Studies Toward the Total Synthesis of Tetrahydrofuran-Containing Natural Products

by

Daniel Kwon

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Name: **Daniel Kwon**

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

Dr. Robert A. Britton
Senior Supervisor
Professor

Dr. David J. Vocadlo
Supervisor
Professor

Dr. Andrew J. Bennet
Supervisor
Professor

Dr. Peter D. Wilson
Internal Examiner
Associate Professor

Date Defended/Approved: July 14, 2016

Abstract

Natural products have played a significant role as leads and inspiration for many novel therapeutics. Among the most common structural fragments found in biologically active natural products is the tetrahydrofuran, a five membered oxygen-containing heterocycle. As oftentimes very little natural product is available from the producing organism, there has been a longstanding interest in the development of efficient and general synthetic methods to access tetrahydrofurans and tetrahydrofuran-containing natural products. This thesis summarizes recent efforts directed towards the total synthesis of amphirionin-4 and biselide A, two tetrahydrofuran-containing natural products with potentially useful biological activities. Amphirionin-4 is a polyketide isolated from *Amphidinium sp*. dinoflagellates, and has demonstrated potent proliferation activity in ST-2 stem cells. Biselide A is a marine macrolide isolated from the Okinawan ascidian *Didemnidae sp.,* and has demonstrated potent cytotoxicity towards a variety of human cancer cell lines. Notably, the unifying element in our synthetic approaches to both of these natural products is a reliance on chlorohydrin-based strategies to access the tetrahydrofuran cores in an efficient, diastereoselective and enantioselective manner.

Keywords: tetrahydrofuran; biselide; amphirionin; total synthesis; natural product

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List of Schemes

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$[\alpha]_D$	Specific Rotation at the sodium D line (589 nm)
°C	Degrees Celsius
AcOH	Acetic Acid
c	Concentration in g/mL
cat.	Catalytic amount
CSA	Camphor-10-sulfonic acid
CuTC	Copper(I) thiophene-2-carboxylate
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DIBAL	Diisobutylaluminum hydride
DIC	N,N'-Diisopropylcarbodiimide
DIPA	Diisopropylamine
DMAP	N,N-Dimethylpyridin-4-amine
DMP	Dess-Martin periodinane
dr	Diastereomeric ratio
e.g.	*Exempli gratia*
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et_2O	Diethyl Ether
EtOAc	Ethyl Acetate
HF·Pyr	Hydrogen fluoride pyridine
HMBC	Heteronuclear multiple bond correlation
HPLC	High-performance liquid chromatography
HSQC	Heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
i.e.	*Id est*
IC_{50}	Half maximal inhibitory concentration
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamine
M	Molar (mol/L)
MeCN	Acetonitrile

MeOH	Methanol
MMTR	4-Methoxytrityl
Ms	Methanesulfonyl
MTPA	α-Methoxy-α-trifluoromethylphenylacetate
MTPA-OH	α-Methoxy-α-trifluoromethylphenylacetic acid
NCS	N-Chlorosuccinimide
NHK	Nozaki-Hiyama-Kishi
nOe	Nuclear Overhauser effect
OTf	Trifluoromethanesulfonate
PG	Protecting Group
PMB	*para*-Methoxybenzyl
PPTS	Pyridinium para-toluenesulfonate
PS-PPh_3	Polymer Supported Triphenylphosphine
PTSA	*para*-Toluenesulfonic acid monohydrate
Pv	Pivalate
Pyr	Pyridine
rt	Room temperature
TBAF	Tetrabutylammonium Fluoride
TBS	tert-Butyldimethylsilyl
TC	Thiophene-2-carboxylate
TCBC	2,4,6-Trichlorobenzoyl chloride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TMSCl	Trimethylsilyl chloride
Trt	Triphenymethyl
δ	Chemical shift (in ppm) from tetramethylsilane

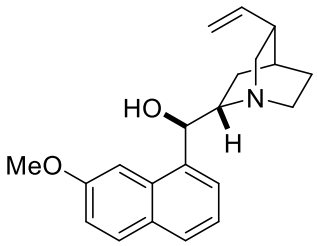
Chapter 1.

Introduction

1.1. Introduction to Natural Products

Mankind has had a long association with natural products, especially those derived from plants.[1] From the administration of crude plant extracts as treatments for various ailments to the synthesis of structural analogues of bioactive natural products, we continue to rely heavily on nature as a primary source of new therapeutic agents.[2] One of the earliest records of natural product-derived medicine comes from the Ebers Papyrus, which was written in Egypt around 1500 BCE and lists over 700 drugs.[3] Rational investigation into the use of herbal extracts as therapeutics was further advanced by the Greeks and Romans. For example, Pedanius Dioscorides, a prominent Greek pharmacologist and physician, kept an extensive record of medicinal plants found while traveling through various territories with the Roman armies.[2] Even today, natural product-based therapeutics such as Traditional Chinese Medicine thrive in various pockets of the world and further exemplify mankind's reliance on natural products for medicines.[4] The WHO estimates that the worldwide herbal medicine market is one of the fastest growing pharmaceutical markets and is presently valued at approximately $43 billion USD per annum.[5]

In recent decades, many natural products have been isolated from a wide range of terrestrial and aquatic organisms. While these secondary metabolites often play vital roles in the survival of the producing organism (*e.g.*, defense against predators or pathogens), they also have the potential to help defend humans against various illnesses and pathogens. For example, quinine (**1**) in Figure 1.1, isolated from the bark of *Cinchona* species, exhibits antipyretic, analgesic and anti-inflammatory properties and is well-known for being utilized as the first effective treatment for malaria.



quinine (**1**)

Figure 1.1. Structure of the anti-inflammatory natural product quinine.

To this day, isolation and medicinal applications of natural products are still pursued and play a large role in drug discovery. From 1981 to 2010, natural products and their analogues comprised of 26% of FDA approved drugs, while totally synthetic drugs based on pharmacophores originally found in a natural product accounted for further a 13%.[6] Unfortunately, the isolation of natural products is often a challenging process that may only afford a few milligrams of the pharmacologically active compound from kilograms of biomass. Thus, the design and execution of an economically viable chemical synthesis of biologically active natural products is often regarded as a more attractive approach and can support lead optimization, pharmacological studies, and clinical trials.

In contemplating the construction of biologically-active and/or structurally complex natural products, the development of new synthetic methodologies is crucial. In particular, methods that facilitate access to stereochemically rich heterocycles have had a significant impact on natural product synthesis and drug discovery.

1.2. Introduction to Tetrahydrofuran-based Natural Products

Tetrahydrofurans are five membered heterocycles containing one oxygen and four carbons, and are found in many classes of terrestrial and marine natural products. Furthermore, an impressive number of these THF-containing natural products demonstrate potent and potentially useful biological activity (Figure 1.2).[7] For example, uvaricin (**2**) is a potent anti-cancer THF-containing natural product first isolated from the roots of the *Uvaria accuminata* plant from the *Annonacae* species and reported in

1982.[8,9] Interest in uvaricin (**2**) stems primarily from its antitumor activity against P-388 lymphocytic leukemia cells.[8] Amphidinolide E (**3**) is another example of a THF-containing natural product, and is a member of the family of amphidinolide polyketides isolated from *Amphidinium* dinoflagellates.[10] Amphidinolide E (**3**) possesses cytotoxic activity against murine leukemia cell lines, with IC_{50} values of 2.0 and 4.8 μg mL^{-1} against L1210 and L5178Y, respectively.[10] Eribulin mesylate (**4**), which is marketed as Halaven™, was developed by Eisai Co. and recently approved by the FDA for the treatment of metastatic breast cancer and contains three THF rings within its macrocyclic structure.[11] Notably, eribulin is the only chemotherapeutic on the market that has shown an increased survival of the population of metastatic breast cancer patients.[11]

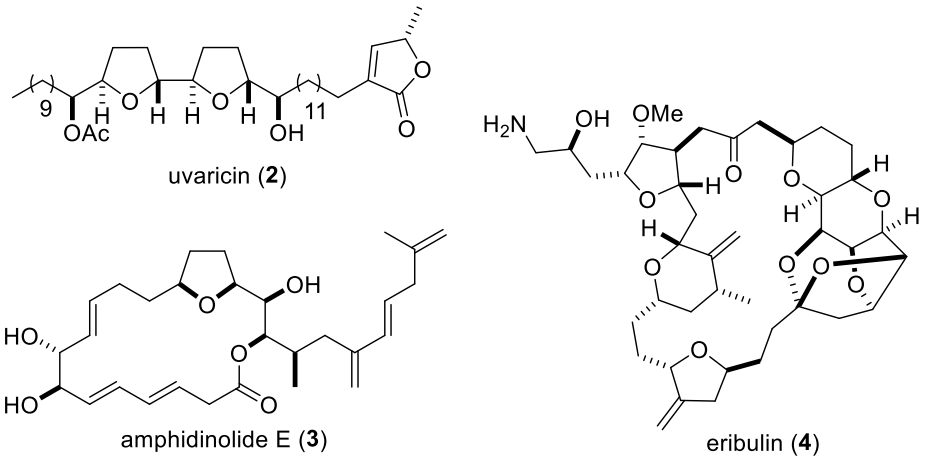
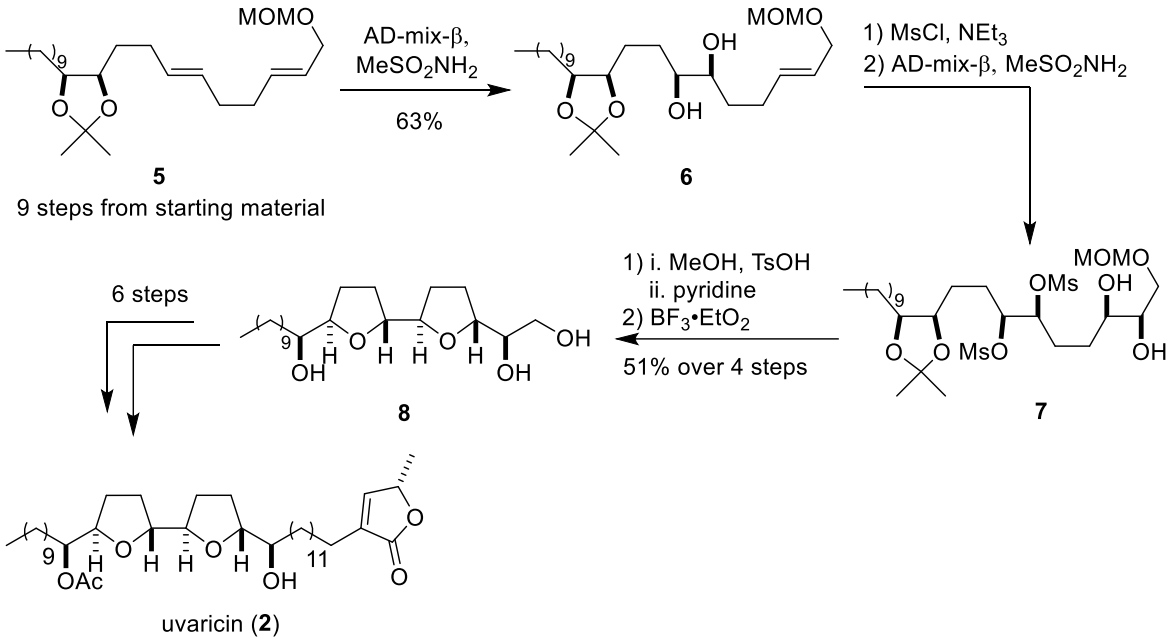


Figure 1.2. Representative natural products containing a THF ring.

1.3. Strategies Towards the Synthesis of Tetrahydrofurans

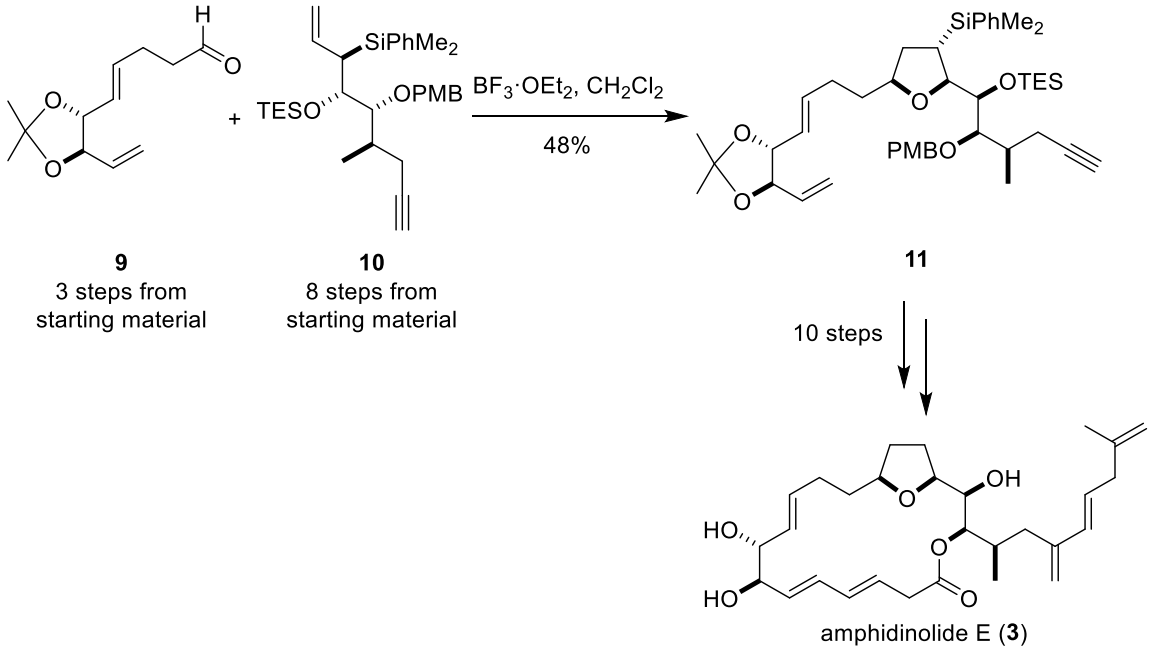
Due to their intriguing biological activity and potential as pharmaceuticals, THF-containing natural products have been the target of a large body of research.[7,12] Furthermore, considering that the biological activity of THF-containing natural products depends significantly on stereochemistry, considerable efforts have been expended on the stereoselective synthesis of tetrahydrofurans. A common strategy employed in the syntheses of annonaceous acetogenin polyketides and exemplified in the synthesis of uvaricin (**2**) by Keinan and co-workers, involves a Sharpless asymmetric dihydroxylation[13–15] to install the required stereogenic centres (Scheme 1.1). A

subsequent mesylation followed by intramolecular displacement provides access to the two desired tetrahydrofurans in **8**.[16] A further sequence of reactions yielded uvaricin (**2**) in 19 steps with an overall yield of 0.16%.



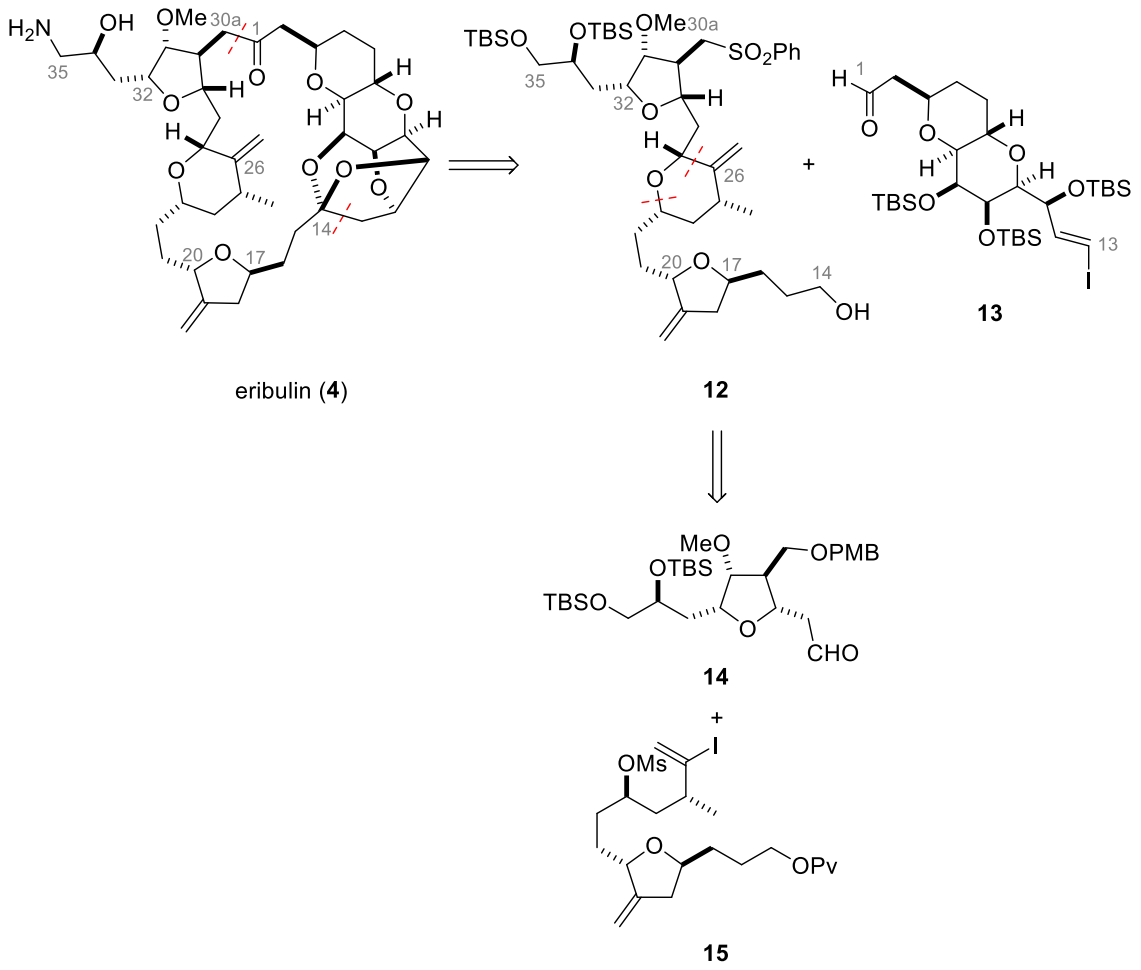
Scheme 1.1. Keinan's method for installing two THF rings stereoselectively in the synthesis of uvaricin (2).

Amphidinolide E (**3**) has been the target of several synthetic studies, culminating in two total syntheses by Roush[17] and Lee.[18] As highlighted below, a key step employed by Roush involved a [3+2] annulation reaction developed by Roush[19] between aldehyde **9** and allysilane **10** in order to construct the tetrahydrofuran moiety (Scheme 1.2).[17] Further elaboration of **11** afforded amphidinolide E (**3**) with a total of 19 steps in its longest linear sequence.



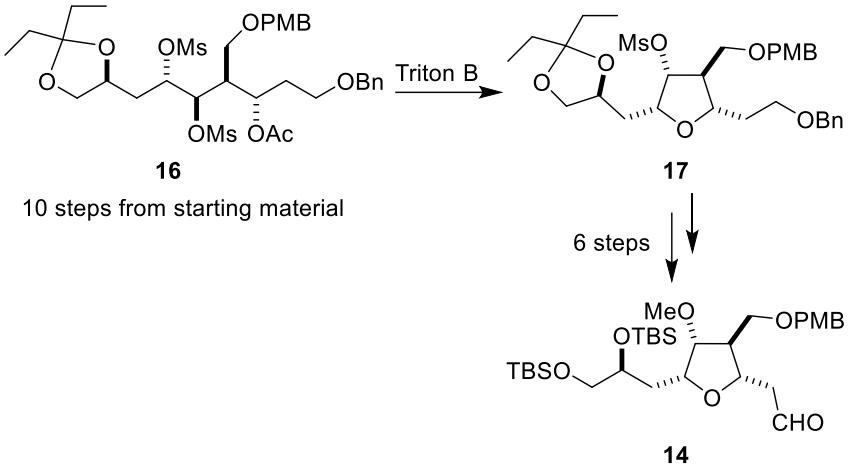
Scheme 1.2. Roush's method in accessing the THF ring *via* a [3+2] annulation in the synthesis of amphidinolide E (3).

Considering the obvious structural and stereochemical complexity of eribulin mesylate (Halaven^{TM}), the synthesis of eribulin (**4**) represents a considerable challenge. While oftentimes the focus of a total synthesis is production of sufficient quantities of material to confirm structure or carry out preliminary biological studies, a scalable synthesis of eribulin (**4**) was necessary for toxicological studies and to support clinical trials and eventually production.[11] Eisai Co.'s process synthesis of eribulin (**4**) focuses on coupling two large fragments **12** (which contain the two THFs) and **13** at C1 and C30a and C13 and C14.[11] Fragment **12** can be accessed via a NHK coupling and subsequent cyclization between THFs **14** and **15**.



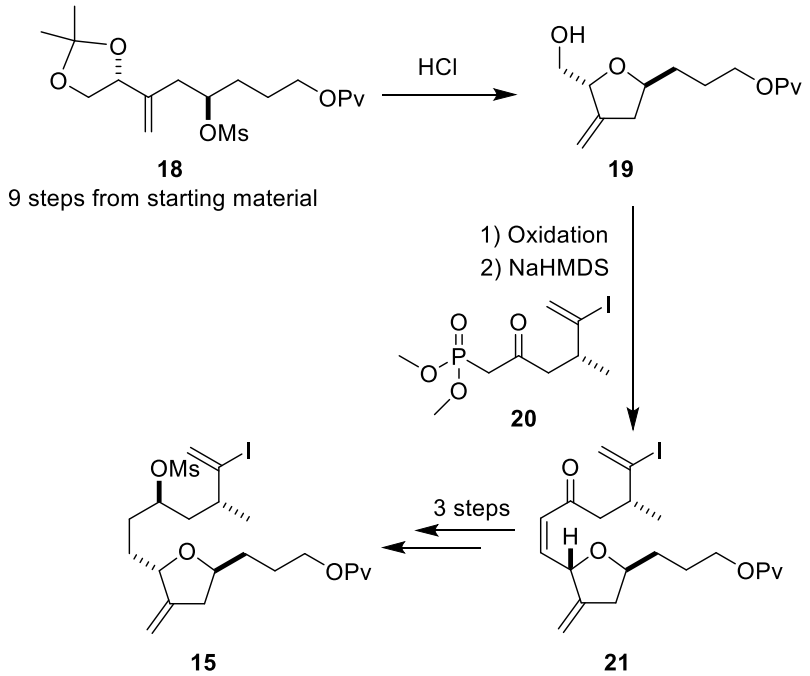
Scheme 1.3. Retrosynthetic analysis of eribulin (4).

To access the first THF fragment **14**, precursor **16** was synthesized from two separate chiral building blocks. Base-induced cyclization of precursor **16** via displacement of a mesylate provided THF **17**, which was further converted to THF fragment **14** following several protection/deprotection and oxidation manipulations with a step count of 17 steps (Scheme 1.4).



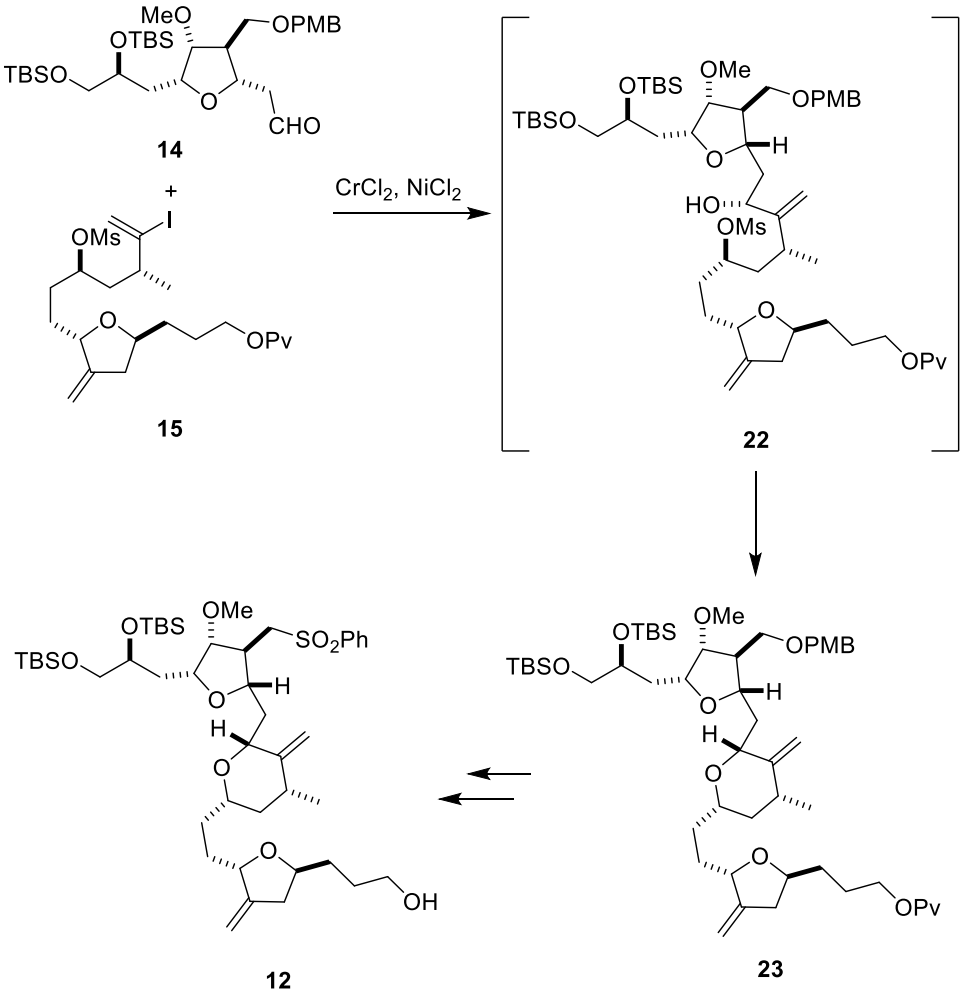
Scheme 1.4. Eisai Co.'s method in accessing the first THF in the synthesis of eribulin (4).

The other THF fragment **15** was formed via an acid-induced acetonide removal and 5-*exo*-tet cyclization from compound **18**. Alcohol **19** was then oxidized to the corresponding aldehyde, which was further reacted with a phosphonate **20** under Horner-Wadsworth-Emmons conditions to prepare compound **21**. Three additional steps furnished THF fragment **15** (Scheme 1.5).



Scheme 1.5. Eisai Co.'s method in accessing the second THF in the synthesis of eribulin (3).

With THF fragments **14** and **15** in hand, these compounds were coupled via a key Nozaki-Hiyama-Kishi reaction,[20,21] which formed the allylic alcohol intermediate **22** that immediately underwent cyclization to form the tetrahydropyran present in compound **23**. Finally, the tetrahydropyran **23** was converted to the desired fragment **12** through a series of functional group manipulations.



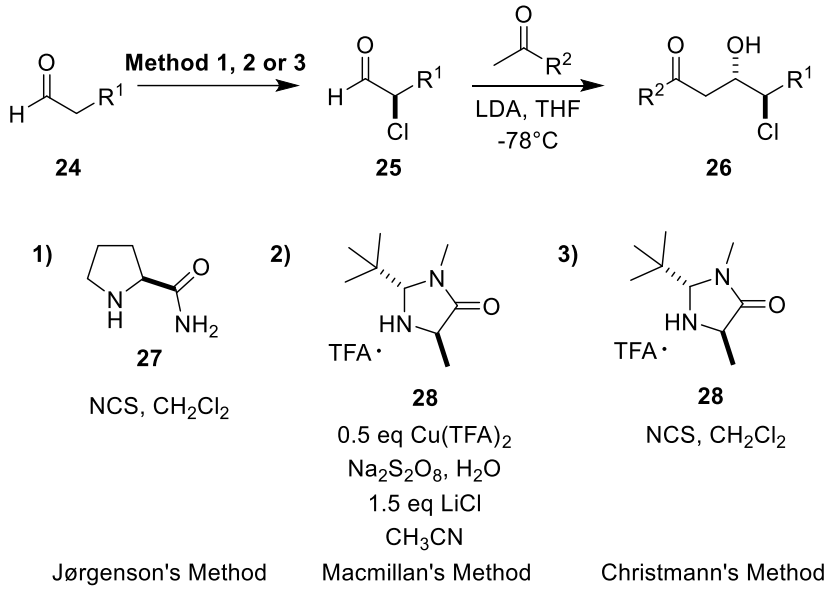
Scheme 1.6. Synthesis of fragment 23 via a key Nozaki-Hiyama-Kishi reaction and cyclization.

As indicated in the examples above, current synthetic strategies rely primarily on lengthy synthetic routes to access THFs that rely on chiral building blocks as well as

numerous protecting group or functional group manipulations. Furthermore, the ability to generate a series of analogues to explore structural activity relationships (SAR) of a specific pharmacophore is crucial in the development of pharmaceuticals. Thus, a reliance on chiral building blocks or chiral reagents make it difficult to further optimize the biological activity. These factors can decrease efficiency with respect to the exploration and optimization of biological activity and impact the scalability of a synthesis.

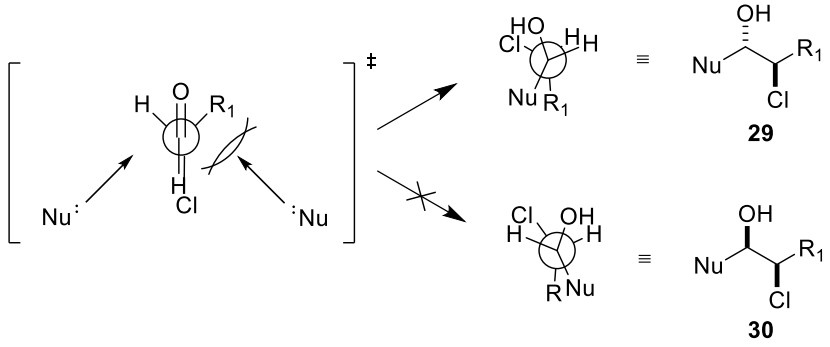
1.4. Accessing Tetrahydrofurans Stereoselectively via an α-Chloroaldehyde Approach

In light of this, the Britton group has developed a strategy for the stereoselective and protecting-group free formation of THF ring systems. This method utilized chlorohydrins as key building blocks that are generally made readily available in 2-3 steps from inexpensive and commercially-available starting materials. Importantly, this strategy allows facile and rapid access to all possible configurational isomers of 2,5-disubstituted-3-tetrahydrofuranols.[22] Specifically, chlorohydrin building blocks are accessed via an aldol reaction between lithium enolates and α-chloroaldehydes (**25**) to provide ketochlorohydrins (*e.g.,* compound **26**) with excellent diastereoselectivity. These latter substances can then undergo sequential stereoselective reduction and cyclization reactions to provide tetrahydrofurans. Notably, the requisite α-chloroaldehydes (**25**) can be synthesized enantioselectively via methods developed by Jørgensen (Method 1)[23] or Macmillian (Method 2)[24] that utilize L-prolinamide (**27**) or imidazolidinone-based organocatalyst (**28**), respectively (Scheme 1.7). More recently, Christmann (Method 3) has reported a simplified protocol that combines the excellent enantioselectivity offered by MacMillan's catalyst (**28**) with the ease of use of NCS as a chlorinating agent.[25]



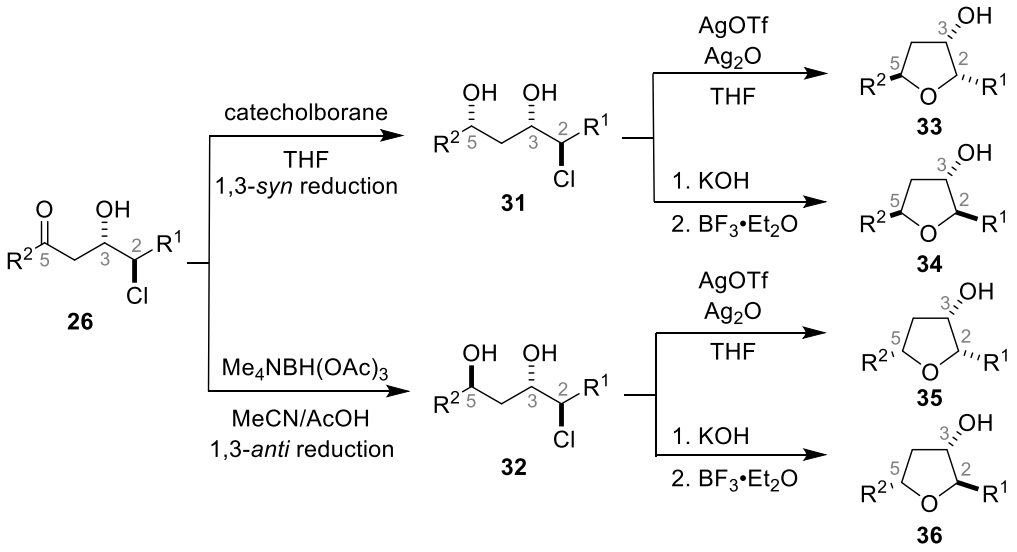
Scheme 1.7. Synthesis of ketochlorohydrins, building blocks for THFs, via α-chloroaldehydes synthesized from Jørgensen's, Macmillan's or Christmann's method.

The diastereoselectivity of the aldol reaction between an α-chloroaldehyde (*e.g.,* **25**) and an enolate derived from a methyl ketone can be rationalized using the well-established Evans-Cornforth model (Scheme 1.8) that predicts the C-O bond of the carbonyl and the adjacent C-Cl bond of the chloromethine will be aligned in opposite directions in order to minimize the net dipole moment. As a result, the facial selectivity of the nucleophilic attack is determined by the relative steric bulk of the two groups on the opposite faces of the aldehyde, resulting in the nucleophilic addition from the less hindered side of the carbonyl to form the *anti*-aldol adduct **29** (Scheme 1.8).[26,27]



Scheme 1.8. Facial selectivity of nucleophilic attack on α-chloroaldehydes as rationalized by the Evans-Cornforth model.

Exploiting the ready access to enantiomerically enriched ketochlorohydrins (*e.g.*, **26**), it was subsequently found that these materials can be reduced stereoselectively in a 1,3-*syn* or -*anti* fashion to provide chlorodiols **31** or **32**.[28–30] Formation of 2,5-disubstituted tetrahydrofuranols (*e.g.*, **33** or **35**) simply involves treating chlorodiols **31** or **32** with a silver(I) salt and Ag_2O, which acts as a mild base. Here, the chloride is displaced by the C5 hydroxyl function via a S_N2 process. Alternatively, formation of an epoxide followed by Lewis acid-catalyzed rearrangement provides the 2,5-disubstituted tetrahydrofuranol (**34** and **36**) with net retention of stereochemistry at the C2 position. Through these complementary cyclization methods, all possible configuration isomers of 2,5-diisubstituted 3-hydroxytetrahydrofurans are accessible (Scheme 1.9).

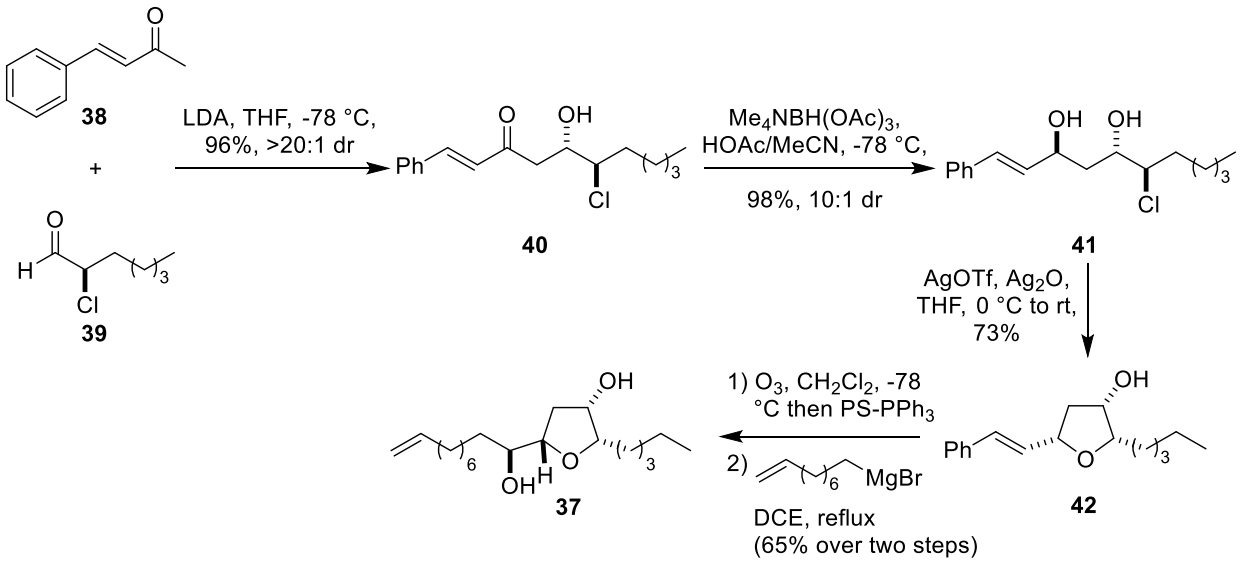


Scheme 1.9. Access to all configurational isomers of 2,5-disubstituted-3-hydroxytetrahydrofurans via the ketochlorhydrin substrate.

