Endeavors in Methodology Development and Natural Product Total Synthesis

by

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This thesis deals with the development of new reaction methodology, as well as total synthesis of natural products.

Chapter 1 describes readily available rhodium(II) salts catalyzed B-H insertion reactions between NHC-boranes (NHC-BH_3) and diazocarbonyl compounds ($N2CR^1COR^2$). Stable α-NHC-boryl carbonyl compounds (NHC-BH_2-CHR^1COR^2) are isolated in good yields. The reaction is a reliable way to make boron-carbon bonds with good tolerance for variation in both the NHC-borane and diazocarbonyl components. It presumably occurs by insertion of a transient rhodium carbene into a boron-hydrogen bond of the NHC-borane. Competition experiments show that a typical NHC-borane is highly reactive toward rhodium carbenes.

Chapter 2 describes the synthetic routes towards the synthesis of tulearin A and tulearin C. Large scale synthesis of the bottom fragments (C1-C12) and the top fragment (C13-C26) for tulearin A was accomplished. Different synthetic routes were tested to accomplish the total synthesis of tulearin A. Some major problems toward the total synthesis of tulearin A were identified and solved. Meanwhile a novel synthetic route towards the total synthesis of tulearin C was developed. New methodologies were applied to make the synthesis more efficient. The total synthesis of tulearin C was not accomplished because of the difficulty of removal of the acetate protecting group at C17.

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1,4-CHD	1,4-cyclohexaldiene
9-trp	9-triptycenecarboxylate
Ac	acetate
ACN	acetonitrile
AIBN	2,2'-azobis(2-methylpropionitrile) (azobisisobutyronitrile)
BAIB	bis(acetoxy)iodobenzene
BDE	bond dissociation energy
Bn	benzyl
Boc	di-*tert*-butyl dicarbonate
BOM	benzyloxymethyl
^{n}Bu	normal butyl
^{t}Bu	tertiary butyl
COSY	correlation spectroscopy
Cp	cyclopentadienyl
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutyl aluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
dipp	2,6-diisopropylphenyl
DMAP	4-dimethylamino pyridine
DME	1,2-dimethoxy ethane

DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMS	dimethyl sulfide
dr	diastereomeric ratio
EI	electron ionization
equiv	equivalents
ESI	electrospray ionization
er	enantiomeric ratio
Et	ethyl
HMBC	heteronuclear multiple bond coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
iPr	isopropyl
Imd	imidazol-2-ylidene
IR	infrared spectrometry
KHMDS	potassium bis(trimethylsilyl)amide
KIE	kinetic isotope effect
LiDBB	lithium 4,4'-di-*tert*-butylbiphenylide
Me	methyl
Mes	2,4,6-triisopropylphenyl
Ms	methylsulfonyl (mesyl)
MTPA	α-methoxytrifluorophenylacetic acid
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NHC	N-heterocyclic carbene
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
nPr	normal propyl
NOE	nuclear Overhauser effect

Ph	phenyl
PMB	*p*-methoxybenzyl
PT	1-phenyl-1*H*-tetrazol-5-yl
Pyr	pyridine
QqTOF	quadrupole time-of-flight
RCM	ring-closing metathesis
Rh_2(5*S*-MEPY)$_4$	tetrakis[methyl 2-pyrrolidone-5(S)-carboxylate]dirhodium
Rh_2(esp)$_2$	bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]
Rh_2(*S*-DOSP)$_4$	tetrakis[(S)-(-)-(p-dodecylphenylsulfonyl)prolinato]dirhodium
Rh_2(*S*-PTAD)$_4$	tetrakis[(S)-(+)-(1-adamantyl)-(N-phthalimido)acetato]dirhodium
rt	room temperature
STY	styrene
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
TES	triethylsilyl
Tf	trifluoromethylsulfonyl (triflyl)
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
TLC	thin layer chromatography
Ts	4-methylphenylsulfonyl (tosyl)

PREFACE

Foremost, I would like to express my gratitude to my supervisor Prof. Dennis Curran for supporting me over the past five and half years, for his patience, motivation, enthusiasm, and immense knowledge. I appreciate all his contributions of time, ideas, and funding to make my Ph.D. experience productive and simulating. I am grateful for the freedom of the scientific research he granted, as well as his help in spectrum analysis and improving my writing skills. I could not be prouder of my academic root and hope that I can in turn pass on the research values and dreams that he has given to me.

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I would like to thank Dr. Damodaran Krishnan and Sage Bowser for maintain out excellent NMR facilities and helped me measure the rotation barrier of NHC-boranes. I am also grateful to Drs. John Williams and Bhaskar Godugu for directing the superb mass-spec facilities.

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1.0 INSERTION OF REACTIVE RHODIUM CARBENES INTO BORON-HYDROGEN BONDS OF STABLE N-HETEROCYCLIC CARBENE BORANES

1.1 INTRODUCTION

1.1.1 N-Heterocyclic carbene boranes

In 1991, Arduengo reported the first isolation and crystal structure analysis of a stable N-heterocyclic carbene (NHC), 1,3-bis(adamantly)imidazole-2-ylidene **1.1** (Figure 1.1).[1] The unusual stability of **1.1** and other NHCs is in part a result of shielding of the carbene carbon by sterically demanding substituents on the ring. However, more important is the electronic stabilization by resonance interaction of the lone pairs of electrons on the nitrogen atoms with empty p orbital of the sp^2 hybridized carbene. Resonance structures and simplified orbital pictures are shown in Figure 1.1. The NHCs are a relatively new class of neutral Lewis bases with properties as strong σ-donors and weak π-acceptors. In the last two decades, NHCs have become ubiquitous ligands in organometallic chemistry[2] and they also act as organocatalysts[3,4] in the absence of metals.

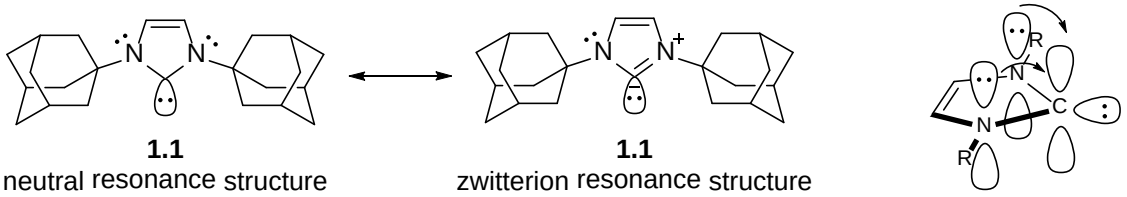
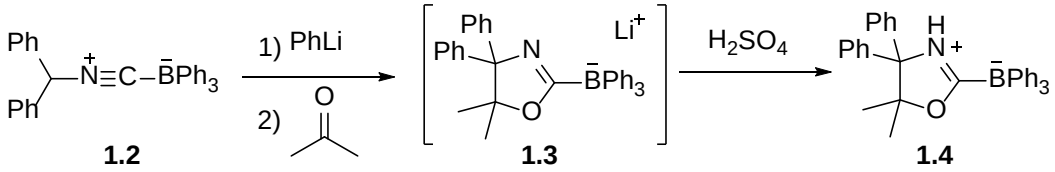


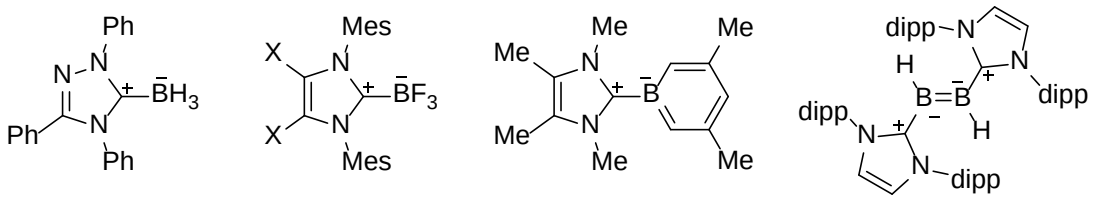
Figure 1.1 Two resonance structures of diAd-Imd **1.1** and simplified orbital picture

Long before free NHCs were isolated, the first NHC-borane complex was prepared in 1967 by Bittner.[5] In-situ generated isonitrile-triphenylborane complex **1.2** reacts with base and acetone to give borate anion **1.3**. It was protonated to produce oxazolidin-2-ylidene triphenylborane complex **1.4** (Scheme 1.1).



Scheme 1.1 The synthesis of the first NHC-borane complex **1.4**

Over the next four decades, there were scattered reports that other NHC-boranes were prepared, including complexes of oxazole-2-ylidenes and N-substituted imidazoles (Figure 1.2). New NHCs were trapped by common boron Lewis acids to obtain new complexes, such as 1,2,4-triazole-5-ylidene-borane **1.5**[6] and BF_3 complexes **1.6a** and **1.6b**[7]. Also, NHCs were used to stabilize unusual and reactive boron species, for example, borabenzene **1.7**[8] and diborene **1.8**.[9]

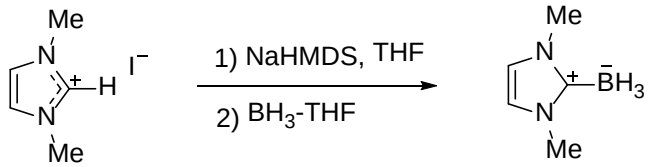


1.5 **1.6a** X = H **1.6b** X = Cl **1.7** **1.8**

Figure 1.2 Representative examples of NHC-borane complexes synthesized before 2007

Starting in 2007, systematic studies of NHC-boranes blossomed rapidly with the research focused on understanding the reactivity of NHC-boranes and on obtaining new functionalized NHC-boranes. NHC-boranes are emerging as attractive reagents for radical,[10] ionic,[11] and organometallic reactions[12] and as co-initiators for polymerizations.[13,14] Meanwhile, much new main group chemistry has appeared with unusual NHC-boranes featured both in stable bonding patterns and in highly reactive intermediates.

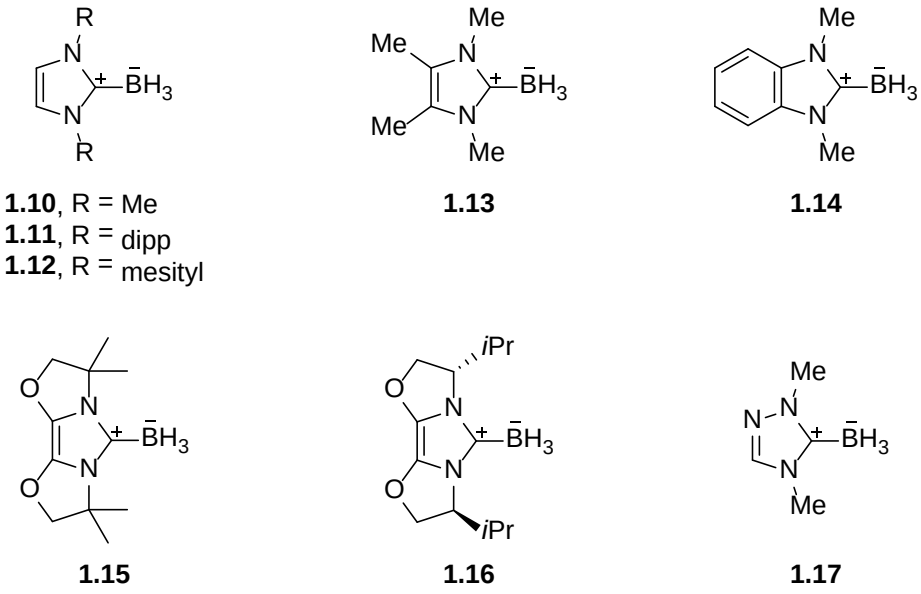
The most common way to prepare NHC-boranes is by direct complexation of a stable carbene with a borane source. Stable imidazolylidene carbenes are the most common, and they are usually generated in situ by the deprotonation of the corresponding imidazolium salt.[15] The preparation of diMe-Imd-BH_3 **1.10** shown in Scheme 1.2 is typical. Deprotonation of salt **1.9** with NaHMDS provides the corresponding carbene. Addition of BH_3-THF then evaporation of solvent provides complex **1.10** as a white solid in 79% yield. NHC-borane complexes are usually purified by crystallization or flash chromatography.



1.9 **1.10**, 79%

Scheme 1.2 Representative synthesis of an NHC-borane

Over the last five years, the Curran and Lacôte groups have prepared a variety of NHC-boranes,[16] and a selection of structures is shown in Figure 1.3. There are imidazolylidene-boranes bearing alkyl (methyl, **1.10**) groups as well as substituted aryl groups (**1.11**, **1.12**). C4- and C5-substituents on the imidazolidene ring are readily incorporated (**1.13**). Additional fused rings can be introduced (**1.14**). Boranes from achiral and chiral Glorius carbenes (**1.15**, **1.16**) as well as triazolylidenes (**1.17**) are also readily accessible.



1.10, R = Me
1.11, R = dipp
1.12, R = mesityl

1.13 **1.14**

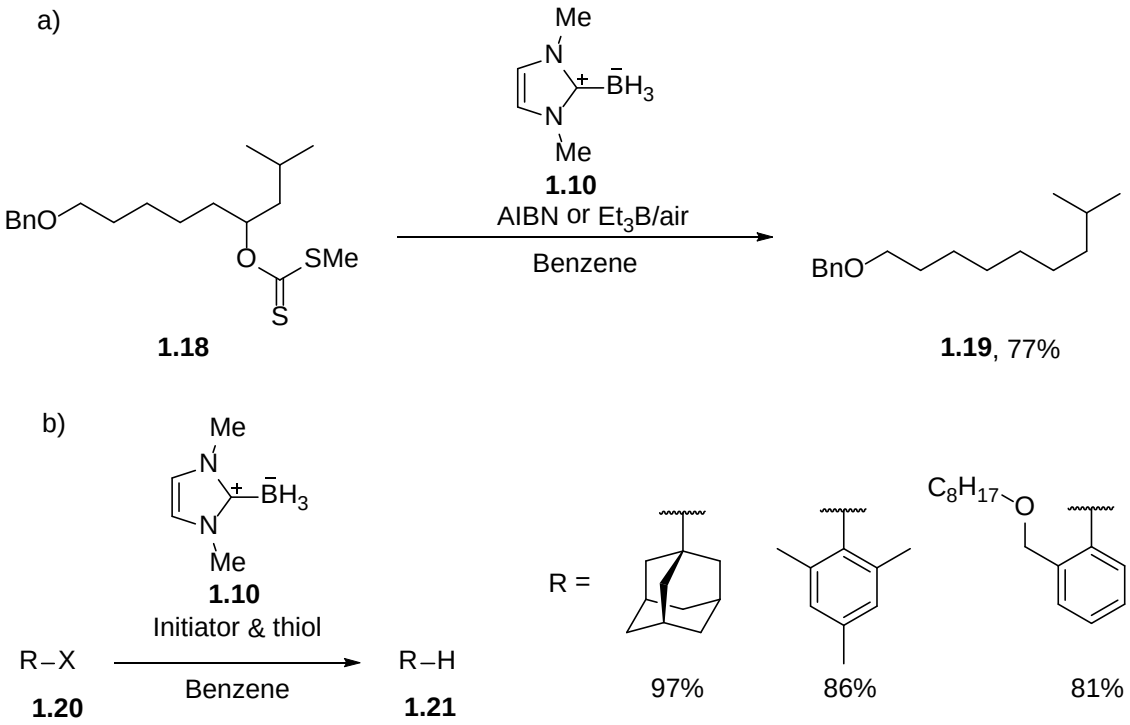
1.15 **1.16** **1.17**

Figure 1.3 Examples of NHC complexes of borane

Complexes of NHC-BH_3 are remarkably robust. They are typically white solids that are stable to air and water, strong base, and mild acid. They resist dissociation to release reactive BH_3 even under relatively forcing conditions. They can be treated as if they were standard organic compounds. These features make them attractive as the reagents for organic synthesis and as the starting points for the preparation of substituted NHC-boranes.

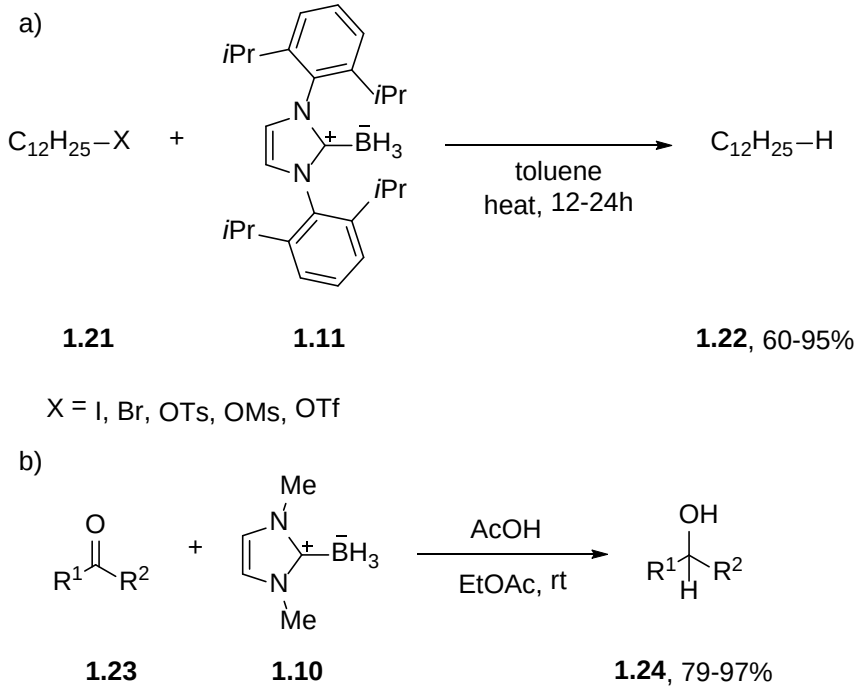
1.1.2 Reactivity and functionalization of NHC-boranes

The first use of NHC-boranes as synthetic reagents was for the radical chain reduction of xanthates and related functional groups.[10] Representative examples are shown in Scheme 1.3. Xanthate **1.18** was reduced to corresponding alkane **1.19** by diMe-Imd-BH_3 **1.10** in good yield (Scheme 1.3a).[17] Radical reductions of the halides by **1.10** are limited to alkyl precursors that have electron-withdrawing groups near the halides. Thiols were used to accelerate the radical hydrogen atom transfer reaction. In this way, adamantyl and aryl halides **1.20** can be reduced efficiently (Scheme 1.3b).[18]



Scheme 1.3 NHC-boranes used in radical reactions

The B-H bonds of NHC-boranes have some hydridic character. So they can also be used as ionic reducing agents. Dipp-Imd-BH_3 **1.11** can reduce aliphatic halides and sulfonates **1.21** simply by heating (Scheme 1.4a).[11] Such reductions occurred in the absence of radical initiators, and radical-probe experiments were negative. These experiments support an ionic mechanism. Horn and Mayr measured the nucleophilicity parameter (*N*) of **1.10** and **1.11** and found that both were good hydride donors.[19] The *N* value for **1.10** is comparable to that of an anionic reagent such as $NaCNBH_3$ and higher than the *N* values of common neutral hydride donors such as silanes, stannanes, dihydropyridines, and amine boranes. Meanwhile, diMe-Imd-BH_3 **1.10** serves as practical hydride donors for the reduction of aldehydes and ketones **1.23** in the presence of acetic acid. Primary and secondary alcohols **1.24** were formed in good yields under ambient conditions (Scheme 1.3b).[20]



Scheme 1.4 NHC-boranes used in ionic reactions

The study of carbene-boranes as reactants has led to the synthesis of diverse stable compounds with unusual boron substituents and bonding patterns. Whenever the needed boranes (BH_2R, BHR^1R^2) are available by hydroboration or other means, direct complexation of NHCs with substituted boranes can be used to introduce additional boron substituents (Figure 1.4, top side).[21] However, because trivalent boranes are Lewis acids, many functional groups are not compatible. So when R is functionalized, the complexation route is often not practical. Functionalization of the parent NHC-BH_3 complexes is the other route to obtain substituted NHC-boranes (Figure 1.4, bottom side). These NHC-borane complexes can undergo various transformations to introduce boron-substituents in place of B-H bonds. Typically, this route is more feasible because the precursor complexes with sp^3-hybridized boron are stable.

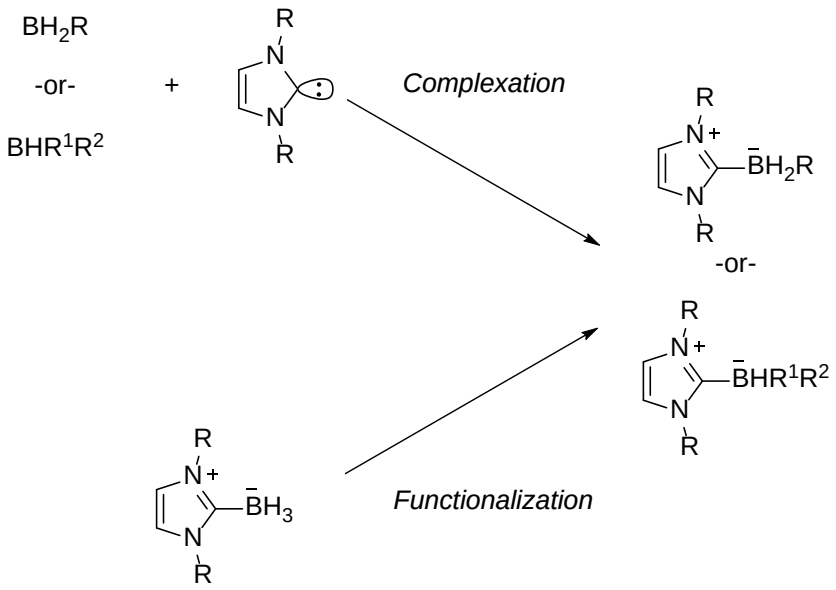
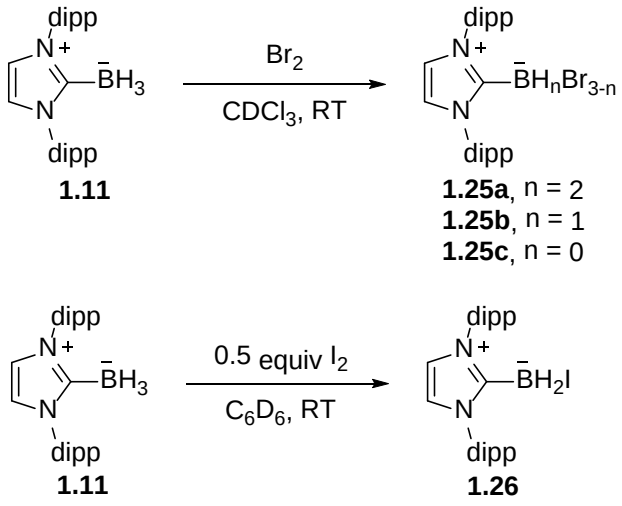


Figure 1.4 Routes to *B*-functionalized NHC-boranes

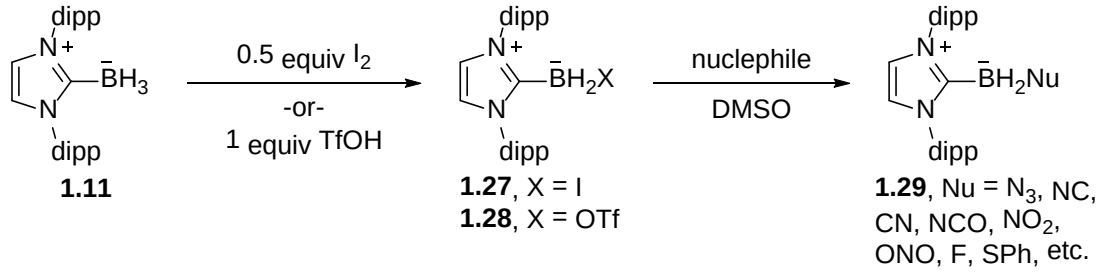
In the last five years, Curran, Lacôte and coworkers have developed several methods to synthesize *B*- functionalized NHC-boranes from parent NHC-BH_3 complexes. NHC-boranes can

react with a diverse array of eletrophiles to give substitution products. For example, dipp-Imd-BH_3 **1.11** reacts with an assortment of halogenating reagents including *N*-bromosuccinimide (NBS), *N*-iodosuccinimide (NIS), bromine, and iodine (Scheme 1.5).[22] Mono-, di-, and trisubstitution reactions are possible, and selectivities are variable.



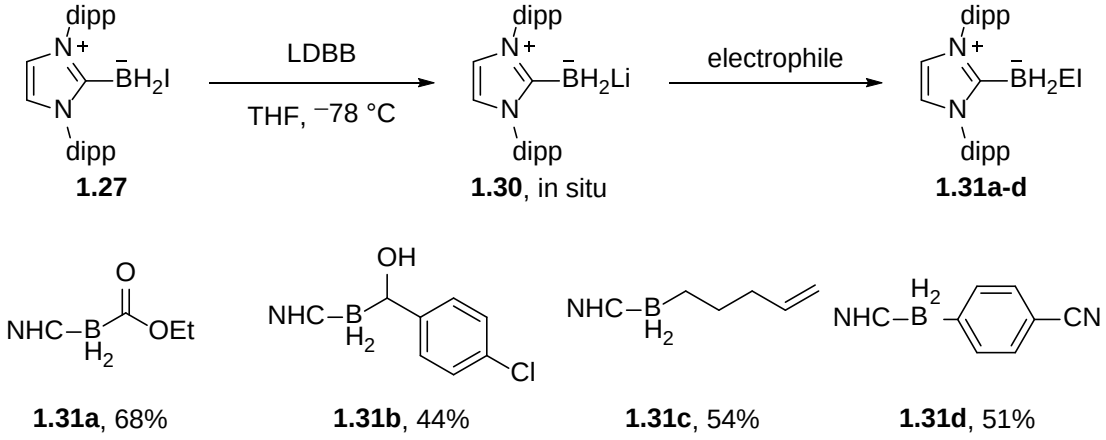
Scheme 1.5 Examples of electrophilic halogenation reactions

Halo- and sulfonate-substituted NHC-boranes **1.27** and **1.28** can undergo nucleophilic substitution on boron to give more *B*-substituted compounds. A diverse collection of substituted NHC-boranes **1.29** become available, including boron halides, cyanides, sulfur derivatives, azides, isonitriles, isocyanates, nitro compounds, nitrous esters and other derivatives (Scheme 1.6).[22]



Scheme 1.6 Examples of nuclephilic substitutions of boron triflate and boron iodide

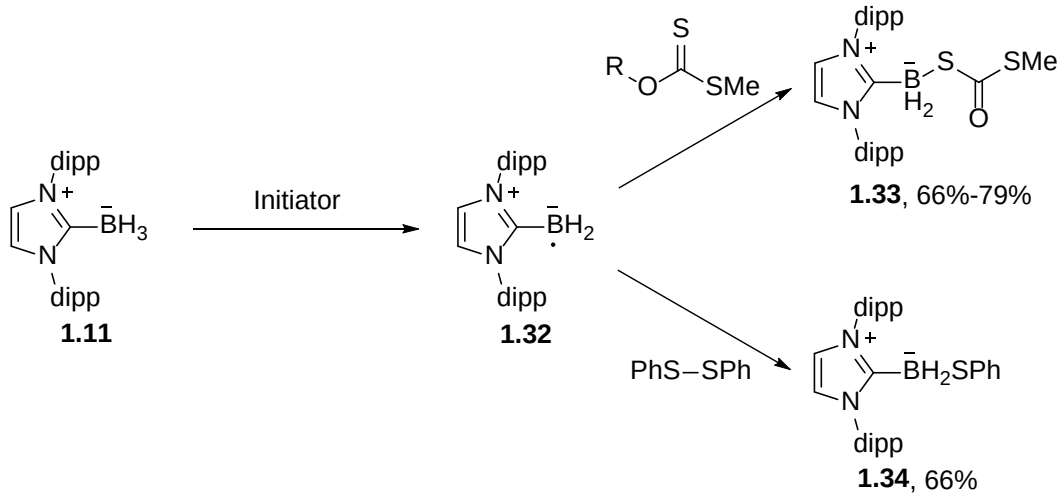
Reactions of NHC-boryl reactive intermediates, such as boryl radicals, boryl anions and borenium ions also offer opportunities to make functionalized NHC-boranes. An NHC-boryl anion can be generated in situ by reductive metalation of **1.38** with lithium di-*tert*-butylbiphenyl (LiDBB). The anion **1.41** was trapped by a wide variety of eletrophiles to provide products **1.42**, including those of acylaction, hydroxyalkylation, alkylation and arylation (Scheme 1.7).[23]



Scheme 1.7 Generation and trapping of an NHC-boryllithium reagent

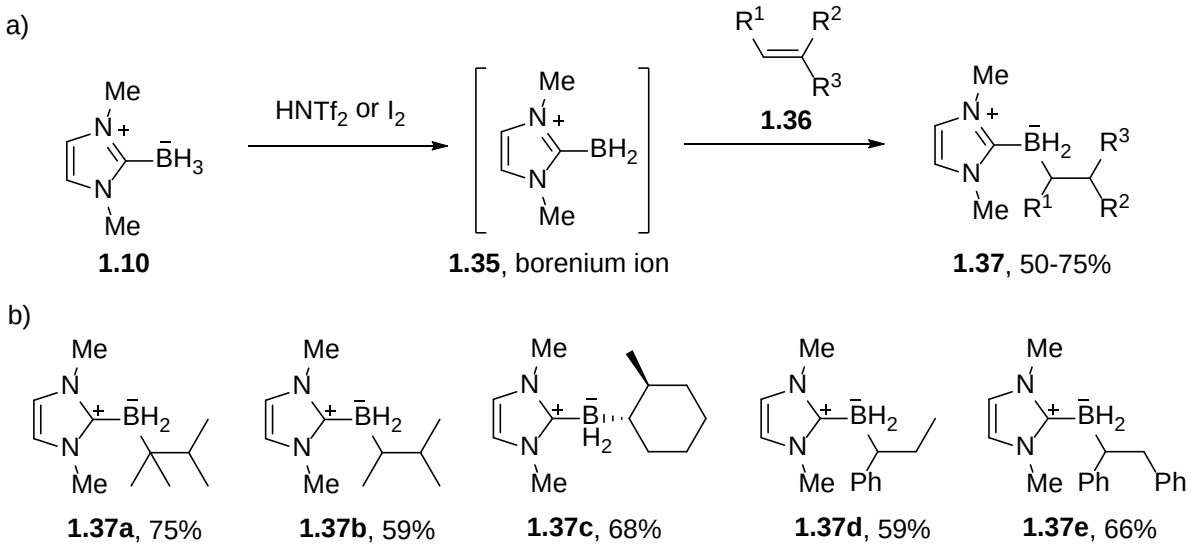
Because of the relatively low bond dissociation energy of B-H bonds of NHC-borane complexes,[24] cleavage of the B-H bonds gives an NHC-boryl radical **1.32**. Sulfur-substituted

NHC-borane **1.33** and **1.34** can be made by radical addition of xanthates[17] and disulfides[25] (Scheme 1.8).



Scheme 1.8 Generation of NHC-boryl radical and its reactions with xanthates and disulfides

NHC-BH_3 complexes do not directly hydroborate alkenes; however, this reaction can be catalyzed by borenium ions. By treating with triflimide ($HNTf_2$)[26] or iodine (I_2),[27] a borenium ion **1.35** or a species that reacts like a borenium ion can be formed. The borenium ion **1.35** reacted with alkenes **1.36** to form the hydroboration products **1.37** in good yield (Scheme 1.9).

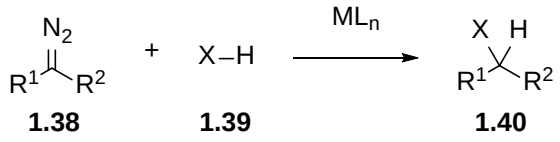


Scheme 1.9 Generation of borenium ion and hydroboration of alkenes

By the methods described above, various stable *B*-functionalized NHC-boranes were obtained. The development of these methods has helped to expand our knowledge about NHC-boranes. At the onset of this project, we wondered whether new B-substituted NHC boranes could be made by B-H insertion reactions of reactive carbenes.

1.1.3 Reactive carbene insertions into X-H bonds

Transition metal catalyzed insertions of in situ generated carbenes from diazocompounds into the element-hydrogen bonds (X-H, X = C, Si, O, N, S, *etc*.) are efficient tools for the construction of carbon-carbon or carbon-heteroatom bonds (Scheme 1.10).[28] Benefiting from mild reaction conditions and high efficiency, transition metal catalyzed X-H insertion reactions have been widely used in organic synthesis.[29–37]



1.38 **1.39** **1.40**

Scheme 1.10 Transition metal catalyzed X-H insertion reactions

A generally accepted insertion mechanism includes the formation of a metal carbene intermediate **1.41** by transition metal mediated decomposition of diazo compound **1.38**. The reactive eletron-deficient metal carbene **1.41** inserts into an X-H bond of **1.39** to give product **1.40** (Figure 1.5, part a). The X-H bond insertions can be divided into two types according to the polarity of the X-H bond (Figure 1.5, part b): low polarity (X = C, Si) and high polarity (X = O, N, S). Insertions of metal carbene into the low polarity bond of C-H or Si-H are proposed by a concerted process through transition state **A**, in which C-C bond (or Si-C bond) formation and C-H bond formation occur simultaneously with the dissociation of metal catalyst, affording product **1.40**. In contrast, the insertions into more polar X-H bonds, such as N-H, O-H, S-H bonds, are conjectured to react in a stepwise process through ylide intermediates **C** followed by a 1,2-proton shift.

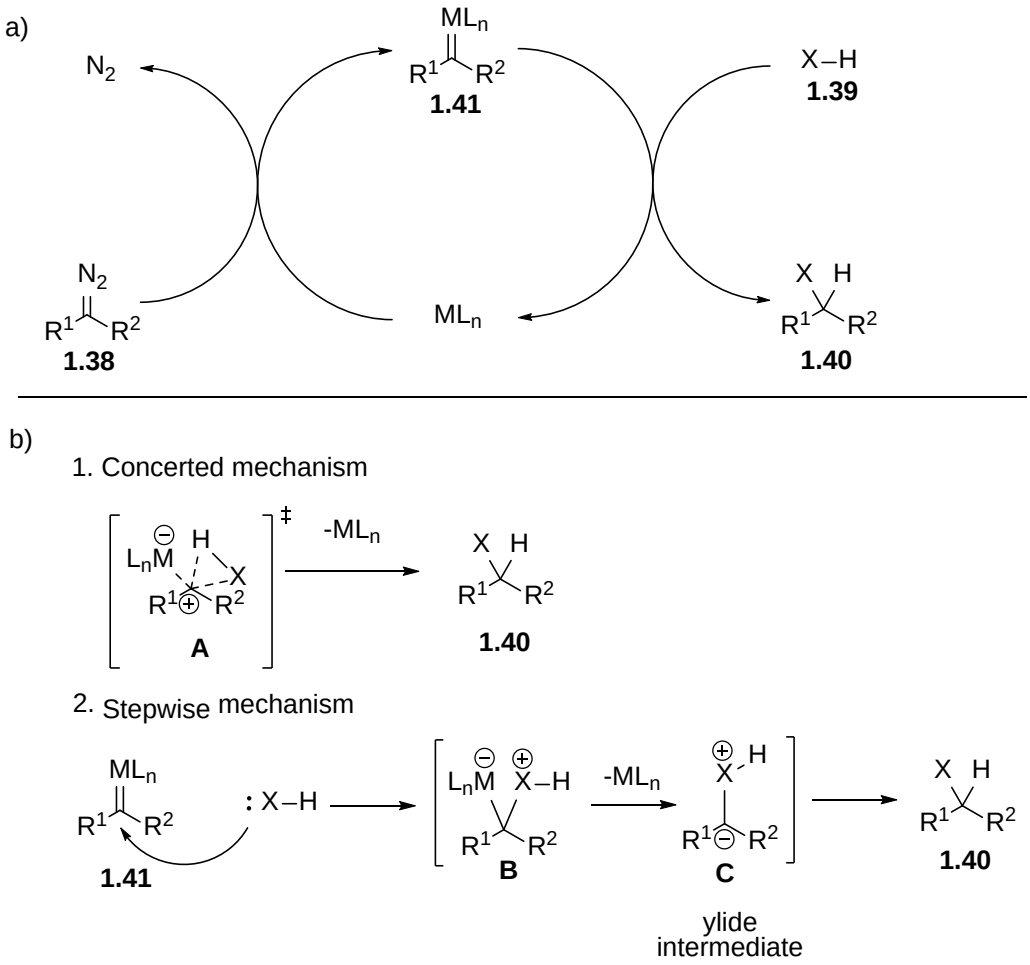


Figure 1.5 Mechanisms of transition metal catalyzed X-H insertion reactions

Among these, the insertion of transient carbenes into C-H bonds has been studied most because of its potential in forming C-C bonds. Reactions of thermally or photochemically generated carbenes have been studied in detail;[38,39] however, few of these reactions have shown good synthetic potential. Meanwhile, carbene generation can occur from diazoalkanes photochemically and thermally[40] or by the use of a transition metal. Copper compounds were initially used,[41–43] but few examples were reported that showed generality or synthetic utility.

In late 1970s, Teyssie reported that the intermolecular C-H insertion reactions of ethyl diazoacetate with alkanes was catalyzed by dirhodium(II) tetracetate and related rhodium

carboxylates (Figure 1.6).[44,45] $Rh_2(tfa)_4$ and $Rh_2(9\text{-trp})_4$ gave higher yield than $Rh_2(OAc)_4$. Four regioisomers were formed in the insertion reactions with alkane **1.42** and the ratio varied depending on the catalysts. These seminal studies demonstrated that the dirhodium tetracarboxylates were superior at inducing C-H insertion compared to the older copper catalysts. They also showed that the regioselectivity of insertion reactions was influenced by the catalysts.

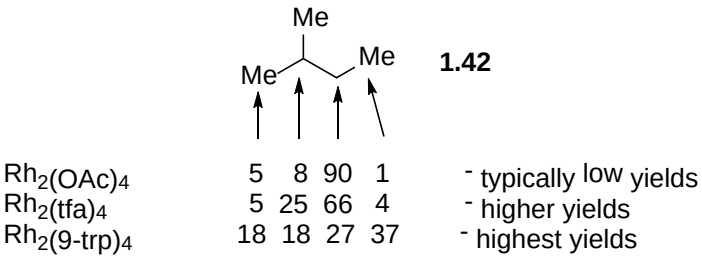
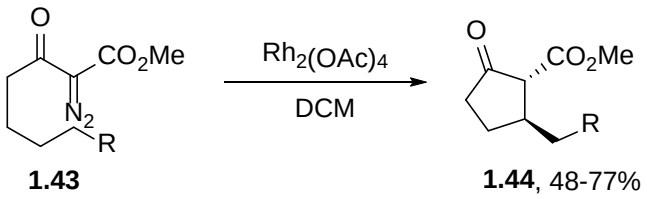


Figure 1.6 Rh-catalyzed reactions of alkanes with ethyl diazoacetate

The substrate **1.42** in Figure 1.6 is solvent and was used in large excess. Because metal carbenes tended to dimerize and mixtures of C-H insertion products were invariably formed in these intermolecular reactions, intermolecular C-H insertions reactions on 1/1 stoichiometries were considered to be not synthetically useful for a time. Wenkert[46] and Taber[47] addressed these problems with a series of investigations on the intramolecular version of these reactions. Diazo compounds **1.43** undergoes C-H insertion reactions to form five-membered ring ketone **1.44** in good yields (Scheme 1.11). These reactions also demonstrated the synthetic advantages of dirhodium tetraacetate as a catalyst.



1.43 **1.44**, 48-77%

Scheme 1.11 Intramolecular C-H insertion catalyzed by $Rh_2(OAc)_4$

In these early years, the extraordinary preference for the formation of five-membered cyclopentanone rings emerged,[48] as did regiochemical preference for insertion into a tertiary C-H bond over a secondary C-H bond.[49] Insertion into a C-H bond of a stereocenter occurred with retention of configuration.[50] And heteroatoms, such as oxygen and nitrogen, activated adjacent C-H bonds for insertion.[51]

The reactivity of metal carbenes is defined by the substituents that adorn the carbenes. Hence the carbenes have been classified according to the substituents adjacent to the carbene center (Figure 1.7).[29] The acceptor- and aceeptor/acceptor-carbenes (**1.45** and **1.46**) are highly reactive species because the acceptor groups do not stabilize the highly electrophilic carbene center. The majority of synthetically useful C-H functionalizations with these types of metal carbenes have been intramolecular versions.[33,52,53] The donor group stabilizes the electron-deficient metal carbene **1.47** through resonance and attenuates its reactivity.[54] A variety of substituted aryl and vinyl groups can be employed as the donor group,[29] and this has allowed the intermolecular C-H insertion to evolve from a synthetically limited reaction to broadly useful transformation.[32]

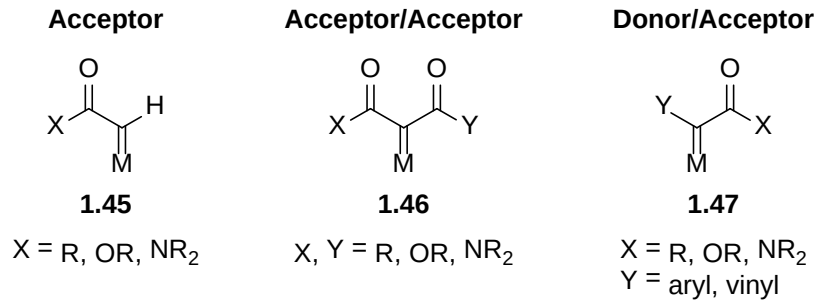
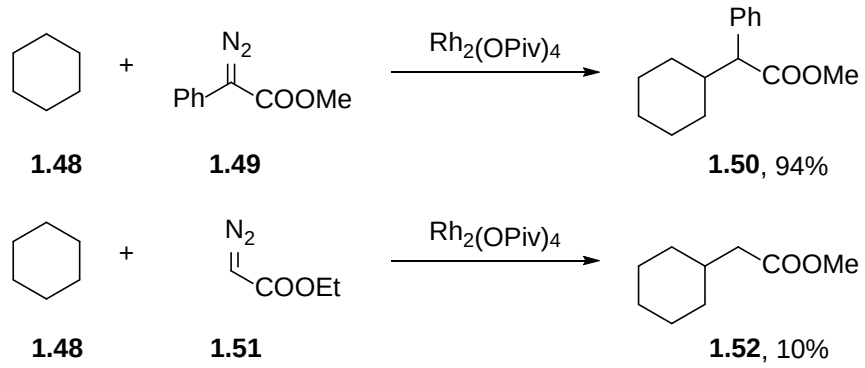


Figure 1.7 The three classes of metal carbenes

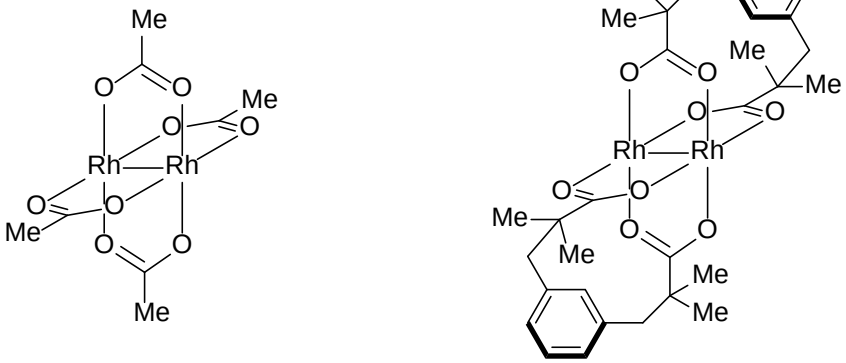
Davies embarked on comprehensive investigations of the scope of the intermolecular C-H insertion reactions.[29,31] It was demonstrated that highly regioselective insertion reactions could be achieved with aryl- and vinyldiazoacetates in metal carbene reactions.[55] By using donor-acceptor diazo compound **1.49**, the C-H insertion product **1.50** was formed in good yield. In contrast, by using ethyl diazoacetate **1.51**, most of the metal carbenes were dimerized, and only 10% desired C-H insertion product **1.52** was obtained (Scheme 1.12).[56]



Scheme 1.12 Intermolecular C-H insertion reactions

Various catalysts have been investigated for the transient carbene insertion reactions of a C-H bond. Copper catalysis dominated the literature before the advent of dirhodium tetraacetate.[42] However, copper catalysts tend to be highly electrophilic. They typically generate

metal carbenes that are too reactive to undergo selective C-H activation reactions. Since the discovery of dirhodium(II) compounds,[57] they have been the most common and most versatile catalysts for C-H insertion reactions.[28,48] A major factor is due to the dirhodium bridge caged within a "lantern" structure, such as $Rh_2(OAc)_4$ **1.53**.[58–60] The structure consists of a Rh-Rh singly bound cluster surrounded by four acetate ligands, each of which is bonded to both rhodium atoms (Figure 1.8). Rhodium carbenes are catalytically generated in situ and the carbene itself is never isolated. The mechanism for the generation of the carbene results from σ-bond formation between the metal and the diazo compound followed by loss of nitrogen to give the carbene intermediate as indicated in Figure 1.9.[61] In the reactions with diazo compounds, only one of the two rhodium atoms functions as a carbene-binding site; the second rhodium atom assists the C-H insertion reaction by acting as an electron sink to enhance the electrophilicity of the carbene moiety and facilitate cleavage of the Rh-C bond on completion of the reaction.



1.53, $Rh_2(OAc)_4$ **1.54**, $Rh_2(esp)_2$

Figure 1.8 Representative achiral rhodium(II) catalysts

The intact "lantern" structure is crucial for catalysis. However, direct evidence has been provided that the dinuclear Rh catalyst undergoes structural changes within minutes of initiating

the reaction. Tetracarboxylate Rh dimers participate freely in ligand exchange reactions. Carboxylate detachment from the dinuclear Rh core is thought to be responsible for catalyst degradation during the insertion reactions.[62,63] In order to avoid the decomposition of the catalysts, $Rh_2(esp)_2$ catalyst **1.54** was developed (Figure 1.8). The joining of two carboxylate ligands through an appropriately spaced linker confers added stability to these complexes because the chelate effect disfavors complete ligand dissociation from the metal center.[62]

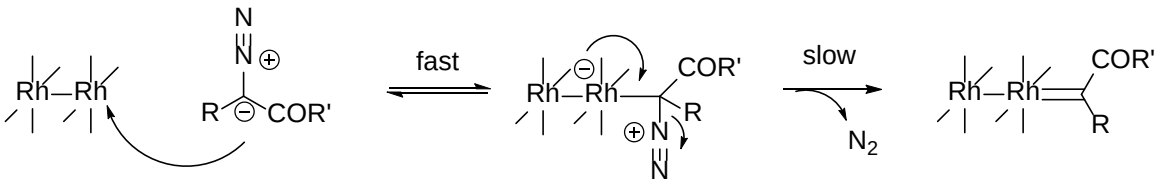
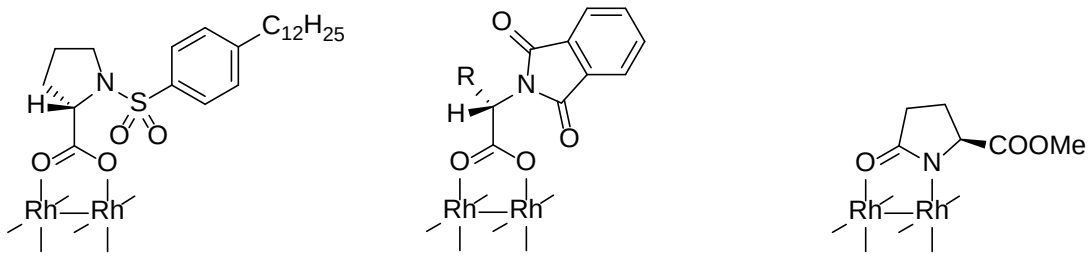


Figure 1.9 Mechanism of rhodium catalyzed carbene formation

Building on initial findings from achiral catalysts, two types of chiral rhodium(II) complexes have been developed for enantioselective catalysis in C-H insertion reactions. They are rhodium(II) carboxylates[64–66] and rhodium(II) carboxamidates.[28] The carboxylates are built upon *N*-protected amino acid templates with four carboxylate ligands symmetrically positioned around the dirhodium framework. Rh_2(*S*-DOSP)$_4$ **1.55**[67] and Rh_2(*S*-PTAD)$_4$ **1.56**[68] are representatives in this category (Figure 1.10). Their reactivities toward diazo decomposition are often greater than those of rhodium acetate or rhodium octanoate. And they are optimal for intermolecular C-H insertion reactions. By using Rh_2(*S*-DOSP)$_4$ **1.55** as the catalyst, donor-acceptor diazo compound **1.58** inserted into the C-H bond next to the nitrogen atom of Boc protected pyrrolidine **1.59** to form product **1.60** in excellent yield and enantioselectivity (Scheme 1.13, part a).[54] The carboxamides are constructed from lactams derived from amino acids. Generally they are more rigid than rhodium carboxylates. And they are often the best catalysts

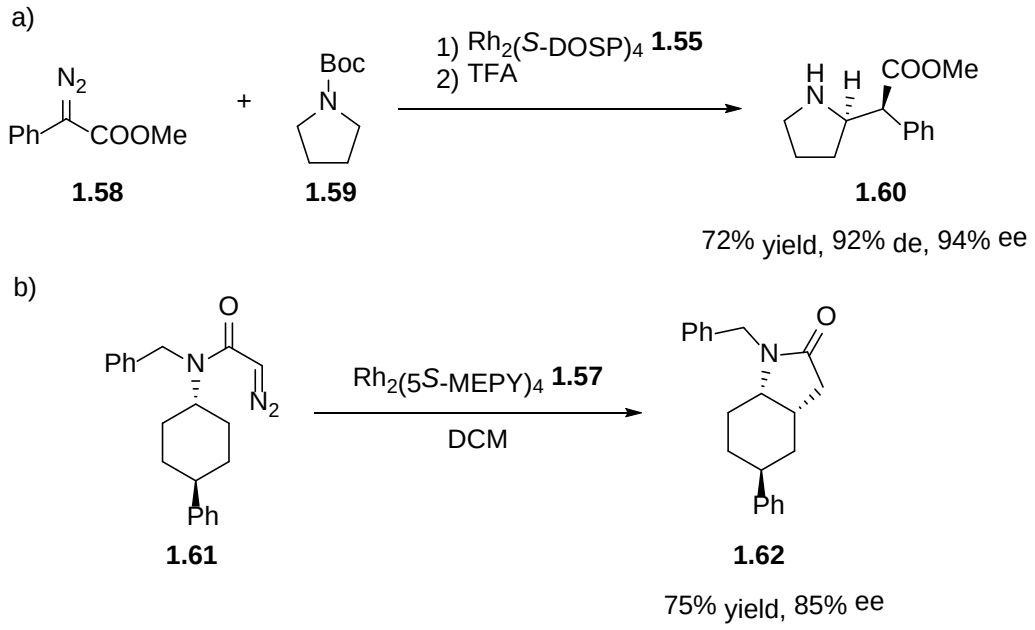
for enantioselective intramolecular C-H insertion reactions.[33] $Rh_2(5S\text{-MEPY})_4$ **1.57** are effective for highly enantioselective intramolecular insertion reactions of diazoacetamides **1.61** to form γ-lactam **1.62** (Scheme 1.13, part b).[69]



1.55, $Rh_2(S\text{-DOSP})_4$ **1.56**, $Rh_2(S\text{-PTAD})_4$ **1.57**, $Rh_2(5S\text{-MEPY})_4$

Figure 1.10 Representative chiral rhodium(II) catalysts

Overall, transient carbene insertions into C-H bonds are powerful reactions to build new C-C bonds. Various catalysts have been developed to promote the reactivity and to construct new stereogenic centers.

