Synthesis of Neopeltolide and Analogs, Sulfur-Containing Heterocycles and Enantioenriched Allylated Chromenes

by

Yubo Cui

B.S., Nanjing University, 2003

M.S., Nanjing University, 2006

Submitted to the Graduate Faculty of the

Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2014

UNIVERSITY OF PITTSBURGH

DIETRICH SCHOOL OF ARTS AND SCIENCES

This dissertation was presented

by

Yubo Cui

It was defended on

Nov 25, 2014

and approved by

Dr. Craig Wilcox, Professor, Department of Chemistry

Dr. Kazunori Koide, Associate Professor, Department of Chemistry

Dr. Xiangqun Xie, Professor, Department of Pharmaceutical Sciences

Dr. Paul E. Floreancig, Professor, Department of Chemistry

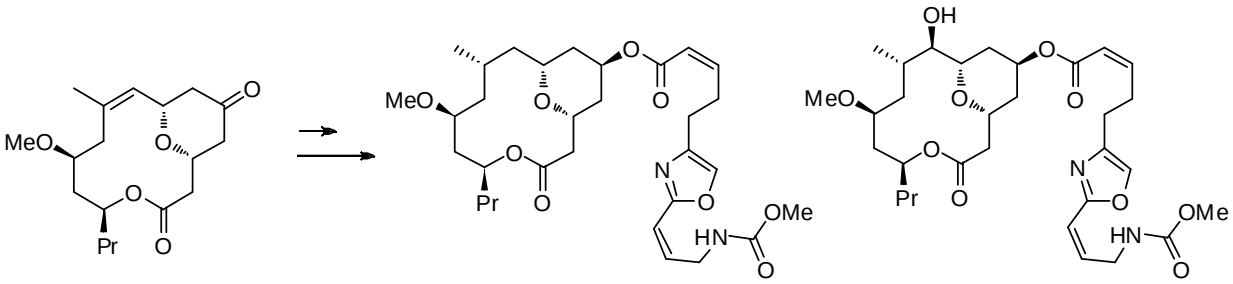
Dissertation Director: Dr. Paul E. Floreancig, Professor, Department of Chemistry

Synthesis of Neopeltolide and Analogs, Sulfur-Containing Heterocycles and Enantioenriched Allylated Chromenes

Yubo Cui, PhD

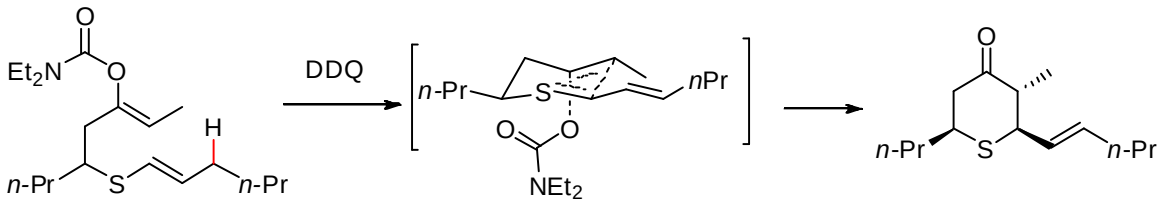
University of Pittsburgh, 2014

Described herein is the total synthesis of neopeltolide and eleven analogs with modifications to its macrolactone and side chain. Preliminary biological assays showed neopeltolide and its analogs are not general cytotoxins as demonstrated by notable cell line selectivity. The introduction of different polar groups to the macrolactone at C8 and C9 positions is tolerated to variable extent, while alternations to the side chain generally lead to significantly diminished potency with the exception of using a furan ring to replace the oxazole ring. Experimental data also indicated p53 to play an auxiliary role in the potent antiproliferative activity of these compounds.

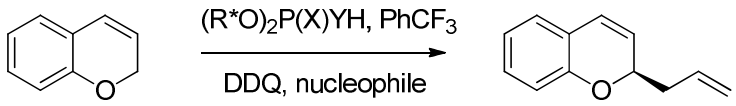


DDQ mediated oxidative C-H bond cleavage has been established as an effective and stereoselective method to prepare sulfur containing six- or five- member rings. The moieties for generating thiocarbenium ions are unsaturated sulfides including allyl sulfides and preferably vinyl sulfides, while the appended nucleophiles include enol acetates, enol carbamates and

allylsilanes. Most cyclization reactions rapidly afford sulfur containing heterocycles with high stereocontrols and in good to excellent yields under very mild conditions.



Also described herein is an enantioselective addition reaction that employs DDQ-mediated carbon-hydrogen bond cleavage. 2*H*-Chromene can undergo oxidative carbon-hydrogen bond cleavage and, in the presence of a chiral Brønsted acid, the resulting acetal intermediate is converted to a chiral ion pair that reacts with intermolecular nucleophiles to prepare enantiomerically enriched products. While the scope of this process is still very limited, we were able to conduct reactions with good enantiocontrol at reasonable catalyst loadings in non-polar aromatic solvents.



R = chiral group, X = O or S, Y = O or NTf

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

9-BBN	9-Borabicyclo[3.3.1]nonane
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
2-CSA	2-Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dba	Dibenzylideneacetone
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
EI	Electron impact ionization
HRMS	High-resolution mass spectrometry
LDA	Lithium diisopropylamide
m-CPBA	*meta*-Chloroperoxybenzoic acid
MsCl	Mesyl chloride

M.S.	Molecule sieves
PyBOP	Benzotriazolyloxy-tris[pyrrolidino]-phosphonium hexafluorophosphate
SET	Single electron transfer
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TRIP	Triisopropylphenyl
TsOH	*p*-Toluenesulfonic acid

PREFACE

I would like to thank my advisor, Professor Paul Floreancig, for his diligent work and thoughtful guidance throughout my PhD studies. What I appreciate most from him is his passion for chemistry, which inspires my understandings of fundamental principles in organic chemistry and encourages me to meet challenges that are more than expected. I also truly appreciate his continuing support after I finished most of my research projects.

I would like to thank Professor Wilcox, Professor Koide, Professor Xie and Professor Brummond for their guidance and advices in comprehensive examination, graduation proposal writing and dissertation studies. Also thank Professor Day and Dr Balachandran from School of Medicine for their biological assays on neopeltolide and its analogs.

To all of past and present group members, I wish to thank you all for your help in the past few years. I am feeling lucky to study and work in such a open and supportive environment, where we share so much to enjoy the fun moment together and face the challenges side by side.

Last but NEVER the least, I would like to thank my beloved wife and our kids. I can never make a meaning life without your love and support. It's for my family why I am trying my best to make the dreams become true. It's also a great moment to express my gratitude to my parents, who have spent the best time of their life for the happiness of me and my sisters, and who are now very glad to see the best scene they could imagine dozens of years ago.

1. TOTAL SYNTHESIS OF NEOPELTOLIDE AND ANALOGS

1.1 INTRODUCTION

1.1.1 Discovery and Biological Activities of Neopeltolide

Secondary metabolites from marine sponges have been found to be rich sources of structurally diverse and biological active compounds largely due to the unique and harsh habitats of the sponges.[1] Among them, marine macrolides having potent cytotoxic properties are especially promising anticancer agents.[2] Unfortunately, these macrolides are typically scarce or even no longer available. This makes further investigation of their mechanism of action and structure-activity relationship difficult, and hinders their potential growth into important lead compounds. Total synthesis of these macrolides and their analogs are thus indispensable for research in cancer research community.

In 2007, Wright and co-workers isolated a new macrolide designated as neopeltolide (**1.1**) from the deep-water sponge *Daedalopelta* belonging to the family *Neopeltidae* off the north Jamaican coast (Figure 1.1).[3] It is a 14-membered macrolide featuring a tri-substituted 2,6-*cis*-tetrahydropyran ring and a highly unsaturated oxazole-containing side chain at C5-position, which is identical to what was found in leucascandrolide A **1.3**.[4] However, the structure **1.1**

originally proposed by Wright based on spectroscopic studies contained several stereochemical misassignments,[3] which were later corrected to be structure **1.2** by Panek[5a] and Scheidt[5b] through their independent work in total synthesis.

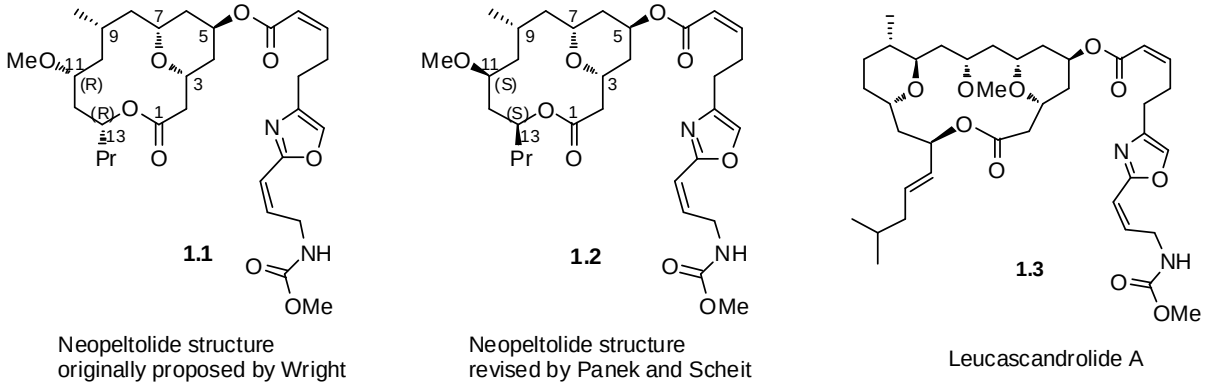


Figure 1.1 Structures of neopeltolide and leucascandrolide A.

Neopeltolide was found to be an extremely potent toxin against a series of tumor cell lines, including P388 murine leukemia, A-549 human lung adenocarcinoma, and NCI-ADR-RES (formerly MCF7/ADR) human ovarian sarcoma (IC_{50} values of 0.56, 1.2, and 5.1 nM, respectively).[3] For PANC-1 pancreatic and DLD-1 colorectal cell lines, neopeltolide also showed strong inhibitory effects but with only 50% cell death over an extended dose range, suggesting a cytostatic effect on these two cell lines. Additionally, neopeltolide is a potent inhibitor of the fungal pathogen *Candida albicans* (MIC value of 0.625 μg/mL in liquid culture), which often poses a severe threat to the health of AIDS patients. In comparison, the structurally more complex leucascandrolide A showed sub-micro molar inhibitory potency on P388 murine leukemia (IC_{50} value of 0.35 μM) and comparable potency on A549 cells and *Candida albicans*.[4]

The structural overlap and similar biological activities between neopeltolide and leucascandrolide suggest the possibility that a common mechanism is responsible for the

inhibition of cellular proliferation by the two compounds. In 2008 Kozmin and co-workers reported a simplified congener **1.4** of leucascandrolide A with the removal of C12, C21 methyl groups and C18-C19 alkene group (Figure 1.2)[5c]. Cellular studies demonstrated this congener and neopeltolide effectively inhibited yeast cell growth, which was substantially enhanced by substituting glucose with galactose or glycerol. Subsequent genetic analysis of determinants of drug sensitivity and suggested these compounds may inhibit mitochondrial ATP synthesis, and evaluation of the activity of the four mitochondrial electron transport chain complexes in yeast and mammalian cells revealed their principal cellular target was the cytochrome bc_1 complex.

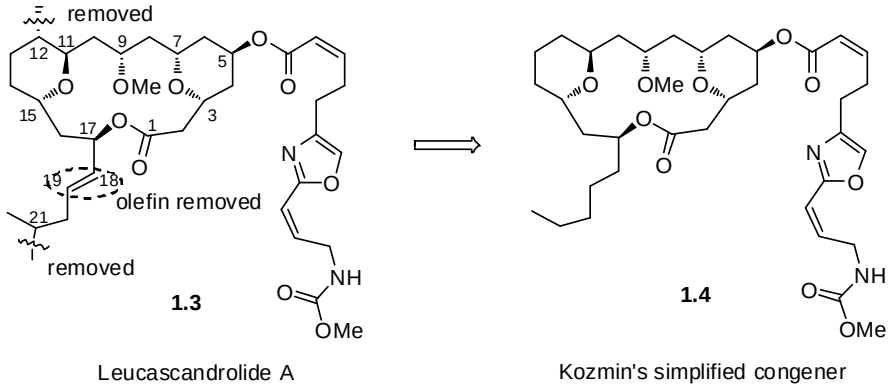
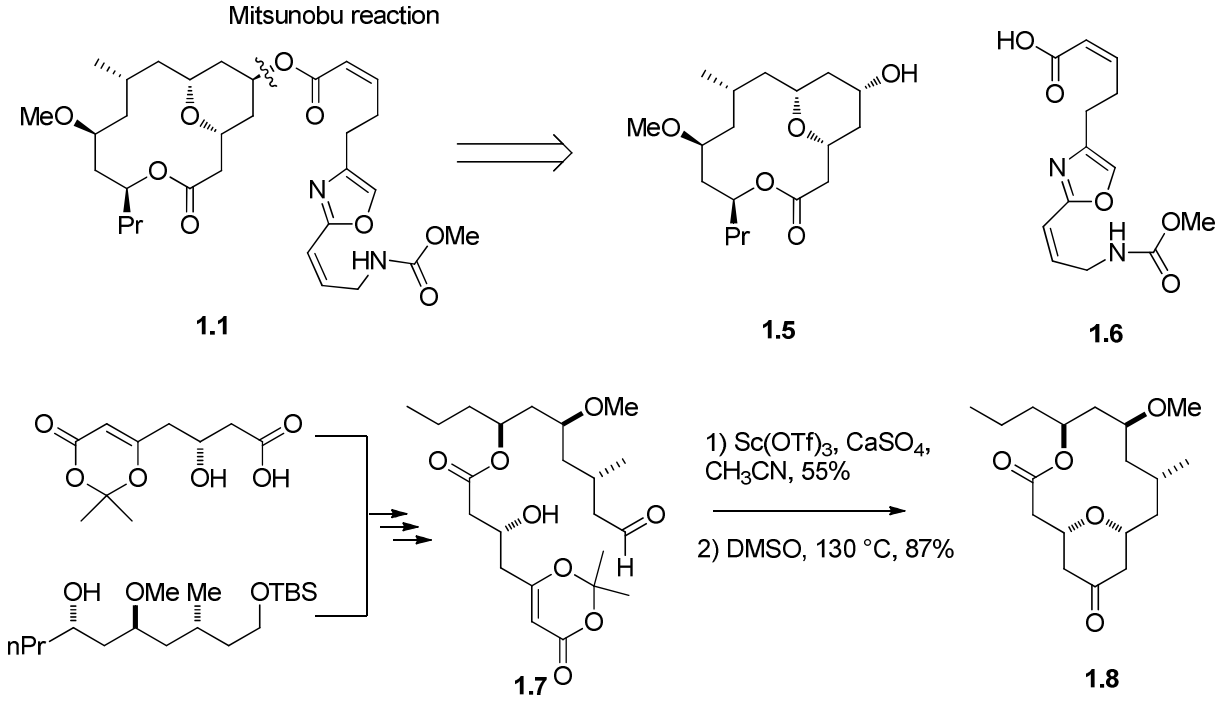


Figure 1.2 Kozmin's design of a simplified congener.

Besides neopeltolide and leucascandrolide, other similar natural macrolides of this class include callipeltosides,[6] lyngbouilloside,[7] auriside[8] and lyngbyaloside,[9] which contain a C-3 hemiketal instead of an ether functionality. However, these compounds exhibit moderate cytotoxicity in comparison to neopeltolide and leucascandrolide.

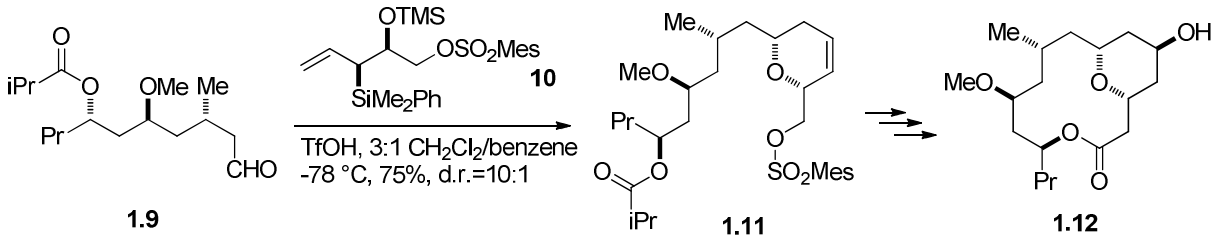
1.1.2 Reported Syntheses of the Macrolactone

Inspired by the potent cytotoxic activities of neopeltolide, several elegant total and formal synthesis have emerged since its discovery in 2007.[5,10] Nearly all total syntheses used a Mitsunobu reaction to connect the macrolactone alcohol and the oxazole side chain acid, while a major difference is the manner of constructing the tetrahydropyran ring (Scheme 1.1). A common approach uses the Prins reaction or its derivations. Syntheses from Scheidt,[5b] Lee[10a] and Yadav[10k] employed the Prins reaction to prepare the macrolactone and the tetrahydropyran in one step. As shown in Scheme 1.1, Scheidt et al. prepared the dioxinone compound **1.7** and treated it with $Sc(OTf)_3$ to give a cyclized intermediate, which released the tetrahydropyrone **1.8** upon heating in DMSO.



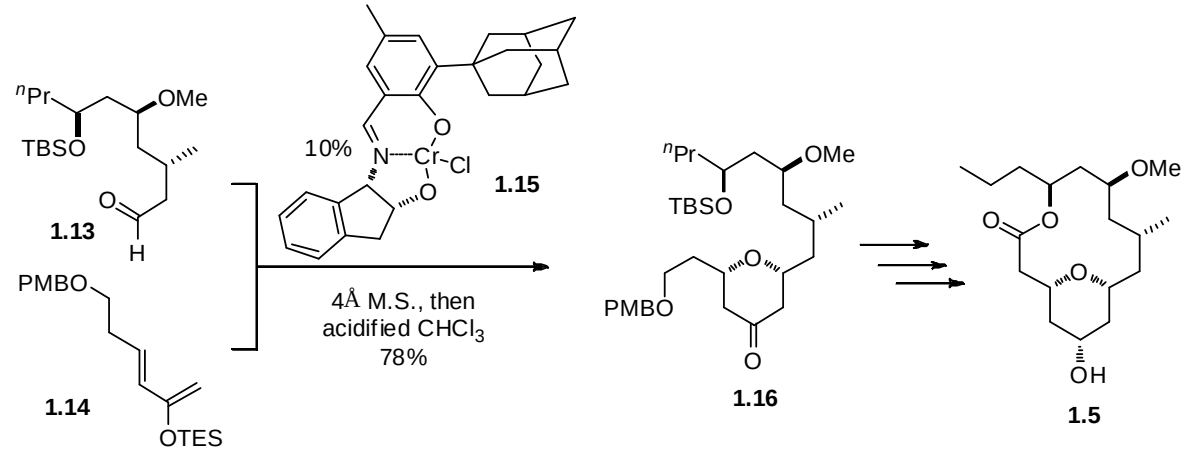
Scheme 1.1 Scheidt's synthesis of the macrolactone by Prins macrocyclization reaction.

Several syntheses assembled the tetrahydropyran ring before the closure of the macrolactone. The synthesis from Panek[5a] used a triflic acid promoted [4+2] annulation to combine aldehyde **1.9** and allylsilane **1.10**. The following oxymercuration installed the hydroxyl group at C5 with the correct stereochemistry (Scheme 1.2). This strategy was also used by Maier[10b] and Kozmin[5c] in similar ways in their syntheses of the macrolactone.



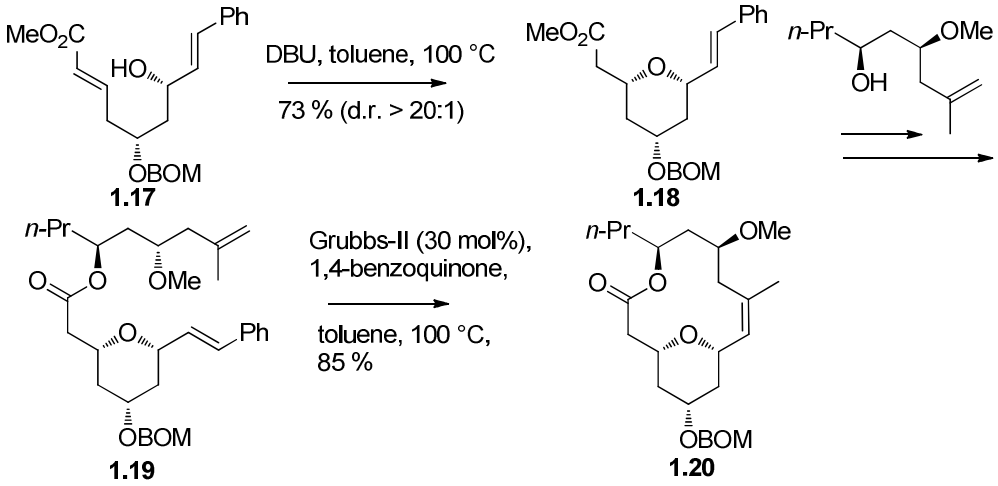
Scheme 1.2 Panek's synthesis of the macrolactone.

Paterson et al. utilized a hetero Diels–Alder reaction to assemble the tetrahydropyran core from siloxydiene **1.14** and aldehyde **1.13** (Scheme 1.3).[10d] The reaction proceeded as expected under the catalysis of chiral tridentate chromium (III) salt **1.15** to provide the *cis*-tetrahydropyrone **1.16** in 78% yield. Two years later Oestreich designed a more flexible route to prepare the linear intermediate **1.13**, facilitating the synthesis of different diastereomeric analogs of neopeltolide.[10p]



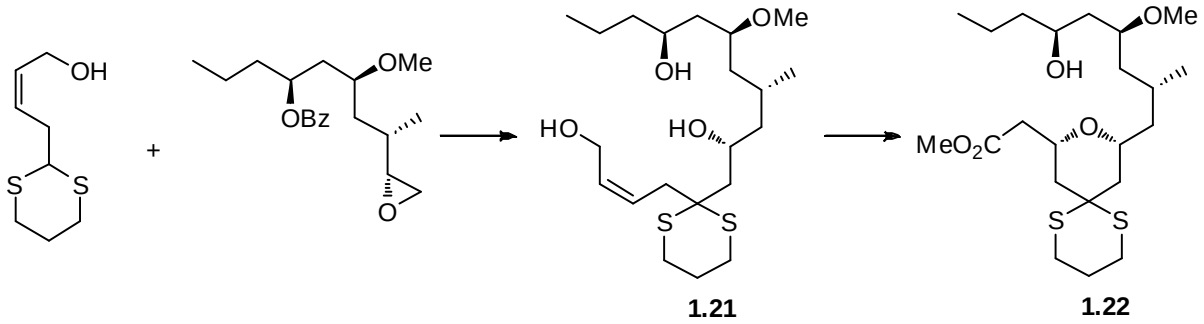
Scheme 1.3 Paterson's synthesis of the macrolactone featured by a *hetero*-Diels-Alder reaction.

Fuwa reported two syntheses of the neopeltolide macrolactone in 2008 and 2010.[10c,10m] The reported optimized route afforded the macrolactone via a concise 12-step synthetic sequence (Scheme 1.4). The key step, an intramolecular oxa-conjugate addition, was accomplished by treatment of **1.17** with DBU in toluene at 100 °C to close the tetrahydropyran ring **1.18** with a 20:1 stereoselectivity and 73% yield, and subsequently olefin metathesis with 30% Grubbs-II catalyst closed the macrolactone ring **1.20**. Similar retro-synthetic strategy was used by Taylor[10e] in a 14-step route utilizing ether transfer methodology and a radical cyclization reaction to establish the requisite stereochemistry of the tetrahydropyran core.



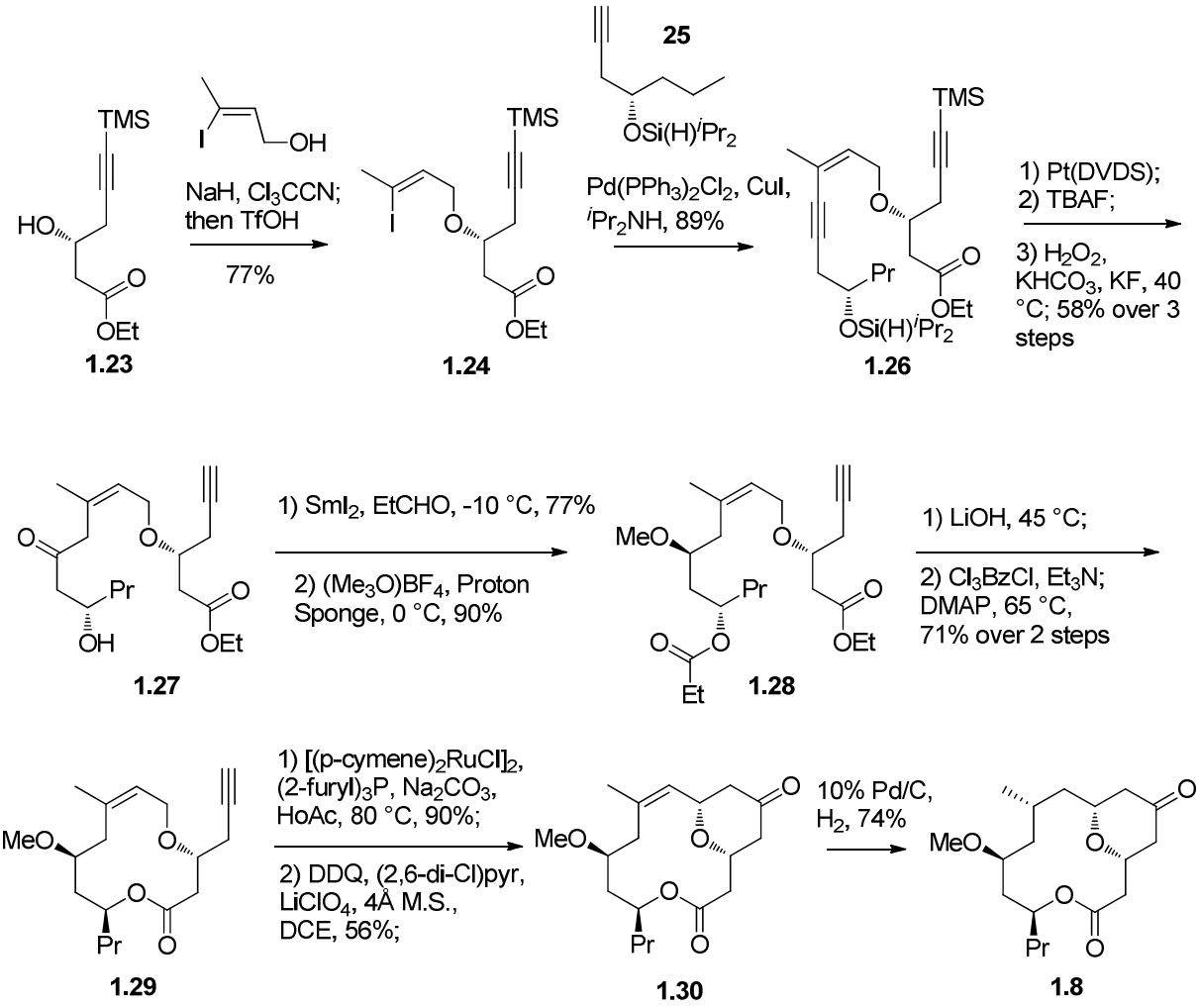
Scheme 1.4 Fuwa's synthesis of macrolactone by oxa-conjugate addition and metathesis.

Hong finished the formal synthesis of the macrolactone featuring a tandem allylic oxidation/oxa-Michael reaction to form the 2,6-*cis* tetrahydropyran ring **1.22** with a 20:1 d.r. and 78% yield (Scheme 1.5).[10i] Roulland utilized a $[CpRu(MeCN)_3]PF_6$-catalyzed tandem alkyne-enal coupling/Michael addition sequence to close the tetrahydropyran ring, finishing the macrolactone in 15 steps.[10h]



Scheme 1.5 Hong's Synthesis by a tandem allylic oxidation/oxa-Michael reaction.

The Floreancig group became interested in neopeltolide for the opportunity of applying our recently developed methodology of oxidative carbenium formation mediated by DDQ. Previous work by Dr. Tu, published in 2009, accomplished the formal synthesis of the macrolactone (Scheme 1.6).[11] The sequence featured the use of Brønsted acid-mediated etherification and Sonogashira reactions to assemble the fragments, an intramolecular hydrosilylation-Tamao oxidation to effect a regioselective alkyne hydration, and a stereoselective hydrogenation to establish the C-9 stereocenter.



Scheme 1.6 Previous work by Dr. Tu in the Floreancig group.

Based on the conformation of the macrocycle as illustrated by the X-ray structure of **1.30**, the sterically more-accessible convex face is the one that should react with H_2 to provide the desired stereoisomer **1.8** (Figure 1.3).[11] Indeed, subjecting **1.30** to H_2 and Pd/C provided **1.8** in 74% yield with a negligible amount (<10%) of C-9 diastereomer.

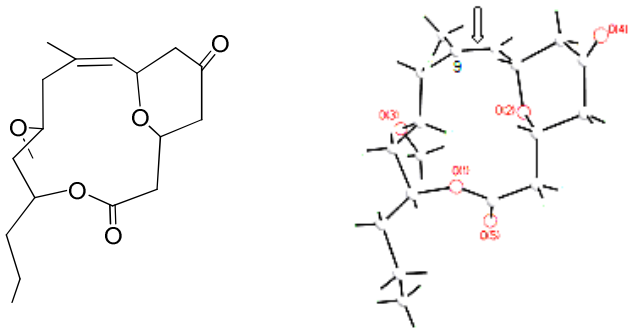
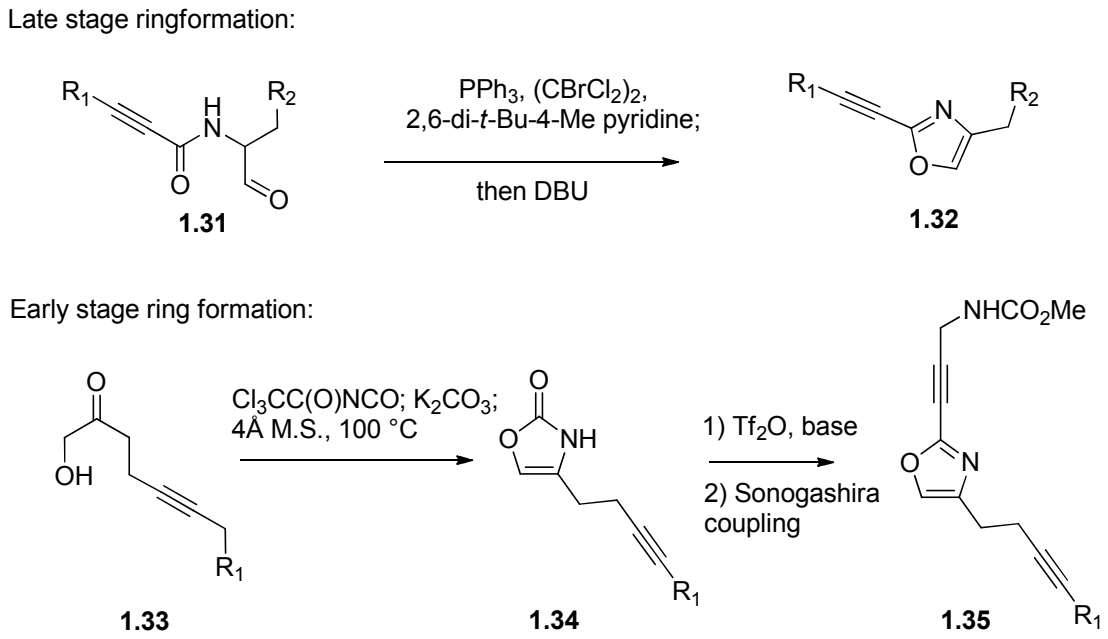


Figure 1.3 Crystal structure of Compound **1.30** in Tu's synthesis.

1.1.3 Reported Syntheses of the Oxazole Side Chain

The first synthesis of the oxazole side chain was reported by Leighton in 2000, though in his synthesis of leucascandrolide A he actually chose a different retro-synthetic strategy instead of using the Mitsunobu reaction as the last step.[12a] Since then, several syntheses have emerged with the most efficient probably being a 9-step route reported by Roulland in 2009 with an estimated overall yield of 18% from commercially available reagents.[10f-h,12b-e]

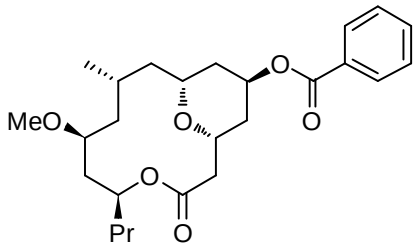
The challenges involved in the synthesis of the side chain include the formation of the oxazole ring and selective reduction of unsaturated bonds. The methods available for direct cyclization to the oxazole ring typically afford low or moderate yields, and the intermediates involved are often unstable and may cause reproducibility problems (Scheme 1.7).[12b] An alternate route is to make oxazolone **1.34** first, use triflic anhydride to convert it into oxazole triflate, and then perform a Sonogashira reaction.[12c] These routes may give better yields than direct cyclization, but the oxazole triflate must be well protected from moisture, and reproducibility is also a problem based on our experience.



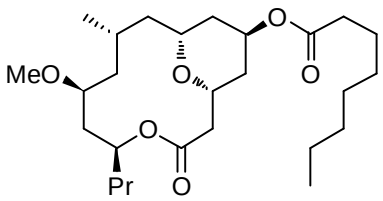
Scheme 1.7 Typical examples to the oxazole side chain.

1.1.4 Reported Approaches to Neopeltolide Analogs

Several research groups have prepared neopeltolide analogs and studied their cytotoxicity to understand the structure-activity relationships of neopeltolide analogs. Scheidt et al. explored the potencies of the macrolactone, the oxazole side chain and two simplified analogs with the modification of oxazole side chain to benzoyl ester **1.37** and octanoyl ester **1.38** against MCF7 and P-388 cells (Figure 1.4).[10g] The macrolactone and side chain alone only show nominal growth inhibition, and the elimination of the oxazole side chain abolishes the vast majority of potency. These results indicate the full potency may rely on a cooperative interaction of the macrolactone and the oxazole side chain.



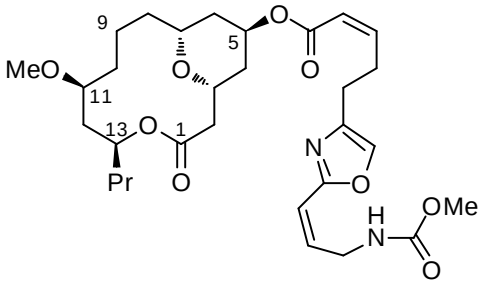
benzyol analog **1.37**



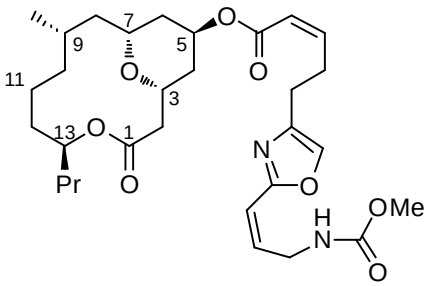
octanoyl analog **1.38**

Figure 1.4 Neopeltolide analogs reported by Scheidt.

Fuwa et al. confirmed the above cooperative interaction by measuring the potencies of slightly different macrolactone structures and the oxazole side chain.[10j] An additional interesting result in his report was that removing the C9 methyl group **1.39** or the C11 methoxy group **1.40** did not dramatically alter its antiproliferative potency (Figure 1.5). The C-9-desmethyl analog **1.39** has slightly better potencies against P388 cells, while C-11-demethoxy analog **1.40** is 80% less potent against P388 cells.



9-demethyl neopeltolide **1.39**



11-demethoxy neopeltolide **1.40**

Figure 1.5 Neopeltolide analogs reported by Fuwa.

Maier et al. prepared 5-epimer **1.41** and 11-epimer **1.42** of neopeltolide by slight modifications to their synthetic route, and these two analogs yielded a 4~50 fold loss of potency on L929 and A549 cells (Figure 1.6).[10f] Furthermore, Maier investigated the structure-activity relationship on

the side chain. The length of the side chain was found to be very important to maintain its potency, with a loss of potency by 6000 fold when two methylene groups were removed (**1.44**), and even greater loss when the homoallyl chain was removed (**1.43**). Additionally, *(E)*-isomers **1.45** or **1.46** lead to a 10~30 fold loss of potency compared with the corresponding *Z* isomers. The best result is the *Z,(E)*-analog **1.47** with an additional double bond, which is equally potent to neopeltolide.

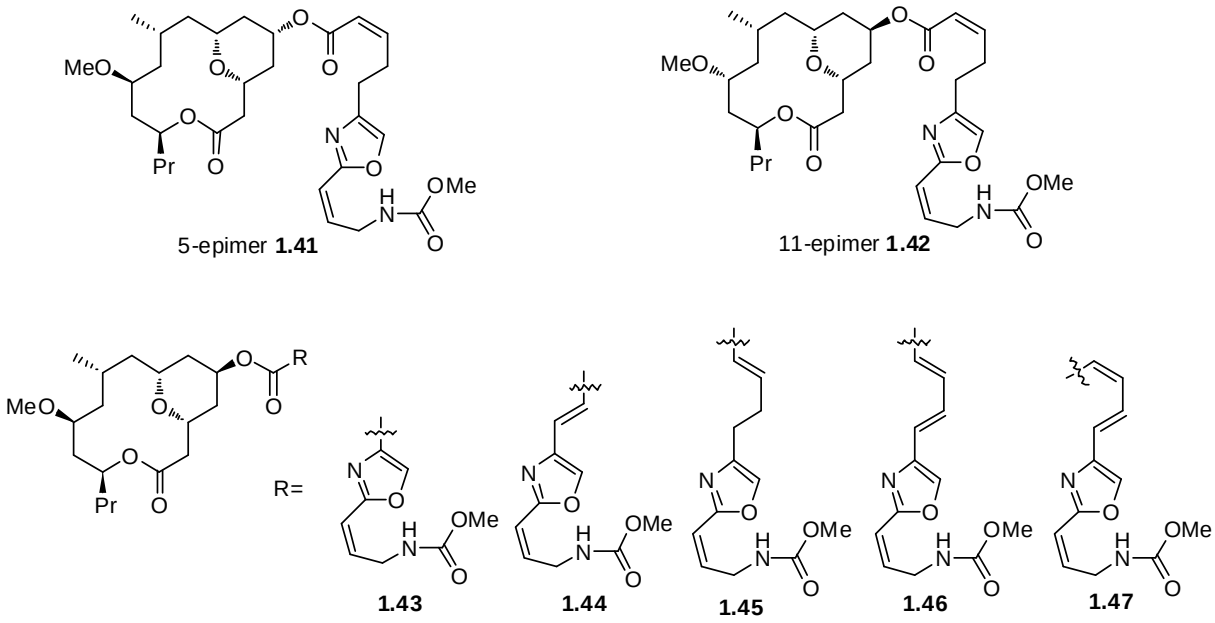


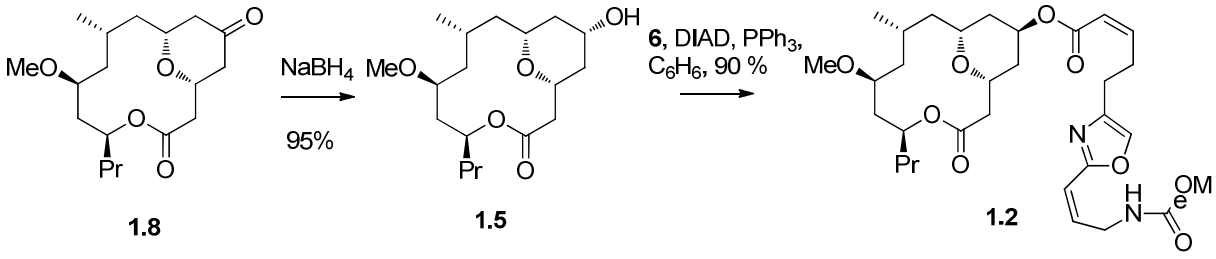
Figure 1.6 Neopeltolide analogs reported by Maier.

1.2 SYNTHESIS OF NEOPELTOLIDE

1.2.1 Completion of Neopeltolide Synthesis

The conversion from the macrolactone to neopeltolide has been reported, but we completed the synthesis to have the natural product for subsequent biological studies. Reduction of **1.8** with

$NaBH_4$ in MeOH at 0 °C followed by Mitsunobu esterification[13] with **1.6** (prepared according to the protocol of Wipf and Graham[12b]) provided the natural product **1.2** (Scheme 1.8). All spectral data matched those reported by the Scheidt group.[5b]



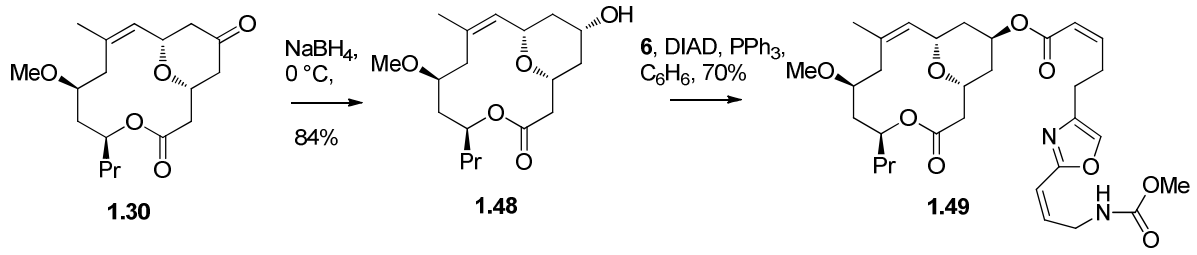
Scheme 1.8 Completion of the neopeltolide synthesis.

1.2.2 Modifications to the Macrolactone

The alkene group in **1.30** gave us a good opportunity to introduce functional groups onto the macrolactone and investigate the potency of the resulting products. These functional groups could alter the physical properties of neopeltolide, hopefully leading to different absorption and distribution profiles as well as providing possibilities to control the drug delivery in future studies. We also believe these studies could further our understanding on the structure-activity relationship of these macrolides.

I. Synthesis of Dehydro-Neopeltolide

Since **1.30** was easily accessed through the sequence, we reduced it with $NaBH_4$, and then appended the oxazole side chain to obtain dehydro-neopeltolide **1.49** (Scheme 1.9). Although this analog is not likely to differ much from neopeltolide, the removal of one step in the sequence makes the macrolide more accessible.



Scheme 1.9 Synthesis of dehydro-neopeltolide.

II. Synthesis of C9-*Epi*-Neopeltolide

We then subjected **1.30** to hydrogenation in the presence of $[Ir(Cod)py(PCy_3)]PF_6$ (Crabtree's catalyst).[14] The reaction proceeded fast with the catalyst promoting reduction preferably from the concave face where the tetrahydropyranyl oxygen rests closer to coordinate the iridium atom (Scheme 1.10 and Figure 1.7). The desired C9-epimer **1.50** was isolated in a reasonable 54% yield, while the diastereoselectivity for this reaction was 1.4:1 based on crude NMR. Reduction with $NaBH_4$ followed by Mitsunobu esterification[14] with **1.6** provided C9-*epi*-neopeltolide **1.51**.

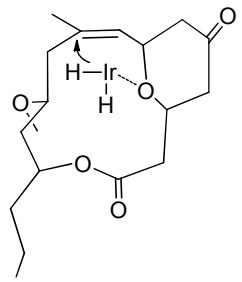
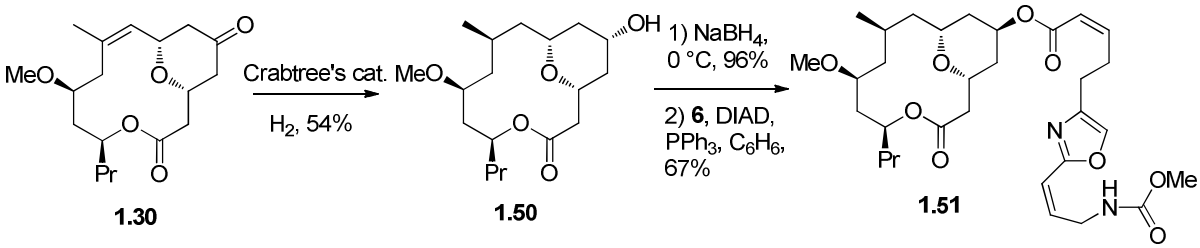


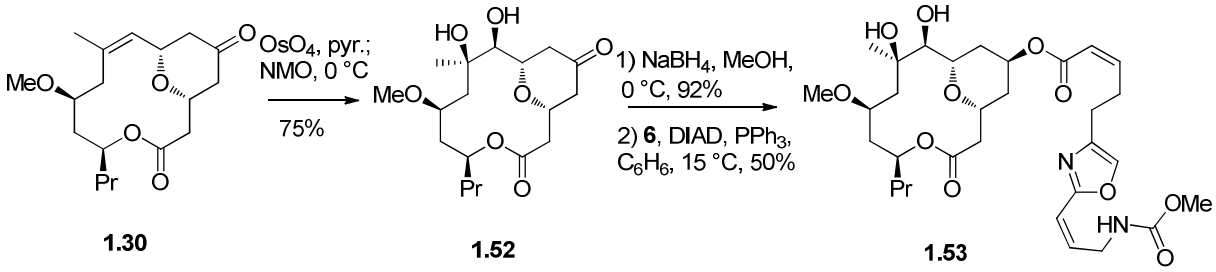
Figure 1.7 Inversion of facial selectivity by utilizing oxygen coordination.



Scheme 1.10 Synthesis of C9-*epi*-neopeltolide.

III. Synthesis of Dihydroxy Neopeltolide

Next we tried to introduce polar groups that could bring useful alterations in the physical properties of the molecule. Exposing **1.30** to OsO_4, followed by osmate ester cleavage with NMO[15] yielded diol **1.52** in 75% yield as a single diastereomer, as expected from the analysis of crystal structure of compound **1.30** (Scheme 1.11). This reaction required stoichiometric OsO_4 to proceed at a reasonable rate on our scale, though when scaled up the OsO_4 loading could conceivably be lowered. After reduction with $NaBH_4$, Mitsunobu esterification with **1.6** provided dihydroxy neopeltolide **1.53** in a moderate 50% yield. This reaction was performed at slightly lowered temperature with a controlled amount of the side chain acid **1.6** to ensure the regioselectivity over the more hindered secondary and tertiary alcohols.



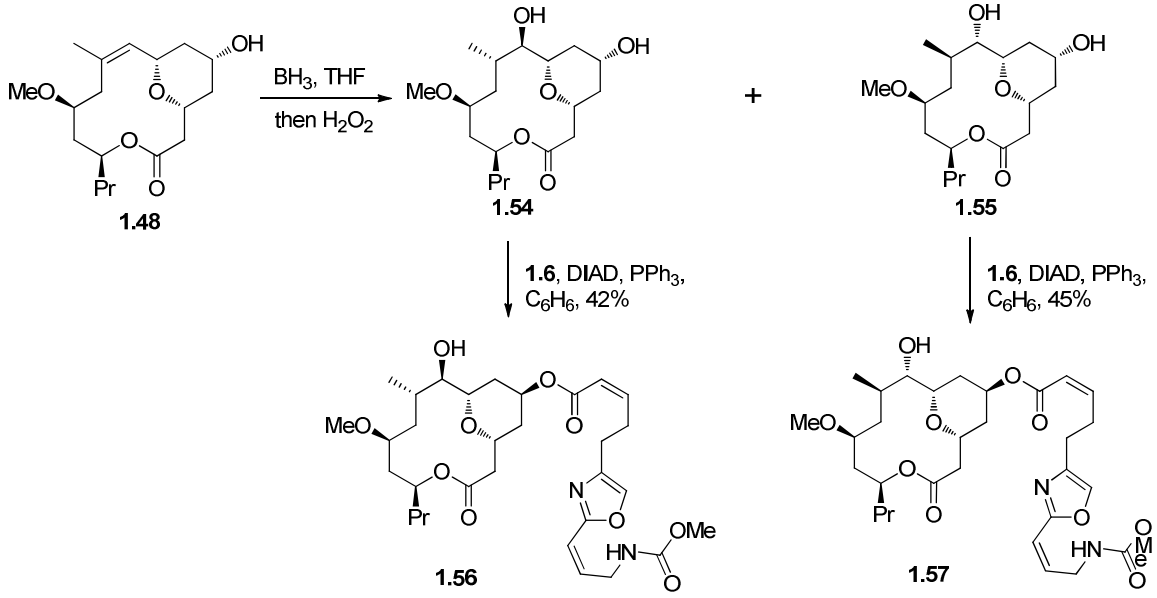
1.30 **1.52** **1.53**

Scheme 1.11 Synthesis of dihydroxy neopeltolide.

IV. Synthesis of Two C8-Hydroxy Neopeltolides

Introducing one hydroxyl group instead of two is also desirable. Under standard reaction conditions with borane, two separable diastereomers **1.54** and **1.55** were obtained from **1.48** with a ratio of nearly 1:1 (Scheme 1.12). The stereochemical assignments for these compounds were

confirmed by NOESY experiments. Lowering the reaction temperature for the borane addition had no effect on the ratio of the two diastereomers. Commonly employed bulkier reagents such as thexylborane and dicyclohexylborane were unreactive toward **1.48**,[16a] but diethylborane reacted efficiently to form **1.54** as a single stereoisomer.[16b] Both diastereomers were coupled regioselectively with **1.6** under Mitsunobu conditions to give two mono-hydroxy neopeltolides **1.56** and **1.57**.

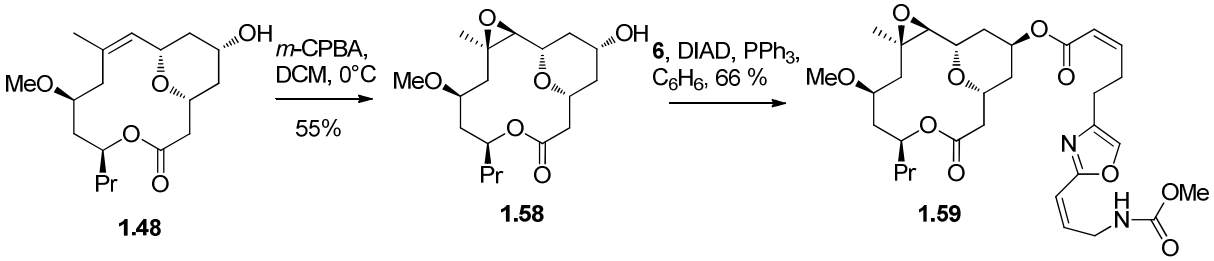


Scheme 1.12 Synthesis of mono-hydroxy neopeltolides.

V. Synthesis of Epoxy Neopeltolide

We were also interested in introducing an epoxide group to neopeltolide. To avert a potential competitive Bayer-Villiger reaction, we first reduced **1.30** with $NaBH_4$, and then subjected the alcohol **1.48** to *m*-CPBA oxidation (Scheme 1.13). The desired epoxide **1.58** was obtained in a moderate yield as a single diastereomer, as expected from the analysis of crystal structure of

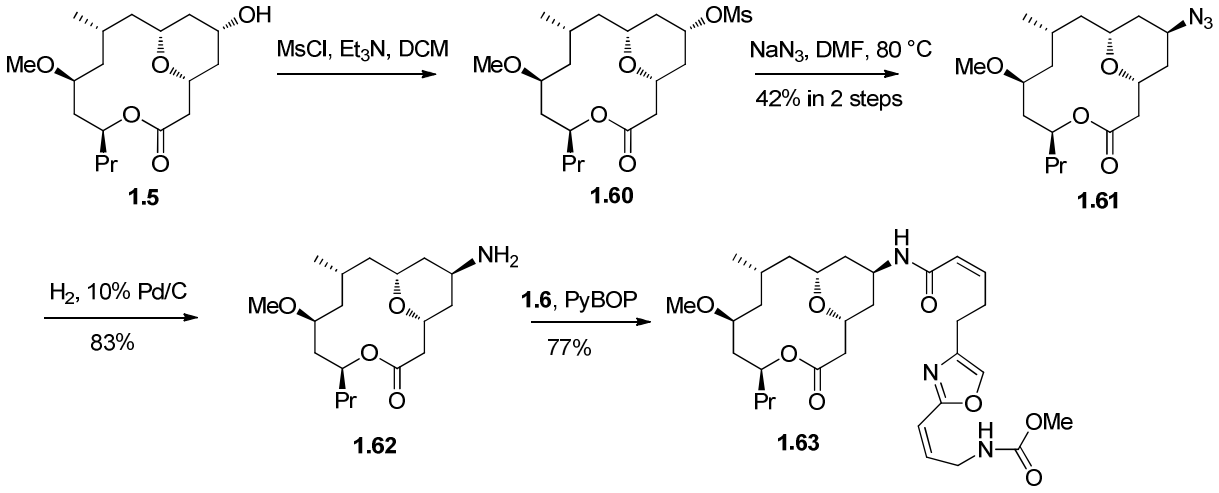
compound **1.30**. Mitsunobu esterification with **1.6** provided epoxyneopeltolide **1.59** in 66% yield.



Scheme 1.13 Synthesis of epoxyneopeltolide.

VI. Synthesis of an Amide Analog

Amide bonds are considerably more stable than ester bonds under normal physiological conditions, and amides have better solubility in aqueous solution compared with esters.[17] We were curious about whether replacing the ester linkage with an amide linkage in neopeltolide would bring a significant variation in terms of potency. Compound **1.5** was treated with MsCl and then sodium azide in DMF,[18] affording the desired azide **1.61** with inverted C5 stereocenter in a moderate yield (Scheme 1.14). Standard hydrogenation provided amine **1.62**, followed by coupling with PyBOP to obtain the desired amide **1.63** in 77% yield.[19]



Scheme 1.14 Synthesis of amide analog.

1.2.3 Simplification to the Side Chain

Results from previous work explain that oxazole-containing side chain is important for the antiproliferative potency of neopeltolide, though it shows no potency on its own.[10g] Changing to benzoate and octanoate esters oversimplifies the structure and diminishes potency,[10g] and shortening the length of the side chain significantly lowers its potency.[10f] However, there has been no attempt to investigate the role of the oxazole ring and the carbamate to our knowledge. Considering the challenges of synthesis posed by the oxazole ring, we tried to use simpler and more accessible aromatic rings to substitute the oxazole ring and investigate the antiproliferative activities of the resulting products (Figure 1.8).

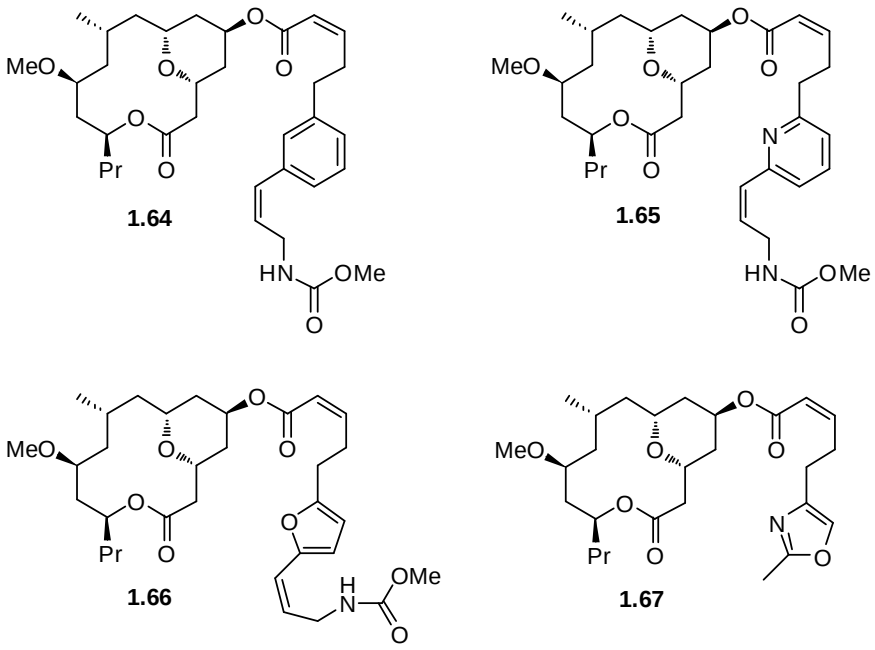
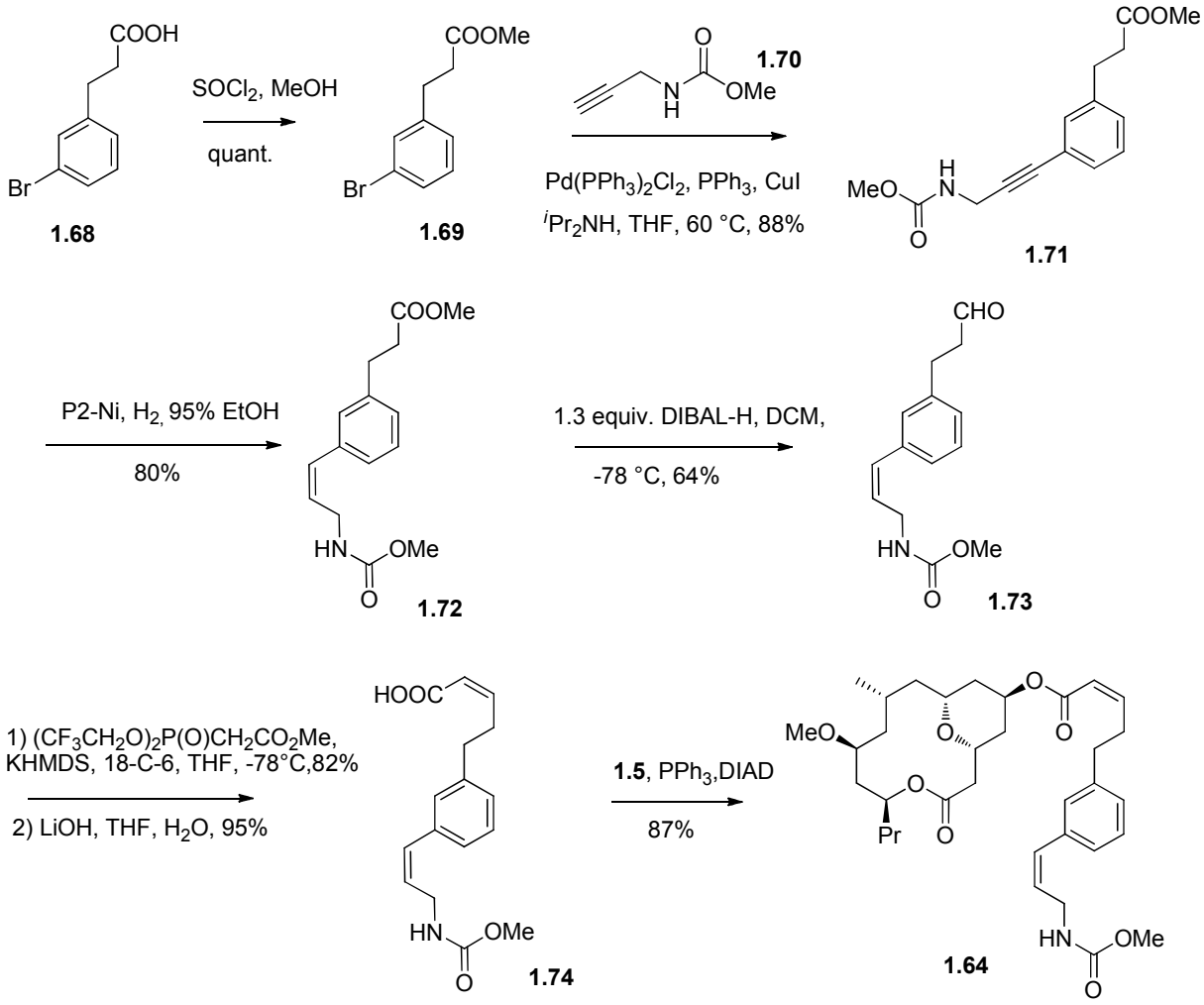


Figure 1.8 Simplification to the side chain of neopeltolide.

