Total Synthesis of Tetrahydrofuranol-Containing Natural Products and Studies Toward Eleutherobin

by

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Abstract

An extension of previously developed methodology towards the synthesis of tetrahydrofuranol rings is demonstrated in the total synthesis of amphirionin-4 in 11 steps comprising the first total synthesis of this natural product. Furthermore, we were able to exploit this methodology toward the total synthesis and structural reassignment of laurefurenyne A. The development of a flexible and concise synthesis allowed for access to the proposed stereostructure of the natural product and, following analysis of spectral data, indicated this structure had been misassigned. Further synthetic efforts completed the synthesis of the correct structure of laurefurenyne A and enabled investigations into the biosynthesis of this natural product.

An additional study describes efforts toward the synthesis of the promising anti-cancer natural product eleutherobin. As part of these efforts we have developed a cyclobutanone α-arylation/ring expansion strategy that affords access to α-tetralones. This methodology has been expanded toward the synthesis of a wide range of α-arylcyclobutanones and α-tetralones including the incorporation of heterocycles. Our efforts towards the synthesis of the core of eleutherobin through an α-tetralone intermediate are detailed including a radical cyclization method to form a vital C-C bond required for a proposed retro-aldol fragmentation.

Furthermore, we have exploited this approach in our efforts toward the total synthesis of coniothyrinone D. While ultimately unsuccessful in accessing the natural product, this synthesis has demonstrated the utility of this approach towards the synthesis of this natural product scaffold.

Keywords: natural products; total synthesis; laurefureynye A; amphirionin-4; coniothyrinone D; eleutherobin

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List of Schemes

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12-C-4	12-Crown-4, 1,4,7,10-tetraoxacyclododecane
μwave	Microwave
$[\alpha]_D$	Specific rotation at the sodium D line (589 nm)
°C	Degrees Celsius
6-MSA	6-methylsalicylic acid
Ac	Acetate
ACP	Acyl carrier protein
aq	Aqueous
AIBN	Azobisisobutyronitrile
AT	Acyltransferase
BAIB	(Diacetoxyiodo)benzene
Bn	Benzyl
Bu	Butyl
Bz	Benzoyl
CAN	Ammonium cerium (IV) nitrate
CBS	Corey-Bakshi-Shibata reduction
CoA	Coenzyme A
COSY	Correlated spectroscopy
Cp	Cyclopentadienyl
CSA	10-Camphorsulfonic acid
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DCE	Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DH	Dehydratase
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DIC	Diisopropylcarbodimide
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N,N*-Dimethylformamide

DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DPPF	1,1'-*bis*(diphenylphosphino)ferrocene
dr	Diastereoisomeric ratio
D*t*BPF	1,1'-*bis*(di-*t*-butylphosphino)ferrocene
E	*Entgegen* (alkene geometry)
ECD	Electronic circular dichromism
ee	Enantiomeric excess
Enz	Enzyme
ER	Enoyl reductase
Et	Ethyl
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
*i*Pr	*Iso*-propyl
KR	Ketoreductase
KS	Ketosynthase
LA	Lewis Acid
LDA	Lithium diisopropylamide
Me	Methyl
MeCN	Acetonitrile
Mes	Mesityl
MOM	Methoxymethyl
MoOPh	Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoramide)
Ms	Mesyl
MTPA	α-Methoxy-α-trifluoromethylphenylacetic acid
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NHK	Nozaki-Hiyama-Kishi
NIS	*N*-iodosuccinimde
NMO	*N*-methylmorpholine-*N*-oxide

NMP	*N*-methyl-2-pyrrolidine
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nuc	Nucleophile
PBB	*para*-Bromobenzyl
Ph	Phenyl
PIFA	[*Bis*(trifluoroacetoxy)iodo]benzene
pin	Pinacol
Piv	Pivaloyl
PKS	Polyketide synthase
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
PNB	*para*-Nitrobenzoyl
R	Substituent
R	*Rectus* (chiral designation)
Red-Al	Sodium bis(2-methoxyethoxy)aluminiumhydride
rt	Room temperature
S	*Sinister* (chiral designation)
S_N2	Bimolecular nucleophilic substitution
SOMO	Singly occupied molecular orbital
TBADT	Tetrabutylammonium decatungstate
TBAF	Tetrabutylammonium fluoride
TBAB	Tetrabutylammonium bromide
TBDPS	*t*-Butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
*t*Bu	*t*-butyl
TC	2-Thiophene carboxylate
TDDFT	Time-dependent density functional theory
TE	Thioesterase
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride

THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
Ts	Tosyl
TS	Transition state
TTMSS	*Tris*(trimethylsilyl)silane
WHO	World Health Organization
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
Z	*Zusammen* (alkene geometry)

Chapter 1.

Introduction

1.1. Natural Products

Natural products comprise the set of chemical compounds produced by living organisms and play essential roles in the survival and growth of these organisms. For example, bacteria use natural products such as erythromycin as antimicrobial agents to reduce competition for limited resources and for protection from other microorganisms while insects rely heavily on volatile hydrocarbons as pheromones for mating and communication.[1,2] In turn, humans have exploited natural products for a variety of uses including dyes, flavours, perfumes, pharmaceuticals and pesticides.[3–6] To date, over 300,000 natural products have been described in the *Super Natural II* database.[7] Considering that less than 10% of organisms have been described let alone investigated for their metabolites, this number should continue to grow in the years to come.[8,9]

1.1.1. Biosynthesis of Natural Products

Natural products range in structural complexity from simple molecules such as ethanol to more elaborate structures such as morphine (**2**) and paclitaxel. In order to access these natural products, organisms have evolved a number of intricate biosynthetic pathways. Broadly speaking, natural products are divided into six classes based on their biosynthetic origin (Figure 1.1): ribosomal and nonribosomal peptides (e.g. **1**), alkaloids (e.g. **2**), carbohydrates (e.g. **3**), phenylpropanoids (e.g. **4**), polyketides (e.g. **5**) and terpenoids and steroids (e.g. **6**).[10] Ribosomal peptides and carbohydrates are generally referred to as primary metabolites due to their role in normal cellular processes, while nonribosomal peptides, alkaloids, phenylpropanoids, polyketides and terpenoids and steroids are classified as secondary metabolites. While secondary

metabolites are generally not critical for standard cellular processes, they still fulfill important ecological functions and are more likely to be unique metabolites of a particular organism. Secondary metabolites often contain more structural complexity and derive from sophisticated and complex biosynthetic pathways.[4]

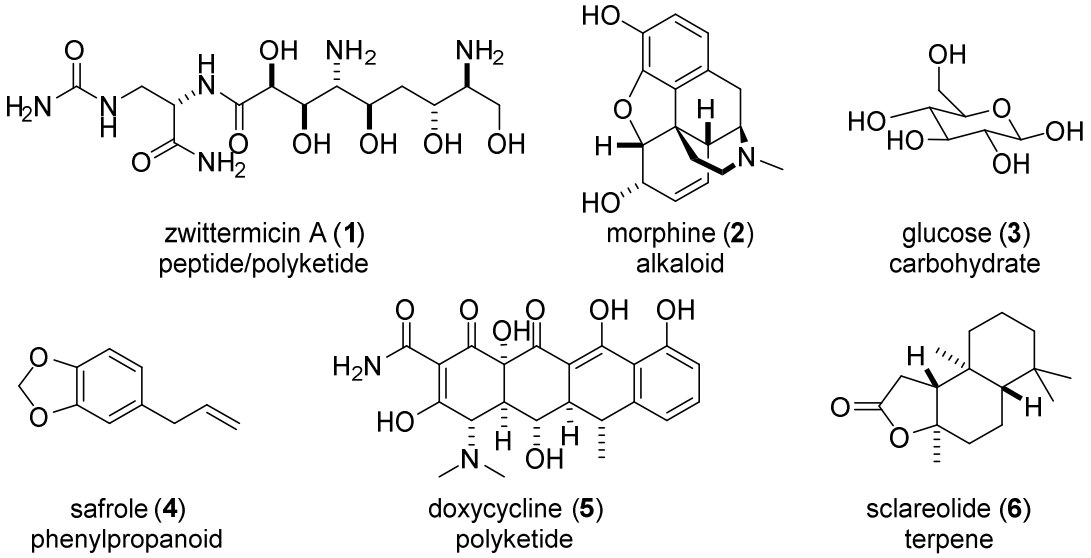
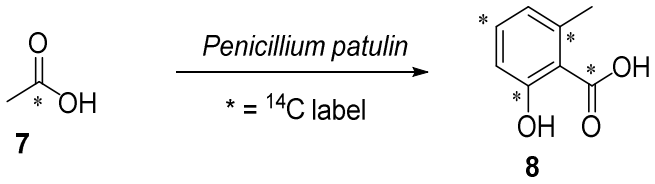


Figure 1.1. Examples of different classes of natural products.

Polyketides are a very large class of natural products that incorporate a wide range of functional groups and structural features including macrocycles or aromatic rings and numerous stereocentres. Biosynthetically, the origin of polyketides was widely debated until Arthur Birch proposed a hypothesis in the 1950's that polyketides arose from acetate or propionate units that underwent sequential condensation reactions.[11] This hypothesis was later proven by Birch through feeding ^{14}C-labelled acetate (**7**) to the fungus *Penicillium patulum* and then observing the production of ^{14}C-labelled 6-methylsalicylic acid (6-MSA, **8**, Scheme 1.1).[11] Importantly, this product had uniform ^{14}C incorporation at specific sites indicating that these products were the result of multiple condensation reactions to form the aromatic ring.

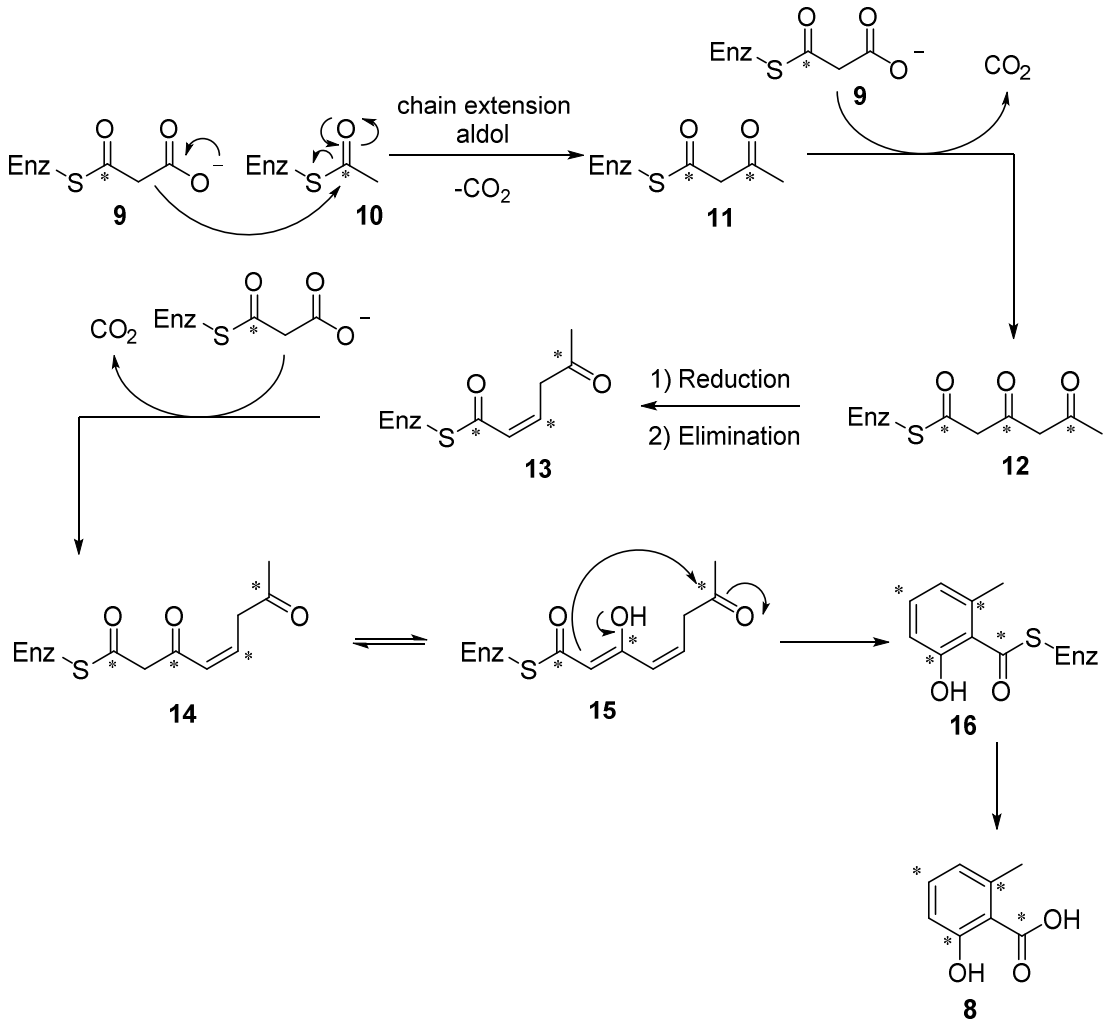
Scheme 1.1. Birch's demonstration that 6-methylsalicylic acid is derived from acetate groups.



7 **8**

Following this discovery, further investigations confirmed the mechanism through which these polyketide compounds are synthesized. The key C-C bond forming event is a decarboxylative Claisen reaction between a malonyl derived intermediate (e.g. **9**) and an enzyme bound thioester (e.g. **10**). The product of this reaction can then undergo further derivatization prior to a subsequent aldol reaction that continues extension of the chain. The proposed pathway for the biosynthesis of 6-MSA is shown in Scheme 1.2.[12] The pathway contains three decarboxylative Claisen reactions as well as a reduction/elimination sequence to convert ketone **12** into alkene **13**, and an intramolecular aldol reaction/elimination to form the aromatic ring **16**. Finally, hydrolysis of the thioester affords ^{14}C-labelled 6-MSA (**8**).

Scheme 1.2. Proposed biosynthetic pathway for the production of ^{14}C labelled 6-MSA.



Later, researchers successfully described the molecular machinery that carries out these transformations.[13] These polyketide natural products are constructed by large multifunctional enzymatic complexes known as polyketide synthases (PKS).[14–16] An example of a type I PKS biosynthesis of erythromycin A (**20**) is shown in Figure 1.2.[17–19] The biosynthetic machinery in this case consists of six modular domains, each of which is responsible for incorporating a single extender unit (**18**) into the growing polyketide chain. Subsequent modifications within each module by ketoreductases (KR), dehydratases (DH) and enoylreductases (ER) builds up significant structural and stereochemical complexity. Ultimately, a thioesterase (TE) cleaves the chain from the

PKS backbone and forms 6-deoxyerythronolide B (**19**). This is subsequently converted by other, non-PKS, enzymes into erythromycin A (**20**) which a potent antibiotic. Researchers have also been able to exploit the molecular machinery that produces these polyketides in the synthesis of unnatural polyketides and analogues of these complex molecules.[20]

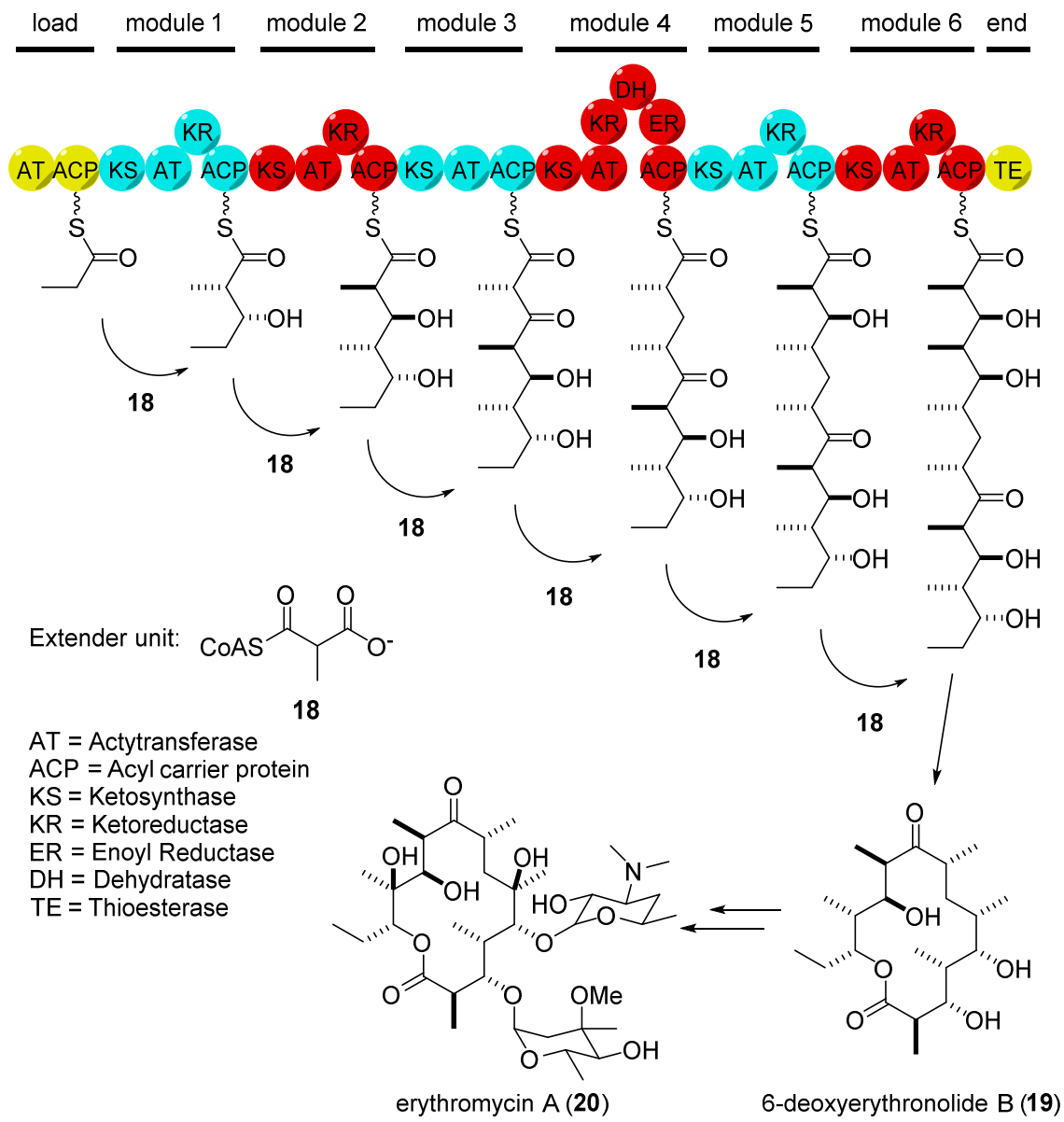


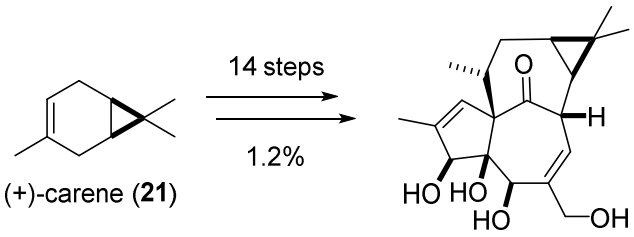
Figure 1.2. Biosynthesis of erythromycin A (20) using a Type I PKS and incorporating 6 propionyl goups.

1.1.2. Natural Product Isolation and Characterization

The isolation and characterization of natural products is not a trivial exercise. Many organisms only produce natural products in small quantities and since many natural products are unique to a single organism, isolation of a single pure sample of a natural product often requires extraction of a large amount of biomass to get sufficient material for characterisation and biological testing. For example, the isolation of eleutherobin (**40**, page 14) only gave the natural product in 0.01% yield from a rare soft coral, which has hindered further exploration of the potential chemotherapeutic uses of this compound.[21] Access to large amounts of biomass can be feasible in some instances especially for terrestrial plant species and fermentable microorganisms but is not a reasonable option for many organisms (e.g. corals or sponges) due to the environmental impact their removal would have or significant challenges in their physical removal. As a result, total synthesis has become a powerful tool in natural product chemistry to enable access to sufficient material for comprehensive biological testing and further compound development.

An example of this approach can be found in Baran's synthesis of (+)-ingenol (Scheme 1.3).[22] This synthesis was achieved in 14 overall steps in a 1.2% overall yield (73% average per step) which compared well with the isolation yield of ingenol of 275 mg/kg (0.028% w/w). Moreover, this synthesis also provided access to analogues of ingenol and supported large scale synthesis to provide an alternative to the currently used isolation process which suffers from low yield.

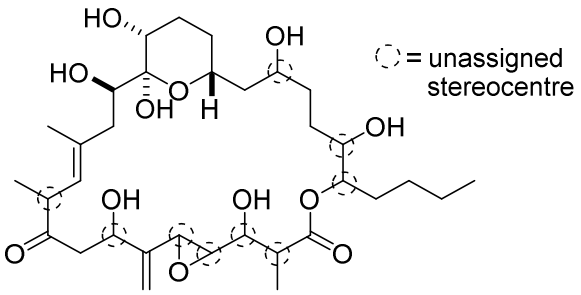
Scheme 1.3. Summary of Baran's synthesis of ingenol (22).



(+)-carene (**21**) (+)-ingenol (**22**)

The subsequent characterisation of an isolated natural product is also non-trivial. The modern natural product chemist has access to a large number of techniques such

as X-ray crystallography, NMR spectroscopy, mass spectrometry and chemical derivatization, which have made structural elucidation much easier than in the past. However, in spite of advances in instrumentation, accurate determination of the structural skeleton of a natural product is still a challenging task and further determination of stereochemistry is even more so. For example, amphidininol 3 (Figure 2.7, **119**) was originally isolated in 1991 but the complete structure was not solved until 1999[23] and has undergone revision since then. The flat structure of amphidinolide N (**23**) has also been assigned, [24] though it still contains too many unassigned stereocentres to consider assignment by total synthesis. There are also many reported cases of incorrectly assigned structures in the natural product literature,[25] which have presented a significant barrier to the development of these compounds for potential applications.



amphidinolide N (**23**)

Figure 1.3. Amphidinolide N with unassigned stereocentres.

The most well-known example highlighting the importance of correct structural assignment comes from the multinational effort to synthesize penicillin during World War II. Due to the critical need for antibiotics, several large groups of researchers were involved in developing a *de novo* synthesis of the penicillins (**26**) that would enable their large-scale production. However, synthetic efforts in this area were unsuccessful due in part to the uncertainty surrounding the actual structure of penicillin at the time (Figure 1.4). Several top experts in the field disagreed over the penicillin structure and it wasn't until 1945 that X-ray crystallography confirmed the structure of penicillin was **26**.[26] The first chemical synthesis of a penicillin was finally achieved in 1957 when Sheehan and co-workers completed the synthesis of penicillin V.[27]

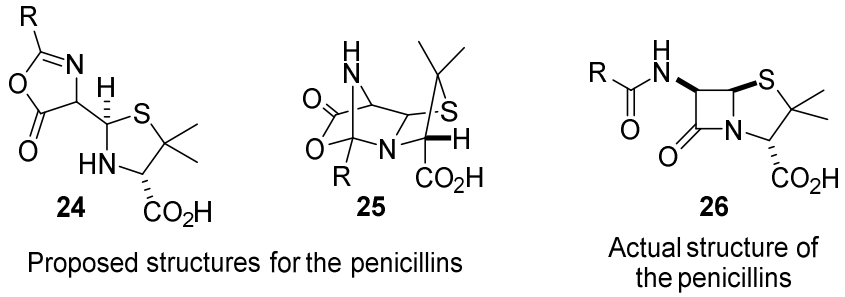


Figure 1.4. Proposed structures for the penicillins during World War II.

One of the most useful tools to confirm the structure of a challenging, non-crystalline natural product is through total synthesis. Two examples are shown in Figure 1.5 where total synthesis was integral in determining that the original assignment was incorrect. Apyroseol-14 was isolated from a sponge, *Aplysilla rosea*, in 1997[28] and assigned as compound **27**. However, when Zaragozá and co-workers attempted to carry out a synthesis of this compound they were unable to effect the final step and instead obtained isomeric compound **28**. Comparisons of the data recorded on isomer **28** with the data reported for the natural product indicated that isomer **28** was in fact the natural product and led to a reassigned structure for apyroseol-14.[29] Robustadial A was originally assigned as structure **29** containing a bicyclo[3.2.0]heptane ring system.[30] However synthesis of the bis(methyl) ether of this compound revealed that it had been misassigned and further spectroscopic analysis and synthesis indicated that the correct structure of robustadial A incorporated a pinane skeleton at the spirocentre (**30**).[31,32]

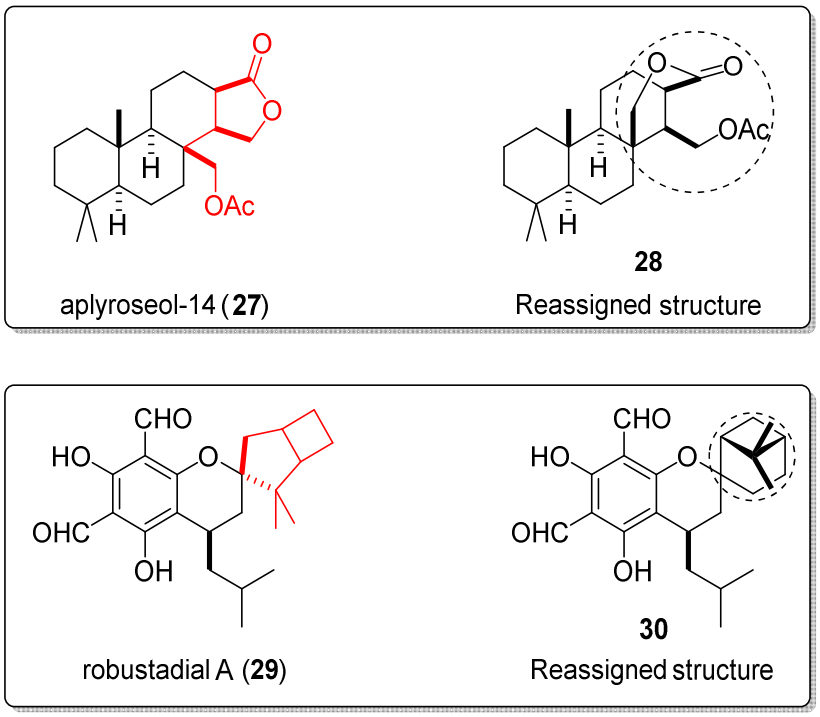
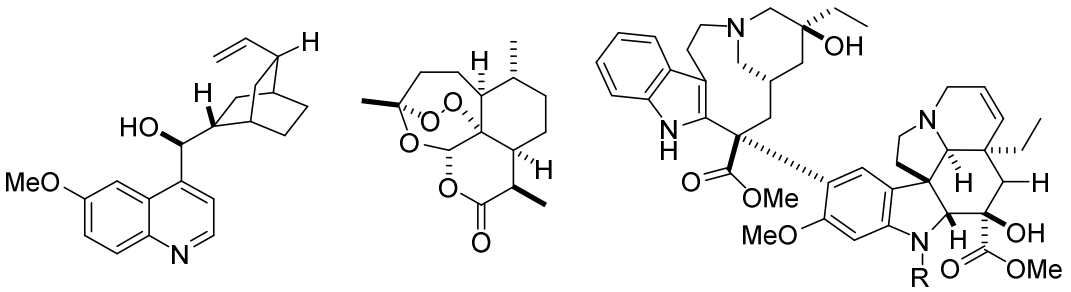


Figure 1.5. Reassigned natural products based upon total synthesis.

1.1.3. Natural Products as Drug Leads

Natural products have historically been the predominant source of pharmaceuticals and still play a critical role in modern drug discovery. Ancient Mesopotamian clay tablets from *c.* 2600 B.C. detail the medicinal uses for oils from several plant sources such as the cypress and cedar trees, which are currently used today for the treatment of multiple illnesses such as coughs and colds,[8] and many cultures still use natural product extracts to treat various ailments. Some examples of natural products that are in current use for the treatment of diseases are shown in Figure 1.6. Quinine (**31**) and artemisinin (**32**) are used for the treatment of malaria throughout much of the world, while the *Vinca* alkaloids (**33**, **34**) are used as potent chemotherapy agents.



quinine (**31**) artemisinin (**32**) R = CH_3; vinblastine (**33**)
R = CHO; vincristine (**34**)

Figure 1.6. Natural products currently in usage as pharmaceuticals.

While natural products often do not make good drugs due to issues of bioavailability, pharmacokinetic properties and difficulties in accessing sufficient material,[33] many more drugs are derived from natural products or contain pharmacophores discovered from a natural product. Figure 1.7 shows the results of a study of new chemical entities that reached the market from 1981-2010 and indicates that 50% of the 1355 drugs that were approved were either natural product derived or synthetic drugs that incorporated a natural product pharmacophore or mimicked a natural product effect on a specific therapeutic target.[34]

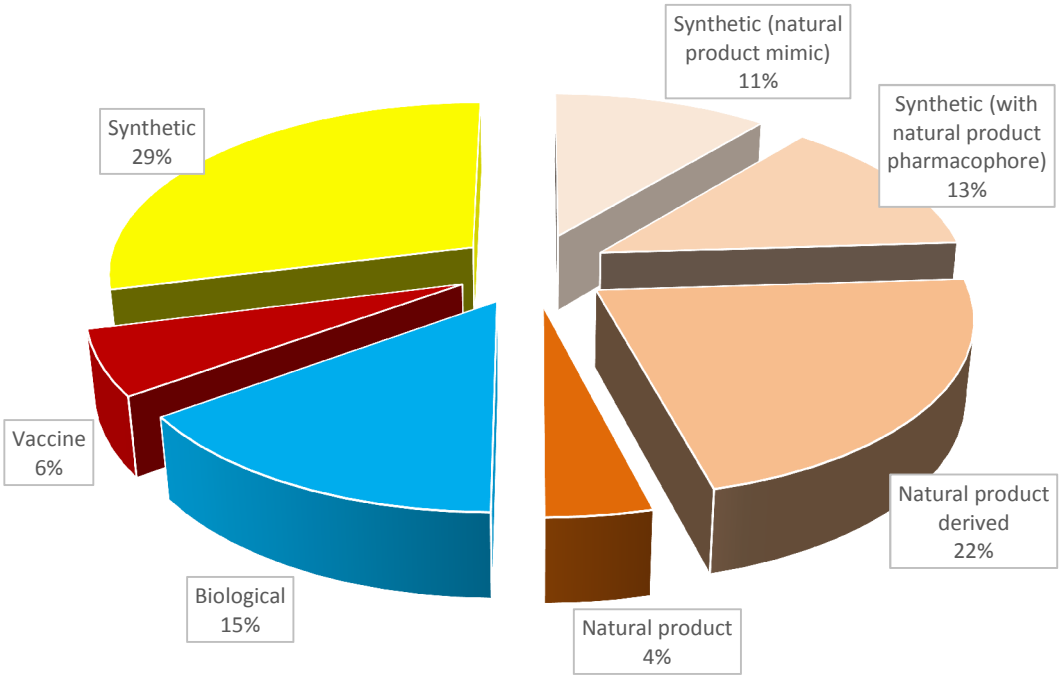


Figure 1.7. Origin of approved drugs from 1981 to 2010.[34]

While considerable resources have been devoted to combinatorial libraries and high-throughput screening efforts over the past few decades, natural products are still considered to be a vital part of drug discovery. Several statistical studies have shown that natural products contain significantly more structural diversity and are more drug-like than combinatorial libraries (Table 1.1).[35–38] Given that there is an ever increasing demand worldwide for new pharmaceutical agents, natural products will continue to provide an important source of new biologically active compounds and insight into potential targets for pharmaceutical development.

Table 1.1. Abundance of selected structural properties in combinatorial libraries vs natural products.[36]

Properties	Drugs	Synthetics[a]	Natural Products[b]
Bridgehead atoms with three ring bonds	25%	9%	49%
Rotatable C-C bonds	74%	48%	66%
Rings per molecule	3.0	2.6	3.3
Chiral centres per molecule	1.2	0.1	3.2
Rotatable bonds per molecule	10.7	8.0	11.1

a) Representative pool of synthetic compounds from Bayer AG; b) Natural products sampled from the *Dictionary of Natural Products*

In order to support the use of natural products in drug discovery efforts, the development of new synthetic methods continues to be an important pursuit. A particular emphasis has been placed recently on the development of syntheses that focus on step economy.[39–41] In general, a low step count increases the overall yield of a reaction sequence (Figure 1.8) and consequently helps to reduce many of the costs associated with total synthesis including reductions in quantities of starting materials, reagents and solvents, and the time involved in carrying out the synthesis.

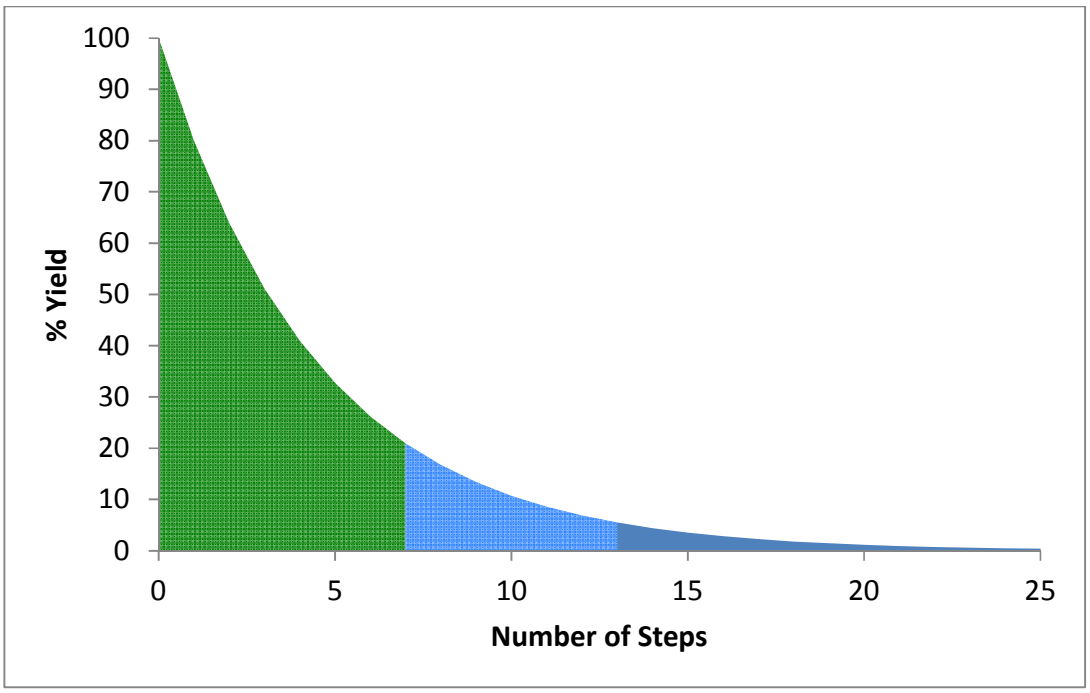


Figure 1.8. Overall yield in a reaction sequence at 80% yield per step.

1.2. Thesis Overview

The primary focus of this thesis is the application of new synthetic methods to the efficient synthesis of marine natural products.

In *Chapter 2*, a discussion of our application of methods developed in the Britton group toward the synthesis of two tetrahydrofuranol-containing natural products is presented. Firstly, the total synthesis of amphirionin-4 (**35**) is reported. This natural product, isolated from an *Amphidinium* dinoflagellate,[42] contains a tetrahydrofuranol ring as its core structure along with a long polyene side chain that includes a synthetically challenging skipped tetraene motif. Secondly, the total synthesis and structural reassignment of laurefurenyne A is presented. This *Laurencia* metabolite includes a 2,2'-bistetrahydrofuranol scaffold as the core of the molecule and questions surrounded the stereochemistry of this compound following the report of its structure by Jaspars in 2010.[43] Through the development of a flexible synthesis utilizing asymmetric aldol reactions with enantiomerically enriched α-chloroaldehydes, we were able to access the proposed stereostructure for laurefurenyne A (**36**) and demonstrate that it required a

configurational reassignment. Further analysis and synthetic efforts led to the first synthesis of the correct structure of laurefurenyne A (**36**) in 14 overall steps.

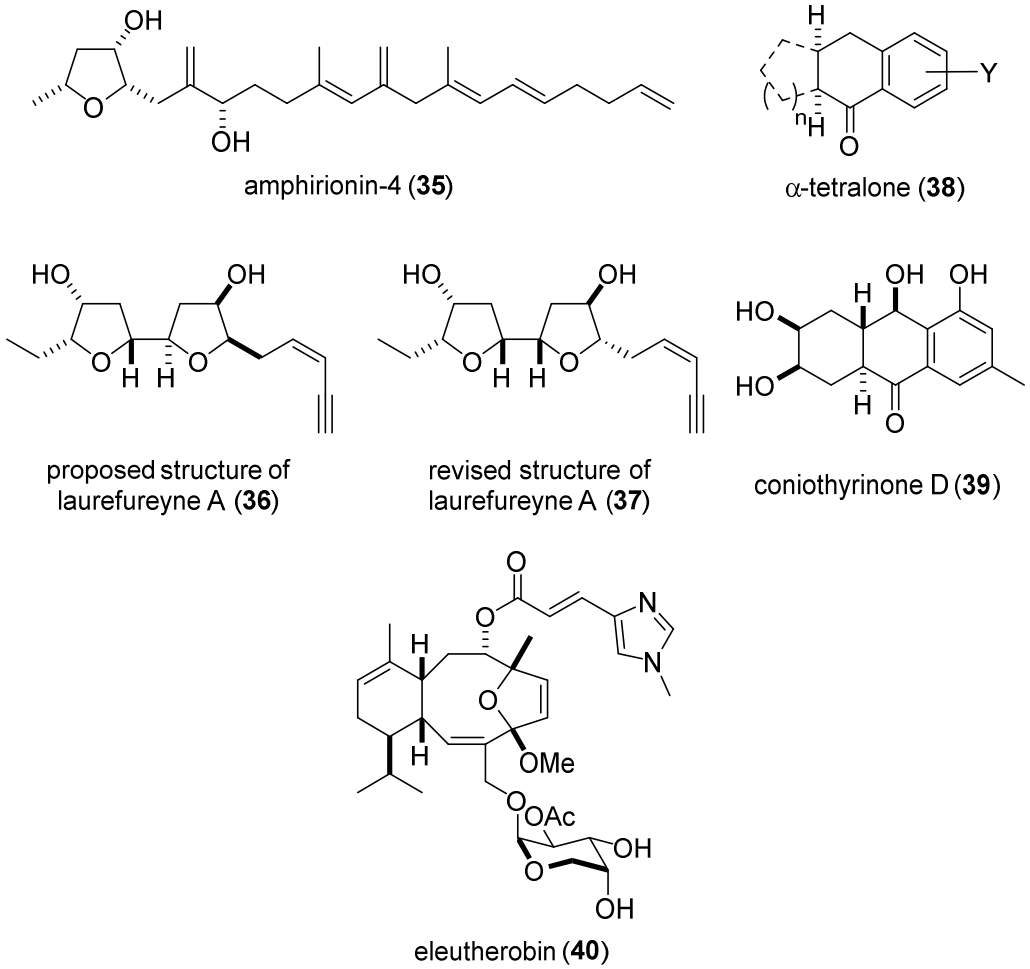


Figure 1.9. Natural product targets in this thesis.

In *Chapter 3*, our most recent efforts towards the synthesis of eleutherobin (**40**) are detailed. Biological studies on eleutherobin (**40**) had shown that this natural product is a potent microtubule stabilizing compound with potential applications in the treatment of cancer. However, efforts in exploiting this activity had been stymied due to the difficulties in accessing sufficient material from the natural source and previous synthetic efforts had not been sufficiently scalable to address this impasse. Accordingly, the development of a concise and efficient synthesis of eleutherobin (**40**) is important for further biological testing and preclinical studies. Previous efforts in the Britton group geared toward the preparation of a key intermediate in the synthesis of eleutherobin had

relied on the development of a new method for the synthesis of α-tetralones that involves a novel α-arylation/ring annulation sequence effected on cyclobutanones. In this chapter, we present the further expansion of this new methodology to include a range of α-aryl cyclobutanones and production of a variety of α-tetralones (**38**). Lastly, this chapter discusses our synthetic efforts towards the synthesis of eleutherobin that exploit this α-tetralone methodology. A radical cyclization approach is shown to afford access to a highly functionalized intermediate in our proposed synthesis of eleutherobin and we envisage that this new route should prove useful for future synthetic efforts this natural product.

In *Chapter* 4, the utility of this method is also demonstrated in our studies toward the total synthesis of coniothyrinone D (**39**), a secondary metabolite isolated from an endophytic species of fungi that was shown to possess antimicrobial activity. While ultimately unsuccessful in accessing the natural product, we were able to synthesise both *O*-methylconiothryinone D and 9-*epi*-coniothyrinone in an efficient manner.

Chapter 2.

Total Synthesis of Tetrahydrofuranol-Containing Natural Products

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

Holmes, M. T.; Britton, R. *Chem. Eur. J.* ***2013****, 19*, 12649; and Holmes, M.; Kwon, D.; Taron, M.; Britton R. *Org. Lett.*, **2015**, *17*, 386

2.1. Introduction

Tetrahydrofuranol rings are a common motif found in many marine natural products. They are encountered in secondary metabolites isolated from sponges, algae, coral and other marine organisms and often form the core of complex and stereochemically rich natural products. As a result, tetrahydrofuranols have been targets of interest for organic synthesis for many years.

2.1.1. Examples of Tetrahydrofuranol-Containing Natural Products

Tetrahydrofuranol rings have been found in a variety of polyketide natural products[10] (Figure 2.1) ranging from large macrolides such as amphidinolide X (**41**)[44] or biselide A (**42**)[45] to smaller macrolides such as laurefurenyne C (**43**)[43] and also to simpler compounds such as (+)-muscarine (**45**) or (+)-goniothalesdiol (**44**).[46]

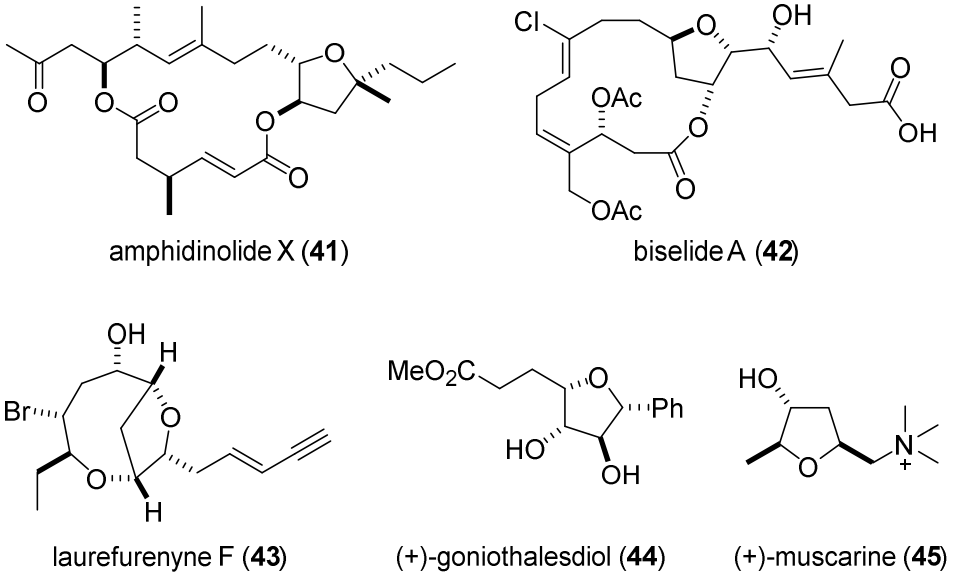
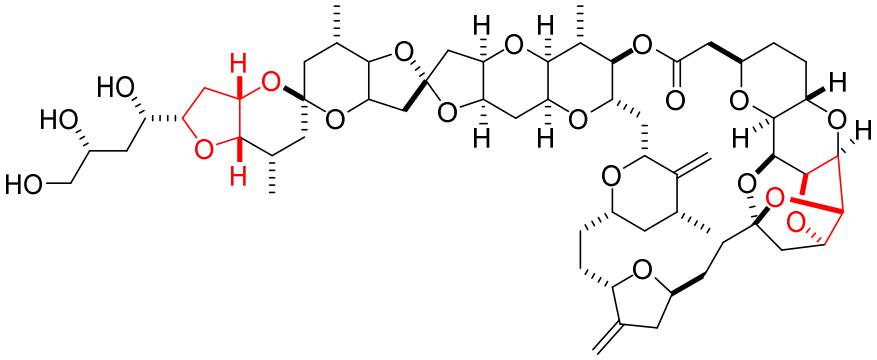
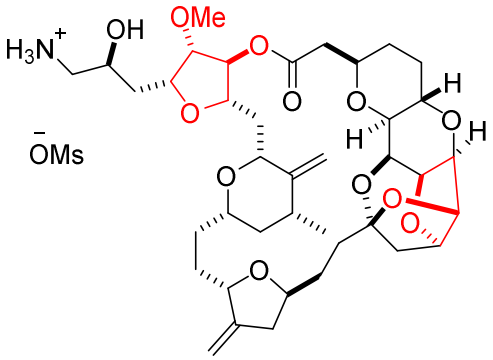


Figure 2.1. Representative tetrahydrofuranol-containing natural products.

These natural products often display interesting biological activity. Amphidinolide X, biselide A and (+)-goniothalesdiol have been demonstrated to have promising cytotoxicity against cancer cell lines,[44–46] while muscarine is a potent agonist of the muscarinic acetylcholine receptor. While there are few drugs containing tetrahydrofuran rings available currently, Eisai Co. has brought the drug Eribulin mesylate (**47**) to market as a chemotherapy agent (Figure 2.2).[47] This complex macrolide is a synthetic analogue of halichondrin B (**46**)[48,49] and contains a tetrahydrofuranol ring in the upper left quadrant that is critical for retaining the biologically active conformation of the macrocycle.



halichondrin B (**46**)



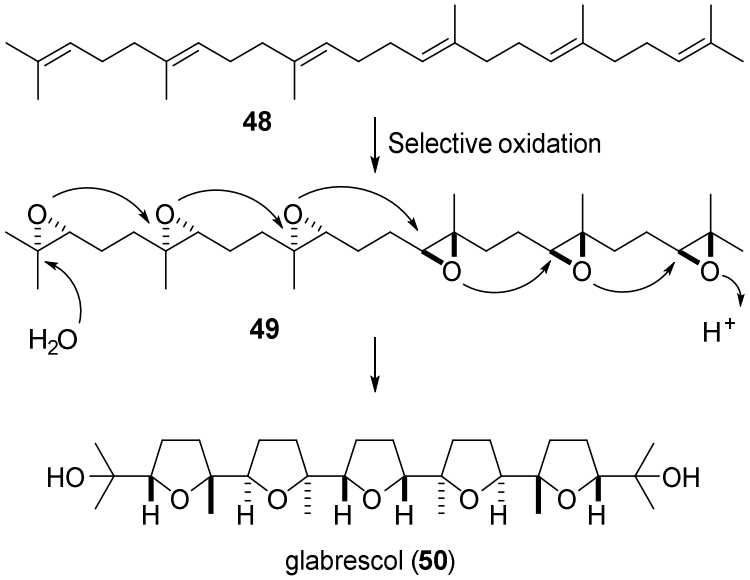
Eribulin mesylate (Halaven, **47**)

Figure 2.2. Eribulin mesylate – a synthetic analogue of halichondrin B containing multiple tetrahydrofuran rings.

2.1.2. Tetrahydrofuran Biosynthesis

Tetrahydrofurans are synthesized in Nature as part of the polyketide synthase sequence discussed in Chapter 1. Unlike many aspects of polyketide biosynthesis, tetrahydrofuran formation is generally considered to be a post-PKS modification where the cyclic ethers are formed after the construction of the carbon backbone.[10,50] There are many available methods for the construction of tetrahydrofuran rings in Nature but the two major pathways are epoxide opening or Michael addition to double bonds to form the cyclic ether. The biosynthesis of glabrescol[51] (**50**) is shown in Scheme 2.1 which begins by the selective enzymatic epoxidation of polyene **48** which is followed by a cascade of epoxide opening reactions initiated by a water molecule to afford the complex set of tetrahydrofurans found in this natural product.

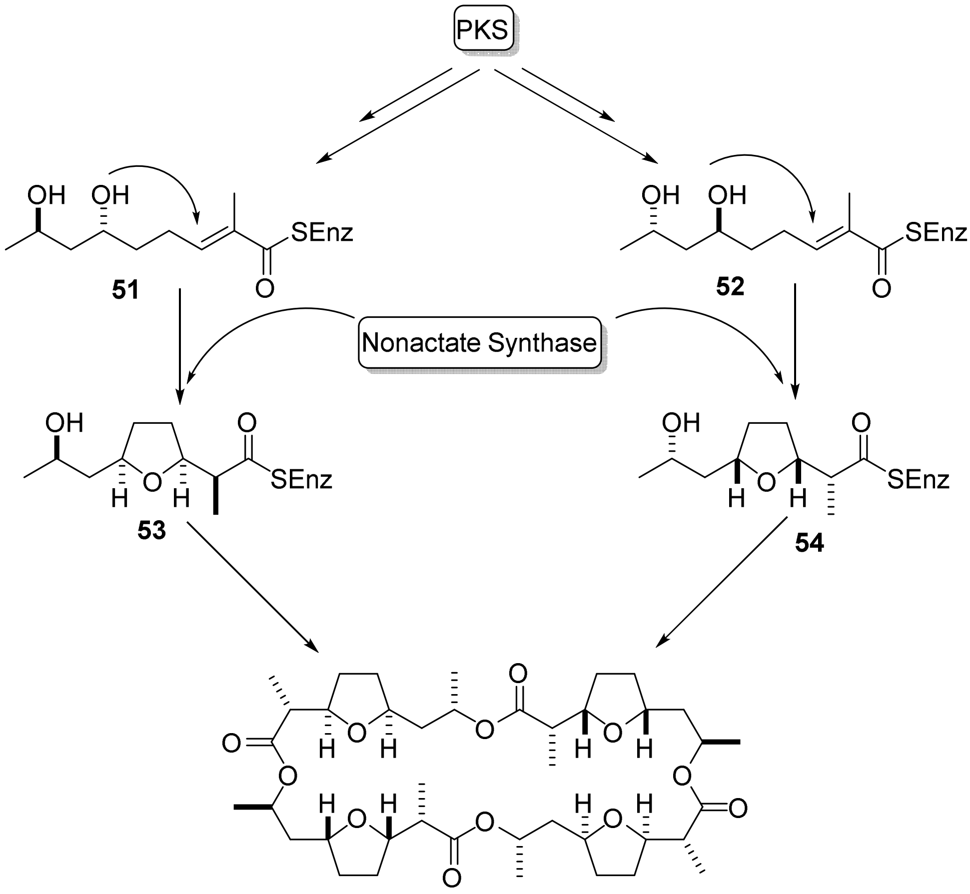
Scheme 2.1. Biosynthesis of THF rings via epoxide opening.



glabrescol (**50**)

The other major biosynthetic pathway to THF rings involves nucleophilic addition of an alcohol function onto an activated alkene. Generally this involves the oxa-Michael addition reaction as shown in Scheme 2.2 for the biosynthesis of nonactin (**55**).[52] This biosynthesis uses the PKS process to obtain intermediates **51** and **52,** which are then cyclized via Michael addition using nonactate synthase to afford the THF rings (**53** and **54**). Further dimerization and combination of the two parts afford the macrolide nonactin (**55**).

Scheme 2.2. Biosynthesis of THF rings via Michael addition.



nonactin (**55**)

2.1.3. Synthetic Methods to Access Tetrahydrofuranol Scaffolds

Tetrahydrofuranol-containing natural products are attractive targets for total synthesis due to their structural complexity, which provides challenges that test the limits of new synthetic methods or strategies, and their potentially useful biological activity. As a result, there have been a significant number of methodologies developed that afford efficient and stereo-controlled access to this scaffold (some select examples are shown in Figure 2.3).[53–55]

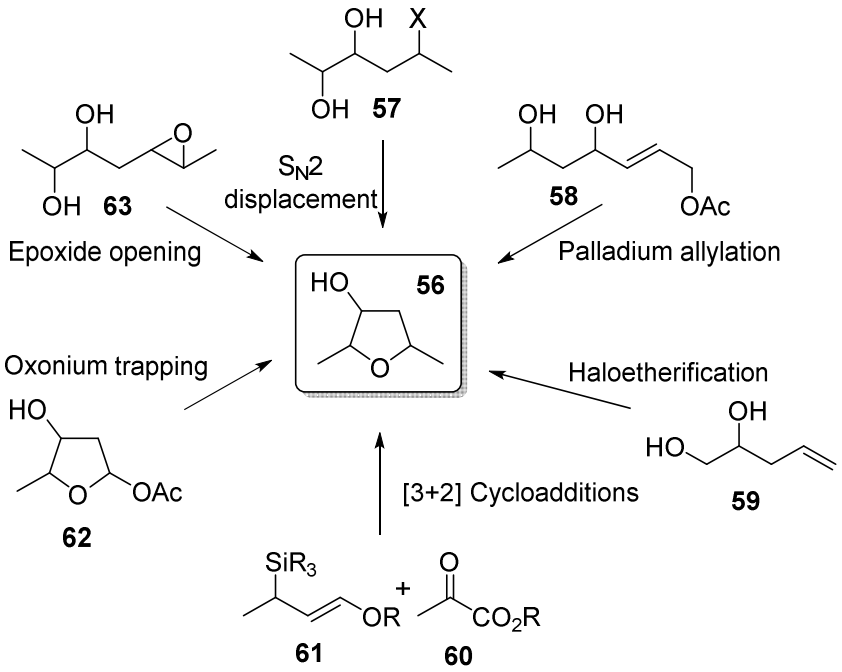
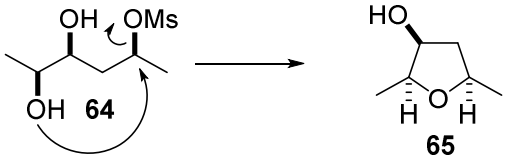


Figure 2.3. Examples of methodologies to access tetrahydrofuranols.

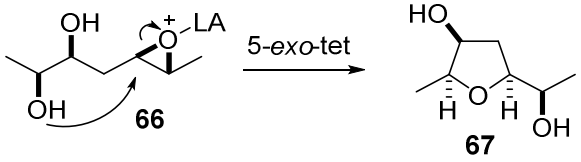
S_N2 displacement of a good leaving group (Br, I, OMs, OTs etc) has been a common way to form tetrahydrofuran rings (Scheme 2.3).[56] While this does allow for a stereocontrolled synthesis of the ring, access to the precursors to this reaction can be challenging and require multiple steps.[57]

Scheme 2.3. Mechanism of S_N2 displacement of a leaving group to form a tetrahydrofuranol.



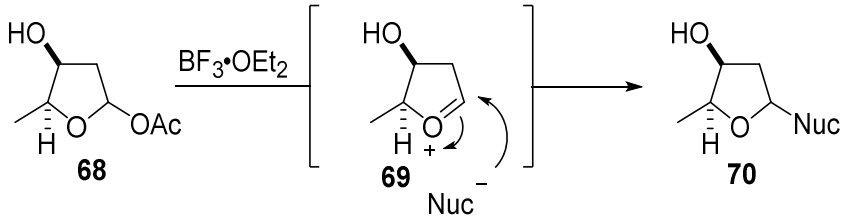
The epoxide opening reaction to form tetrahydrofuranols follows the general mechanism shown in Scheme 2.4.[58–61] Under either Lewis or Brønsted acidic conditions, the epoxide is opened *via* 5-*exo*-tet attack of the alcohol to form the tetrahydrofuranol. This methodology can also be adopted to mimic the biosynthesis of these molecules via a cascade process similar to that shown for glabrescol (Scheme 2.1).[62,63]

Scheme 2.4. Mechanism of epoxide opening for tetrahydrofuranol synthesis.



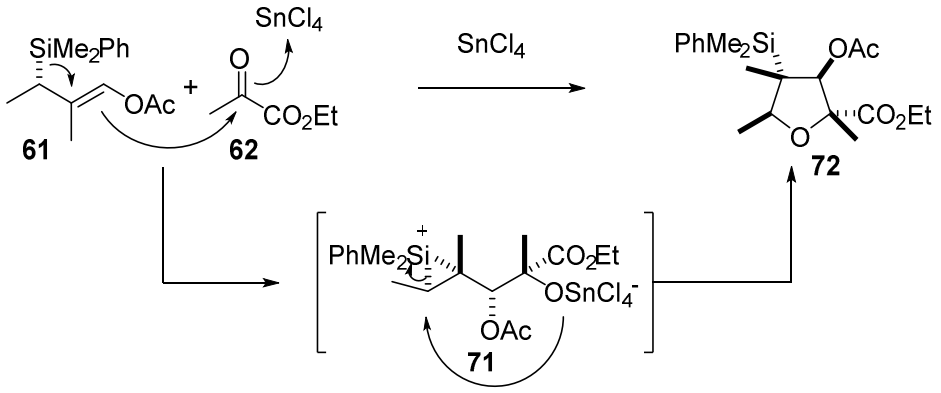
The intra- or intermolecular trapping of oxocarbenium ions is another popular method for forming tetrahydrofuran rings and a demonstrative example is shown in Scheme 2.5.[64–66] Here, a Lewis acid generates an oxocarbenium ion from the γ-lactol (**68**). Subsequent trapping of the oxocarbenium **69** with a nucleophile affords the tetrahydrofuranol **70**. Some degree of stereocontrol can be achieved by careful choice of reaction conditions. However, this method is highly substrate dependent and is not necessarily compatible with many functional groups.[54]

Scheme 2.5. Mechanism of oxonium trapping for tetrahydrofuranol synthesis.



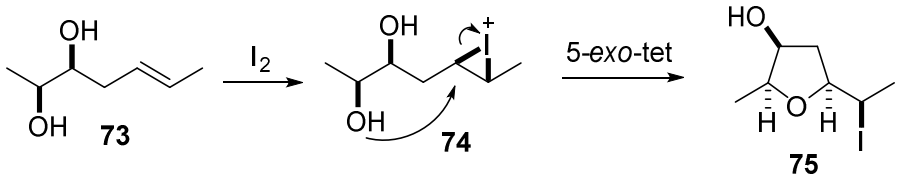
[3+2] Cycloaddition is also a powerful tool and is commonly used to access tetrahydrofuran scaffolds as it can combine two complex components and set multiple stereocentres in a single reaction. One example of this reaction is shown in Scheme 2.6.[67] The first step involves nucleophilic addition of the alkene to the carbonyl group activated by $SnCl_4$ and subsequent capture of the siliranium ion with the generated alkoxide to give tetrahydrofuran **70** as a single diastereoisomer. However [3+2] cycloadditions often only provide access to a small set of diastereoisomers and as such have limited scope.[54]

Scheme 2.6. Mechanism of [3+2] cycloaddition for tetrahydrofuranol synthesis.



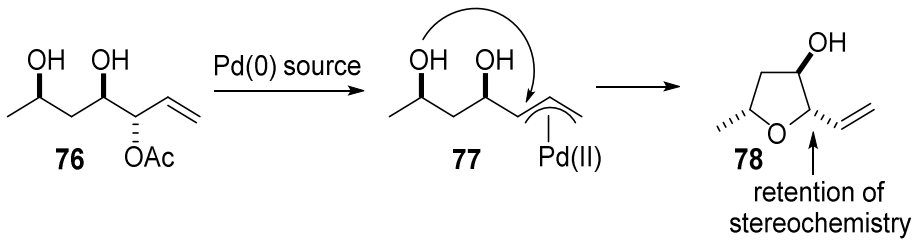
Haloetherification is also commonly used to form tetrahydrofuran rings although controlling the stereochemical outcome of these reactions is non-trivial and often substrate dependent.[68] A general mechanism for this reaction is demonstrated in Scheme 2.7 that is analogous to the epoxidation mechanism shown earlier and favours the 5-*exo*-tet cyclization over the 6-*endo*-tet.

Scheme 2.7. Mechanism of haloetherification for tetrahydrofuranol synthesis.



Recently, transition metal catalyzed reactions have become popular for the synthesis of small heterocycles such as tetrahydrofurans.[69–71] In particular, nucleophilic trapping of allyl palladium intermediates has been used for the formation of tetrahydrofuranols. These reactions initiate with the formation an allyl-palladium complex, which is then trapped by intramolecular alcohol attack. This process affords a tetrahydrofuran ring with net retention of stereochemistry.

Scheme 2.8. Mechanism of ring closure via allyl-palladium intermediate.



In spite of the wide range of methods that are available to to access tetrahydrofuranols, there are still challenges surrounding the efficient and stereoselective syntheses of these ring systems. Oftentimes, multi-step reaction sequences are required to access the acyclic precursors and the stereochemical outcomes are often heavily dependent on the substrate. To address these shortcomings, the Britton group was interested in developing a flexible approach to these important heterocycles that would enable the rapid syntheses of complex natural products with useful biological activity.

2.1.4. α-Chloroaldehydes in Asymmetric Synthesis

α-Chloroaldehydes are attractive building blocks for natural product synthesis due to their bifunctional nature and inherent chirality at the α-centre.[72] For many years after the initial disclosure of their use in substrate controlled addition reactions, α-chloroaldehydes were underutilised perhaps owing to difficulties in accessing these compounds in enantiomerically enriched form.[72] However, in 2004, the research groups of Jørgensen[73] and MacMillan[74] independently reported the synthesis of enantiomerically enriched α-chloroaldehydes (**80**) via the direct organocatalytic chlorination of aldehydes (Figure 2.4) and demonstrated a broad scope for these reactions. Following these seminal publications, MacMillan later reported an improved method for the synthesis of α-chloroaldehydes using organo-SOMO catalysis[75] where LiCl is the chlorine source and $Na_2S_2O_8$ and $Cu(TFA)_2$ are used as oxidizing agents with chiral catalyst **83** as the organocatalyst. Christmann then further developed this work by combining catalyst **83** and *N*-chlorosuccinimide (NCS)[76] which represented a much simpler reaction set-up and work-up procedure while not eroding the enantiomeric excess of the product. These methods permit access to a wide range of enantiomerically enriched α-chloroaldehydes.

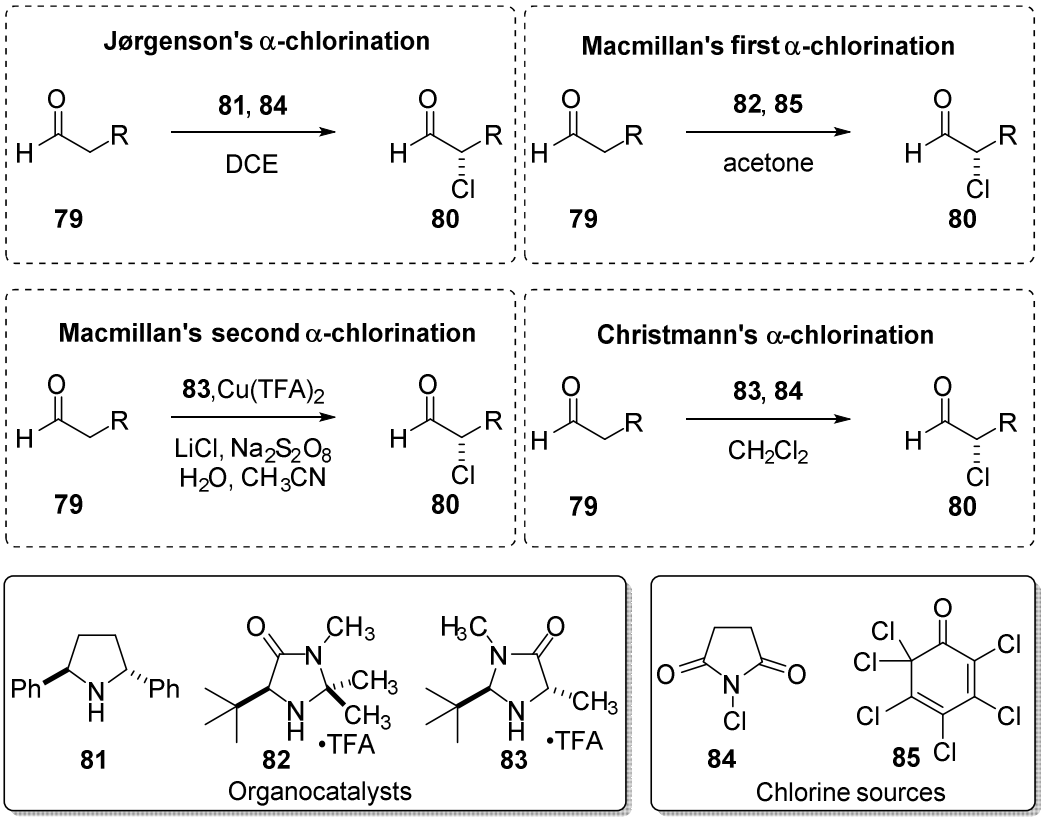


Figure 2.4. Enantioselective synthesis of α-chloroaldehydes.

The reaction of nucleophiles with α-chloroaldehydes is generally considered to be modelled most accurately by the Cornforth model[77,78] (Figure 2.5), where the carbon-chlorine bond is arranged *anti*-periplanar to the C-O bond of the carbonyl group to minimize the overall dipole moment of the molecule in the lowest energy transition structure. The nucleophile then approaches from the least hindered face at the Bürgi-Dunitz angle to give the 1,2-*anti*-chlorohydrin as the major product of the reaction.[79]

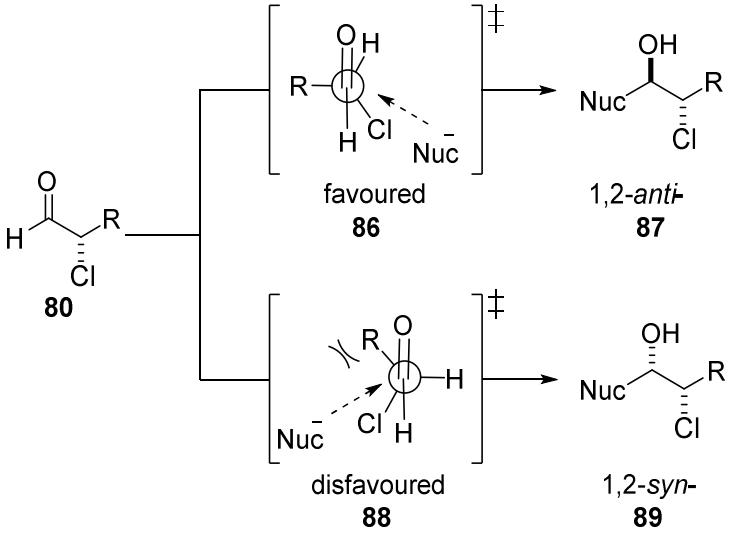


Figure 2.5. Nucleophilic addition to α-chloroaldehydes according to the Cornforth model.

α-Chloroaldehydes have been utilised in the synthesis of a large variety of organic chemistry scaffolds (Figure 2.6). These include epoxides and aziridines (**90** and **91**),[75,76,80,81] α-hydroxyaldehydes (**99**),[82,83] cyclopropanes (**92**),[84] morpholine (**96**)[85] and piperazine (**97**)[85] rings amongst others.

