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Omar Robles-Resendiz Date

Modular Synthesis of Polyketide Natural Products:

Synthesis of the C9-C27 Degradation Product of Aflastatin A

and Total Synthesis of Fostriecin

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By

Omar Robles-Resendiz

B. S., University of Guanajuato, 2003

Advisor: Frank E. McDonald, Ph.D.

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Abstract

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Modular approaches for the synthesis of polyketide natural products were applied to the synthesis of the C9-C27 degradation product of aflastatin A and the total synthesis of fostriecin. The synthesis of the C9-C27 degradation product of aflastatin A featured the cross-coupling of alkynes with epoxides as the key reaction for the union of structurally complex and stereochemically rich polypropionates. For the total synthesis of fostriecin, sequential palladium-catalyzed Negishi cross-coupling reactions were used for the rapid access of an advanced intermediate in gram scale. Then, regio- and stereoselective Sharpless asymmetric dihydroxylation reaction was applied to introduce the C8 and C9 chiral centers at a late stage, providing a concise route to this type of natural products.

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Abbreviations

Ac	acetyl
ACP	acyl carrier protein
AIBN	2,2'-azbisisobutyronitrile
aq	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
Boc	*tert*-butoxycarbonyl
t-BuOOH	*tert*-butylhydroperoxide
n-BuLi	*n*-butyllithium
t-BuLi	*tert*-butyllithium
Bz	benzoyl
Cat	catalytic
CoA	coenzyme A
cod	1,5-cyclooctadienyl
Cy	cyclohexyl
d	doublet
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DH	dehydratase
DIBAL	diisobutylaluminum hydride
DMAP	*N, N*-dimethylaminopyridine
DMF	*N, N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid

DVDS	1,3-divinyl-1,1,3,3-tetramethyldisiloxane
equiv	equivalent
ER	enoyl reductase
EtOAc	ethyl acetate
ESI	electrospray ionization
FAB	fast atom bombardment
FAS	fatty acid synthase
FT-IR	Fourier transform infrared spectroscopy
Fur	furyl
HMG	3-hydroxy-3-methylglutarate
HMPA	Hexamethylphosphoric triamide
HRMS	high resolution mass spectroscopy
IBX	2-Iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
Ipc	isopinocampheyl
Kg	kilogram
KS	ketosynthase
KR	ketoreductase
LA	Lewis acid
LD_{50}	median lethal dose
m	multiplet
MAT	malonyl-acetyl transferase
mg	milligram

MHz	megaHertz
mL	milliliter
mmol	millimole
MS	molecular sieves
NCI	National Cancer Institute
NIS	*N*-iodosuccinimide
nM	nanomolar
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methylpyrrolidone
NMR	nuclear magnetic resonance
Ph	phenyl
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
PP	protein phosphatase
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
PTLC	preparative thin layer chromatography
p-TsOH	*para*-toluenesulfonic acid
pyr	pyridine
q	quartet
RNA	Ribonucleic acid
rt	room temperature
s	singlet

sat	saturated
SD	standard deviation
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TE	thioesterase
TEA	triethylamine
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
μg	microgram
μL	microliter
μM	micromolar

Chapter 1

Introduction to Polyketide Natural Products

1.1 Introduction and Background

Polyketide natural products are a broad and remarkable class of secondary metabolites. These naturally occurring substances exhibit an astonishing range of structural complexity and functional diversity, as well as a plethora of biologically and medicinally important activities that include antibiotic, antifungal, antiparasitic, anticancer, cardiovascular and immunosuppressive properties (figure 1). Polyketides are generally nonessential molecules for the producing organism and are synthesized as secondary metabolites by an iterative sequence of Claisen-type condensations of simple acetate and propionate subunits.[1] In fact, polyketides represent the fourth largest family of natural products that are assembled from common building blocks, along with polynucleotides, polypeptides and polysaccharides. Currently, there are about 50 approved drugs that are polyketide-based, with a wide range of pharmaceutical applications that include antibacterials, antifungals, anticancer, immunosuppressants, cholesterol-lowering among others,[2] and have had combined sales over $15 billion, including six blockbuster drugs: lovastatin, pravastatin and simvastatin (which are HMG-CoA reductase inhibitors, and reduce cholesterol levels), the antibiotics clarithromycin and azithromycin, as well as the immunosuppressant tacrolimus (FK-506).

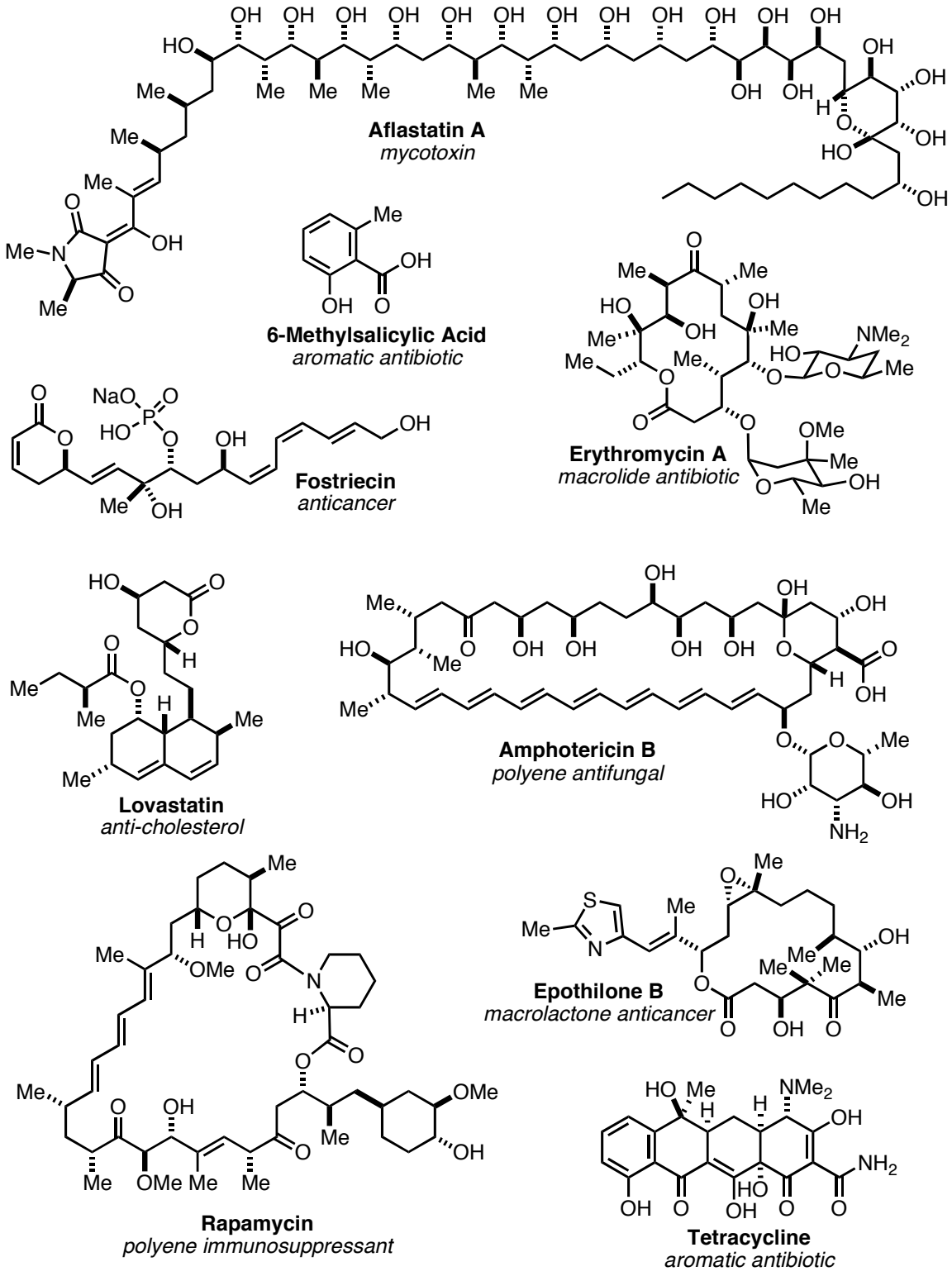
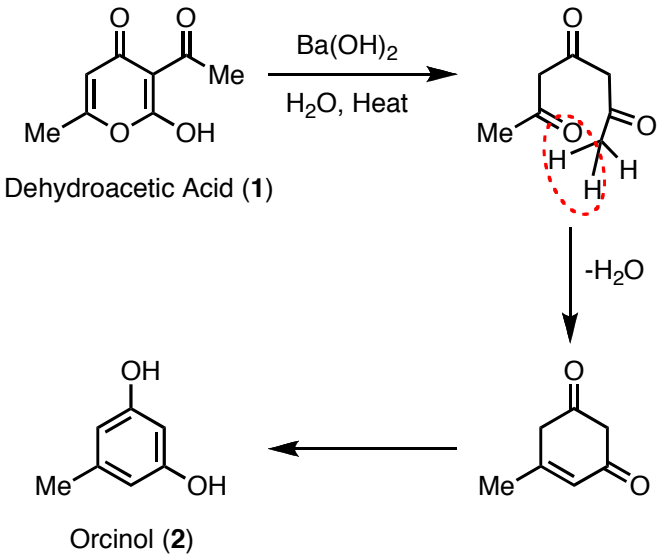


Figure 1. Representative Polyketide Natural Products.

The idea that some aromatic natural products might be derived from simple, linear poly-β-keto intermediates was originally proposed more than a century ago by the English chemist John N. Collie.[3,4] During a series of studies directed to prove the structure of dehydroacetic acid **1** by chemical degradation, he discovered, quite to his surprise, that when heating dehydroacetic acid in the presence of barium hydroxide, one of the products was the aromatic compound orcinol **2** (scheme 1). After correctly assigning the structure of orcinol based on the available analytical data, he came up with a mechanistic explanation for its formation, that was based on the triketone **3** as key intermediate, which would then undergo a intramolecular aldol condensation and aromatization to yield orcinol **2**.



Scheme 1. Collie's synthesis of orcinol.

This was a bold and remarkable proposal, in that it included a mechanistic hypothesis at a time when organic chemists had only vague ideas of reaction pathways and reaction mechanisms were rationalised by "lasso mechanisms" in

which leaving atoms were circled by dotted lines. Indeed, Collie's hypothesis was dismissed by his contemporary chemists and labeled as "premature",[1] and no further attention was given for several decades, until it was validated with the aid of isotope labeling experiments and modern spectroscopic techniques. Birch and coworkers designed a series of experiments that involved the feeding of acetate labelled with ^{14}C at C-1, to the fungus *Penicillium patulum*, which produces the aromatic antibiotic 6-methylsalicylic acid, and was followed by detailed analysis of the samples produced, in order to measure the radioactivity.[5,6] The results concluded that the ^{14}C labels were incorporated in the predicted pattern (figure 2), thus proving that some aromatic natural products are biosynthesized from acetate units.

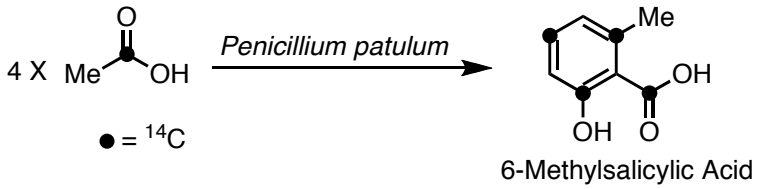


Figure 2. Birch's isotope labeling experiment.

1.2 Biosynthesis of Polyketides

Polyketide natural products are assembled in a modular fashion by iterative Claisen-type condensations of simple acetate (C_2) and/or propionate (C_3) subunits, followed by oxidation-state adjustments that may include keto reduction, dehydration and enoyl reduction, before entering the next cycle of condensation, allowing for a wide range of diversity along the growing chain (figure 3).[1] The enzymes responsible for polyketide biosynthesis are clustered in

multienzyme systems, the polyketide synthases (PKSs). Furthermore, non-PKS enzymes are often involved on the late stage tailoring of polyketide natural products (e.g. glycosidations, oxidations), giving rise to the staggering structural complexity seen on some polyketide natural products. Polyketide synthases share several common features with fatty acid synthases (FASs) which assemble fatty acids in a similar fashion from C_2 acetate units, and were characterized before any PKS was isolated in sufficient purity for definitive characterization. However, in the 1980's, the development of molecular genetic tools greatly facilitated the identification of the genes and subsequently, the enzymes responsible for the biosynthesis of polyketide natural products. All fatty acid synthases have the same set of components: a keto synthase (KS), which catalyzes the Claisen-type condensation; an acyl carrier protein (ACP), which is the chain extender; a keto reductase (KR), that reduces the ketone to the corresponding alcohol; a dehydratase (DH), that catalyzes the elimination of a water molecule; an enoyl reductase (ER), which catalyzes the reduction of the resulting double bond to the fully saturated chain; a thioesterase (TE), that promotes the release of the chain as a free acid or an acyl ester; and also a malonyl-acetyl transferase (MAT), which role is to transfer the building blocks acetate (to start) and malonate (to extend) from the corresponding coenzyme A. In contrast to the biosynthesis of fatty acids, in polyketide biosynthesis the full reductive cycle is not necessary. This allows a virtually unlimited number of possible combinations along the growing chain, increasing the functional diversity and structural complexity of these natural products (figure 3).

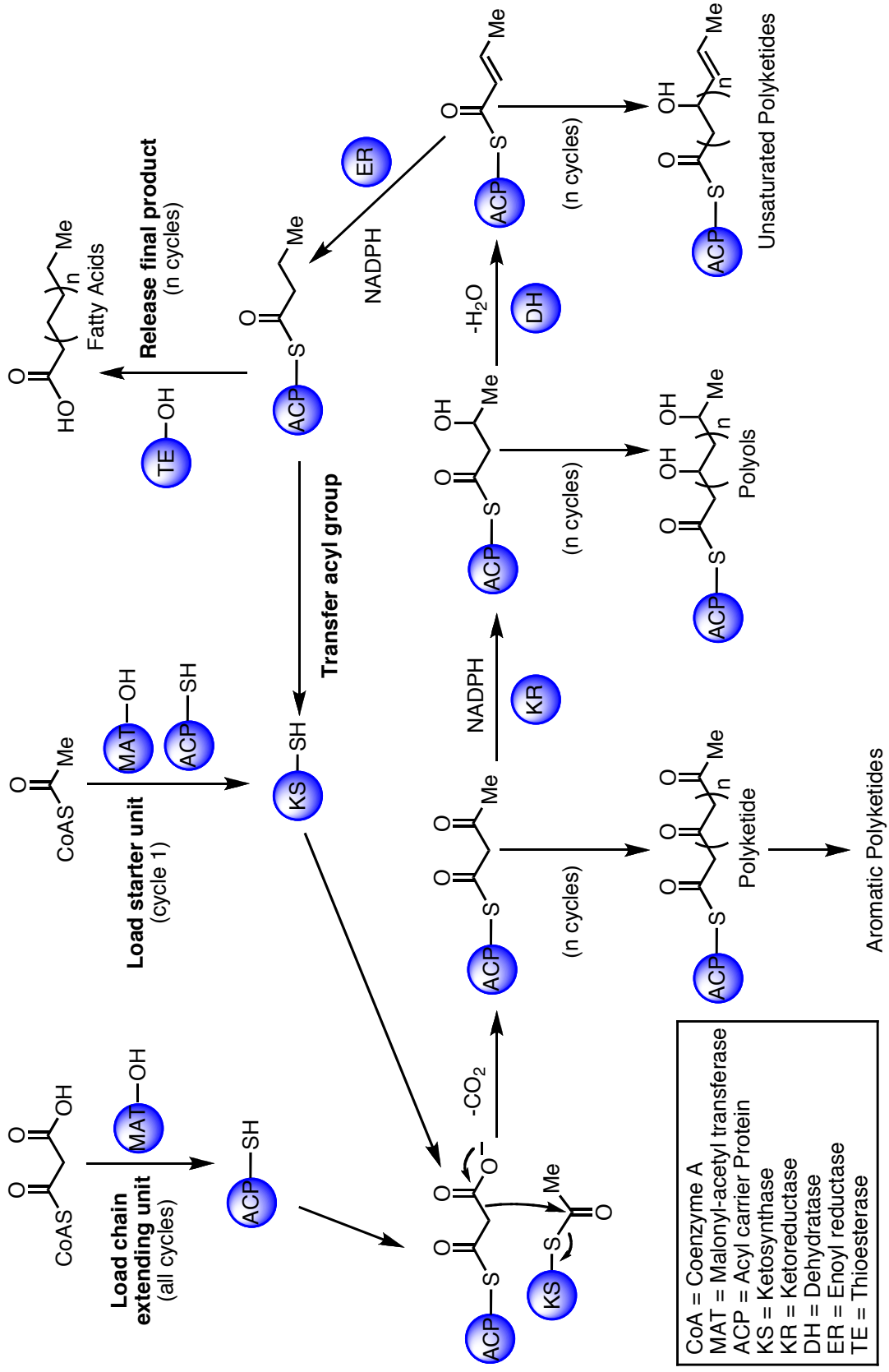


Figure 3. Biosynthesis of fatty acids, polyketides and unsaturated polyketides.

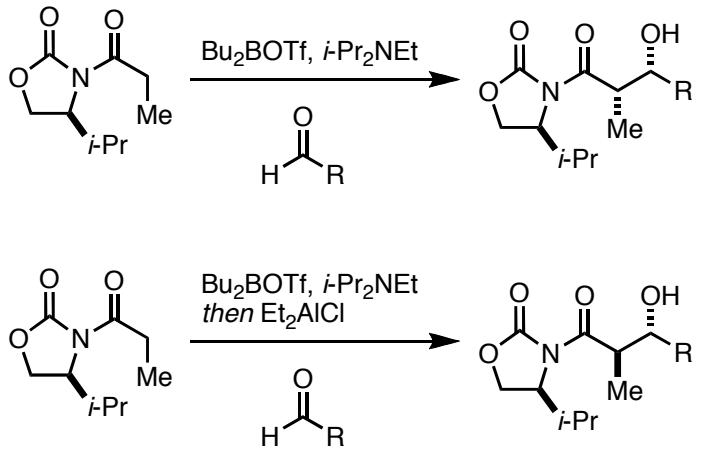
1.3 Synthetic Approaches to Polyketides

The structural diversity and stereochemical complexity present in polyketide natural products has both inspired and challenged organic chemists for several decades to develop methods and strategies to assemble this intriguing natural substances in the laboratory. Indeed, over the course of the last three decades, the pursuit of this goal has yielded tremendous advances in asymmetric synthesis, particularly in the development of new carbon-carbon bond forming reactions with absolute control of the stereochemistry.[7] In fact, some of the most representative polyketide natural products, like erythromycin A, had captured the imagination of synthetic chemists even when methods for stereoselective carbon-carbon bond formations were not available. By 1950's the lack of stereoselective versions of carbon-carbon bond forming processes was illustrated by a quote of R. B. Woodward, who while referring to the synthesis of erythromycin A famously said, *"looks at present time quite hopelessly complex, particularly in view of its plethora of asymmetric centers"*.[8] The first total synthesis of erythromycin A was completed in 1981 by the Woodward laboratory and featured the use of stereoselective aldol reactions.[9] Over the last 30 years, an impressive number of developments in the field of stereoselective carbon-carbon bond reactions have enabled the synthesis of complex polyketide natural products. The most general methods include aldol reactions, allylation and crotylation reactions, as well as cycloaddition reactions. The development of strategies to link large fragments has also played an important role, since often simple reactions fail to give the desired coupled products efficiently, due to the complexity of the reacting

partners. Among the most reliable methods for linking large polyketide substructures are alkyne-epoxide cross couplings, metal catalyzed cross-couplings, dithiane-epoxide cross couplings and directed aldol reactions, among others.

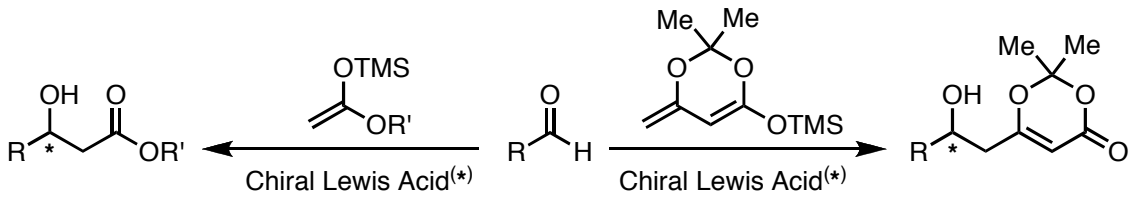
1.3.1 Aldol Reactions in Polyketide Synthesis

The aldol reaction is the most developed reaction in polyketide chemistry and has evolved into a powerful and versatile tool for the carbon-carbon bond formation with control of the stereochemistry of up to two chiral centers, in both cyclic and acyclic systems, and has been extensively studied by Masamune, Heathcock, Evans, Paterson, among others.[7,10] It is particularly useful for the synthesis of small building blocks, where absolute control of the stereochemistry is possible by choosing the right reaction conditions. However, the aldol reaction is also highly sensitive to stereoinduction from both the electrophilic and nucleophilic components. When these effects are reinforced, the result is an effective reaction, but this reaction is not yet general for all possible stereoisomers. Among the most used methods are the Evans' chiral auxiliary approach,[11,12] and chiral Lewis acid catalyzed aldol addition of silyl enol ethers to aldehydes.[13] A classical Evans' *syn*-aldol reaction is shown on scheme 2, as well as Heathcock's variant that produces the *anti*-aldol product. These reactions have been widely applied in polyketide synthesis, since either *syn*- and *anti*-aldol adducts can be generated and both oxazolidinone enantiomers are commercially available, giving acces to all four diastereomers.



Scheme 2. Chiral auxiliary based aldol reactions.

The catalytic enantioselective aldol additions of silyl enol ethers to aldehydes have been developed more recently[7,13] and are generically illustrated on scheme 3.

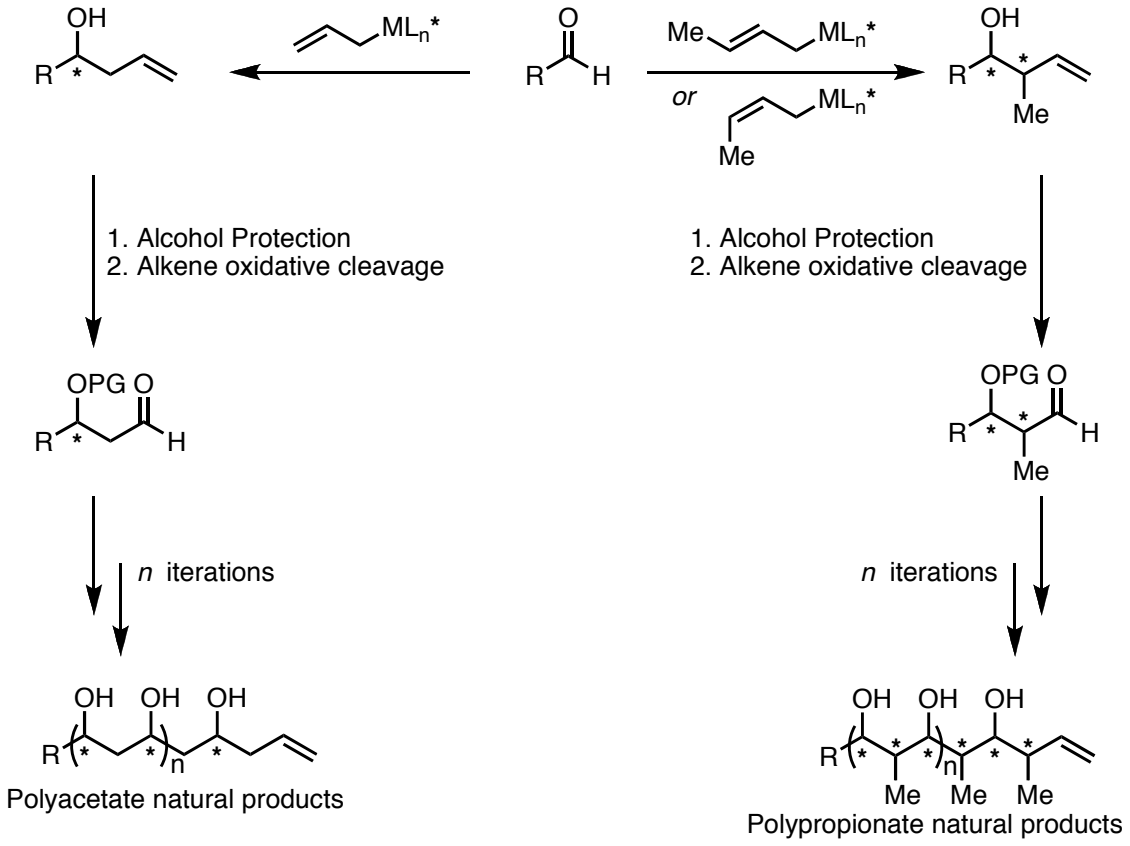


Scheme 3. Enantioselective addition of silyl enol ethers to aldehydes.

1.3.2 Allylation and Crotylation Reactions in Polyketide Synthesis

Over the last three decades, allylation and crotylation reactions have been extensively developed and successfully applied in polyketide synthesis as aldol addition equivalents, and are among of the most used methods for the construction of polyketide natural products.[14,15,16] Several allyl- and crotylmetal reagents are available and include allyl- and crotylboronates, trialkyl-, trihalo- and

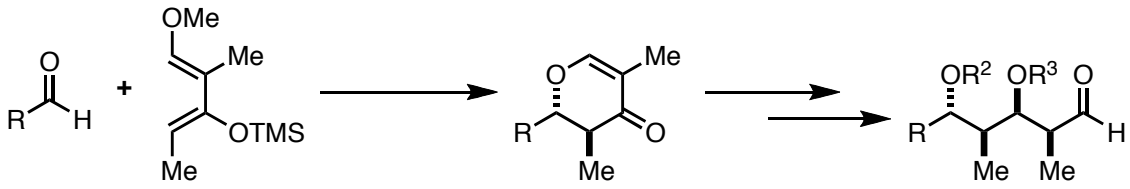
trialkoxysilanes, trialkylstannanes, allylaluminum, crotylzirconium, crotyltitanium, crotylchromium, among others. Several variants of these reactions have been reported, including catalytic enantioselective methods,[16,17] and offer different alternatives that can be selected to better match the substrate. Some of the advantages that these reactions present are a high degree of stereoinduction, acces to all different possible diastereomers and levels of reactivity that can be tuned by careful choice of the metal reagent, as well as products that are amenable for easy iterations and further functionalizations. Scheme 4 illustrates this approach to polyketide structures.



Scheme 4. Allyl and crotyl addition reactions in polyketide natural products.

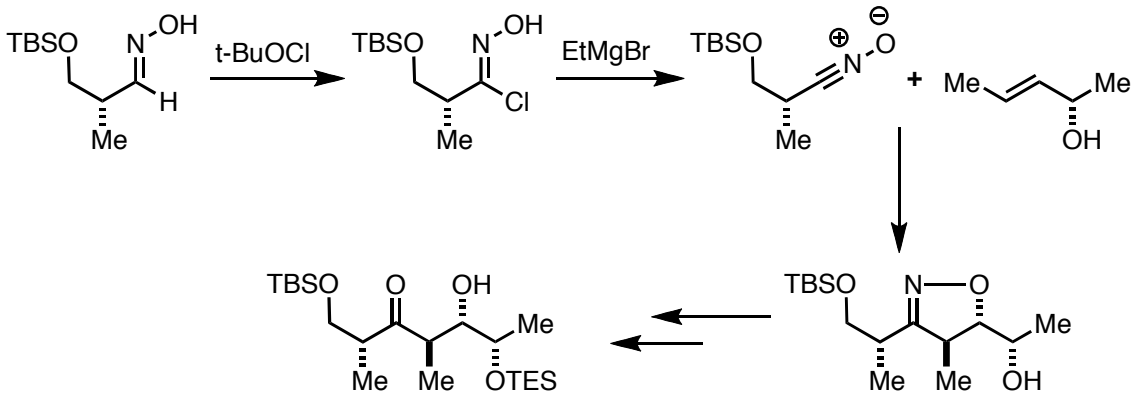
1.3.3 Cycloaddition Reactions in Polyketide Synthesis

Although aldol reactions, as well as allyl and crotyl additions to carbonyl groups are the most widely used transformations in polyketide synthesis, novel approaches have been devised. Among them, hetero Diels-Alder and 1,3-dipolar cycloaddition reactions have been developed as a *non*-aldol alternative for the synthesis of polyketides. Danishefsky and co-workers have pioneered the use of a hetero Diels-Alder reaction to form branched pyranose derivatives (scheme 5), that have been used as five-carbon sythons and have been applied to the synthesis of complex polyketide natural products like 6-deoxyerythronolide B and zincophorin, among others.[18,19]



Scheme 5. Hetero Diels-Alder cycloadditions in polyketide natural products.

The hydroxyl-directed cycloaddition of nitrile oxides to allylic alcohols, initially discovered by Kanemasa,[20] has been developed into a synthetically useful method for polyketide synthesis by Carreira and coworkers (scheme 6).[21,22] This hydroxyl-directed 1,3-dipolar cycloaddition generally displays high degree of regio- and stereoselectivity, and by choosing the proper dipole and dipolarophile, gives access to all diastereomers commonly found in polyketide natural products. This methodology has been applied to the synthesis of epothilone A and B.[22]



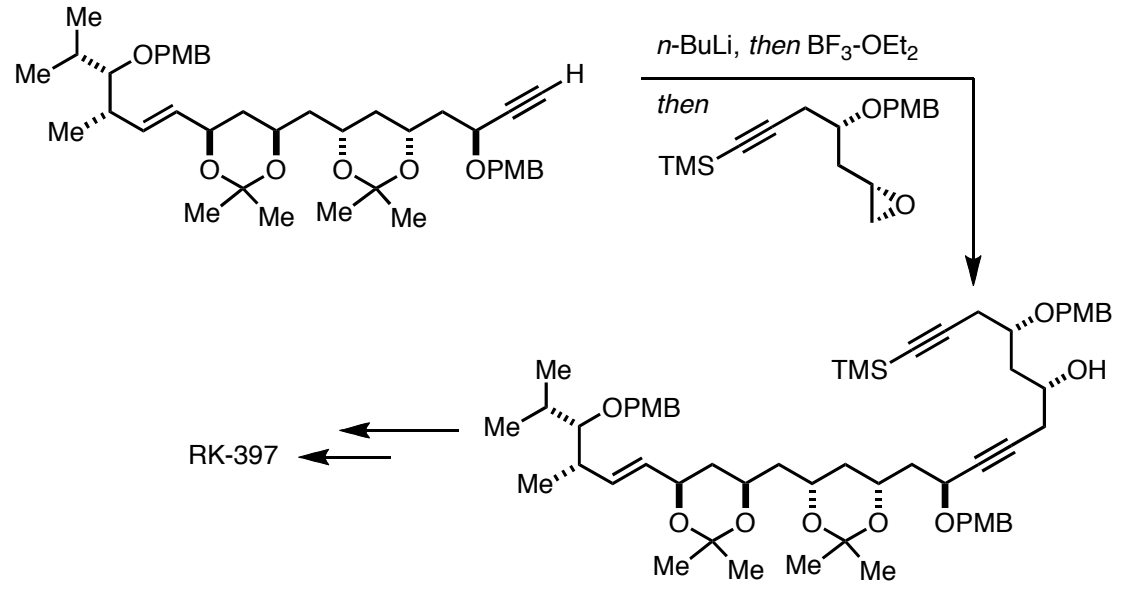
Scheme 6. 1,3-Dipolar cycloadditions in polyketide natural products.

1.3.4 Strategies to Link Large Polyketide Fragments

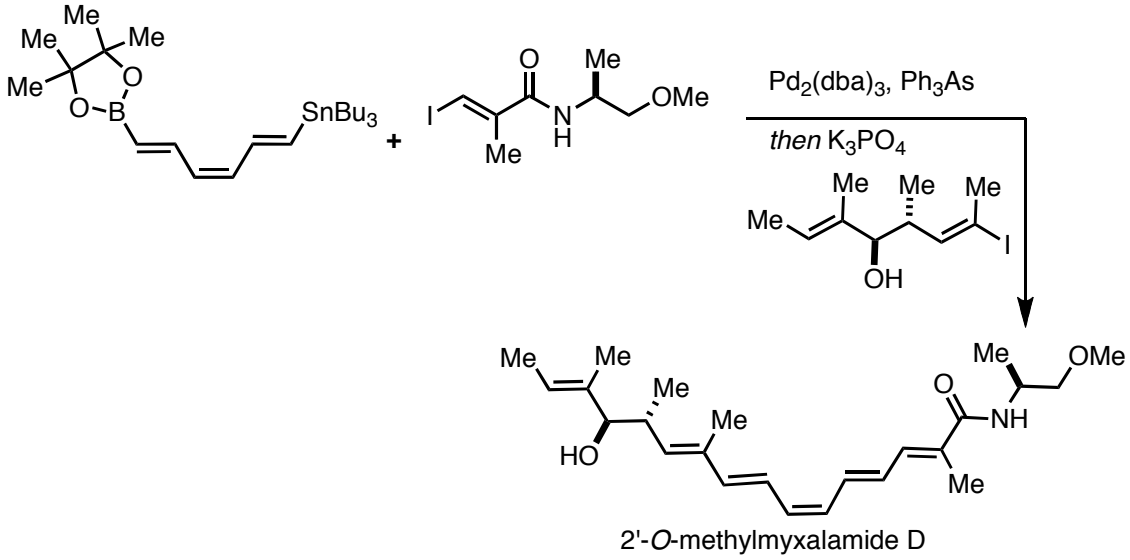
Among the most reliable methods for linking large polyketide substructures are alkyne-epoxide cross couplings, metal catalyzed cross-couplings, dithiane cross couplings, aldol reactions, among others. The McDonald laboratory has developed an alkyne plus epoxide approach,[23,24] based on the cross coupling of nucleophilic alkynes with electrophilic epoxides, followed by functionalization of the resulting internal alkyne, which was applied to the synthesis of the polyene macrolide RK-397 (scheme 7).[24]

Metal catalyzed cross-coupling has emerged as an useful and reliable tool to link complex polyketide substructures, particularly those having diene or polyene moieties.[25,26] Recent developments include the use of a linchpin strategy that takes advantage of sequential Stille/Suzuki-Miyaura reactions,[27] to assemble complex polyketide structures in one-pot. This approach has been demonstrated for the total synthesis of several complex polyketide natural products, including

lucilactaene,[28] strobilurin B,[29] 2'-*O*-methylmyxalamide D (scheme 8),[30] among others.

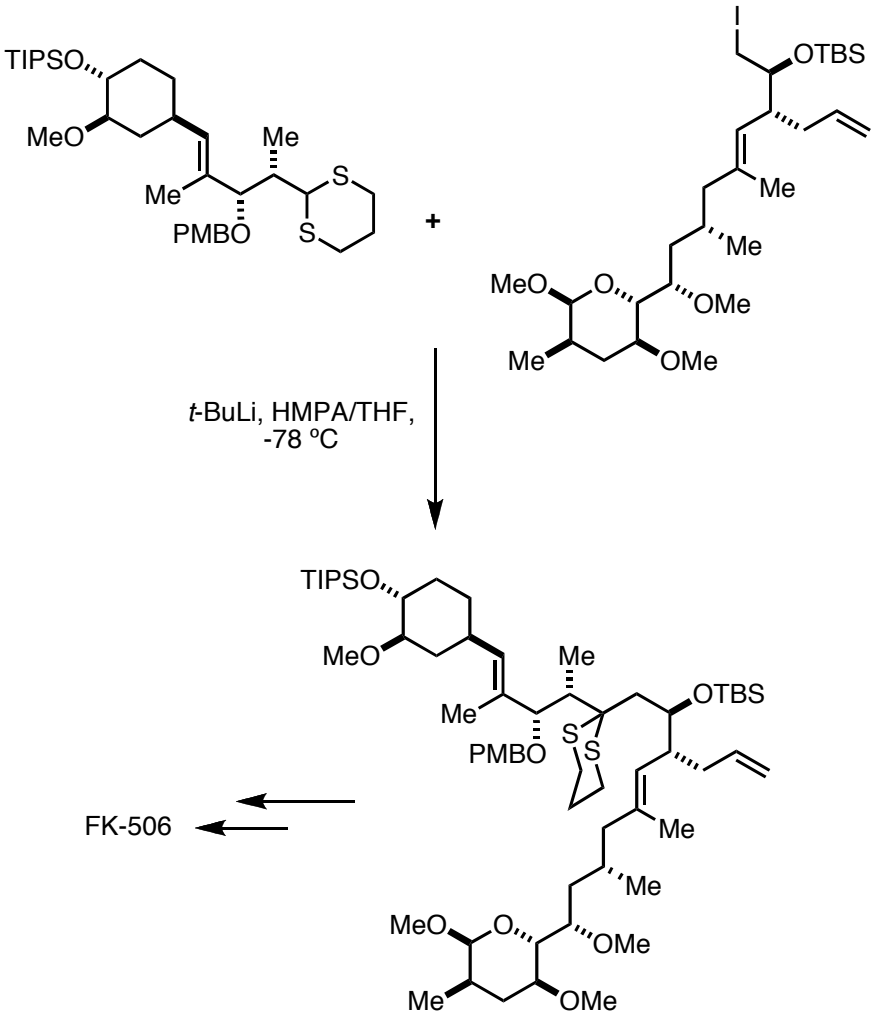


Scheme 7. Alkyne-epoxide cross-couplings in polyketide synthesis.



Scheme 8. Metal catalyzed cross-couplings in polyketide synthesis.

Dithiane-based cross couplings, developed by Smith and coworkers,[31] have evolved into a powerful alternative for the union of advance intermediates in the synthesis of complex natural products. One of the advantage of this methodology is the ability of dithiane anions to react with a wide variety of electrophiles that include aldehydes, ketones, enones, acid chlorides, alkyl halides, epoxides and aziridines. This approach has been showcased in multiple total syntheses of natural products, an example being on the total synthesis of the immunosuppressant FK-506 (scheme 9).[32]



Scheme 9. Dithiane-based cross-couplings in polyketide synthesis.

Chapter 2

Synthesis of the C9-C27 Degradation Product of Aflastatin A

2.1 Introduction and Background

Aflatoxin, a mycotoxin produced by some strains of *Aspergillus parasiticus*, *Aspergillus flavus*, *Aspergillus nomius* and *Aspergillus tamarii*, is one of the most potent environmental carcinogens. It has high carcinogenicity toward mammals and it is a contaminant of agricultural products. Aflatoxins in general are not only recognized as toxic contaminants of agricultural goods, but also as a causative agent in human hepatic and extrahepatic carcinogenesis as well as in lung tumorigenesis.[33,34] Therefore, over the past years, there has been an increasing interest to address the problem of aflatoxin contamination.

Aflastatins A and B (**1**, **2**) are specific inhibitors of aflatoxin production, and were isolated from the mycelia of *Streptomyces sp*. MRI142 during the course of a screening for aflatoxin production inhibition (figure 1).[35] After aflastatin A was reported by Sakuda and coworkers in 1996, the same research group noticed that another natural product; blasticidin A (**3**), which had been isolated as an antibiotic from *Streptomyces griseochromogenes* in 1955 but not structurally characterized,[36] had close homology in the physicochemical properties with aflastatin A. The biological activity of blasticidin A was then reexamined and showed inhibition of aflatoxin production as strongly as aflastatin A.[37]

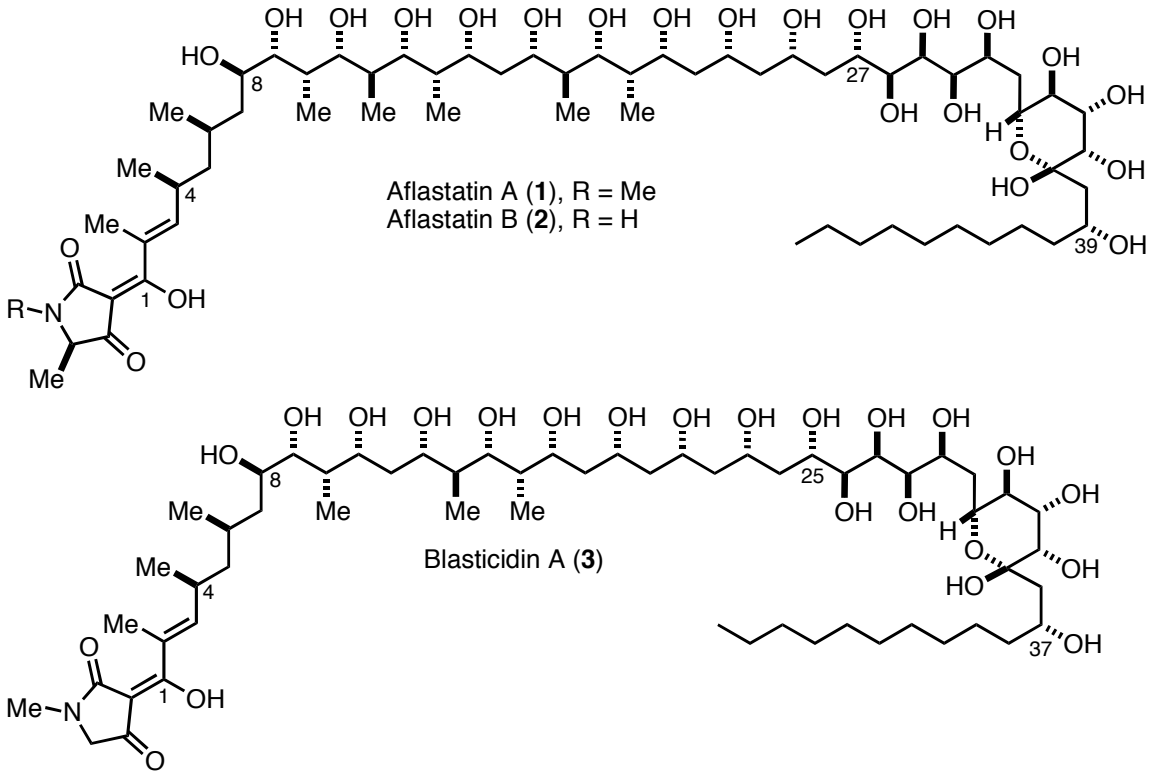


Figure 1. Structures of aflastatins A and B (**1**, **2**) and blasticidin A (**3**).

The aflastatins and blasticidin A inhibit the biosynthesis of aflatoxin by *Aspergillus parasiticus* at low concentrations without essentially affecting the growth of *Aspergillus parasiticus* (table 1). It is known that aflastatin A (**1**) inhibits messenger RNA expression of the genes which code for the biosynthetic enzymes producing aflatoxin in *Aspergillus parasiticus,*[38] as well as melanin biosynthesis by *Colletotrichum lagenarium*.[39] A specific inhibitor for aflatoxin biosynthesis may be a good candidate for a useful drug to protect foods and feeds from aflatoxin contamination, since unlike fungicides, it does not kill the producer of aflatoxin, and so it is expected to depress aflatoxin contamination without rapid spread of drug-resistant strains. Aflastatin A and Blasticidin A have

shown low oral toxicity (LD_{50} > 1000 mg/kg), however, they exhibited higher toxicity to mice upon intraperitoneal injection (LD_{50} for **1**, 6.17 mg/kg). Aflastatin A (**1**) also showed dose-related reduction of adenocarcinoma 755 tumor growth by intraperitoneal injection, but only at higher doses, making it toxic at effective concentrations.

Compound	Concentration (μM)	Mycelial dry weight (m ± S.D., mg/10 mL)	Aflatoxin concentration (m ± S.D., μg/mL)
Control	0	58 ± 2	4.1 ± 0.7
Aflastatin A (**1**)	0.03125	63 ± 8	2.2 ± 0.4
Aflastatin A (**1**)	0.0625	62 ± 5	2.1 ± 0.1
Aflastatin A (**1**)	0.125	62 ± 4	2.0 ± 0.6
Aflastatin A (**1**)	0.25	63 ± 2	1.5 ± 0.3
Aflastatin A (**1**)	0.5	64 ± 5	< 0.1
Control	0	34.0 ± 1.0	4.67 ± 1.33
Aflastatin B (**2**)	0.03	32.7 ± 0.58	1.47 ± 0.34
Aflastatin B (**2**)	0.12	32.3 ± 0.58	0.65 ± 0.57
Aflastatin B (**2**)	0.5	31.7 ± 0.58	< 0.1

Table 1. Aflastatins A and B inhibition of aflatoxin production by *A. parasiticus*.

Sakuda and coworkers also explored the biological activity of some blasticidin derivatives (**4**, **5**) in which the tetramic acid was removed by ozonolysis and subsequent reduction of the resulting aldehyde to the corresponding polyols (figure 2). Compounds **4** and **5** were shown to retain significant activity for the inhibition of aflatoxin production in *Aspergillus parasiticus* (table 2), and also

found that compound **4** was much less toxic to mice than the parent natural products (up to 80 mg/kg, intraperitoneal injection).

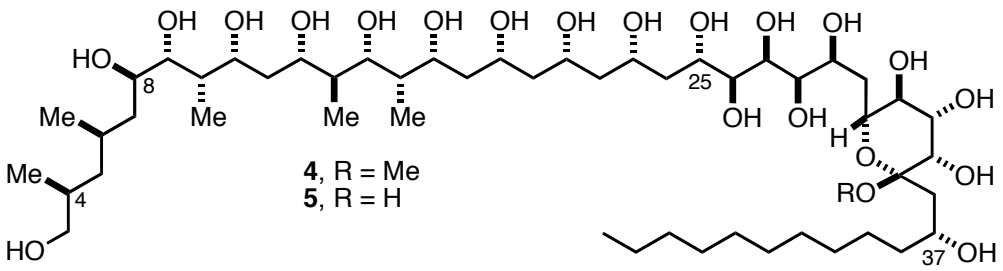


Figure 2. Structures of blasticidin A derivatives **4** and **5**.

Compound	Concentration (μM)	Mycelial dry weight (m ± S.D., mg/10 mL)	Aflatoxin concentration (m ± S.D., μg/mL)
Control	0	24.1 ± 0.7	20.7 ± 2.0
Blasticidin A (**3**)	0.25	24.3 ± 0.3	1.1 ± 0.1
Blasticidin A (**3**)	0.5	23.2 ± 0.6	0.5 ± 0.1
Blasticidin A (**3**)	1.0	11.5 ± 2.1	0.1 ± 0.01
4	10	21.5 ± 0.6	0.7 ± 0.2
5	10	22.1 ± 1.0	0.3 ± 0.1

Table 2. Blasticidin A and derivatives inhibition of aflatoxin production.

