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SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS
OF FOSTRIECIN AND SOME ANALOGS

presented by

Glenn Walton Phillips

has been accepted towards fulfillment
of the requirements for the

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Major Professor's Signature

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SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF FOSTRIECIN AND SOME ANALOGS

By

Glenn Walton Phillips

A DISSERTATION

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ABSTRACT

SYNTHETIC STUDIES TOWARD THE TOTAL SYNTHESIS OF FOSTRIECIN AND SOME ANALOGS

By

Glenn Walton Phillips

The development of a novel aldol reaction between 2-alkynals and methyl [(4R, 5S)-1,5-dimethyl-4-phenyl-2-imidazolidinone] methylene tetracarbonyl chromium (0) and its enantiomer, has provided a unique approach to the total synthesis of fostriecin; an antitumour agent. The synthetic strategy outlined for this natural product is a convergent one and involves a lactone, diene and triol fragment. All three fragments have been successfully prepared in high yields and a formal synthesis of fostriecin has also been accomplished.

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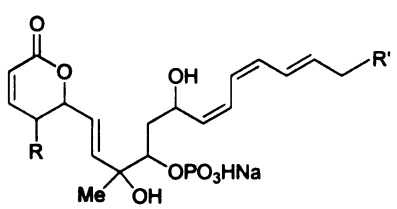
CHAPTER 1

INTRODUCTION TO FOSTRIECIN (CI-920) AND ITS SYNTHETIC APPROACHES

The Discovery of Fostriecin

In 1984 several articles were published describing CI-920 as a structurally novel antitumor compound, that was first isolated from a fermentation broth of ATCC 31906 *fostreus* subspecies of bacteria streptomyces pulveraceus.[1] Initial screenings of the fermentation beer isolates showed strong *in vitro* activity against murine leukemia with ID_{50} versus L1210 cells of 0.073 μg/ mL. This high level of antitumor activity incited a more detailed investigation of this extract. Upon careful characterization three compounds, fostriecin (CI-920), and two others numbered PD 113,270 and PD 113,271 were found (Figure I-1).[2] The maximum yield of fostriecin that could be obtained per mL of fermentation beer was 400 μg.

Figure I-1 Planar Structures of Fostriecin and Related Compounds



1, 1a, 1b

1-Fostriecin R = H, R' = OH

1a-PD 113, 270 R = H, R' = H

1b-PD 113, 271 R = OH, R' = OH

The Biological Activity of Fostriecin

The explanation for the current synthetic interest of fostriecin lies in its biological activity. It displays *in vitro* activity against a plethora of tumor cell lines including lung, breast, and ovarian cancer and displays effacious *in vivo* activity against lymphoid leukemias.[3,4] This novel phosphate ester has also been investigated in a phase one clinical trial at the National Cancer Institute, but was halted due to concerns about stability and purity.[5]

In 1988, fostriecin was found to inhibit *in vitro* purified samples of topoisomerase II (IC_{50} = 40 μM). Based on this observation it was immediately hypothesized that fostriecin had a mode of action analogous to that of etoposide,[6] doxorubicin[7] and amsacrine,[8] leading topoisomerase II inhibitors at the time of fostriecin's discovery. Classical topoisomerase II inhibitors induce irreversible DNA strand cleavage by stabilizing the interaction between topoisomerase II and double-stranded DNA, inadvertently trapping the enzyme-DNA complex.[9] Etoposide and 4'-(9-acidinylamino)methanesulfon-*m*-anisidide (*m*-AMSA) are examples of this type of topo II isomerase inhibitor. The other type of topo II isomerase inhibitors prevent the enzyme from binding to DNA or block additional steps in the enzymes catalytic cycle. Amsacrine and suramin are examples of this type of inhibitor. The mechanism of such inhibitors has not been established as well as the classical topo II isomerase inhibitors. The cytotoxic effect brought about by these inhibitors is as a result of a protein-associated DNA strand cleavage. The activity of fostriecin is weak by comparison to these other topoisomerases, which is inconsistent with the mechanism proposed, since such high levels of antitumor

activity were recorded initially. Further evidence that this hypothesis was incorrect was provided by Fostrina's group in 1992, when they discovered that fostriecin does not inhibit topoisomerase II in mamalian cellular extracts.[10]

This anomaly is remedied by another one of fostriecin's biological characteristics, its ability to inhibit protein phosphatases 1, 2A, and 4 (IC_{50}= 45 μM, 1.5 nM and 3.0 nM, respectively).[11,12,13,14,15,16,17] With respect to this property, fostriecin has the highest selectivity for inhibition of protein phosphatase 1 (PP1) known to date. Compounds possessing this characteristic have the ability to block the mitotic entry check point preceding mitosis.[13] This phenomenon is also known as G_2 arrest, and is the point in cell division where damaged DNA is replaced or its synthesis is completed on entering mitosis.[18] The G_2 arrest hypothesis is based on the observation that fostriecin exerts its cytotoxic effects at low concentrations (0.5-0.15 nM) in Chinese hamster ovary (CHO) cells. At this level PP2A is completely inhibited but not PP1. The existence of PP1 indicates that there is cell damage and the cell cycle will not proceed to the M phase.[12]

Another school of thought suggests that fostriecin induces cells to enter mitosis prematurely, the opposite of G_2 arrest. Characteristics of cells that have entered into prophase are chromosome condensation, separation of spindle poles and formation of asters. Entry into this phase is regulated by the maturation promoting factor (MPF) complex which consists of cyclin B and Ser/Thr kinase $p34^{cdc2}$. When this complex is activated it is thought to stimulate normal chromosome condensation. When 375 μM of fostriecin was administered to baby hamster ovary (BHK) cells in the G2 phase,

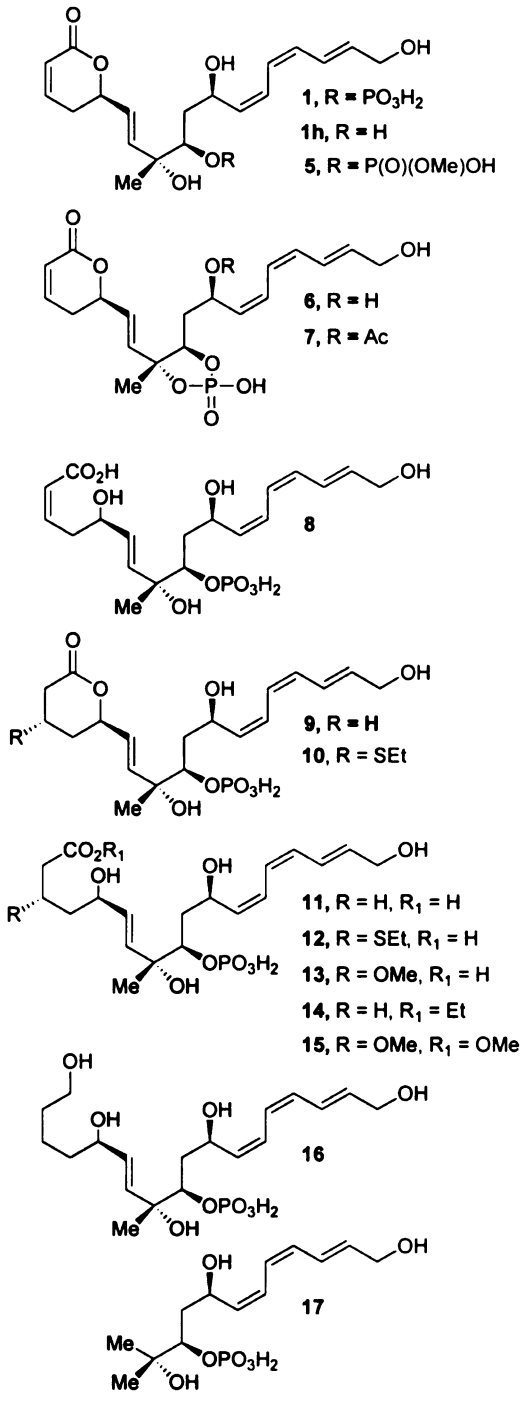
premature mitosis resulted. This was confirmed by the presence of condensed chromatids, separation of spindle poles and aster formation in the cells examined.[13]

The method of transport into tumor cells is via a reduced folate carrier system, which also serves to enhance its selective antitumor properties. In addition, recently it has been found that this unique property as a potent and selective inhibitor of protein phosphatase 2A (PP2A) was shown to limit myocardial infarct size and protect cardiomycytes during ischemia.[19]

Most recently, a structure activity relationship (SAR) study revealed that the protein phosphatase selectivity is probably due to fostriecin's α,β-unsaturated lactone.[20] These results were obtained when fostriecin's structure was compared to the pharmacophore for nonselective PP1 inhibition and its binding was modeled to PP2A utilizing a homology model derived from PP1 X-ray structures. The comparative model revealed that the pharmacophore present in fostriecin includes: (1) a phosphate that binds the metal ions in the active site; (2) a methyl group in close proximity to the phosphonate acid proposed to mimic the substrate phosphothreonine methyl group and (3) an extended hydrophobic segment thought to mimic the substrate hydrophobic residues. The feature that did not correspond to the phamacophore was fostriecin's unsaturated lactone. To test this hypothesis Boger and co-workers synthesized fourteen derivatives seen in Figure I-2 below and examined their protein phosphatase selective inhibition as well as their cytotoxic activity on L1210 cells. The first five **1**, **1h**, **5**, **6** and **7** were designed to examine the importance of the phosphate, while the latter ten compounds **8-17** were designed to test the unsaturated lactone. As may be observed from the table in Figure I-2, the presence of the unsaturated lactone is responsible for an approximate 200-fold

increase in PP2A inhibition. From the model it was suggested that the serine at residue 269 (C269S) is the nucleophile that assist in the active site binding via a Michael addition to the lactone. Supporting this hypothesis was that when the serine was replaced by a phenylalanine the resulting mutant was much less active to fostriecin. Other results obtained confirmed that the presence of the phosphate was even more crucial to the phosphatase inhibition than the α,β-unsaturated lactone, as dephosphorylated fostriecin resulted in a 10^5-fold loss in PP2A inhibition.

Figure I-2 Protein Phosphatase[a] Selectivity and Cytotoxic Activity[b] (IC_{50}, μM) of Fostriecin Derivatives



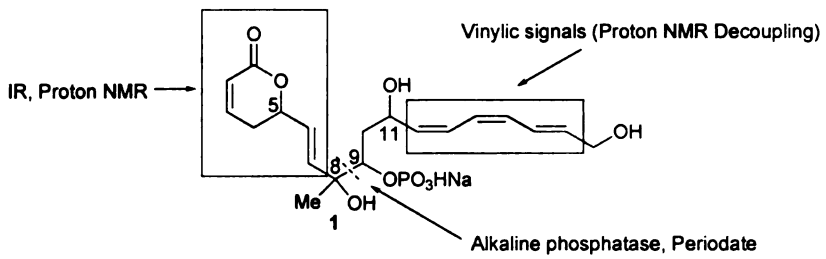
Compound	PP2A	PP1	PP5	L1210	L1210/CI-920
1	0.001 (± 0.0007)	50(± 10)[c]	70 (± 33)	0.3	35
1h	350 (± 100)	> 100	> 100	20	35
5	2.9 (± 1.5)	> 100[c]	> 100	15	> 50
6	3.2 (± 1.1)	> 100	> 100	15	35
7	> 100	> 100	> 100	> 100	> 100
8	73 (± 9)	> 100	> 100	> 25	> 25
9	0.21 (± 0.05)	> 100[c]	> 100	> 50	> 50
10	0.5 (± 0.4)	> 100[c]	> 100	3	> 25
11	> 50	> 100	> 100	> 50	> 50
12	8.8 (± 2.5)	> 100[c]	> 100	> 25	> 25
13	> 100	> 100	> 100	> 25	> 25
14	1.7 (± 0.2)	> 100	> 100	> 25	> 25
15	2.0 (± 2.8)	> 100	> 100	> 25	> 25
16	2.1 (± 0.6)	≥ 100[c,d]	140 (± 50)[d]	> 100	> 100
17	0.19 (± 0.02)	≥ 100[d]	≥ 100[d]	40	60

[a] Assays were conducted with native PP2A (rabbit muscle), rhPP1α and rhPP5 catalytic subunits as detailed.[b] L1210/CI-920 is a cell line resistant to **1** by virtue of an impaired folate transporter required to import **1**. [c] Also assayed with native PP1 (rabbit muscle) with identical results. [d]Enzyme inhibition at 100 μM = 40-50%.

Structural and Stereochemical Determination

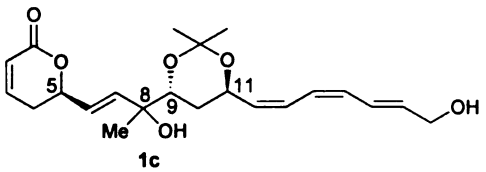
Although the 2-dimensional structure of fostriecin was first published in 1983, it would be fourteen years before the absolute configuration of all four stereocenters would be known. In 1985 Hokanson and French determined several stereochemical assignments of the molecule via proton and carbon-13 experiments, particularly the lactone and triene functionalities (Figure I-3).[21] A periodate cleavage was used to separate the lactone moiety from the rest of the molecule following the removal of the C_9 phosphate monoester via an alkaline phosphatase. The C_5 stereocenter was determined to be *R* by an independent synthesis of the lactone fragment by comparing its optical rotation to that of the lactone derived from the natural product.

Figure I-3 Structural Determination from Spectral Data

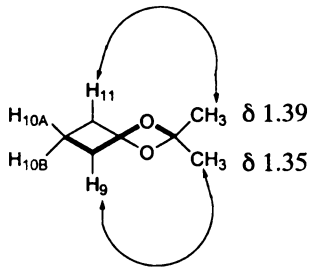


In 1997 Boger's group completed the absolute stereochemical assignment of fostriecin, reaffirming Hokanson and French's partial analysis and assigning the C_8, C_9 and C_{11} stereocenters.[i] Extensive NMR, experiments and chemical degradation were the techniques they used to solve the absolute stereochemistry.

Figure I-4 Boger's Determination of the C_9 and C_{11} Stereochemistry



1c

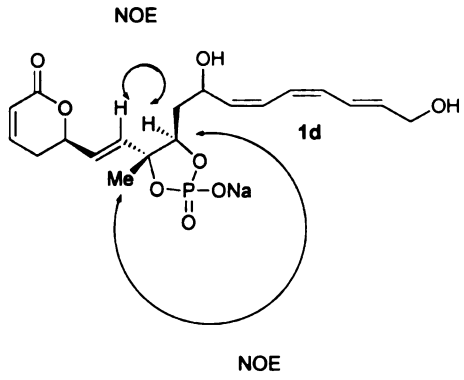


Proton	J (Hz)
9	10.5, 1.9
10A	10.5, 3.7
10B	9.6, 1.9
11	9.6, 3.7

The relative stereochemistry of C_9 and C_{11} was determined to be *trans*, by preparing the acetonide derived dephosphorylated fostriecin. Proton, carbon-13 and 2D proton-proton NOESY NMR experiments all confirmed a twist-boat conformation characteristic of the 1,3-*anti* diol acetonides (Figure I-4).[23]

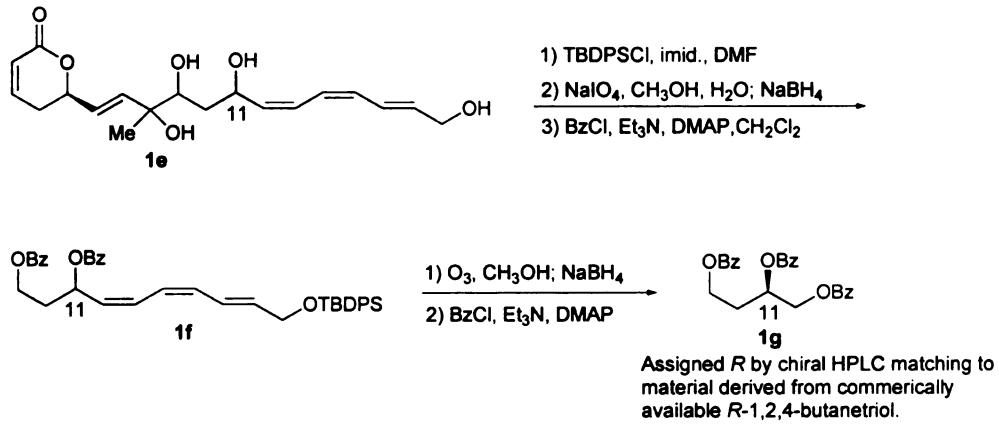
The relative stereochemistry of C_8 and C_9 was determined by converting fostriecin to a five-membered cyclic phosphate diester. ^{31}P NMR and 2D proton-proton ROESY NMR confirmed a 1,2-*syn* relationship (Figure I-5).

Figure I-5 Boger's Determination of the C_8/C_9 Relative Stereochemistry



The absolute stereochemistry of the C_{11} stereocenter was used to confirm chirality at C_8 and C_9. Benzyl protected 1,2,4-butanetriol chemically derived from the dephosphorylated natural product was matched by chiral HPLC to a synthetic sample, prepared from commercially available *R*-1,2,4-butanetriol (Figure I-6). This confirmed the C_{11} chiral center to be R and fostriecin's complete stereochemical assignment to be *5R*, *8R*, *9R*, *11R*.

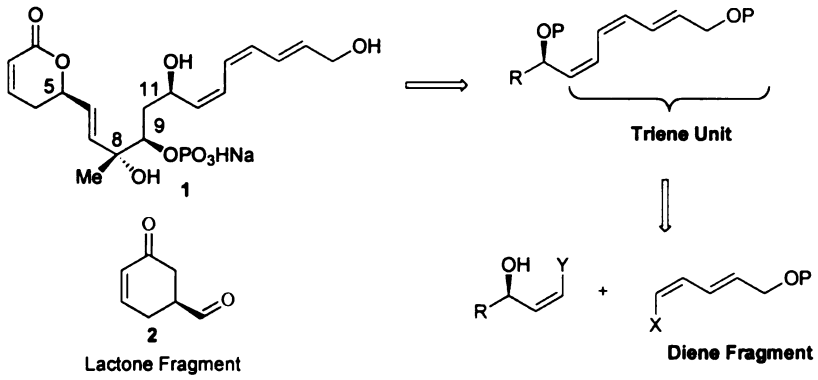
Figure I-6 Boger's Determination of C_{11} Absolute Stereochemistry



Introduction to the Synthetic Approaches to Fostriecin

With the knowledge of fostriecin's biological activity in mind, a profusion of syntheses, formal syntheses and partial syntheses have been reported to date with the vast majority being published in the last four years. Thus far, there have been five total syntheses;[24,25,25,27,28] three formal syntheses;[29,30,31] the synthesis of a dephosphorylated isomer of the natural product,[32] and two partial synthetic analyses – one of a C_8 epimer – reported.[33,34] Both classical and modern organic chemistry have been explored to a large extent. Some key reactions employed are the Wittig and Horner-Wadsworth-Emmons (HWE)[74,93] olefination, Sharpless asymmetric dihydroxylations,[36,94] Felkin and non-Felkin additions, an asymmetric Diels-Alder reaction,[25] asymmetric hydrogenation,[49] diimide reductions,[29] Sonogashira,[55] Stille,[40] and Suzuki couplings,[26,52] Grubb's ring-closing metathesis (RCM),[45] Swern, Dess-Martin and N-morphorline oxide-tetrapropyl ammonium peruthanate (NMO-TPAP) oxidations. In this chapter we shall explore briefly some general methods used to prepare the lactone and triene moieties (Figure I-7) and then examine these eleven approaches in a chronological fashion. This chapter will culminate with a brief look at our retrosynthetic analysis.

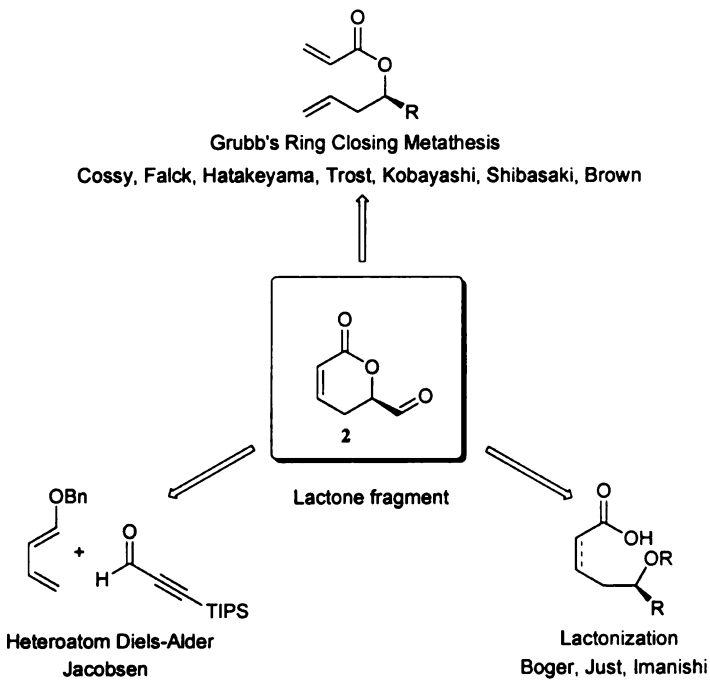
Figure I-7 Identification of Diene Fragment



General Approaches used to Prepare the Lactone Fragment

Even though there have been eleven publications involving synthetic routes to fostriecin, only three different methods have been used to prepare the lactone fragment: Grubb's ring-closing metathesis, a heteroatom Diels-Alder approach and acid mediated lactonization.

Figure I-8 General Approaches to the Lactone Fragment



Grubb's Ring Closing Metathesis

Of the three ways explored to make this moiety, the Grubb's RCM is by far the most popular. Cossy,[33] Falck,[26] Hatakeyama,[28] Trost,[31] Kobayashi,[30] Shibasaki,[29] and Brown[34] all use this technique. As can be seen in Figure I-16, the protection of a secondary homoallyic alcohol with acroyloyl group provided the RCM precursor **55** in high yield and the subsequent metathesis also results in high yields of lactone **56**. This method is most attractive because it avoids having to protect the lactone as an acetal, which is prevalent in all the other approaches.

The Heteroatom Diels-Alder Reaction

The heteroatom Diels-Alder reaction (Figure I-8) has only been exploited on one occasion out of the eleven approaches mentioned to construct this fragment. In Jacobsen's synthesis[25] of fostriecin a chromium based asymmetric catalyst was used to give a greater than a 99%ee and 65% yield of the benzyl acetal precursor after crystallization. The reaction shown in Figure I-19 gives the initial heteroatom Diels-Alder adduct with 89%ee in 90% yield and a 95:5 disatereomeric ratio. Subsequent removal of the TIPS group, epimerization with toluene-sulfonic acid and recrystallization gave **64** with very high enantiomeric purity.

The Acid Laconization Method

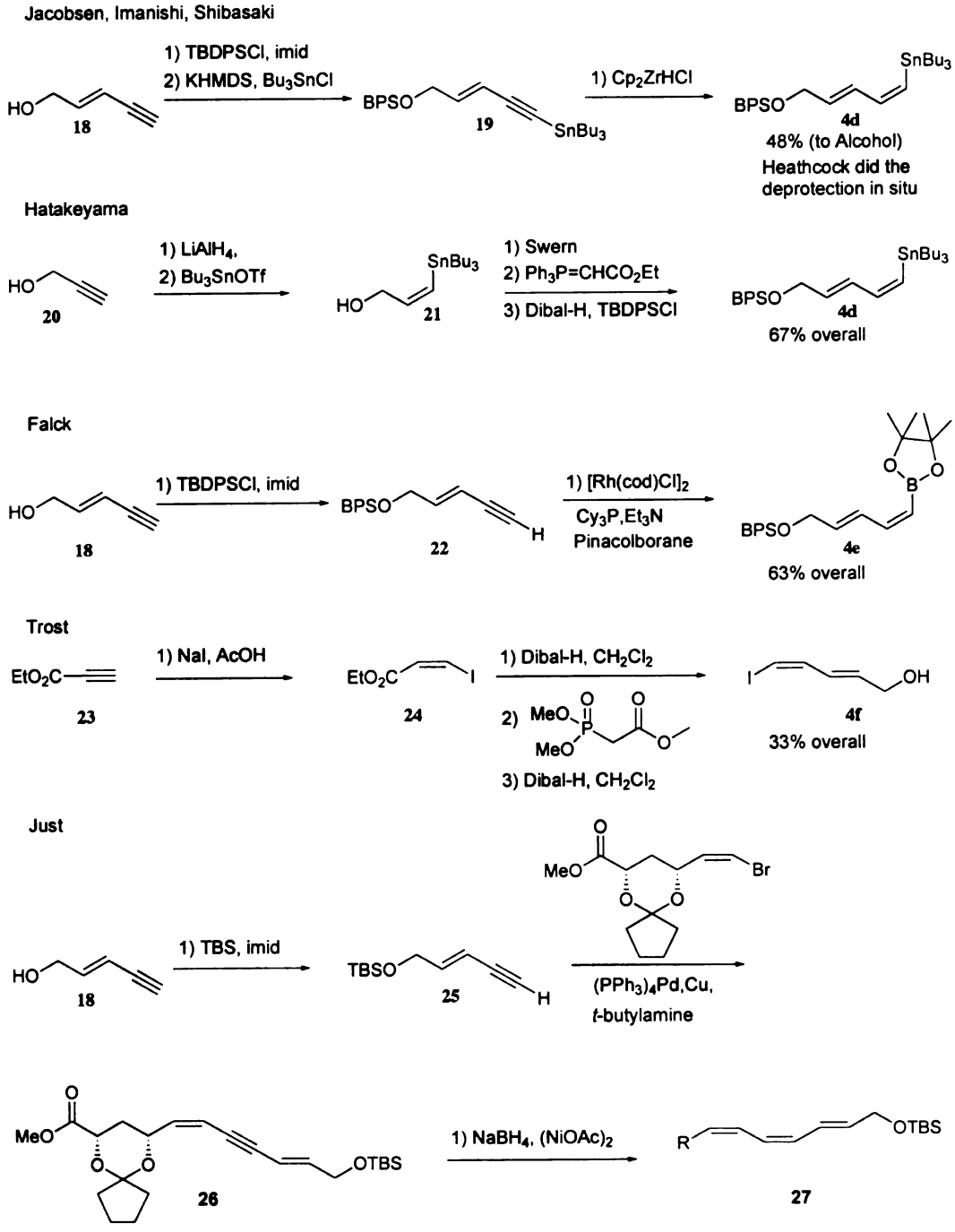
The remaining three publications used acid lactonization to construct the δ–lactone ring. As was mentioned earlier, the protection of the lactone as an acetal was essential to prevent decomposition or low yields. Boger[22] and Just[32] reported obtaining poor yields when attempting to do a Wittig reaction on the lactone aldehyde **2** seen in Figure I-8. The other key feature seen in this method is the introduction of the double bond using selenium chemistry. Our approach adopts the acid lactonization technique but differs at this point, having the double bond already intact prior to cyclization. Chapter 2 will discuss in detail the preparation of this moiety.

General Approaches used to Prepare the Diene Fragment As a Precursor to the Triene Unit.

Even though there have been many approaches to fostriecin, at many of the various pivotal points in these syntheses, synthetic strategies have overlapped. Preparing

the triene (Figure I-7) unit of fostriecin is an archetypal example of this overlap. With eleven synthetic approaches published, only Sonogashira,[55] Stille,[40] Suzuki-Miyaura[26,52] and a Hiyama type coupling[31] are employed to construct the triene unit. In this section we will examine how the diene precursors necessary for these couplings were prepared.

Figure I-9 General Approaches to the Diene Fragment



Heathcock's Method to Prepare the Diene Fragment

Jacobsen,[25] Imanishi,[27] and Shibasaki[29] all adopted a method published by Heathcock for the synthesis of diene **4d** from 2-pentene-4-yn-1-ol (Figure I-9) which was used in the synthesis of myaxlamide A.[102] Heathcock actually employed TBS protection of the primary alcohol was employed and the alkynal stannane was prepared with KHMDS and Bu_3SnCl. Jacobsen,[25] Imanishi,[27] and Shibasaki,[29] however, used a TBDPS group for the initial protection step (see Figure I-9). The proceeding steps after this protection were, however, identical. A hydrozirconation reduction gave the corresponding diene. Heathcock's final product was the deprotected alcohol in 48% yield. No yield was given by these authors for the TBDPS protected precursor.

Hatakeyama's Approach to the Diene Fragment

Hatakeyama, also prepared diene fragment **4d** using Heathcock's procedure but in addition to that approach he presented an alternative strategy to prepare diene **4d**.[28] Starting with 2-propyn-1-ol, a $LiAlH_4$ reduction followed by addition of tributyltin triflate gave the vinyl tin reagent. A Swern oxidation to the corresponding aldehyde followed by a Wittig reaction to a phosphate ester completed the carbon chain with correct stereoselectivity. A DIBAL reduction and TBDPSCl protection gave the desired diene fragment **4d** in 67% yield overall.

Falck's Preparation of the Diene Fragment

Falck's method of choice to assemble the triene moiety was via a Suzuki-Miyaura coupling of the boronic ester **4e**.[26,52] The starting material used and the protection step

were identical to that reported by Jacobsen,[25] Imanishi[27] and Shibasaki.[29] The last step differed, however, with a rhodium-mediated trans addition of pinacolborane to the terminal acetylene **22** to form the vinyl borane **4e**. The overall yield for this approach was 63%.

Just Approach to the Triene Assembly

In Just's approach an alkyne reduction was used to unmask the central olefin of the triene after the coupling had taken place.[32] A Sonogashira[55] coupling of the TBDPS protected 2*E*-penten-4-yne-1-ol to a vinyl bromide provided the triene precursor **26**. The reduction of this alkyne turned out to be one of the most challenging reactions of the synthesis. The author resorted to a nickel boron (NiB) catalyst with one equivalent of hydrogen, a system reported by Brown.[35] To their disappointment this reduction gave only a small amount of desired product **27** along with several over reduced products and some un-reacted starting material.

Trost Approach to the Triene Fragment

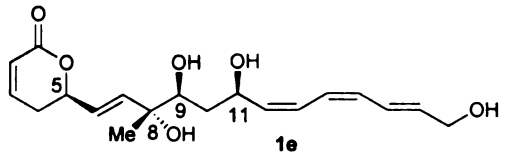
The Trost approach was unique in the sense that the diene moiey **4f** is a vinyl halide instead of an organometallic reagent.[31] All the other preparations of this fragment involved diene units that were either a tin or a boron organometallic compound (see Figure I-9). This diene fragment **4f** was prepared from ethyl propiolate. The vinyl iodide **24** was prepared by treatment of ethyl propiolate with NaI and AcOH in 77% yield. Reduction to the aldehyde was achieved with DIBAL-H. A HWE reaction with trimethyl phosphonoacetate and subsequent DIBAL reduction gave the (2*E*, 4*Z*)-5-Iodopenta-2,4-dien-1-ol **4f** in 33% overall yield.

Synthetic Approaches

Just's Synthetic Approach

The first attempt at the total synthesis of fostriecin was by Just and O'Connor in 1988.[32] It was attempted without knowledge of its absolute configuration, which would only be determined nine years later by Boger and co-workers.[22] Of the eight possible diastereomers, they choose to prepare the 5*R*, 8*R*, 9*S*, 11*R* diastereomer (Figure I-10) and found it to be non-identical to the natural product. Their work narrowed the number of possibilities to just seven.

Figure I-10 Dephosphorylated Isomer of Fostriecin Synthesized by Just



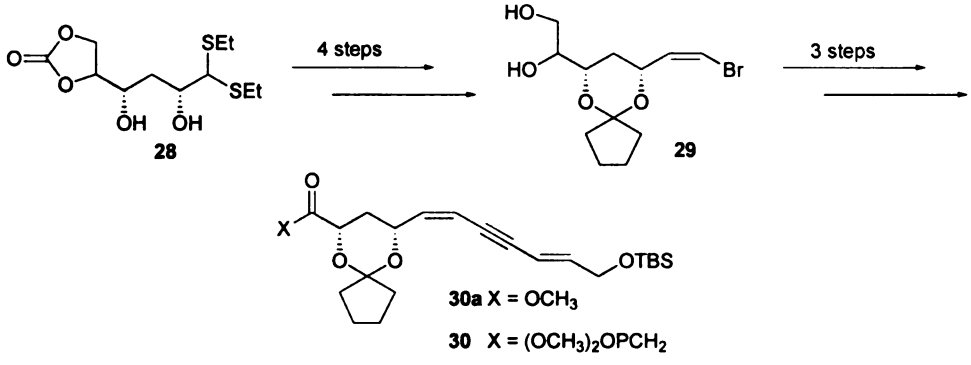
1e

Their approach to the dephosphorylated fostriecin diastereomer **1e** utilized 1,2-O-isopropylidene-*D*-glucofuranose as a chiral starting reagent. The C_5, C_9, and C_{11} stereogenic centers were set in place by this choice of starting material. A few transformations led this synthetic team to a diethyl dithioacetal **28** and a very similar dithioacetal methyl ester **31**. The acetal **28** was used to make the central portion of the molecule, setting stereocenters C_9 and C_{11}, (Figure I-11) and the ester **31** was used to prepare the lactone **2** (Figure I-11) with the C_5 stereocenter. In the preparation of the lactone **2**, the acid catalyzed lactonization gave low yields and the lactone aldehyde **2** proved to be very unstable on silica gel. A Horner-Wadsworth-Emmons (HWE)[74,93] reaction between **30** and **2** connected the lactone to the rest of the molecule. The triene

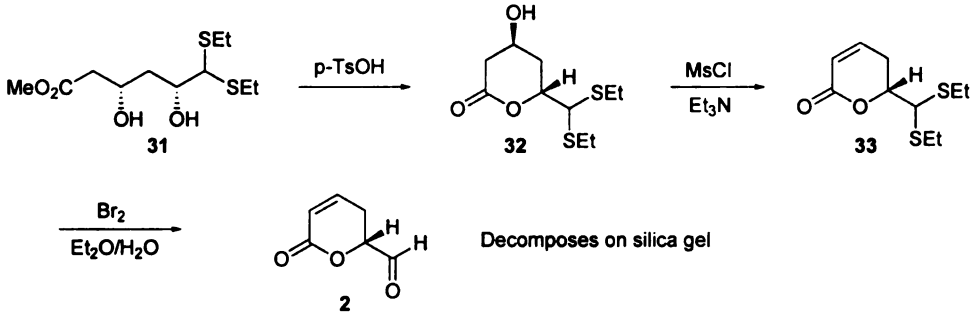
unit was introduced in intermediate **30** by conversion of the dithioacetal **28** to a *cis* vinyl bromide by mercury deprotection of the thioacetal group and a Wittig reaction with bromomethylene triphenyl phosphorane. Sonogashira[55] coupling of that bromide to a tertiary butyl silyl (TBS) protected enynol provided **30.** The last stereogenic center $C_{8.}$ was constructed by asymmetric methylation of the ketone **34**, which gave a 98:2 ratio of alcohol diastereomers in favor of the correct 8*R* isomer.

Figure I-11 Just Synthesis of Fostriecin Isomer 1e

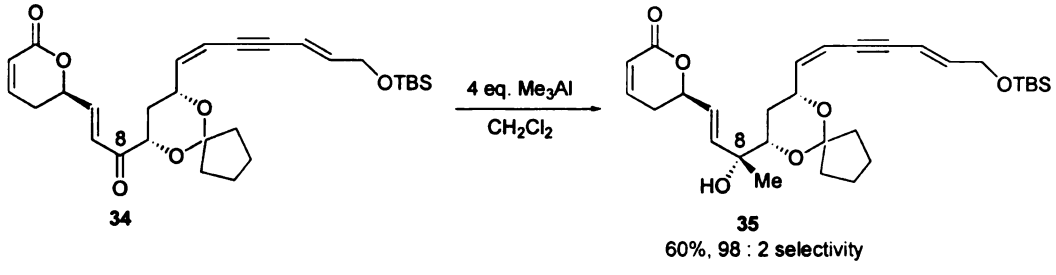
The Central portion



The Lactone Aldehyde



The Methylation Step



A setback in the synthesis occurred at this point. When the hydrogenation of **35** using Lindlar's catalyst was attempted Just and O'Connor obtained a mixture of overreduced products. Having a low supply of compound **35**, Just and O'Connor decided

to carry out this transformation at an earlier stage in the synthesis. Methyl ester **30a** was available in near gram quantities, so hydrogenation was attempted on that substrate. Brown's NiB catalyst system with 1 equivalent of H_2 provided the best results.[18c] The reaction however was still not clean, several products of overreduction and some starting material were also isolated. A yield for this step was not reported. The ensuing steps worked smoothly to give the 5*R*, 8*R*, 9*S*, 11*R* diastereomer of fostriecin.

Boger's Synthetic Approach[24]

Since the Boger group was the first group to tackle the stereochemical determination[22] and complete the total synthesis of natural fostriecin,[24] they were also the first to encounter many of the problems indigenous to this molecule. One key theme which maybe seen throughout this chapter is the use of convergent syntheses instead of a linear one, as a tool to combat the stability issues mentioned in the following chapter.

Boger's retrosynthetic analysis shows three main fragments the C_1-C_6 unit leading to the lactone moiety; the C_8-C_{12} unit leading to the C_8-C_9 *syn* and the C_9-C_{11} *anti* arrangements in the center portion and the C_{16}-C_{18} stannane used in the assembly of the triene fragment (Figure I-12).