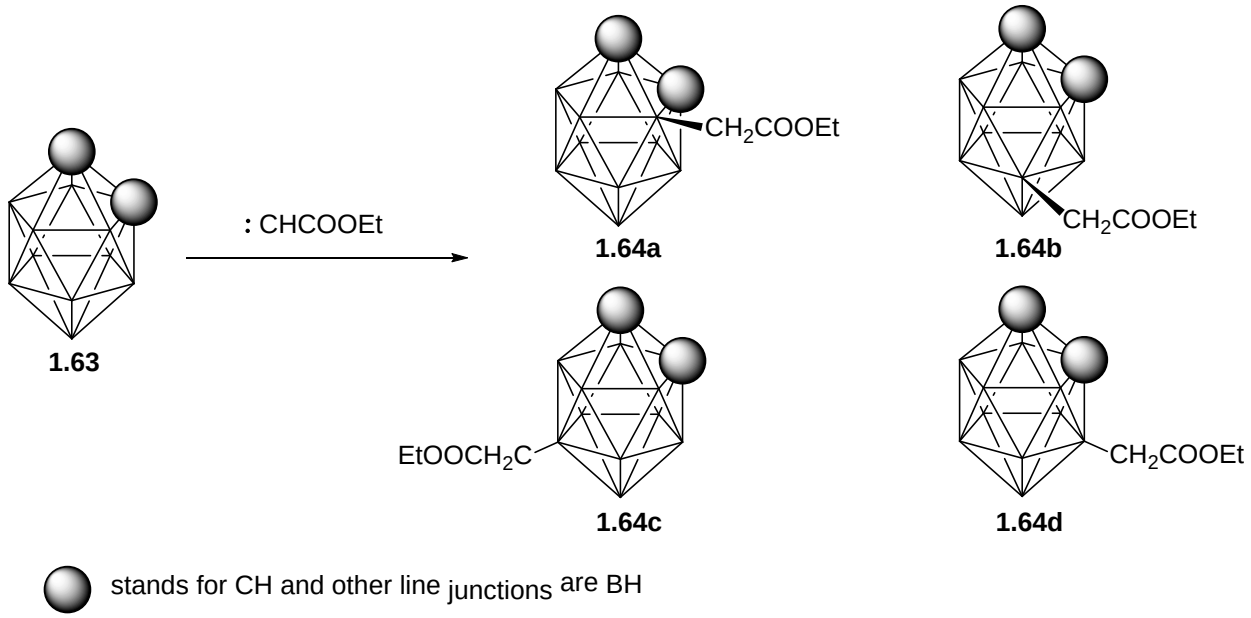


Scheme 1.13 Examples of enantioselective C-H insertion reactions

1.1.4 Carbene insertions of B-H bonds of borane-Lewis base complexes

Compared to C-H bond insertion reactions, the literature on reactions of B-H bonds with carbenes is sparse. The B-H bonds in free boranes are electron-deficient. So they do not readily undergo insertion with electron-deficient Fischer-type metal carbenes.

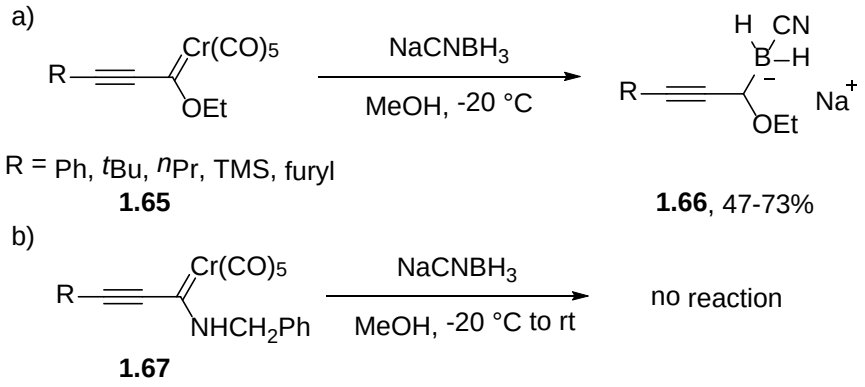
Two isolated examples of insertion reactions of electron-rich B-H bonds have been reported. Irradiation of ethyl diazoacetate (N_2CHCO_2Et) gave carbethoxylcarbene ($:CHCO_2Et$), which then inserted into the B-H bonds of an *o*-carborane **1.65** in low yield (Scheme 1.14).[70] Several regioisomers **1.64a-d** were found, and the product ratio was determined by GC-MS. No C-H insertion products were detected.



Scheme 1.14 B-H bond insertion of *o*-carborane

Fischer alkynylcarbene complexes **1.65** reacted with $NaCNBH_3$ to produce propagyl cyanoborohydrides **1.66** derived from the insertion of the carbene ligand into the B-H bond.[71]

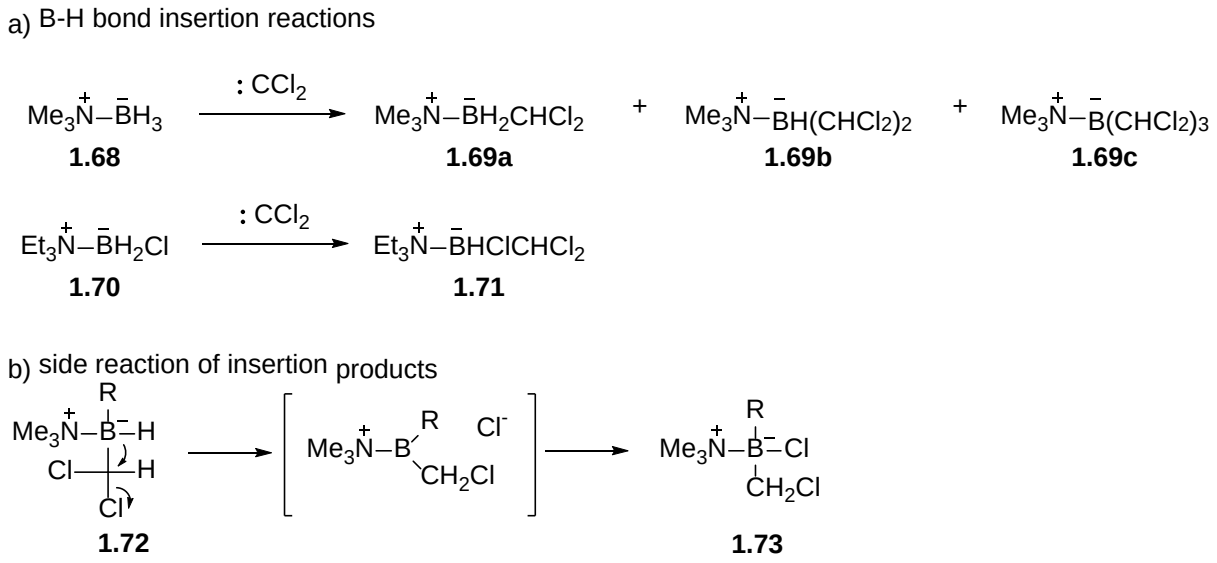
This reaction occurs because of the electrophilicity of alkynylcarbene complexes **1.65** (Scheme 1.15, part a). No reaction took place if the electrophilicity of the carbene carbon was diminished by the presence of a strong electron-donating group. For example, the aminocarbene **1.67** was completely unreactive toward $NaCNBH_3$, even when the reaction was carried out at room temperature (Scheme 1.15, part b).



Scheme 1.15 B-H bond insertion by Fisher alkynylcarbene complexes

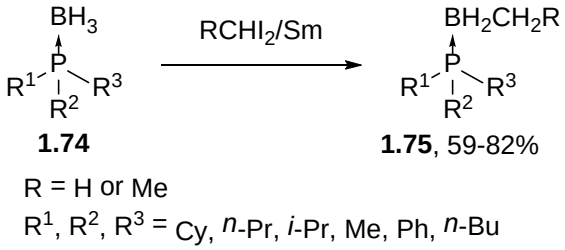
Upon formation of complex with an amine or a phosphine, the B-H bond of borane becomes more electron-rich. These amine-borane or phosphine-borane complexes provide an opportunity to achieve B-H bond insertion with electron-deficient metal carbenes.[72–74] One example is shown in Scheme 1.16a. Treatment of amine-borane **1.68** with a large excess (40 equiv) of dichlorocarbene, which was generated by an α-elimination reaction, gave a mixture of B-H bond insertion products **1.69a-c**. The reaction cannot be stopped after the first insertion for all amine- and phosphine-BH_3 complexes. The presence of a halogen substituent on boron prevented a second insertion of the carbenes. Amine borane complex **1.70** reacted with dichlorocarbene to form only the single insertion product **1.71**. Meanwhile, the resulting

insertion products **1.70** are subject to decomplexation and internal redox reactions (Scheme 1.15, part b) and are not especially stable.[74]



Scheme 1.16 B-H bond insertion of amine- and phosphine-boranes

The samarium carbenes derived from CH_2I_2 and CH_3CHI_2 insert into B-H bonds of phosphine-boranes **1.74** to afford phosphine-monomethylborane **1.75** in good yields although P-H insertions are faster (Scheme 1.17).[75] Again, a large excess (7 equiv) of carbene-generating reagents have to be used.



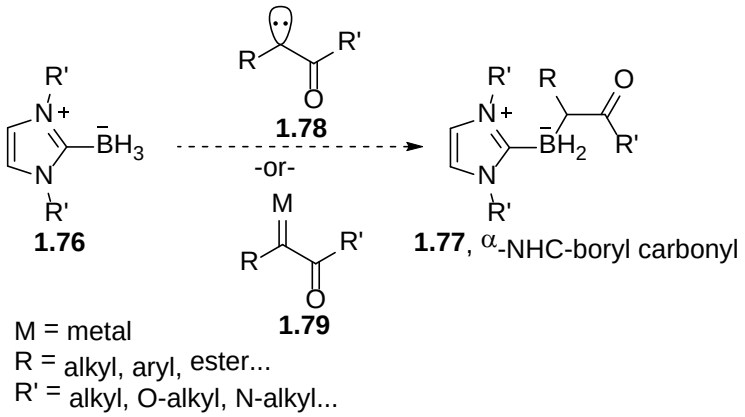
Scheme 1.17 B-H bond insertion of phosphine-boranes with samarium carbenes

In summary, carbene insertions into B-H bonds are rare. The limited examples require a large excess of carbene-generating reagents and sometimes produce unstable insertion products. Just as rhodium catalysts have dramatically improved intermolecular C-H insertion reactions, we hypothesized the B-H insertion reactions can also be promoted by them.

1.2 RESULTS AND DISCUSSION

1.2.1 Reaction design

Compared with amine-boranes, NHC-boranes are a unique class of borane-Lewis base complexes because of their stability. Because NHC-boranes are good hydride donors[19] we hypothesized that they would also be good carbenophiles, reacting especially with transient electrophilic[76] carbenes **1.78** or metal carbenes **1.79** by direct B-H insertion (Scheme 1.18).



Scheme 1.18 Proposed B-H bond insertion of NHC-boranes

The products of such reactions are unknown α-NHC-boryl carbonyl compounds **1.77** with new B-C bonds. These are interesting because these might rearrange by 1,3-boryl shift to boron enolates or behave as nucleophiles themselves on carbon or oxygen.[77] By developing rhodium catalyzed B-H bond insertion reactions of transient carbenes, a new class of *B*-functionalized NHC-boranes could be synthesized. And this new methodology might be a reliable way to make B-C bonds.

1.2.2 Survey of reaction conditions

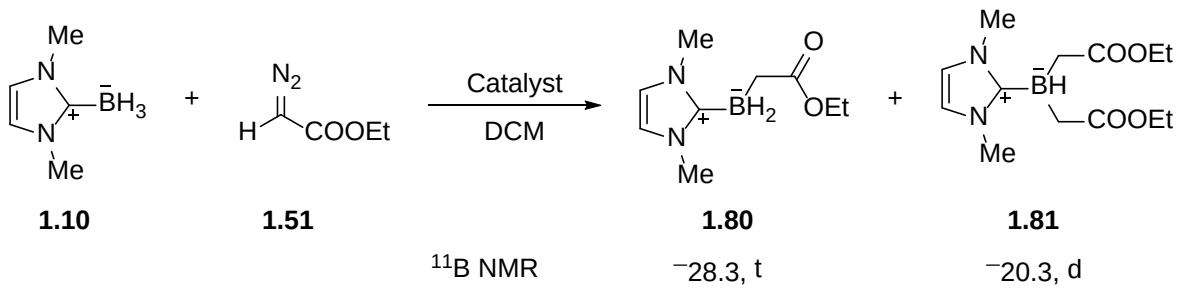
We began the study with the reactions of diMe-Imd-BH_3 **1.10** and commercially available ethyl diazoacetate **1.51**. The common catalyst for C-H insertions $Rh_2(OAc)_4$ **1.53**[58] was tested first. In a typical experiment, a slight excess of diazoacetate **1.51** (1.2 equiv) was added by syringe pump over 4 h to a solution of diMe-Imd-BH_3 **1.10** (1 equiv) and $Rh_2(OAc)_4$ **1.53** (1 mol%) in dichloromethane at 40 °C (Table 1.1, entry 1). The ^{11}B NMR spectrum of the crude product showed a large triplet –28.3 ppm (77%), which we assigned to the insertion product **1.80**. There was also a smaller doublet at –20.3 ppm (17%), which we assigned to the double insertion product **1.81**, along with an even smaller quartet from remaining **1.10** (–37.5 ppm, 6%).

Purification of the crude product by flash chromatography with 1/1 hexane/ethyl acetate provided pure insertion product **1.80** in 62% yield. The resonances for the CH_2 group adjacent to boron and carbonyl group were shielded in both the ^1H (1.62 ppm, broad) and ^{13}C (24.4 ppm, q, J_{CB} = 32 Hz) NMR spectra. The signal of this CH_2 group in the boron-decoupled ^1H NMR spectra is a clear triplet. And the ester carbonyl carbon of **1.80** resonated at 181.1 ppm in ^{13}C NMR spectrum. Meanwhile, the stretch of the carbonyl group on IR showed at 1651 cm^{-1}, which

is also shifted by the boron atom. These observations all support that insertion product **1.80** is an α-NHC-boryl acetate (C-B bond) and not an NHC-boryl enol (O-B bond).

In contrast to the convenient isolation of monoinsertion product **1.80**, the very polar double insertion product **1.81** did not emerge from the column even when 100% ethyl acetate was used as eluent. It is also possible that the double insertion product **1.81** eventually decomposes on the column. This would probably give the corresponding imidazolium salt, which is also very polar. The yield of **1.81** was estimated at 14% based on the ^{11}B NMR spectrum of the crude product.

Table 1.1 Results of representative initial experiments with NHC-borane **1.10** and ethyl diazoacetate **1.51**



1.10 **1.51** **1.80** **1.81**

^{11}B NMR −28.3, t −20.3, d

entry	equiv **1.51**	catalyst (1%)	conv (%)[a]	yield **1.80** (%)[b]	yield **1.81** (%)[a]
1	1.2	$Rh_2(OAc)_4$ **1.53**	94	62	14
2	0.8	$Rh_2(OAc)_4$ **1.53**	75	53	7
3	3.0	$Rh_2(OAc)_4$ **1.53**	96	40	22
4	1.2	$Rh_2(esp)_2$ **1.54**	92	62	12

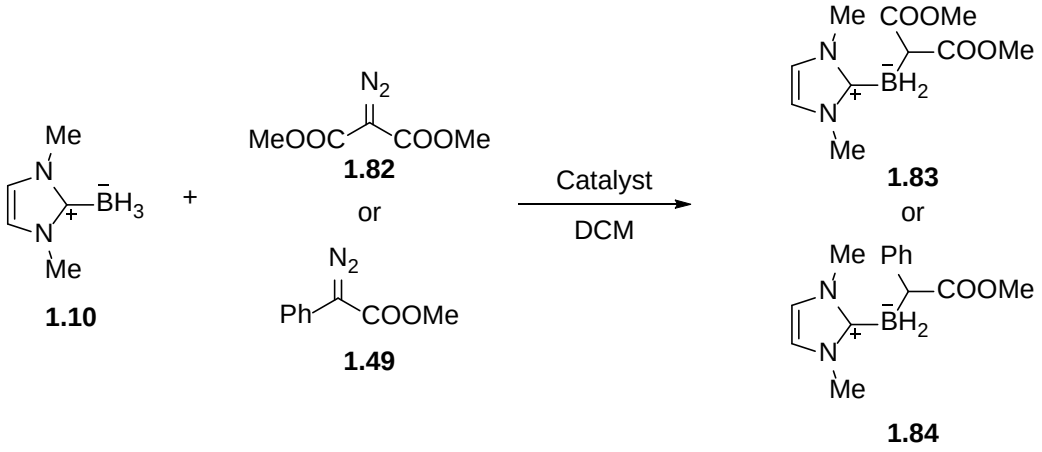
[a] Estimated from the ^{11}B NMR spectrum of the crude product; [b] Isolated by automated flash chromatography

Next we varied the amount of diazoester **1.51** while keeping the catalyst as $Rh_2(OAc)_4$ **1.53**. A reaction with slight deficiency of ethyl diazoacetate **1.80** (0.8 equiv) gave 53% mononisertion product **1.81** and 7% di-insertion product **1.81** along with 25% recovered **1.10** (Table 1.1, entry 2). As before, the yield of **1.80** is isolated by flash chromatography, and the other yields are estimated by ^{11}B NMR spectroscopy. With excess **1.51** (3 equiv, Table 1.1, entry 3), there was less **1.80** (40%), more **1.81** (22%), and only a trace of unreacted **1.10** (4%). On the basis of the results in Table 1.1, we settled on the use of 1.2 equiv of diazo partner for further experiments.

$Rh_2(esp)_2$ **1.54**[78] was also tested with diMe-Imd-BH_3 **1.11** and ethyl diazoacetate **1.80** (Table 1.1, entry 4). It gave similar conversion of diMe-Imd-BH_3 **1.10** (92%) and same yield of single insertion product **1.80** (62%).

These two catalysts, $Rh_2(OAc)_4$ **1.53** and $Rh_2(esp)_2$ **1.54** gave very similar conversion and yield in the reaction of diMe-Imd-BH_3 **1.10** and ethyl diazoacetate **1.51** (compare Table 1.1, entry 1and 4). However, when acceptor-acceptor diazo compound **1.82** reacted with diMe-Imd-BH_3 **1.10**, $Rh_2(OAc)_4$ **1.53** only gave less than 5% conversion to the insertion product **1.83** (Table 1.2, entry 1). When $Rh_2(esp)_2$ **1.54** was applied, we obtained excellent conversion (96%) and good yield of insertion product **1.83** (73%) (Table 1.2, entry 2). Similar results were obtained in the reaction of donor-acceptor diazo compound **1.49** and diMe-Imd-BH_3 **1.10**. With $Rh_2(OAc)_4$ **1.53** as the catalyst, only 11% diMe-Imd-BH_3 **1.10** converted to the insertion product **1.84**, which was isolated in 9% yield (Table 1.2, entry 3). In contrast, excellent conversion (98%) and good yield of insertion product **1.84** (73%) were achieved with $Rh_2(esp)_2$ **1.54**. Therefore, $Rh_2(esp)_2$ **1.54** was chosen as the catalyst for the following reactions.

Table 1.2 Screening catalysts with NHC-borane **1.10** and diazo compound **1.82** and **1.49**



entry	catalyst (1%)	diazo compound	conv (%)[a]	yield **1.83** or **1.84** (%)[b]
1	$Rh_2(OAc)_4$ **1.53**	**1.82**	<5	N.D.[c]
2	$Rh_2(esp)_2$ **1.54**	**1.82**	96	73
3	$Rh_2(OAc)_4$ **1.53**	**1.49**	11	9
4	$Rh_2(esp)_2$ **1.54**	**1.49**	98	74

[a] Estimated from the ^{11}B NMR spectrum of the crude product; [b] Isolated by automated flash chromatography; [c] Not determined

Because the previous reactions all gave high yields, it is difficult to see the effect of the reaction solvents. So reaction solvents were screened in the reaction of diMe-Imd-BH_3 **1.10** and methyl 2-benzyldiazoacetate **1.85**. With dichloromethane as the solvent, the reaction gave **1.86** in 26% yield (Table 1.3, entry 1). The reaction temperature was elevated by switching the solvent from dichloromethane (b.p. = 40 °C) to 1,2-dichloroethane (b.p. = 84 °C). However, the insertion product **1.86** was obtained with lower conversion (22%) and lower yield (20%) (Table 1.3, entry 2). With more polar solvent, acetonitrile, no product was formed (Table 1.3, entry 3). Therefore, we settled on dichloromethane.

Table 1.3 Screening solvents with NHC-borane **1.10** and diazo compound **1.85**

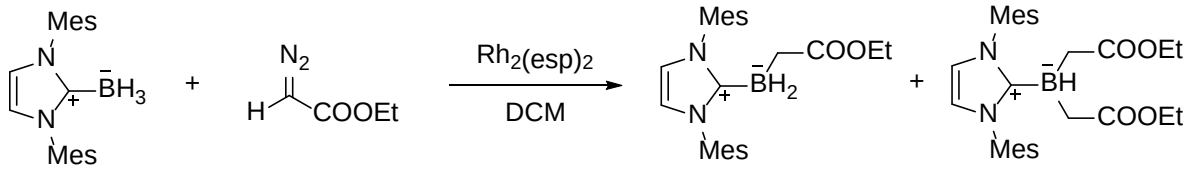
1.10 **1.85**, 1.2 equiv **1.86**

entry	solvent	conv (%)[a]	yield **1.86** (%)[b]
1	dichloromethane	28	26
2	1,2-dichloroethane	22	20
3	acetonitrile	trace	N.D.[c]

[a] Estimated from the ^{11}B NMR spectrum of the crude product; [b] Isolated by automated flash chromatography; [c] Not determined

Finally, we wanted to find out if the conversion of the reaction could be improved by increasing the reaction time. So the reaction with NHC-borane **1.12** and ethyl diazoacetate **1.51** was used to test this parameter. When the reaction time was doubled from 4 h to 8 h, the conversion increased a little from 65% to 71%. But the isolated yield was similar (55% compared with 56%). This increase of conversion without a corresponding increase of yield is because of more significant formation of the double insertion product **1.88**, whose estimated yield increased from 6% to 11% (Table 1.4). As a result, 4 h was used as the optimized reaction time.

Table 1.4 Screening reaction time with NHC-borane **1.12** and ethyl diazoacetate **1.51**



1.12 **1.51**, 1.2 equiv **1.87** **1.88**

entry	reaction time	conv (%)[a]	yield **1.87** (%)[b]	yield **1.88** (%)[a]
1	4 h	65	56	6
2	8 h	71	55	11

[a] Estimated from the ^{11}B NMR spectrum of the crude product; [b] Isolated by automated flash chromatography

Based on the results in Table 1.1-1.4, we settled on the optimal reaction conditions by using a slight excess of diazo compounds (1.2 equiv), 1 mol% $Rh_2(esp)_2$ **1.54** as the catalyst, dichloromethane as the solvent for 4 h reaction time. These conditions were used to study the reaction scope.

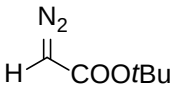
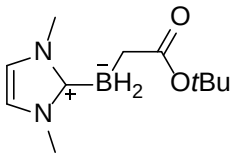
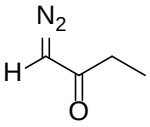
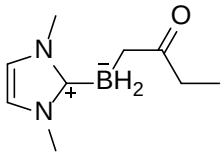
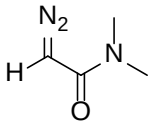
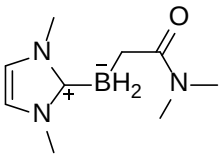
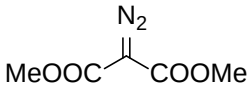
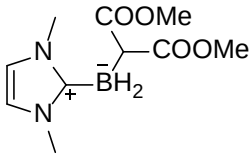
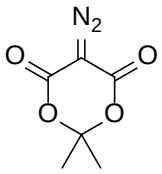
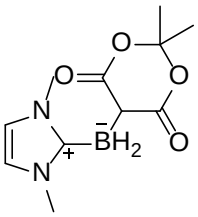
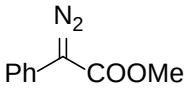
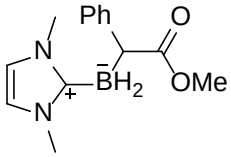
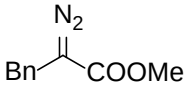
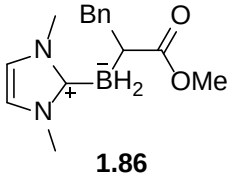
1.2.3 Scope studies

We selected diMe-Imd-BH_3 **1.10** for the initial survey in part because it offered little opportunity for competing bimolecular reaction of the rhodium carbenes with the NHC ring or its sbustituents. We first tested the scope of the reactions of diMe-Imd-BH_3 **1.10** with various diazocarbonyl compounds. The results of representative reactions in this series are summarized in Table 1.5.

When more bulky *tert*-butyl diazoacetate **1.89** was used in the reaction, the conversion was 71% and the yield was 58% (Table 1.5, entry 1). As with substrate **1.51**, small amounts of double insertion products were formed (estimated 11% by ^{11}B NMR spectroscopy) but not isolated. Instead of stabilizing by ester groups, diazo compounds 1-diazobutan-2-one **1.91** and 2-diazo-*N*,*N*-dimethylacetamide **1.93** were stabilized by ketone and amide. The conversion of these two reactions are 66% and 80%, and the yields are 49% and 55%, respectively (Table 1.5, entry 2 and 3). Meanwhile, the yields of double insertion products were estimated as 10% and 19% by ^{11}B NMR spectroscopy. These three single stabilized diazo compounds all gave similar results to ethyl diazoacetate **1.51** (compare Table 1.5, entry 1-3 with Table 1.1, entry 4).

The diazocompounds with additional conjugating substituents were also tested. The acceptor-acceptor diazo compounds, dimethyl diazomalonate **1.82**, produced α-NHC-boryl malonate **1.83** in 96% conversion and 73% isolated yield (Table 1.5, entry 4). The estimated amount of double insertion product was 9%. Similarly, diazodimedone **1.95** provided **1.96** in 83% conversion and 60% isolated yield (Table 1.5, entry 5). And no double insertion product was observed by ^{11}B NMR spectroscopy. The donor-acceptor precursor methyl 2-phenyl-diazoacetate **1.49** gave **1.84** in 98% conversion and 74% isolated yield (Table 1.5, entry 6). The yield of double insertion product was 9% (estimated by ^{11}B NMR spectroscopy). In these three examples, the yield of double insertion products are significantly lower than the previous examples. The two large substituents of the diazo compounds helped slow down the second B-H insertion reaction. Therefore, diazoesters with additional stabilizing substituents gave better conversions and yields.

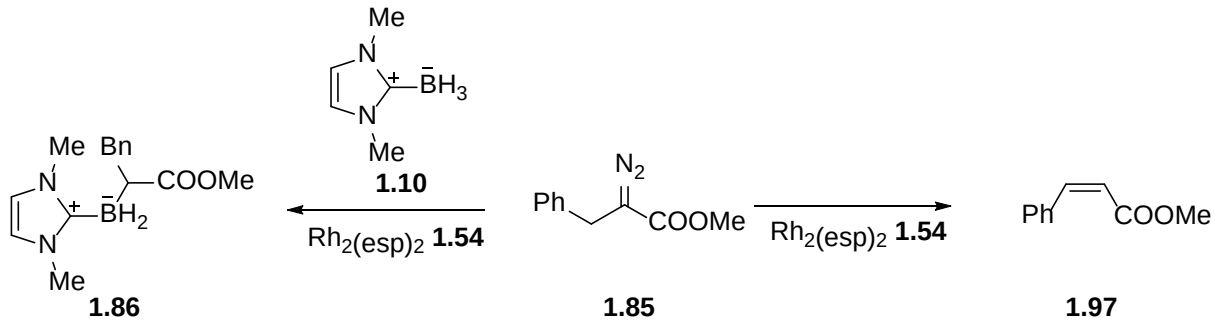
Table 1.5 Scope of the B-H insertion with 1% $Rh_2(esp)_2$: variation of the diazo partner

entry	diazo partner	product	conv.[a]	yield[b]
1	 **1.89**	 **1.90**	71%	58%
2	 **1.91**	 **1.92**	66%	49%
3	 **1.93**	 **1.94**	80%	55%
4	 **1.82**	 **1.83**	96%	73%
5	 **1.95**	 **1.96**	83%	60%
6	 **1.49**	 **1.84**	98%	74%
7	 **1.85**	 **1.86**	28%	26%

[a] Estimated from the ^{11}B NMR spectrum of the crude product

[b] Isolated by automated flash chromatography

In contrast to the success with additional conjugating substituents, the diazo compound bearing an additional alkyl group, methyl 2-benzyldiazoacetate **1.85**, gave **1.86** in only 26% yield (Table 1.5, entry 7). The main problem here is not the formation of di-insertion product but the low conversion; the yield of **1.86** based on recovered starting material is 93% because only 28% of **1.10** was consumed. However, methyl (*Z*)-3-phenylacrylate **1.97** was observed in ^{1}H NMR spectrum of the crude product. Therefore, the reason of the low conversion of **1.10** is the competitive reaction of β-hydride elimination of methyl 2-benzyldiazoacetate **1.85**.[79]



Scheme 1.19 Side reaction of methyl 2-benzyldiazoacetate **1.85**

We next varied the structure of the NHC-carbene partner while holding the diazo partner as ethyl diazoacetate **1.11**. The standard conditions were used with the $Rh_2(esp)_2$ catalyst, and the results are summarized in Table 1.6.

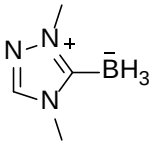
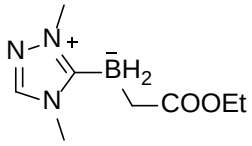
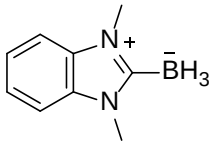
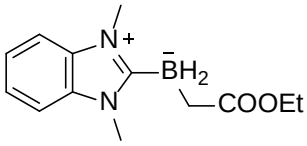
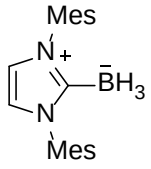
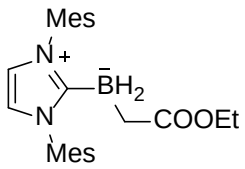
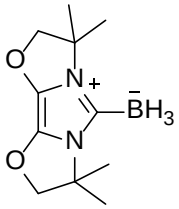
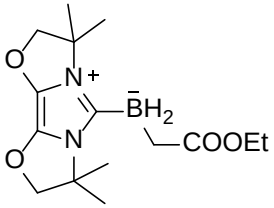
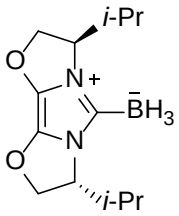
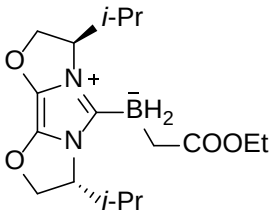
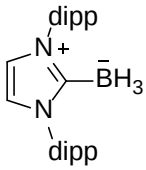
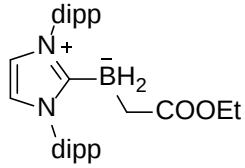
The B-H bond in triazolylidene borane **1.17** is more electron-deficient because of the more electron withdrawing 1,2,4-triazole ring. Conversion was 72% and isolated yield of monoisertion product **1.98** was 52% (Table 1.6, entry 1). Minor amounts of di-insertion products was formed (11% estimated yield). Both the convertion and yield were lower than the ones with diMe-Imd-BH_3 **1.10**. The results of benzimidazolylidene borane **1.14** was similar to dimethylimidazolylidene **1.10**. The reaction of NHC borane **1.14** and ethyl diazoacetate **1.51** gave 80% conversion and 60% isolated yield of monoinsertion products **1.99** (Table 1.6, entry

2). And minor amounts of di-insertion products were formed (19% isolated yield). The similar results (compare Table 1.6, entry 1 and 2 with Table 1.1, entry 4) are because of the comparable steric effect of the substituents on the heterocycles of the NHC-borane partner.

With bulkier substrates dimesitylimidazolylidene borane **1.12**, the conversion of NHC-borane was a bit lower (65%). The isolated yield of monoinsertion product **1.87** (60%) approached the conversions of the precursors (Table 1.6, entry 3). The reaction of tricyclic borane **1.15** and ethyl diazoacetate **1.51** gave 66% conversion and 60% isolated yield of monoinsertion product **1.100** (Table 1.6, entry 4). And with enantiopure tricyclic borane **1.16**, the conversion was 66% and the isolated yield of monoinsertion product **1.101** was 59% (Table 1.6, entry 5, enantiopure). In all these three examples (Table 1.6, entry 3-5), only 5-6% of the di-insertion product was detected in the ^{11}B NMR spectrum of the crude product. Therefore, although the conversions of these reactions were lower with the bulkier substituents on the imidazole ring of NHC, the formation of the di-insertion products were also diminished. In the case of the very hindered dipp borane **1.11**, conversion was 65% and isolated yield of monoinsertion product **1.102** was 63%. And there was no resonance at all for the di-insertion product in the ^{11}B NMR spectrum of the crude product (Table 1.6, entry 6a).

These results suggest that the only significant competing pathway for B-H insertion to **1.11** is reaction of the rhodium carbene with itself or its precursor. This in turn suggests that higher yields might be obtained by increasing the amount of the diazo precursor. This approach failed with the smaller NHC-borane **1.10** because of the di-insertion product was formed competitively (Table 1.1, entry 3). In contrast, a reaction of dipp-Imd-BH_3 **1.11** with 3 equiv of ethyl diazoacetate **1.51** gave complete conversion of **1.11**, and isolated yield of insertion product **1.102** increased from 63% (Table 1.6, entry 6a) to 96% (Table 1.6, entry 6b).

Table 1.6 Scope of the B-H insertion with 1% $Rh_2(esp)_2$: variation of the NHC-borane partner

entry	NHC-BH_3	product	conv.[b]	yield[c]
1	 **1.17**	 **1.98**	72%	52%
2	 **1.14**	 **1.99**	80%	60%
3	 **1.12**	 **1.87**	65%	56%
4	 **1.15**	 **1.100**	66%	60%
5	 **1.16**	 **1.101**	66%	59%
6a 6b[a]	 **1.11**	 **1.102**	65% 100%	63% 96%

[a] 3 equiv of ethyl diazoacetate **1.51**

[b] Estimated from the ^{11}B NMR spectrum of the crude product

[c] Isolated by automated flash chromatography

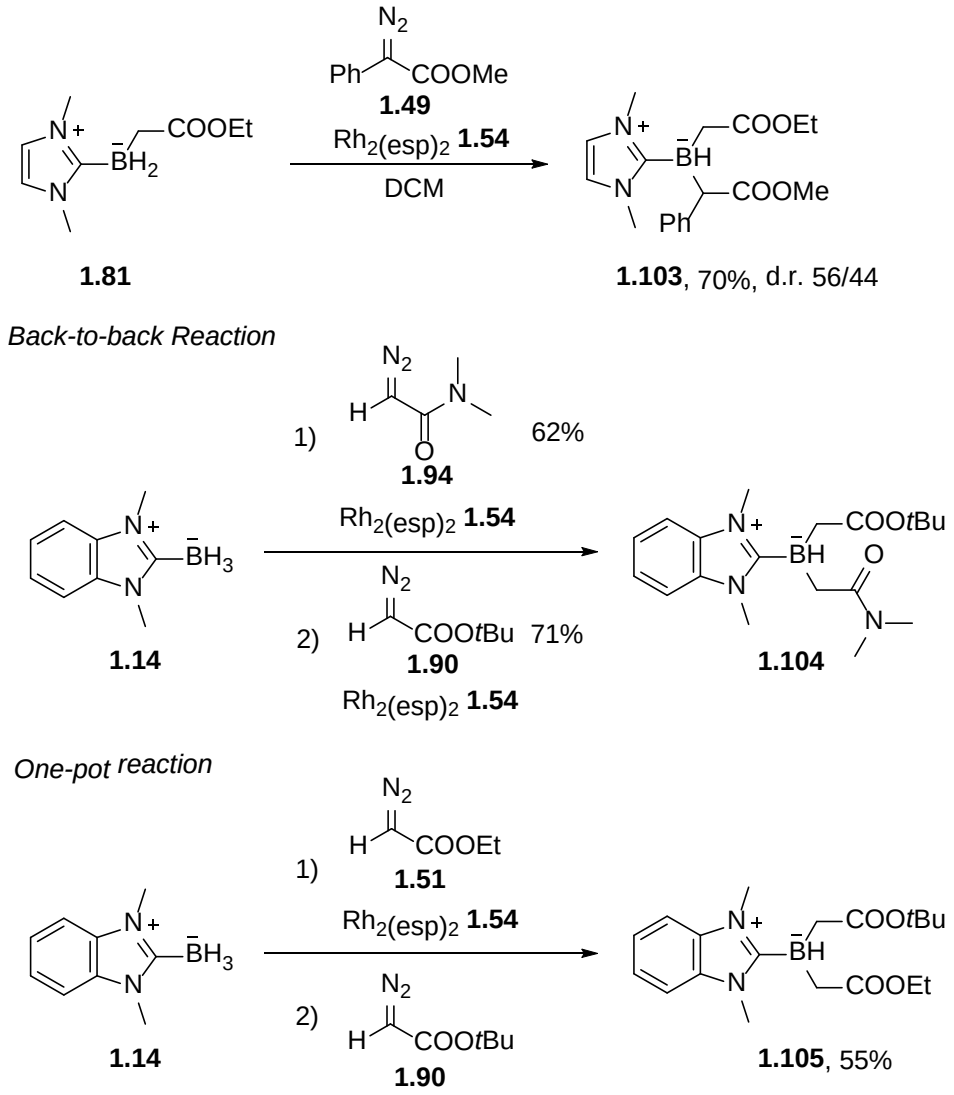
1.2.4 Formation of unsymmetrical double insertion products

Although we did not isolate di-insertion products in the scope study, we know that they were formed from the ^{11}B NMR spectra of crude products. Instead of making symmetrical double insertion products, we investigated the formation of the unsymmetrical double insertion products by treatment of the monoinsertion products from one diazo compound with a second, different diazo compound, as shown in Scheme 1.20. Reaction of insertion product **1.81** with methyl 2-phenyldiazoacetate **1.49** (2 equiv) provided separable diastereomers of the double insertion product **1.103** in 70% combined yield. The diastereomer ratio is 56/44, which was determined by separating the two pure diastereomers. These diastereomers arise because the boron atom and one of the adjacent carbon atoms in **1.103** are both stereogenic centers. The phenyl substituent in this product is important for the purification since related diesters lacking it (for example, **1.81**) did not reliably come off the column.

Back-to-back reaction of benzimidazolylidene borane **1.14** with two different diazo compounds gave a chiral product **1.104** whose only stereocenter is at boron. A first reaction with diazoamide **1.94** and $Rh_2(esp)_2$ **1.54** gave the monoinsertion product, which was isolated in 62% yield. Then a second reaction with *tert*-butyl diazoacetate **1.90** (2 equiv) and the same catalyst was followed to give **1.104** in 71% isolated yield.

The two enantiomers of **1.104** were stable on both silica gel and on an (*S*,*S*)-Whelk-O1 column with chiral stationary phase. A small amount of the racemate (22 mg) was preparatively resolved on the chiral column to give about 10 mg each of the two component enantioners in high enantiopurity. Optical rotations were –34.0 (first eluting enantiomer) and +33.8 (both c = 1, $CHCl_3$). However, the pure enantiomers are not crystalline, and the absolute configuration could not be solved. To the best of our knowledge, this is the first example of isolation and

characterization of stable enantiomers of a chiral carbene-borane whose only stereocenter is on boron.



Scheme 1.20 Stepwise and one-pot formation of double insertion products

Finally, a sequential one-pot reaction was also successful. First, ethyl diazoacetate **1.51** (1.2 equiv) was added by syringe pump over 4 h to benzimidazolylidene borane **1.14** (1 equiv) and 1 mol% $Rh_2(esp)_2$ at 40 °C. Like some of the other reactions, the color of the mixture

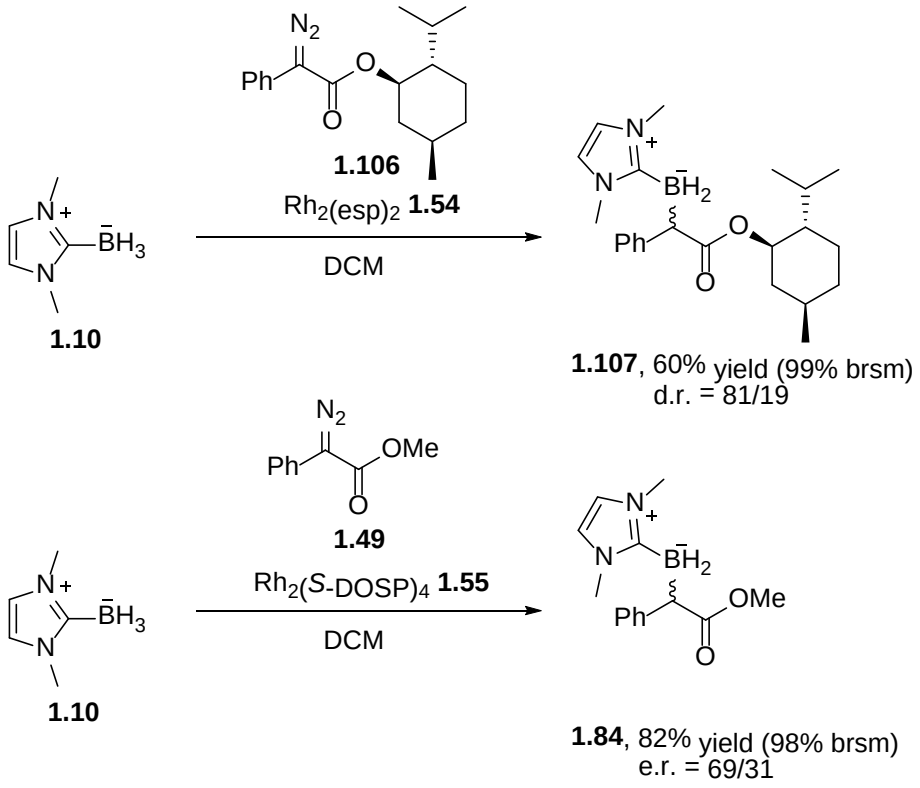
gradually changed from green to orange. Just as the first syringe pump stopped, a second was started and *tert*-butyl diazoacetate **1.90** (2 equiv) was added, again over 4 h at 40 °C. Although the mixture remained orange, TLC analysis showed that the second insertion was progressing during the second syringe pump period. Standard workup and chromatography gave diester **1.105** in 55% isolated yield. This experiment shows that it is not necessary to isolate the single insertion products on the way to double insertion.

1.2.5 Preliminary results of asymmetric B-H insertion reactions

As mentioned before, double insertion product **1.103** has two diastereomers because of the stereogenic centers of the boron atom and one of the adjacent carbon atoms. Therefore, it provides an opportunity to pursue the asymmetric version of B-H insertion reactions. In order to simplify the situation, we decided to investigate the two stereogenic centers separately. We targeted to synthesize the enantiomers with carbon or boron stereogenic centers.

First, we examined the B-H bond insertion reactions to construct carbon stereogenic centers. Preliminary results are shown in Scheme 1.21. In the first approach, a diazoester with a chral auxillary was used. (–)-Menthyl diazoacetate **1.106** was treated with diMe-Imd-BH_3 **1.10** and the standard $Rh_2(esp)_2$ catalyst to provide **1.107** as an 81/19 mixture of diastereomers in 61% conversion and 60% isolated yield. We have not yet succeeded in separating these diastereomers, so their configurations are unassigned. Meanwhile, reactions with chiral Rh(II) catalysts were also tested. Several chiral Rh(II) catalysts have been developed for carbene insertion reactions of C-H bonds. Therefore, we selected commercially available catalyst Rh_2(*S*-DOSP)$_4$ **1.55** in our reactions. The donor-acceptor precursor methyl 2-phenyldiazoacetate **1.49** and diMe-Imd-BH_3 **1.10** were reacted with the chiral catalyst **1.55** to afford the chiral insertion product **1.84** in 84%

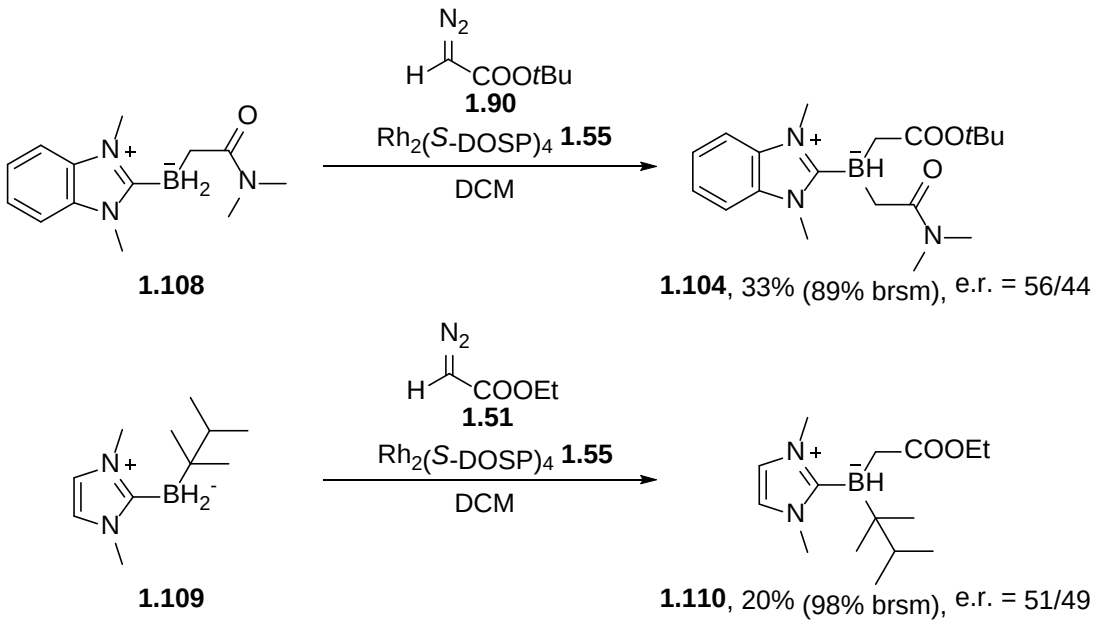
conversion and 82% isolated yield. In contrast to $Rh_2(esp)_2$ catalyst, we have to use freshly distilled DCM to obtain good conversion. The two enantiomers of **1.84** were resolved on the chiral (*S*,*S*)-Whelk-O1 column (25% isopropanol in hexane). The major peak was at 31.2 min and the minor peak showed up at 27.4 min. And the enantiomer ratio was measured as 69/31 based on the peak areas of the two separated enantiomers of **1.84**.



Scheme 1.21 Asymmetric B-H bond insertion reactions to build carbon stereogenic center

In contrast to building carbon stereogenic centers, catalytic asymmetric reactions for constructing boron stereogenic centers have never been reported in the literature. By inserting a different single stabilized diazo compound into single substituted NHC-boranes, it is possible to obtain the chiral double substituted NHC-boranes whose only stereogenic center is on boron.