The structure of aflastatin A (**1**) has been determined by chemical degradation and extensive spectroscopic analysis.[35] It contains a novel tetramic acid derivative with a long polyhydroxylated side chain and a tetrahydropyran ring moiety, and contains 29 chiral centers. The absolute configuration was proposed in 2000,[40] however, Kishi suggested that the stereochemical assignments for the

C8-C9 and C28-C32 should be reversed (figure 3).[41] The Sakuda group later published the revised structure, along with the disclosure of the absolute stereochemistry of blasticidin A (**3**).[42]

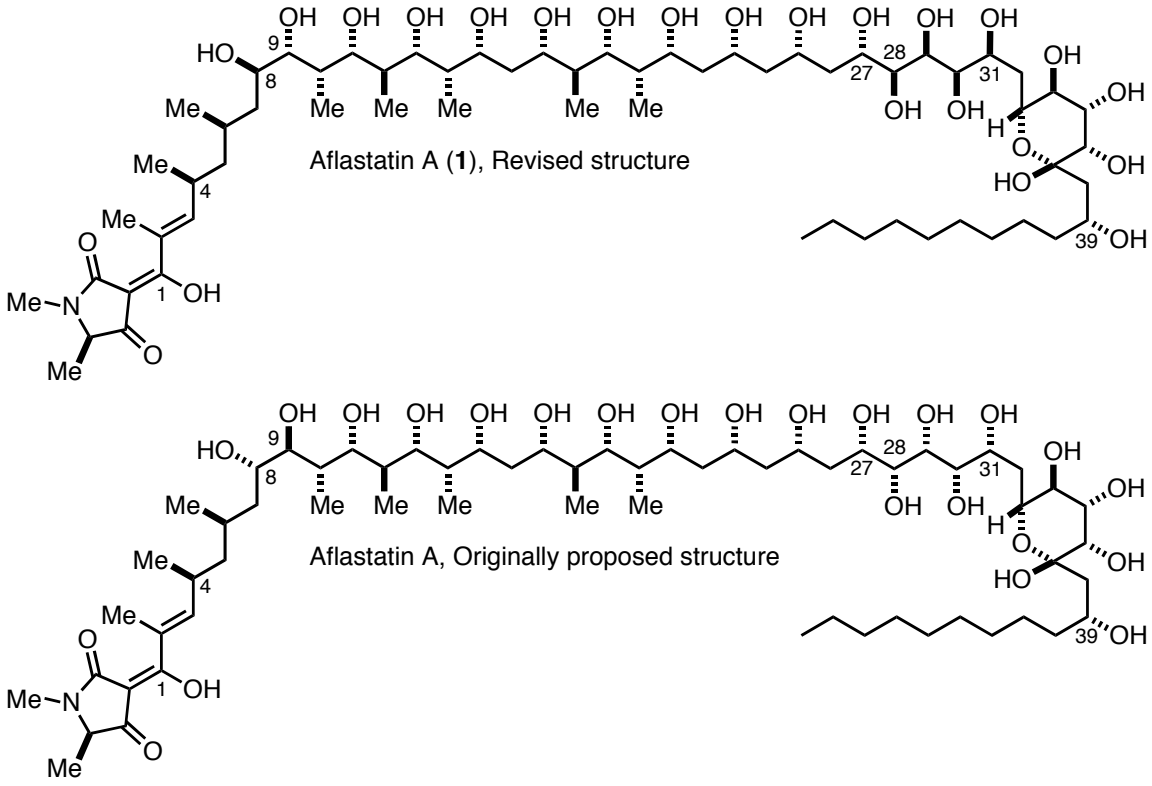
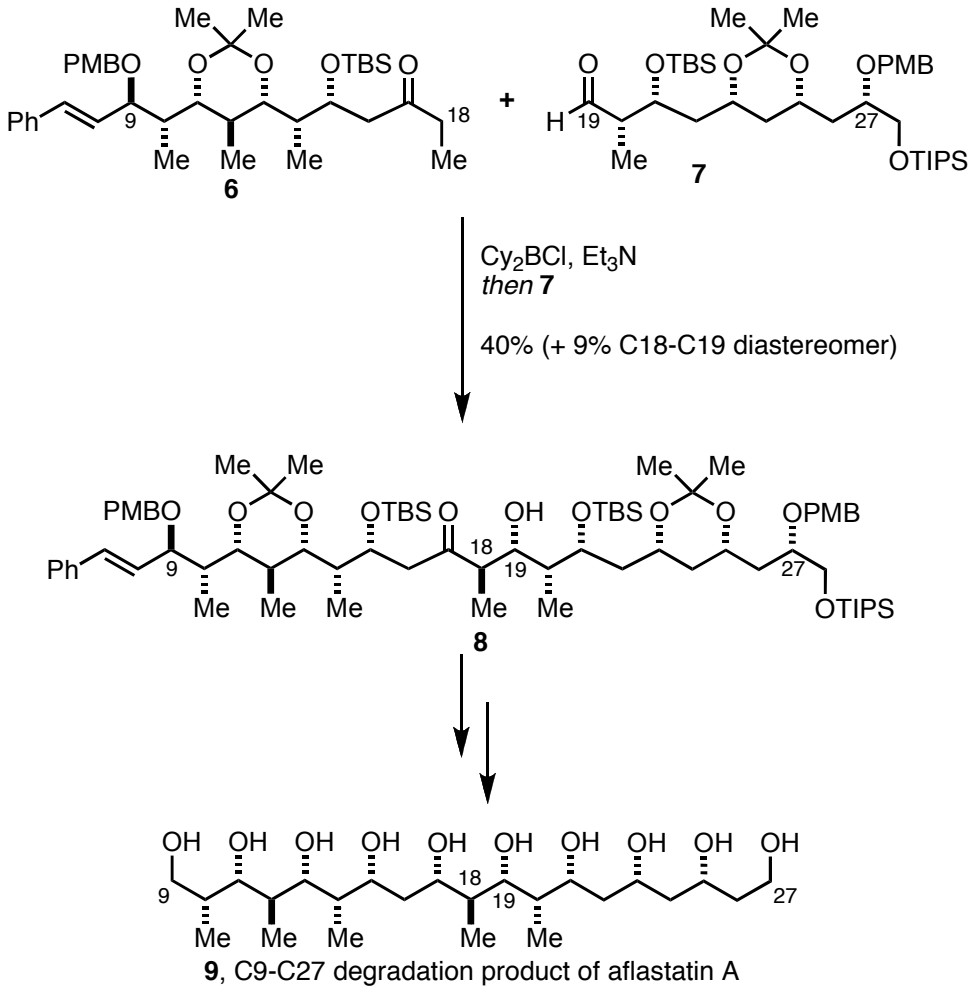


Figure 3. Structures of Aflastatin A (**1**) and originally proposed structure.

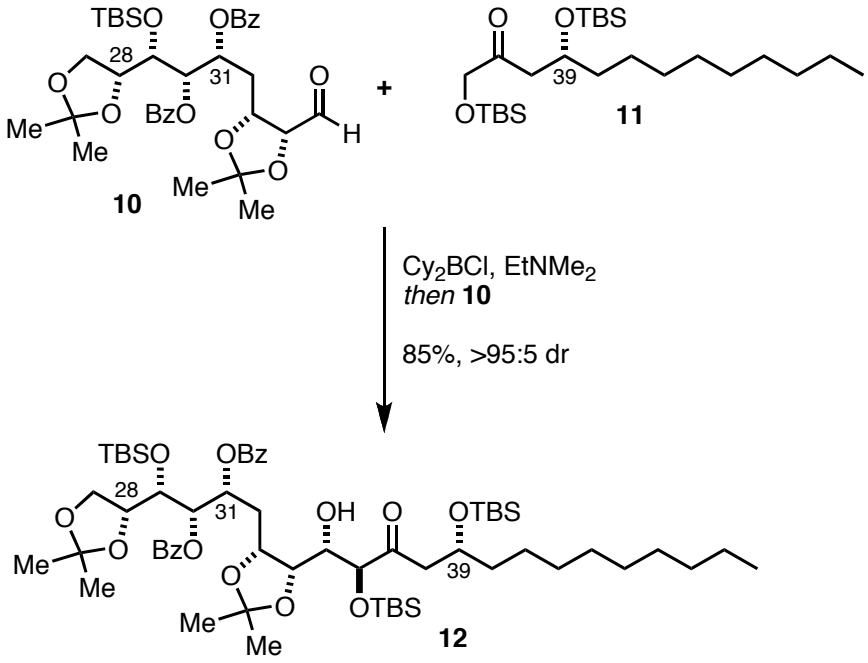
Up to date, no total synthesis of aflastatin A (**1**) has been achieved. Other than our work, the only synthetic activity in this area reported in the chemical literature is the synthesis of the C9-C27 degradation product (scheme 1),[43] by an iterative aldol approach, as well as the synthesis of the C27-C48 sector of aflastatin A,[44] although with the stereochemistry from C28-C31 corresponding to the originally proposed but incorrect structure (scheme 2). For the synthesis of the C9-C27

degradation product, Evans and coworkers utilized several enantio- and diastereoselective aldol reactions to prepare the ketone **6** and aldehyde **7**. These fragments were then coupled through an aldol reaction via the *E*-enol borinate of ethyl ketone **6**, to provide the *anti*-aldol product **8** in 40% yield and modest diastereoselectivity. The aldol adduct **8** was then transformed into the C9-C27 degradation product of aflastatin A in 7 steps.



Scheme 1. Evans' synthesis of the C9-C27 degradation product of aflastatin A.

The synthesis of the C27-C48 sector of aflastatin A (**12**) also relied on the aldol reaction as the key strategy for the union of complex highly oxygenated subunits. The cross-coupling of aldehyde **10** with ketone **11** gave the *anti*-aldol adduct **12** in 85% yield and >95:5 diastereoselectivity (scheme 2).

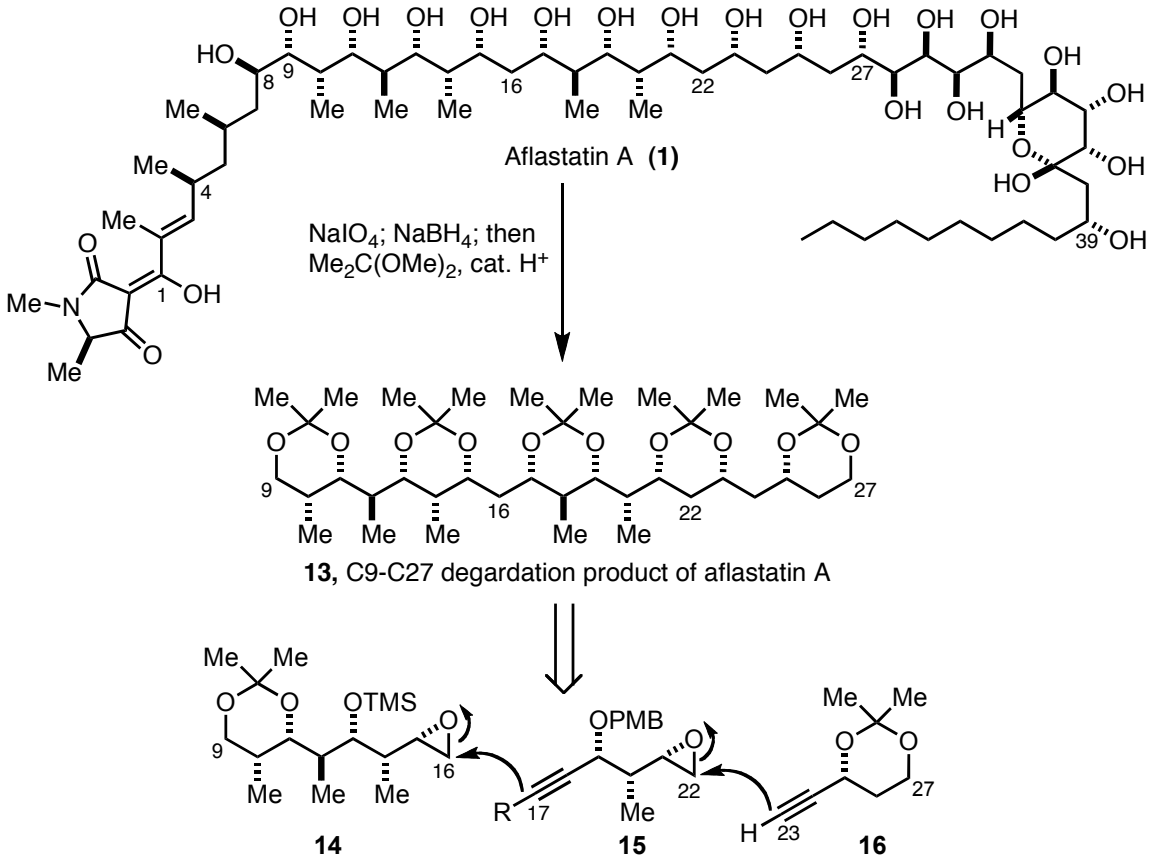


Scheme 2. Evans' synthesis of the C27-C48 sector of aflastatin A.

2.2 Synthetic Strategy

Our approach to the synthesis of the C9-C27 degradation product of aflastatin A is shown on scheme 3. It is based on iterative cross-coupling of nucleophilic alkynes with electrophilic epoxides, followed by functionalization of the internal alkynes, recently developed in the McDonald group.[23] Encouraged by the successful application of this approach to the total synthesis of RK-397,[24] we decided to extend this methodology to the synthesis of structurally complex and

stereochemically rich polypropionates. We chose the pentaacetonide C9-C27 degradation product of aflastatin A (**13**), as our target to demonstrate demonstrate the efficacy of the alkyne-epoxide cross-couplings in complex settings.



Scheme 3. Retrosynthetic analysis for **13**.

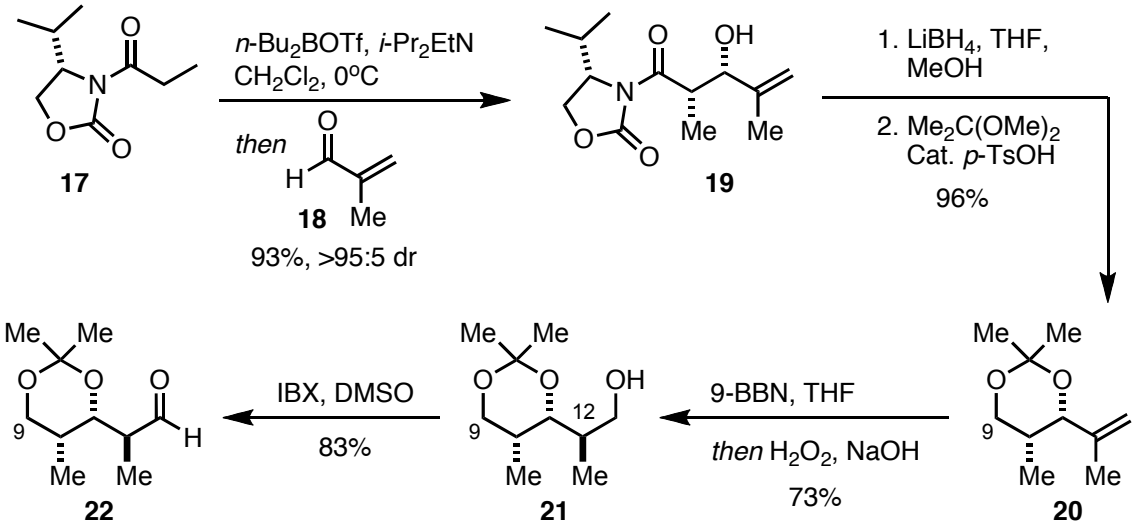
The pentaacetonide C9-C27 degradation product of aflastatin A (**13**) was the larger fragment from chemical degradation of aflastatin A (**1**), and was used to elucidate the relative stereochemistry of the aflastatins backbone.[40] It contains 13 chiral centers, with stereochemically dense C10-C15 and C17-C21 sectors

having six and five continuous asymmetric centers, respectively, making it an attractive target for chemical synthesis. As shown on scheme 3, our retrosynthetic analysis envisioned that the C9-C27 substructure could be efficiently assembled by coupling modules **14**, **15** and **16**. The coupling modules were efficiently prepared utilizing modern methods for stereoselective synthesis in a concise fashion, allowing for *gram* scale syntheses of each module.

2.3 Results and Discussion

2.3.1 Initial approach to the synthesis of Module 14

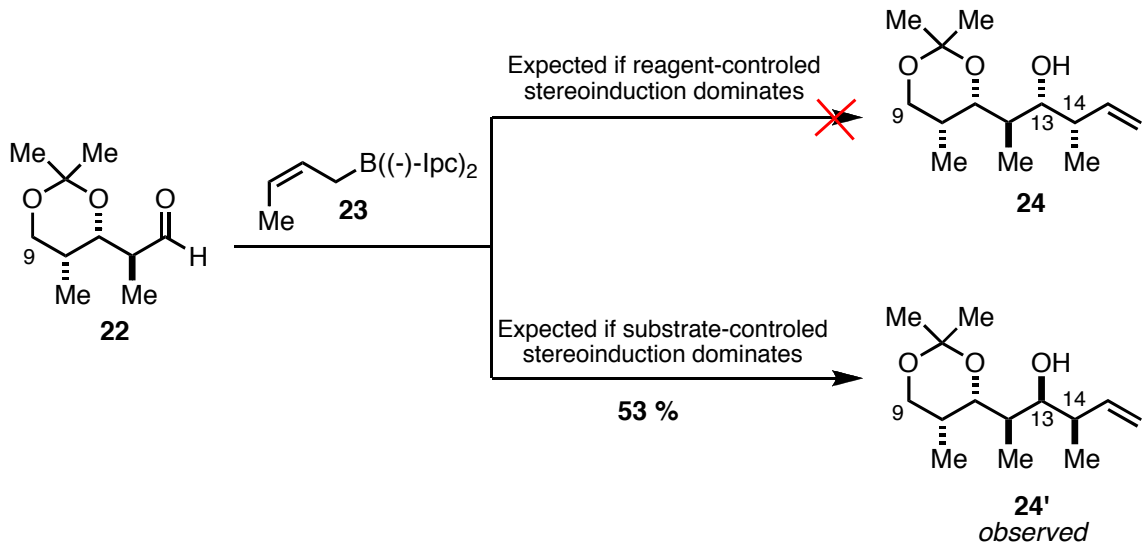
Our initial approach to the synthesis of epoxide **14** is summarized on the schemes below. Our synthesis commenced with an Evans' asymmetric aldol reaction of oxazolidinone **17** and methacrolein **18**,[45] that provided the aldol adduct **19** in 93% yield and excellent diastereoselectivity (scheme 4).



Scheme 4. Synthesis of aldehyde **22**.

Reductive cleavage of the chiral auxiliary in **19** was followed by acetonide protection of the resulting diol to afford the terminal olefin **20**. Diastereoselective hydroboration-oxidation provided the terminal alcohol **21** and set the stereochemistry at C12 selectively. Then, IBX oxidation of the primary alcohol provided the desired aldehyde **22** under mild conditions without epimerization of the C12 chiral center.

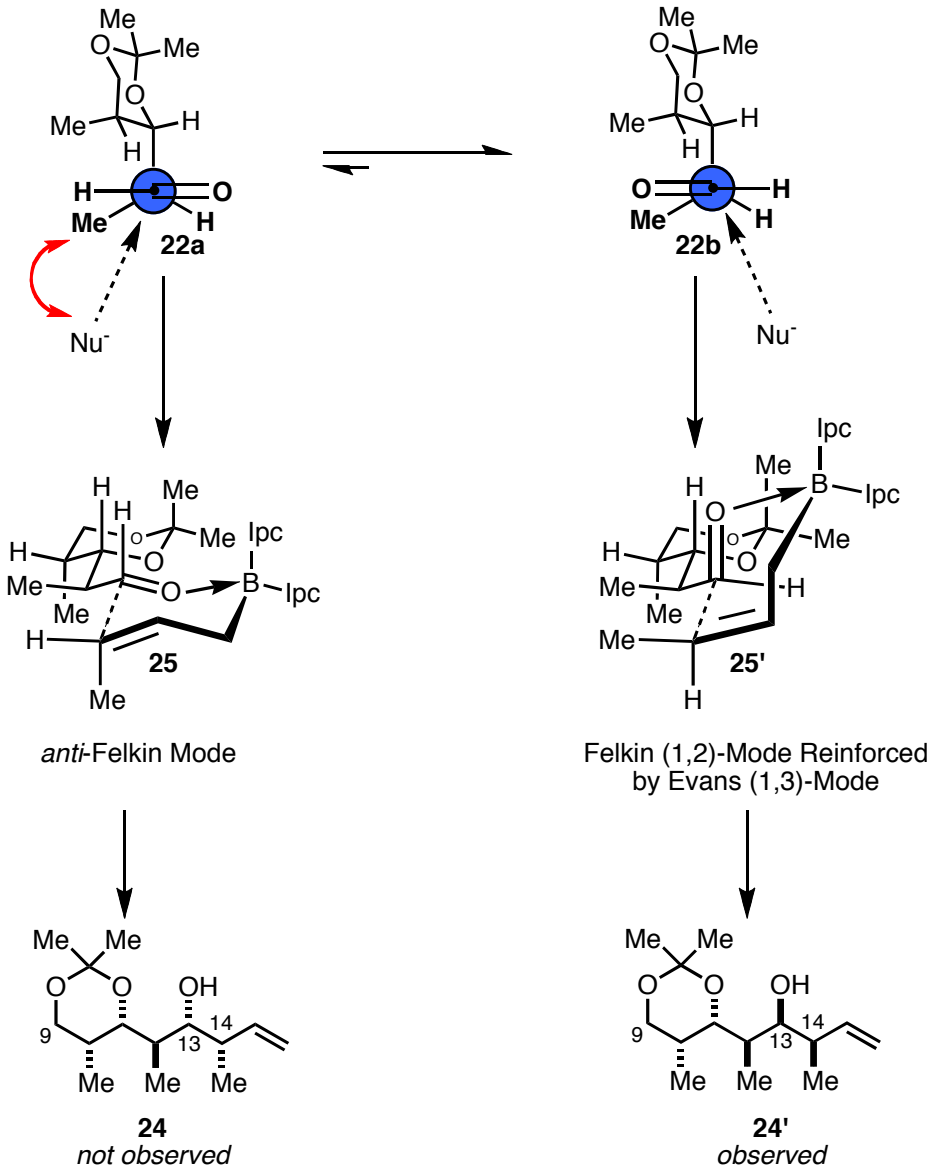
Brown's enantioselective crotylborane addition to aldehyde **22** was then applied to introduce the remaining carbon atoms of module **14** and set the C13 and C14 chiral centers in **24** (scheme 5).[46] To our surprise, the desired homoallylic alcohol **24** was not obtained, which was expected if reagent-controlled stereoinduction dominated (from the chiral crotylborane reagent **23**). Instead the corresponding diastereomer **24'** was the only observed product that corresponded to the case in which substrate-controlled stereoinduction dominated.



Scheme 5. Brown crotylation of aldehyde **22**.

The stereochemical outcome of this reaction can be rationalized by close examination of the stereoinduction models. As illustrated in scheme 6, the aldehyde **22** is an excellent example of the Felkin-Anh model of 1,2-stereoinduction, with clearly defined large (acetonide), medium (methyl group) and small (hydrogen) groups. In this particular case, the stereoinduction sense of the chiral reagent is a mismatched case with the inherent stereoinduction of the substrate. If the reagent-controlled stereoinduction were to dominate (**25**), the incoming nucleophile has to approach the aldehyde through the *anti*-Felkin-Anh conformation **22a**, in which there are substantial steric interactions of the incoming nucleophile with the α-methyl group of the aldehyde. In order to avoid these steric interactions, the preferred reactive conformation is **22b**, that is predicted by the Felkin-Anh model, in which the incoming nucleophile approaches the aldehyde next to the small (hydrogen) substituent, overriding any stereoinduction bias of the chiral reagent. Furthermore, the 1,2-Felkin-Anh model is reinforced by the 1,3-Evans model of stereoinduction, that also predicts that the observed product would be the favored one.

The use of other reaction conditions and/or crotylation reagents also failed to give the homoallylic alcohol with the desired stereochemistry, often giving complex mixtures of products. At this stage we decided to reevaluate our synthetic route to the module **14**, and opted to take advantage of this strong stereoinduction bias of the substrate, and use it to direct the crotylation reaction in the desired direction by redesigning our substrate and choosing the appropriate reaction conditions.

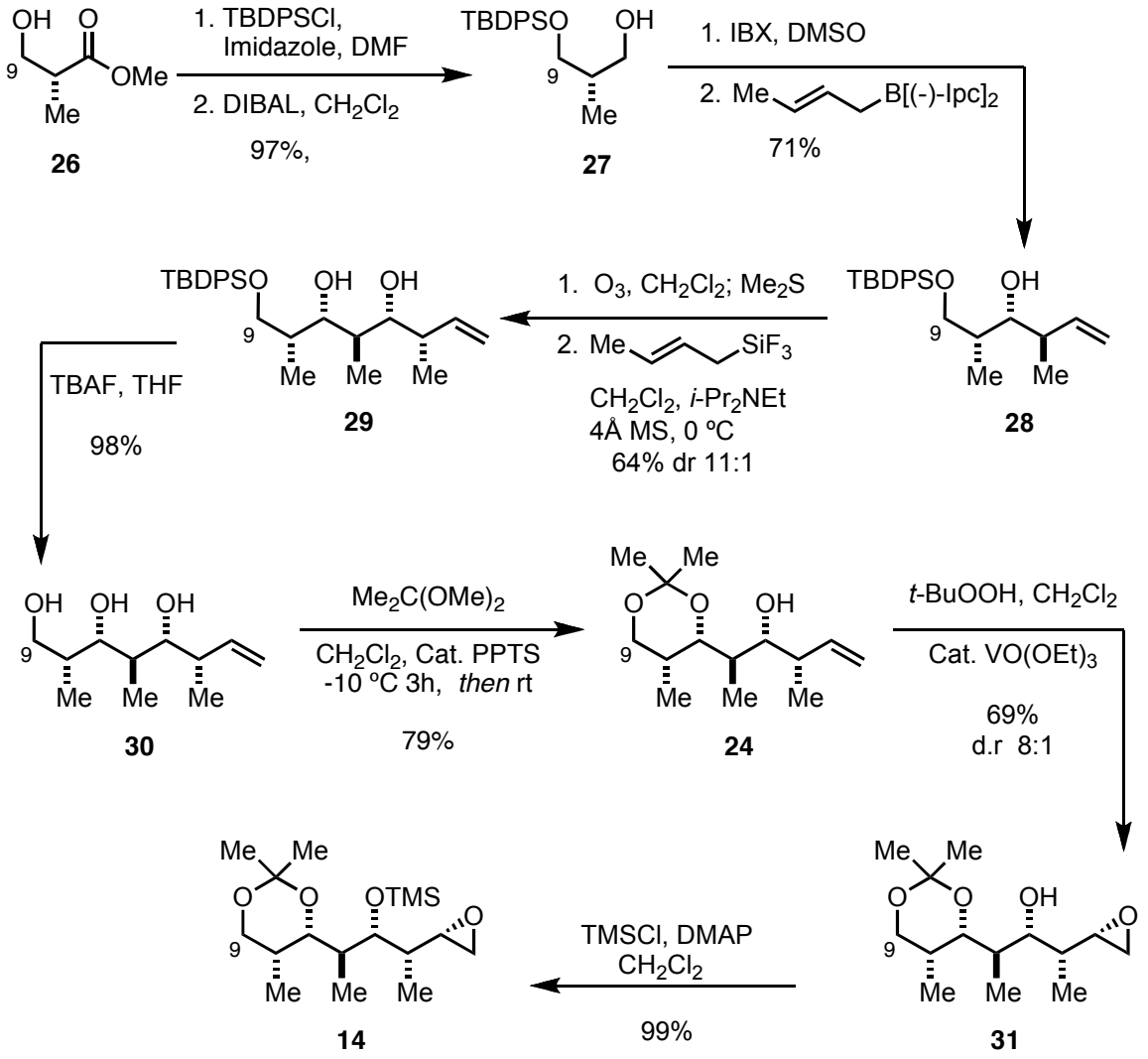


Scheme 6. Stereochemical rationals for the crotylation of aldehyde **22**.

2.3.2 Synthesis of Module 14

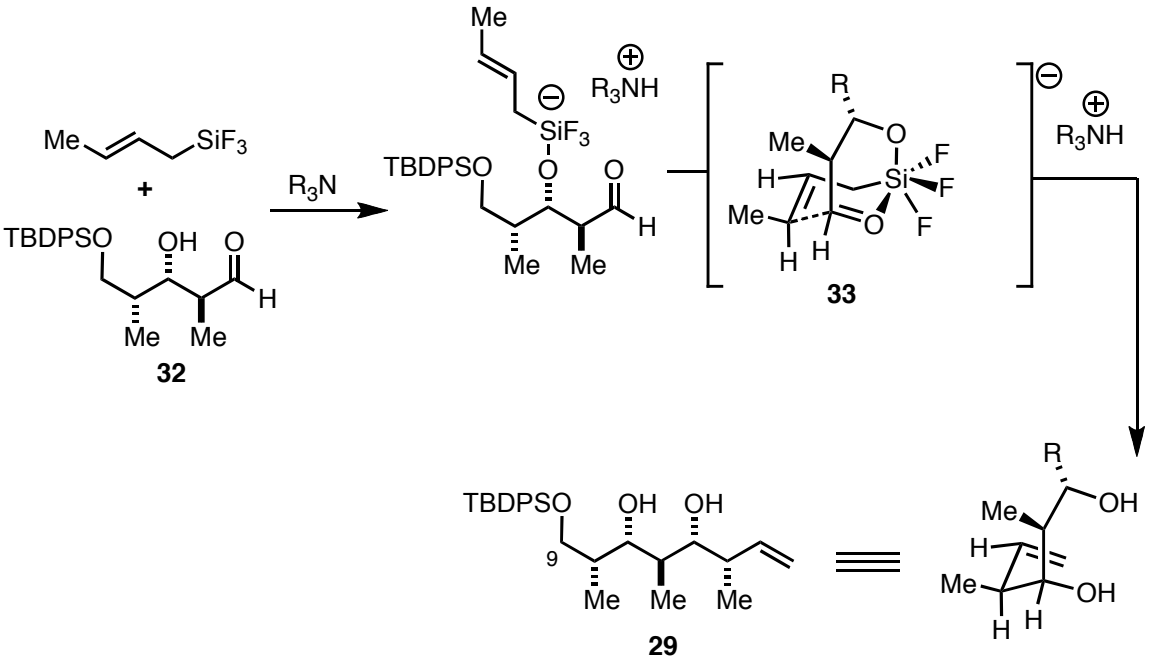
Our revised approach to the synthesis of module started from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate (scheme 7). Protection of the alcohol (**26**) was followed by reduction of the methyl ester to the corresponding alcohol (**27**). IBX oxidation of the primary alcohol provided the corresponding

aldehyde, which was immediately subjected to Brown's enantioselective crotylborane addition to avoid any epimerization. In this case, the sense of stereoinduction of the chiral reagent and substrate was a matched case and reinforced each other, providing the desired homolallylic alcohol **28** as a single diastereomer in 71% yield for the two steps.



Scheme 7. Synthesis of module **14**.

The terminal olefin in **28** was then cleaved by ozonolysis, and the resulting aldehyde underwent diastereoselective reaction with crotyltrifluorosilane to afford the diol **29** in 64% yield and 11:1 diastereoselectivity.[47] This diastereoselective crotyltrifluorosilane addition developed by Chemler and Roush is a remarkable reaction, in that the *E*-crotyltrifluorosilane provides the *syn* product with good disatereoselectivity. Scheme 8 shows the reaction mechanism of this transformation, which passes through a bicyclic transition state **33** that accounts for the observed stereochemistry of the product.[47]



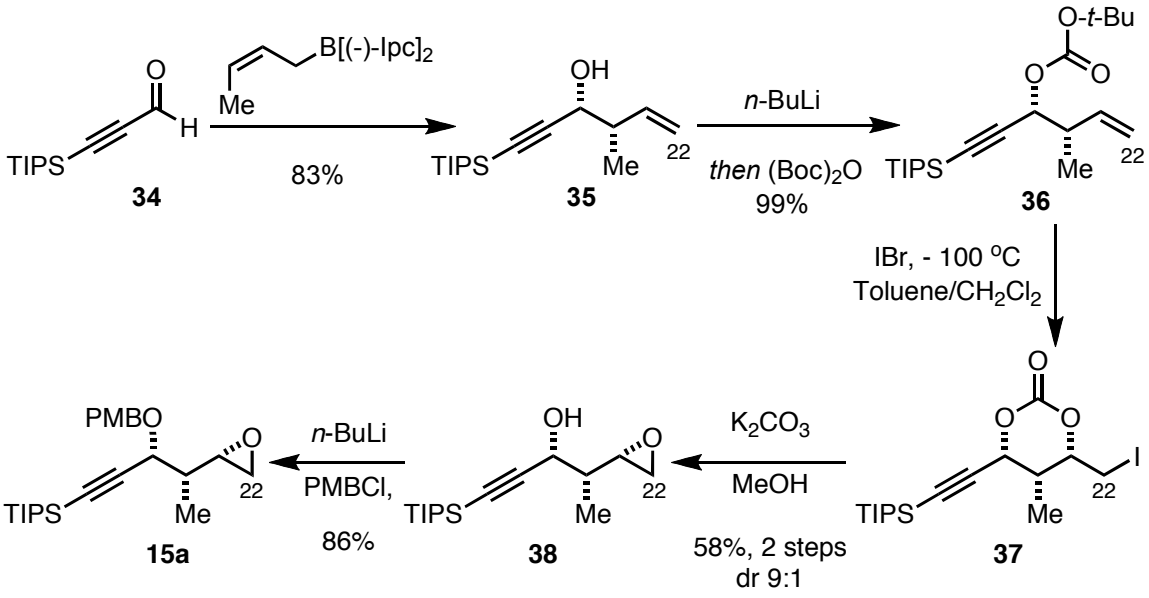
Scheme 8. *E*-crotyltrifluorosilane addition to aldehyde **32**.

The synthesis of module **14** was completed by removal of the silyl protecting group in **29**, followed by selective installation of the terminal acetonide under kinetic conditions, that afforded the alcohol **24** in 78% yield. The free alcohol was

then used to direct a diastereoselective vanadium-catalyzed epoxidation[48] that provided module **14** after TMS protection of the alcohol **31** (scheme 7).

2.3.3 Synthesis of Module 15a

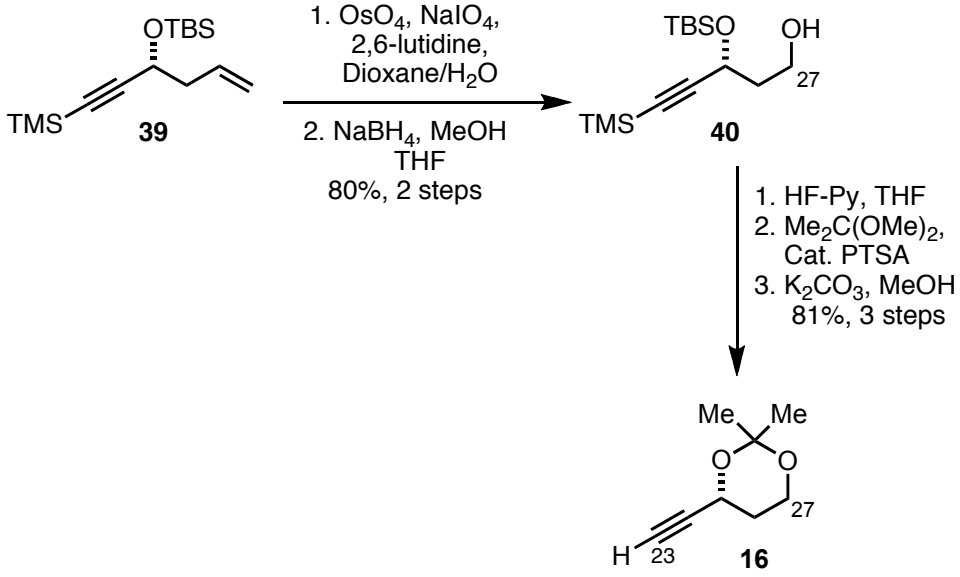
The epoxyalkyne module **15a** was prepared from the known enynol **35**,[49] that arose from Brown's enantioselective crotylborane addition to aldehyde **34**. Boc protection of alcohol **35** provided carbonate **36** in excellent yield. The C21-C22 epoxide was introduced by IBr-promoted cyclization of **36**, followed by basic methanolysis of the resulting cyclic iodocarbonate **37**.[50] Finally, PMB protection of alcohol **38** afforded module **15a** containing a triisopropylsilyl (TIPS) substituent on the alkyne (scheme 9).



Scheme 9. Synthesis of module **15a**.

2.3.4 Synthesis of Module 16

The terminal alkyne module **16** was synthesized from the known enyne **39**,[23] by by oxidative cleavage of the terminal olefin followed by reduction of the resulting aldehyde to provide the diol **40**. Removal of the TBS protecting group under acidic conditions was followed by installation of the acetonide across the diol, and finally, the terminal alkyne **16** was unmasked by removing the TMS under basic methanolysis, in 81% yield for the three steps (scheme 10).

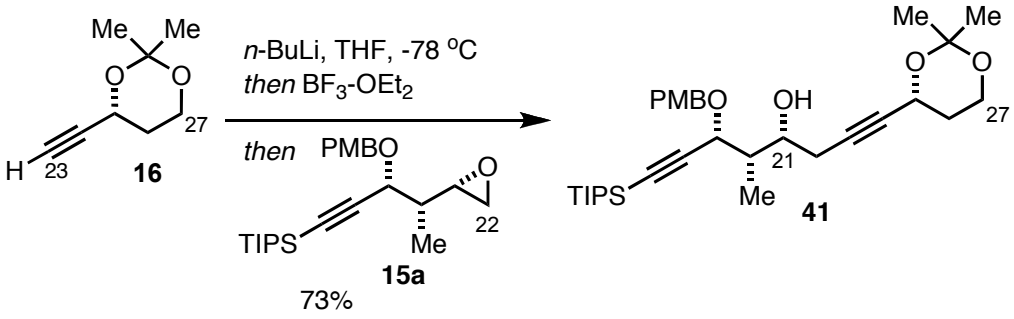


Scheme 10. Synthesis of module **16**.

2.3.5 Cross-Coupling of Modules 15a and 16

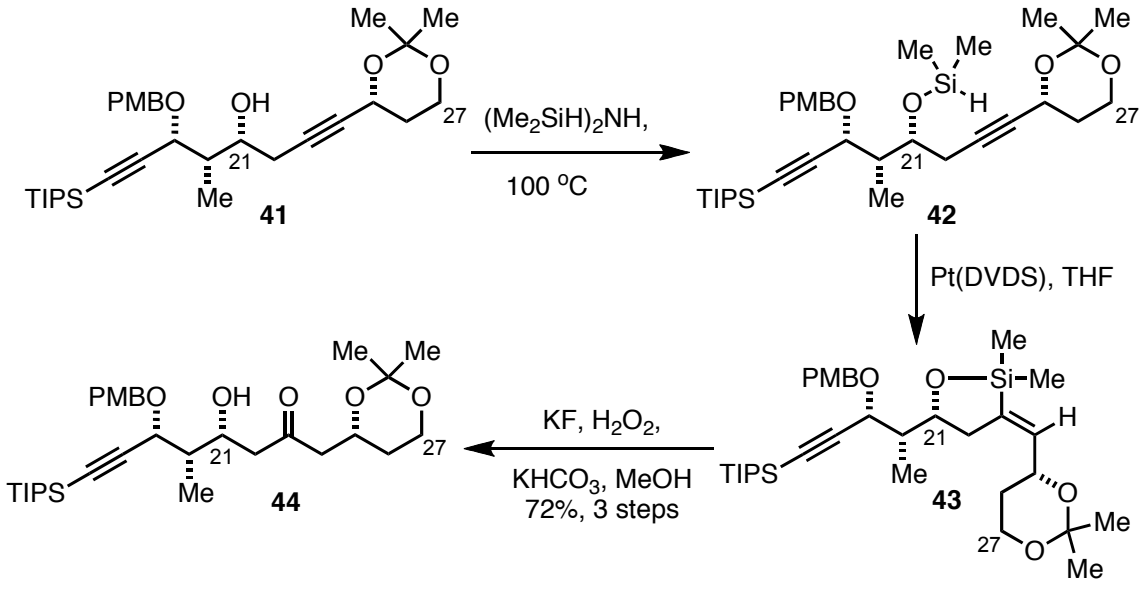
With the modules **14**, **15a** and **16** in hand, we began to assemble the skeleton of the aflastatin C9-C27 degradation product (**13**), by first coupling modules **15a** and **16** (scheme 11). Treatment of **16** with one equivalent of *n*-butyllithium and

BF_3-OEt_2 at -78 ºC,[51] followed by addition of the electrophilic epoxide **15a** provided alkynyl alcohol **41** in 73% isolated yield.



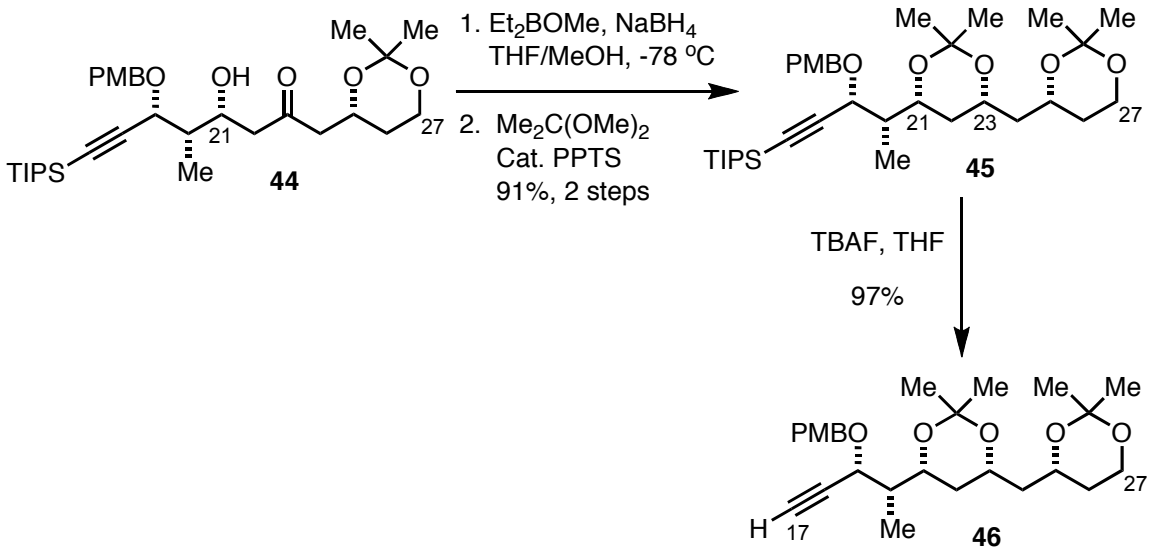
Scheme 11. Cross-coupling of modules **15a** and **16**.

The resulting C21-alcohol was then used to direct the regioselectivity in the hydration of the internal alkyne to the corresponding β-hydroxyketone **44** (scheme 12), via intramolecular platinum-catalyzed hydrosilylation[52] and Tamao-Fleming oxidation.[53]



Scheme 12. Regioselective functionalization of alkyne **41**.

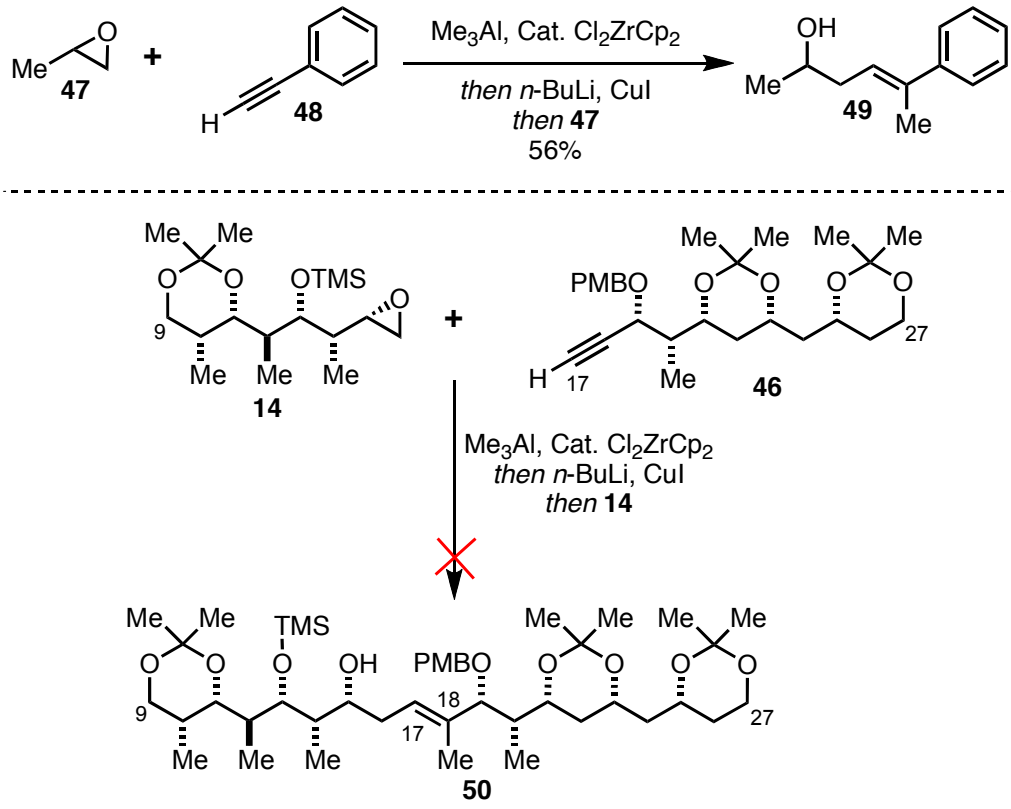
The C21 hydroxyl group also directed the diastereoselective reduction of the ketone **44** to provide the *syn*-C21,C23-diol, which was converted into the corresponding acetonide **45** (scheme 13). Removal of the triisopropylsilyl (TIPS) substituent on the alkyne **45** afforded terminal alkyne **46** in 97% yield, that in turn served as the next nucleophilic coupling partner.



Scheme 13. Diastereoselective reduction of ketone **44**.

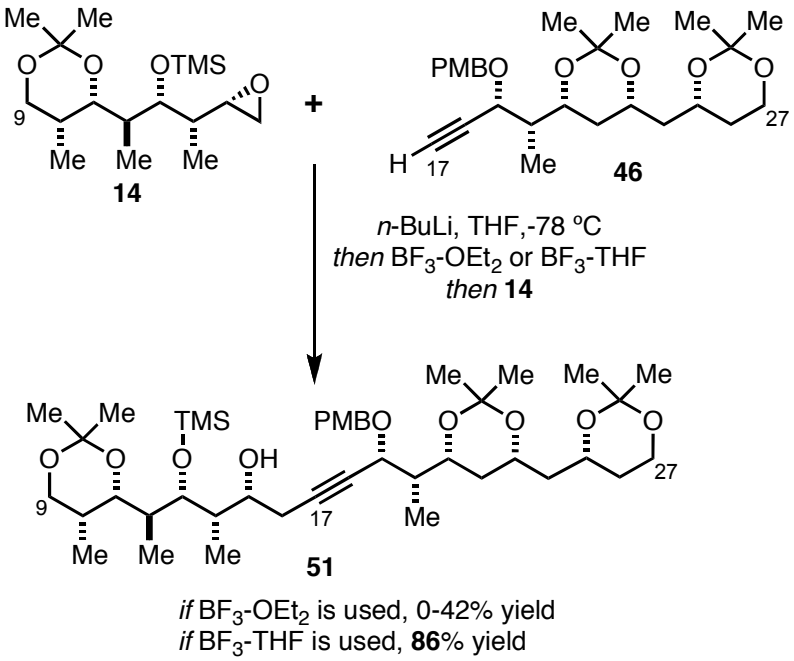
2.3.6 Cross-Coupling of Modules 14 and 46

Our original plan to introduce a methyl group at C18 via carbometallation of the terminal alkyne **46** and subsequent cross-coupling of the resulting vinylcuprate with epoxide **14** failed due to the high degree of functionalization in both coupling patterns (scheme 14), despite the fact that simpler model systems provided the desired trisubstituted olefins in good yield.



Scheme 14. Attempted carbometallation - cross-coupling of **14** and **46**.

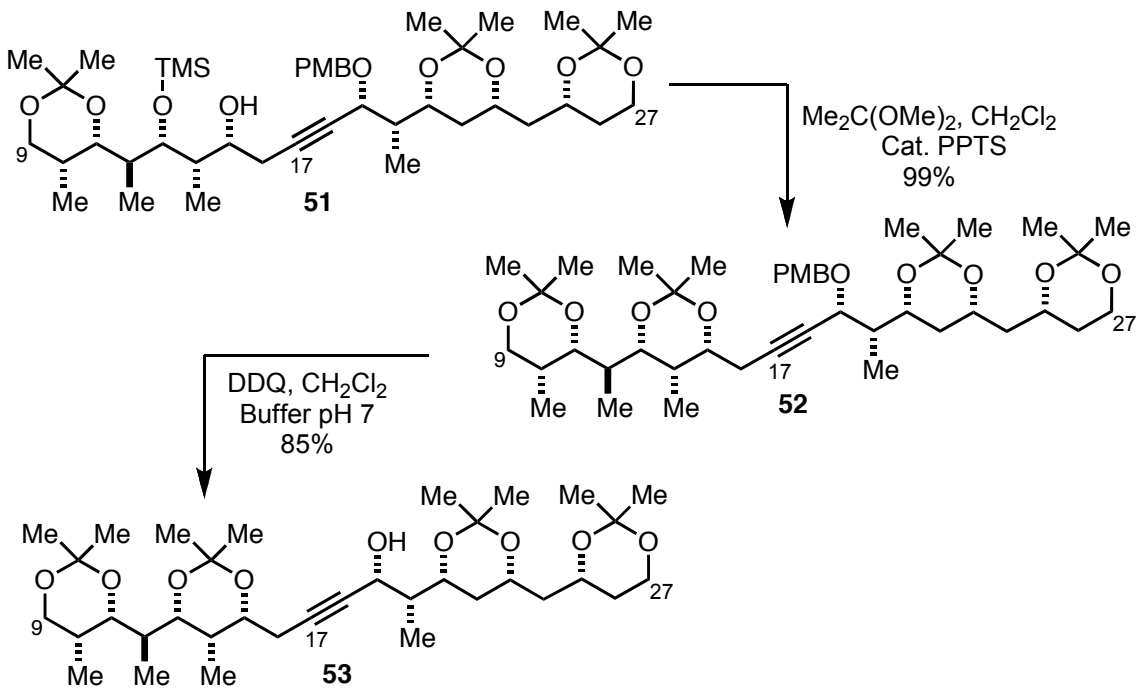
After finding that the carbometallation of the terminal alkyne **46** and subsequent cross-coupling of the resulting vinylcuprate with epoxide **14** was not a viable option, we returned to the reliable cross-coupling of the alkynylboronates with epoxides. Initial studies using one equivalent of *n*-butyllithium and BF_3-OEt_2 at -78 ºC,[51] followed by addition of the electrophilic epoxide provided the desired coupled product **51**, but the yields were low and irreproducible (scheme 15). However, when BF_3-THF was utilized instead of BF_3-OEt_2, the alkynyl alcohol **51** was obtained in excellent yield.[54] The better results obtained by using BF_3-THF can be attributed to its milder reactivity and higher stability as compared to BF_3-OEt_2.



