DDQ-Mediated Oxidative Oxocarbenium Ion Formation – Method Development and Natural Product Total Synthesis

by

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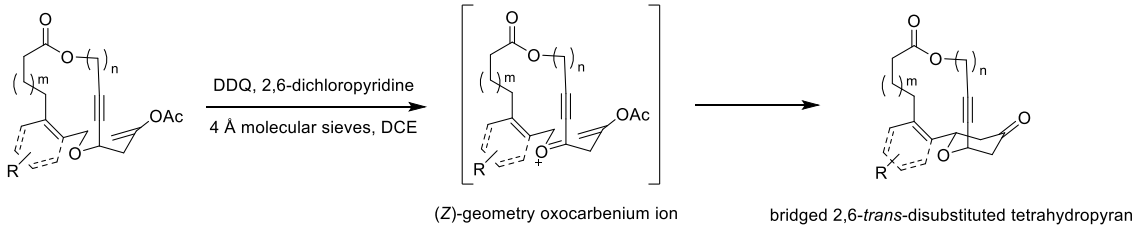
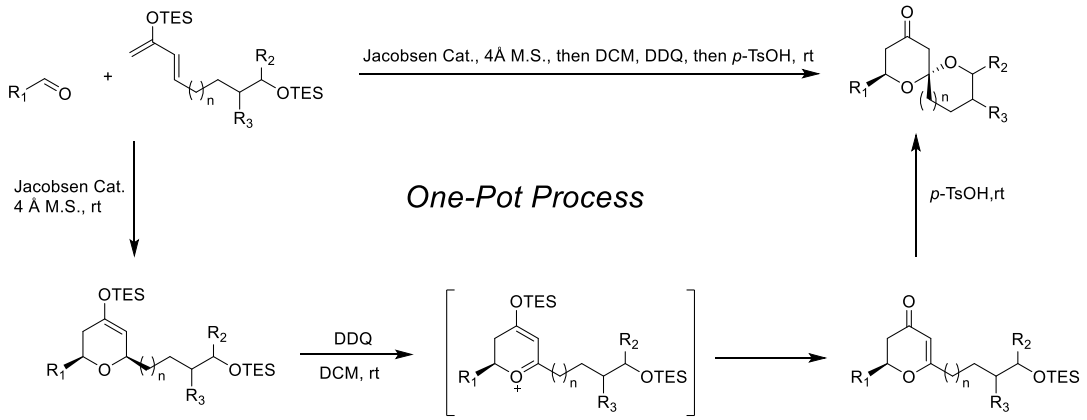
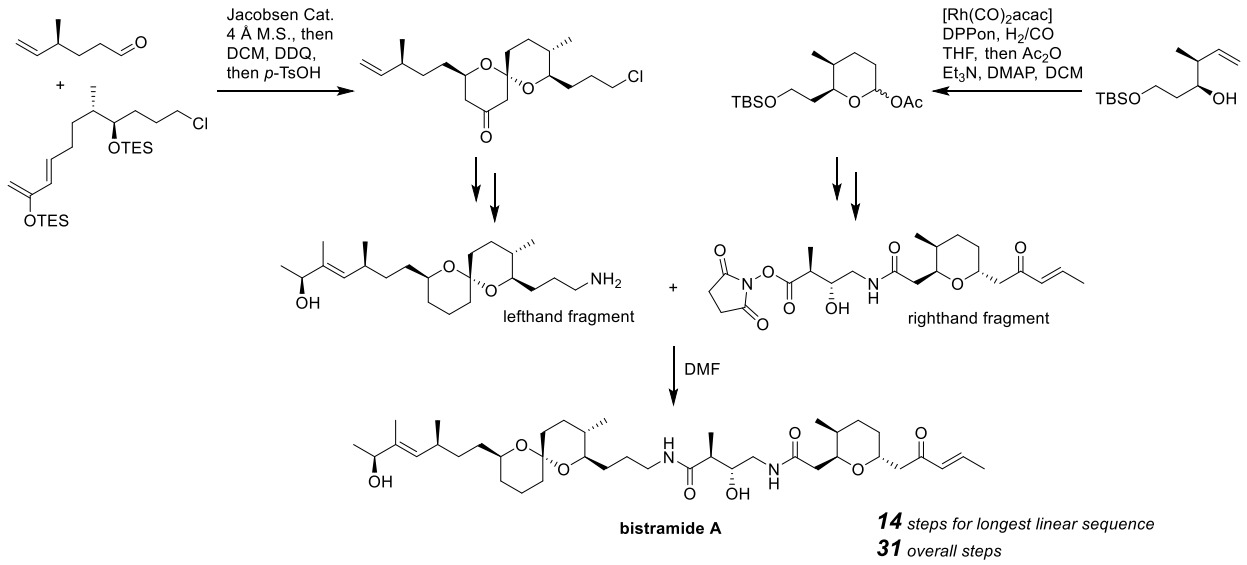
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is an excellent oxidant for cleaving the carbon–hydrogen bond of allylic (or benzylic) ethers to generate oxocarbenium ions. When DDQ oxidation proceeds in a macrocyclic system that contains a sterically undemanding alkynyl group, the (*Z*)-geometry oxocarbenium ion dominates due to the geometric constraint of the macrocyclic core. The following nucleophilic addition of the appending enol acetate to this macrocyclic oxocarbenium ion yields the bridged 2,6-*trans*-disubstituted tetrahydropyran diastereoselectively.



Based on the DDQ oxidation methodology, a one-pot process has been developed to access synthetically challenging spiroketal structures through combining simple dienes and aldehydes. After the initial hetero-Diels-Alder (HDA) reaction, the resulting tetrahydropyranyl enol silyl ethers are subjected to DDQ oxidation. The tetrahydropyranyl oxocarbenium ions are formed immediately, followed by the cleavage of the carbon–silicon bonds to produce the enones that go through an oxa-Michael addition to afford the spiroketals in excellent yields.



This one-pot process has been successfully applied to the construction of the spiroketal core during the convergent total synthesis of bioactive natural product bistramide A. The 2,6-*trans*-tetrahydropyran in the righthand fragment was fast assembled through another novel one-pot process, which is composed of a hydroformylation, cyclization, and acetylation. Currently, our total synthesis of bistramide A holds the shortest synthetic sequence in the literature.



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LIST OF ABBREVIATIONS

Ac	Acetyl
Bn	Benzyl
Bz	Benzoyl
Boc	*tert*-Butyloxycarbonyl
Bu	Butyl
CAN	Cerium(IV) ammonium nitrate
cod	1,5-Cyclooctadiene
Cp^*	Pentamethylcyclopentadienyl
cy	Cyclohexyl
dba	Dibenzylideneacetone
DBU	1,8-Diazabicycloundec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMP	Dess-Martin periodinane

dr	Diastereomeric ratio
DMSO	Dimethylsulfoxide
DTBP	Di-*tert*-butyl peroxide
ee	Enantiomeric excess
EDG	Electron donating group
EWG	Electron withdrawing group
Et	Ethyl
FG	Functional group
Fmoc	Fluorenylmethyloxycarbonyl
HMPA	Hexamethylphosphoramide
HRMS	High-resolution mass spectrometry
HOSu	*N*-Hydroxysuccinimide
Ipc	Isopinocampheyl
LA	Lewis acid
LDA	Lithium diisopropylamide
mCPBA	*meta*-Chloroperoxybenzoic acid
Ms	Methanesulfonyl
M.S.	Molecule sieves
$NMQPF_6$	*N*-methylquinolinium hexafluorophosphate
Nu	Nucleophile
OTf	Trifluoromethanesulfonate
PG	Protecting group

Pht	Phthalimide
PMB	*para*-Methoxybenzyl
Py	Pyridine
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
PPTS	Pyridine-*p*-toluenesulfonate
PTSA	*para*-Toluenesulfonic acid
TBAF	Tetra-*n*-butylammonium
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	Tosyl

ACKNOWLEDGEMENTS

First and foremost, I would like to express my sincere appreciation to my advisor Prof. Paul E. Floreancig for your support for my Ph.D. study. Your advices on both research and career have been invaluable to me. Under your intellectual guidance, I have gained a better understanding of organic chemistry on both breadth and depth and also learned the critical thinking skills, which make me a qualified chemist and become my whole life treasure.

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Last but not the least, I would like to thank my mother and father. They are always supportive throughout my life. I also want to express my special love and acknowledgements to my wife, Dr. Zhiyun Cao. She is always there to support me. Their love provides me inspiration. I wish I could show them how much I love them.

1.0 INTRODUCTION TO OXOCARBENIUM ION FORMATION

Oxocarbenium ions are frequently proposed as intermediates in a number of organic transformations.[1] These intermediates are a classic form of a carbocation that is stabilized by the lone pair on an adjacent oxygen atom. Due to this stabilization, oxocarbenium ions are commonly formed under mild conditions, which allow them to undergo nucleophilic additions from a vast range of nucleophiles and yield substituted ethers. Nevertheless, to date, there are only a few pathways for accessing these synthetically useful carbocations: 1) ethereal bond formation pathway,[2] 2) functional group departure pathway,[3] 3) enol ether functionalization pathway,[4] 4) hydride transfer pathway,[5] and 5) oxidative electron transfer pathway (Figure 1-1).[6] Several representative chemical transformations of the above approaches of oxocarbenium ion formation and their applications in complex molecule synthesis will be briefly discussed.

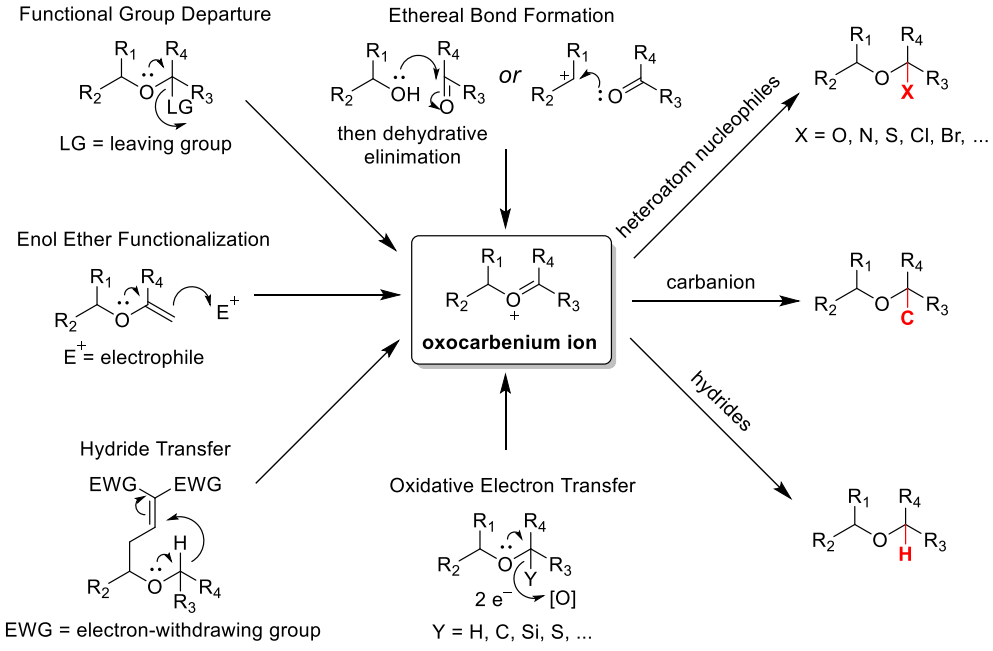
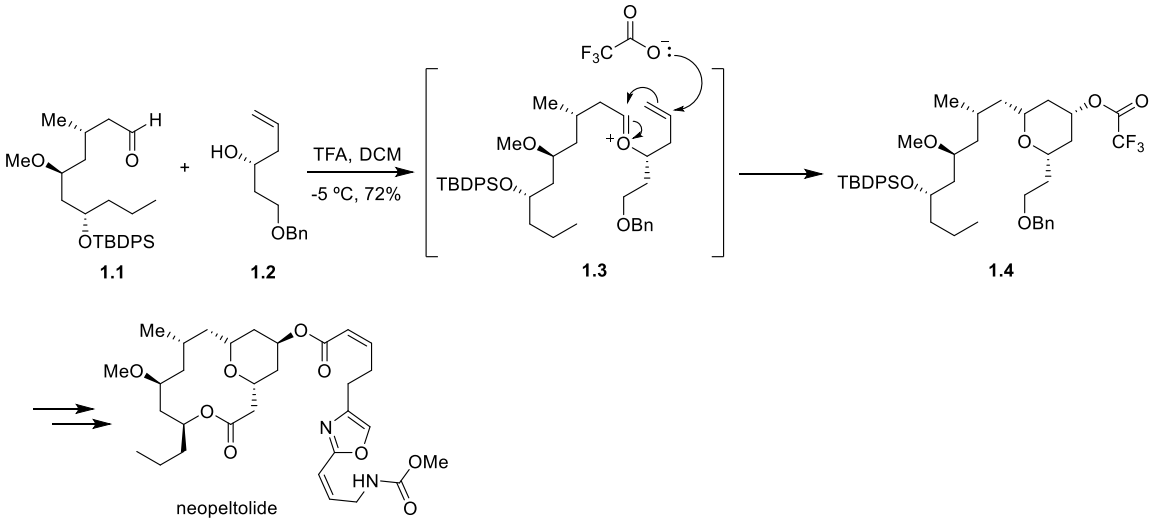


Figure 1-1. Oxocarbenium ion formations and utilities

1.1 ETHEREAL BOND FORMATION

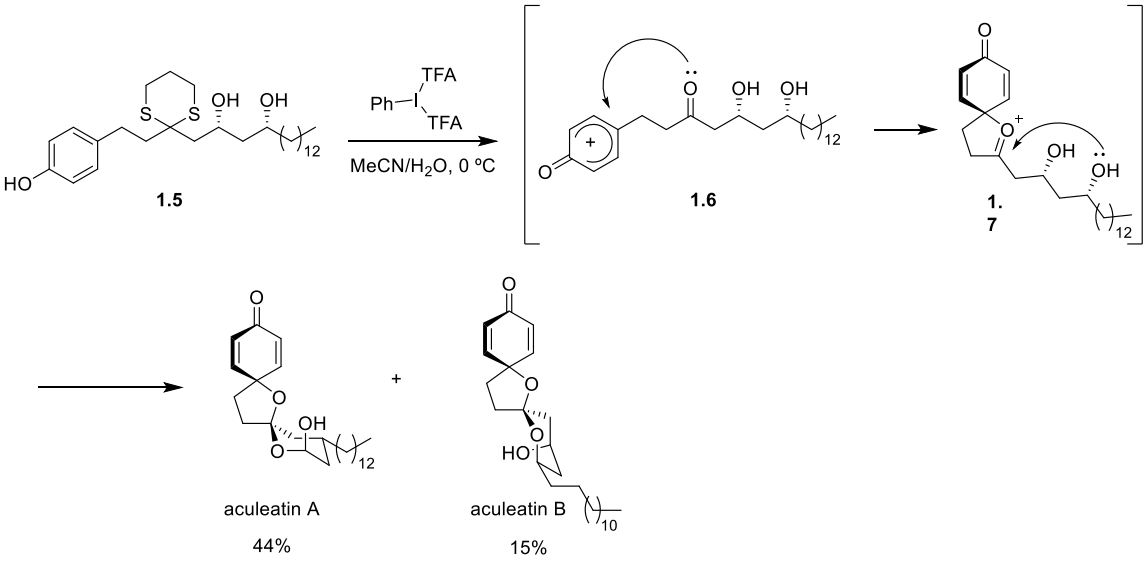
The most common access to oxocarbenium ions is the dehydrative condensation of alcohols or silyl ethers with aldehydes or ketones in the presence of Brønsted or Lewis acids. One example is given by Maier and co-workers during their total synthesis of the cytotoxin neopeltolide (Scheme 1-1).[7] In their route, the oxocarbenium ion **1.3** was formed by the condensation of aldehyde **1.1** with homoallylic alcohol **1.2** in the presence of trifluoroacetic acid. Subsequently attack by the pendent alkene formed the tetrahydropyran (THP) ring. Thereafter, the *in situ* formed tetrahydropyranyl cation was quenched by the trifluoroacetoxy anion to afford THP **1.4** in 72% yield with perfect diastereoselectivity. The installation of the trifluoroacetoxy group served as a useful handle on the THP ring. After removing the trifluoroacetyl group, the unprotected alcohol coupled with the oxazole fragment smoothly under Mitsunobu conditions.



Scheme 1-1. Maier's synthesis of neopeltolide

Wong and co-workers disclosed an oxocarbenium ion formation through the coupling of an internal ketone and an oxidatively generated phenoxonium cation.[8] This method is highlighted in

their convergent synthesis of the antimalarial natural products (±)-aculeatin A and B (Scheme 1-2). Notably, the treatment of racemic substrate **1.6** with the oxidant phenyliodine trifluoroacetate produced the phenoxnium cation and deprotected the dithiane-masked ketone.[9] After the coupling of these two newly generated species, oxocarbenium ion **1.8** was formed, then was captured by the internal alcohol to afford the target products in moderate overall yield.



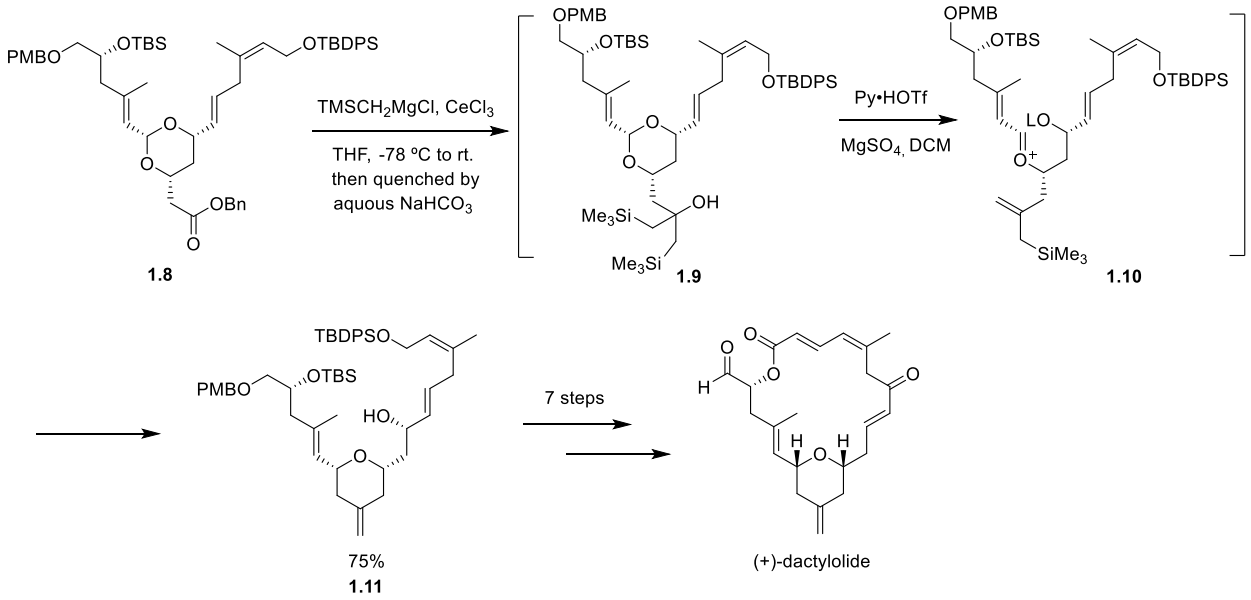
Scheme 1-2. Condensation of ketone and phenoxonium cation

1.2 FUNCTIONAL GROUP DEPARTURE AT THE α-POSITIONS OF ETHERS

The departure of a functional group causes an unsymmetrical cleavage of the carbon–leaving group bond and results the oxocarbenium ion for the following target- or diversity-oriented synthesis.

The precursors, acetals, can be easily converted to the oxocarbenium ions in the presence of Brønsted or Lewis acids, when alkoxy groups act as the leaving groups. This pathway was

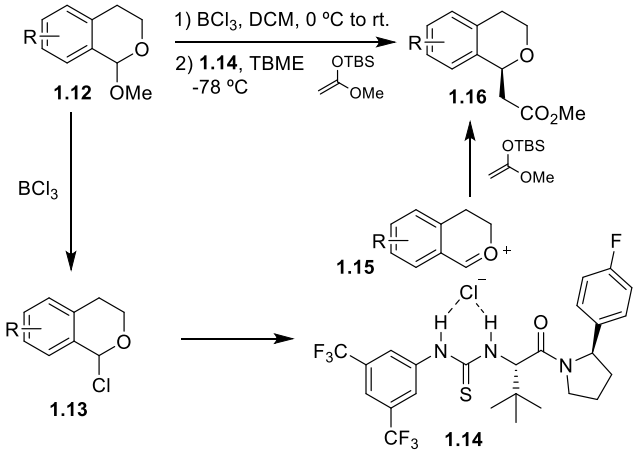
illustrated by the Floreancig group in the total synthesis of (+)-dactylolide (Scheme 1-3).[10] This synthesis is featured by the efficient construction of the THP **1.11** through a Prins-type reaction, in which the oxocarbenium ion **1.10** was generated by Lewis acid-ionization of one acetal oxygen. This transformation is a two-step sequence that started from the cerium(III) chloride-promoted addition of ((trimethylsilyl)methyl)magnesium chloride to the benzyl ester **1.8**. The resulting tertiary alcohol **1.9** was quenched with base and subjected to pyridine/triflic acid and magnesium sulfate for the key Prins-type reaction. The excellent regioselectivity is attributed to the preference for the kinetically facile 6-*endo* cyclizaton over the 8-*endo* cyclization.[11]



Scheme 1-3. Floreancig's total synthesis of (+)-dactylolide

The halogen anion is also a suitable leaving group in the oxocarbenium ion formation process. Jacobson and co-workers reported a chiral thiourea-catalyzed reaction to enantioselectively convert the carbon–chloride bonds on 1-chloroisochromans **1.13** to carbon–carbon bonds (Scheme 1-4).[12] The oxocarbenium ions **1.15** were formed through the dissociation of carbon–chloride bonds under the assistance of hydrogen-bond donor pyrrole-bearing thiourea

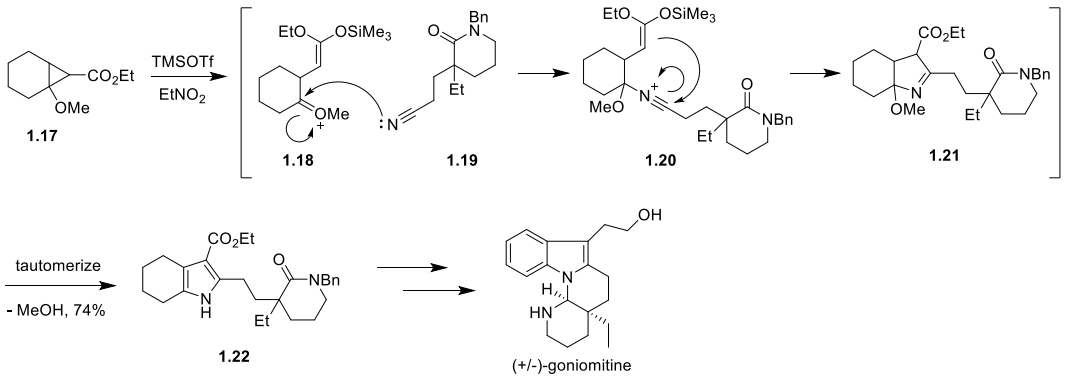
derivative **1.14**, in their proposed mechanism. This anion binding between the oxocarbenium ions and the chiral thiourea-chloride complex enables the nucleophiles to attack **1.15** enantioselectively.



entry	R	time (h)	yield (%)	*ee* (%)
1	H	6	87	85
2	5-Me	7.5	71	90
3	6-Me	7.5	82	84
4	7-Me	7.5	82	87
5	6-F	21	70	90
6	6-MeO	22	96	74

Scheme 1-4. Enantioselective additions to isochroman oxocarbenium ions

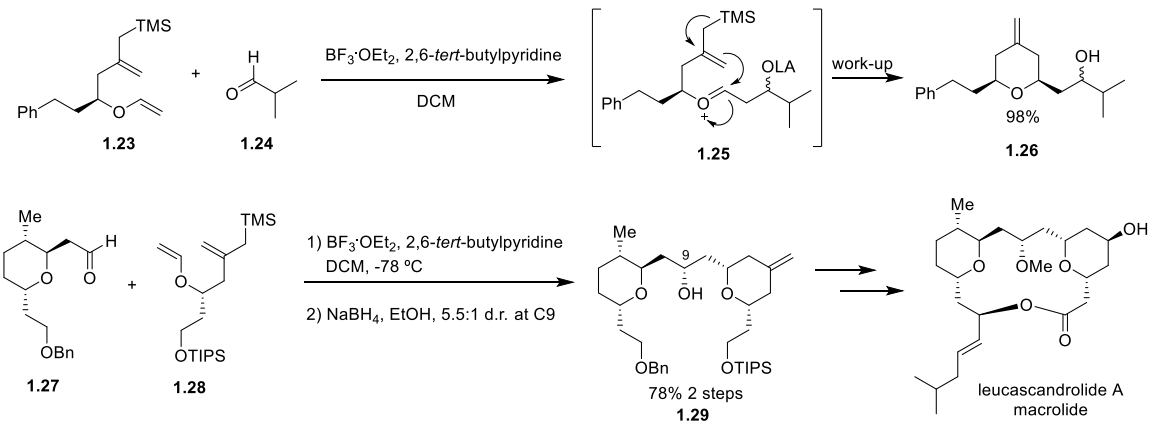
Carbon-centered leaving groups are also able to afford the oxocarbenium ions, which was demonstrated by Pagenkopf and coworkers in their total synthesis of (±)-goniomitine (Scheme 1-5).[13] In the key step, a TMSOTf-assisted cyclopropane ring-opening process was employed to afford oxocarbenium ion **1.18** at the initial stage. Thereafter, nitrile 1**.19** was added onto **1.18** to afford nitrilium ion **1.20**, followed by an intramolecular cyclization to yield the fused skeleton **1.21**. The isolated product **1.22** was obtained in 74% yield after methanol-elimination and tautomerization.



Scheme 1-5. Pagenkopf's synthesis of (±)-goniomitine

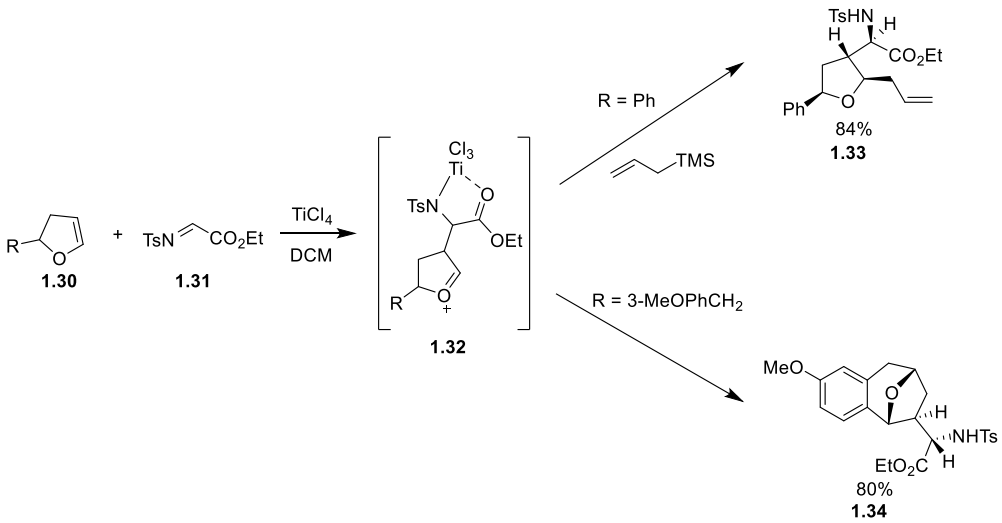
1.3 REACTIONS OF ENOL ETHERS WITH ELETROPHILES

Prins-type reactions will produce oxocarbenium ion intermediates when enol ethers act as nucleophiles in the reactions. Based on extensive studies on the Prins-type reaction, the Rychnovsky group developed a Mukaiyama aldol-Prins cascade reaction.[14] In this reaction, the key oxocarbenium ion **1.25** was formed through a nucleophilic addition of enol ether **1.23** to aldehyde **1.24** in the presence of $BF_3 \cdot OEt_2$ (Scheme 1-6). Consequentially, the intramolecular cyclization and desilylation proceeded to afford THP **1.26** in excellent yields. Subsequently, they applied this methodology as the key step to efficiently couple the fragment **1.27** and **1.28** in their formal syntheses of the bioactive natural product, leucascandrolide A (Scheme 1-6).



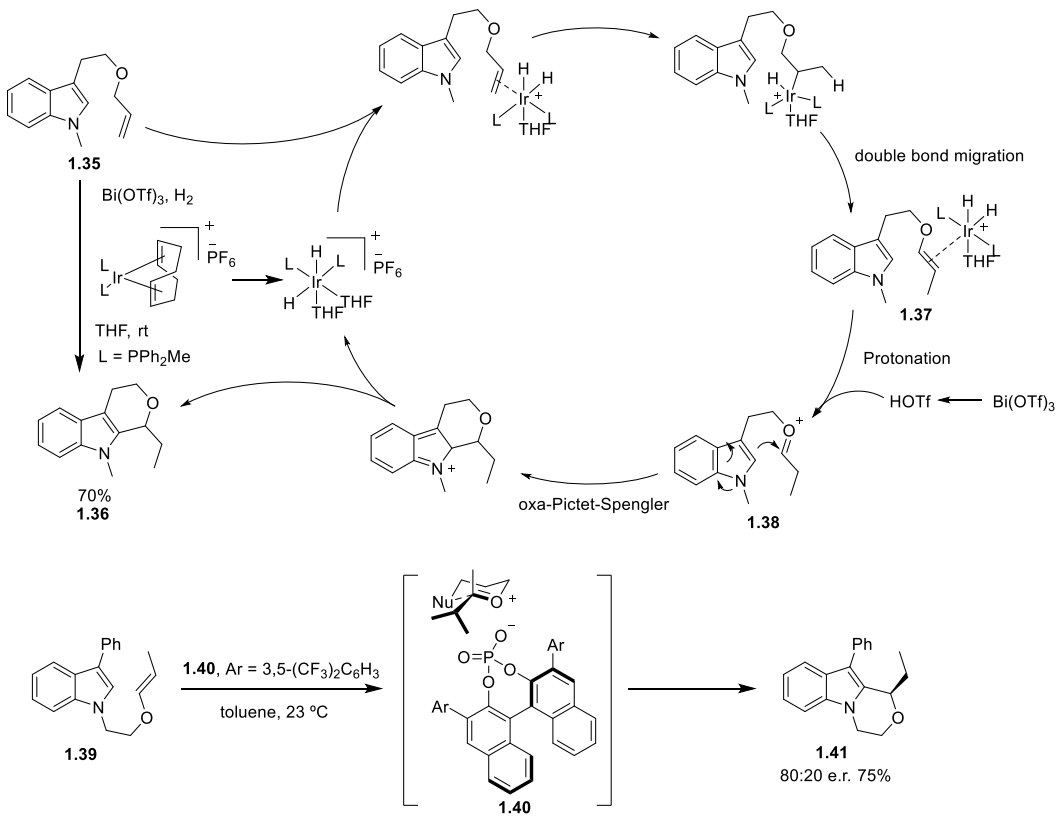
Scheme 1-6. Mukaiyama aldol/Prins reaction and its application in natural product synthesis

Ghosh and co-workers demonstrated that imines are also susceptible to the nucleophilic attacks from enol ethers (Scheme 1-7).[15] In their transformations, dihyrofurans **1.30** were added to the titanium(IV) chloride-activated *N*-sulfonyl imino ester **1.31** to afford oxocarbenium ions **1.32**. Both intermolecular and intramolecular nucleophilic additions to **1.32** diastereoselectively yield multiply substituted tetrahydrofurans **1.33** and benzo-fused 8-oxabicyclo[3.2.1]octane **1.34** in excellent yields respectively.



Scheme 1-7. Ghosh's multiply substituted tetrahydrofuran syntheses

Protonation-mediated ionization of enol ethers is an alternative oxocarbenium formation method. Scheidt and co-workers disclosed a tandem isomerization/oxa-Pictet-Spengler protocol to illustrate this pathway (Scheme 1-8).[16] Allylic ether **1.35** underwent an iridium(III)-catalyzed double bond migration to yield enol ether **1.37**. Then, the *in situ* generated triflic acid protonated **1.37** to furnish key oxocarbenium ion **1.38**, which initiated the oxa-Pictet-Spengler reaction to yield pyran-fused indole **1.36**. Interestingly, the authors observed that the double bond migration process was significantly accelerated when they added the bismuth triflate and iridium pre-catalyst simultaneously, which implies a cooperative catalysis affect in their system. Notably, an asymmetric oxa-Pictet-Spengler example was shown in the same paper by employing the chiral phosphoric acid **1.40** as Brønsted acid. The enantioselectivity is attributed to contact ion-pair interaction.

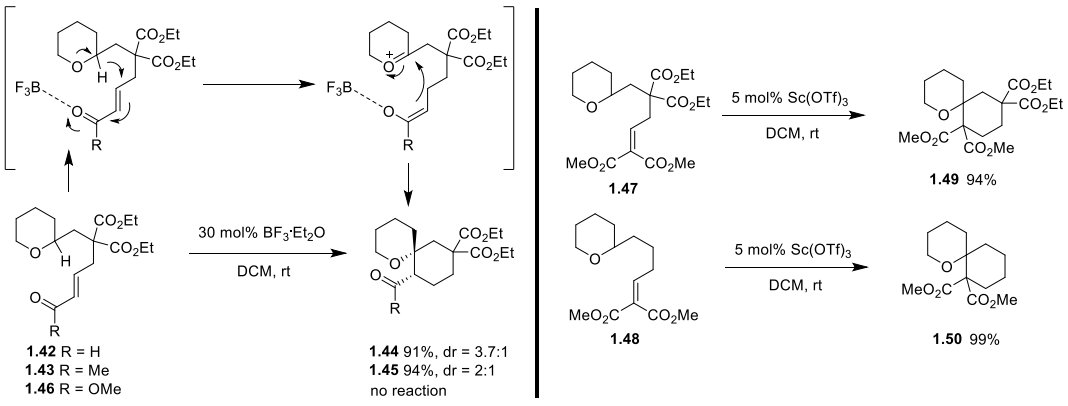


Scheme 1-8. The tandem isomerization/oxa-Pictet-Spengler reaction

1.4 INTRAMOLECULAR HYDRIDE TRANSFER

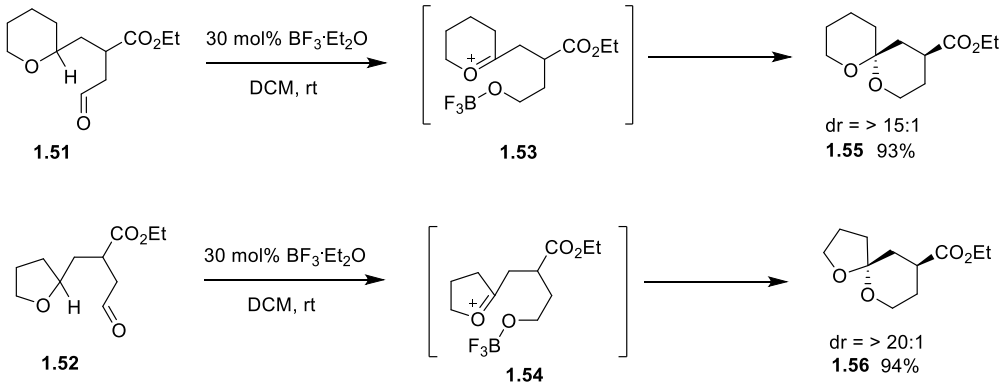
The carbon(sp^3)–hydrogen bonds that are adjacent to the oxygen atoms have the potential to become hydride donors. When there are proper internal hydride acceptor, such as aldehydes, ketones, and esters, those potential hydride donors will transfer a hydride, forming the oxocarbenium ions in the presence of Lewis acids.[5a,17] Due to their "green" nature, the development of hydride transfer reactions is a hot topic in current organic synthesis.

Sames and co-workers disclosed the first example of the intramolecular hydride transfer reactions that involved oxocarbenium ion formation (Scheme 1-9).[17a] They conducted the intramolecular hydroalkylation through the treatment of α,β-unsaturated aldehyde **1.42** and α,β-unsaturated ketone **1.43** with the Lewis acid $BF_3{\cdot}OEt_2$. Excellent yields and moderate diastereoselectivities of the cyclized products **1.44** and **1.45** were obtained. The failure of ester **1.46** in this reaction implies that higher acceptor-electrophilicity is required for the ester substrates. After installing an extra ester group on **1.46**, ester **1.47** could undergo this annulation reaction smoothly in excellent yields. Notably, the geminal substitutions are not necessary for efficient annulation based on the result of substrate **1.48**.



Scheme 1-9. Sames' intramolecular hydride transfer reactions

In connection with the results on α,β-unsaturated aldehydes, ketones, and esters, Sames found that the saturated aldehydes and ketones are also suitable hydride acceptors (Scheme 1-10).[17b] Aldehydes **1.51** and **1.52** underwent the $BF_3{\cdot}OEt_2$-catalyzed hydride transfer process to produce the oxocarbenium ions **1.53** and **1.54**. These oxocarbenium ions were attacked by internal alcohol nucleophiles to afford spiroketals **1.55** and **1.56** respectively in excellent yields. The remarkable diastereoselectivity of these reactions can be explained by the thermodynamical control of the reversible intramolecular cyclization process.

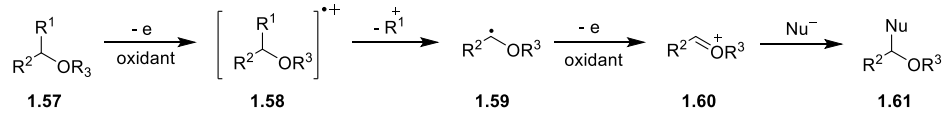


Scheme 1-10. Spiroketal synthesis *via* hydride transfer reactions

1.5 OXIDATIVE ELECTRON TRANSFER

Ethers **1.57** will transfer one electron to proper oxidants and form radical cations **1.58** (Scheme 1-11). Meanwhile, the C–R^1 bonds of **1.57** are significantly weakened and can be cleaved to render radical species **1.59**. After transferring another electron from **1.59**, the oxocarbenium ions **1.60** are formed and ready to undergo the nucleophilic additions. Normally, these oxidative reactions proceed in neutral conditions, which avoid any issues associated with acid- or base-

sensitive functional groups on the substrates. Electrochemical oxidation and chemical reagent-mediated oxidation are two major methods in this approach.



Scheme 1-11. The general mechanism of the oxidative oxocarbenium ion formation

The Yoshida group has contributed pioneering and systematic studies of electrochemical oxidations.[18] During their initial investigations, α-silyl ethers were employed as the substrates (Figure 1-2).[19] They passed a 10mA constant current through an undivided cell that was equipped with a carbon rod anode and cathode and contained a 0.2 M solution of α-silyl ethers **1.62** and the electrolyte tetraethylammonium triflate. During this process, the oxocarbenium ions **1.66** were formed after two equivalents of electrons were transferred from **1.62** to the anode. Subsequent addition of methanol produced acetals **1.63** in good to excellent yields. The silyl groups played a vital role during this reaction. Not only did they significantly lower the oxidation potentials of **1.62**, but they also controlled the reaction chemoselectivity since the carbon–silicon bonds in radical cations **1.64** were largely weakened and selectively cleaved. Based on the success of electrochemical oxidation of α-silyl ethers, Yoshida has extended the substrate scope, including α-stannyl ethers,[20] telluroglycosides,[21] α-germyl ethers,[22] and thioethers[23] (Scheme 1-12).

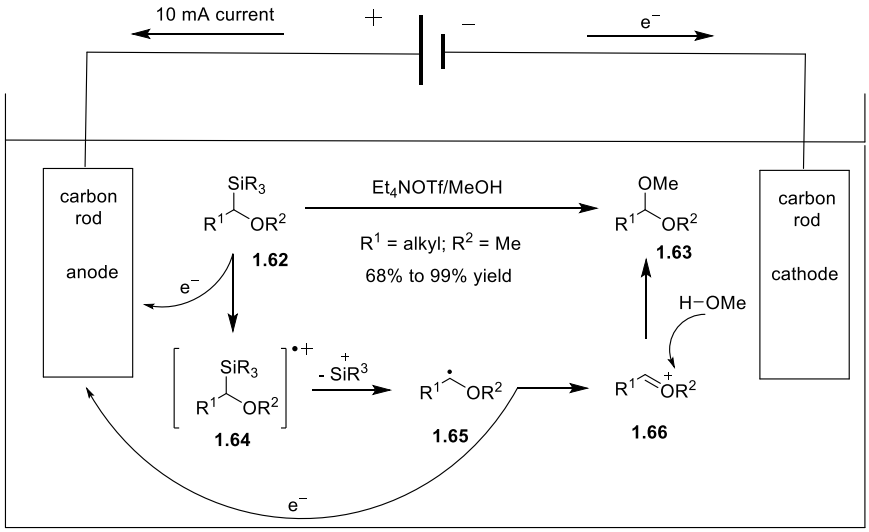
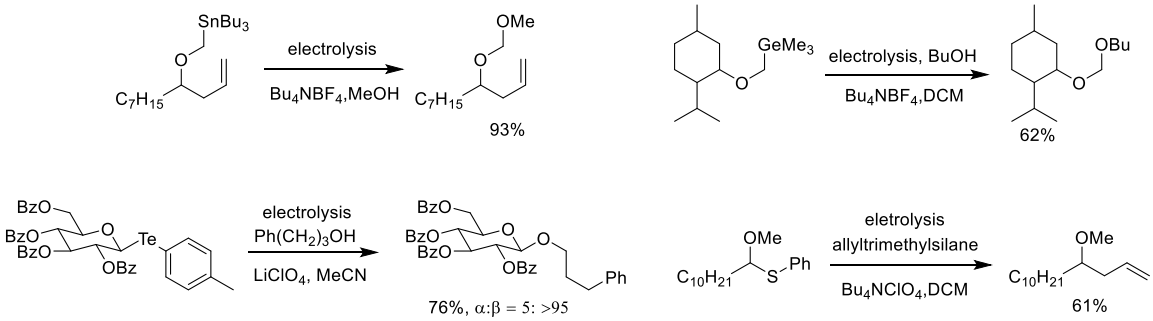
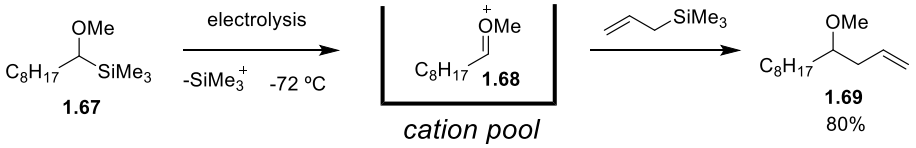


Figure 1-2. Electrochemical oxidation of α-silyl ethers



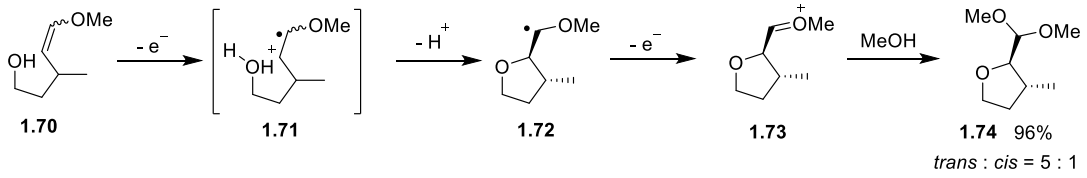
Scheme 1-12. Electrochemical oxidation of substrates other than α-silyl ethers

Recently, Yoshida and co-workers developed a novel "cation pool" method in which oxocarbenium ions are generated by low temperature electrolysis and accumulated in a nucleophile-free environment (Scheme 1-13).[24] This method has effectively filled the deficiency on the characterization of simple alkyloxycarbenium ions in common organic reaction media. The thermal stability investigation showed that the oxocarbenium ion **1.68** is quite stable at temperatures lower than –50 °C, but decomposes dramatically at higher temperatures. In addition, the reaction of the oxocarbenium ion pool with various types of nucleophiles proceeded smoothly in moderate to excellent yield, although the diastereoselectivity is relatively low.



Scheme 1-13. The "cation pool" method

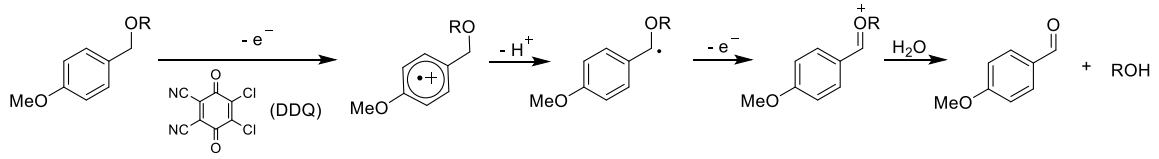
Enol ethers are also electrochemical oxidation substrates. One example is given by Moeller and co-workers (Scheme 1-14).[25] They observed that radical cation **1.71**, generated from the enol ether **1.70** could be trapped by the internal alcohol to afford the tetrahydrofuran radical **1.72**. One electron of **1.72** was removed by electrochemical oxidation to yield the oxocarbenium ion **1.73** that underwent the solvolysis to furnish dimethylacetal **1.74** in excellent yield as a mixture of 5:1 in favor of the *trans*-isomer. THPs could also be synthesized *via* this method; however, this reaction fails to yield seven-membered or larger ring systems.



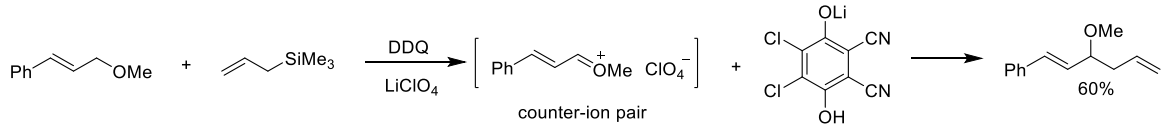
Scheme 1-14. Electrochemical oxidation of the electron-rich enol ether

Besides the electrochemical oxidation protocol, many chemical reagents, such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[26] di-*tert*-butyl peroxide (DTBP),[27] *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$),[28] and ceric ammonium nitrate (CAN),[29] are able to oxidatively activate the carbon-hydrogen (C–H) bonds and carbon-carbon (C–C) bonds to form oxocarbenium ions. For instance, the DDQ-mediated *p*-methoxybenzyl ether deprotection protocol is a typical oxidative C–H bond activation process during which oxocarbenium ions are involved (Scheme 1-15).[26a] Mukaiyama successfully captured the DDQ-generated oxocarbenium

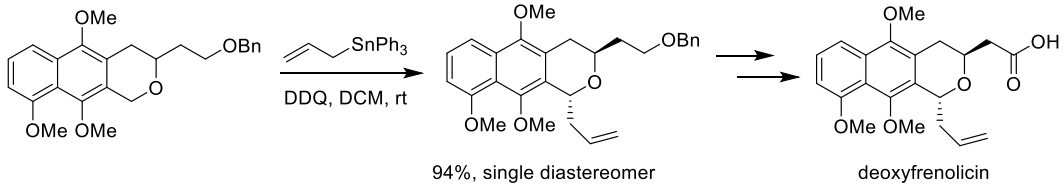
ion with allyltrimethylsilane instead of water to form a new C–C bond (Scheme 1-16).[26b] In this reaction, lithium perchlorate was proven to significantly improve the reaction yield, which was ascribed to the counter-ion effect. Later, Xu and co-workers smoothly installed an allyl group onto the isochroman in excellent yield and diastereoselectivity *via* the DDQ oxidation during their total synthesis of deoxyfrenolicin (Scheme 1-17).[26c] In 2006, a DDQ-based cross-dehydrogenative coupling (CDC) reaction was developed to couple benzyl ethers and carbonyl compounds by Li and co-workers (Scheme 1-18).[26d,26e] Interestingly, in their initial investigation, indium(III) chloride and copper bromide showed a synergistic effect in activating DDQ and the malonate substrate (Eq. (1-1)). Later, they found out that the CDC reaction could even proceed between benzyl ethers and ketones under heat without any other additives (Eq. (1-2)).



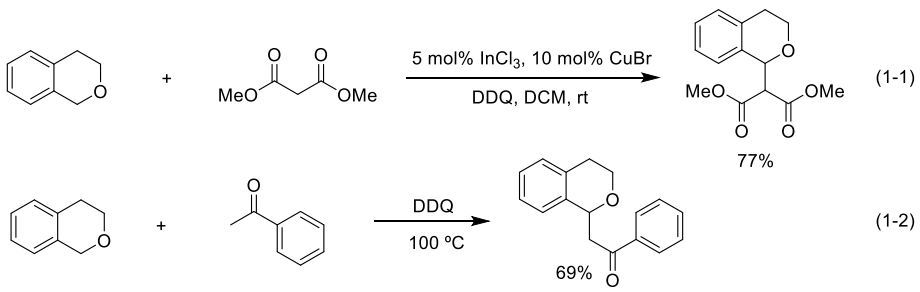
Scheme 1-15. Oxidative deprotection of *p*-methoxybenzyl ether by DDQ



Scheme 1-16. DDQ oxidation by employing allyltrimethylsilane as nucleophile

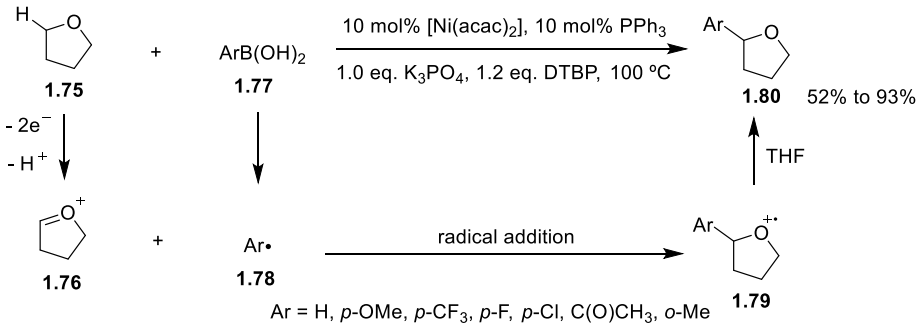


Scheme 1-17. Xu's application of DDQ oxidation to the synthesis of deoxyfrenolicin



Scheme 1-18. Li's results of DDQ-mediated CDC reactions

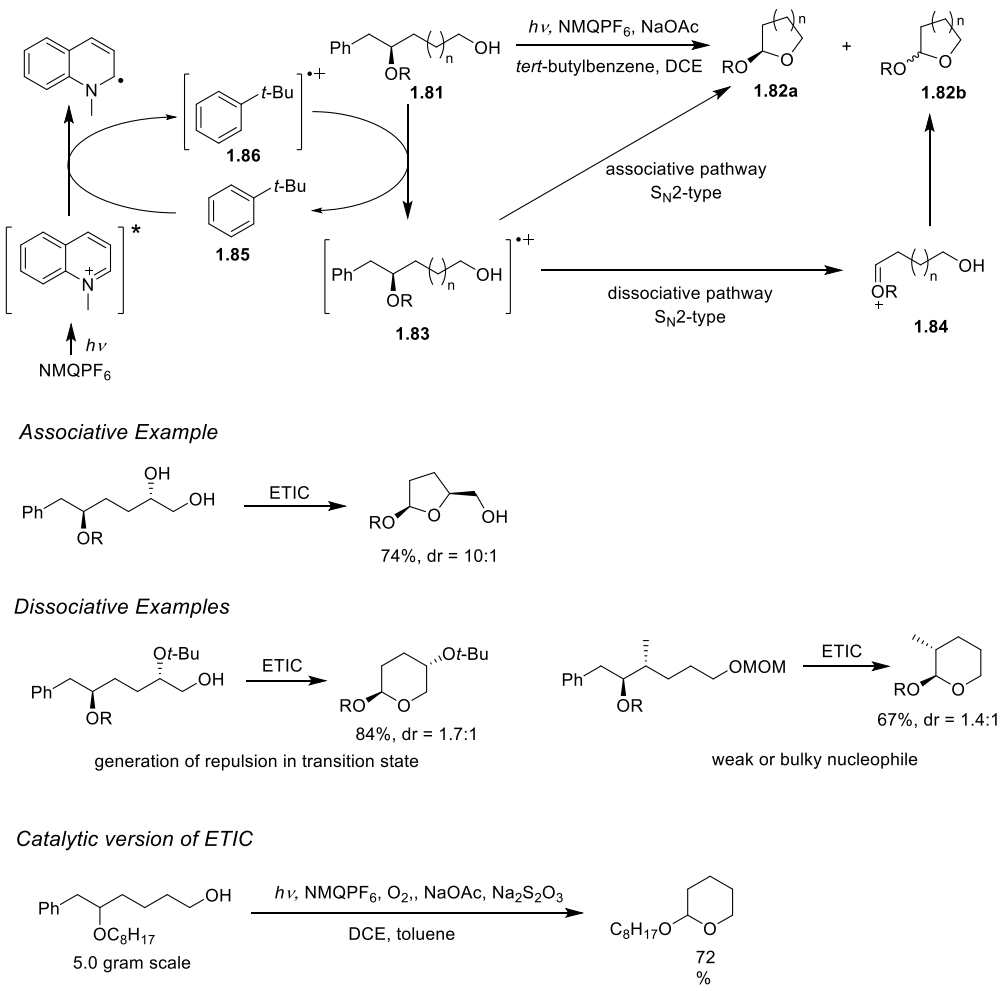
Recently, Lei reported a new method that oxidatively installed the aryl groups onto the carbons adjacent to the oxygen atoms (Scheme 1-19).[27] Under the assistance of nickel catalyst, DTBP oxidatively cleaved the C–H bond at the α-position of the inert solvent tetrahydrofuran **1.75** to yield oxocarbenium ion **1.76**. Simultaneously, the aryl radicals **1.78** were released from the arylboronic acids **1.77** and combined with **1.76**. The resulting radical cations **1.79** underwent a radical abstraction from the solvent and delivered arylsubstituted tetrahydrofurans **1.80** in good to excellent yields. This proposed mechanism is supported by the fact that no desired products were collected when the radical-trapping reagent TEMPO was introduced into the reaction.