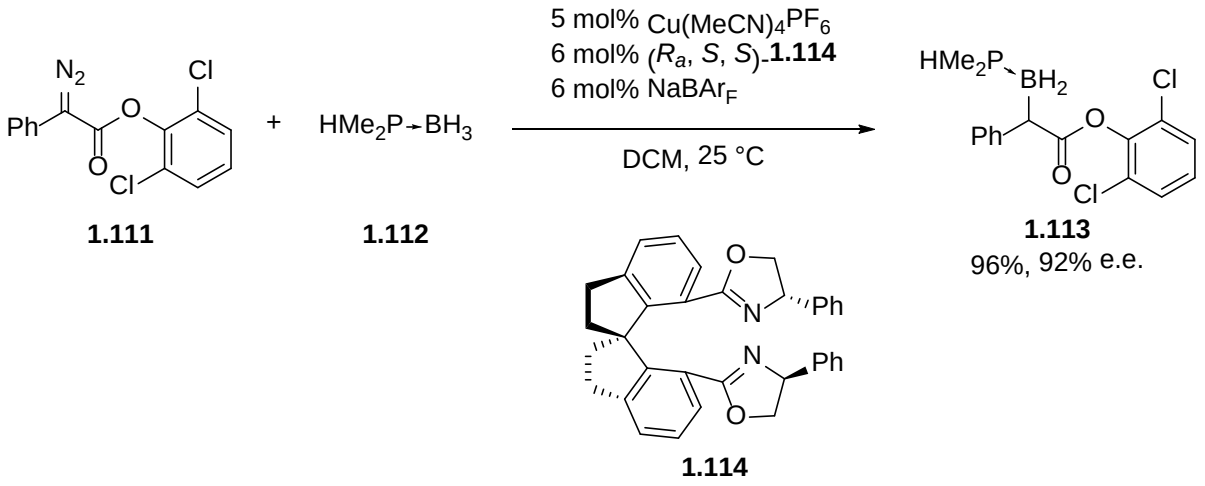
Two examples are shown in Scheme 1.22. Reaction of monoinsertion product **1.108** with *tert*-butyl diazoacetate **1.90** (2 equiv) catalyzed by chiral Rh_2(*S*-DOSP)$_4$ **1.55** provided the chiral double insertion product **1.104** in 33% isolated yield (37% conversion). The enantiomer ratio was measured to be 56/44 by the chiral (*S*,*S*)-Whelk-O1 column. We initially attributed the low enantiomeric excess to the similarity of the two substituents on boron. So a more sterically hindered single substituted NHC-borane **1.109** was tested. With the same chiral catalyst, ethyl diazoacetate **1.51** was inserted into the B-H bond of NHC-borane **1.109**. Double substituted NHC-borane **1.110** was obtained in 20% yield (21% conversion). However, based on the analysis of the chiral (*S*,*S*)-Whelk-O1 column, the insertion product **1.112** was almost racemic (e. r. = 51/49).



Scheme 1.22 Asymmetric B-H bond insertion reactions to build boron stereogenic center

Shortly after we reported our rhodium catalyzed carbene insertion into B-H bonds of *N*-heterocyclic carbene boranes, Zhou reported a similar copper-catalyzed reaction with amine- or

phosphine-borane adducts and diazo compounds.[80] In their cases, with the chiral ligand **1.114**, $Cu(MeCN)_4PF_6$ catalyzed the reaction of diazo compound **1.111** and phosphine-borane **1.112** to form the insertion product **1.113** with excellent yield (96%) and high enantioselectivity (92% e.e.) (Scheme 1.23). The preliminary experiments of asymmetric B-H insertion reactions with rhodium catalysts only gave poor to moderate enantioselectivity. However, by screening reaction conditions, it may be possible to afford high enantioselectivity. For example, many chiral Rh(II) catalysts are available for screening. By using different NHC-boranes with different steric and electronic environment, higher selectivity could be expected. Meanwhile, changing the ester groups on the diazo partner is another route for optimization.

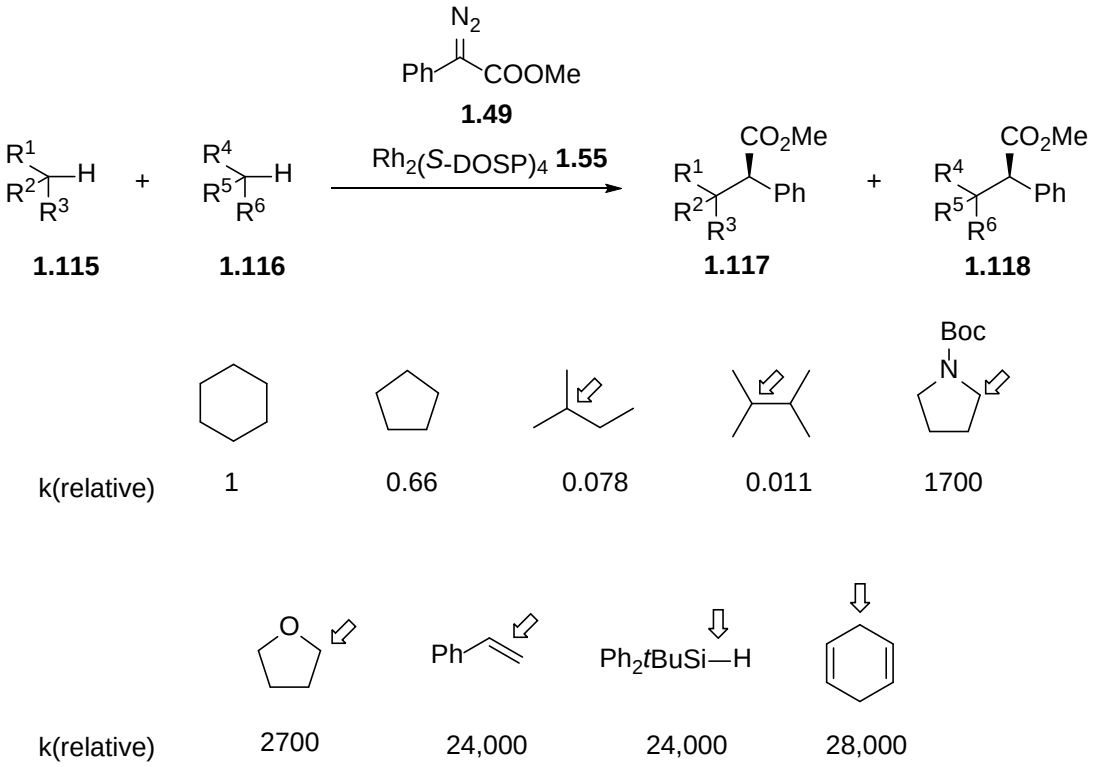


Scheme 1.23 Copper catalyzed enantioselective B-H insertion reaction by Zhou

1.2.6 Competitive rate experiments

The NHC-rings and N-substituents of the precursors in Table 1.6 and Scheme 1.19-1.21 contain various potential sites for reactions of rhodium carbenes, including aromatic rings and activated C-H bonds. However, side products from reaction at sites other than boron have so far not been

isolated. This implies that the B-H bonds of these NHC-boranes are very reactive toward rhodium carbenes. This notion is also supported by the good yields obtained without large excesses of reagents and by the scope of the different diazo compounds that can be used.



Scheme 1.24 Davies C-H insertion reactivity scale

To better address the relative reactivity of NHC-boranes, we tapped into a scale put forth by Davies and co-workers (Scheme 1.24).[54] The scale is for reactions between various carbenophiles and methyl 2-phenyl-diazoaccetate **1.49** catalyzed by Rh_2(*S*-DOSP)$_4$ **1.55**. From these data, it is clear that these C-H insertions display remarkable selectivity. Reactions with THF and *N*-Boc-pyrrolidine are more favorable than reactions with cyclohexane by factors of 1700 and 2400, respectively. C-H insertion of THF is about 10 times less favorable than Si-H

insertion or cyclopropanation of styrene. And the best substrate for C-H insertion is 1,4-cyclohexadiene, which reacts 28,000 times faster than cyclohexane.

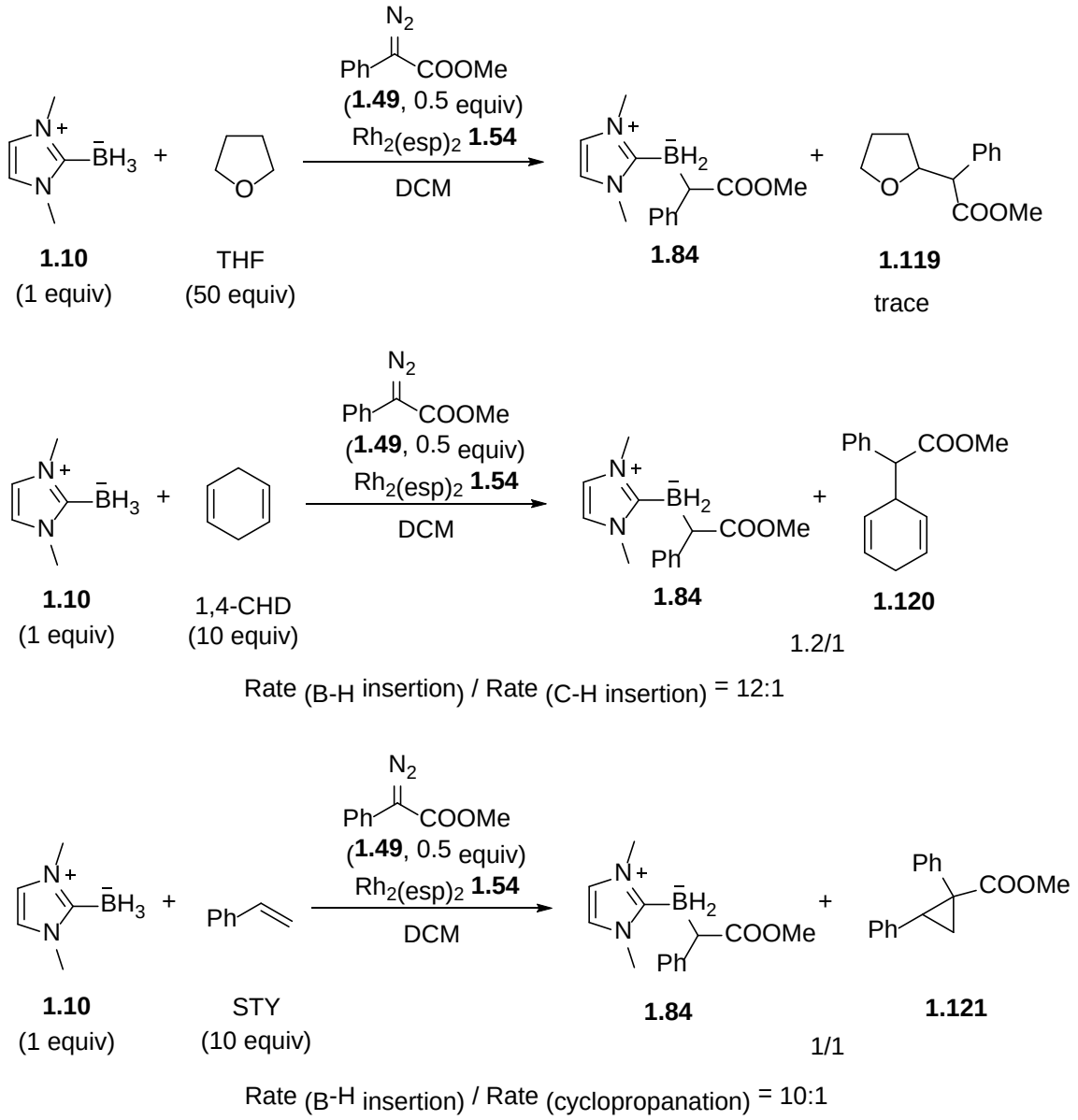
We used the $Rh_2(esp)_2$ catalyst for internal consistency, so we cannot place our results quantitatively on the Davies scale. We started competition experiments with diMe-Imd-BH_3 **1.10** and THF, whose CH_2O groups are considered to be activiated toward C-H insertion of Rh-carbenes. But in the preliminary reactions of methyl 2-phenyl-diazoacetate **1.49**, diMe-Imd-BH_3 **1.10** and THF, the THF insertion product was hardly formed at all even when THF was used in 50-fold excess over **1.10**. The THF did not interfere with the B-H insertion reaction, and **1.84** was the major product as usual. This implies that THF can be used as solvent or cosolvent in the B-H insertion reactions.

We then moved directly to the top of the Davies reactivity scale with 1,4-cyclohexadiene and styrene. Competition of 1 equiv of 1,4-cyclohexadiene and 1 equiv diMe-Imd-BH_3 **1.10** again provided **1.84**, this time with a little of the cyclohexadiene C-H insertion product. Finally, competition of a 10-fold excess of 1,4-cyclohexadiene with diMe-Imd-BH_3 **1.10** provided the B-H insertion product **1.84** and the C-H insertion product **1.120** in a ratio of about 1.2/1, which was measured by the integration in the ^1H NMR spectrum of crude products.

Likewise, reaction of diMe-Imd-BH_3 **1.10** and styrene in a 1/1 ratio gave **1.84** with only a small amount of the styrene cyclopropanation product. Competition of 1 equiv of diMe-Imd-BH_3 **1.10** with 10 equiv of styrene gave **1.84** and **1.121** in about a 1/1 ratio.

These results show that diMe-Imd-BH_3 **1.10** is about 10-12 times more reactive than 1,4-cyclohexadiene and styrene, and it is over 100 times more reactive than THF towards reactive rhodium carbenes. Accordingly, the B-H bonds in diMe-Imd-BH_3 **1.10** are much more reactive than typical activated C-H bonds in bimolecular insertion reactions with rhodium carbenes. In

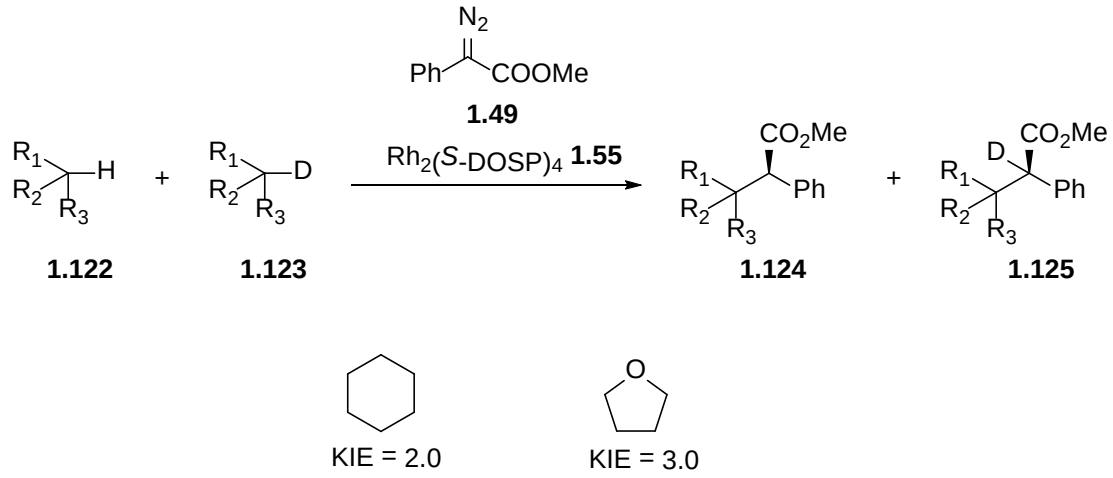
conclusion, NHC-boranes are highly reactive carbenophiles toward electrophilic rhodium carbenes.



Scheme 1.25 Competition experiments of NHC-borane **1.10** with THF, 1,4-cyclohexadiene and styrene

1.2.7 Isotope effect experiments

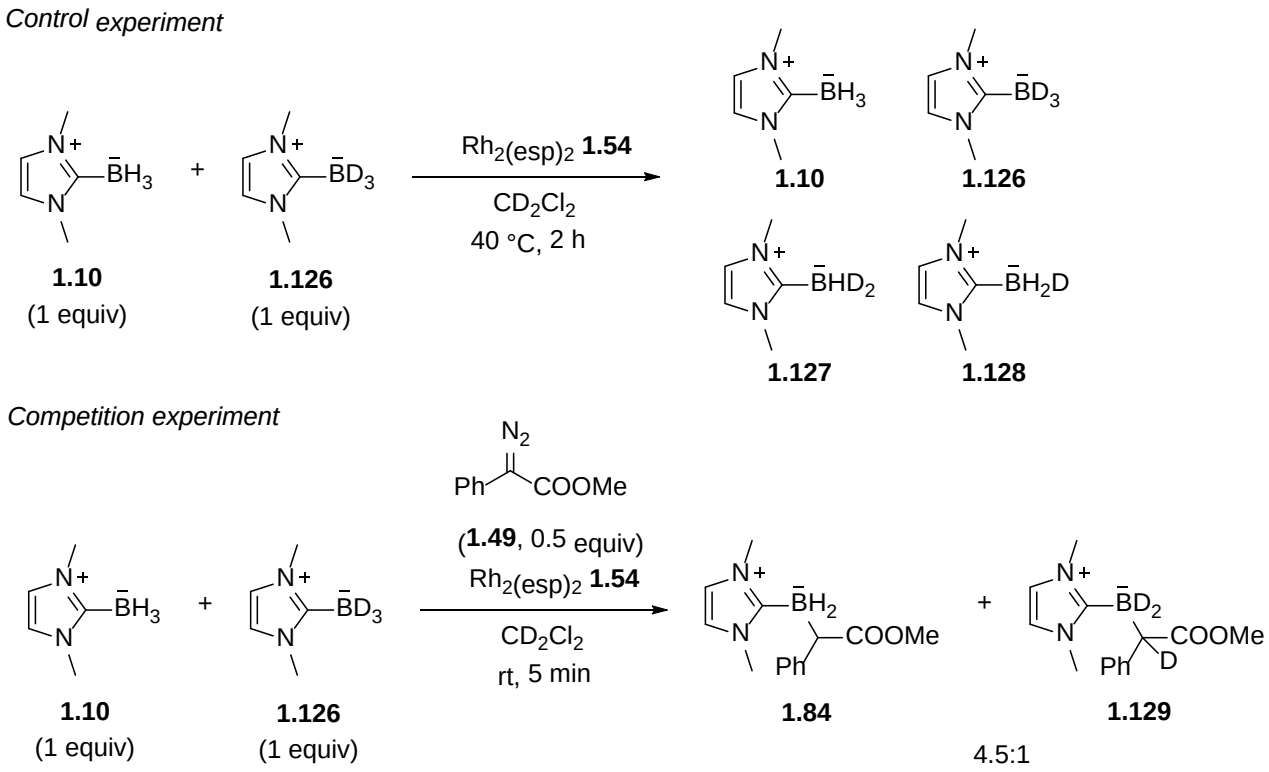
Finally, we conducted simple experiments to estimate the kinetic isotope effect in a typical B-H insertion reaction. Also, Rh_2(*S*-DOSP)$_4$-catalyzed reactions of labeled and unlabeled substrates with methyl 2-phenyl-diazoaceate **1.49** by Davies was used for comparison. In a competition of cyclohexane with cyclohexane-d_{12}, the kinetic isotope effect was about 2. And it was about 3 with THF and THF-d_8 (Scheme 1.26).[54]



Scheme 1.26 Davies C-H insertion isotope effect results

Before the competition experiment of the insertion reaction, a control experiment was conducted with diMe-Imd-BH_3 **1.10**, diMe-Imd-BD_3 **1.126** (>95% D) and $Rh_2(esp)_2$ **1.54** but lacking the diazoester (Scheme 1.27). During the reaction, H/D exchange occurred over 2 h at 40 °C. DiMe-Imd-BHD_2 **1.127** and diMe-Imd-BH_2D **1.128** were detected by ^{11}B NMR because the multiplicities changed due to the differences in spin and coupling constant (*J*) between H and D. However, it was hard to quantitate accurately because of overlapping. No exchange occurred without the catalyst. We propose that the catalyst, which is a Lewis acid, react with the NHC-

borane, perhaps by direct hydride transfer. During this process, a small amount of a borenium ion (NHC-BH_2^+) or its reactive equivalent was formed.[81] This could catalyze the H/D exchange by reversible hydride/deuteride transfer.[26]



Scheme 1.27 Competition experiment to estimate the isotope effect

By running the control experiment at rt for 10 min, no H/D exchange was observed. Therefore, we conducted the competition experiment by rapidly adding a solution of 0.5 equiv of the methyl 2-phenyldiazoacetate **1.49** to a CD_2Cl_2 solution of the catalyst and 1 equiv each of diMe-Imd-BH_3 **1.10** and diMe-Imd-BD_3 **1.126** (Scheme 1.27). The expected insertion products **1.84** and **1.129** were formed after 5 min in a ratio of about 4.5/1. The unreacted boranes at this point were mostly (>90%) diMe-Imd-BH_3 **1.10** and diMe-Imd-BD_3 **1.129**, and the exchanged

products diMe-Imd-BH_2D **1.127** or diMe-Imd-BHD_2 **1.128** were not detected in the ^{11}B NMR spectrum (<10%). Therefore, the kinetic isotope effect of B-H bonds is about 4.5. This means that B-H bond cleavage is likely to be involved in the rate-limiting step.

1.2.8 Mechanism

Based on all these data, a consistent picture of the B-H insertion reactions of rhodium carbenes is formed. By analogy with Si-H and C-H bond insertion reactions, we propose a B-H bond insertion mechanism shown in Figure 1.11. Diazo compound **1.49** reacted with $Rh_2(esp)_2$ to give intermediate **I**. After releasing a molecule of nitrogen, the rhodium carbene **II** was formed. Then it inserted into the B-H bond of the NHC-borane **1.10** through a concerted transition state to form insertion product **1.84** and the catalyst.

The rhodium-carbene C-H insertion reactions are thought to be concerted but not synchronous.[33,36,82] Therefore, the B-H insertions may be similar. In the transition state, because of the large isotope effect, the hydride abstraction by the rhodium carbene to form the new C-H bond is advanced. And the following C-B bond formation lags. In this view, it is reasonable to consider the transition state as having the character of two reactive species: an NHC-borenium ion and a rhodium enolate. After passing the transition state, these two components collapse quickly by *B*-alkylation to form the product **1.84** and return the catalyst.

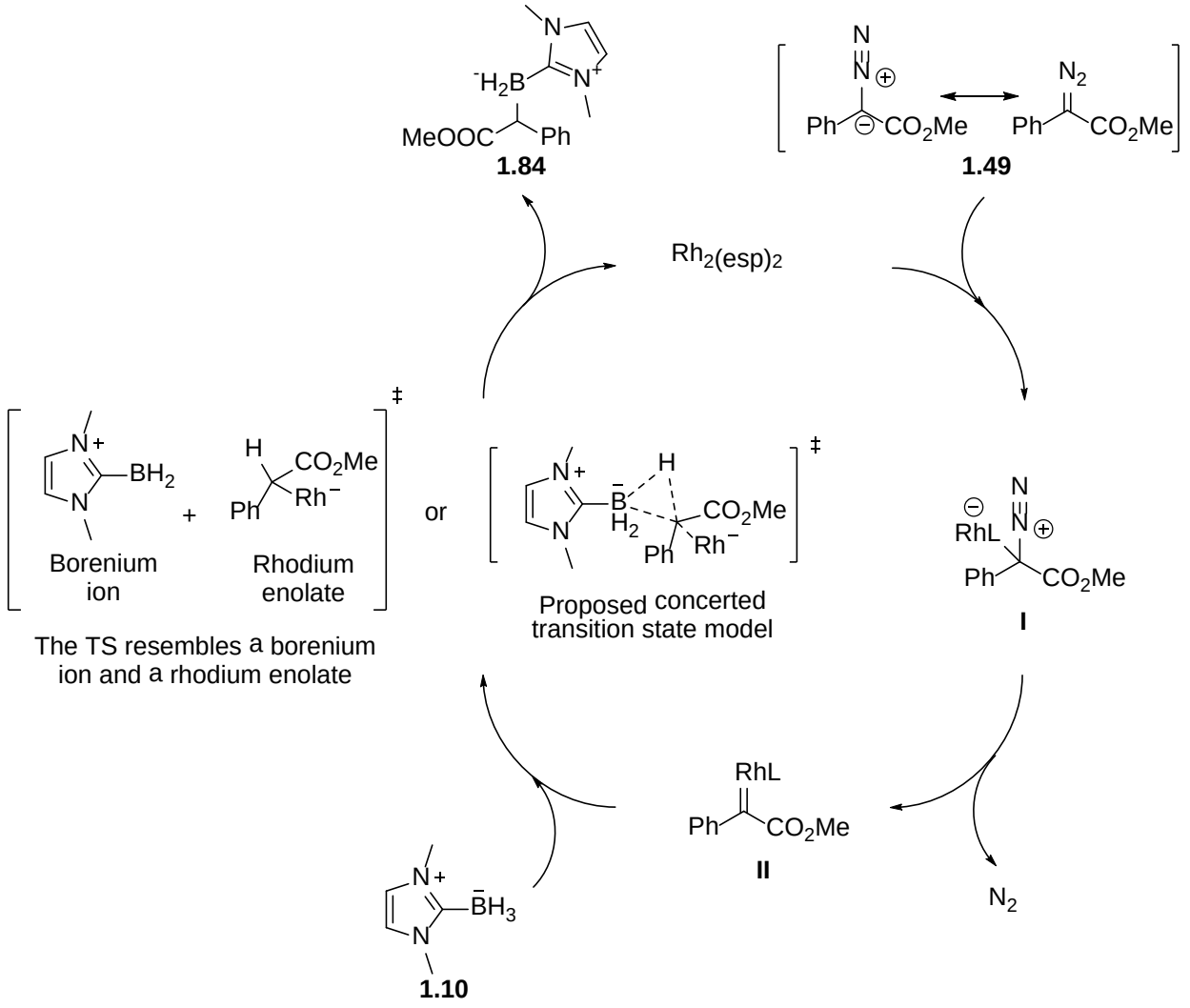


Figure 1.11 Proposed mechanism

Compared to most C-H bonds, the B-H bonds of NHC-boranes are relatively weak (BDE < 85 kcal/mol).[13,14,24] And they are considered as good hydride donors.[19] These electronic effects explain why they are such reactive carbenophiles toward electrophilic rhodium carbenes. However, steric effects may also be important because the second insertion to NHC-BH_2R is slower than the first to NHC-BH_3. And when large *N*-substituents were introduced on NHC parts, the conversion of the insertion reactions dropped significantly and little double insertion products were observed.

1.3 CONCLUSIONS

A rhodium (II) salt catalyzed B-H bond insertion reaction between NHC-boranes and diazocarbonyl compounds is described in this chapter. By using this method, stable α-NHC-boryl carbonyl compounds are synthesized in good yield. It provides a reliable way to make organoboron compounds with boron-carbon bonds from stable NHC-borane complexes. A large number of the NHC-boranes and diazo carbonyl components were tolerated in this reaction. More hindered NHC-boranes give better yields of monoinsertion products because the primary products are not subject to a competing second insertion. These newly formed organoboron compounds may be further used in the subsequent reactions, such as Suzuki-Miyaura coupling reactions. It is also potent to asymmetrically construct new carbon and boron stereogenic centers in this reaction.

The mechanism of this reaction was also briefly investigated. These first reactions of stable carbene-boranes with transient metal carbenes suggest that NHC-boranes are good carbenophiles. It encourages further study of their reactions with other types of reactive carbenes.

1.4 EXPERIMENTAL

General information: All reactions were performed in oven-dried glassware under an argon atmosphere, except where noted. Chemicals and solvents were purchased from commercial suppliers and used as received, excepting as follows. Dichloromethane, THF, ether, and toluene were dried by passing through an activated alumina column.

All reactions were followed by TLC to completion, unless stated otherwise. TLC analysis was performed by illumination with a UV lamp (254 nm) or staining with PMA and heating. All flash chromatography was performed by Combiflash Rf machine with pre-packed silica gel columns purchased from Teledyne Isco Inc.

^{1}H NMR spectra were measured on a Bruker Avance 400 MHz and 500 MHz instruments in $CDCl_3$, and chemical shifts were measured relative to the TMS peak (δ 0.00). The following abbreviations were used to describe coupling: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. ^{13}C NMR spectra were measured on Bruker Avance instruments at 100 MHz, 125MHz or 175 MHz with chemical shifts relative to residual solvent peak (δ 77.0 ($CDCl_3$) or 128.06 (C_6D_6)). The resonances for carbons bonded to boron in the ^{13}C-NMR spectrum are typically weak. The NHC-carbene carbon resonance was generally not observed. The resonance for CH_2 or CH adjacent to boron was observed in some but not all spectra. ^{11}B NMR spectra were measured on Bruker Avance 400 MHz and 500 MHz instruments at 128 MHz and 160 MHz. The ^{11}B chemical shifts are given relative to $BF_3{\cdot}OEt_2$ (^{11}B = 0 ppm).

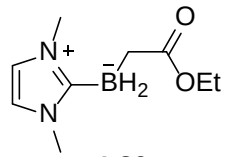
Melting points (mp) were determined with a Mel-Temp II apparatus and are uncorrected. IR spectra were recorded as thin films (CH_2Cl_2) or neat on KBr plates on an ATI Mattson Genesis Series FTIR spectrometer.

High resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) on the Q-Tof Ultima API, Miccromass UK Limited instrument.

Analytical HPLC analysis was conducted using an (*S*,*S*)-Whelk-O 1 column (Pirkle, 250 mm x 4.6 mm ID) eluting with hexanes:iPrOH at 1.0 mL/min, 10-20 μg per injection. Preparatory HPLC resolutions were performed on an (*S*,*S*)-Whelk-O 1 column (Pirkle, 25 cm x

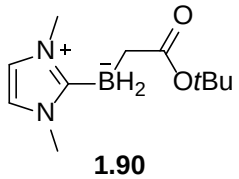
21.1 mm ID) eluting with hexanes:iPrOH at 7.0 mL/min, 40 mg per injection. All HPLC injections were monitored with a Waters model 440 UV detector at wavelength 254 nm.

General procedure for reactions in Tables 1.1-1.6: The NHC-BH_3 (1.0 equiv) and the $Rh_2(esp)_2$ (0.01 equiv) were dissolved in dry DCM (2 mL) under argon. The solution was dark green. The reaction mixture was heated to reflux. A solution of the diazo compound (1.2 equiv) in dry DCM (2 mL) was added via syringe pump over a period of 4 h. The color of the solution turned to orange. After 4 h, the solvent was removed and the crude ^1H and ^{11}B NMR spectra were recorded. The mixture was concentrated and purified by flash chromatography to give the pure product.



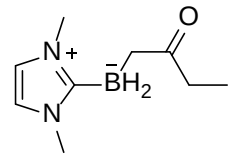
1.80

(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2-ethoxy-2-oxoethyl)dihydroborate (1.80): Reaction of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol), $Rh_2(esp)_2$ (3.4 mg, 0.0045mmol) and ethyl 2-diazoacetate (**1.51**) (0.080 mL, 0.54 mmol) according to the general procedure afforded 54.7 mg (62%) of product **1.80**, isolated as colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H), 3.93 (q, J = 7.2 Hz, 2H), 3.75 (s, 6H), 1.62 (br, 2H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 120.3, 58.8, 35.9, 29.7, 24.4 (q, J_{BC} = 32 Hz), 14.5; ^{11}B NMR (128 MHz, $CDCl_3$) δ –28.3 (t, J_{BH} = 90 Hz); IR (film) 2923, 2853, 2305, 1651, 1574, 1461 cm^{-1}; HRMS (ESI) *m/z* ($2M^+ - H$) calcd for $C_{18}H_{33}B_2N_4O_4$ 391.2682, found 391.2676. The estimated yield of the double insertion product (^{11}B NMR (160 MHz, $CDCl_3$) δ –20.3 (d, J_{BH} = 91 Hz)) is 12%.



1.90

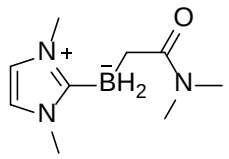
(2-(tert-Butoxy)-2-oxoethyl)(1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)dihydroborate (1.90): Reaction of (1,3-dimethyl-1*H*–imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol), $Rh_2(esp)_2$ (3.4 mg, 0.0045mmol) and *tert*-butyl 2-diazoacetate (**1.89**) (76.8 mg, 0.54 mmol) according to the general procedure afforded 58.5 mg (58%) of product **1.90**, isolated as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 2H), 3.78 (s, 6H), 1.57 (br, 2H), 1.30 (s, 3H); ^{13}C NMR (175 MHz, C_6D_6) δ 180.3, 119.5, 76.3, 35.5, 28.6, 26.0 (br); ^{11}B NMR (128 MHz, $CDCl_3$) δ –28.4 (t, J_{BH} = 88 Hz); IR (film) 2973, 2928, 2333, 1691, 1481 cm^{-1}; HRMS (ESI) *m/z* ($2M^+$ – H) calcd for $C_{22}H_{41}B_2N_4O_4$ 447.3314, found 447.3333. The estimated yield of the double insertion product (^{11}B NMR (160 MHz, $CDCl_3$) δ –20.3 (d, J_{BH} = 88 Hz)) is 11%.



1.92

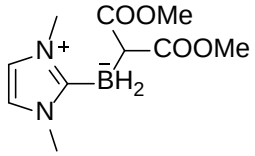
(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2-oxobutyl)dihydroborate (1.92): Reaction of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol), $Rh_2(esp)_2$ (3.4 mg, 0.0045mmol) and 1-diazobutan-2-one (**1.91**) (53.0 mg, 0.54 mmol) according to the general procedure afforded 39.7 mg (49%) of product **1.92**, isolated as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 2H), 3.72 (s, 6H), 2.50 (q, *J* = 7.5 Hz, 2H), 1.87 (br, 2H), 1.01 (t, *J* = 7.5 Hz, 3H) ; ^{13}C NMR (175 MHz, $CDCl_3$) δ 219.8, 120.4, 36.0 (br), 35.9, 34.3, 8.8; ^{11}B NMR (160 MHz, $CDCl_3$) δ –28.3 (t, J_{BH} = 90 Hz); IR (film) 3130, 2936, 2312, 1661, 1575, 1483 cm^{-1};

HRMS (ESI) *m/z* ($2M^+ - H$) calcd for $C_{18}H_{33}B_2N_4O_2$ 359.2790, found 359.2802. The estimated yield of the double insertion product (^{11}B NMR (160 MHz, $CDCl_3$) δ –20.7 (d, J_{BH} = 88 Hz)) is 10%.



1.94

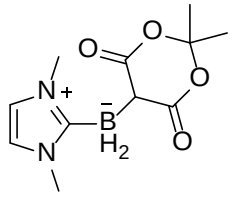
(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2-(dimethylamino)-2-oxoethyl)dihydroborate (1.94): Reaction of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol), $Rh_2(esp)_2$ (3.4 mg, 0.0045mmol) and 2-diazo-*N*,*N*-dimethylacetamide (**1.93**) (61.1 mg, 0.54 mmol) according to the general procedure afforded 48.3 mg (55%) of product **1.94**, isolated as white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 2H), 3.73 (s, 6H), 3.12 (s, 3H), 2.86 (s, 3H), 1.68 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.5, 120.3, 38.2, 35.7, 35.2; ^{11}B NMR (128 MHz, $CDCl_3$) δ –29.1 (t, J_{BH} = 87 Hz); IR (film) 3031, 2927, 2324, 1604, 1469, 1396 cm^{-1}; HRMS (ESI) *m/z* ($M^+ - H$) calcd for $C_9H_{17}BN_3O$ 194.1465, found 194.1463. The estimated yield of the double insertion product (^{11}B NMR (128 MHz, $CDCl_3$) δ –22.0 (d, J_{BH} = 87 Hz)) is 19%.



1.83

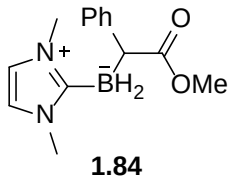
(1,3-Dimethoxy-1,3-dioxopropan-2-yl)(1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)dihydroborate (1.83): Reaction of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol), $Rh_2(esp)_2$ (3.4 mg, 0.0045mmol) and dimethyl 2-diazomalonate (**1.82**) (110.7 mg, 0.54

mmol) according to the general procedure afforded 78.9 mg (73%) of product **1.83**, isolated as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 2H), 3.74 (s, 6H), 3.55 (s, 6H), 3.08 (br, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 120.8, 51.1, 44.0 (br), 36.0; ^{11}B NMR (160 MHz, $CDCl_3$) δ –25.5 (t, J_{BH} = 94 Hz); IR (film) 3170, 3132, 2952, 2326, 1741, 1576, 1486, 1437, 1375 cm^{-1}; HRMS (ESI) *m/z* (M^+ – H) calcd for $C_{10}H_{16}BN_2O_4$ 239.1203, found 239.1217. The estimated yield of the double insertion product (^{11}B NMR (160 MHz, $CDCl_3$) δ –17.7 (d, J_{BH} = 91 Hz)) is 9%.



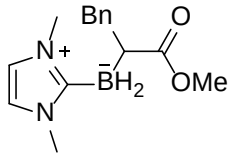
1.96

(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)dihydroborate (1.96): Reaction of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol), $Rh_2(esp)_2$ (3.4 mg, 0.0045mmol) and 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (**1.95**) (91.9 mg, 0.54 mmol) according to the general procedure afforded 68.1 mg (60%) of product **1.96**, isolated as yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 2H), 3.84 (s, 6H), 1.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 161.0, 121.5, 110.9, 103.8, 36.6, 27.0; ^{11}B NMR (160 MHz, $CDCl_3$) δ –18.7 (t, J_{BH} = 93 Hz); IR (film) 3174, 3145, 3001, 2958, 2407, 1722, 1668, 1576, 1485 cm^{-1}; mp 193-195 ℃ (decomposition). There is no double insertion product appeared in the ^{11}B NMR spectrum.



1.84

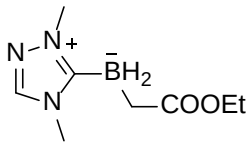
(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2-methoxy-2-oxo-1-phenylethyl)dihydroborate (1.84): Reaction of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol), $Rh_2(esp)_2$ (3.4 mg, 0.0045mmol) and methyl 2-diazo-2-phenylacetate (**1.49**) (95.1 mg, 0.54 mmol) according to the general procedure afforded 86.0 mg (74%) of product **1.84**, isolated as white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.28 (m, 2H), 7.14-7.17 (m, 2H), 7.02-7.05 (m, 1H), 6.78 (s, 2H), 3.62 (s, 3H), 3.47 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 145.4, 127.6, 127.6, 123.9, 120.4, 50.8, 46.0 (br), 35.7; ^{11}B NMR (160 MHz, $CDCl_3$) δ –23.2 (t, J_{BH} = 91 Hz); IR (film) 3170, 3133, 3058, 3019, 2950, 2921, 2342, 2310, 1703, 1599, 1578, 1485, 1453, 1431 cm^{-1}; mp 137-139℃; HRMS (ESI) *m/z* (M^+) calcd for $C_{14}H_{19}BN_2O_2$ 258.1540, found 258.1533. The estimated yield of the double insertion product (^{11}B NMR (160 MHz, $CDCl_3$) δ –14.1 (d, J_{BH} = 96 Hz)) is 9%.



1.86

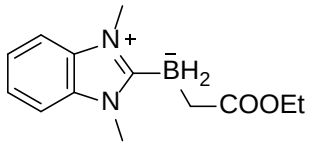
(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(1-methoxy-1-oxo-3-phenylpropan-2-yl)dihydroborate (1.86): Reaction of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol), $Rh_2(esp)_2$ (3.4 mg, 0.0045mmol) and methyl 2-diazo-3-phenylpropanoate (**1.85**) (102.7 mg, 0.54 mmol) according to the general procedure afforded 31.8 mg (26%) of product **1.86**, isolated as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.20 (m, 5H), 6.80 (s, 2H), 3.74 (s, 6H), 3.38 (s, 3H), 3.11 (dd, J_1 = 14.0 Hz, J_2 = 10.0 Hz, 1H), 2.72 (dd, J_1 = 14.0 Hz,

J_2 = 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 128.5, 127.9, 125.0, 120.4, 50.3, 39.1, 36.0, 29.7; ^{11}B NMR (160 MHz, $CDCl_3$) δ –25.1 (t, J_{BH} = 88 Hz); IR (film) 2922, 2299, 1694, 1482, 1437, 1352 cm^{-1}; HRMS (ESI) *m/z* ($2M^+$ – H) calcd for $C_{30}H_{41}B_2N_4O_4$ 543.3308, found 543.3309. There is no double insertion product.



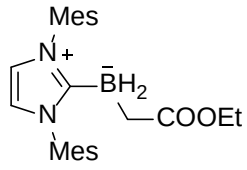
1.98

(1,4-Dimethyl-1*H*-1,2,4-triazol-4-ium-5-yl)(2-ethoxy-2-oxoethyl)dihydroborate (1.98): Reaction of (1,4-dimethyl-1*H*-1,2,4-triazol-4-ium-5-yl)trihydroborate (**1.17**) (50.0 mg, 0.45 mmol), $Rh_2(esp)_2$ (3.4 mg, 0.0045 mmol) and ethyl 2-diazoacetate (**1.51**) (0.080 mL, 0.54 mmol) according to the general procedure afforded 46.1 mg (52%) of product **1.98**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 3.97 (s, 3H), 3.94 (q, *J* = 7.0 Hz, 2H), 3.79 (s, 2H), 1.64 (br, 2H), 1.14 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6, 141.3, 59.0, 38.1, 33.7, 23.0 (br), 14.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ –28.6 (t, J_{BH} = 90 Hz); IR (film) 2924, 2343, 1683, 1552, 142, 1258 cm^{-1}; HRMS (ESI) *m/z* ($2M^+$ – H) calcd for $C_{16}H_{31}B_2N_6O_4$ 393.2593, found 393.2600. The estimated yield of the double insertion product (^{11}B NMR (128 MHz, $CDCl_3$) δ –20.7 (d, J_{BH} = 91 Hz)) is 11%.



1.99

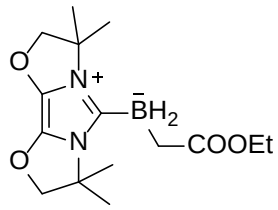
(1,3-Dimethyl-1*H*-benzo[d]imidazol-3-ium-2-yl)(2-ethoxy-2-oxoethyl)dihydroborate (1.99): Reaction of (1,3-dimethyl-1*H*-benzo[d]imidazol-3-ium-2-yl)trihydroborate (**1.14**) (50.0 mg, 0.31 mmol), $Rh_2(esp)_2$ (2.3 mg, 0.0031 mmol) and ethyl 2-diazoacetate (**1.51**) (0.055 mL, 0.37 mmol) according to the general procedure afforded 45.8 mg (60%) of product **1.99**, isolated as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.47 (m, 4H), 3.98 (s, 6H), 3.91 (q, J = 7.0 Hz, 2H), 1.73 (br, 2H), 1.04 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.7, 133.2, 124.2, 110.8, 58.8, 32.2, 14.3; ^{11}B NMR (160 MHz, $CDCl_3$) δ –28.1 (t, J_{BH} = 90 Hz); IR (film) 2923, 2308, 1691, 1468, 1395 cm^{-1}; mp 67-70 ℃; HRMS (ESI) *m/z* (M^+-1) calcd for $C_{13}H_{19}BN_2O_2$ 245.1461, found 245.1457. The isolated yield of the double insertion product (^{11}B NMR (128 MHz, $CDCl_3$) δ –20.0 (d, J_{BH} = 91 Hz)) is 19%.



1.87

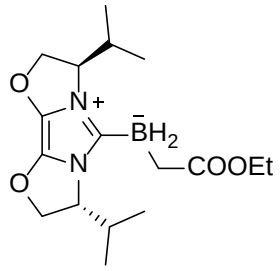
(1,3-Dimesityl-1*H*-imidazol-3-ium-2-yl)(2-ethoxy-2-oxoethyl)dihydroborate (1.87): Reaction of (1,3-dimesityl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.12**) (50.0 mg, 0.16 mmol), $Rh_2(esp)_2$ (1.2 mg, 0.0016 mmol) and ethyl 2-diazoacetate (**1.51**) (0.028 mL, 0.19 mmol) according to the general procedure afforded 36.2 mg (56%) of product **1.87**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 4H), 6.95 (s, 2H), 3.82 (q, J = 7.0 Hz, 2H), 2.34 (s, 6H), 2.12 (s, 12H), 1.03 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.0, 139.2, 135.0, 134.3, 129.1,

121.3, 58.5, 21.1, 17.8, 14.4; ^{11}B NMR (160 MHz, $CDCl_3$) δ –27.2 (t, J_{BH} = 85 Hz); IR (film) 2923, 2854, 2343, 1697, 1489, 1443, 1380 cm^{-1}; mp 179-181 ℃ (decomposition); HRMS (ESI) *m/z* ($2M^+$-1) calcd for $C_{50}H_{65}B_2N_4O_4$ 807.5186, found 807.5178. The estimated yield of the double insertion product (^{11}B NMR (160 MHz, $CDCl_3$) δ –19.8 (br)) is 4%.



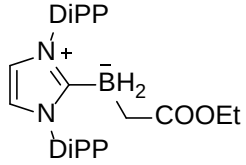
1.100

(2-Ethoxy-2-oxoethyl)(3,3,7,7-tetramethyl-2,3,7,8-tetrahydroimidazo[4,3-b:5,1-b']bis(oxazole)-4-ium-5-yl)dihydroborate (1.100): Reaction of (3,3,7,7-tetramethyl-2,3,7,8-tetrahydroimidazo[4,3-b:5,1-b']bis(oxazole)-4-ium-5-yl)trihydroborate (**1.15**) (50.0 mg, 0.23 mmol), $Rh_2(esp)_2$ (1.7 mg, 0.0023 mmol) and ethyl 2-diazoacetate (**1.51**) (0.041 mL, 0.28 mmol) according to the general procedure afforded 42.5 mg (60%) of product **1.100**, isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 (s, 4H), 4.01 (q, *J* = 7.0 Hz, 2H), 1.73 (s, 6H), 1.62 (br, 2H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6, 123.3, 87.7, 62.6, 58.6, 26.2, 14.5; ^{11}B NMR (160 MHz, $CDCl_3$) δ –28.0 (t, J_{BH} = 88 Hz); IR (film) 2978, 2933, 2336, 1693, 1559, 1430 cm^{-1}; HRMS (ESI) *m/z* ($2M^+$ – H) calcd for $C_{30}H_{49}B_2N_4O_8$ 615.3731, found 615.3728. The estimated yield of the double insertion product (^{11}B NMR (160 MHz, $CDCl_3$) δ –20.2 (d, J_{BH} = 90 Hz)) is 6%.



1.101

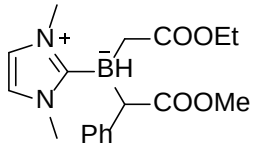
((3*R*,7*R*)-3,7-diisopropyl-2,3,7,8-tetrahydroimidazo[4,3-b:5,1-b']bis(oxazole)-4-ium-5-yl)(2-ethoxy-2-oxoethyl)dihydroborate (1.101): Reaction of ((3*R*,7*R*)-3,7-diisopropyl-2,3,7,8-tetrahydroimidazo[4,3-b:5,1-b']bis(oxazole)-4-ium-5-yl)trihydroborate (**1.16**) (50.0 mg, 0.20 mmol), $Rh_2(esp)_2$ (1.5 mg, 0.0020 mmol) and ethyl 2-diazoacetate (**1.51**) (0.036 mL, 0.24 mmol) according to the general procedure afforded 39.6 mg (59%) of product **1.101**, isolated as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74-4.81 (m, 4H), 4.63-4.65 (m, 2H), 3.93-4.02 (m, 2H), 2.70-2.76 (m, 2H), 1.65 (br, 2H), 1.21 (t, J = 7.2 Hz, 3H); 1.00 (d, J = 6.8 Hz), 0.81 (d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.1, 123.6, 61.3, 58.8, 29.1, 18.8, 14.5, 14.3; ^{11}B NMR (128 MHz, $CDCl_3$) δ –27.4 (t, J_{BH} = 88 Hz); IR (film) 2965, 2876, 2324, 1743, 1692, 1464, 1437, 1406, 1374 cm^{-1}; HRMS (ESI) *m/z* ($2M^+$ – H) calcd for $C_{34}H_{57}B_2N_4O_8$ 671.4357, found 671.4349. The estimated yield of the double insertion product (^{11}B NMR (160 MHz, $CDCl_3$) δ –19.6 (d, J_{BH} = 90 Hz)) is 6%.



1.102

(1,3-Bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-ium-2-yl)(2-ethoxy-2-oxoethyl)dihydroborate (1.102): Reaction of (1,3-bis(2,6-diisopropylphenyl)-1*H*-imidazol-3-

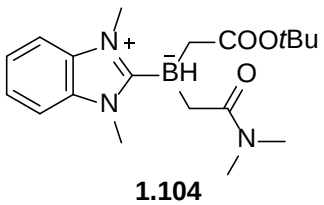
ium-2-yl)trihydroborate (**1.11**) (50.0 mg, 0.12 mmol), $Rh_2(esp)_2$ (1.0 mg, 0.0012 mmol) and ethyl 2-diazoacetate (**1.51**) (0.021 mL, 0.14 mmol) according to the general procedure afforded 36.9 mg (63%) of product **1.102**, isolated as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.47 (m, 2H), 7.25-7.28 (m, 4H), 6.99 (s, 2H), 3.78 (q, *J* = 7.0 Hz, 2H), 2.58 (sep, *J* = 6.5 Hz, 4H), 1.31 (d, *J* = 7.0 Hz, 6H), 1.15 (d, *J* = 7.0 Hz, 6H), 0.99 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 145.4, 134.0, 130.1, 123.9, 122.3, 58.3, 28.7, 25.2, 22.7, 14.3; ^{11}B NMR (160 MHz, $CDCl_3$) δ –26.8 (t, J_{BH} = 86 Hz); IR (film) 3138, 2963, 2928, 2870, 2350, 1691, 1467, 1422, 1384, 1363 cm^{-1}; mp 169-172 ℃ (decomposition); HRMS (ESI) *m/z* ($2M^+$ – H) calcd for $C_{62}H_{89}B_2N_4O_4$ 977.7070, found 975.7049. There is no double insertion product.



