fluorophenyl)-3-((4-nitrophenyl)sulfonyl)-2-phenyloxazolidin-4-one (173c): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 82.3 μL of 4-fluorophenylacetyl chloride (0.6 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 14% EtOAc in hexanes) to yield 101 mg (76%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −68.3 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*= 9.2 Hz, 2H), 7.74 (d, *J*= 9.2 Hz, 2H), 7.51 (t, *J*= 7.2 Hz, 1H), 7.45-7.34(m, 6H), 7.13 (t, *J*= 8.8 Hz, 2H), 6.73 (d, *J*= 1.2 Hz, 1H), 5.50 (s, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 150.9, 142.8, 135.7, 130,7, 129.6, 129.5, 128.9, 128.1, 128.0, 127.5, 123.9, 116.2, 116.0, 91.3, 78.1; IR ν_{max} cm^{-1}: 1758, 1534, 1511, 1384, 1350, 1316, 1229, 1182, 1159, 1111, 1088, 760, 741; HRMS (ASAP with APCI) *m/z* cald for $C_{21}H_{14}N_2O_6FS$ $(M-H)^+$: 441.0557; found: 441.0559; Full characterization of the *anti* compound: $[\alpha]_D^{19}$ +59 (*c* 0.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*= 9.2 Hz, 2H), 7.67 (d, *J*= 8.8 Hz, 2H), 7.52 (t, *J*= 7.2 Hz, 1H), 7.43-7.37 (m, 4H), 7.35-7.32 (m, 2H), 7.08 (appt t, *J*= 8.8 Hz, 2H), 6.63 (d, *J*= 1.6 Hz, 1H), 5.48 (s, 1H); δ ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 150.8, 143.2, 135.3, 130.9, 129.3, 128.7, 128.4, 128.1, 128.0, 124.0, 115.9, 115.7, 90.7, 78.3; IR ν_{max} cm^{-1}: 1759, 1534, 1512, 1385, 1350, 1316, 1223, 1183, 1159, 1088, 742; HRMS (ES+) *m/z*

calcd for $C_{21}H_{15}N_2O_6FNaS$ $(M+Na)^+$: 465.0533; found: 465.0538; The *ee* (>98%) was determined by chiral HPLC employing the *anti* diastereomers. Daicel Chiracel™ OD-H column, flow rate 1.0 ml/min, 20% ^{i}PrOH/80% hexanes, T_r: 29.3 min (2*R*, 5*S*), 37.1 min (2*S*, 5*R*).



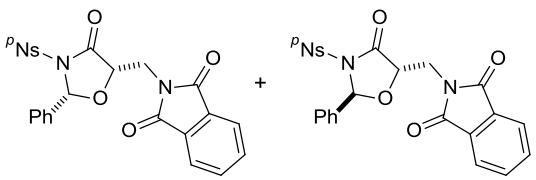
(5*S*)-5-(Naphthalen-1-yl)-3-[(4-nitrophenyl)sulfonyl]-2-phenyloxazolidin-4-one (173d): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 123 mg of 1-naphthaleneacetyl chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 14% EtOAc in hexanes) to yield 113 mg (80%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −25.5 (*c* 1.37, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J*= 8.8 Hz, 2H), 7.99-7.97 (m, 1H), 7.93-7.89 (m, 2H), 7.81 (d, *J*= 8.8 Hz, 2H), 7.61-7.79 (m, 1H), 7.56-7.49 (m, 4H), 7.46-7.42 (m, 4H), 6.76 (d, *J*=0.8 Hz, 1H), 6.23 (s, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 150.9, 143.0, 135.8, 134.0, 131.0, 130.7, 130.5, 129.6, 129.3, 128.92, 128.87, 127.7, 126.9, 126.3, 125.1, 124.9, 124.0, 123.3, 91.1, 77.2; IR ν_{max} cm^{-1}: 1757, 1533, 1382, 1350, 1315, 1228, 1181, 1089, 741; HRMS (ES+) *m/z* calcd for $C_{25}H_{18}N_2O_6NaS$ $(M+Na)^+$: 497.0783; found: 497.0795; Full characterization of the *anti* compound: $[\alpha]_D^{19}$ +140 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J*= 8.8 Hz, 2H), 8.06 (d, *J*= 8.0 Hz, 1H), 7.91-7.87 (m, 2H), 7.69 (d, *J*= 9.2 Hz, 2H), 7.60-7.50 (m, 4H), 7.46-7.38 (m, 5H), 6.75 (d, *J*= 1.6 Hz, 1H), 6.32 (s, 1H); δ