Scheme 15. Cross-coupling of modules **14** and **46**.

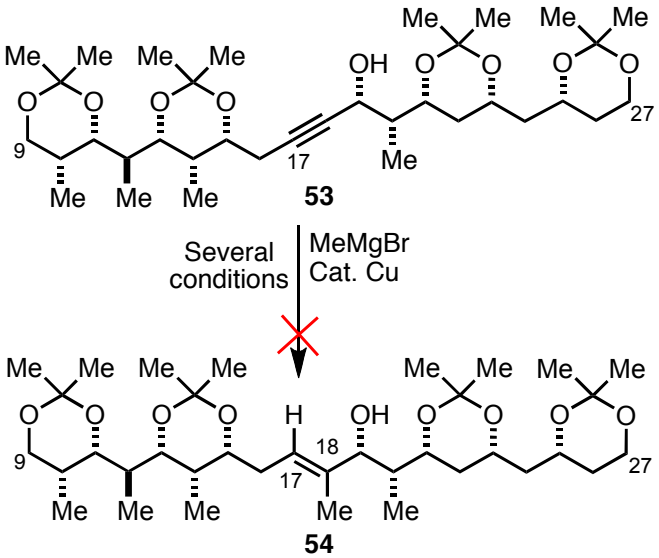
2.3.7 Completion of the Synthesis of 13

The cross-coupling of modules **14** and **46** provided the contiguous carbon chain of the C9-C27 degradation product of aflastatin A (**13**). All that was needed to complete the synthesis of the pentaacetonide C9-C27 degradation product **13** was to execute some protecting group manipulations, and add a methyl group and the elements of water onto the C17-C18 alkyne. Needless to say, this had to be accomplished with the proper regio- and stereoselectivity, which turned out to be a challenging task. To that end, the TMS protecting group in **51** was removed under mild acidic conditions, and in the same pot, the resulting diol was protected as the corresponding acetonide **52** in 99% yield (scheme 16). The PMB group was then removed with DDQ, providing the propargylic alcohol **53** in 85% yield.



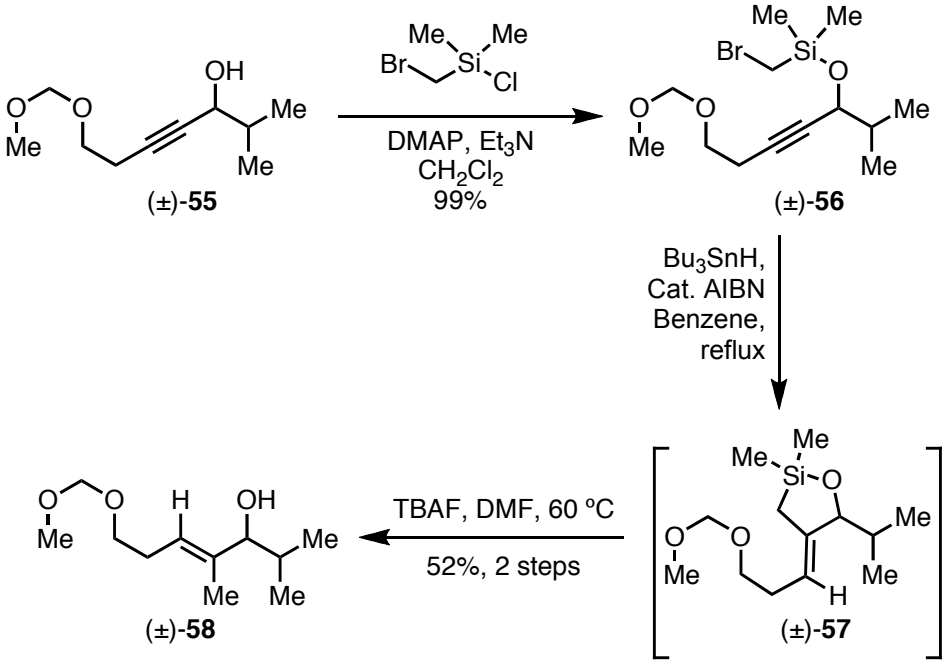
Scheme 16. Synthesis of alkynol **53**.

All attempts to introduce the methyl substituent at C18 via copper catalyzed carbometallation were fruitless, giving only decomposition over extended periods of time (scheme 17).



Scheme 17. Attempted functionalization of alkynol **53**.

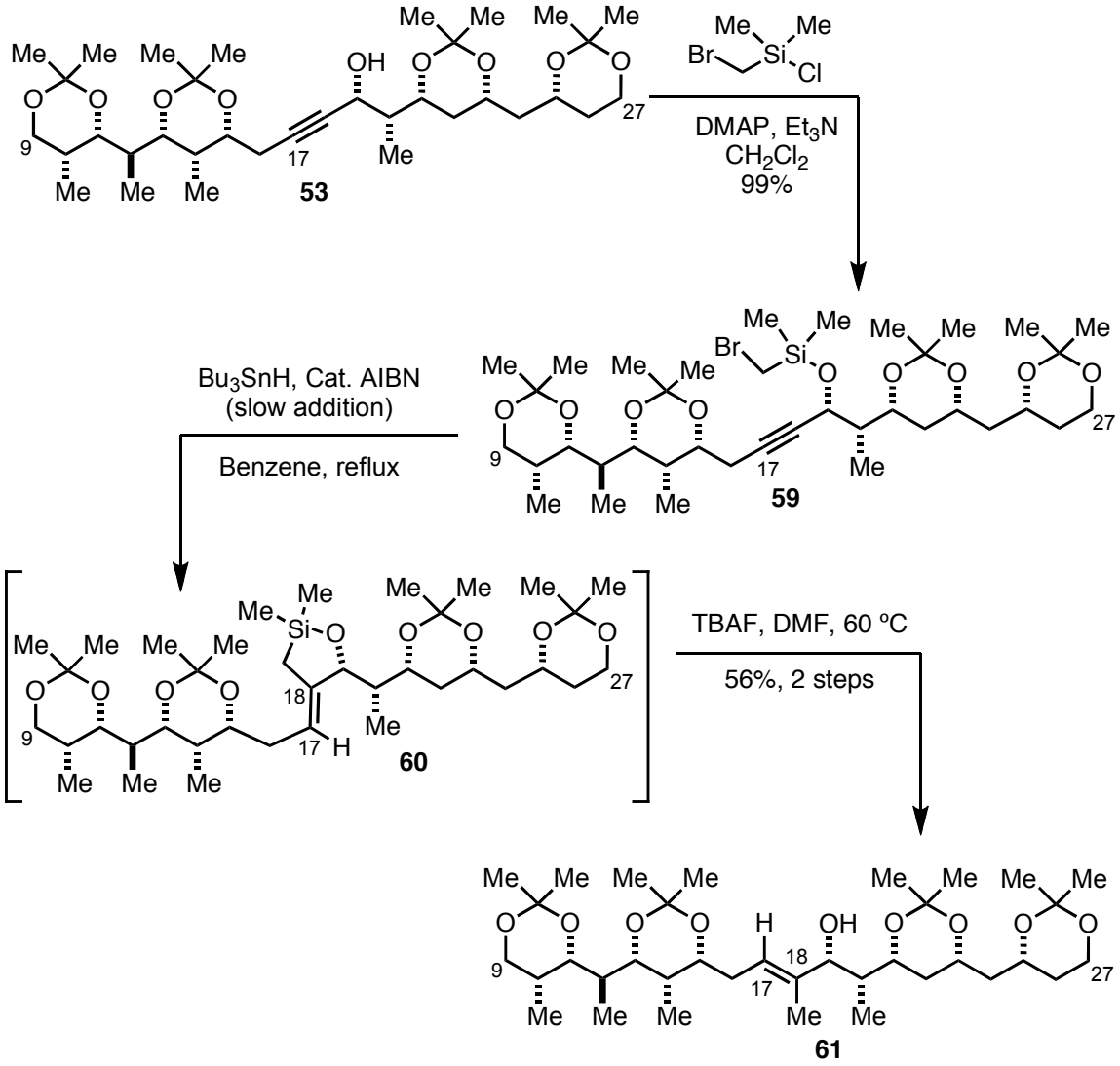
After some experimentation with a model system **55**, we found that the internal alkyne could be functionalized by the radical cyclization of bromomethylsilyl ether **56**, followed by protiodesilylation to afford the *E*-trisubstituted **58** selectively (scheme 18).[55,56]



Scheme 18. Radical cyclization of bromomethylsilyl ether model system (±)-**56**.

Encouraged by the successful functionalization of the internal alkyne on the model system **55**, we applied these reaction conditions to the alkynol **53**. The alkynol was transformed into the corresponding bromomethylsilyl ether **59** (scheme 18). The introduction of the C18-methyl substituent was then accomplished by radical cyclization of the bromomethylsilyl ether **59**, which was followed by protiodesilylation to stereoselectively afford the *E*-trisubstituted alkene **61** (scheme 19). In this complex setting, slow addition of the Bu_3SnH and

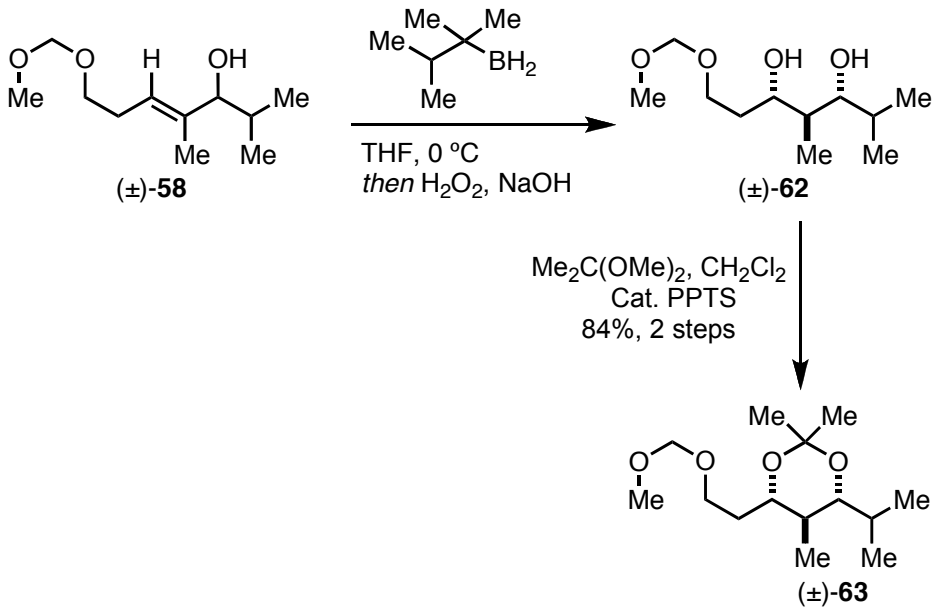
AIBN was crucial to allow carbon-carbon formation and avoid competing reduction of the methylsilyl ether radical to the corresponding trimethylsilyl ether.



Scheme 19. Functionalization of alkynol **53**.

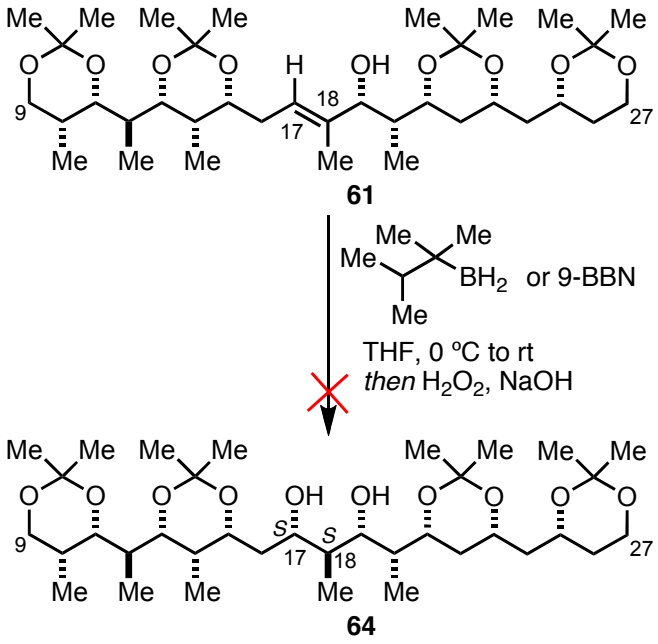
In anticipation for the final hydroboration - oxidation of **61**, reaction conditions were explored with olefin (±)-**58** as model system. We found that the use of thexylborane in THF at 0 ºC provided the *syn*-diol (±)-**62** as a single

diastereomer, consistent with the Still-Barrish model of stereoinduction.[57] The diol (±)-**62** was then converted into the corresponding acetonide (±)-**63**, which was used to confirm the relative stereochemistry (scheme 20).[58]



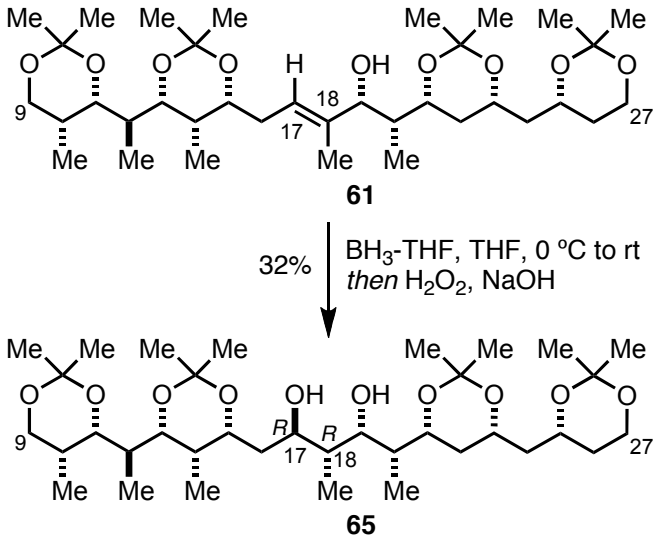
Scheme 20. Hydroboration - oxidation of model system (±)-**58**.

The hydroboration - oxidation reaction of allylic alcohol **61** was then attempted with thexylborane, however, no reaction was observed at appreciable rates, even at room temperature (scheme 21). Other bulky boranes such as 9-BBN also failed to react, and extended reaction times led only to decomposition. The lack of reactivity of allylic alcohol **61** with bulky boranes was attributed to steric hindrance between the reacting centers.



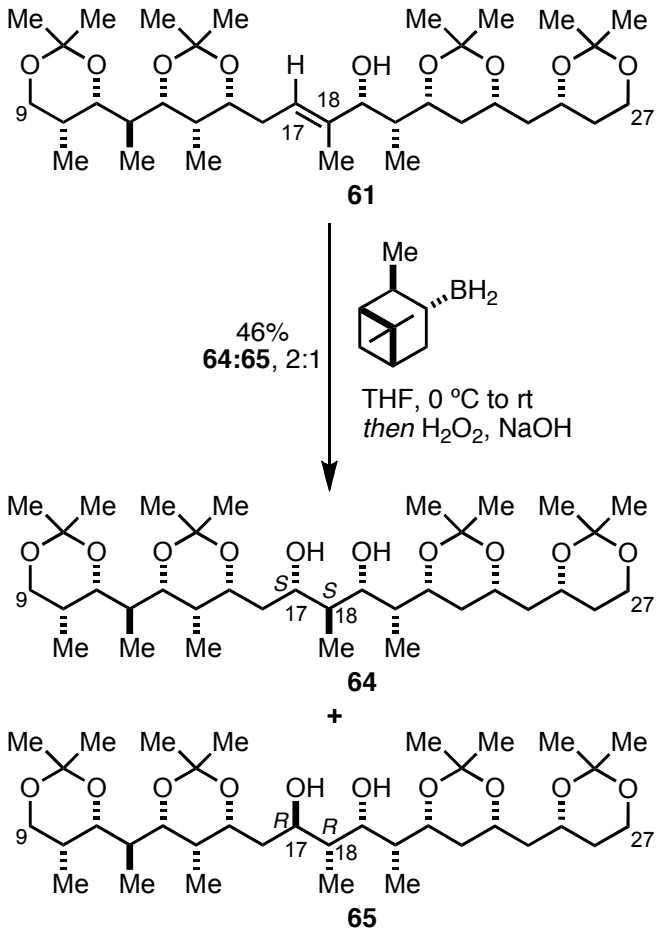
Scheme 21. Hydroboration - oxidation of **61** with bulky boranes.

The hydroboration - oxidation reaction using BH_3-THF was then explored, however, the product obtained was the undesired (17*R*,18*R*)-diastereomer **65** instead of **64** (scheme 22).



Scheme 22. Hydroboration - oxidation of **61** with BH_3-THF.

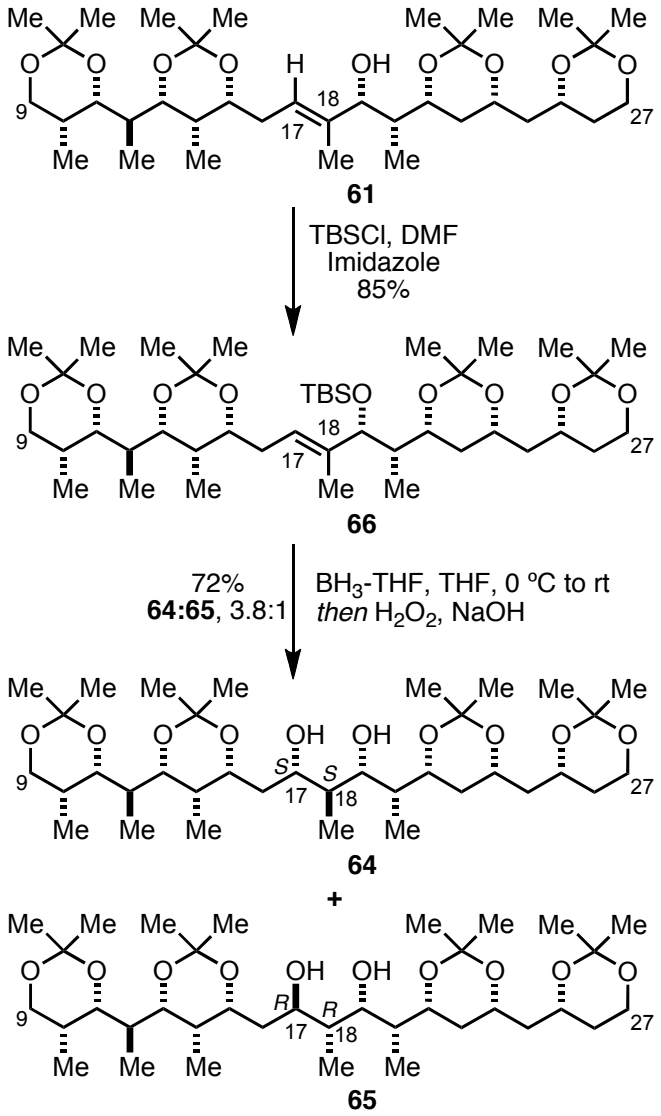
The use of the chiral non-racemic borane (+)-IpcBH$_2$ inverted the preference of stereoisomers to favor the (17*S*,18*S*) configuration of **64**,[59] but with only a 2:1 diastereomeric ratio and 46% yield (scheme 23).



Scheme 23. Hydroboration - oxidation of **61** with (+)-IpcBH$_2$.

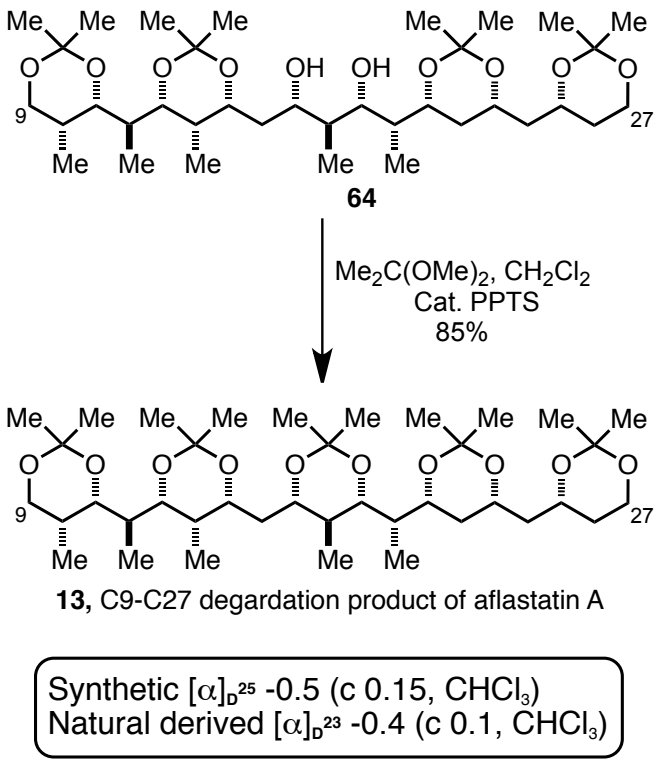
At this stage, it was evident that the conformation of the allylic alcohol **61** favored the hydroboration - oxidation on the undesired face of the olefin, since even the use of the chiral non-racemic borane (+)-IpcBH$_2$ gave a diastereoselectivity of only 2:1. In an attempt to change this trend, the allylic alcohol **61** was

transformed into the silyl ether **66** (scheme 24), which substantially changed the conformation based on ^{1}H NMR observations. The hydroboration - oxidation of **66** with BH_3-THF afforded a separable 3.8 : 1 mixture of C17-C19 diols favoring **64**, in which the TBS ether was lost under the basic oxidation conditions.



Scheme 24. Hydroboration - oxidation of silyl ether **66** with BH_3-THF.

Finally, the diol **64** was transformed into the pentaacetonide C9-C27 degradation product of aflastatin A (**13**), under mild conditions (scheme 25).[60]



Scheme 25. Synthesis of the C9-C27 degradation product of aflastatin A (**13**).

The spectroscopic and physical data of the synthetic pentaacetonide C9-C27 degradation product of aflastatin A (**13**) agreed with the reported data obtained by oxidative degradation of aflastatin A.[40] The ^{1}H NMR and ^{13}C NMR spectral comparison of synthetic with naturally derived **13** are shown of figures 4 and 5, respectively. The table 3 shows a tabular comparisons of ^{1}H and ^{13}C NMR data for synthetic pentaacetonide **13** and compound **13** produced by degradation of aflastatin A.[40]

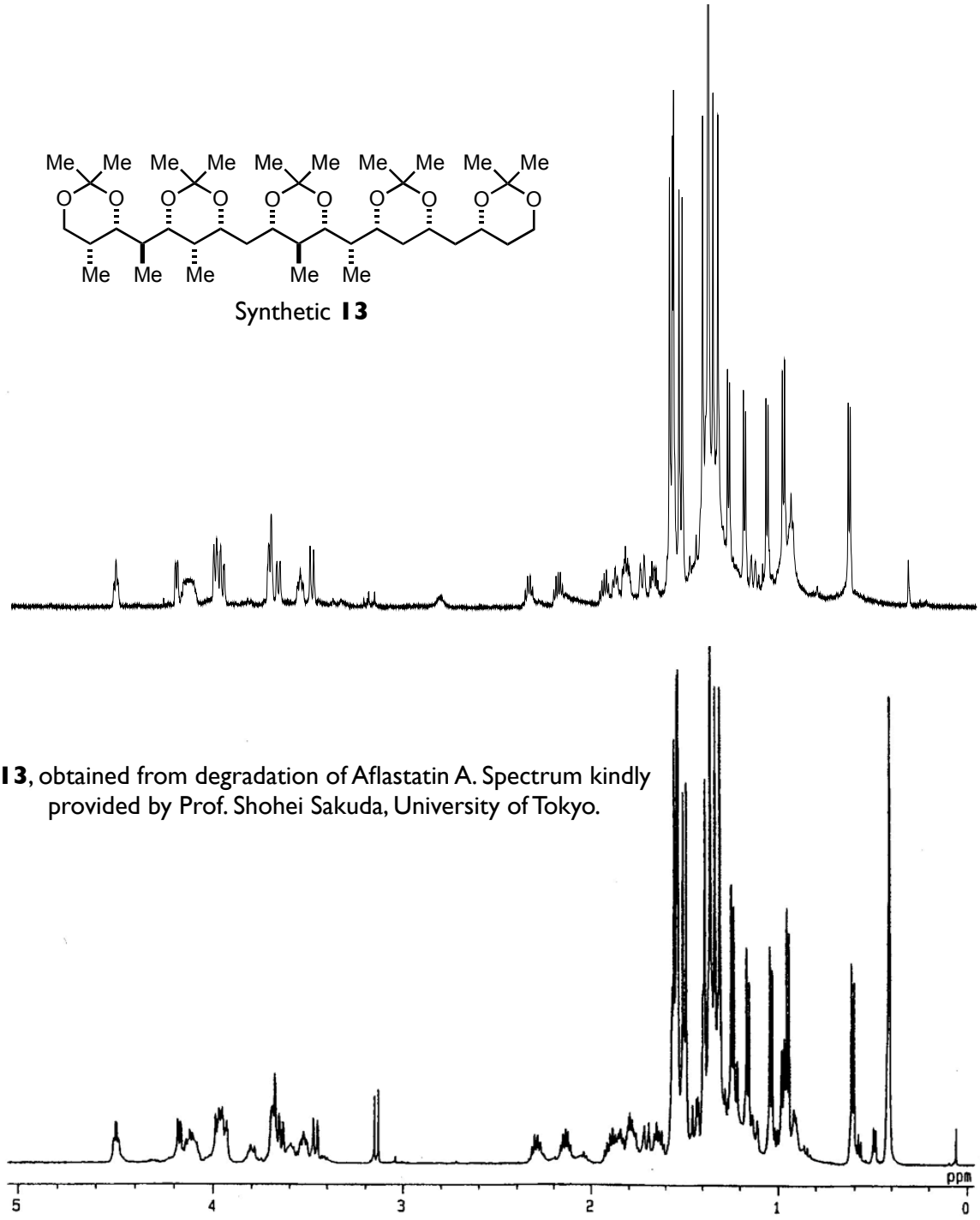
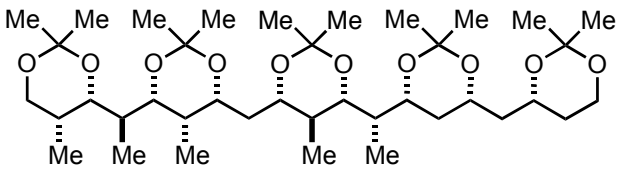
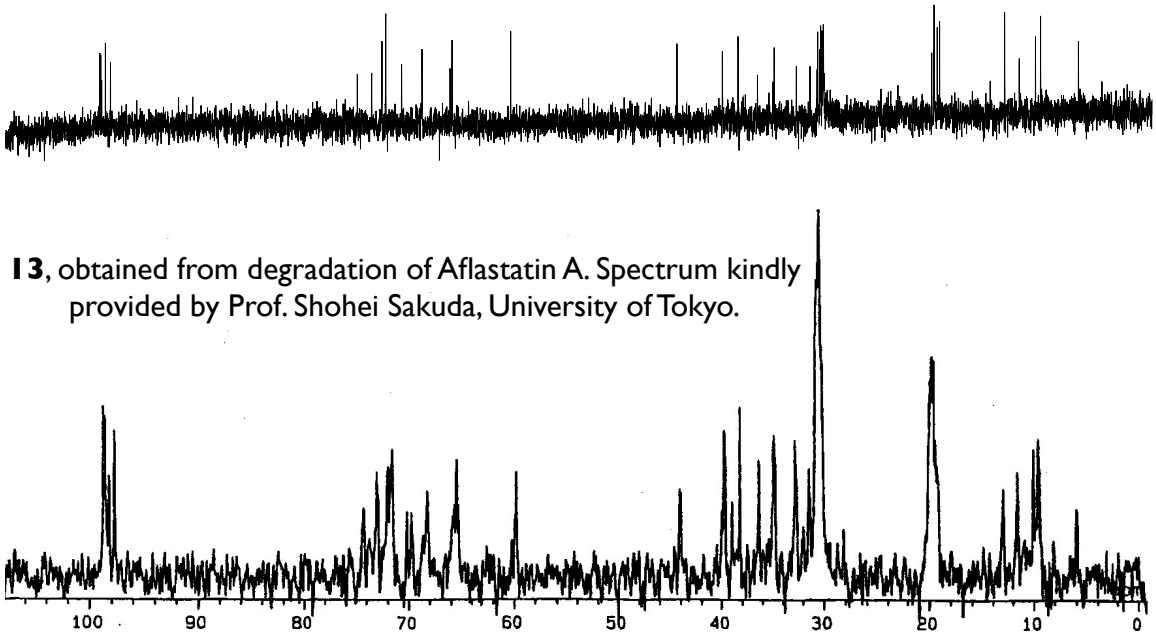


Figure 4. ^{1}H NMR comparison of synthetic with naturally derived **13** in C_6D_6.



Synthetic **13**



13, obtained from degradation of Aflastatin A. Spectrum kindly provided by Prof. Shohei Sakuda, University of Tokyo.

Figure 5. ^{13}C NMR comparison of synthetic with naturally derived **13** in C_6D_6.

^{1}H NMR		**^{13}C NMR**	
synthetic **13** 600 MHz in C_6D_6	from degradation of aflastatin A (ref. 40) 500 MHz in C_6D_6	synthetic **13** 150 MHz in C_6D_6	from degradation of aflastatin A (ref. 40) 125 MHz in C_6D_6
4.52-4.50 (m, 1H)	4.49 (m, 1H)	99.13	98.7
4.18 (d, *J*= 7.8 Hz, 1H)	4.17 (dd, *J*= 2.0, 7.0 Hz, 1H)	99.05	98.7
4.14 (dd, *J*= 1.8, 6.6 Hz, 1H)	4.13 (dd, *J*= 2.5, 6.5 Hz, 1H)	98.97	98.6
4.12-4.09 (m, 1H)	4.09 (m, 1H)	98.61	98.2
3.98 (d, *J*= 9.0 Hz, 1H)	3.98 (dd, *J*= 2.0, 9.0 Hz, 1H)	98.13	97.7
3.95 (m, 1H)	3.95 (m, 1H)	74.73	74.3

^{1}H NMR		^{13}C NMR	
synthetic **13** 600 MHz in C_6D_6	from degradation of aflastatin A (ref. 40) 500 MHz in C_6D_6	synthetic **13** 150 MHz in C_6D_6	from degradation of aflastatin A (ref. 40) 125 MHz in C_6D_6
3.93 (m, 1H)	3.93 (m, 1H)	73.38	73.1
3.69 (m, 1H)	3.69 (m, 1H)	72.40	72.0
3.68 (m, 1H)	3.68 (m, 1H)	72.04	71.6
3.64 (d, *J*= 9.6 Hz, 1H)	3.64 (dd, *J*= 2.0, 8.0 Hz, 1H)	72.04	71.6
3.53 (m, 1H)	3.53 (m, 1H)	70.54	70.2
3.47 (d, *J*= 10.8 Hz, 1H)	3.46 (dd, *J*= 6.5, 1.5 Hz, 1H)	68.60	68.3
2.33-2.30 (m, 1H)	2.30 (m, 1H)	65.94	65.5
2.18-2.14 (m, 1H)	2.14 (m, 1H)	65.76	65.5
1.94-1.89 (m, 1H)	1.90 (m, 1H)	60.20	59.8
1.87-1.84 (m, 1H)	1.84 (m, 1H)	44.48	44.1
1.82-1.80 (m, 1H)	1.80 (m, 1H)	40.13	39.8
1.79-1.78 (m, 1H)	1.77 (m, 1H)	38.64	38.3
1.72-1.70 (m, 1H)	1.70 (m, 1H)	36.80	36.4
1.67-1.63 (m, 1H)	1.63 (m, 1H)	35.35	35.0
1.56 (s, 3H)	1.55 (s, 3H)	35.22	35.0
1.55 (m, 2H)	1.55 (m, 2H)	33.12	32.8
1.55 (s, 3H)	1.55 (s, 3H)	31.82	31.5
1.54 (s, 3H)	1.54 (s, 3H)	31.10	30.7
1.52 (s, 3H)	1.53 (s, 3H)	30.92	30.5
1.50 (s, 3H)	1.50 (s, 3H)	30.86	30.5
1.47-1.45 (m, 1H)	1.47 (m, 1H)	30.82	30.5
1.39 (s, 3H)	1.39 (s, 3H)	30.70	30.5
1.36 (s, 3H)	1.36 (s, 3H)	30.56	30.5
1.36 (s, 3H)	1.36 (s, 3H)	20.29	20.0
1.36-1.33 (m, 2H)	1.34-1.33 (m, 2H)	20.07	19.8
1.34 (s, 3H)	1.33 (s, 3H)	20.07	19.8
1.31 (s, 3H)	1.30 (s, 3H)	19.76	19.6
1.25 (d, *J*= 6.6 Hz, 3H)	1.24 (d, *J*= 6.5 Hz, 3H)	19.54	19.6
1.17 (d, *J*= 6.6 Hz, 3H)	1.16 (d, *J*= 7.0 Hz, 3H)	13.38	13.0
1.05 (d, *J*= 6.6 Hz, 3H)	1.03 (d, *J*= 7.0 Hz, 3H)	11.99	11.6
0.96 (d, *J*= 7.2 Hz, 3H)	0.95 (d, *J*= 7.5 Hz, 3H)	10.45	10.1
0.61 (d, *J*= 6.6 Hz, 3H)	0.61 (d, *J*= 6.5 Hz, 3H)	9.97	9.6
		6.38	6.1

Table 3. Comparisons of ^{1}H and ^{13}C NMR data for synthetic and natural **13**.

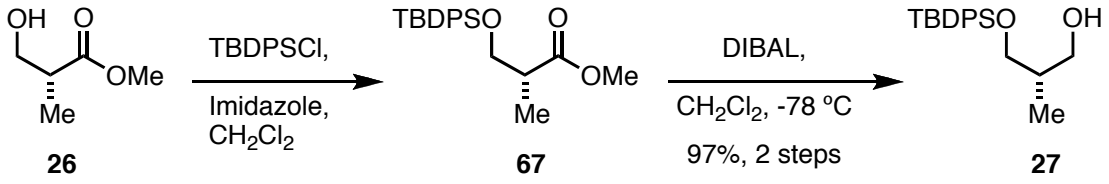
2.4 Conclusions

The synthesis of the C9-C27 degradation product of aflastatin A (**13**) was completed, and featured the cross-coupling of alkynes with epoxides as the key reaction for the union of structurally complex and stereochemically rich polypropionates.[60] Our synthesis of the C9-C27 degradation product of aflastatin A (**13**) demonstrated the efficacy of the alkyne-epoxide cross-couplings in complex settings, as well as the ability to functionalize the resulting internal alkynes into polyol or polypropionate segments. We anticipate the application of this synthetic approach will facilitate the synthesis of other complex polyketide natural products.

2.5 Experimental Section

General Procedures: All reactions were carried out under an argon atmosphere in oven-dried or flame-dried glassware using dry solvents under anhydrous conditions. All anhydrous solvents were dried with activated molecular sieves (3Å or 4Å beads) purchased from Aldrich and tested for trace water content with a Coulometric KF titrator from Denver Instruments. All solvents used for extraction and chromatography procedures were used as received from commercial suppliers without further purification. All reagents were purchased from Aldrich, GFS Chemicals or Strem Chemicals. ^{1}H NMR and ^{13}C NMR spectra were measured in deuterated chloroform ($CDCl_3$) or deuterated benzene (C_6D_6) on Varian Inova 600 or Unity 600 NMR spectrometers. All proton NMR spectra were recorded at 600 MHz and were referenced with residual chloroform (7.27 ppm) or

residual benzene (7.16 ppm), and reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All carbon NMR spectra were measured at 150 MHz and were referenced with residual chloroform (77.23 ppm) or residual benzene (128.39 ppm), and reported in parts per million (ppm). All infrared spectra were recorded on sodium chloride discs on a Mattson Genesis II FT-IR. Abbreviations for signal intensities are as follows: s, strong; m, medium; w, weak, br, broad. High resolution mass spectra (FAB or ESI) were recorded on a VG 70-S Nier Johason Mass spectrometer or a Thermo Finnigan LTQ FT spectrometer. Elemental analyses were performed by Atlantic Microlab Inc, Norcross, GA. Optical rotations were measured at 25 ºC (concentration in g/100 mL) using a 10 cm cell with a Perkin-Elmer 341 polarimeter. Analytical Thin Layer Chromatography (TLC) was performed on precoated glass backed plates purchased from Whatman (silica gel $60F_{254}$; 0.25mm thickness). Flash chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from EM Science.



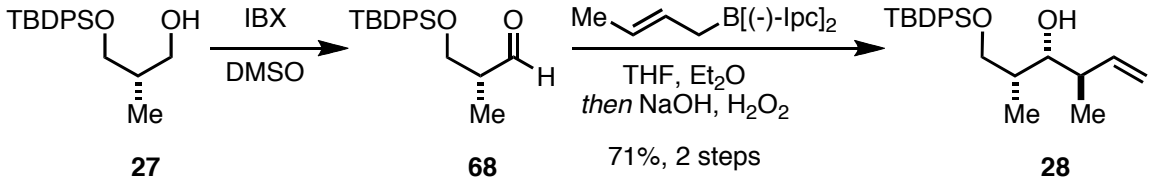
(*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropan-1-ol (27): Imidazole (6.33 g, 93.1 mmol) was dissolved in CH_2Cl_2 (150 mL), and the solution was then cooled down to 0 ºC. TBDPSCl (23.9 mL, 93.1 mmol) was added dropwise and the

mixture was stirred for 15 minutes, after which methyl (*R*)-3-hydroxy-2-methylpropionate **26** (10 g, 84.65 mmol) was added. The reaction was allowed to warm to room temperature and stirred for one hour. The mixture was then diluted with water (150 mL) and ether (200 mL). The mixture was extracted with ether (3 X 200 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure.

The crude silylether **67** was then dissolved in anhydrous CH_2Cl_2 (80 mL), and the solution was cooled to -78 ºC. Then, DIBAL (211.6 mL, 1.0 M in CH_2Cl_2, 211.6 mmol) was added slowly via syringe. The reaction was stirred at -78 ºC until TLC analysis showed completion of the reaction (approximately three hours). EtOAc (20 mL) was then added to quench the reaction, which was further stirred at -78 ºC for 30 minutes. The mixture was then warmed to 0 ºC and treated with saturated Rochelle's salt solution (250 mL), and stirred vigorously until the two phases separated. The mixture was extracted with ether (3 X 200 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes and ethyl acetate (90:10) as eluent to afford the alcohol **27** (27.13 g, 97% yield for two steps), as a colorless viscous oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J*= 6.6 Hz, 4H), 7.47-7.45 (m, 2H), 7.43-7.41 (m, 4H), 3.74 (dd, *J*= 10.8, 4.8 Hz, 1H), 3.69 (dd, *J*= 6.0, 6.0 Hz, 2H), 3.61 (dd, *J*= 10.8, 7.8 Hz, 1H), 2.62 (t, *J*= 6.0 Hz, 1H), 2.04-1.99 (m, 1H), 1.08 (s, 9H), 0.85 (d, *J*= 7.2, Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 135.79, 135.76, 133.30, 130.00, 127.96, 68.98, 67.93, 37.46, 27.03, 19.34, 13.36. **FT-IR** (neat,

cm^{-1}): 3389 (br, m), 3071 (m), 3049 (m), 2958 (s), 2930 (s), 2858 (s), 1471 (m), 1428 (s), 1390 (w), 1361 (w), 1110 (s), 1038 (m). **HRMS** (ESI+): Calcd. for $C_{20}H_{29}O_2Si$ ([M+H]$^+$), 329.1937. Found: 329.1929. **[α]$_D^{25}$** -5.8 (c 1.7, $CHCl_3$); {lit. ***ent*-27 [α]$_D^{20}$** +6.3 (c 1.0, $CHCl_3$)}.[61]



27 **68** **28**

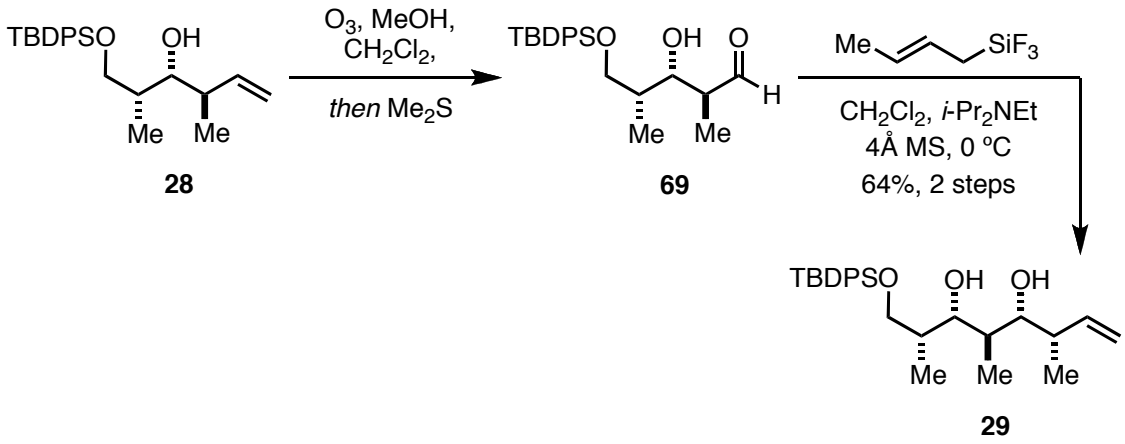
(2*R*,3*R*,4*R*)-1-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylhex-5-en-3-ol (28): IBX (22.1 g, 79.1 mmol) was dissolved in DMSO (150 mL) and then the alcohol **27** (20 g, 60.9 mmol) in THF (50 mL) was added. The reaction mixture was stirred at room temperature and monitored by TLC. After TLC showed completion of the reaction (14 hours), the mixture was cooled to 0 ºC, and a pH 7 phosphate buffer solution (100 mL) was added, followed by ether (200 mL). The mixture was filtered through Celite and then extracted with ether, the combined organic fractions were washed twice with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. To avoid epimerization, the crude aldehyde **68** was used for the next reaction without further purification.

Potassium *tert*-butoxide (8.88 g, 79.1 mmol), which had been dried under vacuum at 80 ºC overnight, was dissolved in THF (35 mL) and then the temperature of the solution was lowered to -78 ºC. The reaction vessel was fitted with a jacketed addition funnel, and after a mixture of acetone-dry ice was added to the addition funnel's jacket, *trans*-2-butene (14.2 mL, 152.2 mmol) was added

to the addition funnel. Condensation of the *trans*-2-butene in the addition funnel facilitated quantification of the reagent which was added dropwise to the reaction vessel, followed by *n*-BuLi (31.65 mL, 2.5 M in hexane, 79.1 mmol) which was also added dropwise through the addition funnel. The reaction was stirred for 60 minutes, after which $[(-)\text{-Ipc}]_2\text{BOMe}$ (26 g, 82.2 mmol, freshly prepared from (-)-α-pinene and BH_3-SMe_2, followed by methanolysis)[46] in ether (120 mL) was added dropwise. The reaction was stirred for 30 minutes, and then BF_3-OEt_2 (10.70 mL, 80.22 mmol) was added dropwise, followed by the crude aldehyde **68** (60.87 mmol). After the final addition the addition funnel was removed. The reaction was stirred at -78 ºC for 3 h at which time the reaction flask was fitted with a reflux condenser, and solutions of NaOH (3N, 70 mL) and H_2O_2 (30%, 30 mL) were added slowly (CAUTION!, EXOTHERMIC REACTION!), and the mixture was allowed to warm to room temperature. The reaction was heated to reflux for one hour to ensure complete oxidation of the organoborane species. After cooling to room temperature, the organic phase was separated, washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. ^{1}H NMR analysis of the crude mixture indicated sinlge diastereomer. The residual oil was purified by flash chromatography using hexanes and ether (90:10) as eluent to afford alcohol **28** as a colorless oil (16.54 g, 71% yield, for two steps).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71-6.69 (m, 4H), 7.46-7.44 (m, 2H), 7.42-7.39 (m, 4H), 5.85 (ddd, *J*= 18.6, 9.6, 8.4 Hz, 1H), 5.14-5.10 (m, 2), 3.74 (d, *J*= 4.8 Hz, 2H), 3.61 (ddd, *J*= 7.2, 2.4, 2.4 Hz, 1H), 2.46 (d, *J*= 2.4 Hz, 1H), 2.33-2.27 (m, 1H), 1.88-1.83 (m, 1H), 1.09 (s, 9H), 0.97 (d, *J*= 6.6 Hz, 6H, overlapping

methyls). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 142.08, 135.88, 135.78, 133.60, 133.45, 129.90, 127.89, 115.59, 76.32, 68.63, 41.95, 36.85, 27.09, 19.42, 16.95, 9.79. **FT-IR** (neat, cm^{-1}): 3497 (br, m), 3071 (m), 3049 (m), 2960 (s), 2930 (s), 2858 (s), 1960 (w), 1886 (w), 1820 (w), 1471 (m), 1461 (m), 1427 (s), 1390 (m), 1111 (s), 997 (m), 823 (m), 739 (m), 701 (s). **HRMS** (ESI+): Calcd. for $C_{24}H_{35}O_2Si$ ($[M+H]^+$), 383.2406. Found: 383.2400. **$[\alpha]_D^{25}$** -6.2 (c 2.18, $CHCl_3$); {lit. ***ent*-28 $[\alpha]_D^{20}$** +4.9 (c 2.8, $CHCl_3$)}.[62]

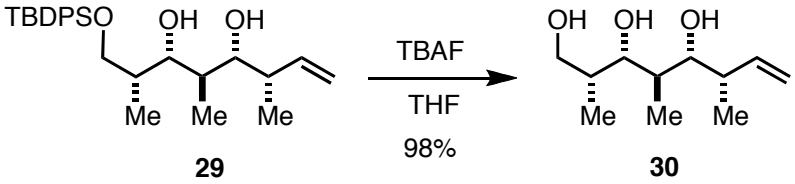


(2*R*,3*S*,4*R*,5*R*,6*S*)-1-(*tert*-butyldiphenylsilyloxy)-2,4,6-trimethyloct-7-ene-3,5-diol (29): The hydroxyalkene **28** (12.0 g, 31.4 mmol) was dissolved in methanol (70 mL) and CH_2Cl_2 (30 mL), and then the solution was cooled to -78 ºC. A stream of ozone was bubbled through the colorless solution until it turned pale blue (ca. 3 min), then O_2 was bubbled through the solution until it turned colorless. A TLC analysis confirmed completion of the reaction. The mixture was then treated with dimethyl sulfide (46.05 mL, 627.3 mmol) and the reaction mixture was allowed to reach room temperature slowly and stirred for 8 hours,

after which the majority of the volatile solvents were removed in vacuo. The residue was taken up in hexanes (100 mL) and this solution was washed with water (2 X 75 mL) and brine, the organic fraction was then dried over $MgSO_4$, filtered and concentrated in vacuo to yield the crude aldehyde **69** as a colorless oil. To avoid epimerization, the crude aldehyde **69** was used immediately for the next reaction without further purification.