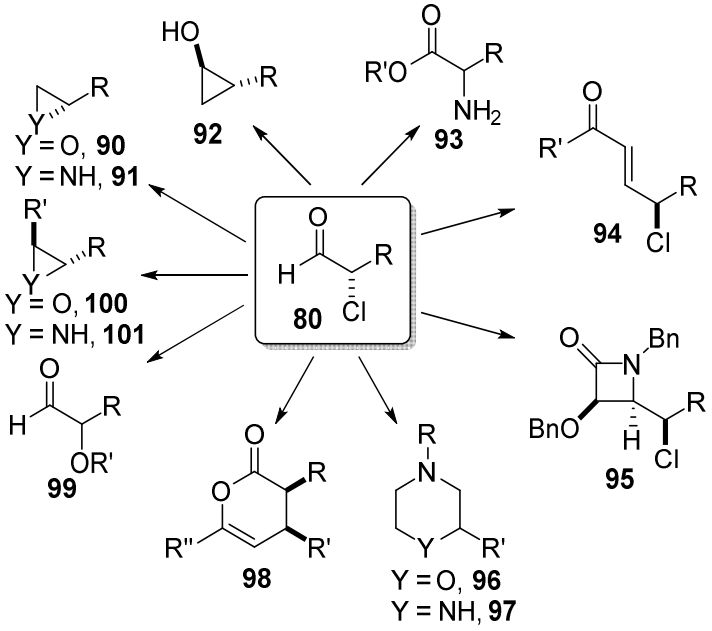
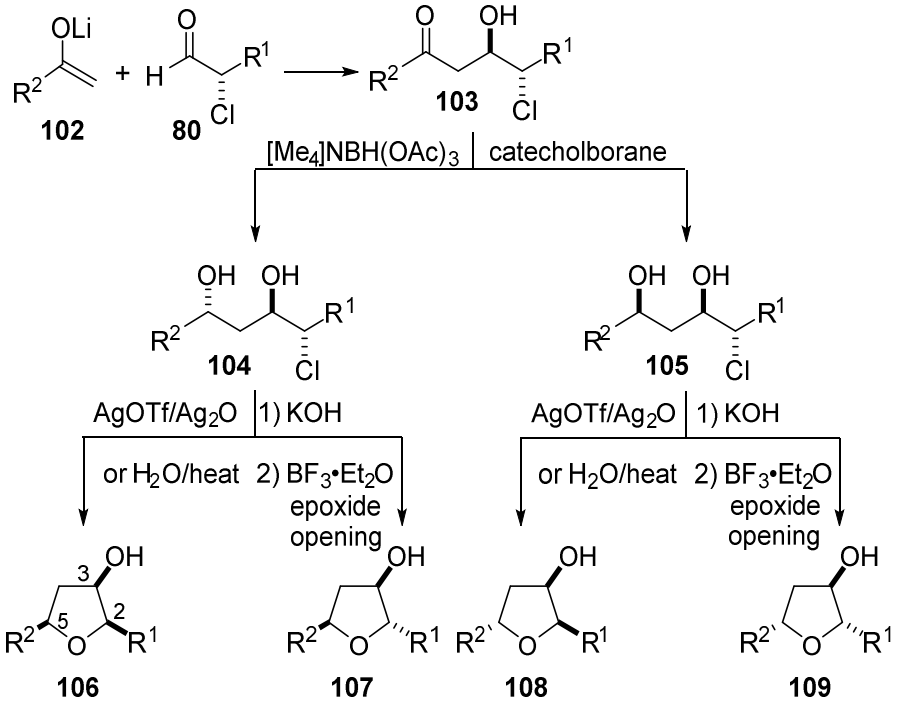


Figure 2.6. Scaffolds readily accessible with α-chloroaldehydes.

2.1.5. Britton Group's Approach to Tetrahydrofuranol Synthesis

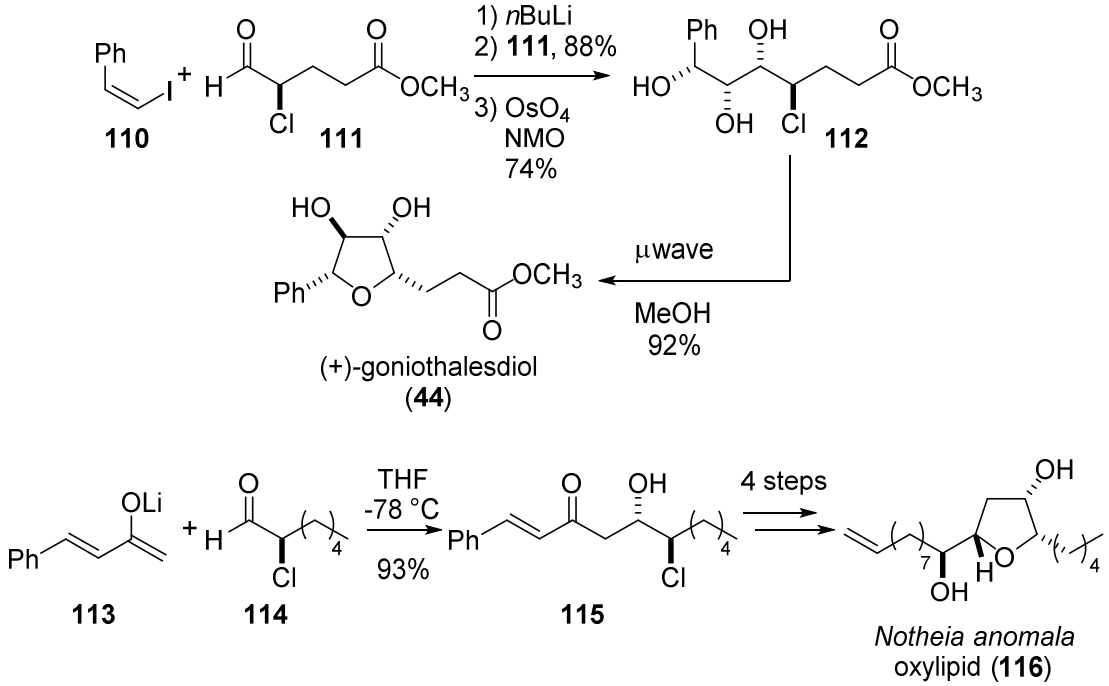
Previous work in the Britton group led to the identification of a synthetic route to tetrahydrofuranols (Scheme 2.9) that allowed ready access to all of the potential 2,5-disubstituted 3-hydroxy tetrahydrofuran diastereoisomers using α-chloroaldehydes as starting materials.[86] The sequence initiates with an asymmetric aldol reaction between a lithium enolate (e.g., **102**) and an α-chloroaldehyde (e.g. **80**) to afford a *syn*-β-ketochlorohydrin (e.g., **103**). A 1,3-*anti*- or 1,3-*syn*-reduction then affords chlorodiols **104** and **105** with excellent levels of diasterocontrol. These diols could then be directly cyclized to the THF ring via S_N2 displacement of the Cl atom by either treatment with stoichiometric amounts of silver (I) oxide (Ag_2O) and silver (I) trifluoromethanesulfonate (AgOTf) or by heating in H_2O or MeOH to afford 2,3-*syn*-tetrahydrofuranols **106** and **107**.[87] Access to the 2,3-*anti*-tetrahydrofuranols **108** and **109** is achieved by a double inversion process involving epoxide formation followed by Lewis acid-promoted rearrangement.

Scheme 2.9. Britton group's synthesis of all diastereoisomers of tetrahydrofuranols from α-chloroaldehydes.



This methodology has been applied to the synthesis of several natural products, including those shown in Scheme 2.10. (+)-Goniothalesdiol (**44**) was accessed in four steps starting with the lithiation of vinyl iodide **110** and subsequent nucleophilic addition into α-chloroaldehyde **111** followed by dihydroxylation and cyclization to afford the natural product in 49% overall yield.[87] Marine oxylipid **116** was synthesized in 6 steps from heptanal using the lithium aldol reaction between **113** and α-chloroaldehyde **114** to establish the core structure of the molecule followed by further elaboration to access the natural product **116**.

Scheme 2.10. Synthesis of tetrahydrofuran-containing natural products (44) and (116).

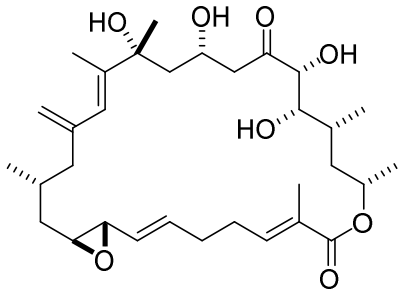


2.2. Total Synthesis of Amphirionin-4

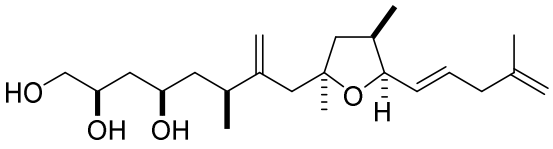
The work contained within this subchapter is the result of a collaboration with colleagues Daniel Kwon and Matthew Taron. Daniel Kwon carried out much of the work involved in the synthesis of the tetrahydrofuran ring including the discovery of the diastereoselective NHK reaction while Matthew Taron was involved in the synthesis of the polyene sidechain.

2.2.1. Introduction

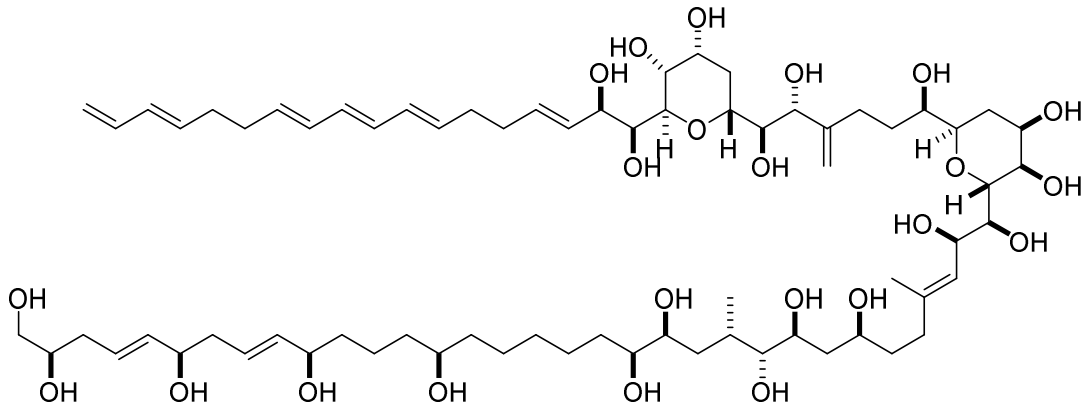
Amphidinium species of marine dinoflagellates have proven to be a rich source of structurally diverse polyketides.[88,89] Generally *Amphidinium* polyketide metabolites fall into three structural classes; the macrolides (e.g. amphidinolide B (**117**)), the linear polyhydroxylated chains (e.g. amphidinol 3 (**119**)) and the non-polar polyketides (e.g. amphidinin A (**118**)). These natural products have been the target of many synthetic efforts due to their unique structures and intriguing biological activity.[23,90–92]



amphidinolide B (**117**)



amphidinin A (**118**)

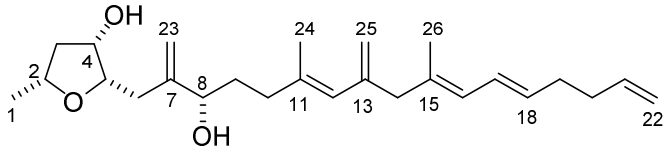


amphidinol 3 (**119**)

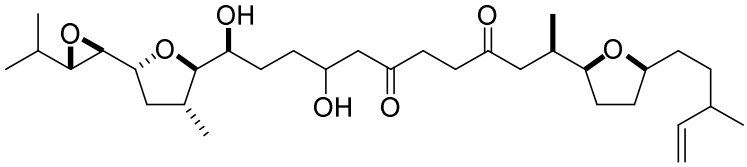
Figure 2.7. ***Amphidinium*** **polyketides.**

In 2014, Tsuda and co-workers reported the isolation of a number of tetrahydrofuran-containing polyketides (**35**, **120**, **121**, Figure 2.8) from the KCA09051 strain of *Amphidinium* collected off the coast of Iriomote Island in the Okinawa archipelago.[42,93,94] Of particular interest to our group was amphirionin-4 (**35**), which was shown to demonstrate potent proliferation activity on murine bone marrow stromal ST-2 cells (+950% growth rate at 0.1 ng/mL). These cells promote the development of

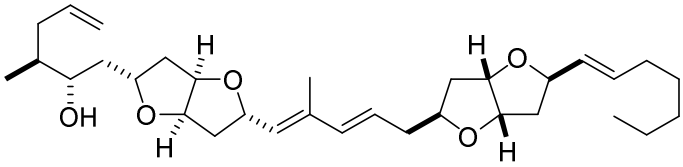
lymphocytes from bone marrow cells and consequently have utility in enhancing immune response and increasing the rate of bone regeneration. The structure itself was also of interest since it contained an all-*syn*-tetrahydrofuranol ring as its core along with an extended polyene side chain, a remote allylic alcohol at C8 and an unusual skipped tetraene motif. Considering the unique structure and potentially useful biological activity, we were interested in exploring whether it would be possible to extend our chlorohydrin-based THF synthesis to access this natural product.



amphirionin-4 (**35**)



amphirionin-5 (**120**)



amphirionin-2 (**121**)

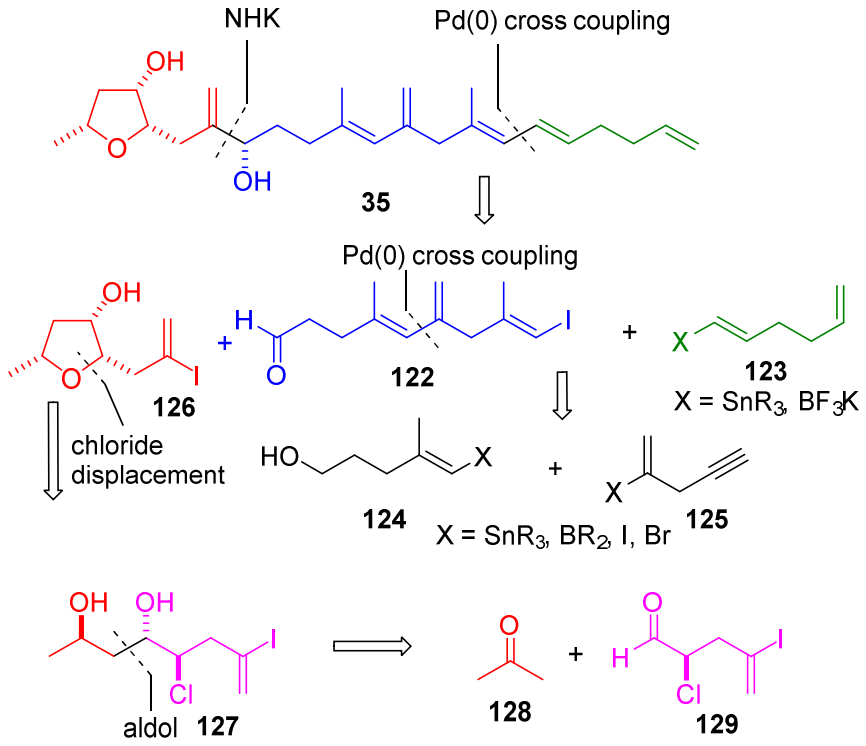
Figure 2.8. Structures of amphirionin-2, -4, and -5, isolated from the KCA09051 strain of *Amphidinium* dinoflagellates.

2.2.2. Retrosynthesis

Our retrosynthetic analysis of amphirionin-4 is depicted in Scheme 2.11 and involves three key disconnections that were envisaged to yield an efficient and convergent synthesis. Specifically, we planned to connect the THF core to the polyene sidechain through a Nozaki-Hiyama-Kishi (NHK) reaction involving vinyl iodide **126** and aldehyde **122**, which would also introduce the remote allylic alcohol at C8.[95,96] An iterative series of Pd-catalyzed cross-coupling reactions could be used to build up the

polyene side chain from easy to access precursors **123**-**125**. Synthesis of the tetrahydrofuranol ring (**126**) would exploit methods developed by Dr Kang and Dr Mowat discussed earlier[86,87] and involve the lithium aldol reaction between acetone (**128**) and α-chloroaldehyde **129** followed by 1,3-*anti*- reduction and cyclization to afford access to the enantiomerically enriched *syn*-tetrahydrofuranol found in amphirionin-4.

Scheme 2.11. Retrosynthetic analysis for amphirionin-4 (35).

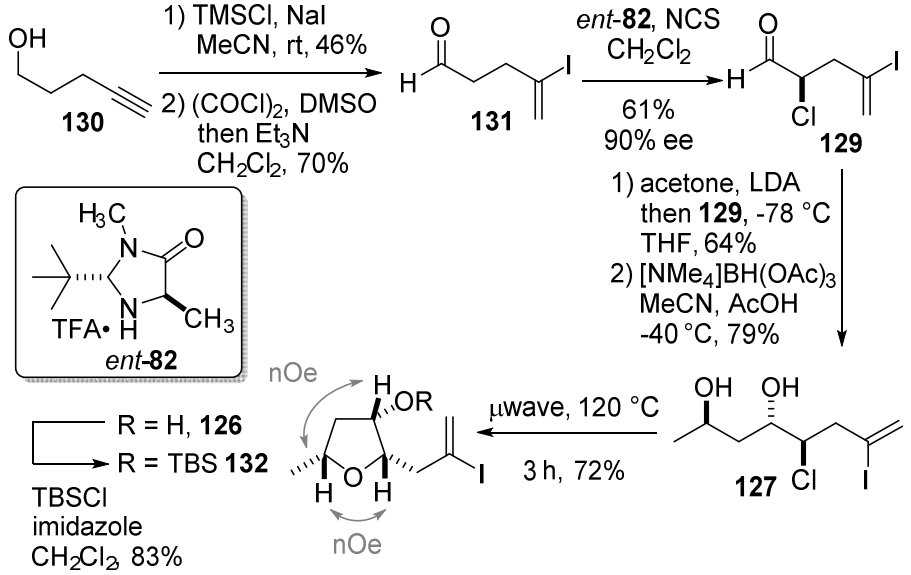


2.2.3. Construction of the THF Ring

The synthesis of the tetrahydrofuranol is described in Scheme 2.12. Our initial attempts focused on use of the α-chloroaldehyde derived from oxidation and chlorination of 4-pentyn-1-ol (**130**). However, the α-chloroaldehyde produced from this process was volatile, which complicated its isolation. Based on this challenge, the plan was revised to instead effect the hydroiodination of the alkyne in the first step which would decrease the volatility of the subsequent synthetic intermediates. Accordingly, hydroiodination of the alkyne function in 4-pentyn-1-ol (**130**) followed by a Swern oxidation[97] afforded aldehyde **131**. The low yield for the hydroiodination reaction is due to the necessary stoppage of

the reaction at ~60% conversion to avoid the production of an inseparable byproduct that was produced after extended reaction times. A subsequent asymmetric α-chlorination of **131** using MacMillan's catalyst *ent*-**82** and NCS gave the α-chloroaldehyde **129** in good enantiomeric excess (90% ee).[76] Care had to be taken with α-chloroaldehyde **129** as it was unstable and prone to racemize during purification by flash chromatography. As a result, this material was reacted directly with the lithium enolate derived from acetone to afford the β-ketochlorohydrin (not shown). A 1,3-*anti*-selective reduction afforded chlorodiol **127** in good yields and high diastereoselectivity.[98] Cyclization by heating the compound in MeOH in a microwave reactor gave clean conversion to the tetrahydrofuranol **126**. Analysis of correlations in 1D NOESY spectra recorded on tetrahydrofuranol **126** confirmed the all-*syn* arrangement of functional groups on the THF ring.

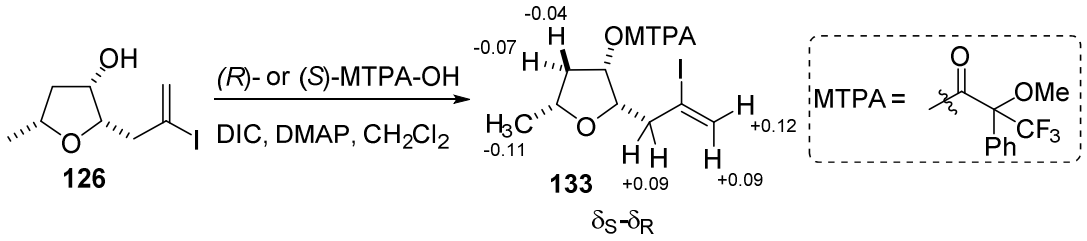
Scheme 2.12. Synthesis of tetrahydrofuranol (126).



In order to establish the absolute stereochemistry of the tetrahydrofuranol **126**, we utilized a modified Mosher's analysis.[99,100] Thus, the (*R*)- and (*S*)-MTPA esters were synthesized and the resulting ^{1}H NMR spectra were analyzed and allowed us to compile a difference plot between the two spectra (Scheme 2.13). This established the stereochemistry to be (2*R*, 4*S*, 5*S*) as shown. Enantiomeric excess was determined by chiral HPLC on the reduced form of α-chloroaldehyde **131** and was found to be 90% in

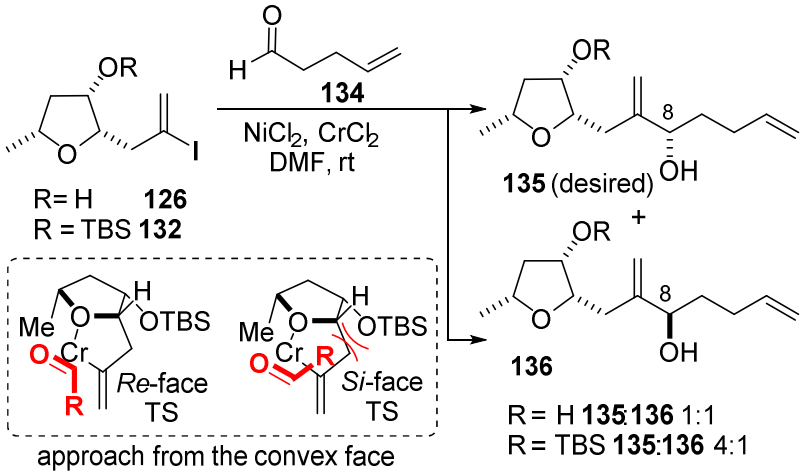
the absence of flash chromatographic purification (see Experimental section for HPLC traces) or 80% after purification on silica gel.

Scheme 2.13. Determination of absolute stereochemistry using Mosher's esters.



With the tetrahydrofuranol **126** in hand, we were interested in exploring the planned NHK reaction with a view towards using the tetrahydrofuran ring to control the stereochemical outcome of this reaction (Scheme 2.14). The NHK reaction of tetrahydrofuranol **126** went cleanly to the allylic alcohol but unfortunately gave a 1:1 mixture of diastereoisomers **135** and **136**. As a result we decided to protect the alcohol functionality in **126** as the silyl ether to block coordination between the alcohol and the putative vinyl chromium intermediate. To our delight, this modification improved the diastereoselectivity of the reaction to 4:1 in favour of the desired stereoisomer **135**. This is a unusual example of 1,4-stereoinduction. We hypothesized that the reaction involves coordination of the vinyl chromium species to the tetrahydrofuran oxygen, which leads to preferential approach of the aldehyde through the pro-*S* TS rather than the pro-*R* TS. (see inset). Presumably, the unprotected alcohol in **126** competes with the tetrahydrofuran oxygen for coordination to the vinyl chromium species and diminishes the diastereoselectivity of the subsequent addition to the aldehyde.

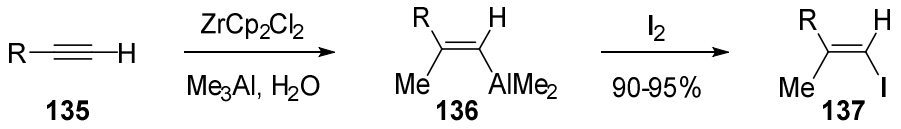
Scheme 2.14. 1,4-Stereoinduction in the NHK reaction of vinyl iodide (132).



2.2.4. Construction of the Side Chain

Having established a method to control the stereochemistry of the allylic alcohol at C8, we then wanted to focus on the synthesis of the pentadecatetraenal sidechain. In order to achieve this we intended to make extensive use of zirconium catalyzed carboalumination reactions to access the desired building blocks. This reaction was initially developed by Negishi in 1978[101,102] and is a powerful method for the stereocontrolled conversion of readily accessible terminal alkynes into vinyl halides which can be further used in Pd-coupling reactions.

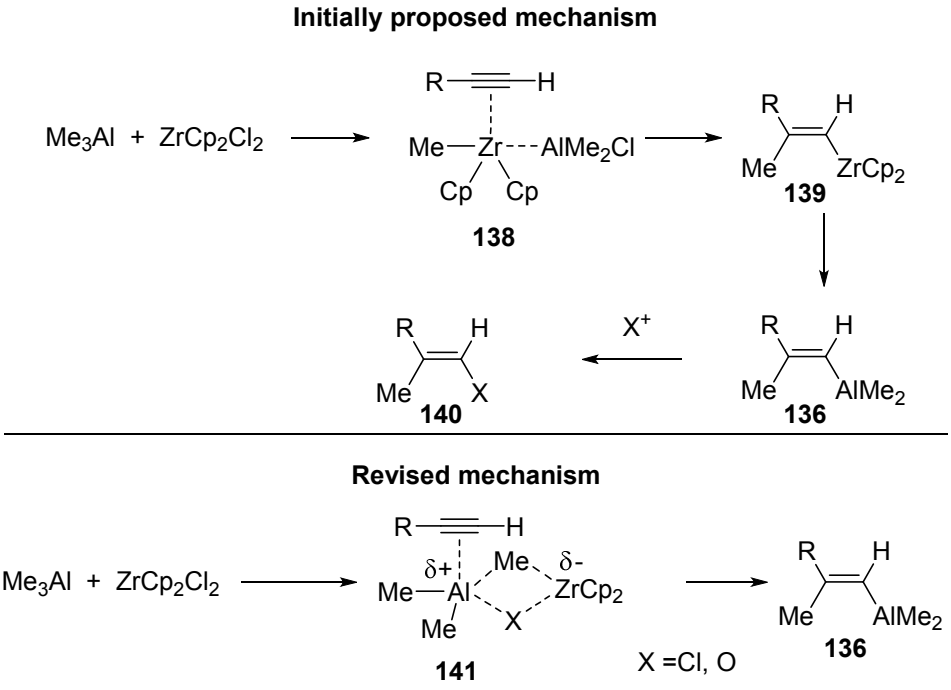
Scheme 2.15. Zirconium-catalyzed carboalumination reaction.



Mechanistically, considerable doubt existed about the pathway followed by this reaction. Both zirconium and aluminum were shown to be essential for the reaction to proceed as the absence of zirconium only afforded trace amounts of the product. The reaction afforded the *cis* alkene in very high (95:5) diastereoselectivity indicating that addition of the methyl group and the metal atom occurred simultaneously. Negishi's first proposal was that the zirconium formed a complex with the trimethylaluminum (**138**) and

added across the alkyne to afford the complex **139**.[103] Transmetallation with the aluminum would then afford the vinyl aluminum species (**136**), which can then undergo a reaction with an electrophile of choice to give the alkene product. However, tests using deuterated $Cp_2Zr(CD_3)Cl$ and $Al(CH_3)_3$ indicated that the methyl group was derived from the aluminum rather than the zirconium. Accordingly, Negishi revised the mechanism and proposed that zirconium formed complex **141** with trimethylaluminum and increased the reactivity of this species sufficiently for it to react with the alkyne and form the vinyl aluminum intermediate **136**.[104] Later studies by Wipf and co-workers showed that the reaction rate could be significantly increased by the addition of 1.5 equivalents of H_2O. While studies are needed to further investigate this observation, the reason for this rate increase is considered to be due to an oxygen replacing the Cl in complex **141** and increasing the subsequent reactivity of this complex.[105]

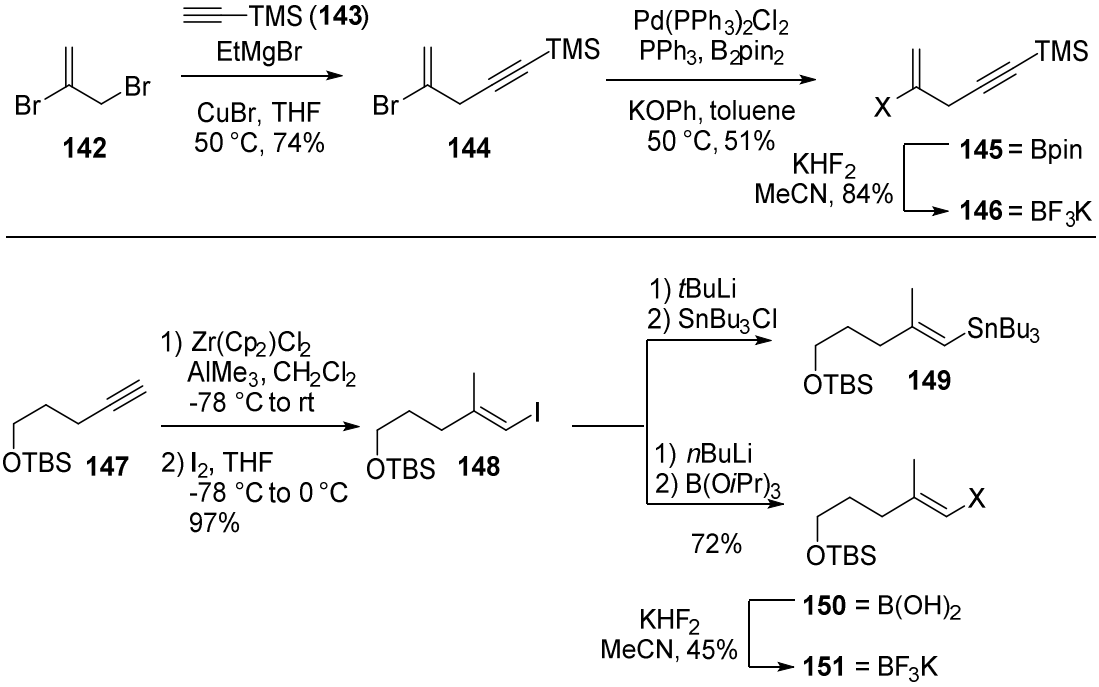
Scheme 2.16. Proposed mechanisms for zirconium catalyzed carboalumination reaction.



Our efforts towards the synthesis of the side chain initiated with the preparation of vinyl bromide **144** via the copper(I) catalyzed reaction of 2,3-dibromopropene (**142**) with the Grignard reagent derived from TMS-acetylene (**143**) (Scheme 2.17).[106] This

vinyl bromide was then further derivatized into the vinyl boron pinacolate **145**. The other coupling partner was synthesized via a zirconium catalyzed carboalumination of silyl ether protected-alkyne **147** followed by reaction with iodine to afford the vinyl iodide **148**. This could be readily converted into a variety of other coupling partners **149** to **151** by lithiation using *n*-BuLi following by trapping with the desired electrophile ($B(OiPr)_3$ or $SnBu_3Cl$). No yield is reported for the vinyl stannane as any attempt to purify this material on silica gel led to complete protodestannylation and as a result, crude **149** was used for subsequent coupling reactions. The vinyl boronic acid **150** was then converted into the vinyl trifluoroborate **151** by treatment with potassium bifluoride. The yield for this reaction was modest due to the propensity of the vinyl boronic acid to undergo hydrodeborylation to afford the terminal alkene.

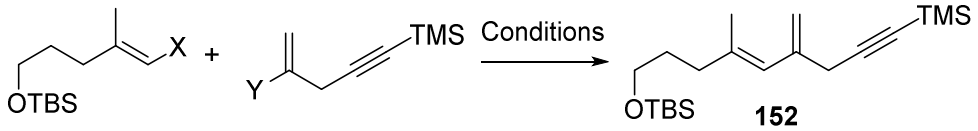
Scheme 2.17. Synthesis of coupling partners (145) to (151).



Our attempts to carry out the coupling between these two fragments are summarized in Table 2.1. While the coupling of vinyl iodide **148** with vinyl boronates **145** and **146** (entries 1-4) did give trace amounts of product, we observed significant degradation of the reactants during the reaction and all attempts to increase the amount of desired product were unsuccessful. Initial coupling reactions using vinyl bromide **144**

and vinyl boronic acid **150** or vinyl stannane **151** also failed to generate any observable product due to complete hydrodeborylation/hydrodestannylation. Considering these results, we decided to investigate the use of vinyl trifluoroborates that have been pioneered by Molander as a stable alternative to boronic acids as coupling partners in Suzuki-Miyaura reactions.[107] These trifluoroborates are more stable than the parent boronic acid and slowly hydrolyze to the boronic acid over the course of the reaction, This ensures that the boronic acid is only present in low concentrations throughout the course of the reaction and reduces the propensity for decomposition prior to transmetallation with the palladium intermediate. Cross coupling of the vinyl trifluoroborate **151** with the vinyl bromide **144** afforded the desired diene **152** in a reproducibly good yield and could be readily scaled up to produce multigram quantities without issues.

Table 2.1. Cross-coupling reactions to access diene (152).



148 X = I
149 X = $SnBu_3$
150 X = $B(OH)_2$
151 X = BF_3K

144 Y = Br
145 Y = Bpin
146 Y = BF_3K

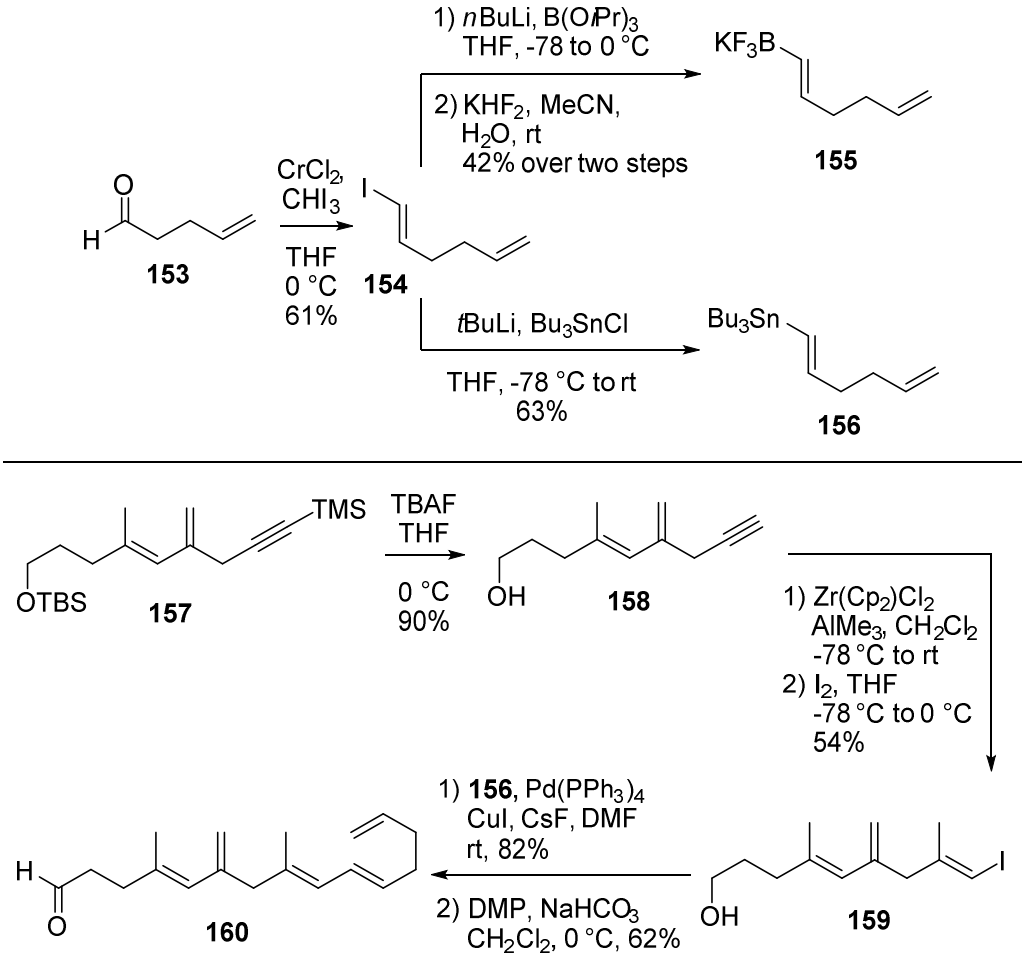
Entry	Reactants	Temperature	Catalyst	Additive	Yield
1	**148+145**	50 °C	$Pd(PPh_3)_4$	Cs_2CO_3[a]	~10%
2	**148+145**	50 °C	$Pd(PPh_3)_4$	$Ba(OH)_2$[a]	<5%
3	**148+145**	50 °C	(D*t*BPF)$PdCl_2$	$Ba(OH)_2$[a]	<5%
4	**148+146**	50 °C	$Pd(PPh_3)_4$	Cs_2CO_3[a]	<5%
5	**149+144**	50 °C	$Pd(PPh_3)_4$	CuI, CsF[b]	<5%
6	**150+144**	55 °C	$Pd(PPh_3)_4$	Cs_2CO_3[c]	<5%
7	**151+144**	55 °C	$Pd(PPh_3)_4$	Cs_2CO_3[a]	68%

Note: a) A 1:1 mixture of THF:H_2O was used as solvent. b) DMF was used as solvent. c- EtOH was used as solvent.

The completion of the synthesis of the side chain is described in Scheme 2.18. A Takai reaction of aldehyde **153** with iodoform afforded vinyl iodide **154** in reasonable yield and disappointingly low dr (2:1).[108] This vinyl iodide was then converted into vinyl trifluoroborate **155** or vinyl tributylstannane **156** by lithium-iodide exchange followed by

treatment with either triisopropylborate followed by potassium hydrogen fluoride or tributyl tin chloride. Meanwhile, TBAF deprotection on alkyne **157** afforded alcohol **158,** which was subsequently converted into the vinyl iodide **159** via a carboalumination reaction followed by treatment with iodine. Our initial efforts to replicate the coupling reaction from Table 2.1 using trifluoroborate **155** were unsuccessful as the basic conditions utilized led to isomerization of the sensitive diene system. However a Stille coupling between vinyl stannane **156** and vinyl iodide **159** did give access to the polyene in good yield.[109,110] Subsequent oxidation using Dess-Martin periodinane (DMP)[111] afforded aldehyde **160** and completed the synthesis of the polyene side chain.

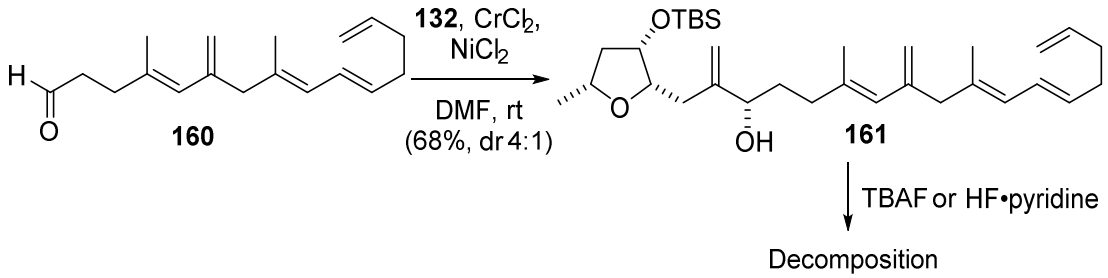
Scheme 2.18. Synthesis of complete side chain.



2.2.5. Completion of Synthesis

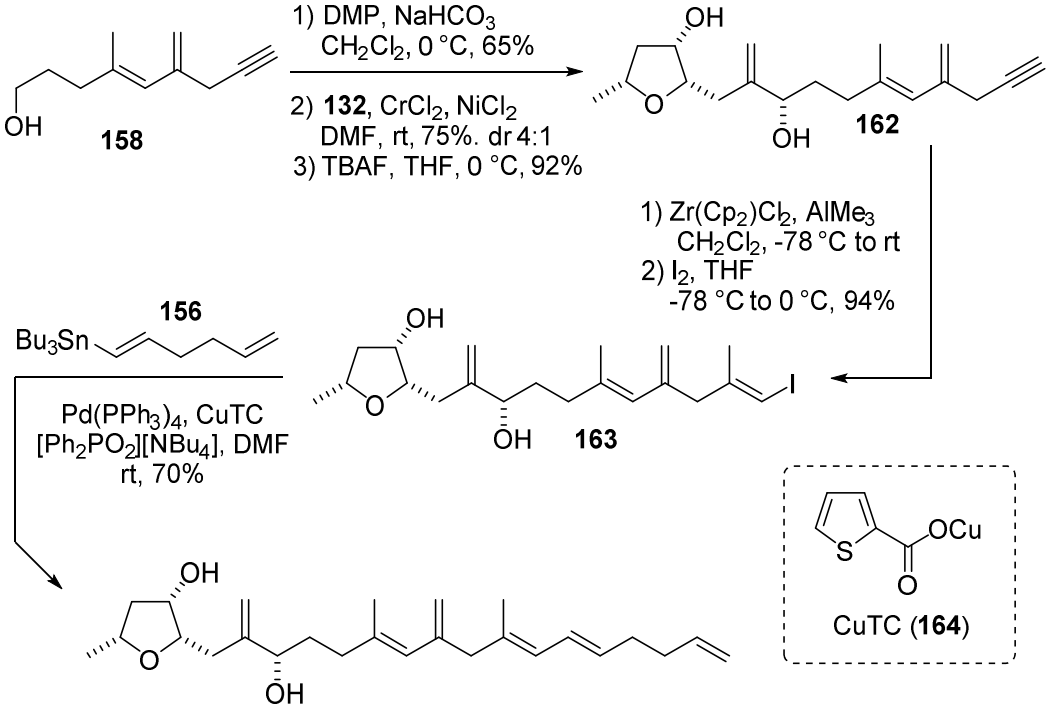
NHK coupling between tetrahydrofuran **132** and aldehyde **160** proceeded cleanly to the desired product **161** with the same diastereoselectivity observed on the test substrate (Scheme 2.14). However, removal of the silyl group from the tetrahydrofuran ring proved to be problematic as the skipped tetraene motif was found to be sensitive to both basic (TBAF) and acidic (HF•pyridine) conditions. Considering the instability of this molecule we decided to modify the synthetic plan and attempt to form the tetraene at a later stage following the NHK coupling with the tetrahydrofuran ring.

Scheme 2.19. First attempt at completing the synthesis of amphirionin-4.



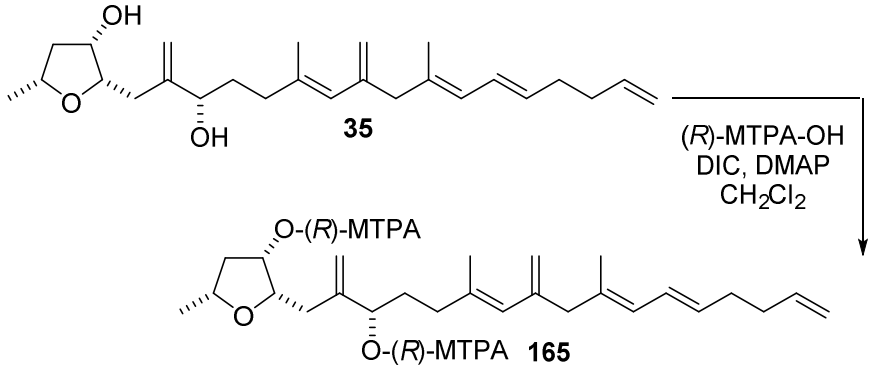
Accordingly, we began the modified and ultimately successful approach (Scheme 2.20) by oxidation of the alcohol in **158** followed by the NHK reaction to afford the tetrahydrofuranol **162** in excellent yield (75%, 4:1 dr) Conversion of the alkyne in **162** into the vinyl iodide **163** using the reactions discussed earlier in the synthesis of **159** proceeded in high yield. However, the subsequent Stille coupling with vinyl stannane **156** proved unsuccessful using the conditions that had previously afforded tetraene **160** and only gave an intractable mixture of products. Fortunately switching the conditions to those pioneered by Fürstner (copper (I) thiophene carboxylate (CuTC), tetrabutylammonium diphenylphosphinate) for use on sensitive substrates[112] that avoid the use of base and elevated temperatures was successful and gave access to amphirionin-4 in excellent yield with the tetraene motif intact.

Scheme 2.20. Modified synthesis to access amphirionin-4.



Both ^{1}H and ^{13}C NMR spectra recorded for synthetic amphirionin-4 were in agreement with that reported for the natural product (see Experimental Section, Table 2.3).[42] However, the specific rotation of synthetic amphirionin-4 (-5.8, *c* 0.34, $CHCl_3$) differed in sign from that reported for the natural product (+6, *c* 0.29, $CHCl_3$). Since the stereochemistry for amphirionin-4 was assigned by analysis of bis(*R*) and bis(*S*)-MTPA esters using the modified Mosher's method, we also converted our synthetic amphirionin-4 into the corresponding bis(*R*)-MTPA ester **165** (Scheme 2.21). The spectral data recorded for this derivative were in complete agreement with those reported by Tsuda for the bis(*R*)-MTPA ester of the natural product and differed significantly from that reported for the corresponding bis(*S*)-MTPA ester of **35**. We consider that the difference in specific rotation between natural and synthetic amphirionin-4 results from its small absolute value and the challenges involved in accurately measuring specific rotation with small sample sizes.

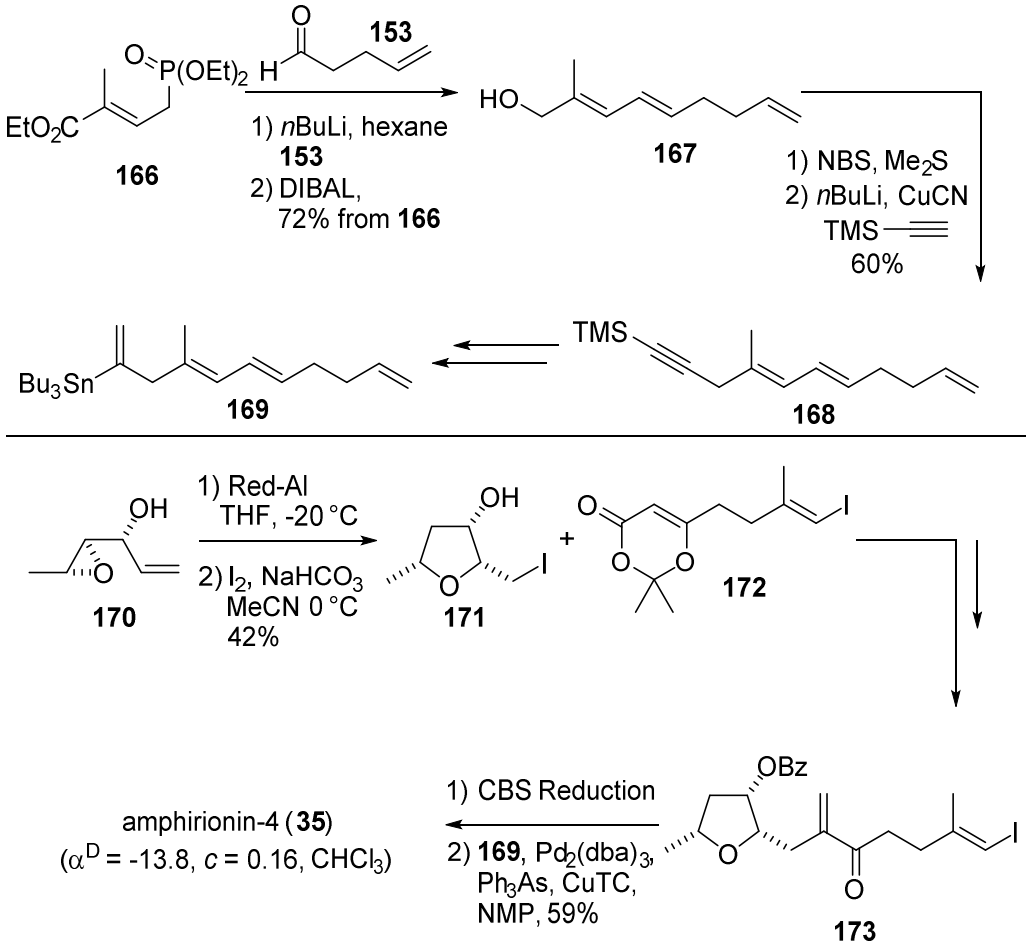
Scheme 2.21. Synthesis of *bis*(*R*)-MTPA ester for confirmation of stereochemistry.



2.2.6. Discussion of Subsequent Syntheses of Amphirionin-4

Following the publication of our synthesis of amphirionin-4 in 2015, two additional syntheses of **35** by Kuwahara[113] and Ghosh in 2016 have been reported.[114] Kuwahara approached the synthesis in a similar manner, breaking up the structure into the tetrahydrofuranol and several fragments for the polyene side chain (Scheme 2.22). In Kuwahara's synthesis, the side chain is accessed through a Horner-Wadsworth-Emmons reaction to afford allyl alcohol **167**, which was subsequently converted to the allyl bromide and displaced with the cuprate derived from TMS acetylene to give alkyne **168**. Further reactions gave vinyl stannane **169** to be used later in the sequence. The tetrahydrofuranol core was synthesized via reductive opening of epoxide **170** with Red-Al followed by cyclization of the resulting alcohol using the iodoetherification method discussed earlier. This process afforded tetrahydrofuranol **171** in moderate yields and with the correct stereochemistry (established by Mosher's ester analysis). Esterification with vinyl iodide **172**, intramolecular alkylation and subsequent conversion to the enone afforded advanced intermediate **173**. Chiral reduction of this enone[115] installed the C8 allylic stereocentre with the desired stereochemistry and then Stille coupling using triphenylarsine was employed to complete the synthesis of amphirionin-4. Importantly, while Kuwahara's specific rotation (-13.8, *c* 0.16, $CHCl_3$) differed in value to that reported by our group, the sign of the rotation matched our own.

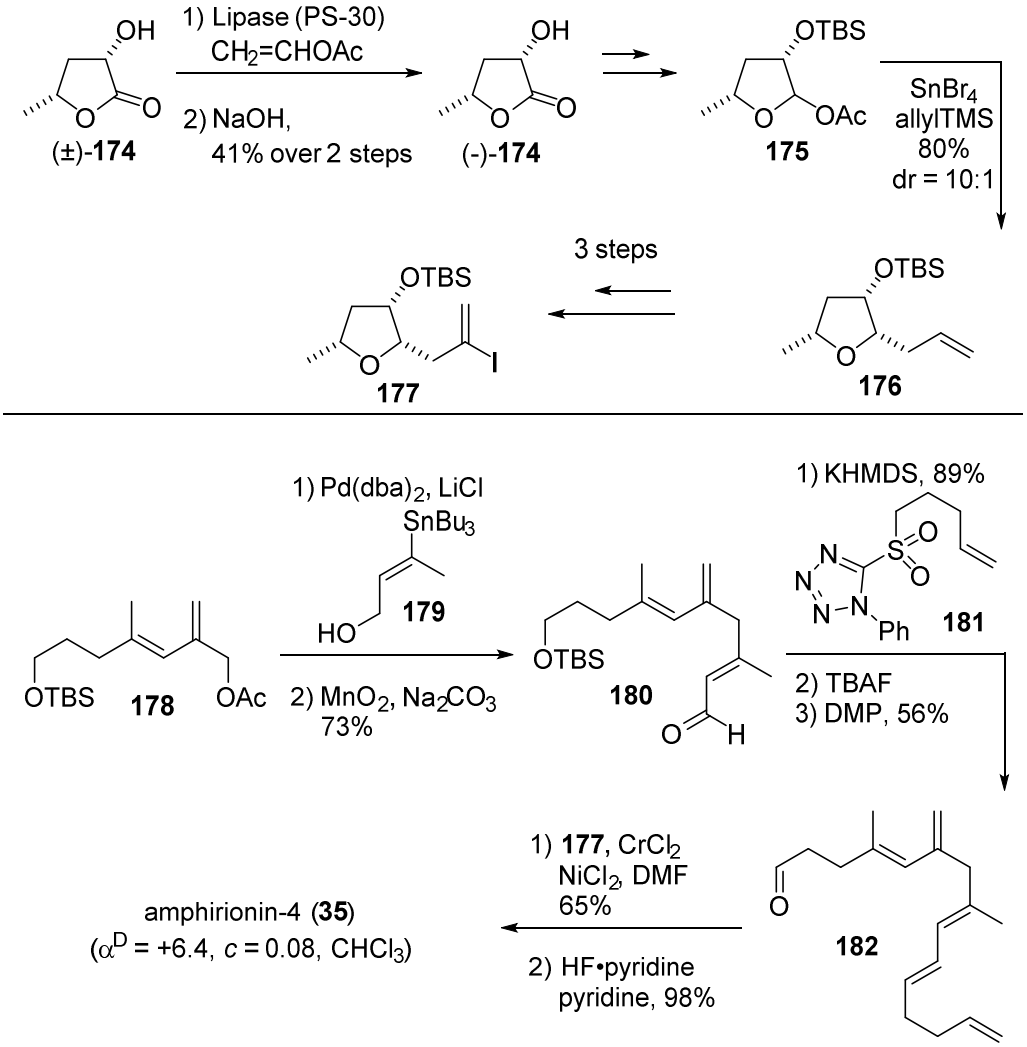
Scheme 2.22. Kuwahara's synthesis of amphirionin-4.



Ghosh published the third synthesis of amphirionin-4 shortly afterwards (Scheme 2.23). In this most recent synthesis, the same diastereselective NHK coupling developed in our synthesis was exploited to connect the tetrahydrofuran and the polyene side chain. The Ghosh synthesis of the tetrahydrofuranol core relies on enzymatic resolution of α-hydroxy lactone **174** followed by reduction of the lactone and an intermolecular trapping of the oxocarbenium ion generated by addition of $SnBr_4$ and allyltrimethylsilane to acetal **175** to afford tetrahydrofuran **176**. Subsequent conversion of the terminal alkene to the vinyl iodide over 3 steps gave access to one coupling partner **177** for the NHK reaction. The synthesis of the polyene sidechain was initiated from 4-pentyn-1-ol which was subsequently converted to allyl acetate **178** and then sequential Stille coupling[109] and Julia-Kocienski[116] reactions gave access to aldehyde **182**. NHK coupling

between the two substrates afforded the desired product in identical diastereoisomeric ratio to that reported by our group and, following silyl deprotection, afforded amphirionin-4. Interestingly, Ghosh reported the specific rotation (+6.4, *c* 0.08, $CHCl_3$) to be identical to that of the natural product and different from that of the two synthetic samples of the natural product. However, Ghosh subsequently published a correction to his original paper where X-ray crystallography indicated that the enzymatic resolution used to access (-)-**174** actually afforded the opposite stereochemistry to that shown and therefore he had completed the synthesis of the enantiomer of amphirionin-4.

Scheme 2.23. Ghosh's synthesis of amphirionin-4.



2.3. Total Synthesis and Structural Reassignment of Laurefurenyne A and B

2.3.1. Introduction

Laurencia species of red algae have been widely studied by natural product chemists and to date there are over 300 unique secondary metabolites that have been isolated and characterized from various *Laurencia* species.[117,118] In particular, these red algae produce a unique set of C_{15} acetogenins. These C_{15} acetogenins have several characteristic structural features that identify them as *Laurencia* metabolites (Figure 2.9). They are generally halogenated in some form, contain either a conjugated enyne or a bromoallene terminus, and contain one or more cyclic ether rings.

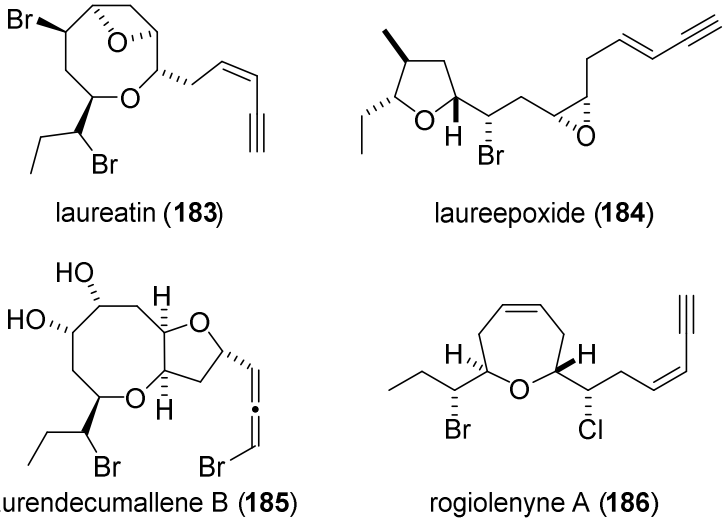
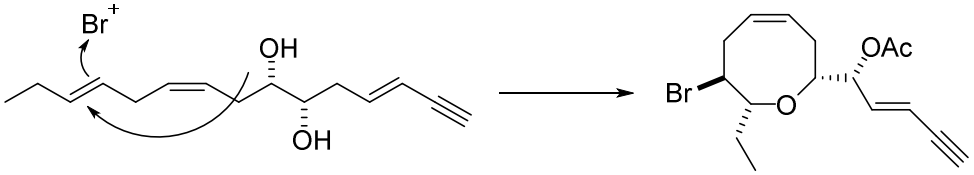


Figure 2.9. Representative *Laurencia* metabolites.

Biosynthetically most *Laurencia* C_{15} acetogenins are believed to derive from laurediol (**187**), from which sequential bromonium/chloronium/epoxide opening events form complex collections of ether rings. The proposed biosynthesis for laurencin (**188**), the first characterized *Laurencia* metabolite, is shown in Scheme 2.24. Murai and co-workers have demonstrated that the treatment of laurediol with a lactoperoxidase in the presence of hydrogen peroxide and sodium bromide generated deacetyllaurencin albeit in low yield.[119] This synthesis relies on the bromonium catalyzed cyclization of laurediol

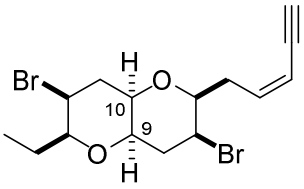
to form the eight-membered ring and generate the requisite stereochemical relationship at the bromomethine centre. Subsequent acetylation affords laurencin (**188**).

Scheme 2.24. Proposed biosynthesis of laurencin.

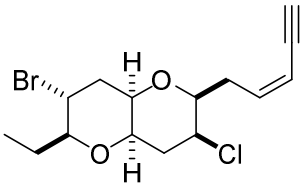


laurediol (**187**) laurencin (**188**)

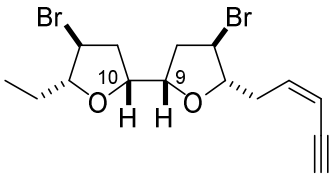
Due to their highly oxidized backbone and complicated structure, the determination of the structure of the various *Laurencia* metabolites has proven to be challenging.[120] In particular, there has been considerable debate regarding the skeletal structure of compounds such as elatenyne (Figure 2.10) which was originally proposed to include a pyrano[3,2-*b*]pyran similar to that present in (*Z*)-dactomelyne (**190**).[121] However, synthesis of the proposed structure **189** demonstrated that elatenyne had been incorrectly assigned.[122] Calculation of the expected ^{13}C NMR chemical shifts by Goodman and Burton indicated that the most likely structure was the bis-tetrahydrofuranol **191** as the ^{13}C NMR chemical shifts for C9 and C10 in the ^{13}C NMR spectra of **189** resonate at >76 ppm, which is not consistent with the expected shifts for C9 and C10 in the pyrano[3,2,*b*]pyran system of **189** (δ_C<76 ppm).[122,123] This hypothesis was later confirmed through total synthesis of **191** in 2012 by Burton and Kim, leading to the reassignment of the structure of elatenyne as compound **191**.[124]



189: originally proposed structure of elatenyne



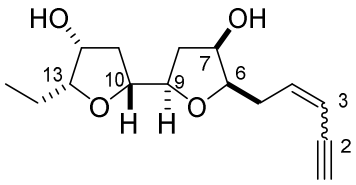
(*Z*)-dactomelyne (**190**)



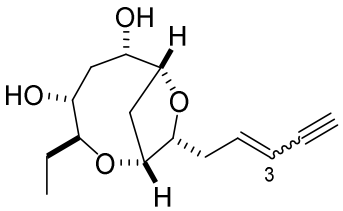
191: reassigned structure of elatenyne

Figure 2.10. Reassignment of the structure of elatenyne.

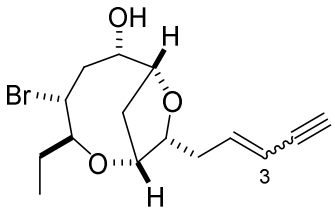
In 2010, Jaspars and co-workers reported the isolation of six new *Laurencia* metabolites, laurefurenynes A-F (**36**, **43**, **192**-**195,** Figure 2.11).[43] These six metabolites consist of three diastereoisomeric pairs and each contain a tetrahydrofuranol scaffold in the structure. Studies of the cytotoxicity of these natural products indicated that laurefurenynes C and F possessed moderate, non-selective cytotoxicity while the other laurefurenynes were inactive.



proposed structures of
3*Z* = **36** (laurefureyne A)
3*E* = **192** (laurefurenyne B)



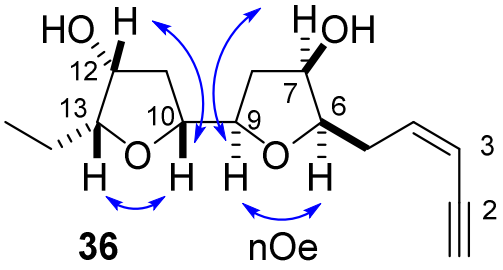
3*Z* = **193** (laurefureyne C)
3*E* = **194** (laurefurenyne D)



3*Z* = **195** (laurefureyne E)
3*E* = **43** (laurefurenyne F)

Figure 2.11. Structures of laurefurenynes A-F.

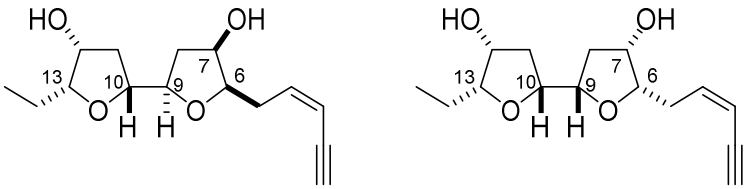
Of particular interest to our group was the structure of laurefurenyne A, which contains the same bis-tetrahydrofuran ring that had complicated the structural assignment of elatenyne. Jaspars assigned the structure of laurefurenyne A as a bis-tetrahydrofuranol based on Burton and Goodman's prior report on elatenyne's structure.[122] Notably, the chemical shifts of C9 and C10 in the ^{13}C NMR spectrum (δ_C = 79.1 and 78.2 respectively) of laurefurenyne A matched with Burton and Goodman's proposal. It is notable that at the time, the elatenyne structural revision had been proposed by not verified through total synthesis, and the fused pyrano[3,2-*b*]pyran system (Figure 2.10) was also considered to be a potential structure for laurefurenyne A. The stereochemistry of each separate ring was established (Figure 2.12) by analysis of a 2D NOESY spectrum that indicated that protons H6, H7 and H9 were oriented *syn* with respect to each other. In a similar manner, H10, H12 and H13 were also found to be all-*syn,* indicating that both rings had all-*syn* stereochemistry.



δ_{C9} = 79.1
δ_{C10} = 78.2

Figure 2.12. Assignment of relative stereochemistry of each ring of laurefurenyne A.

The relative stereochemistry between the two tetrahydrofuran rings proved more challenging to assign as there were no NOESY correlations that differentiated the two possible stereostructures **36** and **196**. Modelling of these two diastereoisomers indicated that the best match to the NOE data was diastereoisomer **36** (Figure 2.13), however due to the inherent uncertainties in this method, diastereoisomer **196** was also a possibility for the structure of laurefurenyne A. The absolute stereochemistry of laurefurenyne A was also not established.

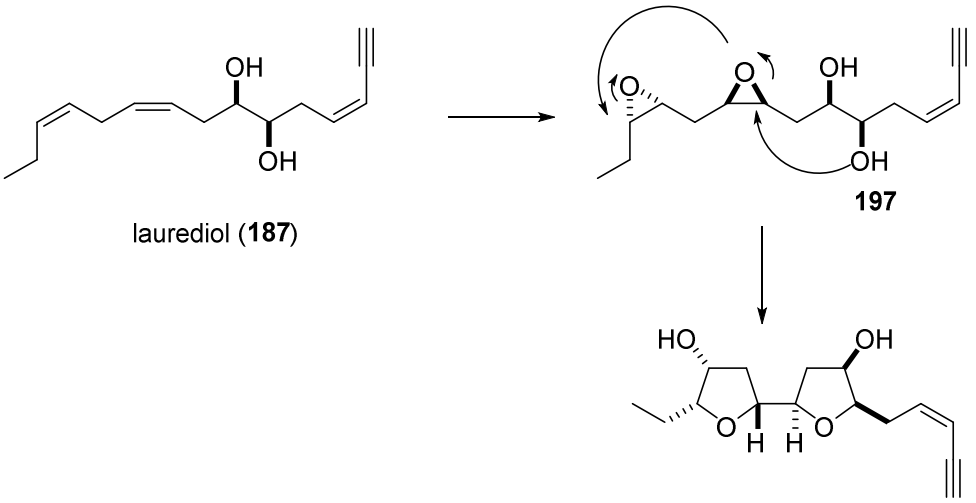


(6*R*, 7*R*, 9*R*):**36** (6*S*, 7*S*, 9*S*):**196**

Figure 2.13. Candidate stereostructures for laurefurenyne A.

Jaspars also proposed a possible biosynthetic route for the production of laurefurenyne A from laurediol (**187**). This route initiated with a double epoxidation reaction on laurediol to form bis-epoxide **197** and then a subsequent epoxide opening cascade would afford direct access to laurefurenyne A (**36**) with the correct stereochemistry. This represented a relatively unusual biosynthetic pathway for *Laurencia* metabolites as there was no requirement for the involvement of bromonium or chloronium ions in the pathway.

Scheme 2.25. Proposed biosynthesis for laurefurenyne A.

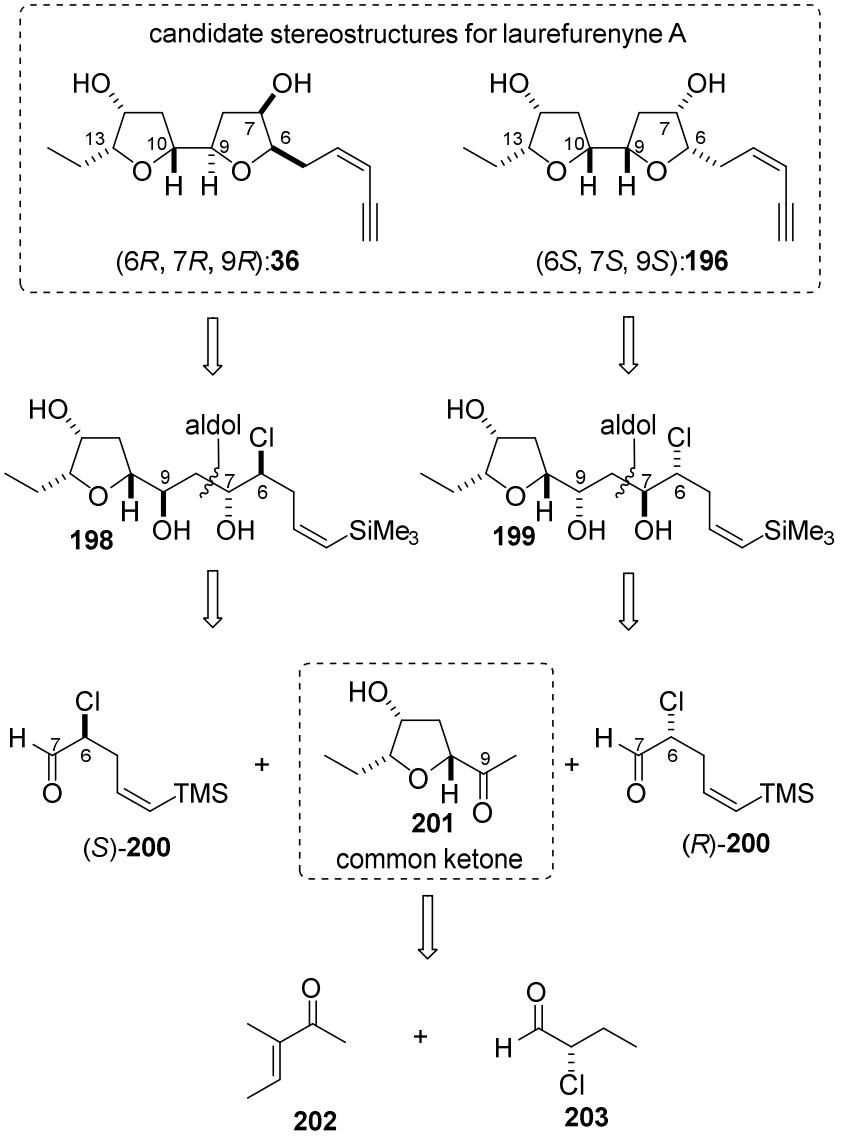


Due to the uncertainty regarding the stereochemistry of laurefurenyne A, we were intrigued to explore the use of our chlorohydrin-based THF synthesis to access this natural product.