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 150.8, 143.3, 135.3, 133.8, 130.9, 130.0, 129.3, 129.1, 128.8, 128.7, 128.6, 126.8, 126.3, 125.1, 124.3, 124.0, 123.5, 90.8, 76.9; IR ν_{max} cm^{-1}: 1759, 1533, 1383, 1350, 1219, 1182, 1088, 760, 741; HRMS (ES+) *m/z* calcd for $C_{25}H_{18}N_2O_6NaS$ $(M + Na)^+$: 497.0783; found: 497.0803. The *ee* (>98%) was determined by chiral HPLC employing the *syn* diastereomers. Daicel Chiracel™ OD-H column, flow rate 1.0 ml/min, 20% ^{i}PrOH/80% hexanes, T_r: 30.0 min (2*R*, 5*S*), 33.0 min (2*S*, 5*R*).



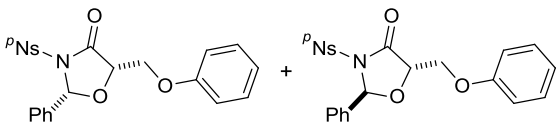
(5*R*)-3-[(4-Nitrophenyl)sulfonyl]-2-phenyl-5-(thiophen-2-yl)oxazolidin-4-one (173k): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 96.4 mg of 2-thiopheneacetyl chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 14% EtOAc in hexanes) to yield 91 mg (70%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −80.7 (*c* 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, *J*= 8.8 Hz, 2H), 7.79 (d, *J*= 8.8 Hz, 2H), 7.50 (t, *J*= 6.8 Hz, 1H), 7.43-7.36 (m, 5H), 7.17 (d, *J*= 3.6 Hz, 1H), 7.06 (dd, *J*= 3.6, 5.2 Hz, 1H), 6.69 (d, *J*= 0.8 Hz, 1H), 5.73 (t, *J*= 0.8 Hz, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 150.9, 142.8, 135.7, 135.4, 130.7, 129.5, 128.9, 127.6, 127.43, 127.38, 126.9, 124.0, 91.1, 75.5; IR ν_{max} cm^{-1}: 1759, 1533, 1404, 1383, 1350, 1316, 1227, 1183, 1087, 741; Satisfactory HRMS data was not obtained; Full characterization of the *anti* compound: $[\alpha]_D^{18}$ +16.4 (*c* 1.22, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J*= 9.2 Hz, 2H), 7.65 (d, *J*= 9.2 Hz, 2H), 7.52-7.48 (m, 1H), 7.38-7.36 (m, 5H), 7.19 (d, *J*= 3.6 Hz, 1H),

7.04 (dd, *J*= 3.6, 5.2 Hz, 1H), 6.60 (d, *J*= 1.6 Hz, 1H), 5.75 (t, *J*= 1.2 Hz, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 150.8, 143.2, 135.6, 135.0, 130.9, 129.2, 128.6, 127.2, 127.1, 124.0, 90.8, 76.1; IR ν_{max} cm^{-1}: 1761, 1533, 1384, 1350, 1219, 1183, 1088, 740; Satisfactory HRMS data was not obtained; The *ee* (>98%) was determined by chiral HPLC employing the the mixture of *syn* and *anti* diastereomers. Daicel Chiracel^{TM} OD-H column, flow rate 1.0 ml/min, 20% EtOH /80% hexanes, T_r: 16.7 min (2*S*, 5*R*), 26.5 min (2*R*, 5*R*), 51.8 min (2*R*, 5*S*), 62.4 min (2*S*, 5*S*).



