Synthesis of the (*E,Z,Z*)-Triene System and Complete Carbon Skeleton of (+)-Neosorangicin A

Dissertation
zur Erlangung des akademischen Grades

Doctor rerum naturalium

(Dr. rer. nat.)

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geb. am 24.08.1991 in Peking, VR China

genehmigt durch die Fakultät für Verfahrens- und Systemtechnik der Otto-von-Guericke-Universität Magdeburg

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Promotionskolloquium am: 15. März. 2024

Abstract

In drug discovery, natural products (NPs) have been the primary source for a very long time, especially for cancer and infectious diseases. Chemical synthesis of NPs has the unique benefits of facilitating the discovery of new antibiotic targets, enhancing chemical complexity, and providing more robust structures for analyzing biological activity.

(+)-Neosorangicin A is a novel macrolactone-type antibiotic that shows a promising inhibition against cell division of Gram-negative and Gram-positive bacteria in biological *in-vitro* tests. Because the biotechnological production of neosorangicin A yield is modest, developing a multi-gram scale synthetic method is of tremendous practical and research interest to the chemistry community. Several research groups developed different methods for the synthesis of (+)-sorangicin A. As this molecule is such complex, almost all research groups have adopted a convergent retrosynthesis strategy, which split this molecule into three building blocks: a dihydropyran (DHP) fragment, a tetrahydrofuran (THP) fragment, and a bicyclo octane (BCO) moiety.

In this work, several palladium-catalyzed coupling reactions have been investigated, including Suzuki, Negishi, and Sonogashira, to generate the *(E,Z,Z)*-triene structure that is observed in (+)-sorangicin A **1** and (+)-neosorangicin A **3**. Nevertheless, the preliminary experiments yielded unfavorable results after modeling studies to mitigate the influence of pollutants and other variables. We had to utilize Stille coupling to construct the *(E,Z,Z)* system. The attempt successfully obtained the *(E,Z,Z)* system of (+)-sorangicin A **1** and (+)-neosorangicin A **3**, upon acquiring the essential blocks **212**, **214,** and **239**. Collaborate with others to achieve the total synthesis of (+)-sorangicin A **1** and (+)-neosorangicin A **3** in the convergent synthesis strategy. We employed cross-metathesis, and scaled up to gram level, to connect the BCO moiety **212** and THP moiety **239**. With further modifications of **215**, vinyl iodide **247** could be obtained via hydrozirconation of the triple bond followed by substituting the intermediate vinyl metal species. In the end, the complete open-form carbon skeleton of (+)-neosorangicin A **3** was synthesized with collaborators.

Zusammenfassung

In der Arzneimittelforschung waren Naturprodukte (NPs) schon seit sehr langer Zeit die Hauptquelle, insbesondere für Krebs und Infektionskrankheiten. Die chemische Synthese von NPs hat einzigartige Vorteile, da sie die Entdeckung neuer Antibiotika-Ziele erleichtert, die chemische Komplexität erhöht und robustere Strukturen für die Analyse biologischer Aktivitäten bereitstellt.

(+)-Neosorangicin A ist ein neuartiges Antibiotikum vom Makrolacton-Typ, das vielversprechende Hemmwirkungen gegen die Zellteilung von Gram-negativen und Gram-positiven Bakterien in biologischen In-vitro-Tests zeigt. Da die biotechnologische Produktion von Neosorangicin A bescheiden ist, ist die Entwicklung einer synthetischen Methode im Multigramm-Maßstab von enormem praktischem und wissenschaftlichem Interesse für die Chemie-Community. Mehrere Forschungsgruppen haben unterschiedliche Methoden zur Synthese von Sorangicin A entwickelt. Da dieses Molekül so komplex ist, haben nahezu alle Forschungsgruppen eine konvergente Retrosynthese-Strategie übernommen, bei der dieses Molekül in drei Bausteine aufgeteilt wird: ein Dihydropyran (DHP)-Fragment, ein Tetrahydrofuran (THP)-Fragment und eine Bicyclooctan (BCO)-Einheit.

In dieser Arbeit wurden mehrere palladiumkatalysierte Kupplungsreaktionen untersucht, einschließlich Suzuki, Negishi und Sonogashira, um die (*E,Z,Z*)-Trienstruktur zu erzeugen, die in Sorangicin A **1** und Neosorangicin A **3** beobachtet wird. Dennoch lieferten die vorläufigen Experimente nach Modellstudien zur Minderung des Einflusses von Schadstoffen und anderen Variablen ungünstige Ergebnisse. Wir mussten den Weg der Verwendung der Stille-Kupplung verfolgen, um das (*E,Z,Z*)-System zu konstruieren. Der Versuch führte erfolgreich zum (*E,Z,Z*)-System von Sorangicin A **1** und Neosorangicin A **3** nach Erwerb der essenziellen Bausteine **212**, **214** und **239**. In Zusammenarbeit mit anderen wurde die Totalsynthese von Sorangicin A **1** und Neosorangicin A **3** in der konvergenten Synthesestrategie erreicht. Wir setzten die Kreuzmetathese ein und skalierten sie auf Gramm-Ebene hoch, um die Bicyclooctan (BCO)-Einheit **212** und die Tetrahydrofuran (THP)-Einheit **239** zu verbinden. Durch weitere Modifikationen von **215** konnte das Vinyliodid **247** durch Hydrozirconierung der Dreifachbindung und Substitution der Zwischenstufe des Vinylmetalls erhalten werden. Schließlich wurde das vollständige offene Kohlengerüst von Neosorangicin A **3** in Zusammenarbeit mit Kollegen synthetisiert.

List of abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
AcOH	Acetic acid
ATR	Attenuated total reflectance
BCO	bicyclooctane
BINOL	1,1′ -Bi-2-naphthol
Bn	Benzyl
Bu	Butyl
BPS	*t*-Butyldiphenylsilyl
Bz	Benzoyl
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
Cbz	Benzyloxycarbonyl
Chx	Cyclohexyl
CM	Cross-metathesis
Cp	cyclopentadienyl
CSA	Camphorsulfonic acid
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DCM	Dichloromethane
DHP	Dihydropyran
DIH	1,3-Diiodo-5,5-Dimethylhydantoin
DIPA	Diisopropylamine
DIPEA	N,N-Diisopropylethylamine
DIAD	Diisopropylazodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPT	Diisopropyl tartrate
DMAP	4-(*N, N*-dimethylamino) pyridine
DME	Dimethyl ethoxy
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMPU	Dimethyltetrahydropyrimidinone
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide

dppf	1,1'-Bis(diphenylphosphino)ferrocene
de	Diastereomeric excess
EA	Ethyl acetate
ee	Enantiomeric excess
Equiv/eq.	Equivalent
Et	Ethyl
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
FTIR	Fourier Transform Infrared Spectroscopy
G2	Grubbs catalyst 2nd Generation
Hex	Hexane
HG2	Hoveyda–Grubbs catalysts 2nd Generation
^{1}H NMR	Proton Nuclear Magnetic Resonance
hrs	Hour(s)
HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum coherence
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectroscopy
KHMDS	Potassium bis(trimethylsilyl)amide
NIS	*N*-Iodosuccinimide
i-Bu	Isobutyl (2-methylpropyl)
i-Pr	Isopropyl
IR	Infrared
LiDBB	Lithium 4',4'-ditert-butylbiphenylide
LDA	Lithium diisopropylamide
m-CPBA	3-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MIDA	*N*-Methyliminodiacetic acid
MeLi	Methyl lithium
MHz	Megahertz
MIC	Minimum inhibitory concentration
min	Minute(s)

MOM	Methoxymethyl
MEM	Methoxyethoxymethyl
MPLC	Medium Pressure Liquid Chromatography
PMB	*p*-Methoxybenzyl
Ph	phenyl
MS	Mass Spectrometry
MsCl	Methanesulphonyl Chloride
MTPA	2-Methoxy-2-(trifluoromethyl)-2-phenylacetic acid
MTPACl	2-Methoxy-2-(trifluoromethyl)-2-phenylacetyl chloride
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
n-BuLi	*n*-Butyl lithium
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Enhancement
OTBS	tert-Butyldimethylsilyloxy
OTf	Trifluoromethanesulfonate
PADC	Potassium azodicarboxylate
PEPPSI	pyridine-enhanced precatalyst preparation stabilization and initiation
Piv	Pivaloyl
PPTS	*p*-Toluenesulfonic acid
PT	1-phenyl-1H-tetrazol-5-yl
Py	Pyridine
RCM	Ring-Closing Metathesis
RNAP	RNA polymerase
RT/rt/r.t.	Room Temperature
Sat.	Saturated
Sec	Second(s)
TBAF	*tetra*-Butylammonium fluoride
TBSCl	*tert*-Butyldimethylsilyl chloride
t-BuLi	*tert*-Butyllithium
TEA	Triethylamine
TES	Triethylsilyl
TESOTf	Triethylsilyltriflate

TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TIPSOTf	Triisopropylsilyl trifluoromethanesulfonate
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl Chloride
TMSCN	Trimethylsilyl Cyanide
TMSOTf	Trimethylsilyl trifluoromethanesulfonate

Contents

1. Introduction

Since the discovery of penicillin by Alexander Fleming in 1928[1], antibiotics have profoundly altered human history and daily life. On the front lines of World War II, it prevented thousands of deaths. Additionally, it made several previously incurable infections caused by different pathogens, such as bacteria, fungi, viruses, and parasites, treatable. Using antibiotics for medical purposes was perhaps one of the 20th century's most significant accomplishments. However, decades of uncontrolled usage have severely weakened the supply of antibiotics. The underdosing usage of antibiotics can apply the selective pressure that induces bacteria to evolve resistance to these drugs. Meanwhile, the prescribing habits, such as using recently developed antibiotics rapidly, possibly delivered another selective pressure to bacteria. Therefore, bacteria are rapidly evolving resistance to antibiotics in recent decades[2].

The so-called *ESKAPE* pathogens (***E****nterococcus faecium,* ***S****taphylococcus aureus,* ***K****lebsiella pneumoniae,* ***A****cinetobacter baumannii,* ***P****seudomonas aeruginosa, and* ***E****nterobacter spp.*) show multidrug-resistant (MDR) and extensively drug-resistant (XDR). The development of novel therapeutics to treat drug-resistant infections, particularly those caused by *ESKAPE* pathogens, is urgently needed. Although alternate treatments for *ESKAPE* infections have been discovered, which prolonged the effectiveness of conventional antimicrobials[3]. The development of new antibiotics has an unparalleled advantage.

Natural products (NPs) have been the key source, especially for cancer and infectious diseases, in drug discovery for a long time. Since the golden age of antibiotics in the middle of the 20th century, natural products have been utilized as potent antibacterial treatments[4]. Despite the giant production of antibiotics from bioprocesses such as fermentation, chemical synthesis has a unique advance to avoid that relevant NPs are ineffective produced when the organism is taken out of the specific habitat. On another side, the synthesis of a challenged nature product not only satisfied the interests of academia, such as developing new methods to solve synthetic problems but also inspired chemists as a strategy towards analog development. They provide access to unexplored chemical space, which offers the potential for discovering new antibiotic targets. One of the primary advantages of the NPs-based drug discovery strategies is that these diverse libraries can be accessed rapidly, as transformations can be carried out on various substrates, thereby increasing chemical complexity and providing more robust structures for probing biological activity.

2. Background

2.1 Chemical Structure of (+)-Sorangicin A and (+)-Neosorangicin A

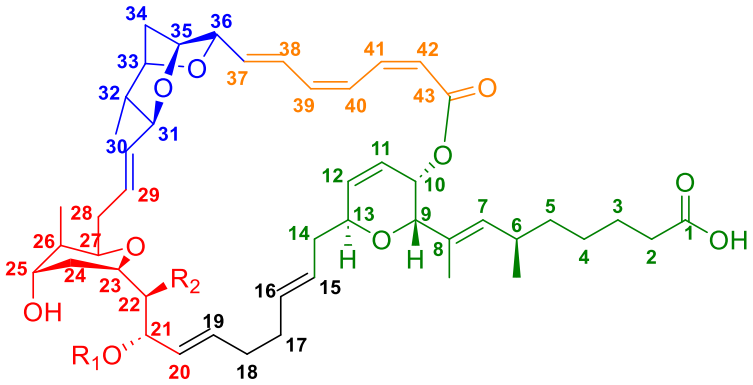


***Figure* 2.1** *Structure of (+)-sorangicin A **1** and B **2** red: tetrahydropyran-ring (THP-ring) blue: bicyclo octane (BCO); orange: (E,Z,Z)-triene ester; dark green: dihydropyran-ring (DHP-ring) and side substrate.*

Höfle *et al.*[5] were the first researchers to successfully isolate and characterize (+)-sorangicin A **1** and B **2** as a novel antibiotically series from the So ce12 strain of myxobacteria (*Sorangium cellulosum*) at the German Research Centre for Biotechnology (GBF, as Helmholtz Centre for Infection Research since 2006) in 1985, Braunschweig. The structure of (+)-sorangicin A **1** was identified by mass spectrometric and NMR spectroscopic analysis and later verified by X-ray structural analysis. Sorangicins belong to the macrolides polyether antibiotics class of natural products. The most abundant metabolite is a 31-membered lactone ring. Incorporated into the macrocycle are a tetrasubstituted tetrahydropyran ring (THP ring), a trisubstituted dihydropyran ring (DHP ring), and a bicyclo octane (BCO) which are rarely found in nature. In addition, the macrocycle contains an (*E,Z,Z*)-trienester function sensitive to isomerization (See *Figure* 2.1). The difference between (+)-sorangicin B **2** and (+)-sorangicin A **1** is the absence of a hydroxy function at C22.

In 2017, Müller *et al.*[6] isolated and patented (+)-neosorangicin A **3** (*Figure* 2.2) from another strain (So ce439) of the myxobacterium. The structural configuration of is very similar to that of (+)-sorangicin A **1** and differs only in the side chain on the DHP ring. The configuration of the methyl group on the C3 (*Figure* 2.2) and C6 carbon (*Figure* 2.1) is inverted. In (+)-sorangicin A **1**, the side chain on the DHP ring consists of eight carbon atoms and end with a terminal carboxylic acid. In (+)-neosorangicin A **3**, there are five carbon atoms with a chiral secondary alcohol function at C2.

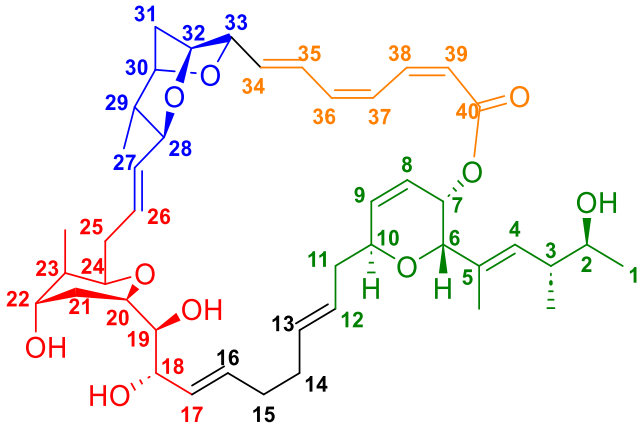


***Figure* 2.2** *Structure of (+)-neosorangicin A **3** red: tetrahydropyran-ring (THP-ring) blue: bicyclo octane (BCO); orange: (E,Z,Z)-triene ester; dark green: dihydropyran-ring (DHP-ring) and side substrate.*

2.1.1 Effective Against Gram-positive and -negative Pathogens

The sorangicins family is an early-stage drug candidate currently in the preclinical phase. They show antibacterial activity towards mainly Gram-positive but also Gram-negative pathogens, such as *Enterococcus spp.*, *Staphylococcus aureus* (MRSA/VISA), *Streptococcus pneumoniae*, *Acinetobacter sp.*, *Pseudomonas aeruginosa*, *Escherichia coli*.[6, 7] Bulk research articles[8] focused on (+)-sorangicin A **1**, so far the most potential candidate, and studied the antibiotic mechanism. Recently, Campbella *et al.*[9] compared the inhibiting mechanism between Rifampicin (Rif), a first-line therapeutic used to treat the infectious disease tuberculosis (TB), and (+)-sorangicin A **1**. They also further investigated the mechanism of Rif-resistant (Rif^R) *Mycobacterium tuberculosis* (Mtb) inhibition by (+)-sorangicin A **1** (Sor). The closing cryo-electron microscopy (cryo-EM) data proves (+)-sorangicin A **1** inhibits wild-type (WT) RNAP by the exact mechanism as Rif, binding to the same compartment located in the β-subunit of RNAP (*Figure 2.3*),[9] preventing the translocation of very short RNAs. But it inhibits Rif^R-

Mtb, such as the β-subunit RNAP with S456>L mutation (S-L RNAP), by a distinct mechanism. The binding of (+)-sorangicin A **1** to RNAP inhibits promoter DNA unwinding, which is a crucial step in the initiation of transcription.

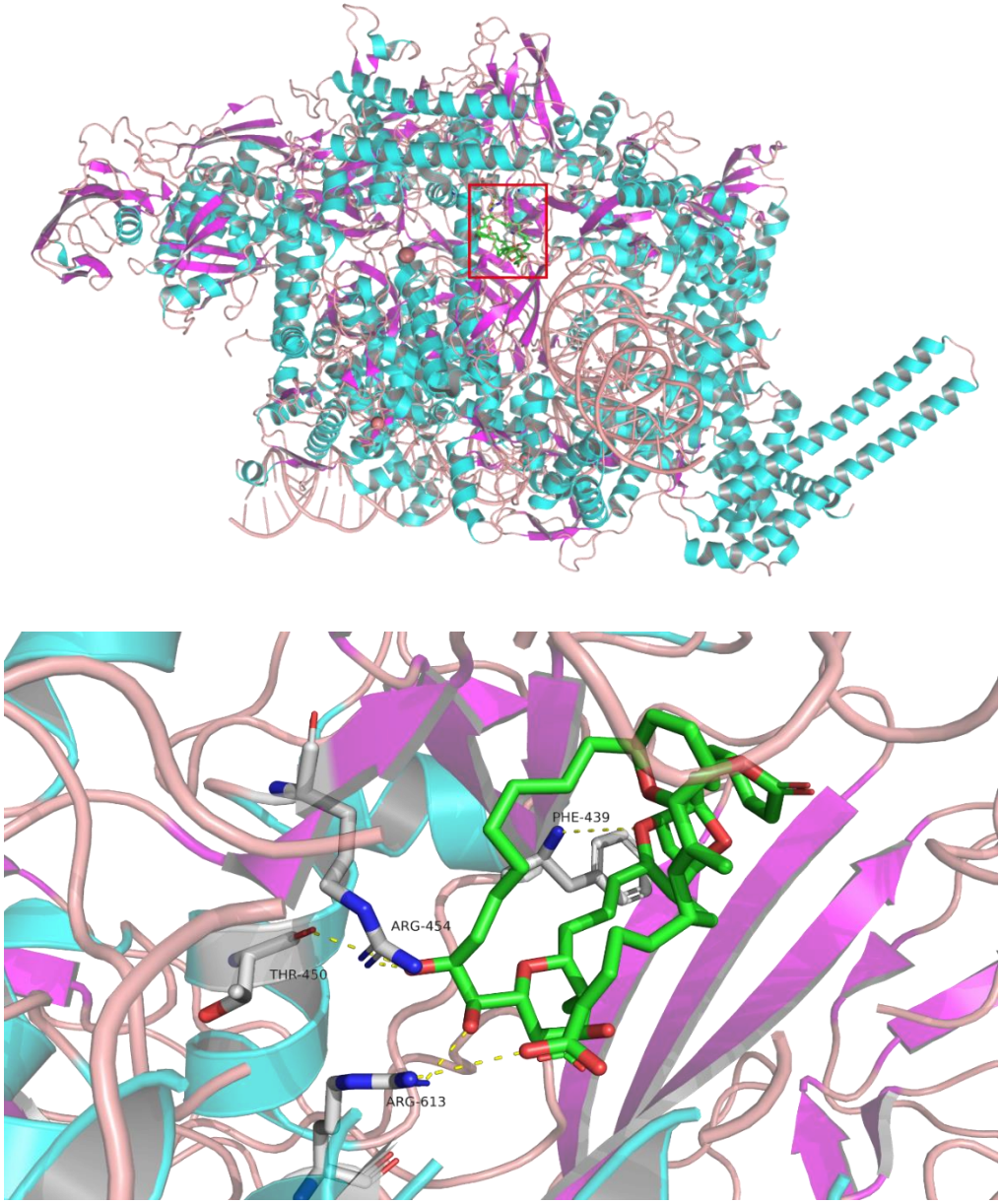


Figure 2.3 *Mycobacterium tuberculosis WT RNAP transcription initiation intermediate structure with (+)-sorangicin A* ***1*** *(above: complete cyro-EM graphic; below: interact between WT RNAP and sor, zoom-in the red box of above; generated with PyMOL. PDB index:6vvx)*

Based on these data, a favor model that explains the effects of Sor on Mtb WT- and S>L-RNAP been presented in *Figure 2.4*. The top row in *Figure 2.4* shows how nucleic acids and apo WT-RNAP or S>L-RNAP rearrange in steps to form the productive elongation complex RPec. The apo RNAPs form RP1 (the initial engagement with DNA complex), proceed to

RP2 (partial bubble intermediate), then to RPo (the fully unwound bubble with the T-strand DNA in the active site), then to RPitc (containing short transcripts), and eventually to RPec. The middle row in *Figure 2.4* illustrates how WT-RNAP with Sor is inhibited at the transition from RPitc to RPec due to steric clashes between Sor and the elongating RNA transcript. The bottom row of *Figure 2.4* shows how the S>L-RNAP in the presence of Sor can proceed to RP2, but the transition to RPo is inhibited. The position of the DNA in RPo imposes constraints on the RNAP fork loop 2 (FL2) position, which in turn is incompatible with the presence of Sor when the S>L substitution is present in FL2, likely explaining this finding. Therefore, comparing the middle row with the bottom, unlike with the WT-RNAP, Sor inhibits the S>L-RNAP at a step upstream of RPitc. Therefore, (+)-sorangicin A **1** provides a new target for drug design and has potential as a starting molecule for designing drugs to treat TB patients with comorbidities who require multiple medications. Additionally, A drug-drug interaction profile[9] reveals that (+)-sorangicin A **1** has more favorable pharmacokinetic properties than Rif. This is important for developing inhibitors to treat TB patients with comorbidities.

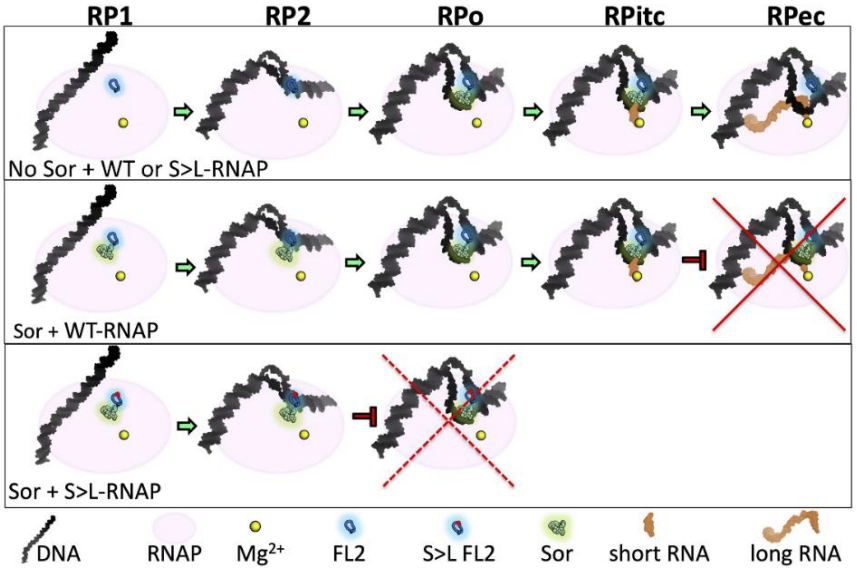


Figure 2.4 *Model of Sor's effect on the transcription of WT- and S>L-RNAPs. By Elizabeth A. Campbella et al.*[9]

As a novel candidate of sorangicins, (+)-neosorangicin A **3** shows a higher and broader spectrum of activity towards Gram-positive and Gram-negative bacteria compared with (+)-sorangicin A **1**. According to the data presented in *Table 2.1*, the minimum inhibitory concentration (MIC) values of (+)-neosorangicin A **3** against various pathogens, such as *Entero-coccus spp.*, *S. aureus*, *S. pneumoniae*, *A. baumannii*, *E. coli*, and *P. aeruginosa*, fall within the mid ng/ml

and low µg/ml range. This suggests that (+)-neosorangicin A **3** exhibits potent inhibitory activity against both Gram-positive and Gram-negative bacteria. (+)-neosorangicin A demonstrates superior activity levels in comparison to (+)-sorangicin A **1**, exhibiting an average potency that ranges from 2 to 10 times greater. Nevertheless, it is worth noting that both (+)-neosorangicin A **3** and (+)-sorangicin A **1** exhibit no activity against rifampicin-resistant *S. aureus Newman*. This observation suggests that both molecules likely target overlapping binding sites on the RNAP. The activity of (+)-neosoranguicin A **3** and (+)-sorangicin A **1** in *Escherichia coli* pathogens is observed to increase when sub-inhibitory amounts of polymyxin B nonapeptide (PMBN) are introduced. In addition, it has been observed that the MIC of (+)-neosorangicin A **3** is reduced in efflux-deficient *Escherichia coli* mutants. The half-inhibitory concentrations (IC_{50}) for (+)-neosorangicin A **3**, (+)-sorangicin A **1**, and Rif were evaluated using *in vitro* assays on *S. aureus* RNA polymerase. The IC_{50} values were found to be 0.06 ± 0.01 µM, 0.21 ± 0.12 µM, and 0.03 ± 0.02 µM, respectively. These findings confirm that (+)-neosorangicin A **3** exhibits more activity in comparison to (+)-sorangicin A **1**.

Table 2.1 *Antimicrobial activity (MIC, mg/mL) of sorangicin A **1** (sor A), neosorangicin A **3** (neosor A),and rifampicin (rif) on various bacteria*[6]

	Bacteria species	Sor A	Neosor A	Rif
Gram-positive	*Enterococcus faecalis* DSM-20478	2	0.5	6.4
	Enterococcus faecium DSM-20477	16	8	>6.4
	Staphylococcus aureus ATCC29213	0.003	0.01	0.01
	Staphylococcus aureus DSM-346	1	0.25	0.006
	Staphylococcus aureus Newman	0.1	0.01	0.01
	Staphylococcus aureus Newman (Rif^R)	>64	>64	>6.4
	Streptococcus pneumoniae DSM-11865	32	0.5	0.1
Gram-negative	*Acinetobacter baumannii* DSM-30008	8	8	1.6
	Escherichia coli DSM-1116	16	8	6.4
	Escherichia coli DSM-1116 + 3 µg/ml PMBN	0.25	0.25	0.4
	Escherichia coli DSM-26863 (tolC3)	8	2	6.4
	Escherichia coli (TolC-deficient)	8	1	6.4
	Klebsiella pneumoniae DSM-30104	16	8	6.4
	Pseudomonas aeruginosa DSM-1128	32	8	>6.4

2.1.2 Biosynthesis of (+)-Sorangicin A and (+)-Neosorangicin A

By feeding experiments with ^{13}C labeled acetate, sodium bicarbonate, and methionine Höfle *et al*[5]. could closer elucidate the biogenesis of **1**. Accordingly, (+)-sorangicin A **1** is constructed by linear condensation from 20 acetate units. The starter - malonyl CoA is to be incorporated into the product and provides the C1 carboxyl group in **1**. All methyl groups originate from methionine.

For the production of (+)-sorangicin A **1**, fermentation is currently the most economical method, especially as it is delivered directly by way of ce12 to the medium and is accessible without cell disruption of direct extraction. Semisynthetic or possibly synthetic approaches would be also required. The cells were first collected by centrifugation from the culture solution and the fermenter supernatant with 1-1.5 Vol.-% were extracted with XAD-1180 adsorption resin to isolate (+)-sorangicin A. Most of the polar co-products could be removed by washing with 60% methanol. After acid-base extraction with ammonia-ether and subsequent azeotropic drying with toluene, the residue was dissolved in dichloromethane and stirred with silica gel as pre-clean, then the contained mass of (+)-sorangicin A could be obtained by crystallization from ethyl acetate. Chromatography of the mother liquor yielded additional (+)-sorangicin A **1**. From the supernatant of a 650 L fermenter 19.9 g (+)-sorangicin A **1** were obtained.

(+)-Neosorangicin A **3**, like (+)-sorangicin A **1**, also can be obtained biotechnologically[6]. *Sorangin-ium cellulosum* strain So ce439 was stored at -80 °C and it was reactivated in 20 ml of liquid medium containing 0.5% soy peptone, 0.2% yeast extract, 0.1% $MgSO_4 \cdot 7H_2O$, 0.1% $CaCl_2 \cdot 2H_2O$, 10% glucose$\cdot 7H_2O$ and 8 mg/l Na-Fe-EDTA. The culture was scaled up to 1 L and used for fermentation of the So ce439 strain in the same liquid medium as above but including also 2% amberlite XAD-16 resin. After completion of the fermentation process the XAD resin (1.71 kg) was sieved out and recovered. The XAD adsorber resin was first extracted with methanol/H_2O (3/7) and then again with pure methanol. The extracts were combined and evaporated to an aqueous mixture, which was diluted with water and extracted three times with ethyl acetate. These organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to yield 5.3 g of crude extract. The crude extract was redissolved in methanol containing 1% H_2O and extracted three times with heptane. After evaporation of the

combined organic layers under reduced pressure, 3.91 g of enriched crude extract were obtained. The enriched crude extract was taken in methanol and filtered through a Strata-column (10 g, 55 µm, 70 Å) two times. Crude extract 3.45 g were isolated after evaporation of methanol. In the end, the crude extract was purified by RP-MPLC and 247 mg of pure (+)-neosorangicin A **3** were obtained.

2.2 Current Studies Toward the Synthesis of (+)-Sorangicin A

As stated in section 2.1.2, the biotechnological synthesis of sorangicins has rather low productivity, particularly in the case of (+)-neosorangicin A **3**. The present findings and conclusions offer encouraging evidence that the synthesis of structural analogues belonging to the sorangicin family could present a new strategy in addressing rifampicin-resistant strains of tuberculosis, along with additional potential applications as the discipline of Medicinal Chemistry progresses. Therefore, exploring an efficient and scalable synthetic pathway with the capability to produce multi-grams of the desired product has emerged as a promising area of research.

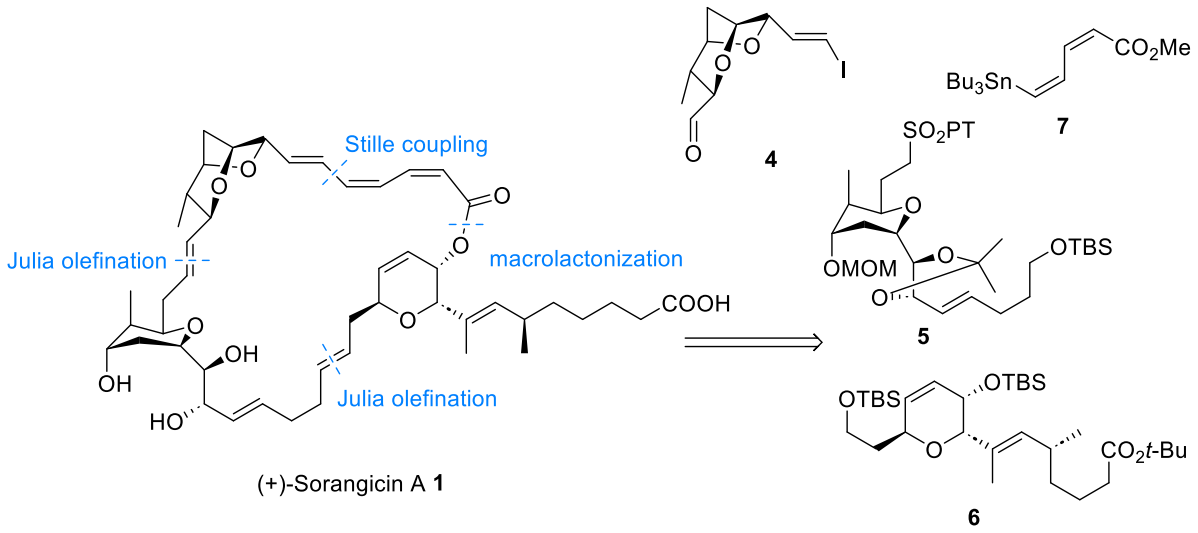
(+)-Neosorangicin A **3** and (+)-sorangicin A **1** exhibit analogical properties owing to their shared chemical characteristics. Both compounds consist of a distinct bicyclic ether structure, specifically a trisubstituted dihydropyran with a carbon side chain (carboxylic in the case of (+)-sorangicin A **1**, and alcoholic in the case of (+)-neosorangicin A **3**), as well as a tetrasubstituted tetrahydropyran moiety. These components are integrated within a 31-membered lactone. Hence, the synthesis of (+)-neosorangicin A **3** can be achieved in a manner that is comparable to the synthesis of (+)-sorangicin A **1**.

Since 2004, there has been a notable interest among the synthetic community regarding (+)-sorangicin A **1** and its analogs. The previous interest has been ignited by groundbreaking research conducted by research groups such as Amos B. Smith III[10-12], Morken[13], Schinzer[14, 15], M. T. Crimmins[16, 17], Lee[18], S. Raghavan[19-21], and Yadav[22] *etc*. Due to the enormous volume of literature available on established (+)-sorangicin A **1** total synthesis and semi-syntheses, the current level of study will be selectively introduced as follows.

2.2.1 Total Synthesis by Amos B. Smith III *et al.*

The Smith group published the synthesis of the four fragments,[10, 23] the first as well as so far the only successful total synthesis of (+)-sorangicin A **1** in 2009.[11] The retrosynthetic analysis

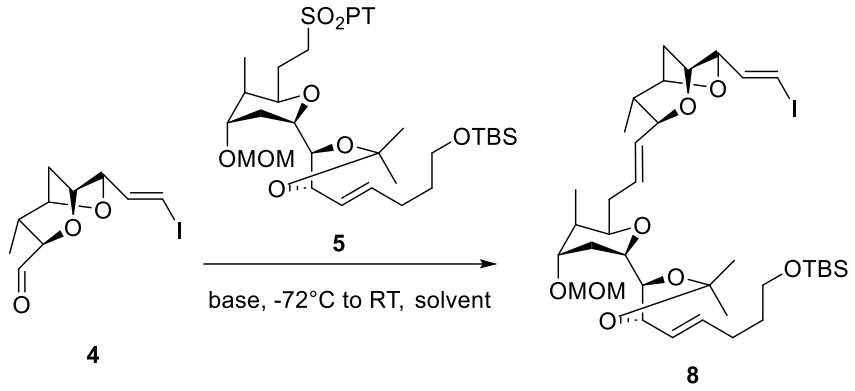
of Smith III (see *Scheme 2.1*) has disconnected (+)-sorangicin A **1** in four fragments. The dioxabicyclooctane fragment **4** was linked via a Julia-Kocienski olefination with the tetrahydropyran **5**, and another Julia-Kocienski olefination with the dihydropyran fragment **6**. For the construction of the triene system, a Stille coupling between **4** and (*Z,Z*)-diene **7** was planned. An appropriate macro-lactonization should close the ring.



Scheme 2.1 *Retrosynthetic analysis of (+)-sorangicin A* ***1*** *by Amos B. Smith III et al.*

The first Julia-Kocienski[24] olefination (*Scheme 2.2*) shown by the Smith III group demonstrated the high substrate dependence of this reaction in practice, in terms of stereoselectivity and yield. Thus, the coupling of **4** and **5** supplied with lithium bases the desired product exclusively in the desired *E*-configuration, but with *t*-BuLi in up to 39% yield. KHMDS in DME gave 54% yield but a low selectivity of 2: 1 for the *E*-isomer. With NaHMDS in DMF / HMPA an improved selectivity of 3.6: 1 was achieved at a slightly deteriorated yield. All results of Julia-Kocienski olefination are summarized in *Table 2.2*. It turns out here that a clear trend towards more excellent selectivity was observed with increasingly closer coordination by the potassium counter ion to lithium, even if strongly aprotic polar solvents are used, this should cause a high degree of ion-pair separation.

Following the olefination of **4** and **5**, the group underwent the second Julia-Kocienski olefination for coupling with dihydropyran **10**. Dihydropyran **10** was carried out from modified fragment **6** with 8 steps, as depicted in *Scheme 2.3*. In contrast to the previous reaction of the same kind, the utilization of KHMDS in DME yielded the most favorable outcome in terms of both yield and stereoselectivity, owing to its status as the least coordinating cation



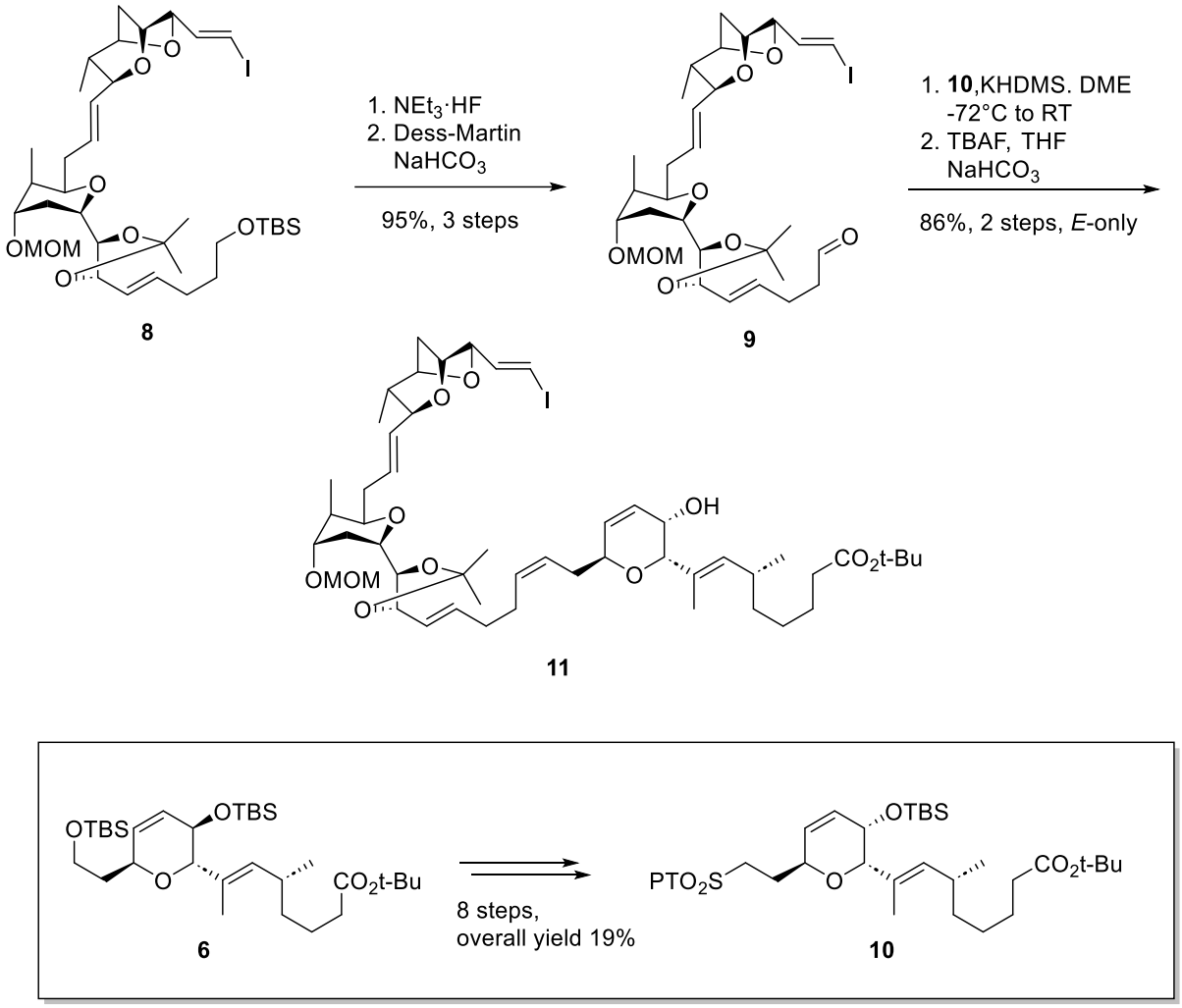
Scheme 2.2 *Julia-Kocienski olefination between* ***4*** *and* ***5***

Table 2.2 *Julia-Kocienski olefination between BCO fragment* ***4*** *and THP fragment* ***5****.*

Base	Solvents	Yield	E/Z Ratio	Recovered Sulfone	Recovered Aldehyde
LiHDMS	DMF/HMPA (3:1)	24%	*E*-only	63%	36%
NaHDMS	DMF/HMPA (3:1)	40%	3.6:1	39%	23%
KHDMS	DME	54%	2.0:1	0%	0%
LDA	DMF/HMPA (3:1)	11%	*E*-only	38%	42%
t-BuLi	DMF/HMPA (3:1)	39%	*E*-only	39%	13%

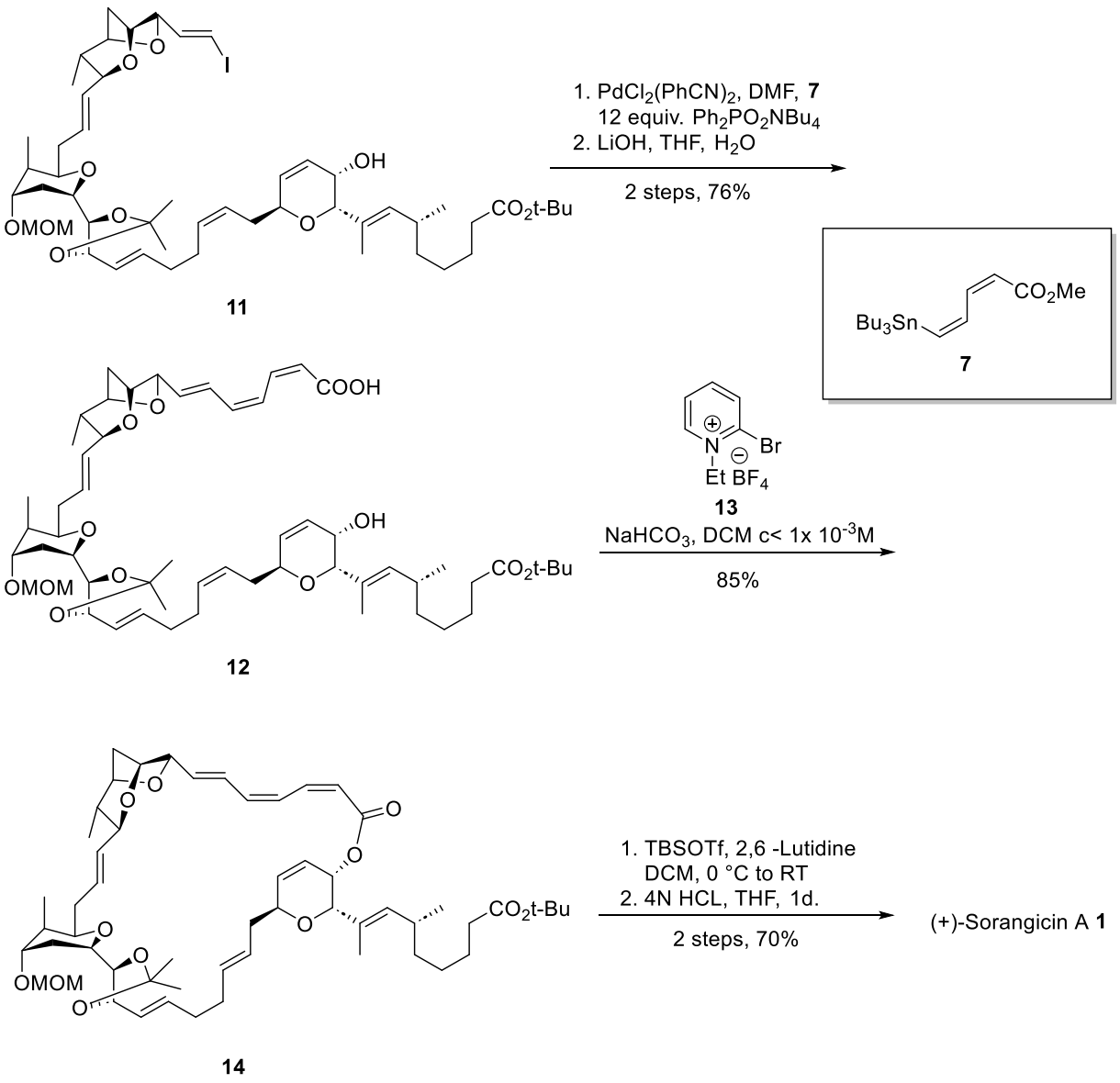
among the series Li, Na, and K. The desired *E*-isomer **11** was produced in 86% yield after cleavage of the silyl protecting group using TBAF in THF. The reaction involving sulfone **10** and aldehyde **9** was initially proposed by Smith III *et al.*[11] Nevertheless, this experimental setup has provided very low yields for KHMDS in DME, approximately 30%, as well as for LiHMDS in DMF/HMPA. Intriguingly, only a 1:1 combination of two stereoisomers was recovered.