1.103

(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2-ethoxy-2-oxoethyl)(2-methoxy-2-oxo-1-phenylethyl)hydroborate (1.103): The (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)(2-ethoxy-2-oxoethyl)dihydroborate (**1.81**) (38.0 mg, 0.19 mmol, 1.0 equiv) and the $Rh_2(esp)_2$ (1.4 mg, 0.0019 mmol, 0.01 equiv) were dissolved in dry DCM (2 mL) under argon. The solution was dark green. The reaction mixture was heated to reflux. A solution of methyl 2-diazo-2-phenylacetate (**1.49**) (66.7 mg, 0.38 mmol, 2.0 equiv) in dry DCM (2 mL) was added via syringe pump over a period of 4 h. The color of the solution turned to be orange. After 4 h, the solvent was removed and the crude ^{1}H NMR and ^{11}B NMR was taken. The mixture was concentrated and purified by flash chromatography (Hex:EA = 1:2) to give two diastereomers as colorless oil. Diastereomer A (25.6 mg, 0.075 mmol, 39%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.20 (m, 2H),

7.06-7.10 (m, 2H), 6.90-6.99 (m, 1H), 6.58 (s, 2H), 3.87 (qd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 2H), 3.62 (s, 3H), 3.47 (s, 6H), 1.98 (br, 1H), 1.75 (br, 2H), 1.03 (t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 178.6, 144.0, 127.5, 127.5, 124.2, 121.0, 58.7, 50.8, 49.0 (br), 36.4, 28.0 (br), 14.4; ^{11}B NMR (128 MHz, $CDCl_3$) δ –16.4 (d, J_{BH} = 96 Hz); IR (film) 2950, 2377, 1703, 1482, 1453, 1434, 1363 cm^{-1}; HRMS (ESI) *m/z* (M^++H) calcd for $C_{18}H_{26}BN_2O_4$ 345.1980, found 345.1974. Diastereomer B (20.1 mg, 0.059 mmol, 31%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.27 (m, 2H), 7.11-7.19 (m, 2H), 6.99-7.02 (m, 1H), 6.73 (s, 2H), 3.74-3.85 (m, 2H), 3.40 (s, 3H), 3.24 (br, 1H), 1.53 (br, 2H), 0.97 (t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 178.9, 143.3, 128.5, 127.6, 124.4, 121.2, 58.6, 50.6, 49.0 (br), 36.7, 26.5 (br), 14.3; ^{11}B NMR (128 MHz, $CDCl_3$) δ –16.5 (d, J = 95 Hz); IR (film) 3134, 2950, 2376, 1703, 1598, 1577, 1481, 1453, 1432 cm^{-1}; HRMS (ESI) *m/z* (M^++H) calcd for $C_{18}H_{26}BN_2O_4$ 345.1980, found 345.1990.



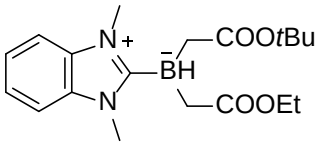
1.104

(2-(*tert*-Butoxy)-2-oxoethyl)(1,3-dimethyl-1*H*-benzo[d]imidazol-3-ium-2-yl)(2-(dimethylamino)-2-oxoethyl)hydroborate (1.104): Reaction of (1,3-dimethyl-1*H*-benzo[d]imidazol-3-ium-2-yl)trihydroborate (**1.14**) (200.0 mg, 1.25 mmol), $Rh_2(esp)_2$ (9.5 mg, 0.013 mmol) and 2-diazo-*N*,*N*-dimethylacetamide (**1.94**) (169.7 mg, 1.50 mmol) according to the general procedure afforded 189.0 mg (62%) of (1,3-Dimethyl-1*H*-benzo[d]imidazol-3-ium-2-yl)(2-(dimethylamino)-2-oxoethyl)dihydroborate, isolated as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.44 (m, 4H), 3.96 (s, 6H), 3.16 (s, 3H), 2.87 (s, 3H), 1.68 (br, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180,9, 133.2, 124.0, 110.8, 38.2, 35.2, 32.0; ^{11}B NMR (128 MHz, $CDCl_3$) δ

–28.8 (t, J_{BH} = 87 Hz); IR (film) 2923, 2851, 2101, 1643, 1405, 1174 cm^{-1}; mp 117-120 ˚C; HRMS (ESI) *m/z* (M^+-1) calcd for $C_{13}H_{20}BN_3O$ 244.1621, found 244.1619.

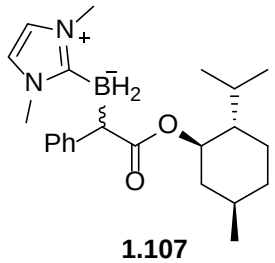
The (1,3-dimethyl-1*H*-benzo[d]imidazol-3-ium-2-yl)(2-(dimethylamino)-2-oxoethyl)dihydroborate (47.0 mg, 0.24 mmol, 1.0 equiv) and the $Rh_2(esp)_2$ (1.8 mg, 0.0024 mmol, 0.01 equiv) were dissolved in dry DCM (2 mL) under argon. The solution was dark green. The reaction mixture was heated to reflux. A solution of *tert*-butyl 2-diazoacetate (**1.90**) (0.067 mL, 0.48 mmol, 2.0 equiv) in dry DCM (2 mL) was added via syringe pump over a period of 4 h. The color of the solution turned to be orange. After 4 h, the solvent was removed and the crude ^1H NMR and ^{11}B NMR was taken. The mixture was concentrated and purified by flash chromatography (pure acetone) to give the product **1.104** (61.0 mg, 0.17 mmol, 71%) as colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.46 (m, 4H), 3.98 (s, 6H), 3.13 (s, 3H), 2.79 (s, 3H), 2.05 (br, 1H), 1.73 (br, 3H), 1.09 (s, 9H); ^{13}C NMR (175 MHz, C_6D_6) δ 179.0, 178.3, 133.5, 123.7, 110.9, 76.7, 37.9, 34.9, 32.3, 30.0 (br), 28.3; ^{11}B NMR (128 MHz, $CDCl_3$) δ –20.8 (d, J_{BH} = 92 Hz); IR (film) 2926, 2854, 2390, 1699, 1613; HRMS (ESI) *m/z* (M^+ – H) calcd for $C_{19}H_{29}BN_3O_3$ 358.2302, found 358.2300.

The two enantionmers were separated by chiral HPLC ((S,S)-Whelk-O column, hexane/iPrOH = 40:60). First eluting enatiomer A: $[\alpha]_D^{25}$ = –34.0 (*c* = 1.13, $CHCl_3$). Second eluting enatiomer B: $[\alpha]_D^{25}$ = +33.8 (*c* = 1.12, $CHCl_3$).



1.105

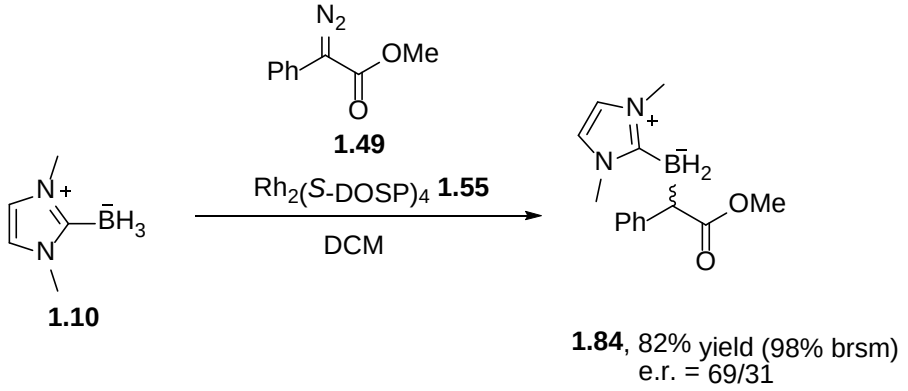
(2-(*tert*-Butoxy)-2-oxoethyl)(1,3-dimethyl-1*H*-benzo[d]imidazol-3-ium-2-yl)(2-ethoxy-2-oxoethyl)hydroborate (1.105): (1,3-Dimethyl-1*H*-benzo[d]imidazol-3-ium-2-yl)trihydroborate (**7**) (50 mg, 0.31 mmol, 1.0 equiv) and the $Rh_2(esp)_2$ (2.3 mg, 0.0031 mmol, 0.01 equiv) were dissolved in dry DCM (2 mL) under argon. The solution was dark green. The reaction mixture was heated to reflux. A solution of ethyl 2-diazoacetate (**1.51**) (0.050 mL, 0.37 mmol, 1.2 equiv) in dry DCM (2 mL) was added via syringe pump over a period of 4 h. Then a solution of *tert*-butyl 2-diazoacetate (**1.90**) (0.10 mL, 0.62 mmol, 2.0 equiv) was added via syringe pump over a period of 4 h. The reaction mixture turned brown. After the addition was complete, the solvent was removed and crude ^{1}H and ^{11}B NMR spectra were taken. The mixture was concentrated and purified by flash chromatography (Hex:EA = 2:1) to give the product **1.105** (61.4 mg, 0.17 mmol, 55%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.48 (m, 4H), 4.01 (s, 6H), 3.83 (q, J = 6.4 Hz, 3H), 1.84 (br, 1H), 1.77 (br, 3H), 1.12 (s, 9H), 0.95 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 179.0, 178.6, 133.7, 124.2, 111.2, 77.0, 58.9, 32.6, 30.0 (br), 28.6, 14.9; ^{11}B NMR (128 MHz, $CDCl_3$) δ –20.1 (d, J_{BH} = 92 Hz); IR (film) 2974, 1697, 1464, 1390, 1364; HRMS (ESI) *m/z* (M^+ + H) calcd for $C_{19}H_{30}BN_2O_4$ 361.2299, found 361.2287.



1.107

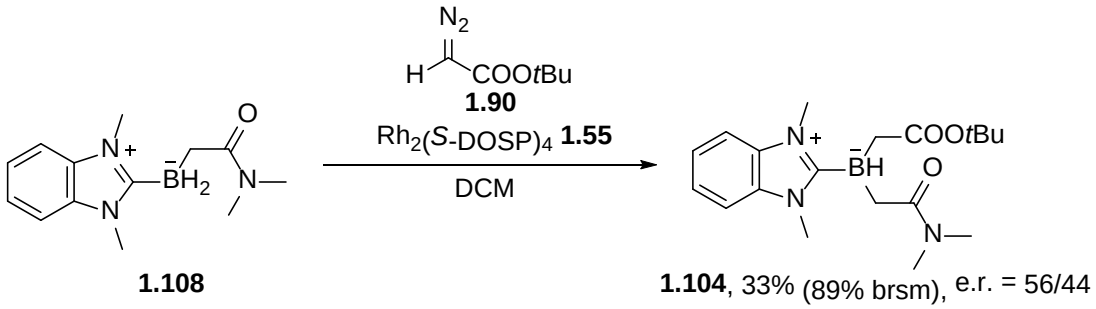
(1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2-(((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl) oxy)-2-oxo-1-phenylethyl)dihydroborate (1.107): The (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol) and $Rh_2(esp)_2$ (3.4 mg, 0.0045mmol) were dissolved in dry DCM (2 mL) under argon. The solution was dark green. The reaction mixture was heated to reflux. A solution of (1*S*,2*R*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-diazo-2-phenylacetate (**1.106**) (162.2 mg, 0.54 mmol) in dry DCM (2 mL) was added via syringe pump over a period of 4 h. The color of the solution turned to be orange. After 4 h, the solvent was removed and the crude ^{1}H and ^{11}B NMR spectra were recorded. The mixture was concentrated and purified by flash chromatography to afford 103.2 mg (60%) of product **1.107**, isolated as white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94-7.32 (m, 5H), 6.74 (s, 0.38H), 6.72 (s, 1.62H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 171.1, 146.0, 145.8, 129.1, 128.4, 127.6, 127.4, 126.8, 123.6, 122.6, 120.3, 72.5, 72.2, 47.2, 47.0, 41.3, 41.0, 36.2, 35.6, 34.4, 34.2, 31.4, 31.3, 26.1, 26.0, 23.5, 23.3, 22.7, 22.1, 21.9, 21.0; ^{11}B NMR (160 MHz, $CDCl_3$) δ –23.2 (t, J_{BH} = 90 Hz); IR (film) 3169, 3134, 3056, 3022, 2954, 2869, 2349, 2308, 1699, 1597, 1575, 1485, 1453, 1406 cm^{-1}; mp 89-92 ℃; HRMS (ESI) *m/z* (M^+) calcd for $C_{23}H_{35}BN_2O_2$ 382.2792, found 382.2790. There is no double insertion product.

Procedure for reaction (2) in Scheme 1.21:



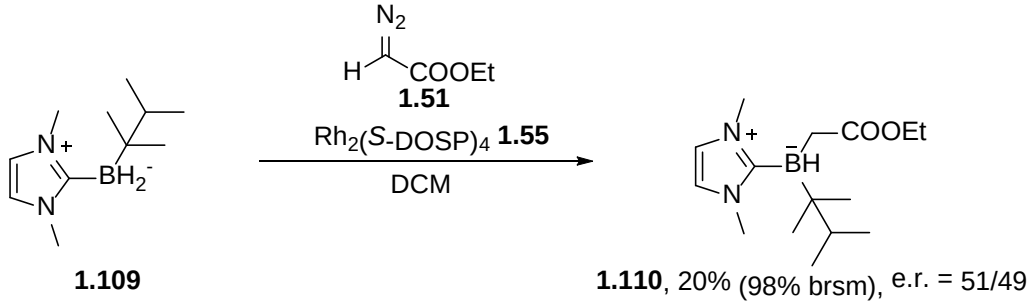
The (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (50.0 mg, 0.45 mmol) and the Rh_2(*S*-DOSP)$_4$ (**1.55**) (8.5 mg, 0.0045 mmol) were dissolved in dry DCM (2 mL) under argon. The solution was dark green. The reaction mixture was stirred at rt. A solution of methyl 2-diazo-2-phenylacetate (**1.49**) (95.1 mg, 0.54 mmol) in dry DCM (2 mL) was added via syringe pump over a period of 4 h. After 4 h, the solvent was removed and the crude ^{1}H and ^{11}B NMR spectra were recorded. The mixture was concentrated and purified by flash chromatography to give 95.3 mg (82%) of the pure product (1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)(2-methoxy-2-oxo-1-phenylethyl)dihydroborate (**1.84**). The characterization data is the same as previous synthesized compound. The two enantionmers were separated by chiral HPLC ((*S*,*S*)-Whelk-O column, hexane/iPrOH = 20:80). The ratio of integrations of the two peaks is 69/31.

Procedure for reaction (1) in Scheme 1.22:



The (1,3-dimethyl-1*H*-benzo[d]imidazol-3-ium-2-yl)(2-(dimethylamino)-2-oxoethyl)dihydroborate (**1.108**) (47.0 mg, 0.24 mmol, 1.0 equiv) and Rh_2(*S*-DOSP)$_4$ (**1.55**) (4.5 mg, 0.0024 mmol) were dissolved in dry DCM (2 mL) under argon. The solution was dark green. The reaction mixture was heated to reflux. A solution of *tert*-butyl 2-diazoacetate (**1.90**) (0.067 mL, 0.48 mmol, 2.0 equiv) in dry DCM (2 mL) was added via syringe pump over a period of 4 h. The color of the solution turned to be orange. After 4 h, the solvent was removed and the crude ^{1}H NMR and ^{11}B NMR was taken. The mixture was concentrated and purified by flash chromatography (pure acetone) to give the product **1.104** (28.4 mg, 0.079 mmol, 33%) as colorless oil. The characterization data is the same as previous synthesized compound. The two enantionmers were separated by chiral HPLC ((*S*,*S*)-Whelk-O column, hexane/iPrOH = 40:60). The ratio of integrations of the two peaks is 56/44.

Procedure for reaction (2) in Scheme 1.22:



1.109 **1.110**, 20% (98% brsm), e.r. = 51/49

The (1,3-dimethyl-1H-imidazol-3-ium-2-yl)(2,3-dimethylbutan-2-yl)dihydroborate (**1.109**) (58.2 mg, 0.30 mmol, 1.0 equiv) and Rh_2(*S*-DOSP)$_4$ (**1.55**) (5.7 mg, 0.0030 mmol) were dissolved in dry DCM (2 mL) under argon. The solution was dark green. The reaction mixture was heated to reflux. A solution of ethyl 2-diazoacetate (**1.51**) (0.089 mL, 0.60 mmol, 2.0 equiv) in dry DCM (2 mL) was added via syringe pump over a period of 4 h. The color of the solution turned to be orange. After 4 h, the solvent was removed and the crude ^{1}H NMR and ^{11}B NMR was taken. The mixture was concentrated and purified by flash chromatography to give the product **1.110** (16.8 mg, 0.06 mmol, 20%) as colorless oil: : ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (ABq, 2H, $\Delta\delta_{AB}$ = 0.012, J_{AB} = 2.0 Hz), 3.94 (s, 3H), 3.84 (q, J = 6.8 Hz, 2H) 3.79 (s, 3H), 1.67-1.76 (m, 2H), 1.36 (sep, J = 6.8 Hz, 2H), 0.98 (t, J = 6.8 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H), 0.74 (s, 3H), 0.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 121.1, 121.0, 58.2, 37.8, 37.4, 37.0, 26.6, 24.9, 18.9, 18.1, 14.4; ^{11}B NMR (128 MHz, $CDCl_3$) δ –16.3 (d, J_{BH} = 87 Hz); IR (film) 3121, 2951, 2857, 2353, 1694, 1472cm^{-1}; HRMS (ESI) *m/z* (M^+) calcd for $C_{15}H_{28}BN_2O_2$ 279.2238, found 279.2229. The two enantionmers were separated by chiral HPLC ((*S*,*S*)-Whelk-O column, hexane/iPrOH = 20:80). The ratio of integrations of the two peaks is 51/49.

Procedure for the competition reactions of NHC-borane 1.10 with THF, 1,4-cyclohexadiene and styrene: A solution of methyl 2-diazo-2-phenylacetate (**1.49**) (20.0 mg, 0.11 mmol, 0.5 equiv) in DCM (2 mL) was added to a stirred solution of $Rh_2(esp)_2$ (3.4 mg, 0.0045 mmol, 0.02 equiv), (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (25.0 mg, 0.23 mmol, 1.0 equiv) and THF (0.93 mL, 11.5 mmol, 50 equiv) or 1,4-cyclohexadiene (0.21 mL, 2.3 mmol, 10 equiv) or styrene (0.28 mL, 2.3 mmol, 10 equiv) in DCM (2 mL) via syringe pump over 2 h at rt. The solvent was removed *in vacuo* and crude ^{1}H-NMR was taken to calculate the ratio of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)(2-ethoxy-2-oxoethyl)dihydroborate (**1.84**) and methyl 2-phenyl-2-(tetrahydrofuran-2-yl)acetate (**1.119**) or methyl 2-(cyclohexa-2,5-dien-1-yl)-2-phenylacetate (**1.120**) or methyl 1,2-diphenylcyclopropanecarboxylate (**1.121**).

Procedure for kinetic isotope studies: (1,3-Dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.10**) (2.6 mg, 0.024 mmol, 1 equiv) and (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)trihydroborate (**1.126**-d_3) (2.7 mg, 0.024 mmol, 1 equiv) were dissolved in CD_2Cl_2 (0.75 mL) in a NMR tube. The ^{11}B-NMR spectrum was taken to determine the initial retio of the two substrates. Then $Rh_2(esp)_2$ (0.2 mg) and a solution of methyl 2-diazo-2-phenylacetate (**1.49**) (2.1 mg, 0.012 mmol, 0.5 equiv) in CD_2Cl_2 (0.25 mL) was added. ^{11}B-NMR was taken after 5 min to calculate the ratio of (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)(2-methoxy-2-oxo-1-phenylethyl)dihydroborate (**1.84**) and (1,3-dimethyl-1*H*-imidazol-3-ium-2-yl)(2-methoxy-2-oxo-1-phenylethyl)dihydroborate (**1.129**).

2.0 PROGRESS TOWARDS THE TOTAL SYNTHESIS OF TULEARINS

2.1 INTRODUCTION

2.1.1 Total synthesis of marine macrolides

Nature has stocked the sea with enormously rich sources of structurally diverse, often highly complex secondary metabolites.[83] These marine natural products exhibit a variety of biological activities including cytotoxicity, neurotoxicity, antiviral, and antifungal activities.[84] Among these fascinating structures, a prominent category are the marine macrolides (macrocyclic lactones). These are highly oxygenated and stereochemically elaborate polyketides which have a macrocyclic lactone as a conformational constraint.[85,86] Many marine macrolides have potent cell growth antiproliferative properties and are considered as promising lead compounds for the development of new anti-cancer chemotherapeutic agents.[87]

Three remarkable marine macrolides are shown in Figure 2.1. Spongistatins, isolated from East Indian Ocean Perifera *Spongia* sp., are bis-spiroacetal-containing marine macrolides with captivating structures.[88] They stand out as the most potent cancer cell growth inhibitory agents tested to date in the U.S. National Cancer Institute's primary panel of 60 human carcinoma cell lines having low nanomolar or picomolar GI_{50} values across the board.[89] Dictyostatin, isolated from a marine sponge of the genus *Spongia* sp., is a 22-membered

macrolide that displays low nanomolar growth inhibitory activity against a number of human cancer cell lines.[90,91] Leucascandrolide A, isolated from the New Caledonian calcareous sponge *Leucascandra caveolata*, is an 18-membered macrolide which exhibited in-vitro cytotoxicity against KB throat epithelial carcinoma and P388 murine leukemia cell.[92]

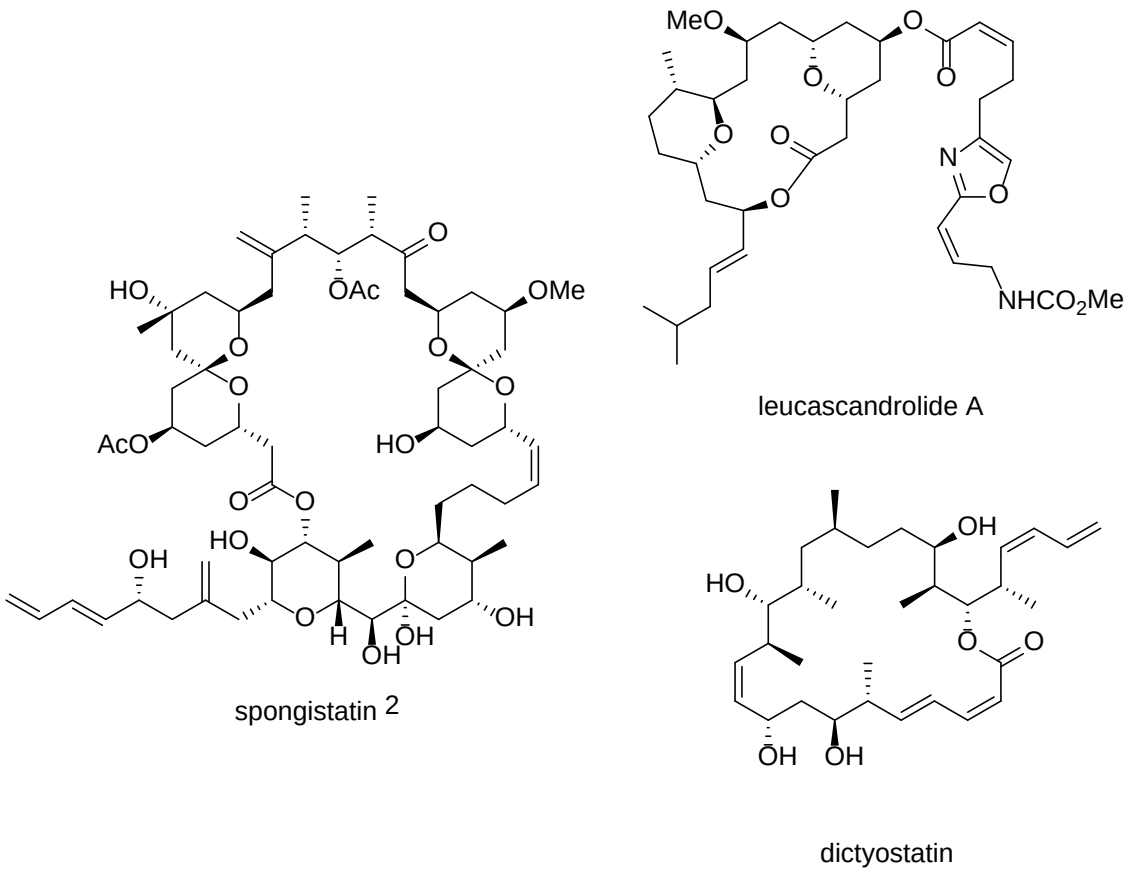


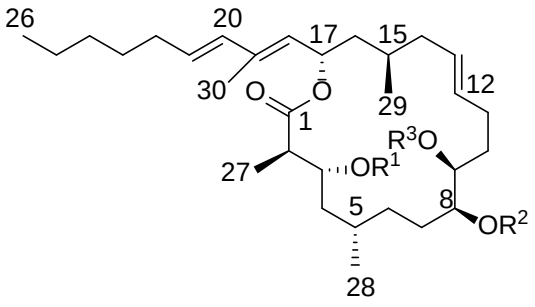
Figure 2.1 Representative marine macrolides

Because of the low natural abundance of these marine macrolides as well as the unacceptable ecological impact of large-scale isolation of the producing organism, the total synthesis of marine macrolides becomes necessary for further biological evaluations and possible future clinical use. Meanwhile, the impressive structures themselves challenge contemporary

organic synthesis with regard to both strategy and methodology for their total synthesis. For example, highly stereoselective reactions need to be applied in order to control a variety of stereocenters in the molecules. Mild reaction conditions are necessary for these kinds of highly oxygenated fragile structures. Efficient coupling reactions are needed for the combination of large fragments at the late stage of synthesis. At the same time, synthesis is also important for structural elucidation, especially for the determination of the full absolute configuration.

2.1.2 Tulearins

Tulearins are a representative family of marine macrolides that were isolated by Kashman and coworkers in 2008. Bioguided (brine shrimp test) separation of the $CHCl_3/CH_3OH$ (1:1) extract of Madagascar *Fascaplysinopsis* sp. sponge collected in Salary Bay north of Tulear provided 6.6 mg of 18-membered macrolactone, tulearin A **2.1**, a yield of 0.019 wt % (Figure 2.2).[93] Two additional tulearins were also isolated in very small quantity and designated as tulearin B **2.2** and C **2.3** (Figure 2.2).[94]



2.1 tulearin A, R^1, R^3 = H, R^2 = $CONH_2$
2.2 tulearin B, R^1, R^2 = $CONH_2$, R^3 = H
2.3 tulearin C, R^1, R^2, R^3 = H
2.4 R^1 = H, R^2, R^3 = -C(O)-

Figure 2.2 Structures of tulearin A, B and C

The effect of tulearin A **2.1** on cell proliferation was determined in two different human leukemic cell lines, K562 and UT7, using the colorimetric methylthiazole tetrazolium bromide (MTT) assay. After 3 days of culture in the presence of 0.5 μg/mL of **2.1**, ~60% of proliferation of K562 cells and ~35% of proliferation of UT7 cells were inhibited.[93]

The molecular formula of tulearin A **2.1** was assigned as $C_{31}H_{53}NO_6$ with six degrees of unsaturation or rings based on the HR-ESIMS (QqTOF) molecular ion peak (*m/z* calcd 558.3771, found 558.3757, $[M + Na]^+$). With 1D and 2D NMR data, tulearin A **2.1** was identified to consist of an *E*,*E* $\Delta^{18,20}$-diene, a nonconjugated *E* alkene (C12, C13), four oxygenated-methine (C3, C8, C9, and C17), a lactone (C1), five methyl groups (C26, C27, C28, C29, and C30) and a carbamate ester. The coupling constant (J = 15.5 Hz) between H20/H21 and the NOEs between H18/H20 and between H30/H21 established the *E*,*E* configuration of $\Delta^{18,20}$-diene. The *E* geometry of isolated double bond between C12 and C13 was assigned based on the line shape simulation.[93]

The complete 2D structure of tulearin A **2.1** was assigned by COSY and HMBC correlations. It is a 2,4,15,19-tetramethylated hexaeicosanoic polyketide acid forming an 18-membered lactone (from C1 to C17), carrying on the macrolide chain, having two hydroxyls (on C3 and C9) and one carbamate (on C8).[93] Particularly, the carbamate group is rare in nature. Only about 150 natural products with carbamate group(s) are listed in the Beilstein database. Among them, less than 20 compounds belong to macrolides, for example, palmerolide A,[95] geldanamycin[96] and saxitoxin.[97]

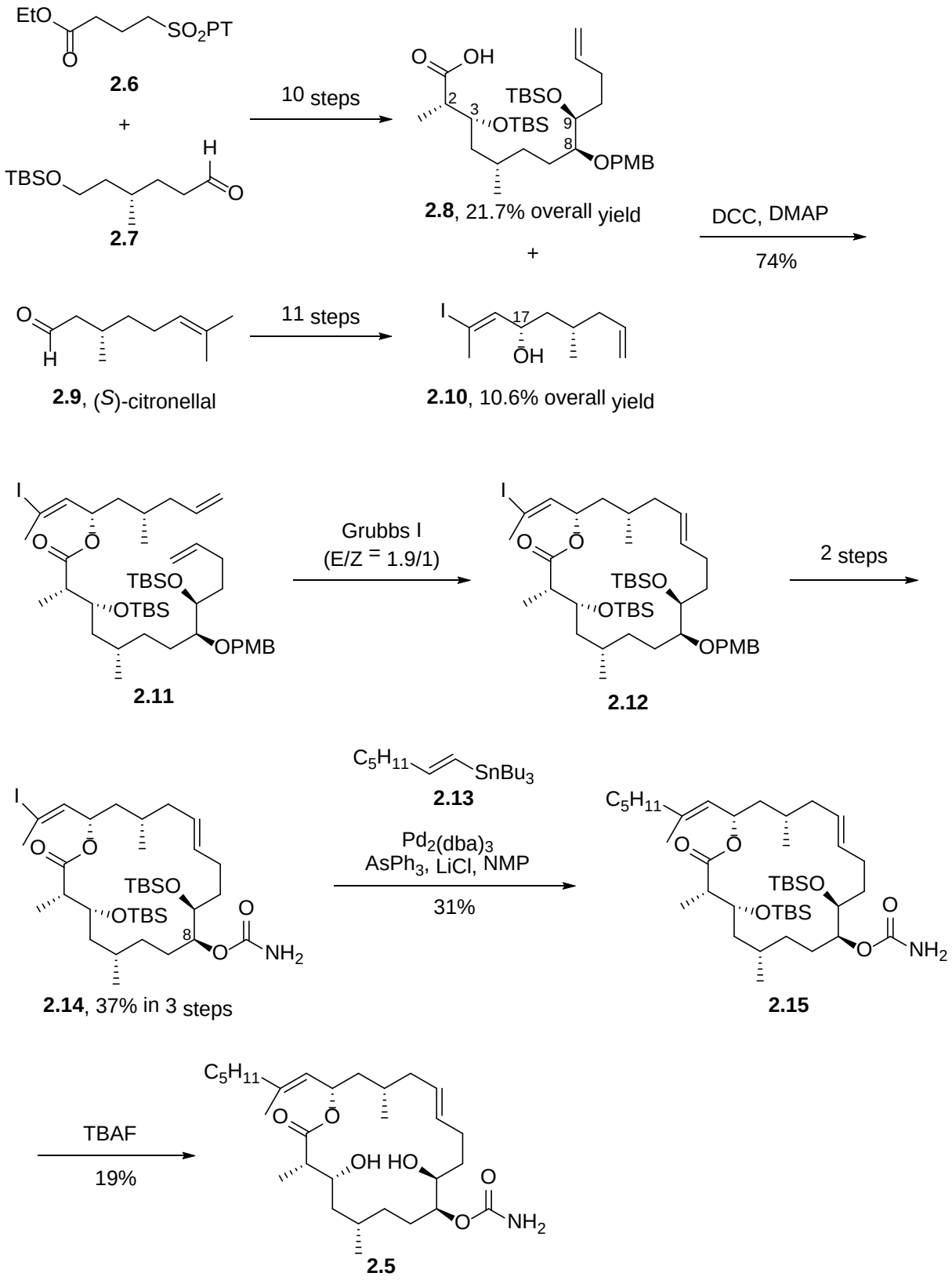
When tulearin A **2.1** was treated with a mixture of aqueous ammonia/MeOH (1:1), a less polar compound **2.4** was afforded as colorless crystals in 83% yield. Compound **2.4** gave crystals suitable for X-ray diffraction analysis, confirming its structure and establishing the relative

configuration of all seven chiral centers of tulearin A **2.1**. Using the modified Mosher's method, the absolute configuration of C9 was assigned as *S*. Hence, based on the X-ray structure, the absolute configuration of **2.1** is 2*R*,3*R*,5*S*,8*S*,9*S*,15*R*, and 17*S* as shown in Figure 2.2.[94]

2.1.3 Previous synthetic studies of Tulearins

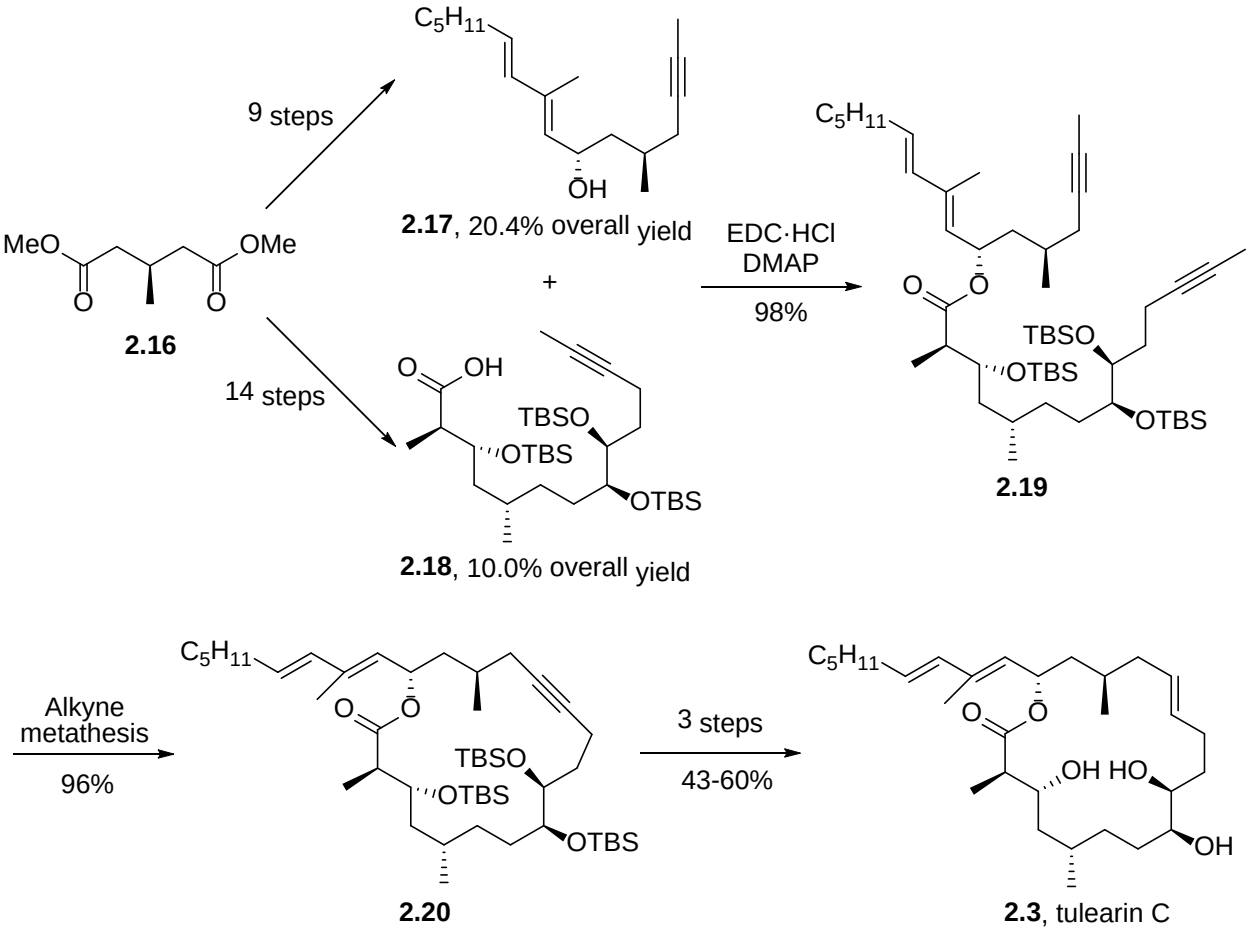
In 2009, a stereoisomer **2.5** of tulearin A **2.1** was synthesized by Cossy, Curran and co-workers (Scheme 2.1).[98] The stereoisomer **2.5** was connected by three fragments, acid **2.8** (C1–C12), vinyl iodide **2.10** (C13–C19), and stannane **2.13** (C20–C26). Acid **2.8** was synthesized from starting material sulfone **2.6** and aldehyde **2.7** in 10 steps. The stereocenters at C2 and C3 were obtained by Crimmins *syn* aldol reaction, and the stereocenters at C8 and C9 were generated from Sharpless asymmetric dihydroxylation reaction. Vinyl iodide **2.10** was obtained from (*S*)-citronellal **2.9** in 11 steps. The stereocenter at C17 was formed by Noyori asymmetric reduction. These two parts were brought together by esterification with a yield of 74%. Ring-closing metathesis was used to afford the macrocycle **2.12** in 43% yield (*E*/*Z* = 1.9/1). The carbamate was installed at the C8 position in two steps. Then Stille coupling was used to introduce the side chain to give compound **2.15** in 31% yield. The TBS group was removed by TBAF in 19% yield to provide one stereoisomer **2.5** of tulearin A **2.1**.

Several drawbacks compromise the efficiency of this route. In particular, the RCM reaction that is used to construct C12/C13 double bond only gives a *E/Z* selectivity of 1.9:1 in 43% yield. Stille coupling of stannane **2.13** with corresponding vinyl iodide only gives 31% yield. Meanwhile, the ^{1}H-NMR and ^{13}C-NMR spectra of the final product **2.5** have unidentified peaks, suggesting that the sample was not pure.



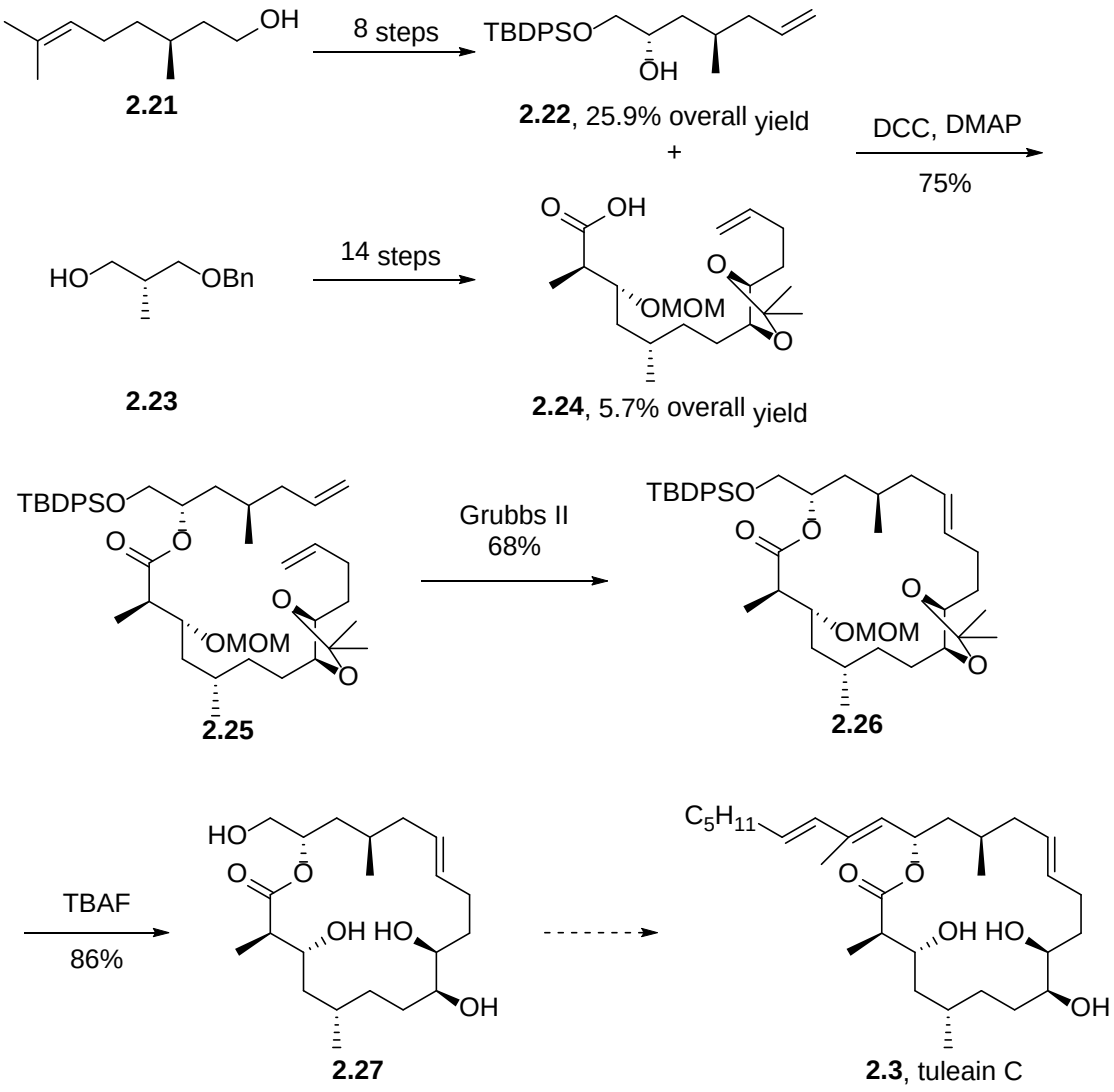
Scheme 2.1 Summary of Cossy and Curran's total synthesis of one isomer of tulearin A

The first total synthesis of tulearin C was reported by Fürstner and co-workers in 2011.[99] The top fragment **2.17** and the bottom fragment **2.18** were synthesized from the common starting material dimethyl 3-methylglutarate **2.16** in 9 steps and 14 steps, respectively. The two fragments were coupled together by esterification in 98% yield. Then the key alkyne metathesis was used for ring closure. Macrocycle **2.20** was obtained with excellent yield. The total synthesis of tulearin C **2.3** was accomplished through three subsequent conversions in 43-60% yield. In this way, the *E*/*Z* selectivity issue during the ring-closing reaction was solved. But as the two hydroxyl groups at C8 and C9 are not differentiated, the synthetic route cannot be used to finish the total synthesis of tulearin A **2.1**.



Scheme 2.2 Fürstner's total synthesis of tulearin C

Another synthetic route has been developed to construct the C1-C18 macrolactone core by Yadav (Scheme 2.3).[100] The strategy is similar to Cossy and Fürstner's total synthesis. Top fragment **2.22** and bottom fragments **2.24** were synthesized from commercially available starting material **2.21** and **2.23** in 8 steps and 14 steps respectively. The two fragments were connected together by esterification. Ring-closing metathesis was applied to finish the macrolactone core synthesis of tulearin C.



Scheme 2.3 Yadav's synthesis of macrolactone core of tulearin C

2.1.4 Synthetic plan of tulearin A

Because of the interesting biological activities and the novel skeleton of tulearins, we set out to develop a more efficient and versatile route to synthesize any stereoisomer or analog of tulearin A. These compounds could be used in biological activity tests to provide information about structure activity relationship (SAR).

There are several challenges for this total synthesis. First, the existence of carbamate group in natural products is quite rare, and there are few methods to install it at late stage of total synthesis. Second, most stereocenters in this molecule are not adjacent. It is difficult to use substrate control methods, which have proved to be quite efficient in total synthesis of macrolides, to introduce stereocenters. Third, the *E*,*E* $\Delta^{18,20}$-diene moiety with the C-17 allylic hydroxy group is chemically sensitive. Therefore no harsh conditions, especially acid conditions, are feasible after introducing this moiety.

The retrosynthetic analysis of tulearin A **2.1** is shown in Figure 2.3. The macrocycle can be synthesized by Yamaguchi lactonization. Julia-Kocienski olefination was used to couple BOM protected sulfone **2.28** and PMB protected aldehyde **2.29** to form the precursor of the macrolactonization.

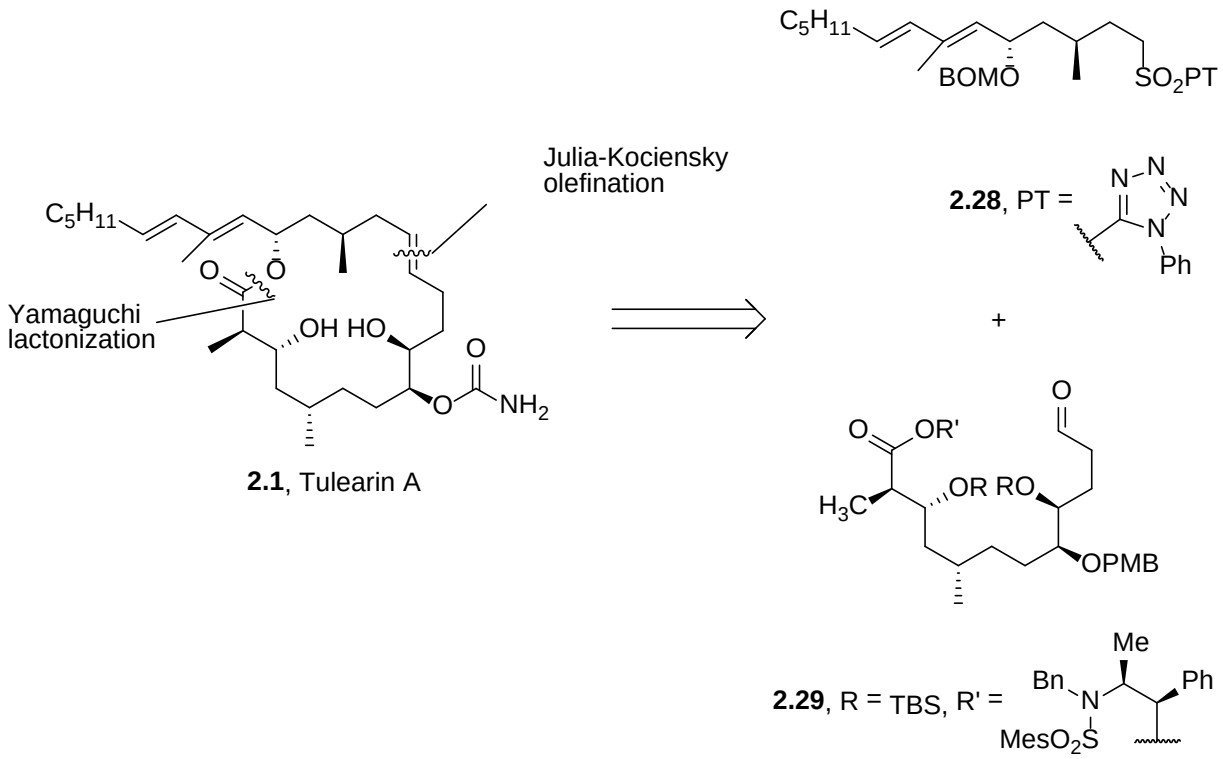


Figure 2.3 Retrosynthetic analysis of tulearin A

As shown in Figure 2.4, the C13-C26 fragment **2.28** can be synthesized by Julia-Kocienski olefination between sulfone **2.30** and aldehyde **2.31** followed by desilylation and sulfone formation. Aldehyde **2.31** can be formed from aldehyde **2.32** by Wittig olefination followed by DIBAL-H reduction and Swern oxidation. Aldehyde **2.32** can be generated from aldehyde **2.33**, which is from commercially available (*R*)-5-methoxy-3-methyl-5-oxopentanoic acid **2.34**, using a Brown allylation to construct the C17 stereocenter.

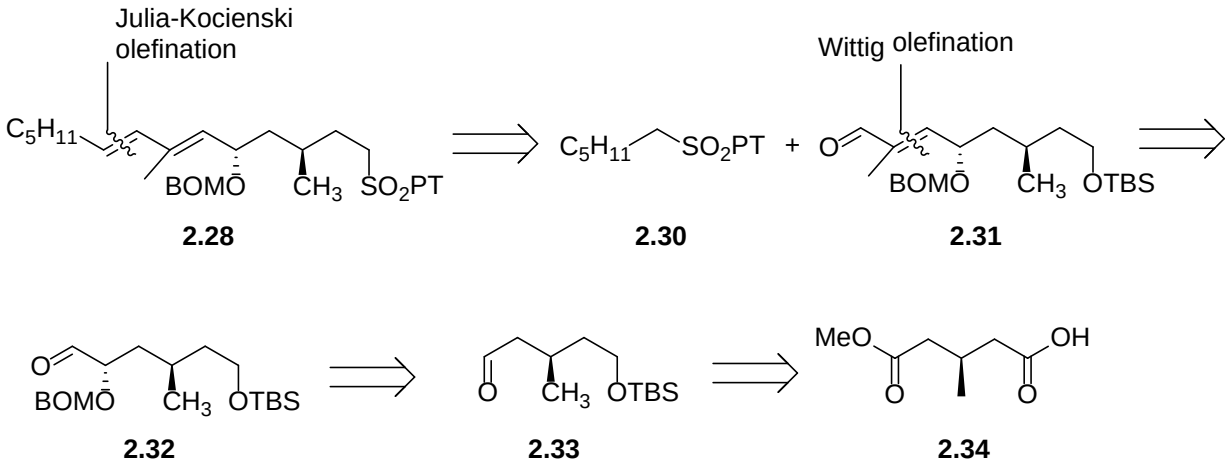


Figure 2.4 Retrosynthetic analysis of sulfone **2.28**

The C1-C12 fragment **2.29** can be obtained from aldehyde **2.35** by Masamune *anti* aldol reaction (Figure 2.5).[101] Aldehyde **2.35** is a key intermediate in Cossy's synthesis,[98] and it can be synthesized from (*S*)-citronellal **2.9** in 10 steps (22% yield).