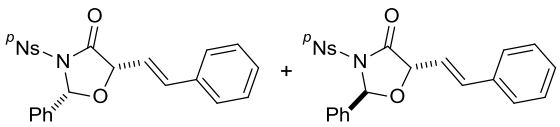
2-{[(5*S*)-3-(4-Nitrophenylsulfonyl)-4-oxo-2-phenyloxazolidin-5-yl]methyl}isoindoline-1,3-dione (173m): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 143 mg of 1-(2-phthalimidopropionyl) chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 30% EtOAc in hexanes) to yield 89 mg (59%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{18}$ −53.1 (*c* 1.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*= 8.8 Hz, 2H), 7.87-7.81 (m, 2H), 7.77-7.71 (m, 4H), 7.44 (t, *J*= 7.2 Hz, 1H), 7.36-7.30 (m, 2H), 7.28-7.26 (m, 2H), 6.62 (d, *J*= 0.8 Hz, 1H), 4.92 (ddd, *J*= 1.2, 5.2, 8.4 Hz, 1H), 4.18-4.06 (m, 2H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 167.5, 150.9, 142.8, 135.5, 134.3, 131.7, 130.6, 129.5, 128.8, 127.5, 124.0, 123.6, 91.3, 74.2, 38.2; IR ν_{max} cm^{-1}: 1759, 1718, 1534, 1463, 1424, 1385, 1350, 1319, 1270, 1231, 1183, 1089, 1000, 859, 739; HRMS (ES+) *m/z* calcd for $C_{24}H_{17}N_3O_8NaS$ $(M + Na)^+$:

530.0634; found: 530.0604. Full characterization of the *anti* compound: $[\alpha]_D^{15}$ −50 (*c* 0.56, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*= 9.2 Hz, 2H), 7.82 (dd, *J*= 2.8, 5.6 Hz, 2H), 7.72 (dd, *J*= 3.2, 5.6 Hz, 2H), 7.63 (d, *J*= 8.8 Hz, 2H), 7.46-7.42 (m, 1H), 7.31-7.30 (m, 4H), 6.44 (d, *J*= 1.2 Hz, 1H), 4.94 (dt, *J*= 1.2, 6.8 Hz, 1H), 4.15 (d, *J*= 6.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2): δ 168.2, 167.9, 151.2, 143.6, 135.2, 134.6, 132.1, 131.1, 129.5, 128.8, 128.7, 124.4, 123.7, 91.6, 74.4, 38.7; IR ν_{max} cm^{-1}: 1759, 1718, 1532, 1384, 1350, 1225, 1182, 1088, 740, 720; HRMS (ES+) *m/z* calcd for $C_{24}H_{17}N_3O_8NaS$ $(M + Na)^+$: 530.0634; found: 530.0637. The *ee* (>98%) was determined by chiral HPLC employing the the mixture of *syn* and *anti* diastereomers. Daicel Chiracel^{TM} OD-H column, flow rate 1.0 ml/min, 35% ^{i}PrOH /65% hexanes, T_r: 34.1 min (2*R*, 5*S*), 41.2 min (2*S*, 5*R*), 49.8 min (2*S*, 5*S*), 75.2 min (2*R*, 5*R*).