5-Hexenoic acid was the starting material employed to make the lactone fragment (Figure I-13). A Sharpless AD[36,94] on the olefin constructs the C_5 chiral center in diol **42** with 92 %ee and 98 %ee after crystallization. After an acid catalyzed lactonization, the internal olefin was introduced using selenium chemistry. The aldehyde lactone as observed by Just and O'Connor's is very unstable. Boger solved this problem by converting it to its isopropyl lactol (Figure I-13).

Figure I-12 Boger's Retrosynthetic Analysis[24]

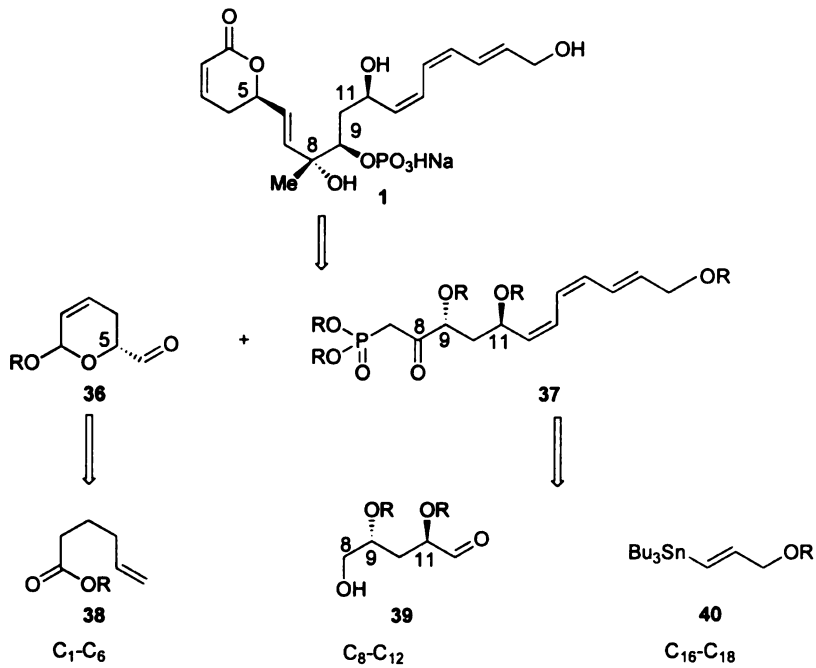
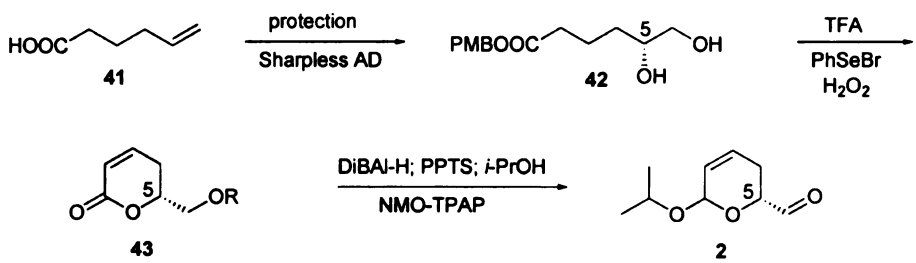


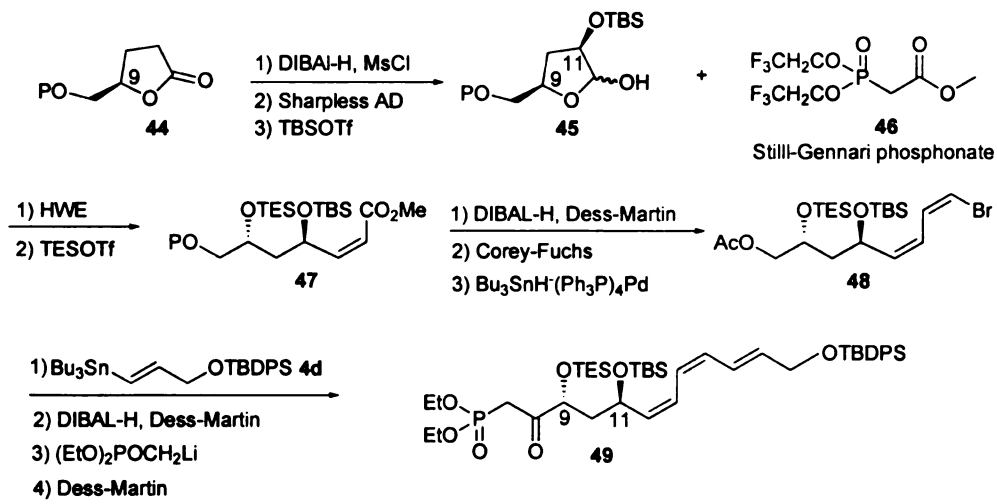
Figure I-13 Boger's Synthesis of the Lactone Fragment[24]



Synthesis of the C_7-C_{18} fragment commenced with a two-step conversion of *D*-glutamic acid to an optically active lactone **44** incorporating the nascent C_9 chiral center

(Figure I-14). This was converted to the corresponding dihyrofuran before the C_{11} alcohol was introduced by Sharpless AD. A subsequent TBS protection of C_{11} gave **45**. Boger then used a stepwise approach to assemble the sensitive *Z,Z,E*-triene. Condensation with a Still- Gennari phosphonate gave the methyl ester **47** and installed the first *Z* olefin.[37] Conversion of the aldehyde derived from this ester to a *cis* vinyl bromide was achieved using Corey-Fuchs two-step procedure and a tributyl tin hydride palladium reduction (Bu_3SnH-$Pd(PPh_3)_4$).[38,39] The last olefin would be constructed using a Stille coupling[40] of the vinyl bromide and the vinyl stannane **40**[41] shown in the retrosynthetic analysis.

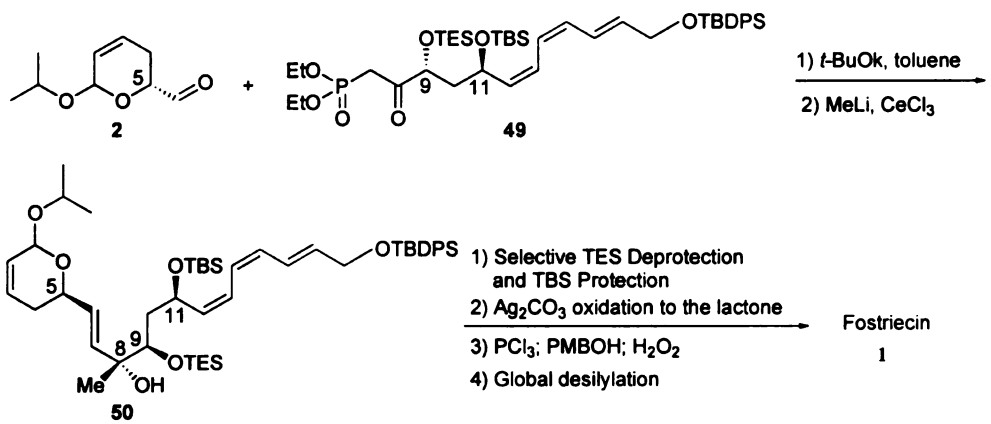
Figure I-14 Boger's Synthesis of the C_7-C_{18} Fragment[24]



A Horner-Wadsworth-Emmons[74,93] was used to couple the isopropyl lactol **2** to the C_7-C_{18} fragment and a methylation of the C_8 ketone with a $MeLi/CeCl_3$ slurry set the last stereocenter (Figure I-15).[42] The latter step only gave a 3:1 ratio of diastereomers in favor of the needed 8*R* isomer, and a 20:1 ratio of 1,2 versus 1,4 products. Separation was accomplished at a later stage in the synthesis. Boger selectively removed the triethyl silyl

(TES) protecting group on C_9 and installed the phosphonate first before doing a global desilylation. PCl_3 followed by *p*-methoxybenzyl alcohol (PMBOH) and subsequent phosphite oxidation with H_2O_2-H_2O was used to introduce the phosphate ester at C_9.[43] Global desilylation was the last step (Figure I-15).

Figure I-15 Boger's Completetion of Fostriecin[24]



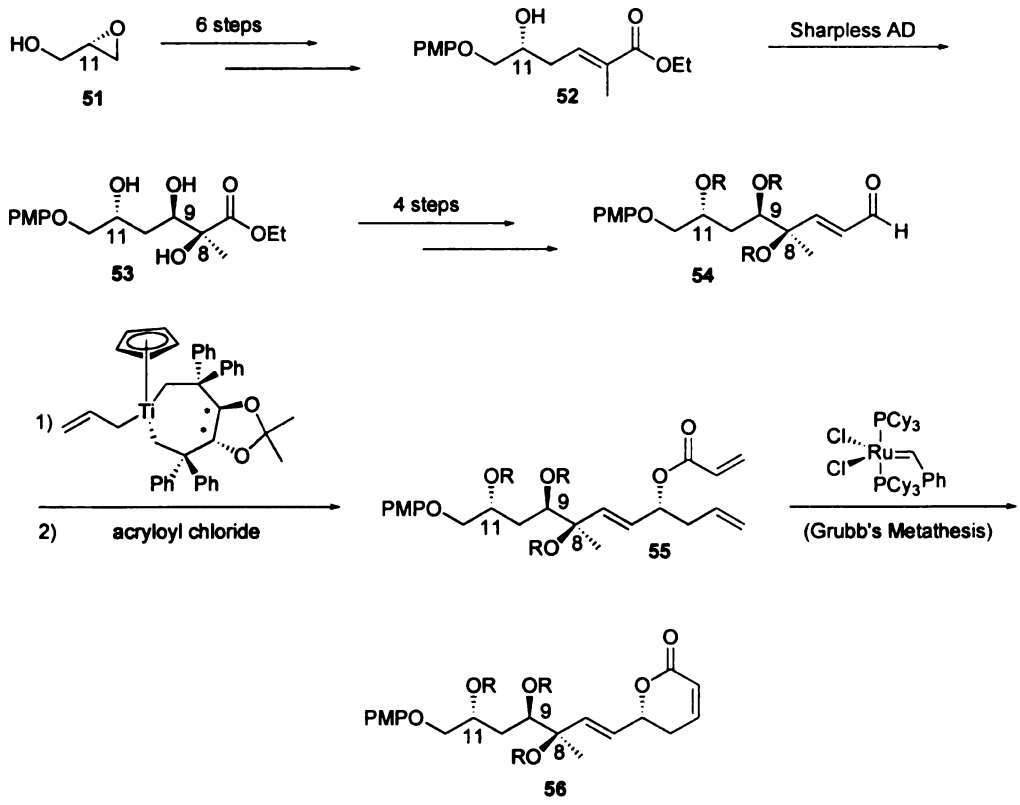
Cossy's Synthetic Approach[33]

A partial synthesis of fostriecin was reported by Janine Cossy and co-workers at the Organic Chemistry Laboratory Association in Paris.[33] Despite the fact that it was just a partial synthesis, (only the C_1-C_{12} fragment) some interesting chemical applications were employed. Using *S*-glycidol as starting material preset the C_{11} stereocenter. A linear sequence of six steps led to the preparation of the C_8 and C_9 stereocenters, which were introduced by a Sharpless AD reaction.[36,94] This method was used to establish the C_5 and

C_{11} chiral centers in Boger's synthesis but was used here to set the two stereocenters C_8 and C_9 simultaneously (Figure I-16).

Another interesting application was the use of an allyltitanium complex to construct the C_5 stereogenic center.[44] This reaction not only accomplishes this, but leads to the lactone in only two additional steps. Protecting the alcohol resulting from allyl addition with acryoyl chloride, set up the two terminal olefins for a Grubbs' metathesis reaction,[45] which proceeded with an 86% yield. This was the first example of this type of lactonization used on route to fostriecin.

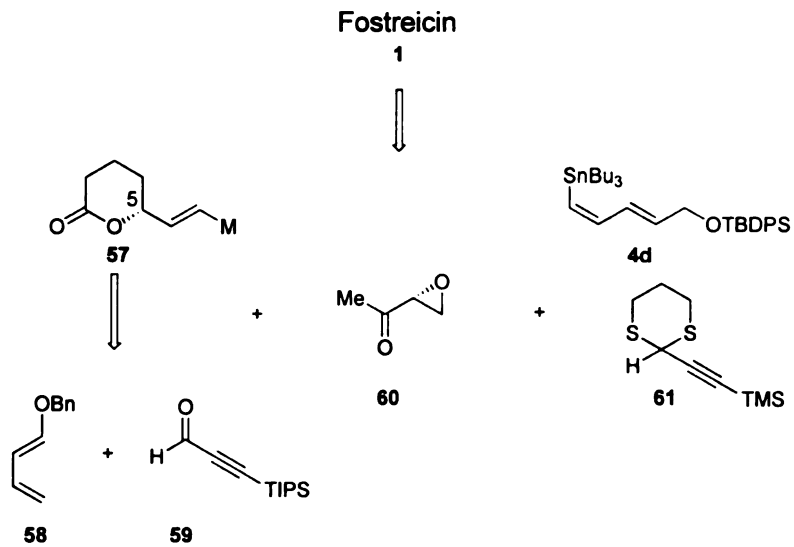
Figure I-16 Cossy Synthesis of the C_1-C_{12} Fragment[33]



Jacobsen's Synthetic Approach[25]

Shortly after Boger's and Cossy's publications, Jacobsen and Chavez achieved a second total synthesis of fostriecin.[25] Their approach was especially interesting because all four stereocenters in the natural product were established differently and none utilizing the chemical methods used by Just, Boger, or Cossy.

Figure I-17 Jacobsen's Retrosynthetic Analysis[25]



The C_5 stereocenter was established via an asymmetric hetero-Diels-Alder reaction catalyzed by a chromium salen complex developed in the Jacobsen laboratory.[46] High yields, enantiomeric excess (ee's) and diastereomeric ratios (dr) were obtained (Figure I-19). The acetylene unit on the protected lactol after hydrozirconation\transmetalation[47] acts as a nucleophile, adding by chelation control to a

chiral epoxy ketone. This addition sets the C_8 stereocenter with greater than 30:1 diastereoselectivity (Figure I-20). The C_9 stereogenic center was also prepared in a unique fashion. A [(salen)Co]-catalyzed hydrolytic kenetic resolution (HKR) reaction was used to prepare enantioenriched *R*-epoxy ketone, this technique was also developed in Jacobsen's laboratory (Figure I-18).[48]

The last chiral center was constructed using Noyori's transfer hydrogenation methodology.[49] The reaction proceeded with a 25:1 diastereomeric ratio. The sensitive triene unit was completed by a Stille[50] coupling of a vinyl iodide **69** to the *Z,E*-stannane **4d** (Figure I-17) to give the fostriecin core. The phosphonate was installed by a method developed by Evans, which was used in Boger's synthetic approach.

Figure I-18 Jacobsen Hydrolytic Kinetic Resolution of Epoxyketone 62[25]

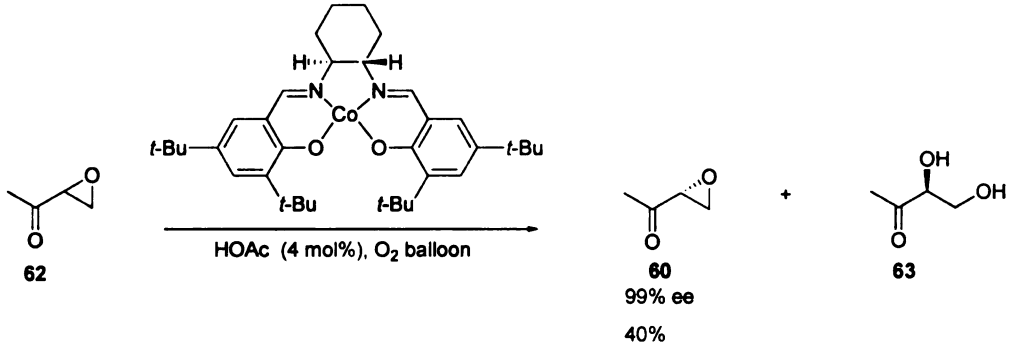


Figure I-19 Jacobsen Asymmetric Hetero-Diels-Alder Reaction[25]

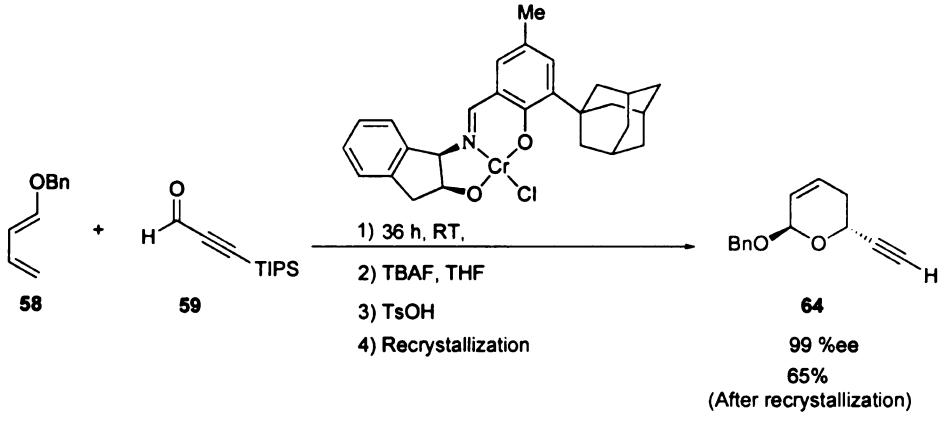
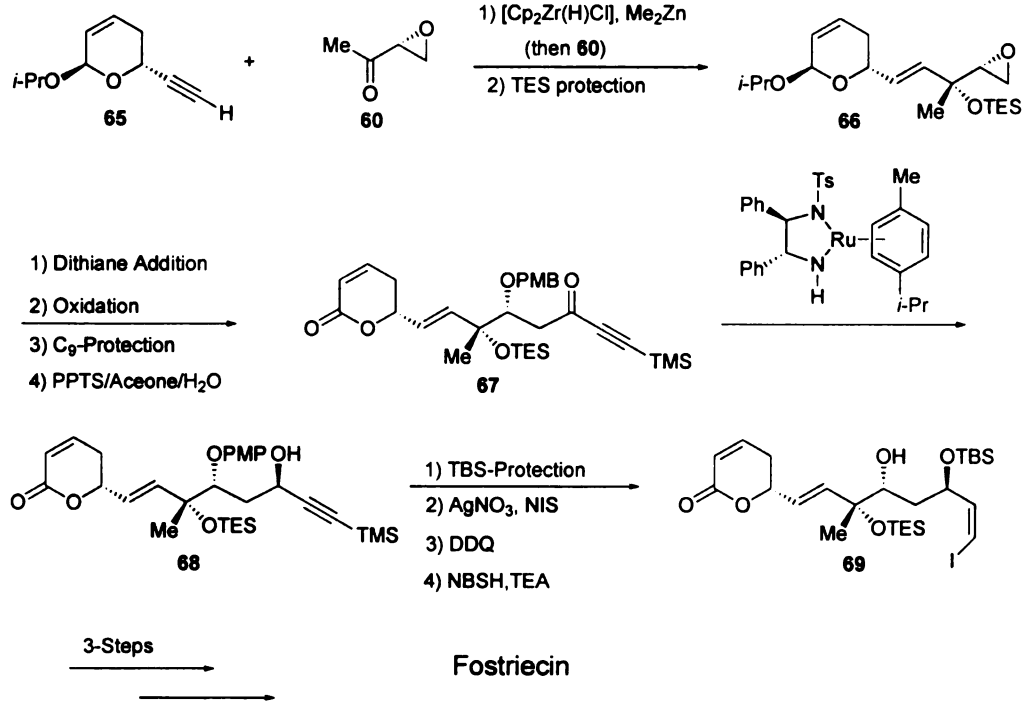


Figure I-20 Jacobsen Synthetic Analysis Continued[25]

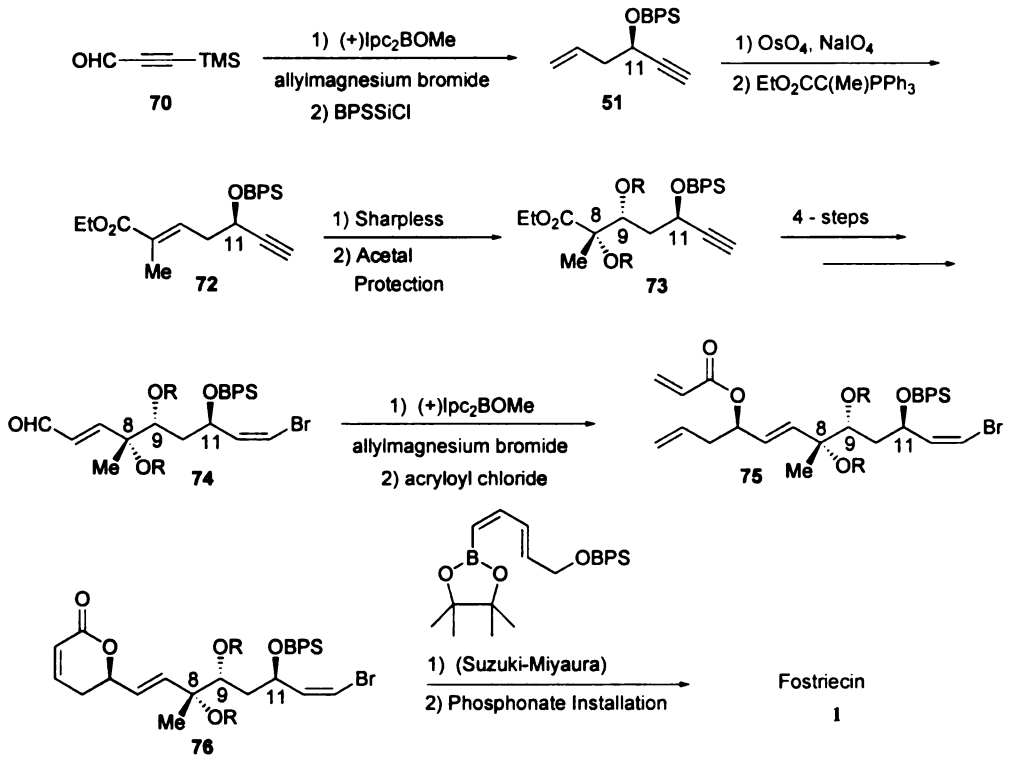


Falck's Synthetic Approach[26]

Reddy and Falck reported the third complete synthesis which had very few steps that would render their strategy unique.[26] Two of their key steps RCM[45] and Sharpless dihyroxylation,[36,94] are identical to Cossy's approach[33]. A third step, allylation of an aldehyde was the same but a different catalyst was used. Reddy and Falck's[26] synthesis began with allylation of **70**. Allylation of the aldehyde **70** with (+)-β–methoxydiisopinocamphenyl borane and allyl magnesium bromide of the aldehyde **70** sets the C_{11} stereocenter with approximately 98 % ee (Figure I-21).[51] Later the same method was used to generate the C_5 chiral center in intermediate **75** which occurred with the same level of induction. This approach to setting the C_5 center is closely related to Cossy's approach with the difference being that Cossy's synthesis[33] required the chiral allyl titanium complex (Figure I-16). Considering this last step, it should come as no surprise that the identical method used to form the lactone in Cossy's synthetic efforts was applied here, the Grubbs' ring closing metathesis.[45] The other two chiral centers were also generated as seen before by Cossy and co-workers,[33] via a Sharpless AD.[36,94]

A Suzuki-Miyaura cross coupling[52] was the strategy utilized by this group to construct the *Z,E,E*- triene moiety, which completed the synthesis of the fostriecin core.

Figure I-21 Falck Synthetic Analysis[26]

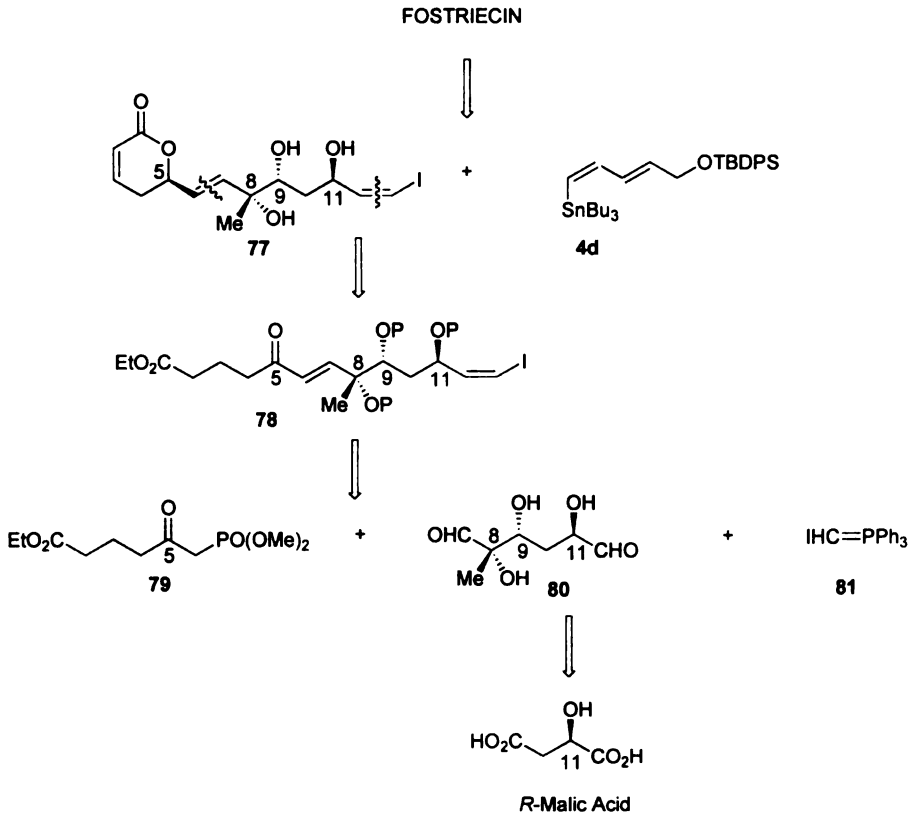


Imanishi Synthetic Approach[27]

In March 2002, sixteen days after Falck's publication,[27] the Imanishi group published yet another total synthesis of fostriecin. Like Falck's synthesis many steps are reminiscent of those seen in previous syntheses (Figure I-22). A Horner-Wadsworth-Emmons[74,93] reaction establishes the C_6- C_7 olefin joining the lactone to the center portion of the molecule, and at the other end a Stille[50] coupling of a *cis* vinyl iodide to a *Z,E*-stannane. The C_8 and C_9 stereocenters were prepared via a Sharpless AD.[36,94] A *R*-Binapthol aluminum hydride (BINAl-H) reduction[53] of **78** was used to construct the C_5

chiral center, with a 20:1 diastereoselectivity. The alcohol resulting from this transformation would complete the acid lactonization in high yield, following the approach used earlier by Boger. The C_{11} stereocenter was obtained using *R*-malic acid as a starting substrate, which was not used as a starting material in any of the earlier synthetic approaches or since.

Figure I-22 Imanishi's Retrosynthetic Analysis of Fostriecin[27]



Kobayashi's Synthetic Approach[30,54]

Shortly after Imanishi's synthesis was published, Kobayashi published his retrosynthetic analysis for dephosphorylated fostriecin which is shown in Figure I-23. The article however delineated the synthesis of the C_3-C_{12} fragment of fostriecin as a mixture of isomers **82**.[54] The C_8 and C_9 stereocenters were introduced by a Sharpless asymmetric dihydroxylation (Figure I-23) and careful optimization with various dienes of type **84** (Figure I-24). Suzuki,[30] Stille[50] and Sonogashira[55] coupling reactions were also utilized in this synthesis in the construction of the C_3-C_{12} fragment of fostriecin **82**. Only the C_8 and C_9 chiral centers were explicitly defined (via a Sharpless AD) the C_5 and the C_{11} centers were present as a mixture of isomers. The author alluded to the fact that these chiral centers could be obtained from commercially available starting materials, so an asymmetric synthesis of fostriecin would be possible with this strategy.

Figure I-23 Kobayashi's Retrosynthetic Analysis[54]

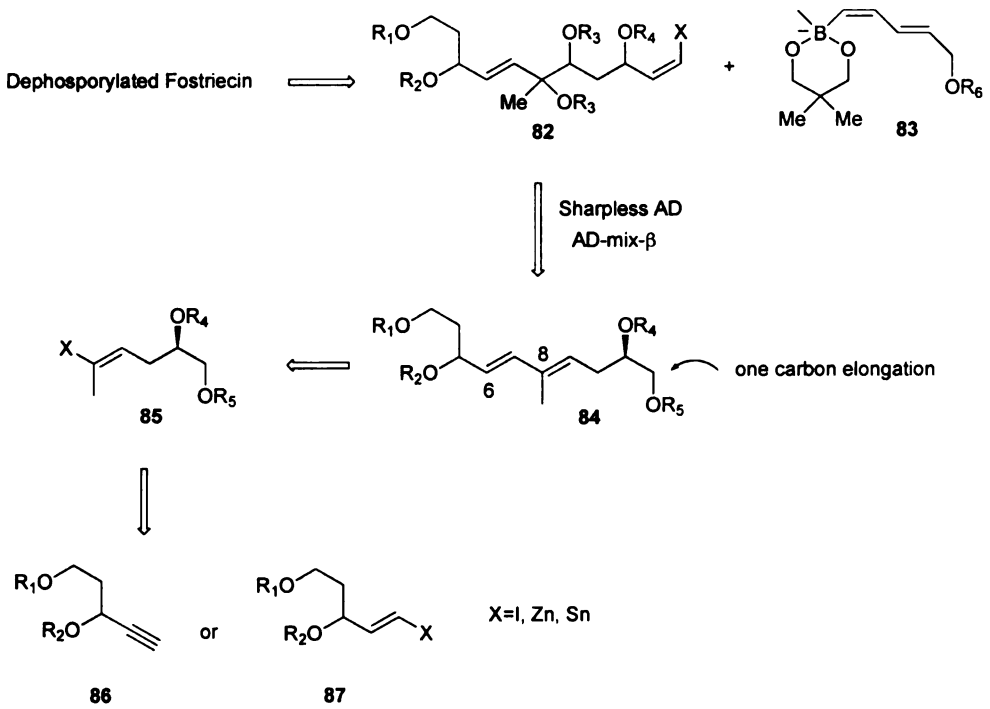
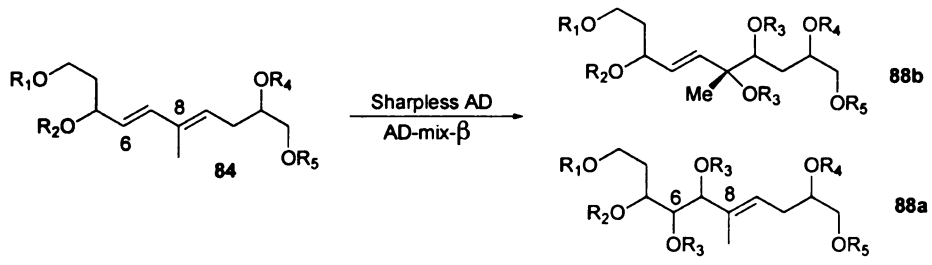


Figure I-24 Optimizing Conditions for the Sharpless AD Reaction[54]



Entry	R_1	R_2	R_4	R_5	ratio (88a:88b)	yield (%)
1	PMB	EE	TBS	PMB	1:1	52 (83% conversion)
2	TBS	EE	TBS	PMB	1:1	<42 (80% conversion)
3	TBS	–	TBS	PMB	1:<1	<20 (complex mixture)
4	PMB	THP	MOM	TBS	1:10	93
5	PMB	EE	– [a]	TBS	1:>17	85
6	PMB	TBS	– [a]	EE	1:3.6	66

All reactions were carried out at room temperature for 2 days.
a - No hydroxyl group was present at that position, just a Hydrogen atom.

In September of the same year, Kobayashi and Wang published a full paper with its contents outlining a formal synthesis of the natural product.[30] The key intermediate targeted is the vinyl iodide **69** (Figure I-26) which was also an intermediate in Jacobsen's, Imanishi's,[25] Shibasaki's,[27] and Hatakeyama's[28] syntheses. Intermediate **69** (Figure I-26) was shown by others to couple to diene fragment **4f** to give the fostriecin core (Figure I-20). Despite the extensive experimentation with Sharpless dihydroxylation of various dienes seen in Kobayashi's earlier work[54] (Figure I-24), he resorted to a kinetic

resolution via Sharpless asymmetric expoxidation[36,94] to install the chiral centers. The scheme below outlines this approach.

Figure I-25 Kobayashi's Formal Synthesis[30]

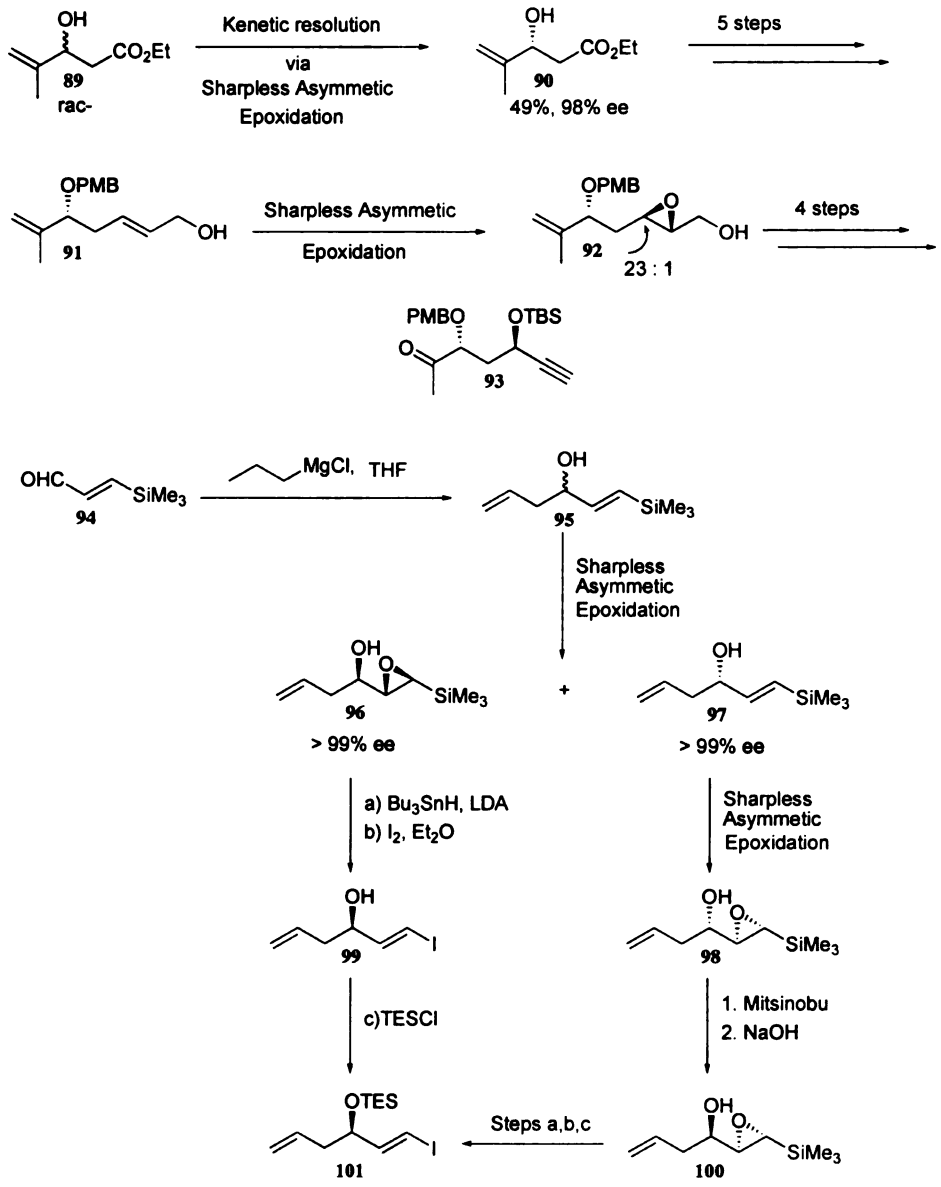
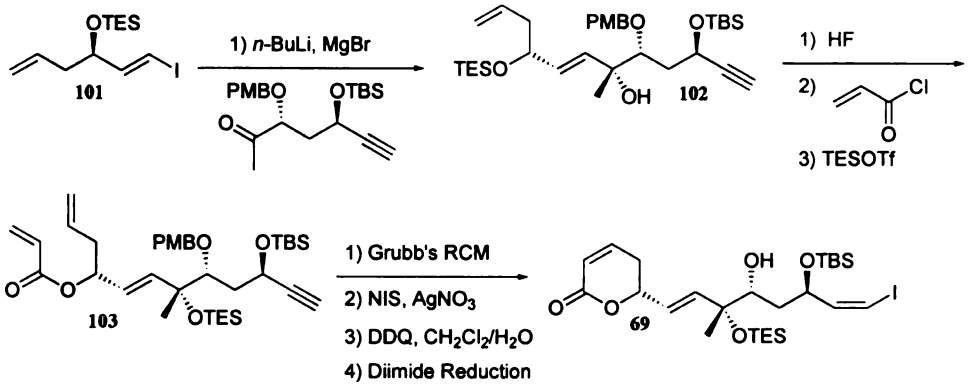


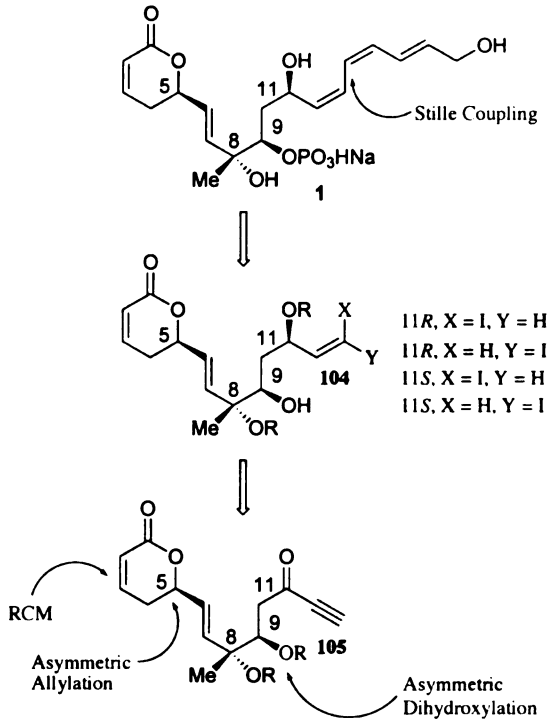
Figure I-26 Kobayashi's Formal Synthesis Continued[30]



Hatakeyama's Synthetic Approach[28]

Other than the USA, publications on synthetic efforts on fostriecin have come primarily from one other country, Japan. Thus far we have examined Imanishi's[27] and Kobayashi's[30,54] syntheses of fostriecin, but more recently two other syntheses surfaced from this country. Hatakeyama's synthesis[28] was the last total synthesis of fostriecin to date. Even more recentl, a formal total synthesis was reported by Shibasaki.[29]

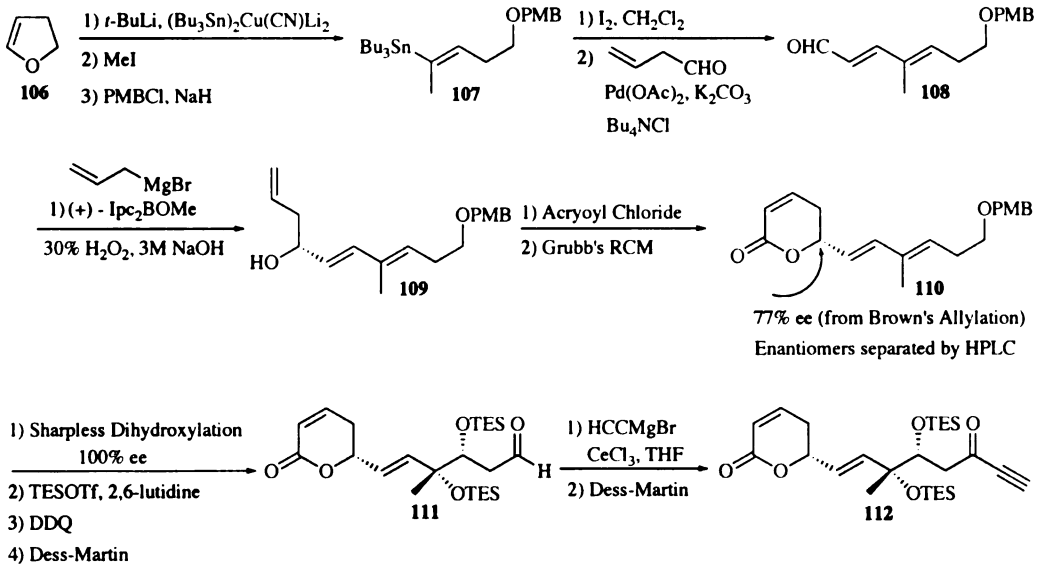
Figure I-27 Hatakeyama's Retrosynthetic Analysis[28]



Hatakeyama's approach is delinated in the (Figure I-27).[28] A key ynone intermediate **105** can be manipulated to prepare fostriecin as well as a number of *E*, *Z* isomers and C_{11} diastereomers. This key intermediate ynone is prepared from dihydrofuran **106**, which when subjected to Aldisson's procedure for stannylation (providing perfect *E* selectivity),[98] para-methoxy-benzyl protection, iodination and Heck coupling[99] gave the *E*, *E*-diene aldehyde **108**. This aldehyde was converted to a secondary alcohol by selective nucleophilic addition of a propenyl boron reagent in 77% ee, and formation of the lactone moiety by Grubb's ring closing metathesis.[45] This lactone was then subjected to a Sharpless dihydroxylation,[36,94] bis TES protection, a

selective PMB deprotection and a Dess-Martin oxidation to give the lactone aldehyde **111** (see Figure I-28). Aldehyde **111** was converted to the key intermediate ynone **112** via the addition of ethynyl Grignard, followed by a Dess-Martin oxidation. In order to complete the total synthesis, the terminal alkyne was converted to a cis vinyl iodide using NaI, AcOH in acetone in a 10:1 ratio, reduced to the secondary alcohol in 84% de and coupled to the *Z*-stannane **4d** prepared by Jacobsen[25], Imanishi[27] and Shibasaki[29] (see Figure I-9). A few hydroxyl group protection and deprotection steps provided the natural product.