The subsequent pivotal phase culminated in the development of the isomerization-sensitive (*E,Z,Z*)-triene configuration (see *Scheme 2.4*). To accomplish this, compound **11** was subjected to a Stille reaction using the known (*Z,Z*)-stannane **7**. The resulting product was analyzed, yielding the corresponding triene as depicted in *Scheme 2.4*. These findings indicated that the tributyltin compound underwent isomerization, resulting in the formation of a triene compound. The suppression of this effect could be achieved through the incorporation of 12 equivalents of $Ph_2PO_2NBu_4$.



Scheme 2.3 *Julia-Kocienski olefination for coupling* ***8*** *and* ***10***

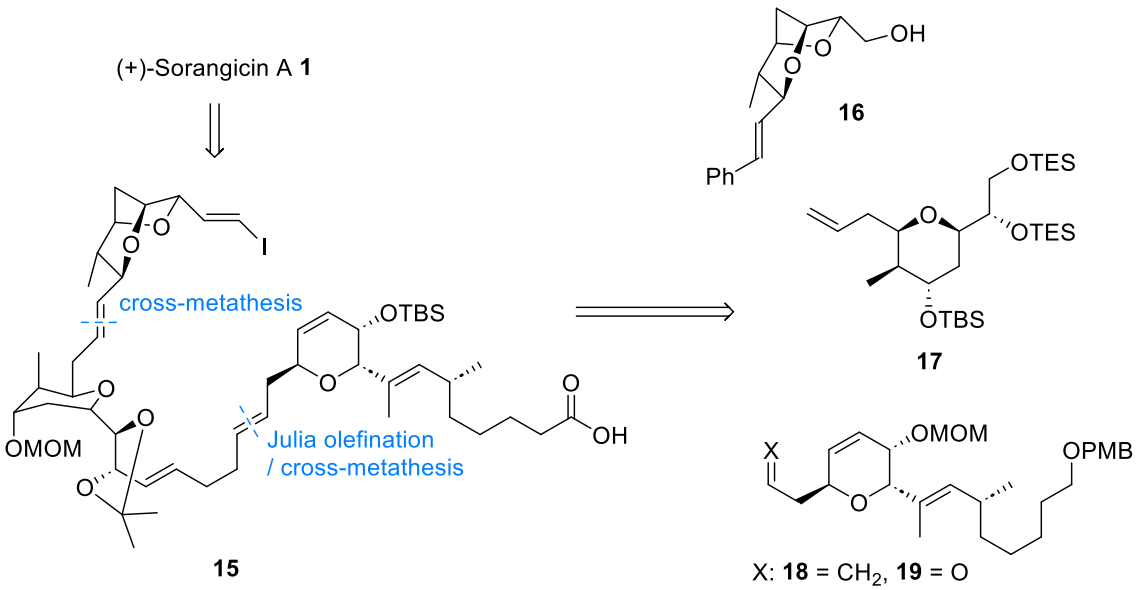
The initial substance required for macrolactonization was obtained (*Scheme 2.4*), after hydrolysis of the ester to the carboxylic acid **12**. The process of lactonization was initially accomplished using a modified version of the Yamaguchi conditions developed by Yonemitsu[25], or alternatively, modified based on Evans' adaptation of the Mukaiyama method.[26] In all instances, the formation of products occurred with mixture of isomeric triene subunits, posing a challenge in separation of the major product. The cause of this is attributed to the reversible Michael addition of DMAP under Yamaguchi or iodide under Mukaiyama conditions to the corresponding activated triene system. The Mukaiyama reagent **13** consists of tetrafluoride borate as a non-nucleophilic counter ion, resulting in a reduction of isomeric forms to below 4%. The MOM-ether protecting group was cleaved and subsequently silylated to the tert-butyl silyl ester using TBSOTf. (+)-Sorangicin A **1** can be liberated by subjecting the crude product to aqueous hydrochloric acid.



Scheme 2.4 *Composition of triene unit and ring-closing*

2.2.2 Formal Synthesis by M. T. Crimmins *et al.*

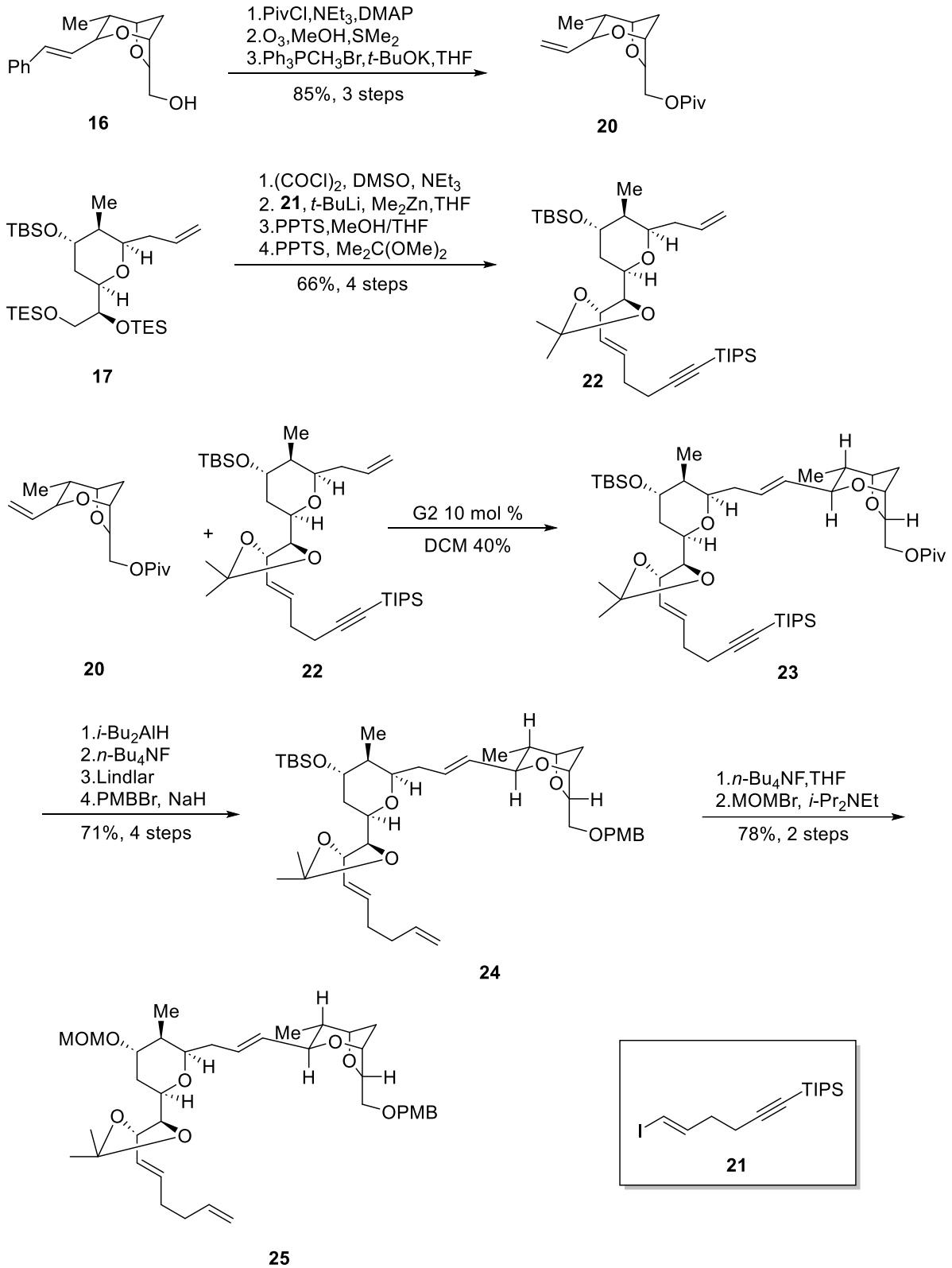
In 2011 M.T. Crimmins *et al*. published a formal synthesis of (+)-sorangicin A **1**.[17] The retro-synthesis plan is presented in *Scheme 2.5*. Similar to Smith's publication in 2009, Crimmins likewise employed a convergent method comprising three essential subunits: bicyclic ether **16**, tetrahydropyran **17**, and dihydropyran **18** and **19**.



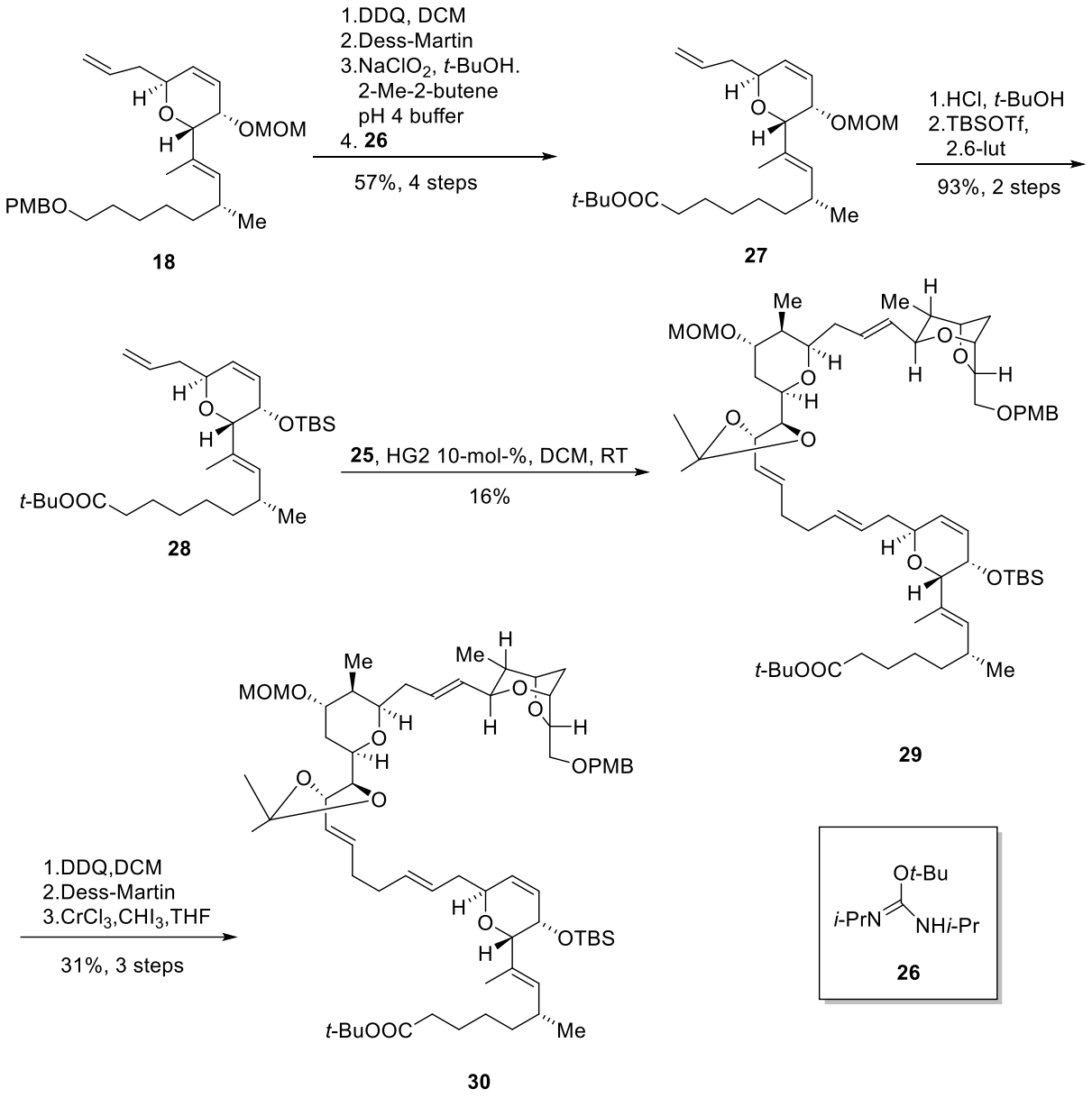
Scheme 2.5 *Retrosynthetic analysis of (+)-sorangicin A* ***1*** *by Michael T. Crimmins et al.*

The initial approach employed in the process of linking is known as cross-metathesis. The bicyclic ether **20** was synthesized from pre-prepared bicyclic ether **16** via a three-step process including acylation, ozonolysis, and methylenation with a yield of 85%. Compound **20** was then used as a substrate for cross-metathesis. Before the essential cross-metathesis reaction, an expansion of THP **17** was additionally conducted. The modified Swern conditions were employed to selectively cleave and oxidize the primary TES ether in THP **17**. The vinyl zinc species, which was formed *in situ* from vinyl iodide **21**, underwent a Felkin-Anh controlled addition to the aldehyde to introduce the C21 stereo-center. The acetonide of the 1,2-diol was subsequently converted through a two-step procedure, resulting in the formation of THP **22** with a yield of 66% over four steps.

Upon dropwise addition of THP **22** at room temperature over several hours to a solution of bicyclic ether **20** and Grubbs' second-generation catalyst, the cross-metathesis reaction was accomplished in 40% yield. Removal of the TIPS protecting group, followed by Lindlar reduction of the alkyne and subsequent adjustment of the TBS protecting groups to MOM provided terminal olefin **25** in 55% yield over the six-step sequence. (*See Scheme 2.6*)



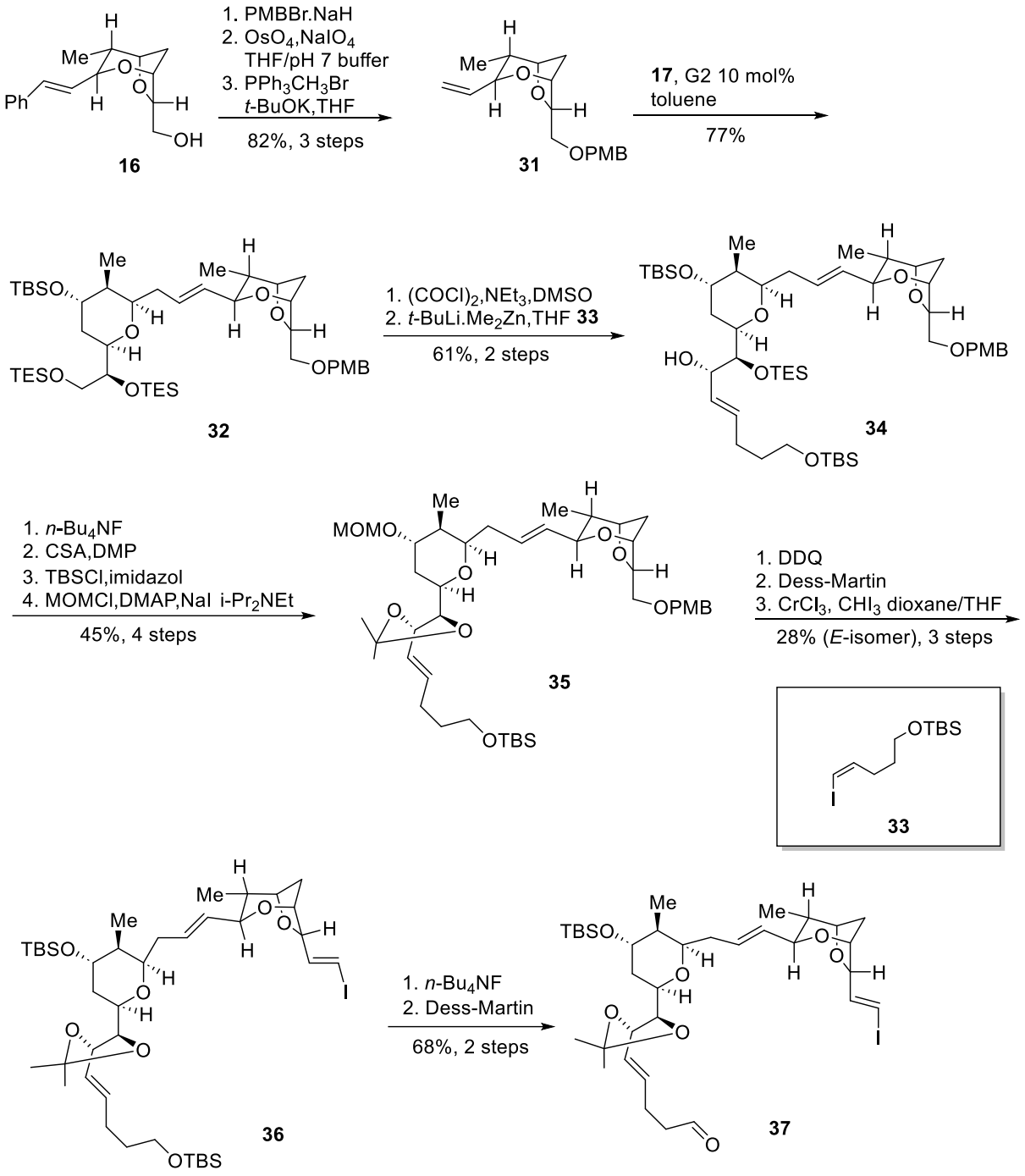
Scheme 2.6 *1st approach of coupling* ***20*** *and* ***22***



***Scheme 2.7** 1st approach of fragment **30** via cross-metathesis reaction*

To achieve the necessary oxidation state on compound **18**, a sequential process consisting of four steps was employed (*Scheme 2.7*). The process involved the cleavage of the PMB ether under oxidative circumstances, followed by Dess-Martin oxidation, Pinnick oxidation, and ultimately ester formation. As a result of this sequence, compound **27** was obtained with 57% yield. Dihydropyran **28** was obtained with a yield of 93% by a two-step method, wherein the MOM ether was substituted with a TBS ether. After the preparation of both cross-metathesis partners, fragments **25** and **28** were subjected to the Hoveyda-Grubbs' second-generation catalyst (HG2). This key bond-forming reaction produces a mixture of cross-metathesis adducts **29**. However, the desired cross-metathesis adduct was obtained with only 16% yield. Despite

the low yield for this key reaction, intermediate **29** was advanced through a three-step sequence to arrive at fragment **30** in 31% yield.



Scheme 2.8 *2nd approach of coupling* ***17*** *and* ***31***

Due to the observed low yield in the cross-metathesis reaction to combine the DHP fragment with the remaining portion of the molecule, Michael T. Crimmins *et al*. decided to explore the use of the Julia-Kocienski olefination method, previously employed by Smith III.[11] In order to

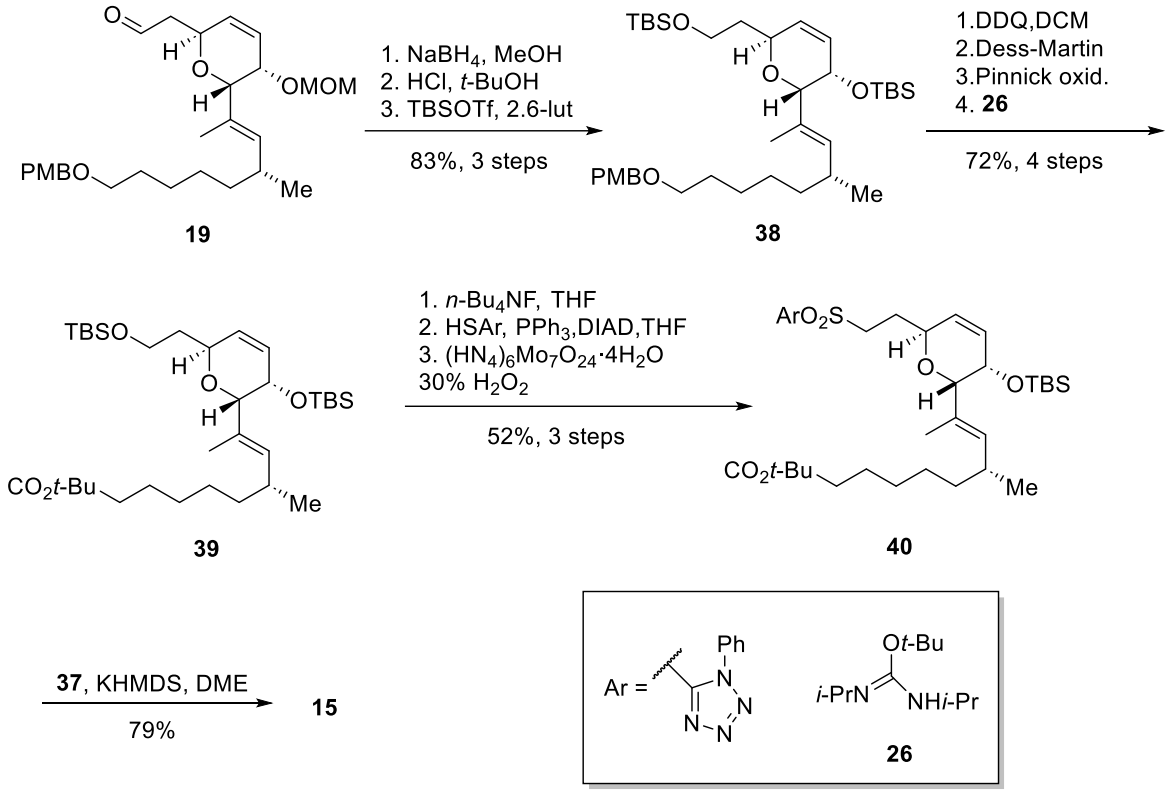
obtain the bicyclic ether/THP and DHP fragment required for the Julia olefination, a modification has been made to the protecting group strategy (*Scheme 2.8*).

The bicyclic ether **16** was subjected to protection as the PMB-ether. Subsequently, the PMB-ether underwent oxidative cleavage using the Johnson-Lemieux protocol[27] and methylene Wittig olefination, resulting in the formation of bicyclic ether **31**. The synthesis of cross-metathesis adduct **32** was achieved by gradually adding THP **17** to a solution containing bicyclic ether **31**, followed by using of Grubbs' second-generation catalyst (G2). The resulting adduct was obtained with yield 77% and exhibited a single identifiable *E*-isomer. The use of modified Swern conditions to TES ether **32** resulted in the targeted oxidation, leading to the formation of an intermediate aldehyde. Subsequent reaction of this aldehyde with the vinyl zinc species derived from vinyl iodide **33** resulted in the formation of bicyclic ether/THP fragment **34**. The overall yield of this two-step sequence was 61%.

To achieve fragment **35**, the silyl protecting groups were eliminated from the vinyl addition product **34** using TBAF, resulting in the exposure of an intermediate tetraol. The tetraol compound was treated with CSA in DMP to induce the formation of an acetonide. As a result, the hydroxyl groups at positions C16 and C25 were protected by introducing TBS and MOM-ethers, respectively. This process led to the production of the completely protected bicyclic ether/THP fragment **35**, with a yield of 45% achieved by the four-step sequence. The cleavage of the PMB ether for a duration of 10 minutes accomplished through oxidative circumstances utilizing DDQ. Subsequently, the resulting alcohol underwent oxidation employing Dess-Martin reagent. The intermediate aldehyde was obtained promptly using a Takai olefination reaction[28], resulting in the formation of *E/Z*-vinyl iodides at a ratio of 4:1. The *E*-vinyl iodide **36** was obtained with yield of 28% over three steps through the efficient separation of vinyl iodides using flash column chromatography. The conversion of vinyl iodide **36** to aldehyde **37**, which is essential for the Julia-Kocienski olefination, was achieved using a well-established two-step process, resulting in a yield of 68%.

With the aldehyde coupling partner in hand, the previously sulfone synthesis process was employed to modified dihydropyran **40** (*Scheme 2.9*). To get the alcohol, aldehyde **19** was reduced using sodium borohydride. Under acidic circumstances, the MOM ether was cleaved from the resulting alcohol to expose an intermediate diol, which was transformed to bis-TBS ether **38** in 83% yield over three steps. The previously employed sequence was used to introduce the desired oxidation state, which was transformed to tertbutyl ester **39** in four steps in

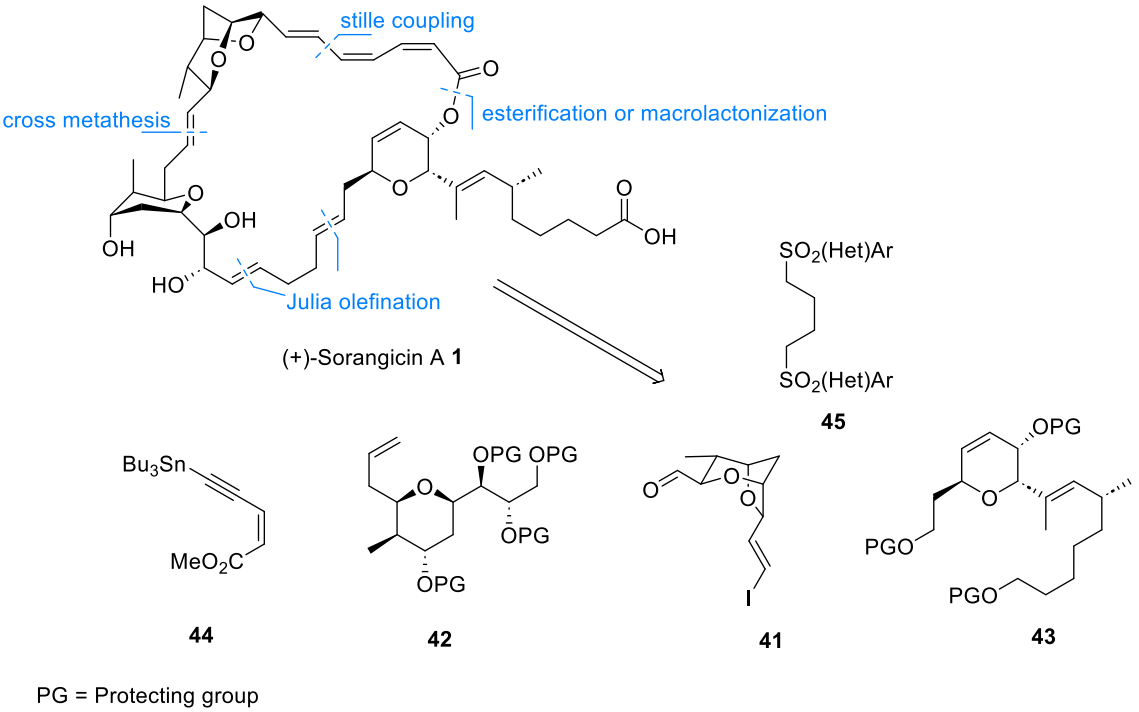
72% yield. As ester **39** corresponds to an intermediate in Smith's synthesis, a well-known three-step sequence was used to selectively cleave the C15 TBS-ether and convert the resulting alcohol to sulfone **40**. Finally, sulfone **40** and aldehyde **37** were used in a Julia-Kocienski olefination under Smith's conditions to generate fragment **15** in 79% yield. Compound **15** matches a late intermediate of Smith III's total synthesis of **1**.



Scheme 2.9 *2nd approach of fragment* ***15*** *via Julia-Kocienski Olefination*

2.2.3 Partial Synthesis by S. Nyalata and S. Raghavan

In 2019, S. Nyalata and S. Raghavan published a new paper[19] for reporting their up-to-date progress of (+)-sorangicin A. They are also using a convergent strategy, disconnecting (+)-sorangicin A **1** into essential subunits: bicyclic ether **41**, tetrahydropyran **42**, and dihydropyran **43** and precursor triene moiety **44** (*Scheme 2.10*). So far, there is no report from this group about total synthesis or semi-syntheses of (+)-sorangicin A **1**. But they have reported successfully bicyclic ether **41**, tetrahydropyran **42**, and dihydropyran **43** fragments, and coupled moiety **41** with **42** via cross-metathesis.

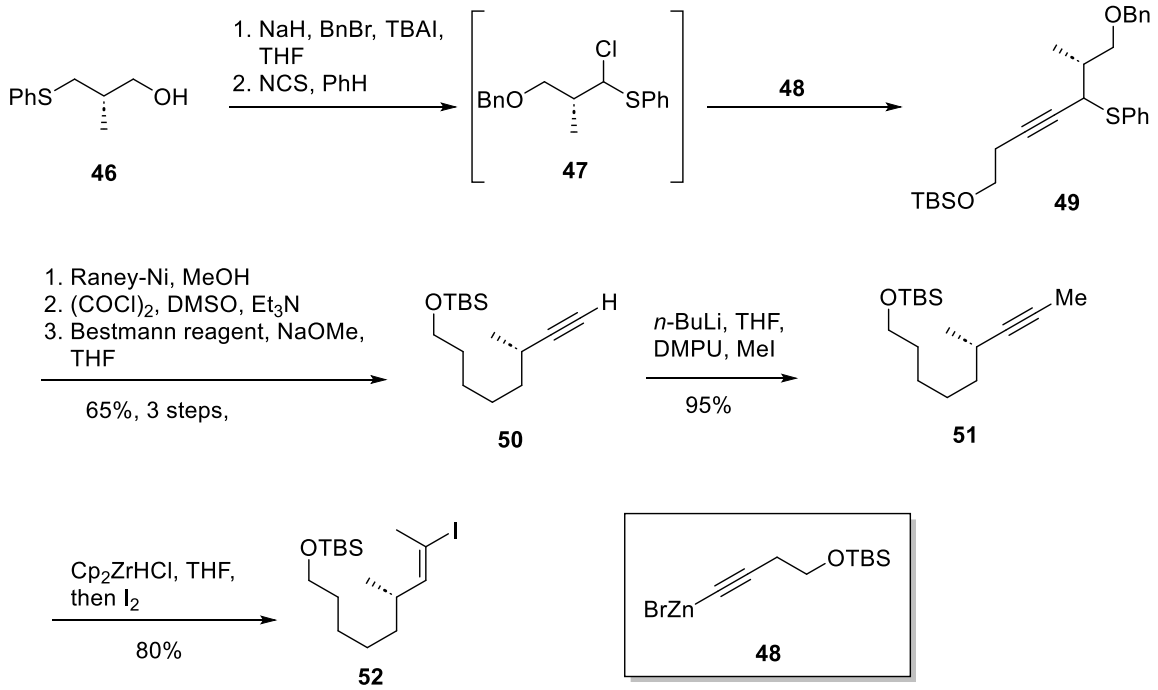


Scheme 2.10 *Retrosynthetic analysis of (+)-sorangicin A* ***1*** *by S. Raghavan et al.*

The synthesis of side chain **52** of dihydropyran fragment **43** commences by employing the previously created sulfide **46** (*Scheme 2.11*).[21] The alcohol function was protected as a benzyl ether, followed by α-chlorination using NCS to yield *α*-chlorosulfide **47**. Subsequently, without isolating compound **47**, it was subjected to a reaction with alkylzinc reagent **48**, resulting in the formation of propargyl sulfide **49**. The triple bond and sulfide function were reduced, and hydrogenolysis was conducted simultaneously to yield an intermediate alcohol. This alcohol was further oxidized to an aldehyde using the Swern oxidation method. Consequently, under the Ohira-Bestmann methodology, alkyne **50** was successfully synthesized with 65% yield using a three-step sequence. The methylation of the lithium acetylide was carried out *in situ* using MeI, resulting in the formation of methyl alkyne **51** with a yield of 84%. The reaction of methylalkyne **51** with an excess of Cp_2ZrClH resulted in the formation of a vinyl zirconium compound. Subsequently, treatment of this compound with iodine led to the conversion into vinyl iodide **52**. Vinyl iodide side chain **52** was consequently obtained with an overall yield of 28% through a series of eight sequential stages.

The synthesis of DHP-core chain **66** (*Scheme 2.13*) originated with the utilization of D-(-)-tartaric acid **53** (*Scheme 2.12*), which underwent a series of four stages to yield chloroacetonide **54**, using established synthesis protocols.[29] The reaction of compound **54** with lithium amide in liquid ammonia as solvent resulted in the formation of alkynol **55** with a yield of

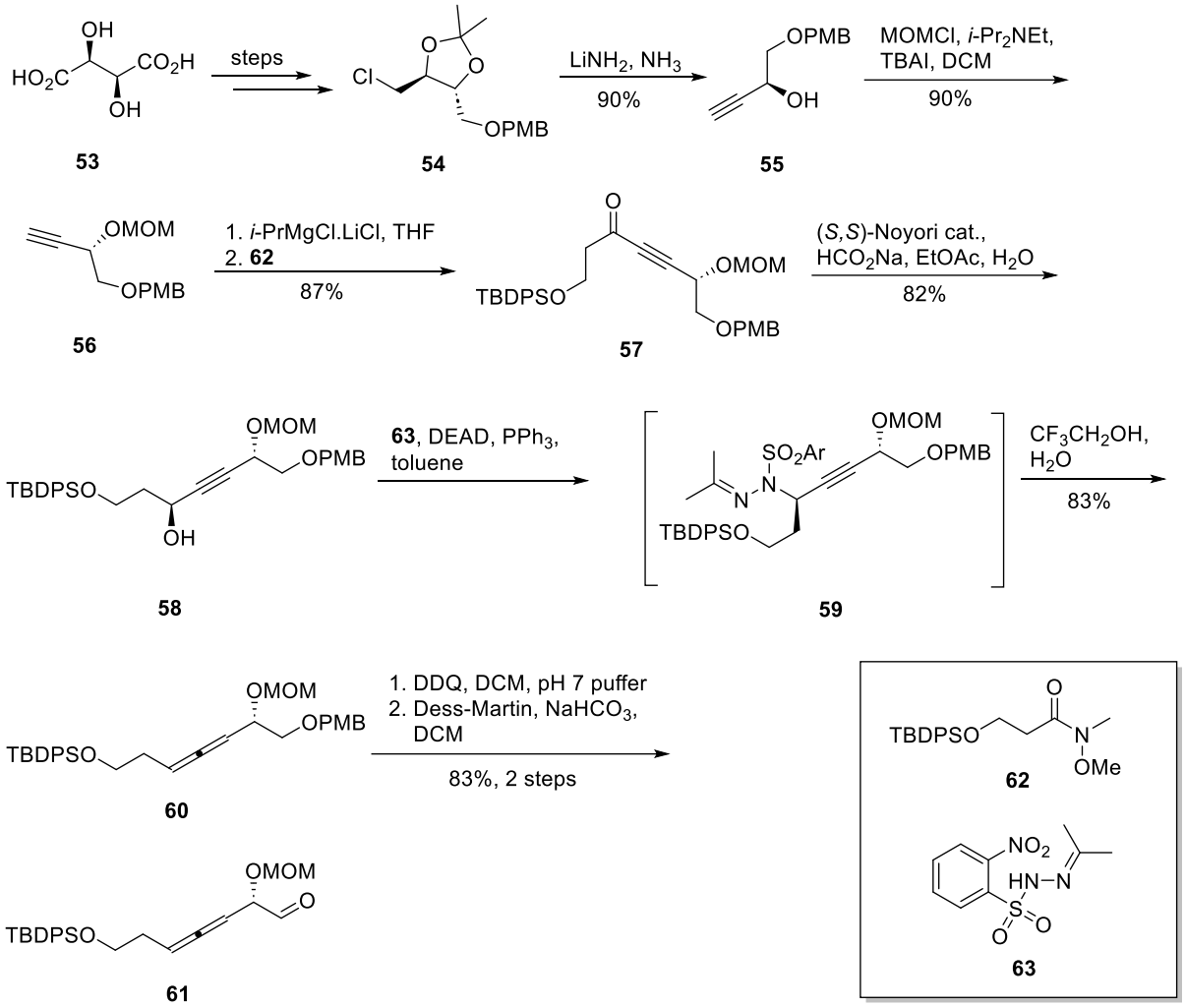
90%. The secondary alcohol was protected as a MOM-ether and then reacted with Weinreb amide **62** under basic condition, resulting in the formation of ketone **57** with 87% yield. The reduction process exhibited stereoselectivity, resulting in the production of alcohol **58** with 82% yield (de = 99%). Allene **60** was synthesized via the application of the Myers-Movassaghi procedure[30], starting from alcohol **58**. The reaction between compound **58** and hydrazone **63**, conducted under Mitsunobu conditions, resulted in the formation of intermediate **59**. Subsequent treatment of compound **59** with an acidic aqueous solution led to the formation of allene **60**, in 83% yield. The PMB ether was deprotected under oxidative circumstances, and the resulting free alcohol was oxidized using Dess-Martin periodinane. This synthesis yielded aldehyde **61** with an overall yield of 38% over a total of nine steps.



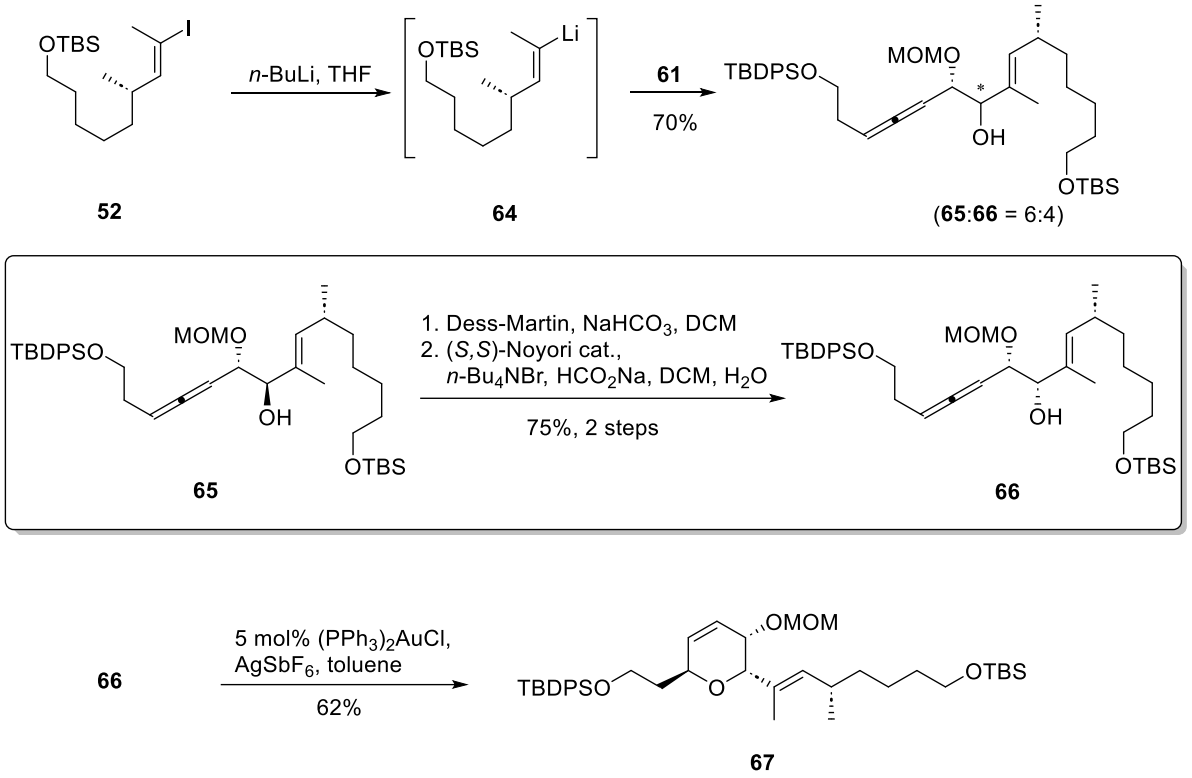
Scheme 2.11 *Synthesis of side chain* ***52*** *of dihydropyran fragment* ***43***

Subsequently, the coupling of vinyl iodide **52** and aldehyde **61** was performed through the utilization of an appropriate organometallic addition, as depicted in *Scheme 2.13*. The isomerization of *in situ* prepared alkyl lithium compound **64** upon reaction with aldehyde **61** at -78 °C resulted the formation of complex mixtures of products. The use of transmetallation to organomagnesium or organozinc compounds did not yield any significant improvement in the given scenario. Ultimately, it was acknowledged that subjecting the mixture of aldehyde **61** and alkyllithium compound **64** to a rapid warming process at 0 °C for 10 minutes. This resulted in

the formation of a distinct combination of compound **65** and **66**, with a ratio of 6:4. Fortunately, the alcohol functionality of the undesirable isomer **65** could be effectively inverted by a two-step process. Isomer **66** was obtained from isomer **65** with a yield of 75% over two steps, with a diastereomeric ratio of 9:1. This transformation involved oxidation using Dess-Martin periodinane and reduction in the presence of (*S,S*)-Noyori catalyst. The conversion of allene alcohol **66** to dihydropyran **67** was catalyzed by $AuCl(PPh_3)_2$, resulting in a clean reaction with 62% yield. Following the successful synthesis of the DHP fragment **67**, the subsequent focus was directed towards addressing the synthesis of the THP fragment **42**, which had previously remained incomplete.