Building on this success, it was also demonstrated that the direct cyclization of chlorodiols to THFs (**33** and **35**) can be effected by heating the former material in various polar solvents in a microwave reactor, thus avoiding the use of stoichiometric amounts of silver(I) reagents.[31] This reaction was shown to be high yielding, regioselective and tolerant to a variety of functional groups.

The development of this methodology has supported the total synthesis of several THF-containing natural products, including the marine oxylipid **37** (Scheme

1.10)[22]. Here, a lithium aldol reaction between (2*S*)-2-chloroheptanal (**39**) and (*E*)-4-phenylbut-3-en-2-one (**38**) yielded chlorohydrin **40** in 93% yield with a diastereomeric ratio greater than 20:1. A 1,3-*anti* reduction of chlorohydrin **40** then afforded diol **41** in 98% yield in a 10:1 diastereomeric ratio, which was readily cyclized with AgOTf and Ag_2O, affording tetrahydrofuranol **42**. Oxidative cleavage followed directly by the addition of 8-nonenylmagnesium bromide at reflux in DCE allowed access to the enantiomerically- enriched marine oxylipid **37.**



Scheme 1.10. Synthesis of marine oxylipid (37) via a chlorohydrin-based strategy.

1.5. Conclusion

With the development of a stereoselective strategy to efficiently access THFs, we were interested in extending this strategy to the total synthesis of several THF-containing natural products that possess interesting biological properties. Our aim was to develop a synthetic route that not only exploited our chlorohydrin-based strategy but also allowed access to sufficient quantities of our targets for further evaluation of their biological activity. In this thesis, work on the synthesis of two tetrahydrofuranol-containing polyketides, amphirionin-4 and biselide A, is presented.

Chapter 2.

The Total Synthesis of Amphirionin-4

The results discussed in Chapter 2 have been reported in part, see:

Holmes, M.; Kwon, D.; Taron, M.; Britton, R. *Org. Lett.* **2015**, *17* (15), 3868–3871.

2.1. Introduction to the Amphirionin Family of Polyketides

The *Amphidinium sp.* are dinoflagellates that are of great interest to the natural products community as a source of secondary metabolites with biologically interesting properties.[32] Notably, three major classes of polyketides have been reported from this species of dinoflagellates, the largest of which is the aforementioned macrocyclic amphidinolide family, including amphidinolide E (**3**) (Figure 2.1). An additional structural class of polyketides isolated from *Amphidinium sp.* is characterized by a long chain unsaturated and polyhydroxylated fragment such as amphidinol 3 (**43**).[33] The third major structural class is composed of polyketides that contain a linear polyketide structure with a characteristically lower molecular weight (< 600 Da) and some oxygenation. Recently, the isolation of a family of THF-containing natural products with these structural characteristics was reported by Tsuda and coworkers.[34] Amphirionins-1,[35] -2 (**44**),[36] -3,[37] -4 (**45**),[34] and -5 (**46**),[38,39] were isolated from various strains of the *Amphidinium* species, and were demonstrated to possess potentially useful biological activity.

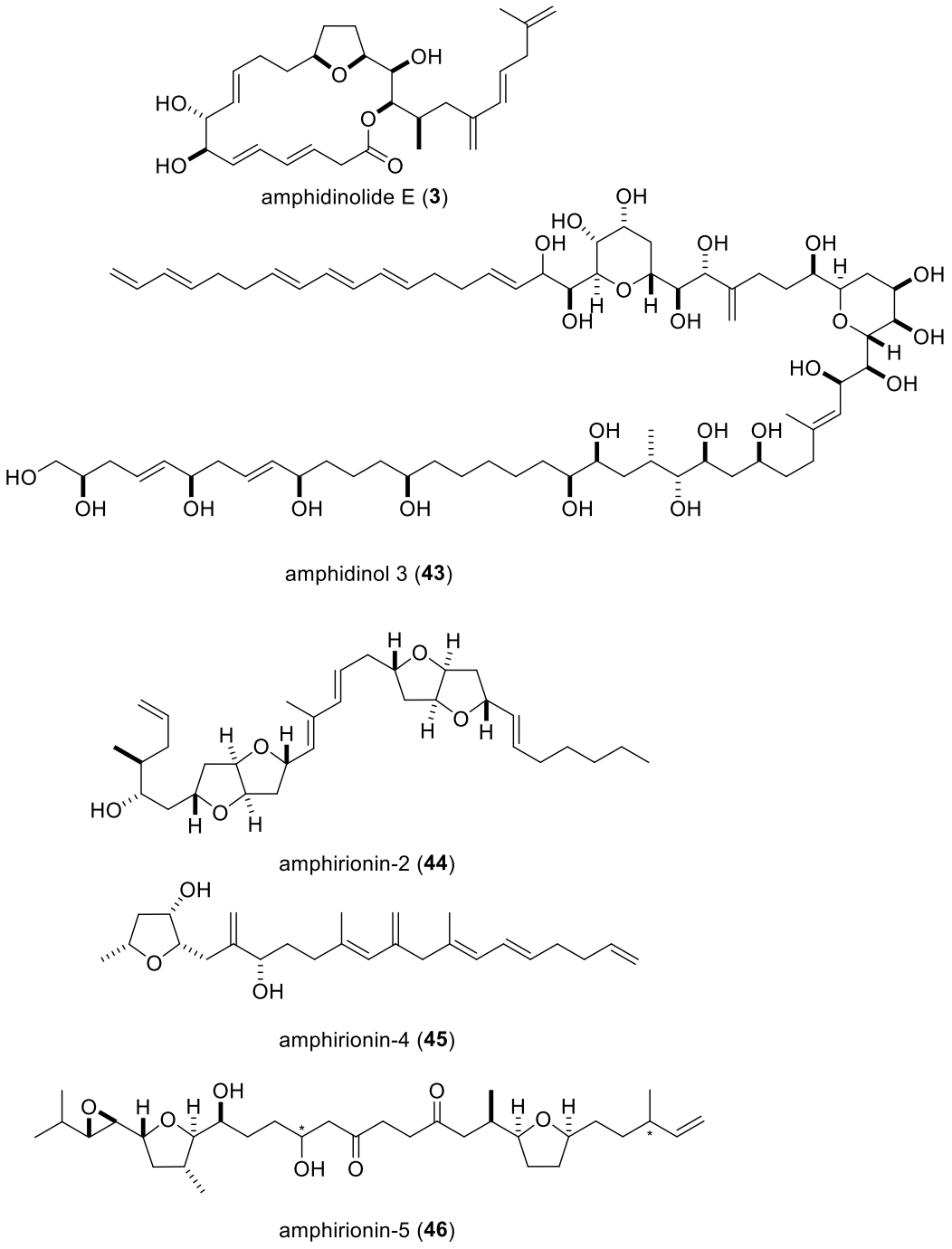


Figure 2.1. Examples from the three structural classes of polyketides isolated from *Amphidinium sp*.

During preliminary biological studies on amphirionin-2 (**44**), Tsuda found that this natural product possessed significant cytotoxicity against Caco-2 human colon carcinoma cells (IC_{50} = 0.1 μg/mL) and A549 human lung adenocarcinoma cells (IC_{50} =

0.6 µg/mL), while showing weaker activity towards HeLa human cervix adenocarcinoma cells (20% inhibition at 1 µg/mL).[36] This activity was attributed to the actin inhibiting properties of amphirionin-2 (**44**).[36]

In contrast, both amphirionin-4 (**45**) and -5 (**46**) showed proliferation activity towards several cell lines. In particular, when tested against ST-2 murine bone-marrow derived stromal cells, MC3T3-E1 murine osteoblastic cells and NIH3T3 murine embryotic fibroblastic cells, amphirionin-5 (**46**) displayed proliferation activity for both ST-2 and MC3T3-E1 cell lines (IC_{50} = 0.001-10 ng/mL).[38] Interestingly, amphirionin-4 (**45**) was only active as a proliferating agent with ST-2 cells (increase in cell growth rate by 950% at a concentration of 0.1 ng/mL).[34] The potency of amphirionin-4 (**45**) makes it a very intriguing target for total synthesis and highlights this natural product as a potential lead candidate for the purposes of bone and cartilage regrowth.[34] The full results are outlined in Table 2-1.[34,38]

Table 2-1 Cell proliferation activities of amphirionin-4 and amphirionin-5 at varying concentrations

	Concentration (ng/mL)	ST-2 (bone marrow)[a]	MC3T3-E1 (osteoblasts)[a]	NIH3T3 (fibroblastic)[a]
amphirionin-4 (**45**)	0.001	610%	90%	90%
amphirionin-4 (**45**)	0.01	880%	90%	100%
amphirionin-4 (**45**)	0.1	950%	80%	100%
amphirionin-4 (**45**)	1.0	630%	80%	100%
amphirionin-4 (**45**)	10.0	510%	80%	90%
amphirionin-5 (**46**)	0.001	170%	180%	110%
amphirionin-5 (**46**)	0.01	230%	280%	120%
amphirionin-5 (**46**)	0.1	230%	260%	110%
amphirionin-5 (**46**)	1.0	170%	180%	130%
amphirionin-5 (**46**)	10.0	270%	320%	200%

[a] % = Rate of proliferation of cells compared to the control

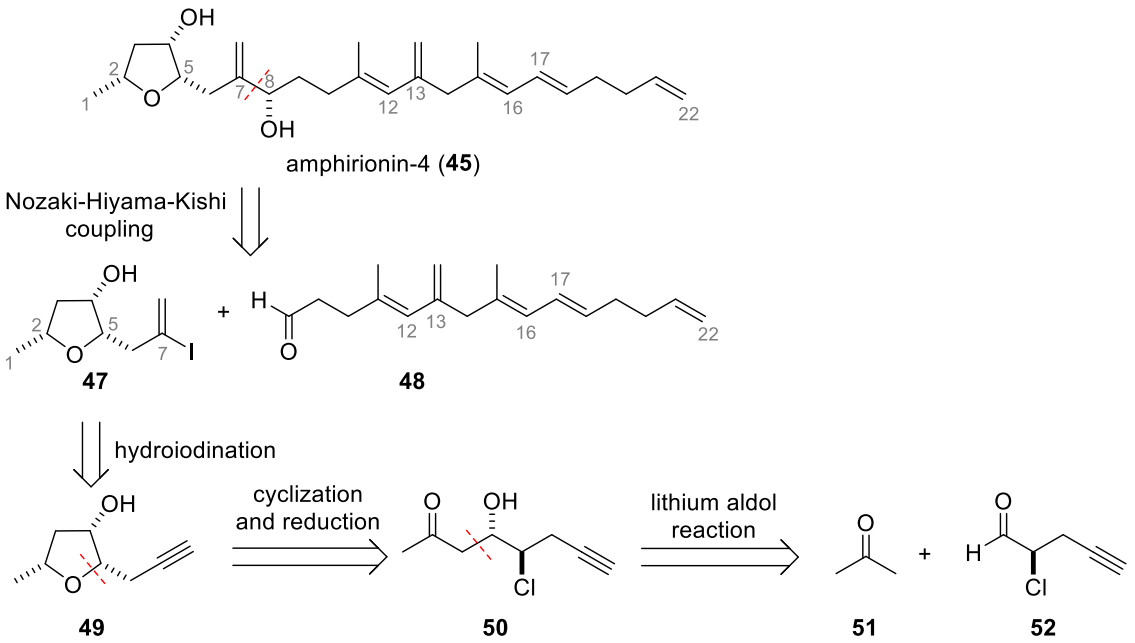
In addition to a densely functionalized THF, amphirionin-4 (**45**) also includes a skipped tetraene motif on a heptadecyl side chain and a remote allylic alcohol, both of which present synthetic challenges. These unique structural features of amphirionin-4

(**45**) coupled with its potent biological activity makes this natural product an intriguing and important synthetic target.

2.2. Synthesis of the *syn*-Tetrahydrofuranol of Amphirionin-4

2.2.1. Retrosynthesis of Amphirionin-4

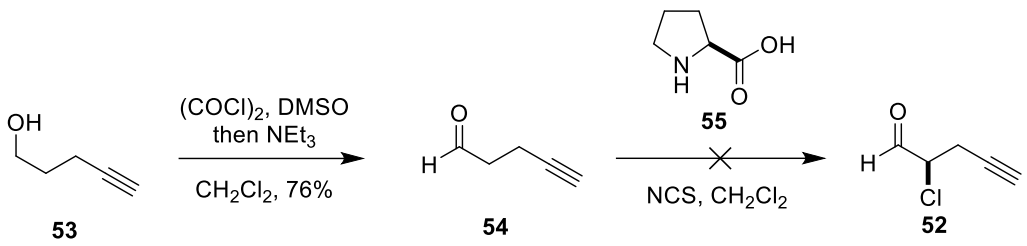
The total synthesis of amphirionin-4 (**45**) was the result of a collaboration between myself and two other graduate students in the Britton group: Michael Holmes and Matthew Taron. Our synthetic strategy aimed at making late-stage connections between three key fragments to ensure an efficient synthesis (Scheme 2.1) and allow late stage access to analogues for medicinal chemistry purposes. Specifically, we envisaged a Nozaki-Hiyama-Kishi reaction would connect the two key fragments **47** and **48** and introduce the remote allylic alcohol at C8. Fragment **48** was independently synthesized by Michael Holmes and Matthew Taron, while the *syn*-tetrahydrofuranol **47** was the target of my research. The vinyl iodide motif in tetrahydrofuranol **47** would be incorporated through hydroiodination of the alkyne function in tetrahydrofuranol **49**. As described in Chapter 1, this compound could be accessed utilising our chlorohydrin-based strategy, initiating from an aldol reaction between an enantiomerically-enriched α-chloroaldehyde **52** and acetone (**51**). Additional key steps would include a 1,3-*anti* reduction of ketochlorohydrin **50** to give an *anti*-chlorodiol and a subsequent cyclization reaction to afford tetrahydrofuranol **49**.



Scheme 2.1. Proposed retrosynthesis of amphirionin-4 (45).

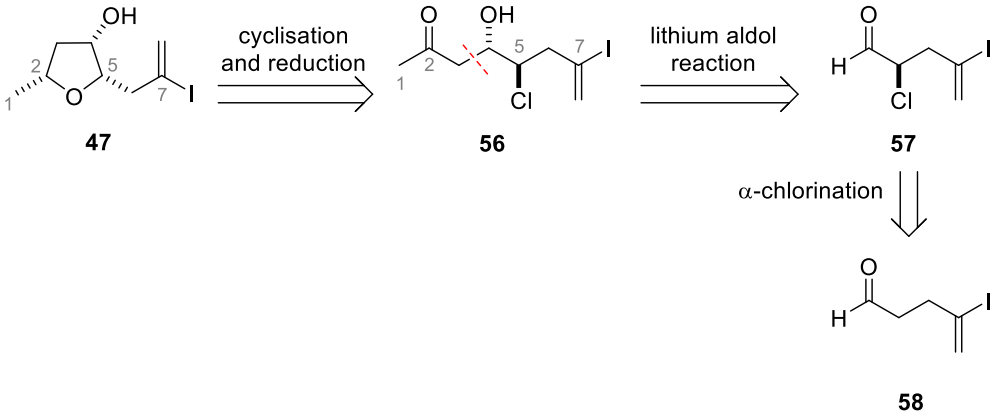
2.2.2. Synthesis of the α-Chloroaldehyde

Our attempts at synthesizing α-chloroaldehyde **52** are summarized in Scheme 2.2. Oxidation of the alcohol function in 4-pentyn-1-ol (**53**) was accomplished using a Swern oxidation,[40] and gave the aldehyde **54** that was used without purification due to its volatility and challenges associated with its purification. Considering the cost of the standard organocatalysts L-prolinamide (**27**) and imidazolidinone **28**,[24] we decided to first explore the α-chlorination using L-proline (**55**) and also evaluate the synthesis of THF **49** using a racemic mixture of α-chloroaldehyde **52**. Unfortunately, attempts to carry out the α-chlorination of aldehyde **54** proved problematic and often delivered an undesirable mixture of starting material, mono-chlorinated aldehyde, and di-chlorinated aldehyde alongside other unidentified side products. This inconsistency was attributed to the presence of impurities carried through from the previous oxidation step. Considering these complications, the synthetic route was modified accordingly.



Scheme 2.2. Attempted synthesis of α-chloroaldehyde 52.

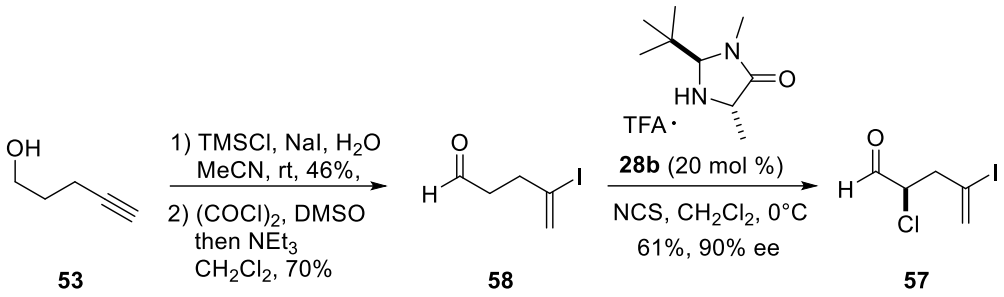
In an effort to decrease the volatility of the aldehyde, which would facilitate purification prior to α-chlorination, we elected to first introduce the vinyl iodide function at C7 prior to oxidation. The revised retrosynthesis of tetrahydrofuranol **47** is shown in Scheme 2.3.



Scheme 2.3. Revised retrosynthesis of tetrahydrofuranol 47.

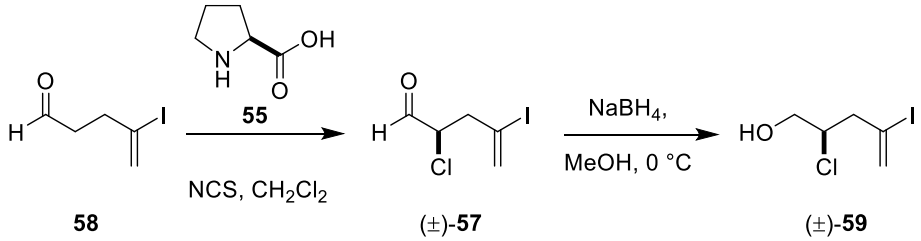
The hydroiodination of 4-pentyn-1-ol (**53**) via *in situ* formation of hydrogen iodide from TMSCl and NaI with the subsequent addition of H_2O, proceeded cleanly on small scale. However, efforts to repeat this reaction on larger scales resulted in the formation of side-products after extended reaction times. Therefore, it was found optimal to stop the reaction at approximately 60% conversion, after which point the product could be readily purified. A Swern oxidation then gave the desired aldehyde **58** cleanly in 70% yield following chromatographic purification. Initial attempts to effect the desired α-chlorination with Macmillan's imidazolidinone-based organocatalyst **28b** were met with difficulties that included challenges in purification, loss of product during aqueous workup, and formation of undesirable side products such as the di-chlorinated product.

After assessing both Macmillan's[41] and Christmann's[25] method, optimal reaction conditions were identified that included stirring the reaction mixture overnight under Christmann's conditions at 0 °C, after which time pentane was added and the by-products were removed by filtration. Purification via flash chromatography with a short silica column then afforded the enantiomerically-enriched α-chloroaldehyde **57** in good yield (Scheme 2.4).



Scheme 2.4. Synthesis of α-chloroaldehyde 57.

Considering the enolizability of the α-chloroaldehyde **57**, there was some concern that purification of this material by flash column chromatography would promote racemization. Using a racemic mixture of the chlorohydrin **59**, obtained from the α-chlorination of aldehyde **58** with L-proline and subsequent reduction (Scheme 2.5), as a standard, the enantiomeric excess of chlorohydrin **59** was determined by chiral HPLC following a variety of purification conditions and reduction, the results of which are summarized in Table 2-2.



Scheme 2.5. Preparation of the racemic chlorohydrin 59 as a standard for the determination of enantiomeric excess values.

Table 2-2 Enantiomeric excess values for several purification conditions.

Entry	Purification Conditions	Enantiomeric Excess %
1	No flash chromatography	90%

2	3 inch silica column	80%
3	3 inch Iatrobead column	83%
4	3 inch NEt_3-treated silica column	Decomposition

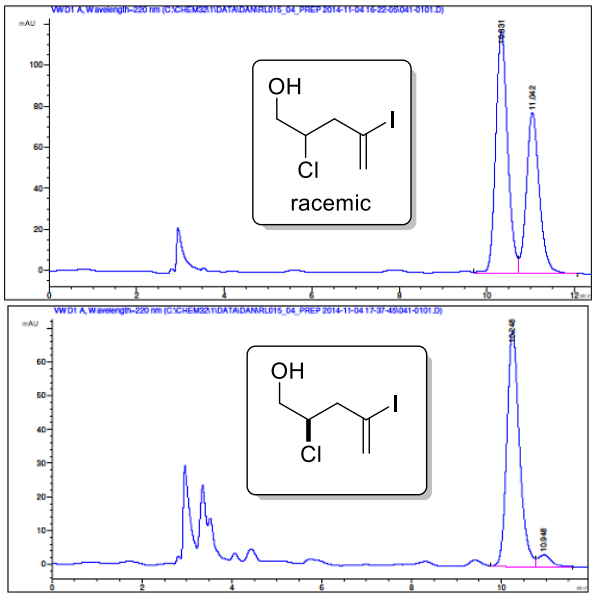
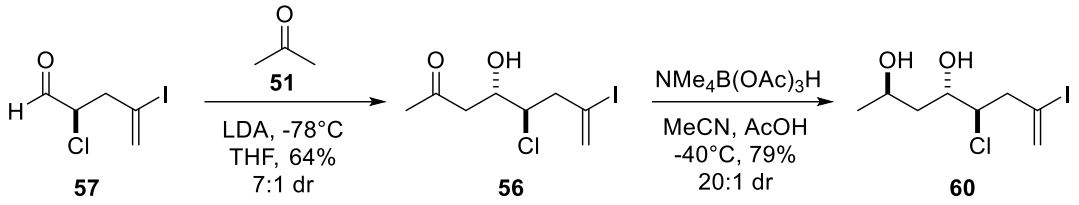


Figure 2.2 Chiral HPLC traces of the racemic chlorohydrin 59 standard and enantiomerically-enriched chlorohydrin 59.

Based on these results, we elected to avoid purification of the α-chloraldehyde **57** at the expense of yield (61% vs 73%) in order to preserve the enantiomeric excess of this material.

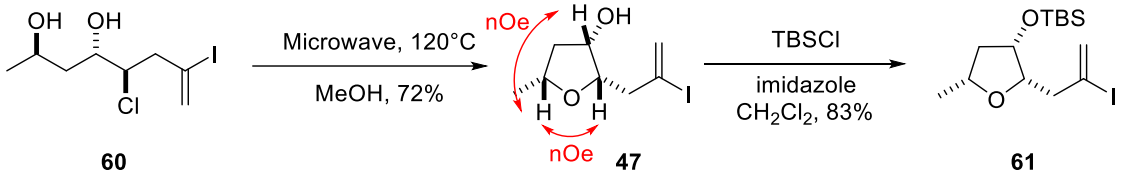
2.3. Completion of the *syn*-Tetrahydrofuranol

Moving forward, the lithium enolate of acetone (**51**) was formed via reaction with LDA and was subsequently treated with α-chloroaldehyde **57**, producing β-ketochlorohydrin **56** in 64% yield and in a 7:1 diastereomeric ratio, favouring the desired *anti* diastereomer. The β-Ketochlorohydrin **56** then underwent an Evans-Saksena reduction,[30,42] giving the 1,3-*anti* diol **60** in a 79% yield (dr = 15:1). Care had to be taken to maintain the reaction temperature at -40 °C as the diastereomeric ratio was found to erode at elevated temperatures (*e.g.*, dr = 7:1 at -20 °C) (Scheme 2.6).



Scheme 2.6. Synthesis of chlorodiol 60.

With the precursor to the desired all *syn*-tetrahydrofuranol **47** in hand, a solution of diol **60** in MeOH was heated to 120 °C for three hours in a microwave reactor to provide the desired tetrahydrofuranol **47**. In this way, the synthesis of the first key fragment of amphirionin-4 was completed (Scheme 2.7). The relative stereochemistry of tetrahydrofuranol **47** was confirmed to be "all *syn*" via analysis of 1D NOESY spectra, while synthesis of the corresponding (*R*)- and (*S*)-MTPA esters and subsequent analysis using Mosher's method[43,44] confirmed the absolute stereochemistry of tetrahydrofuranol **47**. Owing to our uncertainty regarding the effect of the C4 hydroxyl group on the planned Nozaki-Hiyama-Kishi[20,21] coupling reaction, we elected to protect the free hydroxyl group of tetrahydrofuranol **47** as a TBS ether.

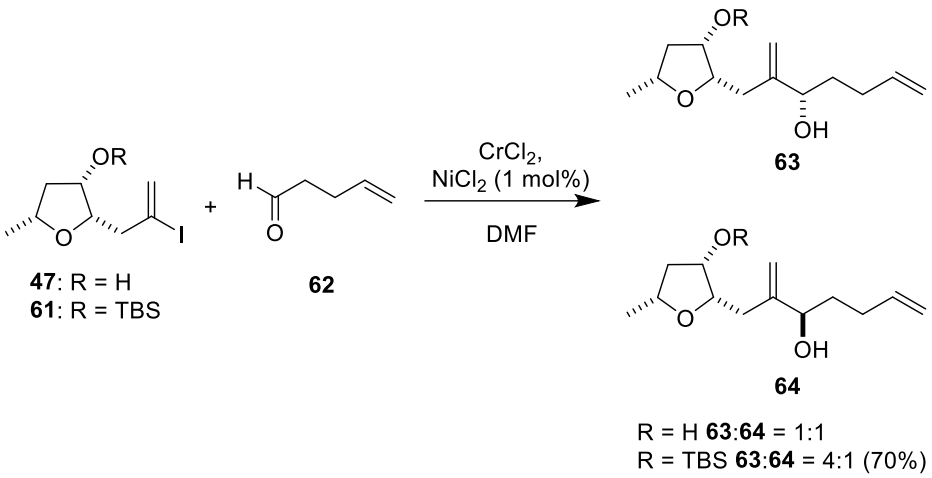


Scheme 2.7. Synthesis of tetrahydrofuranol 47 and 61.

2.4. Diastereoselectivity of the Nozaki-Hiyama-Kishi Coupling Reaction

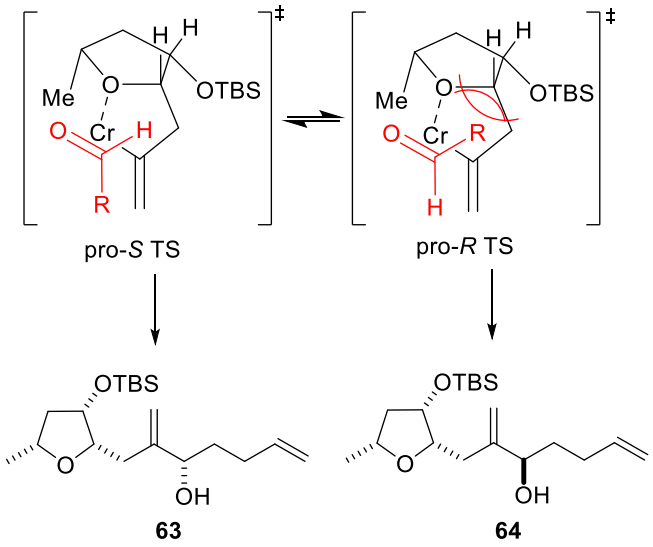
With the correctly configured tetrahydrofuranols **47** and **61** in hand, we were interested in exploring the planned NHK reaction. For this purpose, 4-pentenal (**62**) was used as a model substrate for the NHK reaction. In the event, the NHK reaction between tetrahydrofuranol **47** and 4-pentenal (**62**) proceeded cleanly to afford a 1:1 diastereomeric mixture of **63** and **64.** However, when tetrahydrofuranol **61** and 4-pentenal (**62**) were subjected to the same reaction conditions, we were pleased to observe a 4:1 diastereomeric ratio for the desired allylic alcohol **63** (Scheme 2.8). The

absolute stereochemistry of the allylic alcohol was confirmed following conversion to the (*R*)- and (*S*)-MTPA esters and analysis using Mosher's method.[43,44]



Scheme 2.8. NHK reaction of tetrahydrofuranol 47 and 61 and 4-pentenal (62).

This result is a rare example of 1,4-stereoinduction and our current working model to explain this phenomenon involves the coordination of the vinyl chromium intermediate to the oxygen atom of the tetrahydrofuran, forming a bicyclic intermediate (Scheme 2.9). Notably, in tetrahydrofuranol **46**, the presence of the free hydroxyl group may disrupt this bicyclic intermediate through competing coordination to the vinyl chromium moiety. The aldehyde subsequently adds through the pro-*S* transition structure (see below) in which steric interactions are minimized between the protons on the tetrahydrofuranol and the carbon chain on the aldehyde, imparting a degree of diastereoselectivity to this reaction.

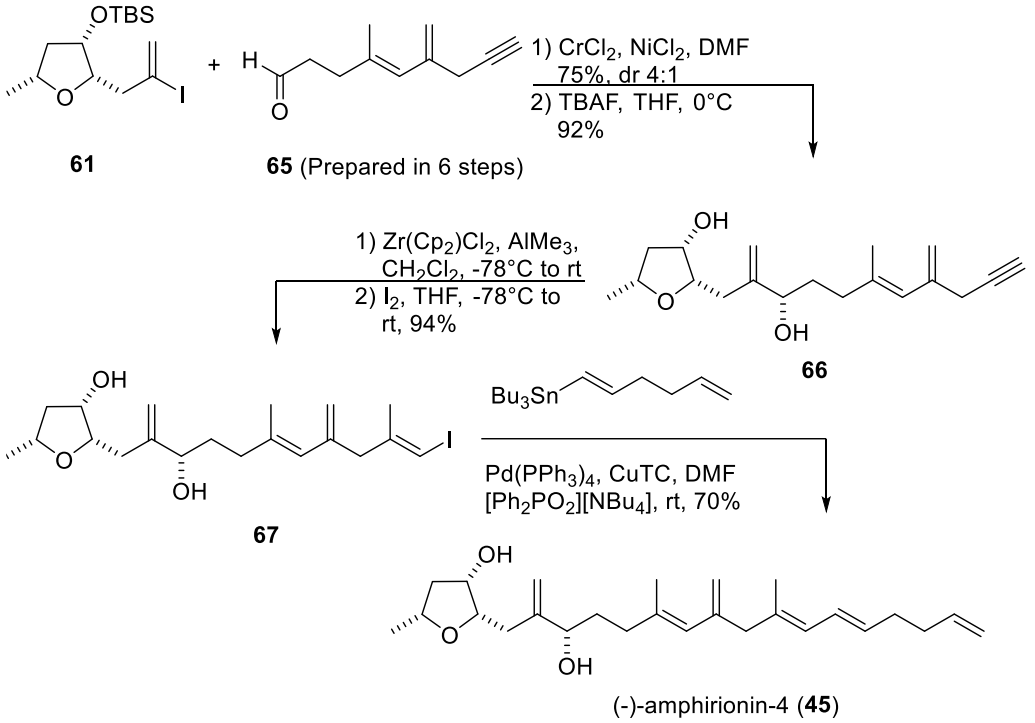


Scheme 2.9. Working model of the NHK reaction explaining the 1,4-stereoinduction effect.

With this exciting result, we had gained selective access to the remote stereocentre of the allylic alcohol present in amphirionin-4 (**45**) and set the stage for a total synthesis that was ultimately completed by Michael Holmes as described below.

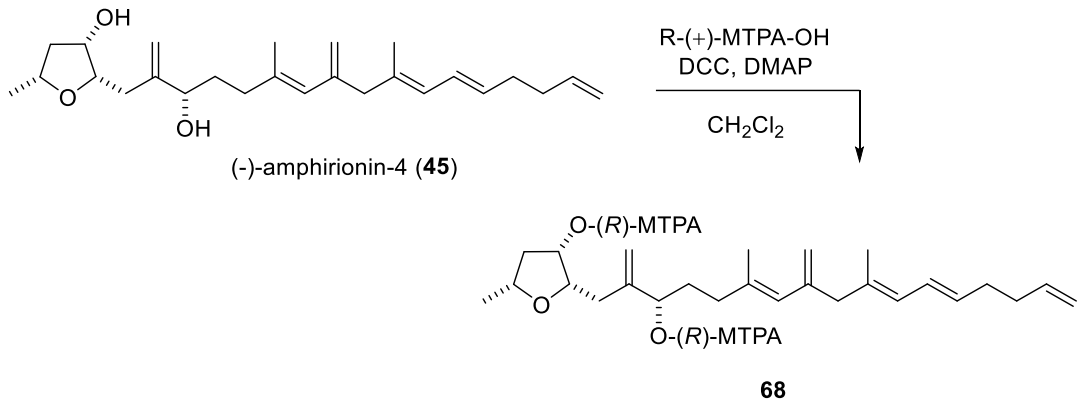
2.5. Completion of the Synthesis of Amphirionin-4

Tetrahydrofuranol **61** and aldehyde **65** (prepared in 6 steps by Michael Holmes and Matthew Taron) were subjected to the same NHK conditions developed earlier, yielding the protected tetrahydrofuranol in 75% yield and in a 4:1 diastereomeric ratio. The TBS ether was then removed cleanly using TBAF in a 92% yield to afford tetrahydrofuranol **66**. The alkyne functionality on THF **66** was subsequently converted into a vinyl iodide **67**, in preparation for the final palladium-catalyzed cross coupling, which would construct the skipped tetraene and finish the synthesis. After much difficulty, it was found that Fürstner's coupling conditions,[45] which are ideal for sensitive substrates, proved effective and yielded access to (–)-amphirionin-4 (**45**) in excellent yield over the final two steps (Scheme 2.10). The total synthesis required 11 steps in its longest linear sequence and confirmed the structure and stereochemistry of amphirionin-4 (**45**).



Scheme 2.10. Completion of the synthesis of amphirionin-4 (45).

Interestingly, while the ^{1}H and ^{13}C NMR spectra recorded on synthetic amphirionin-4 (**45**) were in agreement with that reported for the natural product,[34] the specific rotation (-5.8, *c* 0.34, $CHCl_3$) differed in sign from that of natural amphirionin-4 (+6, *c* 0.29, $CHCl_3$).[34] Considering that the absolute stereochemistry for **45** was originally assigned by analysis of the bis-(*R*)- and bis-(*S*)-MTPA esters using the modified Mosher's method,[43,44] we also converted our synthetic amphirionin-4 into the corresponding bis-(*R*)-MTPA ester **68** (Scheme 2.11). The spectral data for the synthetic bis-(*R*)-MTPA ester **68** was in complete agreement with those reported by Tsuda[34] for the bis-(*R*)-MTPA ester **68** derived from natural amphirionin-4 (**45**) while differing significantly from the spectra reported for the naturally derived bis-(*S*)-MTPA ester (not shown). Considering these facts, the difference in specific rotation of synthetic and natural amphirionin-4 can then only result from its small absolute value and the consequent difficulty in accurately measuring specific rotation with small sample sizes.



68

Scheme 2.11. Synthesis of the bis-(*R*)-MTPA ester 68 to confirm the absolute stereochemistry of amphirionin-4 (45).