Figure I-28 Hatakeyama's Synthetic Approach[28]

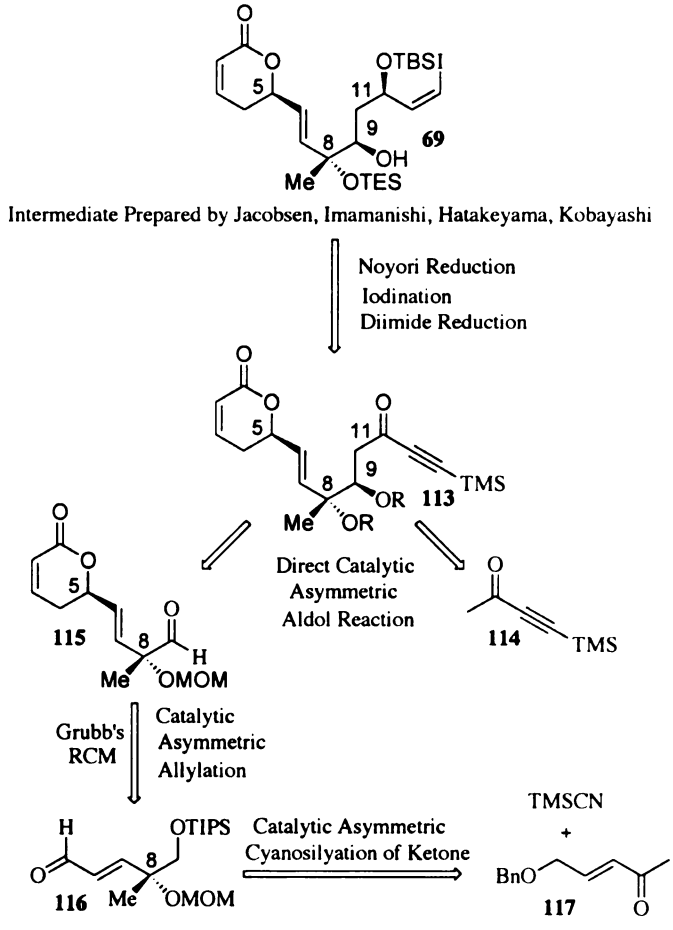


Shibasaki's Synthetic Approach[29]

A couple months after Hatakeyama's publication,[28] Shibasaki and co-workers from the University of Tokyo-Hongo published yet another formal synthesis of fostriecin.[29] Their approach coincided with that of Jacobsen,[25] Imanishi,[27] Kobayashi[30] and Hatakeyama[28] at the *cis*-vinyl iodide Stille coupling precursor **69** (Figure I-29) and

thus constitutes a formal synthesis. The key features of this approach included a Noyori reduction,[53] a direct catalytic asymmetric Aldol reaction, a catalytic asymmetric allylation, and a catalytic asymmetric cyanosilylation of a ketone.

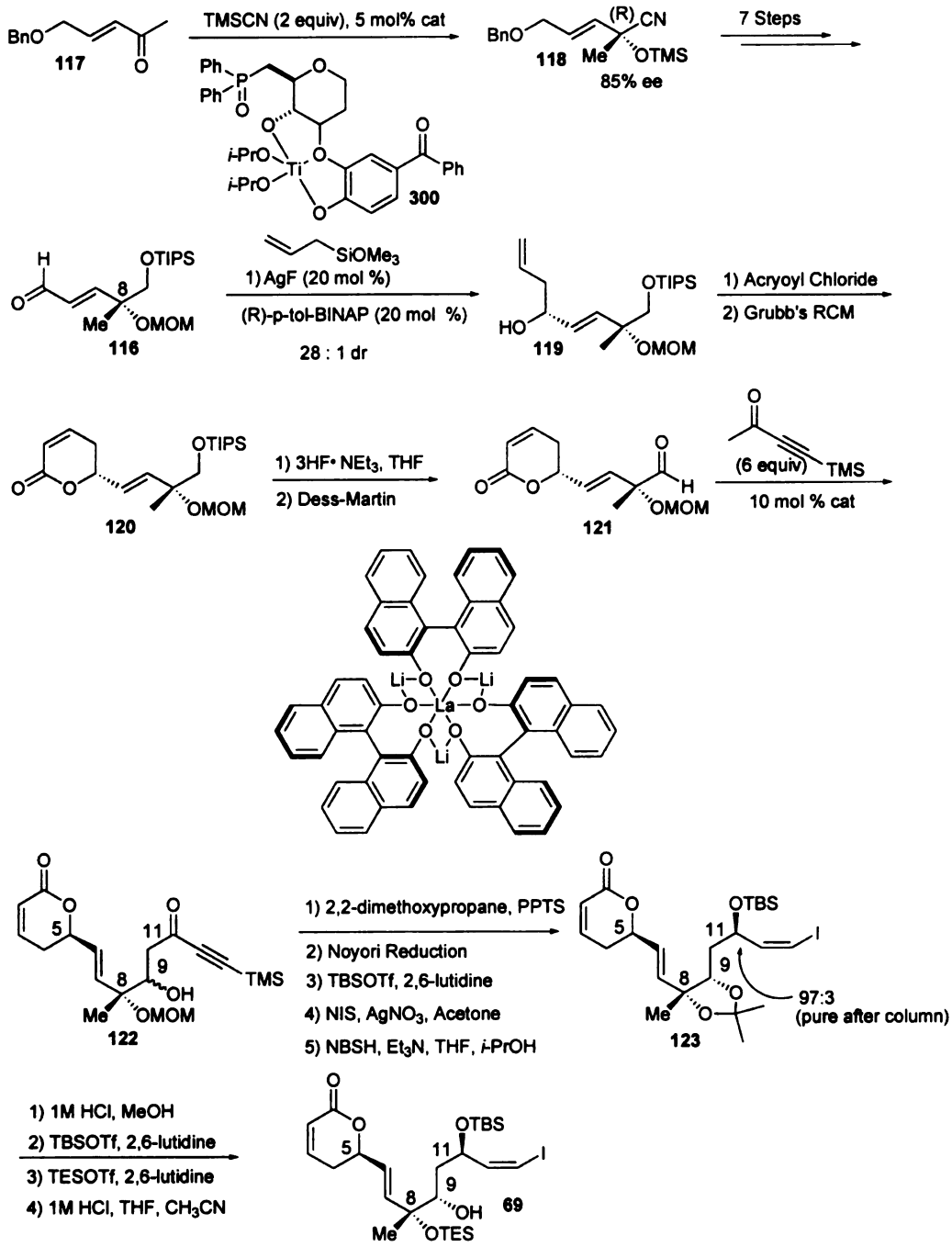
Figure I-29 Shibasaki's Retrosynthetic Analysis[29]



The asymmetric cyanosilylation of **117** was achieved in 85% ee using the titanium catalyst shown in Figure I-30. The resulting (R)-ketone cyanohydrin **118** was converted to a diol which was selectively protected with a TIPS and a MOM group, respectively.

Removal of the benzyl group from the primary allylic alcohol at the other end of the molecule followed by oxidation provided the α,β-unsaturated aldehyde intermediate **116**. At this point a catalytic asymmetric allylation using 20 mol% AgF-(R)-*p*-tol-BINAP complex was achieved in 80% yield with a 28:1 diastereomeric ratio. Lactonization using the Grubb's ring closing metathesis technique was then applied as seen in previous syntheses. The resulting lactone **120** was easily converted to the aldehyde **121** which was the precursor for yet another catalytic asymmetric reaction. Using 6.5 equivalents of a TMS protected 2-but-3-ynone and an (*S*)-Lanthanide Lithium BINOL complex catalyzes this enantioselective aldol reaction proceeded to give **122** in 65% yield with a 3.6:1 ratio of diastereomers. Conversion of this mixture to the corresponding acetonide followed by a Noyori reduction[53] gave a 49% yield of pure desired propargyl alcohol in a 97:3 diastereomeric ratio. Conversion of the TMS protected acetylene to the alkynal iodide followed by diimide reduction gives the vinyl iodide **123** which was easily converted to the desired intermediate **69** by acetonide removal and selective TES protection. While preparing this thesis, Shibasaki and co-workers published a total synthesis of the C_8 epimer of fostriecin.[29] This synthesis retained the same main features described here only varying at the cyanosilylation of ketone **117** (Figure I-30). The variation was using a gadolinium catalyst complex to obtain the (*S*)-stereoisomer at C_8 of **118**, instead of the titanium catalyst seen in Figure I-30.[29]

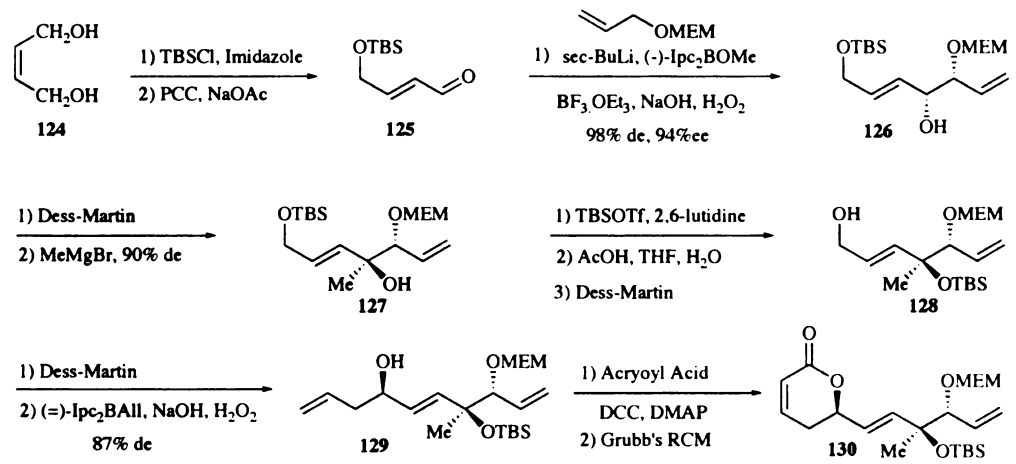
Figure I-30 Shibasaki's Synthetic Approach[29]



Brown's Synthetic Approach[35]

Herbert C. Brown and co-workers joined the fostriecin bandwagon with their publication in August of 2003 of the C_1-C_{11} subunit **130** of 8-*epi*-fostriecin, shown in Figure I-31.[35] The key step in the synthesis of **130** is a chelation controlled addition of a Grignard to an α-oxygenated ketone. As can be seen in Figure I-31 below, *cis*-2-butene-1,4-diol was employed as the starting material. After mono-protection, the resulting alcohol was oxidized to give the *trans*-aldehyde **125** which upon alkoxyallylboration with (-)-β-γ-methoxyethoxymethoxyallyldiisopinocampheylborane gave the homoallylic alcohol **126**, in > 98% de and 94% ee. A Dess-Martin oxidation follwed by a methyl Grignard addition gave the anti tertiary alcohol **127** in 90% de. A few selective deprotection and protection steps leads to the Grubb's ring closing metathesis[45] which gives the lactone **130**. The formation of the lactone via RCM has been seen in earlier synthetic approaches.

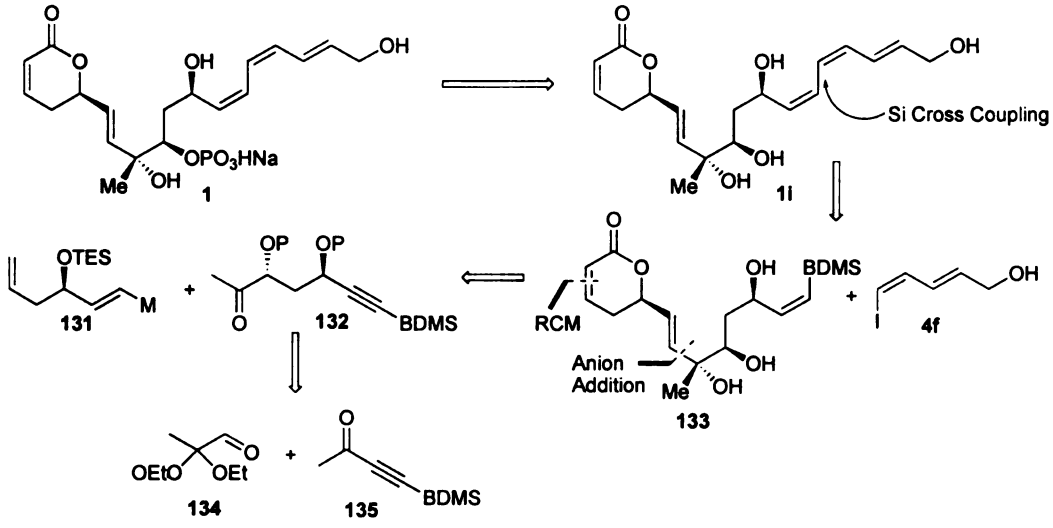
Figure I-31 Brown's Synthetic Approach of the C_1-C_{11} Subunit[35]



Trost's Synthetic Approach[31]

The last publication investigating fostriecin as a synthetic target described the efforts of Barry Trost and co-workers.[31] They used a dinuclear asymmetric zinc complex in an aldol reaction, a chelation controlled Grignard addition and a palladium cross-coupling reaction between an alkenyl silane and a vinyl iodide as key reactions. The synthesis was a formal one, with dephosphorylated fostriecin **1i** being the target. The retrosynthetic analysis is outlined in Figure I-32 below.

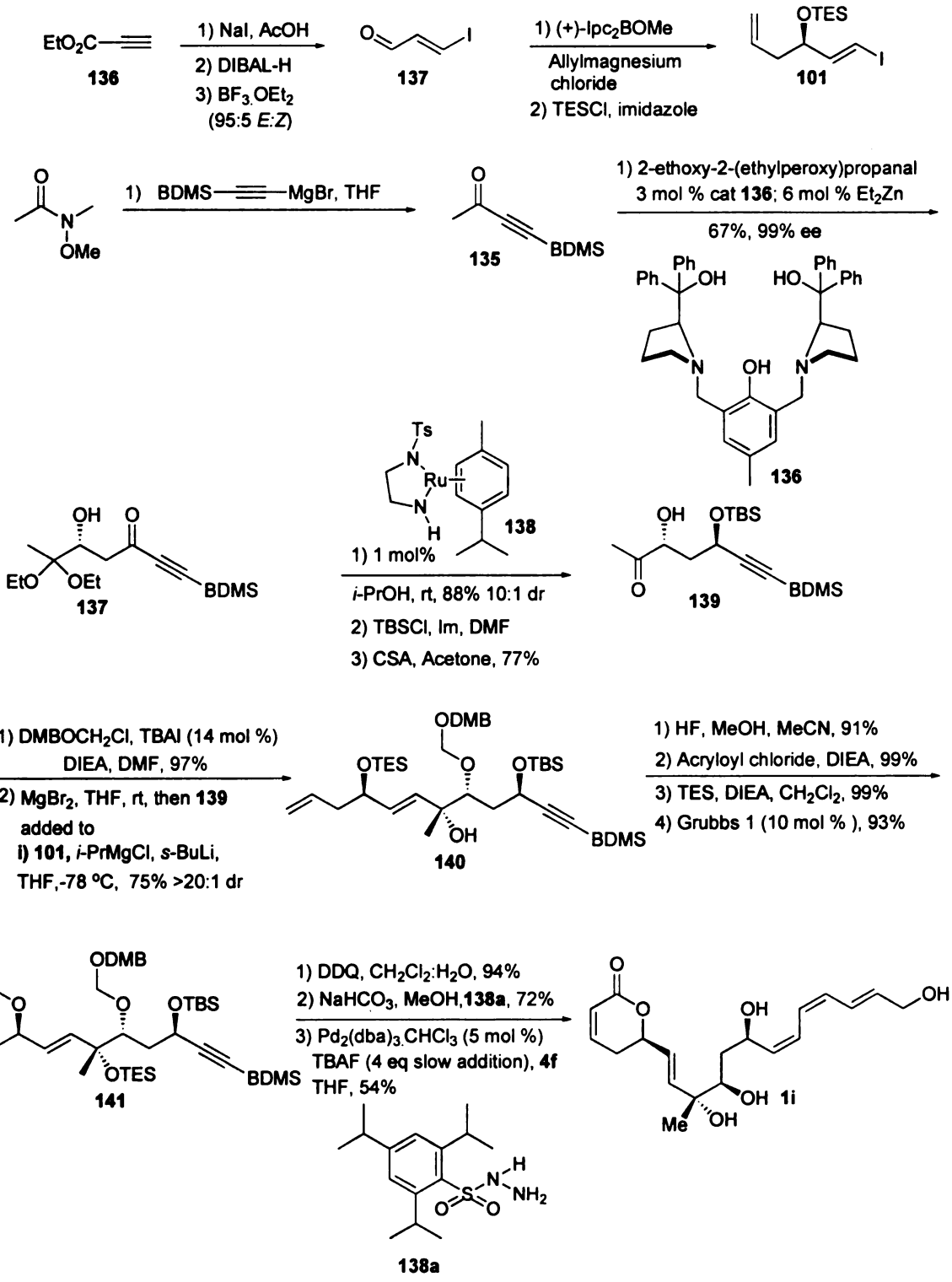
Figure I-32 Trost's Retrosynthetic Analysis[31]



Trost's formal synthesis began with ynone **135**, which was derived from an addition of BDMS protected ethynyl magnesium bromide to the Weinreb's amide of acetic acid. Ynone **135** was subjected to the Zn-catalyzed direct aldol reaction conditions developed in Trost's group to give the desired adduct in 99% ee and 73% yield.

Reduction of the ketone under Noyori's[53] ruthenium-catalyzed transfer hydrogenation followed by selective TBS protection and acetal removal gave intermediate α-hydroxy ketone **139**. After a 3,4-dimethoxybenzyl (DMB) protection of the secondary alcohol, the vinyl magnesium species was added in a chelation-controlled fashion to give tertiary alcohol **140** as a single diastereomer in 75% yield. Removal of the TES-group and acryoyl chloride addition set the stage for the lactone by Grubb's RCM[45] (Figure I-8). This precursor was then subjected to a diimide reduction following a DMB deprotection. The resulting alkenyl silane was coupled to the vinyl iodide **4f** (Figure I-33) in 54% yield with simultaneous deprotection of all the silyl groups furunishing dephosphorylated fostriecin **1i**.

Figure I-33 Trost's Synthetic Approach of the C_1-C_{11} Subunit[31]

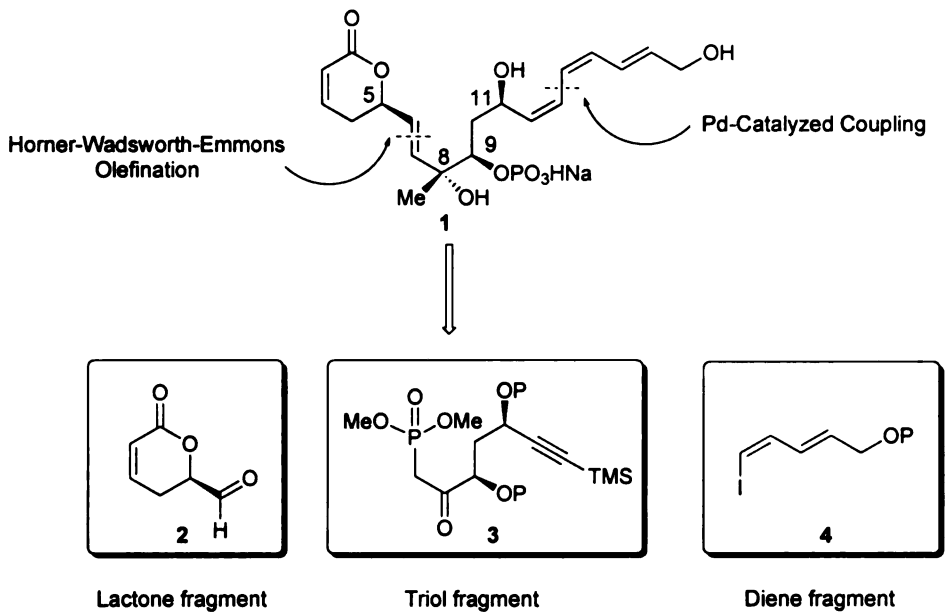


Our Synthetic Approach

At the time our synthetic strategy was planned, only Just and O'Connor's synthesis of the dephosphorylated fostriecin isomer **1e** had been published[32] (Figure I-9). Just's attempt proved to be a valuable asset, and was instrumental in our development of a feasible and practical synthetic approach. The Horner-Wadsworth-Emmons olefination used to connect the lactone to the center portion of the molecule and the Sonogashira[55] coupling used to form the triene moiety, were both tools that were adopted from Just's approach. Some challenges they encountered such as the unstable lactone aldehyde and a sensitive acetylene reduction forced us to design a strategy that would avoid these problems.

As time progressed and as more syntheses were published a few changes in our approach were encured, but the basic strategy remained the same. The following scheme shows our retrosynthetic approach for this molecule and involves the union of lactone **2**, phosphate ester **3**, and diene **4** (Figure I-34). High *E*-selectivity may be achieved from the Horner-Wadsworth-Emmons olefination[74,93] between **2** and **3**, while the Sonogashira[55] coupling of the deprotected acetylene to the vinyl iodide should complete the fostriecin core. A detailed examination of the synthesis of each fragment and their assembly will be given in the following chapters.

Figure I-34 Our Retrosynthetic Analysis of Fostriecin

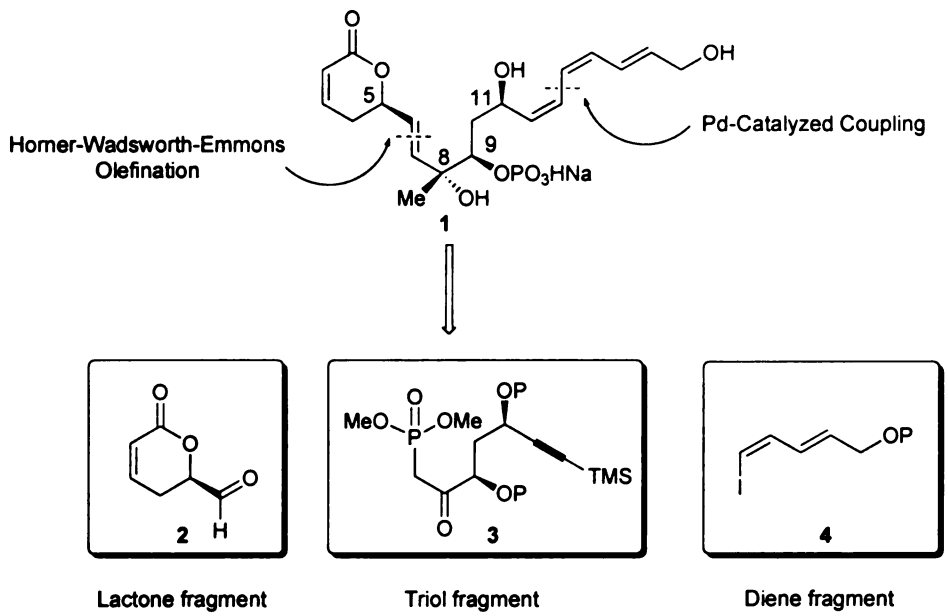


CHAPTER 2

THE SYNTHESIS OF THE LACTONE AND DIENE FRAGMENTS AND A NOVEL ALDOL REACTION

As was outlined in chapter one, our synthetic approach to fostriecin involves the preparation of the three key intermediates, a lactone, a triol and a diene fragment. In this chapter we will examine how the synthesis of the lactone and the triol fragments have been achieved, and look at a novel aldol reaction which is the key step in the triol fragment synthesis. The lactone synthesis was first developed by Mark Parisi[56] and then modified by Su Yu.[57] The synthesis of the diene fragment was developed by Mark Parisi and the aldol reaction of imidazolidinone carbene complexes with 2-alkynals was developed by Dr. Kenneth Wilson.[58]

Figure II-1 Our Retrosynthetic Analysis of Fostriecin

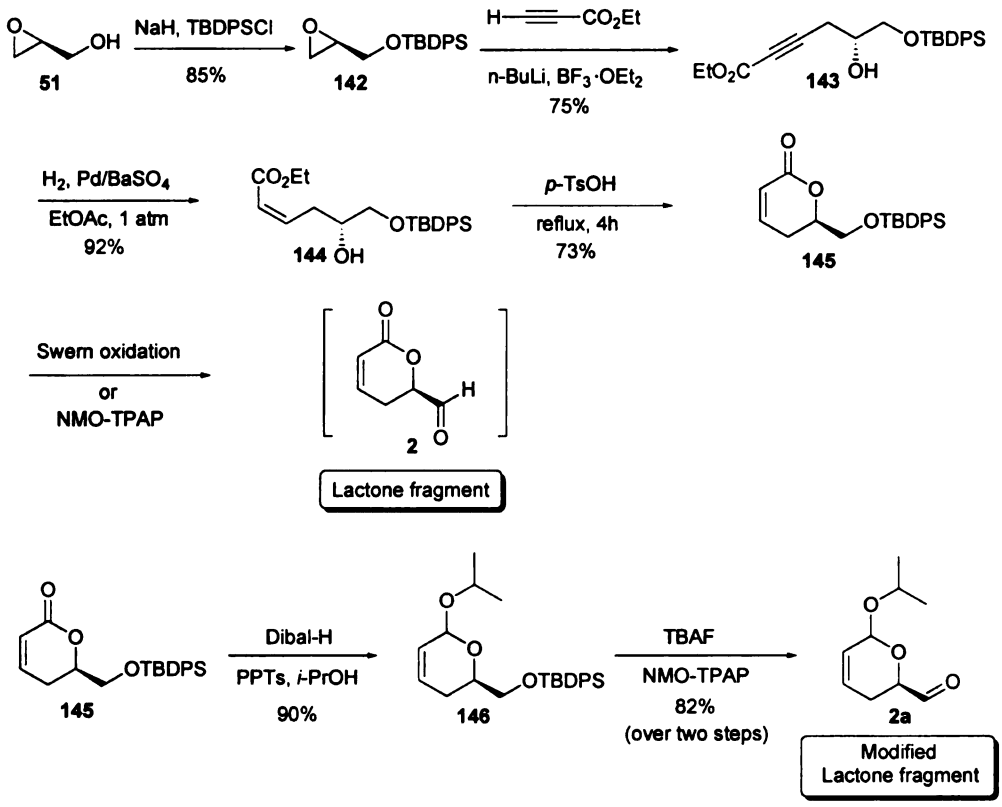


The Lactone Fragment

The lactone fragment possesses one of the four stereocenters found in fostriecin which would ultimately become C_5. This prompted the design of a route using a chiral starting reagent, to set that C_5 stereocenter. Using commerically available *S*-glycidol, a mono-protection of the primary alcohol with tertiary butyl diphenyl silyl chloride (TBDPSCl)[59] initiated the six-step sequence shown in Figure II-2. Nucleophilic ring opening of epoxide **142** with the anion of ethyl propiolate gave alcohol **143** in 75% yield.[60] The anion of ethyl propiolate is not stable above –78 °C and this is the first time that it has been alkylated with an epoxide. This alkynol was then reduced to the *cis*-alkene **144**,[61] and the six-membered ring lactone formed by acid catalysis in an overall yield of 42% for the five steps.[62] The oxidation step was reserved for the next stage of the synthesis as the aldehyde obtained from oxidation is very unstable, and must be made in

situ. In his 1997 paper that established the stereochemistry of the natural product, Boger used a Swern oxidation to obtain this lactone *in situ* which was coupled with a stabilized Wittig reagent.[22] They only obtained a 52% yield for this transformation. Later, in his total synthesis of fostriecin, he prepared the lactone in its isopropyl lactol form, to counteract this low yield.[63,64] This methodology was adopted and the isopropyl lactol **2a** was obtained in 74% yield in three steps from the lactone **145**.

Figure II-2 Synthesis of the Lactone Fragment



Alternative Preparation of *S*-Glycidol

As was mentioned in the previous section *S*-glycidol was choosen as the chiral starting reagent. This compound could be bought from the Aldrich chemical company at a price of $64.20 for 5 grams. Interestingly, racemic glycidol could be obtained from the same company for $88.40 for 500 grams, a factor of about 40 times cheaper. Inspired by this drastic difference in price, we set out to prepare *S*-glycidol or a derivative of *S*-glycidol from its racemic mixture, instead of purchasing the pure chiral material. A technique developed by Jacobsen, namely the hydrolytic kinetic resolution of epoxides provided a solution for the cost efficient preparation of epoxide **142**.[90] Jacobsen has shown that this method also works for glycidols and some examples from his work are shown in Figure II-3. Very small catalyst loadings (0.5-2.0 mol %) of 1,2-cyclohexadiamino-N,N'-bis(3,5-di-t-butylsalicyclidene) cobalt (II) (Co^{II}-Salen) are required to give >99% ee with a variety of substrates. The cost of this catalyst is only $23.00 per gram from Strem Chemicals. In the only example reported by Jacobsen of a silyl derivative of glycidol, the TBS ether gave a 48% yield and >99% ee, with a 0.5 mol% catalyst loading (see figure II-3).

p

p

s

n

c

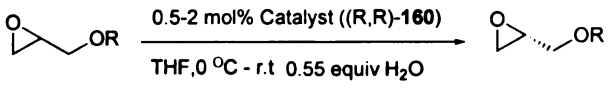
c

w

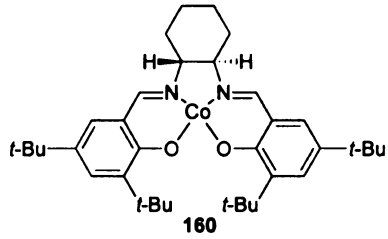
in

an

Figure II-3 Jacobsen's HKR of Gycidyl Derivatives[90]



Substrate	Yield	ee
157 R = H	19% (+oligomers)	>99%
158a R =TBS	48%	>99%
158b R =Bn	47%	>99%
158c R =$CO(CH_2)_2CH_3$	44%	>99%



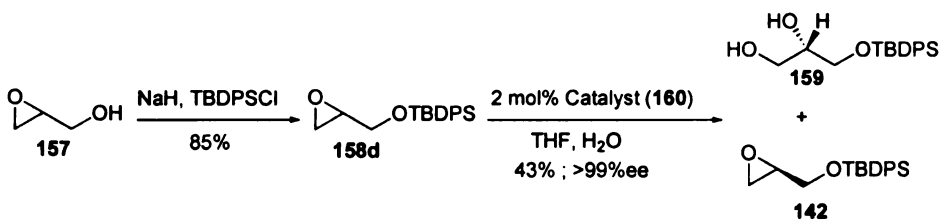
160

Jacobsen's Catalyst

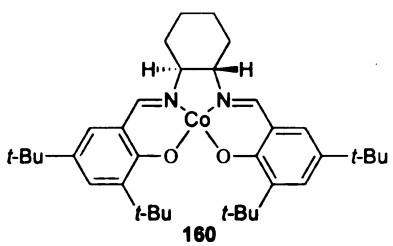
High performance liquid chromatography (HPLC) was used to monitor the progress of the resolution, but because TBS protected glycidol is not UV active, the product had to be derivatized by ring opening with 2-napthalenethiol prior to its subjection to the chiral column. Using TBDPS as a protecting group would allow us to monitor the progress of the reaction without derivatization, providing that the correct conditions for separation could be determined. After a few days of searching, the optimal condition that would separate the two enantiomers of TBDPS protected glycidol **158d** were found using a chiracel-OD column with pure hexanes as the eluent. As can be seen in Figure II-4 the results were comparable to those obtained by Jacobsen for the TBS analog **158a**. The epoxide **142** could be obtained in 43% yield and greater than 99% ee.

In addition the catalyst could be recycled using a protocol described by Jacobsen and in a second run the epoxide **142** was obtained in the same yield and 96% ee. Despite the lost of half the starting glycidol **157**, this method is much more cost efficient than purchasing the chiral material, especially if a large scale synthesis of this fragment is desired.