The crude aldehyde **69** (ca. 31.36 mmol) was dissolved in anhydrous CH_2Cl_2 (400 mL) and then transferred via cannula to a flask containing 4 Å MS (10 g). The mixture was stirred at room temperature for 30 minutes and then cooled to 0 ºC and treated sequentially with (*E*)-crotyltrifluorosilane (13.18 g, 94.08 mmol) and *i*-Pr_2NEt (12.16 g, 94.08 mmol).[47] The resulting mixture was stirred for five days at 0 ºC, then warmed to room temperature and 1N HCl (300 mL) was added and the biphasic mixture was stirred vigorously for 30 minutes. The mixture was then extracted with ether (3 X 300 mL), the combined organic fractions were then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in THF (200 mL) and then 1N NaOH (100 mL) was added, and the mixture was stirred vigorously for one hour. The mixture was then extracted with ether (3 X 300 mL), the combined organic fractions were then dried over Na_2SO_4, filtered and concentrated under reduced pressure. Estimation of the diastereomeric ratio by ^{1}H NMR analysis of the crude mixture indicated 11:1 dr. The residue was purified by flash chromatography using hexanes and ether (90:10) as eluent to yield the diol **29** as a white amorphous solid (8.715 g, 64% yield, for the two steps).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69-6.66 (m, 4H), 7.47-7.44 (m, 2H), 7.43-7.39 (m, 4H), 6.01 (ddd, *J*= 17.1, 10.8, 6.6 Hz, 1H), 5.12-5.09 (m, 2H), 4.11 (bs, 2H), 3.93 (dd, *J*= 9.6, 1.2 Hz, 1H), 3.82 (dd, *J*= 10.8, 3.6 Hz, 1H), 3.72 (dd, *J*= 10.2, 4.8 Hz, 1H), 3.63 (dd, *J*= 9.0, 2.4 Hz, 1H), 2.48-2.43 (m, 1H), 1.85-1.81 (m, 1H), 1.79-1.72 (m, 1H), 1.07 (s, 9H), 1.03 (d, *J*= 7.2 Hz, 3H), 0.99 (d, *J*= 7.2 Hz, 3H), 0.76 (d, *J*= 6.6 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.12, 135.88, 135.76, 133.16, 132.98, 130.09, 130.06, 128.00, 114.22, 79.99, 79.81, 69.61, 40.13, 38.23, 36.52, 27.03, 19.39, 13.25, 11.33, 9.28. **FT-IR** (neat, cm^{-1}): 3413 (br, m), 3071 (m), 3049 (m), 2963 (s), 2932 (s), 2858 (s), 1471 (m), 1428 (s), 1111 (s), 997 (m), 976 (m), 823 (m), 740 (m), 702 (s), 613 (m). **HRMS** (ESI+): Calcd. for $C_{27}H_{41}O_3Si$ ($[M+H]^+$), 441.2825. Found: 441.2815. **$[\alpha]_D^{25}$** -7.6 (c 1.1, $CHCl_3$); {lit. **29 $[\alpha]_D^{25}$** -7.4 (c 1.01, $CHCl_3$)}.[47]

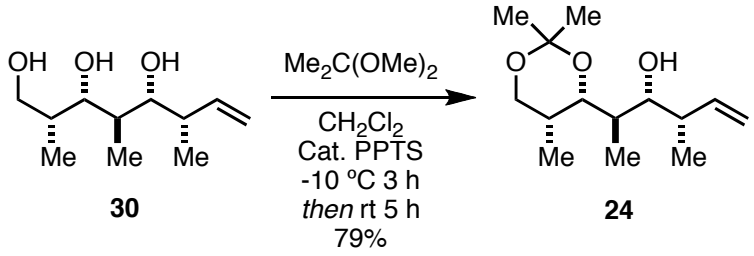


29 **30**

(2*R*,3*S*,4*R*,5*R*,6*S*)-2,4,6-trimethyloct-7-ene-1,3,5-triol (30): The diol **29** (6.5 g, 14.75 mmol) was dissolved in THF (100 mL) and then the TBAF solution (29.5 mL, 1.0 M in THF, 29.5 mmol) was added dropwise via syringe. The reaction mixture was stirred for eight hours at room temperature and then the reaction mixture was diluted with water (150 mL) and CH_2Cl_2 (150 mL). The aqueous fraction was extracted with CH_2Cl_2 (3 X 150 mL), the combined organic fractions were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The

residue was purified by flash chromatography on a short column using a gradient of hexanes and ethyl acetate (80:20 to 10:90) to yield the triol **30** as a colorless oil (2.92 g, 98% yield).

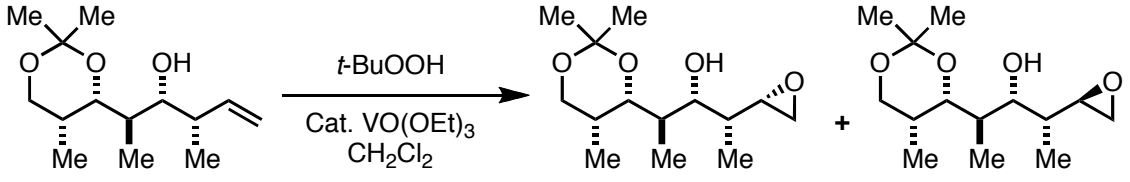
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 (ddd, *J*= 16.8, 10.5, 5.4 Hz, 1H), 5.20 (dd, *J*= 10.2, 1.2 Hz, 1H), 5.15 (dd, *J*= 17.4, 1.2 Hz, 1H), 4.69 (bs, 1H), 3.87 (dd, *J*= 9.0, 1.8 Hz, 1H), 3.82 (dd, *J*= 10.2, 3.0 Hz, 1H), 3.70 (dd, *J*= 10.8, 5.4 Hz, 1H), 3.62 (dd, *J*= 9.0, 3.6 Hz, 1H), 2.96 (bs, 2H), 2.55-2.52 (m, 1H), 1.85-180 (m, 1H), 1.79-1.72 (m, 1H), 1.24 (d, *J*= 11.4 Hz, 3H), 1.00 (d, *J*= 6.6 Hz, 3H), 0.79 (d, *J*= 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 141.81, 115.98, 80.16, 79.84, 68.44, 39.45, 38.04, 36.28, 12.97, 10.12, 8.91. **FT-IR** (neat, cm^{-1}): 3340 (br, s), 2970 (s), 2933 (m), 2879 (m), 1456 (m), 1421 (m), 1380 (w), 1331 (w), 1272 (w), 1233 (w), 1133 (m), 1029 (m), 994 (m), 970 (s), 913 (m). **HRMS** (ESI+): Calcd. for $C_{11}H_{23}O_3$ ($[M+H]^+$), 203.1647. Found: 203.1640. **$[\alpha]_D^{25}$** -25.6 (c 0.75, $CHCl_3$).



(2*R*,3*R*,4*S*)-4-methyl-2-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl)hex-5-en-3-ol (24): The triol **30** (2.9 g, 14.3 mmol) was dissolved in CH_2Cl_2 (60 mL) and then the solution was cooled to -10 ºC. PPTS (100 mg) was then added, followed by 2,2-dimethoxypropane (8.78 mL, 71.7 mmol), and the resulting mixture was stirred for three hours at -10 ºC and then warmed slowly to room temperature

and further stirred for five hours. The reaction mixture was then diluted with water (50 mL) and the mixture was extracted with CH_2Cl_2 (3 X 100 mL), the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes and ethyl acetate as eluents (90:10) to afford the desired terminal acetonide **24** as a colorless oil (2.734 g, 79% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.99 (ddd, *J*= 17.1, 10.8, 6.6 Hz, 1H), 5.08-5.04 (m, 2H), 4.38 (bs, 1H), 4.13 (dd, *J*= 11.4, 3.0 Hz, 1H), 3.94 (dd, *J*= 9.6, 2.4 Hz, 1H), 3.63 (dd, *J*= 12.0, 2.4 Hz, 1H), 3.57 (dd, *J*= 8.7, 1.8 Hz, 1H), 2.38-2.36 (m, 1H), 1.78-1.74 (m, 1H), 1.63-1.60 (m, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 1.11 (d, *J*= 6.6 Hz, 3H), 1.01 (d, *J*= 6.6 Hz, 3H), 0.77 (d, *J*= 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.27, 113.58, 99.12, 80.01, 78.91, 67.29, 40.03, 37.30, 30.26, 29.86, 19.23, 11.49, 11.36, 10.62. **FT-IR** (neat, cm^{-1}): 3492 (br, s), 3072 (w), 2967 (s), 2935 (s), 2873 (s), 1459 (m), 1380 (s), 1270 (m), 1236 (m), 1199 (s), 1178 (m), 1145 (m), 1097 (m), 1008 (s), 958 (m), 910 (m), 848 (s) **HRMS** (ESI+): Calcd. for $C_{14}H_{27}O_3$ ($[M+H]^+$), 243.1960. Found: 243.1955. **$[\alpha]_D^{25}$** +16.0 (c 1.67, $CHCl_3$).



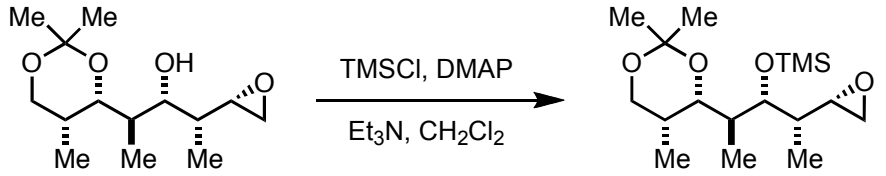
(2*R*,3*S*,4*R*)-2-((*S*)-oxiran-2-yl)-4-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl) pentan-3-ol (31): The homoallylic alcohol **24** (0.95 g, 3.9 mmol) was dissolved in

anhydrous CH_2Cl_2 (10 mL) and the solution was cooled to 0 ºC, and then VO $(OEt)_3$ (70 μL, 0.39 mmol) was added, followed by *t*-BuOOH (1.42 mL, 5.5 M in decane, 7.8 mmol). The reaction mixture was stirred and allowed to warm to room temperature, and the reaction was monitored by TLC. After 36 hours the reaction was completed. To quench the reaction, a saturated solution of $Na_2S_2O_3$ (5 mL) was added and the mixture was stirred for 20 minutes, then extracted with CH_2Cl_2 (3 X 15 mL), the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Estimation of the diastereomeric ratio by ^{1}H NMR analysis of the crude mixture indicated 8:1 dr. The residue was purified carefully by gravity chromatography on silica gel pretreated with 2.5% vol of Et_3N and using hexanes and ethyl acetate (80:20) as eluent to afford the minor diastereomer epoxyalcohol **31b** (77.6 mg, 8% yield), followed by the desired major epoxyalcohol **31** (0.62 g, 61% yield), both as colorless oils.

Data for the major epoxyalcohol **31**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.50 (s, 1H), 4.12 (dd, *J*= 11.4, 3.0 Hz, 1H), 3.93 (dd, *J*= 10.2, 2.4 Hz, 1H), 3.66 (dd, *J*= 9.0, 1.8 Hz, 1H), 3.62 (dd, *J*= 12.0, 1.8 Hz, 1H), 3.05 (ddd, *J*= 7.2, 4.2, 3.0 Hz, 1H), 2.82 (dd, *J*= 4.2, 4.2 Hz, 1H), 2.57 (dd, *J*= 4.8, 3.0 Hz, 1H), 1.79-1.72 (m, 1H), 1.63-1.59 (m, 1H), 1.50 (s, 3H), 1.41 (s, 3H), 1.31-1.26 (m, 1H), 1.11 (d, *J*= 7.2 Hz, 6H, overlapping methyls), 0.68 (d, *J*= 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 99.18, 79.12, 78.42, 67.25, 56.53, 47.27, 40.01, 36.87, 30.26, 29.89, 19.30, 11.31, 10.60, 9.96. **FT-IR** (neat, cm^{-1}): 3478 (br, s), 2987 (s), 2973 (s), 2937 (s), 2877 (m), 1457 (m), 1421 (w), 1380 (s), 1270 (m), 1251 (w), 1238 (m),

1199 (s), 1178 (m), 1145 (m), 1122 (m), 1103 (m), 1008 (s), 958 (m), 862 (m), 848 (m). **HRMS** (ESI+): Calcd. for $C_{14}H_{27}O_4$ ([M+H]$^+$), 259.1909. Found: 259.1905. **[α]$_D^{25}$** +41.2 (c 0.56, $CHCl_3$).

Data for the minor epoxyalcohol **31b**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.49 (s, 1H), 4.13 (dd, *J*= 12.0, 3.0 Hz, 1H), 3.94 (dd, *J*= 10.2, 1.8 Hz, 1H), 3.82 (dd, *J*= 9.0, 1.8 Hz, 1H), 3.62 (dd, *J*= 11.4, 1.2 Hz, 1H), 3.10 (ddd, *J*= 7.2, 4.8, 3.6 Hz, 1H), 2.83 (dd, *J*= 3.6, 3.6 Hz, 1H), 2.52 (dd, *J*= 4.8, 3.6 Hz, 1H), 1.77-1.71 (m, 1H), 1.64-1.60 (m, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.40-1.35 (m, 1H), 1.11 (d, *J*= 6.6 Hz, 3H), 0.94 (d, *J*= 7.2 Hz, 3H), 0.69 (d, *J*= 6.6 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 99.19, 79.26, 76.90, 67.26, 54.72, 47.33, 39.23, 37.03, 30.23, 29.90, 19.29, 11.12, 10.62, 8.17. **FT-IR** (neat, cm^{-1}): 3486 (br, s), 2981 (s), 2935 (s), 2873 (m), 1459 (s), 1409 (m), 1270 (m), 1236 (m), 1199 (s), 1178 (m), 1141 (m), 1120 (m), 1103 (m), 1008 (s), 958 (m), 931 (m), 908 (m), 846 (s). **HRMS** (ESI+): Calcd. for $C_{14}H_{27}O_4$ ([M+H]$^+$), 259.1909. Found: 259.1903. **[α]$_D^{25}$** +25.0 (c 1.275, $CHCl_3$).

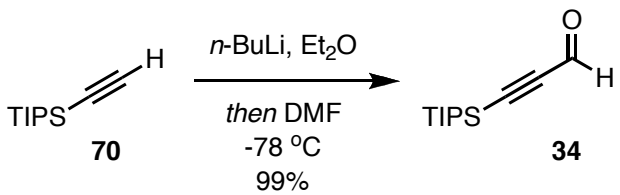


31 **14**

Trimethyl((2*S*,3*S*,4*S*)-2-((*S*)-oxiran-2-yl)-4-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl)pentan-3-yloxy)silane (14): The epoxyalcohol **31** (0.32 g, 1.2 mmol), was dissolved in anhydrous CH_2Cl_2 (5 mL) and then DMAP catalyst (15.1 mg, 0.12 mmol) was added, followed by triethylamine (138 μL, 1.5 mmol), and

finally TMSCl (187 μL, 1.5 mmol). The mixture was stirred at room temperature for 10 minutes, and then quenched with a pH 7 phosphate buffer solution (3 mL). The mixture was extracted with CH_2Cl_2 (3 X 15 mL), the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel pretreated with 2.5% vol of Et_3N and using hexanes and ether as eluents (90:10) to afford the TMS-ether **14** as a colorless oil (0.405 g, 99% yield).

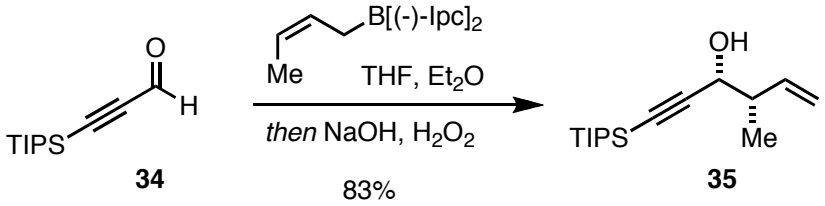
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.08 (dd, *J*= 11.4, 2.4 Hz, 1H), 3.81 (dd, *J*= 5.4, 3.0 Hz, 1H), 3.80 (dd, *J*= 9.6, 1.8 Hz, 1H), 3.60 (dd, *J*= 11.4, 1.2 Hz, 1H), 2.77 (dd, *J*= 4.8, 4.8 Hz, 1H), 2.73 (ddd, *J*= 8.4, 4.8, 3.0 Hz, 1H), 2.62 (dd, *J*= 4.8, 3.0 Hz, 1H), 1.90-1.85 (m, 1H), 1.56-1.50 (m, 1H), 1.46-1.42 (m, 1H), 1.37 (s, 3H), 1.33 (s, 3H), 1.04 (d, *J*= 6.6 Hz, 6H, overlapping methyls), 0.83 (d, *J*= 7.2 Hz, 3H), 0.12 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 98.42, 75.66, 72.49, 67.63, 56.50, 48.45, 40.00, 39.23, 30.03, 29.98, 19.07, 14.59, 12.25, 10.51, 0.76. **FT-IR** (neat, cm^{-1}): 2988 (s), 2964 (s), 2939 (s), 2864 (m), 1458 (m), 1378 (m), 1250 (s), 1198 (m), 1096 (s), 1038 (m), 1008 (s), 958 (w), 879 (m), 839 (s). **HRMS** (ESI+): Calcd. for $C_{17}H_{35}O_4Si$ ($[M+H]^+$), 331.2305. Found: 331.2304. **$[\alpha]_D^{25}$** +7.5 (c 1.0, $CHCl_3$).



3-(Triisopropylsilyl)propiolaldehyde (34): To a stirred solution of TIPS-acetylene **70** (41.1 g, 225 mmol) in ether (200 mL) at 0 °C was added *n*-BuLi

(100 mL, 2.5 M in hexane, 250 mmol) dropwise over 30 minutes. The reaction was stirred one hour at 0 ºC and then cannulated into a solution of freshly distilled DMF (52.2 mL, 675 mmol) in Et_2O (200 mL) at -78 ºC over 30 minutes. The reaction mixture was stirred at -78 ºC for one hour, then it was allowed to warm up slowly to 0 ºC over a period of one hour. The reaction was quenched at 0 ºC by pouring it into a solution of 5% H_2SO_4 (500 mL) at 0 ºC to attain a slightly acidic pH. After stirring one hour, the organic phase was separated and the aqueous phase was extracted exhaustively with ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography using a short silica gel column and pentane and ether (90:10) as eluent to afford 3-(triisopropylsilyl)propiolaldehyde **34** as a colorless oil (46.95 g, 99% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.21 (s, 1H), 1.17-1.11 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 176.76, 104.68, 100.93, 18.62, 11.13. **FT-IR** (neat, cm^{-1}): 2945 (s), 2892 (s), 2868 (s), 2731 (w), 2149 (m), 1669 (s), 1463 (m), 1385 (m), 999 (s), 882 (m). **HRMS** (ESI+): Calcd. for $C_{12}H_{23}OSi$ ($[M+H]^+$), 211.1518. Found: 211.1512.

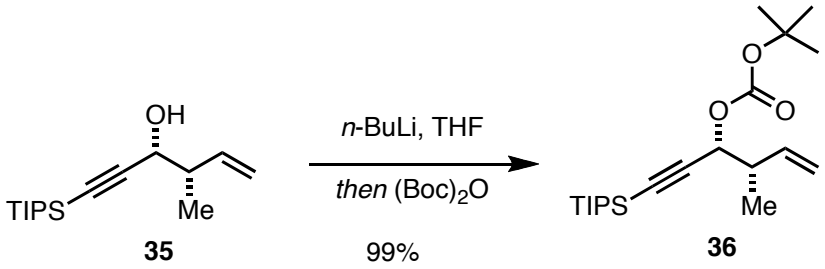


34 **35**

(3*R*,4*S*)-4-methyl-1-(triisopropylsilyl)hex-5-en-1-yn-3-ol (35): Potassium *tert*-butoxide (10.85 g, 96.7 mmol), which had been dried under vacuum at 80 ºC overnight, was dissolved in THF (28 mL) and then the temperature of the solution

was lowered to -78 ºC. The reaction vessel was fitted with a jacketed addition funnel, and after a mixture of acetone-dry ice was added to the addition funnel's jacket, *cis*-2-butene (16.2 mL, 180 mmol) was added to the addition funnel. Condensation of *cis*-2-butene in the addition funnel facilitates quantification of the reagent which was added dropwise to the reaction vessel, followed by *n*-BuLi (38.7 mL, 2.5 M in hexane, 96.7 mmol) which was also added dropwise through the addition funnel. The reaction was stirred for 60 minutes, after which [(-)Ipc]$_2$BOMe (34.8 g, 110 mmol, freshly prepared from (-)-α-pinene and BH_3-SMe_2, followed by methanolysis)[46] in ether (120 mL) was added dropwise. The reaction was stirred for 30 minutes, and then BF_3-OEt_2 (14.35 mL, 114.3 mmol) was added dropwise, followed by 3-(triisopropylsilyl)propiolaldehyde **34** (18.5 g, 87.9 mmol). After the final addition the addition funnel was removed. The reaction was stirred at -78 ºC for three hours at which time the reaction flask was fitted with a reflux condenser, and solutions of NaOH (3N, 70 mL) and H_2O_2 (30%, 30 mL) were added slowly (CAUTION!, EXOTHERMIC REACTION!), and the mixture was allowed to warm to room temperature. The reaction was heated to reflux for one hour to ensure complete oxidation of the organoborane species. After cooling to room temperature, the organic phase was separated, washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Estimation of the diastereomeric ratio by ^{1}H NMR analysis of the crude mixture indicated a ratio greater than 25:1. The residual oil was purified by flash chromatography using hexanes and ethyl acetate (90:10) as eluent to afford alcohol **35**[49] as a colorless oil (19.53 g, 83% yield).

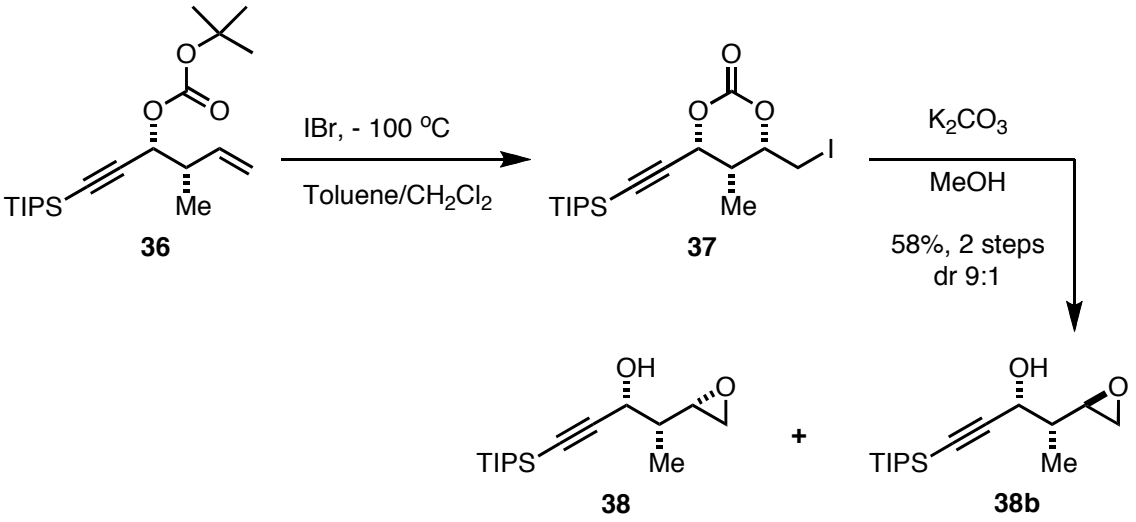
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91-5.85 (m, 1H), 5.19-5.16 (m, 2H), 4.29 (d, *J*= 4.2 Hz, 1H), 2.50-2.44 (m, 1H), 1.95 (bs, 1H), 1.14 (d, *J*= 6.6 Hz, 3H), 1.08-1.07 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 139.00, 117.44, 106.80, 86.90, 66.72, 44.64, 18.78, 16.04, 11.35. **FT-IR** (neat, cm^{-1}): 3386 (m, br), 3080 (w), 2958 (s), 2943 (s), 2891 (s), 2867 (s), 2168 (m), 1462 (s), 1016 (s), 968 (m), 916 (m), 883 (s). **HRMS** (ESI+): Calcd. for $C_{16}H_{31}OSi$ ($[M+H]^+$), 267.2144. Found: 267.2138. **Anal.** Calcd. for $C_{16}H_{30}OSi$: C, 72.11; H, 11.35. Found: C, 72.50; H, 11.52. **$[\alpha]_D^{25}$** +26.0 (c 1.09, $CHCl_3$).



***Tert*-butyl (3*R*,4*S*)-4-methyl-1-(triisopropylsilyl)hex-5-en-1-yn-3-yl carbonate (36):** The alcohol **35** (6.35 g, 23.8 mmol) was dissolved in THF (30 mL), and then the solution was cooled to -78 ºC. *n*-BuLi (10.5 mL, 2.5 M in hexane, 26.2 mmol) was added dropwise via syringe and the reaction mixture was stirred for 45 minutes allowing to warm up slowly to 0 ºC, after which $(Boc)_2O$ (6.2 g, 28.6 mmol) was added dropwise neat. This mixture was allowed to reach room temperature and was stirred for one hour. The mixture was then diluted with water (50 mL) and ether (50 mL). The mixture was extracted with ether (3 X 60 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash

chromatography using hexanes and ethyl acetate (95:5) as eluent to afford the Boc-protected alcohol **36** as a colorless oil (8.619 g, 99% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.95-5.89 (m, 1H), 5.14-5.09 (m, 3H), 2.65-2.59 (m, 1H), 1.49 (s, 9H), 1.15 (d, *J*= 6.6 Hz, 3H), 1.07-1.06 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 152.89, 138.43, 116.42, 102.88, 88.40, 82.64, 71.22, 41.82, 27.94, 18.74, 15.87, 11.30. **FT-IR** (neat, cm^{-1}): 2958 (s), 2942 (s), 2892 (m), 2867 (s), 2177 (w), 1747 (s), 1462 (m), 1369 (m), 1275 (s), 1166 (m), 882 (m). **HRMS** (ESI+): Calcd. for $C_{21}H_{39}O_3Si$ ($[M+H]^+$), 367.2668. Found: 367.2665. **Anal.** Calcd. for $C_{16}H_{30}OSi$: C, 68.80; H, 10.45. Found: C, 68.80; H, 10.54. **$[\alpha]_D^{25}$** +53.4 (c 2.55, $CHCl_3$).



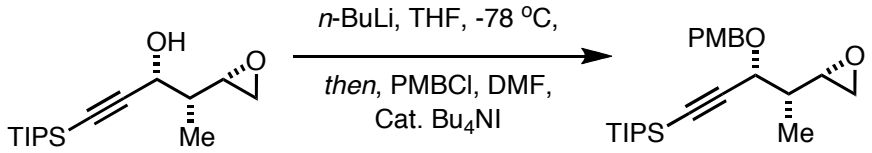
(3*R*,4*R*)-4-((*S*)-oxiran-2-yl)-1-(triisopropylsilyl)pent-1-yn-3-ol (38): The Boc-protected alcohol **36** (5.0 g, 13.65 mmol) was dissolved in toluene (100 mL) and dichloromethane (50 mL), and the solution was then cooled to -100 °C. IBr (27.3 mL, 1.0 M in dichloromethane, 27.3 mmol) was added dropwise via syringe along

the wall of the flask to allow for ample cooling. The solution was stirred for 45 minutes at -100 ºC, and then $Na_2S_2O_3$ (20% aqueous, 50 mL) and $NaHCO_3$ (5% aqueous, 50 mL) were added and the mixture was stirred until it reached room temperature and the solution turned clear. The mixture was extracted with dichloromethane (3 X 150 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue **37** was dissolved in methanol (100 mL) and the solution was cooled to 0 ºC. Potassium carbonate (5.58 g, 40.95 mmol) was added in one portion, the mixture was allowed to warmed to room temperature and stirred for one hour, after which the mixture was diluted with water (100 mL) and ether (100 mL). The mixture was extracted with ether (3 X 150 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Estimation of the diastereomeric ratio by ^{1}H NMR analysis of the crude mixture indicated a 9:1 dr. The residue was purified carefully by gravity chromatography on silica gel pretreated with 2.5% vol of Et_3N and using hexanes and ethyl acetate (90:10) as eluent to afford the minor diastereomer epoxyalcohol **38b** (0.22 g, 6% yield) followed by the desired epoxyalcohol **38** (1.99 g, 52% yield), both as colorless oils.

Data for the major epoxyalcohol **38**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.43 (dd, *J*= 5.4, 4.8 Hz, 1H), 3.01 (ddd, *J*= 7.2, 3.6, 3.0 Hz, 1H), 2.83 (dd, *J*= 4.8, 3.6 Hz, 1H), 2.76 (dd, *J*= 4.8, 3.0 Hz, 1H), 2.06 (d, *J*= 4.8 Hz, 1H), 1.68-1.63 (m, 1H), 1.18 (d, *J*= 6.6 Hz, 3H), 1.08-1.07 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 106.61, 87.78, 65.51, 54.31, 47.43, 42.54, 18.78, 13.05, 11.33. **FT-IR** (neat,

cm^{-1}): 3419 (br, m), 2942 (s), 2891 (s), 2866 (s), 2168 (w), 1462 (m), 1019 (m), 996 (m), 882 (m). **HRMS** (ESI+): Calcd. for $C_{16}H_{31}O_2Si$ ([M+H]$^+$), 283.2088. Found: 283.2087. **Anal.** Calcd. for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 67.99; H, 10.79. **$[\alpha]_D^{25}$** +14.6 (c 1.915, $CHCl_3$).

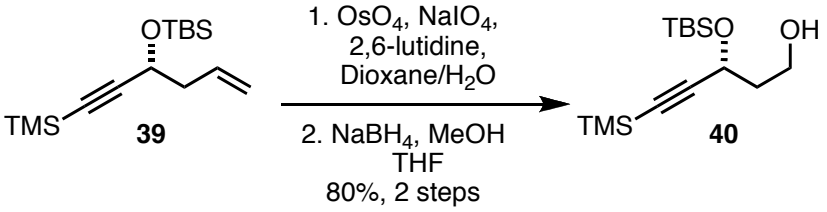
Data for the minor epoxyalcohol **38b**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.53 (dd, *J*= 7.2, 3.0 Hz, 1H), 3.00 (ddd, *J*= 7.2, 4.8, 3.0 Hz, 1H), 2.82 (dd, *J*= 4.8, 4.8 Hz, 1H), 2.56 (dd, *J*= 4.8, 3.0 Hz, 1H), 2.48 (d, *J*= 7.2 Hz, 1H), 1.68-1.63 (m, 1H), 1.10 (d, *J*= 7.2 Hz, 3H), 1.08 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 106.53, 87.29, 66.25, 53.83, 46.00, 42.39, 18.79, 11.93, 11.34. **FT-IR** (neat, cm^{-1}): 3447 (br, m), 2942 (s), 2891 (s), 2865 (s), 2168 (w), 1462 (m), 1020 (m), 992 (m), 882 (m). **$[\alpha]_D^{25}$** +5.5 (c 0.45, $CHCl_3$).



Triisopropyl((3*R*,4*R*)-3-(4-methoxybenzyloxy)-4-((*S*)-oxiran-2-yl)pent-1-ynyl) silane (15a): The epoxyalcohol **38** (1.2 g, 4.37 mmol) was dissolved in THF (10 mL), and the solution was cooled to -78 ºC. Then, the *n*-BuLi (1.92 mL, 2.5 M in hexane, 4.8 mmol) was added dropwise via syringe. After the addition was completed, the reaction mixture was warmed slowly to room temperature and stirred for 30 minutes, after which, the PMBCl (0.89 g, 5.68 mmol) was added dissolved in 10 mL of anhydrous DMF, followed by the addition of Bu_4NI (0.16 g, 0.43 mmol). The reaction mixture was stirred for 24 hours at room temperature,

and then diluted with water (20 mL) and ether (30 mL). The mixture was extracted with ether (3 X 50 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel pretreated with 2.5% vol of Et_3N and using hexanes and ethyl acetate (90:10) as eluent to afford PMB-protected alcohol **15a** (1.51 g, 86% yield), as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J*= 9.0 Hz, 2H), 6.89 (d, *J*= 9.0 Hz, 2H), 4.79 (d, *J*= 11.4 Hz, 1H), 4.49 (d, *J*= 11.4 Hz, 1H), 4.06 (d, *J*= 6.0 Hz, 1H), 3.81 (s, 3H), 3.01 (ddd, *J*= 7.2, 3.6, 3.0 Hz, 1H), 2.79 (dd, *J*= 4.8, 3.6 Hz, 1H), 2.79 (dd, *J*= 4.8, 3.0 Hz, 1H), 1.64-1.59 (m, 1H), 1.19 (d, *J*= 7.2 Hz, 3H), 1.12-1.09 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.42, 130.06, 129.74, 113.92, 104.67, 88.71, 70.98, 70.17, 55.42, 54.45, 47.75, 41.92, 18.81, 13.58, 11.35. **FT-IR** (neat, cm^{-1}): 2942 (s), 2865 (s), 2166 (m), 1612 (m), 1462 (s), 1249 (s), 1070 (m), 10379 (m), 882 (m). **HRMS** (ESI+): Calcd. for $C_{24}H_{39}O_3Si$ ($[M+H]^+$), 403.2663. Found: 403.2662. **Anal.** Calcd. for $C_{16}H_{30}OSi$: C, 71.59; H, 9.51. Found: C, 71.72; H, 9.55. **$[\alpha]_D^{25}$** +105.8 (c 5.9, $CHCl_3$).

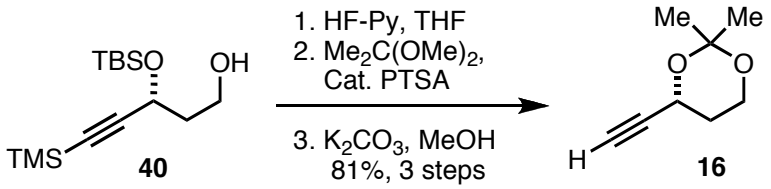


(*R*)-3-(*tert*-butyldimethylsilyloxy)-5-(trimethylsilyl)pent-4-yn-1-ol (40): To a solution of the alkene **39** (20.0 g, 70.8 mmol), in a mixture of dioxane (500 mL) and water (100 mL), was added 2,6-lutidine (16.5 mL, 142 mmol) and OsO_4 (250

mg, 0.98 mmol). The solution was cooled to 0 ºC and then $NaIO_4$ (60.54 g, 283.1 mmol) was added in small portions over a period of 5 minutes while keeping the temperature at 0 ºC. After the addition was completed, the reaction mixture was warmed to room temperature and stirred vigorously for 45 minutes. The reaction mixture was then diluted with dichloromethane (200 mL) and water (200 mL), and extracted with dichloromethane (3 X 300 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in THF (150 mL) and methanol (15 mL). The solution was cooled to 0 ºC and then the $NaBH_4$ (5.3 g, 141.5 mmol) was added. The reaction mixture was stirred vigorously for 30 minutes, after which, the reaction was quenched by the addition of a saturated ammonium chloride solution (100 mL) and the mixture was extracted with dichloromethane (3 X 150 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes and ethyl acetate (90:10) as eluent to afford alcohol **40** as a colorless oil (16.381 g, 80% yield, two steps).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.62 (dd, *J*= 6.6, 4.2 Hz, 1H), 3.93 (dddd, *J*= 4.8, 4.8, 3.6, 3 Hz, 1H), 3.78 (dddd, *J*= 6.6, 6.6, 4.8, 4.2 Hz, 1H), 2.49 (bs, 1H), 1.98-1.93 (m,1H), 1.92-1.86 (m, 1H), 0.91 (s, 9H), 0.17 (s, 3H) 0.16 (s, 9H), 0.15 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 106.78, 90.08, 62.91, 60.42, 40.12, 25.95, 18.33, -0.59, -4.29, -4.90. **FT-IR** (neat, cm^{-1}): 3381 (m, br), 2957 (s), 2930 (s), 2886 (s) 2858 (s), 2172 (m), 1472 (m), 1251 (s), 1092 (s), 1056 (s), 1010 (m),

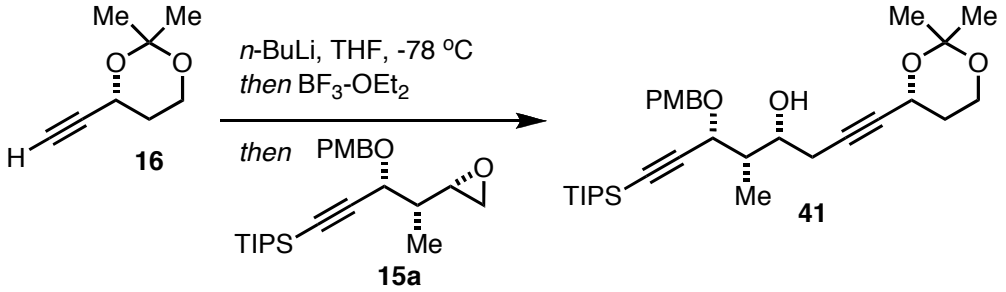
840 (s) 778 (m). **HRMS** (ESI+): Calcd. for $C_{14}H_{31}O_2Si_2$ ($[M+H]^+$), 287.1857. Found: 287.1856. **$[\alpha]_D^{25}$** +71.6 (c 1.04, $CHCl_3$).



(*R*)-4-ethynyl-2,2-dimethyl-1,3-dioxane (16): The TBS-protected alcohol **40** (7.0 g, 24.4 mmol) was dissolved in THF (40 mL) in a plastic tube (Nalgene Brand), and then the HF-Py (1.45 mL, 48.85 mmol) was added dropwise. The reaction mixture was stirred at room temperature for two hours, then cooled to 0 ºC and quenched by the addition of 50 mL of a saturated aqueous solution of $NaHCO_3$. The resulting diol was extracted exhaustively with CH_2Cl_2; the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in 2,2-dimethoxypropane (30 mL), and *p*-toluenesulfonic acid was added (50 mg). The reaction mixture was stirred for eight hours, and then it was quenched by the addition of triethylamine (5 mL), and washed with water. The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then dissolved in methanol (50 mL) and the solution was cooled to 0 ºC, then K_2CO_3 (9.98 g, 73.3 mmol) was added. The solution was allowed to warm to room temperature and stirred for one hour. Then, the mixture was diluted with ether (75 mL) and water (50 mL). The mixture was extracted with ether (3 X 75 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced

pressure. The residue was purified by flash chromatography using pentane and ether (85:15) as eluent to afford (3*R*)-3,5-monoacetonide-1-pentyne **16** (2.76 g, 81% yield, three steps) as a colorless oil.

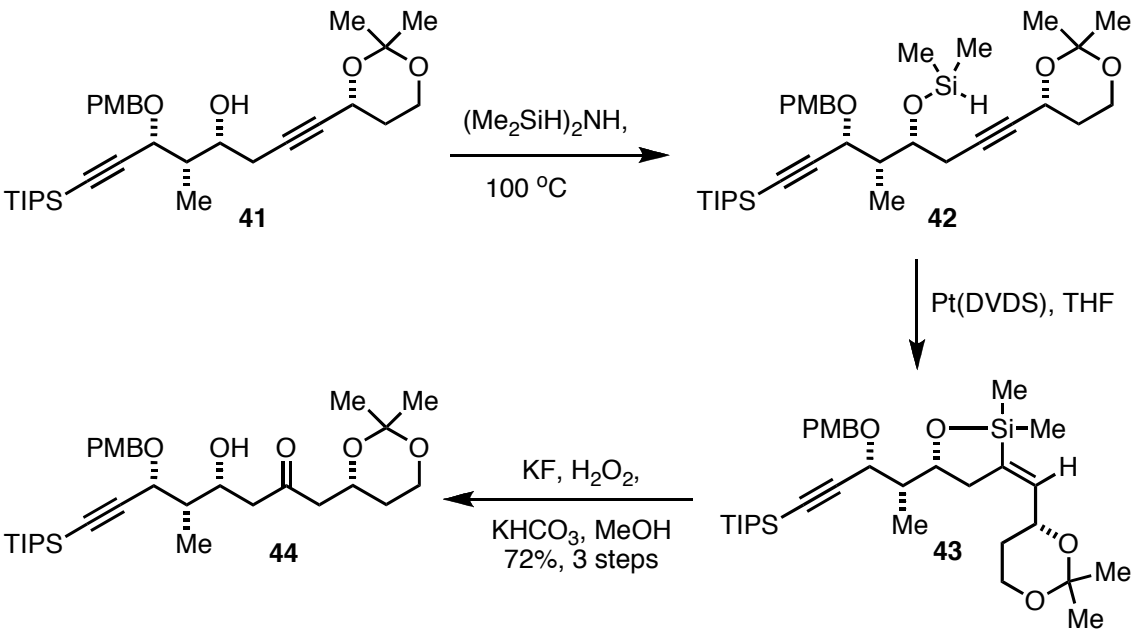
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.69 (ddd, *J*= 11.4, 2.4, 2.4 Hz, 1H), 3.95 (ddd, *J*= 12.0, 12.0, 3.0 Hz, 1H), 3.85 (ddd, *J*= 12.0, 5.4, 2.4 Hz, 1H), 2.47 (d, *J*= 1.8 Hz, 1H), 2.06-1.99 (m, 1H), 1.73-1.69 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 99.25, 82.82, 73.04, 60.24, 59.36, 31.80, 29.66, 19.58. **FT-IR** (neat, cm^{-1}): 3242 (s), 2976 (m), 2936 (m), 2878 (m), 2121 (w), 1380 (s), 1107 (s), 1078 (s), 964 (m), 848 (m). **HRMS** (ESI+): Calcd. for $C_8H_{13}O_2$ ($[M+H]^+$), 141.0910. Found: 141.0909. **Anal.** Calcd. for $C_8H_{13}O_2$: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.56; H, 8.70; O, 22.89. **$[\alpha]_D^{25}$** +16.4 (c 0.7, $CHCl_3$).



(4*R*,5*S*,6*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)-6-(4-methoxybenzyloxy)-5-methyl-8-(triisopropylsilyl)octa-1,7-diyn-4-ol (XX): The alkyne **16** (0.95 g, 6.8 mmol) was dissolved in anhydrous THF (20 mL), and the solution was cooled to -78 ºC. Then, *n*-BuLi (2.85 mL, 2.5 M in hexane, 7.1 mmol) was added dropwise via syringe, and the mixture was stirred for 30 minutes at -78 ºC, after which BF_3-OEt_2 (0.93 mL, 7.4 mmol) was added dropwise and the mixture was stirred for 10

minutes and kept at -78 ºC. Finally, the epoxide **15a** (2.5 g, 6.2 mmol) in anhydrous THF (5 mL) was added via cannula. The mixture was stirred at -78 ºC for two hours, and then quenched with a pH 7 phosphate buffer solution (20 mL). The mixture was extracted with ether (3 X 50 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes and ethyl acetate (80:20) as eluent to afford the coupling product alcohol **41** (2.476 g, 73% yield), as a colorless oil.

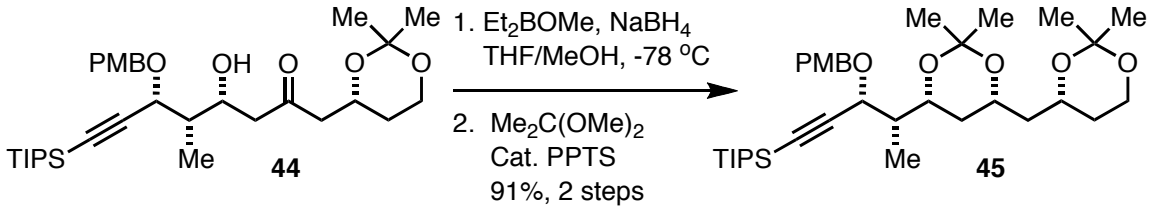
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J*= 9.0 Hz, 2H), 6.88 (d, *J*= 9.0 Hz, 2H), 4.78 (d, *J*= 10.8 Hz, 1H), 4.67 (dd, *J*= 10.8, 2.4 Hz, 1H), 4.47 (d, *J*= 10.8 Hz, 1H), 4.23 (d, *J*= 3.6 Hz, 1H), 4.02 (dd, *J*= 7.2, 7.2 Hz, 1H), 3.93 (ddd, *J*= 12.0, 12.0, 3.0 Hz, 1H), 3.83 (ddd, *J*= 12.0, 4.8, 2.4 Hz, 1H), 3.81 (s, 3H), 2.99 (d, *J*= 1.2 Hz, 1H), 2.47 (ddd, *J*= 16.5, 7.2, 1.8 Hz, 1H), 2.38 (ddd, *J*= 16.5, 7.2, 1.8 Hz, 1H), 2.06-2.04 (m, 1H), 1.99-1.92 (m, 1H), 1.67-1.64 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.11 (m, 21H), 1.10 (d, *J*= 7.8 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.55, 129.96, 129.48, 114.04, 104.92, 99.05, 88.90, 82.15, 80.97, 72.81, 72.52, 70.40, 60.57, 59.51, 55.40, 41.18, 32.27, 29.70, 25.06, 19.54, 18.79, 11.31, 7.85. **FT-IR** (neat, cm^{-1}): 3490 (br, m), 2941 (s), 2865 (s), 2245 (w), 2166 (w), 1612 (m), 1514 (s), 1462 (m), 1380 (m), 1248 (s), 1084 (s), 1037 (s). **HRMS** (Fab+): Calcd. for $C_{32}H_{50}O_5SiNa$ ($[M+Na]^+$), 565.3325. Found: 565.3314. **$[\alpha]_D^{25}$** +74.9 (c 3.91, $CHCl_3$).



(4*R*,5*S*,6*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)-4-hydroxy-6-(4-methoxybenzyloxy)-5-methyl-8-(triisopropylsilyl)oct-7-yn-2-one (44): The alkynyl alcohol **41** (1.7 g, 3.2 mmol) was dissolved in $(Me_2SiH)_2NH$ (6 mL), and then the solution was heated to 100 °C and stirred for 16 hours. After 16 hours, the reaction mixture was cooled to room temperature and the volatiles were removed under high vacuum for 4 hours. The residue **42** was then dissolved in anhydrous THF (10 mL) and a solution of platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex in xylenes (100 μL) was added. The reaction mixture was stirred at ambient temperature for 20 hours, producing a THF solution of the cyclic siloxane **43**. The solution was diluted with methanol (10 mL); $KHCO_3$ (978 mg, 9.7 mmol) and KF (567 mg, 9.7 mmol) were added followed by slow addition of 30% aqueous H_2O_2 (5.8 mL, 50 mmol). The reaction mixture was stirred for 24 hours, and then poured into a cooled saturated Na_2SO_3 aqueous solution and stirred vigorously for two hours. The mixture was then

extracted with ether (3 X 50 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes and ethyl acetate (70:30) as eluent to afford the β-hydroxyketone **44** (1.331 g, 72% yield, three steps), as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J*= 8.4 Hz, 2H), 6.89 (d, *J*= 8.4 Hz, 2H), 4.78 (d, *J*= 12.0 Hz, 1H), 4.46 (d, *J*= 12.0 Hz, 1H), 4.36-4.30 (m, 2H), 4.24 (d, *J*= 3.6 Hz, 1H), 3.98 (ddd, *J*= 12.0, 12.0, 2.4 Hz, 1H), 3.82 (s, 3H), 3.82-3.81 (m, 1H), 3.21 (bs, 1H), 2.74 (dd, *J*= 16.8, 8.4 Hz, 1H), 2.66 (dd, *J*= 16.2, 6.6 Hz, 1H), 2.52 (dd, *J*= 16.8, 3.6 Hz, 1H), 2.43 (dd, *J*= 16.2, 5.4 Hz, 1H), 1.89-1.85 (m, 1H), 1.60-1.53 (m, 1H), 1.50-1.48 (m, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.12-1.11 (m, 24H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 209.28, 159.57, 130.06, 129.73, 114.06, 105.00, 98.69, 88.81, 72.35, 70.50, 69.94, 65.72, 59.94, 55.48, 50.08, 48.46, 42.53, 31.19, 30.06, 19.29, 18.85, 11.37, 9.69. **FT-IR** (neat, cm^{-1}): 3497 (br, m), 2942 (s), 2865 (s), 2165 (w), 1711 (s), 1612 (m), 1513 (s), 1462 (m), 1380 (m), 1248 (s), 1198 (m), 1101 (m), 1036 (s), 883 (m). **HRMS** (Fab+): Calcd. for $C_{32}H_{52}O_6SiNa$ ([M+Na]$^+$), 583.3431. Found: 583.3419. **$[\alpha]_D^{25}$** +61.9 (c 0.93, $CHCl_3$).

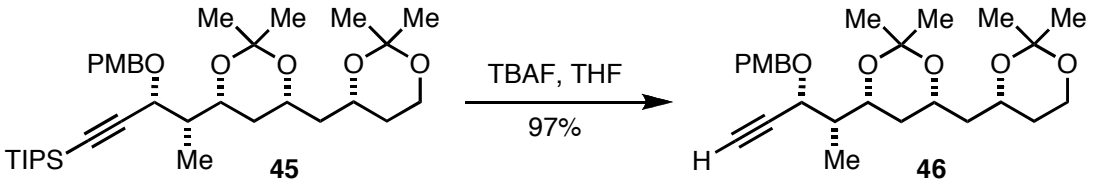


((3*R*,4*S*)-4-((4*R*,6*R*)-6-(((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-(4-methoxybenzyloxy)pent-1-ynyl)

triisopropylsilane (45): The β-hydroxyketone **44** (1.33 g, 2.37 mmol) was dissolved in anhydrous THF (20 mL) and the solution was cooled to -78 ºC. Methanol (2 mL) was added, followed by the Et_2BOMe (2.84 mL, 1 M in THF, 2.84 mmol), and the reaction mixture was stirred for two hours at -78 ºC. The $NaBH_4$ (188.4 mg, 4.98 mmol) was then added and the reaction was stirred for four hours at -78 ºC, and then quenched with 30 % aqueous H_2O_2 (5 mL). The reaction mixture was allowed to warm to room temperature and stirred for one hour, then saturated Na_2SO_3 aqueous solution was added and stirred vigorously for two hours. The mixture was then extracted with CH_2Cl_2 (3 X 50 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in $Me_2C(OMe)_2$ (20 mL) and then the PPTS (25 mg) was added. The reaction mixture was stirred at room temperature for eight hours, then the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes and ethyl acetate (90:10) as eluent to afford the diacetonide **45** (1.309 g, 91% yield, two steps), as a colorless oil and as a single diastereomer.