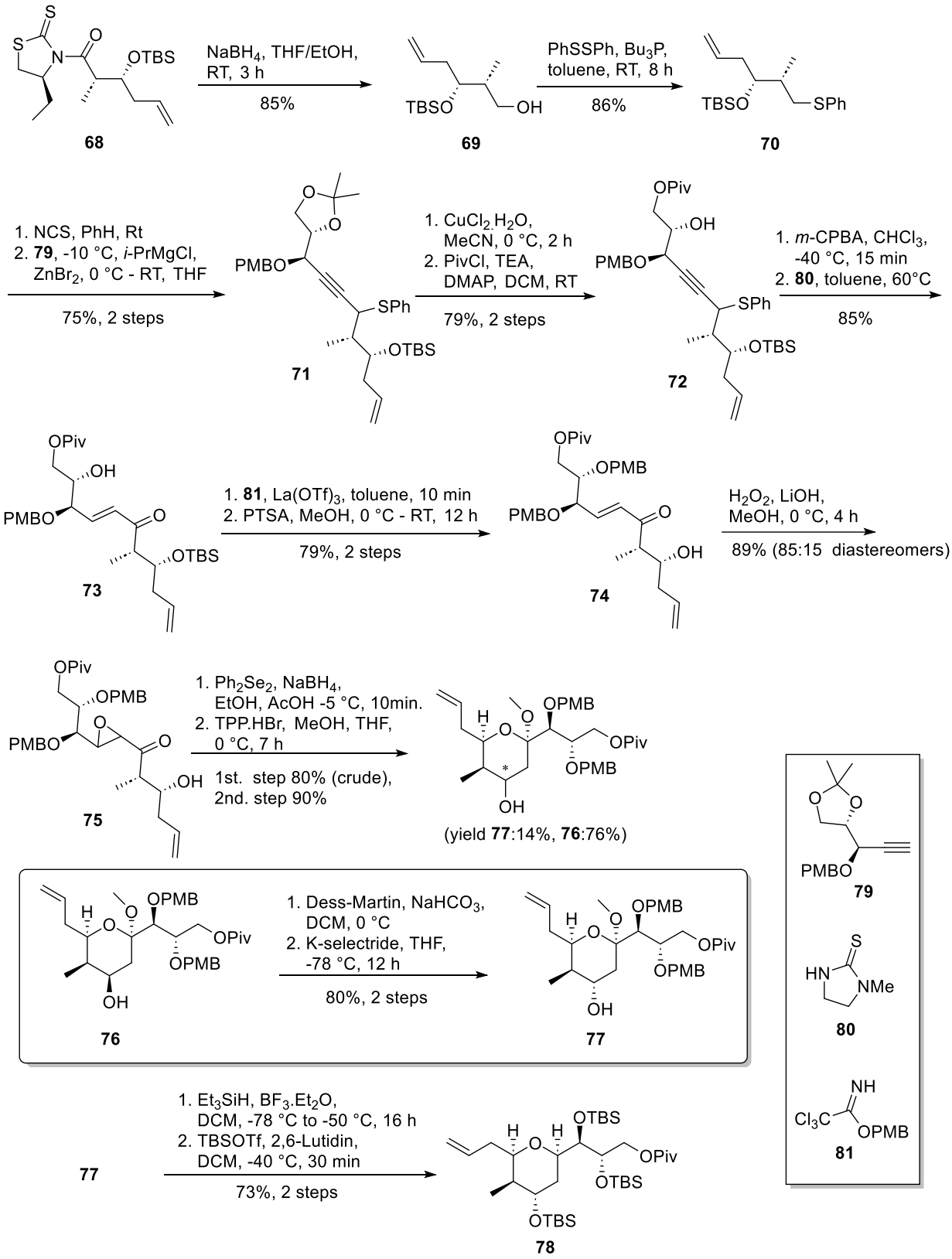


Scheme 2.12 *DHP fragment* ***67*** *synthesis (part 1).*



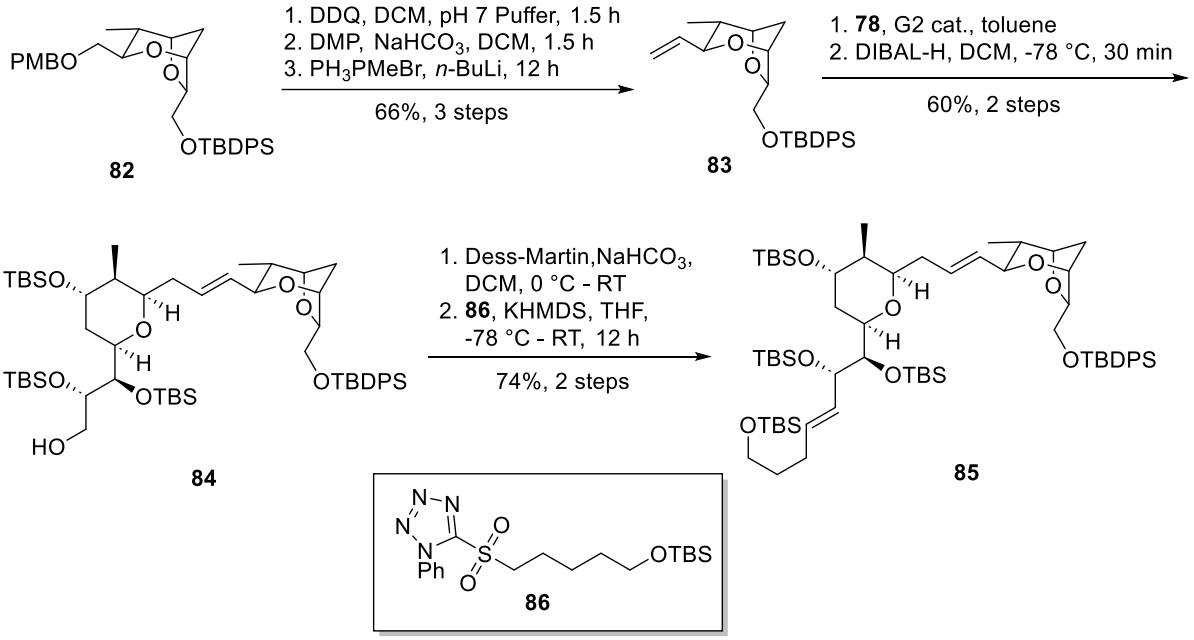
Scheme 2.13 *DHP fragment **67** synthesis (part 2).*

The synthesis of THP moiety **78** commenced with the previously established silyl ether **68** (*Scheme 2.14*). Initially, the Evans auxiliary compound was subjected to cleavage using sodium borohydride, resulting in the formation of alcohol **69**. The reaction was carried out using Hata's protocol[31] to get sulfide **70**. Sulfide **70** reacted with NCS, leading to the formation of an α-chlorosulfide. This α-chlorosulfide was next subjected to a reaction with alkynylzinc bromide, which was derived from compound **79**. A mixture of inseparable epimers of propargyl sulfide **71** (75% yield, dr = 5.5:4.5) was produced. The oxidation of the chiral carbon atom to the prochiral ketone was seen throughout the synthesis process, prompting the execution of the subsequent reactions using the epimeric mixture. The synthesis proceeded by deprotecting acetonide **71** and thereafter protecting the resultant diol selectively as pivalate **72**. The α, β-unsaturated ketone **74** was obtained by subjecting the epimeric sulfide mixture to oxidation, followed by [2,3]-sigmatropic rearrangement. Various approaches were attempted during this stage to determine the optimal course of action for the final steps, only the optimal path is displayed. In this experiment, the α, β-unsaturated ketone **74** transformed using LiOH and H_2O_2, resulting in the formation of isomeric-epoxides **75** that could not be separated. The carbonyl group was reduced, and subsequently, ketal production occurred under acid



Scheme 2.14 *Synthesis of THP fragment* ***78*** *by S. Nayalata and S. Raghavan.*

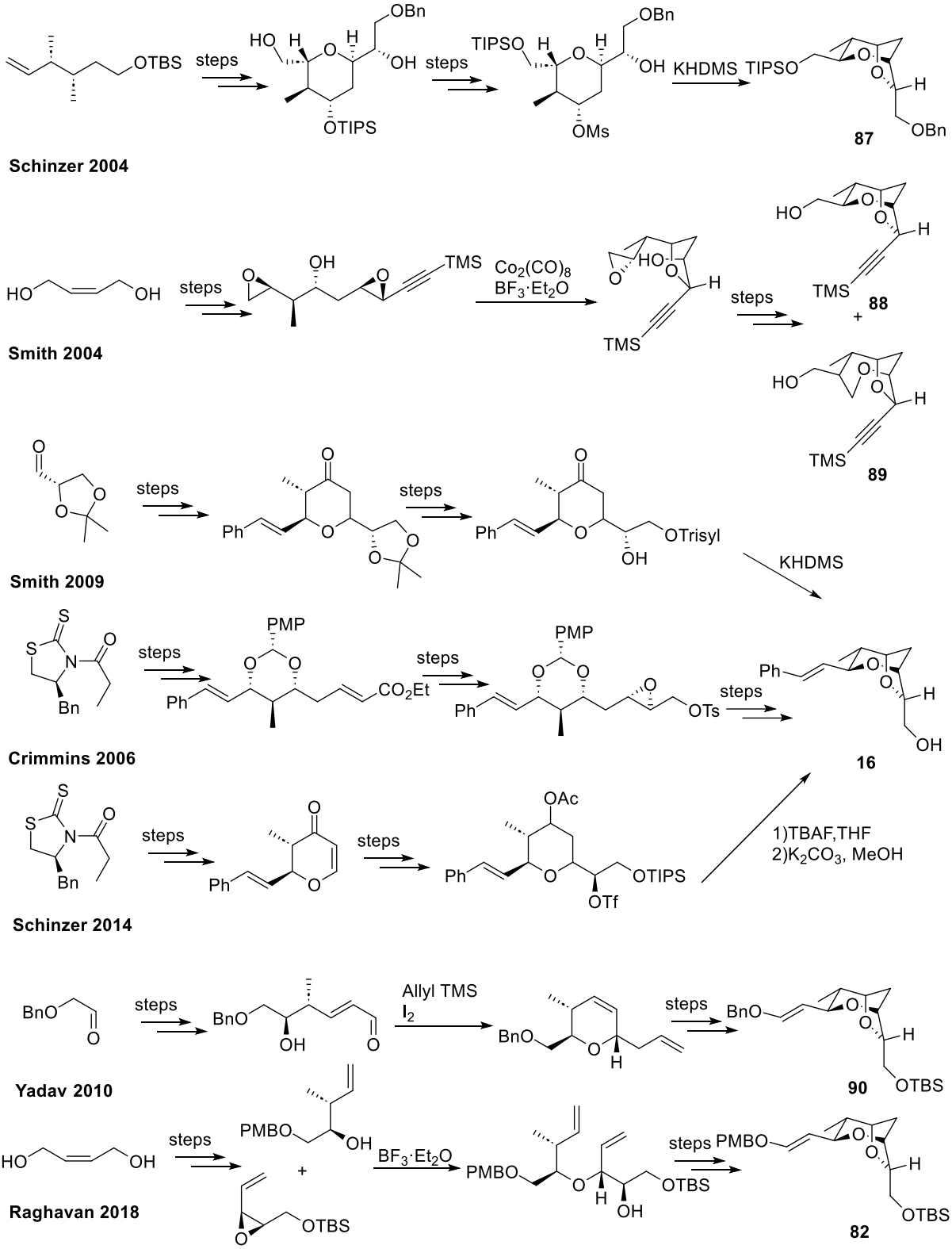
catalyzed conditions. This reaction yielded compounds **76** and **77** in a ratio of 8.5:1.5, with an overall yield of 90%. Regrettably, the unwanted isomer 76 was produced as the predominant outcome. Nevertheless, it is possible to transform this compound into the desired isomer 77 by employing a two-step oxidation/reduction process, achieving a yield of 85% over two steps. The PMB protecting groups were removed using reductive conditions, and subsequently, silylation was performed to obtain the THP fragment **78** as a TBS ether. The overall yield achieved over 15 steps was 13.6%.



Scheme 2.15 *Cross-metathesis coupling between BCO fragment **83** and THP fragment **78**.*

To facilitate the cross-metathesis reaction between BCO fragment **83** and THP fragment **78**, it was necessary to first introduce a terminal double bond in compound **82** (*Scheme 2.15*). The PMB group was removed using oxidative means, followed by the oxidation of the alcohol function using Dess-Martin periodinane. The resulting product was then subjected to a Wittig reaction, resulting in the formation of the terminal alkene **83**. This three-step process obtained 66% yield of the desired product. A mixture was prepared by combining BCO fragment **83** and THP fragment **78** with a 2-mol-% concentration of Grubbs 2nd generation catalyst. The resulting mixture was agitated in toluene for 36 hours. The cross-metathesis product **84** obtained in 60% yield over two steps with subsequent removal of the Piv-ester. The conversion of the alcohol to the aldehyde, followed by the Julia-Kocienski olefination using sulfone **86**, resulted in the synthesis of the ultimate compound **85** in 74% yield.

2.2.4 Selected Synthesis Studies of Bicyclo[3.2.1]octane Subunit



Scheme 2.16 *An up-to-date scheme for the BCO fragment synthesis effort by synthetic community*[12, 14, 15, 20, 32]

As previously stated, bicyclo octane is a distinctive substructure that has garnered considerable attention in pioneering research, with its synthesis being seen as a paramount objective. A schematic representation in *Scheme 2.16* is provided to offer an overview of the key initiatives. These endeavors can be categorized into three goals: firstly, the construction of the pyran precursor using asymmetric synthetic methods, then modification of the precursor by diverse techniques (Schinzer, Smith *etc*.); secondly, the cascade method involving acid-catalyzed epoxide-opening (Crimmins); and finally, the convergent synthesis of the pyran precursor (Raghavan).

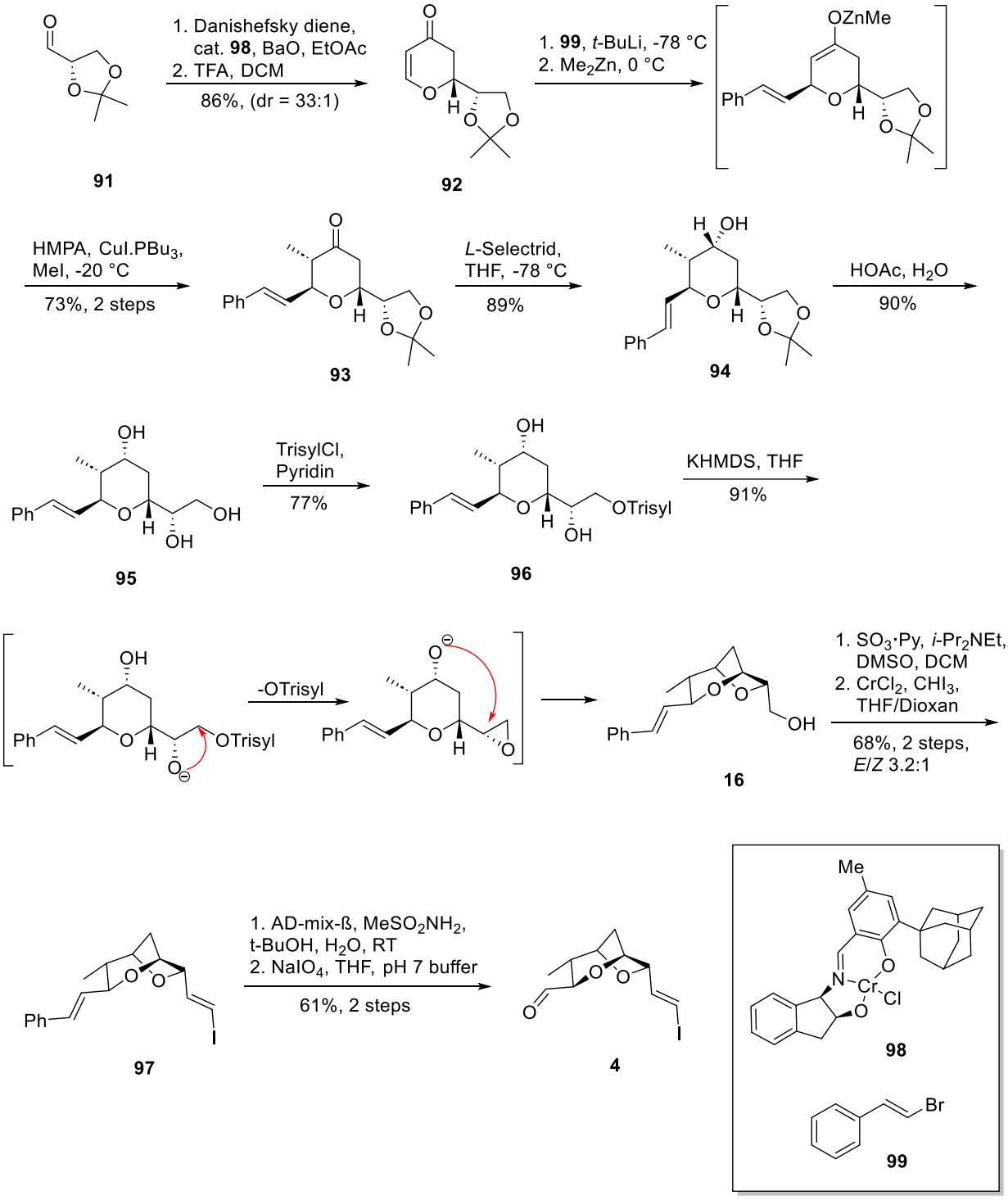
2.2.4.1 An Asymmetric Hetero-Diels-Alder Method Developed by Smith III *et al.*

The initial synthesis of compound **88** was conducted by the research group Amos B. Smith III,[33] as reported in their publication in 2004. However, this synthesis demonstrated limited productivity, yielded only 1.5% of product **89** after a series of 15 steps. Thus, a novel pathway was devised and documented in 2009, demonstrating a substantial reduction of steps and enhanced efficiency for bicyclo octane moiety **16**.[10]

This novel pathway (*Scheme 2.17*) starting with a reported asymmetric Hetero-Diels-Alder reaction by Jacobsen[34] between the Danishefsky diene and aldehyde (−)-**91**, successfully constructs a 2.3-dihydropyranone **92** as the desired product. Danishefsky *et al.*[35] observed the Hetero-Diels-Alder reaction involving zinc chloride in benzene. Under these conditions, aldehyde **91** had a significant impact on the stereochemistry of the resulting Hetero-Diels-Alder product. Furthermore, they determined that the chromium (III)-Schiff base catalyst **98** was unable to successfully counteract this strong influence in cases where there was a mismatch. Based on the Cram model, it has been observed that the product **92** was obtained as a sole stereoisomer with 72% yield. The addition of the absent substituents in pyranone **92** were performed using a conjugate addition in a one-pot process.

The styrene is subsequently guided via the shield located at the bottom of the acetonide in the equatorial position, arranging effectively the stereochemistry of the methyl group. The Noyori three-component prostaglandin coupling protocol[36] was employed, involving Li halogen exchange of bromine in compound **99** using *t*-BuLi at -78 °C. Subsequently, Me_2Zn was added and the reaction mixture was warmed to 0 °C to form a mixed zincate. Then, dihydropyrone **92** was added at -78 °C, followed by the introduction of 10 equivalents of HMPA and subsequent alkylation of the zinc enolate with 10 equivalents of methyl iodide at -40 °C, resulting in a successful conjugate addition. However, **93** was isolated in 51% yield, accompanied by a

bis-alkylation product in 20% yield. This phenomenon can be attributed to the deprotonation of **99**, which is thereafter engaged by the enolate undergoing recurrent alkylation. Subsequently, it was discovered that the utilization of a copper iodide tri-butyl phosphine complex



Scheme 2.17 *Synthesis of bicyclo[3.2.1]octane subunit* ***16*** *by Smith III et al.*

facilitated the transmetalation of the zinc enolate, hence mitigating the aforementioned effect. Although the reactivity drops, reaction duration is extended by a period of two days, resulting in a significant increase in the yield, which reaches 73%.

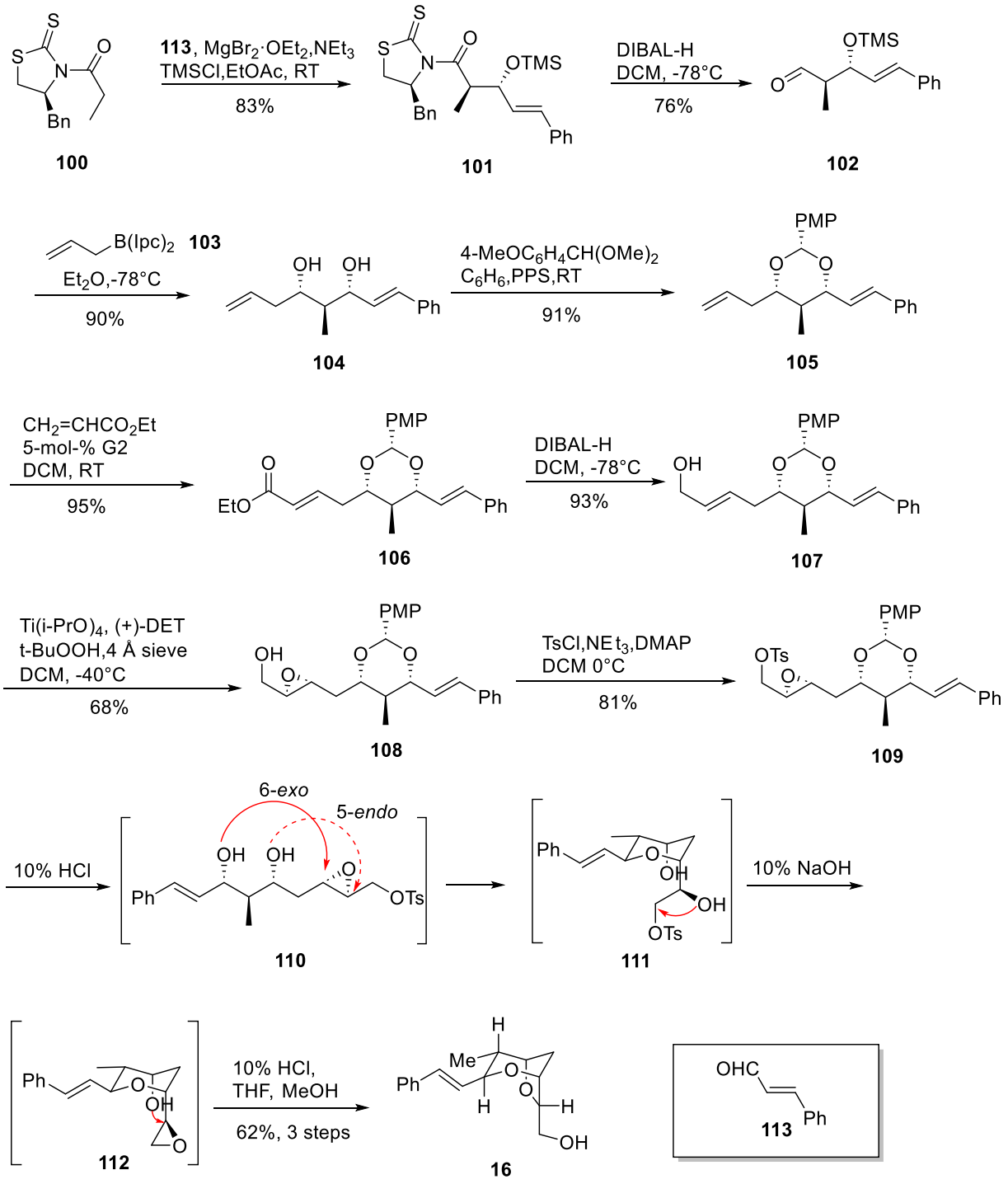
Compound **93** was subjected to reduction using L-selectride, resulting in the formation of axial alcohol **94**. The acetonide protecting group was subsequently removed using aqueous acetic acid, yielding the diol **95** which was selectively sulfonated at the primary alcohol with trisyl chloride, resulting to the formation of compound **96**. The required bicyclo[3.2.1]octane subunit **16** can be initiated through a cascade reaction by treatment **96** with KHMDS, which leads to the *in situ* formation of epoxide followed by intramolecular opening. The oxidation of compound **16** to the aldehyde was achieved under the Parikh-Doering conditions, followed by Takai olefination to generate the required *E*-iodide **97**. The selectivity exhibited a ratio of *E/Z* = 3.2:1 with 68% overall yield. It was determined that the utilization of a mixture of THF and dioxane was imperative for the successful scale-up of the process. The desired fragment **4** was obtained using a two-step process, starting with a selective Sharpless dihydroxylation of electron-rich styrene. This can be facilitated by leveraging the distinct electron densities of the two alkenes followed by oxidative cleavage of the resultant diol using sodium periodate, which resulted **4** in a yield of 61%.

2.2.4.2 A One-pot Acid-catalyzed Epoxide-opening Cascade Method Developed by Crimmins *et al.*

Crimmins and Haley published[16] their solution for the synthesis of dioxabicyclooctan fragment **16**. The methodology involved the utilization of intramolecular epoxide-openings derived from alcohols to facilitate the construction of both the pyran ring and the furan moiety in one-pot.

The process to synthesize compound **16** by Crimmins *et al*. (*Scheme 2.18*) commenced with the utilization of magnesium bromide as a catalyst in the Evans *anti*-aldol reaction. Due to the presence of a thiazolidine thione auxiliary, the TMS-protected aldol product **101** can undergo direct reduction with DIBAL-H, resulting in the formation of the aldehyde **102**. Aldehyde **102** was subjected to an allylation reaction, employing Brown's methodology[37], resulting in a stereoselective conversion. The resulting product **104** was then protected as PMP acetal **105**. Compound **106** can be synthesized using a metathesis reaction utilizing the Grubbs II catalyst and 20 equivalents of ethyl acrylate with **105**, therefore transforming the terminal olefin to

compound **106**. The utilization of the previous PMP acetal protection contributed to the mitigation of competitive forces for RCM. Upon subjecting the allylic alcohol **107** obtained by reduction of **106**, a Sharpless epoxidation reaction was performed, ultimately yielding the desired epoxide **108**.



Scheme 2.18 *Synthesizing BCO fragment* ***16*** *by Crimmins et al.*

Following tosylation of **108**, the subsequent step involves the use of acetal **109**. In this step, the acetal group must be deprotected before undergoing an acid-catalyzed intramolecular epoxide opening, resulting in the formation of pyran **111**. It is important to note that these reactions occur under acidic circumstances. The prevailing expectation was that the 6-*exo* attack would occur in preference to the 5-*endo* attack targeting the alternative hydroxyl group. The destabilization of the relevant transition state for a 5-*endo* attack is caused by both geometric factors (Baldwin rule) and the electron-withdrawing nature of the tosyl group, which are in close spatial proximity. The formation of the second epoxide is thereafter based on the agent. A catalyzed 5-*exo* epoxide opening, which is renewed due to geometrical considerations, occurs in preference to a potential 6-*endo* epoxide opening, to construct the tetrahydrofuran ring. BCO fragment **16** was produced by this streamlined one-pot synthesis, resulting in a yield of 62% across three sequential steps. The synthetic pathway exhibits an overall yield of 19% across a sequence of 10 successive steps.

2.2.4.3 A Short, Convergent Synthesis by S. Nyalata and S. Raghavan

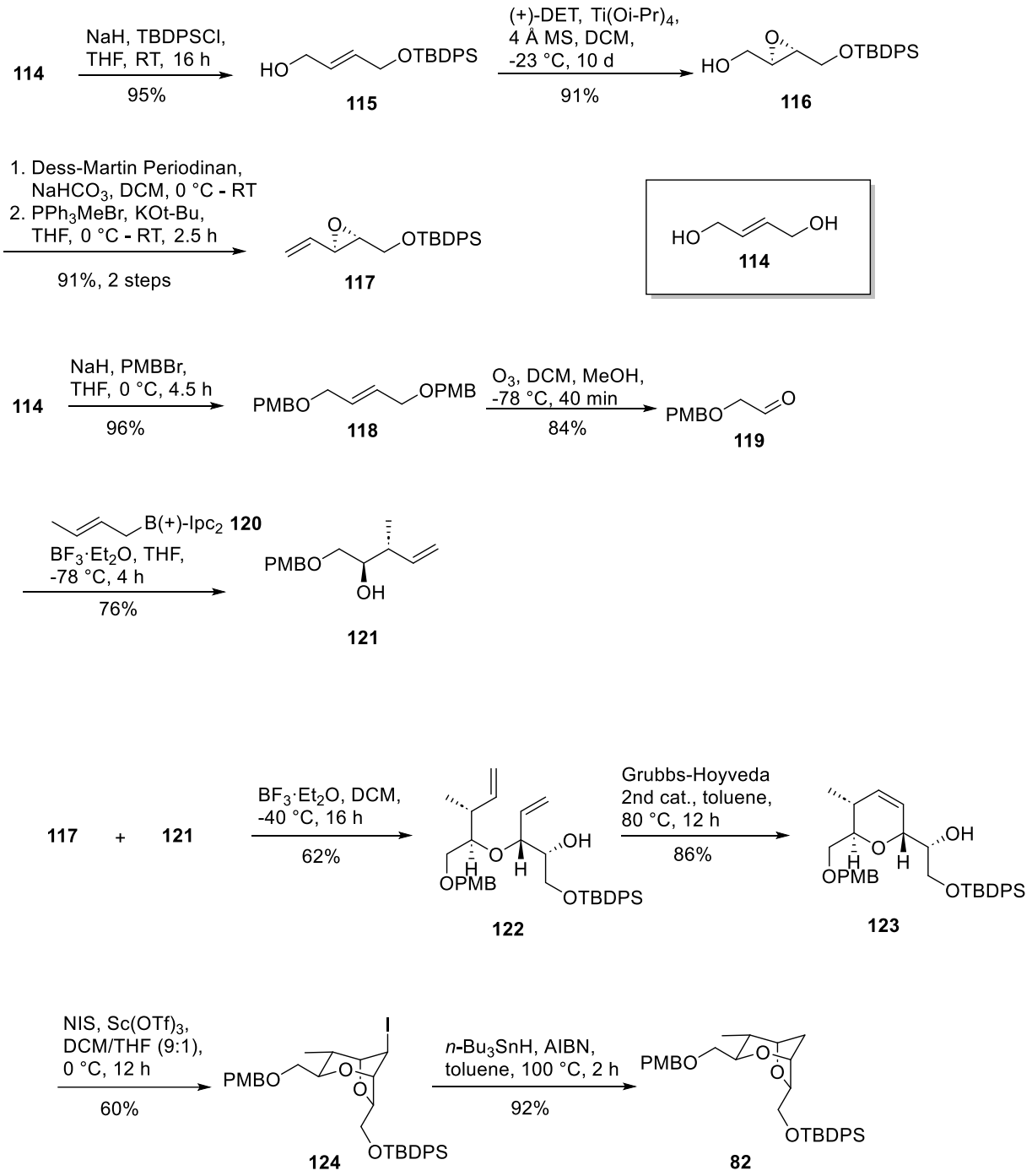
The synthesis of bicyclooctane by S. Raghavan *et al*.[38] (*Scheme 2.19*) involved the preparation of allyl epoxide **117** and homoallyl alcohol **121**. Both syntheses commenced with the utilization of *E*-butenediol **114** as the initial component.

The manufacture of epoxide **117** commenced with the initial step of *mono*-silylation of compound **114** utilizing TBDPSCl. In the subsequent phase, the conversion of alcohol **115** to epoxide **116** achieved with the application of a Sharpless epoxidation. Epoxide **116** undergoes oxidation using Dess-Martin periodinane, following Wittig reaction, resulting in the formation of allyl epoxide **117** with 79% overall yield.

Homoallyl alcohol **121** was synthesized starting with *E*-butenediol **114** followed by dual protection strategy involving the addition of PMB groups. Subsequently, the double bond of compound **118** was cleaved by ozonolysis to obtain aldehyde **119** with 84% yield. A Brown crotylation reaction was employed to manufacture homoallyl alcohol **121**. This reaction demonstrates a favorable yield and exhibits a high level of anti-stereoselectivity, with a 76% yield and a diastereomeric ratio of at least 20:1.

Diene **122** can be efficiently synthesized using a Lewis acid-catalyzed epoxide opening reaction, following the established Mioskowski methodology. The formation of dihydropyran **123** through an RCM reaction, catalyzed by Grubb's 2nd generation catalyst, resulted in 85% yield

to form **123**. Compound **124** was obtained in a yield of 64% using a 5-*endo* iodine-promoted ring closure reaction of **123**, using NIS and catalytic quantities of scandium triflate. The synthesis of the BCO fragment **82** was accomplished by a radical deiodination using tributyltin hydride and AIBN. This synthetic pathway involved a total of eight steps and resulted in an overall yield of 21%.



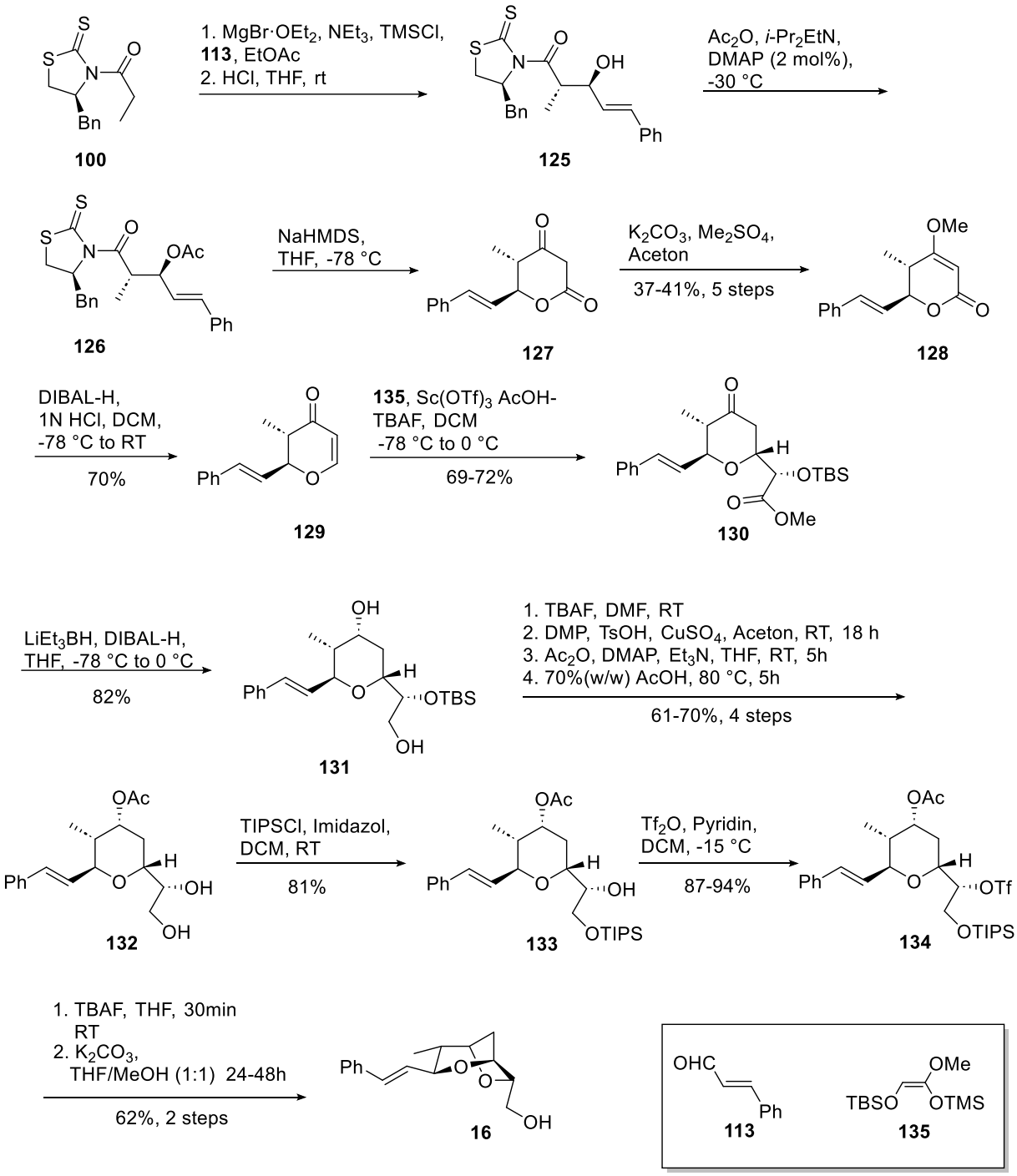
Scheme 2.19 *Synthesis of bicyclooctane* ***82*** *by S. Raghavan et al.*

2.3 Previous Studies by Schinzer *et al.* – The Starting Point

Our lab initially employed an acid-catalyzed epoxide opening strategy to synthesize the dioxabicyclo[3.2.1]octane core. This involved the construction of a tetrahydropyran ring, followed by the closure of the tetrahydrofuran using a Williamson ether synthesis.[39] Nevertheless, the cumulative yield of 1% over 19 steps is deemed inadequate. In 2014, Lars Michaelis[15] developed a more concise and resilient method that produces greater yield. This method was employed to obtain an adequate amount of material for the final investigations on the (*E,Z,Z*)-triene system.

In a revised retrosynthetic investigation of the dioxabicyclo[3.2.1]octane system, Michaelis identified dihydropyranone **129** with 2,3-*anti*-substitution as a viable precursor for a Mukaiyama-Michael addition, which can be utilized to synthesize the necessary tetrahydropyran compound. Upon conducting a stereoselective reduction of the keto group, the corresponding axial alcohol is obtained. Subsequently, a transition towards triflate **134** is carried out. This is followed by a TBAF-mediated deprotection and epoxide formation. Finally, a base-induced intramolecular epoxide opening is performed, resulting in the desired bicyclic system **16**.

The methodology commenced with the utilization of the well-established Evans *anti*-aldol reaction,[40] which yielded the essential trans-configured framework (*Scheme 2.20*). Following the acetylation of the hydroxy group in compound **125**. Subsequent treatment with NaHMDS resulted in the formation of keto lactone **127**, accompanied by the removal of the auxiliary as the leaving group. Dihydropyranone **129** was obtained through the methylation and reduction of keto lactone **127** using DIBAL-H. The addition of ketene acetal **135** to compound **129** was performed in the presence of scandium triflate as catalyst. Quenching with TBAF/AcOH. The major isomer **130** was obtained with a yield ranging from 69% to 72%, accompanied by an overall diastereomeric ratio of 6:1. The stereo-selective reduction of the carbonyl group resulted in the formation of the axial alcohol, while the ester carbonyl group was reduced to yield the primary alcohol. To mitigate the generation of the undesired by-product, a single equivalent of lithium triethyl borohydride was employed, followed by the addition of three equivalents of DIBAL-H. This sequential approach aimed to effectively reduce both the carbonyl group and the ester functionality. Therefore, diol **131** was obtained in high purity using this simple and direct method.



Scheme 2.20 *Synthesis of bicyclooctane* ***16*** *by L. Michaelis*

The TBS group in **131** was removed using TBAF in DMF, while the diol was protected as an acetonide in a single-step procedure. In a further single-step process, the residual hydroxy group was subjected to acetylation, resulting in the hydrolysis of the acetonide and the formation of diol **132** by using acetic acid. Then, the primary alcohol underwent regioselective silylation with TIPSCl, while the secondary alcohol was triflated, resulting in the synthesis of

compound **134**. The cleavage of the silyl ether on **134** with TBAF in THF resulted in the rapid production of an epoxide. Finally, potassium carbonate and methanol were introduced, with the latter being added in such a manner that a mixture of THF and methanol in a 1:1 ratio was obtained. In the given experimental conditions, the deacetylation of the hydroxy group located in the axial position occurred, leading to the subsequent opening of the epoxide ring and resulting in the formation of the intended bicyclic system, denoted as compound **16**.

3. Objective of this Work

Our research group has directed its attention towards the total synthesis of (+)-sorangicin A **1**, an innovative antibiotic from myxobacteria. As previously mentioned, the bicyclooctane fragment and the tetrahydropyran fragment found in sorangicins are identical in (+)-sorangicin A **1** and (+)-neosorangicin A **3** (see *Figure* 2.1 and *Figure* 2.2 in Section 2.1). In the preceding section, Section 2.3 above, extensive research and advancement have been conducted by former members of our team, focusing on the development and examination of dependable synthetic methodologies for these fundamental fragments.

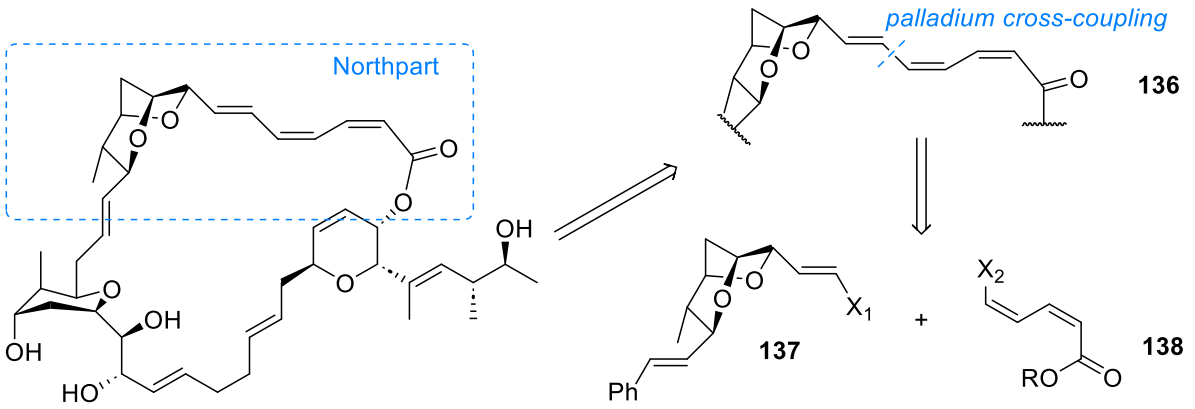
The primary objective of this research is to develop a succinct and robust method for synthesizing the (*E,Z,Z*)-triene sub-structure present in (+)-sorangicin A **1** and (+)-neosorangicin A **3**. In order to generate an adequate amount of material for the subsequent synthesis of the common (*E,Z,Z*)-triene system found in (+)-sorangicin A **1** and (+)-neosorangicin A **3**, it is imperative to expand the employed methodology described in Section 2.3. Furthermore, collaborative efforts will be conducted to achieve a total synthesis of (+)-sorangicin A **1** and (+)-neosorangicin A **3**.

4. Theoretical Part

4.1 Building the (*E,Z,Z*)-Triene System of (+)-Sorangicin A and (+)-Neosorangicin A

4.1.1 Retrosynthesis Planning

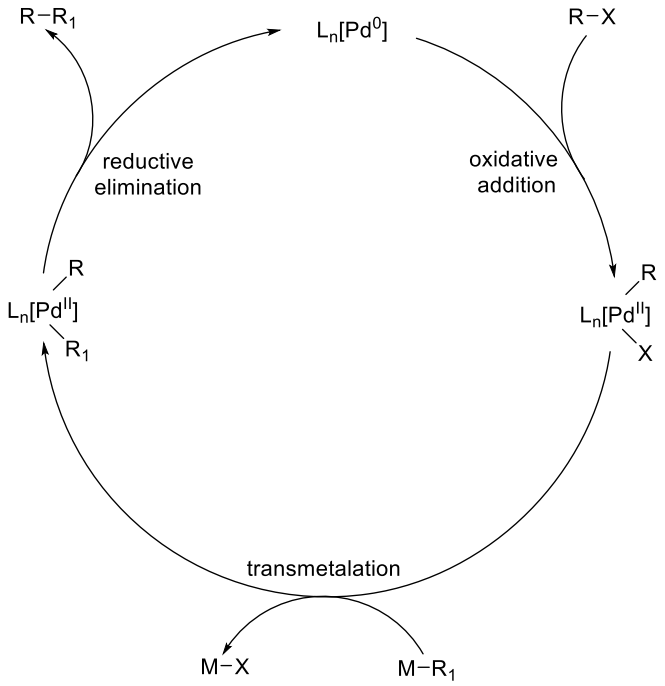
Entirety (+)-neosorangicin A **3** or (+)-sorangicin A **1** can be partitioned into two distinct components: a northern portion, labeled as **136**, which involves an (*E,Z,Z*)-triene system with bicyclo[3.2.1]octane core, and a southern portion consisting of a tetrahydropyran-ring and a dihydropyran-ring (*Scheme 4.1*). According to the experimental findings made by Höfle *et al*[5]. involving the isolation of Sorangicin A **1**, it has been determined that the triene structure is considered to be the most chemically unstable component. Triene **136** exhibits a tendency to undergo isomerization, resulting in the formation of a (*E,E,E*)-triene system, which is thermodynamically more stable. This feature also gave rise to challenges in the palladium cross-coupling method employed by Smith *et al*[12]., as outlined in Section 2.2.1.