2.3.2. Retrosynthesis

Both stereostructures **36** and **196** were potential candidates for the correct structure of laurefurenyne A and because of this we were interested in designing a synthesis that would permit late stage access to either candidate stereostructure (Scheme 2.26). To achieve this, we envisaged utilizing the Ag(I)-promoted cyclization to form the bis-tetrahydrofuran core from chlorodiols **198** and **199** and then subsequent iodine-silicon exchange and Sonogashira coupling to afford the ene-yne functionality. These chlorodiols could both be derived from the same intermediate ketone **201** via a lithium aldol reaction with either enantiomer of readily accessed α-chloroaldehyde **200** and subsequent 1,3-*anti*-selective reduction of the resultant β-hydroxyketone. The common ketone **201** could be accessed through a similar methodology in an enantioselective manner from the α-chloroaldehyde derived from butanal (**203**) and (3*E*)-3-methyl-3-penten-2-one (**202**).

Scheme 2.26. Retrosynthesis of the candidate stereostructures for laurefurenyne A.

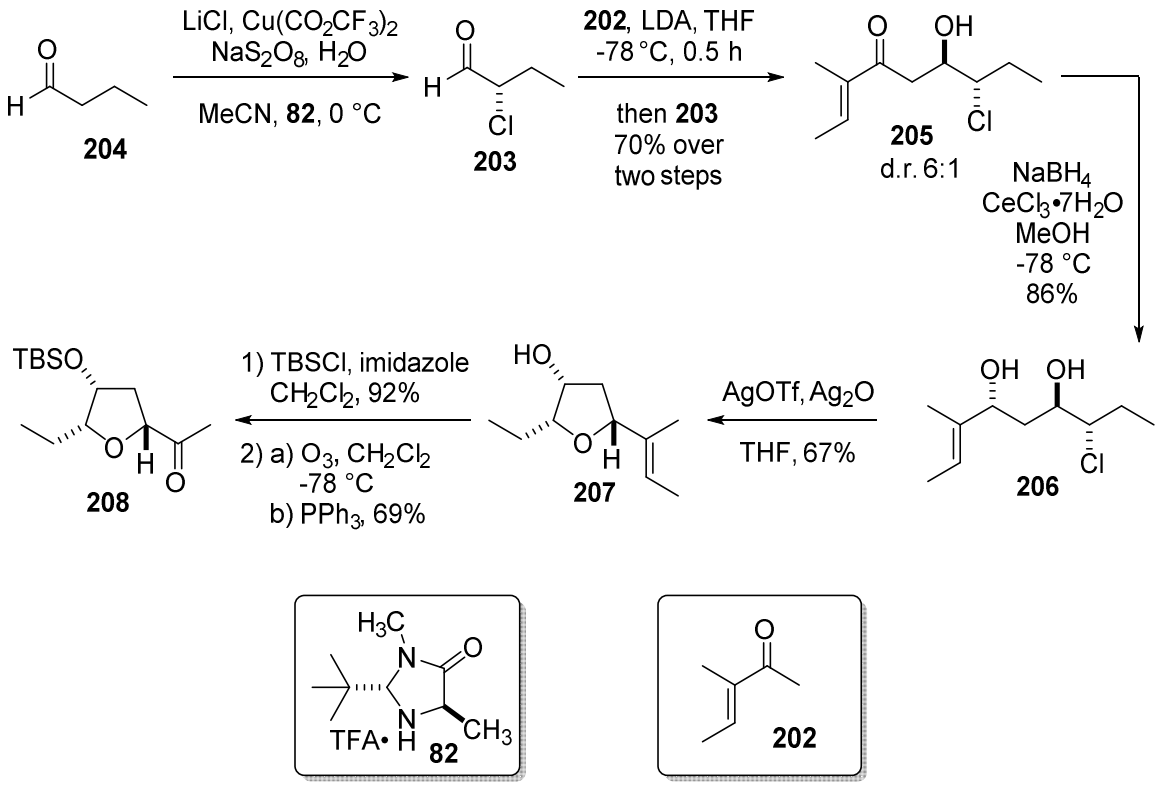


2.3.3. Synthesis of First Candidate Stereostructures

As depicted in Scheme 2.27, the synthesis of the candidate stereostructures **36** and **196** began with the asymmetric α-chlorination of butanal (**204**) using the procedure described by MacMillan.[75] The resulting α-chloroaldehyde **203** was extremely volatile and challenging to purify and so the crude product from this reaction was treated directly with the lithium enolate derived from 3-methyl-3-penten-2-one (**202**) to afford the *anti*-

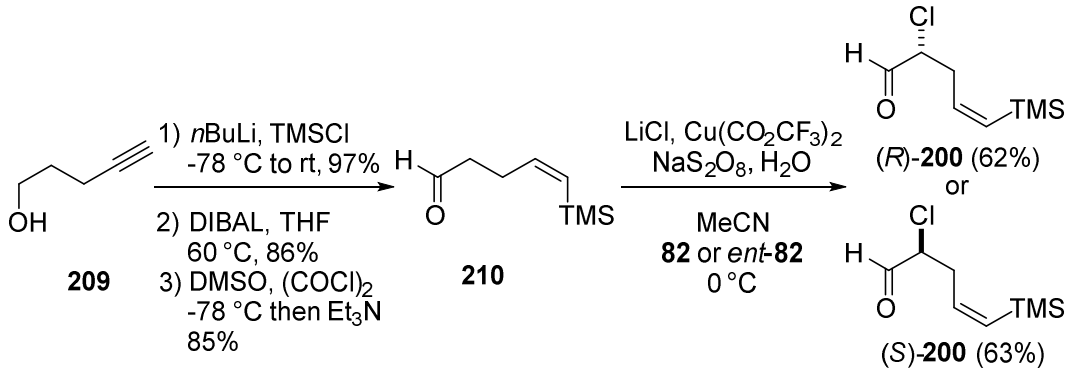
chlorohydrin **205** in good yield (70% over two steps) and dr (6:1, *anti*:*syn*). A subsequent Evans-Saksena[125,126] reduction of the resulting β-ketochlorohydrin unexpectedly gave a 1:1 ratio of 1,3-*syn*-:1,3-*anti*-diols. However a Luche reduction[127] carried out at -78 °C did afford the desired 1,3-*anti*-diol **206** as the major component of an inseparable 5:1 mixture of diastereoisomers. Attempts to carry out the cyclization using a microwave reactor led to the generation of an intractable mixture but cyclization of this material using our AgOTf/Ag_2O conditions cleanly afforded the tetrahydrofuranol **207** and allowed for separation of the diastereoisomers. The relative stereochemistry of **207** was assigned by analysis of 1D NOESY spectra while analysis of the (*R*)- and (*S*)-MTPA esters of **207** and chiral GC (see Experimental section for further details) confirmed both the absolute stereochemistry and the high enantiomeric purity (95% ee). Protection of the alcohol function in tetrahydrofuranol **207** as the TBS ether was followed by ozonolytic cleavage of the alkene to generate the methyl ketone **208** in six steps from butanal (**204**).

Scheme 2.27. Synthesis of methyl ketone (208).



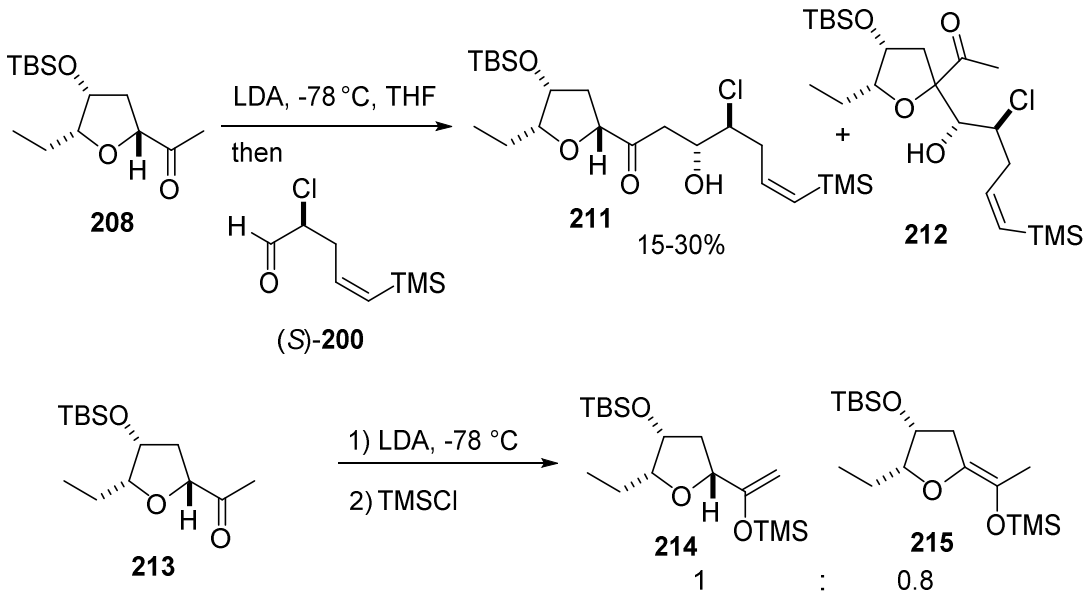
Both (*R*)- and (*S*)-enantiomers of α-chloroaldehyde **200** were obtained from 5-pentyn-1-ol (**209**). Silylation then reduction of the alkyne by DIBAL over five days and subsequent Swern oxidation afforded aldehyde **210** in high yields over the three steps. Chlorination of **210** using either enantiomer of catalyst **82** and Macmillan's SOMO procedure[75] afforded both (*R*)- and (*S*)-**200** in good yield and enantiomeric purity.

Scheme 2.28. Synthesis of α-chloroaldehydes (*R*)-200 and (*S*)-200.



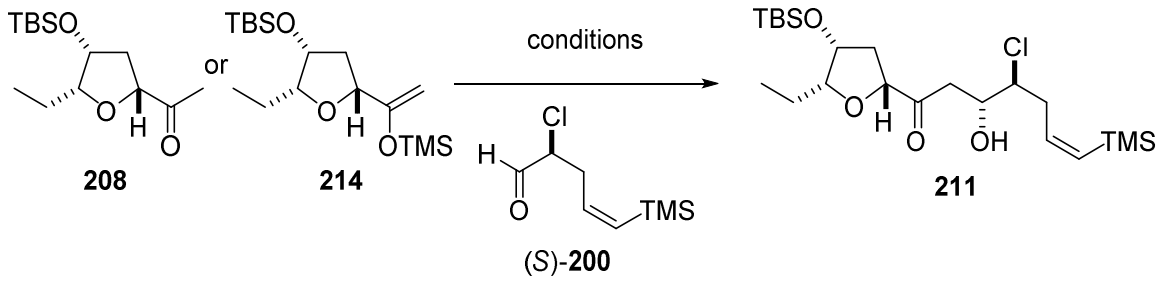
With the two key components in hand, we then focused on combining these two fragments in an aldol reaction. Initial efforts using LDA did afford the desired product but in low and inconsistent yields (Scheme 2.29). Analysis of the ^{1}H NMR spectra derived from **211** revealed that a significant amount of undesired aldol adduct **212** was being produced during the reaction. In order to confirm this, we trapped the intermediate lithium enolate derived from **208** with TMSCl to form the silyl enol ether. Examination of the spectral data for this reaction revealed the formation of two silyl enol ethers **214** and **215** in a 1:0.8 ratio. This surprising result indicated that the deprotonation event was not selective for the methyl group and we speculated that the undesired deprotonation resulted from coordination of the lithium to the tetrahydrofuran etheric oxygen.

Scheme 2.29. Initial efforts to carry out lithium aldol reaction between ketone 208 and α-chloroaldehyde (*S*)-200.



In an effort to improve the yield for this reaction (Table 2.2), we screened a variety of bases and counterions (entries 1 to 3). This screen indicated that LiHMDS was the optimal base and, furthermore, we observed that the use of LiHMDS suppresses formation of undesired adduct **212**. Additional additives (entries 4 and 5) did not further promote the formation of the desired product. We observed a number of degradation products of ketone **208** following treatment with LiHMDS at -78 °C for two hours followed by quenching with NH_4Cl. Accordingly, we explored the formation of the enolate at -40 °C (entry 6) with a significantly decreased reaction time. This gave the desired aldol adduct in an increased yield of 39%, which was reproducible over several reactions. Attempts to carry out a Mukaiyama aldol reaction using silyl enol ether **214** did not provide any of the desired product (entry 8) while an attempt at an amine free reaction by treating silyl enol ether **214** with MeLi to generate the enolate only gave a small amount of the desired aldol adduct **211** (entry 7). A boron aldol between **214** and (*S*)-**200** (entry 9) also led to very little (<5%) of the desired product with significant degradation of the α-chloroaldehyde being observed. Ultimately it was decided that due to the ease of synthesis for the components (**208** and **200**) of this reaction, we would proceed with the synthesis and accept the low yields for this early key aldol step.

Table 2.2. Optimisation of aldol reaction between ketone (208) and α-chloroaldehyde (*S*)-200.



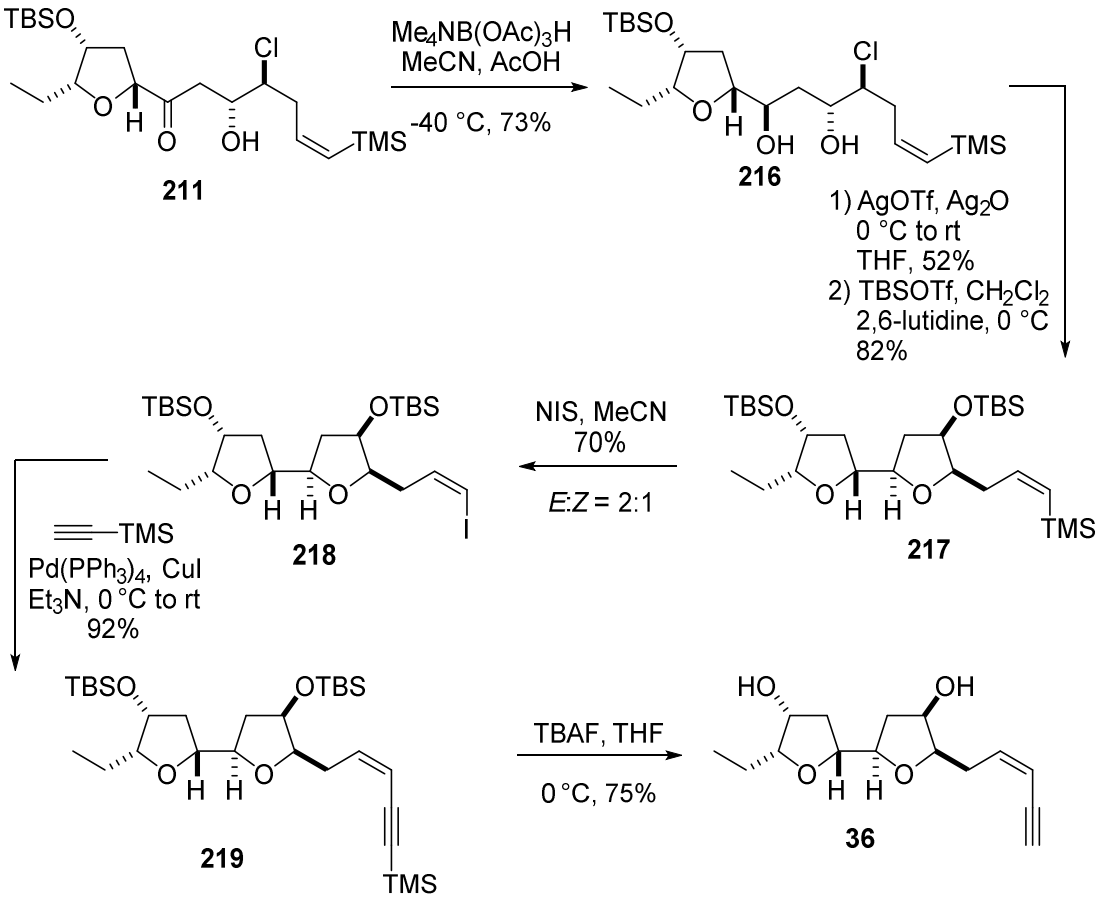
208 **214** (*S*)-**200** **211**

Entry	Substrate	Base	Additives	Time (min)[a]	T (°C)	Yield (211)
1	**208**	LiHMDS	-	30	-78	30%
2	**208**	NaHMDS	-	30	-78	15%
3	**208**	KHMDS	-	30	-78	<5%
4	**208**	LiHMDS	LiCl	30	-78	~25%
5	**208**	LiHMDS	12-C-4	30	-78	~25%
6	**208**	LiHMDS	-	5	-40	39%
7	**214**	MeLi	-	60	-78 to 20	~5%
8	**214**	-	$BF_3•OEt_2$	5	-60	<5%
9	**208**	NEt_3	$(Cy)_2BCl$	180	-78 to 0	<5%

Note: a) Time before the addition of α-chloroaldehyde (*S*)-**200**

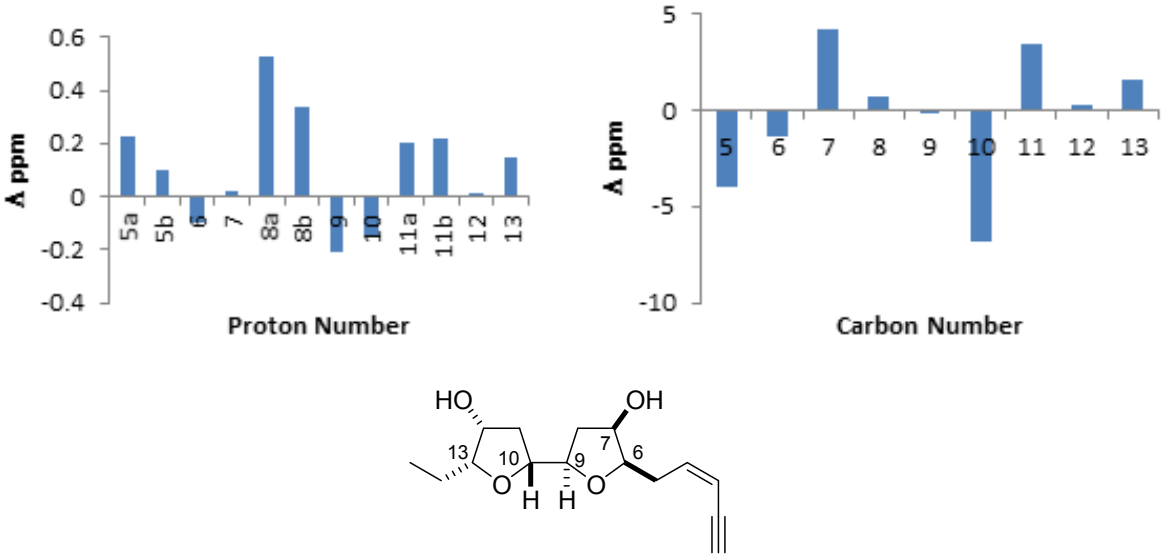
With aldol adduct **211** in hand, we then carried out a 1,3-*anti*-selective Evans-Saksena reduction that afforded the corresponding chlorodiol **216** which was then cyclized using our AgOTf/Ag_2O conditions and protected as the TBS ether to give the 2,2'-bis-tetrahydrofuran **217**. Iodine-silicon exchange gave the (*Z*)-vinyl iodide **218** along with small amounts of the undesired (*E*)-isomer. Following this, a Sonogashira coupling[128] with TMS acetylene and subsequent global deprotection gave access to 2,2'-bis-tetrahydrofuranol **36** which completed the synthesis of the candidate stereostructure **36**. As described in the Experimental section of this chapter, an identical sequence of reactions utilising the enantiomeric α-chloroaldehyde (*S*)-**200** was used to prepare the alternative candidate stereostructure **196**.

Scheme 2.30. Synthesis of candidate stereostructure (36).



2.3.4. Structural Revision

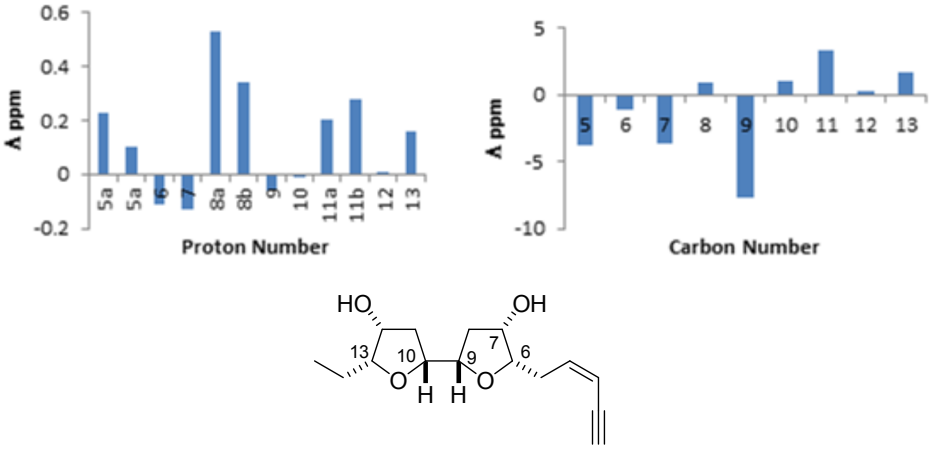
With both candidate stereostructures **36** and **196** in hand, we compared the spectral data derived from these compounds to those reported for the natural product laurefurenyne A. To our surprise, both the ^{1}H and ^{13}C spectra for **36** and **196** were clearly different to those reported for laurefurenyne A (Figure 2.14 and Figure 2.15). In particular, the spectral data showed significant differences in the C6-C9 ring while the C10-C13 ring was a much closer match to the spectral data for the natural product.



(6R, 7R, 9R):**36**

Figure 2.14. Difference plots of ^{1}H and ^{13}C NMR spectral data for candidate stereostructure (36).

Note: Bars in the graphs represent the difference in chemical shift between resonances in the candidate stereostructure **36** and those reported for the natural product.



(6*S*, 7*S*, 9*S*):**196**

Figure 2.15. Difference plots of ^{1}H and ^{13}C NMR spectral data for candidate stereostructure (196).

Note: Bars in the graphs represent the difference in chemical shift between resonances in the candidate stereostructure **196** and those reported for the natural product.

Due to these discrepancies, we re-evaluated the data recorded for the natural product. A close investigation of the original assignment revealed that the key NOE correlation between H9 and H7 that had been used to assign the stereochemistry at C7 could have been an error due to the complete overlap of H10 and H7 in the ^{1}H NMR spectrum (Figure 2.16). As a result, the NOE that was being observed might simply be an NOE correlation between the adjacent protons H9 and H10. With this in mind, we proposed two new candidate stereostructures **37** and **220** that differ from our original structures by having inverted stereochemistry at C7.

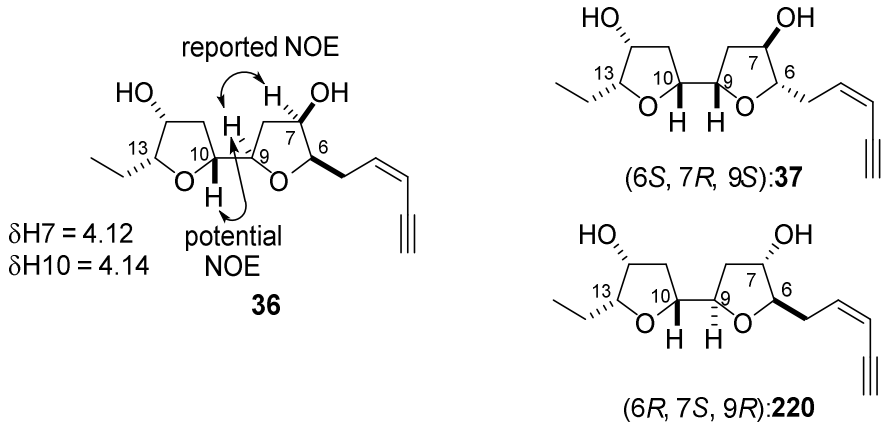
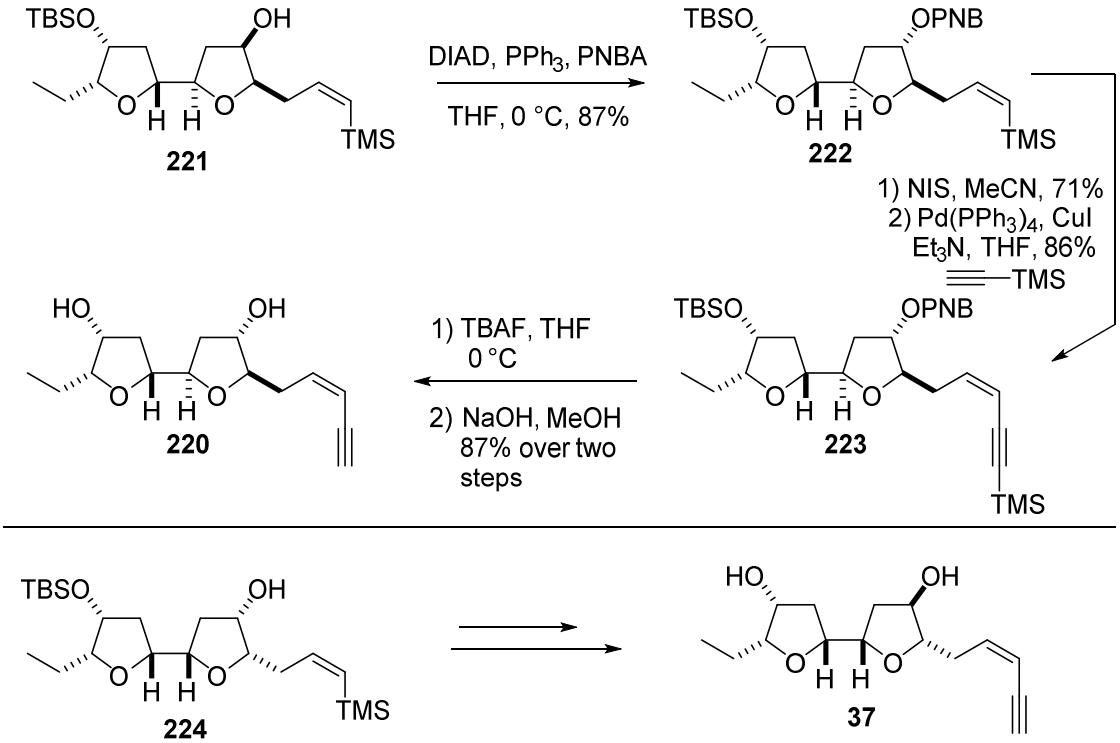


Figure 2.16. Proposed new candidate stereoisomers (37) and (220).

2.3.5. Synthesis of Laurefurenyne A

Fortunately, access to the revised candidate stereostructure **220** could be readily gained from intermediate **221** in our original synthesis of **36**. As shown in Scheme 2.31, a Mitsunobu inversion of the C7 alcohol on **221** using *p*-nitrobenzoic acid (PNBA) as the nucleophile proceeded in very high yield to afford protected tetrahydrofuran **222**. Silicon-iodine exchange followed by Sonogashira coupling[128] with TMS acetylene gave the eneyne **223** in comparable yields to those observed earlier in the synthesis of candidate stereostructure **36**. Sequential deprotections of the silyl and *p*-nitrobenzoyl groups proceeded without any issues to afford the revised stereostructure **220**. As described in the Experimental section of this chapter, an identical sequence of reactions exploiting an intermediate from the original synthesis of stereostructure **196** was used to prepare the alternative candidate stereostructure **37**.

Scheme 2.31. Synthesis of candidate stereostructures (220) and (37).



With these stereostructures in hand, we were delighted to find that the spectral data (^{1}H NMR, ^{13}C NMR, HRMS) for candidate stereostructure **37** were in complete agreement with those reported for the natural product and differed significantly from that recorded on the other candidate **220** (Figure 2.17). In addition, the specific rotation for **37** ($[\alpha]_D$ = -6.2, *c* = 0.2, CH_3OH) was consistent with that reported for laurefurenyne A ($[\alpha]_D$ = -8.0, *c* = 0.1, CH_3OH), establishing the absolute stereochemistry of the natural product to be that shown in Figure 2.17.

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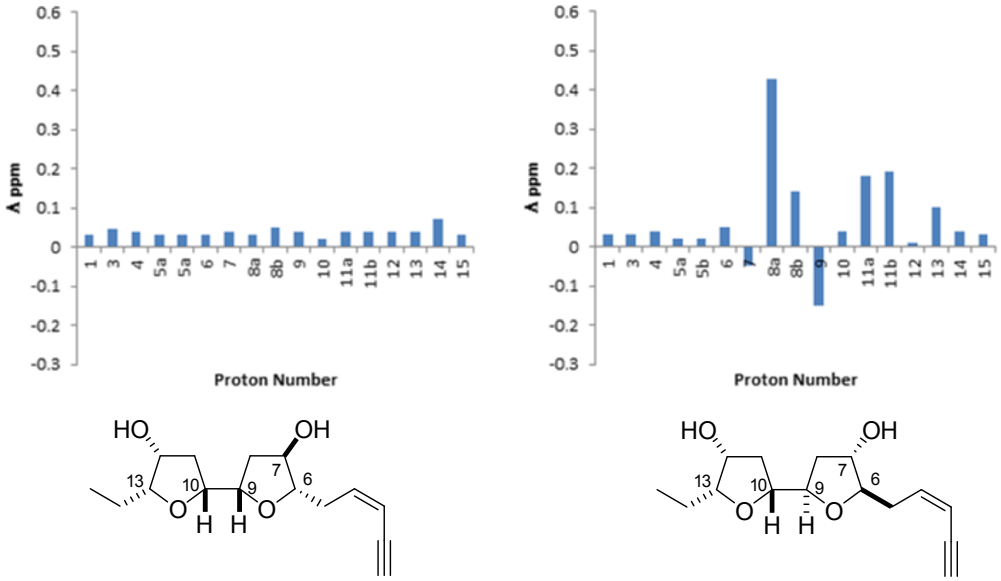


Reassigned structure for laurefurenyne A

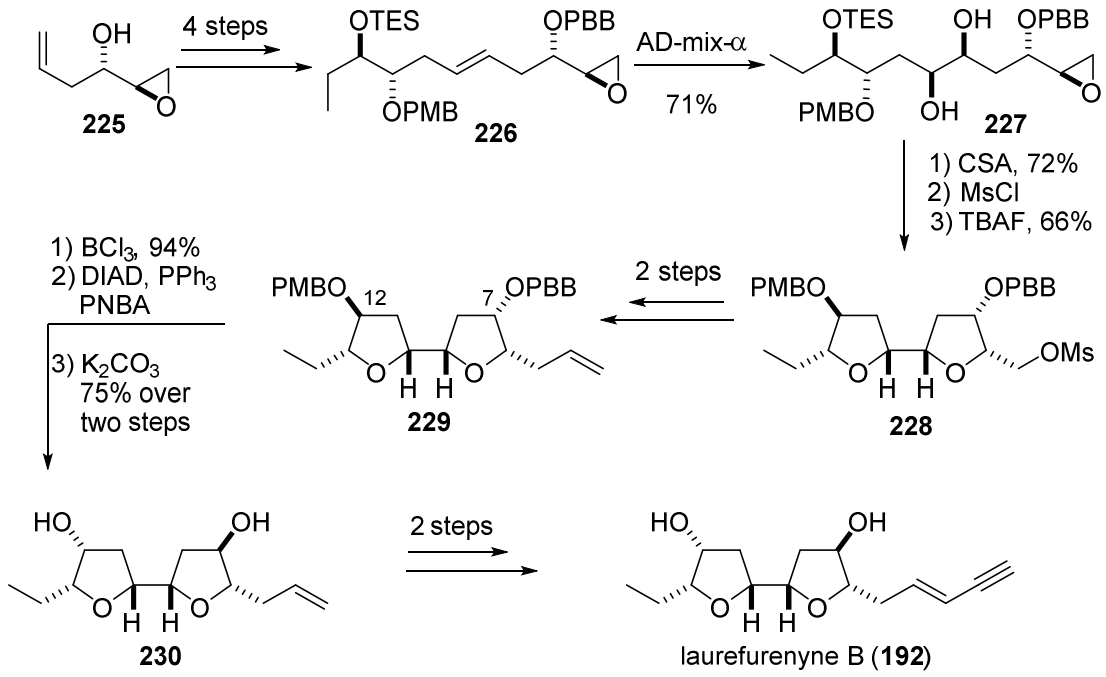
α^{D} =-6.2, *c* = 0.2, CH_3OH

Figure 2.17. Difference plots of ^{1}H NMR spectral data for candidate stereostructures (37) and (220).

2.3.6. Discussion of Burton's Synthesis of Laurefurenyne B

Concurrently with our synthesis of laurefurenyne A, Burton and co-workers were also investigating a synthesis of laurefurenyne B (**192**) following their successful reassignment of the structure of elatenyne (Figure 2.10, **191**).[124] Their synthesis of laurefurenyne B is shown in Scheme 2.32.[129] Dihydroxylation of the alkene function in **226** gave diol **227** which was converted into the bis-tetrahydrofuran **228** by acid-mediated epoxide opening followed by mesylate displacement. Installation of the alkene group followed by double epimerization of the C7 and C12 centres gave bis-tetrahydrofuran **230** with the correct stereochemistry. Conversion of the alkene into the *E*-enyne completed the synthesis of laurefurenyne B (**192**) in 17 overall steps from allyl bromide and acrolein. Gratifyingly, Burton's synthesis and subsequent analysis of spectral data was consistent with our own work and corroborated our structural reassignment.

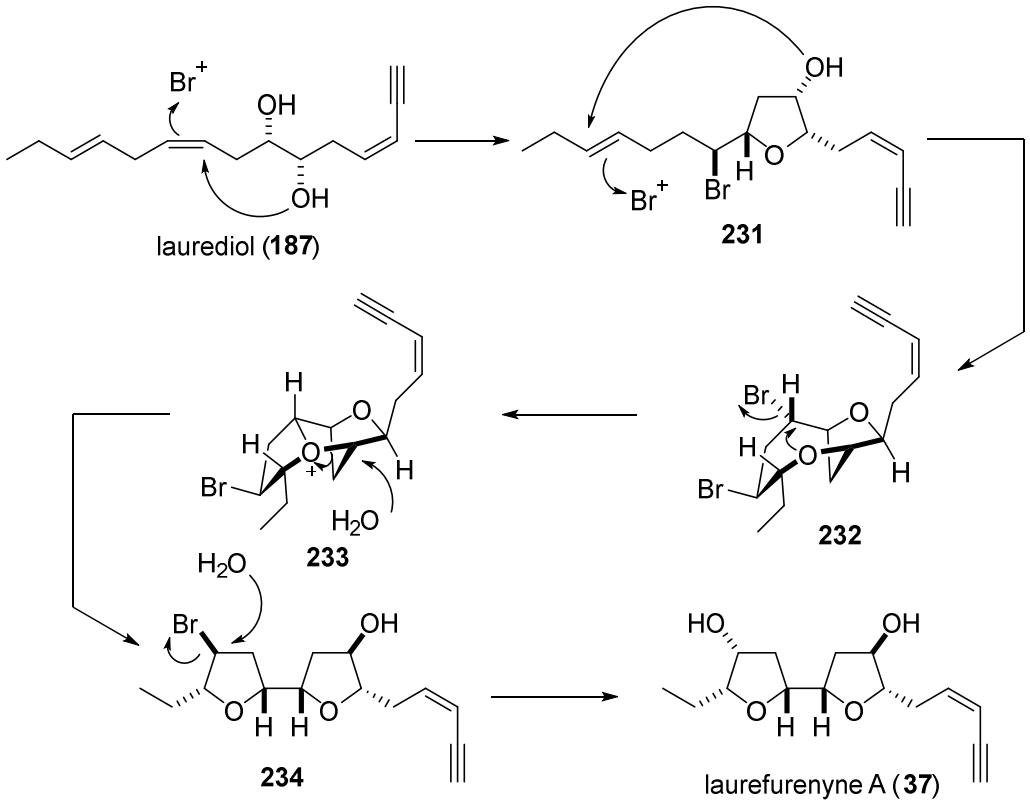
Scheme 2.32. Burton's total synthesis of laurefurenyne B (192).



2.3.7. Revised Biosynthesis

With the reassignment of the structures of laurefurenynes A and B, we proposed a new biogenetic route for the biosynthesis of laurefurenyne A (Scheme 2.33) that is analogous to the proposed biosynthesis of elatenyne (**191**).[124] Starting from laurediol (**187**), two bromonium ion catalyzed cyclization events would afford an 8,5 fused ring intermediate **232**. Intramolecular displacement of the bromide at C10 would form the intermediate oxonium **233** that could be opened by H_2O at C7 to afford the bis-tetrahydrofuranol **234**. Final S_N2 displacement of the bromide at C12 by another H_2O molecule would afford the structure of laurefurenyne A (**37**).

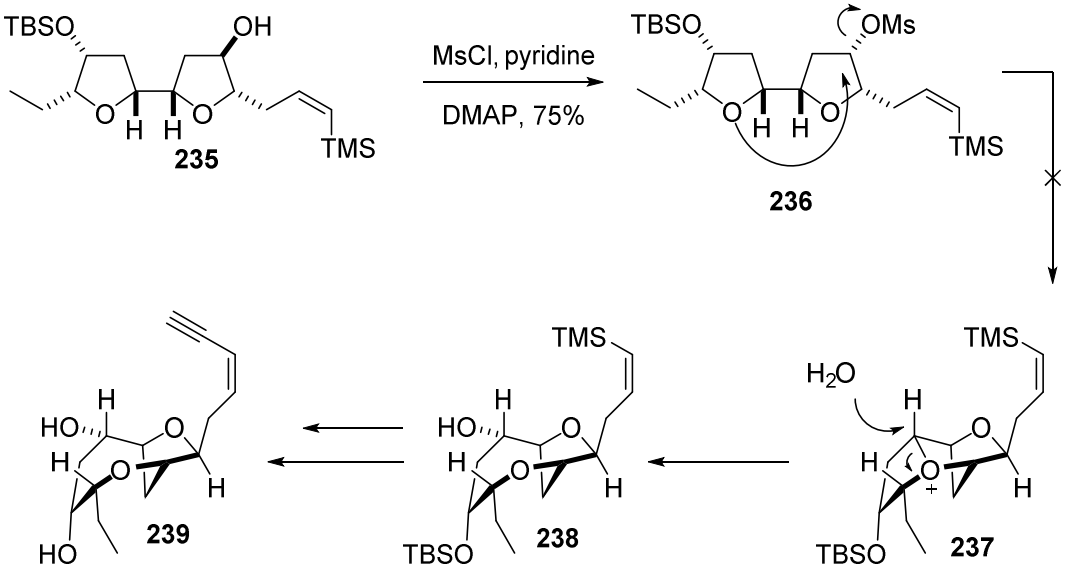
Scheme 2.33. Proposed biosynthesis of laurefurenyne A.

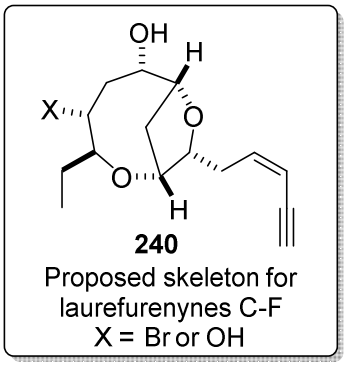


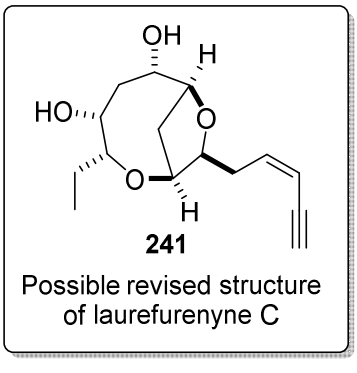
This proposed biosynthesis included an intermediate **232** that contained the same bridged 8,5-system that was found in laurefurenynes C-F (**193**-**195**). Accordingly, we hypothesized that it was possible that all of the laurefurenynes are derived from the same biosynthetic pathway via the common oxonium intermediate (**233**). If correct, stereochemical reassignment of laurefurenynes C-F would be necessary (e.g. from **240** to **241**). In order to probe this hypothesis, we considered that conversion of the bistetrahydrofuranol **235**, prepared previously in the synthesis of laurefurenyne A (**37**), to the cyclic oxonium intermediate **237** followed by addition of H_2O at C10 would afford access to the 8,5 ring system **238** (Scheme 2.34). Subsequent modifications would permit an entry to laurefurenyne C (**241**) and provide further evidence for our proposed biosynthetic pathway. In order investigate this sequence, we would need to install a good leaving group at C7 on intermediate **235**. Efforts to install a tosylate group *via* reaction with tosyl chloride proved to be unsuccessful due to the hindered nature of the alcohol but we were able to incorporate a mesylate group at this position and access the

potential oxonium precursor **236**. However, all efforts to form the oxonium intermediate by intramolecular displacement of the mesylate proved to be unsuccessful with no reaction observed at 60 °C and decomposition of the substrate was observed upon further heating of the reaction mixture. As a result, we were unable to shed further light on the biosynthesis of the laurefurenynes and investigate the structural assignment of laurefurenynes C-F.

Scheme 2.34. Attempt to access laurefurenynes C-F via oxonium intermediate (237).







2.4. Conclusion

In summary, the utility of the Britton group's methodology geared towards accessing tetrahydrofuranol rings has been demonstrated in the synthesis of two marine natural products, amphirionin-4 and laurefurenyne A. The synthesis of amphirionin-4 (**35**) was achieved through an aldol reaction between acetone and an enantiomerically enriched α-chloroaldehyde, a series of Pd-catalyzed coupling reactions to form the side chain and a novel 1,4-diastereoselective NHK coupling. This synthesis was completed in 11 steps as the longest linear sequence and represented the first total synthesis of this natural product. We also completed the first total synthesis of laurefurenyne A (**37**) in 14 linear steps. This synthesis also exploited the use of aldol reactions between methyl ketones and enantiomerically enriched α-chloroaldehydes to develop a flexible synthesis of the bistetrahydrofuran skeleton contained in the proposed structure of laurefurenyne A. Synthesis of this structure indicated that there had been an error in the original assignment and through further synthesis we were able to complete the synthesis of the correct structure of laurefurenyne A and carry out a structural reassignment.

2.5. Experimental Information

2.5.1. General Considerations

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.[130] 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.

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 ethanol/2-propanol bath.

Optical rotations were 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: CDCl3: 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) spectrometers. 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.

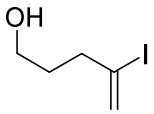
Gas chromatography (GC) analysis was performed on a Hewlett Packard model 6890 gas chromatograph, equipped with a flame ionization detector and a custom made fused chiral silica column with a 1:1 mixture of *heptakis*-(2,6-di-*O*-methyl-3-*O*-pentyl)-*β*-cyclodextrin and OV-1701.

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).

2.5.2. Amphirionin-4 Experimental

Preparation of vinyl iodide 242 (Daniel Kwon)



242

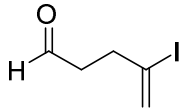
To a stirred solution of NaI (8.99 g, 60 mmol) in MeCN (24 mL) at room temperature was added TMSCl (3.05 mL, 24 mmol) followed by H_2O (0.217 mL, 12 mmol) The resulting reaction mixture was stirred for 10 minutes before 4-pentyn-1-ol (2.24 mL, 24 mmol) was added. The reaction mixture was stirred for 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 **242** (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.

Preparation of aldehyde 131 (Daniel Kwon)



131

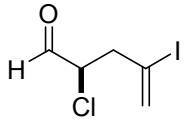
To a cold (-78 °C), stirred solution of DMSO (1.53 mL, 23.8 mmol) in CH_2Cl_2 (22 mL) was added oxalyl chloride (1.01 mL, 11.9 mmol) and the reaction mixture was stirred for 20 minutes at this temperature. Vinyl iodide **242** (1.68 g, 7.92 mmol) was then added and the reaction mixture was stirred for 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 **131** (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.

Preparation of α-chloroaldehyde 129 (Daniel Kwon)



129

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 *ent*-**82** (0.244 g, 0.86 mmol) in CH_2Cl_2 (40 mL) was added aldehyde **131** (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 (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 **129** (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)

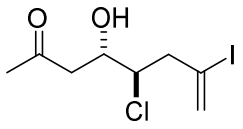
^{13}C NMR (100 MHz, $CDCl_3$) δ: 193.6, 130.6, 103.2, 61.9, 47.3

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

IR: 2923, 2851, 1733, 1617, 1418, 1264, 1118, 1057, 904, 502 cm^{-1}

α_D($CHCl_3$, *c* = 0.10): +72.1

Preparation of β-ketochlorohydrin 243 (Daniel Kwon)



243

To a cold (-78 °C), stirred solution of diisopropylamine (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 (0.194 mL, 2.65 mmol, distilled over K_2CO_3) was added and the resulting mixture was stirred for 30 minutes. α-

chloroaldehyde **129** (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 diastereoisomers. Purification of the crude product by flash chromatography (EtOAc:hexanes 25:75) afforded the β-ketochlorohydrin **243** (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* = 4.8 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)

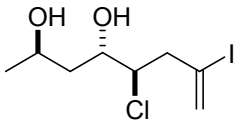
^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.1, 129.4, 105.9, 70.5, 63.0, 63.0, 49.1, 46.1

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

Preparation of diol 127 (Daniel Kwon)



127

To a cold (-40 °C), stirred solution of β-ketochlorohydrin **243** (0.103 g, 0.341 mmol) in MeCN (2mL) 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 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 diastereoisomers. Purification of the crude product by flash chromatography (EtOAc-hexanes 40:60) afforded the diol **127** (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)

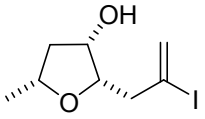
^{13}C NMR (100 MHz, $CDCl_3$) δ: 129.3, 106.5, 71.7, 65.8, 64.7, 48.7, 40.3, 24.1

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.

Preparation of tetrahydrofuranol 126 (Daniel Kwon)



126

To a vial containing MeOH (3 mL) was added diol **127** (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 then concentrated *in vacuo*. Purification of the crude product by flash

chromatography (EtOAc:hexanes 33:66) afforded tetrahydrofuranol **126** (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

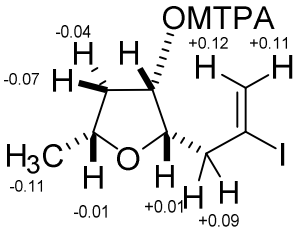
Determination of absolute stereochemistry for tetrahydrofuranol 126

To a stirred solution of tetrahydrofuranol **126** (5 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 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 10:90) afforded the (*S*)-MTPA ester.

Data for the (*S*)-MTPA ester of **126**: ^{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)

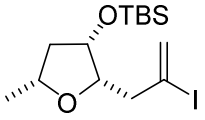
In an analogous manner, the (*R*)-MTPA ester was prepared using (*R*)-(+)-MTPA-OH.

Data for the (*R*)-MTPA ester of **126**: ^{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)



244

Preparation of the tetrahydrofuran 132 (Daniel Kwon)



132

To a cold (0 °C), stirred solution of tetrahydrofuranol **126** (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 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 **132** (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).

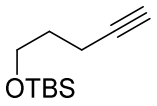
^{13}C NMR (100 MHz, $CDCl_3$) δ: 127.3, 108.5, 81.3, 73.8, 73.3, 46.0, 43.3, 25.8, 22.2, 18.1.

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}.

$\alpha_D(CHCl_3, c = 2.0)$: +0.2

Preparation of the alkyne 22



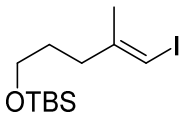
22

To a stirred solution of 4-pentyn-1-ol (2.66 g, 32.0 mmol) in CH_2Cl_2 (64 mL) at room temperature was added imidazole (4.40 g, 64.0 mmol) followed by TBSCl (5.30 g, 35.0 mmol) and stirred for an additional 2 hours then treated with H_2O (20 mL) and the phases were separated. The aqueous phase was washed with CH_2Cl_2 (3 x 15 mL) and the combined organic phases were then washed with brine (20 mL), dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane-Et_2O, 99:1) afforded alkyne **22** (5.91 g, 29.8 mmol, 94%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.70 (t, *J* = 6.0 Hz, 2H), 2.27 (dt, *J* = 2.7, 7.1 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.73 (tt, *J* = 6.0, 7.1 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H).

Reference for known compound: Rudisill, S. *J. Org. Chem.* **1989**, *54*, 5856.

Preparation of the vinyl iodide 148



148

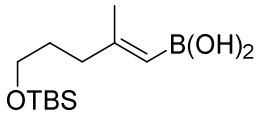
To a cold (-78°C) stirred solution of zirconocene dichloride (1.2 g, 4.1 mmol) in CH_2Cl_2 (34 mL) was added Me_3Al (34.1 mL, 2.0 M in hexanes, 68.3 mmol) followed by H_2O (0.18 mL, 10.3 mmol) and the reaction mixture was then stirred at -78°C for an

additional 30 minutes then warmed to room temperature for an additional 30 minutes. The reaction mixture was then cooled to -78°C, alkyne **147** (4.06 g, 20.5 mmol) was added and the reaction mixture was then stirred at room temperature for an additional 1.5 hours. The reaction mixture was then cooled to -78°C, and I_2 was added (10.4 g, 41 mmol, 0.7M solution in THF). The reaction mixture was stirred at -78°C for 30 minutess and then stirred at 0°C for an additional 30 minutes. The reaction was treated by the slow addition of saturated aqueous $Na_2S_2O_3$ (30 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic phases were washed with brine (50 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (2" column, pentane) afforded vinyl iodide **148** (6.74 g, 29.8 mmol, 97%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.88 (m, 1H), 3.58 (t, *J* = 6.3 Hz, 2H), 2.27 (dt, *J* = 1.0, 7.4 Hz, 2H), 1.84 (d, *J* = 1.0 Hz, 3H), 1.64 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H).

Reference for known compound: Zheng, Y. F.; Oehlschlager, A. C.; Hartman, P. G. *J. Org. Chem.* **1994**, *59*, 5803.

Preparation of the vinylboronic acid 150



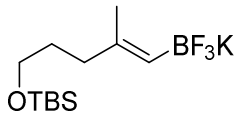
150

To a cold (-78 °C) stirred solution of vinyl iodide **148** (3.3 g, 9.7 mmol) in THF (32 mL) was added 2,2'-bipyridyl (catalytic) followed by the dropwise addition of *n*BuLi (5.5 mL, 15 mmol, 2.63M solution in hexanes) and the reaction mixture was then stirred for an additional 30 minutes. Triisopropylborate (3.6 mL, 16 mmol, freshly distilled from CaH_2) was then added and the reaction mixture stirred at 0 °C for 1 hour then treated with a 1:1 mixture of EtOAc:saturated aqueous NH_4Cl solution (20 mL) and stirred at 0 °C for an additional 30 minutes. The phases were then separated and the aqueous phase extracted with EtOAc (2 x 30 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude

product by flash chromatography (2.5" column, EtOAc:pentane, 1:4) afforded the vinyl boronic acid **150** (1.8 g, 7.0 mmol, 72%) as a colourless oil. This compound was used immediately in the next step due to rapid decomposition.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.24 (br m, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 2.20 (br t, *J* = 7.2 Hz, 2H), 2.11 (br d, *J* = 0.7 Hz, 3H), 1.70 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H).

Preparation of the vinyltrifluoroborate 151



151

To a stirred solution of boronic acid **150** (1.8 g, 6.9 mmol) in MeCN (20 mL) at room temperature was added KHF_2 (2.2 g, 28 mmol) then H_2O (7 mL) and the reaction mixture was stirred for 2 hours then the solvent was removed *in vacuo*. The solids were redissolved in acetone (20 mL), filtered, the solvent was removed *in vacuo,* and the flask placed under high vacuum for 14 hours to afforded the vinyl trifluoroborate **151** as a white solid (0.98 g, 3.1 mmol, 45%) which was used without further purification.

^{1}H NMR (400 MHz, acetone-d_6) δ: 5.08 (m, 1H), 3.61 (t, *J* = 6.6 Hz, 2H), 1.93 (t, *J* = 7.5 Hz, 2H), 1.71 (s, 3H), 1.59 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (150 MHz, acetone-d_6) δ: 140.9, 132.8 (br), 64.2, 39.3, 32.6, 26.3, 19.8, 18.8, -5.0.

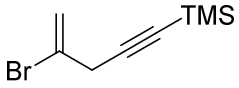
^{19}F NMR (470 MHz, acetone-d_6) δ: -135.80.

HRMS: *m/z* calcd for $C_{12}H_{25}BF_3OSi$: 281.1717 (M+H); Found: 281.1728 (M+H).

IR: 2858, 1255, 928 cm^{-1}.

mp: > 200 °C

Preparation of the enyne 144



144

To a cold (0 °C) stirred solution of TMS acetylene (0.70 mL, 5.0 mmol) in THF (13 mL) was added MeMgI (1.3 mL, 4 mmol, 3.0M solution in Et_2O). The reaction mixture was then heated to 50 °C and stirred for 15 mins then CuBr (71 mg, 0.50 mmol) was added and the reaction mixture stirred at 50 °C for an additional 15 mins. 2,3-dibromoprop-1-ene (0.50 g, 2.5 mmol) was then added and the reaction mixture was stirred for an additional 2 hours at 50 °C then cooled to 0 °C and treated with aqueous NH_4Cl (10 mL), diluted with EtOAc (20 mL) and the phases were separated. The organic phase was washed with H_2O (10 mL). The aqueous phase was washed with EtOAc (2 x 15 mL) and the combined organic phases were washed with brine (20 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane) afforded the vinyl bromide **144** (402 mg, 1.86 mmol, 74%) as a light yellow oil.

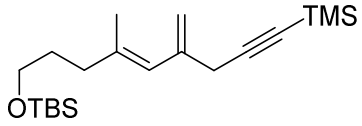
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.02 (dt, *J* = 1.8, 1.8 Hz, 1H), 5.56 (dt, *J* = 1.8, 1.8 Hz, 1H), 3.37 (dd, *J* = 1.8, 1.8 Hz, 2H), 0.18 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 126.7, 117.9, 101.1, 88.9, 32.8, -0.1.

HRMS: *m/z* calcd for $C_8H_{13}BrSi$: 217.0043 (M+H); Found: 217.0047 (M+H).

IR: 2960, 2899, 2181, 1638 cm^{-1}

Preparation of the diene 152



152

To a vial charged with vinyl bromide **144** (340 mg, 1.56 mmol), vinyl trifluoroborate **151** (500 mg, 1.56 mmol), $CsCO_3$ (1.58 g, 4.68 mmol) and $Pd(PPh_3)_4$ (90 mg, 0.08 mmol) was added THF (4 mL) and H_2O (0.4 mL) and the vial was then heated to 55 °C for 4 hrs. The reaction mixture was then diluted with H_2O (4 mL) and EtOAc (6 mL) and the phases were separated. The organic phase was washed with H_2O (4 mL). The combined aqueous phases were then washed with EtOAc (2 x 4 mL) and the combined organic phases were washed with brine (6 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:pentane 2:98) afforded the diene **152** (371 mg, 1.06 mmol, 68%) as a yellow oil.

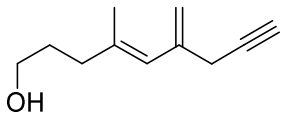
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.61 (br s, 1H), 5.34 (br s, 1H), 4.92 (br s, 1H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.00 (br s, 2H), 2.10 (dd, *J* = 6.6, 8.1 Hz, 2H), 1.79 (s, 3H), 1.66 (m, 2H), 0.90 (s, 9H), 0.17 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.4, 139.3, 124.5, 114.0, 104.0, 87.4, 62.7, 36.6, 31.1, 28.2, 26.0, 18.4, 18.0, 0.09, -5.3.

HRMS: *m/z* calcd for $C_{20}H_{39}OSi_2$: 351.2534 (M+H); Found: 351.2527 (M+H).

IR: 2955, 2178, 1250 cm^{-1}.

Preparation of the alcohol 158



158

To a cold (0 °C), stirred solution of diene **152** (206 mg, 0.59 mmol) in THF (5 mL) was added TBAF (2.06 mL, 2.06 mmol, 1M in THF) and the reaction mixture was stirred at 0 °C for an additional 2 hrs then treated with H_2O (3 mL), diluted with EtOAc (5 mL) and the phases were separated. The organic phase was washed with H_2O (3 mL). The combined aqueous phases were then washed with EtOAc (2 x 3 mL) and the combined organic phases were washed with brine (4 mL), then dried ($MgSO_4$) and

filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:pentane 30:70) afforded the alcohol **158** (87 mg, 0.53 mmol, 90%) as a colourless oil.

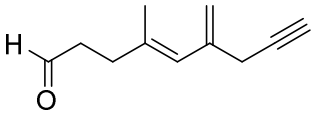
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.57 (br s, 1H), 5.34 (m, 1H), 4.94 (br s, 1H), 3.66 (t, *J* = 6.5 Hz, 2H), 2.97 (br s, 2H), 2.16 (t, *J* = 7.5 Hz, 2H), 2.14 (t, *J* = 2.5 Hz, 1H), 1.81 (d, *J* = 1.0 Hz, 3H), 1.73 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.0, 139.4, 124.6, 114.4, 81.5, 70.7, 62.6, 36.7, 30.7, 26.9, 17.9.

HRMS: *m/z* calcd for $C_{11}H_{17}O$: 165.1274 (M+H); Found: 165.1272 (M+H).

IR: 3295, 2935, 1643, 1418, 1059, 900 cm^{-1}.

Preparation of the aldehyde 245



245

To a cold (0 °C), stirred solution of alcohol **158** (55 mg, 0.33 mmol) in CH_2Cl_2 (3 mL) was added $NaHCO_3$ (55 mg, 66 mmol) followed by Dess-Martin periodinane (184 mg, 0.44 mmol). The solution was stirred at 0 °C for an additional 16 hrs then saturated aqueous $NaHCO_3$ solution (2 mL) was added and the phases were separated. The organic phase was washed with H_2O (2 mL). The combined aqueous phases were then washed with CH_2Cl_2 (2 x 3 mL) and the combined organic phases were washed with brine (3 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:pentane 20:80) afforded the aldehyde **245** (35 mg, 0.21 mmol, 65%) as a colourless oil.

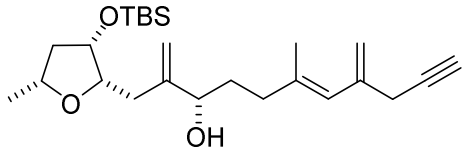
^{1}H NMR (400 MHz, $CDCl_3$ δ: 9.79 (t, *J* = 1.8 Hz, 1H), 5.66 (br s, 1H), 5.36 (dt, *J* = 1.6, 1.6 Hz, 1H), 4.94 (br s, 1H), 2.96 (m, 2H), 2.58 (m, 2H), 2.41 (m, 2H), 2.13 (t, *J* = 3.0 Hz, 1H), 1.81 (d, *J* = 1.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.0, 139.7, 137.5, 125.2, 114.8, 81.3, 70.8, 42.1, 32.5, 26.8, 18.1.

HRMS: *m/z* calcd for $C_{11}H_{15}O$: 163.1117 (M+H); Found: 163.1125 (M+H).

IR: 3293, 2930, 1722, 1419, 1202 cm^{-1}

Preparation of the tetrahydrofuran 246



246

To a cold (0 °C), stirred solution of tetrahydrofuran **132** (86 mg, 0.23 mmol) and aldehyde **245** (39 mg, 0.24 mmol) in DMF (0.4 mL) was added $CrCl_2$ (124 mg, 1.01 mmol) and $NiCl_2$ (1.3 mg, 0.01 mmol) and the reaction mixture was stirred at 0 °C for an additional 16 hours then 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 diastereoisomers. Purification of the crude product by flash chromatography (EtOAc:pentane 20:80) afforded the tetrahydrofuran **246** (60 mg, 0.14 mmol, 61%) as a light yellow oil and single diastereoisomer.

^1H NMR (400 MHz, $CDCl_3$) δ: 5.64 (br s, 1H), 5.34 (dt, *J* = 1.6, 1.6 Hz, 1H), 5.06, (d, *J* = 1.2 Hz), 4.94 (br s, 1H), 4.93 (dd, *J* = 1.3, 1.3 Hz, 1H), 4.27 (ddd, *J* = 3.3, 4.3, 7.5 Hz, 1H), 4.07-3.97 (m, 3H), 3.74 (ddd, *J* = 2.8, 4.4, 10.5 Hz, 1H), 2.96 (m, 2H), 2.52 (dd, *J* = 9.4, 14.1 Hz, 1H), 2.29 (ddd, *J* = 6.1, 7.5, 13.3 Hz, 1H), 2.18 (dd, *J* = 2.8, 14.6 Hz, 1H), 2.13 (t, *J* = 2.5 Hz, 1H), 2.12 (m, 1H), 2.03 (ddd, *J* = 6.4, 9.5, 13.2 Hz, 1H), 1.80 (d, *J* = 1.4 Hz, 3H), 1.76 (m, 1H), 1.65 (m, 1H), 1.55 (ddd, *J* = 3.2, 6.3, 12.9 Hz, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.4, 140.2, 139.7, 124.3, 114.2, 114.1, 84.3, 81.6, 75.3, 74.1, 73.7, 70.7, 43.1, 36.6, 34.6, 31.9, 26.9, 25.8, 22.0, 18.1, -4.6, -5.0.

HRMS: *m/z* calcd for $C_{25}H_{43}SiO_3$: 419.2976 (M+H); Found: 419.2998 (M+H).

IR: 3429, 3309, 2930, 2857, 1472, 1254cm^{-1}

α_D($CHCl_3$, *c* = 1.0): -14.4

Assignment of the absolute stereochemistry of the allylic alcohol in tetrahydrofuran 246

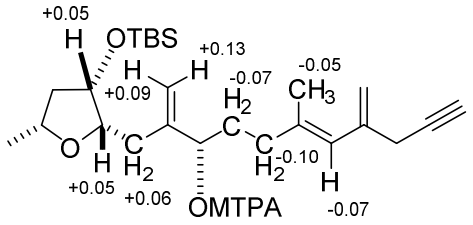
To a stirred solution of tetrahydrofuran **246** (2 mg, 0.005 mmol) in CH_2Cl_2 (0.2 mL) at room temperature was added (*S*)-(-)-MTPA-OH (1.7 mg, 0.007 mmol), *N*,*N*'-diisopropylcarbodiimide (0.0025 mL, 0.015 mmol) and dimethylaminopyridine (catalytic). The reaction mixture was stirred for 16 hrs then the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:pentane 15:85) afforded the (*S*)-MTPA ester.

Data for the (*S*)-MTPA ester of **246**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (m, 2H), 7.39 (m, 3H), 5.51 (br s, 1H), 5.43 (dd, *J* = 6.5, 6.5 Hz, 1H), 5.35 (m, 2H), 5.18 (br s, 1H), 5.13 (br s, 1H), 4.91 (m, 1H), 4.23 (m, 1H), 3.94 (m, 1H), 3.81 (ddd, *J* = 4.2, 6.3, 6.3 Hz, 1H), 3.55 (d, *J* = 1.2 Hz, 3H), 2.94 (m, 2H), 2.36 (m, 2H), 2.28 (m, 1H), 2.13 (t, *J* = 2.6 Hz, 1H), 1.94 (m, 2H), 1.82 (m, 2H), 1.71 (d, *J* = 1.37, 3H), 1.48 (ddd, *J* = 2.9, 6.7, 13.0 Hz, 1H), 1.29 (d, *J* = 6.0 Hz, 3H).

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

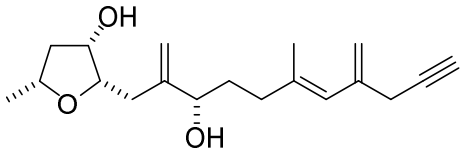
Data for the (*R*)-MTPA ester of **246**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (m, 2H), 7.39 (m, 3H), 5.58 (br s, 1H), 5.38 (dd, *J* = 6.4, 6.4 Hz, 1H), 5.35 (m, 2 H), 5.05 (br s, 1H), 5.04 (br s, 1H), 4.93 (br s, 1H), 4.18 (m, 1H), 3.91 (m, 1H), 3.76 (ddd, *J* = 4.3, 6.8, 6.8 Hz, 1H), 3.55 (d, *J* = 1.3 Hz, 3H), 2.95 (m, 2H), 2.32 (m, 2H), 2.25 (m, 1H), 2.14 (t, *J*

= 3.2 Hz, 1H), 2.07 (m, 2H), 1.89 (m, 2H), 1.77 (d, *J* = 0.9 Hz, 3H), 1.46 (ddd, *J* = 2.8, 6.7, 13.0 Hz, 1H), 1.27 (d, *J* = 6.2 Hz, 3H).



$\delta_S - \delta_R$ **247**

Preparation of the tetrahydrofuranol 162



162

To a cold (0 °C), stirred solution of tetrahydrofuran **246** (18 mg, 0.043 mmol) in THF (1 mL) was added TBAF (0.065 mL, 0.065 mmol, 1M in THF) and the reaction mixture was stirred at 0 °C for an additional 1 hr then treated with H_2O (1 mL), diluted with EtOAc (2 mL) and the phases were separated. The organic phase was then washed with H_2O (1 mL). The aqueous phase was washed with EtOAc (3 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*. Purification of the crude product by flash chromatography (pentane:EtOAc 50:50) afforded the tetrahydrofuran **162** (12 mg, 0.039 mmol, 92%) as a colourless oil.

^{1}H NMR (400 MHz, C_6D_6) δ: 5.71 (br s, 1H), 5.45 (dt, *J* = 1.8, 1.8 Hz, 1H), 5.07 (br s, 1H), (ddt, *J* = 1.8, 1.8, 1.8 Hz, 1H), 4.93 (ddd, *J* = 1.3, 1.3, 1.3 Hz, 1H), 4.16 (dd, *J* = 5.5, 8.1 Hz, 1H), 3.81 (ddd, *J* = 2.6, 4.0, 6.3 Hz, 1H), 3.59 (m, 1H), 3.49 (ddd, *J* = 4.2, 8.8 Hz, 1H), 2.81 (m, 2H), 2.66 (dd, 8.8, 14.5 Hz, 1H), 2.29-2.21 (m, 2H), 2.13 (dddd, *J* = 1.0, 6.1, 10.0, 15.9, 1H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.87 (m, 2H), 1.73 (m, 1H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.22 (ddd, *J* = 2.3, 7.0, 13.2 Hz, 1H), 1.15 (d, *J* = 6.0 Hz, 3H).

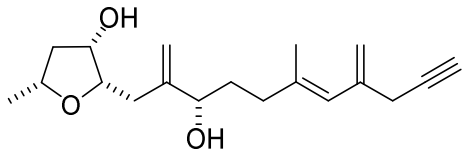
^{13}C NMR (100 MHz, C_6D_6) δ: 150.0, 140.7, 139.7, 125.1, 114.4, 112.9, 84.2, 81.6, 75.3, 73.9, 73.3, 71.4, 43.3, 37.1, 34.9, 31.5, 27.1, 21.9, 18.2.

HRMS: *m/z* calcd for $C_{19}H_{29}O_3$: 305.2111 (M+H); Found: 305.2109 (M+H).