Figure II-4 Preparation of TBDPS Protected *R*-Gycidyl Ether



157 158d 159 142



160

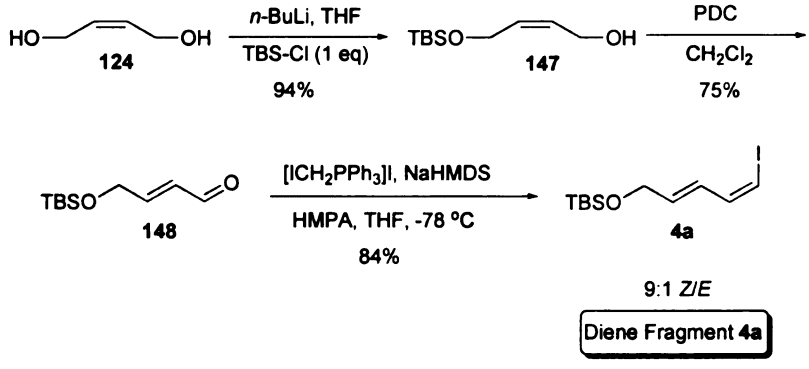
Jacobsen's Catalyst

The Diene Fragment 4a

This fragment was the least difficult to prepare but as reported in Chapter one, it is also the part of the triene unit in fostriecin that is suspected to be responsible for its instability. A late stage coupling of the acetylene of the triol fragment **3** (Figure II-1) to the *Z,E*-iododiene **4a** minimizes the exposure of this sensitive portion of fostriecin to many transformations. If this fragment was to be installed too early, these transformations

might produce undesired products.[56] The synthesis of the diene fragment **4a** is outlined in Figure II-5.

Figure II-5 Synthesis of the Diene Fragment 4a



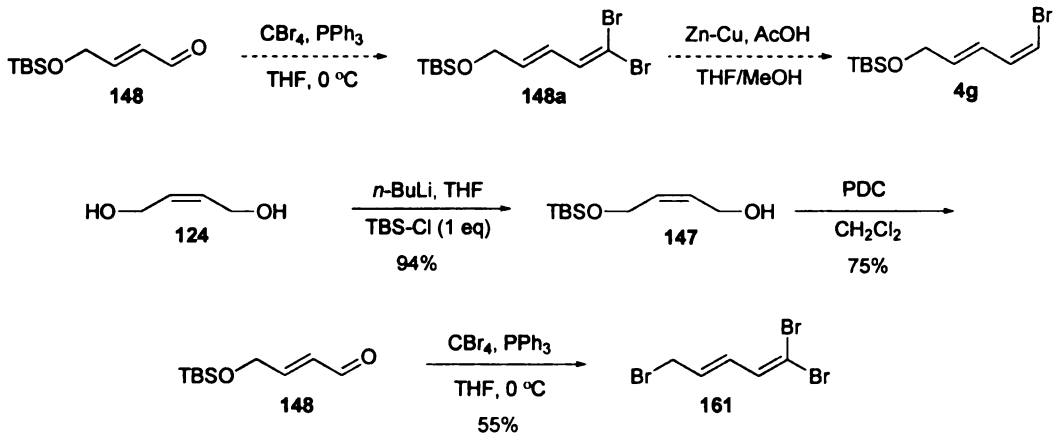
Our synthesis of **4a** commences with the tertiary butyl silyl (TBS) monoprotection of *cis*-2-butene-1,4-diol using Marshall's protocol.[65] The unprotected alcohol group in **147** was then oxidized with pyridinium dichromate (PDC) to form the α,β–unsaturated aldehyde **148** with complete isomerization of the double bond to the desired *trans* stereochemistry.[89] The final step was achieved using Stork's procedure for the synthesis of *cis* iodo-alkenes.[66] A 9:1 ratio of *E*:*Z* isomers was obtained and these isomers of **4a** were easy to separate. The overall yield for these three steps for the mixture of isomers was 59%. It is important to note that compound **4a** was prepared immediately before use. Vinyl iodide **4a** is light sensitive and cannot be stored for any period, otherwise decomposition of the products results.

The Diene Fragments 4b and 4d

The synthetic route used to prepare diene fragment **4a** was a short one, but it involves at least two major problems: the *E*/*Z* selectivity of its formation and its instability to light. Only a 9:1 ratio of *cis* : *trans* isomers of **4a** was obtained, which means that not only is 10% of the material not used, a separation is required. Compound **4a**'s sensitivity only complicated matters because it had to be prepared, purified and used while being meticulously protected from light. A more feasible fragment that should be less prone to this stability issue would be the equivalent vinyl bromide. It has been well established that vinyl bromides are more stable alternatives to vinyl iodides when being handled in the laboratory.[67] The vinyl bromide most likely could be stored and would not have to be used as soon as it was prepared.

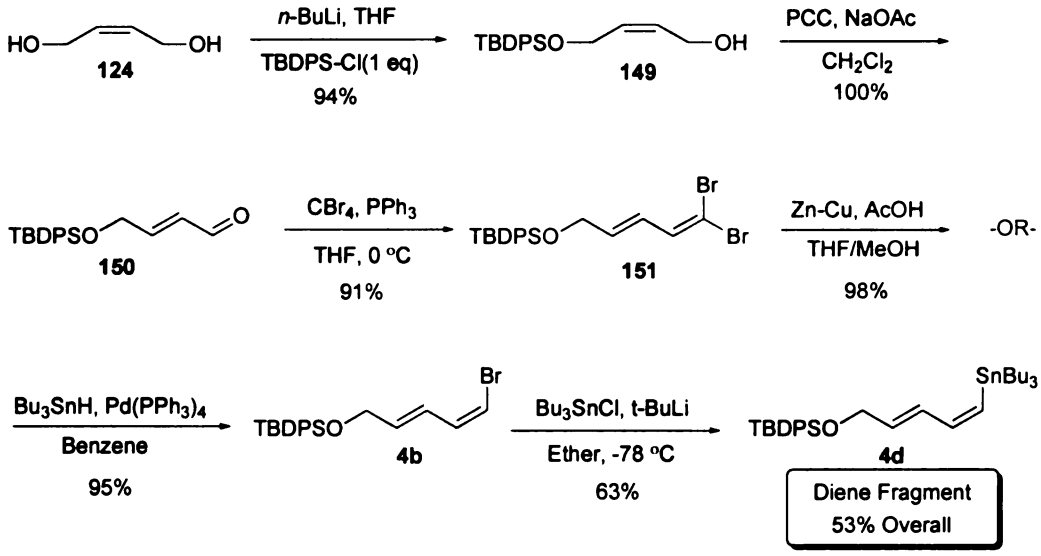
The selectivity issue on the other hand could only be addressed if a different chemical protocol was employed since Stork reported that inferior selectivities are obtained when Ph_3P=CHBr was used instead of Ph_3P=CHI.[66] Using Corey-Fuchs[38] procedure on aldehyde **148** followed by selective reduction[68] of the vinyl dibromide may give higher selectivity for vinyl bromide **4g**. However when Xuejun Lui applied this procedure to aldehyde **148** an undesired product was obtained which was devoid of the TBS group. The product was tentatively assigned as tribromide **161** based on the proton NMR spectrum (see Figure II-6).

Figure II-6 Attempted Synthesis of the Diene Fragment 4g Via Corey-Fuchs Reaction[38]



Failure to convert **148** to **148a** was successfully combated by changing the TBS protecting group to a TBDPS group in the first step of the synthesis. As outlined in Figure II-7 the sequence of reactions proceeded smoothly to give 84% yield of diene fragment **4b** as a single *Z*-isomer by NMR analysis. Vinyl stannane **4d** was also prepared to provide an alternative to coupling **3** to the diene fragment.

Figure II-7 Synthesis of the Diene Fragments 4b and 4d

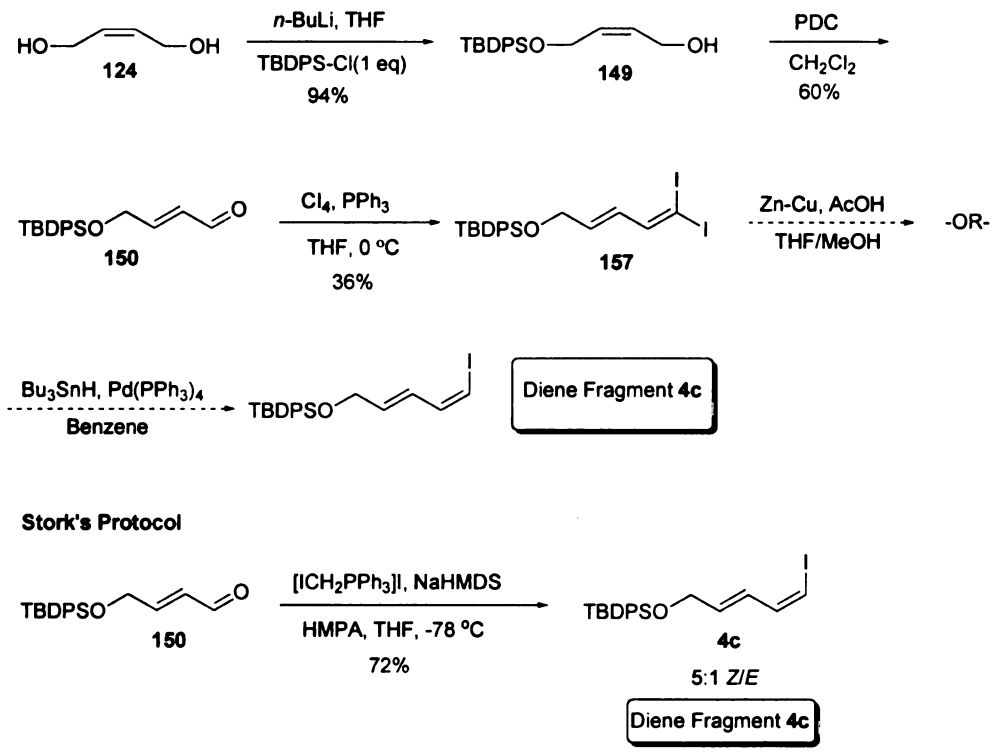


Another minor change that improved the overall yield of fragment **4b** was the use of a combination of pyridinium chlorochromate (PCC) and sodium acetate (NaOAc), instead of pyridinium dichromate PDC as the oxidant for the second step. This change greatly simplified the purification process since filtration over a plug of silica gel gave the product **150** that was pure enough to be used for the next step and pure enough to be completely characterized.

Extending the Corey-Fuchs[38] reduction protocol to vinyl iodide **4c** via diiodide **157** was troublesome. Preparation of the vinyl diiodide **157** using Corey-Fuchs protocol was unreliable, with the optimal yield being 36%. In addition, neither of the two methods successfully employed to do the selective reduction on the dibromide (Figure II-7) worked on the vinyl diiodie **157**. Both the tri-butyl tin hydride[39] and the Zn-Cu[68] couple

reduction methods gave decomposed products. Diene fragment **4c** could however be obtained in a 72% yield with a 5:1 ratio of *cis* : *trans* isomers using Stork's protocol.[66]

Figure II-8 Synthesis of the Diene Fragment 4c



Rationale For The Preparation of Diene Fragment 4d

At an earlier stage in the development of our strategy to fostriecin, some model reactions were carried out with vinyl iodide **4a** and 3-butyn-2-ol (and its TBS derivative) to access whether a Pd-cross coupling reaction with a propargyl alcohol was feasible. And to determine if the alkyne in a *trans*, *cis*-dienyne of the type **153** or **155** could be

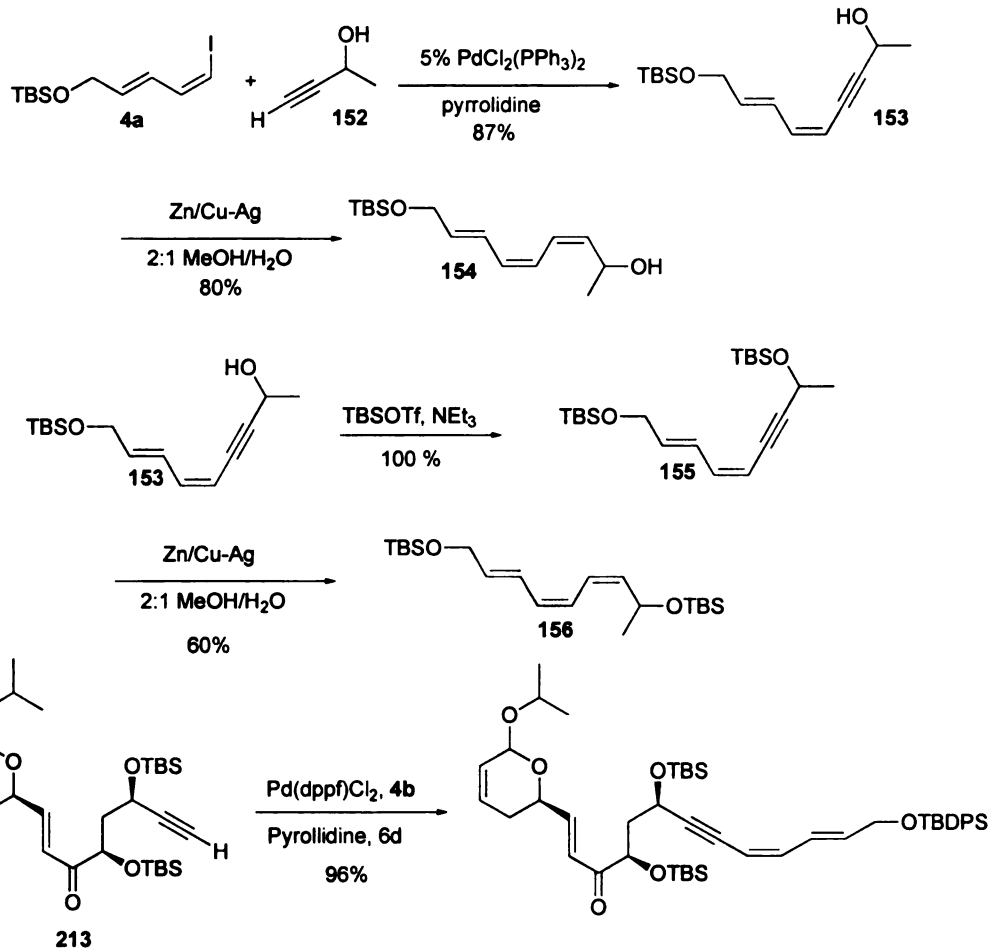
selectively reduced to the *cis*-alkene without any over reduction of the diene unit. Both substrates gave positive results as can be seen in Figure II-9.

Unfortunately, later in the synthetic scheme when diene fragment **4b** (Figure II-7) was coupled to the core **213** (Figure II-9), reaction times of up to six days were necessary to obtain good yields. The synthetic route was modified, and the modification included a change from the vinyl bromide diene fragment **4b** to a tributyl tin derivative **4d** (Figure II-7).[92] The extra step can be seen in Figure II-7, was achieved in 63% yield (unoptimized). Preparing the stannane was not difficult but its purification was a hassle. A common side product was the reduced stannane, which was in abundance if the silica gel column was not buffered with triethyl amine (Et_3N).

Even though preparing the vinyl stannane **4d** requires an extra step lowering the overall yield, there were some advantages to using this as the diene fragment. First it is a known compound making its characterization and the characterization of any unstable intermediates less compulsive;

secondly it increases the weight of this fragment making small scale reactions easier to run; and last it is much more stable than its halide counterparts, being able to be stored for months without any sign of decomposition.

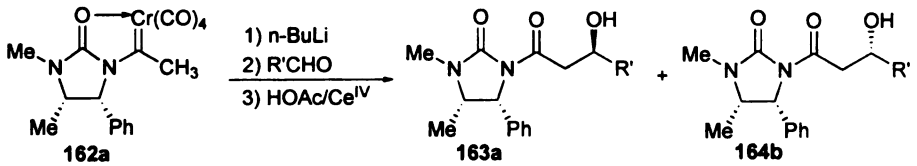
Figure II-9 Palladium Cross-Coupling With Dienes 4a and 4b



A Novel Aldol Reaction

The synthesis of the triol fragment will be discussed in rigorous detail in the following chapter, but the impetus for its construction, a novel aldol reaction will be discussed here.

Figure II-10 Asymmetric Aldol Reactions Using a Chiral Imidazolidinone Fischer Carbene Complex[69]

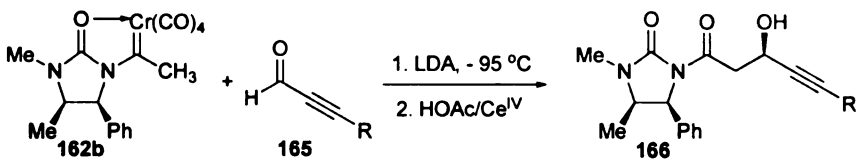


R	temperature (°C)	time (min)	ratio (**163a : 164b**)	yield (%)
n-Pr	- 10	2	91:9	83
	-30	30	89:11	87
	- 30	30	87:13	85 *
i-Pr	-10	10	91:9	83
	- 30	30	95:5	88
Ph	-78 to -30	30	98:2	60

* anion generated with LDA

In 1994 Wulff, Shi, and Wilson published the use of a chiral imidazolidinone Fischer carbene complex developed in our group as a chiral α–unsubstituted acetate enolate synthon for asymmetric aldol reactions.[69] As can be seen in Figure II-10, excellent yields and diastereoselectivities were observed when the enolate anion of complex **162a** was reacted with a variety of alkyl and aryl aldehydes.[71] These encouraging results prompted Dr. Wilson to expand the scope of this reaction to 2-alkynals.[70] He found that the desired propargylic alcohols were prepared in good yields and diastereoselectivities, however the stereoinduction observed in these products was reversed (Figure II-11). This observation was confirmed by X-ray crystallography on **166d**.[58]

Figure II-11 Asymmetric Aldol Reactions of 2-Alkynals Using a Chiral Imidazolidinone Fischer Carbene Complex



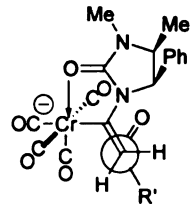
162b **165** **166**

Entry	R	Diastereoselectivity (*anti*:*syn*)	yield (%)
a	CH_2CH_3	13:87	57
b	Ph	17:83	75
c	TMS	9:91	58
d	TBS	9:91	59
e	TIPS	9:91	45

Before one can attempt to explain the anomaly of a change in diastereoselectivity when alkynals of type **165** are used a clear understanding of the scope of the reaction is essential. The chiral auxillary on the carbene complex has three main features that ensure high diastereoselectivity. First the phenyl and methyl groups on the imidazolidinone provides facial selectivity by steric interactions with the incoming aldehyde. The aldehyde will approach from the less sterically hindered face of the enolate. Secondly the bulky ligands on the chromium provide an even more hindered environment. Transition state I was proposed to account for the observed stereoselectivity with aliphatic and aryl aldehydes (Figure II-12). The model has substituent R' of the aldehyde in between the two hydrogens of the enolate carbon. This model predicts that as the size of R' increases, the stereoselectivity should increase. This expection is realized in the data shown in

Figure II-10. The selectivity increases from 53 : 42 acetaldehyde (R' = Me) to 98 : 2 with benzaldehyde (R' = Ph).

Figure II-12 Hypothesized Transition State of Aldol Reaction

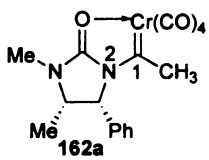


I

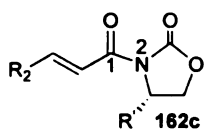
Monomeric Enolate

The third feature that ensures high diastereoselectivity is the chelation of the imidazolidinone oxygen to chromium. Without this feature there would be free rotation around the nitrogen-carbene carbon bond of complex **162a** in Figure II-13. This chelation is necessary to set the orientation of the chiral auxiliary spacially. In other oxazolidinone and imidazolidinone chiral auxiliaries of the type **162c** there is free rotation around the amide bond. Rotation around the amide bond in these systems can be prevented by adding a Lewis acid or chelating transition metal to the system. The beauty of the carbene complex **162a** is that a chelation controlled conformation about the C_1-N_2 bond is built in.[89]

Figure II-13 Preventing Rotation Around the C_3-N_2 Bond In Chiral Auxiliaries



162a



162c

Other Factors that Influence the Asymmetric Aldol Reaction

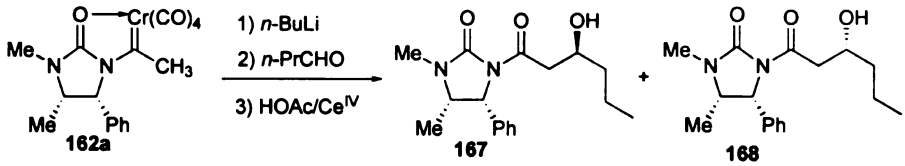
A number of factors were examined by Wulff and Shi in an attempt to obtain a greater understanding of the scope of the asymmetric aldol reaction between alkyl aldehydes and complex **162a**. Already discussed is the effect of the size of the R' group (Figure II-10), but other conditions such as temperature, concentration, type of base used and the effect of additives also investigated and their findings are summarized.

Temperature and Concentration

To examine the effect of temperature and concentration on the asymmetric aldol reaction, butanal was chosen as the alkyl aldehyde. As can be seen in Figure II-14 from entries 1 through 3 as the temperature is lowered from –10 °C to –78 °C there is an erosion of diastereoselectivity. An *anti* : *syn* ratio of 93 : 7 was observed at –10 °C and an *anti* : *syn* ratio of 55:45 at –78 °C. In addition, at –95 °C (entry 5) a reversal of selectivity is observed with the *anti* : *syn* ratio of aldol adduct **167** to aldol adduct **168** being 28 : 72. Entries 3 and 4 examined the effect of concentration. A 10 fold decrease in concentration results in a change in selectivity from 55 : 45 to 73 : 27, favoring the *anti* product **167**.

Figure II-14 The Effects of Temperature and Concentration on the

Asymmetric Aldol Reaction



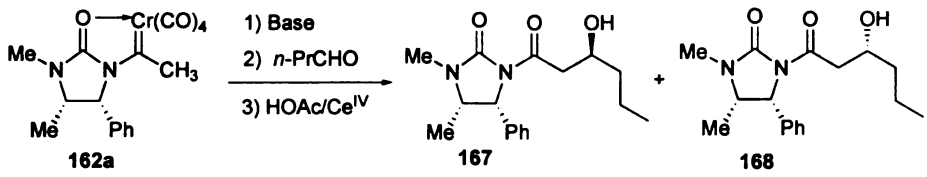
Entry	R	temperature (°C)	ratio (*anti*:*syn*)	yield (%)
1	*n*-Pr	-10	93:7	83
2	*n*-Pr	-50	84:16	83
3	*n*-Pr	- 78	55:45	85
4	*n*-Pr[a]	-78	73:27	85
5	*n*-Pr	-95	28:72	60

[a] This reaction was performed with the enolate concentration at 0.007 M. All others in table-were carried out at 0.07 M.

Type of Base Used

The choice of base used in the asymmetric aldol reaction between complex **162a** and butanal affected the selectivities dramatically. In Figure II-15 entries 2 and 3 show that using sodium or potassium instead of a lithium based base results in almost complete erosion of selectivity. Both entries 2 and 3 gave almost equal amounts of the *anti* and *syn* products, **167** and **168**, while in entry 1 where LiN(TMS) is used as the base, a 90 : 10 *anti* : *syn* ratio of products was observed.

Figure II-15 The Effects of Other Cations on the Asymmetric Aldol Reaction



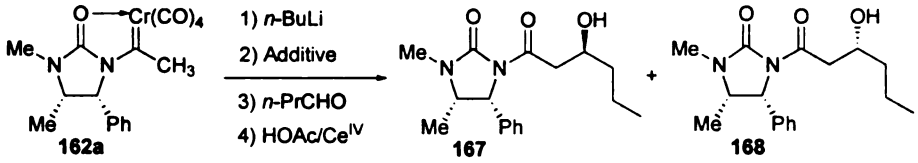
162a **167** **168**

Entry	Base	temperature (°C)	ratio (*anti*:*syn*)	yield (%)
1	$LiN(TMS)_2$	-30	90:10	76
2	$NaN(TMS)_2$	-30	55:45	61
3	$KN(TMS)_2$	- 30	53:47	58

The Effect of Additives

The effect of additives was also studied by Wulff and Shi and some data are shown in Figure II-16. In the reaction between complex **162a** and butanal, both HMPA and BITMSA improves the selectivity of the reaction, but a more dramatic change occurs at -78 °C than at -30 °C.

Figure II-16 The Effects of Additives on the Asymmetric Aldol Reaction



Entry	Additive	temperature (°C)	ratio (*anti:syn*)	yield (%)
1	none	-78	55:45	85
2	HMPA (1.3)	-78	80:20	81
3	none	- 30	88:12	88
4	HMPA (2.0)	-30	90:10	66
5	BITMSA (3.0)	-78	64:36	75

Analysis of the Factors Affecting the Aldol Reaction of Carbene Complex 162a

When the data from the experiments described above was complied and analyzed it suggested that one possibly for the erosion of selectivity is aggregation of the enolates. The results of Figure II-14, entries 1 and 3 are consistent with the presence of aggregates at lower temperatures. The monomeric enolate transition state (Figure II-12) would be expected to give higher selectivity at lower temperature rather than the reverse. Entries 3 and 4 of Figure II-14 also support this hypothesis, when a 10-fold decrease in concentration occurs selectivity for the formation of aldol adduct **167** is increased. The aggregation of enolates is known to be disrupted with dilution. Less aggregation would be expected at 0.007 M (entry 4) than at 0.07 M (entry 3). Thus a greater proportion of the monomeric enolate would be present and the observation of higher selectivity is consistent with the aggregation of enolate I (Figure II-12) and with a lower selectivity from the reaction of the aggregated enolate than with the monomeric enolate.

The results from Figure II-15 also suggest that at –30 °C the sodium and potassium bases promote the formation of aggregates. The ability of sodium and potassium to form aggregates at higher temperatures can be expected because sodium and potassium are bigger and softer cations. However a more conclusive argument may be reached if these reactions are repeated at –78 °C.

The effect of additives maybe due to disruption of aggregates shown in Figure II-16. It is known that lithium aggregates maybe disrupted using bases such as hexamethylphosphoramine (HMPA) or tetramethylethylenediamine (TMEDA).[72] In the reaction with *n*-butanal, extensive studies were carried out to determine if aggregates were involved in this asymmetric aldol reaction. Figure II-16 entries 1-4 suggest that lithium aggregates are being formed at very low temperatures, because using HMPA at –78 °C improves the diastereoselectivity dramactically in favor of the *anti* product, **167**. At -30 °C, however very little change in diastereoselectivity is observed.

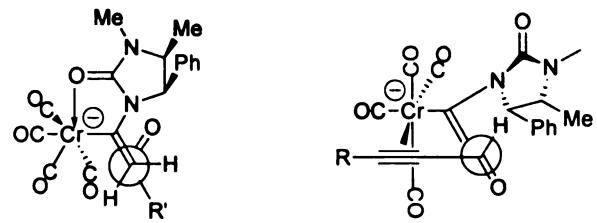
Rationale For The Reversal of Diastereoselctivity in Alkynals

Only aldehydes that cannot chelate to the chromium have been discussed so far. These results might imply that the alkynals ability to chelate to the metal center might not have an effect on the selectivities observed, but rather, are the results of sterics and aggregation alone. However, Figure II-16 entry 5 shows that bistrimethylsilylacetylene (BTMSA) can have a small effect on the selectivity. An analysis of all this data and more that has not been presented here has been summarized.[71,56,73]

While the mechanism of the reaction is not known in detail, the stereoselectivity in alkyl aldehydes appear to be dependant on the aggregation state of the enolate where the

least aggregated species favor the *anti*-adduct and the more aggregated form of the enolate favors the *syn*-adduct. If the least aggregated form is the monomer, then the observed stereoselectivity could be accounted for by the open transition state I where the larger R_1 group leads to high *anti*-selectivity (Figure II-17). The reversal of selectivity in the reaction of the alkynals could be accounted for by their reaction with the more aggregated enolate since these reactions can only be carried out at low temperatures. It is also possible that the alkynals could react via displacement of the imidazolidinone oxygen as in transition state II. The data does not allow for a definitive distinction to be made at this time.

Figure II-17 Hypothesized Transition States of Aldol Reactions

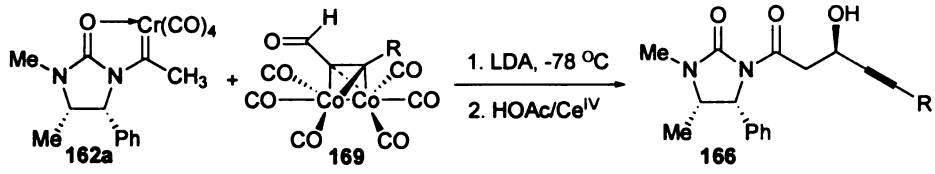


I
Monomeric Enolate

II
Co-ordinated Alkyne enolate

High selectivities are obtained when the reactions are carried out using a dicobalt hexacarbonyl complexed 2-alkynal (Figure II-18).[58] The 3*R* diastereomers are observed which is the same as seen with the aryl and alkyl substrates. As was discussed above, this could be due to a change in the mechanism or to steric factors, since the protected alkyne is much bigger than the 2-alkynals. The diastereoselectivities obtained were higher by comparison to the unprotected alkynals. With this modification both diastereomers can be accessed in high yields and selectivities. This discovery is utilized in the early stages of the triol fragment synthesis to set the C_{11} stereogenic center of fostriecin.

Figure II-18 Asymmetric Aldol Reactions of 2-Alkynal Cobal Complexes with a Chiral Imidazolidinone Fischer Carbene Complex



Entry	R	Diastereoselectivity (*anti*:*syn*)	yield (%)
a	CH_2CH_3	88:12	50
b	Ph	87:13	59
c	TMS	> 99.5:0.5	67
d	TBS	> 99.5:0.5	65
e	TIPS	>99.5:0.5	48

Despite the many experiments carried out so far, the exact mechanism of the aldol reaction of imidazolidinone carbene complexes is still unknown. There is however some evidence to suggest that steric interaction, aggregation, and alkyne chelation to the chromium all could possibly influence the stereochemical outcome of this reaction.

CHAPTER 3

SYNTHESIS OF THE TRIOL FRAGMENT

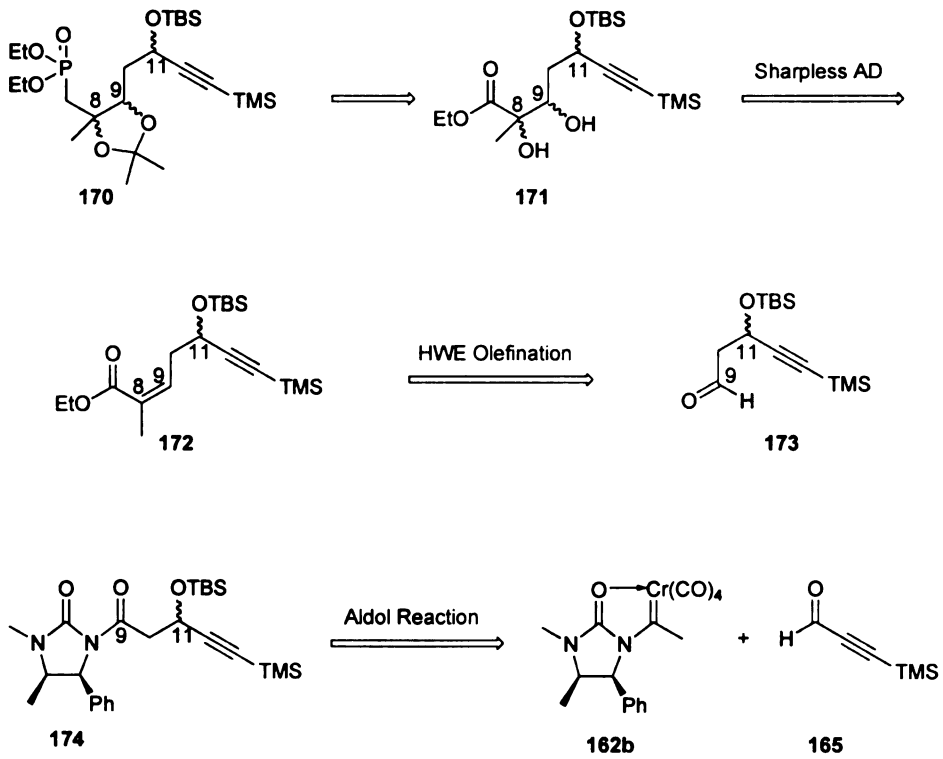
First Generation Synthesis of the Triol Fragment

The initial synthetic strategy of the triol fragment dates back to 1994 and the discovery of the asymmetric aldol reactions of imidazolindinone carbene complexes.[58] At this point the absolute configuration of fostriecin was unknown and as a result the initial and final strategies differ significantly with a few key reactions remaining unaltered.

The lack of knowledge about the stereochemical environment at C_8, C_9 and C_{11}, led to the route seen in Figure III-1. The three key reactions being an asymmetric aldol between a Fischer carbene complex **162b** and a 2-alkynal **165** to construct the C_{11} stereogenic center; a Horner-Wadswoth-Emmons (HWE)[93] olefination to construct either the *E* or *Z* isomer of trisubstituted alkene **172**; and a Sharpless asymmetric dihydroxylation[94] on that alkene to give the C_8 and C_9 stereocenters. The absolute stereochemistry of the asymmetric aldol depends on the choice of the proper enantiomer of the imidazolidinone auxillary in the carbene complex and would afford either of the two C_{11} epimers which when combined with the HWE[93] and Sharpless AD[94] could access any of the eight permutations possible.

This synthetic route was abandoned because of disappointing diastereoselectivities observed in the Sharpless AD[94] reaction. A 2:1 ratio with the PHAL ligand and a 1:1 ratio with the PYR ligand were the best results obtained. Matters became more complex when it was observed that these diastereomers were inseparable by silica gel chromatography and that the physical state of the diol is an oil. Derivatization using 9-fluorenone and *p*-methoxybenzaldehyde failed, so at this point it was decided that designing an alternative strategy would be the better option.

Figure III-1 First Generation Retrosynthesis of Triol Fragment



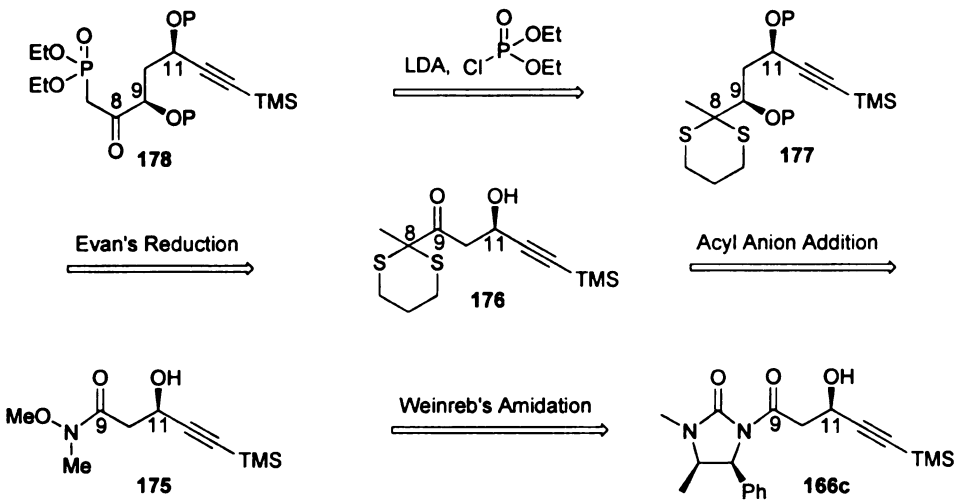
Second Generation Synthesis of the Triol Fragment

In 1997, Boger and co-workers published the absolute stereochemistry of fostriecin.[22] This discovery occurred in a timely fashion because it was right around that time that our second generation synthetic efforts were being developed. In the new approach the HWE[93] and Sharpless AD[94] would be replaced by an acyl anion addition and an Evan's 1,3-*anti* reduction of a β-hydroxy ketone as key reaction steps as outlined in Figure III-2.[75]

The C_9 and C_{11} stereogenic centers were known to be a*nti* and both possessing an R configuration. An Evan's *anti*-reduction[75] of the β- keto alcohol **176** would induce the correct chirality at the C_9 position since the chirality at the C_{11} alcohol would already be

established from the novel asymmetric aldol reaction discussed earlier. The conversion of the Weinreb's amide **175** to the dithiane adduct **176** was planned utilizing the previous work of Leibeskind who demonstrated that Weinreb's amide could be directly alkylated with 2-lithio-1,3-dithiane.[76] The one-step conversion of **166c** to **176** by addition of 2-lithio-1,3-dithiane to **166c** failed. In addition the direct conversion of **166c** to **175** failed. The synthesis of **176** was achieved by initial conversion of **166c** to the methyl ester and then transformed to **176** via **175**.