Scheme 1-19. C–H bond activation of simple furan

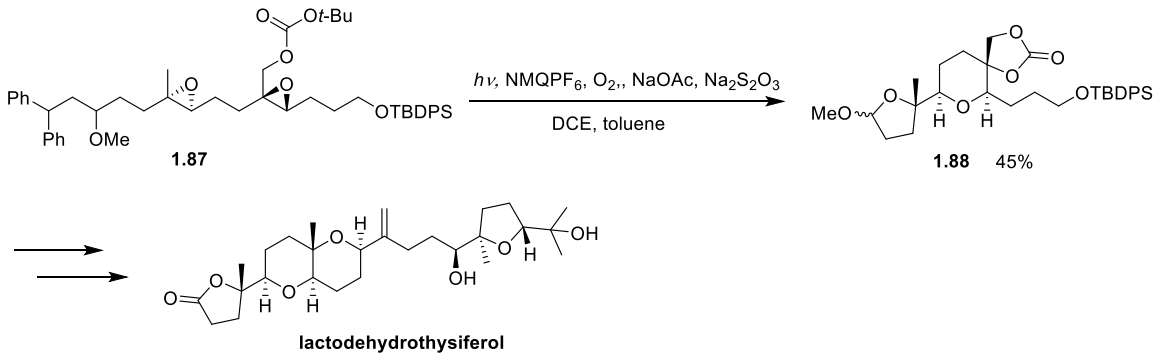
The Floreancig group has conducted extensive studies on oxidative activation of the C–C and C–H bonds.[28,29,30] In 2001, according to the principle that the benzylic C–C bonds will be

significantly weakened in homobenzylic ether radical cations, Dr. Kumar *et al.* developed an electron transfer initiated cyclization (ETIC) to prepare cyclic acetals (Scheme 1-20).[28a] This reaction was initiated by the photo-activation of $NMQPF_6$, which accepts one electron from the cosensitizer **1.85**. The resulting radical cation **1.86** would accept one electron from substrate **1.81** to afford the key intermediate, homobenzylic radical cation **1.83**. Interestingly, at this stage, there are two cyclization pathways, which yield the same product **1.82**: the associative pathway and the dissociative pathway. The former is an S_N2-type cyclization that leads the stereochemical inversion at electrophilic center, whereas the latter is an S_N1-type cyclization that generates the oxocarbenium ion **1.84** and scrambles the substrate stereochemical center. Based on the experimental results, the authors concluded that the dissociative pathway would favor the substrates that bear weak or bulky nucleophiles or could generate steric repulsion in the transition state. Later, a catalytic version of this reaction was developed, which performed more efficiently and enabled gram-scale reaction.[28b]



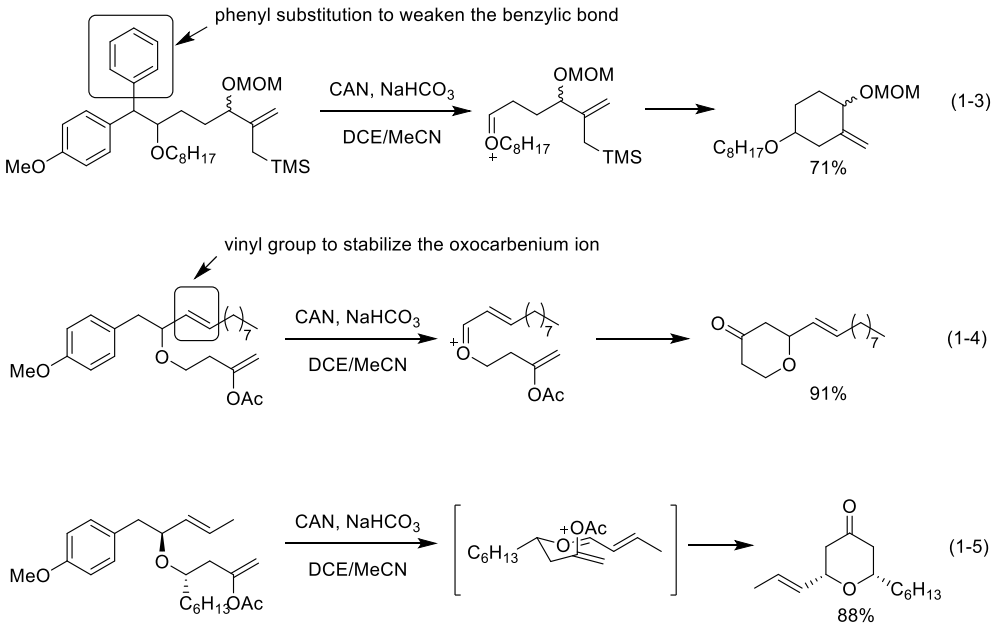
Scheme 1-20. Electron transfer initiated cyclizations

The power of this ETIC reaction was showcased by Dr. Clausen *et al.* in their total synthesis of the protein phosphatase 2A inhibitor, lactodehyrothyrsiferol (Scheme 1-21).[28j] This synthetic route is highlighted by the $NMQPF_6$-mediated cascade cyclization of the diepoxide **1.87**, which regio- and stereo-selectively converted the linear molecule to the tricyclic intermediate **1.88** in moderate yield. Although this reaction terminated before the consumption of starting material, recycling the diepoxide **1.87** enabled the production of gram quantities of **1.88**.



Scheme 1-21. Photoinitiated cyclization in the synthesis of lactodehydrothyrsiferol

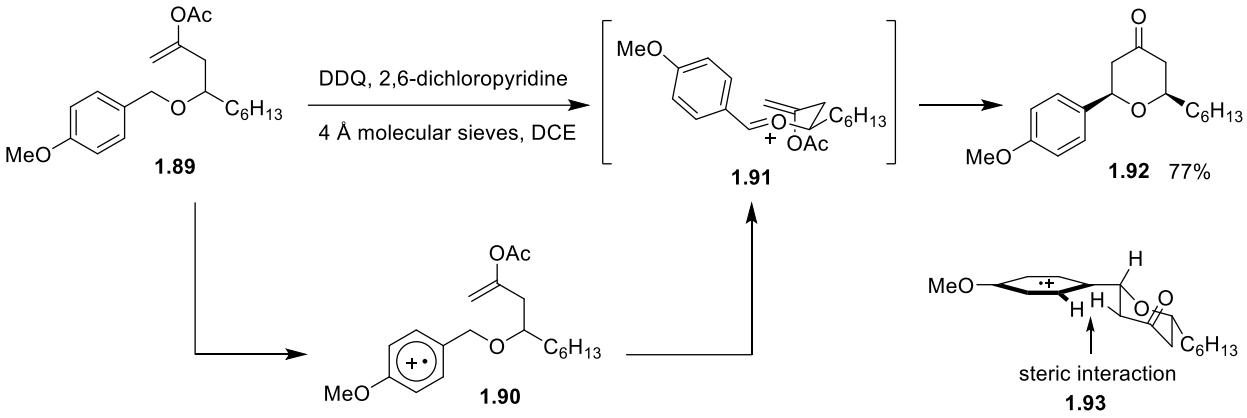
Although the ETIC reaction has shown excellent efficiency for substrates with oxygen-centered nucleophiles, the applications to the substrates with carbon-centered nucleophiles, such as the electron-rich enol ethers, were unsuccessful. It is reasoned that the low oxidation potentials of enol ethers might reduce the chemoselectivity by transferring the electrons to the oxidants prior to the arene electroauxiliaries. However, directly lowering the oxidation potentials of the arene groups by placing electron-rich substitutions on the aromatic rings would lead to strengthening the benzylic bonds and obstructing the cleavage of these bonds. Dr Wang *et al.* devised two strategies to tackle this issue: 1) adding substitutions at benzylic position to weaken the benzylic bonds (Eq. (1-3)), 2) placing a vinyl group at the homobenzylic position to stabilize the oxocarbenium ions (Eq. (1-4)) (Scheme 1-22).[29b,29b] Moreover, the non-photoinitiated oxidant, CAN, was proven to have a higher efficiency than other oxidants during this process, which is attributed to the inner sphere electron-transfer mechanism. The CAN-mediated oxidation exhibited an excellent stereochemical selectivity in 6-*endo*-cyclization to yield the 2,6-*cis*-disubstituted THP as a single diastereomer (Eq. (1-5)). This observation is explained by the strong preference for chair transition states and an (*E*)-configuration for the oxocarbenium ions during the cyclization.[31]



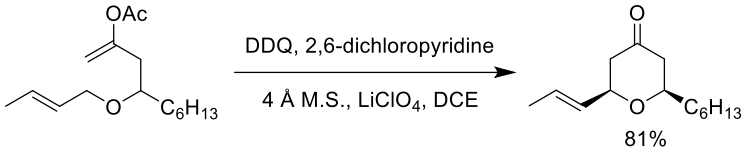
Scheme 1-22. Carbon-carbon bond formation *via* ETIC

During the Floreancig group's exploration for a more atom-economic oxidation system, Dr. Tu *et al.* found that DDQ is an efficient oxidant to promote a cyclization of *p*-methoxybenzylic ether **1.89** to afford 2,6-*cis*-disubstituted THP **1.92** as single diastereomer in excellent yield (Scheme 1-23).[30a] This oxidation was initiated by an electron transfer from **1.89** to DDQ to form radical cation **1.90**, which underwent either hydrogen atom abstraction pathway or proton abstraction then electron transfer pathway to form the chair-like oxocarbenium ion **1.91**. Due to the oxocarbenium ion's preference for an (*E*)-configuration, the *trans*-THP **1.92** was yielded exclusively in this reaction. A steric interaction was proposed to effectively restrict the conversion from radical cation **1.93** to corresponding oxocarbenium ion which could lead to the overoxidation product.[33] Comparing to the harsh conditions and limited substrates scope of the DDQ-mediated C–C bond formations from other groups, this DDQ oxidation reaction can smoothly proceed at

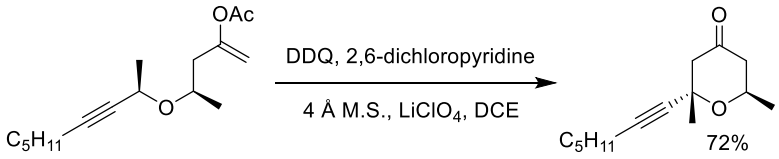
room temperature and accommodate a wide scope of substrates, such as benzyl ethers,[30b,30l] allylic ethers,[30d,30e,30f,30n] and propargylic ethers.[30d,30e,30o]



Allylic ether example:

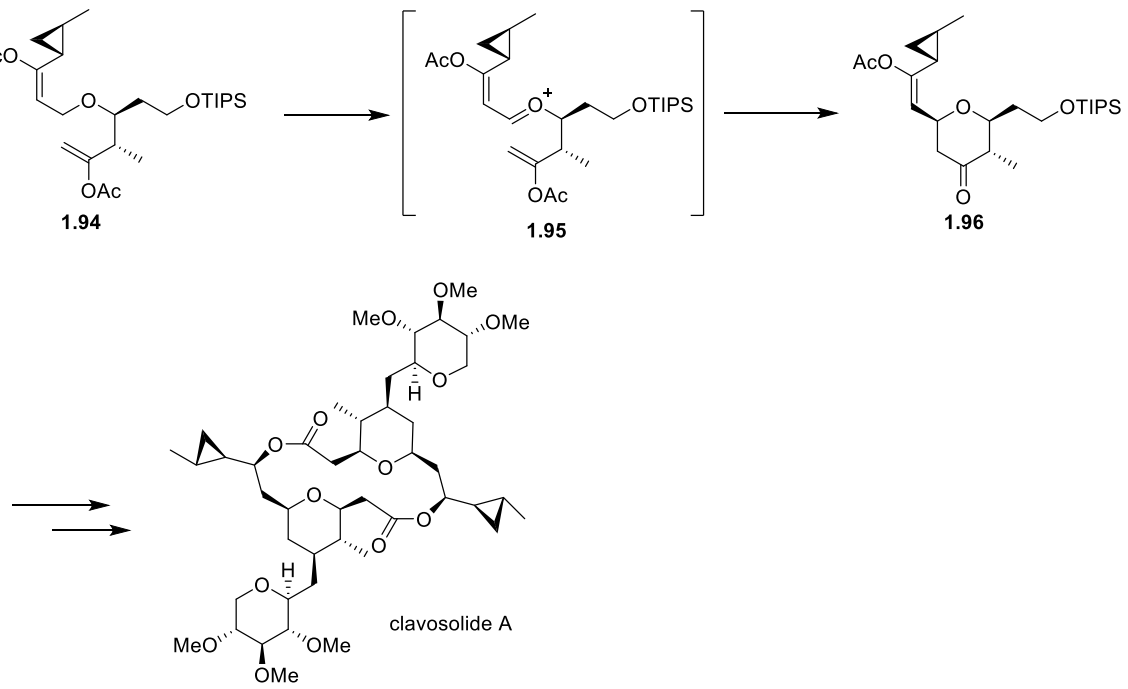


Propargylic ether example:



Scheme 1-23. C–H bond activation by DDQ oxidation

Dr. Peh has successfully applied this DDQ-activated C–H functionalization to the total synthesis of clavosolide A (Scheme 1-24).[30n] This sequence is highlighted by the oxidative generation of vinylogous cyclopropyl carbinyl cation **1.95**, which is considered to be acid-labile and will undergo a ring-opening process in the presence of Lewis acids. However, under the mild DDQ-mediated neutral environment, oxocarbenium ion **1.95** is sufficiently stable to furnish THP **1.96**.



Scheme 1-24. Dr. Peh's synthesis of clavosolide A

2.0 SYNTHESIS OF MACROLACTONES BEARING BRIDGED 2,6-*TRANS*-TETRAHYDROPYRANS THROUGH OXIDATIVE C–H BOND ACTIVATION

2.1 INTRODUCTION

Macrolides occupy a significant portion of biologically important natural products and pharmaceuticals.[33] The structural diversities of macrolides, which are brought by various types of substructures on the large rings, induce the great interest among chemists to explore accesses toward these molecules. 2,6-*trans*-Disubstituted tetrahydropyrans (THPs) are commonly present in many bioactive macrolides (Figure 2-1).[34] However, synthetic approaches to these *trans*-THP-contained macrolides are limited due to the challenges introduced by the thermodynamically unfavored *trans*-THPs. A frequently used strategy is to construct the *trans*-THP fragments through known methodologies before the macrolactonization. One representative example of this protocol is illustrated in Floreancig group's formal synthesis of leucascandrolide A (Scheme 2-1).[35]

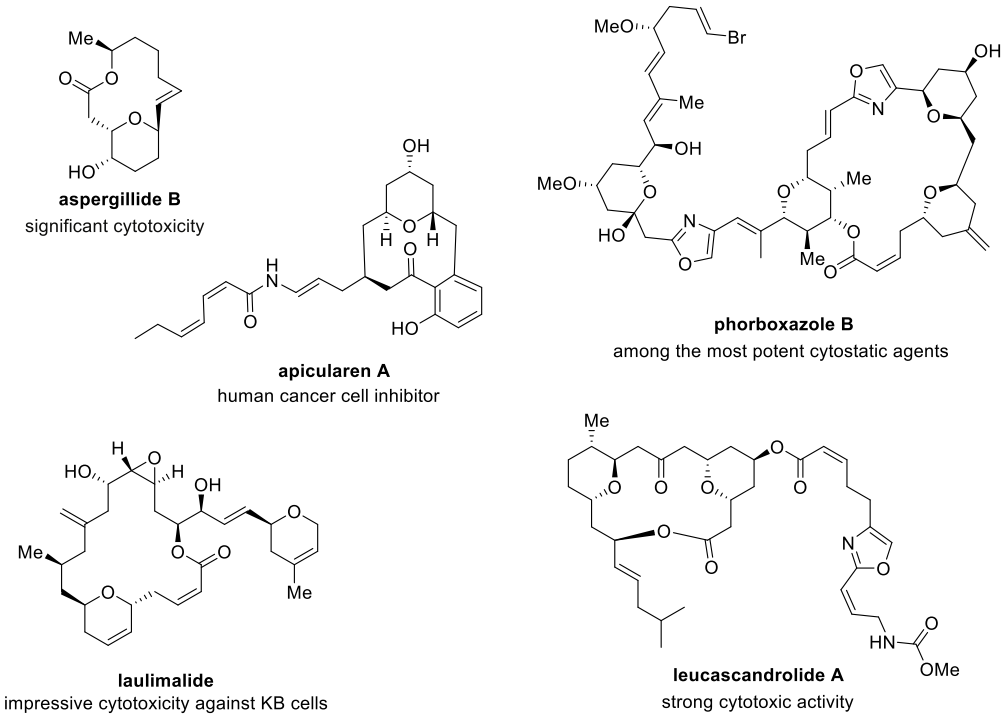
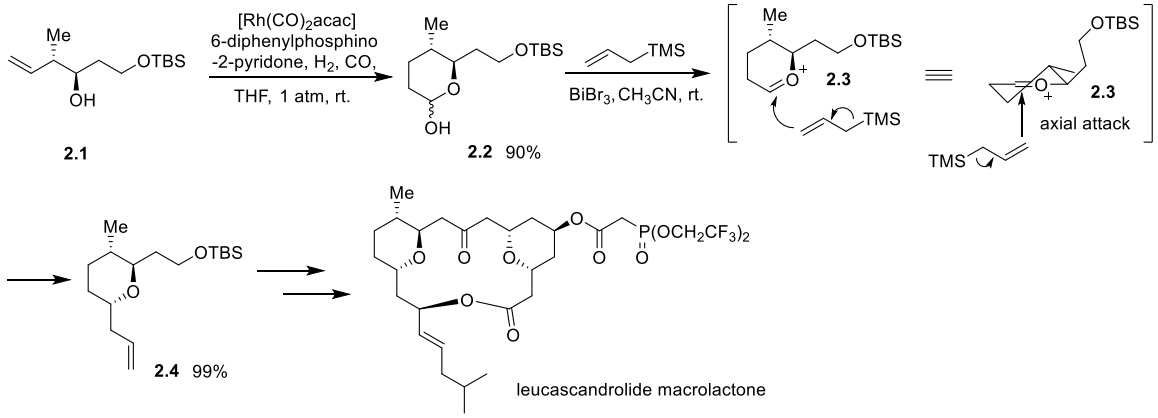


Figure 2-1. Examples if bioactive macrolides bearing bridged 2,6-*trans*-THPs

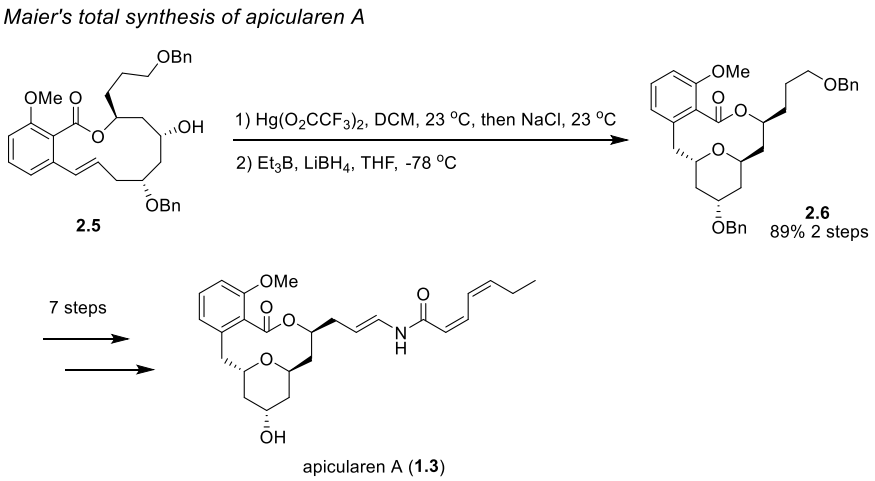


Scheme 2-1. Floreanicg group's formal synthesis of leucascandrolide A

In this synthesis, the *trans*-THP fragment **2.4** was accessed from homoallylic alcohol **2.1**, which underwent a tandem hydroformylation/THP ring cyclization to afford THP **2.2** with a stereochemically undefined acetal carbon. The following dehydration proceeded smoothly with

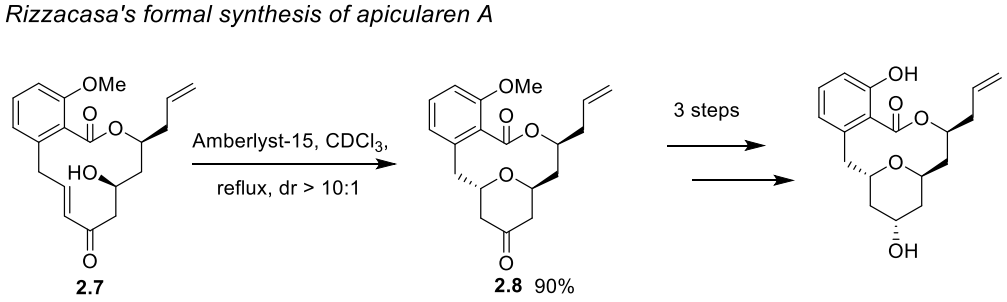
the assistance of strong Lewis acid, bismuth(III) bromide, to yield key oxocarbenium ion **2.3**. The allytrimethylsilane preferred an axial attack to this newly formed carbocation, thus yielded 2,6-*trans*-disubstituted THP **2.4** as single stereoisomer in nearly quantitative yield. Later, a rhenium(VII) oxide-catalyzed macrolactonization confined this *trans*-THP subunit on the macrocycle of leucascandrolide A.

Alternatively, transannular cyclization is a promising but barely developed protocol for direct formation of bridged 2,6-*trans*-disubstituted THPs on macrocyclic scaffolds.[36] In 2004, the Maier group and the Rizzacasa group independently showed two different transannular cyclization reactions during their synthesis towards the natural product, apicularen A.[37] In Maier's route, the macrocyclic *trans*-THP **2.6** was constructed by a mercuric trifluoroacetate-promoted transannular cyclization across the 12-membered macrolactone **2.5** (Scheme 2-2).[37a] The high *trans*-selectivity in this reaction is attributed to the transition state of the kinetically controlled cyclization being product-like, thus leading to the less strained product.



Scheme 2-2. Maier's total synthesis of apicularen A

Rizzacasa's transannular cyclization relied on the assistance of Amberlyst-15, which promoted the cyclization of enone **2.7** and distereoselectively delivered the *trans*-THP **2.8** in 90% yield (dr >10:1) (Scheme 2-3).[37b] Interestingly, both *trans*- and *cis*-THP products were formed at the initial stage, but the *cis*-isomer converted to the *trans*-isomer after 18 hours.



Scheme 2-3. Rizzacasa's formal synthesis of apicularen A

The *trans*-THP products are rarely observed during the Floreancig group's previous studies on THP synthesis through the oxidative carbon–hydrogen (C–H) bond or carbon–carbon (C–C) bond functionalization reactions.[30] This is ascribed to the significant energy gap between the (*E*)-geometry oxocarbenium ion and (*Z*)-geometry oxocarbenium ion, which are the *cis*-THP precursor and *trans*-THP precursor respectively (Figure 2-2).[38]

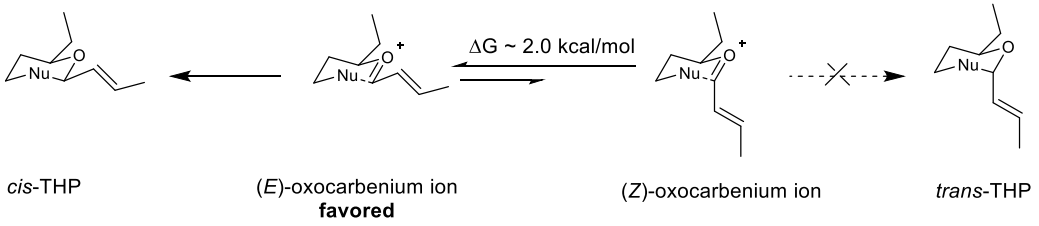
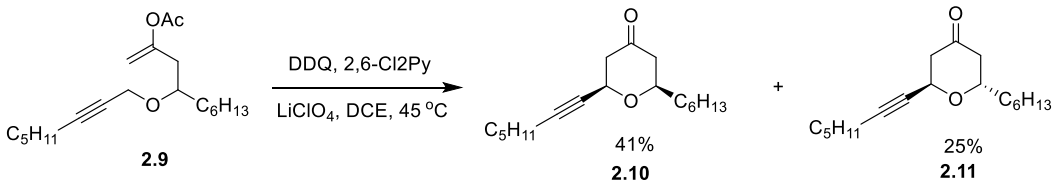


Figure 2-2. Energy gap between (*E*) and (*Z*)-geometry oxocarbenium ions

However, a significant percent yield of *trans*-THP **2.11** was observed by Dr. Liu when he was examining the propargylic ether **2.9** in the DDQ-mediated C–H bond activation reaction

(Scheme 2-4).[30d] In this process, the energetic difference between the (*E*)- and (*Z*)-oxocarbenium ions is expected to be minimized by the sterically undemanding nature of the alkynyl group, which explains the 25% isolated yield of **2.11** (Figure 2-3).



Scheme 2-4. Dr. Liu's observation of the *trans*-THP product through DDQ oxidation

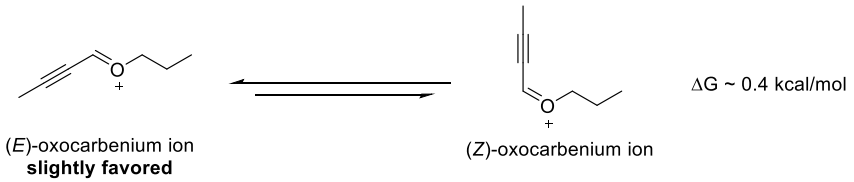


Figure 2-3. Explanation for the observation of *trans*-THP

This observation inspired us to make an assumption that, for certain tether lengths, the geometric constraints of macrocyclic oxocarbenium ions could coerce alkynyl substitutents to adapt an axial orientation, which leads to producing the desired *trans*-THP containing bicyclic products (Figure 2-4). This chapter will demonstrate this assumption by employing DDQ as the oxidant and the macrocycles with appending nucleophiles as substrates.

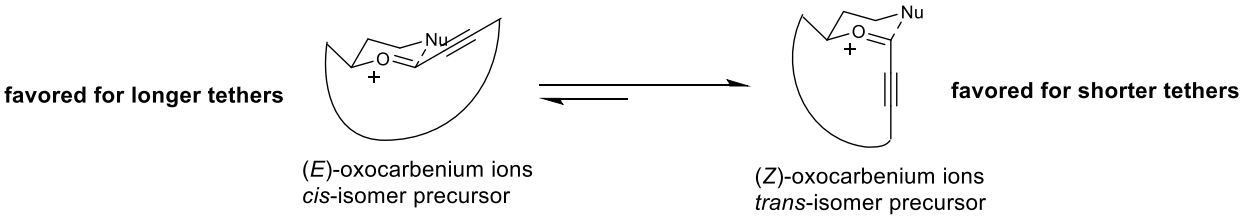


Figure 2-4. Our strategy to access the *trans*-THP in the macrocyclic system

2.2 SUBSTRATE PREPARATION

Three general types of substrates (Figure 2-5) were proposed for the investigation of the oxidative transannular cyclization. Acyclic Type I substrates (**2.12** to **2.14**) were designed for detailed studies of the effect of alkynyl groups in DDQ-mediated C–H bond cleavage reactions. Type II substrates (**2.15** to **2.19**) were macrocyclic benzylic and allylic ethers bearing alkynyl groups for testing the *trans*-THP-oriented strategy. Type III macrocycles (**2.20** to **2.25**) were relatively inert propargylic ethers for exploring the scope of the oxidative transannular cyclization.

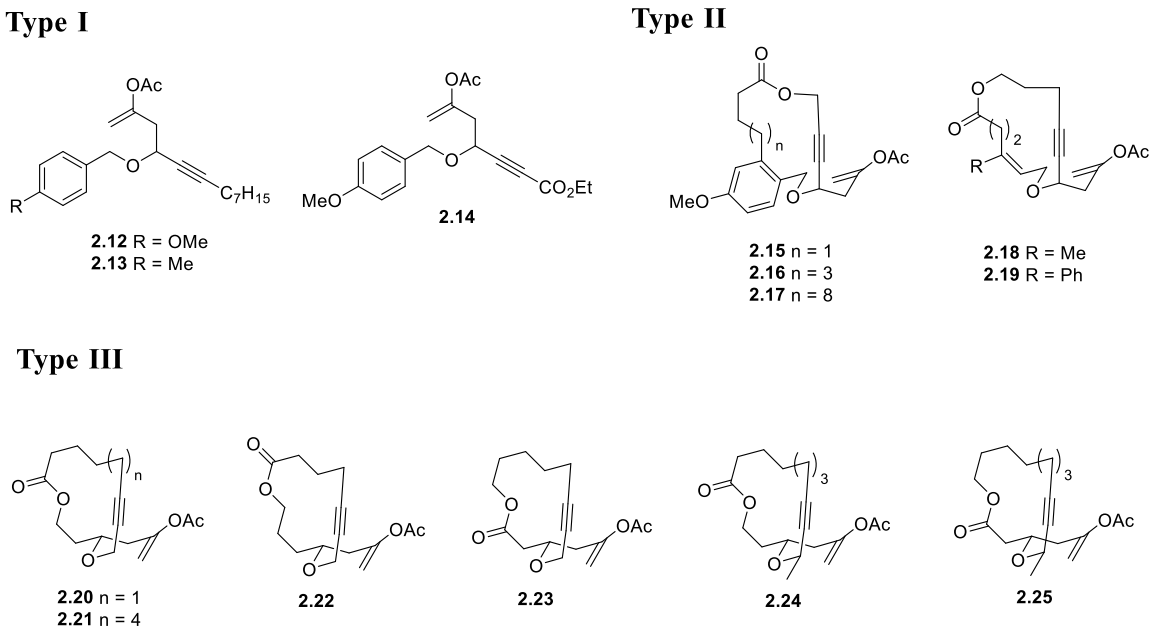
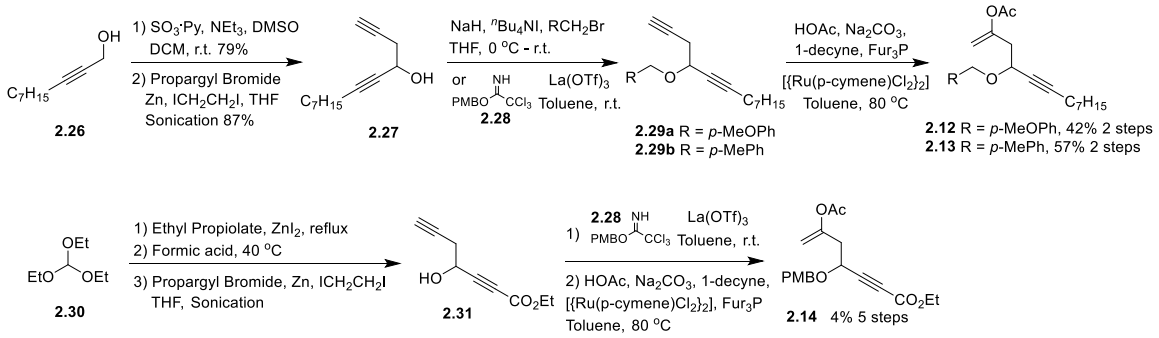


Figure 2-5. Three types of proposed substrates

Benzylic ethers **2.12** and **2.13** were accessed from propargylic alcohol **2.26** (Scheme 2-5). This primary alcohol was converted to secondary alcohol **2.27** through a sequential Parikh-Doering oxidation[39] and a sonochemical Barbier-type reaction.[40] A $La(OTf)_3$-catalyzed etherification[41] and a Williamson etherification[42] were employed to convert **2.27** to ether **2.29a** and **2.29b** respectively.

A ruthenium(II)-catalyzed enol acetate formation[43] furnished the desired substrates from ethers **2.29** in moderate yields.

The preparation of **2.14** was initiated by forming an acetal intermediate through refluxing triethyl orthoformate and ethyl propiolate with a catalytic amount of ZnI_2 (Scheme 2-5).[44] This newly generated acetal was deprotected by formic acid and followed by a sonochemical reaction to give homopropargyl alcohol **2.31**, which was subjected to sucessive $La(OTf)_3$-catalyzed etherification and enol acetate formation to yield substrate **2.14**.

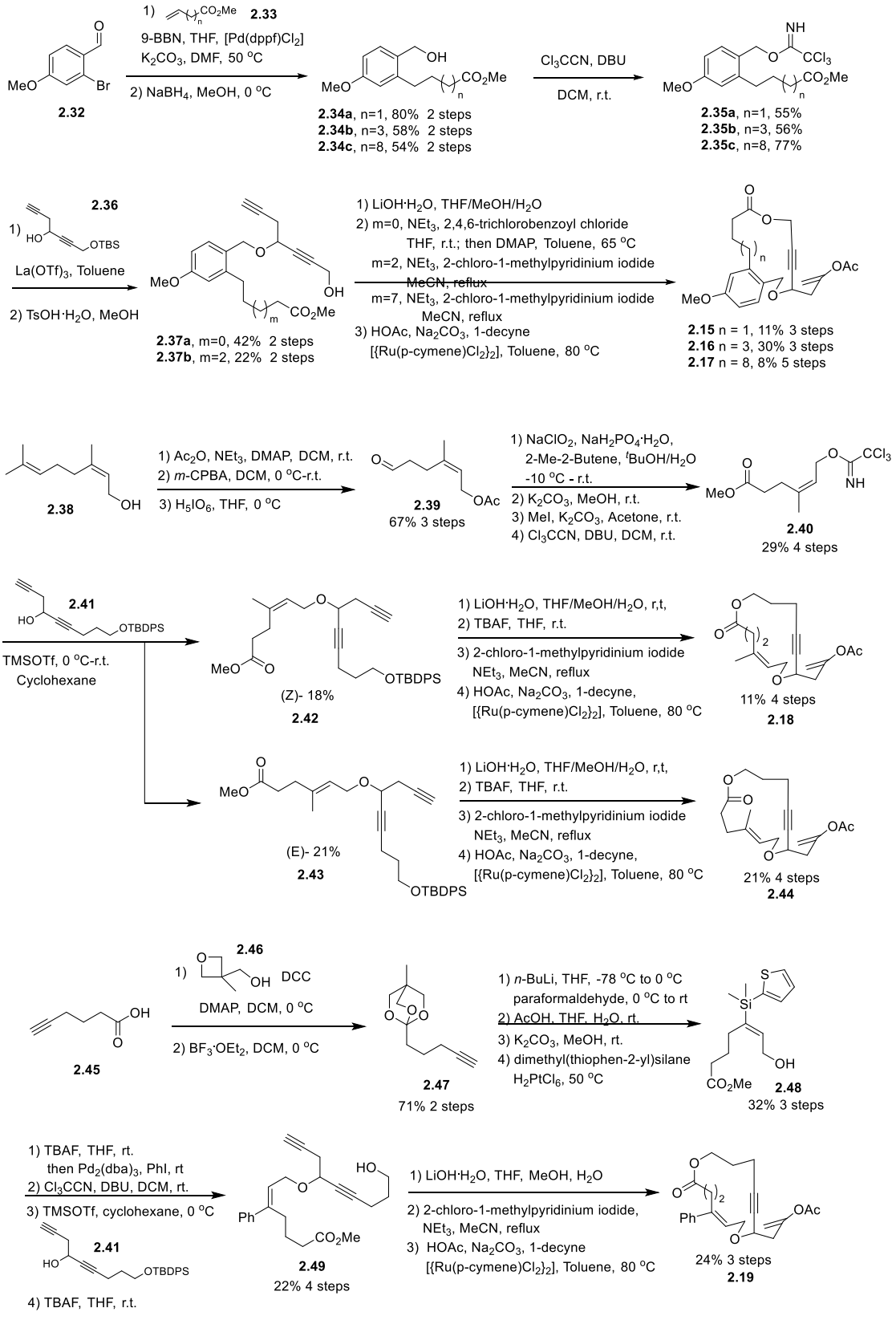


Scheme 2-5. Synthesis of Type I substrates

The synthesis of substrates **2.15**, **2.16** and **2.17** shared a similar route as shown in Scheme 2-6. Suzuki coupling[45] between the known aldehyde **2.32** and esters **2.33** afforded the *ortho*-substituted anisaldehydes, which were reduced by $NaBH_4$ to give benzyl alcohols **2.34**. These benzyl alcohols were treated with Cl_3CCN and DBU to yield trichloroacetimidates **2.35**, followed by $La(OTf)_3$-promoted etherification and desilylation to afford the macrolactonization precursors **2.37**. After hydrolysis, the carboxylic acid from ester **2.37a** was subjected to a Yamaguchi macrolactonization[46] and enol acetate formation successively to yield the marcocycle **2.15** in fair yield. Considering the low efficiency of Yamaguchi macrolactionization, we turned to the Mukaiyama protocol,[47] which led to a significant improvement of the yields.

The (*Z*)-configured alkenyl group on macrocycle was accessed by taking advantage of natural extract, nerol (**2.38**), which was converted to aldehyde **2.39** through acetylation, epoxidation, and oxidation procedures (Scheme 2-6).[48] Subsequently, aldehyde **2.39** was further oxidized to the carboxylic acid, which was esterified with iodomethane after a deacetylation. The union of trichloroacetimidate **2.40** and fragment **2.41** was catalyzed by TMSOTf to produce both (*Z*)-allylic ether **2.42** and (*E*)-allylic ether **2.43**. These two isomers were subjected to the regular macrolactone formation sequence and enol acetate formation reaction to deliver the desired substrate **2.18** and its *E*-isomer **2.44**.

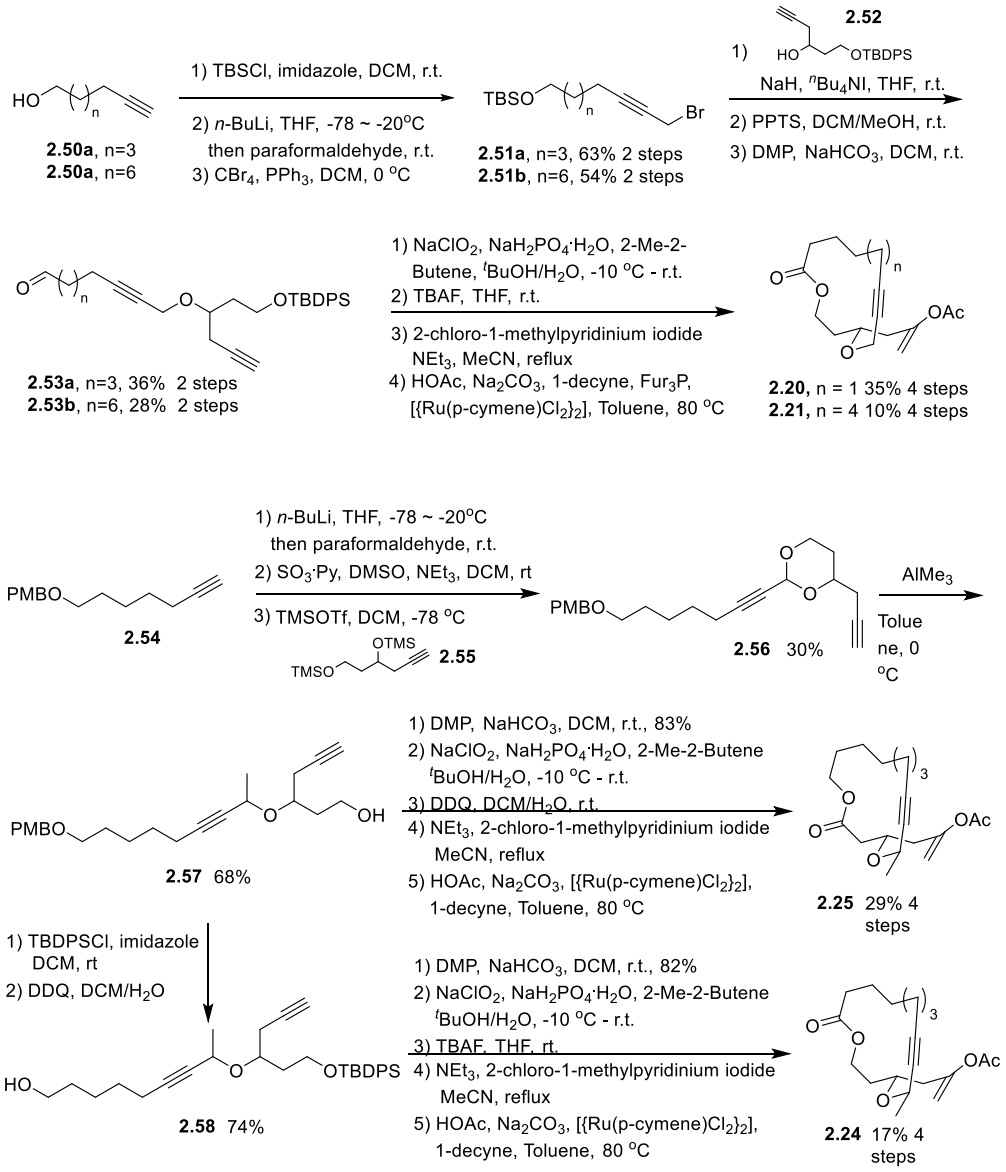
The preparation of the phenyl-substituted allylic ether **2.19** began with a carboxylic acid protection protocol that would facilitate the following homologation process (Scheme 2-6). The homologation product underwent the carboxylic acid deprotection, methylation, and hydrosilylation successively to form vinylsilane **2.48**, which was subjected to the Hiyama coupling[49] in the presence of iodobenzene. The resulting vinylphenyl intermediate was converted to the trichloroacetimidate and coupled with fragment **2.41**, followed by a TBAF-promoted desilylation to furnish the macrolactonization precursor **2.49**. Mukaiyama macrolactonization and enol acetate formation completed the synthesis of **2.19**.



Scheme 2-6. Synthesis of Type II substrates

The assemblies of substrates **2.20** and **2.21** shared the same route (Scheme 2-7). Alcohols **2.50** were converted into propargyl bromides **2.51** in good yields by successive alcohol protection, homologation, and bromination. The Williamson ether synthesis was utilized to couple the bromides **2.51** with homopropargyl alcohol **2.52**, followed by selective desilylation and Dess-Martin oxidation[50] to afford aldehydes **2.53**. The syntheses of substrates **2.20** and **2.21** were achieved after a mild oxidation, desilylation, Mukaiyama macrolactonization, and enol acetate formation. Substrates **2.22** and **2.23** shared a similar synthetic sequence with **2.20** and **2.21**, except for some minor modifications of the starting materials. During the synthesis of **2.22**, **2.50a** and **2.52** were replaced by but-3-yn-1-ol and 7-((*tert*-butyldiphenylsilyl)oxy)hept-1-yn-4-ol. During the synthesis of **2.23**, the primary alcohol of **2.51a** was protected with TBDPS instead of TBS, and the secondary alcohol of **2.52** was protected with TBS instead of TBDPS.

The synthetic sequences for substrates **2.24** and **2.25** are shown in Scheme 2-7, which are highlighted by the $AlMe_3$-promoted methylation of the cyclic acetal **2.56**.[51] The methylated product **2.57** was converted to substrates **2.24** and **2.25** after several functional group manipulations, macrolactonization, and enol acetate formation.

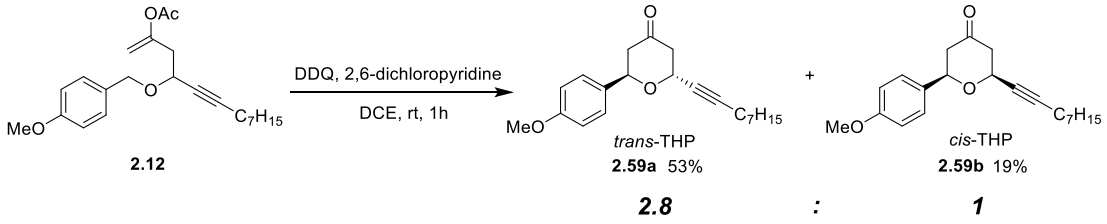


Scheme 2-7. Synthesis of Type III substrates

2.3 RESULTS AND DISCUSSION

p-Methoxybenzylic ether **2.12** was treated with DDQ in 1,2-dichloroethane (DCE) at room temperature. The reaction went to completion in one hour as expected, and it furnished a mixture

of *trans*- and *cis*-THPs with a surprising ratio of nearly three to one of *trans*-THP **2.59a** to *cis*-THP **2.59b** (Scheme 2-8).



Scheme 2-8. DDQ-mediated oxidation of *p*-methoxybenzylic ether **2.12**

The initial results strongly demonstrated that the alkynyl groups are able to adapt the axial orientation in the oxocarbenium ion transition state. Moreover, an electrostatic interaction between the π-electrons of the alkynyl group and the partially positive charged hydrogen at the α-position of the ether is proposed to promote the *trans*-stereochemical selectivity (Figure 2-6).[52] This electrostatic model is validated by the performance of different benzylic ether analogs and solvents in the DDQ oxidative cyclization (Table 2-1).

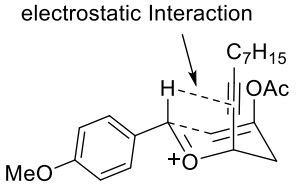
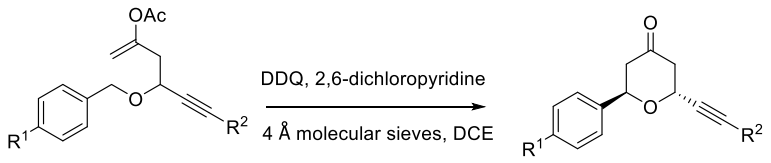


Figure 2-6. The hypothesized electrostatic interaction during the transition state

Table 2-1. Investigation of the electronic effects[a]



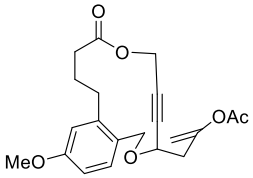
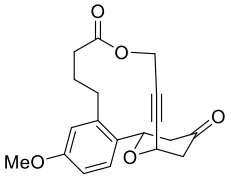
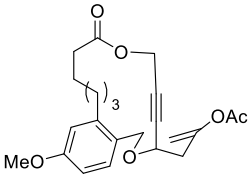
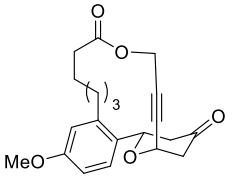
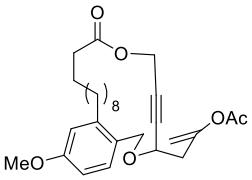
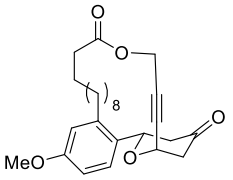
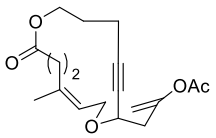
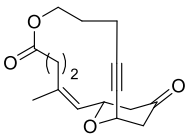
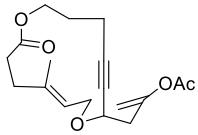
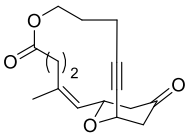
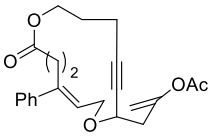
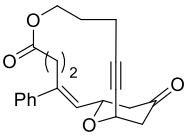
entry	substrate	R^1	R^2	product	solvent	ratio[b] (*trans*/*cis*)	yield[c] (%)
1	**2.12**	OMe	C_7H_{15}	**2.59**	DCE	2.8/1	72
2	**2.13**	Me	C_7H_{15}	**2.60**	DCE	3.3/1	72
3	**2.14**	OMe	CO_2Et	**2.61**	DCE	1.6/1	45
4	**2.12**	OMe	C_7H_{15}	**2.59**	CH_3NO_2	1.6/1	50

a). Representative procedure: DDQ (2 eq.), 4 Å molecular sieves and 2,6-dichloropyridine (4 eq.) were added to a solution of substrate in solvent (0.1 M) at rt. The resulting mixture was stirred at rt. b). Ratio is based on ^{1}H NMR integral of characteristic peak. c). Both of *trans* and *cis* products are included.

A slight increase of the *trans*-selectivity was observed through replacing the *para*-substitution of arene from methoxyl group to methyl group (entry 1 *vs* entry 2). It is reasoned that the weaker electron-donating nature of methyl group destabilizes the intermediate cation. This destabilization increases the partial positive charge on the α-hydrogen in the electrostatic model and results a stronger interaction between the α-hydrogen and π-electrons. A reduction of the *trans*-selectivity was expected for the cyclization of ester **2.14** (entry 3). The terminal electron-withdrawing group of the alkynyl group lowers the π-electron density, and thus decreases its ability to participate in the electrostatic interaction. In addition, when the reaction was conducted in the polar solvent nitromethane instead of DCE, the *trans*-selectivity diminished (entry 4). It is attributed to that the increase in attractive interaction between the α-hydrogen and solvent weakens the electrostatic interaction between the α-hydrogen and π-electrons, which is an additional support for our proposed electrostatic model.

The preference for the axial orientation of the alkynyl groups was confirmed, which strongly encouraged us to move the pursuit of *trans*-selectivity forward to the macrocyclic substrates. The initial results are shown in Table 2-2. To our delight, *p*-methoxybenzylic ether **2.17** underwent DDQ-mediated transannular cyclization smoothly at room temperature and afforded the desired 2,6-*trans*-disubstituted-THP **2.65** as a single diastereomer in 72% yield (entry 1). Higher substrate reactivity was observed when the *p*-methoxybenzylic ether analogs with longer tether lengths were subjected to the cyclization reaction (entries 2 and 3). This is attributed to the reduction of strain in these macrocyclic systems, which stabilizes the intermediate oxocarbenium ions.[53] Interestingly, the 2,6-*cis*-isomer was observed as a minor product in the reaction of the 20-membered ring substrate **2.19** (entry 2). This is consistent with the initial *trans*-selectivity-oriented strategy shown in Figure 2-4. The allylic ethers were also effective substrates for the DDQ oxidation. All of them can be cyclized at room temperature to furnish the *trans*-THPs as single diastereomers (entries 4 to 6). However, the reaction rates vary significantly based on the substrate oxidation potentials and the stability of the intermediate cations.[54] Due to the higher oxidation potential of allylic ethers than *p*-methoxybenzylic ethers, substrate **2.18** exhibited a much slower rate and yield **2.65** (entry 4). Its corresponding *E*-isomer **2.44** produced the same product as the only diastereomer with slower reaction rate (entry 5), which is ascribed to the strain-induced destabilization of the intermediate cation. Moreover, the product configuration of isomer **2.44** also suggests that the rotation of the π-bonds is facile in oxocarbenium ions. The addition of an oxocarbenium ion-stabilizing group, such as a phenyl group, on the alkene elevated the reaction rate dramatically (entry 6).

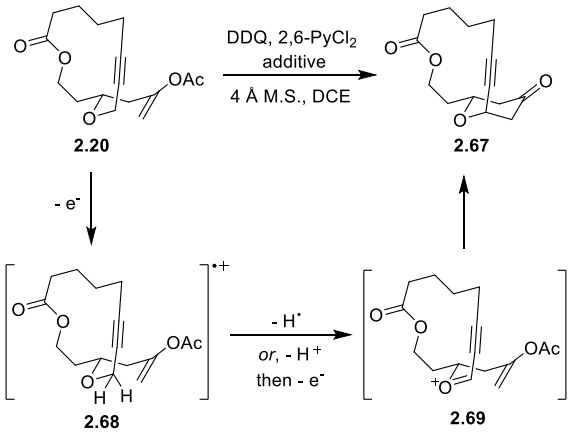
Table 2-2. Synthesis of the macrolactions bearing bridged 2,6-*trans*-disubstituted THPs[a]

entry	substrate	ring size	time (h)	product	yield[b] (%)
1	 **2.15**	13	4	 **2.62**	72
2	 **2.16**	15	1	 **2.63**	81
3	 **2.17**	20	0.67	 **2.64**	65 (dr = 6:1)[c]
4	 **2.18**	14	26	 **2.65**	54
5	 **2.44**	14	43	 **2.65**	35
6	 **2.19**	14	0.25	 **2.66**	72

a).Representative procedure: DDQ (2 to 3 eq.), 4 Å molecular sieves, 2,6-dichloropyridine (4 eq.) and $LiClO_4$ (0.2 eq.) were added to a solution of substrate in DCE (0.1 M) at rt. The resulting mixture was stirred at rt. *b*). Combined yield of diastereomers. *c*). Determined by ^1H NMR integral of characteristic peak.

Encouraged by the success of the cyclizations of benzylic and allylic ethers, the substrate scope exploration was expanded to the propargylic ethers that exhibited lower reactivity in the DDQ oxidation (Table 2-3).

Table 2-3. DDQ-mediated cyclization of macrocyclic substrate **2.20**[a]



entry	additive	temperature	time	yield (%)
1	N/A	50 ºC	62h	30
2[b]	$LiClO_4$	50 ºC	62h	36
3	$LiClO_4$	reflux	18h	9
4[c]	$LiClO_4$	r.t.	31d	28

a). Representative procedure: DDQ (4 to 8 eq.), 4 Å molecular sieves, additive and 2,6-dichloropyridine (4 eq.) were added to a solution of **2.20** in DCE (0.1 M) at rt. The resulting mixture was stirred at appropriate temperature. *b*).The starting material beared a 3.5/1 ratio of substrate **2.20**/enol acetate regioisomer and the yield is based on the purity of starting material.*c*).The starting material beared a 4/1 ratio of substrate **2.20**/enol acetate regioisom. The yield is based on the purity of starting material.

Macrocycle **2.20** was subjected to the oxidative cyclization at 50 °C with four equivalents of DDQ. After a prolonged period (62 hours), **2.20** was fully consumed and afford 2,6-*trans*-disubstituted THP **2.67** in 30% yield as single diastereomer (entry 1). The structure and stereochemistry of **2.67** were confirmed by single crystal diffraction (Figure 2-7). No by-product was collected from this reaction, which hints that the modest yield could be attributed to nonspecific decomposition of carbocations rather than the overoxidation. The addition of lithium perchlorate slightly improved the reaction yield (entry 2), which is explained by the formation of a more electrophilic carbocation-perchlorate ion-pair.[26b] Higher temperatures significantly shortened the reaction time, but diminished the reaction yield (entry 3). A slightly lower yield was obtained after one-month stirring of the reaction at room temperature (entry 4).

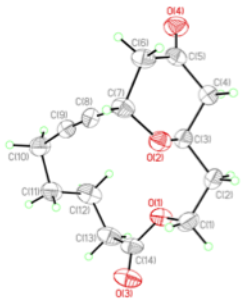


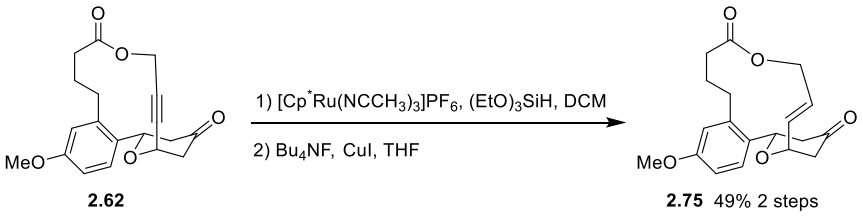
Figure 2-7. Single crystal diffraction of 2,6-*trans*-disubstituted THP **2.67**

The low reactivity of proparylic ether **2.20** in the DDQ oxidation can be attributed to two reasons: 1) The relatively higher oxidation potentials of alkynes make the proparylic substrates more resistant to losing electrons than corresponding benzylic and allylic substrates. 2) The macrocyclic constrains limit radical cation **2.68** from adopting a coplanar geometry of the alkynyl π-system, C-H bond at α-position of ether, and the lone electron pair on the ether oxygen atom, which slows down the oxocarbenium formation.[32]

The scope of propargylic substrates was explored and shown in Table 2-4. As we observed in Table 2-2, the substrate with longer tether length exhibits higher reactivity. Compare to substrate **2.20**, the 16-membered macrocycle **2.21** underwent the oxidative transannular cyclization at lower temperature and rendered THP products in a higher yield, in which the *cis*-isomer was present as minor product (entries 1 and 2). Moving the lactone group one carbon away from the oxocarbenium ion did not bring about any visible impact to either reactivity or yield (entry 1 *vs* entry 3). However, a significant reactivity reduction was observed when the carbonyl group of the lactone was moved closer to the oxocarbenium ion (entry 1 vs entry 4, entry 5 *vs* entry 6). It was interpreted that the carbonyl group has a greater contribution to intermediate carbocation destabilization compared to the oxygen atom. The methyl groups at α-position of ethers are

proposed to provide stabilization impact to the intermediate oxocarbenium ions. Therefore, tertiary ethers **2.22** and **2.23** reacted at lower temperature in this oxidation reaction than other substrates and but afforded the desired *trans*-THPs with similar yields (entries 5 and 6).

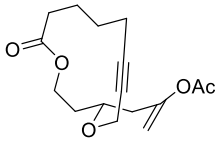
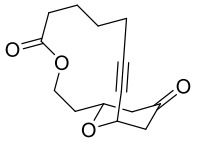
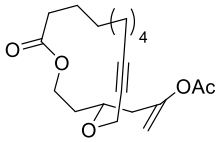
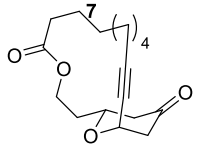
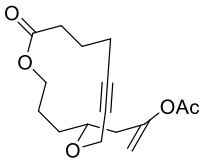
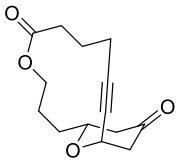
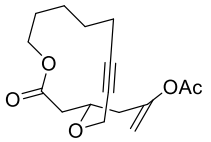
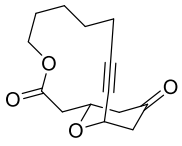
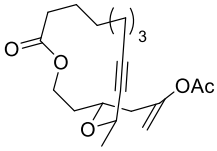
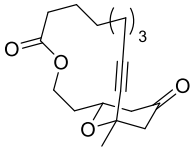
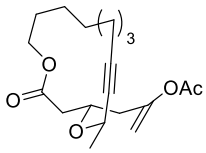
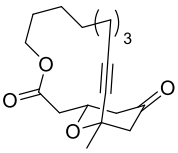
Although alkynyl groups rarely appear in the macrolides, they are able to accept versatile functionalizations and be subjected to diversity-oriented synthesis. Herein, we provided a "formal *E*-selective hydrogenation" example to demonstrate the utilities of the alkyne-contained macrocycles. Alkyne **2.62** underwent a hydrosilylation/desilylation-based reduction[55] sequence to access the synthetically challenging (*E*)-alkene **2.75** in 49% yield.



