Studies Toward the Total Synthesis of Biselide A

by

Matthew W. Taron

B.Sc. (Hons.), University of British Columbia, 2011

Thesis Submitted in Partial Fulfillment of the
Requirements for the Degree of
Master of Science

in the
Department of Chemistry
Faculty of Science

SIMON FRASER UNIVERSITY

Summer 2015

Approval

Name: **Matthew W. Taron**

Degree: **Master of Science**

Title: ***Studies Toward The Total Synthesis of Biselide A***

Examining Committee: **Chair:** Dr. Hua-Zhong Yu
Professor

Dr. Robert A. Britton
Senior Supervisor
Associate Professor _____

Dr. Peter D. Wilson
Supervisor
Associate Professor _____

Dr. David J. Vocadlo
Supervisor
Professor _____

Dr. Robert N. Young
Internal Examiner
Professor _____

Date Defended/Approved: May 12, 2015

Abstract

The use of natural products for medicinal purposes is a tradition dating back to ancient times. To this day bioactive natural products continue to inspire a large proportion of the new pharmaceuticals that are developed each year. Many natural products serve as drug leads and inspire the synthesis and development of more potent analogues. The biselides and haterumalides are two members of a class of recently described bioactive polyketide natural products that have been found in Okinawan ascidians.

Many of the biselides and haterumalides exhibit anticancer activity, yet very little material is available from the natural sources. Of particular interest is biselide A, which is the only member of this class to demonstrate selective killing of human cancer cells over healthy cells. It has been proposed that C20 oxygenation in biselide A confers this selectivity and thus, derivatives with C20 oxygenation are also of pharmaceutical interest. While multiple syntheses of haterumalides have been published, biselide A has not yet been synthesized.

This thesis highlights recent efforts towards a scalable total synthesis of biselide A. Three different approaches have been explored: the first incorporates a Horner-Wadsworth-Emmons reaction as a key step, and the second and third use a cross metathesis key step. While the Horner-Wadsworth-Emmons approach was ultimately unsuccessful, our successes in the cross metathesis approach should now yield access to this potentially important natural product.

Keywords: Total synthesis; biselide; haterumalide; macrolide; natural products; cross metathesis

Acknowledgements

I would like to thank my supervisor, Dr. Robert Britton, for allowing me the opportunity to explore deeper into the field of organic synthesis. I am grateful for his confidence in me to test my own ideas, his enthusiasm and optimism during sometimes stressful days in the lab, and his patience and attitude which have truly made the last 2 years enjoyable.

I would like to thank Profs. Peter Wilson and David Vocadlo for agreeing to serve as my supervisory committee and for providing insightful suggestions which helped spark new curiosities throughout my project.

I would like to thank Colin Zhang and Dr. Andrew Lewis for NMR services, as well as past and present departmental secretaries Lynn Wood, Evon Khor, and Nathalie Fournier for their assistance.

I would like to thank past and present members of the Britton group: Dr. Matthew Nodwell, Dr. Jake Goodwin-Tindall, Dr. Robbie Zhai, Dr. Ajay Naidu, Dr. Shira Halperin, Jason Draper, Vijay Dhand, Hope Fan, Stanley Chang, Milan Bergeron-Brlek, Michael Holmes, Steve Hur, Abhi Bagai, Chris Adamson, and Daniel Kwon; you all have been inviting since day one and this allowed for a fun and productive 2 years. I would also like to thank members of the Young research group for their assistance in everything from borrowing chemicals to providing scientific insight.

I would like to thank my family for their continued support and encouragement to pursue my interests and goals. Additionally, I would like to thank my friends for their support along my journey.

Lastly, I would like to thank my previous supervisor at the University of British Columbia Okanagan, Dr. Ed Neeland, who first introduced me to the excitement and power of organic chemistry. His continued support and mentorship has enlightened me on numerous occasions.

Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

$[\alpha]_D$	Specific rotation at the sodium D line (589 nm)
°C	Degrees Celsius
δ	Chemical shift (in ppm) from tetramethylsilane
2,2-DMP	2,2-Dimethoxypropane
9-BBN	9-Borabicyclo[3.3.1]nonane
Ac	Acetyl
addn	Addition
aq	Aqueous
BCE	Before common era
Bu	Butyl
BuLi	*n*-Butyllithium
c	Concentration in g/mL
cat.	Catalytic amount
COSY	Correlation spectroscopy
D	Dextrorotatory
DCC	*N,N'*-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	Diisobutylaluminum hydride
DIPA	Diisopropylamine
DIC	*N,N'*-Diisopropylcarbodiimide
DIPEA	*N,N*-Diisopropylethylamine
DMAP	*N,N*-Dimethyl-4-aminopyridine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodinane
dpephos	(Oxydi-2,1-phenylene)*bis*(diphenylphosphine)
dr	Diastereomeric ratio
E	Entgegen (*trans*)
ee	Enantiomeric excess
eq.	Equivalents
Et	Ethyl

Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
equiv.	Equivalents
FT-IR	Fourier transform infrared
GC	Gas chromatography
G-II	Grubbs II
HG-II	Hoveyda-Grubbs II
HMBC	Heteronuclear multiple bond correlation
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i	Iso-
i.e.	*Id est* (that is)
IC_{50}	Half maximal inhibitory concentration
imid.	Imidazole
KHMDS	Potassium hexamethyldisilazide
L	Levorotatory
LC	Liquid chromatography
LD	Lethal dosage
LDA	Lithium diisopropylamide
lit.	Literature
M	Molar (mol/L)
m.p.	Melting point
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
mmol	Millimole(s)
mol	Mole(s)
MPM	4-Methoxyphenyl methyl
MS	Mass spectrometry

Ms	Mesyl
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NHK	Nozaki-Hiyama-Kishi
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
OTf	Trifluoromethanesulfonate
Ph	Phenyl
pH	$-\log_{10}[H^+]$
PMB	Paramethoxybenzyl
ppm	Parts-per-million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
pyr.	Pyridine
r.t.	Room temperature
RCM	Ring-closing metathesis
RRCM	Relay ring-closing metathesis
SAR	Structure-activity relationship
SCUBA	Self-contained underwater breathing apparatus
SM	Starting material
SOMO	Singly-occupied molecular orbital
t	Tertiary
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMS	Trimethylsilyl

TOF	Time-of-flight
Ts	Tosyl
Z	Zusammen (*cis*)

Chapter 1.

Introduction

1.1. Natural Products Used in Medicine

For thousands of years, humans primarily used plants as a source of medicines for the treatment of disease and illness.[1] The use of these plants were so important to health and survival that entire medicinal systems were created around them, with the earliest records from Mesopotamia dating back as far as 2600 BCE.[2] These records document the medicinal uses of approximately 1000 plant-based substances, some of which include *Glycyrrhiza glabra* (licorice) and *Papaver somniferum* (poppy juice).[2] Records of many other plant-based medicinal systems have been discovered from Egypt ("Ebers Papyrus", 1500 BCE), China ("Wu Shi Er Bing Fang", 1100 BCE), and India ("Charaka", 1000 BCE).[2]

Plants and other organisms produce secondary metabolites which are small molecules that are often produced to exhibit a specific biological activity. These compounds are also known as natural products. Over the past century, a tremendous effort has been expended in determining the structure of the active natural products that have been traditionally used as medicines. For example, extracts from the bark of a willow tree were traditionally used to treat pain and fever. The medicinal properties of willow bark extract can be attributed to the natural product salicin (**1**), which was later modified to become the synthetic analogue, acetylsalicylic acid (**2**) (aspirin).[3] Similarly, *Ephedra sinica* is a Chinese plant that produces ephedrine (**3**), a drug that was traditionally used to treat asthma and is currently used as a decongestant.[2] The use of ephedrine as a bronchodilator eventually led to the discovery of a more potent synthetic derivative, salbutamol (**4**).[4] A further and significant natural product discovery was that of paclitaxel (**5**), found in the stem bark of the Pacific Yew tree (*Taxus brevifolia*) and first

isolated in 1967.[5] Paclitaxel is still an important cancer chemotherapeutic today, and presently well over 1 million patients have received treatment with this drug for breast and ovarian cancers.[6]

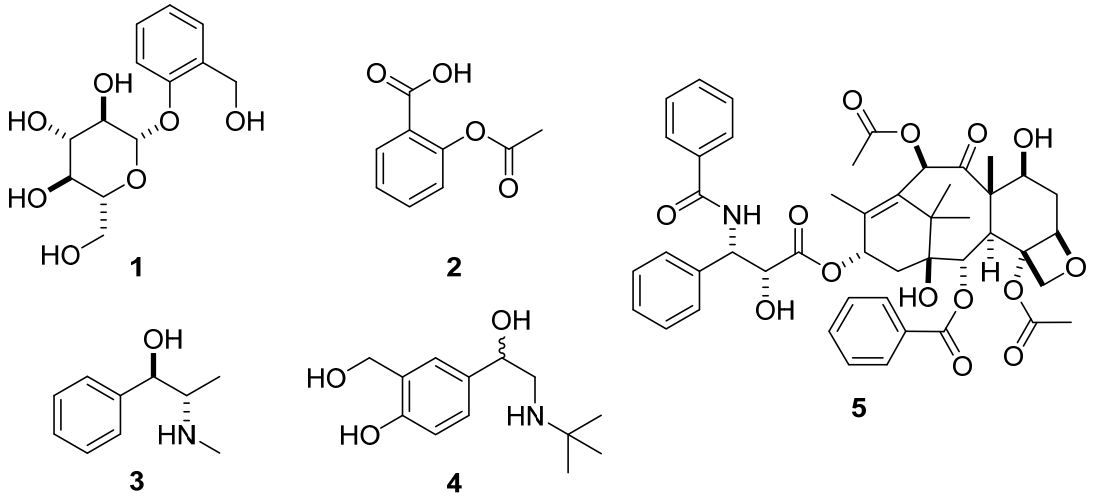


Figure 1.1. Natural products used as drugs: salicin (1), acetylsalicylic acid (2), ephedrine (3), salbutamol (4), and paclitaxel (5). [3,4,7]

Clearly the natural product world has gifted us with many important pharmaceutical compounds and lead candidates for drug discovery efforts. A study published by Newman and Cragg in 2010 further highlights the continued importance of natural products to the pharmaceutical sector by categorizing the sources of new drugs entering the market over the past 30 years.[8] This study reports that over half of the drugs brought to market in the 30 year timeframe were natural products or were derived from, inspired by, or mimicked by the properties/structure of natural products (Table 1.1).[8]

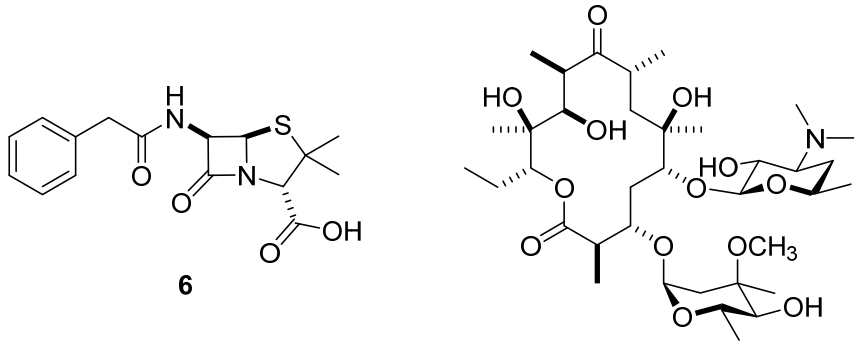
Table 1.1. Sources of New Pharmaceutical Drugs from 1981 – 2010[8,9]

Source of new drug	Number of drugs	Percentage of total (%)
Biological (usually a large peptide or protein)	144	12.7
Natural product	47	4.2
Natural product "botanical" (botanical "defined mixtures")	3	0.3
Natural product derivative (usually made by semisynthesis)	247	21.9
Synthetic (usually found by random screening)	325	28.8
Synthetic but pharmacophore is/was from a natural product	50	4.4
Vaccine	68	6.0
Natural product mimic	246	21.8
Total	1130	100%

While traditional natural product research has focused on terrestrial plant sources, many recent discoveries have relied on microorganisms as a source of bioactive natural products. One of the most popular antibiotics, penicillin (**6**) is a natural product isolated from the fungi *Penicillium notatum*, and erythromycin (**7**) is a macrolide produced by the bacteria *Saccharopolyspora erythraea*.[3] Additionally, in the 1950's marine environments became more accessible for natural products discovery due to the introduction of SCUBA and small submarines.[10] Efforts to discover new bioactive compounds from the ocean have resulted in the development of a growing number of pharmaceutical drugs. One example of a potent marine natural product is bryostatin 1 (**8**), which is currently in clinical trials for the treatment of cancer, Alzheimer's disease, and HIV/AIDS eradication.[11] Bryostatin 1 (**8**) was first isolated and characterized in 1982 from a marine invertebrate, *Bugula neritina*. In this case, 500 kg of the bryozoan was collected to extract and isolate the natural product.[12] The epothilones (**9**) are another class of marine macrolides isolated from a myxobacteria, *Sorangium cellulosum*.[13] In this case, 230 L of production strain culture was required to yield just 4.8 g of epothilone A (**9**, R = H) and 2.1 g of epothilone B (**9**, R = CH_3).[13] The discovery of the epothilones eventually led to a number of drug candidates, of which ixabepilone (**10**) was created and approved for the treatment of breast cancer in 2007.[14]

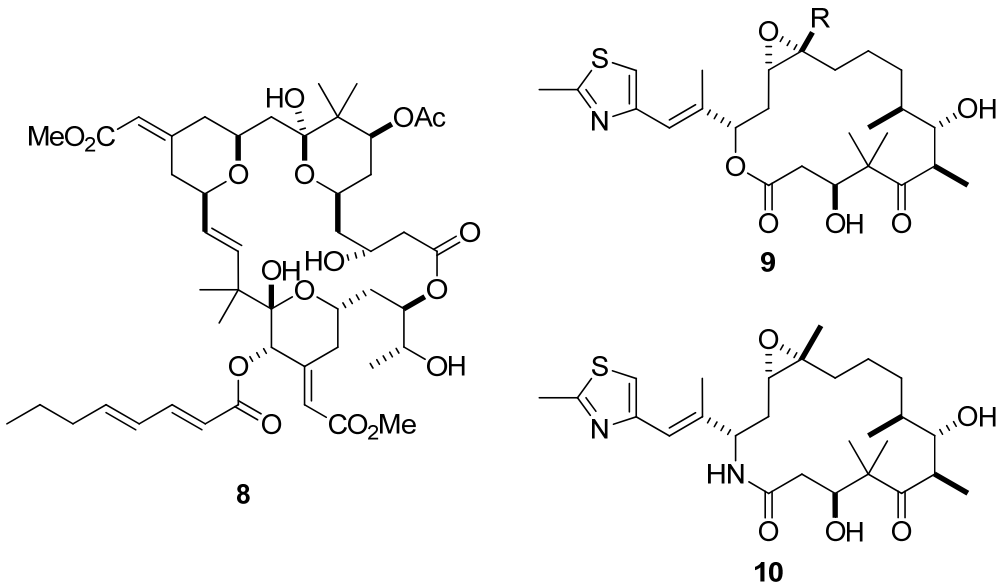
The collection of marine plants and organisms often requires considerable resources and large quantities (multi kilograms) of biomass to isolate very small

amounts of pure natural products, which represents an environmental concern. Additionally, obtaining small amounts of natural products from marine collections often precludes derivatization for medicinal chemistry purposes, clinical trials, or pharmaceutical production. Consequently, an important goal for synthetic organic chemistry is the design and total synthesis of bioactive natural products that allow for the derivatization and scale up of nature's most valuable and important molecules.



6 **7**

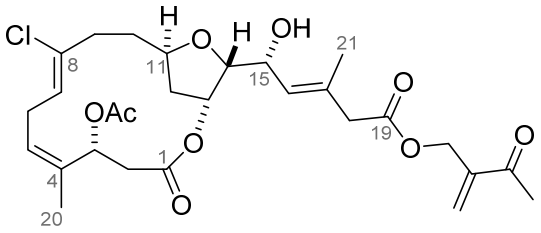
Figure 1.2 **Natural products found in organisms: penicillin (6) and erythromycin (7).[3]**



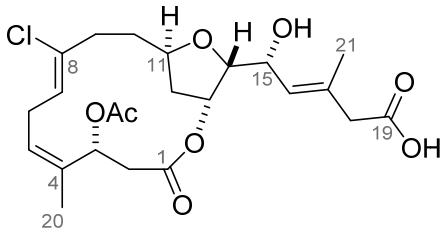
8 **9** **10**

Figure 1.3 **Marine macrolide natural products: bryostatin 1 (8), epothilone A (9, R = H), epothilone B (9, R = CH_3), and ixabepilone (10).[12,13,15]**

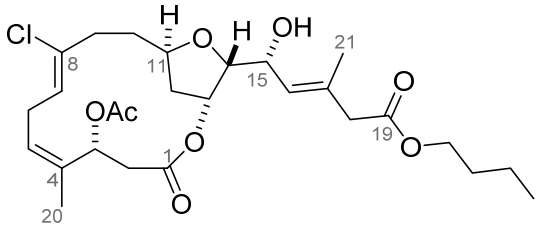
The first haterumalides were discovered from two species of Okinawan marine organisms in 1999.[16,17] Hu *et. al.* reported the isolation (1.5 mg) and structure determination of haterumalide B (**11**), which was found in extracts of the Okinawan ascidian *Lissoclinum sp.*[17] In the same year, Uemura *et al.* published the isolation and structures of haterumalides NA (**12**), NB (**13**), NC (**14**), ND (**15**), and NE (**16**) from an Okinawan sponge, *Ircinia sp.*[16] Additionally, Strobel *et. al.* reported the discovery of a chlorinated macrocyclic lactone in 1999, which was isolated from a strain of *Serratia marcescens* bacteria.[18] This compound was reported as oocydin A, however, was later determined to be identical to haterumalide NA (**12**). In 2001, haterumalide X was discovered and determined to be the *Z* isomer at the C16 alkene of haterumalide NA.[19] This discovery was published by Levenfors who reported also finding haterumalides NA, B, and NE all from a soil bacterium *Serratia plymuthica.*[19]



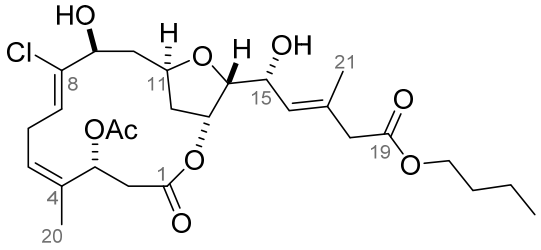
11 (haterumalide B)



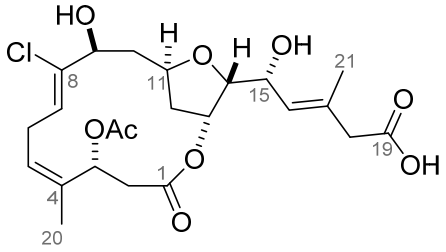
12 (haterumalide NA)



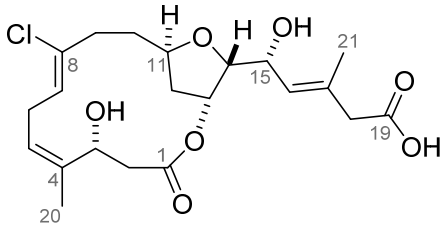
13 (haterumalide NB)



14 (haterumalide NC)



15 (haterumalide ND)



16 (haterumalide NE)

Figure 1.4 Structures of haterumalide natural products.[20]

Members of the biselide family are structurally similar to the haterumalides, with the notable additional C20 oxygenation. It wasn't until 2004 that biselides were first discovered by Kigoshi *et. al.* with the isolation of biselides A (**17**) and B (**18**) from the Okinawan ascidian *Didemnidae sp.*[21] In 2005 Kigoshi *et al.* additionally discovered biselides C (**19**), D (**20**), and E (**21**) from the same organism.[22]

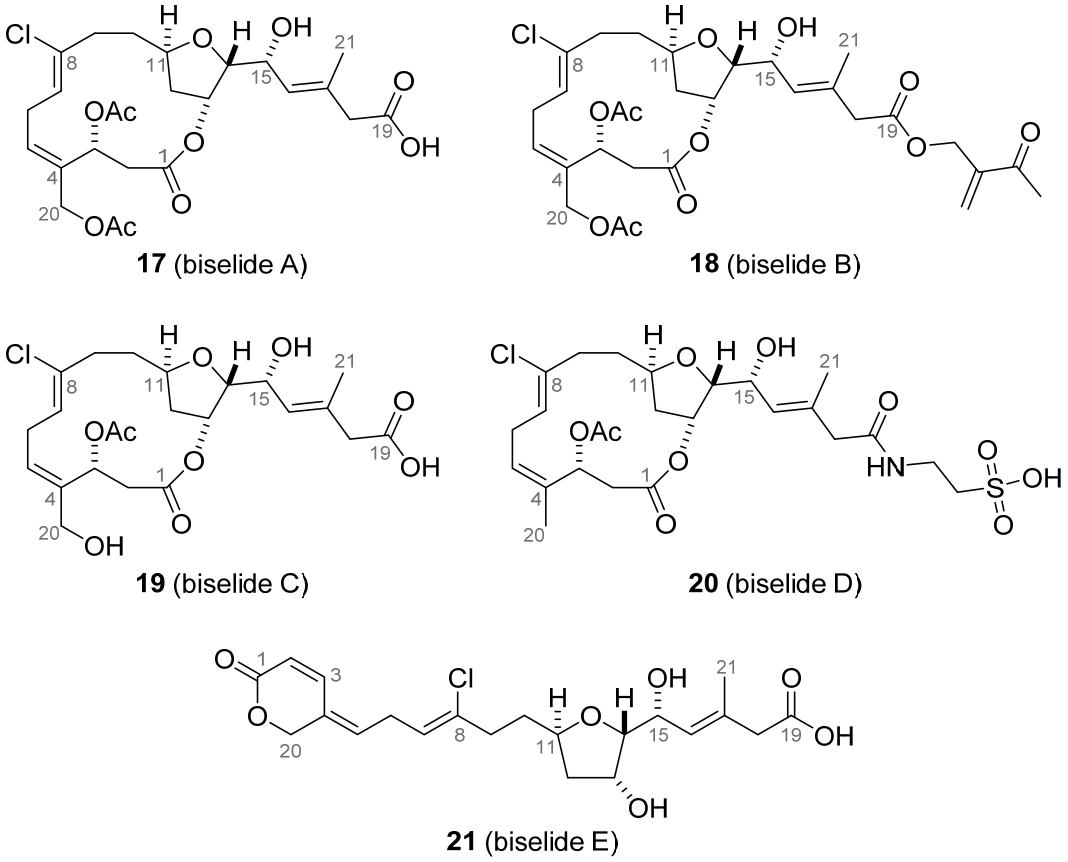


Figure 1.5 Structures of biselide natural products.[20]

Structurally, the haterumalides and biselides are all 14-membered macrolactones containing a trisubstituted 3-hydroxytetrahydrofuran moiety, and differ only by substitutions at C3, C9, C19, and C20, with the exception of biselide E which is a linear analogue. All of these molecules have 5 stereogenic centres except for biselide E which has 4 stereogenic centres. Halogenated marine macrolides are rare and thus, the presence of the vinyl chloride moiety further contributes to the unique structure of these two classes of compounds.[17]

1.2. Biological Activity of Haterumalides and Biselides

Many of the haterumalides and biselides have been tested for biological activity and a variety of effects have been reported. After haterumalide B (**11**) was isolated, Ueda and Yu discovered that it is capable of inhibiting the cell division of fertilized sea urchin eggs with complete inhibition observed at 0.01 μg/mL.[17] Haterumalides B (**11**), NA (**12**), and NE (**16**) all exhibit antifungal properties by preventing spore germination of multiple types of filamental fungi, including oomycetes (water molds).[19] Uemura *et. al.* tested haterumalide NA (**12**) against P388 leukemia cancer cells and cytotoxic effects were observed with an IC_{50} of 0.32 μg/mL.[16] Additionally, haterumalide NA (**12**) was shown to be moderately toxic towards mice, exhibiting an LD_{99} of 0.24 g/kg.[16]

To date, Kigoshi has published the most in depth bioactivity studies and compared biselides A (**17**) and C (**19**) and haterumalide NA methyl ester to the commercial chemotherapy drugs cisplatin and doxorubicin against an array of human cancer cell lines (Table 1.2).[22] These results suggest that biselide A (**17**) and haterumalide NA methyl ester exhibit a cytotoxicity towards human cancer cells similar to that of chemotherapy drugs cisplatin and doxorubicin. While the structurally similar biselide C (**19**) also exhibits cytotoxicity, it is less effective when compared to biselide A (**17**) and haterumalide NA methyl ester. Kigoshi additionally carried out *in vivo* toxicity studies in brine shrimp.[22] Biselides A (**17**) and C (**19**) showed no toxicity against brine shrimp at levels up to 50 μg/mL.[22] Haterumalide NA methyl ester was tested against brine shrimp and interestingly showed strong toxicity, with an LD_{50} of 0.6 μg/mL.[22] These results suggest that oxygenation at C20 in biselides A (**17**) and C (**19**), and notably absent in haterumalide NA, may confer selectivity towards the killing of cancer cells.