I. Simplification with Phenyl Group

The phenyl-containing side chain acid was accessed starting from commercially available, inexpensive 3-(3-bromophenyl)propionic acid **1.68** (Scheme 1.15)**.** An esterification was effected in quantitative yield using two equivalents of thionyl chloride in methanol. The carbamate group was introduced through a Sonogashira reaction in an excellent yield in the presence of bis(triphenylphosphine)palladium(II) dichloride, triphenylphosphine and copper(I) iodide.[20] Without the presence of triphenylphosphine, there was no coupling even at an elevated temperature. A possible explanation was that the alkyne group in **1.70** could not reduce the Pd(II) to form the effective Pd(0) catalyst.

To convert the alkyne **1.71** to the *cis*-alkene **1.72,** a standard Lindlar hydrogenation was initially used. Although the desired *cis*-alkene was obtained in 44% yield, the reaction also produced *trans*-alkene and over-reduced alkane products that caused some difficulties in the purification process. Later experiments revealed P2-nickel catalyst could perform this reduction to provide **1.72** in a very clean and efficient manner.[21] The colloidal P2-nickel catalyst was easily prepared from nickel(II) acetate tetrahydrate and sodium borohydride, and had to be used immediately after preparation. Sometimes the P2-nickel reaction stalled before complete conversion, and another batch of freshly prepared catalyst had to be added. The ester group was selectively reduced with 1.3 equivalents of DIBAL-H to form aldehyde **1.73** in 64% yield along with a minor amount of over-reduced alcohol. A Still-Gennari condensation[22] followed by hydrolysis afforded the phenyl-containing side chain acid **1.74**, which was coupled with **1.5** to provide **1.64** under Mitsunobu conditions.



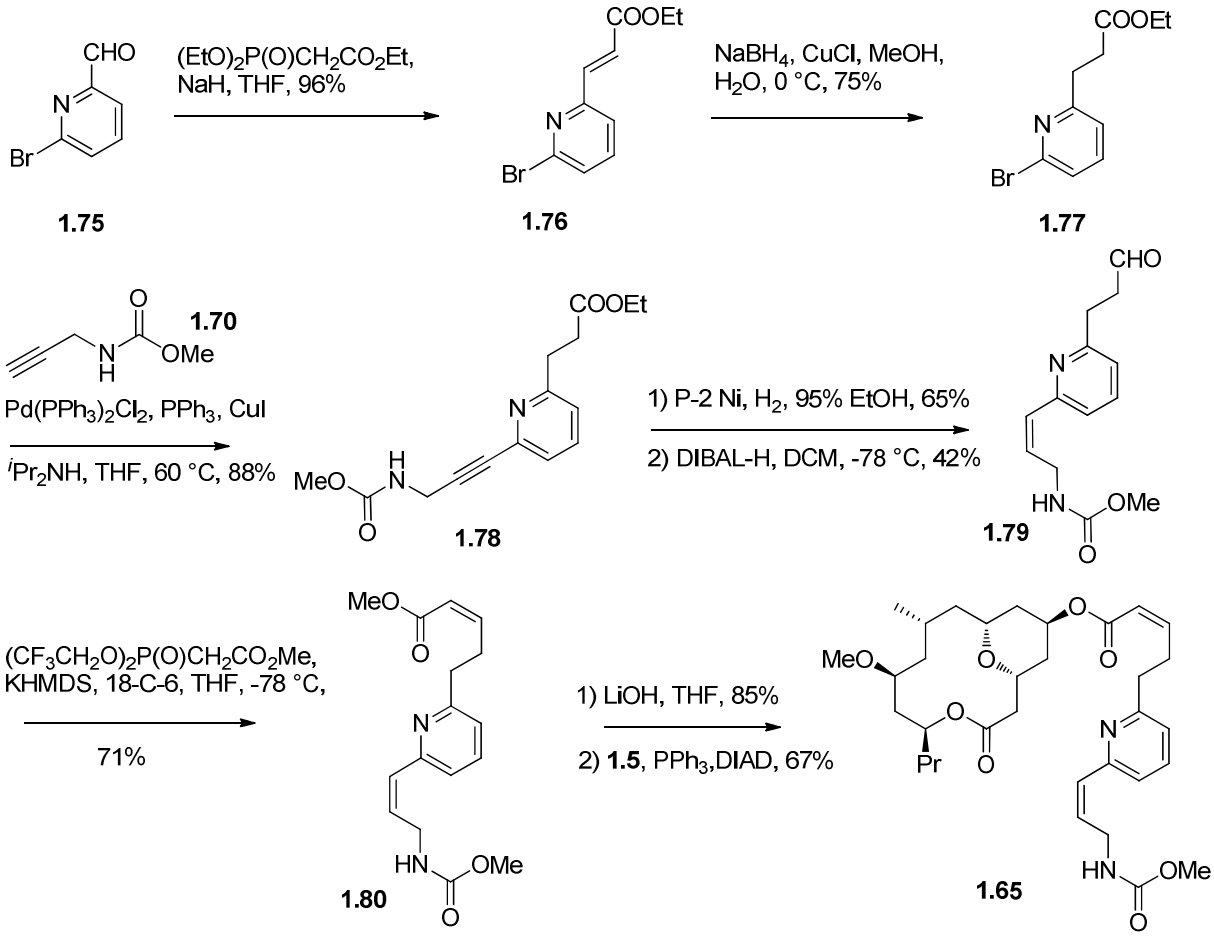
Scheme 1.15 Synthesis of the phenyl analog.

II. Simplification with Pyridyl Group

We chose commercially available 6-bromo-2-pyridinecarboxaldehyde **1.75** as our starting material to prepare the pyridine-containing analog **1.65** (Scheme 1.16). Chain extension through a Horner-Wadsworth-Emmons reaction[23] proceeded nearly quantitatively. Initially we used 10% palladium on charcoal to reduce the newly-formed double bond in compound **1.76**.

Unfortunately, the palladium catalyst led to a significant debromination. Suppressors previously reported to be effective in eliminating debromination, including diphenyl sulfide[24] and zinc bromide,[25] were tried but with little improvement. Finally, sodium borohydride in the presence of CuCl[26] effected a chemoselective reduction of the newly-formed double bond to provide **1.76** in 75% yield, and no debrominated product was found in this reaction.

A Sonogashira coupling was then performed to afford **1.78** in an excellent yield. Standard Lindlar hydrogenation on **1.78** led to complete over-reduction in 3 hours. Samarium(II) iodide in the presence of bis(triphenylphosphine)cobalt(II) dichloride[27] led to an undesired dimerized product in 78% yield. Again the P2-nickel catalyst reduced the alkyne group in **1.78** to provide the *cis*-alkene group in **1.79** in 65% yield with no *trans*-isomer. DIBAL-H was used to reduce **1.78** to provide the aldehyde **1.79** in a moderate 42% yield along with 37% of an over-reduced alcohol. Still-Gennari condensation afforded the desired ester **1.80** in 71% yield, which was then hydrolyzed by lithium hydroxide. However, the zwitterionic nature of the hydrolytic product made its purification and characterization difficult, so it was used directly into the next Mitsunobu reaction to form the pyridine-containing analog **1.65**.



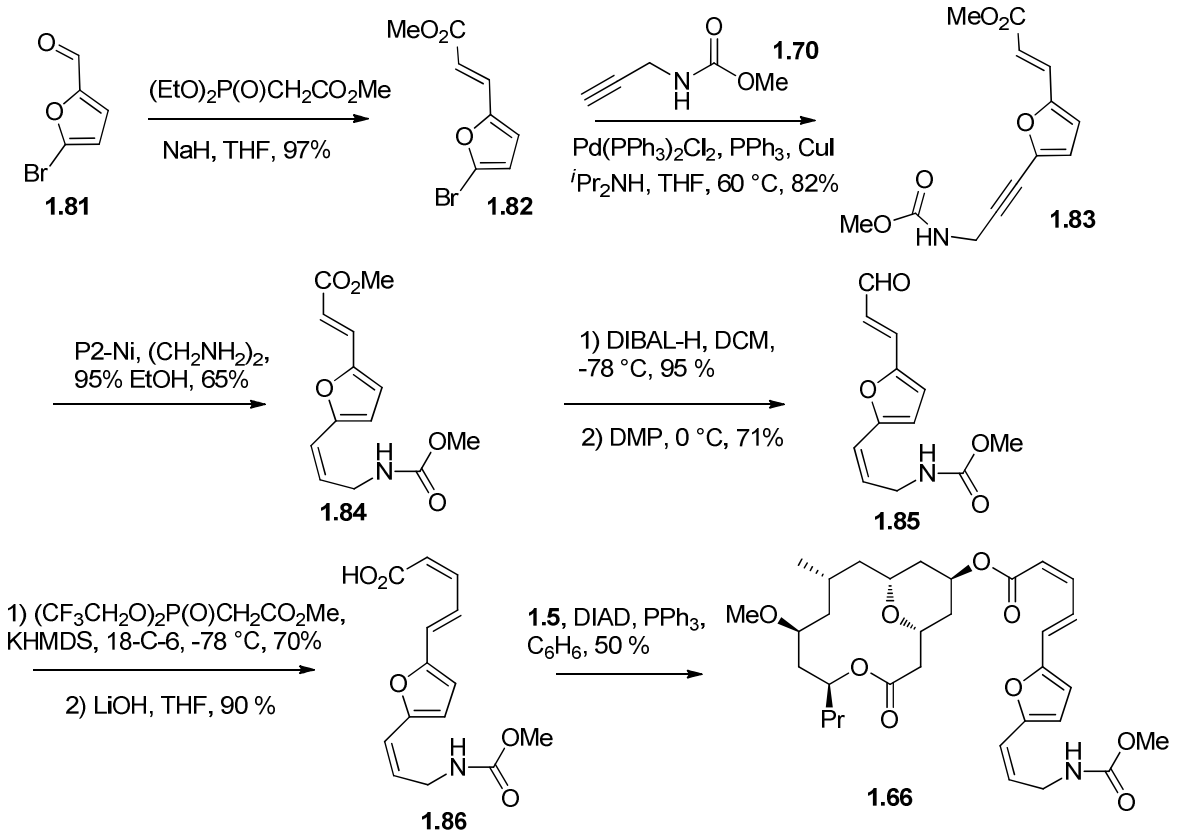
Scheme 1.16 Synthesis of the pyridine-containing analog.

III. Simplification with Furanyl Group

The sequence for furanyl analog started from commercially available reagent 5-bromo-2-furaldehyde **1.81** (Scheme 1.17). Chain extension through a Horner-Wadsworth-Emmons reaction produced **1.82** nearly quantitatively. While the newly-formed conjugated double bond could be easily reduced with the $NaBH_4$-CuCl system, a significant amount of debromination occurred. We thought the $NaBH_4$-CuCl system would preferably occur on a *trans*-alkene and we might evade this problem by first performing a Sonogashira reaction. Thus a Sonogashira coupling was performed to introduce the carbamate fragment in 82% yield. Much to our surprise,

treatment of the Sonogashira product **1.83** with $NaBH_4$-CuCl led to a complete reduction from the alkyne to an alkane before the reduction of the desired *trans*-alkene. Considering the result reported by Maier[10f] that the analog **1.47** with an additional *trans*-double bond was equally potent to the natural product, we decided to retain this double bond.

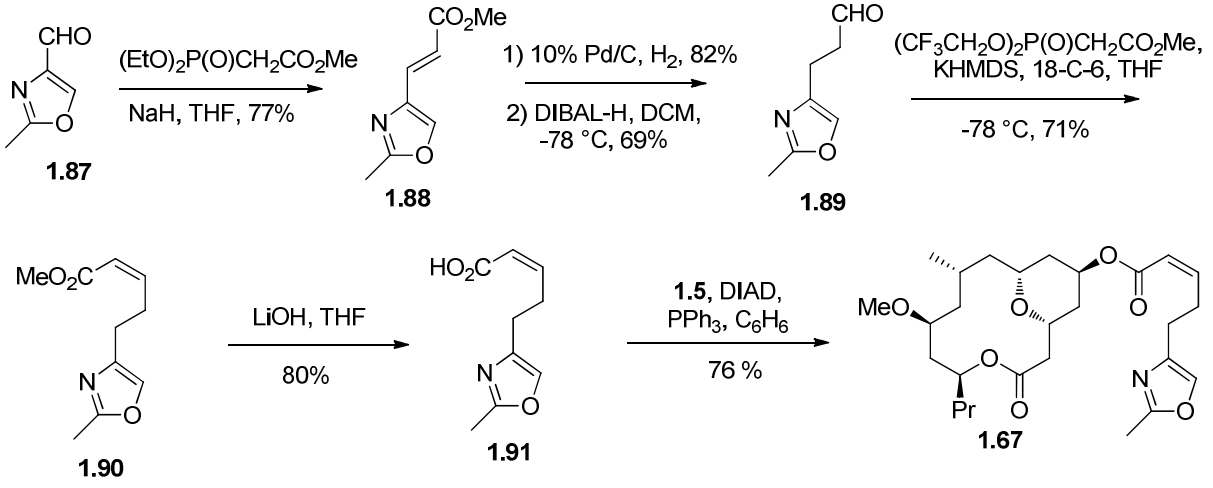
Thus, the Sonogashira product **1.83** was reduced with the P2-nickel catalyst to afford the desired *cis*-alkene **1.84** in 65% yield. DIBAL-H reduction led to a complete reduction of the conjugated ester to the corresponding alcohol, which was then oxidized with Dess-Martin reagent[28] to afford the aldehyde **1.84**. Still-Genarri condensation followed by hydrolysis yielded the conjugated side chain acid **1.86**, which went through a Mitsunobu esterification to provide the final furanyl analog **1.66**.



Scheme 1.17 Synthesis of the furanyl analog.

IV. Simplification with Des-Carbamate Side Chain

The sequence to prepare the shortened oxazole side chain without the carbamate group was smoothly completed in 5 steps (Scheme 1.18). The commercially available starting material, 2-methyloxazole-4-carboxaldehyde **1.87**, underwent a Horner-Wadsworth-Emmons reaction to prepare the chain extended product **1.88** in 77% yield. Hydrogenation with 10% Pd/C followed by a selective reduction provided the aldehyde **1.89** in good yield. Still-Genarri condensation afforded the *cis*-alkene **1.90** in 71% yield, which under hydrolysis produced the shortened oxazole side chain acid **1.91** in 80% yield. Finally a Mitsunobu reaction with the macrolactone alcohol **1.5** furnished the des-carbamate analog **1.67** in a good yield.



Scheme 1.18 Synthesis of the des-carbamate analog.

1.3 BIOLOGICAL STUDIES

Next we sought to explore the potency of neopeltolide **1.2**, the macrolactone modified analogs **(1.49**, **1.51**, **1.53**, **1.56**, **1.57**, **1.59** and **1.63)** and the side chain modified analogs (**1.64-1.67**). The biological assays were conducted by Dr. Balachandran in the research group of Professor Billy

Day from School of Medicine, University of Pittsburgh. Human colon carcinoma cell line (HCT116) and an isogenic p53 knock-out control of HCT116 cells with p53 knock-out were used to evaluate the antiproliferative potency of these compounds. An MCF-7 breast carcinoma cell line obtained from Georgetown University was also studied, and this cell line is known to be more resistant than the commonly used MCF7 (ATCC® HTB-22™). The obtained GI_{50} values are listed in Table 1.1.

To confirm that the synthetic neopeltolide **1.2** is the same as previously reported, we evaluated its potency against the HCT116 cell line. Compound **1.2** inhibited growth of HCT116 cells with a GI_{50} of 0.77 nM, which is in close agreement with the data reported by Kozmin (0.50 nM).[5c]

Next we analyzed the effect of macrolactone modifications to their potencies. The two structurally closest analogs, the alkene analog **1.49** and C9-*epi* analog **1.51**, were slightly less potent than neopeltolide. The C8-hydroxy analogs **1.56** and **1.57**, epoxy analog **1.59** and amide analog **1.63**, showed 20~100 fold loss of potency against HCT116 cells, while the dihydroxy analog **53** showed 1000 times less potency against HCT116 cells. Interestingly, the profile of potency against HCT116-P53KO cells was different from against HCT116 cells. Neopeltolide **1.2** and analogs **1.49** and **1.51** were roughly 10 times less potent when P53 was knocked out, which suggests an important role of P53 in their mechanism against HCT116 cells. On the other hand, more polar analogs **1.53**, **1.56**, **1.57**, **1.59** and **1.63**, showed little loss of potency in P53KO cells, or even some gain.

In the MCF-7 cell line obtained from Georgetown University, neopeltolide **1.2** showed an effective inhibition with a GI_{50} of 6.96 μM, indicating a significant loss of potency when compared with the nanomolar potency in the commonly used MCF7 cells from ATCC. The C9-*epi* analog **1.51** and dihydroxy analog **1.53** were found to be more effective than the natural product. The sharp contrast of relative potencies between HCT116 and MCF-7 for the dihydroxy analog **1.53** might be additional evidence suggesting the selectivity of this class of macrolides against different cell lines, and this selectivity may be highly dependent on their subtle structural differences.

Table 1.1 Biological activities of neopeltolide and the analogs.

Compound	HCT116 GI_{50} [nM]	HCT116-P53KO GI_{50} [nM]	MCF-7 GI_{50} [nM]	Description
1.2	0.77	9.9	6960	neopeltolide
1.49	5.4	49	30000	alkene analog
1.51	6.6	50	1180	C9-*epi* analog
1.53	4300	4300	2770	dihydroxy analog
1.56	17	13	43600	C8-hydroxy analog
1.57	48	49	>50000	C9-*epi*-C8-*epi*-hydroxy analog
1.59	24	48	>50000	epoxy analog
1.63	66	68	>50000	amide analog
1.64	100	73	>50000	phenyl analog
1.65	2900	2300	4480	pyridine-containing analog
1.66	24	52	34800	Furanyl analog
1.67	730	550	>50000	des-carbamate analog

When analyzing the modification on the side chain, we found that for HCT116 cells phenyl analog **1.64** and furanyl analog **1.66** showed roughly 20~100 fold less potency than neopeltolide, but comparable potency when p53 was knocked out. The pyridine-containing analog **1.65** showed a significant loss against HCT116 cells, but better potency against MCF-7 cell line than the natural product. The des-carbamate analog **1.67** showed significant loss of potency in all the cell lines tested, suggesting the essential role of the carbamate group for the full potency of neopeltolide.

1.4 SUMMARY

The total synthesis of neopeltolide was completed, together with the synthesis of eleven analogs with modifications focusing on the macrolactone and the side chain (Figure 1.9). Preliminary biological assays showed the selectivity of these analogs against different cancer cell lines. The potent antiproliferative activity of neopeltolide was found to be at least partly related to P53. The introduction of polar groups to the macrolactone and the introduction of simplified aromatic ring to the side chain led to different profiles of antiproliferative potencies against different cell lines, ranging from significant loss to appreciable gain.

The changes to C9 stereocenter (**1.49** and **1.51**), and the introduction of polar functional groups to the macrolactone (**1.56**, **1.57**, **1.59** and **1.63**), are both tolerated. Considering the overall antiproliferative potency and ease of modification, the C8-hydroxy analog **1.56** may be a good start point for further research of targeted drug delivery. The analog with two vicinal hydroxyl groups **1.53** is essentially inactive to HCT116 cells. The substitution of the oxazole ring with

simpler aromatic rings **1.64**, **1.65** and **1.67** is tolerated to a certain extent, and five-membered furan ring **1.67** provides antiproliferative GI_{50} values closest to those of the natural product **1.2**. The removal of the carbamate group **1.67** leads to a significant loss of potency. This clearly underscores the importance of the carbamate group to the potency of neopeltolide.

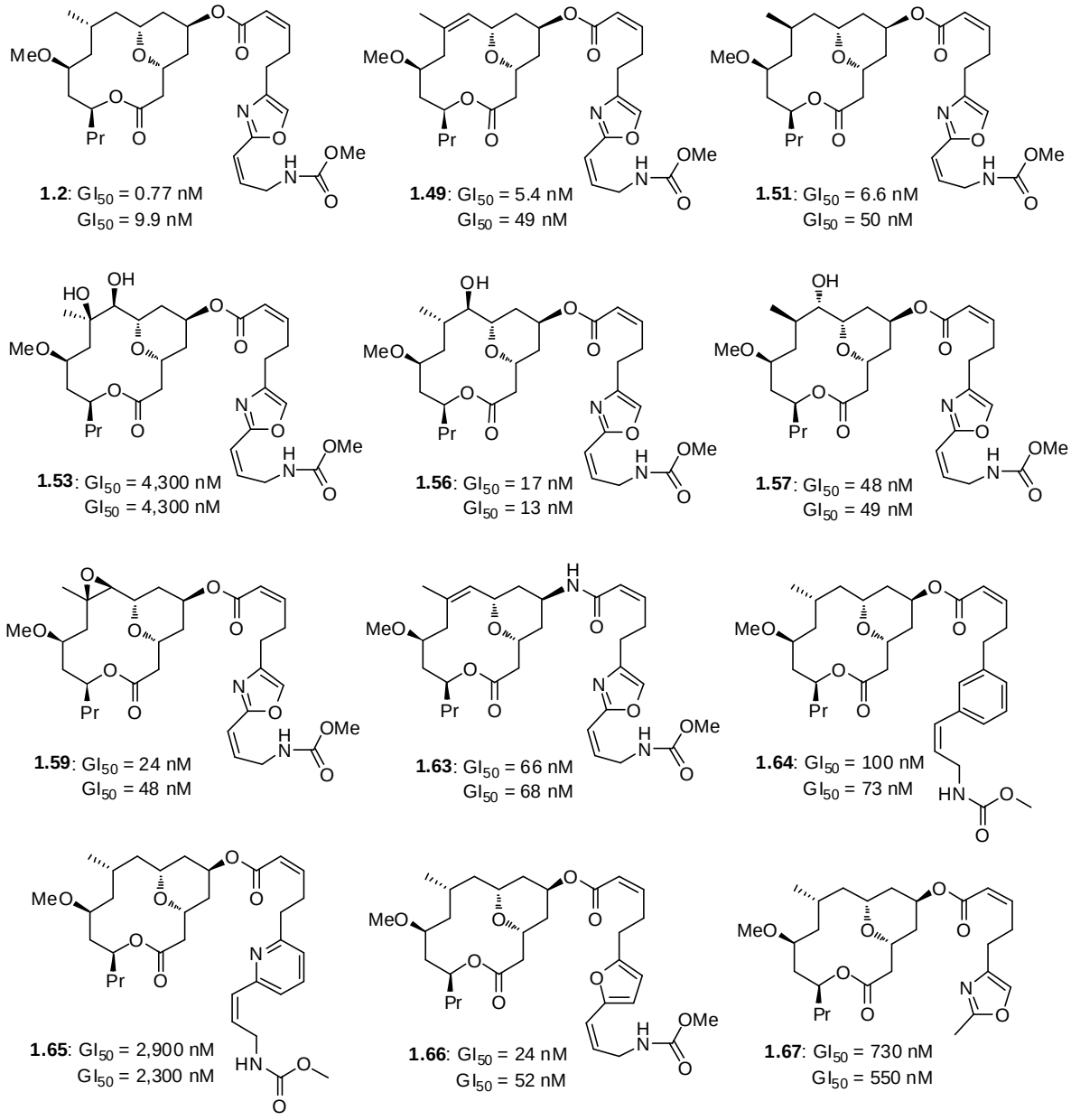


Figure 1.9 Neopeltolide and analogs.

top GI_{50} against HCT116; below GI_{50} against HCT116 with p53 knock-out

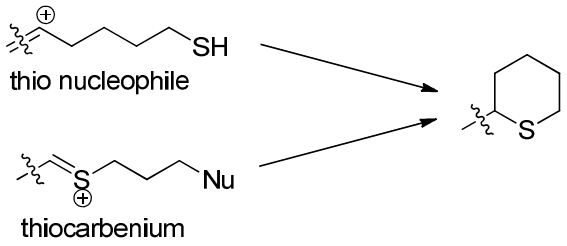
2. SYNTHESIS OF SULFUR-CONTAINING HETEROCYCLES THROUGH OXIDATIVELY GENERATED THIOCARBENIUM IONS

2.1 INTRODUCTION

2.1.1 Previous Methods for Synthesis of Sulfur-Containing Heterocycles

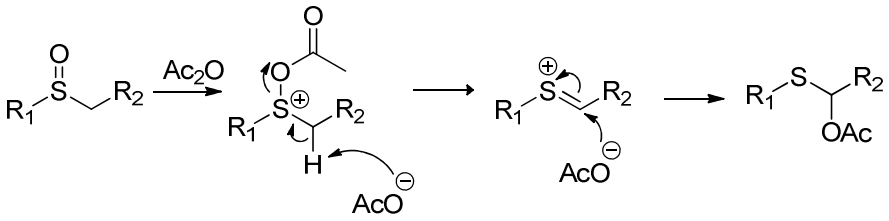
Organic sulfides are widely recognized as versatile functional groups in organic chemistry. Compared with theire oxygen counterparts, organic sulfides are more nucleophilic and less basic, and can be easily transformed into a variety of derivatives via hydrogenolysis, oxidation, olefination and rearrangement,[29] thus providing additional opportunities for structural diversification. The versatility of sulfur has been demonstrated in the construction of a number of synthetic targets.[30] Sulfur is also among one of the most abundant elements of life, primarily being an essential component in many proteins and cofactors.[31] In some other cases, sulfur exists in heterocycles that are important structural subunits in many biologically active molecules.[32]

In contrast to ethers,[33] methods for the synthesis of sulfur containing heterocycles are relatively limited. Of various methods reported for the synthesis of sulfur containing heterocycles,[34-36] the two most successful strategies utilize the nucleophilic nature of thio species[35] and the intermediacy of thiocarbenium ions[36] (Scheme 2.1).



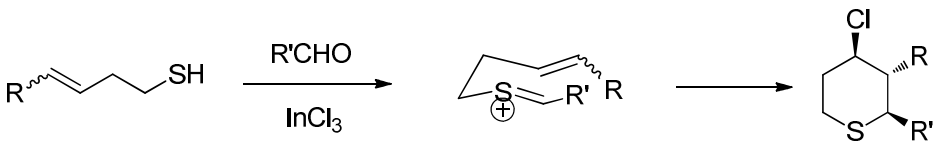
Scheme 2.1 Two major synthetic strategies for sulfur containing heterocycles.

Thiocarbenium ions are attractive intermediates for the synthesis of sulfur-containing compounds.[37] Traditionally, the Pummerer reaction has been utilized to generate thiocarbenium ions (Scheme 2.2)[38]. The classic Pummerer reaction involves an acylation of a sulfoxide by an anhydride, followed by elimination to form the thiocarbenium ion and thus to expose the reactive site on the adjacent carbon. The thiocarbenium ion is then trapped with acetate or other nucleophiles where applicable. The classic Pummerer reaction generally requires harsh acidic initiators, and in most cases forms *exo* product when appended nucleophiles are used.[39]



Scheme 2.2 Pummerer reaction.

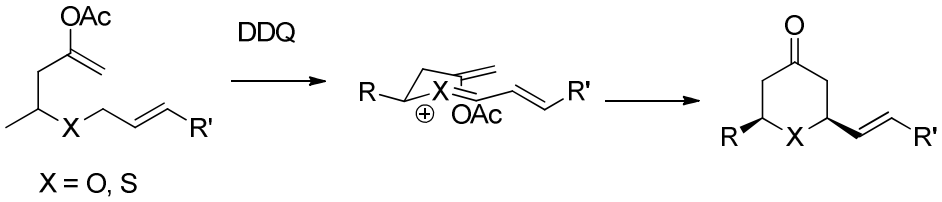
Another way to generate thiocarbenium ion strategy is via thia-Prins-type reactions in which ring formation occurs through homoallylic mercaptans with aldehydes in the presence of an acid catalyst (Scheme 2.3). This method was first described by Li,[36a] and further developed by other research groups.[36b-i]



Scheme 2.3 Thia-Prins type reaction.

2.1.2 Oxidative C-H Bond Cleavage

Selective and efficient oxidative activation of the C-H bond adjacent to a heteroatom (such as N or O) has been widely investigated and successfully used in the synthesis of a number of natural products and pharmaceuticals.[40] Dr. Tu and Dr. Liu in the Floreancig group have developed a stereoselective synthetic route for the preparation of tetrahydropyrones, whereby allylic or benzylic ethers are oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to generate oxocarbenium ions that react with appended enol acetate nucleophiles(Scheme 2.4).[41] In the postulated chair transition state, the substituent R assumes an equatorial position and the α,β-unsaturated oxocarbenium ion exists in (*E*)- geometry. Therefore, the reaction generates 2,6-*cis* disubstituted tetrahydropyrones with excellent stereocontrol.

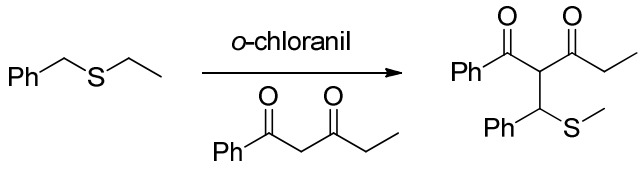


Scheme 2.4 Six-membered heterocycle synthesis through oxidative C-H bond cleavage.

By a simple analogy to their oxygen counterparts, the desired thiocarbenium ions may also be oxidatively generated from corresponding allyl sulfides. Sulfur is larger than oxygen, so the orbital overlap between sulfur and the adjacent carbon in thiocarbenium ions may not be as good as the orbital overlap between oxygen and carbon in oxocarbenium ions. On the other hand, sulfur atom is less electronegative. A few studies have shown that the energetic difference between thiocarbenium ions and oxocarbenium ions is small.[42] With respect to stereoselectivity, due to the fact that carbon-sulfur bonds are significantly longer than carbon-oxygen bonds,[43a] the

energy penalty of *(Z)*-geometry of the thiocarbenium ions over *(E)*-geometry [43b] may be smaller than the corresponding oxocarbenium geometries. Therefore it is reasonable to assume lower stereoselectivities from thiocarbenium ions intermediates.

In 2007, Zhiping Li and coworkers [44] attempted a similar approach, whereby *o*-chloranil instead of DDQ was utilized to effect a C−H bond oxidation on benzyl sulfides to generate thiocarbenium ions, followed by an intermolecular nucleophilic attack (Scheme 2.5). Though limited by the scope of substrates and nucleophiles, this method sheds light onto the feasibility of synthesizing sulfur containing heterocycles via DDQ mediated oxidative C-H bond cleavage.



Scheme 2.5 C-H bond oxidation of benzyl sulfide with o-chloranil.[44]

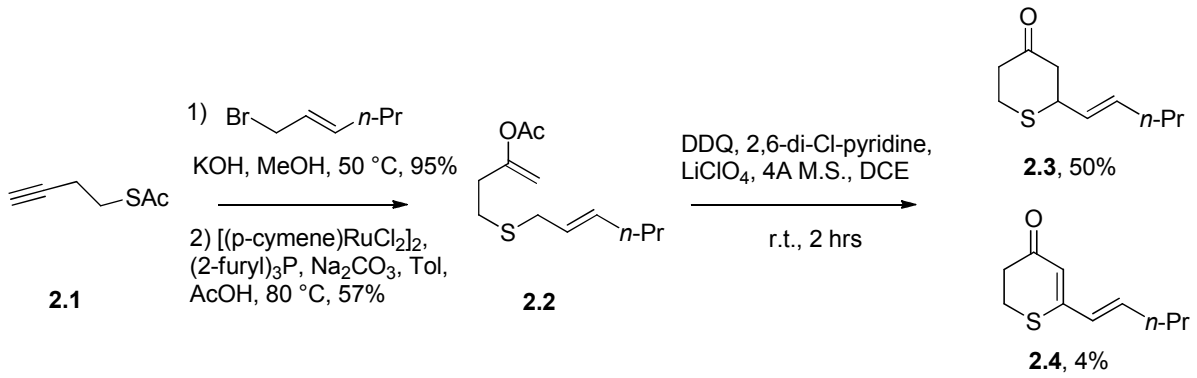
2.2 SYNTHESIS OF SULFUR CONTAINING HETEROCYCLES THROUGH DDQ MEDIATED OXIDATIVE C-H BOND CLEAVAGE

To provide a new alterative in addition to the limited number of synthetic methods for sulfur containing heterocycle synthesis, we decided to approach tetrahydrothiopyrones and tetrahydrothiophenes through oxidatively generated thiocarbenium ions and appropriate appended nucleophiles. We investigated the types of sulfides that are used to generate

thiocarbenium ions and the types of appended nucleophiles, and synthesized a series of substrates for the development of this synthetic methodology.

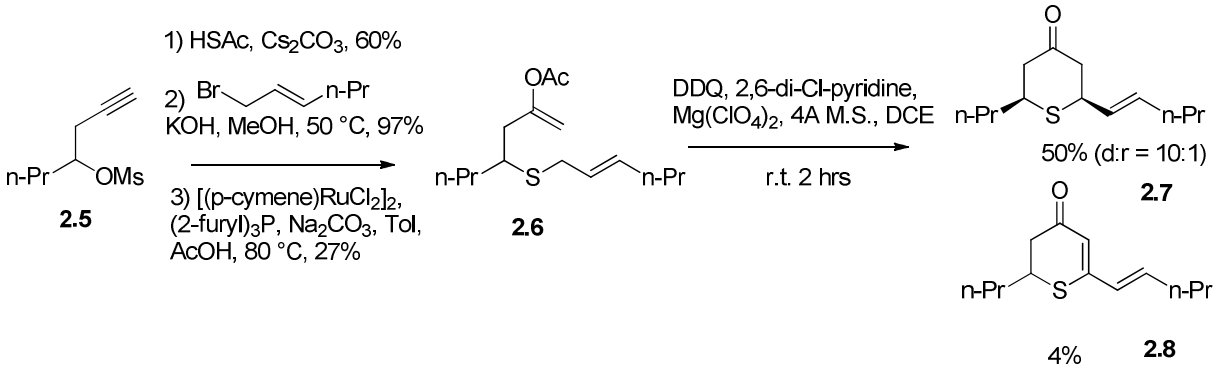
2.2.1 Synthesis of Tetrahydrothiopyrone Using Thiocarbenium Ions Generated from Allylic and Benzylic Sulfides

Our initial approach was to mimic our route to the formation of tetrahydropyrones developed by former group members Dr. Wang and Dr. Liu. The strategy involved the oxidative C-H bond cleavage of allylic or benzylic ethers with DDQ to yield oxocarbenium ions, and the incorporation of an enol acetate as an appended nucleophile that had been proved to be compatible with DDQ mediated oxidative cyclization. Thus, substrate 2.2 was prepared and subjected to the DDQ oxidation conditions (Scheme 2.6). A simple nucleophilic substitution of (*E*)-1-bromohex-2-ene with but-1-yn-4-yl thioacetate **2.1** afforded the allyl sulfide intermediate in an excellent yield. The alkynyl group was then converted to the enol acetate **2.2** in 57% yield via a ruthenium-catalyzed Markovnikov addition with AcOH.[45] Substrate **2.2** was then treated with DDQ in 1,2-dichloroethane (DCE) in the presence of 4Å molecular sieves as the water scavenger and 2,6-dichloropyridine as the base. The cyclization was complete within 2 hours at room temperature, providing the desired tetrahydrothiopyranone **2.3** in 50% yield and over-oxidation side product **2.4** in 4% yield. The addition of $LiClO_4$ to the reaction mixture is believed to help reducing the formation of **2.4**, presumably due to the stabilization of the radical anion of DDQ that forms from the initial single electron transfer. Besides $LiClO_4$, $Mg(ClO_4)_2$ was also found to be as effective in this role.



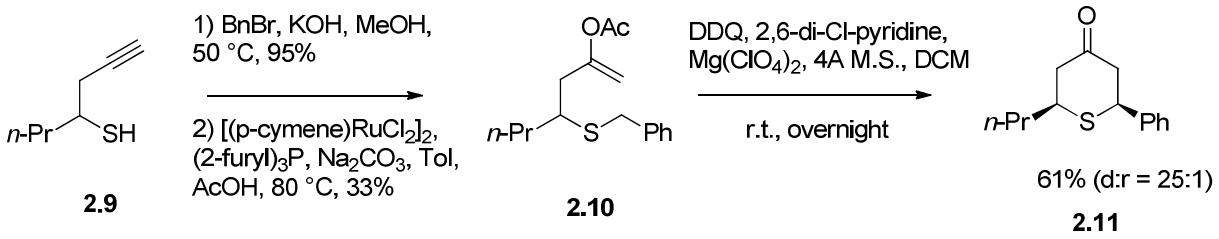
Scheme 2.6 Synthesis of a simple allyl sulfide and its cyclization reaction.

To investigate the stereoselectivity of the reaction, secondary allyl sulfide **2.6** was synthesized in a very similar route as illustrated in Scheme 2.7. It should be noted that the ruthenium-catalyzed Markovnikov addition afforded the desired internal enol acetate in only 27% yield, while the major products were terminal enol acetates. Substrate **2.6** reacted with DDQ to yield **2.7** as a diastereomeric mixture at 10:1 ratio with *cis*-product being preferred, confirming that the (*E*)-thiocarbenium ion is the dominant reactive species in the reaction process. The over-oxidation side product **2.8** was also isolated from this reaction.



Scheme 2.7 Synthesis of substituted allyl sulfide and its cyclization reaction.

Benzyl sulfide **2.10** was similarly synthesized and subjected to the cyclization reaction (Scheme 2.8). The cyclization reaction with benzyl substrate **2.10** afforded the desired *cis*-tetrahydrothiopyranone **2.11** in higher yield (60%) than the reaction with allyl sulfide substrate **2.6**, with an excellent diastereomeric ratio of 25:1. No over-oxidation was observed even after the reaction was allowed to proceed at room temperature overnight. We postulate that the benzylic carbonhydrogen bond in the product does not overlap the *p*-orbitals of the aromatic ring, thereby greatly slowing further oxidation of the desired product.



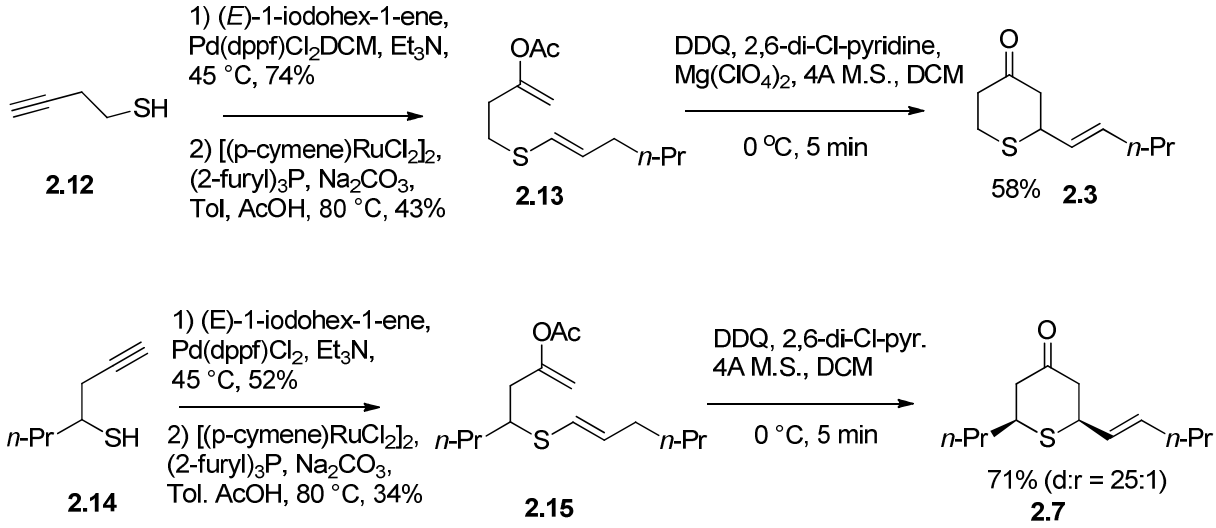
Scheme 2.8 Synthesis of substituted benzyl sulfide and its cyclization reaction.

2.2.2 Synthesis of Tetrahydrothiopyrone Using Thiocarbenium Ions Generated from Vinyl Sulfides

The over-oxidation problem observed with allyl sulfide substrates is believed to be related to the similar oxidation potentials between the substrates and the desired products, and thus comparable oxidation rates of the two species to form thiocarbenium ions. Previous mechanistic studies in the Floreancig group and other groups revealed that vinyl substrates have lower oxidation potential than allyl substrates, and usually lead to faster generation of corresponding oxocarbenium ion intermediates.[46] Therefore we postulated that vinyl sulfides would overcome the over-oxidation problem and improve the efficiency of the reaction. Additionally, vinyl

sulfides are attractive substrates because these structures can be accessed through a number of new metal mediated protocols.[47]

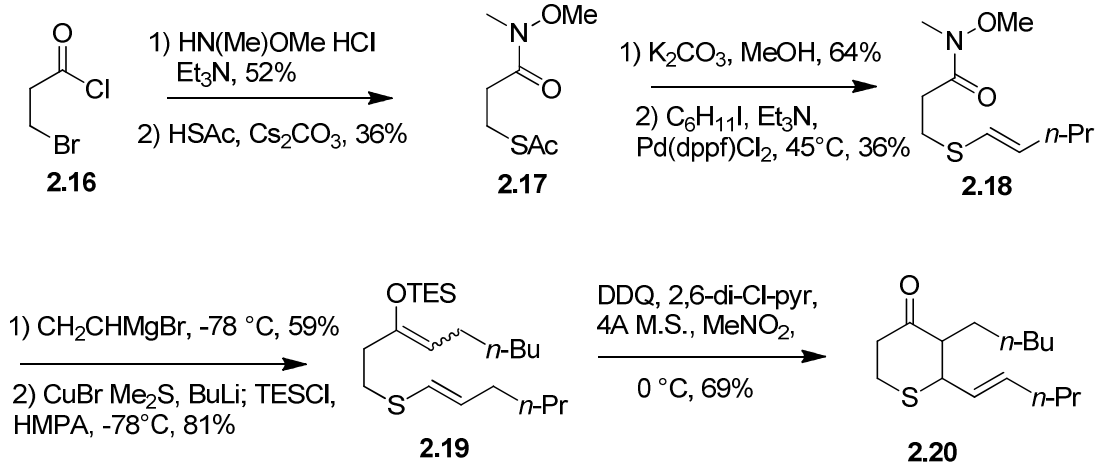
Vinyl substrates **2.13** and **2.15** were synthesized and subjected to the DDQ oxidation reactions as illustrated in Scheme 2.9. An efficient palladium-mediated coupling reaction[48] between but-3-yne-1-thiol **2.12** and (*E*)-1-iodohex-1-ene led to the formation of a vinyl sulfide structure, which was subjected to the ruthenium catalyzed Markovnikov addition conditions to afford the desired substrate **2.13**. Exposing **2.13** to DDQ provided **2.3** in 58% isolated yield within 5 min at 0 °C with no observable formation of the over-oxidation side product **2.4**. Secondary vinyl sulfide **2.15** was prepared from **2.14** and subjected to the DDQ mediated reaction conditions to afford the desired *cis*- cyclization product **2.7** in 71% yield with an excellent 25:1 dr. Compared with the aforementioned allyl sulfides, both of these vinyl sulfides substrates require lower reaction temperature and much shorter reaction time, yet afford the desired products in better yields and higher stereoselectivity when secondary sulfides are used.



Scheme 2.9 Synthesis of vinyl sulfides and their cyclization reactions.

2.2.3 Synthesis of Tetrahydrothiopyrone with 2,3-Stereoselectivity Using Enol Silane and Enol Carbamates

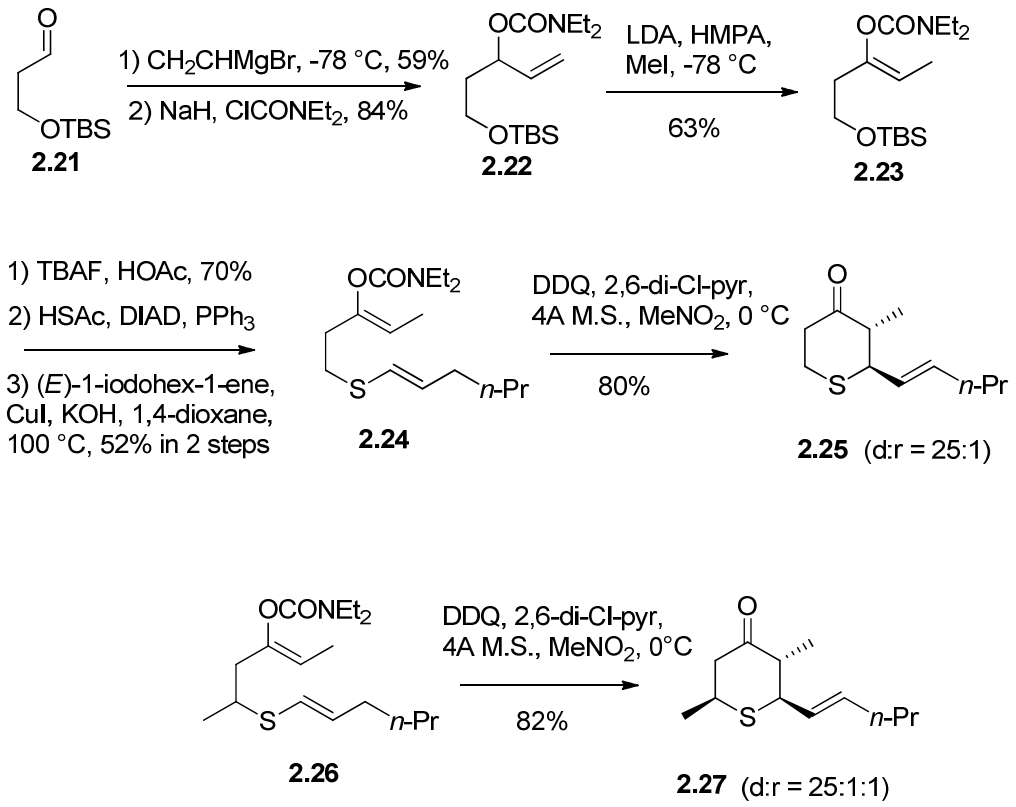
Employing substituted nucleophiles instead of unsubstituted enol acetates may lead to the formation of 2,3-disubstituted cyclization products, thus expanding the scope and versatility of this method. Initially we demonstrated this concept by using substituted enol silanes as a *Z/E* mixture, as shown in Scheme 2.10. Commercially available 3-bromopropanoyl chloride **2.16** was reacted with *N,O*-dimethylhydroxylamine hydrochloride to form a Weinreb amide, followed by a nucleophilic replacement with potassium thioacetate to obtain intermediate **2.17**. The thioacetate group was hydrolyzed and coupled with (*E*)-1-iodohex-1-ene to yield vinyl sulfide **2.18**. The Weinreb amide group was then converted to enone by reacting with vinyl magnesium bromide at low temperature, followed by a cupper(I) mediated silylation reaction to afford the desired substituted enol silanes **2.19** with 1.2:1 *Z/E* ratio. The cyclization reaction of this *Z/E* substrate mixture afforded the desired 2,3-disubstituted tetrahydrothiopyranone in good yield as an inseparable mixture with a 1:0.6 *trans:cis* ratio.



Scheme 2.10 Synthesis of vinyl sulfide with appended enol silane as a *Z/E* mixture and its cyclization reactions

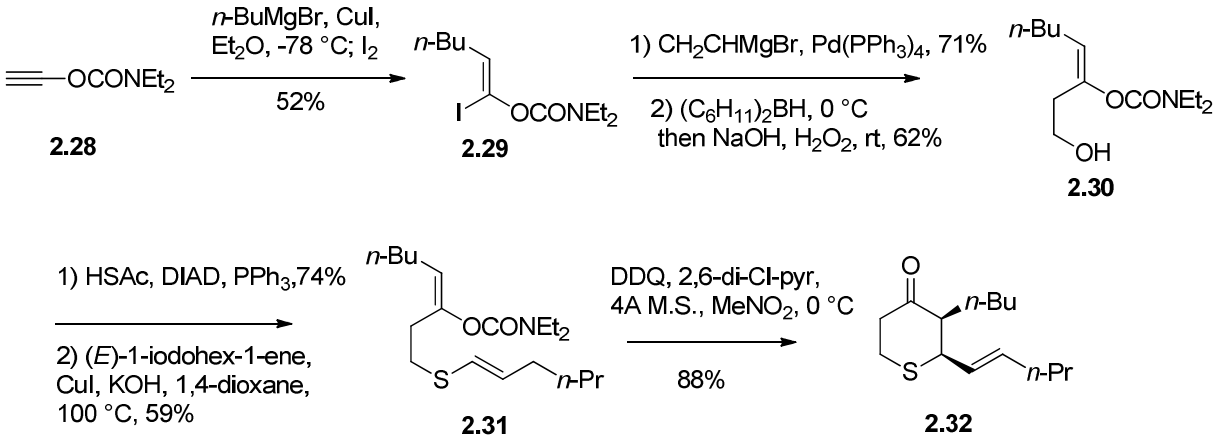
To precisely control the stereochemical outcome of the 2,3-disubstituted cyclization product, the substituted nucleophiles in the substrates need to be prepared with a high degree of geometrical control. The geometries of internal enol acetates and internal enol silanes are difficult to control. Several different approaches to achieve the desired geometry on these two species were tried, but none of them afforded satisfactory geometrical selectivity. Finally we were able to solve this problem by preparing the desired *(Z)*- and *(E)*- enol carbamates through two different routes (Scheme 2.11 and 2.12).

The preparation and cyclization of *(Z)*-enol carbamate **2.24** is shown in Scheme 2.11. A Grignard reaction between aldehyde **2.21** and vinyl magnesium bromide at low temperature, followed by a straightforward acylation, led to the formation of allyl carbamate **2.22**. Upon treatment with LDA in the presence of HMPA at low temperature,[49] the allyl carbamate **2.22** isomerized to the desired *(Z)*-enol carbamate **2.23**. The silyl ether protecting group was cleaved with TBAF (buffered with acetic acid), replaced with thioacetic acid under Mitsunobu conditions,[50] and coupled with (*E*)-1-iodo-1-hexene under the catalysis of copper(I) iodide and potassium hydroxide[51] to form **2.24**. Although the coupling reaction conditions were originally developed for thiols, we found thioesters could be used with similar efficiency, presumably due to *in situ* cleavage of thioesters with potassium hydroxide. Therefore the necessity of converting thioesters to thiols was eliminated. Treatment of the *(Z)*-enol carbamate substrate **2.24** with DDQ rapidly afforded the cyclization product **2.25** in 80% yield with 25:1 dr favoring 2,3-*trans* product. When branched substrate **2.26** was used, the reaction also ran very smoothly with high stereocontrol favoring 2,3-*trans* and 2,6-*cis* stereochemical outcome.



Scheme 2.11 Synthesis of vinyl sulfides with *(Z)*-enol carbamate and cyclization reactions.

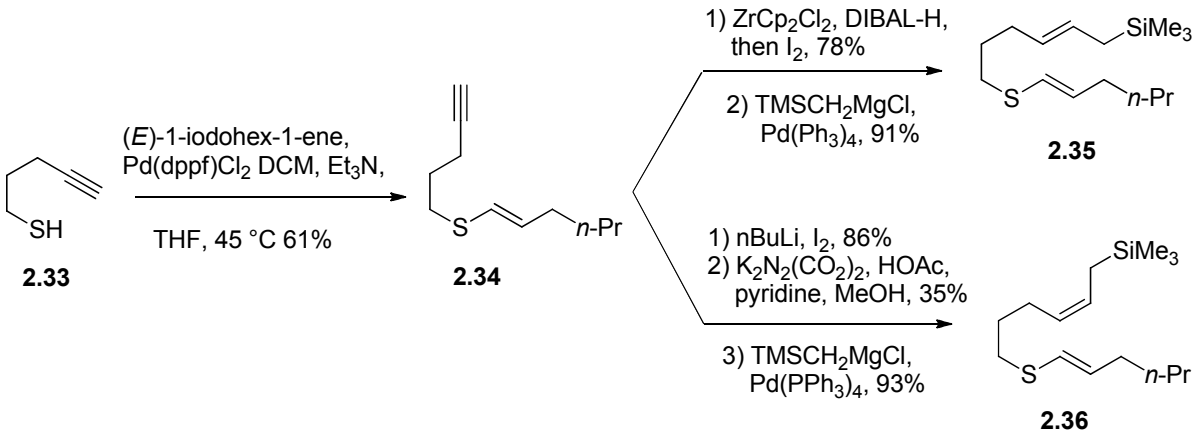
For the *(E)*-enol carbamate substrate **2.31**, a different synthetic route was designed as illustrated in Scheme 2.12. Vinyl iodide **2.29** with the desired geometry was prepared by exposing alkynyl carbamate **2.28** to Marek's carbocupration/iodination sequence.[52] The following Kumada coupling, hydroboration, Mitsunobu reaction and copper catalyzed coupling reaction provided the *(E)*-enol carbamate substrate **2.31**. Exposing **2.31** to DDQ oxidation afforded 2,3-*cis*-product **2.32** in 88% yield as a single stereoisomer (as determined by NMR) within a few minutes at 0 °C.



Scheme 2.12 Synthesis of vinyl sulfide with *(E)*-enol carbamate and cyclization reaction.

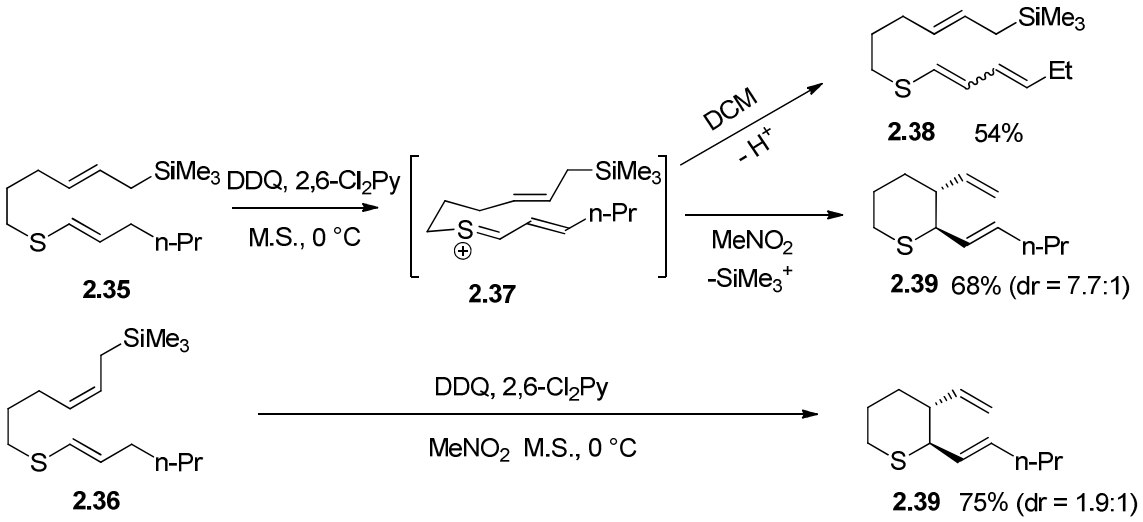
2.2.4 Synthesis of Tetrahydrothiopyran Derivatives with 2,3-Stereocontrol Using Allylsilane

Another way to achieve 2,3-stereoselectivity is through using π nucleophiles such as allylsilanes, which were shown to be efficient nucleophiles in similar reactions.[53] Palladium catalyzed coupling between thiol **2.33** and (*E*)-1-iodo-1-hexene afforded the common intermediate **2.34** for preparing both *trans*- and *cis*- allylsilane substrates. Treatment of the alkynyl group with *in situ* prepared Schwartz's reagent followed by iodine quenching[54] and a subsequent palladium catalyzed Kumada coupling with trimethylsilyl methylmagnesium chloride,[55] afforded *trans*-allylsilane **2.35** in high yields. For *cis*-allylsilane substrate **2.36**, the alkynyl group was first converted to an alkynyl iodide, then reduced with *in situ* generated diimide to obtain the desired *cis*- geometry and coupled under Kumada conditions to introduce the allylsilane moiety.



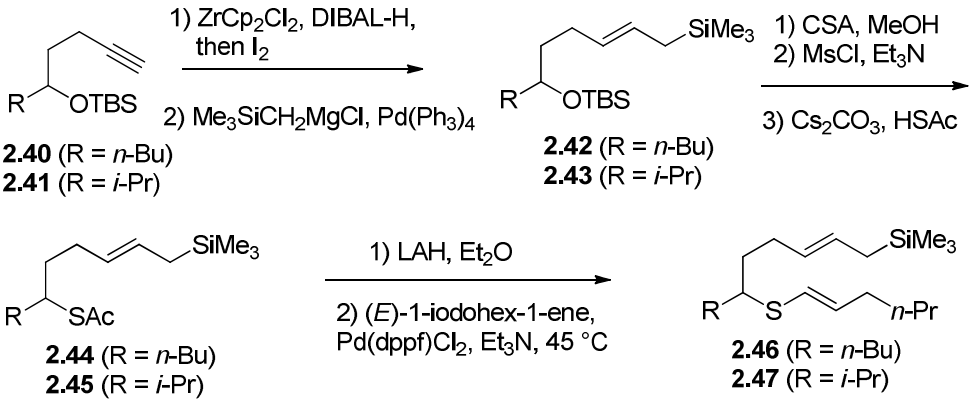
Scheme 2.13 Synthesis of vinyl sulfides with allylsilane nucleophile.

Oxidative cyclization with allylsilanes nucleophiles are greatly affected by the choice of solvent. When methylene chloride was used, dienyl sulfide **2.38** was the major product of the reaction, probably resulting from the deprotonation of thiocarbenium ion **2.37** (Scheme 2.14). When more polar solvent $MeNO_2$ was used, the oxidation of *trans*-allylsilane substrate **2.35** led to the formation of 2,3-*trans* tetrahydrothiopyran derivatives **2.39** in 68% yield with a 7.7:1 dr. With *cis*-allylsilane substrate **2.36**, the cyclization reaction also led to the formation of 2,3-*trans* tetrahydrothiopyran **2.39** as the main product but with only 1.9:1 dr.