2.62 **2.75** 49% 2 steps

Scheme 2-9. (*E*)-selective formal hydrogenation of macrocyclic alkyne

Table 2-4. Examination of the macrocyclic propargylic ethers in DDQ-mediated cyclization[a]

entry	substrate	ring size	temp	time (h)	product	yield[b] (%)
1	 **2.20**	13	50 ºC	62	 **2.67**	36
2	 **2.21**	16	40 ºC	60	 **2.70**	46 (dr = 2:1)[c]
3	 **2.22**	13	40 ºC	77	 **2.71**	36
4[d]	 **2.23**	13	50 ºC	192	 **2.72**	24
5	 **2.24**	15	30 ºC	48	 **2.73**	40
6	 **2.25**	15	30 ºC	96	 **2.74**	39

a).Representative procedure: DDQ (4 to 8 eq.), 4 Å molecular sieves, 2,6-dichloropyridine (4 eq.) and $LiClO_4$ (0.2 eq.) were added to a solution of substrate in DCE (0.1 M) at rt. The resulting mixture was stirred at rt. *b*). Combined yield of diastereomers. *c*). Determined by ^1H NMR integral of characteristic peak.*d*) 8 eq. DDQ was employed.

2.4 SUMMARY

Bridged 2,6-*trans*-disubstituted THPs were synthesized through the DDQ-promoted transannular cyclization reactions in macrocyclic systems. The excellent stereoselectivity of this reaction is ascribed to ring strains that coerce the sterically undemanding alkynyl groups to adapt axial orientations in the intermediate oxocarbenium ions. Macrocyclic benzylic, allylic, and propargylic substrates were examined. Although all of them produced the desired *trans*-THPs as major or single diastereomers, the reactivities were quite different. The benzylic and allylic ethers were highly reactive and produced the *trans*-THPs in good to excellent yields under mild conditions. Interestingly, the alkynyl groups in this type of substrates exhibited an electrostatic interaction with the α-hydrogen of oxocarbenium ions, which further favored the axial orientation of the alkynyl groups. The macrocyclic propargylic ethers were quite inert toward DDQ oxidation. Harsher reaction conditions were employed to furnish the *trans*-THPs in significantly lower yields compared to the benzylic and allylic ethers. In addition, the high functionalization potential of the alkynyl groups enable the transannular cyclization products to be extremely useful intermediates for the preparation of a number of compounds.

3.0 ONE-POT STRATEGY FOR SPIROKETAL SYNTHESIS

3.1 INTRODUCTION

Spiroketals are abundant in numerous biologically important natural products (Figure 3-1).[56] In the past decades, a significant number of approaches have been developed for both target- and diversity-oriented spiroketal syntheses.[57] These methods can be classified into two general categories: 1) a cascade process that cyclizes a functionalized linear molecule in the presence of Brønsted or Lewis acids;[58] 2) a stepwise protocol that constructs the two rings of a spiroketal separately.[59] Several examples are briefly discussed below.

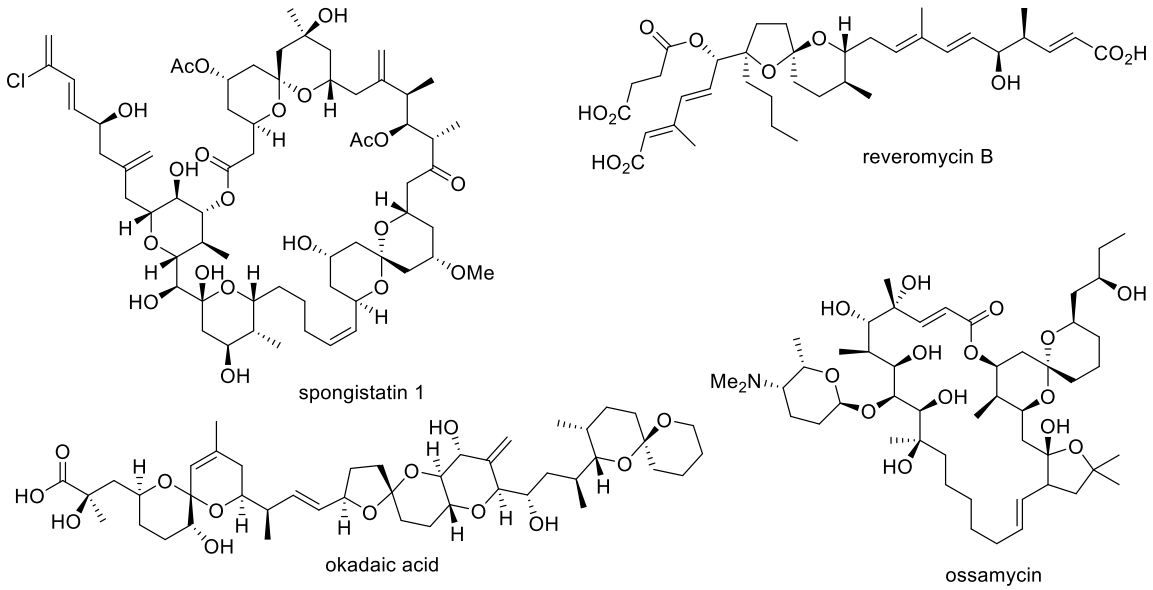
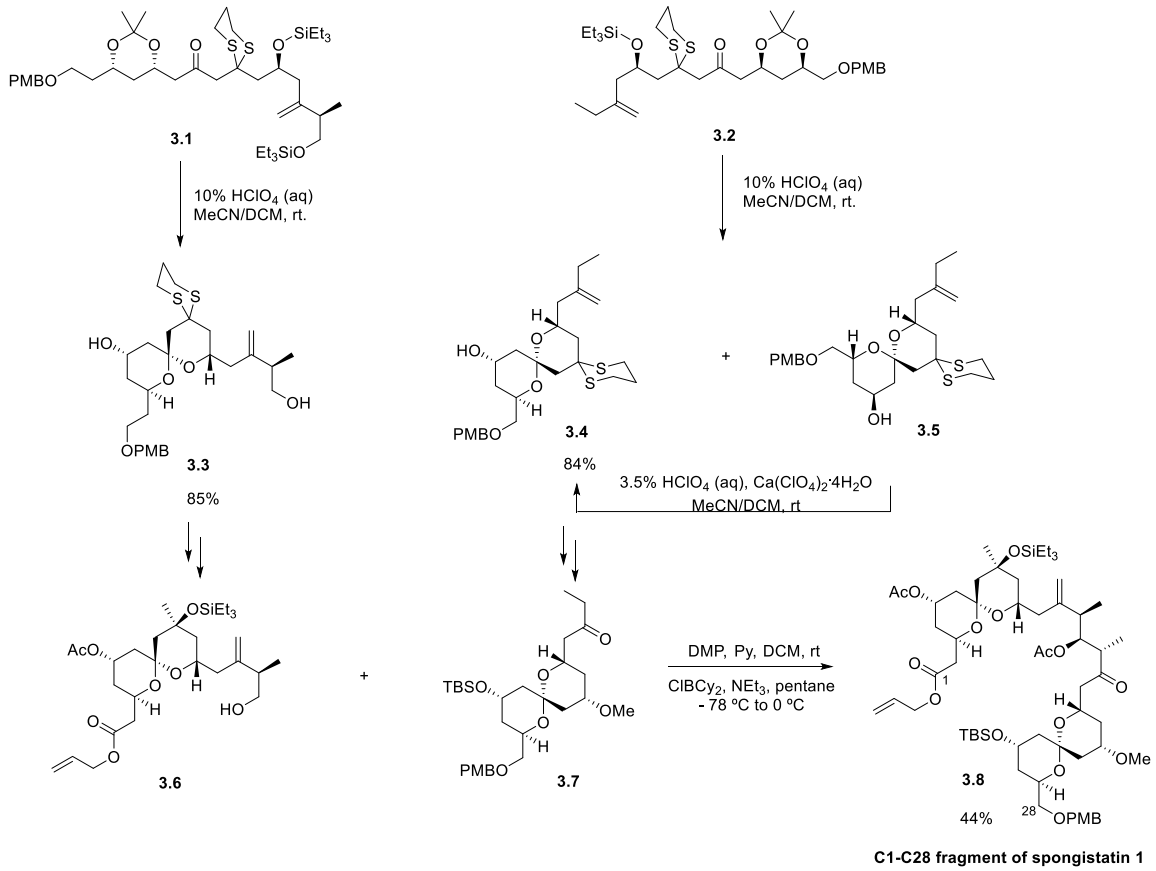


Figure 3-1. Selected natural products that contain spiroketal substructures

3.1.1 Cascade Cyclization of Functionalized Linear Molecules

As the most common spiroketal precursors, dihydroxyketones can be easily converted to spiroketals through an acid-catalyzed dehydrative cyclization. Ley and co-workers illustrated this method during the synthesis of the C1-C28 fragment **3.8** of the natural product, spongistatin 1 (Scheme 3-1).[60] Both of the spiroketal scaffolds with different configurations in **3.8** were constructed from β-ketodithianes in the presence of perchloric acid. β-Ketodithiane **3.1** produced the double-anomerically stabilized spiroketal **3.3** smoothly as a single diastereomer in excellent yield. Whereas the dehydrative cyclization of β-ketodithiane **3.2** yielded a mixture of the desired partially anomerically stabilized spiroketal **3.4** and its stereoisomer **3.5** in a ratio of 1:4. Based on Smith's protocol, the distribution of **3.4** and **3.5** can be re-equilibrated as a 2.2:1 mixture in favor of **3.4** with the assistance of Ca^{2+} ions.[61] Thus, spiroketal **3.4** was collected in 84% yield after three rounds of the calcium(II)-catalyzed epimerization. Moreover, the 1,3-dithiane units are crucial to the spiroketalizations. The corresponding 1,3-dione performed capriciously in this spiroketalization reaction.

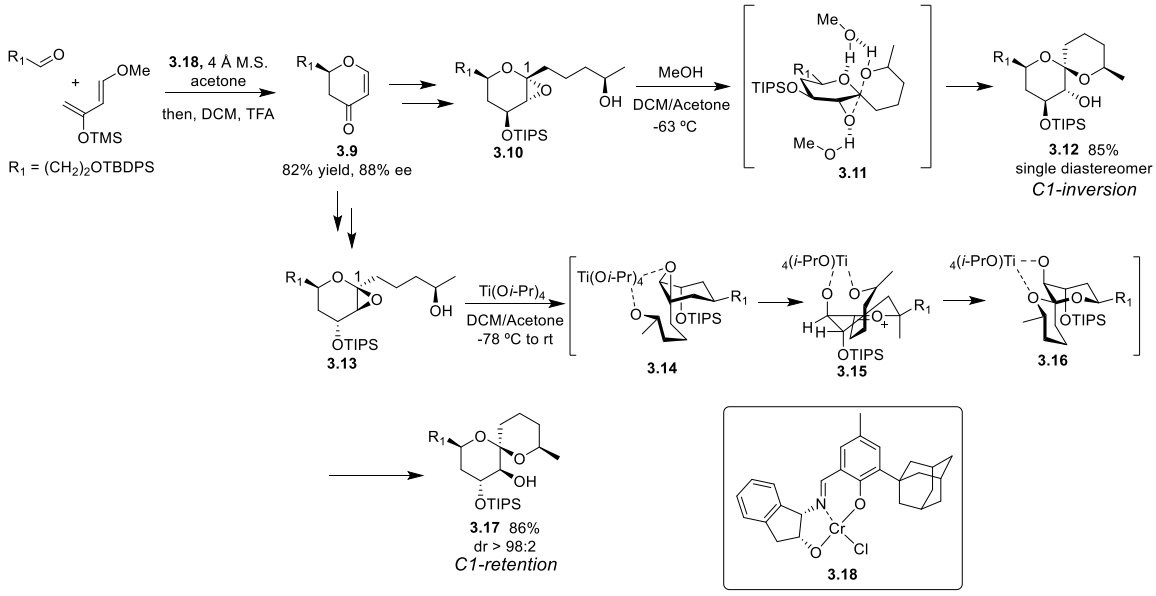


Scheme 3-1. Ley's synthesis of the C1-C28 fragment of spongistatin 1

3.1.2 Stepwise Protocol for Spiroketal Formation

Compared to the one-step spiroketalization approach, the stepwise protocol can assemble the two rings of spiroketals through different cyclization methods, which enables a wider scope of spiroketals to be synthetically accessible. Tan and co-workers developed a spirocyclization reaction to kinetically control the configurations of the spiroketal products (Scheme 3-2).[62] Their construction of spiroketals began with an asymmetric hetero-Diels-Alder (HDA) reaction that stereoselectively formed the first ring **3.9**. After several modifications on **3.9**, the resulting epoxides **3.10** and **3.13** underwent a methanol-induced or Lewis acid-catalyzed epoxide ring-

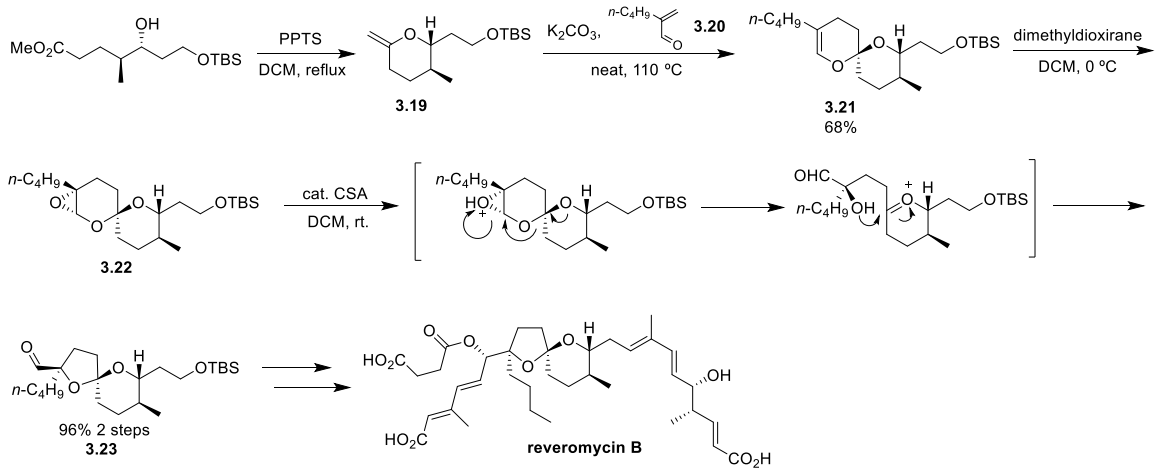
opening/cyclization process to selectively furnish the C1-inversion and C1-retention spiroketals **3.12** and **3.17** respectively. The methanol-involved process was proposed to undergo a S_N2 or S_N2-like pathway, in which the hydrogen-bonding model **3.11** was proposed to explain the diastereoselectivity.[62b] From this model, the two hydrogen-bonds contributed by the upper methanol and both the tetrahydropyran oxygen and side chain oxygen disfavor the oxocarbenium ion-mediated S_N1 pathway. When the spirocyclization proceeds in the presence of titanium isopropoxide, the S_N1 pathway is preferred.[62c] During this process, the Lewis acid not only opens the epoxide, but also serves as a noncovalent tether that connects the epoxide oxygen and side chain oxygen to facilitate the kinetic formation of **3.17**.



Scheme 3-2. Spirocyclization of glycal epoxides

Rizzacasa and co-workers sequentially employed an acid-promoted lactonization and inverse electron demand HDA to construct the 6,6-spiroketal **3.21** in their synthesis of reveromycin B (Scheme 3-3).[63] During the HDA reaction, the oxygen atom of aldehyde **3.20** predominantly approached to THP **3.19** in axial manner due to the anomeric effect, which explains the high

distereoselectivity of this reaction. Interestingly, after the epoxidation of **3.21**, the labile product **3.22** underwent a rearrangement to form more thermodynamically stable 5,6-spiroketal **3.23** in excellent yield under acidic conditions. A mechanism containing a ring-opening/carbocation-formation/re-cyclization process was proposed to illustrate this rearrangement.



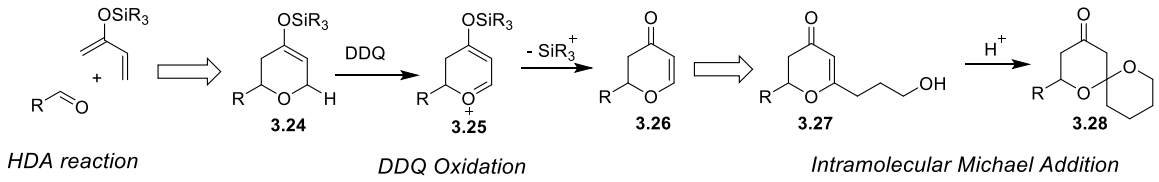
Scheme 3-3. Rizzacasa's access toward 5,6-spiroketal in the synthesis of reveromycin B

3.1.3 Designing a One-Pot Strategy for Spiroketal Formation

Although the stepwise protocol significantly expands the scope of synthetically accessible spiroketals, it lengthens the synthetic sequence by at least one step. We were exploring a solution to this issue, which could allow us to construct the two rings of a spiroketal through different cyclization reactions but in a one-pot process.

Based on the Floreancig group's previous studies on DDQ oxidation,[30] we predicted that the C–H bond at α-position of the enol silane **3.24** could be oxidatively cleaved by DDQ to form the oxocarbenium ion **3.25** (Scheme 3-4). In the absence of a nucleophile, **3.25** will rapidly convert to enone **3.26**, which is an excellent Michael acceptor. We envisioned that if the enone contained

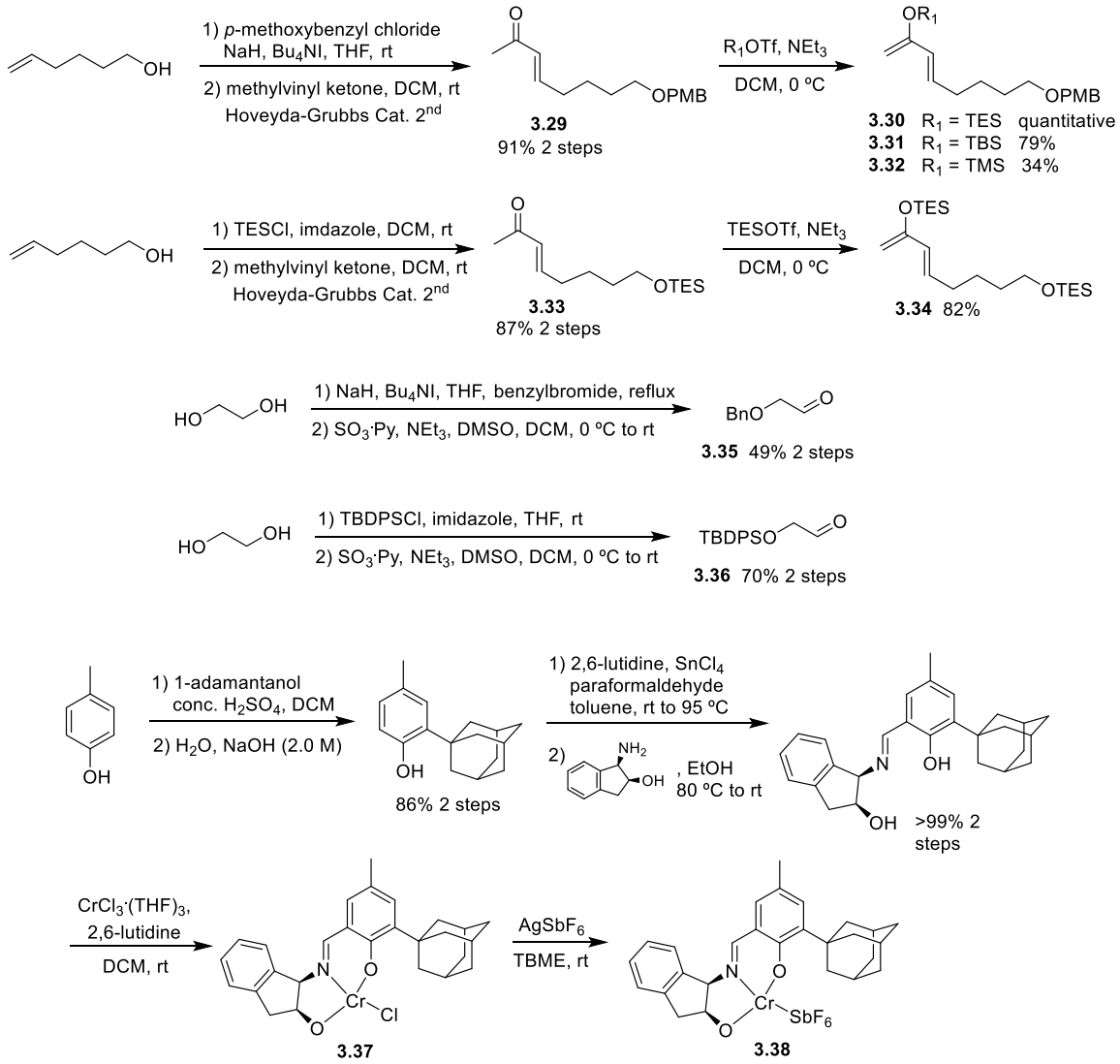
a side chain with an alcohol group at the end, such as enone **3.27**, spiroketal scaffold **3.28** would be easily furnished under acidic conditions. Additionally, the THP-based enol silyl ethers are readily available from a transition metal-catalyzed HDA reaction.[64] Thus, a one-pot strategy that combines these three reactions was conceived.



Scheme 3-4. One-pot strategy for spiroketal formation

3.2 SYNTHESIS OF SPIROKETALS THROUGH A ONE-POT PROCESS

Dienes **3.30** to **3.32** and **3.34**, aldehydes **3.33** and **3.34**, and Jacobsen catalysts **3.37** and **3.38** were prepared for initial investigation (Scheme 3-5). Synthesis of these dienes followed the sequence of alcohol protection, alkene cross-metathesis,[65] and enol silane formation. The preparation of aldehydes **3.35** and **3.36** started with a single alcohol protection of ethylene glycol, followed by a Parikh-Doering oxidation.[39] Catalysts **3.37** and **3.38** were assembled by known procedures.[66]

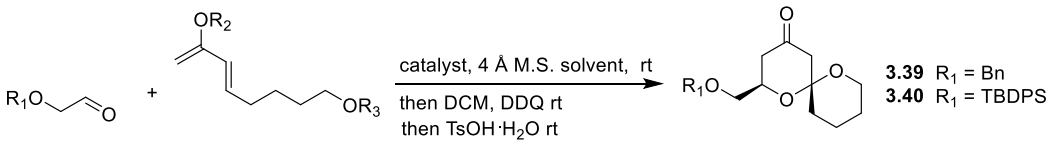


Scheme 3-5. Substrates and catalysts for initial investigation

The initial results are shown in Table 3-1. The first attempt of the one-pot process began with the addition of catalyst **3.37** into the mixture of diene **3.30**, aldehyde **3.35**, molecular sieves, and acetone. The resulting slurry was stirred at room temperature until diene **3.30** was consumed, then was diluted by dichloromethane. The diluted reaction mixture was treated with DDQ in one portion, followed by the addition of PTSA when the TLC indicated the completion of enone formation and PMB deprotection. The resulting mixture was stirred at room temperature until the

desired spiroketal was fully formed. After purification, spiroketal **3.39** was isolated in a moderate yield as a single diastereomer (entry 1). Different enol silyl groups did not significantly impact the yield of this reaction (entries 1, 2, and 4). Acetone as the solvent is unnecessary for the HDA reaction (entry 1 vs entry 3). The employment of catalyst **3.38** led to a slight decrease of yield, which might be attributed to the acceleration of the side reactions, such as aldehyde condensation and diene decomposition, due to the stronger Lewis acidity of **3.38** (entry 4 vs entry 5). In order to suppress the possible oxidative decompositions in the reaction, a lower loading amount of oxidant is preferred. Thus, TES was employed instead of PMB as the protecting group of the primary alcohol of diene substrate, which reduced the loading amount of DDQ by half, and thus led to a significant improvement of yield (entry 6). This observation might also be reasoned by the higher efficiency of TES deprotection as compared to PMB deprotection. Aldehyde **3.36** bearing a TBDPS protecting group brought a significant improvement of product *ee* value and also a slight increase in reaction yield (entry 7).

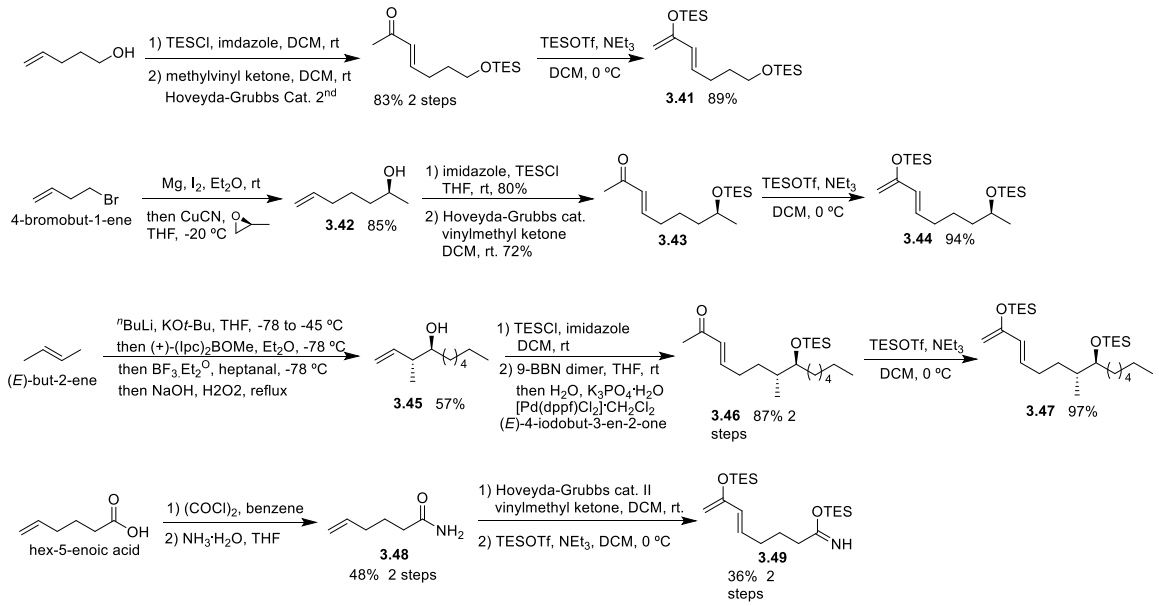
Table 3-1. Initial investigation of the one-pot spiroketal formation reaction[a]



entry	R_1	R_2	R_3	catalyst	solvent	yield[b] (%)	ee[c] (%)
1	Bn	TES	PMB	**3.37**	acetone	39	n.d.[d]
2	Bn	TMS	PMB	**3.37**	acetone	36	n.d.
3	Bn	TES	PMB	**3.37**	N/A	39	n.d.
4	Bn	TBS	PMB	**3.37**	N/A	38	n.d.
5	Bn	TBS	PMB	**3.38**	N/A	31	n.d.
6	Bn	TES	TES	**3.37**	N/A	73	73
7	TBDPS	TES	TES	**3.37**	N/A	78	91

a).Representative procedure: a mixture of diene (1.0 eq.), aldehyde (1.5 to 2.0 eq), 4 Å molecular sieves, and solvent was stirred at rt for certain time. Then the reaction system was diluted with DCM and treated with DDQ (1.1 to 2.2 eq). The resulting solution was stirred at rt for certain time, followed by adding tosyl acid (1.5 to 2.0 eq).*b*) isolated yield. *c*) determined by HPLC. *d*) not determined.

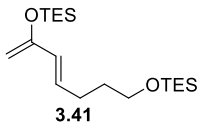
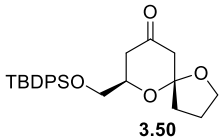
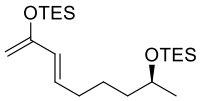
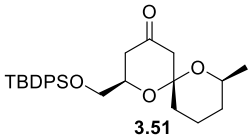
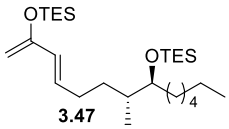
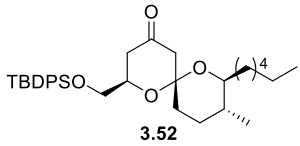
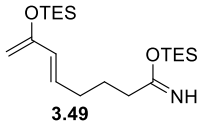
Several representative dienes were designed and synthesized in order to comprehensively evaluate the potential synthetic value of this spiroketal formation reaction (Scheme 3-6). Diene **3.41** shared a similar synthetic route with diene **3.34**. The *in situ* generated Grignard reagent from 4-bromobut-1-ene opened the ring of (*S*)-(–)-propylene oxide to afford secondary alcohol **3.42**, which underwent a silyl protection, alkene cross-metathesis, and enol silane formation to yield diene **3.44**. Diene **3.47** was accessed from (*E*)-but-2-ene, which underwent a Brown crotylation,[67] silyl protection, Suzuki coupling,[45] and enol silane formation to deliver the desire substrate. The hex-5-enoic acid was converted to amide **3.48** by a two-step amination,[68] which was followed by an alkene cross-metathesis and enol silane formation to furnish diene **3.49**.



Scheme 3-6. Synthesis of the diene substrates

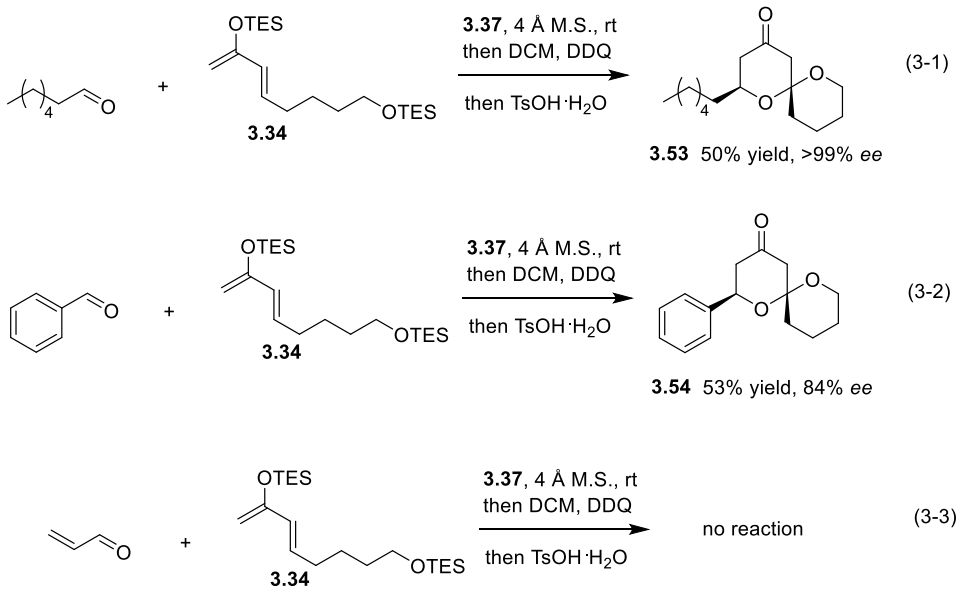
The performances of these dienes with aldehdye **3.36** in the one-pot process are listed in Table 3-2. All of the spiroketals were isolated as single diastereomers. Diene **3.41** with shortened carbon chain can undergo the HDA, DDQ oxidation, and oxa-Michael cyclization smoothly to afford 5,6-spiroketal **3.50** in similar yield with diene **3.34** (entry 1). The excellent yields of spiroketals **3.44** and **3.47** imply that the secondary alcohols are as effective nucleophiles as the primary alcohols in oxa-Michael cyclization; and the multiple substituted dienes are also suitable substrates for the spiroketal formation process (entries 2 and 3). Moreover, spiroketals **3.51** and **3.52** are nearly enantiopure compounds because an *ee* enhancement occurs when two enantiomerically enriched molecules are coupled, which is referred as the Horeau principle.[69] The one-pot process was most likely obstructed at the initial stage for diene **3.49** (entry 4), which might be attributed to the possible coordination effect between transition metal catalyst and the nitrogen atom of amide.

Table 3-2. Diene scope exploration[a]

entry	diene	product	*ee* (%)	yield[b] (%)
1	 **3.41**	 **3.50**	85[c]	72
2	 **3.44**	 **3.51**	>99	71
3	 **3.47**	 **3.52**	>99	75
4	 **3.49**	no desired product		

a).Representative procedure: a mixture of diene (1.0 eq.), aldehyde (1.5 to 2.0 eq), 4 Å molecular sieves, and solvent was stirred at rt for certain time. Then the reaction system was diluted with DCM and treated with DDQ (1.0 eq).The resulting solution was stirred at rt for certain time, followed by adding tosyl acid (1.5 to 2.0 eq).*b*) isolated yield. *c*) *ee* value of product is determine by HPLC

Different types of aldehydes were also subjected to our spiroketal formation protocol. The results are shown in Scheme 3-7. Although a prolonged HDA reaction was necessary, heptanal, a nonfunctionalized aliphatic aldehyde was able to yield spiroketal **3.53** in moderate yield but with an extremely high *ee* value (Eq (3-1)). Benzaldehyde also required a long period to undergo the HDA reaction, followed by rapid oxidation and cyclization to afford spiroketal **3.54** in moderate yield and with a slightly lower *ee* value (Eq (3-2)). The attempt of acrolein was unsuccessful (Eq (3-3)). The volatile aldehyde disappeared rapidly from the reaction mixture, leaving behind the unreacted diene, which gradually decomposed in the presence of the catalyst. The [4+2] cyclized product from diene **3.34** and the acrolein alkene was not observed either.



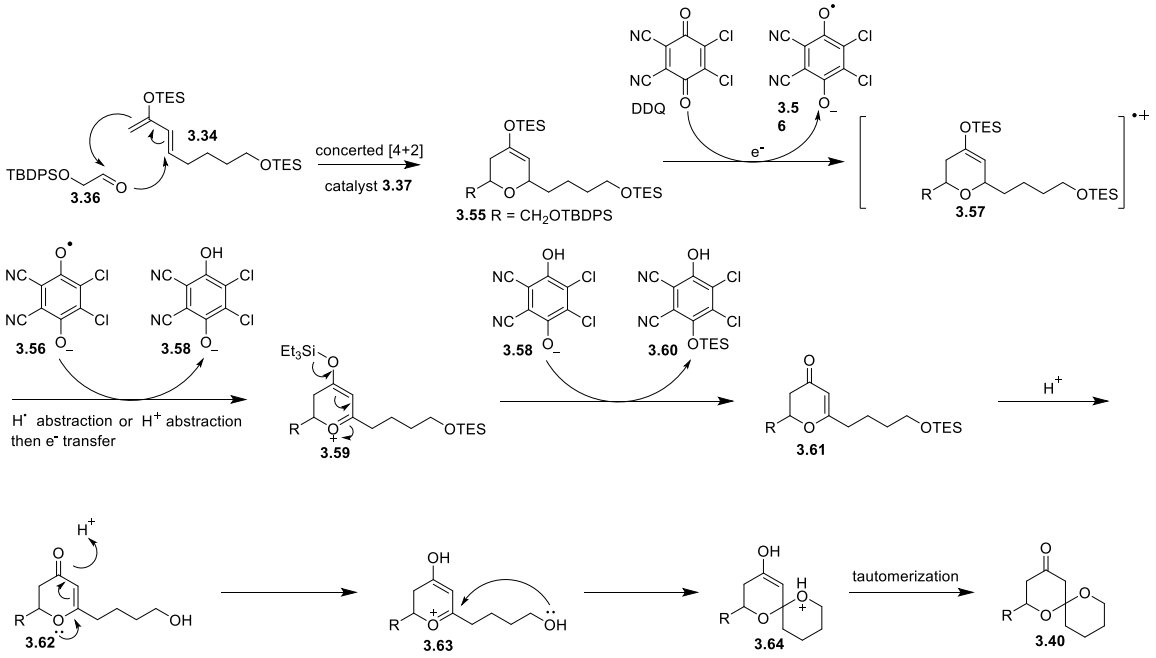
Scheme 3-7. Performances of different aldehydes in the spiroketal formation reaction

3.3 DISCUSSION

3.3.1 Proposed Mechanism for the One-Pot Process

A proposed mechanism of the spiroketal formation reaction is shown in Scheme 3-8. At the HDA stage, diene **3.34** and aldehyde **3.36** are combined to form enol silylether **3.55** in a concerted [4+2] manner. The Jacobsen group ruled out the possibility of the Mukaiyama aldol condensation mechanism for this [4+2] cyclization through treating the intermediacy of a Mukaiyama aldol condensation adduct with Jacobsen catalyst, which failed to yield any cyclized product.[70] The second stage is initiated by a one-electron transfer from **3.55** to DDQ, which generates radical cation **3.57** and radical anion **3.56**. Oxocarbenium ion **3.59** was formed through either a hydrogen atom abstraction pathway, or a successive proton abstraction and electron

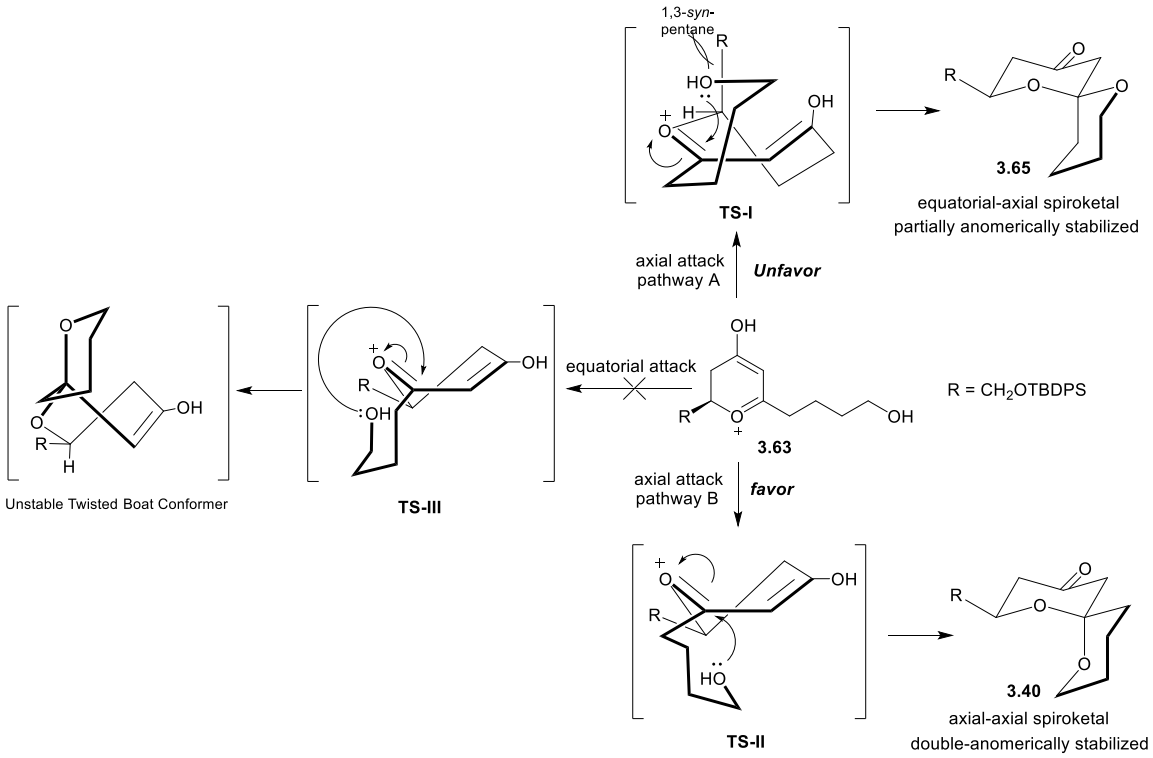
transfer pathway. During this process, radical anion **3.56** is further reduced to anion **3.58**. A rapid desilylation of oxocarbenium ion **3.59** furnishes enone intermediate **3.61** and mono-silylated 1,4-dihydroxybenzene **3.60**. During the last stage, the TES group of **3.61** is selectively removed due to its acid lability. The resulting enone **3.62** is protonated and forms oxocarbenium ion **3.63**, which is attacked by the free internal alcohol to give the spiroketal scaffold **3.64**. The desired spiroketal **3.40** is formed after the tautomerization of **3.64**. Interestingly, the stoichiometric amount of 1,4-dihydroxybenzene **3.60** derived from DDQ creates a buffer-like system in the reaction, thus requiring more than one equivalent of PTSA to initiate the oxa-Michael cyclization.



Scheme 3-8. Proposed mechanism for the one-pot spiroketal formation

3.3.2 Stereochemical Analysis

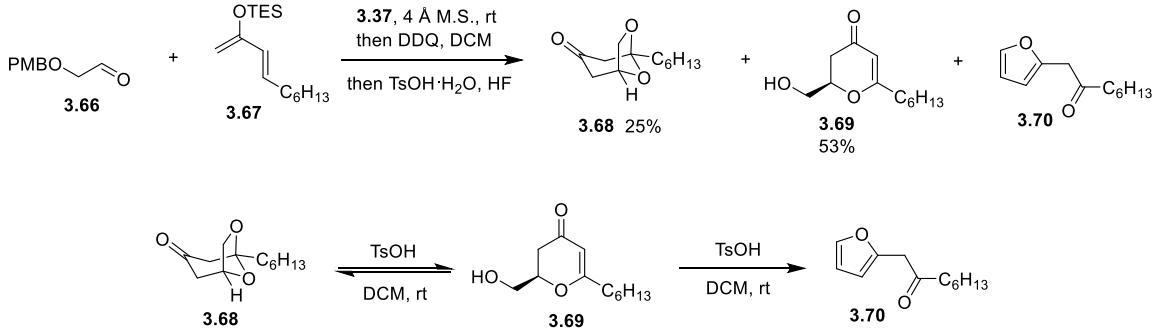
The one-pot process exhibits exclusive diastereoselectivity because the oxa-Michael cyclization undergoes a pathway that is both kinectically and thermodynamically favored (Scheme 3-9). For the intermediate **3.63**, the equatorial attack by internal alcohol on the oxocarbenium ion is disfavored due to the generation of the unstable twisted-boat conformer. There are two possible axial-attack pathways as shown in Scheme 3-9. The 1,3-*syn*-pentane interaction kinetically disfavors pathway A.[71] Moreover, compared to the double-anomerically stabilized spiroketal **3.40** obtained through pathway B, partially anomerically stabilized spiroketal **3.65** is considered as the thermodynamically unfavored product. Therefore, pathway A is fully suppressed during the oxa-Michael cyclization.



Scheme 3-9. Analysis of the diastereoselectivity of oxa-Michael cyclization

3.3.3 Synthesis of Bridged Bicyclic Ethers through the One-Pot Process

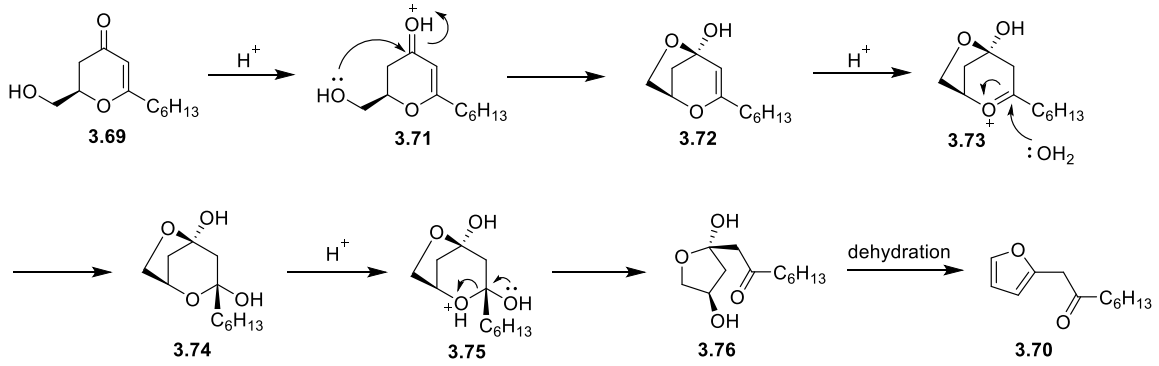
We also initiated a simple trial of the one-pot process that was targeted to yield a bridged bicyclic ether (Scheme 3-10). Successively treating aldehyde **3.66** and diene **3.67** with catalyst **3.37**, DDQ, PTSA, and HF, the desired bicyclic ether **3.68** was obtained in a 25% yield, while the uncyclized precursor **3.69** was also collected in a 53% yield. Interestingly, a silyl transfer was observed during the DDQ oxidation. The TES group from the enol silyl moiety transferred to the PMB deprotected alcohol, which could not be desilylated until HF was added. With a prolonged time, furan **3.70** was obtained, accompanied by a significant consumption of **3.68** and **3.69**. Moreover, when pure isolated **3.68** or **3.69** was treated with PTSA, both **3.68** and **3.69** were observed and **3.70** would also be formed after several hours. We proposed that there is a labile equilibrium between **3.68** and **3.69** and **3.69** is irreversibly converted to **3.70** under acidic conditions.



Scheme 3-10. Access toward bridged bicyclic ethers through the one-pot process

The proposed furan formation mechanism is shown in Scheme 3-11. After the nucleophilic attack of the alcohol to the protonated carbonyl group, bicyclic hemi-acetal **3.72** is formed. This intermediate is protonated to form oxocarbenium ion **3.73**, which accepts the nucleophilic attack by water to afford diol **3.74**. The THP ring of **3.74** opens under acidic conditions to form

tetrahydrofuran **3.76**. Two dehydrations convert **3.76** to the furan that was collected in the one-pot process.



Scheme 3-11. Proposed mechanism for the formation of furan **3.70**

3.4 SUMMARY

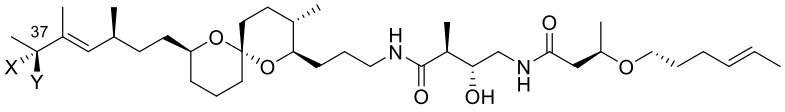
We have demonstrated that the synthetically useful spiroketals can be easily and diastereoselectively accessed through a one-pot process that combines a HDA reaction, a DDQ oxidation, and an oxa-Michael cyclization. Non-cyclic dienes and aldehydes were employed as the starting materials, which were easily prepared. The multiple-substituted dienes performed excellently in the spiroketal formation reaction as well as the diene bearing a shorter tether length. Both of the non-functionalized aldehydes and aromatic aldehydes are suitable substrates, although a prolonged time is necessary for the initial HDA reaction. For the mechanism proposal, we hypothesized that the telescoped DDQ oxidative C–H bond activation of the concerted [4+2] cyclization product generates oxocarbenium ion intermediates, which are rapidly converted to enones. The oxa-Michael cyclization occurs to yield the desired products when the acid is added. The stereoselectivity is attributed to the kinetically and thermodynamically favored pathway.

Moreover, an attempt to produce the bridged bicyclic ether was initiated, and a moderate yield of the desired product was collected.

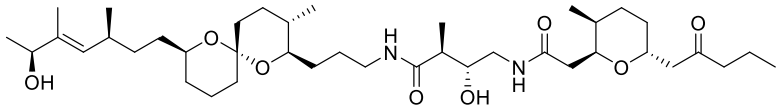
4.0 TOTAL SYNTHESIS OF BISTRAMIDE A

4.1 INTRODUCTION OF BISTRAMIDE A

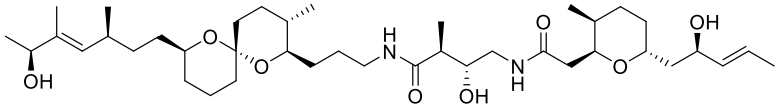
The bistramide family represents a novel class of bioactive cyclic polyethers from the marine ascidian *Lissoclinum bistratrum*.[72] To date, five members of this family have been isolated and characterized (Figure 4-1). Bistramide A was first discovered by the Gouiffès group in 1988,[72a,72b] while the isolation of the other four members were conducted by the Biard group in 1994.[72c]



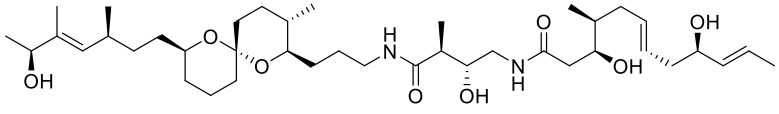
4.1 bistramide A: X = H, Y = OH
4.2 bistramide C: X = Y = O



4.3 bistramide B



4.4 bistramide D



4.5 bistramide K

Figure 4-1. Members of the bistramide family

The Gouiffès group conducted the initial structure determination of bistramide A through extensive 2D NMR analysis.[72a] A linear structure for bistramide A was suggested based on the assignments of all crucial connectivity assisted by ^{1}H-^{13}C and ^{1}H-^{1}H COSY in combination with ^{1}H-^{13}C COLOC and relayed ^{1}H-^{1}H-^{13}C COSY. Later, the Hawkins group claimed a structure revision for bistramide A according to their observation of three key long-range ^{1}H-^{13}C correlations (Figure 4-2).[72b] They proposed an alternative three-dimensional structure that contains two bridged macrocycles and one bridged furan. The correct structure of bistramide A was not revealed until the Ireland group published their reassignment of bistramide A based on the automated analysis of a 2D INADEQUATE experiment data.[73]

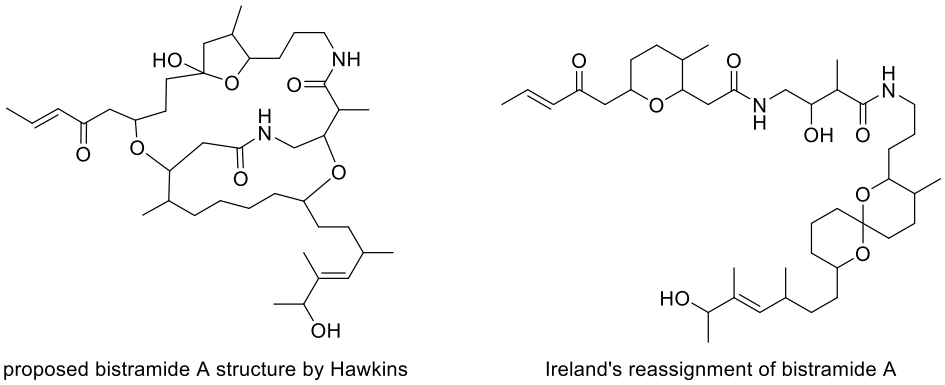


Figure 4-2. Structure determination of bistramide A

However, Ireland's bistramide A structure does not provide any information related to the absolute configuration, which is extremely important for the effective exploration of its biological activities. In 2000, Solladié *et al.* determined the absolute configuration of C4 in bistrmide D *via* Mosher's method.[74] Moreover, they also assigned the relative configurations of the tetrahydropyran ring and spiroketal skeleton based on the NOESY spectral data (Figure 4-3). Later, the Wipf group fully assigned the absolute configuration of bistramide C through the combination

of organic synthesis and NMR spectroscopy.[75] Kozmin's first total synthesis of bistramide A uncovered the C37 stereochemistry and confirmed Wipf's assignment.[76]

Figure 4-3. Relative configuration determination of the substructures of bistramide A

Bistramide A is initially demonstrated to possess significant cytotoxicity towards P388 leukemia, B16 melanoma, HT29, and non-small-cell lung carcinoma (NSCLC-N6) cell lines with an IC_{50} of 0.4 to 4.5 nM, and is able to selectively activate the δ isotype of protein kinase C (PKCδ) in human promyelocytic leukemia (HL-60) and human malignant melanoma (MM96E), which leads to the inhibition of cytokinesis and growth arrest.[77] However, Kozmin showed the low bind affinity between bistramide A and PKCδ recently, and proved the existence of the interaction between bistramide A and actin by crystallographic studies, which explains the potent antipoliferative effects of bistramide A and makes it be a potential antitumor drug.[78] Therefore, the total synthesis of this promising potential drug has attracted the attention of many synthetic groups.[76,79]

4.2 PREVIOUS TOTAL SYNTHESIS OF BISTRAMIDE A

Five groups have independently reported total syntheses of bistramide A.[76,79] These five routes shared the similar retrosynthetic plans that disconnected bistramide A at the two amide bonds (Figure 4-4). However, the resulting three subunits were constructed through different routes. Each bistramide A synthesis is summarized in this section chronologically.

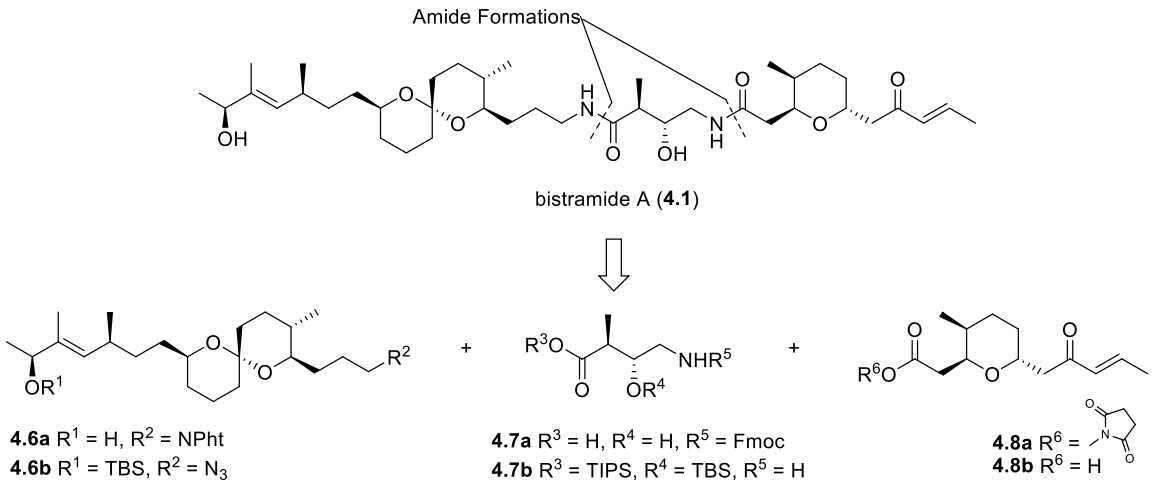
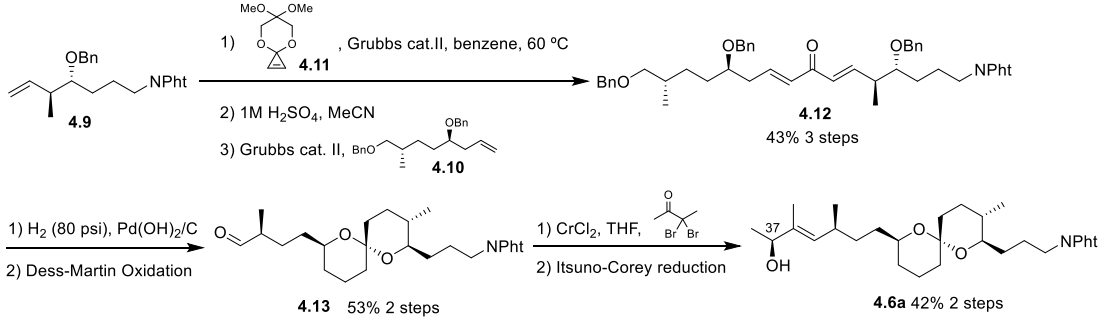


Figure 4-4. General retrosynthetic analysis of the previous total syntheses of bistramide

4.2.1 Kozmin's Total Synthesis of Bistramide A

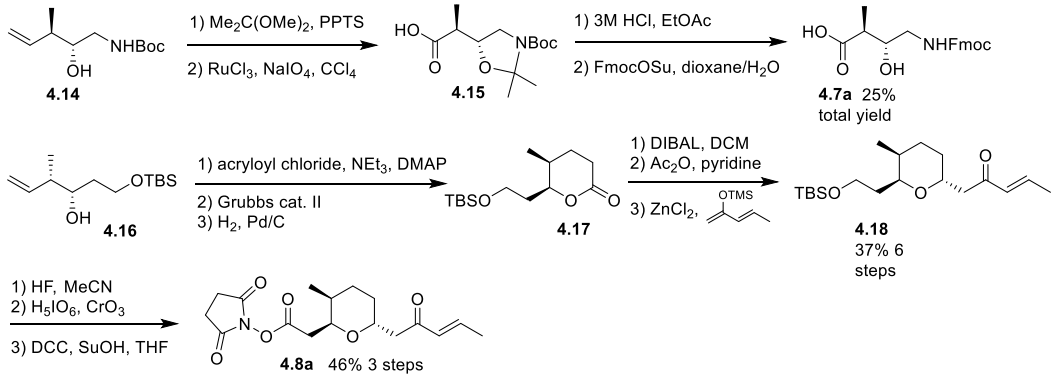
Kozmin and co-workers accomplished the first total of bistramide A in 2004.[76] During their efforts toward spiroketal fragment **4.6a**, homoallylic alcohols **4.9** and **4.10** were connected through cyclopropene acetal **4.11** in the presence of Grubbs catalyst (2nd generation) (Scheme 4-1). The resulting dienone **4.12** was exposed to hydrogen gas and palladium to generate the dihydroxyketone intermediate *in situ*, which underwent a spiraketalization reaction and subsequent Dess-Martin oxidation to yield the key spiroketal scaffold **4.13**. After a Cr(II)-mediated

olefination,[80] the Itsuno-Corey reduction[81] introduced the desired stereochemistry at carbon C37, and completed the synthesis of fragment **4.6a**.