Table 1.2 Cytotoxicity of Biselides A, C, and Haterumalide NA Methyl Ester Compared to Cisplatin and Doxorubicin*

Cell Line	Biselide A (17)	Biselide C (19)	Haterumalide NA methyl ester	Cisplatin	Doxorubicin
MDA-MB-231 (breast)	3.72	25.5	0.406	4.83	0.186
HOP18 (lung)	9.35	82.7	0.739	4.08	0.159
NCI-H460 (lung)	3.53	18.0	0.135	0.600	0.00823
A498 (renal)	1.79	16.3	0.335	4.01	0.166
PC-3 (prostate)	2.07	18.2	0.539	4.01	0.357
DLD-1 (colon)	0.513	17.1	0.141	2.11	0.190
HCT116 (colon)	3.01	18.0	0.292	2.23	0.0629
P388 (leukemia)	3.72	21.2	0.408	0.0754	0.0252
P388/ADR (leukemia)	7.78	34.6	0.621	0.271	5.79
Mean	3.94	27.9	0.402	2.47	0.772

*IC_{50} values in μM

Researchers at Fujisawa Pharmaceutical Co. were investigating an active compound they identified as FR177391 (haterumalide NA, **12**) for the treatment of hyperglyceridemia.[23,24] In this study, FR177391 was also oxidized to 20-hydroxy FR177391 (biselide C, **19**) via microbial conversion.[24] Both compounds were discovered to bind to protein phosphatase 2A (PP2A), which inhibits phosphatase activity to reduce blood levels of triglycerides and induce adipogenesis.[23,24] This discovery indicates that haterumalides and biselides may additionally show promise as leads for the treatment of hyperglyceridemia. Additionally, PP2A has also been shown to play a role in suppression of oncoproteins and cancer cell proliferation.[25]

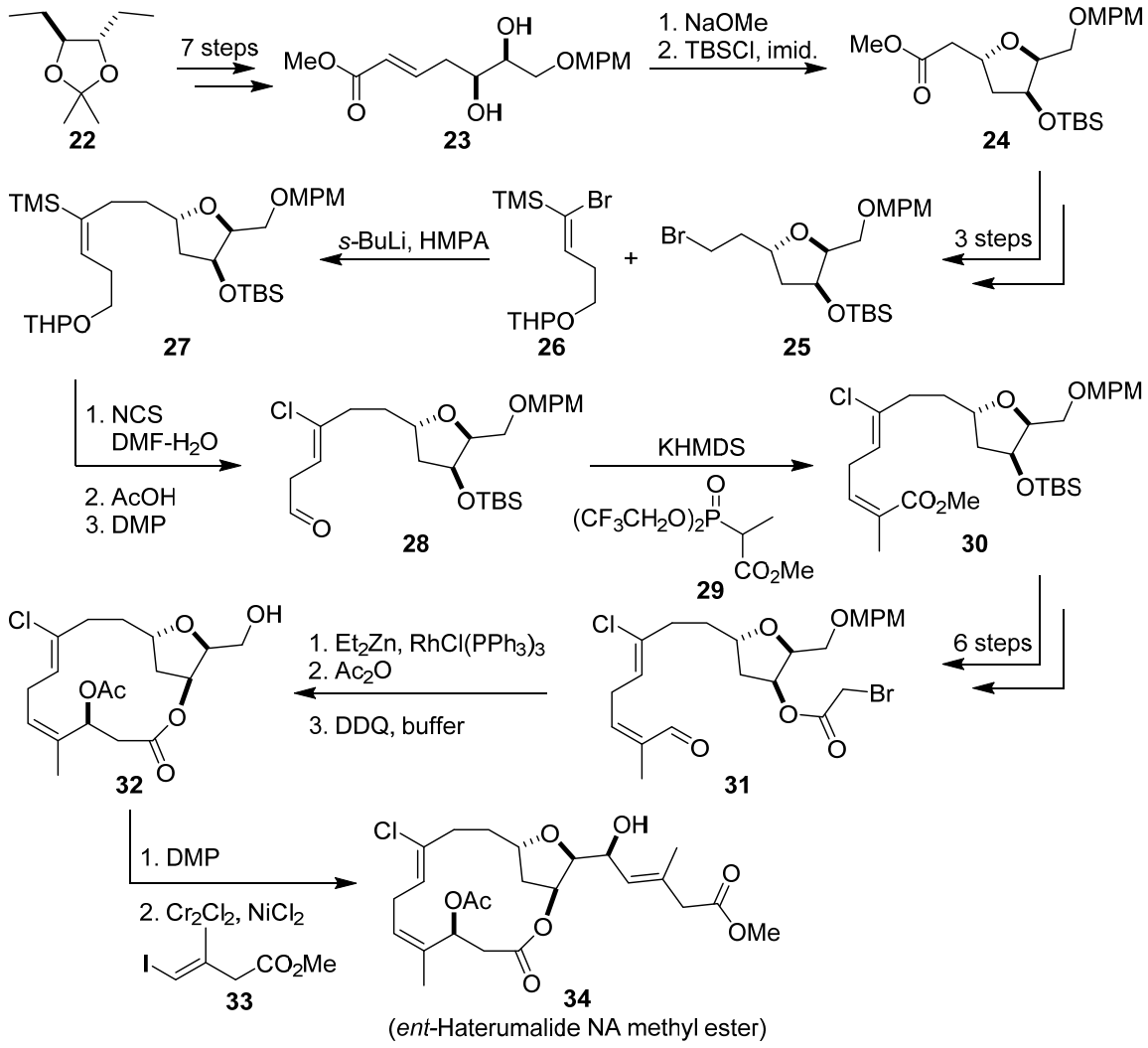
1.3. Previous Syntheses of Haterumalides and Biselides

1.3.1. *Ent*-haterumalide NA Methyl Ester, Kigoshi 2003

Kigoshi reported the first total synthesis of any member of the haterumalides and biselides, completing the asymmetric synthesis of *ent*-Haterumalide NA methyl ester (**22**) in 2003 (Scheme 1.1).[26] This synthesis led to the revision of the assigned stereochemistry in haterumalide NA and also established the absolute stereochemistry.

The synthesis commenced from (+)-2,3-*O*-isopropylidene-L-threitol (**22**) which is converted to the mono-MPM ether **23** in 7 steps. A Michael addition/cyclization sequence of diol **23** followed by hydroxyl protection with *tert*-butyldimethylsilyl chloride allowed access to the desired *trans*-tetrahydrofuran **24**, as a 5:1 diastereomeric mixture. The methyl ester moiety of tetrahydrofuran **24** was converted to the alkyl bromide **25** in 3 steps. Compound **25** was coupled with the carbanion generated from the *Z*-bromoalkenylsilane **26** (accessed in 4 steps from 3-butyn-1-ol) on treatment with *sec*-butyllithium to produce the vinyl silane **27**. This material was then transformed to the corresponding vinyl chloride following a modified Tamao procedure.[27] Following a simple acid hydrolysis and Dess-Martin oxidation, aldehyde **28** was prepared and subjected to a Still-modified Horner-Wadsworth-Emmons reaction[28] with phosphonate **29** to access the *Z*-conjugated ester **30**. In 6 steps, ester **30** was prepared for the subsequent Reformatsky-type reaction which was carried out under Honda's conditions.[29] This reaction required the addition of acetic anhydride to trap the reactive products and allow for isolation of the product, albeit in low yield (9%). Subsequent treatment with DDQ unveiled the primary hydroxyl group to access macrolide **32**. Alcohol **32** was oxidized to the corresponding aldehyde and subsequently underwent a Nozaki-Hiyama-Kishi coupling[30,31] with vinyl iodide **33** to generate the target compound, *ent*-Haterumalide NA methyl ester in good isomeric ratio of 11:1. The major isomer matched NMR data for the natural product, although the optical rotation was opposite in sign. Overall, the total synthesis of the enantiomer of the natural product was completed in 26 steps and in 0.2% overall yield.

Scheme 1.1 Kigoshi's Synthesis of *Ent*-Haterumalide NA Methyl Ester (34)

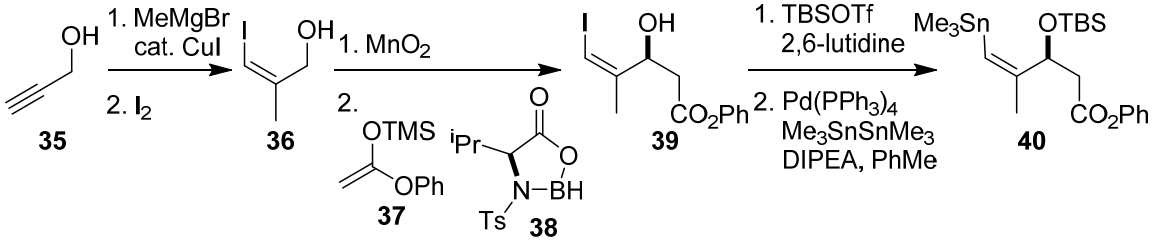


1.3.2. *Ent*-Haterumalide NA Methyl Ester, Snider 2003

Just months after Kigoshi's synthesis of *ent*-Haterumalide NA methyl ester was published, Snider published an alternative total synthesis of this particular haterumalide.[32] A key step of this synthesis incorporated a Stille coupling reaction between two halves of the macrocycle, followed by macrolactonization in order to provide a more convergent route to the target. Vinylstannane **40** was synthesized by first treating propargyl alcohol **35** with methylmagnesium bromide and copper(I) iodide, and quenching with molecular iodine to generate the allylic alcohol **36** (Scheme 1.2).[33] The

alcohol **36** was then oxidized and subjected to an asymmetric aldol reaction with the silyl enol ether **47** and Kiyooka's oxazaborolidinone **38**[34] to provide the phenyl ester **39** in 80% enantiomeric excess. Protection of the hydroxyl group with *tert*-butyldimethylsilyl trifluoromethanesulfonate and cross-coupling with hexamethylditin cleanly converted vinyl iodide **39** to vinylstannane **40**.

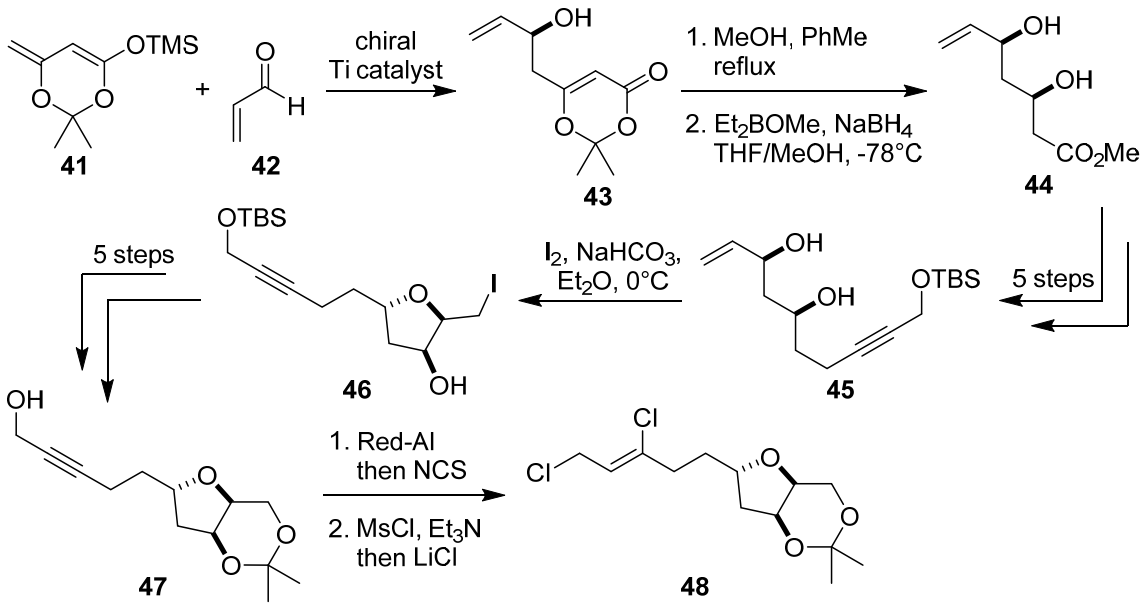
Scheme 1.2 Snider's Synthesis of Vinylstannane (40)



35 **36** **37** **38** **39** **40**

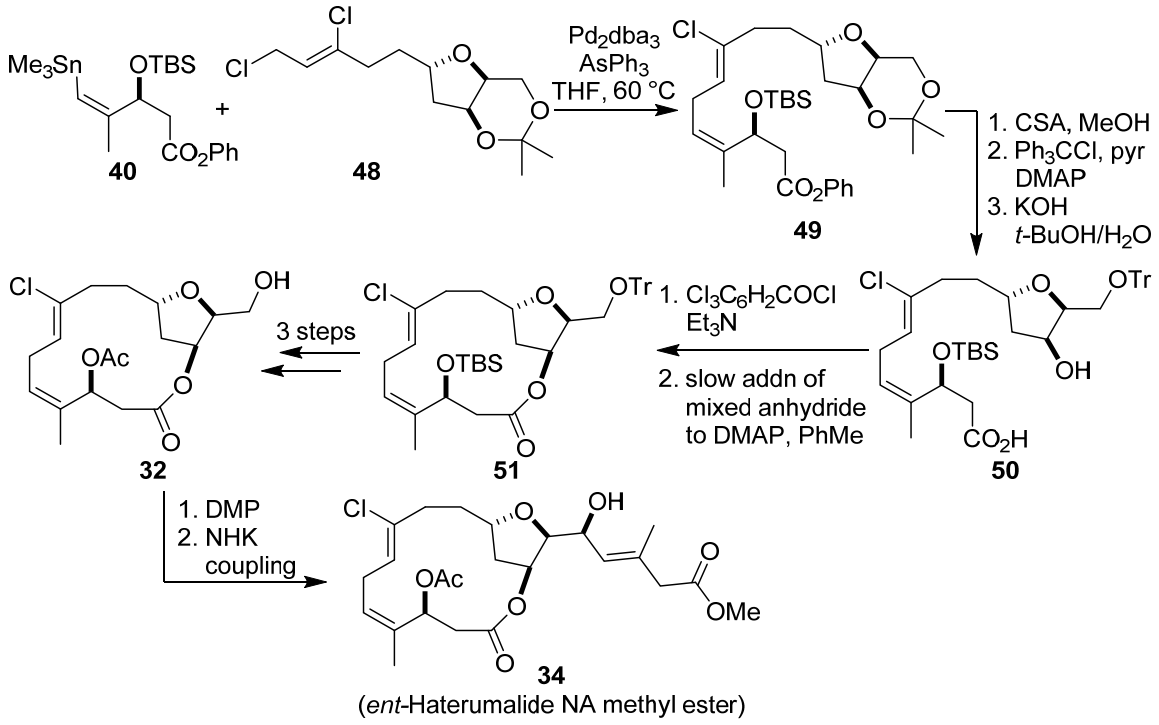
Alcohol **43** was synthesized via an asymmetric aldol reaction between compound **41** and acrolein (**42**), and utilized Carreira's chiral titanium catalyst[35] to generate the desired *S* stereochemistry at the hydroxyl group (Scheme 1.3). Heating alcohol **43** in methanol and toluene provided a keto ester and subsequent reduction afforded the *syn*-diol **44**. Upon conversion of ester **44** to alkyne **45** in 5 steps, iodoetherification provided access to tetrahydrofuran **46** in >95% de. This latter material was then converted into the acetonide-protected tetrahydrofuran **47** in 5 steps. The alkyne function in tetrahydrofuran **47** was then reduced and the intermediate vinyl aluminium species was treated with NCS to generate a vinyl chloride, following which the allylic alcohol was converted into a chloride to afford dichloride **48**, the precursor for a subsequent Stille coupling.

Scheme 1.3 Snider's Synthesis of Dichloride (48)



Upon completion of the synthesis of vinylstannane **40** and dichloride **48**, a Stille coupling[36] reaction using Farina's conditions[37] proceeded to give the desired skipped diene **49** in 65% yield (Scheme 1.4), with an additional 10% of *E*-isomer being produced. From diene **49**, a series of reactions involving acetonide deprotection, tritylation of the primary alcohol, and hydrolysis afforded the hydroxy acid **50**. Macrolactonization of compound **50** was carried out under Yamaguchi's protocol,[38] which provided macrolide **51** in 65% yield and also gave 15% of unwanted dimer and trimer. After manipulating protecting groups on macrolide **51**, the intermediate compound **32** was accessed, further oxidized to the aldehyde, and subjected to the Nozaki-Hiyama-Kishi coupling previously reported by Kigoshi to complete the synthesis.[26] Haterumalide NA methyl ester (**34**) was completed by Snider in 28 steps and 0.7% overall yield.

Scheme 1.4 Completion of Snider's *Ent*-Haterumalide NA Methyl Ester (34) Synthesis

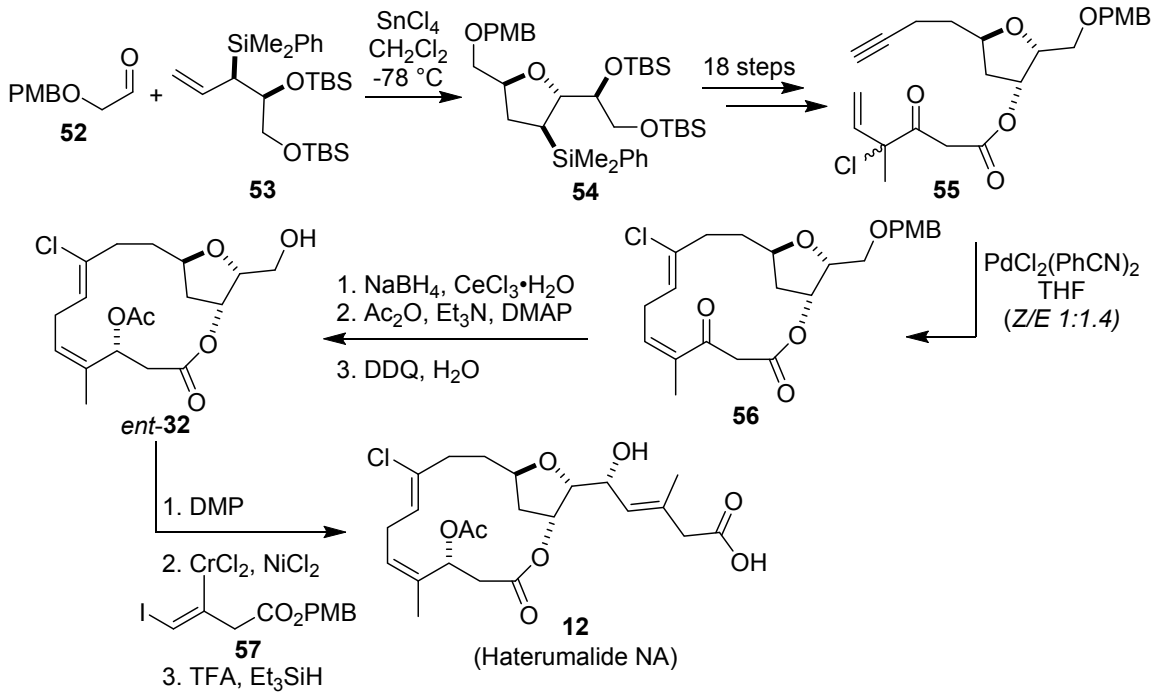


1.3.3. Haterumalide NA, Hoye 2005

In 2005, Hoye reported the first total synthesis of the correct enantiomer of Haterumalide NA (Scheme 1.5).[39] The beginning of the synthesis follows methods previously reported by Roush and Micalizio to access tetrahydrofuran **54** via a tin(IV) chloride-catalyzed [3+2] annulation of aldehyde **52** and allylsilane **53**.[40] The allylsilane **53** was accessed in 6 steps from commercially available materials. From tetrahydrofuran **54**, 18 steps were required to construct eneyne **55**, the precursor for the key Kaneda chloroallylation/macrocyclization.[41] The chloroallylation reaction required a *bis*(benzonitrile)palladium chloride catalyst to provide macrocycle **56**, unfortunately with the minor isomer (*Z*) being the desired product. From macrocycle **56**, a 3 step sequence involving Luche reduction[42], acetylation, and PMB deprotection with DDQ afforded the enantiomer of Kigoshi's intermediate (*ent*-**32**). Subsequent DMP oxidation and NHK coupling followed Kigoshi's strategy, and vinyl iodide **57** contains a PMB ester which was deprotected in TFA to unveil the carboxylic acid and ultimately, haterumalide NA

(**12**). Hoye's total synthesis provided the natural product in 32 steps and 0.2% overall yield.

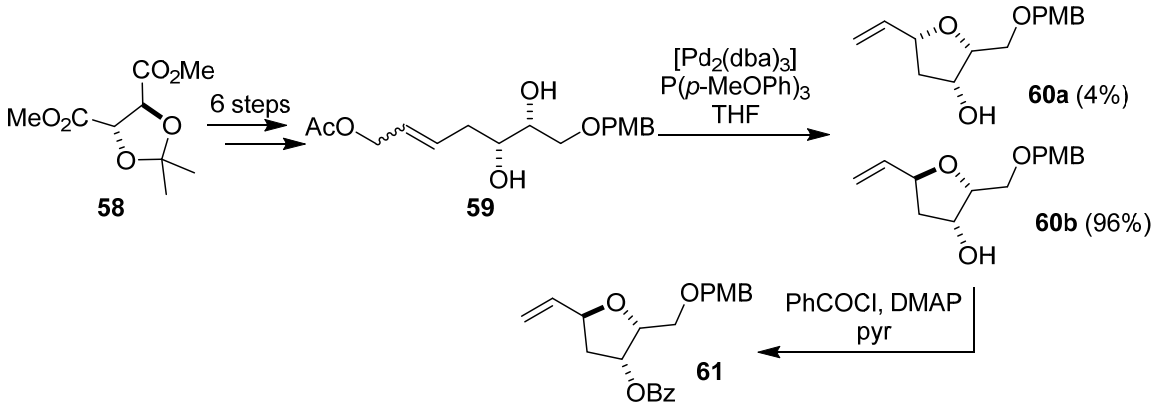
Scheme 1.5 Hoye's Synthesis of Haterumalide NA (12)



1.3.4. Haterumalide NA, Roulland 2008

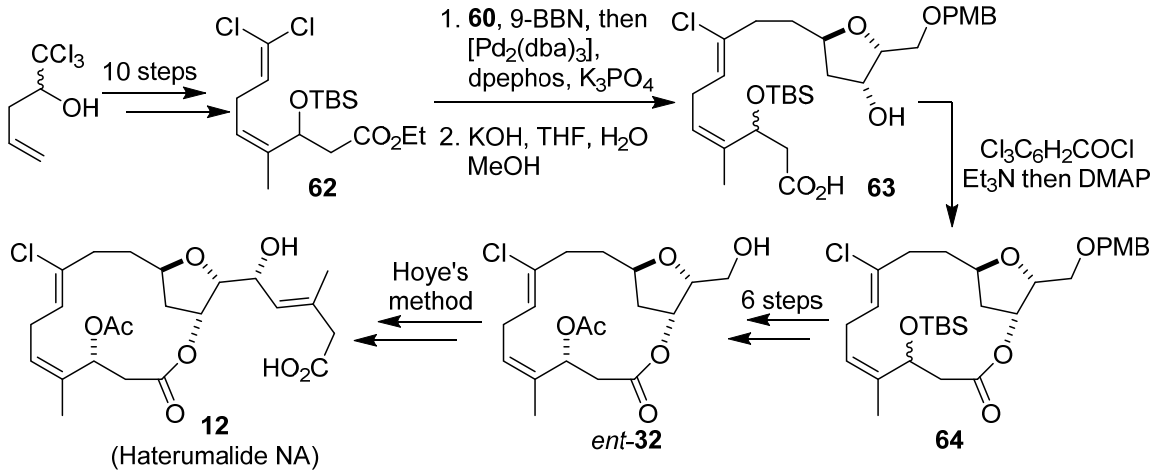
It was 3 years after the initial synthesis of haterumalide NA, that a second synthesis was published by Roulland which featured a Suzuki-Miyaura cross-coupling reaction.[43] By utilizing a chiral pool approach starting from D-tartrate ester **9**, a 6 step sequence transformed the latter compound to diol **59** with a favourable *E*/*Z* ratio of 95:5 (Scheme 1.6). This material was cyclized via a palladium-catalyzed etherification reaction and the addition of *tris*-(4-methoxyphenyl)phosphine produced tetrahydrofuranol **60** in quantitative yield with a 24:1 diastereoselectivity. Subsequent benzoylation of the major product provided tetrahydrofuran **61**.

Scheme 1.6 Roulland's Synthesis of Tetrahydrofuran (61)



The second coupling partner for the Suzuki-Miyaura cross coupling[44] was constructed from 1,1,1-trichloro-4-penten-2-ol which was transformed over 10 steps into ethyl ester **62** (Scheme 1.7). With both subunits in hand, the cross-coupling between tetrahydrofuranol **60** and ethyl ester **62** was implemented and following hydrolysis gave the seco acid **63**. Compound **63** was then subjected to Yamaguchi's conditions[38] to provide macrolide **64**. From the macrolide, 6 steps were required to access *ent*-**32** which was carried forward to complete haterumalide NA (**12**) following Hoye's methods.[39] In summary, Roulland's synthesis of haterumalide NA was completed in 22 linear steps and in 6.1% overall yield.