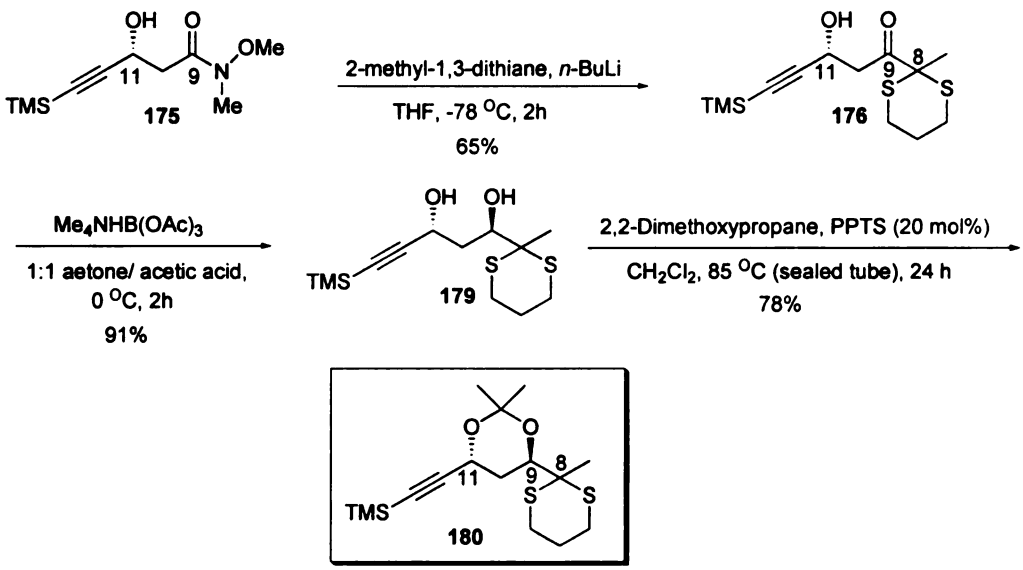
Figure III-2 Second Generation Retrosynthesis of Triol Fragment

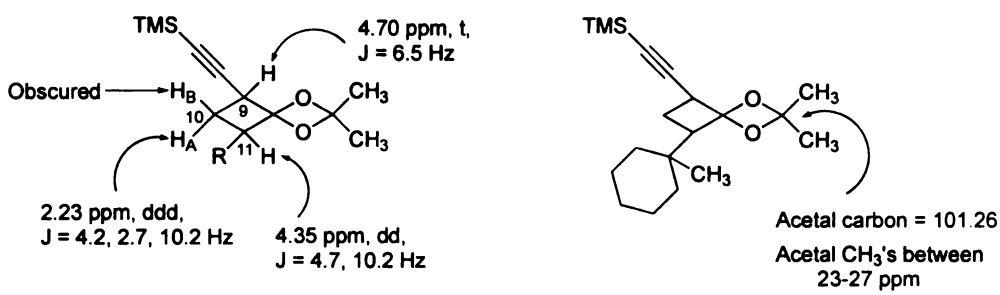


As shown in Figure III-3, the reduction of **176** with Evan's procedure gave a single diastereomer by proton NMR, which was presumed to be the *anti*-diol **179**. The *anti*-stereochemistry was confirmed by Mark Parisi upon derivatization of diol **179** with 2,2-dimethoxypropane to give **180** and subsequent proton and carbon-13 studies.[56] The C_{11} proton adjacent to the alkyne is a triplet at 4.70 ppm with a coupling constant of 6.5 Hz. The C_9 proton adjacent to the dithiane is a doublet of doublets at 4.35 ppm with coupling constants of 4.7 and 10.2 Hz. The C_{10A} proton *syn* to the C_9 proton is a doublet of doublet of doublets at 2.23 ppm, with coupling constants of 2.7 (geminal coupling), 4.2 and 10.2 Hz. The C_{10B} proton *syn* to the C_{11} proton is obscured by signals from the dithiane ring, so its coupling constants could not be determined. The observable 10.2 Hz coupling constant between C_9 and C_{10A} is consistent with the twist-boat confirmation, characteristic of *anti* diol acetonides. The carbon-13 NMR spectrum of the acetonide **180** in Figure III-3 provided additional verification of the relative stereochemistry of the two alcohols.[23,77] The chemical shift of the acetal carbon is 101.26 ppm, within the range

reported by Rychnovsky[77] for *anti* diol acetonides (*syn* acetonides usually have chemical shifts near 99.0 ppm), and well outside the 99.5-100.5 ppm range where and assignment could be ambiguous. The methyl groups on the acetonide are located between 21 and 27 ppm, also well within the range reported by Rychnovsky[77] for *anti* acetonides (*syn* acetonides have methyl group shifts at 19.5 and 30.0 ppm).

Figure III-3 Addition of Dithiane, Reduction, and Acetonide Formation[75,76,77]





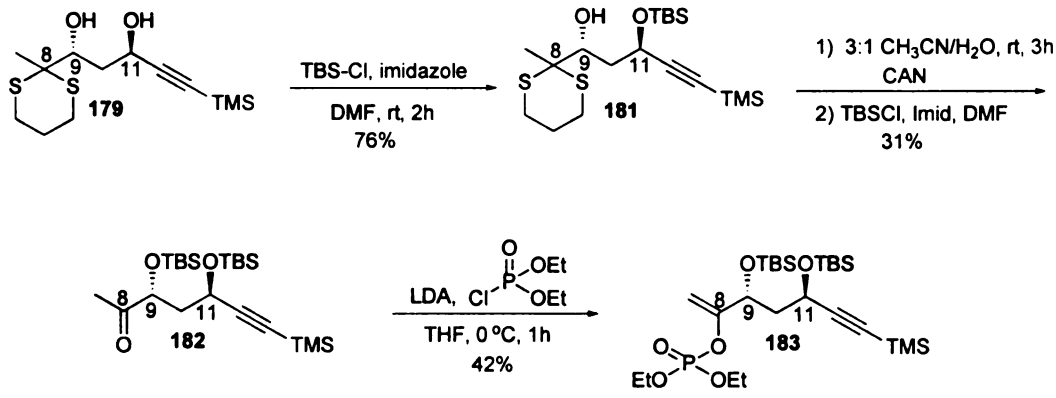
Proton NMR Analysis

Carbon-13 NMR Analysis

With the stereochemistry of the C_9 stereocenter verified, the second generation synthesis of the triol fragment was pursued by Mark Parisi. A tertiary butyl silyl (TBS) protection of the diol only gave the mono-protected product. The product expected from the TBS protection of **179** was the bis silyl ether. This was shown by Su Yu to be the mono-silyl ether **181** correcting an error that had been made in Mark Parisi's thesis. The second TBS protection was only achieved after the cerium ammonium nitrate (CAN)

oxidation was carried out on dithiane **181** and these two steps gave the ketone **182** in moderate yields.[95] Alkylation of the enolate of **182** with diethyl chloro phosphonate was found to give the O-alkylated product **183** and not the desired C-alkylated product.

Figure III-4 Protection, Oxidation and Phosphonate Addition



In addition to the above problem of O-alkylation of **182**, it was also realized that the C_9 and C_{11} alcohols would need to be protected with different groups because later in the synthesis the C_9 would have to be phosphorylated selectively. It was found that while selective protection of the C_{11} was possible, it proved difficult to protect C_9, presumably due to the presence of the methyl group on the dithiane. So again another strategy was sought at this point.

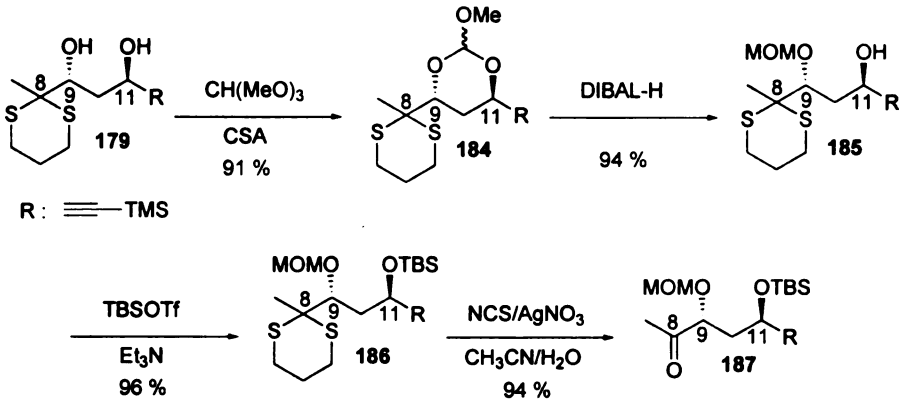
Third Generation Synthesis of the Triol Fragment

Fortunately, the third route retains the same key steps. A change of the C_9 protecting group was required as well as and an efficient and successful method for introduction of the phophonate ester.

Finding an appropriate protecting group on C_9 proved problematic. The 2-methyl-1,3-dithiane unit in **179** provides a much more sterically hindered environment for the C_9 hydroxyl than does the acetylene unit for its neighboring hydroxyl. Hence after mono-protection of the less hindered C_{11} by a TBS group, an attempt to introduce a tri-ethyl silyl (TES) group and a methoxy methyl (MOM) group on the C_9 alcohol failed. A TES and MOM combination was also attempted but proved unsuccessful.

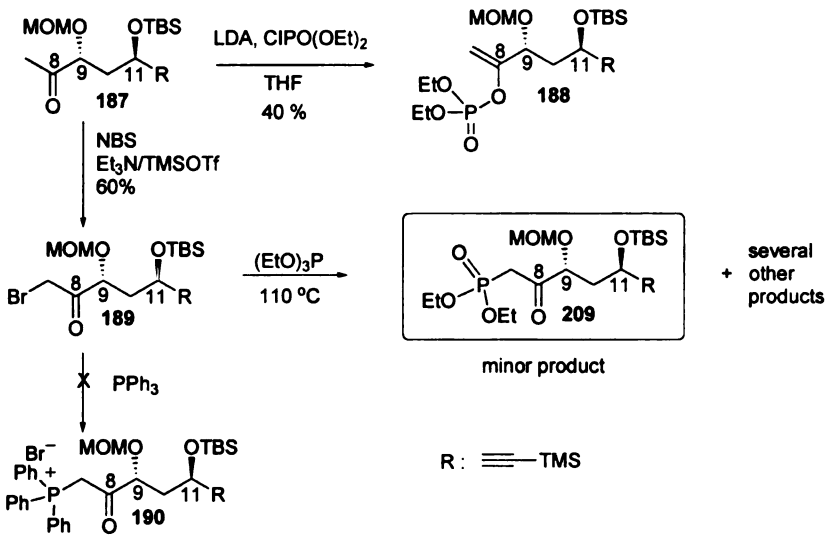
Su Yu, a post doctoral fellow in the Wulff group, utilized a trimethyl ortho ester formation between the C_9 and C_{11} alcohols of diol **184** and its reductive cleavage as a solution to this problem (Figure III-5).[78,79] Reductive cleavage of **184** with DIBAL-H placed the MOM group on the more hindered C_9 alcohol, and a subsequent TBS protection of the C_{11} alcohol followed smoothly. It is of interest to note that DIBAL-H in hexanes and dichloromethane provide the desired product but DIBAL-H in tetrahydrofuran results in only recovery of starting material.

Figure III-5 Selective Protection of Diol[78,79]



With the problem of selective protection of C_9 vs C_{11} solved, attention was turned to the problem of C vs O phosphorylation. It was envisioned that *O*-phosphorylation could be reduced if the ketone **187** was converted to an alpha bromo ketone and the Arbuzov's[96] reaction perfomed. Xuejun Lui in our group found that the reaction of the bromo ketone **189** with triethyl phosphite gave several products with the desired phosphonate **209** as a minor product (see Figure III-6). Conversion to the triphenyl phosphonium salt **190** by reaction of the alpha bromo ketone **189** with triphenyl phosphine also failed. This reaction gave primarily reduction of **189** to **187**.

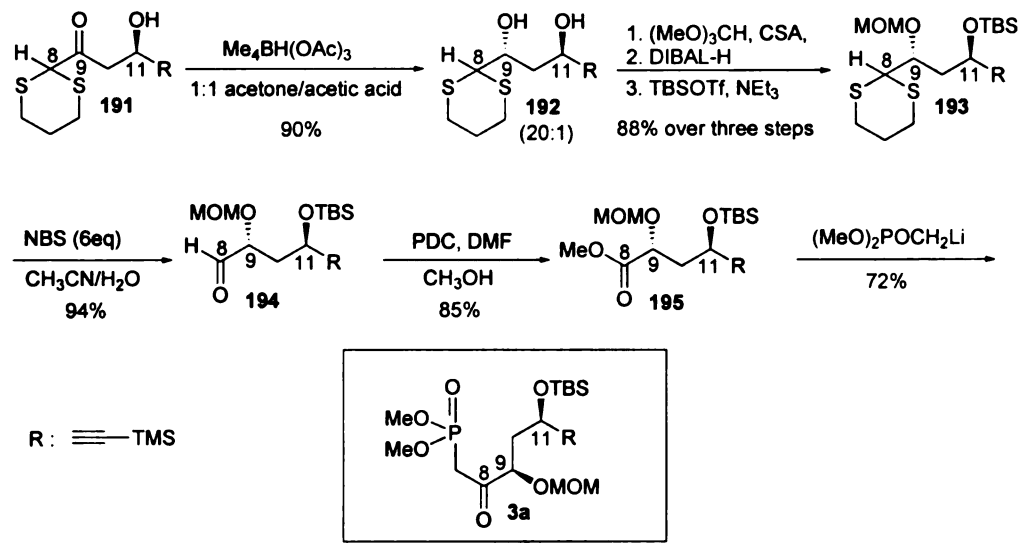
Figure III-6 Preparation of Phosphonate 209



In 2001 Xuejun Lui suggested that the methylene unit alpha to the phosphonate in the triol fragment could be installed via nucleophilic addition of a phosphonate enolate to a methyl ester 195 (Figure III-7) to give phosphonate. This meant that instead of using 2-methyl-1,3-dithiane as an acyl anion equivalent 1,3-dithiane would have to be used. This

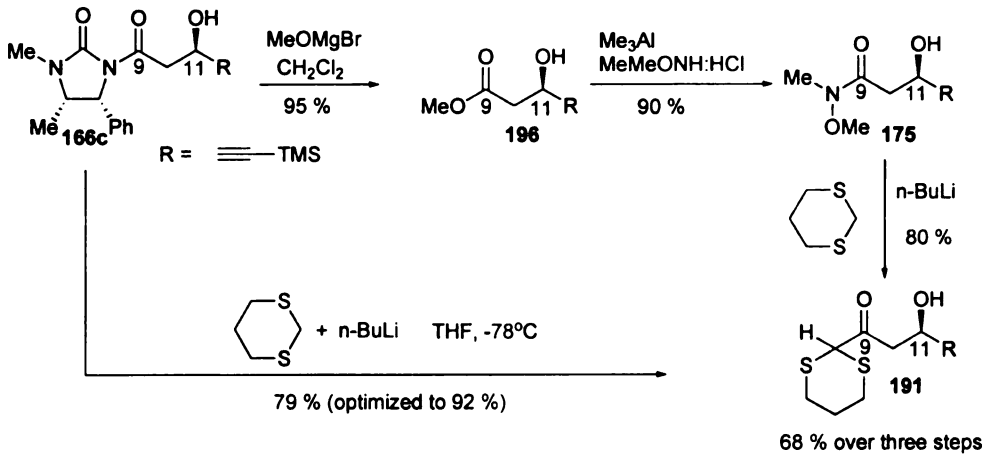
reaction sequenced worked smoothly to produce the desired phosphonate **3a** in a 7.6% yield over 15 steps from chromium hexacarbonyl.

Figure III-7 New Approach to the Phosphonate 3a



This change in acyl anion equivalents also provided the solution to another problem encountered in the first generation synthesis, namely the direct conversion of imidazolidinone **166c** to the dithiane derivative **176** (Figure III-2). Xuejun successfully achieved the related transformation of **166c** to **191** in 79% yield as shown in Figure III-8. Success in this case may be due to the smaller steric demand of 2-lithio-1,3-dithiane vs 2-methyl-2-lithio-1,3-dithiane. This removed two steps in the preparation of **3a** to provide a 13 step synthesis in 8.8% overall yield. The conversion of **166c** to **191** was later optimized to 92% increasing the overall yield of **3a** to 10.2% from chromium hexacarbonyl.

Figure III-8 Improved Acyl Anion Equivalent Addition



Preparation of TES Protected Triol Fragment 3b

The first total synthesis of fostiecin (CI-920) was achieved by Boger and co-workers[24] around the same time our triol fragment was completed and being scaled up. Boger's approach was related to ours in that an HWE[74,93] reaction was used to couple the lactone fragment to the rest of the molecule by the introduction of the chiral center at C_8 via addition of a methyl organo metallic compound to a ketone. It became apparent that in order to achieve the correct diastereomer in the methylation step a Felkin-Ann non-chelation control addition would be necessary (Figure III-9). Boger achieved this using a MeLi-$CeCl_3$ mixture resulting in a 3:1 diastereomeric ratio of C_8 epimers, and with a 20:1 ratio of 1,2 versus 1,4 addition products.[24,97] The protecting group used in Boger's synthesis was a triethyl silyl group which is known to promote non-chelation controlled additions. Our triol fragment possessed a MOM group on the C_9 alpha to the C_8 carbonyl, this is known to give the chelation controlled diastereomer as the major product. This meant our synthetic approach had to be modified to avoid this problem (Figure III-10).

Figure III-9 Boger Non-Chelation Controlled Methylation Conditions[24]

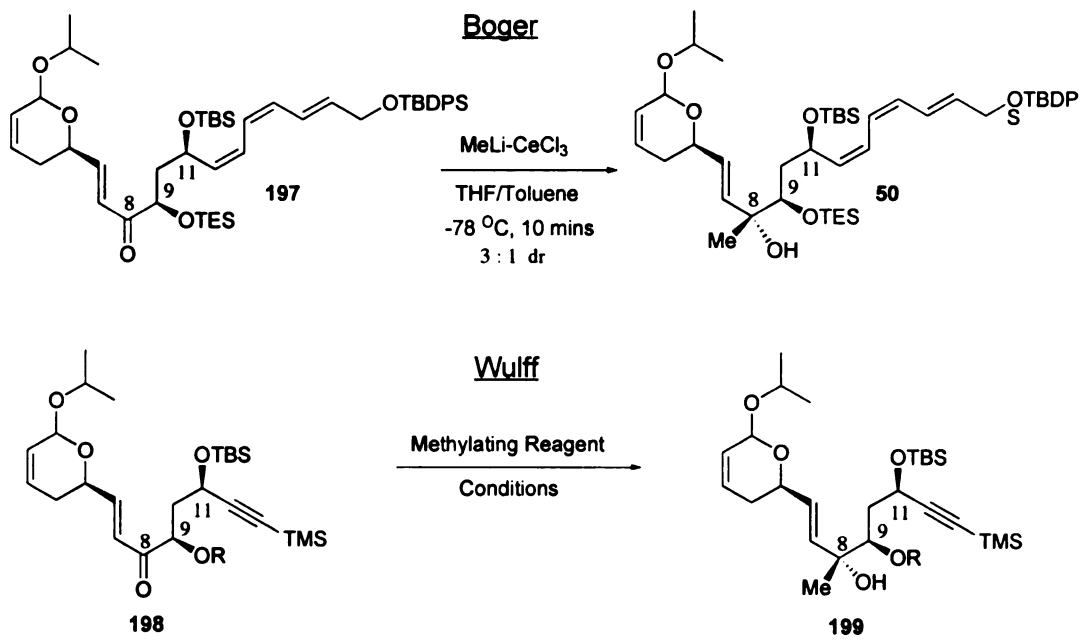
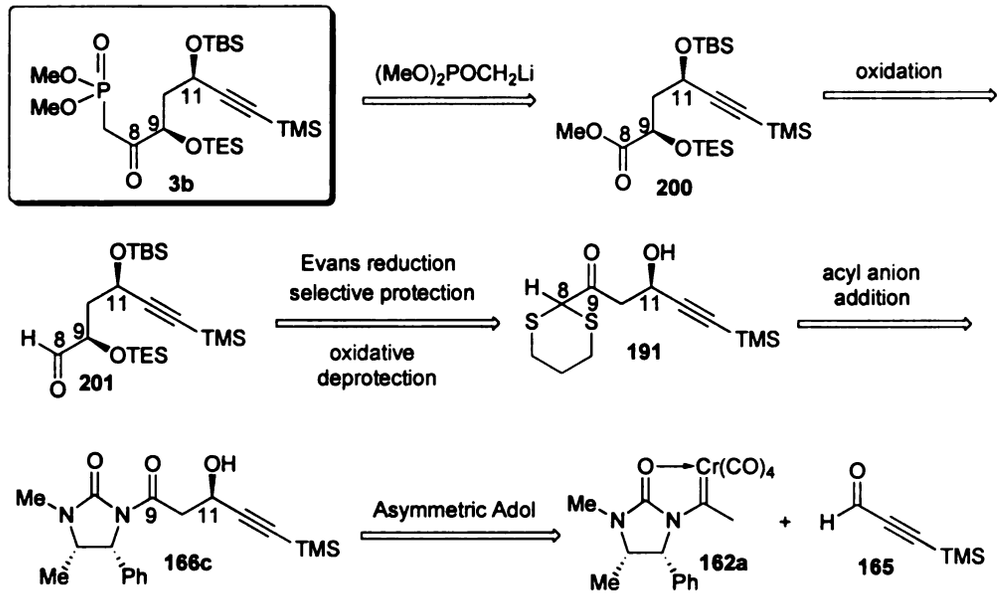


Figure III-10 Retrosynthetic Analysis of Triol Fragment 3b



Problems Encountered in Modification - Preparation of Phosponate 3b

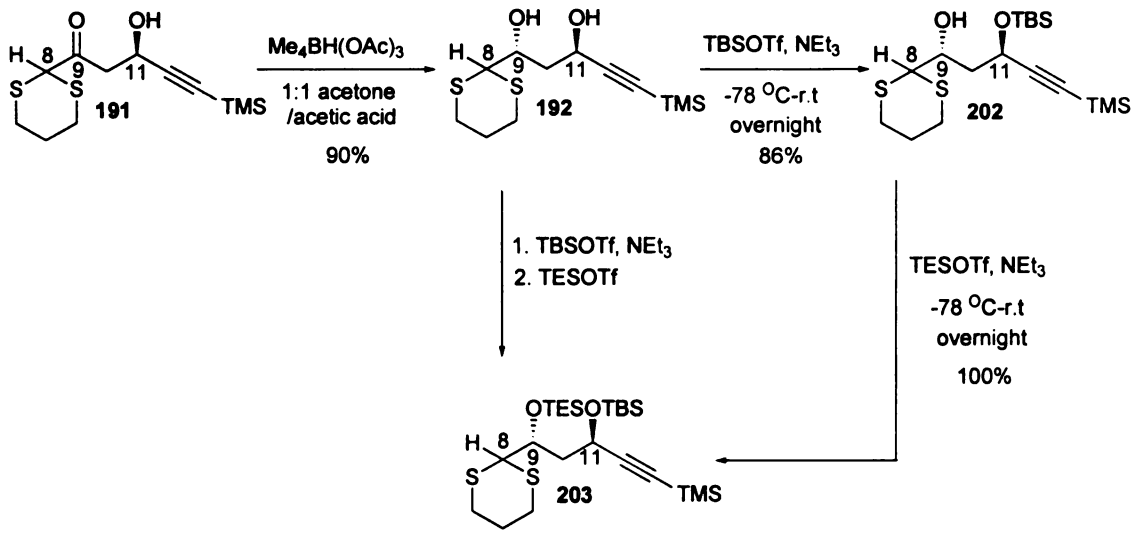
At first glance, it may seem like a trivial task to change the protecting group at the C_9 alcohol in phosphonate **3a** (Figure III-7) from a MOM group to a TES group. However, many challenges were encountered and they were mainly due to the lability of the TES group.

Since there was a ready supply of the MOM protected intermediate **193**, the most efficient approach to **203** (Figure III-11) would be to develop a protocol for the removal of this MOM group from **193** and then reprotection with a TES group.[81] Unfortunately, removal of the MOM group with magnesium bromide etherate ($MgBr_2.OEt_2$) in 1,4-butanethiol gave a mixture of undesired compounds. Better luck was obtained when the ortho ester **184** (Figure III-5) was cleaved to the diol **192** using boron triflouride etherate ($BF_3.OEt_2$) in mercaptoethanol.[82] This reaction gave an 86% yield, but at this point there

was insufficient material to continue to investigate the remaining steps. Thus the protection protocol for the diol **192** was modified.

With the change from disubstituted dithiane **179** (Figure III-5) to the monosubstituted dithiane **192** (Figure III-11) it was conceived that the slightly less hindered environment at C_9 might make the required stepwise selective protection feasible. Using this change to our advantage we protected the C_{11} alcohol with TBS to give **202**, and subsequently web were in fact able to protect the C_9 alcohol with the TES group to give **203**. The results were encouraging with an overall yield of 86% for the two steps. As can be seen from Figure III-11, the conditions required for protection of C_9 and C_{11} were similar, hence, we decided a one-pot procedure might be convenient. To our surprise not only was the reaction successful, but a dramatic increase in the overall yield was observed producing **203** essentially quantitatively.

Figure III-11 Improved Selective Protection of Diol Fragment



Oxidative removal of dithiane using *N*-bromosuccinamide (NBS) in acetonitrile and water was very successful when the MOM protecting group was on the C_9 alcohol **193** (Figure III-7, see experimental for details).[83] However, repeating this protocol with the TES protected **203** gave a mixture of products and recovered starting material. Solubility seemed to be a problem. An attempt to solve this problem was made by substituting acetonitrile with propionitrile in the solvent system. However, this also gave a mixture of products with at least six spots on a thin layer chromatography (TLC) plate. There was also an attempt to solve this problem by reversing the order of addition of the reagents, i.e the NBS solution was added to the protected diol, but to no avail.

At this point a series of reactions were set up to screen various conditions as seen in Table III-1. Two of the five reactions screened gave a clean crude proton NMR of the desired product.[84] In entry 5, one can see that using the same conditions developed before for the MOM derivative **193** with the addition of $CaCO_3$ gave a good result. Based on

this observation, it appears that a base had to be used in order for this transformation to be successful. The source of the problem is presumed to be the generation of hydrogen bromide (HBr) which under the conditions leaves the MOM group unharmed, but results in the cleavage of the TES group.

Table III-1 Oxidative Deprotection Screening Reactions

Entry	Reagents	Temperature/ ^{O}C	Solvent System [a]	Results
1	$NaHCO_3$, MeI	70	CH_3CN:H_2O	Failed
2	$CaCO_3$, MeI	70	$(CH_3)_2CO$:H_2O	Failed
3	$CaCO_3$, Hg_2Cl_2	25	$(CH_3)_2CO$:H_2O	Failed
4	$BaCO_3$, NBS	25	$(CH_3)_2CO$:H_2O	Good NMR
5	$CaCO_3$, NBS	25	CH_3CN:H_2O	Good NMR

a- A 9:1 ratio of solvent to H_2O was used in each case.

Preparation of the Methyl Ester 200 and Completion of Phosponate 3b

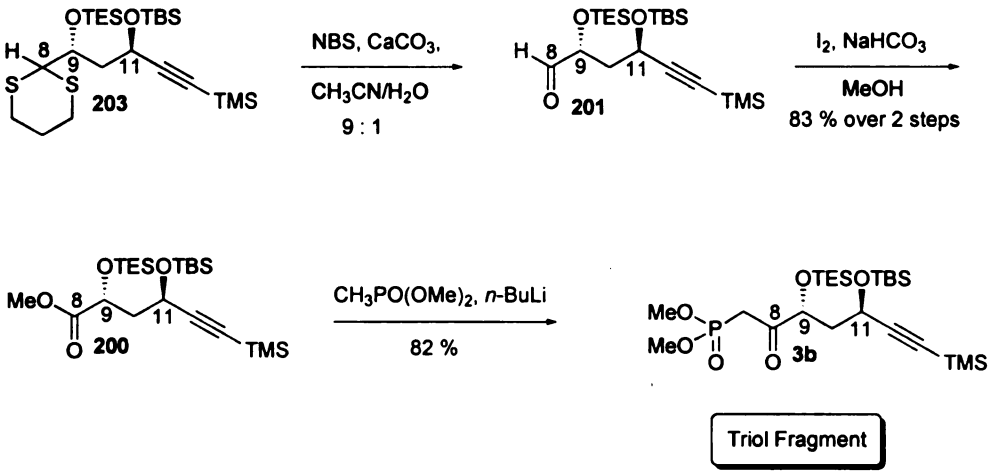
Having overcome the set back of the removal of diathiane in the presence of TES protected alcohol, the synthesis was continued as planned. A pyridinium dichromate (PDC) oxidation of the MOM protected aldehyde **194** in methanol (MeOH) and dimethyl formamide (DMF) proved successful in the preparation of ester **195** (Figure III-7).[85] As with the dithiane deprotection problems were encountered when the PDC oxidation protocol was applied to the TES protected aldehyde **201**. This reaction gave a 44% yield of a methyl ester similar to **200** but which had lost its TES protecting group.

The solution to this predicament came via a *Leibegs Ann. Chemistry* 1992 publication by König and coworkers.[86] Involving an iodine (I_2) oxidation in MeOH in the

presence of sodium bicarbonate ($NaHCO_3$) they reported a procedure for conversion of aldehydes to methyl esters.

The stability of the aldehydes over prolonged periods of times is of a general concern to organic chemists. Anticipating this, a sequential approach from the dithiane **203** to the methyl ester **200** was attempted and found to work. It was found that purification of the aldehyde **201** via chromatography was unnecessary to obtain good yields. A simple work-up of **201** with a saturated solution of sodium thiosulfate (Na_2SO_3), filtration, extraction with ether and drying was sufficient to proceed to the next step. The two steps done sequentially gave an 83% yield of **200**.

Figure III-12 Oxidative Deprotection and Triol Fragment Completion



With the knowledge that the TES group is unstable in even mild acids, the conditions for the introduction of the phosphonate were taken into account. This step should not be a problem since no acid is generated in the reaction. Thus the conditions developed from our earlier synthetic efforts on the conversion of **195** to **3a** (Figure III-7) were attempted on ester **200**.[87] The reaction was however not complete after 48h. This

was suprising since the MOM protected derivative **195** only required 2h. Increasing the reaction temperature to 25 ^{o}C overnight gave **3b** in an 82% yield for a total of 14.2% yield over 10 steps from chromium hexacarbonyl.

While repeating the sequence in Figure III-12, other problems were incurred that were not seen in the first time through. The *n*-butyl lithium used must have an accurate titer otherwise the TES group is lost. In addition when performing silica gel chromatography on the intermediates a solvent system containing 0.5-1% triethyl amine should be used a precautionary measure to avoid any loss of the TES group.

Preparation of Phosponate 3c

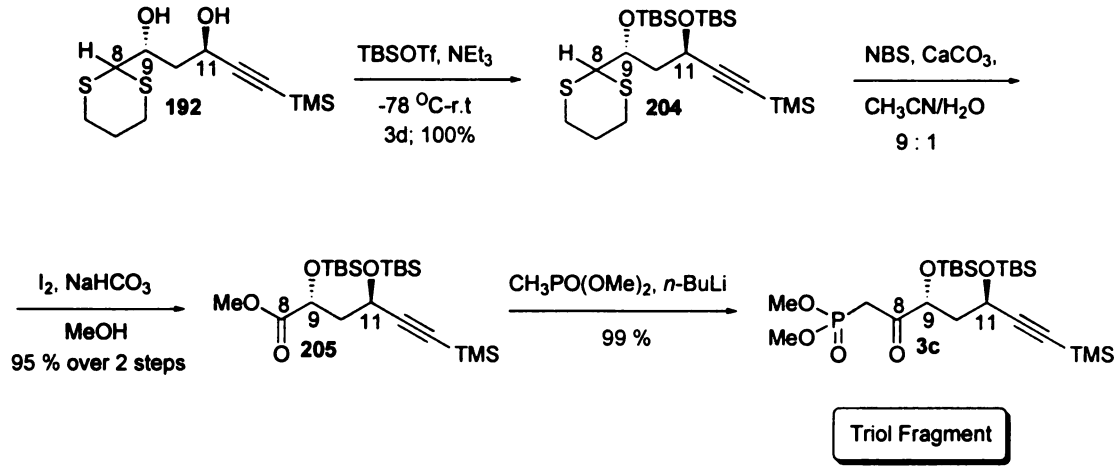
Inspite of a very successful synthesis of the triol fragment **3b**, two major problems still plagued this synthetic pathway. First using TES as a C_9 hydroxyl protecting group meant that extreme care would have to be taken when performing any transformations in which mild acid is generated. On two occasions thus far $CaCO_3$ and $NaHCO_3$ had to be used to prevent deprotection (Figure III-12). In addition each silica gel column would have to be pre-treated with Et_3N amine beginning at the point that TES is first introduced as a protecting group up until the point of its removal.

A second and more serious issue was the low selectivity obtained by Boger when the C_8 carbonyl is methylated. As was mentioned previously (Figure III-9) this is a Felkin-Ann non-chelation addition to the C_8 carbonyl where the selectivity should be a function of the size of the protecting group on the C_9-oxygen. When protected by a TES group only a 3:1 diastereomeric ratio was observed (Figure III-9).

We thought that perhaps both these problems could be addressed if a bulkier and more acid stable silyl alternative was used. Other silyl protecting groups that would have these characteristics are the triisopropyl silyl (TIPS), tert-butyl dimethyl silyl (TBS), and *tert*-butyl diphenyl silyl (TBDPS) groups. The results from the work of Mark Parasi, Su Yu and Xuejun Lui suggested that trying to protect the C_9 hydroxyl group on dithiane **181** with very bulky protecting groups would not work (Figure III-4). However, using dithiane **192** instead of dithiane **181** might be expected to relieve some steric constraints (because the methyl group on the α carbon has been replaced by a smaller moiety, a hydrogen atom). Nonetheless, we reasoned the large TBDPS group would probably still not be a viable option. The choice between the two other silyl protecting groups was made simple when Boger's publication was carefully examined. In his report a C_9 and C_{11} di-TBS protected intermediate was published. This derivative was only made after the C_8 methylation step and interestingly after the accidental removal of TES from the C_9 hydroxyl. We anticipated that the larger TBS group would give better selectivity for the methylation step and any similar or identical compounds made could be compared to the intermediates reported in Boger's publication.

Fortunately, the change of silyl protecting groups from TES to TBS proceeded uneventfully. As can be seen in Figure III-13 a quantitative yield of **204** is obtained for the TBS protection of the diol **192** and the two remaining steps gave over 90% yield. This change improved the yield of the triol fragment from 14.2% to 19.8% for the ten-step sequence starting from chromium hexacarbonyl.

Figure III-13 Oxidative Deprotection and Triol Fragment 3c Completion



Accidental Preparation of Phosponate 3c

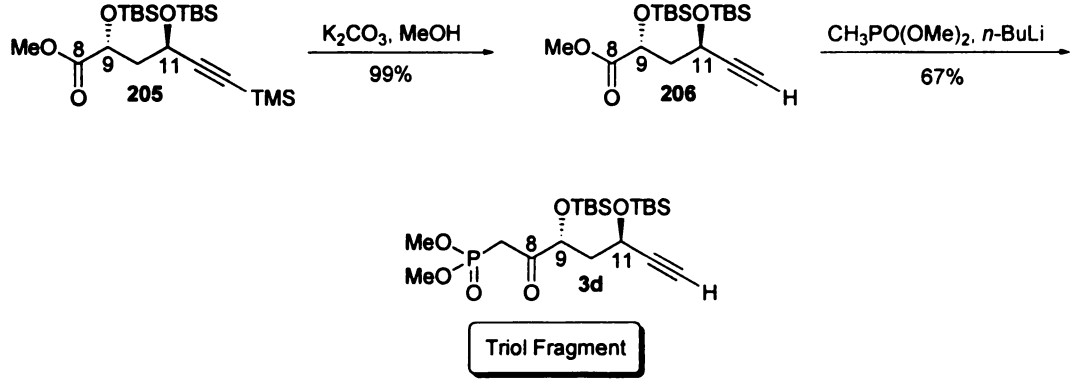
While preparing triol fragment **3b** (Figure III-12), an unexpected transformation occurred. When dithiane **203** was sequentially treated with *n*-bromosuccinimide (NBS) and calcium carbonate ($CaCO_3$) in a 9 : 1 mixture of acetonitrile : water and iodine (I_2), sodium bicarbonate ($NaHCO_3$) and methanol (MeOH) (Figure III-12) a 50% yield of a new product was observed. After rigourous NMR, IR and MS analysis this compound was identified as methyl ester **205**, which has two TBS protecting groups. It became apparent that in the work-up of this reaction, the TES group was cleaved and a TBS from another molecule of **204** underwent intermolecular exchange. This transformation could occur via a direct protection of the C_9 hydroxyl by the TBS of another molecule of **204**, or first an intramolecular silyl migration from C_{11} to C_9 followed by a reprotection of C_{11} from another molecule of dithiane **204**.

Preparation of Phosponate 3d

While trying to optimize the reaction conditions for the last step in the preparation of phosphonate **3c** (Figure III-13), a phosphonate side product was isolated in 10% yield which proved to be the alkyne desilylated material **3d**. Varying the ratio of *n*-BuLi : dimethyl phosphonate led in some instances to the removal of TMS from the acetylene. In order to couple the diene fragment **4** to the triol fragment **3c** this step would be essential (Figure IV-13). If a one-pot procedure for these two steps could be developed it would create a more attractive route towards the natural product. Unfortunately further experimentation on the ratio of phosphonate to *n*-BuLi did not improve the yield of this product but resulted in only reduced yields of triol fragment **3c**.

The removal of TMS from phosphonate **3c** was also attempted with potassium carbonate (K_2CO_3) in MeOH but this only produced decomposed material. Larger quantities of this phosphonate fragment **3d** could, however, be prepared by performing the alkyne deprotection prior to phosphonate addition. The first step is high yielding as can be seen from Figure III-14. However, the dimethyl phosphonate addition to **200** could only be optimized to 67% yield, a result that was not always reproduced.