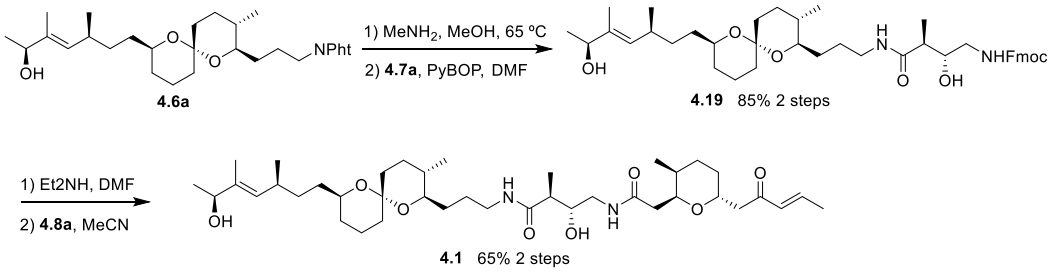
Scheme 4-1. Spiroketal fragment synthesis in Kozmin's synthesis

The γ-amino acid **4.7a** was assembled from the oxidative cleavage of terminal alkene **4.14**, followed by the removal of Boc and acetonide protecting groups and installation of an Fmoc group on the amine. The 2,6-*trans*-disubstituted THP ring of fragment **4.8a** was constructed through a consecutive acrylation, ring-closing metathesis, hydrogenation, reduction, acylation, and S_N1 substitution process in a 37% overall yield from homoallylic alcohol **4.16**. After the desilylation of **4.18**, the unprotected alcohol was exposed to periodic acid to afford the carboxylic acid intermediate, which was converted to **4.8a** by coupling with *N*-hydroxysuccinimide.



Scheme 4-2. Syntheses of subunits **4.7a** and **4.8a**

After the removal of the phthalimide group, spiroketal **4.6a** was combined with Fmoc protected amino acid **4.7a** to furnish **4.19**. An Fmoc deprotection of amide **4.19** enabled this fragment to be coupled with t*rans*-THP **4.8a** and complete the total synthesis of bistramide A.

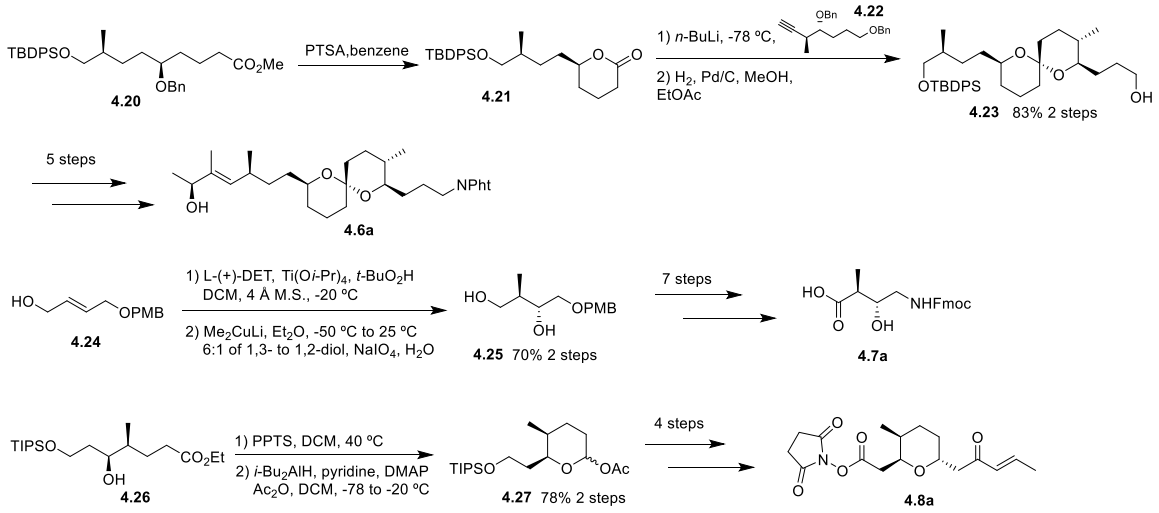


Scheme 4-3. Completion of Kozmin's bistramide A synthesis

4.2.2 Crimmins' Total Synthesis of Bistramide A

Two years after Kozmin's accomplishment of bistramide A synthesis, Crimmins and co-workers published their route toward this natural product.[79a] They trisected bistramide A into the three same pieces as Kozmin's synthesis. Spiroketal **4.6a** was constructed through a stepwise strategy (Schme 4-4). The lactonization of hydroxyester **4.20** in the presence of PTSA constructed the first ring of the spiroketal and results the lactone **4.22**, on which an alkynyl chain was installed. Subsequently, a palladium-catalyzed hydrogenation reduced the alkynyl group, deprotected the benzyl group, and cyclized the second ring of spiroketal **4.23**. Subunit **4.6a** was formed after a few side chain functional group manipulations on **4.23**. The chiral centers of subunit **4.7a** were introduced to allylic alcohol **4.24** by a Sharpless epoxidation, followed by a methylation to open the resulting epoxide to yield diol **4.25**. The THP scaffold of subunit **4.8a** was also formed by a PTSA-catalyzed lactonization of hydroxyester **4.26**. The resulting THP **4.27** was converted to **4.8a**

in four steps. In the end, these three pieces were coupled by two simple amide formation reactions to yield bistramide A.

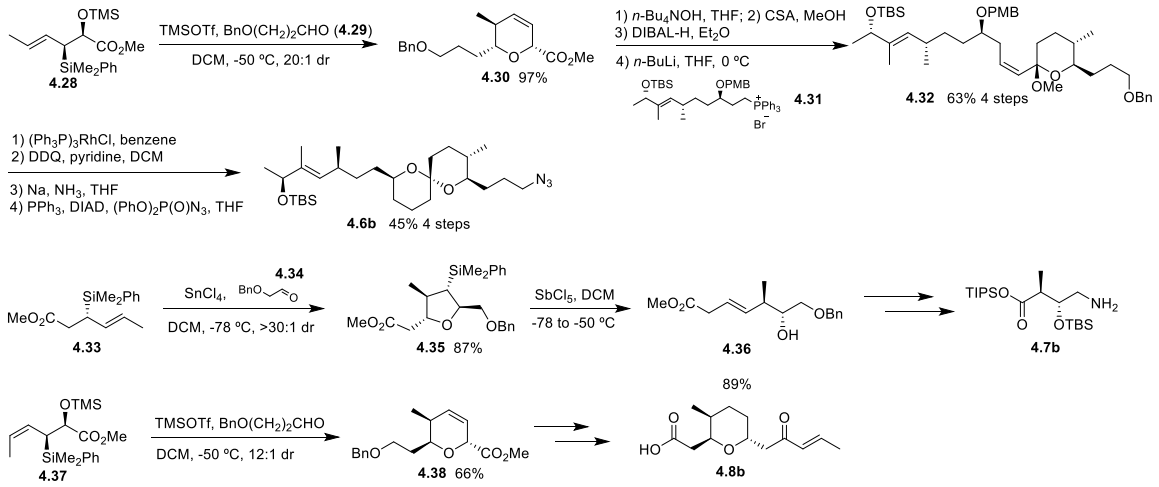


Scheme 4-4. Crimmins' protocol toward the synthesis of bistramide A

4.2.3 Panek's Total Synthesis of Bistramide A

The Panek group established the total synthesis of bistramide A as a perfect showcase of their [4+2] and [3+2] annulations between allylsilanes and aldehydes (Scheme 4-5).[79a,79b,82] Spiroketal **4.6b** was sourced from allylsilane **4.28**, which underwent a [4+2] annulation with aldehyde **4.29** to diastereoselectively afford *cis*-THP **4.30** in excellent yield. This THP was coupled with fragment **4.31** to form alkene **4.32** after several functional group manipulations. Wilkinson's catalyst selectively reduced the less hindered double bond of **4.32**, followed by an oxidative deprotection of the PMB group, which facilitated the spirocyclization reaction. The resulting spiroketal intermediate underwent a Birch reduction and a Mitsunobu reaction to yield the desired spiroketal subunit. Allylsilane **4.33** was subjected to a [3+2] annulation with aldehyde **4.34** to afford tetrahydrofuran **4.35**, which underwent an $SbCl_5$-catalyzed ring-opening process to

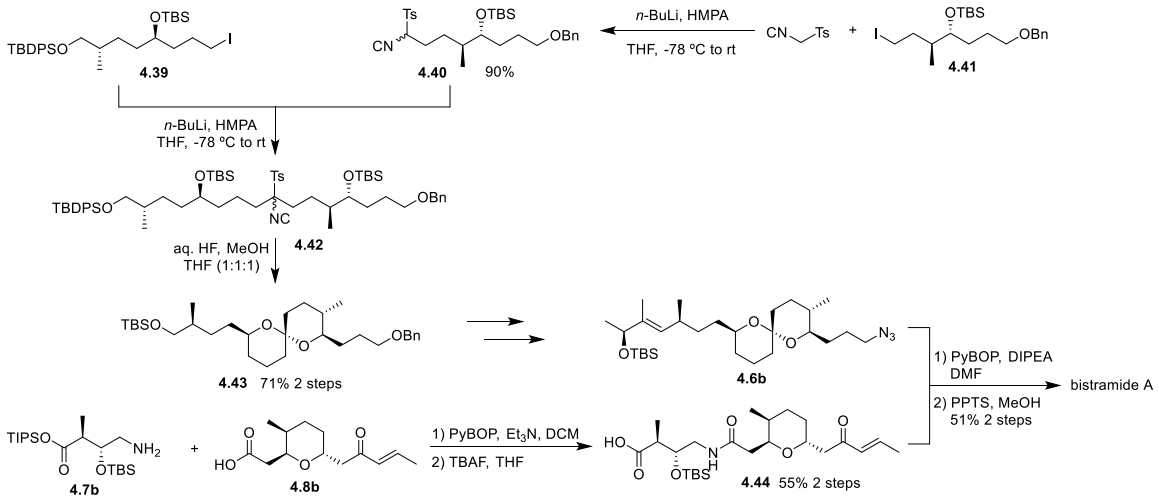
yield ester **4.36**. After a few modifications, **4.36** was successfully converted to amino acid **4.7b**. The *trans*-THP subunit **4.8b** was also synthesized from a [4+2] annulation of allylsilane **4.37** and aldehyde **4.29**.



Scheme 4-5. Showcase of the annulation reactions in the total synthesis of bistramide A

4.2.4 Yadav's Total Synthesis of Bistramide A

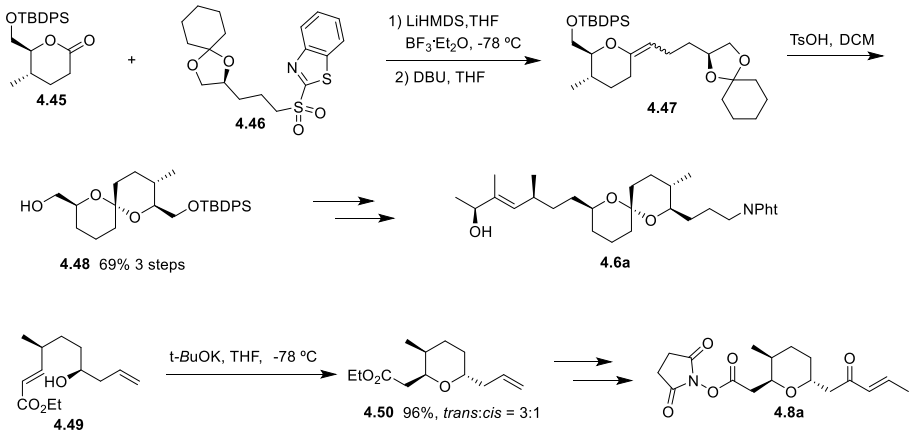
Yadav's synthesis of bistramide A is highlighted by employing dialkylated tosylmethyl isocyanide derivative **4.42** as the surrogate of the dihydroxyketone to rapidly construct the spiroketal **4.43** in excellent yield (Scheme 4-6).[79c,83] This spiroketalization precursor was synthesized by two successive butyllithium-promoted alkylations that installed iodides **4.39** and **4.41** on the tosylmethyl isocyanide. Spiroketal **4.43** was converted to subunit **4.6b** through several side chain manipulations. The amino acid fragment **4.7b** and *trans*-THP fragment **4.8b** were combined with the assistance of PyBOP, followed by another PyBOP-promoted amide formation to couple with subunit **4.6b** to yield silyl protected bistramide A. A simple desilylation smoothly removed the silyl groups to furnish bistramide A in good yield.



Scheme 4-6. Yadav's alcomplishment of bistramide A synthesis

4.2.5 Lord and Goekjian's Total Synthesis of Bistramide A

Recently, Lord and Goekjian published their approach toward the synthesis of bistramide A.[79e] Their total synthesis is highlighted by a novel enol ether-forming reaction for spirocyclization and a *trans*-oriented kinetic oxa-Michael cyclization (Scheme 4-7). Under the optimized conditions, lactone **4.45** and Julia-Kocienski reagent **4.46** joined together to form the enol ether **4.47**, followed by PTSA-promoted cyclization to yield spiroketal **4.48**. The *trans*-THP ring was formed by an oxa-Michael cyclization of substrate **4.49**. During this reaction, a nearly quantitative yield of cyclized products was collect as a 3:1 mixture of isomers in favor of *trans*-THP **4.50**, which was converted to subunit **4.8a** in 7 steps. The synthesis of amino acid **4.7a** was similar to Kozmin's protocol.



Scheme 4-7. Lord and Goekjian's synthesis of bistramide A

However, the current synthetic sequences for bistramide A are quite long. Even the shortest sequence that comes from Kozmin's group needs 17 steps for the longest linear sequence and 45 overall steps from commercially available starting materials. A more convergent synthetic route is necessary to access to this potential drug candidate. The one-pot spiroketal formation process that was described previously in Chapter 3 will significantly shorten the sequence through dramatically increasing the molecular complexity in one step. Moreover, the 2,6-*trans*-THP fragment can also be assembled more efficiently through another novel one-pot process, which subsequently proceeds a hydroformylation, a cyclization, and an acetylation. We believe these two strategies will provide us a highly concise synthetic protocol to synthesize bistramide A.

4.3 RETROSYNTHETIC ANALYSIS

Our retrosynthetic analysis is shown in Figure 4-5. We envisioned bistramide A could be obtained through a simple amide formation that couples amine **4.51** and succinimide-activated carboxylic acid **4.52**. Aldehyde **4.53** and diene **4.54** were designed to undergo a one-pot spiroketal

formation process that was described previously in Chapter 3. Diene **4.54** can be further dissected into vinyl iodide **4.55** and secondary alcohol **4.56**. For the righthand fragment synthesis, we planed to disconnect it at the amide linkage, separating it into amino acid subunit **4.57** and *trans*-THP subunit **4.59**. Subunit **4.57** can be easily accessed from secondary alcohol **4.58** through a ruthenium(III) chloride-mediated terminal alkene oxidation. The THP ring of **4.59** can be constructed through a successive hydroformylation/cyclization/subsitition process that began with secondary alcohol **4.60**.

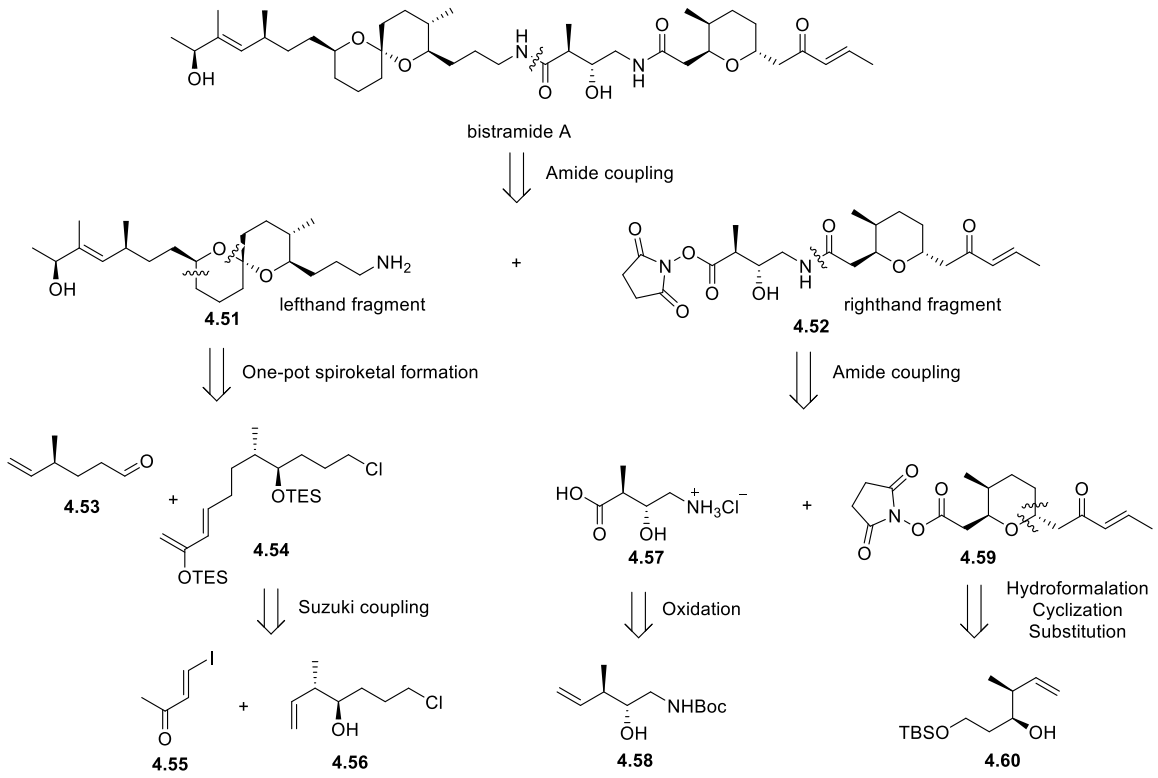
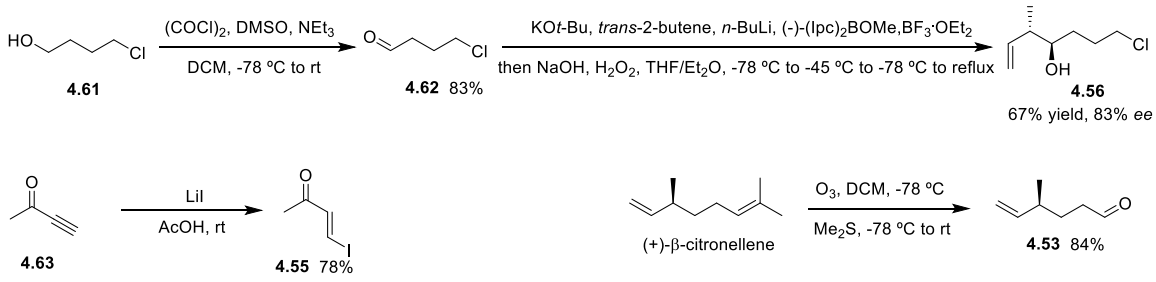


Figure 4-5. Retrosynthetic plan of bistramide A

4.4 TOTAL SYNTHESIS OF BISTRAMIDE A

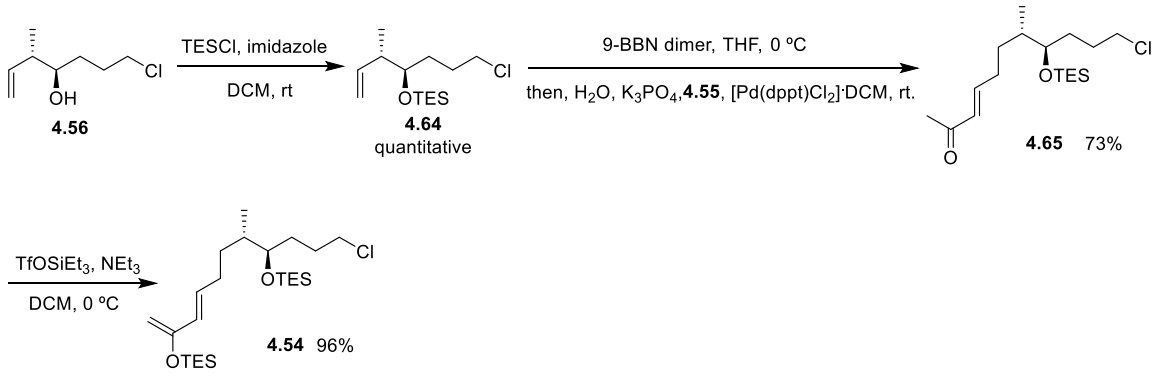
4.4.1 Lefthand Fragment Synthesis

Commercially available alcohol **4.61** underwent Swern oxidation[84] to afford aldehyde **4.62** in excellent yield (Scheme 4-8). Secondary alcohol **4.56** was collected in 67% yield and 83% *ee* value that was determined by Mosher ester analysis[85] through Brown crotylboration[67] of aldehyde **4.62**. Vinyl iodide **4.55** was generated through a facile hydroiodination of ketone **4.63**.[86] In order to access the chiral center on aldehyde **4.53**, we took the advantage of natural extract (+)-β-citronellene by conducting a regioselective ozonolysis.[87]



Scheme 4-8. Synthesis of fundamental units **4.53**, **4.55**, and **4.56** for the lefthand fragment

Diene **4.54** was easily accessed through a straightforward sequence that consisted of a silyl protection, a Suzuki coupling,[45] and an enol silane formation (Scheme 4-9). Water was proven to be crucial in this Suzuki coupling. It quenched the hydroboration reaction and prevented the palladium catalysis cycle from being deactivated by the unreacted borane.

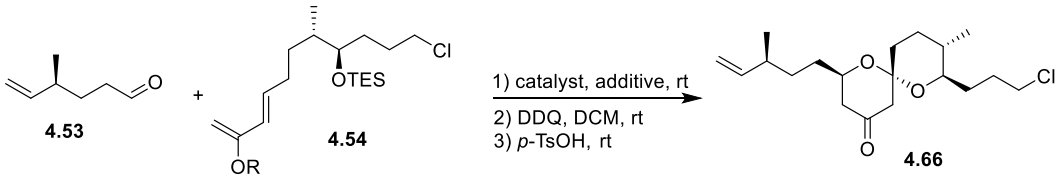


Scheme 4-9. Synthesis of diene **4.54**

With diene **4.54** and aldehyde **4.53** in hand, we were able to initiate our investigation of the key step, the spiroketal formation (Table 4-1). To our delight, desired spiroketal **4.66** was collected as a single diastereomer during our first attempt, in which diene **4.54** was simply mixed with aldehyde **4.53** and catalyst **4.67** and stirred at room temperature for 60 hours before being treated with DDQ and PTSA (entry 1). The relatively long time for the HDA reaction was attributed to the low reactivity of aliphatic aldehyde **4.53**. Several side reactions were proposed to occur during the HDA reaction. Under the highly concentrated conditions, aldehyde **4.53** might undergo a condensation process with the assistance of Lewis acid to form oligomers or polymers that stayed at the baseline of the TLC plates. Simultaneously, catalyst **4.67** would promote the cleavage of then enol silane on diene **4.54** to form enone intermediate **4.69** due to the presence of adventitious water in the system (Scheme 4-10). This enone was subjected to PTSA to yield a significant amount of by-product **4.70**. Adding molecular sieves and increasing the equivalents of aldehyde **4.53** effectively improved the yield of the desired spiroketal (entry 2). Interestingly, catalyst **4.68** significantly shortened the HDA reaction time, but still afforded the spiroketal with similar yield (entry 3). It might be rationalized by the stronger Lewis acidity of **4.68**, which accelerated both the spiroketal formation reaction and the side reactions. Replacing the enol silane

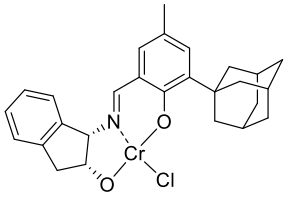
with silyl groups that are less labile to the acids did not bring any significant improvement to the results (entries 4 and 5). A sight increase of the yield was obtained by adjusting the detailed procedure of the HDA reaction (entry 6). Molecular sieves, catalyst **4.68**, and two equivalents of aldehyde **4.53** were mixed and stirred for 5 minutes before adding diene **4.54** and another two equivalents of aldehyde **4.53** in order to evenly distribute the catalyst and pre-activate the aldehyde.

Table 4-1. Construction of the key spiroketal core[a]

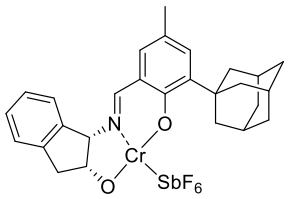


entry	R	catalyst	equiv. of aldehyde	additive	time[b] (h)	yield[c] (%)
1	TES	**4.67**	2	N/A	60	30
2	TES	**4.67**	4	4 Å MS	48	51
3	TES	**4.68**	4	4 Å MS	10	53
4	TBS	**4.68**	4	4 Å MS	10	51
5	TIPS	**4.68**	4	4 Å MS	36	45
6[d]	TES	**4.68**	4	4 Å MS	10	58

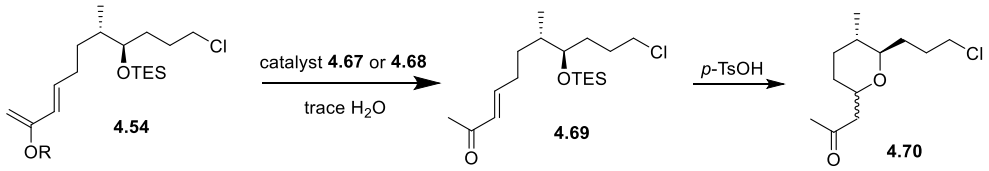
a) Representative procedure:Jacobsen catalyst was added to the mixture of aldehyde **4.53**, diene **4.54**, and additive. The resulting mixture was stirred at room temperature for certain hours until it reached the full consumption of diene **4.54**. DDQ and PTA were added successively to form the desired spiroketal. *b*) The time for HDA reaction. *c*) Isolated yield. *d*) Catalyst **4.68** was added to the mixture of 4 Å MS and 2 equiv. aldehyde **4.53**. The mixture is stirred for 5 min, then diene **4.54** and another 2 equiv aldehyde **4.53** were loaded.



4.67

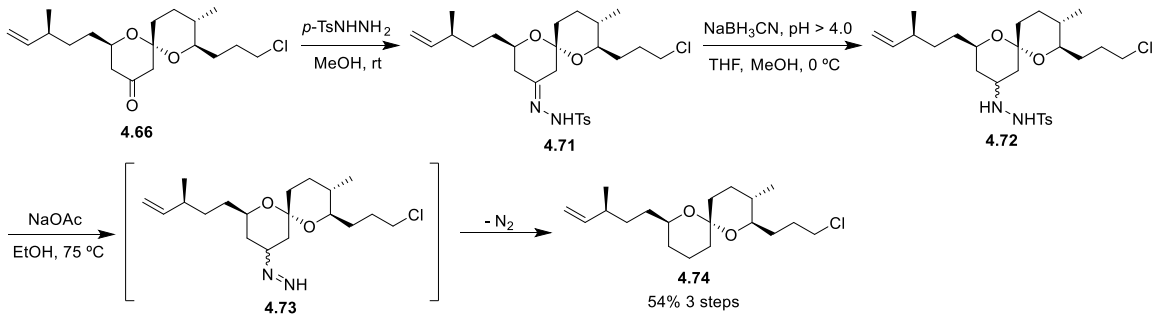


4.68



Scheme 4-10. Generation of by-product **4.70** in the spiroketal formation reaction

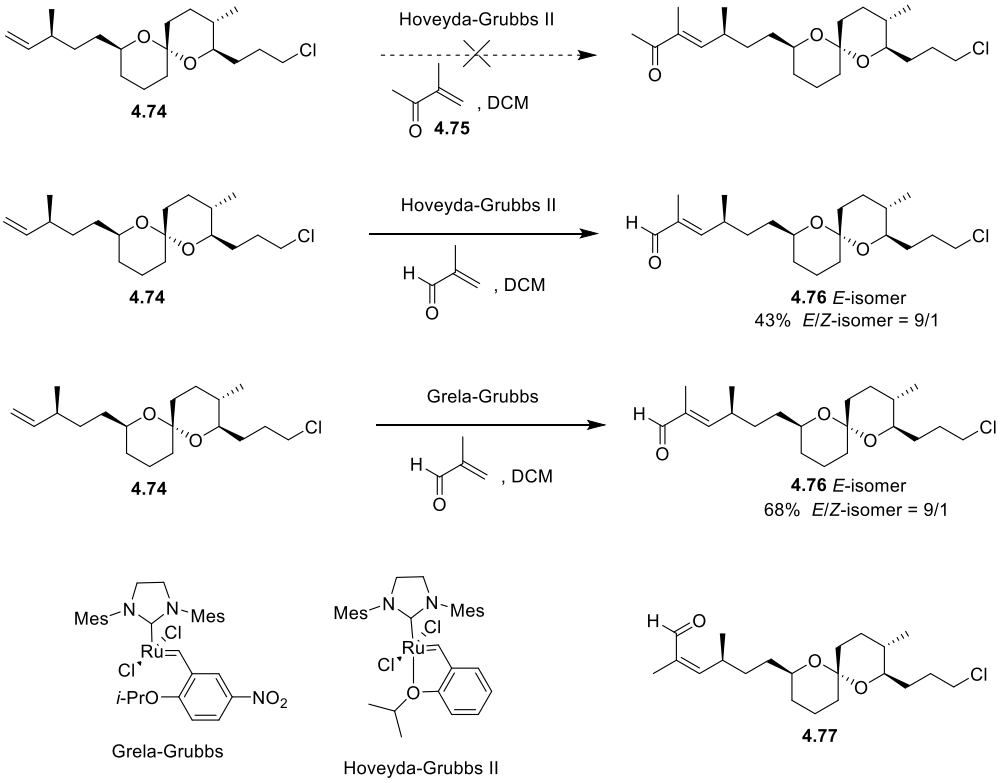
A mild variant of the Wolff-Kishner reduction,[88] known as Caglioti reaction,[89] was employed to deoxygenate the ketone on the spiroketal core (Scheme 4-11). It is a three-step sequence that started with the treatment of spiroketal **4.66** with *p*-tosylhydrazine to afford tosylhydrazone intermediate **4.71**, followed by a hydride reduction to render tosylhydrazine derivative **4.72**. The resulting tosylhydrazine eliminated a *p*-toluenesulfinic acid (TsH) under slightly basic condition with heat to form diazene intermediate **4.73**, which decomposed to desired hydrocarbon **4.74**.



Scheme 4-11. Deoxygenation of ketone **4.66** through Caglioti

The deoxygenation product **4.74** was sequentially subjected to alkene cross metathesis reaction to couple with ketone **4.75**, which turned out to be unsuccessful (Scheme 4-12). When methacrolein was employed in the presence of Hoveyda-Grubbs catalyst (2nd generation),[65e] a moderate yield of coupling product **4.76** was collected. Moreover, Grela-Grubbs catalyst significantly lifted the efficiency of the metathesis reaction to produce **4.76** in 68% yield.[90]

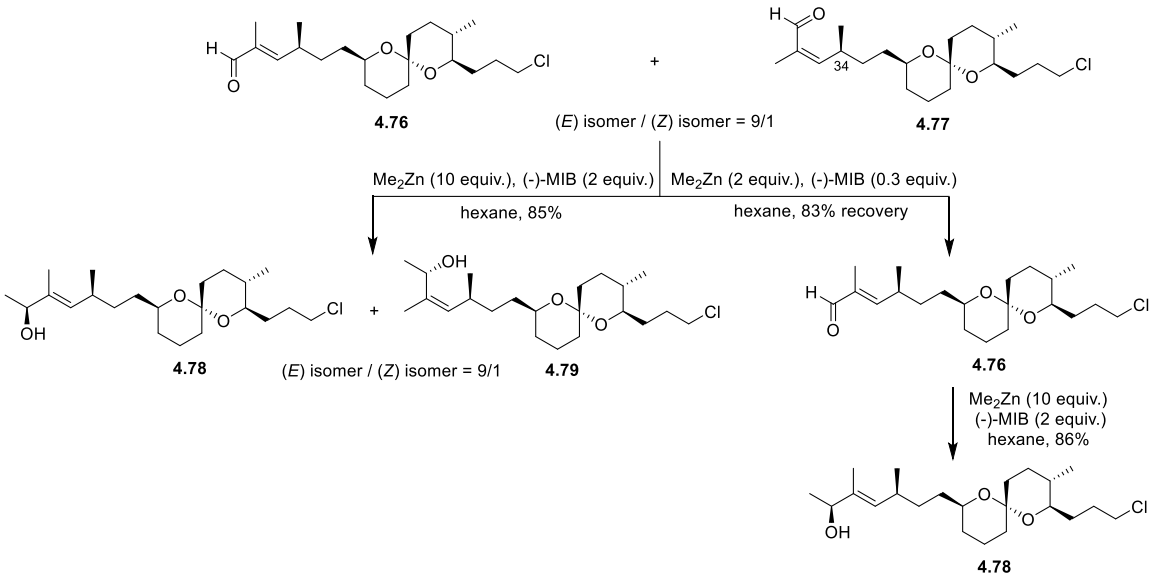
However, regardless of the Grubbs catalyst chosen, this metathesis reaction generated an inseparable *Z*-isomer **4.77** that had an approximate 1:9 ratio with **4.76**.



Scheme 4-12. Installation of methacrolein onto **4.74** via alkene cross metathesis reaction

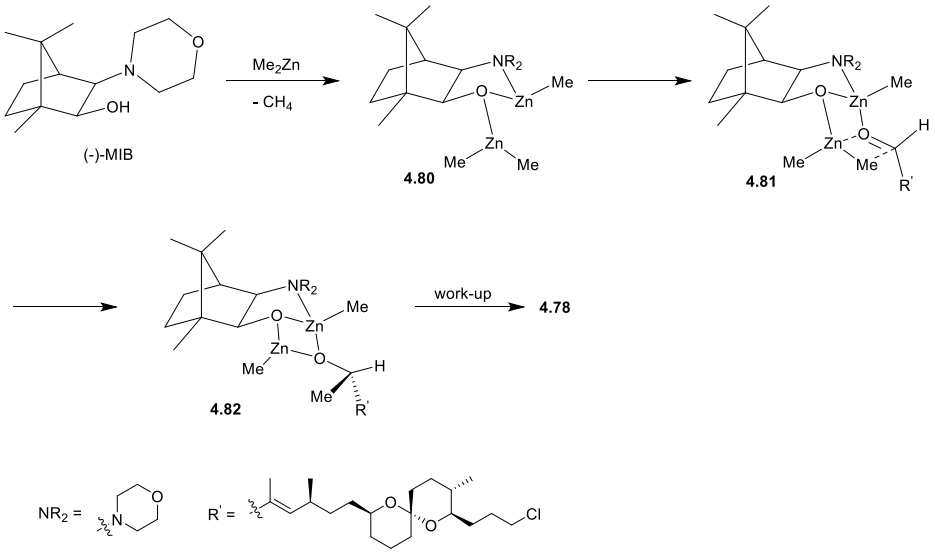
Treating the α,β-unsaturated aldehyde **4.76** (with contaminant **4.77**) with dimethyl zinc reagent in the presence of (–)-morpholino isoborneol (MIB) asymmetrically added a methyl group on the aldehyde, which afforded a mixture of diastereomers **4.78** and **4.79** in 85% yield (Scheme 4-13).[91] However, (*Z*)-isomer **4.79** was still unable to be isolated under normal laboratory technologies. Unfortunately, when the mixture of **4.78** and **4.79** were directly subjected to the following steps, the undesired isomer was still inseparable. Through analyzing the structures of isomers **4.76** and **4.77**, we hypothesized that (*Z*)-isomer **4.77** might have a much higher reactivity in the methylation than (*E*)-isom*e*r **4.76** in order to relieve the steric interaction between the

carbonyl group and C34 methyl group. Thus, the mixture of **4.76** and **4.77** were subjected to the methylation with reduced loading amount of dimethyl zinc and (–)-MIB. As expected, pure (*E*)-isomer **4.76** was obtained in an 83% recovery, which was re-subjected to methylation to afford pure **4.78** in 86% yield.

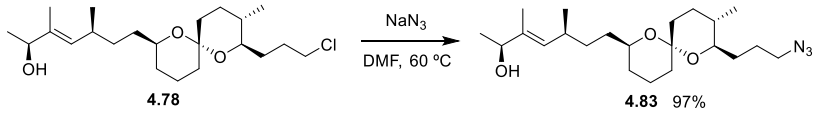


Scheme 4-13. Dimethylzinc-mediated asymmetric methylation

The proposed mechanism for the asymmetric methylation is also shown in Scheme 4-14.[92] The (–)-MIB reacts with one equivalent of dimethyl zinc and coordinates with another molecule of dimethyl zinc to form the bimetallic intermediate **4.80**. When aldehyde **4.76** coordinates to this bimetallic intermediate, the larger group occupies the less hindered position and orients the hydrogen upwards as shown in model **4.81**. Then, the addition of the internal methyl group forms the desired chiral center in model **4.82**, which converted to **4.78** upon work up. Due to the reported instability of the lefthand fragment,[79d] the synthesis of this fragment was temporarily halted at azide **4.83** which was formed by the convertion of the chloride on **4.78** to an azido group (Scheme 4-15).[93]



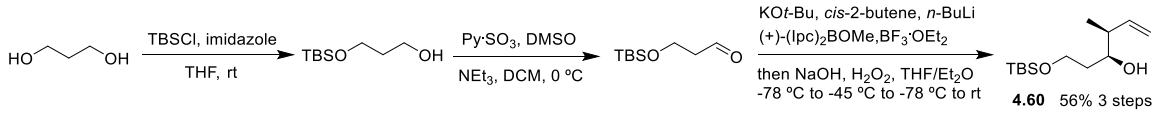
Scheme 4-14. Proposed mechanism of asymmetric



Scheme 4-15. Synthesis of the precursor of the lefthand fragment

4.4.2 Righthand Fragment Synthesis

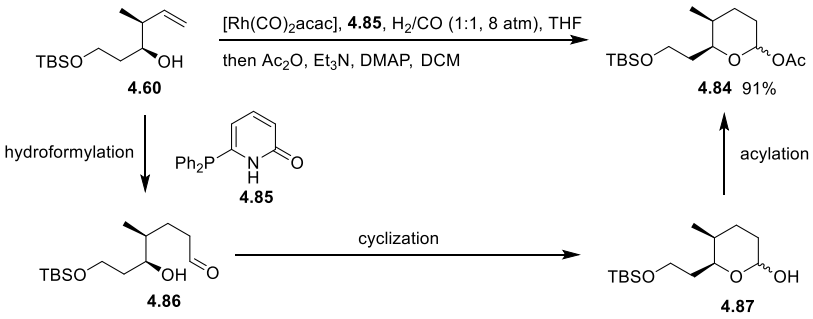
The righthand fragment synthesis began with the assembly of chiral homoallylic alcohol **4.60**, which was sourced from 1,3-propanediol, followed by monosilylation, Parikh-Doering oxidation, and Brown crotylation (Scheme 4-16).



Scheme 4-16. Synthesis of homoallylic alcohol **4.60**

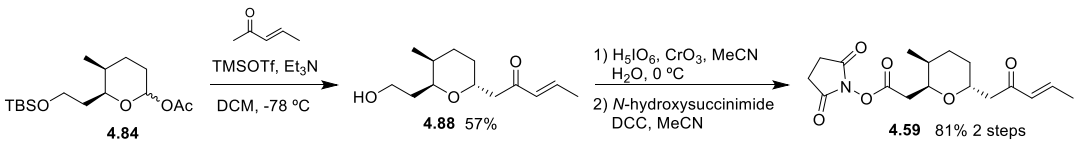
Inspired by the *trans*-THP construction during the formal synthesis of leucascandrolide A in the Floreancig group (Scheme 2-1),[35] a creative one-pot process was invented to directly convert

homoallylic alcohol **4.60** to THP **4.84** (Scheme 4-17). At the initial stage, the hydroformylation extended the carbon chain of **4.60** by one carbon with the assistance of rhodium catalyst in the presence of Breit's exceptional DPPon ligand **4.85**.[94] The resulting aldehyde **4.86** cyclized to form THP intermediate **4.87**, which was treated with acetic anhydride to yield THP **4.84** as a mixture of diastereomers. Compared to Kozmin's four-step sequence that constructed the same THP product (Scheme 4-2), this one-pot process is exceedingly more efficient.



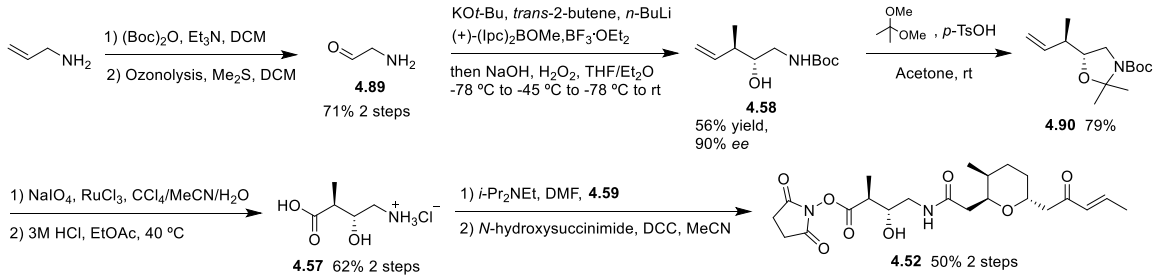
Scheme 4-17. The one-pot process to access THP **4.84**

The substitution of the acetoxy group of **4.84** with an α,β-unsaturated ketone was promoted by TMSOTf (Scheme 4-18). This reagent generated the tetrahydropyranyl carbocation intermediate from **4.84**, which accepted the nucleophilic attack from the *in situ* generated enol trimethylsilyl ether to form a 2,6-*trans*-THP intermediate. Moreover, during the quenching process, TMSOTf was hydrolyzed by water and released triflic acid that deprotected the silyl group to yield alcohol **4.88**. A CrO_3/H_5IO_6 oxidation converted the resulting alcohol to the carboxylic acid, which was subsequently activated by *N*-hydroxysuccinimide to form **4.59**.



Scheme 4-18. Synthesis of *trans*-THP **4.59**

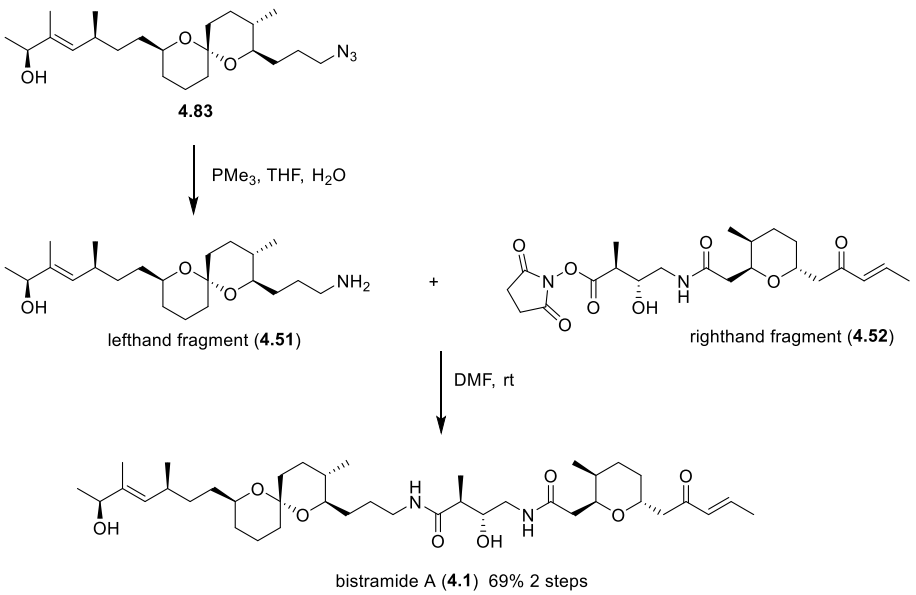
The synthesis of γ-amino acid hydrochloride salt **4.57** essentially followed Kozmin's protocol except the Fmoc protection step, which was unnecessary for our total synthesis (Scheme 4-19). Neutralizing **4.57** with Hünig's base enabled it to couple with *trans*-THP **4.59** smoothly. The resulting carboxylic acid was activated by coupling with *N*-hydroxysuccinimide to form the righthand fragment **4.52**.



Scheme 4-19. Synthesis of amino acid hydrochloride salt **4.57** and righthand fragment **4.52**

4.4.3 Completion of the Total Synthesis

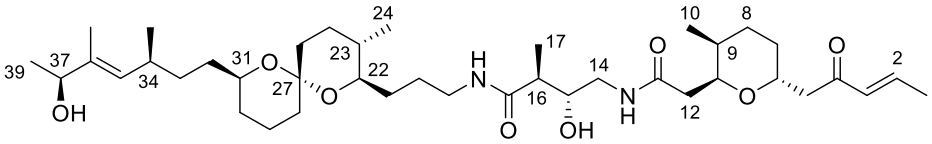
The end game of this total synthesis was initiated by reductively converting the azido group of lefthand fragment to the primary amino group in the presence of trimethylphosphine, followed by coupling with righthand fragment without any assisting reagent (Scheme 4-20). This two-step sequence delivered natural product bistramide A in a 68% overall yield.



Scheme 4-20. Completion of total synthesis of bistramide A

The spectroscopic data (^{1}H NMR and ^{13}C NMR) for the synthetic bistramide A were closely matched with those data for natural bistramide A (Table 4-2),[72c] which indicates the success of the total synthesis of bistramide A.

Table 4-2. Comparison of the NMR data of natural bistramide A to synthetic bistramide



Carbon #	Natural Bistramide A, ^{13}C NMR, ppm, 100 MHz	Synthetic Bistramide A, ^{13}C NMR, ppm, 125 MHz	Natural Bistramide A, ^{1}H NMR, ppm, 400 MHz	Synthetic Bistramide A, ^{1}H NMR, ppm, 400 MHz
1	18.43	18.63	1.91 (dd, 3H, *J* = 1.4, 6.8 Hz)	1.93 (dd, 3H, *J* = 1.6, 6.8 Hz)
2	144.50	144.72	6.90 (dq, 1H, *J* = 6.8, 15.7 Hz)	6.91 (dd, 1H, *J* = 6.8, 15.6 Hz)
3	132.07	132.33	6.15 (dq, 1H, *J* = 1.5, 15.7Hz)	6.13 (dd, 1H, *J* = 1.6, 15.6 Hz)
4	198.89	199.13	—	—
5	45.24	45.49	2.91 (dd, 1H, *J* = 8.8, 17.0 Hz), 2.53 (dd, 1H, *J* = 3.0, 17.0 Hz)	2.91 (dd, 1H, *J* = 8.8, 16.8 Hz), 2.53 (dd, 1H, *J* = 2.8, 17.2 Hz)
6	64.80	64.98	4.20-4.19 (m, 1H)	4.22-4.18 (m, 1H)
7	30.78	31.10	1.73-1.42 (m, 1H), 1.41-1.29 (m, 1H)	1.86-1.42 (m, 1H), 1.41-1.12 (m, 1H)
8	26.52	26.73	1.73-1.42 (m, 1H), 1.41-1.29 (m, 1H)	1.86-1.42 (m, 1H), 1.41-1.12 (m, 1H)
9	33.32	33.55	1.92 (m, 1H)	1.86-1.42 (m, 1H)
10	17.14	17.36	0.86 (d, 3H, *J* = 7.0 Hz, 3H)	0.89 (d, 3H, *J* = 6.8 Hz)

11	74.82	75.05	4.06 (dd, 1H, *J* = 4.8, 11.2 Hz)	4.07 (dd, 1H, *J* = 4.8, 11.2 Hz)
12	32.33	32.52	2.75 (dd, 1H, *J* = 11.7, 15.1 Hz)	2.76 (dd, 1H, *J* = 11.6, 14.8 Hz)
13	173.42	173.72	—	—
14	44.85	44.92	3.50 (dt, 1H, *J* = 5.8, 14.0 Hz), 3.24 (dt, 1H, *J* = 5.7, 14.0 Hz)	3.51 (dt, 1H, *J* = 5.4, 14.0 Hz), 3.24 (dt, 1H, *J* = 6.0, 14.0 Hz)
15	73.81	74.10	3.72 (dt, 1H, *J* = 10.3, 5.1 Hz)	3.72 (q, 1H, *J* = 4.8 Hz)
16	43.36	43.56	2.38 (dq, 1H, *J* = 5.0, 7.0 Hz)	2.42-2.34 (m. 1H)
17	15.57	15.78	1.26 (d, 3H, *J* = 7.0 Hz)	1.26 (t, 3H, *J* = 6.8 Hz)
18	175.14	175.37	—	—
19	39.49	39.71	3.30 (dt, 2H, *J* = 6.8, 12.7 Hz)	3.31 (dt, 2H, *J* = 6.8, 12.8 Hz)
20	25.86	26.09	1.83-1.82 (m, 1H), 1.73-1.42 (m, 1H)	1.86-1.42 (m, 2H)
21	30.44	30.66	1.73-1.42 (m, 1H), 1.41-1.29 (m, 1H)	1.86-1.42 (m, 1H), 1.41-1.12 (m, 1H)
22	74.26	74.47	3.15 (dt, 1H, *J* = 1.8, 9.6 Hz)	3.16 (dt, 1H, *J* = 2.0, 9.6 Hz)
23	34.89	35.09	1.41-1.29 (m, 1H)	1.41-1.12 (m, 2H)

24	17.94	18.22	0.76 (d, 3H, *J* = 6.6 Hz)	0.82 (d, 3H, *J* = 6.4 Hz)
25	27.87	28.12	1.73-1.42 (m, 2H)	1.86-1.42 (m, 2H)
26	36.10	36.31	1.73-1.42 (m, 2H)	1.86-1.42 (m, 2H)
27	95.44	95.67	—	—
28	35.47	35.70	1.73-1.42 (m, 1H), 1.41-1.29 (m, 1H)	1.86-1.42 (m, 1H), 1.41-1.12 (m, 1H)
29	19.23	19.44	1.83-1.82 (m, 1H), 1.73-1.42 (m, 1H)	1.86-1.42 (m, 2H)
30	31.34	31.56	1.73-1.42 (m, 1H), 1.13 (m, 1H)	1.86-1.42 (m, 1H), 1.41-1.12 (m, 1H)
31	69.07	69.29	3.45 (m, 1H)	3.45 (m, 1H)
32	34.09	34.32	1.73-1.42 (m, 1H), 1.41-1.29 (m, 1H)	1.86-1.42 (m, 1H), 1.41-1.12 (m, 1H)
33	33.48	33.69	1.41-1.29 (m, 2H)	1.41-1.12 (m, 2H)
34	31.88	32.09	2.36 (m, 1H)	2.42-2.34 (m. 1H)
35	20.97	21.17	0.96 (d, 3H, *J* = 6.8 Hz)	0.96 (d, 3H, *J* = 6.8 Hz)
36	131.32	131.61	5.20 (d, 1H, *J* = 9.2 Hz)	5.19 (d, 1H, *J* = 9.6 Hz)
37	137.16	137.39	—	—

38	11.82	12.01	1.62 (d, 3H, *J* = 1.3 Hz)	1.63 (d, 3H, *J* = 1.2 Hz)
39	73.26	73.53	4.20-4.19 (m, 1H)	4.22-4.18 (m, 1H)
40	21.75	21.96	1.25 (d, 3H, *J* = 6.3 Hz)	1.26 (t, 3H, *J* = 6.8 Hz)
NH (13/14)			7.30 (br.t, 1H, *J* = 5.8 Hz)	7.32 (br.t, 1H, *J* = 6.0 Hz)
NH (18/19)			6.95 (br.t, 1H, *J* = 5.5 Hz)	6.96-6.94 (br.m, 1H)
OH (4)			—	—
OH (11)			—	—
OH (15)			4.61 (d, OH, *J* = 5.3 Hz)	4.62 (br.s, 1H)
OH (39)			3.70 (br)	—

4.5 SUMMARY

We have established a convergent route toward the biologically active natural product bistramide A. It is currently the shortest synthetic sequence to access this molecule, which takes 14 steps from commercially available starting materials for the longest linear sequence and 31 total steps from commercially available starting materials for the total synthesis. The corresponding steps for the shortest previous synthesis are 17 steps and 45 steps.

Our total synthesis of bistramide A is highlighted by two one-pot processes. The one-pot spiroketal formation process successfully combined two relatively simple acyclic pieces to form

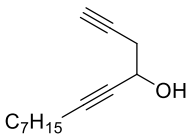
the highly complex spiroketal in good yield, which is also a perfect showcase of the spiroketal formation methodology illustrated in Chapter 3. The one-pot hydroformylation, cyclization, and acetylation process significantly accelerated the assembly of the 2,6-*trans*-disubstituted-THP ring. Additionally, a kinetic separation was conducted during the asymmetric methylation process, which isolated the undesired *Z*-isomer and ensured the purity of the final natural product.

APPENDIX A

SYNTHESIS OF MACROLACTONES BEARING BRIDGED 2,6-*TRANS*-TETRAHYDROPYRANS THROUGH OXIDATIVE C–H BOND ACTIVATION

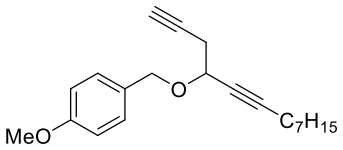
General Experimental: Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz. The chemical shifts are reported in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; qunit = quintet; sept = septet; dd = doublet of doublets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublet; td = triplet of doublets; dtd = doublet of triplet of doublets; br = broad). High resolution and lowresolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Methylene chloride was distilled under N_2 from CaH_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, toluene and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All products in this manuscript are racemic mixtures but are drawn as single enantiomers to indicate their relative stereochemistry.

Trideca-1,5-diyn-4-ol (2.27)



To a solution of dec-2-yn-1-ol (2.6 g, 17 mmol) and NEt_3 (6.9 mL, 50 mmol) in dry DMSO (16 mL) and dry CH_2Cl_2 (12 mL) was added sulfur trioxide pyridine complex (4.0 g, 25 mmol) in one portion at rt. The dark brown solution was stirred for 1.5 h, then was quenched with H_2O. The aqueous layer was extracted with ether (3x). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 25:1) to give dec-2-ynal as a yellow oil (2.0 g, 79%). A mixture of zinc powder (4.3 g, 66 mmol), 1,2-diiodoethane (3.7 g, 13 mmol), dec-2-ynal (2.0 g, 13 mmol), and 3-bromo-1-propyne (2.3 g, 20 mmol) in anhydrous THF (60 mL) was sonicated in a commercial ultrasonic cleaning bath for 2 h, then was quenched with 1.0 M HCl solution, followed by the extraction with ether (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1 to 12:1) to give **2.27** as a yellow oil (2.2 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (qt, 1H, *J* = 2.1, 6.0 Hz), 2.58-2.52 (m, 3H), 2.18 (td, 2H, *J* = 1.8, 6.9 Hz), 2.08 (t, 1H, *J* = 2.7 Hz), 1.50-1.43 (m, 2H), 1.37-1.24 (m, 8H), 0.86 (t, 3H, *J* = 6.3 Hz).

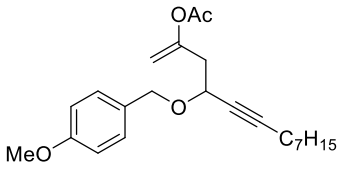
1-Methoxy-4-((trideca-1,5-diyn-4-yloxy)methyl)benzene (2.29a)



A solution of trichloroacetimidate **2.28** (2.1 g, 7.5 mmol) and homopropargyl alcohol **2.27** (0.96 g, 5.0 mmol) in toluene (120 mL) was treated with $La(OTf)_3$ (142 mg, 0.250 mmol). The resulting suspension was stirred at rt for 1.5 h, then was quenched with silica gel. After filtration, the filtrate was concentrated *in vacuo* and purified by flash chromatography (hexanes:EtOAc = 50:1) to afford desired ether **2.29a** (1.5 g, 94%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 2H, *J* =

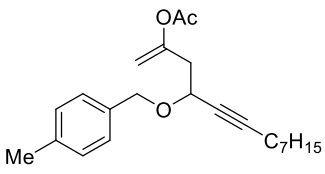
8.4 Hz), 6.92 (d, 2H, *J* = 8.7 Hz), 4.79 (d, 1H, *J* = 11.4 Hz), 4.54 (d, 1H, *J* = 11.4 Hz), 4.25 (tt, 1H, *J* = 1.8, 6.6 Hz), 3.82 (s, 3H), 2.65 (ddd, 2H, *J* = 1.5, 2.7, 6.6 Hz), 2.31 (td, 2H, *J* = 1.8, 6.9 Hz), 2.10 (t, 1H, *J* = 2.4 Hz), 1.62-1.58 (m, 2H), 1.52-1.41 (m, 2H), 1.38-1.28 (m, 6H), 0.95 (t, 3H, *J* = 7.2 Hz).