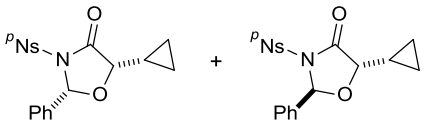
(5*S*)-3-[(4-Nitrophenyl)sulfonyl]-5-(phenoxymethyl)-2-phenyloxazolidin-4-one (173j): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 111 mg of 3-phenoxypropanoyl chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 20% EtOAc in hexanes) to yield 111 mg (82%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{18}$ −80.5 (*c* 1.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J*= 8.8 Hz, 2H), 7.87 (d, *J*= 9.2 Hz, 2H), 7.50-7.47 (m, 1H), 7.42-7.41 (m, 4H), 7.30-7.26 (m, 2H), 7.01 (t, *J*= 7.2 Hz, 1H), 6.81 (d, *J*= 8.0 Hz, 2H), 6.68 (d, *J*= 0.8 Hz, 1H), 4.82 (d, *J*= 1.2 Hz, 1H), 4.35 (d, *J*= 1.6 Hz, 2H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6,

157.7, 150.8, 143.0, 136.6, 130.6, 129.6, 129.5, 128.8, 127.5, 124.0, 122.1, 115.0, 92.7, 77.2, 68.5; IR ν_{max} cm^{-1}: 1758, 1600, 1533, 1495, 1458, 1403, 1383, 1350, 1315, 1228, 1182, 1108, 1088, 1063, 1037, 856, 739; HRMS (ES+) *m/z* calcd for $C_{22}H_{18}N_2O_7NaS$ $(M + Na)^+$: 477.0732; found: 477.0761. Full characterization of the *anti* compound: $[\alpha]_D^{18}$ +72.1 (*c* 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J*= 8.8 Hz, 2H), 7.63 (d, *J*= 8.8 Hz, 2H), 7.52-7.51 (m, 2H), 7.46 (t, *J*= 7.2 Hz, 1H), 7.34-7.25 (m, 4H), 6.99 (t, *J*= 7.2 Hz, 1H), 6.76 (d, *J*= 8.0 Hz, 2H), 6.56 (d, *J*= 0.8 Hz, 1H), 4.87 (d, *J*= 1.2 Hz, 1H), 4.39-4.38 (m, 2H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 157.8, 150.7, 143.6, 135.2, 130.7, 129.6, 129.0, 128.8, 128.3, 123.9, 121.8, 114.5, 91.0, 77.1, 66.2; IR ν_{max} cm^{-1}: 1760, 1533, 1496, 1384, 1350, 1313, 1222, 1182, 1088, 755, 741; HRMS (ES+) *m/z* calcd for $C_{22}H_{18}N_2O_7NaS$ $(M+Na)^+$: 477.0732; found: 477.0736. The *ee* (>98%) was determined by chiral HPLC employing the *syn* diastereomers. Daicel Chiracel™ OD-H column, flow rate 1.0 ml/min, 20% ^{i}PrOH/80% hexanes, T_r: 45.8 min (2*R*, 5*S*), 51.0 min (2*S*, 5*R*).



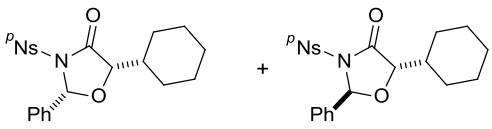
(5*S*)-3-[(4-Nitrophenyl)sulfonyl]-2-phenyl-5-[(E)-styryl]oxazolidin-4-one (173l): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 108 mg of *trans*-styrylacetyl chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 13% EtOAc in hexanes) to yield 86.4 mg (64%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{18}$ −47 (*c* 0.87, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ

8.21 (d, *J*= 8.8 Hz, 2H), 7.77 (d, *J*= 8.8 Hz, 2H), 7.49 (t, *J*= 7.2 Hz, 1H), 7.42-7.29 (m, 9H), 6.82 (dd, *J*= 1.6, 16.0 Hz, 1H), 6.66 (d, *J*= 1.2 Hz, 1H), 6.21 (dd, *J*= 6.0, 16.0 Hz, 1H), 5.17 (dt, *J*= 6.0, 1.2 Hz, 1 H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 150.8, 142.9, 135.8, 135.3, 135.1, 130.6, 129.4, 128.84, 128.80, 128.7, 127.5, 126.9, 124.0, 120.3, 91.1, 78.1; IR ν_{max} cm^{-1}: 2923, 1756, 1533, 1383, 1350, 1315, 1225, 1182, 1109, 1088, 969, 740; HRMS (ASAP with APCI) *m/*z calcd for $C_{23}H_{19}N_2O_6S$ $(M+H)^+$: 451.0964; found: 451.0953. Full characterization of the *anti* compound: $[\alpha]_D^{18}$ +31 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*= 8.8 Hz, 2H), 7.65 (d, *J*= 8.8 Hz, 2H), 7.50 (t, *J*= 6.8 Hz, 1H), 7.39-7.28 (m, 9H), 6.76 (dd, *J*= 1.2, 16.0 Hz, 1H), 6.58 (d, *J*= 0.8 Hz, 1H), 6.22 (dd, *J*= 5.6, 16.0 Hz, 1H), 5.17 (dt, *J*= 5.6, 1.2 Hz, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 150.8, 143.2, 135.6, 135.3, 135.2, 130.7, 129.3, 128.7, 128.6, 128.4, 126.9, 124.0, 120.7, 90.9, 78.4; IR ν_{max} cm^{-1}: 1757, 1533, 1383, 1350, 1315, 1219, 1183, 1088, 740; HRMS (ASAP with APCI) *m/z* calcd for $C_{23}H_{19}N_2O_6S$ $(M+H)^+$: 451.0964; found: 451.0963. The *ee* (>98%) was determined by chiral HPLC employing the *syn* diastereomers. Daicel Chiracel^{TM} OD-H column, flow rate 1.0 ml/min, 20% ^{i}PrOH/80% hexanes, T_r: 28.8 min (2*R*, 5*S*), 44.3 min (2*S*, 5*R*).



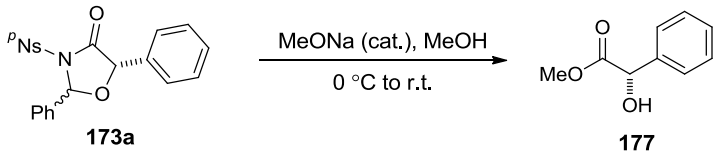
(5*S*)-5-Cyclopropyl-3-[(4-nitrophenyl)sulfonyl]-2-phenyloxazolidin-4-one (173i): General procedure A was followed employing 91.8 mg of *N*-nosyl oxaziridine (0.300 mmol, 1 equiv), 24.0 mg of TMSQn (0.0600 mmol, 20 mol %), 0.11 mL of *N*,*N*-diisopropylethylamine (0.60 mmol, 2 equiv), and 71.2 mg of cyclopropylacetyl chloride (0.600 mmol, 2 equiv). The crude product was purified via flash chromatography (6% to 13% EtOAc in hexanes) to yield 82.0 mg (70%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers