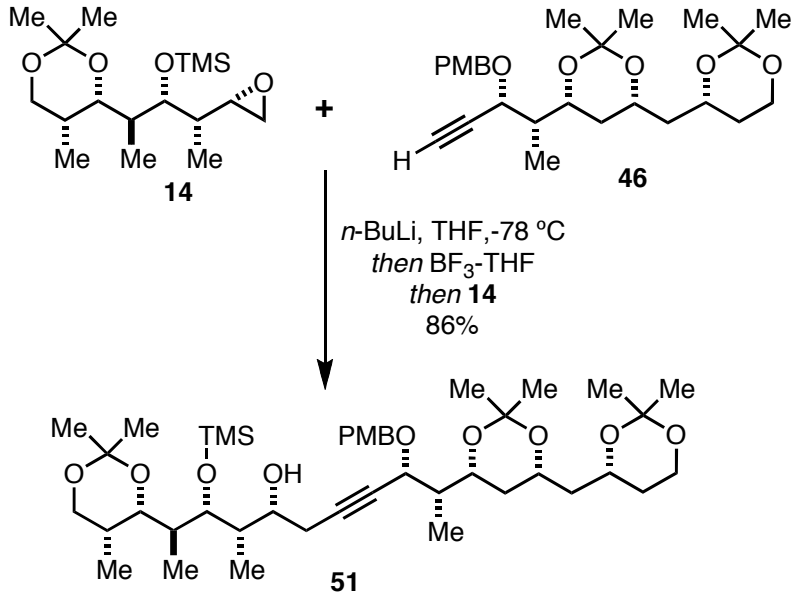
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J*= 8.4 Hz, 2H), 6.80 (d, *J*= 8.4 Hz, 2H), 4.75 (d, *J*= 11.4 Hz, 1H), 4.41 (d, *J*= 11.4 Hz, 1H), 4.12 (d, *J*= 5.4 Hz, 1H), 4.08-4.01 (m, 2H), 3.98-3.92 (m, 2H), 3.83 (dd, *J*= 12.0, 5.4 Hz, 1H), 3.81 (s, 3H), 1.80-1.75 (m, 2H), 1.63-1.56 (m, 1H), 1.44-1.38 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.30-1.24 (m, 2H), 1.11-1.10 (m, 21H), 1.08 (d, *J*= 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.41, 130.40, 129.82, 113.91, 106.06, 98.56, 98.36, 87.67, 70.95, 70.47, 70.39, 65.51, 65.46, 60.19, 55.48,

43.63, 42.97, 34.79, 31.17, 30.41, 30.21, 20.05, 19.44, 18.86, 11.42, 11.29. **FT-IR** (neat, cm^{-1}): 2992 (m), 2942 (s), 2864 (s), 2164 (w), 1612 (m), 1513 (s), 1462 (m), 1379 (s), 1248 (s), 1198 (s), 1172 (m), 1102 (m), 1037 (m), 969 (m), 881 (m), 820 (m). **HRMS** (ESI+): Calcd. for $C_{35}H_{59}O_6Si$ ($[M+H]^+$), 603.4081. Found: 603.4071. **$[\alpha]_D^{25}$** +46.8 (c 0.65, $CHCl_3$).



(4*R*,6*R*)-4-(((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-6-((2*S*,3*R*)-3-(4-methoxybenzyloxy)pent-4-yn-2-yl)-2,2-dimethyl-1,3-dioxane (46): The TIPS-protected alkyne **45** (1.3 g, 2.17 mmol) was dissolved in THF (22 mL), and the solution was cooled down to 0 ºC. A 1M solution of TBAF in THF (4.342 mL, 4.342 mmol) was added dropwise via syringe. After the addition was completed, the reaction mixture was allowed to warm to room temperature and stirred for one hour, then diluted with water and ether. The mixture was extracted with ether (3 X 50 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes and ethyl acetate (90:10) as eluent to afford the unprotected terminal alkyne **46** (0.945 g, 97% yield), as a colorless oil.

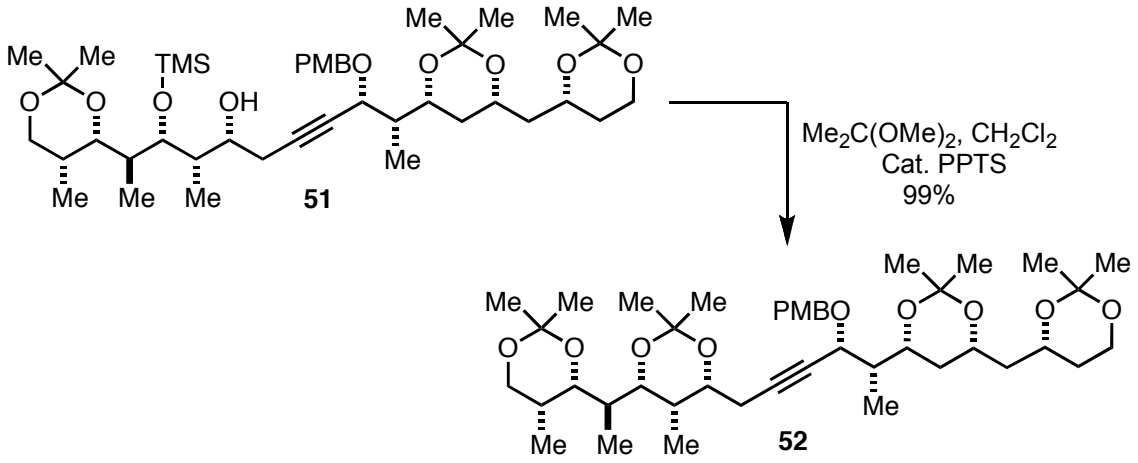
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (d, *J*= 8.4 Hz, 2H), 6.88 (d, *J*= 8.4 Hz, 2H), 4.74 (d, *J*= 11.4 Hz, 1H), 4.39 (d, *J*= 11.4 Hz, 1H), 4.10 (dd, *J*= 6.0, 2.4 Hz, 1H), 4.07-4.02 (m, 2H), 3.98 (dd, *J*= 12.0, 2.4 Hz, 1H), 3.94 (dd, *J*= 7.2, 2.4 Hz, 1H), 3.84 (dd, *J*= 12.0, 6.0 Hz, 1H), 3.81 (s, 3H), 2.49 (d, *J*= 2.4 Hz, 1H), 1.80-1.72 (m, 2H), 1.63-1.56 (m, 1H), 1.44 (s, 3H), 1.43-1.39 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.29-1.26 (m, 2H), 1.08 (d, *J*= 12.0 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.45, 130.15, 129.82, 113.92, 98.58, 98.37, 82.35, 74.70, 70.65, 70.23, 69.95, 65.51, 65.45, 60.17, 55.47, 43.23, 42.97, 34.32, 31.11, 30.36, 30.22, 19.92, 19.46, 10.79. **FT-IR** (neat, cm^{-1}): 3286 (m), 2991 (s), 2942 (s), 2917 (s), 2871 (s), 2109 (w), 1612 (m), 1513 (s), 1380 (s), 1249 (s), 1198 (s), 1172 (s), 1101(m), 1036 (m), 970 (m), 821 (m). **HRMS** (ESI+): Calcd. for $C_{26}H_{39}O_6$ ($[M+H]^+$), 447.2747. Found: 47.2747. **$[\alpha]_D^{25}$** +48.0 (c 0.825, $CHCl_3$).



(2*S*,3*R*,4*S*,5*R*,9*R*,10*S*)-10-((4*R*,6*R*)-6-(((*R*)-2,2-dimethyl-1,3-dioxan-4-yl) methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-9-(4-methoxybenzyloxy)-4-methyl-2-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl)-3-(trimethylsilyloxy)undec-7-yn-5-ol (46): The alkyne **46** (0.155 g, 0.348 mmol) was dissolved in anhydrous THF (5 mL), and the solution was cooled to -78 ºC. Then, *n*-BuLi (0.146 mL, 2.5 M in hexane, 0.365 mmol) was added dropwise via syringe, and the mixture was stirred for 30 minutes at -78 ºC, after which BF_3-THF (42 μL, 0.38 mmol) was added dropwise and the mixture was stirred for 10 minutes and kept at -78 ºC. Finally, the epoxide **14** (0.115 g, 0.348 mmol) dissolved in anhydrous THF (1 mL + 1 mL wash) was added via cannula. The mixture was stirred at -78 ºC for two hours, and then quenched with a pH 7 phosphate buffer solution (20 mL). The mixture was extracted with ether (3 X 50 mL), the organic fractions were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using hexanes and ethyl acetate (80:20) as eluent to afford the coupling product alcohol **51** (0.233 g, 86% yield), as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J*= 8.4 Hz, 2H), 6.87 (d, *J*= 8.4 Hz, 2H), 4.71 (d, *J*= 10.8 Hz, 1H), 4.35 (dd, *J*= 10.8, 2.4 Hz, 1H), 4.08 (d, *J*= 6.0 Hz, 1H), 4.05 (dd, *J*= 11.4, 2.4 Hz, 1H), 4.04-3.99 (m, 3H), 3.97-3.91 (m, 3H), 3.48-3.81 (m, 2H), 3.80 (s, 3H) 3.69 (dd, *J*= 11.4, 1.2 Hz, 1H), 3.19 (d, *J*= 2.4 Hz, 1H), 2.47 (ddd, *J*= 16.8, 7.3 1.8 Hz, 1H), 2.38 (ddd, *J*= 16.8, 7.3 1.8 Hz, 1H), 2.00-1.96 (m, 1H), 1.95-1.90 (m, 1H), 1.78-1.74 (m, 1H), 1.71-1.65 (m, 1H), 1.62-1.55 (m, 1H), 1.45-1.42 (m, 2H), 1.43 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.35 (s,

3H), 1.33 (s, 3H), 1.25-1.21 (m, 3H), 1.06 (d, *J*= 7.2 Hz, 3H), 1.05 (d, *J*= 6.6 Hz, 3H), 0.94 (d, *J*= 7.2 Hz, 3H), 0.85 (d, *J*= 7.2 Hz, 3H), 0.15 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.34, 130.47, 129.63, 113.86, 98.64, 98.50, 98.35, 84.29, 80.03, 76.85, 73.07, 72.89, 70.41, 70.35, 70.12, 67.52, 65.48, 65.44, 60.15, 55.46, 43.62, 42.98, 39.16, 38.56, 34.41, 31.07, 30.38, 30.22, 30.04, 29.94, 25.14, 19.96, 19.45, 19.09, 12.59, 10.91, 10.54, 9.15, 0.77. **FT-IR** (neat, cm^{-1}): 3478 (br, m), 2989 (s), 2939 (s), 2916 (s), 2873 (s), 1612 (w), 1513 (m), 1461 (m), 1379 (s), 1249 (s), 1198 (s), 1172 (s), 1034 (s), 1009 (m), 971 (m), 874 (m), 840 (s), 752 (m). **HRMS** (ESI+): Calcd. for $C_{43}H_{73}O_{10}Si$ ($[M+H]^+$), 777.4973. Found: 777.4968. **$[\alpha]_D^{25}$** +39.3 (c 1.57, $CHCl_3$).

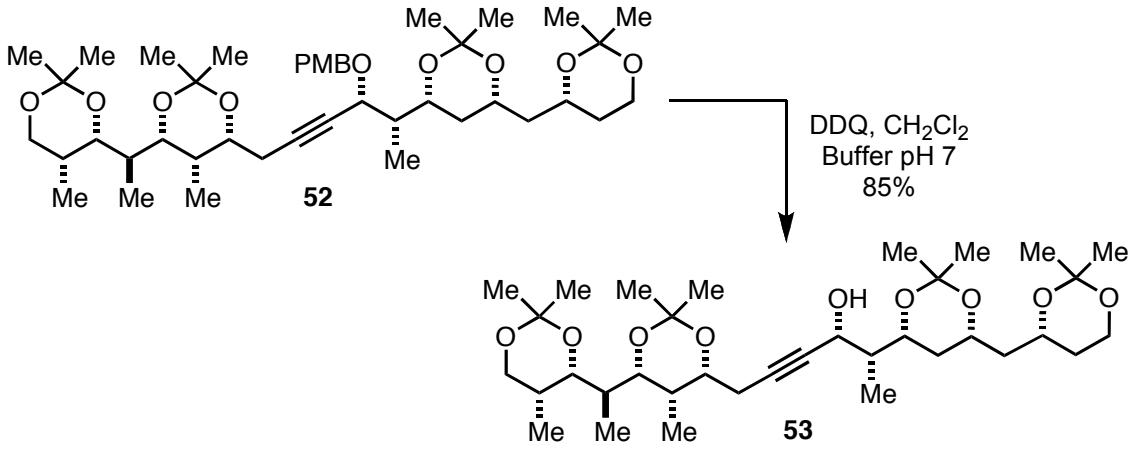


(4*R*,5*S*,6*R*)-4-((4*R*,5*S*)-5-((4*R*,6*R*)-6-(((*R*)-2,2-dimethyl-1,3-dioxan-4-yl) methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-(4-methoxybenzyloxy)hex-2-ynyl)-2,2,5-trimethyl-6-((*S*)-1-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl) ethyl)-1,3-dioxane (52): The alcohol **51** (0.209 g, 0.269 mmol) was dissolved in CH_2Cl_2 (3 mL) and then PPTS (10 mg) was added, followed by 2,2-

dimethoxypropane (3 mL), and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was the diluted with water (5 mL) and the mixture was extracted with CH_2Cl_2 (3 X 20 mL), the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes and ethyl acetate as eluents (90:10) to afford the desired tetraacetonide **52** as a viscous colorless oil (0.199 g, 99% yield).

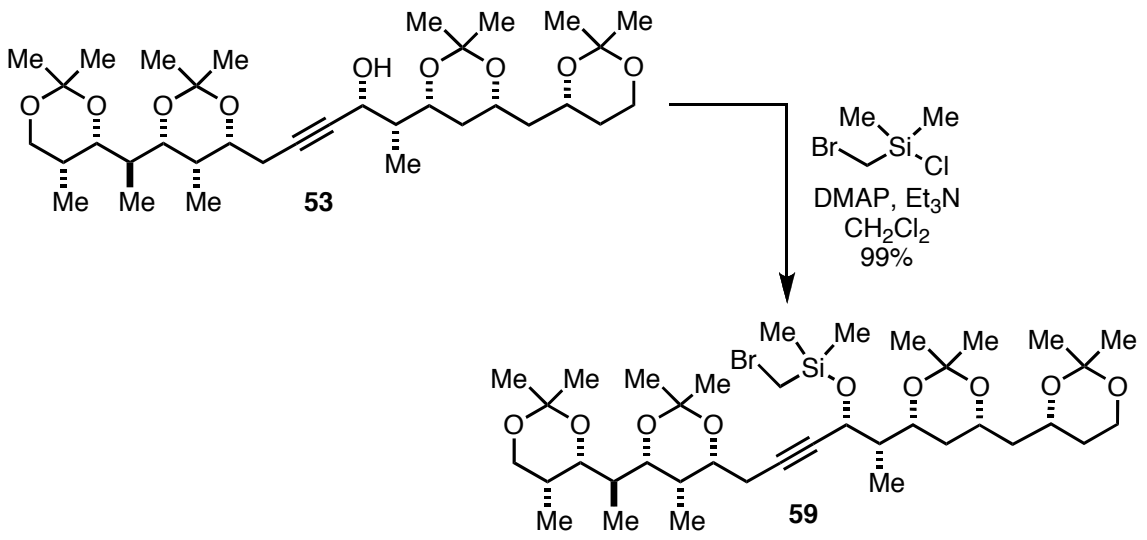
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, *J*= 9.0 Hz, 2H), 6.87 (d, *J*= 9.0 Hz, 2H), 4.69 (d, *J*= 10.8 Hz, 1H), 4.35 (d, *J*= 10.8 Hz, 1H), 4.08 (dd, *J*= 8.4, 1.8 Hz, 1H), 4.06-4.0 (m, 4H), 3.98-3.97 (m, 1H), 3.95 (dd, *J*= 12.0, 2.4 Hz, 1H), 3.93-3.89 (m, 1H), 3.88 (dd, *J*= 8.4, 1.8 Hz, 1H), 3.83 (dd, *J*= 12.0, 5.4 Hz, 1H), 3.81 (s, 3H), 3.56 (d, *J*= 11.4, 1H), 2.49 (ddd, *J*= 16.8, 6.6, 1.8 Hz, 1H), 2.38 (ddd, *J*= 16.8, 8.4, 1.8 Hz, 1H), 2.06-2.01 (m, 1H), 1.78-1.73 (m, 2H), 1.69-1.66 (m, 1H), 1.67-1.53 (m, 2H), 1.50-1.45 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.40 (s, 6H, overlapping methyls), 1.39 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.28-1.21 (m, 3H), 1.13 (d, *J*= 7.2 Hz, 3H), 1.06 (d, *J*= 6.6 Hz, 3H), 0.91 (d, *J*= 7.2 Hz, 3H), 0.86 (d, *J*= 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.39, 130.36, 129.66, 113.88, 99.23, 98.77, 98.50, 98.34, 82.75, 80.18, 77.02, 74.11, 72.86, 72.04, 70.36, 70.20, 70.15, 68.34, 65.46, 60.15, 55.46, 43.62, 42.97, 37.80, 34.41, 32.01, 31.06, 30.40, 30.38, 30.22, 30.07, 30.05, 23.28, 19.97, 19.83, 19.46, 19.28, 12.56, 10.94, 9.96, 5.57. **FT-IR** (neat, cm^{-1}): 2990 (s), 2938 (s), 2919 (s), 2868 (s), 1612 (m), 1513 (m), 1461 (m), 1379 (s), 1249 (s), 1199 (s), 1173 (s), 1105 (s), 1039 (m), 1010 (m), 969 (m), 851 (w), 821 (w), 733 (w).

HRMS (ESI+): Calcd. for $C_{43}H_{69}O_{10}$ ([M+H]$^+$), 745.4891. Found: 745.4879. **[α]$_D^{25}$** +28.1 (c 1.95, $CHCl_3$).



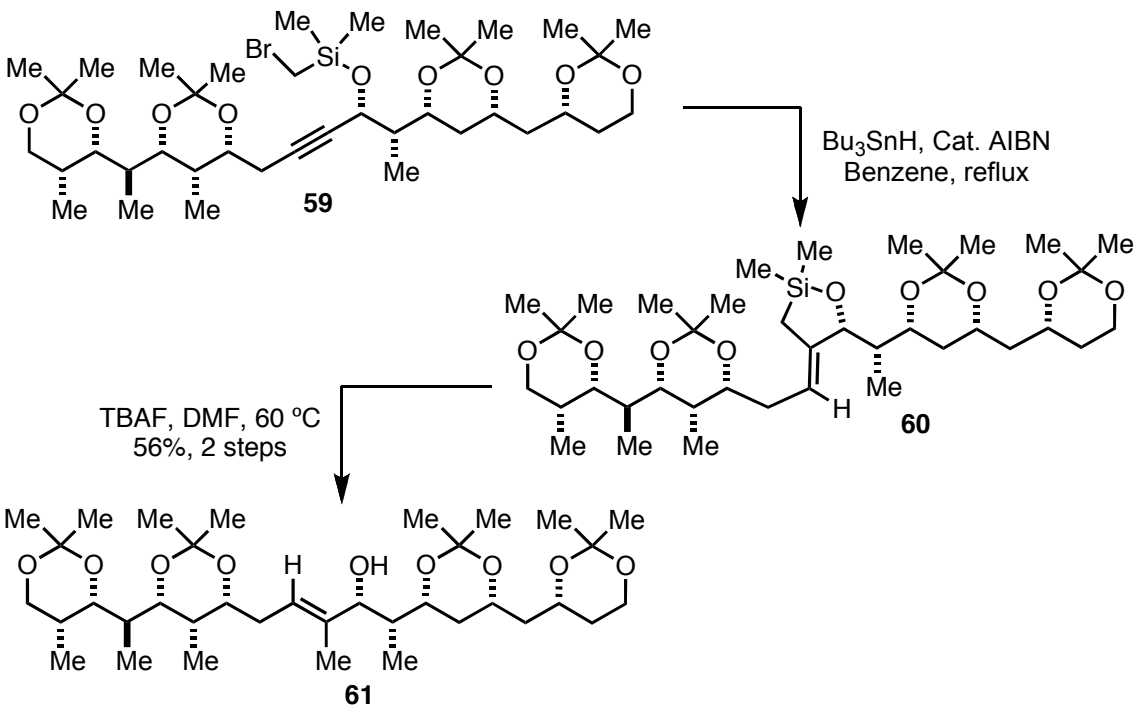
(2*R*,3*R*)-2-((4*R*,6*R*)-6-(((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-6-((4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-((*S*)-1-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxan-4-yl)hex-4-yn-3-ol (53): The PMB-ether **52** (0.199 g, 0.267 mmol) was dissolved in CH_2Cl_2 (6 mL), and then a pH 7 phosphate buffer solution (3 mL) was added. The mixture was stirred vigorously and then DDQ (0.12 g, 0.53 mmol) was added at once. The reaction mixture was stirred at room temperature and monitored closely by TLC. The reaction was completed after one hour. The reaction mixture was diluted quickly with CH_2Cl_2 and water, and then extracted with extracted with CH_2Cl_2 (3 X 20 mL), the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes and ethyl acetate as eluents (70:30) to afford the propargylic alcohol **53** as a viscous colorless oil (0.142 g, 85% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.56 (bs, 1H), 4.10 (d, *J*= 11.4 Hz, 2H), 4.07-4.01 (m, 4H), 3.97 (ddd, *J*= 12.0, 12.0, 2.4 Hz, 1H), 3.88 (d, *J*= 8.4 Hz, 1H), 3.84 (dd, *J*= 12.0, 4.8 Hz, 1H), 3.57 (d, *J*= 11.4 Hz, 1H), 2.78 (d, *J*= 3.0 Hz, 1H), 2.44 (dd, *J*= 16.8, 6.0 Hz, 1H), 2.34 (dd, *J*= 16.8, 8.4 Hz, 1H), 2.06-2.00 (m, 1H), 1.83-1.79 (m, 1H), 1.73-1.69 (m, 2H), 1.65-1.58 (m, 2H), 1.56-53 (m, 1H), 1.50-1.46 (m, 2H), 1.45 (s, 3H), 1.44 (s, 6H, overlapping methyls), 1.41 (s, 6H, overlapping methyls), 1.39 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.27-1.25 (m, 1H), 1.13 (d, *J*= 7.2 Hz, 3H), 1.09 (d, *J*= 6.6 Hz, 3H), 0.88 (d, *J*= 6.0 Hz, 3H), 0.87 (d, *J*= 6.6 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 99.25, 98.79 (2 carbons), 98.39, 82.11, 81.40, 73.97, 72.77, 72.63, 72.08, 68.36, 66.42, 65.55, 65.36, 60.15, 43.60, 42.79, 37.84, 33.93, 31.82, 31.15, 30.41, 30.31, 30.20, 30.06 (2 carbons), 23.13, 20.05, 19.85, 19.46, 19.23, 12.46, 9.94, 8.31, 5.64. **FT-IR** (neat, cm^{-1}): 3447 (br, m), 2989 (s), 2937 (s), 2919 (s), 2874 (s), 1460 (m), 1379 (s), 1267 (m), 1242 (m), 1198 (s), 1172 (s), 1105 (s), 1009 (m), 968 (m), 852 (m). **HRMS** (ESI+): Calcd. for $C_{35}H_{61}O_9$ ($[M+H]^+$), 625.4316. Found: 625.4307. **$[\alpha]_D^{25}$** -8.6 (c 0.6, $CHCl_3$).



(Bromomethyl)((2*S*,3*R*)-2-((4*R*,6*R*)-6-(((*R*)-2,2-dimethyl-1,3-dioxan-4-yl) methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-6-((4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-((*S*)-1-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxan-4-yl)hex-4-yn-3-yloxy)dimethylsilane (59): Propargylic alcohol **53** (106 mg, 0.169 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL), and then DMAP catalyst (2 mg, 0.016 mmol) was added followed by triethylamine (24 μL, 0.25 mmol), and finally (bromomethyl)dimethylchlorosilane (34 μL, 0.25 mmol). The mixture was stirred at room temperature for 30 minutes, and then quenched with a pH 7 phosphate buffer solution. The mixture was extracted with CH_2Cl_2 (3 X 15 mL), the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel pretreated with 2.5% vol of Et_3N and using hexanes and ethyl acetate as eluents (90:10) to afford the bromomethylsilyl ether **59** as a colorless oil (130 mg, 99% yield).

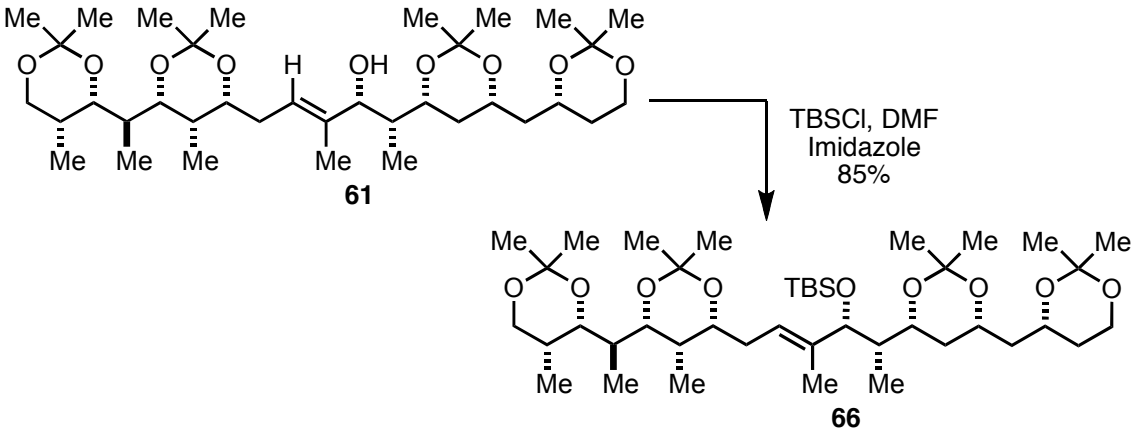
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.45 (d, *J*= 5.4 Hz, 1H), 4.10 (dd, *J*= 11.4, 1.8 Hz, 1H), 4.08-3.96 (m, 6H), 3.86-3.82 (m, 2H), 3.57 (d, *J*= 11.4 Hz, 1H), 2.56 (d, *J*= 13.2 Hz, 1H), 2.53 (d, *J*= 13.2 Hz, 1H), 2.44 (ddd, *J*= 16.8, 6.0, 1.2 Hz, 1H), 2.32 (dd, *J*= 16.8, 7.8 Hz, 1H), 2.05-2.00 (m, 1H), 1.83-1.79 (m, 1H), 1.70-1.67 (m, 1H), 1.64-1.54 (m, 4H), 1.48-1.45 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.39 (s, 6H, overlapping methyls), 1.38 (s, 3H), 1.35 (s, 3H), 1.29-1.24 (m, 2H), 1.44 (d, *J*= 7.2 Hz, 3H), 1.00 (d, *J*= 7.2 Hz, 3H), 0.88 (d, *J*= 6.6 Hz, 3H), 0.87 (d, *J*= 6.6 Hz, 3H), 0.31 (s, 6H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 99.25, 98.79, 98.50, 98.38, 82.18, 82.11, 74.23, 72.81, 72.03, 69.87, 68.43, 65.57, 65.46, 64.93, 60.16, 45.20, 43.10, 37.78, 34.44, 32.15, 31.14, 30.47, 30.38, 30.25, 30.07 (2 carbons), 23.32, 19.95, 19.82, 19.52, 19.31, 16.63, 12.69, 10.37, 9.99, 5.51, -2.32 (2 carbons) **FT-IR** (neat, cm^{-1}): 2989 (s), 2939 (s), 2871 (m), 1459 (m), 1378 (s), 1255 (s), 1199 (s), 1170 (s), 1105 (s), 1051 (m), 1010 (m), 968 (m), 840 (m), 817 (m). **HRMS** (ESI+): Calcd. for $C_{38}H_{68}BrO_9Si$ ($[M+H]^+$), 775.3816. Found: 775.3829. **$[\alpha]_D^{25}$** +11.5 (c 0.5, $CHCl_3$).



(2*R*,3*R*,*E*)-2-((4*R*,6*R*)-6-(((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methyl-6-((4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-((*S*)-1-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxan-4-yl)hex-4-en-3-ol (61): The bromomethylsilyl ether **59** (100 mg, 0.129 mmol) was dissolved in anhydrous benzene (10 mL) and the solution was heated to reflux. Then Bu_3SnH (49 mg, 0.167 mmol) and AIBN (6.3 mg, 0.038 mmol) were dissolved in benzene (total volume 1 mL) and added with a syringe pump over 4 hours at a rate of 0.25 mL per hour. After the addition was completed, the reaction mixture was further stirred and refluxed for 4 additional hours. The reaction mixture was then cooled down to room temperature and the volatiles were removed under reduced pressure. The residue **60** was dissolved in DMF (5 mL) and then the TBAF (0.644 mL, 1.0 M in THF, 0.644 mmol) was added dropwise via syringe. The mixture was then heated to 60 ºC and stirred for 20 hours. After cooling down to

room temperature, the reaction mixture was quenched with a saturated solution of NH_4Cl (5 mL) and then diluted with CH_2Cl_2 and water. The mixture was then extracted with CH_2Cl_2 (3 X 15 mL), the combined organic fractions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using a gradient of hexanes and ethyl acetate (90:10 to 70:30) as eluent to afford the desired trisubstituted olefin **61** as a viscous colorless oil (46.4 mg, 56% yield for the two steps).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.47 (t, *J*= 7.2 Hz, 1H), 4.20 (bs, 1H), 4.13-4.09 (m, 2H), 4.07-4.04 (m, 3H), 3.98 (ddd, *J*= 12.0, 12.0. 2.4 Hz, 1H), 3.89 (ddd, *J*= 7.2, 7.2, 1.8 Hz, 1H), 3.86-3.84 (m, 2H), 3.56 (dd, *J*= 11.4, 1.2 Hz, 1H), 3.12 (bs, 1H), 2.31- 2.27 (m, 1H), 2.20-2.15 (m, 1H), 2.05-2.00 (m, 1H), 1.86-1.80 (m, 1H), 1.67-1.61 (m, 2H), 1.58 (s, 3H), 1.55-1.48 (m, 4H), 1.46, (s, 6H, 2 overlapping methyls), 1.44 (s, 3H), 1.40 (s, 9H, 3 overlapping methyls), 1.39 (s, 3H), 1.38 (s, 3H), 1.32-1.26 (m, 2H), 1.13 (d, *J*= 6.6 Hz, 3H), 0.89 (d, *J*= 6.6 Hz, 3H), 0.85 (d, *J*= 6.6 Hz, 3H), 0.84 (d, *J*= 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 136.75, 119.88, 98.97, 98.81, 98.75, 98.40, 79.14, 74.41, 74.17, 73.89, 71.99, 68.48, 65.58, 65.35, 60.16, 42.83, 39.53, 37.84, 34.22, 32.48, 31.33, 31.17, 30.45, 30.36, 30.22, 30.06, 29.92, 20.17, 19.85, 19.48, 19.26, 14.42, 12.71, 9.97, 5.97, 5.83. **FT-IR** (neat, cm^{-1}): 3488 (br, m), 2989 (s), 2917 (s), 2858 (s), 1461 (m), 1378 (m), 1267 (s), 1241 (m), 1199 (s), 1172 (s), 1137 (m), 1105 (s), 1008 (s), 968 (m), 854 (m). **HRMS** (ESI+): Calcd. for $C_{36}H_{65}O_9$ ($[M+H]^+$), 641.4629. Found: 641.4629. **$[\alpha]_D^{25}$** -20.0 (c 0.15, $CHCl_3$).

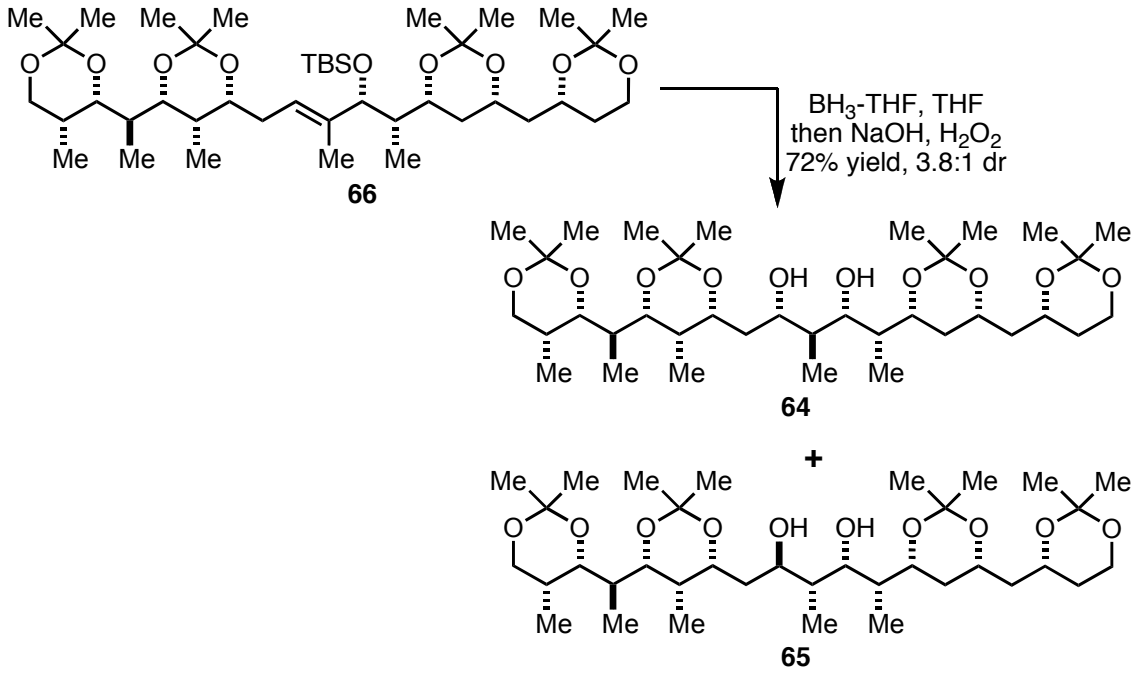


61 **66**

***Tert*-butyl((2*S*,3*R*,*E*)-2-((4*R*,6*R*)-6-(((*R*)-2,2-dimethyl-1,3-dioxan-4-yl) methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methyl-6-((4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-((*S*)-1-((4*S*,5*R*)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxan-4-yl)hex-4-en-3-yloxy)dimethylsilane (66):** The allylic alcohol **61** (27 mg, 0.042 mmol) was dissolved in DMF (4 mL) and then the imidazole (6 mg, 0.084 mmol) was added followed by TBSCl (13 mg, 0.084 mmol). The mixture was stirred for 72 hours, and the mixture was then diluted with water (5 mL) and CH_2Cl_2 (200 mL). The mixture was extracted with CH_2Cl_2 (3 X 15 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes and ethyl acetate (90:10) as eluents to afford the TBS-protected olefin **66** as a viscous colorless oil (28 mg, 88% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.27 (t, *J*= 7.2 Hz, 1H), 4.11-4.03 (m, 3H), 3.99-3.91 (m, 3H), 3.86-3.82 (m, 2H), 3.78 (d, *J*= 9.0 Hz, 1H), 3.68 (d, *J*= 12.0 Hz, 1H), 3.55 (d, *J*= 10.8 Hz, 1H), 2.35-2.30 (m, 1H), 2.05-2.00 (m, 2H), 1.82-1.72 (m, 2H), 1.63-1.54 (m, 2H), 1.56 (s, 3H), 1.52-1.48 (m, 2H), 1.47-1.46 (m, 1H), 1.45 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.39 (s, 6H, overlapping methyls), 1.38 (s, 3H),

1.34 (s, 3H), 1.30 (s, 3H), 1.28-1.23 (m, 2H), 1.13 (d, *J*= 6.6 Hz, 3H), 0.91 (d, *J*= 6.6 Hz, 3H), 0.90 (d, *J*= 9.0 Hz, 3H), 0.89 (s, 9H), 0.85 (d, *J*= 7.2 Hz, 3H), 0.03 (s, 3H), -0.03 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 138.46, 122.50, 98.96, 98.81, 98.37, 98.27, 79.34, 74.62, 73.87, 71.82, 68.94, 68.57, 65.65, 65.43, 60.17, 43.08, 41.94, 37.78, 34.72, 32.74, 31.47, 31.14, 30.52, 30.43, 30.23 (2 carbons), 30.19, 30.07, 29.93, 26.11, 19.92, 19.77, 19.49, 19.33, 18.43, 12.99, 12.34, 9.96, 9.70, 5.64. **FT-IR** (neat, cm^{-1}): 2989 (s), 2929 (s), 2858 (s), 1461 (m), 1378 (s), 1251 (m), 1197 (s), 1172 (m), 1105 (s), 1045 (m), 1008 (m), 968 (m), 871 (w), 836 (m), 775 (m). **HRMS** (ESI+): Calcd. for $C_{42}H_{79}O_9Si$ ($[M+H]^+$), 755.5493. Found: 755.5493. **$[\alpha]_D^{25}$** -7.8 (c 0.35, $CHCl_3$).

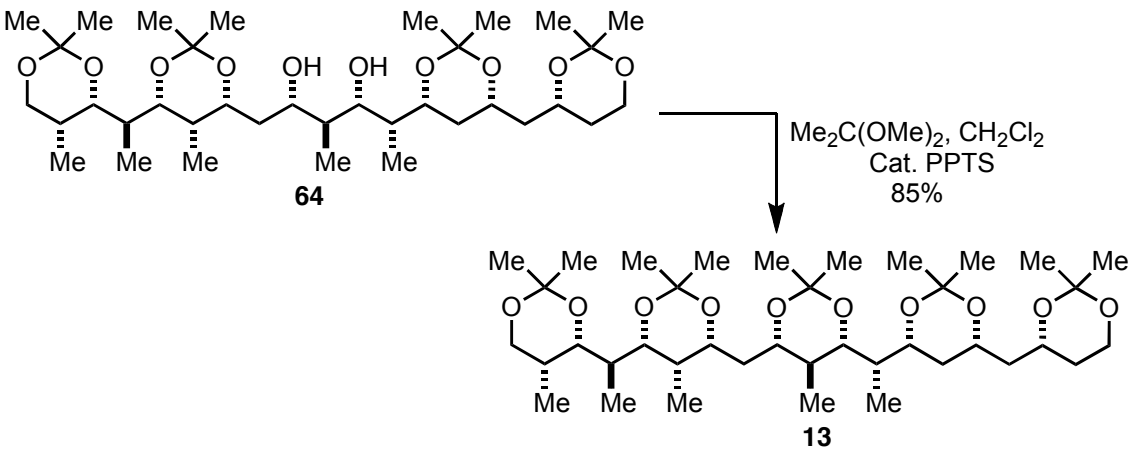


(2*S*,3S,4*S*,5*R*)-5-((4*R*,6*R*)-6-(((*R*)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methyl-1-((4*R*,5*S*,6*R*)-2,2,5-trimethyl-6-((*S*)-1-((4*S*,5*R*)-2,2,5,5-trimethyl-1,3-dioxan-4-yl)ethyl)-1,3-dioxan-4-yl)hexane-2,4-diol (64): The trisubstituted olefin **66** (16 mg, 0.021 mmol) was dissolved in anhydrous THF (2 mL) and the solution was cooled to 0 ºC. BH_3-THF (42 μL, 1M in THF, 0.042 mmol) was then added and the reaction mixture was allowed to warm to room temperature and stirred at room temperature for 5 days. The reaction mixture was then cooled to 0 ºC and treated with NaOH (0.3 mL, 3N) and H_2O_2 (0.3 mL), and stirred vigorously for two hours at room temperature. Saturated Na_2SO_3 aqueous solution (1 mL) was then added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 X 10 mL), the combined organic fractions were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography using a gradient of hexanes and ethyl acetate (80:20 to 40:60) to afford the desired diol **64** (8 mg, 57% yield) and the minor diastereomer **65** (2.1 mg, 15% yield), as colorless viscous oils.

Data for the major diol **64**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.28 (bs, 1H), 4.22 (d, *J*= 4.8 Hz, 1H), 4.18 (bs, 1H), 4.11 (d, *J*= 11.4 Hz, 1H), 4.07-4.03 (m, 4H), 3.98 (ddd, *J*= 12.0, 12.0, 2.4 Hz, 1H), 3.90-3.87 (m, 2H), 3.84 (dd, *J*= 12.0, 5.4 Hz, 1H), 3.69 (d, *J*= 9.6 Hz, 1H), 3.57 (d, *J*= 11.4 Hz, 1H), 2.05-1.99 (m, 1H), 1.84-1.79 (m, 1H), 1.76-1.67 (m, 2H), 1.64-1.59 (m, 3H), 1.57-1.49 (m, 4H), 1.46 (s, 6H, overlapping methyls), 1.44 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H), 1.38 (s, 6H, overlapping methyls), 1.34-1.30 (m, 2H), 1.26 (s, 3H), 1.13 (d, *J*= 6.6 Hz, 3H),

0.97 (d, *J*= 6.6 Hz, 3H), 0.92 (d, *J*= 6.6 Hz, 3H), 0.86 (d, *J*= 6.6 Hz, 3H), 0.76 (d, *J*= 6.6 Hz, 3H). **FT-IR** (neat, cm^{-1}): 3452 (br, m), 2927 (s), 2858 (s), 2796 (w), 1461 (m), 1378 (m), 1267 (w), 1241 (w), 1199 (m), 1112 (s), 1008 (m), 968 (m). **HRMS** (ESI+): Calcd. for $C_{36}H_{67}O_{10}$ ($[M+H]^+$), 659.4734. Found: 659.4729. $\mathbf{[\alpha]_D^{25}}$ -1.2 (c 0.13, $CHCl_3$).

Data for the minor diastereomer diol **65**: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.20 (d, *J*= 10.2 Hz, 1H), 4.10 (dd, *J*= 11.4, 2.4 Hz, 1H), 4.07-4.01 (m, 3H), 4.00-3.94 (m, 3H), 3.90 (dd, *J*= 1.8, 9.0 Hz, 1H), 3.84 (ddd, *J*= 1.2, 4.8, 12 Hz, 1H), 3.82-3.81 (m, 1H), 3.57 (dd, *J*= 1.2, 11.4 Hz, 1H), 3.07 (bs, 1H), 2.89 (bs, 1H), 2.07-2.00 (m, 2H), 1.84-1.75 (m, 2H), 1.74-1.59 (m, 5H), 1.56-1.52 (m, 2H), 1.56-1.52 (m, 2H), 1.50-1.46 (m, 2H), 1.46 (s, 3H), 1.43 (s, 6H, overlapping methyls), 1.41 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.26 (s, 3H), 1.13 (d, *J*= 7.2 Hz, 3H), 1.02 (d, *J*= 7.2 Hz, 6H, overlapping methyls), 0.90 (d, *J*= 7.2 Hz, 3H), 0.87 (d, *J*= 7.2 Hz, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 99.04, 98.81, 98.56, 98.40, 75.37, 74.48, 72.55, 72.44, 71.96, 70.77, 68.45, 65.59, 65.35, 60.16, 42.88, 40.92, 39.79, 38.36, 37.77, 34.16, 33.60, 31.17, 30.47, 30.35, 30.22, 30.07, 29.93, 20.11, 19.99, 19.48, 19.30, 12.69, 11.94, 9.93, 8.58, 6.26. **FT-IR** (neat, cm^{-1}): 3434 (br, m), 2935 (s), 2858 (s), 2798 (w), 1461 (m), 1378 (m), 1255 (w), 1201 (m), 1162 (m), 1110 (s), 1008 (m), 970 (m). **HRMS** (ESI+): Calcd. for $C_{36}H_{67}O_{10}$ ($[M+H]^+$), 659.4734. Found: 659.4727. $\mathbf{[\alpha]_D^{25}}$ -4.0 (c 0.12, $CHCl_3$).



C9-C27 Pentaacetonide Degradation Product of Aflastatin A (13): The diol **64** (4 mg, 0.006 mmol) was dissolved in CH_2Cl_2 (1 mL) and then PPTS (1 mg) was added, followed by 2,2-dimethoxypropane (1 mL), and the resulting mixture was stirred at room temperature for 72 hours. Triethylamine (0.5 mL) was then added, and the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes and ethyl acetate as eluents (90:10) to afford the desired pentaacetonide **13** as a white solid (3.6 mg, 85% yield).

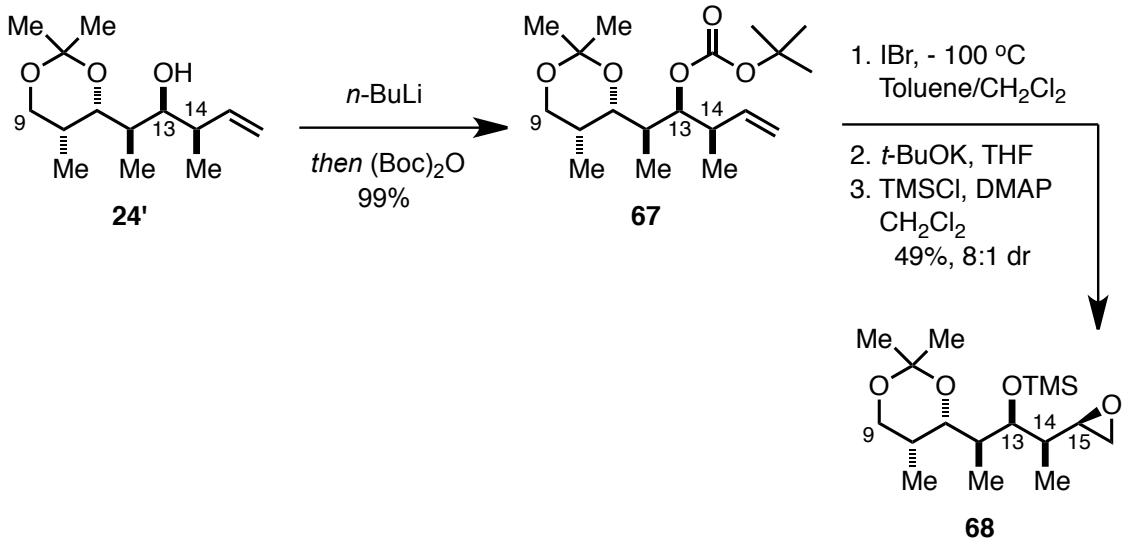
^{1}H NMR (600 MHz, C_6D_6) δ 4.52-4.50 (m, 1H), 4.18 (d, *J*= 7.8 Hz, 1H), 4.14 (dd, *J*= 1.8, 6.6 Hz, 1H), 4.12-4.09 (m, 1H), 3.98 (d, *J*= 9.0 Hz, 1H), 3.95 (m, 1H), 3.93 (m, 1H), 3.69 (m, 1H), 3.68 (m, 1H), 3.64 (d, *J*= 9.6 Hz, 1H), 3.53 (m, 1H), 3.47 (d, *J*= 10.8 Hz, 1H), 2.33-2.30 (m, 1H), 2.18-2.14 (m, 1H), 1.94-1.89 (m, 1H), 1.87-1.84 (m, 1H), 1.82-1.80 (m, 1H), 1.79-1.78 (m, 1H), 1.72-1.70 (m, 1H), 1.67-1.63 (m, 1H), 1.56 (s, 3H), 1.55 (m, 2H), 1.55 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H), 1.50 (s, 3H), 1.47-1.45 (m, 1H), 1.39 (s, 3H), 1.36 (s, 6H, overlapping methyls), 1.36-1.33 (m, 2H), 1.34 (s, 3H), 1.31 (s, 3H), 1.25 (d, *J*= 6.6 Hz, 3H), 1.17 (d, *J*= 6.6 Hz, 3H), 1.05 (d, *J*= 6.6 Hz, 3H), 0.96 (d, *J*= 7.2 Hz, 3H), 0.61 (d,

J= 6.6 Hz, 3H). **^{13}C NMR** (150 MHz, C_6D_6) δ 99.13, 99.05, 98.97, 98.61, 98.13, 74.73, 73.38, 72.40, 72.04 (2 carbons), 70.54, 68.60, 65.94, 65.76, 60.20, 44.48, 40.13, 38.64, 36.80, 35.35, 35.22, 33.12, 31.82, 31.10, 30.92, 30.86, 30.82, 30.70, 30.56, 20.29, 20.07 (2 carbons), 19.76, 19.54, 13.38, 11.99, 10.45, 9.97, 6.38. **FT-IR** (neat, cm^{-1}): 2989 (s), 2966 (s), 2937 (m), 1502 (w), 1461 (m), 1434 (w), 1378 (s), 1261 (m), 1199 (s), 1174 (s), 1103 (s), 1049 (m), 1010 (m), 970 (m). **HRMS** (ESI+): Calcd. for $C_{39}H_{71}O_{10}$ ($[M+H]^+$), 699.5047. Found: 699.5050. **$[\alpha]_D^{25}$** -0.5 (c 0.15, $CHCl_3$); {lit. natural derived **13 $[\alpha]_D^{23}$** -0.4 (c 0.1, $CHCl_3$)}.[40]

2.6 Appendix. Synthesis of the 13-*epi*, 14-*epi*, 15-*epi*-C9-C27 Degradation Product of Aflastatin A

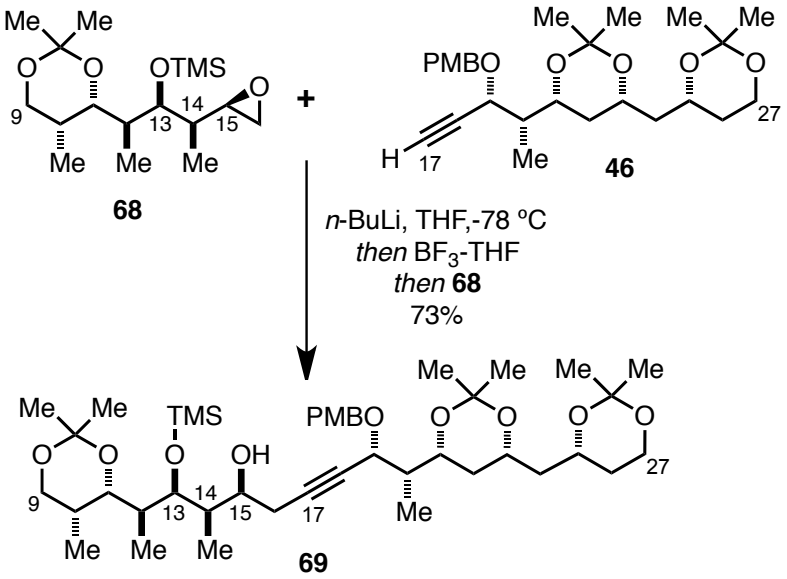
Although the stereochemistry at C13 and C14 in the homoallylic alcohol **24'** is inverted with respect to the stereochemistry in the C9-C27 degradation product of Aflastatin A (**13**), compound **24'** was used as an excellent model system to explore reaction conditions that eventually were used in the synthesis of the C9-C27 degradation product of Aflastatin A (**13**).