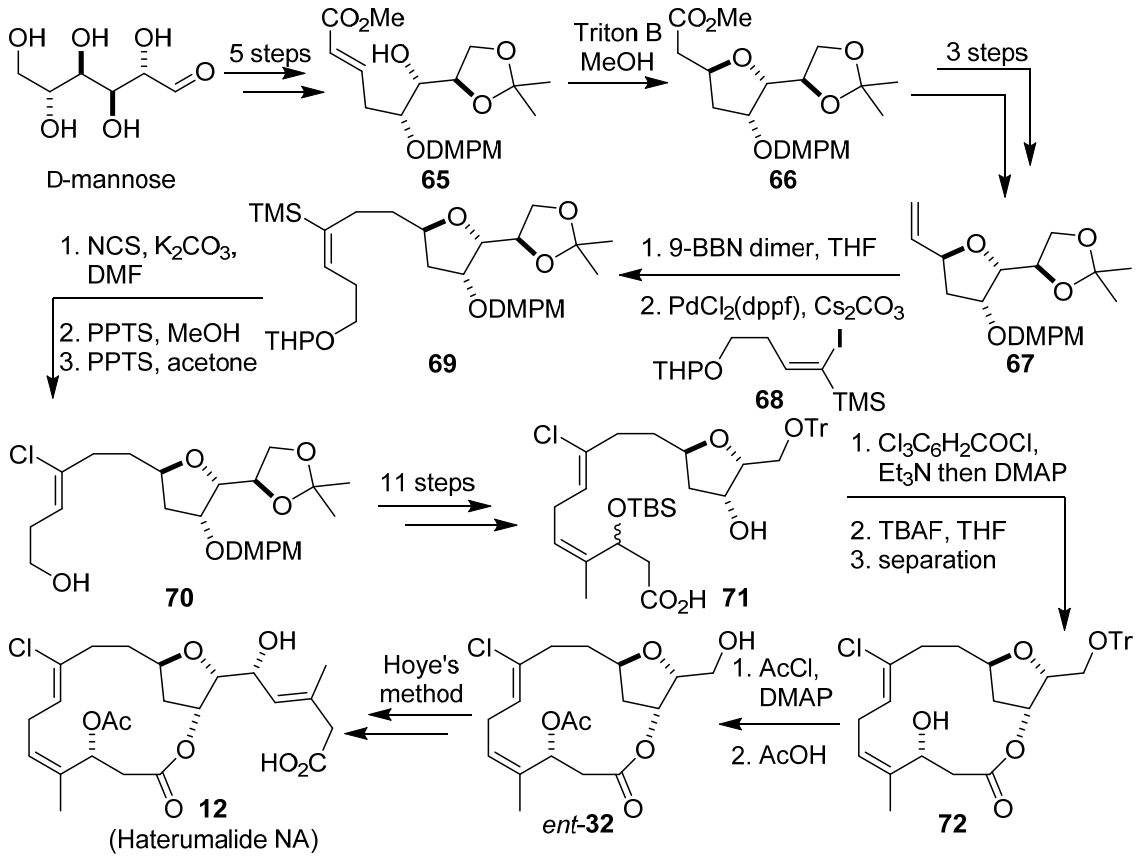
Scheme 1.7 Completion of Roulland's Haterumalide NA (12) Synthesis



1.3.5. Haterumalide NA, Kigoshi 2008

Kigoshi's second synthesis of haterumalide NA was published 5 years after his first reported total synthesis of *ent*-haterumalide NA methyl ester.[45] Similar to the strategy developed by Roulland,[43] Kigoshi incorporated a Suzuki-Miyaura coupling form the C8-C9 bond (Scheme 1.8).[44] The synthesis starts by transforming D-mannose into the *α,β*-unsaturated ester **65**, which was then subjected to an intramolecular oxy-Michael cyclization reaction promoted by Triton B to provide tetrahydrofuran **66**.[46] In 3 further steps, the Suzuki-Miyaura coupling partner **67** was prepared, which contains a terminal olefin that underwent hydroboration with 9-BBN. The *β*-alkyl Suzuki-Miyaura coupling reaction was carried out with this intermediate and alkenylsilane **68** to give tetrahydrofuran **69** in quantitative yield.[44] Attempts to convert the vinyl TMS moiety into a vinyl chloride under modified Tamao conditions,[27] as Kigoshi previously reported[26], resulted in a low, irreproducible yield, and new conditions requiring NCS in DMF and K_2CO_3 were found to improve on this result. Acid hydrolysis with PPTS removed the acetonide and THP protecting groups, and the resulting diol was reprotected as the acetonide yielding compound **70**. Over 11 further steps this material was transformed into seco acid **71** which was subjected to a Yamaguchi macrolactonization reaction.[38] Treatment of the latter compound with TBAF removed the silyl protecting group to give 2 diastereoisomers that were separable by silica gel chromatography. The undesired isomer was converted to the desired isomer **72** by oxidation of the hydroxyl group and subsequent Luche reduction.[42] Acetylation of the C3 hydroxyl group followed by removal of the trityl protecting group gave intermediate compound *ent*-**32** which was once again converted to haterumalide NA (**12**) following Hoye's method.[39] Kigoshi's synthesis of haterumalide NA (**12**) was completed in 33 steps and in 1.2% overall yield. Using this method, Kigoshi also completed the total synthesis of haterumalide B in 2009, by using a slightly different coupling partner for the Nozaki-Hiyama-Kishi coupling.[30,31]

Scheme 1.8 Kigoshi's Synthesis of Haterumalide NA (12)

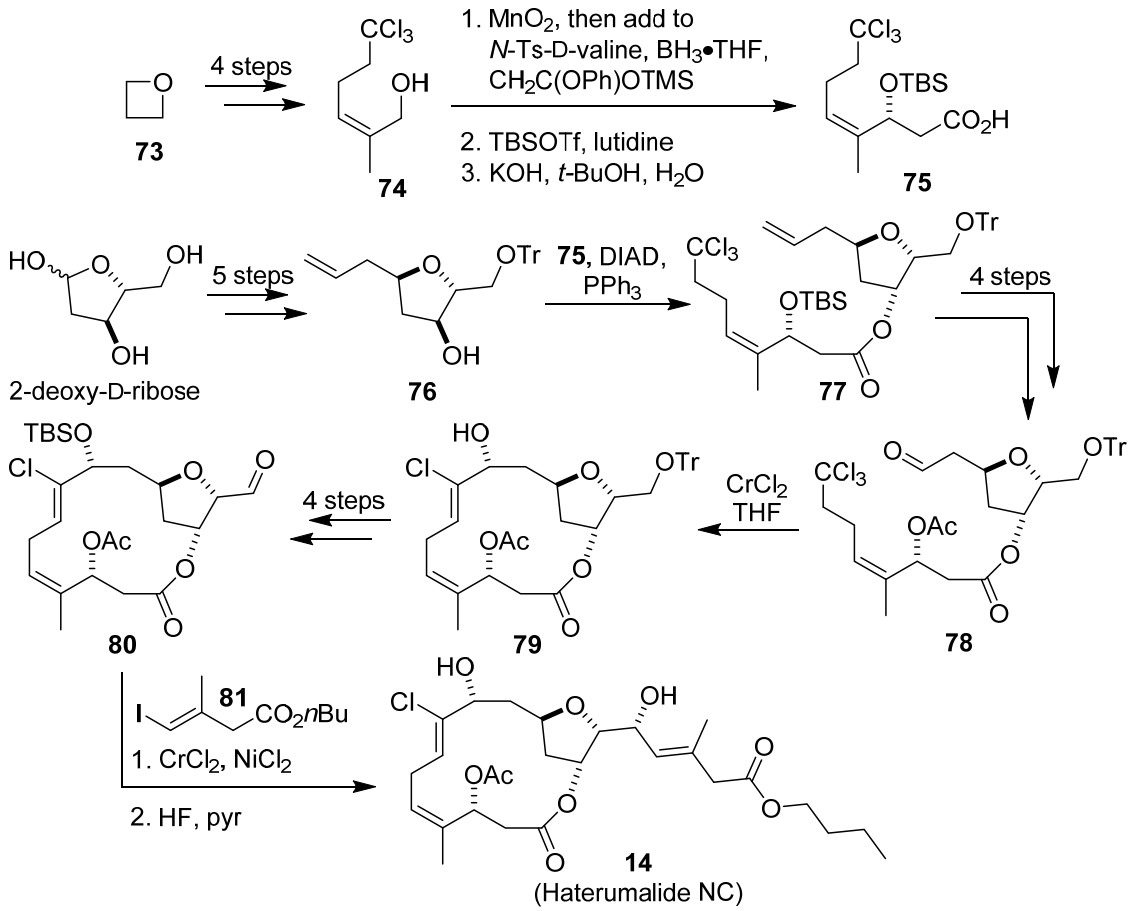


1.3.6. Haterumalide NC, Borhan 2008

In 2008, Borhan *et al.* published the first total synthesis of haterumalide NC (**14**) (Scheme 1.9); using this strategy the formal synthesis of haterumalide NA (**12**) was also reported.[47] This synthetic route was inspired by reactions of chlorovinylidene chromium carbenoids developed by Falck and Mioskowski.[48,49] The synthesis begins with the conversion of trimethylene oxide (**73**) to alcohol **74** over 4 steps. Oxidation to an aldehyde with manganese(IV) oxide followed by an asymmetric Mukaiyama aldol reaction, silylation, and hydrolysis gave the seco acid **75** in good yield and in 80% enantiomeric excess.[50] Separately, alcohol **76** was prepared in 5 steps from 2-deoxy-D-ribose and subjected to a Mitsunobu esterification reaction with seco acid **75** to afford compound **77**. In 4 subsequent steps, aldehyde **78** was synthesized and reacted with chromium(II) chloride in a chromium carbenoid-mediated macrocyclization to provide

macrocycle **79** as the major product with the desired stereochemistry at C9 in a 4:1 ratio. Protecting group manipulation of macrolide **79** and oxidation allowed access to aldehyde **80** in 4 steps. The latter compound was then coupled to vinyl iodide **81** under Nozaki-Hiyama-Kishi conditions[30,31] and subsequent desilylation with HF-pyridine afforded haterumalide NC (**14**). The total synthesis of haterumalide NC (**14**) was completed with the longest linear sequence being 16 steps and 6% overall yield. The formal synthesis of haterumalide NA was completed through a Barton-McCombie deoxygenation[51] of macrocycle **79**, subsequent removal of the trityl protecting group and oxidation to the aldehyde (*ent*-**32**). This aldehyde (*ent*-**32**) is a common intermediate in the synthesis of haterumalide NA (**12**) following Hoye's protocol.[39]

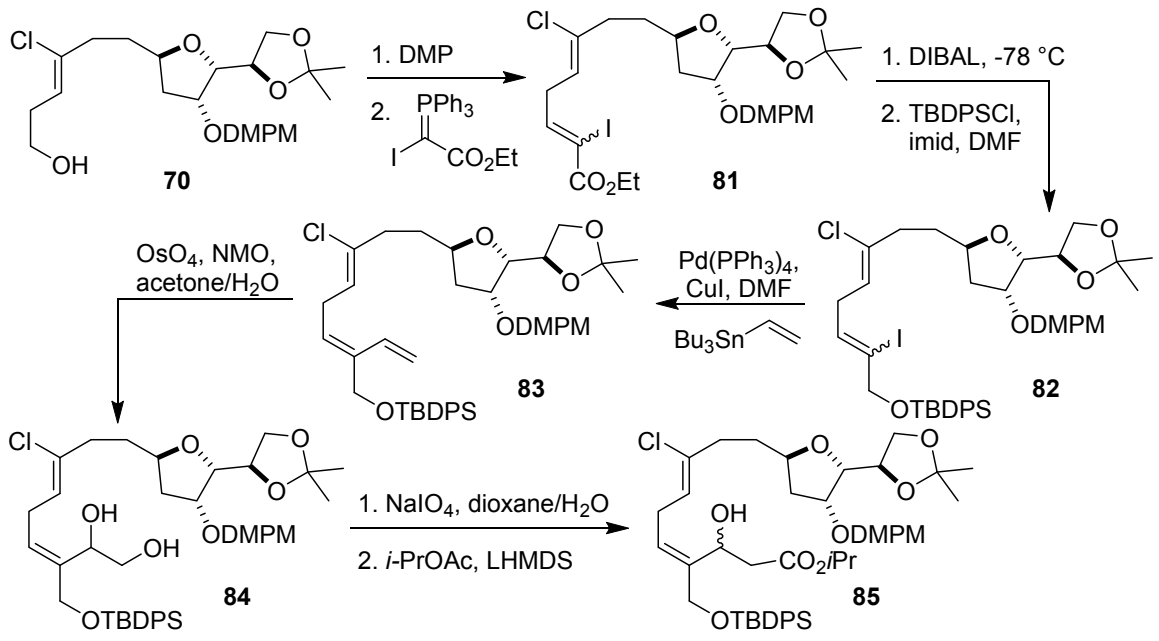
Scheme 1.9 Borhan's Synthesis of Haterumalide NC (14)



1.3.7. Further Studies Toward Biselides, Kigoshi 2012

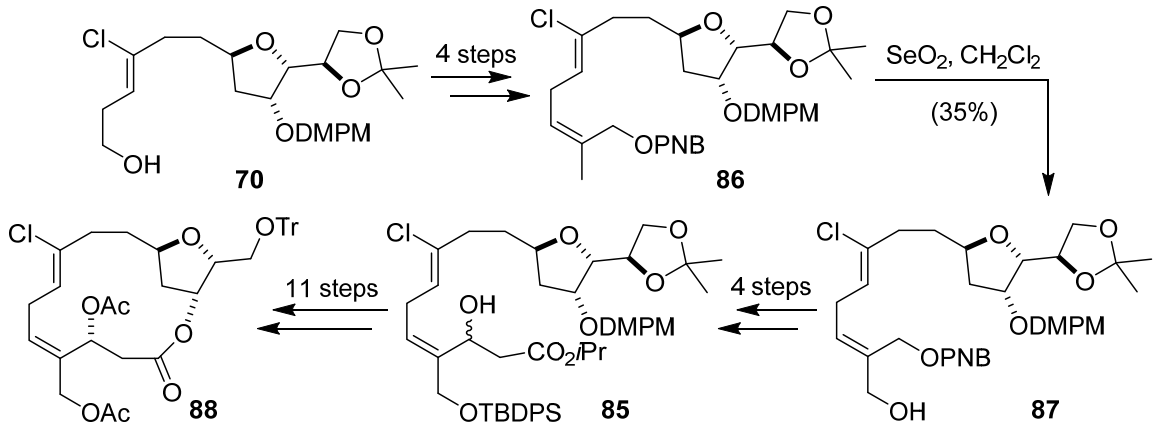
In 2012, Kigoshi's group published results in 2 parts which further highlight their efforts to synthesize the biselides. A Stille coupling[36] was incorporated in part 1 to elaborate the biselide carbon core prior to macrolactonization (Scheme 1.10).[52] Starting from the previously reported intermediate **70**, the terminal alkene was oxidized with Dess-Martin periodinane and converted into vinyl iodide **81** with an iodo Wittig reagent to produce a 3:1 mixture of *Z/E* isomers.[53] The ethyl ester was then reduced to the corresponding primary alcohol with DIBAL and subsequently protected as a silyl ether. The key Stille coupling step[36] with a vinylstannane afforded the skipped triene **83**. Subsequent dihydroxylation of compound **83** proved to be problematic due to the low regioselectivity for the terminal alkene and provided diol **84** in only 30% yield. Oxidative cleavage of compound **84** gave a *α,β*-unsaturated aldehyde which was reacted in an acetate aldol with isopropyl acetate to access ester **85**. Due to the poor yield and selectivity of the dihydroxylation reaction the synthesis was not completed, however, ester **85** contains all of the carbon atoms in the biselide macrocycle, and is a viable intermediate that could provide access to biselides A and B.

Scheme 1.10 Kigoshi's Recent Synthesis of the Biselide Core using Stille Coupling



The second part of Kigoshi's report highlights their attempts to synthesize the macrolactone using an allylic oxidation reaction (Scheme 1.11).[54] Again from intermediate **70**, 4 steps were required to access tetrahydrofuran **86**. The electron withdrawing properties of the *p*-nitrobenzoate on compound **86** was reported to enhance the regioselectivity of the allylic oxidation reaction, which was accomplished in 35% yield to give allyl alcohol **87**. The poor yield for this reaction was attributed to the formation of a side product with no oxygenation at C3 and an aldehyde at C20. In several steps from compound **87**, *β*-hydroxy ester **85** could be accessed and further manipulated to form macrolide **88**. The synthesis did not progress beyond compound **88**, due to an inability to remove the trityl protecting group in the presence of the two acetates. This research published by Kigoshi provides yet another means to access the biselide core through an allylic oxidation approach.

Scheme 1.11 Kigoshi's Recent Synthesis of the Biselide Core using Allylic Oxidation



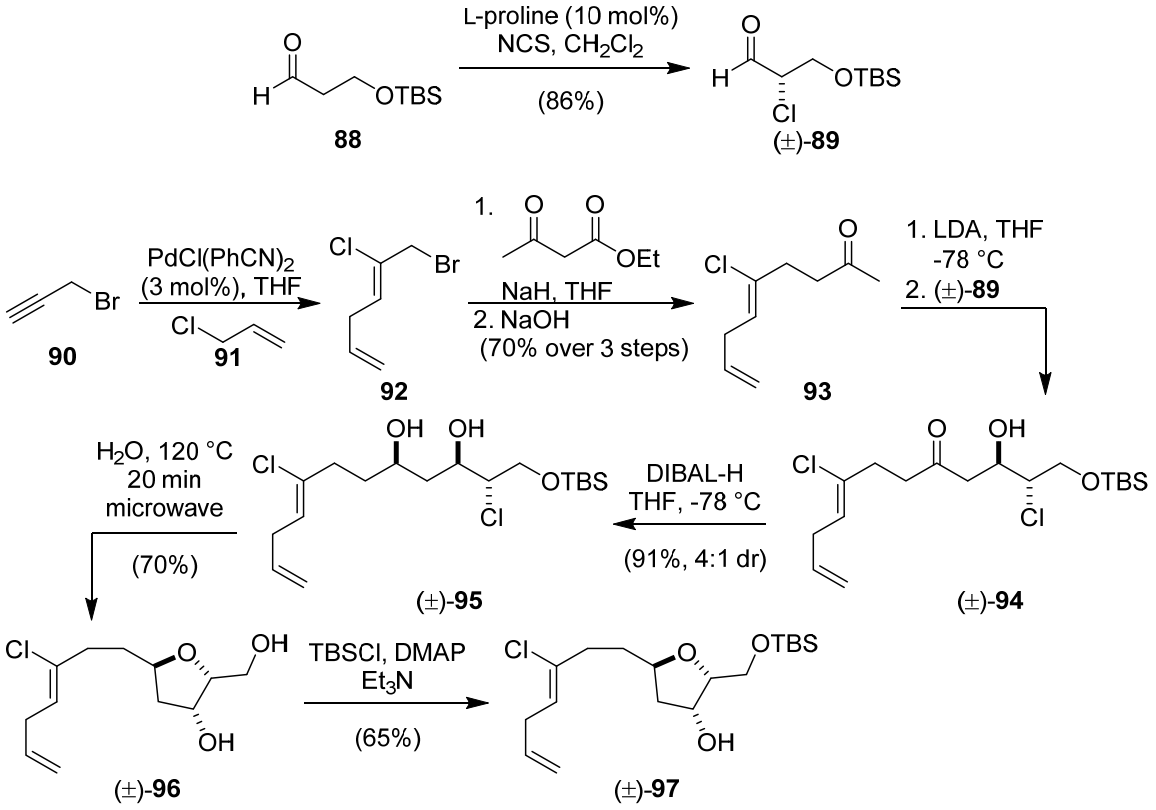
1.4. Previous Strategies for the Total Synthesis of Biselide A

1.4.1. Ring-Closing Metathesis

Initial attempts to synthesize biselide A in the Britton group were led by Dr. Baldip Kang.[55] The proposed strategy incorporated the group's previously reported chloropolyol cyclization methodology[56–58] to allow access to the 2,5-disubstituted-3-oxygenated

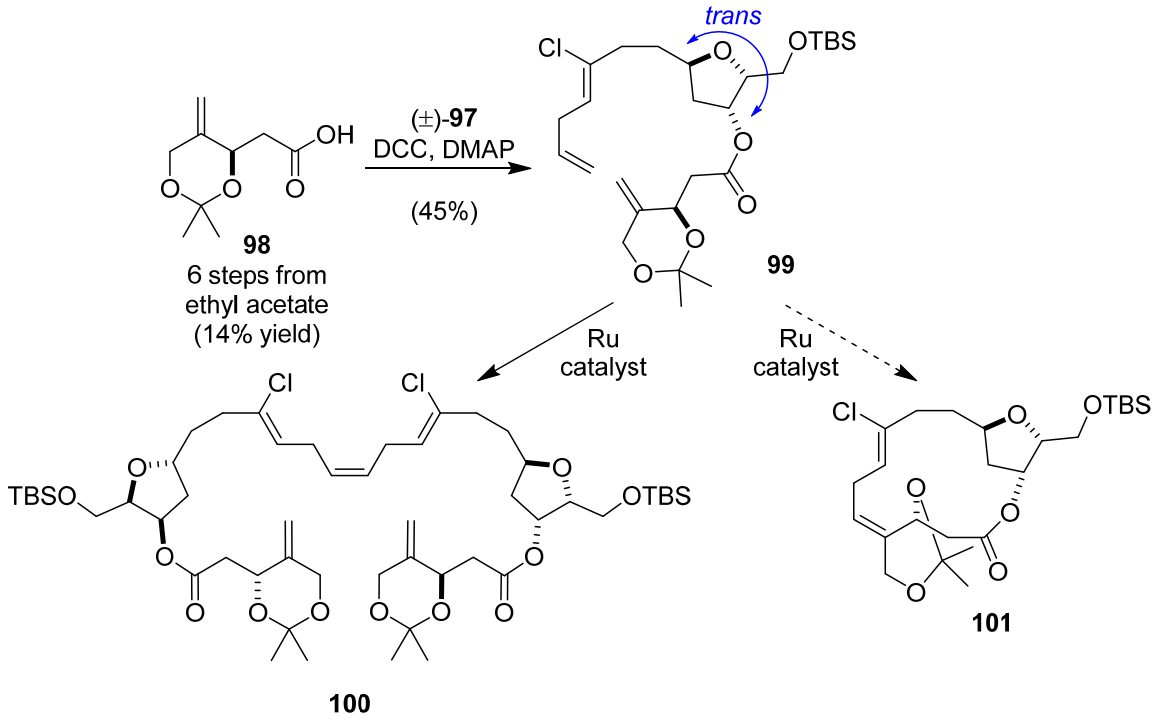
tetrahydrofuran moiety as well as a ring closing metathesis (RCM) key step that would construct the C4-C5 alkene of the macrocycle. Kang constructed *α*-chloroaldehyde **89** by α-chlorination of aldehyde **88** with catalytic amount of L-proline and NCS,[59] which expectedly proceeded with low levels of enantioselectivity (Scheme 1.12). Separately, propargyl bromide (**90**) and allyl chloride (**91**) were subjected to a Kaneda chloroallylation reaction[41] to generate skipped diene **92**. This intermediate was further subjected to an alkylation reaction with ethyl acetoacetate and decarboxylation afforded the methyl ketone **93**.[60] A lithium aldol reaction between methyl ketone **93** and *α*-chloroaldehyde (±)-**89** produced racemate (±)-**94**,[58] which was reduced to the 1,3-*syn*-diol with DIBAL (d.r. = 4:1) to give compound (±)-**95**.[56] Thermal cyclization in water gave tetrahydrofuranol (±)-**96** and subsequent re-silylation of the primary hydroxyl group provided access to compound (±)-**97**.

Scheme 1.12 Kang's Synthesis of Tetrahydrofuranol ((±)-97)



Acid **98** was synthesized in 6 steps and was coupled to tetrahydrofuranol (±)-**97** with DCC and DMAP to provide the precursor for a RCM reaction (i.e. ester **99**) (Scheme 1.13). Kang attempted the RCM reaction of ester **99** using various ruthenium metathesis catalysts and conditions without observing the desired product **101**.[55] The major product from this reaction was determined to be dimer **100**, the formation of which was attributed to the reactivity differences between the two alkenes, and the *trans*-relationship of the two side chains on the THF ring that presumably also prevents the two alkenes from engaging in the required RCM.

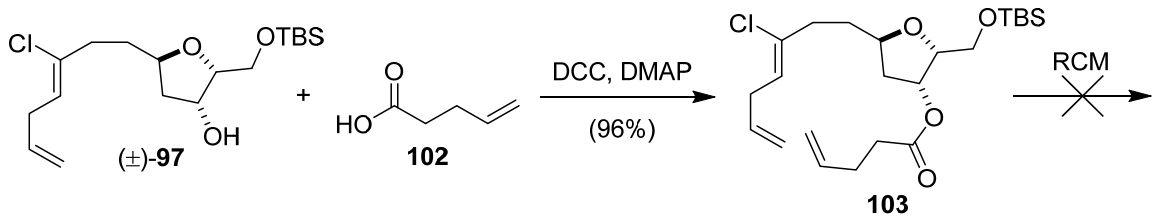
Scheme 1.13 Kang's Synthesis of Precursor (99) and RCM Products



In order to verify that the reactivity differences in the alkenes had an effect on the RCM reaction, a simplified monosubstituted olefin **102** was coupled to tetrahydrofuranol (±)-**97** to construct precursor **103** (Scheme 1.14). Submitting compound **103** to various Grubbs metathesis catalysts either resulted in no reaction or small amounts of dimer. From this study it was concluded that the *trans* orientation of the side chains on the THF ring prevented the alkenes from engaging a RCM reaction, and that the reactivity

differences between the two alkenes did not play a substantial role in the success of the RCM process.

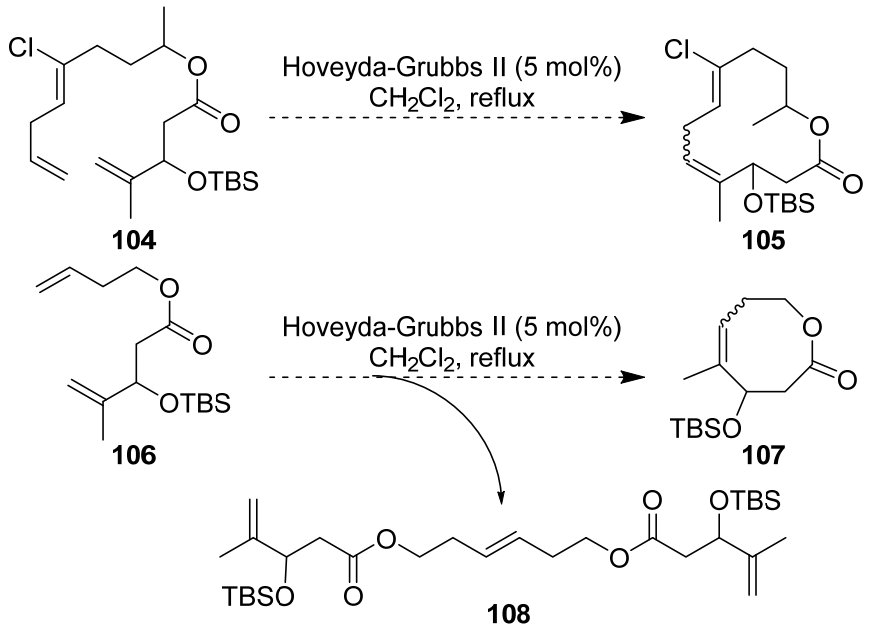
Scheme 1.14 Kang's Monosubstituted Olefin RCM Attempt



1.4.2. Relay Ring-Closing Metathesis

The unexpected outcome of the ring-closing metathesis strategy encouraged Hope Fan, another former student of the Britton group, to investigate a revised approach to biselide A (**17**).[61] Fan proposed that if the *trans*-relationship between side chains off the THF ring was preventing RCM, the cyclization/THF formation step can occur after RCM. This would allow for the necessary flexibility required for RCM and a proof-of-concept study was carried out with compounds **104** and **106**, which were expected to form RCM products **105** and **107**, respectively (Scheme 1.15). In the event, no reaction occurred between compound **104** and Grubbs-Hoveyda II catalyst. Similar metathesis reaction conditions with substrate **106** generated only small amounts of the dimer **108**. Attempts to optimize these reactions by screening concentration, solvent, and catalyst were not successful. The experiments carried out by Kang and Fan suggested that the failure of the RCM reaction was a result of a complex combination of incompatible stereochemical relationship between the side chains on the THF ring, and reactivity differences of the terminal alkenes.

Scheme 1.15 Proof-Of-Concept Studies for RCM with Less Rigid Substrates



Reports of a relay ring-closing metathesis (RRCM) by Hoye[39,62] and Porco[63] demonstrated this approach can be successful for accessing similar macrocycles in which RCM was affected by rigidity and/or reactivity of alkenes. In a typical RRCM event, a 6-carbon relay chain is added to the more substituted alkene in order to promote reactivity (Figure 1.6).

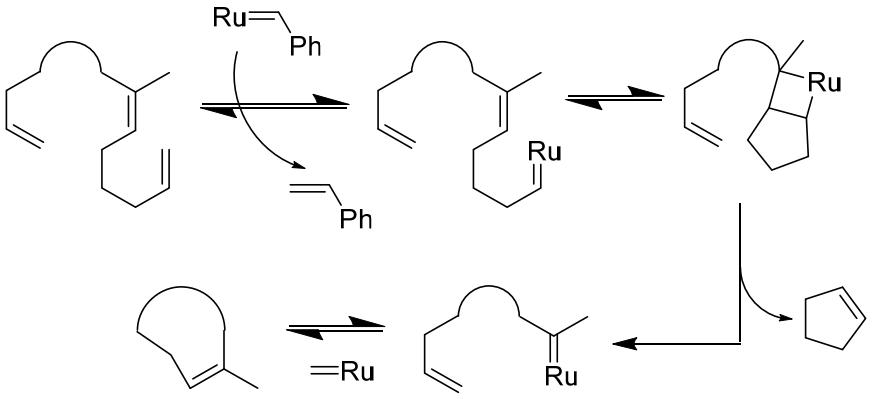
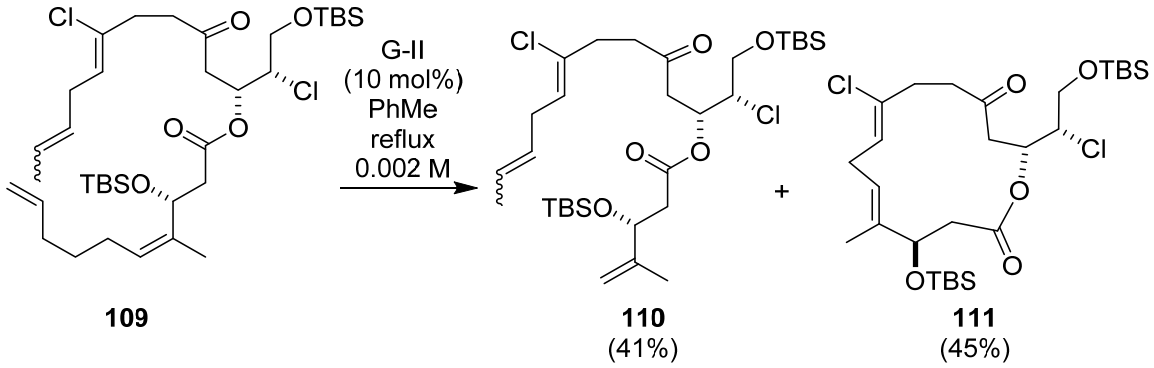


Figure 1.6 The relay ring-closing metathesis mechanism.