4-(4-Methoxybenzyloxy)tridec-1-en-5-yn-2-yl acetate (2.12)



To a suspension of [(*p*-cymene)$RuCl_2$]$_2$ (115 mg, 0.190 mmol), Na_2CO_3 (75 mg, 0.71 mmol), tri(2-furyl)phosphine (87 mg, 0.38 mmol), and 1-decyne (0.85 mL, 4.7 mmol) in toluene (30 mL) was added the first portion of acetic acid (0.55 mL, 9.4 mmol). The mixture was heated to 80 °C and stirred for 1 h. The second portion of acetic acid (0.55 mL, 9.4 mmol) and **2.29**a (1.5 g, 4.7 mmol) in toluene (5 mL) were added into the reaction through syringe. The reaction was stirred at the 80 °C for 3 h. Then crude mixture was loaded onto a small plug of silica gel and eluted with EtOAc (3x). The residue was concentrated and purified by flash chromatography (hexanes:EtOAc = 40:1 to 20:1) to give the desired enol acetate (0.78 g, 45%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 6.90-6.87 (m, 2H), 4.85 (s, 2H), 4.72 (d, 1H, *J* = 11.4 Hz), 4.45 (d, 1H, *J* = 11.4 Hz), 4.22 (ddt, 1H, *J* = 2.1, 6.3, 7.2 Hz), 3.81 (s, 3H), 2.66 (dd, 2H, *J* = 5.4, 7.2 Hz), 2.25 (td, 2H, *J* = 1.8, 6.9 Hz) 2.05 (s, 3H), 1.59-1.49 (m, 2H), 1.44-1.29 (m, 8H), 0.90 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 159.4, 152.3, 130.1, 129.9, 113.9, 104.3, 87.4, 78.2, 70.1, 66.1, 55.5, 40.6, 32.0, 29.0, 28.9, 22.8, 21.2, 18.9, 14.3; IR (neat) 2930, 2857, 1758, 1667, 1613, 1586, 1514, 1464, 1369, 1341, 1302, 1249, 1206, 1137, 1081, 1036, 965, 875, 823, 758, 721 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{32}O_4Na$ $[M+Na]^+$ 395.2198, found 395.2190.

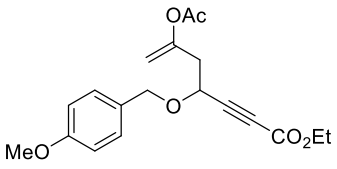
4-(4-Methylbenzyloxy)tridec-1-en-5-yn-2-yl acetate (2.13)



NaH (60%, 84 mg, 2.1 mmol) was added to a solution of homopropargyl alcohol **2.27** (0.26 g, 1.4 mmol) in anhydrous THF (5 mL) at 0 °C. The resulting suspension was stirred at rt for 30 min, followed by adding *n*-Bu_4NI (52 mg, 0.14 mmol) and *p*-methyl benzyl bromide (0.26 g, 1.4 mmol) successively. The resulting mixture was stirred at rt for 24 h, then was quenched with water. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to give ether **2.29b** (0.47 g, 99%). To a suspension of [(*p*-cymene)$RuCl_2$]$_2$ (18 mg, 0.029 mmol), Na_2CO_3 (11 mg, 0.11 mmol), tri(2-furyl)phosphine (14 mg, 0.058 mmol) and 1-decyne (0.13 mL, 0.72 mmol) in toluene (6.5 mL) was added the first portion of acetic acid (0.080 mL, 1.4 mmol). The mixture was heated to 80 °C and stirred for 1 h. The second portion of acetic acid (0.080 mL, 1.4 mmol) and ether **2.29b** (0.21 g, 0.72 mmol) in toluene (1 mL) were added to the reaction through syringe. The reaction was stirred at the 80 °C for 3 h. Then crude mixture was loaded onto a small plug of silica gel and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography to give the desired enol acetate (149 mg, 58%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H, *J* = 8.0 Hz), 7.15 (d, 2H, *J* = 8.0 Hz), 4.85 (s, 2H), 4.74 (d, 1H, *J* = 11.6), 4.48 (d, 1H, *J* = 11.6 Hz), 4.23 (t, 1H, *J* = 6.8 Hz), 2.66 (app dd, 2H, *J* = 6.8, 8.0 Hz), 2.35 (s, 3H), 2.24 (app dd, 2H, *J* = 5.6, 6.8 Hz), 2.05 (s, 3H), 1.56-1.49 (m, 2H), 1.42-1.37 (m, 2H), 1.34-1.26 (m, 6H), 0.90 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 152.3, 137.5, 135.0, 129.2, 128.4, 104.3, 87.5, 78.2, 70.3, 66.3, 40.6, 32.0, 29.0, 28.9, 22.9, 21.4, 21.3, 18.9, 14.3; IR (neat) 2928, 2857, 1759, 1668, 1458, 1433, 1369,

1340, 1204, 1083, 1020, 874, 803 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{32}O_3Na$ $[M+Na]^+$ 379.2249, found 379.2222

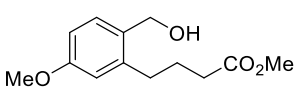
Ethyl 6-acetoxy-4-(4-methoxybenzyloxy)hept-6-en-2-ynoate (2.14)



Ethyl propynoate (5.0 g, 51 mmol), triethyl orthoformate (11 g, 74 mmol), and ZnI_2 (0.2 g) were placed in a fractional distillation apparatus. The reaction was carefully heated for 2.5 h to maintain the distillate temperature between 50 to 100 °C. Then the thick brown residue was cooled down and poured to hexane (100 mL). After filtration, the filtrate was concentrated *in vacuo*. The residue was purified by the fractional distillation under reduced pressure to give target acetal, ethyl 4,4-diethoxybut-2-ynoate (4.3 g, b.p. 90 °C/2-7 torr) as a colorless liquid. A mixture of ethyl 4,4-diethoxybut-2-ynoate (2.0 g, 10 mmol) and formic acid (4 mL) was stirred at 40 ºC for 3 h, then was poured to ice water. The resulting mixture was neutralized by $NaHCO_3$ powder, and followed by extraction with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude aldehyde (10 mmol) was re-dissolved in anhydrous THF (40 mL). To the resulting solution were added propargyl bromide (1.8 g, 15 mmol), Zn powder (3.2 g, 50 mmol), and 1,2-diiodoethane (2.8 g, 10 mmol) successively. The resulting suspension was sonicated in a commercial ultrasonic cleaning bath for 2 h. After the sonication, the reaction was quenched with 1.0 M HCl solution and followed by extraction with ether (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give the desired homopropargyl alcohol 2.31 (466 mg, with impurities) as a yellow oil. To the solution of alcohol **2.31** (0.50 g, 3.0 mmol) and trichloroacetimidate **2.28** (1.3 g, 4.5 mmol) in toluene (60 mL) was

added $La(OTf)_3$ (88 mg, 0.15 mmol) in one portion. The resulting suspension was stirred for 12 hours at rt, and then quenched with silica gel. After filtration, the filtrate was concentrated and purified by flash chromatography (hexanes:EtOAc = 20:1) to give the target benzylic ether (with impurities). To a suspension of $[(p\text{-cymene})RuCl_2]_2$ (33 mg, 0.054 mmol), Na_2CO_3 (21 mg, 0.20 mmol), tri(2-furyl)phosphine (25 mg, 0.11 mmol) and 1-decyne (0.24 mL, 1.3 mmol) in toluene (12 mL) was added the first portion of acetic acid (0.15 mL, 2.7 mmol). The mixture was heated to 80 °C and stirred for 1 h. The second portion of acetic acid (0.15 mL, 2.7 mmol) and the newly formed benzylic ether (0.38 g, 1.3 mmol) in toluene (3 mL) were added into the reaction through syringe. The reaction was stirred at the 80 °C for 4 h. Then crude mixture was loaded onto a small plug of silica gel and eluted with EtOAc. The filtrate was concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1 to 15:1) to give the desired enol acetate (170 mg, 4% over 5 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, 2H, *J* = 8.5 Hz), 6.89 (d, 2H, *J* = 9.0 Hz), 4.90 (d, 1H, *J* = 2.0 Hz), 4.89 (s, 1H), 4.75 (d, 1H, *J* = 11.0 Hz), 4.46 (d, 1H, *J* = 11.0 Hz), 4.33 (t, 1H, *J* = 6.5 Hz), 4.26 (q, 2H, *J* = 7.0 Hz), 3.81 (s, 3H), 2.73-2.72 (m, 2H), 2.06 (s, 3H), 1.34 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 159.7, 153.4, 150.9, 130.1, 129.1, 114.0, 105.3, 85.0, 78.2, 71.1, 65.5, 62.4, 55.5, 39.5, 21.2, 14.2; IR (neat) 2938, 2869, 2839, 2235, 1757, 1713, 1669, 1613, 1514, 1465, 1369, 1301, 1250, 1208, 1086, 1034, 882, 823, 752 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}O_6Na$ $[M+Na]^+$ 369.1314, found 369.1331.

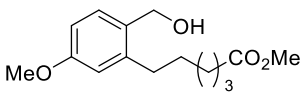
Methyl 4-(2-(hydroxymethyl)-5-methoxyphenyl)butanoate (2.34a)



To a solution of methyl but-3-enoate (1.2 g, 12 mmol) in anhydrous THF (6.7 mL) at 0 °C was added 9-BBN (35 mL, 0.5 M in THF, 17 mmol). The reaction was warmed to rt and stirred for 4 h, then was diluted with anhydrous DMF (67 mL)

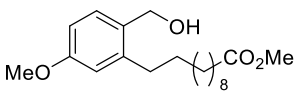
and treated with $PdCl_2(dppf)•CH_2Cl_2$ (0.27 g, 0.33 mmol), 2-bromo-4-methoxybenzaldehyde (2.3 g, 11 mmol), and K_2CO_3 (3.0 g, 22 mmol). The mixture was heated to 50 °C and stirred overnight. The reaction was quenched by pouring the crude mixture into H_2O. The aqueous layer was extracted with EtOAc (3x). The combined organic layer was washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1) to give the desired product (2.7 g, contaminated by borate derivatives). The crude product was dissolved in MeOH (25 mL) and treated with $NaBH_4$ (0.43 g, 11 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min, then was quenched with sat. aq. $NaHCO_3$. The crude mixture was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 4:1) to give **2.34a** (2.1 g, 80% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 1H, *J* = 8.4 Hz), 6.76 (s, 1H), 6.75 (d, 1H, *J* = 16.0 Hz), 4.66 (d, 2H, *J* = 5.6 Hz), 3.82 (s, 3H), 3.68 (s, 3H), 2.73 (t, 2H, *J* = 8.0 Hz), 2.42 (t, 2H, *J* = 7.2 Hz), 2.04 (t, 1H, *J* = 5.6 Hz), 1.97 (p, 2H, *J* = 7.6 Hz).

Methyl 6-(2-(hydroxymethyl)-5-methoxyphenyl)hexanoate (2.34b)



Same procedure with the preparation of **2.34a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 1H, *J* = 7.5), 6.75-6.72 (m, 2H), 4.65 (s, 2H), 3.81 (s, 3H), 3.67 (s, 3H), 2.68 (t, 2H, *J* = 7.8 Hz), 2.33 (t, 2H, *J* = 7.2 Hz), 1.73-1.59 (m, 4H), 1.48-1.37 (m, 2H).

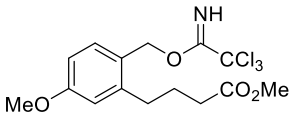
Methyl 11-(2-(hydroxymethyl)-5-methoxyphenyl)undecanoate (2.34c)



Same procedure with the preparation of **2.34a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 1H, *J* = 8.4 Hz), 6.77-6.72 (m, 2H), 4.65 (d, 2H, *J* =

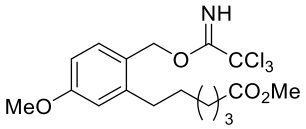
5.6 Hz), 3.81 (s, 3H), 3.67 (s, 3H), 2.67 (t, 2H, *J* = 8.0 Hz), 2.31 (t, 2H, *J* = 7.6 Hz), 1.64-1.56 (m, 4H), 1.45 (t, 1H, *J* = 5.6 Hz), 1.39-1.29 (m, 12H).

Methyl 4-(5-methoxy-2-((2,2,2-trichloro-1-iminoethoxy)methyl)phenyl)butanoate (2.35a)



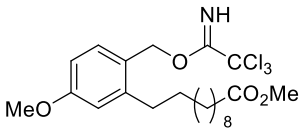
To a solution of **2.34a** (345 mg, 1.45 mmol) in CH_2Cl_2 (3 mL) were added DBU (0.32 mL, 2.2 mmol) and Cl_3CCN (0.44 mL, 622 mg) at 0 °C. The reaction mixture was warmed to rt and stirred for 1 h at this temperature. The mixture was directly concentrated *in vacuo* and purified by flash chromatography (hexanes:EtOAc = 15:1, hexane contained 1% NEt_3) to give **2.35a** (304 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.35 (d, 1H, *J* = 8.1 Hz), 6.78-6.75 (m, 2H), 5.28 (s, 2H), 3.82 (s, 3H), 3.68 (s, 3H), 2.73 (t, 2H, *J* = 7.8 Hz), 2.39 (t, 2H, *J* = 7.5 Hz), 1.98 (p, 2H, *J* = 7.8 Hz).

Methyl 6-(5-methoxy-2-((2,2,2-trichloro-1-iminoethoxy)methyl)phenyl)hexanoate (2.35b)



Same procedure with the preparation of **2.35a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.35 (d, 1H, *J* = 8.4 Hz), 6.78-6.73 (m, 2H), 5.28 (s, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 2.69 (t, 2H, *J* = 7.8 Hz), 2.32 (t, 2H, *J* = 7.5 Hz), 1.72-1.61 (m, 4H), 1.47-1.36 (m, 2H).

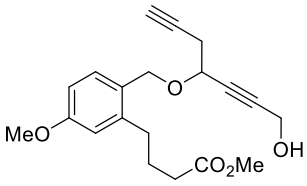
Methyl 11-(5-methoxy-2-((2,2,2-trichloro-1-iminoethoxy)methyl)phenyl) undecanoate (2.35c)



Same procedure with the preparation of **2.35a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.34 (d, 1H, *J* = 8.4 Hz), 6.79 (d, 1H, *J* = 2.8 Hz),

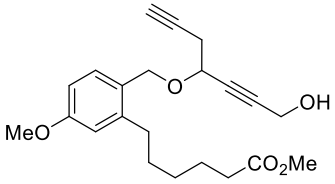
6.75 (dd, 1H, *J* = 2.8, 8.4 Hz), 5.30 (d, 2H, *J* = 12.0 Hz), 3.82 (s, 3H), 3.67 (s, 3H), 2.67 (t, 2H, *J* = 8.0 Hz), 2.31 (t, 2H, *J* = 7.2 Hz), 1.66-1.59 (m, 4H), 1.37-1.28 (m, 12H).

Methyl 4-(2-((7-hydroxyhepta-1,5-diyn-4-yloxy)methyl)-5-methoxyphenyl)butanoate (2.37a)



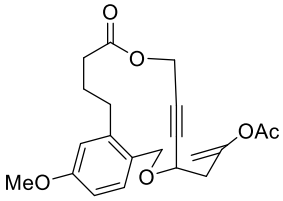
Trichloroacetimidate **2.35a** (1.6 g, 4.1 mmol) and secondary alcohol **2.36** (0.98 g, 4.1 mmol) were dissolved in anhydrous toluene (70 mL) at rt. $La(OTf)_3$ (0.12 g, 0.2 mmol) was added. The resulting mixture was stirred overnight. The reaction was quenched with silica gel, then was filtered using Et_2O as the eluant. The filtrate was concentrated and purified by flash chromatography (hexanes:EtOAc = 20:1 to 10:1) to give the desired homopropargylic ether (1.0 g, contaminated by some impurities). The crude was dissolved in MeOH (30 mL) and treated with $TsOH•H_2O$ (200 mg) at rt. After stirring for 30 min, the solution was concentrated and purified by flash chromatography (hexanes:EtOAc = 10:1 to 1:1) to give the desired product (595 mg, 42% over two steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.26 (m, 1H), 6.75 (s, 1H), 6.73 (dd, 1H, *J* = 2.7, 8.1 Hz), 4.80 (d, 1H, *J* = 11.1 Hz), 4.48 (d, 1H, *J* = 11.1 Hz), 4.36 (d, 2H, *J* = 4.5 Hz), 4.28 (tt, 1H, *J* = 1.8, 5.4 Hz), 3.80 (s, 3H), 3.70 (s, 3H), 2.74 (dd, 1H, *J* = 0.9, 9.3 Hz), 2.72 (d, 1H, *J* = 9.3 Hz), 2.64 (ddd, 2H, *J* = 1.5, 2.7, 6.6 Hz), 2.48 (t, 1H, *J* = 6.6 Hz), 2.42 (t, 2H, *J* = 7.2 Hz), 2.06 (t, 1H, *J* = 2.7 Hz), 1.96 (p, 2H, *J* = 7.8 Hz).

Methyl 6-(2-((7-hydroxyhepta-1,5-diyn-4-yloxy)methyl)-5-methoxyphenyl)hexanoate (2.37b)



Same procedure with the preparation of **2.37a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 1H, *J* = 8.4 Hz), 6.75-6.69 (m, 2H), 4.78 (d, 1H, *J* = 11.1 Hz), 4.46 (d, 1H, *J* = 11.1 Hz), 4.37 (d, 2H, *J* = 1.5 Hz), 4.27 (tt, 1H, *J* = 1.5, 6.6 Hz), 3.80 (s, 3H), 3.68 (s, 3H), 2.69 (t, 2H, *J* = 8.1 Hz), 2.63 (ddd, 2H, *J* = 1.2, 2.7, 6.6 Hz), 2.34 (t, 2H, *J* = 7.2 Hz), 2.06 (t, 1H, *J* = 2.7 Hz), 1.74-1.59 (m, 4H), 1.48-1.38 (m, 2H).

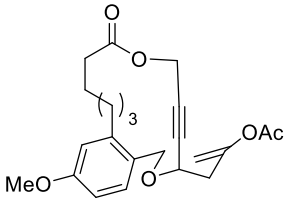
Macrolactone substrate 2.15



To a solution of **2.37a** (0.1 g, 0.3 mmol) in a mixed solvent of THF, MeOH, and H_2O (0.9 mL, 0.3 mL, and 0.3 mL respectively) at rt was added LiOH•H_2O (50 mg, 1.2 mmol). The resulting mixture was stirred at rt for 1 h, then was acidified with 0.5 M HCl until the pH fell into the range of 3 to 4. The aqueous solution was extracted with EtOAc (3x), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was re-dissolved in anhydrous THF (2 mL), followed by the addition of anhydrous NEt_3 (0.2 mL) at rt. The mixture was stirred for 20 min, then a solution of trichlorobenzoyl chloride (106 mg, 0.43 mmol) in anhydrous THF (2 mL) was added. Precipitates were formed after a few minutes. The mixture was stirring for 2 h at rt, followed by a filtration. The precipitates were washed with toluene (135 mL total). The toluene solution of filtrate was added dropwise into a solution of DMAP (146 mg, 1.2 mmol) in toluene (40 mL) at 65 °C over a period of 4 h. After addition, the mixture was concentrated, re-dissolved in Et_2O, and washed with sat. aq. $NaHCO_3$. The organic layer was dried

over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography to give the desired macrolactone (27 mg, 29% over 2 steps). To a mixture of [(*p*-cymene)$RuCl_2$]$_2$ (8.3 mg, 0.014 mmol), Na_2CO_3 (5.4 mg, 0.051 mmol), tri(2-furyl)phosphine (6.5 mg, 0.028 mmol), and 1-decyne (60 μL, 0.34 mmol) in toluene (2.2 mL) was added the first portion of acetic acid (39 μL, 0.68 mmol). The mixture was heated to 80 °C and stirred for 1 h. The second portion of acetic acid (39 μL, 0.68 mmol) and the newly prepared macrolactone (106 mg, 0.34 mmol) in toluene (1 mL) were added into the reaction through syringe. The reaction was stirred at the 80 °C for 3 h. Then crude mixture was loaded onto a small plug of silica gel and eluted with EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 10:1) to give enol acetate **2.15** (49 mg, 11% over 3 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, 1H, *J* = 7.8 Hz), 6.74-6.70 (m, 2H), 4.89 (s, 1H), 4.85 (d, 1H, *J* = 1.5 Hz), 4.77 (d, 2H, *J* = 2.1), 4.76 (d, 1H, *J* = 9.6 Hz), 4.30 (tt, 1H, *J* = 2.1, 6.9 Hz), 4.17 (d, 1H, *J* = 9.3 Hz), 2.93-2.83 (m, 1H), 2.68 (dd, 1H, *J* = 6.9, 15.0), 2.62-2.37 (m, 3H), 2.08 (s, 3H), 2.00-1.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 169.0, 160.0, 151.4, 143.1, 132.7, 127.1, 115.4, 111.2, 104.6, 84.8, 81.2, 68.0, 67.1, 55.2, 52.0, 39.4, 34.4, 31.2, 29.3, 21.1; IR (neat) 2922, 2852, 1745, 1667, 1611, 1579, 1503, 1461, 1439, 1368, 1324, 1258, 1215, 1132, 1110, 1044, 1025 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{24}O_6Na$ $[M+Na]^+$ 395.1471, found 395.1475.

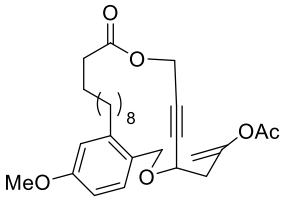
Macrolactone substrate 2.16



To a solution of **2.37b** (94 mg, 0.25 mmol) in a mixed solvent of THF, MeOH, and H_2O (0.78 mL, 0.26 mL, and 0.26 mL, respectively) at rt was added LiOH•H_2O (42 mg, 1.0 mmol). The resulting mixture was stirred at rt for 1 h, and then was acidified with 0.5 M HCl until the pH fell in the range of 3 to 4. The

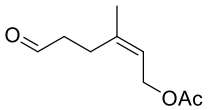
aqueous solution was extracted with EtOAc (3x), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was re-dissolved in anhydrous MeCN (200 mL), followed by the addition of anhydrous NEt_3 (0.35 mL) at rt. The resulting mixture was added to a refluxing solution of 2-chloro-1-methylpyridinium iodide (322 g, 1.26 mmol) in MeCN (400 mL) over 10 h. The resulting brown solution was cooled down and concentrated *in vacuo*. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1) to afford the desired macrolactone (61 mg). To a mixture of $[(p\text{-cymene})RuCl_2]_2$ (5.1 mg, 0.0084 mmol), Na_2CO_3 (3.3 mg, 0.032 mmol), tri(2-furyl)phosphine (3.9 mg, 0.017 mmol) and 1-decyne (37 μL, 0.21 mmol) in toluene (2 mL) was added the first portion of acetic acid (24 μL, 0.42 mmol). The mixture was heated to 80 °C and stirred for 1 h. The second portion of acetic acid (24 μL, 0.42 mmol) and the newly prepared macrolactone (71 mg, 0.21 mmol) in toluene (1 mL) were added into the reaction through syringe. The reaction was stirred at the 80 °C for 5 h. Then crude mixture was loaded onto a small plug of silica gel and eluted with EtOAc. The filtrate was concentrated and the residue purified by flash chromatography (hexanes:EtOAc = 20:1 to 10:1) to give the enol acetate **2.16** (36 mg, 30% over 3 steps) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, 1H, J = 8.8 Hz), 6.72-6.69 (m, 2H), 4.91 (s, 1H), 4.88 (d, 1H, J = 1.6 Hz), 4.84 (d, 1H, J = 10.4 Hz), 4.79 (d, 2H, J = 2.0 Hz), 4.36 (tt, 1H, J = 2.0, 6.4 Hz), 4.33 (d, 1H, J = 10.6 Hz), 3.79 (s, 3H), 2.77-2.71 (m, 2H), 2.65 (dd, 1H, J = 6.0, 14.8 Hz), 2.60-2.52 (m, 1H), 2.42-2.38 (m, 2H), 2.09 (s, 3H), 1.78-1.72 (m, 2H), 1.65-1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 169.3, 159.6, 151.7, 143.5, 130.8, 127.6, 115.1, 110.9, 104.9, 84.4, 81.0, 68.6, 66.8, 55.4, 51.7, 39.9, 33.8, 33.1, 30.4, 28.8, 24.5, 21.3; IR (neat) 2923, 2853, 1745, 1667, 1610, 1579, 1502, 1462, 1369, 1325, 1259, 1209, 1135, 1111, 1067, 1032 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{28}O_6Na$ $[M+Na]^+$ 423.1784, found 423.1768.

Macrolactone substrate 2.17



Same procedure with the preparation of **2.16**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 1H, *J* = 7.6 Hz), 6.73-6.71 (m, 2H), 4.88 (d, 2H, *J* = 3.6 Hz), 4.79 (d, 1H, *J* = 10.8 Hz), 4.76 (s, 2H), 4.36 (d, 1H, *J* = 10.8 Hz), 4.38-4.35 (m, 1H), 3.80 (s, 3H), 2.70 (dd, 2H, *J* = 7.2, 13.2 Hz), 2.64 (dd, 2H, *J* = 6.8, 10.0 Hz), 2.38 (t, 2H, 6.4 Hz), 2.06 (s, 3H), 1.72-1.68 (m, 2H), 1.62-1.58 (m, 2H), 1.38-1.26 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 169.3, 159.5, 151.8, 143.4, 130.9, 127.7, 115.1, 111.1, 104.9, 85.2, 80.7, 68.4, 67.1, 55.4, 52.4, 40.2, 33.9, 33.2, 31.5, 29.2, 28.2, 27.8, 27.6, 27.5, 27.2, 24.5, 21.3; IR (neat) 2928, 2856, 1753, 1668, 1611, 1579, 1503, 1461, 1370, 1342, 1207, 1114, 1077, 1023, 875, 818 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{28}H_{38}O_6Na$ $[M+Na]^+$ 493.2566, found 493.2559.

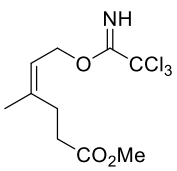
(*Z*)-3-Methyl-6-oxohex-2-enyl acetate (2.39)



To a solution of nerol (9.3 g, 60 mmol) in CH_2Cl_2 (30 mL) were added NEt_3 (16.7 mL, 120 mmol) and DMAP (188 mg, 1.54 mmol), followed by a slow addition of Ac_2O (8.4 mL, 90 mmol). The reaction mixture was stirred at rt for 1 h, then was diluted with Et_2O. The mixture was washed with sat. aq. $CuSO_4$ (3x), H_2O, and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford (*Z*)-3,7-dimethylocta-2,6-dienyl acetate (17.6 g, 100%) as a pale yellow oil. *m*-CPBA (5.6 g, 33 mmol) was added to a solution of (*Z*)-3,7-dimethylocta-2,6-dienyl acetate (5.8 g, 30 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was allowed to warm to rt slowly, and stirred at rt for 4 h. The reaction was quenched with aq. NaOH (3.0 M, 50 mL), extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 15:1 to 10:1) to afford (*Z*)-3,7-dimethyl-6,7-epoxyoct-2-enyl acetate (4.8 g, 76%) as a clear oil.

A solution of H_5IO_6 (5.7 g, 25 mmol) in water (20 mL) was added to the solution of (*Z*)-3,7-dimethyl-6,7-epoxyoct-2-enyl acetate (4.8 g, 23 mmol) in THF (34 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, then was concentrated *in vacuo*. The residue was diluted with Brine, then was extracted with Et_2O (3x). The combined organic layers were washed with aq. $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography to afford desired product (3.4 g, 88%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, 1H, *J* = 1.6 Hz), 5.41 (t, 1H, *J* = 7.2 Hz), 4.59 (d, 2H, *J* = 7.2 Hz), 2.59-2.55 (m, 2H), 2.44 (t, 2H, *J* = 7.6 Hz), 2.06 (s, 3H), 1.77 (d, 3H, *J* = 1.2 Hz).

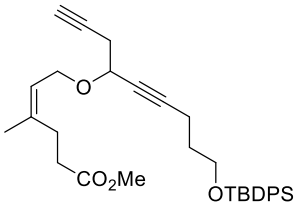
(*Z*)-Methyl 4-methyl-6-(2,2,2-trichloro-1-iminoethoxy)hex-4-enoate (2.40)



A mixture of aldehyde **2.39** (6.0 g, 35 mmol), NaH_2PO_4 (11 g, 78 mmol), 2-methyl-2-butene (12.4 g, 176 mmol), ^{t}BuOH (120 mL), and H_2O (60 mL) was cooled to -10 °C in salt-ice bath. $NaClO_2$ (12.8 g, 141 mmol) was added in 3 portions over 30 min. The mixture was allowed to warm to rt slowly over 3 h, then was added sat. aq. $Na_2S_2O_3$. The resulting mixture was stirred for 20 min at rt. After extraction with EtOAc (3x), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude acid (35 mmol) was re-dissolved in MeOH (100 mL) and treated with K_2CO_3 (7.3 g, 53 mmol). After stirring at rt for 2 h, the reaction was quenched with 1.0 M HCl and extracted with EtOAc (3x). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The residue was re-dissolved in acetone (160 mL). K_2CO_3 (5.4 g, 39 mmol) and MeI (2.8 mL, 46 mmol) were added successively. The resulting suspension was stirred for 25 h at rt, followed by a filtration through a pad of Celite®. The filtrate was concentrated *in vacuo* and purified by flash chromatography to afford desired (*Z*)-allylic alcohol (2.4 g, with impurities) as yellowish oil. Cl_3CCN (4.4 mL, 46

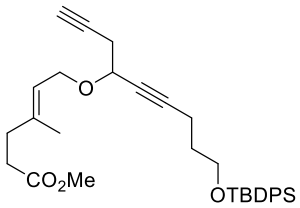
mmol) and DBU (2.8 mL, 20 mmol) were added successively to the solution of the newly generated allylic alcohol (2.4 g, 15 mmol) in anhydrous CH_2Cl_2 (28 mL). The resulting black mixture was stirred at rt for 3 h, then was concentrated under reduced pressure. The residue was purified through flash chromatography (hexanes:EtOAc = 10:1, 1% NEt_3 in hexane) to give trichloroacetimidiate **2.40** (2.8 g, 29% over 4 steps) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 5.54 (t, 1H, *J* = 6.8 Hz), 4.81 (d, 2H, *J* = 6.8 Hz), 3.68 (s, 3H), 2.47-2.45 (m, 4H), 1.80 (s, 3H).

(*Z*)-Methyl 6-(9-(*tert*-butyldiphenylsilyloxy)nona-1,5-diyn-4-yloxy)-4-methylhex-4-enoate (2.42)



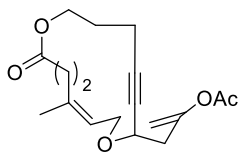
To a solution of trichloroacetimidiate **2.40** (1.7 g, 5.7 mmol) and secondary alcohol **2.41** (2.3 g, 5.7 mmol) in anhydrous cyclohexane (36 mL) was added TMSOTf (0.1 mL, 0.6 mmol) at 0 °C. The resulting mixture was allowed to warm to rt slowly and stirred at rt for 2 h, then was filtered and concentrated. The residue was purified by flash chromatography to afford both (*Z*)-product **2.42** (549 mg, 18%) and (*E*)-product **2.43** (632 mg, 21%). **3.45**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.45-7.37 (m, 6H), 5.40 (t, 1H, *J* = 6.8 Hz), 4.21-4.16 (m, 2H), 4.02 (dd, 1H, *J* = 7.6, 11.2 Hz), 3.75 (t, 2H, *J* = 6.0 Hz), 3.65 (s, 3H), 2.57-2.50 (m, 2H), 2.47-2.29 (m, 6H), 1.98 (t, 1H, *J* = 2.8 Hz), 1.79 (p, 2H, *J* = 6.4 Hz), 1.75 (s, 3H), 1.05 (s, 9H).

(*E*)-Methyl 6-(9-(*tert*-butyldiphenylsilyloxy)nona-1,5-diyn-4-yloxy)-4-methylhex-4-enoate (2.43)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (m, 4H), 7.45-7.36 (m, 6H), 5.35 (t, 1H, *J* = 6.8 Hz), 4.22-4.12 (m, 2H), 4.03 (dd, 1H, *J* = 7.6, 12.0 Hz), 3.76 (t, 2H, *J* = 6.0 Hz), 3.68 (s, 3H), 2.57-2.54 (m, 2H), 2.47-2.33 (m, 6H), 1.99 (t, 1H, *J* = 2.4 Hz), 1.78 (p, 2H, *J* = 6.4 Hz), 1.68 (s, 3H), 1.05 (s, 9H).

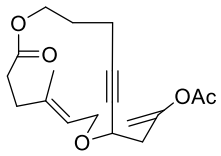
Macrolactone substrate 2.18



To a solution of **2.42** (0.55 g, 1.0 mmol) in a mixed solvent of THF, MeOH, and H_2O (3 mL, 1 mL, and 1 mL, respectively) at rt was added LiOH•H_2O (174 mg, 4.12 mmol). The resulting mixture was stirred at rt for 2 hours, and then was acidified with 1.0 M HCl until the pH was between 3 and 4. The aqueous solution was extracted with EtOAc (3x), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Then the crude acid was re-dissolved in anhydrous THF (15 mL) followed by an addition of TBAF (1.0 M in THF, 2.6 mL, 2.6 mmol). The resulting organic solution was stirred at rt for 1.5 h, then was acidified by 1.0 M HCl until the pH fell into the range of 3 to 4. The aqueous solution was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in anhydrous MeCN (100 mL) contained NEt_3 (1.4 mL, 10 mmol). The resulting solution was added dropwise to a refluxing solution of 2-chloro-1-methylpyridinium iodide (1.3 g, 5.2 mmol) in MeCN (500 mL) over 6 h. The resulting brown solution was cooled down and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 10:1) give desired macrolactone (78 mg, contaminated by TBDPS derivatives) as yellowish oil. To a suspension of [(*p*-cymene)$RuCl_2$]$_2$ (7.3 mg, 0.012

mmol), Na_2CO_3 (4.8 mg, 0.045 mmol), tri(2-furyl)phosphine (5.6 mg, 0.024 mmol), and 1-decyne (54 μL, 0.30 mmol) in toluene (2 mL) was added first portion of acetic acid (34 μL, 0.60 mmol). The mixture was heated to 80 °C and stirred for 1 h. The second portion of acetic acid (34 μL, 0.60 mmol) and the newly obtained macrolactone (78 mg, 0.30 mmol) in toluene (1 mL) were added into the reaction through syringe. The reaction was stirred at the 80 °C for 4.5 h. The crude mixture was loaded onto a small plug of silica gel and eluted with EtOAc (3x). The filtrate was concentrated. The residue purified by flash chromatography (hexanes:EtOAc = 25:1 to 10:1) to give the enol acetate **2.18** (36 mg, 11%, over four steps) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (td, 1H, *J* = 1.2, 7.6 Hz), 4.88 (s, 1H), 4.85 (d, 1H, *J* = 1.6 Hz), 4.30-4.17 (m, 4H), 3.95 (dd, 1H, *J* = 7.2, 10.4 Hz), 2.62 (dd, 2H, *J* = 4.8, 6.4 Hz), 2.59-2.49 (m, 3H), 2.47-2.43 (m, 2H), 2.42-2.35 (m, 1H), 2.14 (s, 3H), 1.90-1.84 (m, 2H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 169.3, 152.2, 142.6, 121.8, 104.3, 86.4, 79.3, 66.1, 64.6, 64.0, 40.4, 34.7, 28.2, 26.8, 23.4, 21.3, 17.2; IR (neat) 2924, 2856, 1755, 1733, 1667, 1433, 1369, 1338, 1249, 1203, 1065, 1019, 969, 879 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{24}O_5Na$ $[M+Na]^+$ 343.1521, found 343.1566.

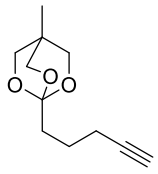
Macrolactone substrate 2.44



Same procedure with the preparation of **2.18**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (td, 1H, *J* = 1.2, 6.4 Hz), 4.85 (s, 1H), 4.84 (d, 1H, *J* = 1.6 Hz), 4.37 (dd, 1H, *J* = 6.0, 14.0 Hz), 4.27-4.12 (m, 3H), 4.02 (dd, 1H, *J* = 6.0, 14.0 Hz), 2.62-2.56 (m, 2H), 2.53-2.47 (m, 2H), 2.46-2.42 (m, 2H), 2.38-2.35 (m, 2H), 2.14 (s, 3H), 1.79 (p, 2H, *J* = 6.0 Hz), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 169.3, 152.2, 134.8, 124.0, 104.4, 84.1, 81.9, 67.8, 67.5, 62.3, 40.8, 35.1, 32.5, 25.0, 21.3, 16.1, 15.4; IR (neat) 2924, 2856, 1734,

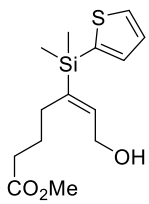
1669, 1574, 1433, 1368, 1343, 1206, 1069, 1022, 969, 882 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{24}O_5Na$ $[M+Na]^+$ 343.1521, found 343.1515.

4-Methyl-1-(pent-4-ynyl)-2,6,7-trioxabicyclo[2.2.2]octane (2.47)



To a solution of hex-5-ynoic acid (10 g, 89 mmol), (3-methyloxetan-3-yl)methanol (10 g, 98 mmol), and DMAP (1.1 g, 8.9 mmol) in CH_2Cl_2 (150 mL) was added DCC (18 g, 89 mmol) in one portion at 0 °C. White precipitates were formed. The mixture was stirred at ice bath for 1.5 h, then was filtered through a Celite® pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 6:1, hexane contained 2% NEt_3) to give the desired ester (19.5 g) as colorless oil. This freshly prepared ester (19.5 g) was re-dissolved in CH_2Cl_2 (100 mL). BF_3•OEt_2 (3.1 mL, 25 mmol) was added to this solution slowly at 0 °C. The resulting solution was warmed to rt slowly and stirred at rt for 8 h. The reaction was quenched with NEt_3 (15 mL) and diluted with Et_2O (250 mL). The precipitates were filtered through a Celite® pad. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 20:1, hexane contained 2% NEt_3) to give pure product (12.4 g, 71% over 2 steps) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 6H), 2.22 (td, 2H, *J* = 2.4, 7.2 Hz), 1.94 (t, 1H, *J* = 2.4 Hz), 1.82-1.77 (m, 2H), 1.74-1.65 (m. 2H), 0.80 (s, 3H).

(*E*)-Methyl 5-(dimethyl(thiophen-2-yl)silyl)-7-hydroxyhept-5-enoate (2.48)

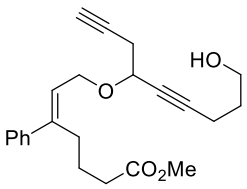


To a solution of **2.47** (12.4 g, 63.2 mmol) in THF (130 mL) was added *n*-BuLi (1.6 M in hexane, 43.4 mL, 69.5 mmol) at -78 °C. The resulting solution was allowed to warm to 0 °C slowly over 1.5 h. Paraformaldehyede (5.7 g, 0.19 mol) was added in

one portion at 0 °C. The resulting suspension was warmed to rt and stirred overnight. The reaction was quenched with aq. NH_4Cl. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford the desired propargyl alcohol (12 g, 85%). The newly formed propargyl alcohol (6.4 g, 28 mmol) was dissolved in a mixed solvent AcOH/THF/H_2O (160 mL/80 mL/40 mL). The resulting solution was stirred at rt for 2 h, then was concentrated *in vacuo*. The residue was re-dissolved in THF (200 mL), then was concentrated *in vacuo*. Repeated 2 more times to remove H_2O from the product. The product was dissolved in MeOH (200 mL) and treated with K_2CO_3 (8.5 g, 62 mmol) in one portion. After being stirred at rt for 2 h, the reaction mixture was diluted with CH_2Cl_2, then was filtered through a silica gel pad. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography to give pure ester (3.8 g, 85%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 (d, 2H, *J* = 2.0 Hz), 3.68 (s, 3H), 2.45 (t, 2H, *J* = 7.2 Hz), 2.32-2.28 (m, 2H), 1.84 (p, 2H, *J* = 7.2 Hz), 1.76 (s, 1H). To a solution of this newly formed ester (1.7 g, 11 mmol) and dimethyl(thiophen-2-yl)silane (3.1 g, 22 mmol) in THF (10 mL) was added H_2PtCl_6 solution ($1.0x10^{-3}$ M in THF, 5.4 mL, $5.4x10^{-3}$ mmol) dropwise at rt. The resulting solution was stirred at 50 °C for 3.5 h, then was cooled to 0 °C. 1.0 M HCl aq. (5 mL) was added and the reaction was stirred for 5 min at 0 °C before $NaHCO_3$ aq. was poured in. The aqueous layer was extracted with EtOAc (3x). The combined organic phases were dried over Na_2SO_4, filtered, concentrated. The residue was purified by flash chromatography to give desired product **2.48** (1.47 g, 45%) as yellowish oil. (The corresponding *Z*-isomer (1.38 g, 42%) was also separated.) **2.48**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, 2H, *J* = 4.8 Hz), 7.27 (d, 2H, *J* = 3.6 Hz), 7.19 (dd, 2H, *J* = 3.6, 4.8 Hz), 6.07 (t, 1H, *J* = 6.0 Hz), 4.28 (d,

2H, *J* = 6.0 Hz), 3.66 (s, 3H), 2.24 (t, 2H, *J* = 7.2 Hz), 2.18 (t, 2H, *J* = 8.0 Hz), 1.68 (s, 1H), 1.59-1.52 (m, 2H), 0.44 (s, 6H).

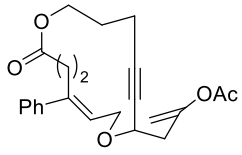
(*E*)-Methyl 7-(9-hydroxynona-1,5-diyn-4-yloxy)-5-phenylhept-5-enoate (2.49)



To a solution of **2.48** (1.6 g, 5.4 mmol) in THF (45 mL) was added TBAF (1.0 M in THF, 11.9 mL, 11.9 mmol) at rt under argon. The resulting solution was stirred for 10 min, then was treated with PhI (1.3 g, 6.5 mmol) and $Pd_2(dba)_3$ (494 mg, 0.540 mmol). The resulting mixture was stirred at rt for 30 min, then was filtered through a pad of silica gel. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography to give the desired allylic alcohol (0.96 g, 76%) as yellow oil. Cl_3CCN (1.2 mL, 12 mmol) and DBU (0.75 mL, 5.3 mmol) were added successively to the solution of the newly generated allylic alcohol (0.96 g, 4.1 mmol) in anhydrous CH_2Cl_2 (13 mL). The resulting black mixture was stirred at rt for 1 h, then was concentrated under reduced pressure. The residue was purified through flash chromatography (hexanes:EtOAc = 20:1 to 15:1, 2% NEt_3 in hexane) to give desired trichloroacetimidiate (1.4 g, 92%) as yellow oil. TMSOTf (69 µL, 0.38 mmol) was added to a solution of homopropargyl alcohol **2.41** (2.2 g, 5.6 mmol) and the freshly prepared trichloroacetmidiate (1.4 g, 3.8 mmol) in anhydrous cyclohexane (30 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 20 min, then was filtered through a pad of Celite®. The filtrate was concentrated and the residue was purified through flash chromatography (hexanes:EtOAc = 30:1 to 20:1) to give the desired ether (925 mg, 40%) as yellowish oil. The newly generated ether (925 mg, 1.52 mmol) was dissolved in THF (20 mL) and treated with TBAF (1.0 M in THF, 2.3 mL, 2.3 mmol). After stirring at rt for 30 min, the reaction solution was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 4:1 to 2:1)

to give desired alcohol **2.49** (434.5 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.25 (m, 5H), 5.87 (t, 1H, *J* = 6.8 Hz), 4.20 (dd, 1H, *J* = 6.0, 12.4 Hz), 4.30-4.22 (m, 2H), 3.79 (t, 2H, *J* = 6.0 Hz), 3.66 (s, 3H), 2.64-2.60 (m, 4H), 2.42 (td, 2H, *J* = 1.6, 6.8 Hz), 2.31 (t, 2H, *J* = 7.2 Hz), 2.08 (t, 1H, *J* = 2.4 Hz), 1.80 (p, 2H, *J* = 6.8 Hz), 1.74-1.64 (m, 3H).

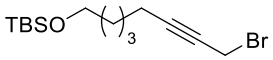
Macrolactone substrate 2.19



To a solution of **2.49** (0.22 g, 0.61 mmol) in a mixed solvent of THF, MeOH, and H_2O (3 mL, 1 mL, and 1 mL, respectively) at rt was added LiOH•H_2O (0.10 g, 2.4 mmol). The resulting mixture was stirred at rt for 2 h, then was acidified with 1.0 M HCl until the pH was below 3. The aqueous solution was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude acid was dissolved in anhydrous MeCN (20 mL) that contained NEt_3 (0.85 mL, 6.1 mmol). The resulting solution was added dropwise to a refluxing solution of 2-chloro-1-methylpyridinium iodide (779 mg, 3.05 mmol) in MeCN (500 mL) over 7 h. After addition, the brown solution was cooled down and concentrated. The residue was purified by flash chromatography to give the desired macrolactone (94 mg, 46% over 2 steps) as yellowish oil. To a suspension of [(*p*-cymene)$RuCl_2$]$_2$ (6.7 mg, 0.011 mmol), Na_2CO_3 (4.4 mg, 0.042 mmol), tri(2-furyl)phosphine (5.1 mg, 0.022 mmol) and 1-decyne (50 μL, 0.28 mmol) in toluene (2 mL) was added first portion of acetic acid (32 μL, 0.56 mmol). The mixture was heated to 80 °C and stirred for 1 h. The second portion of acetic acid (32 μL, 0.56 mmol) and the newly obtained macrolactone (94 mg, 0.28 mmol) in toluene (1 mL) were added into the reaction through syringe. The reaction was stirred at the 80 °C for 4.5 h. Then crude mixture was loaded onto a small plug of silica gel and eluted with EtOAc. The filtrate was concentrated and the residue was purified by flash

chromatography to give the desired enol acetate **2.19** (59 mg, 53%) as yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 5.82 (t, 1H, *J* = 6.4 Hz), 4.90 (s, 1H), 4.87 (d, 1H, *J* = 1.6 Hz), 4.39 (dd, 1H, *J* = 6.8 12.0 Hz), 4.35-4.28 (m, 3H), 4.18 (dd, 1H, *J* = 6.8, 12.0 Hz), 2.68-2.61 (m, 4H), 2.59-2.43 (m, 2H), 2.40-2.28 (m, 2H), 2.13 (s, 3H), 1.96-1.84 (m, 2H), 1.81-1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 169.3, 152.1, 143.4, 141.6, 128.6, 127.6, 126.7, 125.2, 104.6, 85.4, 80.0, 66.2, 64.9, 63.5, 40.3, 33.5, 28.8, 25.8, 24.1, 21.3, 16.2; IR (neat) 2929, 1755, 1730, 1667, 1493, 1433, 1368, 1245, 1204, 1080, 1020, 964, 917, 880, 761 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{28}O_5Na$ $[M+Na]^+$ 419.1834, found 419.1841.

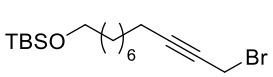
(8-Bromooct-6-ynyloxy)(*tert*-butyl)dimethylsilane (2.51a)



To a solution of hept-6-yn-1-ol (1.5 g, 13 mmol) in CH_2Cl_2 (30 mL) were added imidazole (2.3 g, 34 mmol) and TBSCl (4.0 g, 27 mmol) at rt. The resulting suspension was stirred at rt for 2 h. The reaction was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography to yield the TBS protected alcohol (3.0 g, 100%) as colorless oil. A solution of this TBS protected alcohol (9.7 g, 43 mmol) in anhydrous THF (84 mL) was cooled to -78 °C, followed by the addition of *n*-BuLi (1.6 M in hexane, 31 mL, 49 mmol). The resulting brown mixture was allowed to warm to 0 °C over 1 h. Paraformaldehyde (4.10 g, 136 mmol) was added to the solution at 0 °C in one portion. The mixture was warmed to rt slowly and stirred overnight. The reaction was quenched with aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3x). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1) to give the desired alcohol (10 g, 94% over 2 steps) as a colorless oil. A solution of the newly

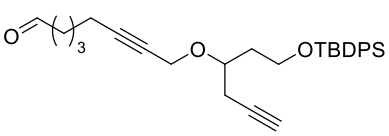
obtained alcohol (10 g, 39 mmol) in CH_2Cl_2 (400 mL) was treated with PPh_3 (11 g, 43 mmol) and CBr_4 (16 g, 47 mmol) at 0 °C. The resulting solustion was stirred at 0 °C for 1 h, then was quenched with H_2O. The aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with H_2O, brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 100:0 to 100:1) to give product **2.51a** (9.2 g, 74%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (t, 2H, *J* = 2.0 Hz), 3.61 (t, 2H, *J* = 6.4 Hz), 2.25 (tt, 2H, *J* = 2.0, 6.8 Hz), 1.56-1.49 (m, 4H), 1.47-1.38 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.3, 75.6, 63.2, 32.5, 28.4, 26.2, 25.3, 19.2, 18.6, 15.9, -5.1; IR (neat) 2932, 2858, 1463, 1388, 1254, 1210, 1099, 1006, 836, 776 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}OBr$ $[M]^+$ 319.1093, found 319.1084.

(11-Bromoundec-9-ynyloxy)(*tert*-butyl)dimethylsilane (2.51b)



Same procedure with the preparation of **2.51a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (t, 2H, *J* = 2.4 Hz), 3.60 (t, 2H, *J* = 6.8 Hz), 2.24 (tt, 2H, *J* = 2.4, 7.2 Hz), 1.51 (p, 4H, *J* = 7.2 Hz), 1.40-1.35 (m, 2H), 1.33-1.30 (m, 6H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.5, 75.5, 63.5, 33.0, 29.5, 29.3, 29.0, 28.6, 26.2, 26.0, 19.2, 18.6, 16.0, -5.0.

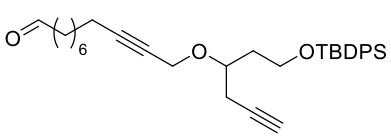
8-(1-(*tert*-Butyldiphenylsilyloxy)hex-5-yn-3-yloxy)oct-6-ynal (2.53a)



NaH (60%, 0.38 g, 9.5 mmol) was added to a solution of secondary alcohol **2.52** (3.0 g, 8.6 mmol) in anhydrous THF (30 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 30 min, then was added *n*-Bu_4NI (266 mg, 0.72 mmol) and bromide **2.51a** (2.3 g, 7.2 mmol). The brown mixture was allowed to warm

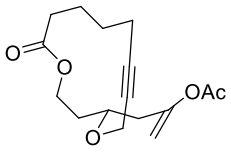
to rt slowly and stirred at rt overnight. The reaction was quenched with H_2O. The aqueous phase was extracted with Et_2O (3x). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*, followed by flash chromatography purification (hexanes:EtOAc = 100:1 to 50:1) to give the desired ether as a yellow oil (2.8 g, 66%). This ether (5.1 g, 8.6 mmol) was re-dissolved in a mixture of CH_2Cl_2 (40 mL) and MeOH (40 mL), followed by the addition of PPTS (2.4 g, 9.5 mmol) in one portion. After stirring at rt for 2 h, the solution was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 6:1) to give desired alcohol as a colorless oil (3.1 g, 76%). The TBS deprotected product (2.1 g, 4.4 mmol) was dissolved in CH_2Cl_2 (100 mL), followed by the addition of $NaHCO_3$ (1.8 g, 22 mmol) and DMP (2.8 g, 6.6 mmol). The resulting mixture was stirred for 1 h at rt., then was added aq. sat. $Na_2S_2O_3$ (75 mL) and aq. sat. $NaHCO_3$ (75 mL). After stirring for 1 h, the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexane: EtOAc, 20:1) to give the desired aldehyde as a colorless oil (1.5 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, 1H, *J* = 1.6 Hz), 7.72-7.69 (m, 4H), 7.44-7.38 (m, 6H), 4.22 (dt, 2H, *J* = 2.0, 6.4 Hz), 3.97-3.92 (m, 1H), 3.91-3.84 (m, 1H), 3.82-3.76 (m, 1H), 2.49 (dd, 2H, *J* = 2.4, 5.6 Hz), 2.42 (td, 2H, *J* = 1.6, 7.2 Hz), 2.22 (tt, 2H, *J* = 1.6, 7.2 Hz), 2.02 (t, 1H, *J* = 2.8 Hz), 1.98-1.83 (m, 2H), 1.76-1.68 (m, 2H), 1.56-1.50 (m, 2H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 135.6, 133.9, 133.8, 129.7, 129.7, 127.8, 85.9, 80.9, 76.8, 73.5, 70.3, 60.3, 57.3, 43.4, 36.8, 28.0, 27.0, 23.9, 21.3, 19.3, 18.6; IR (neat) 3292, 3070, 3049, 2932, 2858, 2720, 1724, 1471, 1428, 1110, 1006, 967, 823, 739, 705 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{30}H_{38}O_3SiNa$ $[M+Na]^+$ 497.2488, found 497.2492.

11-(1-(*tert*-Butyldiphenylsilyloxy)hex-5-yn-3-yloxy)undec-9-ynal (2.53b)



Same procedure with the preparation of **2.53a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, 1H, *J* = 1.6 Hz), 7.70-7.66 (m, 4H), 7.45-7.36 (m, 6H), 4.20 (dt, 2H, *J* = 2.4, 5.6 Hz), 3.94-3.88 (m, 1H), 3.87-3.83 (m, 1H), 3.79-3.74 (m, 1H), 2.48 (dd, 2H, *J* = 2.8, 5.6 Hz), 2.43 (td, 2H, *J* = 1.6, 7.2 Hz), 2.17 (tt, 2H, *J* = 2.0, 6.8 Hz), 2.00 (t, 1H, *J* = 2.8 Hz), 1.96-1.81 (m, 2H), 1.63 (p, 2H, *J* = 7.2 Hz), 1.48 (p, 2H, *J* = 7.2 Hz), 1.40-1.25 (m, 6H), 1.06 (s, 9H).

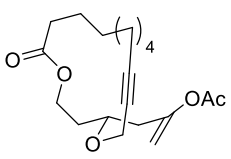
Macrolactone substrate 2.20



A mixture of aldehyde **2.53a** (1.5 g, 3.2 mmol), NaH_2PO_4 (1.0 g, 7.0 mmol), 2-methyl-2-butene (1.1 g, 16 mmol), *t*-BuOH (11 mL), and H_2O (5.5 mL) was cooled to -10 °C in salt-ice bath. $NaClO_2$ (1.1 g, 13 mmol) was added in 3 portions over 30 min. The mixture was allowed to warm to rt slowly over 3 h, then was quenched at rt by adding sat. aq. $Na_2S_2O_3$. The resulting mixture was stirred at rt for 20 min, then extracted with EtOAc (3x). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude was re-dissolved in THF (40 mL) and treated with TBAF (1.0 M in THF, 7.9 mL, 7.9 mmol). The resulting solution was stirred at rt overnight, then was acidified with 0.5 M HCl until the pH fell into the range of 3 to 4. The aqueous layer was extrated with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude hydroxyl acid was re-dissolved in MeCN (250 mL) and followed by adding NEt_3 (4.4 mL, 32 mmol). The resulting solution was added dropwise to a refluxing solution of 2-chloro-1-methylpyridinium iodide (4.0 g, 16 mmol) in MeCN (500 mL) over 8 h. After addition, the brown solution was cooled down and concentrated. The residue was purified by flash chromatography

(hexanes:EtOAc = 15:1 to 10:1) to afford the desired macrolactone (525 mg, contaminated by TBDPS derivatives) as a yellowish oil. To a suspension of [(*p*-cymene)$RuCl_2$]$_2$ (55 mg, 0.090 mmol), Na_2CO_3 (36 mg, 0.34 mmol), tri(2-furyl)phosphine (42 mg, 0.18 mmol), and 1-decyne (0.40 mL, 2.2 mmol) in toluene (20 mL) was added the first portion of acetic acid (257 μL, 4.50 mmol). The mixture was heated to 80 °C and stirred for 1 h. The second portion of acetic acid (257 μL, 0.6 mmol) and the newly obtained macrolactone (525 mg, 2.20 mmol) in toluene (5 ml) were added into the reaction through syringe. The reaction was stirred at the 80 °C for 5 h. Then crude mixture was loaded onto a small plug of silica gel and eluted with EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 10:1) to give the enol acetate **2.20** (321 mg, 35%, over four steps) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (d, 1H, *J* = 1.2 Hz), 4.83 (s, 1H), 4.30-4.19 (m, 2H), 4.14-4.05 (m, 3H), 2.58 (ddd, 1H, *J* = 2.0, 7.6, 14.4 Hz), 2.47 (t, 2H, *J* = 4.8 Hz), 2.37 (dddd, 1H, *J* = 2.8, 5.6, 8.4, 17.2 Hz), 2.22-2.17 (m, 1H), 2.17 (s, 3H), 2.16-2.00 (m, 2H), 1.90 (ddt, 1H, *J* = 3.2, 12.0, 14.8 Hz), 1.83-1.76 (m, 1H), 1.74-1.67 (m, 2H), 1.51-1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 169.2, 153.0, 104.3, 86.0, 77.1, 69.6, 60.5, 56.8, 37.8, 35.0, 33.8, 27.7, 23.5, 21.3, 17.9; IR (neat) 2926, 2854, 1755, 1731, 1665, 1434, 1369, 1259, 1200, 1152, 1053 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_5Na$ $[M+Na]^+$ 317.1365, found 317.1365.