Thus, homoallylic alcohol **24'** was transformed into module **68** by first installing a Boc group on the free alcohol to provide carbonate **67** in excellent yield. The C15-C16 epoxide was introduced by IBr-promoted cyclization of **67**, followed by opening of the resulting cyclic iodocarbonate under basic conditions that provided the corresponding epoxide.[50] Finally, TMS protection of the free alcohol afforded module **68** (scheme 26).



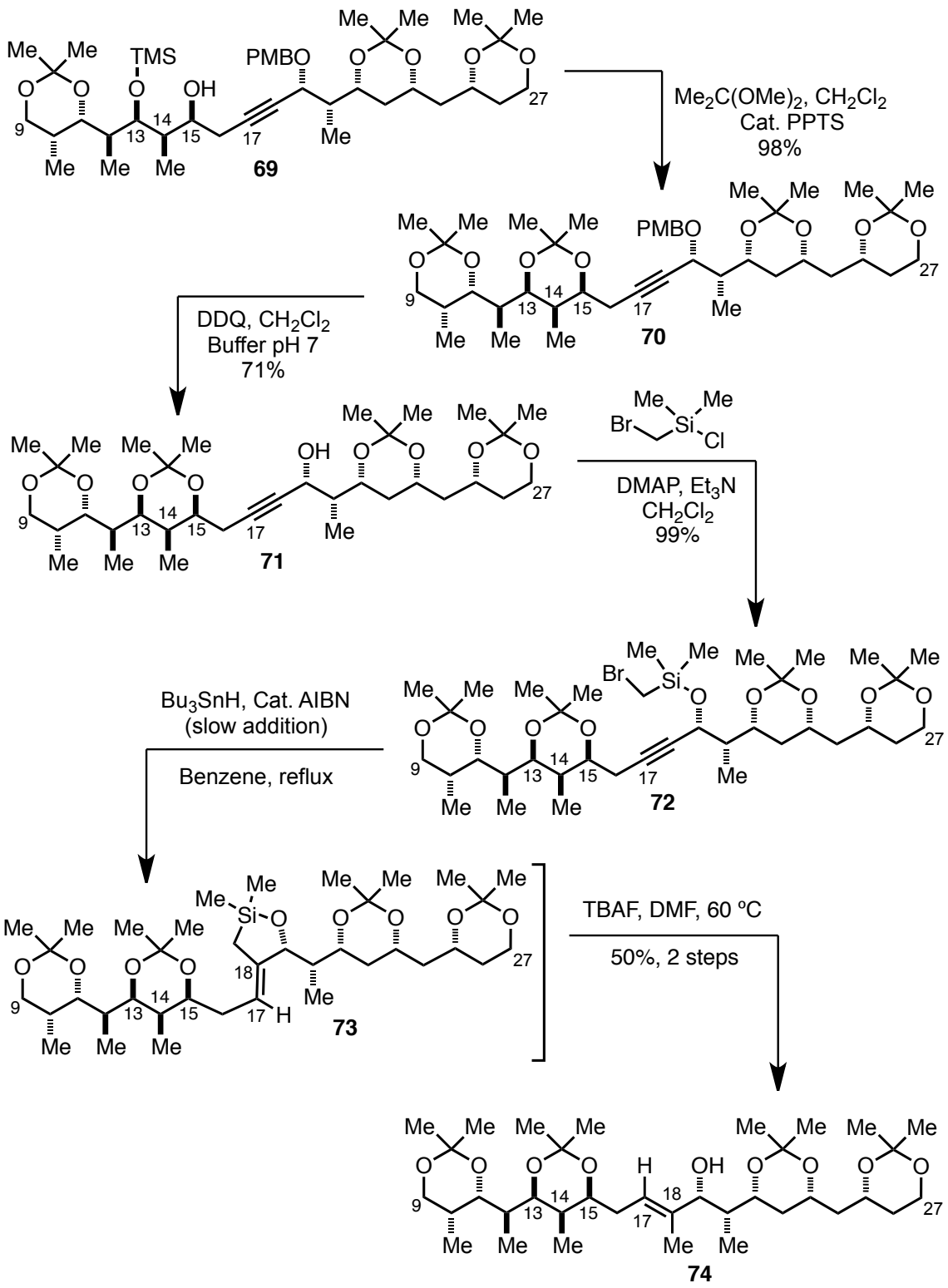
Scheme 26. Synthesis of module **68**.

The epoxide **68** was then coupled with alkyne **46**. Treatment of **46** with one equivalent of *n*-butyllithium and BF_3-THF at -78 ºC, followed by addition of the electrophilic epoxide **68** provided alkynyl alcohol **69** in 73% isolated yield (scheme 27).



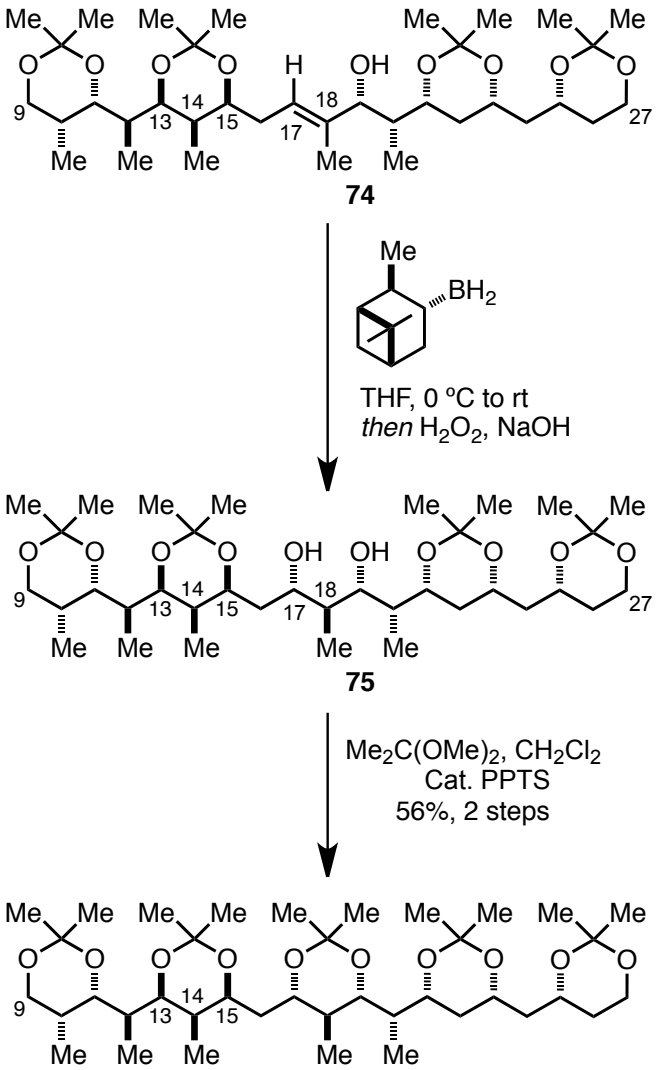
Scheme 27. Cross-coupling of modules **68** and **46**.

The TMS protecting group in **69** was removed under mild acidic conditions, and in the same pot, the resulting diol was protected as the corresponding acetonide **70** in 98% yield (scheme 28). The PMB group was then removed with DDQ, providing the propargylic alcohol **71** in 71% yield. The introduction of the C18-methyl substituent was then accomplished by radical cyclization of the bromomethylsilyl ether **72**, which was followed by protiodesilylation to stereoselectively afford the *E*-trisubstituted alkene **74** (scheme 28).



Scheme 28. Functionalization of alkynol **69**.

The synthesis of 13-*epi*, 14-*epi*, 15-*epi*-C9-C27 degradation product of Aflastatin A (**76**) was then accomplished by stereoselective hydroboration - oxidation of the olefin **74** using the chiral non-racemic borane (+)-IpcBH$_2$, that provided the diol **75** as a single diastereomer and finally installation of the remaining acetonide afforded the pentaacetonide **76** in 56% yield for the two steps. The ^{1}H NMR spectral comparison of synthetic **13** with **76** in C_6D_6 is shown in figure 6.



74

75

76, 13-*epi*, 14-*epi*, 15-*epi*-C9-C27 degardation product of aflastatin A

Scheme 29. Synthesis of pentaacetonide **76**.

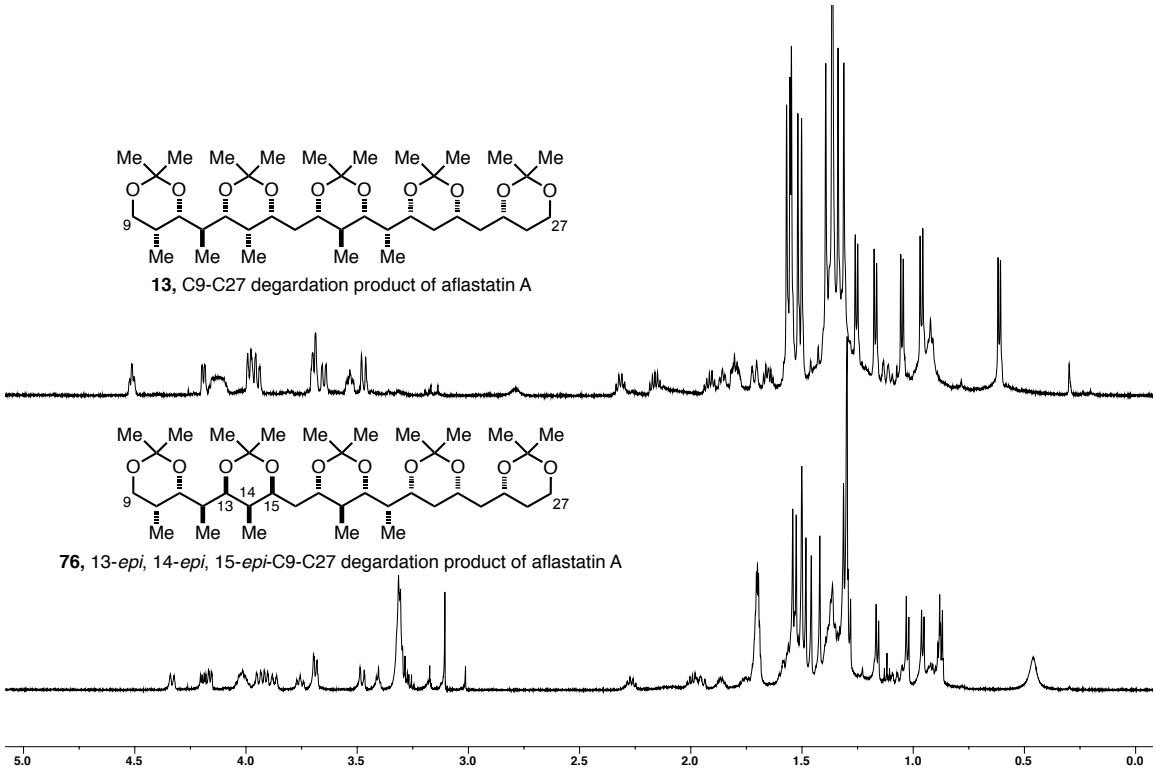


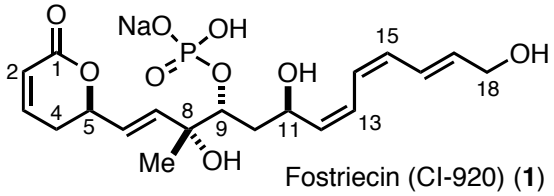
Figure 6. ^{1}H NMR spectral comparison of synthetic **13** with **76** in C_6D_6.

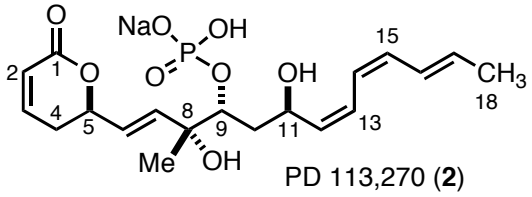
Chapter 3

Total Synthesis of Fostriecin

3.1 Introduction and Background

Fostriecin (**1**, CI-920) is a phosphate ester metabolite produced by *Streptomyces pulveraceus*. It was originally isolated, along with some related compounds PD 113,270 (**2**) and PD 113,271 (**3**), from the fermentation broth of an unidentified actinomycete from a Brazilian soil sample in 1983 (figure 1).[63,64] The producing microorganism was later characterized as *Streptomyces pulveraceus* subspecies *fostreus* ATCC 31906.





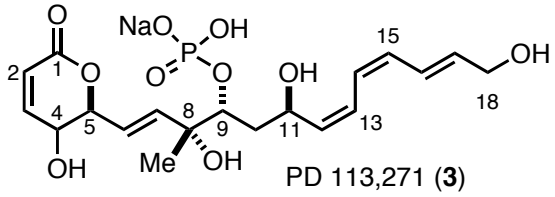


Figure 1. Structures of fostriecin and related compounds.

Fostriecin was found to exhibit potent activity *in vitro* against leukemia (L1210, IC_{50} = 0.46 μM), lung, breast and ovarian cancer cells, as well as effective *in vivo* antitumor activity in the murine tumor models.[65] The biological activity of this

promising molecule was investigated in a Phase I clinical trial at NCI, however it was halted before dose-limiting toxicities or therapeutic plasma levels were reached due the lack of available compound from natural sources and concerns regarding the purity and stability of the molecule, since it was found that fostriecin and related compounds were unstable above pH 8 and very sensitive to dilute acids (pH below 5.5).[65]

Fostriecin was shown to inhibit DNA topoisomerase II (IC_{50} = 40 μM) through a novel, non-DNA-strand cleavage mechanism, however, the activity was weak and it did not induced G2 arrest like other more potent topoisomerase II inhibitors,[66] which suggested that the DNA topoisomerase II was unlikely the target responsible for the anticancer activity of fostriecin.

Fostriecin was then shown to inhibit the mitotic entry check point by the potent and selective inhibition of certain serine/threonine protein phosphatases, particularly protein phosphatases 1 (PP1), 2A (PP2A) and 4 (PP4), with IC_{50} = 45 μm, 1.5 nM, and 3 nM, respectively. Quite remarkably, fostriecin exhibited a 10^4-fold selectivity on its inhibitory activity for PP2A/PP4 over PP1, making fostriecin the most selective protein phosphate inhibitor known to date (table 1), in contrast to several other potent protein phosphatase inhibitors such as microcystin-LA (**4**), tautomycin (**5**), calyculin (**6**), okadaic acid (**7**), and cantharidin (**8**) among others (figure 2).

Inhibitor	IC_{50}/PP1	IC_{50}/PP2A	Selectivity PP1/PP2A
Fostriecin (**1**)	45 μM	1.5 nM	10^4-10^5
Microcystin-LA (**4**)	0.1 nM	0.1-1 nM	1-0.1
Tautomycin (**5**)	0.2 nM	1 nM	0.2
Calyculin (**6**)	0.5-2 nM	0.1-1 nM	ca. 1
Okadaic acid (**7**)	20 nM	0.2 nM	100
Cantharidin (**8**)	470 μM	40 μM	10

Table 1. Selective inhibitors of PP1 and PP2A protein phosphatases.

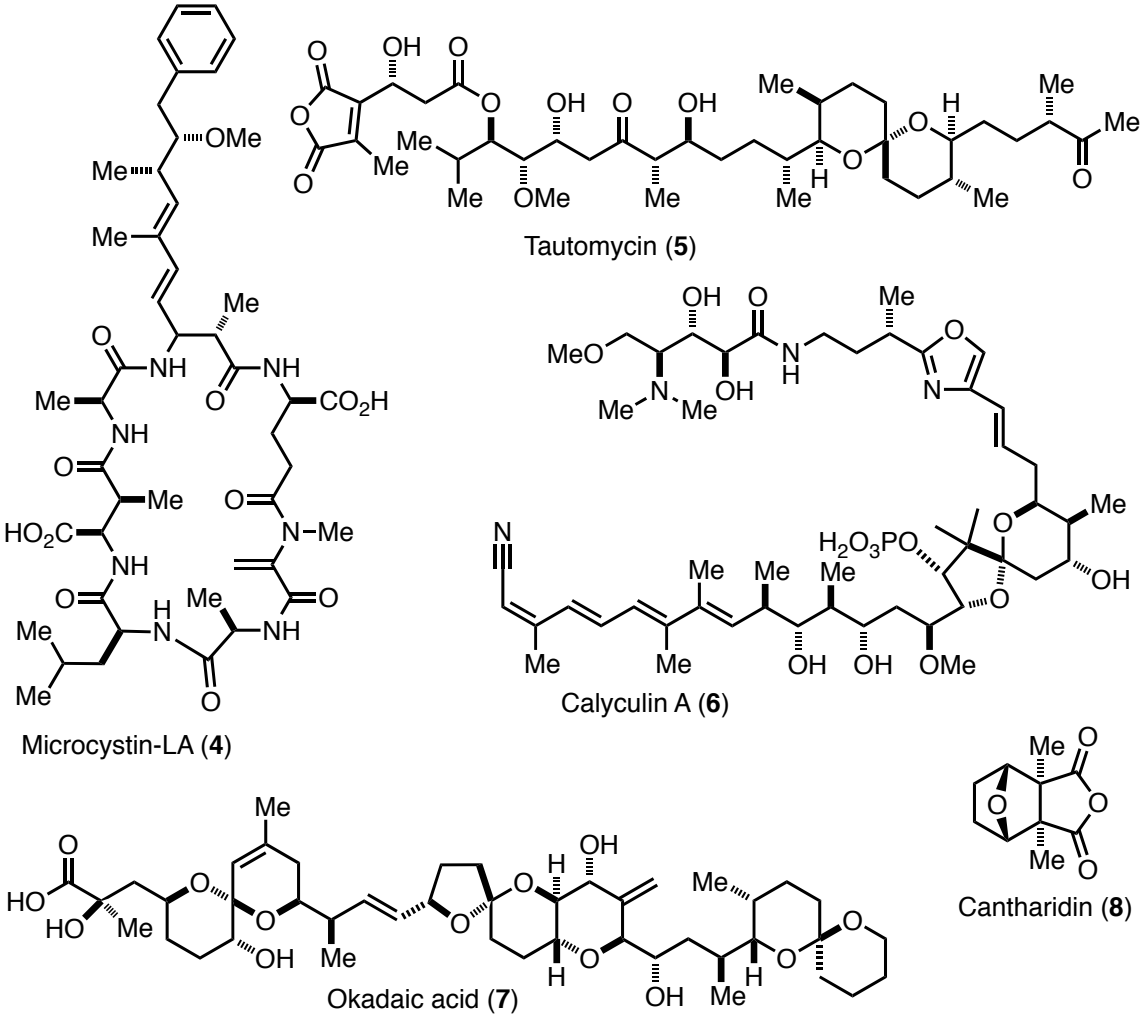
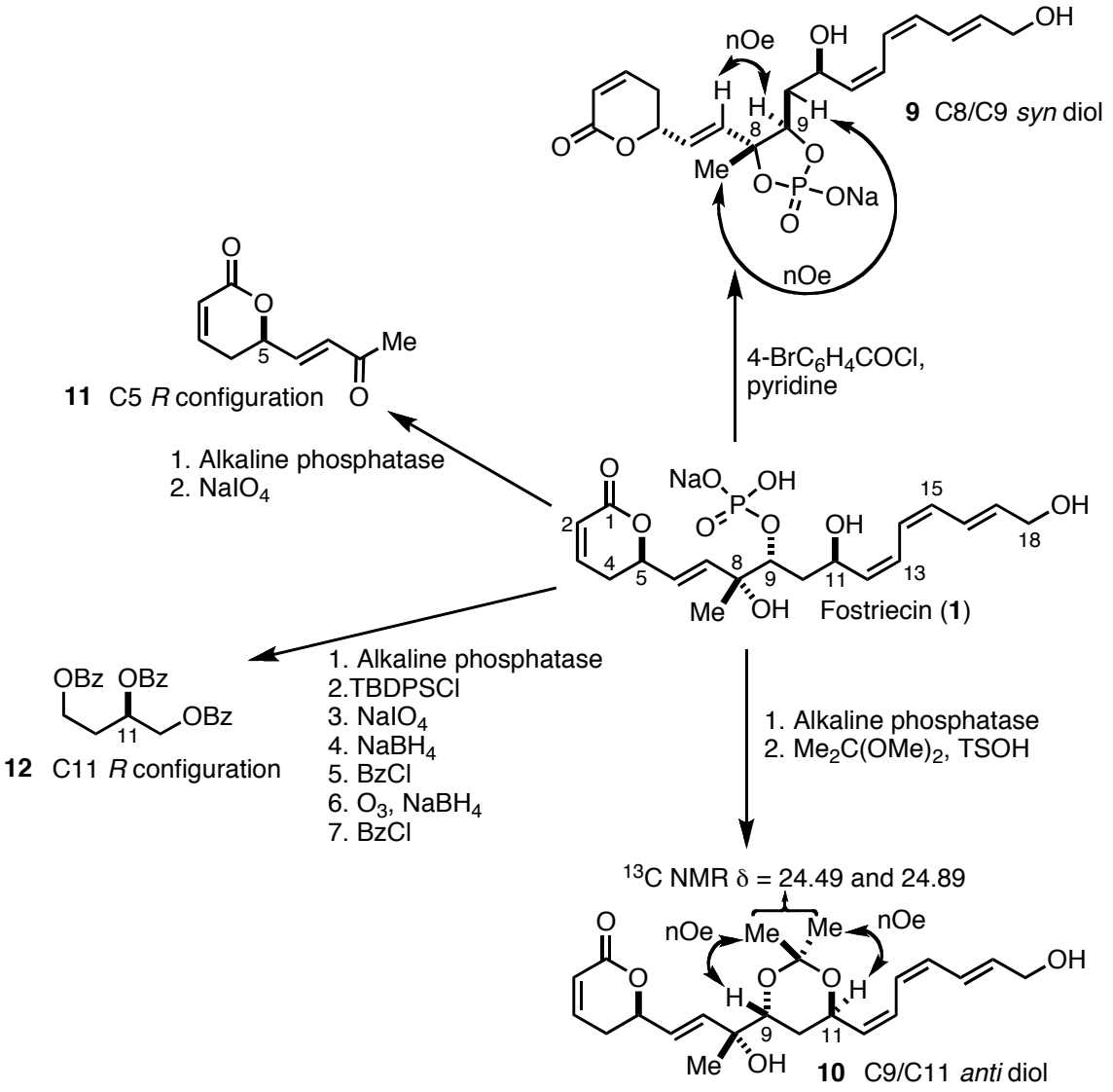


Figure 2. Structures of selective protein phosphatases inhibitors.

The gross structure of fostriecin was proposed in 1983,[63] however, the relative and absolute stereochemistry was determined until 1997 by Boger and coworkers by chemical degradation and extensive spectroscopic analysis.[67] Key intermediates used to establish the absolute stereochemistry included the cyclic phosphate ester **9**, the acetonide **10**, lactone **11** and tribenzoate **12** (scheme 1).



Scheme 1. Elucidation of relative and absolute stereochemistry for fostriecin.

Since the isolation and structural characterization of fostriecin, several other related natural products have been isolated (figure 3) and their biological activities have been explored and compared to that of fostriecin (table 2).[68-71]

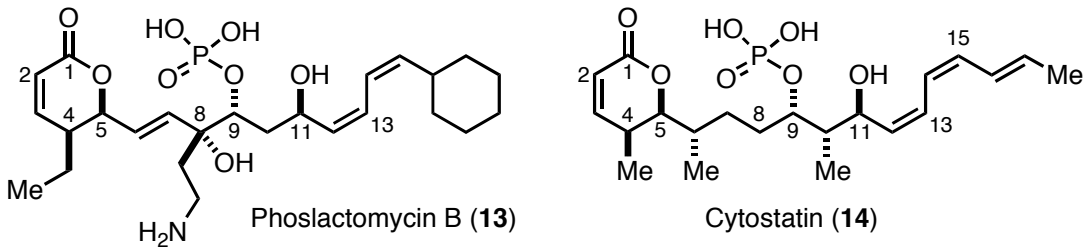


Figure 3. Structures of phoslactomycin B and cytostatin.

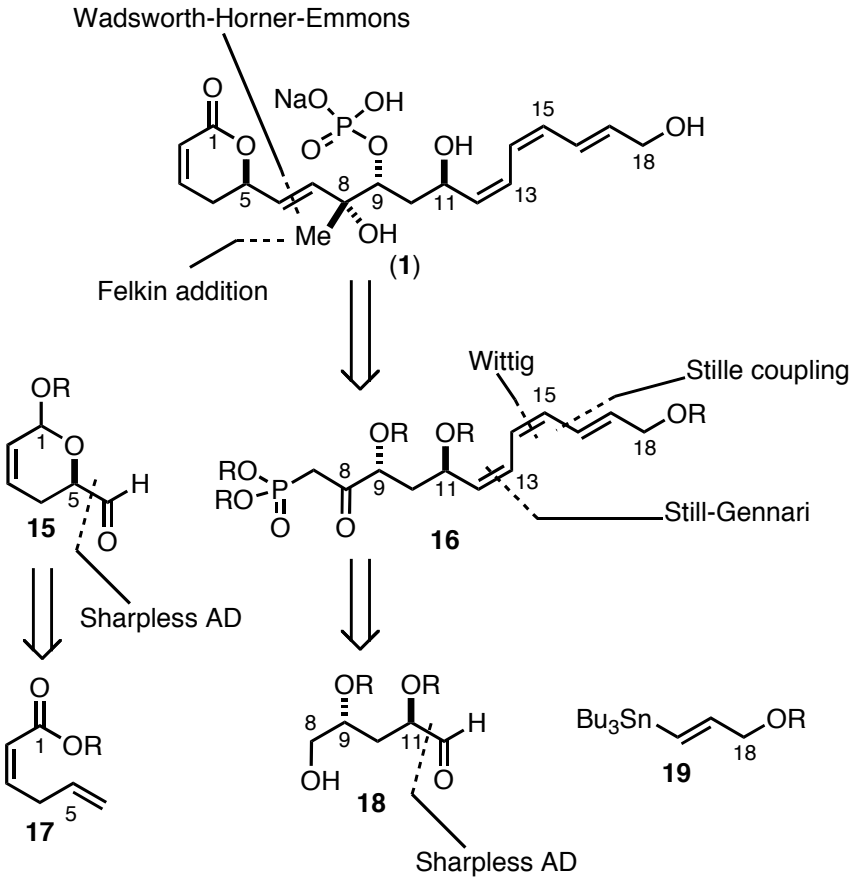
Inhibitor	Protein phosphatase inhibition		Cytotoxicity IC_{50}/L1210
	IC_{50}/PP1	IC_{50}/PP2A	
Fostriecin (**1**)	131 μM	3.2 nM	0.46 μM
Phoslactomycin B (**13**)	>1000 μM	5.8 μM	2 μM
Cytostatin (**14**)	>250 μM	0.21 μM	0.6 μM

Table 2. Inhibition of PP1 and PP2A protein phosphatases by **13** and **14**.

The structural features of fostriecin as well as its impressive biological profile, stimulated an intense activity in the synthetic community towards the synthesis of fostriecin. Boger and coworkers achieved the first total synthesis in 2001,[72] and was followed by total syntheses by Jacobsen,[73] Falck,[74] Imanishi,[75,76] Hatakeyama,[77] Shibasaki,[78,79] and formal syntheses by Cossy,[80] Kobayashi,[81]

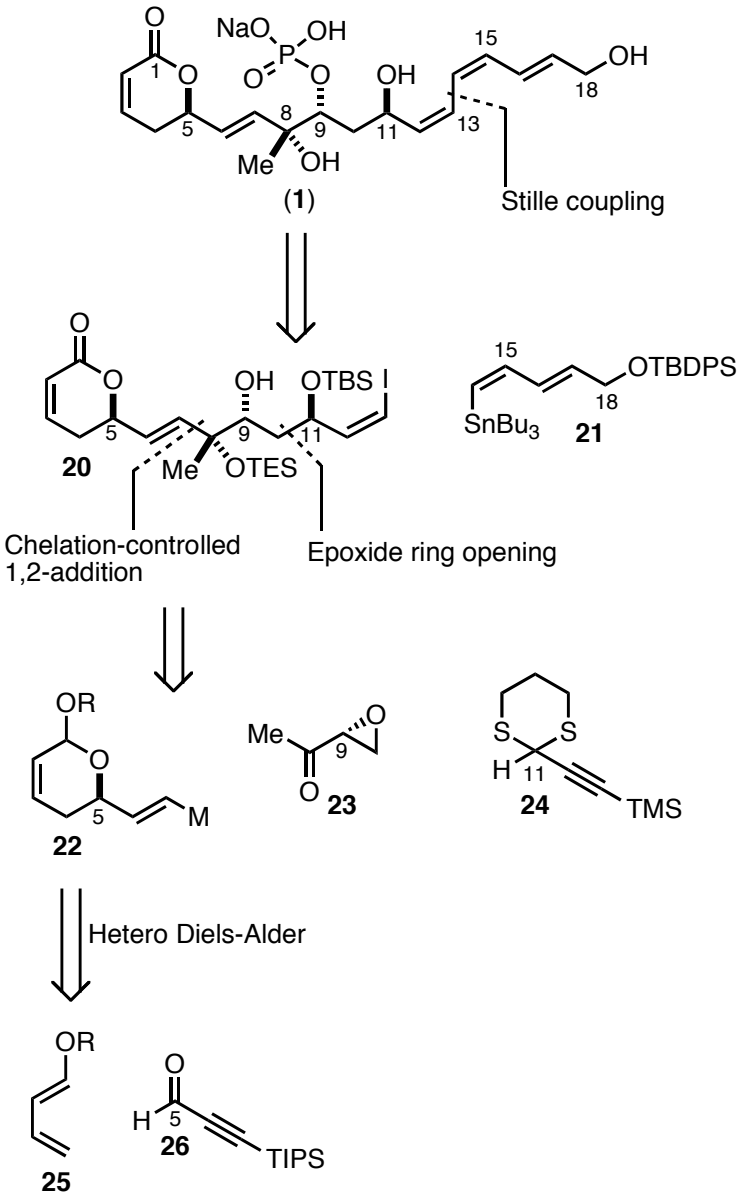
Trost,[82] and Hayashi,[83] and have been extensively reviewed,[65,84] and so only a couple of these synthesis are discussed in this introduction.

The key transformations in Boger's synthesis of fostriecin are illustrated on scheme 2. The synthesis required 27 steps for the longest linear sequence, starting from *D*-glutamic acid (C9 center), and included late-stage introduction of the C9 phosphate and global deprotection, Felkin-Anh addition of addition of the C8-methyl substituent (albeit with 3:1 diastereoselectivity), introduction of the C-terminus lactone via a Wadsworth-Horner-Emmons that installed the C6-C7 *trans* double bond, and stepwise construction of the *Z*,*Z*,*E*-triene.



Scheme 2. Boger's approach to fostriecin.

Jacobsen's approach also featured late-stage introduction of the C9 phosphate and global deprotection,[73] but the *Z*,*Z*,*E*-triene was assembled through a Stille cross-coupling between vinyl iodide **20** and stannane **21** (scheme 3). This disconnection has been used by multiple groups (Imanishi, Hatakeyama, Falck, Trost), and the vinyl iodide **20** has been the common intermediate of Jacobsen, Imanishi, Hatakeyama, Kobayashi and Shibasaki.

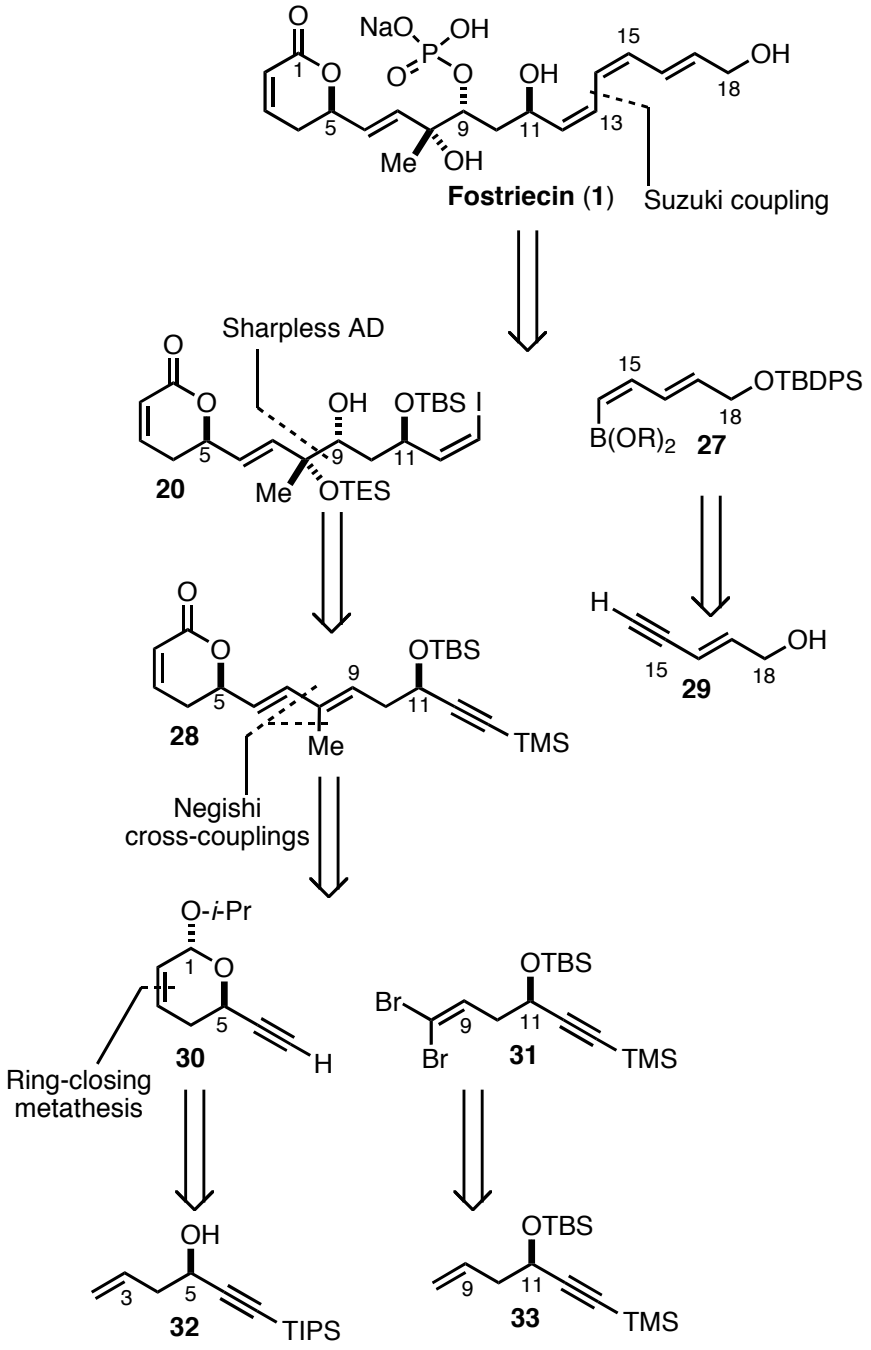


Scheme 3. Jacobsen's approach to fostriecin.

The synthesis of vinyl Iodide **20** featured a epoxide ring opening reaction to form the C10-C11 bond, and a chelation-controlled vinyl addition to ketone **23**. The key building blocks **22** and **23** were prepared by catalytic enantioselective hetero-Diels-Alder and hydrolytic kinetic resolution reactions. The longest linear sequence in the Jacobsen synthesis of fostriecin was 17 steps.

3.2 Synthetic Strategy

The possibility of improvements in the synthetic chemistry directed towards fostriecin and other analogs prompted us to develop a robust, but yet flexible approach to this type of polyketide natural products. Our approch to fostriecin is based on the use of reliable palladium-catalyzed cross-couplings to assemble the carbon skeleton in a concise manner, followed by a regio- and stereoselective dihydroxylation reaction (Scheme 4). Our synthesis also targeted vinyl iodide **20** as the common intermediate for the synthesis of fostriecin, as well as a platform for the synthesis of fostriecin analogs. Our synthetic strategy was designed to be flexible enough to allow the synthesis of any possible diastereomer and to introduce different substituents at C8. Each module was prepared in multigram scale, from readily available starting materials. Modules **27** and **28** were quickly assembled from known enynes **30**[85] and **31**[23,24,60] by ring closing metathesis and oxidative-cleavage - Corey-Fuchs reactions, respectively.

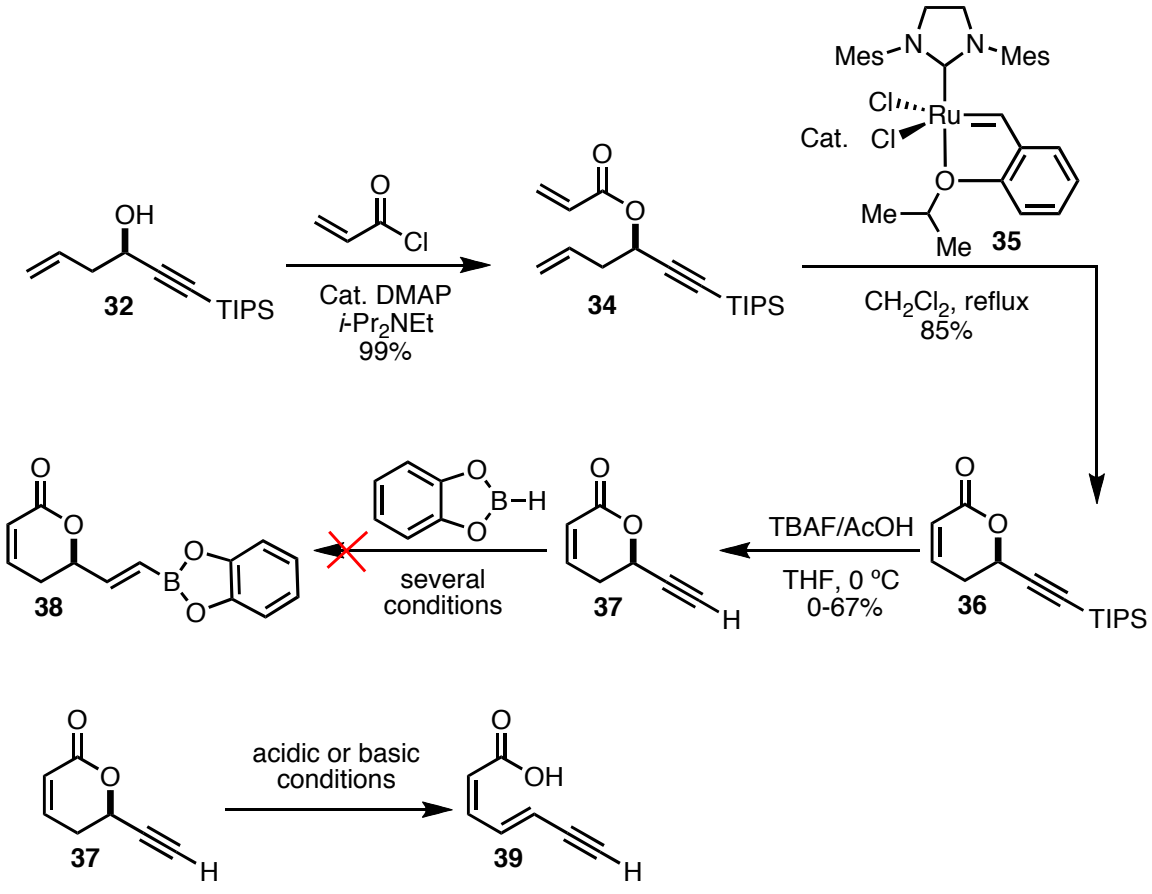


Scheme 4. Retrosynthetic analysis for Fostriecin (**1**).

3.3 Results and Discussion

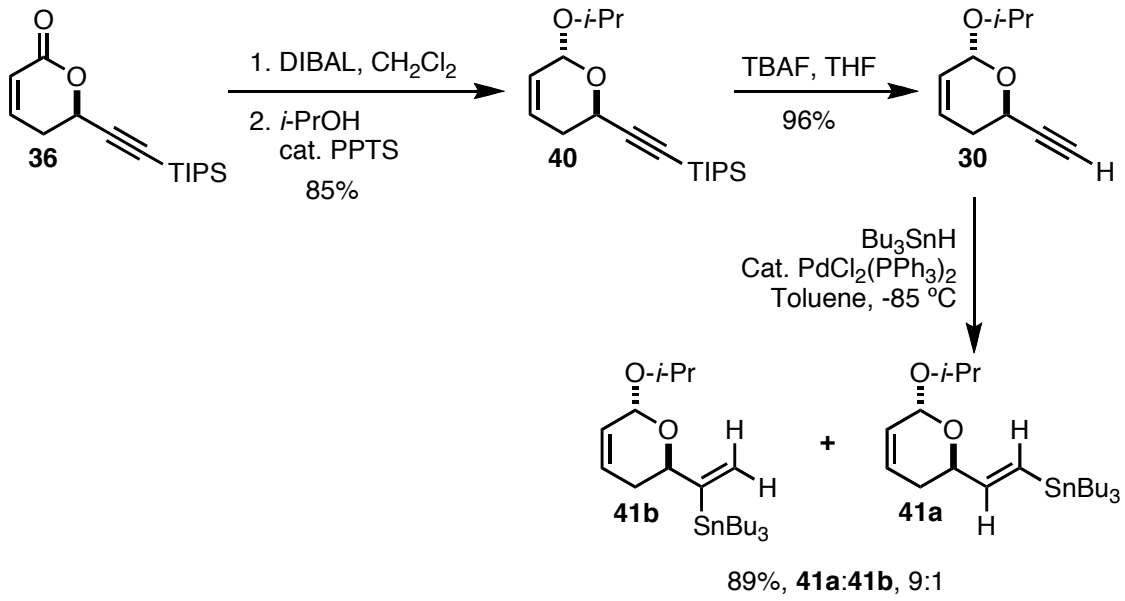
3.3.1 Synthesis of Module 30

Our initial approach was to prepare a boronic ester derivative **36** with the lactone oxidation state, in anticipation for subsequent Suzuki coupling. Thus, acylation of alcohol **32** provided acrylate **34** that underwent ring-closing metathesis to provide the known lactone **36** in 85% yield.[85] The TIPS protecting group was then removed under carefully buffered conditions, to avoid elimination of the lactone to the corresponding acid **39**. All attempts to hydroborate the alkyne **37** failed, and forcing conditions produced only the acid **39** as side product (scheme 5).



Scheme 5. Attempted synthesis of boronic ester **38**.

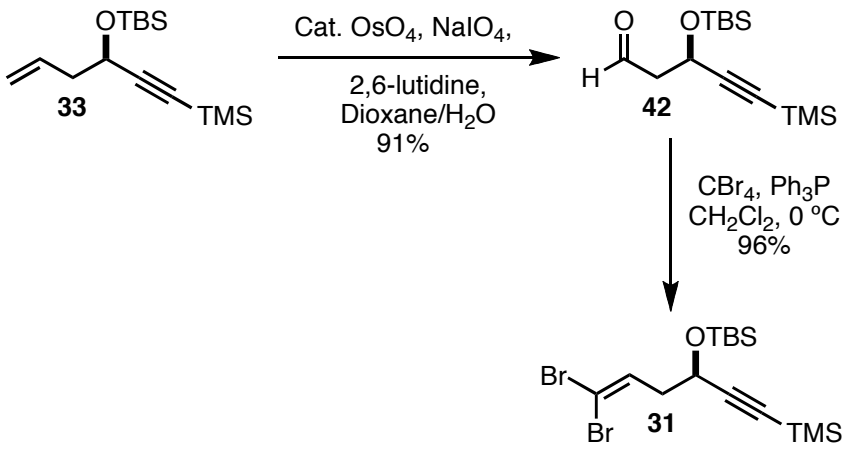
The lack of reactivity of the alkyne was attributed to the electron withdrawing effect of the lactone. In order to increase the reactivity of the alkyne and avoid the elimination side reaction, the lactone **36** was transformed into the corresponding acetal **40**, which after removal of the TIPS protecting group afforded the acetal **30** in excellent yield.[85] The terminal alkyne was then functionalized into the vinyl stannane **42a**, by palladium-catalyzed hydrostannylation (scheme 6). The use of toluene as solvent and low reaction temperature were crucial in order to observe good regioselectivity (9:1).



Scheme 6. Synthesis of acetal **30** and stannane **41a**.

3.3.2 Synthesis of Module 31

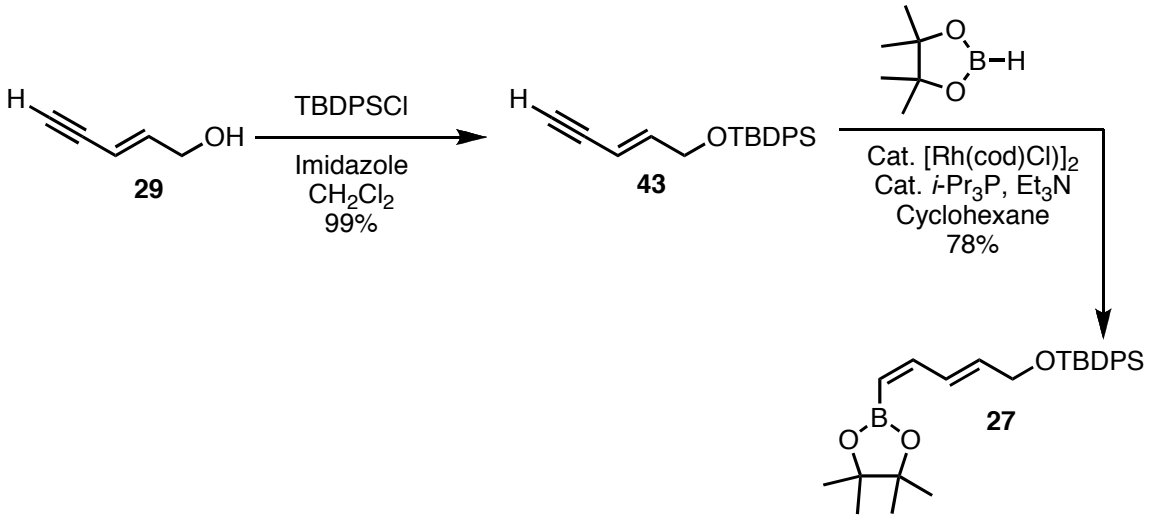
The synthesis of module **31** was achieved in two steps from the known enyne **33**.[23] Oxidative cleavage of the terminal olefin, followed by Corey-Fuchs reaction[86] afforded the desired dibromide **31** in 96 % yield (scheme 7).



Scheme 7. Synthesis of dibromide **31**.