IR: 3400, 3306, 2928, 1645, 1442, 1264, 1067 cm^{-1}

α_D($CHCl_3$, *c* = 1.0): +20.8

Preparation of the vinyl iodide 163



162

To a cold (-78 °C), stirred solution of tetrahydrofuranol **162** (10 mg, 0.033 mmol) and zirconocene dichloride (1.9 mg, 0.0066 mmol) in CH_2Cl_2 (0.2 mL) was added Me_3Al (0.1 mL, 0.198 mmol, 2M in hexanes) followed by H_2O (0.6 μL, 0.034 mmol). The reaction mixture was stirred at -78 °C for 30 mins then warmed to room temperature and stirred for an additional 3 hrs. The reaction mixture was then cooled to -78 °C and iodine (17 mg, 0.066 mmol) in THF (0.2 mL) was added. The reaction mixture was then stirred at -78 °C for 30 mins then warmed to 0 °C for an additional 30 mins then treated by the slow addition of saturated aqueous $Na_2S_2O_3$ solution (0.5 mL), diluted with CH_2Cl_2 (1 mL) and the phases were separated. The organic phase was then washed with H_2O (1 mL). The aqueous phase was washed with EtOAc (6 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*. Purification of the crude product by flash chromatography (pentane:EtOAc 50:50) afforded the vinyl iodide **163** (13.8 mg, 0.031 mmol, 94%) as a light yellow oil.

^1H NMR (600 MHz, C_6D_6) δ: 5.77 (m, 1H), 5.61 (br s, 1H), 5.08 (br s, 1H), 4.93 (br s, 1H), 4.89 (br s, 1H), 4.88 (br s, 1H), 4.13 (dd, *J* = 6.3, 8.0 Hz, 1H), 3.75 (m, 1H), 3.57 (m, 1H), 3.48 (ddd, *J* = 4.3, 9.0, 9.0 Hz, 1H), 2.66 (m, 2H), 2.64 (dd, *J* = 9.2, 15.0

Hz, 1H), 2.23 (m, 2H), 2.13 (ddd, *J* = 6.2, 9.9, 14.2 Hz, 1H), 1.84 (m, 2H), 1.72 (m, 1H), 1.70 (m, 6H), 1.18 (ddd, *J* = 2.2, 7.0, 13.5 Hz, 1H), 1.13 (d, *J* = 6.2 Hz, 3H).

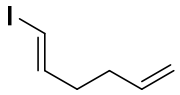
^{13}C NMR (150 MHz, C_6D_6) δ: 150.2, 145.9, 142.8, 139.5, 125.4, 115.2, 112.9, 84.2, 76.9, 75.2, 73.9, 73.4, 47.8, 43.3, 37.1, 35.2, 31.6, 23.6, 22.0, 18.0.

HRMS: *m/z* calcd for $C_{20}H_{32}IO_3$: 447.1391 (M+H); Found: 447.1374 (M+H).

IR: 3388, 2925, 2854, 1646, 1442, 1377 cm^{-1}.

α_D($CHCl_3$, *c* = 1.0): -7.4.

Preparation of the vinyl iodide 154



154

To a cold (0 °C), stirred solution of chromium (II) chloride (8.9 g, 72.8 mmol) in THF (24 mL) was added iodoform (5.2 g, 13.3 mmol). The solution was stirred at 0 °C for an additional 5 mins then 4-pentenal (1.02 g, 12.1 mmol) was added and the solution was stirred at 0 °C for an additional 2 hours then treated with H_2O (20 mL), diluted with Et_2O (40 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 20 mL), brine (20 mL), then dried ($MgSO_4$) and filtered, and the majority of the solvent was carefully removed *in vacuo*. Purification of the crude product by flash chromatography (pentane) afforded the vinyl iodide **154** (1.54 g, 7.40 mmol, 61%) as a yellow oil and a mixture of *E*/*Z* isomers (5:1).

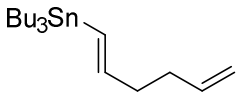
^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.52 (m, 1H), 6.02 (d, *J* = 14.0 Hz, 1H), 5.78 (m, 1H), 5.03 (ddt, *J* = 1.5, 1.5, 17.1 Hz, 1H), 5.00 (ddt, 1.5, 1.5, 10.2 Hz, 1H), 2.15 (m, 4H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 145.7, 137.2, 115.5, 75.0, 35.4, 32.4.

HRMS: *m/z* calcd for C_6H_9I: 207.9749 (M); Found: 207.9771(M). (EI)

IR: 3076, 2923, 1640, 1436 cm^{-1}.

Preparation of the vinyl stannane 156



156

To a cold (-78 °C), stirred solution of vinyl iodide **154** (400 mg, 1.92 mmol) in THF (19 mL) was added *t*BuLi (2.5 mL, 4.23 mmol, 1.7M in pentane) and the reaction mixture was stirred for an additional 20 mins at -78 °C. Bu_3SnCl (0.57 mL, 2.11 mmol) was then added and the reaction mixture warmed to room temperature and stirred for 30 mins. The reaction mixture was then cooled to -78 °C and treated with H_2O (10 mL) followed by 1N NaOH solution (20 mL). The reaction mixture was then stirred for 1 hr at room temperature then diluted with Et_2O (40 mL) and the phases were separated. The organic phase was washed with H_2O (3 x 20 mL), brine (20 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (pentane) afforded the vinyl stannane **156** (452 mg, 1.21 mmol, 63%) as a colourless oil.

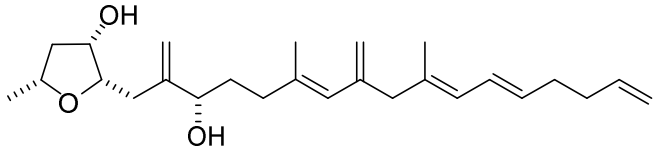
^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.93 (t, *J* = 4.9 Hz, 1H), 5.91 (s, 1H), 5.82 (m, 1H), 5.01 (ddt, *J* = 1.6, 2.0, 17.5 Hz, 1H), 4.95 (ddt, *J* = 1.2, 2.0, 10.1 Hz, 1H), 2.26-2.12 (m, 4H), 1.48 (m, 8H), 1.31 (m, 8H), 0.95-0.82 (m, 20H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 148.6, 138.4, 127.7, 114.5, 37.1, 33.2, 29.1, 27.3, 13.7, 9.4.

HRMS: Did not pass MS using EI or ESI techniques

IR: 2957, 2924, 1641, 1599 cm^{-1}.

Preparation of amphirionin-4 (35)



1

To a vial charged with vinyl iodide **163** (2.8 mg, 0.006 mmol) was added vinyl stannane **156** (2.2 mg, 0.006 mmol) followed by $[Ph_2PO_2][NBu_4]$ (4.1 mg, 0.009 mmol) in degassed, dry DMF (0.1 mL). Copper (I) thiophene-2-carboxylate (1.5 mg, 0.008 mmol) was then added followed by a solution of $Pd(PPh_3)_4$ (0.3 mg, 0.0003 mmol) in DMF (0.1 mL). The reaction mixture was stirred at room temperature for an additional 1 hr then diluted with H_2O (0.5 mL) and EtOAc (0.5 mL) and the phases were separated. The organic phase was then washed with H_2O (2 x 0.5 mL). The aqueous phase was washed with EtOAc (3 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*. Purification of the crude product by flash chromatography (pentane:EtOAc 50:50) afforded amphirionin-4 (**35**) (1.7 mg, 0.0042 mmol, 71%) as a colourless oil.

^{1}H NMR (600 MHz, C_6D_6) δ: 6.34 (ddt, *J* = 1.3, 12.1, 15.1 Hz, 1H), 5.98 (br d, *J* = 10.7 Hz, 1H), 5.81 (br s, 1H), 5.77 (ddd, *J* = 6.2, 10.4, 16.5 Hz, 1H), 5.57 (br dt, *J* = 6.2, 15.2 Hz, 1H), 5.08 (br s, 1H), 5.05 (br s, 1H), 5.02 (ddt, *J* = 1.8, 1.8, 16.1 Hz, 1H), 5.00 (br s, 1H), 4.98 (ddt, *J* = 1.5, 2.0, 9.3 Hz, 1H), 4.92 (br s, 1H), 4.12 (dd, *J* = 4.8, 7.8 Hz, 1H), 3.75 (br s, 1H), 3.57 (ddq, *J* = 1.6, 5.8, 6.8 Hz, 1H), 3.47 (ddd, *J* = 3.8, 4.5, 8.6 Hz, 1H), 3.09 (br s, 1H), 2.82 (br s, 2H), 2.62 (ddd, *J* = 0.8, 8.8, 14.9 Hz, 1H), 2.25 (ddd, *J* = 6.8, 6.8, 8.5 Hz, 1H), 2.21 (dd, *J* = 4.9, 15.2 Hz, 1H), 2.15 (ddd, *J* = 6.8, 9.9, 19.8 Hz, 1H), 2.10 (t, *J* = 5.7 Hz, 2H), 2.06 (br t, *J* = 5.7 Hz, 2H), 1.84 (m, 2H), 1.80 (d, *J* = 1.0 Hz, 3H), 1.73 (m, 1H), 1.69 (br s, 3H), 1.18 (ddd, *J* = 2.5, 6.6, 13.4, 1H), 1.12 (d, *J* = 6.2 Hz, 3H).

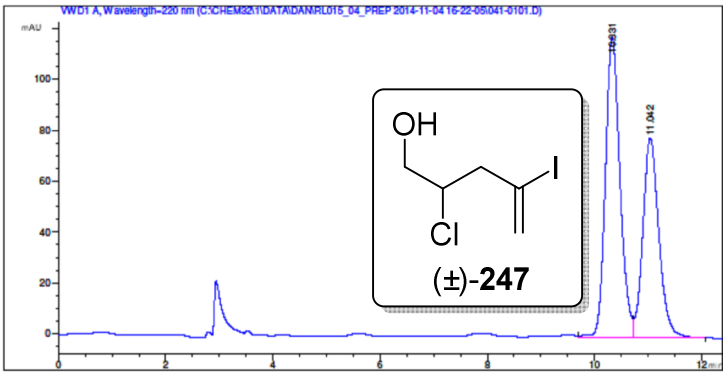
^{13}C NMR (150 MHz, C_6D_6) δ: 150.2, 144.3, 138.7, 138.5, 134.2, 132.15, 132.11, 127.7, 127.4, 126.3, 114.9, 114.8, 112.8, 84.1, 75.2, 73.8, 73.4, 48.8, 43.2, 37.2, 35.0, 34.2, 32.8, 31.6, 22.0, 18.1, 16.4.

HRMS: *m/z* calcd for $C_{26}H_{40}O_3$: 401.3050 (M+H); Found: 401.3049 (M+H).

IR: 3394, 2926, 1641, 1441 cm^{-1}.

$\alpha_D(CHCl_3, c = 0.34)$: -5.8.

Figure 2.18. Chiral HPLC traces to establish enantiomeric excess of α-chloroaldehyde 129

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

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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
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----|-------|----|-------|----------|----------|--------|
   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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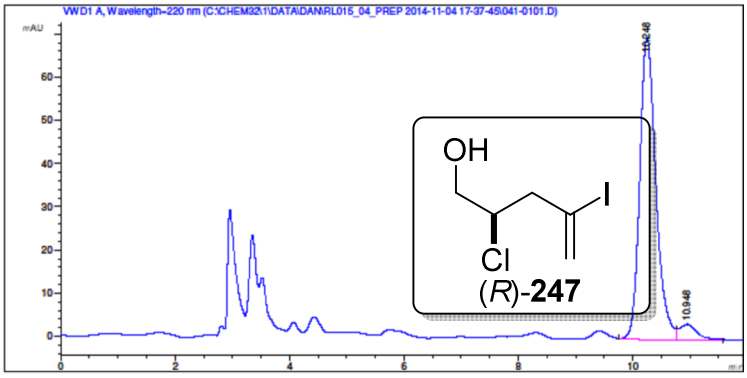


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================================================================================
                            Area Percent Report
================================================================================

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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   ]      %
----|-------|----|-------|----------|----------|--------|
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   2  10.948 VB    0.3100   73.78009    3.54235   5.1297