Scheme 4.1 *Retrosynthesis Planning of the north part* ***136***

Consequently, it makes sense to incorporate the triene into the molecule as late as feasible during total synthesis. Palladium (0)-catalyzed carbon-carbon cross-coupling is a chemical process that facilitates the formation of new carbon-carbon bonds between two molecules

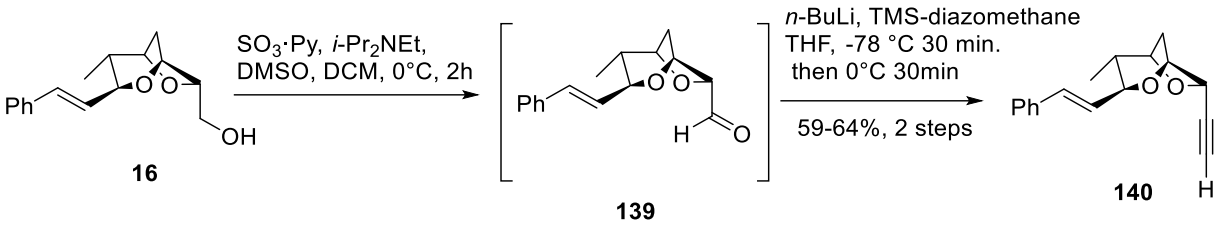
containing carbon atoms. Organic synthesis extensively employs this method for the production of various organic substances, encompassing pharmaceuticals and agricultural commodities. Based on extant research papers, it is obvious that techniques involving palladium C-C coupling have been acknowledged promising for the synthesis of the (*E, Z, Z*)-triene system. Notably, the Stille reaction, as successfully demonstrated by Smith III, has garnered considerable attention in this respect. Organotin compounds are highly poisonous and unstable under typical ambient conditions. Further investigation of palladium-catalyzed couplings, such as Suzuki,[41] Negishi,[42] and Sonogashira,[43] continues to retain significant research significance. While they have a similar mechanism (*Scheme 4.2*).



Scheme 4.2 *General mechanisim of palladium C-C- coupling*

One possible approach to construct an (*E,Z,Z*)-triene system is coupling a metal-substituted *E*-olefin on BCO block **137** with iodide **142**. Alternatively, coupling halogen-substituted *E*-olefin on BCO block with a metal-substituted (*Z,Z*)-olefin could also be a viable method. Terminal alkynes can conduct hydrometallation reactions to provide functionalized *E*-olefins on BCO block **137**. Due to the syn-additive characteristic of these processes, they result in strong *E*-selectivity. Terminal alkynes can conduct hydroborations,[44] hydrozirconations,[45] and hydrosilylations.[46] Furthermore, these hydrometallation products can, *in situ*, undergo further reactions in the presence of palladium catalysts to cross-coupling reactions.

The first step involved the identification of a suitable terminal alkyne. To initiate the process, aldehyde **139**, which was obtained from oxidation of compound **16** under Parikh–Doering condition. Themethods were studied frist by L. Michaelis[47],involving to utilizing the Seyferth-Gilbert[48] reagent or its modified version suggested by Bestmann and Ohira[49], together with the two-step Corey-Fuchs sequence[50]. However, none of the aforementioned methods are capable of achieving the desired alkyne. The reaction involving lithiated TMS-diazomethane, known as the Colvin rearrangement, was examined, and yielded up to 64% **140** after two steps (*Scheme 4.3*). BCO **140** can be conveniently crystallized by evaporating its toluene solution, resulting in crystals that are appropriate for XRD analysis. Therefore, the configuration of the building block could be verified (*Figure 4.1*).



Scheme 4.3 *Synthesis of terminal alkyne* ***140***

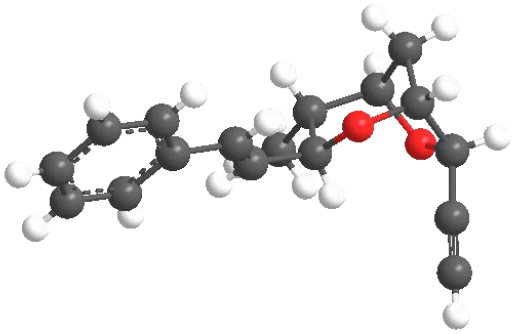
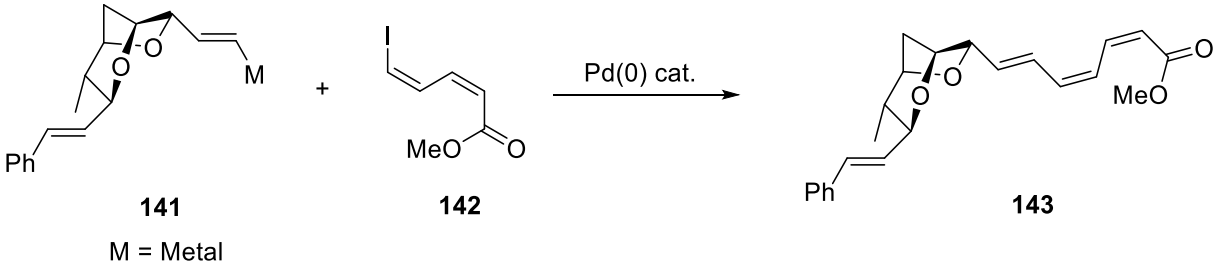


Figure 4.1 *Absolute configuration of* ***140***

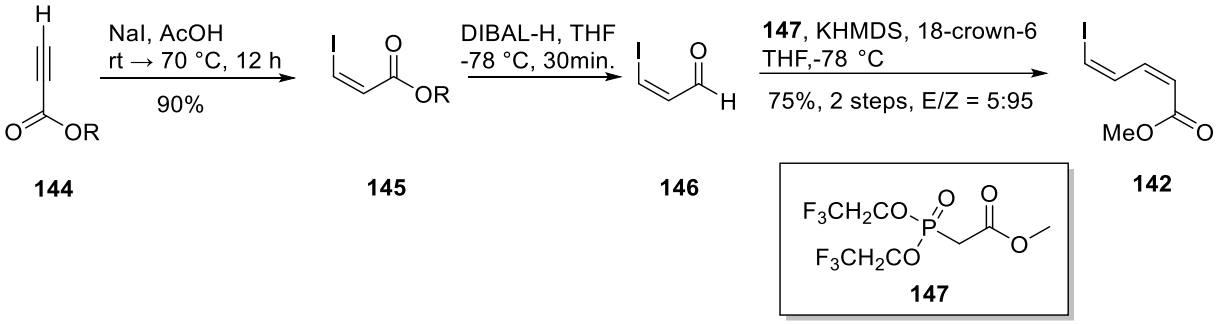
4.1.2 Early Testing for Building the Triene System through C-C Coupling

To examine the initial option, compound **142**, which contains iodine, was produced and afterwards connected to a suitable (*E*)-olefin **141** via a palladium-catalyzed coupling procedure. There are established pathways in literature for the synthesis of compound **142** (*Scheme 4.4*). The compound utilized for **142** is derived from (*Z*)-ethyl- or methyl-3-iodoacrylate **145**, which can be readily synthesized from ethyl or methyl propiolate using NaI and acetic acid at

elevated temperatures[51]. The compound **145** can be reduced using DIBAL-H to obtain the corresponding aldehyde **146**. This aldehyde can then be reacted with a Still-Gennari olefination to yield compound **142**. With several iterations, the yield of this method can be enhanced to 75% (*Scheme 4.5*), but the literature indicates a yield of 95%.



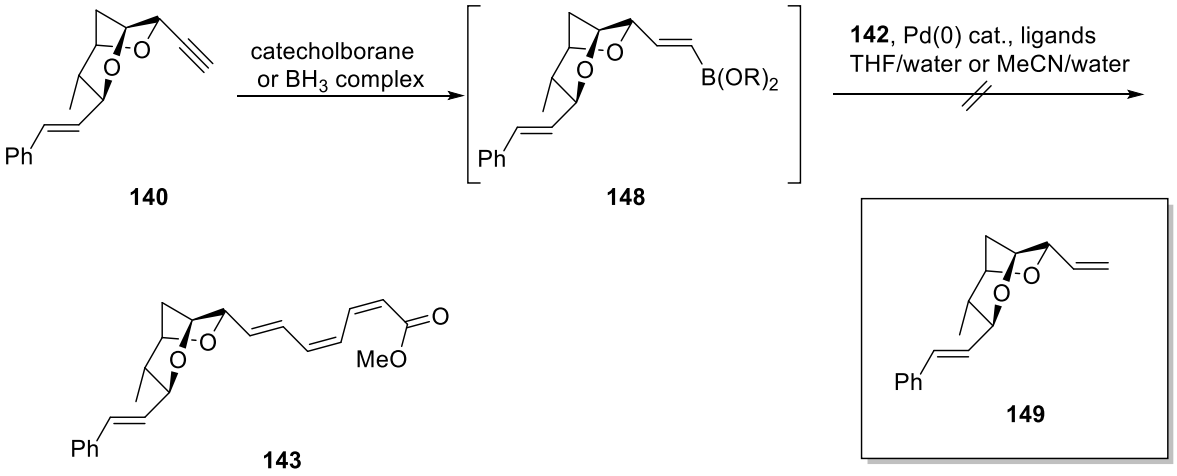
Scheme 4.4 *coupling a metal-substituted E-olefin on BCO block* ***141*** *with iodide* ***142***



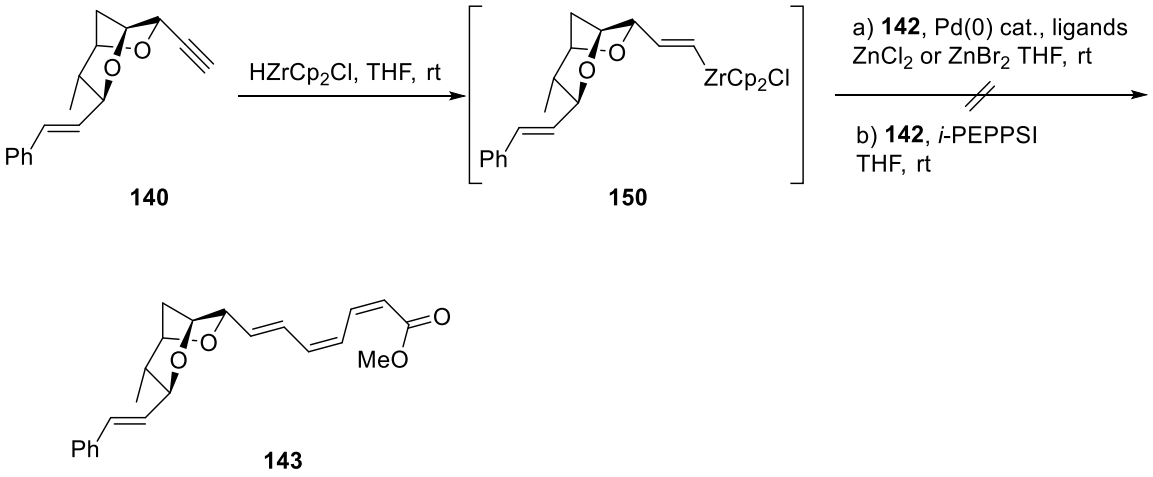
Scheme 4.5 *Synthesis of* ***142*** *(R = ethyl* ***145a*** *or methyl* ***145b*** *)*

Following the initial formation of **142**, the alkyne **140** will conduct hydroboration using a one-pot approach. Subsequently, it will be converted into triene **143** through a Suzuki coupling reaction (*Scheme 4.6*). The hydroboration reaction was carried out utilizing either catecholborane or BH_3 complex, and it yielded positive results in both instances. Following the reaction, the appropriate alkene **149** was isolated in each case through the process of aqueous work-up, which implied a protodeboronation. An endeavor was undertaken to carry out coupling by employing DIPA as the base, in a solution comprising of THF or MeCN and water, utilizing either $Pd(PPh_3)_4$ or $PdCl_2(dppf)_2$ or $Pd(OAc)_2$ as catalysts, along with a range of ligands. Unfortunately, it was not possible to obtain the desired chemical **143** under any circumstances, although in some cases traces of **143** can be found with LCMS.

Schwartz's reagent has demonstrated its efficacy in the hydrozirconation of terminal alkynes. This reaction can also be selectively performed adjacent to alkenes, making it highly suitable for the current situation. After multiple trials, the alkyne **140** was successfully treated with Schwartz's reagent, resulting in isolation of only olefin **149**. This outcome serves as evidence of a successful addition. The second step of coupling, following trans-metalation with zinc chloride or zinc bromide for Negishi coupling (condition a in *Scheme 4.7*), failed.



Scheme 4.6 *Suzuki coupling between* ***141*** *and* ***148***



Scheme 4.7 *Negishi coupling between* ***141*** *and* ***148***

An alternative development of Negishi coupling involves the use of *i*-PEPPSI as the palladium precatalyst without trans-metalation (condition b in *Scheme 4.7*), reported in the literature. As earlier pointed out, isolation of olefin **149** suggests that molecule **150** may exist *in*

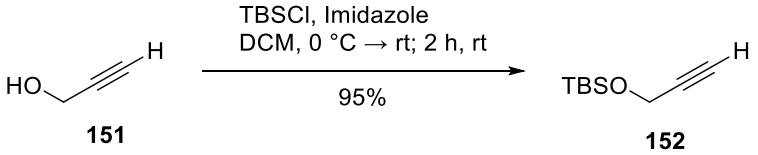
situ. However, **143** was not achieved. The results of conditions that were tested in the early stage have been collected and presented in *Table 4.1*.

Table 4.1 *Conditions tested in early stage*

Entry	Metal	Conditions
1	catecholborane	DIPA, MeCN/Water (10:1), TPPTS, $Pd(OAc)_2$, rt
2	BH_3·THF	DIPA, MeCN/Water (10:1), (*o*-Tol)$_3$P, $Pd(PPh_3)_4$, rt
3	BH_3·*N,N*-diethylaniline	DIPA, MeCN/Water (10:1), TPPTS, $PdCl_2(dppf)_2$, rt
4	$HZrCp_2Cl/ZnBr_2$	THF, (*o*-Tol)$_3$P, $Pd(OAc)_2$, rt
5	$HZrCp_2Cl/ZnCl_2$	THF, (*o*-Tol)$_3$P, $Pd(OAc)_2$, rt
6	$HZrCp_2Cl$	THF, *i*-PEPPSI, rt

4.1.3 Model Studies of Building the Triene System through C-C Coupling

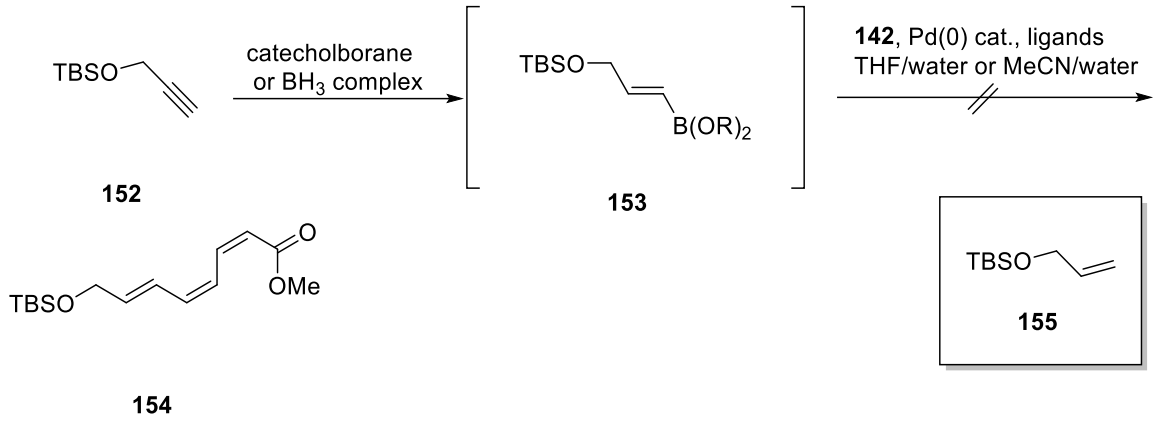
Because of the unsolved problem during the expansion of production of the BCO component, and the time-consuming nature of the BCO preparation procedure, more investigations were required to solve the formation of the triene system. In addition, the early experiments gave unfavorable results. Conducting systematic and rational modeling research is crucial to eliminating the influence of contaminants and similar factors. A TBS-protected propargyl alcohol **152** could be a reasonable model for investigation, while it is easy to prepare and contains in ether similar to **141**.



Scheme 4.8 *Preparation of TBS protected propargyl alcohol **152***

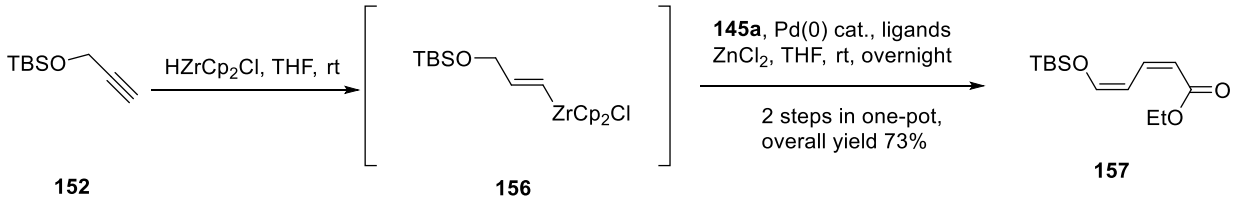
Compound **152** can be produced simply under room temperature from propargyl alcohol **151** with TBSCl and Imidazole, which gave quantitive yield (*Scheme 4.8*). After having the model molecule for investigation in hand, we conduct of the same one-pot hydroboration approach to construct triene **143** through a Suzuki coupling reaction (*Scheme 4.9*). Again, it was not possible to obtain the desired compound **154** under any circumstances. The hydroboration reaction was carried out, and it yielded same positive results in both instances, the appropriate

alkene **155** was also observed in each case through the process of aqueous work-up by crude NMR, which implied the protodeboronation.



Scheme 4.9 *Suzuki coupling between **152** and **142***

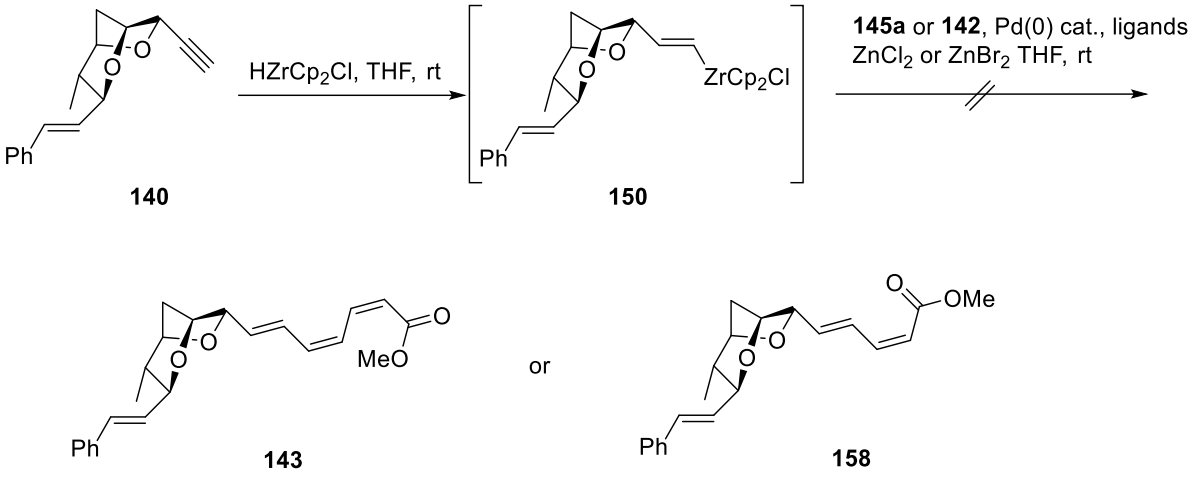
It is worth noting that moisture may be introduced by using self-prepared iodide **142** throughout the aqueous workup. We experimented to examine the hydrozirconation of the terminal alkyne. This was done and followed by trans-metalation with zinc chloride, then addition of iodide **145a** instead of iodide **142**. Fortunately, this one-pot Negishi reaction was effective, yielding 73% diene **157** after purification (*Scheme 4.10*). This significant finding suggests that the other substances participating in the process were free from any impurities. All reagents were used in high purity grade standards for the Negeshi reaction. After producing freshly prepared iodide **142** and removing any water content, we promptly conducted the Negeshi reaction utilizing iodide **142, 145a** and BCO fragment under identical conditions. Regrettably, the desired reactions from the modeling experiments were not effectively achieved, only corresponding olefin **149** was isolated (*Scheme 4.11*).



Scheme 4.10 *Model studies of Negeshi reaction*

According to the results presented above, the failure of the palladium-catalyzed coupling is not attributable to the lack of purity of the reagents or water that was included in the reagents

that were self-prepared. Moreover, the unsuccessful PEPPSI-catalyzed coupling using zirconium complexes suggests that the trans-metalation step of the coupling reaction in the one-pot method was hindered by the distinctive structure of the BCO building block. As a result, only the corresponding terminal alkene could be produced.



Scheme 4.11 *Negeshi coupling between* ***141*** *and* ***145a, 142***

Table 4.2 *Conditions tested in model studies*

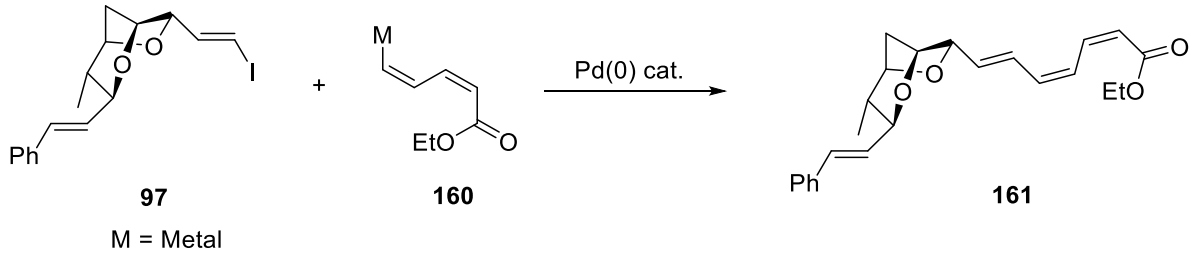
Entry	Metal	Conditions	Result
1	catecholborane	DIPA, MeCN/Water (10:1), TPPTS, $Pd(OAc)_2$, **142** or **145a**, rt	No C-C coupling, only reducted **152** isolated
2	BH_3·THF	DIPA, MeCN/Water (10:1), (*o*-Tol)$_3$P, $Pd(PPh_3)_4$, **142** or **145a**, rt	No C-C coupling, only reducted **152** isolated
3	BH_3·*N,N*-diethylaniline	DIPA, MeCN/Water (10:1), TPPTS, $PdCl_2(dppf)_2$, **142** or **145a**, rt	No C-C coupling, only reducted **152** isolated
4	$HZrCp_2Cl/ZnCl_2$	THF, $Pd(PPh_3)_4$, $Pd(OAc)_2$, in one-pot, **145a**, rt, overnight	Isolated **157** with 73% yield

During the modeling study, in addition to the tests that were indicated above, we also examined several other conditions (*Table 4.2*). The method, Zr-mediated hydroboration, published by Wang *et al*[52]. is the most valuable one among the various conditions that were reported in the literature but were not examined. This is because the model molecules that were utilized in the modeling study are capable of reacting under mild conditions, as was documented in

the relevant research. However, to achieve greater yields when working with complicated substituents, like BCO building block, reflux is necessary. In addition, these conditions will not applicable in the late stage of the synthesis.

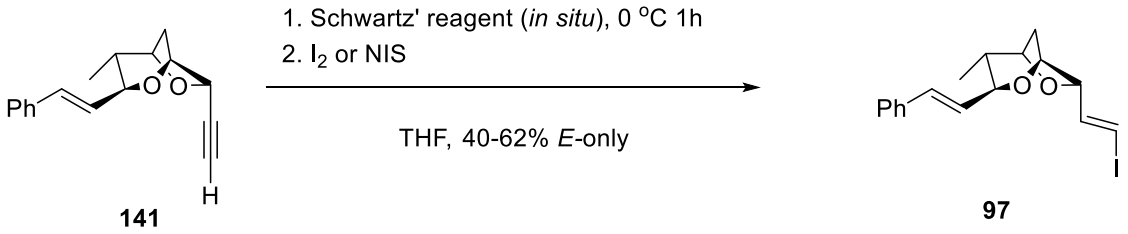
4.1.4 Towards the Attempts with Halogen-elaborated BCO Moiety

The initial surprise arises from the failure of the coupling reaction in all instances, despite the fact that a cross-coupling should be feasible. While it is accurate to say that coupling with a (*Z*)-iodide is less preferred and slower than an (*E*)-iodide, the reaction should not completely fail. The key to success in testing is finding an appropriate mix of palladium catalyst, base, and temperature. Thus, the alternative route, coupling of a halogen-substituted (*E*)-olefin to the BCO fragment with a metal-substituted (*Z,Z*)-olefin could be the only possible route (*Scheme 4.12*).



Scheme 4.12 *Coupling halogen-substituted E-olefin on BCO block* ***97*** *with a metal-substituted* ***160***

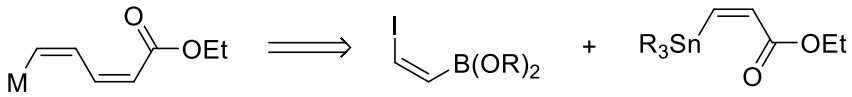
To investigate this possibility, compound **97**, which contains an (*E*)-iodide, was synthesized and subsequently linked to a suitable (*Z,Z*)-olefin **160** using a palladium-catalyzed coupling method. There are well-defined routes in the literature documented by Smith III *et al*. (*Scheme 2.17*). Compound **97** is obtained from the BCO fragment **16** by a modified Takai olefination. While the reaction exhibits a preference for (*E*)-olefin, it lacks practical effectiveness. Smith III observed a selectivity of just 3.2:1 ratio of the *(E)* and *(Z)* isomers. Given our prior confidence with hydrozirconation, employing a metal-halogen approach appears to be a logical and potentially more selective way. Consequently, we conducted an experiment using a one-step hydrozirconation procedure, followed by an iodide exchange. In order to ensure optimal selectivity of hydrozirconation, compound **141** was pre-treated with super hydride at 0 °C. Subsequently, it was *in situ* combined with freshly generated Schwartz reagent. By using an iodine source such as I_2 or NIS, it was possible to isolate compound **97** with up to 62% yield, exclusively obtaining the (*E*)-isomer of the double bond (*Scheme 4.13*).



141 **97**

Scheme 4.13 *Synthesis of **97** via hydrozirconation*

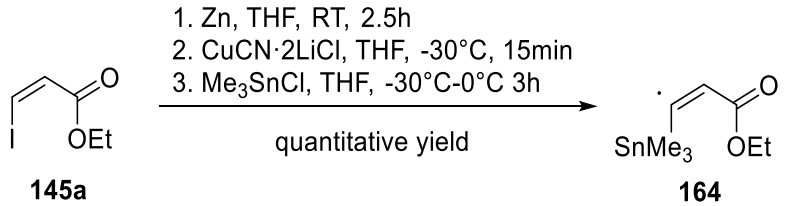
Upon synthesizing **97**, our primary objective is to obtain a suitable (*Z,Z*)-olefin as one coupling partner. We have been inspired by Kobayashi 's use of a one-pot technique in his concise total synthesis of
(-)-myxalamide A to construct the (*E,Z,E*)-triensystems[53]. The (*E,Z,Z*)-olefin **161** can be synthesized using a Stille-coupling reaction, which links **162** and **163**, followed by a Suzuki coupling reaction to produce a C-C bond between the (*Z,Z*)-olefin **160** and **97**. Since we have already produced quantities of ethyl (*Z*)-3-iodoacrylate **145a** in prior trials, it is highly cost-effective and logical to convert it to **163** through metal halogen exchange.



160 **162** **163**

Scheme 4.14 *Retrosynthesis of **160**, R = Alkyl*

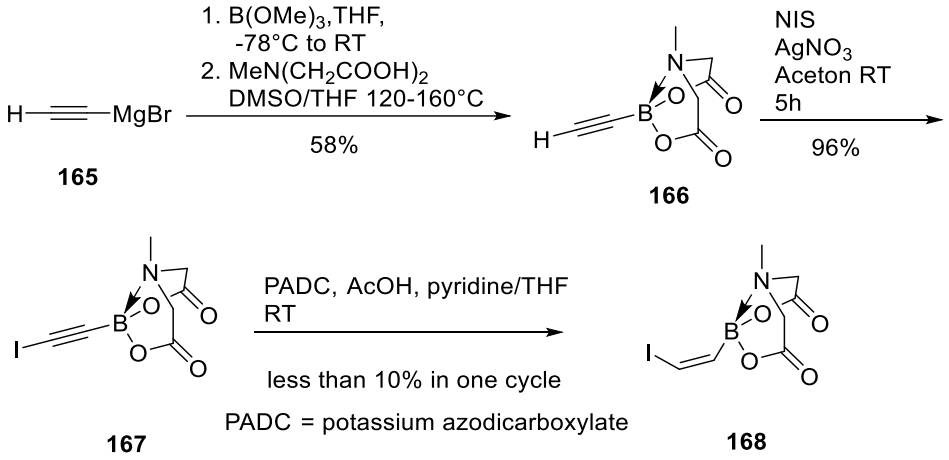
Knochel *et al*[54]. have reported a facile process for converting vinyl iodide into a tin substrate with high stereoselectivity. Compound **145a** was treated with zinc dust, and formation of a *E: Z* mixture (11:89) of a organo-zinc intermediate was observed. Then treatment of this mixture with CuCN·2LiCl followed by the addition of Me_3SnCl leads to the formation of pure (*Z*)-ethyl 3-(trimethylstannyl) acrylate **164** in quantitative yield (*Scheme 4.15*). This compound should be stored at -20°C due to the decomposition at ambient temperatures.



145a **164**

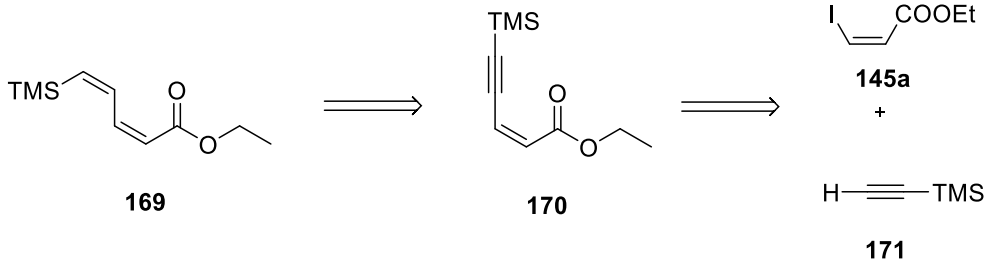
Scheme 4.15 *Synthesis of (Z)-ethyl 3-(trimethylstannyl) acrylate **164***

Many boronic acids are highly unstable and prone to breakdown, which hampers their effectiveness in coupling reactions and makes long-term storage challenging. Thus, Kobayashi *et al*.[53] use MIDA boronates in their work. The boronate esters protected by MIDA exhibit excellent handling properties, long-term stability when stored on a laboratory bench exposed to air, compatibility with chromatography techniques, and lack of reactivity under typical anhydrous cross-coupling conditions. The bifunctional MIDA boronate building block **168** was first reported by Lee[55] (*Scheme 4.16*). The compound is derived from the ethynyl MIDA boronate **166**, which can be acquired using the readily available Grignard reagent **165**. Nevertheless, our attempts to reproduce the maximum yield for ethynyl MIDA boronate **166** were unsuccessful in our experimental trials. One probable explanation is that the preparation was done under nitrogen rather than argon. The process of using silver[56] to boost the addition of iodine to an alkyne was utilized to get a high yield of compound **167**. However, the partial reduction mediated by PADC, which utilizes diimide as the active species, only converts a portion of **167** into **168**. Due to the unavailability of MPLC, the separation of the crude product from diimide reduction using PADC has been attempted using silver ion flash chromatography, but with limited efficiency.



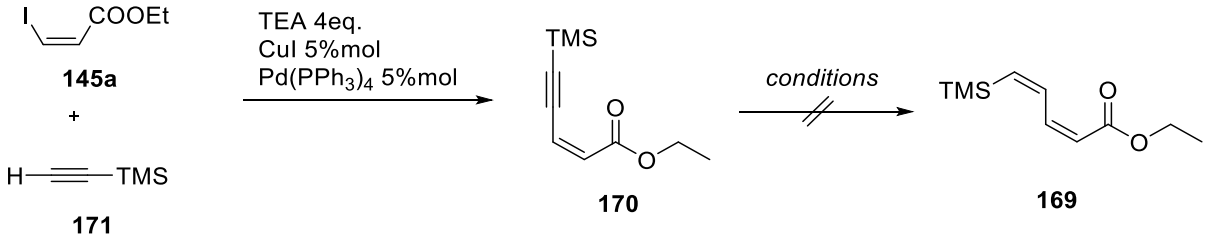
Scheme 4.16 *Synthesis of bifunctional MIDA boronate building blocks*

Due to the unattainability of **168** with the required level of purity in our laboratory's circumstances, we were compelled to discard this approach. There are limited alternative coupling reactions available apart from Stille coupling. The Hiyama coupling[57] represents a potential option. Consequently, it is necessary to synthesize a (*Z,Z*)-diene like **169** specifically for Hiyama coupling. Compound **169** can be synthesized from **170** through a process of selective reduction of an alkyne. The alkynoate **170** can be obtained from **145a** and TMS acetylene **171** by employing a Sonogashira coupling [43] (*Scheme 4.17*).



Scheme 4.17 *Retrosynthesis of* ***169***

The Sonogashira coupling reaction between compound **145a** and compound **171** was conducted under mild conditions, resulting in a high yield. Regarding its properties, **170** exhibits stability when in contact with silica for purification. The attempted reduction of diene **169** was unsuccessful (*Table 2.1*). The Lindlar reduction[58] is a chemical reaction that specifically converts alkynes into (*Z*)-alkenes by a *syn*-hydrogenation process. This occurs because the catalyst used in the reaction is lowered in its reactivity to avoid over reduction. In the current situation, no desired transformation was detected in any instance.



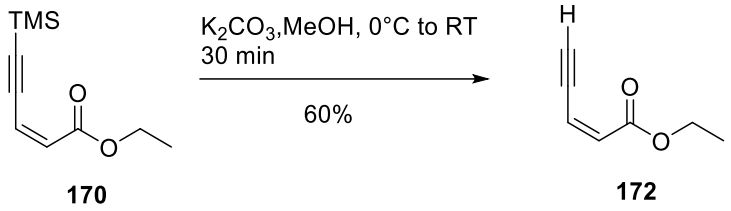
Scheme 4.18 *Sonogashira coupling between* ***145a*** *and* ***171***

Table 4.3 *Conditions on the hydrogenation of* ***170*** *to the Z,Z-diene* ***169***

Entry	Conditions	Result
1	H_2 (1atm), Lindlar catalyst 5-mol%, quinoline 10-mol%., DCM	No recation
2	H_2 (1atm), Lindlar catalyst 5-mol%, quinoline 10-mol%., MeOH	No recation
3	H_2 (1atm), Pd/Ba_2SO_4 5-mol%, quinoline 10-mol%., MeOH	No recation
4	H_2 (1atm), Pd/Ba_2SO_4 5-mol%, MeOH	Over-reduction of **170** by ^{1}H NMR

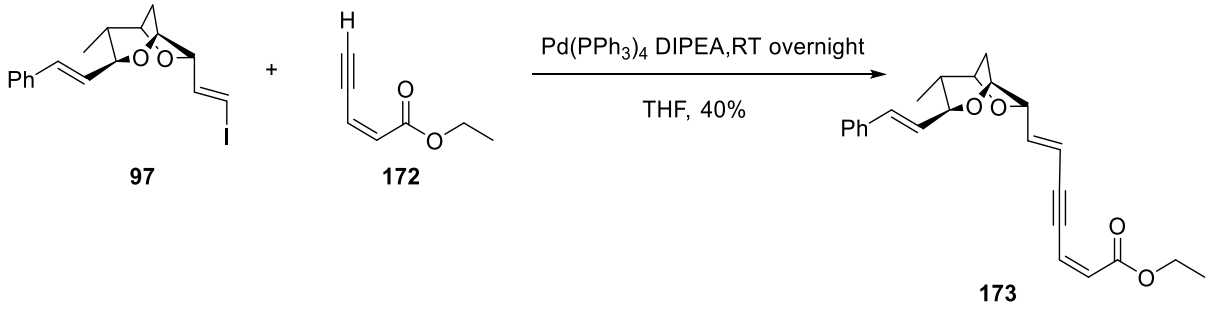
After extensive literature search, it has been demonstrated that utilizing a Hiyama coupling at late stage has the potential dangers of isomerization and decomposition, as well as previous attempts to synthesize **169** have proven unsuccessful. Therefore, this method had to be discarded. Currently, beyond the Stille coupling revealed by Smith III, the Sonogashira coupling

remains deserving of additional investigation. Compound **170** can be readily converted into acetylene **172** through desilylation using either TBAF or K_2CO_3/MeOH. Yet the yield obtained with TBAF is not consistent, as decomposition may take place during the addition process. The conventional procedure, employing K_2CO_3/MeOH, is highly dependable, on temperature and reaction time being critical factors to consider. Elevated temperature can cause decomposition, while a prolonged reaction period can result in transesterification with MeOH, yielding inseparable impurities.



Scheme 4.19 *Synthesis of acetylene **172***

After the successful synthesis of compound **172**, a Sonogashira reaction was carried out between compounds **97** and **172** using identical conditions (*Scheme 4.20*), which were used in the synthesis of compound **170**. But the amine base was replaced with DIPEA. The desired cross-coupling intermediate **173** is obtained as a result of this process with 40% crude yield. ^1H and ^{13}C NMR data were identical with the literature and the mass was confirmed by LCMS.



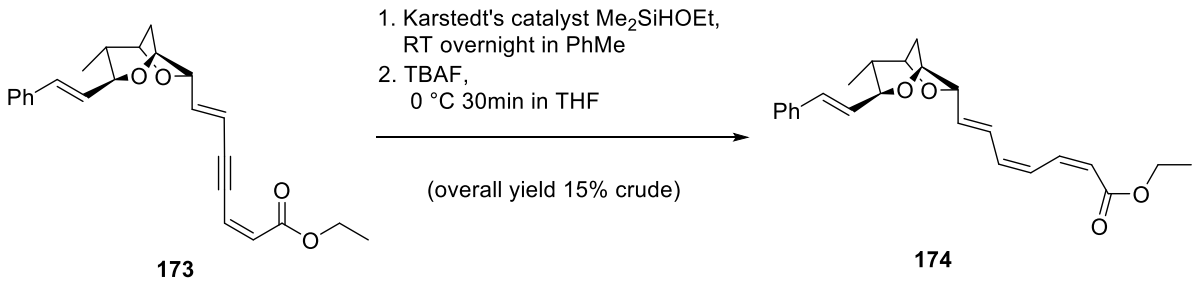
Scheme 4.20 *Sonogashira reaction between compounds **97** and **172***

The process of selectively reducing a triple bond structure to a double bond remains a challenging task. Smith III *et al.*[12] reported a similar trienoate was obtained through semi-hydrogenation using a 5% Pd/ $CaCO_3$ catalyst that was poisoned with Pb/quinoline. However, any attempts to remove quinoline under acidic conditions led to rapid isomerization. Therefore, if

some reduction method can avoid the purification process under acidic conditions, it is possible to achieve the (*E,Z,Z*)- trienoate. Following a thorough literature review, T. V. Hansen *et al*.[59] conducted experiments using several reduction methods, which present a promising opportunity for further exploration.

During their research of RvD1[60], they successfully transformed an internal alkyne using Karstedt's catalyst (2%) and an excess of dimethylethoxy silane. As a result, a mixture of regioisomeric mono-(*Z*)-substituted alkene dimethylsilylethoxy ethers were produced. Gratifyingly, subjecting this combination to TBAF in THF resulted the intended (*Z*)-olefin. Additionally, they investigated the protocol described by Boland and colleagues[59]. The initial approach utilizes a mixture of zinc, copper, and silver in a solution of methanol and water. However, extended periods for reaction and/or increased temperatures are frequently required. These conditions frequently decrease the (*Z*)-stereoselectivity due to isomerization towards the thermodynamically more stable (*E*)-alkene(s). After using TMSCl as an additive in their exploration, short reaction times at ambient temperature, good yields, and high (*Z*)-selectivity have been achieved.

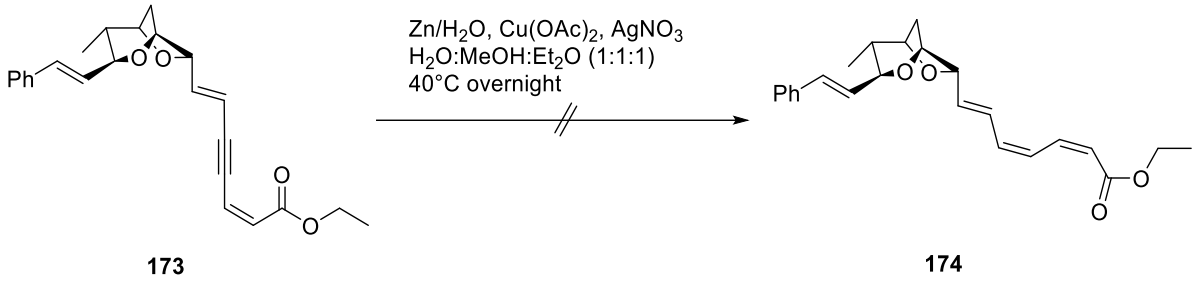
Initially, we experimented with Karstedt's catalyst for the purpose of semi-reduction (*Scheme 4.21*). Compound **173** was mixed with toluene and then stirred for an extended period of time with Karstedt's catalyst and dimethylethoxysilane. After performing a rapid filtration process using Celite® and evaporation of the solvent, the residue was dissolved in THF and then cooled to 0 °C. Subsequently, TBAF was introduced and stirred for a duration of 30 minutes. Ultimately, a total of 15% (w/w) of crude product was successfully retrieved. Regrettably, despite successful detection of the mass of the target molecule using LCMS, the ^{1}H NMR results were highly contaminated, suggesting that compound **173** is prone to decomposition in this stage.



173 174

Scheme 4.21 *Semi-reduction of* ***173*** *using Karstedt's catalyst*

Afterwards, we attempted the Boland protocol (*Scheme 4.22*). Considering that TMSCl can be regarded as an acid additive. Additionally, it is worth noting that our group achieved success in the total synthesis of disorazole C_1 by employing the original Boland methodology as a crucial step for semi-reduction.[61] Thus, we employed the classical Boland approach in this case. The pre-prepared Boland reagent was subjected at a temperature of 40 °C for an extended period after the addition of **173**. The conclusive ^{1}H NMR shown a mixture of product and educt, which are not separable with flash chromatography.