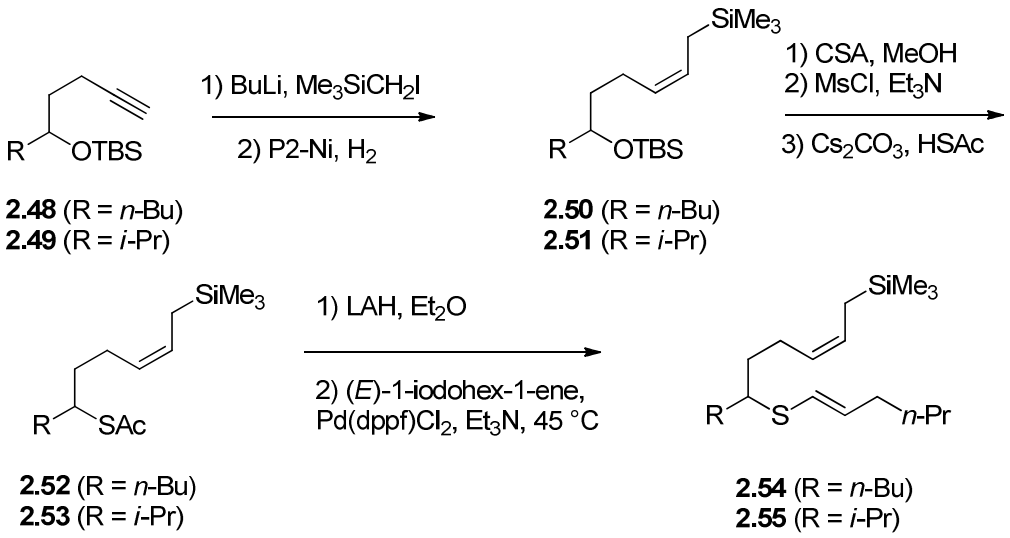
Scheme 2.14 Cyclization reaction of vinyl sulfides with allylsilane nucleophile.

To further derivatize the cyclization products and expand the scope of the reaction, several other substituted allylsilane substrates were prepared and investigated. Scheme 2.15 shows a modified synthetic route for substituted *trans* allylsilane substrates. The allylsilane group was first installed in **2.42/2.43** using hydrozirconation/iodination [54] and Kumada coupling,[55] followed by deprotection of the silyl ether, mesylation and thiolation to obtain intermediate **2.44/2.45**. Reduction with lithium aluminum hydride and subsequent palladium catalyzed coupling reaction afforded the desired *trans*-substrates **2.46/2.47**.



Scheme 2.15 Synthesis of secondary vinyl sulfides with *trans*-allylsilane nucleophiles.

For the preparation of substituted *cis*- allylsilane substrates **2.54/2.55** (Scheme 2.16), the desired *cis*- geometry in **2.50/2.51** was installed by a partial hydrogenation of the corresponding propargyl silane catalyzed with *in situ* prepared P2 nickel.[21] The silyl protected alcohol was then converted to vinyl sulfide **2.54/2.55** by deprotection, mesylation, thiolation, reduction and palladium catalyzed coupling reaction.

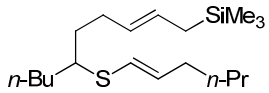
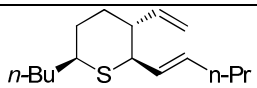
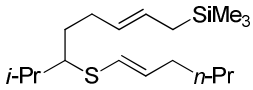
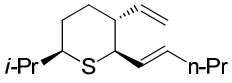
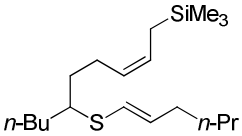
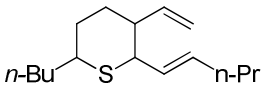
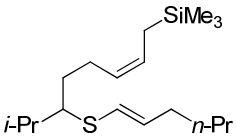
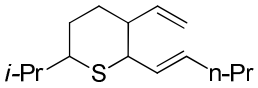


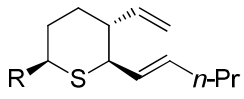
Scheme 2.16 Synthesis of secondary vinyl sulfides with *cis*-allylsilane nucleophile.

The results of oxidative cyclization in $MeNO_2$ on the substituted *trans*-/*cis*- allylsilanes in Scheme 2.15 and 2.16 are summarized in table 2.1. The additional *n*-butyl or *i*-propyl substituents in these substrates led to the formation of four diastereomeric products as shown in Figure 2.1 denoted as *o-trans-m-cis* **2.58**, *o-trans-m-trans* **2.59**, *o-cis-m-cis* **2.60** *and o-cis-m-trans* products **2.61**. The cyclization of substituted *trans*- allylsilanes afforded good stereoselectivities, with the expected *o-trans-m-cis* products being major products. However, the cyclization of substituted *cis*- allylsilanes led to the formation of a mixture of *o-trans-m-cis* and *o-cis-m-trans* products in a nearly 1:1 ratio and other minor diastereomers. The stereo structures of these products were determined by NOESY and coupling constant analysis. Also note that

increasing the size of the substituent on the *cis*- allylsilanes from *n*-butyl to *i*-propyl has no effect in improving *o*-selectivity.

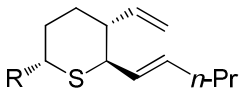
Table 2.1 Cyclization of substituted allylsilane substrates.

Substrate	Major product	Total yield (%)	dr (*o-t-m-c: o-t-m-t: o-c-m-c: o-c-m-t*)
 **2.46**	 **2.56**	68	1.0: 0.18:0.09:0.05
 **2.47**	 **2.57**	79	1.0: 0.14: 0.09: 0.04
 **2.54**		87	1.0: 0.17 : 0.17 : 0.80
 **2.55**		72	1.0: 0.14 : 0.12 : 1.0



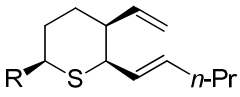
2.58

o-trans-m-cis



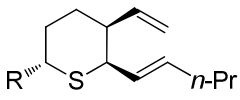
2.59

o-trans-m-trans



2.60

o-cis-m-cis



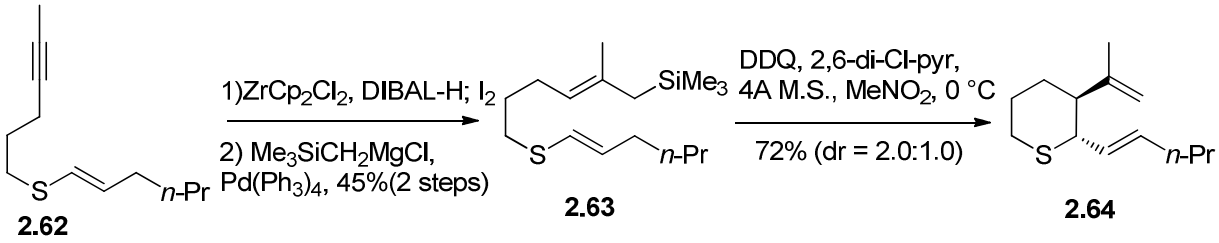
2.61

o-cis-m-trans

Figure 2.1 Four diastereomeric products resulting from substituted allylsilanes.

R: *n*-butyl, *iso*-propyl

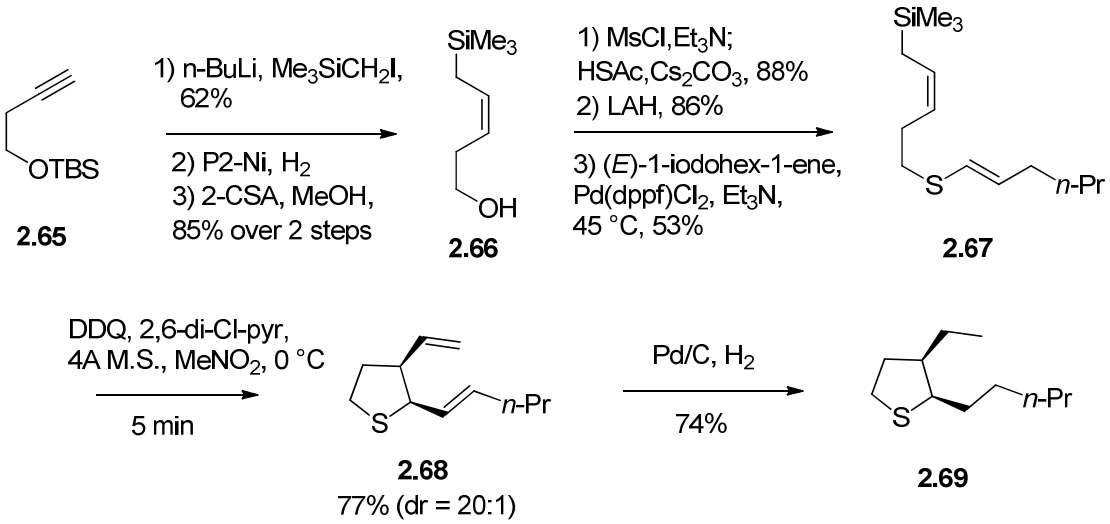
Tri-substituted allylsilane **2.63** was prepared in two steps from **2.62** (Scheme 2.17). The following cyclization reaction led to the formation of **2.64** in a 72% yield with a 2:1 dr favoring 2,3-*trans* product. The diastereomeric ratio was fairly close to the *(Z)*-allylsilane substrate **2.36** as described in Scheme 2.14.



Scheme 2.17 Cyclization of tri-substituted allylsilane.

2.2.5 Synthesis of Tetrahydrothiophene

Tetrahydrothiophenes could also be accessible through the present oxidative cyclization reaction with one less carbon atom in the substrate structures. We investigated their synthesis by only choosing substrates with vinyl sulfide and allylsilane functionalities. As shown in Scheme 2.18, (*Z*)-allylsilane substrate **2.67** was synthesized and oxidatively cyclized in a very similar route. Homopropargyl silyl ether **2.65** was deprotonated and reacted with trimethylsilyl methyl iodide, followed by a partial hydrogenation of the triple bond catalyzed with *in situ* prepared P2 nickel catalyst[21] and deprotection of the silyl ether to afford **2.66**. A standard sequence of mesylation, reduction and coupling reaction led to the formation of the desired substrate **2.67**. The cyclization reaction rapidly afforded tetrahydrothiophene **2.68** in a 20:1 diastereomeric ratio favoring 2,3-*cis* stereochemistry. The 2,3-*cis* stereochemistry was confirmed by further hydrogenation to **2.69** and compared with literature reported NMR data.[56]



Scheme 2.18 Synthesis of tetrahydrothiophene through *cis*-allylsilane.

2.3 DISCUSSION

2.3.1 Proposed Mechanism for Reactions with Allyl and Vinyl Sulfides

The approach of extending the DDQ mediated oxidative C-H bond cleavage strategy from allyl or vinyl ether substrates to their sulfur counterparts has proved to be very successful. Under similar reaction conditions to allyl ethers or vinyl ethers, the cyclizations on allyl sulfides and vinyl sulfides proceed smoothly as expected with moderate to good yields and, in many cases, excellent stereoselectivities.

A proposed mechanism for the cyclization of allyl sulfide **2.2** and the formation of side product is shown in Figure 2.2. A single electron transfer reaction on **2.2** generates the radical cation **2.70**,

followed by a hydrogen atom abstraction by the DDQ radical anion **2.71** to form the α,β-unsaturated thiocarbenium ion **2.72**. An intramolecular nucleophilic attack from the enol acetate group, via a chair transition state, leads to the formation of the cyclization product **2.3**. The resulting acylium ion (not shown) was quenched by 2,6-dichloropyridine, thus facilitating the cyclization process. During the reaction, $LiClO_4$ presumably stabilizes the radical anion **2.70** and acts as a catalyst. Due to comparable oxidation potentials of the starting material **2.2** and the desired product **2.3**, **2.3** may be further oxidized by DDQ under the reaction conditions to form undesired thiocarbenium ion **2.74** and eventually afford the side product **2.4**.

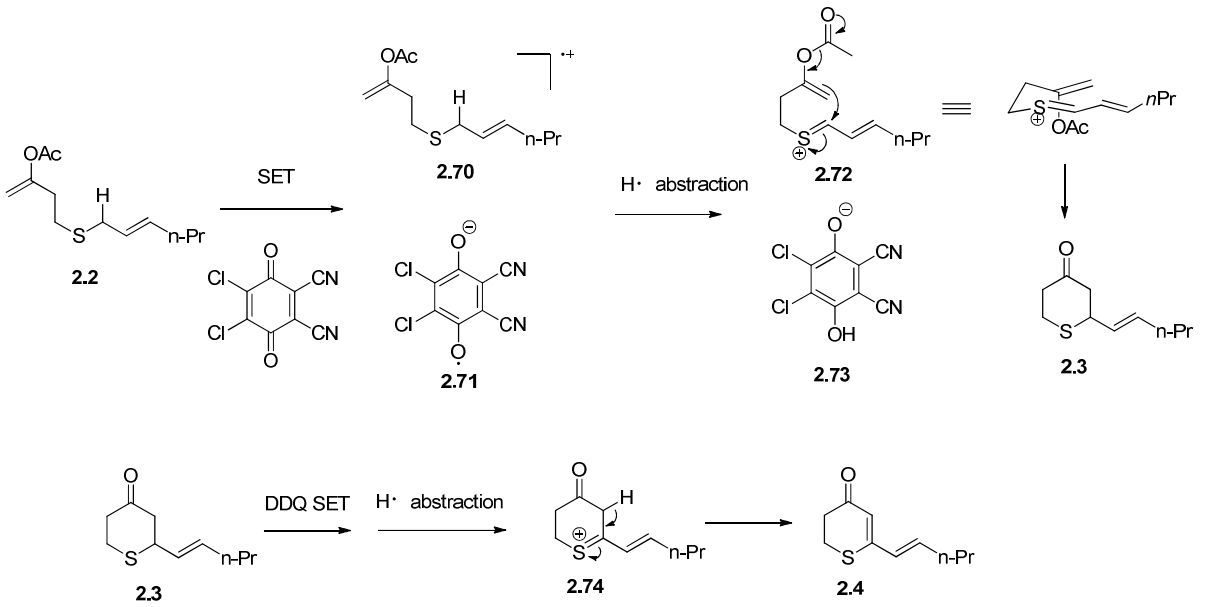


Figure 2.2 A proposed mechanism of DDQ-mediated cyclization of allyl sulfide **2.2**.

Compared with allyl sulfide **2.2**, the reaction of vinyl sulfide **2.13** is much faster even at lower temperature with a higher yield of **2.3** and a negligible amount of side product **2.4**. This indicates the same α,β-unsaturated thiocarbenium ion intermediate **2.72** is formed in the reaction pathway (Figure 2.3). A plausible explanation for the reactivity difference is that vinyl sulfide **2.13** has much lower oxidation potential than the substrate allyl sulfide **2.2** and the desired product **2.3**

(also an allyl sulfide). Therefore at lower temperature the oxidation reaction on vinyl sulfide **2.13** is much faster than on allyl sulfide **2.2** and the desired product **2.3** (which leads to the formation of undesired over-oxidation product **2.4**). This observation is in agreement with the conclusions from previous mechanistic studies.[45]

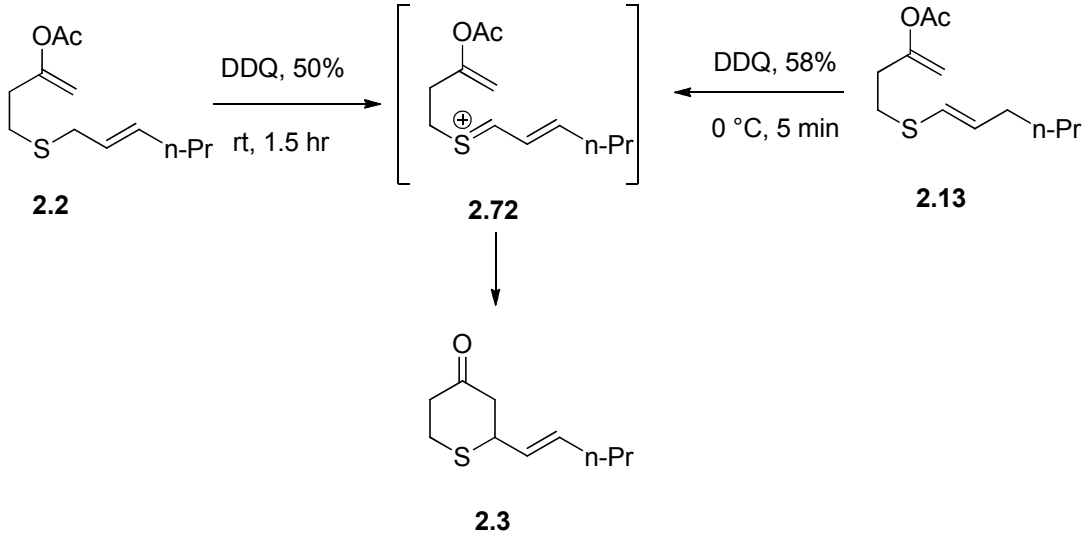


Figure 2.3 A comparison between allyl sulfide **2.2** and vinyl sulfide 2.**13**.

2.3.2 Stereocontrol with Enol Acetate and Enol Carbamate Nucleophiles

For secondary sulfides substrates **2.6**, **2.10** or **2.15**, 2,6-*cis* cyclization products are the major products with satisfactory to excellent diastereomeric ratios. In the postulated chair transition states, the substituent R assumes an equatorial position, and the *(E)*-thiocarbenium ion **2.75** is the dominant reactive species in the reaction mechanism (Figure 2.4), thus favoring the formation of 2,6-*cis* product **2.76**. In the less favored *(Z)*-thiocarbenium ion **2.77** greater steric hindrance is expected, and therefore 2,6-*trans* product **2.78** is formed as a minor product. Compared with their oxygen counterparts, the stereoselectivities from the cyclization reactions with sulfides are

generally lower, indicating the longer bonds between carbon and sulfur have an adverse affect to the preference of the *(E)*-geometry of thiocarbenium ions. It should be also noted that though the *(Z)*-thiocarbenium ion explains the minor 2,6-*trans* product nicely, we cannot exclude the possibility of the minor product arising from a possible less favored boat transition state.

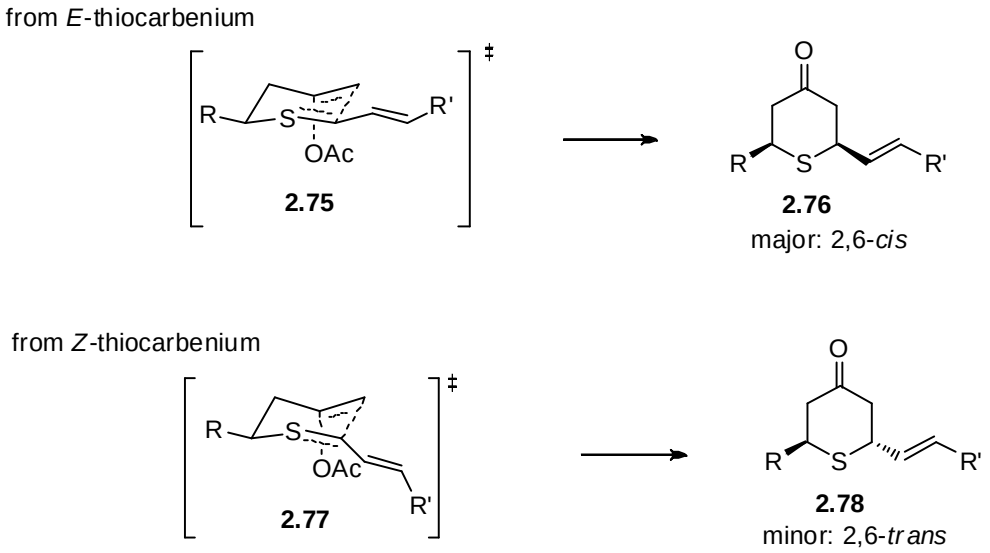


Figure 2.4 Stereocontrol of 2,6-disubsituted tetrahydrothiopyranone.

For secondary sulfides substrate **2.24** with a *(Z)*-vinyl carbamate, the 2,3-*trans* cyclization product **2.25** is the major product with an excellent ratio of 25:1. Similar to the mechanism of 2,6-disubstitution products, the substituents at the 2- and 3-positions assume equatorial orientations in the postulated chair transition states, and the *(E)*-thiocarbenium ion **2.79** is the dominant reactive species in the reaction mechanism (Figure 2.5), thus favoring the formation of 2,3-*trans* product **2.25**. The less favored *(Z)*-thiocarbenium **2.80** presumably leads to the formation of the minor product **2.81.** We have also demonstrated that complementary

stereocontrol result can be accessed through *(E)*-vinyl carbamate **2.31**, leading to 2,3-*cis* product **2.32** as the major product through the same mechanism.

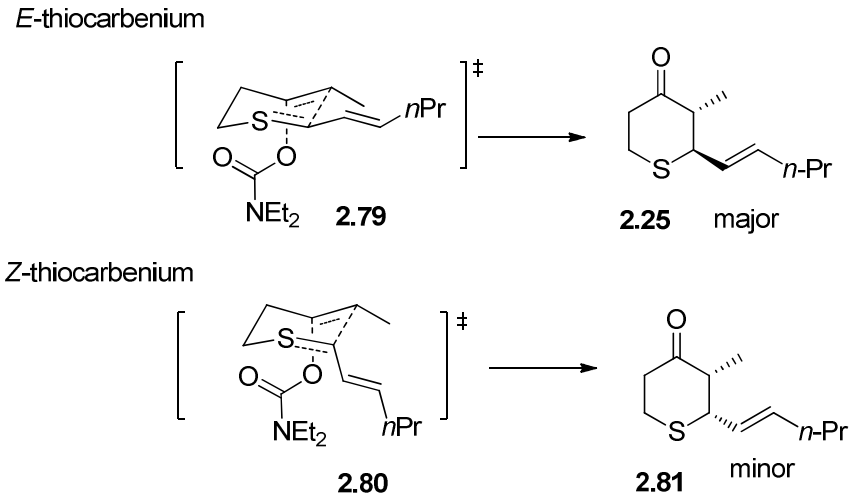


Figure 2.5 Stereocontrol of 2,3-disubsituted THTP from (*Z*)-vinyl carbamate.

2.3.3 Mechanisms and Stereocontrols with Allylsilane

Allylsilanes have also proved to be very efficient nucleophiles in these oxidative cyclization reactions, but the solvent of choice is the more polar $MeNO_2$ instead of dichloromethane to avoid the formation of diene product **2.38**. Presumably allylsilanes are slightly weaker nucleophiles than enol acetates and enol carbamates, and therefore the thiocarbenium ion **2.37** has a longer life in the reaction system. The use of more polar solvent greatly helps to stabilize **2.37** and suppress the unwanted deprotonation pathway to form the diene product **2.38**.

Both *(E)*- and *(Z)*- unsubstituted allylsilane afford 2,3-*cis* products as the major products which may be explained by the same mechanism as illustrated in Figure 2.6 (only *(E)*-allylsilane structures are illustrated), where *(E)*-thiocarbenium **2.37** is more favored than *(Z)*-thiocarbenium **2.82**. It should be noted that the *trans:cis* stereoselectivities from *(E)*-allylsilane **2.35** (7.7:1) and

(Z)-allylsilane **2.36** (1.9:1) are lower than those from the enol carbamate substrates. A reasonable reason which may explain the lower stereoselectivity of *(E)*-allylsilane **2.35** is solvent effect due to the necessary replacement of dichloromethane with $MeNO_2$, however it cannot explain the difference between *(E)*- and *(Z)*-allylsilanes**.**

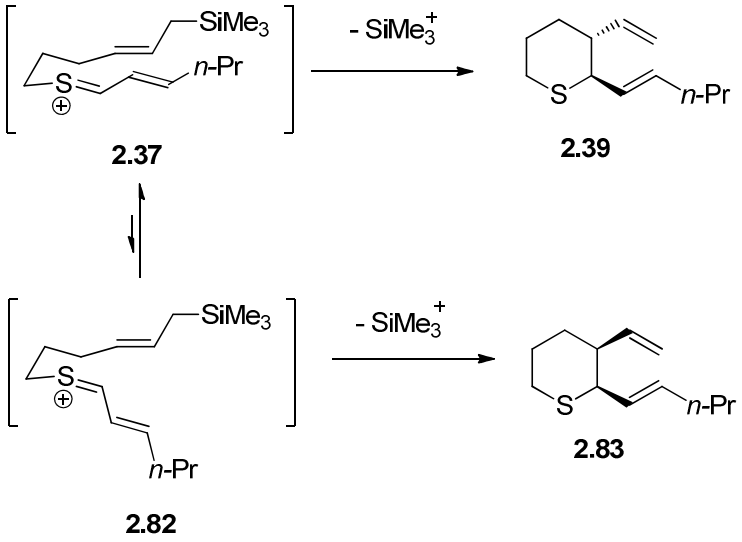


Figure 2.6 Formation of 2,3-*trans* products from *(E)*-allylsilanes.

When secondary allyl sulfides are used, four diastereomeric products are formed (Figure 2.1, **2.58** to **2.61**), again with the (*E*)-allylsilane substrates reacting with much higher levels of stereocontrol than the corresponding (*Z*)-allylsilane substrates. For (*Z*)-allylsilane substrates, *o-trans-m-cis* product **2.58** and *o-cis-m-trans* product **2.61** are formed in a nearly 1:1 ratio (Figure 2.7). Our experimental data revealed that the ratios of four diastereomeric products are not very relevant to the size of the R- substituents (Table 2.1), indicating a boat transition state is unlikely to be responsible for the much lower stereoselectivity from the cyclization of (*Z)*-allylsilanes. The most plausible pathway is through the (*Z*)-thiocarbenium ion intermediate **2.85** with the conjugated alkenyl group occupying a pseudoaxial orientation.

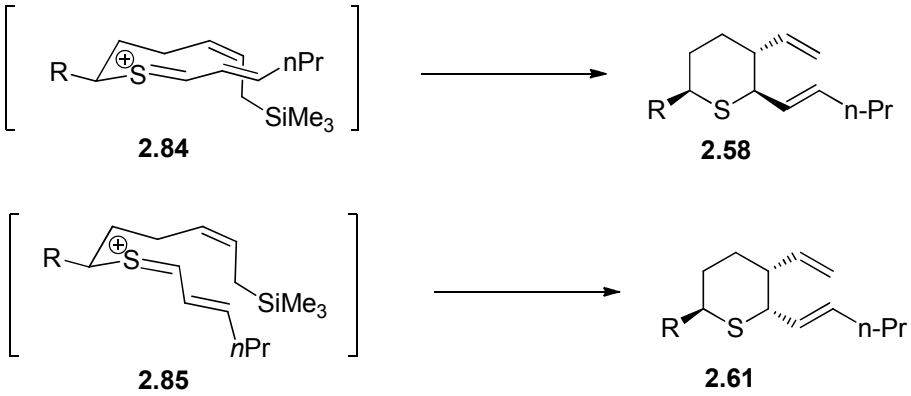


Figure 2.7 Formation of the two major diastereomeric products from (*Z*)-allylsilanes.

The oxidative cyclization from *cis*-allylsilane **2.67** to tetrahydrothiophene **2.68** is also very efficient with excellent stereoselectivity (dr 20:1) (Scheme 2.18). Carbon-sulfur double bonds are known to be longer than carbon-oxygen double bonds,[43a] which may explain this unusual 5-*endo* cyclization reaction. The strong preference towards 2,3-*cis* product from *(Z)*-allylsilane may be related by the lower energy of the *(E)*-thiocarbenium ion **2.86** compared with the *(Z)*-thiocarbenium **2.87**, but we do not fully understand the origin of the stereochemistry (Figure 2.8).

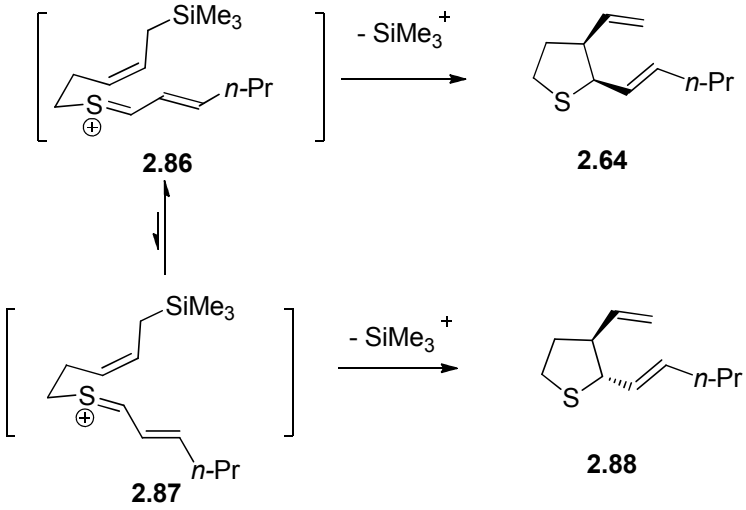


Figure 2.8 Formation of the two diastereomeric THT products from (*Z*)-allylsilanes.

2.4 SUMMARY

We have discovered DDQ mediated oxidative C-H bond cleavage to be an effective and stereoselective method to synthesize sulfur containing six- or five- member rings. The moieties for generating thiocarbenium ions are unsaturated sulfides including allyl sulfide and preferably vinyl sulfide, both of which can be easily accessed, while the appended nucleophiles include enol acetate, enol carbamate and allylsilane.

With vinyl sulfides these cyclization reactions rapidly afford sulfur containing six-membered rings with high stereocontrol and in good to excellent yields under very mild conditions. Enol acetates and enol carbamate nucleophiles tend to afford tetrahydrothiopyranones with the best stereochemical outcomes. With unsubstituted enol acetates as the nucleophiles, *cis*-2,6-disubstituted tetrahydrothiopyranones are the preferred products from cyclizations of secondary sulfides. With substituted enol carbamates as the nucleophiles, *trans*-2,3-disubstituted tetrahydrothiopyranones are the preferred products from cyclizations of *(Z)*-enol carbamates, and *cis*-2,3-disubstituted tetrahydrothiopyranones are the preferred products from cyclizations of *(E)*-enol carbamates. Allylsilane nucleophiles afford slightly inferior stereocontrols, and the stereochemical outcomes are also affected by the geometry of the nucleophiles. While the exact explanation for different stereocontrol from *(E)*- and *(Z)*- allylsilanes remains to be explored, the experimental studies tend to indicate the possibility of a concerted interaction between the thiocarbenium ion and the allylsilane moiety. In the meanwhile, we have also demonstrated that *(E)*- and *(Z)*- allylsilanes could be used to prepare tetrahydrothiophenes with moderate to high stereocontrol in good yields under very mild conditions.

The combination of unique synthetic approach, good functional group compatibility and excellent diastereoselectivity highlights this oxidative cyclization methodology from other

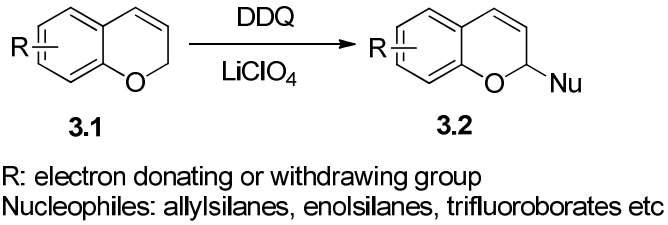
common synthetic strategies for approaching sulfur containing six- or five- member rings. The synthetic methodology described here may also find applications in accessing complex molecules in pharmaceutical and special chemical industry.

3. ASYMMETRIC BIMOLECULAR COUPLING REACTIONS THROUGH OXIDATIVELY GENERATED AROMATIC CATIONS: SCOPE AND LIMIT

3.1 INTRODUCTION

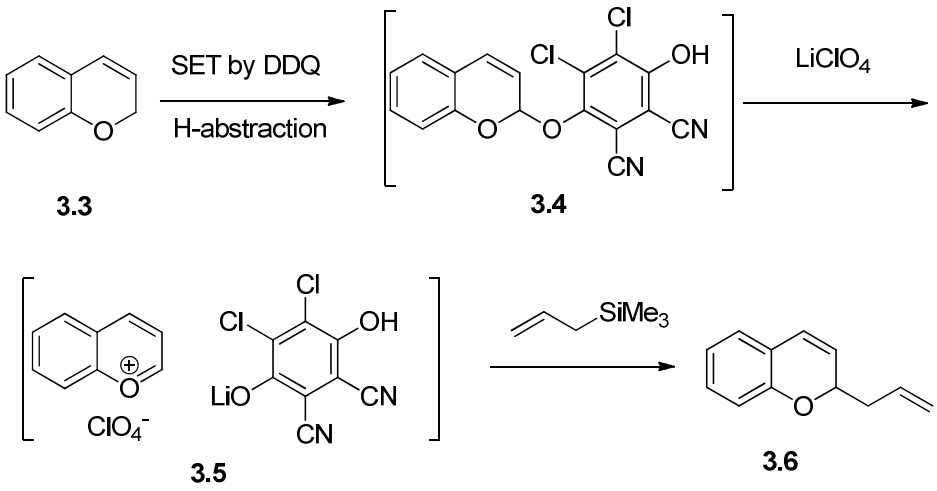
Fragment-based screening has become increasingly popular to design high-affinity ligands and sub-units in search of biologically active molecules.[57] This protocol generally requires the rapid preparation of libraries of low molecular weight compounds with diverse structures. Access to these libraries would be facilitated by the development of new fragment coupling reactions that allow structural variability and, preferably, incorporation of one or more heteroatoms and stereocenters. One strategy to generate these fragments is through oxidative carbon-hydrogen bond cleavage, which is characterized by the oxidative formation of stabilized carbocations followed by intermolecular nucleophilic attack to accomplish the bimolecular coupling process.[58] A significant challenge in this strategy is the stabilized carbocations must have sufficient lifetime to accommodate the addition rates of the intermolecular nucleophile. For this reason, most bimolecular coupling reactions through oxidative carbon-hydrogen bond cleavage are based on readily oxidized substrates, such as tetrahydroisoquinolines, electron-rich alkenes, isochromans and xanthenes.[59]

The Floreancig group has developed a number of stereoselective cyclization reactions based on the oxidation of ethers, amides, and sulfides with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidant.[11,41,46] These processes proceed through oxidative carbon-hydrogen bond cleavage to form stabilized carbocations followed by intramolecular additions of appended π-nucleophiles. Recently, Clausen and Villafane in the Floreancig group have successfully extended this approach to bimolecular coupling reactions, and prepared a number 2*H*-chromene derivatives (Scheme 3.1).[60]



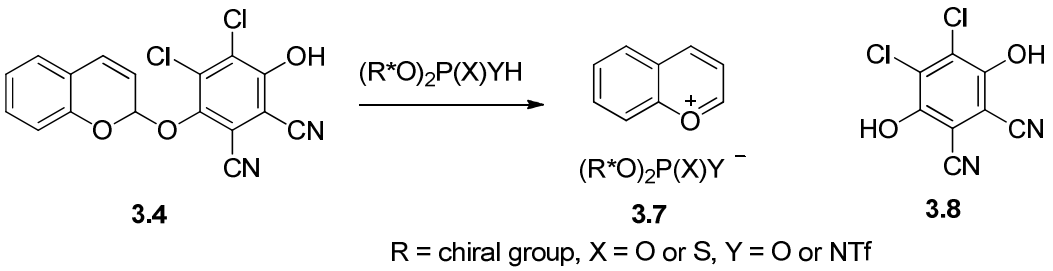
Scheme 3.1 Achiral bimolecular coupling on chromene substrates.

A plausible pathway for these bimolecular coupling reactions are shown in Scheme 3.2. The incorporation of aromatic ring lowers the oxidation potential of these substrates and assures easier access to the intermediate **3.4**. On the other hand, the aromatic ring also leads to higher stability of the oxidation intermediate, and thus necessitates a catalyst to promote its dissociation to form an intermediate with higher reactivity. Lithium perchlorate has been found to greatly improve the efficiency of the reaction, presumably by promoting the dissociation of the acetal **3.4** and the formation of a more reactive ion pair **3.5**, which reacts with an intermolecular nucleophile to afford **3.6**.



Scheme 3.2 The formation of ion pairs in achiral bimolecular coupling.

The possible formation of an achiral ion pair in the reaction mechanism encouraged us to explore the potential of replacing $LiClO_4$ with a chiral Brønsted acid. Thus a chiral ion pair **3.7** may be generated and available for further nucleophilic addition to afford enantiomerically enriched products (Scheme 3.3). Chiral phosphoric acids were selected for their catalytic activities to promote asymmetric additions through oxocarbenium ion intermediates.[59i,j] The association between the oxocarbenium ion and phosphoric acid has been attributed to C—H···X hydrogen bonds rather conventional hydrogen bonds.[61] Though there are a few examples of asymmetric additions into oxidatively generated carbocations in the literature, all of these examples employ chiral nucleophiles to achieve enantioselectivity.[59g,62] To the best of our knowledge, this postulated strategy is very unique in generating a chiral center from oxidatively generated carbocations and achiral nucleophiles.



3.4 **3.7** **3.8**

R = chiral group, X = O or S, Y = O or NTf

Scheme 3.3 Chiral ion pair from an oxidatively generated intermediate.

3.2 ASYMMETRIC BIMOLECULAR COUPLING REACTIONS THROUGH OXIDATIVELY GENERATED AROMATIC CATIONS

In the postulated strategy, the co-existence of the racemic acetal **3.4** and the chiral iron pair **3.7** dictates the competition between the uncatalyzed background reaction which leads to racemic products, and the postulated catalyzed reaction which leads to enantiomerically enriched products. Our first approach was to identify the reaction conditions that may suppress the background reaction. We anticipated the choice of solvent may have a significant impact on the background reaction rate as well as the distance of the counterions in the chiral pair. So we performed the bimolecular coupling reaction between **3.3** and allyltrimethylsilane in the absence of $LiClO_4$ in different solvents, expecting the disappearance of intermediate **3.4** on TLC to reflect the background reaction rate (Table 3.1). Compared with acetonitrile and dichloromethane, the background reaction rate was considerably slower in toluene presumably due to its lower polarity. So toluene was selected for further screening experiments.

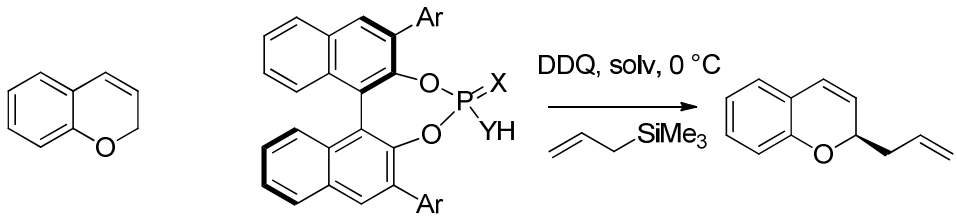
Table 3.1 Initial solvent screening results (without $LiClO_4$).

Solvent	Nucleophile	Temperature °C	TLC Consumption
acetonitrile	AllylTMS	0	1.5 hours
dichloromethane	AllylTMS	0	2 hours
toluene	AllylTMS	0	12 hours

To screen for the optimal catalyst, several BINOL-based phosphoric acids and phosphoryl triflimides **3.9-3.12**, as well as their thio counterparts **3.13-3.14**, were synthesized according to literature procedure and screened for optimal enantioselectivities.[63] Specifically, substrate **3.3** was exposed to DDQ oxidation in the presence of stoichiometric amounts of catalysts at 0°C to generate the relatively stable acetal intermediates in approximately 30 minutes, followed by the addition of allyltrimethylsilane to consume the intermediates and finish the coupling process. After disappearance of the stable intermediates on TLC, the crude reaction mixture was purified by column chromatography, and the enantiomeric excess was measured by chiral HPLC using a Lux Cellulose 3 column. The screening results were summarized in Table 3.2 (entry 1 to 6 for catalyst screening). Triisopropylphenyl (TRIP) substituted phosphoryl triflimide **3.11** was found to be the optimal catalyst, affording **3.15** in 62% ee at stoichiometric loading (entry 3). The absolute stereochemistry of **3.15** was determined through an independent synthetic approach (discussed later in Scheme 3.4),[65] and confirmed with optical rotations and HPLC retention times. Phosphoryl triflimide groups were superior to phosphoric acid groups presumably due to their higher acidity. Thiophosphoric acid **3.13** and thiophosphoryl triflimide **3.14** afforded very low ee. Replacement of toluene with dichloromethane led to 34% ee (entry 7), while replacement with α,α,α-trifluorotoluene further improved the stereocontrol to 77% ee (entry 8). α,α,α-Trifluorotoluene was usually believed to behave similarly as dichloromethane, so the sharp

difference in stereocontrol between these two solvents further suggests the presence of aromatic interactions between the chiral ion pair **3.7** and the aromatic solvent, which are beneficial to the stereochemical outcome.

Table 3.2 Screening results with stoichiometric loading of catalysts.



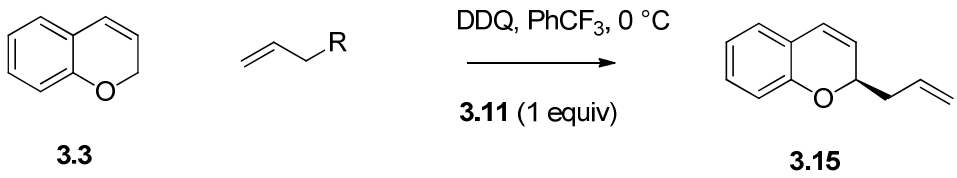
3.3 **3.9-3.14** **3.15**

Entry	Catalyst	Ar	X	Y	Solvent	ee %
1	**3.9**	2,4,6-Triisopropylphenyl	O	O	Tol	26
2	**3.10**	3,5-Ditrifluoromethylphenyl	O	O	Tol	4
3	**3.11**	2,4,6-Triisopropylphenyl	O	NTf	Tol	62
4	**3.12**	2,6-Diisopropyl-4-(9-anthracenyl)phenyl	O	NTf	Tol	31
5	**3.13**	2,4,6-Triisopropylphenyl	S	O	Tol	4
6	**3.14**	2,4,6-Triisopropylphenyl	S	NTf	Tol	13
7	**3.11**	2,4,6-Triisopropylphenyl	O	NTf	DCM	34
8	**3.11**	2,4,6-Triisopropylphenyl	O	NTf	$PhCF_3$	77

To further improve the enantioselectivity of the reaction, we screened several other nucleophiles besides allyltrimethylsilane (Table 3.3). These reactions were conducted in α,α,α-trifluorotoluene with stoichiometric amount of **3.11** at 0 °C. Allyl phenyl dimethylsilane and allyltriphenyltin provided 92% ee and 89% ee respectively (entry 1 and 3), while allyltributyltin provided 48% ee

(entry 2). While nucleophilicity difference seems to be a reasonable explanation, it should be noted allyltriphenyltin is more nucleophilic than allyl trimethylsilane.[64] Again we believe the higher enantioselectivities may be resulting from possible aromatic interactions between the chiral iron pair **3.7** and those nucleophiles containing phenyl groups.

Table 3.3 Screening results at stoichiometric loading of catalysts.

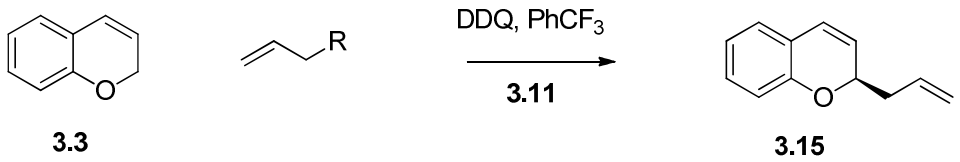


3.3 **3.15**

Entry	Catalyst	M	ee %
1	**3.11**	$SiMe_2Ph$	92
2	**3.11**	$SnBu_3$	48
3	**3.11**	$SnPh_3$	89

To test the efficiency of the catalyst, we performed a series of reactions with allyltriphenyltin and allyl phenyl dimethylsilane with substoichiometric amount of catalyst **3.11** (Table 3.4). Lowering catalyst **3.11** from stoichiometric amount to 20% at 0 °C resulted in nearly 30% drop in enantioselectivity, with both nucleophiles affording 62% ee (entry 1 and 5). Lowering the nucleophilic reaction temperature from 0 °C to -25 °C (the freezing point of α,α,α-trifluorotoluene is -29 °C) improved the enantioselectivity significantly, with allyltriphenyltin adding in 81% ee and 66% yield (entry 2), and allyl phenyl dimethylsilane adding in 86% ee and 56% yield (entry 6). It should be noted the lower yields were partially affected by the scales of these reactions and the evaporation loss of the products.

Table 3.4 Screening results at one equivalent loading of catalysts.

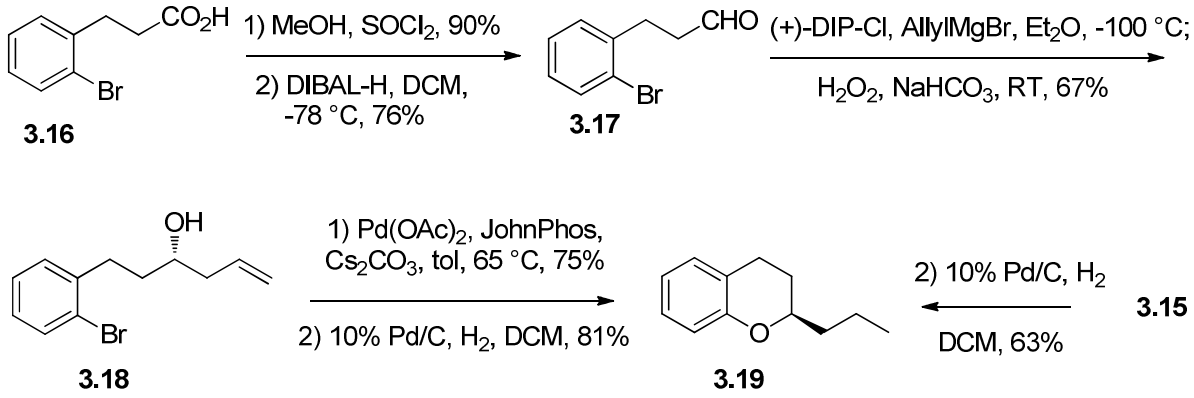


3.3 3.15

Entry	R	Temperature (°C)	Cat loading (mol%)	Ee (%)	Yield (%)
1	Ph_3Sn	0	20	62	-
2	Ph_3Sn	-25	20	81	66
3	Ph_3Sn	-25	10	68	66
4	Ph_3Sn	-25	5	31	57
5	$PhMe_2Si$	0	20	62	-
6	$PhMe_2Si$	-25	20	86	56
7	$PhMe_2Si$	-25	10	79	52
8	$PhMe_2Si$	-25	5	17	53

Further reducing the catalyst loading to 10% resulted in slightly lower enantioselectivity, with allyltriphenyltin adding in 68% ee and 66% yield (entry 3), and allyl phenyl dimethylsilane adding in 79% ee and 52% yield (entry 7). Reducing the catalyst loading to 5% resulted in significant drops in enantioselectivity, with 31% ee and 57% yield from allyltriphenyltin (entry 4), and 17% ee and 53% yield from allyl phenyl dimethylsilane (entry 8). These substoichiometric results indicate the turn-over rate of the BINOL catalyst is not impressively high, and at lower catalyst loading the uncatalyzed background reaction can become competitive, but useful enantioselectivities can still be obtained with 10% to 20% loading of the catalyst.

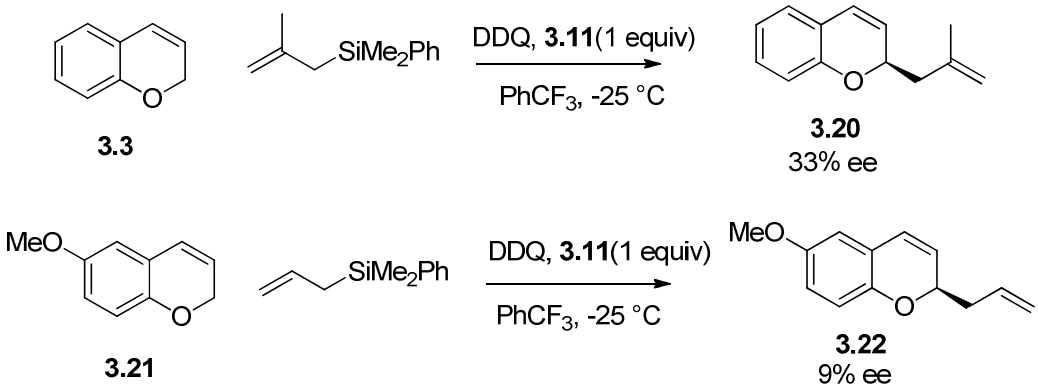
Compound **3.15** has not been prepared in enantiomerically pure form in literature. Therefore its absolute stereochemistry has to be determined through an independent synthetic route (Scheme 3.4). Commercially available *o*-bromohydrocinnamic acid **3.16** was converted to its methyl ester, and partially reduced to obtain the corresponding aldehyde **3.17**. The key stereocenter in **3.18** was then introduced using a well-known Brown allylation reaction with predictable stereochemical outcome.[65] A palladium-mediated cyclization[66] followed by hydrogenation of the alkene group provided **3.19** (observed $[\alpha]_D$ + 99.1). Another hydrogenation on the alkene **3.15**, which was prepared with the present methodology (73% ee before hydrogenation), afforded the same product with an observed $[\alpha]_D$ + 73.0. Retention times with both products as well as racemic products also matched very well.



Scheme 3.4 Synthetic approach to determine absolute stereochemistry.

We attempted to expand the scope of the present methodology, but the results were not successful. Scheme 3.5 demonstrates two of such examples. Replacing allyl phenyl dimethylsilane with methallyl phenyl dimethylsilane on **3.3**, with stoichiometric amount of the optimal catalyst **3.11** under optimal conditions, afforded **3.20** in 33% ee. When an methoxy group was installed on the substrate, also with stoichiometric amount of the optimal catalyst **3.11**

under optimal conditions, the reaction afforded **3.22** only in 9% ee. We noticed that the background reactions for both processes were quite fast in the absence of catalyst. We postulate that the enhanced nucleophilicity of the methallyl phenyl dimethylsilane in comparison to the allyl phenyl dimethylsilane creates the potential for the competitive reaction with intermediates related to **3.4** (Scheme 3.2). The electron donation from the methoxy group stabilizes the intermediate cation and weakens its interaction with the chiral counterion.



Scheme 3.5 Unsuccessful attempts to expand the reaction scope.

3.3 SUMMARY

We have discovered that DDQ-mediated carbon-hydrogen bond cleavage reactions, in the presence of a chiral Brønsted acid, can be used to generate chiral aromatic electrophiles that react with intermolecular nucleophiles to prepare enantiomerically enriched products. Mechanistic studies implicate the formation of a mixed acetal intermediate upon cation formation that ionizes in the presence of chiral phosphoric acids to generate chiral ion pairs with reactive oxocarbenium

cations, despite the absence of conventional hydrogen bonding sites. While the scope of this process is still very limited, several interesting observations have been noted. The uncatalyzed background reaction to form racemic addition products is a significant competitive process, but can be suppressed by choosing non-polar solvent at low temperature. For higher enantioselectivity the best solvent is non-polar aromatic solvent (with $PhCF_3$ being the best), and the best nucleophile are allyl phenyl dimethylsilane and allyltriphenyltin. These facts indicate possible aromatic interactions between the chiral ion pairs, nucleophiles and solvent which are beneficial for the enantioselective outcome. We postulate the best enantioselectivity requires a delicate balance of electronic effects and aromatic interactions in the chiral ion pair intermediates. Despite these limitations we were able to conduct reactions with good enantiocontrol at reasonable catalyst loadings. These processes are, to the best of our knowledge, the first examples of enantioselective reactions with chiral electrophiles that arise from oxidative carbon-hydrogen bond cleavage.

APPENDIX A

TOTAL SYNTHESIS OF NEOPELTOLIDE AND ANALOGS

Experimental

General Experimental

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometer at 300 MHz and 75 MHz， respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Tetramethylsilane (TMS) or the solvent peak was used as a reference value, for ^{1}H NMR: TMS (in $CDCl_3$) = 0.00 ppm, CD_3OD =3.31, for ^{13}C NMR: TMS (in $CDCl_3$) = 0.00, CD_3OD = 49.00. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. 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. 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. Methylene chloride was distilled under N_2 from CaH_2.

Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Benzene was dried with 4A molecular sieves. THF was distilled from sodium. Other reagents were obtained from commercial source without further purification. All reactions were performed in oven or flame-dried glassware with magnetic stirring unless otherwise noted.

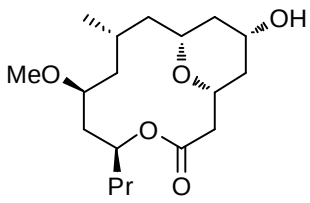
General protocol for the preparation of macrocyclic alcohol from macrocyclic ketone with $NaBH_4$ (general protocol A)

To a one-dram vial charged with macrocyclic ketone (0.020 mmol) was added MeOH (0.5 mL). The reaction mixture was cooled to 0 °C and $NaBH_4$ (0.040 mmol) was added. After 10 min, AcOH (0.40 mmol) was added and the reaction was concentrated under vacuum. The resulting residue was purified by flash column chromatography to afford the desired macrocyclic alcohol.

General protocol for the Mitsunobu coupling (general protocol B)

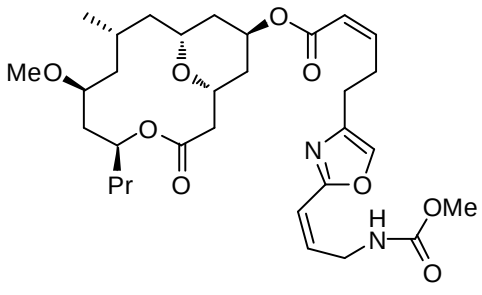
To a one-dram vial charged with macrocyclic alcohol (0.019 mmol), oxazolic acid (0.078 mmol) and PPh_3 (0.086 mmol) was added benzene (0.5 mL). To the reaction mixture was added DIAD (0.086 mmol). After ten minutes the reaction was concentrated under vacuum. The resulting residue was purified by flash column chromatography to afford the desired product.

(1*R*,5*S*,7*S*,9*S*,11*R*,13*S*)-13-hydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (1.5)



General protocol A was followed, starting from the macrocyclic ketone **1.8** (6.5 mg, 0.020 mmol) and $NaBH_4$ (1.6 mg, 0.042 mmol). Flash column chromatography (50% EtOAc in hexanes) yielded 6.2 mg (95%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 5.12-5.21(m, 1H), 3.75-3.87(m, 1H), 3.73(ddd, *J* = 2.0, 4.4, 10.9 Hz, 1H), 3.59(t, *J* = 9.4 Hz, 1H), 3.32(s, 3H), 3.18(t, *J* =9.3 Hz, 1H), 2.63(dd, *J* = 4.4, 14.5 Hz, 1H), 2.44(dd, *J* = 10.7, 14.5 Hz, 1H), 1.99(ddd, *J* = 1.8, 1.8, 11.5 Hz, 1H), 1.81-1.92(m, 2H), 1.43-1.78(m, 5H), 1.12-1.41(m, 6H), 1.0(d, *J* = 6.7 Hz, 3H), 0.92(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.8, 78.6, 75.6, 73.3, 72.3, 68.1, 56.2, 44.1, 42.2, 42.2, 41.9, 40.7, 40.0, 36.9, 31.2, 25.5, 19.0, 13.9; IR (film) 3416, 2918, 2871, 1730, 1650, 1459, 1087 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{32}O_5Na$ ([M+Na]+): 351.2147, found 351.2159; $[\alpha]_D^{25}$ = +17.1 ($CHCl_3$, c = 0.2).

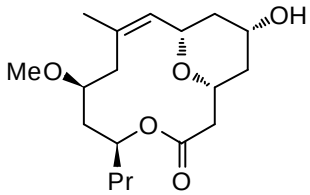
(*Z*)-(1*R*,5*S*,7*S*,9*S*,*11R*,13*R*)-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1] pentadecan-13-yl 5-(2-((*Z*)-3-((methoxycarbonyl)amino)prop-1-en-1-yl)-oxazol-4-yl)pent-2-enoate (1.2)



General protocol B was followed, starting from the macrocyclic alcohol **1.5** (6.2 mg, 0.019 mmol), the oxazolic acid **1.6** (22.0 mg, 0.078 mmol), PPh_3 (11.4 mg, 0.086 mmol) and DIAD (16.8 μL, 0.086 mmol). Flash column chromatography (30% EtOAc in hexanes) yielded 10.5 mg (93%) of neopeltolide. ^{1}H NMR (300MHz, CD_3OD) δ 7.66(s,1H), 6.32-6.41(m,

1H), 6.28(dt, *J* = 2.1, 13.8 Hz, 1H), 6.03(pentet, *J* = 6.0 Hz, 1H), 5.88(d, *J* = 11.6 Hz, 1H), 5.20(t, *J* = 2.8 Hz, 1H), 5.12-5.22(m, 1H), 4.30(dd, *J* = 1.4, 4.2 Hz, 2H), 4.06(t, *J* = 9.3 Hz, 1H), 3.70(s, 1H), 3.65(s, 3H), 3.56(t, *J* = 9.0 Hz, 1H), 3.28(s, 3H), 3.01(dd, *J* = 7.6, 15.1 Hz, 2H), 2.71(s, 1H), 2.70(dt, *J* = 4.4, 14.7 Hz, 1H), 2.23(dd, *J* = 11.0, 14.7 Hz, 1H), 1.73-1.90(m, 2H), 1.65-1.73(m, 2H), 1.44-1.60(m, 5H), 1.26-1.44(m, 6H), 1.07-1.18(m, 1H), 0.97(d, *J* = 6.3 Hz, 3H), 0.92(d, *J* = 13.6 Hz, 3H); ^{13}C NMR (75MHz, CD_3OD) δ 173.1, 166.9, 161.9, 159.5, 150.0, 142.3, 139.3, 136.0, 121.7, 116.0, 77.2, 77.1, 74.0, 71.4, 69.2, 56.4, 52.6, 45.3, 43.5, 43.3, 41.1, 38.0, 37.6, 37.4, 36.2, 32.6, 29.0, 26.4, 26.0, 20.0, 14.2; IR (film) 3357, 2954, 2922, 2854, 1719, 1646, 1537, 1458, 1376, 1342, 1249, 1178, 1064, 994, 777cm^{-1}; HRMS (ESI) calc. for $C_{31}H_{47}N_2O_9Na$ ([M+Na]$^+$): 613.3101, found 613.3076; $[\alpha]_D^{25}$ = +17.5 (MeOH, c = 0.24).

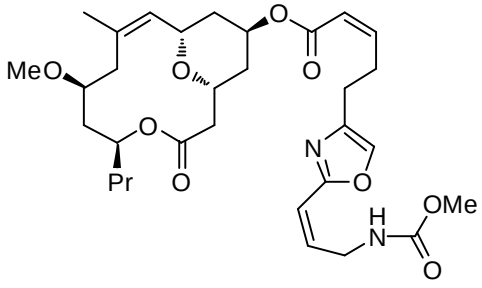
(1*R*,5*S*,7*S*,11*S*,13*R*,*Z*)-13-hydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1] pentadec-9-en-3-one (1.48)



General protocol A was followed, starting from the alkene ketone **1.30** (14.9 mg, 0.046 mmol) and $NaBH_4$ (3.6 mg, 0.095 mmol). Flash column chromatography (50% EtOAc in hexanes) yielded 12.6mg (84%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 5.31-5.37(m, 1H), 5.30(d, *J* =7.2 Hz, 1H), 3.82-3.93(m, 3H), 3.49-3.56(m, 1H), 3.36(s, 3H), 2.63(dd, *J* = 3.8, 15.1 Hz, 1H), 2.51(dd, *J* = 11.1, 15.1 Hz, 1H), 2.33(d, *J* = 13.3 Hz, 1H), 1.95-2.05(m, 3H), 1.86(d, *J* = 0.6 Hz, 3H), 1.81-1.89(m, 1H), 1.64-1.74(m, 1H), 1.47-1.59(m, 2H), 1.44(s, 1H), 1.18-1.40(m, 3H), 0.92(t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.3, 146.9, 125.1, 81.8, 74.1, 72.4, 72.0, 68.1, 57.9, 43.3, 42.1 ,41.8, 40.5, 40.3, 37.4, 25.2, 18.7, 13.9; IR (film) 3422, 2959, 2923, 2854, 1732, 1654,

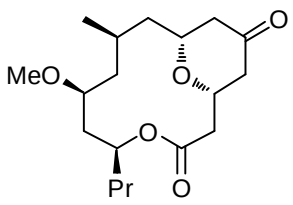
1454, 1373, 1315, 1264, 1195, 1080, 1035, 981, 939, 842, 755 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{30}O_5Na$ ($[M+Na]^+$): 349.1991, found 349.1992; $[\alpha]_D^{25}$ = -47.0 ($CHCl_3$, c = 0.38).