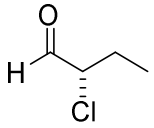
Totals :                  1438.30292   73.43463
```

Table 2.3. Comparison of ^{1}H and ^{13}C NMR data between synthetic and natural amphirionin-4

Position	^{13}C(natural product)	^{13}C (synthetic)	Difference	^{1}H (natural product)	^{1}H (synthetic)	Difference
1	21.7	22.0	-0.03	1.17	1.12	0.05
2	73.7	73.8	-0.01	3.61	3.57	0.04
3	43.0	43.2	-0.02	1.88	1.84	0.04
				1.24	1.18	0.06
4	73.1	73.4	-0.03	3.80	3.75	0.05
5	83.9	84.1	-0.02	3.51	3.47	0.04
6	31.2	31.6	-0.04	2.67	2.62	0.05
				2.26	2.21	0.05
7	149.6	150.2	-0.06			
8	75.2	75.2	0	4.16	4.12	0.04
9	34.6	35.0	-0.04	1.89	1.84	0.05
				1.77	1.73	0.04
10	36.9	37.2	-0.03	2.29	2.25	0.04
				2.20	2.15	0.05
11	138.3	138.5	-0.02			
12	126.1	126.3	-0.02	5.85	5.81	0.04
13	144.0	144.3	-0.03			
14	48.5	48.8	-0.03	2.87	2.82	0.05
15	133.9	134.2	-0.03			
16	127.1	127.4	-0.03	6.03	5.98	0.05
17	127.5	127.7	-0.02	6.38	6.34	0.04
18	131.9	132.1	-0.02	5.62	5.57	0.05
19	32.5	32.8	-0.03	2.14	2.10	0.04
20	33.9	34.2	-0.03	2.10	2.06	0.04
21	138.3	138.7	-0.04	5.81	5.77	0.04
22	114.6	114.9	-0.03	5.06	5.02	0.04
				5.02	4.98	0.04
23	112.6	112.8	-0.02	5.10	5.05	0.05
				4.95	4.92	0.03
24	17.9	18.1	-0.02	1.85	1.80	0.05
25	114.5	114.8	-0.03	5.13	5.08	0.05
				5.04	5.00	0.04
26	16.2	16.4	-0.02	1.74	1.69	0.05

2.5.3. Laurefurenyne A Experimental

Preparation of (2*S*)-2-chlorobutanal (203)

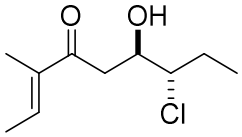


203

To a cold (0 °C), stirred solution of (2*R*,5*S*)-2-*tert*-butyl- 3,5,dimethylimidazolidin-4-one trifluoroacetate (3.2 g, 11 mmol), lithium chloride (**82**, 3.5 g, 83 mmol), copper (II) trifluoroacetate hydrate (8.6 g, 28 mmol) and sodium persulfate (13 g, 56 mmol) in MeCN (100 mL) was added H_2O (2.2 mL, 122 mmol). The resulting solution was stirred at 0 °C for 10 min. After this time, butyraldehyde **204** (5.0 mL, 56 mmol) was added dropwise and the resulting mixture was stirred for an additional 20 h. The reaction mixture was then treated with H_2O (75 mL) diluted with Et_2O-CH_2Cl_2 (3:1, 150 mL) and the phases were separated. The aqueous phase was washed with Et_2O (2 x 150 mL) and the combined organic phases were washed with H_2O (100 mL) and brine (6 x 100 mL), after which the majority of the MeCN was removed (determined by ^{1}H NMR spectroscopy). The remaining solution was then cooled to 0 °C and concentrated by rotary evaporator (ice bath) to approximately 50 mL to afford the chloroaldehyde **203** as a solution in Et_2O-CH_2Cl_2 which was used directly in the next step without further purification. The optical purity of the chloroaldehyde **203** was determined to be 95% ee following its conversion to the tetrahydrofuranol **207** (see below).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.50 (d, *J* = 2.4 Hz, 1H), 4.11 (ddd, *J* = 2.4, 5.6, 8.0 Hz, 1H), 2.10 – 1.83 (m, 2H), 1.08 (t, *J* = 7.5 Hz, 3H).

Preparation of ketochlorohydrin 205



205

To a cold (-78 °C), stirred solution of diisopropylamine (5.70 mL, 41 mmol) in THF (200 mL) at -78 °C was added a solution of *n*-butyllithium (14.6 mL, 39 mmol, 2.66 M in hexanes) dropwise. The solution was warmed to 0 °C for 30 min then cooled to -78 °C. 3-Methyl-3-penten-2-one (**202**, 4.5 mL, 37 mmol) was then added dropwise as a solution in THF (10 mL) and the reaction mixture was stirred for 30 min. Chloroaldehyde **203** was then added as a solution in Et_2O-CH_2Cl_2 (see above) and the reaction mixture was stirred for an additional 60 min. The reaction mixture was then quenched by addition of saturated aqueous NH_4Cl solution (30 mL) and warmed to rt. The mixture was then diluted with EtOAc (150 mL) and H_2O (150 mL) and the phases were separated. The organic phase was washed with H_2O (150 mL). The aqueous phase was washed with EtOAc (2 x 150 mL) and the combined organic phases were washed with brine (150 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product (6:1, dr) by flash chromatography (hexanes-EtOAc, 5:1) afforded the ketochlorohydrin **205** (5.3 g, 26 mmol, 70%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.83 (qq, *J* = 1.3, 7.0 Hz, 1H), 4.12 (m, 1H), 3.87 (m, 1H), 3.61 (d, 1H), 3.12 (dd, *J* = 2.5, 17.1 Hz, 1H), 2.95 (dd, *J* = 8.6, 17.4 Hz, 1H), 2.01 (m, 1H), 1.89 (dq, *J* = 0.9, 7.0 Hz, 3H) 1.79 (m, 3H), 1.72 (m, 1H), 1.07 (t, *J* = 7.4 Hz, 3H).

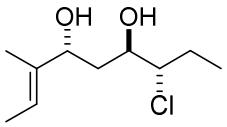
^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.2, 139.8, 138.8, 71.5, 67.9, 67.9, 39.8, 27.5, 15.3, 11.1.

HRMS: *m/z* calcd for $C_{10}H_{17}ClO_2$: 227.0809 (M+Na); Found: 227.0796 (M+Na).

IR (neat): 3477, 2972, 2935, 1658, 1380, 1233, 1074, 909, 733 cm^{-1}.

$[\alpha]_D^{20}$ = +32 (*c* 1.0 in $CHCl_3$).

Preparation of the diol 206



206

To a stirred solution of the ketochlorohydrin **205** (5.3 g, 26 mmol) in MeOH (250 mL) at rt was added cerium(III)trichloride heptahydrate (9.5 g, 26 mmol).After 5 min, the reaction mixture was cooled to -78 °C and sodium borohydride (1.02 g, 27 mmol) was added in a single portion. The reaction mixture was stirred for 20 min at -78 °C then allowed to warm to rt over the course of 20 min. The resulting mixture was quenched by the addition of saturated aqueous NH_4Cl solution (20 mL) and diluted with EtOAc (200 mL). The organic layer was separated and the solvent removed *in vacuo*. The resulting oil was dissolved in EtOAc (150 mL) and washed with H_2O (1 x 100 mL). The combined aqueous layers were washed with EtOAc (2 x 100 mL) and the combined organic phases were then washed with brine (100 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 3:1) afforded the diol **206** (4.6 g, 22 mol, 86%, ratio of 1,3-*anti:syn* isomers 4:1) as a white solid (mp = 60-63 °C).

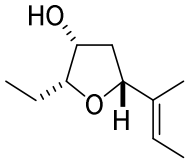
Data for **206** (only data for the major (1,3-*anti*) isomer is listed): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.57 (m, 1H), 4.38 (dd, *J* = 5.4, 7.3 Hz, 1H), 3.95 (m, 1H), 3.93 (m, 1H), 1.93 (m, 1H), 1.81 (m, 1H), 1.71 (m, 1H), 1.61 (m, 6H), 1.07 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 137.7, 119.9, 74.3, 71.8, 69.5, 36.6, 26.6, 13.0, 12.1, 11.2.

HRMS: *m/z* calcd for $C_{10}H_{19}ClO_2$: 229.0966 (M+Na); Found: 229.0967 (M+Na).

IR (neat): 3378, 2971, 1382, 1051, 913, 813.93 cm^{-1}.

Preparation of the tetrahydrofuranol 207



207

To a cold (0 °C), stirred solution of diol **206** (4.6 g, 22 mmol) in THF (200 mL) was added silver(I) oxide (5.6 g, 24 mmol) and silver(I) trifluorosulfonate (6.2 g, 5.6 mmol). The reaction mixture was allowed to warm to rt and stir for an additional 36 h. The resulting mixture was filtered through Celite®, diluted with EtOAc (200 mL) and was washed with saturated aqueous $NaHCO_3$ solution (2 x 80 mL) and H_2O (2 x 100 mL). The combined aqueous layers were washed with EtOAc (2 x 100 mL). The combined organic phases were then washed with brine (2 x 150 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 3:1) afforded the tetrahydrofuranol **207** (2.5 g, 15 mmol, 67%,) as a white solid (mp = 60-62 °C). The optical purity of the tetrahydrofuranol **207** was determined to be 95% ee by chiral GC analysis. For this purpose, the enantiomeric tetrahydrofuranol *ent*-**207**was prepared following an identical series of reactions to those presented above with the exception that (2*S*,5*R*)-2-*tert*-butyl-3,5,dimethylimidazolidin-4-one trifluoroacetate (*ent*-**82**) was employed as the catalyst for the asymmetric α-chlorination of butyraldehyde (i.e., **204** → *ent*-**203**). The enantiomeric tetrahydrofuranols **207** and *ent*-**207** were separable by chiral GC using a CDX-3 chiral column and a constant temperature of 140 °C (injection temperature = 250 °C, pressure = 10 psi). The retention time of the tetrahydrofuranol **207** is 17.42 min and the retention time of the enantiomeric tetrahydrofuranol *ent*-**207** is 16.88 min. See chromatogram below.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.64 (m, 1H), 4.22 (m, 1H), 4.18 (m, 1H), 3.55 (dt, *J* = 3.4, 6.9 Hz, 1H), 2.33, (m, 1H), 1.77, (m, 1H), 1.72, (m, 2H), 1.63, (m, 3H), 1.62 (m, 3H), 1.45 (d, *J* = 8.67 Hz, 1H), 1.01 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.2, 120.0, 84.8, 81.9, 72.8, 40.2, 21.8, 13.1, 12.0, 10.6.

HRMS: *m/z* calcd for $C_{10}H_{18}O_2$: 193.1199 (M+Na); Found: 193.1190 (M+Na).

IR (neat): 3440, 2969, 2877, 1455, 1052, 1022, 830 cm^{-1}.

$[\alpha]_D^{20}$ = -26.4 (*c* 0.3 in $CHCl_3$).

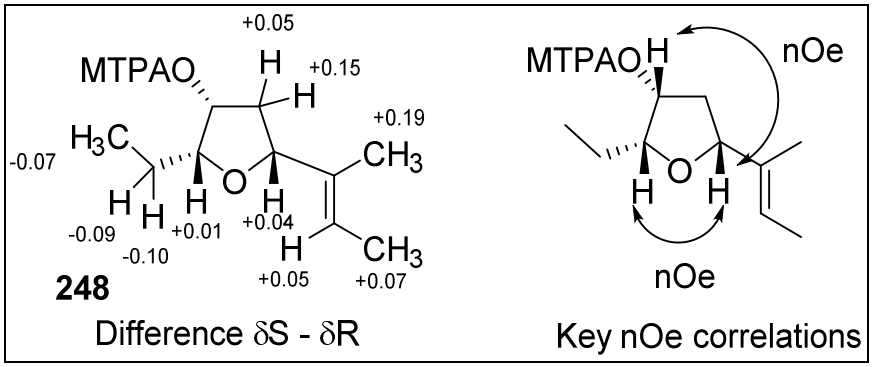
Assignment of the relative and absolute stereochemistry for the tetrahydrofuranol 207

To a cold (0 °C), stirred solution of tetrahydrofuran **207** (2.5 mg, 0.015 mmol) in dry CH_2Cl_2 (0.2 mL) was added (*S*)-(-)-MTPA-OH (5.2 mg, 0.022 mmol), *N,N'*-Diisopropylcarbodiimide (0.0066 mL, 0.042 mmol) and dimethylaminopyridine (catalytic). The reaction mixture was stirred for 24 h then the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 5:1) afforded the (*S*)-MTPA ester.

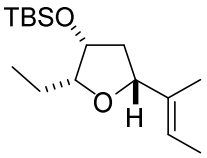
^1H NMR (500 MHz, $CDCl_3$) δ: 7.53 (m, 2H), 7.42-7.38 (m, 3H), 5.58 (q, *J* = 6.8 Hz, 1H), 5.45 (ddd, *J* = 1.7, 3.8, 5.8, 1H), 4.22 (t, *J* = 8.2 Hz, 1H), 3.66 (dt, *J* = 3.8, 6.9 Hz, 1H), 3.54 (q, *J* = 1.1 Hz, 3H), 2.53 (ddd, *J* = 7.2, 8.3, 15.3 Hz, 1H), 1.76 (ddd, *J* = 2.2, 8.1, 10.0 Hz, 1H), 1.65 – 1.46 (m, 2H) 1.59 (d, *J* = 6.8 Hz), 1.53 (s, 3H), 0.86 (t, *J* = 7.4 Hz).

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

^1H NMR (500 MHz, $CDCl_3$) δ: 7.53 (m, 2H), 7.42-7.38 (m, 3H), 5.51 (q, *J* = 6.8 Hz, 1H), 5.41 (ddd, *J* = 1.7, 3.8, 5.8, 1H), 4.18 (t, *J* = 8.2 Hz, 1H), 3.65 (dt, *J* = 3.8, 6.9 Hz, 1H), 3.55 (q, *J* = 1.1 Hz, 3H), 2.49 (ddd, *J* = 7.2, 8.3, 15.3 Hz, 1H), 1.75-1.57 (m, 3H), 1.54 (d, *J* = 6.8 Hz), 1.34 (s, 3H), 0.93 (t, *J* = 7.4 Hz).



Preparation of the silyl-protected tetrahydrofuranol 249



249

To a cold (0 °C), stirred solution of the tetrahydrofuran **207** (2.5 g, 15 mmol) in CH_2Cl_2 (150 mL) was added *tert*-butyldimethylsilyl chloride (3.4 g, 22 mmol) then imidazole (2.0 g, 30 mmol). The solution was allowed to warm to rt and stir for 14 h. The reaction mixture was washed with H_2O (2 x 100 mL) and brine (100 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 15:1) afforded the silyl-protected tetrahydrofuranol **249** (3.9 g, 14 mmol, 92%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.53 (m, 1H), 4.25 (m, 1H), 4.17 (t, *J* = 7.8 Hz, 1H), 3.50 (m, 1H), 2.22 (m, 1H), 1.66 (m, 1H), 1.65 (m, 1H), 1. 64 (d, *J* = 1.0 Hz, 3H), 1.60 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

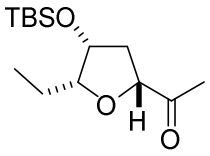
^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.8, 121.4, 84.7, 82.8, 73.0, 40.5, 25.8, 22.2, 18.1, 13.2, 11.1, 10.8, -4.4, -5.2.

HRMS: *m/z* calcd for $C_{16}H_{32}O_2Si$: 285.2244 (M+H); Found: 285.2212 (M+H).

IR (neat): 2956, 2935, 2855, 1257, 1093, 941, 840, 776 cm^{-1}.

$[\alpha]_D^{20}$ = -18.9 (*c* 1.0 in $CHCl_3$).

Preparation of the ketone 208



208

Through a cold (-78 °C), stirred solution of silyl-protected tetrahydrofuranol **249** (3.9 g, 14 mmol) in CH_2Cl_2 (140 mL) was bubbled ozone until the solution turned blue (approx. 15 min). Dinitrogen was then bubbled through the solution until it turned colourless (approx. 10 min) following which triphenylphosphine (4.3 g, 16 mmol) was added. The reaction mixture was stirred at rt for 12 h then the solvent was removed *in vacuo*. The resulting solids were diluted with Et_2O (50 mL) and cooled to -78 °C. The solution was filtered and the residue was washed with cold (0 °C) Et_2O (20 mL). This process was repeated on the filtrate one time and then the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 10:1) afforded the ketone **208** (2.58 g, 9.5 mmol, 69%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.25 (dd, *J* = 2.6, 10.1 Hz, 1H), 4.12 (t, *J* = 3.0 Hz, 1H), 3.74 (dt, *J* = 2.8, 6.8 Hz, 1H), 2.32 (m, 1H), 2.28 (s, 3H), 2.19 (m, 1H), 1.75 (m, 1H), 1.66 (m, 1H), 1.00 (t, *J* = 7.5 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

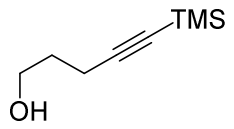
^{13}C NMR (125 MHz, $CDCl_3$) δ: 214.3, 86.8, 82.4, 71.6, 40.7, 25.7, 22.6, 18.0, 10.7, -4.7, -5.3.

HRMS: *m/z* calcd for $C_{14}H_{28}O_3Si$: 273.1880 (M+H); Found: 273.1884 (M+H).

IR (neat): 2961, 2936, 2857, 1723, 1463, 1354, 1258, 1114, 1065, 1040, 838 cm^{-1}.

$[\alpha]_D^{20}$ = + 1.5 (*c* 1.0 in $CHCl_3$).

Preparation of 5-(trimethylsilyl)pent-4-yn-1-ol (250)



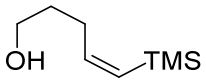
250

To a cold (-78 °C), stirred solution of 4-pentyn-1-ol (3 mL, 33 mmol) in THF (150 mL) was added a solution of *n*-butyllithium (27 mL, 67 mmol, 2.5M in hexanes) dropwise over 30 min and the reaction mixture was then stirred for 40 min at (-78 °C). Chlorotrimethylsilane (10 mL, 81 mmol) was then added dropwise over 10 min and the solution was allowed to warm to rt and stir for an additional 14 h. A 1N aqueous solution of HCl (50 mL) was then added and the mixture was stirred for 2 h. The resulting mixture was diluted with EtOAc (150 mL), and washed with H_2O (2 x 100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous layers were washed with EtOAc (2 x 100 mL) and the combined organic phases were washed with brine (150 mL), dried ($MgSO_4$) and filtered, and the solvent removed *in vacuo* to afford the alkyne **250** (5.0 g, 32 mmol, 98%) as a colourless oil that required no further purification. The spectral data derived from **250** was consistent with that reported in the literature for this material.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.76 (t, *J* = 6.0 Hz, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 1.78 (m, 2H), 0.15 (s, 9H).

Reference for known compound: Bunce, R. A.; Hertzler, D. V. *J. Org. Chem.*, **1986**, *51*, 3451-3453.

Preparation of (4*Z*)-5-(trimethylsilyl)pent-4-en-1-ol (251)



251

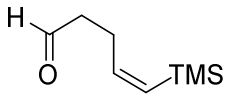
To a cold (0 °C), stirred solution of alkyne **250** (5.0 g, 32 mmol) in THF (150 mL) was added a solution of DIBAL (33 mL, 33 mmol, 1M in THF) slowly over 10 min. The reaction mixture was stirred for 20 min then heated to reflux and maintained at reflux for

36 h. Additional DIBAL (33 mL, 33 mmol, 1M in THF) was added and the reaction mixture heated at reflux for an additional 24 h. Additional DIBAL solution (49 mL, 49 mmol, 1M in THF) was then added and the reaction mixture heated at reflux for an additional 72 h. The reaction mixture was then cooled to 0 °C and quenched by the sequential addition of H_2O (4.6 mL), 15% aqueous NaOH solution (4.6 mL) and then H_2O (12 mL). The mixture was then warmed to rt and $MgSO_4$ (30 g) was added. The resulting slurry was stirred for 20 min before the solids were removed by filtration and the filtrate was concentrated *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 5:1) afforded the *(Z)*-alkene **251** (4.5 g, 28 mmol, 86%) as a colourless oil. The spectral data derived from **251** was consistent with that reported in the literature for this material.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.31 (td, *J* = 7.4, 14.0 Hz, 1H), 5.52 (dt, *J* = 1.4, 14.0 Hz, 1H), 3.67 (q, *J* = 5.4 Hz, 2H), 2.22 (dq, *J* = 1.4, 7.4 Hz, 2H), 1.67 (m, 2H), 1.26 (t, *J* = 5.4 Hz, 1H), 0.12 (s, 9H).

Reference for known compound: Miura, K.; Okajima, S.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Am. Chem. Soc*. **2000**, *122,* 11348-11357.

Preparation of (4*Z*)-5-(trimethylsilyl)pent-4-enal (210)



210

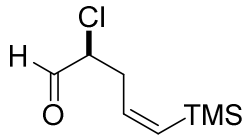
To a cold (-78 °C), stirred solution of dimethylsulfoxide (6.2 mL, 87 mmol) in CH_2Cl_2 (250 mL) was added oxalyl chloride (5.0 mL, 58 mmol) dropwise over 20 min. The reaction mixture was stirred for 30 min then alcohol **251** (4.5 g, 28 mmol) was added dropwise over 10 min. The reaction mixture was then stirred for an additional 30 min then triethylamine (20 mL, 140 mmol) was added and the solution was allowed to warm to rt over 20 min. The mixture was washed with H_2O (2 x 100 mL) and brine (100 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 12:1) afforded aldehyde

210 (3.9 g, 25 mmol, 85%) as a light yellow oil. The spectral data derived from **210** was consistent with that reported in the literature for this material.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.79 (t, *J* = 1.5 Hz, 1H), 6.24 (td, *J* = 7.4, 14.0 Hz, 1H), 5.57 (dt, *J* = 1.4, 14.0 Hz, 1H), 2.49 (m, 4H), 0.13 (s, 9H).

Reference for known compound: Miura, K.; Okajima, S.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Am. Chem. Soc*. **2000**, *122,* 11348-11357.

Preparation of (2*S*,4*Z*)-2-chloro-5-(trimethylsilyl)pent-4-enal ((*S*)-200)



(*S*)-200

To a cold (0 °C), stirred solution of (2*S*,5*R*)-2-tert-butyl- 3,5,dimethylimidazolidin-4-one trifluoroacetate (**82**, 0.36 g, 1.3 mmol), lithium chloride (0.41 g, 9.6 mmol), copper (II) trifluoroacetate hydrate (0.98 g, 3.2 mmol) and sodium persulfate (1.5 g, 6.4 mmol) in MeCN (50 mL) was added H_2O (0.25 mL, 14.1 mmol). The resulting solution was stirred at 0°C for 10 min. After this time, aldehyde **210** (1.0 g, 6.4 mmol) was added dropwise and the resulting mixture was stirred for an additional 20 h. The reaction mixture was then quenched with H_2O (30 mL) and the mixture was diluted with CH_2Cl_2 (50 mL) and the phases were separated. The aqueous phases was washed with CH_2Cl_2 (2 x 50 mL) and the combined organic phases were washed with water (80 mL) and brine (80 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, 1:1) afforded the (*S*)-chloroaldehyde (*S*)-**200** as a light yellow oil (1.13 g, 5.9 mmol, 62%).

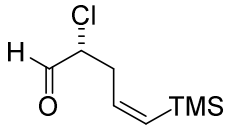
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.53 (d, *J* = 2.1 Hz), 6.25 (td, *J* = 7.4, 14.0 Hz, 1H), 5.77 (dt, *J* = 1.4, 14.0 Hz, 1H), 4.20 (ddd, *J* = 2.1 Hz, 5.5, 8.1 Hz, 1H), 2.87 – 2.81 (m, 1H), 2.70 – 2.64 (m, 1H), 0.14 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.8, 140.4, 134.7, 63.0, 35.6, 0.04.

IR (neat): 2957, 2900, 1732, 1249, 1066, 837, 764 cm^{-1}.

$[\alpha]_D^{20}$ = - 22.4 (*c* 1.0 in $CHCl_3$).

Preparation of (2*R*,4*Z*)-2-chloro-5-(trimethylsilyl)pent-4-enal ((*R*)-200)



(*R*)-200

To a cold (0 °C), stirred solution of (2*R*,5*S*)-2-tert-butyl- 3,5,dimethylimidazolidin-4-one trifluoroacetate (*ent*-**82**, 0.54g, 1.9 mmol), lithium chloride (0.61 g, 14 mmol), copper (II) trifluoroacetate hydrate (1.5 g, 4.8 mmol) and sodium persulfate (2.3 g, 9.6 mmol) in MeCN (100 mL) was added H_2O (0.38 mL, 21 mmol). The resulting solution was stirred at 0°C for 10 min. After this time, aldehyde **210** (1.5 g, 9.6 mmol) was added dropwise and the resulting mixture was stirred for an additional 20 h. The reaction mixture was then quenched with H_2O (30 mL), the mixture was diluted with CH_2Cl_2 (50 mL) and the phases were separated. The aqueous phases was washed with CH_2Cl_2 (2 x 50 mL) and the combined organic phases were washed with water (80 mL) and brine (50 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, 1:1) afforded the (*R*)-chloroaldehyde (*R*)-**200** as a light yellow oil (0.77 g, 4.1 mmol, 63%).

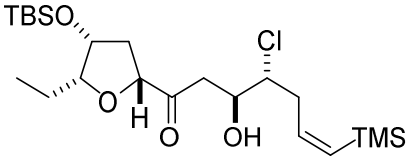
^{1}H NMR (500 MHz, $CDCl_3$) δ: 9.53 (d, *J* = 2.1 Hz), 6.25 (td, *J* = 7.4, 14.0 Hz, 1H), 5.77 (td, *J* = 1.4, 14.0 Hz, 1H), 4.20 (ddd, *J* = 2.1 Hz, 5.5, 8.1 Hz, 1H), 2.87 – 2.81 (m, 1H), 2.70 – 2.64 (m, 1H), 0.14 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.8, 140.4, 134.7, 63.0, 35.6, 0.04.

IR (neat): 2957, 2900, 1732, 1249, 1066, 837, 764 cm^{-1}.

$[\alpha]_D^{20}$ = +22.1 (*c* 1.0 in $CHCl_3$).

Preparation of the ketochlorohydrin 252



252

To a cold (-78 °C), stirred solution of hexamethyldisilazane (0.74 mL, 3.5 mmol) in THF (30 mL) was added a solution of *n*-butyllithium (1.2 mL, 3.2 mmol, 2.5 M in hexanes) dropwise over 10 min. The solution was allowed to warm to rt over 15 min and then cooled to -40 °C. Ketone **208** (800 mg, 2.9 mmol) was then added dropwise over 10 min as a solution in THF (5 mL). The reaction mixture was stirred for 20 min at -40 °C then cooled to -78 °C and chloroaldehyde (*R*)-**200** (670 mg, 3.5 mmol) was added. The solution was stirred for an additional 30 min then quenched by the addition of saturated aqueous NH_4Cl (10 mL) and warmed to rt. The mixture was diluted with EtOAc (30 mL) and washed with H_2O (2 x 30 mL). The combined aqueous phases were washed with EtOAc (2 x 30 mL) and the combined organic extracts were washed with brine (50 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 10:1) afforded the ketochlorohydrin **252** (520 mg, 1.1 mmol, 39%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.36 (m, 1H), 5.69 (td, *J* = 1.3, 14.1 Hz, 1H), 4.31 (dd, *J* = 2.6, 10.2 Hz, 1H), 4.18 (m, 1H), 4.15 (m, 1H), 3.92 (m, 1H), 3.75 (m, 1H), 3.29 (dd, *J* = 3.0, 17.9 Hz, 1H), 3.21 (d, *J* = 4.3 Hz, 1H), 2.90 (dd, *J* = 9.3, 17.9 Hz, 1H), 2.77-2.71 (m, 1H), 2.56-2.47 (m, 1H), 2.36 (m, 1H), 2.22 (ddd, *J* = 1.2, 2.5, 13.2 Hz, 1H), 1.81-1.59 (m, 2H), 1.01 (t, 7.4 Hz, 3H), 0.86 (s, 9H), 0.13 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

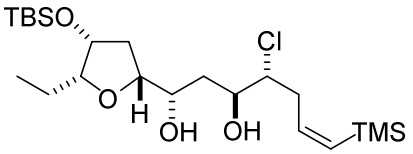
^{13}C NMR (150 MHz, $CDCl_3$) δ: 215.6, 143.4, 132.6, 86.9, 82.2, 71.8, 70.5, 65.4, 41.3, 40.5, 36.9, 25.8, 22.5, 10.8, 0.1, -4.7, -5.2.

HRMS: *m/z* calcd for $C_{22}H_{43}O_4Si_2$: 485.2281 (M+Na); Found: 485.2299 (M+Na).

IR (neat): 2971, 2901, 1702, 1393, 1250, 1066, 837 cm^{-1}.

$[\alpha]_D^{20}$ = -3.2 (*c* 1.0 in $CHCl_3$).

Preparation of the diol 253



253

To a cold (-40 °C), stirred solution of tetramethylammonium triacetoxyborohydride (880 mg, 3.4 mmol) in MeCN (3 mL) was added acetic acid (3 mL) followed by ketochlorohydrin **252** (390 mg, 0.84 mmol) as a solution in MeCN (1.5 mL).The reaction mixture was stirred at -40 °C for 12 h then saturated aqueous sodium potassium tartrate solution (5 mL) was added and the reaction mixture was allowed to warm to rt and stir for an additional 2 h. The mixture was then diluted with CH_2Cl_2 (10 mL) and washed with H_2O (2 x 10 mL). The combined aqueous phases were washed with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were washed with brine (15 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo.* Purification of the crude product by flash chromatography (hexanes-EtOAc, 5:1) afforded diol **253** (220 mg, 0.48 mmol, 57%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.38 (m, 1H), 5.68 (td, *J* = 1.3, 14.2 Hz, 1H), 4.21 (m, 1H), 4.18 (m, 1H), 4.04-3.99 (m, 2H), 3.92 (m, 1H), 3.58 (d, *J* = 7.6 Hz, 1H), 3.52 (m, 1H), 3.34 (s, 1H), 2.91 (m, 1H), 2.56-2.47 (m, 1H), 2.15 (m, 1H), 1.94 (dd, *J* = 3.9, 13.9 Hz, 1H), 1.85 (ddd, *J* = 3.0, 6.4, 14.2 Hz, 1H), 1.71 (m, 3H), 0.97 (t, *J* = 7.6 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.9, 132.3, 85.0, 80.5, 72.8, 72.4, 69.4, 64.9, 37.3, 35.1, 34.9, 29.7, 25.7, 22.0, 10.8, 0.1, -4.6, -5.1.

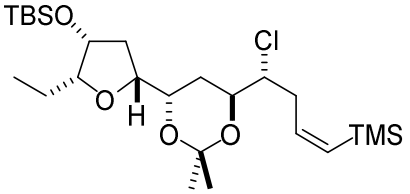
HRMS: *m/z* calcd for $C_{22}H_{45}ClO_4Si_2$: 465.2618 (M+H); Found: 465.2612 (M+H).

IR (neat): 3487, 2969, 2906, 1393, 1250, 1066, 837 cm^{-1}.

$[\alpha]_D^{20}$ = -10.0 (*c* 0.3 in $CHCl_3$).

Assignment of the relative stereochemistry for diol 253

Preparation of acetonide 254



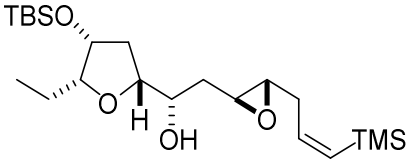
254

To a solution of diol 253 (5 mg, 0.011 mmol) at rt in acetone (0.5 mL) was added dimethoxypropane (0.039 mL, 0.32 mmol) and camphorsulfonic acid (1.3 mg, 0.0050 mmol). The reaction mixture was stirred for 4 h then treated with triethylamine (0.006 mL, 0.044 mmol). The resulting mixture was concentrated *in vacuo.* Purification of the crude product by flash chromatography (hexanes-EtOAc, 20:1) afforded the acetonide **254**. In the ^{13}C NMR spectrum recorded on acetonide **254**, the two methyl groups of the acetonide function resonate at δ = 24.9 and 24.9 ppm, indicating the relative stereochemistry of the two alcohol functions in the diol **253** is 1,3-*anti* as indicated.[131]

^1H NMR (600 MHz, $CDCl_3$) δ: 6.37 (td, *J* = 7.3, 13.5 Hz, 1H), 5.67 (td, *J* = 1.4, 14.1 Hz, 1H), 4.21 (m, 1H), 3.88 (m, 1H), 3.84-3.79 (m, 3H), 3.56 (m, 1H), 2.79 (dddd, *J* = 1.5, 3.5, 6.9, 15.3 Hz, 1H), 2.46 (m, 1H), 2.22 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.74 (m, 1H), 1.61 (m, 2H), 1.35 (s, 6H), 0.93 (t, *J* = 7.8 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.5, 132.5, 85.3, 79.6, 72.4, 69.7, 69.5, 64.6, 38.5, 37.4, 32.2, 25.8, 24.9, 24.9, 22.3, 10.7, 0.1, -4.4, -5.2.

Preparation of epoxide 255

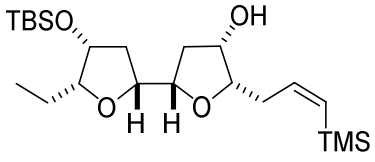


255

To a cold (0 °C), stirred solution of diol **253** (10 mg, 0.022 mmol) in EtOH (0.2 mL) was added an aqueous solution of sodium hydroxide (0.013 mL, 0.026 mmol, 2N) and the reaction mixture was stirred for 30 min. The reaction mixture was then diluted with EtOAc (0.5 ml) and was washed with H_2O (2 x 0.5 mL) and brine (0.5 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*.. Purification of the crude product by flash chromatography (hexanes-EtOAc, 5:1) afforded the epoxide **255**. In the ^{1}H NMR spectrum recorded on epoxide **255**, the observed coupling constants between the two resonances corresponding to the epoxide protons at δ = 2.91 and 2.78 was 2.2 Hz consistent with that of a *trans* epoxide.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.31 (td, *J* = 7.3, 14.2 Hz, 1H), 5.66 (td, *J* = 1.4, 14.2 Hz, 1H), 4.18 (m, 1H), 4.05-3.99 (m, 2H), 3.51 (m, 1H), 2.91 (ddd, *J* = 2.2, 4.1, 6.7 Hz, 1H), 2.78 (ddd, *J* = 2.2, 5.6, 7.8 Hz, 1H), 2.40 (m, 2H), 2.11 (ddd, *J* = 5.4, 9.4, 14.3 Hz, 1H), 1.86 (ddd, *J* = 1.1, 4.5, 13.8, 1H), 1.76 (ddd, *J* = 4.1, 8.2, 14.0 Hz, 1H), 1.69-1.46 (m, 3H), 0.96 (t, *J* = 7.6 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

Preparation of the bistetrahydrofuran 224



34

To a cold (0 °C), stirred solution of diol **253** (200 mg, 0.44 mmol) in THF (5 mL) was added silver(I) oxide (200 mg, 0.88 mmol) and silver(I) trifluorosulfonate (170 mg, 0.66 mmol). The reaction mixture was sonicated and stirred for 12 h with the bath

temperature eventually reaching 40 °C. The reaction mixture was then filtered through Celite® and diluted with EtOAc (5 mL). The mixture was washed with saturated $NaHCO_3$ solution (2 x 5 mL) and H_2O (2 x 5 mL). The combined aqueous phases were washed with EtOAc (2 x 10 mL) and the combined organic extracts were washed with brine (10 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 5:1) afforded **224** (72 mg, 0.17 mmol, 38 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.39 (m, 1H), 5.61 (td, *J* = 1.4, 14.0 Hz, 1H), 4.22-4.09 (m, 4H), 3.99 (ddd, *J* = 2.5, 5.2, 11.3 Hz, 1H), 3.63 (dt, *J* = 2.7, 7.2 Hz), 3.59 (m, 1H), 2.54 (m, 2H), 2.37 (dd, *J* = 2.5, 14.0 Hz, 1H), 2.29 (ddd, *J* = 6.8, 9.5, 15.0 Hz, 1H), 2.13 (m, 1H), 1.79 – 1.57 (m, 2H), 1.41 (dd, *J* = 1.6, 7.0, 14.0 Hz, 1H), 0.97 (t, *J* = 7.5 Hz), 0.90 (s, 9H), 0.13 (s, 9H), 0.053 (s, 6H), 0.047 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.9, 131.3, 85.9, 84.5, 79.6, 78.4, 72.3, 71.0, 38.7, 33.6, 33.4, 25.8, 21.6, 18.1, 10.8, 0.1, -4.5, -5.2.

HRMS: *m/z* calcd for $C_{22}H_{45}O_4Si_2$: 429.2851 (M+H); Found: 429.2830 (M+H).

IR (neat): 3433, 2953, 2857, 1462, 1249, 1060, 835, 774 cm^{-1}.

$[\alpha]_D^{20}$ = -5.3 (*c* 1.0 in $CHCl_3$).

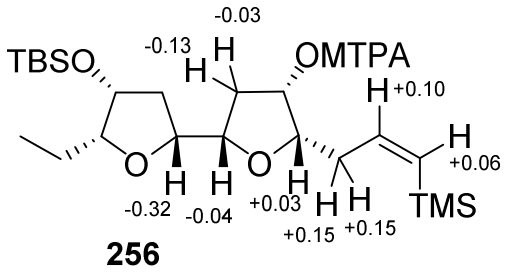
Assignment of the relative and absolute stereochemistry for the bistetrahydrofuran 224

To a cold (0 °C), stirred solution of tetrahydrofuran **224** (3 mg, 0.007 mmol) in dry CH_2Cl_2 (0.2 mL) was added (*S*)-(-)-MTPA-OH (2.5 mg, 0.011 mmol), *N,N'*-diisopropylcarbodiimide (0.0033 mL, 0.021 mmol) and dimethylaminopyridine (catalytic). The reaction mixture was stirred for 24 h then the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 7:1) afforded the (*S*)-MTPA ester.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 (m, 2H), 7.39 (m, 3H), 6.26 (ddd, *J* = 6.4, 8.2, 14.0 Hz, 1H), 5.61 (dt, *J* = 1.2, 14.0 Hz, 1H), 5.3 (m, 1H), 4.14 (m, 1H), 3.88 (m, 1H), 3.76 (ddd, *J* = 3.8, 5.3, 8.6 Hz, 1H), 3.53 (s, 3H), 3.49 (dt, *J* = 5.3, 8.1 Hz, 1H), 3.43 (dt, *J* = 3.6, 6.4 Hz, 1H), 2.52 (m, 2H), 2.34 (m, 1H), 2.09 (ddd, *J* = 6.2, 8.1, 14.0 Hz, 1H), 1.98 (ddd, *J* = 1.6, 5.9, 14.9 Hz, 1H), 1.79 (ddd, *J* = 1.9, 5.0, 13.4 Hz, 1H), 1.55 (m, 2H), 0.90 (t, *J* = 7.8 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 9H), -0.04 (s, 3H), -0.03 (s, 3H).

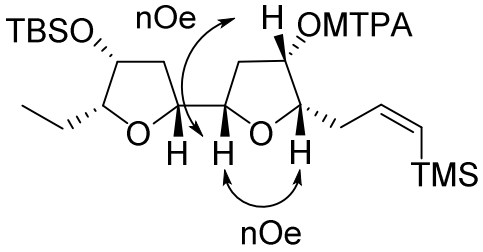
In an analogous manner, the (*R*)-MTPA ester was prepared using (*R*)-(-)-MTPA-OH.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 (m, 2H), 7.39 (m, 3H), 6.26 (ddd, *J* = 6.4, 8.2, 14.0 Hz, 1H), 5.61 (dt, *J* = 1.2, 14.0 Hz, 1H), 5.3 (m, 1H), 4.14 (m, 1H), 3.88 (m, 1H), 3.76 (ddd, *J* = 3.8, 5.3, 8.6 Hz, 1H), 3.53 (s, 3H), 3.49 (dt, *J* = 5.3, 8.1 Hz, 1H), 3.43 (dt, *J* = 3.6, 6.4 Hz, 1H), 2.52 (m, 2H), 2.34 (m, 1H), 2.09 (ddd, *J* = 6.2, 8.1, 14.0 Hz, 1H), 1.98 (ddd, *J* = 1.6, 5.9, 14.9 Hz, 1H), 1.79 (ddd, *J* = 1.9, 5.0, 13.4 Hz, 1H), 1.55 (m, 2H), 0.90 (t, *J* = 7.8 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 9H), -0.04 (s, 3H), -0.03 (s, 3H).



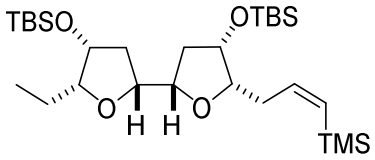
256

Difference δS - δR



Key nOe correlations

Preparation of the TBS protected bistetrahydrofuran 257



257

To a cold (0 °C), stirred solution of **224** (20.0 mg, 0.047 mmol) in CH_2Cl_2 (1 mL) was added 2,6-lutidine (0.009 mL, 0.071 mmol) and *tert*-butyldimethylsilyl triflate (0.013

mL, 0.056 mmol). The reaction mixture was stirred at 0 °C for 2 h and then quenched by the addition of H_2O (1 mL). The layers were separated and the organic layer was washed with H_2O (1 x 1 mL) and brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 15:1) afforded the product **257** (19.0 mg, 0.036 mmol, 77%) as a colourless oil.

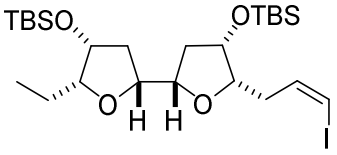
^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.39 (m, 1H), 5.58 (td, *J* = 1.3, 14.1 Hz, 1H), 4.25 – 4.19 (m, 2H), 3.87-3.79 (m, 2H), 3.63 (m, 1H), 3.49 (dt, *J* = 4.2, 6.8 Hz, 1H), 2.51 – 2.31 (m, 2H), 2.26 (m, 2H), 1.94 – 1.83 (m, 2H), 1.60 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.11 (s, 9H), 0.073 (s, 3H), 0.056 (s, 3H), 0.052 (s, 3H), 0.038 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 145.8, 130.6, 85.0, 83.3, 80.6, 80.1, 73.2, 72.8, 39.4, 39.0, 33.9, 29.7, 25.8, 22.4, 18.1, 18.0, 10.7, 0.1, -4.5, -4.6, -5.1, -5.2.

HRMS: *m/z* calcd for $C_{28}H_{58}O_4Si_3$: 565.3560 (M+Na); Found: 565.3535 (M+Na).

IR (neat): 2957, 2890, 2860, 1253, 1102, 1064, 838, 775 cm^{-1}

Preparation of the vinyl iodide 258



258

To a solution of the silyl-protected bis-tetrahydrofuran **257** (19.0 mg, 0.036 mmol) in MeCN (1 mL) was added N-iodosuccinimide (20.0 mg, 0.074 mmol) and the resulting solution was stirred for 14 h. The reaction mixture was then quenched by the addition of saturated $Na_2S_2O_3$ solution (1 mL) and the resulting solution was stirred until it turned colourless (approx. 5 min). EtOAc (2 mL) was then added and the mixture was washed with H_2O (2 x 1 mL). The combined aqueous phases were washed with EtOAc (2 mL) and the combined organic layers were washed with brine (1.5 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by

flash chromatography (hexanes-EtOAc, 10:1) afforded the vinyl iodide **258** (15.0 mg, 0.025 mmol, 70 %, ratio of *Z*:*E* isomers = 3:1) as a light yellow oil.

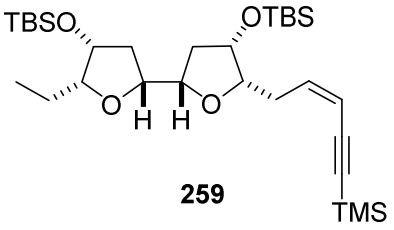
Data for **258** (only data for the major (*Z*) isomer is listed): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.36 (q, *J* = 7.0 Hz, 1H), 6.28 (td, *J* = 1.4, 7.0 Hz, 1H), 4.30 (m, 1H), 4.24 (m, 1H), 3.88 (m, 1H), 3.86 (m, 1H), 3.77 (dt, *J* = 4.7, 7.7 Hz, 1H), 3.53 (m, 1H), 2.50 – 2.23 (m, 4H), 1.93 (m, 1H), 1.87 (m, 1H), 1.63 (dt, *J* = 7.4, 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.93 (s, 9H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.088 (s, 3H), 0.070 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 138.8, 85.1, 83.4, 81.4, 80.4, 80.0, 73.2, 72.7, 39.1, 38.8, 35.8, 25.8, 22.4, 18.1, 10.7, -4.5, -4.6, -5.0, -5.1.

HRMS: *m/z* calcd for $C_{25}H_{50}IO_4Si_2$: 597.2287 (M+H); Found: 597.2302 (M+H).

IR (neat): 2955, 2932, 2857, 1471, 1254, 1065, 835, 775 cm^{-1}.

Preparation of the ene-yne 259



259

To a cold (0 °C), stirred solution of $Pd(PPh_3)_4$ (catalytic) and CuI (catalytic) in THF (1.5 mL) was added triethylamine (0.014 mL, 0.17 mmol). A solution of the vinyl iodide **258** (10 mg, 0.017 mmol) in THF (0.5 mL) was then added dropwise followed by. trimethylsilylacetylene (0.024 mL, 0.17 mmol) and the reaction mixture was stirred for 14 h at rt. The solvent was then removed *in vacuo.* Purification of the crude product by flash chromatography (hexanes-EtOAc, 10:1) afforded the product **259** (8.0 mg, 0.014 mmol, 82%, ratio of *Z*:*E* isomers 3:1) as a colourless oil.

Data for **259** (only data for the major (*Z*) isomer is listed): ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.08 (td, *J* = 6.8, 10.6 Hz, 1H), 5.54 (td, *J* = 1.2, 10.6 Hz, 1H), 4.26 (m, 1H), 4.21 (m, 1H), 3.87-3.83 (m, 2H), 3.70 (ddd, *J* = 5.1, 8.2, 9.3 Hz, 1H), 3.51 (dt, *J* = 4.0,

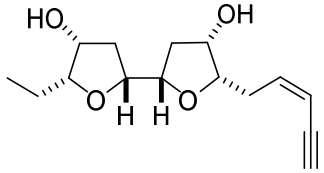
6.6 Hz, 1H), 2.63-2.55 (m, 2H), 2.30-2.22 (m, 2H), 1.94-1.80 (m, 2H), 1.60 (dq, *J* = 7.6, 7.6 Hz), 0.93 (t, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.18 (s, 9H), 0.08 (s,3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 142.7, 110.1, 102.1, 98.9, 85.1, 82.1, 80.4, 80.1, 73.3, 72.7, 39.2, 39.0, 31.3, 25.9, 25.8, 22.4, 18.1, 10.7, 0.1, -4.4, -4.6, -5.0, -5.1.

HRMS: *m/z* calcd for $C_{30}H_{59}O_4Si_3$: 567.3716 (M+H); Found: 567.3685 (M+H).

IR (neat): 2957, 2928, 2857, 1253, 1065, 838, 779 cm^{-1}.

Preparation of the bistetrahydrofuranol 196



196

To a cold (0 °C), stirred solution of **259** (8.0 mg, 0.014 mmol) in THF (0.3 mL) was added tetrabutylammonium fluoride solution (0.060 mL, 0.057 mmol, 1M in THF) and the solution was stirred for an additional 12 h. EtOAc (1 mL) was then added and the organic layer was removed and washed with H_2O (2 x 0.5 mL). The aqueous phases were washed with EtOAc (2 x 0.5 mL) and the combined organic layers were washed brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 1:2) afforded the product **196** (1.8 mg, 0.007 mmol, 52%).

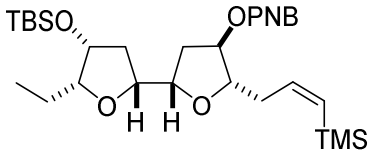
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.11 (ddd, *J* = 1.2, 7.5, 10.8 Hz, 1H), 5.57 (m, 1H), 4.20-4.12 (m, 4H), 3.74 (ddd, *J* = 2.8, 7.2, 7.2 Hz, 1H), 3.60 (ddd, *J* = 2.9, 7.1, 7.1 Hz, 1H), 3.15 (d, *J* = 1.6 Hz, 1H), 2.81 (m, 1H), 2.73 (m, 1H), 2.36 (s, 1H), 2.28 (ddd, *J* = 5.9, 9.6, 14.6 Hz, 1H), 1.94 (dd, *J* = 4.9, 14.4 Hz, 1H), 1.89 (dd, *J* = 4.7, 14.1 Hz, 1H), 1.72 (m, 2H), 1.0 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 141.2, 110.3, 85.8, 82.9, 82.6, 80.0, 79.1, 78.8, 71.5, 71.3, 35.7, 35.5, 31.8, 21.5, 10.6.

HRMS: *m/z* calcd for $C_{15}H_{22}O_4$: 289.1410 (M+Na); Found: 289.1410 (M+Na).

IR (neat): 3406, 2971, 2901, 1393, 1250, 1066, 1057, 892 cm^{-1}

Preparation of the bistetrahydrofuran 260



260

To a stirred solution of triphenylphosphine (49 mg, 0.19 mmol) in THF (0.5 mL) was added *para*-nitrobenzoic acid (32 mg, 0.19 mmol). The bifuran **224** (20 mg, 0.046 mmol) was then added as a solution in THF (0.5 mL) and the reaction mixture cooled to 0 °C. Diisopropyl azodicarboxylate (0.037 mL, 0.19 mmol) was added and the reaction mixture stirred for 1 h. The solvent was then removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 10:1) afforded the product **260** (23 mg, 0.040 mmol, 87%*)* as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 6.36 (m, 1H), 5.67 (td, *J* = 1.1, 14.2 Hz, 1H), 5.28 (m, 1H), 4.23 (m, 2H), 4.11 (m, 1H), 3.89 (m, 1H), 3.59 (m, 1H), 2.47 (m, 2H), 2.31 – 2.16 (m, 3H), 1.84 (ddd, *J* = 1.9, 5.2, 13.5, 1H), 1.63 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

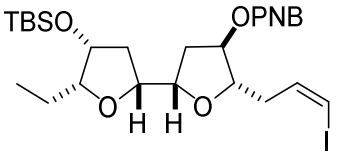
^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.1, 150.6, 142.9, 135.5, 132.3, 130.7, 123.5, 85.5, 83.9, 81.3, 79.8, 79.5, 72.5, 39.0, 37.8, 34.9, 25.8, 22.3, 22.3, 18.1, 10.8, 0.1, -4.5, -5.2.

HRMS: *m/z* calcd for $C_{29}H_{47}NNaO_7Si_2$: 600.2783 (M+Na); Found: 600.2789 (M+Na).

IR (neat): 2954, 2894, 2856, 1727, 1530, 1349, 1273, 1117, 1102, 836, 774, 720 cm^{-1}.

$[\alpha]_D^{20}$ = -37.1 (*c* 0.5 in $CHCl_3$).

Preparation of the vinyl iodide 261



261

To a solution of **260** (18.0 mg, 0.031 mmol) in MeCN (1 mL) was added N-iodosuccinimide (14.0 mg, 0.062 mmol) and the resulting solution was stirred for 14 h. The reaction mixture was then quenched by the addition of saturated $Na_2S_2O_3$ solution (1 mL) and the resulting solution was stirred until it turned colourless (approx. 5 min). EtOAc (2 mL) was then added and the mixture was washed with H_2O (2 x 2 mL). The combined aqueous phases were washed with EtOAc (2 mL) and the combined organic layers were washed with brine (2 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 10:1) afforded the product **261** (12.0 mg, 0.019 mmol, 61 %, ratio of *Z*:*E* isomers 4:1) as a colourless oil.

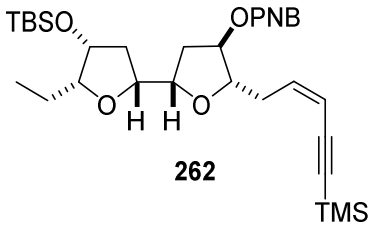
Data for **261** (only data for the major (*Z*) is listed): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 8.9 Hz, 2H), 8.19 (d, *J* = 8.9 Hz, 2H), 6.40 – 6.33 (m, 2H), 5.29 (m, 1H), 4.29-4.21 (m, 2H), 4.19 (dt, *J* = 1.8, 6.7 Hz, 1H), 3.92 (m, 1H), 3.60 (m, 1H), 2.50 (m, 2H), 2.32 – 2.23 (m, 3 H), 1.84 (ddd, *J* = 1.9, 4.9, 13.5 Hz, 1H), 1.70 – 1.58 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.2, 150.7, 141.4, 136.8, 135.4, 130.8, 123.6, 85.6, 85.0, 82.7, 81.5, 79.8, 79.5, 72.6, 39.4, 38.9, 34.7, 25.8, 22.4, 10.8, -4.5, -5.1.

HRMS: *m/z* calcd for $C_{26}H_{38}INNaO_7Si_2$: 654.1354 (M+Na); Found: 654.1365 (M+Na).

IR (neat): 2971, 290, 1725, 1529, 1381, 1271, 1066, 891, 775 cm^{-1}.

Preparation of the ene-yne 262



262

To a cold (0 °C), stirred solution of $Pd(PPh_3)_4$ (catalytic) and CuI (catalytic) in THF (1.5 mL) was added triethylamine (0.024 mL, 0.17 mmol). A solution of the vinyl iodide **261** (12.0 mg, 0.017 mmol) in THF (0.5 mL) was then added dropwise followed by. trimethylsilylacetylene (0.024 mL, 0.17 mmol) and the reaction mixture was stirred for 14 h at rt. The solvent was then removed *in vacuo.* . Purification of the crude product by flash chromatography (hexanes-EtOAc, 10:1) afforded the ene-yne product **262** (9.7 mg, 0.016 mmol, 95%, ratio of *Z:E* isomers 5:1). Further purification isolated the (*Z*)-ene-yne **262** (8.0 mg, 0.013 mmol) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 9.1 Hz, 2H), 8.19 (d, *J* = 9.1 Hz, 2H), 6.05 (td, *J* = 7.6, 11.0 Hz, 1H), 5.63 (td, *J* = 1.2, 11.0 Hz, 1H), 5.33 (dt, *J* = 1.6, 5.7 Hz, 1H), 4.23 (m, 2H), 4.16 (dt, *J* = 1.8, 6.4 Hz, 1H), 3.88 (m, 1H), 3.59 (m, 1H), 2.65 (m, 2H), 2.31 – 2.25 (m, 2H), 2.17 (m, 1H), 1.88 (ddd, *J* = 2.0, 5.1, 13.5 Hz, 1H), 1.63 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.90 (s, 9H), 0.19 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H).

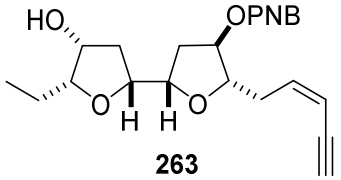
^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.0, 150.6, 139.5, 135.5, 130.8, 123.6, 111.9, 101.5, 99.7, 85.5, 83.3, 81.5, 80.0, 79.8, 72.5, 39.1, 35.2, 35.1, 25.8, 22.4, 10.8, -0.06, -4.5, -5.1.

HRMS: *m/z* calcd for $C_{31}H_{47}NO_7Si_2$: 624.2783 (M+Na); Found: 624.2816 (M+Na).

IR (neat): 2955, 2901, 1728, 1530, 1273, 1101, 843, 774, 720 cm^{-1}.

$[\alpha]_D^{20}$ = +46.1 (*c* 0.2 in $CHCl_3$).

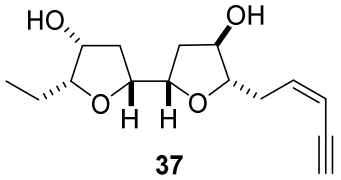
Preparation of the bistetrahydrofuranol 263



263

To a cold (0 °C), stirred solution of **262** (8.0 mg, 0.013 mmol) in THF (0.2 mL) was added tetrabutylammonium fluoride solution (0.040 mL, 0.040 mmol, 1M in THF) and the solution was stirred for an additional 12 h. EtOAc (1 mL) was then added and the organic layer was removed and washed with H_2O (2 x 0.5 mL). The aqueous phases were washed with EtOAc (2 x 0.5 mL) and the combined organic layers were washed brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to give the crude product **263** which was used in the next step without purification.

Preparation of the bistetrahydrofurandiol 37



37

To a solution of bifuranol **263** in MeOH (0.3 mL) at rt was added aqueous NaOH solution (0.065 mL, 0.065 mmol, 1N) and the resulting mixture was stirred for 1 h. Following this, a saturated aqueous solution of NH_4Cl (0.2 mL) was added followed by dilution with EtOAc (1 mL). The organic layer was washed with H_2O (2 x 0.5 mL) and the combined aqueous layers were washed with EtOAc (2 x 0.5 mL). The combined organic layers were then washed with brine (1 mL), dried ($MgSO_4$) and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 1:3) afforded the product **37** (3.0 mg, 0.011 mmol, 87% over two steps) as a white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.09 (td, *J* = 7.5, 10.8 Hz, 1H), 5.62 (ddt, *J* = 1.5, 2.0, 10.8 Hz, 1H), 4.41 (ddd, *J* = 1.8, 5.9, 10.3 Hz, 1H), 4.16 (m, 2H), 4.02 (ddd, *J* = 2.3, 5.6, 11.0 Hz, 1H), 3.94 (ddd, *J* = 3.5, 6.4, 6.4 Hz, 1H), 3.53 (ddd, *J* = 2.4, 6.9, 6.9 Hz,

1H), 3.38 (d, *J* = 11.2, 1H), 3.13 (d, *J* = 2.0 Hz, 1H), 2.64 (m, 2H), 2.23 (ddd, *J* = 5.6, 10.1, 14.4 Hz, 1H), 1.89 (ddd, *J* = 2.9, 6.1, 13.4 Hz, 1H), 1.85 (dd, *J* = 3.2, 13.9 Hz, 1H), 1.76-1.66 (m, 4H), 0.97 (t, *J* = 7.5 Hz, 3H).

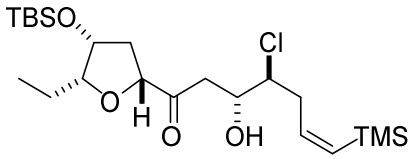
^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.9, 111.4, 85.7, 85.6, 82.5, 80.0, 79.3, 78.3, 75.0, 70.9, 37.3, 34.7, 34.1, 29.7, 21.7, 10.5.

HRMS: *m/z* calcd for $C_{15}H_{22}O_4$: 289.1410 (M+Na); Found: 289.1393 (M+Na).

IR (neat): 3409, 3293, 2967, 2923, 1393, 1250, 1066, 892 cm^{-1}.

$[\alpha]_D^{20}$ = -7.6 (*c* 0.2 in $CHCl_3$).

Preparation of the ketochlorohydrin 211



211

To a cold (-78 °C), stirred solution of hexamethyldisilazane (0.49 mL, 2.2 mmol) in THF (20 mL) was added a solution of *n*-butyllithium (0.8 mL, 2.0 mmol, 2.5 M in hexanes) dropwise over 10 min. The solution was allowed to warm to rt over 15 min and then cooled to -40 °C. Ketone **208** (500 mg, 1.8 mmol) as a solution in THF (5 mL) was then added dropwise over 10 min. The reaction mixture was stirred for 20 min at -40 °C then cooled to -78 °C and chloroaldehyde (*S*)-**200** (420 mg, 2.2 mmol) was added. The solution was stirred for an additional 30 min then quenched by the addition of saturated aqueous NH_4Cl (10 mL) and warmed to rt. The mixture was diluted with EtOAc (30 mL) and washed with H_2O (2 x 30 mL). The combined aqueous phases were washed with EtOAc (2 x 30 mL) and the combined organic extracts were washed with brine (50 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 8:1) afforded the product **211** (330 mg, 0.70 mmol, 40%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.36 (m,1H), 5.69 (td, *J* = 1.5, 14.2 Hz, 1H), 4.31 (dd, *J* = 2.3, 10.0 Hz, 1H), 4.14 (m, 1H), 4.08 (m, 1H), 3.91 (ddd, *J* = 3.4, 6.0, 9.7 Hz , 1H), 3.78 (m, 1H), 3.51 (d, *J* = 5.2 Hz, 1H), 3.16 (dd, *J* = 9.2, 17.4 Hz, 1H), 3.07 (dd, *J* = 3.1, 17.4 Hz, 1H), 2.75 (dddd, *J* = 1.5, 3.5, 6.4, 15.0 Hz, 1H), 2.50 (m, 1H), 2.38 (ddd, *J* = 3.9, 9.9, 13.3 Hz, 1H), 2.26 (ddd, *J* = 1.0, 2.3, 13.3 Hz, 1H), 1.82 – 1.59 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.85 (s, 9H), 0.14 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H).

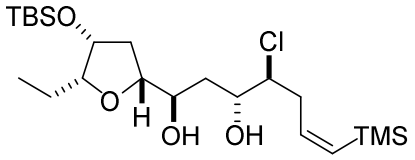
^{13}C NMR (100 MHz, $CDCl_3$) δ: 215.8, 143.3, 132.8, 87.0, 82.3, 71.8, 65.4, 41.1, 37.1, 25.7, 22.5, 18.1, 11.0, 0.1, -4.7, -5.2.

HRMS: *m/z* calcd for $C_{22}H_{43}O_4Si_2$: 485.2281 (M+Na); Found: 485.2299 (M+Na).

IR (neat): 3474, 2955, 2858, 1714, 1463, 1250, 1064, 1037, 857, 837, 776 cm^{-1}.

$[\alpha]_D^{20}$ = +5.9 (*c* 0.3 in $CHCl_3$).

Preparation of the diol 216



216

To a cold (-40 °C), stirred solution of tetramethylammonium triacetoxyborohydride (730 mg, 2.8 mmol) in MeCN (3 mL) was added acetic acid (3 mL) followed by ketochlorohydrin **211** (320 mg, 0.69 mmol) as a solution in MeCN (1.5 mL).The reaction mixture was stirred at -40 °C for 12 h then saturated aqueous sodium potassium tartrate solution (5 mL) was added and the reaction mixture was allowed to warm to rt and stir for an additional 2 h. The mixture was then diluted with CH_2Cl_2 (10 mL) and washed with H_2O (2 x 10 mL). The combined aqueous phases were washed with CH_2Cl_2 (2 x 10 mL) and the combined organic layers were washed with brine (15 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo.* Purification of the crude product by flash chromatography (hexanes-EtOAc, 5:1) afforded diol **216** (230 mg, 0.50 mmol, 73%) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.38 (m, 1H), 5.68 (dt, *J* = 1.2, 14.1 Hz, 1H), 4.18 (m, 1H), 4.03 – 3.94 (m, 3H), 3.88 (m, 1H), 3.57 (ddd, *J* = 3.2, 6.0, 8.3 Hz, 1H), 3.46 (d, *J* = 6.5 Hz, 1H), 3.34 (d, *J* = 4.1 Hz, 1H), 2.87 (dddd, *J* = 1.6, 3.4, 6.3, 15.3 Hz, 1H), 2.53 (m, 1H), 2.29 (ddd, *J* = 5.3, 9.5, 13.5 Hz, 1H), 1.93 (ddd, *J* = 2.6, 10.1, 14.5 Hz, 1H), 1.83 (ddd, *J* = 2.6, 7.1, 14.5 Hz, 1H), 1.80 (ddd, *J* = 1.2, 4.1, 13.8 Hz, 1H), 1.70 – 1.54 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H), 0.90 (s, 9H), 0.13 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.0, 132.3, 85.5, 80.1, 72.5, 72.5, 71.0, 65.7, 38.4, 37.0, 35.8, 25.8, 22.2, 18.1, 10.8, 0.12, -4.6, -5.1.

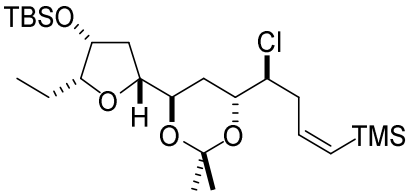
HRMS: *m/z* calcd for $C_{22}H_{45}ClO_4Si_2$: 465.2618 (M+H); Found: 465.2608 (M+H).

IR (neat): 3443, 2957, 2900, 1407, 1251, 1066, 837, 775 cm^{-1}.

$[\alpha]_D^{20}$ = -15.2 (*c* 0.8 in $CHCl_3$).

Assignment of the relative stereochemistry for diol 216

Preparation of acetonide 264



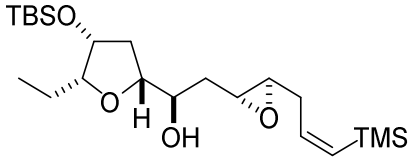
264

To a solution of diol **216** (5 mg, 0.011 mmol) at rt in acetone (0.5 mL) was added dimethoxypropane (0.039 mL, 0.32 mmol) and camphorsulfonic acid (1.3 mg, 0.0050 mmol). The reaction mixture was stirred for 4 h then treated with triethylamine (0.006 mL, 0.044 mmol). The resulting mixture was concentrated *in vacuo.* Purification of the crude product by flash chromatography (hexanes-EtOAc, 20:1) afforded the acetonide **264**. In the ^{13}C NMR spectrum recorded on acetonide **264**, the two methyl groups of the acetonide function resonate at δ = 24.5 and 24.2 ppm, indicating the relative stereochemistry of the two alcohol functions in the diol **216** is 1,3-*anti* as indicated.[131]

^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.37 (dt, *J* = 7.3, 13.5 Hz, 1H), 5.68 (dt, *J* = 1.4, 14.1 Hz, 1H), 4.26 (m, 1H), 3.92 (m, 1H), 3.87-3.81 (m, 2H), 3.77 (m, 1H), 3.63 (m, 1H), 2.80 (dddd, *J* = 1.5, 3.5, 6.9, 15.3 Hz, 1H), 2.43 (m, 1H), 2.16 (m, 1H), 1.80-1.59 (m, 5H) 1.38 (s, 3H), 1.37 (s, 3H), 0.93 (t, *J* = 7.8 Hz, 3H), 0.90 (s, 9H), 0.12 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 143.1, 132.5, 84.8, 79.1, 72.0, 70.0, 69.2, 64.7, 37.5, 36.9, 32.3, 25.8, 24.5,24.2, 22.6, 10.5, 0.07, -4.4, -5.2.

Preparation of epoxide 265

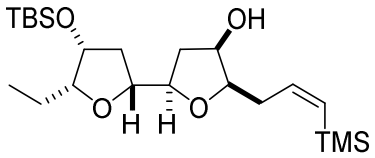


265

To a cold (0 °C), stirred solution of diol **216** (10 mg, 0.022 mmol) in EtOH (0.2 mL) was added an aqueous solution of sodium hydroxide (0.013 mL, 0.026 mmol, 2N) and the reaction mixture was stirred for 30 min. The reaction mixture was then diluted with EtOAc (0.5 ml) and was washed with H_2O (2 x 0.5 mL) and brine (0.5 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*.. Purification of the crude product by flash chromatography (hexanes-EtOAc, 5:1) afforded the epoxide **265**. In the ^{1}H NMR spectrum recorded on epoxide **265**, the observed coupling constants between the two resonances corresponding to the epoxide protons at δ = 2.91 and 2.78 was 2.4 Hz consistent with that of a *trans* epoxide.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.32 (dt, *J* = 7.4, 14.1 Hz, 1H),5.65 (dt, *J* = 1.3, 14.1 Hz, 1H), 4.19 (m, 1H), 3.92 (m, 1H), 3.74 (m, 1H), 3.56 (ddd, *J* = 3.3, 6.2, 7.3 Hz, 1H), 3.03 (d, *J* = 4.8 Hz, 1H), 2.97 (ddd, *J* = 2.4, 4.2, 6.9 Hz, 1H), 2.77 (ddd, *J* = 2.4, 5.4, 7.8 Hz, 1H), 2.41 (m, 2H), 2.25 (ddd, *J* = 5.1, 9.1, 14.4 Hz, 2H), 1.89 (ddd, *J* = 4.4, 9.2, 14.1 Hz, 1H), 1.81 (ddd, *J* = 1.4, 4.3, 13.7 Hz, 1H), 1.68-1.52 (m, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

Preparation of the bistetrahydrofuran 266



266

To a cold (0 °C), stirred solution of diol **216** (220 mg, 0.44 mmol) in THF (5 mL) was added silver(I) oxide (220 mg, 0.96 mmol) and silver(I) trifluorosulfonate (190 mg, 0.75 mmol). The reaction mixture was sonicated and stirred for 12 h with the bath temperature eventually reaching 40 °C. The reaction mixture was then filtered through Celite® and diluted with EtOAc (5 mL). The mixture was washed with saturated $NaHCO_3$ solution (2 x 5 mL) and H_2O (2 x 5 mL). The combined aqueous phases were washed with EtOAc (2 x 10 mL) and the combined organic extracts were washed with brine (10 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 5:1) afforded **266** (110 mg, 0.26 mmol, 54 % ratio of *E*:*Z* isomers 6:1) as a colourless oil.

Data for **266** (only data for the major (*Z*) is listed): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.40 (td, *J* = 7.4, 14.0 Hz, 1H), 5.60 (td, *J* = 1.3, 14.0 Hz, 1H), 4.32 (dt, *J* = 5.4, 6.7 Hz, 1H), 4.07 (dt, *J* = 2.4, 10.3 Hz, 1H), 4.02 (m, 2H), 3.74 (ddd, *J* = 2.7, 7.2, 9.5 Hz, 1H), 3.67 (m, 1H), 3.62 (dt, *J* = 5.8, 7.2 Hz, 1H), 2.52 (m, 2H), 2.34 (m, 1H), 2.14-1.94 (m, 3H), 1.67-1.59 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.13 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.0, 131.1, 84.7, 84.3, 76.5, 72.8, 71.2, 37.8, 36.9, 33.3, 25.8, 22.4, 18.1, 10.9, 0.2, -4.6, -5.1.