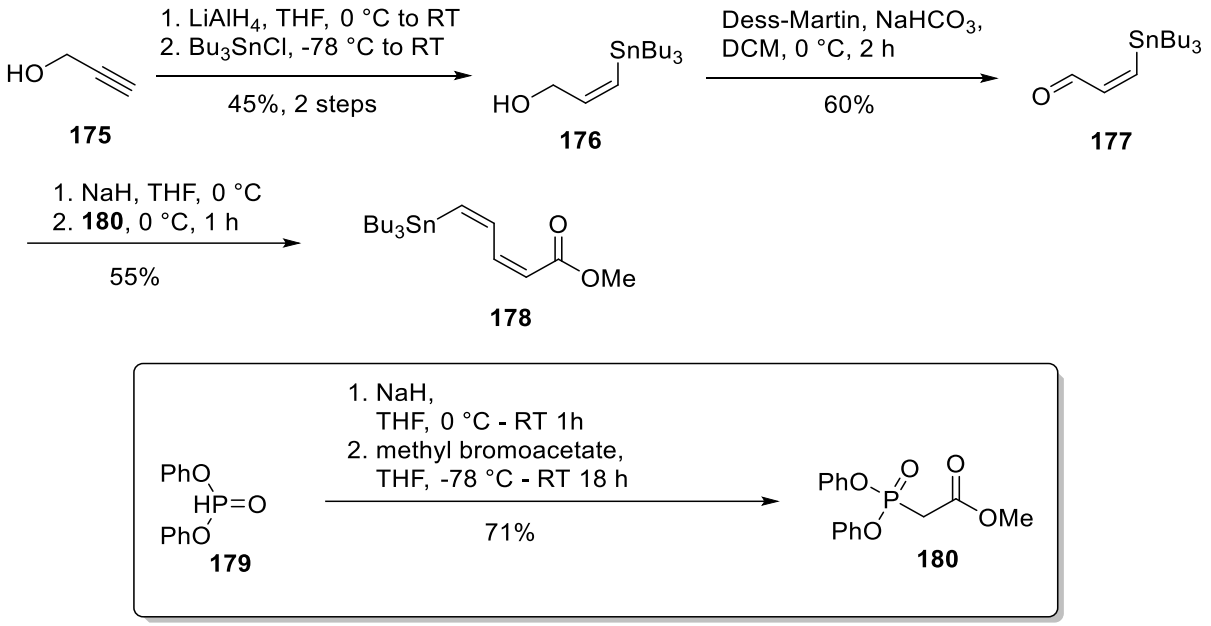
173 **174**

Scheme 4.22 *Semi-reduction of **173** using Boland protocol*

Since none of the previous attempts proved to be fruitful, eventually, we had to follow the path outlined by Smith III, utilizing Stille coupling as a method to construct the (*E,Z,Z*) system. Employing **164** can be easily considered, and further reduction and Still-Gennari olefination[62] can be considered to prepare the (*Z,Z*)-diene tin ester. But relying on empirical evidence and research publications, the selectivity of this synthetic pathway is inadequate. Experiments conducted by K. Ando[63] have demonstrated that specific reaction conditions are necessary to achieve a high level of (*Z*)-selectivity in the synthesis of (*Z*)-tin diene **178**. Multiple circumstances were examined, including the Still-Gennari variation using KHMDS, 18-Crown-6 in THF, Triton ® B in THF, and DBU with NaI. All systems tested exhibited a consistent and significant preference for (*Z*)-selectivity, except for the (*Z*)-tin acrylaldehyde **177**. K. Ando was the first to disclose adjusted conditions that enable high (*Z*)-selectivity for this category of aldehydes as well. The phosphonate group's substituents were altered specifically for this objective, utilizing aryloxyl residues. As a base, either NaH or Triton ® B in THF was employed.

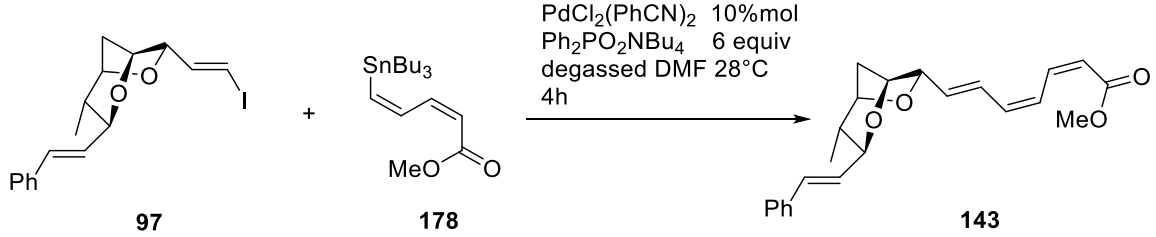
To obtain (*Z,Z*)-tributyltin diene **178**, it is necessary to synthesize Ando's reagent **180** and (*Z*)-tributyltin acrylaldehyde **177** (*Scheme 4.23*). The synthesis of **180** starts with diphenyl phosphonate **179**, which was reacted with NaH in THF to give deprotonated diphenyl phosphonate *in situ*. This was directly reacted with methyl bromoacetate to give methyl diphenylphospho-

ryl acetate **180**, which was isolated in 71% yield in a one-pot reaction for two steps. (*Z*)-tributyltin acrylaldehyde **177** could be prepared via a three-step synthesis from propargyl alcohol **175**.[64] Propagyl alcohol **175** was first hydroaluminated with $LiAlH_4$ in THF. The resulting nucleophilic alanide could be reacted with *t*-tributyltin chloride in the next step to give (*Z*)-tributyltin acrylaldehyde **176** in 45% yield over two steps. After Dess-Martin oxidation, (*Z*)-tributyltin acrylaldehyde **177** was obtained in 60% yield. Once phosphonate **180** and aldehyde **177** were successfully synthesized, Ando's conditions were conducted with NaH at 0 °C, obtaining **178** after flash chromatography with 55% yield.



Scheme 4.23 *Synthesis of (Z, Z)-tributyltin diene **178***

Once having the (*Z,Z*)-tributyltin diene **178** in hand, the Stille couping had been tested (*Scheme 4.24*). By utilizing bis(benzonitrile)-dichloropalladium(II) as the catalyst in DMF, in conjunction with an excess of $Ph_2PO_2NBu_4$ (6 equivalents) as a tin scavenger to inhibit *Z/E* isomerization, (+)-**143** was generated with a 71% yield as a single isomer, exhibiting a ratio greater than 20:1, which is comparable as reported by Smith III.

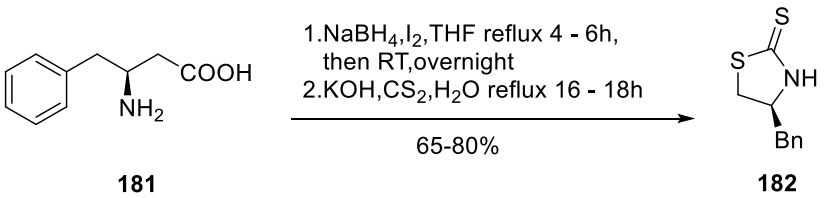


Scheme 4.24 *Stille coupling between **97** and **178***

4.2 Studies Towards Bicyclo[3.2.1]octane Building Block

4.2.1 Scale-up the Synthesis Route Developed by L. Michaelis

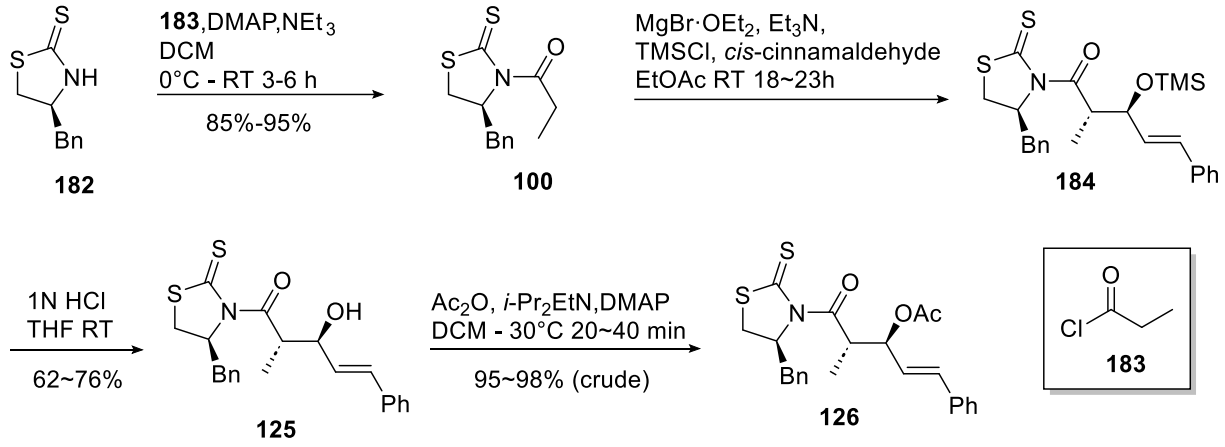
As mentioned earlier in Section 2.3, our research team has successfully devised a reliable approach for the synthesis of the bicyclo[3.2.1]octane building block **16**. Due to its limited accessibility, to conduct the experiments defined in Section 4.1 and explore the ultimate objective of total synthesis, it is imperative to upscale the previous method of synthesis.
According to L. Michaelis' dissertation[47], it has been identified that the most economically efficient initial substance is *(S)*-4-benzyl-1,3-thiazolidine-2-thione **182**. This compound can be made from the readily available and affordable *L*-phenylalanine **181**. The cost of the auxiliary is 230 € for 1 gram, which exceeds the affordability for direct acquisition. The synthesis can be conveniently conducted in two steps on a 100-gram scale, without the need for chromatographic purification. The only disadvantage in this context is the incidental generation of hydrogen sulfide. The reduction of *L*-Phenylalanine **181** is achieved by employing *in situ* generated diborane, resulting in the production of phenylalaninol. This process offers the advantage of being conducted securely and inexpensively on multigram scale. Unlike the reported, it was necessary to apply heat for an extended period after the iodine addition in order to achieve a consistently high yield. However, it is deemed superfluous to subject the mixture to reflux for a duration beyond 18 hours, as has been previously documented in other scholarly articles. The reflux process can be terminated upon the formation of milky suspensions in the mixture, typically occurring after around 4 to 6 hours. Subsequently, the mixture can be agitated at ambient temperature for an extended duration overnight. Afterwards, the phenylalaninol, in white paste form, underwent subsequent reactions without undergoing an additional purifying step.



Scheme 4.25 *Synthesis of (S)-4-benzyl-1,3-thiazolidine-2-thione 182*

According to Le Corre[65], in the subsequent cyclization process involving carbon disulfide in a caustic potash solution, the addition of carbon disulfide to the amino group occurs initially.

Following the removal of hydrogen sulfide, the process of cyclization can take place, resulting in the formation of auxiliary **182**. An alternative possible approach is the hydroxyl group undergoes attachment with another molecule of carbon disulfide. This results in the formation of a leaving group, which facilitates the process of cyclization through a sulfur atom, leads to the formation of **182**. Multiple scale-up studies have demonstrated that the concentration of alkali has a substantial effect on the yield. The recommended concentration range for potassium hydroxide is 0.8 to 1.2 mol/L. Following a reflux process lasting around 16-18 hours, the color of the reaction mixture has transitioned from a red plum hue (referred to as kobai-iro) to either a transparent yellow or a transparent brilliant green shade. After neutralization of the reaction solution using hydrochloric acid, the auxiliary **182** can be easily extracted from water with DCM and further purification by recrystallization from ethanol.

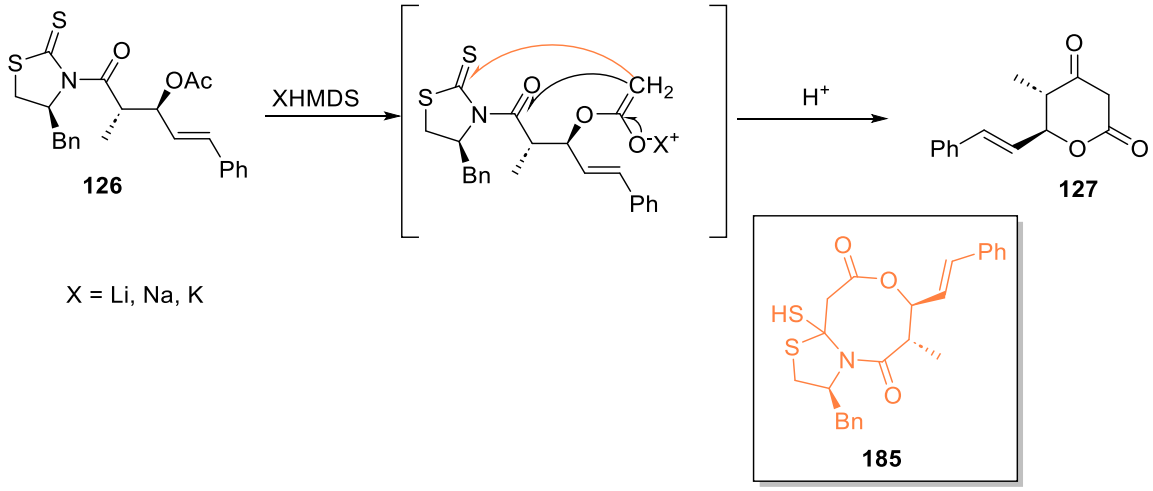


Scheme 4.26 *Synthesis of* ***126***

In contrast to the L. Michaelis' dissertation, milder conditions, wherein without using *n*-BuLi, has been employed for the synthesis **100**. The reaction was initiated by the use of a catalytic amount of DMAP, which was afterwards followed by the addition of triethylamine and propionyl chloride at 0°C. The present condition exhibits favorable characteristics for scalability, primarily because of its ability to be executed at room temperature. Additionally, if required, the purification process can be easily facilitated through recrystallization from acetonitrile after aqueous work-up, thus enhancing its feasibility for scale-up. The diastereoselective synthesis of anti-aldol product **184** is achieved by an *anti*-aldol reaction that was originally developed by Evans *et al.*[40], using 10-mol% $MgBr{\cdot}OEt_2$, cinnamaldehyde, and triethylamine. Under these conditions, a state of equilibrium is established between aldol and *retro*-aldol reactions. Thus, TMSCl has been utilized to selectively sequester and eliminate the anti-aldol product from the equilibrium state. During the experimental practicing, it was observed that

less than 10 mol% catalyst was inadequate, resulting in the recovery of the *retro*-aldol product only. Crude **184** has been used directly under acid conditions to cleave the TMS-protecting group to obtain **125**. In the context of multi-gram scale, it is required to eliminate the excess of cinnamaldehyde by flash chromatography. Failure to do so might impede the subsequent acylation reaction.

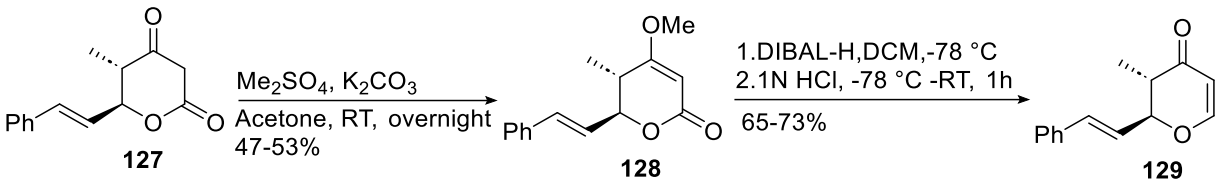
The optimal acetylation conditions for **126** is below -30 °C with Hünig's base, acetic anhydride, and DMAP, which yields NMR pure product with a minor by-product shown on TLC. The crude product was cyclized directly without further purification, and an exact yield was not determined at this point. It is worth noting that L. Michaelis has suggested that the purification step may be omitted to save time.



Scheme 4.27 *Dieckmann condensation for ketolactone **127***

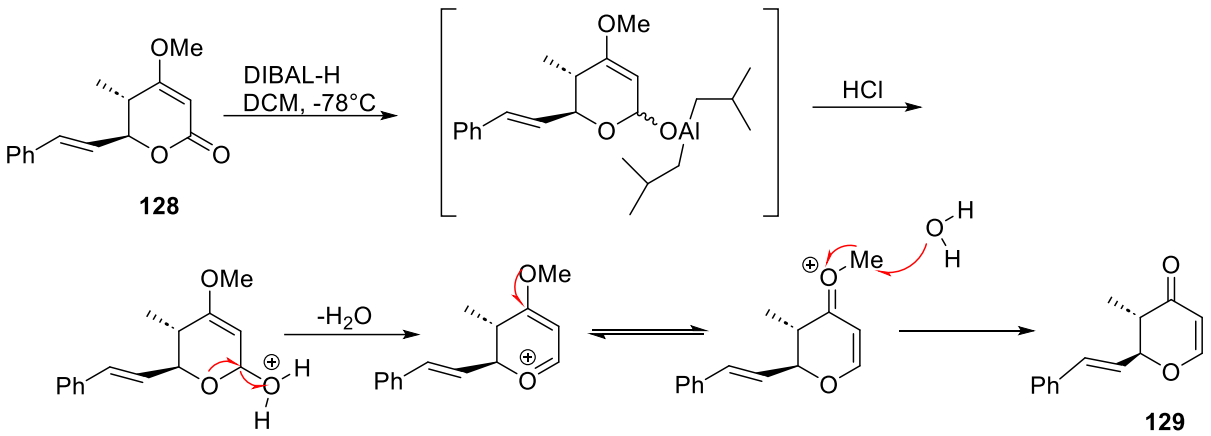
L. Michaelis found that the subsequent cyclization process indicated that the combination of NaHMDS as the base and THF as the solvent was the most advantageous. The conversion process was deemed complete after the addition of approximately two equivalents of base. However, other hexamethyldisilazide bases, such as LiHMDS and KHMDS, have also been explored in the context of scale-up investigations. In contrast to L. Michaelis' dissertation, it is shown that all hexamethyldisilazide bases have the potential to generate the desired compound **127**, as evidenced by identification using ^{1}H NMR spectroscopy. However, it is certain that all hexamethyldisilazides will certainly produce the byproduct **185** due to the enolates attack on the auxiliary, as reported by H Leijonmarck *et al*[66] (*Scheme 4.27*). For workup, the pH of the solution was initially reduced using a 1 N HCl/methanol solution, ensuring the separation of ketolactone and auxiliary with byproduct **185**. Both ketolactone and the slightly acidic

auxiliary were recovered by extraction with a saturated potassium carbonate solution. Following the process of re-acidification of the water extraction, the resultant product is the crude ketolactone with slightly acidic auxiliary and traces **185** in THF-water mixture. While KHDMS has demonstrated a higher yield, ranging from 5-10% more compared to NaHDMS, in milligram scale tests. NaHDMS possesses a distinct edge when it comes to multi-gram scale production. This benefit lies in its ability to be easily prepared within a timeframe of 5 hours by heating hexamethyldisilazane and NaH neat to 120-130 °C. It provided a great economic advantage during the constraints of logistics. Therefore, Dieckmann condensation reaction was performed using NaHDMS, resulting in a product with yield up to 60% in multi-gram scale, after purification by chromatography. To save time, considering the potential occurrence of keto-enol tautomerism, it is feasible to omit chromatographic purification at this particular stage, especially when working on multi-gram scale. Consequently, the unpurified ketolactone proceeded with direct methylation using dimethyl sulfate and potassium carbonate to obtain **128**.



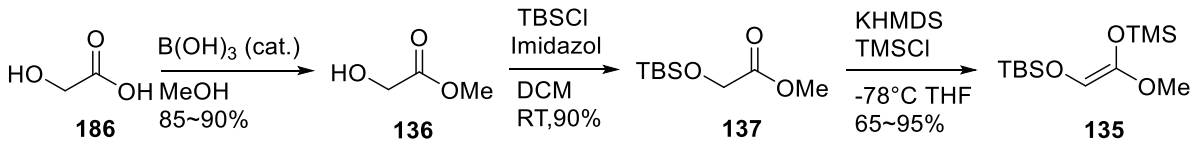
Scheme 4.28 *Synthesis of lactone core **129** from dieckmann condensation intermediate*

Following an overnight methylation process conducted at room temperature, the vinylogous ester **128** underwent reduction using DIBAL-H, resulting in the formation of dihydropyranone **129** with a yield ranging from 65% to 73%. In terms of its mechanism, the addition of a DIBAL-H molecule occurs initially to the lactone. Upon the introduction of hydrochloric acid, a lactol is generated from the pre-existing intermediate. This lactol is promptly protonated and likely transformed into an oxonium ion, accompanied by the liberation of a water. Finally, an α, β-unsaturated carbonyl group is formed yielding a functionalized pyranone **129**. However, it should be noted that the mechanism also suggests that an excessive amount of DIBAL-H has the potential to over-reduce compound **128**, resulting in the formation of a ring-opening byproduct (*Scheme 4.29*). This particular by-product has the potential to significantly impact the next Mukaiyama-Michael reaction. Fortunately, the compound **129** can be effectively refined by a two-solvent recrystallization method using pentane and diethyl ether. This process yields colorless needle-shaped crystals. The mother liquor, which is either yellow or bright-yellow in color, can be purified by flash chromatography.



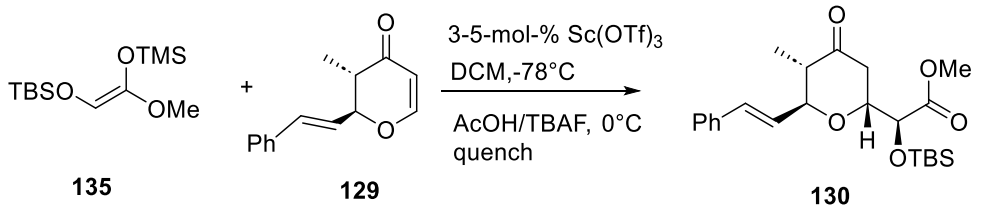
Scheme 4.29 *Possible mechanism for the formation of* ***129***

With the enhanced availability of the requisite dihydropyran, it became viable to commence the upscaling of the obligatory ketal. The aforementioned ketal has been reported and can be conveniently amalgamated through a sequential procedure commencing with methyl glycolate. TBS-protection of methyl glycolate, a reaction with KHMDS and TMSCl leads to the formation of the TMS ketal **135** (*Scheme 4.30*). This intermediate compound can subsequently participate in further processes. The first reported yield of 86% for the synthesis of the ketal compound, as reported in the literature, could not be reproduced. Nevertheless, it was possible to increase the initial yields of 30-40% to a greater percentage by implementing a modified water phase work-up technique. In practical, it has been observed that compound **135** achieves an acceptable level of purity after the evaporation of solvent, as determined by the analysis of ^{1}H NMR spectrum. Hence, when considering quantities beyond 50 grams, the utilization of vacuum distillation purification can be disregarded. In addition, a borane acid catalyst reaction has been employed for the purpose of synthesizing methyl glycolate. This strategy offers a flexible method for obtaining ketene acetal, particularly in situations where logistical constraints may arise.



Scheme 4.30 *Synthesis of silyl ketene acetal* ***135***

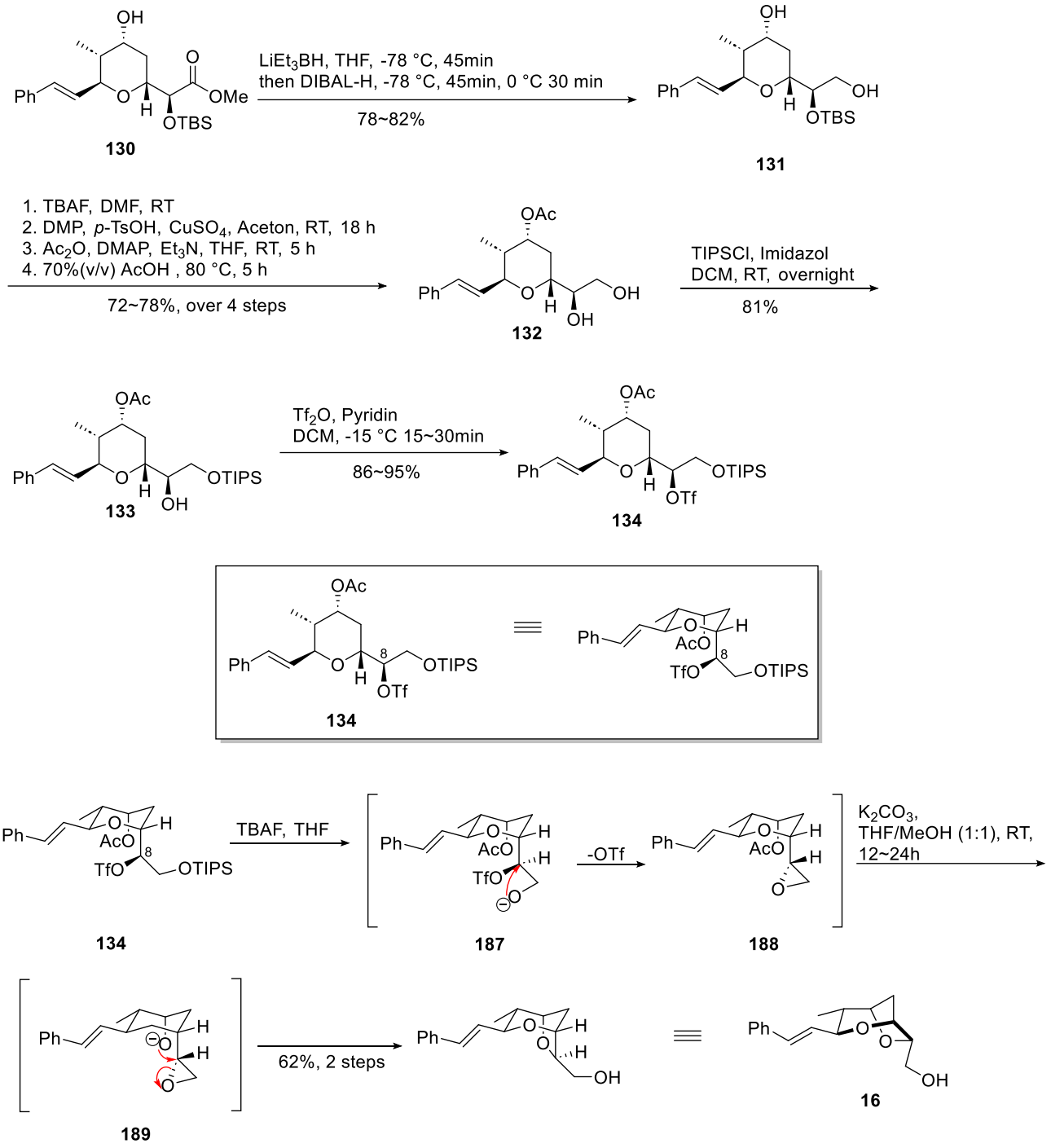
Subsequently, the Mukaiyama-Michael addition was established. In order to achieve the desired outcome, a combination of dihydropyranone **129** and 5-mol-% scandium triflate was introduced under -78 °C. According to L. Michaelis, the Mukaiyama-Michael addition can be achieved by gradually introducing a diluted solution of the ketal in dichloromethane. However, this method proves to be inadequate for achieving complete consumption of the starting material on a multigram scale. In such cases, it is necessary to add an additional, unspecified quantity of the silyl ketal until the starting material is practically undetectable using thin-layer chromatography. But the term "gradually adding" or "very slowly" lacks a clear and precise definition. Hence, this particular step poses the greatest challenge in the process of scaling up. After conducting many screenings, an optical condition suitable for scales over 15 grams has been created. The experimental procedure involved the gradual addition of approximately 6-10 equivalents of ketal using a syringe pump at a flow rate up to 6 ml/h. This addition was carried out in a mixture containing well-diluted **129** and 5 to 10-mol-% scandium triflate at -78 °C. The quantity of **129** can be fully consumed. A colorless oil was obtained after flash chromatography, which then transformed into colorless crystals when left at room temperature overnight.



135 **129** **130**

Scheme 4.31 *Mukaiyama-Michael reaction for coupling **129** and **135***

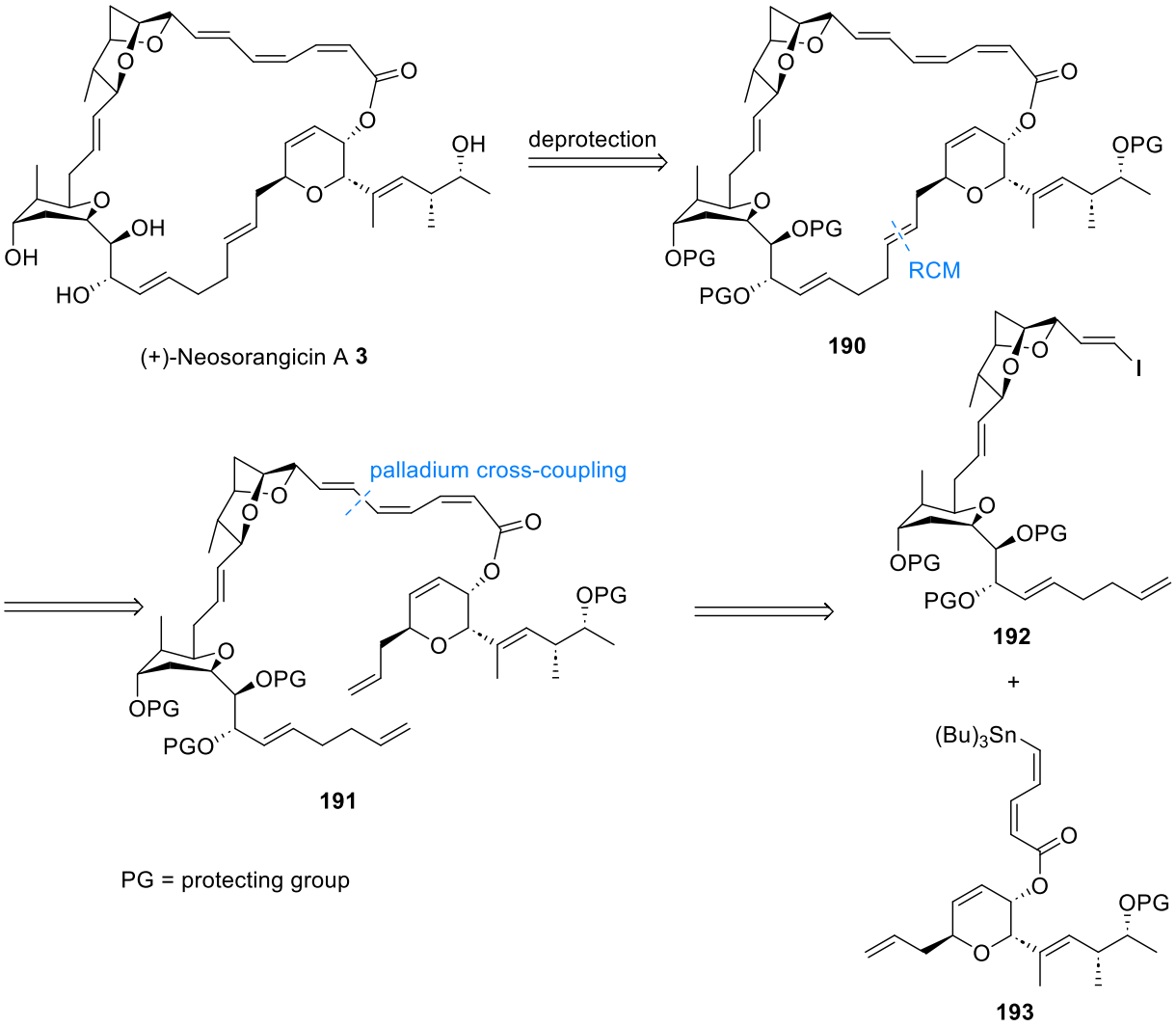
The ring closure to tetrahydropyranone was performed using tetrahydropyranone **130**, following L. Michaelis' protocol. The technology operates effectively at a multi-gram scale without requiring any modifications. It is important to acknowledge that the protecting group technique from **130** to obtain **16** cannot be operated with trisylation like Smith III[10] did, because the wrong configuration would result (*Scheme 4.32*).



Scheme 4.32 *Ring closure to furan from* ***130***

4.3 "Endgame" of (+)-Neosorangicin A

4.3.1 Retrosynthesis Planning



Scheme 4.33 *Retrosynthesis of (+)-neosorangicin A* ***3***

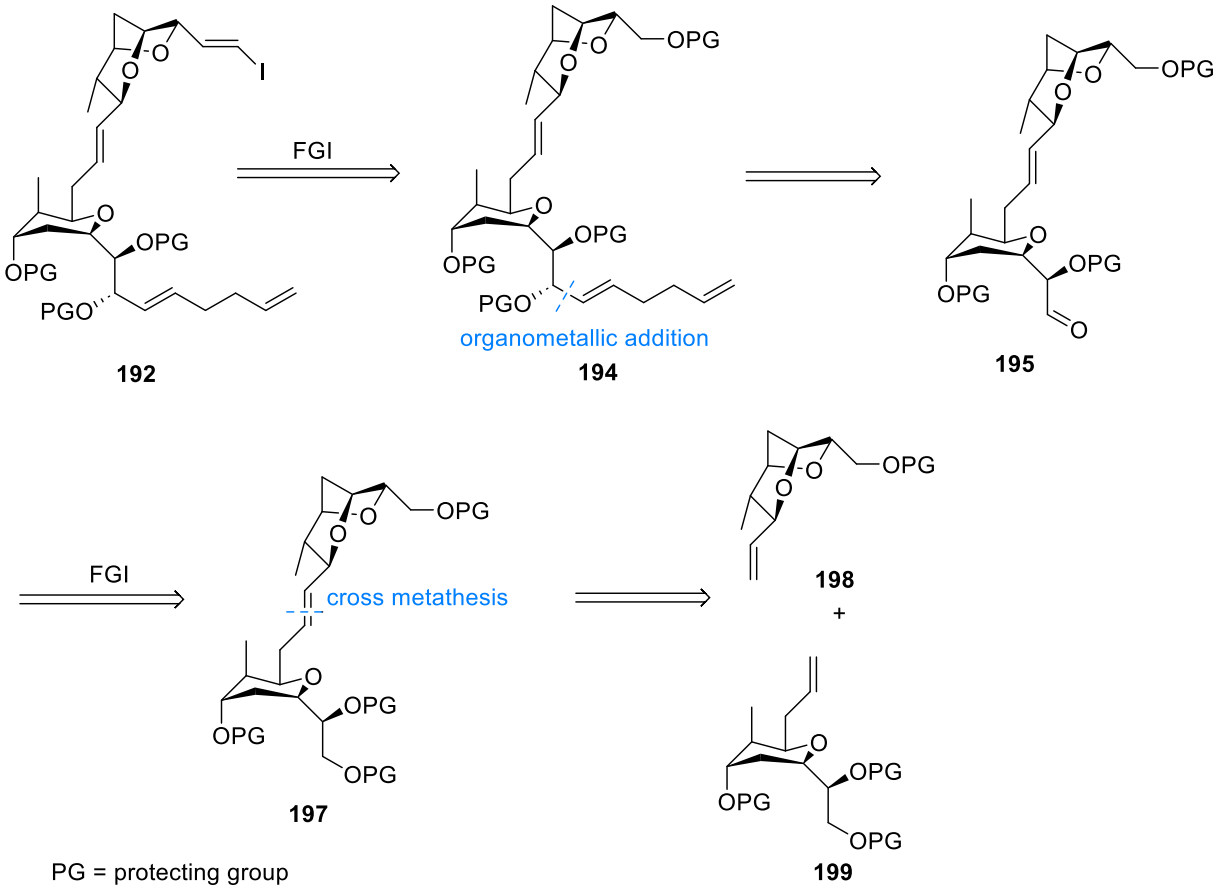
After many attempts with collaborators, we finally chose the following strategy for retrosynthesis analysis. The "end game" of (+)-neosorangicin A **3** should proceed via ring closing metathesis (RCM) and a final global deprotection of all protecting groups (*Scheme 4.33*). Under suitable reaction conditions, it should be possible to remove all three protecting groups simultaneously. In the critical ring closing metathesis, a smooth transformation is expected including a preference for the required (*E*)-isomer. RCM precursor **191** is to be synthesized from vinyl iodide **192** and tin diene ester **193** using a modified Stille coupling should provide the full

carbon skeleton of (+)-neosorangicin A. In this process, possible isomerization of the (*Z*) double bonds was primarily suspected as a potential source of problems.

4.3.2 Connecting BCO and THP Fragments via Cross-metathesis

4.3.2.1 Retrosynthesis Planning

Vinyl iodide **192** was obtained under suitable conditions via cross-metathesis from BCO ether **198** and THP ether **199** (*Scheme 4.34*). A stereoselective organometallic addition should add the C6 side chain to aldehyde **195** and provide the secondary alcohol in the correct configuration. After removal of the protecting group, the diol function should be protected with an appropriate protecting group to allow orthogonal removal at the late stage of the synthesis. Aldehyde **195** was synthesized from cross-metathesis product **197** via a one-pot deprotection/oxidation sequence. BCO ether **198** and THP ether **199** are expected to be prepared via two respective linear synthetic routes over 19 steps and 15 steps.



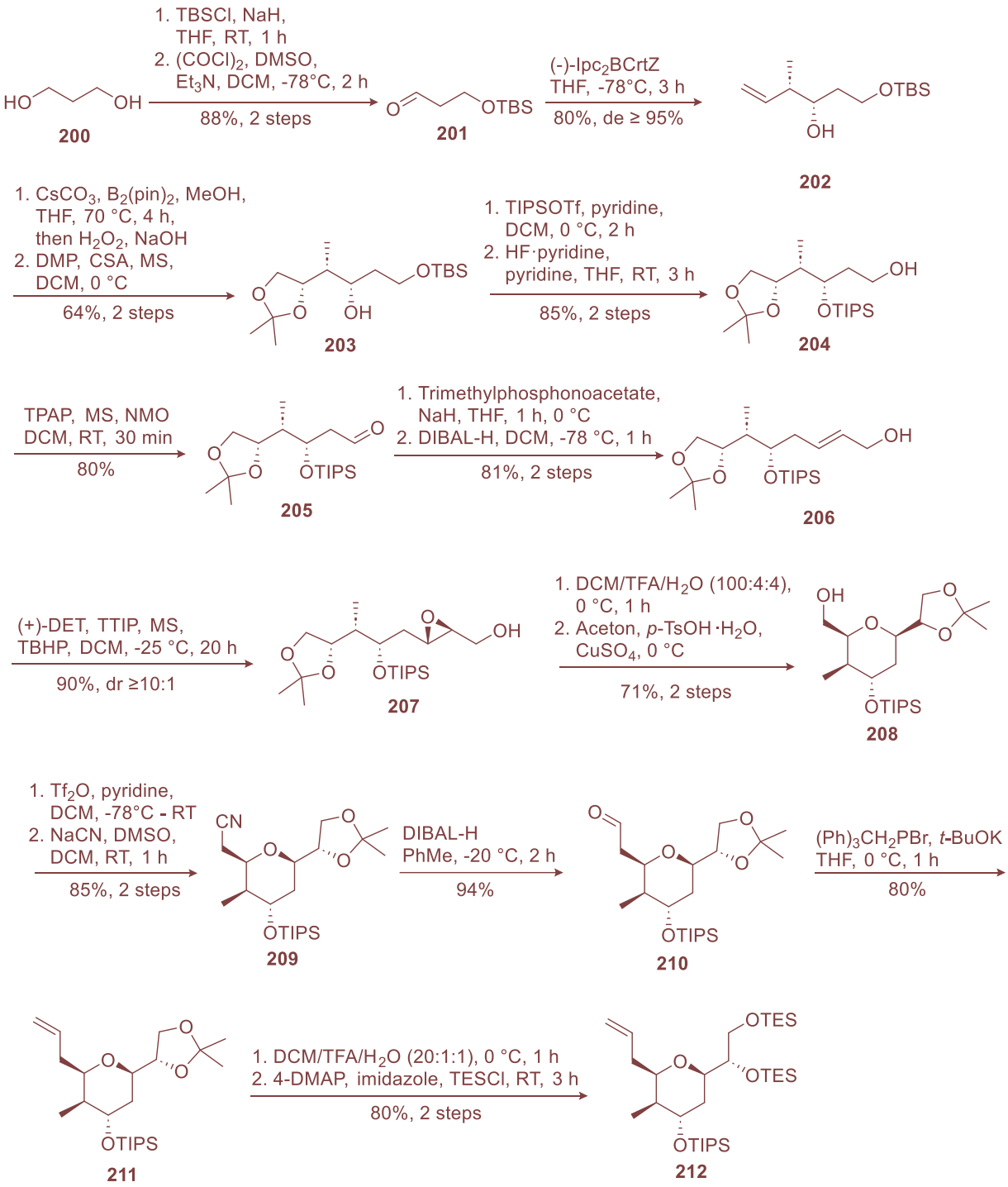
Scheme 4.34 *Retrosynthesis of Vinyl iodide* ***192***

4.3.2.2 Synthesis of the Tetrahydropyran Fragment 212

The new synthesis route of THP fragment **212** was carried out from our group by M. Munt[67] and will be briefly summarized here (*Scheme 4.35*). The process commences with mono-silylation of propanediol **200**. Upon treatment with NaH, monosodium salt is generated by deprotonation and forms a gray precipitate, effectively inhibiting any subsequent deprotonation and silylation reactions. The alcohol, which was mono-silylated, was directly oxidized under Swern conditions, resulting in the formation of aldehyde **201** with a yield of 88% across two sequential steps. Homoallyl alcohol **202** was synthesized through the utilization of a crotylation reaction as reported in the publication authored by H. C. Brown *et al*[68]. with a yield of 80% and a diastereomeric excess of de ≥ 95%. The stereoselective dihydroxylation method, as described by P. Morken *et al*. in a publication from 2014[69], was employed to insert the alcohol functional groups of homoallyl alcohol **202** in the appropriate configuration. To facilitate the subsequent differentiation of the four alcohol functionalities, a strategic decision was made to selectively protected the triol at the 1,2-diol position using dimethylacetonide. The experiment yielded **203** with a percentage of 64% after two steps. The hydroxyl group of acetonide **203**, which is a secondary alcohol, was protected by converting it into a TIPS ether using pyridine and TIPSOTf. Next, TIPS-protected **203** was subjected to direct treatment with an HF-pyridine complex, along with the addition of pyridine, in order to cleave the primary TBS ether. These two steps resulted in 85% yield of **204**. The Ley oxidation[70], known for its ease of performance, has been employed for the conversion of **204** to the aldehyde **205** effectively. The observed yield of the process is approximately 80%. The aldehyde **205** was subsequently transformed into the α, β-unsaturated carboxylic acid methyl ester by the utilization of a Horner-Wadsworth-Emmons[71] reaction. Aferwards, the (*E*)-α, β-unsaturated carboxylic acid methyl ester was subjected to reduction utilizing DIBAL-H at -78 °C, resulting in the formation of the allyl alcohol **206**. The use of Sharpless asymmetric epoxidation was deemed appropriate for the introduction of the final two stereocenters in THP fragment **212**. Under the conditions of -25 °C for a duration of 20 hours in DCM, it was possible to achieve the isolation of the required epoxide **207** with a notable selectivity of up to 10:1 and an exceptionally high overall yield of 90%.

Following the successful preparation of an appropriate quantity of epoxide **207**, the functionalized THP ring was formed using a mixture of DCM, TFA, and H_2O in a volume ratio of 100:4:4 at 0 °C. This reaction provided satisfactory results in terms of product yield. The reaction occurs spontaneously in a 6-*exo*-*tet* manner, as proposed by the Baldwin[72] rules. The 1,2-

diol functionality of the THP fragment was protected by introducing an acetonide group, resulting **208** with 71% yield after two steps and flash chromatography. The alcohol **208** underwent a successful triflation process, resulting in the formation of the desired triflate. The triflate was converted into nitrile **209** by a substitution reaction using NaCN in DMSO.