2.6. Conclusion

In conclusion, the first synthesis of amphirionin-4 (**45**) was completed in part through efficient access to the all *syn*-tetrahydrofuranol via the established chlorohydrin-based strategy. Furthermore, the stereogenic centre of the allylic alcohol was introduced using a Nozaki-Hiyama-Kishi reaction that proceeds via a rare remote 1,4-stereoinduction effect. We are now currently investigating the biological activity of amphirionin-4 (**45**) in collaboration with Professor Underhill at UBC.

2.7. Experimental

2.7.1. General

All reactions described were performed under an atmosphere of dry nitrogen using oven-dried glassware unless otherwise specified. Flash chromatography was carried out with 230-400 mesh silica gel (Silicycle, SiliaFlash® P60) following the technique described by Still.[46] Concentration and removal of trace solvents was done via a Büchi rotary evaporator using dry ice/acetone condenser and vacuum applied from a Büchi V-500 pump.

All reagents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, TCI America or Strem and were used without further purification. All solvents

were purchased from Sigma Aldrich, EMD, Anachemia, Caledon, Fisher or ACP and used with further purification unless otherwise specified. Diisopropylamine and CH_2Cl_2 were freshly distilled over CaH_2. THF was freshly distilled over Na metal/benzophenone. Acetone was freshly distilled over 3Å molecular sieves. Cold temperatures were maintained by use of the following conditions: 5 °C, fridge (True Manufacturing, TS-49G); 0 °C, ice-water bath; −40 °C, acetonitrile-dry ice bath; −78 °C, acetone-dry ice bath; temperatures between −78 °C and 0 °C required for longer reaction times were maintained with a Neslab Cryocool Immersion Cooler (CC-100 II) in a EtOH/2-propanol bath.

Optical rotation was measured on a Perkin Elmer 341 Polarimeter at 589 nm.

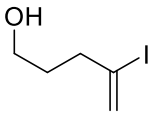
Nuclear magnetic resonance (NMR) spectra were recorded using chloroform-d ($CDCl_3$), benzene-d_6 (C_6D_6) or acetone-d_6 ($(CD_3)_2CO$). Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent (^{1}H NMR: $CDCl_3$: δ 7.26, C_6D_6: δ 7.16, $(CD_3)_2CO$: δ 2.05; ^{13}C NMR: $CDCl_3$: δ 77.16, C_6D_6: δ 128.06, $(CD_3)_2CO$: δ 29.84). 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; q, quartet; quint, quintet; m, multiplet; b, broad), coupling constants, number of protons. NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Bruker 500 (500 MHz), or Bruker 400 (400 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of 1H- 1H COSY, HSQC, HMBC, TOCSY and 1D NOESY spectra, where applicable.

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two™ Fourier transform spectrometer with neat samples. Only selected, characteristic absorption data are provided for each compound.

High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS using ESI-MS or was carried out by the Notre Dame University Mass Spectrometry Department using EI technique.

High performance liquid chromatography (HPLC) were performed on an Agilent 1200 Series equipped with a variable wavelength UV-Vis detector (λ = 220 nm) and Daicel Chemical Industries, Ltd. Chiralpak® AD chiral column (4.6 × 250 mm).

2.7.2. Preparation of 4-iodopent-4-en-1-ol (69)



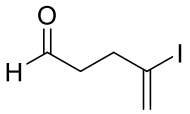
To a stirred solution of NaI (8.99 g, 60 mmol) in MeCN (24 mL) at room temperature was added TMSCl (3.05 mL, 24 mmol) followed by H_2O (0.217 mL, 12 mmol) The resulting reaction mixture was stirred for 10 minutes before 4-pentyn-1-ol (**52**) (2.24 mL, 24 mmol) was added. The reaction mixture was stirred for an additional 1 hour at room temperature until analysis of aliquots of the reaction mixture by ^{1}H NMR spectroscopy indicated 60% conversion. The reaction mixture was then treated with H_2O (20 mL), diluted with diethyl ether (40 mL) and the phases were separated. The organic phase was washed with saturated $Na_2S_2O_3$ (50 mL) then the combined aqueous phases were washed with Et_2O (2 x 20 mL). The combined organic phases were washed with brine (80 mL) then dried ($MgSO_4$) and filtered, and the solvent was carefully removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:CH_2Cl_2, 8:92) afforded the vinyl iodide **69** (2.34 g, 11.0 mmol, 46%) as a light yellow oil which was stored with copper wire under an inert atmosphere at -20 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.07 (dt, *J* = 1.6, 1.4 Hz, 1 H), 5.72 (dt, *J* = 1.5, 0.7 Hz, 1 H), 3.68 (q, *J* = 6.2 Hz, 2 H), 2.51 (dt, *J* = 7.1, 1.0 2 H) 1.78 (tt, *J* = 7.6, 6.4 Hz, 2 H), 1.27 (br t, *J* = 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 126.1, 111.6, 61.4, 41.8, 32.1.

Reference for known compound: Gao, F.; Hoyveda, A.H. *J. Am. Chem. Soc.* **2010**, *132*, 10961-10963.

2.7.3. Preparation of 4-iodopent-4-enal (58)



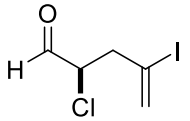
To a cold (-78 °C), stirred solution of DMSO (1.53 mL, 23.8 mmol) in CH_2Cl_2 (22 mL) was added oxalyl chloride (1.01 mL, 11.9 mmol) and the reaction mixture was stirred for 20 minutes at this temperature. Vinyl iodide **69** (1.68 g, 7.92 mmol) was then added and the reaction mixture was stirred for an additional 40 minutes at -78 °C. NEt_3 (5.18 mL, 39.6 mmol) was then added and the reaction mixture was allowed to warm to room temperature over 10 minutes. The reaction mixture was then treated with saturated aqueous NH_4Cl solution (20 mL) and diluted with CH_2Cl_2 (20 mL). The phases were separated and the aqueous phase was washed with CH_2Cl_2 (2 x 30 mL) and then the combined organic phases were washed with H_2O (2 x 40 mL), brine (40 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:CH_2Cl_2, 65:35) afforded the aldehyde **58** (1.16 g, 5.52 mmol, 70%) as a light yellow oil which was stored with copper wire under an inert atmosphere at -20 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.80 (t, *J* = 1.2 Hz, 1 H), 6.11 (dt, *J* = 1.7, 1.3 Hz, 1 H), 5.75 (dt, *J* = 1.8, 0.7 Hz, 1 H), 2.75 (m, 2 H), 2.69 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.2, 127.0, 109.1, 43.5, 38.1.

Reference for known compound: Fujii, T.; Orimoto, K.; Nakada, M. *Tetrahedron Lett.* **2014**, *55*, 1100-1103.

2.7.4. Preparation of (*R*)-2-chloro-4-iodopent-4-enal (57)



To a cold (0 °C) stirred solution of *N*-chlorosuccinimide (0.571 g, 4.27 mmol) and (2*R*,5*S*)-2-*tert*-butyl-3,5,dimethylimidazolidin-4-one trifluoroacetate (**28b**) (0.244 g, 0.86 mmol) in CH_2Cl_2 (40 mL) was added aldehyde **58** (0.90 g, 4.27 mmol) and the reaction mixture was stirred at 0 °C for an additional 18 hours. More (2*R*,5*S*)-2-*tert*-butyl-3,5,dimethylimidazolidin-4-one trifluoroacetate (**28b**) (0.122 g, 0.43 mmol) was then added and the reaction mixture was stirred for an additional 1 hour. The reaction mixture was then diluted with pentane (40 mL), filtered and concentrated *in vacuo*. Purification of the crude product by flash chromatography (CH_2Cl_2) in a 3" silica column afforded the α-chloroaldehyde **57** (0.65 g, 2.62 mmol, 61%) as a yellow oil, which was stored with a copper wire under an inert atmosphere at -20 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.62 (d, *J* = 1.4 Hz, 1 H), 6.24 (dt, *J* = 1.0, 1.6 Hz, 1 H), 5.92 (dd, *J* = 1.0, 1.7 Hz, 1 H), 4.48 (ddd, *J* = 1.4, 4.6, 9.5 Hz, 1 H), 3.18 (dddd, *J* = 1.0, 1.6, 4.6, 15.2 Hz, 1 H), 2.73 (ddd, *J* = 1.0, 9.5, 15.2 Hz, 1 H).

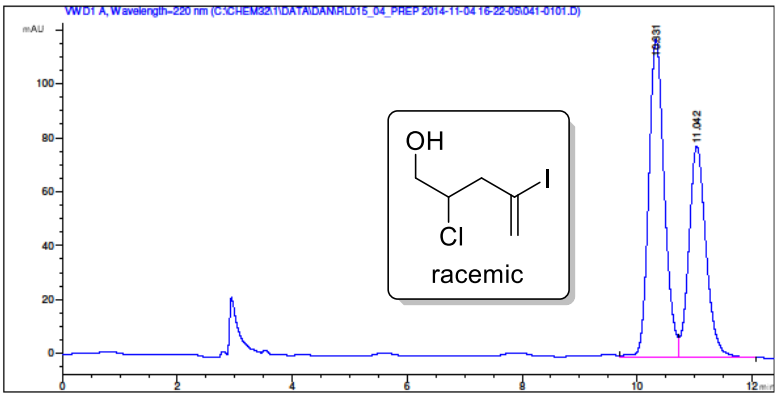
^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 130.6, 103.2, 61.9, 47.3.

HRMS: *m/z* calcd for C_5H_6ClIO: 243.9152 (M); Found: 243.9173 (M).

IR: 2923, 2851, 1733, 1617, 1418.14, 1264, 1118, 1057, 904, 502 cm^{-1}.

α_D($CHCl_3$, c 0.10): +72.1

Chiral HPLC Traces

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================================================================================
                          Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|-------|
   1  10.331 VV    0.2890 2229.85303  117.94742  57.8799
   2  11.042 VB    0.3159 1622.70129   78.36033  42.1201

Totals :                  3852.55432  196.30775
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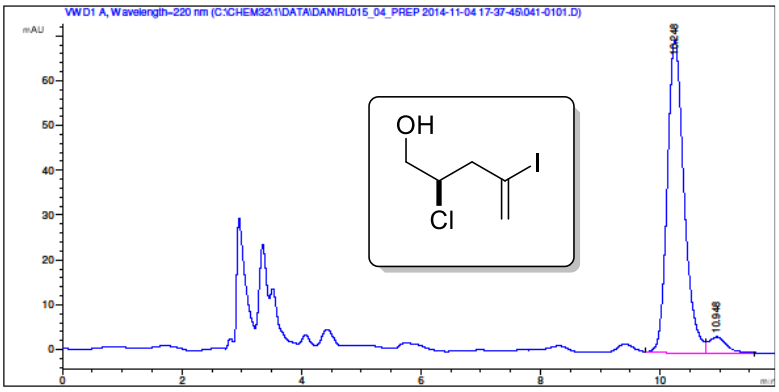


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================================================================================
                          Area Percent Report
================================================================================

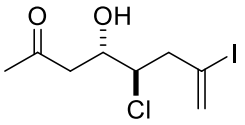
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|-------|
   1  10.248 VV    0.2977 1364.52283   69.89229  94.8703
   2  10.948 VB    0.3100   73.78009    3.54235   5.1297