HRMS: *m/z* calcd for $C_{22}H_{45}O_4Si_2$: 429.2851 (M+H); Found: 429.2851 (M+H).

IR (neat): 3432, 2953, 2894, 2857, 1462, 1407, 1248, 1097, 1052, 836 cm^{-1}.

$[\alpha]_D^{20}$ = -36.8 (*c* 0.9 in $CHCl_3$).

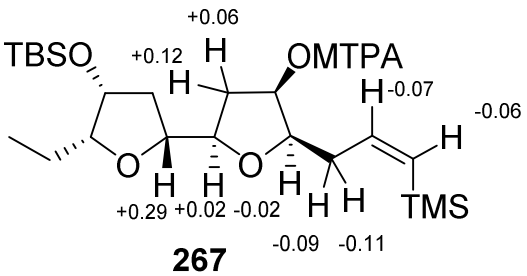
Assignment of the relative and absolute stereochemistry for the bistetrahydrofuran 266

To a cold (0 °C), stirred solution of tetrahydrofuran **266** (3.0 mg, 0.007 mmol) in dry CH_2Cl_2 (0.2 mL) was added (*S*)-(-)-MTPA-OH (2.5 mg, 0.011 mmol), *N,N'*-diisopropylcarbodiimide (0.0033 mL, 0.021 mmol) and dimethylaminopyridine (catalytic). The reaction mixture was stirred for 24 h then the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 7:1) afforded the (*S*)-MTPA ester of **266**.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53 (m, 2H), 7.39 (m, 3H), 6.15 (ddd, *J* = 6.4, 8.2, 14.0 Hz, 1H), 5.55 (dt, *J* = 1.2, 14.0 Hz, 1H), 5.39 (m, 1H), 4.19 (m, 1H), 3.97 (m, 1H), 3.76 (m, 2H), 3.56 (m, 1H), 3.53 (s, 3H), 2.52 (m, 2H), 2.31 (m, 1H), 2.13 (ddd, *J* = 5.9, 8.3, 13.8 Hz, 1H), 1.66 (m, 2H), 1.59 (ddd, *J* = 1.7, 6.9, 14.4 Hz, 1H), 1.46 (ddd, *J* = 2.4, 6.5, 13.4 Hz, 1H), 0.93 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

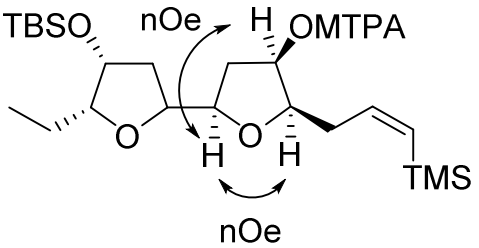
In an analogous manner, the (*R*)-MTPA ester was prepared using (*R*)-(-)-MTPA-OH.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 (m, 2H), 7.40 (m, 3H), 6.22 (ddd, *J* = 6.4, 8.2, 14.0 Hz, 1H), 5.61 (dt, *J* = 1.2, 14.0 Hz, 1H), 5.39 (m, 1H), 4.12 (m, 1H), 3.94 (ddd, *J* = 7.0, 8.9, 8.9 Hz, 1H), 3.78 (ddd, *J* = 3.5, 7.0, 7.0 Hz, 1H), 3.53 (s, 3H), 3.49-3.45 (m, 2H), 2.61 (m, 1H), 2.46 (m, 1H), 2.40 (m, 1H), 1.95 (ddd, *J* = 6.0, 7.9, 14.0 Hz, 1H), 1.63 (m, 2H), 1.47 (ddd, *J* = 1.1, 6.0, 14.7 Hz, 1H), 1.34 (ddd, *J* = 2.3, 6.4, 13.2 Hz, 1H), 0.90 (t, *J* = 7.9 Hz, 3H), 0.87 (s, 9H), 0.08 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).



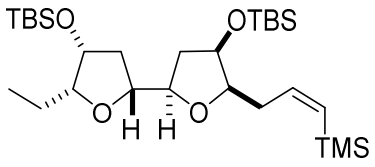
267

Difference δS - δR



Key nOe correlations

Preparation of the TBS protected bistetrahydrofuran 217



217

To a cold (0 °C), stirred solution of **266** (20.0 mg, 0.047 mmol) in CH_2Cl_2 (1 mL) was added 2,6-lutidine (0.009 mL, 0.071 mmol) and *tert*-butyldimethylsilyl triflate (0.013 mL, 0.056 mmol). The reaction mixture was stirred at 0 °C for 2 h and then quenched by the addition of H_2O (1 mL). The layers were separated and the organic layer was washed with H_2O (1 x 1 mL) and brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 15:1) afforded the product **217** (21.0 mg, 0.038 mmol, 81%, ratio of *Z:E* isomers 6:1) as a colourless oil.

Data for **217** (only data for the major (*Z*) is listed): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.40 (dt, *J* = 7.5, 14.0 Hz, 1H), 5.56 (dt, *J* = 1.5, 14.0 Hz, 1H), 4.22 (m, 2H), 3.94 (m, 2H), 3.67 (m, 1H), 3.56 (dt, *J* = 3.9, 6.6 Hz, 1H), 2.57 – 2.39 (m, 2H), 2.19 (m, 2H), 1.66 (m, 2H), 1.51 (m, 2H), 0.93 (t, *J* = 7.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.10 (s, 9H), 0.05 (s, 6H), 0.04 (s, 6H).

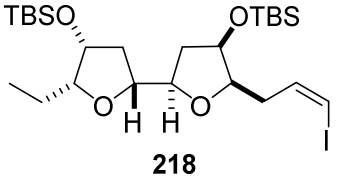
^{13}C NMR (150 MHz, $CDCl_3$) δ: 145.6, 130.7, 85.3, 83.6, 80.8, 80.5, 72.5, 72.2, 38.6, 38.5, 33.6, 25.8, 22.3, 18.0, 10.7, 0.1, -4.5, -4.5, -5.0, -5.1.

HRMS: *m/z* calcd for $C_{28}H_{58}O_4Si_3$: 565.3560 (M+Na); Found: 565.3535 (M+Na).

IR (neat): 2956, 2928, 2901, 1471, 1393, 1254, 1065, 835, 774 cm^{-1}.

$[\alpha]_D^{20}$ = -48.8 (*c* 0.25 in $CHCl_3$).

Preparation of the vinyl iodide 218



218

To a solution of **217** (16.4 mg, 0.030 mmol) in MeCN (1 mL) was added N-iodosuccinimide (13.0 mg, 0.048 mmol) and the resulting solution was stirred for 14 h. The reaction mixture was then quenched by the addition of saturated $Na_2S_2O_3$ solution (1 mL) and the resulting solution was stirred until it turned colourless (approx. 5 min). EtOAc (2 mL) was then added and the mixture was washed with H_2O (2 x 1 mL). The combined aqueous phases were washed with EtOAc (2 mL) and the combined organic layers were washed with brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 10:1) afforded the product **218** (12.7 mg, 0.021 mmol, 70 %, ratio of *Z*:*E* isomers = 2:1). Further purification isolated the (*Z*)-ene-yne (8.0 mg, 0.013 mmol).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.38 (dt, *J* = 6.5, 7.1 Hz, 1H), 6.24 (dt, *J* = 1.5, 7.1 Hz, 1H), 4.24 (m, 1H), 4.19 (m, 1H), 3.94 (m, 2H), 3.78 (m, 1H), 3.57 (dt, *J* = 3.8, 6.7, 1H), 2.51 – 2.39 (m, 2H), 2.2 (m, 2H), 1.67 (m, 2H), 1.51 (m, 2H), 0.92 (t, *J* = 7.7 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 6H).

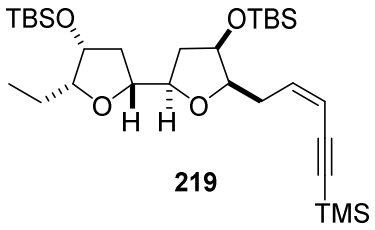
^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.2, 85.8, 83.8, 82.1, 81.2, 80.9, 73.0, 72.5, 39.0, 38.7, 36.1, 26.2, 26.1, 22.6, 11.1, -4.1, -4.2, -4.6, -4.7.

HRMS: *m/z* calcd for $C_{25}H_{49}IO_4Si_2$: 619.2106 (M+Na); Found: 619.2120 (M+Na).

IR (neat): 2956, 2929, 2899, 2858, 1472, 1249, 1065, 835, 774 cm^{-1}.

$[\alpha]_D^{20}$ = -14.4 (*c* 0.4 in $CHCl_3$).

Preparation of the ene-yne 219



219

To a cold (0 °C), stirred solution of $Pd(PPh_3)_4$ (catalytic) and CuI (catalytic) in THF (1 mL) was added triethylamine (0.019 mL, 0.14 mmol). A solution of the vinyl iodide **218** (8.0 mg, 0.013 mmol) in THF (0.3 mL) was then added dropwise followed by. trimethylsilylacetylene (0.020 mL, 0.14 mmol) and the reaction mixture was stirred for 14 h at rt. The solvent was then removed *in vacuo.* . Purification of the crude product by flash chromatography (hexanes-EtOAc, 10:1) afforded the ene-yne product **219** (7.0 mg, 0.012 mmol, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.12 (m, 1H), 5.52 (dt, *J* = 1.5, 11.0 Hz, 1H), 4.24 (m, 1H), 4.21 (m, 1H), 3.93 (m, 2H), 3.74 (m, 1H), 3.57 (dt, *J* = 4.0, 6.6 Hz, 1H), 2.66 (m, 2H), 2.20 (m, 2H), 1.67 (m, 2H), 1.51 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.18 (s, 9H), 0.064 (s, 3H), 0.058 (s, 3H), 0.044 (s, 6H).

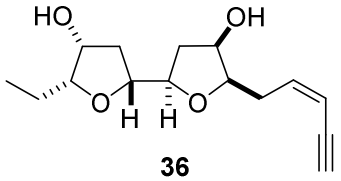
^{13}C NMR (150 MHz, $CDCl_3$) δ: 142.5, 110.0, 102.1, 98.9, 85.4, 82.6, 81.0, 80.7, 72.7, 72.2, 38.7, 31.2, 29.7, 25.8, 25.8, 22.3, 10.7, 0.1, -4.5,-4.6 -4.9, -5.1.

HRMS: *m/z* calcd for $C_{30}H_{58}O_4Si_3$: 589.3535 (M+Na); Found: 589.3566 (M+Na).

IR (neat): 2958, 2903, 1396, 1249, 1066, 842, 779 cm^{-1}.

$[\alpha]_D^{20}$ = -5.4 (*c* 0.1 in $CHCl_3$).

Preparation of the bistetrahydrofurandiol 36



36

To a cold (0 °C), stirred solution of **219** (6.4 mg, 0.011 mmol) in THF (0.3 mL) was added tetrabutylammonium fluoride solution (0.045 mL, 0.045 mmol, 1M in THF) and the solution was stirred for an additional 12 h. EtOAc (1 mL) was then added and the organic layer was removed and washed with H_2O (2 x 0.5 mL). The aqueous phases were washed with EtOAc (2 x 0.5 mL) and the combined organic layers were washed brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 1:3) afforded the product **36** (2.2 mg, 0.007 mmol, 75 %) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.09 (td, *J* = 7.7, 10.9 Hz, 1H), 5.57 (m, 1H), 4.30 (d, *J* = 11.5 Hz, 1H), 4.14 (m, 2H), 4.03 – 3.98 (m, 3H), 3.80 (ddd, *J* = 2.3, 6.8, 8.1 Hz, 1H), 3.65 (dt, *J* = 1.7, 7.0 Hz, 1H), 3.11 (d, *J* = 1.96, 1H), 2.83 (m, 1H), 2.71 (m, 1H), 2.39 (m, 2H), 2.03 (ddd, *J* = 2.3, 7.9, 14.2 Hz, 2H), 1.77 (m, 2H), 0.98 (t, *J* = 7.62, 3H).

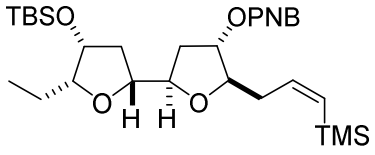
^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.8, 110.6, 86.9, 84.2, 82.3, 79.9, 79.3, 78.9, 71.1, 70.7, 37.6, 37.5, 29.9, 29.7, 21.7, 10.4.

HRMS: *m/z* calcd for $C_{15}H_{22}O_4$: 267.1589 (M+H); Found: 267.1592 (M+H).

IR (neat): 3414, 2968, 1455, 1393, 1250, 1066, 1049 cm^{-1}.

$[\alpha]_D^{20}$ = -23.9 (*c* 0.3 in $CHCl_3$).

Preparation of the bistetrahydrofuran 268



268

To a stirred solution of triphenylphosphine (73 mg, 0.28 mmol) in THF (0.5 mL) was added *para*-nitrobenzoic acid (47 mg, 0.28 mmol). The bifuran **266** (30 mg, 0.070 mmol) was then added as a solution in THF (0.5 mL) and the reaction mixture cooled to 0 °C. Diisopropyl azodicarboxylate (0.054 mL, 0.28 mmol) was added and the reaction mixture stirred for 1 h. The solvent was then removed *in vacuo*. Purification of the crude

product by flash chromatography (hexanes-EtOAc, 10:1) afforded the product **268** (35 mg, 0.061 mmol, 87 % ratio of *Z:E* isomers 6:1*)* as a colourless oil.

Data for **268** (only data for the major (*Z*) is listed): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 8.7 Hz, 2H), 6.37 (td, *J* = 7.4, 14.0 Hz, 1H), 5.66 (td, *J* = 1.4, 14.0 Hz, 1H), 5.24 (m, 1H), 4.31 (m, 1H), 4.22 (m, 2H), 3.92 (m, 1H), 3.61 (dt, *J* = 6.6, 3.7 Hz, 1H), 2.63 – 2.41 (m, 2H), 2.25 (ddd, *J* = 5.6, 8.6, 13.5 Hz, 1H), 2.07 – 1.94 (m, 2H), 1.68 (m, 2H), 1.60 (ddd, *J* = 2.3, 5.6, 13.5 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.86 (s, 9H), 0.13 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

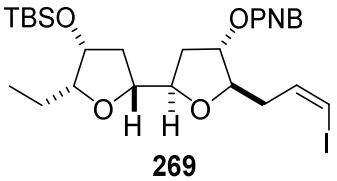
^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1, 150.7, 142.7, 135.3, 132.4, 130.7, 123.5, 85.6, 84.1, 81.5, 79.8, 79.2, 72.1, 38.3, 37.6, 34.8, 25.7, 22.3, 18, 10.8, 0.1, -4.5, -5.1.

HRMS: *m/z* calcd for $C_{29}H_{47}NO_7Si_2$: 600.2783 (M+Na); Found: 600.2781 (M+Na).

IR (neat): 2956, 2930, 2900, 2858, 1726, 1530, 1272, 1102, 1066, 836, 720 cm^{-1}.

$[\alpha]_D^{20}$ = +5.4 (*c* 0.7 in $CHCl_3$).

Preparation of the vinyl iodide 269



269

To a solution of **268** (26.0 mg, 0.045 mmol) in MeCN (1 mL) was added N-iodosuccinimide (20.0 mg, 0.090 mmol) and the resulting solution was stirred for 14 h. The reaction mixture was then quenched by the addition of saturated $Na_2S_2O_3$ solution (1 mL) and the resulting solution was stirred until it turned colourless (approx. 5 min). EtOAc (2 mL) was then added and the mixture was washed with H_2O (2 x 2 mL). The combined aqueous phases were washed with EtOAc (2 mL) and the combined organic layers were washed with brine (2 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography

(hexanes-EtOAc, 10:1) afforded the product **269** (20.0 mg, 0.032 mmol, 71 %, ratio of *Z*:*E* isomers = 2:1).

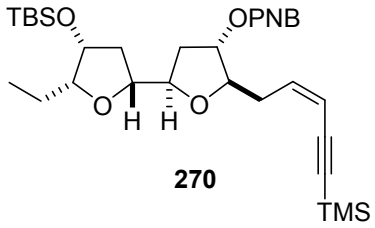
Data for **269** (only data for the major (*Z*) is listed): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 9.2 Hz, 2H), 8.19 (d, *J* = 9.2 Hz, 2H), 6.40-6.34 (m, 2H), 5.25 (m, 1H), 4.36-4.22 (m, 3H), 3.92 (m, 1H), 3.62 (dt, *J* = 3.8, 6.7 Hz, 1H), 2.61-2.44 (m, 2H), 2.26 (ddd, *J* = 5.6, 8.7, 13.8, 1H). 2.10-2.00 (m, 2H), 1.70-1.57 (m, 3H), 0.96 (t, *J* = 7.5 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.2, 150.8, 141.3, 136.8, 135.3, 130.9, 123.7, 85.6, 85.1, 83.0, 81.7, 79.9, 79.3, 72.1, 39.3, 38.3, 34.5, 25.7, 22.3, 10.8, -4.5, -5.1.

HRMS: *m/z* calcd for $C_{26}H_{38}INO_7Si$: 654.1354 (M+Na); Found: 654.1367 (M+Na).

IR (neat): 2968, 2927, 1725, 1528, 1393, 1272, 1066, 836, 719 cm^{-1}.

Preparation of the ene-yne 270



270

To a cold (0 °C), stirred solution of $Pd(PPh_3)_4$ (catalytic) and CuI (catalytic) in THF (1.5 mL) was added triethylamine (0.037 mL, 0.27 mmol). A solution of the vinyl iodide **269** (17.0 mg, 0.027 mmol) in THF (0.5 mL) was then added dropwise followed by. trimethylsilylacetylene (0.038 mL, 0.27 mmol) and the reaction mixture was stirred for 14 h at rt. The solvent was then removed *in vacuo.* . Purification of the crude product by flash chromatography (hexanes-EtOAc, 10:1) afforded the ene-yne product **270** (14.2 mg, 0.023 mmol, 86%, ratio of *Z:E* isomers 2:1). Further purification isolated the (*Z*)-ene-yne **270** (9.5 mg, 0.016 mmol) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 9.1 Hz, 2H), 8.18 (d *J* = 9.1 Hz, 2H), 6.08 (dt, *J* = 7.8, 10.7 Hz, 1H), 5.63 (dt, 1.3, 10.7 Hz, 1H), 5.30 (m, 1H), 4.31 (ddd, *J* =

5.5, 7.7, 10.8 Hz, 1H) , 4.27-4.21 (m, 2H), 3.91 (ddd, *J* = 5.6, 7.8, 8.6 Hz, 1H), 3.63 (dt, *J* = 3.8, 6.6 Hz, 1H), 2.77-2.64 (m, 2H), 2.24 (ddd, *J* = 5.6, 8.5, 13.6 Hz, 1H), 2.05 (ddd, *J* = 1.3, 5.7, 13.9 Hz, 1H), 1.98 (ddd, *J* = 5.9, 10.7, 13.5 Hz, 1H), 1.68 (m, 2H), 1.60 (ddd, *J* = 2.2, 5.4, 13.5, 1H), 0.95 (t, *J* = 7.6 Hz, 3H), 0.86 (s, 9H), 0.18 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

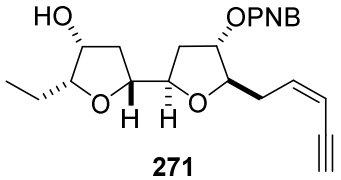
^{13}C NMR (150 MHz, $CDCl_3$) δ: 164.0, 150.7, 139.4, 135.3, 130.8, 123.5, 112.0, 101.5, 99.7, 85.6, 83.6, 81.8, 80.1, 79.4, 72.1, 38.4, 34.9, 34.8, 25.8, 22.4, 18.0, 10.8, -0.1, -4.5, -5.1.

HRMS: *m/z* calcd for $C_{31}H_{47}NO_7Si_2$: 624.2783 (M+Na); Found: 624.2774 (M+Na).

IR (neat): 2970, 2901, 1727, 1529, 1393, 1250, 1066, 842 cm^{-1}.

$[\alpha]_D^{20}$ = +46.1 (*c* 0.1 in $CHCl_3$).

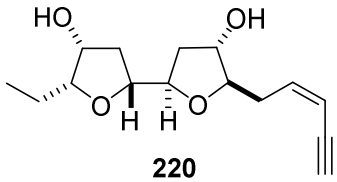
Preparation of the bistetrahydrofuranol 271



271

To a cold (0 °C), stirred solution of **270** (5.6 mg, 0.0093 mmol) in THF (0.3 mL) was added tetrabutylammonium fluoride solution (0.028 mL, 0.028 mmol, 1M in THF) and the solution was stirred for an additional 12 h. EtOAc (1 mL) was then added and the organic layer was removed and washed with H_2O (2 x 0.5 mL). The aqueous phases were washed with EtOAc (2 x 0.5 mL) and the combined organic layers were washed brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to give the crude product **271** which was used in the next step without purification.

Preparation of the bistetrahydrofurandiol 220



220

To a solution of bifuranol **271** in MeOH (0.3 mL) at rt was added aqueous NaOH solution (0.05 mL, 0.05 mmol, 1N) and the resulting mixture was stirred for 1 h. Following this, a saturated aqueous solution of NH_4Cl (0.2 mL) was added followed by dilution with EtOAc (1 mL). The organic layer was washed with H_2O (2 x 0.5 mL) and the combined aqueous layers were washed with EtOAc (2 x 0.5 mL). The combined organic layers were then washed with brine (1 mL), dried ($MgSO_4$) and filtered, and the solvent removed *in vacuo*. Purification of the crude product by flash chromatography (hexanes-EtOAc, 1:2) afforded the product **220** (2.1 mg, 0.0079 mmol, 85% over two steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.09 (ddt, *J* = 0.8, 7.0, 10.9 Hz, 1H), 5.60 (ddt, *J* = 1.4, 2.3, 10.9 Hz, 1H), 4.23 (m, 1H), 4.18 (ddd, *J* = 1.3, 6.3, 9.4 Hz, 1H), 4.08 (ddd, *J* = 1.3, 2.4, 10.4 Hz, 1H), 3.99 (ddd, *J* = 2.4, 5.1, 11.4 Hz, 1H), 3.95 (dt, *J* = 2.9, 6.7 Hz, 1H), 3.87 (d, *J* = 11.4 Hz, 1H), 3.59 (dt, *J* = 2.5, 7.0 Hz, 1H), 3.12 (dd, *J* = 0.8, 2.3 Hz, 1H), 2.72-2.54 (m, 2H), 2.39 (ddd, *J* = 5.3, 10.5, 13.9 Hz, 1H), 2.29 (ddd, *J* = 5.7, 9.3, 13.7 Hz, 1H), 1.99 (dd, *J* = 2.5, 13.9 Hz, 1H), 1.84 (ddd, *J* = 2.8, 6.3, 13.1 Hz, 1H), 1.72-1.61 (m, 3H), 0.97 (t, *J* = 7.4 Hz, 3H).

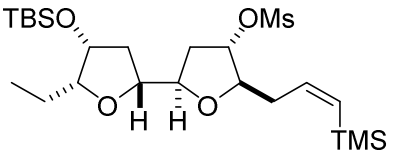
^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.2, 110.0, 86.0, 85.7, 82.4, 82.4, 80.5, 76.4, 75.5, 70.9, 38.1, 35.8, 34.6, 22.1, 10.5.

HRMS: *m/z* calcd for $C_{15}H_{22}O_4$: 267.1591 (M+H); Found: 267.1592 (M+H).

IR (neat): 2409, 3301, 2968, 2903, 1394, 1066, 1128, 1031 cm^{-1}.

$[\alpha]_D^{20}$ = -10.7 (*c* 0.3 in $CHCl_3$).

Preparation of mesylate 236



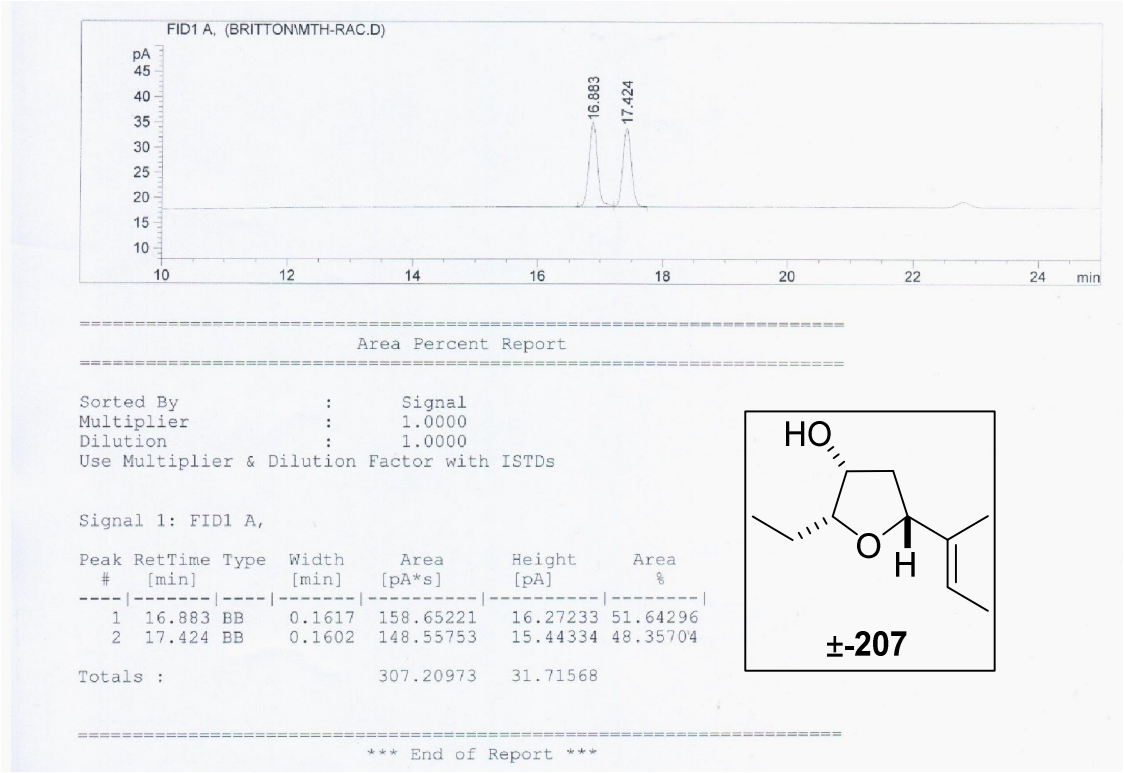
236

To a stirred solution of bistetrahydrofuran **235** (7 mg, 0.016 mmol) in pyridine (0.4 mL) was added DMAP (catalytic amount) and MsCl (0.004 mL, 0.048 mmol) and the reaction mixture was stirred at room temperature for 16 hours. CH_2Cl_2 (1 mL) was then added and the mixture was washed with H_2O (2 x 1 mL). The combined aqueous phases were washed with CH_2Cl_2 (1 mL) and the combined organic layers were washed with brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (15% EtOAc in hexanes) afforded the mesylate **236** (6.1 mg, 0.012 mmol, 75 %) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.35 (ddd, *J* = 7.9, 7.9, 13.2 Hz, 1H), 5.70 (dt, *J* = 1.7, 13.2 Hz, 1H), 4.97 (ddd, *J* = 2.6, 2.6, 5.2 Hz, 1H), 4.24 (m, 1H), 4.20 (m, 1H), 4.12 (ddd, *J* = 3.5, 6.1, 6.1 Hz, 1H), 3.9 (m, 1H), 3.59 (dt, *J* = 4.4, 10.5 Hz, 1H), 3.03 (s, 3H), 2.46 (m, 2H), 2.26 (m, 2H), 1.77 (ddd, *J* = 0.8, 5.2, 14.1 Hz, 1H), 1.64 (m, 2H), 0.97 (t, *J* = 7.1 Hz, 3H), 0.93 (s, 9H), 0.16 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).

HRMS: *m/z* calcd for $C_{23}H_{47}O_6SSi_2$: 507.2626 (M+H); Found: 507.2664 (M+H).

Figure 2.19. HPLC traces for determination of enantiomeric excess for tetrahydrofuran 207



Area Percent Report

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Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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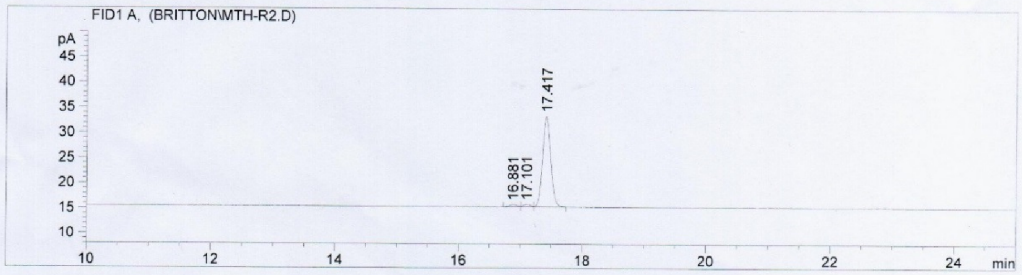
Totals :				307.20973	31.71568	

*** End of Report ***

±-207



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Area Percent Report

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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

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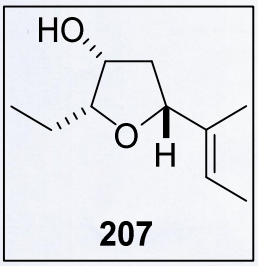
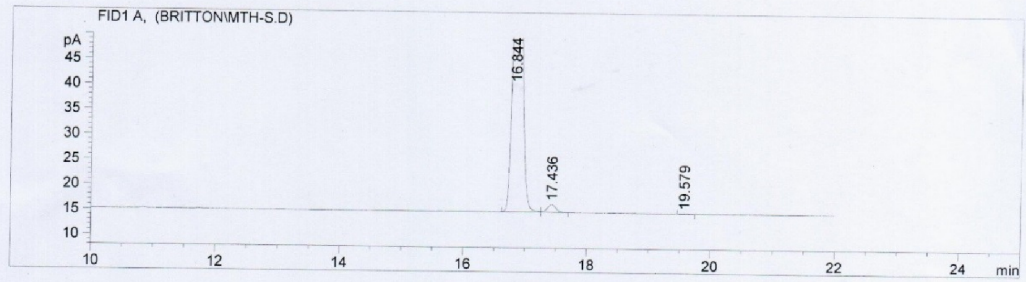
2	17.101	VV	0.0998	3.99380	4.76353e-1	2.30785
3	17.417	VB	0.1143	165.23602	17.97041	95.48286

Totals : 173.05307 18.87997



207



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Area Percent Report

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Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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2	17.436	BB	0.1257	15.19137	1.54565	2.02016
3	19.579	BB	0.1075	6.65074e-1	7.49640e-2	0.08844

Totals : 751.98682 81.45203

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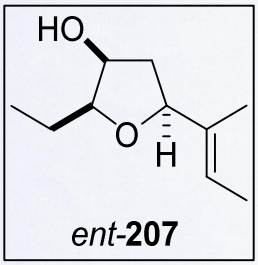
*** End of Report ***



ent-**207**

Chapter 3.

Studies Toward the Total Synthesis of Eleutherobin

3.1. Introduction

Cancer has become one of the leading causes of mortality worldwide and the WHO estimates that there were approximately 14 million new cases and 8.2 million cancer related deaths in 2012.[132] The number of new cases is expected to increase by 70% over the next 2 decades and the development of new oncology drugs is a high priority in the pharmaceutical industry.

3.1.1. Antimitotics as Chemotherapy Agents

Natural products have traditionally proven to be a rich source of novel chemotypes that interfere with cell division and mitosis. Due to the fact that cancer is often characterized by the uncontrolled proliferation of cells, drugs targeting cell division offer opportunities to disproportionately affect cancerous cells.[133] In particular, many antimitotic drugs work by binding to and interfering with microtubule dynamics.[134] Currently, the most well established antimitotics are Taxol® (**272**)[135] and the *Vinca* alkaloids (**33**, **34**)[136] (Figure 3.1). Taxol binds to a pocket located in the second globular domain in the beta-tubulin subunit and stabilizes the subsequent polymerization process while the *Vinca* alkaloids bind to a separate pocket and destabilize microtubules.[137] The interference of these compounds with the kinetics of the polymerization process lead to apoptosis of the dividing cell.[138]

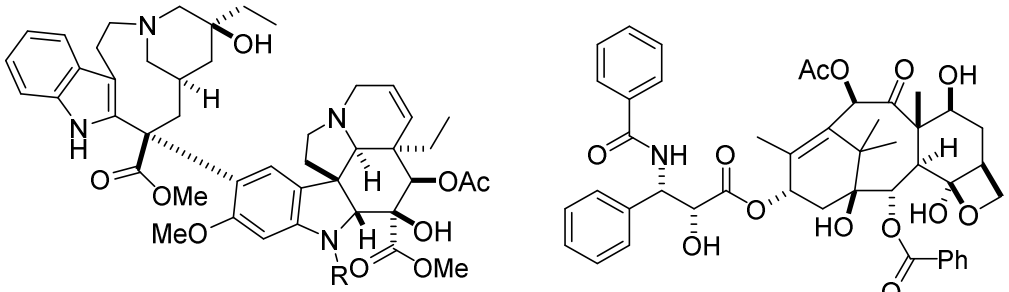


Figure 3.1. Antimitotic drugs used to treat cancer.

While these drugs have been used in the treatment of a variety of different cancers, there are two major factors that have limited their effectiveness.[133] Patient resistance to these drugs, in particular to Taxol,[139] is frequently observed and off-target toxicity is also a major concern, as the effect of these drugs on the function of healthy cells can lead to suppression of the immune system and neuropathy. As a result, the development of new antimitotic agents would afford clinicians more options for patients who respond poorly to current treatments.

3.1.2. Eleutherobin

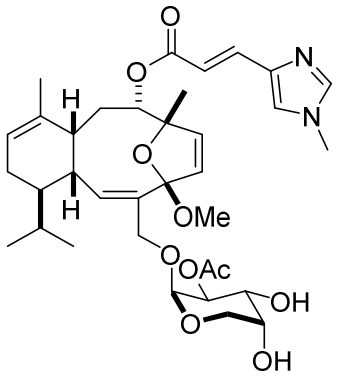
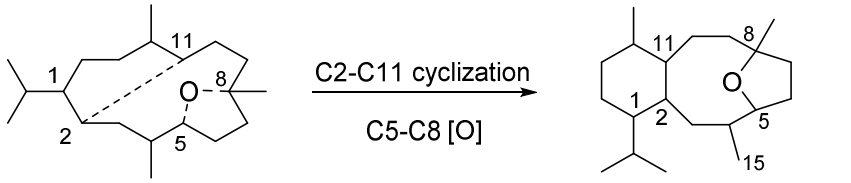


Figure 3.2. Structure of eleutherobin (40).

In 1997, eleutherobin (**40**) was reported from a rare *Eleutherobin sp.* soft-coral collected off the coast of Western Australia.[21,140] The structure was elucidated through a variety of 1D and 2D NMR experiments while the relative stereochemistry was

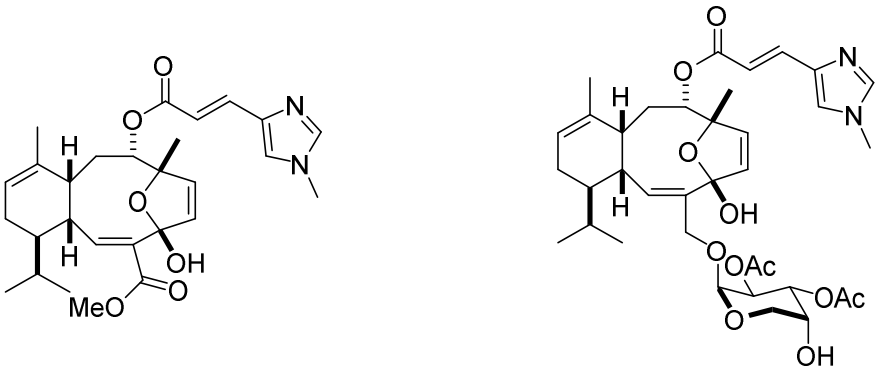
determined by extensive analysis of 1D NOESY experiments. The absolute stereochemistry was later established by total synthesis (*vide infra*).[141,142] The diterpenoid carbocyclic core contains a bicyclo[8.4.0]tetradecane skeleton (**274**) that is characteristic of the sarcodyctin family of natural products. The sarcodyctins are considered to derive from a cembrane intermediate (**273**) through a C2-C11 cyclization event followed by oxidative formation of an ether linkage between C5 and C8 (Figure 3.3).[143,144]



cembrane skeleton (**273**) sarcodyctin skeleton (**274**)

Figure 3.3. Proposed biogenesis for the sarcodyctin family (274).

While the sarcodyctin family is small, currently consisting of only 15 members, they have been shown to have interesting biological properties. Other members of the family include eleuthoside A (**276**) and sarcodyctin A (**275**) (Figure 3.4).[145,146] Structurally, these members are often differentiated by the appendages surrounding the skeletal core and on eleutherobin, these comprise of an *N*-methylurocanic ester at C8 and an acetylated D-arabinopyranose residue at C15.



sarcodyctin A (**275**) eleuthoside A (**276**)

Figure 3.4. Representative members of the sarcodyctin family of natural products.

When eleutherobin was assayed for biological activity, it demonstrated significant cytotoxic effects and inhibited the proliferation of a number of different cancer cell lines

(Table 3.1).[147] Comparisons with Taxol indicated that eleutherobin was nearly as potent as Taxol in both HCT116 and A2780 cancer cell lines. Importantly, when eleutherobin was screened against the Taxol resistant A2780/Tax22 cell line containing mutated tubulin, eleutherobin was found to have a 4.3-fold increase in IC_{50} value as opposed to the 13-fold increase seen for Taxol. This finding indicates that eleutherobin may have real clinical use for patients who have developed Taxol resistance. Eleutherobin was also shown to displace [^{3}H]Taxol with the same IC_{50} value as Taxol (2 μM) indicating that both compounds share a common binding site on tubulin and mode of action.

Table 3.1. ***In vitro*** **cytotoxicity of eleutherobin compared to Taxol.**

Compound	HCT116[a]	A2780[a]	A2780/Tax22[a]
Eleutherobin	10.7	13.7	59 (4.3)[b]
Taxol	4.6	6.7	90 (13.4)[b]

Note: a) IC_{50} values (nM); b) values in parentheses indicate n–fold resistance relative to parent cell line

While there have been efforts to explore the structure activity relationship (SAR) for eleutherobin,[148] the amount of material that could be accessed from the natural source (14 mg from several kilograms of dry coral) was insufficient for detailed SAR or *in vivo* studies.

3.2. Previous Syntheses of Eleutherobin

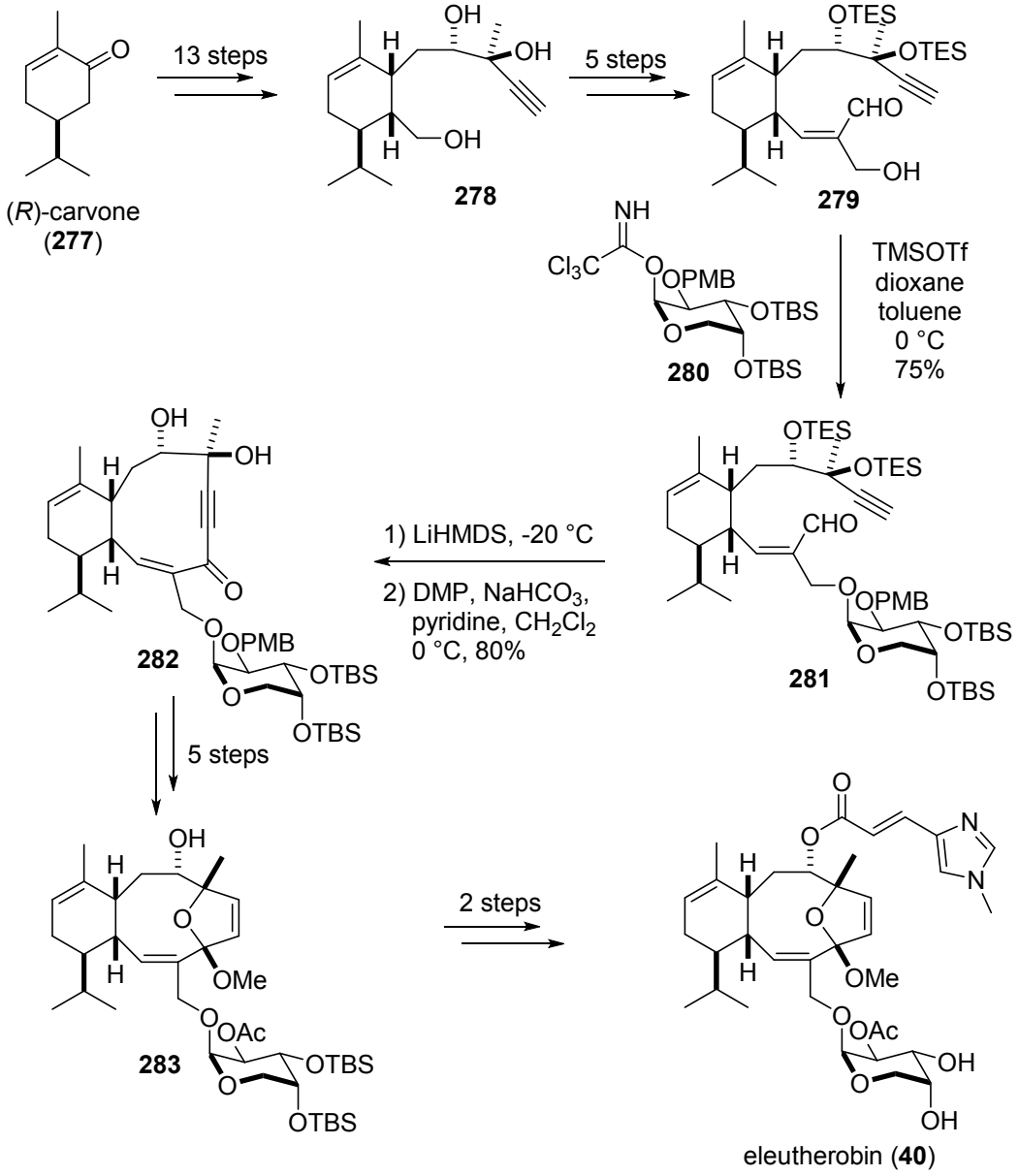
As a result of the interesting biological properties of eleutherobin, there has been significant interest from the synthetic community at achieving an efficient and scalable synthesis of this natural product. However, to date, there have only been two successful total syntheses of eleutherobin, reported by Nicolaou and Danishefsky, and one formal synthesis disclosed by Gennari. A brief discussion of each synthesis is contained hereafter.

3.2.1. Nicolaou's Total Synthesis of Eleutherobin

Nicolaou and co-workers carried out the first reported total synthesis of eleutherobin in 1997.[142,149,150] This synthesis utlilized carvone (**277**) as the original chiral building block which was converted this into alkyne **278** through a sequence involving

hydroxymethylation, Claisen rearrangement and subsequent organometallic additions to access the desired product in 13 steps (Scheme 3.1). Further functional group manipulations and a Knoevenagel condensation gave hydroxyaldehyde **279**. At this point, the D-arabinose unit was coupled with the primary alcohol on alkyne **279** by treatment of trichloroacetimidate **280** in the presence of TMSOTf to afford the β-anomer. The macrocycle was then closed by lithiation of the alkyne by LiHMDS and intramolecular nucleophilic attack on the aldehyde function in compound **281** followed by oxidation to give the 10 membered ring **282**. Subsequent protecting group manipulations and hydrogenation of the alkyne using Lindlar's catalyst gave acetal **283** which completed the synthesis of the carbon skeleton of eleutherobin. Completion of the synthesis by installing the *N*-methylurocanic ester and deprotection of the arabinose group gave 11 mg of eleutherobin (**40**) in 28 overall steps and <1% overall yield. This synthesis confirmed the relative and absolute chemistry of eleutherobin to be the same as that originally proposed by Fenical and co-workers. Nicolaou also adapted this apporach to the preparation of closely related compounds, eleuthosides A (**276**) and B.

Scheme 3.1. Nicolaou's total synthesis of eleutherobin (40).

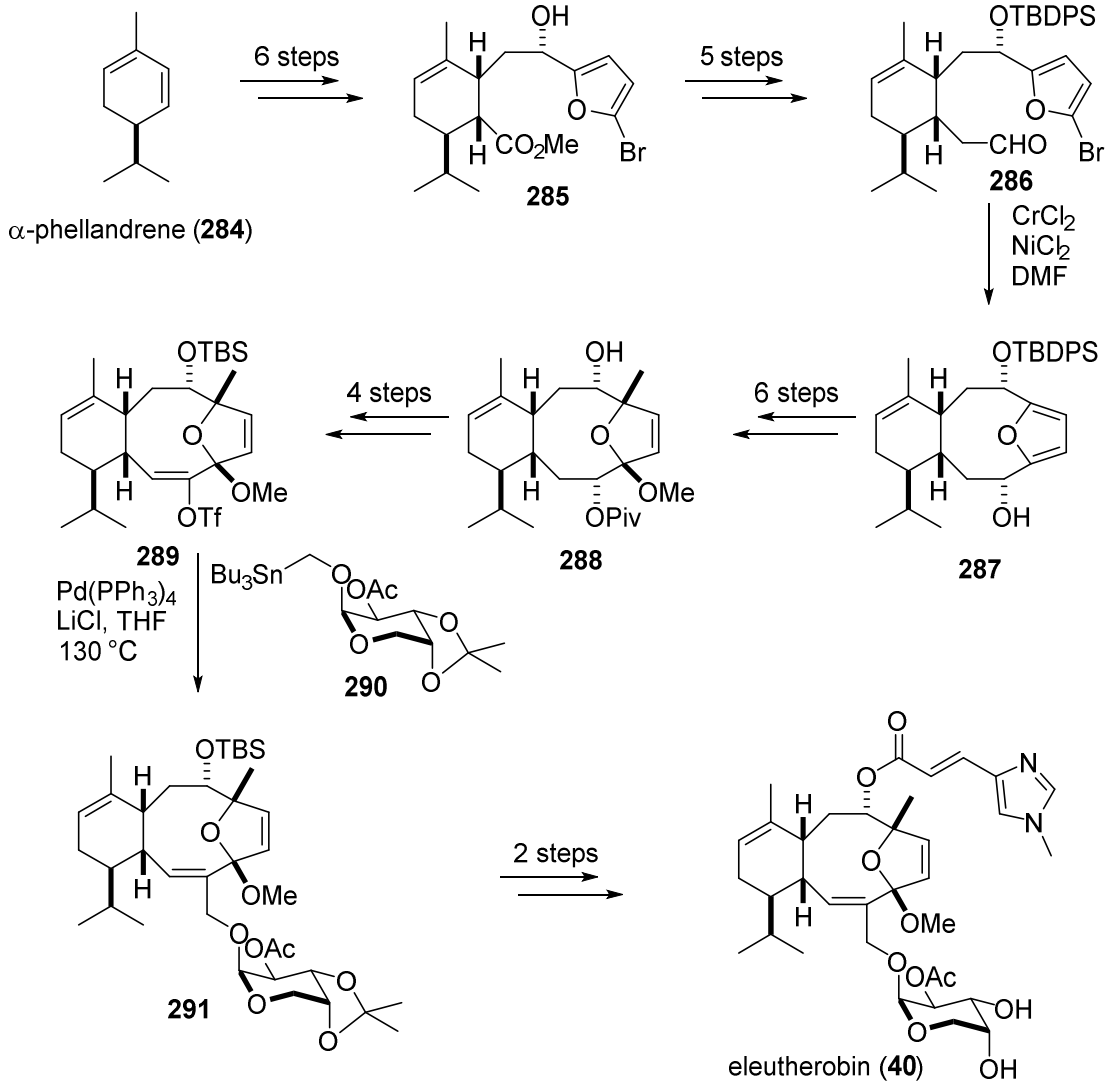


3.2.2. Danishefsky's Total Synthesis of Eleutherobin

Danishefsky and co-workers reported the second total synthesis of eleutherobin in 1997,[151,152] shortly after Nicolaou's report. This synthesis used the chiral terpene (*R*)-α-phellandrene (**284**) as the initial chiral building block, which was elaborated over 6 steps into bromofuran **285** (Scheme 3.2). A one carbon homologation and subsequent

protecting group manipulations gave macrocyclic precursor **288**. A subsequent NHK reaction using stoichiometric $NiCl_2$ gave the advanced intermediate **287** in good yield and diastereoselectivity. Hydroxyl directed DMDO oxidation of furan **287**, MeLi addition and an acid catalyzed ring contraction of intermediate **296** (Scheme 3.3) gave compound **288**, containing the structural core of eleutherobin. The pivaloyl group was then converted into vinyl triflate **289** which was subjected to an unusual sp^2-sp^3 Stille coupling with alkyl stannane **290** to afford the β-anomer of the D-arabinose unit. Completion of the synthesis by deprotection of the acetonide and installation of the *N*-methylurocanic ester gave 60 mg of eleutherobin in 25 steps with <1% overall yield.

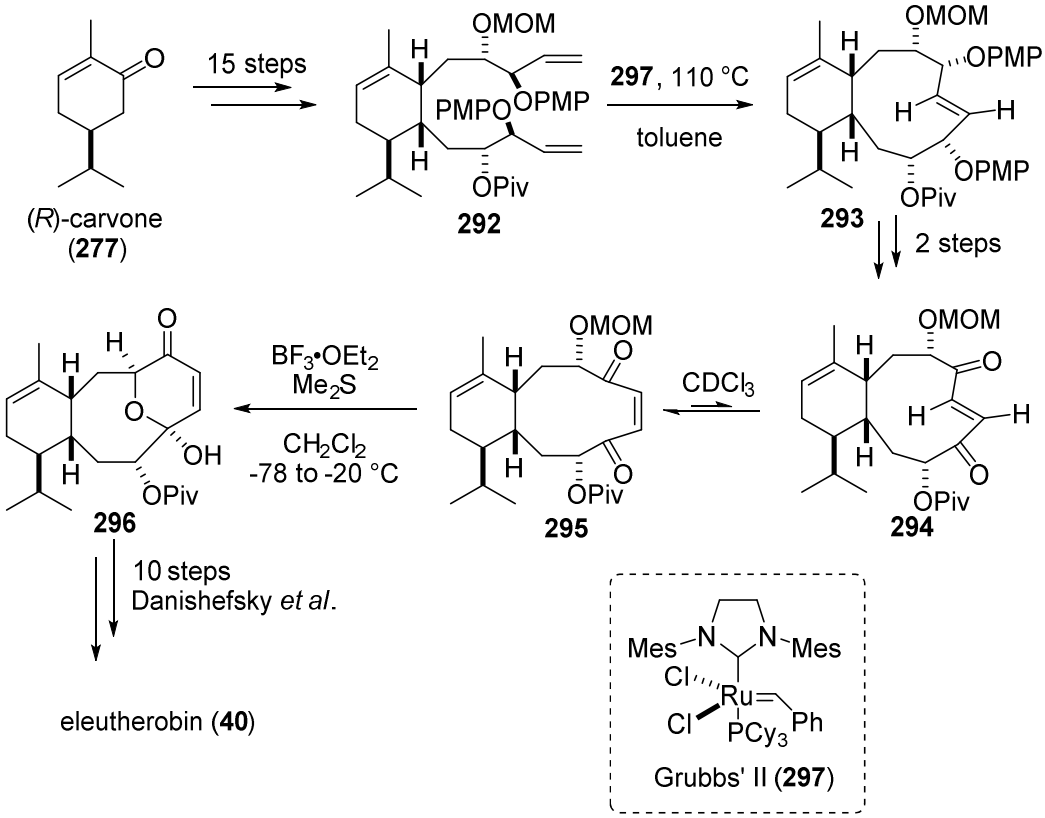
Scheme 3.2. Danishefsky's total synthesis of eleutherobin (40).



3.2.3. Gennari's Formal Synthesis of Eleutherobin (40)

Gennari and co-workers reported a formal synthesis of eleutherobin in 2005[153,154] that intercepted an intermediate in Danishefsky's total synthesis. Similar to Nicolaou, Gennari used (*R*)-carvone (**277**) as the chiral building block. Multiple stereoselective Hafner-Duthaler oxyallylations[155] enabled the synthesis of diene **292** in 15 steps. Ring closing metathesis using Grubbs' second generation catalyst afforded the (*E)*-macrocycle **293**. However, following protecting group removal and oxidation, the (*E*)-enedione **294** was readily isomerized to the (*Z)*-enedione **295**. Further functional group manipulations led to pyranose **296**, which is an advanced intermediate in Danishefsky's synthesis. In total, this synthesis required 20 steps from carvone to access intermediate **296** in 4% overall yield.

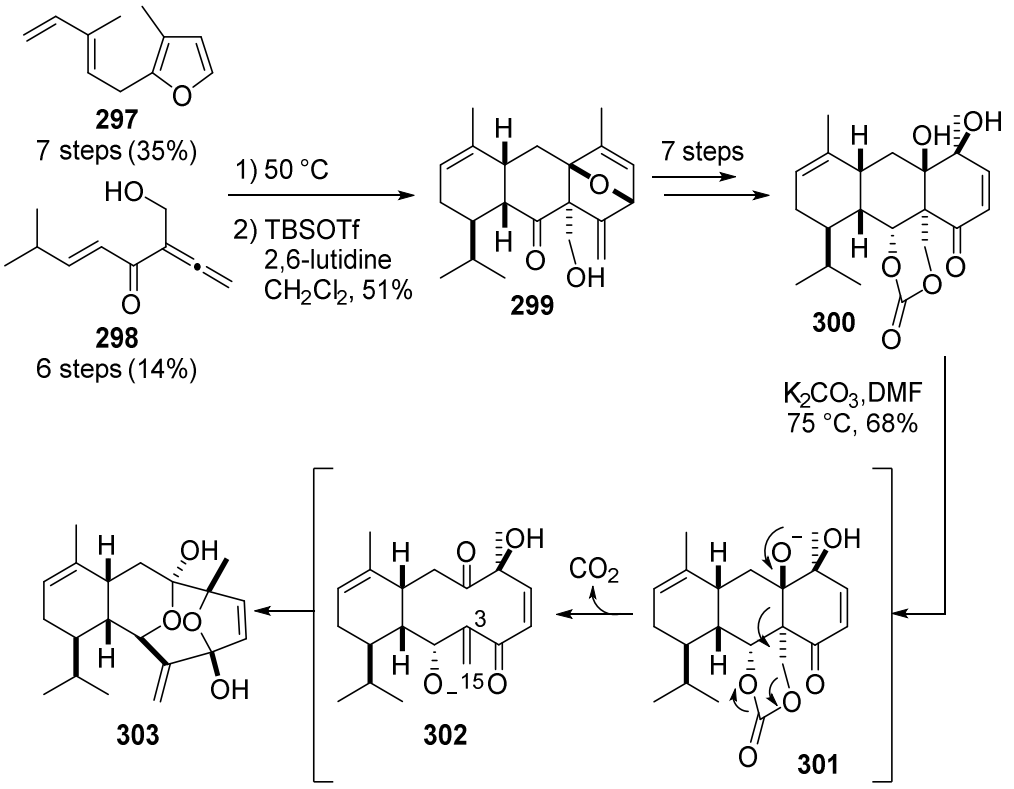
Scheme 3.3. Gennari's formal synthesis of eleutherobin.



3.2.4. Winkler's Approach to the Synthesis of Eleutherobin

In 2003, Winkler and co-workers reported their attempts to carry out the total synthesis of eleutherobin utilizing an interesting tandem Diels-Alder cycloaddition to form the core of the molecule.[156] Unfortunately, they were unable to complete the synthesis but their key Grob fragmentation inspired our synthetic efforts.[157] Winkler's synthesis began with the tandem Diels-Alder reaction between allene **298** and dienylfuran **297** to give racemic **299** after silyl protection. Subsequent derivatization to the carbonate **300** through a series of functional group manipulations and radical opening of the bicyclic ether was carried out in seven steps. Heating the carbonate **300** with potassium carbonate in DMF led to the formation of alkoxide **301** which then underwent the desired Grob fragmentation to break the C3-C8 bond but also led to simultaneous elimination of carbon dioxide to form intermediate **302**. This intermediate then underwent acetalization to give bishemiacetal **303** in 68% overall yield. The structure of hemiacetal **303** was confirmed by X-ray crystallography. Unfortunately, Winkler was unable to suppress the elimination of CO_2 and the formation of the undesired alkene between C3 and C15 and this route was eventually abandoned. However, the success of the Grob fragmentation demonstrated that a ring expansion strategy may well serve as a platform for the synthesis of eleutherobin.

Scheme 3.4. Winkler's approach to eleutherobin and undesired elimination of carbon dioxide during Grob fragmentation.



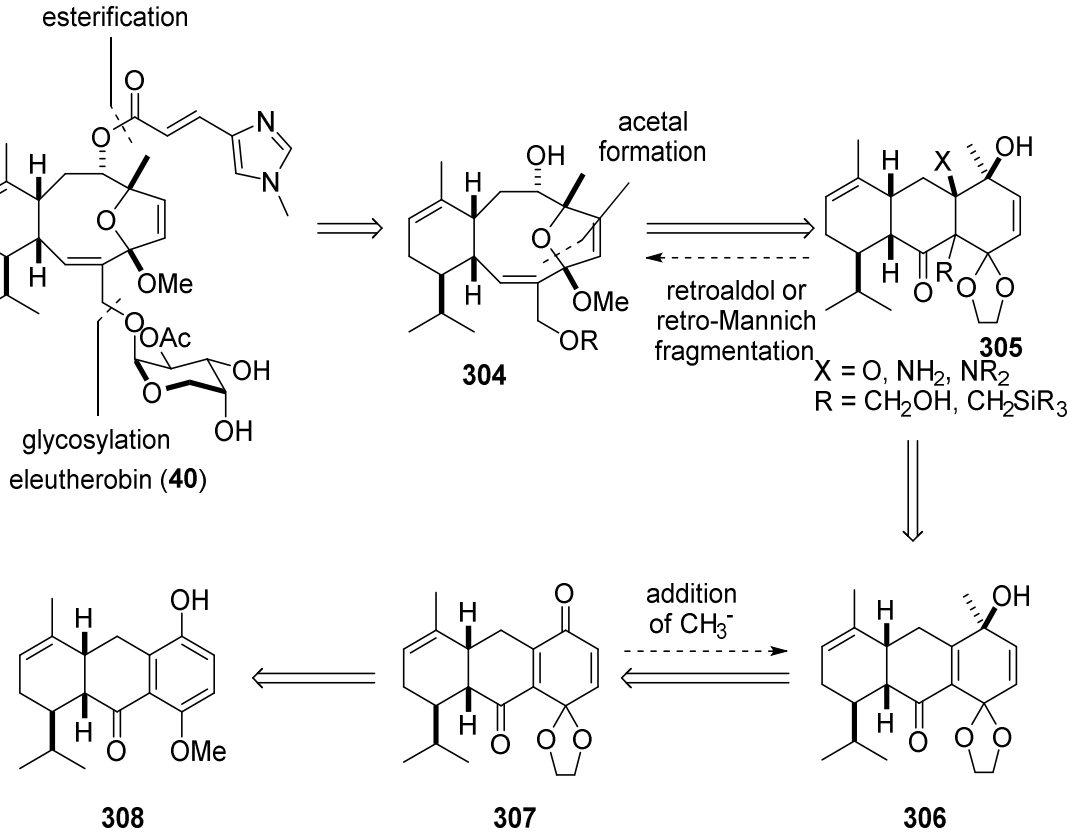
3.3. Previous Approaches in the Britton Group

While the previous syntheses of eleutherobin were successful in accessing the natural product, the overall length of these syntheses (25-35 steps) has hindered their application to the production of sufficient quantities of eleutherobin to advance preclinical trials. Since extraction of eleutherobin from natural sources also remains impractical, the development of a concise (≤15 steps) and economic synthesis of eleutherobin represents the best option to further explore its antimitotic properties.

The Britton group's original approach to eleutherobin focused on constructing the 10 membered macrocyclic core of eleutherobin by a fragmentation reaction. Scheme 3.5 details the proposed retrosynthesis where the installation of the *N*-methyl urocanic ester and D-arabinose units would take place following the construction of the core of eleutherobin (**304**). The macrocyclic core would arise from a retroaldol/Mannich reaction

that would effectively break the central C-C bond and be followed by followed by ketal deprotection and spontaneous acetal formation. Compound **305** would require the installation of a heteroatom (O or N) at C8 and a single carbon fragment at C3 of the tetrasubsitituted olefin in compound **306** to provide the precursor for the retroaldol/Mannich fragmentation. The tertiary alcohol in **306** could be synthesized *via* diastereoselective addition of a methyl nucleophile into ketone **307**. Ketone **307** could then be accessed by a hypervalent iodine mediated oxidative dearomatization reaction on tetralone **308**. In contrast to Winkler's racemic synthesis, tetralone **308** could be synthesized in an enantiomerically enriched form from (*R*)-α-phellandrene (**284**).

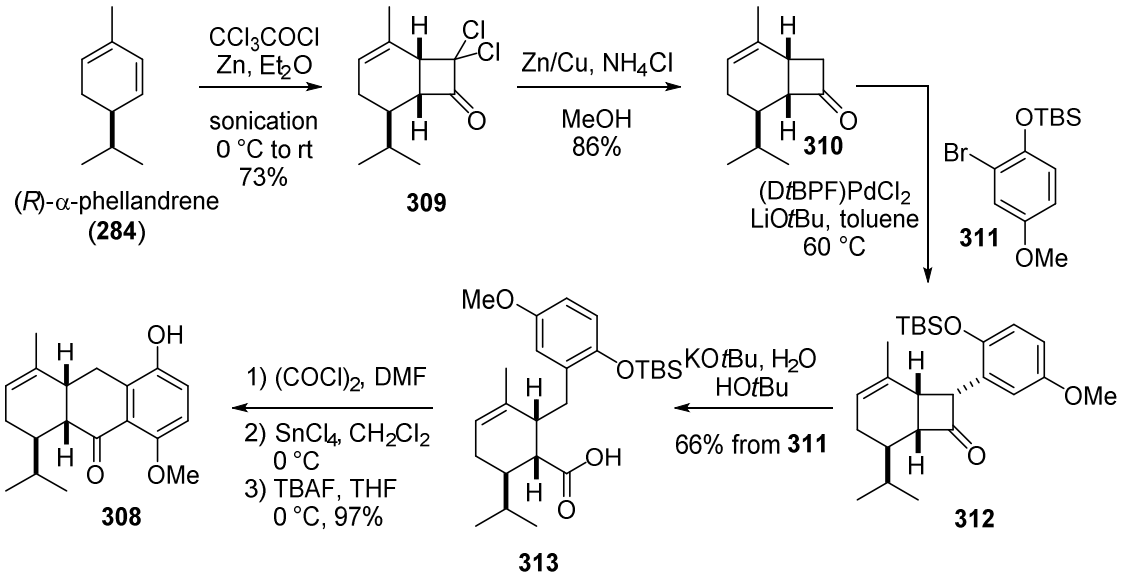
Scheme 3.5. Britton group's proposed retrosynthesis of eleutherobin.



The development of a synthesis of α-tetralones (e.g. **308**) was carried out by Dr. Jeffrey Mowat.[158] Dr. Mowat investigated several different strategies towards accessing **308** including an electrocyclization, Pd-catalyzed ring expansion of cyclobutanol and

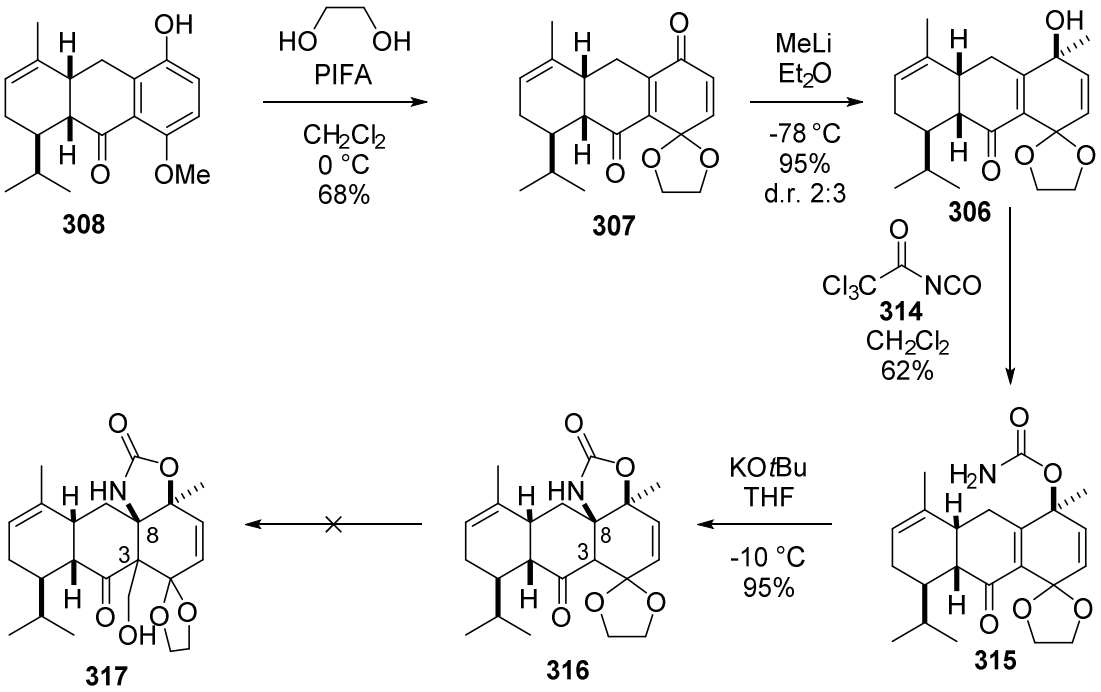
ketene [2+2] cycloaddition. Fortunately, an efficient and flexible synthesis that yielded access to a wide range of α-tetralones was eventually realized. As shown in Scheme 3.6, this sequence begins with the cycloaddition reaction between α-phellandrene (**384**) and the ketene generated from the reaction of trichloroacetylchloride with zinc to afford dichlorocyclobutanone **309**. Dechlorination of **309** by treatment with zinc-copper couple in the presence of ammonium chloride gave cyclobutanone **310**. Cyclobutanone **310** was also an intermediate in the synthesis of eleutherobin by Danishefsky and co-workers.[151] At this stage, the Pd-catalyzed α-arylation reaction between cyclobutanone **310** and aryl bromide **311** was investigated. Efforts using the conditions developed by Colacot and coworkers ((D*t*BPF)$PdCl_2$, KO*t*Bu, toluene, 115 °C)[159] gave only a 15% yield of α-aryl cyclobutanone **312** and further attempts to carry out this reaction led to variable and poor yields. While changes in temperature and solvent did not improve this result, the replacement of KO*t*Bu by LiOtBu as the base gave the α-arylcyclobutanone **312** in high yield. Haller-Bauer fragmentation[160,161] of **312** using KOtBu in the presence of water afforded the arylcarboxylic acid **313** in 66% yield over 2 steps from arylbromide **311**. An intramolecular Friedel-Crafts acylation sequence followed by silyl deprotection with TBAF afforded α-tetralone **308** in 97% yield over 3 steps.

Scheme 3.6. Synthesis of α-tetrolone (308) *via* a novel α-arylation/ring expansion sequence.



Having established an efficient synthesis of α-tetralones, Dr. Stanley Chang attempted to convert tetralone **308** into the precursor for the proposed retroaldol/Mannich fragmentation sequence.[162] His efforts towards this end goal are summarized in Scheme 3.7. Oxidative dearomatization of phenol **308** using [bis(trifluoroacetoxy)iodo]benzene (PIFA) and ethane-1,2-diol gave diene-dione **307** in good yield. Subsequent treatment with methyllithium gave tertiary alcohol **306** as a 2:3 mixture of diastereoisomers. The reaction of tertiary alcohol **306** with trichloroacetyl isocyanate (**314**)[163] gave carbamate **315**, which then underwent aza-Michael addition into the enone at C8 upon treatment with KO*t*Bu in tetrahydrofuran to give cyclic carbamate **316** in good yield. Despite Dr. Chang's success in reaching this intermediate, he was unable to further elaborate the skeleton by functionalization at C3 with a hydroxymethyl group (**317**). As a result, ultimately his efforts to access the precursor for the retro-Mannich reaction were unsuccessful and the effectiveness of the fragmentation strategy remained unknown. Nevertheless, the work up to this point included a novel and efficient synthetic approach to α-tetralones and had demonstrated that further elaboration of the scaffold of tetralone **308** was possible.

Scheme 3.7. Most advanced synthetic approach to eleutherobin by Britton and Chang.



3.4. Synthesis of α-Tetralones

Note: The work in this subchapter is the result of a collaboration with Dr. Jeffrey Mowat and Dr. Stanley Chang. Dr. Jeffrey Mowat originally developed this reaction and discovered the key role that lithium plays in this process, while Dr. Stanley Chang carried out the subsequent optimization and was responsible for preparing approximately half of the substrates present in Scheme 3.11 and Scheme 3.12.

3.4.1. Introduction to α-Tetralones

α-Tetralones (e.g. **325**) are important scaffolds and building blocks for medicinal chemistry. The synthesis of several drugs utilize α-tetralones as a key intermediate. For example, the synthetic route to the antidepressant drug sertraline hydrochloride (**318**) (Figure 3.5) relies on the reductive amination of an α-tetralone[164] while ABT-200 (**319**), another antidepressant, is also accessed from an α-tetralone.[165] Several other drugs incorporate α-tetralone derivatives as part of their pharmacophore, including the antibiotic tetracycline (**320**)[166,167] and the antiviral podophyllotoxin (**321**).[168] Several natural products also contain this structural motif including tetrahydroaltersolanol B (**322**),[169] crossogumerin C (**324**)[170] and vismione B (**323**).[171,172]

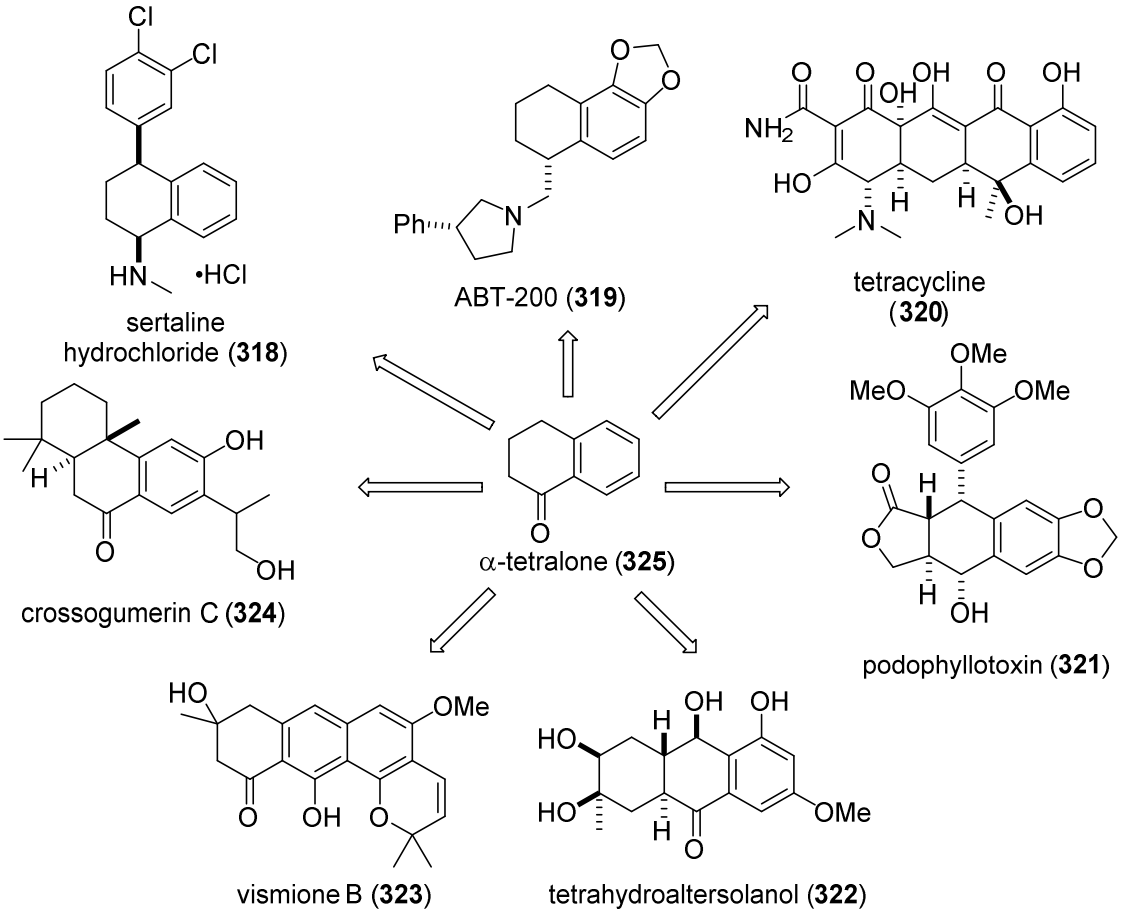
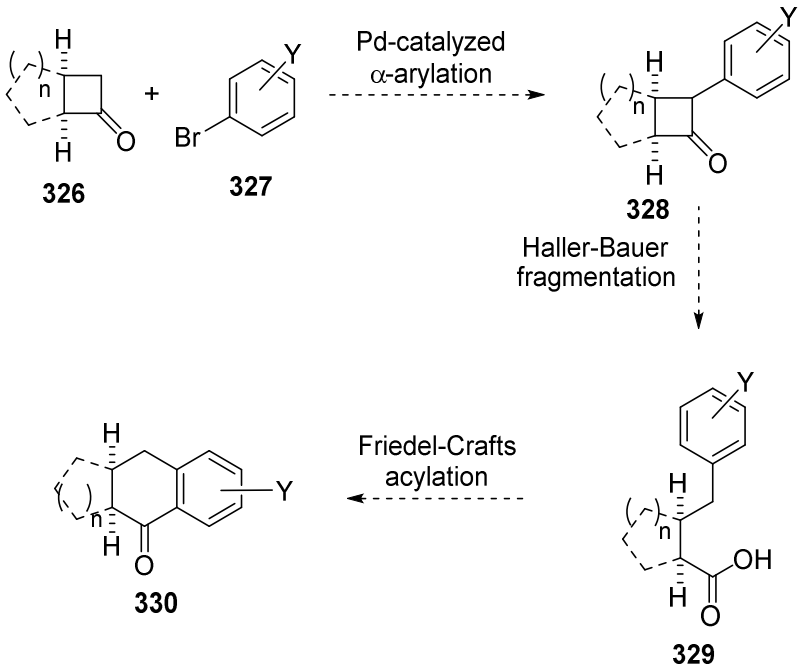


Figure 3.5. Examples of α-tetralone-containing drugs and natural products.

As a result of the broad utility of α-tetralone scaffolds, there have been a number of synthetic sequences developed to access these systems. These include the oxidation of tetrahydronapthalenes,[173] radical addition to arenes,[174] arene-siloxyalkyne carbocyclizations[175] and the Friedel-Craft reaction of 4-aryl butyrylchlorides.[176–179] However in spite of these efforts, the synthesis of densely functionalized or further annulated α-tetralones remains a challenge. Accordingly, we considered that the α-arylation/ring expansion sequence developed by Dr. Mowat (Scheme 3.6) could be adapted towards the synthesis of a wide range of α-tetralones. Our proposed reaction sequence is outlined in Scheme 3.8.

Scheme 3.8. Proposed synthesis of α-tetralones *via* an α-arylation/ring annulation sequence.

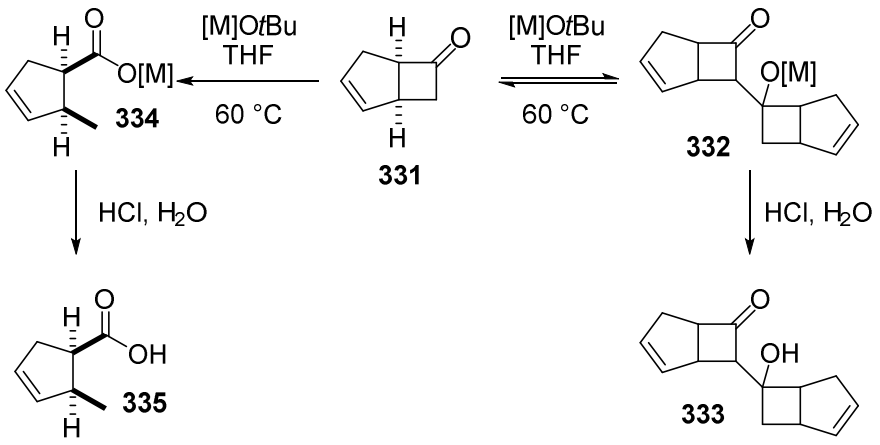


3.4.2. α-Arylation of Cyclobutanones

While Miura,[180] Buchwald,[181,182] Hartwig[183–185] and others[186–189] have demonstrated Pd-catalyzed α-arylation reactions on a wide range of substrates including acyclic ketones, cyclopenta-, cyclohexa- and cycloheptanones, the α-arylation of cyclobutanones had not been reported. As shown previously (Scheme 3.6), Dr. Jeffrey Mowat demonstrated the first example of an α-arylation reaction on a cyclobutanone using (D*t*BFP)$PdCl_2$ and LiO*t*Bu in THF to access this scaffold. Of particular note was the requirement for the counterion to be lithium rather than potassium in order to carry out the transformation in a reasonable yield. In order to determine the cause for this unusual counterion effect, we explored the reactions of cyclobutanone **331** with Li-, Na- and KO*t*Bu in THF. As summarized in Scheme 3.9, both NaO*t*Bu and KO*t*Bu promoted rapid and irreversible fragmentation of the cyclobutanone **331** to afford carboxylic acid **335** as the major product. Conversely, reaction of cyclobutanone **331** with LiO*t*Bu led to the rapid formation of diastereoisomeric aldol products **333** with little carboxylic acid **335** observed. However, after extended reaction times (90 mins), we observed the formation

of the carboxylic acid **335**, indicating that formation of the aldol product **332** is a reversible process. This result suggests that the aldol adducts serve to protect the cyclobutanone **331** from fragmentation while slowly generating the Li-enolate required for the α-arylation reaction *via* a retroaldol reaction.

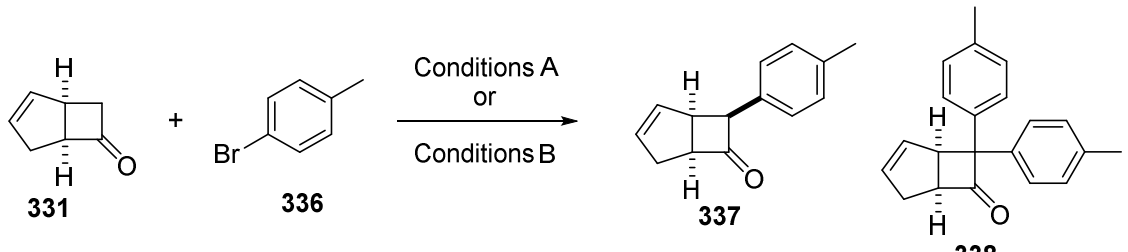
Scheme 3.9. Background reactions of cyclobutanone (331) with different bases.



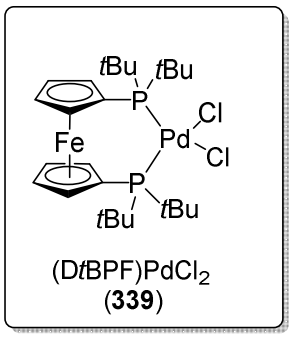
[M] = K: **335**:**333** = >20:1 (reaction time = 15 min)
[M] = Na: **335**:**333** = 20:1 (reaction time = 15 min)
[M] = Li: **335**:**333**= 1:20 (reaction time = 15 min)
[M] = Li: **335**:**333** = 20:1 (reaction time = 90 min)

Optimization of this reaction led to the development of two separate reaction conditions that afford α-arylcyclobutanones.[162] The first set of conditions ((D*t*BPF)$PdCl_2$ (**339**), LiO*t*Bu, THF, 60 °C, conditions B) effect the α-arylation of cyclobutanone **331** with 4-bromotoluene (**336**) in 59% yield.[159] A significant complicating process ecountered in many α-arylations involves the formation of diarylated products (e.g. **338**), and here the choice of THF as solvent proved to be critical as the use of other solvents such as dimethoxyethane or 1,4-dioxane resulted in significantly more diarylated product **338**. Having established that LiO*t*Bu was essential for the success of the reaction, we also investigated the ligands pioneered by Buchwald.[182] This investigation revealed that a combination of XPhos (**340**), $PdCl_2$ and LiO*t*Bu (conditions A) also led to the production of α-arylcyclobutanone **337** in high (76%) yield with a minimal amount of the diarylated compound being formed.

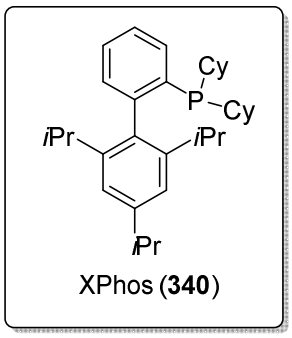
Scheme 3.10. Pd-catalyzed α-arylation of cyclobutanone (331).



Conditions A: 76%, **337**:**338** = 17.5:1
Conditions B: 59%, **337**:**338** = 7.5:1



(D*t*BPF)$PdCl_2$
(**339**)

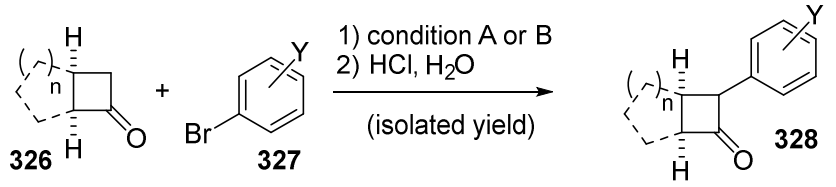


XPhos (**340**)

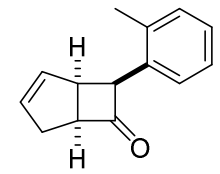
Note: Conditions A: $PdCl_2$ (5 mol%), XPhos (5 mol%), LiO*t*Bu (2.3 equiv.), THF, 60 °C.
Conditions B: (D*t*BPF)$PdCl_2$ (5 mol%), LiO*t*Bu (2.3 equiv.), THF, 60 °C.

Having established two optimal conditions for the synthesis of α-arylcyclobutanones we next investigated the scope of this reaction. As shown in Scheme 3.11, this methodology proved to be applicable to the synthesis of a wide range of α-arylcyclobutanones (**341** to **358**). Notably, the reaction is equally effective with cyclobutanones annulated to 5-, 6- or 8-membered rings. Aryl bromides containing either electron donating groups (e.g. OMe) or electron withdrawing groups (e.g trifluoromethyl, chloride) reacted cleanly to form α-arylcyclobutanones (**342**, **343**, **347)**. Also we demonstrated that the reaction is tolerant of substitution around the ring, and *ortho*-, *meta*- and *para*-substitution on the aryl bromide had little effect on the reaction yield (e.g. **341**, **344**, **345**). We also explored the α-arylation with heterocycles and were delighted to discover that the furan **349**, thiophene **350**, pyridine **351** and pyrimidine **352** were all accessible in reasonable yields.

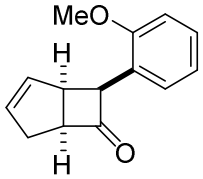
Scheme 3.11. Synthesis of α-arylcyclobutanones (341) to (358).



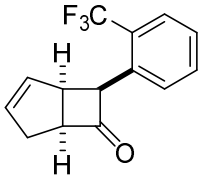
326 **327** **328**



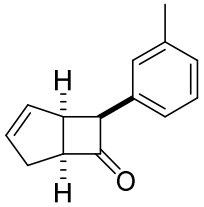
341: (59%[a], 54%[b])



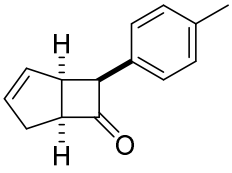
342: (48%[a], 52%[b])



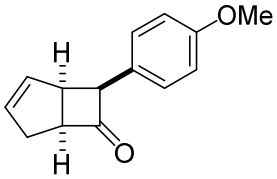
343: (53%[b])[c]



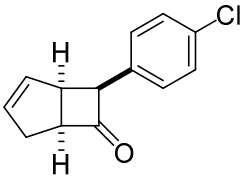
344: (56%[a])



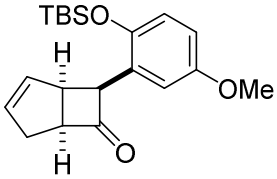
345: (76%[a], 59%[b])



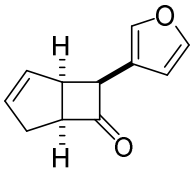
346: (66%[a], 44%[b])



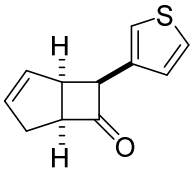
347: (63%[a])



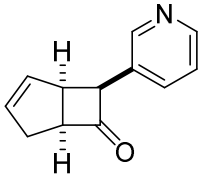
348: (59%[b])



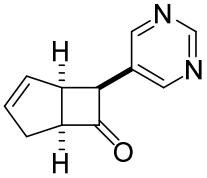
349: (52%[b])



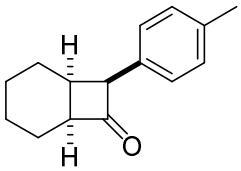
350: (65%[b])



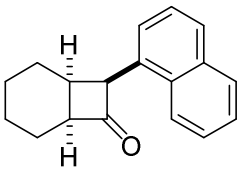
351: (56%[b])



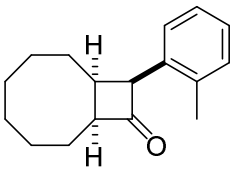
352: (40%[b])



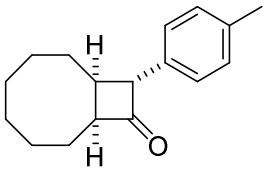
353: (58%[a], 66%[b])



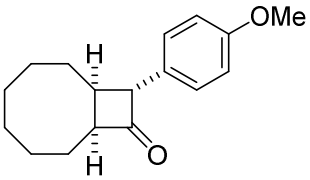
354: (30%[a])



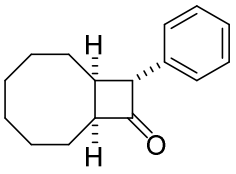
355: (54%[a], 74%[b])



356: (64%[a], 58%[b])



357: (69%[a], 66%[b])



358: (80%[b])

Note: Conditions A: $PdCl_2$ (5 mol%), XPhos (5 mol%), LiO*t*Bu (2.3 equiv.), THF, 60 °C. Conditions B: (D*t*BPF)$PdCl_2$ (5 mol%), LiO*t*Bu (2.3 equiv.), THF, 60 °C. Only the major diastereoisomeric product is depicted. c – 2 equivalents of cyclobutanone **331** were used

The stereochemical outcome of this reaction indicates that the all-*cis*-diastereoisomer is a favoured product. This preference is considered to be the result of formation of a lithium enolate following the α-arylation event and subsequent protonation of the enolate from the convex face of the bicyclic system. Interestingly, products **356**, **357** and **358** were isolated as the *trans*-products, which may suggest a rapid epimerization of the α-centre and formation of the more thermodynamically stable diastereoisomer during or after reaction work up. Analysis of 1D NOESYs was used to determine the cyclobutanone stereochemistry and we discovered that the chemical shift of the proton highlighted in Figure 3.6 was diagnostic for assigning stereochemistry among annulated α-arylcyclobutanones.

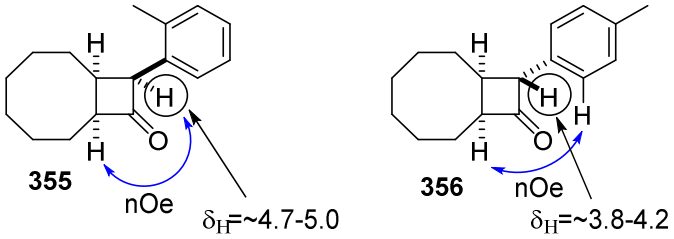
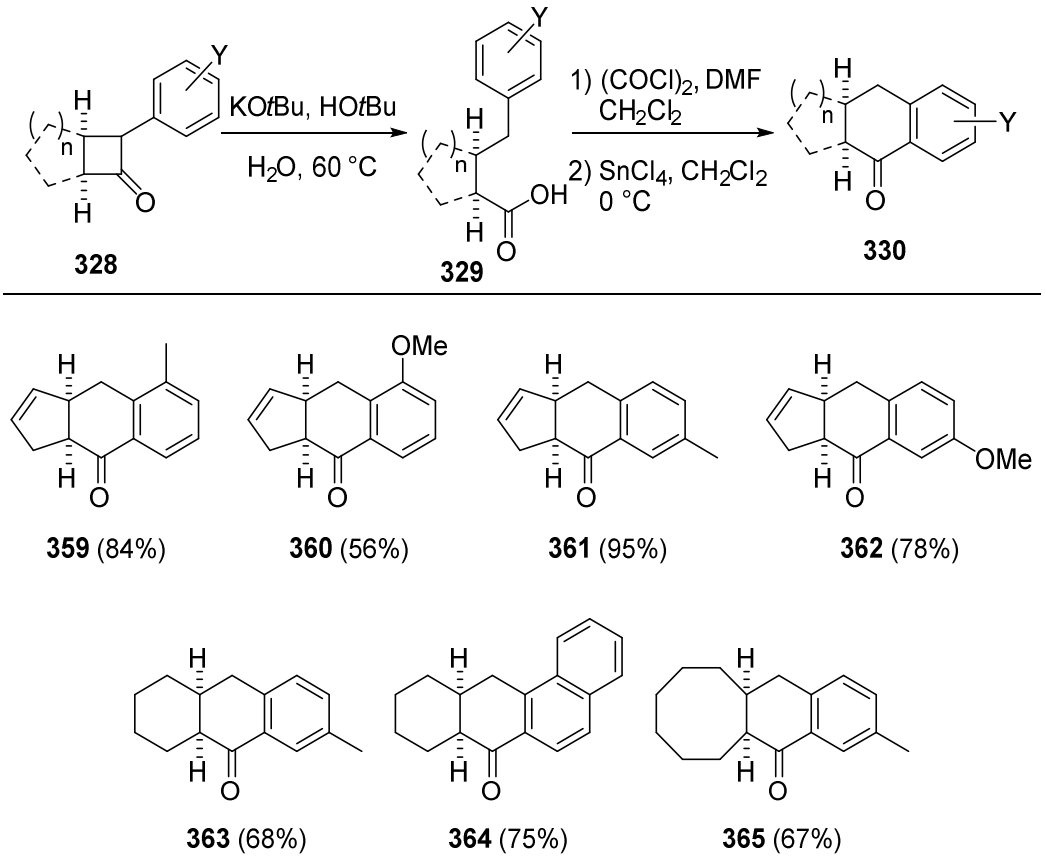


Figure 3.6. Characteristic ^{1}H NMR shifts for different diastereoisomers.

3.4.3. Synthesis of α-Tetralones

Having established a robust synthesis of α-arylcyclobutanones, we then investigated the annulative ring expansion process presented in Scheme 3.8. As summarized in Scheme 3.12, treatment of α-arylcyclobutanones with aqueous KO*t*Bu led cleanly to the aryl acid **329**. Degassing of this reaction mixture was essential to avoid oxidation at the benzylic position of the fragmented product prior to quenching the reaction. Subsequent formation of the acyl chloride by treatment with oxalyl chloride and DMF followed by an intramolecular Friedel-Crafts acylation[190] promoted by tin (IV) chloride afforded α-tetralones **359** to **365** in good to excellent yield over the three steps.

Scheme 3.12. Synthesis of α-tetralones (359) to (365) by an annulative ring expansion sequence.



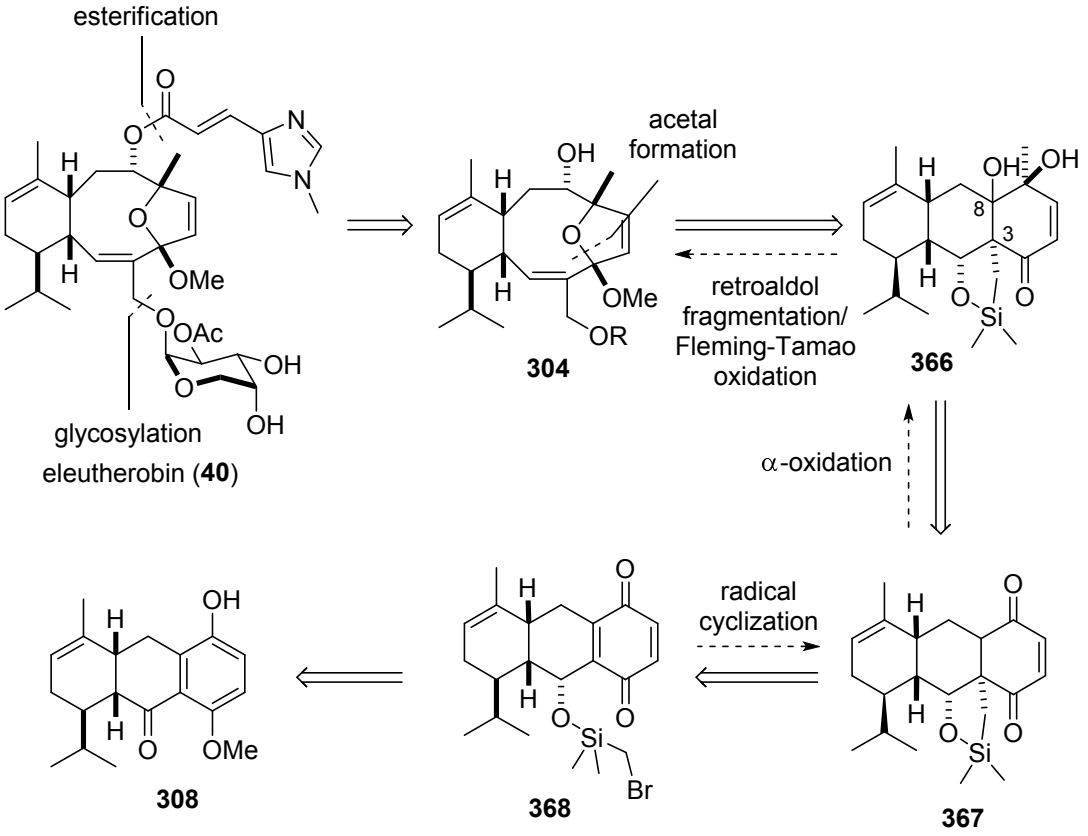
3.5. Studies Toward the Total Synthesis of Eleutherobin

3.5.1. Retrosynthesis

Since Dr. Chang had been unable to incorporate a hydroxymethyl group into his advanced intermediate **316** (Scheme 3.7), we decided to approach the challenge from a different direction. Accordingly, we planned to incorporate the hydroxymethyl group at C3 by Tamao-Kumada-Fleming oxidation of the C-Si group in silafuran **366** (Scheme 3.13).[191,192] The hydroxyl group at C8 could be installed by oxidation of the α-carbonyl position in dione **367**. We considered that dione **367** could be synthesized by radical cyclization of the radical formed by cleavage of the C-Br bond in quinone **368** and subsequent 1,4-addition to the enone. Quinone **368** could then be accessed by oxidative

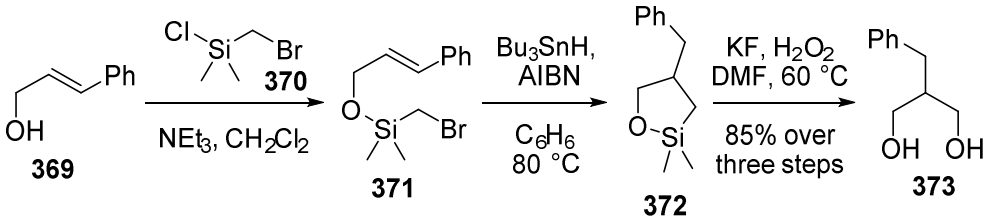
dearomatization of α-tetralone **308** which was an intermediate in our previous attempted syntheses.

Scheme 3.13. Revised retrosynthesis of eleutherobin (40).



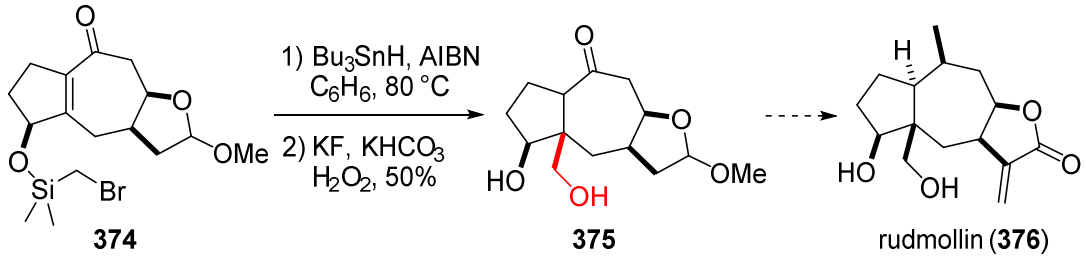
The bromomethyldimethylsilyl group has seen considerable synthetic use since the seminal publications by Nishiyama[193] and Stork[194] in the mid 1980's. This group is particularly useful for radical reactions as Wilt had shown that halogen abstraction from α-halosilanes to be much more facile than the corresponding haloalkanes.[195] Nishiyama demonstrated a simple protocol for the synthesis of 1,3-diols from allylic alcohols (Scheme 3.14). This procedure initiates with the formation of silyl ether **371** by condensation of allylic alcohol **369** with bromomethylchlorodimethylsilane (**370**). Subsequent submission of silyl ether **371** to standard radical cyclization conditions (Bu_3SnH, AIBN, benzene) then affords the silafuran **372**. Tamao-Kumada oxidation using H_2O_2 and KF then give the 1,3-diol **373** in 85% yield over the sequence.

Scheme 3.14. Nishiyama's synthesis of 1,3-diols utilizing bromomethyldimethylsilyl ethers.



Following these seminal works, this strategy has been applied in the synthesis of a number of natural products.[196–202] One such example is shown in Scheme 3.15 where Little and co-workers were attempting to carry out the synthesis of rudmollin (**376**).[203] Here, treatment of bromomethyldimethylsilyl ether **374** with AIBN and Bu_3SnH gave the intermediate silafuran after 1,4-addition into the enone. Subsequent Tamao-Kumada oxidation gave the 1,3-diol function found in the natural product and resulted in the generation of a new quaternary centre (**375**). While Little was unable to complete the synthesis of rudmollin using this route, we considered that this result demonstrated the utility of this approach for forming a quaternary centre by 1,4-addition into an enone followed by a late stage oxidation to unveil the hydroxymethyl group.

Scheme 3.15. Little's hydroxymethyl incorporation by 1,4-radical addition to an enone.

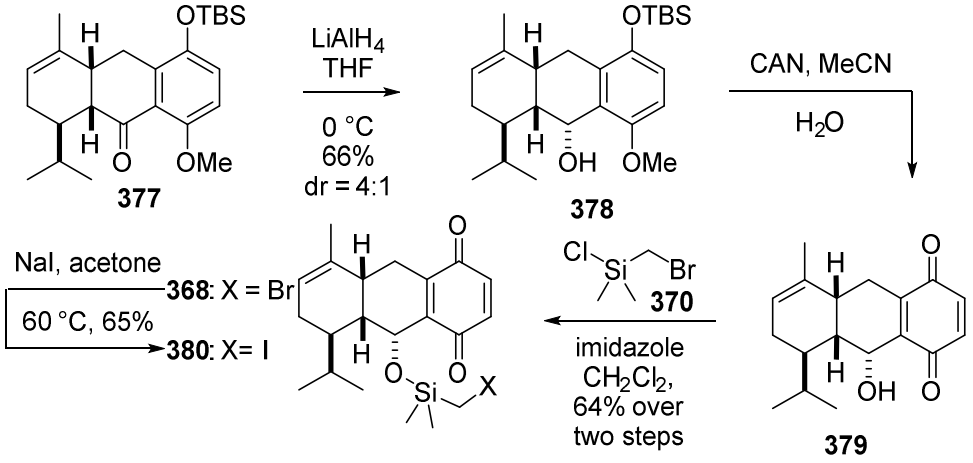


3.5.2. Studies Toward the Synthesis of the Retroaldol Precursor

Our investigation into the feasibility of this route began with the previously synthesized α-tetralone intermediate **377** (Scheme 3.6). Subsequent reduction of the carbonyl using $LiAlH_4$ gave alcohol **378** in 66% yield for the desired diastereoisomer. The facial selectivity of this reaction is rationalized based on approach of the reducing

agent from the concave face of the tricyclic ring system. Removal of the silyl ether from the phenol was a not a prerequisite for aromatic oxidation,[204] so we then carried out the dearomatization by directly treating this material with ammonium cerium (IV) nitrate (CAN). This afforded the quinone **379** in very high yield (~90%). Formation of the quinone was confirmed by analysis of its ^{1}H NMR spectra which showed two proton resonances at 6.80 ppm and 6.75 ppm characteristic of a quinone. The ^{13}C NMR spectra also showed the presence of two carbonyl carbons and the compound was bright orange in colour, a common feature of many quinones. With quinone **379** in hand, we then incorporated the bromomethyldimethylsilyl ether by treatment with chlorosilane **370** and imidazole to afford radical precursore **368**. Since iodine-carbon bonds are weaker than bromine-carbon bonds and more susceptible to homolysis[205] we also carried out a Finkelstein reaction on **368** to access iodide **380**.[206,207]

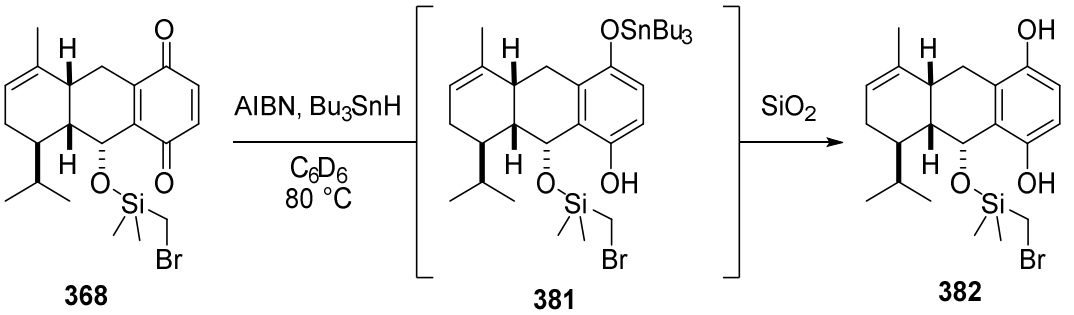
Scheme 3.16. Synthesis of radical cyclization precursors (368) and (380).



With the precursor to the radical cyclization in hand, we then attempted to effect this cyclization (Scheme 3.17). Initial efforts using the standard radical conditions in d_6-benzene indicated the formation of a single major product. However all attempts to isolate this compound were unsuccessful and instead, we isolated hydroquinone **382** as the major product. Due to similarities in the ^{1}H NMR spectra of **382** and the unknown product, we considered that this later material was likely the O-Sn protected version of hydroquinone **381** which would then destannylate upon exposure to silica gel to afford