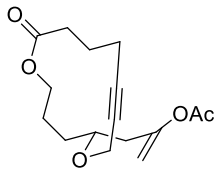
Macrolactone substrate 2.21



Same procedure with the preparation of **2.20**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (s, 2H), 4.30-4.14 (m, 4H), 4.04 (p, 1H, *J* = 6.0 Hz), 2.47 (d, 2H, *J* = 5.6 Hz), 2.34 (t, 2H, *J* = 6.8 Hz), 2.29-2.28 (m, 2H), 2.14 (s, 3H), 1.91-1.82 (m, 2H), 1.78-1.65 (m, 2H), 1.57-149 (m, 4H), 1.44-1.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

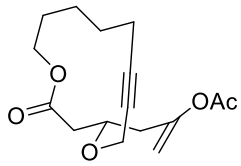
174.1, 169.2, 152.8, 104.5, 86.9, 76.4, 70.7, 60.8, 55.9, 36.6, 33.9, 33.3, 27.4, 26.9, 26.5, 26.0, 24.0, 21.3, 18.2; IR (neat) 2930, 2857, 1756, 1733, 1666, 1435, 1369, 1199, 1065, 1022, 965, 878 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{29}O_5$ $[M]^+$ 337.2015, found 337.1962.

Macrolactone substrate 2.22



Similar procedure with the preparation of substrate **2.20**. ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (s, 2H), 4.34 (ddd, 1H, *J* = 3.6, 5.2, 11.2 Hz), 4.28 (dt, 1H, *J* = 2.0, 16.4 Hz), 4.12 (td, 1H, *J* = 2.8, 10.4 Hz), 4.04 (dt, 1H, *J* = 2.0, 16.4 Hz), 3.84 (p, 1H, *J* = 6.0 Hz), 2.48-2.44 (m, 2H), 2.43-2.31 (m, 4H), 2.16 (s, 3H), 2.02-1.84 (m. 3H), 1.83-1.73 (m, 2H), 1.61-1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 169.3, 153.4, 103.9, 84.8, 78.8, 75.0, 64.1, 57.5, 38.2, 33.7, 31.1, 23.7, 21.9, 21.3, 18.4; IR (neat) 2929, 2855, 2032, 1962, 1754, 1732, 1666, 1574, 1436, 1369, 1201, 1159, 1069, 1019, 881 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_5Na$ $[M+Na]^+$ 317.1365, found 317.1325.

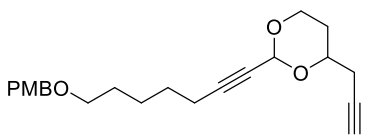
Macrolactone substrate 2.23



Smilar procedure with the preparation of **2.20**. ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (d, 1H, *J* = 1.6 Hz), 4.83 (d, 1H, *J* = 1.6 Hz), 4.40-4.30 (m, 2H), 4.25 (dt, 1H, *J* = 2.4, 16.4 Hz), 4.07-4.02 (m, 2H), 2.61 (dd, 1H, *J* = 2.0, 14.4 Hz), 2.56 (dd, 1H, *J* = 4.8, 15.2 Hz), 2.45 (dd, 1H, *J* = 10.0, 14.4 Hz), 2.38 (dd, 1H, *J* = 7.2, 15.6 Hz), 2.34-2.26 (m, 1H), 2.22-2.16 (m, 1H), 2.16 (s, 3H), 1.81-1.70 (m, 2H), 1.68-1.52 (m, 3H), 1.51-1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 169.2, 152.4, 104.7, 86.3, 72.4, 62.9, 56.6, 41.5, 37.7, 26.8, 25.1, 22.5, 21.3, 18.2; IR (neat) 2926, 2865, 1738, 1666, 1580, 1454, 1370, 1245,

1192, 1072, 1021, 963 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}O_5Na$ $[M+Na]^+$ 317.1365, found 317.1369.

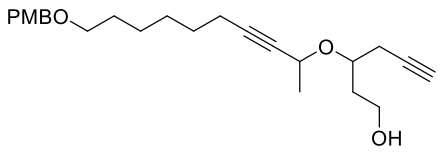
2-(8-(4-Methoxybenzyloxy)oct-1-ynyl)-4-(prop-2-ynyl)-1,3-dioxane (2.56)



PMB protected alcohol **2.54** (11 g, 44 mmol) was dissolved in anhydrous THF (80 mL) and cooled to -78 °C, then was added *n*-BuLi (1.6 M in hexane, 30 mL, 48 mmol) dropwise. The resulting brown mixture was allowed to warm to 0 °C over 1 h. Paraformaldehyde (3.9 g, 0.13 mol) was added to the solution at 0 °C in one portion. The resulting mixture was warmed to rt slowly and stirred at rt overnight, then was quenched with aq. NH_4Cl. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography to give the desired product (6.0 g, 50%) as colorless oil. The newly generated alcohol (6.0 g, 22 mmol) was re-dissolved in a mixture of CH_2Cl_2 (16 mL), DMSO (22 mL), and NEt_3 (9.1 mL). Sulfur trioxide pyridine complex (5.2 g, 33 mmol) was added in one portion. The resulting brown mixture was stirred at rt for 2 h, then was quenched with H_2O. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, concentrated. The residue was purified by flash chromatography to give 9-(4-methoxybenzyloxy)non-2-ynal (3.9 g, 66%) as brown oil. To a stirring solution of hex-5-yne-1,3-diol (420 mg, 3.70 mmol) in anhydrous DMF (25 mL) was added imidazole (1.3 g, 18 mmol). The reaction mixture was stirred for 5 min, then was added chlorotrimethylsilane (884 mg, 8.10 mmol) and 4-dimethylaminopyridine (26 mg) successively. The reaction mixture was stirred for 18 h, then was quenched with ice chips. The reaction mixture was extracted into hexanes and the aqueous layer was washed with hexanes. The combined organic layers were dried over Na_2SO_4,

filtered, and concentrated. The residue was re-dissolved in CH_2Cl_2 (28 mL). The resulting solution was cooled to -78 °C and added 9-(4-methoxybenzyloxy)non-2-ynal (1.0 g, 3.7 mmol) and TMSOTf (82 mg, 0.37 mmol). The reaction mixture was stirred for 30 min, followed by the addition of 0.1 eq. TMSOTf (82 mg, 0.37 mmol). The resulting mixture was stirred for 2.5 h, then was quenched with pyridine (0.1 ml), warmed to rt, and washed with sat. aq. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford the desired acetal **2.56** (410 mg, 30%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 2H, *J* = 8.0 Hz), 6.88 (d, 2H, *J* = 8.4 Hz), 5.23 (s, 1H), 4.43 (s, 2H), 4.18 (dd, 1H, *J* =4.8, 11.6 Hz), 3.87-3.77 (m, 2H), 3.81 (s, 3H), 3.42 (t, 2H, *J* = 6.4 Hz), 2.61 (ddd, 1H, *J* = 2.4, 4.8, 16.8 Hz), 2.40 (ddd, 1H, *J* = 2.8, 8.4, 16.8 Hz), 2.24 (t, 2H, *J* = 6.8 Hz), 2.03 (t, 1H, *J* = 2.8 Hz), 1.84-1.71 (m, 2H), 1.62-150 (m, 4H), 1.42-1.36 (m, 4H).

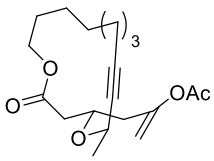
3-(10-(4-methoxybenzyloxy)dec-3-yn-2-yloxy)hex-5-yn-1-ol (2.57)



To a solution of **2.56** (410 mg, 1.10 mmol) in toluene (20 mL) was added $AlMe_3$ (2.0 M in hexane, 6.6 mL, 13 mmol) dropwise at 0 °C. The resulting solution was stirred at the same temperature for 2 h, then was poured to aq. NaOH (2.0 M, 100 mL). The aqueous layer was extracted with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 4:1) to afford the desired product (0.29 g, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, 2H, *J* = 8.4), 6.88 (d, 2H, *J* = 8.4 Hz), 4.44 (s, 2H), 4.29 (q, 1H, *J* = 6.8 Hz), 3.93-3.87 (m, 1H), 3.81-3.76 (m, 2H), 3.81 (s, 3H), 3.44 (t, 2H, *J* = 6.4 Hz), 2.73 (dt, 1H, *J* = 3.2, 16.8 Hz), 2.49 (ddd, 1H, *J* = 2.8, 8.4, 16.8 Hz), 2.20 (t, 2H, *J* = 6.8 Hz), 2.08 (t, 1H, *J* = 5.2 Hz), 2.01 (t, 1H, *J* = 2.8 Hz),

2.04-1.96 (m, 1H), 1.89-1.80 (m, 1H), 1.65-1.58 (m, 2H), 1.53-1.48 (m, 2H), 1.40 (d, 3H, *J* = 6.8 Hz), 1.41-1.38 (m, 4H).

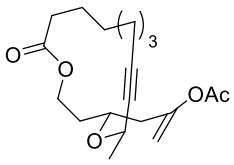
Macrolactone substrate 2.25



To a solution of alcohol **2.57** (0.29 g, 0.75 mmol) in CH_2Cl_2 (15 mL) at rt were added $NaHCO_3$ (315 mg, 3.75 mmol) and Dess-Martin periodinane (477 mg, 1.13 mmol) successively. The resulting suspension was stirred for 1.5 h, then was added sat. aq. $NaHCO_3$ (10 mL) and sat. aq. $Na_2S_2O_3$ (10 mL). The resulting mixture was stirred at rt for 1 h, then the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated. The residue was purified by flash chromatography to give the desired aldehyde (0.24 g, 83%) as colorless oil. A mixture of newly formed aldehyde (0.24 g, 0.62 mmol), NaH_2PO_4 (189 mg, 1.37 mmol), 2-methyl-2-butene (217 mg, 3.10 mmol), ^{t}BuOH (2.3 mL), and H_2O (1.2 mL) was cooled to -10 °C in salt-ice bath. $NaClO_2$ (224 mg, 2.48 mmol) was added in 2 portions over 20 min. The mixture was allowed to warm to rt slowly over 3 h, then was quenched with sat. aq. $Na_2S_2O_3$. The resulting mixture was stirred for 20 min and acidified with 1.0 M aq. HCl until pH was below 3. The aqueous layer was extracted with EtOAc (3x). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude acid was re-dissolved in CH_2Cl_2 (6 mL) and treated with water (0.3 mL) and DDQ (155 mg, 0.680 mmol). After stirring at rt for 4 h, the reaction was quenched with sat. aq. $NaHCO_3$. The aqueous layer was washed with EtOAc, then was acidified until pH was below 3. The acidified aqueous layer was extracted with EtOAc (3x). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was re-dissolved in MeCN (60 mL) that contained NEt_3 (0.9 ml, 6 mmol). The resulting solution was added dropwise to a

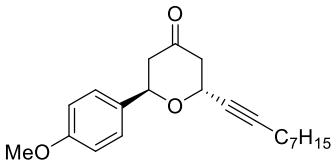
refluxing solution of 2-chloro-1-methylpyridinium iodide (792 mg, 3.10 mmol) in MeCN (600 mL) over 6 hours. After addition, the brown solution was cooled down and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 15:1) to give desired macrolactone (78 mg, 48% over 3 steps) as a yellowish oil. To a suspension of [(*p*-cymene)$RuCl_2$]$_2$ (6.9 mg, 0.011 mmol), Na_2CO_3 (4.5 mg, 0.042 mmol), tri(2-furyl)phosphine (5.1 mg, 0.022 mmol) and 1-decyne (51 μL, 0.28 mmol) in toluene (2 mL) was added the first portion of acetic acid (32 μL, 0.56 mmol). The mixture was heated to 80 °C and stirred for 1 h. The second portion of acetic acid (32 μL, 0.56 mmol) and the newly formed macrolactone (78 mg, 0.30 mmol) in toluene (1 mL) were added into the reaction through syringe. The reaction was stirred at 80 °C for 3.5 h. Then crude mixture was loaded onto a small plug of silica gel and eluted with EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 40:1 to 10:1) to give enol acetate **2.25** (59 mg, 61%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (d, 1H, *J* = 1.2 Hz), 4.85 (d, 1H, *J* = 1.2 Hz), 4.64-4.58 (m, 1H), 4.44 (ddt, 1H, *J* = 2.0, 6.4, 12.8 Hz), 4.25 (ddd, 1H, *J* = 2.8, 8.0, 11.2 Hz), 4.12-4.07 (m, 1H), 2.71 (dd, 1H, *J* = 4.8, 14.0 Hz), 2.50 (d, 2H, *J* = 6.4 Hz), 2.41 (dd, 1H, *J* = 6.8, 14.0 Hz), 2.30 (td, 2H, *J* = 1.6, 6.0 Hz), 2.15 (s, 3H), 1.80-1.45 (m, 8H), 1.36 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.2, 152.8, 104.2, 87.2, 80.1, 69.8, 65.6, 62.5, 40.0, 39.8, 27.4, 26.8, 26.7, 26.0, 22.6, 21.4, 18.3; IR (neat) 2933, 2859, 1756, 1733, 1668, 1434, 1370, 1332, 1194, 1091, 1050, 1021, 877 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{27}O_5$ $[M]^+$ 323.1858, found 323.1856.

Macrolactone substrate 2.24



Similar procedure with the preparation of **2.25**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (s, 1H), 4.83 (d, 1H, *J* = 1.2 Hz), 4.50 (ddt, 1H, *J* = 2.0, 6.4, 12.8 Hz), 4.35-4.26 (m, 2H), 4.16 (td, 1H, *J* = 2.4, 11.6 Hz), 2.67 (dd, 1H, *J* = 3.2, 15.2 Hz), 2.43-2.37 (m, 3H), 2.30-2.18 (m, 3H), 2.14 (s, 3H), 1.71-1.57 (m, 4H), 1.54-1.46 (m, 4H), 1.37 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 169.3, 153.4, 103.8, 86.9, 80.3, 69.1, 61.9, 60.8, 38.1, 34.4, 31.4, 27.1, 26.8, 24.3, 22.8, 21.4, 18.2; IR (neat) 2933, 2862, 1754, 1731, 1667, 1436, 1369, 1332, 1202, 1085, 1021, 966, 874 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}O_5Na$ $[M+Na]^+$ 345.1678, found 345.1668.

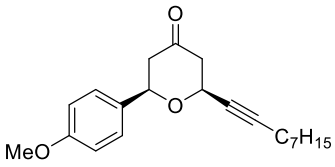
***Trans*-2-(4-Methoxyphenyl)-6-(non-1-yn-1-yl)tetrahydro-4*H*-pyran-4-one (2.59a)**



To a suspension of substrate 2.12 (152 mg, 0.410 mmol), 2,6-dichloropypyridine (241 mg, 1.60 mmol), and 4 Å molecular sieves (304 mg) in anhydrous DCE (4 mL) was added DDQ (186 mg, 0.820 mmol) in one portion at rt. The mixture was stirred at rt for 1 h, then was quenched with NEt_3 (0.1 mL). The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 30:1 to 15:1) to give the cyclized products (97 mg, total mass, *trans*-isomer/*cis*-isomer = 2.8/1, 72% total yield). 2.59a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.30 (m, 2H), 6.94-6.89 (m, 2H), 5.26 (dd, 1H, *J* = 5.4, 8.4 Hz), 5.18 (ddt, 1H, *J* = 1.5, 1.8, 6.6 Hz), 3.82 (s, 3H), 2.81 (dd, 1H, *J* = 6.9, 14.1 Hz), 2.64-2.61 (m, 2H), 2.53 (d, 1H, *J* = 14.1 Hz), 2.23 (td, 2H, *J* = 2.1, 6.9 Hz), 1.54-1.47 (m, 2H), 1.40-1.26 (m, 8H), 0.89 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 159.7, 132.8, 127.7, 114.2, 90.6, 76.6, 73.7, 65.8, 55.5, 49.4, 47.6, 31.9, 29.0, 29.0, 28.7,

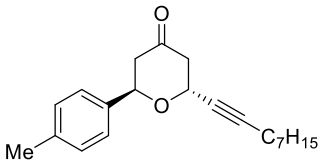
22.8, 18.9, 14.3; IR (neat) 2929, 2856, 1724, 1613, 1515, 1463, 1367, 1334, 1304, 1248, 1177, 1104, 1054, 1035, 946, 829 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{29}O_3$ $[M]^+$ 329.2117, found 329.2116.

Cis-2-(4-Methoxyphenyl)-6-(non-1-yn-1-yl)tetrahydro-4*H*-pyran-4-one (2.59b)



^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.29 (m, 2H), 6.93-6.88 (m, 2H), 4.58 (dd, 1H, *J* = 3.3, 10.8 Hz), 4.53 (ddt, 1H, *J* = 1.8, 3.3, 11.1 Hz), 3.81 (s, 3H), 2.80-2.54 (m, 4H), 2.23 (td, 2H, *J* = 2.1, 7.2 Hz), 1.55-1.47 (m, 2H), 1.38-1.26 (m, 8H), 0.89 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 159.8, 132.4, 127.7, 114.2, 88.0, 78.6, 67.8, 55.6, 53.6, 49.4, 48.5, 31.9, 29.0, 29.0, 28.6, 22.8, 19.0, 14.3; IR (neat) 2926, 2854, 1723, 1613, 1515, 1462, 1344, 1302, 1250, 1177, 1161, 1043, 952, 830 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{29}O_3$ $[M]^+$ 329.2117, found 329.2108.

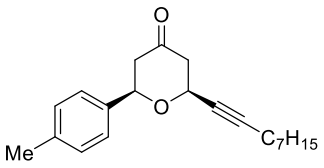
Trans-2-(Non-1-yn-1-yl)-6-(*p*-tolyl)tetrahydro-4*H*-pyran-4-one (*trans*-2.60)



To a suspension of substrate 2.13 (29 mg, 0.08 mmol), 2,6-dichloropypyridine (47 mg, 0.32 mmol), 4 Å molecular sieves (57 mg) in anhydrous DCE (1 mL) was added DDQ (36 mg, 0.16 mmol) in one portion at rt. The mixture was stirred at rt for 6 h, then was quenched with NEt_3 (0.1 mL). The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography to give the desired product (18 mg, total mass, *trans*/*cis* = 3.3/1, 72% total yield) as yellowish oil. *trans*-2.60: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, 2H, *J* = 8.4 Hz), 7.20 (d, 2H, *J* = 8.0 Hz), 5.27 (dd, 1H, *J* = 4.0, 10.0 Hz), 5.20 (ddt, 1H, *J* = 1.6, 2.4, 5.2 Hz), 2.89 (dd, 1H, *J* = 6.8, 14.0 Hz), 2.68-2.57 (m, 2H), 2.54 (dt, 1H, *J* = 1.6, 14.4 Hz), 2.36 (s, 3H), 2.23 (td, 2H, *J* = 2.0, 7.2 Hz), 1.55-1.47 (m, 2H),

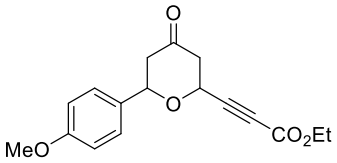
1.39-1.33 (m, 2H), 1.31-1.28 (m, 6H), 0.89 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 138.1, 137.7, 129.5, 126.2, 90.7, 76.5, 73.9, 65.8, 49.5, 47.6, 32.0, 29.0, 29.0, 28.7, 22.8, 21.4, 18.9, 14.3; IR (neat) 2927, 2856, 1724, 1516, 1459, 1415, 1365, 1333, 1225, 1161, 1104, 1055, 1021, 945, 809 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{29}O_2$ $[M]^+$ 313.2168, found 313.2161.

Cis-2-(Non-1-yn-1-yl)-6-(_p_-tolyl)tetrahydro-4_H_-pyran-4-one (_cis_-2.60)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, 2H, J = 8.0 Hz), 7.19 (d, 2H, J = 8.0 Hz), 4.60 (dd, 1H, J = 3.2, 10.8 Hz), 4.53 (ddt, 1H, J = 2.0, 2.8, 8.4 Hz), 2.76 (dd, 1H, J = 11.6, 14.4 Hz), 2.68-2.57 (m, 3H), 2.35 (s, 3H), 2.24 (td, 2H, J = 2.0, 7.2 Hz), 1.57-1.49 (m, 2H), 1.37-1.33 (m, 2H), 1.31-1.28 (m, 6H), 0.89 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5, 138.3, 137.3, 129.5, 126.2, 88.0, 78.8, 77.6, 67.8, 49.4, 48.5, 31.9, 29.0, 29.0, 28.6, 22.8, 21.4, 19.0, 14.3; IR (neat) 2927, 2856, 1724, 1516, 1460, 1380, 1344, 1305, 1246, 1161, 1135, 1054, 953, 811, 719 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{29}O_2$ $[M]^+$ 313.2168, found 313.2169.

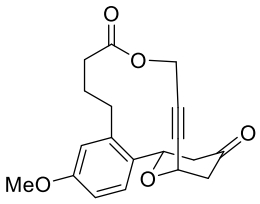
Ethyl 3-(6-(4-methoxyphenyl)-4-oxotetrahydro-2_H_-pyran-2-yl)propiolate (2.61)



To a suspension of substrate 2.14 (56 mg, 0.16 mmol), 2,6-dichloropypyridine (96 mg, 0.65 mmol), 4 Å molecular sieves (113 mg) in anhydrous DCE (1.6 mL) was added DDQ (75 mg, 0.33 mmol) in one portion at rt. The mixture was stirred at rt for 9.5 h, then was quenched with NEt_3 (0.1 mL). The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 8:1) to give the desired product (22 mg, total mass, *trans*/*cis* = 1.6/1, 45% total yield) as colorless oil. Mixture of *trans*-2.61 and *cis*-2.61: ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.34-7.30 (m, 2H), 6.94-6.91 (m, 2H), 5.29 (dd, 0.6H, *J* = 2.0, 7.6 Hz), 5.22 (dd, 0.6H, *J* = 5.2, 9.2 Hz), 4.68 (dd, 0.4H, *J* = 3.2, 11.6 Hz), 4.62 (dd, 0.4H, *J* = 3.2, 10.8 Hz), 4.25 (q, 2H, *J* = 7.2 Hz), 3.82 (s, 1.8H), 3.82 (s, 1.2H), 2.94 (dd, 0.6H, *J* = 7.6, 14.8 Hz), 2.82 (dd, 0.4H, *J* = 12.0, 14.8 Hz), 2.75-2.62 (m, 3H), 1.33 (t, 1.8H, *J* = 6.8 Hz), 1.31 (t, 1.2H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 203.5, 160.0, 159.9, 153.1, 152.9, 131.8, 131.7, 127.7, 127.5, 114.3, 83.0, 82.6, 80.2, 79.1, 78.0, 74.8, 66.7, 64.9, 62.6, 62.6, 55.5, 49.2, 49.0, 46.5, 45.7, 14.2; IR (neat) 2980, 2934, 2840, 1716, 1643, 1613, 1587, 1516, 1464, 1367, 1337, 1302, 1252, 1178, 1152, 1059, 1033, 950, 833, 751 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}O_5$ $[M]^+$ 303.1232, found 303.1238.

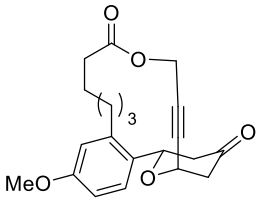
Macrocyclic benzylic ether 2.62



To a suspension of macrolactone substrate **2.15** (46 mg, 0.12 mmol), 2,6-dichloropypyridine (77 mg, 0.52 mmol), 4 Å molecular sieves (92 mg) in anhydrous DCE (1.3 mL) was added DDQ (59 mg, 0.26 mmol) in one portion at rt. The mixture was stirred at rt for 4 h, then was quenched with NEt_3 (0.1 mL). The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 5:1 to 3:1) to give the desired product (29 mg, 72%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, 1H, *J* = 8.4 Hz), 6.81 (dd, 1H, *J* = 2.8, 8.8 Hz), 6.76 (d, 1H, *J* = 2.8 Hz), 5.36 (dd, 1H, *J* = 2.0, 12.4 Hz), 5.10 (dt, 1H, *J* = 1.2, 7.2 Hz), 4.84 (dd, 1H, *J* = 3.2, 15.2 Hz), 4.69 (dd, 1H, *J* = 1.6, 14.8 Hz), 3.81 (s, 3H), 2.98-2.81 (m, 3H), 2.62-2.49 (m, 4H), 2.40 (ddd, 1H, *J* = 3.6, 11.2, 12.4 Hz), 2.01-1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 172.6, 159.9, 142.5, 128.3, 127.4, 115.8, 111.8, 84.2, 82.6, 69.2, 65.5, 55.2, 51.7, 46.8, 46.2, 34.5, 31.4, 29.1; IR (neat) 2923, 2851,

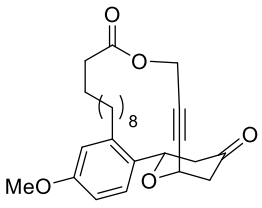
1740, 1611, 1579, 1504, 1441, 1368, 1334, 1275, 1255, 1233, 1158, 1131, 1110, 1048, 1024, 996, 952, 818, 733 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{20}O_5Na$ $[M+Na]^+$ 351.1208, found 351.1199.

Macrocyclic benzylic ether 2.63



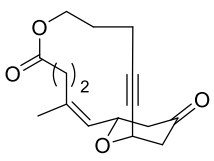
To a suspension of macrolactone substrate **2.16** (32 mg, 0.080 mmol), 2,6-dichloropypyridine (48 mg, 0.32 mmol), 4 Å molecular sieves (65 mg) in anhydrous DCE (0.85 mL) was added DDQ (37 mg, 0.16 mmol) in one portion at rt. The mixture was stirred at rt for 1 h, then was quenched with NEt_3 (0.1 mL). The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 8:1 to 3:1) to give the desired product (23 mg, 81%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, 1H, *J* = 8.8 Hz), 6.80 (dd, 1H, *J* = 2.8, 8.4 Hz), 6.71 (d, 1H, *J* = 2.8 Hz), 5.43 (dd, 1H, *J* = 2.8, 11.6 Hz), (d, 1H, *J* = 6.8 Hz), 4.83 (dd, 1H, *J* = 2.0, 15.2 Hz), 4.72 (dd, 1H, *J* = 3.2, 15.6 Hz), 3.80 (s, 3H), 2.92 (dd, 1H, *J* = 7.2, 14.4 Hz), 2.73-2.52 (m, 5H), 2.39 (t, 2H, *J* = 6.4 Hz), 1.81-1.75 (m, 1H), 1.73-1.57 (m, 3H), 1.53-1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 172.7, 159.7, 142.0, 130.0, 127.2, 115.0, 111.8, 83.2, 82.5, 70.7, 65.7, 55.4, 51.6, 49.1, 46.6, 33.7, 33.2, 30.7, 28.6, 24.4; IR (neat) 2934, 2861, 1739, 1610, 1580, 1503, 1458, 1371, 1333, 1266, 1229, 1158, 1113, 1056, 1023, 984, 947, 816, 731 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{24}O_5Na$ $[M+Na]^+$ 379.1521, found 379.1543.

Macrocyclic benzylic ether *trans*-2.64



To a suspension of macrolactone substrate **2.17** (50 mg, 0.11 mmol), 2,6-dichloropypyridine (63 mg, 0.42 mmol), 4 Å molecular sieves (100 mg) in anhydrous DCE (1.3 mL) was added DDQ (48 mg, 0.21 mmol) in one portion at rt. The mixture was stirred at rt for 40 min, then was quenched NEt_3 (0.1 mL). The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 15:1 to 5:1) to give the desired product (30 mg, *trans*/*cis* = 6/1, 65% total yield) as yellow oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, 1H, *J* = 8.4 Hz), 6.80 (dd, 1H, *J* = 2.8, 8.4 Hz), 6.74 (d, 1H, *J* = 2.8 Hz), 5.47 (dd, 1H, *J* = 2.8, 11.2 Hz), 5.25 (d, 1H, *J* = 6.0 Hz), 4.80 (dd, 1H, *J* = 1.2, 16.0 Hz), 4.70 (dd, 1H, *J* = 2.0, 16.0 Hz), 3.81 (s, 3H), 2.94 (dd, 1H, *J* = 7.2, 14.0 Hz), 2.77-2.70 (m, 2H), 2.63-2.55 (m, 3H), 2.39 (t, 2H, *J* = 6.8 Hz), 1.72-1.58 (m, 4H), 1.41-1.26 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 173.4, 159.6, 142.5, 129.8, 127.7, 115.3, 111.8, 83.6, 83.4, 70.6, 65.5, 55.5, 52.3, 48.9, 46.9, 33.7, 33.2, 31.8, 29.7, 28.3, 27.5, 27.2, 26.9, 26.2, 24.1; IR (neat) 2928, 2855, 1739, 1610, 1579, 1504, 1461, 1335, 1230, 1160, 1052, 946, 816, 732, 705 cm^{-1}; $C_{26}H_{35}O_5$ $[M]^+$ 427.2484, found 427.2493.

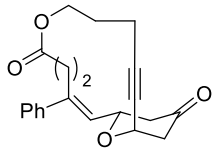
Macrocyclic allylic ether 2.65



To a suspension of macrolactone substrate **2.18** (36 mg, 0.11 mmol), 2,6-dichloropypyridine (100 mg, 0.674 mmol), $LiClO_4$ (3.0 mg, 0.028 mmol), 4 Å molecular sieves (72 mg) in anhydrous DCE (1.4 mL) was added DDQ (76 mg, 0.34 mmol) in one portion at rt. The mixture was stirred at rt for 23 h, then 1.0 equiv. DDQ (26 mg , 0.11 mmol) was added. The resulting mixture was stirred for 3 h at rt, then was quenched

with NEt_3 (0.1 mL). The black mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 6:1) to give the desired *trans*-product **2.65** (17 mg, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (dd, 1H, *J* = 1.2, 8.8 Hz), 5.08 (dd, 1H, *J* = 1.2, 7.6 Hz), 4.95 (td, 1H, *J* = 5.6, 8.8 Hz), 4.28-4.23 (m, 1H), 4.14-4.09 (m, 1H), 2.78 (dd, 1H, *J* = 7.2, 14.0 Hz), 2.57-2.32 (m, 9H), 1.90-1.83 (m, 2H), 1.80 (d, 3H, *J* = 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 172.8, 142.7, 125.4, 89.1, 77.8, 68.5, 65.9, 64.4, 48.2, 47.0, 34.7, 29.1, 26.2, 23.5, 16.9; IR (neat) 2922, 2852, 1731, 1436, 1380, 1332, 1249, 1154, 1106, 1051, 937, 893 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{20}O_4Na$ $[M+Na]^+$ 299.1259, found 299.1248. To a suspension of macrocyclic substrate **2.44** (20 mg, 0.062 mmol), 2,6-dichloropypyridine (55 mg, 0.37 mmol), $LiClO_4$ (1.7 mg, 0.016 mmol), 4 Å molecular sieves (40 mg) in anhydrous DCE (0.8 mL) was added DDQ (42 mg, 0.19 mmol) in one portion at rt. The mixture was stirred at rt for 43 h, then was quenched with NEt_3 (0.1 mL). The black mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography to give the *trans*-product **2.65** (6.0 mg, 35%).

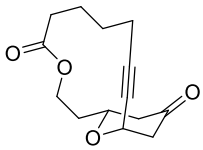
Macrocyclic allylic ether 2.66



To a suspension of macrolactone **2.19** (38 mg, 0.096 mmol), 2,6-dichloropypyridine (57 mg, 0.38 mmol), $LiClO_4$ (3 mg, 0.03 mmol), and 4 Å molecular sieves (76 mg) in anhydrous DCE (1 mL) was added DDQ (44 mg, 0.19 mmol) in one portion at rt. The mixture was stirred at rt for 15 min, then was quenched with NEt_3 (0.1 mL). The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash

chromatography (hexanes:EtOAc = 8:1 to 4:1) to give the desired product **2.66** (24 mg, 72%). **22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.73 (d, 1H, *J* = 8.4 Hz), 5.14-5.10 (m, 2H), 4.37-4.24 (m, 2H), 2.83 (dd, 1H, *J* =7.2, 14.0 Hz), 2.63 (td, 2H, *J* = 4.0, 7.6 Hz), 2.56-2.37 (m, 6H), 2.32-2.25 (m, 1H), 1.93-1.81 (m, 2H), 1.80-1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 173.6, 144.6, 141.2, 128.7, 128.0, 127.3, 126.9, 88.5, 78.3, 69.2, 65.9, 63.4, 48.2, 47.2, 33.9, 29.5, 25.8, 23.9, 16.1; IR (neat) 2926, 1726, 1493, 1444, 1358, 1334, 1246, 1227, 1157, 1112, 1047, 937, 887, 764 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_4Na$ $[M+Na]^+$ 375.1572, found 375.1584.

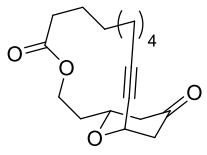
Macrocyclic propargylic ether 2.67



To a suspension of macrolactone substrate **2.20** (177 mg, 0.60 mmol, **2.20**/enol acetate regioisomer = 8/1), 2,6-dichloropypyridine (888 mg, 6.0 mmol), $LiClO_4$ (51 mg, 0.48 mmol), 4 Å molecular sieves (355 mg) in anhydrous DCE (7 mL) was added DDQ (817 mg, 3.6 mmol) in one portion at rt. The mixture was stirred at 50 °C for 41.5 h, then was added DDQ (0.27 g 1.2 mmol) and $LiClO_4$ (19 mg, 0.18 mmol). The resulting mixture was stirred at the same temperature for 20.5 h, then was quenched with NEt_3 (1.5 mL). The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 4:1) to give the desired product **2.67** (49 mg, 36%) as colorless crystal. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09-5.07 (m, 1H), 4.62-4.55 (m, 1H), 4.39-4.33 (m, 1H), 4.06 (dt, 1H, *J* = 4.0, 10.8 Hz), 2.74 (dd, 1H, *J* = 8.0, 14.8 Hz), 2.49 (ddd, 1H, *J* = 3.2, 6.8, 14.0 Hz), 2.45 (dt, 1H, *J* = 1.2, 14.4 Hz), 2.42-2.37 (m, 2H), 2.33-2.18 (m, 2H), 2.04 (ddt, 1H, *J* = 2.0, 11.2, 16.8 Hz), 1.96-1.79 (m, 4H), 1.76-1.66 (m, 1H), 1.51-1.40 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.4, 173.2, 89.0,

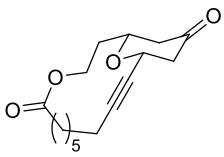
77.8, 67.2, 65.7, 60.0, 48.4, 46.2, 35.2, 34.4, 28.1, 24.7, 18.8; IR (neat) 2921, 2851, 1724, 1704, 1334, 1258, 1230, 1152, 1109, 1057, 1026, 860, 780 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_4Na$ $[M+Na]^+$ 273.1103, found 273.1097.

Macrocyclic propargylic ether *trans*-2.70



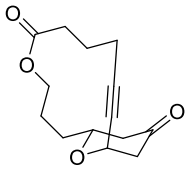
To a suspension of macrolactone substrate **2.21** (30 mg, 0.090 mmol), 2,6-dichloropypyridine (53 mg, 0.36 mmol), $LiClO_4$ (2.8 mg, 0.03 mmol), 4 Å molecular sieves (60 mg) in anhydrous DCE (1 mL) was added DDQ (81 mg, 0.36 mmol) in one portion at rt. The mixture was stirred at 40 °C for 60 h, then quenched with NEt_3. The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 4:1) to give both *trans*- and *cis*-products (12 mg total mass, *trans*/*cis* = 2/1, 46% total yield) as pale yellow oil. ***Trans*-2.70**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (dd, 1H, *J* = 1.6, 6.8), 4.48 (ddt, 1H, *J* = 2.4, 8.8, 13.6 Hz), 4.26-4.17 (m, 2H), 2.80 (dd, 1H, *J* = 6.8, 13.6 Hz), 2.49-2.43 (m, 2H), 2.34 (t, 2H, *J* = 6.8 Hz), 2.32-2.29 (m, 2H), 2.21 (dd, 1H, *J* = 7.2, 14.0 Hz), 2.04-1.96 (m, 1H), 1.90-1.82 (m, 1H), 1.71 (p, 2H, *J* = 6.8 Hz), 1.51-1.44 (m, 4H), 1.41-1.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 174.0, 90.0, 77.1, 68.3, 66.0, 59.7, 47.9, 47.8, 35.7, 33.6, 27.8, 26.8, 26.7, 26.0, 24.4, 18.0; IR (neat) 2929, 2857, 1729, 1459, 1337, 1226, 1187, 1147, 1097, 1053, 980, 932, 863 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{25}O_4$ $[M]^+$ 293.1753, found 292.1720.

Macrocyclic propargylic ether *cis*-2.70



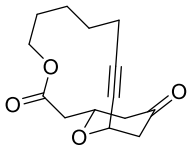
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38-4.21 (m, 3H), 3.78 (ddt, 1H, *J* = 2.4, 9.2, 11.2 Hz), 2.63-2.52 (m, 2H), 2.46-2.38 (m, 2H), 2.36-2.24 (m, 4H), 2.13-2.04 (m, 1H), 1.85-1.68 (m, 3H), 1.60-1.34 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 174.4, 86.7, 78.8, 67.5, 62.1, 48.1, 47.7, 35.2, 33.7, 26.4, 25.7, 24.8, 24.5, 22.5, 17.9; HRMS (ESI) *m/z* calcd for $C_{17}H_{24}O_4$ $[M]^+$ 292.1675, found 292.1700.

Macrocyclic propargylic ether 2.71



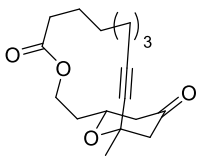
To a suspension of macrolactone substrate **2.22** (36 mg, 0.12 mmol), 2,6-dichloropypyridine (72 mg, 0.49 mmol), $LiClO_4$ (3.9 mg, 0.037 mmol), 4 Å molecular sieves (72 mg) in anhydrous DCE (1.5 mL) was added DDQ (56 mg, 0.25 mmol) in one portion at rt. The mixture was stirred at rt for 24 h, then was added DDQ (56 mg, 0.25 mmol). The resulting mixture was stirred for 53 h at 40 °C, then quenched with NEt_3 (0.1 mL). The black mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography to give the desired product **2.71** (11 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (app d, 1H, *J* = 7.2 Hz), 4.57 (ddd, 1H, *J* = 3.2, 4.8, 11.6 Hz), 4.42 (ddt, 1H, *J* = 2.4, 10.4, 11.6 Hz), 3.95 (td, 1H, *J* = 1.6, 11.2 Hz), 2.73 (dd, 1H, *J* = 7.6, 14.4 Hz), 2.52 (ddd, 1H, *J* = 2.8, 8.8, 16.8 Hz), 2.14 (app d, 2H, *J* = 14.4 Hz), 2.38-2.17 (m, 4H), 2.06-1.97 (m, 1H), 1.92-1.77 (m, 2H), 1.65-1.57 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 173.8, 87.6, 78.6, 70.9, 67.0, 65.6, 49.2, 47.0, 35.5, 33.0, 23.3, 21.1, 18.8; IR (neat) 2922, 2852, 1727, 1554, 1452, 1390, 1341, 1230, 1196, 1159, 1110, 1052, 967, 910 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{19}O_4$ $[M]^+$ 251.1283, found 251.1314.

Macrocyclic propargylic ether 2.72



To a suspension of macrolactone substrate **2.23** (51 mg, 0.17 mmol, **2.23**/enol acetate regioisomer = 4/1), 2,6-dichloropypyridine (102 mg, 0.690 mmol), $LiClO_4$ (5.5 mg, 0.050 mmol), 4 Å molecular sieves (112 mg) in anhydrous DCE (2 mL) was added DDQ (157 mg, 0.69 mmol) in one portion at rt. The mixture was stirred at 50 °C for 119.5 h, then was added DDQ (78 mg, 0.35 mmol). After stirring at the same temperature for a period of 54.5 h, another 78 mg DDQ (0.35 mmol) was added. The resulting mixture was stirred for 18 h at 50 °C, then was quenched with NEt_3 (0.5 mL). The mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and purified by flash chromatography (hexanes:EtOAc = 10:1 to 4:1) to give the desired *trans*-product **2.72** (8.0 mg, 24% extrapolated yield) as white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (dd, 1H, *J* = 0.8, 8.0 Hz), 4.85 (ddt, 1H, *J* = 3.2, 9.6, 11.2 Hz), 4.44-4.38 (m, 1H), 3.91 (dt, 1H, *J* = 4.0, 11.2 Hz), 2.74 (dd, 1H, *J* = 8.0, 15.2 Hz), 2.61-2.50 (m, 2H), 2.47-2.35 (m, 3H), 2.30-2.15 (m, 2H), 1.74-1.55 (m, 5H), 1.53-1.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 170.1, 88.6, 78.6, 69.7, 65.7, 63.8, 48.0, 45.7, 42.2, 27.4, 26.4, 23.3, 18.5; IR (neat) 2928, 2863, 1818, 1731, 1420, 1379, 1337, 1313, 1272, 1232, 1153, 1110, 1066, 1040, 972, 940, 868, 823 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_4Na$ $[M+Na]^+$ 273.1105, found 273.1097.

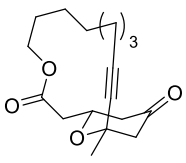
Macrocyclic propargylic ether 2.73



To a suspension of macrolactone substrate **2.25** (40 mg, 0.12 mmol), 2,6-dichloropypyridine (73 mg, 0.50 mmol), $LiClO_4$ (4.0 mg, 0.037 mmol), 4 Å molecular sieves (80 mg) in anhydrous DCE (1.5 mL) was added DDQ (56 mg, 0.25 mmol) in one portion at rt. The mixture was stirred at rt for 8 h, then was warmed to 30 °C.

After the reaction was stirred at 30 °C for 26 h, 27 mg DDQ (0.12 mmol) was added. The resulting mixture was stirred for 14 h at 30 °C, then quenched with NEt_3. The black mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography to give the desired product **2.73** (13.4 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50-4.37 (m, 2H), 4.05 (dt, 1H, *J* = 4.0, 11.2 Hz), 2.53 (dd, 1H, *J* = 2.0, 14.0 Hz), 2.48-2.36 (m, 3H), 2.36-2.25 (m. 2H), 2.24-2.20 (m, 1H), 2.18-2.12 (m, 1H), 1.93-1.88 (m, 2H), 1.72-1.61 (m, 2H), 1.58 (s, 1H), 1.56-1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 173.9, 87.5, 80.7, 72.4, 68.3, 60.3, 54.0, 47.5, 34.9, 34.7, 30.2, 27.2, 26.8, 24.8, 18.1; IR (neat) 2928, 2859, 1728, 1441, 1357, 1303, 1254, 1166, 1142, 1085, 1033, 1001, 865, 784 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{23}O_4$ $[M]^+$ 279.1596, found 279.1582.

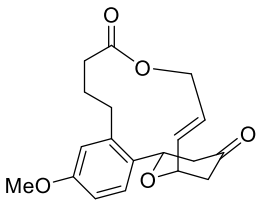
Macrocyclic propargylic ether 2.74



To a suspension of macrolactone substrate **2.25** (36 mg, 0.11 mmol), 2,6-dichloropypyridine (66 mg, 0.45 mmol), $LiClO_4$ (3.6 mg, 0.034 mmol), 4 Å molecular sieves (72 mg) in anhydrous DCE (1.4 mL) was added DDQ (51 mg, 0.22 mmol) in one portion at rt. The mixture was stirred at rt for 10 h, then was warmed to 30 °C. After stirring at 30 °C for 43 h, 25 mg DDQ (0.11 mmol) was added. The resulting mixture was stirred for 43 h at 30 °C, then quenched with NEt_3 (0.1 mL). The black mixture was loaded directly onto a short plug of silica gel and eluted with CH_2Cl_2 and EtOAc. The filtrate was concentrated and the residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 8:1) to give the desired product **2.74** (12.4 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80-4.73 (m, 1H), 4.21-4.07 (m, 2H), 2.57 (d, 1H, *J* = 1.6 Hz), 2.56 (s, 1H), 2.52 (dd, 1H, *J* = 2.0, 14.0 Hz), 2.43 (d, 1H, *J* = 13.6 Hz), 2.39 (dt, 1H, *J* = 2.0, 14.0 Hz), 2.27-2.20 (m, 3H), 1.84-1.75 (m, 1H), 1.68-1.62 (m, 3H),

1.59 (s, 3H), 1.56-1.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.2, 170.3, 87.3, 80.7, 72.6, 70.2, 64.5, 53.6, 47.1, 42.7, 30.6, 27.6, 26.7, 26.3, 24.8, 17.5; IR (neat) 2920, 2858, 1731, 1468, 1449, 1426, 1375, 1316, 1275, 1259, 1204, 1162, 1129, 1100, 1071, 1029, 968 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{22}O_4$ $[M]^+$ 278.1518, found 278.1505.

Macrocyclic *E*-alkene 2.75



To a solution of macrocyclic benzylic ether **2.62** (14 mg, 0.044 mmol) in dry CH_2Cl_2 (0.1 mL) was added $HSi(OEt)_3$ (9.7 µL, 0.053 mmol) under argon atmosphere. The resulting solution was cooled to 0 °C and added $[Cp^*Ru(NCCH_3)_3]PF_6$ (cat.). The reaction was warmed to rt and stirred at rt for 30 min before diluted with dry Et_2O (2 mL). The resulting mixture was filtered through a plug of Florisil® (2 cm), wash with dry Et_2O (2 mL), and concentrated *in vacuo*. The residue was re-dissolved in dry THF (0.3 mL). Under argon atmosphere, CuI (1mg, cat.) was added, followed by the addition of TBAF (84 µL, 0.084 mmol) at rt. The resulting mixture was stirred at rt for 4 h, then was diluted with EtOAc, filtered through a pad of silica gel and the filtrate was concentrated in vacuum. The residue was purified by flash chromatography (hexanes:EtOAc = 6:1 to 4:1) to give the desired alkene **2.75** (7.2 mg, 49%) as yellowish oil. ^{1}H NMR (400 MHz, C_6D_6) δ 7.25 (d, 1H, *J* = 8.4 Hz), 6.68 (dd, 1H, *J* = 2.8, 8.4 Hz), 6.59 (d, 1H, *J* = 2.8 Hz), 5.92 (ddd, 1H, *J* = 0.8, 4.4, 16.0 Hz), 5.81 (dddd, 1H, *J* = 0.8, 4.4, 5.6, 16.4 Hz), 4.90 (dd, 1H, *J* = 2.4, 12.0 Hz), 4.44-4.43 (m, 1H), 4.36 (dd, 1H, *J* = 6.4, 12.4 Hz), 4.07 (ddt, 1H, *J* = 1.2, 4.4, 12.0 Hz), 2.61-2.48 (m, 2H), 2.43-2.29 (m, 4H), 2.04 (ddd, 1H, *J* = 3.2, 9.6, 12.4 Hz), 1.94 (ddd, 1H, *J* = 3.2, 9.6, 12.4 Hz), 1.62-1.58 (m, 1H), 1.50-1.43 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 205.0, 172.8, 160.4, 142.4, 135.7, 131.9, 130.6, 116.0, 112.3, 72.6, 67.6, 61.5, 55.1, 48.6, 43.5, 34.8, 32.1, 30.6, 29.2; IR (neat)

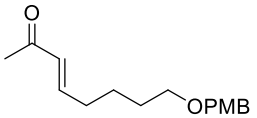
2923, 2852, 1730, 1611, 1579, 1504, 1459, 1375, 1264, 1235, 1156, 1133, 1101, 1042, 995, 954, 810 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{19}H_{22}O_5Na$ $[M+Na]^+$ 353.1365, found 353.1374.

APPENDIX B

ONE-POT STRATEGY FOR SPIROKETAL SYNTHESIS

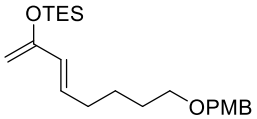
General Experimental: Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz. The chemical shifts are reported in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, C_6D_6 = 7.16 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23, C_6D_6 = 128.4 ppm. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; qunit = quintet; sept = septet; dd = doublet of doublets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublet; td = triplet of doublets; dtd = doublet of triplet of doublets; br = broad). High resolution and lowresolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Methylene chloride was distilled under N_2 from CaH_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, toluene and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography.

(*E*)-8-((4-Methoxybenzyl)oxy)oct-3-en-2-one (3.29)



To a solution of hex-5-en-1-ol (5.2 mL, 43 mmol) in THF (80 mL) was added NaH (60% in mineral oil, 1.7 g, 43 mmol) in one portion at rt. The resulting mixture was stirred for 30 min at rt, followed by the addition of $^{n}Bu_4NI$ (1.6 g, 4.3 mmol) and *p*-methoxybenzyl chloride (5.9 mL, 43 mmol). The reaction mixture was stirred at rt overnight, then was quenched with NH_4Cl aq. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 50:1) to afford 1-((hex-5-en-1-yloxy)methyl)-4-methoxybenzene (9.6 g, quantitative). To a solution of 1-((hex-5-en-1-yloxy)methyl)-4-methoxybenzene (15.8 g, 71.7 mmol) in CH_2Cl_2 (250 mL) were added vinylmethylketone (15.1 g, 215 mmol) and Hoveyda-Grubbs catalyst (2nd generation, 45 mg, 0.072 mmol). The resulting solution was stirred at rt for 21 h, then was concentrated directly. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1 to 10:1 to 6:1) to afford the desired product (17 g, 91%) as an oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, 2H, *J* = 7.2 Hz), 6.89 (d, 2H, *J* = 8.4 Hz), 6.79 (td, 1H, *J* = 6.8, 16.0 Hz), 6.07 (d, 1H, *J* = 16.0 Hz), 3.81 (s, 3H), 3.46 (t, 2H, *J* = 6.0 Hz), 2.27-2.22 (m, 5H), 1.67-1.53 (m, 4H).

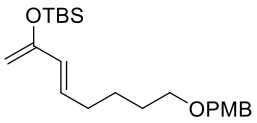
(*E*)-Triethyl((8-((4-methoxybenzyl)oxy)octa-1,3-dien-2-yl)oxy)silane (3.30)



To a solution of **3.29** (1.1 g, 4.1 mmol) and NEt_3 (1.1 mL, 8.2 mmol) was added TESOTf (1.0 mL, 4.5 mmol) dropwise at 0 °C. The resulting solution was stirred at 0 °C for 2 h, then was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 100:1, hexanes contained 1%

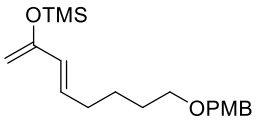
NEt_3) to afford desired product (1.4 g, quantitative) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 6.90-6.87 (m, 2H), 6.00 (td, 1H, *J* = 6.8, 15.2 Hz), 5.87 (td, 1H, *J* = 0.8, 15.2 Hz), 4.44 (s, 2H), 4.21 (d, 2H, *J* = 12.8 Hz), 3.81 (s, 3H), 3.45 (t, 2H, *J* = 6.4 Hz), 2.11 (q, 2H, *J* = 7.2 Hz), 1.67-1.60 (m, 2H), 1.52-1.45 (m, 2H), 1.00 (t, 9H, *J* = 8.4 Hz), 0.73 (q, 6H, *J* = 8.0 Hz); ^{1}H NMR (400 MHz, $CDCl_3$) δ 159.3, 155.3, 131.5, 131.0, 129.4, 128.2, 114.0, 93.8, 72.7, 70.1, 55.5, 32.1, 29.5, 26.0, 7.0, 5.2.

(*E*)-*tert*-Butyl((8-((4-methoxybenzyl)oxy)octa-1,3-dien-2-yl)oxy)dimethylsilane (3.31)



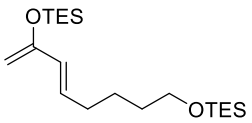
Same procedure with the preparation of **3.30**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.26 (m, 2H), 6.90-6.87 (m, 2H), 5.99 (td, 1H, *J* = 6.8, 15.2 Hz), 5.87 (d, 1H, *J* = 15.2 Hz), 4.44 (s, 2H), 4.21 (d, 2H, *J* = 4.0 Hz), 3.81 (s, 3H), 3.45 (t, 2H, *J* = 6.8 Hz), 2.11 (q, 2H, *J* = 7.2 Hz), 1.66-1.59 (m, 2H), 1.52-1.45 (m, 2H), 0.97 (s, 9H), 0.18 (s, 6H).

(*E*)-((8-((4-Methoxybenzyl)oxy)octa-1,3-dien-2-yl)oxy)trimethylsilane (3.32)



Same procedure with the preparation of **3.30**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.21 (m, 2H), 6.84-6.79 (m, 2H), 6.19 (td, 1H, *J* = 7.2, 15.3 Hz), 5.93 (td, 1H, *J* = 1.2, 15.3 Hz), 4.31 (d, 2H, *J* = 14.1 Hz), 4.30 (d, 2H, *J* = 15.3 Hz), 3.31 (s, 3H), 3.29 (t, 2H, *J* = 6.3 Hz), 2.02 (q, 2H, *J* = 7.5 Hz), 1.62-1.50 (m, 2H), 1.49-1.40 (m, 2H), 0.03 (s, 9H).

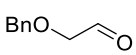
(*E*)-3,3,13,13-Tetraethyl-5-methylene-4,12-dioxa-3,13-disilapentadec-6-ene (3.34)



To the solution of hex-5-en-1-ol (2.0 mL, 17 mmol) in CH_2Cl_2 (40 mL) were added imidazole (1.7 g, 25 mmol) and TESCl (3.3 mL, 20 mmol) at rt. The resulting mixture was stirred at rt for 5 h, then was quenched with H_2O. The aqueous layer was

extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 200:1 to 100:1) to afford triethyl(hex-5-en-1-yloxyl)silane (4.0 g, quantitative) as a colorless oil. To the solution of vinylmethylketone (1.8 mL, 22 mmol) and triethyl(hex-5-en-1-yloxyl)silane (1.6 g, 7.5 mmol) in CH_2Cl_2 (40 mL) was added Hoveyda-Grubbs catalyst (2^{nd} generation, 24 mg, 0.038 mmol) at rt. The resulting solution was stirred at rt for 1.5 h, then was concentrated directly. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1) to afford desired enone **3.33** (1.7 g, 87%). To a solution of enone **3.33** (1.6 g, 6.2 mmol) in dry CH_2Cl_2 (10 mL) was added NEt_3 (1.7 mL, 12 mmol) and TESOTf (1.5 mL, 6.9 mmol) successively at 0 °C. The resulting solution was stirred at the same temperature for 30 min, then was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (pre-treated with 1% NEt_3 in hexanes) to afford diene **3.34** (2.3 g, 99%). ^{1}H NMR (400 MHz, C_6D_6) δ 6.24 (td, 1H, *J* = 7.2, 15.2 Hz), 5.93 (d, 1H, *J* = 15.2 Hz), 4.32 (s, 1H), 4.25 (s, 1H), 3.52 (t, 2H, *J* = 6.0 Hz), 2.05 (q, 2H, *J* = 7.2 Hz), 1.56-1.41 (m, 4H), 1.04-0.99 (m, 18H), 0.70 (q, 6H, *J* = 8.0 Hz), 0.59 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 155.7, 131.6, 128.6, 93.6, 62.7, 32.8, 32.2, 26.0, 7.1, 7.0, 5.4, 4.9; IR (neat) 2955, 2912, 2878, 1591, 1459, 1414, 1382, 1319, 1239, 1100, 1017, 964, 808, 743 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{43}O_2Si_2$ $[M+H]^+$ 371.2802, found 371.2813.