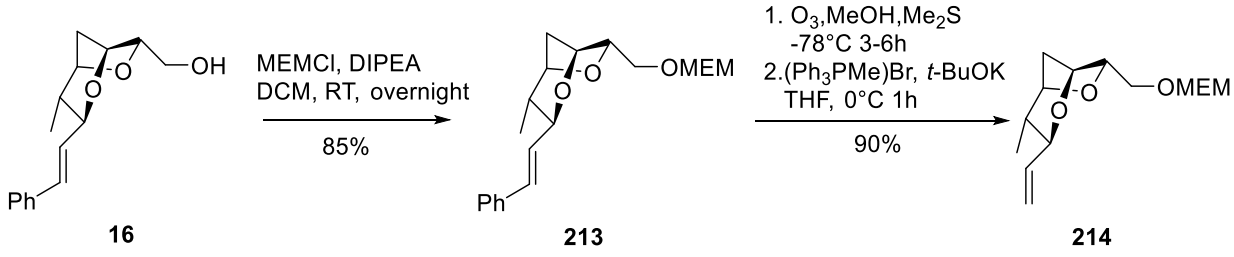


Scheme 4.35 *Synthesis route of THP fragment* ***212*** *(red = taken from collaborator)*

The nitrile **209** was subsequently subjected to reduction by gradually adding DIBAL-H -78 °C, resulting in the formation of aldehyde **210** with a high yield exceeding 90%. Olefin **211** was later synthesized through Wittig reaction, utilizing methyl triphenyl phosphonium bromide and *t*-BuOK as the base, resulting with a yield of 81%. To accomplish the synthesis of THP fragment **212**, it was necessary to change the protecting group again using a more robust ketal for subsequent synthesis. A mixture of DCM, TFA, and water in a volume ratio of 20:1:1, was utilized to cleave the acetonide at 0 °C. Subsequently, the 1,2-diol was protected using TESCl, following the methodology described by Crimmins *et al.*[17]. This synthetic approach yielded compound **212** in 80% yield after two steps. The overall yield across all 19 steps is 8%.

4.3.2.3 Studies of Cross-metathesis of THP Fragment 212 and BCO Fragment 214

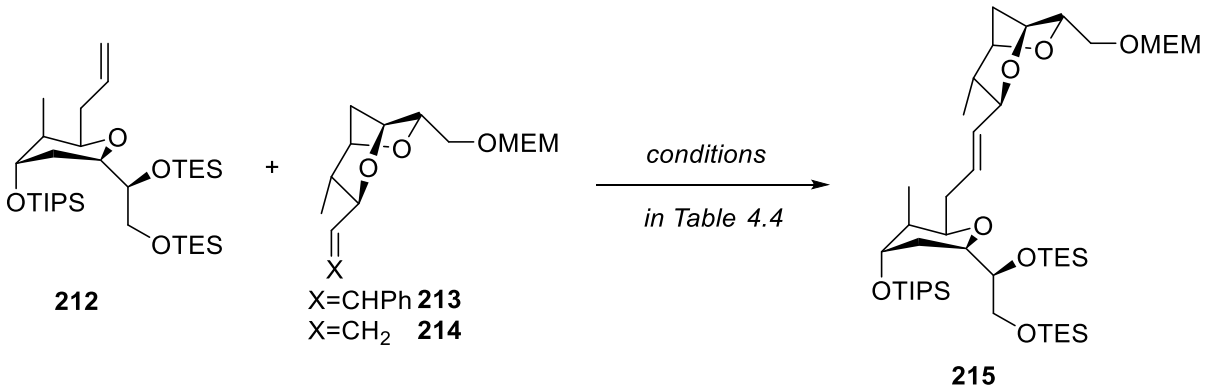
Following the methodology proposed by Crimmins *et al.*[17], we utilized cross-metathesis to link the BCO moiety with the THP moiety. Therefore, it is crucial to modify the BCO fragment **16**. The alcohol was protected as MEM ether through the utilization of MEMCl. The phenyl group was cleaved using ozonolysis, followed by a Wittig reaction to provide the terminal olefin as precursor for metathesis, which theoretically provides the highest reaction rate and selectivity[73]. To acquire the MEM ether **213**, a solution is prepared by dissolving **16** and DIPEA in DCM, which is then followed by the addition of MEMCl. This protection exhibited with slightly high yield, although with an extended reaction time. No noticeable reduction in time was observed while increasing the quantity of base and using either MEMCl or DMAP. The MEM ether **213** was dissolved in methanol and exposed to ozone at -78 °C. Upon addition of Me_2S, the mixture gradually elevated approaching room temperature for an additional period. In contrast to the report, ozonolysis required shorter time, showed by TLC analysis that the conversion of compound **213** was fully completed within a shorter period of 3-6 hours. The resulting aldehyde was utilized in a Wittig reaction using methyltriphenylphosphonium bromide and *t*-BuOK at 0°C. This reaction gave the terminal olefin **214** with a yield of 90% over 2 steps.



Scheme 4.36 *Synthesis of BCO-MEM ether fragment* ***214***

With MEM ether **214** and THP fragment **212** in hand, we conducted an initial evaluation of cross metathesis on a 10 mg scale. The initial attempts proved unsuccessful. The cross-metathesis product was not obtained until the reaction was transferred to a glove box and the catalyst was dissolved in toluene and added in portions. The molar yield, calculated concerning the THP fragment **212** (same as below), was 67%. This suggests that solvent deoxygenation is crucial. Furthermore, there were no instances of homodimer products observed during this stage. In addition, apart from cross-metathesis with **214** at this stage, there was also an attempt to directly **213** in a cross-metathesis to shorten the sequencing. However, the reaction involving **213** reaches a stagnant state and heating did not enhance its formation (*see Table 4.4, entry 4*). A possible explanation for this phenomenon is that the products of metathesis have reached some kind of equilibrium. Meanwhile, the homodimer of THP **212** can be observed in the crude ^{1}H NMR spectrum.

Upon discovering the optimal conditions, we attempted to synthesize a quantity of **215** up to gram scales. Unfortunately, identical conditions failed to replicate the comparable molar yield. Just 45% of **215** had been isolated, with 12% homodimer of **212.** Surprisingly, no homodimer of **214** can be isolated. Therefore, we made further attempts on a larger scale by changing the solvent, increasing the amount of BCO ether **214**, and the quantity of catalyst, heating, and other parameters in order to eliminate the homodimer and reduce the duration of the reaction. Thus, we made other attempts on a larger magnitude by changing the solvent, further increasing the amount of BCO **214**, increasing the quantity of catalyst, using heat, and other methods to eliminate the formation of homodimers and reduce the duration of the reaction. The best conditions at this scale were determined as follows: To a degassed toluene solution containing 1.5 equivalents of BCO **214**, at concentration of roughly 0.4 mmol/ml, a diluted THP **212** solution with a concentration of around 0.2 mmol/ml at room temperature was slowly added to the BCO **214** solution drop by drop, along with the 10 to 15-mol-% G2 catalyst dissolved in solvent with concentration of around 0.1 mmol/ml, using a syringe pump. The duration of this process was around 6 hours. Afterwards, the reaction mixture was allowed to proceed at ambient temperature for approximately 12 hours, resulting in the formation of the cross-metathesis product **215** with a molar yield of 60%. The homodimer of **212** is present in the crude ^{1}H NMR of the unpolar chromatography fraction, along with unreacted **212**. However, the molar yield of the homodimer, as evaluated by ^{1}H NMR, was less than 10%. Homodimer of **212** can be easily transformed to **212** through the same metathesis procedure. All attempted representative conditions are summarized in the *Table 4.4*.



Scheme 4.37 *Cross metathesis between THP* ***212*** *and BCO* ***214*** *or* ***213***

Table 4.4 *Conditions of cross metathesis between THP* ***212*** *and BCO* ***214*** *or* ***213***

Entry	conditions	CM product 215 yield	Homodiemer of THP 111 yield
1	1.0 eq. **212**, 1.2 eq **214**, 5% G2 PhMe, RT, 10 mg scale, 16h	67%	none
2	1.0 eq. **212**, 1.2 eq **214**, 5% G2 PhMe, RT, gram scale, 16h	45%	45%
3	1.0 eq. **212**, 1.2 eq **214**, 10% G2 DCM, microwave 100℃, 10 mg scale, 0.5h	40%	22%
4	1.0 eq. **213**, 1.2 eq **214**, 5% G2 PhMe, RT, 10 mg scale, 16h	35%	25%
5	1.0 eq. **212**, 1.5 eq **214**, 10% G2 in three portion, PhMe, RT, gram scale, 12h	55%	33%
6	1.0 eq. **212**, 1.5 eq **214**, 5-10% G2 added simultaneously, PhMe, RT, gram scale, 6+12h	60%	<10% by ^{1}H NMR

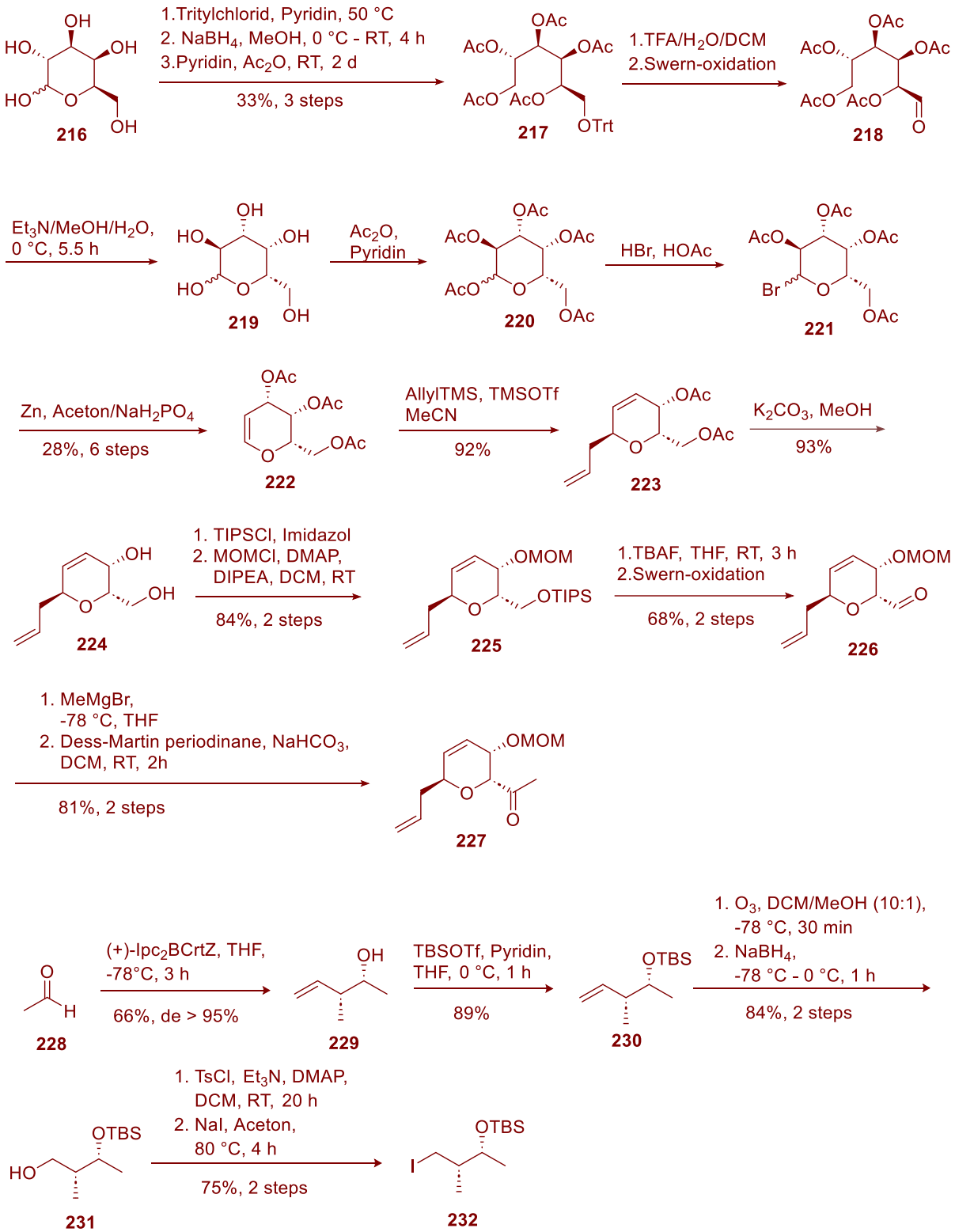
4.3.3 Elaboration of the Complete Carbon Skeleton of (+)-Neosorangicin A 3

4.3.3.1 Synthesis of the Dihydropyran Fragment 193

Following the successful cross-metathesis reaction, the resulting coupling product **215**, was obtained from the combination of BCO fragment **214** and THP fragment **212**. Another coupling partner which contains the fully elaborated DHP fragment **193** must be synthesized. The synthesis of this DHP core was initially established and subsequently advanced R. Stoykova[74] and M. Munt[67]. Consequently, an overview of the synthesis will be provided.

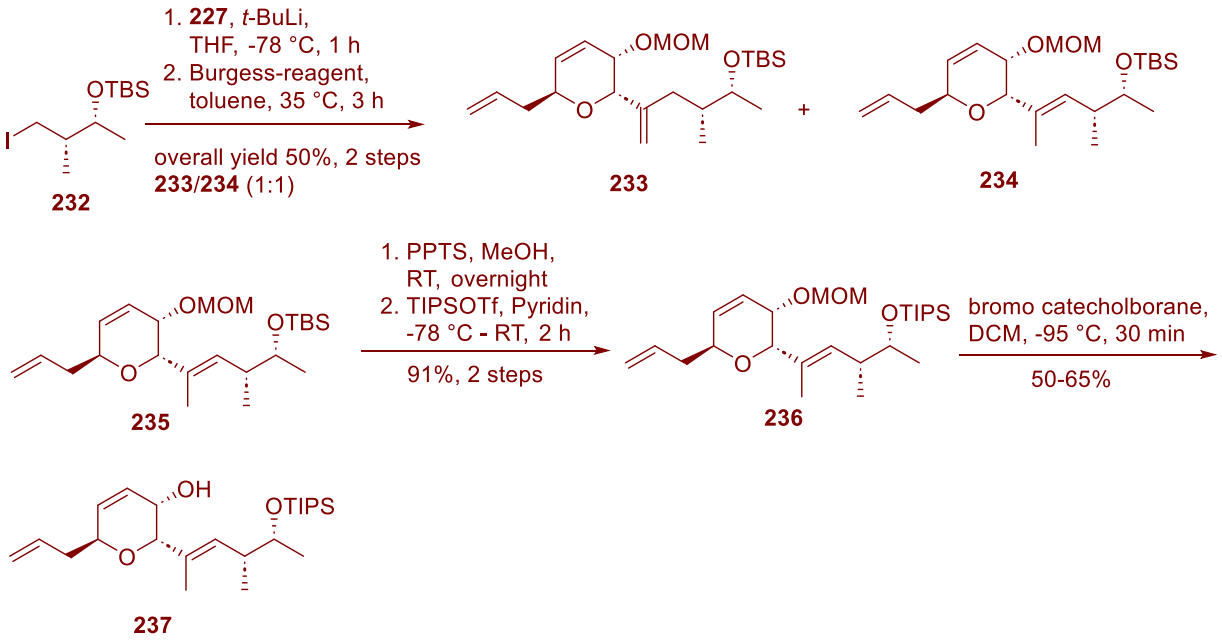
The synthesis initiates by inverting the stereocenters of naturally existing D-galactose **216**, resulting in the formation of L-galactose **219** with a series of six synthetic steps. Otherwise, it would be a very expensive starting material. The first prescription was published by Orii *et al.*[75], and was subsequently refined for our synthesis to enhance both yield and practicality. The primary hydroxyl group of D-galactose **216** is firstly protected through a selective reaction with trityl chloride in pyridine at 50°C, resulting in the formation of a trityl ether. Afterward, the lactol function was reducted using sodium borohydride in methanol, followed by acetylation of the resulting free hydroxyl groups using acetic anhydride in pyridine. This synthetic pathway yielded compound **217** with 33% overall yield across the three-step process. The primary hydroxyl, which was protected by a trityl group, was effectively regenerated by using TFA and subsequently oxidized to aldehyde **218** employing Swern conditions. The method of Zemplén deacetylation[76] results in the restoration of the hemiacetal and yields L-galactose **219**. Afterwards, acetylation of all alcohol functionalities was carried out using acetic anhydride in the presence of pyridine, resulting in the formation of penta-acetate **220**. The reaction with HBr in acetic acid resulted in the substitution of an acetate group, ultimately yielding **221**. Dihydropyran **222** was obtained through reductive elimination of bromide in the presence of zinc. The synthesis of compound **222**, originating from compound **217**, can be achieved by a six-step process with a yield of 28% (*Scheme 4.38*).

The utilization of a Ferrier rearrangement[77] with allyltrimethylsilane, facilitated by TMSOTf, resulted in the stereoselective formation of allyl DHP core **223** in 92% yield . The deacetylation reaction resulted in the formation of diol **224** with a high yield of 93%. The primary alcohol group was selectively protected using TIPSCl and imidazole in dichloromethane, resulting in the formation of a TIPS ether. Compound **225** was obtained in following the preservation of the secondary alcohol function with MOMCl, in 84% yield over two steps. The cleavage of TIPS ether using TBAF resulted in the regeneration of the primary alcohol. This alcohol was oxidized using Swern conditions, leading to the formation of aldehyde **226** in 73% yield. Diastereomeric alcohols were obtained by a typical Grignard reaction using methyl magnesium bromide. These alcohols were subsequently oxidized with Dess-Martin periodinane, allowing in the direct formation of methyl ketone **227** without further purification. In summary, the synthesis of dihydropyran fragment **227** from D-galactose **219** involved a total of 17 steps, resulting in a yield of 4.3%. The synthesis of the functionalized side chain **232** can be achieved by a concise synthetic pathway consisting of six steps, exhibiting exceptional selectivity and an overall yield of 37%. The process commences with a Brown[68] crotylation of acetaldehyde **228** (as depicted in *Scheme 4.38*). Homoallyl alcohol **229** is produced with high selectivity



Scheme 4.38 *Synthesis of dihydropyran fragment* ***227*** *and side chain* ***232*** *(red = taken from collaborator)*

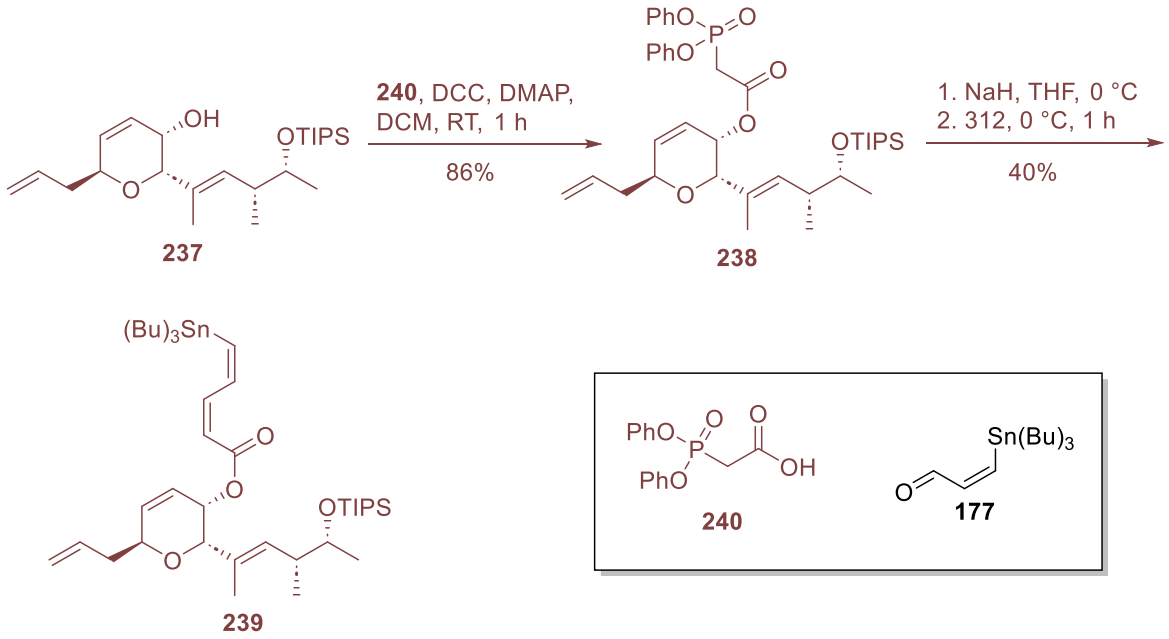
and a yield of 66%. The alcohol functionality was protected by employing TBSOTf in THF at 0 °C, resulting in the formation of TBS-olefin **230**. The ozonolysis reaction was conducted using a solvent mixture of DCM and methanol. A less harsh reducing agent, $NaBH_4$, was employed in the two-step process, resulting in a favorable yield of 89%. The alcohol **231** was initially subjected to tosylation, followed by the substitution of the resultant tosylate with NaI in acetone under reflux. This technique has demonstrated a substantial increase in yield, reaching a minimum of 75% of **232** after two steps.



Scheme 4.39 *Coupling of DHP core **227** and side chain **232** (red = taken from collaborator)*

Coupling of the two compounds, **227** and **232**, to introduce the trisubstituted (*E*) double bond in the correct geometry and acceptable yield is a challenge. many attempts had been tested such as Wittig reaction, HWE reaction, Julia-Kocienski olefination. But unfortunately, none of them effect as expected. Thus, after these sobering results, an organometallic addition of the side chain and subsequent dehydration of the resulting alcohol was tackled. Iodide **232** and methyl ketone **227** were dissolved in dry THF and cooled to -78 °C. Subsequently, *t*-BuLi was slowly added and stirred for 1 h at -78 °C. After aqueous workup, the crude product obtained was dissolved in dry toluene, Burgess reagent[78] was added and stirred for 3 h at 35 °C. Using this method, an overall yield of 50% was obtained over two steps at a ratio of 1:1 (**233**:**234**). Although selectivity is not achieved, a major advantage of this method is that the (*Z*)-isomer is not formed, which is inseparable from the (*E*)-isomer.

After having the coupled compound **235**, the MOM protecting group had to be selectively removed first. However, this selective cleavage could not be achieve under various conditions. Since double de-protection of the compound was often observed as a by-product, it was decided to replace the TBS group by the more stable TIPS group. Thus, TBS was cleaved with PPTS in MeOH. Then TIPSOTf and pyridine in DCM was used to introduce the TIPS protecting group. TIPS-protected DHP fragment **236** could thus be obtained in 91% yield over two steps. Compound **236** was dissolved in DCM, cooled to -95 °C, and 2 eq. of bromocatecholborane, dissolved in some DCM, was slowly added. With this method, alcohol **237** was isolated with a reproducible yield of 50-60%.



Scheme 4.40 *Last modification of **237** for Stille coupling (red = taken from collaborator)*

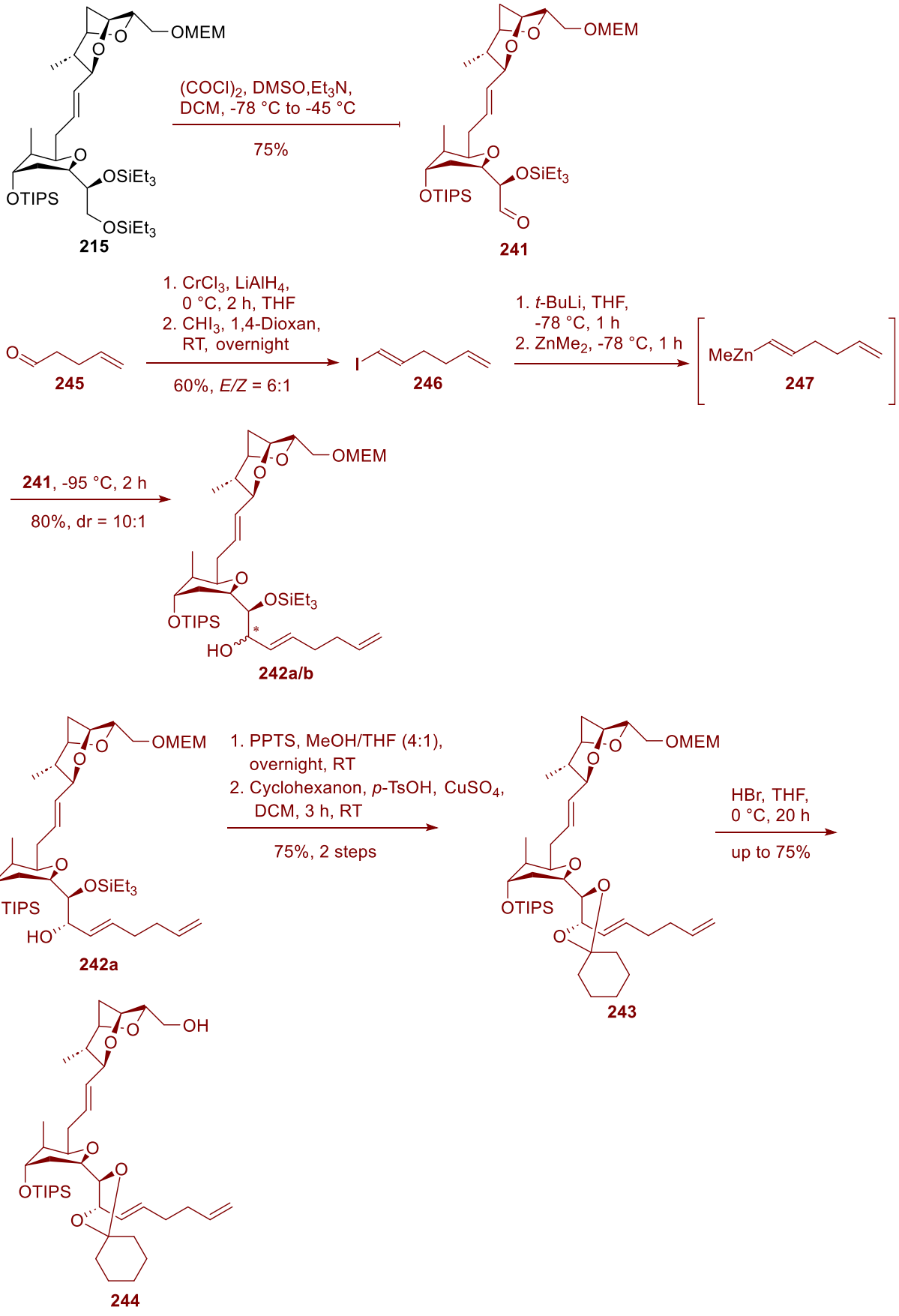
The last modification of **237** to get the precursor for the Stille coupling was done using the same conditions, we mentioned already in section 4.1.4. diphenoxyphosphorylcarboxylic acid **240** had to be synthesized first. Reaction of **240** with DHP alcohol **237** under Steglich esterification condition afforded compound **238** in excellent yield of 86%. For the next step, (*Z*)-tributyltin acrylaldehyde **177** was used. Phosphonate **238** was placed in dry THF and NaH was added. After stirring at 0 °C for 1 h, aldehyde **177** dissolved in dry THF was added to the deprotonated phosphonate. The desired (*Z,Z*)-tin dihydropyran diene ester **239** was obtained with a yield of 40% and a selectivity of *E/Z* = 1:2. The (*E*)-isomer can be easily recovered as DHP alcohol **237** after hydrolysis with K_2CO_3 in methanol. Thus, (*Z,Z*)-tin dihydropyran diene ester **239** was successfully synthesized over 24 steps with an overall yield of 0.22%.

4.3.3.2 Final Modifications of the Cross-coupled Fragment 215 and Stille Coupling for Achieving (*E,Z,Z*)-Triene System

After having the modified DHP fragment **239** for Stille coupling ready, the final modification of the cross-couped fragment **215** were performed to obtain vinyl iodide **192**. Cross-coupling product **215** was oxidized to aldehyde **241** under modified Swern conditions. For this, 5 eq of oxalyl chloride and 10 eq of DMSO were used. After 1 h at -45 °C, a complete deprotection/oxidation sequence was achieved. Cooling to -78 °C and slow addition of triethylamine afforded aldehyde **241** in 75% yield over two steps. Following the methodology of Crimmins *et al*.[17], the subsequent procedure involved the introduction of the zinc compound of vinyl iodide **246** into aldehyde **241** using a Cram-chelate controlled addition (*Scheme 4.41*). Here, vinyl iodide **246** underwent a transformation to generate the intermediate vinylzinc species **247**. Vinyl iodide **247** can be produced using a one-step process using 4-pentenal **245** and the Takai reaction[79]. The optimal selectivity/yield ratio was achieved through a series of optimization experiments using 3 equivalents of vinyl iodide, 6 equivalents of *t*-BuLi, and 4.5 equivalents of dimethylzinc in THF at a temperature of -95 °C. The diastereomeric alcohols **242a** can be obtained with an 80% yield and a selectivity of at least 10:1 favoring the correct diastereomer.

Before the deprotection of the MEM group could be envisioned, a change of protecting groups of the diol had to be performed in order to get a stable system to survive the MEM deprotection. First, PPTS in MeOH/THF (4:1) was used to remove the secondary TES group. Then cyclohexanone and PPTS in DCM at RT gave cyclohexenyl ketal **243** in 75% yield. Alcohol **244** could be isolated cleanly right away with HBr in THF at 0 °C. After some optimization work, a reproducible yield of up to 75% could be obtained with HBr (33% in acetic acid) in THF at 0 °C for 20 h. This is a very critical step and it is very important not to let the HBr concentration get above a threshold value, if possible, otherwise side reactions can be observed. This was achieved by slow addition at hourly time intervals. Also, the reaction mixture should be kept meticulously around 0 °C, otherwise HBr will react with THF in an acid-induced nucleophilic ring opening.

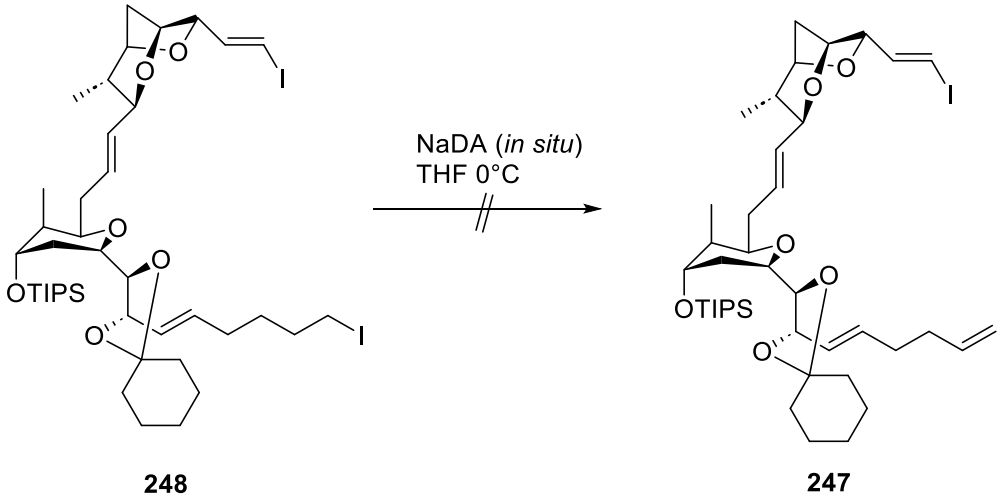
The primary alcohol function of **244** was then oxidized to an aldehyde under Parikh-Doering conditions (*Scheme 4.43*). This, because of its susceptibility to epimerization, was converted directly by Colvin rearrangement[80] to the terminal alkyne **245**. After several failed experiments, with very low yields, it was realized that residual pyridine or triethylamine from the previous oxidation strongly affects the Colvin rearrangement. For this reason, care must be



Scheme 4.41 *Modifications of the cross-couped fragment* ***215*** *part 1 (red = taken from collaborator)*

taken to thoroughly remove the amine. For the Colvin rearrangement, TMS-diazomethane was deprotonated with *n*-BuLi at -78 °C. After addition of the aldehyde and stirring for one hour, alkyne **245** could be isolated with an overall yield of 30-50% over two steps. Careful attention must be paid to water exclusion during the subsequent hydrozirconation.

The vinyl iodide **247** could actually be obtained via hydrozirconation of the triple bond followed by substitution of the intermediate vinyl metal species **246**. In this process, the Schwarz reagent was generated *in situ* in the presence of light and reacted with alkyne **245**, and the intermediate zirconium vinyl species **246** was formed. After the addition was complete, 3 eq. NIS were added and stirred again for 30 min at ambient temperature. To prevent hydrozirconation of the terminal olefin function in **245**, which leads to by-product **248**, an excess of 1.5 eq of Schwarz reagent must not be exceeded, the temperature should also be controlled when adding NIS, because NIS dissolves in THF under exothermic conditions. Vinyl iodide **247** could thus be synthesized up to 55% yield over two steps from alkyne **245**. The (*Z*)-isomer cannot be observed by this method for mechanistic reasons as we explored in Section 4.1.4. Thus, the final coupling product **247** was prepared in a 30-step synthesis with an overall yield of about 0.2%.

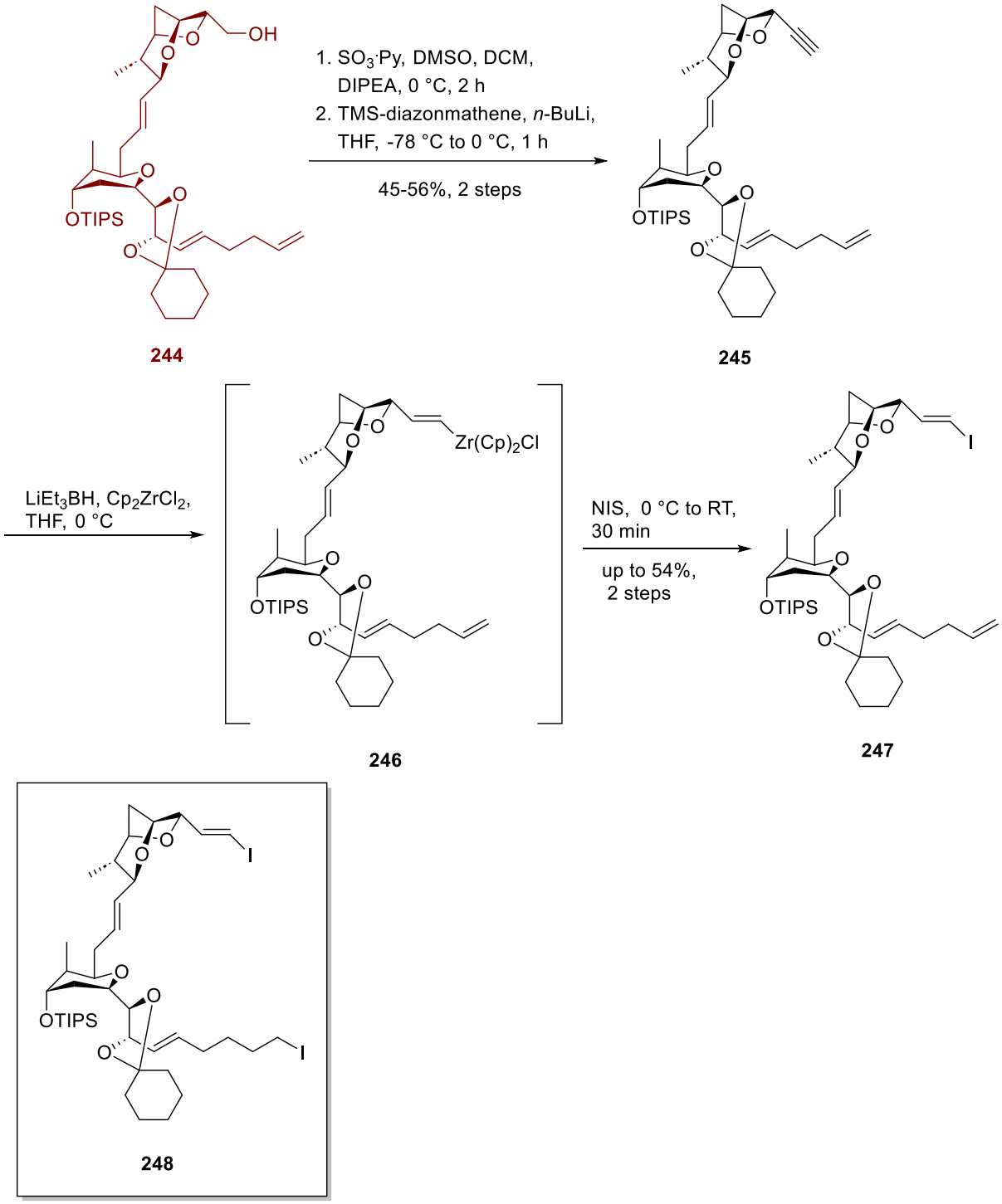


248 **247**

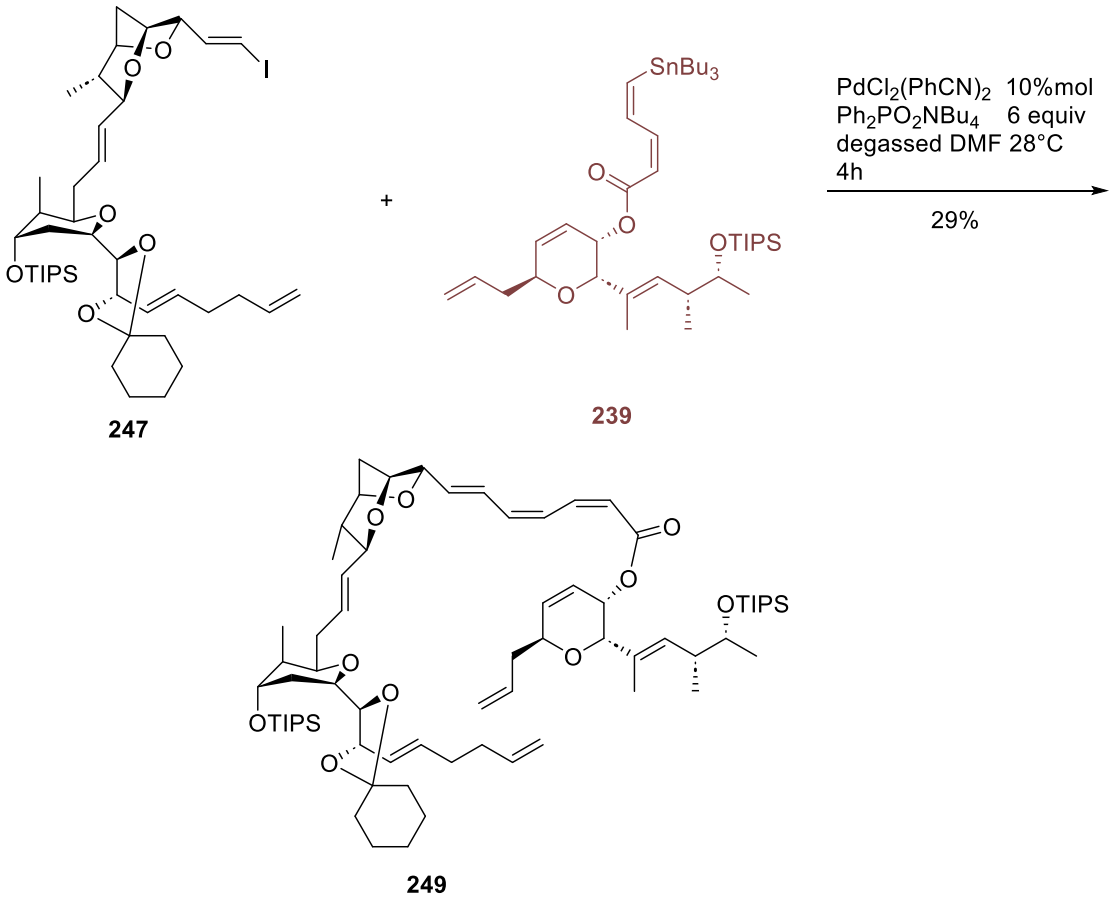
Scheme 4.42 *Elimination of **248***

Due to the challenging nature of acquiring **247**, we aimed to discover a method of converting the byproduct **248** into **247**. D. B. Collum *et al*. [81], published a technique for eliminating haloalkanes by employing NaDA produced *in situ* by the reaction of a sodium suspension and *N,N*-dimethylethylamine. Unfortunately, attempts to employ this approach did not produce the intended outcomes for **247**. Proton NMR studies indicated that this elimination process lacked selectivity. Furthermore, the current laboratory conditions do not allow for the separation of a

combination of **247** and **248**. Consequently, the retrieval of the byproduct had to be discontinued.



Scheme 4.43 *Modifications of the cross-couped fragment* ***215*** *part 2 (red = taken from collaborator)*



Scheme 4.44 *Stille coupling between* ***247*** *and* ***239***

After successfully modifying both fragments, the synthesis of (+)-neosorangicin A **3** entered its final phase. Compound **249** (*Scheme 4.44*) was synthesized using the Stille coupling method, which entailed the stepwise connection of vinyl iodide **247** and tin diene ester **239**. In order to reduce the probability of isomerization in the sensitive diene or triene system, the coupling technique included the addition of $Ph_2PO_2NBu_4$. The substance in concern had already been employed by Smith III[10] in the production of (+)-sorangicin A **1**, and we examined it in section 4.1.4. The reaction proceeded well, nevertheless, it is disappointing that the reported high yield of 90%, as found in Smith III model study, could not be reproduced. Although the result was quite modest, with a 30% yield. Considering the intricate molecular composition at play, this outcome can be deemed satisfactory. The collaborative endeavor has achieved the synthesis of the complete open-form carbon skeleton of (+)-neosorangicin A **3** in, including all carbon atoms and precisely generated 16 asymmetric centers! This offers the arena to the final step to close the complex 31-memberd macrolide ring of (+)-neosorangicin A **3** via RCM reaction.

5. Summary and Outlooks

5.1 Summary

The sorangicin family includes preclinical therapeutic candidates. These compounds usually affect Gram-positive pathogens but also inhibit Gram-negative pathogens. In the case of (+)-neosorangicin A **3**, the present findings and conclusions suggest that the synthesis of structural analogues of the sorangicin family may offer a new approach to treating rifampicin-resistant tuberculosis and other potential applications as medicinal chemistry advances. Developing an effective and scalable synthetic method that can create multi-grams of the target product is a highly important research subject.

The objective of this study was to develop a method that is both efficient and dependable in generating the (*E,Z,Z*)-triene structure that is observed in (+)-sorangicin A **1** and (+)-neosorangicin A **3**. In order to ensure that subsequent inquiries into the (*E,Z,Z*)-triene system, provide adequate material, it was necessary to expand the methodology outlined in Section 2.3. The possible approach to construct an (*E,Z,Z*)-triene system in coupling a metal-substituted (*E*)-olefin **137** to the iodide **142**. Alternatively, coupling halogen-substituted (*E*)-olefin on BCO fragment with a metal-substituted (*Z,Z*)-olefin could also be a viable method.