hydroquinone **382**. This pathway presumably involves reduction of one of the ketones by Bu_3SnH and subsequent isomerization to afford the aromatic compound.

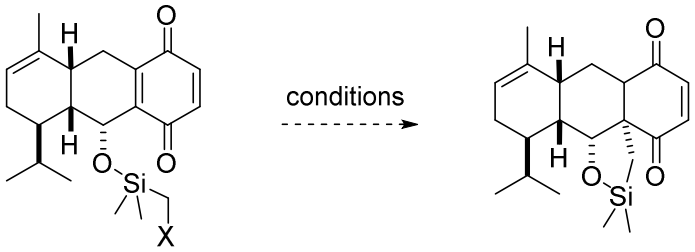
Scheme 3.17. Production of undesired hydroquinone (382) by reduction with Bu_3SnH.



368 **381** **382**

Accordingly, we screened a number of conditions designed to effect the desired radical cyclization (Table 3.2). Since Bu_3SnH reduced the quinone, we replaced it with tris(trimethyl)silylsilane (TTMSS) under similar conditions.[208] However, we were unable to observe any reaction under these conditions. When these same conditions were applied towards the iodide **380** (entry 2), a significant amount of degradation was observed. Since there are examples of photolysis of C-I bonds to initiate radical reactions rather than relying on thermal decomposition of initiators such as AIBN, we irradiated iodide **380** in the presence of Bu_3SnH as the radical propagator. However, this compound was not stable to extended periods of photoirradiation as significant degradation was observed as well as alkene isomerization. With our efforts to carry out a direct radical cyclization meeting with little success, we next explored a Barbier coupling using zinc powder. Unfortunately, this reaction afforded hydroquinone **382** as the sole product through reduction of the carbonyl. Lastly, we attempted a lithium-halogen exchange to form the corresponding carbanion which we hoped would then undergo 1,4-addition to the quinone. However quinone **380** proved to be unstable to these conditions and an intractable mixture of degradation products was isolated.

Table 3.2. Efforts towards cyclization of quinones (368) and (380).



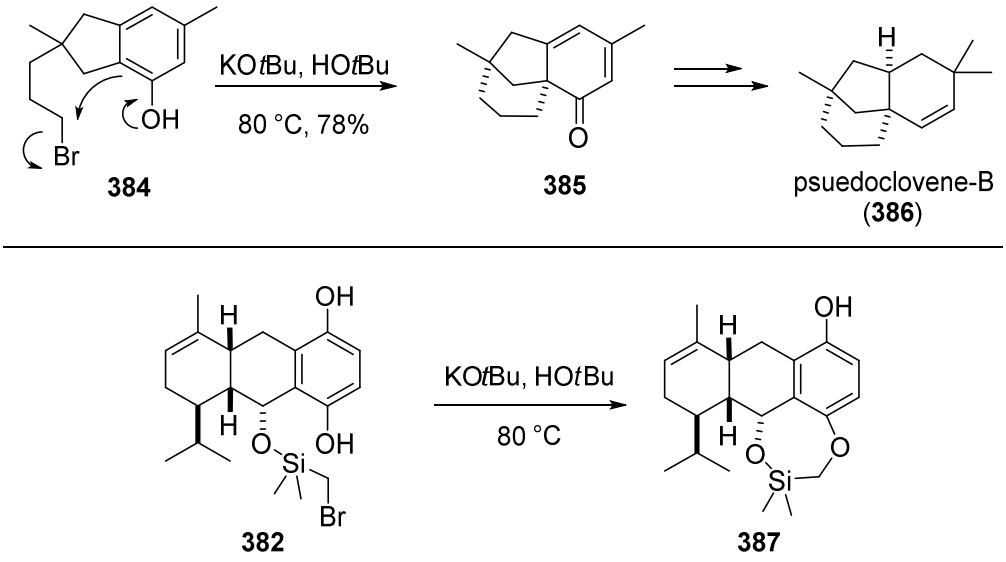
X = Br, **368**
X = I, **380**

383

Entry	X	Conditions	Product
1	Br	TTMSS, AIBN, 80 °C	No reaction
2	I	TTMSS, AIBN, 80 °C	Decomposition
3	Br	Bu_3SnH, hv	Mixture of products – reaction at alkene
4	I	Zn, NH_4Cl, H_2O, THF	Hydroquinone
5	I	*t*BuLi, THF, -78 °C	Decomposition

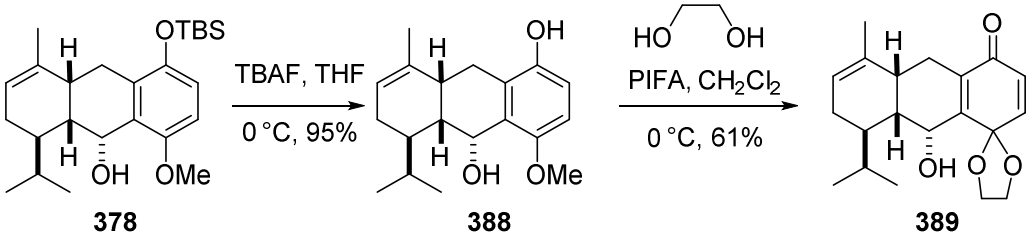
While radical cyclization of quinone **368** was unsuccessful, several groups have shown that phenols can undergo *C*-alkylation under anionic conditions to form cyclic ring systems.[209–211] Mukherjee used this approach while carrying out the racemic synthesis of pseudoclovene B (**386**)[212,213] where the anionic cyclization of intermediate **384** by S_N2 displacement of the bromide to afford the quaternary carbon centre and dearomatized the ring (Scheme 3.18). While a common requirement for the success of this reaction is that *O*-alkylation be impossible, we considered that the irreversible formation of a 5-membered ring vs the formation of the 7-member ring might be competitive. However treatment of hydroquinone **382** with KO*t*Bu in HO*t*Bu gave clean access to the 7-membered ring **387** *via* alkylation of the phenol.

Scheme 3.18. Mukherjee's total synthesis of pseudoclovene-B *via* an anionic phenol cyclization and application of this towards the cyclization of hydroquinone (382).



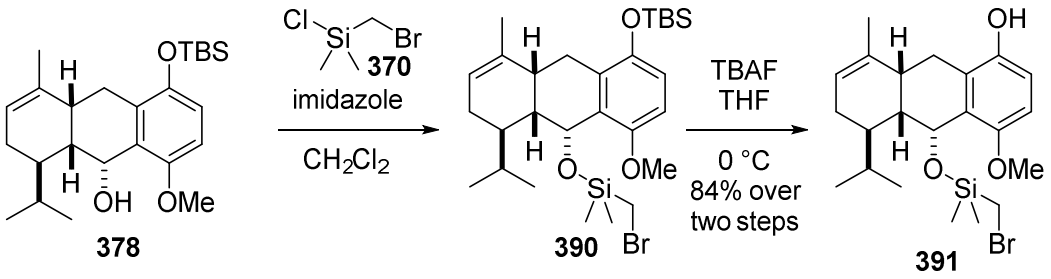
Given that quinone **368** was not compatible with the radical cyclization conditions, we decided to slightly modify the strategy to include a protecting group on the quinone and reduce its propensity for rearomatization. Accordingly, TBAF deprotection of alcohol **378** gave phenol **388** cleanly and then treatment with [bis(trifluoroacetoxy)iodo]benzene (PIFA) and ethylene glycol afforded enone **389**. Unfortunately, attempts to introduce the bromomethyldimethylsilyl ether at this stage were unsuccessful and only afforded starting material. We considered the lack of reactivity is related to steric hindrance from the acetal group shielding the alcohol functionality.

Scheme 3.19. Synthesis of enone (389).



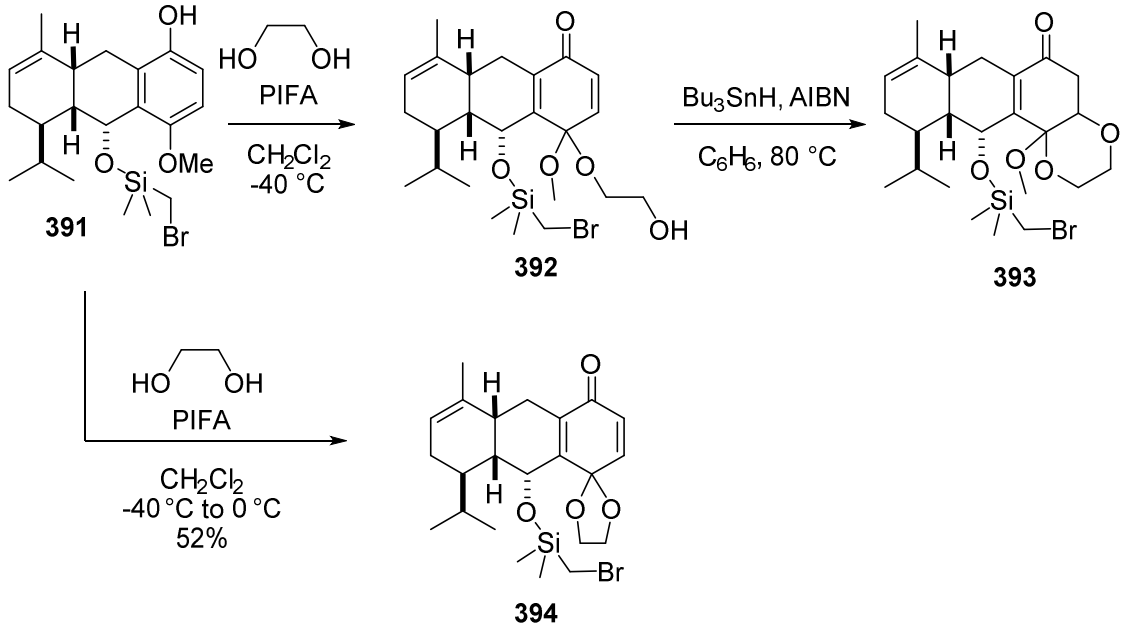
Since incorporation of the bromomethyldimethylsilyl ether was not successful following dearomatization, we decided to install this group prior to dearomatization. Thus, reaction of alcohol **378** with bromomethylchlorodimethylsilane afforded compound **390**. Gratifyingly, treatment of compound **390** with a single equivalent of TBAF cleanly afforded phenol **391** with only traces (<10%) of the free alcohol being detected. This observation is consistent with a report by Finch where TBAF was used to selectively deprotect phenolic TBS ethers in the presence of alcoholic TBS ethers under controlled conditions.[214]

Scheme 3.20. Synthesis of compound (391).



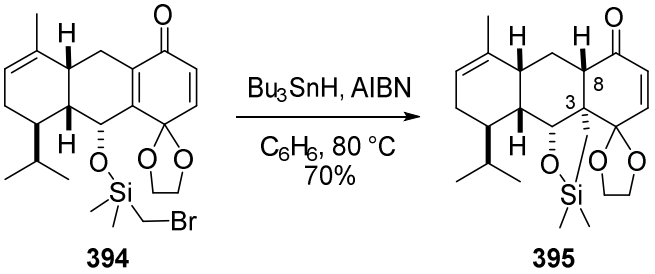
With free phenol **391** in hand, we attempted to carry out the dearomatization to give the desired enone **394**. Treatment with (diacetoxyiodo)benzene (BAIB) and ethylene glycol lead to a complex mixture of products as did reaction with PIFA and ethylene glycol at 0 °C. However, lowering the temperature of the reaction to -40 °C led to the isolation of enone **392** as the major product. Subjection of enone **392** to radical cyclization conditions however led to oxa-Michael addition of the free alcohol into the enone to form compound **393** as determined by the disappearance of the characteristic ^{1}H NMR resonances at 6.70 and 6.17 ppm. Since the low temperature of the dearomatization reaction was likely the reason why the acetal in **392** did not form the expected 1,3-dioxolane, we repeated this reaction at -40 °C and gradually warmed the reaction mixture to 0 °C over a period of 1 hr. Gratifyingly, this revised process afforded the desired enone **394** albeit in moderate yield.

Scheme 3.21. Successful dearomatization of phenol (391).



With enone **394** in hand, it was subjected to the radical cyclization conditions as shown in Scheme 3.22. To our delight, the major product isolated from this reaction was the desired silafuran **395** resulting from 1,4-addition into the enone.

Scheme 3.22. Successful radical cyclization to form silafuran (395).



Analysis of the ^{1}H NMR recorded on silafuran **395** showed two diastereotopic proton resonances at 0.4 and 1.15 ppm characteristic of the methylene protons at C15 (Figure 3.7). Further analysis using 2D NMR experiments (COSY, HSQC, HMBC) showed the new resonance at 3.05 ppm was the proton at C8 adjacent to the carbonyl.

This exciting result represents the first incorporation of the critical hydroxymethyl group surrogate at C3 using our synthetic approach.

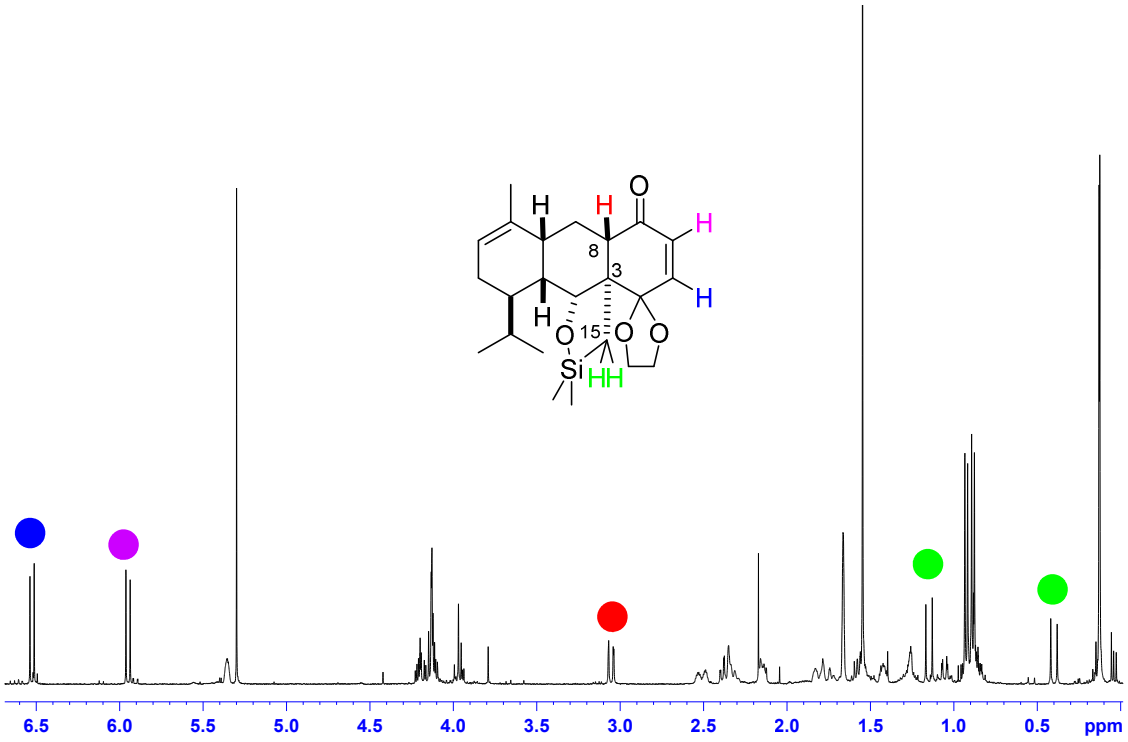
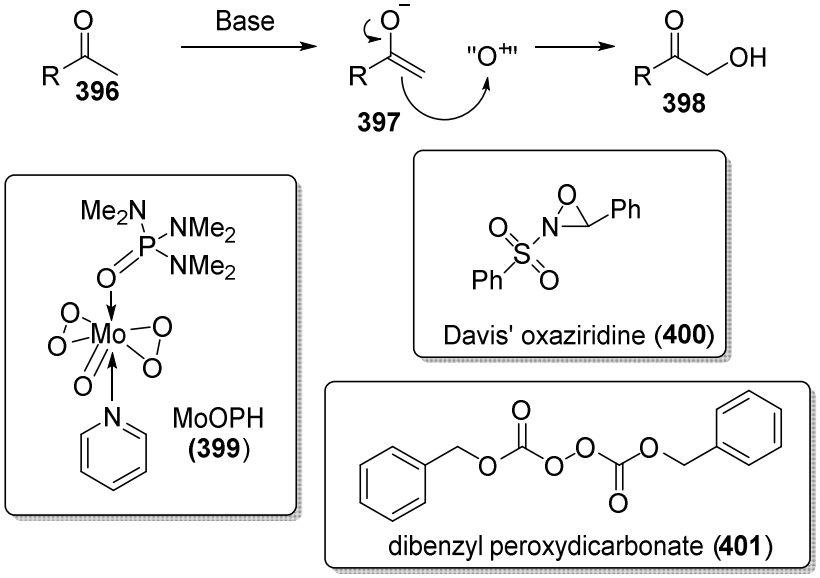


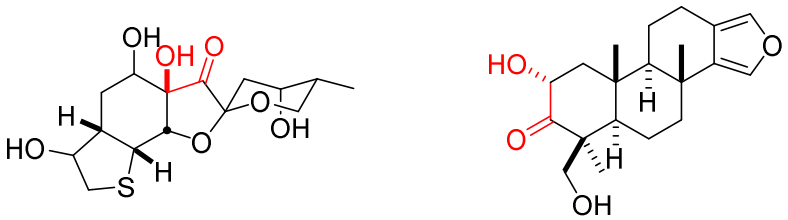
Figure 3.7. **^{1}H NMR spectrum of silafuran (395).**

With silafuran **395** in hand, we then investigated the incorporation of an oxygen atom at C8. α-Oxidation of ketones is a well-established synthetic strategy for the formation of α-hydroxyketones (Scheme 3.23).[215] In general, these reactions rely on the formation of an enolate and subsequent reaction of this enolate with an electrophilic source of oxygen such as O_2,[216,217] dibenzyl peroxydicarbonate (**401**),[218] Davis' oxaziridine (**400**)[219,220] or MoOPh (**399**).[221,222]

Scheme 3.23. General method for the formation of α-hydroxyketones (398).



This strategy has been integral in the synthesis of many natural products including Smith's synthesis of (±)-breynolide (**402**)[223] and Zoretic's synthesis of isospongiadiol (**403**)[224] (Figure 3.8). In both of these syntheses, the installation of the α-hydroxy group was carried out by oxidation adjacent to the ketone and was a critical step in the synthesis.



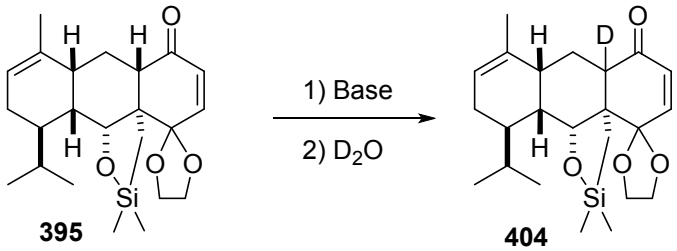
(±)-breynolide (**402**) isospongiadiol (**403**)

Figure 3.8. Natural product syntheses requiring installation of an α-hydroxy function next to the carbonyl.

In order to establish whether this would be a viable stategy, we subjected silafuran **395** to a number of different bases followed by a quench with deuterium oxide to determine if the desired enolate was indeed being formed.(Table 3.3). Unforutnately, treatment with LDA, LiHMDS and KHMDS at -78 °C (entries 1 to 3) followed by treatment with D_2O provided none of the deuterated compound **404**. In an effort to

facilitate deprotonation of this clearly problematic substrate, we increased the temperature of the reaction but this only led to decomposition of the starting material with a number of new products being observed.

Table 3.3. Attempts to form enolate of silafuran (395).

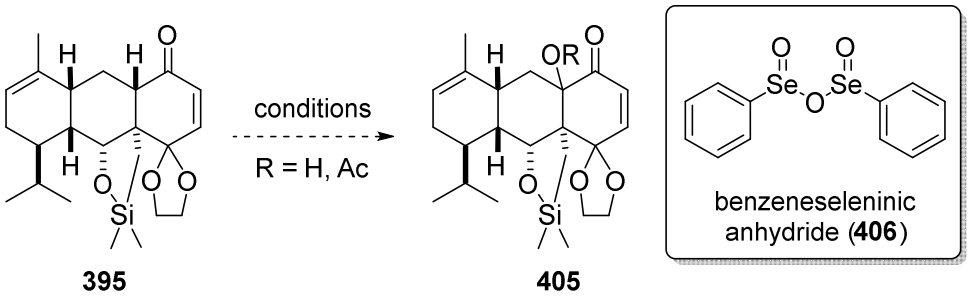


395 **404**

Entry	Base	Temperature	Result
1	LDA	-78 C°	No reaction
2	LiHMDS	78 C°	No reaction
3	KHMDS	78 C°	No reaction
4	KHMDS	-40 °C	Decomposition plus starting material
5	KHMDS	0 °C	Decomposition

While the reaction of an enolate with an electrophilic source of oxygen is the predominant way to form α-hydroxyketones, there have been several other methods developed to effect this transformation. Rubottom oxidation[225–227] of a silyl enol ether is a common method to access these compounds. Accordingly, we attempted to access the silyl enol ether of **395**. Since the formation of the enolate was not a viable approach, we used TMSOTf and NEt_3 as a combination to attempt this reaction. However, these conditions did not provide any enol silyl ether and largely returned starting material. Our further efforts to carry out this oxidation are shown in Table 3.4. Both $Mn(OAc)_3$[228,229] and $Pb(OAc)_4$[230] have been shown to install α-acetoxy groups adjacent to enones. However both these reagents are also known to react with alkenes to form γ-lactones, and treatment of silafuran **395** with these reagents under the standard conditions led to reaction at the isolated alkene affording the lactones along with other products including rearrangement of the alkene to the tetrasubstituted position. Benzeneseleninic anhydride (**406**) has also been shown to oxidize angular positions next to carbonyls,[231,232] but these conditions also proved to be incompatible with the alkene and so further investigation of these reagents was abandoned.

Table 3.4. Efforts to oxidize silafuran (395).

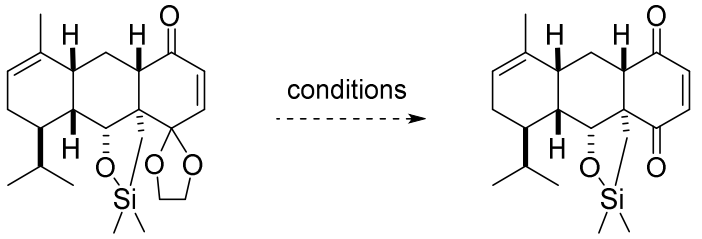


395 **405**

Entry	Conditions	Major Product
1	$Mn(OAc)_3.2H_2O$, C_6H_6, 80 °C	Alkene rearrangement
2	$Mn(OAc)_3.2H_2O$, Et_3N, C_6H_6, 80 °C	No reaction
3	$Mn(OAc)_3.2H_2O$, $NaHCO_3$, C_6H_6, 80 °C	No reaction
4	$Mn(OAc)_3$, C_6H_6, 80 °C	Reaction at alkene
5	$Pb(OAc)_4$, C_6H_6, 80 °C	Reaction at alkene
6	Benzeneseleninic anhydride, toluene, 100 °C	Reaction at alkene

Our explanation for our inability to oxidize the C8 centre is based on models of **395**, which indicate that the enolate/enol tautomeric form of the ketone in compound **395** would be challenging to form due to the presence of the quarternary carbon at C3 and the large, bulky acetal group at C4 blocking deprotonation. However, we considered that removal of the acetal group and formation of the enedione **407** would enable the formation of the required enolate. Table 3.5 summarizes our attempts to carry out this deprotection. Efforts using conditions that were employed effectively by Dr. Chang during his efforts to functionalize the C3 position of intermediate **316** (Scheme 3.7) afforded starting material (entry 1). Increasing the temperature of this reaction led to decomposition and the observation of several new aldehyde peaks in the spectrum, likely due to a retroaldol process occurring after the deprotection of the acetal (Scheme 3.24). Efforts using other acids (entries 3-5) also failed to afford the desired product with only recovered starting material or retroaldol decomposition products observed. Huet and co-workers had previously demonstrated that wet oxalic acid on silica gel is a mild method to deprotect α,β-unsaturated acetals[233] but our efforts to apply this strategy to the deprotection of **395** (entry 6) were unsuccessful, likely to the electron withdrawing nature of the enone in this system.

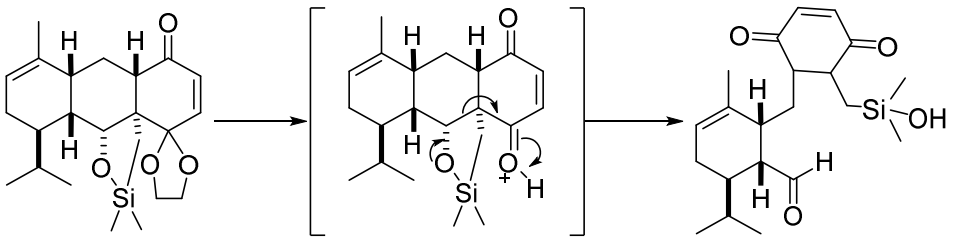
Table 3.5. Attempts to unveil ketone function by removal of the acetal on silafuran (395).



395 407

Entry	Conditions	Result
1	TsOH, H_2O, acetone, rt	Starting material
2	TsOH, H_2O, acetone, 60 °C	Decomposition
3	1N HCl, THF, 60 °C, 2 h	Starting material
4	1N HCl, THF, 60 °C, 12 h	Decomposition
5	PPTS, THF, H_2O, 60 °C	Starting material plus decomposition
6	SiO_2, oxalic acid, H_2O , CH_2Cl_2, rt	Starting material

Scheme 3.24. Proposed retroaldol decomposition of intermediate (408).

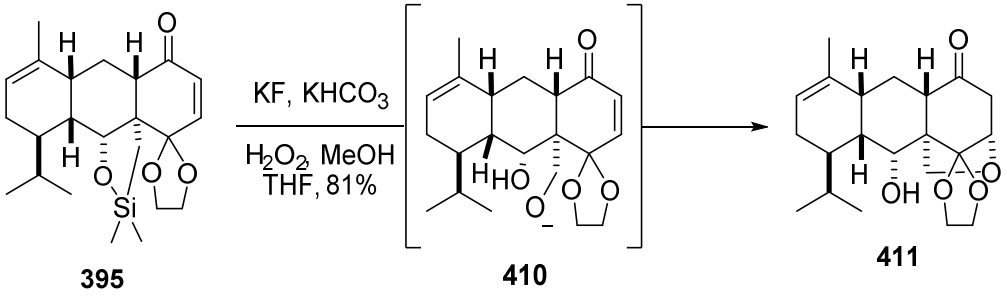


395 408 409

Since removal of the acetal on **395** proved to be challenging, we considered whether cleavage of the silafuran might reduce the steric crowding and allow formation of the enolate. Accordingly, we attempted to carry out a Tamao oxidation using the standard conditions (KF, $KHCO_3$, H_2O_2)[191] to oxidise the C-Si bond (Scheme 3.25). Since these conditions are similar to those used to epoxidize an enone, we were concerned about the potential for the formation of undesired side products. However, we isolated a single product from the reaction mixture. Analysis of ^{1}H NMR spectra showed the silyl group was no longer present but also the resonances at 6.53 and 5.95 ppm corresponding to the enone were no longer visible. The observation of new methylene

signals led us to conclude that the product was compound **411** which is the result of oxa-Michael addition into the enone after oxidation of the C-Si bond. While this result was not productive in terms of advancing the synthesis, we were happy to observe that Tamao oxidation of the silafuran proceeded cleanly and was compatible with the rest of the molecule.

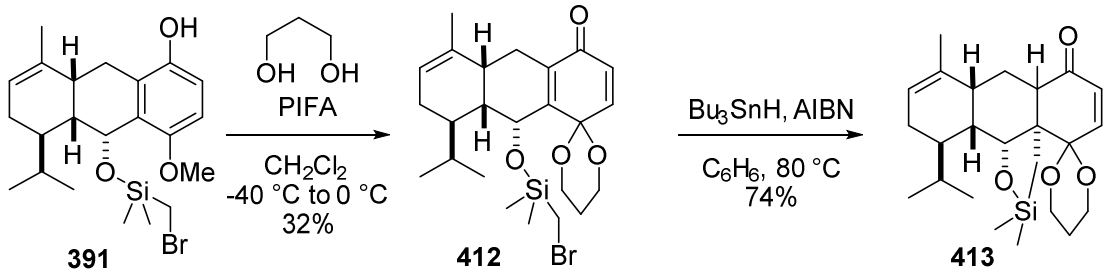
Scheme 3.25. Tamao oxidation on silafuran (395).



395 **410** **411**

Given that acetal on **395** had proved to be challenging to remove, we attempted to incorporate a different acetal protecting group in the dearomatization step. While efforts to make the acyclic dimethyl acetal were ultimately unsuccessful due to instability of the resulting product to flash chromatography, we were able to incorporate a 1,3-dioxane ring at that position although in a significantly reduced yield compared to the 1,3-dioxolane (Scheme 3.26). Newman has shown that the rate of cleavage of 1,3-dioxanes is about an order of magnitude greater than the rate of cleavage for 1,3-dioxolanes.[234] However, while radical cyclization gave the desired product **413**, attempts to remove the acetal were also unsuccessful and did not afford the desired enedione.

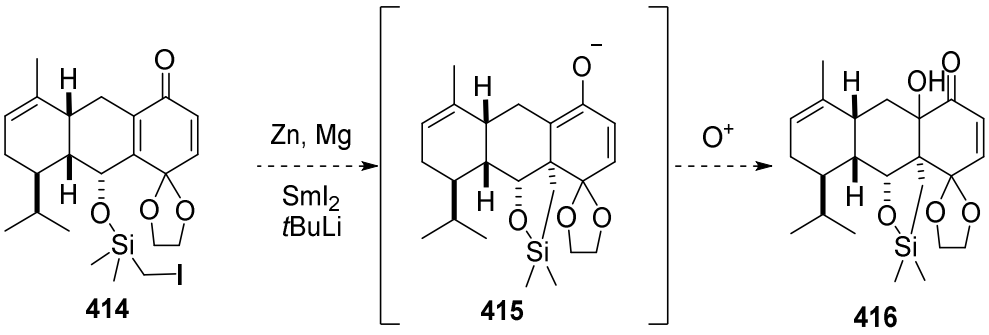
Scheme 3.26. Synthesis of silafuran (413) containing a 1,3-dioxane ring.



391 **412** **413**

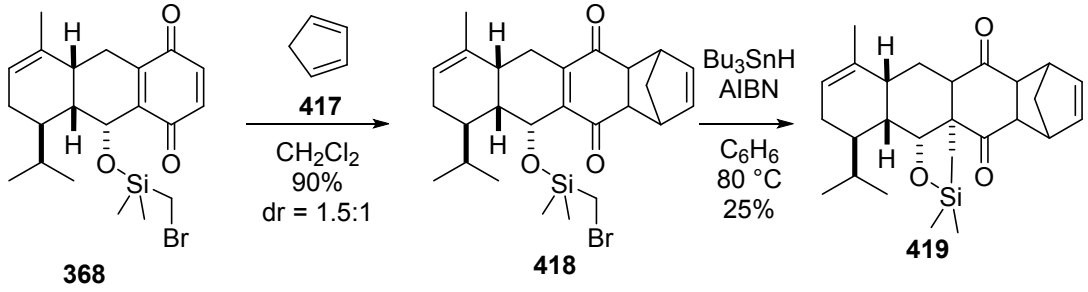
Since direct deprotonation to form the enolate had been unsuccessful, we wanted to investigate whether anionic cyclization from the iodide of enone **414** would give the desired enolate that could then be trapped prior to working up the reaction (Scheme 3.27). Attempts to form the anion by treatment with Mg, Zn or SmI_2 simply led to a mixture of rearomatized products consistent with our observations earlier with quinone **368** (Table 3.2). However treatment of compound **414** with *t*BuLi provided a complex mixture of products that included the desired product **415** (~5%) and showed that anionic cyclization may well be a solution to this impasse. However, efforts to optimize this reaction were unsuccessful and we did not pursue it further.

Scheme 3.27. Efforts towards anionic cyclization of iodide (414).



Since radical cyclization of the quinone **368** had not been successful, we also considered that protection of the quinone **368** as the Diels-Alder adduct might avoid the rearomatization issues encountered earlier. To this end we treated quinone **368** with cyclopentadiene (**417**) in CH_2Cl_2. This reaction gave the desired adduct **418** as a 1.5:1 mixture of diastereoisomers in excellent yield (90%). A radical cyclization then gave a mixture of compounds including some of the desired compound **419**. However heating **419** in toluene at reflux did not lead to the retro-Diels-Alder product and increasing the temperature to 140 °C in xylenes only led to degradation of this material. Given that the radical cyclization did not afford the desired compound in a high yield, this route was abandoned.

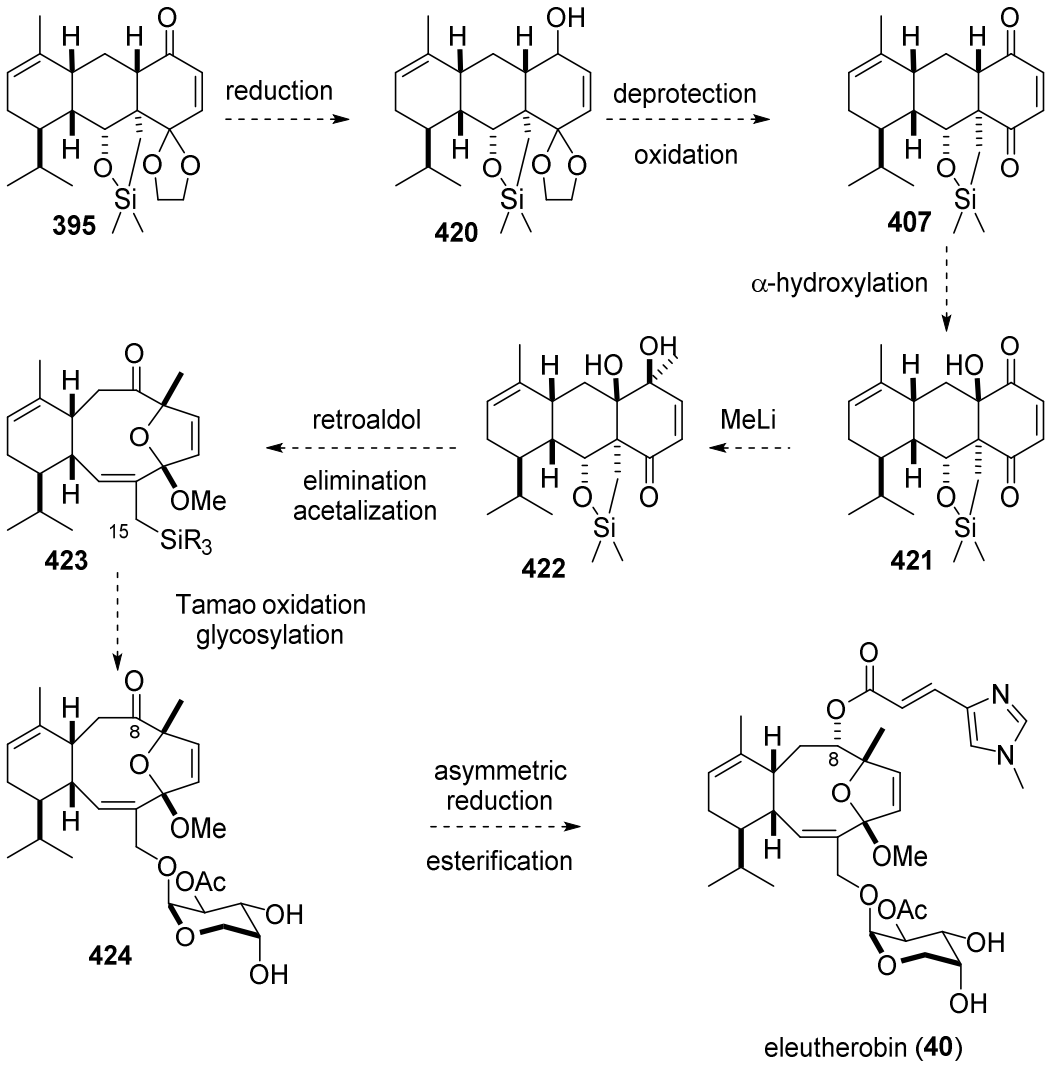
Scheme 3.28. Diels-Alder protection of quinone (368).



3.5.3. Future Work

While our efforts to functionalize the silafuran **395** have not yet been successful, the fact that we have successfully formed the critical C-C bond and installed the quarternary carbon required for the retroaldol fragmentation represents a significant advance in the synthesis. We still consider that the acetal present in **395** is the primary reason why formation of the enolate has been unsuccessful and removal of this acetal a priority. Since the conjugated enone is highly electron withdrawing and thus significantly destabilizes the oxonium intermediate required for acetal deprotection, we are interested in investigating whether reduction of the carbonyl in **395** would remove this electronic hindrance and allow for deprotection using milder conditions. Subsequent reoxidation of the alcohol would give access to the desired intermediate **407**. This compound should readily form the enolate and allow for the installation of the required α-hydroxy function in **421**. The stereochemistry of the tertiary alcohol in **421** can then be used to control the stereoselectivity of the MeLi addition to give diol **422**. A subsequent retroaldol fragmentation/elimination/acetalization would give the core of eleutherobin **423**. Tamao oxidation and glycosylation at C15 would give advanced intermediate **424** then asymmetric reduction of the carbonyl at C8 and installation of the urocanic ester would complete the synthesis of eleutherobin (**40**) in 18 steps. This synthesis should be sufficiently scalable to permit the production of the quantities of material required for further exploration of the biological activity of eleutherobin including animal studies.

Scheme 3.29. Proposed further functionalization of the silafuran (431) towards the synthesis of eleutherobin (40).



3.6. Conclusion

In summary, we have expanded the scope of the α-arylation reaction developed by Dr. Jeffrey Mowat and Dr. Stanley Chang for the synthesis of a wide range of α-arylcyclobutanones including the incorporation of heterocycles such as thiophene and pyridine. A number of these α-arylcyclobutanones were also converted into the corresponding α-tetralones in a short and efficient synthesis. Building on this work, we investigated the synthesis of the core of eleutherobin (**40**) through a proposed retro-aldol

fragmentation reaction. We were able to install the key quartenary carbon centre bearing a hydroxymethyl surrogate via radical addition into an enone which represents a significant advance over previous synthetic efforts in the Britton group. While attempts to carry out the α-oxidation of the resulting ketone were unsuccessful and we have not yet been able to access the desired retro-aldol precursor, the successful synthesis of intermediate **395** should provide a useful starting point for the further development of a scalable and efficient synthesis of eleutherobin and further exploration of its antimitotic activity and application in the treatment of cancer.

3.7. Experimental Information

3.7.1. General Considerations

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.[130] 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, AK Scientific 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. 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 ethanol/2-propanol bath.

Optical rotations were 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: CDCl3: 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) spectrometer. 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.

Gas chromatography (GC) analysis was performed on a Hewlett Packard model 6890 gas chromatograph, equipped with a flame ionization detector and a custom made fused chiral silica column with a 1:1 mixture of heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-*β*-cyclodextrin and OV-1701.

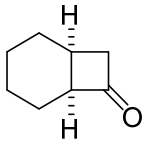
High resolution mass spectra were performed on an Agilent 6210 TOF LC/MS using ESI-MS or was carried out by the Notre Dame University Mass Spectrometry Department using EI technique.

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).

Single crystal X-ray crystallographic analysis was performed on a Bruker X8 APEX II diffractometer with graphite monochromated Mo-K*α* radiation.

3.7.2. Synthesis of α-Tetralones

Preparation of bicyclo[4.2.0]octan-7-one (425)



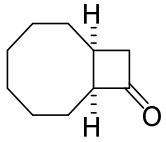
425

To a cold (0 °C), stirred solution of cyclohexene (4.00 mL, 38.4 mmol), Zn powder (5.15 g, 79.0 mmol) in Et_2O (128 mL) was drop-wise added a solution of trichloroacetyl chloride (5.30 mL, 47.5 mmol) in Et_2O (32.0 mL) over 1.5 hours. The resulting suspension was stirred with sonication for 1 hour, then without sonication overnight for 14.5 hours. After this time, the reaction mixture was filtered through a Celite® cake, and was rinsed with Et_2O (100 mL). The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (70 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 100 mL), and the combined organic phases were washed with brine (100 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford crude 8,8-dichlorobicyclo[4.2.0]octan-7-one, which was used in the next step without further purification.

To a stirred solution of crude 8,8-dichlorobicyclo[4.2.0]octan-7-one in methanol (110 mL) was added Zn/Cu couple (13.4 g, ~0.205 mol) and ammonium chloride (11.3 g, 0.211 mol), and the resulting suspension was stirred for 21 hours. After this time, the reaction mixture was filtered through a Celite® cake, and was rinsed with Et_2O (200 mL). The solvent was removed *in vacuo* to afford crude cyclobutanone **461**. Purification of the crude material by flash chromatography (EtOAc:hexanes, 5:95→15:85) provided bicyclo[4.2.0]octan-7-one **425** (2.28 g, 46% yield over two steps) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.27 (m, 1H), 3.13 (dddd, *J* = 9.1, 9.1, 9.1, 3.0 Hz, 1H), 2.51-2.40 (m, 2H), 2.15 (m, 1H), 1.96 (m, 1H), 1.61-1.50 (m, 2H), 1.43 (m, 1H), 1.28-1.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.2, 56.8, 52.3, 29.6, 22.8, 22.7, 22.5, 21.4; IR (neat): 2927, 2854, 1771, 1448 cm^{-1}; HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_8H_{13}O$: 125.0961; found: 125.0970.

Preparation of bicyclo[6.2.0]decan-9-one (426)



426

To a stirred solution of 10,10-dichlorobicyclo[6.2.0]decan-9-one[235,236] (2.05 g, 9.26 mmol) in methanol (26.5 mL) was added Zn/Cu couple (3.14 g, ~48.1 mmol) and ammonium chloride (2.68 g, 50.0 mmol), and the resulting suspension was stirred for 24 hours. After this time, the reaction mixture was filtered through a Celite® cake, and was rinsed with Et_2O (50 mL). The solvent was removed *in vacuo* to afford crude cyclobutanone **426**. Purification of the crude material by flash chromatography (EtOAc:hexanes, 5:95→15:85) provided bicyclo[6.2.0]decan-9-one **426** (1.01 g, 72% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 3.27 (m, 1H), 3.12 (m, 1H), 2.53-2.43 (m, 2H), 1.83-1.75 (m, 2H), 1.74-1.62 (m, 3H), 1.61-1.51 (m, 3H), 1.38-1.23 (m, 4H);

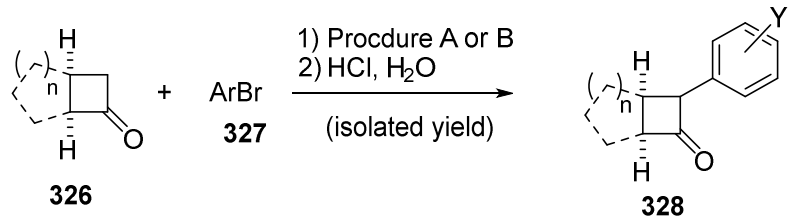
^{13}C NMR (150 MHz, $CDCl_3$) δ: 213.4, 62.6, 52.6, 30.4, 30.0, 29.8, 28.7, 26.2, 25.6, 22.2.

IR (neat): 2917, 2851, 1774, 1464 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{10}H_{17}O$: 153.1274; found: 153.1252.

α-Arylation of Cyclobutanones

General procedure for α-arylation of cyclobutanones



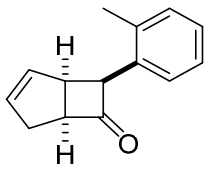
Procedure A:

To a warm (60 °C), stirred suspension of $PdCl_2$ (0.02 mmol), XPhos (0.02 mmol), and Li*O*t*B*u (1.0 M solution in THF or hexanes, 0.92 mmol) was purged with N_2 for 5 minutes. After 30 minutes at 60 °C, a solution of arylbromide (1.25 M in THF, 0.40 mmol) was added to the reaction mixture in one portion. A solution of cyclobutanone (1.25 M in THF, 1.1 equiv,) was added to the reaction mixture in one portion, and the resulting dark brown solution was stirred for the time indicated. The reaction was quenched with 1 M HCl (1 mL), diluted with EtOAc (2 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 3 mL), and the combined organic phases were washed with brine (3 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (silica gel).

Procedure B:

To a warm (60 °C), stirred suspension of (D*t*BPF)$PdCl_2$ (0.02 mmol), Li*O*t*B*u (1.0 M solution in THF or hexanes, 0.92 mmol) was purged with N_2 for 5 minutes. After 30 minutes at 60 °C, a solution of arylbromide (1.25 M in THF, 0.40 mmol) was added in one portion. A solution of cyclobutanone (1.25 M in THF, 1.1 equiv,) was added in one portion to the reaction mixture, and the resulting dark brown solution was stirred for the time indicated. The reaction was quenched with 1 M HCl (1 mL), diluted with EtOAc (2 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 3 mL), and the combined organic phases were washed with brine (3 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography.

Preparation of cyclobutanone 341



341

Procedure A:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95→25:75). Yield: 59%; light yellow oil.

Procedure B:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95→25:75). Yield: 54%; light yellow oil.

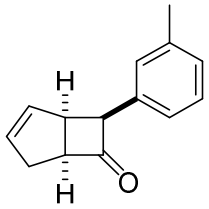
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23 (m, 1H), 7.16-7.13 (m, 2H), 7.10 (m, 1H), 5.83 (m, 1H), 5.29 (m, 1H), 4.85 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.01 (m, 1H), 3.91 (dddd, *J* = 8.2, 8.2, 2.4, 1.3 Hz, 1H), 2.78 (m, 1H), 2.52 (qq, *J* = 9.2, 2.1 Hz, 1H), 2.32 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.0, 135.3, 134.6, 133.3, 130.4, 130.0, 128.0, 127.2, 125.8, 66.6, 59.6, 44.5, 34.8, 19.7;

IR (neat): 3058, 1767, 1146, 743 cm^{-1};

HR-MS (ESI of $[M+Na]^+$): *m/z* calc'd for $C_{14}H_{14}NaO$: 221.0937; found: 221.0954.

Preparation of cyclobutanone 344



344

Procedure A:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95→20:80). Yield: 56%; light yellow oil.

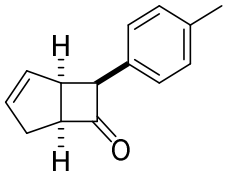
^{1}H NMR (MHz, $CDCl_3$) δ: 7.17 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.06-6.96 (m, 3H), 5.86 (m, 1H), 5.53 (m, 1H), 4.76 (dd, *J* = 8.2, 3.1 Hz, 1H), 3.97-3.88 (m, 2H), 2.82-2.74 (m, 1H), 2.54-2.45 (m, 1H), 2.32 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.2, 138.1, 134.7, 134.7, 130.6, 128.9, 128.3, 128.0, 125.3, 68.8, 59.5, 44.9, 34.5, 21.6;

IR (neat): 3058, 2919, 2853, 1772, 1607, 1051 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{14}H_{15}O$: 199.1117; found: 199.1129.

Preparation of cyclobutanone 345



345

Procedure A:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 2.5:97.5→12.5:87.5). Yield: 76%; yellow oil.

Procedure B:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 2.5:97.5→12.5:87.5). Yield: 59%; yellow oil.

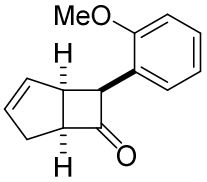
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.09 (d, *J* = 8.1 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 5.86 (m, 1H), 5.52 (m, 1H), 4.75 (dd, *J* = 8.4, 3.2 Hz, 1H), 3.95-3.88 (m, 2H), 2.78 (m, 1H), 2.49 (m, 1H), 2.31 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$) δ: 212.4, 136.8, 134.7, 131.7, 130.6, 129.1, 128.2, 68.6, 59.6, 45.0, 34.5, 21.3;

IR (neat): 3054, 2920, 1773, 1515, 1146 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{14}H_{15}O$: 199.1117; found: 199.1126.

Preparation of cyclobutanone 342



342

Procedure A:

Reaction time: 4.5 h. Flash chromatography (EtOAc:hexanes, 5:95→20:80). Yield: 48%; light yellow oil.

Procedure B:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95→20:80). Yield: 52%; light yellow oil.

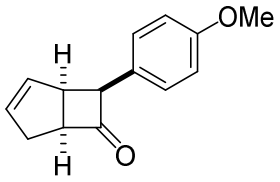
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.21 (ddd, *J* = 7.8, 1.6 Hz, 1H), 6.89-6.81 (m, 2H), 5.81 (m, 1H), 5.35 (dddd, *J* = 5.7, 2.2, 2.2, 2.2 Hz, 1H), 5.00 (dd, *J* = 9.2, 2.5 Hz, 1H), 4.02-3.95 (m, 1H), 3.91-3.84 (m, 1H), 3.83 (s, 3H), 2.76 (m, 1H), 2.49 (ddddd, *J* = 17.0, 9.2, 2.0, 2.0, 2.0 Hz, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.4, 156.5, 134.2, 131.0, 128.9, 128.2, 123.3, 120.3, 110.0, 63.4, 59.6, 55.4, 44.8, 34.8;

IR (neat): 3060, 2939, 1767, 1492, 1244, 1024, 752 cm^{-1};

HR-MS (ESI of $[M+Na]^+$): *m/z* calc'd for $C_{14}H_{14}NaO_2$: 237.0886; found: 237.0906.

Preparation of cyclobutanone 346



346

Procedure A:

Reaction time: 3 h. Flash chromatography (EtOAc:hexanes, 10:90→30:70). Yield: 66%; yellow oil.

Procedure B:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 10:90→30:70). Yield: 44%; yellow oil.

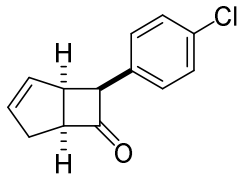
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11-7.07 (m, 2H), 6.84-6.80 (m, 2H), 5.87 (m, 1H), 5.51 (m, 1H), 4.73 (dd, *J* = 6.6, 4.0 Hz, 1H), 3.93-3.88 (m, 2H), 3.77 (s, 3H), 2.78 (dq, *J* = 17.0, 2.1 Hz, 1H), 2.49 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.5, 158.7, 134.6, 130.6, 129.4, 126.9, 113.8, 68.3, 59.5, 55.3, 45.1, 34.4;

IR (neat): 3060, 2935, 1767, 1511, 1246, 1030, 839 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{14}H_{15}O_2$: 215.1067; found: 215.1076.

Preparation of cyclobutanone 347



347

Procedure A:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95→15:85). Yield: 63% (dr = 4:1); yellow oil.

(*major*)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.2-7.23 (m, 2H), 7.14-7.09 (m, 2H), 5.89-5.85 (m, 1H), 5.49-5.45 (m, 1H), 4.74 (dd, *J* = 7.1, 4.6 Hz, 1H), 3.96-3.90 (m, 2H), 2.81-2.73 (m, 1H), 2.54-2.45 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.4, 135.1, 133.2, 133.0, 130.1, 129.6, 128.6, 67.9, 59.8, 44.8, 34.5;

IR (neat): 3054, 2919, 2851, 1777, 1492, 1091 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{13}H_{11}ClNaO$: 241.0391; found: 241.0361.

(*minor*)

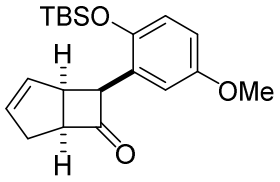
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33-7.29 (m, 2H), 7.21-7.17 (m, 2H), 6.00 (dddd, *J* = 5.6, 2.3, 2.3, 2.3 Hz, 1H), 5.89 (m, 1H), 4.04-3.98 (m, 2H), 3.65-3.59 (m, 1H), 2.84-2.77 (m, 1H), 2.66-2.56 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.7, 135.1, 133.0, 132.7, 132.4, 129.1, 128.3, 72.0, 60.9, 44.7, 35.4;

IR (neat): 3054, 2921, 2855, 1774, 1491, 1092 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{13}H_{11}ClNaO$: 241.0391; found: 241.0369.

Preparation of cyclobutanone 348



348

Procedure B:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95→10:90). Yield: 59%; yellow oil.

Major product:

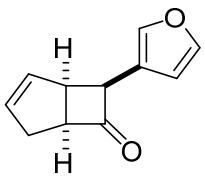
^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (d, *J* = 2.7 Hz, 1H), 6.70 (d, *J* = 9.0 Hz, 1H), 6.64 (dd, *J* = 2.7, 9.0 Hz, 1H), 5.83 (m, 1H), 5.41 (m, 1H), 4.95 (dd, *J* = 2.7, 9.3 Hz, 1H), 3.96 (m, 1H), 3.89 (m, 1H), 3.71 (s, 3H), 2.76 (br d, *J* = 17 Hz, 1H), 2.49 (m, 1H), 1.03 (s, 9H), 0.24 (s, 3H), 0.21 (s, 3H) ;

^{13}C NMR (100 MHz, $CDCl_3$) δ: 213.2, 153.3, 146.6, 134.3, 130.8, 126.1, 118.4, 114.8, 113.0, 63.8, 59.6, 55.6, 44.8, 34.7, 25.9, 18.2, -4.0, -4.2;

IR (neat): 2955, 2857, 1773, 1495, 1222, 1046 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{20}H_{29}O_3Si$: 345.1880; found: 345.1859.

Preparation of cyclobutanone 349



349

Procedure B

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 52%; yellow oil.

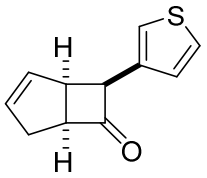
^{1}H NMR (400 MHz, C_6D_6) δ: 7.26 (m, 1H), 7.05 (dd, *J* = 1.8, 1.8 Hz, 1H), 6.08 (d, *J* = 1.8 Hz, 1H), 5.47 (m, 1H), 5.32 (m, 1H), 3.98 (dd, *J* = 2.1, 9.1 Hz, 1H), 3.28 (m, 1H), 3.18 (m, 1H), 2.6 (m, 1H), 2.0 (m, 1H).

^{13}C NMR (100 MHz, C_6D_6) δ: 208.9, 142.9, 140.4, 134.4, 130.6, 118.5, 110.7, 60.5, 60.0, 44.2, 34.5.

IR (neat): 2914, 1773, 1501, 1156, 1024 cm^{-1}.

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{11}H_{11}O_2$: 175.0754; found: 175.0750.

Preparation of cyclobutanone 350



350

Procedure B

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95→10:90). Yield: 65%; colourless oil.

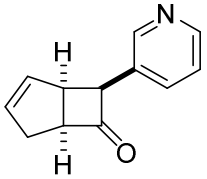
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (dd, *J* = 3.1, 5.0 Hz, 1H), 7.12 (m, 1H), 6.90 (dd, *J* = 1.1, 5.0 Hz, 1H), 5.87 (m, 1H), 5.55 (m, 1H), 4.81 (dd, *J* = 2.7, 8.8 Hz, 1H), 3.92 (m, 2H), 2.77 (m, 2H), 2.49 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.5, 134.6, 134.4, 130.4, 127.3, 125.3, 122.2, 64.4, 59.7, 44.6, 34.3.

IR (neat): 2914, 1775, 1351, 1145, 998 cm^{-}1.

HR-MS (ESI of [M+H]+): m/z calc'd for $C_{11}H_{11}OS$: 191.0525; found: 191.0540.

Preparation of cyclobutanone 351



351

Procedure B:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 30:70→50:50). Yield: 56% (dr = 3:1, inseparable mixture); light yellow oil.

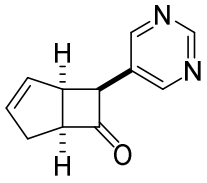
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.50 (dd, *J* = 1.8, 5.4 Hz, 1H), 8.43 (d, *J* = 1.8 Hz, 1H), 7.57 (ddd, *J* = 1.8, 1.8, 7.0 Hz, 1H), 7.26 (dd, *J* = 5.4, 7.0 Hz, 1H), 5.92 (m, 1H), 5.47 (m, 1H), 4.80 (dd, *J* = 2.7, 8.6 Hz, 1H), 4.00 (m, 2H), 2.81 (m, 1H), 2.53 (ddq, *J* = 2.2, 8.5, 17.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.4, 148.8, 147.8, 136.3, 135.6, 129.5, 123.5, 65.9, 60.3, 44.6, 34.5.

IR (neat): 2922, 3854, 1775, 1479, 1243, 1146 cm^{-1}.

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{12}H_{12}NO$: 186.0913; found: 186.0926.

Preparation of cyclobutanone 352



352

Procedure B:

Reaction time: 2 h. Flash chromatography (EtOAc:hexanes, 50:50→70:30). Yield: 40% (dr = 4:1, inseparable mixture); light yellow oil.

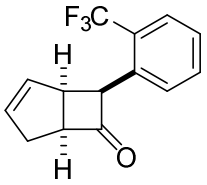
Major product:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.13 (s, 1H), 8.57 (s, 2H), 5.99 (m, 1H), 5.48 (m, 1H), 4.77 (dd, *J* = 1.9, 9.1 Hz, 1H), 4.08 (m, 1H), 4.01, (m, 1H), 2.85 (m, 1H), 2.55 (ddq, *J* = 2.3, 9.0, 17.1 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 209.00, 157.4, 156.5, 155.3, 136.8, 129.0, 63.8, 61.0, 44.4, 34.8.

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{11}H_{11}N_2O$: 187.0866; found: 187.0875.

Preparation of cyclobutanone 343



343

Procedure B:

Reaction time: 2.5 h. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 53%; colourless oil. 2 equivalents of cyclobutanone were used to obtain higher conversion and 3.3 equivalents of Li*O*t*Bu were used.

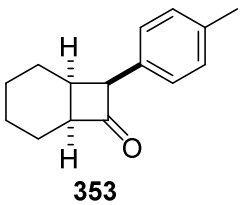
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.34 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 5.88 (m, 1H), 5.27 (m, 1H), 5.10 (dd, *J* = 2.1, 9.2, Hz, 1H), 4.00 (m, 1H), 3.94 (m, 1H), 2.81 (br d, 17.6 Hz, 1H), 2.55 (ddq, *J* = 2.1, 9.1, 17.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.5, 135.0, 132.6 (q, *J* = 1.8 Hz), 131.6 (q, *J* = 1.2 Hz), 130.3, 130.1, 127.9 (q, *J* = 28.0 Hz), 127.2, 126.0 (q, 5.6 Hz), 124.4 (q, *J* = 273 Hz), 65.3 (q, *J* = 0.9 Hz), 59.6, 46.4 (q, 1.2 Hz), 34.8.

IR (neat): 2920, 1778, 131, 1156, 1109 cm^{-1}.

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{14}H_{12}F_3O$: 253.0835; found: 253.0831.

Preparation of cyclobutanone 353



353

Procedure A:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95→20:80). Yield: 58% (dr = 4:1 inseparable mixture); yellow oil.

Procedure B:

Reaction time: 2.5 h. Flash chromatography (EtOAc:hexanes, 5:95→20:80). Yield: 66% (dr = 9:1 inseparable mixture); yellow oil.

Major product:

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28-7.24 (m, 2H), 7.14-7.10 (m, 2H), 4.59 (app d, *J* = 9.1 Hz, 1H), 3.35 (dd, *J* = 8.4, 8.4 Hz, 1H), 2.85-2.76 (m, 1H), 2.32 (s, 3H), 2.14-2.08 (m, 1H), 1.77-1.70 (m, 1H), 1.61-1.50 (m, 2H), 1.48-1.39 (m, 1H), 1.14-1.04 (m, 2H), 0.88-0.78 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.2, 136.4, 132.2, 129.0, 128.2, 64.0, 54.0, 28.3, 26.4, 22.8, 22.7, 21.3, 21.0;

IR (neat): 2925, 2853, 1767, 1515, 1024 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{15}H_{19}O$: 215.1430; found: 215.1437.

Minor product:

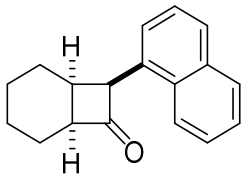
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.28-7.24 (m, 2H), 7.14-7.10 (m, 2H), 4.29 (dd, *J* = 7.3, 1.7 Hz, 1H), 3.29-3.23 (m, 1H), 2.70-2.62 (m, 1H), 2.32 (s, 3H), 2.05-1.95 (m, 1H), 1.88-1.79 (m, 1H), 1.76-1.67 (m, 2H), 1.58-1.50 (m, 3H), 1.43-1.33 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 209.4, 136.6, 133.8, 129.5, 127.0, 66.2, 53.9, 30.6, 26.1, 22.6, 22.1, 21.5, 21.2;

IR (neat): 2925, 2853, 1767, 1515, 1024 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{15}H_{19}O$: 215.1430; found: 215.1437.

Preparation of cyclobutanone 354



354

Procedure A:

Reaction time: 3 h. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 30%; yellow oil.

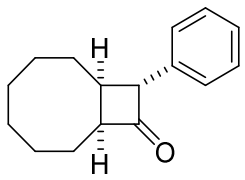
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (ddd, *J* = 7.2, 1.0, 1.0 Hz, 1H), 7.97-7.93 (m, 1H), 7.87-7.83 (m, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.54-7.46 (m, 2H), 7.44 (dd, *J* = 8.2, 7.2 Hz, 1H), 5.08 (d, *J* = 8.8 Hz, 1H), 3.53 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.20-3.08 (m, 1H), 2.21-2.14 (m, 1H), 1.63-1.55 (m, 1H), 1.53-1.39 (m, 3H), 1.20-1.00 (m, 2H), 0.87-0.74 (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 208.9, 133.6, 131.7, 131.4, 128.9, 127.6, 126.2, 126.0, 125.7, 125.5, 123.1, 62.0, 54.9, 29.8, 25.3, 22.7, 22.5, 21.2;

IR (neat): 3048, 2927, 2853, 1767, 1677, 1447, 1173 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{18}H_{19}O$: 251.1430; found: 251.1428.

Preparation of cyclobutanone 358



358

Procedure B:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 81% (dr = 3.5:1); light yellow oil.

Major product:

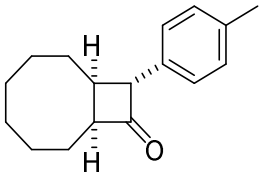
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35-7.31 (m, 2H), 7.26 (m, 3H), 3.99 (dd, *J* = 2.6, 7.9 Hz, 1H), 3.19 (dddd, *J* = 11.8, 9.6, 2.2, 2.3 Hz, 1H), 2.57 (dddd, *J*= 11.8, 9.9, 8.0, 2.3 Hz, 1H), 2.04-1.74 (m, 5H), 1.71-1.55 (m, 3H), 1.52-1.21 (m, 4H);

^{13}C NMR (105 MHz, $CDCl_3$) δ: 212.3, 136.5, 128.7, 126.9, 69.1, 61.4, 37.8, 29.8, 29.4, 28.2, 25.9, 25.2, 23.9;

IR (neat): 2924, 1760, 1448, 698 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{16}H_{21}O$: 229.1587; found: 229.1588.

Preparation of cyclobutanone 356



356

Procedure A:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 64% (dr = 3:1); yellow oil.

Procedure B:

Reaction time: 2.5 h. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 58% (dr = 6:1); yellow oil.

Major product:

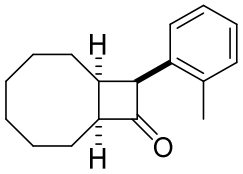
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 3.94 (dd, *J* = 2.7, 7.7 Hz, 1H), 3.17 (dddd, *J* = 2.2, 2.2, 9.6, 12.2 Hz, 1H), 2.52 (m, 1H), 2.33 (s, 3H), 2.02-1.72 (m, 5H), 1.68-1.55 (m, 3H), 1.51-1.33 (m, 3H), 1.23 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.6, 136.6, 135.6, 129.4, 126.9, 68.9, 61.4, 38.0, 29.8, 29.5, 28.2, 26.0, 25.2, 24.0, 21.1.

IR(neat): 2919, 2852, 1774, 1515, 1463 cm^{-1}.

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{17}H_{23}O$: 243.1743; found: 243.1727.

Preparation of cyclobutanone 355



355

Procedure A:

Reaction time: 1 h. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 54% (dr = 5:1 inseparable mixture); yellow oil.

Procedure B:

Reaction time: 0.5 h. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 74% (dr = 1:1 inseparable mixture); yellow oil.

Major product:

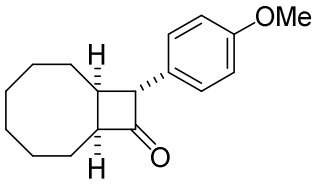
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 6.4 Hz, 1H), 7.18-7.11 (m, 3H), 4.75 (dd, *J* = 2.2, 10.2 Hz, 1H), 3.30 (dddd, *J* = 2.7, 2.7, 9.6, 12.3, 1H), 2.88 (m, 1H), 2.20 (s, 3H), 1.94 (m, 1H), 1.78-1.64 (m, 4H), 1.61-1.33 (m, 3H), 1.30-0.97 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 211.8, 135.8, 132.9, 129.9, 128.2, 127.1, 125.8, 63.3, 60.3, 35.8, 30.6, 27.7, 26.1, 25.9, 25.7, 20.6, 19.6.

IR(neat): 2922, 2852, 1769, 1492, 1463 cm^{-1}.

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{17}H_{23}O$: 243.1743; found: 243.1732.

Preparation of cyclobutanone 357



357

Procedure A:

Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 10:90). Yield: 69% (dr = 3:1); yellow oil.

Procedure B:

Reaction time: 0.5 h. Flash chromatography (EtOAc:hexanes, 10:90). Yield: 66% (dr = 2.5:1); yellow oil.

Major product:

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.92 (dd, *J* = 3.0, 7.9 Hz, 1H), 3.78 (s, 3H), 3.16 (dddd, *J* = 2.0, 2.0, 9.5, 12.4 Hz), 2.44 (m, 1H), 2.01-1.73 (m, 5H), 1.69-1.55 (m, 3H), 1.51-1.32 (m, 3H), 1.26 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 212.9, 158.6, 128.8, 128.1, 114.2, 68.5, 61.4, 55.3, 38.2, 29.9, 29.4, 28.1, 25.9, 25.2, 24.0.

IR(neat): 2920, 2851, 1773, 1513, 1248 cm^{-1}.

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{17}H_{23}O_2$: 259.1693; found: 259.1665.

Preparation of α-Tetralones

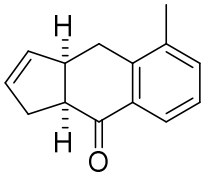
General procedure for tetralone formation:

To a stirred solution of cyclobutanone (1 equiv) in HO*t*Bu (0.2 M) was added H_2O (4 equiv) and KO*t*Bu (2 equiv), and the resulting mixture was purged with N_2 for 5 minutes. The resulting mixture was heated at 60 °C for 1 hour. After this time, the reaction mixture was treated with 1 M HCl until pH = 1, and was diluted with EtOAc and H_2O. The phases were separated, and the aqueous phase was extracted with EtOAc (3×). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude acid was used in the next step without further purification.

To a cold (0 °C), stirred solution of crude acid (1.0 equiv) in CH_2Cl_2 (0.3 M) was added oxalyl chloride (3 equiv) and DMF (cat). The resulting mixture was stirred for 45 minutes. After this time, the solvent was removed *in vacuo* to afford crude acyl chloride, which was used in the next step without purification.

To a cold (0 °C), stirred solution of acyl chloride in CH_2Cl_2 (0.3 M) was drop-wise added a solution of $SnCl_4$ (1.2 equiv) in CH_2Cl_2 (0.43 M) over 1 minute. The resulting mixture was stirred for 1 hour, and was then treated with a saturated aqueous solution of $NaHCO_3$, H_2O, and EtOAc. The phases were separated, and the aqueous phase was extracted with EtOAc (3×). The combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude tetralone product was purified by flash chromatography (silica gel).

Preparation of α-tetralone 359



359

Starting material amount: 0.23 mmol. Flash chromatography (EtOAc:hexanes, 5:95→20:80). Yield: 84%; yellow oil.

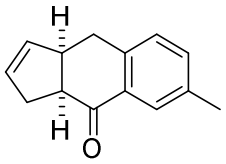
^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.78 (d, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.18 (app t, *J* = 7.6 Hz, 1H), 5.83-5.79 (m, 1H), 5.75-5.71 (m, 1H), 3.41-3.35 (m, 1H), 3.17-3.11 (m, 1H), 3.03 (dd, *J* = 16.3, 5.9 Hz, 1H), 2.88-2.81 (m, 1H), 2.74 (dd, *J* = 16.3, 7.1 Hz, 1H), 2.72-2.66 (m, 1H); 2.33 (s, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) δ: 202.1, 140.3, 135.9, 135.0, 134.9, 133.9, 131.3, 126.2, 125.0, 47.9, 42.7, 36.7, 27.7, 19.6;

IR (neat): 3054, 2912, 2851, 1674, 1593, 1286 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{14}H_{15}O$: 199.1117; found: 199.1115.

Preparation of α-tetralone 361



361

Starting material amount: 73 μmol. Flash chromatography (EtOAc:hexanes, 5:95→20:80). Yield: 95%; light yellow oil.

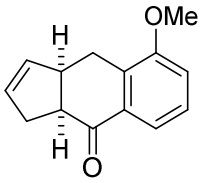
^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.70 (s, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 5.81-5.78 (m, 1H), 5.73-5.71 (m, 1H), 3.40-3.34 (m, 1H), 3.19-3.13 (m, 1H), 3.03 (dd, *J* = 15.8, 5.7 Hz, 1H), 2.86 (m, 1H), 2.77 (dd, *J* = 15.8, 7.3 Hz, 1H), 2.66 (m, 1H), 2.35 (s, 3H);

^{13}C NMR (150 MHz, $CDCl_3$) δ: 202.1, 139.1, 136.6, 134.7, 134.5, 133.7, 131.3, 128.5, 127.3, 48.5, 43.3, 36.7, 31.4, 21.1;

IR (neat): 3052, 2921, 1671, 1610, 1413, 821 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{14}H_{15}O$: 199.1117; found: 199.1128.

Preparation of α-tetralone 360



360

Starting material amount: 0.14 mmol. Flash chromatography (EtOAc:hexanes, 5:95→20:80). Yield: 56%; colorless oil.

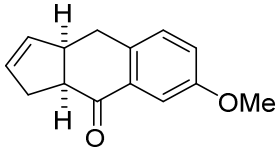
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 (d, *J* = 7.9 Hz, 1H), 7.24 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.02 (d, *J* = 8.1 Hz, 1H), 5.81-5.77 (m, 1H), 5.74-5.71 (m, 1H), 3.86 (s, 3H), 3.40-3.31 (m, 1H), 3.17-3.05 (m, 2H), 2.88-2.76 (m, 2H), 2.74-2.65 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.0, 156.7, 135.1, 134.7, 131.2, 131.0, 126.9, 118.9, 114.7, 55.9, 48.1, 42.6, 36.8, 23.7;

IR (neat): 3055, 2948, 2841, 1675, 1584, 1261 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{14}H_{15}O_2$: 215.1067; found: 215.1079.

Preparation of α-tetralone 362



362

Starting material amount: 0.26 mmol. Flash chromatography (EtOAc:hexanes, 5:95→20:80). Yield: 78%; yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 2.8 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.05 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.82-5.78 (m, 1H), 5.74-5.70 (m, 1H), 3.83 (s, 3H), 3.41-

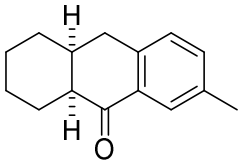
3.33 (m, 1H), 3.16 (ddd, *J* = 9.2, 7.8, 5.8 Hz, 1H), 3.02 (dd, *J* = 15.9, 5.9 Hz, 1H), 2.91-2.82 (m, 1H), 2.76 (dd, *J* = 15.9, 7.4 Hz, 1H), 2.71-2.63 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.7, 158.6, 134.7, 134.5, 134.5, 131.2, 129.8, 121.6, 109.5, 55.6, 48.3, 43.2, 36.7, 30.8;

IR (neat): 3054, 2910, 2840, 1673, 1609, 1281 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{14}H_{15}O_2$: 215.1067; found: 215.1077.

Preparation of α-tetralone 363



363

Starting material amount: 0.27 mmol. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 68%; off-white solid (m.p. = 91-93 °C).

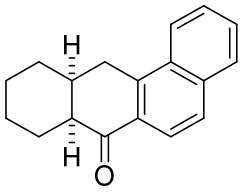
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (s, 1H), 7.30-7.25 (m, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 2.99 (dd, *J* = 16.6, 4.9 Hz, 1H), 2.90 (dd, *J* = 16.6, 6.3 Hz, 1H), 2.70-2.65 (m, 1H), 2.44-2.35 (m, 1H), 2.36 (s, 3H), 2.23-2.12 (m, 1H), 1.67-1.36 (m, 7H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.7, 140.1, 136.2, 134.5, 131.7, 129.3, 127.4, 48.5, 36.0, 33.0, 29.0, 25.5, 23.9, 23.6, 21.1;

IR (neat): 2926, 2852, 1676, 1612, 1271 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{15}H_{19}O$: 215.1430; found: 215.1440.

Preparation of α-tetralone 364



364

Starting material amount: 0.13 mmol. Flash chromatography (EtOAc:hexanes, 5:95) Yield: 75%; light yellow oil.

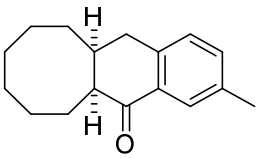
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19-8.15 (m, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.89-7.84 (m, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.64-7.56 (m, 2H), 3.41 (d, *J* = 6.1 Hz, 2H), 2.84-2.78 (m, 1H), 2.64-2.56 (m, 1H), 2.20-2.08 (m, 1H), 1.74-1.63 (m, 1H), 1.63-1.46 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.8, 141.2, 136.0, 131.9, 129.1, 128.9, 128.3, 127.0, 126.7, 124.9, 123.1, 47.8, 35.1, 29.4, 29.3, 25.4, 23.8, 23.7;

IR (neat): 3059, 2928, 2851, 1671, 1236 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{18}H_{19}O$: 251.1430; found: 251.1429.

Preparation of α-tetralone 365



365

Starting material amount: 0.23 mmol. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 67%; light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 1.0 Hz, 1H), 7.27 (dd, *J* = 1.6, 7.7 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 2.86 (m, 2H), 2.46 (m, 2H), 2.35 (s, 3H), 1.87 (m, 1H), 1.75-1.60 (m, 8H), 1.59-1.46 (m, 4H).

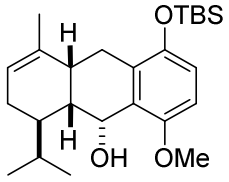
^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.3, 140.3, 136.1, 134.2, 131.8, 128.7, 127.5, 48.7, 36.7, 34.6, 31.2, 28.1, 26.8, 26.2, 25.4, 25.3, 21.0.

IR (neat): 2917, 2852, 1676, 1612, 1445, 1284 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{17}H_{23}O$: 243.1743; found: 243.1732.

3.7.3. Studies Toward the Synthesis of Eleutherobin

Preparation of benzylic alcohol 378



378

To a cold (0 °C), stirred solution of tetralone **377** (853 mg, 2.06 mmol) in THF (20 mL) was added $LiAlH_4$ (117 mg, 3.09 mmol) and the reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was then treated with 1N HCl (20 mL), diluted with EtOAc (20 mL) and the layers were separated. The organic phase was washed with H_2O (2 x 20 mL) and then the combined aqueous phases were washed with EtOAc (2 x 20 mL). The combined organic phases were then washed with brine (20 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:hexanes, 10:90) afforded the benzylic alcohol **378** (555 mg, 1.33 mmol, 66%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.69 (d, *J* = 8.8 Hz, 1H), 6.62 (d, *J* = 6.62 Hz, 1H), 5.59 (m, 1H), 5.13 (dd, *J* = 4.4, 5.0 Hz, 1H), 3.81 (s, 3H), 2.96 (dd, *J* = 6.4, 17.4 Hz, 1H), 2.78 (dd, *J* = 7.5, 17.4 Hz, 1H), 2.50 (d, *J* = 5.0 Hz, 1H, *O*-H), 2.35 (m, 1H), 2.29 (m, 1H),

2.05 (m, 1H), 1.96 (m, 1H), 1.89 (m, 1H), 1.85 (m, 1H), 1.73 (br s, 3H), 1.02 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 6H), 0.20 (s, 3H), 0.19 (s, 3H).

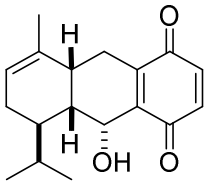
^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.22, 146.6, 137.5, 129.5, 129.4, 123.5, 117.5, 108.5, 67.7, 55.9, 39.8, 39.6, 34.6, 25.9, 25.8, 25.6, 21.2, 21.1, 18.7, 18.3, -4.1, -4.2.