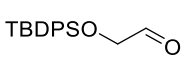
2-(Benzyloxy)acetaldehyde (3.35)



To a solution of ethane-1,2-diol (11.2 g, 200 mmol) in THF (120 mL) was added NaH (60% in mineral oil, 2.8 g, 67 mmol) in one portion at rt. The resulting mixture was stirred for 30

min at rt, followed by addition of $^{n}Bu_4NI$ (2.4 g, 6.7 mmol) and benzyl bromide (11 mL, 200 mmol). The reaction mixture was refluxed overnight, then was quenched with NH_4Cl aq. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 4:1) to afford 2-(benzyloxy)ethan-1-ol (8.3 g, 81%). To a solution of 2-(benzyloxy)ethan-1-ol (1.7 g, 11 mmol), NEt_3 (4.7 mL, 34 mmol), and DMSO (11 mL) in CH_2Cl_2 (7.8 mL) was added SO_3•Py (2.7 g, 17 mmol) in one portion at rt. The resulting yellow solution was stirred at rt for 1 h, then was quenched with H_2O. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1) to afford desired product (1.0 g, 61%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, 1H, *J* = 0.8 Hz), 7.40-7.31 (m, 5H), 4.64 (s, 2H), 4.11 (d, 2H, *J* = 0.8 Hz).

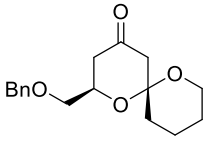
2-((*tert*-Butyldiphenylsilyl)oxy)acetaldehyde (3.36)



To a solution of ethane-1,2-diol (5.6 mL, 100 mmol) were added imidazole (2.0 g, 30 mmol) and TBDPSCl (5.2 mL, 30 mmol) at rt. The resulting mixture was stirred at rt for 24 h, then was quenched with H_2O. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 4:1) to afford 2-((*tert*-butyldiphenylsilyl)oxy)ethan-1-ol (5.1 g, 85%) as a colorless oil. To a solution of 2-((*tert*-butyldiphenylsilyl)oxy)ethan-1-ol (1.2 g, 4.0 mmol) in CH_2Cl_2 (2.8 mL) were added NEt_3 (1.7 mL, 12 mmol), DMSO (3.9 mL), and SO_3•Py (0.95 g, 6.0 mmol) at rt successively. The resulting solution was stirred at rt for 2 h, then was quenched with H_2O. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were dried over Na_2SO_4, filtered, and

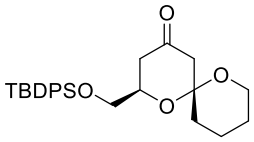
concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1 to 10:1) to afford the desired aldehyde (0.98 g, 82%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, 1H, *J* = 0.8 Hz), 7.70-7.65 (m. 4H), 7.48-7.39 (m, 6H), 4.22 (d, 2H, *J* = 0.8), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 135.7, 132.7, 130.3, 128.1, 70.2, 53.6, 26.9, 19.5; IR (neat) 3071, 2932, 2892, 2858, 1738, 1472, 1428, 1362, 1113, 899, 823, 741, 702, 611 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{23}O_2Si$ $[M+H]^+$ 299.1462, found 299.1454.

(2*R*,6*R*)-2-((Benzyloxy)methyl)-1,7-dioxaspiro[5.5]undecan-4-one (3.39)



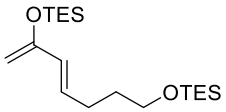
To a mixture of diene **3.34** (0.37 g, 1.0 mmol), aldehyde **3.35** (300 mg, 2.0 mmol), and 4 Å molecular sieves was added Jacobsen catalyst **3.37** (26 mg, 0.05 mmol) at rt. The resulting slurry was stirred at rt for 18 h, then was diluted with CH_2Cl_2 (8 mL). DDQ (0.23 g, 1.0 mmol) was added in one portion. The resulting mixture was stirred at rt for 0.5 h. Then, *p*-TsOH•H_2O (0.38 g, 2.0 mmol) was added to the reaction in one portion. The resulting mixture was stirred at rt for 1.5 h, then was filtered through a short pad of silica gel. The filtrate was concentrated, then was purified by flash chromatorgraphy (hexanes:EtOAc = 20:1 to 15:1 to 10:1 to 5:1) to afford desired spiroketal **3.39** (212 mg, 73% yield, 73% *ee* as determined by HPLC with a Lux cellulose-3 column). $[\alpha]^{25}_D$ -39.1 (*c* 1.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 4.65 (d, 2H, *J* = 2.4 Hz), 4.16-4.10 (m, 1H), 3.67-3.59 (m, 4H), 2.48-2.33 (m, 4H), 2.00-1.87 (m, 2H), 1.66-1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9, 138.3, 128.6, 127.8, 127.7, 73.6, 72.4, 68.6, 61.3, 52.0, 43.3, 34.8, 24.6, 18.8; IR (neat) 2943, 1722, 1602, 1453, 1364, 1311, 1273, 1174, 1074, 1045, 989, 951, 739, 699 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}O_4$ $[M+H]^+$ 291.1591, found 291.1580.

(2*R*,6*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-1,7-dioxaspiro[5.5]undecan-4-one (3.40)



4 Å molecular sieves (150 mg) and Jacobsen's catalyst **3.37** (13 mg, 0.025 mmol) were added into the mixture of diene **3.34** (0.18 g, 0.50 mmol) and aldehyde **3.36** (0.30 mg, 1.0 mmol) successively under argon at rt. The resulting mixture was stirred overnight at rt, then was diluted with CH_2Cl_2 (5 mL). DDQ (0.14 g, 0.61 mmol) was added in one portion. The resulting mixture was stirred at rt for 20 min, then was added *p*-TsOH•H_2O (0.19 g, 1.0 mmol). After stirring at rt for 2 h, the reaction was quenched with NEt_3 and filtered through a short pad of silica gel. The filtrate was concentrated and the residue was purified by flash column chromatography to afford the desired spiroketal **3.40** (0.17 g, 78% yield, 91% *ee* as determined by HPLC with a Lux cellulose-3 column based on (2*R*,6*R*)-2-(benzyloxymethyl)-1,7-dioxaspiro[5.5]undecan-4-one). $[\alpha]^{25}_D$ -23.0 (*c* 1.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 4H, *J* = 6.8 Hz), 7.47-7.38(m, 6H), 4.06 (q, 1H, *J* = 4.8 Hz), 3.84-3.77 (m, 2H), 3.66-3.56 (m, 2H), 2.46-2.37 (m, 4H), 2.00-1.91 (m, 1H), 1.86 (d, 1H, *J* = 13.6 Hz), 1.66-1.60 (m, 2H), 1.55-1.47 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 135.9, 135.8, 133.7, 133.6, 130.0, 127.9, 99.2, 69.9, 66.6, 61.2, 52.2, 43.2, 35.0, 27.0, 24.6, 19.5, 18.8; IR (neat) 3050, 3071, 2999, 2932, 2858, 1738, 1589, 1472, 1428, 1391, 1362, 1261, 1113, 1008, 939, 900, 823, 741, 703, 611 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{35}O_4Si$ $[M + H]^+$ 439.2287, found 439.2305..

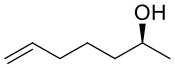
(*E*)-3,3,12,12-Tetraethyl-5-methylene-4,11-dioxa-3,12-disilatetradec-6-ene (3.41)



Same procedure with the preparation of **3.34**. ^{1}H NMR (400 MHz, C_6D_6) δ 6.28 (td, 1H, *J* = 7.2, 15.2 Hz), 5.97 (d, 1H, *J* = 15.2 Hz), 4.34 (s, 1H), 4.26 (s, 1H), 3.54 (t, 2H, *J* = 6.4 Hz), 2.19 (q, 2H, *J* = 7.2 Hz), 1.66-1.59 (m, 2H), 1.04-0.99 (m, 18H), 0.71 (q, 6H, *J* = 7.6 Hz), 0.60 (q, 6H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 155.6, 131.2,

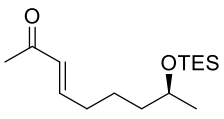
128.8, 93.6, 62.2, 32.8, 28.7, 7.1, 7.0, 5.4, 4.8; IR (neat) 2955, 2912, 2877, 1591, 1459, 1414, 1382, 1320, 1239, 1103, 1017, 963, 806, 744 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{41}O_2Si_2$ $[M+H]^+$ 356.2645, found 356.2644.

(*S*)-Hept-6-en-2-ol (3.42)



To a suspension of magnesium (0.19 g, 7.7 mmol) and iodine (cat.) in Et_2O (5 mL) was added 4-bromobut-1-ene (1.0 g, 7.4 mmol) dropwise. The resulting suspension was refluxing spontaneously and stirred for 1 h. The freshly prepared Grignard reagent was added to a solution of CuCN (66 mg, 0.74 mmol) in THF (6 mL) at –20 °C. The resulting mixture was stirred at –20 °C for 20 min, then (*S*)-(–)-propylene oxide (0.41 mL. 5.9 mmol) was added to this mixture. The reaction was warmed to 0 °C and stirred at this temperature for 12 h. The reaction was quenched with NH_4Cl aq. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 10:1 to 8:1) to afford desired alcohol **3.42** (0.57 g, 85% yield, >99% *ee* as determined by Mosher ester analysis). ^1H NMR (400 MHz, $CDCl_3$) δ 5.82 (dddd, 1H, *J* = 6.8, 6.8, 10.4, 17.2 Hz), 5.02 (tdd, 1H, *J* = 1.6, 2.0, 17.2 Hz), 4.96 (tdd, 1H, *J* = 1.2, 2.0, 10.0 Hz), 3.85-3.78 (m, 1H), 2.09 (dq, 2H, *J* = 1.2, 7.2 Hz), 1.56-1.40 (m, 4H), 1.20 (d, 3H, *J* = 6.4 Hz).

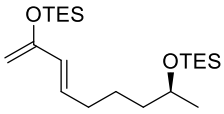
(*S*,*E*)-8-((Triethylsilyl)oxy)non-3-en-2-one (3.43)



To a solution of **3.42** (0.57 g, 5.0 mmol) in THF (10 mL) were added imidazole (0.68 g, 10 mmol) and TESCl (1.1 g, 7.5 mmol) at rt. The resulting mixture was stirred at rt for 1.5 h, then was quenched with H_2O. The aqueous layer was extracted with

Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 100:1) to afford (*S*)-triethyl(hept-6-en-2-yloxy)silane (0.92 g, 80%). To a solution of (*S*)-triethyl(hept-6-en-2-yloxy)silane (0.92 g, 4.0 mmol) and vinylmethylketone (0.84 g, 12 mmol) in CH_2Cl_2 (16 mL) was added Hoveyda-Grubbs catalyst (2nd generation, 25 mg, 0.04 mmol). The resulting solution was stirred at rt for 13 h, then was concentrated directly. The residue was purified by flash chromatography (hexanes:EtOAc = 20:1) to afford enone **3.43** (0.78 g, 72%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (td, 1H, *J* = 6.8, 16.0 Hz), 6.08 (td, 1H, *J* = 1.6, 16.0 Hz), 3.83-3.79 (m, 1H), 2.25 (s, 3H), 2.27-2.21 (m, 2H), 1.64-1.56 (m, 1H), 1.54-1.41 (m, 3H), 1.15 (d, 3H, *J* = 6.0 Hz), 0.97 (t, 9H, *J* = 8.0 Hz), 0.60 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 148.5, 131.6, 68.3, 39.4, 32.7, 27.1, 24.5, 24.1, 7.1, 5.2.

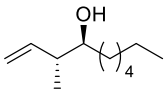
(*S*,*E*)-3,3,13,13-Tetraethyl-11-methyl-5-methylene-4,12-dioxa-3,13-disilapentadec-6-ene (3.44)



To a solution of enone **3.43** (0.18 g, 0.67 mmol) in dry CH_2Cl_2 (2 mL) was added NEt_3 (0.19 mL, 1.3 mmol) and TESOTf (0.17 mL, 0.73 mmol) successively at 0 °C. The resulting solution was stirred at the same temperature for 30 min, then was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (pre-treated with 1% NEt_3 in hexanes) to afford diene **3.44** (0.24 g, 94%). $[\alpha]^{25}_D$ +3.3 (*c* 1.37, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.28 (td, 1H, *J* = 7.2, 15.2 Hz), 5.97 (d, 1H, *J* = 15.2 Hz), 4.35 (s, 1H), 4.28 (s, 1H), 3.74-3.67 (m, 1H), 2.06 (q, 1H, *J* = 2.8 Hz), 1.59-1.46 (m, 2H), 1.44-1.33 (m, 2H), 1.10 (d, 3H, *J* = 6.4 Hz), 1.04 (t, 9H, *J* = 8.0

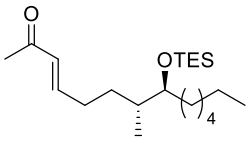
Hz), 1.03 (t, 9H, *J* = 8.0 Hz), 0.72 (q, 6H, *J* = 8.0 Hz), 0.61 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (400 MHz, C_6D_6) δ 155.7, 131.7, 128.6, 128.2, 93.6, 68.5, 39.7, 32.5, 25.8, 24.1, 7.2, 7.0, 5.5, 5.4; IR (neat) 2954, 1655, 1592, 1459, 1414, 1377, 1318, 1239, 1137, 1095, 1016, 963, 817, 744, 672 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{45}O_2Si_2$ $[M+H]^+$ 385.2960, found 385.2958.

(3*R*,4*S*)-3-Methyldec-1-en-4-ol (3.45)



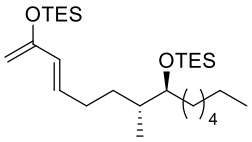
To a suspension of KO^{t}Bu (3.8 g, 34 mmol) in THF (18 mL) was added (*E*)-but-2-ene (5.2 mL, 60 mmol) at –78 °C, followed by addition of ^{n}BuLi (1.6 M in THF, 19 mL, 30 mmol) at the same temperature. The reaction was warmed to –45 °C and stirred at –45 °C for 20 min, then was cooled to –78 °C. A pre-cooled (–30 °C) solution of (+)-$(Ipc)_2$BOMe (11 g, 35 mmol) in Et_2O (25 mL) was added to the reaction mixture dropwise. The resulting mixture was stirred at –78 °C for 30 min, then BF_3•OEt_2 (4.8 mL) was added. After addition, the reaction mixture was stirred at –78 °C for 4.5 h, then NaOH (aq., 3.0 M, 21 mL) and H_2O_2 (aq., 30%, 9 mL) were added. The reaction was refluxed for 1 h, then was poured into a separatory funnel. The organic layer was collected, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 100:1 to 50:1 to 20:1) to afford desired alcohol **3.45** (2.9 g, 57% yield, 83% *ee* as determined by Mosher ester analysis) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddd, 1H, *J* = 8.4, 11.2, 16.8 Hz), 5.11 (s, 1H), 5.09-5.07 (m, 1H), 3.40-3.36 (m, 1H), 2.20 (dq, 1H, *J* = 6.8, 14.0 Hz), 1.63 (s, 1H), 1.54-1.40 (m, 2H), 1.38-1.28 (m, 10H), 1.02 (d, 3H, *J* = 6.8 Hz), 0.88 (t, 3H, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.8, 48.0, 47.9, 42.0, 39.2, 38.4, 34.6, 27.9, 23.9, 20.9.

(5*R*,6*S*,*E*)-5-Methyl-6-((triethylsilyl)oxy)dodec-3-en-2-one (3.46)



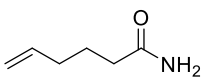
To a solution of **3.45** (1.0 g, 5.9 mmol) were added imidazole (0.80 g, 12 mmol) and TESCl (1.5 mL, 8.8 mL) at rt. The resulting solution was stirred at rt for 2 h, then was quenched with H_2O. The aqueous layer was extracted with Et_2O and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 500:1) to afford triethyl(((3*R*,4*S*)-3-methyldec-1-en-4-yl)oxy)silane (1.5 g, 87%) as a colorless oil. To a solution of 9-BBN dimer (448 mg, 1.84 mmol) in THF (2 mL) was added a solution of triethyl(((3*R*,4*S*)-3-methyldec-1-en-4-yl)oxy)silane (580 mg, 2.04 mmol) in THF (2 mL) at rt under argon. The resulting solution was stirred at rt for 4.5 h, then was quenched with H_2O (0.5 mL). To the reaction mixture were added a solution of K_3PO_4•H_2O (705 mg, 3.06 mmol) in H_2O (1 mL), a solution of (*E*)-4-iodobut-3-en-2-one (799 mg, 4.08 mmol) in THF (3 mL), and [Pd(dppf)Cl_2]•CH_2Cl_2 (83.3 mg, 0.102 mmol) at rt. The resulting dark brown mixture was stirred at rt for 16 h, then was quenched with H_2O. The aqueous layer was extracted with Et_2O (3x) and combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 50:1) to afford enone **3.46** (720 mg, 99%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (td, 1H, *J* = 6.8, 16.0 Hz), 6.09 (d, 1H, *J* = 16.0 Hz), 3.54-3.51 (m, 1H), 2.41-2.27 (m, 1H), 2.25 (s, 3H), 2.21-2.14 (m, 1H), 1.58-1.51 (m, 3H), 1.42-1.32 (m, 2H), 1.28-1.21 (m, 8H), 0.96 (t, 9H, *J* = 12.0 Hz), 0.90 (t, 3H, *J* = 6.8 Hz), 0.59 (q, 6H, *J* = 8.0 Hz).

(10*R*,11*S*,*E*)-3,3,13,13-Tetraethyl-11-hexyl-10-methyl-5-methylene-4,12-dioxa-3,13-disilapentadec-6-ene (3.47)



To a solution of enone **3.46** (0.15 g, 0.41 mmol) in dry CH_2Cl_2 (1 mL) was added NEt_3 (0.12 mL, 0.83 mmol) and TESOTf (0.10 mL, 0.46 mmol) successively at 0 °C. The resulting solution was stirred at the same temperature for 30 min, then was quenched with H_2O and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (pre-treated with 1% NEt_3 in hexanes) to afford diene **3.47** (0.18 g, 92%). $[\alpha]^{25}_D$ -1.7 (*c* 1.30, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 6.30 (td, 1H, *J* = 7.2, 15.2 Hz), 6.00 (d, 1H, *J* = 15.2 Hz), 4.35 (s, 1H), 4.27 (s, 1H), 3.62-3.58(m, 1H), 2.25-2.16(m, 1H), 2.11-2.02(m, 1H), 1.73-1.66 (m, 1H), 1.61-1.45 (m, 3H), 1.40-1.22 (m, 9H), 1.06 (t, 9H, *J* = 8.0 Hz), 1.04 (t, 9H, *J* = 8.0 Hz), 0.96 (d, 3H, *J* = 6.8 Hz), 0.92 (t, 3H, *J* = 6.8 Hz), 0.73 (q, 6H, *J* = 8.0 Hz), 0.67 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (400 MHz, C_6D_6) δ 155.7, 131.7, 128.6, 93.4, 76.5, 38.4, 32.9, 32.5, 32.4, 30.4, 30.0, 26.3, 23.1, 14.8, 14.3, 7.3, 7.0, 5.7, 5.4; IR (neat) 2955, 2876, 1591, 1459, 1414, 1378, 1318, 1238, 1120, 1016, 964, 809, 742, 673 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{56}O_2Si_2$ $[M]^+$ 468.3819, found 468.3822.

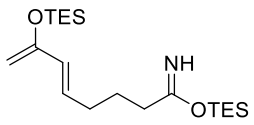
Hex-5-enamide (3.48)



To a solution of hex-5-enoic acid (1.0 mL, 8.4 mmol) in benzene (16 mL) was added oxalyl chloride (1.4 mL, 17 mmol) dropwise at 0 °C. The resulting solution was stirred at rt for 1 h. Then the solvent was removed under reduced pressure. The residue was re-dissolved in THF (16 mL) and treated with aqueous ammonium hydroxide (16 mL) dropwise at 0 °C. The resulting mixture was stirred at rt for 18 h, then was diluted with H_2O and

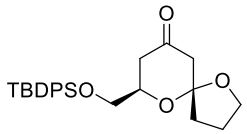
EtOAc. The aqueous layer was extracted with EtOAc (3x) and combined organic layers (included the original portion of organic layer) were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography to afford desired amide (0.46 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 1H), 6.02 (s, 1H), 5.72 (tdd, 1H, *J* = 6.8, 10.0, 12.8 Hz), 4.96 (dd, 1H, *J* = 1.2, 13.2 Hz), 4.92 (d, 1H, *J* = 10.4 Hz), 2.16 (t, 2H, *J* = 7.6 Hz), 2.04 (q, 2H, *J* = 7.2 Hz), 1.66 (quint, 2H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 137.8, 115.4, 35.1, 33.1, 24.6.

Triethylsilyl (*E*)-7-((triethylsilyl)oxy)octa-5,7-dienimidate (3.49)



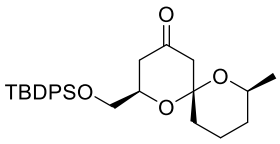
To a solution of **3.48** (47 mg, 0.42 mmol) and vinylmethylketone (0.1 mL, 1.26 mmol) in CH_2Cl_2 (1.7 mL) was added Hoveyda-Grubbs catalyst (2nd generation, 1.3 mg, 0.0021 mmol) at rt. The resulting solution was stirred at rt for 2 h, then was concentrated directly. The residue was purified by flash chromatography to afford (*E*)-7-oxooct-5-enamide (30 mg, 46%). This freshly prepared enone (30 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (0.5 mL). To this solution were added NEt_3 (0.1 mL, 0.76 mmol) and TESOTf (106 mg, 0.40 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 1 h, then was quenched with H_2O and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography to afford desired diene **3.49** (58 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (td, 1H, *J* = 6.8, 15.2 Hz), 5.95 (d, 1H, *J* = 15.2 Hz), 4.34 (s, 1H), 4.26 (s, 1H), 4.17 (s, 1H), 2.06 (q, 2H, *J* = 6.8 Hz), 1.86 (t, 2H, *J* = 7.2 Hz), 1.69 (quint, 2H, *J* = 7.2 Hz), 1.03-0.98 (m, 18H), 0.76-0.67 (m, 12H).

(5*R*,7*R*)-7-((*tert*-Butyldiphenylsilyloxy)methyl)-1,6-dioxaspiro[4.5]decan-9-one (3.50)



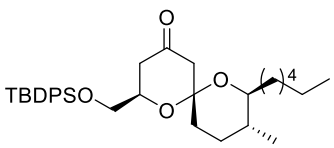
4 Å molecular sieves (80 mg) and Jacobsen's catalyst **3.37** (13 mg, 0.02 mmol) were added into the mixture of diene **3.41** (0.14 g, 0.39 mmol) and aldehyde **3.36** (0.23 g, 0.78 mmol) successively under argon at rt. The resulting mixture was stirred overnight at rt, then was diluted with CH_2Cl_2 (3.2 mL). DDQ (0.11 g, 0.47 mmol) was added in one portion. The resulting mixture was stirred at rt for 20 min, then was added *p*-TsOH•H_2O (0.15 g, 0.78 mmol). After stirring at rt for 2 h, the reaction was quenched with NEt_3 (0.1 mL) and filtered through a short pad of silica gel. The filtrate was concentrated and the residue was purified by flash column chromatography to afford the desired spiroketal **3.50** (0.12 g, 72% yield, 85% *ee* as determined by HPLC with a Lux cellulose-3 column based on (5*R*,7*R*)-7-(benzyloxymethyl)-1,6-dioxaspiro[4.5]decan-9-one). $[\alpha]^{25}_D$ -24.1 (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 4H, *J* = 6.8 Hz), 7.46-7.37 (m, 6H), 4.16-4.13 (m, 1H), 3.94 (q, 1H, *J* = 7.2 Hz), 3.85 (q, 1H, *J* = 7.2 Hz), 3.79-3.72 (m, 2H), 2.74 (d, 1H, *J* = 14.4 Hz), 2.47 (d, 1H, *J* = 14.4 Hz), 2.44-2.42 (m, 2H), 2.20-2.14 (m, 1H), 2.11-2.05 (m. 1H), 1.94-1.92 (m, 1H), 1.77 (q, 1H, *J* = 9.6 Hz), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.1, 135.9, 135.8, 133.7, 133.7, 129.9, 127.9, 127.8, 107.8, 70.1, 67.8, 66.6, 49.5, 43.3, 37.7, 27.0, 23.7, 19.5; IR (neat) 3070, 3049, 2958, 2930, 2890, 2857, 1726, 1472, 1461, 1428, 1362, 1335, 1292, 1256, 1113, 1082, 1000, 823, 741, 704, 610 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{33}O_4Si$ $[M + H]^+$ 425.2148, found 425.2138.

(2*R*,6*R*,8*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-8-methyl-1,7-dioxaspiro[5.5]undecan-4-one (3.51)



4 Å molecular sieves (70 mg) and Jacobsen's catalyst **3.37** (6.7 mg, 0.013 mmol) were added into the mixture of diene **3.44** (0.10 g, 0.26 mmol) and aldehyde **3.36** (0.16 g, 0.52 mmol) successively under argon at rt. The resulting mixture was stirred overnight at rt, then was diluted with CH_2Cl_2 (2 mL). DDQ (71 mg, 0.31 mmol) was added in one portion. The resulting mixture was stirred at rt for 20 min, then was added *p*-TsOH•H_2O (74 mg, 0.39 mmol). After stirring at rt for 2 h, the reaction was quenched with NEt_3 (0.1 mL) and filtered through a short pad of silica gel. The filtrate was concentrated and the residue was purified by flash column chromatography to afford the desired spiroketal **3.51** (84 mg, 71% yield). $[\alpha]^{25}_D$ -22.3 (*c* 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.72 (m, 4H), 7.47-7.38 (m, 6H), 4.02-3.95 (m, 1H), 3.83-3.68 (m, 3H), 2.46-2.36 (m, 4H), 1.96 (tq, 1H, *J* = 4.0, 13.2 Hz), 1.83 (d, 1H, *J* = 13.2 Hz), 1.64 (d, 1H, *J* = 12.8 Hz), 1.55 (d, 1H, *J* = 15.2 Hz), 1.46 (dt, 1H, *J* = 4.8, 13.2 Hz), 1.25-1.14 (m, 1H), 1.08 (d, 3H, *J* = 4.8 Hz), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.5, 135.9, 135.8, 133.7, 133.6, 130.0, 127.9, 99.6, 69.6, 66.6, 66.5, 52.2, 43.2, 34.4, 32.0, 27.0, 21.8, 19.5, 19.2; IR (neat) 3071, 2931, 2857, 1724, 1472, 1428, 1383, 1304, 1256, 1220, 1177, 1113, 1083, 996, 965, 823, 798, 741, 703 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{27}H_{37}O_4Si$ $[M + H]^+$ 425.2461, found 453.2450.

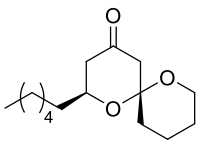
(2*R*,6*R*,8*S*)-2-((*tert*-Butyldiphenylsilyloxy)methyl)-8-methyl-1,7-dioxaspiro[5.5]undecan-4-one (3.52)



4 Å molecular sieves (100 mg) and Jacobsen's catalyst **3.37** (14 mg, 0.026 mmol) were added into the mixture of diene **3.47** (0.25 g, 0.53

mmol) and aldehyde **3.36** (0.32 g, 1.1 mmol) successively under argon at rt. The resulting mixture was stirred overnight at rt, then was diluted with CH_2Cl_2 (5 mL). DDQ (0.14 g, 0.64 mmol) was added in one portion. The resulting mixture was stirred at rt for 20 min, then was added *p*-TsOH•H_2O (0.20 g, 1.1 mmol). After stirring at rt for 2 h, the reaction was quenched with NEt_3 (0.1 mL) and filtered through a short pad of silica gel. The filtrate was concentrated and the residue was purified by flash column chromatography to afford the desired spiroketal **3.52** (0.21 g, 75% yield). $[\alpha]^{25}_D$ -32.2 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.72 (m, 4H), 7.47-7.37 (m, 6H), 4.08-4.02 (m, 1H), 3.80 (dd, 1H, *J* = 5.6, 10.4 Hz), 3.74 (dd, 1H, *J* = 3.6, 10.4 Hz), 3.26 (dt, 1H, *J* = 2.4, 9.6 Hz), 2.46-2.35 (m, 4H), 1.90-1.86 (m, 1H), 1.74-1.63 (m, 1H), 1.60-1.52 (m, 2H), 1.48-1.41 (m, 1H), 1.36-1.23 (m, 10H), 1.08 (s, 9H), 0.88 (t, 3H, *J* = 6.8 Hz), 0.82 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 135.9, 133.6, 133.6, 130.0, 129.9, 129.9, 128.0, 127.9, 99.3, 75.8, 69.9, 66.7, 53.6, 52.1, 43.2, 35.5, 34.2, 33.0, 32.1, 29.8, 28.2, 27.0, 26.8, 25.4, 22.9, 19.5, 17.9, 14.3; IR (neat) 3049, 2930, 2858, 1727, 1589, 1461, 1428, 1361, 1310, 1247, 1113, 998, 822, 794, 741, 703, 606 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{33}H_{49}O_4Si$ $[M + H]^+$ 537.3400, found 537.3390.

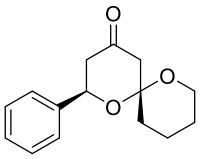
(2*S*,6*R*)-2-Hexyl-1,7-dioxaspiro[5.5]undecan-4-one (3.53)



4 Å molecular sieves (150 mg) and Jacobsen's catalyst **3.37** (39 mg, 0.075 mmol) were added into the mixture of diene **3.34** (0.18 g, 0.50 mmol) and freshly distilled heptanal (0.14 mL, 1.0 mmol) successively under argon at rt. The resulting mixture was stirred at rt for 13 h, 1.0 equiv. heptanal (0.07 mL, 0.5 mmol) was added to the reaction. The resulting reaction mixture was stirred at rt for 24 h, then was diluted with CH_2Cl_2 (4 mL). DDQ (0.11 g, 0.50 mmol) was added in one portion. The resulting mixture was stirred at

rt for 20 min, then was added *p*-TsOH•H_2O (0.19 g, 1.0 mmol). After stirring at rt for 2 h, the reaction was quenched with NEt_3 (0.1 mL) and filtered through a short pad of silica gel. The filtrate was concentrated and the residue was purified by flash column chromatography to afford the desired spiroketal **3.53** (65 mg, 50% yield, >99% *ee* as determined by HPLC with a Lux cellulose-3 column). $[\alpha]^{25}_D$ -70.7 (*c* 1.42, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92-3.86 (m, 1H), 3.60-3.58 (m, 2H), 2.43-2.34 (m, 3H), 2.19 (dd, 1H, *J* = 7.6, 14.0 Hz), 1.91 (td, 1H, *J* = 4.4, 12.8 Hz), 1.85-182 (m, 1H), 1.70-1.48 (m, 7H), 1.41-1.26 (m, 7H), 0.90 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 99.0, 69.1, 61.2, 52.3, 47.4, 36.5, 35.2, 32.0, 29.5, 25.8, 24.7, 22.8, 19.0, 14.3; IR (neat) 2931, 2858, 1726, 1464, 1362, 1309, 1275, 1251, 1208, 1173, 1096, 1074, 1045, 988, 949 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{27}O_3$ $[M + H]^+$ 255.1960, found 255.1942.

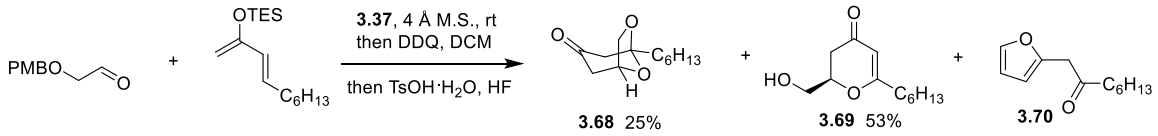
(2*R*,6*R*)-2-Phenyl-1,7-dioxaspiro[5.5]undecan-4-one (3.54)



4 Å molecular sieves (150 mg) and Jacobsen's catalyst **3.37** (39 mg, 0.075 mmol) were added into the mixture of diene **3.47** (0.25 g, 0.53 mmol) and freshly distilled benzaldehyde (0.11 g, 1.0 mmol) successively under argon at rt. The resulting mixture was stirred at rt for 72 h, then was diluted with CH_2Cl_2 (4 mL). DDQ (0.11 g, 0.50 mmol) was added in one portion. The resulting mixture was stirred at rt for 20 min, then was added *p*-TsOH•H_2O (0.19 g, 1.0 mmol). After stirring at rt for 2 h, the reaction was quenched with NEt_3 (0.1 mL) and filtered through a short pad of silica gel. The filtrate was concentrated and the residue was purified by flash column chromatography to afford the desired spiroketal **3.54** (65 mg, 53% yield, 84% *ee* as determined by HPLC with a Lux cellulose-3 column). $[\alpha]^{25}_D$ -19.7 (*c* 2.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.39 (m, 4H), 7.36-7.32 (m, 1H), 4.99 (dd, 1H, *J* = 1.2, 11.6 Hz), 3.67 (dd, 1H, *J* = 2.0, 9.2 Hz), 2.69-2.64 (m, 1H), 2.57-2.50 (m, 3H), 2.01-1.89 (m,

2H), 1.68-1.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.6, 141.1, 128.8, 128.1, 126.0, 99.5, 70.7, 61.4, 52.2, 48.7, 35.2, 24.6, 18.9; IR (neat) 2944, 2872, 1725, 1452, 1370, 1310, 1258, 1212, 1172, 1132, 1077, 1039, 985, 948, 872, 750 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{19}O_3$ $[M + H]^+$ 247.1334, found 247.1324.

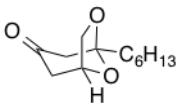
Synthesis of the bridged bicyclic ether through the one-pot process



Jacobsen's catalyst **3.37** (20 mg, 0.042 mmol) was added into the mixture of 4 Å molecular sieves (300 mg), (*E*)-(deca-1,3-dien-2-yloxy)triethylsilane (0.23 g, 0.84 mmol), and 2-((4-methoxybenzyl)oxy)acetaldehyde (0.23 g, 1.3 mmol) successively under argon at rt. The resulting mixture was stirred at rt for 18 h, then was added 0.5 equiv. of 2-((4-methoxybenzyl)oxy)acetaldehyde (76 mg, 0.42 mmol). The resulting mixture was stirred at rt for 28 h, then was diluted with dry CH_2Cl_2 (4 mL). The first portion of DDQ (0.19 g, 0.84 mmol) was added. After stirring at rt for 5 min, the second portion of DDQ (0.29 g, 1.3 mmol) was added and the reaction was diluted with wet CH_2Cl_2 (2 mL). The resulting mixture was stirred at rt for 14 h, followed by the addition of the third portion of DDQ (0.19 g, 0.84 mmol). The reaction was stirred at rt for 2 h, then was added HF (70% in pyridine, 0.05 mL) and *p*-TsOH•H_2O (80 mg, 0.42 mmol). After stirring at rt for 30 min, to the reaction were added 1.0 equiv. *p*-TsOH•H_2O (0.16 g, 0.84 mmol), HF (70% in pyridine, 0.1 mL), and 1.0 equiv. *p*-TsOH•H_2O (0.16 g, 0.84 mmol) successively. The resulting reaction mixture was stirred at rt for 1.5 h, then was quenched with NEt_3 (0.1 mL) and filtered through a short pad of silica gel. The filtrate was concentrated and the residue was purified by flash column chromatography to afford bridged bicyclic ether **3.68** (44

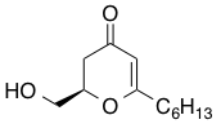
mg, 25%), enone **3.69** (95 mg, 53%), and trace amount of furan **3.70** (a significant amount of furan **3.70** was obtained when the reaction was stirred at rt overnight).

(1*R*,5*S*)-5-Hexyl-6,8-dioxabicyclo[3.2.1]octan-3-one (3.68)



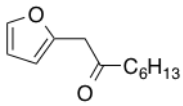
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (t, 1H, *J* = 4.8 Hz), 3.89 (ddd, 1H, *J* = 2.0, 4.8, 7.2 Hz), 3.84 (d, 1H, *J* = 7.2 Hz), 2.74 (ddd, 1H, *J* = 2.0, 5.2, 16.8 Hz), 2.60 (dd, 1H, *J* = 0.8, 16.8 Hz), 2.54 (d, 1H, *J* = 16.4 Hz), 2.44 (td, 1H, *J* = 1.2, 16.4 Hz), 1.86-1.74 (m, 2H), 1.50-1.42 (m, 2H), 1.38-1.26 (m, 6H), 0.90 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.7, 109.2, 73.3, 70.6, 51.6, 46.4, 37.3, 31.9, 29.5, 23.2, 22.8, 14.3; IR (neat) 2929, 2858, 1727, 1466, 1378, 1317, 1280, 1241, 1186, 1156, 1079, 1040, 1008 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{21}O_3$ $[M + H]^+$ 213.1485, found 213.1479.

(*R*)-6-Hexyl-2-(hydroxymethyl)-2,3-dihydro-4*H*-pyran-4-one (3.69)



^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 4.45 (tdd, 1H, *J* = 3.2, 5.2, 14.0 Hz), 3.90 (dd, 1H, *J* = 3.2, 12.4 Hz), 3.78 (dd, 1H, *J* = 5.2, 12.0 Hz), 2.63 (dd, 1H, *J* = 14.0, 16.0 Hz), 2.59 (br, 1H), 2.32 (ddd, 1H, *J* = 0.8, 3.6, 12.8 Hz), 2.25 (dt, 2H, *J* = 2.8, 7.2 Hz), 1.58-1.51 (m, 2H), 1.33-1.23 (m, 6H), 0.87 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 177.9, 104.3, 79.6, 64.1, 37.1, 34.9, 31.6, 28.9, 26.5, 22.6, 14.2; IR (neat) 3408, 2956, 2929, 2859, 1654, 1601, 1459, 1404, 1340, 1239, 1026, 984, 919, 811 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{21}O_3$ $[M + H]^+$ 213.1485, found 213.1477.

1-(Furan-2-yl)octan-2-one (3.70)

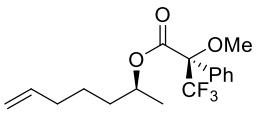


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, 1H, *J* = 0.4, 1.2 Hz), 6.35 (dd, 1H, *J* = 2.0, 3.2 Hz), 6.20 (dd, 1H, *J* = 0.4, 2.8 Hz), 3.70 (s, 2H), 2.45 (t, 2H, *J* = 7.2 Hz), 1.60-1.53 (m, 2H), 1.32-1.24 (m, 6H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.7, 148.6, 142.3, 110.9, 108.4, 42.7, 42.1, 31.8, 29.0, 23.8, 22.7, 14.2; IR (neat) 2957, 2928, 2857, 1721, 1598, 1505, 1464, 1380, 1287, 1146, 1075, 1011, 936, 731, 413 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{12}H_{19}O_2$ $[M + H]^+$ 195.1380, found 195.1376.

General procedure for the Mosher ester analysis

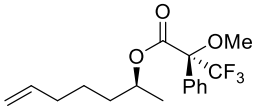
The secondary alcohol substrate (1.0 eq.) was treated with Mosher acid solution in dry CH_2Cl_2 (0.12 M, 1.5 eq.), DCC solution in dry CH_2Cl_2 (0.069 M, 2.0 eq.), and DMAP solution in dry CH_2Cl_2 (0.11 M, 0.1 eq.) successively at rt. The resulting mixture was stirred at rt overnight, then filtered through a Celite® pad. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the desired Mosher ester.

(*R*)-((*S*)-Hept-6-en-2-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S3.1)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.43-7.38 (m, 3H), 5.77-5.66 (m, 1H), 5.22-5.14 (m, 1H), 5.00-4.94 (m, 2H), 3.58 (d, 3H, *J* = 1.2 Hz), 2.03-1.97 (m, 2H), 1.69-1.47 (m, 2H), 1.35 (d, 3H, *J* = 6.0 Hz), 1.33-1.27 (m, 2H).

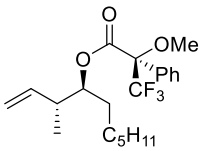
(*S*)-((*S*)-Hept-6-en-2-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S3.2)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.43-7.39 (m, 3H), 5.82-5.72 (m, 1H), 5.20-5.12 (m, 1H), 5.04-4.96 (m, 2H), 3.56 (d, 3H, *J* = 0.8

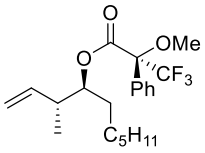
Hz), 2.07 (q. 2H, *J* = 7.2 Hz), 1.76-1.66 (m, 1H), 1.63-1.55 (m, 1H), 1.53-1.40 (m, 1H), 1.38-1.31 (m, 1H), 1.27 (d, 3H, *J* = 6.0 Hz).

(*R*)-((3*R*,4*S*)-3-Methyldec-1-en-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S3.3)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.56 (m, 2H), 7.42-7.38 (m, 3H), 5.72-5.63 (m, 1H), 5.09-5.04 (m, 2H), 5.01 (s, 1H), 3.56 (d, 3H, *J* = 1.2 Hz), 2.52-2.43 (m, 1H), 1.67-1.51 (m, 2H), 1.29-1.25 (m, 8H), 0.95 (d, 3H, *J* = 5.6 Hz), 0.88 (t, 3H, *J* = 6.8 Hz).

(*S*)-((3*R*,4*S*)-3-Methyldec-1-en-4-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S3.4)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.56 (m, 2H), 7.42-7.38 (m, 3H), 5.77-5.68 (m, 1H), 5.09-5.05 (m, 3H), 3.56 (d, 3H, *J* = 0.8 Hz), 2.56-2.47 (m, 1H), 1.62-1.47 (m, 2H), 1.29-1.16 (m, 8H), 1.03 (d, 3H, *J* = 6.8 Hz), 0.87 (t, 3H, *J* = 7.2 Hz).

HPLC data

==== Shimadzu LCsolution Analysis Report ====

Peak Table

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.469	346344	38987	13.505	27.856
2	4.067	1136936	44140	44.334	31.538
3	4.302	334693	23000	13.051	16.433
4	5.099	21614	3354	0.843	2.396
5	5.207	38418	3897	1.498	2.784
6	9.677	345523	14897	13.473	10.644
7	11.645	340946	11684	13.295	8.348
Total		2564474	139959	100.000	100.000

<Chromatogram>

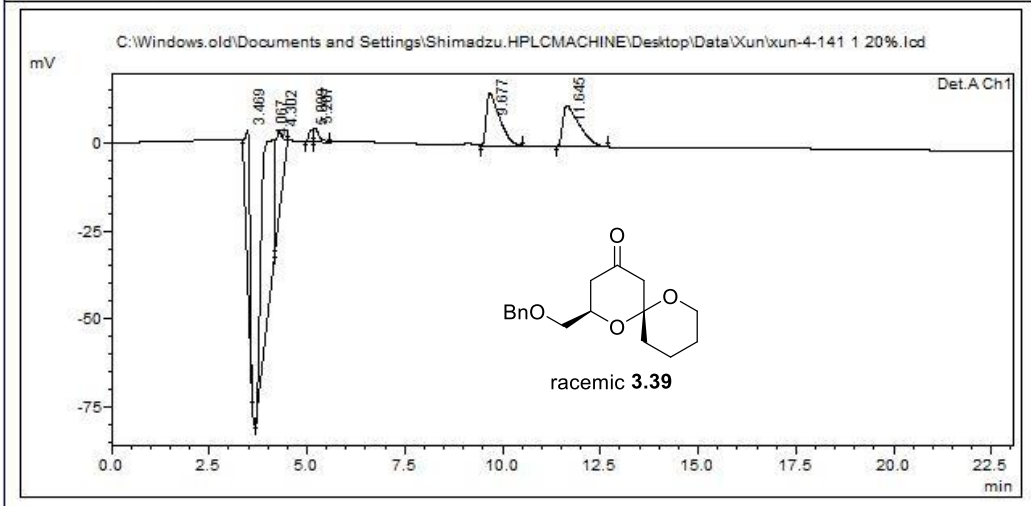


Figure S3-1. HPLC anaylsis report of racemic **3.39**

==== Shimadzu LCsolution Analysis Report ====

PeakTable

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.471	293835	32496	8.595	19.902
2	4.150	1370482	47704	40.090	29.217
3	4.318	614182	37821	17.966	23.163
4	4.627	200488	15736	5.865	9.637
5	9.965	815132	24892	23.845	15.245
6	12.547	124373	4630	3.638	2.836
Total		3418491	163279	100.000	100.000

<Chromatogram>

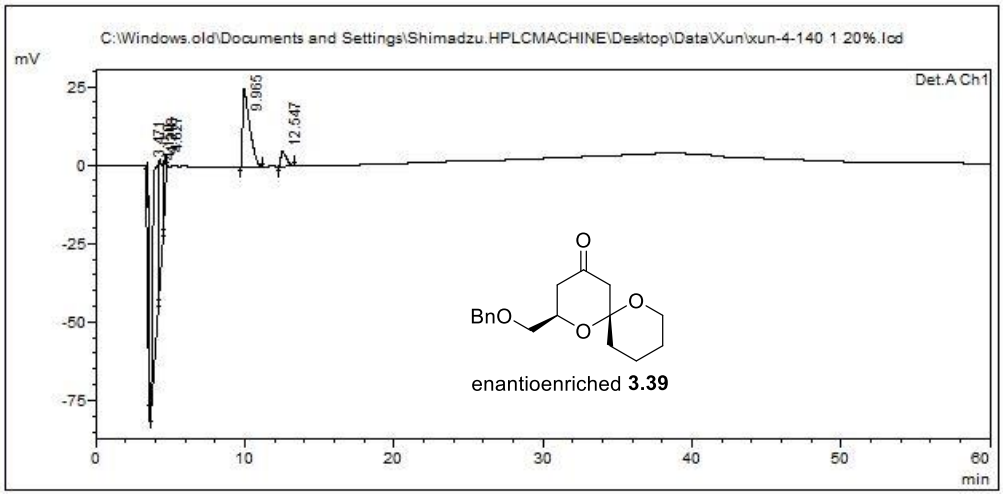


Figure S3-2. HPLC anaylsis report of enantioenriched **3.39**

==== Shimadzu LCsolution Analysis Report ====

PeakTable

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	4.278	1242004	136203	15.782	47.753
2	5.267	4636474	74857	58.915	26.245
3	5.597	981738	52497	12.475	18.405
4	6.225	374141	8955	4.754	3.140
5	17.291	329017	7403	4.181	2.596
6	23.510	306372	5311	3.893	1.862
Total		7869748	285227	100.000	100.000

<Chromatogram>

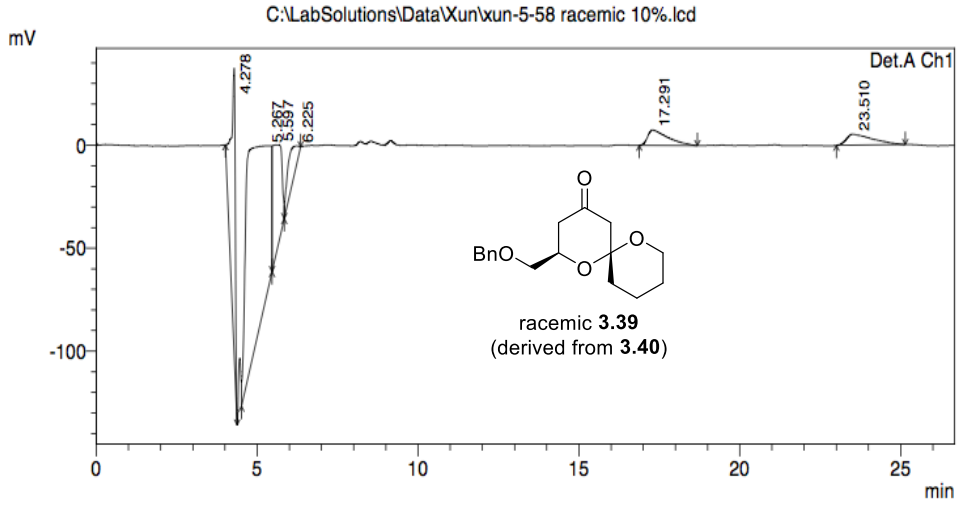


Figure S3-3. HPLC anaylsis report of racemic **3.39** (derived from **3.40**)

==== Shimadzu LCsolution Analysis Report ====

PeakTable

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.892	424487	35252	3.118	6.787
2	4.269	1932270	133981	14.194	25.797
3	4.470	371531	46700	2.729	8.992
4	5.392	5795831	117957	42.576	22.712
5	5.721	2394025	91903	17.586	17.695
6	6.164	1281982	55492	9.417	10.685
7	6.580	798514	22721	5.866	4.375
8	9.101	37228	2649	0.273	0.510
9	11.955	92221	2416	0.677	0.465
10	17.037	464030	9626	3.409	1.853
11	24.369	20878	674	0.153	0.130
Total		13612996	519372	100.000	100.000

<Chromatogram>

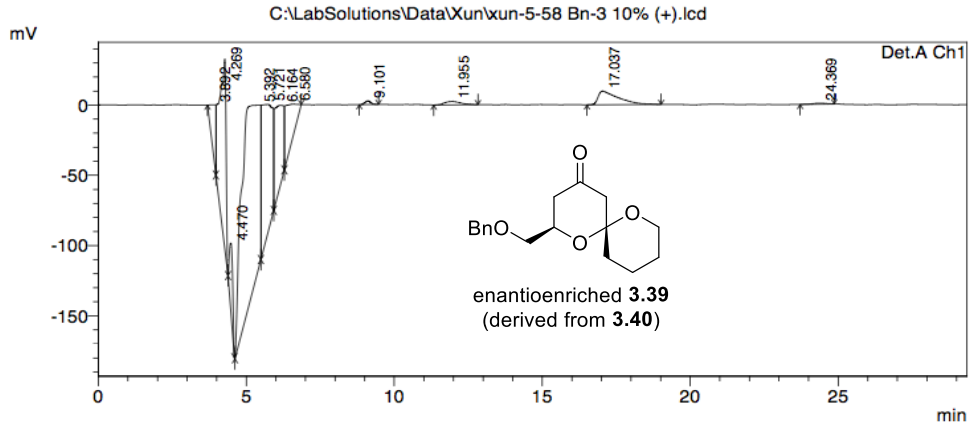


Figure S3-4. HPLC anaylsis report of enantioenriched **3.39** (derived from **3.40**)

==== Shimadzu LCsolution Analysis Report ====

PeakTable

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.274	368707	43524	32.755	64.838
2	12.599	380015	12629	33.759	18.814
3	14.223	376933	10974	33.486	16.348
Total		1125656	67128	100.000	100.000

<Chromatogram>

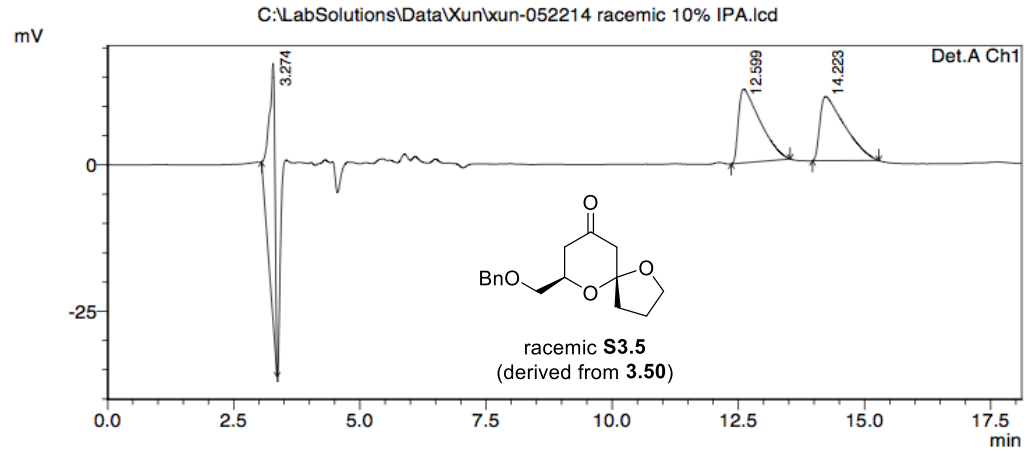


Figure S3-5. HPLC anaylsis report of racemic **S3.5** (derived from **3.50**)

==== Shimadzu LCsolution Analysis Report ====

PeakTable

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.258	478746	52064	53.961	76.659
2	10.628	65012	4336	7.328	6.384
3	12.655	318384	10348	35.886	15.236
4	14.794	25068	1168	2.826	1.720
Total		887211	67916	100.000	100.000

<Chromatogram>

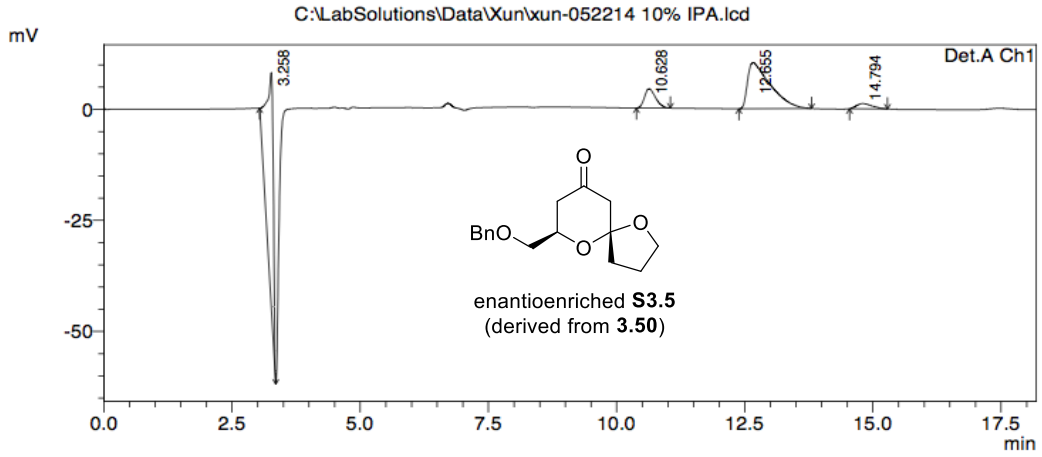


Figure S3-6. HPLC anaylsis report of enantioenriched **S3.5** (derived from **3.50**)

==== Shimadzu LCsolution Analysis Report ====

PeakTable

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.594	333551	64438	51.066	74.124
2	5.527	160671	12000	24.598	13.803
3	6.406	158955	10495	24.336	12.073
Total		653176	86932	100.000	100.000

<Chromatogram>

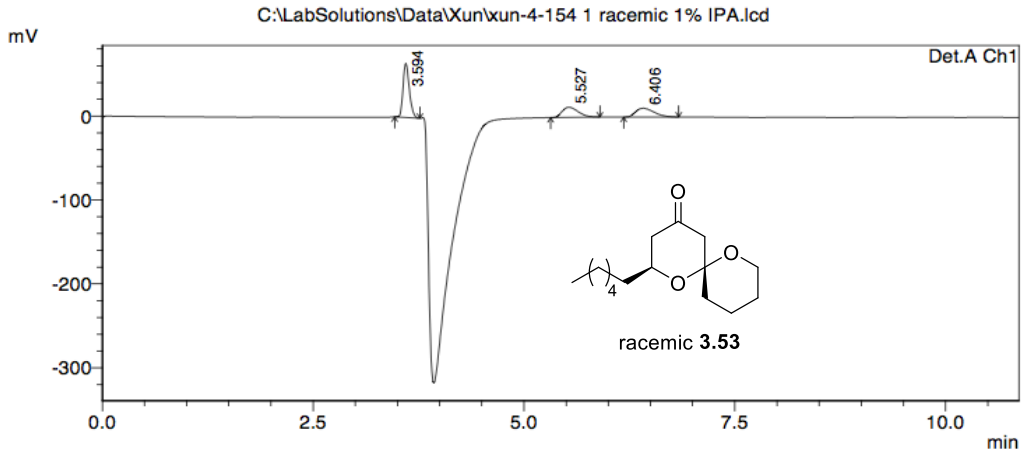


Figure S3-7. HPLC anaylsis report of racemic **3.53**

==== Shimadzu LCsolution Analysis Report ====

PeakTable

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.595	3765869	181245	49.904	67.876
2	4.555	3341808	57494	44.285	21.532
3	5.476	438503	28283	5.811	10.592
Total		7546181	267022	100.000	100.000

<Chromatogram>

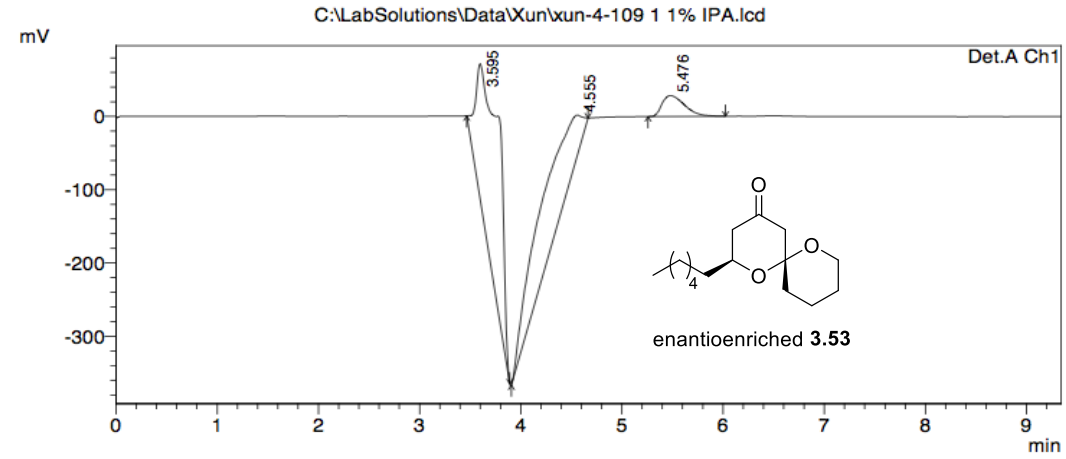


Figure S3-8. . HPLC anaylsis report of enantioenriched **3.53**

==== Shimadzu LCsolution Analysis Report ====

PeakTable

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.529	629447	131339	40.520	75.930
2	8.757	461999	22727	29.741	13.139
3	10.666	461974	18907	29.739	10.931
Total		1553420	172973	100.000	100.000

<Chromatogram>

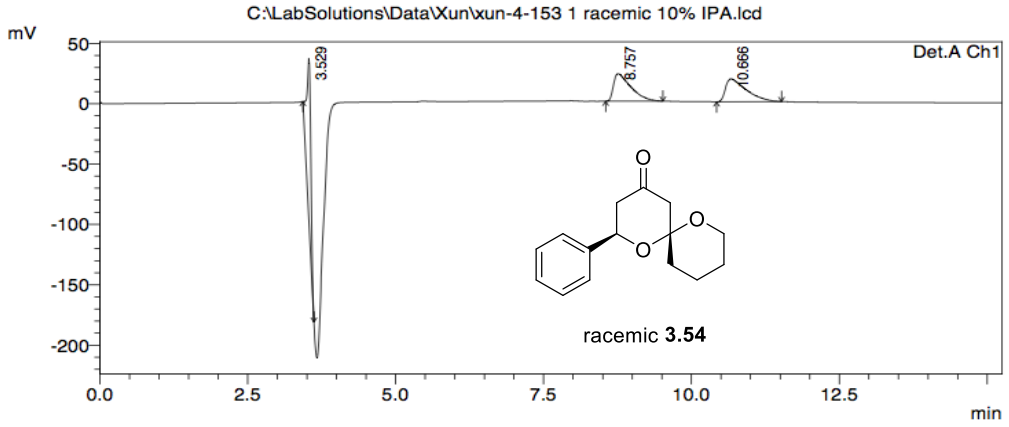


Figure S3-9. HPLC anaylsis report of racemic **3.54**

==== Shimadzu LCsolution Analysis Report ====

PeakTable

Detector A Ch1

Peak#	Ret. Time	Area	Height	Area %	Height %
1	3.550	732761	141449	42.032	77.404
2	8.804	928686	37560	53.271	20.554
3	11.206	81875	3731	4.696	2.042
Total		1743321	182740	100.000	100.000

<Chromatogram>

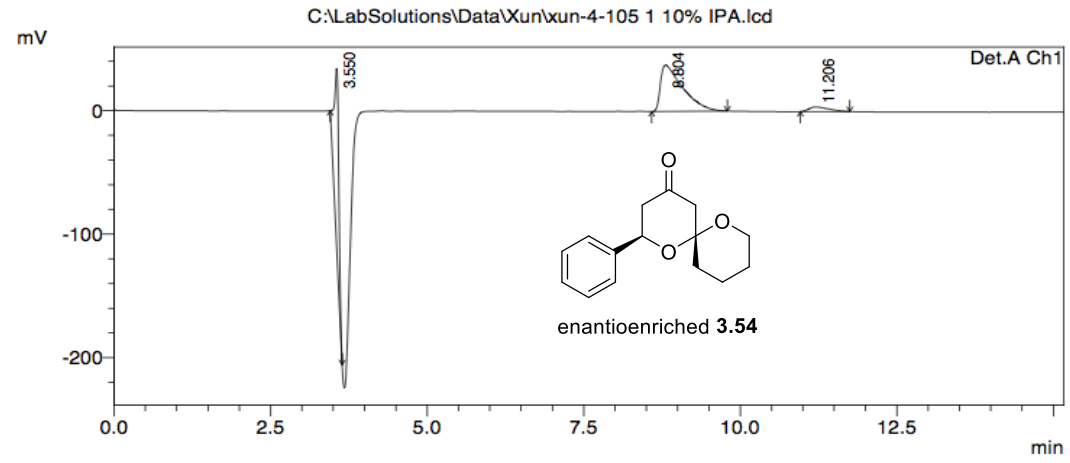


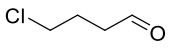
Figure S3-10. HPLC anaylsis report of enantioenriched **3.54**

APPENDIX C

TOTAL SYNTHESIS OF BISTRAMIDE A

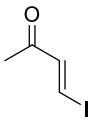
General Experimental: Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker Avance 300 spectrometer at 300 MHz and 75 MHz, a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, a Bruker Avance 500 spectrometer at 500 MHz and 125 MHz. The chemical shifts are reported in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, C_6D_6 = 7.16 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23, C_6D_6 = 128.4 ppm. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; sept = septet; dd = doublet of doublets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublet; td = triplet of doublets; dtd = doublet of triplet of doublets; br = broad). High resolution and lowresolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Methylene chloride was distilled under N_2 from CaH_2. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, toluene and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography.