Inspired by the demonstrated success of a RRCM reaction in total synthesis efforts, Fan's revised strategy for the synthesis of the biselides and haterumalides would

exploit this reaction to induce the key macrocyclization event, followed by ketone reduction and thermal cyclization to form the THF ring.[61] Upon synthesizing RRCM precursor **109**, Grubbs II catalyst was used to catalyze the metathesis reaction and two major compounds were isolated (Scheme 1.16). Surprisingly, the macrocyclic product **111** was formed exclusively with the undesired *E* geometry of the new alkene. Fan explored an exhaustive number of reaction conditions using compound **109** and diastereomers of compound **109** in hope that the *Z* alkene could be formed via RRCM, but these studies ultimately proved unsuccessful and the RRCM strategy was no longer pursued.

Scheme 1.16 Fan's RRCM of Compound (109)



109 **110** (41%) **111** (45%)

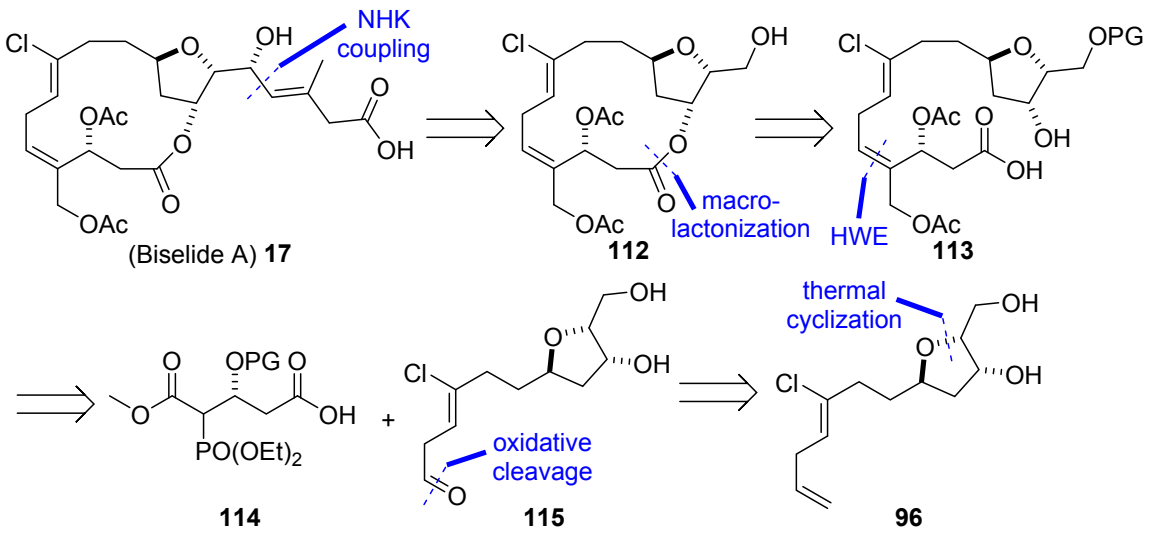
Chapter 2.

Revised Strategy for the Total Synthesis of Biselide A

2.1. Horner-Wadsworth-Emmons Strategy

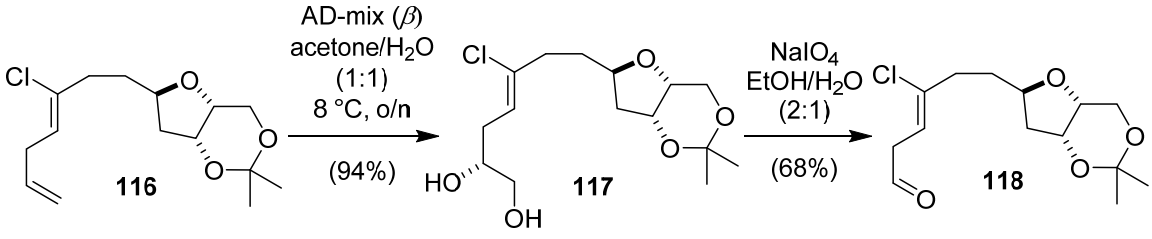
With unsuccessful attempts to synthesize biselide A in our group by Kang using RCM,[55] and Fan using RRCM,[61] we decided to focus our attention away from metathesis processes and towards a new strategy that would allow us to build upon the terminal alkene at C4 of our readily available intermediate **96**. We were inspired by Kigoshi's second generation synthesis of haterumalide NA[45] that incorporated a *Z*-selective Horner-Wadsworth-Emmons (HWE)[64] reaction to form the C4-C5 trisubstituted alkene as a single isomer in high yield. Thus, our third generation approach involved the use of a Horner-Wadsworth-Emmons key step to elaborate the C4-C5 alkene (Scheme 2.1). Based on Hoye's synthesis of haterumalide NA,[39] we planned to install the sidechain through a Nozaki-Hiyama-Kishi coupling reaction during late stages of the synthesis.[30,31] We envisaged accessing the C20 oxygenated macrocycle **112** by cyclization under Yamaguchi conditions in accordance with previous syntheses of haterumalides.[38] The Horner-Wadsworth-Emmons key step with phosphonate **114** would then allow access to the precursor for macrolactonization. Finally, aldehyde **115** would be accessed through a selective oxidative cleavage reaction of the terminal alkene present in tetrahydrofuranol **96**, an intermediate which has previously been prepared by Kang.[55]

Scheme 2.1 Retrosynthesis for the Horner-Wadsworth-Emmons Strategy



We commenced a synthesis of aldehyde **118** by examining the selective oxidative cleavage of the terminal alkene on substrate **116** (Scheme 2.2). Tetrahydrofuran **116** was accessed through a simple acetonide protection of compound **96**. Subjecting tetrahydrofuran **116** to AD-mix (*β*) overnight cleanly afforded diol **117**, with no indication of oxidation of the trisubstituted alkene. Subsequent diol cleavage with sodium periodate produced aldehyde **118**.

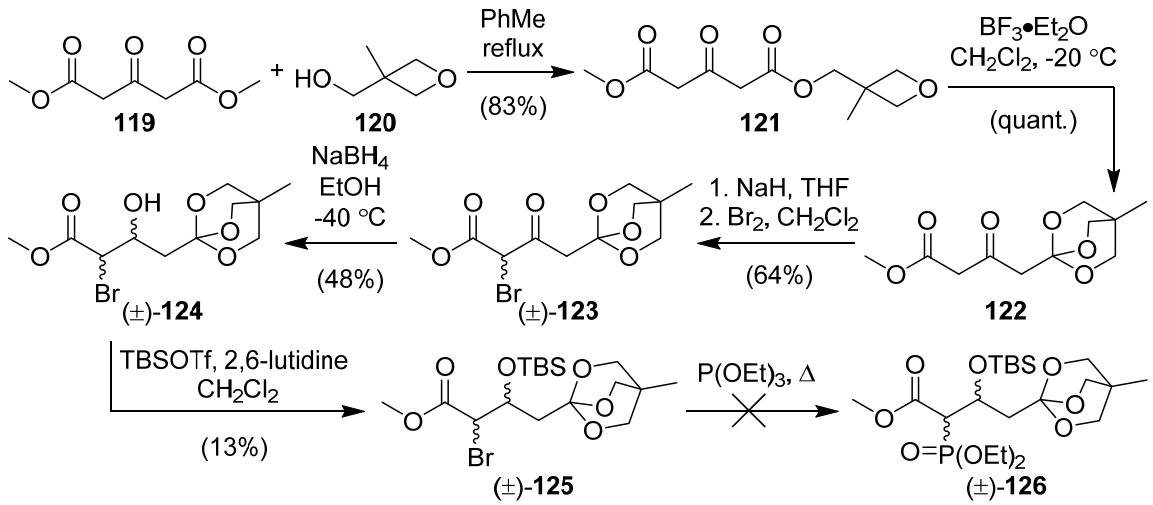
Scheme 2.2 Oxidative Cleavage of Compound (116)



With aldehyde **118** in hand, a phosphonate derivative similar to compound **114** was required for the key HWE step. We envisioned the carboxylic acid being masked as an orthoester and a simple silyl ether protecting the hydroxyl function. The synthesis of the requisite phosphonate began with dimethyl-1,3-acetone dicarboxylate **119**, which underwent transesterification with oxetane **120** to afford compound **121**. Following protocols developed by Corey *et. al.*,[65] oxetane **121** was reacted with boron trifluoride

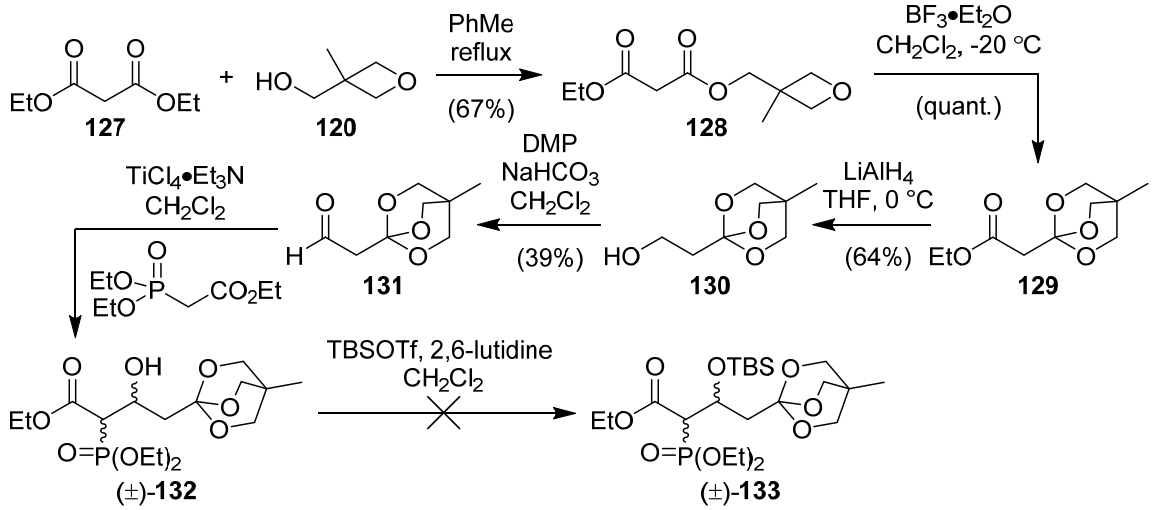
etherate to generate orthoester **122**. Deprotonation of compound **122** followed by immediate treatment with bromine provided a racemic mixture of compound **123**. Notably, this bromination reaction was first explored using L-proline and *N*-bromosuccinimide[66] but only returned starting material. Reduction of the ketone in compound (±)-**123** was accomplished by exposure to sodium borohydride to give bromohydrin (±)-**124**. This material was initially subjected to standard conditions for TBS protection of the alcohol function using *tert*-butyldimethylsiliyl chloride and imidazole, however no product was observed. Using *tert*-butyldimethylsiliyl triflate and 2,6-lutidine produced the TBS-protected compound (±)-**125**, albeit in a low 13% yield. The difficulty in protecting the alcohol function in bromohydrin (±)-**124** may be due to steric congestion. Nevertheless, formation of the target phosphonate (±)-**126** was attempted in a reaction with compound (±)-**125** and neat triethylphosphite at room temperature and then under reflux. In either case only starting material was recovered from this reaction. Considering the lack of reactivity of compound **125**, it was also treated with sodium iodide in an attempt to convert the alkyl bromide into a more labile alkyliodide. Disappointingly, several attempts to effect this Finkelstein reaction also failed to provide any desired product.[67] In addition, attempts to react compound (±)-**125** with dimethyl phosphite and sodium metal were equally unsuccessful. Here, again, it was believed that steric congestion prevented both the phosphite and the iodide from undergoing S_N2 attack at the *α*-carbon. Consequently, this synthetic strategy to access to our target phosphonate (±)-**126** was abandoned.

Scheme 2.3 Initial Strategy for the Synthesis of ((±)-126)



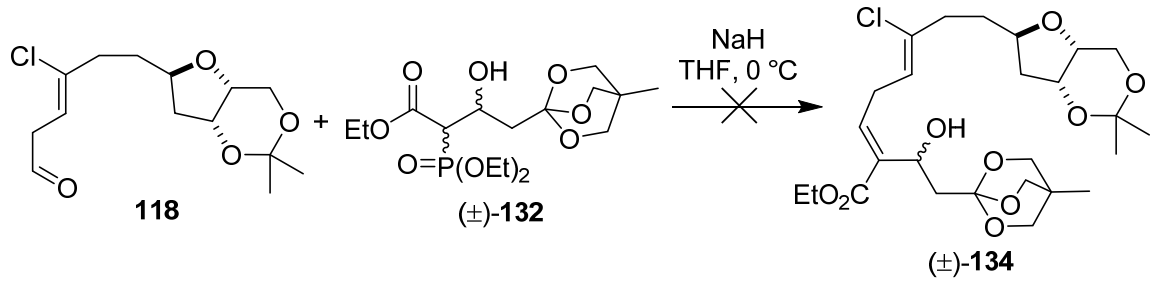
Considering the failures of our first approach to phosphonate **126**, a new route for the synthesis of a similar phosphonate was envisioned that would make use of many of the steps already optimized and depicted in Scheme 2.3. This strategy was initiated with a transesterification reaction involving diethyl malonate (**127**) and oxetane **120** (Scheme 2.4). Orthoester **129** was accessed using the same conditions discussed above for compound **122**. A reduction reaction of ethyl ester **129** with lithium aluminum hydride afforded alcohol **130**, which was subsequently oxidized with Dess-Martin periodinane to provide aldehyde **131**. A titanium-catalyzed aldol coupling[68] between aldehyde **131** and triethyl phosphonoacetate proceeded to give phosphonate (±)-**132**. Protection of the hydroxyl function of this latter material with *tert*-butyldimethylsilyl trifluoromethanesulfonate failed and only elimination to form an *α,β*-unsaturated ester was observed.

Scheme 2.4 Revised Strategy for the Synthesis of ((±)-133)



Following several failed attempts to protect the hydroxyl function in (±)-**132**, we elected to attempt the HWE reaction with aldehyde **118** to assess the viability of this route. Thus, ester **132** was treated with sodium hydride followed by the aldehyde **118**. Upon workup and purification of the crude reaction mixture via flash chromatography, no desired product was observed. Multiple degradation products due to elimination of the phosphonate were observed in the ^{1}H NMR spectra that were recorded on the crude reaction mixture and purified fractions. In the absence of any desired product from this HWE reaction, and our inability to protect the hydroxyl on the phosphonate, which would potentially avoid undesired side reactions from elimination, we sought an alternative strategy for the formation of the C4-C5 alkene function.

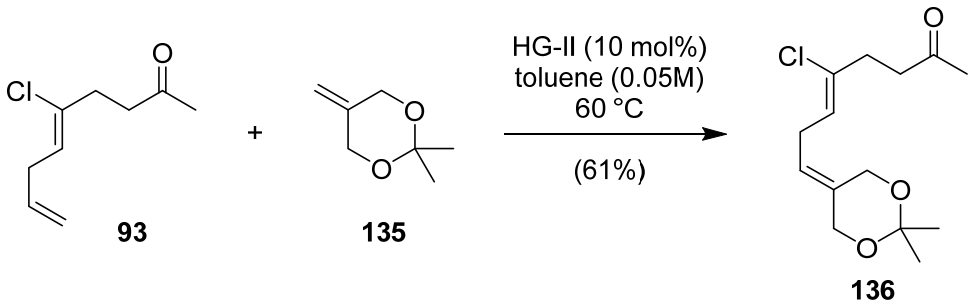
Scheme 2.5 Horner-Wadsworth-Emmons Attempt



2.2. Cross Metathesis Strategy

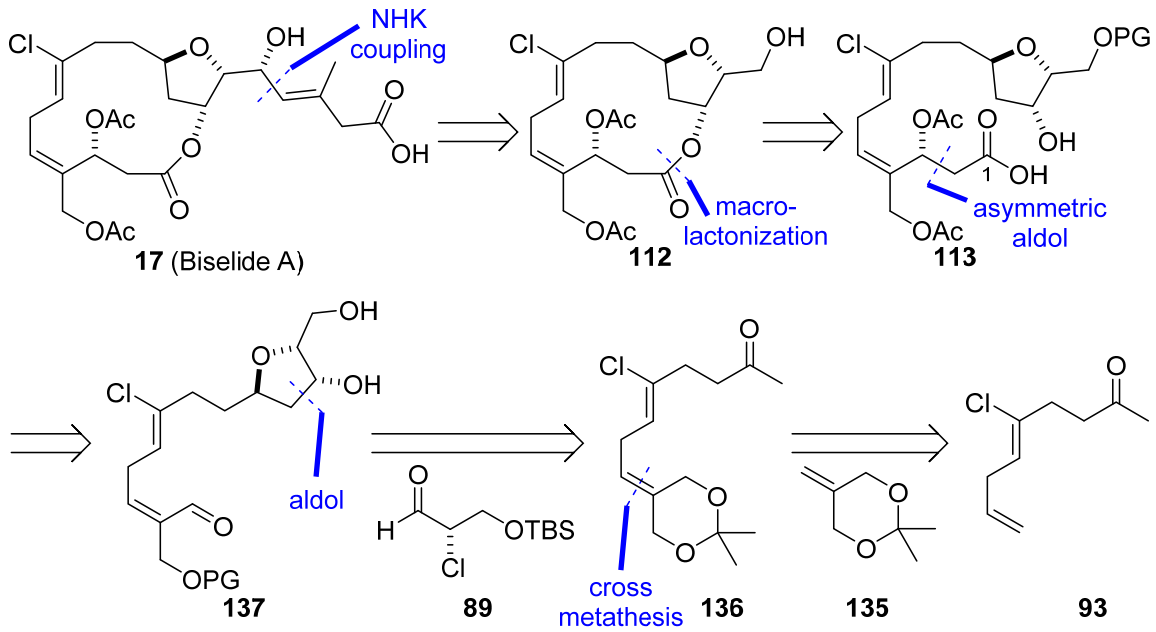
Previous work by Fan led to the identification of a compatible alkene **135** for cross metathesis with methyl ketone **93** (Scheme 2.6). Further, it was found that use of the Hoveyda-Grubbs II catalyst in toluene at 60 °C was optimal for this transformation.

Scheme 2.6 Cross Metathesis with Methyl Ketone (93) and Dioxane (135)



Considering the failings of the HWE approach, we decided to build upon this result and explore a strategy that would incorporate this cross metathesis as a key step (Scheme 2.7). It was expected that the final stages of the synthesis would remain unchanged and involve Yamaguchi macrolactonization[38] and NHK coupling reactions,[30,31] both of which are well-precedented processes. An asymmetric acetate aldol reaction would then be used to install the C1 and C2 fragment of the macrocycle and provide access to the requisite carboxylic acid for macrolactonization. Again, tetrahydrofuranol **137** would be accessed through the aldol-reduction-cyclization sequence previously established in our laboratory. A cross metathesis between compound **93** and dioxane **135** would then provide a route to methyl ketone **136**, which would ultimately require deprotection and regioselective protection of the *E*-allyl alcohol function.

Scheme 2.7 Retrosynthesis for Cross Metathesis Strategy



Towards this goal, deprotection of acetonide **136** with PPTS provided a diol in quantitative yield (Scheme 2.8). We realized that the major challenge in this route would be the regioselective protection of one alcohol function in the newly generated diol, and a variety of conditions were tested in order to assess selectivity, conversion, and yield of this transformation (Table 2.1).

Scheme 2.8 Acetonide Deprotection and Hydroxyl Protection

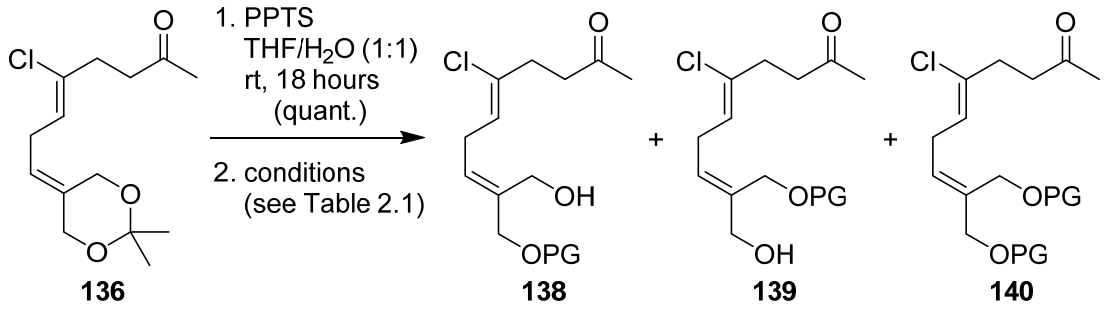
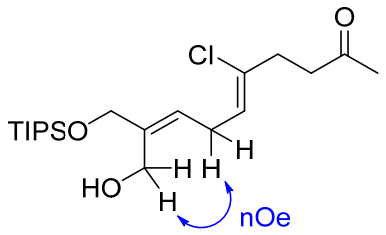


Table 2.1 Conditions for Chemoselective Hydroxyl Protection of 1,3-Diol

Entry	Protecting group	Conditions	Products
1	TBS	TBSCl (1.2 eq), imidazole, CH_2Cl_2, rt, o/n	47% **140** (major)
2	TBS	TBSCl (0.9 eq added dropwise), imidazole, CH_2Cl_2, -78 °C → rt,	**136** isolated as major compound
3	Ac	Acetic acid (1.5 eq), DIC, DMAP, CH_2Cl_2, rt	51% **140** (major)
4	Ac	PPL, 1,4-dioxane, rt	No reaction
5[69]	TIPS	TIPSCl (1.0 eq), $AgNO_3$, pyridine, rt, o/n	2.4:1 **138/139**, 48% conversion
6	TIPS	TIPSCl (1.1 eq), NEt_3, DMAP, CH_2Cl_2, 0 °C → rt, o/n	12% **138**, 12% **139** – no selectivity
7	TIPS	Same as entry 6 but larger scale	29% **138**, 2% **139**, 32% **140**
8	TIPS	TIPSCl (1.0 eq), NEt_3, DMAP, CH_2Cl_2, 0 °C → rt, o/n	32% **138**, 8% **139**

As summarized in Table 2.1 (entries 1 and 2), we first explored a selective protection strategy by reacting the diol intermediate with *tert*-butyldimethylsilyl chloride hoping that selectivity could be attained based on the different steric environments of the two alcohol functions generated upon deprotection of acetonide **136** with PPTS. No selectivity was observed and large amounts of *bis*-silylated material and starting material were also isolated from these reactions. Entries 3 and 4 highlight additional attempts to effect selective acylation of the *E*-allyl alcohol function. Disappointingly, reaction with acetic acid and *N,N'*-diisopropylcarbodiimide showed no selectivity and primarily produced the corresponding *bis*-acetylated product along with recovered starting material. An interesting report from Imai describes selective *E* acetylation of related substrates using porcine pancreas lipase (PPL) and vinyl acetate.[70] Using these conditions, however, no desired product was formed. Finally, our efforts to use the more sterically bulky TIPS protecting group in entries 5-8, showed some selectivity for the *E*-allyl alcohol function. Our best conditions are summarized in entry 8. Here we found a 4:1 selectivity, albeit in low product yield. The mono-TIPS protected *E* and *Z* isomers were distinguished by analysis of 1D NOESY experiments. For example, a correlation

was observed between the protons on the hydroxy methylene and the *bis*-allylic protons in the *E* protected product (Figure 2.1).

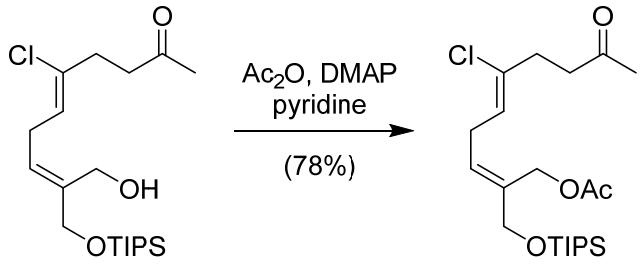


138

Figure 2.1 NOe correlations for methyl ketone (138).

Despite the poor yield for the selective protection of the diol function, we carried forward with this material keeping in mind that further optimization of this step would be required at a later point. With scarce material remaining, methyl ketone **138** was acetylated to afford the orthogonally-protected compound **139** (Scheme 2.9).