3.3.3 Synthesis of Module 27

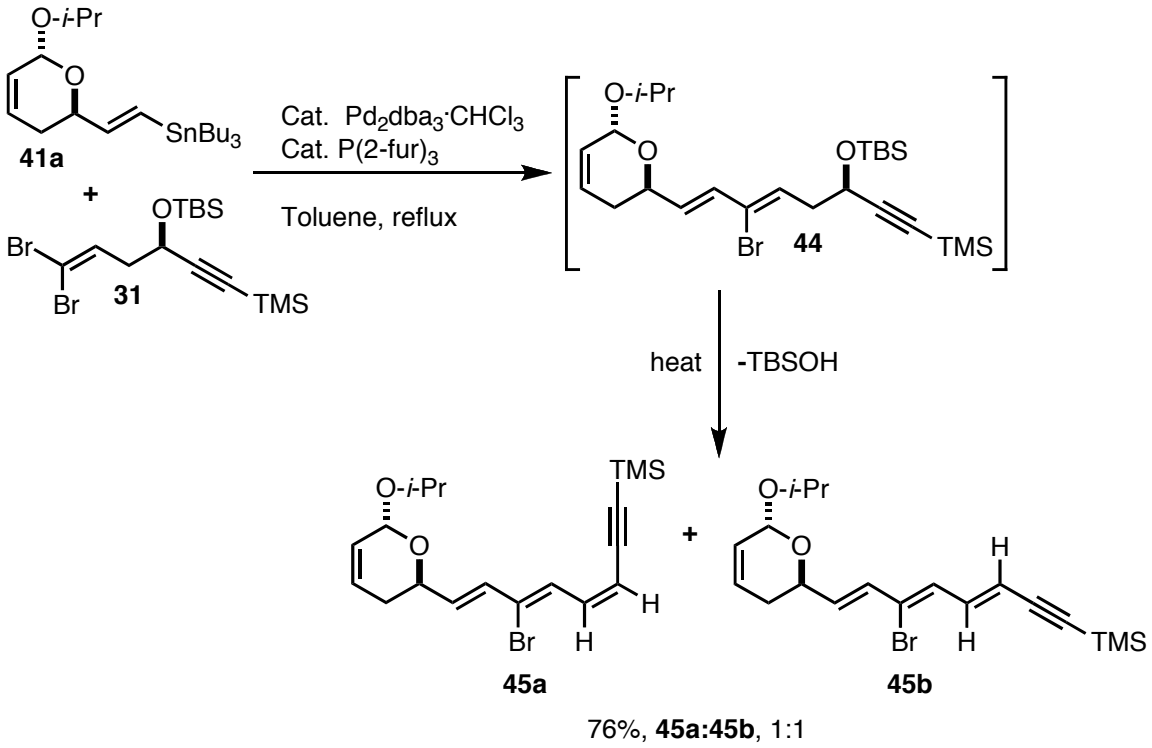
The known boronic ester **27** was synthesized in two steps according to the literature precedent,[74] from commercially available alkynol **29**. TBDPS protection of the alcohol provided silyl ether **43**, which then underwent rhodium-catalyzed *trans*-hydroboration to afford the desired *Z*-boronate selectively (scheme 8).[87]



Scheme 8. Synthesis of boronic ester **27**.

3.3.4 Stille Cross-Coupling of Module 41a and 31

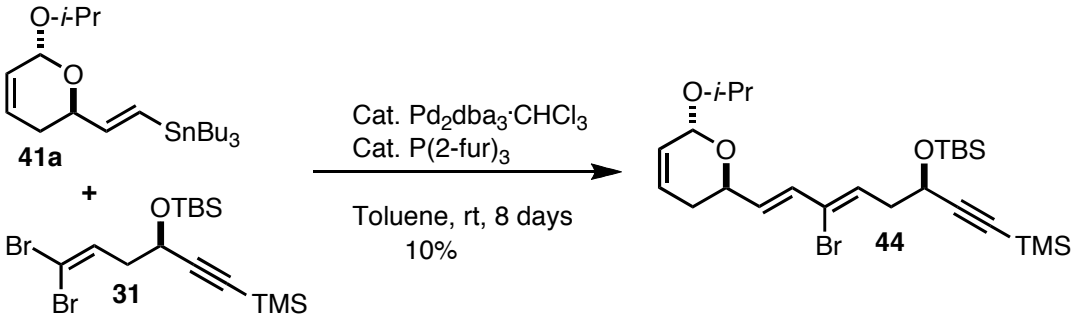
With the modules in hand we began to assemble the carbon skeleton of fostriecin by first coupling modules **41a** and **31** through a palladium-catalyzed Stille reaction.[88] In the event, vinyl stannane **41a** and dibromide **31** were treated with catalytic amounts of $Pd_2dba_3{\cdot}CHCl_3$ and $P(2\text{-fur})_3$ in toluene at reflux (scheme 9). The reaction was completed in just 30 minutes, however, the product of the reaction was ***not*** the expected bromodiene **44**, but rather a 1:1 mixture of trienes **45a-b** in 76% combined yield, which were the products of the elimination of OTBS group in the bromodiene **44**.



Scheme 9. Stille cross-coupling of **31** and **41a**.

Although the outcome of this experiment was not the desired one, it provided us with valuable information. Specifically, we learned that the Stille cross-coupling had proceeded selectively with *mono* alkylation of the dibromide under this reaction conditions, and that the bromodiene product was thermally unstable.

The cross-coupling was then tried at room tempearature, but the reaction was extremely slow, since after 8 days, only 10% of the desired bromodiene was obtained (Scheme 10), and the vinyl stannane was observed to decompose over time.



Scheme 10. Stille cross-coupling of **31** and **41a** at room temperature.

Encouraged by this result, several reaction conditions, catalyst systems and additives were explored, and the results are summarized in the table 3. The best results (61% in 6 days, entry 4) were obtained when $Pd_2dba_3{\cdot}CHCl_3$, $P(2\text{-fur})_3$ and the additive $Ph_2PO_2NBu_4$ salt,[89] in toluene at room temperature were used. The use of copper iodide (entries 6, 7), base (entry 9) or $Pd_2Cl_2(CH_3CN)_2$ (entries 3,10) led only to protiodestannylation (**46**). Interestingly, the use of polar solvents like NMP (entry 8) or the electron-rich caltalyst $Pd(t\text{-}Bu_3P)_2$ (entries 11-13)

produced bisalkyne compound **47**, which is generated by initial oxidative addition on dibromide **31**, followed by β-hydride elimination to produce a bromoalkyne, which was then coupled with the vinyl stannane **41a**.[90]

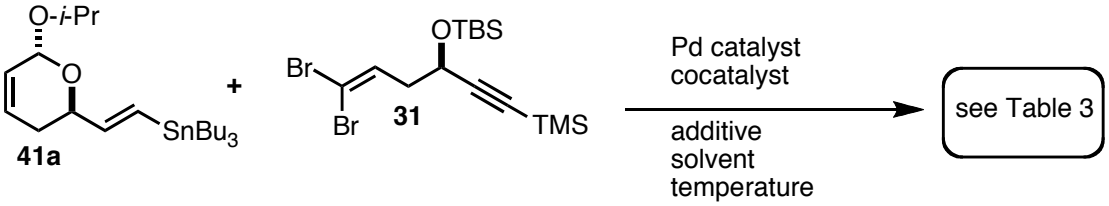
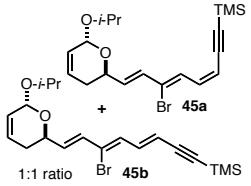
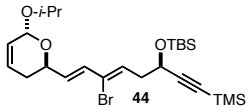
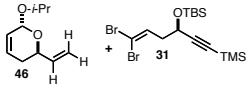
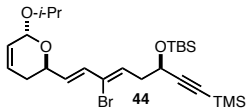
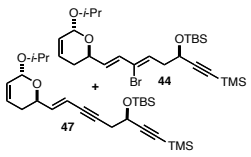
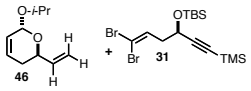
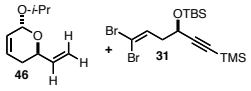
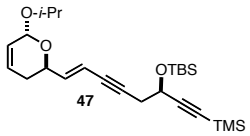
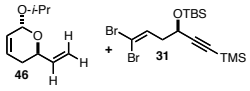
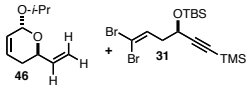
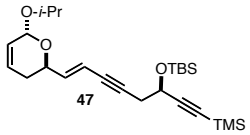
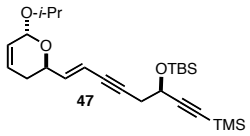
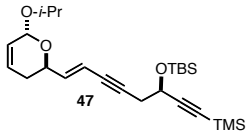


Table 3. Optimization of the Stille cross-coupling.

Entry	Catalyst	Co-catalyst	Additive	Solvent	Temp	Time	Product(s)	Yield
1	$Pd_2dba_3{\cdot}CHCl_3$ $P(2\text{-fur})_3$	none	none	toluene	100 °C	30 min		**76%**
2	$Pd_2dba_3{\cdot}CHCl_3$ $P(2\text{-fur})_3$	none	none	toluene	rt	8 days		**10%**
3	$PdCl_2(CH_3CN)_2$	none	none	DMF	rt	5 days		**N.D.**
4	$Pd_2dba_3{\cdot}CHCl_3$ $P(2\text{-fur})_3$	none	$Ph_2PO_2NBu_4$	toluene	rt	6 days		**61%**
5	$Pd_2dba_3{\cdot}CHCl_3$ $P(2\text{-fur})_3$	none	$Ph_2PO_2NBu_4$	DMF	rt	5 days		**52%**
6	$Pd_2dba_3{\cdot}CHCl_3$ $P(2\text{-fur})_3$	CuI	$Ph_2PO_2NBu_4$	toluene	rt	7 days		**N.D.**
7	$Pd_2dba_3{\cdot}CHCl_3$ $P(2\text{-fur})_3$	CuI	none	toluene	rt	7 days		**N.D.**

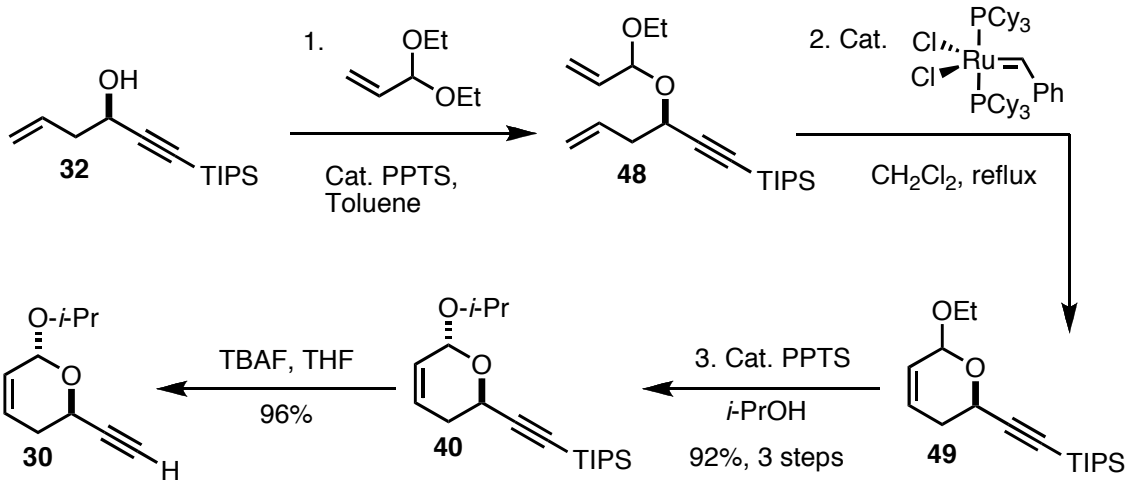
Entry	Catalyst	Co-catalyst	Additive	Solvent	Temp	Time	Product(s)	Yield
8	$Pd_2dba_3{\cdot}CHCl_3$ $P(2\text{-fur})_3$	none	$Ph_2PO_2NBu_4$	NMP	rt	5 days		**48%**
9	$Pd_2dba_3{\cdot}CHCl_3$ *i*-Pr_2NEt	none	$Ph_2PO_2NBu_4$	NMP	rt	6 days		**N.D.**
10	$PdCl_2(CH_3CN)_2$	none	$Ph_2PO_2NBu_4$	NMP	rt	3 days		**N.D.**
11	Pd(*t*-$Bu_3P)_2$	CuTc	$Ph_2PO_2NBu_4$	toluene	rt	8 days		**N.D.**
12	Pd(*t*-$Bu_3P)_2$	none	$Ph_2PO_2NBu_4$	toluene	rt	8 days		**N.D.**
13	Pd(*t*-$Bu_3P)_2$	CuTc	$Ph_2PO_2NBu_4$	NMP	rt	3 days		**N.D.**

Abbreviations: NMP, N-methyl-2-pyrrolidinone; CuTc, Copper(I) thiophene-2-carboxylate, N.D., not determined.

Although entry 4 provided a good yield of the desired bromodiene **44**, it still required 6 days for completion and the purification was somewhat complicated due to the formation of side products. Other alternatives for the coupling of modules **30** and **31** were then explored and the results are described below. Also, during the course of the optimization of the Stille cross-coupling, an improved synthesis of module **30** was developed.

3.3.5 Improved Synthesis of Module 30

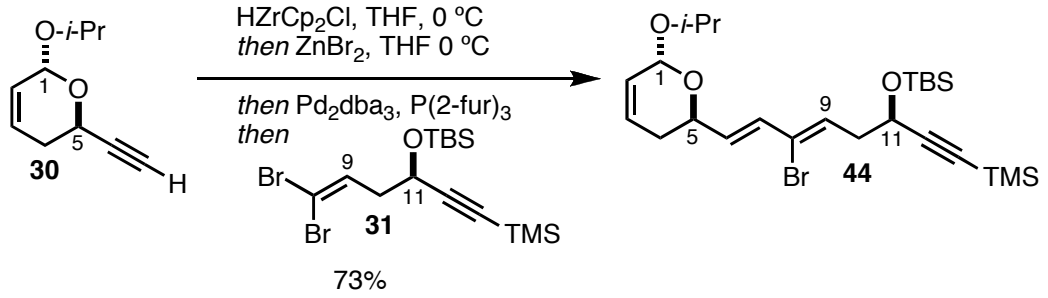
The improved synthesis of module **30** required only 4 steps from alcohol **32** and just two chromatographic purifications. The alcohol **32** was transformed into the mixed acetal **48**, which was subjected to ring-closing metathesis using the first generation Grubbs' catalyst. The crude acetal **49** was then subjected to transacetalization to provide acetal **40** as a single anomer in 92% yield for the three steps. Removal of the TIPS protecting group in **40** provided module **30** in 96% yield.



Scheme 11. Improved synthesis of module **30**.

3.3.6 Negishi Cross-Coupling of Module 30 and 31

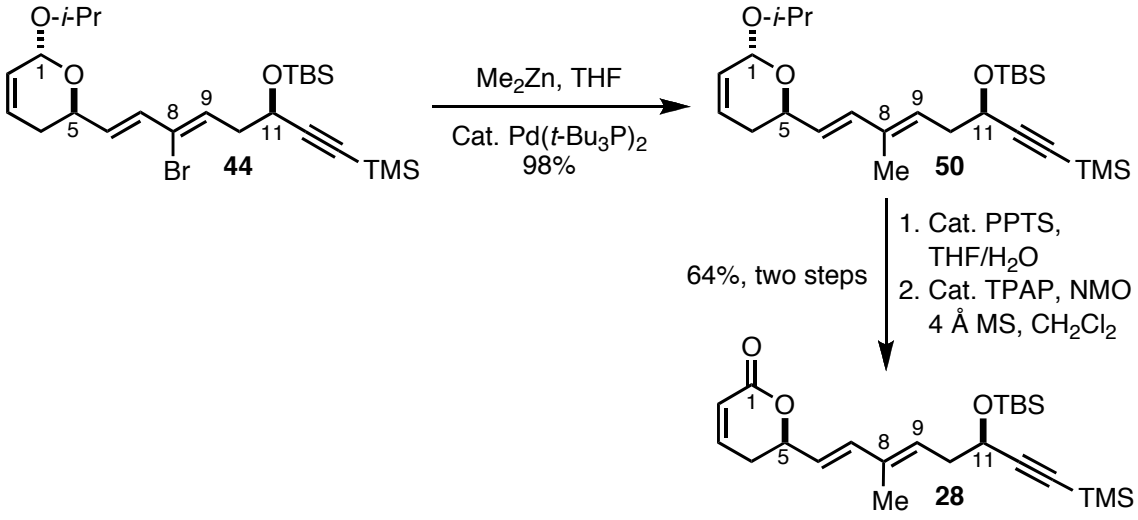
After some experimentation, we found that module **30** could be coupled to module **31** in a single operation via hydrozirconation of the terminal alkyne, followed by transmetallation to the corresponding organozinc species, which then underwent Negishi cross-coupling to afford the desired bromodiene **44** in 73% isolated yield (scheme 12).[85,91]



Scheme 12. Negishi cross-coupling of **30** and **31**.

Some of the advandages that this approach offered over the Stille coupling were complete regioselectivity in the functionalization of the alkyne **30**, shorter reaction times, and better yields.

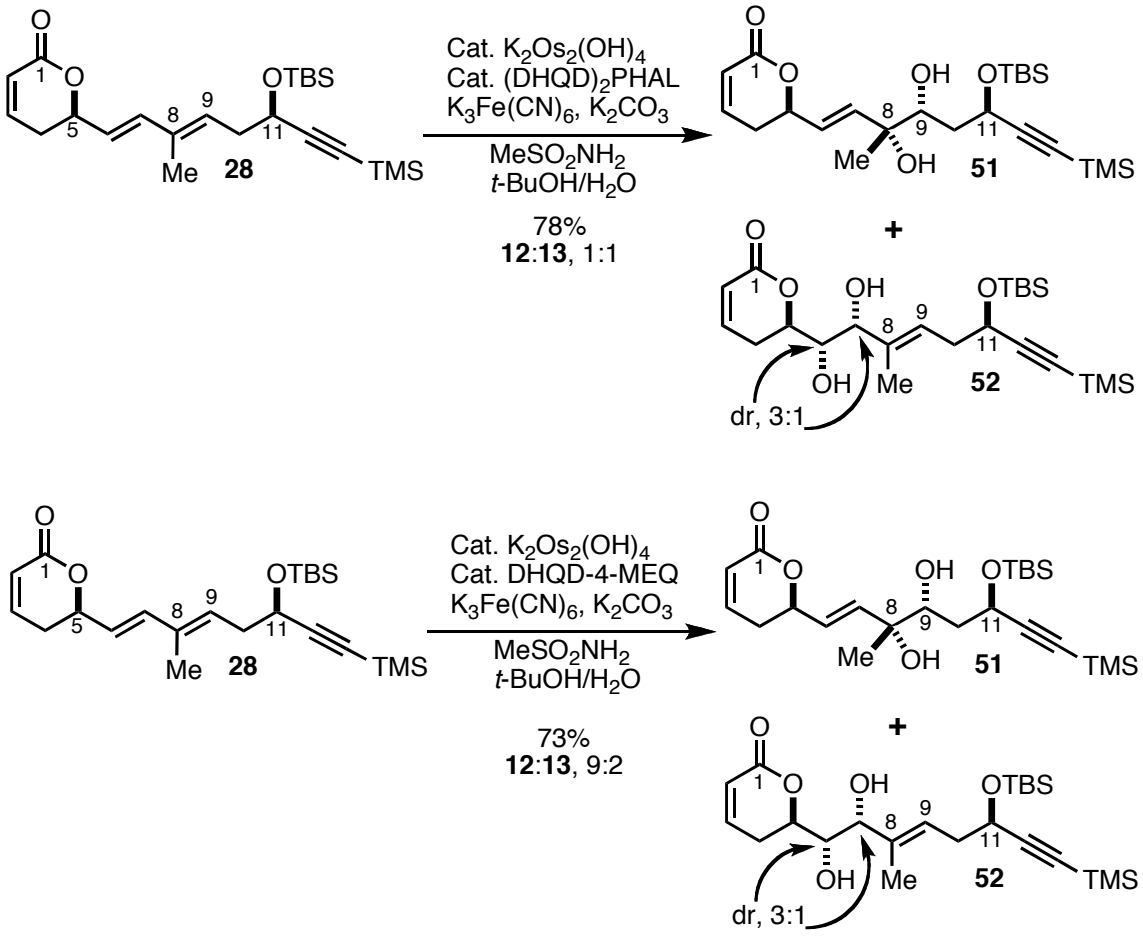
The C8-methyl substituent was then installed by a second Negishi cross-coupling of bromodiene **44** and methylzinc that afforded diene **50** in excellent yield. The oxidation state at C1 was then corrected by mild hydrolysis of the acetal **50**, followed by oxidation of the corresponding lactol to lactone **28** (scheme 13).



Scheme 13. Synthesis of lactone **28**.

3.3.7 Sharpless Asymmetric Dihydroxylation of lactone 28

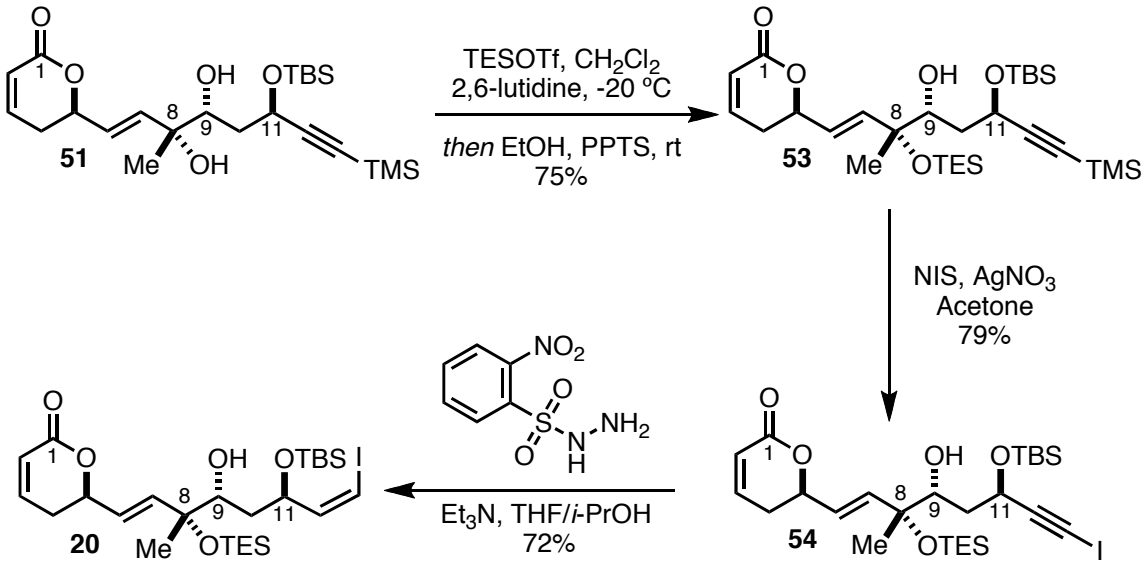
With lactone **28** in hand, we then explored the key Sharpless asymmetric dihydroxylation to install the remaining C8 and C9 chiral centers. Initial studies using $(DHQD)_2PHAL$ as the chiral ligand (AD-mix β) provided a 1:1 mixture of regioisomeric diols **51** and **52** (the dr of **52** was ~3:1,) in 78% combined yield. However, the use of monomeric ligand DHQD-4-MEQ provided a 9:2 mixture in 73% combined yield, favoring the desired regioisomer **51** (Scheme 14).[92]



Scheme 14. Sharpless asymmetric dihydroxylation of lactone **28**.

3.3.8 Synthesis of Vinyl Iodide 20, and Formal Synthesis of Fostriecin

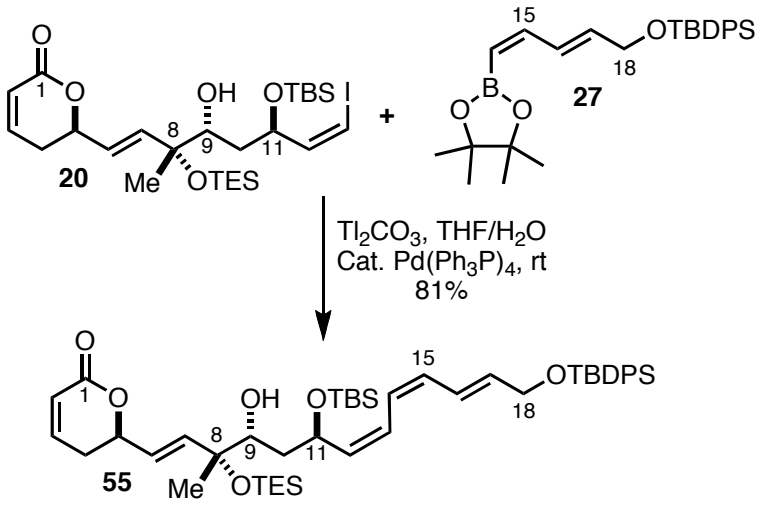
The diol **51** was transformed into the key vinyl iodide intermediate **20** in three steps (scheme 15). Regioselective protection of the tertiary alcohol was achieved by first forming the C8, C9 bis-TES silyl ethers *in situ* and then selectively removing the more labile C9 secondary TES under mild acidic conditions that provided compound **53** in 75% yield. Treatment of TMS-alkyne **53** with NIS and $AgNO_3$ in acetone afforded iodoalkyne **54** in 79% yield. Compound **54** was an intermediate on Jacobsen's synthesis of fostriecin,[73] and thus at this stage, our synthesis of iodoalkyne **54** represented a formal synthesis of fostriecin. Our spectroscopic and physical data for compound **54** agreed with the data reported by Jacobsen. Chemo- and stereoselective reduction of the iodoalkyne **54** provided vinyl iodide **20** in 72% yield, as previously described by Jacobsen.



Scheme 15. Synthesis of Vinyl Iodide **20**.

3.3.9 Suzuki Coupling of Vinyl Iodide 20 and Boronic Ester 27

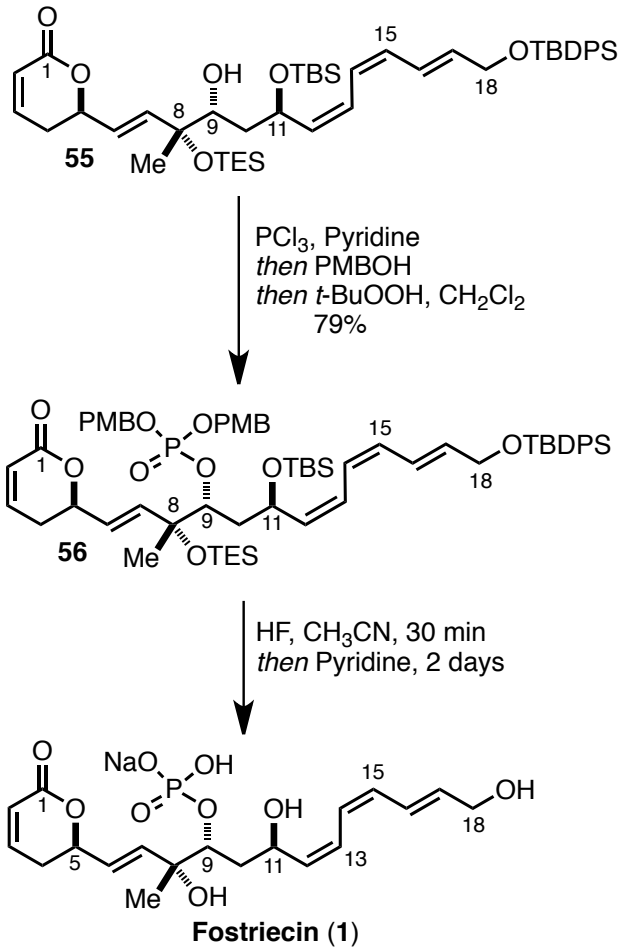
The complete carbon skeleton of fostriecin was assembled by Suzuki cross-coupling of vinyl iodide and boronic ester **27** (scheme 16).[25,74] The best results were obtained when thallium carbonate was used as the base, since other mild bases like silver oxide provided lower yields and slower reaction rates. Under this reaction conditions, the compound **55** was obtained in 81% yield.



Scheme 16. Suzuki coupling of vinyl iodide **20** and boronic ester **27**.

3.3.10 Completion of the Synthesis of Fostriecin

The total synthesis of fostriecin was completed by installing the C9 phosphate group and global deprotection, following the protocol described by Boger and coworkers.[72] Treatment of alcohol **55** with PCl_3 in pyridine was immediately followed by the addition of PMBOH to form the corresponding phosphite, that was then oxidized to the phosphate **56** in 79% overall yield (scheme 17). Global deprotection under mild conditions afforded Fostriecin (**1**).



Scheme 17. Completion of the Synthesis of Fostriecin (**1**).

3.4 Conclusions

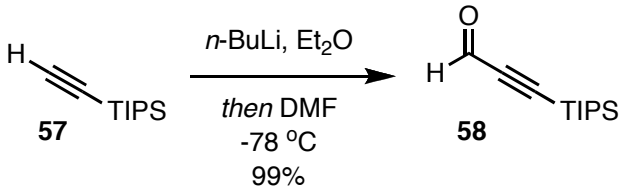
The total synthesis of fostriecin was completed in a concise manner. Our approach used sequential palladium-catalyzed Negishi cross-coupling reactions for the rapid access of an advanced intermediate **28** in gram scale. A regio- and stereoselective Sharpless asymmetric dihydroxylation reaction was applied to introduce the C8 and C9 chiral centers at a late stage. Our synthetic strategy is robust, but yet is flexible enough to allow for the synthesis of virtually any possible diastereomer and to introduce different substituents at C8. We anticipate

that this approach will open the doors to the rapid acces of fostriecin synthetic analogs, in the search for more stable but highly bioactive molecules.

3.5 Experimental Section

General Procedures: All reactions were carried out under an argon atmosphere in oven-dried or flame-dried glassware using dry solvents under anhydrous conditions. All anhydrous solvents were dried with activated molecular sieves (3Å or 4Å beads) purchased from Aldrich and tested for trace water content with a Coulometric KF titrator from Denver Instruments. All solvents used for extraction and chromatography procedures were used as received from commercial suppliers without further purification. All reagents were purchased from Aldrich, GFS Chemicals or Strem Chemicals. ^{1}H NMR and ^{13}C NMR spectra were measured in deuterated chloroform ($CDCl_3$) or deuterium oxide (D_2O) on Varian Inova 600 or Unity 600 NMR spectrometers. All proton NMR spectra were recorded at 600 MHz and were referenced with residual chloroform (7.27 ppm) and reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All carbon NMR spectra were measured at 150 MHz and were referenced with residual chloroform (77.23 ppm) and reported in parts per million (ppm). All infrared spectra were recorded on sodium chloride discs on a Mattson Genesis II FT-IR. Abbreviations for signal intensities are as follows: s, strong; m, medium; w, weak, br, broad. High resolution mass spectra (FAB or ESI) were recorded on a VG 70-S Nier Johason Mass spectrometer or a Thermo Finnigan LTQ FT spectrometer.

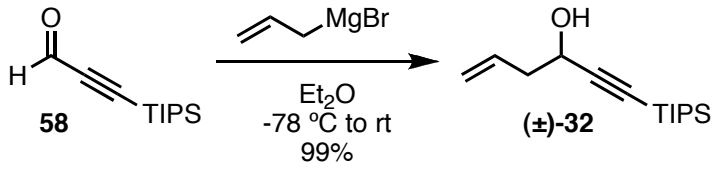
Optical rotations were measured at 25 ºC (concentration in g/100 mL) using a 10 cm cell with a Perkin-Elmer 341 polarimeter. Analytical Thin Layer Chromatography (TLC) was performed on precoated glass backed plates purchased from Whatman (silica gel $60F_{254}$; 0.25mm thickness). Flash chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from EM Science.



3-(Triisopropylsilyl)-1-propynal (58): To a stirred solution of TIPS-acetylene **57** (41.1 g, 225 mmol) in ether (200 mL) at 0 ºC was added *n*-BuLi (100 mL, 2.5 M in hexane, 250 mmol) dropwise over 30 minutes. The reaction was stirred one hour at 0 ºC and then cannulated into a solution of freshly distilled DMF (52.2 mL, 675 mmol) in Et_2O (200 mL) at -78 ºC over 30 minutes. The reaction mixture was stirred at -78 ºC for one hour, then it was allowed to warm up slowly to 0 ºC over a period of one hour. The reaction was quenched at 0 ºC by pouring it into a solution of 5% H_2SO_4 (500 mL) at 0 ºC to attain a slightly acidic pH. After stirring one hour, the organic phase was separated and the aqueous phase was extracted exhaustively with ether. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was purified by flash chromatography using a short silica gel column and pentane and

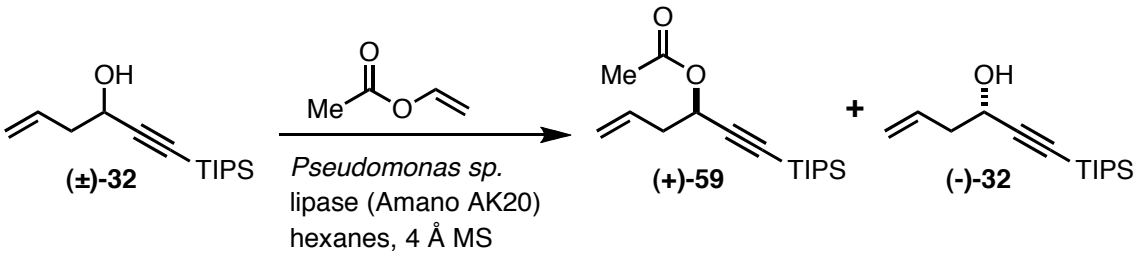
ether (90:10) as eluent to afford 3-(triisopropylsilyl)-1-propynal (**58**) as a colorless oil (47.1 g, 99% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.21 (s, 1H), 1.17-1.11 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 176.65, 104.65, 100.75, 18.57, 11.11. **FT-IR** (neat, cm^{-1}): 2945 (s), 2892 (s), 2868 (s), 2731 (w), 2149 (m), 1669 (s), 1463 (m), 1385 (m), 999 (s), 882 (m). **HRMS** (ESI+): Calcd. for $C_{12}H_{23}OSi$ ($[M+H]^+$), 211.1518. Found: 211.1512.



1-(Triisopropylsilyl)hex-5-en-1-yn-3-ol (±)-(32): To a stirred solution of aldehyde **58** (47 g, 223.4 mmol) in THF (200 mL) at -78 ºC was added allylmagnesiumbromide (235 mL, 1.0 M in ether, 235 mmol) dropwise over 30 minutes. After the addition was completed, the reaction mixture was allowed to warm slowly to 0 ºC and stirred for two hours. The reaction was quenched at 0 ºC with a saturated aqueous solution of NH_4Cl (200 mL), and then warmed to room temperature. The organic phase was separated and the aqueous phase was extracted with ether (2 X 200 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was filtered through a short silica gel column using hexane and ether (80:20) as eluent to yield the desired alcohol **(±)-32** as a light yellow oil (55.80 g, 99% yield).

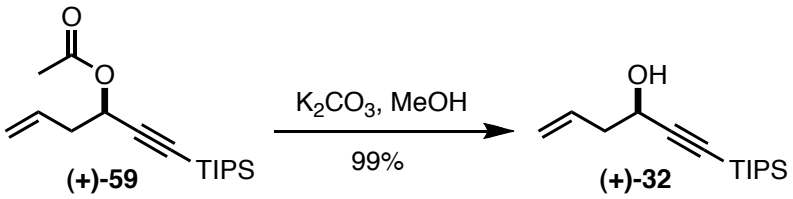
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.94-5.87 (m, 1H), 5.21-5.17 (m, 2H), 4.45 (dd, *J*= 12.0, 6.0 Hz, 1H), 2.53-2.45 (m, 2H), 2.00 (d, *J*= 6.0 Hz, 1H), 1.08-1.06 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 133.17, 119.12, 108.19, 86.12, 62.25, 42.56, 18.76, 11.32. **FT-IR** (neat, cm^{-1}): 3326 (br, m), 3079 (w), 2942 (s), 2892 (s), 2865 (s), 2169 (w), 1663 (w), 1463 (s), 1382 (m), 1334 (w), 1245 (w), 1120 (w),1029 (s), 995 (s), 968 (w), 917 (m), 883 (s), 676 (s). **HRMS** (ESI+): Calcd. for $C_{15}H_{29}OSi$ ($[M+H]^+$), 253.1988. Found: 253.1986.



Enzymatic kinetic resolution of 1-(Triisopropylsilyl)hex-5-en-1-yn-3-ol (±)-(32): To a solution of alcohol **(±)-32** (55 g, 217.89 mmol) in dry hexanes (1000 mL), 4 Å molecular sieves (55 g, powder), *Pseudomonas sp.* lipase Amano AK 20 (20 g) and vinyl acetate (40 mL, 433.96 mmol) were added. The reaction was stirred at room temperature and the reaction was monitored by 1H NMR analysis. After 72 hours, the reaction mixture was filtered through a glass filter and concentrated. The residue was purified by flash chromatography using hexanes and ether as eluents (90:10) to provide acetate ester (*R*)-**59** (30.82 g, 48% yield) and (*S*)-1-(triisopropylsilyl)hex-5-en-1-yn-3-ol (*S*)-**32** (26.74 g, 49% yield, ≥95:5 er).

Data for **(*R*)-1-(triisopropylsilyl)hex-5-en-1-yn-3-yl acetate (59): ^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.86-5.80 (m, 1H), 5.44 (t, *J*= 6.0 Hz, 1H), 5.17-5.11 (m, 2H), 2.52 (t, *J*= 7.2 Hz, 2H), 2.06 (s, 3H), 1.08-1.04 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 169.89, 132.47, 118.78, 104.35, 87.22, 63.88, 39.68, 21.15, 18.71, 11.27. **FT-IR** (neat, cm^{-1}): 3081 (w), 2944 (s), 2892 (m), 2865 (s), 2177 (w), 1747 (s), 1643 (w), 1463 (m), 1371 (m), 1344 (w), 1228 (s), 1120 (w), 1070 (m), 1020 (s), 995 (m), 962 (w), 919 (m), 883 (m), 786 (w), 676 (m). **HRMS** (ESI+): Calcd. for $C_{17}H_{31}O_2Si$ ($[M+H]^+$), 295.2093. Found: 295.2097. **$[\alpha]_D^{25}$** +85.8 (c 1.6, $CHCl_3$).

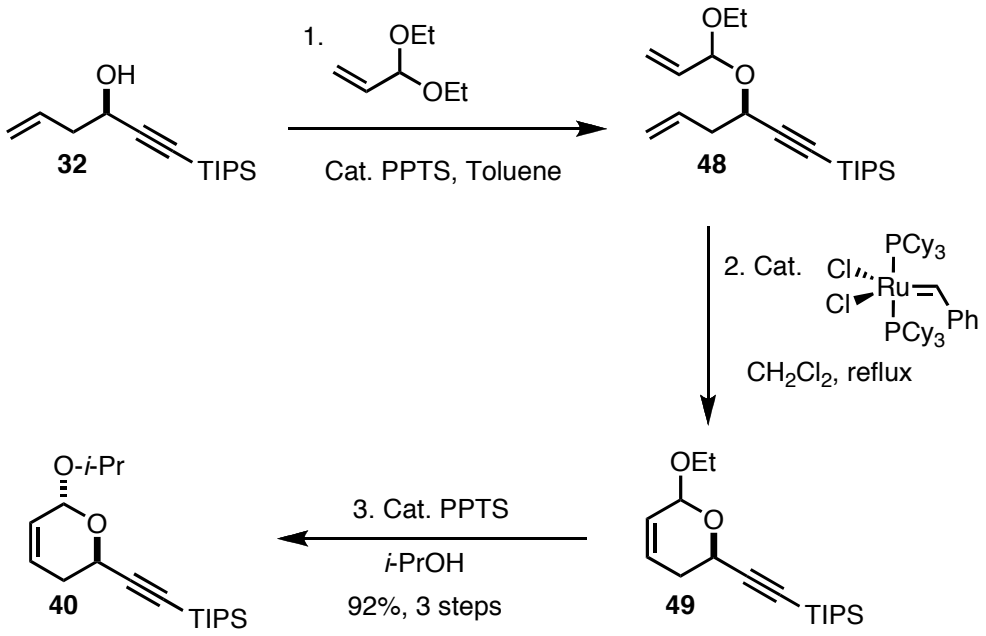
Data for **(*S*)-1-(triisopropylsilyl)hex-5-en-1-yn-3-ol (32): ^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.94-5.87 (m, 1H), 5.21-5.17 (m, 2H), 4.45 (dd, *J*= 12.0, 6.0 Hz, 1H), 2.53-2.45 (m, 2H), 2.00 (d, *J*= 6.0 Hz, 1H), 1.08-1.06 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 133.17, 119.12, 108.19, 86.12, 62.25, 42.56, 18.76, 11.32. **FT-IR** (neat, cm^{-1}): 3326 (br, m), 3079 (w), 2942 (s), 2892 (s), 2865 (s), 2169 (w), 1663 (w), 1463 (s), 1382 (m), 1334 (w), 1245 (w), 1120 (w),1029 (s), 995 (s), 968 (w), 917 (m), 883 (s), 676 (s). **HRMS** (ESI+): Calcd. for $C_{15}H_{29}OSi$ ($[M+H]^+$), 253.1988. Found: 253.1986. **$[\alpha]_D^{25}$** -27.1 (c 1.2, $CHCl_3$).



(*R*)-1-(Triisopropylsilyl)hex-5-en-1-yn-3-ol (32): To a solution of the acetate ester **59** (27 g, 91.68 mmol) in methanol (250 mL), potassium carbonate (6.34 g,

45.84 mmol) was added. The reaction mixture was stirred at room temperature for six hours, and then diluted with water (250 mL) and ether (250 mL). The aqueous phase was extracted with ether (2 X 250 mL), the organic fractions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was filtered through a pad of silica gel using hexanes as eluent, then concentrated under reduced pressure and then dried azeotropically with toluene, to yield the desired alcohol **(+)-59** as a light yellow oil (23.1 g, 99% yield, ≥95:5 er).

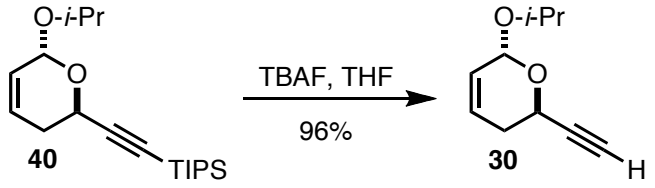
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.94-5.87 (m, 1H), 5.21-5.17 (m, 2H), 4.45 (dd, *J*= 12.0, 6.0 Hz, 1H), 2.53-2.45 (m, 2H), 2.00 (d, *J*= 6.0 Hz, 1H), 1.08-1.06 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 133.17, 119.12, 108.19, 86.12, 62.25, 42.56, 18.76, 11.32. **FT-IR** (neat, cm^{-1}): 3326 (br, m), 3079 (w), 2942 (s), 2892 (s), 2865 (s), 2169 (w), 1663 (w), 1463 (s), 1382 (m), 1334 (w), 1245 (w), 1120 (w),1029 (s), 995 (s), 968 (w), 917 (m), 883 (s), 676 (s). **HRMS** (ESI+): Calcd. for $C_{15}H_{29}OSi$ ($[M+H]^+$), 253.1988. Found: 253.1986. **$[\alpha]_D^{25}$** +27.4 (c 1.0, $CHCl_3$).



(((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)ethynyl)triisopropylsilane (40): The alcohol **32** (10 g, 39.62 mmol) was dissolved in dry toluene (120 mL) and then the acrolein diethyl acetal (30.3 g, 198.08 mmol) was added, followed by the PPTS (0.9955 g, 3.96 mmol). The reaction mixture was stirred at room temperature for one hour and then the ethanol by product was removed azeotropically by rotating the reaction mixture in a rotary evaporator (~ 80 mbar) at 30 ºC. The reaction was monitored by TLC , and the volume of the solution was kept constant by occasional addition of dry toluene. After completion of the reaction (~ two hours), the mixture was diluted with ether (150 mL) , washed with a saturated aqueous solution of $NaHCO_3$ (2 X 150 mL), and water (2 X 150 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residual oil was then dried azeotropically with toluene, and then dissolved in dry CH_2Cl_2 (400 mL), and degassed. The solution was

heated to reflux under argon and then the Grubbs I catalyst (0.978 g, 1.1884 mmol) was added in two portions (489 mg at the beginning, and 489 mg after one hour, each in 10 mL of CH_2Cl_2) via cannula. The reaction mixture was refluxed for four hours after the addition of the last portion of the catalyst. After cooling to room temperature, air was bubbled through the solution for one hour to quench the catalyst. The solution was concentrated and then the residue was redissolved in a mixture of hexanes and ether (8:2, 50 mL) and then filtered over a short pad of silica gel (which was pretreated with 2.5% Et_3N) and then concentrated under reduced pressure. The residue was dissolved in *i*-PrOH (200 mL) and then the PPTS was added (0.9955 g, 3.96 mmol). The reaction mixture was stirred at room temperature for 18 hours and then the solution was concentrated under reduced pressure. The residue was redissolved in ether (150 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 X 150 mL), and water (2 X 150 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using silica gel (which was pretreated with 2.5% Et_3N in hexanes) and hexanes and ether as eluents (90:10), to afford the desired acetal **40** as a light yellow oil as a single anomer (11.8 g, 92% yield for the three steps). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.95 (dddd, *J*= 9.6, 5.4, 1.8, 1.2 Hz, 1H), 5.70 (dddd, *J*= 9.6, 3.0, 2.4, 1.8 Hz, 1H), 5.14 (bs, 1H), 4.72 (dd, *J*= 10.8, 3.6 Hz, 1H), 4.04 (sept, *J*= 6.0 Hz, 1H), 2.40 (dddd, *J*= 18.0, 10.8, 4.8, 2.4 Hz, 1H), 2.23 (dddd, *J*= 18.0, 5.4, 3.6, 1.2 Hz, 1H), 1.28 (d, *J*= 6.0 Hz, 3H), 1.18 (d, *J*= 6.0 Hz, 3H), 1.09-1.06 (m, 21H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 128.08, 126.19, 106.75,

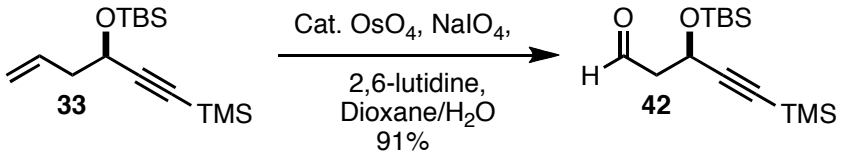
93.47, 85.53, 70.33, 57.87, 32.00, 23.95, 22.39, 18.78, 11.33. **FT-IR** (neat, cm^{-1}): 3043 (w), 2960 (m), 2942 (s), 2894 (m), 2865 (s), 1463 (m), 1382 (w), 1367 (w), 1315 (w), 1180 (m), 1126 (m), 1097 (m), 1058 (m), 1025 (s), 998 (s), 883 (m). **HRMS** (ESI+): Calcd. for $C_{19}H_{35}O_2Si$ ($[M+H]^+$), 323.2406. Found: 323.2405. **$[\alpha]_D^{25}$** +74.0 (c 0.2, $CHCl_3$).



(2*R*,6*R*)-2-ethynyl-6-isopropoxy-3,6-dihydro-2H-pyran (30): The acetal **40** (10.5 g, 32.55 mmol) was dissolved in THF (100 mL) and the solution was cooled to 0 ºC. The TBAF (39.06 mL, 1.0 M in THF, 39.06 mmol) was then added dropwise via syringe. The reaction mixture was stirred at 0 ºC and then diluted with water (150 mL) and ether (150 mL). The aqueous phase was extracted with ether (2 X 150 mL), the organic fractions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using silica gel (which was pretreated with 2.5% Et_3N in hexanes) and pentane and ether as eluents (90:10), to afford the desired acetal **30** as a colorless volatile oil (5.2 g, 96% yield).

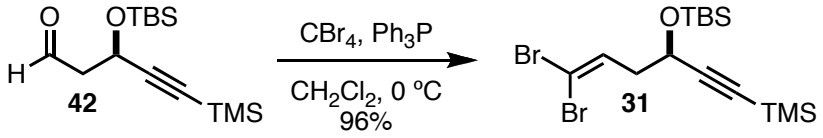
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.94 (dd, *J*= 9.6, 6.0 Hz, 1H), 5.68 (ddd, *J*= 9.6, 3.0, 3.0 Hz, 1H), 5.10 (bs, 1H), 4.66 (ddd, *J*= 11.4, 3.0, 2.4 Hz, 1H), 4.03 (sept, *J*= 6.0 Hz, 1H), 2.45 (d, *J*= 2.4 Hz, 1H), 2.39 (ddd, *J*= 18.0, 11.4, 1.8 Hz, 1H), 2.19 (ddd, *J*= 18.0, 4.8, 4.8 Hz, 1H), 1.25 (d, *J*= 6.0 Hz, 3H), 1.16 (d, *J*= 6.0 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 127.69, 126.09, 93.06, 82.89, 72.83, 70.06, 57.08, 31.39, 23.95, 22.09. **FT-IR** (neat, cm^{-1}): 3293 (m), 3046 (w), 2971 (s), 2929 (m), 2877 (m), 1463 (w), 1402 (m), 1380 (m), 1317 (m), 1182 (m), 1126 (m), 1099 (m), 1052 (m), 1024 (s), 1000 (s), 966 (m), 944 (m), 858 (m), 719 (m). **HRMS** (ESI+): Calcd. for $C_{10}H_{15}O_2$ ($[M+H]^+$), 167.1072. Found: 167.1065. **$[\alpha]_D^{25}$** +114.5 (c 0.8, $CHCl_3$); {lit.[85] **30 $[\alpha]_D$** +83.8 (c 0.14, $CHCl_3$)}.