4-Chlorobutanal (4.62)



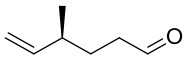
To a solution of oxalyl chloride (5.9 mL, 69 mmol) in dry CH_2Cl_2 (200 mL) was added a solution of DMSO (6.8 mL, 92 mmol) in dry CH_2Cl_2 (35 mL) dropwise at –78 °C under an atmosphere of argon. The resulting solution was stirred at -78 °C for 30 min, then a solution of 4-chlorobutan-1-ol (5.0 g, 46 mmol) in dry CH_2Cl_2 (70 mL) was added dropwise. The resulting mixture was stirred at –78 °C for 30 min, then NEt_3 (32 mL, 230 mmol) was added dropwise. The reaction was allowed to warm to rt. After stirring at rt for 30 min, the mixture was quenched with H_2O and extract with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (Pentane:Et_2O =10:1 to 4:1) to afford desired aldehyde (4.1 g, 83% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 3.57 (t, 2H, *J* = 6.4 Hz), 2.64 (t, 2H, *J* = 6.8 Hz), 2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 44.3, 41.1, 25.0; IR (neat) 2962, 2831, 2728, 1724, 1439, 1411, 1391, 1371, 1310, 1205, 1160, 1120, 1065, 934, 676, 648 cm^{-1}.

(*E*)-4-Iodobut-3-en-2-one (4.55)



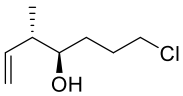
LiI (1.6 g, 12 mmol) was dissolved in AcOH (10 mL) under argon, followed by the addition of but-3-yn-2-one (0.78 mL, 10 mmol) at rt. The resulting mixture was stirred at rt for 18.5 h, then was quenched with H_2O. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were wash with H_2O, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc = 50:1 to 20:1) to afford desired product **4.55** (1.5 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 1H, *J* = 15.2 Hz), 7.16 (d, 1H, *J* = 14.8 Hz), 2.25 (s, 3H).

(*S*)-4-Methylhex-5-enal (4.53)



Ozone was bubbled into the solution of (+)-β-citronellene (4.7 g, 34 mmol) in CH_2Cl_2 (200 mL) at –78 °C until the trisubstituted double bond was fully consumed. 5 mL of Me_2S was added. The resulting solution was warmed to rt slowly, then was stirred at rt for 7 h. The reaction mixture was concentrated directly and the residue was purified by flash chromatography (pentane:Et_2O = 10:1) to afford desired aldehyde **4.53** (3.2 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 5.64 (quint, 1H, *J* = 9.3 Hz), 5.00 (d, 1H, *J* = 6.6 Hz), 4.96 (s, 1H), 2.44 (t, 2H, *J* = 7.5 Hz), 2.21-2.11 (m, 1H), 1.74-1.53 (m, 2H), 1.03 (d, 3H, *J* = 6.6 Hz).

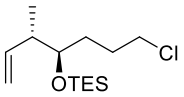
(3*S*,4*R*)-7-Chloro-3-methylhept-1-en-4-ol (4.56)



To a suspension of KO^{t}Bu (6.3 g, 56 mmol) in THF (25 mL) were added *trans*-2-butene (10 mL) and ^{n}BuLi (35 mL, 1.6 M in hexanes, 56 mmol) dropwise successively at –78 °C under an atmosphere of argon. The resulting mixture was warmed to –45 °C and stirred at –45 °C for 10 min. The mixture was cooled to –78 °C again and a solution of (–)-$(Ipc)_2BOMe$ (17.8 g, 56.3 mmol) in Et_2O (30 mL) was added dropwise over 20 min. The resulting mixture was stirred at –78 °C for 30 min, then BF_3•Et_2O (17.4 mL, 84.5 mmol) and a solution of **4.62** (9.0 g, 84 mmol) in Et_2O (10 mL) were added dropwise successively. After stirring at –78 °C for 8.5 h, NaOH (3M, 30 mL) was added into the reaction, followed by H_2O_2 (30%, 15 mL). Then reaction was refluxed for 1 h. After cooling to rt, the organic layer was separated and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 100:1 to 20:1) to afford desired product (6.1 g, 67% yield, 83% *ee* as determined by Mosher ester

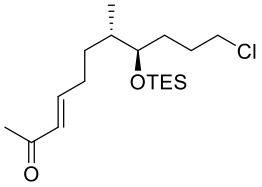
analysis). $[\alpha]^{25}_{D}$ +2.6 (*c* 2.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74 (ddd, 1H, *J* = 8.4, 10.4, 16.8 Hz), 5.16-5.15 (m, 1H), 5.13-5.10 (m, 1H), 3.59 (dt, 2H, *J* = 1.2, 6.4 Hz), 3.43-3.38 (m, 1H), 2.24-2.16 (m, 1H), 2.05-1.95 (m, 1H), 1.91-1.81 (m, 1H), 1.76-1.68 (m, 1H), 1.66 (s, 1H), 1.53-1.44 (m, 1H), 1.04 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 117.0, 74.1, 45.5, 44.7, 31.6, 29.2, 16.4; IR (neat) 3400, 2962, 2873, 1639, 1446, 1418, 1375, 1302, 1116, 1083, 1000, 917, 724, 650 cm^{-1}.

((3*S*,4*R*)-7-Chloro-3-methylhept-1-en-4-yloxy)triethylsilane (4.64)



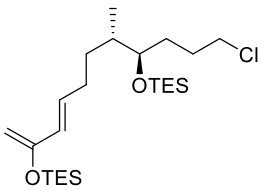
To a solution of **4.56** (4.3 g, 26 mmol) and imidazole (3.6 g, 53 mmol) in CH_2Cl_2 (50 mL) was added TESCl (5.8 mL, 34 mmol) dropwise at rt. The resulting suspension was stirred at rt for 3 h, was quenched with H_2O, extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 200:1 to 100:1) to afford desired product (7.3 g, quantitative). $[\alpha]^{25}_{D}$ +1.8 (*c* 1.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83-5.74 (m, 1H), 5.05-5.03 (m, 1H), 5.01-5.00 (m, 1H), 3.64-3.60 (m, 1H), 3.53 (dt, 2H, *J* = 0.4, 6.4 Hz), 2.35-2.27 (m, 1H), 1.93-1.82 (m, 1H), 1.80-1.69 (m, 1H), 1.55-1.48 (m, 2H), 1.02 (d, 3H, *J* = 6.8 Hz), 0.98 (t, 9H, *J* = 8.0 Hz), 0.62 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.0, 114.8, 75.5, 45.6, 43.6, 31.0, 29.4, 14.9, 7.2, 5.4; IR (neat) 2957, 2912, 2877, 1459, 1416, 1377, 1239, 1089, 1041, 1006, 914, 741, 654 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{28}OSiCl$ $[M - H]^+$ 275.1598, found 275.1606.

(7*S*,8*R*,*E*)-11-Chloro-7-methyl-8-(triethylsilyloxy)undec-3-en-2-one (4.65)



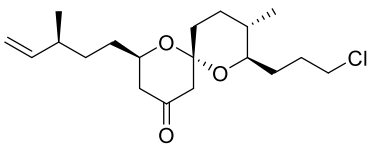
To a solution of 9-BBN dimer (1.7 g, 6.8 mmol) in THF (10 mL) was added a solution of **4.64** (2.1 g, 7.6 mmol) in THF (10 mL) dropwise at 0 °C under an atmosphere of argon. The resulting mixture was stirred for 4 h at rt, and then quenched with H_2O (1.0 mL). An aqueous solution of K_3PO_4•H_2O (2.6 g, 11 mmol, in 4 mL H_2O) was added into the mixture, followed by **4.55** (1.6 g, 8.0 mmol) and [Pd(dppf)Cl_2]•CH_2Cl_2 (62 mg, 0.076 mmol). The flask was covered with alumina foil. After stirring at rt for 2 h, the mixture was poured into H_2O and extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 50:1 to 10:1) to afford desired product (1.9 g, 73% yield). $[\alpha]^{25}_D$ +2.0 (*c* 1.53, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (td, 1H, *J* = 6.8, 16.0 Hz), 6.09 (d, 1H, *J* = 16.0 Hz), 3.57-3.56 (m, 3H), 2.37-2.28 (m, 1H), 2.25 (s, 3H), 2.21-2.12 (m, 1H), 1.93-1.85 (m, 1H), 1.80-1.69 (m, 1H), 1.61-1.49 (m, 3H), 1.31-1.22 (m, 1H), 0.96 (t, 9H, *J* = 8.0 Hz), 0.89 (d, 3H, *J* = 6.4 Hz), 0.59 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8, 148.5, 131.6, 75.6, 45.7, 38.4, 31.3, 30.7, 30.0, 29.1, 27.0, 14.5, 7.2, 5.4; IR (neat) 2955, 2876, 1698, 1677, 1627, 1571, 1459, 1415, 1361, 1252, 1085, 1008, 980, 742 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{36}O_2SiCl$ $[M + H]^+$ 347.2168, found 347.2151.

(10*S*,11*R*,*E*)-11-(3-Chloropropyl)-3,3,13,13-tetraethyl-10-methyl-5-methylene-4,12-dioxa-3,13-disilapentadec-6-ene (4.54)



To a solution of **4.65** (0.39 g, 1.1 mmol) and NEt_3 (0.32 mL, 2.2 mmol) was added TESOTf (0.28 mL, 1.2 mmol) at 0 °C. The resulting solution was stirred for 30 min at 0 °C. Then the reaction was quenched with H_2O and extracted with CH_2Cl_2 (2x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 200:1 to 100:1, column was pre-treated with 1% NEt_3 hexanes solution) to afford desired product (0.50 g, 96% yield). $[\alpha]^{25}_D$ +1.6 (*c* 1.31, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6): δ 6.27 (td, 1H, *J* = 7.0, 15.5 Hz), 5.98 (d, 1H, *J* = 15.0 Hz), 4.35 (s, 1H), 4.28 (s, 1H), 3.48-3.45 (m, 1H), 3.23-3.15 (m, 2H), 2.19-2.12 (m, 1H), 2.05-1.97 (m, 1H), 1.82-1.74 (m, 1H), 1.63-1.55 (m, 2H), 1.49-1.30 (m, 3H), 1.20-1.13 (m, 1H), 1.04 (t, 9H, *J* = 8.0 Hz), 1.01 (t, 9H, *J* = 8.0 Hz), 0.86 (d, 3H, *J* = 7.0 Hz), 0.73 (q, 6H, *J* = 8.0 Hz), 0.60 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ 154.6, 130.5, 127.7, 92.5, 74.7, 44.3, 37.4, 31.6, 29.3, 28.8, 28.4, 13.3, 6.2, 6.0, 4.6, 4.4; IR (neat) 2955, 2877, 1656, 1591, 1459, 1414, 1379, 1317, 1239, 1085, 1016, 964, 813, 742, 672 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{50}O_2Si_2Cl$ $[M + H]^+$ 461.3032, found 461.3016.

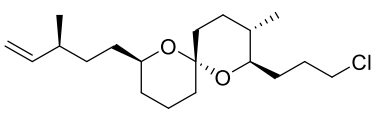
(2*R*,6*R*,8*R*,9*S*)-8-(3-Chloropropyl)-9-methyl-2-((*S*)-3-methylpent-4-enyl)-1,7-dioxaspiro[5.5]undecan-4-one (4.66)



A flame dried 10 ml round-bottom flask was charged with 4 Å molecular sieves (150 mg) and **4.68** (24 mg, 0.033 mmol), and aldehyde **4.53** (247 mg, 2.2 mmol). The resulting mixture was stirred for 5 min at rt under argon. Diene **4.54** (507 mg, 1.1 mmol) was added through a 1 mL syringe. Another 2.0 eq. of aldehyde

4.53 (2467 mg, 2.2 mmol) was used to rinse the one drum vial that contained **4.54**, and then transferred into the reaction. The brown slurry was stirred at rt for 24 h, then was diluted with CH_2Cl_2 (8 mL) and treated with DDQ (300 mg, 1.32 mmol). The resulting mixture was stirred at rt for 30 min, then TsOH•H_2O (418 mg, 2.2 mmol) was added in one portion. The brown suspension was stirred at rt for 2 h then was quenched with NEt_3 (0.5 mL). The black slurry was filtered by a short silica gel pad and further purified by flash column chromatography (hexanes:EtOAc = 20:1 to 10:1) to afford desired spiro ketal **4.66** (218.1 mg, 58% yield). $[\alpha]^{25}_D$ +42.7 (*c* 1.30, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (ddd, 1H, *J* = 7.6, 10.4, 17.6 Hz), 5.01-4.95 (m, 2H), 3.79-3.72 (m, 1H), 3.59-3.47 (m, 2H), 3.16 (dt, 1H, *J* = 2.8, 9.6 Hz), 2.39 (s, 1H), 2.36 (dd, 1H, *J* = 2.8, 14.4 Hz), 2.20 (dd, 1H, *J* = 11.6, 14.4 Hz), 2.20-2.14 (m, 1H), 2.01-1.91 (m, 1H), 1.87-1.83 (m, 1H), 1.82-1.75 (m, 1H), 1.70-1.62 (br.m, 2H), 1.62-1.50 (br.m, 6H), 1.49-1.26 (br.m, 3H), 1.04 (d, 3H, *J* = 6.8 Hz), 0.87 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.4, 144.4, 113.3, 99.2, 75.5, 69.1, 52.1, 47.4, 45.8, 37.9, 35.5, 34.1, 34.0, 32.5, 30.5, 28.7, 28.1, 20.5, 18.0; IR (neat) 2925, 2853, 1726, 1458, 1378, 1312, 1245, 1176, 1082, 1031, 981, 911 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{32}O_3Cl$ $[M + H]^+$ 343.2040, found 343.2040.

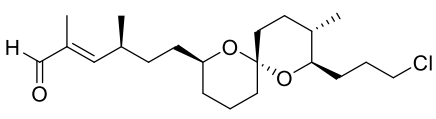
(2*R*,3*S*,6*S*,8*S*)-2-(3-Chloropropyl)-3-methyl-8-((*S*)-3-methylpent-4-enyl)-1,7-dioxaspiro[5.5]undecane (4.74)



To a solution of **4.66** (292 mg, 0.85 mmol) in MeOH (11 mL) was added $TsNHNH_2$ (317, 1.70 mmol) in one portion. The resulting solution was stirred at rt for 6 h, then was concentrate under reduced pressure. The residue was diluted with 30% EtOAc hexanes solution and filtered through a short silica gel pad. The filtrate was concentrated and re-dissolved in MeOH/THF (1/1, 16 mL). A solution of $NaBH_3CN$ (53 mg,

0.85 mmol) in MeOH (0.9 mL) was added at 0 °C. To the resulting solution was carefully added a 1N HCl stock solution in EtOH dropwise at 0 °C until TLC analysis indicated the total consumption of starting material. The reaction was diluted with Et_2O and washed with H_2O, sat. $NaHCO_3$, and brine successively. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in EtOH (20 mL) and degassed with N_2 for 5 min. NaOAc (1.8 g) was added, followed by 1.5 mL H_2O. The resulting mixture was degassed for another 5 min with N_2 and then transferred into a pre-heated oil bath (75 ^oC). The reaction was stirred at 75 ^oC for 30 min, then was cooled to rt, diluted with Et_2O, then washed with H_2O and brine successively. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 100:1 to 50:1) to afford the desired product (151 mg, 54% yield for three steps). $[\alpha]^{25}_D$ +39.9 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76-5.68 (m, 1H), 4.97 (d, 1H, *J* = 18.0 Hz), 4.93 (d, 1H, *J* = 10.8 Hz), 3.66-3.54 (m, 2H), 3.48-3.40 (m, 1H), 3.18 (t, 1H, *J* = 10.0 Hz), 2.14-2.08 (m, 2H), 1.84-1.74 (m, 3H), 1.64-1.38 (m, 11H), 1.35-1.26 (m, 3H), 1.21-1.12 (m, 1H), 1.01 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 112.8, 95.7, 74.3, 69.4, 45.9, 37.9, 36.3, 35.7, 35.2, 34.2, 32.9, 31.6, 30.9, 29.5, 28.1, 20.4, 19.4, 18.2; IR (neat) 2930, 2867, 1457, 1385, 1272, 1225, 1181, 1094, 1033, 987, 956, 910 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{34}O_2Cl$ $[M + H]^+$ 329.2247, found 329.2250.

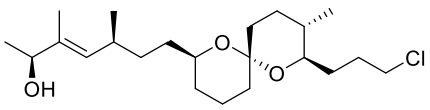
(*S*,*E*)-6-((2*S*,6*S*,8*R*,9*S*)-8-(3-Chloropropyl)-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)-2,4-dimethylhex-2-enal (4.76)



To a solution of **4.74** (28 mg, 0.085 mmol) in freshly distilled methacrolein/dry CH_2Cl_2 (5/1, 1.2 mL) was added Grela-

Grubbs metathesis catalyst (7.1 mg, 0.011 mmol). The reaction was stirred at 40 °C for 4 h, then was cooled to rt and stirred overnight. The resulting dark green solution was concentrated and purified by flash column chromatography (hexanes:EtOAc = 50:1 to 20:1) to afford **4.76** (21.7 mg, E/Z = 8.8/1, 68% yield). $[\alpha]^{25}_{D}$ +18.6 (*c* 1.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (s, 1H), 6.28 (d, 1H, *J* = 10.0 Hz), 3.66-3.53 (m, 2H), 3.48-3.43 (m, 1H), 3.15 (dt, 1H, *J* = 2.0, 10.0 Hz), 2.74-2.67 (m, 1H), 2.16-2.10 (m, 1H), 1.88-1.73 (m, 2H), 1.76 (s, 3H), 1.64-1.26 (m, 15H), 1.21-1.11 (m, 1H), 1.09 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 160.5, 138.3, 95.7, 74.4, 69.1, 45.8, 36.2, 35.6, 35.2, 34.4, 33.8, 33.0, 31.5, 30.9, 29.5, 28.1, 20.1, 19.3, 18.2, 9.7; IR (neat) 2932, 2870, 1690, 1640, 1457, 1386, 1272, 1225, 1183, 1095, 1030, 987, 957, 918, 878, 820, 652 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{36}O_3Cl$ $[M + H]^+$ 371.2353, found 371.2344.

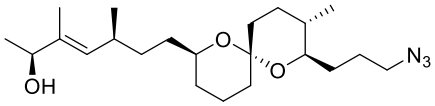
(2*S*,5*S*,*E*)-7-((2*S*,6*S*,8*R*,9*S*)-8-(3-Chloropropyl)-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)-3,5-dimethylhept-3-en-2-ol (4.78)



A flame dried Schlenk flask was charged with (–)-MIB (38 mg, 0.16 mmol), hexanes (0.5 mL), and a freshly prepared solution of $ZnMe_2$ (75 mg, 0.79 mmol) in hexanes (0.5 mL) successively at rt under argon. A solution of **4.76** (29 mg, 0.079 mmol) in hexanes (0.5 mL) was added dropwise at rt. The resulting milky mixture was stirred at rt overnight. The reaction was quenched by adding sat. NH_4Cl (1 mL), then was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAt = 10:1 to 4:1) to afford desired product (26 mg, 86%). $[\alpha]^{25}_{D}$ +33.0 (*c* 0.66, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (d, 1H, *J* = 9.6 Hz), 4.25-4.20 (m, 1H), 3.66-3.54 (m, 2H), 3.46-3.41 (m,

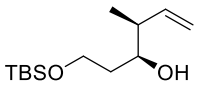
1H), 3.17 (dt, 1H, *J* = 2.4, 10.0 Hz), 2.40-2.33 (m, 1H), 2.19-2.08 (m, 1H), 1.87-1.76 (m, 3H), 1.64 (d, 3H, *J* = 1.6 Hz), 1.62-1.45 (m, 5H), 1.44-1.29 (m, 9H), 1.26 (d, 3H, *J* = 6.4 Hz), 0.97 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 131.8, 95.7, 74.3, 73.8, 69.3, 45.8, 36.3, 35.7, 35.2, 34.4, 33.8, 32.1, 31.6, 30.9, 29.5, 28.1, 21.9, 21.2, 19.4, 18.2, 11.8; IR (neat) 3419, 2931, 2868, 1456, 1386, 1272, 1225, 1182, 1090, 1032, 986 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{40}O_3Cl$ $[M + H]^+$ 387.2547, found 387.2666.

(2*S*,5*S*,*E*)-7-((2*S*,6*S*,8*R*,9*S*)-8-(3-Azidopropyl)-9-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)-3,5-dimethylhept-3-en-2-ol (4.83)



To a solution of **4.78** (10 mg, 0.027 mmol) in DMF (0.2 mL) was added NaN_3 in one portion. The resulting mixture was stirred at 60 °C for 8 h, then was purified directly by flash chromatography (hexanes:EtOAc = 10:1 to 5:1) to afford **4.83** (10.6 mg, quantitative). $[\alpha]^{25}_D$ +28.7 (*c* 0.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (d, 1H, *J* = 9.2 Hz), 4.22 (q, 1H, *J* = 6.4 Hz), 3.46-3.44 (m, 1H), 3.40-3.27 (m, 2H), 3.17 (dt, 1H, *J* = 2.4 Hz), 2.38-2.33 (m, 1H), 2.00-1.90 (m, 1H), 1.88-1.71 (m, 2H), 1.64 (d, 3H, *J* = 1.2 Hz), 1.63-1.29 (m, 15H), 1.26 (d, 3H, *J* = 6.4 Hz), 0.97 (d, 3H, *J* = 6.8 Hz), 0.85 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.4, 131.8, 95.7, 74.4, 73.7, 69.4, 52.2, 36.3, 35.6, 35.2, 34.4, 33.8, 32.1, 31.6, 30.6, 28.1, 25.7, 21.9, 21.2, 19.4, 18.2, 11.8; IR (neat) 3424, 2930, 2867, 1456, 1385, 1225, 1095, 1034, 985 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{38}O_2N_3$ $[M - OH]^+$ 376.2964, found 376.2964.

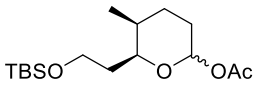
(3*S*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-methylhex-5-en-3-ol (4.60)



To a solution of 1,3-propanediol (10 mL, 0.14 mol) in THF (150 mL) were added imidazole (3.8 g, 0.055 mol) and TBSCl (4.2 g, 0.028 mol) successively. The resulting mixture was stirred at rt overnight, then quenched with H_2O and extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography to afford 3-(*tert*-butyldimethylsilyloxy)propan-1-ol (5.1 g, 95% yield) as colorless oil. This freshly prepared mono-protected diol was re-dissolved in CH_2Cl_2 (20 mL) and treated with DMSO (26 mL), NEt_3 (11 mL, 0.081 mol), SO_3•Py (6.4 g, 0.04 mol) successively. The resulting yellow solution was stirred at rt for 4 h, then was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and purified by flash column chromatography (hexanes:EtOAc = 50:1 to 20:1) to afford 3-(*tert*-butyldimethylsilyloxy)propanal (4.5 g, 88% yield). To a suspension of KO^{t}Bu (2.2 g, 20 mmol) in THF (45 mL) were added *cis*-2-butene (8 mL, 90 mmol) and ^{n}BuLi (1.6 M in hexanes, 12 mL, 20 mmol) successively at –78 °C under argon. The resulting orange solution was warmed to –45 °C and stirred for 10 min at this temperature. The reaction was cooled to –78 °C and a solution of (+)-$(Ipc)_2$BOMe (6.3 g, 20 mmol) in THF (20 mL) was added dropwise. After stirring at –78 °C for 30 min, BF_3•OEt_2 (2.5 mL, 20 mmol) was added dropwise, followed by 3-(*tert*-butyldimethylsilyloxy)propanal (3.4 g, 18 mmol). The resulting mixture was stirred at –78 °C for 3.5 h. Then NaOH (3.0 M aqueous solution, 25 mL) and H_2O_2 (30%, 15 mL) were added successively and the reaction was stirred at rt overnight. The organic layer was separated and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 100:1 to 20:1) to afford desired product (2.94 g, 67% yield, 87% *ee* as

determined by Mosher ester analysis). $[\alpha]^{25}_D$ –6.2 (*c* 1.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 5.79 (ddd, 1H, *J* = 7.6, 10.4, 17.6 Hz), 5.09-5.02 (m, 2H), 3.93-3.88 (m, 1H), 3.82-3.78 (m, 1H), 3.68 (ddd, 1H, *J* = 2.4, 6.0, 8.8 Hz), 3.36 (s, 1H), 2.31-2.22 (m, 1H), 1.73-1.57 (m, 2H), 1.07 (d, 3H, *J* = 6.8 Hz), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 115.0, 75.6, 63.2, 44.2, 35.7, 26.1, 18.4, 15.4, –5.3, –5.3; IR (neat) 3450, 2956, 2930, 2858, 1471, 1388, 1362, 1256, 1086, 1005, 939, 912, 836, 777 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{27}OSi$ $[M - OH]^+$ 227.1816, found 227.1831.

(5*S*,6*S*)-6-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-5-methyltetrahydro-2*H*-pyran-2-yl acetate (4.84)

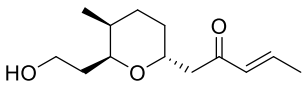


Warning: The CO/H_2 mixture must be handled in a well-ventilated fume hood and the reaction should be conducted behind a blast shield because high pressure is required.

To a solution of 6-diphenylphosphanyl-2-pyridone **4.85** (6-DPPon, 1.94 g, 6.95 mmol) in THF (40 mL) was added $[Rh(CO)_2acac]$ (359 mg, 1.39 mmol) in three portions, followed by a solution of **4.60** (6.8 g, 28 mmol) in THF (10 mL). The resulting dark brown mixture was sealed in a high-pressure reactor under an atmosphere of CO/H_2 gas (1/1, 120 psi) and stirred at rt for 48 h. The mixture was exposed in air and diluted with CH_2Cl_2 (200 mL). NEt_3 (5.8 mL, 42 mmol), DMAP (170 mg, 1.4 mmol) and Ac_2O (3.2 mL, 33 mmol) were added successively at rt. The resulting brown solution was stirred for 3 h at rt, then quenched with sat. $NaHCO_3$, extracted with Et_2O (3x). The combined organic layers were dried over Na_sSO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 20:1 to 10:1) to afford desired product (8.0 g, d.r. = 6/1, 91% yield) as a pale yellow oil. $[\alpha]^{25}_D$ (*c* , $CHCl_3$); ^1H NMR (400 MHz,

$CDCl_3$): δ 6.02 (d, 0.16H, *J* = 3.2 Hz), 5.61 (dd, 1H, *J* = 3.2, 8.4 Hz), 4.10-4.06 (m, 0.16H), 3.75 (ddd, 1H, *J* = 2.4, 4.0, 9.2 Hz), 3.69-3.59 (m, 2.32 H), 2.04 (s, 3H), 2.02 (s, 0.48H), 1.81-1.48 (m, 8.12H), 0.93 (d, 3H, *J* = 7.2 Hz), 0.93 (d, 0.48H, *J* = 7.2 Hz), 0.85 (s, 10.6H), 0.01 (d, 6.96H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 169.3, 95.5, 92.6, 75.8, 69.6, 59.7, 59.6, 36.1, 35.9, 30.4, 30.2, 29.1, 26.0, 25.5, 25.5, 21.3, 18.4, 18.4, 12.1, 11.3, –5.2, –5.3, –5.3; IR (neat) 2952, 2739, 1754, 1471, 1440, 1364, 1304, 1235, 1038, 1008, 955, 888, 838, 777, 734, 681, 663, 605 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{32}O_4NaSi$ $[M + Na]^+$ 339.1962, found 339.1954.

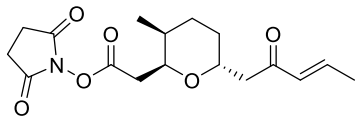
(*E*)-1-((2*R*,5*S*,6*S*)-6-(2-Hydroxyethyl)-5-methyltetrahydro-2*H*-pyran-2-yl)pent-3-en-2-one (4.88)



To a solution of (*E*)-pent-3-en-2-one (40 mg, 0.48 mmol) in dry CH_2Cl_2 (3 mL) was added freshly distilled NEt_3 (0.11 mL, 0.80 mmol) and freshly distilled TMSOTf (0.12 mL, 0.64 mmol) successively at 0 °C under an atmosphere of argon. The resulting solution was stirred at 0 °C for 1 h, then the reaction was cooled to -78 °C, and a solution of **4.84** (102 mg, 0.32 mmol) in dry CH_2Cl_2 (4 mL) was added. After stirring at -78 °C for 10 min, freshly distilled TMSOTf (0.07 mL, 0.38 mmol) was added. The resulting solution was stirred at -78 °C for 10 min, then was quenched with sat. NH_4Cl and extracted with CH_2Cl_2 (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 4:1 to 2:1) to afford the desired product (41 mg, 57%). $[\alpha]^{25}_D$ -50.8 (*c* 1.08, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93-6.84 (m, 1H), 6.15 (dd, 1H, *J* = 1.2, 16.0 Hz), 4.21-4.14 (m, 1H), 3.95-3.91 (m, 1H), 3.75 (td, 2H, *J* = 1.6, 5.2 Hz), 2.87 (dd, 1H, *J* = 8.8, 15.6 Hz), 2.77 (t, 1H, *J* = 2.4 Hz), 2.53 (dd, 1H, *J* = 4.4, 15.6 Hz), 2.02-1.93 (m, 1H), 1.90 (dd, 3H, *J* = 1.2, 6.8 Hz), 1.87-1.81 (m, 1H), 1.77-1.71 (m, 1H), 1.67-1.61

(m, 1H), 1.50-1.39 (m, 2H), 1.36-1.26 (m, 1H), 0.84 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 143.8, 132.4, 75.6, 66.3, 60.9, 45.8, 33.2, 30.4, 28.8, 26.7, 18.5, 16.6; IR (neat) 3436, 2932, 1672, 1630, 1440, 1380, 1292, 1057, 970 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{13}H_{23}O_3$ $[M + H]^+$ 227.1647, found 227.1665.

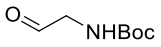
2,5-Dioxopyrrolidin-1-yl 2-((2*S*,3*S*,6*R*)-3-methyl-6-((*E*)-2-oxopent-3-enyl)tetrahydro-2*H*-pyran-2-yl)acetate (4.59)



To a solution of **4.88** (142 mg, 0.625 mmol) in wet CH_3CN (0.75 v %, water, 3.4 mL) was slowly added a stock solution of H_5IO_6/CrO_3 in wet CH_3CN (5.7 g H_5IO_6 and 12.5 mg CrO_3 in 57 mL wet CH_3CN, 3.4 mL) dropwise at 0 °C over 30 min. The resulting mixture was stirred at 0 °C for 30 min. A solution of Na_2HPO_4 (0.8 g) in H_2O (10 mL) was added, followed by EtOAc (20 mL). The reaction mixture was stirred at rt for 1 h. The organic layer was separated. The remaining aqueous layer was acidified by conc. HCl (0.3 mL) and extract with EtOAc (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was re-dissolved in CH_3CN (7.4 mL) and treated with *N*-hydroxysuccinimide (79 mg, 0.69 mmol) and DCC (129 mg, 0.625 mmol) successively. The resulting mixture was stirred at rt for 11 h then was filtered. The filtrate was concentrated and purified by flash column chromatography (DCM:MeOH = 50:1) to afford desired product (172 mg, 81% yield). $[\alpha]^{25}_D$ -41.6 (*c* 1.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.90-6.82 (m, 1H), 6.11 (d, 1H, J = 16.0 Hz), 4.37-4.36 (m, 1H), 4.13-4.09 (m, 1H), 3.05-2.95 (m, 2H), 2.82 (s, 4H), 2.71-2.60 (m, 2H), 2.04-2.00 (m, 1H), 1.89 (d, 3H, J = 6.8 Hz), 1.82 (d, 1H, J = 12.8 Hz), 1.68 (d, 1H, J = 12.4 Hz), 1.44-1.24 (m, 2H), 0.87 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 168.9, 167.0, 143.3, 132.5, 73.7, 67.0, 45.3, 32.5, 30.4, 29.8, 26.3, 25.6, 18.3, 16.4; IR (neat)

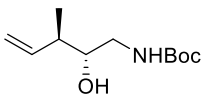
2934, 2876, 1815, 1785, 1741, 1693, 1668, 1630, 1435, 1364, 1294, 1205, 1065, 992, 972, 867, 815, 648 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NO_6Na$ $[M + Na]^+$ 360.1423, found 360.1416.

tert-Butyl 2-oxoethylcarbamate (4.89)



To a solution of allylamine (9.0 g, 0.16 mol) in CH_2Cl_2 (250 mL) was slowly added di-*tert*-butyl dicarbonate (28.6 mL, 0.158 mol) at rt, followed by NEt_3 (20.7 mL, 0.148 mol). The resulting solution was stirred at rt overnight, then was concentrated under reduced pressure to yield *tert*-butyl allylcarbamate (24.6 g, quantitative) as white crystal. The allylcarbamate (10 g, 0.064 mol) was dissolved in CH_2Cl_2 (200 mL). The reaction solution was cooled to -78 °C, then ozone gas was bubbled into the solution until it turned to blue. Me_2S (9.4 mL, 0.13 mol) was added in one portion. After stirring at rt for 4 h, the reaction mixture was concentrated and purified by flash columne chromatography (hexanes:EtOAc = 4:1 to 2:1) to afford the desired product (7.2 g, 71% yield for two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 5.22 (br.s, 1H), 4.06 (d, 2H, *J* = 5.2 Hz), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 155.8, 80.4, 51.6, 28.5; IR (neat) 3361, 2979, 2933, 1693, 1519, 1456, 1393, 1368, 1251, 1170, 1090, 1040, 974, 855, 782 cm^{-1}.

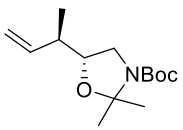
tert-Butyl (2*R*,3*R*)-2-hydroxy-3-methylpent-4-enylcarbamate (4.58)



To a suspension of KO^{t}Bu (2.3 g, 20.7 mmol) in THF (50 mL) under argon was added *trans*-2-butene (10 mL, 113 mmol) and ^{n}BuLi (1.6 M in hexanes, 12.9 mL, 20.7 mmol) successively at –78 °C. The resulting orange solution was warmed to –45 °C and stirred for 10 min at this temperature. Then the reaction was cooled to –78 °C and a solution of (+)-$(Ipc)_2$BOMe (6.5 g, 21 mmol) in THF (20 mL) was added dropwise. After stirring at –78 °C for 30 min, BF_3•OEt_2 (2.6 mL, 21 mmol) was added dropwise, followed by a solution of **4.89** (3.0

g, 19 mmol) in THF (8 mL). The resulting mixture was stirred at –78 °C for 3 h. Then NaOH (3.0 M aqueous solution, 20 mL) and H_2O_2 (30%, 20 mL) were added successively and the reaction was stirred at rt overnight. The organic layer was separated and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 8:1 to 2:1) to afford desired product (2.27 g, 56% yield, 90% *ee* as determined by Mosher ester analysis). $[\alpha]^{25}_D$ -1.9 (*c* 1.19, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81-5.72 (m, 1H), 5.16 (s, 1H), 5.13-5.11 (m, 1H), 4.94 (br.s, 1H), 3.49 (dt, 1H, *J* = 2.8, 7.2 Hz), 3.38-3.35 (m, 1H), 3.08 (ddd, 1H, *J* = 4.8, 8.0, 14.0 Hz), 2.29-2.20 (m, 1H), 1.45 (s, 9H), 1.06 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 140.1, 117.0, 79.7, 74.4, 44.5, 42.6, 28.6, 16.3; IR (neat) 3374, 3076, 2976, 2932, 1692, 1518, 1455, 1392, 1367, 1252, 1172, 1095, 1042, 1002, 915, 887, 781 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{22}O_3N$ $[M + H]^+$ 216.1600, found 216.1586.

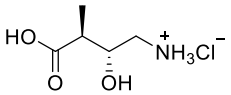
(*R*)-*tert*-Butyl 5-((*R*)-but-3-en-2-yl)-2,2-dimethyloxazolidine-3-carboxylate (4.90)



To a solution of **4.89** (170 mg, 0.79 mmol) in 2,2-dimethoxypropane (2.0 mL) and acetone (8.0 mL) was added *p*-TsOH•H_2O (15 mg, 0.08 mmol) in one portion. The resulting solution was stirred at rt for 5 min, then was quenched with sat. $NaHCO_3$, extracted with Et_2O, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (hexanes:EtOAc = 100:1 to 50:1) to afford desired product (159 mg, 79% yield). $[\alpha]^{25}_D$ -16.9 (*c* 1.33, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88-5.80 (m, 1H), 5.11-5.06 (m, 2H), 3.92 (td, 1H, *J* = 6.4, 9.6Hz), 3.65-3.52 (m, 1H), 3.18-3.10 (m, 1H), 2.41-2.33 (m, 2H), 1.52 (t, 3H, *J* = 15.2 Hz), 1.47 (s, 12H), 1.03 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5, 152.6, 152.1, 94.2, 93.2, 80.7, 80.0, 74.5, 48.6, 48.4, 43.3, 43.1, 28.6, 27.3, 26.3, 25.4, 24.5, 13.1,

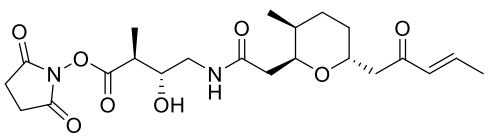
12.8; IR (neat) 3080, 2978, 2935, 2876, 1703, 1642, 1478, 1457, 1394, 1255, 1214, 1178, 1095, 1053, 1005, 916, 876, 770, 679 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{14}H_{26}O_3N$ $[M + H]^+$ 256.1913, found 256.1894.

(2*R*,3*S*)-3-Carboxy-2-hydroxybutan-1-aminium chloride (4.57)



To a solution of **4.90** (1.01 g, 3.96 mmol) in CH_3CN (7.3 mL) was added CCl_4 (7.3 mL), H_2O (9.1 mL), $NaIO_4$ (3.46 g, 16.2 mmol) and $RuCl_3$ (41 mg, 0.20 mmol) at rt. The resulting mixture was stirred at rt overnight, then was diluted with CH_2Cl_2 and H_2O. After filtering through a Celite® pad, the organic layer in the filtrate was separated and aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers (include the original organic layer) were dried over $MgSO_4$, filtered, and concentrated. A short silica column (CH_2Cl_2:MeOH = 20:1 to 10:1) was used to purify the crude acid. The residue was re-dissolved in EtOAc (15 mL) and treated with 3 N HCl (aq., 15 mL). After stirred at 35 °C for 1 h, the reaction mixture was diluted with EtOAc and H_2O. The aqueous layer was washed with EtOAc three times, then was concentrated under reduced pressure to afford the desired salt (415 mg, 62% yield for two stpes). ^{1}H NMR (400 MHz, D_2O): δ 4.03 (ddd, 1H, *J* = 2.8, 7.6, 10.4 Hz), 3.29 (dd, 1H, *J* = 2.4, 13.2 Hz), 3.06 (dd, 1H, *J* = 10.4, 13.2 Hz), 2.70 (quint., 1H, *J* = 7.2 Hz), 1.21 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, D_2O): δ 178.1, 69.2, 44.2, 42.4, 12.8.

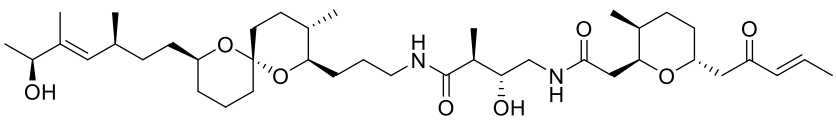
(2*S*,3*R*)-2,5-Dioxopyrrolidin-1-yl 3-hydroxy-2-methyl-4-(2-((2*S*,3*S*,6*R*)-3-methyl-6-((*E*)-2-oxopent-3-enyl)tetrahydro-2*H*-pyran-2-yl)acetamido)butanoate (4.52)



To a solution of **4.57** (70 mg, 0.41 mmol) in DMF (3 mL) was added diisopropylethylamine (0.48 mL, 2.7 mmol)

and a solution of **4.59** (92 mg, 0.27 mmol) in DMF (1 mL) successively at rt. The resulting mixture was stirred at rt for 1.5 h, then was diluted with EtOAc and H_2O. The aqueous layer was separated and acidified with 0.05 M aq. HCl. The aqueous layer was extracted with EtOAc (3x). The combined organic layers (not included the original organic layer) were dried over Na_2SO_4, filtered, and concentrated. The residue was re-dissolved in CH_3CN (5 mL). *N*-Hydroxysuccinimide (34 mg, 0.30 mmol) and DCC (56 mg, 0.27 mmol) were added successively. The resulting suspension was filtered after stirred at rt for 16.5 h then was filtrated. The filtrate was concentrated and purified by flash column chromatography (CH_2Cl_2:MeOH = 50:1) to afford desired product (62 mg, 50% yield). $[\alpha]^{25}_D$ -18.4 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4 (s, 1H), 6.96-6.87 (m, 1H), 6.15 (dd, 1H, *J* = 1.6, 16.0 Hz), 4.21 (t, 1H, *J* = 9.6 Hz), 4.08 (dd, 1H, *J* = 4.8, 11.6 Hz), 4.00 (dt, 1H, *J* = 2.0, 7.2 Hz), 3.69 (ddd, 1H, *J* = 2.4, 6.0, 14.0 Hz), 3.38-3.32 (m, 1H), 2.97-2.88 (m, 2H), 2.84 (s, 4H), 2.80 (dd, 1H, *J* = 11.6, 15.2 Hz), 2.56 (dd, 1H, *J* = 2.4, 16.8 Hz), 2.18 (dd, 1H, *J* = 1.2, 15.6 Hz), 1.92 (dd, 3H, *J* = 1.2, 6.8 Hz), 1.69-1.61 (m, 2H), 1.43 (d, 3H, *J* = 3.6 Hz), 1.41-1.22 (m, 3H), 0.87 (d, 3H, *J* = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.6, 173.7, 170.2, 169.3, 145.1, 132.3, 75.1, 73.2, 64.8, 45.6, 43.9, 42.5, 33.6, 32.2, 31.1, 29.9, 26.7, 25.8, 18.6, 17.5, 13.8; IR (neat) 3321, 2925, 2849, 1811, 1780, 1736, 1623, 1535, 1434, 1365, 1310, 1259, 1204, 1065, 801, 641 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{33}N_2O_8$ $[M + H]^+$ 453.2237, found 453.2231.

Bistramide A (4.1)



To a solution of **4.83** (7.0 mg, 0.018 mmol) in THF/H_2O (3/1, 1.2 mL) was added PMe_3 (1.0 M in THF, 0.089 mL, 0.089 mmol) at rt. The resulting solution was stirred for 1 h and poured into brine. The aqueous layer was extracted with Et_2O (3x). The

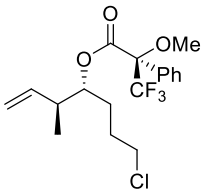
combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in DMF (0.9 mL) and **4.52** (8.0 mg, 0.018 mmol) was added in one portion. The resulting light yellow solution was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O (2x). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (CH_2Cl_2:MeOH = 30:1 to 15:1) to afford bistramide A (8.7 mg, 69% yield). $[\alpha]^{25}_D$ +6.1 (*c* 0.61, CH_2Cl_2), the reported optical rotation value for natural Bistramide A is +10 (*c* 0.5, CH_2Cl_2); 1H NMR (400 MHz, CDCl3): δ 7.32 (br.t, 1H, *J* = 6.0 Hz), 6.96-6.94 (br.m, 1H), 6.91 (dd, 1H, *J* = 6.8, 15.6 Hz), 6.13 (dd, 1H, *J* = 1.6, 15.6 Hz), 5.19 (d, 1H, *J* = 9.6 Hz), 4.62 (br.s, 1H), 4.22-4.18 (m, 2H), 4.07 (dd, 1H, *J* = 4.8, 11.2 Hz), 3.72 (q, 1H, *J* = 4.8 Hz), 3.51 (dt, 1H, *J* = 5.4, 14.0 Hz), 3.45 (m, 1H), 3.31 (dt, 2H, *J* = 6.8, 12.8 Hz), 3.24 (dt, 1H, *J* = 6.0, 14.0 Hz), 3.16 (dt, 1H, *J* = 2.0, 9.6 Hz), 2.91 (dd, 1H, *J* = 8.8, 16.8 Hz), 2.76 (dd, 1H, *J* = 11.6, 14.8 Hz), 2.53 (dd, 1H, *J* = 2.8, 17.2 Hz), 2.42-2.34 (m. 2H), 2.15 (dd, 1H, *J* = 1.2, 15.2 Hz), 1.93 (dd, 3H, *J* = 1.6, 6.8 Hz), 1.86-1.30 (br.m, 28H), 1.26 (t, 6H, *J* = 6.8 Hz), 0.96 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J* = 7.6 Hz), 0.82 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1, 175.4, 173.7, 144.7, 137.4, 132.3, 131.6, 95.7, 75.0, 74.5, 74.1, 73.5, 69.3, 65.0, 45.5, 44.9, 43.6, 39.7, 36.3, 35.7, 35.1, 34.3, 33.7, 33.6, 32.5, 32.1, 31.6, 31.0, 30.7, 28.1, 26.7, 26.1, 22.0, 21.2, 19.4, 18.6, 18.2, 17.4, 15.8, 12.0; IR (neat) 3600-3200 (brs), 2927, 2856, 1649, 1550, 1456, 1378, 1295, 1225, 986, 733 cm^{-1}; HRMS (ES) *m/z* calcd for $C_{40}H_{69}N_2O_8$ $[M + H]^+$ 705.5054, found 705.5065.

General procedure for the Mosher ester analysis

The secondary alcohol substrate (1.0 eq.) was treated with Mosher acid solution in dry CH_2Cl_2 (0.12 M, 1.5 eq.), DCC solution in dry CH_2Cl_2 (0.069 M, 2.0 eq.), and DMAP solution in dry

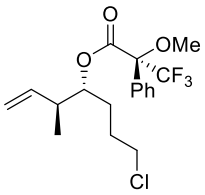
CH_2Cl_2 (0.11 M, 0.1 eq.) successively at rt. The resulting mixture was stirred at rt overnight, then filtered through a Celite® pad. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the desired Mosher ester.

(*R*)-((3*S*,4*R*)-7-Chloro-3-methylhept-1-en-4-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S4.1)



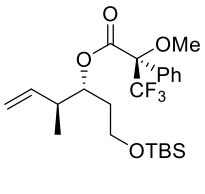
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.55 (m, 2H), 7.43-7.39 (m, 3H), 5.72 (ddd, 1H, *J* = 8.0, 10.0, 17.6 Hz), 5.12-5.07 (m, 3H), 3.56 (d, 3H, *J* = 1.2 Hz), 3.44 (t, 2H, *J* = 6.0 Hz), 2.57-2.48 (m, 1H), 1.78-1.60 (m, 4H), 1.04 (d, 3H, *J* = 6.8 Hz).

(*S*)-((3*S*,4*R*)-7-Chloro-3-methylhept-1-en-4-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S4.2)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.44-7.40 (m, 3H), 5.68 (ddd, 1H, *J* = 8.0, 10.0, 18.0 Hz), 5.11-5.06 (m, 2H), 5.03 (d, 1H, *J* = 0.4 Hz), 3.55 (d, 3H, *J* = 1.2 Hz), 3.53-3.50 (m, 2H), 2.53-2.45 (m, 1H), 1.79-1.76 (m, 4H), 0.96 (d, 3H, *J* = 6.8 Hz).

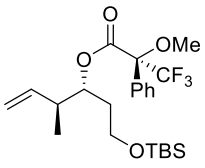
(*R*)-((3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-methylhex-5-en-3-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S4.3)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.43-7.38 (m, 3H), 5.87 (ddd, 1H, *J* = 7.2, 10.4, 17.6 Hz), 5.23 (quint. 1H, *J* = 4.4 Hz), 5.01 (td, 1H, *J* = 1.6, 11.2 Hz), 4.97 (td, 1H, *J* = 1.6, 17.2 Hz), 3.68-3.58 (m, 2H), 3.57-3.56 (m, 1H),

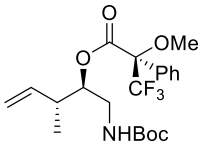
3.55 (d, 3H, *J* = 1.2 Hz), 2.58-2.53 (m, 1H), 1.90-1.76 (m, 2H), 1.00 (d, 3H, *J* = 6.8 Hz), 0.89 (s, 9H), 0.02 (s, 6H).

(*S*)-((3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-methylhex-5-en-3-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S4.4)



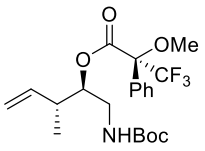
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H), 7.41-7.38 (m, 3H), 5.80 (ddd, 1H, *J* = 6.8, 10.4, 17.2 Hz), 5.24 (quint., 1H, *J* = 4.4 Hz), 5.10 (td, 1H, *J* = 1.6, 6.8 Hz), 5.06 (td, 1H, *J* = 1.6, 13.6 Hz), 3.58-3.53 (m, 2H), 3.55 (d, 3H, *J* = 1.2 Hz), 3.51-3.44 (m, 1H), 2.65-2.58 (m, 1H), 1.85-1.73 (m, 2H), 1.04 (d, 3H, *J* = 6.8 Hz), 0.89 (s, 9H), 0.02 (d, 6H, *J* = 3.6 Hz).

(*R*)-((2*R*,3*R*)-1-(*tert*-Butoxycarbonylamino)-3-methylpent-4-en-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S4.5)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.44-7.42 (m, 3H), 5.67 (ddd, 1H, *J* = 8.4, 10.4, 18.4 Hz), 5.21-5.16 (m, 1H), 5.07 (d, 1H, *J* = 9.6 Hz), 5.03 (s, 1H), 4.55 (br.s, 1H), 3.53 (d, 3H, *J* = 1.2 Hz), 3.45-3.41 (m, 1H), 3.27-3.20 (m, 1H), 2.53-2.48 (m, 1H), 1.44 (s, 9H), 0.99 (d, 3H, *J* = 6.8 Hz).

(S)-((2R,3R)-1-(tert-Butoxycarbonylamino)-3-methylpent-4-en-2-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (S4.6)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.56 (m, 2H), 7.44-7.41 (m, 3H), 5.74 (ddd, 1H, *J* = 8.4, 10.0, 18.4 Hz), 5.22-5.18 (m, 1H), 5.11 (d, 1H, *J* = 8.0 Hz), 5.08 (s,

1H), 4.37 (br.s, 1H), 3.57 (d, 3H, *J* = 1.2 Hz), 3.47-3.42 (m. 1H), 3.10 (ddd, 1H, *J* = 5.6, 8.4, 14.4 Hz), 2.56-2.51 (m, 1H), 1.44 (s, 9H), 1.08 (d, 3H, *J* = 6.8 Hz).

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