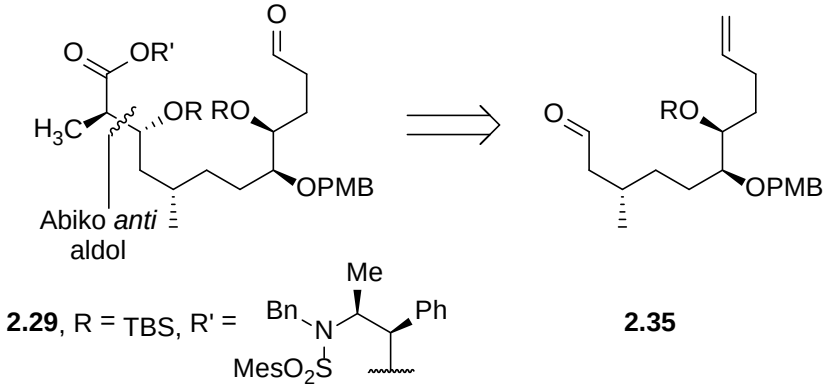
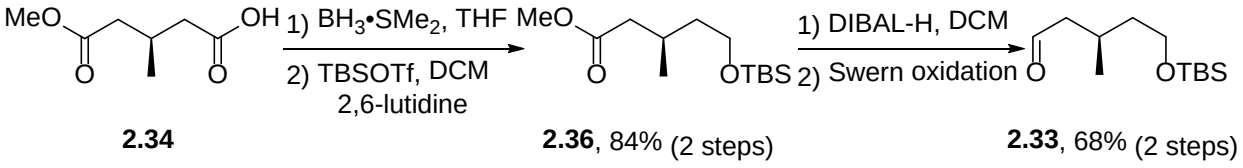


Figure 2.5 Retrosynthetic analysis of aldehyde **2.29**

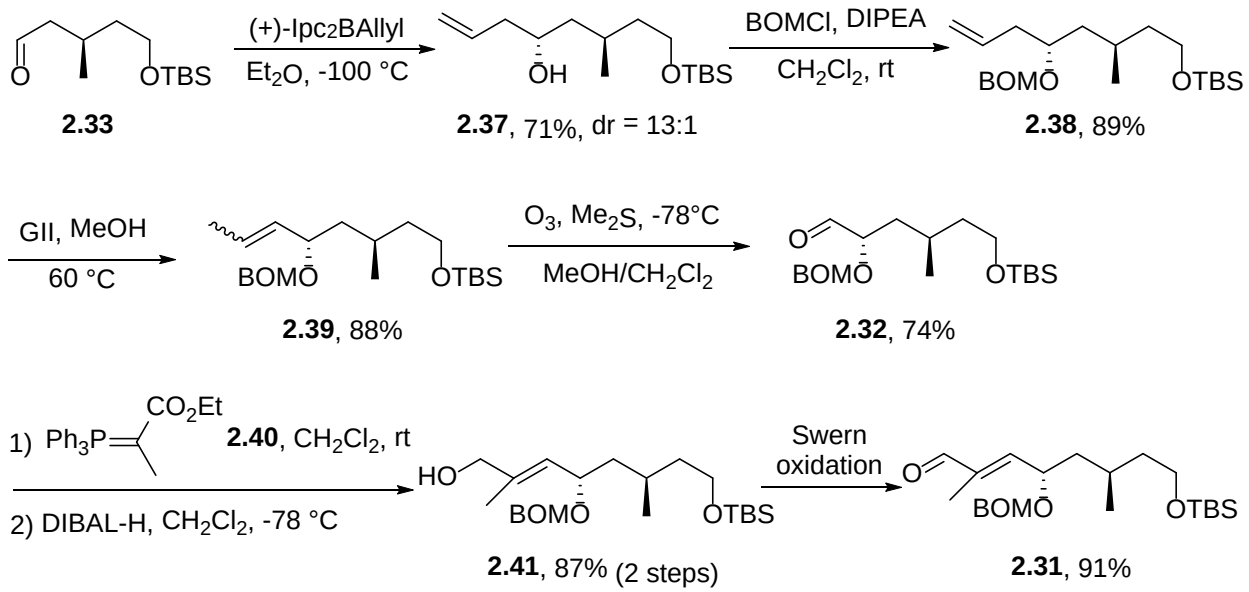
2.1.5 Dr. Sui's progress toward the total synthesis of tulearin A

Dr. Bin Sui's synthesis of sulfone **2.28** started from commercially available enantiomerically pure half-ester **2.34**. Selective reduction of acid in **2.34** provided a crude alcohol, which was protected with TBS group to give ester **2.36** in 84% yield over two steps.[102] Ester **2.36** was then reduced to an alcohol by DIBAL-H. Subsequent Swern oxidation of this alcohol afforded aldehyde **2.33** in 68% yield over two steps (Scheme 2.4).



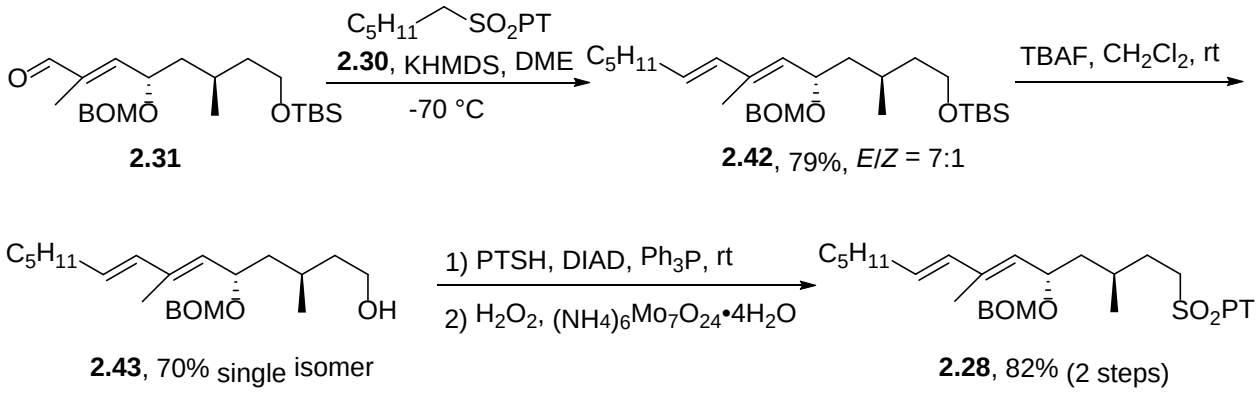
Scheme 2.4 Synthesis of aldehyde **2.33**

Alkene **2.37** was synthesized by Brown asymmetric allylation from aldehyde **2.33** with moderate selectivity (d.r. = 13:1).[103] The two diastereomers could not be separated at this step and were used together in the following reactions. Compound **2.37** was treated with benzyl chloromethyl ether (BOMCl) and Hünig's base to give protected ether **2.38**. The terminal double bond of **2.38** was isomerized by treatment with second-generation Grubbs catalyst resulting in the formation of allylic ether **2.39** in 88% yield.[104] After the double bond of **2.39** was oxidatively cleaved with ozone, aldehyde **2.32** was obtained in 74% yield. Next **2.32** was subjected to Wittig olefination with commercially available ylide **2.40** to afford an (*E*)-α,β-unsaturated ester, which was immediately reduced by DIBAL-H to provide alcohol **2.41** in 87% yield over two steps. After the Swern oxidation, the aldehyde **2.31** was obtained in 91% yield (Scheme 2.5).



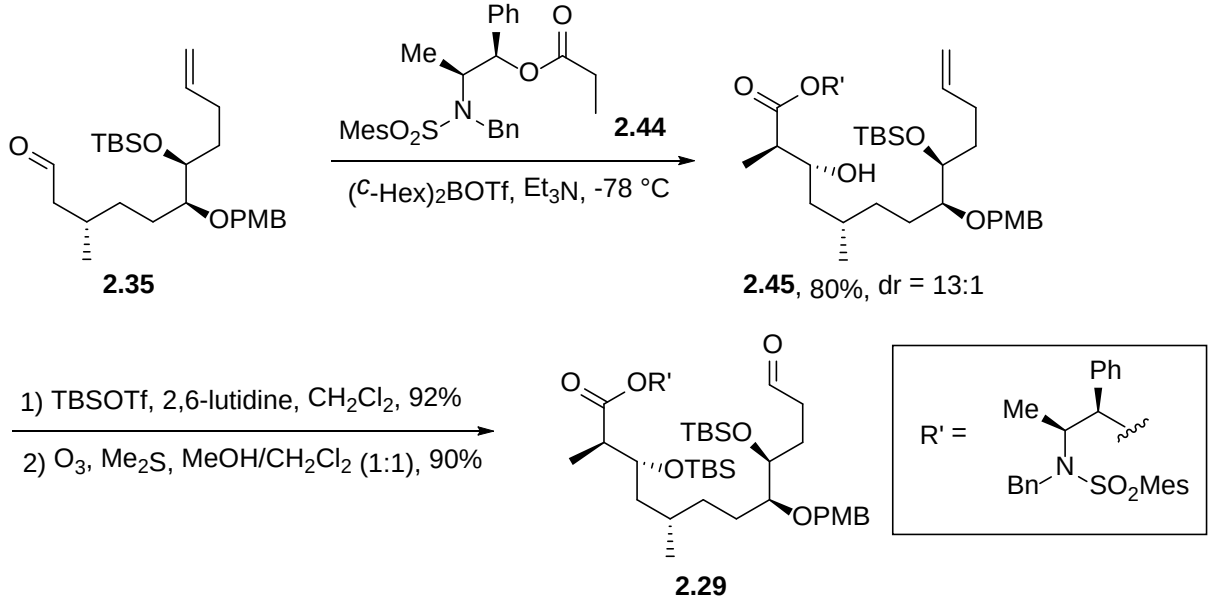
Scheme 2.5 Synthesis of aldehyde **2.31**

Julia-Kocienski olefination[105] was used to couple sulfone **2.30** and aldehyde **2.31**. The conjugated diene **2.42** was obtained in 79% yield with *E/Z* ratio of 7:1. After removal of TBS group of **2.42** with TBAF and careful purification to remove the C17 diastereomer and the *Z*-Δ^{20} isomer, the target *E*,*E*-1,3-diene **2.43** was obtained in 70% yield as a single isomer. The alcohol **2.43** was converted to the sulfide by Mitsunobu reaction (1-phenyl-1*H*-tetrazole-thiol, diisopropyl azodicarboxylate, and Ph_3P). The sulfide was oxidized with H_2O_2 in the presence of catalytic amount of $(NH_4)_6Mo_7O_{24}$ in ethanol to afford sulfone **2.38** in 82% yield over two steps.[106] Thus, fragment C13–C26 **2.38** was gained in 10.2% over 15 steps (Scheme 2.6).



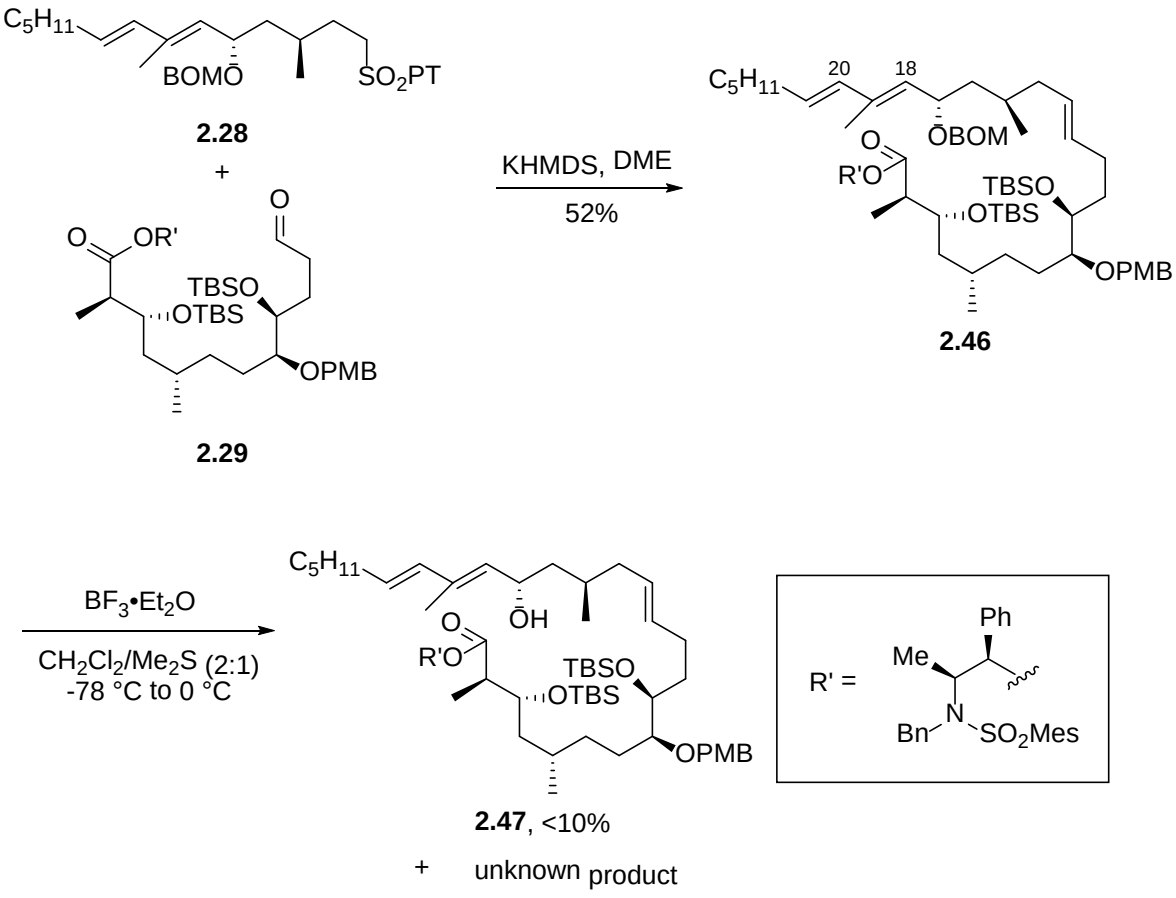
Scheme 2.6 Synthesis of C13-C26 fragment sulfone **2.28**

The synthesis of aldehyde **2.29** is summarized in Scheme 2.7. The key intermediate **2.35** can be synthesized in 22% over 10 steps followed by Cossy's synthetic route.[98] Aldehyde **2.35** was subjected to Masamune's *anti* aldol reaction to afford the desired product in 80% yield with d.r. of 13:1.[101] After protection of the free alcohol at C3 with TBSOTf in 92% yield, the double bond was oxidatively cleaved with ozone to provide aldehyde **2.29** in 90% yield. Thus, the C1–C12 fragment **2.29** was obtained in 14.4 % yield over 13 steps.



Scheme 2.7 Synthesis of C1-C12 fragment aldehyde **2.29**

As shown in Scheme 2.8, the top fragment sulfone **2.28** and the bottom fragment aldehyde **2.29** were coupled by Julia-Kocienski olefination in 52% yield with excellent *E* selectivity.[105] However, when compound **2.46** was treated with BF_3•Et_2O in CH_2Cl_2/Me_2S (2/1) at −78 °C to deprotect the BOM group,[107] the alcohol **2.47** was isolated in less than 10% yield. The major product was an unidentified compound without the *E*,*E* $\Delta^{18,20}$-diene moiety.



Scheme 2.8 Efforts towards synthesis of tulearin A

Dr. Bin Sui made significant progress, but several problems still need to be solved in order to accomplish the total synthesis of tulearin A. First, because of the low yield of the deprotection of BOM group, efficient methods are needed to remove this protecting group.

Otherwise, another protecting group should be used so that it can be removed under mild conditions. Second, the linear synthetic sequence of the top fragment is too long. A more convergent synthetic route should be developed in order to make the synthesis more efficient. Third, the selectivities of the asymmetric Brown allylation used to create the C17 stereocenter and the Julia-Kocienski olefination used to form C20/C21 double bond are moderate. As a result, purification of the product became an issue, especially for large-scale synthesis.

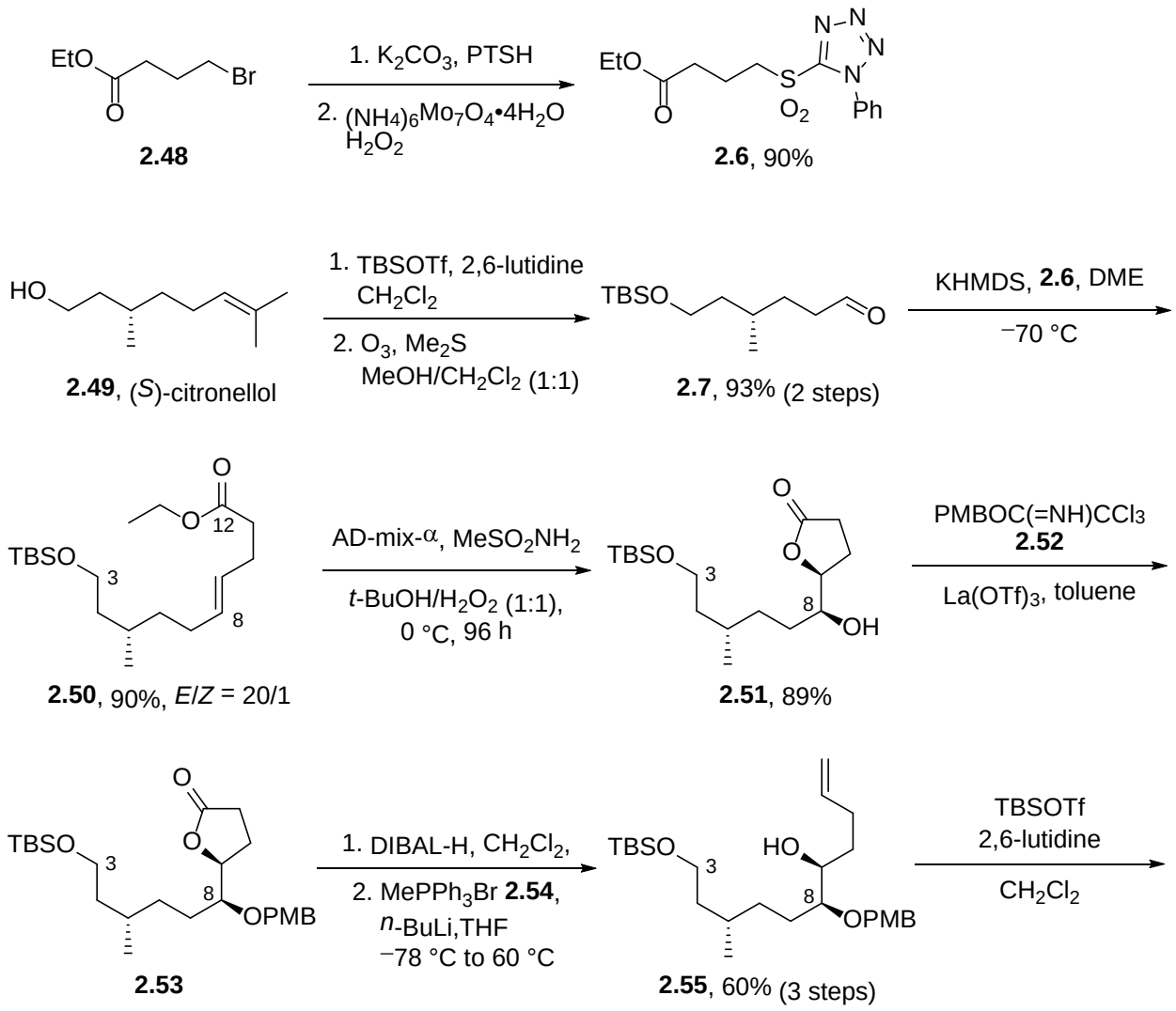
2.2 RESULTS AND DISCUSSION

2.2.1 Large-scale synthesis of the bottom fragment (C1-C12 fragment) of tulearin A

The large-scale synthesis of aldehyde **2.29** followed Dr. Bin Sui's synthetic route, as shown in Scheme 2.9. Sulfone **2.6** was obtained by substitution of ethyl 4-bromobutyrate **2.48** with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH), followed by oxidation with H_2O_2 in the presence of catalytic amount of $(NH_4)_6Mo_7O_{24}$ in ethanol in 90% yield over two steps.[106] Protection of the free hydroxyl group in commercially available (*S*)-citronellol **2.49** with a TBS group followed by ozonolysis of the double bond afforded the known aldehyde **2.7** in 93% yield over two steps.[108]

Julia-Kocienski olefination between aldehyde **2.7** and sulfone **2.6** was performed by treating with KHMDS in DME at –70 °C to give alkene **2.50** in 90% yield with good *E* selectivity (E/Z = 20:1).[105] The selectivity was determined by ^{1}H-NMR analysis of the crude product, and the Z isomer was separated by column chromatography. Sharpless asymmetric dihydroxylation[109] of alkene **2.50** with AD-mix-α and methanesulfonamide in *t*-BuOH/H_2O (1:1) at 0 °C for 96 h gave rise to a diol that spontaneously cyclized to form the five-membered

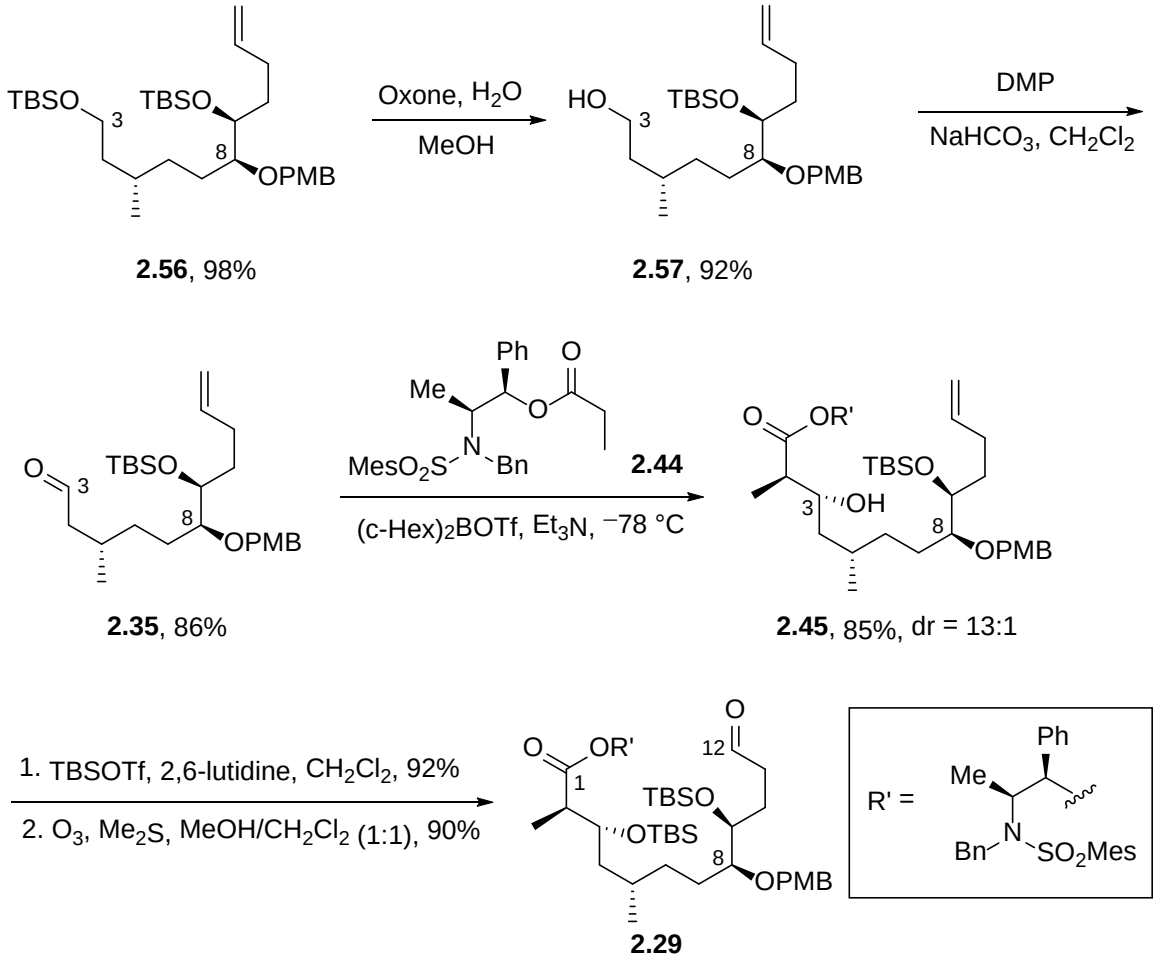
lactone **2.51** in 89% yield. Thus, the two hydroxyl groups (C8 and C9) were differentiated in preparation for later introduction of the carbamate group at C8. The stereochemistry of C8 and C9 was assigned as 8*S* and 9*S* based on the Sharpless AD model.[110]



Scheme 2.9 Synthesis of C1-C12 fragment aldehyde **2.29**

The free hydroxyl group at C8 in lactone **2.51** was protected with a PMB group by treating it with 4-methoxylbenzyl-2,2,2-trichloroacetimide **2.52** in the presence of lanthanum

triflate to give lactone **2.53**.[111] The lactone **2.53** was directly reduced by DIBAL-H at –78 °C and the resulting hemiacetal was treated with methyltriphenylphosphonium bromide **2.54** and *n*-BuLi to provide alkene **2.55** in 60% yield over three steps. Protection of the free hydroxyl group at C9 in alkene **2.55** as a TBS ether gave the fully protected alkene **2.56** in 98% yield. The primary TBS group at C3 in alkene **2.56** was deprotected selectively with Oxone to give alcohol **2.57** in 92% yield.[112] The free hydroxyl group in alcohol **2.57** was then oxidized with Dess-Martin periodinane (DMP) to afford aldehyde **2.35** in 86% yield.



Scheme 2.10 Synthesis of C1-C12 fragment aldehyde **2.29** (Cont.)

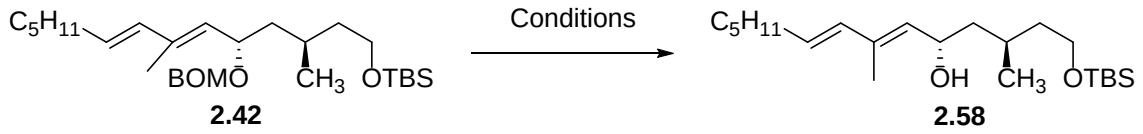
Abiko chiral auxiliary **2.44** was chosen to construct the final two stereocenters and conditions were used to provide the *anti* aldol product.[101] Chiral auxiliary **2.44** was treated with dicyclohexylboron triflate ((*c*-hex)$_2$BOTf) and triethylamine (Et_3N) to give an enolate intermediate that was reacted with aldehyde **2.35** to afford the aldol product **2.45** in 85% yield with good diastereoselectivity (d.r. = 13:1) based on analysis of ^{1}H-NMR spectra. The stereochemistry at C2 and C3 was assigned by Abiko's model as 2*R* and 3*R*.[113] After protection of the free hydroxyl group at C3 as TBS ether in 92% yield, the double bond was oxidatively cleaved with ozone to provide the aldehyde **2.29** in 90% yield. Thus, the C1-C12 fragment **2.29** was obtained in 24.4% yield over 13 steps in gram scale. This work shows that the synthetic route to the bottom fragment is practical and scalable.

2.2.2 New synthetic route for top fragment (C13-C26 fragment)

2.2.2.1 Attempts for removal of BOM group at C17

As shown in Dr. Bin Sui's work (Scheme 2.8), when the advanced intermediate **2.46** was treated with BF_3•Et_2O in CH_2Cl_2/Me_2S (2/1) at −78 °C, alcohol **2.47** was isolated in less than 10% yield. Therefore, suitable conditions are needed to remove the BOM group without touching the PMB group. However, after literature searching, only the strong Lewis acid BF_3 and potential reducing reagent lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB) can potentially be used. To study whether the BOM ether at C17 can be cleaved in the presence of the *E*,*E* $\Delta^{18,20}$-diene moiety under these conditions, a model study was applied to BOM ether **2.42**. When this was subjected to the same conditions as before (BF_3•Et_2O, CH_2Cl_2/Me_2S = 2:1, −78 °C),[107] only 18% target product **2.58** was isolated, and 50% starting material **2.42** was recovered. When ethanethiol was used instead of dimethyl sulfide,[114] the substrate **2.42** decomposed quickly. Meanwhile,

treatment of **2.42** with lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB) in THF at −78 °C for 5 min[115] gave a crude product that lacked signal of the diene moiety in ^{1}H NMR spectrum.



2.42 **2.58**

Conditions:
1. BF_3•Et_2O, DCM/Me_2S = 2:1, -78ºC, 20 min, 18% yield (36% based on recovering starting material)
2. BF_3•Et_2O, DCM/EtSH = 8:1, -78ºC, 5 min, decomposition
3. LiDBB, THF, -78ºC, 5 min, decomposition

Scheme 2.11 Deprotection of BOM Group

Based on these results, we decided to replace the BOM group at C17 by another protecting group that can be removed under milder conditions. The acetate group is a potential candidate because it can be removed when the chiral auxiliary is cleaved. In Dr. Bin Sui's synthetic route, it is difficult to change the BOM group because it was installed at early stage. Accordingly, we designed a more convergent and more stereoselective synthetic route to form C13-C26 fragment.

2.2.2.2 Retrosynthetic analysis of synthesis of sulfone 2.59

As shown in scheme 2.12, sulfone **2.59** can be synthesized by asymmetric Nozaki-Hiyama-Kishi (NHK) reaction between aldehyde **2.33** and vinyl iodide **2.61** followed by introducing protecting groups, desilylation and sulfone formation. With the key intermediate **2.60**, it is easier to try different protecting groups. Vinyl iodide **2.61** can be formed by zirconium catalyzed $AlMe_3$ addition to alkyne **2.62**.[116] Enyne **2.62** can be generated by Sonogashira coupling from vinyl iodide **2.63**, which can be obtained from commercially available 1-heptyne **2.64**.[117]

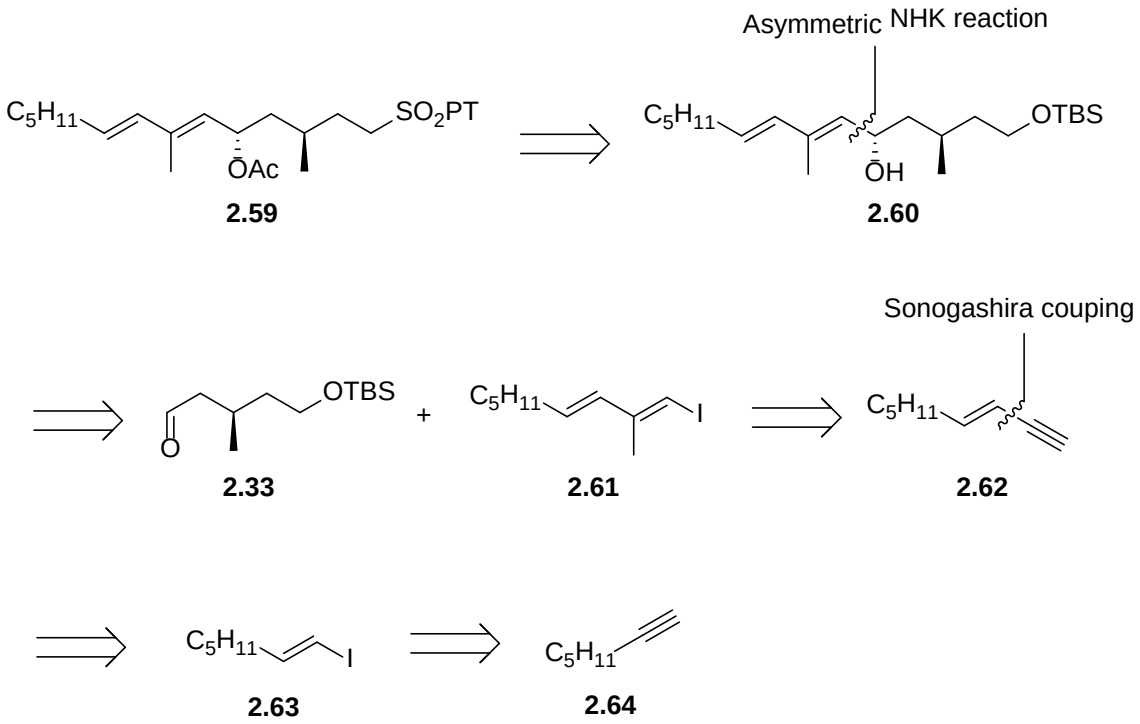
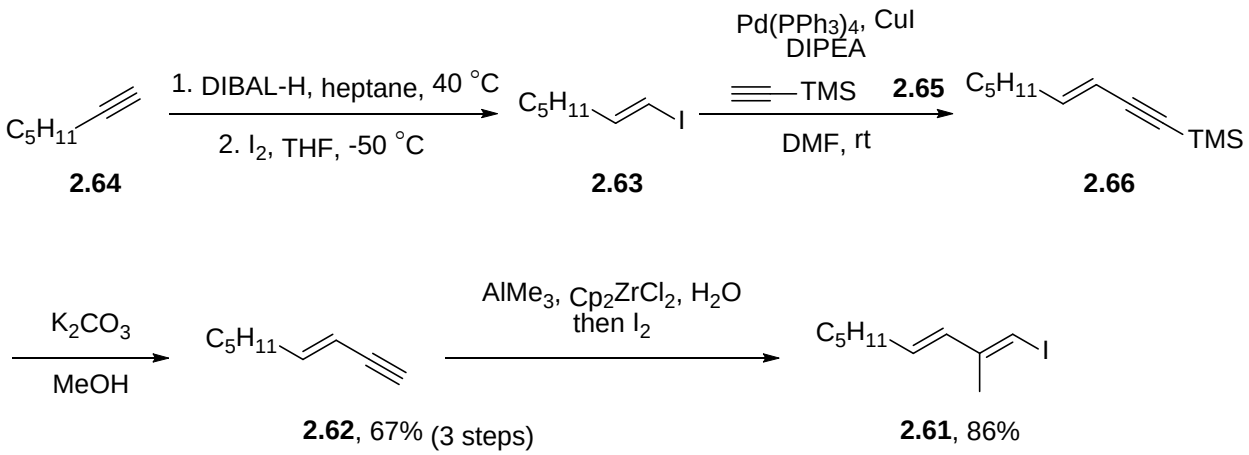


Figure 2.6 Retrosynthetic analysis of sulfone **2.59**

2.2.2.3 Synthesis of sulfone 2.59

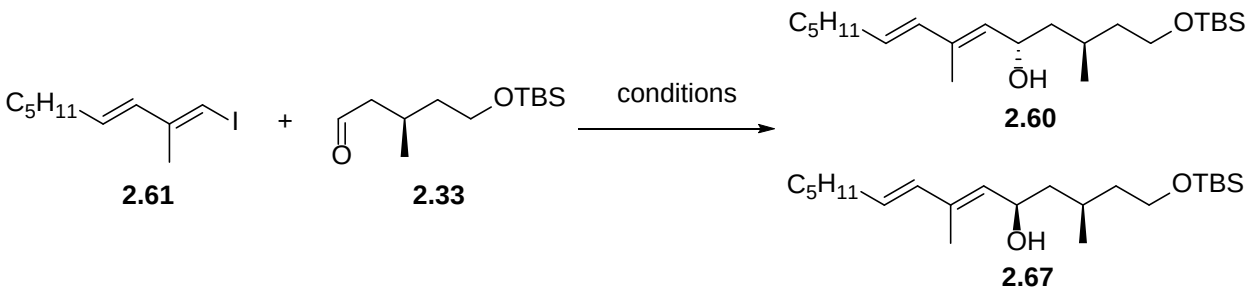
The synthesis of vinyl iodide **2.61**, shown in scheme 2.13, started from commercially available compound 1-heptyne **2.64**. This was treated with DIBAL-H at 40 °C in heptane to form the vinyl aluminum compound, which was quenched by I_2 at –50 °C in THF to afford vinyl iodide **2.63**.[117] Sonogashira coupling between vinyl iodide **2.63** and ethynyltrimethylsilane **2.65** catalyzed by $Pd(PPh_3)_4$ and CuI with Hünig's base (*N*,*N*-diisopropylethylamine, DIPEA)[118] gave TMS-protected enyne **2.66**. Then this was treated with potassium carbonate in methanol to remove TMS group to produce enyne **2.62**, which was purified by distillation in 67% yield over three steps. Enyne **2.62** was subjected to trimethylaluminum ($AlMe_3$) addition which was catalyzed by bis(cyclopentadienyl)zirconium(IV) dichloride ($ZrCl_2Cp_2$) and promoted by water to give vinyl

iodide **2.61** in 86% yield.[116] The *E,E* $\Delta^{18,20}$-diene moiety was formed as a single isomer, and the route was scaled up to provide about 10 g of vinyl iodide **2.61**.



Scheme 2.12 Synthesis of vinyl iodide **2.61**

Aldehyde **2.33** was obtained through Dr. Bin Sui's synthetic route described in Scheme 2.4. When Nozaki-Hiyama-Kishi reaction ($CrCl_2$, $NiCl_2$)[119] was used to couple aldehyde **2.33** and vinyl iodide **2.61**, only trace amount of the expected alcohol **2.60** or **2.67** was isolated. When aldehyde **2.33** was treated with vinyllithium reagent which derived from lithium-halogen exchange of vinyl iodide **2.61** and *t*-BuLi at –78 °C,[120] the coupled product **2.60** and its C17 diastereomer **2.67** were synthesized in a ratio of 1.1:1 as determined by ^{1}H-NMR analysis. The two diasteromers **2.60** and **2.67** can be separated by column chromatography. The isolated yields of **2.60** and **2.67** were 38% and 35%, respectively. So no further improvement was made to increase the diastereoselectivity of the coupling reaction between vinyl iodide **2.61** and aldehyde **2.33**.



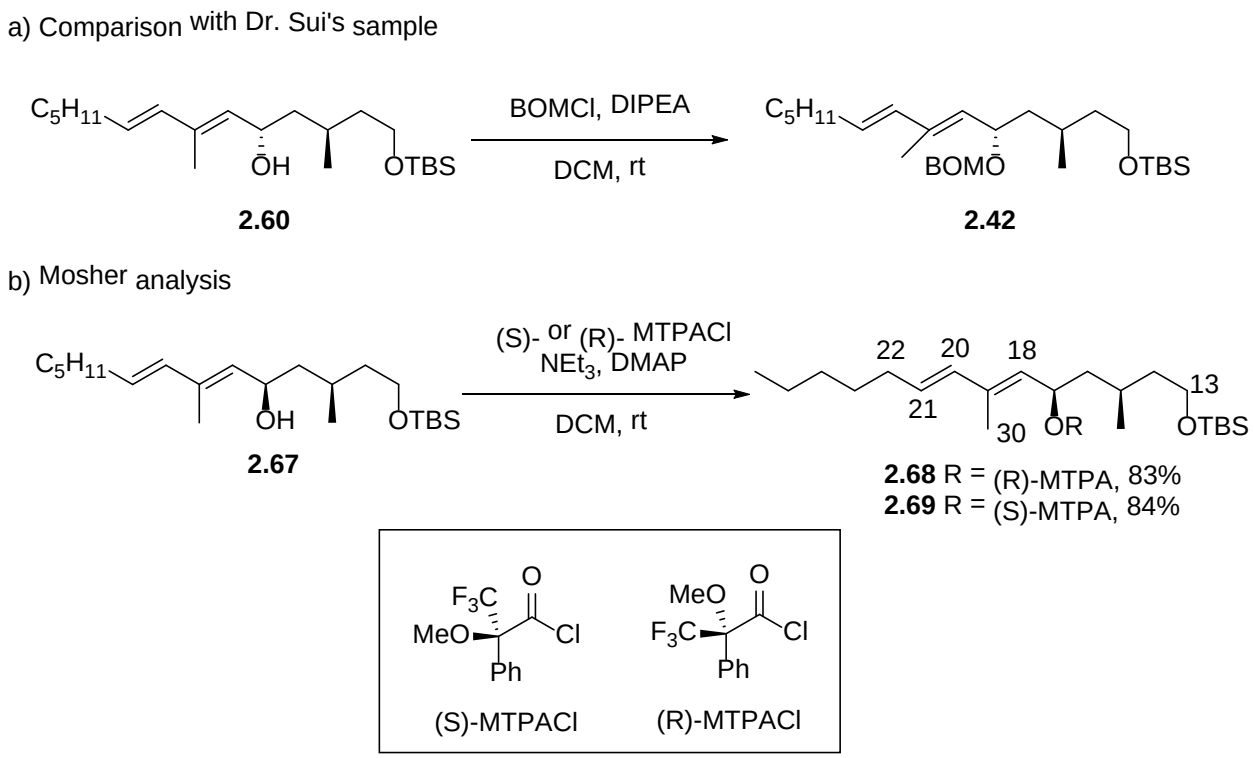
2.61 **2.33** **2.60** **2.67**

Condtions:

1. t-BuLi, Et_2O, $^{-}78\ ^{\circ}C$, 73%, **2.60**:**2.67** = 1.1:1
2. $CrCl_2$, $NiCl_2$, DMF, trace

Scheme 2.13 Coupling reactions between vinyl iodide **2.61** and aldehyde **2.33**

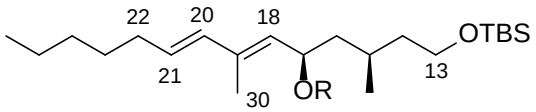
The configuration of C17 in alcohol **2.60** was determined by two methods. Alcohol **2.60** was protected by benzyloxymethyl chloride (BOMCl) with Hünig's base (*N*,*N*-diisopropylethylamine, DIPEA) in CH_2Cl_2 to afford the BOM ether **2.42** in 97% yield. In Dr. Bin Sui's synthetic route, the stereocenter at C17 in the same compound **2.42** was assigned by the model of asymmetric Brown allylation.[103] The new sample shared the same analytical data (^{1}H-NMR, ^{13}C-NMR and optical rotation) with Dr. Bin Sui's compound **2.42**.



Scheme 2.14 Determination of stereochemistry at C17

Meanwhile, the stereocenter of C17 in alcohol **2.60** was confirmed with Mosher ester method in order to make sure the Brown's model was valid. When undesired alcohol **2.67** was treated with (*S*)- and (*R*)- MTPACl (structures shown in scheme 2.15), the corresponding Mosher esters **2.68** ((*R*)-MTPA) and **2.69** ((*S*)-MTPA) were obtained. The chemical shift differences of the protons on C13, C18, C20, C21, C22 and C30 are listed in Table 2.1. The absolute configuration was assigned as *R* in the diastereomer **2.67** by applying the advanced Mosher rule.[121]

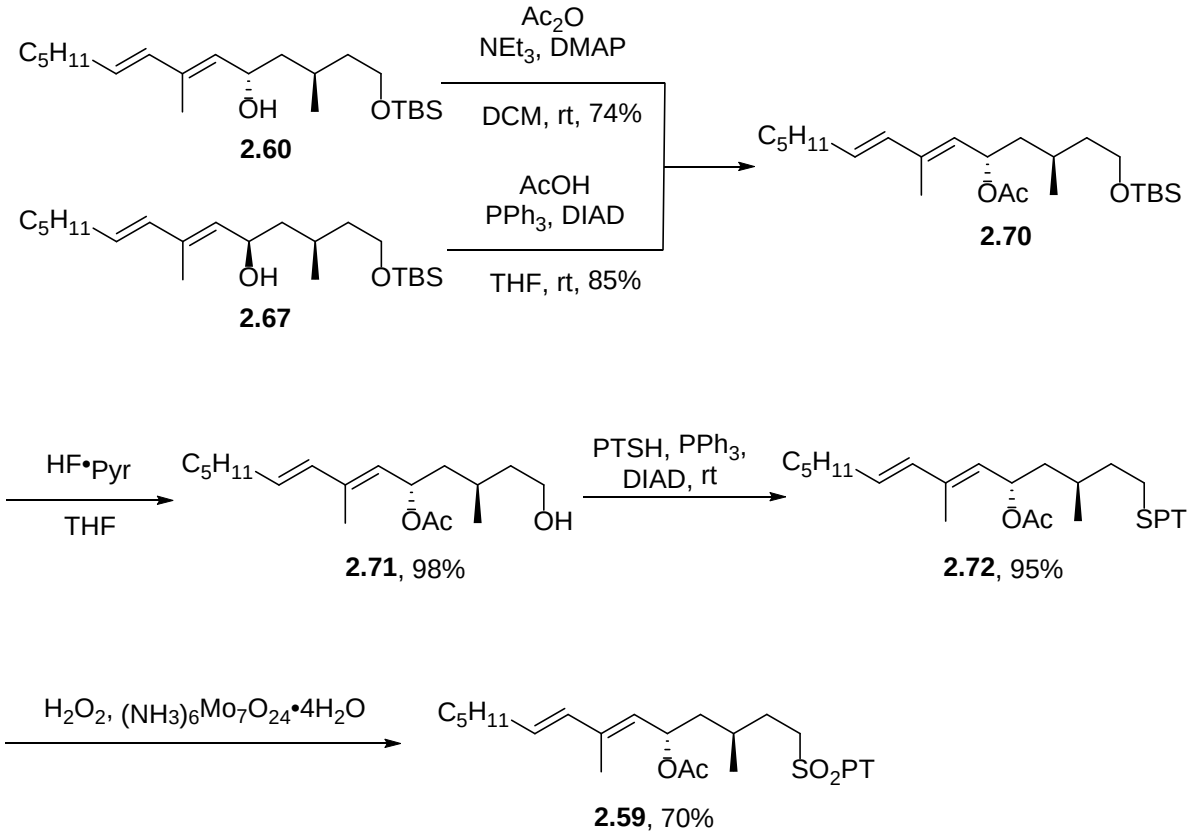
Table 2.1 ^{1}H NMR chemical shift of (*S*)- MTPA **2.68** and (*R*)- MTPA **2.69** in ppm, solvent $CDCl_3$



2.68 R = (*R*)-MTPA, 83%
2.69 R = (*S*)-MTPA, 84%

Atom No.	18	30	20	21	22	13
δ((*S*)-MTPA)	5.114	1.886	5.973	5.751	2.092	3.615
δ((*R*)-MTPA)	5.263	1.897	6.026	5.769	2.103	3.562
Δ((*S*)-(*R*))	-0.149	-0.011	-0.053	-0.018	-0.011	+0.053

With a confident assignment of the stereochemistry, alcohol **2.60** was acetylated to give the acetate-protected **2.70** by using Ac_2O, Et_3N and DMAP in DCM in 74% yield. Meanwhile, the diastereomer **2.67** was transferred to the same compound **2.70** by Mitsunobu reaction with AcOH, diisopropyl azodicarboxylate (DIAD), and Ph_3P to invert the stereocenter at C17 in 86% yield. HF/Pyridine in THF was used to remove TBS group of compound **2.70** to form alcohol **2.71** in 98% yield. Alcohol **2.71** was converted to sulfide **2.72** by Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-thiol (PTSH), diisopropyl azodicarboxylate (DIAD), and Ph_3P in 95% yield. The sulfide **2.72** was oxidized with H_2O_2 in the presence of catalytic amount of $(NH_4)_6Mo_7O_{24}$ in ethanol to afford sulfone **2.59** in 70% yield.[106]

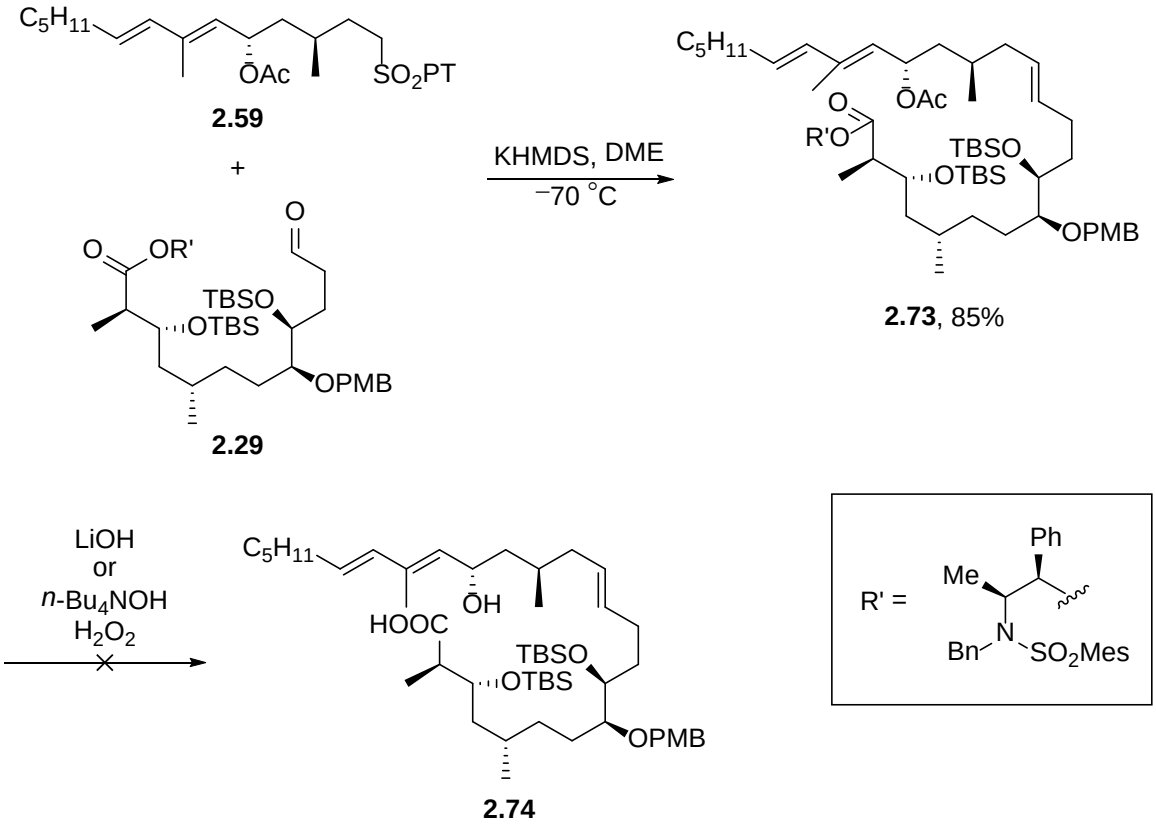


Scheme 2.15 Synthesis of C13–C26 fragment sulfone **2.59**

The synthesis of C13-C26 fragment sulfone **2.59** was accomplished in 22% yield over 13 steps. The longest linear synthetic route takes 9 steps, which is 6 steps shorter than Dr. Bin Sui's route. Meanwhile, the protecting group at C17 was introduced after the carbon skeleton was constructed. The *E,E* $\Delta^{18,20}$-diene moiety is formed as a single isomer. The single isomer **2.59** with the correct C17 stereocenter configuration was synthesized in gram scale.