Scheme 2.9 Acetylation of Methyl Ketone (138)

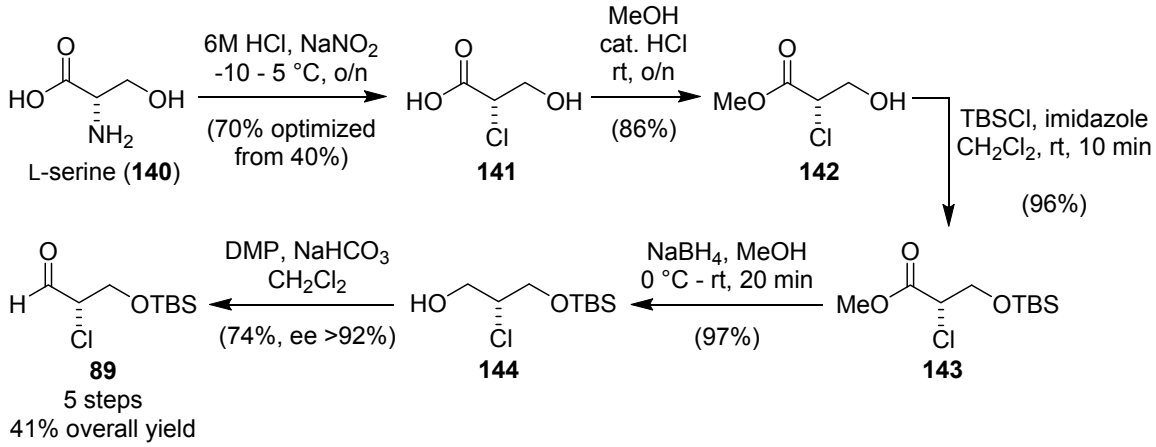


138 **139**

With the synthesis of the methyl ketone complete, our attention turned to the preparation of *α*-chloroaldehyde **89**. Kang had previously developed the synthesis of *α*-chloroaldehyde **89**, and Fan later optimized the final oxidation step in this sequence by use of Dess-Martin periodinane to prevent racemization at the chloromethine centre.[55,61] Following this protocol, the synthesis of *α*-chloroaldehyde **89** commenced from L-serine (**140**) (Scheme 2.10) using a chlorination procedure previously reported by DeKimpe.[71] Thus, L-serine was converted to the chlorinated acid (**141**) with retention of stereochemistry. The stereochemical outcome of this reaction involves two consecutive S_N2 displacement reactions, whereby the amine function is converted to a diazonium salt

and subsequently displaced by the hydroxyl to form an epoxide. Acid-induced epoxide opening with chloride installs the halogen moiety in compound **141**. While Fan reported a yield of only 40% for this reaction, we discovered that the low yield was related to the polarity of the product, which hindered isolation under the previously optimized conditions. Bearing this in mind, we were able to optimize the isolation of carboxylic acid **141** by employing a repetitive sequence of extractions. Following this revised isolation protocol, the yield for this reaction was increased from 40% to 70%. Esterification of carboxylic acid **141** in methanol cleanly generated methyl ester **142**, which was directly silylated with *tert*-butyldimethylsilyl chloride to afford methyl ester **143**. Reduction of compound **143** with sodium borohydride provided alcohol **144**. Importantly, following several modifications to the sequence of reactions required to access alcohol **144**, we were able to produce up to 28 grams of alcohol **144** from 30 grams of L-serine (**140**). Finally, Dess-Martin periodinane was used to oxidize compound **144** while preserving the stereogenic centre, which provided the desired *α*-chloroaldehyde **89** in good yield. Following this route, the enantiomeric excess of *α*-chloroaldehyde **89** was previously determined to be greater than 92% by chiral GC analysis.[61]

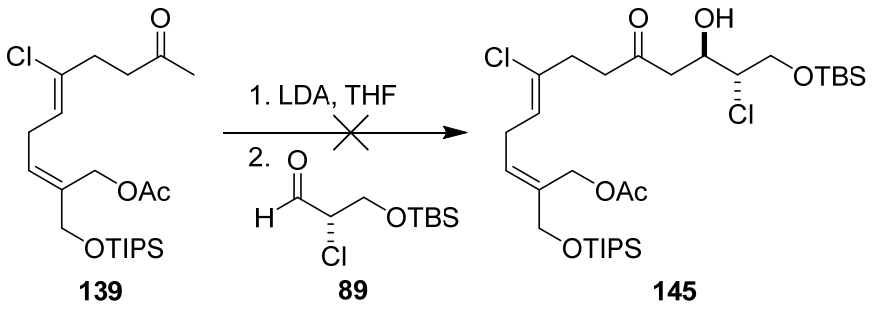
Scheme 2.10 Synthesis of *α*-Chloroaldehyde (89) via Fan's Strategy[61]



With the *α*-chloroaldehyde (**89**) in hand, we attempted the aldol reaction with methyl ketone **139** (Scheme 2.11). Unfortunately, no reaction was observed and the two starting materials were isolated upon work up. Due to the complications in producing the methyl ketone **139**, we were only able to investigate this aldol reaction on small scale

(<20 mg of methyl ketone), which most likely contributed to the lack of success of this reaction.

Scheme 2.11 Attempted Aldol Reaction Between Methyl Ketone (139) and *α*-Chloroaldehyde (89)



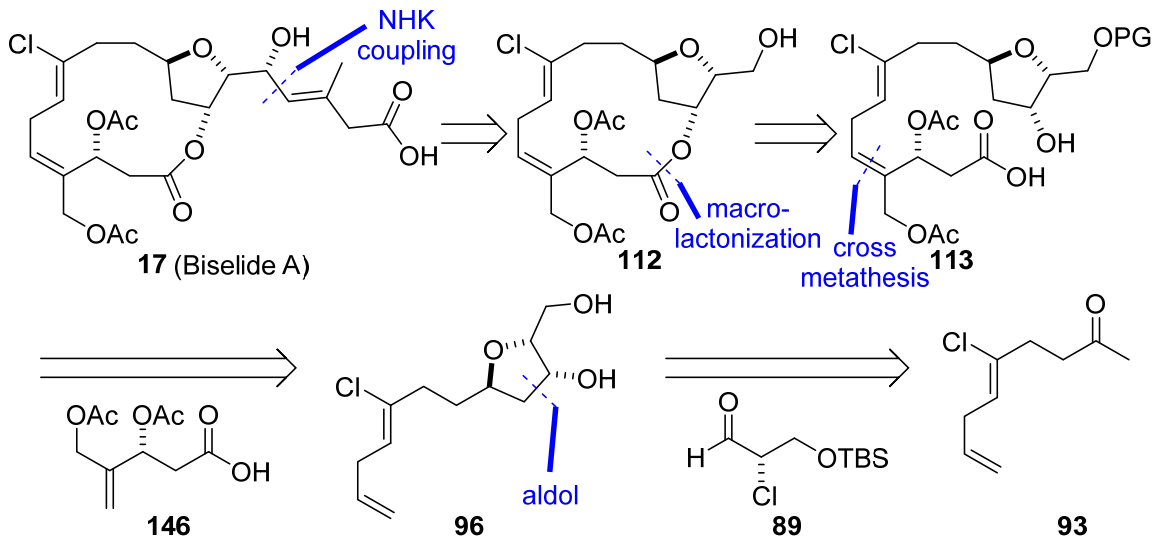
139 **89** **145**

Considering the challenges in preparing the methyl ketone **139**, we realized that the synthesis could be simplified if the tetrahydrofuran was formed before cross metathesis. For example, the acetylation of methyl ketone **138** (Scheme 2.9) was only necessary to protect the alcohol during the aldol reaction and would not be necessary if cross metathesis was performed later. Additionally, the amount of Grubbs-Hoveyda II catalyst required for the cross metathesis at an early stage was cost-prohibitive. Thus, the scale-up of this route required to access sufficient amounts of methyl ketone **139** and properly explore the aldol reaction was not initiated and, instead, a more economical strategy was pursued.

2.3. Revised Cross Metathesis Strategy

Our plans for the revised synthetic route follow the same endgame strategy from carboxylic acid **113** through to the target compound biselide A (**17**, Scheme 2.12). Compound **113** would then be constructed through a cross-metathesis reaction with an advanced building block such as diacetate **146**, in a reaction with tetrahydrofuranol **96**. The latter compound would be synthesized from an aldol reaction between methyl ketone **93** and *α*-chloroaldehyde **89**, followed by reduction of the ketone and subsequent cyclization.

Scheme 2.12 Retrosynthesis for Revised Cross Metathesis Strategy



Following methods developed by Kang, diol **95** was accessed in good yield over 2 steps from methyl ketone **93**.[55] Continuing with this sequence, thermal cyclization proceeded to give the desired tetrahydrofuranol **96** in 70% yield. On larger scales (>200 mg) we observed a noticeable decline in the yield of compound **96**, and the reaction was optimized on a gram scale which ultimately required the use of methanol as the solvent and higher temperatures for a much longer period of time (Scheme 2.13). After producing the diol **96** in high yield, it was protected as the corresponding acetonide on reaction with 2,2-dimethoxypropane and *p*-toluenesulfonic acid to access tetrahydrofuranol **147**, and secure one of the coupling partners for the cross metathesis reaction.

Scheme 2.13 Optimized Cyclization Reaction and Subsequent Silyl Protection

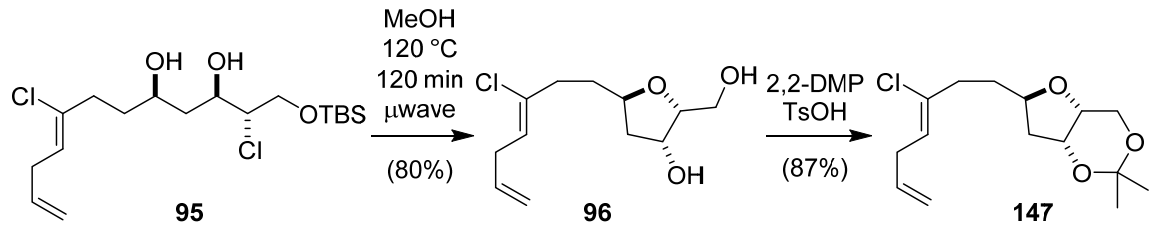


Figure 2.2 displays the ^{1}H NMR spectrum of tetrahydrofuranol **147**. The resonance at δ 5.03 ppm (multiplet) corresponds to the two terminal alkene protons, while the resonances at δ 5.79 ppm (multiplet) and δ 5.54 ppm (triplet, *J* = 7.1 Hz) correspond to the two remaining vinyl protons in the compound. The presence of the acetonide is confirmed by the resonances at δ 1.43 ppm (singlet) and δ 1.38 ppm (singlet), representative of the two methyl groups.

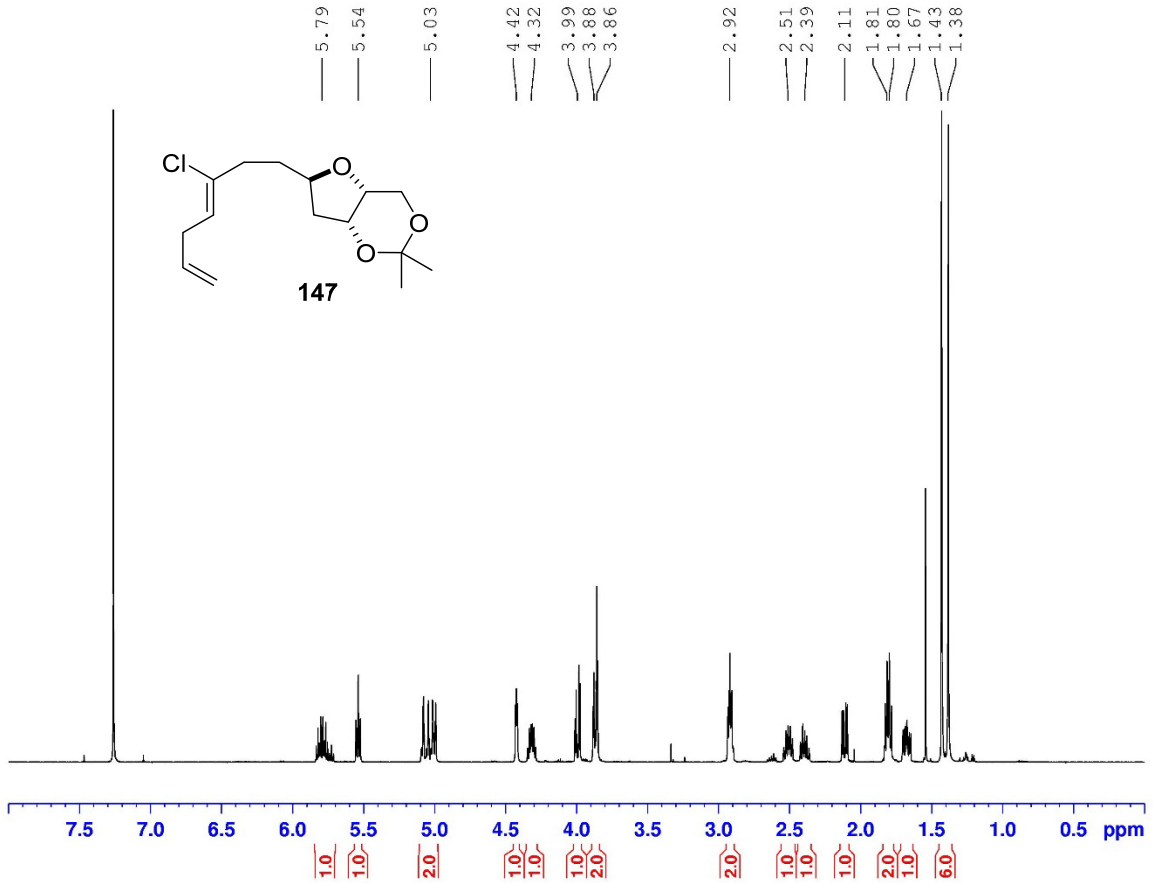
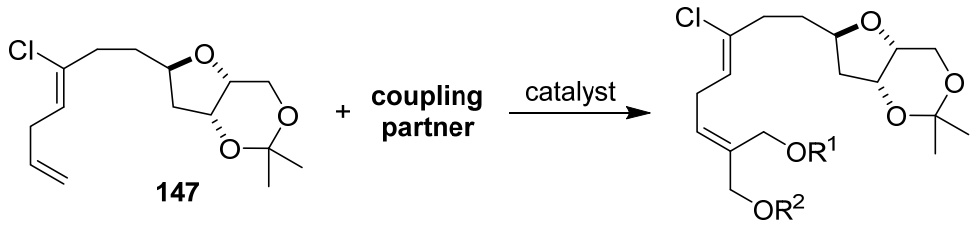
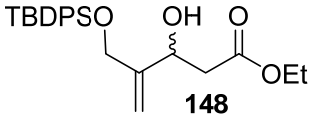
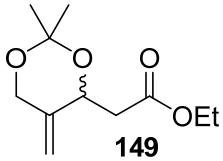
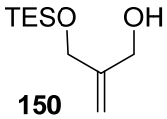
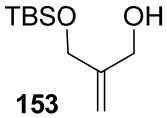
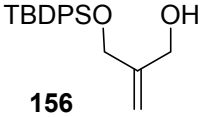
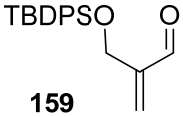


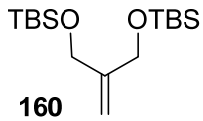
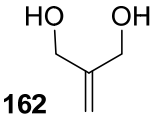
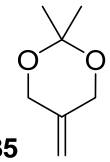
Figure 2.2 ^{1}H NMR spectrum of tetrahydrofuranol (147).

With the acetonide-protected tetrahydrofuranol **147** in hand we carried out the synthesis and screening of various alkene partners for the cross metathesis step (Table 2.2). The standard reaction conditions used for the synthesis of compound **136** were maintained, and in some instances the Stewart-Grubbs catalyst was additionally tested.[72]

Table 2.2 Compounds Screened in Cross Metathesis Reaction with Tetrahydrofuranol (147)*



Entry	Coupling Partner	Catalyst	*E/Z* selectivity	Product (Yield %)
1	 **148**	HG-II	N/A	(0)
2		Stewart Grubbs	N/A	(0)
3	 **149**	HG-II	N/A	(0)
4	 **150**	HG-II	1:1	**151**: R^1 = H, R^2 = TES (15) **152**: R^1 = TES, R^2 = H (15)
5	 **153**	HG-II	1:1.5	**154**: R^1 = H, R^2 = TBS (13) **155**: R^1 = TBS, R^2 = H (20)
6	 **156**	HG-II	1:1	**157**: R^1 = H, R^2 = TBDPS (29)
7		Stewart Grubbs	1:2	**157**: R^1 = H, R^2 = TBDPS (20) **158**: R^1 = TBDPS, R^2 = H (47)
8	 **159**	HG-II	N/A	(0)
9		Stewart Grubbs	N/A	(0)

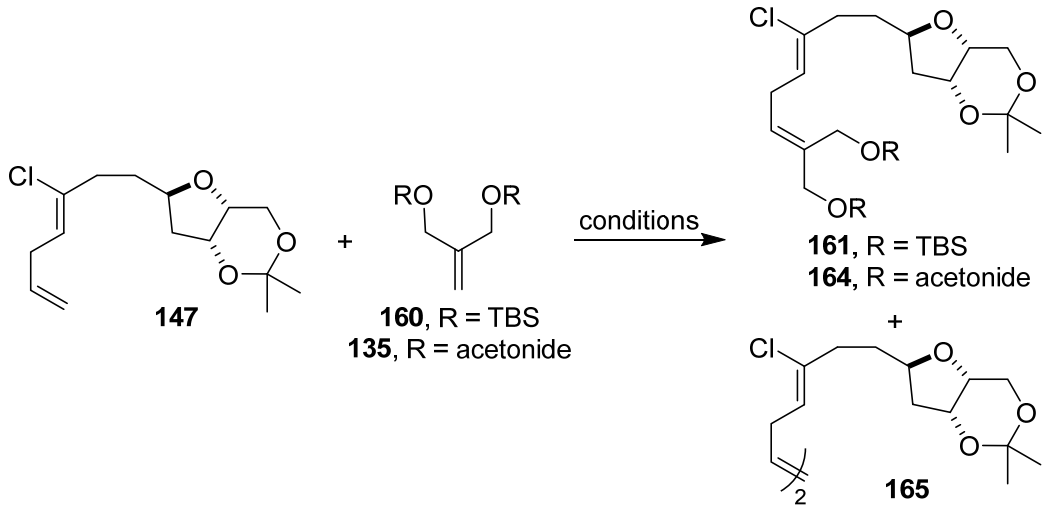
Entry	Coupling Partner	Catalyst	*E/Z* selectivity	Product (Yield %)
10	 **160**	HG-II	N/A	**161**: R^1 = TBS, R^2 = TBS (16)
11	 **162**	HG-II	N/A	**163**: R^1 = H, R^2 = H (17)
12	 **135**	HG-II	N/A	**164**: R^1, R^2 = acetonide (60)

*Reaction conditions: **147** [0.05M] in PhMe, 5 equiv. coupling partner, N_2 sparge, heat to 60 °C, then add 5 mol% catalyst.

After exploring various coupling partners and catalysts, the original dioxane **135** and original conditions with Grubbs-Hoveyda II still gave the best yield. We attempted to monitor reactions of alkene **160** under different conditions to gain further insight into the reaction (Table 2.3). Analyzing reactions periodically by ^{1}H NMR spectroscopy, we found that reaction progress halted after ~2 hours (entry 1). In an effort to re-initiate the metathesis reaction, more catalyst was added at 2 hour intervals (entry 2) and with more careful monitoring (every 15 min) we determined that reaction progress stalled after only 15 min and that adding catalyst at 2 hour intervals did not re-initiate the metathesis process. Using the Stewart-Grubbs catalyst (entry 3) we observed a similar outcome. In an effort to assess the effect of concentration, the reaction was repeated at ten times the concentration (entry 4), but this change resulted only in dimerization of tetrahydrofuranol **147** to produce compound **165**. To gain further insight into the dimerization process and in an effort to determine whether the dimer was in fact a precursor to product, the reaction described in entry 4 was repeated and stopped at 30 and 60 minutes (entries 5 and 6, respectively). The results from these experiments suggested that the first step in this reaction is indeed dimerization, which occurs rapidly and is followed by cross metathesis with the protected diol coupling partner. In an effort to mitigate dimer

formation, the alkene **147** was added dropwise, which only slightly improved the outcome (entry 7). Finally, for comparison purposes, we tested the original conditions with dioxane **135** and again, this reaction produced the best result. Similar to Fan's attempts at improving the relay ring-closing metathesis,[61] changes to the cross metathesis conditions did not offer any noticeable improvements and the best results were obtained using the reaction conditions summarized in entry 8.

Table 2.3 Monitored Cross Metathesis Reactions



Entry	Conditions	Time	R	Major product	Comments	Conversion (%)
1	A[a]	4 h	TBS	**147**	Rxn did not progress further after 2 h	25
2	B[b]	4 h	TBS	**165**	Rxn did not progress further after 15 min	57
3	C[c]	4 h	TBS	**165**	Rxn did not progress further after 15 min	54
4	D[d]	3 h	TBS	**165**	N/A	82
5	E[e]	30 min	TBS	**165**	N/A	55
6	E[e]	1 h	TBS	**165**	N/A	59
7	F[f]	3 h	TBS	**165**	N/A	77
8	G[g]	16 h	acetonide	**164**	N/A	77

[a] Grubbs-Hoveyda II (5 mol%), 60 °C PhMe, 0.05 M, 5 equiv. coupling partner; [b] Same as A but added 5 mol% cat. every 2 h; [c] Same as B but with Stewart-Grubbs catalyst; [d] Same as A but 0.5M, after 2 h added another 5 mol% cat.; [e] Same as A but 0.5M; [f] Same as A but added compound **147** dropwise over 20 minutes; [g] Same as A but 10 equiv. compound **135**, after 4h cool to r.t. o/n.

The observation of dimer **165** suggested that this compound may in fact be an intermediate that undergoes further cross metathesis with the protected diol **135**. The dimer (**166**) was isolated and the ^{1}H NMR spectrum compared to the starting material **147** (Figure 2.3). As indicated in Figure 2.3, there is a significant difference in the alkene

region of the ^{1}H NMR spectra. For example, resonances at δ 5-6 ppm in the ^{1}H NMR spectrum of the dimer indicate only two alkene protons. Additionally, the multiplet at δ 5.05 ppm in the ^{1}H NMR spectrum of the starting material is clearly absent in that of the dimer while all other resonances were present. In addition to this ^{1}H NMR data, high resolution mass spectrometric analysis of the dimer included a signal at m/z 567.2273 amu (calculated m/z 567.2251 amu), consistent with the chemical formula $C_{28}H_{42}Cl_2NaO_6$ corresponding to the dimer plus a sodium ion.

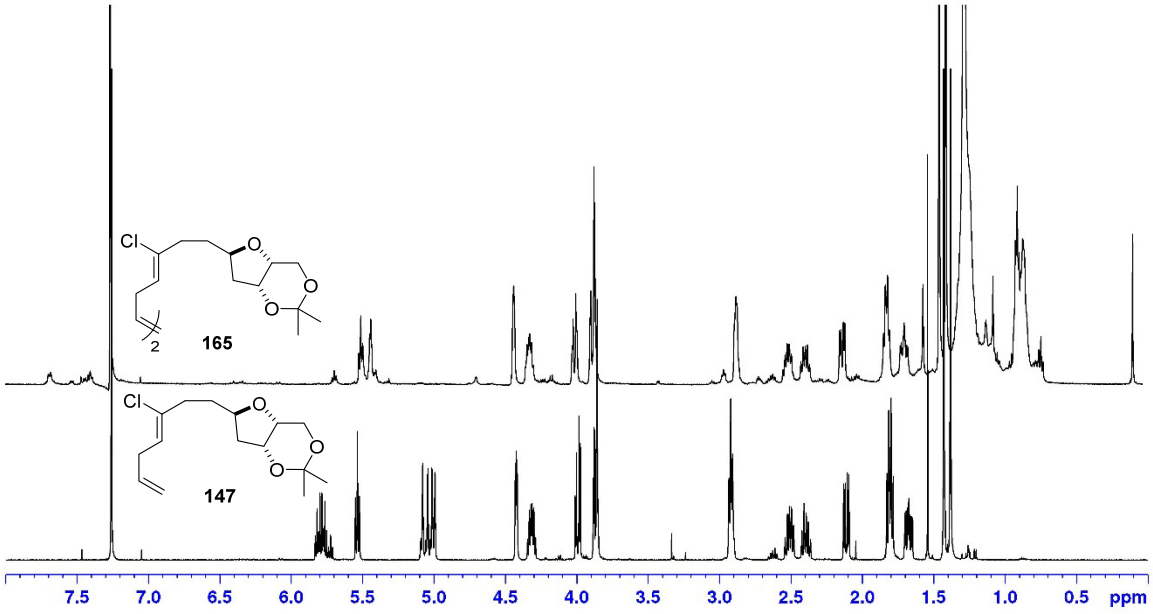
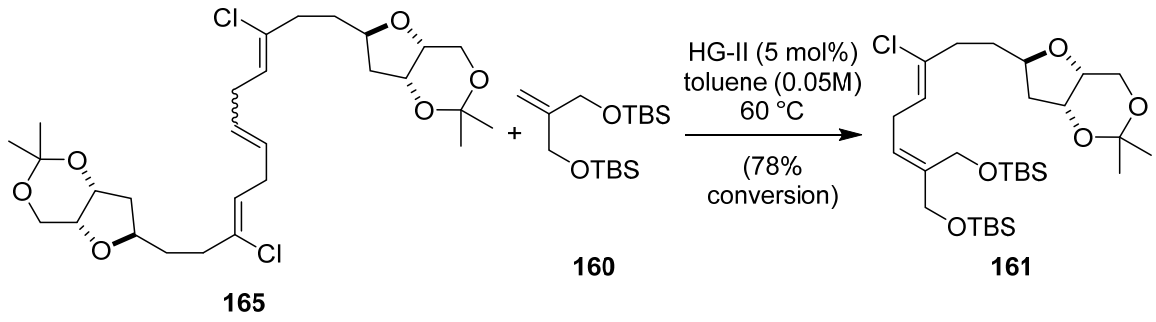


Figure 2.3 ^{1}H NMR spectrum comparing dimer (165) and monomer (147).

With dimer **165** in hand, cross metathesis was carried out with alkene **160** (Scheme 2.14). As expected, the desired metathesis product was produced, indicating that the dimer is in fact an intermediate in the cross metathesis reaction and that further optimization of this reaction may lead to improved conversion to the desired diene **161**. This reaction was tested on small scale (<10 mg) and converted 78% of starting material **165** to give tetrahydrofuran **161**.

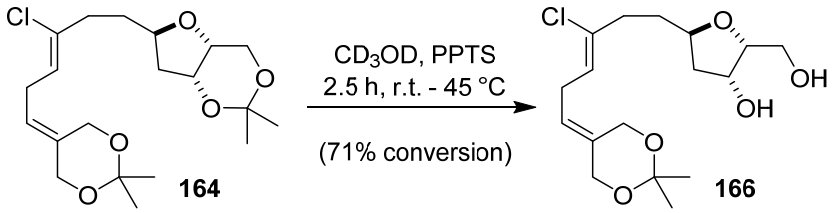
Scheme 2.14 Cross Metathesis with Dimer (165)



165 **160** **161**

Returning to the total synthesis of biselide A, the bisacetonide **164** was subjected to mildly acidic conditions in hope that the tetrahydrofuranol acetonide would be left untouched while the acetonide protecting group for the *bis*-allyl alcohol function would be removed selectively (Scheme 2.15). Unfortunately, the undesired diol **166** was formed exclusively under these conditions in 71% conversion based on remaining starting material **164**. This result was confirmed by analysis of the ^{1}H NMR spectra recorded on the only product isolated from the crude reaction mixture (Figure 2.4). For example, two resonances at δ 1.33 and 1.46 ppm (each integrating for 3 protons) are characteristic for the tetrahydrofuranol acetonide (in methanol-d_4). Conversely, the two methyl groups on the terminal diol acetonide protecting group typically resonate at δ 1.32 ppm (integrate for 6 protons). On monitoring the deprotection step by ^{1}H NMR spectroscopy, it was clear that the tetrahydrofuranol acetonide was removed.