could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −64.0 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J*= 8.8 Hz, 2H), 7.75 (d, *J*= 8.8 Hz m, 2H), 7.45 (t, *J*= 8.8 Hz, 1H), 7.35 (t, *J*= 8.0 Hz, 2H), 7.26-7.24 (m, 2H), 6.57 (d, *J*= 0.8 Hz, 1H), 4.11 (dd, *J*= 0.8, 7.2 Hz, 1H), 1.28-1.20 (m, 1H), 0.76-0.45 (m, 4H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 150.8, 143.0, 136.2, 130.4, 129.4, 128.8, 127.3, 123.9, 91.0, 80.2, 12.3, 1.8, 1.6; IR ν_{max} cm^{-1}: 1757, 1535, 1382, 1350, 1232, 1180, 741; HRMS (ASAP with APCI) *m/z* calcd for $C_{18}H_{15}N_2O_6S$ $(M-H)^+$ 387.0651; found: 387.0647; Full characterization of the *anti* compound: $[\alpha]_D^{19}$ +49.5 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J*= 8.8 Hz, 2H), 7.67 (d, *J*= 8.8 Hz, 2H), 7.48 (t, *J*= 6.8 Hz, 1H), 7.38-7.31 (m, 4H), 6.41 (d, *J*= 1.2 Hz, 1H), 3.94 (dd, *J*= 1.2, 7.6 Hz, 1H), 1.21-1.12 (m, 1H), 0.78-0.72 (m, 1H), 0.67-0.55 (m, 2H), 0.54-0.46 (m, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 150.7, 143.5, 135.5, 130.7, 129.2, 128.6, 128.3, 124.0, 90.3, 81.3, 11.9, 2.1, 1.8; IR ν_{max} cm^{-1}: 1759, 1534, 1402, 1381, 1351, 1317, 1291, 1222, 1181, 1089, 1049, 1012, 859, 740; HRMS (ASAP with APCI) *m/z* calcd for $C_{18}H_{17}N_2O_6S$ $(M+H)^+$ 389.0807; found: 389.0855; The *ee* (>98%) was determined by chiral HPLC employing the *syn* diastereomers. Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH/90% hexanes, T_r: 21.1 min (2*R*, 5*S*), 24.7 min (2*S*, 5*R*).



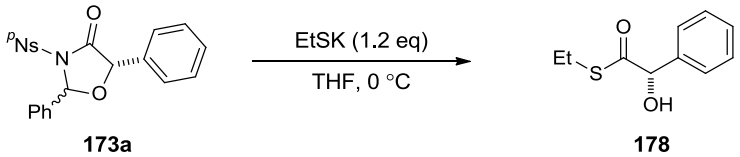
(5*S*)-5-Cyclohexyl-3-((4-nitrophenyl)sulfonyl)-2-phenyloxazolidin-4-one (173n): General procedure A was followed employing 184 mg of *N*-nosyl oxaziridine (0.600 mmol, 1 equiv), 24.0 mg of TMSQn (0.120 mmol, 20 mol %), 0.21 mL of *N*,*N*-diisopropylethylamine (1.2 mmol, 2 equiv), and 0.18 mL of cyclohexylacetyl chloride (1.2 mmol, 2 equiv). The crude product was purified via flash chromatography (6% EtOAc in

hexanes) to yield 73.4 mg (29%) of the compound as a mixture of two diastereomers. Effective separation of these two diastereomers could be achieved by using MPLC for characterization purpose. Full characterization of the *syn* compound: $[\alpha]_D^{19}$ −63.9 (*c* 2.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*= 9.2 Hz, 2H), 7.71 (d, *J*= 8.8 Hz, 2H), 7.45 (t, *J*= 7.2 Hz, 1H), 7.35 (t, *J*= 7.2 Hz, 2H), 7.28-7.25 (m, 2H), 6.54 (d, *J*= 1.6 Hz, 1H), 4.38 (dd, *J*= 4.0, 1.6Hz, 1H), 1.93-1.85 (m, 1H), 1.79-1.77 (m, 3H), 1.71-1.61 (m, 2H), 1.37-1.14 (m, 5H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 150.7, 143.1, 136.7, 130.4, 129.4, 128.8, 127.4, 123.8, 91.7, 81.7, 41.0, 28.5, 26.5, 25.9, 25.8, 25.7; IR ν_{max} cm^{-1}: 2929, 2855, 1754, 1534, 1456, 1403, 1383, 1350, 1314, 1230, 1181, 1107, 1088, 856, 740; HRMS (ES+) *m/z* cald for $C_{21}H_{23}N_2O_6S$ $(M+H)^+$: 431.1277; found: 431.1268; Full characterization of the *anti* compound: $[\alpha]_D^{19}$ +1.85 (*c* 1.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J*= 8.8 Hz, 2H), 7.69 (d, *J*= 9.2 Hz, 2H), 7.48 (t, *J*= 7.6 Hz, 1H), 7.36 (t, *J*= 7.6 Hz, 2H), 7.32-7.27 (m, 2H), 6.38 (d, *J*= 1.2 Hz, 1H), 4.27 (d, *J*= 3.6, 1.6 Hz, 1H), 1.96-1.88 (m, 1H), 1.82-1.73 (m, 3H), 1.67-1.64 (m, 1H), 1.57-1.54 (m, 1H), 1.39-1.09 (m, 5H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 150.7, 143.8, 135.4, 130.6, 129.0, 128.5, 128.4, 124.0, 90.4, 81.5, 39.2, 28.8, 26.8, 26.0, 25.8; IR ν_{max} cm^{-1}: 2929, 2855, 1757, 1534, 1458, 1384, 1350, 1314, 1289, 1218, 1181, 1089, 1026, 855, 740; HRMS (ES+) *m/z* cald for $C_{21}H_{23}N_2O_6S$ $(M+H)^+$: 431.1277; found: 431.1267; The *ee* (>98%) was determined by chiral HPLC employing the *anti* diastereomers. Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH/90% hexanes, T_r: 19.0 min (2*R*, 5*S*), 21.0 min (2*S*, 5*R*).