Several palladium-catalyzed coupling reactions have been investigated, including Suzuki[41], Negishi[42], and Sonogashira[43]. Nevertheless, the preliminary experiments yielded unfavorable results. Therefore, we engaged in systematic and rigorous model experiments to mitigate the influence of pollutants and other such variables. The model research of **152** determined that borylation of acetylene, which has an oxygen functional group at the α-position, is not feasible. While Negishi coupling showed success in subsequent modeling investigations, the outcomes could not be replicated on BCO fragments using the same conditions. A possible explanation is that the unique structure of the BCO fragment may act as a cage, grab the metal, preventing the transmetalation step of the coupling process to occur. Thus, attempts were made to couple a halogen-substituted (*E*)-olefin on the BCO fragment with a metal-substituted (*Z,Z*)-olefin. Moreover, this technique was replete with significant challenges. Eventually, we have to follow the path outlined by Smith, utilizing a Stille coupling as a method to construct the (*E,Z,Z*) system. The attempt was successful to obtain the (*E,Z,Z*) system represented in (+)-sorangicin A **1** and (+)-neosorangicin A **3**.

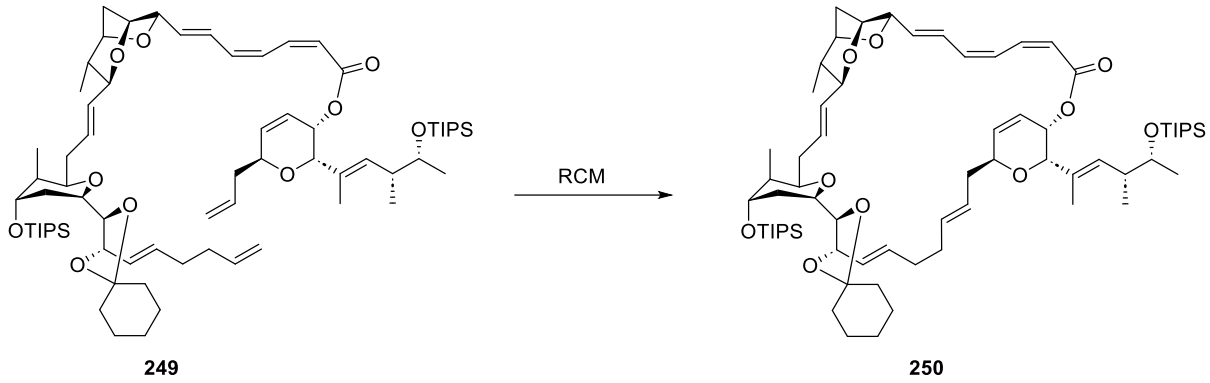
Due to the limited accessibility of BCO fragment **16**, scale-up experiments were conducted on the second-generation synthetic pathway which was developed by our group. The key step in this pathway involved the synthesis of the crucial intermediate **130** through the implementation of the Mukaiyama-Michael reaction. Ultimately, reaction conditions were discovered on a scale greater than 10 grams, thereby resolving unclear operating procedures that were present in previous studies.

Upon acquiring the essential fragments **212**, **214** and **239** in collaboration with M. Munt[67] and R. Stoykova[74] to achieve the total synthesis of (+)-sorangicin A **1** and (+)-neosorangicin A **3** in a convergent synthesis strategy, we employed cross-metathesis, as suggested by Crimmins *et al*.[17], to connect the BCO moiety **212** and THP moiety **239**, following their methods. After several attempts, the optimal conditions for this complex and important coupling were finally achieved. A gram-scale preparation of **215**, which is the key intermediate in the convergent synthesis strategy, was accomplished under these conditions with 60% yield.

With further modifications of **215**, the vinyl iodide **247** could actually be obtained via hydrozirconation of the triple bond followed by substitution of the intermediate vinyl metal species. The complete carbon skeleton of (+)-neosorangicin A **3** (*Scheme 4.44*) was synthesized using the Stille coupling method, which entailed the stepwise connection of vinyl iodide **247** and tin diene ester **239**. Despite the outcome being rather modest, with a yield of 30%. Given the complex molecular composition involved, this result can be considered satisfactory. The united effort has successfully accomplished the open-form of (+)-neosorangicin A **3** carbon skeleton synthesis, encompassing all carbon atoms and precisely created 16 asymmetric centers.

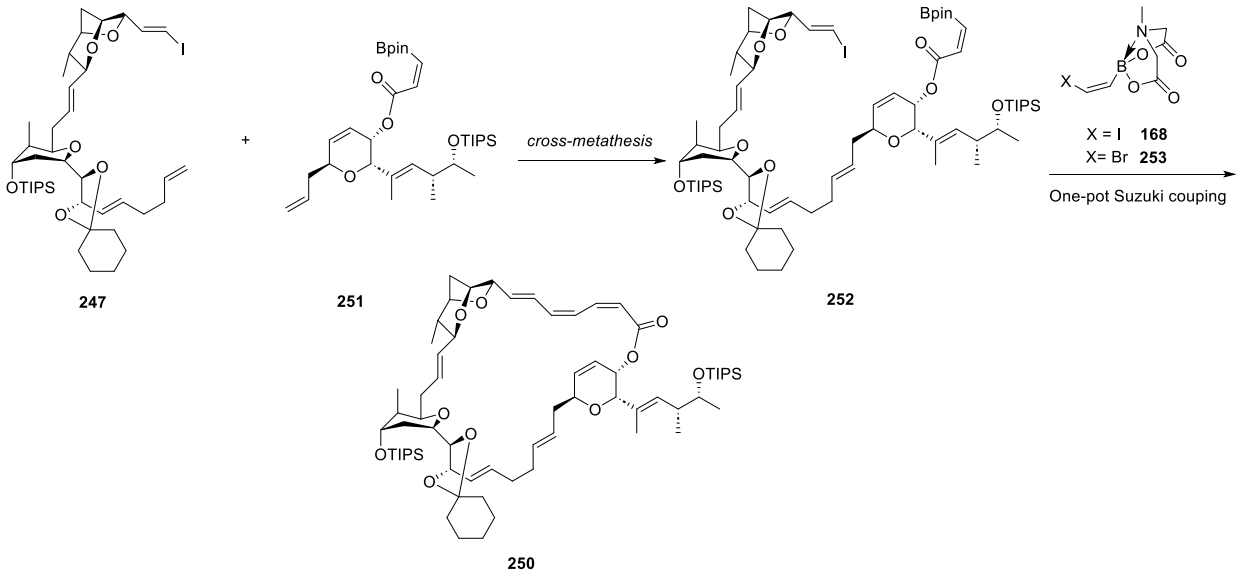
5.2 Outlooks

In this study, we successfully obtained the whole open-form carbon framework of (+)-neosorangicin A **3**. However, there remains potential for additional investigation. In order to fully accomplish the total synthesis, it is necessary to conduct further tests on the RCM to accomplish the closed ring of (+)-neosorangicin A **3**. Although from a thermodynamic perspective, the utilization of the prevalent Grubbs catalysts for RCM promotes the formation of (*E*)-selective products. However, additional research is required to identify RCM catalysts that possess appropriate ligands capable of enhancing selectivity, optimizing reaction conditions, and facilitating post-processing.



Scheme 5.1 *RCM to obtain the closed ring intermediate* ***250***

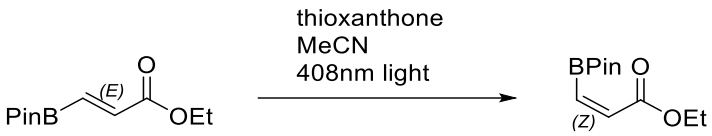
Given the perilous and unstable nature of organotin reagents, an alternative approach for ring closing shows greater potential for future research endeavors. The proposed method involves using the DHP fragment **251**, which is derived from the alteration of **237**, together by the cross-metathesis coupling with **247**. This technique, as shown in scheme 5.2, allows for the production of the open-form skeleton **252**. Subsequently, the Suzuki reaction was utilized to acquire the intermediate **250** using a one-pot methodology.



Scheme 5.2 *Alternative approach for obtain the closed ring intermediate* ***250***

To obtain the prospected building block **251**, a photochemistry method reported by R. Gilmour [82] *et al*., could achieve a boron-enabled geometric isomerization of alkenes with selective energy-transfer catalysis, such as thioxanthone. This discovery highlights the utilization

of Suzuki couplings. The issue of preparing boron substituents encountered in this work is expected to be resolved with a high probability by this discovery. Initial parallel experiments have also shown the capability of this photocatalytic process.



Scheme 5.3 *Boron-enabled geometric isomerization via energy-transfer catalysis*

Simultaneously, as the mentioned close-form intermediate is being carried out, it would be worthwhile to explore enhancements to the current work as a potential avenue for future study. Such as utilizing an asymmetric *trans*-selective hetero Diels–Alder strategy to obtain **129** with a BINOL catalyst as reported by Yamashita[83] *et al*.

Additionally, there is still potential for reassessing the protecting group strategy in the late stage of the synthesis. Specifically, the process of removing the MEM protecting group of **251**. Although the utilization of HBr is effective, the introduction of an acidic environment through this approach can readily result in the degradation of the “high-end” BCO fragment. The optimal conditions of the hydrozirconation to obtain vinyl iodide **247** could also need further investigations.

6. Experimental part

6.1 General Techniques

Reactions with air and moisture-sensitive compounds were performed under an atmosphere of dry nitrogen or Argon. Solids were dried under an oil pump vacuum with heating if necessary.

Liquid reagents and solutions were added with commercial material syringes and injected through a septum or in the nitrogen countercurrent.

Acquired commercial **fine chemicals** were generally used without further purification. For the performance of reactions came only dried, absolute solvent. In the case of Tetrahydrofuran, it was distilled under nitrogen atmosphere over sodium with benzophenone as an indicator. Dichloromethane was distilled over calcium hydride before use. In the case of acetone, it was dried with calcium sulfate, and distilled under a vacuum. All other solvents used were dried over a molecular sieve or optionally in the reagent and a set-without further purification.

For **column chromatographic** purification of the products, the silica gel MN60 (particle size 0.25 mm) from Fluka was used. Chromatography was possibly accelerated with slight overpressure (<0.1 bar). The specified solvent mixing ratio was determined by thin-layer chromatography.

For analytical purposes, the **pre-made thin layer chromatography** films POLYGRAM SIL G / UV254 have been used with fluorescent indicator from Macherey-Nagel. Irradiation with UV light of wavelength 254 nm. Staining with $KMnO_4$ or vanillin reagent and then heating with the heat gun permitted the detection of the separated substances.

Vanillin reagent: 8.6 g vanillin was dissolved in 200 ml of ethanol and mixed slowly with 2.5 ml concentered sulfuric acid.
Potassium permanganate reagent: 3 g $KMnO_4$, 20 g of K_2CO_3 were dissolved in 300 ml water then added 5 ml of 5% sodium hydroxide solution.

For the **^{1}H** and **^{13}C NMR** spectra, a Bruker AVIII 400 MHz and a Bruker AV Neo 600 MHz spectrometer were used to acquire fid data. The spectra were recorded respectively with an internal standard as an internal standard for the invariably dissolved substances in $CDCl_3$ with tetramethyl silane for **^{1}H** (0.0 ppm and 77.01 ppm for **^{13}C**). Peak multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiples, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, dq = doublet of quartet, br = broad signal

For **high-resolution Mass spectra (HRMS)**, a Waters Xevo G2 TOF spectrometer with ESI technique or a Finnigan MAT 95 spectrometer with EI technique has been used to acquire data.

For **IR-spectra,** a Vertex 70V with has been used with attenuated total reflection technique. The position of the absorption bands is given in wavenumber $\tilde{\nu}$ [cm^{-1}]. The relative intensity of the bands is abbreviated as follows: w = weak, m = medium, s = strong, br = broad singal.

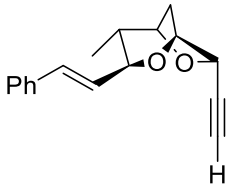
For **melting point (MP)**, a BÜCHI B-540 melting point apparatus has been used to acquire data.

For **specific optical rotations**, an Anton Paar MCP150 polarimeter at 589 nm has been used to acquire data at a concentration of g/100ml.

6.2 Experimental Procedures

6.2.1 Procedures for 4.1

Preparation of (*3S,4R,7S*)-7-ethynyl-4-methyl-3-((*E*)-styryl)-2,6-dioxabicyclo [3.2.1]octane 140



0.304 g (1.17 mmol) of **16**, 0.61 ml (3.59 mmol) of DIPEA, and 0.43 ml of DMSO were dissolved in 10 ml of dichloromethane and 0.365 g (2.29 mmol) of sulfur trioxide-pyridine complex was added at 0 °C. After 2 h at 0 °C, it was diluted with diethyl ether, washed with water, 1 M $KHSO_4$, water and brine. The organic phase was dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was dissolved in 5 ml of THF and slowly heated at 78 °C to give a solution, of 1.386 mmol (0.693 ml, 2 M in hexane), previously mixed for 30 min at this temperature with 1.352 mmol (0.845 ml, 1.6 M in hexane) of *n*-Buli deprotonated trimethylsilyl diazomethane dropped into 10 ml of THF. It was stirred at -78° C for 30 min, at 0 °C for 30 min, and room temperature for 30 min. Then it was quenched with saturated Ammonium chloride solution, the phases were separated and extracted three times with diethyl ether. The combined organic phases were dried over magnesium sulfate and the solvent was removed in vacuo. After flash chromatographic purification (diethyl ether/pentane 1:1), 0.186 g (0.731 mmol, 62% over 2 steps) **140** as white solid was obtained.

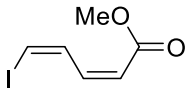
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.43-7.45 (d, J = 7.32 Hz, 2H), 7.33-7.37 (t, J = 7.46 Hz, 2H), 7.26-7.31 (m, 1H), 6.68-6.72 (d, J = 15.8 Hz, 1H), 6.18-6.23 (dd, J = 15.8, 7.52 Hz, 1H), 4.7-4.71 (t, J = 2.51 Hz, 1H), 4.62-4.66 (dd, J = 9.29, 7.86 Hz, 1H),4.54-4.55 (q, J = 2.22 Hz, 1H), 4.36-4.37 (m, 1H), 2.71-2.72 (d, J = 2.32 Hz, 1H), 2.03-2.07 (m, 2H), 1.55-1.63 (m, 2H), 1-1.01 (d, J = 6.77 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 136.66, 132.74, 128.47, 128.43, 127.66, 126.54, 80.19,78.78, 78.74, 76.52, 76.13, 71.04, 41.18, 38.49, 14.96.

HRMS: $C_{17}H_{18}O_2$; M: calc.: 254.1307, found: 254.1309

$[\alpha]_D^{20}$ = -95° (c = 0,16 in $CHCl_3$)

Preparation of Methyl (*2Z,4Z*)-5-iodopenta-2,4-dienoate 142



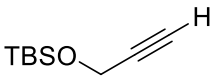
To a solution of 0.452 g (2 mmol) (*Z*)-ethyl 3-iodoacrylate **145a** in 4.6 ml dichloromethane, was added, at 78 °C, 2.2 ml (1 M, 2.2 mmol) of a solution of DIBAL-H in hexane, so that the

temperature did not exceed 75 °C. The solution was then quenched with 1 ml methanol. After 15 min, quenching was performed at die- ser temperature with 1 ml of methanol, followed by the addition of 5 ml of a 20% solution of potassium sodium tartrate in water. The cooling bath was removed, and 5 ml of diethyl ether was added and stirred at room temperature for one hour. It was filtered through Celite, the organic phase was washed with saturated saline and dried over potassium carbonate. After removal of the solvent, the residue, dissolved in 5 ml THF, at 78 °C, was added to a solution, previously at 78 °C for 5 min, with 4 ml (0.5 M, 2mmol) of a solution of KHMDS in toluene deprotonated 0.636 g (2 mmol) acetic acid [bis(2,2,2- trifluoromethoxy)phosphinyl]methyl ester and 2.64 g (10 mmol) 18-crown-6 in 35 ml THF. After 30 min at 78 °C, quenching was performed with 5 ml of saturated ammonium chloride solution and diluted with diethyl ether. To this was added 20 ml of saturated saline and after phase separation, the aqueous phase was extracted with diethyl ether. The combined organic phases were dried over sodium sulfate and the solvent was removed in vacuo. After flash chromatographic purification (1%-10% diethyl ether/hexane), 85 mg (0.357 mmol, 18% over 2 steps) of product **142** was obtained as a yellow oil, as a mixture of *E/Z* isomers (*E*:*Z*=5:95).

^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 7.99-8.04 (ddd, J = 10.49, 7.76, 1.14 Hz, 1H), 6.84-6.87 (dt, J = 7.74, 1.26 Hz, 1H), 6.7-6.76 (m, 1H), 5.88-5.92 (dt, ^{3}J =11.42, 1.29 Hz, 1H), 3.74 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 166.21, 142.97, 134.59, 121.23, 93.95, 51.49.

Preparation of *tert*-butyldimethyl(prop-2-yn-1-yloxy)silane 152



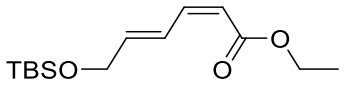
Add imidazole (18.92 g, 250 mmol, 2.2 equiv.), propargyl alcohol **151** (7 g, 125 mmol, 1 equiv.) and anhydrous DCM (150 mL) to a flame dry flask with stir bar. Place this flask in an ice bath and allow to cool prior to the portion wise addition of TBSCl (19.31 g, 128 mmol, 1.05 equiv). Allow the reaction to warm to room temperature and monitor by TLC, observe where a white suspension. After 2h, remove the stir bar and concentrate the reaction through rotary evaporation to remove the DCM and obtain an oily white residue. Dilute the residue with pentanes (250 mL) and vacuum filter through a silica gel plug. After rinsing the plug

with pentane, concentrate the combined organics through rotary evaporation, yield 20.19g (95%) of **152** as colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 4.31 (d, J=2.4Hz,2H), 2.38 (t, J=2.4Hz,1H), 0.91 (s,9H), 0.13 (s,6H).

The ^{1}H NMR data were in agreement with the literature.[84]

Preparation of ethyl (*2Z,4E*)-6-((tert-butyldimethylsilyl)oxy)hexa-2,4-dienoate 157



To a suspension of HCp_2ZrCl (89.4 mg, 0.35 mmol) in 1.0 mL THF, was added dropwise a solution of **152** (53.4 mg, 0.31 mmol) dropwise. The clear solution was stirred at room temperature for 1 h and the THF solution (0.5 mL) of anhydrous $ZnCl_2$ (47.9 mg, 0.35 mmol) was added dropwise. After 5 min, a THF solution (0.5 mL) of vinyl iodide **145a** (0.72mg, 0.31 mmol) and $Pd(OAc)_2$, (18.4mg 0.016 mmol), $Pd(PPh_3)_4$ was added. After stirring at rt for 1 h, solvent was removed *in vacuo* and the residue was diluted with 5 mL of ether/pentane, filtered and concentrated in vacuo. The crude product was purified with flash column chromatography (5% EA/Hex) to provide *E,Z*-diene ester **157** (61.9mg, 0.23 mmol, 74%) as pale yellow oil.

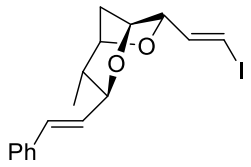
^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 7.50 (ddtd, J = 15.3, 11.4, 1.8, 1.0 Hz, 1H), 6.56 (td, J = 11.4, 0.7 Hz, 1H), 6.08 (dtt, J = 15.4, 5.0, 0.8 Hz, 1H), 5.62 (dp, J = 11.4, 0.8 Hz, 1H), 4.32 – 4.28 (m, 2H), 4.18 (q, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 166.29, 143.87, 142.62, 125.75, 117.45, 63.33, 60.38, 25.91, 18.38, 14.32, -5.20.

HRMS: $C_{14}H_{26}O_3SiNa$ $[M+Na]^+$; calc.: 293.1543; found: 293.1533.

The NMR data were in agreement with the literature.[85]

Preparation of (*3S,4R,7S*)-7-((*E*)-2-iodovinyl)-4-methyl-3-((*E*)-styryl)-2,6-dioxabicyclo[3.2.1]octane 97



309 mg **104** (1 eq, 1.21 mmol) was dissolved in 2 ml dry THF, cooled to 0 °C and 1 eq 1M Superhydrid was added. In a separate flask (covered in aluminum foil). 810 mg Zr Cp_2Cl_2 (2 eq, 2.42 mmol) was suspended in 2 ml THF and 2.5 ml 1M Superhydrid in THF (2 eq, 2.5 mmol) was added. After 1 h of stirring the alkyne solution was added to the fresh generated Schwarz regent. After another 30 mins at rt, 680 mg NIS (2.5 eq, 3 mmol) was added in portion and stirred for 15 min at ambient temperature. The reaction was quenched with saturated $NaHCO_3$ solution, the water phase extracted with EtOAc, and the combined organic phase was washed with saturated brine. After drying over $MgSO_4$, the crude material was purified via column chromatography (hexanes/EtOAc 2:1) to isolate 300 mg white solids (59% yield).

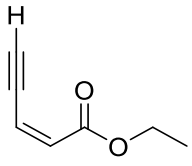
^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 7.43 – 7.36 (m, 2H), 7.35 – 7.27 (m, 2H), 7.27 – 7.20 (m, 1H), 6.89 (dd, J = 14.5, 4.9 Hz, 1H), 6.62 (dd, J = 14.5, 1.8 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.10 (dd, J = 15.8, 7.6 Hz, 1H), 4.47 – 4.41 (m, 1H), 4.37 (dt, J = 4.6, 2.2 Hz, 1H), 4.33 (d, J = 6.3 Hz, 1H), 4.12 (dd, J = 9.6, 7.5 Hz, 1H), 2.08 – 2.01 (m, 1H), 1.97 (d, J = 1.6 Hz, 1H), 1.58 – 1.48 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H)..

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 141.11, 136.68, 132.88, 128.81, 128.64, 128.61, 127.87, 126.71, 126.65, 83.67, 79.69, 79.61, 79.05, 75.88, 41.56, 38.77, 15.20..

HRMS $C_{17}H_{20}IO_2$ $[M+H]^+$ calc.: 383.0508; found: 383.0515.

The data were in agreement with the literature[10].

Preparation of ethyl (*Z*)-pent-2-en-4-ynoate 172



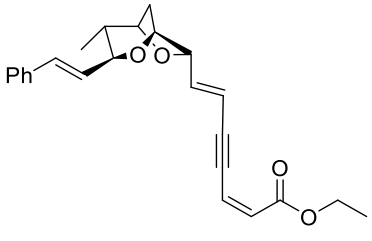
A solution of vinyl iodide **145a** (226 mg, 1.0 mmol) in THF (2 mL) was sparged with nitrogen and then Pd $(PPh_3)_4$ (58 mg, 0.05 mmol) CuI (10 mg, 0.05 mmol) and triethylamine (558 µl, 4 mmol) were sequentially added at 0°C, followed by trimethylsilyacetylene **171** (166 µl, 1.2 mmol). After 1h stirring, the reaction mixture was allowed to warm to room temperature for over 12 h and then quenched with saturated ammonia chloride solution. The mixture was extracted with ether and the organic phase was dried over $MgSO_4$, then concentrated in vacuo to afford a crude oil, which was purified by silica gel column chromatography (EA :Hex = 5:100) to afford enyne ester **170** (200 mg, 99%) as pale-yellow oil.

To a solution of **170** (200mg, 1.1mmol) in 3ml MeOH, 153mg K_2CO_3 (1.0eq) was added at 0°C. The reaction mixture was allowed to warm to room temperature for over 30 min and then quenched with water. The mixture was extracted with ether and the organic phase was dried over $MgSO_4$, then concentrated in vacuo to afford pale yellow oil **172** (82mg, 66%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 6.20 (dd, J = 11.6, 0.9 Hz, 1H), 6.12 (dd, J = 11.5, 2.6 Hz, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.61 (dd, J = 2.6, 0.9 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 164.93, 130.49, 122.31, 79.61, 77.36, 60.51, 14.30.

Preparation of ethyl (*2Z,6E*)-7-((*3S,4R,7S*)-4-methyl-3-((*E*)-styryl)-2,6-dioxabicyclo[3.2.1]octan-7-yl)hepta-2,6-dien-4-ynoate 173

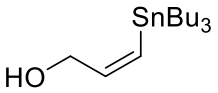


A solution of vinyl iodide **97** (10 mg, 0.03 mmol) in THF (1 mL) was sparged with nitrogen and then Pd $(PPh_3)_4$ (2 mg, 0.0015 mmol) CuI (0.3 mg, 0.0015 mmol) and DIPEA (17 µl, 0.03 mmol) were sequentially added at 0°C, followed by acetylene **172** (3.9 mg, 0.03 mmol). After 1h stirring, the reaction mixture was allowed to warm to room temperature for over 12 h and then quenched with saturated ammonia chloride solution. The mixture was extracted with ether and the organic phase was dried over $MgSO_4$, then concentrated in vacuo to afford a crude **170** 4 mg, as yellow oil.

diagnostic peaks in the **^{1}H NMR** ($CDCl_3$, 600 MHz) δ[ppm] = 6.89 (dd, J = 14.5, 4.9 Hz, 1H), 6.62 (dd, J = 15.5, 4.2 Hz, 1H), 6.57 (d, J = 15.8 Hz, 1H), 6.31 (dd, J = 11.4, 2.6 Hz, 1H), 6.27 – 6.23 (m, 1H), 6.10 (d, J = 11.3 Hz, 1H). **^{13}C NMR** ($CDCl_3$, 100 MHz) of the unpurified material: δ[ppm] = 141.41[BCO-(C)=C-C≡C-C=C-COOEt], 123.33[BCO-C=(C)-C≡C-C=C-COOEt], 99.85[BCO-C=C-(C)≡C-C=C-COOEt], 83.55[BCO-C=C-C≡(C)-C=C-COOEt], 126.58[BCO-C=C-C≡C-(C)=C-COOEt], 126.55[BCO-C=C-C≡C-C=(C)-COOEt]

HRMS $C_{24}H_{26}O_4$ $[M+H]^+$ calc.: 379.1909; found: 379.1916; $[M+Na]^+$ calc.: 401.1729; found: 401.1732; $[M+NH_4]^+$ calc.: 396.2175; found: 396.2175.

Preparation of (*Z*)-3-(tributylstannyl) prop-2-en-1-ole 176



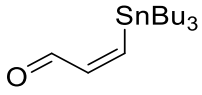
1.51 ml Propargyl alcohol (3.5 eq, 25.9 mmol) was dissolved in 30 ml dry THF and cooled to 0 °C. 500 mg $LiAlH_4$ (1.75 eq, 12.9 mmol) was added slowly and the mixture was stirred overnight. After cooling to -78 °C 2 ml Bu_3SnCl (1 eq, 7.4 mmol) was added dropwise. The mixture was warmed slowly to rt and stirred overnight. The reaction was quenched then with 10 ml MeOH and 10 ml 1 M NaOH. The water phase was extracted with diethyl ether, the combined org. the phase was washed with brine and dried over $MgSO_4$. The solvent was evaporated and the crude material was purified by column chromatography. 1.1 g (43%, 2 steps) clear oil was isolated.

^{1}H NMR ($CDCl_3$, 400 MHz) δ[ppm] = 6.69 (dt, J = 12.9, 5.8 Hz, 1H), 6.08 (dt, J = 12.8, 1.1 Hz, 1H), 4.11 (dt, J = 5.8, 1.1 Hz, 2H), 1.58 - 1.43 (m, 6H), 1.37 - 1.22 (m, 6H), 0.95 - 0.84 (m, 15H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ[ppm] = 146.22, 131.81, 66.14, 29.16, 27.16.

HRMS $C_{15}H_{32}OSnH$ $[M+H]^+$; calc.:341.1580, found: 341.1587.

Preparation of (*Z*)-3-(tributylstannyl) acrylaldehyde 177



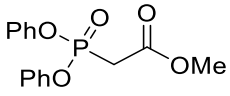
540 mg (Z)-3-(tributylstannyl) prop-2-en-1-ole (1 eq, 1.55 mmol) was dissolved in 15 ml DCM (saturated with water) and cooled to 0 °C. a mixture of 1 g Dess-Martin-regent (1.5 eq, 2.36 mmol) and 430 mg $NaHCO_3$ (3.3 eq, 5.12 mmol) was added. The mixture was stirred for 2 h at 0 °C, then water was added. The water phase was extracted with DCM, the combined org. the phase was washed with brine and dried over MgSO4. The solvent was evaporated and the crude material was purified by column chromatography. 300 mg (56%) aldehyde as a clear oil was isolated.

^{1}H NMR ($CDCl_3$,400 MHz) δ[ppm] = 9.50 (dt, J = 6.9, 1.8 Hz, 1H), 7.69 (d, J = 12.9 Hz, 1H), 6.98 (dd, J = 12.9, 6.9 Hz, 1H), 1.59 - 1.42 (m, 6H), 1.36 - 1.23 (m, 6H), 1.06 - 0.97 (m, 6H), 0.92 - 0.82 (m, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ[ppm] =194.67, 162.89, 145.55, 28.96, 27.18, 13.60, 11.33.

HRMS $C_{15}H_{30}OSnH$ $[M+H]^+$: calc.: 339.1423, found: 339.1431.

Preparation of methyl 2-(diphenoxyphosphoryl)acetate 180

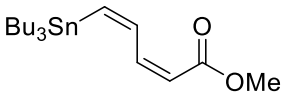


To a dry three-neck round-bottom flask fitted with addition funnel was added sodium hydride (1.57 g, 60% dispersion in mineral oil, 39.2 mmol) and tetrahydrofuran (15 mL). The suspension was stirred at 0 °C before adding a solution of diphenyl phosphite (7.5 mL, 39.2 mmol, impurities ca. 15% phenol) in tetrahydrofuran (5 mL) dropwise via addition funnel. The reaction mixture was stirred for an additional 1 h before adding a solution of methyl bromoacetate (3.7 mL, 39.2 mmol) in tetrahydrofuran (10 mL) over 1 h via addition funnel. The resulting white suspension was stirred at RT for an additional 18 h. Saturated aqueous NH_4Cl (10 mL), H_2O (10 mL), and diethyl ether (20 mL) were sequentially added to the mixture. The aqueous phase was separated and extracted with ethyl acetate (3 x 10 mL). Combined organic phase was washed with saturated aqueous NaCl (40 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by silica gel flash column chromatography (ethyl acetate-hexanes, 1:4 to 1:2, v/v) to obtain methyl 2-(diphenoxyphosphoryl)acetate (8.49 g, 27.7 mmol, 71%) as a hygroscopic colorless oil.

^{1}H NMR ($CDCl_3$, 600 MHz): δ[ppm] = 7.33 (m, 4H), 7.26-7.14 (m, 6H), 3.76 (s, 3H), 3.28 (d, J = 21.7 Hz, 2H),

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 165.31, 165.27, 150.49, 150.45, 129.68, 125.65, 125.60, 120.14, 53.14, 52.89, 34.30, 33.39.

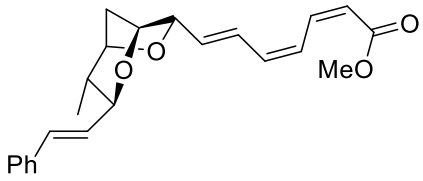
Preparation of methyl (*2Z,4Z*)-5-(tributylstannyl)penta-2,4-dienoate 178



625 mg (diphenoxyphosphoryl)acetate **180** (1.5 eq, 2.04 mmol) was dissolved in 10 ml dry THF and cooled to 0 °C. 76 mg NaH (1.4 eq, 1.9 mmol) was added and stirred for 15 min at 0 °C. It was then cooled to -78 °C and then 469 mg aldehyde **177** was added slowly. The solution was stirred at -78 C for 30 min, then warmed to 0 °C and stirred again for 30 min. The reaction was quenched with NH_4Cl solution and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated on the rotary evaporator. The crude product was purified by column chromatography (pentane/diethyl ether 50:1) to give 298 mg of **178** (55% yield) of a clear oil.

^{1}H NMR ($CDCl_3$, 600 MHz): δ[ppm] = 6.72 (d, J = 10.2 Hz, 1H), 6.40 (t, J = 11.2 Hz, 1H), 6.22 (m, 1H), 5.90 (dd, J = 10.3, 0.7 Hz, 1H), 3.75 (s, 1H), 1.45-1.25 (m, 6H), 0.92-0.84 (m, 7H).

Preparation of methyl (*2Z,4Z,6E*)-7-((*3S,4R,7S*)-4-methyl-3-((*E*)-styryl)-2,6-dioxabicyclo[3.2.1]octan-7-yl)hepta-2,4,6-trienoate 143



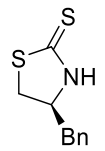
A 15 mL round bottom flask was charged with dienoate **178** (31 mg, 0.0744 mmol), vinyl iodide **97** (15 mg, 0.0395 mmol), and $Ph_2PO_2NBu_4$ (216 mg, 0.471 mmol), and dissolved in degassed DMF (1.2 mL). $PdCl_2(PhCN)_2$ (0.5 mg, 0.00132 mmol) was added and the reaction mixture was purged with argon in glove box, and stirred at rt in the dark overnight. The reaction mixture was diluted with hexanes (4 mL), filtered through Celite plug into brine (5 mL), and rinsed with Et_2O: hexanes (1:1, 20 mL). The mixture was extracted with Et_2O: hexanes (1:1, 3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give a crude residue, which was purified by flash chromatography (10% to 30% EtOAc:hexanes, silica gel was pretreated with 1% Et_3N) to afford trienoate **143** (10 mg, 71%) as a pale yellow oil.

diagnostic trienoate peaks in the **^{1}H NMR** of the unpurified material ($CDCl_3$, 600 MHz) δ[ppm] = 7.34 [dd, J = 12.0, 11.4 Hz, 1 H, [BCO-CH=CH-CH=C(H)-CH=CH-COOMe]], 7.09 [dd, J = 12.0, 11.4 Hz, 1 H, [BCO-CH=CH-CH=CH-C(H)=CH-COOMe]], 6.99 [dd, J = 15.0, 12.0 Hz, 1 H, [BCO-CH=C(H)-CH=CH-CH=CH-COOMe]], 6.43 [dd, J = 12.0, 11.4 Hz, 1 H, [BCO-CH=CH-C(H)=CH-CH=CH-COOMe]], 6.19 [dd, J = 15.0, 5.4 Hz, 1 H, [BCO-C(H)=CH-CH=CH-CH=CH-COOMe]], 5.64 [d, J = 11.4 Hz, 1H, [BCO-CH=CH-CH=CH-CH=C(H)-COOMe]];

HRMS $C_{23}H_{26}O_4Na$ $[M+Na]^+$: calc.: 389.1728; found: 389.1722.

6.2.2 Procedures for 4.2

Preparation of (*S*)-4-benzylthiazolidine-2-thione 182



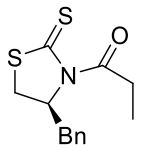
To a solution of *L*-phenylalanine **181** (30 g, 182 mmol) and $NaBH_4$ (3.35g, 104.5mmol, 2.3 Equiv.) in 125 ml THF at -0 ° C has added a solution of Iodine in THF dropwise (0.45M, 100 ml, 1 Equiv.). After gas evolution stopped, the mixture was heated to reflux for 4-6 hours and stirred overnight at room temperature. Then the mixture was cooled to room temperature and MeOH (100ml) was slowly added until a clear solution emerged. After concentrating under vacuum the white residue was dissolved in aqueous NaOH (2M, 200ml) and stirred at room temperature for 4~8 h. The water phase was extracted with dichloromethane (3×100ml) and the combined organic layers were dried with Na_2SO_4. After removal of the solvent, the *L*-phenyl alaninol as a white paste (28g, 99% raw) was afforded and used for the next step without further purification.

The white paste was mixed with aqueous KOH (1.0M, 1L, 6 Equiv.). After adding CS_2 (13.86ml, 229.68mmol, 5 Equiv.), the mixture was heated under reflux until the red-pink solution turned clear and the red-pink color disappear. Then the reaction mixture was cooled to room temperature and extracted with dichloromethane (3×150ml). The organic layers were combined, dried over Mg_2SO_4, and concentrated *in vacuo*. After recrystallizing of the residue with 50ml ethanol, 26.15g (70%) **182** as white solid was isolated.

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] 7.41-7.22 (m, 3H), 7.26-7.16 (m, 2H), 4.52-4.39 (m, 1H), 3.61 (ddd, J = 11.2, 7.6, 0.9 Hz, 1H), 3.34 (dd, J = 11.2, 6.9 Hz, 1H), 3.08-2.91 (m, 2H).

HRMS $C_{10}H_{12}NS_2$ cal. $[M+H]^+$ 210.0411 found: $[M+H]^+$ 210.0409

Preparation of (*S*)-1-(4-benzyl-2-thioxothiazolidin-3-yl) propan-1-one 100



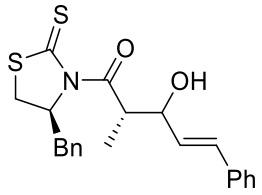
Method A: To a solution of **182** (15.83 g, 75.64 mmol) in 100 ml THF at -78 ° C was added dropwise to a solution of *n*-butyl lithium in hexane (31.8 ml, 2.5 M, 79.42 mmol) over 20 minutes. After 20 min. of stirring, 7.92ml (90.77 mmol) of propionyl chloride was added dropwise and then the temperature was raised to 0 ° C. The reactor was warmed to room temperature after a further 30 min. and stirring was continued until complete conversion was observed by TLC. Semi-saturated potassium carbonate solution was added and the layers mixed. THF was removed in a vacuum and the residue was extracted three times with dichloromethane. The organic phase was dried over sodium sulfate, then the solvent was removed under vacuum. These obtained yellow solid (19.88 g 74.89 mmol, 99% crude) was used without further purification.

Method B: To a solution of **182** (15.83 g, 75.64 mmol) in 100 ml DCM at -78 ° C was added dropwise to a solution of propionyl chloride in DCM (31.8 ml, 2.5 M, 79.42 mmol) over 15 minutes. After 20 min. the reactor was warmed to room temperature after a further 30 min. and stirring was continued until complete conversion was observed by TLC (ca. 4-6 h). the organic phase was washed with 1xHCl, 1x $NaHCO_3$, 1x brine and dried over sodium sulfate, then the solvent was removed under vacuum. These obtained yellow solid was recrystallized once in acetonitrile and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] 7.40-7.23 (m, 5H), 5.38 (dddd, J = 11.2, 7.2, 3.8, 0.7 Hz, 1H), 3.50-3.36 (m, 1H), 3.41-3.33 (m, 1H), 3.27-2.99 (m, 3H), 2.88 (dd, J = 11.5, 0.7 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H).

HRMS $C_{13}H_{16}NOS_2$ cal. $[M+H]^+$ 266.0673 found: 266.0664

Preparation of (*2S, E*)-1-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-2-methyl-5-phenylpent-4-en-1-one 125



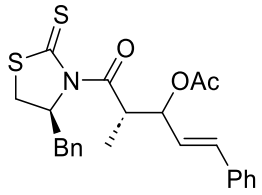
100 (76.8mmol) was dissolved directly in a 0.5-liter round-bottom flask in 156 ml of dry ethyl acetate, then cinnamaldehyde (10.7ml, 84.4 mmol), magnesium bromide ethyl etherate (2.0 g, 7.7 mmol), trimethylamine (21.4 ml, 153.4 mmol) and trimethylsilyl chloride (14.2 ml,115 mmol) was added. After 18 ~ 48 hours stirring at room temperature, the reaction mixture was filtered directly through silica and silica was washed with ca. 150 ml ether. The filtrate was concentrated under reduced pressure and dissolved in 280 ml of THF. After the addition of 1 N HCl (80 ml) and stirring for 1 h at room temperature, the mixture was diluted with diethyl ether and water. The phases were separated and the aqueous phase was extracted three times with 100 ml diethyl ether each. The combined organic phases were washed once each with saturated sodium bicarbonate and brine and dried over sodium sulfate. After removing the solvent under vacuum and flash chromatography (gradient, 10%-30% diethyl ether/pentane) 22.8 g (57.36 mmol, yield 76%) **125** was obtained as a yellow foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] 7.42-7.17 (m, 10H), 6.64 (dd, J = 16.0, 1.2 Hz, 1H), 6.21 (dd, J = 15.9, 6.2 Hz, 1H), 5.25-5.13 (m, 1H), 4.64 – 4.42 (m, 2H), 3.30-3.16 (m, 2H), 3.04 (dd, J = 13.2, 10.6 Hz, 1H), 2.82 (dd, J = 11.4, 0.7 Hz, 1H), 2.49 (s, 1H), 1.32 (d, J = 6.8 Hz, 3H).

HRMS $C_{22}H_{23}NO_2S_2$ cal. $[M+H]^+$ 398.1248, $[M+NH_4]^+$ 415.1541 found $[M+H]^+$ 398.1239, $[M+NH_4]^+$ 415.1515

The ^{1}H NMR data were in agreement with the literature.

Preparation of (*4S, E*)-5-((*S*)-4-benzyl-2-thioxothiazolidin-3-yl)-4-methyl-5-oxo-1-phenylpent-1-en-3-yl acetate 126



125 (22.80 g, 57.36 mmol) was dissolved in 230 ml of dichloromethane. 8.39 ml (60.22 mmol) of DIPEA and 0.140 g (1.15 mmol) of DMAP were added and cooled to -30°C. then Acetic anhydride (5.64 ml, 60.22 mmol) was added. After 1h., 80 ml of 1N hydrochloric acid was added and the mixture was stirred for additional 15 min. After mixing and subsequent separation of the phases, the organic phase was washed with saturated sodium bicarbonate solution and was dried over sodium sulfate. After removal of the solvent *in vacuo*, the yellow-orange residue **126** was used for next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] 7.40-7.24 (m, 11H), 6.71-6.75 (d, J = 15.8 Hz, 1H), 6.07-6.01 (dd, J = 15.9, 8.0 Hz, 1H), 5.67-5.63 (t, J = 8.3 Hz, 1H), 5.26-5.21 (ddd, J = 6.8, 3.9, 3.9 Hz, 1H), 3.34 – 3.29 (dd, J = 11.5, 7.0 Hz, 1H), 3.27 – 3.23 (dd, J = 13.2, 3.8 Hz 1H), 3.08-3.03 (dd, J = 13.2, 10.6 Hz, 1H), 2.93-2.90 (d, J = 11.5 Hz, 1H), 2.02 (s, 3H), 1.27-1.26 (d, J = 6.8 Hz, 3H).

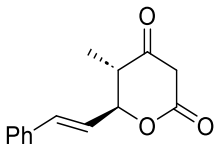
^{13}C NMR (100 MHz, $CDCl_3$) δ[ppm] 201.20, 175.60, 169.42, 136.36, 135.82, 135.54, 129.50, 128.93, 128.62, 128.32, 127.27, 126.73, 124.57, 77.42, 69.06, 42.99, 36.65, 32.51,21.15, 14.36.