Totals :                  1438.30292   73.43463
```

2.7.5. Preparation of (*4S*,*5R*)-5-chloro-4-hydroxy-7-iodooct-7-en-2-one (56)



To a cold (-78 °C), stirred solution of DIPA (0.482 mL, 3.44 mmol, distilled over CaH_2) in THF (24 mL) was added *n*BuLi (1.10 mL, 2.91 mmol, 2.63 M in hexanes) and the reaction mixture was warmed to 0 °C and stirred for 15 minutes. The reaction mixture was then cooled to -78 °C, acetone (**51**) (0.194 mL, 2.65 mmol, distilled over K_2CO_3) was added and the resulting mixture was stirred for 30 minutes. α-chloroaldehyde **57** (0.650 g, 2.65 mmol) was then added and the reaction mixture was stirred for an additional 20 minutes at -78 °C, then quenched by the addition of saturated aqueous NH_4Cl solution (15 mL) and diluted with EtAOc (15 mL). The phases were separated and the organic phase was washed with NH_4Cl (30 mL) and H_2O (30 mL). The combined aqueous phases were then washed twice with EtOAc (15 mL). The combined organic phase was washed with brine (50 mL), dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*, giving the crude product as a 7:1 dr mixture of diastereomers. Purification of the crude product by flash chromatography (EtOAc:hexanes, 25:75) afforded the β-ketochlorohydrin **56** (0.512 g, 1.70 mmol, 64%) as a yellow oil, which was stored with a copper wire under an inert atmosphere at -20 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.19 (dt, *J* = 0.9, 1.6 Hz, 1 H), 5.87 (dd, *J* = 1.0, 1.6 Hz, 1 H), 4.17 (m, 1 H), 4.10 (ddd, *J* = 3.3, 6.8, 10.2 Hz, 1 H), 3.34 (d, *J* = 4.78 Hz, 1 H), 3.14 (dddd, *J* = 1.2, 1.6, 3.1, 15.1 Hz, 1 H), 2.92 (dd, *J* = 2.8, 17.9 Hz, 1 H), 2.80 (dd, *J* = 8.4, 17.9 Hz, 1 H), 2.59 (ddd, *J* = 0.8, 9.9, 15.1 Hz, 1 H), 2.24 (s, 1 H).

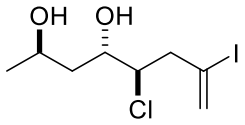
^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.1, 129.4, 105.9, 70.5, 63.0, 63.0, 49.1, 46.1.

HRMS: *m/z* calcd for $C_8H_{12}ClINaO_2$: 324.9463 (M+Na); Found: 324.9463 (M+Na).

IR: 3419.23, 2922.52, 2852.08, 1710.41, 1618.70, 1417.16, 1364.07, 1192.70, 1074.4, 902.64, 706.12, 539.48, 498.33 cm^{-1}.

α_D($CHCl_3$, c 0.196): -1.53

2.7.6. Preparation of (2R,4S,5R)-5-chloro-7-iodooct-7-ene-2,4-diol (60)



To a cold (-40 °C), stirred solution of β-ketochlorohydrin **56** (0.103 g, 0.341 mmol) in MeCN (2 mL) and AcOH (1 mL) was added $[NMe_4]B(OAc)_3H$ (0.360 g, 1.36 mmol) the reaction mixture was stirred at -40 °C for an additional 16 hours treated with saturated aqueous solution of Rochelle's salt (3 mL) and was stirred for an additional 1 hour at room temperature. The reaction mixture was then diluted with EtOAc (5 mL) and the phases were separated. The organic layer was then washed with saturated aqueous $NaHCO_3$ solution (5 mL), H_2O (5 mL), and brine (5 mL), dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*, giving the crude product as a 15:1 mixture of diastereomers. Purification of the crude product by flash chromatography (EtOAc:hexanes, 40:60) afforded the diol **60** (0.072 g, 0.269 mmol, 79%) as a colourless oil which was then stored with copper wire under an inert atmosphere at -20 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.19 (dt, *J* = 1.6, 1.0 Hz, 1 H), 5.87 (dd, *J* = 1.0, 1.6 Hz, 1 H), 4.24 (m, 1 H), 4.20 (ddd, *J* = 3.2, 5.4, 10.2 Hz, 1 H), 4.10 (m, 1 H), 3.04 (ddd, *J* = 0.5, 1.0, 15.0 Hz, 1 H), 3.0 (d, *J* = 5.8 Hz, 1 H), 2.64 (dd, *J* = 0.8, 10.1, 15.1 Hz, 1 H), 1.85 (ddd, *J* = 3.0, 8.6, 14.5 Hz, 1 H), 1.77 (d, *J* = 4.4 Hz, 1 H), 1.68 (ddd, *J* = 2.7, 8.6, 14.5 Hz, 1 H), 1.30 (d, *J* = 6.4 Hz).

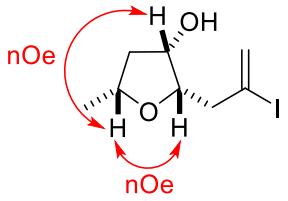
^{13}C NMR (100 MHz, $CDCl_3$) δ: 129.3, 106.5, 71.7, 65.8, 64.7, 48.7, 40.3, 24.1.

HRMS: *m/z* calcd for $C_8H_{14}ClINaO_2$: 326.9619 (M+Na); Found: 326.9619 (M+Na).

IR: 3376, 2966, 2923, 1618, 1489, 1375, 1250, 1118, 901, 702 cm^{-1}.

α_D($CHCl_3$, c 0.8): +2.88

2.7.7. Preparation of (*2S*,*3S*,*5R*)-2-(2-iodoallyl)-5-methyltetrahydrofuran-3-ol (47)



To a vial containing MeOH (3 mL) was added diol **60** (0.068 g, 0.224 mmol) and the vial was sealed in a CEM Discover LabMate microwave reactor. The reaction mixture was heated to 120 °C (as monitored by a vertically focused IR temperature sensor) for 3 hours and then concentrated *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:hexanes, 33:66) afforded tetrahydrofuranol **47** (0.044 g, 0.164 mmol, 72%) as a light yellow solid and was stored under an inert atmosphere at -20 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.23 (q, *J* = 1.36, 1 H), 5.83 (dt, *J* = 0.6, 1.4 Hz, 1 H), 4.29 (tdd, *J* = 2.1, 3.4, 6.5 Hz, 1 H), 3.98 (ddq, *J* = 1.6, 6.3, 6.4 Hz, 1 H), 3.83 (ddd, *J* = 3.5, 6.4, 6.8 Hz, 1 H), 2.83, (ddd, *J* = 0.9, 6.4, 15.2 Hz, 1 H), 2.78 (ddd, *J* = 1.0, 6.8, 14.6 Hz, 1 H), 2.48 (ddd, *J* = 7.8, 6.4, 14.4 Hz, 1 H), 1.52 (ddd, *J* = 2.1, 6.7, 13.9 Hz, 1 H), 1.47 (d, *J* = 6.8 Hz, 1 H), 1.34 (*J* = 6.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 128.2, 106.7, 81.7, 73.9, 73.0, 44.7, 43.4, 22.3.

HRMS: *m/z* calcd for $C_8H_{14}IO_2$: 269.0033 (M+H); Found: 269.0027 (M+H).

IR: 3419, 2970, 2900, 1618, 1393, 1228, 1066, 897 cm^{-1}.

α_D($CHCl_3$, c 0.88): +2.39

Mp: 35-38 °C

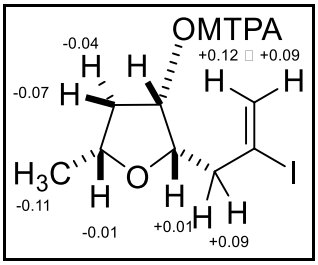
2.7.8. Determination of absolute stereochemistry for (*2S*,*3S*,*5R*)-2-(2-iodoallyl)-5-methyltetrahydrofuran-3-ol (47)

To a stirred solution of tetrahydrofuranol **47** (5.0 mg, 0.0187 mmol) in CH_2Cl_2 (0.4 mL) at room temperature was added (*S*)-(-)-MTPA-OH (6.6 mg, 0.0281 mmol), *N*,*N*'-diisopropylcarbodiimide (0.0088 mL, 0.0562 mmol) and DMAP (catalytic). The reaction mixture was stirred for 16 hrs then the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:pentane, 10:90) afforded the (*S*)-MTPA ester.

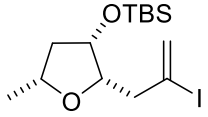
Data for the (*S*)-MTPA ester of **69**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.51 (m, 2H), 7.43 (m, 3H), 6.01 (d, *J* = 1.3 Hz, 1H), 5.75 (m, 1H), 5.38 (ddd, *J* = 2.0, 3.9, 5.8 Hz, 1H), 4.04 (m, 1H), 4.02 (m, 1H), 3.52 (d, *J* = 1.0 Hz, 3H), 2.63 (m, 1H), 2.60 (m, 1H), 1.52 (ddd, *J* = 1.9, 6.4, 12.4 Hz, 1H), 1.15 (d, *J* = 6.2 Hz, 3H)

In an analogous manner, the (*R*)-MTPA ester was prepared using (*R*)-(+)-MTPA-OH.

Data for the (*R*)-MTPA ester of **70**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (m, 2H), 7.43 (m, 3H), 5.89 (d, *J* = 1.4 Hz, 1H), 5.66 (m, 1H), 5.38 (ddd, *J* = 1.9, 3.75, 5.7 Hz, 1H), 4.03 (m, 2H), 3.57 (d, *J* = 1.3 Hz, 3H), 2.64 (m, 1H), 2.54 (d, *J* = 6.2 Hz, 2H), 1.59 (ddd, *J* = 2.0, 6.7, 14.5 Hz, 1H), 1.26 (d, *J* = 6.1 Hz, 3H)



2.7.9. Preparation of *tert*-butyl(((*2S*,*3S*,*5R*)-2-(2-iodoallyl)-5-methyltetrahydrofuran-3-yl)oxy)dimethylsilane (61)



To a cold (0 °C), stirred solution of tetrahydrofuranol **47** (67 mg, 0.25 mmol) in CH_2Cl_2 (1 mL) was added imidazole (25 mg, 0.38 mmol) followed by TBSCl (41 mg, 0.28 mmol) and the reaction mixture was stirred at 0 °C for an additional 16 hrs and then treated with H_2O (1 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 1 mL), brine (1 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. This afforded the protected tetrahydrofuran **61** (79 mg, 0.21 mmol, 83%) which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.17 (ddd, *J* = 1.6, 1.6, 1.6 Hz, 1H), 5.79 (m, 1H), 4.28 (ddd, *J* = 3.3, 4.5, 7.8 Hz, 1H), 4.00 (m, 1H), 3.91 (ddd, *J* = 4.6, 7.5, 7.5 Hz, 1H), 2.67 (m, 2H), 2.32 (ddd, *J* = 6.1, 7.4, 13.1 Hz, 1H), 1.51 (ddd, *J* = 3.3, 6.6, 13.1 Hz, 1H), 1.30 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

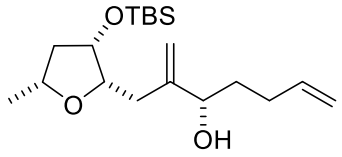
^{13}C NMR (100 MHz, $CDCl_3$) δ: 127.3, 108.5, 81.3, 73.8, 73.3, 46.0, 43.3, 25.8, 22.2, 18.1.

HRMS: *m/z* calcd for $C_{14}H_{28}IO_2Si$: 383.0898 (M+H); Found: 383.0892 (M+H).

IR: 2955, 2929, 2857, 1620, 1472, 1369, 1254, 1111, 1089 cm^{-1}.

α_D($CHCl_3$, c 2.0): +0.2

2.7.10. Preparation of (S)-2-(((2S,3S,5R)-3-((tert-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)methyl)hepta-1,6-dien-3-ol (63)



To a stirred solution of tetrahydrofuran **61** (7.7 mg, 0.02 mmol) and aldehyde **62** (1.5 mg, 0.017 mmol) in DMF (0.3 mL) at room temperature was added $CrCl_2$ (9.3 mg, 0.076 mmol) and $NiCl_2$ (0.093 mg, 0.00076 mmol) and the reaction mixture was stirred at room temperature for an additional 16 hours and then treated with saturated aqueous

NH_4Cl solution (0.5 mL), diluted with EtOAc (1.5 mL) and the phases were separated. The organic phase was washed with H_2O (1 mL). The combined aqueous phases were then washed with EtOAc (5 x 1 mL) and the combined organic phases were washed with brine (2 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to afford the crude mixture as a 4:1 mixture of diastereomers. Purification of the crude product by flash chromatography (EtOAc:pentane, 20:80) afforded the tetrahydrofuran **63** (4 mg, 0.012 mmol, 71%) as a light yellow oil and single diastereomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.84 (ddt, *J* = 6.5, 10.1, 17.1 Hz, 1H), 5.05 (s, 1H), 5.02 (ddt, *J* = 1.6, 2.0, 17.2 Hz, 1H), 4.95 (m, 1H), 4.94 (m, 1H), 4.27 (ddd, *J* = 3.3, 4.3, 7.6 Hz, 1H), 4.13-3.95 (m, 3H), 3.74 (ddd, *J* = 2.8, 4.4, 10.4 Hz, 1H), 2.51 (dd, *J* = 10.3, 14.5 Hz, 1H), 2.29 (ddd, *J* = 6.0, 7.4, 13.2 Hz 1H), 2.17 (dd, *J* = 2.5, 14.5 Hz, 1H), 2.14-2.00 (m, 2H), 1.71 (m, 1H), 1.59 (m, 1 H), 1.55 (m, 1 H), 1.31 (d, *J* = 6.3 Hz, 3 H), 0.9 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H).

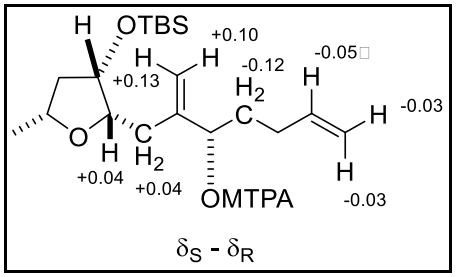
2.7.11. Determination of absolute stereochemistry for (*2S*,*3S*,*5R*)-2-(2-iodoallyl)-5-methyltetrahydrofuran-3-ol (63)

To a stirred solution of tetrahydrofuranol **63** (2 mg, 0.006 mmol) in CH_2Cl_2 (0.2 mL) at room temperature was added (*R*)-(+)-MTPA-OH (2.1 mg, .009 mmol), *N*,*N*'-diisopropylcarbodiimide (0.00276 mL, 0.018 mmol) and dimethylaminopyridine (catalytic). The reaction mixture was stirred for 16 hrs then the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:pentane, 5:95) afforded the (*R*)-MTPA ester (**71**).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (m, 2H), 7.38 (m, 3H), 5.78 (m, 1H), 5.40 (t, *J* = 6.3 Hz, 1H), 5.05 (m, 1H), 5.03 (br s, 1H), 5.00 (m, 1H), 4.98 (m, 1 H), 4.18 (m, 1H), 3.91 (m, 1H), 3.77 (dt, *J* = 4.1, 6.2 Hz, 1H), 3.55 (d, *J* = 1.0, 3H), 2.32 (d, *J* = 6.4 Hz, 1 H), 2.30 (m, 1 H), 2.27 (m, 1H), 2.08 (m, 2H), 1.85 (m, 2H), 1.47 (ddd, *J* = 3.1, 6.7, 13.2 Hz, 1 H), 1.27 (d, *J* = 6.2 Hz), 0.89 (s, 9H), 0.03 (d, *J* = 12 Hz, 6H).

In an analogous manner, the (*S*)-MTPA ester (**72**) was prepared using (*S*)-(-)-MTPA-OH.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (m, 2H), 7.38 (m, 3H), 5.72 (m, 1H), 5.45 (dd, *J* = 5.4, 7.4 Hz, 1H), 5.17 (br s, 1H), 5.13 (d, *J* = 1.25 Hz, 1H), 4.97 (m, 1H), 4.94 (m, 1 H), 4.23 (m, 1H), 3.93 (m, 1H), 3.80 (dt, *J* = 4.6, 9.0 Hz, 1H), 3.54 (d, *J* = 1.1 Hz, 3 H), 2.36 (m, 2H), 2.27 (m, 1H), 2.11-1.89 (m, 2H), 1.87-1.68 (m, 2 H), 1.48 (ddd, *J* = 3.1, 6.7, 13.0 Hz, 1 H), 1.28 (d, *J* = 6.2 Hz), 0.88 (s, 9H), 0.03 (d, *J* = 12.3 Hz, 6H).



Chapter 3.

Studies Towards the Total Synthesis of Biselide A

3.1. Haterumalide and Biselide Family of Chlorinated Marine Macrocyclic Polyketides

3.1.1. Isolation and Biological Activity of Haterumalides and Biselides

The haterumalides are a family of macrocyclic polyketides that have been isolated from a number of organisms. Members of the haterumalide family (haterumalides NA (**73**), B (**74**), NB (**75**), NC (**76**), ND (**77**) and NE (**78**)) (Figure 3.1), isolated from the Okinawan ascidian *Lissoclinium sp.* and Okinawan sea sponge *Ircinia sp.,* were first reported in 1999.[47,48] Soon afterwards, the isolation of haterumalide NA (**73**) from two strains of bacteria *Serratia marcencens*[49] and *Serratia liquefaciens*[50] was reported in 1999 and 2005, respectively. Interestingly, the differences in reported optical rotations between isolated haterumalide NA from the bacterial species and those from the isolated metabolite of the sea sponge have raised questions regarding its absolute stereochemistry.[7] The isolation of other members of the haterumalides, including haterumalides B (**74**), and NE (**75**) from *Serratia plymuthica,* have also been disclosed.[50–53]

Structurally, members of the haterumalide family of natural products all contain a characteristic macrocyclic core with the same stereochemistry, olefination pattern and oxidation at C3, C4, C8, C15 and C19. One notable difference among the members of the haterumalide family is oxidation at C9; only haterumalides NC (**76**) and ND (**77**) are oxidized at this position. Furthermore, members of the haterumalide family possess different functional groups at C19. Thus, while haterumalides NA (**73**), ND (**77**) and NE

(**78**) contain carboxylic acids, haterumalides NB (**75**), NC (**76**), and B (**74**) contain two different esters. With respect to absolute stereochemistry, the initial stereochemical assignment of haterumalide NA by Takada was revised by Kigoshi and coworkers following total synthesis of the methyl ester derivative of *ent*-haterumalide NA. Specifically, they reported the stereochemical revision based on comparisons of optical rotations derived from the CD spectrums of the natural and synthetic samples.[47,54]

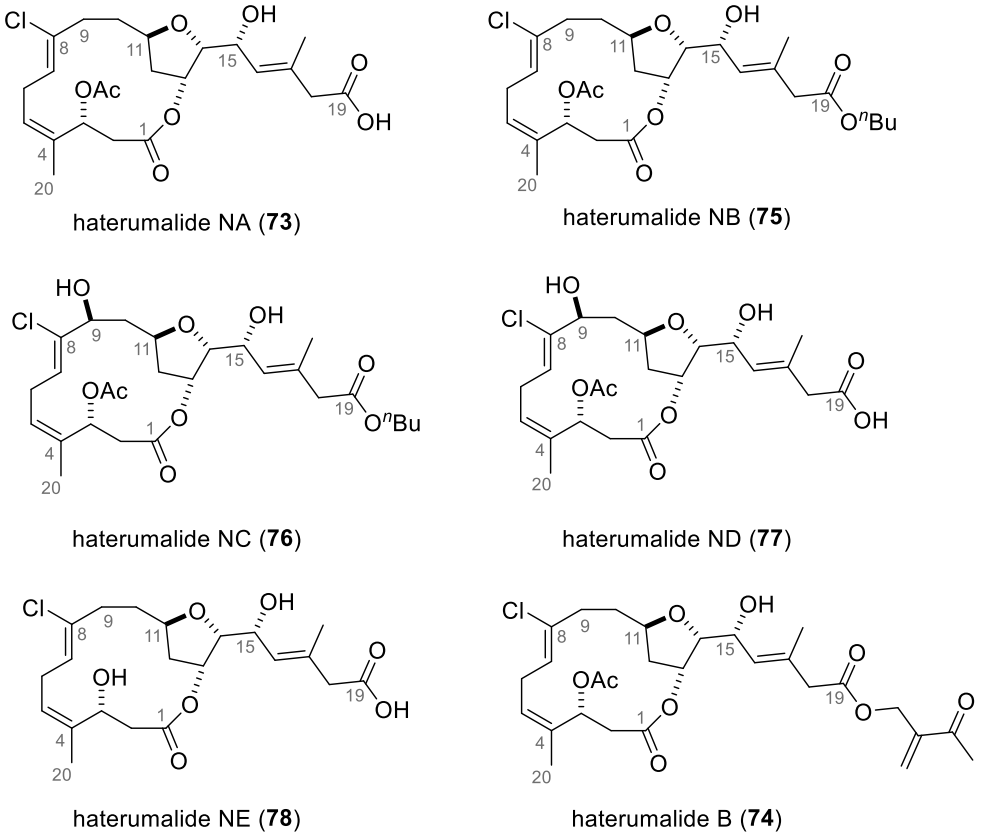


Figure 3.1 Structures of the members of the haterumalide family of macrocyclic polyketides.

Interest in the total syntheses of haterumalides stems from the significant cytotoxicity that haterumalide NA (**73**) displayed against various cancer cell lines, including activity against BT-20 breast cancer cells (IC_{50} = 0.2 µg/mL), MCF-7 breast cancer cells (IC_{50} = 0.42 µg/mL), and P388 leukemia cells (IC_{50} = 0.32 µg/mL).[47,49] Further studies by Kigoshi indicated that haterumalide NA methyl ester (**79**) shows cytotoxicity that is comparable to currently used chemotherapeutic treatments (Table

3-1).[55] However, its toxicity against normal mammary cells (IC_{50} = 0.6 µg/mL), mice (LD_{99} = 0.24 g/kg) and brine shrimp (LD_{50} = 0.6 µg/mL) limits its potential as a pharmaceutical lead due to the lack of cancer specificity and potential toxicity towards humans.[49]

In 2004, two congeners of the haterumalide family were reported: biselides A (**80**) and B (**81**). These marine macrolides possess a very similar structural core to that of the haterumalides and were isolated from an Okinawan ascidian *Didemnidae sp.*[56] In the following year, the isolation of three additional members of the biselide family: biselides C (**82**), D (**83**), and E (**84**) was reported (Figure 3.2). Notably, biselides A-C (**80**, **81**, and **82**) include an additional oxidized carbon at C20 while biselide D (**83**) incorporates an amide linkage at C19. The most structurally distinct of these new compounds is biselide E (**84**), which possesses a linear carbon skeleton rather than the characteristic macrocycle found in other members of the haterumalides and biselides.

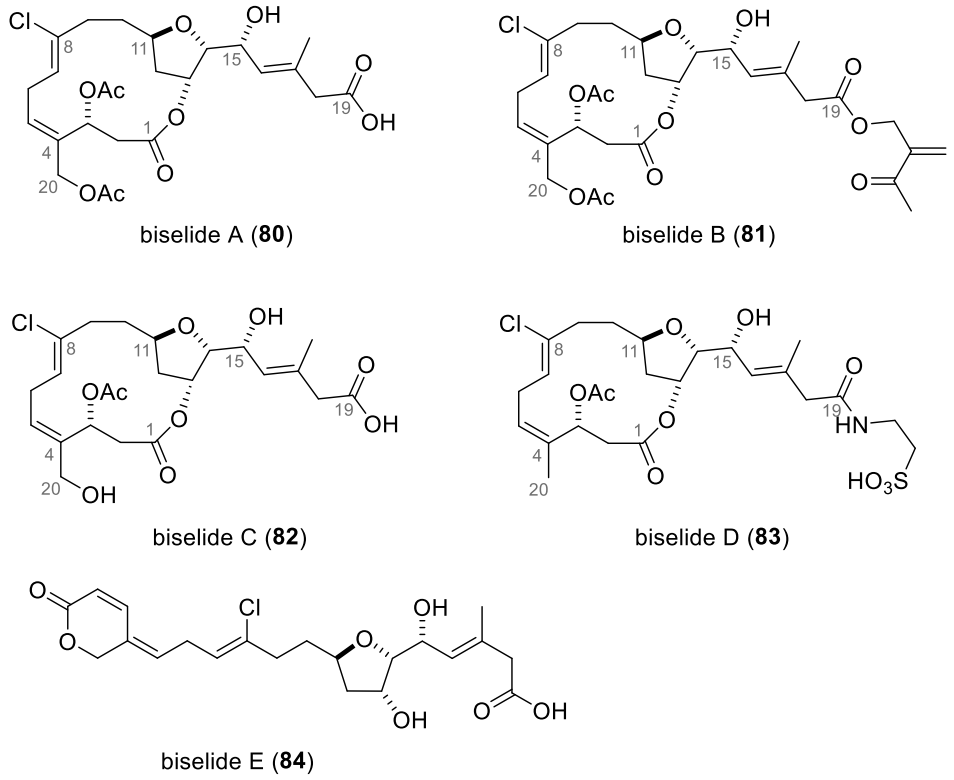


Figure 3.2. Structures of the members of the biselide family of macrocyclic polyketides.

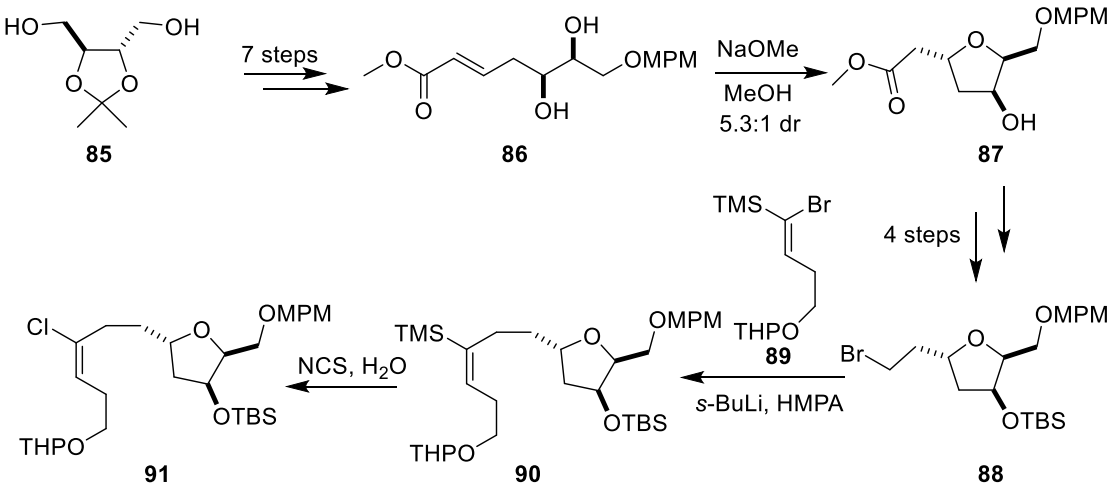
Several members of the biselide family have shown potent and potentially useful biological activity. While sufficient quantities of biselides B (**81**), D (**83**), and E (**84**) could not be obtained for detailed biological analysis, biselides A (**80**) and C (**82**) showed significant cytotoxicity towards various cancer cell lines. Notably, biselide A (**80**) possesses activity comparable to commercially available chemotherapeutic drugs (Table 3-1).[55] Furthermore, biselide A (**80**) displayed potent cytotoxicity against DLD-1 colon cancer line (IC_{50} of 0.513 μM), PC-3 prostate cancer line (IC_{50} of 2.07 μM) and A498 renal cancer line (IC_{50} of 1.79 μM). Interestingly, unlike haterumalide NA methyl ester (**79**), biselides A (**80**) and C (**82**) do not show cytotoxicity towards brine shrimp at concentrations up to 50 μg/mL.[55] Despite this promising preliminary biological data, owing to the very limited amounts of biselides available from the natural source, further pharmacological development of biselides A and C will ultimately rely on material accessed through total synthesis efforts.[57,58]

Table 3-1 Comparison of IC_{50} values between biselides A, C, haterumalide NA methyl ester and conventional chemotherapeutic drugs.

Cell Line	Biselide A (80) *(μM)*	Biselide C (82) *(μM)*	Haterumalide NA methyl ester (79) *(μM)*	Cisplatin *(μM)*	*Doxorubicin (μM)*
MDA-MB-231 (Breast Cancer)	3.72	25.5	0.406	4.83	0.186
HOP18 (Lung Cancer)	9.35	82.7	0.739	4.08	0.159
NCI-H460 (Lung Cancer)	3.53	18.0	0.135	0.600	0.00823
A498 (Renal Cancer)	1.79	16.3	0.335	4.01	0.166
PC-3 (Prostate Cancer)	2.07	18.2	0.539	4.01	0.357
DLD-1 (Colon Cancer)	0.513	17.1	0.141	2.11	0.190
P388 (Leukemia)	3.72	21.2	0.408	0.0754	0.0252
P388/ADR (Leukemia)	7.78	35.6	0.621	0.271	5.79
Mean	3.97	27.9	0.402	2.47	0.772

3.1.2. Previous Total Syntheses of Members of the Haterumalide Family

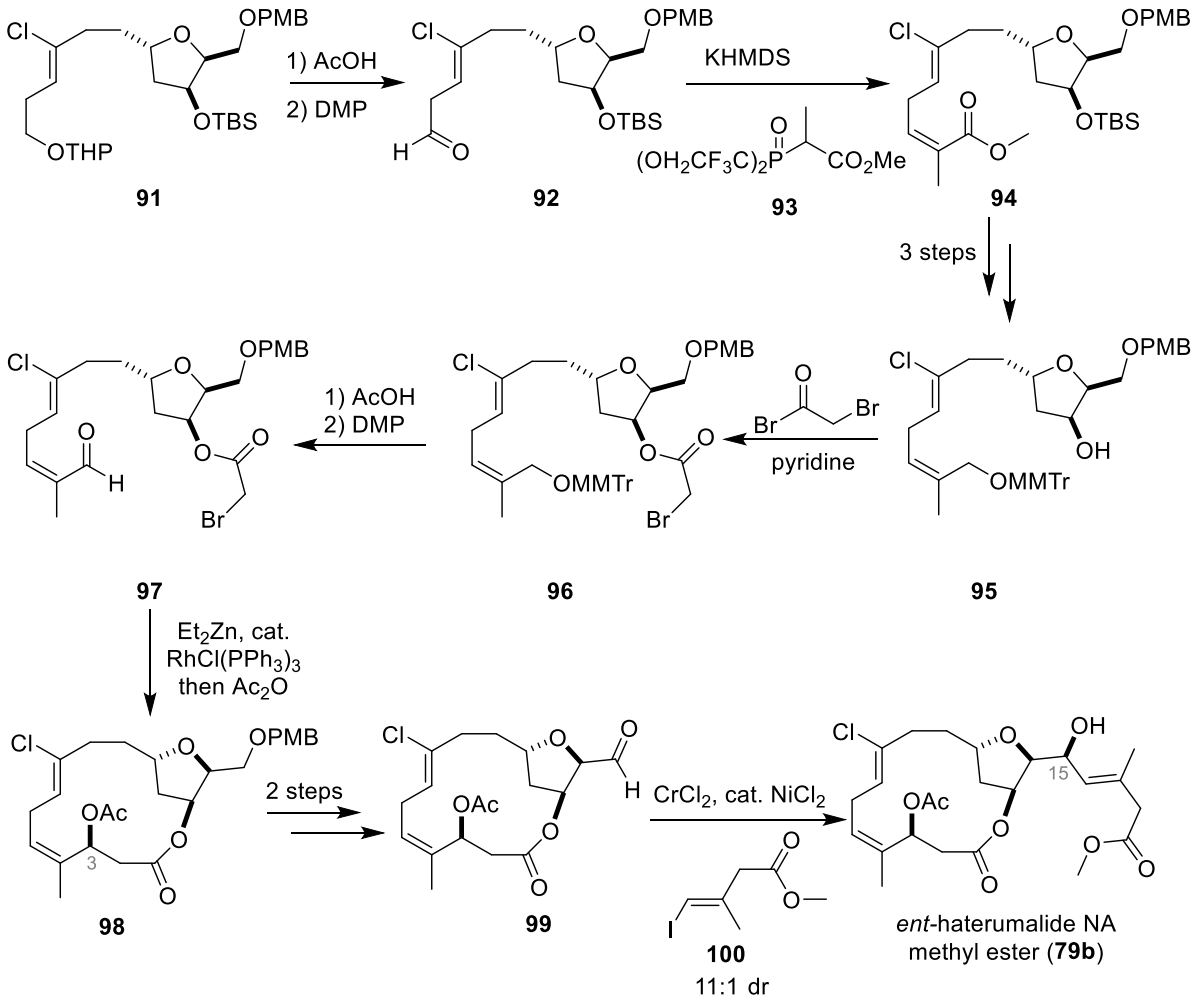
The first efforts toward the total synthesis of a member of the haterumalide family of natural products was undertaken by Kigoshi and coworkers in 2003[54] and directed towards the synthesis of the originally assigned structure of haterumalide NA. Critically, this work led to the reassignment of the absolute stereochemistry of haterumalide NA through the synthesis of *ent*-haterumalide NA methyl ester (**79b**) though ultimately did not provide access to the natural product *ent*-haterumalide NA (**73b**). Strategically, the synthesis involved an intramolecular Reformatsky reaction to construct the macrocycle. As shown in Scheme 3.1, synthesis of the THF ring began with (+)-2,3-*O*-isopropylidene-L-threitol (**85**), which was converted into diol **86** in 7 steps. Diol **86** then underwent an intramolecular oxa-Michael addition to provide tetrahydrofuran **87**, which was further elaborated into bromide **88** in 4 steps. Bromide **88** was then coupled to alkenyl bromide **89** (prepared in 4 steps), affording vinyl silane **90**, which underwent stereoselective halogenation to yield vinyl chloride **91**.[59]



Scheme 3.1. Synthesis of the tetrahydrofuran 91 of *ent*-haterumalide NA methyl ester (79b).

Removal of the THP protecting group and oxidation of the resulting alcohol afforded aldehyde **92**, which was subjected to a Still-Genari modified Horner-Wadsworth-Emmons reaction[60] to afford the *Z*-alkene methyl ester **94**. Tetrahydrofuranol **95**, accessed in 3 steps, underwent esterification with bromoacetyl bromide, affording

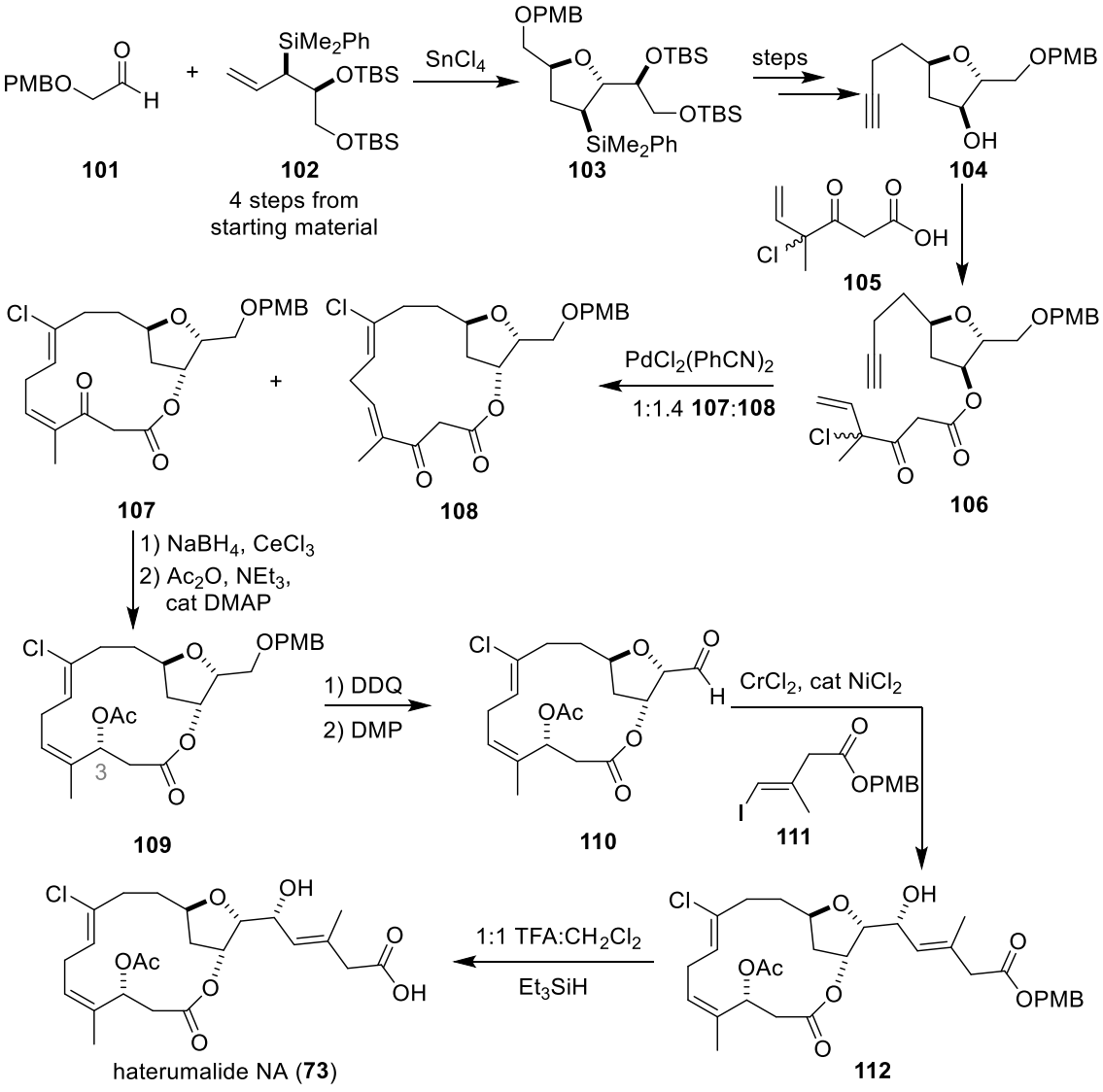
bromo ester **96**. Deprotection of the 4-monomethoxytrityl group and oxidation to aldehyde **97** set the stage for the key Reformatsky-type macrocyclization. Under conditions previously described by Honda,[61] addition of acetic anhydride effectively trapped the β-lactone intermediate, which would normally decompose upon work up, yielding macrocycle **98**, completing the synthesis of the macrocyclic core of haterumalide NA (**73**). However, this macrocyclization yielded a 5:1 diastereomeric ratio of products in favour of the wrong configurational isomer at C3. Deprotection and oxidation then yielded coupling partner **99**, which underwent a NHK reaction[20,21] with the vinyl iodide **100** completing the total synthesis of *ent*-haterumalide NA methyl ester (**79b**). The diastereoselectivity observed in the NHK reaction was attributed to chelation between chromium, the endocyclic oxygen atom present on the THF, and the aldehyde oxygen, facilitating the addition of **100** from the β–face of intermediate **99**. Unfortunately, all attempts at hydrolysis of the methyl ester to obtain *ent*-haterumalide NA (**79b**) failed. The final product, while having the same spectral properties of that of the natural product, had the opposite sign in the CD spectrum (δε -0.72 for the synthetic haterumalide NA methyl ester versus δε +0.62 for the natural haterumalide NA methyl ester). Synthesis of the (*R*)- and (*S*)-MTPA esters of *ent*-haterumalide NA methyl ester (**79b**) using the Mosher's method proved vital in assigning the absolute stereochemistry at the C15 stereocentre and consequently that of the natural product (Scheme 3.2).[54]