Figure III-14 Preparation of Triol Fragment 3d



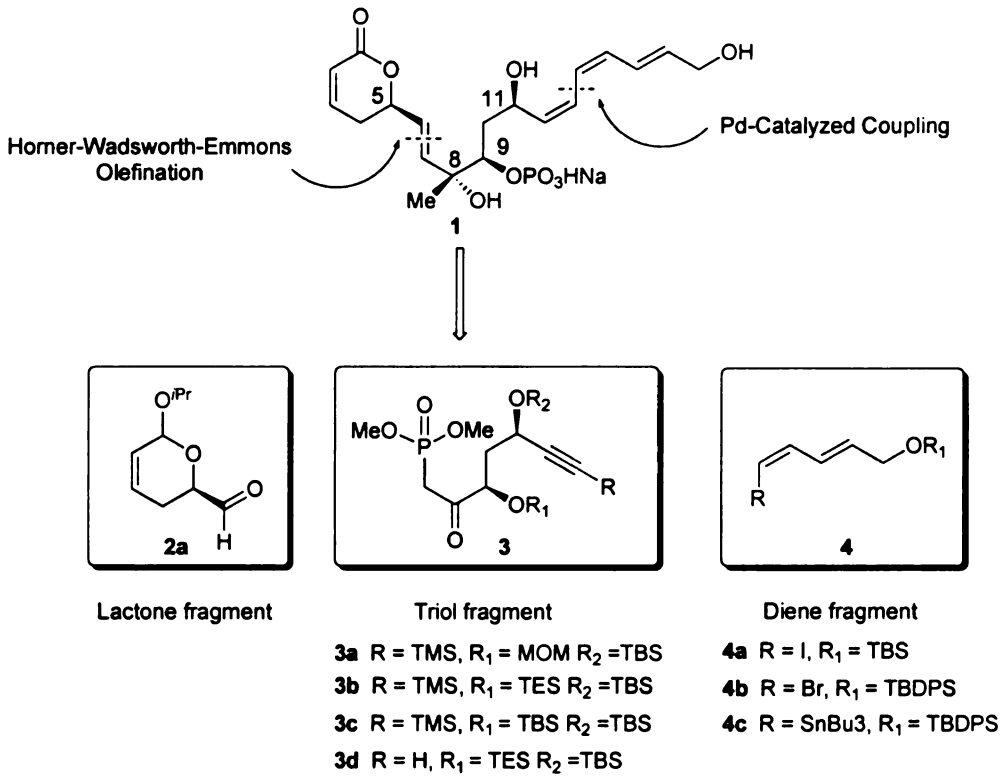
CHAPTER 4

ASSEMBLY OF FRAGMENTS AND THE

INHERENT PREDICAMENTS

With the three fragments in hand, it was planned that the lactone and triol fragments would be assembled first by utilizing a Horner-Wadworths-Emmons (HWE) reaction.[74,93] Methyl addition to C_8 of ketone **212** (Figure IV-3) followed by deprotection of the acetylene and a palladium cross coupling to the diene fragment **4b** should afford the fostriecin core. The subsequent steps have been accomplished by the Boger group on an almost identical compound. There is a Z-olefin in Boger's intermediate **50** (Figure IV-4) at C_{12} versus a triple bond at C_{12} in compound **212** (Figure IV-3). In addition the silyl groups on the C_9 secondary alcohol differ, a TBS group in our fostriecin core versus a TES group in Boger's.

Figure IV-1 Our Retrosynthetic Analysis of Fostriecin



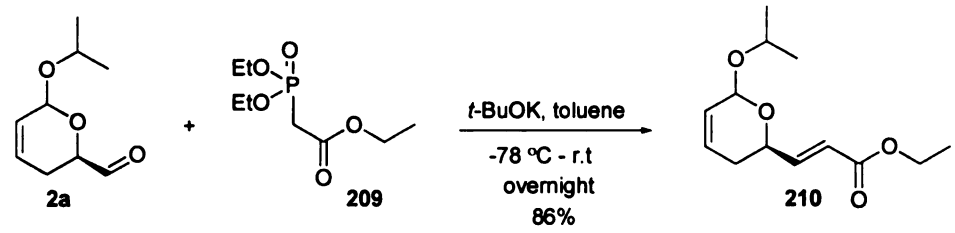
The Horner-Wadsworth-Emmons Reaction

The retrosynthesis shown in Figure IV-1, like the synthesis by Boger[24] and the synthesis by Just and O'Connor, employs a Horner-Wadsworth-Emmons[74,93] reaction as a key reaction necessary to obtain the *E*-configuration at C_5-C_6 double bond. At the time only triol fragments **3a** and **3b** had been prepared and **3a** was predicted to give the wrong stereochemistry upon methylation of the C_8 carbonyl (see section entitled Preparation of TES Protected Triol Fragment **3b**). Phosphonate **3b** was chosen as the Horner-Wadsworth-Emmons precursor. Attempts to repeat Bogers'[24] protocol for the Horner-Wadsworth-Emmons[74,93] reaction gave a disappointing 12% yield as the best result (Figure IV-2, entry 1). In order to test whether the substrate **3b** was sensitive to these

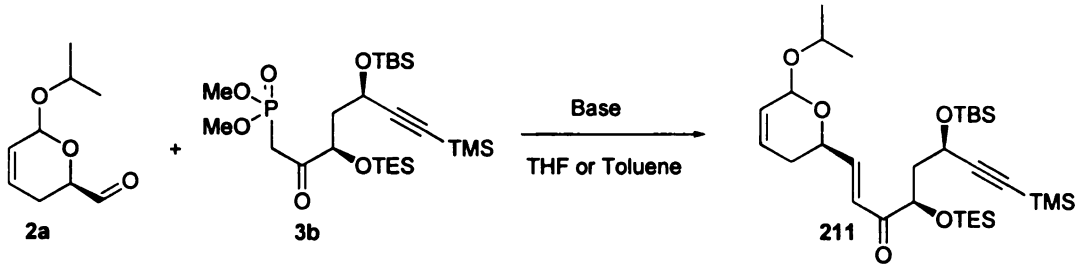
conditions, the reaction was repeated with the simple phosphonate **209** as the substrate which gave the *E*-olefin **210** was obtained in 86% yield. Thus, it is likely that the TMS-protected acetylene unit in **3b**, which is not present in the phosphonate used by Boger,[24] is sensitive to potassium tertiary butoxide (*t*-BuOK) under these conditions. Other bases were screened as shown in Figure IV-2. A triethylamine-lithium chloride (Et_3N-LiCl) combination provided the best results with a 94 % yield for this step.[77,78]

Figure IV-2 Attempts at Horner-Wadsworth-Emmons Coupling

Model Reaction



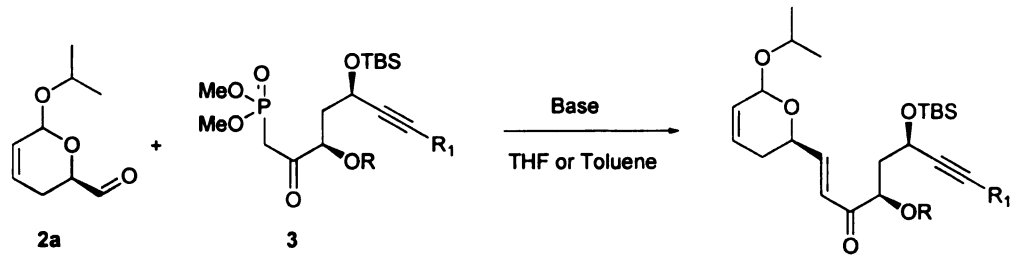
Screening Reactions and Conditions



Conditions	Yield (%)
1) i) *t*-BuOK, toluene, -78 °C - r.t, overnight	12
2) i) LDA, THF, **3b**, -78 °C, 45 min, ii) then aldehyde, -78 °C, 45 min, r.t, 2h	45
3) i) LiCl, THF, **3b**, 5 min, ii) 0 °C; Et_3N, warm to r.t, 30 min iii) 0°C, aldehyde, warm to r.t, 24 h	94

The conditions developed above for the coupling of aldehyde **2a** and phosphonate **3b** were also successful when applied to phosphonates **3c** and **3d**. Over 90% yield of exclusively the *E*-isomers **211, 212,** and **213** was obtained (see Figure IV-3).

Figure IV-3 Horner-Wadsworth-Emmons Coupling of Triol Fragments 3



2a **3**

	Conditions	Yield (%)
1)	i) LiCl, THF, **3b**, 5 min, ii) 0 °C; Et_3N, warm to r.t, 30 min iii) 0 °C, aldehyde, warm to r.t, 24 h; R=TES; R_1=TMS	**211** (94)
2)	i) LiCl, THF, **3c**, 5 min, ii) 0 °C; Et_3N, warm to r.t, 30 min iii) 0 °C, aldehyde, warm to r.t, 24 h; R=TBS; R_1=TMS	**212** (99)
3)	i) LiCl, THF, **3d**, 5 min, ii) 0 °C; Et_3N, warm to r.t, 30 min iii) 0 °C, aldehyde, warm to r.t, 24 h; R=TBS; R_1=H	**213** (90)

The Methylation Step

Of the many total syntheses and synthetic strategies towards fostriecin that have been published, there are only four fundamental methods used to establish the proper stereochemical relationship between the chiral centers at the C_8 and C_9 carbons (see Figure IV-4). These four methods are: the addition of a methyl organometallic reagent to the C_8 ketone of **214**; the addition of a vinyl organometallic reagent to the methyl ketone of **60** which becomes C_8 in the natural product; a Sharpless AD[36] of a trisubstituted olefin bearing a methyl group as one of the three substituents; and a catalytic asymmetric cyanosilylation of methyl ketone of C_8.[29]

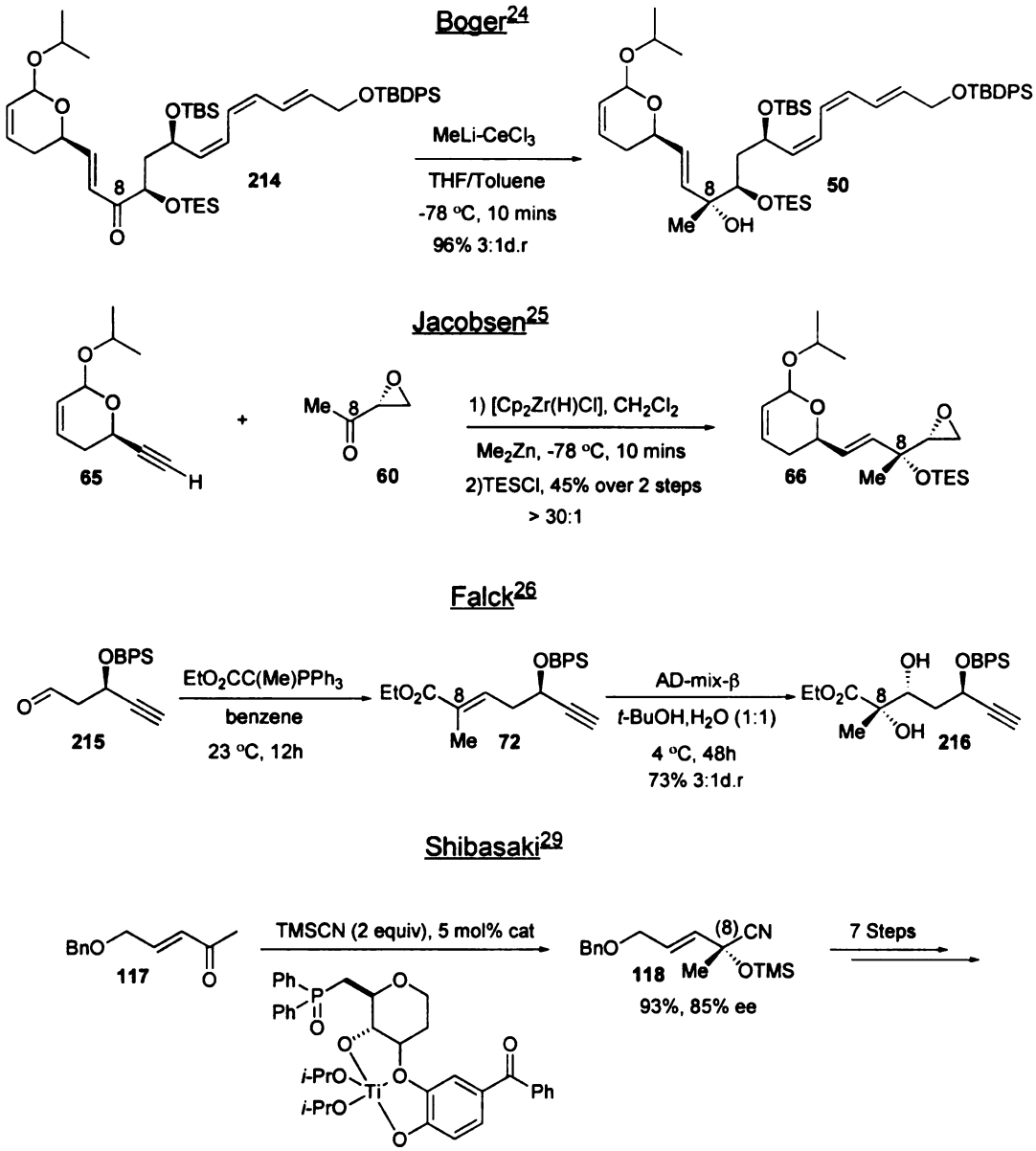
Boger's[24] and Jacobsen's[25] syntheses are both examples of the addition of organometallic reagents to set the relative stereochemistry at C_8 and C_9. These approaches are complimentary in regard to whether the bond being made is part of the carbon backbone (Jacobsen's)[25] or not (Boger's).[24] In entry 1 of Figure IV-4 we see that Boger's synthesis adds a methyl group to the C_8 ketone of compound **214**, an intermediate in which all the other carbons of fostriecin are already in place. In entry 2, however, the situation is reversed; it is the carbon skeleton that is used as the nucleophile on methyl ketone **60** to set the C_8 and C_9 relative stereochemistry.

The approach used by Shibasaki[29] is also complimentary to that used by Jacobsen,[25] but not in the same way that Boger's[24] approach is. Both Shibasaki[29] and Jacobsen[25] use a methyl ketone as a synthon, but Jacobsen[25] adds the carbon skeleton of an early fostriecin intermediate to the methyl ketone **60** continuing a linear sequence of events. Shibasaki[29] however begins his linear synthesis with this event via an asymmetric cyanosilylation of methyl ketone **117** (see Figure IV-4). Ketone **117** is used as a lynchpin in Shibasaki's synthesis and the cyanosilylation of ketone **117** initiates a series of transformations that will occur at both ends of tertiary alcohol **118** (see Chapter I Figure I-29).

The most popular method seen in almost every other synthesis was a Sharpless AD[36]. Falck synthesis exemplifies this is entry 3[26]. Sharpless AD[36] is attractive because both the C_8 and C_9 stereogenic centers are set in one step.

The approach taken by the Wulff group is similar to Boger's since the C_8 ketone to be alkylated is already present in the carbon skeleton. The best result Boger obtained with the addition of a methyl cerium reagent to the ketone **214** was a 3:1 diastereomeric ratio of C_8 epimers and with a 20:1 ratio of 1,2 to 1,4 addition products (Figure IV-4).[24] This reagent was prepared by the addition of 18.2 equivalents of MeLi to 18.8 equivalents of anhydrous $CeCl_3$. The $CeCl_3$ had to be dried thoroughly before the lithium reagent could be added. It was dried under vacuum at 80 °C-90 °C for 2 h, then at 130 °C-140 °C overnight. THF was added and the slurry stirred for 10 h, before titrating with *t*-BuLi which removes any residual moisture (see experimental for details).[24] Impassioned to improve upon this selectivity, it was decided to try a more bulky methylating agent. Addition of methyl titanium tris(isopropoxide) to ketone **211** resulted in an 80% recovery of starting material (Figure IV-5). This outcome was not too discouraging because we knew beforehand that Boger[24] had also been unsuccessful at his attempt with this less reactive reagents on ketone **214** (Figure IV-4). An attempt to reduce the steric bulk by using dimethyl titanium bis(isopropoxide) was considered. In addition this reagent would be expected to be a more reactive nucleophile. However, this reaction also resulted in only recovery of starting material (Figure IV-5).

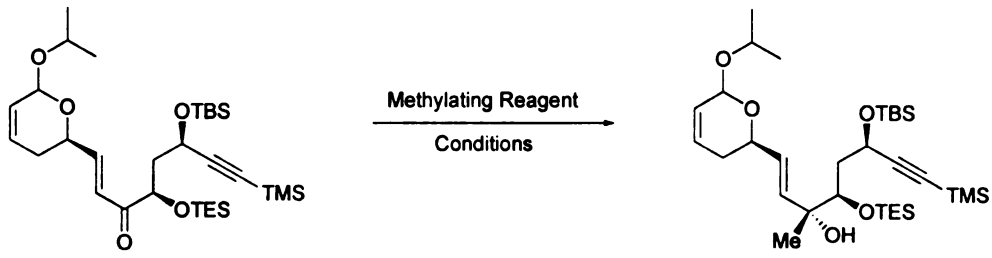
Figure IV-4 Strategies Used for Constructing the C_8 Chiral Center



Given the unreactivity of the methyl titanium reagents, attention was turned to the methyl cerium reagent prepared according to Boger's procedure. The ketone **211** was chosen and using the conditions outlined by Boger,[24] this reaction gave only the recovery of the starting material in 57% yield. The failure of the addition of the methyl cerium reagent to ketone **211** was perplexing because the molecule containing the ketone used by

the Boger group differed from ours only in the side chain attached to C_{11}. This position is three carbons removed from the reaction site. The Boger group accomplished the methylation of ketone **214** after the side chain with the *Z,Z,E*-trienol at C_{12} was already intact (Figure IV-4), while ketone **211** (Figure IV-5) contained a TMS protected acetylene at C_{11}. At this point a model system was devised using α-tetralone as the model substrate (Figure IV-6). This reaction failed as well. It was hypothesized that these failures were probably due to the inadequate preparation of dry $CeCl_3$.

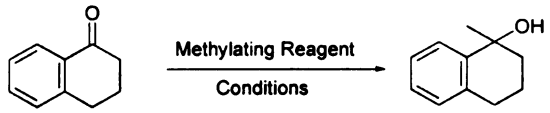
Figure IV-5 Attempts at Methylation



Entry	Methylating Reagent	Conditions	Results
1	$ClTi(i\text{-}PrO)_3$, MeLi(1eq)	-40 °C,1.5 h, add **211**, warm to r.t, 3 days	80 % starting material recovered
2	$ClTi(i\text{-}PrO)_3$, MeLi(2eq)	-30 °C,10 mins,add **211** warm to r.t, 3 days	83 % starting material without TES recovered
3	MeLi-$CeCl_3$	-78 °C,10 mins, 0 °C, 10 mins, -78 °C, add **211**, r.t	57% starting material recovered

There is one example of stereoselective methyl addition to a ketone at C_8 in efforts directed to a fostriecin synthesis and this is to be found in the synthesis of the fostriecin diastereomer **1e** from the work published by Just in 1988 (Figure I-11).[26] In their synthetic plan trimethylaluminium ($AlMe_3$) was the methylating reagent they gainfully employed. A 98:2 diastreomeric ratio in favor of the C_8 *R* isomer **35** was obtained in 60% yield. The problem was that they obtained the chelation controlled tertiary alcohol product **35** using $AlMe_3$ (Figure I-11). The C_9 and C_{11} alcohol groups in ketone **34** were protected with an acetonide which promotes this type of stereocontrol. The C_9-*S* stereogenic center of ketone **34** (Figure I-11) gave the correct C_8-*R* stereochemistry upon methylation. It was thus hypothesized that in order to maintain the correct stereochemistry at C_8, while using C_9-*R* chiral center found in **220**, **221** or **222**, a non-chelation controlled approach would be necessary.

Figure IV-6 Model Methylation Reactions



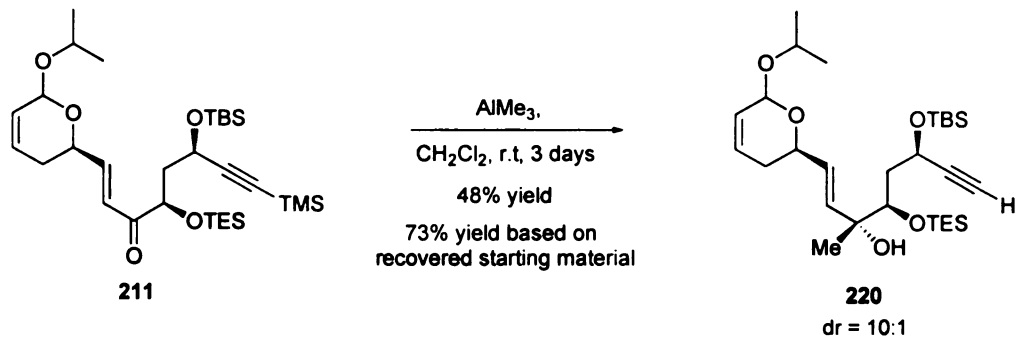
218 219

Entry	Methylating Reagent	Conditions	Results
1	$MeLi\text{-}CeCl_3$	-78 °C, 10 mins, 0 °C, 10 mins, -78 °C, add **218**, r.t	No reaction
2	$AlClMe_2$	-15 °C, add **218** warm to r.t, 3 days	No reaction
3	$AlMe_3$	-15 °C, add **218** warm to r.t, 3 h	99 % **219**

Inspired by the work of Just and O'Connor,[26] the reaction of trimethyl aluminum ($AlMe_3$) and dimethylaluminium chloride ($AlClMe_2$) with α-tetralone were examined as a model system (Figure IV-6). The results obtained using $AlClMe_2$ were disappointing since after three days there was only starting material as indicated by TLC. In contrast the reaction of α-tetralone with $AlMe_3$ was quite facile giving a 99% yield of **219** in three hours. When this methodology was applied to our desired substrate ketone **211**, a 48% yield of tertiary alcohol **220** was obtained (Figure IV-7) as a 10:1 mixture of diastereomers. This ratio of products could be obtained by integrating the hydroxyl protons which are singlets at 2.23 ppm (major isomer) and 2.26 ppm (minor isomer). The stereochemistry of the major diastereomer is assigned that shown in Figure IV-7 on the basis of chemical correlation. This reaction is rather sluggish by comparison to the model

reaction with α-tetralone **218** since it required three days for a 60 % conversion to **220** (Figure IV-7).

Figure IV-7 Methylation of Ketone 211 with $AlMe_3$



There were at least three other advantages to using $AlMe_3$ as a methylating reagent on ketone **211**. First, no 1,4 addition product was observed as reported by Boger.[24] He reported a 20:1 ratio of 1,2 versus 1,4 addition products using the MeLi-$CeCl_3$ system discussed on page 57. This observation is consistent with the results obtained by Just (Figure I-11),[26] in which compound **34** gave a 98:2 ratio of C_8 epimers with no 1,4 addition product being reported.

Secondly, the diastereomeric ratio of tertiary alcohol **220** was improved from a 3:1 ratio as reported for **50** Boger's intermediate (Figure IV-3) to a 10:1 ratio in compound **220**. The TES protecting group on C_9 in **211** (Figure IV-7) provides a more hindered environment around the ketone at C_8 than does the acetonide which protects the C_8 and C_9 alcohols in compound **34** (Figure I-11). This difference in size may prevent chelation and lead to the correct stereochemistry at C_8.

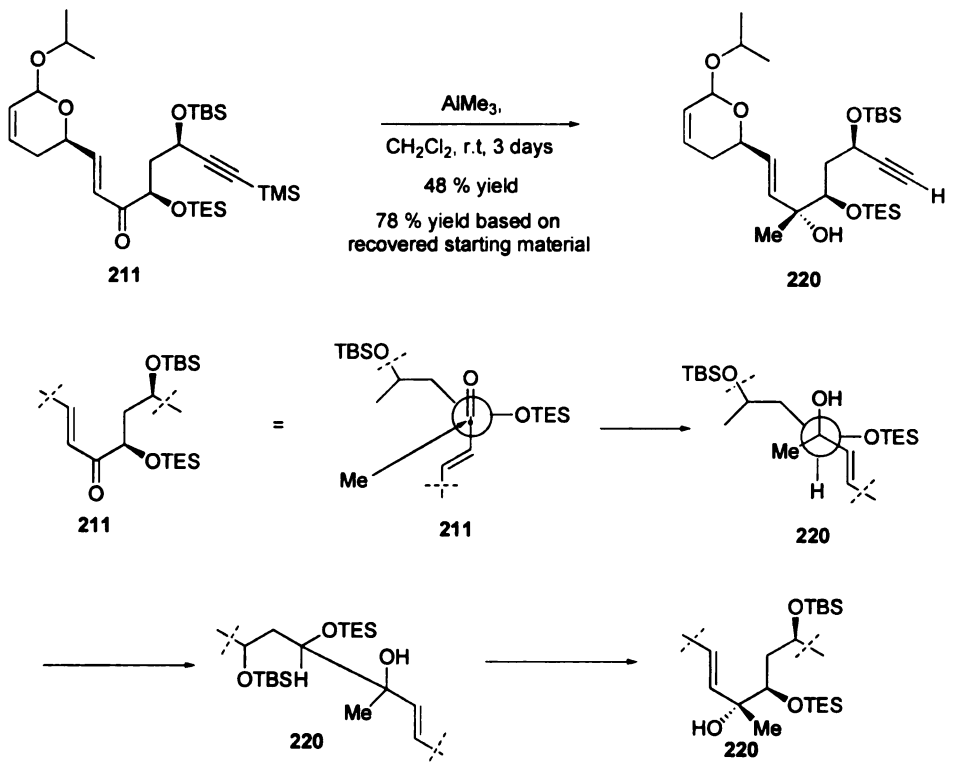
The last, but certainly not the least, advantage was that the TMS group on acetylene **211** was cleaved during this reaction (Figure IV-7). The product of this reaction

was expected to retain the TMS protection of the acetylene in **211**. A deprotection of TMS would have been required prior to the palladium cross coupling reaction as indicated by model studies for this coupling in Figure IV-13. This result evades that step. The loss of the TMS group was confirmed by the appearance of an acetylenic proton as a doublet (J = 2.2 Hz) at 2.41 ppm, in the ^{1}H NMR and the disappearance of the nine trimethyl protons of TMS at 0.04 ppm.

Determining the Stereochemistry at C_8

One of the advantages of using $AlMe_3$ as a methylation reagent mentioned above was the improvement in diastereoselectivity which was confirmed by proton NMR. According to Figure IV-8 the non-chelation controlled Felkin-Ahn product is predicted to be the diastereomer **220**. The bulky TES protecting group should prevent chelation control and thus the desired stereoisomer **220** should be formed. Boger obtained a 3:1 mixture of diastereomers for this step, with the Felkin-Ahn product **50** as the major diastereomer (Figure IV-8).

Figure IV-8 Predicted Model for C_8 Methylation



In Chapter 3 under the section entitled Preparation of Phosphonate **3c** a hypothesis on improving the selectivity of the methylation step was discussed. The primary conclusion was that bulkier silyl protecting groups on the C_9 hydroxyl should favor non-chelation controlled products and increase the selectivity at C_8. Even though we obtained a 10:1 ratio of product **220** when TES protects the C_9 hydroxyl group, it was predicted that an even higher selectivity should result when the TBS protected derivatives **212** and **213** are reacted with $AlMe_3$ (Figure IV-9). To our chagrin only a 3:1 ratio of diastereomers was obtained in 48% yield when ketone **212** was reacted with $AlMe_3$ to give **221**. This unexpected result in selectivity could be explained if there is a competing

steric interaction in ketone **212** which disfavors conformation present in the non-chelated transition state and favors the conformation that would be present in a chelated intermediate. The two TBS groups on the hydroxyls of C_9 and C_{11} could be responsible for the observed selectivity. This steric interaction must also place the TMS protected acetylene in a more hindered environment, preventing the cleavage of TMS as was observed in the case of compound **211** the TES protected derivative. Computational model studies on these intermediates need to be created in order to better understand these results.

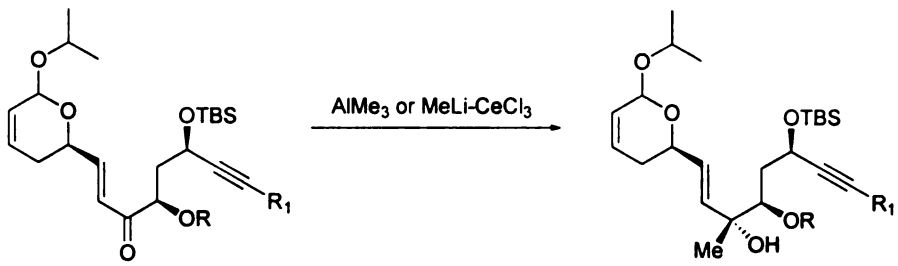
Thus far it was only hypothesized that the correct stereochemistry at C_8 was obtained using the Felkin-Ahn model. A more accurate method of determination would be to subject ketone **211** to the conditions used by Boger[24] enlisting a MeLi-$CeCl_3$ complex as the reagent and comparing the results we would obtain to those obtained by Boger. Since our predictions about the stereoselectivity so far had failed, resolving this challenge before any further synthetic steps were attempted seemed imperative. Using the protocol described by Boger was unsucessful even with the model study (see Figure IV-6). Using commercially available anhydrous $CeCl_3$ may have been the problem. At the prompting of Professor Maleczka a method for preparing anhydrous $CeCl_3$ was attempted instead of using commercially available anhydrous cerium trichloride. Using cerium trichloride heptahydrate ($CeCl_3.7H_2O$) and heating it slowly under high vacuum for three hours from 70 °C - 100 °C, then heating it overnight at 130 °C - 140 °C gave a white powder. This was different in color to the anhydrous $CeCl_3$ that was bought from Aldrich Chemicals which was off-white. The powder was cooled to room temperature under

argon and stirred in dry THF for ten hours as reported by Boger.[24] Following the rest of Boger's protocol gave no reaction. However, removal of the *tert*-butyl lithium (*t*-BuLi) from the protocol gave the desired compound **221** in 90% yield and with a 3:1 dr. *t*-BuLi was used by Boger to remove any traces of water. In the present case which uses 18.2 equivalents of methyl lithium (MeLi) in the reaction (see experimental for details) this step seemed unnecessary.

At the time of this investigation only ketone **212** had been prepared and thus its selectivity was determined first. It was suprising to find that it reacted to give a 7:1 ratio of the respective diastereomers of **221** and in almost quantitative yield. Based on Boger's observation (Figure IV-4) this suggested that the major isomer obtained from ketone **212** using $AlMe_3$ was indeed the one predicted and shown in Figure IV-9. Equally important is that this result indicated that a change from TES to TBS on the C_9 hydroxyl facilitates higher selectivity when the MeLi-$CeCl_3$ complex is used. What supports this hypothesis even more was that later when ketone **211** was prepared and reacted with the MeLi-$CeCl_3$ complex only a 3:1 ratio of diastereomers were obtained. This diastereoselectivity ratio is identical to that reported by Boger on compound **214**[24] (Figure IV-4). Since Boger's product of the methylation alcohol **50** (Figure IV-4) has the identical environment around C_8 as compound **217** (Figure IV-6), we compared the spectra of diastereomers **217** (Figure IV-9) to **50** (Figure IV-4). The C_9 proton and the hydroxyl proton at C_8 were the only two protons that would provide any useful information about the stereochemistry of C_8 and were thus chosen to do the analysis. Unfortunately the proton at C_9 in both compounds **50** and **217** are multiplets, hence Boger did not report any coupling constants

and a comparison could not be made. In addition the hydroxyl proton at C_8 is a singlet at 2.83 ppm in tertiary alcohol **50** but a doublet at 2.83 ppm in tertiary alcohol **217** with a coupling constant of 2.4 Hz. Only the location of these protons could be compared the proton at C_9 in **50** occurs at 3.65 ppm and in **217** at 3.63 ppm. This was not enough evidence to confirm the stereochemistry at C_8.

Figure IV-9 Methyl Addition to Ketones 211, 212 and 213



Entry	R/R_1	Methylating Reagent	Results (Yield: d.r.)[a]
1	**211**, R=TES, R_1= TMS	$AlMe_3$	**220**, 48 % 10:1 R=TES, R_1= H
2	**212**, R=TBS, R_1= TMS	$AlMe_3$	**221**, 48 % 3:1, R=TBS, R_1= TMS
3	**213**, R=TBS, R_1= H	$AlMe_3$	Experiment not done
4	**211**, R=TES, R_1= TMS	MeLi-$CeCl_3$	**217**, 90 % 3:1, R=TES, R_1= TMS
5	**212**, R=TBS, R_1= TMS	MeLi-$CeCl_3$	**221**, 99 % 7:1, R=TBS, R_1= TMS
6	**213**, R=TBS, R_1= H	MeLi-$CeCl_3$	**222**, 98 % 7:1, R=TBS, R_1= H

a- Isolated yields. The yield of **220** was 73% based on unrecovered starting material.

Alkyne Deprotection and Silyl Migration

The deprotection of the TMS from the protected alkynes was only achieved on intermediate **211**. Alkyne **212** retained its TMS group regardless of the method used to methylate C_8 (Figure IV-9). Therefore a method to remove the TMS group from **221** had to be developed. The table in Figure IV-10 below illustrates a number of methods employed to achieve this transformation. All the reagents used gave a mixture of products, with the desired product **222** being obtained in approximately 60% yield in each case. A side product with almost the identical R_f value of **222** was also isolated in approximately 40% yield. This side-product appeared to result from the migration of a TBS from a protected hydroxyl to the unprotected hydroxyl at C_8 in **222**. Thus the likely structure for this side product is either **223** or **224** (Figure-IV-12).

Figure IV-10 TMS Removal and Silyl Migration of Alkyne 221

221 **222**

Entry	Deprotection Reagents	Conditions	Yield **222** + **X**	Ratio **222**:**X**
1	MeOH, K_2CO_3, H_2O	0 °C, 3h	95-100 %	1.5:1
2	MeOH, K_2CO_3, H_2O	0 °C-r.t, overnight	95-100 %	1.5:1
3	$AgNO_3$, KCN, EtOH, H_2O	0 °C-r.t, 3.5h	95-100 %	1.5:1
4	Amberlyst resin, (Cl^- form)	0 °C-r.t, overnight	95-100 %	1.5:1
5	Amberlyst resin, (Cl^- form)	0 °C-70°C, overnight	95-100 %	1.5:1

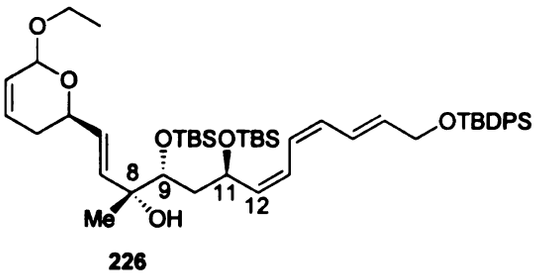
After analyzing the proton and carbon NMR of the unknown tertiary alcohol **X** it became obvious that a TBS migration had occurred. With three alcohols and two TBS groups there were only three possible structures. Alcohol **222** was already identified as our desired substrate, with its proton and carbon NMR spectra closely resembling that of the starting tertiary alcohol. The protons at C_9 and C_{11} in this structure are a triplet at 3.68 ppm (J = 5.2 Hz) and a multiplet at 4.38-4.52 ppm respectively; while in the starting tertiary alcohol **221** they are a triplet at 3.67 ppm (J = 5.2 Hz) and a multiplet at 4.36-4.50 ppm respectively. In addition terminal alkyne **222** had been synthesized in an alternative manner earlier from ketone **213** (see Figure IV-9 entry 6) and its ^{1}H NMR spectrum matched the major compound isolated in the alkyne deprotection of alcohol **221**. Alcohol **222** retained the TBS groups located on C_9 and C_{11} hydroxyls (Figure IV-12). The other product could only be the secondary alcohol **223** with the C_8 and C_{11} hydroxyls protected (R_1 = TBS, R_2 = H, R_3 = TBS) or the secondary alcohol **224** with the C_8 and C_9 hydroxyls protected (R_1 = TBS, R_2 = TBS, R_3 = H) (Figure IV-12).

Of the two remaining possibilities for the unknown alcohol **X**, **224** the compound possessing the TBS groups on C_8 and C_{11} hydroxyls protected would be a very attractive intermediate since in the natural product the C_9 hydroxyl is phosphorylated. The migration producing **224** would eliminate one step in the synthesis, as this C_9 hydroxyl would no longer have to be selectively deprotected. Another advantage of alcohol **224** is that several of Boger's intermediates at the end of his synthesis possessed this framework; subsequently a formal synthesis could be achieved at an earlier stage of our synthetic plan and the intermediates could be readily compared. A last, but certainly not

the least advantage of gaining access to **224** would be that upon arrival at a formal synthesis our intermediates would retain a higher selectivity at C_8. Boger only obtained a 3:1 ratio in tertiary alcohol **50** after methyl addition to ketone **214** (Figure IV-3) whereas compound **224** has a diastereomeric ratio of 7:1.

With great expectancy, the ^1H NMR of the unknown compound **X** was analyzed. Protons H_9 and H_{11} in the product were assigned as a doublet at 3.68 ppm (J = 9.3 Hz) and a multiplet at 4.57-4.65 ppm respectively (see Figure IV-12). Disappointingly this change in ppm values for H_{11} from 4.38 to 4.57 (0.19 ppm) implied that the TBS was migrating from the C_{11} hydroxyl to the C_8 hydroxyl. Boger reported two similar intermediates in his synthetic approach; compound **226** bearing TBS groups on the C_9 and C_{11} hydroxyls and compound **244** bearing TBS groups on the C_8 and C_{11} hydroxyls[24] (Figure IV-11). In these compounds H_9 is reported as a multiplet with only a small change in the ppm value from 3.75 ppm in **226** to 3.73 ppm in **244** being observed. H_{11} showed no change retaining its value of 4.80 ppm in both compounds **226** and **244**. This chemical correlation strongly suggested that an alternative silyl migration was occurring.