HRMS: *m/z* calcd for $C_{25}H_{40}NaO_3Si$:439.2639 (M+Na); Found: 439.2624 (M+Na)

IR: 3508, 2956, 2858, 1483, 1253, 1082, 860 cm^{-1}

α_D($CHCl_3$, c 1.0): +37.7

Preparation of quinone 379

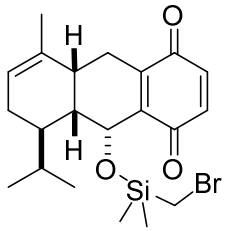


379

To a cold (0 °C), stirred solution of benzylic alcohol **378** (502 mg, 1.21 mmol) in MeCN (12 mL) was added ammonium cerium (IV) nitrate (1.45 g, 2.65 mmol) in H_2O (12 mL) and the reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was then diluted with EtOAc (20 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 10 mL) and then the combined aqueous phases were washed with EtOAc (2 x 20 mL). The combined organic phases were then washed with brine (20 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to afford the crude quinone **379** as a bright orange oil. This compound was then used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.78 (d, *J* = 10.2 Hz, 1H), 6.75 (d, *J* = 10.2 Hz, 1H), 5.57 (m, 1H), 4.89 (m, 1H), 3.61 (d, *J* = 4.8 Hz, 1H), 2.72 (ddd, *J* = 1.9, 6.4, 20.5 Hz, 1H), 2.62 (ddd, *J* = 2.2, 7.1, 20.5 Hz, 1H), 2.40 (br m, 1H), 2.24 (br m, 1H), 2.12 (m, 1H), 2.08 (m, 1H), 1.92 (m, 1H), 1.86 (m, 1H), 1.72 (br d, *J* = 1.0 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 7.3 Hz, 3H).

Preparation of bromomethyldimethylsilyl-protected quinone 368



368

To a cold (0 °C) stirred solution of quinone **379** (1.21 mmol) in CH_2Cl_2 (12 mL) was added imidazole (164 mg, 2.42 mmol) followed by bromomethylchlorodimethylsilane (0.25 mL, 1.82 mmol) and the reaction mixture was stirred at 0 °C for 30 minutes. The reaction mixture was then diluted with H_2O (10 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 10 mL) and then the combined aqueous phases were washed with CH_2Cl_2 (2 x 10 mL). The combined organic phases were then washed with brine (10 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:hexanes, 5:95) afforded the silyl protected quinone **368** (338 mg, 0.77 mmol, 64%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.77 (d, *J* = 10.1 Hz, 1H), 6.73 (d, *J* = 10.1 Hz, 1H), 5.50 (m, 1H), 4.98 (d, *J* = 3.4 Hz, 1H), 3.01 (dd, *J* = 7.6, 17.7 Hz, 1H), 2.46 (dd, *J* = 8.4, 17.7 Hz, 1H), 2.35 (d, *J* = 12.6 Hz, 1H), 2.30 (d, *J* = 12.6 Hz, 1H), 2.28 (m, 1H), 2.22 (m, 1H), 1.83 (m, 1H), 1.78 (m, 1H), 1.75 (m, 1H), 1.73 (s, 3H), 1.60 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 1H), 0.20 (s, 3H), 0.17 (s, 3H).

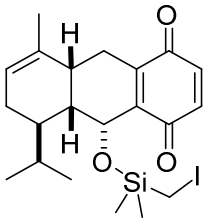
^{13}C NMR (150 MHz, $CDCl_3$) δ: 187.3, 185.9, 144.7, 142.7, 134.6, 136.3, 135.9, 122.3, 65.8, 41.1, 40.3, 33.0, 30.0, 24.8, 24.0, 21.3, 21.2, 19.1, 16.5, -2.7, -2.9.

HRMS: *m/z* calcd for $C_{21}H_{30}IO_3Si$: 437.1142 (M+H); Found: 437.1099 (M+H)

IR: 2958, 1653, 1601, 1299, 1253, 1058, 837 cm^{-1}

α_D($CHCl_3$, c 0.86): +0.6

Preparation of iodide 380



380

To a stirred solution of quinone **368** (40 mg, 0.09 mmol) in acetone (0.5 mL) was added sodium iodide (141 mg, 0.94 mmol) and the reaction mixture was heated to reflux for one hour. The reaction mixture was then cooled to room temperature, diluted with EtOAc (1 mL), treated with saturated aqueous sodium thiosulfate (0.5 mL) The organic phase was washed with H_2O (2 x 1 mL) and then the combined aqueous phases were washed with EtOAc (2 x 1 mL). The combined organic phases were then washed with brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:hexanes, 10:90) afforded the iodide **480** (28 mg, 0.058 mmol, 64%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.78 (d, *J* = 11.3 Hz, 1H), 6.73 (d, *J* = 11.3 Hz, 1H), 5.51 (m, 1H), 4.97 (d, *J* = 3.5 Hz, 1H), 3.02 (dd, *J* = 6.9, 17.4 Hz, 1H), 2.47 (dd, *J* = 8.1, 17.4 Hz, 1H), 2.28 (m, 1H), 2.23 (m, 1H), 1.91 (d, *J* = 12.1 Hz, 1H), 1.85 (d, *J* = 12.1 Hz, 1H), 1.78 (m, 1H), 1.73 (m, 5H), 1.60, (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.23 (s, 3H), 0.18 (s, 3H).

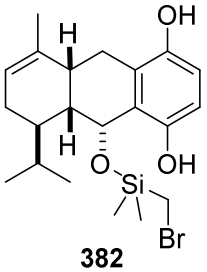
^{13}C NMR (150 MHz, $CDCl_3$) δ: 187.2, 185.9, 144.8, 142.7, 136.4, 135.92, 135.91, 122.2, 65.8, 41.2, 40.3, 33.0, 30.0, 24.8, 24.0, 21.3, 21.2, 19.1, -2.0, -2.5.

HRMS: *m/z* calcd for $C_{21}H_{30}IO_3Si$: 485.1003 (M+H); Found: 485.0987 (M+H)

IR: 2958. 1653, 1600, 1464, 1300, 1252, 1089, 835 cm^{-1}

α_D($CHCl_3$, c 0.66): -7.5

Preparation of hydroquinone 382



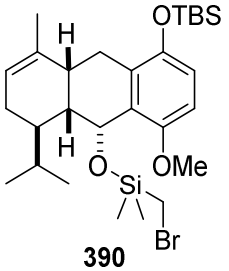
382

To a stirred solution of zinc powder (9 mg, 0.14 mmol) in saturated aqueous ammonium chloride (0.8 mL) was added quinone **368** (30 mg, 0.071 mmol) in THF (1 mL) and the reaction was stirred vigorously for 2 hours. The reaction mixture was then filtered through Celite, diluted with EtOAc (1 mL) and washed with H_2O (1 mL). The combined organic phases were then washed with brine (1 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (EtOAc:hexanes, 25:75) afforded the hydroquinone **382** (28 mg, 0.058 mmol, 64%) as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (br s, 1H, Ph-O*H*), 6.58 (d, *J* = 8.7 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 5.36 (d, *J* = 3.7 Hz, 1H), 5.34 (m, 1H), 4.46 (br s, 1H, Ph-O*H*), 2.84 (dd, *J* = 8.4, 17.3 Hz, 1H), 2.62 (dd, *J* = 7.5, 17.3 Hz, 1H), 2.58 (d, *J* = 13.5 Hz, 1H), 2.54 (d, *J* = 13.5 Hz, 1H), 2.47 (m, 1H), 2.09 (m, 1H), 1.89 (m, 1H), 1.87 (m, 1H), 1.82 (m, 1H), 1.74 (br q, *J* = 1.51 Hz, 3H), 1.50 (m, 1H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.77 (d, *J* = 7.1 Hz, 3H), 0.42 (s, 3H), 0.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.7, 145.4, 136.8, 123.3, 121.3, 121.0, 114.6, 114.3, 77.7, 42.6, 38.3, 36.7, 27.4, 26.3, 25.6, 24.1, 21.7, 21.6, 17.3, 14.9, -2.8, -2.9.

Preparation of silyl-protected alcohol 390



390

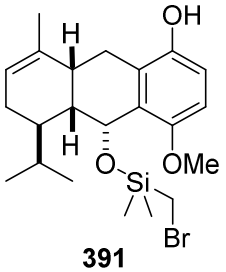
To a stirred solution of benzylic alcohol **378** (215 mg, 0.52 mmol) in CH_2Cl_2 (3 mL) was added imidazole (53 mg, 0.78 mg) and the reaction mixture was cooled to 0 °C. Bromomethylchlorodimethylsilane (0.070 mL, 0.57 mmol) was then added and the reaction mixture was stirred at 0 °C for 20 minutes. The reaction mixture was then diluted with H_2O (3 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 3 mL) and then the combined aqueous phases were washed with CH_2Cl_2 (2 x 3 mL). The combined organic phases were then washed with brine (10 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. The crude compound was used in the next step without purification. Purification of a small amount of the crude product by flash chromatography (EtOAc:hexanes, 5:95) afforded the silyl-protected alcohol **390** as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.71 (d, *J* = 9.1 Hz, 1H), 6.58 (d, *J* = 9.1 Hz, 1H), 5.56 (m, 1H), 5.41 (d, *J* = 4.4 Hz, 1H), 3.79 (s, 3H), 3.27 (dd, *J* = 5.23, 13.9 Hz, 1H), 2.37 (dd, *J* = 13.3, 13.9 Hz, 1H), 2.20 (m, 1H), 2.14 (s, 2H), 2.08 (m, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.78 (m, 1H), 1.76 (s, 3H), 1.02 (s, 9H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).

HRMS: *m/z* calcd for $C_{28}H_{47}BrNaO_3Si_2$: 589.2139 (M+Na); Found: 589.2124 (M+Na).

α_D($CHCl_3$, c 1.0): +6.6

Preparation of phenol 391



391

To a cold (0 °C), stirred solution of compound **390** (0.52 mmol) in THF (5 mL) was added TBAF (1M in THF, 0.47 mL, 0.47 mmol) and the reaction mixture was stirred for 5 minutes. The reaction mixture was then diluted with H_2O (3 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 3 mL) and then the combined aqueous phases were washed with EtOAc (2 x 3 mL). The combined organic phases were then washed with brine (10 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification by flash chromatography (EtOAc:hexanes, 10:90) afforded the phenol **391** (198 mg, 0.44 mmol, 84%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.72 (d, *J* = 9.9 Hz, 1H), 6.60 (d, *J* = 9.9 Hz, 1H), 5.56 (m, 1H), 5.40 (d, *J* = 3.6 Hz, 1H), 4.44 (s, 1H, PhO*H*), 3.79 (s, 3H), 3.14 (dd, *J* = 5.4, 13.4 Hz, 1H), 2.49 (dd, *J* = 11.7, 13.4 Hz, 1H), 2.23 (m, 1H), 2.15 (m, 1H), 2.13 (s, 2H), 1.87 (m, 3H), 1.78 (br s, 3H), 1.75 (m, 1H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 6.2 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H).

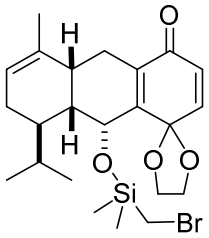
^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.07, 145.5, 135.8, 129.9, 128.5, 122.5, 114.8, 108.3, 66.7, 55.5, 40.1, 39.9, 36.2, 28.5, 24.5, 24.1, 23.8, 22.1, 21.8, 18.1, 16.7, 14.2, -3.1, -3.5.

HRMS: *m/z* calcd for $C_{22}H_{33}BrNaO_3Si$: 475.1275 (M+Na); Found: 475.1251 (M+Na).

IR: 3379, 2957, 1491, 1258, 1090, 1048, 991 cm^{-1}.

α_D($CHCl_3$, c 1.0): -0.7

Preparation of enone 394



394

To a solution of phenol **391** (200 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was added ethylene glycol (0.25 mL, 4.4 mmol) and the reaction mixture was cooled to -40 °C. PIFA (208 mg, 0.49 mmol) was then added dropwise as a solution in CH_2Cl_2 (2 mL) over 5 minutes then the reaction mixture was stirred at -40 °C for 10 minutes then warmed to 0 °C and stirred for an additional 30 minutes. The reaction mixture was then stirred at room temperature for a further 1 hour before being treated with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 3 mL) and then the combined aqueous phases were washed with CH_2Cl_2 (2 x 3 mL). The combined organic phases were then washed with brine (3 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification by flash chromatography (EtOAc:hexanes, 15:85) afforded the enone **394** (110 mg, 0.23 mmol, 52%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.67 (d, *J* = 9.4 Hz, 1H), 6.14 (d, *J* = 9.4 Hz, 1H), 5.48 (m, 1H), 4.57 (d, *J* = 4.0 Hz, 1H), 4.32-4.09 (m, 4H), 3.08 (dd, *J* = 9.4, 9.4, 9.4 Hz, 1H), 2.49 (d, *J* = 13.4 Hz, 1H), 2.38 (d, *J* = 13.4 Hz, 1H), 2.18 (m, 3H), 1.81 (m, 1H), 1.77 (m, 1H), 1.73 (s, 3H), 1.57 (m, 2H), 0.91 (d, *J* = 7.3 Hz, 3H), 0.83 (d, *J* = 7.3 Hz, 3H), 0.20 (s, 3H), 0.18 (s, 3H).

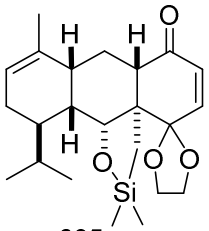
^{13}C NMR (150 MHz, $CDCl_3$) δ: 184.6, 150.9, 141.3, 138.6, 127.4, 121.7, 99.7, 69.3, 65.8, 65.7, 41.4, 40.8, 34.3, 29.0, 24.3, 23.5, 18.4, 16.7, -2.7, -3.1.

HRMS: *m/z* calcd for $C_{23}H_{34}BrO_4Si$: 481.1404 (M+H); Found: 481.1425 (M+H)

IR: 3435, 2959, 1653, 1253, 1103, 965 cm^{-1}.

α_D($CHCl_3$, c 0.36): +17.2

Preparation of silafuran 395



395

To a stirred solution of enone **394** (51 mg, 0.11 mmol) in benzene (2 mL) was added AIBN (2 mg, 0.11 mmol) and Bu_3SnH (0.028 mL, 0.11 mmol) and the reaction mixture was sparged with N_2 for 15 minutes. The reaction mixture was then heated to 80 °C in a sealed vial for 3 hours. More AIBN (2 mg, 0.11 mmol) and Bu_3SnH (0.028 mL, 0.11 mmol) was then added and the reaction was heated at 80 °C for a further 3 hours. The solvent was then removed *in vacuo*. Purification by flash chromatography (EtOAc:hexanes, 15:85) afforded the silafuran **395** (31 mg, 0.077 mmol, 70%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.53 (d, *J* = 9.9 Hz, 1H), 5.95 (d, *J* = 9.9 Hz, 1H), 5.36 (m, 1H), 4.22-4.09 (m, 4H), 3.97 (m, 1H), 3.06 (dd, *J* = 1.9, 12.3 Hz, 1H), 2.51 (m, 1H), 2.37 (m, 1H) 2.34 (m, 1H), 2.14 (m, 1H), 1.83 (m, 1H), 1.66 (s, 3H), 1.58 (m, 1H), 1.42 (m, 1H), 1.15 (d, *J* = 15.3 Hz, 1H), 1.05 (dd, *J* = 1.8, 11.8 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.40 (d, *J* = 15.3 Hz, 1H), 0.13 (s, 3H), 0.12 (s, 3H).

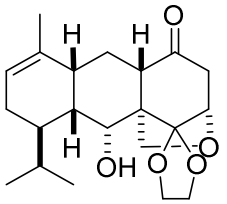
^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.2, 143.8, 135.3, 128.9, 121.2, 110.0, 82.2, 65.6, 65.4, 54.8, 51.1, 44.0, 38.3, 33.0, 31.6, 30.0, 25.0, 21.7, 21.6, 20.8, 19.1, 0.1, -0.7.

HRMS: *m/z* calcd for $C_{23}H_{35}O_4Si$: 403.2299 (M+H); Found: 403.2273 (M+H)

IR: 2958, 1692, 1256, 1037, 816 cm^{-1}

α_D($CHCl_3$, c 0.5): -18.0

Preparation of tetrahydrofuran 411



411

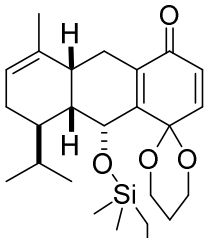
To a stirred solution of silafuran **395** (5 mg, 0.012 mmol) in THF (0.1 mL) and MeOH (0.1 mL) at room temperature was added $KHCO_3$ (3.6 mg, 0.036 mmol) and $KF.2H_2O$ (2.3 mg, 0.025 mmol) followed by H_2O_2 (30% in H_2O, 0.014 mL, 0.12 mmol) and the reaction mixture was stirred for 2 hours. The reaction mixture was then diluted with H_2O (0.5 mL) and EtOAc (0.5 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 0.5 mL) and then the combined aqueous phases were washed with EtOAc (2 x 0.5 mL). The combined organic phases were then washed with brine (0.5 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification by flash chromatography (EtOAc:hexanes, 40:60) afforded the tetrahydrofuran **411** (3.4 mg, 0.0094 mmol, 78%) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.36 (m, 1H), 4.43 (dd, *J* = 2.1, 9.6 Hz, 1H), 4.31 (m, 1H), 4.30 (s, 1H, O*H*), 4.27 (d, *J* = 5.3 Hz, 1H), 4.17 (m, 2H), 4.08 (m, 1H), 3.96 (d, *J* = 9.6 Hz, 1H), 3.94 (dd, *J* = 1.7, 3.8 Hz, 1H), 2.80 (dd, *J* = 2.4, 11.1 Hz, 1H), 2.73 (ddd, *J* = 1.5, 1.5, 16.5 Hz, 1H), 2.61 (dd, *J* = 3.8, 16.5 Hz, 1H), 2.53 (m, 1H), 2.10 (m, 1H), 2.08 (m, 1H), 1.93 (m, 1H),1.79 (m, 2H), 1.66 (br s, 3H), 1.42 (m, 1H), 1.23 (m, 1H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.1 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 207.6, 135.4, 121.5, 115.5, 75.1, 74.1, 67.3, 65.9, 64.7, 53.2, 50.1, 45.8, 40.9, 40.1, 37.6, 29.7, 28.5, 27.7, 26.9, 24.5, 23.4, 21.8, 21.7, 17.5, 15.8, 13.6.

HRMS: *m/z* calcd for $C_{21}H_{31}O_5$: 363.2166 (M+H); Found: 363.2155 (M+H)

Preparation of enone 412



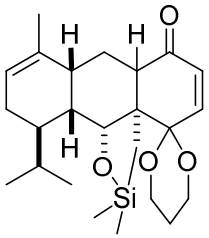
412

To a solution of phenol **491** (100 mg, 0.22 mmol) in CH_2Cl_2 (3 mL) was added 1,3-propanediol (0.023 mL, 0.33 mmol) and the reaction mixture was cooled to -40 °C. PIFA (114 mg, 0.26 mmol) was then added dropwise as a solution in CH_2Cl_2 (2 mL) over 5 minutes then the reaction mixture was stirred at -40 °C for 10 minutes then warmed to 0 °C and stirred for an additional 30 minutes. The reaction mixture was then stirred at room temperature for a further 1 hour before being treated with saturated aqueous $NaHCO_3$ (3 mL) and the phases were separated. The organic phase was washed with H_2O (2 x 3 mL) and then the combined aqueous phases were washed with CH_2Cl_2 (2 x 3 mL). The combined organic phases were then washed with brine (5 mL), then dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo*. Purification by flash chromatography (EtOAc:hexanes, 15:85) afforded the enone **412** (35 mg, 0.070 mmol, 32%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 10.6 Hz, 1H), 6.23 (d, *J* = 10.6 Hz, 1H), 5.47 (m, 1H), 4.90 (d, *J* = 2.9 Hz, 1H), (4.26 (ddd, *J* = 3.1,13.4, 13.4 Hz, 1H), 4.17 (ddd, *J* = 2.1, 12.4, 12.4 Hz, 1H), 4.03 (m, 1H), 3.97 (m, 1H), 3.09 (ddd, *J* = 12.4, 12.4, 12.4 Hz, 1H), 2.44 (d, *J* = 13.4 Hz, 1H), 2.34 (d, *J* = 13.4 Hz, 1H), 2.22 (m, 1H), 2.1 (m, 2H), 1.77 (m, 3H), 1.72 (s, 3H), 1.59 (m, 2H), 0.92 (d, *J* = 7.2 Hz, 3H), 0.87 (m, 1H), 0.84 (d, *J* = 6.2 Hz, 3H), 0.20 (s, 3H), 0.17 (s, 3H).

HRMS: *m/z* calcd for $C_{24}H_{36}BrO_4Si$: 495.1561 (M+H); Found: 495.1570 (M+H)

Preparation of silafuran 413



413

To a stirred solution of enone **412** (13 mg, 0.026 mmol) in benzene (0.5 mL) was added AIBN (1 mg, catalytic) and Bu_3SnH (0.011 mL, 0.039 mmol) and the reaction mixture was sparged with N_2 for 15 minutes. The reaction mixture was then heated to 80 °C in a sealed vial for 3 hours. More AIBN (~1 mg) and Bu_3SnH (0.007 mL, 0.026 mmol) was then added and the reaction was heated at 80 °C for a further 3 hours. The solvent was then removed *in vacuo*. Purification by flash chromatography (EtOAc:hexanes, 15:85) afforded the silafuran **412** as a mixture of two diasteromers (8.1 mg, 0.019 mmol, 74% dr = 4:1) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, *J* = 10.9 Hz, 1H), 6.01 (d, *J* = 10.9 Hz, 1H), 5.37 (m, 1H), 4.52 (d, *J* = 2.4 Hz, 1H), 4.25-3.86 (m, 4H), 3.10 (dd, *J* = 2.4, 10.9 Hz, 1H), 2.49 (m, 1H), 2.34 (m, 2H), 2.13 (m, 1H), 1.81-1.49 (m, 6H), 1.73 (s, 3H), 1.07 (d, *J* = 15.7 Hz, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.25 (d, *J* = 15.7 Hz, 1H), 0.10 (s, 3H), 0.09 (s, 3H).

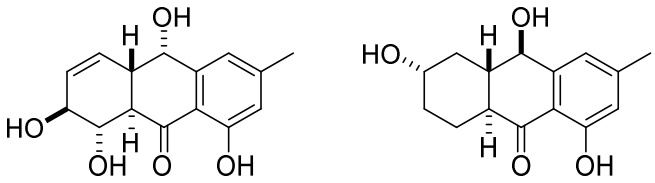
HRMS: *m/z* calcd for $C_{24}H_{37}O_4Si$: 417.2456 (M+H); Found: 417.2432 (M+H).

Chapter 4.

Studies Toward the Total Synthesis of Coniothyrinone D

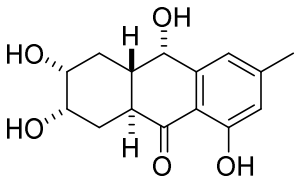
4.1. Introduction

In 2013, Zhang and co-workers reported the isolation of four new hydroxyanthraquinone derivatives from an endophytic *Coniothyrium* sp. of fungi, isolated from the plant *Salsola oppostifolia* in the Canary Islands.[237] These metabolites, coniothyrinones A-D (**39**, **425**-**427**, Figure 4.1) represent the first report of anthraquinone derivatives from a *Coniothyrium* species. These natural products all contain an annulated α-tetralone scaffold along with significant stereochemical complexity. The structure of these natural products was assigned through the analysis of 1D and 2D NMR spectra while 2D NOESY experiments confirmed the relative stereochemistry to be that shown. The absolute configurations of coniothyrinones A (**425**), B (**426**), and D (**39**) were determined on the basis of time-dependent density functional theory[238] (TDDFT) calculations of electronic circular dichromism (ECD) spectra.[239]

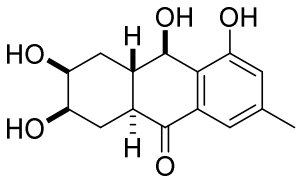


coniothyrinone A (**425**)

coniothyrinone B (**426**)



coniothyrinone C (**427**)



coniothyrinone D (**39**)

Figure 4.1. Anthraquinone derivatives coniothyrinones A-D (39, 425-427) isolated from a *Coniothryium* sp. of endophytic fungi.

Coniothyrinones A-D (**39**, **425**-**427**) were tested in an agar diffusion assay against a number of different fungi and bacteria (Table 4.1). All four compounds showed antimicrobial activity comparable to commercially available antimicrobial agents.

Table 4.1. Antimicrobial activity of coniothyrinones A-D in an agar diffusion assay.

Compound	*M. violaceum*[a]	*S. tritici*[a]	*E. coli*[b]	*B. megaterium*[c]
Coniothyrinone A (**425**)	7.5	6	7.5	8
Coniothyrinone B (**426**)	6	6	6	10
Coniothyrinone C (**427**)	8	5	7.5	10
Coniothyrinone D (**39**)	7.5	5	6	10
Penicillin	6	8	10	26
Streptomycin	7.5	6	0	13

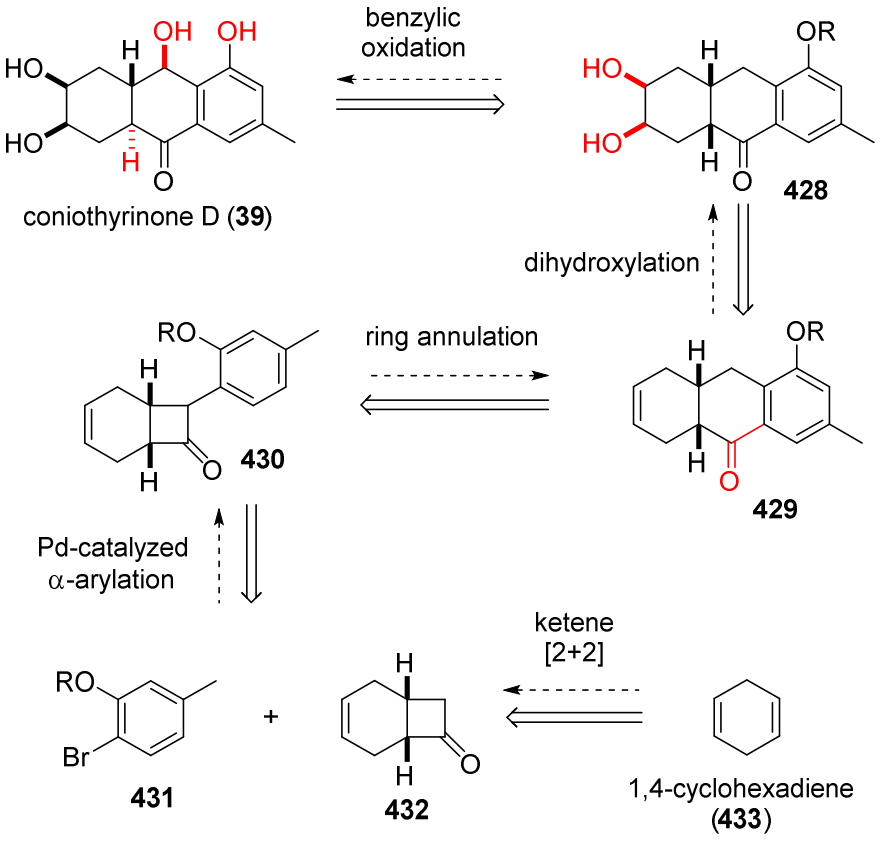
Note: 50 µg of the substances dissolved in acetone were applied to a filter disc and sprayed with the respective test organism. Radii of the zones of inhibition are given in mm. a) Fungi; b) Gram-negative bacterium; c) Gram-positive bacterium.

Having established an efficient synthesis of α-tetralones, we endeavoured to demonstrate this process in the context of a total synthesis coniothyrinone D which would constitute the first total synthesis of a member of this class of natural products.

4.2. Proposed Retrosynthesis

Our retrosynthetic approach to coniothyrinone D (**39**) is outlined in Scheme 4.1. We envisaged that the benzylic alcohol would be introduced by oxidation of the equivalent position in intermediate **428**. The diol would derive from dihydroxylation from the convex face of the decalin ring system of tetralone **429**. This later material would in turn be accessed by the α-arylation/fragmentation/annulation procedure discussed earlier from cyclobutanone **432** and aryl bromide **431**. Cyclobutanone **432** had previously been synthesized from 1,4-cyclohexadiene (**433**) over two steps[240] while 2-bromo-5-methylphenol was commercially available.

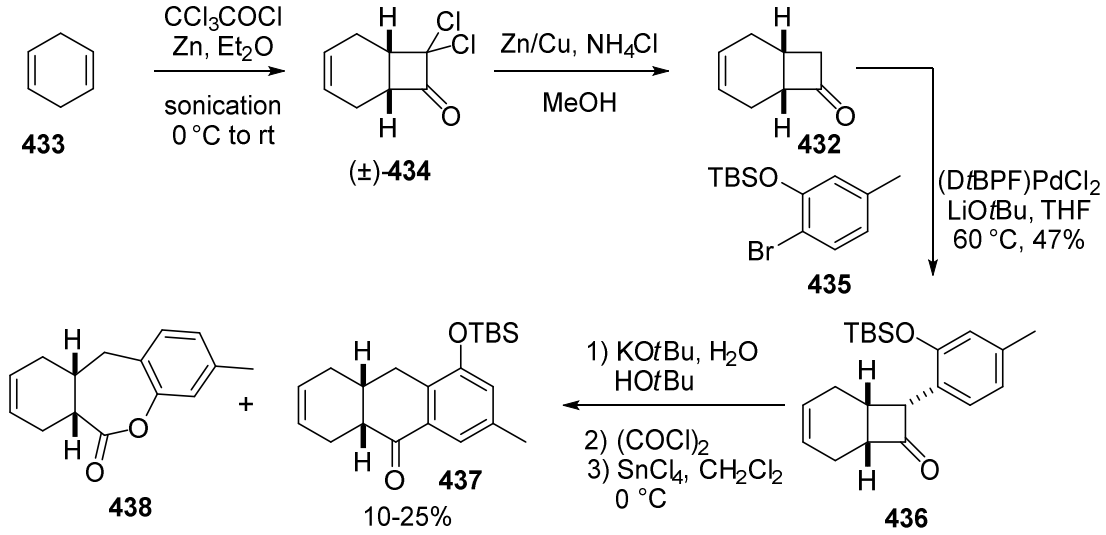
Scheme 4.1. Retrosynthetic approach to coniothryinone D (39).



4.3. Synthetic Attempts

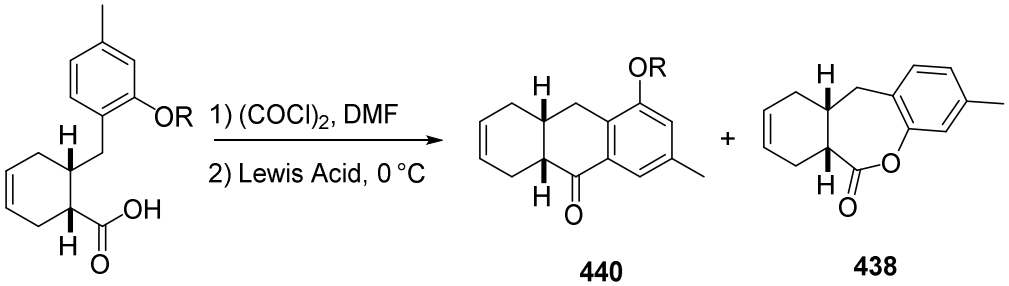
Our attempted synthesis of coniothyrinone D initiated with the [2+2] cycloaddition of the ketene formed from the reaction of trichloroacetyl chloride and zinc with 1,4 cyclohexadiene (**433**). This reaction proceeded cleanly to afford dichlorocyclobutanone **434** which was then dechlorinated by zinc-copper couple in the presence of ammonium chloride to afford cyclobutanone **432** as a single diastereoisomer in 60% yield over two steps. Since removal of the phenol protecting group was one of the last steps in our proposed route, we decided to initially pursue use of a silyl-protected phenol **435** as cleavage of the silyl protecting group was expected to be facile. Initial efforts to carry out the Pd-catalyzed α-arylation between cyclobutanone **432** and silyl-protected phenol **435** using the XPhos/$PdCl_2$/Li*O*t*Bu* conditions developed earlier only afforded the desired α-arylcyclobutanone **436** in very low yield (~10%). However, using the alternative (D*t*BPF)$PdCl_2$/Li*O*t*Bu* conditions, we were able to prepare α-arylcyclobutanone **436** in moderate yield (47%) alongside some recovered aryl bromide **435**. However when we carried out the Haller-Bauer fragmentation using K*O*t*Bu*/H_2O, we observed a significant amount of silyl deprotection (~50%). Furthermore, following acid chloride formation and Friedel Crafts acylation, we only accessed tetralone **437** in a low yield (10-25%) over three steps from α-arylcyclobutanone **436**. This compares poorly to the typical yields for this sequence (Scheme 3.12). The major byproduct from this last step was the formation of lactone **438** which we presume arises from silyl deprotection followed by attack of the phenol into the acid chloride.

Scheme 4.2. Attempted synthesis of α-tetralone (437).



As a result of the low yield for this initial route, we decided to investigate the use of other protecting groups for this sequence. These efforts are summarized in Table 4.2. While the formation of the α-arylcyclobutanones proceeded cleanly in all cases, we encountered significant difficulties in accessing the desired α-tetralone **440** in reasonable yields with the major product being the undesired lactone in most cases. The triisopropylsilyl (TIPS) protecting group (entry 1) was used due to the increased stability of TIPS over TBS to Lewis acids.[241] However, we observed significant decomposition in this reaction and the yield of α-tetralone **440** was not improved. The use of a *para*-methoxybenzyl (PMB) group (entry 2) gave clean conversion to the lactone **439** with no desired product observed. Surprisingly, even the use of the comparatively stable benzyl protecting group (entry 3) gave predominantly the lactone **438** as the major product. In an attempt to determine whether this byproduct resulted from the use of the strong Lewis acid $SnCl_4$, we screened several different reagents to effect the Friedel-Crafts cyclization including Lewis acids (entries 4 to 10) and Brønsted acids (entry 11). Disappointingly, none of these conditions led to the production of the desired product in any appreciable yield. Switching to the methyl protecting group (entry 12), however, did lead to α-tetralone **440** in high yield (71% from the α-cyclobutanone) with no lactone **438** observed.

Table 4.2. Efforts toward the synthesis of α-tetralone (440).



439 **440** **438**

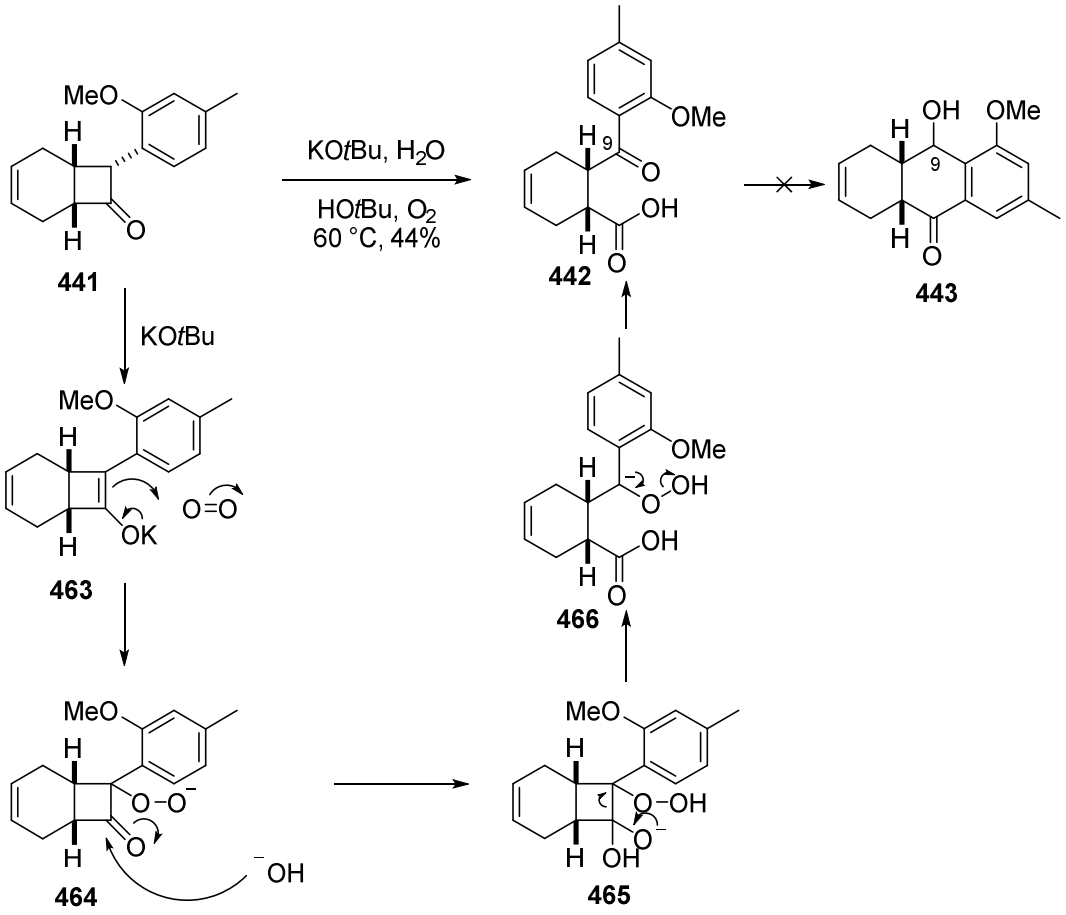
Entry	R	Lewis Acid	Tetralone (440):Lactone (438)
1	TIPS	$SnCl_4$	1:6
2	PMB	$SnCl_4$	0:1
3	Bn	$SnCl_4$	0:1
4	Bn	$FeCl_3$	0:1
5	Bn	$Yb(OTf)_3$	0:1
6	Bn	$AgNO_3$	1:10
7	Bn	$BF_3{\bullet}OEt_2$	0:1
8	Bn	$AlCl_3$	0:1
9	Bn	Et_2AlCl	0:1
10	Bn	$Sc(OTf)_3$	0:1
11	Bn	TFAA, H_3PO_4[a]	0:1
12	Me	$SnCl_4$	1:0

Note: a – reaction used acid **439** as the substrate without forming the acid chloride

Having demonstrated that the OMe was stable to the Friedel Craft acylation conditions, we were interested in moving forward with the synthesis. We had previously observed that degassing the solvent and removing all traces of oxygen was essential during the fragmentation step to avoid oxidation of the product to the benzylic ketone. Since coniothyrinone D was oxygenated at C9, we were interested in investigating whether this undesired process could afford access to the oxidised skeleton of the natural product. As shown in Scheme 4.3, fragmentation of the α-arylcyclobutanone **441** using KO*t*Bu/H_2O under an oxygen atmosphere afforded keto-acid **442**. Here, it is likely that initial trapping of the enolate **463** with O_2 gives peroxide **464**. Subsequent attack by $^{-}$OH at the ketone and fragmentation with expulsion of $^{-}$OH gives the keto-acid **442**. Unfortunately attempts to utilize this compound further in the synthesis were unsuccessful as the acid chloride/Friedel-Crafts sequence led to the formation of an

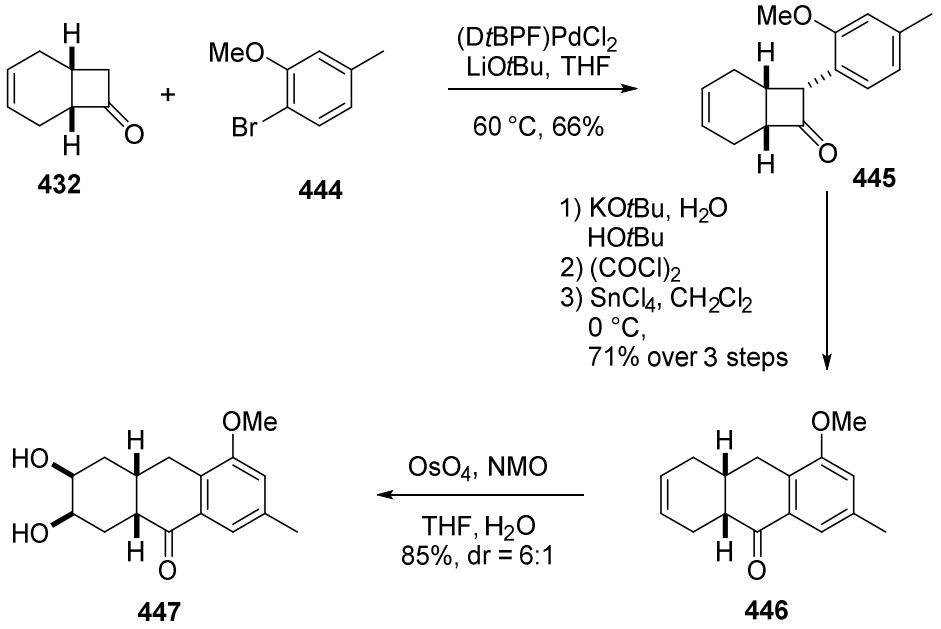
aromatic ring and reduction of the ketone prior to effecting this reaction sequence did not afford the desired product **443** in any appreciable yield.

Scheme 4.3. Oxidation/fragmentation sequence in attempt to access oxidised intermediate (443).



Since oxidation of intermediate **441** was not successful, we next explored the synthesis of tetralone **446** (Scheme 4.4), which proceeded cleanly and in high yields. With α-tetralone **446** in hand, we carried out an Upjohn dihydroxylation of the alkene function.[242] Gratifyingly, this reaction proceeded smoothly (85% yield) and with execellent diastereoselectivity (dr = 6:1) by dihydroxylation from the convex face of the molecule. Interestingly, considerable peak broadening was observed in the ^{1}H and ^{13}C NMR spectra of diol **447** which may result from conformational changes occurring on the order of the NMR timescale.

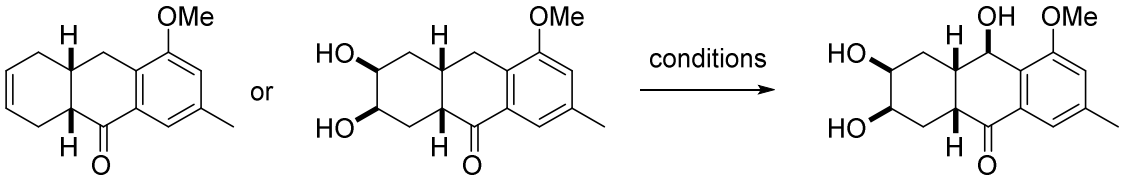
Scheme 4.4. Synthesis of diol (447) *via* Upjohn hydroxylation.



With a scalable route to diol **447** in hand, we then attempted to carry out the critical benzylic oxidation. While many examples of benzylic oxidation have been reported,[243–248] the benzylic oxidation of an α-tetralone has little precedent. Our attempts to effect this reaction are summarized in Table 4.3. Lead tetraacetate has been previously reported to effect benzylic oxidation[249,250] under both thermal and UV irradiation conditions. However, efforts to apply this methodology to α-tetralone **446** (entries 1 and 2) led to the formation of a number of unidentified products. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has also been reported to effectively oxidize highly electron rich benzylic positions.[251] When applied to our substrate, we did not observe any reaction, presumably owing to the fact that the benzylic ketone deactivates the aromatic ring and prevents reaction with this relatively weak oxidising agent. Radical benzylic bromination is also a well-established method of forming benzyl bromides[252] and some researchers have reported that the inclusion of H_2O in the reaction mixture leads to the generation of benzylic alcohols through S_N2 displacement of the bromide.[253] Unfortunately, when our substrate was subjected to these conditions, we observed to incorporation of bromine α to the carbonyl as a result of enol formation followed by reaction with NBS. The Britton group has demonstrated that polyoxometallate catalysts

such as tetrabutylammonium decatungstate (TBADT) can be used to abstract benzylic hydrogen atoms and form the corresponding radical.[254] Oxidation is a commonly observed byproduct of this reaction, and we considered that running this reaction under an O_2 atmosphere might afford the desired product. However, the substrate was not compatible with the conditions and afforded an intractable mixture of products. Finally, we explored the use of ammonium cerium (IV) nitrate (CAN) to effect this benzylic oxidation. These conditions have been reported previously for the installation of alcohols in positions *ortho* to an oxygenated function on the benzene ring.[255] To our delight, when diol **447** was reacted with excess CAN in water/acetonitrile, we were able to obtain the benzyl alcohol **448** in good yield (65%) and very high diastereoselectivity (>20:1 dr).

Table 4.3. Benzylic oxidation efforts to access triol (448).

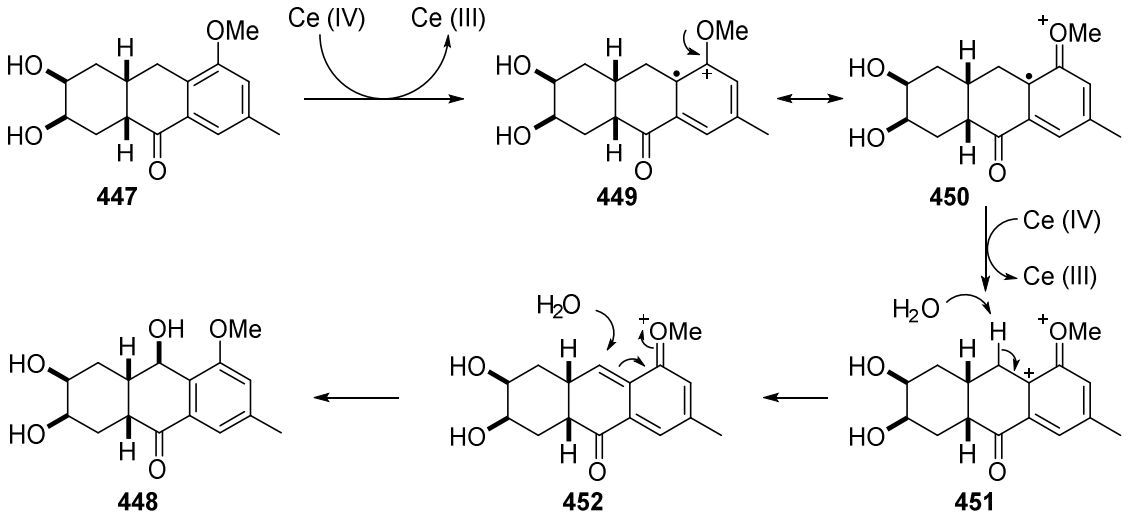


446 **447** **448**

Entry	Substrate	Conditions	Outcome
1	Alkene **446**	$Pb(OAc)_4$, hv, AcOH	Decomposition
2	Alkene **446**	$Pb(OAc)_4$, AcOH, 60 °C	Decomposition
3	Alkene **446**	DDQ	No reaction
4	Diol **447**	NBS, AIBN, H_2O, CCl_4, 80 °C	Bromine incorporation α to carbonyl
5	Alkene **446**	TBADT, O_2, hv	Decomposition
6	Diol **447**	CAN, H_2O, MeCN	Benzyl alcohol **448** (65%)

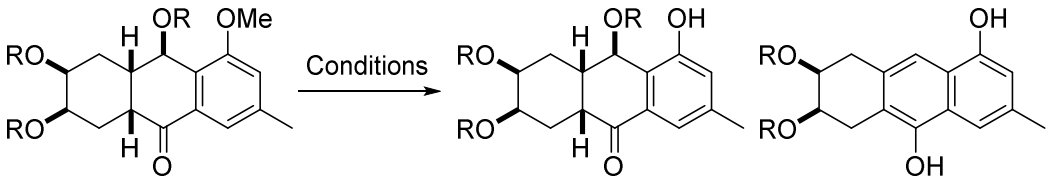
A proposed mechanism for this benzylic oxidation is shown in Scheme 4.5. Single electron transfer to the cerium (IV) converting it to cerium (III) generates the radical carbocation **449**. The cation is stabilized by resonance with the lone pair on the oxygen (**450**). Subsequently, a second single electron transfer occurs from another cerium (IV) species to give the carbocation **451**. Deprotonation then affords the highly activated enone **452** and subsequent H_2O attack from the convex face affords alcohol **448** with high diastereoselectivity.

Scheme 4.5. Proposed mechanism for benzylic oxidation of (447) by ammonium cerium (IV) nitrate.



With the benzylic alcohol **448** in hand, we then investigated deprotection of the phenol to access the natural product. Unfortunately, a screen of conditions to remove the methyl protecting group on the phenol proved to be unsuccessful (Table 4.4). Standard conditions involving the use of BBr_3[256] provided a complicated mixture of undesired products while nucleophilic conditions involving thiols (entries 3 and 4) were not productive.[257,258] Other conditions reported in the literature also proved too harsh for this sensitive substrate (entries 5 and 6).[259,260] In order to determine whether protection of the alcohol functions would increase the stability of this intermediate, we installed TBS ethers and accessed the silyl-protected compound **455**. While this compound was also unstable to Lewis acids (e.g BBr_3, entry 7), when subjected to thiophenol/NaH in DMF (entry 9) at 150 °C we did not observe immediate decomposition. However, after reaction for 12 hours, we recovered undesired byproduct **454** from the reaction along with some starting material (**454**:**455** 1:2). Compound **454** presumably arises from phenol deprotection followed by silyl migration and subsequent elimination of the unprotected alcohol function to give the napthol ring.

Table 4.4. Attempts to access phenol (453).



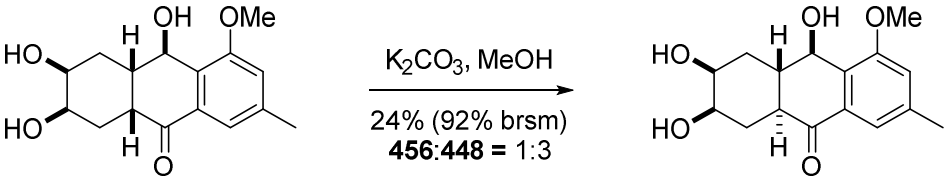
453 **454**

R = H, **448**
R = TBS, **455**

Entry	R	Conditions	Result
1	H	BBr_3, CH_2Cl_2, 0 °C	Decomposition
2	H	BBr_3, CH_2Cl_2, -40 °C	Decomposition
3	H	PhSH, NaH, DMF, 150 °C	Decomposition
4	H	EtSH, $AlCl_3$, CH_2Cl_2, 0 °C	Napthol **454**
5	H	LiCl, DMF, 110 °C	Decomposition
6	H	TMSI, $CDCl_3$	Decomposition
7	TBS	BBr_3, CH_2Cl_2, -40 °C	Decomposition
8	TBS	TMSI, $CDCl_3$	Decomposition
9	TBS	PhSH, NaH, DMF, 150 °C	Starting material plus napthol products

While attempts to remove the methyl group were unsuccessful, we were able to epimerise the α-keto position to access correctly configured O-methylconiothryinone D (**456**). Interestingly, efforts to epimerise this position resulted in the formation of a thermodynamic mixture favouring the *cis*-fused ring system. This is in contrast to epimerisation prior to benzylic oxidation which affords the *trans*-fused ring as the major (5:1) product.

Scheme 4.6. Synthesis of O-methylconiothyrinone D (456).



448

O-methylconiothyrinone D
(**456**)

Stereochemical assignment of these two diastereoisomers was accomplished by analysis of 2D NOESY spectra (Figure 4.2). In particular, the NOESY spectra of **397** displayed clear NOE correlations between the protons in the axial positions around the ring and confirmed the stereochemistry to be as shown.

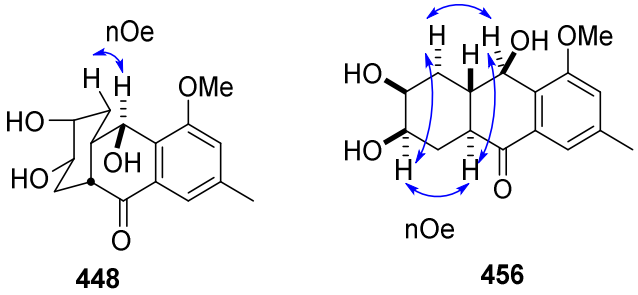
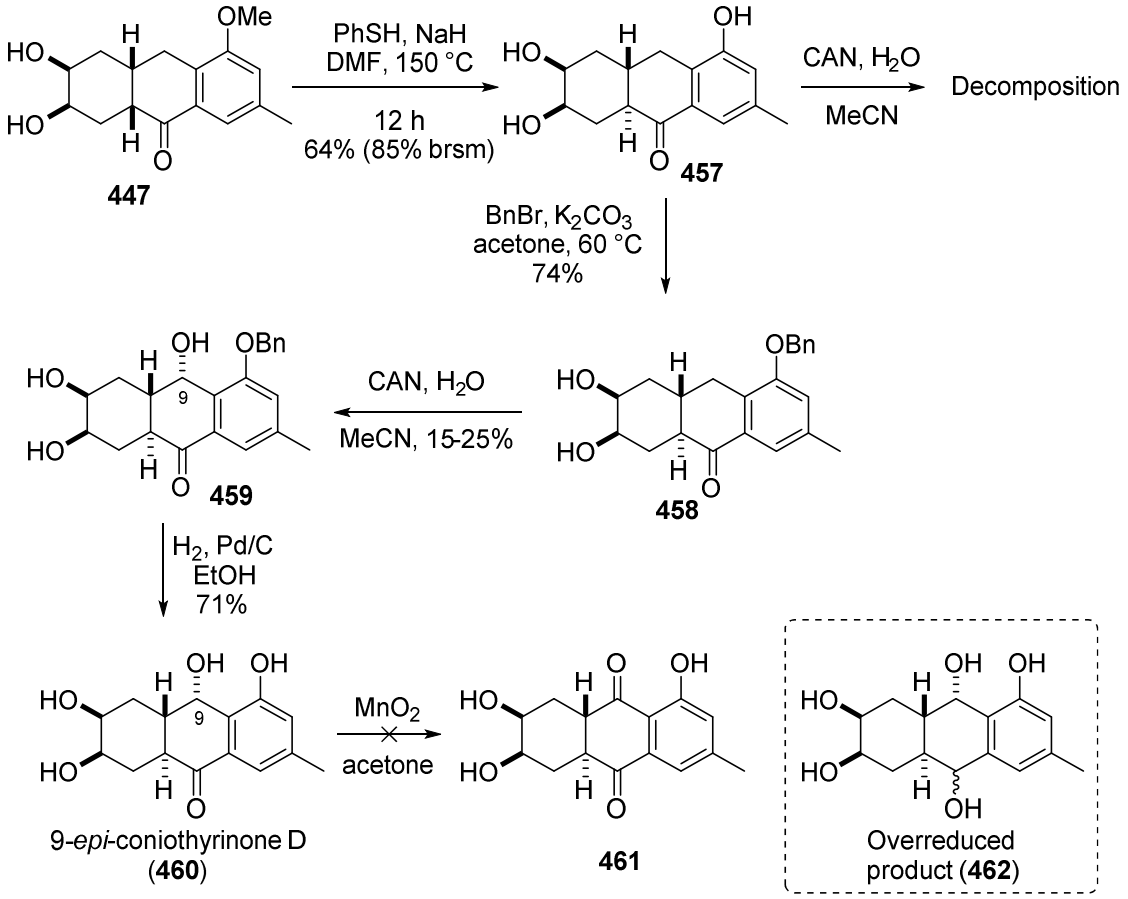


Figure 4.2. NOESY analysis of diastereoisomers (448) and (456).

As efforts to remove the methyl group were unsuccessful, we investigated the removal of the methyl group at an earlier stage in the synthesis. Accordingly, we subjected diol **447** to several different conditions to determine the feasibility of this plan. While BBr_3 proved to be incompatible with the diol function, treatment with thiophenolate in DMF at 150 °C afforded direct access to phenol **457** in 82% yield. This reaction also led to epimerization of the α-carbonyl centre to afford the *trans*-ring junction found in the natural product. Attempts to carry out the benzylic oxidation on this phenol using the CAN conditions demonstrated above provided none of the desired product, presumably due to further oxidation events. As a result, we elected to protect the phenol with a benzyl protecting group and accessed compound **458** in good yield. Benzylic oxidation of compound **458** using CAN afforded the benzyl alcohol **459** in only 20% yield. Further analysis of the crude reaction mixture indicated that the benzyl group was unstable to the oxidative conditions, as significant quantities of benzyl alcohol were also detected in the crude reaction mixture. Despite this fact, we subjected compound **460** to hydrogenation to remove the benzyl protecting group. Care had to be taken as extended reaction times led to reduction of the ketone and formation of overreduced compound **462**. However, careful monitoring of the reaction progress allowed us to access compound **460**. Unfortunately, the ^{1}H and ^{13}C NMR spectra recorded on **460** differed from that reported for coniothyrinone D (**39**) (Figure 4.3). Analysis of 1D NOESY spectra of compound **460** indicated that the stereochemistry at C9 was epimeric to that of the

natural product. The different stereochemical outcome of the benzylic oxidation is likely due to the presence of the *trans*-fused ring system as opposed to the *cis*-fused system shown in Table 4.3. We considered that an oxidation/reduction sequence might afford the correct stereochemistry at C9 but manganese dioxide oxidation did not afford the desired product **461** and only led to the formation of undesired byproducts after extended reaction times.

Scheme 4.7. Alternative approach to 9-*epi*-coniothyrinone D (460).



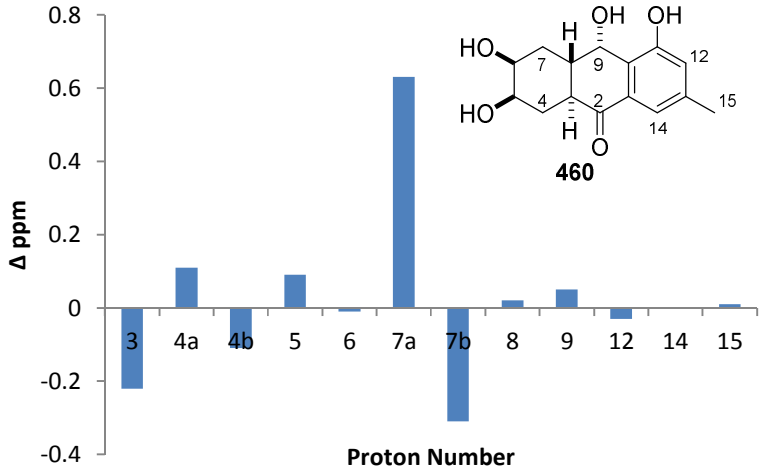


Figure 4.3. **^{1}H NMR difference plot between 9-*epi*-coniothyrinone D (460) and coniothyrinone D (39).**

4.4. Conclusion

To date, we have not been able to complete the synthesis of coniothyrinone D. However we have completed syntheses of *O*-methyl-coniothyrinone D (**456**) and 9-*epi*-coniothyrinone D (**460**) that exploit the methodology developed for the synthesis of tetralones and demonstrates the application of these methods in an efficient and short synthesis of the core structure of the coniothyrinone class of natural products. This represents the first synthesis of the coniothyrinone scaffold to date and should enable further exploration of the potential uses of these compounds.

4.5. Experimental Information

4.5.1. General Considerations

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.[130] 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. 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.

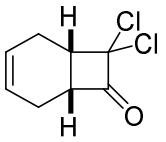
Optical rotation was measured on a Perkin Elmer 341 Polarimeter at 589 nm.

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: CDCl3: 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.

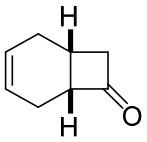
Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two™ Fourier transform spectrometer with neat samples. Only selected, characteristic absorption data are provided for each compound.

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.

Preparation of cyclobutanone 432



434



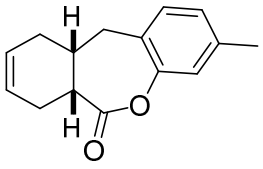
432

To a cold (0 °C), stirred solution of 1,4-cyclohexadiene (1.0 g, 12.5 mmol), Zn powder (1.64 g, 25 mmol) in Et_2O (30 mL) was drop-wise added a solution of trichloroacetyl chloride (1.8 mL, 16.3 mmol) in Et_2O (20 mL) over 1.5 hours. The resulting suspension was stirred with sonication for 1 hour, then warmed to rt and stirred for an additional 2 hours. After this time, the reaction mixture was filtered through a Celite® cake, and was rinsed with Et_2O (30 mL). The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (30 mL), and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 20 mL), and the combined organic phases were washed with brine (30 mL), and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford crude dichlorocyclobutanone **434**, which was used in the next step without further purification.

To a stirred solution of crude dichlorocyclobutanone **434** in methanol (25 mL) was added Zn/Cu couple (4.4 g, 67.6 mmol) and ammonium chloride (3.7 g, 68.9 mmol), and the resulting suspension was stirred for 21 hours. After this time, the reaction mixture was filtered through a Celite® cake, and was rinsed with Et_2O (50 mL). The solvent was removed *in vacuo* to afford crude cyclobutanone **373**. Purification of the crude material by flash chromatography (silica gel, EtOAc:hexanes, 15:85) provided cyclobutanone **432** (0.78 g, 6.34 mmol, 51% yield over two steps) as a colorless oil. The spectral data matched the data reported in the literature.[240]

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.87 (m, 2H), 3.45 (m, 1H), 3.22 (ddd, *J* = 4.0, 8.9, 17.8 Hz, 1H), 2.80 (m, 1H), 2.55 (ddd, *J* = 3.2, 4.8, 18.5 Hz, 1H), 2.38 (m, 1H), 2.33 (m, 1H), 2.16 (m, 1H), 2.08 (m, 1H).

Lactone 438



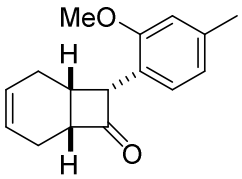
438

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.08 (d, *J* = 7.8 Hz, 1H), 6.97 (br d, *J* = 7.8 Hz, 1H), 6.91 (br s, 1H), 5.73 (m, 2H), 2.98 (dd, *J* = 6.7, 6.7 Hz, 1H), 2.87 (dd, *J* = 6.7, 13.4 Hz, 1H), 2.58 (dd, *J* = 11.1, 13.4 Hz, 1H), 2.40 (m, 2H), 2.36 (m, 1H), 2.35 (s, 3H), 2.11 (m, 1H), 2.00 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.9, 138.6, 152.0, 129.2, 126.6, 126.4, 124.6, 125.4, 120.0, 36.84, 36.79, 36.09, 30.2, 25.6, 21.08,

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{15}H_{17}O_2$: 229.1223; found: 229.1215.

Preparation of the α-arylcyclobutanone 445



445

This was prepared using general procedure B for the α-arylation.

Starting material (294 mg, 2.40 mmol). Reaction time: 1.5 h. Flash chromatography (EtOAc:hexanes, 5:95). Product (320 mg, 1.32 mmol, 66%) was a yellow oil.

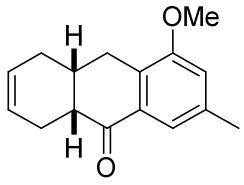
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, *J* = 7.6 Hz, 1H), 6.67 (dd, *J* = 1.2, 7.6 Hz, 1H), 6.65 (d, *J* = 1.2 Hz, 1H), 5.79 (m, 1H), 5.19 (m, 1H), 4.80 (dd, *J* = 2.6, 10.5 Hz, 1H), 3.79 (s, 3H), 3.54 (m, 1H), 3.18 (m, 1H), 2.52 (m, 1H), 2.33 (s, 3H), 2.17-2.08 (m, 2H), 1.69 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ: 214.2, 156.6, 138.2, 129.3, 127.23, 127.16, 120.9, 119.1, 110.9, 59.9, 55.3, 54.2, 28.5, 22.2, 21.6, 21.4.

IR (neat): 3030, 2918, 2836, 1768, 1613, 1507, 1261, 1040 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{16}H_{19}O_2$: 243.1380; found: 243.1389.

Preparation of α-tetralone 446



446

This was prepared using the general procedure for the tetralone synthesis.

Starting material amount: 1.32 mmol. Flash chromatography (EtOAc:hexanes, 5:95). Yield: 71%; light yellow oil.

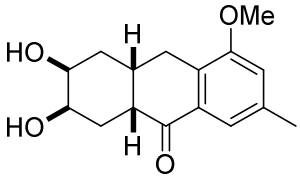
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (s, 1H), 6.84 (s, 1H), 5.73 (m, 1H), 5.63 (m, 1H), 3.85 (s, 3H), 2.91 (dd, *J* = 5.0, 17.7 Hz, 1H), 2.86 (m, 1H), 2.83 (dd, *J* = 7.5, 17.7 Hz, 1H), 2.61 (m, 1H), 2.51 (m, 1H), 2.36 (s, 3H), 2.17 (m, 2H), 1.97 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.4, 157.2, 136.7, 131.9, 128.8, 125.6, 125.3, 119.1, 115.5 55.6, 45.3, 31.7, 28.4, 26.1, 23.8, 21.5.

IR (neat): 2899, 2836, 1682, 1609, 1285, 1065 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{16}H_{19}O_2$: 243.1380; found: 243.1372.

Preparation of diol 447



447

To a cold (0 °C), stirred solution of tetralone **446** (100 mg, 0.41 mmol) and *N*-methylmorpholine oxide (72 mg, 0.62 mmol) in THF (3 mL) and H_2O (1 mL) was added OsO_4 (5 mg, 2.5 wt% in *t*-BuOH) and the reaction mixture was stirred for 14 hours at room temperature. Saturated aqueous Na_2SO_3 (2 mL) was then added and the reaction mixture stirred for a further 2 hours. EtOAc (4 mL) and H_2O (1 mL) was then added and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 2 mL), and the combined organic phases were washed with brine (3 mL), dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by flash chromatography (MeOH:CH_2Cl_2, 5:95) afforded diol **447** (66 mg, 0.24 mmol, 59%) as a white solid along with a 1:1 mixture of **447** and *bis*-*epi*-**447** (30 mg, 0.12 mmol, 26%).

Note: NMR peaks are broad due to conformers ^{1}H NMR (500 MHz, acetone-d6) δ: 7.39 (s, 1H), 7.05 (s, 1H), 3.89 (s, 3H), 3.87 (br m, 1H), 3.67 (br m, 1H), 3.50 (br s, 1H, O-H), 2.95 (dd, *J* = 5.4, 18.5 Hz, 1H), 2.85 (m, 2H), 2.75 (br m, 1H), 2.36 (s, 3H), 2.27 (br m, 1H), 1.78 (ddd, *J* = 3.7, 9.2, 13.4 Hz, 1H), 1.73 (br m, 1H), 1.49 (br m, 1H).

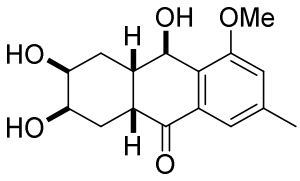
^{13}C NMR (150 MHz, acetone-d6) δ: 198.5, 157.1, 136.0, 132.1, 127.9, 117.7, 115.2, 68.1, 67.1, 54.8, 44.6, 32.6, 29.2, 27.8, 25.7, 20.1.

IR (neat): 3415, 2933, 1675, 1608, 1287, 1049 cm^{-1}.

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{16}H_{21}O_4$: 277.1434; found: 277.1439.

MP: 182-184 °C.

Preparation of triol 448



448

To a stirred solution of diol **447** (30 mg, 0.11 mmol) in MeCN (1 mL) and H_2O (1 mL) was added ammonium cerium(IV) nitrate (238 mg, 0.43 mmol) and the solution was stirred at room temperature for 1 hour. A colour change from orange to yellow was observed. The majority of the solvent was then removed *in vacuo* and the reaction mixture was diluted with brine (2 mL) and EtOAc (2 mL) and the phases were separated. The aqueous phase was washed with EtOAc (3 x 2 mL) and the combined organic phases were washed with brine (2 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by flash chromatography (MeOH:CH_2Cl_2, 5:95 to 10:90) afforded triol **448** (21 mg, 0.072 mmol, 65%) as a white solid.

^{1}H NMR (500 MHz, acetone-d6) δ: 7.38 (s, 1H), 7.12 (s, 1H), 4.95 (br s, 1H), 4.18 (d, *J* = 4 Hz, 1H, O*H*), 3.89 (s, 3H), 3.85 (br m, 1H), 3.70 (d, *J* = 6.8 Hz, 1H, O*H*), 3.49 (m, 1H), 3.47 (m, 1H, O*H*), 3.24 (m, 1H), 2.81 (m, 1H), 2.49 (m, 1H), 2.38 (s, 3H), 1.77 (m, 1H), 1.72 (dd, *J* = 4.7, 11.2 Hz, 1H), 1.10 (ddd, *J* = 2.4, 2.4, 14.1 Hz, 1H).

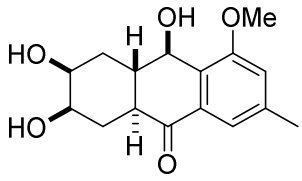
^{13}C NMR (150 MHz, acetone-d6) δ: 198.5, 158.2, 139.1, 131.7, 128.3, 118.2, 116.6, 68.5, 67.8, 64.0, 55.3, 41.2, 36.8, 32.4, 27.5, 20.7.

IR (neat): 3387, 2940, 1681, 1606, 1295, 1051 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{16}H_{21}O_5$: 293.1384; found: 293.1410

MP: 93-97 °C.

Preparation of *O*-methylconiothyrinone D (456)



456

To a stirred solution of triol **448** (8.5 mg, 0.029 mmol) in MeOH (0.2 mL) was added K_2CO_3 (19 mg, 0.14 mmol) and the reaction mixture was stirred for 2 hours. Saturated aqueous NH_4Cl (0.3 mL) and EtOAc (0.3 mL) was then added and the phases were separated. The aqueous phase was washed with EtOAc (2 x 0.3 mL) and then the combined organic phases were washed with brine (0.3 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash chromatography (MeOH:CH_2Cl_2, 8:92) afforded O-methylconiothyrinone D (**456**) (2.0 mg, 0.0068 mmol, 24%) as a white solid along with recovered starting material (5.8 mg, 0,020 mmol, 68%).

^{1}H NMR (500 MHz, acetone-d6) δ: 7.31 (br s, 1H), 7.15 (br s, 1H), 4.76 (dd, *J* = 1.5, 9.0 Hz, 1H), 4.45 (d, *J* = 1.5 Hz, 1H, O*H*), 3.98 (s, 3H), 3.97 (br m, 1H), 3.69 (br m, 1H, O*H*), 3.67 (m, 1H), 3.39 (br m, 1H, O*H*), 2.64 (ddd, *J* = 3.7, 3.7, 13.9 Hz, 1H), 2.37, (m, 1H), 2.37 (br d, *J* = 0.7 Hz, 3H), 2.12 (m, 2H), 1.75 (ddd, *J* = 13.0, 13.0, 13.0 Hz, 1H), 1.50 (ddd, *J* = 2.2, 11.9, 13.9 Hz, 1H).

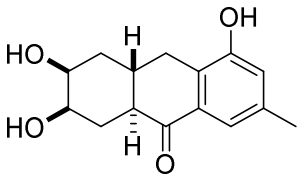
^{13}C NMR (150 MHz, acetone-d6) δ: 197.1, 157.2, 138.1, 132.0, 130.4, 118.2, 116.1, 70.2, 67.7, 55.1, 45.6, 38.0, 34.8, 27.4, 20.1.

IR (neat): 3425, 2939, 1683, 1610, 1279, 1057 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{16}H_{21}O_5$: 293.1384; found: 293.1361

MP: 203-205 °C.

Preparation of the phenol 457



457

To a stirred solution of diol **447** (105 mg, 0.36 mmol) in dry DMF (3 mL) was added benzenethiol (0.37 mL, 3.6 mmol) followed by NaH (77 mg, 1.8 mmol, 60% dispersion in mineral oil). The solution was sparged with nitrogen for 15 mins then the vial was sealed and heated to 150 °C for 36 hours. The reaction mixture was then quenched by the addition of aqueous NH_4Cl solution (2 mL), diluted with EtOAc (3 mL) and brine (2 mL) and the layers were separated. The aqueous phase was washed with EtOAc (~6 x 3 mL) until TLC indicated no remaining product was present and then the combined organic phases were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. Purification by flash chromatography (MeOH:CH_2Cl_2, 10:90) afforded phenol **457** (60 mg, 0,23 mmol, 64%) as a white solid along with some unreacted *epi*-diol **447** (21 mg, 0.077 mmol, 21%).

^{1}H NMR (400 MHz, MeOD) δ: 7.27 (s, 1H), 6.83 (s, 1H), 3.98 (ddd, *J* = 2.7, 4.7, 12.3 Hz, 1H), 3.06 (dd, *J* = 3.8, 16.7 Hz, 1H), 2.27 (s, 3H), 2.32-.29 (m, 3H), 2.07 (m, 2H), 1.66 (ddd, *J* = 13.6, 13.6, 13.6 Hz, 1H), 1.59 (m, 1H).

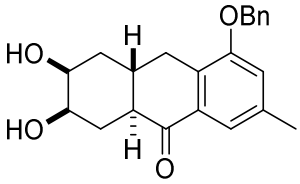
^{13}C NMR (150 MHz, MeOD) δ: 201.5, 155.9, 137.8, 134.1, 129.2, 121.1, 119.1, 72.6, 69.9, 50.4, 39.6, 33.3, 30.6, 28.7, 21.2.

IR (neat): 3395, 2930, 1668, 1613, 1040 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{15}H_{19}O_4$: 263.1278; found: 263.1287.

MP: >250 °C.

Preparation of diol 458



458

To a stirred solution of phenol **457** (54 mg, 0.21 mmol) in acetone (2 mL) was added K_2CO_3 (29 mg, 0.21 mmol) and benzyl bromide (0.025 mL, 0.21 mmol) and the reaction was heated to 60 °C for 4 hours. The solvent was then removed *in vacuo*. Purification by flash chromatography (MeOH:CH_2Cl_2, 5:95) afforded diol **458** (55 mg, 0.16 mmol, 74%) as a white solid.

^{1}H NMR (400 MHz, MeOD) δ: 7.46 (d, *J* = 10.3 Hz, 2H), 7.39 (m, 2H), 7.38 (s, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.07 (s, 1H), 5.14 (d, *J* = 11.7 Hz, 1H), 5.10 (d, *J* = 11.7 Hz, 1H), 3.96 (br m, 1H), 3.67 (ddd, *J* = 3.9, 5.2 ,13.2 Hz, 1H), 3.14 (dd, *J* = 3.9, 16.9 Hz, 2.34 (s, 3H), 2.33 (m, 1H), 2.24 (m, 1H), 2.06 (m, 1H), 1.66 (ddd, *J* = 10.3, 10.3, 10.3 Hz, 1H), 1.58 (m, 1H).

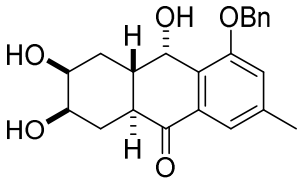
^{13}C NMR (100 MHz, MeOD) δ: 201.1, 157.2, 138.5, 138.1, 133.9, 131.3, 129.6, 129.0, 128.5, 120.0, 118.3, 72.6, 71.4, 69.9, 50.3, 39.6, 33.2, 30.6, 28.6, 21.5.

IR (neat): 3420, 2926, 1679, 1609, 1291, 1053 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{22}H_{25}O_4$: 353.1747; found: 353.1771.

MP: 185-188 °C

Preparation of the triol 459



459

To a stirred solution of α-tetralone **458** (41 mg, 0.12 mmol) in MeCN (2 mL) and H_2O (2 mL) was added ammonium cerium (IV) nitrate (255 mg, 0.47 mmol) and the reaction mixture was stirred for 30 minutes. More CAN (130 mg, 0.24 mmol) was then added and the reaction mixture stirred for an additional 30 minutes. The reaction mixture was then diluted with EtOAc (5 mL) and brine (2 mL) and the phases were separated. The aqueous layer was washed with EtOAc (3 x 3 mL) and then the combined organic phases were washed with brine (2 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography on Iatrobeads® (MeOH:CH_2Cl_2, 5:95) afforded triol **459** (9.3 mg, 0.025 mmol, 21%) as a yellow oil.

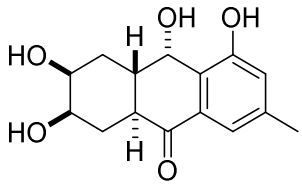
^{1}H NMR (400 MHz, MeOD) δ: 7.52 (d, *J* = 7.9 Hz, 2H), 7.41 (s, 1H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.16 (s, 1H), 5.22 (d, *J* = 12.0 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 2.9 Hz, 1H), 4.04 (br m, 1H), 3.64 (ddd, *J* = 3.3, 4.3, 11.8 Hz, 1H), 2.75 (ddd, *J* = 3.3, 12.0, 12.0 Hz, 1H), 2.37 (s, 3H), 2.27 (m, 1H), 2.17 (m, 1H), 1.95 (ddd, *J* = 3.3, 15.0, 15.0 Hz, 1H), 1.89 (m, 1H), 1.65 (ddd, *J* = 12.0 Hz, 1H)..

^{13}C NMR (100 MHz, MeOD) δ: 201.0, 157.7, 140.8, 138.5, 133.0, 131.6, 129.6, 129.0, 128.6, 120.0, 119.4, 72.5, 71.6, 70.1, 63.9, 43.1, 38.0, 28.6, 21.6, 18.4.

IR (neat): 3420, 2924, 1680, 1606, 1454, 1053 cm^{-1};

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{22}H_{25}O_5$: 369.1697; found: 369.1721.

Preparation of 9-*epi*-coniothryinone D (460)



460

To a stirred solution of triol **459** (7.6 mg, 0.021 mmol) in EtOH (0.2 mL) was added Pd/C (~5 mg) and hydrogen gas was bubbled through the solution for 2 hours. The reaction mixture was then filtered through Celite and the solvent removed *in vacuo*.

Purification by flash chromatography (MeOH:CH_2Cl_2 5:95 to 10:90) afforded 9-*epi*-coniothryinone (**460**, 4.1 mg, 0.15 mmol, 71%) as a light yellow solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 9.68 (s, 1H, PhO*H*), 7.14 (s, 1H), 6.88 (s, 1H), 4.84 (d, *J* = 6.1 Hz, 1H, O*H*), 4.69 (dd, *J* = 1.3, 4.7 Hz, 1H), 4.48 (d, *J* = 6.2 Hz, 1H, O*H*), 4.17 (d, *J* = 2.1 Hz, 1H, O*H*), 3.82 (m, 1H), 3.41 (m, 1H), 2.58 (m, 1H), 2.25 (s, 3H), 2.04 (m, 2H), 1.79 (br dd, *J* = 14.0, 14.0 Hz, 1H), 1.68 (ddd, *J* = 3.7, 3.7, 14.0 Hz, 1H), 1.44 (ddd, *J* = 12.2, 12.2, 12.2 Hz, 1H).

^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ: 198.0, 155.7, 136.6, 133.6, 129.8 120.5, 116.8, 70.3, 67.8, 61.3, 41.1, 36.4, 34.0, 27.8

HR-MS (ESI of $[M+H]^+$): *m/z* calc'd for $C_{15}H_{19}O_5$: 279.1227; found: 279.1231.

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