Scheme 3.2. Kigoshi's synthesis of *ent*-haterumalide NA methyl ester (79b).

In 2005, Hoye and Wang reported the first total synthesis of haterumalide NA (**73**) (Scheme 3.3).[62] This total synthesis utilized a Kaneda chloroallylation strategy[63] in order to close the macrocycle and introduce the vinyl chloride function. Employing the Roush THF synthesis,[19] Hoye and Wang began with aldehyde **101** and allyl silane **102**, which underwent a [3+2] annulation reaction to form the THF **103** that was subsequently converted into tetrahydrofuranol **104**. Coupling chloroacid **105** to the hydroxyl group of tetrahydrofuranol **104** allowed access to the macrocyclization precursor. Slow addition of the THF **106** to a mixture of $PdCl_2(PhCN)_2$ in THF promoted macrocyclization via coupling of the alkyne function to the alkyl chloride, forming a 1:1.4 mixture of geometric isomers **107**:**108**. Luche reduction of macrocycle **107** proceeded with exceptional

diastereoselectivity to provide the desired alcohol, which was acetylated to give macrocycle **109**. Oxidative cleavage of the PMB ether followed by oxidation of the primary alcohol then provided aldehyde **110**. Hoye and Wang also found that the methyl ester could not be hydrolyzed following the NHK reaction so instead employed the corresponding PMB ester **111**, which could be cleanly hydrolyzed following NHK reaction to complete the first synthesis of haterumalide NA (**73**).



Scheme 3.3. Hoye and Wang's total synthesis of haterumalide NA (73) featuring a Kaneda chloroallylation macrocyclization.

Other strategies directed towards the macrocyclic core of the haterumalides are summarized in Figure 3.3. Borhan and Schomaker utilized a chromium-mediated macrocyclization to form the macrocyclic core of haterumalide NC (**76**).[64] A more popular strategy of macrolactonization was first utilized by Snider and Gu in their synthesis of *ent*-haterumalide NA methyl ester (**79b**), who also noted that a TBS ether at C3 was essential for macrolactone formation under Yamaguchi macrolactonization conditions.[65] This strategy was later used by Kigoshi[66] and Roulland[67] in their respective syntheses of haterumalide NA (**73**).

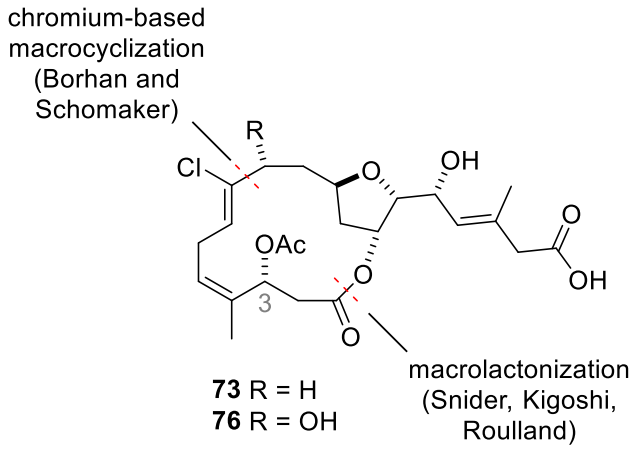


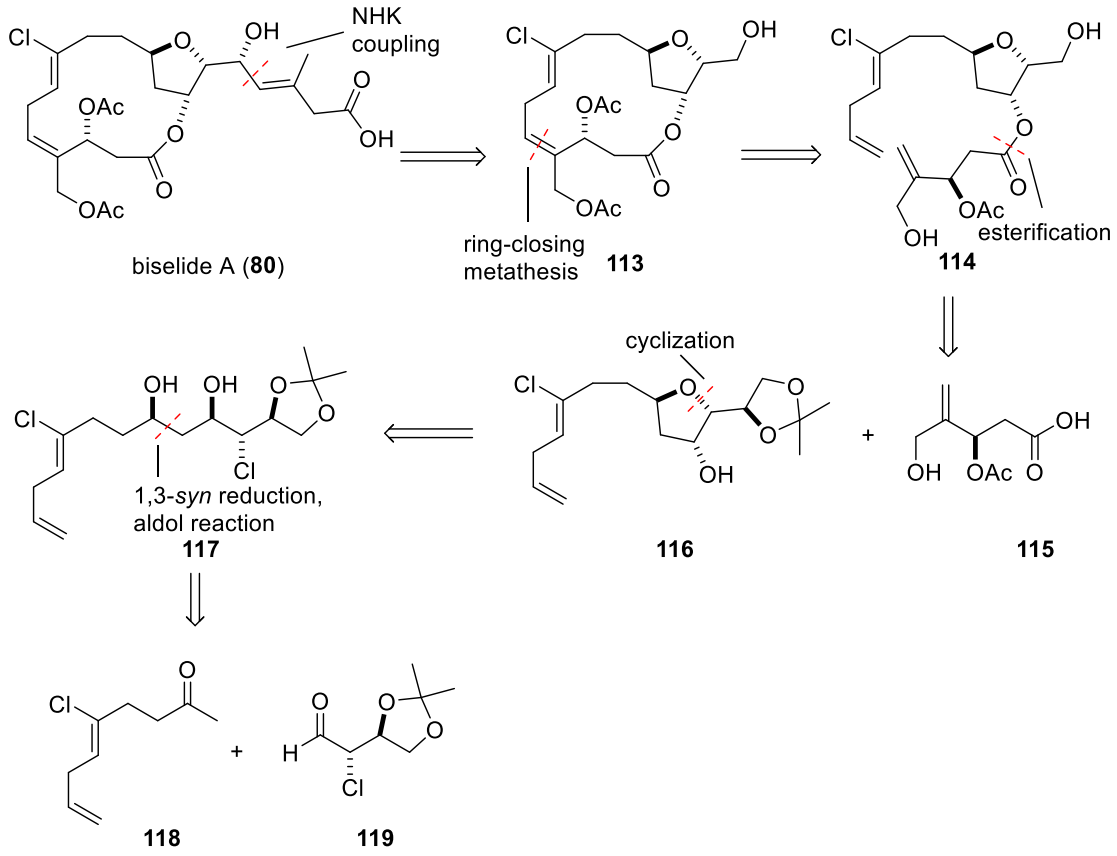
Figure 3.3. Other macrocyclization strategies used in previous total syntheses of haterumalides.

3.2. Previous Strategies Towards the Total Synthesis of Biselide A in the Britton Group

3.2.1. A Ring-Closing Metathesis-based Strategy Towards the Synthesis of Biselide A

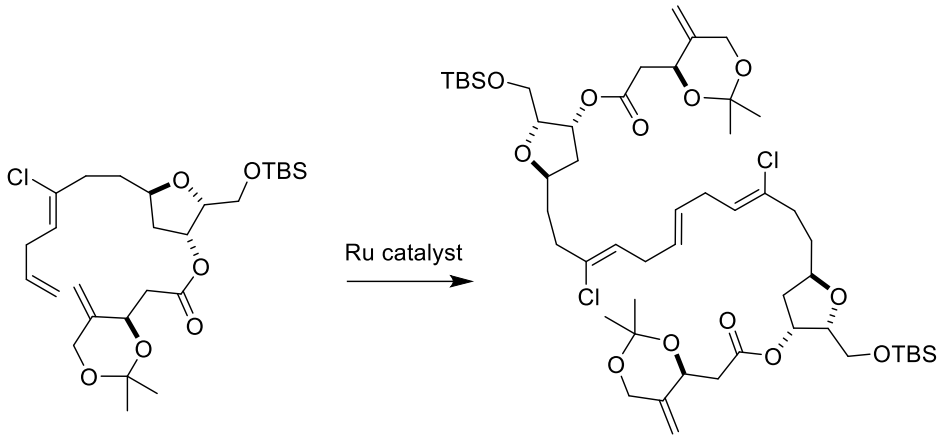
The synthesis of biselide A (**80**) has previously been studied in the Britton group by Dr. Baldip Kang, Hope Fan and Matthew Taron. Dr. Baldip Kang investigated a ring-closing metathesis strategy for the formation of the macrocycle. The synthesis of the

THF intermediate relied on the aforementioned chlorohydrin-cyclization methodology (Scheme 3.4).[68]



Scheme 3.4. A ring-closing metathesis and chlorohydrin-based strategy towards the synthesis of biselide A (80).

Unfortunately, complications arising from intermolecular dimerization complicated the ring-closing metathesis reaction and ultimately led to the abandonment of this route (Scheme 3.5).[68]

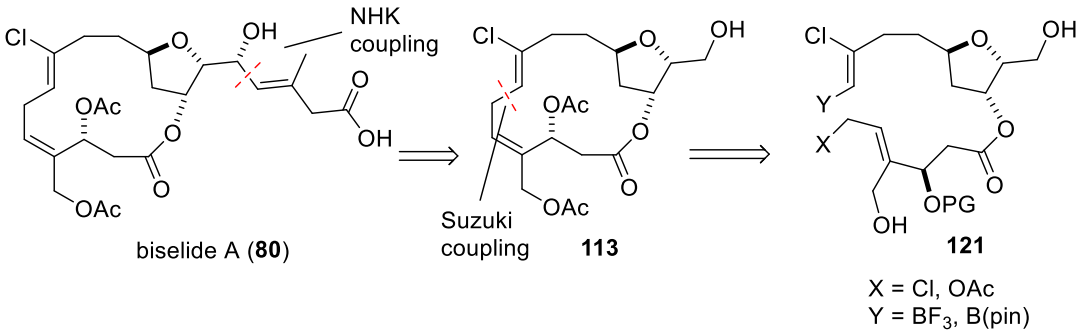


114 **120**

Scheme 3.5. Attempted ring-closing metathesis resulted only in intermolecular dimerization.

3.2.2. A Suzuki Coupling-based Strategy Towards the Synthesis of Biselide A

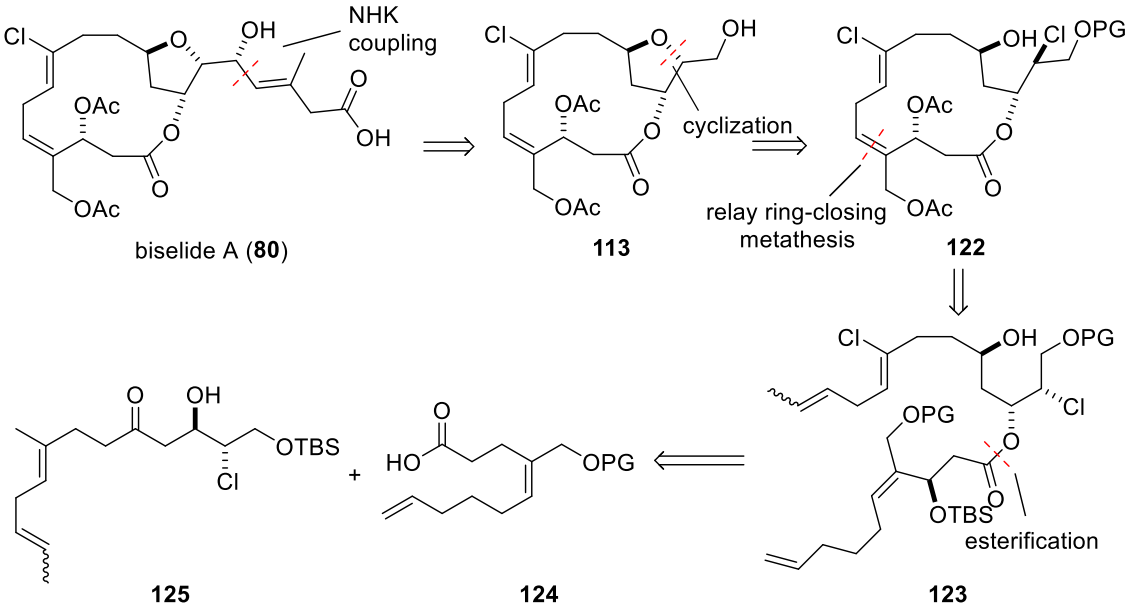
A second strategy investigated by Dr. Baldip Kang relied on a Suzuki coupling reaction[69] between a vinyl trifluoroborate or vinyl dioxaborole with an allyl chloride or acetate to create the macrocyclic structure of biselide A (**80**) (Scheme 3.6).[68] Unfortunately, initial experiments showed only decomposition of the starting material.



Scheme 3.6. A Suzuki coupling-based strategy towards the macrocyclization of biselide A (80).

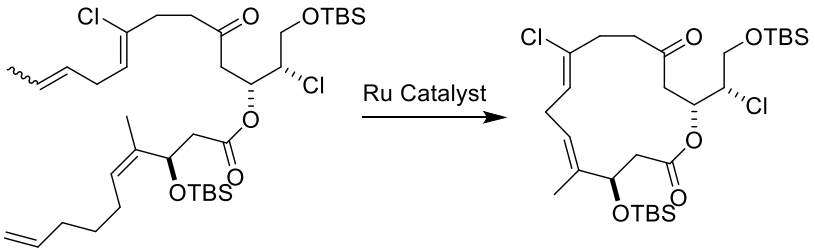
3.2.3. A Relay Ring-Closing Metathesis-based Strategy Towards the Synthesis of Biselide A

The continuation of the synthesis of biselide A (**80**) was led by Hope Fan. A revised strategy was inspired by studies from Hoye, whose relay ring-closing metathesis reaction was employed effectively in the synthesis of haterumalide NA and indicated that the removal of the THF ring may provide flexibility in the carbocyclic backbone and allow macrocyclization to occur.[62,70] To test this theory, Hope Fan initially investigated a model ring-closing metathesis and found that the lack of reactivity of the disubstituted alkene and strain from the formation of these macrocycles were significant factors preventing ring-closing metathesis.[71] In light of this, a revised strategy was envisioned whereby a relay ring-closing metathesis would provide access to an expanded macrocycle prior to THF formation (Scheme 3.7).



Scheme 3.7. Relay ring-closing metathesis-based strategy towards the macrocyclization of biselide A (80).

Unfortunately, the major product from the relay ring-closing metathesis on a model substrate was the undesired (*E*)-alkene, which precluded application of this strategy in a synthesis of biselide A (**80**) (Scheme 3.8).[71]

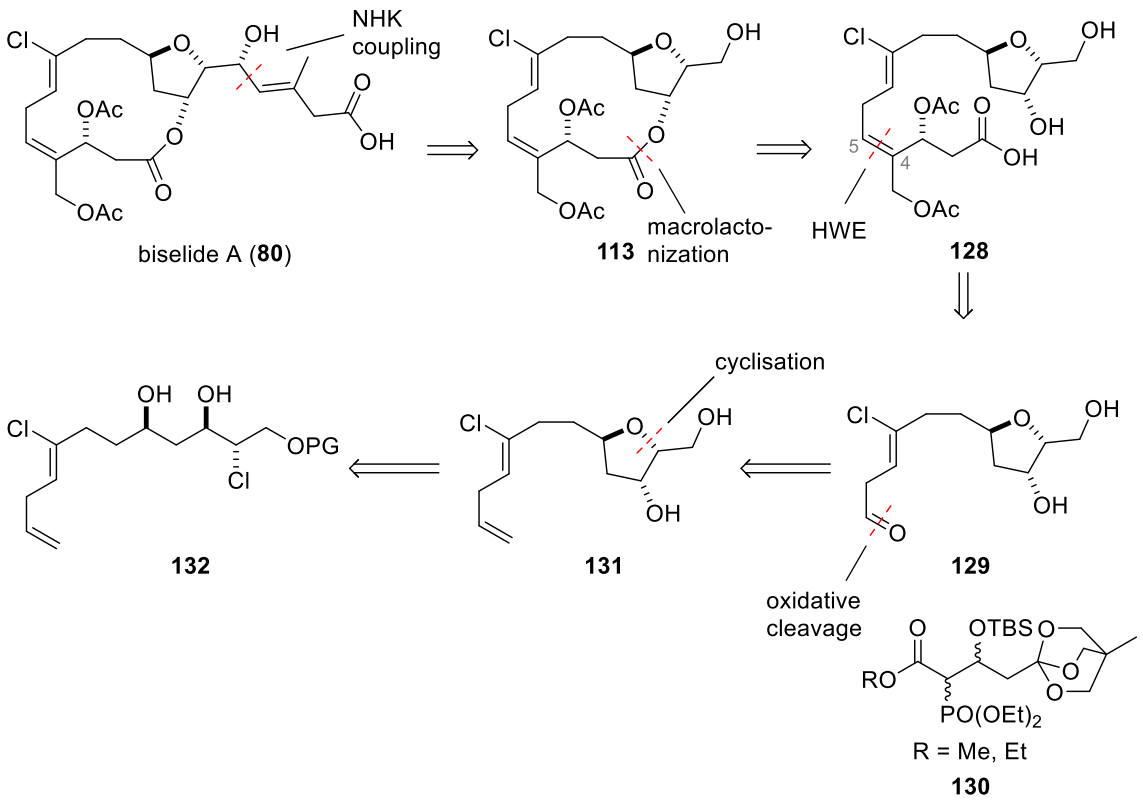


126 **127**

Scheme 3.8. The relay ring-closing metathesis reaction resulting in the wrong geometric isomer.

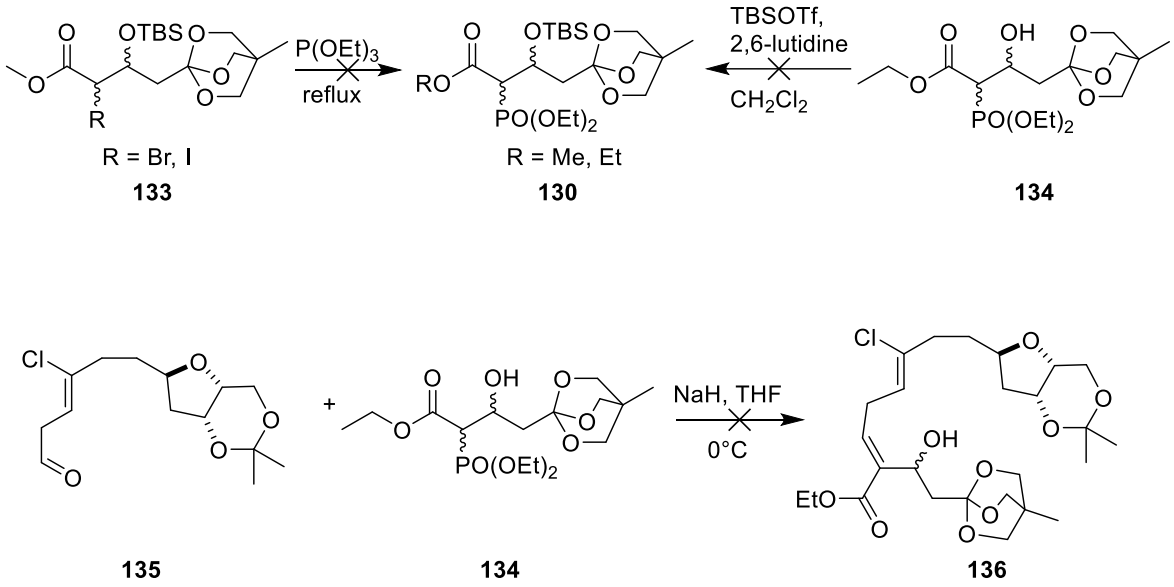
3.2.4. A Horner-Wadsworth-Emmons Reaction and Macrolactonization-based Strategy Towards the Synthesis of Biselide A

Moving away from ring-closing metathesis as a solution to macrocyclization, the next synthetic strategy attempted by Matthew Taron involved macrolactonization and would exploit a Horner-Wadsworth-Emmons (HWE) reaction[72,73] to install the C4-C5 alkene (Scheme 3.9).



Scheme 3.9. A Horner-Wadsworth-Emmons and macrolactonization-based strategy towards the synthesis of biselide A (80).

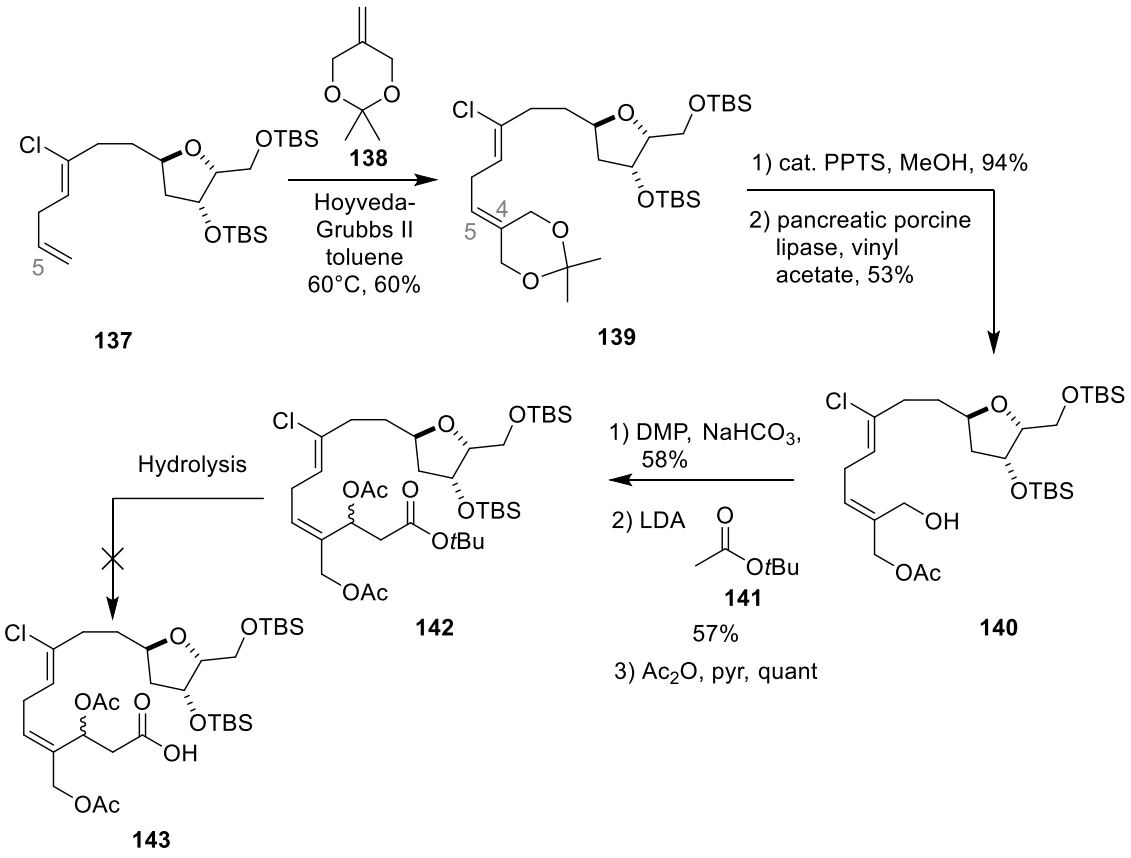
Unfortunately, all attempts to access phosphonate **130** failed due to challenges associated with the synthesis of phosphonates **133** and **134**. Moreover, an attempt to employ phosphonate **134** with a free hydroxyl group in the HWE reaction resulted primarily in decomposition through elimination of the phosphonate (Scheme 3.10).[74]



Scheme 3.10. Failure to access the TBS-protected phosphonate 130 and Horner-Wadsworth-Emmons attempt with phosphonate 134.

3.2.5. A Cross Metathesis and Macrolactonization-based Strategy Towards the Synthesis of Biselide A

Building on the lessons learned in previous routes to the haterumalide/biselide natural products, a revised strategy was investigated by Hope Fan and Matthew Taron that involved a cross-metathesis to access the macrolactone precursor of biselide A (i.e., **128**). Here, they found that the cross metathesis of acetonide-protected olefin **138** with alkene **137** permitted access the desired C4-C5 alkene and yielded tetrahydrofuranol **139** (Scheme 3.11).[71,74] Cleavage of the acetonide and regioselective enzymatic acetylation, using conditions reported by Imai and coworkers,[75] allowed access to acetate **140** in 53% yield. Oxidation, followed by an aldol reaction using the lithium enolate derived from *tert*-butyl acetate (**141**) and acetylation furnished *tert*-butyl ester **142**. However, efforts to access the carboxylic acid **143** by hydrolysis of the ester were unsuccessful. To take advantage of the successful aspects of this work, further efforts would focus on developing a strategy that permits access to the *seco* acid and exploration of the macrolactonization.

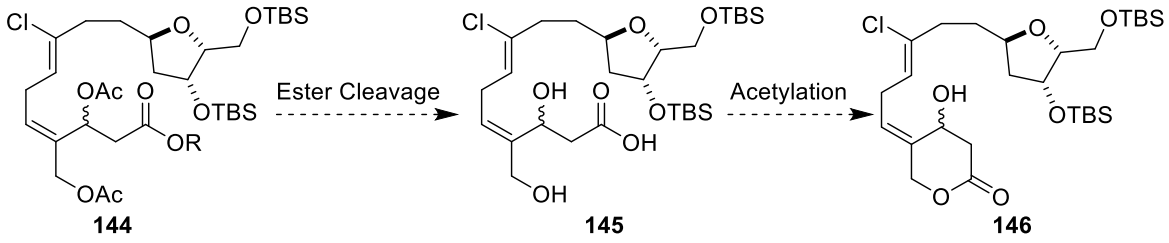


Scheme 3.11. Synthesis of intermediate 142 utilizing a cross metathesis approach to biselide A (80).

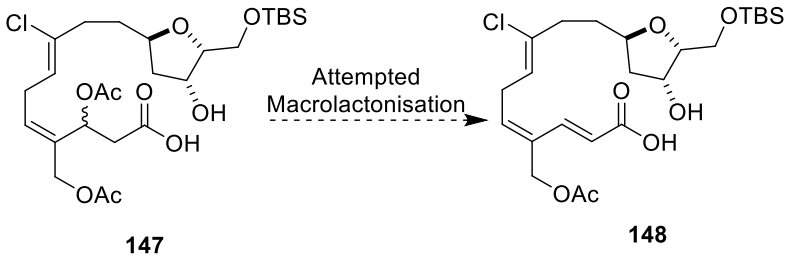
3.3. Revised Macrolactonization Strategy for the Synthesis of Biselide A

Considering our results from several generations of unsuccessful synthetic approaches to haterumalides and biselides, there are two major hurdles complicating a macrolactonization-based synthesis of biselide A (**80**). Namely, i) the identification of an acid protecting group that could be removed under sufficiently mild conditions that avoids hydrolysis of the acetate groups; and ii) identification of conditions that promote macrolactonization without effecting elimination of the β-acetoxy group. (Scheme 3.12). This latter point is particularly concerning considering that the most common macrolactonizations involve high temperatures and/or strongly basic reaction conditions (*e.g.*, Yamaguchi macrolactonization with DMAP and triethylamine at reflux temperatures) (Scheme 3.13). Indeed, Kigoshi was unable to effect macrolactonization

of a β-acetoxy-containing *seco* acid due to competing decomposition[54] and Snider has speculated that this decomposition is in part related to elimination of the β-acetoxy group[65]. While there are methods for macrolactonization that rely on acidic or mildly basic reaction conditions, this requirement significantly limits the number of conditions that could be explored in a synthesis of biselide A.



Scheme 3.12. Hydrolysis of the ester and acetates and subsequent formation of a six-membered lactone.



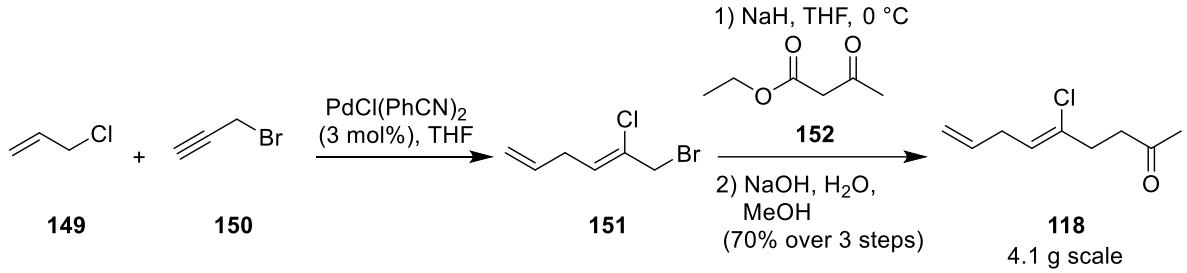
Scheme 3.13. Possible elimination of the β-acetoxy group under basic conditions.

3.3.1. Optimization and Scale-Up of the Synthetic Route to Aldehyde 163

Work up to the synthesis of tetrahydrofuranol **137** was completed by Dr. Baldip Kang, Hope Fan and Matthew Taron

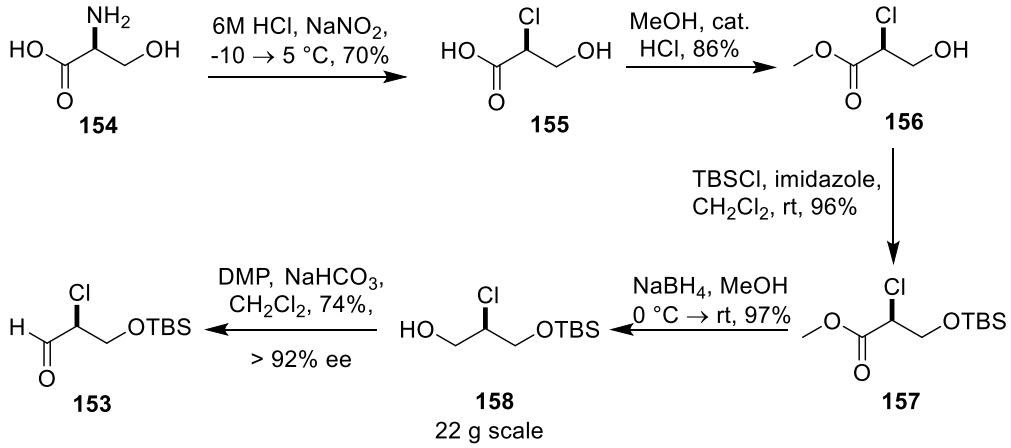
Our efforts began with the adaptation of previous synthetic routes to biselide A. Specifically, to support detailed investigation of macrolactonization strategies, it was necessary to scale up the previously reported synthesis. Towards this goal, methyl ketone **118** was accessed on gram-scale (Scheme 3.14)[68,76] through coupling propargyl bromide (**150**) with allyl chloride (**149**) under Kaneda chloroallylation conditions[63] to give the vinyl chloride **151**. This later material was then was used to alkylate

ethylacetoacetate (**152**). Subsequent hydrolysis of the ethyl ester and decarboxylation generated the methyl ketone **118** in 70% yield over three steps.



Scheme 3.14. A scalable synthesis of methyl ketone 118.

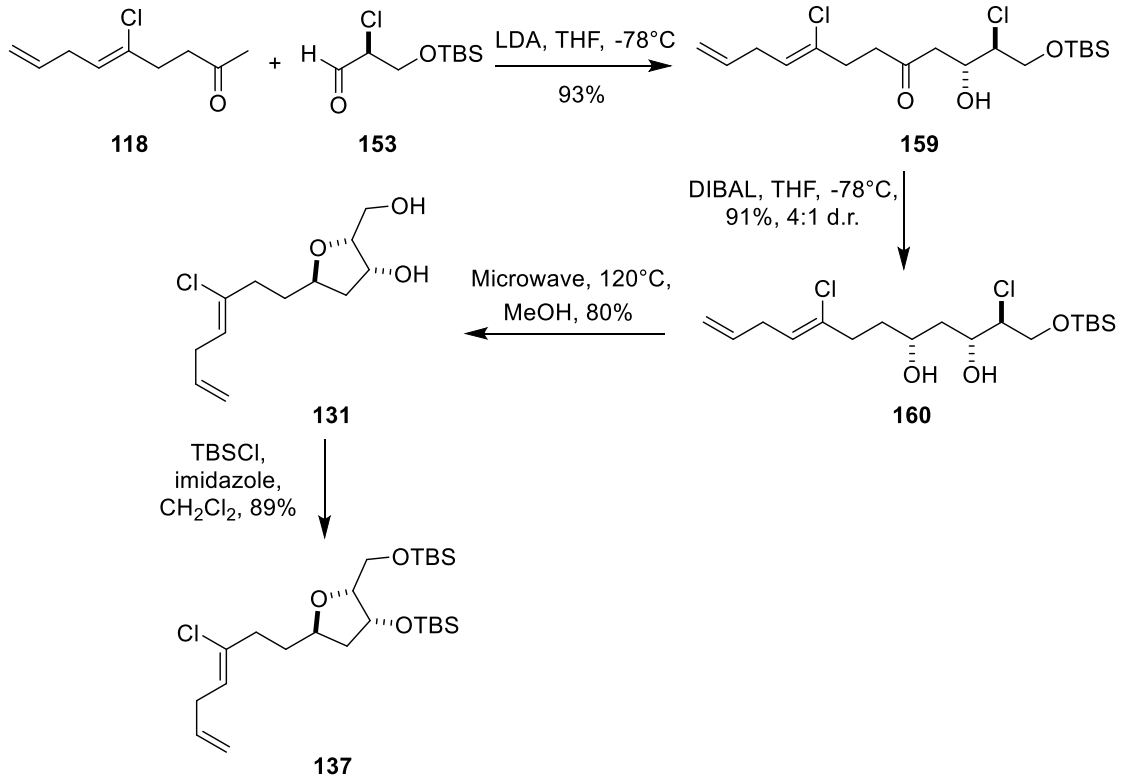
The synthesis of α-chloroaldehyde **153** began with L-serine and exploits methods reported by De Kimpe[77] (Scheme 3.15).[68,71] Thus, L-serine (**154**) was converted into the chloroacid (**155**) with retention of the stereochemistry. A subsequent Fisher esterification proceeded smoothly in MeOH to afford the methyl ester **156**. The free hydroxyl group was then converted into a TBS ether and the ester function was reduced via treatment with sodium borohydride to generate chlorohydrin **158**. This material was then oxidized to α-chloroaldehyde **153** by using Dess-Martin periodinane as required.



Scheme 3.15. Synthesis of the α-chloroaldehyde 153.

With these two components in hand, an aldol reaction between the lithium enolate derived from methyl ketone **118** and α-chloroaldehyde **153** provided the desired β-ketochlorohydrin **159**. A 1,3 *syn*-reduction[28,29] using DIBAL gave the chlorodiol **160** in

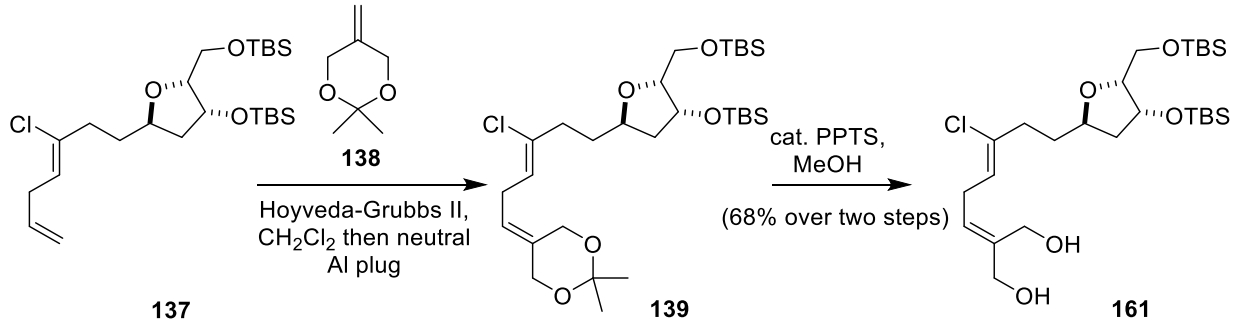
a 91% yield and in a 4:1 diastereomeric ratio. A subsequent thermal cyclization in MeOH furnished the tetrahydrofuranol **131** in good yield.[31] Protection of the primary alcohol and secondary alcohol as TBS ethers then afforded the elaborated THF **137** in preparation for the key cross metathesis reaction (Scheme 3.16).



Scheme 3.16. Access to the bis-silyl tetrahydrofuranol 137 as the cross-metathesis precursor.

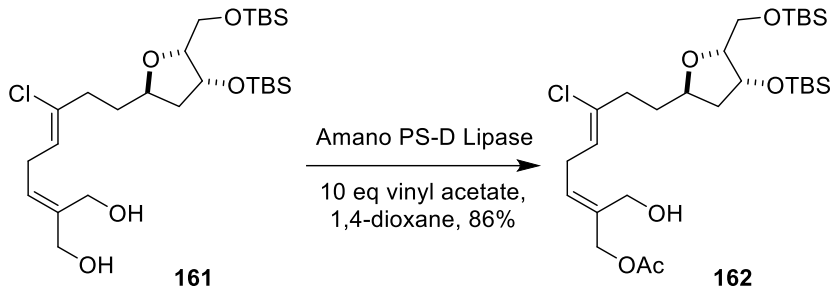
Unfortunately, the previously developed cross-metathesis conditions gave inconsistent results with respect to both yield and conversion. Furthermore, varying the reaction temperature or using anoxic and anhydrous toluene did not improve the reproducibility of this reaction. Fortunately, using Grubbs' conditions that are specifically designed for the synthesis of sterically hindered tri-substituted olefins[78] (3 mol% Hoyveda Grubbs II, 3 equivalents of acetonide **138**, 0.25 M concentration in CH_2Cl_2, reflux), the reproducibility of the reaction improved as well as conversion and yield. Notably, care must be taken to keep the reaction oxygen-free to ensure full conversion to product. Curiously, it was also found that the acetonide protecting group and the TBS protecting group on the primary alcohol both hydrolyze while stirring in methanol under

mildly acidic conditions. Careful examination of the ^{1}H NMR spectra recorded before and after purification via flash column chromatography with silica gel indicated that tetrahydrofuran **139** is stable as part of the crude reaction mixture but undergoes deprotection following flash chromatography. It was speculated that hydrolysis occurs due to acidic impurities derived from the silica gel and, as a result, the purification procedure was improved by filtering the crude reaction mixture through a neutral aluminum plug, which prevents removal of the TBS protecting group, following which the crude material was treated with a catalytic amount of PPTS in MeOH to effect the selective removal of the acetonide protecting group (Scheme 3.17). In this way, the diol **161** could be accessed reproducibly in excellent overall yield.



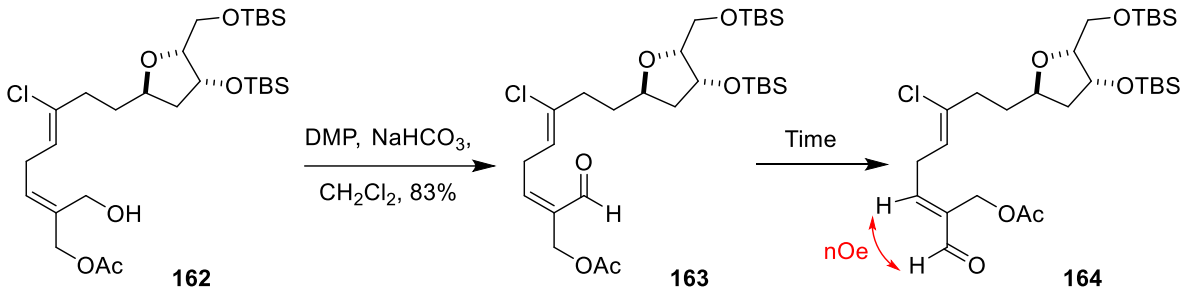
Scheme 3.17. Optimization of the cross-metathesis reaction.

On repeating the enzyme-catalyzed regioselective acetylation of compound **161** on larger scales, it was found that again both the conversion and reaction yields were inconsistent from batch to batch. This inconsistency was attributed to the quality of the porcine pancreatic lipase, which also varied from batch to batch. Takabe and co-workers have demonstrated this same regioselective acetylation utilising instead the lipase Amano PS-D from *Pseudomonas cepacia.*[79] Fortunately, using this enzyme with anhydrous 1,4-dioxane and freshly distilled vinyl acetate, we were able to achieve both consistent and good conversion as well as a good yield for this reaction (Scheme 3.18). With the discovery of these optimized conditions, we could access approximately 300 mg of the monoacetylated compound **162** from 1 g of the methyl ketone **118**, a more than 5 fold improvement in overall yield.



Scheme 3.18. Optimization of the regioselective lipase-catalyzed acetylation of the diol 161.

With the allylic alcohol **162** in hand, oxidation using Dess-Martin periodinane under buffered conditions ($NaHCO_3$) provided aldehyde **163** in good yield (Scheme 3.19). Unfortunately, it was found that even at -20 °C the desired *cis*-isomer **163** isomerizes to the *trans*-isomer **164**. While we had hoped that this isomerization could be reversed, unfortunately the addition of variety of reagents including nucleophilic bases (e.g., DABCO, DMAP) or phosphines (*e.g.*, PPh_3) and silica failed to effect a favourable isomerization of the *trans*-alkene back to the desired *cis*-alkene. Realising that *trans*-isomer **164** is likely the more stable isomer, care had to be taken to immediately subject aldehyde **163** to the subsequent coupling reaction.

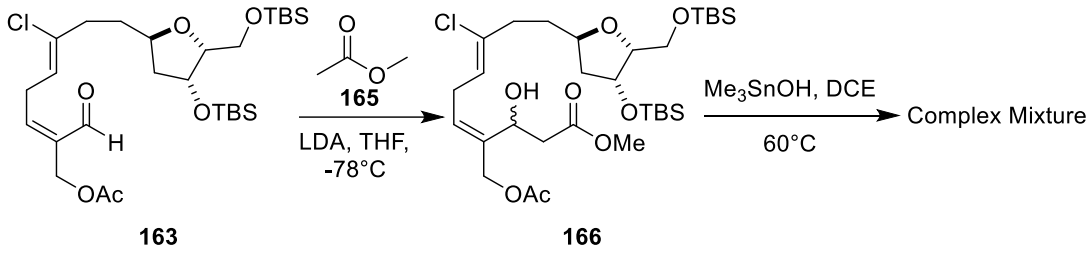


Scheme 3.19. Synthesis of aldehyde 163 and subsequent isomerization to the *trans*-isomer 164.

3.3.2. Investigation into the Selective Cleavage of Ester to Access the *Seco* Acid

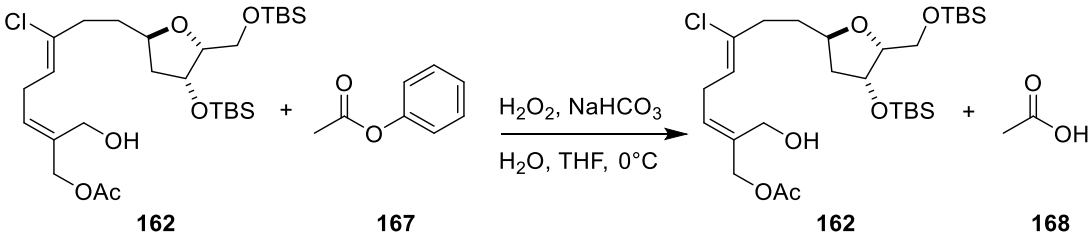
With the optimized synthesis of aldehyde **163** complete, we were interested in exploring routes to access *seco* acid **147**. Our first efforts began with a lithium-aldol

reaction between aldehyde **163** and methyl acetate (**165**) to afford methyl ester **166**. While methyl esters are generally difficult to hydrolyze outside of strongly basic conditions, Nicolaou and co-workers have developed a mild method of cleaving methyl esters that uses trimethyltin hydroxide (Scheme 3.20).[80] However, employing these conditions resulted in formation of an intractable mixture of products. Furthermore, Hoye and Wang had previously attempted a similar hydrolysis during their synthesis of haterumalide NA (**73**) and were also unable to cleave the methyl ester on their haterumalide NA methyl ester (**79**).[62]



Scheme 3.20. Attempted cleavage of the methyl ester using trimethyltin hydroxide.

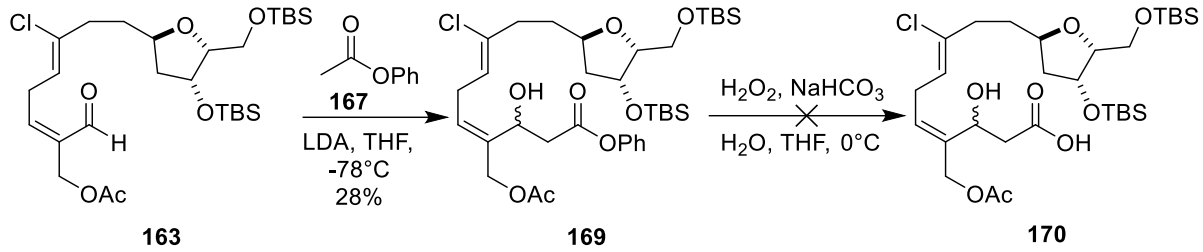
Next, we envisaged that use of a phenyl ester would afford access to the desired *seco* acid owing to their well-documented ability to hydrolyze under mildly basic conditions (*e.g.*, H_2O_2 and $NaHCO_3$, 0 °C).[81] In order to determine whether the acetate function would be stable under these reaction conditions, a 1:1 mixture of phenyl acetate (**167**) and monoacetate **162** was stirred in a mixture of THF, H_2O and H_2O_2 with $NaHCO_3$ (Scheme 3.21). Analysis of the crude ^1H spectrum indicated that the allylic acetate was not affected while the phenyl acetate was successfully and completely hydrolyzed.



Scheme 3.21. Successful cleavage of the phenyl acetate (167) while preventing hydrolysis of the 162.

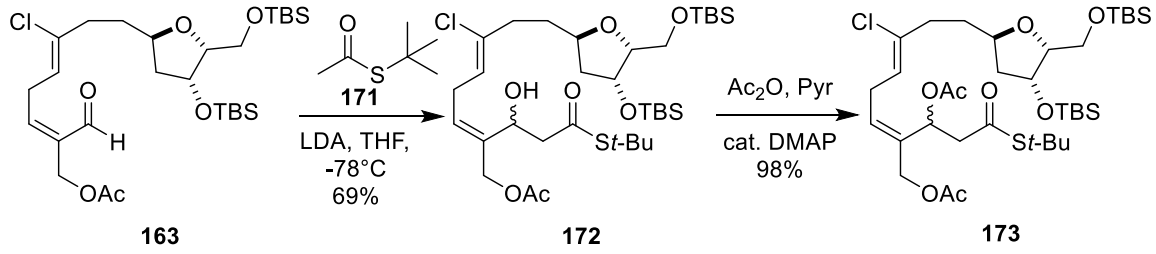
Unfortunately, following synthesis of the phenyl ester **169**, it was found that subjecting this material to the aforementioned conditions resulted in the formation of an

intractable mixture of products (Scheme 3.22). Furthermore, the yield of the aldol reaction between aldehyde **163** and phenyl acetate **167** was low, which would also complicate scale up efforts. Therefore, this synthetic route was abandoned.



Scheme 3.22. Attempted hydrolysis of the phenyl ester 169 under basic conditions.

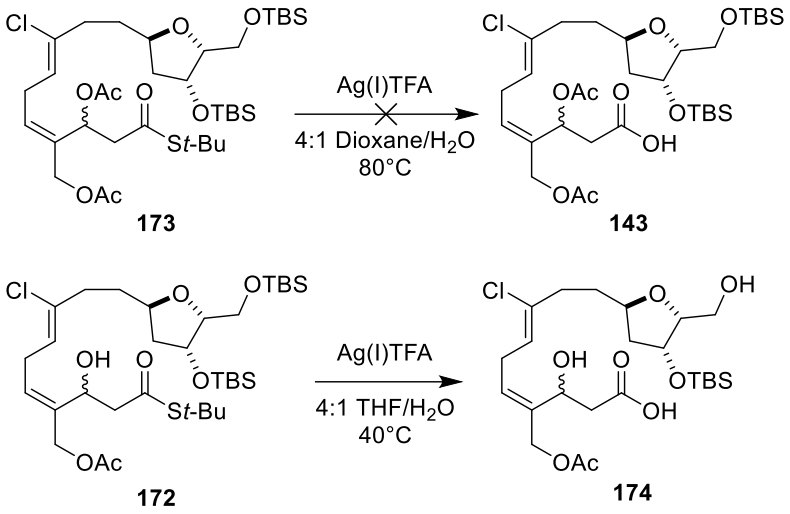
It was apparent from the results presented above that the allylic acetate was not stable to even mildly basic reaction conditions and that ester cleavage would need to be accomplished under neutral or acidic conditions. In light of this, the use of a thioester became a viable option, as thioester cleavage is primarily accomplished utilising silver salts (*e.g.*, silver (I) trifluoroacetate) under aqueous conditions. Accordingly, thioester **173** was synthesized via an aldol reaction between *tert*-butyl thioacetate (**171**) and aldehyde **163** and subsequent acetylation (Scheme 3.23).



Scheme 3.23. Synthesis of thioester 173.

Unfortunately, hydrolysis of the *tert*-butyl thioester proved difficult. While reaction at room temperature showed no progression (monitoring by TLC), slowly heating the reaction mixture to 80 °C led to competitive elimination of the β-acetoxy group, hydrolysis of the TBS ethers and hydrolysis of the *tert*-butyl thioester. Repetition of this reaction at 40 °C for extended periods of time led to hydrolysis of both the *tert*-butyl

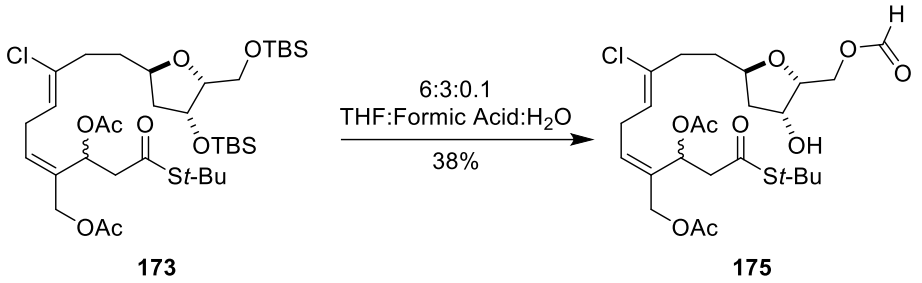
thioester and silyl protecting group on the primary alcohol in low yield (Scheme 3.24). Therefore, this synthetic route to access the *seco* acid was also abandoned.



Scheme 3.24. Attempted hydrolysis of the *tert*-butyl thioester 173 and 172.

3.3.3. Investigation of Masamune Macrolactonization Reaction

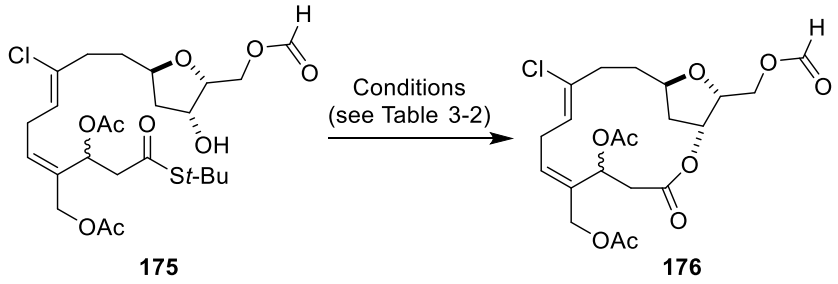