(*Z*)-(1*R*,5*S*,7*S*,11*S*,13*S*,*Z*)-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1] pentadec-9-en-13-yl 5-(2-((*Z*)-3-((methoxycarbonyl)amino)prop-1-en-1-yl)-oxazol-4-yl)pent-2-enoate (1.49)



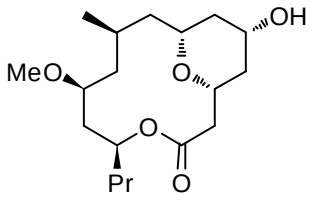
General protocol B was followed, starting from the alkene alcohol **1.48** (6.8 mg, 0.021 mmol), the oxazolic acid (23.0 mg, 0.083 mmol), PPh_3 (23.5 mg, 0.090 mmol) and DIAD (17.8 μL, 0.090mmol). Flash column chromatography (30% EtOAc in hexanes) yielded 8.6 mg (70%) of the alkene analog. ^{1}H NMR (300MHz, CD_3OD) δ 7.67(s, 1H), 6.34-6.43(m, 1H), 6.28(dt, *J* = 2.0, 12.0 Hz, 1H), 6.05(pentet, *J* = 6.0 Hz, 1H), 5.90(dt, *J* = 1.5, 11.5 Hz, 1H), 5.25-5.33(m, 1H), 5.27(t, *J* = 2.8 Hz, 1H), 5.22(d, *J* = 6.7 Hz, 1H), 4.31(d, *J* = 4.7 Hz, 2H), 4.19-4.28(m, 2H), 3.66(s, 3H), 3.58-3.65(m, 1H), 3.34(s, 3H), 3.03(ddd, *J* = 1.4, 7.7, 7.7 Hz, 2H), 2.73(t, *J* = 7.0 Hz, 2H), 2.69(dd, *J* = 3.4, 10.2 Hz, 1H), 2.27-2.38(m, 2H), 1.95(dd, *J* = 10.4, 13.6 Hz, 1H), 1.84(s, 3H), 1.62-1.88(m, 5H), 1.49-1.58(m, 3H), 1.23-1.30(m, 3H), 0.95(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75MHz, CD_3OD) δ 172.7, 166.9, 162.0, 159.7, 150.1, 148.0, 142.3, 139.3, 136.0, 127.0, 121.8, 116.0, 83.4, 75.2, 71.3, 71.1, 69.1, 58.2, 52.7, 44.2, 43.3, 42.5, 41.1, 38.5, 36.3, 35.9, 29.1, 26.5, 25.8, 19.9, 14.3; IR (film) 3351, 2957, 2923, 1719, 1521, 1458, 1268, 1170, 1097, 1072, 892, 818, 776 cm^{-1}; HRMS (ESI) calc. for $C_{31}H_{44}N_2O_9Na$ ($[M+Na]^+$): 611.2945, found 611.2997; $[\alpha]_D^{25}$ = -44.1 (MeOH, c = 0.56).

(1*S*,5*S*,7*S*,9*R*,11*R*)-7-methoxy-9-methyl-5-propyl-15-oxabicyclo[9.3.1]pentadecane-3,13-dione (1.50)



To a 10 mL flask containing the alkene ketone **1.30** (6.1 mg, 0.019 mmol) was added Crabtree's catalyst (3.2 mg, 0.004 mmol). The flask was quickly evacuated and backfilled with H_2, and this process was repeated for three times. Then CH_2Cl_2 (0.2 mL) was charged and the reaction mixture was well stirred at room temperature for 30 min. The reaction mixture was then filtered through Celite, concentrated and purified with flash chromatography (5% Et_2O in CH_2Cl_2) to afford 3.3 mg (54%) of the diastereomeric ketone. ^{1}H NMR (300MHz, $CDCl_3$) δ 5.14-5.22(m, 1H), 3.93-4.02(m, 1H), 3.69(ddd, *J* = 2.6, 6.5, 20.6 Hz, 1H), 3.32(s, 3H), 3.23-3.31(m, 1H), 2.72(dd, *J* = 4.5, 14.4 Hz, 1H), 2.46(dd, *J* = 8.5, 14.4 Hz, 1H), 2.42(dd, *J* = 4.1, 7.0 Hz, 1H), 2.31(d, *J* = 7.8 Hz, 2H), 1.92(dt, *J* = 2.2, 14.8 Hz, 1H), 1.74-1.83(m, 1H), 1.43-1.73(m, 4H), 1.16-1.39(m, 6H), 0.94(d, *J* = 6.8 Hz, 3H), 0.92(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 206.4, 179.8, 80.4, 75.0, 73.8, 72.6, 56.3, 48.2, 46.8, 41.7, 41.6, 40.1, 39.0, 37.7, 28.6, 20.9, 18.7, 13.9; IR (film) 2956, 2923, 2853, 1723, 1459, 1370, 1330, 1252, 1185, 1105, 1081, 844, 799 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{30}O_5Na$ ([M+Na]$^+$): 349.1991, found 349.1974; $[\alpha]_D^{25}$ = -7.9 ($CHCl_3$, c = 0.17).

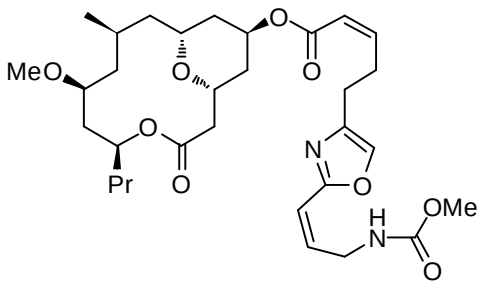
(1*R*,5*S*,7*S*,9*R*,11*R*,13*S*)-13-hydroxy-7-methoxy-9-methyl-5-propyl-15-oxabicyclo[9.3.1]-pentadecan-3-one



General protocol A was followed, starting from the diastereomeric ketone **1.50** (3.3 mg, 0.010 mmol) and $NaBH_4$ (1.1 mg, 0.029 mmol). Flash column chromatography (35% EtOAc in hexanes) yielded 3.2

mg (96%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 5.11-5.20(m, 1H), 3.80-3.86(m, 1H), 3.69(tdd, *J* = 1.9, 4.6, 11.0 Hz, 1H), 3.78(tt, *J* = 2.4, 8.7 Hz, 1H), 3.31(s, 3H), 3.27(dt, *J* = 2.0, 9.1 Hz, 1H), 2.64(dd, *J* = 4.6, 14.3 Hz, 1H), 2.41(dd, *J* = 9.0, 14.3 Hz, 1H), 1.90-1.99(m, 2H), 1.83-1.88(m, 2H), 1.60-1.80(m, 3H), 1.43-1.60(m, 3H), 1.13-1.40(m, 4H), 0.89-0.93(m, 6H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.5, 80.5, 74.6, 72.4, 71.5, 68.4, 56.4, 41.8, 41.7, 41.5, 40.3, 39.6, 39.4, 37.7, 28.7, 21.1, 18.7, 13.9; IR (film) 3363, 3296, 2916, 2852, 1718, 1490, 1457, 1364, 1274, 1256, 1220, 1160, 1108, 1074, 1036, 931 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{32}O_5Na$ ($[M+Na]^+$): 351.2147, found 351.2166; $[\alpha]_D^{25}$ = -9.6 ($CHCl_3$, c = 0.32).

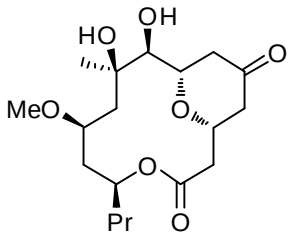
(*Z*)-(1*R*,5*S*,7*S*,9*R*,11*R*,13*R*)-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1]-pentadecan-13-yl 5-(2-((*Z*)-3-((methoxycarbonyl)amino)prop-1-en-1-yl)- oxazol-4-yl)pent-2-enoate (1.51)



General protocol B was followed, starting from the diastereomeric alcohol (3.1 mg, 0.0095 mmol), the oxazolic acid **1.6** (10.5 mg, 0.038 mmol), PPh_3 (10.7 mg, 0.041 mmol) and DIAD (8.1 μL, 0.041 mmol). Flash column chromatography (30% EtOAc in hexanes) yielded 3.8 mg (67%) of the diastereomeric analog. ^{1}H NMR (300MHz, CD_3OD) δ 7.65(s, 1H), 6.36(dt, *J* = 7.4, 11.6 Hz, 1H), 6.26(dt, *J* = 2.0, 11.8 Hz, 1H), 6.02(pentet, *J* = 6.1 Hz, 1H), 5.86(dt, *J* = 1.6, 11.5 Hz, 1H), 5.22(t, *J* = 2.8 Hz, 1H), 5.11-5.20(m, 1H), 4.29(dd, *J* = 1.5, 5.8 Hz, 2H), 3.95-4.05(m, 1H), 3.76(t, *J* =6.0 Hz, 1H), 3.64(s, 3H), 3.29(s,3H), 2.99(dd, *J* = 7.1, 7.1 Hz, 2H), 2.69(t, *J* = 7.7 Hz, 2H), 2.65(dd, *J* = 4.4, 9.4 Hz, 1H), 2.24(dd, *J* = 9.2, 14.4 Hz, 1H), 1.90(d, *J* = 8.9 Hz, 1H), 1.75-1.84(m, 3H), 1.39-1.68(m, 4H), 1.23-1.39(m, 6H), 1.22(t, *J* = 7.2

Hz, 2H), 1.09-1.19(m, 1H), 0.91(t, *J* = 7.3 Hz, 3H), 0.89(d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75MHz, CD_3OD) δ 172.6, 166.9, 161.9, 159.6, 150.0, 142.2, 139.2 135.9, 121.7, 115.9, 82.1, 75.8, 70.8, 70.6, 69.4, 68.9, 56.5, 52.6, 42.6, 41.0, 40.9, 40.5, 38.8, 37.0, 35.8, 30.0, 29.0, 26.4, 21.5, 19.8, 14.2; IR (film) 2923, 2854, 1716, 1519, 1458, 1375, 1249, 1179, 1103, 817 cm^{-1}; HRMS (ESI) calc. for $C_{31}H_{46}N_2O_9Na$ ([M+Na]$^+$): 613.3101, found 613.3075; $[\alpha]_D^{25}$ = +0.2 (MeOH, c = 0.20).

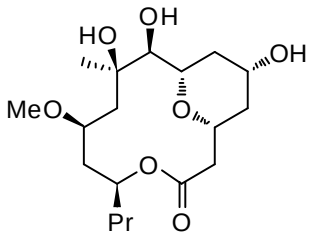
(1*R*,5*S*,7*R*,9*R*,10*S*,11*S*)-9,10-dihydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo-[9.3.1]pentadecane-3,13-dione (1.52)



To a one-dram vial charged with osmium tetroxide (6.1 mg, 0.024 mmol) and pyridine (61 μL, 0.76 mmol) was added THF (0.2 mL). The reaction mixture was cooled to 0 °C and the alkene ketone **1.30** (5.3 mg, 0.016 mmol) in THF (0.2 mL) was added drop wise. After 10 min, 4-Methylmorpholine N-oxide monohydrate (4.3 mg, 0.032 mmol) was added and the reaction was allowed to room temperature over 30 min. The reaction was quenched by 1 mL saturated $Na_2S_2O_3$ at 0 °C and extracted with three 2 mL portions of EtOAc. The organic layer was concentrated under vacuum and purified by flash column chromatography (5% MeOH in CH_2Cl_2) to afford 4.4 mg (75%) of the diol. ^{1}H NMR (300MHz, $CDCl_3$) δ 5.03-5.14(m, 1H), 4.04(tt, *J* = 3.4, 11.2 Hz, 1H), 3.66(tt, *J* = 3.0, 11.2 Hz, 1H), 3.59(s, 1H), 3.54-3.58(m, 1H), 3.39(s, 3H), 3.28(t, *J* = 7.4 Hz, 1H), 2.84(d, *J* = 7.2 Hz, 1H), 2.71(dt, *J* = 1.8, 15.0, 1H), 2.65(dd, *J* = 3.8, 14.5 Hz, 1H), 2.50(dd, *J* = 11.1, 14.3 Hz, 2H), 2.40(dd, *J* = 12.2, 15.1 Hz, 1H), 2.27(dd, *J* = 11.5, 13.5 Hz, 1H), 2.15(ddd, *J* = 1.3, 3.5, 14.4 Hz, 1H), 1.92(dd, *J* = 2.9, 15.2 Hz, 1H), 1.63(dd, *J* = 10.5, 14.8 Hz, 2H), 1.42-1.62(m, 2H), 1.15-1.39(m, 5H), 0.92(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 205.5, 169.5, 77.8, 77.7, 73.3, 73.0, 72.9, 56.2, 47.1, 45.0, 42.7, 41.5,

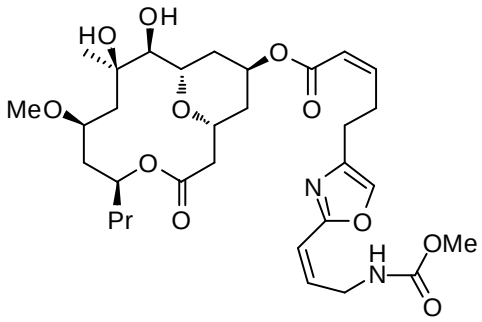
38.2, 37.5, 24.8, 18.4, 13.9; IR (film) 3441, 2923, 1721, 1555, 1460, 1377, 1267, 1183, 1100, 1069, 964, 934, 817 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{30}O_7Na$ ($[M+Na]^+$): 381.1889, found 381.1902; $[\alpha]_D^{25}$ = -28.5 (MeOH, c = 0.13).

(1*R*,5*S*,7*R*,9*R*,10*S*,11*S*,13*R*)-9,10,13-trihydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one



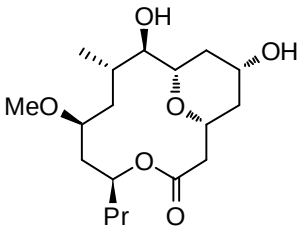
General protocol A was followed, starting from the diol **1.52** (3.6 mg, 0.010 mmol) and $NaBH_4$ (1.1 mg, 0.029 mmol). Flash column chromatography (5% MeOH in CH_2Cl_2) yielded 3.3 mg (92%) of the desired triol. ^{1}H NMR (300MHz, CD_3OD) δ 5.09-5.18(m, 1H), 3.70-3.83(m, 2H), 3.49-3.55(m, 1H), 3.46(ddd, *J* = 1.7, 7.1, 11.1, 1H), 3.32(s, 3H), 3.28(s, 1H), 2.76(dd, *J* = 4.6, 14.1 Hz, 1H), 2.30(dd, *J* = 8.8, 14.1 Hz, 1H), 2.12(dt, *J* = 2.2, 12.4 Hz, 1H), 1.97(t, *J* = 14.8 Hz, 2H), 1.91-1.95(m, 1H), 1.68(dd, *J* = 10.8, 14.7 Hz, 2H), 1.50-1.65(m, 3H), 1.20(dd, *J* = 11.1, 23.4 Hz, 2H), 1.28-1.40(m, 7H), 0.97(t, *J* =7.2 Hz, 3H); ^{13}C NMR (75MHz, CD_3OD) δ 171.2, 77.0, 76.6, 76.5, 74.1, 74.0, 72.0, 67.5, 55.0, 45.4, 41.2, 40.6, 39.9, 37.6, 37.4, 25.6, 18.2, 12.8; IR (film) 3397, 2924, 1729, 1457, 1373, 1263, 1195, 1099, 1044, 937, 731 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{32}O_7Na$ ($[M+Na]^+$): 383.2046, found 383.2034; $[\alpha]_D^{25}$ = -8.6 (MeOH, c = 0.32).

(*Z*)-(1*R*,5*S*,7*R*,9*R*,10*S*,11*S*,13*S*)-9,10-dihydroxy-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-13-yl 5-(2-((*Z*)-3-((methoxycarbonyl)-amino)prop-1-en-1-yl)oxazol-4-yl)pent-2-enoate (1.53)

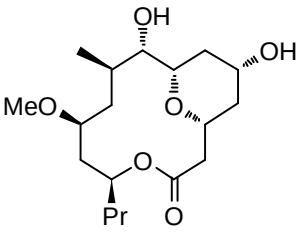


To a one-dram vial charged with triol (3.5 mg, 0.01 mmol), oxazole acid **1.6** (4.1 mg, 0.015 mmol) and PPh_3 (4.2 mg, 0.016 mmol) was added benzene (0.2 mL). The reaction mixture was cooled to 15 °C and DIAD (3.2 μL, 0.016 mmol) in benzene (0.1 mL) was added drop wise. One hour later an additional PPh_3 (1.4 mg, 0.005 mmol) and DIAD (1.07μL, 0.005 mmol) in benzene (0.1 mL) was added sequentially. The reaction was quenched with 1 drop of water after 20 min, concentrated under vacuum and purified with flash chromatography (5% MeOH in CH_2Cl_2) to afford the desired product (3.0 mg, 50%).^{1}H NMR (300MHz, $CDCl_3$) δ 7.40(s, 1H), 6.26-6.34(m, 2H), 6.09(pentet, *J* = 6.4 Hz, 1H), 5.90(dt, *J* = 1.7, 11.5 Hz, 1H), 5.57(br, 1H), 5.32(t, *J* = 2.8 Hz, 1H), 5.06-5.14(m, 1H), 4.31(t, *J* = 6.1 Hz, 2H), 4.00(tdd, *J* = 1.9, 1.9, 9.3 Hz, 1H), 3.69(s, 3H), 3.59-3.67(m, 2H), 3.40(s, 1H), 3.37(s, 3H), 3.35(s, 1H), 3.16(dd, *J* = 5.7, 8.4 Hz, 1H), 3.04(ddt, *J* = 1.9, 7.4, 7.4 Hz, 2H), 2.90(d, *J* = 6.0 Hz, 1H), 2.72(t, *J* = 7.2 Hz, 2H), 2.54(dd, *J* = 3.8, 14.4 Hz, 1H), 2.36(dd, *J* = 11.2, 14.4 Hz, 1H), 2.01-2.11(m, 3H), 1.83(d, *J* = 9.6 Hz, 1H), 1.68(dt, *J* = 3.0, 11.5 Hz, 1H), 1.50-1.65(m, 5H), 1.35(t, *J* = 7.3 Hz, 2H), 1.27(s, 3H), 0.91(t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75MHz, CD_3OD) δ 171.5, 165.5, 148.6, 140.8, 137.8, 134.6, 120.3, 114.5, 77.3, 76.8, 74.0, 73.9, 73.6, 69.5, 67.6, 54.9, 45.1, 41.1, 40.1, 37.4, 34.5, 32.5, 27.5, 25.6, 24.9, 18.2, 12.8; IR (film) 3358, 2957, 2922, 2853, 2500, 1715, 1635, 1553, 1460, 1396, 1262, 1169, 1095, 1052, 1019, 816, 795, 780 cm^{-1}; HRMS (ESI) calc. for $C_{31}H_{46}N_2O_{11}Na$ ($[M+Na]^+$): 645.2999, found 645.2996; $[\alpha]_D^{25}$ = -2.1 (MeOH, c = 0.16).

(1*R*,5*S*,7*S*,9*S*,10*R*,11*S*,13*R*)-10,13-dihydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (54) and (1*R*,5*S*,7*S*,9*R*,10*S*,11*S*,13*R*)-10,13-dihydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (1.55)



1.54



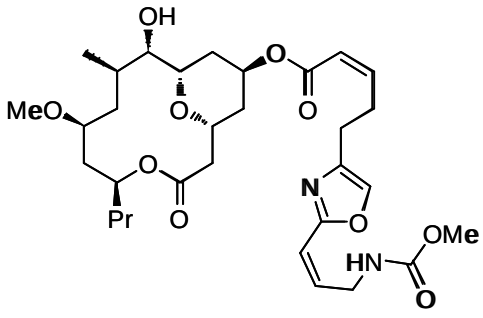
1.55

To a solution of **1.48** (11.5 mg, 0.035 mmol) in THF (0.4 mL) at -78 °C, was added dropwise 1M BH_3/THF solution (135 μL, 0.135 mmol), and then the reaction was allowed to room temperature overnight. A 10% NaOH solution (60 μL) and a 30% aqueous H_2O_2 solution (150 μL) were successively added dropwise at 0 °C. After three hours at room temperature, the resulting mixture was extracted with Et_2O and the combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (5% MeOH in DCM) to afford 4.2 mg (35%) of 1.**54** and 3.9 mg (32%) of **1.55**.

1.54: ^{1}H NMR (300MHz, $CDCl_3$) δ 4.80-4.88 (m, 1H), 3.69-3.88(m, 2H), 3.33-3.39(m, 1H), 3.32(s, 3H), 3.12(apt, *J* = 9.3 Hz, 1H), 2.59(dd, *J* = 4.6, 13.6 Hz, 1H), 2.39(dd, *J* = 9.8, 13.6 Hz, 1H), 2.22-2.27(m, 1H), 1.97-2.06(m, 2H), 1.73-1.83(m, 2H), 1.48-1.62(m, 4H), 1.19-1.37(m, 6H), 0.97(d, *J* = 7.0 Hz, 3H), 0.92(t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.8, 79.2, 75.6, 72.1, 68.1, 62.8, 56.3, 42.2, 40.9, 38.6, 38.2, 37.8, 37.0, 34.7, 29.8, 19.0, 16.2, 13.9; IR (film) 3358, 2957, 2925, 2872, 1727, 1454, 1374, 1262, 1186, 1148, 1084, 1027, 799 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{32}O_6Na$ ($[M+Na]^+$): 367.2097, found 367.2084; $[\alpha]_D^{25}$ = +0.7 ($CHCl_3$, c = 0.58).

1.55: ^{1}H NMR (300MHz, $CDCl_3$) δ 5.19-5.27(m, 1H), 3.85-3.94(m, 2H), 3.35-3.44(m, 1H), 3.33(s, 3H), 3.27-3.33(m, 2H), 2.66(dd, *J* = 3.8, 15.2 Hz, 1H), 2.50(dd, *J* = 11.2, 15.4 Hz, 1H), 2.18(s, 1H), 2.14(dd, *J* = 3.5, 4.6 Hz, 1H), 2.00(ddd, *J* = 2.4, 2.4, 12.4 Hz, 1H), 1.81-1.93(m, 2H), 1.77(dd, *J* = 3.4, 10.7 Hz, 1H), 1.45-1.68(m, 5H), 1.15-1.45(m, 4H), 1.08(d, *J* = 7.0 Hz, 3H), 0.91(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.4, 80.0, 78.5, 72.9, 72.8, 67.9, 56.6, 41.9, 40.3, 39.3, 38.8, 37.2, 35.8, 33.8, 24.0, 18.8, 13.9; IR (film) 3400, 2956, 2922, 1727, 1457, 1366, 1263, 1153, 1089 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{32}O_6Na$ ($[M+Na]^+$): 367.2097, found 367.2089; $[\alpha]_D^{25}$ = +2.7 ($CHCl_3$, c = 0.26)

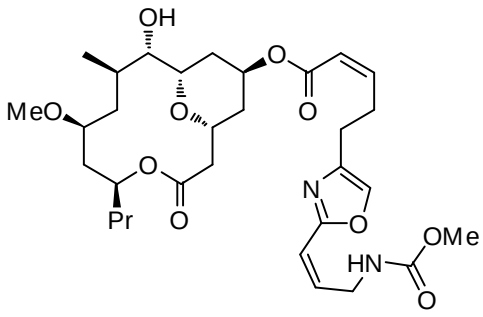
(*Z*)-(1*R*,5*S*,7*S*,9*S*,10*R*,11*S*,13*S*)-10-hydroxy-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-13-yl 5-(2-((*Z*)-3-((methoxycarbonyl)amino)-prop-1-en-1-yl)oxazol-4-yl)pent-2-enoate (1.56)



To a one-dram vial charged with **1.54** (5.8 mg, 0.017 mmol), the oxazole acid **6** (7.0 mg, 0.025 mmol) and PPh_3 (8.8 mg, 0.034 mmol) was added benzene (0.4 mL). The reaction mixture was cooled to 15 °C and DIAD (6.7 μL, 0.034 mmol) in benzene (0.1 mL) was added drop wise. Two hours later the reaction was quenched with 1 drop of water, concentrated under vacuum and purified with flash chromatography (30% THF in pentane) to afford the desired product (4.5 mg, 42%). ^{1}H NMR (400MHz, MeOD) δ 7.70(s, 1H), 6.39(dt, *J* = 7.7, 12.0 Hz, 1H), 6.31(d, *J* = 11.9 Hz, 1H), 6.06(dt, *J* = 6.1, 12.2 Hz, 1H), 5.90(d, *J* = 10.6 Hz, 1H), 5.31(aps, 1H), 4.33(d, *J* = 5.6 Hz, 2H), 4.07(dd, *J* = 6.8, 9.4 Hz, 1H), 3.75(apt, *J* = 6.1 Hz, 1H), 3.67(s, 3H), 3.49(apt, *J* = 10.1 Hz, 1H), 3.39-3.43(m, 1H), 3.33(s, 3H), 3.19(dd, *J* = 2.0, 8.5 Hz,

1H), 3.04(dt, *J* = 7.4, 7.4 Hz, 2H), 2.74(t, *J* = 7.4 Hz, 2H), 2.66(dd, *J* = 4.2, 13.7 Hz, 1H), 2.30(dd, *J* = 10.1, 13.6 Hz, 1H), 2.05(apq, *J* = 12.7 Hz, 2H), 1.76-1.90(m, 3H), 1.51-1.67(m, 4H), 1.22-1.38(m, 4H), 0.97(d, *J* = 7.2 Hz, 3H), 0.94(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100MHz, MeOD) δ 173.1, 167.0, 162.0, 150.1, 142.4, 139.3, 136.1, 121.8, 116.1, 78.7, 77.9, 77.6, 71.1, 69.0, 68.9, 56.6, 52.7, 43.3, 41.2, 40.0, 39.7, 38.3, 36.7, 36.0, 33.8, 29.1, 26.5, 20.2, 17.0, 14.3; IR (film) 3366, 2958, 2924, 2873, 1714, 1520, 1461, 1417, 1264, 1182, 1154, 1091, 820 cm^{-1}; HRMS (ESI) calc. for $C_{31}H_{46}N_2O_{10}Na$ ([M+Na]$^+$): 629.3050, found 629.3055; $[\alpha]_D^{25}$ = +13.3 ($CHCl_3$, c = 0.36).

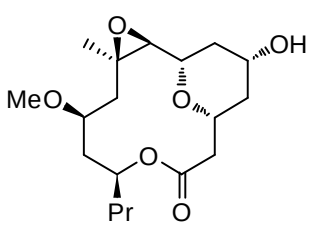
(*Z*)-(1*R*,5*S*,7*S*,9*R*,10*S*,11*S*,13*S*)-10-hydroxy-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-13-yl 5-(2-((*Z*)-3-((methoxycarbonyl)amino)-prop-1-en-1-yl)oxazol-4-yl)pent-2-enoate (1.57)



To a one-dram vial charged with **1.55** (2.6 mg, 0.0075 mmol), the oxazole acid **1.6** (3.6 mg, 0.013 mmol) and PPh_3 (4.4 mg, 0.017 mmol) was added benzene (0.2 mL). The reaction mixture was cooled to 15 °C and DIAD (3.4 μL, 0.017 mmol) in benzene (0.1 mL) was added drop wise. Two hours later the reaction was quenched with 1 drop of water, concentrated under vacuum and purified with flash chromatography (30% THF in pentane) to afford the desired product (2.1 mg, 45%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39(s, 1H), 6.34(dt, *J* = 7.3, 11.5 Hz, 1H), 6.29(dt, *J* = 1.5, 11.6 Hz, 1H), 6.10(dt, *J* = 6.3, 11.9 Hz, 1H), 4.89(dt, *J* = 1.6, 11.4 Hz, 1H), 5.52(brs, 1H), 5.20-5.28(m, 2H), 4.32(t, *J* = 5.8 Hz, 2H), 4.22(apt, *J* = 14.9 Hz, 1H), 3.69(s, 3H), 3.65(dd, *J* = 1.7, 12.1 Hz, 1H), 3.79-3.42(m, 1H), 3.32(s, 3H), 3.21(d, *J* = 9.7 Hz, 1H),

3.04(dtd, *J* = 1.6, 7.5, 7.5 Hz, 2H), 2.72(t, *J* = 7.1 Hz, 2H), 2.61(dd, *J* = 3.8, 15.4 Hz, 1H), 2.42(dd, *J* = 11.4, 15.4 Hz, 1H), 2.10-2.17(m, 1H), 2.00(ddd, *J* = 3.0, 12.1, 15.7 Hz, 1H), 1.80-1.88(m, 2H), 1.60-1.69(m, 2H), 1.41-1.56(m, 4H), 1.25-1.38(m, 4H), 1.07(d, *J* = 7.1 Hz, 3H), 0.92(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.4, 165.3, 149.6, 136.4, 133.9, 133.1, 120.5, 116.7, 78.3, 72.9, 70.4, 67.5, 56.6, 53.4, 42.0, 39.3, 37.3, 35.7, 34.9, 33.7, 33.2, 31.9, 27.7, 25.6, 23.9, 22.7, 18.8, 13.9; IR (film) 3406, 2956, 2923, 2853, 1713, 1643, 1533, 1377, 1261, 1151, 1117, 798 cm^{-1}; HRMS (ESI) calc. for $C_{31}H_{46}N_2O_{10}Na$ ($[M+Na]^+$): 629.3050, found 629.3079; $[\alpha]_D^{25}$ = +6.7 ($CHCl_3$, c = 0.21)

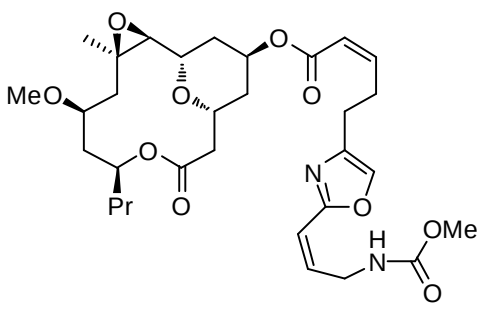
(1*S*,2*S*,4*R*,6*R*,8*S*,12*R*,14*R*)-14-hydroxy-6-methoxy-4-methyl-8-propyl-3,9,16-trioxatricyclo-[10.3.1.02,4]hexadecan-10-one (1.58)



To a one-dram vial charged with the alkene alcohol **1.48** (5.9 mg, 0.018 mmol) and $NaHCO_3$ (5.8 mg, 0.069 mmol) was added CH_2Cl_2 (1 mL). The reaction mixture was cooled to 0 °C and recrystallized *m*-CPBA (4.5 mg, 0.026 mmol) was added in one portion. The reaction was maintained at 0 °C for 4 hours, and then allowed to room temperature overnight. The reaction was quenched by the addition of 0.7 mL saturated $Na_2S_2O_3$ solution and 0.7 mL saturated $NaHCO_3$ solution at 0 °C, and extracted with three 1 mL portions of ethyl acetate. Flash chromatography with (50% EtOAc in hexanes) afforded 3.4 mg (55%) of the epoxy alcohol. ^{1}H NMR (300MHz, $CDCl_3$) δ 5.32-5.42(m, 1H), 3.8(br, 1H), 3.76(tdd, *J* = 1.5, 3.8, 10.9 Hz, 1H), 3.65(dd, *J* = 5.4, 8.9 Hz, 1H), 3.06(ddd, *J* = 2.0, 8.0, 10.9 Hz, 1H), 2.71(d, *J* = 7.8 Hz, 1H), 2.58(dd, *J* = 3.8, 15.1 Hz, 1H), 2.50(dd, *J* = 10.8, 15.2 Hz, 1H), 2.25(dt, *J* = 2.4, 12.4 Hz, 1H), 2.12(dd, *J* = 11.2, 14.6 Hz, 1H), 1.86-2.00(m, 3H), 1.43-1.62(m, 5H), 1.34(s, 3H), 1.24-

1.39(m, 6H), 0.91(t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.2, 73.9, 73.4, 67.4, 64.6, 61.8, 57.2, 44.4, 41.8, 41.6, 39.8, 39.3, 37.3, 23.3, 22.7, 18.7, 13.9; IR (film) 3435, 2924, 2854, 1732, 1459, 1374, 1262, 1200, 1078, 942, 799cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{30}O_6Na$ ($[M+Na]^+$): 365.1940, found 365.1932; $[\alpha]_D^{25}$ = -23.5 ($CHCl_3$, c = 0.33).

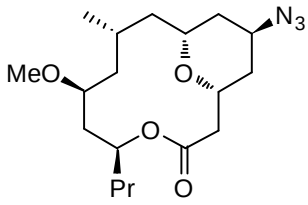
(*Z*)-(1*S*,2*S*,4*R*,6*R*,8*S*,12*R*,14*S*)-6-methoxy-4-methyl-10-oxo-8-propyl-3,9,16-trioxatricyclo[10.3.1.02,4]hexadecan-14-yl 5-(2-((*Z*)-3-((methoxycarbonyl)amino)prop-1-en-1-yl)oxazol-4-yl)pent-2-enoate (1.59)



General protocol B was followed, starting from the epoxy alcohol **1.58** (3.1 mg, 0.009 mmol), the oxazolic acid **1.6** (11.2 mg, 0.040 mmol), PPh_3 (11.4 mg, 0.044 mmol) and DIAD (8.6 μL, 0.044 mmol). Flash column chromatography (30% EtOAc in CH_2Cl_2) yielded 3.6 mg (66%) of the epoxy analog. ^{1}H NMR (300MHz, CD_3OD) δ 7.65(s, 1H), 6.36(dt, *J* = 4.1, 7.3 Hz, 1H), 6.27(dt, *J* = 2.1, 11.9 Hz, 1H), 6.03(pentet, *J* = 6.0 Hz, 1H), 5.89(dt, *J* = 1.6, 11.6 Hz, 1H), 5.27-5.39(m, 1H), 5.28(t, *J* = 3.0 Hz, 1H), 4.30(dd, *J* = 1.8, 6.1 Hz, 2H), 4.08-4.18(m, 1H), 3.72(dd, *J* = 5.3, 10.0 Hz, 1H), 3.65(s, 3H), 3.34-3.42(m, 1H), 3.37(s, 3H), 3.00(ddd, *J* = 1.7, 7.4, 7.4 Hz, 2H), 2.71(t, *J* = 7.1 Hz, 2H), 2.63-2.70(m, 2H), 2.33(dd, *J* = 11.6, 15.2 Hz, 1H), 2.04(dd, *J* = 10.4, 14.7 Hz, 2H), 1.74-1.96(m, 4H), 1.47-1.66(m, 4H), 1.26-1.40(m, 4H), 1.30(s, 3H), 0.93(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75MHz, CD_3OD) δ 172.4, 166.7, 161.9, 150.2, 142.2, 139.1, 136.0, 121.6, 116.0, 77.8, 74.9, 72.2, 68.2, 66.1, 63.0, 57.0, 44.8, 42.7, 42.0, 38.4, 35.4, 34.9, 29.0, 26.4, 23.7, 19.7, 14.1; IR (film) 3352, 2960, 2924, 1724, 1644, 1521, 1440, 1380, 1266,

1253, 1173, 1126, 1077, 1006, 968, 778 cm^{-1}; HRMS (ESI) calc. for $C_{31}H_{46}N_2O_{10}Na$ ($[M+Na]^+$): 627.2894, found 627.2910; $[\alpha]_D^{25}$ = -11.3 (MeOH, c = 0.34).

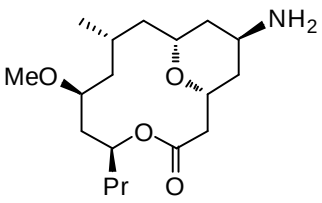
(1*R*,5*S*,7*S*,9*S*,11*R*,13*R*)-13-azido-7-methoxy-9-methyl-5-propyl-4,15-dioxa-bicyclo[9.3.1]-pentadecan-3-one (1.61)



To a mixture of the macrocyclic alcohol **1.5** (11.3 mg, 0.031 mmol), triethylamine (48 μL, 0.34 mmol) and dichloromethane (0.5 mL) at 0 °C was added MsCl (8.0 μL, 0.10 mmol). The reaction was kept at 0 °C for 30 minutes, allowed to room temperature and stirred for 4 hours. Then the reaction mixture was cooled to 0 °C, treated with 1N HCl, and extracted with dichloromethane for three times. The organic extracts were dried with $MgSO_4$, filtered and concentrated under vacuum to afford **1.60**. ^{1}H NMR (300MHz, $CDCl_3$) δ 5.12-5.20(m, 1H), 4.82(ddd, J = 5.0, 11.3, 16.3 Hz, 1H), 3.80(dddd, J = 2.2, 4.3, 11.2, 11.2 Hz, 1H), 3.52(apt, J = 8.9 Hz, 1H), 3.31(s, 3H), 3.23(apt, J = 10.0 Hz, 1H), 3.03(s, 3H), 2.65(dd, J = 4.4, 14.5 Hz, 1H), 2.44(dd, J = 10.7, 14.5 Hz, 1H), 2.12-2.19(m, 1H), 2.03-2.08(m, 1H), 1.84(dd, J = 10.5, 13.4 Hz, 1H), 1.61-1.73(m, 2H), 1.45-1.59(m, 5H), 1.10-1.41(m, 7H), 0.99(d, J = 6.7 Hz, 3H), 0.91(t, J = 7.2 Hz, 3H). This residual crude product was re-dissolved in DMF (1 mL) and treated with sodium azide (16.9 mg, 0.26 mmol) at 80 °C overnight. The reaction mixture was dispersed between water and diethyl ether, and the organic layer was concentrated under vacuum. Flash chromatography (30% ethyl acetate in pentane) afforded the desired azide (4.9mg, 42% over two steps). ^{1}H NMR (300MHz, $CDCl_3$) δ 5.19 (ddd, *J* = 4.5, 10.0, 10.0 Hz, 1H), 4.02-4.09(m, 2H), 3.54(apt, *J* = 9.5 Hz, 2H), 3.30(s, 3H), 2.61(dd, *J* = 4.3, 14.5 Hz, 1H), 2.35(dd, *J* = 10.8, 14.6 Hz, 1H), 1.84(dd, *J* = 10.9, 14.7 Hz, 1H), 1.63-1.76(m, 2H), 1.46-1.61(m, 6H), 1.31-1.43(m, 5H), 1.11-1.25(m, 3H), 0.99(d, *J* = 6.4

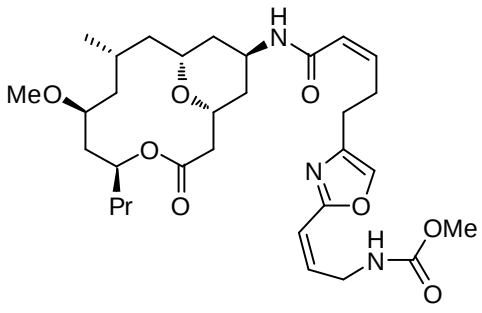
Hz, 3H), 0.92(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.6, 75.6, 75.3, 73.0, 69.4, 56.2, 44.0, 42.2, 40.1, 37.0, 35.9, 34.8, 31.3, 25.6, 19.0, 13.9; IR (film) 2956, 2922, 2871, 2100, 1731, 1460, 1438, 1382, 1272, 1244, 1197, 1165, 1086, 1032, 992, 797 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{33}N_3O_4Na$ ($[M+Na]^+$): 376.2212, found 376.2239; $[\alpha]_D^{25}$ = +39.1 ($CHCl_3$, c = 0.45)

(1*R*,5*S*,7*S*,9*S*,11*R*,13*R*)-13-amino-7-methoxy-9-methyl-5-propyl-4,15-dioxa-bicyclo[9.3.1]-pentadecan-3-one (1.62)



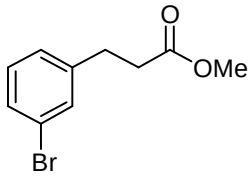
A mixture of **1.61** (4.9 mg, 0.013 mmol) and 10% Pd/C (4.9 mg) in ethanol (0.5 mL) was stirred under hydrogen atmosphere for 5 hours. The mixture was then filtered through Celite and purified on a flash column (10% MeOH in dichloromethane with 1% ammonium hydroxide) to give 3.9 mg (83%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 5.14-5.23(m, 1H), 4.09-4.21(m, 1H), 3.63(m, 2H), 3.44(app s, 1H), 3.31(s, 3H), 2.57(dd, *J* = 3.8, 14.7 Hz, 1H), 2.35(dd, *J* = 10.8, 14.0 Hz, 1H), 2.17(s, 1H), 1.86(dd, *J* = 10.6, 14.6 Hz, 1H), 1.30-1.40(m, 5H), 1.42-1.75(m, 8H), 1.14(t, *J* = 11.6 Hz, 2H), 0.98(d, *J* = 6.1 Hz, 3H), 0.91(t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 171.2, 75.6, 74.7, 72.8, 69.0, 56.2, 44.3, 42.6, 42.3, 40.2, 39.5, 38.3, 37.0, 31.4, 25.7, 19.9, 13.9; IR (film) 3372, 2956, 2923, 2869, 1728, 1460, 1439, 1382, 1341, 1275, 1196, 1157, 1088, 1029, 795 cm^{-1}; HRMS (ESI) calc. for $C_{18}H_{33}NO_4Na$ ($[M+Na]^+$): 350.2307, found 350.2320; $[\alpha]_D^{25}$ = +21.8 ($CHCl_3$, c = 0.38).

Methyl (*Z*)-3-(4-((*Z*)-5-((1*R*,5*S*,7*S*,9*S*,11*R*,13*R*)-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxa-bicyclo[9.3.1]pentadecan-13-ylamino)-5-oxopent-3-enyl)oxazol-2-yl)allylcarbamate (1.63)



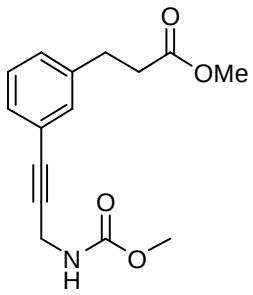
The macrolactone amine **1.62** (3.8 mg, 0.012 mmol), the oxazole acid **1.6** (7.6 mg, 0.027 mmol), diisopropylethylamine (9 μL, 0.052 mmol) and DCM (0.8 mL) were mixed and cooled to 0 °C. PyBOP (19.0 mg, 0.036 mmol) was added, and it was allowed to room temperature overnight. The reaction mixture was then concentrated and purified through a flash column (60% ethyl acetate in pentane) to afford 5.3 mg (77%) of the desired amide. ^{1}H NMR (300MHz, MeOD) δ 7.67(s, 1H), 6.30(dt, *J* = 2.1, 11.9 Hz, 1H), 6.10(dt, *J* = 7.1, 11.5 Hz, 1H), 6.06(d, *J* = 11.9 Hz, 1H), 5.99(dt, *J* = 1.4, 11.5 Hz, 1H), 5.16-5.25(m, 1H), 4.33(dd, *J* = 1.7, 5.8 Hz, 2H), 4.16-4.22(m, 1H), 4.08(dddd, *J* = 1.3, 1.3, 10.9, 10.9 Hz, 1H), 3.71(app t, *J* = 8.8 Hz, 1H), 3.68(s, 3H), 3.56(app t, *J* = 9.7 Hz, 1H), 3.31(s, 3H), 3.01(dt, *J* = 7.4, 7.4 Hz, 2H), 2.71(t, *J* = 7.4 Hz, 2H), 2.67-2.74(m, 1H), 2.32(dd, *J* = 10.9, 14.8 Hz, 1H), 1.91(dd, *J* = 10.9, 14.8 Hz, 1H), 1.69-1.79(m, 2H), 1.45-1.61(m, 7H), 1.10-1.43(m, 6H), 1.02(d, *J* = 6.5 Hz, 3H), 0.96(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75MHz, MeOD) δ 173.2, 168.9, 161.9, 145.0, 142.6, 139.2, 136.1, 124.3, 116.0, 77.2, 77.1, 73.9, 56.5, 52.7, 45.5, 44.9, 43.6, 43.5, 41.2, 41.1, 38.1, 173.2, 168.9, 161.9, 145.0, 142.6, 139.2, 136.1, 124.3, 116.0, 77.2, 77.1, 73.9, 56.5, 52.7, 45.5, 44.9, 43.6, 43.5, 41.2, 41.1, 38.1, 37.4, 36.2, 32.7, 28.7, 26.7, 26.1, 20.1, 14.2; IR (film) 3413, 2922, 2851, 1725, 1711, 1660, 1631, 1550, 1533, 1462, 1377, 1260, 1086, 1018, 798 cm^{-1}; HRMS (ESI) calc. for $C_{31}H_{47}N_3O_8Na$ ([M+Na]$^{+}$): 612.3261, found 612.3264; $[\alpha]_D^{25}$ = +10.7 (MeOH, c = 0.53).

Methyl 3-(3-bromophenyl)propanoate (1.69)



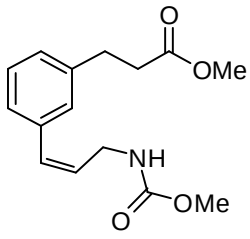
To a solution of 3-(3-bromophenyl)propanoic acid (1.603 g, 7.0 mmol) in methanol (20 mL) was added dropwise $SOCl_2$ (1.03 mL, 14.2 mmol) at 0 °C. The reaction was allowed to room temperature and stirred overnight. Concentration at reduced temperature and flash chromatography (20% ethyl acetate in hexanes) afforded 1.727 g (quantitative yield) of the desired ester. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.35(s, 1H), 7.34(d, J = 7.4 Hz, 1H), 7.12-7.19(m, 2H), 3.68(s, 3H), 2.92(t, J = 7.6 Hz, 2H), 2.62 (t, J = 7.9 Hz, 2H).

Methyl 3-(3-(3-(methoxycarbonyl)prop-1-ynyl)phenyl)propanoate (1.71)



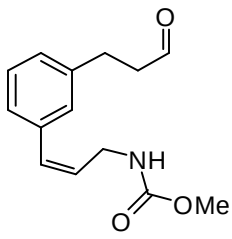
To a flame-dried 50 mL round bottom flask was charged methyl 3-(3-bromophenyl)propanoate **1.69** (122 mg, 0.50 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.050 mmol), PPh_3 (26 mg, 0.10 mmol), CuI (9.5 mg, 0.050 mmol) , distilled diisopropylamine (0.64 mL, 4.5 mmol) and distilled THF (2 mL). The reaction was degassed with argon for 15 minutes, and then methyl prop-2-ynylcarbamate **1.70** (124 mg, 1.1 mmol) was added drop wise with a syringe. The reaction mixture was heated to 55 °C overnight with argon protection. Flash chromatography with 40% ethyl acetate in hexanes gave 121 mg (88%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.14-7.26(m, 4H), 5.12(brs, 1H), 4.16(d, *J* = 4.9 Hz, 2H), 3.71(s, 3H), 3.67(s, 3H), 2.91(t, *J* = 7.8 Hz, 2H), 2.61(t, *J* = 7.7 Hz, 2H).

(*Z*)-methyl 3-(3-(3-(methoxycarbonyl)prop-1-enyl)phenyl)propanoate (1.72)



To a 25 mL round bottom flask was charged nickel acetate tetra hydrate (21.7 mg, 0.087 mmol) and 95% ethanol (1 mL), and hydrogen atmosphere was applied. Then 0.11 mL $NaBH_4$ solution (1N, 0.11 mmol) in 95% ethanol (with 0.1N NaOH) was added to the flask within 10 seconds. After three minutes ethylenediamine (11.7 μL, 0.175 mmol) was added, followed by another three minutes of stirring. Methyl 3-(3-(3-(methoxycarbonyl)prop-1-ynyl)phenyl)propanoate **1.71** (55 mg, 0.20 mmol) was added. After 1.5 hours the reaction mixture was partitioned between diethyl ether and water. The organic phase was dried with sodium sulfate, filtered and concentrated under vacuum. Flash chromatography with 50% ethyl acetate in hexanes gave 44.1 mg (80%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.27(t, J= 7.0 Hz, 1H), 7.04-7.11(m, 3H), 6.54(d, *J* = 11.6 Hz, 1H), 5.67(dt, *J* = 6.6, 11.5 Hz, 1H), 4.86(brs, 1H), 4.06(t, *J* = 5.4 Hz, 2H), 3.68(s, 3H), 3.67(s, 3H), 2.95(t, *J* = 7.8 Hz, 2H), 2.64(t, *J* = 7.5 Hz, 2H).

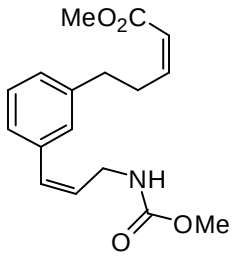
(*Z*)-methyl 3-(3-(3-oxopropyl)phenyl)allylcarbamate (1.73)



To a 25 mL round bottom flask was charged (*Z*)-methyl 3-(3-(3-(methoxycarbonyl)prop-1-enyl)phenyl)propanoate **1.72** (44.1 mg, 0.159 mmol) and dichloromethane (3 mL). The reaction was cooled to -78 °C, and 1M DIBAL-H (0.21 mL, 0.21 mmol) solution in hexanes was added drop wise under nitrogen. After 1 hour of stirring at -78 °C, The reaction was quenched with saturated ammonium chloride aqueous solution. Flash chromatography with 40% ethyl acetate in hexanes gave 25.2 mg (64%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 9.82(s, 1H), 7.26(t, *J*

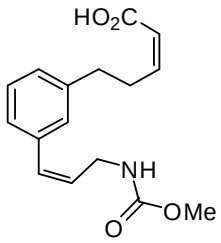
= 4.0 Hz, 1H), 7.02-7.11(m, 3H), 6.54(d, *J* = 11.6 Hz, 1H), 5.67(dt, *J* = 6.6, 11.6 Hz, 1H), 4.81(brs, 1H), 4.07(t, *J* = 5.3 Hz, 2H), 3.68(s, 3H), 2.96(t, *J* = 7.4 Hz, 2H), 2.79(t, *J* = 7.6 Hz, 2H).

(*Z*)-methyl 5-(3-((*Z*)-3-(methoxycarbonyl)prop-1-enyl)phenyl)pent-2-enoate



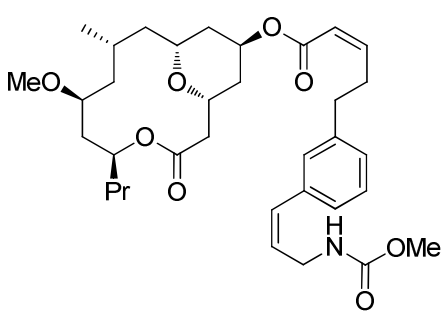
To a 25 mL round bottom flask was charged methyl bis(trifluoroethyl)phosphonoacetate (27 μL, 0.13 mmol), 18-crown-6 (102 mg, 0.39 mmol) and THF (1 mL). The mixture was cooled to -78 °C, and KHMDS (19 mg, 0.095 mmol) in 2 mL THF was added drop wise under nitrogen. After 30 minutes of stirring the (*Z*)-methyl 3-(3-(3-oxopropyl)phenyl)allylcarbamate **1.73** (16.7 mg, 0.068 mmol) in 2 mL THF was added drop wise, followed by 4 hours of stirring at -78 °C. The reaction was quenched with saturated NH_4Cl aqueous solution and extracted with ethyl acetate. Flash chromatography with 30% ethyl acetate in hexanes gave 16.8 mg (82%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.27(t, *J* = 7.6 Hz, 1H), 7.12(d, *J* = 7.7 Hz, 1H), 7.07(s, 1H), 7.06(d, *J* = 8.1 Hz, 1H), 6.54(d, *J* = 11.6 Hz, 1H), 6.26(dt, *J* = 7.5, 11.5 Hz, 1H), 5.80(dt, *J* = 1.6, 11.5 Hz, 1H), 5.67(dt, *J* = 6.7, 11.8 Hz, 1H), 4.84(brs, 1H), 4.08(t, *J* = 5.2 Hz, 2H), 3.70(s, 3H), 3.68(s, 3H), 2.99(td, *J* = 1.3, 7.6 Hz, 2H), 2.76(t, *J* = 8.0 Hz, 2H);); ^{13}C NMR (75MHz, $CDCl_3$) δ 166.7, 149.2, 141.2, 136.4, 131.5, 128.9, 128.4, 127.4, 126.5, 120.0, 52.2, 51.1, 39.3, 35.0, 30.4; IR (film) 3399, 1719, 1643, 1570, 1453, 1251, 1147, 1071, 1023, 819 cm^{-1}; HRMS (ESI) calc. for $C_{17}H_{21}NO_4Na$ ([M+Na]+): 326.1368, found 326.1360.

(Z)-5-(3-((Z)-3-((methoxycarbonyl)amino)prop-1-en-1-yl)phenyl)pent-2-enoic acid (1.74)



The (*Z*)-methyl 5-(3-((*Z*)-3-(methoxycarbonyl)prop-1-enyl)- phenyl)-pent-2-enoate (14.1 mg, 0.046 mmol) was dissolved in THF (0.22 mL) at room temperature. After 1N LiOH aqueous solution (0.45 mL, 0.45 mmol) was added, the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was acidified with 2N HCl drop wise at 0 °C to pH 3, and extracted with three 2 mL portions of ethyl acetate. The organic phase was dried with Na_2SO_4, filtered and concentrated under vacuum. Flash chromatography with 5% methanol in dichloromethane gave 12.7 mg (95%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.26(t, *J* = 7.8 Hz, 1H), 7.03-7.10(m, 3H), 6.55(d, *J* = 11.6 Hz, 1H), 6.34(dt, *J* = 7.5, 11.3 Hz, 1H), 5.81(d, *J* = 11.5 Hz, 1H), 5.64(dt, *J* = 6.5, 11.8 Hz, 1H), 4.84(brs, 1H), 4.09(app s, 2H), 3.69(s, 3H), 3.00(dt, *J* = 7.5, 7.5 Hz, 2H), 2.77(t, *J* = 7.6 Hz, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 169.9, 157.2, 150.5, 141.0, 136.4, 131.6, 128.8, 128.3, 128.1, 127.6, 126.6, 120.2, 52.4, 39.6, 34.9, 30.6; IR (film) 3336, 2924, 1700, 1641, 1531, 1435, 1260, 1194, 1152, 803 cm^{-1}; HRMS (ESI) calc. for $C_{16}H_{19}NO_4Na$ ([M+Na]+): 312.1212, found 312.1215.

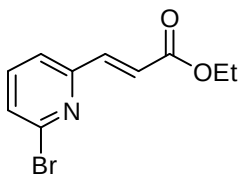
(*Z*)-(1*R*,5*S*,7*S*,9*S*,*11R*,13*R*)-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1]-pentadecan-13-yl 5-(3-((*Z*)-3-((methoxycarbonyl)amino)prop-1-en-1-yl)-phenyl)pent-2-enoate (1.64)



General protocol B was followed, starting from the macrocyclic alcohol **1.5** (2.2 mg, 0.0067 mmol), the phenyl acid **1.74** (7.1 mg, 0.024 mmol), PPh_3 (7.0 mg, 0.027 mmol) and DIAD (5.4 μL, 0.027 mmol). Flash column

chromatography (30% THF in hexanes) yielded 3.5 mg (87%) of the desired product. ^{1}H NMR (400MHz, CD_3OD) δ 7.27(t, *J* = 7.8 Hz, 1H), 7.13(d, *J* = 5.8 Hz, 1H), 7.13(s, 1H), 7.09(d, *J* = 7.8 Hz, 1H), 6.52(d, *J* = 11.6 Hz, 1H), 6.36(dt, *J* = 7.6, 11.6 Hz, 1H), 5.85(dt, *J* = 1.5, 11.6 Hz, 1H), 5.65(dt, *J* = 6.5, 11.6 Hz, 1H), 5.14-5.20(m, 2H), 4.02-4.07(m, 1H), 3.99(apd, *J* = 5.3, 2H), 3.66(apt, *J* = 9.7 Hz, 1H), 3.64(s, 3H), 3.54(apt, *J* = 9.5 Hz, 1H), 3.27(s, 3H), 3.00(dt, *J* = 7.8, 7.8 Hz, 2H), 2.79(t, *J* = 7.4 Hz, 2H), 2.67(dd, *J* = 4.3, 14.8 Hz, 1H), 2.28(dd, *J* = 11, 14.8 Hz, 1H), 1.75-1.89(m, 3H), 1.61-1.73(m, 2H), 1.44-1.60(m, 4H), 1.25-1.42(m, 5H), 1.11(ddd, J= 2.0, 11.0, 13.0 Hz, 1H), 0.96(d, *J* = 6.7 Hz, 3H), 0.93(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100MHz, CD_3OD) δ 173.1, 166.9, 150.6, 142.6, 138.0, 131.8, 130.0, 129.4, 128.4, 127.6, 121.4, 77.1, 77.0, 73.9, 71.3, 69.1, 56.4, 52.4, 45.3, 43.5, 43.2, 41.1, 40.4, 38.0, 37.4, 36.2, 36.0, 32.6, 31.9, 26.0, 22.3, 20.0, 14.1; IR (film) 3338, 2956, 2923, 2854, 1717, 1643, 1527, 1460, 1375, 1250, 1180, 1156, 1111, 1084, 1033, 800 cm^{-1}; HRMS (ESI) calc. for $C_{34}H_{49}NO_8Na$ ($[M+Na]^+$): 622.3356, found 622.3322; $[\alpha]_D^{25}$ = +14.2 (MeOH, c = 0.33).

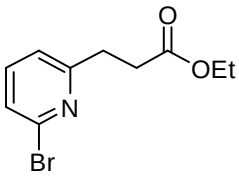
(*E*)-ethyl 3-(6-bromopyridin-2-yl)acrylate (1.76)



To a suspension of 60% sodium hydride (135 mg, 3.38 mmol) in THF (10 mL) $(EtO)_2P(O)CH_2CO_2Et$ (0.62 mL, 3.1 mmol) was added drop wise at 0 °C under nitrogen. Thirty minutes later, 6-bromopicolinaldehyde **1.75** (465 mg, 2.5 mmol) in 2 mL THF was added dropwise, and the reaction mixture was allowed to room temperature afterwards. After 1 hour, the reaction mixture was partitioned between diethyl ether and water. The organic phase was dried, filtered and concentrated under vacuum. Flash chromatography with 20% diethyl ether in hexanes gave 615 mg (96%) of the desired product.

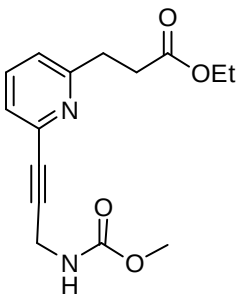
^{1}H NMR (300MHz, $CDCl_3$) δ 7.57(t, *J* = 7.3 Hz, 1H), 7.53(d, *J* = 15.5 Hz, 1H), 7.44(d, *J* = 7.7 Hz, 1H), 7.46(d, *J* = 7.5 Hz, 1H), 6.95(d, *J* = 15.6 Hz, 1H), 4.22(q, *J* = 7.1 Hz, 2H), 1.33(t, *J* = 7.1 Hz, 3H).