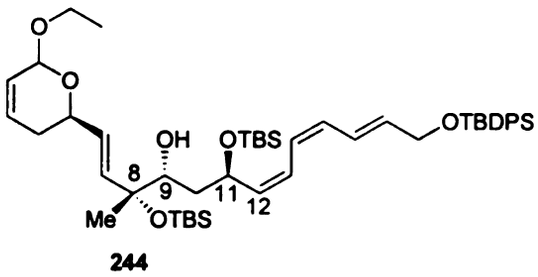
Figure IV-11 Comparing H_9 and H_{11} of Alcohol 226 to Alcohol 244



226

H_9-3.75 (m)

H_{11}-4.80 (m)



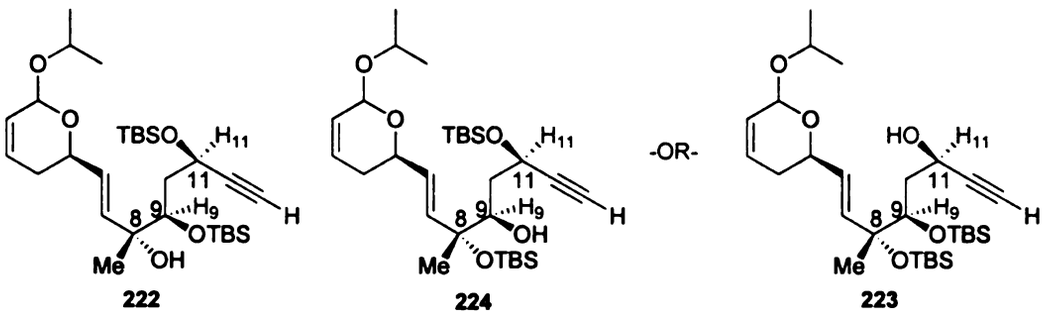
244

H_9-3.73 (m)

H_{11}-4.80 (m)

A more accurate way of determining the correct structure would be to compare the free hydroxyl proton's coupling constant to H_9 and H_{11}. If the hydroxy proton was coupled it would appear as a doublet and thus its coupling partner could be identified as the structure of **X** and could be assigned. Unfortunately, the free hydroxyl proton shows up as a singlet on the 300 MHz Gemini NMR unit so this comparison could not be made. Thus the structure of **X** was tentatively assigned as **223** on the basis of the chemical shift observed for H_{11}. Later however, the unknown alcohol **X** was proven to be **224**.

Figure IV-12 Comparing H_9 and H_{11} of Alcohol 222 to Alcohol 223/224



H_9-3.68 (t , J = 5.2 Hz)
H_{11}-4.38-4.52 (m)

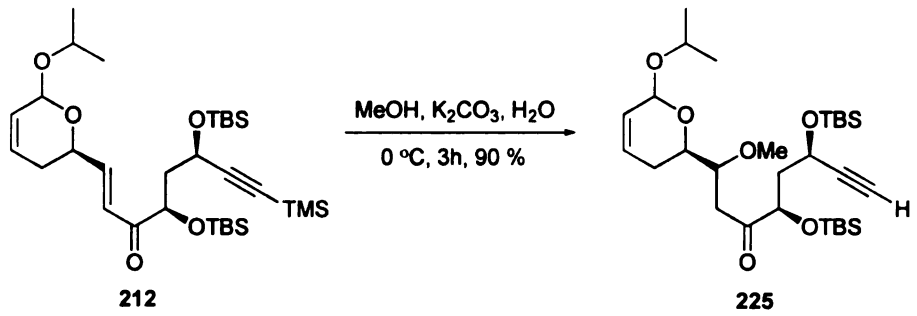
H_9-3.68 (d , J = 9.3 Hz)
H_{11}-4.57-4.65 (m)

Alkyne Deprotection and Michael Addition

Amazingly not only did the alkyne deprotection of the tertiary alcohol **221** gave unexpected results (Figure IV-10), deprotection of ketone **212** provided an unanticipated outcome as well. All the methods of deprotection listed above in Figure IV-10 were tried on ketone **212**, but none gave the desired TMS-deprotected product. All products that were formed had lost the TMS group, however the α,β-unsaturated olefin protons at C_6-C_7 had also disappeared in the ^1H NMR spectrum. The product obtained when K_2CO_3 in $MeOH/H_2O$ was used for the deprotection of ketone **212** was analyzed and upon careful

charaterization it was assigned as the Michael addition product **225** (see Figure IV-13). The nucleophile in this case was the methoxy anion adding to the 4 position of the α,β-unsaturated system. The other conditions listed in Figure IV-10, provided other nucleophiles such as ethoxide and cyanide that were presumed to account for the other unknown products by Michael addition as well. These other products were, however, not characterized.

Figure IV-13 TMS Removal from ketone 212



212 225

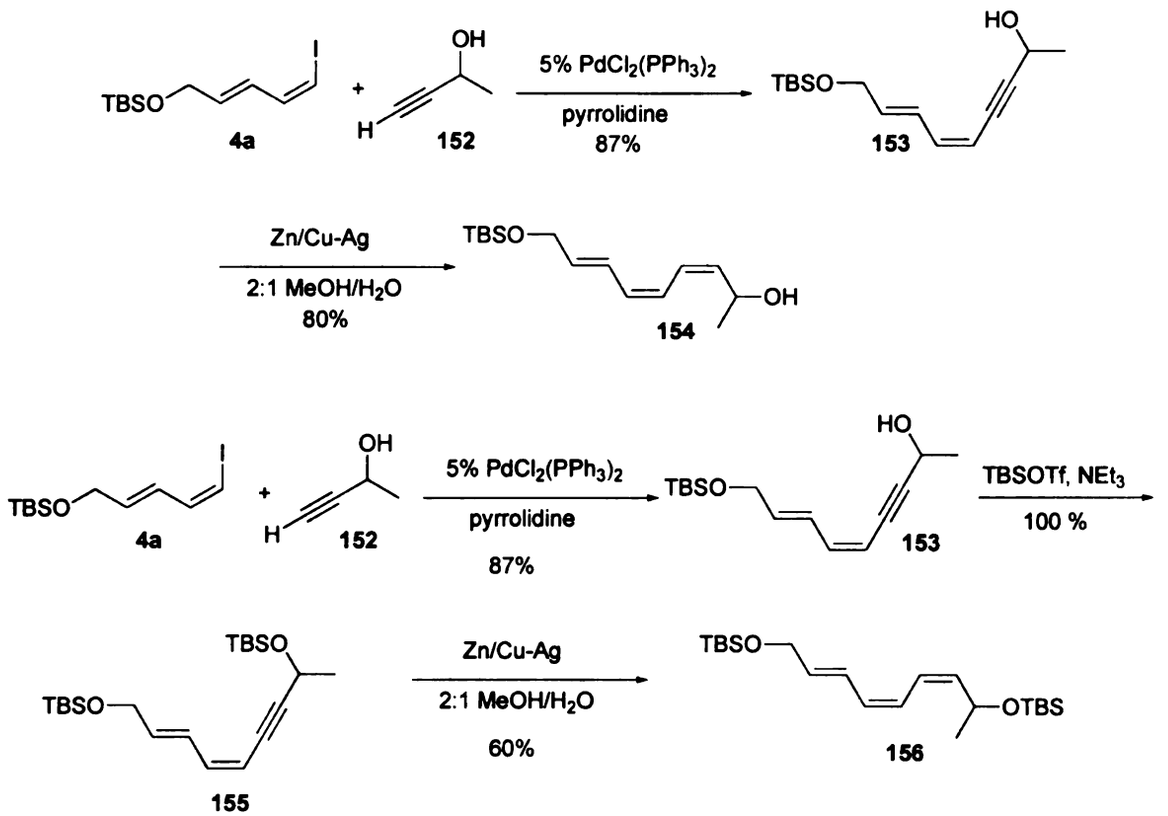
Model Palladium Cross Coupling

With less than 10-steps remaining and a limited amount of substrate, it was decided that a model study of the planned construction of the C_{10}-C_{18} triene unit was essential. Just reported having over-reduced products when reducing the C_{14} internal acetylene of the dienyne system present in compound **35** (Chapter 1, Figure I-11).[32] Our projected substrate **234** (Figure IV-18) has a slightly different arrangement of the dienyne. The alkyne in **234** is at C_{12} instead of at C_{14} as in Just's intermediate **35**. We believed, however, that there was still a strong possibility of getting over-reduced products if the right reduction protocol was not chosen. Hence the model study outlined in Figure IV-14 was established to look at this challenge and inpart in Chapter 2.

Subjecting the aldehyde **148** to Stork's protocol[64] for the synthesis of *cis*-iodo-alkenes, the *Z,E*-iododiene **4a** was obtained in 84% yield with a 9:1 ratio of separable *cis* and *trans* isomers (Chapter 2 Figure II-5). Due to its light sensitivity, the major *Z,E*-isomer of **4a** was used immediately after purification. In the model study shown in Figure IV-14 the palladium cross coupling of **4a** with 1-butyn-3-ol gave an 87% yield of dieyne **227**.[79] The subsequent reduction[68] proceeded cleanly to give the *Z,Z,E*-triene **228** with no evidence of over reduced products or starting material as indicated by its carbon-13 spectrum.

It is known that the Zn/Cu-Ag reduction of acetylenes is influenced by the environment around the acetylene.[68] The model compound **227** possesses a free propargyl alcohol (Figure IV-14). This is different from the desired substrate compound **220** (Figure IV-9) which has a TBS protected propargyl alcohol. To ensure that this difference would not change the outcome of the Zn/Cu-Ag reduction, compound **227** was protected with TBS giving the TBS protected dienyne **229** in quantitative yield. The reduction of **229** was successful giving an unoptimized yield of 60% for the conversion of dienyne **229** to the *Z,Z,E*-triene **230**. No evidence for any over-reduced products could be found in the crude ^{1}H or ^{13}C NMR.

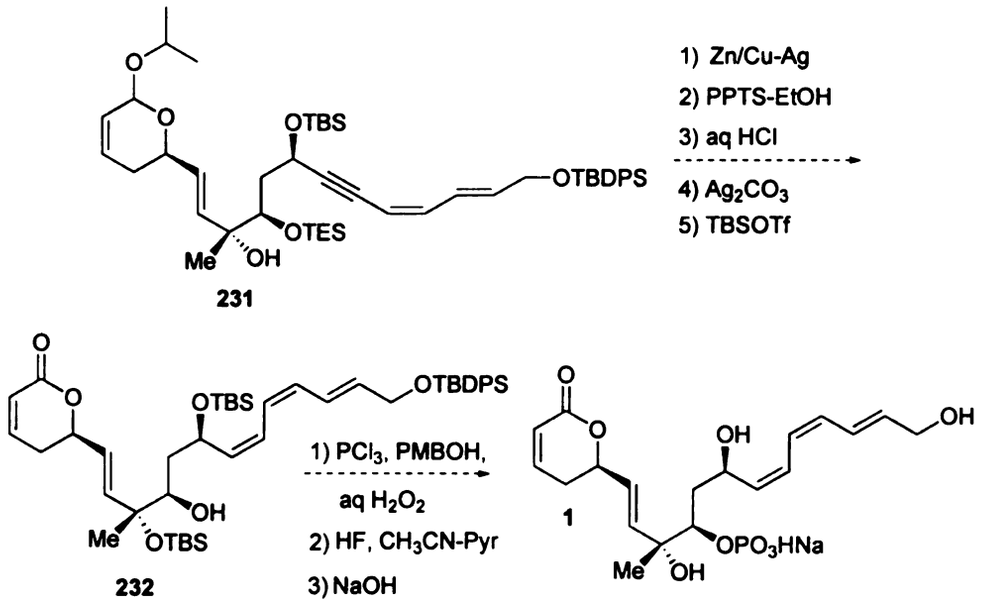
Figure IV-14 Model Study for Diene Triol Coupling



Palladium Cross Coupling

This successful model study for the alkyne reduction was encouraging and gave us confidence that these steps could be extended to the actual substrates of the type **220** or **222** in high yields. If the alkyne **220** (Figure IV-9) was used the coupling product would give the fostriecin core **231** shown in Figure IV-15. A reduction of the internal alkyne of **231** followed by conversion of the acetal to the lactone, a couple of protecting and deprotecting steps, and finally the installation of the phosphate group on C_9 would give the natural product fostriecin (Figure IV-15).

Figure IV-15 Plan for Completion of the Total Synthesis of Fostriecin



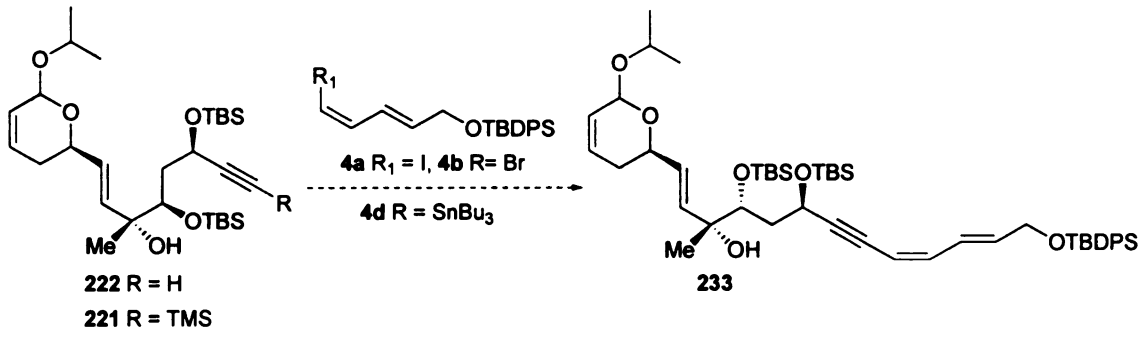
Ketone **211** gave the highest diastereoselectivity for the methyl addition to C_8 which involved the use of $AlMe_3$ as the source of the methyl. A 10:1 ratio of diastereomers were produced concomitant with deprotection of the alkyne to give **220** in good yields (Figure IV-9). The next best result was a 7:1 diastereoselectivity with ketone **213** (Figure IV-9) using the MeLi-$CeCl_3$ complex to add a methyl nucleophile to C_8. The methyl addition occurred in almost quantitative yield but the preparation of ketone **213** had some low yielding steps (see Chapter III-Preparation of Phosphonate **3d**, Figure III-14). Naturally tertiary alcohol **220** would be the most desirable intermediate to bring forward and the conditions used for the palladium cross-coupling model study were applied. The coupling reaction of **220** with the dienyl iodide **4a** (not shown) was attempted under the conditions used in the model study (Figure IV-14). This reaction failed to give any desired product. In addition the yields of **211** often dropped off. This drop was due to TES cleavage from the intermediates made (see chapter III-Accidental

Preparation of Phosphonate **3c**). A second problem was that when $AlMe_3$ used as the methylating reagent, the results were inconsistent, sometimes giving no desired product.

Given the failure to effect the coupling of **220** and **4a**, the possibility of bringing the analogous TBS protected derivative **222** forward in the synthesis was investigated. The coupling of **222** with **4a** was attempted under the same conditions, but as with **220**, no evidence for the coupled product was observed even with a reaction time of 6 days (Figure IV-16 entry 3). At this point it became clear that the conditions developed for the model study would not work on the actual desired systems. This meant only a few options were available: (i) use a different alkyne precusor; (ii) use a different diene; or (iii) change the reaction conditions. In addition the use of the TES protected tertiary alcohol **220** was ruled out because its synthesis was problematic.

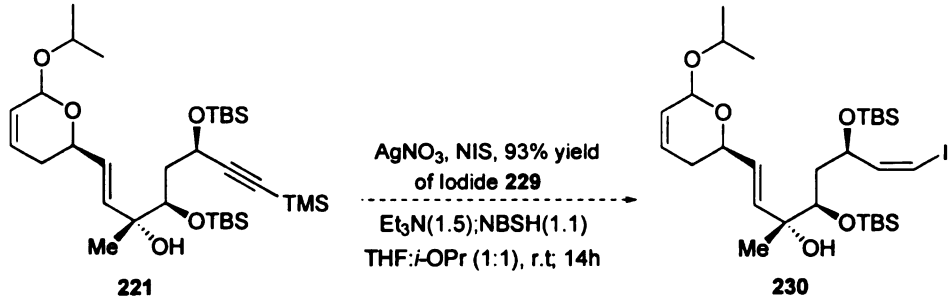
Changing the conditions and/or using a different diene (**4b** or **4d** Figure II-7) were the easier options since there was already a moderate supply of tertiary alcohol **222** available. Hence a few different ligands for the palladium catalyst were screened as well as different solvents and both diene fragments **4b** and **4d** and the results from this extensive effort are presented in Figure IV-16. However, as the data in Figure IV-16 indicates, none of these variations lead to the formation of the desired coupling product **233**. Thus, the only alternative that seemed reasonable at this point was that a different alkynal substrate would have to be used as the vinyl halide's coupling partner.

Figure IV-16 Attempts at Diene Triol Coupling



	R	R_1	Coupling Conditions	Results
1)	H	I	5% $Pd(PPh_3)_4$; Pyrrolidine, r.t; 16h	Diene decomposed and alkyne starting material recovered.
2)	H	Br	5% $Pd(PPh_3)_2Cl_2$; Pyrrolidine, r.t; 16h	Diene and alkyne starting material recovered.
3)	H	Br	30% $Pd(PPh_3)_2Cl_2$; Pyrrolidine, r.t; 6d	Diene decomposed and a new TBDPS protected alkynol was recovered;
4)	H	Br	30% $Pd(PPh_3)_2Cl_2$; Diisopropyl amine, r.t; 6d	Diene decomposed and a new TBDPS protected alkynol was recovered.
5)	H	Br	30% $Pd(dppf)Cl_2$; Pyrrolidine, r.t; 6d	Diene decomposed and a new TBDPS protected alkynol was recovered.
6)	H	Br	20% S-Phos[104]; 10% $Pd(OAc)_2$, Pyrrolidine, r.t; 6d	Diene decomposed and starting alkyne was recovered.
7)	H	Br	40% $Pd(P\text{-}tBu_3)_2Cl_2$[105]; Pyrrolidine, r.t; 6d	Both starting materials were not recovered.
8)	H	Br	10% $Pd(PPh_3)_2Cl_2$; 20% CuI, Et_2NH, r.t; 16h	Diene and alkyne starting material recovered.
9)	TMS	Br	CuCl (2.2eq), Bu_3N; DMI r.t -120 °C; Overnight	Diene and alkyne decomposed.
10)	$SnBu_3$	Br	————	Alkynal stannane was not made.
11)	I	$SnBu_3$	20% $Pd(PPh_3)_4$; 75% CuI, DMF, r.t; 2d	Alkynal iodide made in 93% yield, but no desired product isolated.

Figure IV-17 An Attempt at Alkyne Reduction of Iodide 229

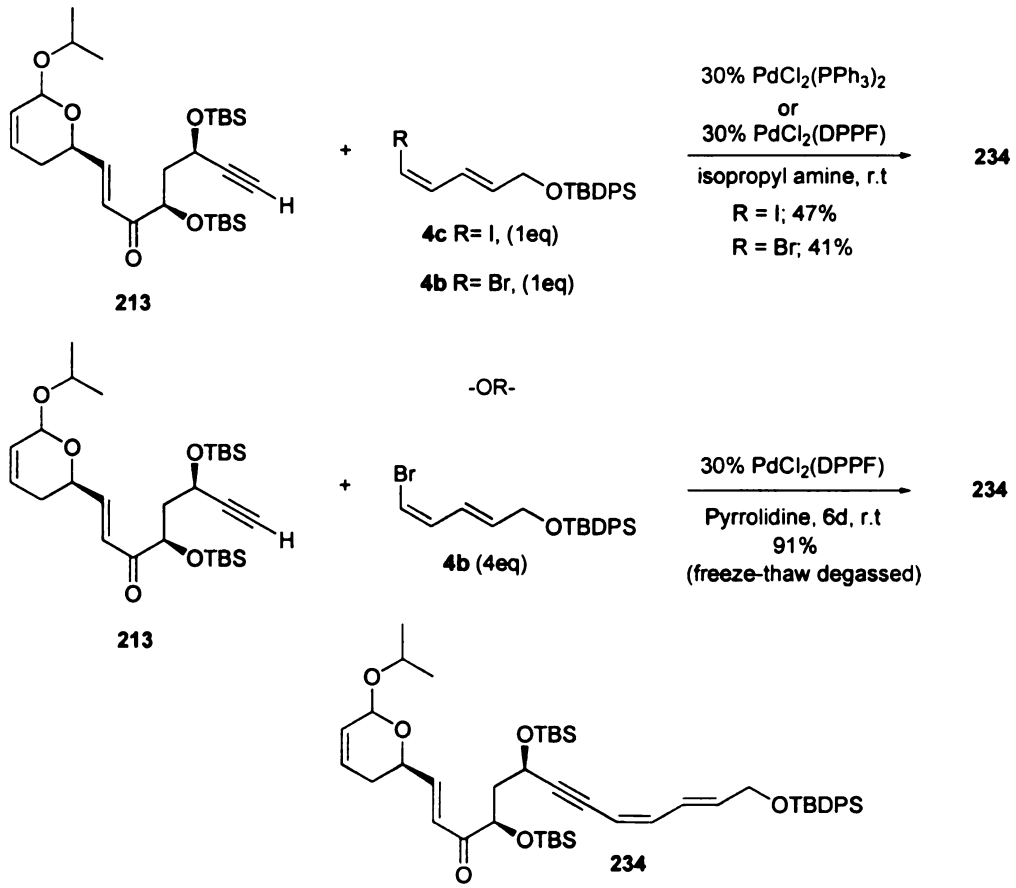


During the screening reactions shown in Figure IV-16 we noticed that one product isolated resembled starting alkyne **222** but possessed a TBDPS group. It is believed that an intermolecular silyl migration of the TBDPS group on the primary alcohol of the diene fragment **4b** was migrating to the alkyne **222**. Proton NMR of this isolated product showed peaks at 7.36-7.52 ppm and 7.66-7.78 ppm in a 6:4 ratio, as well as a singlet at 1.28 integrating to nine protons. This product had lost one of its TBS group but had a TBDPS group present. The product of this reaction was not fully characterized as there are three alcohols that these two silyl protecting groups could possibly be protecting. However, this gave us a pertinent piece of information, which is that in the presence of excess base, a competing and faster reaction was occurring, namely, the shuffling of silyl groups. If the tertiary alcohol at C_8 of **222** could be protected or a precursor of **222** in which the methylation step has not yet been accomplished is used, the cross coupling might be successful. Indeed protecting the C_8 alcohol of **222** would increase the number of linear steps by two, but if an alkyne intermediate could be deprotected earlier then no extra steps would be required.

As was mentioned previously, repeating the steps to prepare tertiary alcohol **220** gave side products which were the result of intermolecular scrambling of silicon

protecting groups which involved exchange of a TES group for a TBS group. One such product was methyl ester **206** (Figure III-14), which was used to prepare the α,β-unsaturated ketone **213** (Figure IV-3). When ketone **213** was subjected to the coupling conditions shown in Figure IV-18, both vinyl bromide **4b** and vinyl iodide **4c** gave a compound that was tentatively assigned by ^{1}H NMR as compound **234** in moderate yields. Later the reaction was optimized to give a 91% yield of compound **234** when 4 equivalents vinyl bromide **4b** were used and the mixture refluxed in pyrrolidine for six days in the presence of 30% $Pd(dppf)Cl_2$.

Figure IV-18 Attempts at the Palladium Cross Coupling

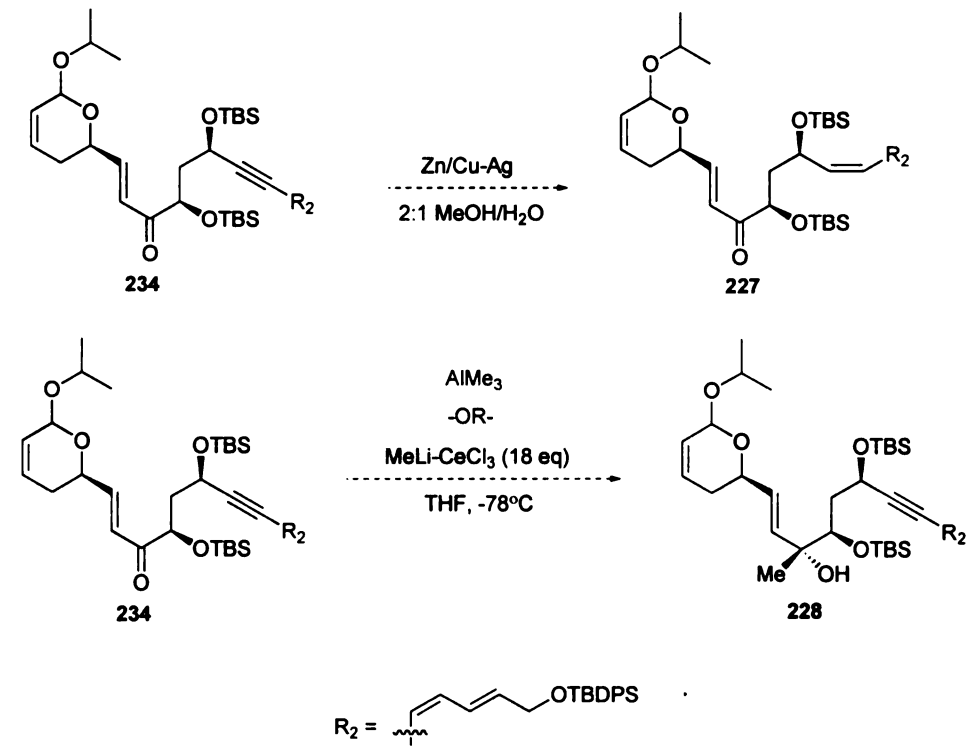


Attempted Alkyne Reduction and Methyl Addition of 234

A quick glance at fostriecin core presented in **234** produced after the palladium cross-coupling reaction of **213** and **4b** indicates that it differs from Boger's intermediate ketone **214** (Figure IV-4) at C_9 and C_{11}. There is a *Z* olefin at C_{11} in Boger's intermediate and an internal alkyne in compound **234**. In addition, there is a TES protected C_9 hydroxyl in ketone **214**, while at the C_9 hydroxyl in compound **234** there is a TBS group. Reduction of the internal alkyne of ketone **234** to the *Z*-olefin would allow for a direct comparison of the effect of the C_9 hydroxyl protecting group on the diastereoselectivity of the methyl addition to the C_8 ketone. In the preliminary study outlined in Figure IV-9

(entries 5 and 6) reaction of the MeLi-$CeCl_3$ combination with ketones **211** and **212**, gave a 3:1 ratio with the TES protected C_9 hydroxy ketone and a 7:1 ratio with the TBS protected C_9 hydroxy ketone. These results were encouraging and gave us confidence that if the reduction of the alkyne in **234** were to occur to give **227**, then we might expect to see a higher diastereoselectivity in methyl addition to **227** than the 3:1 ratio seen by Boger for the addition to **214** (Figure IV-4). So the Zn-Cu reduction was attempted on **234** with the method outlined in the earlier model study (Figure IV-14). Unfortunately, no desired *Z*-alkyne was obtained. The material isolated proved to be a complex mixture. Reversing the order of reactions with methyl addition to the C_8 ketone of **234** first followed by the Zn-Cu-Ag reduction was also attempted. Using either a MeLi-$CeCl_3$ complex or $AlMe_3$ to perform the methyl addition to C_8 of ketone **234** failed to give any desired product. Starting material and decomposed material were the only entities recovered after a number of attempts.

Figure IV-19 Attempts at Methyl Addition and Reduction of 234



Conclusion

The results obtained from the attempts to methylate ketone **234** or reduce its internal alkyne were not only strange but also very discouraging and eventually led us to change our synthetic approach. Compound **234** very closely resembles ketone **214** Boger's intermediate. Ketones **211** and **212** (Figure IV-9) show clearly that whether the C_9 hydroxyl is protected by TES or TBS that methylation with MeLi-$CeCl_3$ is very feasible. It also shows that having an alkyne at C_{11} instead of a triene unit should not prevent this methylation from being successful. Chapter 5 outlines a different approach to fostriecin but this approach needs to be re-visited. Possible sources of error could be that compound **234** has not been completely characterized to verify that it is the structure presented in Figure IV-19 although this is unlikely. The MeLi-$CeCl_3$ needs to be

prepared with a new bottle of $CeCl_3.7H_2O$ since after one year this reagent is reported to become inactive.[102]

CHAPTER 5

The Formal Total Synthesis of Fostriecin

In the previous chapter a series of successful transformations were reported in high yields to provide a structure tentatively assigned **234** and was to serve as an advanced intermediate in the synthesis of fostriecin (Figure IV-18). A HWE reaction between aldehyde **2a** and phosphonates **3b**, **3c** and **3d** (Figure IV-3); a palladium cross coupling reaction with ketone **213** and diene **4b** (Figure IV-18); and a methyl addition to the C_8 of ketones **211**, **212** and **213** with high diastereoselectivity (Figure IV-9) are a few of the key successful transformations. However, at the end of the chapter two disappointing results were described with this approach: first the reduction of the C_{12}-C_{13} triple bond in dienyne **234** failed to give any desired product and the methylation of the ketone at C_8 of this same compound gave starting material back. As outlined in chapter one over ten syntheses of, or synthetic approaches towards fostriecin were reported in just a short period of four years. This myriad of syntheses provided tactical solutions to inherent challenges found in fostriecin's construction. One such challenge was obtaining the *Z,Z,E*- triene unit (Figure I-7). Inspired by the work of Jacobsen,[25] Kobayashi[30] and Shibasaki[29] a diimmide reduction was selected as the method of choice to construct the C_{12}-C_{13} *cis*-double bond. In their reports an alkynal iodide was reduced to a *cis*-vinyl iodide and this iodide was coupled to stannane **4d** (Figure V-1). Our current synthetic approach did not incorporate an alkynyl or vinyl iodide and would have to be

reconstructed to adopt these intermediates. A new retrosynthetic analysis was designed in which only the triol fragment would have to be changed. Figure V-1 below outlines this approach.

Figure V-1 The New Retrosynthetic Analysis of Fostriecin

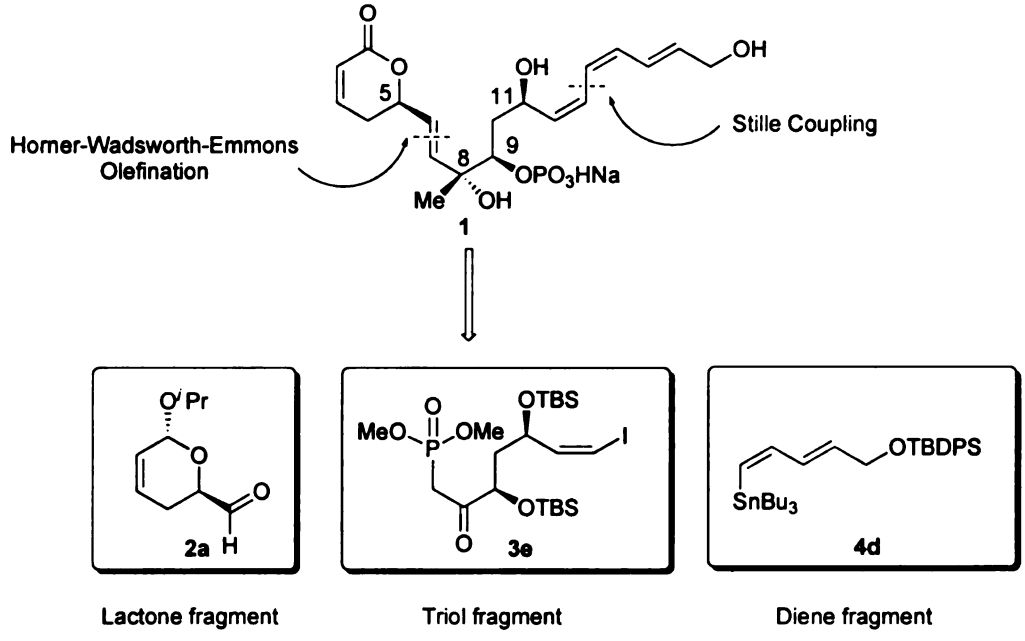
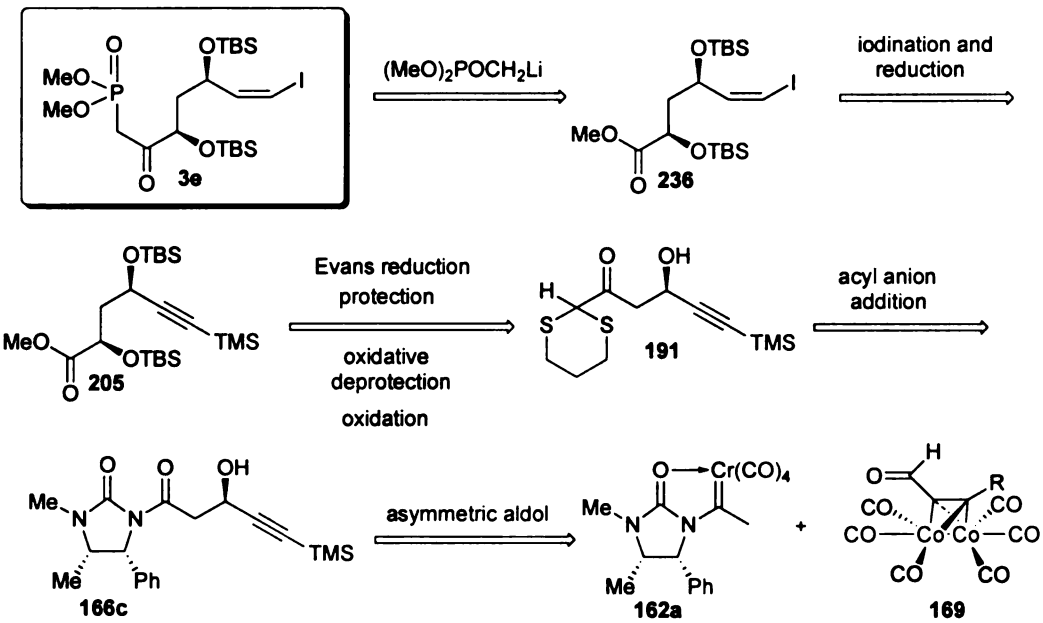


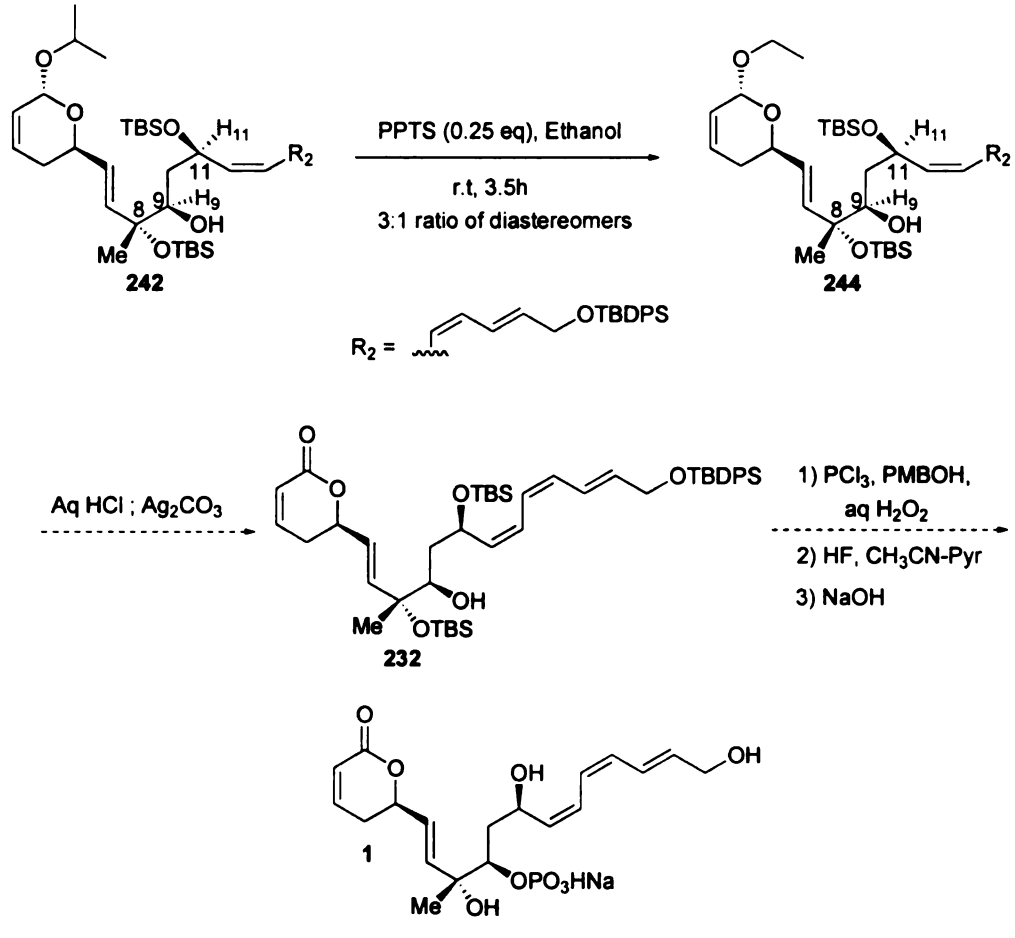
Figure V-2 Retrosynthetic Analysis of Triol Fragment 3e



As shown in Figure V-2, the TMS protected alkyne **205** is the last common intermediate of the triol fragmens **3d** and **3e** in the retrosynthetic analysis. TMS protected alkyne **205** could be converted to an alkynyl iodide **235** (Figure V-3) and this alkynyl iodide reduced with *p*-nitrobenzenesulfonylhydrazide (NBSH)[100] and Et_3N to the *cis*-vinyl iodide **236**. Exposure of the methyl ester of vinyl iodide **236** to nucleophilic addition of the dimethyl methyl phosphonate anion should provide triol fragment **3e**. Triol fragment **3e** could then be coupled to stannane **4d** and a HWE[74,93] reaction of the product would give ketone **239**. Ketone **239** is three steps away from a formal synthesis of fostriecin. As outlined in Figure V-3, a methyl addition to the C_8 ketone of **239** followed by a TBS migration from the C_9 oxygen to the C_8 tertiary alcohol and finally an oxidation of an isopropyl acetal to the lactone would give intermediate **232** a compound which was made by Boger[24] (Figure V-3). This intermediate lactone **232** is two steps

away from the total synthesis of fostriecin and the ensuing steps were published by Boger and co-workers[24].