Masamune has demonstrated that thioesters can be activated using Ag(I), Cu(I) and Hg(II) salts and directly engaged in macrolactonization reactions,[82] and his group has used this method to access a variety of macrolactones (*e.g.,* cytochalasins A and B).[83] Given that we were unable to access the *seco* acid in a reasonable yield, macrolactonization via activation of the *tert*-butyl thioester would be a desirable alternative. Towards this goal, we attempted to remove the two TBS protecting groups in thioester **173**. Unfortunately, this deprotection proved difficult as TBAF promoted the elimination of the β-acetoxy group and a mixture of TBAF and acetic acid only effected the removal of the silyl protecting group on the primary alcohol. Perusal of various methods for silyl ether cleavage identified formic acid in a mixture of THF as a potential solution. Notably, these deprotection conditions were demonstrated in the total synthesis of lankacidin C where they proved uniquely effective on a sensitive substrate.[84] Surprisingly, treating thioester **173** with aqueous formic acid not only hydrolyzed both TBS groups but also formed a formate ester of the primary hydroxyl group and gave direct access to the thioester **175** (Scheme 3.25). This serendipitous result allowed us to avoid a potentially difficult chemoselective protection of the primary alcohol.



173 175

Scheme 3.25. Access to thioester 175 via a one-pot acidic deprotection and formate protection step.

With thioester **175** in hand, macrolactonization of thioester **175** with several Cu(I) and Ag(I) salts was attempted. However, under a variety of conditions only starting material or diol were recovered from the crude reaction mixture ultimately leading us to abandon this route (Table 3-2).



175 176

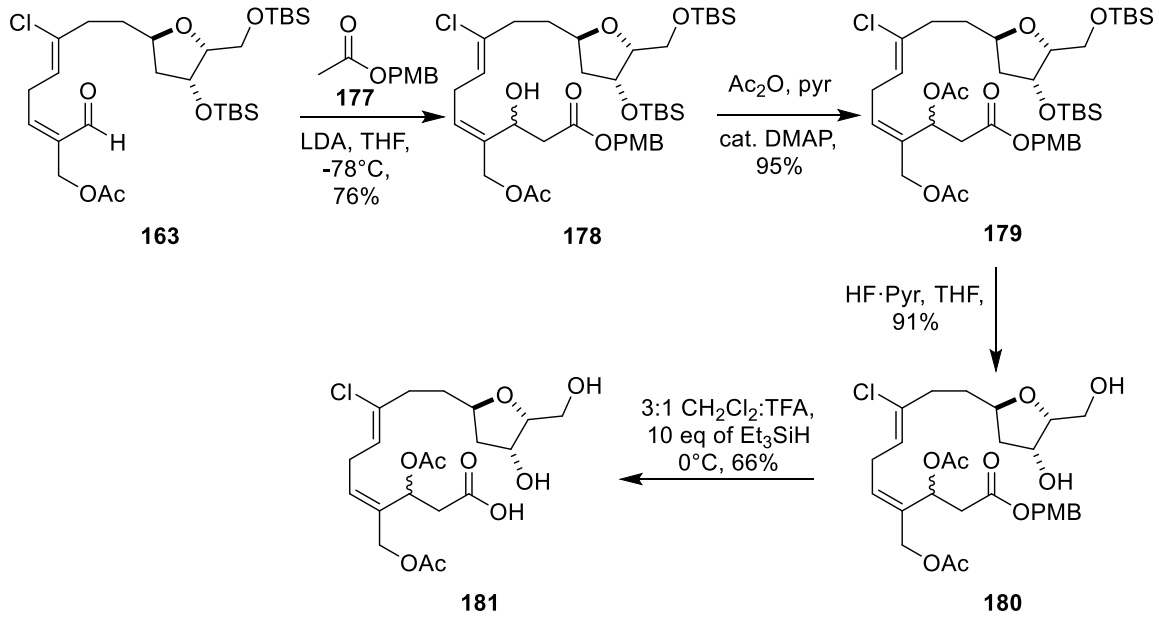
Table 3-2 Conditions for Macrolactonization of Thioester 175.

Entry	Conditions	Products
1	Ag(I)CF_3COO (4 eq), NaH_2PO_4, THF, reflux	Starting material
2	CuTC (5 eq), benzene, reflux	Starting material
3	Cu(I)OTf (5 eq), NaH_2PO_4, benzene/THF (10:3), 60°C	Starting material (major) + formate deprotection

3.3.4. Access to the *Seco* Acid via Selective Deprotection of a PMB Ester

At this point we returned to the challenge of accessing the *seco* acid and considered use of a PMB ester, a protecting group that was employed by Hoye to great effect to complete the first synthesis of haterumalide NA.[62] While haterumalide NA lacks

a primary allylic acetate, Hoye's deprotection protocol did not result in hydrolysis of the β-acetoxy group present on both haterumalide NA and biselide A and, therefore, it stood to reason that a PMB ester may serve our purpose. Thus, an aldol reaction between aldehyde **163** and PMB acetate **177** and subsequent acetylation provided access to the PMB ester **179**. Removal of the silyl protecting groups was accomplished by treatment with HF·Pyr to afford diol **180.** We were delighted to find then that subjecting diol **180** to a 3:1 solution of CH_2Cl_2:TFA and 10 equivalents of Et_3SiH furnished the desired *seco* acid **181** without any observed hydrolysis of the primary allylic acetate (Scheme 3.26).



Scheme 3.26. Synthesis of *seco* acid 181.

Curiously, the ^1H NMR spectrum of **181** in $CDCl_3$ showed significant differences in the chemical shifts of protons assigned to the two diastereomers. These chemical shift differences had not been observed prior to removal of the PMB ester (Figure 3.4). Furthermore, a significant deviation in the chemical shift of the protons on the diastereomeric THFs was observed. Considering that these diastereomers differ only in the configuration of the remote C3 stereocentre, this observation was unexpected and warranted further investigation.

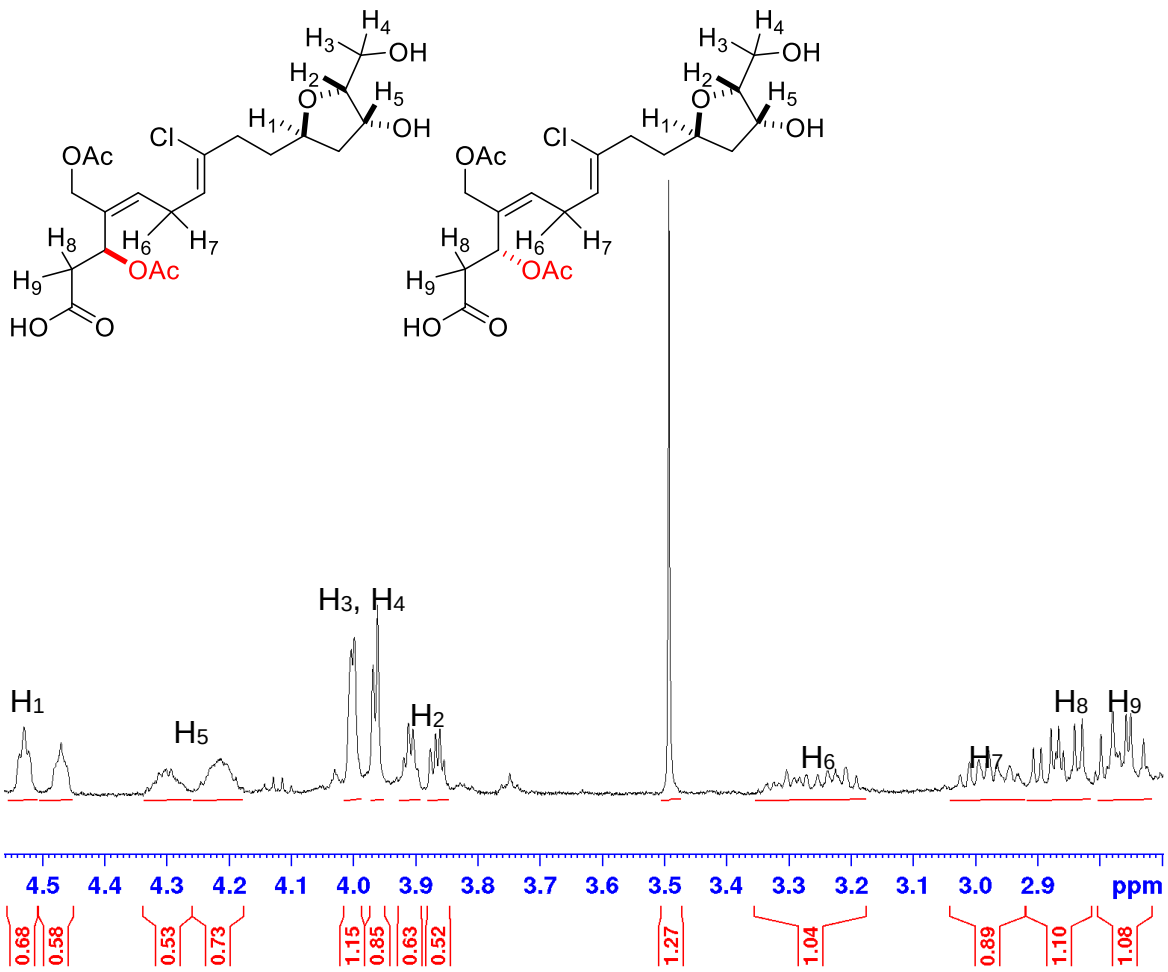
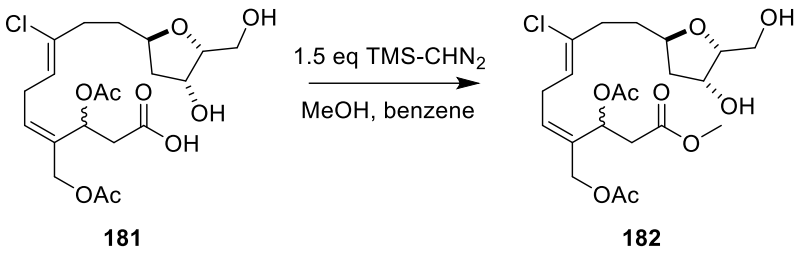


Figure 3.4. **^{1}H NMR spectrum of *seco* acid 181.**

When *seco* acid **181** was subjected to TMS-CHN_2 in a mixture of toluene and methanol to methylate the carboxylic acid, the methyl ester **182** was produced cleanly (Scheme 3.27). Analysis of the ^{1}H NMR spectrum of methyl ester **182** was clearly different from that of the *seco* acid. Specifically, the resonances attributed to the two diastereomers were now superimposed, suggesting that the carboxylic acid function in the *seco* acid is interacting with the THF core in a different way that leads to large ^{1}H NMR spectral differences for the diastereomers of *seco* acid **181**.



181 182

Scheme 3.27. Selective methylation of *seco* acid 181 to give methyl ester 182.

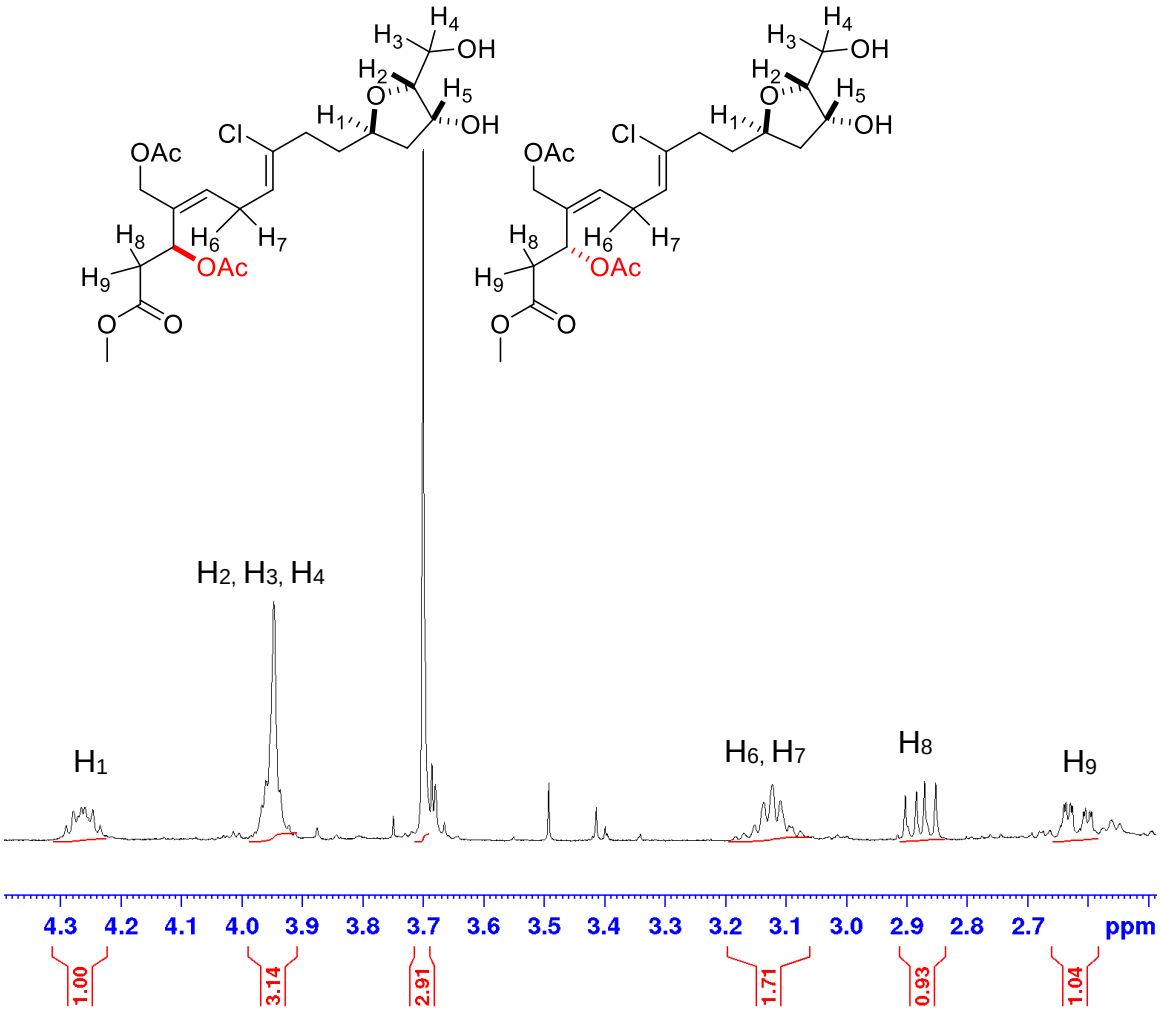


Figure 3.5. ^{1}H NMR spectrum of methyl ester 182.

Specifically, we hypothesized that the spectral properties for the two diastereomers **181a** and **181b** resulted from the formation of a macrocyclic conformation in one or both of these diastereomers that involves hydrogen bonding between the

carboxylic acid and the tetrahydrofuranol. In this way, the stereochemical relationship between the remote stereocentres may well influence the global chemical shifts of each diastereomer. To test this hypothesis, *seco* acid **181** was dissolved in MeOD to disrupt intramolecular hydrogen bonding and the ^{1}H NMR spectrum was recorded. As depicted in Figure 3.6, and in line with our hypothesis, the ^{1}H NMR spectrum of **181** in MeOD showed no significant difference in chemical shifts for the two diastereomers (Figure 3.6).

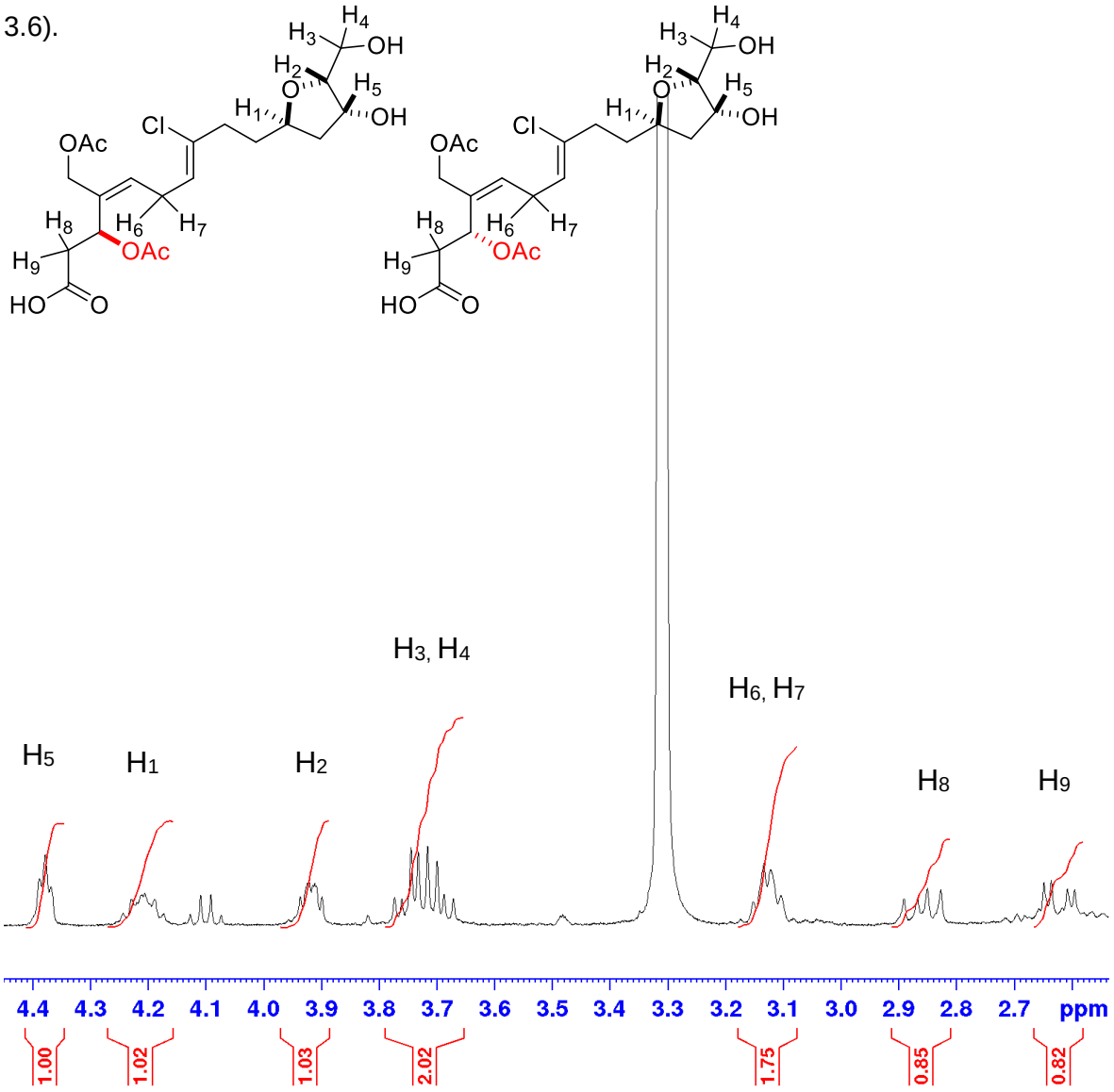


Figure 3.6. ^{1}H NMR spectrum of *seco* acid 181 in MeOD.

In light of this result, we tentatively propose that the carboxylic acid in *seco* acid **181** interacts with one or more of the oxygenated functionalities on the tetrahydrofuranol

as shown in Figure 3.7. It is uncertain to what degree each oxygenated functionality coordinates to the carboxylic acid and it must be noted that the carbonyl function may also coordinate to one of the protons on the hydroxyl groups. To further probe this hypothesis, TBS ethers **147** and **183** were synthesized. Interestingly, the two diastereomers of **147** and **183** again displayed observably different ^{1}H NMR spectral properties, suggesting that hydrogen bonding between the carboxylic acid and the THF core is key.

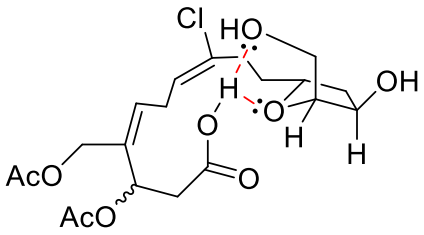
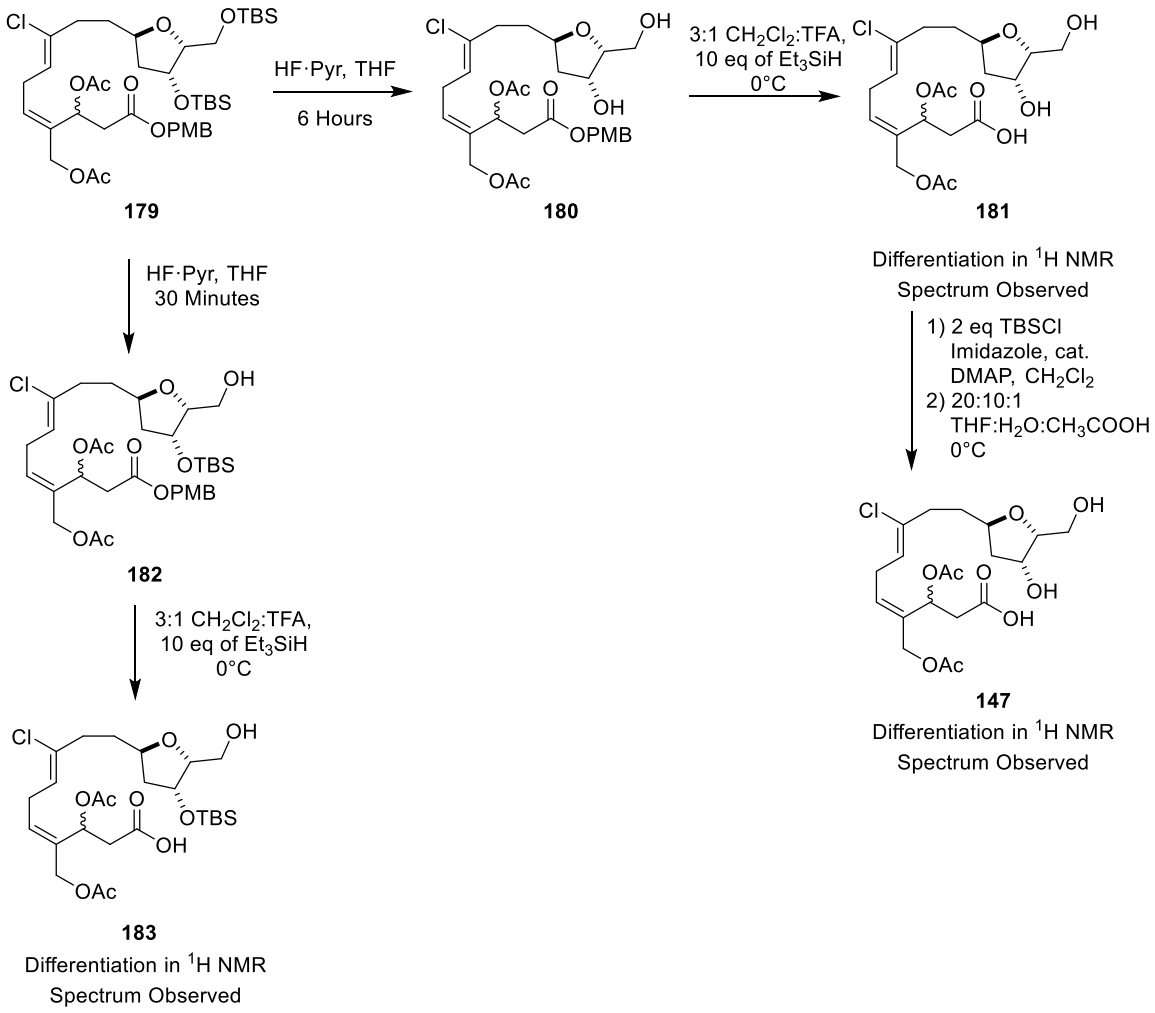


Figure 3.7. Proposed conformation of *seco* acid 181.

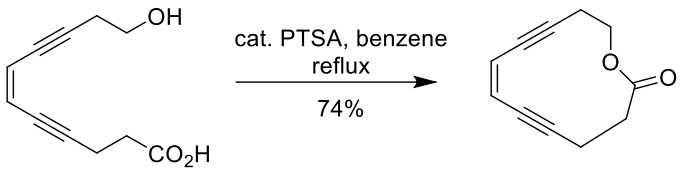


Scheme 3.28. Synthesis of *seco* acid 181 derivatives.

3.3.5. A Novel Acid-Catalyzed Template Macrolactonization

Given that *seco* acid **181** appears to adopt a preferred conformation in $CDCl_3$, we were interested in investigating whether we could exploit this structural feature and induce macrolactonization via simple acid catalysis. In general, the key hindrance to large ring macrocyclizations is entropy, while enthalpic factors generally do not play as significant of a role as large rings often have little strain. Therefore, in macrolactonizations, a significant degree of activation of either the carboxylic acid or the hydroxyl group is required for the requisite ring to form.[85] In our case, however, the adoption of a fairly rigid macrocyclic structure by *seco* acid **181** would help overcome

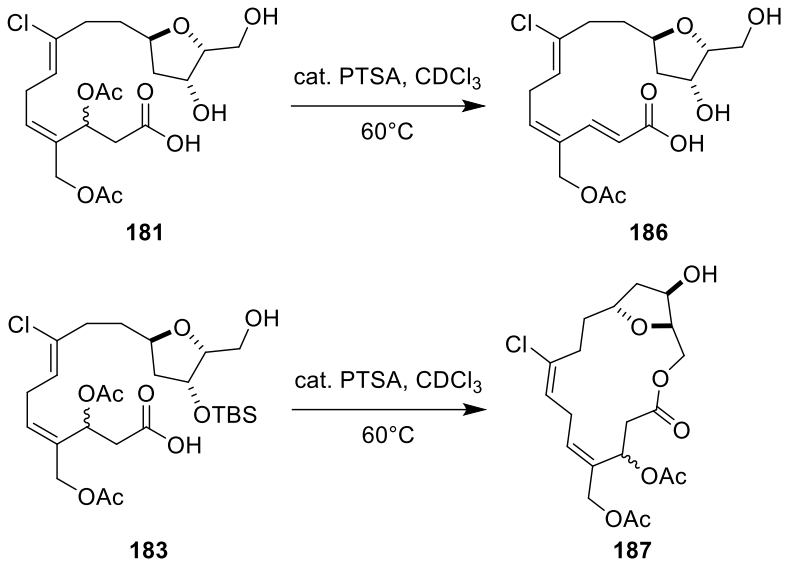
entropic factors. Therefore, it stood to reason that acid catalysis could activate the carboxylic acid sufficiently and, with the hydroxyl group in close proximity, induce macrolactonization via this presumed hydrogen bonding template. It is notable that there are very few examples of macrolactonizations induced by acid catalysis and that the primary examples rely on conformationally strained substrates such as **184** (Scheme 3.29).[86] Thus, this would be the first example of a simple, acid-catalyzed macrolactonization in the context of structurally complex natural product synthesis.



184 **185**

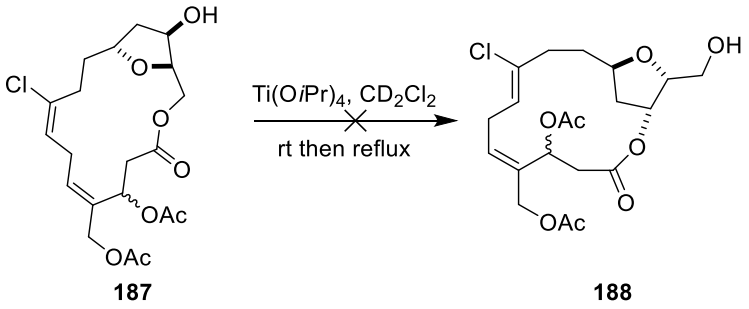
Scheme 3.29. Macrolactonization via acid catalysis on a conformationally rigid substrate.

With the intramolecular hydrogen bonding predicted to be most relevant in the *seco* acid **181** based on the magnitude of difference in chemical shift of the protons in the two diastereomers, acid-catalyzed macrolactonization was first attempted on this substrate but yielded only the enone (Scheme 3.30). Next, *seco* acid **183** with a TBS group on the secondary hydroxyl group was subjected to the same reaction conditions and to our delight, we were able to isolate the primary macrolactone **187** as the major reaction product. This remarkable result stands as a unique example of hydrogen bond-templated macrolactonization.



Scheme 3.30. Acid-catalyzed macrolactonization of TBS-protected *seco* acid 183.

With the primary macrolactone **187** in hand, we attempted to induce a translactonization to access the desired secondary macrolactone **188**. Translactonizations have been employed in the context of several total syntheses by Corey (Bronsted acid)[87] and Paterson (Lewis acid)[88] that leverage the thermodynamic preferences for macrolactone ring size. Given that the initial macrolactonization to form macrolactone **187** was effected using similar conditions to those of Corey's (*i.e.*, PTSA), we explored Paterson's large ring isomerization by adding $Ti(O\textit{i}Pr)_4$ to macrolactone **187** in CD_2Cl_2 (Scheme 3.31). Unfortunately, after stirring at room temperature overnight there was no indication of isomerization and only decomposition of macrolactone **187** occurred.



Scheme 3.31. Attempted translactonization of primary macrolactone 187 to secondary macrolactone 188.

In considering this result, the translactonization may be an improbable prospect for the synthesis of biselide A as studies by Hoye have shown the desired macrolactone suffers from severe ring strain.[62,70] Further, it may be difficult for the larger ring lactone to adopt a conformation where the lone pair of the secondary hydroxyl group can engage in nucleophilic addition to the carbonyl necessary for translactonization (i.e., there may be poor orbital overlap between the lone pair on the alcohol and the C=O π* bond (Figure 3.8)).

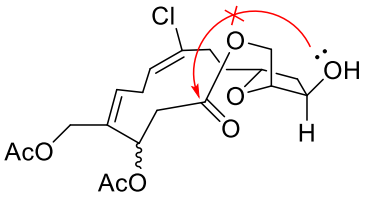
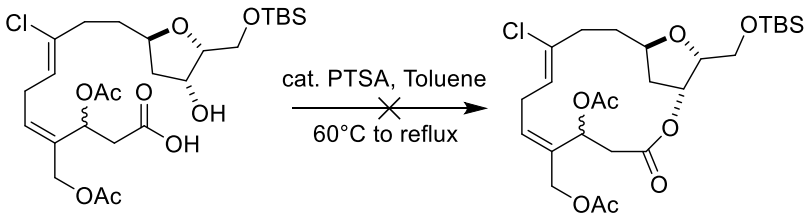


Figure 3.8. Inability of the secondary hydroxyl group to attack the carbonyl due to conformation of macrolactone 187.

Given the inability to exploit translactonization, we turned our attention to directly macrolactonization of the primary TBS *seco* acid **147**. As we had also observed large differences in the ^{1}H NMR spectra for the two diastereomers, acid-catalyzed macrolactonization was attempted (Scheme 3.32). To prevent the hydrolysis of the sensitive primary TBS group, toluene that was freshly distilled from sodium wire and benzophenone was used. Unfortunately, heating this reaction mixture resulted in no formation of the desired macrolactone and after extended periods of time, decomposition products appeared.



147 **189**

Scheme 3.32. Macrolactonization attempt of 183 via acid catalysis.

3.3.6. Investigations into Macrolactonization of *Seco* Acid 147.

Considering the challenges in effecting a hydrogen-bond templated macrolactonization, standard macrolactonization conditions were also explored on *seco* acid **147**. As summarized below, a variety of macrolactonization methods were screened that include base-catalyzed methods [Yamaguchi[89] (entry 1 and 2), Boden-Keck[90] (entry 3)], acid-catalyzed methods [Trost[91] (entry 5), Yamamoto[92] (entry 6)], and neutral or near-neutral methods [modified Mukaiyama[93–95] (entry 7-9), Corey-Nicolaou[96] (entry 4)] (Table 3-3).

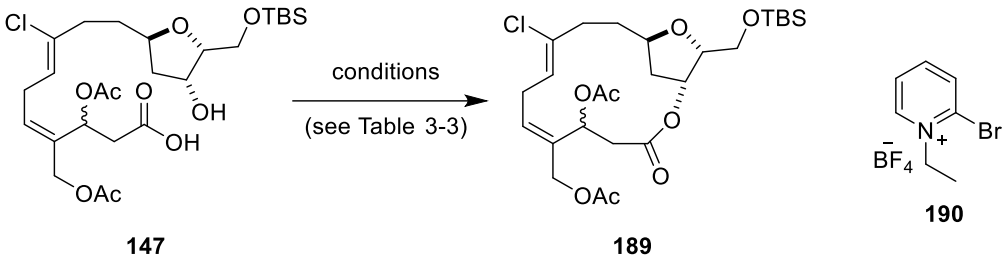


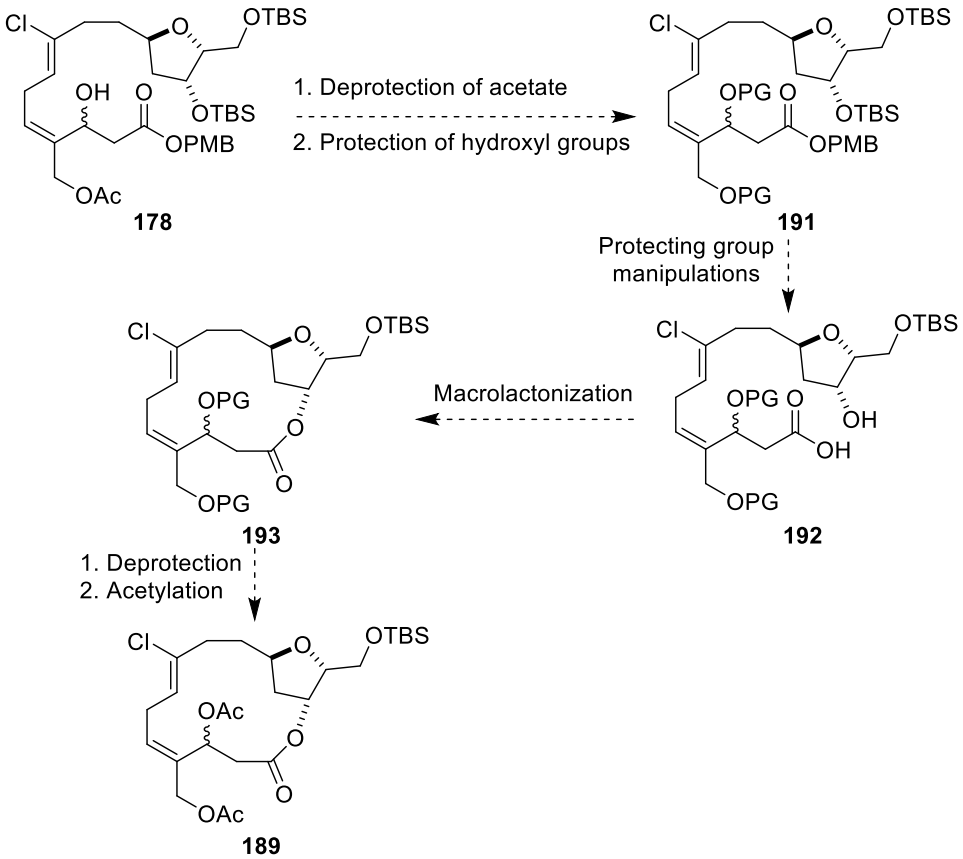
Table 3-3 Conditions for Macrolactonization of *Seco* Acid 147

Entry	Conditions	Products
1	NEt_3, TCBC, THF, rt then slow addition to DMAP, rt	Decomposition, no product detected
2	NEt_3, TCBC, THF, rt then slow addition to DMAP, 80°C	Decomposition, no product detected
3	Slow addition to EDCI•HCl, DMAP, CH_2Cl_2, reflux	Decomposition, no product detected
4	PPh_3, $(2\text{-PyS})_2$, THF, rt then slow addition to Ag(OTf), toluene, rt → 80°C	Decomposition and starting material, no product detected
5	Ethoxyacetylene, $[RuCl_2(p\text{-cymene})_2]_2$, then slow addition to CSA in CH_2Cl_2	Decomposition and starting material, no product detected
6	Slow addition to paranitrobenzoic anhydride, $Sc(OTf)_3$, MeCN, rt	Decomposition, no product detected
7	Slow addition to **190**, $NaHCO_3$	Starting Material
8	Slow addition to **190**, 2,6-lutidine, benzyltrimethylammonium chloride,	Decomposition, no product detected

9	CH_2Cl_2 reflux Slow addition to **190**, DMAP, $NaHCO_3$, molecular sieves, rt	Starting Material

While the Yamaguchi macrolactonization is one of the most popular methods to form macrolactones,[97] using these conditions decomposition of **147** occurred even at room temperature (entry 1 and 2). The sensitivity of **147** under these and other base-catalyzed macrolactonization conditions is most likely related to the presence of two base-sensitive acetoxy groups. Similarly, the Keck macrolactonization, a popular alternative, also resulted in decomposition, likely due to DMAP-promoted elimination of the β-acetoxy group (entry 3). Moving away from methods that rely on relatively strong bases, the Corey-Nicolau macrolactonization involves initial formation of a pyridyl thioester that undergoes an internal proton transfer under silver-catalyzed or thermal conditions, leading to a macrolactone (entry 4).[98] Unfortunately, these conditions also promoted only decomposition of starting material. A mild macrolactonization protocol was described by Trost and Chisholm[91] that utilizes a ruthenium catalyst to form an ethoxyvinyl ester, which is subsequently activated and displaced under acidic conditions to form macrolactones (entry 5). While this reaction has been was used to great effect on a number of sensitive substrates, in our case only a mixture of decomposition products and starting material could be observed in the ^{1}H NMR spectrum recorded on the crude reaction mixture. The Yamamoto macrolactonization, while not having been demonstrated in a natural product synthesis, is described as “the most selective monomeric lactonization method available,”[99] with impressive yields of medium- and large-ring lactones. However, for *seco* acid **147**, these conditions led to slow removal of the TBS protecting group and subsequent decomposition of the *seco* acid. Finally, the modified Mukaiyama salt (**190**)[95] was explored based on promising results reported by Smith during the synthesis of sorangicin A,[93] which possesses a sensitive (*Z,Z,E*)-configured trienone that readily isomerized under most macrolactonization conditions. Unfortunately, while no decomposition occurred using this modified Mukaiyama salt at room temperature, no macrolactone was detected either, with starting material being recovered unreacted. Further heating of the reaction mixture with 2,6-lutidine, a fairly weak base, resulted in decomposition.

With these results in mind, it is clear that the *seco* acid **147** is too sensitive to engage in macrolactonization under standard conditions. The presence of a skipped diene and two allylic acetoxy groups precludes the use of base, most notably DMAP, which severely narrows the scope of macrolactonization methods that may be used. While a possible work-around would involve removal of the acetate from the primary alcohol after the aldol reaction, re-protection of both hydroxyl groups (*e.g.*, as TIPS ethers) and subsequent deprotection/acetylation following macrolactonization (Scheme 3.33), this would add considerably to the length of the synthesis and ultimately impact our ability to exploit this synthesis for supporting biological testing or SAR studies. Therefore, we sought an alternative method to form the macrolactone.

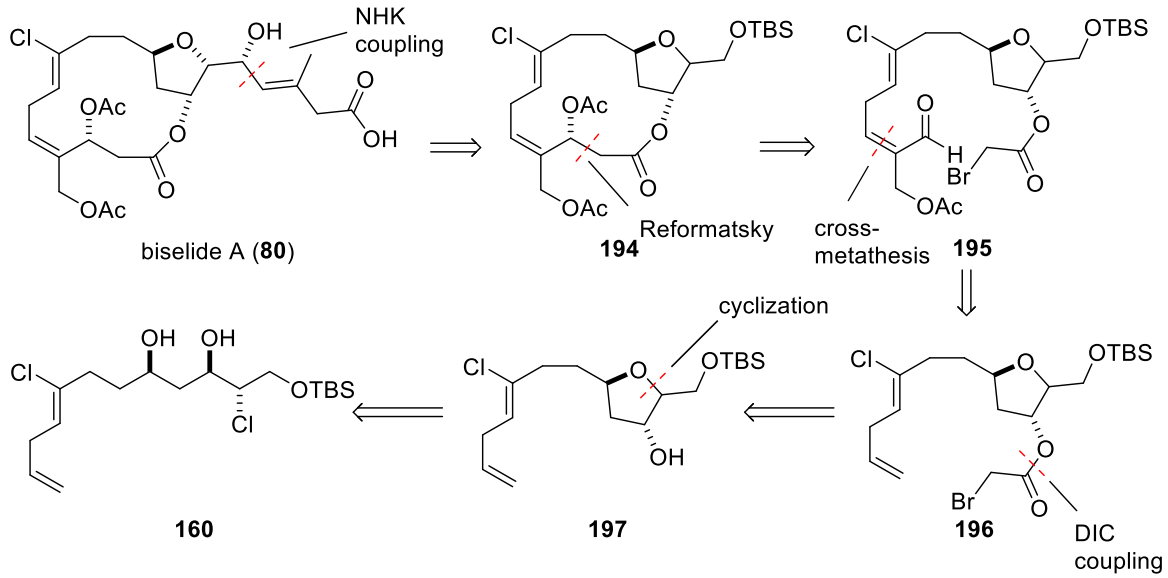


Scheme 3.33. Proposed alternative route to macrolactone 189 via protecting group manipulations.

3.4. Reformatsky-based Strategy for the Synthesis of Biselide A

3.4.1. Retrosynthetic Analysis

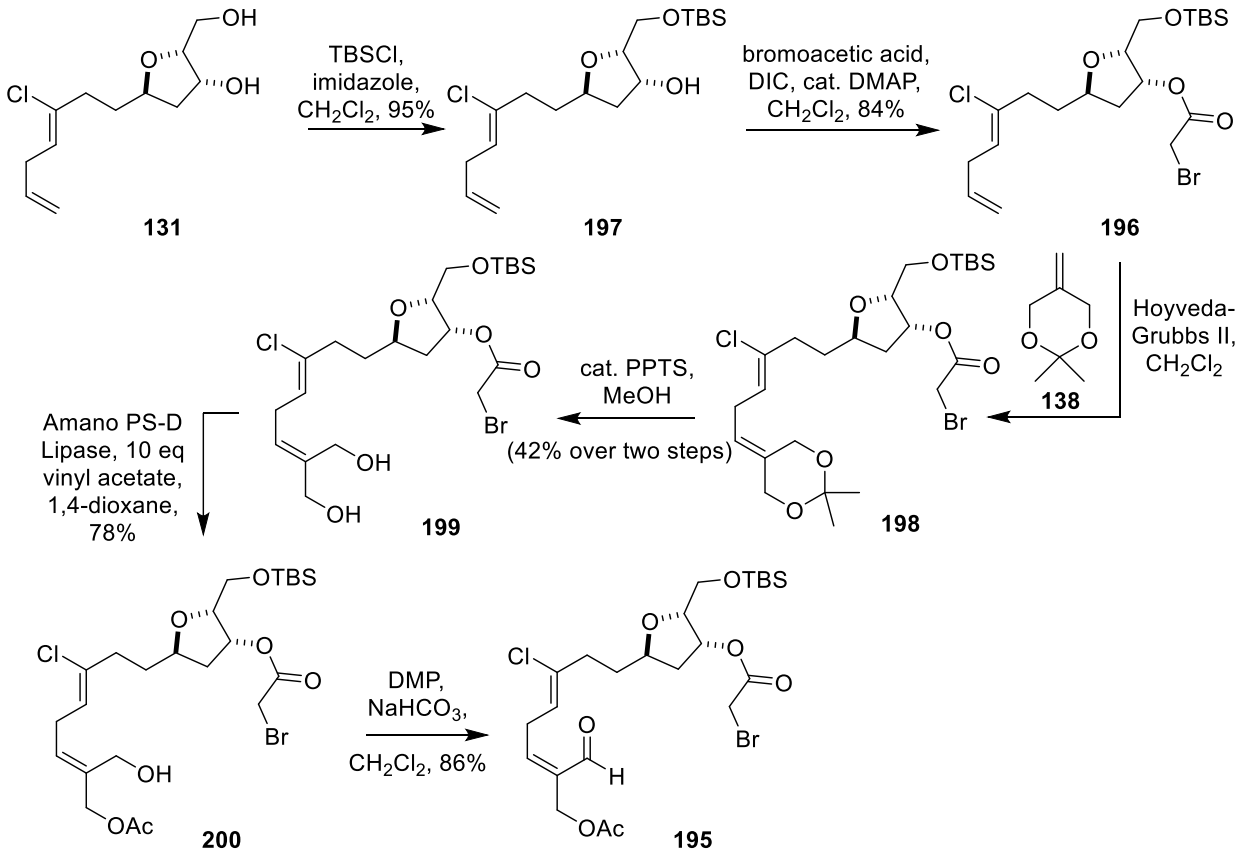
Considering our inability to form the biselide macrolactone via several established macrolactonization methods, we turned instead to the Reformatsky reaction to perform the key macrocyclization reaction (Scheme 3.34). With the same endgame strategy demonstrated by Hoye,[62] the macrocycle would be formed via an intramolecular Reformatsky reaction between the α,β-unsaturated aldehyde and bromoacetate as previously demonstrated by Kigoshi in his synthesis of *ent*-haterumalide NA methyl ester.[54] The α,β-unsaturated aldehyde would be introduced in the same manner as previously described while the bromoacetate would be incorporated via a DIC coupling reaction between a mono-protected TBS-tetrahydrofuranol **197** and bromoacetic acid.



Scheme 3.34. Retrosynthesis for the revised intramolecular Reformatsky reaction strategy.

3.4.2. Synthesis of Aldehyde 195

As shown in Scheme 3.35, beginning with tetrahydrofuranol **131**, mono-silylation with TBSCl and imidazole allows access to the mono-silylated tetrahydrofuranol **197**, which can later be coupled to bromoacetic acid to form bromoacetate **196** in good yield, generating one partner of the Reformatsky reaction. The bromoacetate **196** was then subjected to the cross metathesis conditions used previously to yield diene **198**. The crude diene **198**, after being passed through a plug of neutral alumina, was immediately subjected to mild acidic conditions, with a catalytic amount of PPTS in MeOH, affording diol **199** in 42% yield over two steps. Due to time constraints, these two steps have not yet been optimized for conversion or yield. Diol **199** was then regioselectively acetylated to yield monoacetate **200** using the aforementioned conditions in 72% yield (Scheme 3.35). Oxidation using Dess-Martin periodinane and $NaHCO_3$ then afforded the desired aldehyde **195**, ready for the intramolecular Reformatsky reaction.

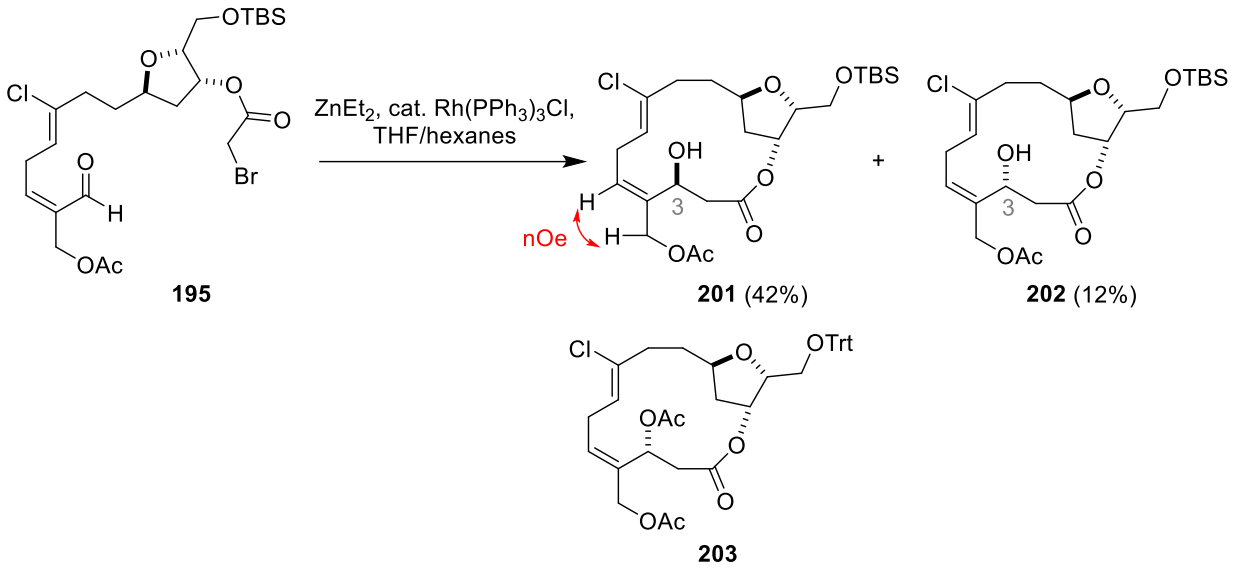


Scheme 3.35. Synthesis of the aldehyde 195 for the intramolecular Reformatsky reaction.

3.4.3. Investigation into the Intramolecular Reformatsky Reaction

Previous work by Kigoshi suggests that the intramolecular Reformatsky reaction of aldehyde **195** will likely generate the undesired diastereomer at the newly formed C3 stereogenic centre.[54] In most cases, inversion of this stereogenic centre could be accomplished by a Mitsunobu reaction, which would form the β-acetoxy macrocycle, or by oxidation, reduction and acetylation of the β-hydroxyl group, as was demonstrated by Hoye.[62] However, Kigoshi found that the formed β-hydroxy macrocycle decomposes on work up, and circumvented this complication by adding acetic anhydride into the reaction mixture to form directly the β-acetoxy macrocycle.[55] Thus, access to the desired diastereomer could prove troublesome, as Kigoshi does not report any success in converting the undesired C3 acetoxy epimer into the desired diastereomer.

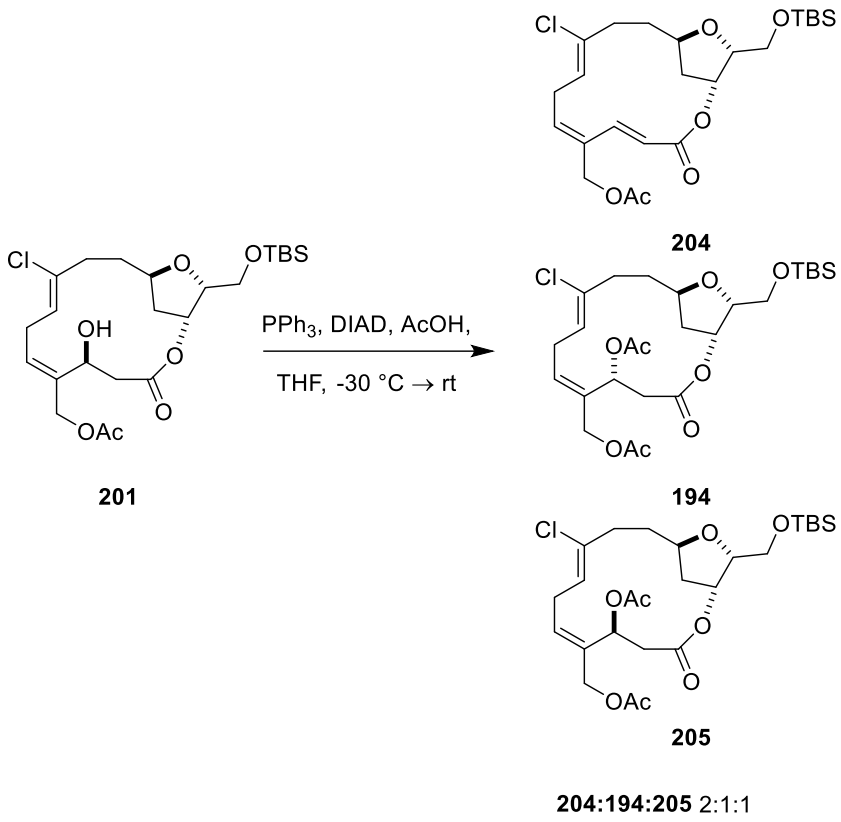
Fortunately, in our case, we were able to isolate both the undesired and desired diastereomer of the β-hydroxyl macrocycle **201** and **202** when subjecting aldehyde **195** to the conditions developed by Honda.[61] Thus, slow addition of aldehyde **195** into a mixture of Wilkinson's catalyst, $ZnEt_2$ in THF/hexanes at 0 °C formed the macrocycle with a 42% yield for the undesired diastereomer **201** and a 12% yield for the desired diastereomer **202** (Scheme 3.36). Substituting THF for CH_2Cl_2 in an attempt to change the diastereomeric ratio resulted primarily in decomposition along with formation of a small amount (<5 %) of the desired diastereomer **202**. Importantly, we found that treatment of the crude reaction mixture with a saturated aqueous solution of NH_4Cl, prevented decomposition that had been reported by Kigoshi and allowed us to avoid direct acetylation of the diastereomeric mixture of alcohols. Comparison of spectral data recorded on macrocycle **201** with that reported by Kigoshi for a very similar compound (**203**)[58] allowed for confident assignment of the stereochemistry of this material. Additionally, analysis of a 2D NOESY spectrum in combination with $^3J_{H,H}$ coupling constants provided further support for this configurational assignment.