Ethyl 3-(6-bromopyridin-2-yl)propanoate (1.77)



In a 25 mL round bottom flask (*E*)-ethyl 3-(6-bromopyridin-2-yl)acrylate **1.76** (595 mg, 2.32 mmol) and CuCl (241 mg, 2.43 mmol) was dissolved in 80% methanol (13.5 mL) at 0 °C under nitrogen. $NaBH_4$ (92.0 mg, 2.32 mmol) was added, 1 hour later another $NaBH_4$ (92.0 mg, 2.32 mmol), and an additional hour later a third $NaBH_4$ (46.0 mg, 1.16 mmol) was added. After 30 minutes the reaction mixture was partitioned between diethyl ether and water, and the organic phase was dried, filtered and concentrated under vacuum. Flash chromatography with 20% diethyl ether in dichloromethane gave 448 mg (75%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.45(t, *J* = 7.6 Hz, 1H), 7.31(d, *J* = 7.8 Hz, 1H), 7.16(d, *J* = 7.4 Hz, 1H), 4.13(q, *J* = 7.2 Hz, 2H), 3.08(t, *J* = 7.4 Hz, 2H), 2.78(t, *J* = 7.4 Hz, 2H), 1.24(t, *J* = 7.2 Hz, 3H).

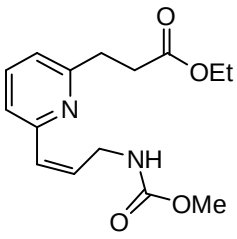
Ethyl 3-(6-(3-(methoxycarbonyl)prop-1-ynyl)pyridin-2-yl)propanoate (1.78)



To a flame-dried 50 mL round bottom flask was charged ethyl 3-(6-bromopyridin-2-yl)propanoate **1.77** (194 mg, 0.75 mmol), $PdCl_2(PPh_3)_2$ (52 mg, 0.074 mmol), PPh_3 (39 mg, 0.15 mmol), CuI (14.4 mg, 0.076 mmol) , distilled diisopropylamine (0.96 mL, 6.8 mmol) and distilled THF (3 mL). The reaction was degassed with argon for 15 minutes, and then methyl prop-2-ynylcarbamate **1.70** (186 mg, 1.65 mmol) was added drop wise with a syringe. The

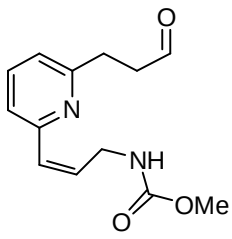
reaction mixture was heated at 50 °C for 1.5 hours with argon protection. Flash chromatography with 40% ethyl acetate in hexanes gave 206 mg (91%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.56(t, *J* = 7.8 Hz, 1H), 7.26(d, *J* = 7.8 Hz, 1H), 7.16(d, *J* = 7.8 Hz, 1H), 5.28(brs, 1H), 4.24(d, *J* = 5.7 Hz, 2H), 4.11(q, *J* = 7.2 Hz, 2H), 3.71(s, 3H), 3.09(t, *J* = 7.5 Hz, 2H), 2.78(t, *J* = 7.5 Hz, 2H), 1.23(t, *J* = 7.2 Hz, 3H).

(*Z*)-ethyl 3-(6-(3-(methoxycarbonyl)prop-1-enyl)pyridin-2-yl)propanoate



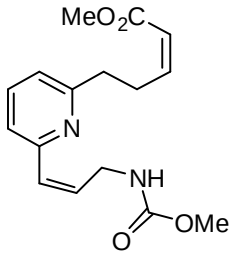
To a 25 mL round bottom flask was charged nickel acetate tetra hydrate (30.6 mg, 0.123 mmol) and 95% ethanol (1 mL), and hydrogen atmosphere was applied. Then 0.15 mL $NaBH_4$ solution (1N, 0.15 mmol) in 95% ethanol (with 0.1N NaOH) was added to the flask within 10 seconds. After three minutes ethylenediamine (16.5 μL, 0.25 mmol) was added, followed by another three minutes of stirring. Ethyl 3-(6-(3-(methoxycarbonyl)prop-1-ynyl)pyridin-2-yl)propanoate **1.78** (90 mg, 0.31 mmol) was added. After 1 hour the reaction mixture was partitioned between diethyl ether and water. The organic phase was dried with sodium sulfate, filtered and concentrated. Flash chromatography with 40% ethyl acetate in hexanes gave 58.8 mg (65%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.57(t, *J* = 7.7 Hz, 1H), 7.05(d, *J* = 6.9 Hz, 1H), 7.02(d, *J* = 6.6 Hz, 1H), 6.46(d, *J* = 11.7 Hz, 1H), 5.97(dt, *J* = 6.9, 11.5 Hz, 1H), 5.97(brs, 1H), 4.30(t, *J* = 6.1 Hz, 2H), 4.15(q, *J* = 7.1 Hz, 2H), 3.68(s, 3H), 3.13(t, *J* = 7.4 Hz, 2H), 2.82(t, *J* = 7.3 Hz, 2H), 1.22(t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 173.0, 159.3, 157.1, 154.9, 136.6, 133.0, 129.9, 122.1, 120.9, 60.3, 51.8, 39.2, 32.9, 32.7, 14.0.

(*Z*)-methyl 3-(6-(3-oxopropyl)pyridin-2-yl)allylcarbamate (1.79)



To a 25 mL round bottom flask was charged (*Z*)-ethyl 3-(6-(3-(methoxycarbonyl)prop-1-enyl)pyridin-2-yl)propanoate (79.9 mg, 0.273 mmol) and dichloromethane (3.5 mL). The reaction was cooled to -78 °C, and 1M DIBAL-H (0.33 mL, 0.33 mmol) solution in hexanes was added drop wise under nitrogen. After 2 hour of stirring at -78 °C, The reaction was quenched with saturated ammonium chloride aqueous solution. Flash chromatography with 40% ethyl acetate in hexanes gave 28.4 mg (42%) of the desired product, together with 14 mg (18%) of recycled starting material and 25 mg (37%) of over-reduced alcohol. ^{1}H NMR (300MHz, $CDCl_3$) δ 9.88(t, *J* = 1.2 Hz, 1H), 7.57(t, *J* = 7.7 Hz, 1H), 7.05(d, *J* = 7.5 Hz, 1H), 7.03(d, *J* = 7.7 Hz, 1H), 6.45(d, *J* = 11.7 Hz, 1H), 5.95(dt, *J* = 6.6, 11.7 Hz, 1H), 5.76(brs, 1H), 4.31(td, *J* = 1.6, 6.5 Hz, 2H), 3.68(s, 3H), 3.15(t, *J* = 6.8 Hz, 2H), 2.98(t, *J* = 7.2 Hz, 2H).

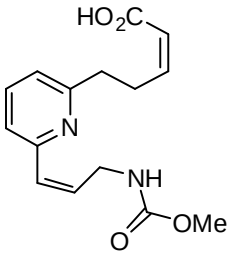
(*Z*)-methyl 5-(6-((Z)-3-(methoxycarbonyl)prop-1-enyl)pyridin-2-yl)pent-2-enoate (1.80)



To a 25 mL round bottom flask was charged methyl bis(trifluoroethyl)phosphonoacetate (44 μL, 0.21 mmol), 18-crown-6 (165 mg, 0.624 mmol) and THF (2 mL). The mixture was cooled to -78 °C, and KHMDS (30 mg, 0.15 mmol) in 3 mL THF was added drop wise under nitrogen. After 30 minutes of stirring (*Z*)-methyl 3-(6-(3-oxopropyl)pyridin-2-yl)allylcarbamate **1.79** (27.0 mg, 0.109 mmol) in 3 mL THF was added drop wise, followed by 4 hours of stirring at -78 °C. The reaction was quenched with saturated NH_4Cl aqueous solution and extracted with ethyl acetate. Flash chromatography with 10% THF in dichloromethane gave 23.6 mg (71%) of

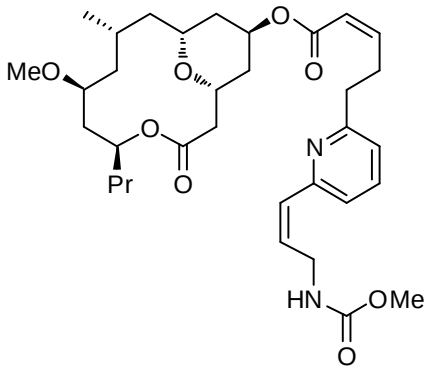
the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.57(t, *J* = 7.7 Hz, 1H), 7.04(d, *J* = 7.1 Hz, 1H), 7.02(d, *J* = 6.7 Hz, 1H), 6.48(d, *J* = 11.7 Hz, 1H), 6.30(dt, *J* = 7.5, 11.5 Hz, 1H), 6.06(brs, 1H), 6.01(dt, *J* = 6.1, 11.4 Hz, 1H), 5.81(dt, *J* = 1.6, 11.5 Hz, 1H), 4.29(t, *J* = 6.3 Hz, 2H), 3.70(s, 3H), 3.67(s, 3H), 3.12(dtd, *J* = 1.0, 7.4, 7.4 Hz, 2H), 2.95(t, *J* = 7.8 Hz, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 166.7, 160.2, 157.3, 155.0, 149.2, 136.8, 132.9, 130.4, 122.1, 120.9, 120.0, 52.0, 51.1, 39.1, 37.4, 28.7; IR (film) 3399, 1719, 1643, 1570, 1530, 1453, 1521, 1147, 1023, 819 cm^{-1}; HRMS (ESI) calc. for $C_{16}H_{20}N_2O_4Na$ ($[M+Na]^+$): 327.1321, found 327.1302.

(Z)-5-(6-((Z)-3-(methoxycarbonyl)prop-1-enyl)pyridin-2-yl)pent-2-enoic acid



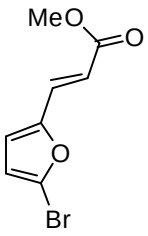
(*Z*)-methyl 5-(6-((*Z*)-3-(methoxycarbonyl)prop-1-enyl)pyridin- 2-yl)pent-2-enoate **1.80** (18.2 mg, 0.060 mmol) was dissolved in THF (0.35 mL) at room temperature. After 1N LiOH aqueous solution (0.90 mL, 0.90 mmol) was added, the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was adjusted to pH 8 at 0 °C, and extracted with 2 mL of ethyl acetate. The aqueous layer was continued to be acidified to pH 2, with ethyl acetate extraction at every 2 pH intervals. The combined organic phase was dried with $MgSO_4$, concentrated, re-dissolved in 10% methanol in dichloromethane, filtered through a thin plug of silica gel and concentrated under vacuum. The salts was obtained in 14.8 mg (85%) and used directly in the next Mitsunobu reaction without further purification.

(*Z*)-(1*R*,5*S*,7*S*,9*S*,11*R*,13*R*)-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1]-pentadecan-13-yl 5-(6-((*Z*)-3-((methoxycarbonyl)amino)prop-1-en-1-yl)-pyridin-2-yl)pent-2-enoate (1.65)



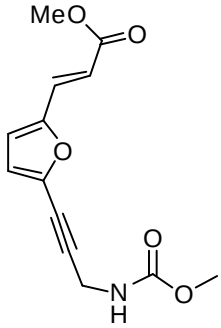
General protocol B was followed, starting from the macrocyclic alcohol **1.5** (2.6 mg, 0.008 mmol), the pyridal acid (9.8 mg, 0.034 mmol), PPh_3 (16.8 mg, 0.064 mmol) and DIAD (12.5 μL, 0.064 mmol). Flash column chromatography (first with 30% THF in pentane, then a second column with 50% EtOAc in pentane) yielded 3.2 mg (67%) of the desired analog. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.59(t, *J* = 7.7 Hz, 1H), 7.00-7.09(m, 3H), 6.49(d, *J* = 11.7 Hz, 1H), 5.94-6.04(m, 1H), 5.94(dt, *J* = 1.4, 15.6 Hz, 1H), 5.10-5.21(m, 2H), 5.04(brs, 1H), 4.31(t, *J* = 6.5 Hz, 2H), 4.06(tdd, *J* = 2.2, 4.2, 11.3 Hz, 1H), 3.69(s, 3H), 3.51-3.60(m, 2H), 3.32(s, 3H), 2.99(t, *J* = 8.0 Hz, 2H), 2.72(dd, *J* = 6.8, 14.9 Hz, 2H), 2.58(dd, *J* = 4.4, 9.3 Hz, 1H), 2.36(dd, *J* = 7.0, 10.8 Hz, 1H), 1.85-1.96(m, 1H), 1.62-1.79(m, 3H), 1.45-1.58(4H), 1.11-1.43(m, 10H), 0.98(d, *J* = 6.4 Hz, 3H), 0.92(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.9, 165.8, 159.7, 157.2, 155.2, 148.5, 136.9, 133.1, 130.3, 122.3, 121.9, 120.9, 75.6, 75.4, 73.4, 69.8, 67.8, 56.2, 52.0, 44.0, 42.4, 42.3, 40.0, 36.9, 36.5, 36.2, 35.3, 31.7, 31.0, 25.6, 19.0, 13.9; IR (film) 2955, 2923, 1722, 1651, 1570, 1455, 1375, 1264, 1182, 1085, 1031, 966, 820 cm^{-1}; HRMS (ESI) calc. for $C_{33}H_{48}N_2O_8Na$ ($[M+Na]^+$): 623.3308, found 623.3356; $[\alpha]_D^{25}$ = +22.4 ($CHCl_3$, c = 0.32).

(*E*)-methyl 3-(5-bromofuran-2-yl)acrylate (1.82)



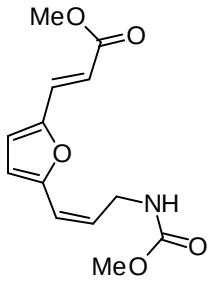
To a suspension of 60% sodium hydride (63.0 mg, 1.58 mmol) in THF (5 mL) $(EtO)_2P(O)CH_2CO_2Me$ (0.41 mL, 2.53 mmol) was added drop wise at 0 °C under nitrogen. One hour later, 5-bromofuran-2-carbaldehyde **1.81** (204 mg, 1.17 mmol) in 5 mL THF was added drop wise, and the reaction mixture was allowed to room temperature over 0.5 hour. The reaction mixture was partitioned between diethyl ether and water. The organic phase was dried, filtered and concentrated under vacuum. Flash chromatography with 20% diethyl ether in hexanes gave 261 mg (97%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.32(d, *J* = 15.7 Hz, 1H), 6.54(d, *J* = 2.9 Hz, 1H), 6.40(d, *J* = 3.0 Hz, 1H), 6.29(d, *J* = 15.7 Hz, 1H), 3.78(s, 3H). ^{13}C NMR (75MHz, CDCl3) δ 166.9, 152.5, 129.7, 125.3, 116.6, 115.7, 114.0, 51.5.

(*E*)-methyl 3-(5-(3-(methoxycarbonyl)prop-1-ynyl)furan-2-yl)acrylate (1.83)



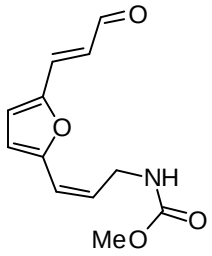
To a flame-dried 25 mL round bottom flask was charged **1.82** (310 mg, 1.34 mmol), $PdCl_2(PPh_3)_2$ (93.1 mg, 0.133 mmol), PPh_3 (69.8 mg, 0.266 mmol), CuI (25.8 mg, 0.136 mmol), distilled triethylamine (1.70 mL, 12.2 mmol) and distilled THF (5 mL). The reaction was degassed with argon for 15 minutes, and then methyl prop-2-ynylcarbamate **1.70** (310 mg, 2.75 mmol) was added drop wise with a syringe. The reaction mixture was heated at 50 °C for 1.5 hours under argon protection. Flash chromatography with 40% ethyl acetate in hexanes gave 289 mg (82%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.34(d, *J* = 15.7 Hz, 1H), 6.59(d, *J* = 3.5 Hz, 1H), 6.57(d, *J* = 3.5 Hz, 1H), 6.33(d, *J* = 15.7 Hz, 1H), 5.79(brs, 1H), 4.25(d, *J* = 5.6 Hz, 2H), 3.78(s, 3H), 3.71(s, 3H).

(*E*)-methyl 3-(5-((*Z*)-3-(methoxycarbonyl)prop-1-enyl)furan-2-yl)acrylate (1.84)



To a 25 mL round bottom flask was charged nickel acetate tetra hydrate (46.6 mg, 0.187 mmol) and 95% ethanol (1 mL), and hydrogen atmosphere was applied. Then 0.25 mL $NaBH_4$ solution (1N, 0.25 mmol) in 95% ethanol (with 0.1N NaOH) was added to the flask within 10 seconds. After three minutes ethylenediamine (26 μL, 0.37 mmol) was added, followed by another three minutes of stirring. To the resulting black colloidal **1.83** (123 mg, 0.467 mmol) was added via a syringe followed by washing with 95% EtOH. After 1.5 hour the reaction mixture was filtered through a pad of silica gel and concentrated under vacuum. Flash chromatography with 30% THF in hexanes gave 80.3 mg (65%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.40(d, *J* = 15.7 Hz, 1H), 6.62(d, *J* = 3.5 Hz, 1H), 6.35(d, *J* = 3.5 Hz, 1H), 6.27(d, *J* = 15.6, 1H), 6.22(d, *J* = 10.4 Hz, 1H), 5.68(dt, *J* = 6.4, 11.8 Hz, 1H), 5.11(brs, 1H), 4.29(t, *J* = 5.4 Hz, 2H), 3.79(s, 3H), 3.70(s, 3H).

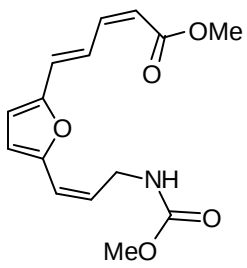
Methyl (*Z*)-3-(5-((*E*)-3-oxoprop-1-enyl)furan-2-yl)allylcarbamate (1.85)



A solution of **1.84** (60.0 mg, 0.226 mmol) in dichloromethane (3 mL) was cooled to -78 °C under nitrogen. Then DIBAL-H (1.34 mL, 1M in hexanes) was added drop wise, followed by one hour of stirring at the same temperature. The reaction was quenched with saturated ammonium chloride solution, extracted with ethyl acetate for three times, and concentrated under vacuum. Flash chromatography with 70% ethyl acetate in hexanes gave 50.8 mg (95%) of the alcohol. The alcohol was dissolved in dichloromethane (3.3 mL) and acetonitrile (1.2 mL) and cooled to 0 °C. Pyridine (28 μL, 0.35 mmol) was added, followed by Dess-Martin reagent (144 mg, 0.34 mmol).

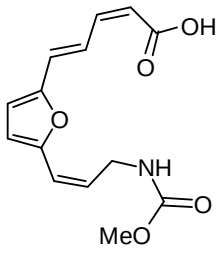
After two hours of stirring at 0 °C , the reaction mixture was concentrated and purified with 40% ethyl acetate in hexanes to afford 34.7 mg (71%) of the desired aldehyde. ^{1}H NMR (300MHz, $CDCl_3$) δ 9.63(d, *J* = 7.9 Hz, 1H), 7.20(d, *J* = 15.6 Hz, 1H), 6.79(d, *J* =3.5 Hz, 1H), 6.55(dd, *J* = 7.9, 15.6 Hz, 1H), 6.43(d, *J* = 3.5 Hz, 1H), 6.26(d, *J* = 11.8 Hz, 1H), 5.75(dt, *J* = 6.3, 11.8 Hz, 1H), 5.07(brs, 1H), 4.30(t, *J* = 5.8 Hz, 2H), 3.71(s, 3H).

(2*Z*,4*E*)-methyl 5-(5-((*Z*)-3-(methoxycarbonyl)prop-1-enyl)furan-2-yl)penta-2,4- dienoate



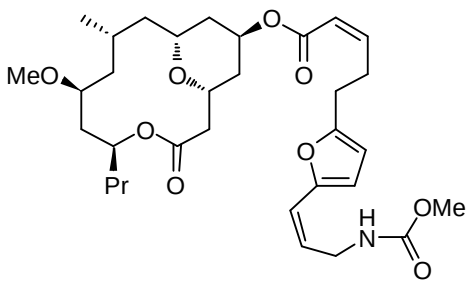
To a 25 mL round bottom flask was charged methyl bis(trifluoroethyl)phosphonoacetate (86 μL, 0.41 mmol), 18-crown-6 (330 mg, 1.23 mmol) and THF (4 mL). The mixture was cooled to -78 °C, and KHMDS (60.8 mg, 0.29 mmol) in 2 mL THF was added drop wise under nitrogen. After 30 minutes of stirring methyl (*Z*)-3-(5-((*E*)-3-oxoprop-1-enyl)furan-2-yl)allylcarbamate (**1.85**) (34.6 mg, 0.15 mmol) in 4 mL THF was added drop wise, followed by 3 hours of stirring at -78 °C. The reaction was quenched with saturated NH_4Cl aqueous solution, extracted with ethyl acetate and concentrated under vacuum. Flash chromatography first with 30% ethyl acetate in pentane, and then 20% ethyl acetate in toluene gave 30 mg (70%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.93(dd, *J* = 11.9, 15.5 Hz, 1H), 6.66(dd, *J* = 11.6, 11.6 Hz, 1H), 6.56(d, *J* = 15.5 Hz, 1H), 6.49(d, *J* = 3.5 Hz, 1H), 6.32(d, *J* = 3.5 Hz, 1H), 6.22(d, *J* = 11.6 Hz, 1H), 5.69(d, *J* = 11.2 Hz, 1H), 5.60-5.70(m, 1H), 5.12(brs, 1H), 4.29(td, *J* = 1.5, 6.2 Hz, 2H), 3.75(s, 3H), 3.69(s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 166.9, 157.1, 153.3, 152.3, 143.8, 128.5, 127.1, 123.8, 118.1, 117.2, 113.6, 113.0, 52.1, 51.2, 40.0; IR (film) 3340, 2950, 1708, 1608, 1528, 1438, 1253, 1197, 1169, 1020, 785 cm^{-1}; HRMS (ESI) calc. for $C_{15}H_{17}NO_5Na$ ([M+Na]+): 314.1004, found 314.1028.

(2*Z*,4*E*)-5-(5-((*Z*)-3-((methoxycarbonyl)amino)prop-1-en-1-yl)furan-2-yl)penta-2,4-dienoic acid (1.86)



(2*Z*,4*E*)-methyl 5-(5-((*Z*)-3-(methoxycarbonyl)prop-1-enyl)furan-2-yl)penta-2,4-dienoate (23.3 mg, 0.080 mmol) was dissolved in THF (0.45 mL) at room temperature. After 1N LiOH aqueous solution (0.9 mL, 0.9 mmol) was added, the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was carefully acidified with 3N HCl drop wise at 0 °C to pH 3, and extracted with three 5 mL portions of ethyl acetate. The organic phase was dried with Na_2SO_4, filtered and concentrated under vacuum. Flash chromatography (EtOAc : DCM : MeOH 1 : 1: 0.2) gave 24.9 mg (90%) of the desired product. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.01(dd, *J* = 12.0, 15.4 Hz, 1H), 6.78(t, *J* = 11.5 Hz, 1H), 6.60(d, *J* = 15.5 Hz, 1H), 6.50(d, *J* = 3.5 Hz, 1H), 6.33(d, *J* = 3.3 Hz, 1H), 6.23(d, *J* = 11.9 Hz, 1H), 5.73(d, *J* = 11.2 Hz, 1H), 5.66(dt, *J* = 6.4, 11.9 Hz, 1H), 5.12(brs, 1H), 4.32(app s, 1H), 3.70(s, 3H). ^{13}C NMR (400MHz, $CDCl_3$) δ 170.7, 157.3, 153.5, 152.3, 145.1, 128.6, 127.1, 124.2, 117.9, 117.1, 113.8, 112.9, 52.2, 40.3; IR (film) 3452, 2941, 1701, 1524, 1253, 1189, 1173, 788 cm^{-1}; HRMS (ESI) calc. for $C_{14}H_{15}NO_5Na$ ([M+Na]+): 300.0848, found 300.0859.

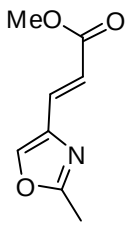
(1*R*,5*S*,7*S*,9*S*,11*R*,13*S*)-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxa-bicyclo[9.3.1]-pentadecan-13-yl methanesulfonate (1.66)



General protocol B was followed, starting from the macrocyclic alcohol **1.5** (2.2 mg, 0.0067 mmol), **1.86** (5.6 mg, 0.013 mmol), PPh_3 (3.9 mg, 0.015 mmol) and DIAD (3.0 μL, 0.015 mmol). Flash column chromatography (50% EtOAc pentane) afforded 2.0 mg

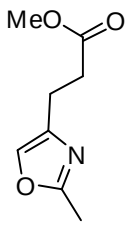
(50%) of the desired analog.. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.01(dd, *J* = 12.0, 16.0 Hz, 1H), 6.74(t, *J* = 11.7 Hz, 1H), 6.60(d, *J* = 15.6 Hz, 1H), 6.51(d, *J* = 3.4 Hz, 1H), 6.33(d, *J* = 3.5 Hz, 1H), 6.24-6.28(m, 1H), 5.76(d, *J* = 11.1 Hz, 1H), 5.60-5.69(m, 1H), 5.23-5.26(m, 1H), 5.12-5.19(m, 1H), 5.07(brs, 1H), 4.28(t, *J* = 6.6 Hz, 2H), 4.10(apt, *J* = 11.4 Hz, 1H), 3.70(s, 3H), 3.57-3.62(m, 2H), 3.32(s, 3H), 2.60(dd, *J* = 4.4, 14.5 Hz, 1H), 2.36(dd, *J* = 10.8, 14.1 Hz, 1H), 1.82-1.94(m, 2H), 1.70-1.75(m, 2H), 1.45-1.62(m, 4H), 1.23-1.39(m, 6H), 1.12-1.19(m, 1H), 0.98(d, *J* = 6.5 Hz, 3H), 0.92(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100MHz, MeOD) δ 173.1, 167.1, 154.8, 145.2, 130.1, 128.7, 125.1, 118.7, 114.9, 114.3, 77.1, 77.0, 73.9, 71.3, 69.1, 56.4, 52.5, 45.2, 43.5, 41.1, 40.4, 37.9, 37.4, 36.0, 32.6, 26.0, 20.0, 14.1; IR (film) 2947, 2854, 1713, 1528, 1376, 1249, 1190, 1064, 994 cm^{-1}; HRMS (pending); $[\alpha]_D^{25}$ = +5.1 (MeOH, c = 0.20).

(*E*)-methyl 3-(2-methyloxazol-4-yl)acrylate (1.88)



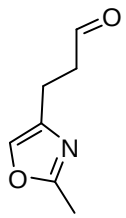
To a suspension of 60% sodium hydride (63 mg, 1.358 mmol) in THF (5 mL) $(EtO)_2P(O)CH_2CO_2Me$ (0.41 mL, 2.53 mmol) was added drop wise at 0 °C under nitrogen. Thirty minutes later, 2-methyloxazole-4-carbaldehyde **1.87** (107 mg, 0.96 mmol) in 2 mL THF was added dropwise, and the reaction mixture was kept at 0 °C for 1.5 hour. The reaction mixture was partitioned between diethyl ether and water. The organic phase was dried, filtered and concentrated under vacuum. Flash chromatography with 5% diethyl ether in hexanes gave 151 mg (93%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.69(s, 1H), 7.47(d, *J* = 15.6, 1H), 6.58(dt, *J* = 2.6, 15.8 Hz, 1H), 3.78(s, 3H), 2.49(s, 1H).

methyl 3-(2-methyloxazol-4-yl)propanoate



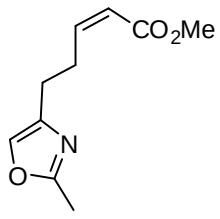
A mixture of (*E*)-methyl 3-(2-methyloxazol-4-yl)acrylate **1.88** (71 mg, 0.42 mmol) and 10% Pd/C (71 mg) in methanol (10 mL) was stirred under hydrogen atmosphere for 2 hours. The mixture was then filtered through Celite and purified on a flash column with 40% ethyl acetate in hexanes to give 59 mg (82%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.30(t, *J* = 1.1 Hz, 1H), 3.68(s, 3H), 2.81(t, *J* = 7.5 Hz, 2H), 2.65(td, *J* = 1.1, 7.1 Hz, 2H), 2.42(s, 3H).

3-(2-methyloxazol-4-yl)propanal (1.89)



To a 25 mL round bottom flask was charged methyl 3-(2-methyloxazol-4-yl)propanoate (48 mg, 0.28 mmol) and dichloromethane (3 mL). The reaction was cooled to -78 °C, and 1M DIBAL-H (0.42 mL, 0.42 mmol) solution in hexanes was added drop wise under nitrogen. After 1.5 hour of stirring at -78 °C, The reaction was quenched with saturated ammonium chloride aqueous solution. Flash chromatography with 40% ethyl acetate in hexanes gave 27 mg (69%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 9.82(s, 1H), 7.29(t, *J* = 5.2 Hz, 1H), 2.81(app s, 4H), 2.42(s, 1H).

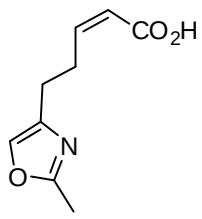
(*Z*)-methyl 5-(2-methyloxazol-4-yl)pent-2-enoate (1.90)



To a 25 mL round bottom flask was charged methyl bis(trifluoroethyl)phosphonoacetate (114 μL, 0.54 mmol), 18-crown-6 (430 mg, 1.63 mmol) and THF (5 mL). The mixture was cooled to -78 °C and KHMDS (80 mg, 0.40 mmol) in 5 mL THF was added drop wise under nitrogen. After 30 minutes of stirring 3-(2-methyloxazol-4-yl)propanal **1.89** (26.2 mg, 0.19

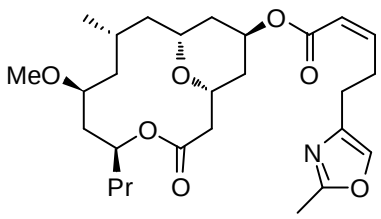
mmol) in 5 mL THF was added drop wise, followed by 5 hours of stirring at -78 °C. The reaction was quenched with saturated NH_4Cl aqueous solution and extracted with ethyl acetate. Flash chromatography with 30% ethyl acetate in pentane gave 23.2 mg (71%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.29(s, 1H), 6.26(dt, *J* = 7.3, 11.5 Hz, 1H), 5.82(dt, *J* = 1.7, 11.5 Hz, 1H), 3.71(s, 3H), 2.98(dtd, *J* = 1.6, 7.2, 7.2 Hz, 2H), 2.64(dd, *J* = 6.9, 7.6 Hz, 2H), 2.42(s, 3H); ^{13}C NMR (300MHz, $CDCl_3$) δ 166.7, 161.3, 149.1, 139.7, 133.9, 120.1, 51.1, 27.5, 25.6, 13.9; IR (film) 2921, 1722, 1646, 1581, 1439, 1201, 1177, 1096, 820 cm^{-1}; HRMS (ESI) calc. for $C_{10}H_{13}NO_3Na$ ($[M+Na]^+$): 218.0793, found 218.0786;.

(*Z*)-5-(2-methyloxazol-4-yl)pent-2-enoic acid (1.91)



(*Z*)-methyl 5-(2-methyloxazol-4-yl)pent-2-enoate **1.90** was dissolved in THF (0.6 mL) at room temperature. After 1N LiOH aqueous solution (1.1 mL, 1.1 mmol) was added, the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was acidified with 3N HCl drop wise at 0 °C to pH 3, and extracted with three 5 mL portions of ethyl acetate. The organic phase was dried with Na_2SO_4, filtered and concentrated under vacuum. Flash chromatography with 10% methanol in dichloromethane gave 13.7 mg (80%) of the desired product. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.31(s, 1H), 6.25(dt, *J* = 7.3, 11.1 Hz, 1H), 5.85(d, *J* = 11.0 Hz, 1H), 2.97(dt, *J* = 7.1, 7.1 Hz, 2H), 2.68(t, *J* = 7.0 Hz, 2H), 2.45(s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 170.0, 161.8, 148.6, 139.1, 134.1, 121.2, 27.5, 24.9, 13.7; IR (film) 3139, 2922, 2537, 1700, 1643, 1577, 1437, 1203, 1096, 1017, 935, 822 cm^{-1}; HRMS (EI) calc. for $C_9H_{11}NO_3$ (M+): 181.073893, found 181.073688.

(*Z*)-(1*R*,5*S*,7*S*,9*S*,11*R*,13*R*)-7-methoxy-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-13-yl 5-(2-methyloxazol-4-yl)pent-2-enoate (1.67)



General protocol B was followed, starting from the macrocyclic alcohol **5** (2.2 mg, 0.0067 mmol), **1.91** (4.9 mg, 0.027 mmol), PPh_3 (9.4 mg, 0.036 mmol) and DIAD (7.1 μL, 0.036 mmol). Flash column chromatography (20% EtOAc in DCM, then switched to 40% EtOAc in hexanes) yielded 2.5 mg (76%) of the desired analog. ^{1}H NMR (400MHz, MeOD) δ 7.54(t, *J* = 1 Hz, 1H), 6.34(dt, *J* = 7.4, 11.5 Hz, 1H), 5.88(dt, *J* = 1.7, 11.5 Hz, 1H), 5.14-5.20(m, 2H), 4.07(dddd, *J* = 2.2, 2.2, 11.5, 11.5 Hz, 1H), 3.67(app t, *J* = 9.7, 1H), 3.57(app t, *J* = 10.8 Hz, 1H), 3.28(s, 3H), 2.97(dtd, *J* = 1.6, 7.1, 7.1 Hz, 2H), 2.70(dd, *J* = 4.3, 14.8 Hz, 1H), 2.64(t, *J* = 7.3, 2H), 2.30(dd, *J* = 11.0, 14.8 Hz, 1H), 1.87(dd, *J* = 10.9, 14.0 Hz, 1H), 1.80-1.86(m, 1H), 1.66-1.76(m, 2H), 1.46-1.62(m, 4H), 1.26-1.44(m, 6H), 1.29(s, 3H), 1.12(ddd, *J* = 1.8, 11.0, 12.8 Hz, 1H), 0.97(t, *J* = 5.8 Hz, 3H), 0.94(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100MHz, MeOD) δ 173.0, 167.7, 164.4, 150.8, 141.6, 136.9, 122.5, 78.0, 77.9, 74.8, 72.2, 70.0, 57.3, 46.1, 44.3, 44.1, 41.9, 38.8, 38.3, 37.1, 33.4, 29.8, 27.1, 26.8, 20.9, 15.0, 14.4; IR (film) 2956, 2922, 2836, 1718, 1642, 1580, 1458, 1382, 1334, 1261, 1175, 1087, 1030, 797 cm^{-1} ; HRMS (ESI) calc. for $C_{27}H_{41}NO_7Na$ ($[M+Na]^+$): 514.2781, found 514.2766; $[\alpha]_D^{25}$ = +27.8 (MeOH, c = 0.21).

APPENDIX B

SYNTHESIS OF SULFUR-CONTAINING HETEROCYCLES THROUGH OXIDATIVELY GENERATED THIOCARBENIUM IONS

General protocols

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 300/400/500/600 MHz and 75/100/125/150 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Tetramethylsilane (TMS) or the solvent peak was used as a reference value, for ^{1}H NMR: TMS (in $CDCl_3$) = 0.00 ppm, CD_3OD =3.31, for ^{13}C NMR: TMS (in $CDCl_3$) = 0.00, CD_3OD = 49.00. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). 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. Analytical TLC was performed on pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash column chromatography was done using 32-63 60 Å silica gel. Methylene chloride was distilled under N_2 from CaH_2. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were used as purchased for chromatography. Benzene was dried with 4Å molecular sieves. THF was distilled from sodium. Other reagents were obtained from commercial sources

without further purification. All reactions were performed in oven or flame-dried glassware with magnetic stirring under nitrogen unless otherwise noted.

General protocol for allyl or benzyl sulfide synthesis (general protocol C)

The corresponding thiol or thioacetate was added dropwise into the solution of potassium hydroxide (2.5 equiv) in methanol (~0.25 M) at 0 °C, and the reaction mixture was stirred vigorously for 20 minutes. The corresponding allyl or benzyl bromide (~1.2 equiv) was added dropwise, and the reaction was heated at 50 °C for 2 hours. White precipitates were formed during the process. The reaction mixture was cooled, concentrated under vacuum and dissolved in diethyl ether. The ether solution was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash column chromatography with 3% ethyl acetate in hexanes afforded the desired allyl sulfide.

General protocol for enol acetate synthesis (general protocol D)

The corresponding alkyne, $[(p\text{-cymene})RuCl_2]_2$ (4 mol%), $(2\text{-furyl})_3P$ (8 mol%), Na_2CO_3 (15 mol%), acetic acid (2 equiv) and toluene were mixed and stirred at 80 °C overnight. Flash column chromatography with 10% ethyl acetate in hexanes afforded the desired enol acetate.

General protocol E1 for thioacetate synthesis (the Mitsunobu reaction) (general protocol E1)

To a solution of PPh_3 (2.3 equiv) in THF (~0.1 M solution) at 0 °C, DIAD (2.3 equiv) was added drop wise over 10 minutes, and the resulting white suspension was stirred for 20 minutes. Thioacetic acid (2.5 equiv) and the corresponding alcohol was added successively. The white precipitates disappeared after 0.5 hours, and the solution was stirred overnight at RT. The

reaction mixture was concentrated and purified by flash column chromatography with 10% diethyl ether in hexanes to afford the desired thioacetate.

General protocol E2 for thioacetate synthesis (general protocol E2)

To a mixture of the corresponding mesylate or bromide and Cs_2CO_3 (2.4 equiv) in DMF (~0.25 M) at 0 °C, Thioacetic acid (2.7 equiv) was added dropwise. The reaction mixture was stirred either at RT overnight (for primary mesylates) or at 40 °C overnight (for secondary mesylates). The reaction was then diluted with diethyl ether, washed with brine for three times and concentrated. Flash column chromatography with appropriate solvents afforded the desired thioacetate.

General protocol F1 for vinyl sulfide synthesis (general protocol F1)

In a round bottom flask the corresponding thioacetate, KOH (2.5 equiv), CuI (0.1 equiv) and vinyl iodide (1.5 equiv) were mixed in dioxane (~0.4 M). The reaction mixture was heated overnight at 100 °C, resulting a dark brown heterogeneous mixture. Then it was cooled to room temperature, concentrated under vacuum and subjected to Flash column chromatography with appropriate solvents to afford the desired vinyl sulfide.

General protocol F2 for vinyl sulfide synthesis (general protocol F2)

To a flame-dried round bottom flask were added *(E)*-1-iodohex-1-ene (1.2 equiv), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ complex (0.05 equiv), distilled Et_3N (2.7 equiv) and THF (~0.2 M). The mixture was stirred for 15 minutes at RT and then 15 minutes at 45°C. The corresponding thiol was added drop wise into the mixture, and the reaction was stirred overnight at 45°C.

Concentration and Flash column chromatography with appropriate solvents afforded the desired vinyl sulfide.

General protocol for the cyclization of allyl or benzyl sulfide substrates (general protocol G1)

The enol acetate, 2,6-dichloropyridine (4 equiv), $LiClO_4$ or $Mg(ClO_4)_2$ (0.2 equiv) and 4 Å molecular sieves (3 mass equiv) were dissolved in anhydrous DCM or DCE to give a ~0.09 M solution. The mixture was stirred for 15 minutes, then DDQ (2.0 equiv) was added in one portion. The reaction was monitored by TLC at room temperature unless specified, and quenched by Et_3N when the starting material was gone. After concentration under vacuum, the residue was purified with Flash column chromatography to give the desired product.

General protocol for the cyclization of vinyl sulfide and allylsilanes (general protocol G2)

The enol acetate, 2,6-dichloropyridine (2 equiv) and 4 Å molecular sieves (3 mass equiv) were dissolved in anhydrous $MeNO_2$ or DCM to give a ~0.09 M solution. The mixture was stirred at 0 °C for 15 minutes, then DDQ (1.05 equiv) was added in one portion. The starting material disappeared in 5 minutes as monitored by TLC. After concentration under vacuum, the residue was purified by Flash column chromatography with appropriate solvents to give the desired product.

General protocol for the synthesis of vinyl iodide (general protocol H)

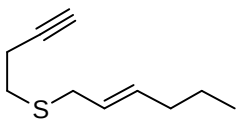
To a suspension of $ZrCp_2Cl_2$ (1.1 equiv) in distilled THF (~0.35 M) protected with argon, 1M DIBAL-H solution (1.1 equiv) was added drop wise at 0 °C. White precipitates were formed in a few minutes, and the mixture was stirred for 30 minutes. Then the alkyne was added drop wise,

followed by THF rinsing. The reaction mixture was allowed to RT and stirred for 1 hr, during which the reaction mixture became clear and green. The reaction was cooled to -78 °C, I_2 (1.1 equiv) in THF was added dropwise, and it was then allowed to -10 °C. The reaction was quenched with 1:1 saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$, extracted with diethyl ether twice and concentrated under vacuum. Flash column chromatography with appropriate solvents afforded the corresponding vinyl iodide.

General protocol for Kumada coupling (general protocol I)

To a suspension of $Pd(PPh_3)_4$ (0.1 equiv) in distilled THF (~3 M solution) protected with argon, 1M trimethylsilyl methylmagnesium chloride (1.5 equiv) was added drop wise at RT. Fifteen minutes later, the corresponding vinyl iodide was added drop wise, followed by another 15 minutes of stirring. The reaction mixture was then quenched with saturated NH_4Cl solution at 0 °C, extracted twice with ether and concentrated under vacuum. Flash column chromatography with appropriate solvents afforded the corresponding ally silane.

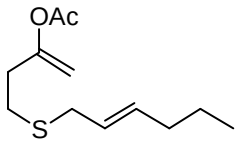
(*E*)-but-3-yn-1-yl(hex-2-en-1-yl)sulfane



General protocol C for allyl sulfide synthesis was followed, starting from *S*-but-3-yn-1-yl ethanethioate (**2.1**) (486 mg, 3.6 mmol), potassium hydroxide (430 mg, 7.7 mmol) and (*E*)-1-bromohex-2-ene (550 mg, 3.1 mmol). Flash column chromatography with 3% ethyl acetate in hexanes afforded 542 mg (95%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dt, *J* =15.2, 6.5 Hz, 1H), 5.40 (dtt, *J* = 15.2, 7.1, 1.0), 3.14 (dd, *J* = 7.0 Hz, 2H), 2.64 (td, *J* = 7.4, 0.9 Hz, 2H), 2.45 (tdd, *J* = 7.4, 2.6, 0.7 Hz, 2H), 2.06-1.99 (m, 3H), 1.46-1.34 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7,

125.6, 82.5, 69.1, 34.1, 33.7, 29.0, 22.3, 19.5, 13.5; IR (film) 3309, 2958, 2930, 2872, 1461, 1427, 1379, 1230, 967 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{10}H_{16}S$ [M] 168.0973, found 168.0978.

(*E*)-4-(hex-2-en-1-ylthio)but-1-en-2-yl acetate (2.2)



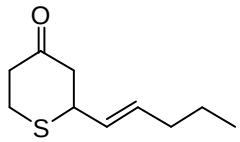
General protocol D for enol acetate synthesis was followed, starting from the above alkyne (169 mg, 1.0 mmol), $[(p\text{-cymene})RuCl_2]_2$ (24.5 mg, 0.04 mmol), $(2\text{-furyl})_3P$ (18.5 mg, 0.08 mmol), Na_2CO_3 (15.1 mg, 0.15 mmol) and acetic acid (0.11 mL, 2.0 mmol). Flash column chromatography with 10% ethyl acetate in hexanes afforded 129 mg (57%) of the desired enol acetate **2.2**.

(*E*)-4-(hex-2-en-1-ylthio)but-1-en-2-yl acetate (**2.2**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58-5.46 (dt, *J* = 15.1, 6.4 Hz, 1H), 5.39 (dtt, *J* = 15.1, 6.9, 1.2 Hz, 1H), 4.88-4.65 (m, 2H), 3.11 (dd, *J* = 6.9, 0.8 Hz, 2H), 2.58 (ddd, *J* = 8.3, 6.7, 1.8 Hz, 2H), 2.48 (m, 2H), 2.15 (s, 3H), 2.02 (dt, *J* = 6.6, 6.6 Hz, 2H), 1.48-1.32 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 154.3, 133.6, 125.7, 102.3, 34.2, 33.7, 33.5, 27.1, 22.4, 20.9, 13.5; IR (film) 2959, 2927, 2872, 1759, 1666, 1434, 1370, 1197, 1020, 966, 914, 876 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{12}H_{20}O_2SNa$ $[M+Na]^+$ 251.1082, found 251.1077.

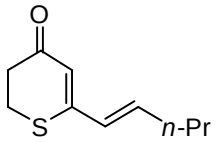
(*E*)-2-(pent-1-en-1-yl)dihydro-2*H*-thiopyran-4(3*H*)-one (2.3) AND (*E*)-6-(pent-1-en-1-yl)-2*H*-thiopyran-4(3*H*)-one (2.4)

General protocol G1 for the cyclization of allyl sulfide substrates was followed, starting from compound 1 (80 mg, 0.35 mmol), DDQ (200 mg, 0.88 mmol), 2,6-dichloropyridine (261 mg, 1.76 mmol), $LiClO_4$ (7.5 mg, 0.07 mmol), 4Å M.S. (240 mg) and 1,2-dichloroethane (5 mL). The reaction was quenched with triethylamine 100 minutes after the addition of DDQ. Flash

column chromatography with 10% ethyl acetate in hexanes afforded 32.3 mg (50%) of the desired cyclization product **2.3** and 2.6 mg (4%) of the over-oxidized product **2.4**.

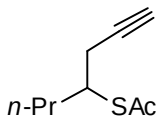


(*E*)-2-(pent-1-en-1-yl)dihydro-2*H*-thiopyran-4(3*H*)-one (**2.3**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70-5.57 (dtd, *J* = 15.4, 6.7, 1.1 Hz, 1H), 5.46 (ddt, *J* = 15.4, 6.8, 1.3 Hz, 1H), 3.84-3.68 (m, 1H), 3.02-2.86 (m, 2H), 2.77 (ddd, *J* = 14.1, 3.9, 0.8 Hz, 1H), 2.72-2.59 (m, 3H), 2.01 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.48-1.33 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1, 133.2, 128.5, 49.3, 45.1, 43.1, 34.2, 27.6, 22.1, 13.4; IR (film) 2957, 2927, 2871, 1713, 1421, 1317, 1262, 970 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{10}H_{16}OS$ [M] 184.0922, found 184.0937.



(*E*)-6-(pent-1-en-1-yl)-2*H*-thiopyran-4(3*H*)-one (**2.4**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (dt, *J* = 15.5, 7.0 Hz, 1H), 6.19 (d, *J* = 15.7 Hz, 1H), 6.08 (s, 1H), 3.18 (t, *J* = 6.8 Hz, 2H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.19 (dtd, *J* = 7.2, 7.2, 1.3 Hz, 2H), 1.55-1.41 (m, 2H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 156.9, 136.9, 130.2, 113.8, 37.6, 34.04, 26.5, 21.8, 13.6; IR (film) 3122, 2947, 1689, 1441, 1282, 1212, 1147, 931 cm^{-1}; HRMS (EI) m/z calcd. for $C_{10}H_{14}OS$ [M] 182.0765, found 182.0782.

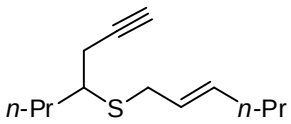
_S_-Hept-1-yn-4-yl ethanethioate



Hept-1-yn-4-yl methanesulfonate (855 mg, 4.5 mmol) was reacted with HSAc (0.87 mL, 9.75 mmol) and Cs_2CO_3 (3.52 g, 8.86 mmol) according to the general protocol E2. Flash column chromatography with 3% diethyl ether in hexanes afforded the desired thioacetate (453 mg, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (ddd, *J* = 11.3, 8.4, 6.0 Hz, 1H), 2.65-2.44 (m, 2H), 2.34 (s, 3H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.82-1.55 (m, 2H), 1.51-

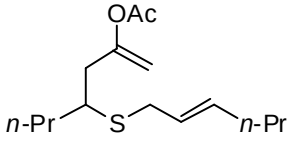
1.31 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 79.3, 70.3, 42.3, 36.1, 34.9, 30.7, 24.8, 13.7.

(*E*)-hept-1-yn-4-yl(hex-2-en-1-yl)sulfane



S-hept-1-yn-4-yl ethanethioate (372 mg, 2.18 mmol) was reacted with *(E)*-1-bromohex-2-ene (469 mg, 2.61 mmol), KOH (245 mg, 4.36 mmol) in methanol (10 mL) according to the general protocol C to afford the desired allyl sulfide (444 mg, 97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dt, J = 15.2, 6.5 Hz, 1H), 5.43 (dt, J = 14.1, 6.8 Hz, 1H), 3.16 (dd, J = 6.7, 2.5 Hz, 2H), 2.75 (ddd, J = 12.6, 7.1, 5.5 Hz, 1H), 2.55 (ddd, J = 16.9, 5.2, 2.6 Hz, 1H), 2.43 (ddd, J = 17.0, 7.1, 2.6 Hz, 1H), 2.11-1.89 (m, 3H), 1.80-1.63 (m, 1H), 1.62-1.34 (m, 6H), 0.91 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.4, 126.2, 81.7, 69.8, 69.7, 42.3, 35.8, 34.2, 33.3, 25.2, 19.8, 13.8, 13.6; IR (film) 3309, 2958, 2930, 2872, 1461, 1427, 1379, 1230, 967 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{13}H_{22}S$ [M] 210.1442, found 210.1431.

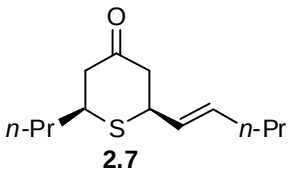
(*E*)-4-(hex-2-en-1-ylthio)hept-1-en-2-yl acetate (2.6)



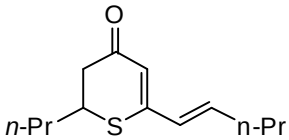
General protocol D for enol acetate synthesis was followed, starting from (*E*)-hept-1-yn-4-yl(hex-2-en-1-yl)sulfane (252.5 mg, 1.2 mmol), $[(p\text{-cymene})RuCl_2]_2$ (30.8 mg, 0.05 mmol), $(2\text{-furyl})_3P$ (22.0 mg, 0.10 mmol), Na_2CO_3 (18.1 mg, 0.18 mmol) and acetic acid (0.13 mL, 2.4 mmol). Flash column chromatography with 10% ethyl acetate in hexanes afforded 86 mg (27%) of the desired enol acetate **2.6**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (dt, J = 14.9, 6.2 Hz, 1H), 5.47-5.35 (m, 1H), 4.86-4.76 (m, 2H), 3.11 (d, J = 6.7 Hz, 2H), 2.75-2.67 (m, 1H), 2.53 (dd, J = 15.3, 6.9 Hz, 1H),

2.45 (dd, *J* = 15.3, 6.9 Hz, 1H), 2.14 (s, 3H), 2.01 (dt, *J* = 6.6, 6.6 Hz, 2H), 1.52-1.32 (m, 6H), 0.90 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 153.7, 133.3, 126.4, 103.7, 40.8, 39.5, 36.2, 34.3, 33.1, 22.5, 21.1, 19.7, 13.9, 13.7; IR (film) 2958, 2930, 2872, 1758, 1665, 1461, 1432, 1369, 1199, 1020, 966, 874 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{26}O_2SNa$ $[M+Na]^+$ 293.1551, found 293.1522.

(2*S*,6*S*)-2-((*E*)-pent-1-en-1-yl)-6-propyldihydro-2*H*-thiopyran-4(3*H*)-one (2.7) and (*E*)-6-(pent-1-en-1-yl)-2-propyl-2*H*-thiopyran-4(3*H*)-one (2.8)



2.7

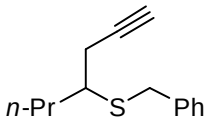


2.8

General protocol G1 for the cyclization of allyl sulfide substrates was followed, starting from the substrate **2.6** (77.3 mg, 0.29 mmol), DDQ (130 mg, 0.57 mmol), 2,6-dichloropyridine (213 mg, 1.46 mmol), $LiClO_4$ (6.1 mg, 0.06 mmol), 4Å M.S. (200 mg) and DCE (4 mL). The reaction was quenched with triethylamine 100 minutes after the addition of DDQ. Flash column chromatography with 10% ethyl acetate in hexanes afforded 32.0 mg (50%) of the desired cyclization product **2.7** with a *cis*:*trans* ratio of 11:1. **2.7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (dtd, *J* = 15.2, 6.8, 0.8 Hz, 1H), 5.40 (ddt, *J* = 15.2, 7.6, 1.4 Hz, 1H), 3.65 (ddd, *J* = 12.4, 7.6, 4.2 Hz, 1H), 3.10 (dtd, *J* = 12.2, 6.7, 2.9 Hz, 1H), 2.75-2.63 (m, 2H), 2.52 (dd, *J* = 19.7, 6.4 Hz, 1H), 2.37 (dd, *J* = 19.3, 6.9 Hz, 1H), 2.01 (dtd, *J* = 7.9, 7.9, 1.1 Hz, 2H), 1.64-1.53 (m, 2H), 1.52-1.44 (m, 2H), 1.44-1.36 (m, 2H), 0.92 (t, *J* =7.6 Hz, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 133.5, 128.1, 50.0, 49.8, 45.3, 43.6, 37.9, 34.2, 22.1, 19.8, 13.8, 13.5; IR (film) 2958, 2930, 2872, 1712, 1461, 1249, 967 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{13}H_{22}SO$ [M] 226.1391, found 226.1388.

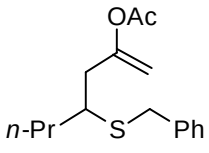
2.8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.44 (dt, *J* = 15.4, 7.1 Hz, 1H), 6.15 (d, *J* = 15.4 Hz, 1H), 6.07 (s, 1H), 3.16 (dtd, *J* = 12.2, 6.6, 2.9 Hz, 1H), 2.76-2.65 (m, 2H), 2.19 (dtd, *J* = 7.6, 7.6, 1.1 Hz, 2H), 1.68-1.44 (m, 4H), 1.44-1.36 (m, 2H), 0.91 (t, *J* =7.5 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 156.9, 136.7, 130.1, 113.8, 49.8, 43.6, 37.6, 33.8, 21.8, 19.8, 13.6; IR (film) 2957, 2849, 1686, 1431, 1281, 1231, 1082, 867 cm^{-1}; HRMS (EI) m/z calcd. for $C_{13}H_{20}OS$ [M] 224.1235, found 224.1247.

Benzyl(hept-1-yn-4-yl)sulfane



Hept-1-yne-4-thiol (413 mg, 2.41 mmol, prepared by LAH reduction of the corresponding thioacetate) was reacted with benzyl bromide (0.37 mL, 3.14 mmol), KOH (336 mg, 2.5 mmol) in methanol (10 mL) according the general protocol C, except the reaction was carried out at RT overnight. Flash column chromatography with 10% dichloromethane in hexanes afforded the desired benzyl sulfide (453 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 3.75 (s, 2H), 2.64 (tt, *J* = 7.6, 5.4 Hz, 1H), 2.45 (dddd, *J* = 17.0, 9.7, 6.2, 2.6 Hz, 2H), 2.01 (t, *J* = 2.6 Hz, 1H), 1.66 (ddt, *J* = 13.7, 9.7, 5.8 Hz, 1H), 1.58-1.20 (m, 3H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.7, 128.3, 126.8, 81.6, 69.9, 42.9, 35.6, 35.4, 25.1, 19.7, 13.6; IR (film) 3299, 3028, 2958, 2929, 2871, 1494, 1454, 1238, 915 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{14}H_{18}S$ [M] 218.1129, found 218.1128.

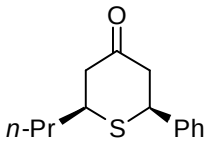
4-(Benzylthio)hept-1-en-2-yl acetate (2.10)



General protocol D for enol acetate synthesis was followed, starting from the above benzyl sulfide (391 mg, 1.79 mmol), $[(p\text{-cymene})RuCl_2]_2$ (43.8 mg, 0.07 mmol), $(2\text{-furyl})_3P$ (32.4 mg, 0.14 mmol), Na_2CO_3 (27.2 mg, 0.26 mmol)

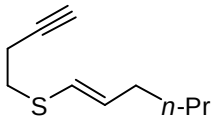
and acetic acid (0.20 mL, 3.6 mmol). Flash column chromatography with 5% diethyl ether in hexanes afforded 164 mg (33%) of the desired enol acetate **2.10**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.18 (m, 5H), 4.85-4.67 (m, 2H), 3.72 (d, *J* = 4.3 Hz, 2H), 2.65-2.55 (m, 1H), 2.53 (dd, *J* = 6.3, 0.6 Hz, 1H), 2.43 (dd, *J* = 14.1, 7.4 Hz, 1H), 2.06 (s, 3H), 1.61-1.50 (m, 1H), 1.50-1.38 (m, 2H), 1.38-1.27 (m, 1H), 0.88-0.68 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 153.4, 138.4, 128.9, 128.3, 126.9, 103.7, 41.1, 39.4, 35.9, 35.1, 21.0, 19.6, 13.7; IR (film) 2958, 2930, 2871, 1757, 1665, 1454, 1370, 1200, 1021, 876 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{22}O_2SNa$ $[M+Na]^+$ 301.1238, found 301.1248.

(2*S*,6*S*)-2-phenyl-6-propyldihydro-2*H*-thiopyran-4(3*H*)-one (2.11)



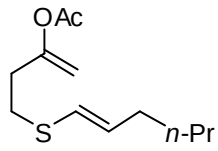
General protocol G1 was followed, starting from compound **2.10** (59.1 mg, 0.21 mmol), DDQ (119 mg, 0.53 mmol), 2,6-dichloropyridine (156 mg, 1.06 mmol), $MgClO_4$ (8.8 mg, 0.04 mmol), 4Å M.S. (180 mg) and dichloromethane (4 mL). The reaction mixture was stirred overnight at RT. The reaction afforded 30.4 mg (61% yield) of the desired cyclization product **2.11** with a *cis*:*trans* ratio of 25:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.25 (m, 5H), 4.16 (dd, *J* = 11.9, 3.6 Hz, 1H), 3.26-3.15 (m, 1H), 2.95-2.84 (m, 2H), 2.76 (dd, *J* = 13.5, 2.0 Hz, 1H), 2.49 (apt, *J* = 12.4, 1H), 1.62 (dd, *J* = 15.1, 7.3 Hz, 2H), 1.54-1.41 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 139.7, 128.8, 127.9, 127.1, 77.3, 77.0, 76.6, 50.8, 50.1, 47.6, 44.4, 37.8, 19.8, 13.8.; IR (film) 2958, 2930, 2872, 1710, 1454, 1247 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{14}H_{18}SO$ [M] 234.1078, found 234.1076.

(*E*)-but-3-yn-1-yl(hex-1-en-1-yl)sulfane



General protocol F2 was followed, starting from 3-butyn-1-thiol **2.12** (534 mg, 2.40 mmol), *(E)*-1-iodohex-1-ene (420 mg, 1.91 mmol), Pd(dppf)Cl_2·DCM complex (82mg, 0.095 mmol) and distilled Et_3N (0.72 mL, 5.1 mmol). Flash column chromatography with 3% diethyl ether in hexanes afforded 238 mg (74%) of the desired vinyl sulfide. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 15.0, 1.2 Hz, 1H), 5.77-5.64 (dt, *J* = 15.0, 7.8 Hz, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.50 (td, *J* = 7.5, 2.6 Hz, 2H), 2.08 (m, 2H), 2.04 (t, *J* = 2.6 Hz, 1H), 1.40-1.21 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 121.3, 82.4, 69.4, 32.8, 31.7, 31.3, 22.1, 19.6, 13.9; IR (film) 3305, 2958, 2927, 2871, 2858, 1459, 1436, 946 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{10}H_{16}S$ [M] 168.0973, found 168.0967.