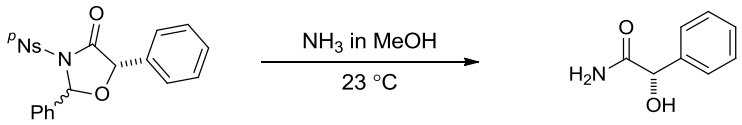
173a 177

(*S*)-(+)-Methyl mandelate (177): To a stirred solution of oxazolidinone **173a** (84.9 mg, 0.200 mmol, 1 equiv) in 2 mL of MeOH was added 2 mg of MeONa (0.2 equiv, 0.04 mmol) at 0 °C. The resulting mixture was stirred at this temperature for 2h and then warmed to ambient temperature and stirred overnight. After full consumption of **173a** which could be monitored by TLC, 2 mL of HCl in MeOH (5%) was added into the reaction to hydrolyze the imine byproduct. The resulting mixture was stirred for 10 min at ambient temperature and diluted with EtOAc and washed with water. The organic layer was separated and the aqueous layer was extracted 3x with EtOAc and the combined organic extracts were dried over $MgSO_4$ and concentrated. The crude material was purified via flash chromatography (20% EtOAc in hexanes) to yield 23 mg (70%) of the titled compound **177** as a wax solid. $[\alpha]_D^{17}$+173 (*c* 0.75, $CHCl_3$); Separating the enantiomers by GLC [flow rate 3.5 mL/min, method: 80 °C for 10 min, ramp @ 0.5 °C/min to 130 °C, hold for 5 min; T_r: 59.9 min (*R*), 61.8 min (*S*)] provided the enantiomer ratio *S* : *R* = 4.0 : 96.0 (92% *ee*).