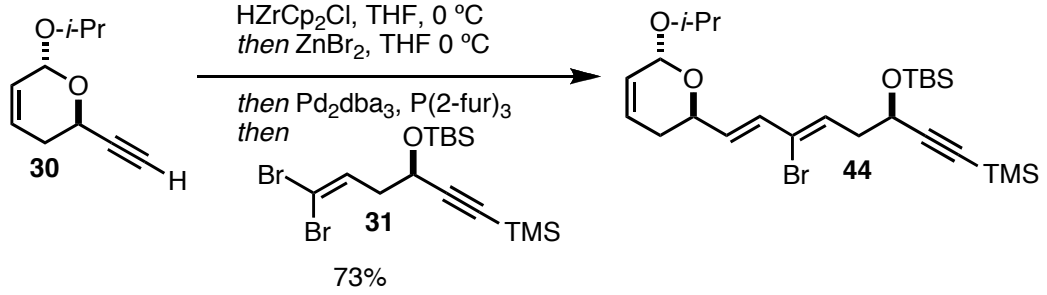
(*R*)-3-(*tert*-butyldimethylsilyloxy)-5-(trimethylsilyl)pent-4-ynal (42): To a solution of the alkene **33** (25 g, 88.47 mmol), in a mixture of dioxane (900 mL) and water (300 mL), was added 2,6-lutidine (20.61 mL, 176.95 mmol) and OsO_4 (250 mg, 0.88 mmol). The solution was cooled to 0 ºC and then $NaIO_4$ (75.7 g, 353.9 mmol) was added in small portions over a period of 5 minutes while keeping the temperature at 0 ºC. After the addition was completed, the reaction mixture was warmed to room temperature and stirred vigorously for 45 minutes. The reaction mixture was then diluted with dichloromethane (500 mL) and water (200 mL). The aqueous fraction extracted with dichloromethane (3 X 500 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes and ether as eluents (90:10), to provide aldehyde **42** as a color less oil (22.90 g, 91% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 9.80 (t, *J*= 2.4 Hz, 1H), 4.85 (dd, *J*= 7.2, 4.8 Hz, 1H), 2.76 (ddd, *J*= 16.8, 7.2, 2.4 Hz, 1H), 2.65 (ddd, *J*= 16.8, 4.8, 2.4 Hz, 1H), 0.88 (s, 9H), 0.16 (s, 9H), 0.16 (s, 3H), 0.13 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 200.55, 105.61, 90.74, 58.86, 51.39, 25.85, 18.29, -0.13, -4.32, -4.89. **FT-IR** (neat, cm^{-1}): 2958 (s), 2931 (s), 2898 (m), 2858 (s), 2719 (w), 2175 (w), 1729 (s), 1471 (m), 1463 (m), 1405 (w), 1390 (w), 1361 (w), 1336 (m), 1251 (s), 1209 (w), 1097 (s), 1051 (m), 995 (m), 842 (s), 779 (m), 761 (m). **HRMS** (ESI+): Calcd. for $C_{14}H_{29}O_2Si_2$ ($[M+H]^+$), 285.1706. Found: 285.1702. **$[\alpha]_D^{25}$** +70.3 (c 2.0, $CHCl_3$).



(*R*)-*tert*-butyl(6,6-dibromo-1-(trimethylsilyl)hex-5-en-1-yn-3-yloxy) dimethylsilane (31): Ph_3P (55.31 g, 210.87 mmol) was dissolved in CH_2Cl_2 (530 mL) and the solution was cooled to 0 ºC. The CBr_4 (34.96 g, 105.43 mmol) was then added and the mixture was stirred for five minutes at 0 ºC. The aldehyde **42** (15.0 g, 52.72 mmol) was then added dropwise dissolved in dry CH_2Cl_2 (53 mL). The reaction mixture was stirred for five minutes at 0 ºC after the addition was completed and then diluted carefully with a saturated aqueous solution of $NaHCO_3$ (500 mL). The aqueous fraction was extracted with dichloromethane (2 X 500 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using hexanes and ether as eluents (90:10), to provide dibromide **31** as a color less oil (22.31 g, 96% yield).

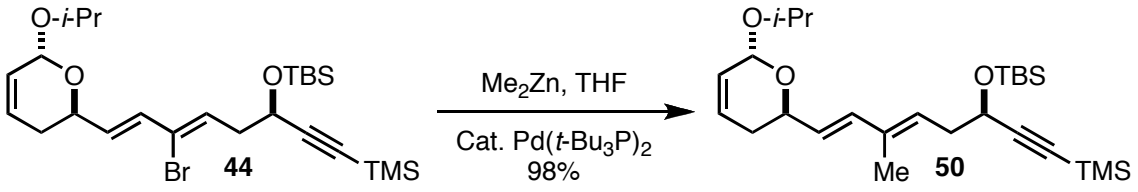
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.50 (t, *J*= 7.2 Hz, 1H), 4.43 (t, *J*= 6.0, Hz, 1H), 2.49-2.45 (m, 2H), 0.91 (s, 9H), 0.18 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 134.63, 106.24, 90.90, 89.99, 61.63, 42.12, 25.97, 18.45, -0.01, -4.33, -475. **FT-IR** (neat, cm^{-1}): 3035 (w), 2956 (s), 2929 (s), 2896 (m), 2858 (s), 2173 (m), 1629 (w), 1471 (m), 1407 (w), 1361 (m), 1342 (m), 1251 (s), 1203 (m), 1093 (s), 1022 (m), 939 (s), 896 (m), 840 (s), 779 (s). **HRMS** (ESI+): Calcd. for $C_{15}H_{29}OBr_2Si_2$ ([M+H]$^+$), 439.0124. Found: 439.0119. **$[\alpha]_D^{25}$** +17.6 (c 1.0, $CHCl_3$).



((*R*,5*Z*,7*E*)-6-bromo-3-(*tert*-butyldimethylsilyloxy)-8-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)octa-5,7-dien-1-ynyl)trimethylsilane (44): The alkyne **30** (2.0 g, 12.03 mmol) was added to a stirred suspension of $HZrCp_2Cl$ (3.72 g, 14.44 mmol) in THF (60 mL) at 0 ºC under argon. The reaction mixture was allowed to warm to room temperature slowly and stirred until consumption of **30** was complete as monitored by TLC (~ one hour). Separately, $ZnBr_2$ (2.98 g, 13.23 mmol) was flame dried and dissolved in THF (13.23 mL). The $ZnBr_2$ solution was cannulated into the organozirconium mixture at 0 ºC and then the reaction mixture was stirred at room temperature. After 30 minutes, a

solution containing dibromide **31** (5.3 g, 12.03 mmol), Pd_2dba_3 (275 mg, 0.300 mmol), and $P(2\text{-fur})_3$ (419 mg, 1.80 mmol) in THF (11 mL) was added via cannula to the organozinc solution. The reaction was protected from light and stirred at room temperature for two days. The reaction was quenched with water and then diluted with ether. The aqueous phase was extracted with ether (2 X 150 mL), the organic fractions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure (at 20 ºC or lower temperature). The residue was purified by quick flash chromatography using silica gel (which was pretreated with 2.5% Et_3N in hexanes) and hexanes and ether as eluents (90:10), to afford the desired vinyl bromide **44** as a yellow oil (4.612 g, 73% yield).

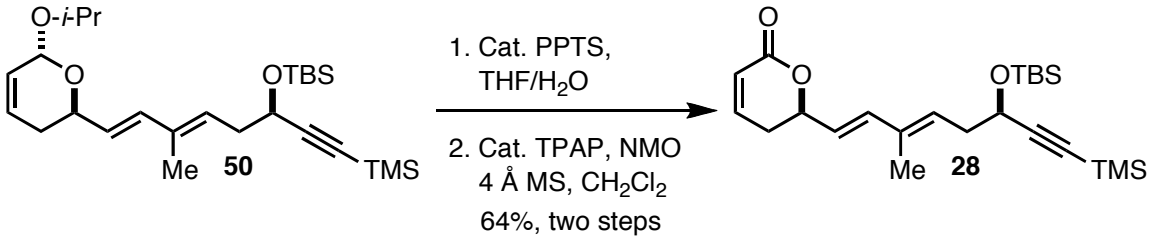
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.33 (d, *J*= 14.4 Hz, 1H), 6.12 (dd, *J*= 14.4, 5.4 Hz, 1H), 6.10-6.08 (m, 1H), 6.03-6.01 (m, 1H), 5.75 (ddd, *J*= 10.2, 4.2, 3.0 Hz, 1H), 5.15 (d, *J*= 1.2 Hz, 1H), 4.58 (ddd, *J*= 9.6, 4.8, 4.8 Hz, 1H), 4.45 (dd, *J*= 6.6, 6.0 Hz, 1H), 4.02 (sept, *J*= 6.0, 1H), 2.73-2.66 (m, 2H), 2.15-2.05 (m, 2H), 1.23 (d, *J*= 6.0 Hz, 3H), 1.19 (d, *J*= 6.0 Hz, 3H), 0.90 (s, 9H), 0.16 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 134.13, 130.12, 129.45, 128.58, 126.64, 126.37, 106.85, 93.45, 89.55, 69.93, 65.91, 62.33, 40.95, 31.06, 25.99, 24.08, 22.31, 18.48, 0.00, -4.33, -4.73. **FT-IR** (neat, cm^{-1}): 3043 (w), 2958 (s), 2929 (s), 2896 (m), 2858 (m), 2173 (w), 1656 (w), 1463 (m), 1400 (m), 1382 (m), 1317 (m), 1251 (s), 1182 (m), 1124 (m), 1097 (s), 1029 (s), 1000 (s), 952 (m), 889 (m), 842 (s), 779 (m), 761 (m). **HRMS** (ESI+): Calcd. for $C_{25}H_{44}O_3BrSi_2$ ($[M+H]^+$), 527.2012. Found: 527.2024. **$[\alpha]_D^{25}$** +47.5 (c 1.5, $CHCl_3$).



***Tert*-butyl((*R*,5*E*,7*E*)-8-((2*R*,6*R*)-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)-6-methyl-1-(trimethylsilyl)octa-5,7-dien-1-yn-3-yloxy)dimethylsilane (50:** The vinyl bromide **44** (4.5 g, 8.53 mmol) was dissolved in THF (85 mL) and then the Pd(*t*-$Bu_3P)_2$ (217.9 mg, 0.426 mmol). The solution was cooled to 0 ºC and then the Me_2Zn (10.23 mL, 1.0 M in heptane, 10.23 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature slowly, protected from light and stirred for 12 hours. The reaction was quenched with water and then diluted with ether. The aqueous phase was extracted with ether (2 X 100 mL), the organic fractions were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a short column using silica gel (which was pretreated with 2.5% Et_3N in hexanes) and hexanes and ether as eluents (90:10), to afford the desired diene **50** as a yellow oil (3.86 g, 98% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.31 (d, *J*= 15.6 Hz, 1H), 6.02 (dd, *J*= 9.6, 5.4 Hz, 1H), 5.74 (ddd, *J*= 9.6, 3.0, 3.0 Hz, 1H), 5.64 (dd, *J*= 15.6, 6.0 Hz, 1H), 5.56 (dd, *J*= 7.8, 6.6 Hz, 1H), 5.13 (bs, 1H), 4.51-4.48 (m, 1H), 4.35 (t, *J*= 6.6, 1H), 4.02 (sept, *J*= 6.0, 1H), 2.54-2.51 (m, 2H), 2.13 (ddd, *J*= 18.0, 10.8, 1.2 Hz, 1H), 2.04 (ddd, *J*= 18.0, 4.8, 4.8 Hz, 1H), 1.78 (s, 3H), 1.25 (d, *J*= 6.0 Hz, 3H), 1.19 (d, *J*= 6.0 Hz, 3H), 0.90 (s, 9H), 0.16 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H). **^{13}C NMR** (150

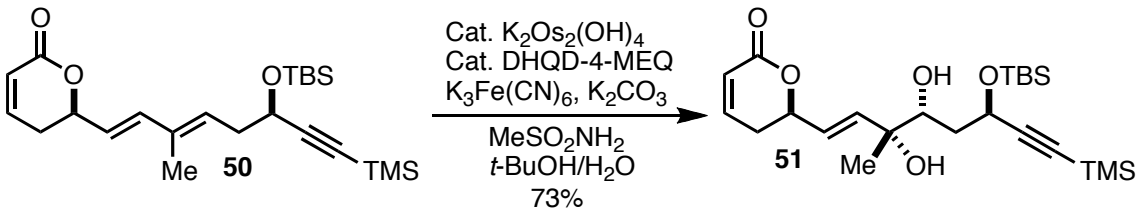
MHz, $CDCl_3$) δ 136.18, 135.47, 128.81, 128.35, 127.19, 126.32, 107.54, 93.45, 89.02, 69.77, 67.22, 63.43, 37.86, 31.17, 26.01, 24.10, 22.31, 18.53, 12.91, 0.03, -4.34, -4.69. **FT-IR** (neat, cm^{-1}): 3041 (w), 2958 (s), 2929 (s), 2894 (m), 2858 (m), 2173 (w), 1656 (w), 1463 (m), 1400 (m), 1380 (m), 1363 (m), 1317 (m), 1251 (s), 1180 (m), 1124 (m), 1095 (s), 1029 (s), 1000 (s), 964 (m), 941 (m), 894 (m), 840 (s), 777 (m). **HRMS** (ESI+): Calcd. for $C_{26}H_{47}O_3Si_2$ ($[M+H]^+$), 463.3064. Found: 463.3063. **$[\alpha]_D^{25}$** +26.1 (c 0.75, $CHCl_3$).



(*R*)-6-((*R*,1*E*,3*E*)-6-(*tert*-butyldimethylsilyloxy)-3-methyl-8-(trimethylsilyl) octa-1,3-dien-7-ynyl)-5,6-dihydro-2H-pyran-2-one (28): The acetal **50** (2.0 g, 4.32 mmol) was dissolved in a mixture of THF and water (120 mL, 3:1) and then the PPTS (271.5 mg, 1.08 mmol) was added. The reaction mixture was stirred at room temperature for 36 hours and then diluted with water and ether. The aqueous phase was extracted with ether (2 X 100 mL), the organic fractions were combined, washed with a saturated aqueous solution of $NaHCO_3$ (2 X 150 mL), and water (2 X 150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and then cannulated into a mixture containing TPAP (379.6 mg, 1.08 mmol), NMO (1.52 g,

12.96 mmol) and 4 Å MS (2.16 g) in CH_2Cl_2 (22 mL) at 0 ºC. The reaction mixture was allowed to warm to room temperature and stirred for 10 hours. The reaction mixture was then filtered through a short pad of silica gel using CH_2Cl_2 as eluent. After concentration, the residue was purified by flash chromatography using silica gel and hexanes and ethyl acetate as eluents (8:2), to afford the desired lactone **28** as a light yellow oil (1.157 g, 64% yield, two steps).

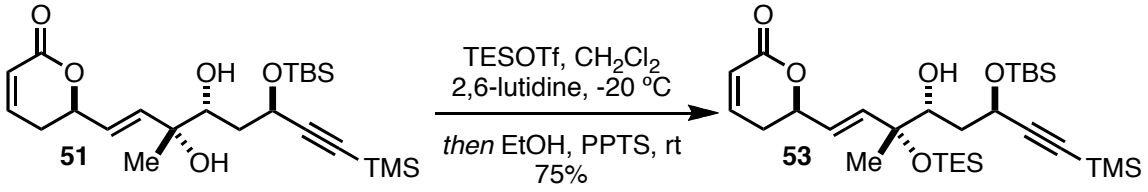
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.90 (ddd, *J*= 9.6, 4.2, 4.2 Hz, 1H), 6.37 (d, *J*= 15.6 Hz, 1H), 6.06 (ddd, *J*= 9.6, 1.8, 1.8 Hz, 1H), 5.67 (dd, *J*= 15.6, 7.2 Hz, 1H), 5.61 (t, *J*= 7.2 Hz, 1H), 5.01-4.97 (m, 1H), 4.36 (t, *J*= 6.6 Hz, 1H), 2.54-2.51 (m, 2H), 2.48-2.46 (m, 2H), 1.77 (s, 3H), 0.89 (s, 9H), 0.16 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 164.29, 144.89, 138.37, 134.86, 130.19, 123.43, 121.85, 107.37, 89.14, 78.69, 63.21, 37.87, 30.25, 25.99, 18.48, 12.88, 0.01, -4.34, -4.70. **FT-IR** (neat, cm^{-1}): 2956 (s), 2927 (s), 2856 (s), 2171 (w), 1725 (s), 1650 (w), 1463 (m), 1421 (s), 1380 (m), 1361 (w), 1338 (w), 1249 (s), 1147 (w), 1087 (s), 1027 (m), 1008 (m), 964 (m), 939 (w), 896 (w), 840 (s), 815 (m), 779 (m), 759 (m). **HRMS** (ESI+): Calcd. for $C_{23}H_{39}O_3Si_2$ ([M+H]$^+$), 419.2438. Found: 419.2439. **$[\alpha]_D^{25}$** +37.0 (c 0.25, $CHCl_3$).



(*R*)-6-((3*R*,4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-3,4-dihydroxy-3-methyl-8-(trimethylsilyl)oct-1-en-7-ynyl)-5,6-dihydro-2H-pyran-2-one (51): The $K_2OsO_2(OH)_4$ (13.2 mg, 0.0358 mmol), DHQD-4-MEQ (83.7 mg, 0.1791 mmol), $K_3Fe(CN)_6$ (1.1794 g, 3.5823 mmol), K_2CO_3 (495.1 mg, 3.5823 mmol) and $MeSO_2NH_2$ (147.6 mg, 1.5523 mmol) were dissolved in a mixture of *t*-BuOH/H_2O (1/1, 24 mL) and stirred vigorously for 15 minutes at room temperature and then cooled to 0 ºC. The diene **50** (500 mg, 1.1941 mmol) was then added and the reaction mixture was stirred at 0 ºC for 36 hours. The reaction mixture was then diluted with CH_2Cl_2 and quenched with a saturated solution of Na_2SO_3 and stirred at room temperature for 15 minutes. The reaction mixture was extracted with CH_2Cl_2 (3 X 50 mL), the organic fractions were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. ^{1}H NMR analysis of the crude mixture showed a 9:2 regioselectivity, favoring the desired regioisomer. The residue was purified by careful gravity column chromatography using silica gel and a hexanes:ethyl acetate gradient (8:2 to 6:1) as eluents, to afford the undesired regioisomeric diol (71.2 mg) and upon further elution, the desired diol **51** as a colorless oil (321 mg, 73% combined yield, 9:2 regioselectivity).

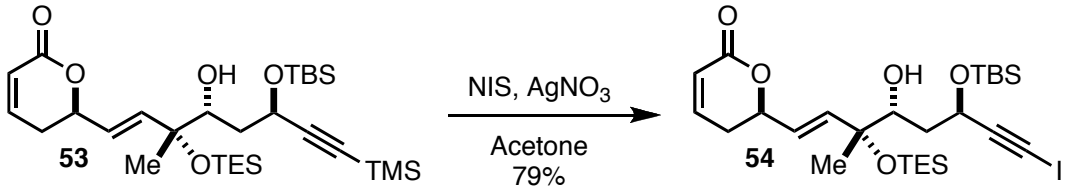
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (m, 1H), 6.06 (dd, *J*= 9.6, 1.8 Hz, 1H), 5.99 (d, *J*= 15.6 Hz, 1H), 5.93 (dd, *J*= 15.6, 5.4 Hz, 1H), 4.98 (ddd, *J*= 10.2, 10.2, 5.4 Hz, 1H), 4.73 (dd, *J*= 4.8, 4.2 Hz, 1H), 3.96 (d, *J*= 9.6 Hz, 1H), 3.50 (bs, 1H), 2.51-2.41 (m, 2H), 2.47 (bs, 1H), 1.84-1.76 (m, 2H), 1.25 (s, 3H), 0.91 (s, 9H), 0.17 (s, 9H), 0.17 (s, 3H), 0.15 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 164.14, 144.89, 138.75, 126.33, 121.78, 106.04, 90.59, 77.62, 74.45, 74.39, 62.57,

38.21, 30.09, 25.93, 22.87, 18.28, -0.04, -4.39, -5.03. **FT-IR** (neat, cm^{-1}): 3444 (br, m), 2956 (s), 2929 (s), 2898 (m), 2856 (m), 2171 (w), 1720 (s), 1463 (w), 1384 (m), 1361 (w), 1342 (w), 1251 (s), 1149 (w), 1064 (s), 971 (w), 840 (s), 779 (m), 759 (w). **HRMS** (ESI+): Calcd. for $C_{23}H_{41}O_5Si_2$ ($[M+H]^+$), 453.2493. Found: 453.2494. **$[\alpha]_D^{25}$** +81.8 (c 0.5, $CHCl_3$).



(*R*)-6-((3*R*,4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-4-hydroxy-3-methyl-3-(triethylsilyloxy)-8-(trimethylsilyl)oct-1-en-7-ynyl)-5,6-dihydro-2H-pyran-2-one (53): The diol **51** (140 mg, 0.3092 mmol) was dissolved in CH_2Cl_2 (5 mL) and then the solution was cooled to -20 ºC. The 2,6-lutidine (79 μL, 0.6803 mmol) was then added, followed by the TESOTf (149 μL, 0.6494 mmol). The reaction mixture was stirred at -20 ºC and monitored by TLC. Once the diol was completely converted into the bis-TES ether (~ one hour, monitored by TLC), EtOH (15 mL) was added and the reaction mixture was allowed to warm to room temperature slowly and then the PPTS (19.4 mg, 0.0773 mmol) was added and the reaction mixture was stirred for 16 hours (monitored by TLC). The reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 X 50 mL), and water (2 X 50 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The

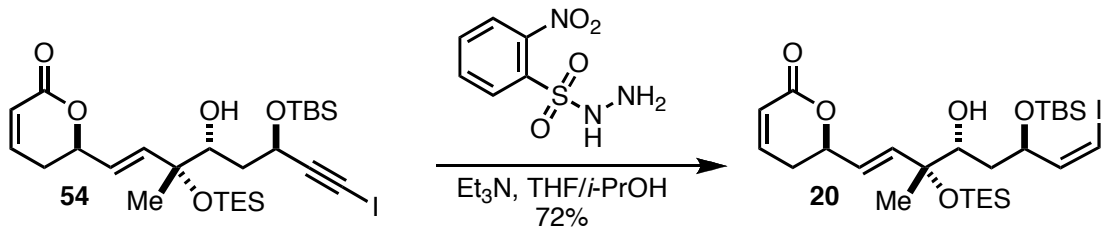
residue was purified by flash chromatography using silica gel (which was pretreated with 2.5% Et_3N in hexanes) and hexanes and ethyl acetate as eluents (90:10), to afford the desired alcohol **53** as a colorless oil (131 mg, 75% yield). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.89 (ddd, *J*= 10.8, 4.8, 4.8 Hz, 1H), 6.06 (dd, *J*= 10.8, 2.4 Hz, 1H), 5.91 (d, *J*= 15.6 Hz, 1H), 5.82 (dd, *J*= 15.6, 6.0 Hz, 1H), 4.99-4.95 (m, 1H), 4.67 (dd, *J*= 7.2, 3.6 Hz, 1H), 3.77 (d, *J*= 10.8 Hz, 1H), 3.04 (d, *J*= 1.8 Hz, 1H), 2.46-2.44 (m, 2H), 1.85 (dd, *J*= 14.4, 7.2 Hz, 1H), 1.51 (ddd, *J*= 14.4, 10.8, 3.6 Hz, 1H), 1.37 (s, 3H), 0.95 (t, *J*= 7.8 Hz, 9H), 0.90 (s, 9H), 0.61 (q, *J*= 7.8 Hz, 6H), 0.16 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 164.17, 144.68, 137.89, 126.76, 121.92, 107.00, 89.65, 77.76, 77.06, 75.44, 62.11, 38.99, 29.82, 25.99, 23.02, 18.37, 7.34, 6.96, -0.03, -4.38, -4.99. **FT-IR** (neat, cm^{-1}): 3511 (br, m), 2956 (s), 2933 (s), 2877 (m), 2858 (m), 2171 (w), 1727 (s), 1461 (m), 1413 (m), 1382 (m), 1382 (m), 1249 (s), 1079 (s), 1002 (s), 894 (w), 840 (s), 779 (m), 744 (m), 727 (m). **HRMS** (ESI+): Calcd. for $C_{29}H_{55}O_5Si_3$ ($[M+H]^+$), 567.3357. Found: 567.3358. **$[\alpha]_D^{25}$** +67.6 (c 1.15, $CHCl_3$).



(*R*)-6-((3*R*,4*R*,6*R*,*E*)-6-(*tert*-butyldimethylsilyloxy)-4-hydroxy-8-iodo-3-methyl-3-(triethylsilyloxy)oct-1-en-7-ynyl)-5,6-dihydro-2H-pyran-2-one (54: The alkyne **53** (100 mg, 0.1763 mmol) was dissolved in acetone (3 mL). Freshly

ground $AgNO_3$ (15 mg, 0.0882 mmol) and *N*-iodosuccinimide (51.6 mg, 0.2292 mmol) were added together in one portion. The reaction was stirred in the dark for two hours and then concentrated. The residue was dissolved in ether (15 mL) and washed with brine (2 X 15 mL), and water (15 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using silica gel (which was pretreated with 2.5% Et_3N in hexanes) and hexanes and ethyl acetate as eluents (80:20), to afford the desired iodoalkyne **54** as a light yellow oil (86.2 mg, 79% yield).

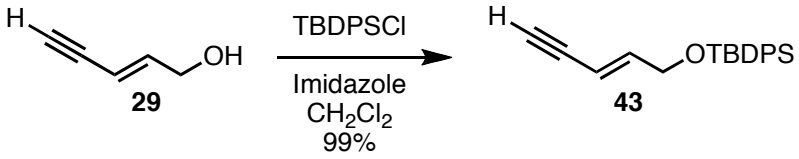
^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (ddd, *J*= 9.6, 5.4, 3.6 Hz, 1H), 6.07 (ddd, *J*= 9.6, 1.8, 1.8 Hz, 1H), 5.91 (dd, *J*= 15.6, 1.2 Hz, 1H), 5.82 (dd, *J*= 15.6, 6.0 Hz, 1H), 4.99-4.95 (m, 1H), 4.80 (dd, *J*= 7.2, 3.6 Hz, 1H), 3.77 (dd, *J*= 10.8, 1.8 Hz, 1H), 2.94 (d, *J*= 1.8 Hz, 1H), 2.47-2.44 (m, 2H), 1.87 (ddd, *J*= 14.4, 7.2, 1.8 Hz, 1H), 1.52 (ddd, *J*= 14.4, 10.8, 3.6 Hz, 1H), 1.37 (s, 3H), 0.96 (t, *J*= 7.8 Hz, 9H), 0.90 (s, 9H), 0.61 (q, *J*= 7.8 Hz, 6H), 0.16 (s, 3H), 0.13 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 164.12, 144.65, 137.77, 126.84, 121.91, 95.68, 77.68, 77.02, 75.30, 63.11, 39.31, 29.83, 25.95, 22.96, 18.34, 7.35, 6.98, 1.70, -4.46, -5.12. **FT-IR** (neat, cm^{-1}): 3488 (br, m), 2954 (s), 2931 (s), 2875 (s), 2858 (m), 2181 (w), 1722 (s), 1577 (w), 1461 (m), 1413 (m), 1382 (m), 1249 (s), 1079 (s), 1002 (s), 975 (m), 896 (w), 836 (s), 813 (m), 779 (m), 744 (m), 727 (m). **HRMS** (ESI+): Calcd. for $C_{26}H_{46}IO_5Si_2$ ($[M+H]^+$), 621.1928. Found: 621.1924. **$[\alpha]_D^{25}$** +61.5 (c 1.0, $CHCl_3$).



(*R*)-6-((1*E*,3*R*,4*R*,6*R*,7*Z*)-6-(*tert*-butyldimethylsilyloxy)-4-hydroxy-8-iodo-3-methyl-3-(triethylsilyloxy)octa-1,7-dienyl)-5,6-dihydro-2H-pyran-2-one (20): The iodoalkyne **54** (80 mg, 0.1289 mmol) was dissolved in THF/isopropanol (1:1, 3 mL) and then the 2-nitrobenzenesulfonyl hydrazide (56 mg, 0.2578 mmol) was added followed by the triethylamine (36 μL, 0.2578 mmol). The reaction mixture was stirred in the dark for 36 hours and then diluted with ether (15 mL) and washed with brine (2 X 15 mL), and water (15 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using silica gel (which was pretreated with 2.5% Et_3N in hexanes) and hexanes and ethyl acetate as eluents (80:20), to afford the desired vinyl iodide **20** as a light yellow oil (58.1 mg, 72% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.89 (ddd, *J*= 9.0, 4.8, 3.0 Hz, 1H), 6.33 (t, *J*=7.8 Hz, 1H), 6.22 (dd, *J*= 7.8, 1.2 Hz, 1H), 6.06 (ddd, *J*= 9.0, 1.8, 1.8 Hz, 1H), 5.90 (dd, *J*= 15.6, 1.2 Hz, 1H), 5.80 (dd, *J*= 15.6, 6.0 Hz, 1H), 4.99-4.95 (m, 1H), 4.67-4.64 (m, 1H), 3.63 (ddd, *J*= 10.2, 2.4, 1.2 Hz, 1H), 3.01 (d, *J*= 2.4 Hz, 1H), 2.46-2.43 (m, 2H), 1.71 (ddd, *J*= 13.2, 7.2, 1.1 Hz, 1H), 1.37 (ddd, *J*= 13.2, 10.8, 3.0 Hz, 1H), 1.34 (s, 3H), 0.94 (t, *J*= 8.4 Hz, 9H), 0.88 (s, 9H), 0.58 (q, *J*= 8.4 Hz,

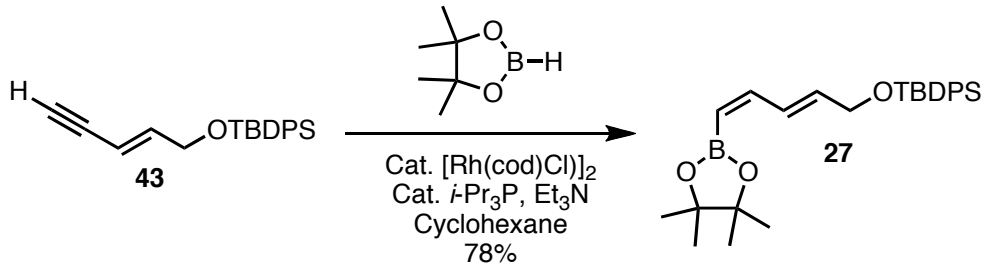
6H), 0.11 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 164.10, 144.64, 144.20, 138.01, 126.98, 121.91, 80.09, 77.82, 77.29, 75.05, 74.34, 37.18, 29.85, 25.99, 22.69, 18.19, 7.32, 6.95, -4.19, -4.79. **FT-IR** (neat, cm^{-1}): 3494 (br, m), 2954 (s), 2931 (s), 2877 (s), 2858 (m), 1725 (s), 1461 (m), 1413 (m), 1382 (m), 1361 (m), 1280 (m), 1247 (s), 1195 (w), 1149 (w), 1079 (s), 1002 (s), 975 (m), 898 (w), 836 (s), 813 (m), 779 (m), 742 (m), 725 (m), 667 (m). **HRMS** (ESI+): Calcd. for $C_{26}H_{47}IO_5Si_2Na$ ([M+Na]$^+$), 645.1904. Found: 645.1899. **$[\alpha]_D^{25}$** +38.0 (c 0.2, $CHCl_3$).



(*E*)-*Tert*-butyl(pent-2-en-4-ynyloxy)diphenylsilane (43): Imidazole (9.12 g, 133.98 mmol) was dissolved in CH_2Cl_2 (120 mL) and then the solution was cooled to 0 ºC. The TBDPSCl (34.3 mL, 133.98 mmol) was then added dropwise followed by the alcohol **29** (10 g, 121.80 mmol). The reaction mixture was allowed to warm to room temperature slowly and stirred for 8 hours. The reaction mixture was diluted with CH_2Cl_2 (130 mL) and water (250 mL), washed with a saturated aqueous solution of $NaHCO_3$ (2 X 250 mL), and water (2 X 250 mL). The organic fraction was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using silica

gel and hexanes and ethyl acetate as eluents (90:10), to afford the desired silyl ether **43** as a colorless oil (39.0 g, 99% yield).

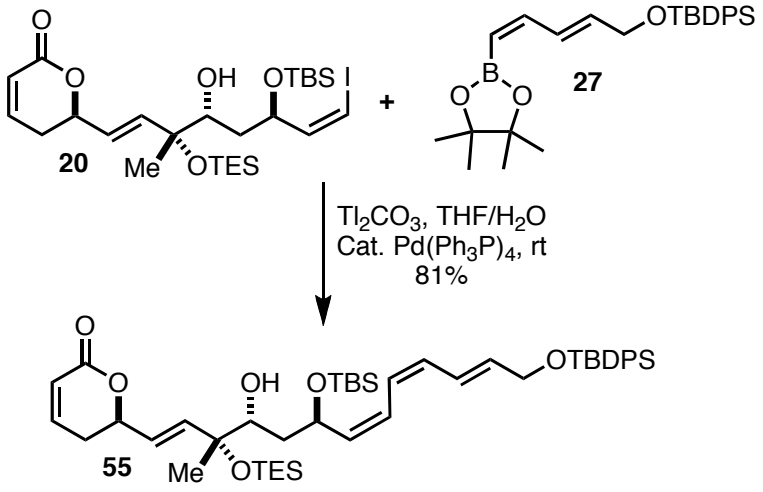
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71-7.69 (m, 4H), 7.47-7.41 (m, 6H), 6.33 (dt, *J*= 15.6, 4.2 Hz, 1H), 5.95 (dq, *J*= 15.6, 2.4 Hz, 1H), 4.29 (dd, *J*= 4.2, 2.4 Hz, 2H), 2.92 (d, *J*= 2.4 Hz, 1H), 1.10 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 144.08, 135.65, 133.37, 130.01, 127.97, 107.84, 82.34, 77.70, 63.59, 26.98, 19.48. **FT-IR** (neat, cm^{-1}): 3293 (s), 3131 (w), 3070 (s), 3050 (s), 2954 (s), 2931 (s), 2892 (s) 2858 (s), 2723 (w), 2105 (w), 1959, (w), 1893 (w), 1824 (w), 1778 (w), 1724 (w), 1658 (w), 1635 (w), 1589 (m), 1565 (w), 1469 (s), 1427 (s), 1376 (s), 1307 (w), 1257 (m), 1187 (m), 1114 (s), 1079 (s), 1010 (m), 956 (s), 821 (s), 802 (s), 740 (m), 705 (s), 617 (s), 489 (s). **HRMS** (ESI+): Calcd. for $C_{21}H_{24}OSiNa$ ([M+Na]$^+$), 343.1494. Found: 343.1492.



***Tert*-butyldiphenyl((2*E*,4*Z*)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) penta-2,4-dienyloxy)silane (27):** Pinacolborane (1.13 mL, 7.81 mmol) was added to a solution of $[Rh(cod)Cl]_2$ (57.8 mg, 0.1172 mmol), *i*-Pr_3P (89.5 μL, 0.4688 mmol) and triethylamine (5.45 mL, 39.07 mmol) in cyclohexane at room temperature. The reaction mixture was stirred for 30 minutes and then the alkyne **43** (3.01 g, 9.38 mmol) was added neat dropwise. The reaction mixture was

stirred at room temperature for 4 hours and then the volatiles were removed under reduced pressure. The residue was purified by flash chromatography using silica gel (which was pretreated with 2.5% Et_3N in hexanes) and a gradient of hexanes and ether as eluents (90:10 to 70:30), to afford the desired boronic ester **27** as a light yellow viscous oil (2.73 g, 78% yield).

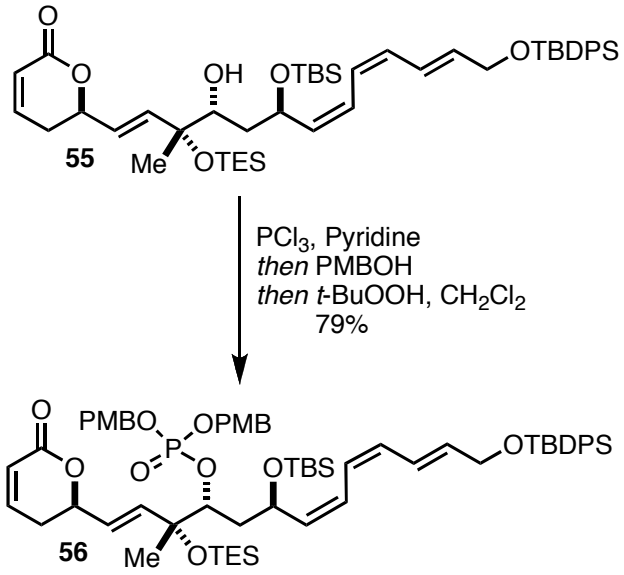
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74-7.72 (m, 4H), 7.46-7.39 (m, 6H), 7.33-7.28 (m, 1H), 6.92 (t, *J*= 12.0 Hz, 1H), 5.92 (dt, *J*= 15.6, 4.2 Hz, 1H), 5.39 (d, *J*= 13.2 Hz, 1H), 4.33 (d, *J*= 2.4 Hz, 2H), 1.29 (s, 12H), 1.13 (s, 9H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 150.47, 137.45, 135.78, 133.71, 129.84, 129.45, 127.88, 83.22, 63.86, 27.09, 25.05, 19.49. **FT-IR** (neat, cm^{-1}): 3070 (m), 3046 (m), 2977 (s), 2931 (s), 2892 (s), 2858 (s), 2730 (w), 1959 (w), 1893 (w), 1832 (w), 1646 (m), 1592 (s), 1469 (m), 1427 (s), 1376 (s), 1330 (s), 1295 (m), 1257 (s), 1211 (m), 1145 (s), 1110 (s), 1041 (w), 1010 (m), 968 (s), 879 (w), 825 (m), 740 (m), 701 (s). **HRMS** (ESI+): Calcd. for $C_{27}H_{38}BO_3Si$ ($[M+H]^+$), 449.2683. Found: 449.2679.



(*R*)-6-((1*E*,3*R*,4*R*,6*R*,7*Z*,9*Z*,11*E*)-6-(*tert*-butyldimethylsilyloxy)-13-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-3-methyl-3-(triethylsilyloxy) trideca-1,7,9,11-tetraenyl)-5,6-dihydro-2H-pyran-2-one (55): The vinyl iodide **20** (75 mg, 0.1204 mmol) and the boronic ester **27** (81 mg, 0.1806 mmol) were dissolved in dry degassed THF/H_20 (3 mL/0.5 mL) and then the $Pd(Ph_3P)_4$ (14 mg, 0.012 mmol) and Tl_2CO_3 (113 mg, 0.2408 mmol) were added. The reaction was stirred in the dark for five days and then filtered through celite and concentrated under reduced pressure. The residue was purified by flash chromatography using silica gel (which was pretreated with 2.5% Et_3N in hexanes) and hexanes and ethyl acetate as eluents (80:20), to afford the desired coupled product **55** as a light yellow oil (80.2 mg, 81% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69-7.68 (m, 4H), 7.45-7.42 (m, 2H), 7.40-7.38 (m, 4H), 6.89 (ddd, *J*= 5.4, 3.0, 3.0 Hz, 1H), 6.77 (dd, *J*= 13.2, 12.6 Hz, 1H), 6.35 (t, *J*= 11.4 Hz, 1H), 6.16 (t, *J*= 12.0 Hz, 1H), 6.08-6.05 (m, 2H), 5.90 (d, *J*= 16.2 Hz, 1H), 5.84 (dt, *J*= 16.2, 4.8 Hz, 1H), 5.81 (dd, *J*= 15.6, 6.0 Hz, 1H), 5.55 (t, *J*= 9.6 Hz, 1H), 4.99-4.93 (m, 2H), 4.30 (d, *J*= 4.2 Hz, 2H), 3.70 (d, *J*= 10.2 Hz, 1H), 3.03 (bs, 1H), 2.48-2.42 (m, 2H), 1.67 (dd, *J*= 13.8, 7.8 Hz, 1H), 1.38-1.32 (m, 1H), 1.33 (s, 3H), 1.09 (s, 9H), 0.94 (t, *J*= 7.8 Hz, 9H), 0.89 (s, 9H), 0.58 (q, *J*= 7.8 Hz, 6H), 0.08 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 164.13, 144.63, 138.10, 135.75, 134.49, 133.78, 130.27, 129.88, 127.89, 126.95, 124.67, 123.36, 122.49, 121.94, 77.81, 77.37, 75.16, 67.26, 64.38, 39.17, 29.83, 27.04, 26.06, 22.44, 19.47, 18.31, 7.29, 6.94, -4.11, -4.86. **FT-IR** (neat, cm^{-1}): 3467 (br, m), 3070 (w), 3046 (m), 2954 (s), 2931 (s), 2877 (s), 2858 (s), 1963 (w), 1897

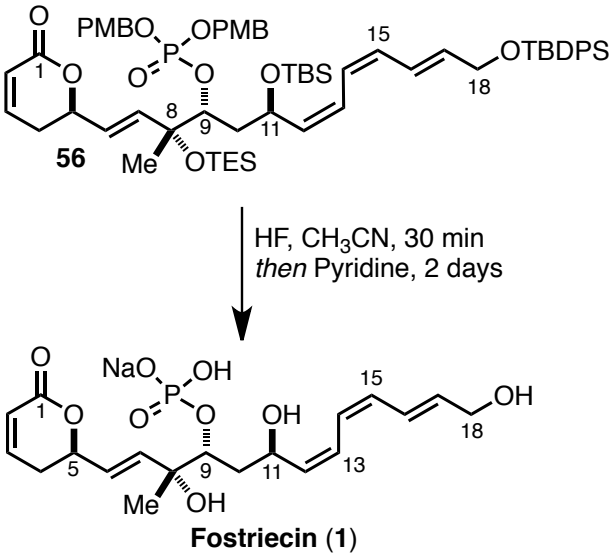
(w), 1820 (w), 1727 (s), 1627 (w), 1589 (w), 1465 (m), 1427 (m), 1380 (m), 1303 (w), 1249 (s), 1191 (w), 1110 (s), 1068 (s), 1006 (s), 971 (m), 941 (m), 833 (s), 779 (m), 740 (s), 705 (s). **HRMS** (ESI+): Calcd. for $C_{47}H_{73}O_6Si_3$ ($[M+H]^+$), 817.4715. Found: 817.4721. $[\alpha]_D^{25}$ -2.5 (c 1.0, $CHCl_3$).



(5*R*,6*R*,8*R*,9*Z*,11*Z*,13*E*)-8-(*Tert*-butyldimethylsilyloxy)-3,3-diethyl-5,18,18-trimethyl-5-((*E*)-2-((*R*)-6-oxo-3,6-dihydro-2H-pyran-2-yl)vinyl)-17,17-diphenyl-4,16-dioxa-3,17-disilanonadeca-9,11,13-trien-6-yl bis(4-methoxybenzyl) phosphate (56): The alcohol **55** (20 mg, 0.0245 mmol) was dissolved in dry pyridine (1 mL) and then the PCl_3 (4.7 μL, 0.0538 mmol) was added and the reaction mixture was stirred for 15 minutes at room temperature. The PMBOH (17 μL, 0.1370 mmol) was added then and the mixture was further stirred for one hour. The reaction mixture was then diluted with CH_2Cl_2 (2 mL) and treated with *t*-BuOOH (20.5 μL, 5.0 M in decane, 0.1027 mmol). The reaction mixture was stirred at room temperature for six hours and the quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL), extracted with CH_2Cl_2 (3 X 5 mL).

The organic fractions were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by PTLC (which was pretreated with 5% Et_3N in hexanes) using hexanes and ethyl acetate as eluents (60:40), to afford the desired phosphate **56** as a pale yellow oil (22 mg, 79% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J*= 8.4 Hz, 4H), 7.45-7.42 (m, 2H), 7.40-7.38 (m, 4H), 7.28-7.26 (m, 4H), 6.87 (d, *J*= 8.4 Hz, 2H), 6.86 (d, *J*= 8.4 Hz, 2H), 6.83 (ddd, *J*= 9.0, 4.2, 4.2 Hz, 1H), 6.72 (dd, *J*= 14.4, 12.0 Hz, 1H), 6.29 (t, *J*= 12.0 Hz, 1H), 6.14 (t, *J*= 12.0 Hz, 1H), 6.03 (d, *J*= 9.6 Hz, 1H), 5.85-5.76 (m, 4H), 5.41 (t, *J*= 9.6 Hz, 1H), 5.02-4.96 (m, 1H), 4.95 (s, 2H), 4.94 (s, 2H), 4.88-4.85 (m, 1H), 4.45 (t, *J*= 9.0 Hz, 1H), 4.29 (d, *J*= 4.2 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 2.37-2.35 (m, 2H), 2.03-1.94 (m, 2H), 1.39 (s, 3H), 1.08 (s, 9H), 0.95 (t, *J*= 7.8 Hz, 9H), 0.89 (s, 9H), 0.60 (q, *J*= 7.8 Hz, 6H), 0.13 (s, 3H), 0.03 (s, 3H). **^{13}C NMR** (150 MHz, $CDCl_3$) δ 164.24, 159.99, 144.89, 137.01, 136.40, 135.75, 134.21, 133.77, 130.17, 130.08, 130.02, 129.90, 129.08, 128.88, 127.90, 126.97, 124.80, 123.82, 122.49, 121.77, 114.11, 82.68 (*J*= 6.45 Hz), 77.81, 76.41, 76.24, 69.23 (*J*= 5.1 Hz), 69.20 (*J*= 5.1 Hz), 65.26, 64.43, 55.49, 40.59, 29.93, 27.05, 26.20, 25.29, 19.48, 18.27, 7.39, 7.01, -3.78, -4.13. **FT-IR** (neat, cm^{-1}): 3070 (w), 2923 (s), 2854 (s), 1731 (m), 1612 (w), 1515 (w), 1461 (m), 1376 (w), 1299 (w), 1249 (m), 1172 (w), 1110 (w), 1076 (w), 998 (m), 968 (m), 887 (m), 821 (w), 779 (w), 740 (w), 725 (w), 701 (m). **HRMS** (ESI+): Calcd. for $C_{63}H_{89}O_{11}PSi_3Na$ ($[M+Na]^+$), 1159.5348. Found: 1159.5354. **$[\alpha]_D^{25}$** +16.0 (c 0.1, $CHCl_3$).



Fostriecin (**1**): Phosphate **56** (20 mg, 0.017 mmol) was placed in a Nalgene tube and then HF/CH_3CN was added (2 mL, from a freshly prepared stock solution of 0.5mL 48% HF and 9.5 mL CH_3CN) and the solution stirred for 30 min. Pyridine (1 mL) was then added immediately and the reaction stirred for 2 days. The reaction was quenched with saturated $NaHCO_3$ (3 mL), extracted with EtOAc (3 x 3 mL). The aqueous phase was concentrated by lyophilization. The residue was purified by reverse phase chromatography using C18 silica gel and a gradient of water:acetonitrile (100:0 to 80:20) as eluent to provide fostriecin (**1**).

^{1}H NMR (600 MHz, D_2O) δ 7.09 (m, 1H), 6.75 (dd, *J*= 15.0, 11.4 Hz, 1H), 6.54 (t, *J*= 12.0 Hz, 1H), 6.33 (t, *J*= 12.0 Hz, 1H), 6.14 (t, *J*= 10.8 Hz, 1H), 5.99-6.01 (m, 1H), 5.87-5.94 (m, 2H), 5.52 (t, *J*= 10.2 Hz, 1H), 5.05-5.10 (m, 1H), 4.87-4.91 (m, 1H), 4.14 (d, *J*= 5.4 Hz, 1H), 4.10-4.12 (m, 1H), 2.56-2.62 (m, 1H), 2.46-251 (m, 1H), 1.58 (t, *J*= 12.6 Hz, 1H), 1.48-1.52 (m, 1H), 1.26 (s, 3H).

HRMS (ESI+): Calcd. for $C_{19}H_{26}O_9P$ ($[M-Na]^+$), 429.1314. Found: 429.1323.

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