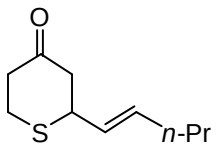
(E)-4-(hex-1-en-1-ylthio)but-1-en-2-yl acetate (2.13)



General protocol D for enol acetate synthesis was followed, starting from the above vinyl sulfide (232 mg, 1.38 mmol), [(p-cymene)$RuCl_2$]$_2$ (32.7 mg, 0.06 mmol), (2-furyl)$_3$P (24.7 mg, 0.12 mmol), Na_2CO_3 (20.2 mg, 0.20 mmol) and acetic acid (0.15 mL, 2.7 mmol). Flash column chromatography with 5% diethyl ether in hexanes afforded 135 mg (43%) of the desired enol acetate **2.13**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (dt, *J* = 15.0, 1.3 Hz, 1H), 5.67 (dt, *J* = 14.9, 7.0 Hz, 1H), 4.86-4.68 (m, 2H), 2.75 (t, *J* = 7.2 Hz, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.14 (s, 3H), 2.12-2.03 (m, 2H), 1.42-1.23 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 154.0, 132.2, 121.5, 102.4, 33.5, 32.6, 31.2, 29.4, 21.9, 20.8, 13.7; IR (film) 2958, 2927, 2857, 1759, 1666, 1434, 1370, 1197,

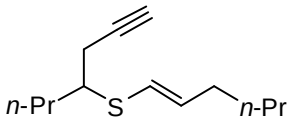
1020, 947, 876 cm^{-1}; HRMS (ESI) *m/z* calcd. For $C_{12}H_{20}O_2SNa$ $[M+Na]^+$ 251.1082, found 251.1079.

(E)-2-(pent-1-en-1-yl)dihydro-2H-thiopyran-4(3H)-one (2.3)



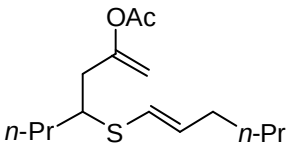
General protocol G2 was followed, starting from the enol acetate **2.13** (45.4 mg, 0.20 mmol), DDQ (47.7 mg, 0.21 mmol), 2,6-dichloropyridine (59.2 mg, 0.40 mmol) and 4Å M.S. (140 mg) in DCM (2 mL). Flash column chromatography with 10% diethyl ether in hexanes afforded 21.4 mg (58%) of the desired cyclization product **2.3**.

(E)-hept-1-yn-4-yl(hex-1-en-1-yl)sulfane



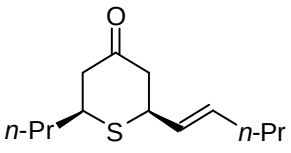
General protocol F2 was followed, starting from hept-1-yne-4-thiol **2.14** (406 mg, 2.37 mmol), *(E)*-1-iodohex-1-ene (430 mg, 1.95 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ complex (82mg, 0.10 mmol) and distilled Et_3N (0.74 mmol, 5.3 mmol). Flash column chromatography with 1% diethyl ether in hexanes afforded 212.2 mg (52%) of the desired vinyl sulfide. ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 15.0, 0.9 Hz, 1H), 5.80 (dt, *J* = 14.9, 6.7 Hz, 1H), 2.88 (tt, *J* = 7.7, 5.3 Hz, 1H), 2.58 (ddd, *J* = 17.0, 5.2, 2.7 Hz, 1H), 2.43 (ddd, *J* = 17.0, 7.5, 2.6 Hz, 1H), 2.08 (dt, *J* = 6.8, 6.8 Hz, 2H), 2.03 (t, *J* = 2.6 Hz, 1H), 1.84-1.67 (m, 1H), 1.64-1.38 (m, 4H), 1.38-1.25 (m, 4H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 120.4, 81.6, 69.9, 45.2, 35.4, 32.8, 31.2, 25.1, 22.0, 19.9, 13.8, 13.7.

(E)-4-(hex-1-en-1-ylthio)hept-1-en-2-yl acetate (2.15)



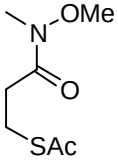
General protocol D for enol acetate synthesis was followed, starting from the above vinyl sulfide (204.2 mg, 0.97 mmol), $[(p\text{-cymene})RuCl_2]_2$ (24.5 mg, 0.04 mmol), $(2\text{-furyl})_3P$ (18.5 mg, 0.08 mmol), Na_2CO_3 (15.1 mg, 0.15 mmol) and acetic acid (0.11 mL, 2.0 mmol). Flash column chromatography with 3% diethyl ether in hexanes afforded 89.1 mg (34%) of the desired enol acetate **2.15**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 14.9, 1.0 Hz, 1H), 5.78 (dt, *J* = 14.9, 6.8 Hz, 1H), 4.88-4.74 (m, 2H), 2.87-2.80 (m, 1H), 2.55 (ddd, *J* = 15.0, 6.6, 0.7 Hz, 1H), 2.45 (ddd, *J* = 15.0, 6.6, 0.7 Hz, 1H), 2.14 (s, 3H), 2.08 (dt, *J* = 6.6, 6.6 Hz, 2H), 1.68-1.58 (m, 1H), 1.58-1.45 (m, 3H), 1.43-1.23 (m, 5H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 153.4, 135.3, 120.2, 103.8, 43.7, 39.4, 36.0, 32.8, 31.2, 22.0, 21.0, 20.0, 13.8, 13.7; IR (film) 2958, 2928, 2872, 1759, 1666, 1461, 1436, 1370, 1200, 1020, 952 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{26}O_2SNa$ $[M+Na]^+$ 293.1551, found 293.1561.

(2*S*,6*S*)-2-((*E*)-pent-1-en-1-yl)-6-propyldihydro-2H-thiopyran-4(3*H*)-one (2.7)



General protocol G2 was followed, starting from the above enol acetate **2.15** (36.2 mg, 0.13 mmol), DDQ (29.5 mg, 0.13 mmol), 2,6-dichloropyridine (38.4 mg, 0.26 mmol) and 4Å M.S. (140 mg) in DCM (1.5 mL). The reaction afforded 21.4 mg (71% yield) of the desired cyclization product **2.7** with a *cis*: *trans* ratio of 25:1.

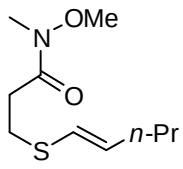
***S*-(3-(methoxy(methyl)amino)-3-oxopropyl) ethanethioate (2.17)**



To a vigorously stirred solution of Me(OMe)NH HCl (2.77 g, 28.4 mmol) and 3-bromopropanoyl chloride **2.16** (4.43 g, 25.8 mmol) in dichloromethane (50 mL) at 0 °C, Et_3N (7.89 mL, 56.7 mmol) was added over three hours, and then the reaction mixture was stirred at RT for 24 hours. The reaction mixture was concentrated under vacuum, dissolved in 150 mL diethyl ether, and washed twice with 200 mL brine. The organic phase was dried with Na_2SO_4, filtered and concentrated under vacuum. Flash column chromatography with 15% acetone in hexanes afforded 2.63 g (52%) the desired product. ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.71 (s, 3H), 3.64 (t, *J* = 6.8 Hz, 2H), 3.21 (s, 3H), 3.05 (t, *J* = 6.8, 2H).

The above bromide (2.05 g, 10.4 mmol) was reacted with HSAc (2.05 mL, 28.7 mmol) and Cs_2CO_3 (8.31 g, 25.5 mmol) according to the general protocol E2. Flash column chromatography with 15% acetone in hexanes afforded the desired thioacetate **2.17** (0.95 g, 48% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.19 (s, 3H), 3.14 (t, *J* = 7.0 Hz, 2H), 2.77 (t, *J* = 6.5 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 171.0, 60.3, 31.1, 29.4, 23.0.

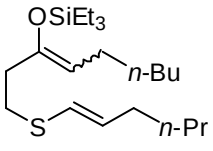
(*E*)-*N*-methoxy-*N*-methyl-3-(pent-1-en-1-ylthio)propanamide (2.18)



The above thioacetate **2.17** (191 mg, 1 mmol) was treated with K_2CO_3 (204 mg, 1.5 mmol) in methanol (3 mL) at RT for 40 minutes. The reaction mixture was diluted with 15 mL diethyl ether, washed successively with 14 mL of 1N HCl and 15 mL brine and concentrated under vacuum. . Flash column chromatography with 15% acetone in pentane afforded 117 mg (78%) of the desired thiol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.20 (s, 3H), 2.85-2.78 (m, 4H), 1.71 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 60.7, 35.4, 31.4, 18.9.

General protocol F2 was followed, starting from the above thiol (625 mg, 4.19 mmol), *(E)*-1-iodohex-1-ene (1.32 g, 6.29 mmol), Pd(dppf)Cl_2·CH_2Cl_2 complex (342mg, 0.42 mmol) and distilled Et_3N (1.46 mL, 10.5 mmol). Flash column chromatography with 15% acetone in hexanes afforded 403 mg (42%) of the desired vinyl sulfide **2.18.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (dt, *J* = 15.0, 1.2 Hz, 1H), 5.69 (dt, *J* = 15.0, 7.0 Hz, 1H), 3.70 (s, 3H), 3.19 (s, 3H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.08 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.39-1.27 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 131.2, 121.8, 61.1, 32.7, 32.1, 31.3, 27.3, 21.9, 13.7.

Triethyl((1-((*E*)-hex-1-en-1-ylthio)non-3-en-3-yl)oxy)silane (2.19)

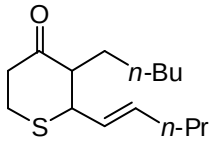


To a stirred solution of the Weinreb amide **2.18** (112 mg, 0.48 mmol) in THF (3 mL) at -78 °C, 1M vinyl magnesium bromide solution (1.45 mL, 1.45 mmol) in THF was added drop wise. The reaction mixture was allowed to RT over 1 hr, quenched with 0.2 mL saturated NH_4Cl solution and concentrated under vacuum. Flash column chromatography with 10% acetone in hexanes afforded 56.2 mg (59%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (dd, *J* = 18.0, 10.4 Hz, 1H), 6.24 (d, *J* = 17.6 Hz, 1H), 5.91-5.86 (m, 2H), 5.68 (dt, *J* =14.8, 7.2 Hz, 1H), 2.92-2.78 (m, 4H), 2.08 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.77-1.69 (m, 1H), 1.65-1.48 (m, 1H), 1.54-1.48 (m, 1H), 1.33-1.28 (m, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 136.3, 132.6, 128.6, 121.7, 39.4, 34.1, 32.8, 26.6, 22.1, 14.0.

To a suspension of CuBr Me_2S (206 mg, 1.0 mmol) in THF (1 mL) was added 1.6M butyl lithium solution (1.25 mL, 2.0 mmol) in hexanes at -40 °C. The mixture was stirred for 0.5 h and then cooled to -78 °C. To this solution were added TES-Cl (190 mg, 1.26 mmol), HMPA (0.22

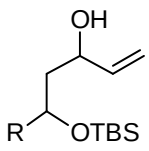
mL, 1.26 mmol), and the enone (25 mg, 0.126 mmol) in THF (1 mL) in this order. The mixture was stirred at this temperature for 40 minutes and then quenched with 1 mL saturated NH_4Cl solution. The mixture was extracted with ethyl acetate. The extracts were washed with water, dried over Na_2SO_4, and concentrated under vacuum. Flash column chromatography with 10% acetone in hexanes afforded 37.7 mg (81%) of the desired product mixture **2.19** with a *Z:E* ratio of 1.21:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95-5.84 (m, 1H), 5.66 (dtd, *J* = 15.0, 7.0, 0.8 Hz, 1H), 4.65 (t, *J* = 7.6 Hz, 0.5 H), 4.47 (t, *J* = 7.0 Hz, 0.4 H), 3.61 (t, *J* = 6.7 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H), 2.81-2.69 (m, 2H), 2.37 (dd, *J* = 8.9, 6.6 Hz, 1H), 2.29 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.08 (qdd, *J* = 8.4, 2.8, 1.3 Hz, 2H), 2.03-1.96 (m, 1H), 1.95-1.82 (m, 2H), 1.79-1.67 (m, 1H), 1.64-1.56 (m, 2H), 1.54-1.47 (m, 2H), 1.02-0.91 (m, 10H), 0.91-0.84 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 148.2, 131.6, 131.1, 122.3, 122.3, 109.5, 108.1, 65.8, 62.6, 37.3, 35.0, 34.6, 34.5, 32.9, 31.94, 31.7, 31.6, 31.5, 31.4, 30.6, 30.3, 29.4, 29.3, 26.8, 25.2, 22.6, 22.5, 22.3, 22.1, 20.6, 19.0, 15.2, 14.1, 14.0, 13.9, 6.7, 6.4, 5.50, 5.0, 4.4; IR (film) 2956, 2925, 2875, 1668, 1460, 1377, 1238, 1179, 1122, 1005, 942 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{43}OSSi$ $[M+H]^+$ 371.2804, found 371.2817.

(*E*)-2-(pent-1-en-1-yl)-3-pentyldihydro-2H-thiopyran-4(3*H*)-one (2.20)



General protocol G2 was followed, starting from the above enol silyl ether **2.19** (41.2 mg, 0.11 mmol), DDQ (25.0 mg, 0.11 mmol), 2,6-dichloropyridine (32.6 mg, 0.22 mmol) and 4Å M.S. (130 mg) in $MeNO_2$. Flash column chromatography with 10% diethyl ether in hexanes afforded 21.7 mg (78%) of the inseparable cyclization product mixture **2.20** with a *trans:cis* ratio 1:0.63. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65-5.54 (m, 1H), 5.47-5.39 (m, 0.4H), 5.37-5.29 (m, 0.6H), 3.75 (dd, *J* =8.2, 4.7 Hz, 0.6H),

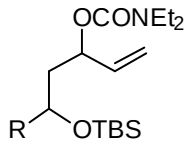
3.49 (t, *J* =7.2 Hz, 0.4H), 3.12 (ddd, *J* =13.8, 8.3, 5.5 Hz, 0.6 H), 3.00-2.82 (m, 2H), 2.75-2.66 (m, 2H), 2.65-2.58 (m, 1H), 2.11-1.90 (m, 2H), 1.89-1.68 (m, 2H), 1.45-1.33 (m, 2H), 0.99-0.94 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 210.4, 134.0, 133.8, 128.7, 125.7, 56.7, 50.4, 49.2, 43.4, 42.5, 34.3, 31.8, 29.1, 26.4, 22.4, 22.2, 14.0, 13.5; IR (film) 2956, 2926, 1710, 1627, 1464, 1281, 1128 cm^{-1}; HRMS (EI) m/z calcd. for $C_{15}H_{26}OS$ [M] 254.1704, found 254.1748.



5-((*tert*-butyldimethylsilyl)oxy)pent-1-en-3-ol (R = H): To a stirred solution of the aldehyde **2.21** (2.8 g, 14.9 mmol) in THF (20 mL) at -78 °C, 1M vinyl magnesium bromide solution (22.3 mL, 22.3 mmol) in THF was added drop wise. The reaction mixture was allowed to RT over 1 hr, and was quenched with 1 mL saturated NH_4Cl solution. Flash column chromatography with 10% ethyl acetate in hexanes afforded 56.2 mg (59%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddd, *J* = 17.2, 10.5, 5.4 Hz, 1H), 5.24 (dt, *J* = 17.2, 1.6 Hz, 1H), 5.07 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.32 (brs, 1H), 3.86 (ddd, *J* = 10.5, 6.0, 4.6 Hz, 1H), 3.78 (ddd, *J* = 10.2, 7.5, 4.4 Hz, 1H), 3.39 (brs, 1H), 1.80-1.60 (m, 2H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 114.0, 72.2, 61.7, 38.2, 25.7, -5.6.

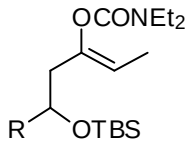
5-((*tert*-butyldimethylsilyl)oxy)hex-1-en-3-ol (R = methyl): Prepared similarly as the above intermediate, starting from 3-((*tert*-butyldimethylsilyl)oxy)butanal. The yield was 54%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98-5.74 (m, 1H), 5.26 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 4.44 (brs, 0.4 H), 4.33-4.23 (m, 0.6 H), 4.21-4.17 (m, 1H), 4.13-4.05 (m, 1H), 3.44 (s, 1H), 3.31 (s, 1H), 1.71-1.55 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 1.2H), 1.19 (d, *J* = 6.1 Hz, 1.8 H), 0.90 (d, *J* = 3.1 Hz, 9H), 0.11 (d, *J* = 4.9 Hz, 3.6H), 0.09 (d, *J* = 2.4 Hz, 2.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

141.1, 140.6, 113.9, 113.7, 72.1, 69.5, 69.4, 67.1, 45.8, 44.3, 25.7, 24.5, 23.0, 17.9, 17.8, -3.8, -4.4, -4.8, -5.0.



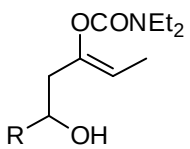
5-((*tert*-butyldimethylsilyl)oxy)pent-1-en-3-yl diethylcarbamate (**2.22**) (R = H): To a stirred solution of the above alcohol (0.55 g, 2.54 mmol) and N,N-diethylcarbamoyl chloride (0.80 mL, 6.4 mmol) in THF (5 mL) was added 60% NaH (256 mg, 6.4 mmol) carefully at 0 °C. The reaction was stirred overnight at room temperature, treated with H_2O (10 mL) and diethyl ether (2 X 10 mL), separated and concentrated under vacuum. Flash column chromatography with 10% ether in hexanes afforded 670 mg (84%) of the desired product **2.22**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 16.7, 10.5, 6.0 Hz, 1H), 5.31-5.15 (m, 2H), 5.11 (d, *J* = 10.6 Hz, 1H), 3.66 (t, *J* = 6.6 Hz, 2H), 3.25 (brs, 4H), 1.90-1.79 (m, 2H), 1.10 (t, *J* = 7.1 Hz, 6H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 137.4, 115.3, 72.2, 59.2, 37.5, 25.8, 18.1, -5.5; IR (film) 3090, 2861, 1703, 1474, 1423, 1380, 1272, 1172, 1098, 986, 838, 776 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{34}NO_3Si$ $[M+H]^+$ 316.2308, found 316.2312.

5-((*tert*-Butyldimethylsilyl)oxy)hex-1-en-3-yl diethylcarbamate (R = Methyl): Prepared similarly as above, and the yield was 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.18 (d, *J* = 17.5 Hz, 1H), 5.08 (d, *J* = 10.6 Hz, 1H), 3.99-3.78 (m, 1H), 3.23 (brs, 4H), 1.70-1.65 (m, 2H), 1.10 (t, *J* = 6.9 Hz, 6H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 138.0, 115.0, 72.4, 64.9, 44.8, 25.8, 25.6, 24.3, 17.9, -3.6, -4.4, -5.0.



(*Z*)-5-((*tert*-butyldimethylsilyl)oxy)pent-2-en-3-yl diethylcarbamate (2.23) (R = H): To a stirred solution of freshly prepared LDA (2.75 mmol) in THF (6 mL) was added successively HMPA (0.69 mL, 4.0 mmol) and the substrate **2.22** (687 mg, 2.18 mmol) in THF (3 mL) at -78 °C. The reaction was stirred for 15 minutes, after which MeI (0.21 mL, 3.4 mmol) was added. The reaction was allowed to -30 °C and treated with water (20 mL) and diethyl ether (20 mL). The organic layer was separated, dried and concentrated under vacuum. Flash column chromatography with 10% ether in hexanes afforded 434 mg (63%) of the desired product **2.23**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 (q, *J* = 6.8 Hz, 1H), 3.69 (t, *J* = 6.9 Hz, 2H), 3.31 (q, *J* = 7.1 Hz, 4H), 2.41 (t, *J* = 6.9 Hz, 2H), 1.50 (d, *J* = 6.8 Hz, 3H), 1.16-1.12 (m, 6H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 146.3, 112.3, 60.7, 37.6, 31.5, 25.8, 22.6, 18.2, 14.0, 10.5, -5.4; IR (film) 3070, 2862, 1703, 1648, 1474, 1423, 1380, 1273, 1172, 1098, 986, 937, 838, 777 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{34}NO_3Si$ $[M+H]^+$ 316.2308, found 316.2310.

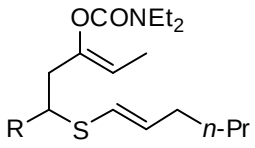
(*Z*)-5-((*tert*-butyldimethylsilyl)oxy)hex-2-en-3-yl diethylcarbamate (R = Methyl): Prepared similarly as above with a yield of 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.07 (q, *J* = 6.8 Hz, 1H), 3.96-3.89 (m, 1H), 3.33 (q, *J* = 6.7 Hz, 4H), 2.35 (dd, *J* = 14.3, 7.1 Hz, 1H), 2.27 (dd, *J* = 14.2, 5.7 Hz, 1H), 1.51 (d, *J* = 6.7 Hz, 3H), 1.16 (t, *J* = 6.5 Hz, 6H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 113.0, 77.3, 77.2, 77.0, 76.7, 66.1, 44.7, 25.8, 23.7, 18.1, 10.6, -4.7, -4.9.



(*Z*)-5-hydroxypent-2-en-3-yl diethylcarbamate (R = H): The above product (410 mg, 1.30 mmol) was treated with a mixture of 1M TBAF (3.9 mL, 3.9 mmol) and HOAc (0.15 mL, 2.6 mmol) at RT for two hours. Flash column

chromatography with 50% ethyl acetate in hexanes afforded 184 mg (70%) of the desired alcohol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (q, *J* = 7.0 Hz, 1H), 3.61 (aps, 2H), 3.39-3.32 (m, 4H), 2.38 (t, *J* = 5.1 Hz, 2H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 137.5, 115.4, 72.3, 59.3, 37.6, 25.9, -5.5; IR (film) 3454, 2873, 1697, 1475, 1424, 1379, 1276, 1219, 1167, 1098, 1054, 973 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{10}H_{19}NO_3Na$ $[M+Na]^+$ 224.1263, found 224.1271.

(*Z*)-5-hydroxyhex-2-en-3-yl diethylcarbamate (R = Methyl): Prepared similarly as above with a yield of 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (qd, *J* = 6.8, 1.2 Hz, 1H), 3.82-3.71 (m, 1H), 3.28 (q, *J* = 6.9 Hz, 4H), 2.32-2.19 (m, 1H), 2.08 (dd, *J* = 14.2, 10.0 Hz, 1H), 1.45 (dd, *J* = 6.8, 1.6 Hz, 3H), 1.15-1.07 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 146.0, 114.7, 63.5, 44.9, 42.0, 41.6, 22.0, 14.0, 13.1, 10.5.

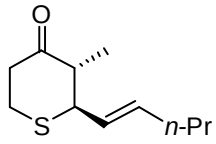


(*Z*)-5-((*E*)-hex-1-en-1-ylthio)pent-2-en-3-yl diethylcarbamate (2.24) (R = H):: General protocol E1 was followed, starting from the above alcohol (184 mg, 0.91 mmol), thioacetic acid (0.16 mL, 2.27 mmol), PPh_3 (544 mg, 2.07 mmol) and DIAD (0.42 mL, 2.12 mmol). Flash column chromatography with 20% diethyl ether in hexanes afforded 174 mg (73%) of the desired thioacetate. Then general protocol F1 was followed, starting from the thioacetate (213 mg, 0.82 mmol), *(E)*-iodo-1-hexene (260 mg, 1.24 mmol), CuI (31 mg, 0.16 mmol) and KOH (115 mg, 2.06 mmol). Flash column chromatography with 5% ethyl acetate in hexanes afforded 128.6 mg (52%) of the desired product **2.24**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 15.0, 1.2 Hz, 1H), 5.55 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.11 (q, *J* = 6.8 Hz, 1H), 3.34 (q, *J* = 7.0 Hz, 4H), 2.74 (dd, *J* = 8.3, 6.8 Hz, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 206 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.54 (dd, *J* = 6.8, 0.9 Hz, 4H), 1.38-1.23

(m, 4H), 1.12-1.14 (m, *6*H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3, 147.3, 131.6, 122.0, 112.0, 34.2, 32.7, 31.3, 30.0, 22.0, 21.9, 13.8, 10.5; IR (film) 2960, 1714, 1473, 1423, 1379, 1265, 1160, 1055, 1002, 946 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{16}H_{29}NO_2S$ [M] 299.1919, found 299.1891.

(*Z*)-5-((*E*)-hex-1-en-1-ylthio)hex-2-en-3-yl diethylcarbamate (2.26) (R = methyl): Prepared similarly as above with a yield of 37% over two steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 15.0, 1.2 Hz, 1H), 5.75 (dt, *J* = 15.0, 6.8 Hz, 1H), 5.10 (q, *J* = 6.8 Hz, 1H), 3.34 (q, *J* = 7.1 Hz, 4H), 3.08-2.91 (m, 1H), 2.60 (ddt, *J* = 14.7, 5.9, 1.0 Hz, 1H), 2.33 (dd, *J* = 14.7, 8.4 Hz, 1H), 2.13-2.00 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.54 (dt, *J* = 6.7, 0.9 Hz, 3H), 1.42-1.25 (m, 7H), 1.20 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 146.6, 134.4, 134.4, 120.8, 113.1, 41.9, 41.6, 38.8, 32.8, 31.3, 22.0, 20.6, 15.1, 13.8, 10.6, 10.6; IR (film) 2961, 2927, 2871, 1714, 1457, 1378, 1267, 1159, 991 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{17}H_{31}NO_2S$ [M] 313.2076, found 313.2108.

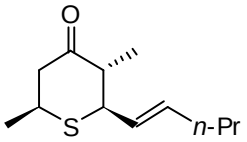
(2*R*,3*S*)-3-methyl-2-((*E*)-pent-1-en-1-yl)dihydro-2*H*-thiopyran-4(3*H*)-one (2.25) (R = H):



General protocol G2 was followed, starting from the *(Z)*-vinyl carbamate **2.24** (52.4 mg, 0.17 mmol), DDQ (41.8 mg, 0.18 mmol), 2,6-dichloropyridine (50.3 mg, 0.34 mmol) and 4Å M.S. (150 mg) in $MeNO_2$ (1.5 mL). The reaction afforded 27.8 mg (80%) of the cyclization product **2.25** with a *trans:cis* ratio of 25:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.36 (ddt, *J* = 15.2, 8.7, 1.4 Hz, 1H), 3.37 (dd, *J* = 9.2, 9.2 Hz, 1H), 2.98 (ddd, *J* = 15.4, 9.3, 5.4 Hz, 1H), 2.90 (ddd, *J* = 13.6, 5.2, 5.2 Hz, 1H),), 2.71 (dd, *J* = 9.4, 4.6 Hz, 2H), 2.67 (dd, *J* = 9.4, 6.5 Hz, 1H), 2.02 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.48-1.30 (m, 2H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 4H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 210.3, 134.6, 128.0, 52.9, 51.9, 43.2, 34.2, 28.8, 22.1, 13.5, 13.1; IR (film) 3583, 2871, 1712, 1651, 1453, 1328, 1277, 1225, 1156, 968 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{11}H_{17}OS$ $[M-H]^+$ 197.1000 , found 197.1003.

(2*R*,3*S*,6*S*)-3,6-dimethyl-2-((*E*)-pent-1-en-1-yl)dihydro-2*H*-thiopyran-4(3*H*)-one (2.27)



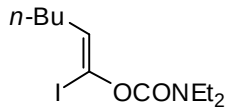
General protocol G2 was followed, starting from the *(Z)*-vinyl carbamate **2.26** (40.8 mg, 0.13 mmol), DDQ (31.0 mg, 0.14 mmol), 2,6-dichloropyridine (38.6 mg, 0.26 mmol) and 4Å M.S. (80 mg) in $MeNO_2$(1.2 mL).. The reaction afforded 22.6 mg (82%) of the cyclization product **2.27** with a *ortho-trans:cis* ratio of 25:1 and a meta-*cis:trans* ratio of 25:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 (dt, *J* = 15.6, 6.8 Hz, 1H), 5.29 (dd, *J* = 15.5, 9.2 Hz, 1H), 3.33 (dd, *J* = 10.2, 10.2 Hz, 1H), 3.22 (dqd, *J* = 13.3, 6.7, 2.9 Hz, 1H), 2.69 (dd, *J* = 12.5, 2.8 Hz, 1H), 2.56 (dq, *J* = 10.9, 6.6 Hz, 1H), 2.48 (dd, *J* = 12.4, 12.4 Hz, 1H), 2.02 (dt, *J* = 6.8, 6.8 Hz, 2H), 1.47-1.36 (m, 2H), 1.30-1.26 (m, 4H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 135.1, 127.6, 52.6, 52.4, 51.3, 39.3, 34.2, 31.5, 22.6, 22.1, 21.2, 14.1, 13.5, 12.2; IR (film) 2959, 2870, 1711, 1646, 1451, 1376, 1331, 1274, 1219, 1106, 965 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{12}H_{19}OS$ $[M-H]^+$ 211.1157, found 211.1153.

Ethynyl diethylcarbamate (2.28)

Diisopropylamine (4.33 mL, 30.7 mmol) was dissolved in dry THF (20 mL) and the solution was cooled to −78 °C. N-BuLi (19.2 mL, 30.7 mmol; 1.6 M solution in hexane) was added dropwise and stirred for 30 min. 2,2,2-tribromoethyl N,N-diethylcarbamate (2.55 g, 6.67 mmol) in THF (8 mL) was added dropwise over five minutes, and the mixture was stirred for 4

hrs. After addition of MeOH (0.81 mL), the reaction mixture was stirred for 2 hrs and then allowed to warm to 0 °C. The reaction mixture was treated with water and diethyl ether. The organic layer was dried ($MgSO_4$), filtered, and concentrated under vacuum to afford the crude product. Flash column chromatography on silica gel (10:1 pentane/ether) furnished of the 1-alkynyl carbamate **2.28** (537 mg, 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41-3.16 (m, 4H), 2.10 (s, 1H), 1.19 (td, *J* = 7.2, 2.7 Hz, 6H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.3, 80.8, 44.1, 36.7, 22.8; IR (film) 3390, 2968, 2859, 1456, 1273, 1141, 1081 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_7H_{11}NO_2$ [M] 141.0790, found 141.0831.

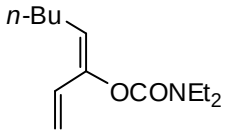
(*Z*)-1-iodohex-1-en-1-yl diethylcarbamate (2.29)



To a stirred suspension of CuI (838 mg, 4.4 mmol) in dry Et_2O(5 mL), 4.4 mL of freshly prepared solution of *n*-BuMgBr in ether (1M, 4.4 mmol) was added drop wise at -78 °C. The reaction mixture was warmed to -25 °C and stirred for 30 minutes. The reaction mixture was cooled to -78 °C, and the alkynyl carbamate **2.28** (282 mg, 2.0 mmol) in dry Et_2O (1 mL) was added drop wise. After 90 minutes, I_2 (1.27 g, 5.0 mmol) in dry Et_2O (5 ml) was added at -78 °C. The reaction mixture was warmed to room temperature, stirred for 15 minutes and quenched with 1:1 saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$. The mixture was separated, extracted with diethyl ether, combined and concentrated under vacuum. Flash column chromatography with 5% E_2O in hexanes afforded 340 mg (52%) of the desired product **2.29**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (t, *J* = 7.2 Hz, 1H), 3.34-3.26 (m, 4H), 2.07 (dt, *J* = 7.6, 7.6 Hz, 2H), 1.72-1.35 (m, 4H), 1.18 (t, *J* = 7.2 Hz, 6H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 128.9, 101.9, 34.6, 31.6, 25.2, 22.6, 14.1; IR

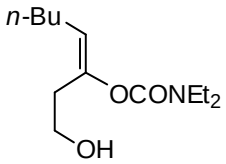
(film) 2872, 1731, 1459, 1420, 1269, 1151, 1096, 1012 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{11}H_{20}NO_2I$ [M] 325.0539 , found 325.0561.

(*E*)-octa-1,3-dien-3-yl diethylcarbamate



To a 25 mL flame-dried round bottom flask was added $Pd(PPh_3)_4$ (202 mg, 0.175 mmol) , followed by argon exchange and protection. Distilled THF(0.6 mL) and 1M vinyl magnesium bromide (3.0 mL, 3.0 mmol) was charged, and the resulting suspension was stirred for 15 minutes at °C. The substrate **2.29** (570 mg, 1.75 mmol) in THF (1 mL) was then added drop wise, and the reaction mixture was stirred for 30 minutes. The reaction was cooled to 0 °C, quenched with saturated aqueous NH_4Cl solution (0.1 mL), and concentrated under vacuum. Flash column chromatography with 10% Et_2O in hexanes afforded 300 mg (71 %) of the desired diene. ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (dd, *J* = 17.1, 11.0 Hz, 1H), 5.31 (dd, *J* = 8.4, 7.7 Hz, 1H), 5.23 (d, *J* = 17.0 Hz, 1H), 5.13 (dt, *J* = 11.0, 1.4 Hz, 1H), 3.37 (q, *J* = 6.7 Hz, 4H), 2.21 (dt, *J* = 14.8, 7.4 Hz, 2H), 1.46-1.12 (m, 12H), 0.91 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 145.2, 127.4, 122.3, 113.6, 31.6, 25.9, 22.1, 13.8.

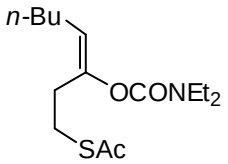
(*E*)-1-hydroxyoct-3-en-3-yl diethylcarbamate (2.30)



To a solution of 1M BH_3 in THF (1.29 mL, 1.29 mmol) at 0 °C, cyclohexene (0.28 mL, 2.58 mmol) was added dropwise. White precipitates were formed in several minutes. Thirty minutes later, the diene (194 mg, 0.86 mmol) was added drop wise. The reaction mixture became clear in 15 minutes and was stirred for 1.5 hours at 0 °C. A 10% solution of sodium hydroxide (2.8mL) and 33% hydrogen peroxide (1.1 mL were added carefully and successively, and the reaction mixture was stirred for 1 hr at room

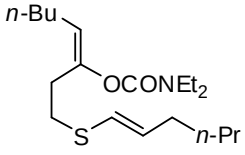
temperature. Following the addition of Et_2O, the organic layer was separated, re-extracted, combined and concentrated under vacuum. Flash column chromatography with 40% EtOAc in hexanes afforded 130 mg (62%) of the desired alcohol **2.30**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.28 (t, *J* = 7.8 Hz, 1H), 3.73-3.54 (m, 4H), 3.32 (brs, *J* = 3.5 Hz, 4H), 2.47 (t, *J* = 5.7 Hz, 2H), 2.10 (dt, *J* = 7.4, 7.4 Hz, 2H), 1.99-1.80 (m, 4H), 1.78-1.70 (m, 4H), 1.63-1.53 (m, 2H), 1.43-1.32 (m, 4H), 1.33-1.24 (m, 6H), 1.18 (d, *J* = 19.9 Hz, 8H), 0.90 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 145.3, 122.0, 70.2, 58.8, 35.5, 33.4, 31.8, 26.3, 25.4, 24.1, 22.2, 13.8; IR (film) 3456, 2960, 2931, 2873, 1697, 1475, 1424, 1276, 1167, 1053 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{13}H_{25}NO_3$ [M] 243.1834, found 243.1861.

(*E*)-S-(3-((diethylcarbamoyl)oxy)oct-3-en-1-yl) ethanethioate



General protocol E1 was followed, starting from the above alcohol (120 mg, 0.49 mmol), thioacetic acid (0.17 mL, 2.5 mmol), PPh_3 (603 mg, 2.3 mmol) and DIAD (0.45 mL, 2.3 mmol). Flash column chromatography with 5% ethyl acetate in hexanes afforded 110 mg (74%) of the desired thioacetate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (t, *J* = 7.8 Hz, 1H), 3.31 (q, *J* = 7.1 Hz, 4H), 2.98 (t, *J* = 7.6, 2H), 2.57 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 2.06 (dt, *J* = 7.2, 7.2 Hz, 2H), 1.90-1.49 (m, 4H), 1.16 (t, *J* = 6.5 Hz, 6H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 154.4, 146.4, 119.4, 41.8, 31.8, 30.5, 29.4, 26.6, 26.2, 22.2, 14.0.

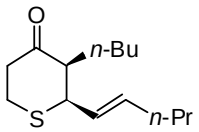
(*E*)-1-((*E*)-hex-1-en-1-ylthio)oct-3-en-3-yl diethylcarbamate (2.31)



General protocol F1 was followed, starting from the above thioacetate (105 mg, 0.35 mmol), CuI (13.3 mg, 0.07 mmol) and KOH (493 mg, 0.88

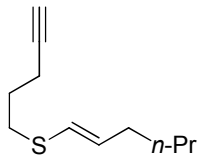
mmol). Flash column chromatography with 5% ethyl acetate in hexanes afforded 70.5 mg (59%) of the desired product **2.31**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 15.0, 1.3 Hz, 1H), 5.66 (dt, *J* = 15.0, 6.9 Hz, 1H), 5.20 (t, *J* = 7.8 Hz, 1H), 3.30 (q, *J* = 7.0 Hz, 4H), 2.81-2.69 (m, 2H), 2.60 (dd, *J* = 11.0, 4.4 Hz, 2H), 2.18-1.99 (m, 4H), 1.42-1.24 (m, 8H), 1.15 (t, *J* = 7.1 Hz, 6H), 0.91-0.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 146.7, 131.7, 122.0, 119.0, 32.8, 31.8, 31.4, 30.0, 29.6, 26.2, 22.2, 22.0, 13.8; IR (film) 2958, 2928, 2872, 1712, 1468, 1421, 1379, 1270, 1159, 1104 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{19}H_{35}NO_2S$ [M] 341.2389, found 341.2413.

(2*R*,3*R*)-3-butyl-2-((*E*)-pent-1-en-1-yl)dihydro-2*H*-thiopyran-4(3*H*)-one (2.32)



General protocol G2 was followed, starting from the *(E)*-vinyl carbamate 19 (49.3 mg, 0.14 mmol), DDQ (33.4 mg, 0.14 mmol), 2,6-dichloropyridine (41.4 mg, 0.28 mmol) and 4Å M.S. (150 mg) in $MeNO_2$ (1.5 mL). The reaction afforded 30.6 mg (88%) of the cyclization product **2.32** as a single diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (dt, *J* = 15.2, 6.6 Hz, 1H), 5.32 (ddt, *J* = 15.2, 8.6, 0.8 Hz, 1H), 3.76 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.12 (ddd, *J* = 13.8, 8.1, 5.8 Hz, 1H), 2.96-2.82 (m, 2H), 2.77-2.64 (m, 2H), 2.10-1.93 (m, 2H), 1.89-1.78 (m, 1H), 1.45-1.33 (m, 2H), 1.33-1.24 (m, 4H), 1.24-1.16 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4, 133.9, 125.6, 56.5, 49.1, 43.4, 34.3, 31.5, 27.2, 26.8, 22.6, 22.2, 14.0, 13.8, 13.4; IR (film) 2828, 1709, 1565, 1432, 1161, 1136, 966, 791 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{14}H_{25}OS$ $[M+H]^+$ 241.1626, found 241.1607.

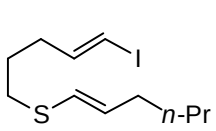
(*E*)-hex-1-en-1-yl(pent-4-yn-1-yl)sulfane (2.34)



General protocol F2 was followed, starting from 4-pentyn-1-thiol **2.33** (5.72 g, 25.7 mmol), *(E)*-1-iodohex-1-ene (4.49 g, 21.4 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ complex (874mg, 1.07 mmol) and Et_3N (7.7 mL, 55.3 mmol, pre-soaked with

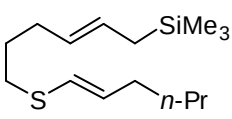
molecular sieves). Flash column chromatography with 2% diethyl ether in hexanes afforded 2.36 g (61%) of the desired vinyl sulfide product **2.34**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 15.0, 1.3 Hz, 1H), 5.67 (dt, *J* = 15.0, 6.9 Hz, 1H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.33 (td, *J* = 6.9, 2.6 Hz, 2H), 2.08 (dtd, *J* = 7.1, 7.1, 1.2 Hz, 2H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.87-1.80 (m, 2H), 1.39-1.21 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.2, 122.0, 83.0, 68.8, 32.6, 31.2, 28.0, 21.8, 17.0, 13.6; IR (film) 3304, 2956, 2926, 2857, 1454, 1433, 1254, 944 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{11}H_{18}S$ [M] 182.1129, found 182.1139.

(*E*)-hex-1-en-1-yl((E)-5-iodopent-4-en-1-yl)sulfane



General protocol H for the synthesis of vinyl iodide was followed, starting from the substrate **2.34** (638 mg, 3.5 mmol), $ZrCp_2Cl_2$(1.13 g, 3.85 mmol) and 1M DIBAL-H (3.85 mL, 3.85 mmol). Flash column chromatography with 2% dichloromethane in hexanes afforded 967 mg (78%) of the desired product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (dt, *J* = 14.4, 7.2 Hz, 1H), 6.06 (dt, *J* = 14.4, 1.4 Hz, 1H), 5.87 (dt, *J* = 15.0, 1.3 Hz, 1H), 5.65 (dt, *J* = 15.0, 7.0 Hz, 1H), 2.62 (t, *J* = 7.3 Hz, 2H), 2.17 (dtd, *J* = 7.5, 7.5, 1.3 Hz, 2H), 2.06 (dtd, *J* = 7.0, 7.0, 1.1 Hz, 2H), 1.75- 1.68 (m, 2H), 1.40-1.26 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 131.1, 122.0, 75.5, 34.5, 32.6, 31.5, 31.2, 27.7, 12.8, 13.7; IR (film) 2954, 2925, 2854, 1606, 1453, 1435, 1256, 1213, 942 cm^{-1}.

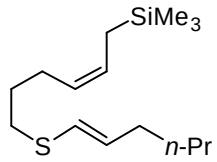
((*E*)-6-((*E*)-hex-1-en-1-ylthio)hex-2-en-1-yl)trimethylsilane (2.35)



General protocol I for Kumada coupling reaction was followed, starting from the above vinyl iodide (468 mg, 1.5 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) and 1M trimethylsilyl methylmagnesium chloride (2.25 mL, 2.25 mmol). Flash column

chromatography with 2% Dichloromethane in hexanes afforded 373 mg (91%) of the desired product **2.35**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (dt, *J* = 15.0, 1.3 Hz, 1H), 5.62 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.41 (dtt, *J* = 15.0, 8.0, 1.2 Hz, 1H), 5.21 (dt, *J* = 15.1, 6.8 Hz, 1H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.11-2.04 (m, 4H), 1.69-1.62 (m, 2H), 1.42-1.26 (m, 4H), 0.89 (t, *J* = 7.6 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.7, 127.4, 127.2, 122.6, 32.8, 32.0, 31.7, 31.5, 29.6, 22.6, 22.0, 13.8, -2.0; IR (film) 2954, 2926, 1454, 1437, 1247, 1155, 964, 940, 852 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{30}SSiNa$ $[M+Na]^+$ 293.1735, found 293.1729.

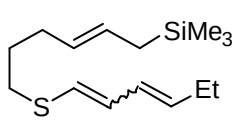
((*Z*)-6-((*E*)-hex-1-en-1-ylthio)hex-2-en-1-yl)trimethylsilane (2.36)



To a solution of the substrate **2.34** (365 mg, 2.0 mmol) in THF (12 mL) cooled at -78 °C was added drop wise 1.6 M BuLi solution (1.38 mL, 2.2 mmol). The reaction mixture was allowed to -20 °C, stirred for 15 minutes, and cooled back to -78 °C. Iodine (609 mg, 2.4 mmol) in THF (5 mL) was added dropwise, and the reaction mixture was slowly allowed to 0 °C. The reaction was quenched with 1:1 saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$, extracted with diethyl ether twice and concentrated under vacuum. Flash column chromatography with 10% dichloromethane in hexanes afforded 529 mg (86%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (d, *J* =15.0 Hz, 1H), 5.67 (dt, *J* = 15.0, 7.0 Hz, 1H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.80 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.86-1.79 (m, 2H), 1.40-1.26 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). To a 25 mL round bottom flask was charged the above ethynyl iodide (374 mg, 1.21 mmol), $K_2N_2(CO_2)_2$ (704 mg, 3.63 mmol), pyridine (0.6 mL, 7.4 mmol) and methanol (1.4 mL). Acetic acid (0.44 mL, 7.7 mmol) diluted with methanol (1.7 mL) was added via a syringe pump over 8 hours at RT. The reaction mixture was carefully quenched with water, extracted twice with diethyl ether

and concentrated under vacuum. Flash column chromatography with 10% dichloromethane in hexanes afforded 124 mg (33%) of the desired *(Z)*-vinyl iodide. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (dt, *J* = 7.4, 0.8 Hz, 1H), 6.18 (dt, *J* = 7.0, 6.9 Hz, 1H), 5.90 (dt, *J* = 15.0, 1.3 Hz, 1H), 5.66 (dt, *J* = 15.0, 6.9 Hz, 1H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.26 (dt, *J* = 7.5, 7.5 Hz, 2H), 2.08 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.84-1.67 (m, 2H), 1.42-1.27 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H). General protocol I for Kumada coupling reaction was followed, starting from above *(Z)*-vinyl iodide (168.5 mg, 0.543 mmol), $(PPh_3)_4$ (63.3 mg, 0.055 mmol) and 1M trimethylsilyl methylmagnesium chloride (0.82 mL, 0.82 mmol). Flash column chromatography with 2% Dichloromethane in hexanes afforded 137 mg (93%) of the desired *(Z)*-allylsilane **2.36**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 15.0, 1.3 Hz, 1H), 5.64 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.44 (dtt, *J* = 10.2, 8.6, 1.6 Hz, 1H), 5.30-5.18 (m, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.13-2.05 (m, 4H), 1.77-1.61 (m, 2H), 1.48 (d, *J* = 12.6 Hz, 2H), 1.40-1.23 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.9, 126.4, 126.1, 122.5, 32.8, 32.3, 31.4, 29.4, 26.0, 22.0, 18.4, 13.9, -1.8; IR (film) 3006, 2928, 2856, 1645, 1456, 1419, 1392, 1248, 1150, 856 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{31}SSi$ $[M+H]^+$ 271.1916, found 271.1929.

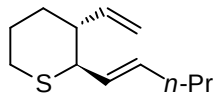
((2*E*)-6-(hexa-1,3-dien-1-ylthio)hex-2-en-1-yl)trimethylsilane (2.38)



General protocol G1 was followed, starting from the *trans*- allylsilane **2.35** (55.9 mg, 0.21 mmol), DDQ (49.3 mg, 0.22 mmol), 2,6-dichloropyridine (0.43 mg, 0.75 mmol) and 4Å M.S. (150 mg) in DCM (2.5 mL). The reaction afforded 30.1 mg (54% yield) of the diene mixture **2.38** with a *trans*: *cis* ratio of about 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (ddd, *J* = 14.9, 11.0, 1.1 Hz, 0.5H), 6.22-6.05 (m, 1.5 H), 6.05-5.97 (m, 0.5H), 5.92 (dd, *J* = 16.9, 6.2 Hz, 0.5H), 5.59 (dt, *J* = 14.5, 6.6 Hz, 0.5H), 5.46-5.36 (m, 1H), 5.33-5.25

(m, 0.5H), 5.25-5.15 (m, 1H), 2.75-2.60 (m, 2H), 2.20-2.11 (m, 1H), 2.13-2.04 (m, 3H), 1.77-1.61 (m, 2H), 1.41 (d, *J* = 8.0 Hz, 2H), 1.00 (td, *J* = 7.5, 1.8 Hz, 3H), -0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.7, 131.0, 128.5, 128.4, 127.8, 127.5, 127.4, 127.3, 127.2, 126.9, 125.1, 123.5, 32.0, 31.9, 31.7, 29.6, 29.5, 25.6, 22.7, 21.0, 14.2, 13.6, -2.0; IR (film) 3378, 2952, 2360, 1713, 1411, 1247, 1134, 1009, 844 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{29}SSi$ $[M+H]^+$ 269.1759, found 269.1775.

(2*R*,3*R*)-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran (2.39)

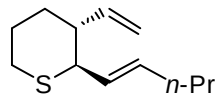


General protocol G2 was followed, starting from the *trans*- allylsilane **2.35** (97.1 mg, 0.36 mmol), DDQ (85.5 mg, 0.38 mmol), 2,6-dichloropyridine (111.6 mg, 0.75 mmol) and 4Å M.S. (290 mg) in $MeNO_2$. The reaction afforded 46.8 mg (68% yield) of the desired cyclization product **2.39** with a *trans*: *cis* ratio of 7.7:1.

(2*R*,3*R*)-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran (**2.39**) (*trans*-product): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.65 (ddd, *J* = 13.7, 8.7, 6.2 Hz, 1H), 5.58 (dd, *J* = 12.8, 5.8 Hz, 1H)., 5.26 (ddt, *J* = 15.3, 8.8, 1.4 Hz, 1H), 5.01-4.92 (m, 2H), 3.13 (dd, *J* = 9.4, 9.4 Hz, 1H), 2.71 (ddd, *J* = 12.4, 12.4, 2.8 Hz, 1H), 2.54 (dddd, *J* = 13.4, 3.6, 3.6, 1.3 Hz, 1H), 2.17 (dddd, *J* = 10.2, 10.2, 10.2, 3.2 Hz, 1H), 2.08-1.94 (m, 3H), 1.91-1.81 (m, 1H), 1.72-1.63 (m, 1H), 1.38 (dt, *J* = 14.6, 4.1 Hz, 2H), 1.30-1.24 (m, 1H), 0.87 (t, *J* =7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 133.6, 129.7, 114.3, 48.2, 47.8, 34.3, 32.4, 29.6, 27.0, 22.2, 13.5; IR (film) 2957, 2926, 2847, 1639, 1451, 1287, 1145, 990, 963 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{12}H_{21}S$ $[M+H]^+$ 197.1364, found 197.1368.

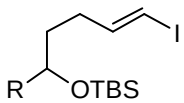
(2*R*,3*S*)-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran (*cis*-product): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (ddd, *J* = 17.2, 10.5, 7.8 Hz, 1H), 5.61 (dt, *J* = 15.2, 6.8 Hz, 1H), 5.52 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.08-4.97 (m, 2H), 3.39 (dd, *J* = 7.8, 3.3 Hz, 1H), 2.72 (ddd, *J* = 13.4, 8.1, 3.4 Hz, 1H), 2.64-2.53 (m, 2H), 2.06-1.90 (m, 3H), 1.79-1.70 (m, 1H), 1.70-1.62 (m, 2H), 1.48-1.33 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 132.9, 127.5, 114.8, 46.1, 44.8, 34.4, 29.4, 26.7, 24.6, 22.4, 13.6; IR (film) 3008, 2853, 1726, 1659, 1451, 1377, 1134, 1017, 891 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{12}H_{21}S$ $[M+H]^+$ 197.1364, found 197.1374.

(2*R*,3*R*)-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran (2.39)



General protocol G2 was followed, starting from the *cis*-allylsilane **2.36** (78.3 mg, 0.29 mmol) DDQ (68.9 mg, 0.30 mmol), 2,6-dichloropyridine (89.6 mg, 0.61 mmol) and 4Å M.S. (240 mg) in $MeNO_2$. The reaction afforded 42.6 mg (75% yield) of the desired cyclization products **2.39** with a *trans*: *cis* ratio of 1.9:1.

(*E*)-*tert*-butyl((1-iodonon-1-en-5-yl)oxy)dimethylsilane and (*E*)-*tert*-butyl((7-iodo-2-methylhept-6-en-3-yl)oxy)dimethylsilane



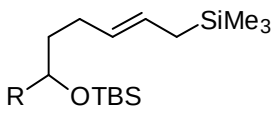
General protocol H for the synthesis of vinyl iodide was followed, starting from the corresponding alkyne **2.40** or **2.41**. Flash column chromatography with 5% Dichloromethane in hexanes afforded the corresponding vinyl iodide.

(*E*)-*tert*-butyl((1-iodonon-1-en-5-yl)oxy)dimethylsilane R: *n*-Bu: 73% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (dt, *J* = 14.2, 7.1 Hz, 1H), 5.98 (dt, *J* = 14.3, 1.4 Hz, 1H), 3.81-3.53 (m, 1H), 2.41-1.83 (m, 2H), 1.69-1.38 (m, 4H), 1.38-0.99 (m, 4H), 0.99-0.84 (m, 12H), 0.04 (s, 3H),

0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 74.3, 71.4, 36.7, 35.5, 31.9, 27.4, 25.9, 22.8, 18.1, 14.1, -4.4, -4.5.

(*E*)-*tert*-butyl((7-iodo-2-methylhept-6-en-3-yl)oxy)dimethylsilane R: *i*-pro: 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (dt, *J* = 14.4, 7.2 Hz, 1H), 5.99 (dt, *J* = 14.4, 1.5 Hz, 1H), 3.42 (dd, *J* = 11.1, 5.1 Hz, 1H), 1.91-2.20 (m, 2H), 1.65-1.75 (m, 1H), 1.43-1.51 (m, 2H), 0.89 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 76.1, 74.3, 32.8, 32.2, 31.3, 25.9, 18.1, 18.0, 17.6, -4.3, -4.4.

(*E*)-*tert*-butyldimethyl((10-(trimethylsilyl)dec-8-en-5-yl)oxy)silane (2.42) and (*E*)-*tert*-butyldimethyl((2-methyl-8-(trimethylsilyl)oct-6-en-3-yl)oxy)silane (2.43)



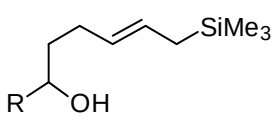
General protocol I for Kumada coupling reaction was followed, starting from the above vinyl iodide. Flash column chromatography with 5% Dichloromethane in hexanes afforded the corresponding allylsilane.

(*E*)-*tert*-butyldimethyl((10-(trimethylsilyl)dec-8-en-5-yl)oxy)silane (**2.42**) R: *n*-Bu: 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (dtt, *J* = 15.2, 7.6, 1.0 Hz, 1H), 5.23 (dt, *J* = 15.2, 6.8 Hz, 1H), 3.64 (app t, *J* = 5.8 Hz, 1H), 2.09-1.92 (m, 2H), 1.50-1.36 (m, 6H), 1.28 (tt, *J* = 10.1, 3.8 Hz, 4H), 0.92-0.80 (m, 12H), 0.04 (s, 3H), 0.04 (s, 3H), -0.02 (m, 9H); 13C NMR (100 MHz, $CDCl_3$) δ 128.3, 125.9, 71.9, 37.5, 36.7, 28.7, 27.5, 25.9, 22.9, 22.6, 18.2, 14.1, -2.0, -4.4.

(*E*)-*tert*-butyldimethyl((2-methyl-8-(trimethylsilyl)oct-6-en-3-yl)oxy)silane (**2.43**) R: *i*-pro: 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (dt, *J* = 15.2, 8.0 Hz, 1H), 5.23 (dt, *J* = 15.2, 6.8 Hz, 1H), 3.45 (apq, *J* = 5.2 Hz, 1H), 1.91-2.05 (m, 2H), 1.67-1.75 (m, 1H), 1.42-1.46 (m, 1H), 1.39 (d, *J* = 8.0 Hz, 2H), 0.89 (s, 9H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 3H),

0.03 (s, 3H), -0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.9, 125.9, 76.3, 33.5, 32.5, 28.7, 25.9, 22.6, 18.2, 18.1, 17.5, -2.0, -4.2, -4.5.

(*E*)-10-(trimethylsilyl)dec-8-en-5-ol and (*E*)-2-methyl-8-(trimethylsilyl)oct-6-en-3-ol

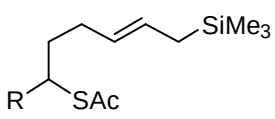


The above allylsilane was stirred with 9-CSA (0.1 equiv) in methanol (~0.4 M) at RT overnight. Flash column chromatography with 20% ethyl acetate in hexanes afforded the corresponding alcohol.

(*E*)-10-(trimethylsilyl)dec-8-en-5-ol R: *n*-Bu: 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.24 (dt, *J* = 15.0, 7.0 Hz, 1H), 3.58 (br, 1H), 1.99-2.14 (m, 2H), 1.65 (t, *J* = 12.0, 1H), 1.26-1.48 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H), -0.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.3, 126.6, 71.4, 37.5, 37.1, 29.1, 27.8, 22.7, 22.6, 14.0, -2.1.

(*E*)-2-methyl-8-(trimethylsilyl)oct-6-en-3-ol R: *i*-pro: 95% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (dtt, *J* = 15.5, 7.5, 1.3 Hz, 1H), 5.26 (dt, *J* = 15.0, 7.0 Hz, 1H), 3.36-3.39 (m, 1H), 2.11-2.15 (m, 1H), 2.01-2.08 (m, 1H), 1.61-1.67 (m, 1H), 1.47-1.53 (m, 1H), 1.38 (d, *J* = 8.5 Hz, 2H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), -0.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.4, 126.8, 76.2, 34.2, 33.4, 29.4, 22.6, 18.8, 17.1, -2.0.

(*E*)-S-(10-(trimethylsilyl)dec-8-en-5-yl) ethanethioate (2.44) and (*E*)-S-(2-methyl-8-(trimethylsilyl)oct-6-en-3-yl) ethanethioate (2.45)



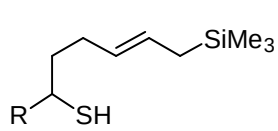
The above alcohol was reacted with mesyl chloride (2 equiv) and Et_3N (3 equiv) in dichloromethane (~0.5 M solution) from -40 °C to RT over two hours. The reaction mixture was acidified with 1N hydrochloric acid, washed twice with water, dried with $MgSO_4$ and concentrated under vacuum. The resulting crude product (100% yield)

was reacted with HSAc (2.7 equiv) and Cs_2CO_3 (2.4 equiv) according to the general protocol E2. Flash column chromatography with 5% ethyl acetate in hexanes afforded the desired thioacetate.

(*E*)-S-(10-(trimethylsilyl)dec-8-en-5-yl) ethanethioate (**2.44**) R: *n*-Bu: 66% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.37 (dt, *J* = 15.0, 8.0 Hz, 1H), 5.19 (dt, *J* = 15.0, 7.0 Hz, 1H), 3.47-3.53 (m, 1H), 2.29 (s, 3H), 1.95-2.09 (m, 2H), 1.47-1.64 (m, 4H), 1.38 (d, *J* = 8.0 Hz, 2H), 1.23-1.33 (m, 4H), 0.86 (t, *J* = 7.0 Hz, 3H), -0.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.8, 127.6, 126.9, 44.1, 35.1, 34.5, 30.8, 30.1, 28.8, 22.6, 22.5, 13.9, -2.1.

(*E*)-S-(2-methyl-8-(trimethylsilyl)oct-6-en-3-yl) ethanethioate (**2.45**) R: *i*-pro: 47% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (dt, *J* = 14.8, 8.0 Hz, 1H), 5.21 (dt, *J* = 14.8, 6.8 Hz, 1H), 3.51 (dt, *J* = 9.6, 4.4 Hz, 1H), 2.33 (s, 3H), 2.04-2.14 (m, 1H), 1.95-2.03 (m, 1H), 1.87-1.95 (m, 1H), 1.47-1.65 (m, 2H), 1.39 (d, *J* = 8.0 Hz, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 127.6, 126.9, 50.4, 32.8, 31.9, 30.7, 30.3, 22.6, 19.9, 18.5, -2.1.