Scheme 3.36. Synthesis of the β-hydroxyl macrocycle (201 and 202) via the intramolecular Reformatsky reaction.

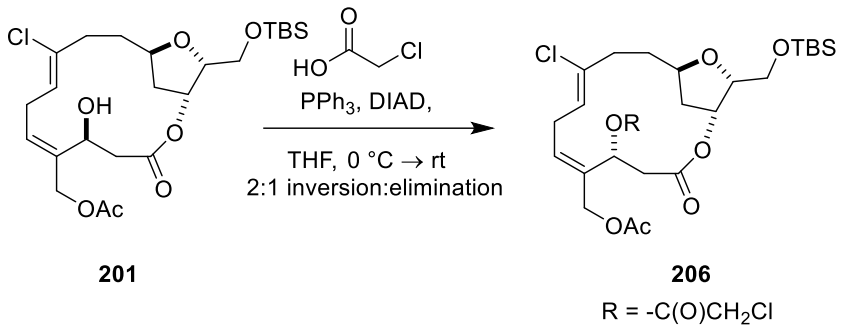
3.4.4. Investigation into Inverting the C3 Sterechemistry

While the undesired diastereomer **201** was found to be the major product of this macrocyclic Reformatsky reaction, either a Mitsunobu inversion[100] or a series of reactions involving oxidation of the allylic alcohol followed by a Luche reduction and acetylation could generate the desired diastereomer **194**. As a Mitsunobu inversion would provide direct access to the desired acetylated macrocycle, this process was tried first. Unfortunately, a Mitsunobu inversion involving macrocycle **201** provided a 2:1:1 mixture of elimination product **204**: inversion product **194**: retention products **205** (Scheme 3.37). Purification of this mixture was complicated by the fact that **194**, **204** and **205** proved inseparable by flash column chromatography.



Scheme 3.37. Mitsunobu inversion of 201 with acetic acid results in a 2:1:1 mixture of 204:194:205.

The formation of the retention product **205** is perhaps not surprising, as it is well established that acetic acid is a poor reagent in the Mitsunobu reaction of sterically hindered alcohols due to its higher pK_a (pK_a = 4.75) compared to the commonly utilized *p*-nitrobenzoic acid (pK_a = 3.41). However several groups have had success using chloroacetic acid (pK_a = 2.86) as an acetic acid surrogate.[101] Therefore, macrocycle **201** was subjected to Mitsunobu conditions with chloroacetic acid, which yielded a 2:1 mixture of inversion product **206** to elimination product **204**, which could be separated via flash chromatography (Scheme 3.38). Notably, even at 0 °C this reaction was complete within seconds and if repeated at lower temperatures it may be possible to avoid elimination completely and further improve the yield for the desired product **206**.

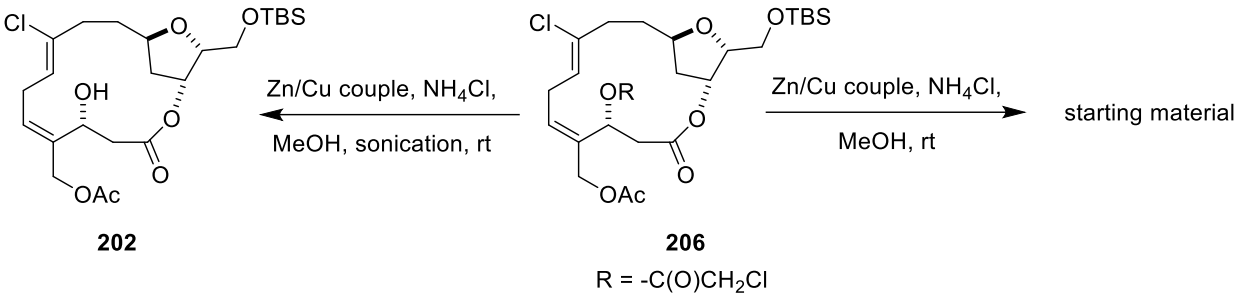


201 **206**

R = -C(O)CH_2Cl

Scheme 3.38. Successful inversion of macrocycle 201 to form the chloroacetate 206.

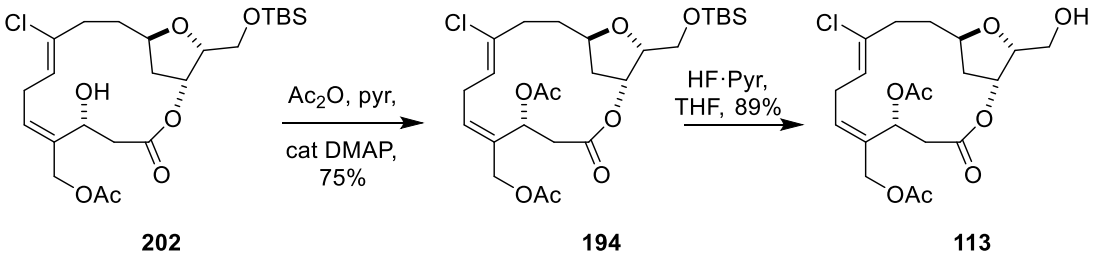
Reduction of α-halo-carbonyl compounds have been accomplished through radical-based methods,[102] metal-based methods via metal insertion and hydrolysis[103] and even photocatalytic methods.[104] Unfortunately, stirring chloroacetate **206** in a solution of Zn/Cu couple and NH_4Cl in methanol returned unreacted starting material. Repetition of this reaction with sonication, resulted in hydrolysis of the chloroacetate, and yielded the β-hydroxyl macrocycle **202**, now with the correct stereochemistry at C3. Due to time constraints, no further attempts were made to reduce chloroacetate **206**.



Scheme 3.39. Attempted reduction of chloroacetate 206.

3.4.5. Completion of the Advanced Macrocycle Intermediate 113

The desired diastereomer **202** generated in the Reformatsky reaction was subsequently acetylated and subjected to HF-pyridine to remove the TBS group, furnishing macrocycle **113** (Scheme 3.40), an advanced intermediate in the synthesis of biselide A. While oxidation, NHK coupling and deprotection (*i.e.*, completion of the synthesis of biselide A) are fairly well established, with sub-milligram amounts of material, a decision was made to stop at this point having secured a viable route to the advanced macrocyclic alcohol **113**.

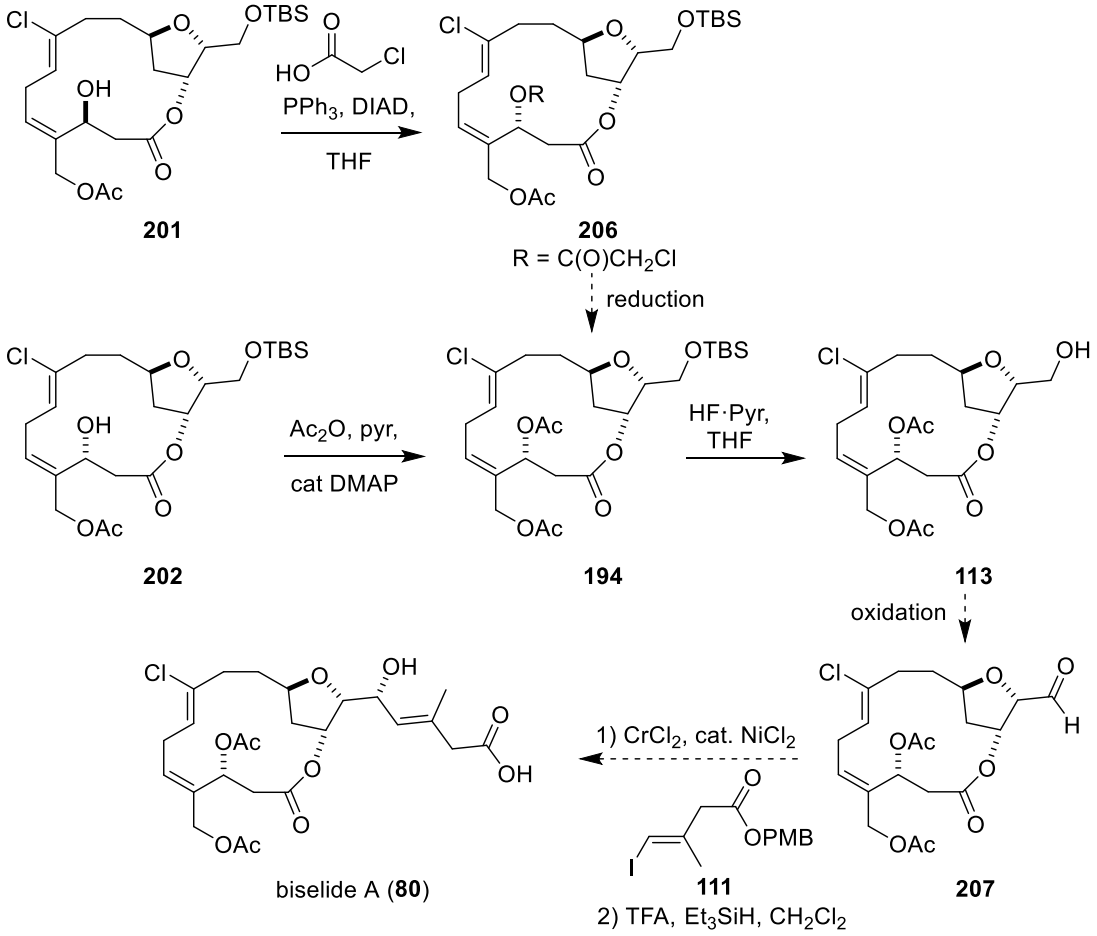


Scheme 3.40. Synthesis of macrocycle 113, three steps away from biselide A.

3.5. Future Studies

With the completion of the total synthesis of biselide A (**80**) close at hand and a route to the macrocycle established, two challenges must be addressed in order to advance material and explore the endgame. Firstly, the intramolecular Reformatsky reaction should be optimized for both yield and diastereoselectivity. Modifying the

reaction temperature or solvent or attempting a different Reformatsky-type reaction conditions may lead to improvements in both yield and ratio of diastereomers. Should the diastereomeric ratio not improve, the chloroacetic acid Mitsunobu reaction should be optimized to avoid elimination and reduction of the α-chloroacetate should be explored. Finally, oxidation of the primary alcohol to give **207** followed by NHK coupling reaction with vinyl iodide **111** and deprotection of the PMB ester should allow access to our target compound biselide A (**80**) in sufficient quantities for biological testing (Scheme 3.41).



Scheme 3.41. Final steps to the completion of biselide A (80).

3.6. Conclusion

In conclusion, an advanced macrocyclic synthetic precursor to biselide A has been accessed, which represents a significant step towards the first total synthesis of

this natural product. In accessing this advanced synthetic intermediate, we also demonstrated the utility of our chlorohydrin-based strategy for tetrahydrofuran synthesis in the rapid and highly diastereoselective preparation of the tetrahydrofuranol core of biselide A. Furthermore, while ultimately unsuccessful, our attempts to effect the macrolactonization of an advanced *seco* acid revealed an unexpected conformational rigidity in $CDCl_3$ that is maintained by hydrogen bonding between the tetrahydrofurandiol and carboxylic acid. Further, we were able to exploit this knowledge and the proximity of the carboxylic acid and alcohol functions by effecting a straightforward Brønsted acid-catalyzed macrolactonization. While Brønsted acid-catalyzed macrolactonization delivered the undesired macrolactone, we were ultimately able to access the 14-membered ring of biselide A through an intramolecular Reformatsky reaction. Notably, following this strategy, the macrolactone was made available in 15 steps and it is expected that the further optimization of the cross metathesis and Reformatsky reactions should result in a substantial increase in the overall yield of this process. Furthermore, the projected number of steps in this total synthesis is 20, which represents one of the most step efficient synthesis of any member of the haterumalides or biselides. The overall efficiency of this biselide A synthesis suggests that it should also support production of sufficient amounts of material to enable further evaluation of its biological properties and explore its utility as an anti-cancer therapeutic.

3.7. Experimental

3.7.1. General

All reactions described were performed under an atmosphere of dry nitrogen using oven dried glassware unless otherwise specified. Flash chromatography was carried out with 230-400 mesh silica gel (Silicycle, SiliaFlash® P60 or E. Merck, Silica Gel 60) following the technique described by Still.[46] Concentration and removal of trace solvents was done via a Büchi rotary evaporator using dry ice/acetone condenser and vacuum applied from a Büchi V-500 pump.

All reagents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, TCI America or Strem and were used without further purification. All solvents

were purchased from Sigma Aldrich, EMD, Anachemia, Caledon, Fisher or ACP and used with further purification unless otherwise specified. Diisopropylamine and CH_2Cl_2 were freshly distilled over CaH_2. THF was freshly distilled over Na metal/benzophenone. 1,4-Dioxanone was dried over activated 3 Å sieves. Cold temperatures were maintained by use of the following conditions: 5 °C, fridge (True Manufacturing, TS-49G); 0 °C, ice-water bath; −78 °C, acetone-dry ice bath; temperatures between −78 °C and 0 °C required for longer reaction times were maintained with a Neslab Cryocool Immersion Cooler (CC-100 II) in a EtOH/2-propanol bath.

Optical rotation was measured on a Perkin Elmer 341 Polarimeter at 589 nm.

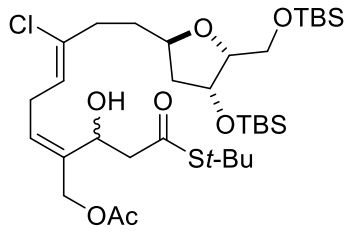
Nuclear magnetic resonance (NMR) spectra were recorded using chloroform-d ($CDCl_3$), or methanol-d_4 (CD_3OD). Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent (^{1}H NMR: $CDCl_3$: δ 7.26, CD_3OD: δ 3.35; ^{13}C NMR: $CDCl_3$: δ 77.16, CD_3OD: δ 49.3. 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; q, quartet; quint, quintet; m, multiplet; b, broad), coupling constants, number of protons. NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Bruker 500 (500 MHz), or Bruker 400 (400 MHz). Assignments of ^{1}H and ^{13}C NMR spectra are based on analysis of COSY, HSQC, HMBC, TOCSY and 1D and 2D NOESY spectra, where applicable.

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two™ Fourier transform spectrometer with neat samples. Only selected, characteristic absorption data are provided for each compound.

High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS using ESI-MS or was carried out by the Notre Dame University Mass Spectrometry Department using EI technique.

High performance liquid chromatography (HPLC) were performed on an Agilent 1200 Series equipped with a variable wavelength UV-Vis detector (λ = 220 nm) and Daicel Chemical Industries, Ltd. Chiralpak® AD chiral column (4.6 × 250 mm).

3.7.2. Preparation of (*2Z*,*5Z*)-8-((*2R*,*4R*,*5R*)-4-((tert-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-2-(3-(*tert*-butylthio)-1-hydroxy-3-oxopropyl)-6-chloroocta-2,5-dien-1-yl acetate (172)



To a cold (0 °C) stirred solution of DIPA (125 µL, 0.89 mmol) in dry tetrahydrofuran (10 mL) was added *n*-butyllithium (2.5 M in hexane, 0.330 mL, 0.814 mmol). The reaction mixture was stirred for 15 min. After this time, the solution was cooled to -78 °C and S-(*tert*-butyl) ethanethioate (**171**) (99.6 mg, 0.74 mmol) was added. The reaction mixture was then stirred at -78 °C for 30 minutes to prepare a 0.071 M stock solution of the ester enolate. Separately, aldehyde **163** (13.0 mg, 0.0226 mmol) was stirred in dry tetrahydrofuran (0.2 mL) and cooled to -78 °C. The enolate mixture (0.46 mL, 0.071 M, 0.033 mmol) was added to the solution of aldehyde and the reaction mixture was then stirred at -78 °C for 30 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:EtOAc, 17:3) afforded compound **172** (11 mg, 0.016 mmol, 69%) as a light yellow oil.

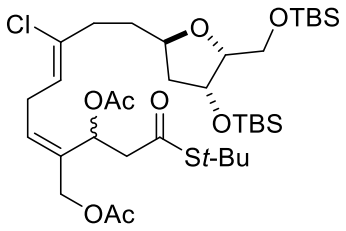
^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.59 (t, *J* = 7.5 Hz, 1 H), 5.45 (t, *J* = 7.2 Hz, 1 H), 5.09 (bd, *J* = 9.8 Hz, 1 H), 4.67 (d, *J* = 12.7 Hz, 1 H), 4.57 (d, *J* = 12.4 Hz, 1 H), 4.37 (t, *J* = 3.1 Hz, 1 H), 4.14 (m, 1 H), 3.86 (dt, *J* = 3.5, 6.0 Hz , 1 H), 3.77 (dd, *J* = 6.3, 10.3 Hz, 1 H), 3.69 (dd, *J* = 5.8, 10.3 Hz), 2.99 (m, 2 H), 2.87 (dd, *J* = 9.7, 15.7 Hz, 1 H), 2.62 (dd, *J* = 3.3, 15.7 Hz, 1 H), 2.49 (m, 1 H), 2.36, (m, 1 H), 2.08, (s, 3 H), 1.93 (dd, *J* = 5.5, 12.2 Hz, 1 H), 1.76 (m, 2 H), 1.63 (ddd, *J* = 4.0, 9.9, 13.7 Hz, 1 H), 1.48 (s, 9 H), 0.89 (d, *J* = 2.2 Hz, 18 H), 0.65 (s, 6 H), 0.58 (d, *J* = 3.0 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 199.8, 170.8, 136.1, 136.1, 135.3, 135.3, 130.1, 130.1, 122.3, 122.2, 122.0, 83.4, 76.8, 72.7, 66.4, 65.1, 62.0, 50.1, 48.8, 42.2, 36.5, 34.2, 29.9, 27.3, 26.2, 25.9, 21.3, -4.6, -4.9, -5.0, -5.1

IR: 3452, 2955, 2929, 2857, 1741, 1682, 1472, 1363, 1250, 1057, 836, 776 cm^{-1}.

HRMS: m/z calcd for $C_{34}H_{63}ClO_7SSi_2$: 729.3414 (M+Na); Found: 729.3403 (M+Na).

3.7.3. Preparation of (*Z*)-2-((*Z*)-6-((*2R*,*4R*,*5R*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-chlorohex-3-en-1-ylidene)-5-(*tert*-butylthio)-5-oxopentane-1,3-diyl diacetate (173)



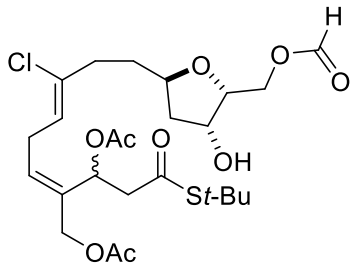
To a stirred solution of thioester **172** (25 mg, 0.0354 mmol) in acetic anhydride (0.5 mL) and pyridine (0.5 mL) was added a catalytic amount of DMAP. The reaction mixture was stirred for 1 hour at room temperature and then the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:EtOAc, 19:1) afforded compound **173** (26 mg, 0.0347 mmol, 98%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.05 (dd, *J* = 5.3, 9.2 Hz, 1 H), 5.64 (t, *J* = 7.5 Hz, 1 H), 5.48 (t, *J* = 7.0 Hz, 1 H), 4.57 (d, *J* = 12.5 Hz, 1 H), 4.50 (d, *J* = 12.2 Hz, 1 H), 4.36 (t, *J* = 3.2 Hz, 1 H), 4.16 (m, 1 H), 3.86 (dt, *J* = 3.6, 6.1 Hz , 1 H), 3.77 (dd, *J* = 6.3, 10.2 Hz, 1 H), 3.69 (dd, *J* = 5.9, 10.2 Hz), 3.1 (t, *J* = 7.6 Hz, 2 H), 2.98 (dd, *J* = 9.1, 15.2 Hz, 1 H), 2.70 (dd, *J* = 5.2, 15.2 Hz, 1 H), 2.48 (m, 1 H), 2.34, (m, 1 H), 2.08, (s, 3 H), 2.02, (s, 3 H), 1.94 (ddd, *J* = 1.3, 5.5, 12.7 Hz, 1 H), 1.76 (m, 2 H), 1.61 (m, 1 H), 1.45 (s, 9 H), 0.89 (d, *J* = 1.7 Hz, 18 H), 0.64 (s, 6 H), 0.56 (d, *J* = 2.2 Hz, 6 H).

IR: 2954, 2929, 2857, 1746, 1364, 1250, 1225, 1086, 1022, 836, 776 cm^{-1}.

HRMS: m/z calcd for $C_{36}H_{65}ClO_8SSi_2$: 771.3519 (M+Na); Found: 771.3506 (M+Na).

3.7.4. Preparation of (*Z*)-5-(*tert*-Butylthio)-2-((*Z*)-4-chloro-6-((*2R*,*4R*,*5R*)-5-((formyloxy)methyl)-4-hydroxytetrahydrofuran-2-yl)hex-3-en-1-ylidene)-5-oxopentane-1,3-diyl diacetate (175)

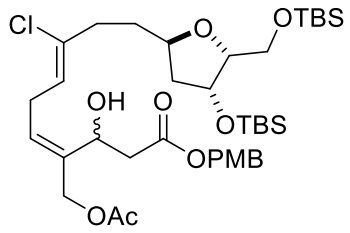


To a vial containing thioester (**173**) (3.3 mg, 0.00441 mmol) was added a mixture of 6:4:1 THF:formic acid:H_2O (0.1 mL). The reaction mixture was stirred for 48 hours at which the solution was diluted with EtOAc (0.5 mL) and added to a solution of saturated sodium bicarbonate (0.5 mL) at 0 °C. The mixture was extracted with EtOAc (3 x 0.5 mL) and the combined organic phases were dried over anhydrous magnesium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:EtOAc, 1:1, then ethyl acetate) afforded compound **175** (1.5 mg, 0.00273 mmol, 62%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.1 (d, *J* = 0.7 Hz, 1 H), 6.05 (ddd, *J* = 2.5, 5.5, 8.6 Hz, 1 H), 5.66 (m, 1 H), 5.51 (m, 1 H), 4.57 (dd, *J* = 4.7, 12.6 Hz, 1 H), 4.52 (d, *J* = 3.8, 9.1 Hz, 1 H), 4.50 (m, 1 H), 4.40 (dd, *J* = 4.0, 8.0 Hz,1 H), 4.26 (m, 1 H), 4.25 (m, 1 H), 4.07 (dt, *J* = 3.4, 6.2 Hz, 1 H), 3.76 (m, 0.5 H), 3.62 (m, 0.5 H), 3.12 (m, 2 H), 2.98 (dd, *J* = 8.9, 15.2 Hz, 1 H), 2.70 (dd, *J* = 5.2, 15.2 Hz, 1 H), 2.60-2.36 (m, 3 H), 2.08, (s, 3 H), 2.03, (s, 3 H), 1.90-1.72 (m, *3* H), 1.46 (s, 9 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 196.1, 196.1, 170.9, 170.9, 170.0, 169.9, 161.3, 135.6, 135.6, 132.9, 132.8, 131.7, 131.7, 122.7, 122.6, 79.5, 79.5, 76.8, 72.7, 72.7, 68.1, 68.1, 65.0, 65.0, 62.7, 62.6, 47.8, 41.7, 41.6, 36.2, 36.2, 33.5, 33.5, 29.8, 27.5, 21.2.

3.7.5. Preparation of 4-Methoxybenzyl (*4Z*,*7Z*)-4-(acetoxymethyl)-10-((*2R*,*4R*,*5R*)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-8-chloro-3-hydroxydeca-4,7-dienoate (178)

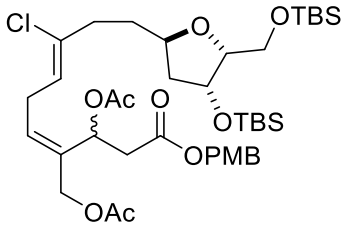


To a cold (0°C) stirred solution of DIPA (125 µL, 0.89 mmol) in dry tetrahydrofuran (10 mL) was added *n*-butyllithium (2.2 M in hexane, 0.405 mL, 0.814 mmol). The reaction mixture was then stirred for 15 min. After this time, the reaction mixture was cooled to -78 °C and 4-methoxybenzyl acetate (**177**) (170 µL, 0.74 mmol) was added. The reaction mixture was stirred at -78 °C for 30 minutes to prepare a 0.071 M stock solution of ester enolate. Separately, aldehyde **163** (21.0 mg, 0.0365 mmol) was stirred in dry tetrahydrofuran (0.35 mL) and cooled to -78 °C. The enolate mixture (0.74 mL, 0.071 M, 0.055 mmol) was added to the solution of the aldehyde and the reaction mixture was stirred at -78 °C for 30 minutes. The reaction was then quenched with saturated aqueous ammonium chloride (0.5 mL). The mixture was extracted with ethyl acetate (3 x 1.0 mL) and the combined organic phases were washed with water (0.8 mL), brine (0.8 mL), then dried with anhydrous magnesium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:EtOAc, 75:25) afforded compound **178** (21 mg, 0.028 mmol, 76%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 6.9 Hz, 2 H), 5.57 (t, *J* = 7.4 Hz, 1 H), 5.44 (t, *J* = 7.0 Hz, 1 H), 5.1 (dd, *J* = 5.0, 6.8 Hz, 1 H), 5.04 (s, 3 H), 4.68 (d, *J* = 12.2 Hz, 1 H), 4.62 (m, 1 H), 4.57 (d, *J* = 12.2 Hz, 1 H), 4.36 (t, *J* = 3.7 Hz, 1 H), 4.15 (m, 1 H), 3.86 (m, 1 H), 3.77 (dd, *J* = 7.0, 10.8 Hz, 1 H), 3.68 (dd, *J* = 6.0, 10.2 Hz), 2.97 (m, 2 H), 2.77 (dd, *J* = 9.8, 16.5 Hz, 1 H), 2.51 (m, 1 H), 2.48 (dd, *J* = 3.2, 16.5 Hz, 1 H), 2.35 (m, 1 H), 2.08, (s, 3 H), 1.93 (dd, *J* = 5.0, 12.1 Hz, 1 H), 1.74 (m, 2 H), 1.63 (m, 1 H), 0.89 (d, *J* = 1.4 Hz, 18 H), 0.65 (s, 6 H), 0.56 (d, *J* = 2.2 Hz, 6 H).

HRMS: m/z calcd for $C_{38}H_{63}ClO_9Si_2$: 777.3591 (M+Na); Found: 777.3590 (M+Na).

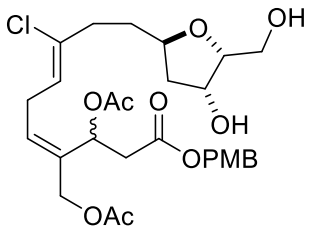
3.7.6. Preparation of (*Z*)-2-((*Z*)-6-((*2R*,*4R*,*5R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4-chlorohex-3-en-1-ylidene)-5-((4-methoxybenzyl)oxy)-5-oxopentane-1,3-diyl diacetate (179)



To a stirred solution of PMB ester **178** (8.0 mg, 0.0106 mmol) in acetic anhydride (0.1 mL) and pyridine (0.1 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*. Purification of the crude product by flash chromatography (pentane:EtOAc, 85:15) afforded compound **179** (8.0 mg, 0.010 mmol, 95%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 6.9 Hz, 2 H), 5.57 (t, *J* = 7.4 Hz, 1 H), 5.44 (t, *J* = 7.0 Hz, 1 H), 5.1 (dd, *J* = 5.0, 6.8 Hz, 1 H), 5.04 (s, 3 H), 4.68 (d, *J* = 12.2 Hz, 1 H), 4.62 (m, 1 H), 4.57 (d, *J* = 12.2 Hz, 1 H), 4.36 (t, *J* = 3.7 Hz, 1 H), 4.15 (m, 1 H), 3.86 (m, 1 H), 3.77 (dd, *J* = 7.0, 10.8 Hz, 1 H), 3.68 (dd, *J* = 6.0, 10.2 Hz), 2.97 (m, 2 H), 2.77 (dd, *J* = 9.8, 16.5 Hz, 1 H), 2.51 (m, 1 H), 2.48 (dd, *J* = 3.2, 16.5 Hz, 1 H), 2.35 (m, 1 H), 2.08, (s, 3 H), 1.93 (dd, *J* = 5.0, 12.1 Hz, 1 H), 1.74 (m, 2 H), 1.63 (m, 1 H), 0.89 (d, *J* = 1.4 Hz, 18 H), 0.65 (s, 6 H), 0.56 (d, *J* = 2.2 Hz, 6 H).

3.7.7. Preparation of (*Z*)-2-((*Z*)-4-Chloro-6-((*2R*,*4R*,*5R*)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)hex-3-en-1-ylidene)-5-((4-methoxybenzyl)oxy)-5-oxopentane-1,3-diyl diacetate (180)



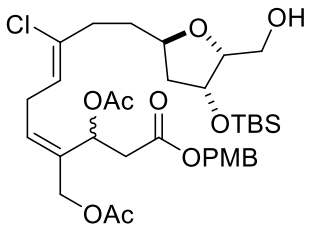
To a stirred solution of PMB ester **179** (80 mg, 0.100 mmol) in THF (1 mL) was added HF·Pyr (1 mL). The reaction mixture was stirred for 6 hours before EtOAc (5 mL) was added and quenched with a saturated aqueous solution of $NaHCO_3$ (4 mL). The mixture was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were dried with anhydrous magnesium sulfate, and filtered, and the solvent removed *in vacuo*, affording compound **180** (51 mg, 0.090 mmol, 91%). The crude mixture was used directly in the next reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 10.7 Hz, 2H), 6.05 (dd, *J* = 5.2, 9.4 Hz, 1H), 5.65 (m, 1H), 5.47 (t, *J* = 6.9 Hz, 0.5 H), 5.10 (d, *J* = 12 Hz, 1H), 5.04 (t, *J* = 11.0 Hz, 0.5 H) 5.04 (d, 12.1 Hz 1H), 4.56 (d, *J* = 12.6 Hz, 1H), 4.50 (m, 1H) 4.49 (d, *J* = 12.4 Hz, 1H), 4.25 (m 1H), 3.96 (m, 1H), 3.95 (m, 2H), 3.83 (s, 3H), 3.09 (m, 2H), 2.89 (dd, *J* = 9.4, 15.9 Hz, 1H), 2.62 (dd, *J* = 5.1, 15.9 Hz, 1H), 2.45 (m, 2H) , 2.30 (m, 1H), 2.11 (m, 1H), 2.03 (s, 3H), 1.95 (s, 3H), 1.88-1.69 (m, 2H)

IR: 3452, 2926, 2855, 1740, 1516, 1443, 1373, 1230, 1165, 1031, 824 cm^{-1}.

HRMS: *m/z* calcd for $C_{28}H_{37}ClO_{10}$: 591.1967 (M+Na); Found: 591.1972 (M+Na).

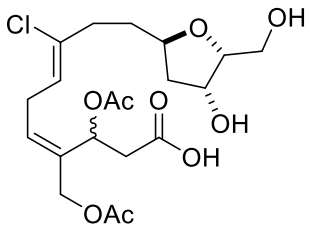
3.7.8. Preparation of (*Z*)-2-((*Z*)-6-((*2R*,*4R*,*5R*)-4-((*tert*-Butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-chlorohex-3-en-1-ylidene)-5-((4-methoxybenzyl)oxy)-5-oxopentane-1,3-diyl diacetate (182)