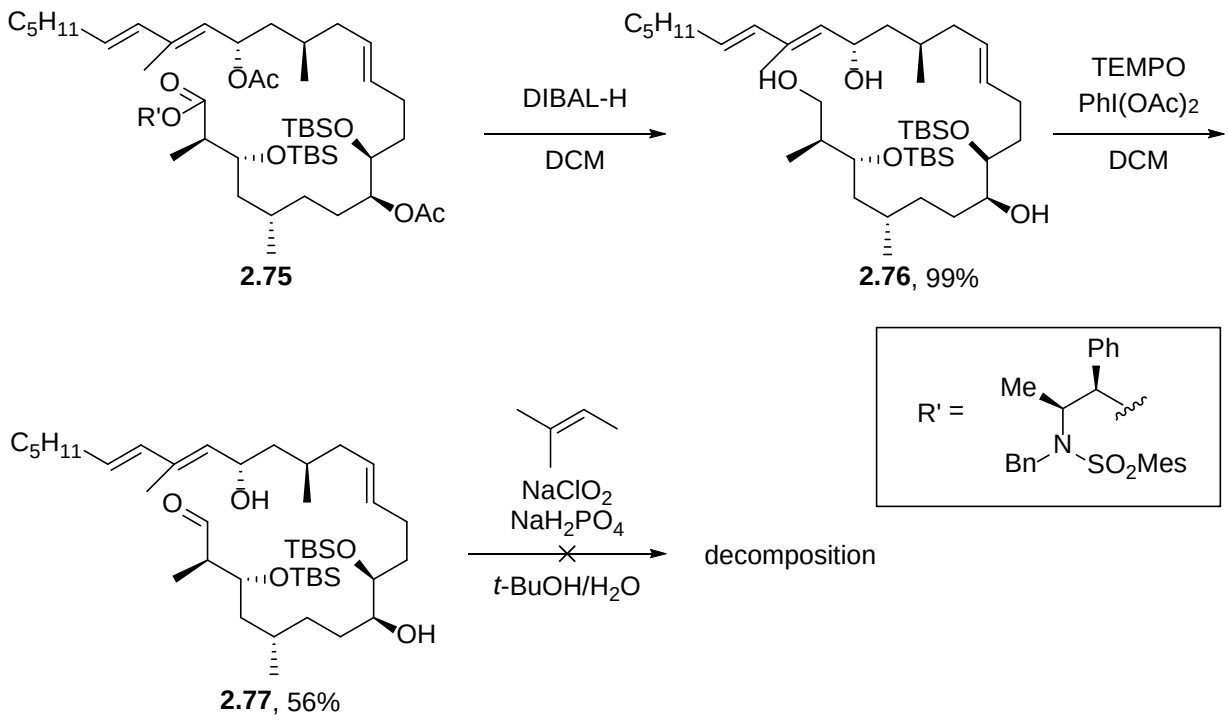
2.2.3 Coupling two fragments and following reactions toward the total synthesis of tulearin A

As shown in Scheme 2.17, acetate-protected top fragment **2.59** and aldehyde **2.29** were coupled by Julia-Kocienski olefination by treating with KHMDS in DME at –70 °C to afford the coupled product **2.73** in 85% yield with excellent *E* selectivity, which was assigned by the analysis of ^{1}H-NMR spectrum. When the coupled compound **2.73** was subjected to LiOH•H_2O in THF/H_2O = 2/1 at room temperature for seven days,[101] the chiral auxiliary was not hydrolyzed. When **2.73** was treated with a stronger base (*n*-Bu_4NOH, H_2O_2) in DME,[122] acid **2.74** was not formed. In these reactions crude ^{1}H-NMR spectra and TLC analysis showed decomposition of the substrate.



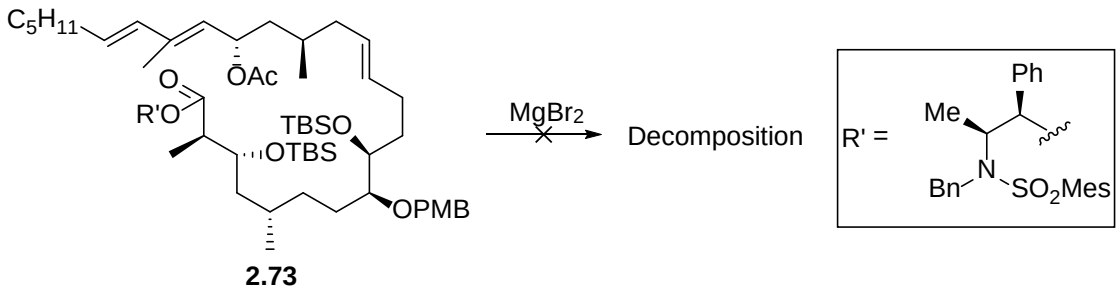
Scheme 2.16 Efforts toward the total synthesis of tulearin A with PMB group at C8

Based on the difficulties of removal of the chiral auxiliary under basic conditions, reduction conditions such as DIBAL-H were considered as alternatives (Scheme 2.17). Coupled compound **2.75** was treated with excess DIBAL-H in DCM at –78 °C to reduce the ester to primary alcohol, as well as to deprotect the acetate group at C17 to give alcohol **2.75** in 92% yield. Then the bulk oxidant (TEMPO, $PhI(OAc)_2$)[123] was used in order to control the selectivity. The primary alcohol **2.76** was oxidized selectively under this condition to form aldehyde **2.77** in 74% yield. However, when aldehyde **2.77** was treated with $NaClO_2$, NaH_2PO_4 and 2-methyl-2-butene in *t*-BuOH/H_2O,[124] the ^{1}H-NMR spectrum of the crude products showed decomposition of the starting material. A possible reason is that the reactive byproduct HOCl reacts with the *E*,*E* $\Delta^{18,20}$-diene moiety of the substrate instead of the scavenger, 2-methyl-2-butene.



Scheme 2.17 Removal the chiral auxiliary by reduction

Meanwhile, a model reaction was tested with **2.73** to find out whether the PMB group at C8 can be removed at later stage of the total synthesis (Scheme 2.18). Because of the existence of *E,E* $\Delta^{18,20}$-diene moiety, DDQ cannot be used to remove the PMB group. Therefore, advanced intermediate **2.73** was treated with weak Lewis acid $MgBr_2$.[125] The ^{1}H-NMR spectrum of the crude product shown *E,E* $\Delta^{18,20}$-diene moiety was absent while PMB group was present. This suggested that under Lewis acid conditions, the PMB group at C8 is more stable than the *E,E* $\Delta^{18,20}$-diene. Therefore, PMB group at C8 is not a suitable protecting group when the *E,E* $\Delta^{18,20}$-diene moiety exists.

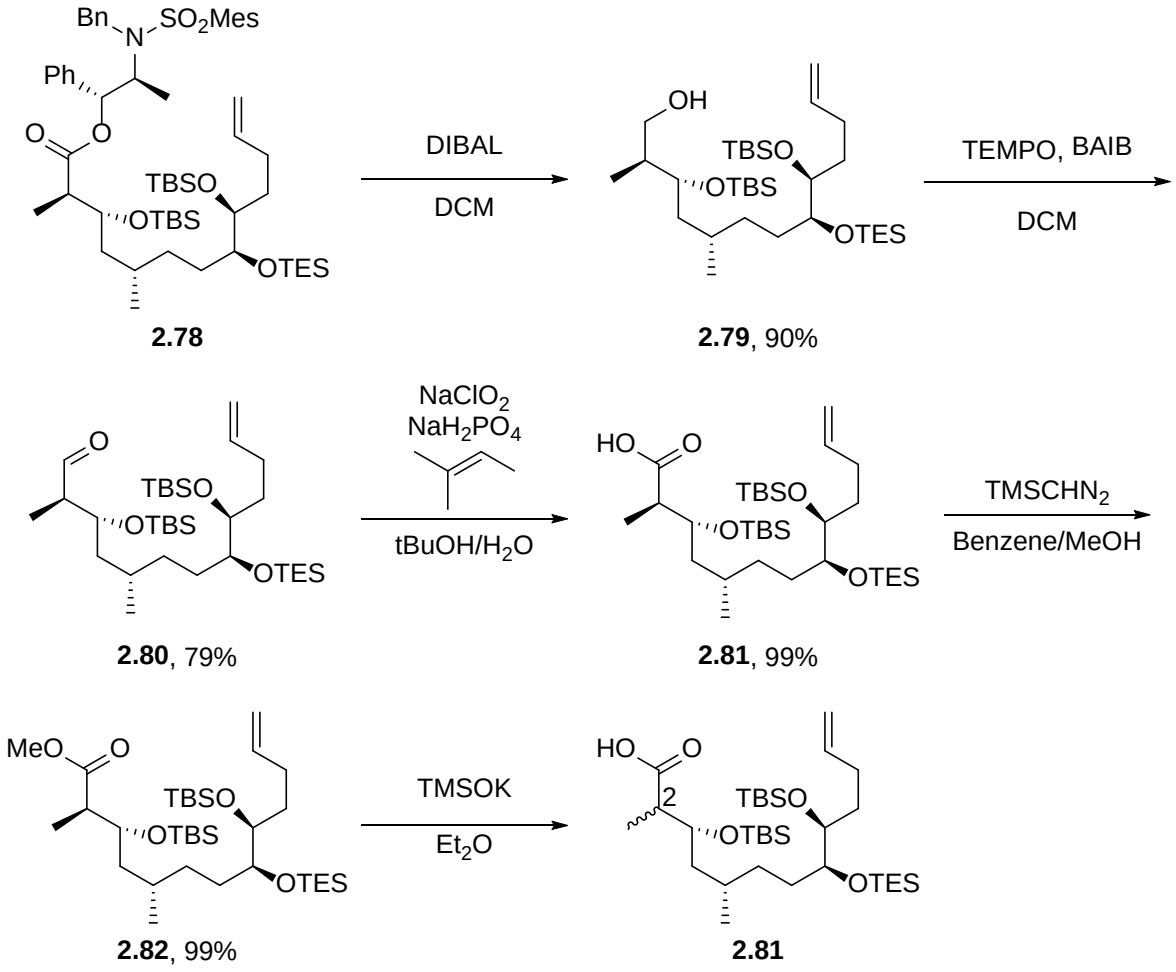


2.73

Scheme 2.18 Model study of removing C8 PMB group

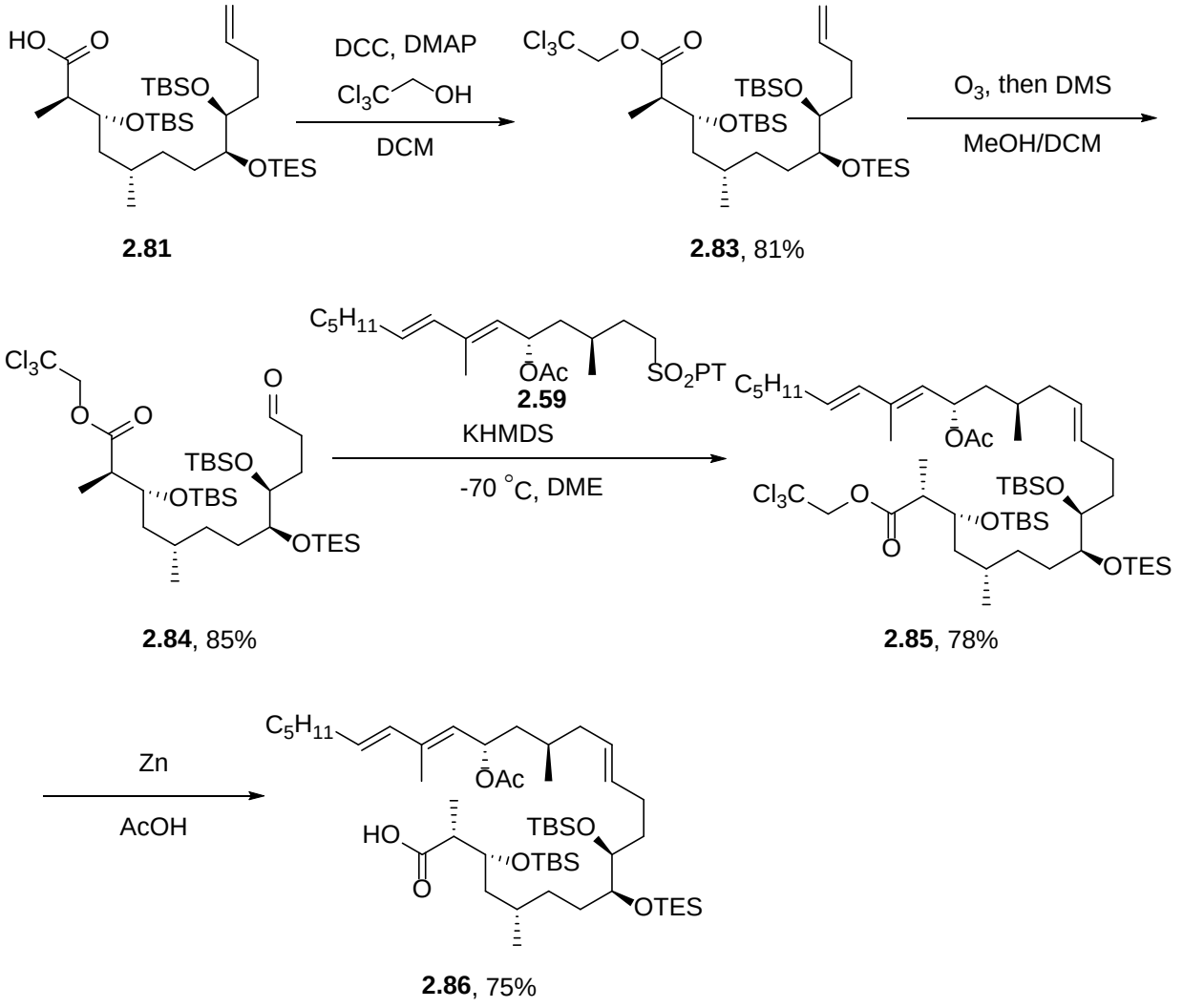
Therefore, it is necessary to remove the chiral auxiliary before coupling with the fragile top fragment. Meanwhile, TES group was chosen as the protecting group at C8 because 1) the conditions required to remove TES group are relatively mild, and 2) the TES group is orthogonal to TBS groups so it can be removed selectively.[126] By using the previous methods, advanced intermediate **2.78** with TES protecting group at C8 was synthesized. Modification of the bottom fragment is shown in Scheme 2.20. Newly synthesized bottom fragment **2.78** with TES protecting group at C8 was treated with excess DIBAL-H to give alcohol **2.79** in 90% yield. TEMPO and $PhI(OAc)_2$ were used to oxidize alcohol **2.79** to aldehyde **2.80** in 79% yield.[123]

Aldehyde **2.80** was further oxidized to acid **2.81** in 80% yield.[124] Acid **2.81** was converted to methyl ester **2.82** quantitatively by treating with $TMSCHN_2$.[127] With ester **2.82** in hand, model reactions were set up to test the reaction conditions of hydrolyzing the methyl ester after coupling with the top fragment **2.59**. Again, when ester **2.82** was subjected to $LiOH•H_2O$ in THF/H_2O = 2/1 at room temperature, no desired acid **2.81** was formed. TMSOK[128] was able to hydrolyze methyl ester **2.82** to acid **2.81**. However, a mixture of the two diastereomers of acid **2.81** with 1/1 ratio was observed in ^{13}C NMR spectrum. The methyl group at C2 position was isomerized due to the basic conditions.



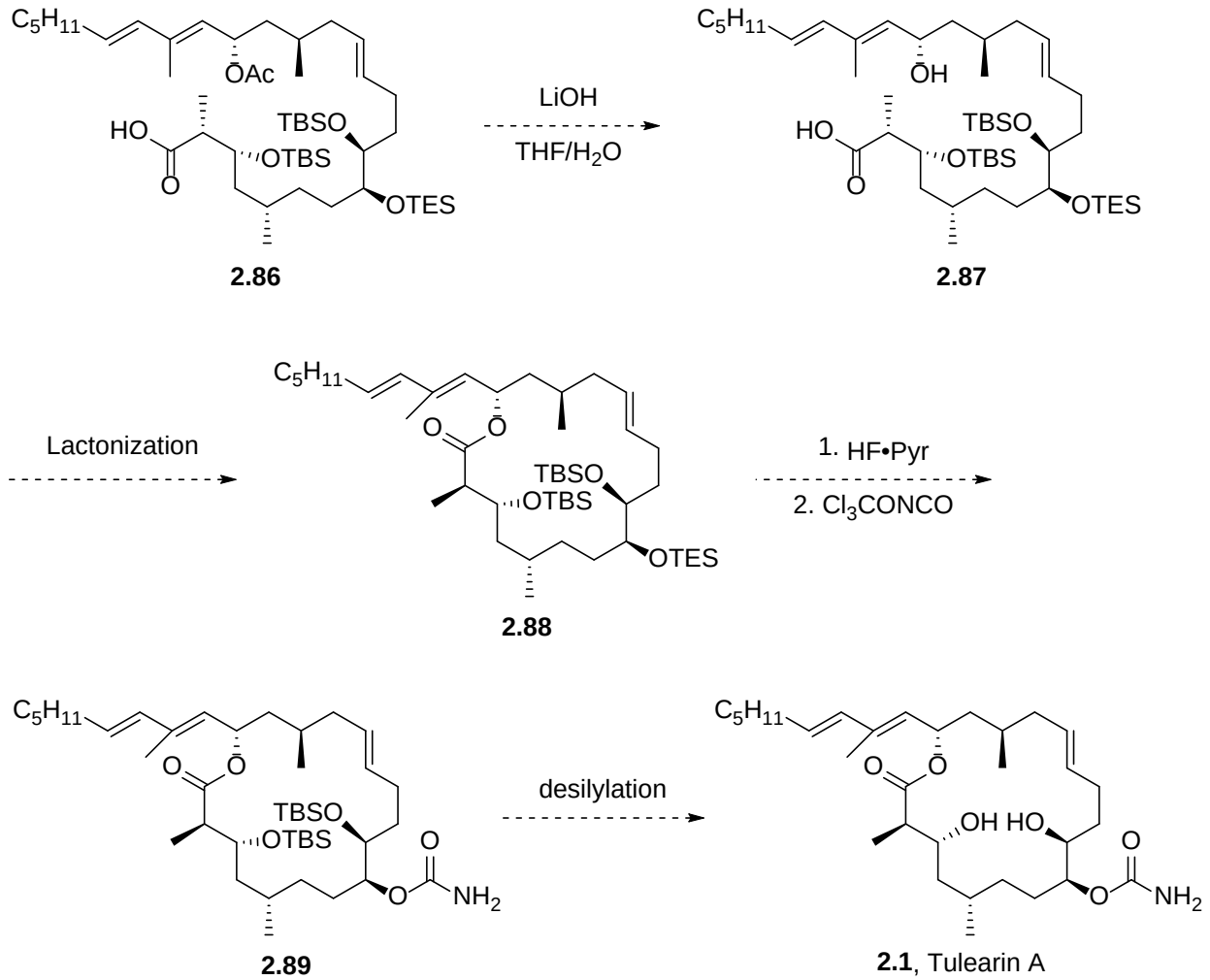
Scheme 2.19 Modification of bottom fragment

As a result, a new protecting group for the acid is needed. The TCE (2,2,2-trichloroethyl) group was chosen (Scheme 2.21).[129] Esterification of acid **2.81** and 2,2,2-trichloroethan-1-ol gave ester **2.83** in 81% yield. The terminal double bond was oxidatively cleaved with ozone to provide the aldehyde **2.84** in 85% yield. Top fragment **2.59** and aldehyde **2.84** was coupled by Julia-Kocienski olefination by treating with KHMDS in DME at –70 °C to afford the coupled product **2.85** in 78% yield. The coupled compound **2.85** was subjected to Zn dust in AcOH to afford acid **2.86** in 75% yield.[129]



Scheme 2.20 Modified end-game synthetic route

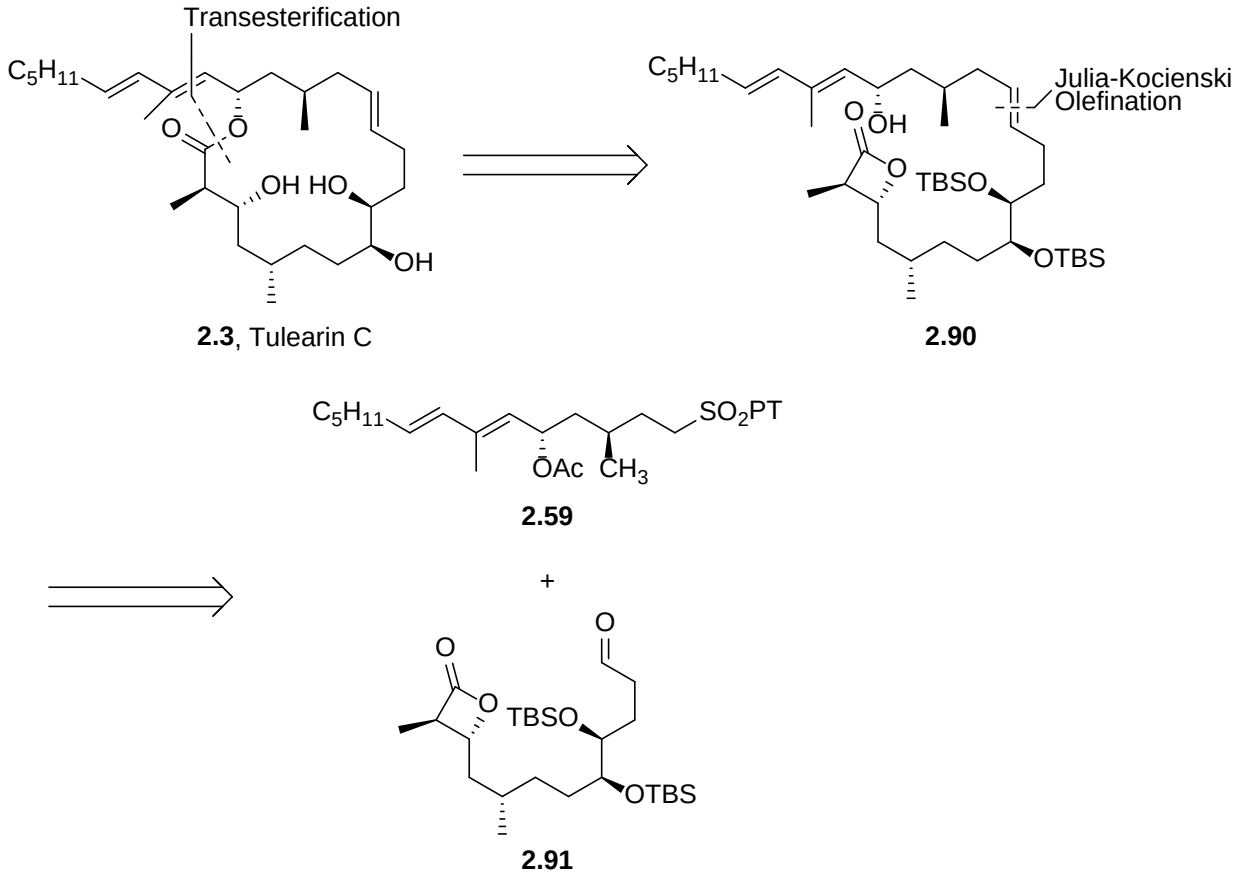
At this point, we had only small amounts of acid **2.86** and efforts were switched to another project. However, acid **2.86** is a promising intermediate to finish the total synthesis. With acid **2.86** in hand, the acetate group will be hydrolyzed to give alcohol **2.87**. Lactonization of corresponding acid and alcohol will provide macrocylic product **2.88**.[130] TES group will be removed using described method (HF·Pyr),[126] the alcohol will be converted to carbamate **2.89**. Finally, globe desilylation will give the tulearin A (Scheme 2.22).[98]



Scheme 2.21 Proposed synthesis of tulearin A

2.2.4 Retrosynthetic analysis of tulearin C

Although the first total synthesis of tulearin C was reported by Fürstner and co-workers in 2011,[99] the synthetic route is relatively long. The longest linear route took 19 steps to finish the total synthesis. Therefore, based on our experience towards the total synthesis of tulearin A, we plan to develop a more efficient synthetic route to accomplish the total synthesis of tulearin C. Tulearin C is simpler to make than tulearin A because selective alcohol protection is not needed.



2.3, Tulearin C

2.90

2.59

2.91

Figure 2.7 Retrosynthetic analysis of tulearin C

The retrosynthetic analysis of tulearin C **2.3** is shown in Figure 2.7. The macrocycle can be synthesized by transesterification from precursor **2.90** bearing a β-lactone moiety.[131] Julia-Kocienski olefination[105] was used to couple sulfone **2.59**, which is a common intermediate in total synthesis of tulearin A, and aldehyde **2.29** with β-lactone to form the precursor of the transesterification.

As shown in Figure 2.8, the C1-C12 fragment **2.91** can be synthesized by acyl halide-aldehyde cyclocondensation[132] from aldehyde **2.92** followed by ozonolysis. Aldehyde **2.92** can be formed by Julie-Kociensky olefination[105] between sulfone **2.94** and aldehyde **2.95** followed by Swern oxidation.[133] Sulfone **2.94** can be synthesized from pent-4-en-1-ol **2.96**. Aldehyde **2.95** can be generated from commercially available (*S*)-citronellol **2.49**.

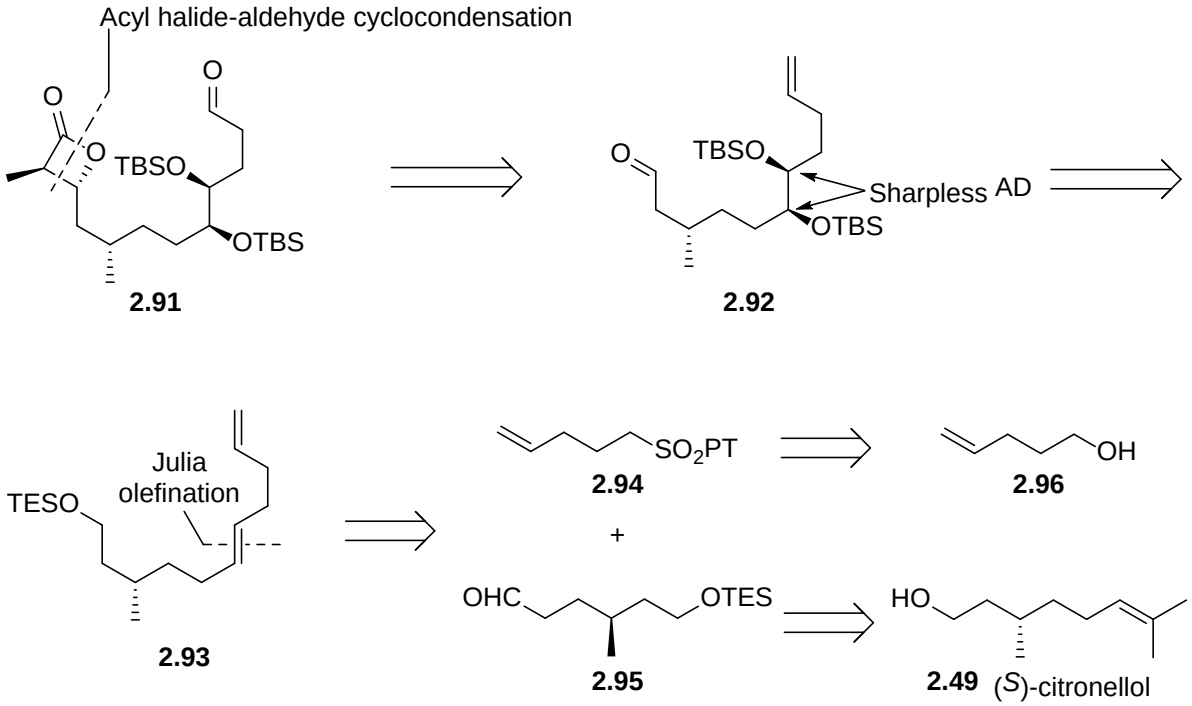
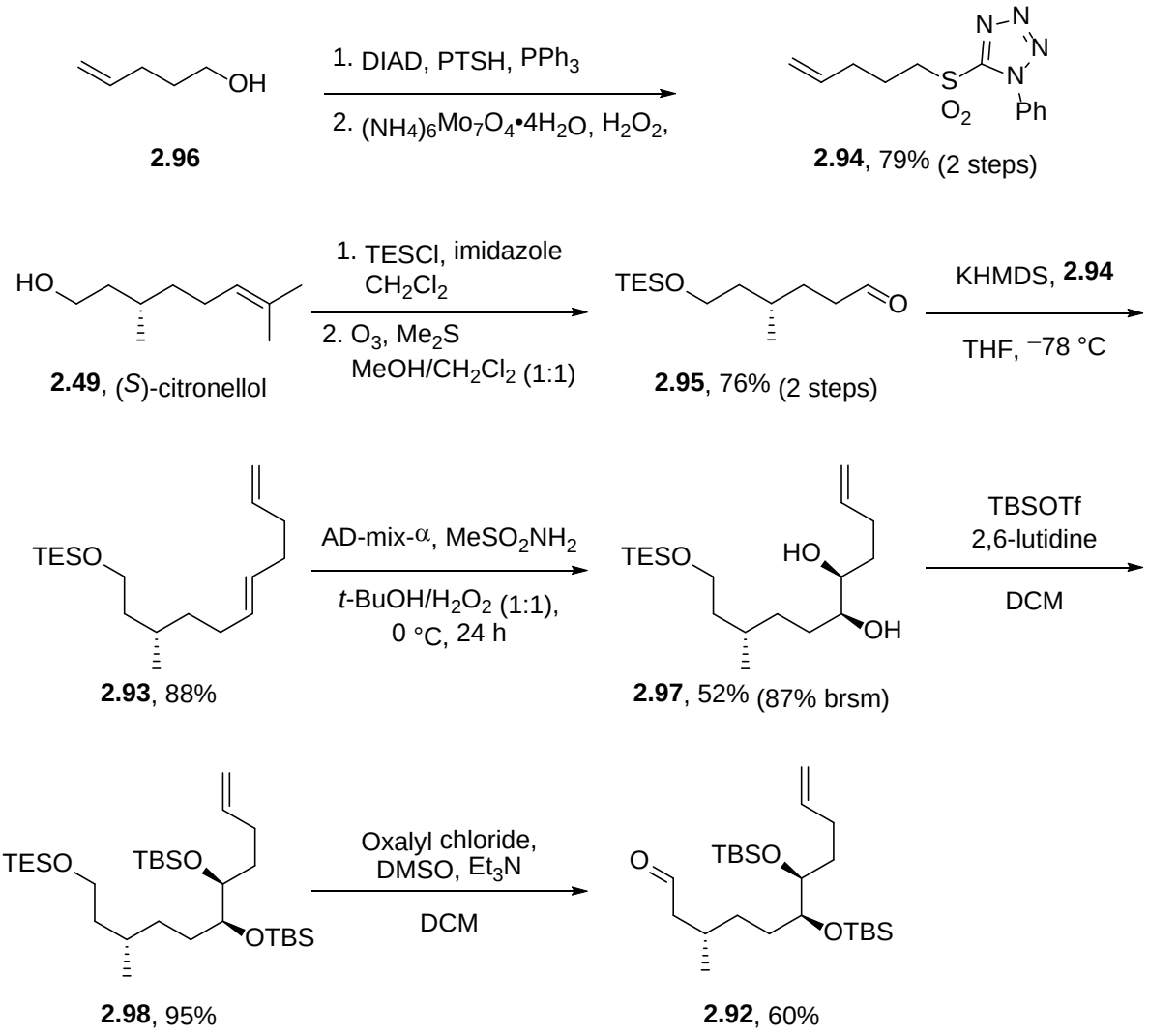


Figure 2.8 Retrosynthetic analysis of aldehyde **2.91**

2.2.5 Progress toward the total synthesis of tulearin C

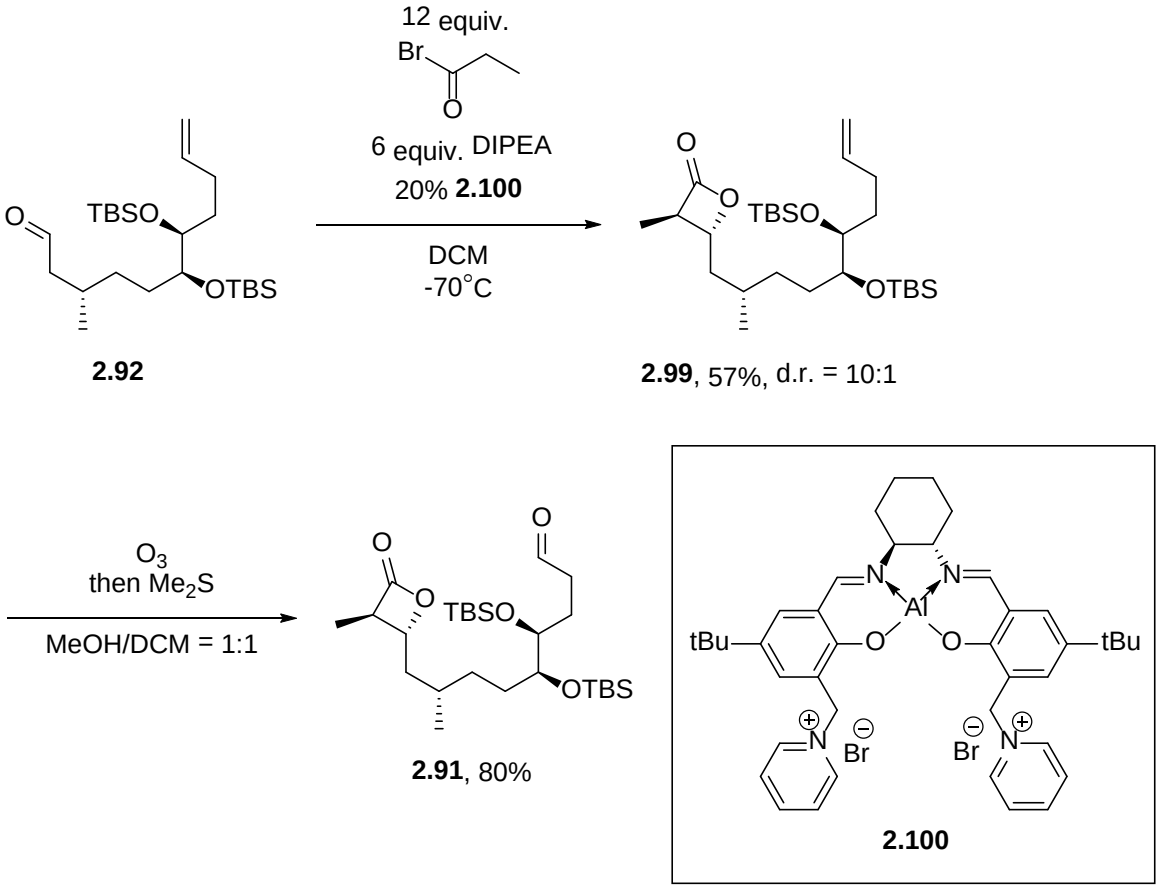
Sulfone **2.94** was obtained by Mitsunobu reaction of pent-4-en-1-ol **2.96** with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH), diisopropyl azodicarboxylate (DIAD), and Ph_3P followed by oxidation with H_2O_2 in the presence of catalytic amount of $(NH_4)_6Mo_7O_{24}$ in ethanol in 79% yield over two steps.[106] Protection of the free hydroxyl group in commercially available (*S*)-citronellol **2.49** with a TES group followed by ozonolysis of the double bond afforded aldehyde **2.95** in 76% yield over two steps.

Julia-Kocienski olefination[105] between aldehyde **2.95** and sulfone **2.94** was performed by treating with KHMDS in THF at –78 °C to give alkene **2.93** in 88% yield with excellent *E* selectivity, which was assigned by the analysis of ^{1}H-NMR spectrum of alkene **2.93**. Sharpless asymmetric dihydroxylation of alkene **2.93** with AD-mix-α and methanesulfonamide in *t*-BuOH/H_2O (1:1) at 0 °C for 24 h selectively formed the diol **2.97** at more electron rich olefin moiety in 52% yield.[134] Meanwhile, 40% alkene **2.93** was recovered after the reaction. The stereochemistry of C8 and C9 was assigned as 8*S* and 9*S* based on the Sharpless AD model.[110] The two hydroxyl groups in diol **2.97** were both protected with TBS to give fully protected **2.98**. Swern oxidation was used to convert the TES protected alcohol **2.98** to aldehyde **2.92** in one step in 60% yield.[133]



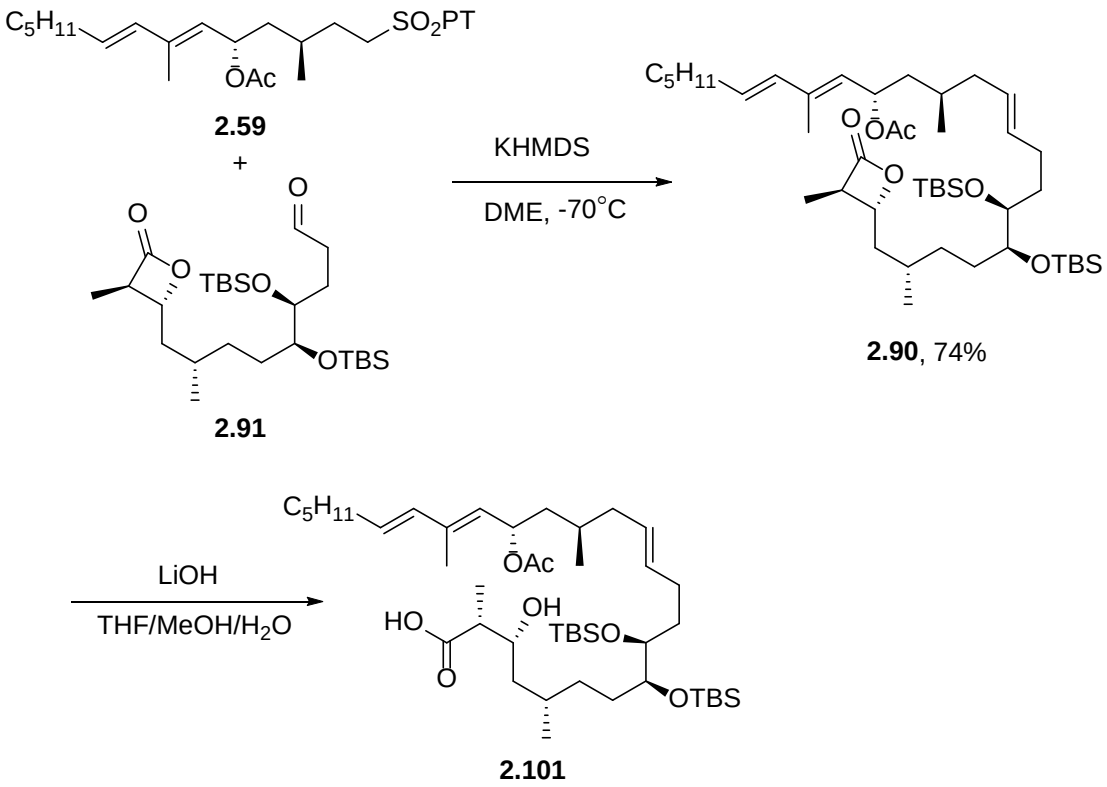
Scheme 2.22 Synthesis of aldehyde **2.92**

Trans-selective catalytic asymmetric [2+2] cyclocondensation of propionyl bromide and aldehyde **2.92** was used to form β-lactone **2.99** by the catalysis of Lewis acid **2.100** in 57% yield with good diastereoselectivity (d.r. = 10:1) based on analysis of ^{1}H-NMR spectra.[132] The stereochemistry at C2 and C3 was assigned by Peters' model as 2*R* and 3*R*. Then the terminal double bond was oxidatively cleaved with ozone to provide the aldehyde **2.91** in 80% yield.



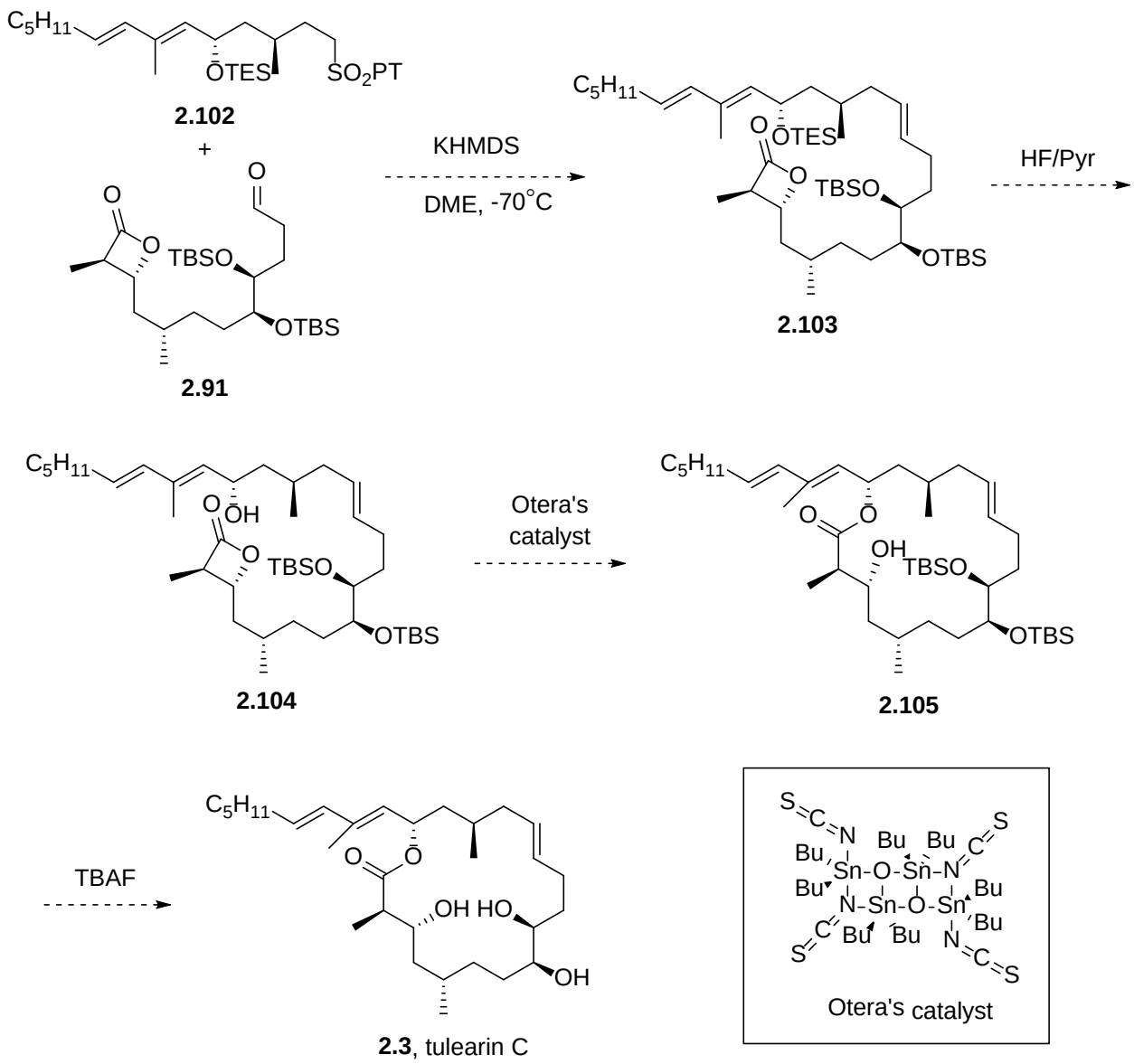
Scheme 2.23 Synthesis of C1-C12 fragment **2.91**

As shown in Scheme 2.24, acetate-protected top fragment **2.59** and aldehyde **2.91** was coupled by Julia-Kocienski olefination by treating with KHMDS in DME at –70 °C to afford the coupled product **2.90** in 74% yield with excellent *E* selectivity,[105] which was assigned by the analysis of ^{1}H-NMR of advanced intermediate **2.90**. When the coupled compound **2.90** was subjected to LiOH•H_2O in THF/MeOH/H_2O = 1/1/1 at room temperature for 30 min, the β-lactone was opened to give **2.101** with the acetate group intact. Therefore, new protecting group was needed for the top fragment.



Scheme 2.24 Efforts toward the total synthesis of tulearin C

The new TES protected sulfone **2.102** need to be prepared to solve this problem. At this point, we do not have time to prepare this new top fragment and we were focused on another project. However, this is a promising route to accomplish the total synthesis. Sulfone **2.102** will be coupled with aldehyde **2.91** by Julia-Kocienski olefination to form coupled intermediate **2.103**.[105] TES group at C17 will be selectively removed by using HF·Pyr to form **2.104**.[126] The transesterification of β-lactone **2.104** will happen with Otera's catalyst to close the macrocycle.[131] Finally, global desilylation of macrolactone **2.105** will give the tulearin C (Scheme 2.25).



Scheme **2.25** Proposed synthesis of tulearin C

2.3 CONCLUSIONS

A new route to the synthesis of tulearin A was investigated. Large scale synthesis of the bottom fragment (C1-C12) was accomplished through Dr. Bin Sui's synthetic route. Synthesis of the top fragment (C13-C26) was modified, and it can now be synthesized in 22% yield over 13 steps totally and 9 linear steps.

Different synthetic routes were tested to accomplish the total synthesis of tulearin A, and the major problems toward the total synthesis of tulearin A were identified. The *E,E* $\Delta^{18,20}$-diene moiety is sensitive in acidic conditions. Basic hydrolysis of the ester group at C1 will epimerize the methyl group at C2. As a result, a new strategy was developed to take a detour. With the current route, the total synthesis of tulearin A could in principle be completed in 5 steps from advanced intermediate **2.86**.

Meanwhile, a new route was developed towards the total synthesis of tulearin C. The synthesis of bottom fragment **2.91** was achieved in 17% yield over 8 linear steps highlighting the catalytic asymmetric [2+2] cyclocondensation to form the β-lactone moiety. However, the total synthesis of tulearin C was not finished because of the difficulty of removal of the acetate protecting group at C17. Our observations suggest that, with new TES protected top fragment, the total synthesis of tulearin C could be finished from advanced intermediate **2.91** in 3 steps.

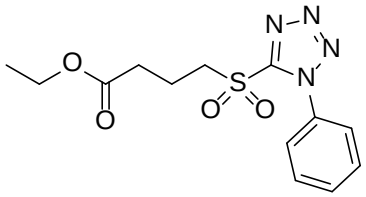
2.4 EXPERIMENTAL

General Information:

All reactions were performed under an atmosphere of argon unless otherwise noted. Reaction solvents were freshly dried either by distillation or by passing through an activated alumina column. THF and toluene were freshly distilled from Na/benzophenone. Methylene chloride and Et_2O were dried by activated alumina according to literature. All other reagents were purchased commercially and used without further purification unless stated otherwise. Reaction mixtures were magnetically stirred and reaction progress was monitored by TLC with 0.25 mm E. Merck precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040 – 0.063 mm) supplied by Sorbent Technologies or by combiflash.

Products and reactions are analyzed by ^{1}H NMR, ^{13}C NMR, COSY, FT-IR, high and low resolution mass spectroscopy, and HPLC. NMR spectra were taken on a Bruker WH-300, IBM AF-300, a Bruker Avance^{TM} 400 NMR, a Bruker Avance^{TM} 600 NMR, and a Bruker Avance^{TM} 700 NMR spectrometer. Spectra were recorded at room temperature in the indicated deuteriated solvents and chemical shifts were reported in parts per million (ppm) downfield relative to TMS using the residual solvent proton resonance of $CDCl_3$ (7.26 ppm) or central $CDCl_3$ carbon peak (77.0 ppm) as the internal standard. In reporting spectral data, the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet, dd = doublet doublet, dt = doublet triplet, td = triplet doublet, qd = quartet doublet, ddt = doublet doublet triplet, dtd = doublet triplet double. Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film on NaCl plate. Peaks are reported in wave numbers (cm^{-1}). Low resolution mass spectra were obtained on Fision Autospec. High resolution mass spectra were

obtained on a V/G 70/70 double focusing machine and were reported in units of *m/z*. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the Na D-line (λ = 589 nm) using a 1 dm cell. HPLC analyses were performed on a Waters 600 E system with a Waters 2487 dual λ absorption detector.

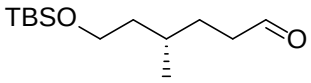


2.6

Ethyl 4-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)butanoate (2.6): K_2CO_3 (18.8 g, 135.3 mmol) was added to a stirred solution of ester **2.48** (10.7 mL, 71.2 mmol) and PTSH (14.0 g, 78.8 mmol) in acetone (120 mL) at rt. After stirring vigorously at 40 °C for 3 h and at rt for 16 h, the precipitate was filtered and washed with acetone. The filtrate was evaporated to give brown oil, which was dissolved in DCM and H_2O. The organic layer was separated and washed with H_2O, dried over Na_2SO_4, and concentrated under vacuum. The crude product was used in next step without further purification.