(*E*)-10-(trimethylsilyl)dec-8-ene-5-thiol and (*E*)-2-methyl-8-(trimethylsilyl)oct-6-ene-3-thiol



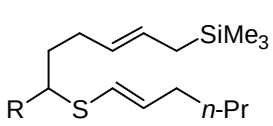
The above thioacetate was reacted with lithium aluminum hydride (2 equiv) in diethyl ether (~0.15 M solution) from 0 °C to RT for 30 minutes. The resulting slurry was treated successively with water (1 mL per mol of LAH), 10% NaOH solution (1 mL per mol of LAH) and saturated Na_2SO_4 solution (3 mL per mol of LAH), and extracted with ether to concentrated under vacuum. Flash column chromatography with 5% diethyl ether in hexanes afforded the desired thiol.

(*E*)-10-(trimethylsilyl)dec-8-ene-5-thiol R: *n*-Bu: 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.19 (dt, *J* = 15.0, 6.5 Hz, 1H), 2.74-2.81 (m, 1H), 2.13-2.20 (m, 1H),

2.05-2.13(m, 1H), 1.61-1.72 (m, 2H), 1.42-1.52 (m, 3H), 1.40 (d, *J* = 8.0 Hz, 2H), 1.26-1.33 (m, 2H), 0.90 (t, *J* = 7.0 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.5, 127.0, 40.4, 39.2, 38.6, 30.3, 29.2, 22.6, 22.5, 14.0, -2.0.

(*E*)-2-methyl-8-(trimethylsilyl)oct-6-ene-3-thiol R: *i*-pro: 89% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (dt, *J* = 15.0, 8.0 Hz, 1H), 5.19 (dt, *J* = 15.0, 7.0 Hz, 1H), 2.71-2.77(m, 1H), 2.18-2.25 (m, 1H), 2.04-2.12 (m, 1H), 1.81-1.87 (m, 1H), 1.59-1.67 (m, 1H), 1.45-1.54 (m, 1H), 1.40 (d, *J* = 8.0 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.6, 127.1, 47.1, 36.5, 33.4, 30.7, 22.6, 20.4, 17.2, -2.0.

((*E*)-6-((*E*)-hex-1-en-1-ylthio)dec-2-en-1-yl)trimethylsilane (2.46) and ((*E*)-6-((*E*)-hex-1-en-1-ylthio)-7-methyloct-2-en-1-yl)trimethylsilane (2.47)

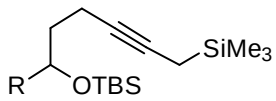


General protocol F2 was followed, starting from the above thiols, *(E)*-1-iodohex-1-ene (1.5 equiv), Pd(dppf)Cl_2·CH_2Cl_2 complex (0.1 equiv) and distilled Et_3N (2.5 equiv). Flash column chromatography with 1% diethyl ether in hexanes afforded the desired vinyl sulfides.

((*E*)-6-((*E*)-hex-1-en-1-ylthio)dec-2-en-1-yl)trimethylsilane (**2.46**) (R = *n*-Bu): 63% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (d, *J* = 15.0 Hz, 1H), 5.74 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.41 (dt, *J* = 15.0, 7.5 Hz, 1H), 5.21 (dt, *J* = 15.0, 7.0 Hz, 1H), 2.66-2.71 (m, 1H), 2.12 (dt, *J* = 7.5, 7.5 Hz, 2H), 2.07 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.52-1.60 (m, 4H), 1.41 (d, *J* = 8.5 Hz, 2H), 1.28-1.37 (m, 6H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.8, 127.9, 126.8, 121.2, 46.6, 35.1, 34.5, 32.9, 31.4, 30.0, 29.0, 22.6, 22.1, 14.0, 13.9, -2.0; IR (film) 3583, 3063, 1455, 1247, 1155, 964, 848 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{39}SSi$ $[M+H]^+$ 327.2542, found 327.2522.

((*E*)-6-((*E*)-hex-1-en-1-ylthio)-7-methyloct-2-en-1-yl)trimethylsilane (**2.47**) (R = *i*-pro): 77% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (d, *J* = 15.0 Hz, 1H), 5.70 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.41 (dt, *J* = 15.5, 8.0 Hz, 1H), 5.20 (dt, *J* = 15.0, 7.0 Hz, 1H), 2.61 (dt, *J* = 9.5, 4.5 Hz, 1H), 2.16-2.23 (m, 1H), 2.08-2.13 (m, 1H), 2.05 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.89-1.96(m, 1H), 1.56-1.63 (m, 1H), 1.46-1.53 (m, 1H), 1.41 (d, *J* = 8.0 Hz, 2H), 1.27- 1.36 (m, 4H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H), -0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.3, 128.0, 127.0, 123.2, 54.3, 32.9, 32.3, 32.1, 31.4, 30.6, 22.7, 22.1, 19.7, 18.9, 13.0, -2.0; IR (film) 3336, 2872, 1715, 1464, 1385, 1368, 1247, 1156, 1013,841 cm^{-1}; HRMS (EI) m/z calcd. for $C_{18}H_{36}SSi$ [M] 312.2307 , found 312.2349.

***tert*-Butyldimethyl((10-(trimethylsilyl)dec-8-yn-5-yl)oxy)silane and *tert*-butyldimethyl((2-methyl-8-(trimethylsilyl)oct-6-yn-3-yl)oxy)silane**

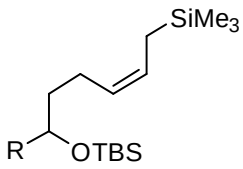


To a solution of the corresponding alkyne in THF (~0.5 M solution) cooled at -40 °C was added drop wise 1.6 M *n*-BuLi solution (1.3 equiv). The reaction mixture was allowed to 0 °C, stirred for 15 minutes, and trimethylsilyl methyl iodide (1.5 equiv) was added dropwise. The reaction was heated at 50 °C for 6 hours to complete the conversion. After cooling to 0 °C, the reaction was quenched saturated NH_4Cl solution, extracted twice with diethyl ether and concentrated under vacuum. Flash column chromatography with 10% dichloromethane in hexanes afforded the corresponding propargyl silane.

tert-Butyldimethyl((10-(trimethylsilyl)dec-8-yn-5-yl)oxy)silane R: *n*-Bu intermediate: 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77-3.72 (m, 1H), 2.24-2.16 (m, 2H), 1.57 (dt, *J* = 6.9, 6.9 Hz, 2H), 1.42-1.41 (m, 4H), 0.91-0.87 (m, 12H), 0.03 (s, 6H), 0.00 (s, 9H).

tert-Butyldimethyl((2-methyl-8-(trimethylsilyl)oct-6-yn-3-yl)oxy)silane R: *i*-pro intermediate: 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58 (dd, *J* = 11.1, 5.7 Hz, 1H), 2.13-2.21 (m, 2H), 1.67-1.78 (m, 1H), 1.50-1.57 (m, 2H), 1.42 (t, *J* = 2.6 Hz, 2H), 0.89 (s, 9H), 0.86 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 7.2 Hz, 3H), 0.09 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

(*Z*)-*tert*-butyldimethyl((10-(trimethylsilyl)dec-8-en-5-yl)oxy)silane (2.50) and (*Z*)-*tert*-butyldimethyl((2-methyl-8-(trimethylsilyl)oct-6-en-3-yl)oxy)silane (2.51)



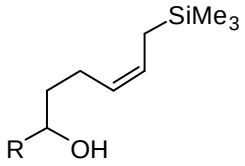
To a 25 mL round bottom flask was charged nickel acetate tetra hydrate (0.4 equiv) and 95% ethanol, and hydrogen atmosphere was applied. Then a freshly prepared 1M $NaBH_4$ solution (0.5 equiv) in 95% ethanol (with 0.1M NaOH) was added to the flask with vigorous stirring within 10 seconds. After three minutes ethylenediamine (0.8 equiv) was added, followed by another three minutes of stirring. The above propargyl silane was added, and the reaction mixture was stirred for 1 hours at RT. After completion of the reaction, the mixture was partitioned between diethyl ether and water. The organic phase was dried with sodium sulfate, filtered and concentrated under vacuum. Flash column chromatography with 10% dichloromethane in hexanes afforded the desired *cis*-ally silane.

(*Z*)-*tert*-butyldimethyl((10-(trimethylsilyl)dec-8-en-5-yl)oxy)silane (**2.50**) R: *n*-Bu: 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (dt, *J* = 10.5, 8.7 Hz, 1H), 5.26 (dt, *J* =10.5, 7.1 Hz, 1H), 3.68-3.62 (m, 1H), 2.10-2.04 (m, 1H), 1.98-1.90 (m, 1H), 1.48-1.42 (m, 6H), 1.32-1.28 (m, 2H), 0.90-0.87 (m, 12H), 0.05 (s, 6H), 0.00 (s, 9H).

(*Z*)-*tert*-butyldimethyl((2-methyl-8-(trimethylsilyl)oct-6-en-3-yl)oxy)silane (**2.51**) R: *i*-pro: 91% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.38 (dtt, *J* = 10.5, 8.5, 1.5 Hz, 1H), 5.26 (dtt, *J* = 10.5, 7.0,

1.5 Hz, 1H), 3.45 (apq, *J* = 5.5 Hz, 1H), 2.08 (dddd, *J* = 15.0, 7.5, 7.5, 7.5 Hz, 1H), 1.89 (dddd, *J* = 15.0, 7.5, 7.5, 7.5 Hz, 1H), 1.68-1.77 (m, 1H), 1.46 (d, *J* = 8.0 Hz, 2H), 1.39-1.43 (m, 2H), 0.90 (s, 9H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.00 (s, 9H).

(*Z*)-10-(trimethylsilyl)dec-8-en-5-ol and (*Z*)-2-methyl-8-(trimethylsilyl)oct-6-en-3-ol

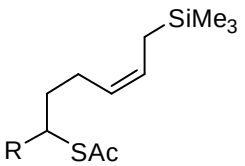


The above allylsilane was stirred with 9-CSA (0.1 equiv) in methanol (~0.4 M) at RT overnight. Flash column chromatography with 20% ethyl acetate in hexanes afforded the corresponding alcohol.

(*Z*)-10-(trimethylsilyl)dec-8-en-5-ol R: *n*-Bu intermediate: 98% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (dt, *J* = 10.7, 8.4 Hz, 1H), 5.27 (dt, *J* = 10.7, 7.0 Hz, 1H), 3.58-3.62 (m, 1H), 2.02-2.18 (m, 2H), 1.55-1.28(m, 10H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.02 (s, 9H).

(*Z*)-2-methyl-8-(trimethylsilyl)oct-6-en-3-ol R: *i*-pro intermediate: 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (dtt, *J* = 10.5, 8.5, 1.5 Hz, 1H), 5.28 (dtt, *J* = 10.5, 7.0, 1.3 Hz, 1H), 3.36-3.40 (m, 1H), 2.13-2.20 (m, 1H), 2.06 (dddd, *J* = 14.5, 7.0, 7.0, 7.0 Hz, 1H), 1.68-1.78 (m, 1H), 1.39-1.55 (m, 5H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.5, 125.4, 77.7, 33.0, 32.8, 25.6, 23.3, 18.4, 18.2, 17.9, 17.7, -1.8, -4.3, -4.4.

(*Z*)-*S*-(10-(trimethylsilyl)dec-8-en-5-yl) ethanethioate (2.52) and (*Z*)-*S*-(2-methyl-8-(trimethylsilyl)oct-6-en-3-yl) ethanethioate (2.53)



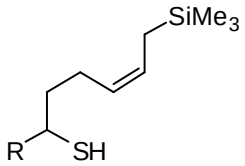
The above alcohol was reacted with mesyl chloride (2 equiv) and Et_3N (3 equiv) in dichloromethane (~0.5 M solution) from -40 °C to RT over two hours. The reaction mixture was acidified with 1N hydrochloric acid,

washed twice with water, dried with $MgSO_4$ and concentrated under vacuum. The resulting crude product (100% yield) was reacted with HSAc (2.7 equiv) and Cs_2CO_3 (2.4 equiv) according to the general protocol E2. Flash column chromatography with 5% ethyl acetate in hexanes afforded the desired thioacetate.

(*Z*)-*S*-(10-(trimethylsilyl)dec-8-en-5-yl) ethanethioate (**2.52**) R: *n*-Bu intermediate: 76% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (dt, *J* = 10.7, 8.4 Hz, 1H), 5.22 (dt, *J* = 10.7, 7.0 Hz, 1H), 3.55-3.49 (m, 1H), 2.31 (s, 3H), 2.02-2.18 (m, 2H), 1.55-1.28(m, 10H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.00 (s, 9H).

(*Z*)-*S*-(2-methyl-8-(trimethylsilyl)oct-6-en-3-yl) ethanethioate (**2.53**) R: *i*-pro intermediate: 47% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40 (dtt, *J* = 10.5, 9.0, 1.5 Hz, 1H), 5.23 (dtt, *J* = 10.5, 7.0, 1.3 Hz, 1H), 3.36-3.40 (dt, *J* = 9.5, 4.5 Hz, 1H), 2.33(s, 3H), 1.98-2.09 (m, 2H), 1.89-1.97 (m, 1H), 1.58-1.65 (m, 1H), 1.45-1.55 (m, 1H), 1.45 (d, *J* = 7.5 Hz, 2H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.00 (s, 9H);; ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.0, 126.3, 126.2, 50.9, 32.4, 32.0, 30.8, 24.8, 19.9, 18.9, 18.5, -1.8.

(*Z*)-10-(trimethylsilyl)dec-8-ene-5-thiol and (*Z*)-2-methyl-8-(trimethylsilyl)oct-6-ene-3-thiol

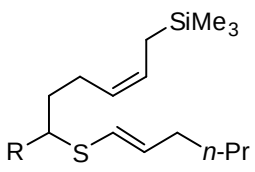


The above thioacetate was reacted with lithium aluminum hydride (2 equiv) in diethyl ether (~0.15 M solution) from 0 °C to RT for 30 minutes. The resulting slurry was treated successively with water (1 mL per mol of LAH), 10% NaOH solution (1 mL per mol of LAH) and saturated Na_2SO_4 solution (3 mL per mol of LAH), and extracted with ether to concentrated under vacuum. Flash column chromatography with 5% diethyl ether in hexanes afforded the desired thiol.

(*Z*)-10-(trimethylsilyl)dec-8-ene-5-thiol R: *n*-Bu thiol: 79% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.41 (dt, *J* = 11.0, 7.0 Hz, 1H), 5.22 (dt, *J* = 11.0, 6.8 Hz, 1H), 2.85-2.76 (m, 1H), 2.20-2.05 (m, 2H), 1.75-1.60 (m, 2H), 1.55-1.25 (m, 6H), 0.91 (t, *J* = 7.6 Hz, 3H), 0.01 (s, 9H); IR (film) 3005, 2858, 1721, 1463, 1379, 1247, 1137, 1017, 855 cm^{-1}.

(*Z*)-2-methyl-8-(trimethylsilyl)oct-6-ene-3-thiol R: *i*-pro thiol: 100% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (apq, *J* = 9.2 Hz, 1H), 5.22 (dt, *J* = 10.8, 7.2 Hz, 1H), 2.73 (ddd, *J* = 13.2, 8.0, 4.0), 2.16-2.26(m, 1H), 2.09 (dddd, *J* = 13.6, 6.8, 6.8, 6.8 Hz, 1H), 1.79-1.91 (m, 1H), 1.61-1.70(m, 1H), 1.43-1.55(m, 3H), 1.13 (d, *J* = 6.8 Hz, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.4, 126.3, 47.6, 36.4, 33.6, 25.1, 20.3, 18.5, 17.3, -1.8.

((*Z*)-6-((*E*)-hex-1-en-1-ylthio)dec-2-en-1-yl)trimethylsilane (2.54) and ((*Z*)-6-((*E*)-hex-1-en-1-ylthio)-7-methyloct-2-en-1-yl)trimethylsilane (2.55)



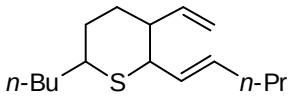
General protocol F2 was followed, starting from the corresponding thiol, *(E)*-1-iodohex-1-ene (1.5 equiv), Pd(dppf)Cl_2·CH_2Cl_2 complex (0.1 equiv) and distilled Et_3N (2.5 equiv). Flash column chromatography with 1% diethyl ether in hexanes afforded the desired vinyl sulfide.

((*Z*)-6-((*E*)-hex-1-en-1-ylthio)dec-2-en-1-yl)trimethylsilane (**2.54**): R: *n*-butyl substrate: 52% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ δ 5.90 (dt, *J* = 15.0, 1.2 Hz, 1H), 5.75 (dt, *J* = 14.9, 6.9 Hz, 1H), 5.46-5.37 (m, 1H), 5.27-5.20 (m, 1H), 2.73-2.65 (m, 1H), 2.17-2.02 (m, 4H), 1.61-1.54 (m, 4H), 1.51-1.28 (m, 9H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 126.6, 126.0, 121.2, 46.9, 34.8, 34.5, 32.9, 31.4, 29.0, 24.3, 22.6,

22.0, 18.4, 14.0, 13.8, -1.8.; IR (film) 3399, 2927, 1721, 1463, 1247, 1137, 1017, 855 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{39}SSi$ $[M+H]^+$ 327.2542, found 327.2515.

((*Z*)-6-((*E*)-hex-1-en-1-ylthio)-7-methyloct-2-en-1-yl)trimethylsilane (**2.55**): R: *i*-propyl substrate: 46% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 5.89 (d, *J* = 14.8 Hz, 1H), 5.71 (dt, *J* = 14.8, 6.8 Hz, 1H), 5.42 (dt, *J* = 10.4, 8.8 Hz, 1H), 5.23 (dt, *J* = 10.8, 7.2 Hz, 1H), 2.60 (dt, *J* =9.2, 4.4 Hz, 1H), 2.09-2.05 (m, 2H), 2.05(dt, *J* = 6.8, 6.8 Hz, 2H), 1.89-1.97 (m, 1H), 1.57-1.66 (m, 1H), 1.42-1.56 (m, 3H), 1.26-1.37 (m, 4H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.95(d, *J* = 6.8 Hz, 3H), 0.88(t, *J* = 7.2 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3, 126.7, 126.2, 123.3, 54.7, 32.9, 32.2, 32.1, 31.4, 25.0, 22.1, 19.6, 19.0, 18.5, 13.9, -1.8; IR (film) 3582, 2927, 1713, 1464, 1384, 1247, 1150, 1104, 856 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{18}H_{36}SSiNa$ $[M+Na]^+$ 335.2205, found 335.2194.

The cyclization of *n*-butyl substituted *trans*-allylsilane



General protocol G2 was followed, starting from the *n*-butyl substituted *trans*-allylsilane **2.46** (123 mg, 0.38 mmol) in $MeNO_2$. The reaction afforded 64.2 mg (68% yield) of the cyclization products with a *o-trans-m-cis : o-trans-m-trans : o-cis-m-cis : o-cis-m-trans* 1: 0.18:0.09:0.05.

(2*R*,3*R*,6*S*)-6-butyl-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran (**2.56**): *n*-butyl *o-trans-m-cis* : ^1H NMR (600 MHz, $CDCl_3$) δ 5.1 (ddd, *J* = 17.5, 10.5, 8.0 Hz, 1H), 5.59 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.24 (ddt, *J* = 15.2, 8.9, 1.4 Hz, 1H), 4.98 (ddd, *J* = 17.0, 1.5, 1.0 Hz, 1H), 4.96 (ddd, *J* = 10.5, 2.0, 0.6 Hz, 1H), 3.17 (dd, *J* = 9.6 Hz, 1H), 2.78 (dddd, *J* = 13.5, 7.2, 6.0, 2.5, 1H), 2.10 (dtd, *J* = 11.0, 8.0, 3.0 Hz, 1H), 2.06-2.00 (m, 1H), 1.97 (dtt, *J* = 7.5, 7.5, 1.7 , 2H), 1.89 (ddd, *J* = 13.7, 6.9, 3.2 Hz, 1H), 1.53-1.18 (m, 13H), 0.89 (t, *J* = 7.5 Hz, 3H, 0.88 (t, *J*

= 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.7, 133.6, 129.5, 114.5, 48.9, 48.0, 43.6, 35.7, 34.5, 34.4, 33.0, 29.0, 22.7, 22.2, 14.0, 13.6; IR (film) 3077, 2859, 1638, 1461, 1263, 1153, 963, 912 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{29}S$ $[M+H]^+$ 253.1990, found 253.2009.

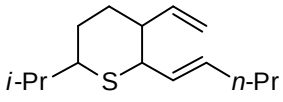
(2*R*,3*R*,6*R*)-6-butyl-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran: *n*-butyl o-*trans*-m-*trans* : ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.8, 10.5, 7.7 Hz, 1H), 5.60 (dt, 15.0, 7.0 Hz, 1H), 5.33 (ddt, *J* = 15.0, 8.5, 1.0 Hz, 1H), 5.03-4.98 (m, 2H), 3.23 (dd, *J* = 8.5, 8.5 Hz, 1H), 2.73-2.64 (m, 1H), 2.22 (dddd, *J* = 9.7, 8.7, 8.7, 3.5 Hz, 1H), 2.03-1.95 (m, 2H), 1.94-1.80 (m, 2H), 1.75-1.65 (m, 2H), 1.64-1.27 (m, 4H), 0.89 (dt, *J* = 14.8, 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.8, 133.0, 129.9, 114.3, 46.6, 44.2, 39.9, 34.4, 34.0, 30.6, 30.1, 26.6, 22.5, 22.3, 14.1, 13.6; IR (film) 3076, 2954, 1638, 1460, 1186, 991, 963, 912 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{29}S$ $[M+H]^+$ 253.1990, found 253.1991.

(2*S*,3*R*,6*R*)-6-butyl-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran: *n*-butyl o-*cis*-m-*cis* : ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34 (ddd, *J* = 17.3, 10.4, 8.3 Hz, 1H), 5.62 (dtd, *J* = 15.3, 6.8, 0.8 Hz, 1H), 5.32 (ddt, *J* = 15.3, 8.0, 1.2 Hz, 1H), 5.18-5.02 (m, 2H), 3.61 (dd, *J* = 8.1, 2.8 Hz, 1H), 2.82 (dddd, *J* = 13.5, 7.2, 6.0, 3.6 Hz, 1H), 2.45-2.55 (m, 1H), 1.96 (dtd, *J* = 7.2, 7.2, 1.2 Hz, 2H), 1.91-1.84 (m, 1H), 1.73-1.62 (m, 3H), 1.57-1.45 (m, 6H), 1.39-1.26 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 132.7, 129.4, 116.0, 48.7, 44.2, 42.9, 37.4, 35.9, 34.4, 33.4, 28.9, 28.5, 22.7, 22.3, 14.0, 13.6; IR (film) 3023, 2854, 1614, 1434, 1342,1149, 984 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{29}S$ $[M+H]^+$ 253.1990, found 253.1998.

(2*R*,3*S*,6*R*)-6-butyl-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran: *n*-butyl o-*cis*-m-*trans*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (ddd, *J* = 17.2, 10.4, 6.0 Hz, 1H), 5.66 (dd, *J* = 15.1, 7.9 Hz, 1H), 5.58 (dt, *J* = 15.1, 6.6 Hz, 1H), 5.01-4.96 (m, 2H), 3.28 (dd, *J* = 8.2, 3.8 Hz, 1H),

2.87 (dddd, *J* = 10.0, 7.0, 7.0, 2.7 Hz, 1H), 2.60 (dddd, *J* = 11.2, 7.4, 3.7, 3.7 Hz, 1H), 2.11-1.97 (m, 3H), 1.70-1.66 (m, 1H), 1.52-1.24 (m, 6H), 0.95-0.83 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.0, 132.9, 126.6, 114.0, 46.1, 45.6, 37.7, 35.5, 34.5, 29.1 ,26.9, 22.6, 22.5, 14.1, 14.0, 13.7; IR (film) 2941, 2859, 1643, 1431, 1382, 1198, 913 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{29}S$ $[M+H]^+$ 253.1990, found 253.1981.

The cyclization of 6-*iso*-propyl substituted *trans*-allylsilane



General protocol G2 was followed, starting from the *iso*-propyl substituted *trans*-allylsilane **2.47** (75.6 mg, 0.24 mmol), DDQ (57.2 mg, 0.25 mmol), 2,6-dichloropyridine (74.0 mg, 0.50 mmol) and 4Å M.S. (230 mg) in $MeNO_2$. The reaction afforded 45.7 mg (79% yield) of the cyclization products with a o-*trans*-m-*cis* : o-*trans*-m-*trans* : o-*cis*-m-*cis* : o-*cis*-m-*trans* ratio of 1.00 : 0.14 : 0.09 : 0.04.

(2*R*,3*R*,6*R*)-6-isopropyl-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran (**2.57**): 6-*iso*-propyl o-*trans*-m-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (ddt, *J* = 17.5, 10.5, 8.0 Hz, 1H), 5.60 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.25 (dd, *J* = 15.3, 9.0 Hz, 1H), 4.99-4.95 (m, 2H), 3.16 (dd, *J* = 9.7, 9.7 Hz, 1H), 2.70 (ddd, *J* = 11.7, 5.5, 2.3 Hz, 1H), 2.14-2.04 (m, 1H), 2.03-1.88 (m, 4H), 1.79-1.68 (m, 1H), 1.52-1.44 (m, 1H), 1.43-1.31 (m, 2H), 1.25 (qd, *J* = 13.5, 2.9 Hz, 1H), 0.99 (dd, *J* = 6.8, 1.6 Hz, 6H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.7, 133.6, 129.7, 114.5, 50.7, 49.0, 48.0, 34.4, 33.3, 32.8, 31.0, 22.2, 19.9, 19.7, 13.6; IR (film) 3061, 2923, 2868, 1532, 1422, 1261, 931 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{27}S[M+H]^+$ 239.1833, found 239.1845.

(2*R*,3*R*,6*S*)-6-isopropyl-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran : 6-*iso*-propyl *o-trans-m-trans*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 (ddd, *J* = 17.8, 10.5, 7.7 Hz, 1H), 5.61 (dtd, *J*

= 15.2, 6.8, 0.8 Hz, 1H), 5.39 (ddt, *J* = 15.2, 8.1, 1.4 Hz, 1H), 5.04-4.97 (m, 2H), 3.22 (t, *J* = 8.0 Hz, 1H), 2.44-2.36 (m, 1H), 2.23-2.29 (m, 1H), 2.05-1.94 (m, 2H), 1.87-1.93(m, 1H), 1.88-1.80 (m, 1H), 1.77-1.59 (m, 2H), 1.55-1.45 (m, 1H), 1.41-1.28 (m, 2H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 133.6, 129.7, 114.5, 48.2, 47.7, 34.3, 32.4, 29.6, 27.0, 22.2, 19.9, 19.7, 13.5; IR (film) 3051, 2943, 2859, 1621, 1482, 1431, 1153, 1091, 923 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{27}S[M+H]^+$ 239.1833, found 239.1839.

(2*R*,3*S*,6*R*)-6-isopropyl-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran: 6-*iso*-propyl o-*cis*-m-*cis*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (ddd, *J* = 17.3, 10.4, 8.4 Hz, 1H), 5.61 (dtd, *J* = 15.2, 6.8, 0.8 Hz, 1H), 5.32 (ddt, *J* = 15.3, 8.3, 1.4 Hz, 1H), 5.18-5.05 (m, 2H), 3.61 (dd, *J* = 8.2, 2.8 Hz, 1H), 2.73 (ddd, *J* = 11.3, 5.5, 2.6 Hz, 1H), 2.46-2.51 (m, 1H), 2.05-1.94 (m, 2H), 1.77-1.59 (m, 2H), 1.55-1.45 (m, 3H), 1.41-1.28 (m, 2H), 1.09 (d, *J* = 6.6 Hz, 6H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 133.6, 129.4, 116.0, 49.7, 46.2, 44.0, 34.5, 33.1, 31.0, 22.2, 20.0, 19.7, 13.6; IR (film) 3076, 2871, 1638, 1462, 1384, 1286, 992, 962, 914 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{27}S[M+H]^+$ 239.1833, found 239.1848.

(2*R*,3*S*,6*S*)-6-isopropyl-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydro-2*H*-thiopyran: 6-*iso*-propyl o-*cis*-m-*trans:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75-5.63 (m, 2H), 5.58 (dt, *J* = 15.1, 6.5 Hz, 1H), 5.05-4.91 (m, 2H), 3.30 (dd, *J* = 8.1, 3.9 Hz, 1H), 2.78 (ddd, *J* = 11.2, 5.6, 2.4 Hz, 1H), 2.59 (dddd, *J* = 11.6, 7.2, 3.7, 3.7 Hz, 1H), 2.17-1.95 (m, 3H), 1.72 (m, 2H), 1.61-1.49 (m, 2H), 1.45-1.35 (m, 2H), 0.98 (dd, *J* = 6.8, 4.3 Hz, 6H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 132.8, 126.5, 113.9, 77.3, 77.0, 76.6, 46.2, 45.5, 44.4, 34.5, 32.4, 31.0, 27.0, 22.4, 20.0, 19.7, 13.6; IR (film) 2971, 2863, 1641, 1502, 1333, 1187, 961, 913cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{27}S[M+H]^+$ 239.1833, found 239.1844.

The cyclization of *n*-butyl substituted *cis*-allylsilane

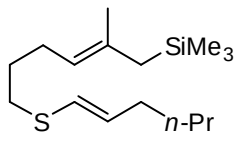
General protocol G2 was followed, starting from the *n*-butyl substituted *cis*-allylsilane **2.54** (50.0 mg, 0.15 mmol), DDQ (35.7 mg, 0.15 mmol), 2,6-dichloropyridine (44.4 mg, 0.30 mmol) and 4Å M.S. (150 mg) in $MeNO_2$. The reaction afforded 33.5 mg (87% yield) of the cyclization products with a *o-trans-m-cis : o-trans-m-trans : o-cis-m-cis : o-cis-m-trans* ratio of 1: 0.17 : 0.17 : 0.80.

The cyclization of 6-*iso*-propyl substituted *cis*-allylsilane

General protocol G2 was followed, starting from the *iso*-propyl substituted *cis*-allylsilane **2.55** (82.8 mg, 0.26 mmol), DDQ (62.0 mg, 0.27 mmol), 2,6-dichloropyridine (77.0 mg, 0.52 mmol) and 4Å M.S. (240 mg) in $MeNO_2$. The reaction afforded 45.5 mg (72% yield) of the cyclization product with a *o-trans-m-cis : o-trans-m-trans : o-cis-m-cis : o-cis-m-trans* 1 : 0.14 : 0.12 : 1.0.

Cyclization of trisubstituted allylsilane

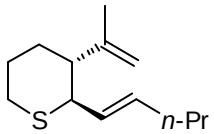
((*E*)-6-((*E*)-hex-1-en-1-ylthio)-2-methylhex-2-en-1-yl)trimethylsilane (2.63)



General protocol H for the synthesis of vinyl iodide was followed, starting from the corresponding alkyne **2.62** (224 mg, 1.0 mmol), $ZrCp_2Cl_2$(323 mg, 1.1 mmol) and 1M DIBAL-H (1.1 mL, 1.1 mmol). Flash column chromatography with 5% dichloromethane in hexanes afforded the corresponding vinyl iodide. This intermediate was reacted with *(E)*-1-iodohex-1-ene (315 mg, 1.5 mmol), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ complex (40.8 mg, 0.05 mmol) and distilled Et_3N (0.42 mL, 3.0

mmol).according to general protocol I to afford 128 mg (45% in two steps) of the desired allylsilane substrate **2.63**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (dt, *J* = 15.0, 1.3 Hz, 1H), 5.62 (dt, *J* = 15.0, 7.0 Hz, 1H), 4.91 (t, *J* = 7.2 Hz, 1H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.07 (m, 4H), 1.76-1.55 (m, 9H), 1.47 (s, 2H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 131.0, 122.5, 110.0, 39.0, 37.3, 32.9, 31.5, 29.0, 26.6, 22.3, 22.1, 13.9, -1.1; IR (film) 3068, 2927, 1715, 1650, 1454, 1376, 1247, 1025, 842 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{16}H_{33}SSi$ $[M+H]^+$ 285.2072, found 285.2070.

(2*S*,3*S*)-2-((*E*)-pent-1-en-1-yl)-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (2.64) (*trans*-product)



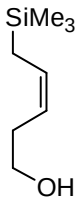
General protocol G2 was followed, starting from the above *trans*-allylsilane **2.63** (72.1 mg, 0.25 mmol), DDQ (59.0 mg, 0.26 mmol), 2,6-dichloropyridine (74.0 mg, 0.50 mmol) and 4Å M.S. (220 mg) in $MeNO_2$. The reaction afforded 38.3 mg (72%) of the desired cyclization products **2.64** with a *trans*: *cis* ratio of 1:0.53. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62-5.53 (dt, *J* = 15.2, 7.2 Hz, 1H), 5.22 (ddt, *J* = 15.2, 8.9, 1.4 Hz, 1H), 4.69 (m, 2H), 3.30 (dd, *J* = 9.8, 9.8 Hz, 1H), 2.78 (ddd, *J* = 13.2, 13.2, 2.8 Hz, 1H), 2.53 (dtd, *J* = 13.4, 3.4, 1.5 Hz, 1H), 2.22 (ddd, *J* = 12.1, 10.5, 2.9 Hz, 1H), 2.09-2.00 (m, 2H), 1.99-1.89 (m, 2H), 1.83-1.64 (m, 3H), 1.61 (s, 3H), 1.38 (dt, *J* = 14.6, 4.1 Hz, 2H), 0.87 (t, *J* =7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 133.1, 129.2, 111.4, 53.4, 52.6, 47.0, 34.3, 32.3, 29.9, 27.7, 22.3, 19.4, 13.4; IR (film) 3072, 2958, 1643, 1438, 1451, 1374, 1287, 962, 889 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{23}S$ $[M+H]^+$ 211.1520, found 211.1523.

(2*R*,3*S*)-2-((*E*)-pent-1-en-1-yl)-3-(prop-1-en-2-yl)tetrahydro-2*H*-thiopyran (*cis*-product of **2.64**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67-5.1 (m, 2H), 4.83-4.74 (m, 1H), 4.65-4.59 (m, 1H), 3.45-

3.38 (m, 1H), 2.87-2.79 (m, 1H), 2.59-2.50 (m, 1H), 2.38 (dt, *J* = 13.6, 3.6 Hz, 1H), 2.16-2.09 (m, 1H), 2.04-1.98 (m, 2H), 1.85-1.75 (m, 1H), 1.72 (dd, *J* = 3.3, 2.7 Hz, 3H), 1.69-1.61 (m, 1H), 1.49-1.42 (m, 2H), 1.04 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 133.4, 129.0, 111.3, 52.4, 52.1, 47.0, 34.4, 32.0, 29.5, 28.1, 22.6, 19.6, 13.9, 13.2; IR (film) 3008, 2858, 1726, 1642, 1451, 1376, 1133, 891 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{23}S$ $[M+H]^+$ 211.1520, found 211.1527.

Synthesis of tetrahydrothiophenes

(*Z*)-5-(trimethylsilyl)pent-3-en-1-ol (2.66)

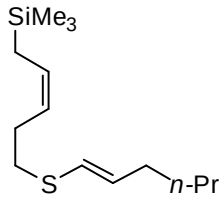


To a solution of the alkyne **2.65** in THF (~0.5 M solution) cooled at -40 °C was added drop wise 1.6 M BuLi solution (10.0 mL, 16.0 mmol). The reaction mixture was allowed to 0 °C, stirred for 15 minutes, and trimethylsilyl methyl iodide (3.93 g, 18.3 mmol) was added dropwise. The reaction was heated at 50 °C for 6 hours to complete the conversion. After cooling to 0 °C, the reaction was quenched saturated NH_4Cl solution, extracted twice with diethyl ether and concentrated under vacuum. Flash column chromatography with 10% dichloromethane in hexanes afforded 2.0 g (62%) of the corresponding propargyl silane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (t, *J* = 7.4 Hz, 2H), 2.36 (tt, *J* = 7.3, 2.7 Hz, 2H), 0.89 (s, 9H), 0.08 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.7, 75.4, 62.7, 25.9, 23.3, 18.3, 6.9, -2.1, -5.2.

To a 25 mL round bottom flask was charged nickel acetate tetrahydrate (386 mg, 1.55 mmol) and 95% ethanol (3 mL), and hydrogen atmosphere was applied. Then a freshly prepared 1M $NaBH_4$ solution (1.94 mL) in 95% ethanol (with 0.1M NaOH) was added to the flask with vigorous stirring within 10 seconds. After three minutes ethylenediamine (0.21 mL, 3.10 mmol) was

added, followed by another three minutes of stirring. The above propargyl silane (1.05 g, 3.88 mmol) was added, and the reaction mixture was stirred for 1 hours at RT. After completion of the reaction, the mixture was partitioned between diethyl ether and water. The organic phase was dried with sodium sulfate, filtered and concentrated under vacuum, and then the crude product was treated with 2-CSA (85.8 mg, 0.4 mmol) in methanol (9 mL) at RT overnight. Flash column chromatography with 20% ethyl acetate in hexanes afforded 519 mg (85% for two steps) of the desired alcohol **2.66**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (dtt, *J* = 10.3, 8.7, 1.5 Hz, 1H), 5.26 (dtt, *J* = 10.3, 7.3, 1.5 Hz, 1H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.27 (dt, *J* = 6.7, 6.7 Hz, 2H), 1.57-1.40 (m, 3H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.0, 122.5, 62.4, 30.5, 18.6, -1.8.

((*Z*)-5-((*E*)-hex-1-en-1-ylthio)pent-2-en-1-yl)trimethylsilane (2.67)

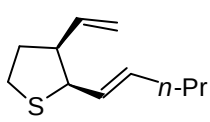


The above alcohol **2.66** (498 mg, 3.1 mmol) and Et_3N (1.31 mL, 9.3 mmol) were mixed in dichloromethane (9 mL) and cooled to -50 °C. Mesyl chloride (0.72 g, 6.3 mmol) was added drop wise, white precipitates were formed in a few minutes, and the resulting suspension was slowly allowed to 0 °C over 1 hour. The reaction mixture was acidified with 1N hydrochloric acid, washed twice with water, dried with $MgSO_4$ and concentrated under vacuum. The resulting crude product (803 mg, 100% yield) was reacted with HSAc (0.27 mL, 3.78 mmol) and Cs_2CO_3 (1.23 g, 3.78 mmol) according to the general protocol E2. Flash column chromatography with 3% diethyl ether in hexanes afforded the desired thioacetate (607 mg, 89% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (dtt, *J* = 10.1, 8.7, 1.4 Hz, 1H), 5.22 (dtt, *J* = 10.1, 7.1, 1.4 Hz, 1H), 2.87 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 2.26 (dt, *J* = 7.1, 7.1 Hz, 2H), 1.47 (d, *J* = 8.7 Hz, 2H), 0.00 (d, *J* = 3.0 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 127.9, 124.4, 30.6, 29.1, 27.0, 18.6, -1.8.

The above thioacetate (585 mg, 2.71 mmol) was reacted with lithium aluminum hydride (205 mg, 5.42 mmol) in diethyl ether (10 mL) from 0 °C to RT for 30 minutes. The resulting slurry was treated successively with water (5.0 mL), 10% NaOH solution (5.0 mL) and saturated Na_2SO_4 solution (15.0 mL), and extracted with ether to concentrated under vacuum. Flash column chromatography with 5% diethyl ether in pentane afforded 407 mg (86%) of the desired thiol. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.54 (dtt, *J* = 10.6, 8.7, 1.6 1H), 5.25 (dtt, *J* = 10.6, 7.1, 1.4 1H), 2.54 (dt, *J* = 7.5, 7.5 Hz, 2H), 2.31 (dt, *J* = 7.0, 7.0 Hz, 2H), 1.49 (d, *J* = 8.6 Hz, 2H), 1.43 (t, *J* = 7.7 Hz, 1H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.0, 122.5, 62.4, 30.5, 18.6, -1.8.

General protocol F2 was followed, starting from the above thiol (391 mg, 2.25 mmol), *(E)*-1-iodohex-1-ene (790 mg, 3.75 mmol), Pd(dppf)Cl_2·CH_2Cl_2 complex (102mg, 0.125 mmol) and distilled Et_3N (1.05 mL, 7.5 mmol). Flash column chromatography with 10% DCM in hexanes afforded 308 mg (53%) of the desired vinyl sulfide **2.67**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (dt, *J* = 15.0, 1.3 Hz, 1H), 5.65 (15.0, 11.0 Hz, 1H), 5.54-5.41 (m, 1H), 5.37-5.19 (m, 1H), 2.64 (t, *J* = 7.4 Hz, 2H), 2.30 (dt, *J* = 8.1, 8.1 Hz, 2H), 2.08 (dtd, *J* = 7.1, 7.1, 1.3 Hz, 2H), 1.51-1.46 (m, 3H), 1.41-1.17 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.01 (d, *J* = 3.0 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.2, 127.3, 124.8, 122.4, 38.6, 32.8, 31.4, 27.2, 22.0, 18.6, 13.8, -1.8; IR (film) 3009, 2955, 1643, 1419, 1248, 1150, 851 cm^{-1}; HRMS (ESI) *m/z* calcd. For $C_{14}H_{29}SiS$ $[M+H]^+$ 257.1759, found 257.1743.

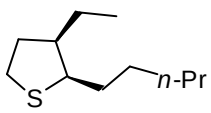
(2*R*,3*S*)-2-((*E*)-pent-1-en-1-yl)-3-vinyltetrahydrothiophene (2.68)



General protocol G2 was followed, starting from the above ally silane 34 (100 mg, 0.39 mmol), DDQ (93.3 mg, 0.41 mmol), 2,6-dichloropyridine (121.5

mg, 0.82 mmol) and 4Å M.S. (300 mg) in $MeNO_2$ (4 mL). The reaction afforded 54.8 mg (77% yield) of the desired tetrahydrothiophene **2.68** with a *cis*: *trans* ratio of 20:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.3, 10.3, 8.1 Hz, 1H), 5.47 (dt, *J* = 14.9, 6.4 Hz, 1H), 5.38 (dd, *J* = 15.0, 9.2 Hz, 1H), 5.14-4.96 (m, 2H), 3.90 (dd, *J* = 9.1, 6.3 Hz, 1H), 2.99 (ddd, *J* = 10.3, 7.2, 4.9 Hz, 1H), 2.93-2.85 (m, 1H), 2.85-2.74 (m, 1H), 2.11 (ddt, *J* = 11.9, 6.8, 5.0 Hz, 1H), 2.01-1.89 (m, 3H), 1.45-1.32 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 131.8, 129.3, 115.8, 53.2, 52.0, 34.9, 34.2, 30.6, 22.3, 13.5; IR (film) 2963, 2931, 1754, 1718, 1648, 1554, 1370, 1196, 1019, 798 cm^{-1}; HRMS (ESI) *m/z* calcd. For $C_{11}H_{19}S$ $[M+H]^+$ 183.1207, found 183.1248.

(2*R*,3*R*)-3-ethyl-2-pentyltetrahydrothiophene (2.69)



A mixture of **2.68** (30 mg, 0.16 mmol) and 10% Pd/C (30 mg) in methanol (1 mL) was stirred under a hydrogen atmosphere overnight. The mixture was purified by flash column chromatography (10% DCM in pentane) to give 22.1 mg (74%) of the product **2.69**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.26 (dt, *J* = 9.6, 4.7 Hz, 1H), 2.85-2.76 (m, 2H), 2.09-1.92 (m, 2H), 1.84-1.69 (m, 1H), 1.69-1.57 (m, 2H), 1.52-1.43 (m, 2H), 1.38-1.21 (m, 6H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.5, 49.0, 33.2, 31.8, 29.6, 28.3, 22.6, 21.3, 14.1, 12.9; IR (film) 2957, 2928, 2859, 1460, 1378, 1261 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{11}H_{22}S$ [M] 186.1442, found 186.1418.

APPENDIX C

ASYMMETRIC BIMOLECULAR COUPLING REACTIONS THROUGH OXIDATIVELY GENERATED AROMATIC CATIONS: SCOPE AND LIMIT

Experimental

General Experimental

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 300/400 MHz and 75/100MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Solvent peaks were used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.26, CD_2Cl_2 = 5.32, for ^{13}C NMR: $CDCl_3$ = 77.0, CD_2Cl_2 = 54.0. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). 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. Analytical TLC was performed on pre-coated (25 mm) silica gel 60F-254 plates. Flash column chromatography was done using 32-63 60 Å silica gel. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument with a Lux Cellulose 3 column.

Methylene chloride was distilled under N_2 from CaH_2. Toluene was dried with 4Å molecular sieves. Anhydrous α,α,α-trifluorotoluene was purchased from Sigma-Aldrich. 2*H*-chromene and related derivatives were prepared following the Stratakis protocol.[67] Chiral phosphate derivatives

were prepared following Yamamoto, Akiyama and Terada protocol, respectively.[68] The 4Å molecular sieves powder is activated at 110 °C at least for 24 hours before use. Other reagents were obtained from commercial sources without further purification. All reactions were performed in oven or flame-dried glassware with magnetic stirring under nitrogen unless otherwise noted.

Representative procedure

To a solution of 2*H*-chromene (1.0 equiv) in a corresponding solvent (0.1 M concentration) at 0 °C were added 4Å molecular sieves powder (60 mg/mL) and the corresponding catalyst (0.05 to 1 equiv). DDQ (1.4 equiv) was added to the reaction mixture, and it was stirred until TLC analysis showed complete consumption of the substrate. After cooling to the corresponding specified temperature, the nucleophile (2~3 equiv) was added, and the reaction was stirred until TLC analysis showed complete consumption of the oxidized intermediate. The reaction was quenched with 10% aqueous $NaHCO_3$ solution, extracted three times with diethyl ether (10 mL), and carefully concentrated under reduced pressure. Flash column chromatography with 3% Et_2O/pentane afforded the desired product. An aliquot was taken and analyzed by chiral HPLC for enantiomeric excess.

Allyl phenyl dimethylsilane

To a round bottom flask was charged magnesium turnings (1.94 g, 81 mmol, 3.75 equiv) and diethyl ether (5 mL). Allyl bromide (2.8 mL, 32.3 mmol, 1.5 equiv) in diethyl ether (30 mL) was added dropwise over 50 min with external water bath at room temperature. After an additional 30 min stirring at room temperature, the reaction mixture was cooled to 0 °C, and

phenyldimethylsilyl chloride (3.68 g, 21.5 mmol, 1.0 equiv) was added dropwise. The reaction was stirred overnight at room temperature, quenched with saturated NH_4Cl solution, extracted two times with diethyl ether (20 mL), dried and concentrated under reduced pressure. Flash column chromatography with 3% Et_2O/pentane afforded at least 3.02 g (80%) of the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.41-7.44 (m, 2H), 7.25-7.29 (m, 3H), 5.68 (ddt, J = 16.5, 10.2, 8.1 Hz, 1H), 4.75-4.81 (m, 2H), 1.66 (dt, J = 8.1, 1.0 Hz, 2H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 134.5, 133.6, 129.0, 127.7, 113.4, 23.7, -3.5.

Reaction Optimization: Solvent screening

To investigate the background reaction rate in the absence of $LiClO_4$, three common solvents, dichloromethane, acetonitrile and toluene were used to perform the reaction. Thus, the representative procedure was followed in each corresponding solvent on a 50 mg scale of 2*H*-chromene but without using $LiClO_4$ or chiral catalyst, and TLC observation was performed. The oxidized intermediate disappeared at 1.5 hours in acetonitrile and 2 hours in DCM. At two hours in toluene there was a significant amount of oxidized intermediate present, and after 12 hours the oxidized intermediate completely disappeared. No actual separation of the addition product was performed.

Reaction Optimization: Catalyst Screening

Stoichiometic reaction with triisopropyl-substituted (TRIP) phosphoric acid (3.9): The reaction was performed at 0 °C for 45 min, using 2*H*-chromene **3.3** (5.3 mg, 40 μmol, 1.0 equiv), TRIP phosphoric acid (**3.9**) (30 mg, 40 μmol, 1.0 equiv), 4Åmolecular sieves (30 mg), DDQ (12.7 mg, 56μmol, 1.4 equiv), allyltrimethylsilane (14 mg, 120 μmol, 3.0 equiv) and toluene (0.4

mL). The enantiomeric excess was determined to be 26% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Stoichiometic reaction with ditrifluoromethylphenyl-substituted phosphoric acid (3.10): The reaction was performed at 0 °C for 45 min, using 2H-chromene **3.3 (**11.9 mg, 90 μmol, 1.0 equiv), ditrifluoromethylphenyl-substituted phosphoric acid (**3.10)** (70 mg, 90 μmol, 1.0 equiv), 4Å molecular sieves (30 mg), DDQ (28.7 mg, 126μmol, 1.4 equiv), allyltrimethylsilane (31 mg, 270 μmol, 3.0 equiv) and toluene (0.4 mL). The enantiomeric excess was determined to be 4% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Stoichiometic reaction with TRIP phosphoramide (3.11)*:* The reaction was performed at 0 °C for 45 min, using 2H-chromene **3.3 (**7.1 mg, 54 μmol, 1.0 equiv), TRIP phosphoramide (**3.11**) (48.5 mg, 54 μmol, 1.0 equiv), 4Å molecular sieves (30 mg), DDQ (17.2 mg, 76μmol, 1.4 equiv), allyltrimethylsilane (19 mg, 160 μmol, 3.0 equiv) and toluene (0.4 mL). Thick precipitates were observed during the oxidation step, and additional solvent (0.3 mL) was used to facilitate stirring. The precipitates disappeared soon after the addition of the nucleophile. The enantiomeric excess was determined to be 62% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Stoichiometic reaction with 4-(anthracen-9-yl)-2,6-diisopropylpheny substituted phosphoramide (3.12): The reaction was performed at 0 °C for 45 min, using 2H-chromene **3.3 (**5.3 mg, 40 μmol, 1.0 equiv), 4-(anthracen-9-yl)-2,6-diisopropylphenyl-substituted phosphoramide (**3.12)** (46 mg, 40 μmol, 1.0 equiv), 4Å molecular sieves (30 mg), allyltrimethylsilane (14 mg, 120 μmol, 3.0 equiv) and toluene (0.4 mL).. The enantiomeric

excess was determined to be 31% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Stoichiometic reaction with TRIP thiophosphoric acid (3.13): The reaction was performed at 0 °C for 45 min, using 2H-chromene **3.3** (6.8 mg, 52 μmol, 1.0 equiv), TRIP thiophosphoric acid (**3.13)** (40 mg, 52 μmol, 1.0 equiv), 4Å molecular sieves (30 mg), DDQ (16.5 mg, 73μmol, 1.4 equiv), allyltrimethylsilane (18 mg, 160 μmol, 3.0 equiv) and toluene (0.4 mL). The enantiomeric excess was determined to be 4% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Stoichiometic reaction with TRIP thiophosphoramide (3.14)*:* The reaction was at 0 °C for 45 min, using 2H-chromene **3.3 (**5.3 mg, 40 μmol, 1.0 equiv), TRIP thiophosphoramide (**3.14)** (36 mg, 40 μmol, 1.0 equiv), 4Å molecular sieves (30 mg), DDQ (12.7 mg, 56μmol, 1.4 equiv), allyltrimethylsilane (14 mg, 120 μmol, 3.0 equiv) and toluene (0.4 mL). The enantiomeric excess was determined to be 13% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Reaction Optimization: Solvent Refinement

Stoichiometic TRIP phosphoramide (3.11) reaction in DCM*:* The reaction was performed in dichloromethane (0.3 mL) at 0 °C for 45 min, using 2H-chromene **3.3 (**4.4 mg, 33 μmol), 100% loading of TRIP phosphoramide (**3.11**) (29.5 mg, 33 μmol) and allyltrimethylsilane (12 mg, 100 μmol). Thick precipitates were observed during the oxidation step, and additional solvent (0.3 mL) was used to facilitate stirring. The precipitates disappeared soon after the addition of the nucleophile. The enantiomeric excess was determined to be 34% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min).

Stoichiometic TRIP phosphoramide (3.11) reaction in *α,α,α*-trifluorotoluene*:* The reaction was performed in α,α,α-trifluorotoluene (0.3 mL) at 0 °C for 45 min, using 2H-chromene **3.3 (**4.7 mg, 36 μmol), 100% loading of TRIP phosphoramide (**3.11**) (32.4 mg, 36 μmol) and allyltrimethylsilane (13 mg, 110 μmol). Thick precipitates were observed during the oxidation step, and additional solvent (0.3 mL) was used to facilitate stirring. The precipitates disappeared soon after the addition of the nucleophile. The enantiomeric excess was determined to be 77% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min).

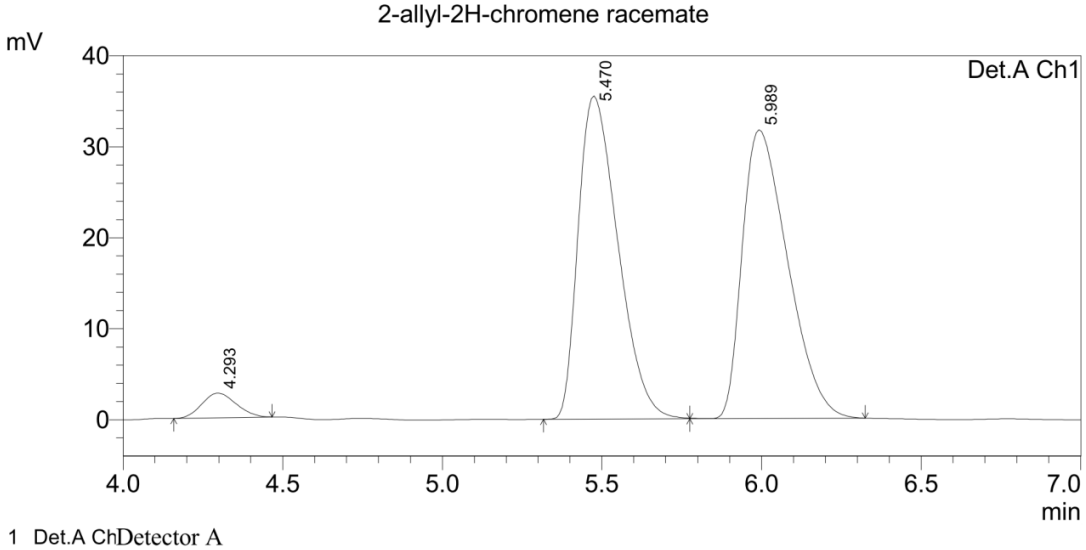
Reaction Optimization: Influence of nucleophile

Stoichiometic TRIP-phosphoramide reaction with allylphenyldimethylsilane: The reaction was performed at 0 °C for 45 min, using 2H-chromene **3.3 (**4.4 mg, 33 μmol), 100% loading of TRIP phosphoramide (**3.11**) (29.5 mg, 33 μmol), DDQ (10.5 mg, 46 μmol), allylphenyldimethylsilane (18 mg, 100 μmol) and α,α,α-trifluorotoluene (0.3 mL). The enantiomeric excess was determined to be 92% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Stoichiometic TRIP-phosphoramide reaction with allyltributyltin: The reaction was performed at 0 °C for 45 min, using 2H-chromene **3.3 (**4.4 mg, 33 μmol), 100% loading of TRIP phosphoramide (**3.11**) (29.5 mg, 33 μmol), DDQ (10.5 mg, 46μmol), allyltributyltin (33 mg, 100 μmol) and α,α,α-trifluorotoluene (0.3 mL). The enantiomeric excess was determined to be 48% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Stoichiometic TRIP-phosphoramide reaction with allyltriphenyltin: The reaction was performed at 0 °C for 45 min, using 2H-chromene **3.3 (**5.0 mg, 38 μmol, 1.0 equiv), 100%

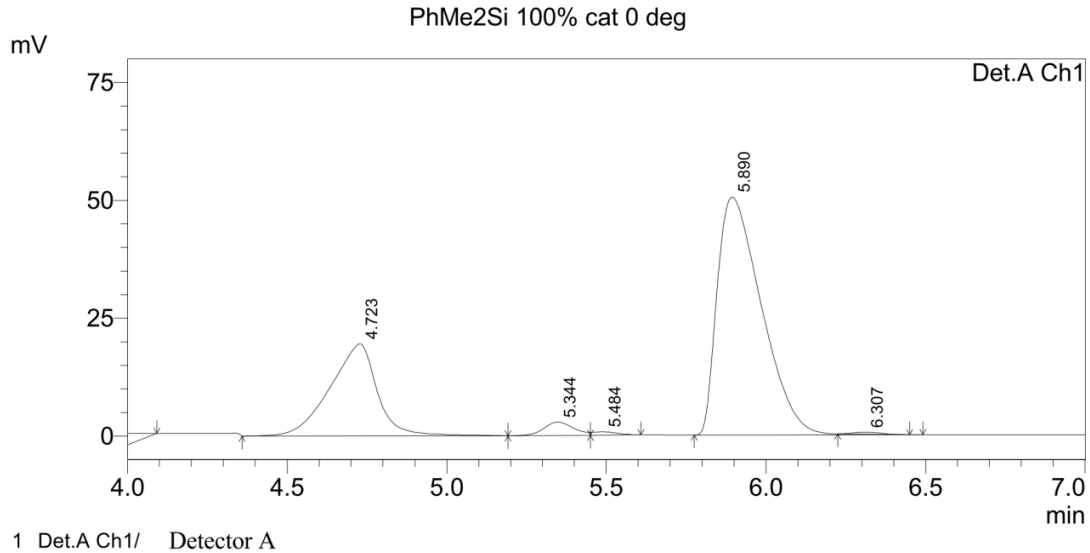
loading of TRIP phosphoramide (**3.11**) (34.5 mg, 38 μmol), DDQ (12 mg, 53μmol, 1.4 equiv), allyltriphenyltin (27 mg, 69 μmol, 1.8 equiv) and α,α,α-trifluorotoluene (0.3 mL). The enantiomeric excess was determined to be 89% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.