Scheme 2.15 Selective Acetonide Deprotection of Compound (164)



164 **166**

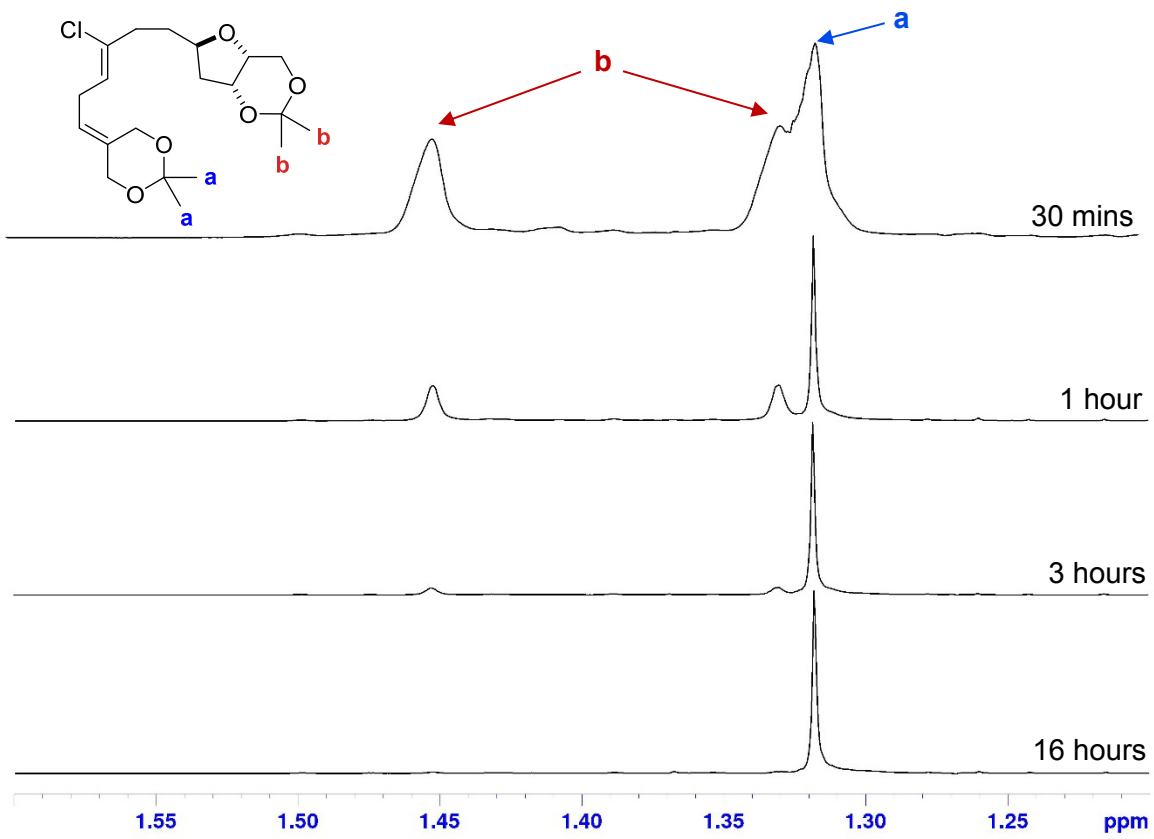
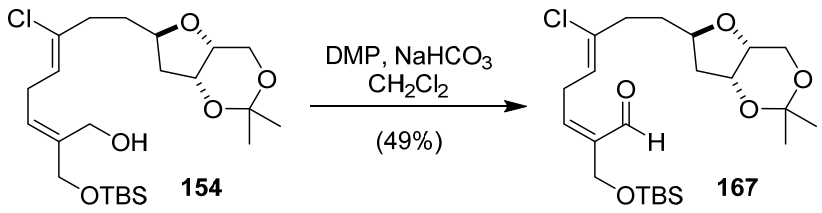


Figure 2.4 **^{1}H NMR spectrum indicating reaction progress (Scheme 2.15) at 30 minutes, 1 hour, 3 hours, and 16 hours.**

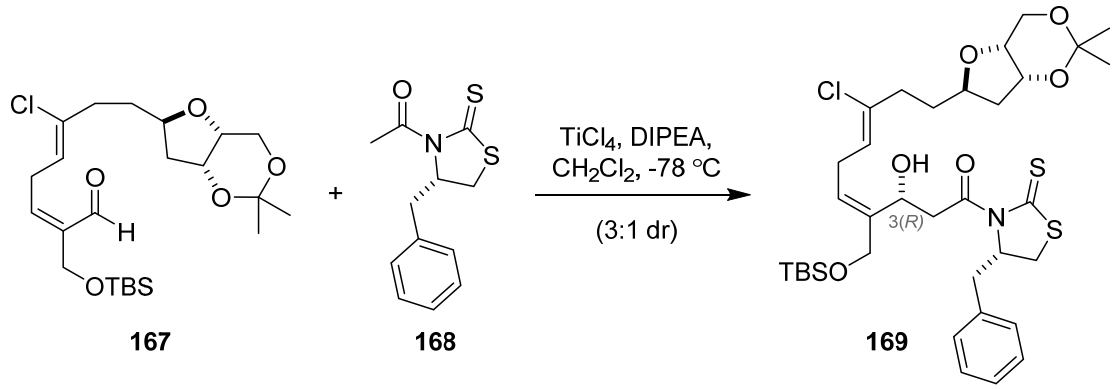
Considering the inability to selectively deprotect the desired acetonide in compound **164**, we turned our attention to the *E*-TBS protected product **154**, which was isolated from cross metathesis with coupling partner **153**. Oxidation of the primary alcohol function with Dess-Martin periodinane produced the desired *α,β*-unsaturated aldehyde (**167**, Scheme 2.16), which was appropriately functionalized for a subsequent acetate aldol reaction to install the remaining two carbon atoms of the biselide macrocycle.

Scheme 2.16 Oxidation of Alcohol (154) to Aldehyde (167)



Within the context of a total synthesis of biselide A, it was essential to control the relative stereochemistry of the required aldol reaction. For this purpose, we sought an auxiliary controlled acetate aldol reaction and considered that the auxiliary should be readily available and easily removed under relatively mild conditions. For these reasons we elected to explore the use of the Crimmins acetylthiazolidinethione **168**, which has previously been employed successfully by Skaanderup and Jensen in the total synthesis of the macrocyclic natural product (-)-pladienolide B.[73] Further, this auxiliary is highly crystalline and often times the aldol products derived from this auxiliary are also crystalline, which allows for purification and improved long term storage. The synthesis of chiral auxiliary **168** was achieved in 3 steps and 54% overall yield from L-phenylalanine following standard procedures.[73,74] The key aldol reaction was carried out with the chiral enolate of acetate **168** which was formed using Vilarrasa's conditions (Scheme 2.17).[75] Employing these conditions, aldol adduct **169** was generated in a 3:1 diastereoisomeric ratio in favour of the desired C3(*R*) stereochemistry. The absolute configuration of the newly formed carbinol stereocentre was tentatively assigned based on previous literature.[73] Since this exploratory reaction was executed on small scale (10 mg), an accurate yield is difficult, although it was estimated at 25%. In addition to the desired product, several side products were generated which indicate that this reaction will certainly require further optimization.

Scheme 2.17 Asymmetric Acetate Aldol Reaction

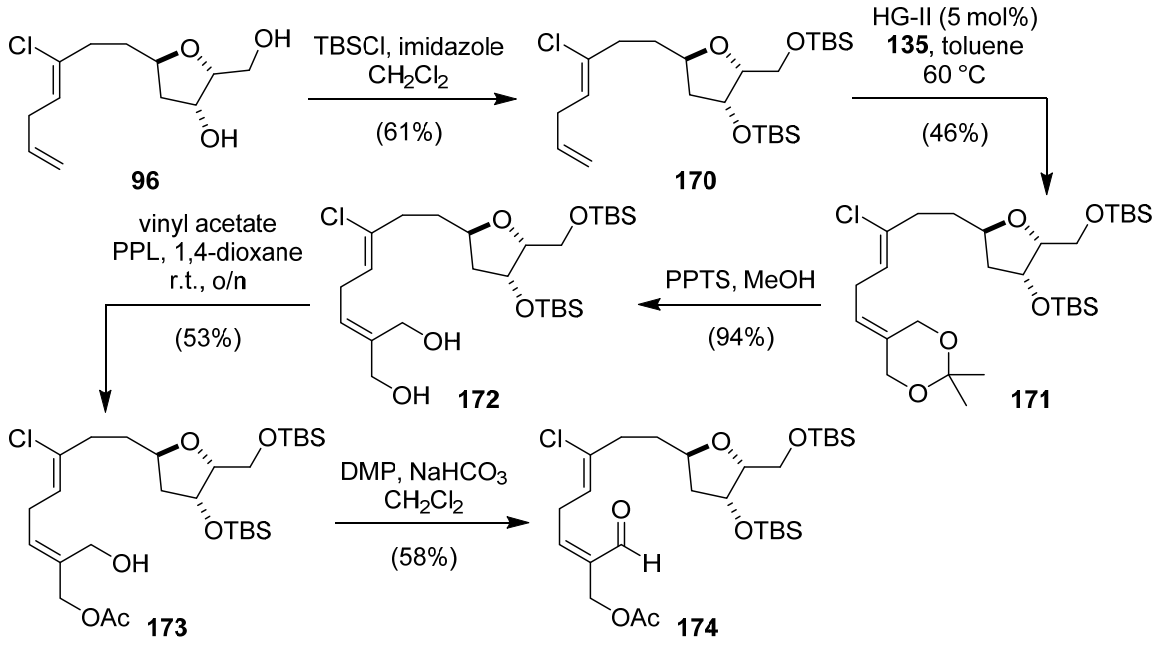


167 **168** **169**

While this route had provided access to small amounts of an advanced precursor to biselide A (**17**), with little material remaining, we returned to the cross metathesis reaction and, based on the improved yield of cross metatheses involving the

dioxane **135** (Table 2.2), elected to proceed with cross metatheses involving this alkene. Considering the challenges encountered previously in the attempted selective deprotection of the bisacetonide **164**, we instead elected to protect the tetrahydrofuranol **96** as the corresponding *bis*-TBS ether. Thus, as depicted in Scheme 2.18, the tetrahydrofuranol **96** was converted into the *bis*-TBS ether **170** under standard conditions and in good yield. A subsequent cross metathesis reaction using our optimized reaction conditions with acetonide **135** afforded the diene **171**. With the two diol functions now orthogonally protected, the allylic diol was selectively deprotected under acidic conditions to access the diol **172**. Based on precedent for the selective acetylation of allylic diols by Imai,[70] the *trans*-hydroxyl function of compound **172** was acetylated by reaction with porcine pancreas lipase and vinyl acetate. We were delighted to find that this highly diastereoselective reaction proceeded cleanly to give a mixture of the desired product accompanied by starting material. Subsequent oxidation of the remaining allylic alcohol function with Dess-Martin periodinane afforded the aldehyde **174**.

Scheme 2.18 Synthesis of Aldehyde (174) from Tetrahydrofuranol (96)



Acetylation of the *trans*-hydroxyl function of diol **172** was confirmed by analysis of 1D NOESY NMR experiments. As indicated in Figure 2.5, irradiation of the acetoxy

methylene resonance at δ 4.64 ppm (singlet) in compound **173** showed an enhancement of the vinyl proton at δ 5.63 ppm (triplet, *J* = 7.5 Hz).

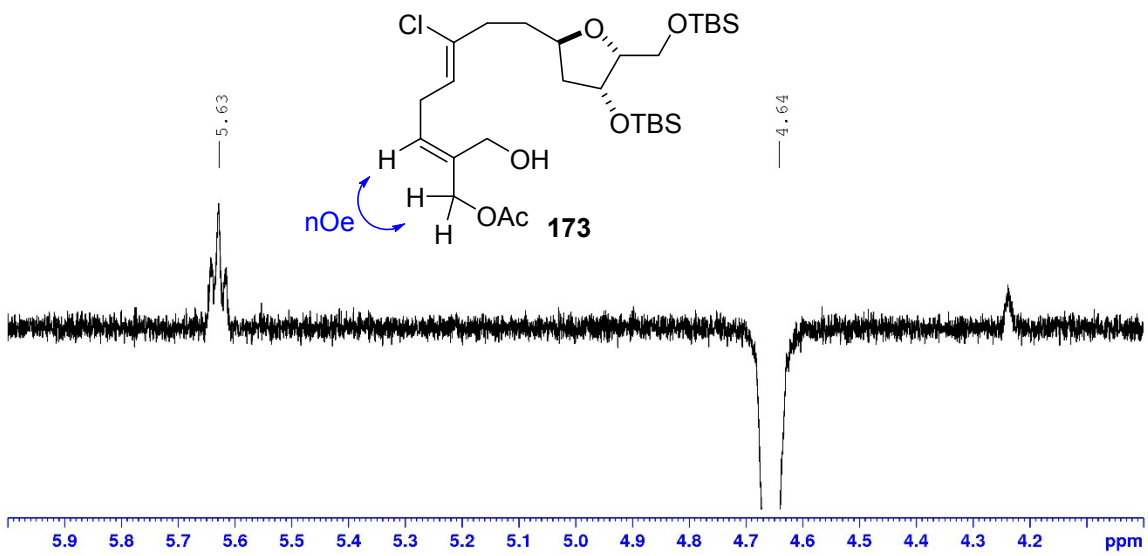


Figure 2.5 1D NOESY NMR spectrum showing nOe correlation on acetate (173).

The ^{1}H NMR spectrum for acetate **173** is depicted in Figure 2.6. The C3 methylene shows a resonance at δ 4.23 ppm (singlet), while the C20 methylene shows a resonance at δ 4.64 ppm (singlet). Additionally, the three *α*-protons of the acetate function are assigned to the resonance at δ 2.09 ppm (singlet), indicating that the acetylation had occurred.

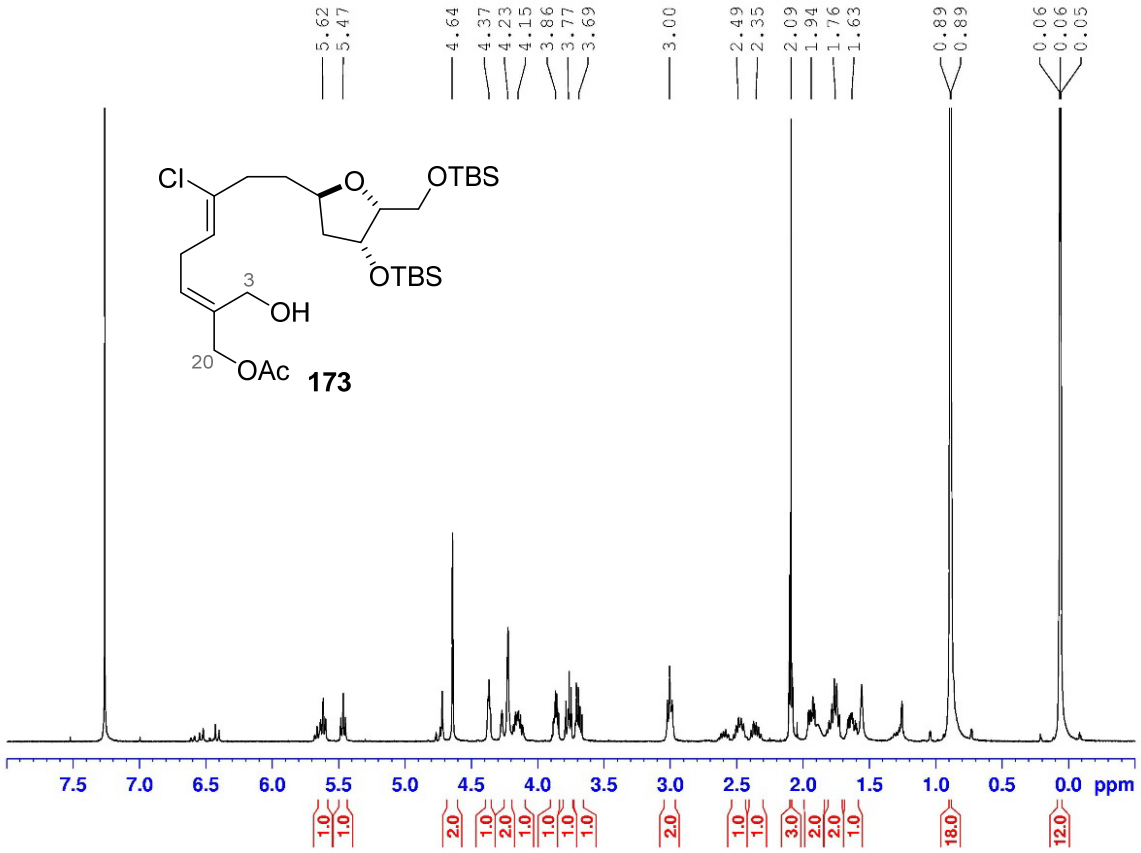
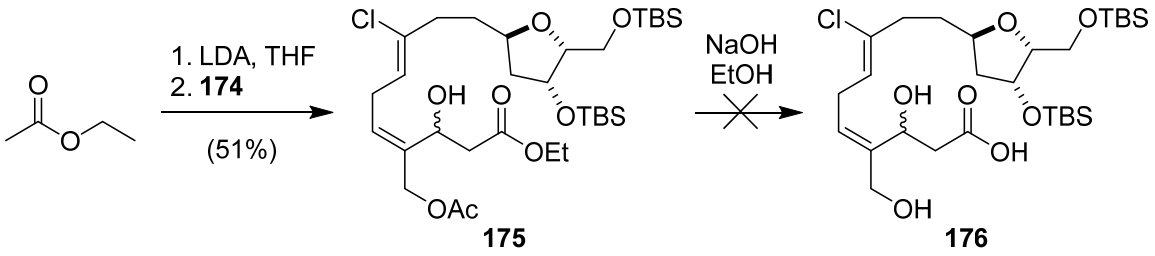


Figure 2.6 **^{1}H NMR spectrum of acetate (173).**

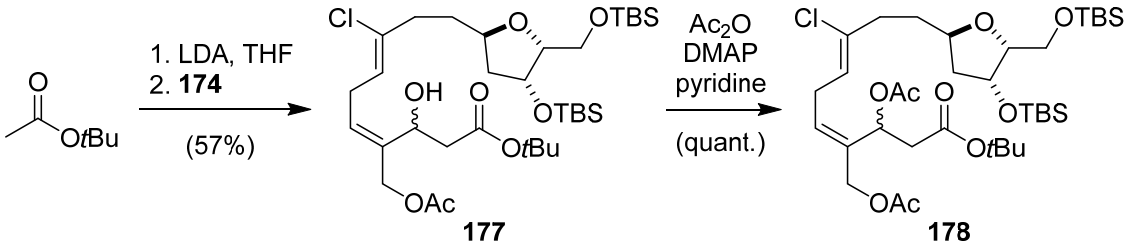
Considering the number of by-products observed in the reaction of the related enal **167** with Crimmins acetylthiazolidinethione **168** (Scheme 2.17), for the purpose of exploring the final steps required for macrocycle formation, we first explored the lithium aldol reaction between ethyl acetate and the aldehyde **174** (Scheme 2.19). In this event, we were delighted that the reaction proceeded to give a diastereomeric mixture of the ethyl esters **175**. Upon subjecting this material to hydrolysis conditions required to eventually access the seco acid, we only observed formation of multiple inseparable compounds that contained additional alkene functions (as observed by analysis of ^{1}H NMR spectra). This outcome suggested that elimination of the *β*-hydroxy group was occurring in preference to ester hydrolysis.

Scheme 2.19 Aldol Raction with Aldehyde (174) and Ethyl Acetate and Attempted Hydrolysis



In considering that the aldol product **175** underwent elimination under basic hydrolysis reaction conditions, we elected to repeat the aldol reaction using instead an acetate ester that was prone to hydrolysis under acidic conditions. Thus, the lithium aldol reaction was repeated with the enolate derived from *tert*-butyl acetate and aldehyde **174** to form *tert*-butyl ester **177** as a diastereoisomeric mixture, which was successively acetylated to provide the diacetate **178** in good overall yield.

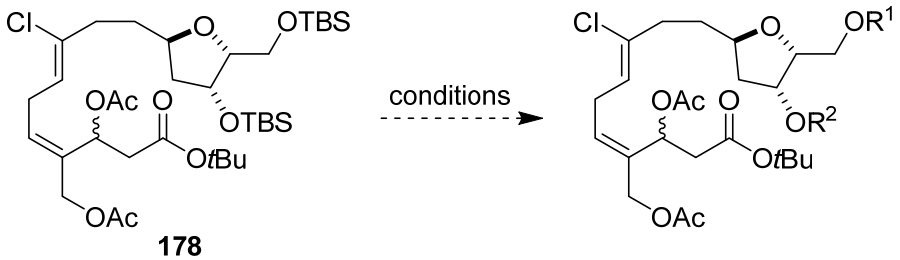
Scheme 2.20 Aldol Reaction with (174) and *tert*-Butyl Acetate and Subsequent Acetylation



With ester **178** in hand, we attempted to hydrolyze the *tert*-butyl ester following several standard sets of reaction conditions (Table 2.4)[76]. Formic acid effected only the removal of the silyl protecting groups without hydrolysis of the *tert*-butyl ester. Further heating of this reaction mixture to 100 °C led predominantly to decomposition. While Kigoshi had success in hydrolyzing a similar *tert*-butyl ester, our attempts to replicate these reported conditions (entry 2) provided only unreacted starting material even after heating the reaction mixture to reflux. When additional amounts of TFA were added this reaction mixture (entry 3) only the silyl protecting groups were removed. In an effort to monitor the hydrolysis by ^{1}H NMR spectroscopy, a reaction of compound **178** with

excess (9 equiv.) of TFA was carried out in dichloromethane-d_2, however, under these conditions 3 products were formed (entry 4). Two of these products still had the *tert*-butyl group, and the remaining product did not show the expected resonance for the *tert*-butyl group in the ^{1}H NMR spectrum, but was also not found to have the correct mass when analyzed by mass spectrometry. For example, the parent ion observed for this product had a mass to charge ratio of 447, while the expected mass for the product was calculated to be 449. Considering the limited amounts of material, one final attempt was made to hydrolyze the *tert*-butyl ester using Kigoshi's conditions with the exception that the reaction was executed at a much higher concentration of both the 2,6-lutidine and trimethylsilyl trifluoromethanesulfonate. Again, no evidence for hydrolysis of the ester was observed in NMR spectra recorded on the crude reaction mixture and, while two new products were formed, they both displayed resonances characteristic of the *tert*-butyl group in their ^{1}H NMR spectra (δ = 1.43 ppm). In the end, hydrolysis of both the ethyl ester and the *tert*-butyl ester were not achieved. Thus, in future studies, an alternate acetate derivative will be required for the aldol reaction that can be readily hydrolyzed using mild conditions, and ideally provide stereoselectivity at the C3 hydroxyl.

Table 2.4 Conditions Attempted for *tert*-Butyl Hydrolysis



178

Entry	Conditions	Time	Temperature	Product
1	A[a]	N/A	r.t.-100 °C	**179**: R^1 = H, R^2 = H
2	B[b,26]	30 min	r.t.-reflux	No reaction
3	C[c]	2 h	r.t.-reflux	**179**: R^1 = H, R^2 = H **180**: R^1 = TBS, R^2 = H
4	D[d]	18 h	r.t.	Complex mixture
5	E[e]	3h	0 °C – r.t.	Complex mixture

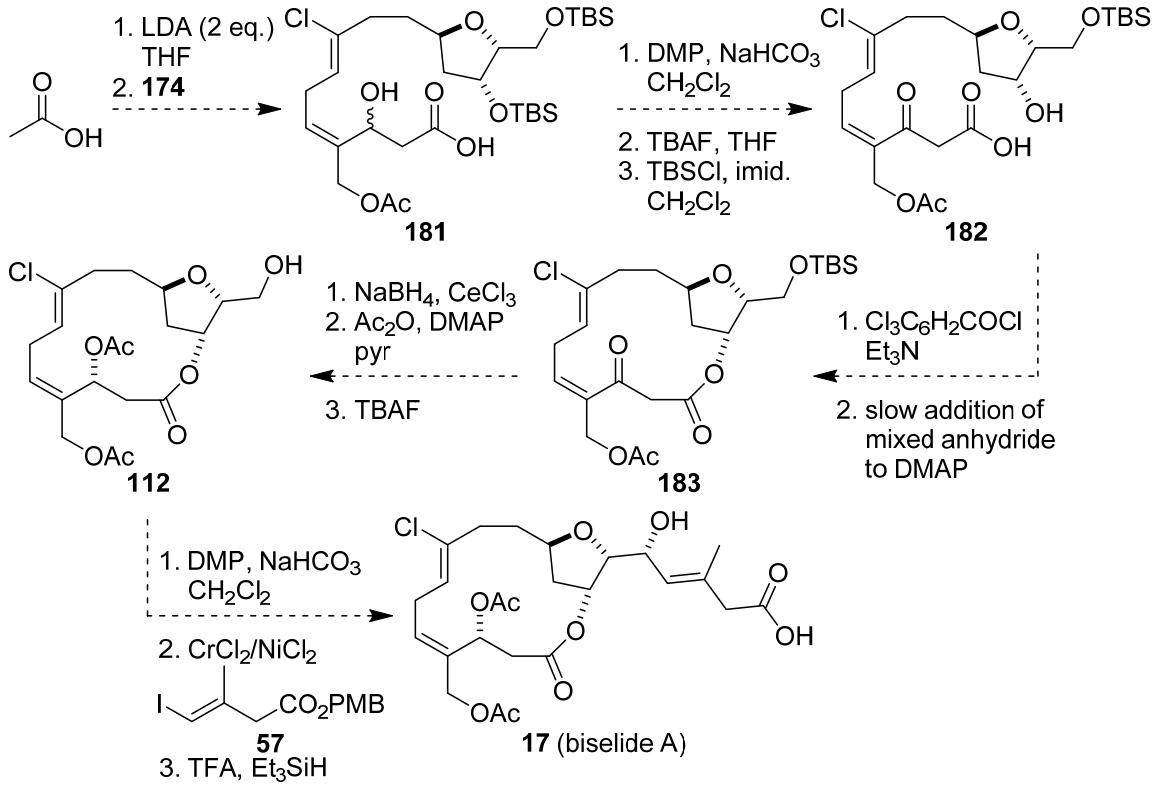
[a]HCO_2H/CH_2Cl_2 (1:1); [b]2,6-lutidine (1.2 equiv), TMSOTf (1.2 equiv), CD_2Cl_2; [c]Conditions B then add TFA (1 equiv.) at r.t. for 30 min, reflux for 30 min, add TFA (4 equiv.), reflux for 30 min; [d]TFA (9 eq), CD_2Cl_2; [e]2,6-lutidine (11 equiv.), TMSOTf (10 equiv.), CD_2Cl_2.

2.4. Future Studies

Two alternative acetate aldol reactions should be considered as potential solutions to the challenges encountered in the route to biselide A (**17**) presented above. Specifically, to avoid the difficult hydrolysis of ethyl and *tert*-butyl esters, an aldol reaction involving the dianion generated from acetic acid[77] would provide the desired carboxylic acid **181** directly (Scheme 2.21). The allylic alcohol could then be subjected to oxidation, to avoid carrying a mixture of diastereoisomers throughout the synthesis. Desilylation followed by a selective mono-silylation of the primary alcohol function would then generate the seco acid **182**. This material could be subjected to a Yamaguchi macrolactonization[38] and subsequently the ketone could undergo a stereoselective Luche reduction based on precedent established by Hoye.[39] Acetylation of the secondary alcohol function followed by TBS removal with TBAF would then afford

intermediate **112**.[39] From macrolide **112**, the hydroxyl would be oxidized to the corresponding aldehyde with Dess-Martin periodinane that would finally be reacted with vinyl iodide **57** in a Nozaki-Hiyama-Kishi coupling reaction. Removal of the PMB protecting group using established conditions from several haterumalide syntheses should allow access to our target compound, biselide A (**17**) in 24 total linear steps.