A solution of $(NH4)_6Mo_7O_{24}·4H_2O$ (18.54 g, 15.0 mmol) in 30% H_2O_2 (116.2 mL) was added to a solution of the above sulfide (21.93 g, 75.0 mmol) in EtOH (300 mL) at 0 °C. After 12 h stirring at rt, a yellow solid had crashed out of the mixture. The mixture was poured into brine and extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to reveal a sludgy yellow and white biphasic residue. The residue was purified by flash chromatography (hexane:EtOAc = 7:1) to give the title compound **2.6** (21.84 g, 90%) a colorless oil, which was solidified under vacuum to get white solid: m.p. 63–66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.68 (m, 2H), 7.65–7.60 (m,

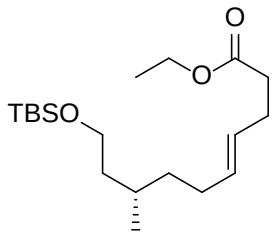
3H), 4.16 (q, J = 7.2 Hz, 1H), 3.89–3.84 (m, 2H), 2.56 (t, J = 6.9 Hz, 1H), 2.34–2.25 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 153.2, 132.9, 131.4, 129.6, 125.0, 60.8, 54.9, 31.8, 17.7, 14.1; IR (film) 3054, 2986, 1731, 1421, 1344, 1265, 1156, 1041, 909, 740; MS (EI) m/z 325 (M^+ + 1); HRMS (ESI) m/z (M^+ + 1) calcd for $C_{13}H_{17}N_4O_4S$ 325.0971, found 325.0984.



2.7

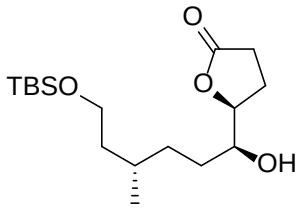
(*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-4-methylhexanal (2.7): TBSOTf (8.96 mL, 39.0 mmol) was added to a solution of (*S*)-citronellol **2.49** (5.48 mL, 30.0 mmol) and 2,6-lutidine (5.55 mL, 45.0 mmol) in DCM (60 mL) at 0 °C dropwise. The resulting mixture was stirred for 2 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (50 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was used in next step without further purification.

Ozone was bubbled through a solution of the above TBS ether (7.33 g, 30.0 mmol) in DCM/MeOH (v/v = 1:1, 90 mL), containing pyridine (0.6 mL) at −78 °C until blue color appear. Excess of ozone was purged out of flask with argon before Me_2S was added dropwise at −78 °C. The reaction was slowly warmed to 20 °C overnight. The mixture was concentrated under vacuum. The residue was purified by flash chromatography (hexane:EtOAC = 20:1) to give the title compound **33** (7.12 g, 93%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, J = 2.1 Hz, 1H), 3.69–3.60 (m, 2H), 2.47–2.38 (m, 2H), 1.72–1.32 (m, 5H), 0.91–0.88 (m, 12H), 0.04 (s, 6H); IR (film) 3020, 2958, 1721, 1521, 1472, 1215, 1091, 929, 770.



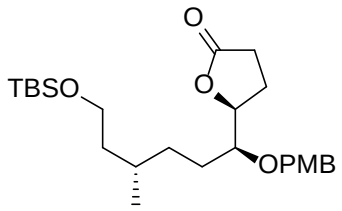
2.50

(*S*,*E*)-Ethyl 10-((*tert*-butyldimethylsilyl)oxy)-8-methyldec-4-enoate (2.50): A solution of KHMDS (3.12 g, 15.6 mmol) in DME (30 mL) was added to a solution of sulfone **2.6** (5.46 g, 16.8 mmol) in DME (60 mL) at −70 °C (isopropyl ether/dry ice). The resulting orange solution was stirred for 30 min before a solution of aldehyde **2.7** (2.94 g, 12.0 mmol) in DME (30 mL) was added dropwise. After stirring for 1 h at −70 °C, the mixture was warmed to rt slowly during the overnight stirring (some white precipitate was observed). The reaction was quenched by adding water, the organic layer was separated, the aqueous layers were extracted with Et_2O (3 × 100 mL). The combined organic layers were deried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (hexane:Et_2O = 40:1) to give the title compound **2.50** (3.68 g, 90%) as a colorless oil: $[\alpha]_D^{25}$ = −0.86 (*c* =1.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51–5.35 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.69–3.60 (m, 2H), 2.38–2.27 (m, 4H), 2.03–1.94 (m, 2H), 1.60–1.49 (m, 2H), 1.39–1.10 (m, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.91–0.88 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 131.8, 127.8, 61.4, 60.2, 39.8, 36.8, 34.4, 29.9, 29.0, 27.9, 25.9, 19.5, 18.3, 14.2, −5.3; IR (film) 3020, 1726, 1520, 1424, 1216, 1035, 929, 756; MS (EI) m/z 327 (M^+ − CH_3); HRMS (ESI) m/z (M^+ − CH_3) calcd for $C_{18}H_{35}O_3Si$ 327.2355, found 327.2350.



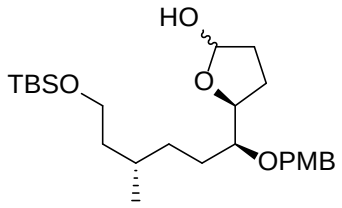
2.51

(*S*)-5-((1*S*,4*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-hydroxy-4-methylhexyl)dihydrofuran-2(3*H*)-one (2.51): AD-Mix-α (28.2 g) and $MeSO_2NH_2$ (1.92 g, 20.1 mmol) were added to a solution of alkene **2.50** (6.90 g, 20.1 mmol) in the solution of *t*-BuOH/H_2O (v/v = 1:1, 100 mL) at 0 °C. The resulting orange solution was stirred at 0 °C for 96 h (the color was changed from orange to yellow). The reaction was quenched with solid Na_2SO_3 (30.0 g) and warmed to rt over an hour. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with KOH (2M aq), brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (hexane:EtOAc = 2:1) to give the title compound **2.51** (5.91 g, 89%) as a colorless oil: $[\alpha]_D^{25}$ = +16.6 (*c* = 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45–4.38 (m, 1H), 3.71–3.60 (m, 2H), 3.59–3.51 (m, 1H), 2.67–2.48 (m, 2H), 2.31–2.04 (m, 2H), 1.89 (d, J = 5.7 Hz, 1H), 1.63–1.32 (m, 7H), 0.91–0.88 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 83.0, 73.6, 61.1, 39.7, 32.7, 30.3, 29.2, 28.6, 25.8, 23.9, 19.4, 18.2, −5.4; IR (film) 3020, 2957, 1772, 1521, 1474, 1423, 1216, 1085, 928, 755; MS (EI) m/z 331 (M^+ + 1); HRMS (ESI) m/z ($M^+ - C_4H_9$) calcd for $C_{13}H_{25}O_4Si$ 273.1522, found 273.1509.



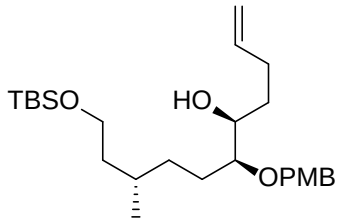
2.53

(*S*)-5-((1*S*,4*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-4-methylhexyl)dihydrofuran-2(3*H*)-one (2.53): *p*-Methoxybenzyltrichloroacetimidate (7.11 mL, 34.8 mmol) and lanthanum triflate (0.51 g, 0.87 mmol) were added to a solution of alcohol **2.51** (5.75 g, 17.4 mmol) in toluene (150 mL) under argon at rt. The reaction mixture was stirred for overnight and then concentrated in vacuo. In order to precipitate tricholoracetamide, the residue oil was taken up in 3:1 cyclohexane/DCM and filtered. The remaining oil was purified by flash chromatography (hexane:EtOAc = 4:1) to yield a clear oil that was still contaminated with some tricholoroacetamide. The precipitation procedure was repeated three more times to yield almost pure product (still has some impurities). The product was used in next step without further purification.



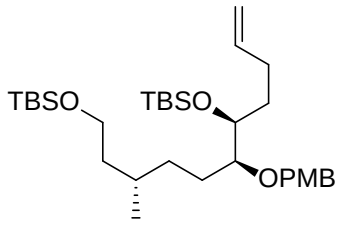
(5*S*)-5-((1*S*,4*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-4-methylhexyl)tetrahydrofuran-2-ol: DIBAL-H (22.4 mL, 1.0 M in hexane, 22.4 mmol) was added to a solution of lactone **2.53** (7.77 g, 17.2 mmol) in DCM (150 mL) at −78 °C. After 1 h, TLC indicated the reaction was complete. The reaction was then quenched by the addition of saturated aqueous potassium sodium tartrate, and warmed to rt and stirred. After an addition 2 h,

the reaction mixture was clear and extracted with DCM (3 × 150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 4:1) to give the title compound as a yellow oil. The product is still contaminated with some impurity. The product was used in the next step without further purification.



(5*S*,6*S*,9*S*)-11-((*tert*-Butyldimethylsilyl)oxy)-6-((4-methoxybenzyl)oxy)-9-methylundec-1-en-5-ol (2.55): *n*-BuLi (29.4 mL, 1.6 M in hexane, 47.1 mmol) was added to a suspension of $MePPh_3Br$ (17.4 g, 48.8 mmol), which was heated to 120 °C for 2 h under vacuum before used in the reaction, in THF (100 mL) at −78 °C. The resulting yellow solution was warmed to rt and stirred for another 40 min. The above lactol (7.35 g, 16.2 mmol) in THF (60 mL) was added to the above solution causing the mixture to become sloppy. The new suspension was heated to 60 °C. After 1.5 h, the TLC indicated the reaction was complete. The mixture was cooled to rt and quenched by saturated NH_4Cl solution. The mixture was extracted with Et_2O (3 × 100 mL) and combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The yellow residue was purified by flash chromatography (hexane:EtOAc = 9:1) to give the title compound **2.55** (4.69 g, 60% over three steps) as a colorless oil: $[\alpha]_D^{25}$ = +10.2 (*c* = 0.71, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2 H), 5.86–5.80 (m, 1H), 5.05–4.96 (m, 2H), 4.60–4.40 (m, 2H), 3.81 (s, 3H), 3.68–3.60 (m, 2H), 3.55–3.51 (m, 1H), 3.24 (q, *J* = 6.0 Hz, 1H), 2.28 (d, *J* = 4.8 Hz, 1H), 2.26–2.22 (m, 1H), 2.15–2.11 (m,

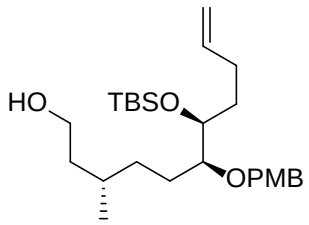
1H), 1.63–1.52 (m, 6H), 1.42–1.32 (m, 2H), 1.23–1.18 (m, 1H), 0.91–0.88 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 138.5, 130.5, 129.5, 114.8, 113.9, 72.1, 72.0, 61.3, 55.3, 39.9, 32.7, 32.2, 30.0, 29.7, 27.6, 26.0, 19.6, 18.3, −5.3; IR (film) 3019, 2930, 1515, 1472, 1423, 1213, 1081, 928, 767, 699.



2.56

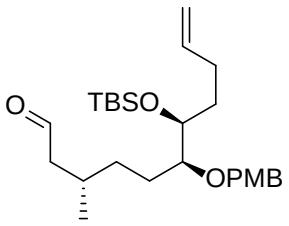
(5*S*,6*S*,9*S*)-5-(But-3-en-1-yl)-6-((4-methoxybenzyl)oxy)-2,2,3,3,9,13,13,14,14-nonamethyl-4,12-dioxa-3,13-disilapentadecane (2.56): TBSOTf (3.0 mL, 13.0 mol) was added to a solution of alcohol **2.55** (4.5 g, 10.0 mmol) and 2,6-lutidine (1.84 mL, 15.0 mmol) in DCM (100 mL) at 0 °C. The resulting mixture was stirred for 2 h at rt. Saturated NH_4Cl solution was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 30:1) to give the title compound **2.56** (5.50 g, 98%) as a colorless oil: $[\alpha]_D^{25}$ = −25.1 (*c* = 1.36, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.86–5.75 (m, 1H), 5.06–4.93 (m, 2H), 4.53–4.42 (m, 2H), 3.80 (s, 3H), 3.79–3.73 (m, 1H), 3.67–3.56 (m, 2H), 3.29–3.22 (m, 1H), 2.23–2.13 (m, 1H), 2.05–1.92 (m, 1H), 1.74–1.26 (m, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.90–0.85 (m, 3H), 0.04 (s, 6H) 0.02(d, *J* = 9.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 139.0, 131.0, 129.3, 114.3, 113.7, 82.2, 72.0, 71.6, 61.4, 55.2, 40.0, 33.9, 30.3, 30.2, 29.4, 26.0, 25.8, 19.6, 18.3, 18.0, −4.4 (d), −5.3; IR (film) 3020, 2955, 2930, 1611, 1513,

1471, 1424, 1216, 1083, 929, 771; HRMS (ESI) m/z (M^+ + Na) calcd for $C_{32}H_{60}O_4NaSi_2$ 587.3928, found 587.3969.



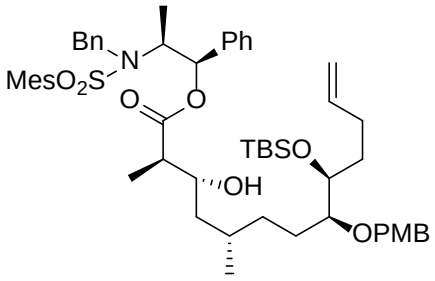
2.57

(3*S*,6*S*,7*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-6-((4-methoxybenzyl)oxy)-3-methylundec-10-en-1-ol (2.57): Oxone (2.02 g, 3.3 mmol) was added to a solution of TBS ether **2.56** (1.70 g, 3.0 mmol) in MeOH (60 mL) and 3 drops of H_2O at rt. After 2 h, TLC indicated the reaction was complete, saturated $NaHCO_3$ solution was added to the mixture, which was extracted with DCM (3 × 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash chromatography (hexane:EtOAc = 4:1 to 1:1) to give the title compound **2.57** (1.13 g, 92%) as a colorless oil: $[\alpha]_D^{25} = -37.6$ (*c* = 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.89–5.75 (m, 1H), 5.06–4.93 (m, 2H), 4.54–4.41 (m, 2H), 3.81 (s, 3H), 3.79–3.75 (m, 1H), 3.70–3.60 (m, 2H), 3.28–3.23 (m, 1H), 2.19–2.16 (m, 1H), 2.06–1.92 (m, 1H), 1.74–1.16 (m, 10H), 0.88 (s, 9H), 0.90–0.85 (m, 3H), 0.02(d, *J* = 9.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.9, 131.0, 129.4, 114.3, 113.7, 82.0, 71.9, 71.6, 61.2, 55.3, 39.0, 33.8, 30.3, 29.5, 25.8, 25.7, 19.5, 18.0, −4.4 (d); IR (film) 3020, 2958, 1611, 1514, 1424, 1216, 1037, 929, 756; HRMS (ESI) m/z (M^+ + Na) calcd for $C_{26}H_{46}O_4NaSi$ 473.3063, found 473.3029.



2.35

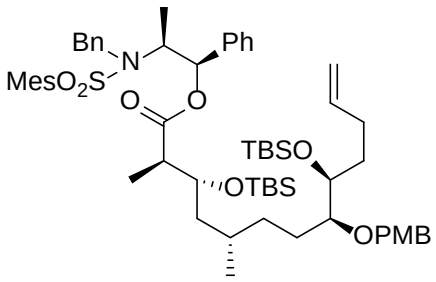
(3*S*,6*S*,7*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-6-((4-methoxybenzyl)oxy)-3-methylundec-10-enal (2.35): DMP (0.565 g, 1.34 mmol) was added to a suspension of alcohol **2.57** (300.0 mg, 0.66 mmol) and $NaHCO_3$ (308.0 mg, 3.66 mmol) in DCM (8.0 mL) at rt under argon. The resulting light yellow solution was stirred for 2 h at rt. Saturated NH_4Cl solution was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The yellow residue was purified by flash chromatography (Hex:EtOAc = 20:1 to 15:1) to give the title compound **2.35** (258 mg, 86%) as a colorless oil: $[\alpha]_D^{25} = -42.6$ (*c* = 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (t, *J* = 2.7 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2 H), 5.85–5.75 (m, 1H), 5.06–4.94 (m, 2H), 4.54–4.40 (m, 2H), 3.81 (s, 3H), 3.79–3.76 (m, 1H), 3.29–3.23 (m, 1H), 2.37 (ddd, J = 16.5, 5.4, 1.8 Hz, 1H), 2.23–2.15 (m, 2H), 2.03–1.96 (m, 2H), 1.72–1.58 (m, 2H), 1.49–1.24 (m, 4H), 0.94 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 0.03 (d, *J* = 9.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 159.2, 138.8, 130.8, 129.3, 114.3, 113.7, 81.7, 71.9, 71.3, 55.1, 50.9, 33.6, 30.2, 30.1, 28.0, 25.8, 19.7, 17.9, −4.5 (d); IR (film) 3020, 1721, 1611, 1514, 1424, 1216, 1037, 929, 757; HRMS (ESI) m/z (M^+ + Na) calcd for $C_{26}H_{44}O_4NaSi$ 471.2907, found 471.2860.



2.45

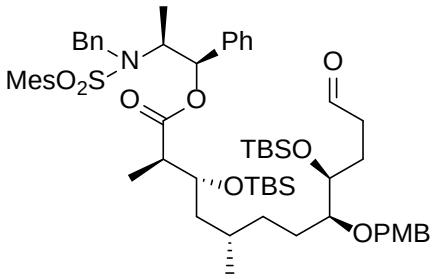
(2*R*,3*R*,5*S*,8*S*,9*S*)-(1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 9-((tert-butyldimethylsilyl)oxy)-3-hydroxy-8-((4-methoxybenzyl)oxy)-2,5-dimethyltridec-12-enoate (2.45): Et_3N was added to a solution of (1*R*,2*S*)-ester **2.44** (291 mg, 0.60 mmol) in DCM (2.5 mL) at rt under argon. After the solution was cooled to −78 °C, a solution of (*c*-Hex)$_2$BOTf (1.34 mL, 1.0 M solution in THF, 1.34 mmol) was added dropwise over 20 min. The resulting solution was stirred at −78 °C for 2 h. a solution of aldehyde **2.35** (227 mg, 0.51 mmol) in DCM (1.5 mL) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C and was warmed to rt over 1 h, then quenched by addition of pH=7 buffer (2.0 mL). The mixture was diluted with MeOH (10.2 mL) and 30% H_2O_2 (1.0 mL) was added carefully. The whole mixture was stirred vigorously overnight and then was concentrated. The residue was partitioned between DCM and H_2O. The aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane:EtOAc = 5:1) to give the title compound **2.45** (400 mg, 85%) as a viscous colorless oil: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.30–7.17 (m, 12H), 6.87–6.85 (m, 6H), 5.84–5.78 (m, 2H), 5.03–4.95 (m, 2H), 4.77–4.42 (m, 4H), 4.14–4.09 (m, 1H), 3.80 (s, 3H), 3.76–3.75 (m, 1H), 3.71–3.70 (m, 1H), 3.25–3.24 (m, 1H), 2.45 (s, 6H), 2.41–2.38 (m, 1H), 2.28 (s, 3H), 2.20–2.17 (m, 1H), 2.02–1.96 (m, 1H), 1.70–1.66 (m, 2H), 1.63–1.57 (m, 1H), 1.44–1.36 (m, 3H), 1.21–1.10 (m, 2H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.88 (s, 9H), 0.85 (d, J = 6.3 Hz, 3H), 0.03 (d, *J* = 25.2 Hz 6H); ^{13}C

NMR (175 MHz, $CDCl_3$) δ 174.6, 159.1, 142.5, 140.3, 138.9, 138.5, 138.1, 133.3, 132.1, 131.0, 129.4, 128.4, 128.3, 127.9, 127.7, 127.2, 114.4, 113.7, 82.2, 78.1, 72.0, 71.6, 70.9, 56.7, 55.3, 48.2, 46.3, 41.7, 34.8, 30.3, 30.2, 29.0, 25.9, 25.7, 22.9, 20.9, 18.7, 18.0, 14.0, 13.5, −4.4 (d).



(2*R*,3*R*,5*S*,8*S*,9*S*)-(1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 3,9-bis((tert-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-2,5-dimethyltridec-12-enoate: TBSOTf (0.14 mL, 0.59 mol) was added to a solution of alcohol **2.45** (420 mg, 0.45 mmol) and 2,6-lutidine (0.09 mL, 0.68 mmol) in DCM (2.5 mL) at 0 °C. The resulting mixture was stirred for 2 h at rt. Saturated NH_4Cl solution was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 10:1) to give the title compound (432 mg, 92%) as a colorless oil: $[\alpha]_D^{25}$ = +10.4 (*c* = 0.96, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33–7.12 (m, 12H), 6.88–6.84 (m, 6H), 5.84–5.78 (m, 1H), 5.77 (d, *J* = 5.4 Hz, 1H), 5.04–4.95 (m, 2H), 4.77–4.42 (m, 4H), 4.14–4.10 (m, 1H), 4.01–3.98 (m, 1H), 3.80 (s, 3H), 3.77–3.74 (m, 1H), 3.24–3.21 (m, 1H), 2.53–2.50 (m, 1H), 2.45 (s, 6H), 2.28 (s, 3H), 2.22–2.16 (m, 1H), 2.02–1.96 (m, 1H), 1.68–1.66 (m, 1H), 1.59–1.55 (m, 1H), 1.46–1.37 (m, 3H), 1.34–1.26 (m, 2H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.65 (d, J = 6.6 Hz, 3H), 0.04 (s, 6H), 0.02 (d, *J* = 18.0 Hz, 6H); ^{13}C NMR δ (150 MHz, $CDCl_3$) 172.1, 159.1,

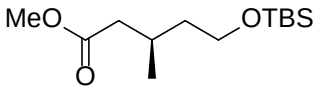
142.4, 140.3, 138.9, 138.3, 138.2, 133.2, 132.1, 131.1, 129.3, 128.4, 128.2, 127.9, 127.7, 126.5, 114.3, 113.7, 82.4, 77.9, 72.1, 71.5, 70.6, 56.6, 55.3, 48.1, 46.1, 40.0, 34.9, 30.3, 30.2, 28.8, 25.8, 22.9, 20.9, 18.9, 18.0, 17.9, 9.8, −4.4 (d), −4.6 (d); IR (film) 3020, 1604, 1515, 1424, 1216, 1042, 929, 763; HRMS (ESI) m/z (M^+ + Na) calcd for $C_{60}H_{91}NO_8NaSi_2$ 1064.5902, found 1064.5920.



2.29

(2*R*,3*R*,5*S*,8*S*,9*S*)-(1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 3,9-bis((tert-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-2,5-dimethyl-12-oxododecanoate (2.29): The above olefine (432 mg, 0.42 mmol) was taken up in DCM/MeOH (v/v = 1: 1, 5 mL) followed by the addition of pyridine (0.51 mL, 4.2 mmol) and SUDAN III (indicator, ~1 mg) at rt under argon. The solution was cooled to −78 °C, and a stream of O_3 was lightly bubbled through the solution until the pink color was disappear (a light yellow color persisted). The DMS was added slowly. The reaction mixture was slowly warmed to rt. After stirring for overnight, the mixture was concentrated under the vacuum. The residue was purified by flash chromatography (Hex:EtOAc = 7:1) to give the title compound **2.29** (260.0 mg, 90%) as a colorless viscous oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.5 Hz, 1H), 7.32–7.12 (m, 12H), 6.88–6.84 (m, 6H), 5.77 (d, *J* = 5.5 Hz, 1H), 4.76–4.42 (m, 4H), 4.16–4.10 (m, 1H), 4.01–3.98 (m, 1H), 3.80 (s, 3H), 3.79–3.76 (m, 1H), 3.25–3.22 (m, 1H), 2.53–2.50 (m, 2H), 2.44 (s, 6H), 2.28 (s, 3H), 1.99–1.92 (m, 1H), 1.64–1.56 (m, 2H), 1.44–1.26 (m, 5H), 1.20 (d, *J* = 7.5 Hz,

3H), 1.07 (d, J = 7.5 Hz, 3H), 0.87 (s, 18H), 0.65 (d, J = 6.5 Hz, 3H), 0.03 (d, J = 5.5 Hz, 6H), 0.01 (d, J = 11.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7, 172.1, 159.2, 142.5, 140.3, 138.3, 138.2, 133.1, 132.1, 130.8, 129.3, 128.4, 128.2, 127.9, 127.7, 126.5, 113.7, 82.2, 77.9, 72.2, 71.1, 70.5, 56.5, 55.3, 48.1, 46.1, 40.7, 39.9, 34.8, 28.8, 25.8, 25.7, 23.5, 22.9, 20.9, 18.8, 18.0, 17.9, 13.9, 9.7, −4.4 (d), −4.7.

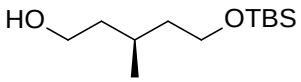


2.36

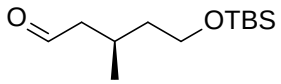
(*R*)-Methyl-5-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate (2.36): A solution of BH_3•SMe_2 (9.4 mL, 2 M solution in THF, 18.8 mmol) was added to a solution of (*R*)-5-methoxy-3-methyl-5-oxopentanoic acid **2.34** (1.72 mL, 12.5 mmol) in THF (60 mL) at 0 °C under Ar. The solution was stirred for 2 h at rt, followed by addition of H_2O. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The crude product was used without further purification.

A solution of the crude alcohol in dry DMF (30 mL) was treated with imidazole (2.38 g, 34.9 mmol) and TBDMSCl (2.19 g, 14.5 mmol) overnight at rt. The mixture was extracted with hexane (3 × 50 mL). The combined organic solution was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc = 30:1) to give the title compound **2.36** (2.74 g, 84% over two steps) as colorless oil: $[\alpha]_D^{25}$ = +1.4 (c = 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68–3.62 (m, 2H), 3.66 (s, 3H), 2.40–2.05 (m, 3H), 1.62–1.40 (m, 2H), 0.96 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 61.0, 51.3, 41.5, 39.4, 27.3, 25.9, 19.8, 18.3, −5.4; IR (film)

3020, 2957, 2931, 1730, 1521, 1473, 1434, 1216, 1086, 1030, 929, 836, 756; MS (EI) m/z 245 ($M^+ - 1$); HRMS (ESI) m/z ($M^+ - CH_3$) calcd for $C_{12}H_{25}O_3Si$ 245.1573, found 245.1572.



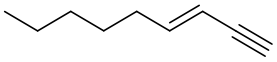
(*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-methylpentan-1-ol: DIBAL-H (25.8 mL, 1.0 M solution in hexane, 25.8 mmol) was added to a solution of ester **18** (2.68 g, 10.3 mmol) in DCM (50 mL) at 0 °C dropwise in 10 min. After 20 min, the mixture was poured into a rapidly stirred mixture of saturated aqueous potassium sodium tartrate (50 mL) and Et_2O (25 mL). The resulting mixture was stirred vigorously for 1 h, at which time the organic layer was clear. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc = 4:1) to give the alcohol (2.21 g, 92.4%) as colorless oil: $[\alpha]_D^{25}$ = +2.6 (*c* = 1.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75–3.59 (m, 4H), 1.78–1.32 (m, 5H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 61.3, 60.8, 39.8, 29.7, 26.4, 25.9, 19.9, 18.3, −5.4; IR (film) 3020, 2958, 2931, 1521, 1473, 1424, 1216, 1086, 1048, 929, 837, 757.



2.33

(*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-methylpentanal (2.33): A solution of DMSO (2.0 mL, 28.5 mmol) in DCM (15 mL) was added to a solution of oxalyl chloride (1.6 mL, 19.0 mmol) in DCM (75 mL) at −78 °C. After 15 min, a solution of above alcohol (2.21 g, 9.5 mmol) in DCM (15 mL) was added dropwise. The resulting solution was stirred for 15 min at the same temp and

Et_3N (6.6 mL, 47.5 mmol) was added. The reaction was maintained at −78 °C for 15 min, then warmed to 0 °C for 30 min stirring. The reaction was quenched with H_2O (30 mL) and the mixture allowed to warm to rt. The mixture was diluted with DCM and organic layer was separated. The aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 20:1) to give title compound **2.33** (1.62 g, 74%) as colorless oil: $[\alpha]_D^{25}$ = +0.7 (*c* = 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, *J* = 2.1 Hz, 1H), 3.65 (td, J = 6.3, 1.5 Hz, 2H), 2.47–2.37 (m, 1H), 2.29–2.16 (m, 2H), 1.61–1.42 (m, 2H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9, 60.8, 50.9, 39.5, 25.9, 29.1, 20.0, 18.3, −5.4; IR (film) 3426, 3020, 1642, 1521, 1475, 1423, 1216, 1032, 929, 726; MS (EI) m/z 231 (M^+ + 1); HRMS (ESI) *m/z* (M^+ + 1) calcd for $C_{12}H_{27}O_2Si$ 231.1780, found 231.1779.



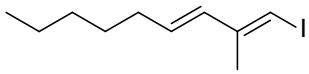
2.62

(E)-Non-3-en-1-yne (2.62): DIBAL-H (69.0 mL, 1.0 M Solution in hexane, 69.0 mmol) was added to a solution of 1-heptyne **2.64** (5.4 g, 65.0 mmol) in heptane (14 mL) while maintaining the temperature below 40 °C. When the initial exothermic reaction had subsided, the reaction mixture was heated for 2 hr at 50 °C. The heptane was then removed in vacuum and residue was diluted with THF (30 mL). Iodine (18.2 g, 69.0 mmol) in THF (30 mL) was added to this vinylalanane solution at -50 °C. After allowing the reaction mixture to warm to room temperature, saturated aqueous potassium sodium tartrate (200 mL) was added, then the mixture was vigorously stirred until it was clear. The mixture was extracted by pentane (3 × 200 mL).

The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The crude (*E*)-1-iodohept-1-ene (14.0 g, 62 mmol) was used without further purification.

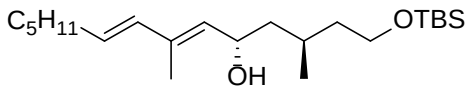
CuI (2.38 g, 12.5 mmol) and DIPEA (21.7 mL, 125 mmol) were added to a solution of crude (*E*)-1-iodohept-1-ene (14.0 g, 62 mmol) and trimethylsilylacetylene (13.3 mL, 93.7 mmol) in dry DMF (100 mL) at room temperature. The reaction mixture was degassed 5 times by freeze-pump-thaw cycles. Then $Pd(PPh_3)_4$ (3.61 g, 3.12 mmol) was added and the degasification was repeated twice. The reaction mixture was stirred at room temperature for 5 h was directly extracted with pentane (3 × 200 mL). The combined pentane layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The crude (*E*)-trimethyl(non-3-en-1-yn-1-yl)silane was used without further purification.

K_2CO_3 (17.9 g, 130 mmol) was added to a solution of crude (*E*)-trimethyl(non-3-en-1-yn-1-yl)silane (12.6 g, 65 mmol) in dry MeOH (150 mL). The reaction mixture was stirred at room temperature for 2 h. Then water was added and the aqueous layer was extracted with pentane. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by reduced pressure distillation (20 mmHg, bp 54 °C to 60 °C) to give the title product **2.62** (5.40 g, 68% over three steps) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (dt, *J* = 15.9 Hz, 6.9 Hz, 1H), 5.46 (tdd, *J* = 15.9 Hz, 3.6 Hz, 1.5 Hz, 1H), 2.79 (d, *J* = 2.1 Hz, 1H), 2.12 (qd, *J* = 6.9 Hz, 1.5 Hz, 2H), 1.58-1.20 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H).



2.61

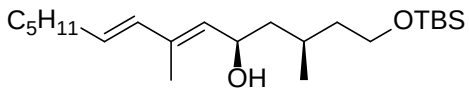
(1*E*,3*E*)-1-Iodo-2-methylnona-1,3-diene (2.61): Cp_2ZrCl_2 (4.15 g, 17.6 mmol) was taken up in DCM (120 mL) followed by the addition of Me_3Al (54.5 mL, 2.0 M solution in hexane, 109 mmol) at –23 °C under argon. H_2O (0.95 mL, 52.7 mmol) was added slowly. After an addtional 20 min of stirring, enyne **2.62** was cannulated in DCM (50 mL). After 10 min, the reaction was quenched with saturated K_2CO_3 solution (10 mL) and 10 min later Na_2SO_4 (20 g) was added to dry the solution. The mixture was filtered and the filtrate was concentrated in vacuum. The crude product was purified by flash chromatography (pure pentane) to give the title product **2.61** (8.00 g, 86%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (s, 1H), 6.15 (d, *J* = 17.4 Hz, 1H), 5.77 (dt, *J* = 15.6 Hz, 6.9 Hz, 1H), 2.07 (q, *J* = 6.9 Hz, 2H), 1.95 (s, 3H), 1.45-1.20 (m, 6H), 0.91 (t, *J* = 6.9 Hz, 3H).



2.60

(3*R*,5*S*,6*E*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyltetradeca-6,8-dien-5-ol (2.60): *t*-BuLi (11.3 mL, 1.7 M solution in pentane, 19.2 mmol) was added to a solution of vinyl iodide **2.61** (3.81 g, 14.4 mmol) in dry Et_2O (50 mL) at –78 °C under argon dropwise. After stirring the reaction mixture at 0 °C for 30 min, it was cooled to –78 °C and a solution of aldehyde **2.33** (2.22 g, 9.62 mmol) in dry Et_2O (20 mL) was cannulated. After additional 1 h stirring at –78 °C, the reaction was quenched by saturated NH_4Cl solution and the mixture was warmed to rt. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under

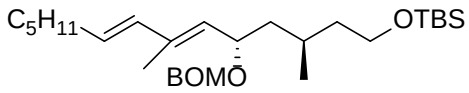
reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 8:1) to give the title compound **2.60** (1.36 g, 38%) as a colorless oil (the upper spot): $[\alpha]_D^{25} = -13.4$ (*c* = 1.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, *J* = 15.6 Hz, 1H), 5.68 (dt, *J* = 15.6 Hz, 6.6 Hz, 1H), 5.34 (d, *J* = 8.7 Hz, 1H), 4.57 (dt, *J* = 13.5 Hz, 5.1 Hz, 1H), 3.69-3.60 (m, 2H), 2.09 (q, *J* = 6.9 Hz, 2H), 1.79 (d, *J* = 0.9 Hz, 3H), 1.75–1.69 (m, 1H), 1.59–1.53 (m, 1H), 1.50–1.38 (m, 3H), 1.34–1.21 (m, 6H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91-0.86 (m, 12H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 134.1, 132.6, 130.5, 66.6, 61.3, 45.0, 40.2, 32.8, 31.4, 29.2, 26.3, 26.0, 22.5, 19.8, 18.3, 14.0, 12.9, –5.3; IR (film) 3364, 2956, 2928, 2857, 1463, 1386, 1254, 1095, 1006, 964, 837, 776.



2.67

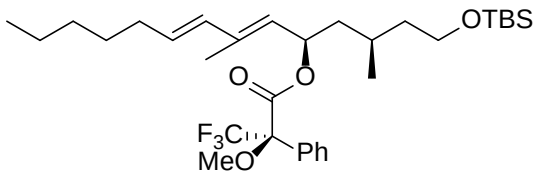
(3*R*,5*R*,6*E*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyltetradeca-6,8-dien-5-ol (2.67): *t*-BuLi (11.3 mL, 1.7 M solution in pentane, 19.2 mmol) was added to a solution of vinyl iodide **2.61** (3.81 g, 14.4 mmol) in dry Et_2O (50 mL) at –78 °C under argon dropwise. After stirring the reaction mixture at 0 °C for 30 min, it was cooled to –78 °C and a solution of aldehyde **2.33** (2.22 g, 9.62 mmol) in dry Et_2O (20 mL) was cannulated. After additional 1 h stirring at –78 °C, the reaction was quenched by saturated NH_4Cl solution and the mixture was warmed to rt. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 8:1) to give the title compound **2.67** (1.24 g, 35%) as a colorless oil (the lower spot): ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (d, *J* = 15.6 Hz, 1H), 5.68 (dt, *J* = 15.6 Hz, 6.6 Hz, 1H), 5.31 (d, *J* = 8.7 Hz,

1H), 4.55 (dt, *J* = 15.3 Hz, 6.9 Hz, 1H), 3.69-3.60 (m, 2H), 2.09 (q, *J* = 6.9 Hz, 2H), 1.80 (d, *J* = 1.2 Hz, 3H), 1.75–1.69 (m, 1H), 1.59–1.53 (m, 1H), 1.50–1.38 (m, 3H), 1.34–1.21 (m, 6H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.91-0.86 (m, 12H), 0.04 (s, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.1, 132.3, 130.5, 66.6, 61.3, 44.9, 39.8, 32.8, 31.4, 29.2, 26.3, 26.0, 22.5, 20.4, 18.3, 14.0, 13.0, –5.3.



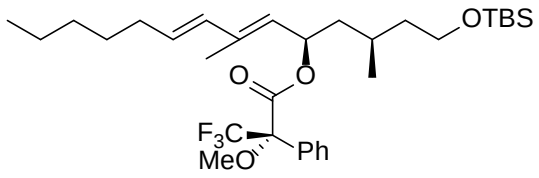
2.42

(5*S*,7*R*)-7,11,11,12,12-Pentamethyl-5-((1*E*,3*E*)-2-methylnona-1,3-dien-1-yl)-1-phenyl-2,4,10-trioxa-11-silatridecane (2.42): BOMCl (0.019 mL, 0.12 mmol) was added to a solution of alcohol **2.60** (18.6 mg, 0.05 mmol) and DIPEA (0.026 mL, 0.15 mmol) in DCM (2 mL) at rt under argon. The resulting mixture was stirred overnight. The mixture was poured into brine and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The crude product was purified by flash chromatography (hexane/EtOAc = 20:1) to give a colorless oil **2.42** (0.024 g, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 4H), 7.30–7.27 (m, 1H), 6.06 (d, *J* = 15.5 Hz, 1H), 5.67 (dt, *J* = 15.5, 7.0Hz, 1H), 5.21 (d, *J* = 9.0 Hz, 1H), 4.74–4.50 (m, 5H), 3.69–3.63 (m, 2H), 2.11 (q, *J* = 7.0 Hz, 1H), 1.81–1.79 (m, 1H), 1.79 (d, *J* = 1.0 Hz, 3H), 1.72–1.64 (m, 1H), 1.62–1.55 (m, 1H), 1.41–1.22 (m, 8H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.90–0.88 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 136.6, 134.0, 130.3, 130.2, 128.4, 127.9, 127.6, 91.6, 69.9, 69.5, 61.3, 43.4, 40.4, 32.9, 31.5, 29.2, 26.0, 22.6, 19.5, 18.3, 14.0, 13.0, −5.3.



2.68

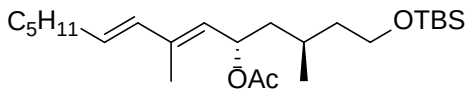
(*R*)-(3*R*,5*R*,6*E*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyltetradeca-6,8-dien-5-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.68): (*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride ((*S*)-MTPACl, 0.012 mL, 0.067 mmol) was added to a solution of alcohol **2.67** (8.2 mg, 0.022 mmol) in pyridine (0.5 mL). The reaction mixture was stirred at rt for 1 h. Then the mixture was purified by flash chromatography (hexane/EtOAc = 10:1) directly to give a colorless oil **2.68** (11.6 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.39-7.36 (m, 3H), 5.97 (d, *J* = 15.6 Hz, 1H), 5.90-5.82 (m, 1H), 5.75 (dt, *J* = 15.6 Hz, 6.9 Hz, 1H), 5.11 (d, *J* = 9.3 Hz, 1H), 3.84-3.57 (m, 2H), 3.54 (s, 3H), 2.09 (q, *J* = 6.9 Hz, 2H), 1.89 (d, *J* = 0.9 Hz, 3H), 1.72-1.55 (m, 5H), 1.47-1.22 (m, 6H), 0.92-0.87 (m, 15H), 0.02 (s, 6H).



2.69

(*S*)-(3*R*,5*R*,6*E*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyltetradeca-6,8-dien-5-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (2.69): (*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl chloride ((*R*)-MTPACl, 0.012 mL, 0.067 mmol) was added to a solution of alcohol **2.67** (8.2 mg, 0.022 mmol) in pyridine (0.5 mL). The reaction mixture was stirred at rt for 1 h. Then the mixture was purified by flash chromatography (hexane/EtOAc = 10:1) directly to give a colorless oil **2.69** (11.6 mg, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.49 (m, 2H),

7.38-7.34 (m, 3H), 6.03 (d, *J* = 15.6 Hz, 1H), 5.96-5.88 (m, 1H), 5.77 (dt, *J* = 15.6 Hz, 6.9 Hz, 1H), 5.26 (d, *J* = 9.3 Hz, 1H), 3.65-3.57 (m, 2H), 3.53 (s, 3H), 2.10 (q, *J* = 6.9 Hz, 2H), 1.90 (d, *J* = 0.9 Hz, 3H), 1.72-1.55 (m, 5H), 1.47-1.22 (m, 6H), 0.92-0.87 (m, 15H), 0.02 (s, 6H).



2.70

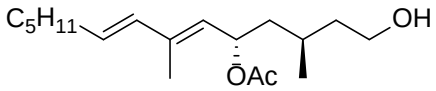
(3*R*,5*S*,6*E*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyltetradeca-6,8-dien-5-yl acetate (2.70):

From (3*R*,5*S*,6*E*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyltetradeca-6,8-dien-5-ol (**2.60**): DMAP (38 mg, 0.31 mmol), Pyridine (0.44 mL, 5.45 mmol) and Ac_2O (0.44 mL, 4.69 mmol) was added to a solution of alcohol **2.60** (0.576 g, 1.56 mmol) in DCM (10 mL) at 0 °C under argon. After stirring the reaction mixture at rt overnight, it was quenched by pH = 7 buffer (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 20:1) to give the title compound **2.70** (474 mg, 76%) as a colorless oil.

From (3*R*,5*R*,6*E*,8*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethyltetradeca-6,8-dien-5-ol (**2.67**): Ph_3P (599 mg, 2.28 mmol) and AcOH (0.13 mL, 2.28 mmol) were added to a solution of alcohol **2.67** (766 mg, 2.08 mmol) in THF (10 mL). After 5 min, the solution was cooled to 0 °C, DIAD (0.45 mL, 2.28 mmol) was added dropwise and the mixture was stirred for 1 h and warmed to rt. After stirred for overnight, the mixture was quenched with saturated $NaHCO_3$ solution. The aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue

was purified by flash chromatography (hexane:EtOAc = 20:1) to give the title compound **2.70** (725 mg, 85%) as a colorless oil.

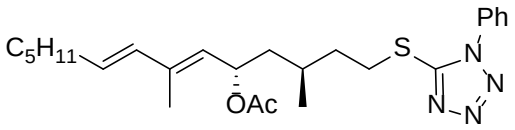
$[\alpha]_D^{25}$ = +11.9 (*c* = 1.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 15.6 Hz, 1H), 5.75-5.65 (m, 2H), 5.20 (d, *J* = 9.2 Hz, 1H), 3.66-3.57 (m, 2H), 2.08 (q, *J* = 6.8 Hz, 2H), 2.00 (s, 3H), 1.84 (d, 0.9 Hz, 3H), 1.60-1.52 (m, 2H), 1.42-1.23 (m, 9H), 0.93-0.82 (m, 15H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 137.5, 133.8, 131.2, 127.7, 69.9, 60.9, 42.0, 40.0, 32.8, 31.4, 29.1, 26.1, 25.9, 22.5, 21.4, 19.7, 18.3, 14.0, 13.1, −5.3; IR (film) 2956, 2928, 2857, 1738, 1462, 1369, 1240, 1097, 1014, 964, 899, 836, 809, 776; HRMS (EI) m/z (M^+) calcd for $C_{24}H_{46}O_3Si$ 410.3216, found 410.3212.



2.71

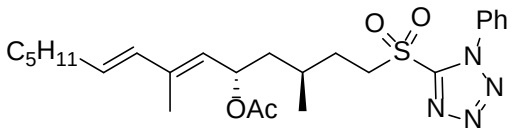
(3*R*,5*S*,6*E*,8*E*)-1-hydroxy-3,7-dimethyltetradeca-6,8-dien-5-yl acetate (2.71): A buffered solution of pyridinum hydrofluoride (5.4 mL, stock solution prepared from 1 mL of pyridinum hydrofluoride, 2 mL of pyridine, and 8 mL of THF) was added to a solution of TBS ether **2.70** (426 mg, 1.08 mmol) in THF (5 mL) at 0 °C under argon. After stirring 5 h at rt, TLC showed the reaction was complete. The reaction was quenched by the addition of pH = 7 buffer (10 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (hexane:EtOAc = 2:1) to give the title compound **2.71** (314 mg, 98%) as a colorless oil: $[\alpha]_D^{25}$ = +27.2 (*c* = 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 15.6 Hz, 1H), 5.76-5.67 (m, 2H), 5.22 (d, *J* = 9.2 Hz, 1H), 3.72-3.59 (m, 2H), 2.07 (q, *J* = 6.8 Hz, 2H), 2.00 (s, 3H), 1.83 (d, *J* = 0.8 Hz, 3H), 1.68-1.48 (m, 4H), 1.41-1.23 (m, 7H), 0.92 (d, *J*

= 6.0 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 137.6, 133.6, 131.4, 127.4, 69.7, 60.6, 42.3, 39.7, 32.8, 31.4, 29.1, 26.0, 22.5, 21.3, 19.8, 14.0, 13.0; IR (film) 3416, 2957, 2927, 2858, 1735, 1457, 1372, 1241, 1056, 1016, 964; HRMS (EI) m/z (M^+) calcd for $C_{18}H_{32}O_3$ 296.2351, found 296.2338.



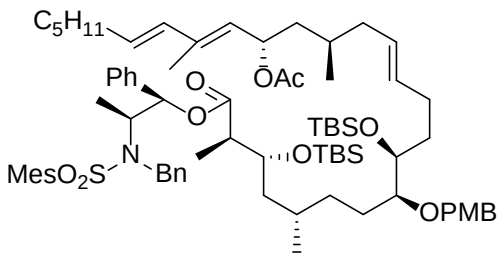
2.72

(3*S*,5*S*,6*E*,8*E*)-3,7-Dimethyl-1-((1-phenyl-1H-tetrazol-5-yl)thio)tetradeca-6,8-dien-5-yl acetate (2.72): Ph_3P (257 mg, 0.98 mmol) and PTSH (183 mg, 1.02 mmol) were added to a solution of alcohol **2.71** (264 mL, 0.89 mmol) in THF (5 mL). After 5 min, the solution was cooled to 0 °C, DIAD (0.19 mL, 0.98 mmol) was added dropwise and the mixture was stirred for 1 h and allowed to warm to rt. After stirred for overnight, the mixture was quenched with pH = 7 buffer. The aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (hexane:EtOAc = 8:1) to give the title compound **2.72** (386 mg, 95%) as a colorless oil: $[\alpha]_D^{25}$ = +27.8 (*c* = 1.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.54 (m, 5H), 6.03 (d, *J* = 15.6 Hz, 1H), 5.79-5.68 (m, 2H), 5.23 (d, *J* = 9.2 Hz, 1H), 3.52-3.33 (m, 2H), 2.11 (q, *J* = 7.2 Hz, 2H), 2.02 (s, 3H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.71-1.59 (m, 4H), 1.43-1.27 (m, 7H), 1.02 (d, *J* = 6.0 Hz, 3H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 154.3, 137.8, 133.7, 133.6, 131.6, 130.0, 129.8, 127.2, 123.8, 69.4, 41.5, 36.0, 32.8, 31.5, 31.0, 29.1, 29.0, 22.5, 21.3, 19.4, 14.0, 13.2; IR (film) 2956, 2926, 2856, 1731, 1597, 1501, 1461, 1385, 1241, 1087, 1015, 965, 761; HRMS (ESI) m/z (M^+ + Na) calcd for $C_{25}H_{36}N_4O_2NaS$ 479.2457, found 479.2491.