1 Det.A ChDetector A

ID#	Name	Ret. Time	Area	Height
1	RT5.470	5.470	307283	35532
2	RT5.989	5.989	314168	31748

Figure S3.1 HPLC of Racemic mixture



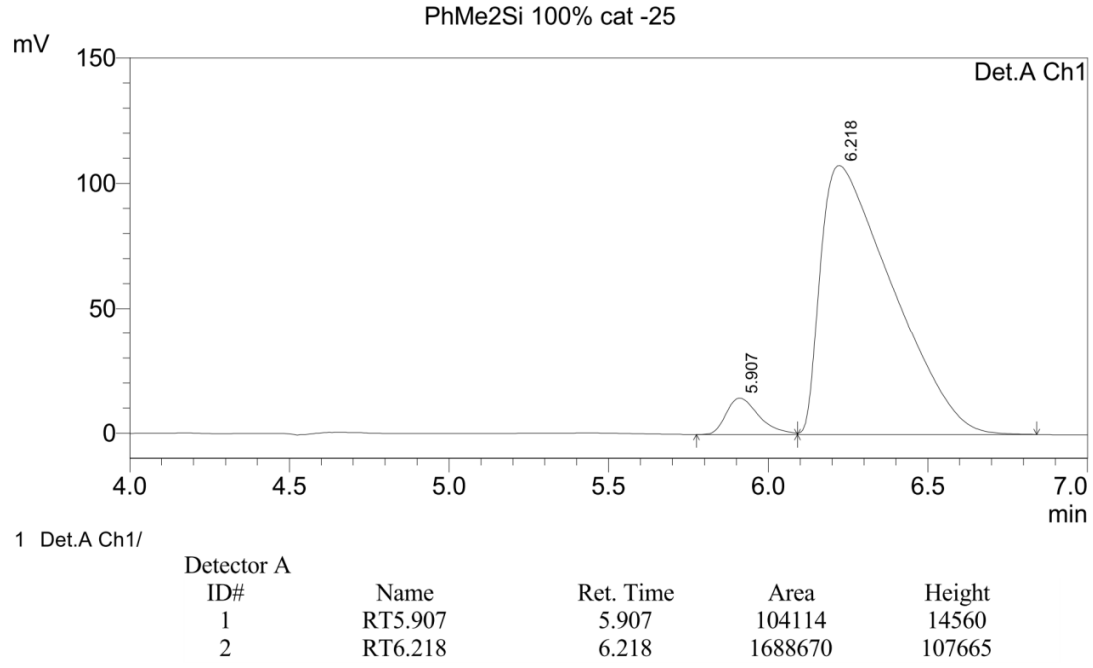
1 Det.A Ch1/ Detector A

ID#	Name	Ret. Time	Area	Height
1	RT5.344	5.344	18526	2846
2	RT5.890	5.890	488087	50510

Figure S3.2 HPLC from allyphenyldimethylsilane at 0 °C

Stoichiometric TRIP-phosphoramide reaction with allylphenyldimethylsilane at low temperature*:* The reaction was performed at -25 °C for 3 hours, using 2H-chromene **3.3 (**37.2 mg, 0.28 mmol), TRIP phosphoramide (**3.11**) (249 mg, 0.028 mmol, 1.0 equiv), 4Å molecular sieves powder (200 mg), DDQ (89 mg, 0.39 mmol, 1.4 equiv), allylphenyldimethylsilane (148 mg, 0.84 mmol, 3 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL). Normal workup and flash column chromatography with 3% Et_2O/pentane afforded 28.9 mg (60%) of the desired product **3.15**. The enantiomeric excess was determined to be 89% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). ^{1}H NMR (300 MHz, $CDCl_3$) δ7.06-7.12 (m, 1H), 6.98 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.84 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.42 (d, *J* = 9.9 Hz, 1H), 5.84-5.96 (m, 1H), 5.71 (dd, *J* = 9.9, 3.3 Hz, 1H), 5.10-5.19 (m, 2H), 4.87-4.93 (m, 1H), 2.44-2.56 (m, 2H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ154.0, 134.1, 129.7,127.0, 125.9, 124.6, 122.6, 121.6, 118.1, 116.4, 75.2, 40.3; IR (film) 2926, 1640, 1605, 1486, 1457, 1230, 1204, 1111, 1038, 917,

769, 753cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{12}H_{11}O$ $[M - H]^+$ 171.0810, found 171.0813; $[\alpha]^{25}_D$ = -174.2 (c = 1.24, CH_2Cl_2).



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT5.907	5.907	104114	14560
2	RT6.218	6.218	1688670	107665

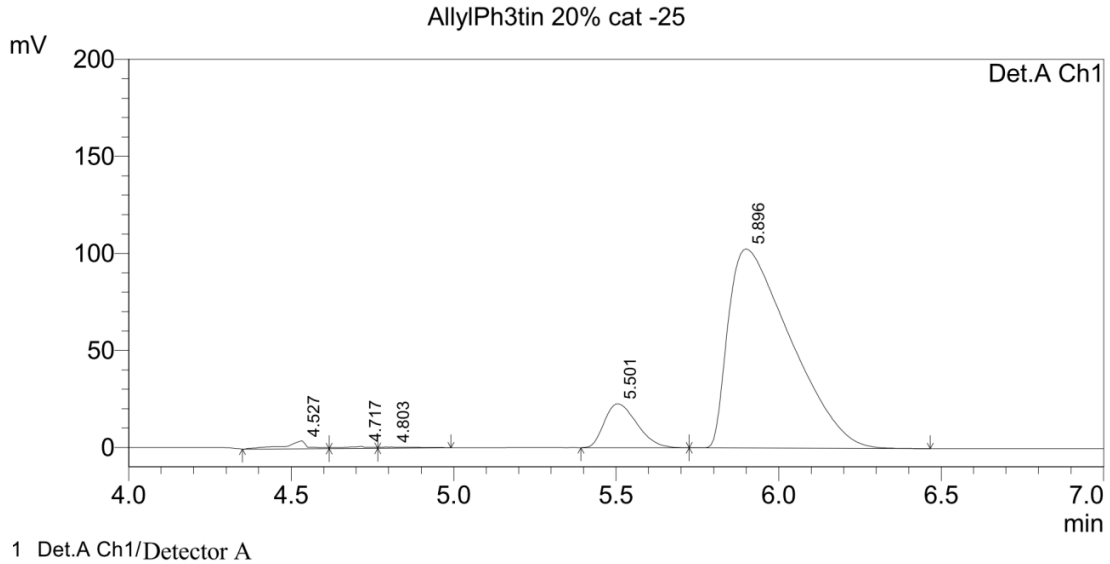
Figure S3.3 HPLC from allyphenyldimethylsilane 100% cat at -25 °C

Reaction Optimization: substoichiometric amount of catalyst

Allyltriphenyltin with 20% of 3.11 at zero degree: The reaction was performed at 0 °C for 45 min, using 2H-chromene **3.3 (**6.6 mg, 0.05 mmol), 20 mol% loading of TRIP phosphoramide (**3.11**) (8.8 mg, 0.01 mmol), DDQ (15.9 mg, 0.07 mmol), allyltriphenyltin (39.1 mg, 0.1 mmol, 2 equiv) and anhydrous α,α,α-trifluorotoluene (0.4 mL). The enantiomeric excess was determined to be 62% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

*Allyltriphenyltin with 20% of **3.11** at low temperature:* The reaction was performed at -25 °C for 3 hours, using 2H-chromene **3.3 (**46.7 mg, 0.35 mmol, 1.0 equiv), TRIP phosphoramide (**3.11**) (62.5 mg, 0.07 mmol, 20% equiv), 4Å molecular sieves powder (200 mg), DDQ (112 mg, 0.50

mmol, 1.4 equiv), allyltriphenyltin (547 mg, 1.4 mmol, 4 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL). The workup procedure is according to Curran's paper.[69] Upon consumption of the oxidized intermediate the reaction mixture was filtered through silica gel and eluted with 10% Et_2O/pentane to give a light yellow filtrate. The filtrate was cooled to 0 °C, and DBU (234 mg, 1.54 mmol) was added. Then a solution of I_2 in diethyl ether was added dropwise until the color of I_2 persisted, during which precipitates were formed. The mixture was filtered through silica gel again using 10% Et_2O/pentane as the eluent and carefully concentrated under reduced pressure. Flash column chromatography with 3% Et_2O/pentane afforded 39.6 mg (66%) of the desired product. The enantiomeric excess was determined to be 81% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.



1 Det.A Ch1/Detector A

ID#	Name	Ret. Time	Area	Height
1	RT5.501	5.501	157665	22594
2	RT5.896	5.896	1370791	102575

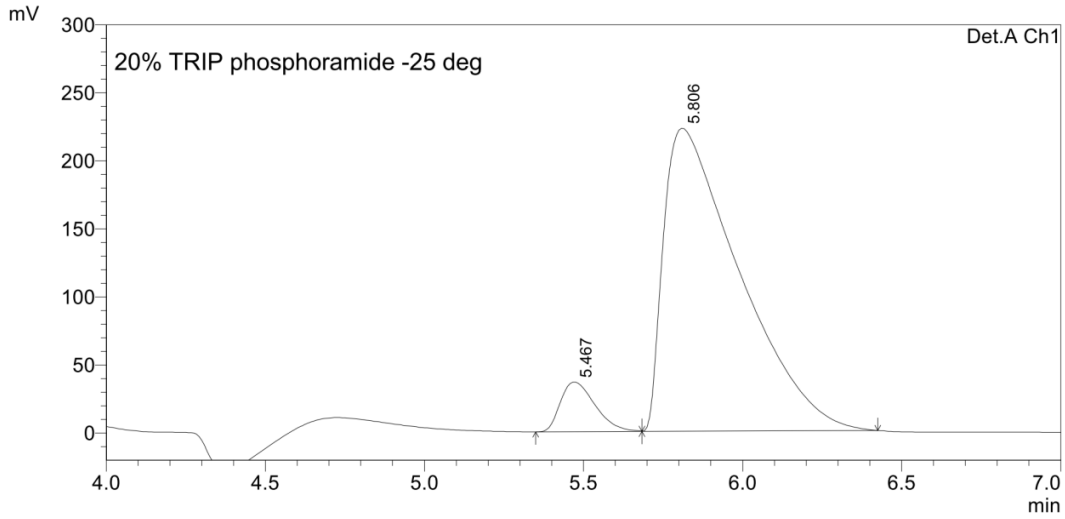
Figure S3.4 HPLC from allyltriphenyltin 20% cat at -25 °C

Allyltriphenyltin with 10% of 3.11 at low temperature: The reaction was performed at -25 °C for 3 hours, using 2H-chromene **3.3 (**45.1 mg, 0.34 mmol), TRIP phosphoramide (**3.11**) (31.7 mg, 0.034 mmol, 10% equiv), 4Å molecular sieves powder (200 mg), DDQ (108.7 mg, 0.48 mmol, 1.4 equiv), allyltriphenyltin (334 mg, 0.86 mmol, 2.5 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL). DBU/I_2 workup and flash column chromatography with 3% Et_2O/pentane afforded 35 mg (66%) of the desired product. The enantiomeric excess was determined to be 68% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Allyltriphenyltin with 5% of 3.11 at low temperature: The reaction was performed at -25 °C for 3 hours, using 2H-chromene **3.3 (**47.5 mg, 0.36 mmol), TRIP phosphoramide (**3.11**) (16.0 mg, 0.018 mmol, 5% equiv), 4Å molecular sieves powder (200 mg), DDQ (115 mg, 0.51 mmol, 1.4 equiv), allyltriphenyltin (352 mg, 0.90 mmol, 2.5 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL). DBU/I_2 workup and flash column chromatography with 3% Et_2O/pentane afforded 35 mg (57%) of the desired product. The enantiomeric excess was determined to be 31% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Allylphenyldimethylsilane with 20% of 3.11 at zero degree: The reaction was performed at 0 °C for 45 min, using 2H-chromene **3.3 (**6.6 mg, 0.05 mmol), 20 mol% loading of TRIP phosphoramide (**3.11**) (8.8 mg, 0.01 mmol), DDQ (15.9 mg, 0.07 mmol), allylphenyldimethylsilane (26 mg, 0.15 mmol, 3 equiv) and anhydrous α,α,α-trifluorotoluene (0.4 mL). The enantiomeric excess was determined to be 62% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Allylphenyldimethylsilane with 20% of 3.11 at low temperature: The reaction was performed at -25 °C for 3 hours, using 2H-chromene **3.3 (**41.5 mg, 0.32 mmol, 1.0 equiv), TRIP phosphoramide (**3.11**) (55.7 mg, 0.063 mmol, 20% equiv), 4Å molecular sieves powder (200 mg), DDQ (100 mg, 0.44 mmol, 1.4 equiv), allylphenyldimethylsilane(169 mg, 0.96 mmol, 3 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL). Normal workup and flash column chromatography with 3% Et_2O/pentane afforded 30.4 mg (56%) of the desired product. The enantiomeric excess was determined to be 86% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.



ID#	Name	Ret. Time	Area	Height
1	RT5.467	5.467	277303	36576
2	RT5.806	5.806	3696651	222827

Figure S3.5 HPLC from allyphenyldimethylsilane 20% at -25 °C

Allylphenyldimethylsilane with 10% of 3.11 at low temperature: The reaction was performed at -25 °C for 3 hours, using 2H-chromene **3.3 (**46.5 mg, 0.35 mmol, 1.0 equiv), TRIP phosphoramide (**3.11**) (31.2 mg, 0.035 mmol, 10% equiv), 4Å molecular sieves powder (200 mg), DDQ (109.5 mg, 0.48 mmol, 1.4 equiv), allylphenyldimethylsilane(185 mg, 1.05 mmol, 3 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL). Normal workup and flash column

chromatography with 3% Et_2O/pentane afforded 31.6 mg (52%) of the desired product. The enantiomeric excess was determined to be 79% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

Allylphenyldimethylsilane with 5% of 3.11 at low temperature: The reaction was performed at -25 °C for 4 hours, using 2H-chromene **3.3 (**48.4 mg, 0.37mmol, 1.0 equiv), TRIP phosphoramide (**3.11**) (16.2 mg, 0.018mmol, 5% equiv), 4Å molecular sieves powder (200 mg), DDQ (117 mg, 0.51 mmol, 1.4 equiv), allylphenyldimethylsilane(194 mg, 1.1mmol, 3 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL). Normal workup and flash column chromatography with 3% Et_2O/pentane afforded 35.4 mg (56%) of the desired product. The enantiomeric excess was determined to be 17% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

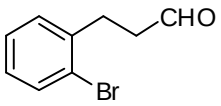
Determination of absolute configuration

A mixture of the chiral 2-allyl-2*H*-chromene **3.15** (30 mg, 0.22 mmol, 73% ee by HPLC, *prepared by the representative procedure in this paper*) and 10% Pd/C (10 mg) in dichloromethane (3 mL) was stirred under a hydrogen atmosphere for 4 hours. Flash column chromatography with 3% Et_2O/pentane afforded 19.6 mg (64%) of the hydrogenated chiral ether **3.19**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03-7.10 (m, 2H), 6.78-6.84 (m, 2H), 3.94-4.04 (m, 1H), 2.72-2.90 (m, 2H), 1.95-2.03 (m, 1H), 1.72-2.02 (m, 2H), 1.45-1.62 (m, 3H), 0.98 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 129.5, 127.1, 122.1, 119.8, 116.7, 75.6, 37.6, 34.1, 27.4, 24.8, 22.3, 18.6, 14.1, 14.0; IR (film) 2957, 2872, 1582, 1488, 1457, 1302, 1232, 1119,

984, 885, 752 m^{-1}; HRMS (EI) m/z calcd for $C_{12}H_{16}O$ [M]+ 176.1201, found 176.1219; $[\alpha]^{25}_D$ = +73.0 (c = 1.96, CH_2Cl_2).

Independent Synthesis With Known Absolute Configuration

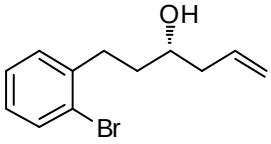
3-(2-Bromophenyl)propanal (3.17)



To a solution of *o*-bromohydrocinnamic acid (**3.16**) (2.29 g, 10.0 mmol) in methanol (20 mL) stirred at 0 °C, thionyl chloride (1.47 mL, 20.0 mmol) was added dropwise, and then the reaction was stirred at room temperature overnight. The reaction was carefully quenched with saturated aqueous $NaHCO_3$ solution (10 mL), neutralized with powder $NaHCO_3$, and extracted three times with 20 mL of diethyl ether. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography with 10% ethyl acetate in hexanes afforded 2.19 g (90%) of the desired ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.20-7.26 (m, 2H), 7.06 (dd, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 3.07 (t, *J* = 7.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 139.5, 132.7, 130.2, 127.9, 124.1, 51.4, 33.7, 31.2.

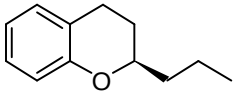
To the solution of methyl 3-(2-bromophenyl)propanoate (1.22 g, 5.0 mmol) in dichloromethane (20 mL) at -78 °C, 1M DIBAL-H solution in hexanes (6 mL, 6.0 mmol) was added dropwise. The reaction was stirred at -78 °C for 1 hour, quenched with methanol (2 mL), and concentrated under reduced pressure. Flash column chromatography with 10% ethyl acetate in hexanes afforded 0.81 g (76%) of the desired aldehyde **3.17**. 1H NMR (300 MHz, $CDCl_3$) δ 9.85 (d, *J* = 0.9 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.24-7.28 (m, 2H), 7.07-7.13 (m, 1H), 3.09 (t, *J* = 7.5 Hz, 2H), 2.82 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 139.6, 132.9, 130.4, 128.0, 127.6, 124.2, 43.6, 28.6.

(S)-1-(2-Bromophenyl)hex-5-en-3-ol (3.18)



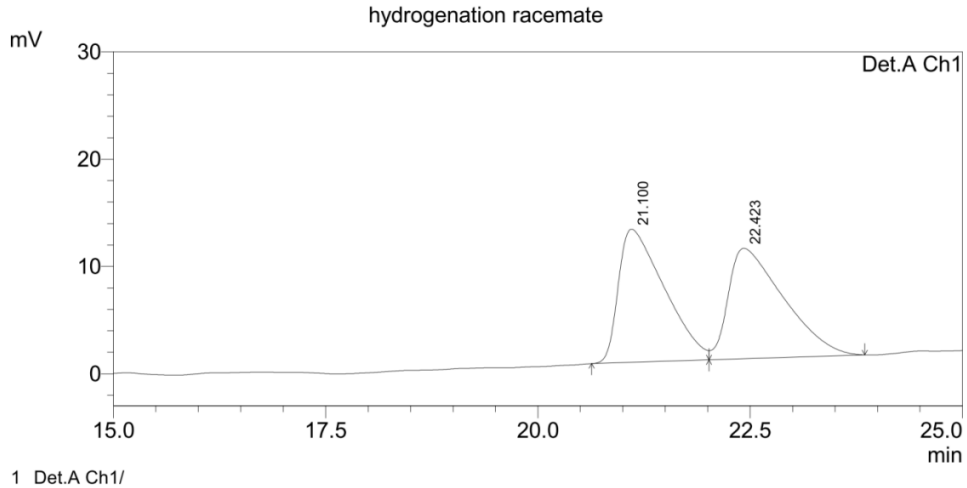
To a solution of (+)-IPC-Cl (1.80 g, 5.6 mmol, 1.87 equiv) in diethyl ether (3 mL) stirred at 0 °C, freshly prepared 0.5M allylmagnesium bromide solution in diethyl ether (10.5 mmol, 5.25 mmol, 1.75 equiv) was added dropwise over 20 min. The reaction was stirred at 0 °C for an additional 30 min, decanted, extracted two times with diethyl ether (5 mL), and concentrated under reduced pressure. The residual oil was dissolved in dry pentane (10 mL), filtered through Millex syringe filter, and added dropwise into a solution of 3-(2-Bromophenyl)propanal **3.17** (640 mg, 3.0 mmol, 1.0 equiv) in diethyl ether (5 mL) at -100 °C over 45 min. The addition was in such a pattern that the allylmagnesium bromide solution touched the inner wall of the reaction flask before entering the solution. After one additional hour at -100 °C, the reaction was quenched with methanol (2 mL) and concentrated under reduced pressure. The residual oil was dissolved in THF (3 mL), cooled to 0 °C, and treated with saturated aqueous $NaHCO_3$ solution (7.0 mL) and 30% H_2O_2 (5.6 mL). After 3 hours at room temperature, the reaction mixture was extracted three time with diethyl ether (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography with 15% ethyl acetate in hexanes afforded 510 mg (67%) of the chiral alcohol (**3.18**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 1H), 7.11-7.17 (m, 2H), 6.93-6.99 (m, 1H), 5.58-5.82 (m, 1H), 5.07 (d, J = 15.6 Hz, 1H), 5.06 (d, J = 11.7 Hz, 1H), 3.58-3.66 (m, 1H), 2.80-2.90 (m, 1H), 2.67-2.77 (m, 1H), 2.22-2.30 (m, 1H), 2.07-2.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 134.5, 132.8, 130.4, 127.6, 127.4, 124.4, 118.3, 70.0, 41.9, 36.8, 32.4; IR (film) 3371, 3072, 2927, 1640, 1567, 1471, 1439, 1045, 1022, 994, 916, 749cm^{-1}; HRMS (ESI) calc. for $C_{12}H_{15}BrONa$ ($[M+Na]^+$): 277.0204, found 277.0197; $[\alpha]^{25}_D$ = -9.7 (c = 2.56, CH_2Cl_2).

(R)-3,4-dihydro-2-propyl-2H-1-benzopyran (3.19)



An round bottom flask was charged with $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 5 mol%), (2-biphenyl)di-*tert*-butylphosphine (18.6 mg, 0.063 mmol, 6.3 mol%), and Cs_2CO_3 (652 mg, 2.0 mmol, 2.0 equiv). The flask was evacuated and back-filled with argon, and (S)-1-(2-Bromophenyl)hex-5-en-3-ol **3.18** (255 mg, 1.0 mmol, 1.0 equiv) in toluene (2 mL) was added via syringe. The flask was then placed into an oil bath pre-heated at 65 °C and stirred overnight. The reaction mixture was then cooled to room temperature, quenched with water (10 mL), and extracted two times with diethyl ether (10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography with 3% Et_2O/pentane afforded 100 mg (75%) of the chiral allyl ether. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 7.4 Hz, 1H), 7.04 (d, J = 7.4 Hz, 1H), 6.80-6.86 (m, 2H), 5.86-6.00 (m, 1H), 5.10-5.20 (m, 2H), 4.02-4.09 (m, 1H), 2.71-2.85 (m, 2H), 2.54-2.61 (m, 1H), 2.37-2.45 (m, 1H), 1.98-2.06 (m, 1H), 1.70-1.79 (m, 1H).

A mixture of (S)-3,4-dihydro-2-allyl-2H-1-benzopyran (83 mg, 0.62 mmol) and 10% Pd/C (20 mg) in dichloromethane (3 mL) was stirred under a hydrogen atmosphere for 4 hours. . Flash column chromatography with 3% Et_2O/pentane afforded 67.4 mg (81%) of the hydrogenated chiral ether **3.19**. $[\alpha]^{25}_D$ = +99.1 (c = 1.96, CH_2Cl_2).

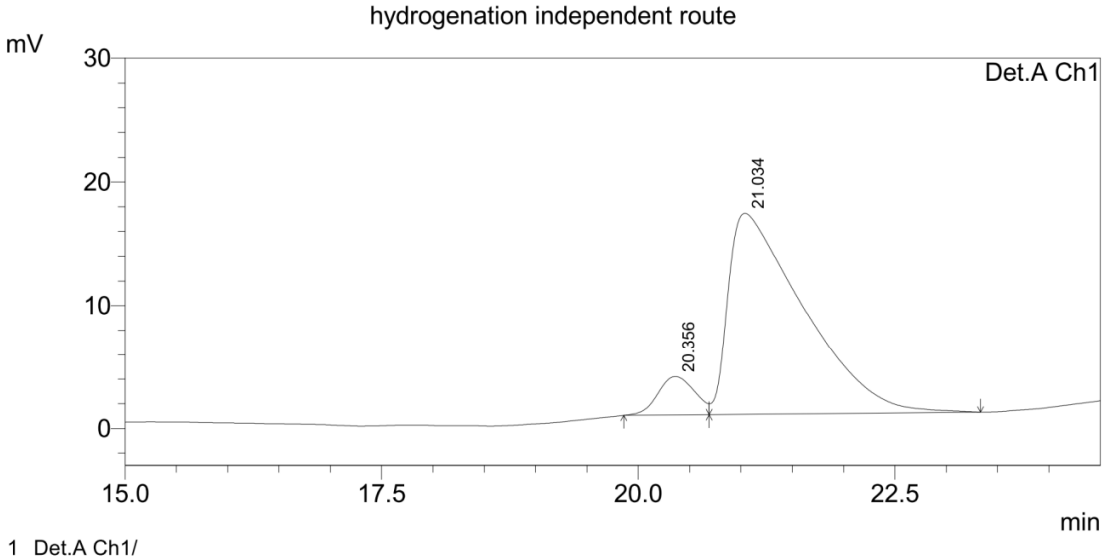


Detector A

ID#	Name	Ret. Time	Area	Height
1	RT21.100	21.100	466475	12416
2	RT22.423	22.423	467034	10307

Figure S3.6 HPLC from hydrogenated racemic mixture

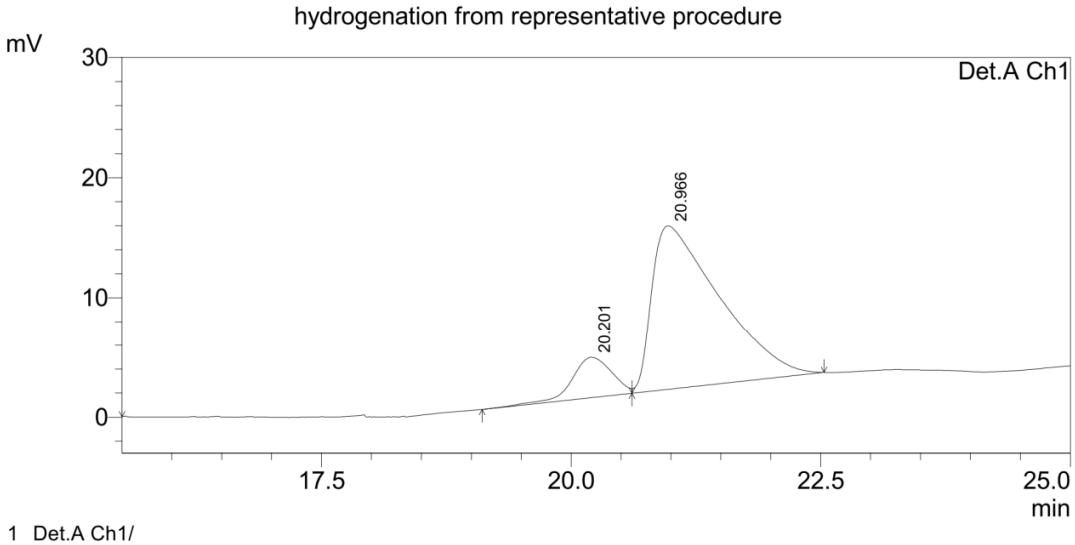
(1.0 mL/min, 80% Methanol in water)



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT20.356	20.356	77856	3118
2	RT21.034	21.034	837583	16323

Figure S3.7 Hydrogenation product from independent route (Brown's reaction)



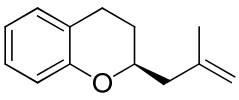
Detector A

ID#	Name	Ret. Time	Area	Height
1	RT20.201	20.201	92597	3355
2	RT20.966	20.966	645291	13683

Figure S3.8 HPLC from hydrogenated product from the present methodology

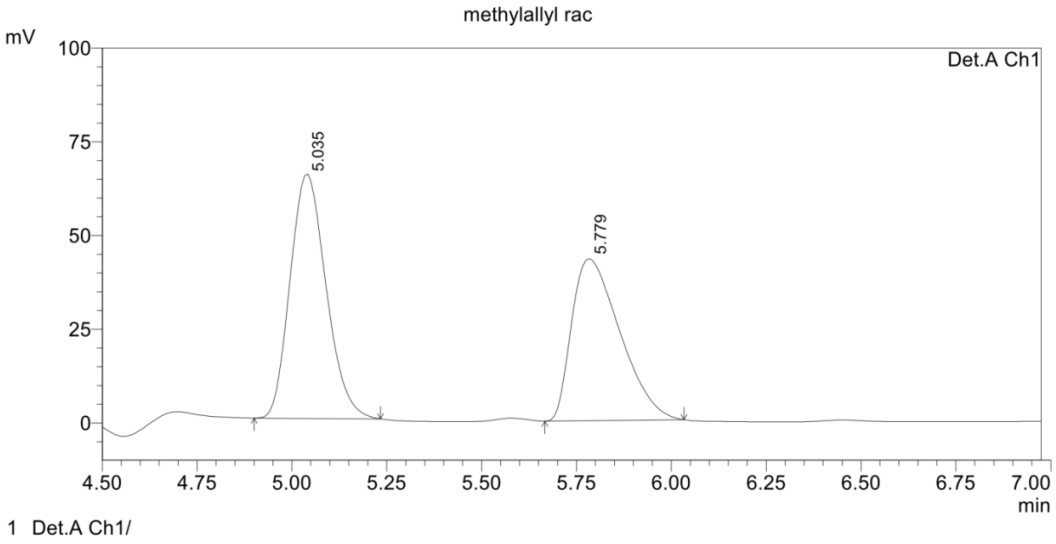
3.4 Attempts To Expand The Scope

(*R*)-2-(2-methylallyl)-2H-benzopyran （3.20）



The reaction was performed at -25 °C for 3 hours, using 2H-chromene **3.3** **(**38 mg, 0.29 mmol, 1.0 equiv), TRIP phosphoramide (**3.11**) (50.9 mg, 0.058mmol, 20% equiv), 4Å molecular sieves powder (200 mg), DDQ (92 mg, 0.41 mmol, 1.4 equiv), methylallylphenyldimethylsilane (162 mg, 0.87 mmol, 3 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL). Normal workup and flash column chromatography with 3% Et_2O/pentane afforded 36.4 mg (68%) of the desired product **3.20**. The enantiomeric excess was determined to be 33% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data

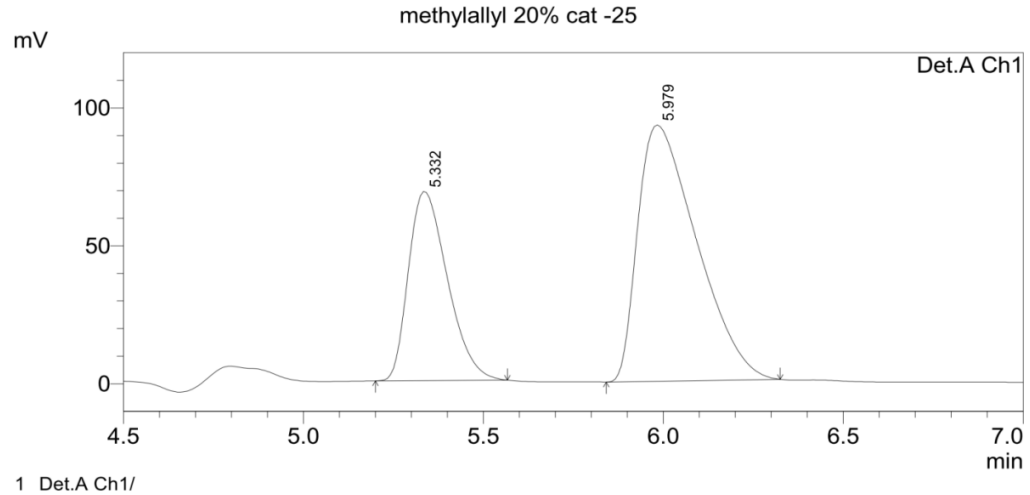
were in agreement with previously reported values. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.12 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 6.98 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.85 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 9.9 Hz, 1H), 5.74 (dd, *J* = 9.9, 3.6 Hz, 1H), 4.96-5.03 (m, 1H), 4.89 (aps, 1H), 4.79 (d, *J* = 0.9 Hz, 1H), 2.56 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.35 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 153.8, 142.2, 129.7, 127.0, 126.3, 124.4, 122.7, 121.6, 116.7, 113.6, 74.2, 43.8, 23.1; IR (film) 3075, 2936, 1640, 1606, 1486, 1457, 1229, 1208, 1113, 1055, 1034, 891, 767, 753 m^{-1}; HRMS (ESI) *m/z* calcd. for $C_{13}H_{13}O$ $[M - H]^+$ 185.0966, found 185.0971; $[\alpha]^{25}_D$ = +55.7 (c = 2.51, CH_2Cl_2).



Detector A

ID#	Name	Ret. Time	Area	Height
1	RT5.035	5.035	430943	65255
2	RT5.779	5.779	382481	43279

Figure S3.9 HPLC from Racemic mixture of **3.20**

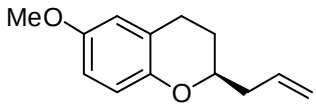


Detector A

ID#	Name	Ret. Time	Area	Height
1	RT5.332	5.332	517488	68566
2	RT5.979	5.979	1057321	92962

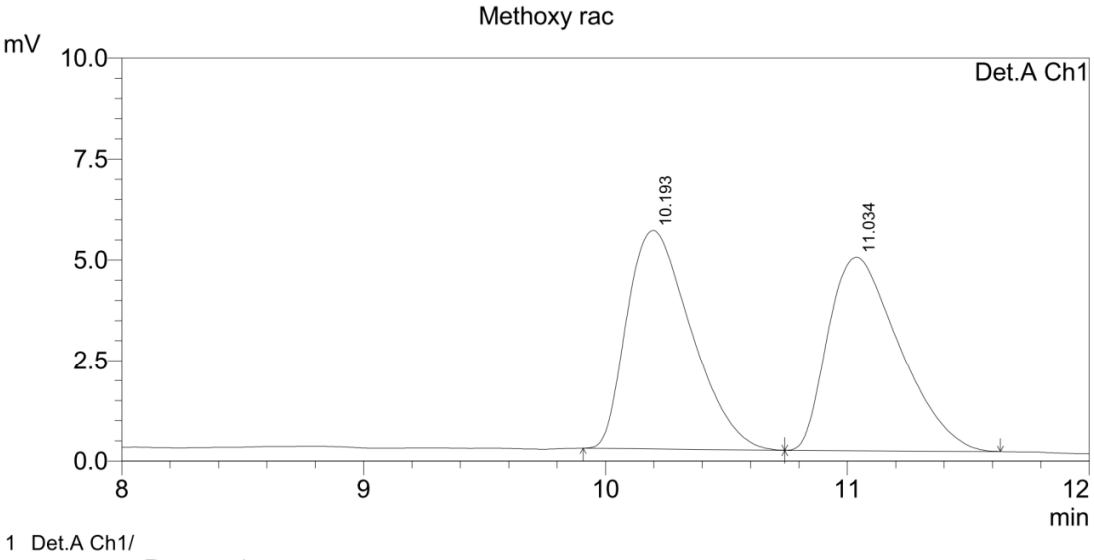
Figure S3.10 HPLC from enantiomerically enriched **3.20**

(*S*)-2-allyl-6-methoxychroman （3.22）



The reaction was performed at -25 °C for 3 hours, using 6-methoxy-2*H*-chromene **3.21** (48 mg, 0.30 mmol, 1.0 equiv), TRIP phosphoramide (**3.11**) (53 mg, 0.06 mmol, 20% equiv), 4Å molecular sieves powder (200 mg), DDQ (95.3 mg, 0.42 mmol, 1.4 equiv), allylphenyldimethylsilane(158 mg, 0.9 mmol, 3 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL). Normal workup and flash column chromatography with 5% Et_2O/pentane afforded 32.4 mg (53%) of the desired product **3.22**. The enantiomeric excess was determined to be 9% by chiral HPLC (1% i-PrOH:hexanes, 1.0 mL/min). Characterization data were in agreement with previously reported values.

^{1}H NMR (400 MHz, $CDCl_3$) δ6.72 (d, *J* = 8.4 Hz, 1H), 6.66 (dd, *J* = 8.8, 2.1 Hz, 1H), 6.54 (d, *J* = 2.8 Hz, 1H), 6.38 (d, *J* = 9.6 Hz, 1H), 5.88 (ddt, *J* = 18.0, 10.4, 7.2 Hz, 1H), 5.74 (dd, *J* = 9.6, 3.2 Hz, 1H), 5.15 (d, *J* = 8.8 Hz, 1H), 5.12 (s, 1H), 4.84 (brs, 1H), 3.75 (s, 3H), 2.53−2.60 (m, 1H), 2.40−2.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.9, 147.1, 133.4, 126.1, 124.3, 122.5, 117.8, 116.5, 114.2, 111.6, 74.3, 55.6, 39.4. $[\alpha]^{25}_D$ = -8.7 (c = 0.33, CH_2Cl_2).

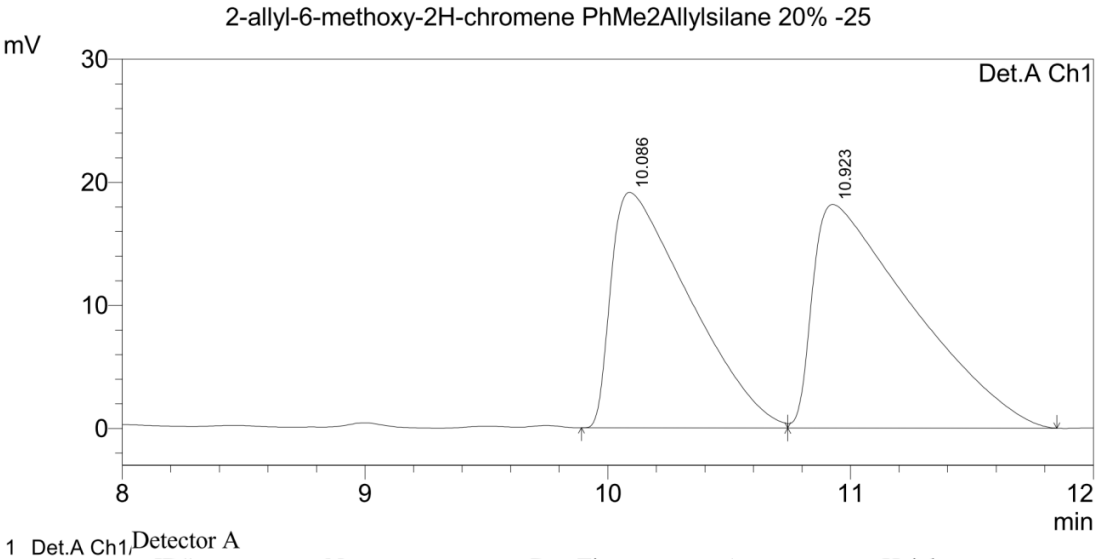


1 Det.A Ch1/

Detector A

ID#	Name	Ret. Time	Area	Height
1	RT10.193	10.193	100630	5434
2	RT11.034	11.034	99139	4814

Figure S3.11 HPLC from racemic **3.22**



1 Det.A Ch1/Detector A

ID#	Name	Ret. Time	Area	Height
1	RT10.086	10.086	430820	19136
2	RT10.923	10.923	520719	18168

Figure S3.12 HPLC from enantiomerically enriched **3.22**

Background reaction with methallylphenyldimethylsilane: The reaction was performed at -25 °C for 1 hour, using 2H-chromene **3.3 (**48.8 mg, 0.37 mmol, 1.0 equiv), 4Å molecular sieves powder (200 mg), DDQ (120 mg, 0.53 mmol, 1.4 equiv), methallylphenyldimethylsilane (206 mg, 1.1 mmol, 3 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL), but without using $LiClO_4$ or chiral catalysts. Normal workup and flash column chromatography with 3% Et_2O/pentane afforded 42 mg (61%) of the desired racemic product.

Background reaction of 6-Methoxy--2H-chromene 3.21: The reaction was performed at -25 °C for 2 hours, using 6-methoxy-2*H*-chromene **3.21** (101 mg, 0.62 mmol, 1.0 equiv), 4Å molecular sieves powder (200 mg), DDQ (198 mg, 0.87 mmol, 1.4 equiv), allylphenyldimethylsilane(334 mg, 1.9 mmol, 3 equiv) and anhydrous α,α,α-trifluorotoluene (3 mL), but without using $LiClO_4$ or chiral catalysts. Normal workup and flash column chromatography with 5% Et_2O/pentane afforded 53.1 mg (42%) of the desired racemic product.

BIBLIOGRAPHY

1. a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.*, **2004**, *67*, 1216. b) Newman, D. J.; Cragg, G. M. *Curr. Med. Chem*. **2004**, *11*, 1693.

2. Napolitano, J. G.; Daranas, A. H.; Norte, M.; Fernandez, J. J. *Anticancer Agents Med Chem.* **2009,** *9*, 122.

3. Wright, A. E.; Botelho, J. C.; Guzman, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. *J. Nat. Prod.* **2007**, *70*, 412.

4. a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51. b) D'Ambrosio, M.; Tató, M.; Poscfalvi, G.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1999**, *82*, 347.

5. a) Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 9211. b) Custar, D. W.; Zabawa, T.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 804. c) Ulanovskya, O. A.; Janjic, J.; Suzuki, M.; Sabharwal, S. S.; Schumaker, P. T.; Kron, S. J.; Kozmin, S. A. *Nature Chem. Biol.* **2008**, *4*, 418

6. Zampella, A.; DAuria, M. V.; Minale, L.; Debitus, C.; Roussakis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11085.

7. Tan, L. T.; Marquez, B. L.; Gerwick, W. H. *J. Nat. Prod.* **2002**, *65*, 925–928.

8. Sone, H.; Kigoshi, H.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 8956.

9 a) Luesch, H.; Yoshida, W. Y.; Harrigan, G. G.; Doom, J. P.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **2002**, *65*, 1945–1948. b) Klein, D.; Braekman, J. C.; Daloze, D.; Hoffmann, L.; Demoulin, V. *J. Nat. Prod.* **1997**, *60*, 1057.

10 a) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3242. b) Vintonyak, V. V.; Maier, M. E. *Org. Lett.* **2008**, *10*, 1239. c) Fuwa, H.; Naito, S.; Goto, T.; Sasaki, M. *Angew.*

Chem., Int. Ed. **2008**, *47*, 4737. d) Paterson, I.; Miller, N. A. *Chemical Commun.* **2008**, 4708. e) Kartika, R.; Gruffi, T. R.; Taylor, R. E. *Org. Lett.* **2008**, *10*, 5047. f) Vintonyak, V. V.; Kunze, B.; Sasse, F.; Maier, M. E. *Chem. Eur. J.* **2008**, *14*, 11132. g) Custar, D. W.; Zabawa, T. P.; Hines, J.; Crews, C. M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2009**, *131*, 12406. h) Guinchard, X.; Roulland, E. *Org. Lett.* **2009**, *11*, 4700. i) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7557. j) Fuwa, H.; Saito, A.; Naito, S.; Konoki, K.; Yotsu-Yamashita, M.; Sasaki, M. *Chem. Eur. J.* **2009**, *15*, 12807. k) Yadav, J. S.; Krishna, G. G.; Kumar, S. N. *Tetrahedron* **2010**, *66*, 480. l) Gallon, J.; Reymond, S.; Cossy, J. *Comp. Rend. Chim.* **2008**, *11*, 1463. m) Fuwa, H.; Saito, A.; Sasaki, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 3041. n) Martinez-Solorio, D.; Jennings, M. P. *J. Org. Chem.* **2010**, *75*, 4095. p) Oestreich, M.; Hartmann, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 6195.

11 Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567.

12 a) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894. b) Wipf, P.; Graham, T. H. *J. Org. Chem.* 2001, *66*, 3242; c) Paterson, I.; Tudge, M. *Tetrahedron*, **2003**, *59*, 6833. d) Wang, Y.; Janjic, J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 13670. e) Dakin, L. A.; Langille, N. F.; Panek, J. S. *J. Org. Chem.* **2002**, *67*, 6812.

13 Mitsunobu, O. *Synthesis* **1981**, 1.

14 Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

15. Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353.

16. a) Brown, H.C. *J. Am. Chem. Soc.* **1975**, *97*, 2791. b) Langer, F.; Devasagayaraj, A.; Chavant, P. Y.; Knochel, P. *Synlett*, **1994**, 410.

17. Barlow, R. B.; Bremner, J. B.; Soh, K. S. *Br. J. Pharmac.*, **1978**, *62*, 39.

18. Ludek, O. R.; Schroeder, G. K.; Liao, C.; Russ, P. L.; Wolfenden, R.; Marquez, V. E. *J. Org. Chem.* **2009**, *74*, 6212.

19. Boss, C.; Rasmussen, P. H.; Wartini, A. R.; Waldvogel, S. R. *Tetrahedron Lett.* **2000**, *41*, 6327.

20. Cho, S. J.; Jensen, N. H.; Kurome, T.; Kadari, S.; Manzano, M. L.; Malberg, J. E.; Caldarone, B.; Roth, B. L.; Kozikowski, A. P. *J. Med. Chem.* **2009**, *52*, 1885.

21. Brown, C. A.; Ahuja, V. K. *J. Org. Chem.*, **1973**, *38*, 2226.

22. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

23. Wadsworth, W. S. *Org. Reactions*, **1977**, *25*, 97.

24. Mori, A.; Mizusaki, T.; Miyakawa, Y.; Ohashi, E.; Haga, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron*, **2006,** *62*, 11925.

25. Wu, G.; Huang, M.; Richards, M.; Poirier, M.; Wen, X.; Draper, R. W. *Synthesis*, **2003**, *11*,1657.

26. Yoshizumi, T. ; et al. *J. Med. Chem.* **2008**, *51*, 4021

27. Vogel, J. C. ; Butler, R. ; Procter, D. J. *Tetrahedron*, **2008**, *64*, 11876.

28. a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277. b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

29. a) Block, E. *Reactions of Organosulfur Compounds*, Academic Press: New York, **1978**. b) Woodward, R. B.; Logusch, E.; Nambiar, K.P.; Sakan, K.; Ward, D. E.; Au-Yeung, B. W.; Balaram, P.; Browne,L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3210. c) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1997**, *53*, 5563. d) Agarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H.; Fieldhouse, R.; Spey, S. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3267. e) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. f) Vedejs, E. *Acc. Chem. Res.* **1984**, *17*, 358.

30. a) Adam, W.; Mitchell, C.M.; Saha-MSller, C.R. *Tetrahedron*, **1994**, *50*, 13121. b) Noda, K.; Hosoya, N.; Irie, R.; Yamashita, Y.; Katsuki, T. *Tetrahedron*, **1994**, *50*, 9609. c) Walker, A.J. *Tetrahedron : Asymmetry*, **1992**, *3*, 961.

31. a) Jacob, C.; Giles, G.I.; Giles, N.M.; Sies, H. *Angew. Chem. Int. Ed.,* **2003,** *42*, 4742. b) Meyer, J. *J. Biol. Inorg. Chem.* **2008**, *13* (*2*), 157.

32. a) Woodward, R. B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer,W.; Ramage, R.; Ranganathan, S.; Vorbruggen, H. *J. Am. Chem. Soc*.**1966**, *88*, 852. b) Casy, G.; Lane, S.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1397. c) Ohuchida, S.; Hamanaka, N.; Hagashi, M.*Tetrahedron Lett.* **1983**, *39*, 4273. d) Kale, V. N.; Clive, D. L. J. *J. Org. Chem.* **1984**, *49*, 1554.

e) Mehta, S.; Andrews, J. S.; Johnston, B. D.; Svensson, B.; Pinto, B. M. *J. Am. Chem. Soc.* **1995**, *117*, 9783.

33. a) H. Qian, X. Han, R. A. Widenhoefer, *J. Am. Chem. Soc.*, **2004**, *126*, 9536. b) H. Qian, X. Han, R. A. Widenhoefer, *J. Am. Chem. Soc.*, **2004**, *126*, 9536. c) E. J. Alvarez-Manzaneda, R. Chabouna, E. Alvarez, E. Cabrera, R. Alvarez-Manzaneda, A. Haidour, J. M. Ramos, *Synlett*, **2006**, 1756. d) A. Dzudza, T. J. Marks, *Org. Lett.*, **2009**, *11*, 1523. e) C.-G. Yang, N. W. Reich, Z. Shi, C. He, *Org. Lett.*, **2005**, *7*, 4553. f) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.*, **2006**, *128*, 9066. g) H. Kim, C. Lee, *Org. Lett.*, **2011**, *13*, 2050. h) A. Guérinot, A. Serra-Muns, C. Gnamm, C. Bensoussan, S. Reymond, J. Cossy, *Org. Lett.*, **2010**, *12*, 1808. i) A. Aponick, B. Biannic, *Org. Lett.*, **2011**, *13*, 1330. J) G.-Q. Tian, M. Shi, *Org. Lett.*, **2007**, *9*, 2405. k) S. N. Chavre, H. Choo, J. K. Lee, A. N. Pae, Y. Kim, Y. S. Cho, *J. Org. Chem.*, **2008**, *73*, 7467. l) M. Barbasiewicz, A. Brud, M. Mąkosza, *Synthesis*, **2007**, 1209. m) K. Tadpetch, S. D. Rychnovsky, *Org. Lett.*, **2008**, *10*, 4839. n) F. Liu, T.-P. Loh, *Org. Lett.*, **2007**, *9*, 2063. o) P. J. Jervis, B. M. Kariuki, L. R. Cox, *Org. Lett.*, **2006**, *8*, 4637. p) L. V. Heumann, G. E. Keck, *Org. Lett.*, **2007**, *9*, 1951. q) G. A. Cortez, C. A. Baxter, R. R. Schrock, A. H. Hoveyda, *Org. Lett.*, **2007**, *9*, 2871. r) Liu, L.; Floreancig, Paul E. *Angew. Chem. Int. Ed.*, **2010**, *49*, 3069.

34. a) Robertson, F.J.; Wu, J. *Journal J. Am. Chem. Soc.*, **2012**, *134*, 2775. b) Li, F.; Calabrese, D.; Brichacek, M.; Lin, I.; Njardarson J.T. *Angew. Chem. Int. Ed.* **2012**, 51, 1938. c) Weïwer, M.; Coulombel, L.; Duñach, E. *Chem. Commun*. **2006**, 332. d) Weïwer, M.; Chaminade, X.; Bayón, J. C.; Duñach, E. *Eur. J. Org. Chem.* **2007**, 2464. e) Tamura, Y.; Choi, H.-D.; Shindo, H.; Uenishi, J.; Ishibashi, H. *Tetrahedron Lett.* **1981**, *22*, 81.

35. a) Ozaki, S.; Matsui, E.; Yoshinaga, H.; Kitagawa, S. *Tetrahedron Lett.* **2000**, *41*, 2621. b) Boullosa, S.; Gandara, Z.; Perez, M.; Gomez, G.; Fall, Y. *Tetrahedron Letters* **2008**, *49*, 4040. c) Hachem, A.; Toupet, L.; Gree, R. *Tetrahedron Lett.* **1995**, *36*, 1849. d) Lei, M.; Xiao, Y.; Liu W.; Fukamizu, K.; Chiba, S.; Ando, K.; Narasaka, K. *Tetrahedron* **2009**, *65*, 6888. e) Gung, B.W. ; Francis, M. *Tetrahedron Letters*, **1995**, 36, 2579. f) Rosiak, A.; Frey, W.; Christoffers, *J. Eur. J. Org. Chem*. **2006**, 4044.

36. a) Yang, X.-F.; Mague, J. T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739; b) Yang, X.-F.; Li, C.-J. *Tetrahedron Lett.* **2000,** *41*, 1321. c) Dobbs, A. P.; Guesne, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *J.* Org. Chem. **2003**, *68*, 7880. d) Kishi, Y.;Nagura, H.; Inagi, S.; Fuchigami, T. *Chem. Commun*. **2008**, 3876. e) Kishi, Y.; Inagi, S.; Fuchigami, T. Eur. *J. Org. Chem*. **2009**, *74*, 103. f) Bondalapati, S.; Gogoi, P.; Indukuri, K.; Saikia, A. K. *J. Org. Chem.* **2012**, *77*, 2508. g) Reddy, B.; Borkar, P.; Yadav, J.;, Sridhar, B.; Gree, R. *J. Org. Chem.* **2011**, *76*, 7677 h) Kishi, Y.; Inagi, S.; Fuchigami, T. *Eur. J. Org. Chem.* **2009**, 103. i) McAllister, L. A.; McCormick, R. A.; Brand, S.; Procter, D. *J. Angew.Chem., Int. Ed.* **2005**, *44*, 452 .

37. a) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832. b) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003. c) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401.

38. a) Pummerer, R. *Chem. Ber*. **1909**, *42*, 2282. Pummerer, R. *Chem. Ber*. **1910**, *43*, 1401. b) De Lucchi, O.; Miotti, U.; Modena, G. *Org. Reactions* **1991**, *40*, 157. c) Padwa, A.; Bur, S. K.; Danca, M. d.; Ginn, J. D.; Lynch, S. M. *Synlett*, **2002,** *6*, 851.

39. A few exceptions where *endo* products are formed: a) Padwa, A.; Gunn, D.E.; Osterhout, M.H.; *Synthesis,* **1997**, 1353; b) Horiguchi, Y.; Sonobe, A.; Saitoh, T.; Toda, J.; Sano, T. *Chem.*

Pharm. Bull. **2001**, *49*(9) 1132. c) Tamura, T.; Choi, H.; Shindo, H.; Uenishi, J.; Ishibashi, H. *Tetrahedron Letters*, **1981**, *22*, 81.

40. a) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci*. **2006**, *103*, 8928. b) Zhang, Y.; Li, C.-*J. Angew. Chem., Int. Ed.* **2006**, *45*, 1949. c) Wan, X.; Xing, D.; Fang, Z.; Li, B.; Zhao, F.; Zhang, K.; Yang, L.;Shi, Z. *J. Am. Chem. Soc*. **2006**, *128*, 12046. d) Maruyama, T.; Suga, S.;Yoshida, J.-I. *J. Am. Chem. Soc.* **2005**, *127*, 7324. e) DeBoef, B.; Pastine,S. J.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 6556. f) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312. g) Chatani, N.; Asaumi, T.; Yorimitsu, S.; Ikeda, T.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2001**, *123*, 10935. h) Yoshida, J.-I.; Suga, S.; Suzuki, S.; Kinomura, N.; Yamamoto, A.; Fujiwara, K. *J. Am. Chem. Soc.* **1999**,*121*, 9546.

41. a) Tu, W.; Liu, L.; Floreancig, P. E. Angew. Chem., Int. Ed. **2008**, *47*, 4184. b) Tu, W.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4567. c) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 3069. d) Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2010,** *49*, 5894.

42. a) Osapay, K.; Delhalle, J.; Nsunda, K. M.; Rolli, E.; Houriet,R.; Hevesi, L. *J. Am. Chem. Soc.* **1989,** *111*, 5028. b) Apeloig, Y.; Karni,M. *J. Chem. Soc., Perkin Trans.* 2 **1988**, 625. c) Gr€utzmacher, H.; Marchand, C. M. *Coord. Chem. Rev*. **1997**, *163*, 287.

43. a) Allen, F. H.; Kennard, R.; Watson, D.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. II*, **1987**, S1-S19. b) Broecker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem.Soc.* **1991**, *113*, 5006.

44. For a similar approach to thiocarbenium ion formation, see: Li, Z.; Li, H.; Guo, X.; Cao, L.; Yu, R.; Li, H.; Pan, S. *Org. Lett.* **2008**, *10*, 803.

45. Goossen, L. J.; Paetzold, J.; Koley, D. Chem. Commun. 2003, 706-707.

46. a) Jung, H. H.; Floreancig, P. E. *Tetrahedron* **2009**, *65*, 10830. b) Schepp, N. P.; Johnston, L. J. *J. Am. Chem. Soc.* **1996**, *118*, 2872. c) Brizgys, G. J.; Jung, H. H.; Floreancig, P. E. *Chem. Sci.* **2012**, *3*, 438. d) Liu, L.; Floreancig, P. E. *Org. Lett.* **2009**, *11*, 3152.

47. a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. b) Bichler, P.; Love, J. A. Top. *Organomet. Chem.* **2010**, *31*, 39.

48. Ciattini, P. G.; Morera, E.; Ortar, G. Tetrahedron Lett. 1995, 36,4133.

49. Hoppe, D.; Hanko, R.; Bronneke, A.; Lichtenberg, F.; van Hulsen, E. *Chem. Ber.* **1985**, *118*, 2822.

50. Mitsunobu, O. *Synthesis* **1981**, 1.

51. Kao, H.-L.; Lee, C.-F. *Org. Lett.* **2011**, *13*, 5204.

52. Chechik-Lankin, H.; Marek, I. *Org. Lett.* **2003**, *5*, 5087.

53. a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. b) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375.

54. Buchwald, S. L.; Lamaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895.

55. Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

56. Filippi, J.; Dunach, E.; Fernandez, X.; Meierhenrich, U. J. *Tetrahedron* **2008**, *64*, 9999.

57. a) Congreve, M.; Chessari, G.; Tisi, D.; Woodhead, A. J. *J. Med. Chem*. **2008**, *51*, 3661; b) Hajduk, P. J.; Greer, J. *Nature Rev. Drug Discovery* **2007**, *6*, 211; c) Congreve, M.; Carr, R.; Murray, C.; Jhoti, H. *Drug Discovery Today* **2003**, *8*, 876; d) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46.

58. a) Liu, L.; Floreancig, P. E. *Curr. Opin. Drug Discovery Dev.* **2010**,*13*, 733; b) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976; c) Davies, H. M. L. *Angew. Chem., Int. Ed.*

2006, *45*, 6422; d) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335; e) Robertson, J.; Pillai, J.; Lush, R. K. *Chem. Soc. Rev.* **2001**, *30*, 94.

59. a) He, Z.; Lin, X.; Zhu, Y.; Wang, Y. *Heterocycles* **2010**, *81*, 965; b) Hayashi, Y.; Itoh, T.; Ishikawa, H. *Angew. Chem., Int. Ed*. **2011**, *50*, 3920; c) Xu, Y.-C.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. *Org. Lett.* **1999**, *1*, 1599; d) Ying, B.-P.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y.-C. *Org. Lett.* **2004**, *6*, 1523; e) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc*. **2006**, *128*, 4242; f) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949; g) Benfatti, F.; Capdevila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G. *Chem. Commun.* **2009**, 5919; h) Zhang, B.; Xiang, S.-K.; Zhang, L.-H.; Cui, Y.; Jiao, N. *Org. Lett.* **2011**, *13*, 5212; i) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997; j) Dubs, C.; Hamashima, Y.; Sasamoto, N.; Seidel, T. M.; Suzuki, S.; Hashizume, D.; Sodeoka, M. J. *Org. Chem.* **2008**, *73*, 5859; k) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc*. **2010**, *132*, 1464; l) Tsang, A. S.-K.; Jensen, P.; Hook, J. M.; Hashmi, A. S. K.; Todd, M. H. *Pure Appl. Chem*. **2011**, *83*, 655; m) Zhang, G.; Zhang, Y.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 10429; n) Alagiri, K.; Devadig, P.; Prabhu, K. R. *Chem. Eur. J.* **2012**, *18*, 5160; o) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094.

60. a) Clausen D.J.; Floreancig, P.E. *J. Org. Chem*. **2012**, *77*, 6574−6582; b) Cui, Y.; Villafane, L.A.; Clausen D.J.; Floreancig, P.E. *Tetrahedron*, **2013**, *69*, 7618.

61. For recent reviews of chiral ion pairs, see: a) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518; b) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **2013**, *52*, 534; c) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603; d) Terada, M. *Synthesis* **2010**, 1929.

62. a) Terada, M.; Tanaka, H.; Sorimachi, K. *J. Am. Chem. Soc.* **2009**, *131*, 3430; b) Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. *Angew. Chem., Int. Ed*. **2009**, *48*, 8572; c) Coric, I.; Vellalath, S.; List, B. *J. Am. Chem. Soc.* **2010**, *132*, 8536; d)

Coric, I.; List, B. *Nature* **2012**, *483*, 315; e) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074.

63. a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626; b) Cheon, C. H.; Yamamoto, H. J. *Am. Chem. Soc*. **2008**, *130*, 9246.

64. Hagen, G.; Mayr, H. *J. Am. Chem. Soc*. **1991**, *113*, 4954.

65. Racherla, U. S.; Brown, H. C. *J. Org. Chem*. **1991**, *56*, 401.

66. Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.

67. Lykakis, I. N.; Efe, C.; Gryparis, C.; Stratakis, M. *Eur. J. Org. Chem.* 2011, 2334.

68. a) Nakashima, D.; Yamamoto, H. *J. Am, Chem. Soc*. 2006, 128, 9627; b) Cheon, C.H; Yamamoto, H. *J. Am. Chem. Soc*., 2008, 130, 9246; c) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* 2004, 43, 1566; d) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc*. 2004, 126, 5356.

69. Curran, D. P.; Chang, C. *J. Org. Chem.* **1989**, *54*, 3140.