To a stirred solution of PMB ester **179** (32 mg, 0.040 mmol) in THF (1 mL) was added HF·Pyr (0.05 mL). The reaction mixture was stirred for 30 minutes before EtOAc (5 mL) was added and quenched with a saturated aqueous solution of $NaHCO_3$ (4 mL). The mixture was extracted with EtOAc (2 x 10 mL) and the combined organic extracts were dried with anhydrous magnesium sulfate, and filtered, and the solvent removed *in vacuo*, affording compound **182** (22 mg, 0.032 mmol, 81%). The crude mixture was used directly in the next reaction.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.05 (dd, *J* = 5.2, 9.4 Hz, 1H), 5.65 (m, 1H), 5.47 (t, *J* = 6.9 Hz, 0.5 H), 5.10 (d, *J* = 12 Hz, 1H), 5.04 (t, *J* = 11.0 Hz, 0.5 H) 5.04 (d, 12.1 Hz 1H), 4.56 (d, *J* = 12.6 Hz, 1H), 4.50 (m, 1H) 4.49 (d, *J* = 12.4 Hz, 1H), 4.18 (dt *J* = 6.3, 14.8 Hz, 1H), 4.01 (q, *J* = 4.7 Hz, 1H), 3.83 (s, 3H), 3.80 (m, 1H), 3.73 (m, 1H), 3.09 (m, 2H), 2.89 (dd, *J* = 9.4, 15.9 Hz, 1H), 2.62 (dd, *J* = 5.1, 15.9 Hz, 1H), 2.46 (m, 1H), 2.36 (m, 1H), 2.3 (m, 1H), 2.03 (s, 3H), 1.97 (m, 1H), 1.95 (s, 3H), 1.83-1.69 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H).

3.7.9. Preparation of (*4Z*,*7Z*)-3-Acetoxy-4-(acetoxymethyl)-8-chloro-10-((2R,4R,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)deca-4,7-dienoic acid (181)



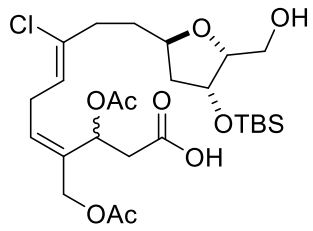
To a solution of diol **180** (8.1 mg, 0.014 mmol) and Et_3SiH (22.3 µL, 0.140 mmol) in CH_2Cl_2 (0.15 mL) at 0 °C was slowly added TFA (0.05 mL). After the reaction mixture was stirred for 15 minutes, while being monitored via TLC, the reaction mixture was diluted with CH_2Cl_2 (2 mL) and quenched with a saturated aqueous solution of $NaHCO_3$ (0.5 mL). The mixture was extracted (3 x 2 mL) and the combined organic phase was dried with anhydrous sodium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (CH_2Cl_2:MeOH, 92:8) afforded compound **181** (4.0 mg, 0.0089 mmol, 64%) as a colourless oil.

^{1}H NMR (600 MHz, MeOD) δ: 6.03 (dd, *J* = 5.3, 9.2 Hz, 1H), 5.70 (t, *J* = 7.4 Hz, 1H), 5.61 (t, *J* = 7.0 Hz, 1 H), 5.10 (d, *J* = 12 Hz, 1H), 4.60 (d, 12.4 Hz 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.38 (t, *J* = 3.9 Hz, 1H) 4.21 (m, 1H), 3.92 (m, 1H), 3.75 (dd, *J* = 5.1, 11.5 Hz, 1H), 3.69 (dd, *J* = 6.5, 11.4 Hz, 1H), 3.13 (m, 2H), 2.86 (dd, *J* = 9.5, 16.2 Hz, 1H), 2.62 (dd, *J* = 5.2, 16.2 Hz, 1H), 2.45 (m, 2H), 2.05 (s, 3H), 2.03 (m, 1H), 2.02 (s, 3H), 1.81-1.72 (m, 3H).

IR: 3364, 2923, 2852, 1737, 1674, 1515, 1435, 1375, 1231, 1029 cm^{-1}.

HRMS: *m/z* calcd for $C_{20}H_{29}ClO_9$: 471.1392 (M+Na); Found: 471.1384 (M+Na).

3.7.10. Preparation of (*4Z*,*7Z*)-3-Acetoxy-4-(acetoxymethyl)-10-((*2R*,*4R*,*5R*)-4-((tert-butyldimethylsilyl)oxy)-5-(hydroxymethyl)tetrahydrofuran-2-yl)-8-chlorodeca-4,7-dienoic acid (183)

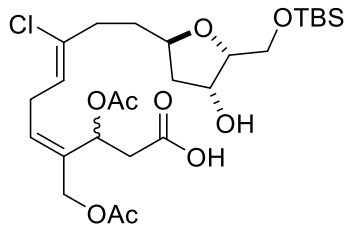


To a solution of PMB ester **182** (4.3 mg, 0.0063 mmol) and Et_3SiH (4.2 µL, 0.063 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was slowly added TFA (0.5 mL). After the reaction mixture was stirred for 15 minutes, while being monitored via TLC, the reaction mixture was diluted with CH_2Cl_2 (2 mL) and quenched with a saturated solution of $NaHCO_3$ (0.5 mL). The mixture was extracted (3 x 2 mL) and the combined organic phase was dried with anhydrous sodium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (CH_2Cl_2:MeOH, 96:4) afforded compound **183** (2.1 mg, 0.0037 mmol, 59%) as a colourless oil.

^{1}H NMR (600 MHz, MeOD) δ: 6.03 (dd, *J* = 5.0, 9.2 Hz, 1H), 5.69 (t, *J* = 7.5 Hz, 1H), 5.60 (t, *J* = 6.7 Hz, 1 H), 5.10 (d, *J* = 12 Hz, 1H), 4.59 (d, 12.6 Hz 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.46 (t, *J* = 3.8 Hz, 1H) 4.18 (m, 1H), 3.95 (dt, *J* = 3.7, 5.8 Hz, 1H), 3.66 (d, *J* = 5.8, 2H), 3.12 (dt, *J* = 7.5, 8.3 Hz, 2H), 2.85 (dd, *J* = 9.4, 16.1 Hz, 1H), 2.61 (dd, *J* = 5.1, 16.3 Hz, 1H), 2.49 (m, 1H), 2.41 (m, 1H), 2.04 (s, 3H), 2.02 (s, 3H), 1.99 (dd, *J* = 6.1, 13.0 Hz, 1H), 1.87-1.70 (m, 3H), 0.91 (s, 9H), 0.10 (d, 6H).

HRMS: *m/z* calcd for $C_{26}H_{43}ClO_9Si$: 585.2257 (M+Na); Found: 585.2242 (M+Na).

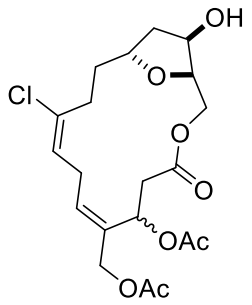
3.7.11. Preparation of (*4Z*,*7Z*)-3-Acetoxy-4-(acetoxymethyl)-10-((*2R*,*4R*,*5R*)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-hydroxytetrahydrofuran-2-yl)-8-chlorodeca-4,7-dienoic acid (147)



To a solution of the *seco* acid **181** (7.0 mg, 0.016 mmol) in CH_2Cl_2 (0.3 mL) was added imidazole (4.2 mg, 0.062 mmol), a catalytic amount of DMAP and then TBSCl (5.9 mg, 0.039 mmol) and stirred for 2 hours while being monitored by TLC. The reaction was then diluted with CH_2Cl_2 (1 mL) and the reaction quenched with a solution of 1M HCl (0.5 mL). The mixture was extracted with CH_2Cl_2 (3 x 1 mL) and the combined organic phases were washed with brine (1 mL), then dried with anhydrous sodium sulfate, and filtered, and the solvent removed in vacuo. This crude mixture was then dissolved in a 2:1 mixture of THF and H_2O and cooled to 0 °C. To this mixture was added acetic acid (10 µL). After the mixture had been stirred for 1 hour, the solvent was removed *in vacuo* and directly purified by flash chromatography (CH_2Cl_2:MeOH, 96:4) afforded compound **147** (4 mg, 0.0071 mmol, 46%) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.03 (m, 1H), 5.92 (t, *J* = 7.8 Hz, 0.5 H), 5.79 (t, *J* = 7.5 Hz, 0.5 H), 5.57 (t, *J* = 7.0 Hz, 0.5 H), 5.47 (t, *J* = 6.7 Hz, 0.5 H), 4.67 (m, 2 H), 4.53 (t, *J* = 3.7 Hz, 0.5 H), 4.42 (t, *J* = 3.5 Hz, 0.5 H), 4.19 (m, 1H), 3.97-3.87 (m, 3 H), 3.20 (m, 1 H), 3.024 (m, 1 H), 2.85 (m, 1H), 2.71 (m, 1 H), 2.56-2.33 (m, 2H), 2.17 (m, 1 H), 2.07 (s, 3H), 2.05 (s, 1.5 H), 2.04 (s, 1.5 H), 1.84-1.63 (m, 3 H), 0.89 (s, 9 H), 0.90 (m, 6 H)

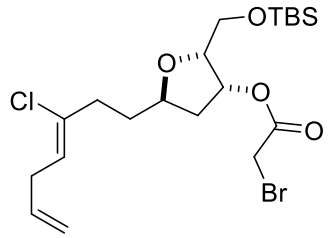
3.7.12. Preparation of ((*1R*,*7Z*,*10E*,*14R*,*16R*)-6-Acetoxy-11-chloro-16-hydroxy-4-oxo-3,17-dioxabicyclo[12.2.1]heptadeca-7,10-dien-7-yl)methyl acetate (187)



A solution of the *seco* acid **183** (2.5 mg, 0.0044 mmol) in $CDCl_3$ (1 mL) was added dropwise to a stirred solution of PTSA (4 mg, 0.023 mmol) in $CDCl_3$ (5 mL) at 60 °C over a period of 1.5 hours. After the addition, the reaction mixture was stirred at 60 °C for 18 hours. The reaction mixture was then cooled to -20 °C and filtered. The solvent was then distilled until solvent remained to obtain a NMR sample, which afforded compound **187** (1 mg, 0.0023 mmol, 53%).

^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.10 (m, 1 H), 5.96 (m, 1 H), 5.60 (t, *J* = 6.7 Hz, 0.5 H), 5.51 (t, *J* = 5.8 Hz, 0.5 H), 4.78-4.52 (m, 2 H), 4.45 (m, 1 H), 4.42 (dd, *J* = 6.1, 11.7 Hz, 1 H), 4.32 (dd, *J* = 3.5, 11.9, 1 H), 4.26 (m, 1 H), 4.09 (m, 1 H), 3.32 (m, 1 H), 2.89 (m, 1 H), 2.86, (m, 1 H), 2.76 (dd, *J* = 6.7, 16.0 Hz, 1 H), 2.60 (dd, *J* = 3.2, 16.5 Hz, 1 H), 2.60 (m, 1 H), 2.39, (m, 1 H), 2.07 (s, 1.5 H), 2.07 (s, 1.5 H), 2.04 (s, 3 H), 2.03 (m, 1 H), 1.85 (m, 1 H), 1.81-1.67 (m, 1 H), 1.58 (m, 1 H)

3.7.13. Preparation of (*2R*,*3R*,*5R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-((*Z*)-3-chlorohepta-3,6-dien-1-yl)tetrahydrofuran-3-yl 2-bromoacetate (196)



To a solution of the mono-TBS tetrahydrofuranol **197** (0.950g, 2.6 mmol) in CH_2Cl_2 (20 mL) was added DMAP (96 mg, 0.79 mmol) and bromoacetic acid (438 mg, 3.15 mmol) and cooled to 0 °C. DIC (0.61 mL, 3.9 mmol) was then added dropwise to the reaction mixture and the reaction was then stirred for 15 minutes. The reaction was then quenched by the addition of H_2O (15 mL) and extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phases were washed with brine (20 mL), then dried with anhydrous sodium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:EtOAc, 95:5) afforded compound **196** (1.05 g, 2.18 mmol, 84%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.78 (ddt, *J* = 6.2, 10.1, 16.3 Hz, 1 H), 5.53 (t, *J* = 7.0 Hz, 1 H), 5.49 (ddd, *J* = 1.1, 3.6, 5.2 Hz, 1 H), 5.03 (m, 2 H), 4.17 (dq, *J* = 6.0, 9.2 Hz, 1 H), 4.09 (ddd, *J* = 3.8, 5.9, 7.1 Hz, 1 H), 3.82 (s, 3 H), 3.79 (m, 1 H), 3.76 (dd, *J* = 2.9, 5.9 Hz, 1 H), 2.92 (t, *J* = 6.6 Hz, 2 H), 2.54-2.35 (m, 2 H), 2.15 (ddd, *J* = 1.4, 6.0, 14.0 Hz, 1 H), 1.86 (m, 1 H), 1.79 (dt, *J* = 6.6, 7.9 Hz, 2 H), 0.87 (s, 9 H), 0.49 (d, *J* = 3.3 Hz, 6 H).

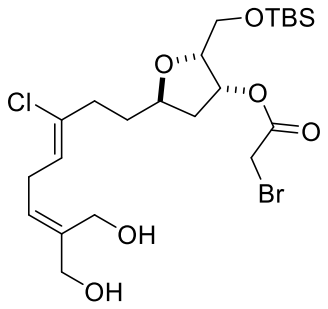
^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.5, 135.4, 135.1, 123.4, 115.5, 80.8, 77.0, 76.5, 61.1, 39.0, 36.4, 33.9, 32.9, 26.0, -5.19, -5.26.

IR: 2928, 1738, 1275, 1089, 836, 777 cm^{-1}.

HRMS: *m/z* calcd for $C_{20}H_{34}BrClO_4Si$: 503.0990 (M+Na); Found: 503.0993 (M+Na).

$[\alpha]_D^{20}$ = -20.0 (*c* = 0.10, $CHCl_3$).

3.7.14. Preparation of (*2R*,*3R*,*5R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-((*Z*)-3-chloro-6-(2,2-dimethyl-1,3-dioxan-5-ylidene)hex-3-en-1-yl)tetrahydrofuran-3-yl 2-bromoacetate (199)



To a 25 mL 3-neck round bottom flask was fitted with a reflux condenser and septa and was charged the Hoyveda-Grubbs II catalyst (18.5 mg, 0.031 mmol). CH_2Cl_2 (4 mL) was added via a syringe and the acetonide **138** (384 mg, 3.09 mmol) and bromoacetate **196** (495 mg, 1.03 mmol) in a solution of CH_2Cl_2 (0.5 mL) were added simultaneously via a syringe to the stirring solution. The solution was heated to reflux for 18 hours after which the reaction mixture was transferred to another round bottom flask and the solvent removed in vacuo. The reaction mixture was then put through a 1.5 inch neutral alumina plug (pentane:EtOAc, 90:10) and the solvent was removed *in vacuo*. To the reaction mixture was then added MeOH (25 mL) and PPTS (20 mg, 0.076 mmol) and stirred for 1 hour after which, EtOAc (40 mL) and H_2O (10 mL) were added. The reaction mixture was extracted with EtOAc (3 x 40 mL) and the combined organic phases were washed with brine (50 mL), then dried with anhydrous sodium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:EtOAc, 60:40) afforded compound **199** (230 mg, 0.424 mmol, 42%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.53 (t, *J* = 7.6 Hz, 1 H), 5.49 (t, *J* = 7.3 Hz, 1 H), 5.47 (t, *J* = 4.0 Hz, 1 H), 4.36 (bs, 2 H), 4.23 (bs, 2 H), 4.18-4.05 (m, 2 H), 3.83 (s, 3 H), 3.79 (m, 1 H), 3.75 (dd, *J* = 2.5, 5.9 Hz, 1 H), 2.97 (t, *J* = 7.4 Hz, 2 H), 2.53-2.32 (m, 2 H), 2.15 (ddd, *J* = 1.1, 5.8, 14.0 Hz, 1 H), 1.85 (m, 1 H), 1.79 (dt, *J* = 7.2, 7.5 Hz, 2 H), 0.87 (s, 9 H), 0.47 (d, *J* = 3.3 Hz, 6 H).

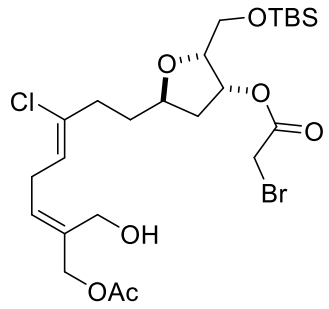
^{13}C NMR (150 MHz, $CDCl_3$) δ: 165.6, 137.5, 134.2, 125.9, 122.3, 79.8, 76.1, 75.6, 66.4, 60.1, 59.1, 38.0, 35.3, 32.8, 26.3, 24.9, -6.2, -6.3.

IR: 3366, 2928, 2856, 1739, 1462, 1277, 1256, 1092, 1007, 838, 778 cm^{-1}.

HRMS: *m/z* calcd for $C_{22}H_{38}BrClO_6Si$: 563.1220 (M+Na); Found: 563.1196 (M+Na).

$[\alpha]_D^{20}$ = -22.7 (*c* = 0.30, $CHCl_3$).

3.7.15. Preparation of (*2R*,*3R*,*5R*)-5-((*3Z*,*6E*)-8-Acetoxy-3-chloro-7-(hydroxymethyl)octa-3,6-dien-1-yl)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-yl 2-bromoacetate (200)



To a stirred solution of the diol **199** (60 mg, 0.11 mmol) in dry 1,4-dioxane (0.3 mL), was added vinyl acetate (30 µL, 0.324 mmol) and Amano PS-D Lipase (6 mg). The reaction mixture was then stirred for 2 hours at room temperature. To this mixture was then added EtOAc (3 mL) and anhydrous magnesium sulfate and then filtered and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:EtOAc,75:25) afforded compound **200** (50 mg, 0.086 mmol, 78%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.62 (t, *J* = 8.0 Hz, 1 H), 5.48 (m, *2* H), 4.65 (bs, 2 H), 4.22 (bs, 2 H), 4.15 (m, 1 H), 4.09 (m, 1 H), 3.83 (s, 2 H), 3.79 (m, 1 H), 3.75 (dd, *J* = 2.1, 5.7 Hz, 1 H), 3.01 (t, *J* = 7.4 Hz, 2 H), 2.53-2.32 (m, 2 H), 2.15 (dd, *J* = 5.9, 14.0 Hz, 1 H), 1.85 (m, 1 H), 1.78 (m, 2 H), 0.87 (s, 9 H), 0.47 (d, *J* = 3.3 Hz, 6 H).

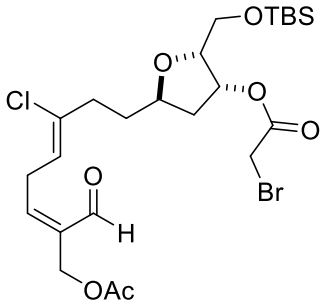
^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.13, 165.3, 134.2, 133.8, 129.2, 122.0, 79.8, 75.9, 75.4, 66.1, 60.1, 57.5, 38.0, 35.3, 32.9, 26.3, 25.0, 24.9, 17.4, -6.2, -6.3.

IR: 3442, 2933, 2857, 1739, 1279, 1257, 1096, 1022, 837 cm^{-1}.

HRMS: *m/z* calcd for $C_{24}H_{40}BrClO_7Si$: 605.1307 (M+Na); Found: 605.1297 (M+Na).

$[\alpha]_D^{20}$ = -5.3 (*c* = 0.30, $CHCl_3$).

3.7.16. Preparation of (*2R*,*3R*,*5R*)-5-((*3Z*,*6Z*)-8-Acetoxy-3-chloro-7-formylocta-3,6-dien-1-yl)-2-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-3-yl 2-bromoacetate (195)

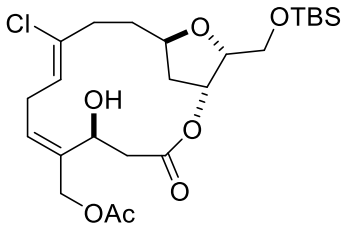


To a stirred solution of the monoacetate **200** (14 mg, 0.024 mmol) and $NaHCO_3$ (6 mg, 0.072 mmol) in CH_2Cl_2 (0.125 mL) was added Dess-Martin periodinane (12.2 mg, 0.029 mmol) and stirred for 1 hour. The reaction mixture was then diluted with pentane (0.15 mL) and purified directly by flash chromatography (pentane then pentane:EtOAc, 85:15), which afforded compound **195** (12 mg, 0.0206 mmol, 86%) as a colourless oil, which was immediately carried on to the next step.

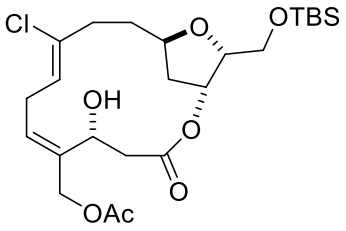
^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.17 (s, 1 H), 6.65 (t, *J* = 7.9 Hz, 1 H), 5.56 (t, *J* = 7.0 Hz, 1 H), 5.49 (t, *J* = 4.2 Hz, 1 H), 4.72 (bs, 2 H), 4.10 (m, 1 H), 3.83 (s, 2 H), 3.82 (m, 1 H), 3.75 (dd, *J* = 1.9, 5.8 Hz, 2 H), 3.49 (t, *J* = 7.7 Hz, 2 H), 2.57-2.32 (m, 2 H), 2.16 (ddd, *J* = 1.2, 5.9, 13.8 Hz, 1 H), 1.87 (m, 1 H), 1.79 (m, 2 H), 0.87 (s, 9 H), 0.47 (d, *J* = 3.4 Hz, 6 H)

HRMS: *m/z* calcd for $C_{24}H_{38}BrClO_7Si$: 603.1151 (M+Na); Found: 603.1149 (M+Na).

3.7.17. Preparation of ((*1R*,*5S*,*6Z*,*9Z*,*13R*,*15R*)-15-(((*tert*-Butyldimethylsilyl)oxy)methyl)-10-chloro-5-hydroxy-3-oxo-2,14-dioxabicyclo[11.2.1]hexadeca-6,9-dien-6-yl)methyl acetate (203) and ((*1R*,*5R*,*6Z*,*9Z*,*13R*,*15R*)-15-(((*tert*-butyldimethylsilyl)oxy)methyl)-10-chloro-5-hydroxy-3-oxo-2,14-dioxabicyclo[11.2.1]hexadeca-6,9-dien-6-yl)methyl acetate (204)



Major



Minor

To a cold (0 °C) solution of $Rh(PPh_3)_3Cl$ (0.48 mg, 0.52 µmol) in THF (0.36 mL) was added $ZnEt_2$ (1 M in hexanes, 0.227 mL, 0.227 mmol) and the resultant mixture was stirred vigorously. A solution of aldehyde **195** (6.0 mg, 0.0103 mmol) in THF (1.5 mL) was then added dropwise over a period of an hour. After addition, the reaction mixture was stirred for 1 hour and 15 minutes at 0 °C. The reaction was then quenched with an aqueous solution of saturated NH_4Cl (1 mL), diluted with EtOAc (2 mL), and filtered through a pad of Celite®. The reaction mixture was extracted with EtOAc (3 x 2 mL) and the combined organic phases were washed with brine (2 mL), then dried with anhydrous sodium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:EtOAc, 85:15 then 70:30) first afforded the minor diastereomer **202** (0.6 mg, 0.0012 mmol, 12%) as a colourless oil and then the major diastereomer **201** (2.2 mg, 0.0044 mmol, 42%) as a colourless oil.

Major Diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.10 (dd, *J* = 7.1, 9.2 Hz, 1 H), 5.55 (t, *J* = 6.9 Hz, 1 H), 5.29 (t, *J* = 3.8 Hz, 1 H), 4.81 (d, *J* = 12.4 Hz, 1 H), 4.79 (m, 1 H), 4.59 (d, *J* = 12.4 Hz, 1 H), 4.18 (dt, *J* = 4.2, 7.2 Hz, 1 H), 3.8 (m, 1 H), 3.72 (dd, *J* = 5.3, 6.2 Hz, 2 H), 3.11 (m, 1

H), 2.89 (m, 1 H), 2.74 (dd, *J* = 7.8, 12.7 Hz, 1 H), 2.67 (dd, *J* = 5.8, 12.7 Hz, 1 H), 2.41 (m, 1 H), 2.32-2.20 (m, 2 H), 2.10 (s, 3 H), 1.59-1.47 (m, 2 H), 0.87 (s, 9 H), 0.06 (d, *J* = 1.6 Hz, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.5, 170.4, 134.4, 134.2, 131.1, 123.2, 80.6, 76.4, 75.9, 66.5, 65.4, 61.2, 41.4, 38.6, 34.0, 29.6, 28.6, 26.3, 22.2, 21.0, 18.31, 14.1, -5.2, -5.4.

HRMS: *m/z* calcd for $C_{24}H_{39}ClO_7Si$: 525.2046 (M+Na); Found: 525.2049 (M+Na).

IR: 3448, 2967, 2932, 2859, 1734, 1472, 1366, 1255, 1234, 1136, 1080, 837, 777 cm^{-1}.

$[\alpha]_D^{20}$ = +6.0 (*c* = 0.10, $CHCl_3$).

Minor Diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.00 (dd, *J* = 7.5, 10.8 Hz, 1 H), 5.24 (t, *J* = 3.1 Hz, 1 H), 5.18 (d, *J* = 8.8 Hz, 1 H), 5.03 (d, *J* = 12.9 Hz, 1 H), 4.71 (m, 1 H), 4.67 (d, *J* = 12.9 Hz, 1 H), 4.12 (t, *J* = 7.0 Hz, 1 H), 3.85 (m, 1 H), 3.77 (d, *J* = 7.2 Hz, 2 H), 3.34 (m, 1 H), 2.86 (dd, *J* = 4.3, 11.7 Hz, 1 H), 2.67 (t, *J* =11.7 Hz, 1 H), 2.66 (m, 1 H), 2.37 (m, 1 H), 2.18 (m, 1 H), 2.10 (s, 3 H), 2.01 (dd, *J* = 3.7, 13.0, 1 H), 1.86 (m, 1 H), 1.49-1.40 (m, 2 H), 0.87 (s, 9 H), 0.04 (d, *J* = 1.1 Hz, 6 H).

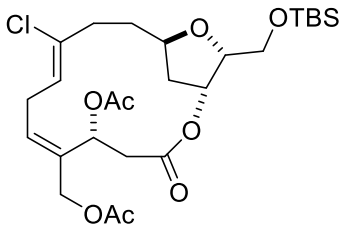
^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.0, 169.0, 136.4, 133.0, 132.8, 124.3, 80.6, 76.3, 75.3, 65.9, 65.3, 61.0, 40.8, 37.8, 35.0, 29.8, 28.1, 26.5, 26.0, 21.3, 15.4, -5.2, -5.3.

IR: 3460, 2955, 2930, 2857, 1737, 1464, 1377, 1250, 1081, 837, 778 cm^{-1}.

HRMS: *m/z* calcd for $C_{24}H_{39}ClO_7Si$: 525.2046 (M+Na); Found: 525.2047 (M+Na).

$[\alpha]_D^{20}$ = -11.7 (*c* = 0.70, $CHCl_3$).

3.7.18. Preparation of ((*1R*,*5R*,*6Z*,*9Z*,*13R*,*15R*)-5-Acetoxy-15-(((*tert*-butyldimethylsilyl)oxy)methyl)-10-chloro-3-oxo-2,14-dioxabicyclo[11.2.1]hexadeca-6,9-dien-6-yl)methyl acetate (194)



To a stirred solution of macrocycle **202** (1.2 mg, 0.0024 mmol) in CH_2Cl_2 (0.1 mL) at room temperature was added a catalytic amount of DMAP, acetic anhydride (25 µL) and pyridine (25 µL). The reaction was stirred for 5 minutes and then was quenched with H_2O (0.2 mL) and reaction mixture was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic phases were washed with brine (1 mL), then dried with anhydrous sodium sulfate, and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (pentane:EtOAc, 85:15) afforded compound **194** (1.0 mg, 0.002 mmol, 75%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.05 (dd, *J* = 6.9, 11.2 Hz, 1 H), 5.82 (dd, *J* = 4.8, 11.8 Hz, 1 H), 5.26 (t, *J* = 3.0 Hz, 1 H), 5.20 (dd, *J* = 2.1, 7.1 Hz, 1 H), 4.96 (d, *J* = 13.2 Hz, 1 H), 4.73 (d, *J* = 13.2 Hz, 1 H), 4.13 (dt, *J* = 4.1, 7.1 Hz, 1 H), 3.90 (dt, *J* = 4.4. 12.3 Hz, 1 H), 3.77 (d, *J* = 7.1 Hz, 2 H), 3.62 (m, 1 H), 2.84 (t, *J* = 11.7 Hz, 1 H), 2.67 (dd, *J* = 4.5, 11.7 Hz, 1 H), 2.66 (m, 1 H), 2.52 (m, 1 H), 2.39 (m, 1 H), 2.18 (m, 1 H), 2.10 (s, 3 H), 2.08 (m, 1 H), 2.04 (s, 3 H), 1.51-1.38 (m, 2 H), 0.86 (s, 9 H), 0.04 (d, *J* = 2.5 Hz, 6 H).

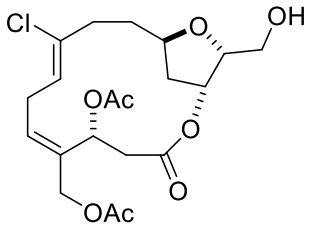
^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.7, 169.4, 168.1, 134.3, 133.1, 132.2, 124.3, 80.7, 76.3, 75.7, 66.5, 64.2, 60.9, 38.0, 37.8, 35.0, 29.9, 28.0, 26.9, 26.0, 21.3, 21.2, 1.2, -5.2, -5.3.

IR: 2959, 2929, 1739, 1433, 1373, 1229, 1079, 838, 780 cm^{-1}.

HRMS: *m/z* calcd for $C_{26}H_{41}ClO_8Si$: 567.2151 (M+Na); Found: 567.2161 (M+Na).

$[\alpha]_D^{20}$ = -14.1 (*c* = 0.31, $CHCl_3$).

3.7.19. Preparation of ((*1R*,*5R*,*6Z*,*9Z*,*13R*,*15R*)-5-Acetoxy-10-chloro-15-(hydroxymethyl)-3-oxo-2,14-dioxabicyclo[11.2.1]hexadeca-6,9-dien-6-yl)methyl acetate (113)



To a stirred solution of macrocycle **194** (1 mg, 0.002 mmol) in THF (0.5 mL) was added HF·Pyr (25 µL). The reaction mixture was stirred for 1 hour before being quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL). The mixture was extracted with EtOAc (3 x 3 mL) and the combined organic extracts were dried with anhydrous magnesium sulfate and concentrated *in vacuo*, affording compound **113** (0.7 mg, 0.002 mmol, 89%) which was characterized without purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.06 (dd, *J* = 7.0, 11.0 Hz, 1 H), 5.81 (dd, *J* = 4.6, 11.5 Hz, 1 H), 5.27 (t, *J* = 3.1 Hz, 1 H), 5.21 (dd, *J* = 1.3, 8.1 Hz, 1 H), 4.90 (d, *J* = 13.2 Hz, 1 H), 4.71 (d, *J* = 13.2 Hz, 1 H), 4.22 (dt, *J* = 4.5, 9.1 Hz, 1 H), 3.91 (m, 1 H), 3.85 (m, 1 H), 3.67 (m, 1 H), 3.55 (m, 1 H), 2.84 (t, *J* = 11.9 Hz, 1 H), 2.74 (dd, *J* = 4.6, 12.3 Hz, 1 H), 2.67 (m, 1 H), 2.54 (m, 1 H), 2.42 (m, 1 H), 2.20 (m, 1 H), 2.09 (s, 3 H), 2.04 (s, 3 H), 1.77 (dd, *J* = 4.0, 8.2 Hz, 1 H), 1.51-1.41 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 170.5, 169.2, 167.9, 134.5. 132.8, 132.0, 124.1, 81.0, 76.0, 75.9, 76.0, 66.1, 64.1, 61.4, 37.8, 37.8, 37.7 34.9, 27.8, 26.7, 21.0

IR: 3454, 2956, 2925, 2855, 1736, 1232, 1047, 930, 838, 777 cm^{-1}.

HRMS: m/z calcd for $C_{20}H_{27}ClO_8$: 453.1283 (M+Na); Found: 453.1283 (M+Na).

$[\alpha]_D^{20}$ = +6.8 (*c* = 0.22, $CHCl_3$).

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