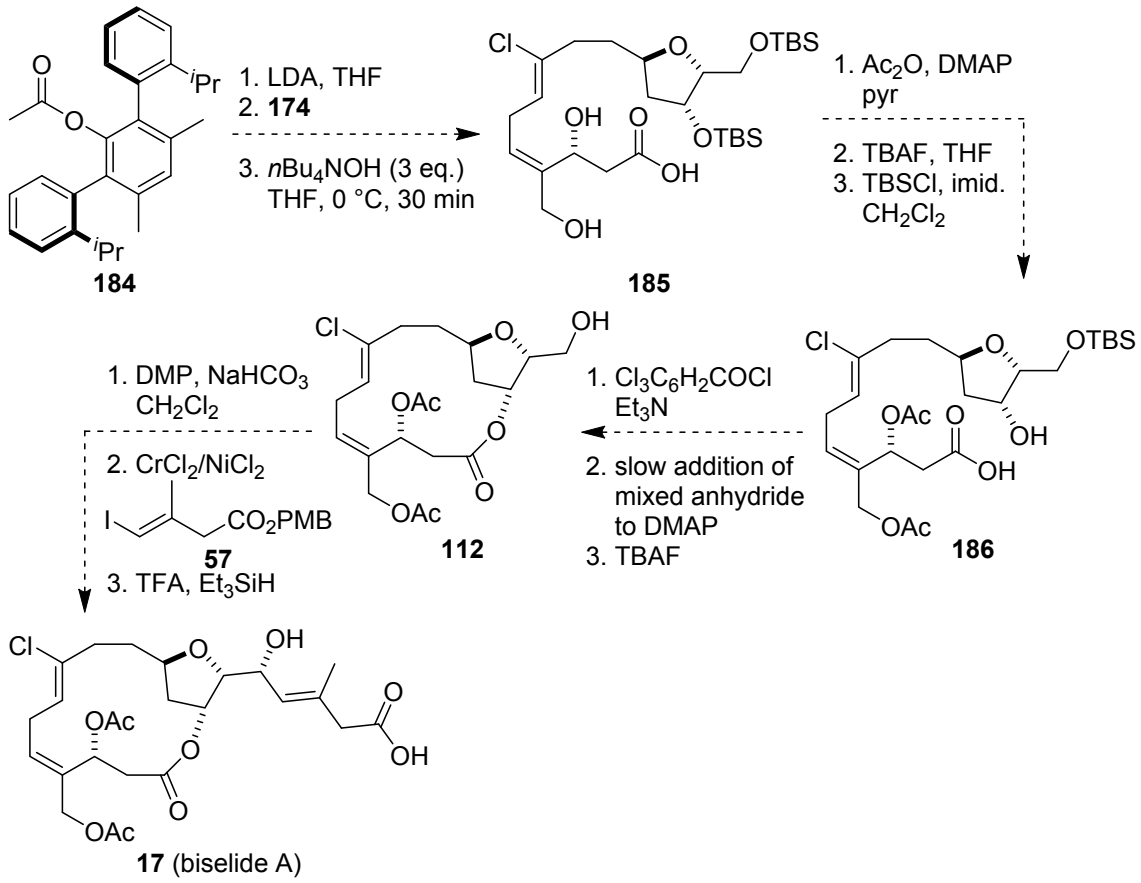
Scheme 2.21 Final Steps to Biselide A (17) from Acetic Acid Aldol Reaction



In an alternate approach, a new acetate chiral auxiliary **184** reported by Yamamoto[78] could be used in a lithium aldol reaction with aldehyde **174** to control the stereochemistry at C3. Subsequent hydrolysis with tetrabutylammonium hydroxide would effect cleavage of both the acetate and chiral auxiliary to afford diol **185**. Both hydroxyl groups would then be acetylated. Following a two-step sequence involving removal of both silyl protecting groups and selective protection of the primary alcohol function as the corresponding TBS ether would access the seco acid **186**. Employing Yamaguchi's macrolactonization conditions[38] would then effect formation of the macrocycle and treatment with TBAF would unveil the primary alcohol group in macrolide **112**. From

macrolide **112**, the synthesis of biselide A (**17**) could be completed following the 3 final steps depicted in Scheme 2.21. This route should provide access to biselide A (**17**) in 23 linear steps from commercially available starting materials.

Scheme 2.22 Final Steps to Biselide A (17) from Asymmetric Acetate Aldol Reaction



2.5. Conclusion

In summary, I have explored various synthetic strategies towards the total synthesis of biselide A and am currently on track to completing the synthesis with a step count that is competitive with previous total syntheses of haterumalides. The 2,5-disubstituted-3-hydroxytetrahydrofuran function present in the biselide and haterumalide natural products has previously presented a synthetic challenge. I have incorporated our chloropolyol cyclization methodology to access this moiety efficiently and in high enantioselectivity, while also building upon the framework of the core structure. Use of this methodology to form the tetrahydrofuranol will allow for a much lower step count compared to conventional methods. The Horner-Wadsworth-Emmons strategy first investigated was not successful due to the challenges in accessing the desired phosphonate coupling partner. Additionally, subjecting the unprotected hydroxyl phosphonate to Horner-Wadsworth-Emmons conditions proved ineffective and instead yielded only a series of intractable by-products. The discovery of an alkene dioxane compound which is compatible for cross metathesis re-invigorated the cross metathesis strategy and was used to build upon the C4-C5 terminal alkene. In the interest of protecting group efficiency, the steps of this sequence were rearranged so that the aldol-reduction-cyclization sequence could be performed prior to cross metathesis, in what we refer to as the revised cross metathesis strategy. While investigating this route, alternate cross metathesis partners were examined with the intention to make the overall synthesis more convergent, however, the previously reported alkene dioxane still proved to be the most efficient. Subsequent studies were carried out to optimize the cross metathesis but improved conditions were not found. With an acetonide-protected tetrahydrofuran compound in hand, I accomplished an asymmetric acetate aldol reaction with a Crimmins-like chiral auxiliary to install the final 2 carbon atoms of the macrocycle while generating the desired C3(*R*)-hydroxyl stereogenic centre. Additional acetate aldol reactions were explored using both ethyl acetate and *tert*-butyl acetate. The product of the former reaction decomposed under basic hydrolysis conditions. Various conditions were explored in attempts to hydrolyze the corresponding *tert*-butyl ester, however, none proved successful. I have established a clear route to the acetate aldol reaction and future studies will investigate alternate acetate sources that allow for ready conversion to the required carboxylic acid functionality. Following this, only two key steps remain to

complete this synthesis. Both of these steps have been used to complete previous syntheses of haterumalides, and therefore, should also provide easy access to biselide A.

2.6. Experimental

2.6.1. General

All reactions described were performed under an atmosphere of dry argon or nitrogen using flame-dried or oven-dried glassware unless otherwise specified. Tetrahydrofuran was freshly distilled over sodium/benzophenone and dichloromethane was dried by distillation from calcium hydride prior to use. All commercially obtained reagents were used as received without further purification unless otherwise noted. Reactions carried out at room temperature were at approximately 22 °C. Flash chromatography was carried out with 230-400 mesh silica gel (E. Merck, Silica Gel 60). Thin layer chromatography was carried out on commercial aluminum backed silica gel 60 plates (E. Merck, type 5554, thickness 0.2 mm). Concentration and removal of trace solvents was performed using a Büchi rotary evaporator using an acetone/dry ice condenser and a Welch vacuum pump.

NMR spectra were recorded using chloroform-d, methanol-d_4, or benzene-d_6 as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane (δ = 0) and were measured relative to the signal of the solvent ($CDCl_3$: δ = 7.26, ^{1}H NMR; δ = 77.16, ^{13}C NMR; CD_3OD: δ = 3.31, ^{1}H NMR; δ = 49.0, ^{13}C NMR; C_6D_6: δ = 7.16, ^{1}H NMR; δ = 128.06, ^{13}C NMR; CD_3CN: δ = 1.94, ^{1}H NMR; δ = 118.26, ^{13}C NMR). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ^{1}H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet), coupling constants, number of protons, assignment (where possible). NMR spectra were recorded on a Bruker Avance II 600 spectrometer equipped with a QNP or TCI cryoprobe (600 MHz), Bruker Avance III 500 spectrometer (500 MHz), or Bruker Avance III 400 spectrometer (400 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of ^{1}H-^{1}H COSY, HMBC, HSQC, TOCSY, and 1D NOESY spectra.

Diastereomeric ratios were determined by analysis of ^{1}H NMR spectra recorded on crude reaction products.

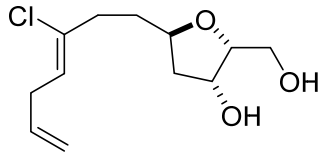
High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS or Bruker micrOTOF-II LC mass spectrometer.

IR spectra were recorded on a PerkinElmer Spectrum Two FT-IR spectrometer equipped with PerkinElmer UATR Two. Only selected, characteristic absorption data are provided for each compound.

Optical rotation was measured on a PerkinElmer 341 polarimeter at 589 nm.

Microwave reactions were performed in a CEM Discover LabMate microwave synthesizer at 2.45 GHz.

2.6.2. Preparation of (2*R*,3*R*,5*R*)-5-[(*Z*)-3-Chlorohepta-3,6-dien-1-yl]-2-(hydroxymethyl)tetrahydrofuran-3-ol (96)



A mixture of (2*S*,3*R*,5*R*,8*Z*)-1-[(*tert*-butyldimethylsilyl)oxy]-2,8-dichlorododeca-8,11-diene-3,5-diol (**95**)[55] and the C-5 epimer (4:1, 2.7 g, 6.8 mmol) were divided into 3 equal amounts. One portion (~900 mg) was placed in a microwave vial, methanol (20 mL) was then added, and the vial was sealed in a CEM Discover LabMate microwave. The reaction mixture was then heated to 120 °C (as monitored by a vertically focused IR temperature sensor) and maintained at this temperature for 120 minutes. After this time, the mixture was removed. This was repeated for the remaining two portions and all mixtures were combined and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (dichloromethane:methanol, 19:1) afforded compound **96** as a single stereoisomer (1.3 g, 5.3 mmol, 80%) as a clear colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.79 (m, 1H), 5.54 (m, 1H), 5.11-4.98 (m, 2H), 4.53 (br s, 1H), 4.28 (m, 1H), 3.96 (m, 3H), 3.10 (d, *J* = 3.9 Hz, 1H), 2.93 (t, *J* = 6.4 Hz, 2H), 2.57-2.36 (m, 2H), 2.24 (m, 1H), 2.11 (ddd, *J* = 1.4, 5.7, 13.2 Hz, 1H), 1.85-1.71 (m, 3H).

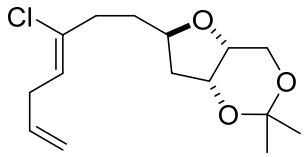
^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.3, 135.2, 123.2, 115.5, 80.5, 77.4, 74.4, 61.9, 42.1, 36.3, 34.0, 32.9.

HRMS: *m/z* calcd for $C_{12}H_{19}ClO_3$: 269.0915 (M+Na); Found: 269.0925 (M+Na).

IR: 3392, 3080, 2931, 1639, 1040 cm^{-1}.

$[\alpha]_D^{20}$: -1.8 (*c* = 1.0, $CHCl_3$).

2.6.3. Preparation of (4*R*,6*R*,7*R*)-6-[(*Z*)-3-Chlorohepta-3,6-dien-1-yl]-2,2-dimethyltetrahydro-4H-furo[3,2-d][1,3]dioxine (116)



To a stirred solution of (2*R*,3*R*,5*R*)-5-[(*Z*)-3-chlorohepta-3,6-dien-1-yl]-2-(hydroxymethyl)tetrahydrofuran-3-ol (**96**) (390 mg, 1.6 mmol) in 2,2-dimethoxypropane (8 mL) was added *p*-toluenesulfonic acid monohydrate (30 mg, 0.2 mmol). The reaction mixture was stirred for 18 hours at room temperature. The reaction was then quenched with brine (8 mL), water (8 mL), and a saturated aqueous solution of sodium bicarbonate (4 mL). The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic phases were washed with brine (15 mL), then dried with anhydrous magnesium sulfate and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 6:1) afforded compound **116** (395 mg, 1.4 mmol, 87%) as a clear colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.79 (m, 1H), 5.54 (t, *J* = 7.1 Hz, 1H), 5.03 (m, 2H), 4.42 (m, 1H), 4.32 (m, 1H), 3.99 (dd, *J* = 4.5, 13.4 Hz, 1H), 3.88 (m, 1H), 3.86 (m, 1H), 2.92 (t, *J* = 6.6 Hz, 2H), 2.51 (dt, *J* = 7.5, 14.5 Hz, 1H), 2.39 (dt, *J* = 7.5, 14.5 Hz, 1H), 2.11

(dd, *J* = 5.4, 13.2 Hz, 1H), 1.81 (m, 1H), 1.80 (m, 1H), 1.67 (ddd, *J* = 4.5, 10.0, 13.2 Hz, 1H), 1.43 (s, 3H), 1.38 (s, 3H).

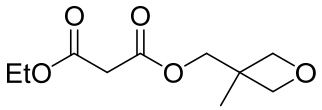
^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.4, 126.2, 123.0, 115.5, 97.8, 77.9, 74.0, 71.4, 61.0, 40.2, 36.5, 34.1, 32.9, 28.2, 20.2.

HRMS: *m/z* calcd for $C_{15}H_{23}ClO_3$: 309.1228 (M+Na); Found: 309.1265 (M+Na).

IR: 3080, 2935, 1639, 1082 cm^{-1}.

$[\alpha]_D^{20}$: -6.5 (*c* = 1.0, $CHCl_3$).

2.6.4. Preparation of Ethyl ((3-Methyloxetan-3-yl)methyl) Malonate (128)



To a stirred solution of diethyl malonate (1.00 mL, 6.56 mmol) in dry toluene (20 mL) was added (3-methyloxetan-3-yl)methanol (0.44 mL, 4.4 mmol). The reaction mixture was stirred at reflux for 3 days and the solvent was then removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes:ethyl acetate, 1:1) afforded compound **128** (635 mg, 2.94 mmol, 67%) as a clear colourless oil.

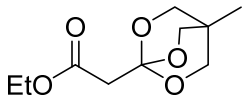
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.52 (d, *J* = 6.0 Hz, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.25 (s, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 2 H), 1.34 (s, 3 H), 1.28 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.8, 166.5, 79.5, 69.7, 61.8, 41.7, 39.2, 21.2, 14.2.

HRMS: *m/z* calcd for $C_{10}H_{16}O_5$: 239.0892 (M+Na); Found: 239.0890 (M+Na).

IR: 2966, 1729, 1030 cm^{-1}.

2.6.5. Preparation of Ethyl 2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]-octan-1-yl)acetate (129)[79]



To a stirred solution of ((3-methyloxetan-3-yl)methyl) malonate (**128**) (635 mg, 2.94 mmol) in dry dichloromethane (29 mL) at -20 °C was added boron trifluoride diethyl etherate (54 µL, 0.44 mmol). The reaction mixture was stirred for 18 hours at -20 °C. The mixture was then quenched with triethylamine (0.3 mL), diluted with diethyl ether (30 mL) and filtered through celite. The solvent was removed *in vacuo* to give **129** (631 mg, 2.92 mmol, 99%) as an amorphous white solid.

^{1}H NMR (400 MHz, CD_3CN) δ: 4.06 (q, *J* = 7.1 Hz, 2H), 3.87 (s, 6H), 2.60 (s, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.76 (s, 3 H).

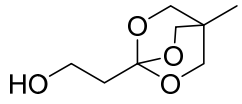
^{13}C NMR (100 MHz, CD_3CN) δ: 168.2, 107.8, 73.2, 61.1, 43.6, 30.9, 14.4, 14.2.

HRMS: *m/z* calcd for $C_{10}H_{16}O_5$: 217.1071 (M+H); Found: 217.1065 (M+H).

IR: 2962, 2936, 1738, 1047 cm^{-1}.

m.p.: 52 - 56 °C.

2.6.6. Preparation of 2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-ol (130)



To a stirred suspension of lithium aluminum hydride (294 mg, 7.75 mmol) in dry tetrahydrofuran (5 mL) at 0 °C was added a solution of ethyl 2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)acetate (**129**) (531 mg, 2.46 mmol) in dry tetrahydrofuran (2 mL). The reaction mixture was stirred for 40 minutes at 0 °C and was then quenched slowly with water (2 mL) and aqueous sodium hydroxide (2 M, 2 mL). The mixture was

diluted with tetrahydrofuran and water and filtered to remove solids. The mixture was extracted with diethyl ether (3 x 20 mL) and the combined organic phases were washed with brine (20 mL), then dried with anhydrous magnesium sulfate and filtered, and the solvent was removed *in vacuo* to give **130** (272 mg, 1.56 mmol, 64%) as a colourless viscous oil.

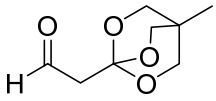
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.91 (s, 6H), 3.74 (t, *J* = 5.1 Hz, 2H), 2.75 (br s, 1H), 1.93 (m, 2H), 0.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 109.3, 72.7, 58.3, 38.7, 30.4, 14.6.

HRMS: *m/z* calcd for $C_8H_{14}O_4$: 175.0965 (M+H); Found: 175.0973 (M+H).

IR: 3427, 2925, 2879, 1045 cm^{-1}.

2.6.7. Preparation of 2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)acetaldehyde (131)



To a stirred solution of 2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-ol (**130**) (33 mg, 0.19 mmol) in dry dichloromethane (2 mL) was added Dess-Martin periodinane (96 mg, 0.23 mmol) and sodium bicarbonate (239 mg, 2.85 mmol). The reaction mixture was stirred for 1 hour at room temperature. The reaction was then quenched with a solution of saturated aqueous sodium bicarbonate (2 mL). The mixture was extracted with dichloromethane (3 x 3 mL) and the combined organic phases were washed with aqueous sodium hydroxide (2 M, 3 mL), water (3 mL), brine (3 mL), then dried with anhydrous magnesium sulfate, and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 3:1) afforded compound **131** (13 mg, 0.076 mmol, 39%) as a colourless viscous oil.

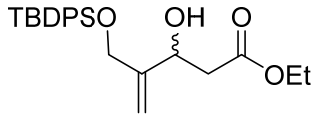
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.70 (t, *J* = 2.8 Hz, 1H), 3.94 (s, 1H), 2.65 (d, *J* = 2.8 Hz, 2H), 0.82 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.9, 107.0, 72.8, 49.8, 30.7, 14.6.

HRMS: *m/z* calcd for $C_8H_{12}O_4$: 173.0808 (M+H); Found: 173.0829 (M+H).

IR: 2919, 1684, 1266 cm^{-1}.

2.6.8. Preparation of Ethyl 4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3-hydroxypent-4-enoate (148)



To a cold (-78 °C) stirred solution of *N,N*-diisopropyl amine (193 µL, 1.38 mmol) in dry tetrahydrofuran (20 mL) was added *n*-butyllithium (2.5 M in hexane, 0.50 mL, 1.3 mmol). The reaction mixture was warmed to 0 °C and stirred for 30 min. After this time, the reaction mixture was cooled to -78 °C and ethyl acetate (113 µL, 1.16 mmol) was added. The reaction mixture was stirred at -78 °C for 30 minutes and 2-(((*tert*-butyldiphenylsilyl)oxy)methyl)acrylaldehyde (**159**) (411 mg, 1.27 mmol) was added. The solution was stirred at -78 °C for 1 hour and the reaction was then quenched with a solution of saturated aqueous ammonium chloride (10 mL). The mixture was extracted with ethyl acetate (3 x 10 mL) and the combined organic phases were washed with water (10 mL), brine (10 mL), then dried with anhydrous magnesium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes:ethyl acetate, 5:1) afforded compound **148** (322 mg, 0.780 mmol, 68%) as a colourless oil.

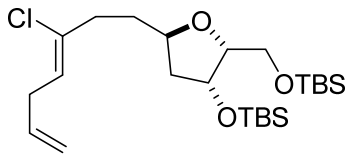
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70-7.65 (m, 4H), 7.47-7.36 (m, 6H), 5.22-5.18 (m, 2H), 4.63 (dt, *J* = 4.7, 7.9 Hz, 1H), 4.26 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.15 (d, *J* = 4.7 Hz, 1H), 2.62 (d, *J* = 4.7, 1H), 2.60 (d, *J* = 8.0 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.06 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.5, 148.1, 135.7, 133.3, 130.0, 127.9, 111.6, 69.5, 65.0, 60.9, 40.8, 26.9, 19.3, 14.3.

HRMS: *m/z* calcd for $C_{24}H_{32}O_4Si$: 435.1962 (M+Na); Found: 435.1940 (M+Na).

IR: 3495, 3072, 2958, 2929, 1734, 1428, 1112 cm^{-1}.

2.6.9. Preparation of *tert*-Butyl[((2*R*,3*R*,5*R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*Z*)-3-chlorohepta-3,6-dien-1-yl)tetrahydrofuran-2-yl)methoxy]dimethylsilane (170)



To a stirred solution of (2*R*,3*R*,5*R*)-5-[(*Z*)-3-chlorohepta-3,6-dien-1-yl]-2-(hydroxymethyl)tetrahydrofuran-3-ol (**96**) (350 mg, 1.4 mmol) in dry dichloromethane (3 mL) was added *tert*-butyldimethylsilyl chloride (450 mg, 2.1 mmol) and imidazole (290 mg, 4.3 mmol). The reaction mixture was stirred for 18 hours at room temperature. The reaction was then quenched with water (2 mL). The mixture was extracted with dichloromethane (3 x 3 mL) and the combined organic phases were washed with brine (4 mL), then dried with anhydrous magnesium sulfate, and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 97:3) afforded compound **170** (410 mg, 0.86 mmol, 61%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84-5.73 (m, 1H), 5.52 (t, *J* = 7.1 Hz, 1H), 5.11-4.96 (m, 2H), 4.37 (m, 1H), 4.16 (m, 1H), 3.87 (dt, *J* = 3.4, 6.1 Hz, 1H), 3.77 (dd, *J* = 6.3, 10.3 Hz, 1H), 3.69 (dd, *J* = 6.0, 10.3 Hz, 1H), 2.91 (m, 2H), 2.54-2.32 (m, 2H), 1.94 (ddd, *J* = 1.3, 5.4, 12.7 Hz, 1H), 1.85-1.70 (m, 2H), 1.63 (ddd, *J* = 4.4, 10.0, 12.7 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07-0.05 (m, 12H).

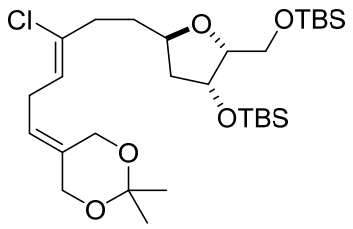
^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.6, 135.4, 122.9, 115.5, 83.4, 76.8, 72.8, 62.0, 42.2, 36.5, 34.1, 32.9, 26.2, 25.9, 18.6, 18.2, -4.6, -5.0, -5.1, -5.1.

HRMS: *m/z* calcd for $C_{24}H_{47}ClO_3Si_2$: 497.2644 (M+Na); Found: 497.2681 (M+Na).

IR: 2953, 2929, 2857, 1472, 1089 cm^{-1}.

$[\alpha]_D^{20}$: -20.1 (*c* = 1.0, $CHCl_3$).

2.6.10. Preparation of *tert*-Butyl[((2*R*,3*R*,5*R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*Z*)-3-chloro-6-(2,2-dimethyl-1,3-dioxan-5-ylidene)hex-3-en-1-yl)tetrahydrofuran-2-yl)methoxy]-dimethylsilane (171)



To a stirred solution of 2,2-dimethyl-5-methylene-1,3-dioxane (**135**) (335 mg, 2.61 mmol) in dry, nitrogen-sparged toluene (2 mL) was added Grubbs-Hoveyda II catalyst (4.2 mg, 0.0067 mmol in 0.6 mL toluene) followed by *tert*-butyl[((2*R*,3*R*,5*R*)-3-((*tert*-butyldimethylsilyl)oxy)-5-((*Z*)-3-chlorohepta-3,6-dien-1-yl)tetrahydrofuran-2-yl)methoxy]dimethylsilane (**167**) (100 mg, 0.2 mmol). The reaction mixture was then heated to 60°C. After 1 hour a second amount of Grubbs-Hoveyda II catalyst was added (2.8 mg, 0.0045 mmol in 0.4 mL toluene) and the reaction mixture was stirred at 60 °C for another 4 hours. The heat was shut off and the reaction left to cool to room temperature overnight while stirring. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography (pentane:diethyl ether, 95:5) to afford compound **171** (56 mg, 0.10 mmol, 46%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.43 (t, *J* = 7.1 Hz, 1H), 5.20 (tt, *J* = 1.5, 7.5 Hz, 1H), 4.43 (s, 2H), 4.37 (m, 1H), 4.22 (s, 2H), 4.15 (m, 1H), 3.86 (dt, *J* = 3.4, 6.1 Hz, 1H), 3.77 (dd, *J* = 6.3, 10.2 Hz, 1H), 3.68 (dd, *J* = 5.9, 10.2 Hz, 1H), 2.83 (t, *J* = 7.1 Hz, 2H), 2.52-2.41 (m, 1H), 2.40-2.29 (m, 1H), 1.93 (ddd, *J* = 1.3, 5.5, 12.7 Hz, 1H), 1.80-1.70 (m, 2H), 1.67-1.57 (m, 1H), 1.43 (s, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06-0.05 (m, 12H).

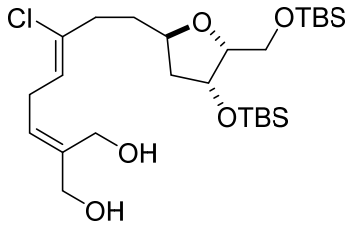
^{13}C NMR (150 MHz, $CDCl_3$) δ: 135.6, 133.3, 122.8, 120.0, 99.3, 83.4, 76.8, 72.8, 64.5, 62.0, 60.0, 42.2, 36.5, 34.1, 26.5, 26.2, 25.9, 24.2, 18.6, 18.2, -4.6, -4.9, -5.0, -5.1.

HRMS: *m/z* calcd for $C_{29}H_{55}ClO_5Si_2$: 597.3169 (M+Na); Found: 597.3189 (M+Na).

IR: 2953, 2928, 2855, 1472, 1082 cm^{-1}.

$[\alpha]_D^{20}$: -11.8 (*c* = 1.0, $CHCl_3$).