173a 178

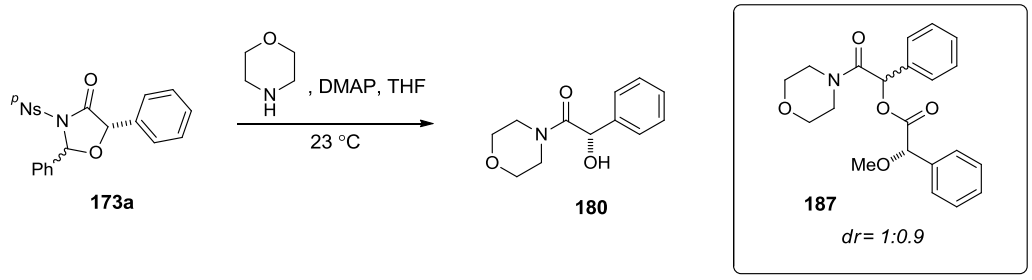
(*S*)-*S*-Ethyl Hydroxy-phenyl-thioacetate (178):[68] To a 0 °C solution of EtSH (17.8 µL, 1.2 equiv, 0.240 mmol) in 2 mL of THF was added KHMDS solution (0.48 mL, 0.5 M in toluene, 0.24 mmol). The reaction was stirred for 5 min at 0 °C and then warmed to ambient temperature and stirred for another 15 min. The resulting milky mixture was cooled to 0 °C and a solution of oxazolidinone **173a** (84.9 mg, 1 equiv, 0.200 mmol) in 1 mL of THF was added dropwise. The resulting mixture was stirred for 4h at 0 °C and warmed to ambient temperature and stirred for another 0.5h. 3 ML of HCl in MeOH (5%) was added into the reaction and stirred for 10 min. The solvent was removed by rotary evaporator and the residue was dissolved in EtOAc and washed with H_2O. The organic layer was separated and the aqueous layer was extracted 3x with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude material was purified by flash column chromatography (14% EtOAc in hexanes) to yield 28 mg (72%) of the titled compound **178** as a clear wax. The *ee* (>98%) was determined by chiral HPLC and only single enantiomer was observed. Daicel Chiracel™ OD-H column, flow rate 0.6 mL/min, 10% ^{i}PrOH/90% hexanes, T_r: 12.3 min (*S*), 17.6 min (*R*).



173a **179**

(*S*)-(+)-Methyl mandelamide (179):[69] NH_3 gas was bubbled into 5 mL of MeOH at 0 °C for 20 min. A solution of oxazolidinone **173a** (84.9 mg, 0.200 mmol, 1 equiv) in 1 mL of CH_2Cl_2 was cannulated into the NH_3/MeOH solution. The reaction was stirred for another 5 min and concentrated under reduced pressure. The crude material was purified by flash chromatography (5% MeOH in CH_2Cl_2) to yield 25 mg (83%) of the titled compound **179** as a white wax solid.

$[\alpha]_D^{17}$+56.7 (*c* 1.20, EtOH). The optical rotation is identical to the reported value of (*S*)-(+)-methyl mandelamide, indicating an excellent *ee* of the ring opened product **179**.



(*S*)-*N*-Mandeloylmorpholine (180):[70] To a stirred solution of oxazolidinone **173a** (84.9 mg, 0.200 mmol, 1 equiv) and DMAP (14.4 mg, 0.100 mmol, 0.5 equiv) in 2mL of THF was added morpholine (0.17 mL, 2.0 mmol, 10 equiv) dropwise at ambient temperature. The reaction was stirred overnight. The reaction was diluted with CH_2Cl_2 and quenched with saturated NH_4Cl aqueous solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude material was purified by flash column chromatography (1/1, EtOAc/Hexanes) to yield 39.8 mg (90%) of the titled compound **180** as white solid. $[\alpha]_D^{15}$ +3.96 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.23 (m, 5H), 5.19 (d, *J*= 6.4 Hz, 1H), 4.72 (d, *J*= 6.4 Hz, 1H), 3.82-3.77 (m, 1H), 3.73-3.67 (m, 1H), 3.64-3.60 (m, 1H), 3.58-3.53 (m, 1H), 3.47 (ddd, *J*= 3.2, 5.6, 11.6 Hz, 1H), 3.30 (ddd, *J*= 2.8, 7.2, 13.2 Hz, 1H), 3.16 (ddd, *J*= 2.8, 5.6, 13.2 Hz, 1H), 3.07 (ddd, *J*= 2.8, 7.2, 10.8 Hz, 1H); δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 139.1, 129.1, 128.7, 127.3, 71.5, 66.5, 65.7, 45.2, 43.1; IR ν_{max} cm^{-1}: 3408, 1643, 1452, 1399, 1272, 1251, 1114, 1068, 1029, 702. The *ee* (5%) was determined by Trost ester analysis upon converting amide **180** to **187**. ^{1}H NMR of **187** showed a 1:0.9 ratio of diastereomers and therefore the *ee* of **180** was 5%.

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