2.59

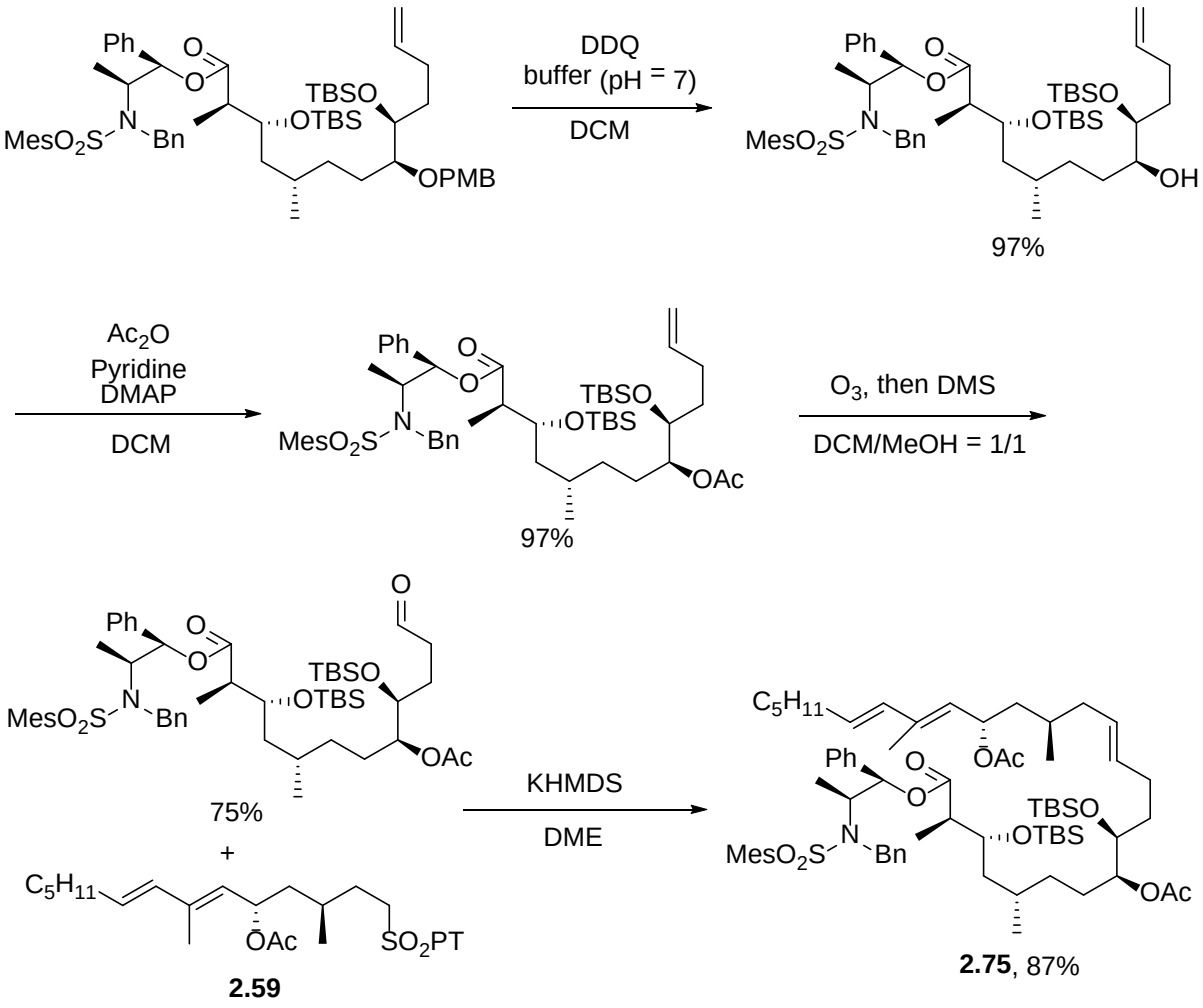
(3*S*,5*S*,6*E*,8*E*)-3,7-Dimethyl-1-((1-phenyl-1H-tetrazol-5-yl)sulfonyl)tetradeca-6,8-dien-5-yl acetate (2.59): A solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (80 mg, 0.065 mmol) in 30% H_2O_2 (0.5 mL) was added to a solution of sulfide **2.72** (148 mg, 0.324 mmol) in EtOH (3 mL) at 0 °C. After 3 h stirring at rt, a yellow solid had crashed out of mixture. The mixture was poured into brine and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum to reveal a sludgy yellow and white biphasic residue. The residue was purified by flash chromatography (hexane:EtOAc = 7:1) to give the title compound **2.59** (111 mg, 70%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73-7.67 (m, 2H), 7.66-7.61 (m, 3H), 6.07 (d, *J* = 15.6 Hz, 1H), 5.66 (dt, *J* = 15.0 Hz, 7.8 Hz, 1H), 5.60 (dt, *J* = 9.0 Hz, 6.6 Hz, 1H), 5.30 (d, *J* = 9.0 Hz, 1H), 3.84-3.72 (m, 2H), 2.17-2.15 (m, 1H), 2.10-2.06 (m, 1H), 2.04 (s, 3H), 2.02-1.99 (m, 1H), 1.84 (d, *J* = 0.6 Hz, 3H), 1.82-1.77 (m, 2H), 1.72-1.66 (m, 1H), 1.55-1.50 (m, 1H), 1.34-1.26 (m, 6H), 1.00 (d, *J* = 6.0 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 153.4, 136.6, 136.3, 133.0, 129.8, 128.8, 127.2, 125.1, 71.3, 54.3, 40.0, 34.9, 32.5, 31.6, 28.1, 24.8, 22.6, 21.4, 19.1, 14.0, 13.2.



2.73

(2*R*,3*R*,5*S*,8*S*,9*S*,12*E*,15*R*,17*S*,18*E*,20*E*)-(1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 17-acetoxy-3,9-bis((tert-butyldimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-2,5,15,19-tetramethylhexacosa-12,18,20-trienoate (2.73): A solution of KHMDS (43.0 mg, 0.216 mmol) in DME (1 mL) was added to a solution of sulfon **2.59** (112 mg, 0.230 mmol) in DME (2 mL) at −70 °C. The resulting orange solution was stirred for 30 min. A solution of aldehyde **2.29** (150 mg, 0.144 mmol) in DME (0.5+0.25 mL) was added to the above solution dropwise. The reaction mixture was stirred for 1 h at −70 °C and warmed to rt slowly. After the mixture was stirred for overnight, H_2O was added to quench reaction. The organic layer was separated, the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane:EtOAc = 10:1) to give the title compound **2.73** (160 mg, 85%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.11 (m, 10H), 6.89–6.83 (m, 6H), 6.02 (d, *J* = 15.3 Hz, 1H), 5.76 (d, *J* = 5.1 Hz, 1H), 5.74-5.68 (m, 2H), 5.45-5.35 (m, 2H), 5.25 (d, *J* = 9.3 Hz, 1H), 4.76 (d, *J* = 16.5 Hz, 1H), 4.53 (d, *J* = 16.5 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.15–4.10 (m, 1H), 4.01-3.98 (m, 1H), 3.81 (s, 3H), 3.78–3.73 (m, 1H), 3.27–3.20 (m, 1H), 2.53–2.50 (m, 1H), 2.45 (s, 6H), 2.29 (s, 3H), 2.12–2.06 (m, 4H), 1.98–1.90 (m, 1H), 1.90–1.83 (m, 1H), 1.81–1.80 (m, 3H), 1.76–1.56 (m, 4H), 1.46–1.35 (m, 6H), 1.35–1.26 (m, 8H), 1.21 (d,

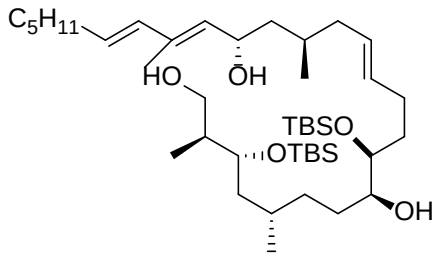
J = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.93–0.87 (s, 24H), 0.65 (d, *J* = 6.0 Hz, 3H), 0.06–0.00 (m, 12H).



Scheme 2.26 Synthesis of compound **2.75**

(2*R*,3*R*,5*S*,8*S*,9*S*,12*E*,15*R*,17*S*,18*E*,20*E*)-(1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropoxy)-3,9-bis((tert-butyldimethylsilyl)oxy)-2,5,15,19-tetramethyl-1-oxohexacosa-12,18,20-triene-8,17-diyl diacetate (2.75): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34-7.12 (m, 8H), 6.89-6.84 (m, 4H), 6.04 (d, *J* = 15.6 Hz, 1H), 5.78 (d, *J*

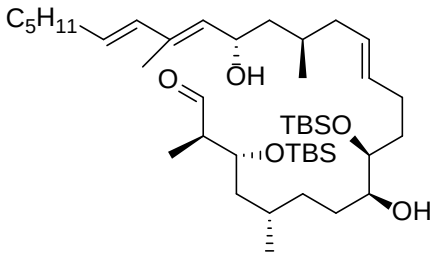
= 4.8 Hz, 1H), 5.77-5.69 (m, 3H), 5.41-5.35 (m, 2H), 5.22 (d, *J* = 9.0 Hz, 1H), 4.77-4.72 (m, 2H), 4.54 (d, *J* = 16.8 Hz, 1H), 4.14-4.12 (m, 1H), 4.00-3.98 (m, 1H), 3.70-3.64 (m, 1H), 2.52-2.48 (m, 1H), 2.46 (s, 6H), 2.30 (s, 3H), 2.12–2.06 (m, 4H), 1.98–1.90 (m, 1H), 1.90–1.83 (m, 1H), 1.81–1.80 (m, 3H), 1.76–1.56 (m, 4H), 1.46–1.35 (m, 6H), 1.35–1.26 (m, 8H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.93–0.87 (s, 24H), 0.65 (d, *J* = 6.0 Hz, 3H), 0.06–0.00 (m, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 170.7, 170.4, 142.5, 140.3, 138.3, 138.2, 137.4, 133.7, 133.2, 132.1, 131.8, 131.3, 128.4, 128.3, 127.9, 127.8 127.3, 126.5, 77.9, 76.4, 71.6, 70.5, 70.0, 56.6, 48.1, 46.1, 41.5, 40.1, 39.9, 34.2, 32.9, 31.9, 31.5, 29.7, 29.5, 29.2, 28.8, 28.7, 25.8, 25.7, 23.0, 22.7, 21.4, 21.2, 20.9, 19.6, 18.8, 18.0, 14.2, 14.1, 14.0, 9.7, –4.5, –4.6.



2.76

(2*S*,3*R*,5*S*,8*S*,9*S*,12*E*,15*R*,17*S*,18*E*,20*E*)-3,9-Bis((*tert*-butyldimethylsilyl)oxy)-2,5,15,19-tetramethylhexacosa-12,18,20-triene-1,8,17-triol (2.76): DIBAL-H (0.29 mL, 1.0 M in hexane, 0.29 mmol) was added to a solution of ester **2.75** (36 mg, 0.029 mmol) in DCM (1 mL) at −78 °C. After 1 h, the reaction was quenched by the addition of saturated aqueous potassium sodium tartrate, and warmed to rt and stirred. After an addition 2 h, the reaction mixture was clear and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 8:1) to give the title compound **2.76** (20 mg, 99%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.06 (d, *J* = 15.6 Hz, 1H), 5.71 (dt, *J* = 15.6 Hz, 7.2

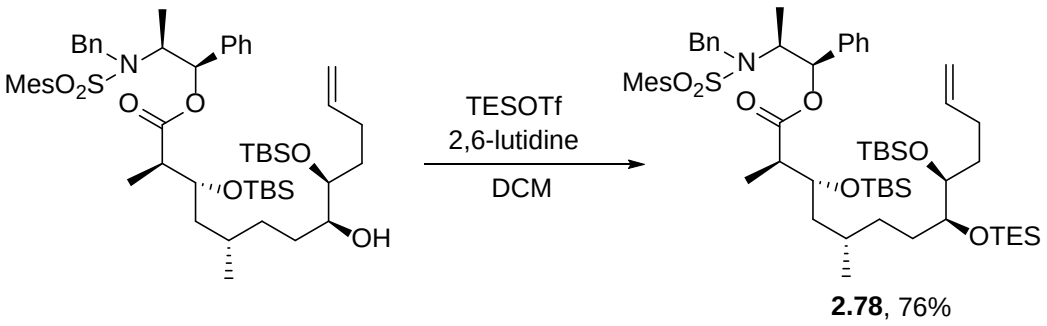
Hz, 1H), 5.42-5.36 (m, 2H), 5.31 (d, *J* = 9.0 Hz, 1H), 4.60 (dd, *J* = 15.6 Hz, 7.2 Hz, 1H), 3.87-3.82 (m, 2H), 3.56-3.51 (m, 2H), 3.45-3.42 (m, 1H), 2.13-2.00 (m, 6H), 1.82 (s, 3H), 1.90-1.81 (m, 1H), 1.72-1.68 (m, 3H), 1.56-1.38 (m, 15H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.92-0.88 (m, 24H), 0.11 (s, 6H), 0.09 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.6, 134.0, 132.3, 131.4, 130.7, 128.8, 74.8, 74.7, 72.7, 66.7, 64.9, 44.3, 42.3, 40.1, 38.5, 33.7, 33.2, 32.8, 31.4, 29.6, 29.2, 29.1, 28.2, 25.9, 22.5, 20.1, 19.9, 18.1, 18.0, 14.4, 14.0, 12.9, –4.1, –4.3, –4.5, –4.6.



2.77

(2*S*,3*R*,5*S*,8*S*,9*S*,12*E*,15*R*,17*S*,18*E*,20*E*)-3,9-Bis((*tert*-butyldimethylsilyl)oxy)-8,17-dihydroxy-2,5,15,19-tetramethylhexacosa-12,18,20-trienal (2.77): $PhI(OAc)_2$ (4.8 mg, 0.015 mmol) and TEMPO (0.2 mg, 0.0014 mmol) were added to a solution of the alcohol **2.76** (9.9 mg, 0.013 mmol) in DCM (0.5 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 8 h. Saturated $Na_2S_2O_3$ solution was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 7:1) to give the title compound **2.77** (5.3 mg, 56%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 6.06 (d, *J* = 15.6 Hz, 1H), 5.72 (dt, *J* = 15.6 Hz, 7.2 Hz, 1H), 5.41-5.34 (m, 2H), 5.30 (d, *J* = 7.2 Hz, 1H), 4.65 (dd, *J* = 15.6 Hz, 7.2 Hz, 1H), 4.12-4.07 (m, 1H), 3.56-3.51 (m, 1H), 3.45-3.42 (m, 1H), 2.56-2.50 (m, 1H), 2.13-2.00 (m, 6H), 1.82 (s, 3H), 1.72-1.68 (m, 2H), 1.56-1.38 (m, 15H), 1.06 (d, *J* = 6.8 Hz, 3H),

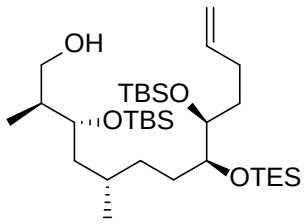
0.92-0.88 (m, 24H), 0.11-0.05 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 135.6, 134.0, 132.3, 131.4, 130.7, 128.8, 74.8, 72.7, 66.7, 64.9, 44.3, 42.3, 40.1, 38.5, 33.7, 33.2, 32.8, 31.4, 29.6, 29.2, 29.1, 28.2, 25.9, 22.5, 20.1, 19.9, 18.1, 18.0, 14.4, 14.0, 12.9, –4.1, –4.3, –4.5, –4.6.



2.78, 76%

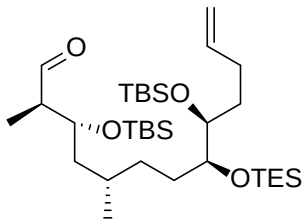
Scheme 2.27 synthesis of compound **2.78**

(2*R*,3*R*,5*S*,8*S*,9*S*)-(1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 3,9-bis((tert-butyldimethylsilyl)oxy)-2,5-dimethyl-8-((triethylsilyl)oxy)tridec-12-enoate (2.78): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.11 (m, 8H), 6.89–6.83 (m, 4H), 5.85-5.82 (m, 1H), 5.80-5.74 (m, 1H), 5.02 (d, *J* = 17.2 Hz, 1H), 4.97 (d, *J* = 10.0 Hz, 1H), 4.76 (d, 16.4 Hz, 1H), 4.53 (d, 16.4 Hz, 1H), 4.15-4.05 (m, 1H), 4.05-4.00 (m, 1H), 3.56-3.44 (m, 2H), 2.53–2.50 (m, 1H), 2.45 (s, 6H), 2.28 (s, 3H), 2.22–2.16 (m, 1H), 2.02–1.96 (m, 1H), 1.68–1.66 (m, 1H), 1.59–1.55 (m, 1H), 1.46–1.37 (m, 3H), 1.34–1.26 (m, 2H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.00-0.85 (m, 27H), 0.68-0.54 (m, 9H), 0.13 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 142.4, 140.2, 138.5, 138.3, 138.2, 133.1, 132.1, 128.3, 128.2, 127.8, 127.7, 127.2, 127.1, 126.4, 114.5, 77.8, 76.3, 71.5, 70.4, 56.5, 48.0, 46.0, 39.8, 34.1, 31.1, 31.0, 29.7, 28.7, 25.8, 25.7, 25.6, 22.9, 22.8, 21.1, 20.8, 18.7, 18.0, 17.9, 13.9, 9.7, –4.6, –4.7.



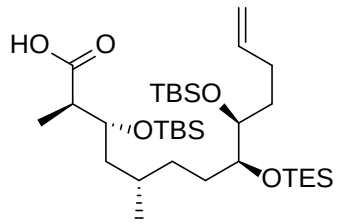
2.79

(2*S*,3*R*,5*S*,8*S*,9*S*)-3,9-Bis((*tert*-butyldimethylsilyl)oxy)-2,5-dimethyl-8-((triethylsilyl)oxy)tridec-12-en-1-ol (2.79): DIBAL-H (0.37 mL, 1.0 M in hexane, 0.37 mmol) was added to a solution of ester **2.78** (95 mg, 0.092 mmol) in DCM (1 mL) at −78 °C. After 1 h, the reaction was quenched by the addition of saturated aqueous potassium sodium tartrate, and warmed to rt and stirred. After an addition 2 h, the reaction mixture was clear and extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 10:1) to give the title compound **2.79** (50 mg, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.77 (m, 1H), 5.02 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 3.89-3.80 (m, 2H), 3.59-3.47 (m, 3H), 2.68 (br, 1H), 2.28-2.18 (m, 1H), 2.03-1.90 (m, 1H), 1.78-1.68 (m, 2H), 1.62-1.50 (m, 4H), 1.42-1.34 (m, 4H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.88-0.86 (m, 21H), 0.62-0.53 (m, 6H), 0.08-0.04 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 114.3, 76.1, 75.2, 75.0, 64.8, 42.2, 38.2, 33.9, 30.8, 29.5, 29.4, 27.0, 25.9, 20.2, 18.0, 14.8, 6.9, 5.2, -4.0, -4.3.



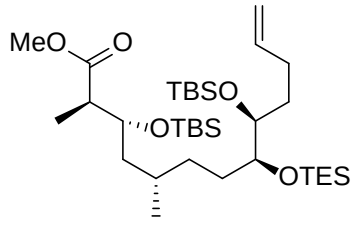
2.80

(2*R*,3*R*,5*S*,8*S*,9*S*)-3,9-Bis((*tert*-butyldimethylsilyl)oxy)-2,5-dimethyl-8-((triethylsilyl)oxy)tridec-12-enal (2.80): $PhI(OAc)_2$ (49 mg, 0.17 mmol) and TEMPO (3 mg, 0.02 mmol) were added to a solution of the alcohol **2.79** (42 mg, 0.066 mmol) in DCM (2 mL) at 0 °C under argon. The reaction mixture was stirred at rt overnight. Saturated $Na_2S_2O_3$ solution was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 20:1) to give the title compound **2.80** (33 mg, 79%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76-9.75 (m, 1H), 5.89-5.79 (m, 1H), 5.04 (d, *J* = 17.2 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 4.10-4.04 (m, 1H), 3.60-3.50 (m, 2H), 2.55-2.48 (m, 1H), 2.29-2.23 (m, 1H), 2.06-1.93 (m, 1H), 1.78-1.18 (m, 9H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.88-0.86 (m, 21H), 0.62-0.53 (m, 6H), 0.08-0.04 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 139.1, 114.3, 76.0, 74.9, 71.3, 52.0, 42.3, 37.1, 34.7, 32.7, 31.9, 30.8, 30.0, 29.7, 29.4, 27.2, 25.8, 22.7, 19.7, 18.0, 14.1, 10.0, 6.9, 5.1, -4.0, -4.2.



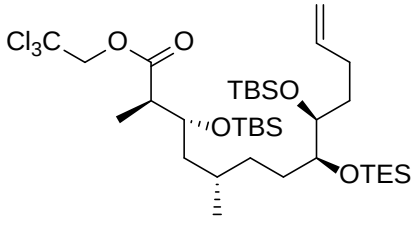
2.81

(2*R*,3*R*,5*S*,8*S*,9*S*)-3,9-Bis((*tert*-butyldimethylsilyl)oxy)-2,5-dimethyl-8-((triethylsilyl)oxy)tridec-12-enoic acid (2.81): $NaH_2PO_4 \cdot H_2O$ (7.6 mg, 0.055 mmol), 2-methyl-2-butene (0.058 mL, 0.55 mmol) and sodium chlorite (7.8 mg, 0.069 mmol) was added to a solution of aldehyde **2.80** (17 mg, 0.027 mmol) in *t*-BuOH (1 mL) and H_2O (0.3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2h. Saturated $NaSO_3$ was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash chromatography (hexane:EtOAc = 10:1 to 5:1) to give the title compound **2.81** (17 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.77 (m, 1H), 5.02 (d, *J* = 17.2 Hz, 1H), 4.95 (d, *J* = 10.2 Hz, 1H), 3.93-3.89 (m, 1H), 3.58-3.47 (m, 2H), 2.71-2.65 (m, 1H), 2.28-2.19 (m, 1H), 2.04-1.90 (m, 1H), 1.71-1.09 (m, 9H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.92-0.88 (m, 21H), 0.62-0.53 (m, 6H), 0.08-0.04 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 139.0, 114.3, 76.0, 74.7, 72.6, 52.1, 42.4, 37.3, 34.5, 32.3, 31.8, 30.8, 30.0, 29.6, 29.4, 27.1, 25.8, 22.5, 19.5, 18.0, 14.3, 10.1, 6.8, 5.1, -4.0, -4.3.



2.82

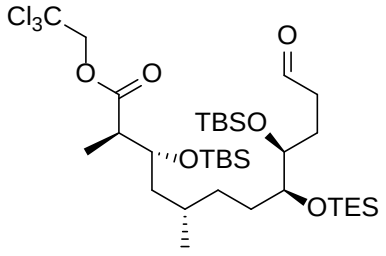
Methyl (2*R*,3*R*,5*S*,8*S*,9*S*)-3,9-bis((*tert*-butyldimethylsilyl)oxy)-2,5-dimethyl-8-((triethylsilyl)oxy)tridec-12-enoate (2.82): Trimethylsilyldiazomethane (0.025 mL, 2.0 M in Et_2O, 0.050 mmol) was added to a solution of acid **2.81** (10.6 mg, 0.017 mmol) in benzene (2 mL) and MeOH (0.5 mL) dropwise. The reaction mixture was stirred at rt for 2 h. TLC shows the reaction was complete. Then the solvent was evaporated and the mixture was purified by flash chromatography (Hex:EA = 20:1) to give the title compound **2.82** (10.7 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, J_1 = 17.1 Hz, J_2 = 10.3 Hz, J_3 = 6.6 Hz, 1H), 5.02 (dq, J_1 = 17.1 Hz, J_2 = 1.7 Hz, 1H), 4.94 (dq, J_1 = 10.3 Hz, J_2 = 1.7 Hz, 1H), 1H), 4.09-4.05 (m, 1H), 3.66 (s, 3H), 3.56-3.48 (m, 2H), 2.69-2.63 (m, 1H), 2.28-2.18 (m, 1H), 1.99-1.90 (m, 1H), 1.75-1.12 (m, 9H), 1.10 (d, J = 6.8 Hz, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.88-0.84 (m, 21H), 0.58 (q, J = 8.0 Hz, 6H), 0.08-0.04 (m, 12H).



2.83

2,2,2-Trichloroethyl (2*R*,3*R*,5*S*,8*S*,9*S*)-3,9-bis((*tert*-butyldimethylsilyl)oxy)-2,5-dimethyl-8-((triethylsilyl)oxy)tridec-12-enoate (2.83): DCC (0.522 g, 2.53 mmol) and DMAP (31 mg, 0.253 mmol) was added to a solution of acid **2.81** (1.065 g, 1.68 mmol) and 2,2,2-

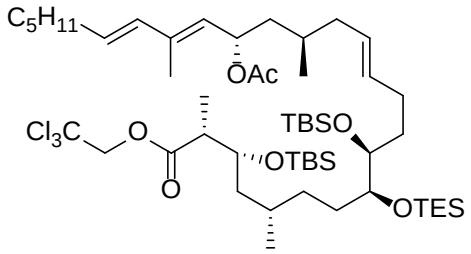
trichloroethanol (0.24 mL, 2.53 mmol) in DCM at rt. The reaction mixture was stirred overnight, concentrated in vacuo, diluted with hexanes, and the DCU precipitate was removed by Buchner filtration. The mother liquor was concentrated in vacuo and the product was purified by flash chromatography on silica gel (Hex: EA = 20:1) to yield the title compound **2.83** (1.043 g, 81%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87-5.78 (m, 1H), 5.02 (d, *J* = 17.2 Hz, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 4.73 (d, *J* = 12.0 Hz, 2H), 4.17-4.14 (m, 1H), 3.59-3.48 (m, 2H), 2.82 (dq, J_1 = 7.0 Hz, J_2 = 4.5 Hz, 1H), 2.27-2.18 (m, 1H), 2.01-1.90 (m, 1H), 1.75-1.52 (m, 4H), 1.42-1.16 (m, 5H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.92-0.88 (m, 21H), 0.62-0.53 (m, 6H), 0.08-0.04 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 139.1, 114.3, 76.0, 75.1, 74.9, 74.0, 71.0, 46.0, 40.5, 35.4, 35.0, 30.8, 29.7, 29.5, 29.2, 27.6, 27.3, 26.0, 25.9, 25.8, 25.8, 19.3, 18.0, 10.5, 6.9, 5.2, -4.0, -4.6.



2.84

2,2,2-Trichloroethyl (2*R*,3*R*,5*S*,8*S*,9*S*)-3,9-bis((*tert*-butyldimethylsilyl)oxy)-2,5-dimethyl-12-oxo-8-((triethylsilyl)oxy)dodecanoate (2.84): The alkene **2.83** (190 mg, 0.25 mmol) was taken up in DCM/MeOH (v/v = 1: 1, 5 mL) followed by the addition of pyridine (0.1 mL, 1.25 mmol) and SUDAN III (indicator, ~1 mg) at rt under argon. The solution was cooled to −78 °C, and a stream of O_3 was lightly bubbled through the solution until the pink color was disappear (a light yellow color persisted). The DMS was added slowly. The reaction mixture was slowly warmed to rt. After stirring for overnight, the mixture was concentrated under the vacuum. The residue

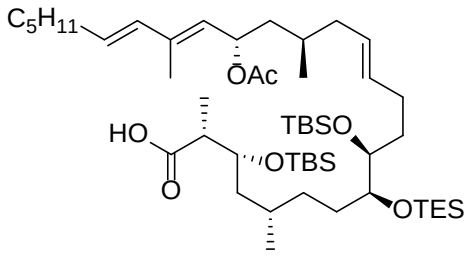
was purified by flash chromatography (Hex:EtOAc = 10:1) to give the title compound **2.84** (161 mg, 89%) as a colorless viscous oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 4.72 (d, J = 12.0 Hz, 2H), 4.17–4.15 (m, 1H), 4.01–3.98 (m, 1H), 3.59–3.51 (m, 2H), 2.81 (dq, J_1 = 7.0 Hz, J_2 = 4.5 Hz, 1H), 2.57–2.50 (m, 1H), 2.43-2.34 (m, 1H), 2.02-1.95 (m, 1H), 1.68–1.51 (m, 4H), 1.40–1.04 (m, 5H), 1.18 (d, J = 7.5 Hz, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.92-0.88 (m, 21H), 0.62-0.53 (m, 6H), 0.08-0.04 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 172.4, 95.0, 75.8, 74.8, 74.0, 70.8, 46.0, 41.2, 40.3, 35.4, 29.1, 27.4, 26.0, 25.8, 23.2, 22.9, 19.2, 18.0, 10.4, 6.9, 5.1, -4.1, -4.5.



2.85

2,2,2-Trichloroethyl (2*R*,3*R*,5*S*,8*S*,9*S*,12*E*,15*R*,17*S*,18*E*,20*E*)-17-acetoxy-3,9-bis((*tert*-butyldimethylsilyl)oxy)-2,5,15,19-tetramethyl-8-((triethylsilyl)oxy)hexacosa-12,18,20-trienoate (2.85): A solution of KHMDS (32 mg, 0.16 mmol) in DME (1 mL) was added to a solution of sulfon **2.59** (85 mg, 0.17 mmol) in DME (2 mL) at −70 °C. The resulting orange solution was stirred for 30 min. A solution of aldehyde **2.84** (95 mg, 0.12 mmol) in DME (0.5+0.25 mL) was added to the above solution dropwise. The reaction mixture was stirred for 1 h at −70 °C and warmed to rt slowly. After the mixture was stirred for overnight, H_2O was added to quench reaction. The organic layer was separated, the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane:EtOAc = 20:1) to give the title compound **2.85** (108 mg, 84%) as a colorless oil: ^{1}H

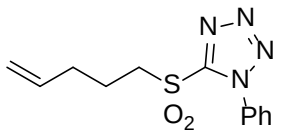
NMR (500 MHz, $CDCl_3$) δ 6.01 (d, *J* = 15.6 Hz, 1H), 5.74-5.68 (m, 2H), 5.40-5.33 (m, 2H), 5.24 (d, *J* = 9.0 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.17–4.14 (m, 1H), 3.51-3.47 (m, 2H), 2.81 (dq, J_1 = 6.9 Hz, J_2 = 4.4 Hz, 1H), 2.20-2.00 (m, 6H), 2.00 (s, 3H), 1.83 (s, 3H), 1.69-1.47 (m, 9H), 1.44-1.24 (m, 12H), 1.18 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.89-0.85 (m, 24H), 0.62-0.53 (m, 6H), 0.08-0.04 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 170.4, 136.6, 133.7, 132.2, 131.1, 128.3, 127.8, 95.0, 73.9, 71.9, 70.8, 69.6, 59.1, 41.8, 40.3, 35.3, 32.8, 31.6, 30.6, 29.7, 29.5, 29.1, 27.2, 25.9, 25.8, 22.5, 21.3, 21.0, 19.1, 18.0, 17.4, 14.2, 14.1, 13.7, 13.0, 6.9, 5.1, -4.0, -4.5.



2.86

(2*R*,3*R*,5*S*,8*S*,9*S*,12*E*,15*R*,17*S*,18*E*,20*E*)-17-Acetoxy-3,9-bis((*tert*-butyldimethylsilyl)oxy)-2,5,15,19-tetramethyl-8-((triethylsilyl)oxy)hexacosa-12,18,20-trienoic acid (2.86): Zn dust (96 mg, 1.46 mmol) was added portionwise to a solution of ester **2.85** (15 mg, 0.0146 mmol) in AcOH (1 mL). The reaction mixture was stirred vigorously under nitrogen for 4 h. After filtration and solvent removal, the residue was taken up in AcOEt and washed with 5% aqueous KHSO4 solution and saturated aqueous NaCl solution. Then it was dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane:EtOAc = 10:1) to give the title compound **2.86** (10.0 mg, 75%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 10.08 (br, 1H), 6.02 (d, *J* = 15.6 Hz, 1H), 5.74-5.56 (m, 2H), 5.42-5.34 (m, 2H), 5.24 (d, *J* = 9.0 Hz, 1H), 3.94-3.84 (m, 1H), 3.51-3.47 (m, 2H), 2.68 (dq, J_1 = 7.1

Hz, J_2 = 3.0 Hz, 1H), 2.36-2.28 (m, 1H), 2.20-1.87 (m, 5H), 2.00 (s, 3H), 1.83 (s, 3H), 1.69-1.47 (m, 9H), 1.44-1.24 (m, 12H), 1.18 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 8.0 Hz, 9H), 0.89-0.85 (m, 24H), 0.62-0.53 (m, 6H), 0.08-0.04 (m, 12H).

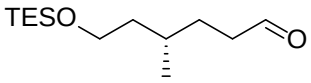


2.94

5-(Pent-4-en-1-ylsulfonyl)-1-phenyl-1H-tetrazole (2.94): Ph_3P (11.54 g, 44 mmol) and PTSH (8.20 g, 46 mmol) were added to a solution of alcohol **2.96** (4.1 mL, 40 mmol) in THF (80 mL). After 5 min, the solution was cooled to 0 °C, DIAD (8.7 mL, 44 mmol) was added dropwise and the mixture was stirred for 1 h and allowed to warm to rt. After stirred for overnight, the mixture was quenched with saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (hexane:EtOAc = 8:1) to give 5-(pent-4-en-1-ylthio)-1-phenyl-1H-tetrazole (8.87 g, 90%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.54 (m, 5H), 5.79 (ddt, J_1 =17.0 Hz, J_2 = 10.3 Hz, J_3 = 6.6 Hz, 1H), 5.09-5.01 (m, 2H), 3.40 (t, J = 7.3 Hz, 2H), 2.22 (dt, J_1 =7.2 Hz, J_2 = 6.8 Hz, 2H), 1.94 (tt, J_1 =7.3 Hz, J_2 = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 136.8, 133.7, 130.1, 129.8, 123.8, 115.9, 32.6, 32.4, 28.2.

A solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (10.565 g, 8.55 mmol) in 30% H_2O_2 (170 mL) was added to a solution of 5-(pent-4-en-1-ylthio)-1-phenyl-1H-tetrazole (10.529 g, 42.7 mmol) in EtOH 420 mL) at 0 °C. After 3 h stirring at rt, a yellow solid had crashed out of mixture. The mixture was poured into brine and extracted with Et_2O (3 × 500 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuum to reveal a sludgy yellow

and white biphasic residue. The residue was purified by flash chromatography (hexane:EtOAc = 7:1) to give the title compound **2.94** (10.4 g, 88%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.57 (m, 5H), 5.76 (ddt, J_1 =17.0 Hz, J_2 = 10.3 Hz, J_3 = 6.7 Hz, 1H), 5.13-5.08 (m, 2H), 3.75-3.71 (m, 2H), 2.27 (dt, J_1 =7.0 Hz, J_2 = 7.0 Hz, 2H), 2.08 (tt, J_1 =7.2 Hz, J_2 = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 135.6, 133.0, 131.4, 129.7, 125.0, 117.1, 55.2, 31.8, 21.1.

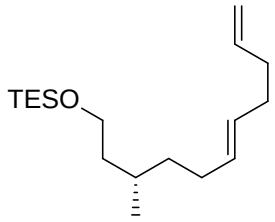


2.95

(*S*)-4-Methyl-6-((triethylsilyl)oxy)hexanal (2.95): A solution of (*S*)-citronellol **2.49** (5.5 mL, 30 mmol) in dry DCM (60 mL) was treated with imidazole (2.65 g, 39 mmol) and TESCl (6.0 mL, 36 mmol) overnight at rt. The mixture was quenched by saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 60 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (hexane:EtOAc = 20:1) to give (*S*)-((3,7-dimethyloct-6-en-1-yl)oxy)triethylsilane (7.3 g, 90%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12-5.08 (m, 1H), 3.69-3.58 (m, 2H), 1.99-1.91 (m, 2H), 1.68 (d, *J* = 0.8 Hz, 3H), 1.60 (s, 3H), 1.62-1.52 (m, 2H), 1.39-1.31 (m, 2H), 1.19-1.10 (m, 2H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.60 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1, 124.9, 61.2, 40.0, 37.2, 29.2, 25.7, 25.5, 19.6, 17.6, 6.79, 4.44.

The above olefine (4.058 g, 15 mmol) was taken up in DCM/MeOH (v/v = 1: 1, 120 mL) followed by the addition of pyridine (6.1 mL, 75 mmol) and SUDAN III (indicator, ~1 mg) at rt under argon. The solution was cooled to −78 °C, and a stream of O_3 was lightly bubbled through the solution until the pink color was disappear (a light yellow color persisted). The DMS was

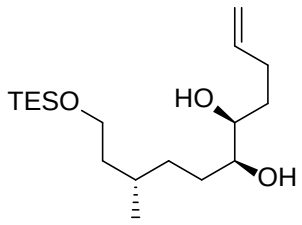
added slowly. The reaction mixture was slowly warmed to rt. After stirring for overnight, the mixture was concentrated under the vacuum. The residue was purified by flash chromatography (Hex:EtOAc = 10:1) to give the title compound **2.95** (3.080 g, 84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, *J* = 1.8 Hz, 1H), 3.70–3.59 (m, 2H), 2.51-2.37 (m, 2H), 1.72-1.33 (m, 5H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.59 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 60.7, 41.6, 39.6, 29.2, 29.0, 19.3, 6.8, 4.4.



2.93

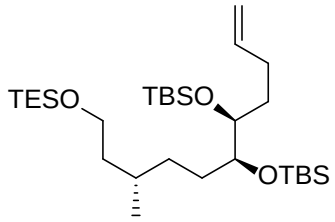
(*S*,*E*)-Triethyl((3-methylundeca-6,10-dien-1-yl)oxy)silane (2.93): A solution of KHMDS (0.863 g, 4.33 mmol) in DME (5 mL) was added to a solution of sulfone **2.94** (1.284 g, 4.62 mmol) in THF (10 mL) at −78 °C. The resulting yellow solution was stirred for 30 min before a solution of aldehyde **2.95** (0.705 g, 2.88 mmol) in DME (5 mL) was added dropwise. After stirring for 1 h at −78 °C, the mixture was warmed to rt slowly during the overnight stirring (some white precipitate was observed). The reaction was quenched by adding water, the organic layer was separated, the aqueous layers were extracted with ethyl acetate (3 × 20 mL). The combined organic layers were deried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash chromatography (hexane:Et_2O = 20:1) to give the title compound **2.93** (0.752 g, 88%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87-5.76 (m, 1H), 5.41-5.40 (m, 2H), 5.01 (dd, J_1 = 17.2 Hz, J_2 = 1.8 Hz, 1H), 4.95 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H), 3.69-3.58 (m, 2H), 2.14-1.92 (m, 6H), 1.63-1.51 (m, 2H), 1.41-1.31 (m, 2H), 1.22-1.13 (m, 1H), 0.96

(t, J = 7.9 Hz, 9H), 0.87 (d, J = 6.6 Hz, 3H) 0.60 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 130.9, 129.3, 114.4, 61.1, 39.9, 37.0, 33.9, 32.0, 30.0, 29.2, 19.5, 6.8, 4.4.



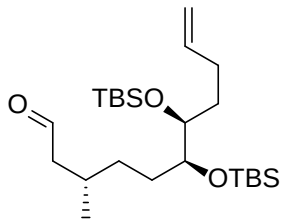
2.97

(5*S*,6*S*,9*S*)-9-Methyl-11-((triethylsilyl)oxy)undec-1-ene-5,6-diol (2.97): AD-Mix-α (19.5 g) and $MeSO_2NH_2$ (1.323 g, 13.9 mmol) were added to a solution of alkene **2.93** (4.126 g, 13.9 mmol) in the solution of *t*-BuOH/H_2O (v/v = 1:1, 100 mL) at 0 °C. The resulting orange solution was stirred at 0 °C for 24 h (the color was changed from orange to yellow). The reaction was quenched with solid Na_2SO_3 (21 g) and warmed to rt over an hour. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with KOH (2M aq), brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (hexane:EtOAc = 5:1) to give the title compound **2.97** (2.392 g, 52%, 87% based on recovery of starting materials) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddt, J_1 = 17.1 Hz, J_2 = 10.3 Hz, J_3 = 6.7 Hz, 1H), 5.07 (dq, J_1 = 17.1 Hz, J_2 = 1.6 Hz, 1H), 5.02 (dq, J_1 = 10.3 Hz, J_2 = 1.6 Hz, 1H), 3.71-3.60 (m, 2H), 3.45-3.41 (m, 2H), 2.31-2.10 (m, 2H), 1.61-1.25 (m, 9H), 0.96 (t, J = 7.9 Hz, 9H), 0.90 (d, J = 6.5 Hz, 3H), 0.60 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 115.0, 74.6, 74.0, 61.0, 39.9, 32.7, 30.9, 30.0, 29.4, 19.6, 6.8, 4.4.



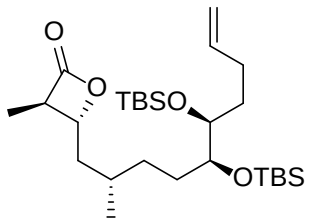
2.98

(5*S*,6*S*,9*S*)-5-(But-3-en-1-yl)-6-((*tert*-butyldimethylsilyl)oxy)-13,13-diethyl-2,2,3,3,9-pentamethyl-4,12-dioxa-3,13-disilapentadecane (2.98): TBSOTf (4.8 mL, 22.5 mol) was added to a solution of alcohol **2.87** (2.127 g, 6.43 mmol) and 2,6-lutidine (3.4 mL, 29.0 mmol) in DCM (20 mL) at 0 °C. The resulting mixture was stirred for 2 h at rt. Saturated NH_4Cl solution was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography (hexane:EtOAc = 20:1) to give the title compound **2.98** (3.417 g, 95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 6.6 Hz, 1H), 5.01 (dq, J_1 = 17.1 Hz, J_2 = 1.7 Hz, 1H), 4.94 (dq, J_1 = 10.2 Hz, J_2 = 1.7 Hz, 1H), 3.68-3.48 (m, 4H), 2.27-2.17 (m, 1H), 2.04-1.91 (m, 1H), 1.75-1.50 (m, 4H), 1.43-1.13 (m, 5H), 0.96 (t, J = 7.9 Hz, 9H), 0.89-0.87 (m, 21H), 0.59 (q, J = 7.9 Hz, 6H), 0.06-0.04 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 114.3, 75.7, 74.8, 61.2, 40.1, 34.3, 30.8, 29.5, 29.5, 27.0, 25.8, 25.7, 19.5, 18.0, 6.8, 4.4, -4.1, -4.5.



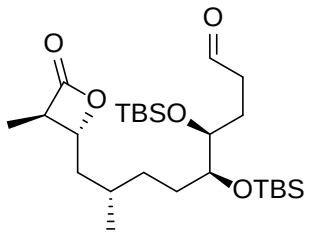
2.92

(3*S*,6*S*,7*S*)-6,7-Bis((*tert*-butyldimethylsilyl)oxy)-3-methylundec-10-enal (2.92): A solution of DMSO (0.065 mL, 0.91 mmol) in DCM (2 mL) was added to a solution of oxalyl chloride (0.052 mL, 0.61 mmol) in DCM (1 mL) at −78 °C. After 15 min, a solution of compound **2.98** (0.17 g, 0.30 mmol) in DCM (2 mL) was added dropwise. The resulting solution was stirred for 15 min at the same temp and Et_3N (0.26 mL, 1.8 mmol) was added. The reaction was maintained at −78 °C for 15 min, then warmed to 0 °C for 30 min stirring. The reaction was quenched with H_2O (5 mL) and the mixture allowed to warm to rt. The mixture was diluted with DCM and organic layer was separated. The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 20:1) to give title compound **2.92** (80 mg, 60%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (t, *J* = 2.4 Hz, 1H), 5.85-5.77 (m, 1H), 5.03-4.99 (m, 1H), 4.97-4.93 (m, 1H), 3.67-3.49 (m, 2H), 2.25-2.18 (m, 2H), 2.07-1.92 (m, 2H), 1.74-1.15 (m, 9H), 0.89-0.86 (m, 21H), 0.06-0.04 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 139.1, 114.4, 75.5, 74.7, 61.2, 51.0, 40.1, 34.3, 30.8, 29.5, 29.5, 27.0, 25.8, 25.7, 19.5, 18.0, -4.1, -4.5.



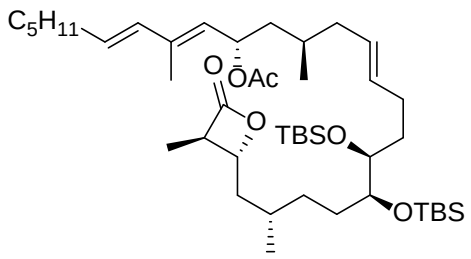
2.99

(3*R*,4*R*)-4-((2*S*,5*S*,6*S*)-5,6-Bis((*tert*-butyldimethylsilyl)oxy)-2-methyldec-9-en-1-yl)-3-methyloxetan-2-one (2.99): Aldehyde **2.92** (0.120g, 0.27 mmol), propionyl bromide (0.29 mL, 3.3 mmol) and diisopropylethylamine (0.24 mL, 1.4mmol) was added to a mixture of complex **2.100** (47 mg, 0.057 mmol) in DCM (3 mL) successively −70 °C. The resulting heterogeneous mixture was stirred at −70 °C for 24 h. The reaction mixture was poured into buffer pH=7 and organic layer was separated. The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/EtOAc = 50:1 to 30:1) to give title compound **2.99** (77 mg, 57%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddt, J_1 = 17.2 Hz, J_2 = 10.2 Hz, J_3 = 6.6 Hz, 1H), 5.02 (dq, J_1 = 17.2 Hz, J_2 = 1.7 Hz, 1H), 4.94 (dq, J_1 = 10.2 Hz, J_2 = 1.7 Hz, 1H), 4.26-4.23 (m, 1H), 3.58-3.53 (m, 1H), 3.50-3.47 (m, 1H), 3.20 (dq, J_1 = 7.5 Hz, J_2 = 4.0 Hz, 1H), 2.25-2.18 (m, 1H), 1.99-1.86 (m, 2H), 1.73-1.52 (m, 5H), 1.42-1.19 (m, 4H), 1.38 (d, J = 7.5 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06-0.03 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 139.0, 114.4, 78.3, 75.5, 74.6, 65.8, 51.2, 41.4, 34.3, 31.9, 30.7, 30.0, 29.4, 26.9, 25.8, 19.2, 18.0, 15.2, 12.4, -4.1, -4.5.



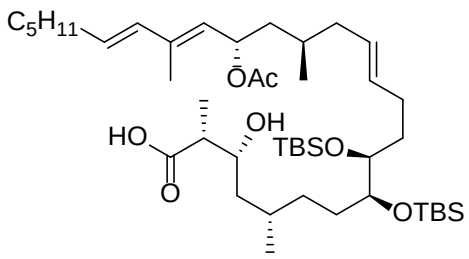
2.91

(4*S*,5*S*,8*S*)-4,5-Bis((*tert*-butyldimethylsilyl)oxy)-8-methyl-9-((2*R*,3*R*)-3-methyl-4-oxooxetan-2-yl)nonanal (2.91): The olefine **2.99** (48 mg, 0.096 mmol) was taken up in DCM/MeOH (v/v = 1: 1, 2 mL) followed by the addition of pyridine (0.039 mL, 0.48 mmol) and SUDAN III (indicator, ~1 mg) at rt under argon. The solution was cooled to −78 °C, and a stream of O_3 was lightly bubbled through the solution until the pink color was disappear (a light yellow color persisted). The DMS was added slowly. The reaction mixture was slowly warmed to rt. After stirring for overnight, the mixture was concentrated under the vacuum. The residue was purified by flash chromatography (Hex:EtOAc = 20:1) to give the title compound **2.91** (38 mg, 80%) as a colorless oil: ^{1}H NMR (700 MHz, $CDCl_3$) δ 9.78 (t, J = 1.6 Hz, 1H), 4.26-4.23 (m, 1H), 3.57-3.55 (m, 1H), 3.53-3.51 (m, 1H), 3.21 (dq, J_1 = 7.5 Hz, J_2 = 4.0 Hz, 1H), 2.57-2.52 (m, 1H), 2.42-2.37 (m, 1H), 2.01-1.96 (m, 1H), 1.90-1.86 (m, 1H), 1.66-1.54 (m, 5H), 1.43-1.41 (m, 1H), 1.39 (d, J = 7.5 Hz, 3H), 1.33-1.28 (m, 4H), 0.95 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.05-0.04 (m, 12H) ; ^{13}C NMR (175 MHz, $CDCl_3$) δ 202.7,172.0, 78.2, 75.4, 74.4, 65.8, 51.3, 41.5, 41.2, 34.4, 30.0, 29.7, 26.9, 25.8, 22.8, 19.2, 18.0, 15.3, 12.4, -4.1, -4.6.



2.90

(6*E*,8*E*,10*S*,12*R*,14*E*,18*S*,19*S*,22*S*)-18,19-Bis((*tert*-butyldimethylsilyl)oxy)-8,12,22-trimethyl-23-((2R,3R)-3-methyl-4-oxooxetan-2-yl)tricosa-6,8,14-trien-10-yl acetate (2.90): A solution of KHMDS (41 mg, 0.21 mmol) in DME (1 mL) was added to a solution of sulfon **2.59** (108 mg, 0.22 mmol) in DME (2 mL) at −70 °C. The resulting orange solution was stirred for 30 min. A solution of aldehyde **2.91** (74 mg, 0.15 mmol) in DME (0.5+0.25 mL) was added to the above solution dropwise. The reaction mixture was stirred for 1 h at −70 °C and warmed to rt slowly. After the mixture was stirred for overnight, H_2O was added to quench reaction. The organic layer was separated, the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane:EtOAc = 20:1) to give the title compound **2.90** (83 mg, 74%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (d, *J* = 15.7 Hz, 1H), 5.76 (d, *J* = 5.1 Hz, 1H), 5.74-5.68 (m, 2H), 5.45-5.35 (m, 2H), 5.25 (d, *J* = 9.3 Hz, 1H), 4.25-4.22 (m, 1H), 3.54-3.47 (m, 2H), 3.21-3.17 (m, 1H), 2.00 (s, 3H), 2.21-1.82 (m, 6H), 1.82 (s, 3H), 1.69-1.19 (m, 18H), (m, 4H), 1.98–1.90 (m, 1H), 1.90–1.83 (m, 1H), 1.81–1.80 (m, 3H), 1.76–1.56 (m, 4H), 1.46–1.35 (m, 6H), 1.37 (d, *J* = 7.5 Hz, 3H), 1.25 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.93–0.87 (m, 21H), 0.05–0.03 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 170.4, 137.1, 135.0, 131.8, 128.7, 127.8, 125.0, 78.2, 75.6, 74.7, 71.4, 60.3, 53.4, 51.2, 41.4, 34.9, 34.3, 33.8, 31.6, 31.4, 30.0, 29.6, 29.1, 27.0, 25.8, 24.7, 22.5, 21.3, 21.0, 19.4, 19.2, 18.0, 14.2, 14.0, 13.1, 12.4, -4.1, -4.5.



2.101

(2*R*,3*R*,5*S*,8*S*,9*S*,12*E*,15*R*,17*S*,18*E*,20*E*)-17-Acetoxy-8,9-bis((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,5,15,19-tetramethylhexacosa-12,18,20-trienoic acid (2.101): LiOH•H_2O (5 mg, 0.12 mmol) was added to a solution of compound **2.90** (9 mg, 0.012 mmol) in THF/MeOH/H_2O (0.5 mL each) at 0 °C. The reaction mixture was stirred for 1h. The TLC showed a more polar spot was formed. The reaction was quenched by pH = 7 buffer and organic layer was separated. The aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by prep TLC to give the title compound **2.101**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (d, *J* = 15.7 Hz, 1H), 5.76 (d, *J* = 5.1 Hz, 1H), 5.74-5.68 (m, 2H), 5.45-5.35 (m, 2H), 5.25 (d, *J* = 9.3 Hz, 1H), 3.78-3.70 (m, 1H), 3.55-3.47 (m, 2H), 2.52-2.43 (m, 1H), 2.00 (s, 3H), 2.21-1.82 (m, 6H), 1.82 (s, 3H), 1.69-1.19 (m, 18H), (m, 4H), 1.98–1.90 (m, 1H), 1.90–1.83 (m, 1H), 1.81–1.80 (m, 3H), 1.76–1.56 (m, 4H), 1.46–1.35 (m, 6H), 1.37 (d, *J* = 7.5 Hz, 3H), 1.25 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.93–0.87 (m, 21H), 0.05–0.03 (m, 12H).

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