2.6.11. Preparation of 2-((*Z*)-6-((2*R*,4*R*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-chlorohex-3-en-1-ylidene)propane-1,3-diol (172)



To a stirred solution of *tert*-butyl[((2*R*,3*R*,5*R*)-3-((*tert*-butyldimethyl-silyl)oxy)-5-((*Z*)-3-chloro-6-(2,2-dimethyl-1,3-dioxan-5-ylidene)hex-3-en-1-yl)tetrahydrofuran-2-yl)methoxy]-dimethylsilane (**171**) (82 mg, 0.14 mmol) in methanol (7 mL) was added PPTS (7 mg, 0.03 mmol). The reaction mixture was stirred for 1 hour at room temperature. The reaction was then quenched with saturated aqueous sodium bicarbonate (3 mL). The mixture was extracted with ethyl acetate (3 x 3 mL) and the combined organic phases were washed with water (4 mL), brine (4 mL), then dried with anhydrous magnesium sulfate, and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes:ethyl acetate, 1:1) afforded compound **172** (72 mg, 0.13 mmol, 94%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.53 (t, *J* = 7.6 Hz, 1H), 5.47 (t, *J* = 7.1 Hz, 1H), 4.36 (m, 3H), 4.22 (d, *J* = 5.4 Hz, 2H), 4.15 (m, 1H), 3.86 (dt, *J* = 3.5, 6.1 Hz, 1H), 3.77 (dd, *J* = 6.3, 10.3 Hz, 1H), 3.69 (dd, *J* = 6.0, 10.3 Hz, 1H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.53-2.43 (m, 1H), 2.41-2.30 (m, 1H), 1.99-1.86 (m, 3H), 1.79-1.71 (m, 2H), 1.63 (ddd, *J* = 4.2, 10.0, 14.0 Hz, 1H), 0.89 (m, 18H), 0.07-0.05 (m, 12H).

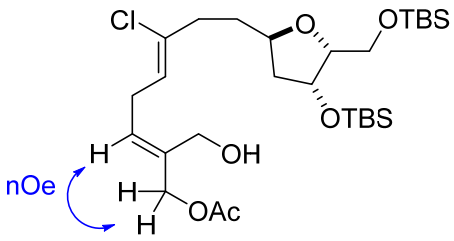
^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3, 135.7, 127.2, 122.8, 83.4, 76.7, 72.8, 67.5, 62.0, 60.2, 42.2, 36.5, 34.1, 27.2, 26.2, 25.9, 18.6, 18.2, -4.6, -4.9, -5.0, -5.1.

HRMS: *m/z* calcd for $C_{26}H_{51}ClO_5Si_2$: 535.3036 (M+H); Found: 535.3006 (M+H).

IR: 3363, 2954, 2928, 1472, 1020 cm^{-1}.

$[\alpha]_D^{20}$: -7.8 (*c* = 1.0, $CHCl_3$).

2.6.12. Preparation of (2*E*,5*Z*)-8-((2*R*,4*R*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-chloro-2-(hydroxymethyl)octa-2,5-dien-1-yl Acetate (173)



To a stirred solution of 2-((*Z*)-6-((2*R*,4*R*,5*R*)-4-((*tert*-butyldimethyl-silyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-furan-2-yl)-4-chlorohex-3-en-1-ylidene)propane-1,3-diol (**172**) (42 mg, 0.078 mmol) in 1,4-dioxane (0.4 mL) was added vinyl acetate (74 µL, 0.80 mmol) and porcine pancreas lipase (42 mg). The reaction mixture was then stirred for 18 hours at room temperature. The reaction was then filtered and diluted with dichloromethane (1 mL) and water (1 mL). The mixture was extracted with dichloromethane (3 x 1 mL) and the combined organic phases were washed with water (1 mL), brine (1 mL), then dried with anhydrous magnesium sulfate, and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes:ethyl acetate, 7:3) afforded compound **173** (24 mg, 0.042 mmol, 53%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.62 (t, *J* = 7.5 Hz, 1H), 5.47 (t, *J* = 7.0 Hz, 1H), 4.64 (s, 2H), 4.37 (m, 1H), 4.22 (s, 2H), 4.15 (m, 1H), 3.86 (m, 1H), 3.77 (dd, *J* = 6.3, 10.3 Hz, 1H), 3.69 (dd, *J* = 6.0, 10.3 Hz, 1H), 3.00 (t, *J* = 7.2 Hz, 2H), 2.49 (dt, *J* = 7.6, 15.2 Hz, 1H), 2.35 (dt, *J* = 7.6, 15.2 Hz, 1H), 2.09 (s, 3H), 1.94 (ddd, *J* = 1.2, 5.5, 12.6 Hz, 1H), 1.89 (br s, 1H), 1.76 (m, 2H), 1.63 (ddd, *J* = 4.5, 9.8, 12.6 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07-0.05 (m, 12H).

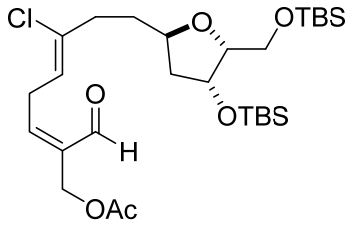
^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.4, 136.0, 134.8, 130.4, 122.5, 83.4, 76.8, 72.8, 67.1, 62.0, 58.5, 42.2, 36.5, 34.1, 27.3, 26.2, 25.9, 21.2, 18.6, 18.2, -4.6, -4.9, -5.0, -5.1.

HRMS: *m/z* calcd for $C_{28}H_{53}ClO_6Si_2$: 577.3142 (M+H); Found: 577.3122 (M+H).

IR: 3457, 2954, 2929, 1472, 1022 cm^{-1}.

$[\alpha]_D^{20}$: -7.9 (*c* = 1.0, $CHCl_3$).

2.6.13. Preparation of (2*Z*,5*Z*)-8-((2*R*,4*R*,5*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-chloro-2-formylocta-2,5-dien-1-yl Acetate (174)



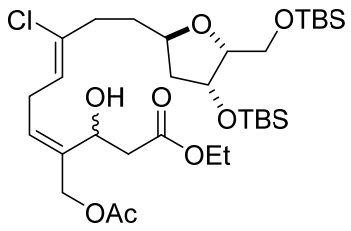
To a stirred solution of (2*E*,5*Z*)-8-((2*R*,4*R*,5*R*)-4-((*tert*-butyldimethyl-silyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydro-furan-2-yl)-6-chloro-2-(hydroxymethyl)octa-2,5-dien-1-yl acetate (**173**) (24 mg, 0.042 mmol) in dry dichloromethane (1.4 mL) was added Dess-Martin periodinane (26 mg, 0.061 mmol) and sodium bicarbonate (53 mg, 0.63 mmol). The reaction mixture was stirred for 45 minutes at room temperature. The reaction was then quenched with a solution of saturated aqueous sodium bicarbonate (1 mL). The mixture was extracted with dichloromethane (3 x 2 mL) and the combined organic phases were washed with an aqueous solution of sodium hydroxide (2 M, 2 mL), water (2 mL), brine (2 mL), then dried with anhydrous magnesium sulfate, and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 9:1) afforded compound **174** (14 mg, 0.024 mmol, 58%) as a colourless oil which was immediately carried on to the next step. Some of the experimental data is listed below.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.17 (s, 1H), 6.65 (t, *J* = 8.2 Hz, 1H), 5.54 (t, *J* = 7.1 Hz, 1H), 4.71 (s, 2H), 4.37 (m, 1H), 4.15 (m, 1H), 3.86 (ddd, *J* = 3.4, 6.1, 6.1 Hz, 1H), 3.77

(dd, *J* = 6.3, 10.3 Hz, 1H), 3.69 (dd, *J* = 6.0, 10.3 Hz, 1H), 3.48 (t, *J* = 7.5 Hz, 2H), 2.53 (dt, *J* = 8.2, 15.4 Hz, 1H), 2.39 (dt, *J* = 8.0, 15.4 Hz, 1H), 2.07 (s, 3H), 1.94 (ddd, *J* = 1.3, 5.5, 12.7 Hz, 1H), 1.76 (m, 2H), 1.64 (ddd, *J* = 4.3, 9.9, 12.7 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07-0.05 (m, 12H).

HRMS: *m/z* calcd for $C_{28}H_{51}ClO_6Si_2$: 575.2985 (M+H); Found: 575.2976 (M+H).

2.6.14. Preparation of Ethyl (4*Z*,7*Z*)-4-(Acetoxymethyl)-10-((2R,4R,5R)-4-((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyl-dimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-8-chloro-3-hydroxydeca-4,7-dienoate (175)



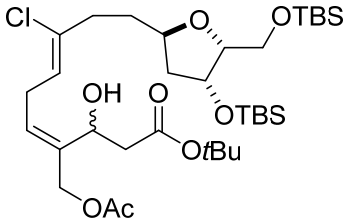
To a cold (-78 °C) stirred solution of *N,N*-diisopropyl amine (440 µL, 3.1 mmol) in dry tetrahydrofuran (26 mL) was added *n*-butyllithium (2.5 M in hexane, 1.2 mL, 2.9 mmol). The reaction mixture was warmed to 0 °C and stirred for 30 min. After this time, the solution was cooled to -78 °C and ethyl acetate (260 µL, 2.7 mmol) was added. The reaction mixture was stirred at -78 °C for 30 minutes to prepare a 0.1 M stock solution of ester enolate. Separately, (2*Z*,5*Z*)-8-((2*R*,4*R*,5*R*)-4-((*tert*-butyldimethyl-silyl)oxy)-5-(((*tert*-butyldimethyl-silyl)oxy)methyl)tetra-hydro-furan-2-yl)-6-chloro-2-formylocta-2,5-dien-1-yl acetate (**174**) (8.2 mg, 0.014 mmol) was stirred in dry tetrahydrofuran (0.2 mL) and cooled to -78 °C. The enolate mixture (0.13 mL, 0.10 M, 0.013 mmol) was added to the entire aldehyde solution and the reaction mixture was stirred at -78 °C for 20 minutes. The reaction was then quenched with a solution of saturated aqueous ammonium chloride (0.4 mL). The mixture was extracted with ethyl acetate (3 x 0.5 mL) and the combined organic phases were washed with water (0.4 mL), brine (0.4 mL), then dried with anhydrous magnesium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 3:1) afforded compound **175** (4 mg, 0.006 mmol, 51%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.76 (t, *J* = 7.5 Hz, 1H), 5.59 (t, *J* = 7.5 Hz, 1H), 5.46 (t, *J* = 6.7 Hz, 1H), 5.44 (t, *J* = 6.7 Hz, 1H), 5.09 (t, *J* = 3.0 Hz, 1H), 5.07 (t, *J* = 3.0 Hz, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 4.60 (s, 1H), 4.57 (s, 1H), 4.37 (t, *J* = 3.5 Hz, 2H), 4.23 – 4.10 (m, 6H), 3.86 (ddd, *J* = 3.5, 6.1, 6.1 Hz, 2H), 3.77 (dd, *J* = 6.3, 10.2 Hz, 2H), 3.68 (dd, *J* = 6.0, 10.2 Hz, 2H), 3.01 (m, 4H), 2.74 (dd, *J* = 10.1, 16.5 Hz, 1H), 2.59 (s, 1H), 2.58 (s, 1H), 2.46 (dd, *J* = 3.4, 16.5 Hz, 2H), 2.35 (m, 2H), 2.08 (s, 3H), 2.07 (s, 3H), 1.94 (ddd, *J* = 1.3, 5.4, 12.7 Hz, 2H), 1.74 (m, 4H), 1.63 (ddd, *J* = 4.4, 9.9, 14.4 Hz, 2H), 1.32-1.24 (m, 6H), 0.89 (s, 18H), 0.89 (s, 18H), 0.07-0.05 (m, 24H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.5, 172.5, 170.8, 136.1, 135.5, 130.5, 130.2, 122.4, 122.2, 83.4, 72.8, 70.8, 65.8, 65.8, 65.1, 62.0, 61.1, 61.0, 59.4, 42.2, 40.8, 40.7, 36.5, 34.2, 34.2, 29.9, 27.5, 27.3, 26.2, 25.9, 22.5, 21.3, 21.2, 18.6, 18.2, 14.3, -4.6, -4.9, -5.0, -5.1.

IR: 3474, 2954, 2929, 1739, 1471, 1023 cm^{-1}.

2.6.15. Preparation of *tert*-Butyl (4*Z*,7*Z*)-4-(Acetoxymethyl)-10-((2*R*,4*R*,5*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyl-dimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-8-chloro-3-hydroxydeca-4,7-dienoate (177)



To a cold (-78 °C) stirred solution of *N,N*-diisopropyl amine (76 µL, 0.54 mmol) in dry tetrahydrofuran (4.5 mL) was added *n*-butyllithium (2.5 M in hexane, 0.20 mL, 0.50 mmol). The reaction mixture was warmed to 0 °C and stirred for 30 min. After this time, the solution was cooled to -78 °C and *tert*-butyl acetate (61 µL, 0.45 mmol) was added. The reaction mixture was stirred at -78 °C for 30 minutes to prepare a 0.1 M stock solution of ester enolate. Separately, (2*Z*,5*Z*)-8-((2*R*,4*R*,5*R*)-4-((*tert*-butyldimethyl-silyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)-methyl)tetra-hydro-furan-2-yl)-6-chloro-2-

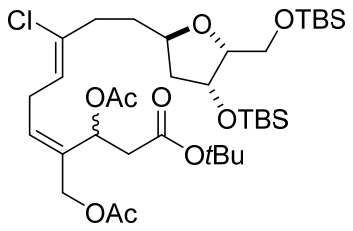
formylocta-2,5-dien-1-yl acetate (**174**) (16 mg, 0.028 mmol) was stirred in dry tetrahydrofuran (0.25 mL) and cooled to -78 °C. The enolate mixture (0.25 mL, 0.10 M, 0.025 mmol) was added to the aldehyde solution and the reaction mixture was stirred at -78 °C for 20 minutes. The reaction was then quenched with a solution of saturated aqueous ammonium chloride (0.4 mL). The mixture was extracted with ethyl acetate (3 x 0.5 mL) and the combined organic phases were washed with water (0.4 mL), brine (0.4 mL), then dried with anhydrous magnesium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 85:15) afforded compound **177** (10 mg, 0.014 mmol, 57%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.75 (t, *J* = 7.5 Hz, 1H), 5.57 (t, *J* = 7.5 Hz, 1H), 5.46 (t, *J* = 7.0 Hz, 1H), 5.44 (t, *J* = 6.8 Hz, 1H), 5.03 (m, 2H), 4.69 (d, *J* = 12.5 Hz, 2H), 4.58 (d, *J* = 12.5 Hz, 2H), 4.37 (m, 2H), 4.15 (m, 2H), 3.86 (ddd, *J* = 3.5, 6.0, 6.0 Hz, 2H), 3.77 (dd, *J* = 6.3, 10.2 Hz, 2H), 3.69 (dd, *J* = 5.9, 10.2 Hz, 2H), 3.00 (m, 4H), 2.64 (dd, *J* = 10.2, 16.4 Hz, 2H), 2.47 (m, 2H), 2.38 (m, 2H), 2.34 (m, 2H), 2.08 (s, 4H), 2.07 (s, 2H), 1.94 (ddd, *J* = 1.1, 5.4, 12.7 Hz, 2H), 1.75 (m, 4H), 1.63 (m, 2H), 1.47 (s, 18H), 0.89 (s, 18H), 0.88 (s, 18H), 0.08-0.05 (m, 24H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.0, 170.8, 136.0, 135.6, 130.3, 129.7, 122.4, 83.4, 81.7, 76.7, 72.7, 66.0, 65.0, 62.0, 42.2, 41.6, 36.5, 34.2, 28.3, 28.3, 28.3, 27.4, 26.2, 25.9, 21.3, 18.6, 18.2, -4.6, -4.9, -5.0, -5.1.

IR: 3464, 2954, 2930, 1738, 1472, 1082 cm^{-1}.

2.6.16. Preparation of (*Z*)-5-(*tert*-Butoxy)-2-((*Z*)-6-((2*R*,4*R*,5*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)-methyl)tetrahydrofuran-2-yl)-4-chlorohex-3-en-1-ylidene)-5-oxopentane-1,3-diyl Diacetate (178)



To a stirred solution of *tert*-butyl (4*Z*,7*Z*)-4-(acetoxymethyl)-10-((2*R*,4*R*,5*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyl-dimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-8-chloro-3-hydroxydeca-4,7-dienoate (**177**) (10 mg, 0.015 mmol) in acetic anhydride (0.3 mL) and pyridine (0.3 mL) was added a catalytic amount of DMAP. The reaction mixture was stirred for 1 hour at room temperature and then the solvent was removed *in vacuo*. The material was then diluted with ethyl acetate (3 mL), washed with a solution of saturated aqueous sodium bicarbonate (3 x 0.5 mL), brine (0.5 mL), and then dried with anhydrous magnesium sulfate, and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:ethyl acetate, 85:15) afforded compound **178** (11 mg, 0.015 mmol, quant.) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.02 (dd, *J* = 4.9, 9.6 Hz, 2H), 5.79 (t, *J* = 7.5 Hz, 1H), 5.64 (t, *J* = 7.2 Hz, 1H), 5.48 (t, *J* = 7.1 Hz, 1H), 5.42 (t, *J* = 7.0 Hz, 1H), 4.58 (d, *J* = 12.3 Hz, 2H), 4.50 (t, *J* = 12.7 Hz, 2H), 4.37 (m, 2H), 4.15 (m, 4H), 3.86 (ddd, *J* = 3.4, 6.2, 6.2 Hz, 2H), 3.77 (dd, *J* = 6.4, 10.2 Hz, 2H), 3.69 (d, *J* = 5.8, 10.2 Hz, 2H), 3.13 (t, *J* = 7.0 Hz, 2H), 3.01 (t, *J* = 7.0 Hz, 1H), 2.75 (dd, *J* = 9.6, 15.6 Hz, 2H), 2.49 (m, 2H), 2.47 (m, 2H), 2.34 (m, 2H), 2.07 (s, 6H), 2.02 (s, 6H), 1.94 (ddd, *J* = 1.3, 5.5, 12.7 Hz, 2H), 1.76 (m, 4H), 1.63 (ddd, *J* = 4.3, 10.2, 12.6 Hz, 2H), 1.43 (m, 18H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07-0.05 (m, 24H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.9, 170.7, 169.8, 169.1, 169.0, 168.8, 136.3, 136.2, 132.8, 122.1, 83.4, 81.3, 76.8, 72.8, 68.2, 65.1, 61.9, 42.2, 40.1, 36.5, 34.3, 28.2, 27.6, 26.2, 25.9, 21.2, 21.0, 18.6, 18.2, -4.6, -4.9, -5.0, -5.1.

HRMS: *m/z* calcd for $C_{36}H_{65}ClO_9Si_2$: 733.3928 (M+H); Found: 733.3931 (M+H).

References

(1) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141–2153.

(2) Cragg, G.; Newman, D. *Biochim. Biophys. Acta (BBA)-General.* **2013**, *1830*, 3670–3695.

(3) Dias, D. A.; Urban, S.; Roessner, U. A Historical Overview of Natural Products in Drug Discovery. *Metabolites*, 2012, *2*, 303–336.

(4) Brittain, R. T.; Farmer, J. B.; Jack, D.; Martin, L. E.; Simpson, W. T. *Nature* **1968**, *219*, 862–863.

(5) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, T. *J. Am. Chem. Soc.* **1971**, *93*, 2325–2327.

(6) One million patients have received treatment with Taxol (paclitaxel) in 10 years since it was first approved. http://www.prnewswire.co.uk/news-releases/one-million-patients-have-received-treatment-with-taxol-paclitaxel-in-10-years-since-it-was-first-approved-154334465.html (accessed Jan 25, 2015).

(7) Gazaliev, A. N.; Zhurinov, M. Z.; Fazylov, S. D.; Balitskii, S. N. *Khimiya Prir. Soedin.* **1989**, 307–319.

(8) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311–335.

(9) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022–1037.

(10) Marris, E. *Nature* **2006**, *443*, 904–905.

(11) Wender, P. A.; Nakagawa, Y.; Near, K. E.; Staveness, D. *Org. Lett.* **2014**, *16*, 5136–5139.

(12) Pettit, G. R.; Herald, C. L.; Doubek, D. L.; Herald, D. L.; Arnold, E.; Clardy, J. *J. Am. Chem. Soc.* **1982**, *104*, 6846–6848.

(13) Hofle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem. Int. Ed.* **1996**, *35*, 1986–1988.

(14) Nicolaou, K. C.; Hale, C. R. H.; Nilewski, C.; Ioannidou, H. *Chem. Soc. Rev.* **2012**, *41*, 5185–5238.

(15) Lee, D.; Sartor, O.; Jain, V. K. *Clin. Prostate Cancer* **2004**, *3*, 80–82.

(16) Takada, N.; Sato, H.; Suenaga, K.; Arimoto, H.; Yamada, K.; Ueda, K.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 6309–6312.

(17) Ueda, K.; Hu, Y. *Tetrahedron Lett.* **1999**, *40*, 6305–6308.

(18) Strobel, G.; Li, J.; Sugawara, F.; Koshino, H.; Harper, J.; Hess, W. M. *Microbiology* **1999**, *145*, 3557–3564.

(19) Levenfors, J. J.; Hedman, R.; Thaning, C.; Gerhardson, B.; Welch, C. J. *Soil Biol. Biochem.* **2004**, *36*, 677–685.

(20) Kigoshi, H.; Hayakawa, I. *Chem. Rec.* **2007**, *7*, 254–264.

(21) Teruya, T.; Shimogawa, H.; Suenaga, K.; Kigoshi, H. *Chem. Lett.* **2004**, *33*, 1184–1185.

(22) Teruya, T.; Suenaga, K.; Maruyama, S.; Kurotaki, M.; Kigoshi, H. *Tetrahedron* **2005**, *61*, 6561–6567.

(23) Yamaoka, M.; Sato, K.; Kobayashi, M.; Nishio, N.; Ohkubo, M.; Fujii, T.; Nakajima, H. *J. Antibiot. (Tokyo).* **2006**, *58*, 654–662.

(24) Kobayashi, M.; Sato, K.; Yoshimura, S.; Yamaoka, M.; Takase, S.; Ohkubo, M.; Fujii, T.; Nakajima, H. *J. Antibiot. (Tokyo).* **2005**, *58*, 648–653.

(25) Tsukamoto, S.; Huang, Y.; Umeda, D.; Yamada, S.; Yamashita, S.; Kumazoe, M.; Kim, Y.; Murata, M.; Yamada, K.; Tachibana, H. *J. Biol. Chem.* **2014**, *289*, 32671–32681.

(26) Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett.* **2003**, *5*, 957–960.

(27) Tamao, K.; Akita, M.; Maeda, K.; Kumadat, M. **1987**, 1100–1106.

(28) Still, W. C.; Gennari, C. *Tetrahedron* **1983**, *24*, 4405–4408.

(29) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549–2551.

(30) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646.

(31) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284.

(32) Gu, Y.; Snider, B. B. *Org. Lett.* **2003**, *5*, 4385–4388.

(33) Duboudin, J. G.; Jousseaume, B.; Bonakdar, A. *J. Organomet. Chem.* **1979**, *168*, 227–232.

(34) Kiyooka, S.; Hena, M. A. *J. Org. Chem.* **1999**, *64*, 5511–5523.

(35) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360–12361.

(36) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833–4840.

(37) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595.

(38) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.

(39) Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 6950–6951.

(40) Micalizio, G. C.; Roush, W. R. **2001**, *3*, 1949–1952.

(41) Kaneda, K.; Uchiyama, T.; Fujiwara, Y.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1979**, *44*, 55–63.

(42) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

(43) Roulland, E. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 3762–3765.

(44) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.

(45) Hayakawa, I.; Ueda, M.; Yamaura, M.; Ikeda, Y.; Suzuki, Y.; Yoshizato, K.; Kigoshi, H. *Org. Lett.* **2008**, *10*, 1859–1862.

(46) Ko, S.; Klein, L.; Pfaff, K.-P.; Kishi, Y. **1982**, *23*, 4415–4418.

(47) Schomaker, J.; Borhan, B. *J. Am. Chem. Soc.* **2008**, *130*, 12228–12229.

(48) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 2179–2181.

(49) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *J. Am. Chem. Soc.* **2001**, *123*, 9196–9197.

(50) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276–2278.

(51) Barton, D.; McCombie, S. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585.

(52) Satoh, Y.; Kawamura, D.; Yamaura, M.; Ikeda, Y.; Ochiai, Y.; Hayakawa, I.; Kigoshi, H. *Tetrahedron Lett.* **2012**, *53*, 1390–1392.

(53) Chenault, J.; Dupin, J.-F. E. *Synthesis (Stuttg).* **1987**, *5*, 498–499.

(54) Satoh, Y.; Yamada, T.; Onozaki, Y.; Kawamura, D.; Hayakawa, I.; Kigoshi, H. *Tetrahedron Lett.* **2012**, *53*, 1393–1396.

(55) Kang, B. Applications of α-Chloroaldehydes toward the Synthesis of Natural Products, 2012, pp. 1–325.

(56) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717–1720.

(57) Kang, B.; Chang, S.; Decker, S.; Britton, R. *Org. Lett.* **2010**, *12*, 1716–1719.

(58) Halperin, S.; Kang, B.; Britton, R. *Synthesis (Stuttg).* **2011**, *2011*, 1946–1953.

(59) Halland, N.; Bruanton, A.; Bachmann, S.; Marigo, M.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.

(60) Bräse, S.; Wertal (nee Nüske), H.; Frank, D.; Vidović, D.; de Meijere, A. *European J. Org. Chem.* **2005**, *2005*, 4167–4178.

(61) Fan, H. Studies toward the Total Synthesis of Biselides & Radical Fluorination of Aliphatic Compounds, 2014, pp. 1–96.

(62) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211.

(63) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. a. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 3601–3605.

(64) Ando, K. *J. Org. Chem.* **1998**, *63*, 8411–8416.

(65) Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571–5574.

(66) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jorgenson, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.

(67) Finkelstein, H. *Ber. Dtsch. Chem. Ges.* **1910**, 1528.

(68) Katayama, M.; Nagase, R.; Mitarai, K.; Misaki, T.; Tanabe, Y. *Synlett* **2006**, 129–132.

(69) Shigeyoshi, N.; Yasuhiro, N.; Hisanao, I.; Yamamotoa, Y. *J. Carbohydr. Chem.* **1986**, *5*, 199–213.

(70) Miura, T.; Kawashima, Y.; Takahashi, M.; Murakami, Y.; Imai, N. *Synth. Commun.* **2007**, *37*, 3105–3109.

(71) D'hooghe, M.; Van Brabandt, W.; Dekeukeleire, S.; Dejaegher, Y.; De Kimpe, N. *Chemistry* **2008**, *14*, 6336–6340.

(72) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441–444.

(73) Skaanderup, P. R.; Jensen, T. *Org. Lett.* **2008**, *10*, 2821–2824.

(74) Granander, J.; Sott, R.; Hilmersson, G. *Tetrahedron* **2002**, *58*, 4717–4725.

(75) Gonzalez, A.; Alguade, J.; Urpi, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949–8952.

(76) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis, Fourth Edition*; 2006; pp. 533–646.

(77) Ziering, D. L.; Pascal, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 834–838.

(78) Saito, S.; Hatanaka, K.; Kano, T.; Yamamoto, H. *Angew. Chem. Int. Ed.* **1998**, *37*, 3378–3381.

(79) Rose, Nicholas, G. W.; Blaskovich, M. A.; Wong, A.; Lajoie, G. A. *Tetrahedron* **2001**, *57*, 1497–1507.