IR (ATR) 3103(w) 3083(w) 3061(w) 3027(w) 2962(w) 2927(w) 2873(m) 2852(w) 1739(s) 1692(m) 1602(w) 1579(w)1495(w) 1452(w) 1367(s) 1341(m) 1319(w) 1292(w) 1259(s) 1226(s) 1190(m) 1163(s) 1136(s) 1113(m) 1057(w) 1016(s) 966(s) 915(w) 884(w) 860(w) 850(w) 832(w) 806(w) 744(s) 693(s) 666(w) 651(w) 613(w) 601(w) 536(w) 532(w) 511(w) 487(w) 465(w) 432(w)

HRMS: $C_{24}H_{25}NO_3S_2$; $[M+H]^+$: calc.: 439.1276 found: 439.1278

$[\alpha]_D^{20}$ = 231.13° (*c* = 1.5 in $CHCl_3$)

Preparation of (*5S,6S*)-5-methyl-6-((*E*)-styryl) dihydro-*2H*-pyran-2,4(*3H*)-dione 127



The crude **126** was dissolved in 300 ml THF and cooled at -78 ° C. Then 86.53 ml 2M solution of NaHMDS in THF (129.8 mmol) was added by a dropping funnel. After the addition, the starting material proved as completely consumed by TLC. Then 400 ml of a 1: 1 mixture of 1N HCl and methanol were added. The cooling bath was removed and the mixture was further adjusted with 1N HCl to pH 5-6. The solution was extracted 3-5 times with saturated sodium carbonate solution (ca. 1 L) and then the brought extract's pH was adjusted to 1-2 with 37% hydrochloric acid. The already partially precipitated product was taken up with dichloromethane extraction and the combined organic phase was further dried with sodium sulfate. The solvent was removed *in vacuo* and residues were used without further purification.

For analytical reason, 15g crude residue was purified by flash chromatography purification (pentane/diethyl ether 20%-50%), yield 4.17 g (18.12 mmol, 29%) product as a yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] 7.43-7.32 (m, 5H), 6.79-6.75 (d, J = 16 Hz, 1H), 6.22-6.17 (dd, J = 16, 7.6 Hz, 1H), 4.92-4.88 (dd, J = 9.6, 7.6 Hz, 1H), 3.64-3.59 (d, J = 19.2 Hz, 1H), 3.54-3.49 (d, J = 19.2 Hz, 1H), 2.63-2.55 (dq, J = 10.0, 7.2 Hz, 1H), 1.22 - 1.20 (d, J= 7.2 Hz, 3H).

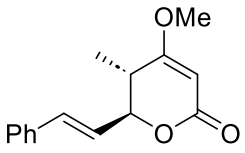
^{13}C NMR (100 MHz, $CDCl_3$) δ[ppm] 201.94, 166.73, 135.98, 135.16, 128.88, 128.81, 126.89, 123.30, 81.50, 47.20, 46.01, 11.21.

IR (ATR) 3780(w), 3723(w), 3698(w), 3680(w), 3660(w), 3640(w), 2980(m), 2887(w), 2378(w), 2349(w), 2314(w), 1726(w), 1709(w), 1636(m), 1560(m), 1482(w), 1451(w), 1381(w), 1360(w), 1285(m), 1262(s), 1240(s), 1213(w), 1162(w), 1121(w), 1089(w), 1074(w), 1052(w), 1019(m), 978(m), 915(w), 857(w), 834(m), 813(w), 755(m), 772(w), 695(m), 670(w), 626(w), 533(w), 504(m), 448(w), 430(m).

HRMS: $C_{14}H_{15}O_3$; $[M+H]^+$: calc.: 231.1021 found: 231.1025

$[\alpha]_D^{20}$ =259.00° (*c* = 1.0 in $CHCl_3$)

Preparation of (*5S,6S*)-4-methoxy-5-methyl-6-((*E*)-styryl)-5,6-dihydro-*2H*-pyran-2-one 128



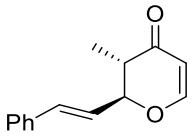
To a solution of **127** (2.75 g,11.94 mmol) in 120 ml acetone at room temperature. Potassium carbonate (1.82 g,13.14 mmol) and dimethyl sulfate (0.96 ml 10.15 mmol) were added. After stirring at room temperature overnight, the mixture was diluted with diethyl ether and water. The phases were separated and the aqua phase was extracted twice with 100ml diethyl ether each. The combined organic phases were dried over sodium sulfate and the solvent was removed under vacuum. After flash chromatography purification (ethyl acetate/pentane 1: 2) 1.72 g (7.04 mmol, 59%) the product was obtained as a white-yellowish solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] 7.44-7.32 (m, 2H), 7.38-7.22 (m, 2H), 6.71 (dd, J = 15.9, 1.1 Hz, 1H), 6.22 (dd, J = 15.9, 7.0 Hz, 1H), 5.16 (d, J = 0.8 Hz, 1H), 4.70 (td, J = 7.2, 1.2 Hz, 1H), 3.75 (s, 3H), 2.64 (pd, J = 7.1, 0.8 Hz, 1H), 1.31-1.20 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ[ppm] 175.42, 171.31, 166.35, 135.92, 134.68, 128.81, 128.59, 128.49, 126.87, 125.40, 89.91, 82.19, 77.49, 77.37, 77.17, 76.85, 60.55, 56.36, 37.28, 29.85, 21.22, 14.35, 14.06.

HRMS $C_{15}H_{17}O_3$ $[M+H]^+$ calc.: 245.1178; found 245.1179.

Preparation of (*2S,3S*)-3-methyl-2-((*E*)-styryl)-2,3-dihydro-*4H*-pyran-4-one 129



128 (11 g, 45 mmol) were dissolved in 150 ml of dichloromethane at -78 ° C and a solution of DIBAL-H in hexane (50 ml, 1 M) was added dropwise. After 50 min. TLC showed the remaining starting material, so another 2 ml DIBAL-H was added. After 10 min., 50 ml of 2N HCl(aq) was added and the cooling bath was removed. The mixture was stirred vigorously for 30 min. The phases were separated and the aqueous phase was extracted twice with dichloromethane. After washing the combined organic phases with water and drying over sodium sulfate, the solvent was removed under vacuum. After recrystallization with ether/pentane 1: 2, 6.5 g **129** was obtained as a colorless solid. the mother liquor was concentrated *in vacuo* and residue was purified by flash chromatography (ether/pentane 1: 2) afforded additional 0.2g **129**. Overall, the yield is 69%.

^{1}H NMR (600 MHz, $CDCl_3$) δ[ppm] =7.44-7.42 (m, 2H), 7.39-7.38 (d, J = 6.0 Hz, 1H), 7.37-7.34 (m, 2H), 7.31-7.29(m, 1H), 6.75-6.73(d, J = 15.9 Hz, 1H), 6.30-6.26(dd, J= 15.9, 7.6 Hz, 1H), 5.46-5.45 (d, J = 6.0 Hz, 1H), 4.66-4.63 (dd, J = 12.4, 7.7 Hz, 1H), 2.64-2.58 (dq, J = 12.2 Hz, 7.0 Hz, 1H), 1.15-1.14 (d, J = 7.0 Hz, 3H).

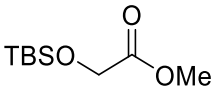
^{13}C NMR (150 MHz, $CDCl_3$) δ[ppm] 194.45, 162.22, 135.63, 135.51, 128.72, 128.57, 126.81, 124.80, 106.47, 85.38, 44.21, 10.70.

IR (ATR) = 3029(w), 3002(w), 2973(w), 2935(w), 2874(w), 1652(s), 1595(s), 1533(w), 1492(w), 1453(w), 1406, 1377(w), 1296(w), 1280(w), 1250(m), 1202(w), 1189(m), 1158(w), 1121(w), 1094(w), 1074(w), 1050(m), 1022(m), 978(m), 940(m), 891(w), 842(m), 825(w), 808(m), 778(m), 749(m), 693(m), 608(w), 587(w), 566(w), 528(m), 500(m), 475(w), 463(w), 411(w).

HRMS: $C_{14}H_{14}O_2$; M+H: calc.: 215.1072 found: 215.1066

$[\boldsymbol{\alpha}]_D^{20}$ = -160.57° (*c* = 0.35 in $CHCl_3$)

Preparation of methyl 2-((*tert*-butyldimethylsilyl)oxy)acetate 137

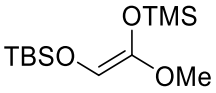


Methyl glycolate **136** (4 g, 44.4 mmol) and imidazole (7.27 g, 106.56 mmol) in 80 ml dichloromethane were treated with TBSCl (8.04 g, 53.28 mmol). After 4 h stirring at room temperature water was added, the phases were separated and the organic phase was washed twice with water and once with brine. After drying over sodium sulfate, the solvent was removed under vacuum (40 ° C, up to 192 mbar) The residue was purified by flash chromatography (diethyl ether/pentane 1:19) to give 8.84 g (43.3 mmol, 97%) **137** a colorless, clear liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] 4.25 (s, 2H), 3.74 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H).

This data is in agreement with that reported by the literature[86].

Preparation of (*Z*)-4-methoxy-2,2,7,7,8,8-hexamethyl-3,6-dioxa-2,7-disilanon-4-ene 135

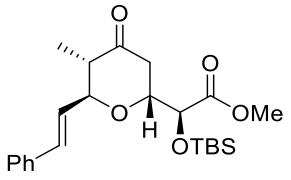


To a dried, 250-mL, 3-necked round-bottomed flask equipped with a magnetic stir bar, a thermometer, a gas inlet tube, and a septum were added KHMDS (3.292 g, 16.5 mmol, 1.1equiv) and THF (90 mL). The solution was cooled to -78 ° C (internal temp.) in a dry ice-acetone bath and then 2-methoxy acetic acid methyl ester (1.486 mL, 15 mmol) was added dropwise via syringe over 5 min. The internal temperature was kept below -70 ° C during addition. After 25 min, TMSCl (2.094 mL, 16.5 mmol, 1.1 equiv) was added dropwise via syringe over 5 min while vigorous stirring was maintained. After 1 h, the dry ice-acetone bath was removed and pentane (60 mL) was added. The reaction mixture was filtered through a glass frit at RT and was concentrated in vacuo (23 ° C, 30 mmHg). The solvent was removed under reduced pressure to give **135** (1.092 g, 41%, 96/4, Z/E) as a colorless oil, which used in following step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] 5.51 (s, 1H), 3.47 (s, 3H), 0.92 (s, 13H), 1.00 – 0.83 (m, 11H).

This data is in agreement with that reported by the literature[86].

Preparation of Methyl (*S*)-2-((tert-butyldimethylsilyl) oxy)-2-((*2R,5S,6S*)-5-methyl-4-oxo-6-((*E*)-styryl) tetrahydro-*2H*-pyran-2-yl) acetate 130



To a solution of 0.5 g (2.33 mmol) **129** and 0.03 g (0.06 mmol, 3-mol-%) scandium (III) triflate in 10 ml dichloromethane was added dropwise via syringe pump, at -78 °C, a solution of 0.942 g (3.51 mmol) **135** in 20 ml dichloromethane. Subsequently, there was an almost complete conversion of the starting material and 0.333 ml (5. 5.82 mmol) of glacial acetic acid was added and warmed up to 0 °C. After the addition of 3.51 ml (1 M, 3.51 mmol) of a solution of TBAF in THF, stirring was continued for about 10 min, diluted with a little dichloromethane and saturated sodium hydrogen carbonate solution was added. After phase separation, the aqueous phase was extracted once with DCM and the combined organic phases were dried over magnesium sulfate. After removal of the solvent under vacuum and flash chromatographic purification (ethyl acetate/pentane 1:5), 0.701 g (1.67 mmol, 72%) of **130** was obtained as a colorless oil that crystallized to a colorless solid overnight at room temperature.

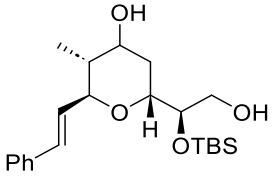
*Note: For this particular step, the optical condition suitable for scales over 15 grams has been created. The experimental procedure involved the gradual addition of approximately 6-10 equivalents (monitored by TLC) of crude ketal **135** using a syringe pump at a flow rate up to 6 ml/h. This addition was carried out in a mixture containing well-diluted **129** and 5 to 10-mol-% scandium triflate at -78 °C. The quantity of **129** can be fully consumed.*

^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 7.27-7.35 (m, 5H), 6.57-6.61 (d, J = 15.88 Hz, 1H), 6.09-6.15 (dd, J = 15.88, 7.16 Hz, 1H), 4.74-4.78 (m, 1H), 4.64-4.67 (m, 1H), 4.36-4.37 (d, 3.31 Hz, 1H), 3.78 (s, 3H), 2.61-2.67 (dd, J = 15.24, 6.86 Hz, 1H), 2.54-2.59 (dd, J = 15.25, 3.79 Hz, 1H), 2.38-2.46 (dq, J = 7.6 Hz, 6.91 Hz, 1H), 1.10-1.12 (d, J =6.81 Hz, 3H), 0.95 (s, 9H), 0.11 (s, 3H), 0.1 (s, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 206.63, 171.37, 136.39, 133.57, 128.54, 127.97, 127.93,126.63, 79.82, 74.76, 52.12, 48.68, 41.02, 25.8, 18.28, 10.92

HRMS: $C_{23}H_{34}O_5Si$; $[M+H]^+$: calc.:419.2254, found: 419.2253 $[M+NH_4]^+$ cal.436.2519 found 436.2522

Preparation of (*2S,3R,6R*)-6-((*R*)-1-((tert-butyldimethylsilyl) oxy)-2-hydroxyethyl)-3-methyl-2-((*E*)-styryl) tetrahydro-*2H*-pyran-4-ol 131



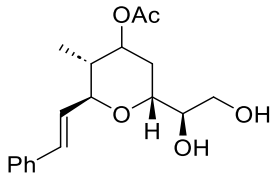
1.662 g (3.97 mmol) of **130** was dissolved in 20 ml of THF and cooling at -78 °C, 4.17 ml (1M, 4.17 mmol) of a solution of lithium triethyl borohydride in THF was slowly added. After 45 min, 11.91 ml (1 M, 11.91 mmol) of a solution of DIBAL-H in hexane was added. After 30 min, the temperature was raised to 0 °C and stirring was continued for another 45 min. Then the reaction was quenched with saturated ammonium chloride solution, followed by a 5-10% (w/w) potassium/sodium tartrate solution. The mixture was stirred vigorously for an additional 1 h at room temperature. The phases were separated and the aqueous phase was extracted with diethyl ether. After drying the combined organic phases over sodium sulfate and removing the solvent *in vacuo*, flash chromatographic (diethyl ether/pentane 4:1) gives 1.282 g (3.26 mmol, 82%) of **131** as colorless oil and respectively white resin.

^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 7.33-7.4 (m, 4H), 7.23-7.27 (m, 1H), 6.58-6.62 (dd, J =16.25,1.69 Hz, 1H), 6.21-6.27 (dd, J = 16.25, 4.93 Hz, 1H), 4.42-4.45 (m,1H), 4.05-4.1 (m, 1H), 3.83-3.93 (m, 2H), 3.72-3.76 (dd, J = 11.13, 5.11 Hz, 1H),3.63-3.67 (dd, J = 11.15, 4.32 Hz, 1H), 2.04-2.1 (ddd, J = 14.12, 7.1, 3.48 Hz, 1H), 1.8-2 (br, 2H), 1.7-1.8 (m, 2H), 1.11-1.12 (d, J = 6.96 Hz, 3H), 0.91 (s,9H), 0.12 (s, 3H), 0.11 (s, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 136.65, 131.97, 128.61, 128.51, 127.71, 126.33, 77.69,73.67, 72.53, 66.89, 63.97, 38.32, 30.85, 25.88, 18.17, 11.76, -4.44, -4.74

HRMS: $C_{22}H_{36}O_4Si$; $[M+H]^+$: calc.: 393.2461 found: 393.2458

Preparation of (*2S,3R,6R*)-6-((*R*)-1,2-dihydroxyethyl)-3-methyl-2-((*E*)-styryl) tetrahydro-*2H*-pyran-4-yl acetate 132



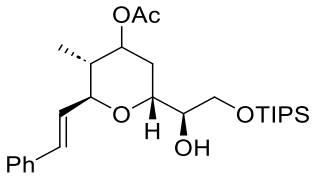
0.473 g (1.17 mmol) of **131** was dissolved in 7 ml of DMF and 1.75 ml (1 M, 1.75 mmol) of a solution of TBAF in THF was added. After stirring for 30 min, at room temperature, 0.676 g (3.55 mmol) of toluene sulfonic acid monohydrate, 3.5 ml of acetone, 2.93 ml (23.77 mmol) of 2,2-DMP, and 1.51 g (9.46 mmol) of anhydrous copper sulfate were added and stirred overnight. Then the reaction solution was slowly added to a saturated sodium bicarbonate solution and diluted with diethyl ether. After filtering off the undissolved copper sulfate, the phases were separated and the organic phase was washed once with water and once with saturated brine and dried over magnesium sulfate. After removing the solvent *in vacuo*, the residue was taken up in 1.5 ml THF, 0.22 ml (2.3 mmol) acetic anhydride, 0.28 ml (2.05 mmol) triethylamine,10 mg (0.08 mmol) DMAP, were added and stirred for 4 h at room temperature. After adding 0.2 ml of methanol and stirring for another 30 min, 15 ml of 70% acetic acid was added and heated to 80 °C for 4 h. The reaction solution was then cooled at room temperature., concentrated *in vacuo,* and azeotropically freed from water and acetic acid residues once with toluene. After flash chromatographic purification (ethyl acetate/pentane 2:1) of the residue, 0.276 g (0.86 mmol, 73%) of **132** was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 7.32-7.34 (m, 2H), 7.24-7.28 (m, 2H), 7.17-7.2 (m, 1H),6.57-6.61 (dd, J = 16.25, 1.24 Hz, 1H), 6.16-6.21 (dd, J = 16.23, 5.25 Hz,1H), 5.11-5.16 (dt, J = 9.95, 4.75 Hz, 1H), 4.37 (m, 1H), 3.82-3.87 (m, 1H), 3.64-3.68 (m, 1H), 3.56-3.61 (m, 1H), 2.15-2.25 (m, 1H), 2.0 (s, 3H), 1.81-1.89 (m, 1H), 1.66-1.71 (dt, J = 13.07, 4.11 Hz, 1H), 1.03-1.04 (d, J = 6.96 Hz, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 170.39, 136.26, 133.12, 128.62, 128, 127.57, 126.53,77.76, 72.93, 71.46, 69.27, 63.76, 35.33, 28.23, 21.19, 12.31

HRMS: $C_{18}H_{24}O_5$; $[M+H]^+$: calc.: 321.1702 found: 321.1710

Preparation of (*2S,3R,6R*)-6-((*R*)-1-hydroxy-2-((triisopropylsilyl)oxy) ethyl)-3-methyl-2-((*E*)-styryl) tetrahydro-*2H*-pyran-4-yl acetate 133



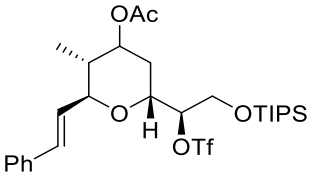
To 0.235 g (0.734 mmol) **132** and 0.101 g (1.47 mmol) imidazole, dissolved in 3.5 ml dichloromethane, were added 0.2 ml (0.954 mmol) triisopropylsilyl chloride and stirred overnight at room temperature. Then ammonium chloride was added and after phase separation, the aqueous phase was extracted with dichloromethane. After drying the combined organic phases over sodium sulfate, the solvent was removed *in vacuo* and the residue was purified by flash chromatography. 0.291 g (0.61 mmol, 83%) **133** was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 7.37-7.39 (m, 2H), 7.29-7.33 (t, J = 7.47 Hz, 2H), 7.22-7.26 (m, 1H), 6.64-6.68 (dd, J = 16.29, 1.23 Hz, 1H), 6.25-6.31 Hz (dd, J = 16.27, 5.08 Hz, 1H), 5.2-5.25 (dt, J = 10.35, 4.58 Hz, 1H), 4.43-4.48 (m, 1H),3.94-3.99 (dt, J = 10.38, 4.28 Hz, 1H), 3.74-3.79 (m, 2H), 3.66-3.72 (m, 1H), 2.51-2.69 (br, 1H), 2.25-2.33 (m, 1H), 2.07 (s, 3H), 1.91-1.99 (m, 1H), 1.71-1.76 (dt, J = 12.9, 3.98 Hz, 1H), 1.11-1.12 (d, J = 6.96 Hz, 3H), 1-1.15 (br, 21H)

^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 170.42, 136.52, 132.72, 128.5, 128.1, 127.78, 126.52,77.93, 73.48, 69.99, 69.71, 63.95, 35.24, 28.30, 21.23, 17.94, 12.3, 11.88

HRMS: $C_{27}H_{45}O_5Si$; $[M+H]^+$: calc.: 477.3036 found: 477.3031

Preparation of (*2S,3R,6R*)-3-methyl-2-((*E*)-styryl)-6-((*R*)-1-(((trifluoromethyl)sulfonyl) oxy)-2-((triisopropylsilyl)oxy) ethyl) tetrahydro-*2H*-pyran-4-yl acetate 134

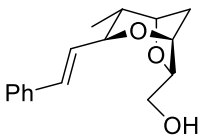


To a solution of 0.256 g (0.537 mmol) **133** and 0.13 ml (1.611 mmol) pyridine in 5 ml dichloromethane, 0.13 ml (0.752 mmol) trifluoromethane sulfonic anhydride was injected at -15 °C. After 15-20 min, the reaction was complete and the reaction solution was washed with 1 N HCl, saturated sodium bicarbonate solution, and brine. The organic phase was dried over sodium sulfate and concentrated under vacuum. The residues dissolved again in toluene, which was again removed *in vacuo*. The last drying with toluene was omitted in later, larger preparations because, if the solvent was completely removed for a longer time, decomposition phenomena occurred. Without further purification, 0.298 g of the product was obtained. In the 1H NMR spectrum, besides the product toluene was also found. Mathematically adjusted for this, 0.286 g (0.47 mmol, 87%) **134**.

^{1}H NMR ($CDCl_3$, 600 MHz): δ[ppm] = 7.38-7.39 (m, 2H), 7.3-7.33 (m, 2H), 7.24-7.26 (m, 2H, phenyl and toluene), 7.17-7.18 (m, 3H, toluene), 6.68-6.71 (dd, J = 16.22, 1.47 Hz,1H), 6.16-6.2 (dd, J = 16.21, 5.3 Hz, 1H), 5.2-5.23 (m, 1H), 5.02-5.05 (m, 1H), 4.43-4.45 (m, 1H), 4.27-4.3 (q, J = 6.35 Hz, 1H), 4.09-4.11 (dd, J = 11.67, 3.83 Hz, 1H),3.93-3.95 (dd, J = 11.65, 4.68 Hz, 1H), 2.36 (s, 3H, toluene), 2.18-2.22 (m, 1H), 2.1 (s, 3H), 1.88-1.9 (m, 2H), 1.0-1.11 (m, br, 24H)

^{13}C NMR ($CDCl_3$, 150 MHz): δ[ppm] = 170.19, 136.45, 133.49, 129.03, 128.52, 128.214, 127.87,127.12, 126.56, 125.288, 90.02, 69.35, 68.45, 62, 35.67, 28.42, 21.18, 17.59, 17.56, 12.48,12.79

Preparation of ((*3S,4R,7S*)-4-methyl-3-((*E*)-styryl)-2,6-dioxabicyclo [3.2.1] octan-7-yl) methanol 16



3.291 g (5.41 mmol) of **134** was dissolved in 40 ml of THF and 6.5 ml (1 M, 6.5 mmol) of a solution of TBAF in THF was added. After stirring for 15 min at room temperature, 40 ml of

methanol was added followed by 7.5 g (54.27 mmol) of potassium carbonate. After stirring overnight, the mixture was diluted with water. The phases were separated, and the aqueous phase was extracted once with ethyl acetate. The combined organic phases were dried over sodium sulfate. After removal of the solvent *in vacuo,* the residue was purified by flash chromatography (ethyl acetate/pentane 1:1). 2.766 g (3.33 mmol, 62%) of **16** was obtained as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ[ppm] = 7.32-7.33 (m, 2H), 7.29-7.33 (m, 2H), 7.21-7.26 (m, 1H),6.56-6.6 (d, J = 15.8 Hz, 1H), 6.09-6.15 (dd, J = 15.8, 7.54 Hz, 1H), 4.44-4.46 (m,1H), 4.31-4.33 (d, J = 6.63 Hz, 1H), 4.04-4.1 (m, 3H), 3.93-3.98 (m, 1H), 2.05-2.1 (ddd, J =11.74, 6.65, 2.73 Hz, 1H), 1.93-1.96 (dd, J = 11.73, 1.54 Hz, 1H),1.5-1.57 (dq, J = 9.12, 6.8 Hz, 1H), 1.24-1.28 (t, J = 7.16 Hz, <1H), 0.94-0.95 (d, J= 6.75 Hz, 3H)

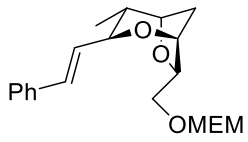
^{13}C NMR ($CDCl_3$, 100 MHz): δ[ppm] = 136.44, 132.1, 128.99, 128.5, 127.74, 126.51, 82.93,79.77, 78.96, 74.4, 60.87, 41.64, 38.76, 15.23

HRMS: $C_{16}H_{20}O_3$; $[M+H]^+$: calc.: 261.1491 found: 261.1488

This data is in agreement with that reported by the literature[10].

6.2.3 Procedures for 4.3

Preparation of (*3S,4R,7S*)-7-(((2-methoxyethoxy) methoxy)methyl)-4-methyl-3-((*E*)-styryl)-2,6-dioxabicyclo[3.2.1]octane 213



202 mg (0.78 mmol) **16** was dissolved in 10 ml DCM at room temperature. 0.27 ml (1.56 mmol) DIPEA and 0.18 ml (1.56 mmol) MEM-Cl were added dropwise. After stirring at room temperature overnight, the mixture was washed once each with 1N HCl and saturated sodium bicarbonate. The organic phase was dried over sodium sulfate, filtered, and the solvent was

evaporated *in vacuo*. After flash chromatography cleaning (ether / pentane 2: 1) 228 mg (0.65 mmol, 85%) **213** was obtained as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ[ppm] = 7.41 – 7.27 (m, 4H), 7.27 – 7.18 (m, 1H), 6.58 (d, J = 15.7 Hz, 1H), 6.11 (dd, J = 15.8, 7.5 Hz, 1H), 4.91 – 4.74 (m, 1H), 4.81 (s, 2H), 4.42 (q, J = 2.2 Hz, 1H), 4.30 (d, J = 6.6 Hz, 1H), 4.15 – 3.89 (m, 4H), 3.84 – 3.67 (m, 3H), 3.65 – 3.53 (m, 3H), 3.56 – 3.34 (m, 2H), 3.39 (s, 3H), 2.06 (ddd, J = 11.7, 6.6, 2.7 Hz, 1H), 1.92 (dd, J = 11.8, 1.6 Hz, 1H), 1.57 – 1.46 (m, 1H), 1.20 (t, J = 7.0 Hz, 1H), 0.93 (d, J = 6.7 Hz, 3H).

^{13}C NMR (CDCl3, 100 MHz) δ[ppm] = 136.70, 132.57, 129.25, 128.64, 126.65, 95.69, 81.48, 79.78, 79.14, 74.87, 71.91, 66.85, 65.64, 59.16, 41.82, 38.84, 15.34.

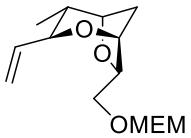
IR (ATR) = 3058(w), 3026(w), 2961(m), 2931(m), 2876(m), 2817(w), 1599(w), 1578(w), 1493(w), 1450(w), 1415(w), 1398(w), 1366(w), 1345(w), 1313(w), 1299(w), 1284(w), 1243(w), 1221(w), 1199(w), 1174(w), 1110(s), 1075(s), 1043(s), 1007(s), 965(s), 920(m), 907(m), 876(m), 846(m), 790(w), 744(m), 694(m), 650(w), 615(w), 607(w), 581(w), 540(w), 515(w), 427(w).

MS(EI**)** m/z (%) = 348.1(M+, 100), 316.1(50), 303.1(48), 291.1(100), 289.1(93), 273.1(17), 272.1(47), 260.1(58),259.1(100),131.0(89), 132.0(22),89.0(88),59.0(82).

HRMS $C_{20}H_{28}O_5$ M calc. 348.1937; found 348.1931

$[\boldsymbol{\alpha}]_D^{20}$ = -36.76° (*c* = 0.74 in $CHCl_3$)

Preparation of (*3S,4R,7S*)-7-(((2-methoxyethoxy)methoxy)methyl)-4-methyl-3-vinyl-2,6-dioxabicyclo[3.2.1]octane 214



A solution of ester **213** (1.12 g, 3.25 mmol) in methanol (32.5 mL) was cooled to -78 °C and ozone was bubbled through the solution until it turned blue, indicating saturation. Oxygen

was then bubbled through the solution for 15 min followed by addition of dimethyl sulfide (4.78 mL, 65 mmol). The reaction mixture was allowed to warm to rt and stir overnight. Volatiles were removed in vacuo and the crude aldehyde was taken on without purification. To a solution of potassium tert-butoxide (1.46 g, 13.0 mmol) in THF (32 mL), cooled to 0°C, was added methyltriphenylphosphonium bromide (5.80 g, 16.3 mmol) and stirred for 0.5 h. A solution of the crude aldehyde was dissolved in THF (8 mL) and added slowly. The solution was allowed to stir for 1 h at 0 °C then quenched with aqueous ammonium chloride (10 mL) followed by addition of DCM (40 mL) and water (20 mL). The phases were separated and the aqueous layer was extracted with DCM (2 x 20 mL). The combined organics were dried over sodium sulfate, filtered, evaporated in vacuo, and purified via column chromatography (30% EtOAc/hexanes) to yield 0.790 g of terminal olefin **214** (2.92 mmol, 90%, 2 steps) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm] = 5.74 (ddd, J = 17.3, 10.3, 7.3 Hz, 1H), 5.22 (dt, J = 17.1, 1.4 Hz, 1H), 5.17 – 5.11 (m, 1H), 4.78 (s, 2H), 4.38 (q, J = 2.2 Hz, 1H), 4.25 (d, J = 6.6 Hz, 1H), 4.07 (td, J = 6.1, 2.2 Hz, 1H), 3.97 – 3.80 (m, 3H), 3.77 – 3.65 (m, 2H), 3.61 – 3.51 (m, 2H), 3.39 (s, 4H), 2.02 (ddd, J = 11.7, 6.6, 2.8 Hz, 1H), 1.88 (d, J = 1.7 Hz, 1H), 1.47 – 1.34 (m, 1H), 0.88 (d, J = 6.7 Hz, 3H).

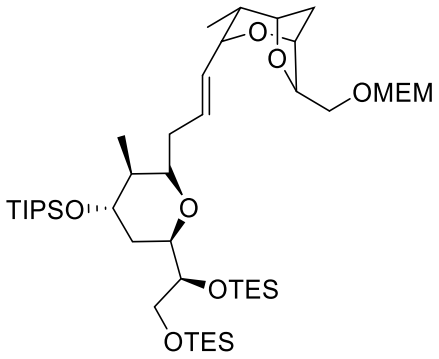
^{13}C NMR (100 MHz, $CDCl_3$) δ[ppm] = 138.03, 117.23, 95.67, 81.45, 80.07, 79.08, 74.74, 71.90, 66.82, 65.65, 59.14, 41.37, 38.79, 15.18.

IR (ATR) = 3078(w), 3018(w), 2932(m), 2876 (m), 2818(w), 1646(w), 1454(w), 1423(w), 1365(w), 1345(w), 1285(w), 1243(w), 1221(w), 1175(w), 1112(s), 1076(s), 1044(s), 918(s), 951(m), 918(m), 900(m), 874(m), 848(m), 827(w), 801(w), 775(w), 638(w), 598(w), 545(w), 519(w), 436(w), 418(w).

HRMS $C_{14}H_{24}O_5$ $[M+H]^+$: calc.: 272.1624 found: 272.1622

$[\boldsymbol{\alpha}]_D^{20}$ = -67.50° (c = 0.45 in $CHCl_3$)

Preparation of 3,3,8,8-tetraethyl-5-((*2R,4S,5S,6R*)-6-((*E*)-3-((*1R,3S,4R,5R*)-7-(((2-methoxyethoxy) methoxy) methyl)-4-methyl-2,6-dioxabicyclo[3.2.1]octan-3-yl)allyl)-5-methyl-4-((triisopropylsilyl)oxy)tetrahydro-*2H*-pyran-2-yl)-4,7-dioxa-3,8-disiladecane 215



In milligram scale: To bicyclic ether **214** (3.12 mg, 0.012 mmol,1.2eq) in 1 mL degassed toluene at room temperature was added tetrahydropyran **212** (6 mg, 0.01 mmol,1.0eq) dropwise over 6 hours as a solution in 0.5 mL toluene via syringe pump. Grubbs 2nd generation catalyst (6 mg, 0.007 mmol) was added in three portions as a solution in 0.3 mL toluene during the addition of tetrahydropyran **212**. Upon completion of the addition of tetrahydropyran 2, the reaction was stirred for 12 hours at room temperature in the glovebox, then opened to air and stirred for 1 hour. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (10-20% EtOAc/Hex) to give cross-metathesis adduct **215** (5.7 mg, 67%) as a colorless oil.

In gram scale: To bicyclic ether **214** (1.64 g, 6.02 mmol,1.6eq) in 15 mL degassed toluene at room temperature was added tetrahydropyran **212** (2.13 g, 3.55 mmol,1.0eq) dropwise over 6 hours as a solution in 15 mL toluene via syringe pump. Grubbs 2nd generation catalyst (452 mg, 0.532 mmol) was dissolved in 4ml degas toluene and added simultaneously with **212** via syringe pump in 6 hours. Upon completion of the addition, the reaction was stirred for 12 hours at room temperature with inert gas, then opened to air and stirred for 1 hour. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (10-20% EtOAc/Hex) to give cross-metathesis adduct **215** (1.81 g, 60%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 600 MHz) δ[ppm] = 5.61 (ddd, J = 14.5, 9.0, 5.0 Hz, 1H), 5.42 (dd, 1H), 4.78 (s, 2H), 4.35 (q, J = 2.1 Hz, 1H), 4.25 (d, J = 6.7 Hz, 1H), 4.07 – 4.05 (m, 1H), 3.98 – 3.86 (m, 5H), 3.84 – 3.77 (m, 2H), 3.75 – 3.70 (m, 2H), 3.62 – 3.53 (m, 3H), 3.47 (dd, J = 10.2, 6.0 Hz, 1H), 3.39 (s, 3H), 2.29 (dddd, J = 12.0, 7.0, 5.1, 1.7 Hz, 1H), 2.08 – 1.97 (m, 3H), 1.85 (dd, J = 11.7, 1.6 Hz, 1H), 1.69 (ddd, J = 14.0, 11.7, 2.6 Hz, 1H), 1.52 – 1.45 (m, 1H), 1.42 – 1.34 (m, 1H), 1.10 – 0.99 (m, 18H), 0.94 (td, J = 8.0, 1.4 Hz, 21H), 0.90 – 0.80 (m, 7H), 0.66 – 0.53 (m, 12H).

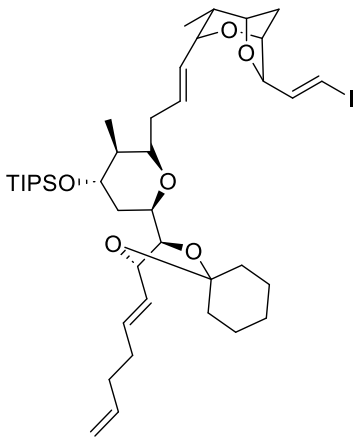
^{13}C NMR ($CDCl_3$,151MHz) δ[ppm] = 131.56, 131.07, 95.71, 81.52, 79.85, 79.14, 76.14, 74.75, 73.57, 73.01, 71.91, 71.34, 66.87, 65.79, 64.60, 59.17, 41.73, 38.88, 38.37, 35.85, 28.99, 18.25, 15.26, 12.37, 10.70, 7.08, 6.94, 5.18, 4.49.

IR(ATR) = 2952(m), 2940(m), 2915(m), 2873 (m), 1968(w), 1460(m), 1414(w), 1379(w), 1343(w), 1315(w), 1297(w), 1285(w), 1239(w), 1199(w), 1143(m), 1115(s), 1077(s), 1049(s), 1005(s), 969(s), 920(w), 903(w), 881(w), 837(w), 803(w), 768(w), 738(s), 726(s), 678(s), 607(w), 568(w), 539(w), 523(w), 501(w),468(w), 444(w), 428(w).

HRMS $C_{44}H_{88}O_9Si_3$ $[M+Na]^+$ calc.: 867.5634; found: 867.5633.

$[\boldsymbol{\alpha}]_D^{20}$ = -3.607° (*c* = 0.61 in $CHCl_3$)

Preparation of (((*2R,3S,4S,6S*)-6-((*2S,3S*)-3-((*E*)-hexa-1,5-dien-1-yl)-1,4-dioxaspiro[4.5]decan-2-yl)-2-((*E*)-3-((*3S,4R,7S*)-7-((*E*)-2-iodovinyl)-4-methyl-2,6-dioxabicyclo[3.2.1]octan-3-yl)allyl)-3-methyltetrahydro-*2H*-pyran-4-yl)oxy)triisopropylsilane 247



40 mg terminal alkyne (1 eq, 0.05 mmol) was dissolved in 1 ml dry THF, cooled to 0 °C and 1 eq Superhydrid was added. In a separate flask (covered in aluminum foil). 20 mg $ZrCp_2Cl_2$ (2 eq, 0.067 mmol) was suspended in 0.5 ml THF and 67 µl Superhydrid (2 eq, 0.067 mmol) was added. After 1 h of stirring the alkin solution was added to the generated Schwarz regent. After another 30 mins at rt, 19 mg NIS (2.5 eq, 0.084 mmol) was added and stirred for 15 min at ambient temperature. The reaction was quenched with sat. $NaHCO_3$ solution, the water phase extracted with diethyl ether, and the combined organic the phase was washed with saturated brine. After drying over $MgSO_4$, the crude material was purified via column chromatography (pentane/diethyl ether 2:1) to isolate 25 mg clear oil (53% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ[ppm]= 6.82 (dd, J = 9.2, 3.3 Hz, 1H), 6.56 (dd, J = 9.7, 1.1 Hz, 1H), 5.87 - 5.76 (m, 2H), 5.58 - 5.52 (m, 2H), 5.41 (dd, J = 10.2, 5.2 Hz, 1H), 5.02 (dd, J = 11.4, 1.1 Hz, 1H), 4.98 - 4.93 (m, 1H), 4.64 - 4.59 (m, 1H), 4.36 - 4.34 (m, 1H), 4.31 (quint, J = 1.8 Hz, 1H), 4.27 - 4.24 (m, 1H), 3.96 (q, J = 1.7 Hz, 1H), 3.90 - 3.85 (m, 4H), 2.30 - 2.23 (m, 1H), 2.19 - 2.14 (m, 4H), 2.12 - 2.07 (m, 1H), 1.88 - 1.84 (m, 1H), 1.75 - 1.69 (m, 1H), 1.65 - 1.49 (m, 10H), 1.40 - 1.33 (m, 4H), 1.06 - 1.01 (m, 21H), 0.84 (d, J = 2.9 Hz, 3H), 0.83 (d, J = 2.7 Hz, 3H).

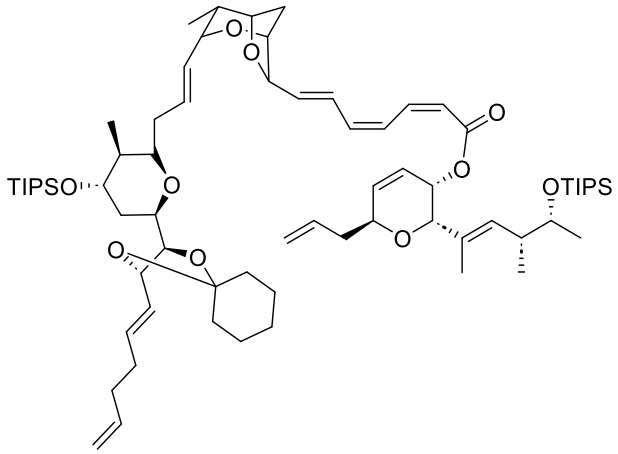
^{13}C NMR (100 MHz, $CDCl_3$) δ[ppm] = 140.96, 138.16, 133.34, 131.56, 130.49, 126.13, 114.79, 108.71, 83.51, 79.51, 79.34, 79.32, 78.77, 78.53, 75.61, 73.02, 71.21, 70.87, 41.27, 38.64, 37.80, 37.66, 35.71, 35.12, 34.17, 33.43, 31.89, 25.20, 24.05, 23.78, 18.12, 15.02, 12.26, 10.46.

HRMS $C_{41}H_{67}IO_6Si$ **[**$M+NH_4]^+$ calc.: 828.4095, found:828.4038.

IR(ATR) 2961(s), 2934(s), 2864(s), 2329(w), 1460(m), 1366(m), 1279(w), 1165(m), 1142(m), 1094(s), 1066(s), 967(s), 939(s), 881(m), 710(w), 678(m), 658(m), 410(w)**.**

$[\boldsymbol{\alpha}]_D^{20}$ = -9.2° (*c* = 1.5, $CHCl_3$).

Preparation of (*2S,3S,6S*)-6-allyl-2-((*4R,5R,E*)-4-methyl-5-((triisopropylsilyl)oxy)hex-2-en-2-yl)-3,6-dihydro-*2H*-pyran-3-yl (*2Z,4Z,6E*)-7-((*1R,3R,4R,5R,7S*)-3-((*E*)-3-((*2S,3S,4S,6R*)-6-((*2R*)-3-((*E*)-hexa-1,5-dien-1-yl)-1,4-dioxaspiro[4.5]decan-2-yl)-3-methyl-4-((triisopropylsilyl)oxy)tetrahydro-*2H*-pyran-2-yl)prop-1-en-1-yl)-4-methyl-2,6-dioxabicyclo[3.2.1]octan-7-yl)hepta-2,4,6-trienoate



A 5 mL tube was charged with stannane **239**, vinyl iodide **247**, $Ph_2PO_2NBu_4$, and dissolved in degassed DMF (1 mL). To this was added $PdCl_2(PhCN)_2$, and delight stirred at RT in the glovebox for 4h. The reaction mixture was diluted with Et2O/hexane (1:1, 2 mL), filtered through a Celite plug into the brine, and rinsed with Et_2O/hexane. The mixture was extracted using Et_2O/hexane (1:1), and the combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to give a crude residue, which was purified by flash chromatography (15% EtOAc/hexane) to afford trienoate **249** with 29% yield.

diagnostic trienoate peaks in the **^{1}H NMR** and **2D ^{1}H NMR** of the unpurified material ($CDCl_3$, 600 MHz)
δ[ppm] = 7.34 [dd, J = 12.0, 11.4 Hz, 1 H, [BCO-CH=CH-CH=C(H)-CH=CH-COOMe]], 7.09 [dd, J = 12.0, 11.4 Hz, 1 H, [BCO-CH=CH-CH=CH-C(H)=CH-COOMe]], 6.99 [dd, J = 15.0, 12.0 Hz, 1 H, [BCO-CH=C(H)-CH=CH-CH=CH-COOMe]], 6.43 [dd, J = 12.0, 11.4 Hz, 1 H, [BCO-CH=CH-C(H)=CH-CH=CH-COOMe]], 6.19 [dd, J = 15.0, 5.4 Hz, 1 H, [BCO-C(H)=CH-CH=CH-CH=CH-COOMe]], 5.64 [d, J = 11.4 Hz, 1H, [BCO-CH=CH-CH=CH-CH=C(H)-COODHP]].

HRMS $C_{70}H_{114}O_{10}Si_2$ $[M+Na]^+$ calc.:1193.785, found:1193.796; $[M+NH_4]^+$ calc.: 1188.829; found: 1188.839.

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8. Appendix

8.1 Catalog of Tables

8.2 Catalog of Schemes

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