Figure V-3 Projected Formal Synthesis of Fostriecin



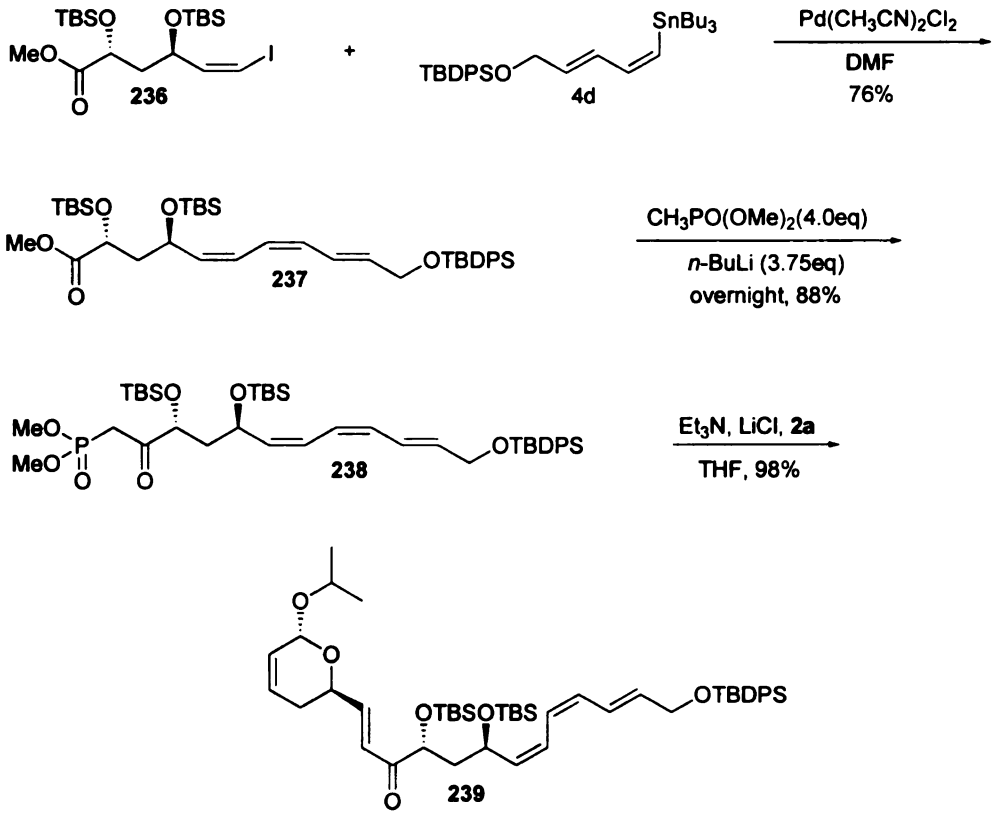
Preparation of Triene 239

The retrosynthetic analysis outlined in Figure V-1 appears to be straightforward, but even these minor changes in our strategy presented some challenges. As outline in Figure V-3 the vinyl iodide **236** could be synthesized from alkyne **205** in 91% over two steps. However when phosphonate addition to **236** was attempted with the anion of $CH_3PO(OMe)_2$, no desired product was obtained and only decomposition of the starting

material was observed. Without dwelling too long on this result the phosphonate addition was postponed until after the Stille[50] coupling between vinyl iodide **236** and stannane **4d**. This step was reminiscent of that seen in Jacobsen's,[25] Hatakeyama's[28] and Shibasaki's[29] syntheses. In addition it was suspected that the conversion of methyl ester triene **237** to phosphonate **238** in Figure V-4 would be a more facile feat than trying to convert iodide **236** to phosphonate **3e**. This suspicion was due to the fact that Boger achieved a similar transformation on an almost identical compound.[24] Nucleophilic addition was performed on an aldehyde in his approach (see Chapter I-Figure I-13) and in our approach methyl ester **237** was the target (Figure V-4). No reaction occurred when THF was used as a solvent but exchanging this solvent for toluene gave an 88% yield of phosphonate triene **238**.

Phosphonate triene **238** was then subjected to the conditions developed for the HWE reaction with **2a** exploited in Chapter 4. A near quantitative yield of **239** was obtained for this step.

Figure V-4 Synthesis of Compound 239

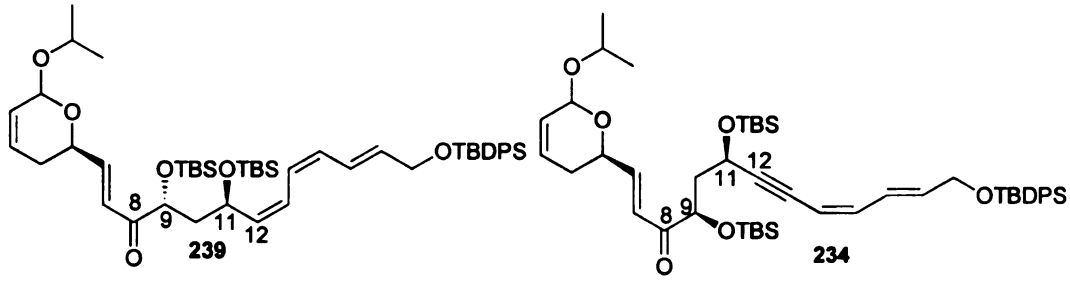


Methylation of Ketone 239

Ketone **239** provided an opportunity to compare how a TBS protected hydroxyl at C_9 and a TES hydroxyl at C_9 in ketone **214** (Figure IV-4) influence the diastereoselectivity when the adjacent C_8 ketone is reacted with MeLi-$CeCl_3$. This reaction appeared to be of a fickle nature because with ketones **212** and **213**, a 7:1 ratio of products were obtained, (Figure V-6) while with ketone **211** (TES protected C_9) only a 3:1 ratio was obtained. However, attempts at methyl addition to ketone **234** (see Chapter 4-Alkyne Reduction and Methylation Attempted) gave only recovered starting material.

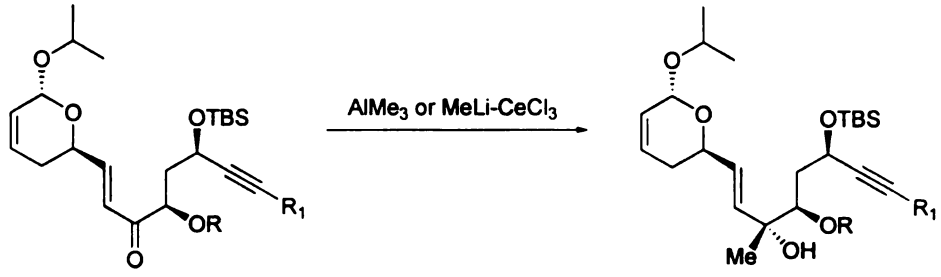
Compound **234** is only different with ketone **239** at C_{12} where the internal alkyne of **234** is now reduced to a *cis*-olefin in **239** (Figure V-5).

Figure V-5 Structures of Ketones 234 and 239 Compared

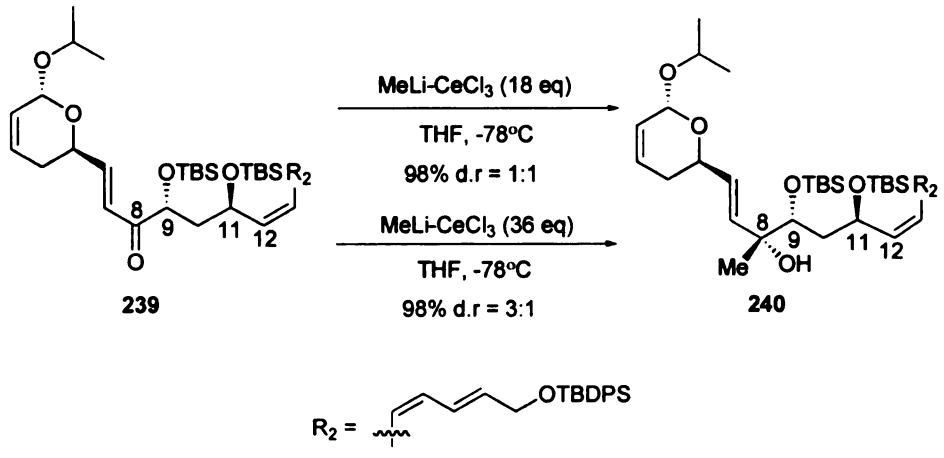


Anxiously, methyl addition to **239** was attempted and gave a 98% yield, however when the diasteroselective ratio was examined only a 1:1 ratio of compounds was obtained. This result was very disappointing as it was expected that at least a 7:1 ratio would be obtained based on the results of ketones **212** and **213** versus **211** (see Figure V-6). In the methyl addition of ketones **212** and **213** the diastereoselectivity is greater than twice of that obtained for ketone **211**. Lowering the temperature of the reaction from -78 °C to -95 °C did not change the selectivity when 18.7 equivalents of $CeCl_3$ and 18.2 equivalents of MeLi was used. The original procedure used by Boger also employs 18.7 equivalents of $CeCl_3$ and 18.2 equivalents of MeLi to get a 3:1 ratio of products at C_8. Even though this is in great excess we decided to double the ratio of each of these starting materials. When 37.4 equivalents of $CeCl_3$ and 36.4 equivalents of MeLi were used, the ratio of diastereomers of **240** increased to 3:1, which was the same ratio of C_8 diastereomers obtained by Boger on the TES protected C_9 ketone **214** (Figure IV-4).[24]

Figure V-6 Diastereoselectivities of Methyl Addition to Ketones 211, 212, 213 and 239



Entry	R/R_1	Methylating Reagent	Results (Yield: d.r.)
1	**211**, R=TES, R_1= TMS	$AlMe_3$	**220**, 78 % 10:1 R=TES, R_1= H
2	**212**, R=TBS, R_1= TMS	$AlMe_3$	**221**, 48 % 3:1, R=TBS, R_1= TMS
3	**213**, R=TBS, R_1= H	$AlMe_3$	Experiment not done
4	**211**, R=TES, R_1= TMS	$MeLi\text{-}CeCl_3$	**217**, 90 % 3:1, R=TES, R_1= TMS
5	**212**, R=TBS, R_1= TMS	$MeLi\text{-}CeCl_3$	**221**, 99 % 7:1, R=TBS, R_1= TMS
6	**213**, R=TBS, R_1= H	$MeLi\text{-}CeCl_3$	**222**, 98 % 7:1, R=TBS, R_1= H



239 **240**

R_2 =

Possible Causes for the Erosion of Selectivity

Even though these reactions have been unexplored mechanistically, it is believed that a combination of two factors led to an erosion of selectivity for the methyl addition to the C_8 ketone from a 3:1 ratio in TES protected alcohol **214** (Figure IV-4) to a 1:1 ratio in the TBS protected alcohol **239** (Figure V-6). These factors are a steric interaction between the TBS groups at C_9 and C_{11} of triene **239** and the special orientation of the triene unit C_{12}-C_{17}.

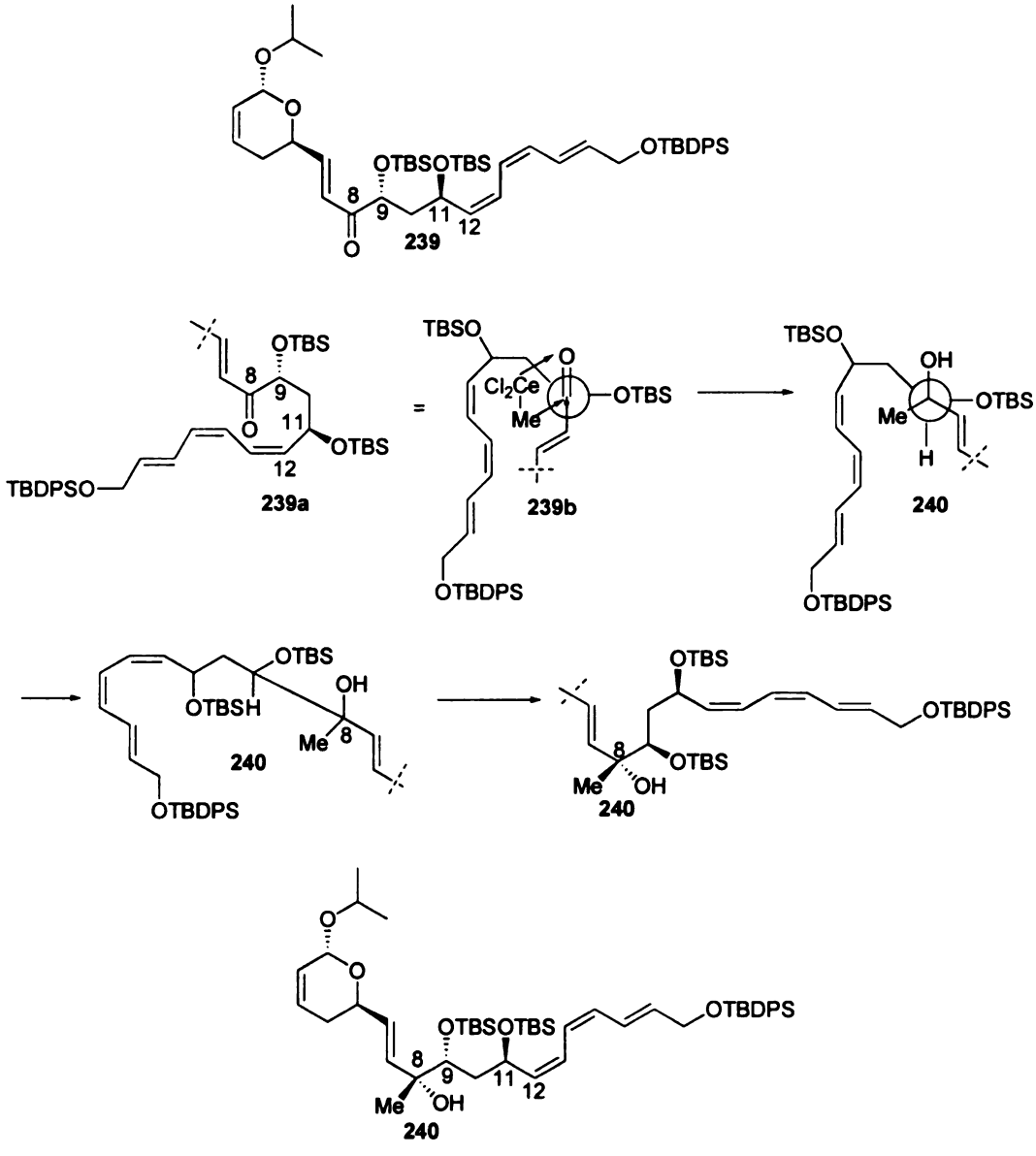
A steric interaction between the C_9 and C_{11} TBS groups is strongly suggested as a reason for the erosion of selectivity because in ketone **214** (Figure IV-4), where the only difference from **239** (Figure V-5) is that C_9 is TES protected a 3:1 ratio is obtained after reaction with MeLi-$CeCl_3$. If this is the only difference between the two structures **214** and **239**, then the interaction between the two TBS groups must play a role in the erosion of selectivity observed.

Another piece of evidence that suggests that the interaction between the C_9 and C_{11} TBS groups is a strained one is that when tertiary alcohols **221** (Figure IV-10) or **240** (Figure V-12) are reacted under basic conditions there is a TBS migration from one of the secondary alcohols to the C_8 tertiary alcohol. This is unusual since tertiary alcohols are inherently more sterically encumbered than secondary alcohols. In order to faciliate a migration of this sort, some competing steric interaction must be present. The C_9 and C_{11} bis-TBS protected alcohols seem to facilitate this type of migration, indicating that this arrangement is indeed a sterically encumbered one.

The steric argument presented above only accounts for the change in selectivity in the methyl addition to the C_8 ketones in **214** and **239** from 3:1 to 1:1, respectively. The change in selectivity between ketones **212/213** (Figure IV-9) and **239** (Figure V-6) upon methyl addition with MeLi-$CeCl_3$ is much more dramatic. When ketones **212/213** which are devoid of the (*Z,E,E*)-triene unit are methylated with MeLi-$CeCl_3$ a 7:1 ratio of C_8 epimers in the products **221** and **222** is observed (Figure IV-9). This is a seven times a greater selectivity at C_8 than is observed when ketone **239** is methylated with MeLi-$CeCl_3$ under the same reaction conditions (Figure V-6). The difference between these structures lie in the nature of the carbon chain attached to C_{11}. In ketone **212** there is a TMS protected alkyne, and in ketone **213** there is a terminal alkyne and in ketone **239** there is a (*Z,E,E*)-triene. At a glance it might not be obvious what the reason for the erosion of selectivity is. When ketone **239** is drawn on paper the triene unit appears to be in the plane of the paper, however when a model of **239** is built, one of the more stable conformers appears to be one whose triene unit partially blocks the *si*-face of the carbonyl. The model for C_8 methyl addition to **239** shown in Figure V-7. The face from which the methyl addition needs to occur in order for the correct C_8-*R* stereochemistry to be obtained is the *si*-face as shown in **239b** (Figure V-7) which is drawn according to the Felkin-Ahn model.[105] With the *re*-face blocked by a bulky TBS group and the *si*-face blocked with a rigid triene unit, the selectivity at C_8 would be expected to be low. In the case of ketones **212** and **213** where there is no triene unit attached at C_{11} the *si*-face would not be blocked hence a higher selectivity for methyl addition to ketones of the type **212** and **213** would be expected.

A change in selectivity brought about by increasing the ratio of MeLi-$CeCl_3$ to ketone **239** is unusual. The fact that even using 18 equivalents of MeLi-$CeCl_3$ complex seems to be necessary, implies that cerium or lithium may have more than one interaction with ketones of type **214** (Figure IV-4) and **239**. They are certainly other oxygens present in ketones **214** and **239**, which despite a very sterically uncompromising environment might still be able to coordinate to cerium in the MeLi-$CeCl_3$ complex. In addition, there are five olefins that could also possibly coordinate to the cerium. Futhermore, the large excess of lithium may also play a role in coordination and or aggregation. Any of these double bonds could cause ketone **239** to have a different orientation spacially than that depicted in Figure V-7, where only the C_8 carbonyl coordinates to the metal. At this point however this reasoning is highly speculative and does not provide a clear explanation for the observed results.

Figure V-7 Predicted model for C_8 Methylation



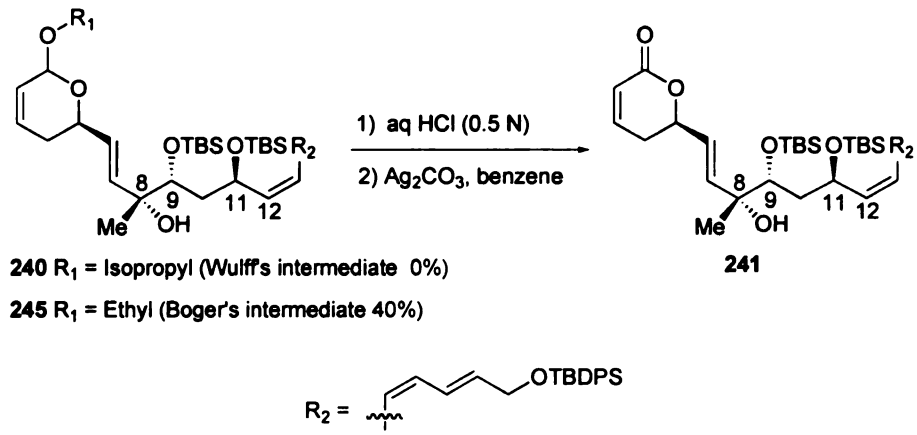
These hypotheses involving metal coordination and/or aggregation are supported by the observation that when ketones **211** and **212** were reacted with $AlMe_3$, they gave completely different selectivities than those resulting from a MeLi-$CeCl_3$ protocol. As can be seen in Figure V-6 entry 1, the TES protected α-hydroxy ketone **211** gave a 10:1

selectivity when $AlMe_3$ was used and only a 3:1 selectivity when MeLi-$CeCl_3$ complex was used (entry 4). In addition, a 7:1 selectivity was obtained with the TBS protected α-hydroxy ketone **212** (entry 5) upon reaction of the MeLi-$CeCl_3$ complex but when $AlMe_3$ was used the selectivity dropped to 3:1 (entry 2). A detailed mechanistic investigation needs to be done to better understand the nature of methyl addition using $AlMe_3$ vs. MeLi-$CeCl_3$ on compounds of the type **211** and **212** and **214** and **239**.

Acetal Removal and TBS Migration

After successful methyl addition to ketone **239** was achieved with a 3:1 ratio of inseparable C_8 epimers, oxidation of the isopropyl acetals **240** to the lactones **241** became the next feat (The major epimer at C_8 is indicated in all figures). This step was essential at this point in our synthetic approach because Boger had shown that after this transformation the diastereomers could be separated (Figure I-14). In order to prevent having to characterize any future intermediates as mixtures, this step was attempted prior to silyl migration. As can be seen in Figure V-8, using mild acid followed by a Fetizon's[101] oxidation gave only decomposed material. This procedure was used by Boger on the ethyl acetals **245** (see Figure V-8) and gave a 40% yield for the two steps.

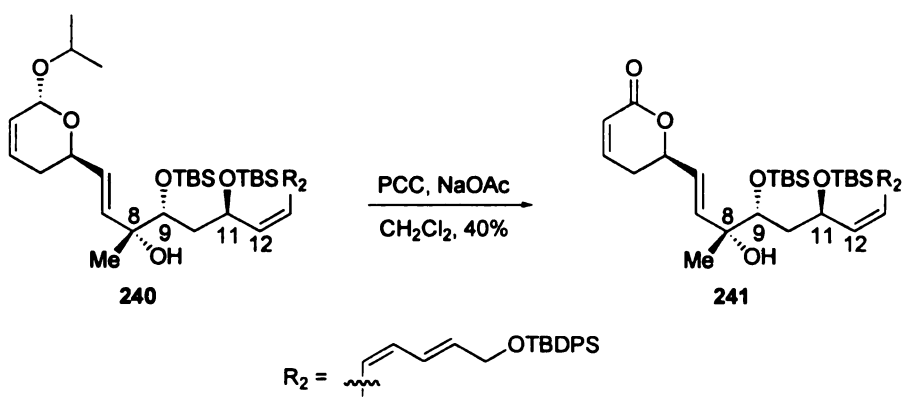
Figure V-8 Acetal Removal With HCl and Ag_2CO_3



The removal of the isopropyl group was also attempted using pyridinium para-toulene sulfonic acid (PPTS) in an acetone/water mixture but upon analysis of the reaction mixture after the oxidation, no desired product was obtained.

Eventually some success came when isopropyl acetals **240** (3:1 diastereomeric ratio) were subjected directly to a pyridinium chlorochromate (PCC) sodium acetate mixture (NaOAc). A 40% yield for the lactones **241** was obtained (characterization was based on ^1H NMR only) and could be separated. Lactones **241** were not very stable and were used immediately for the next step (Figure V-9).

Figure V-9 Acetal Removal With PCC

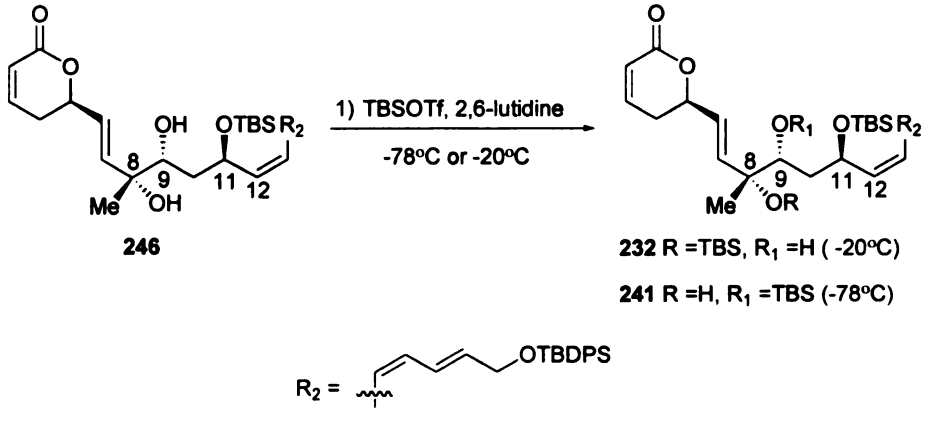


TBS Migration

The migration of TBS from the C_9 oxygen to the C_8 tertiary hydroxyl is essential because in the natural product the C_9 alcohol contains a phosphate group. This migration was not accomplished before but was suggested by an observation made by Boger on a related transformation in his synthetic investigations.[24] Alcohol **246** could be protected selectively either at the C_8 or C_9 alcohol depending on the temperature at which the reaction was done (Figure V-10). At -78 °C hydroxyl protection at C_9 was favored but at -20 °C protection at C_8 was observed. It is possible that silyl migration occurs from the C_9 oxygen to the C_8 alcohol at higher temperatures prior to quenching.

Applying these conditions to lactones **241** gave no desired product but instead just decomposed materials. Enlisting a variety of bases such as Et_3N, imidazole, NaH and amberlyst A-26 (chloride ion form) all gave no desired product. The products isolated were almost all devoid of the α,β-unsaturated olefin in the lactone ring.

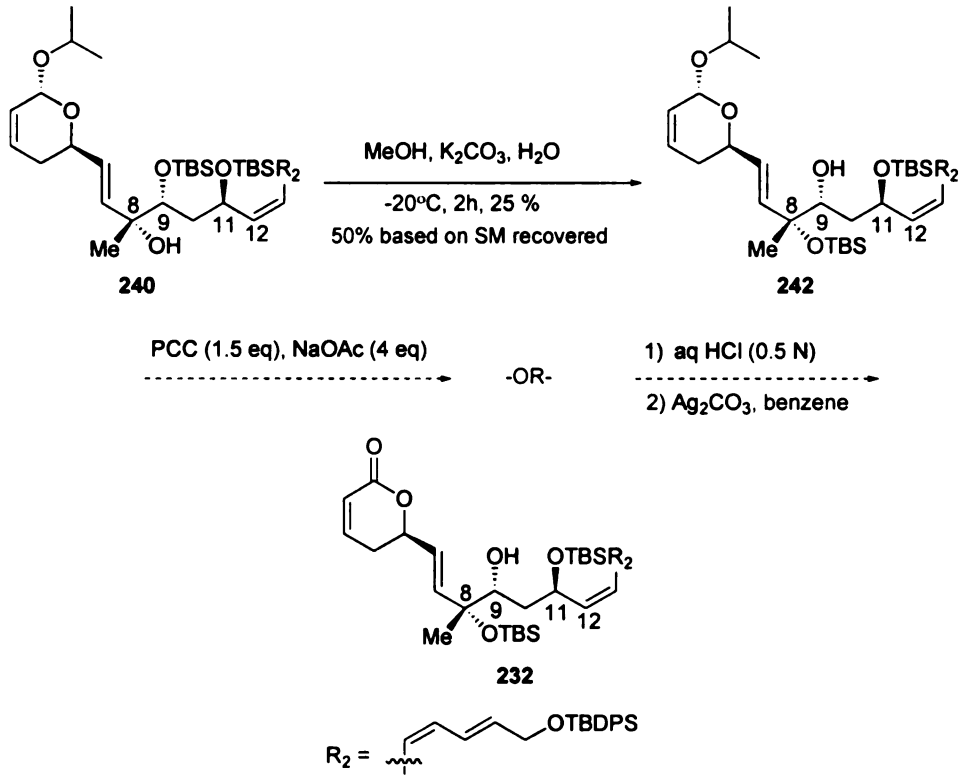
Figure V-10 Selective TBS Protection



Eventually it was hypothesized that a Michael addition to the lactone of **246** was a competing reaction to the silyl migration. If this were true, the order of PCC oxidation and TBS migration would have to be reversed to avoid this problem.

Unfortunately, reversing the order of reactions posed a very crucial problem. PCC is widely used as an oxidizing agent for the conversion of 1° and 2° alcohols to the corresponding aldehydes and ketones.[102] Performing the migration on isopropyl acetals **240** (Figure V-9) first would mean that the C_9 secondary alcohol that is prone to oxidation would be unprotected. Instead of just cleaving the isopropyl group and oxidizing the resulting lactol to lactone **232**, the C_9 alcohol would also be oxidized (Figure V-11). This problem could be solved if the HCl hydrolysis followed by Fetizon's[101] oxidation were applied to isopropy acetals **242** (Figure V-11).

Figure V-11 Migration of TBS Followed by Lactone Preparation

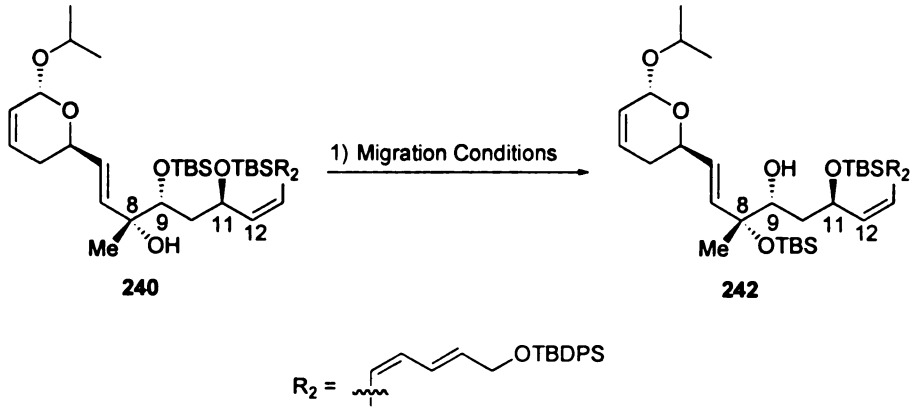


This approach would leave the C_9 alcohol of **242** unharmed but would selectively convert the isopropyl acetals **242** to lactones **232**. It was already shown however that with isopropyl acetals **240**, HCl hydrolysis followed by Fetizon's[101] oxidation failed (Figure V-8). Contrastingly however, with ethyl acetals **245** this transformation was successful (Figure V-8). If isopropyl acetals **242** could be converted to ethyl acetals **244** then the hydrolysis and oxidation would be feasible, and that would constitute formal synthesis.

Thus far, TBS migration was only attempted on lactones **241** and this was unsuccessful, so before an attempt to exchange the isopropyl group on **240** for an ethyl group was made, a series of reactions were screened to actualize the silyl migration on isopropyl acetals **240** (Figure IV-12).

As is shown in Figure V-12 there were at least two sets of conditions that gave the desired compounds **242**, NaH in THF and K_2CO_3 in MeOH and H_2O. A mixture of at least five fractions was seen on TLC and the separation of these fractions was painstakingly difficult. Each preparative TLC plate was buffered with Et_3N and all work-up procedures and isolation done in the dark. Isopropyl acetals **242** could be isolated as a 3:1 diastereomeric mixture in 25% yield. The other products isolated were thought to be TBS deprotected diols and C_{15}-C_{16} *trans*-isomers **243**. Only the C_{15}-C_{16} *trans*-isomers could be isolated long enough to obtain sufficient data for characterization. Separation of acetals **242** could be achieved here but this separation was postponed until the next step because Boger reported an easier separation occurred with lactones **232**.[24] The isopropyl acetals **242** were used immediately for the next step because these products are very unstable. Even freezing in benzene under an argon atmosphere in the freezer (-30 °C) was not enough to keep acetals **242** pure. Interestingly, the isopropyl acetals **240** could be stored for relatively long periods (a month) under these conditions without significant decomposition.

Figure V-12 Screening Conditions for TBS Migration on Alcohol 240



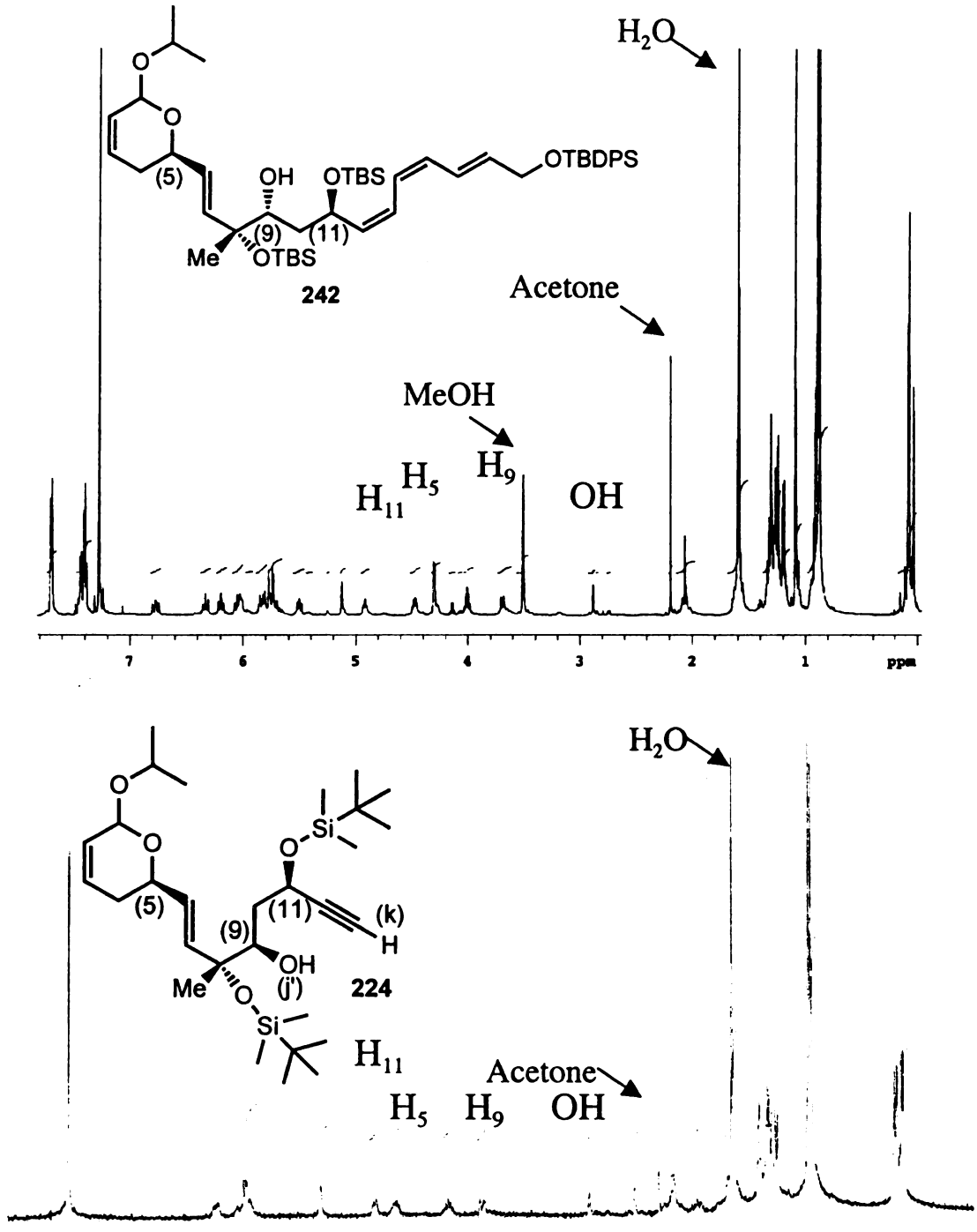
Entry	Bases	Conditions	Results
1	NaH, 7eq, THF	-78 °C, 3h	25%, 40%SM Recovered
2	MeOH:H_2O, (10:1), K_2CO_3 (2.5 eq)	-20 °C-2h	25%, 50%SM Recovered
3	Et_3N (2 eq), CH_2Cl_2	0 °C-r.t, 3.5h	80% SM recovered
4	Imidazole (1 -15eq), THF	0 °C-r.t, overnight	20-80% SM recovered
5	2,6-lutidine (4 - 8 eq), CH_2Cl_2	0 °C-r.t, overnight	20-80% SM recovered

Migration Anomaly

In order to confirm that the migration from the C_9 2° alcohol to C_8 3° alcohol had taken place, we compared the spectral data of products **242** to the isopropyl acetal **X** isolated earlier (Figure IV-10). As reported in Chapter 4, this product was assigned as the alcohol **223** which had its C_8 and C_9 hydroxyls protected with TBS and its C_{11} 2° alcohol unprotected. Structure **223** was supposed to be derived from the migration of TBS group from the oxygen at C_{11} to that at C_8. The result obtained from the comparison of spectral data of **242** with **223** was disturbing initially as the chemical shift changes for **242** were identical to those described for **223** in Chapter 4. The proton H_9 had not shifted and the

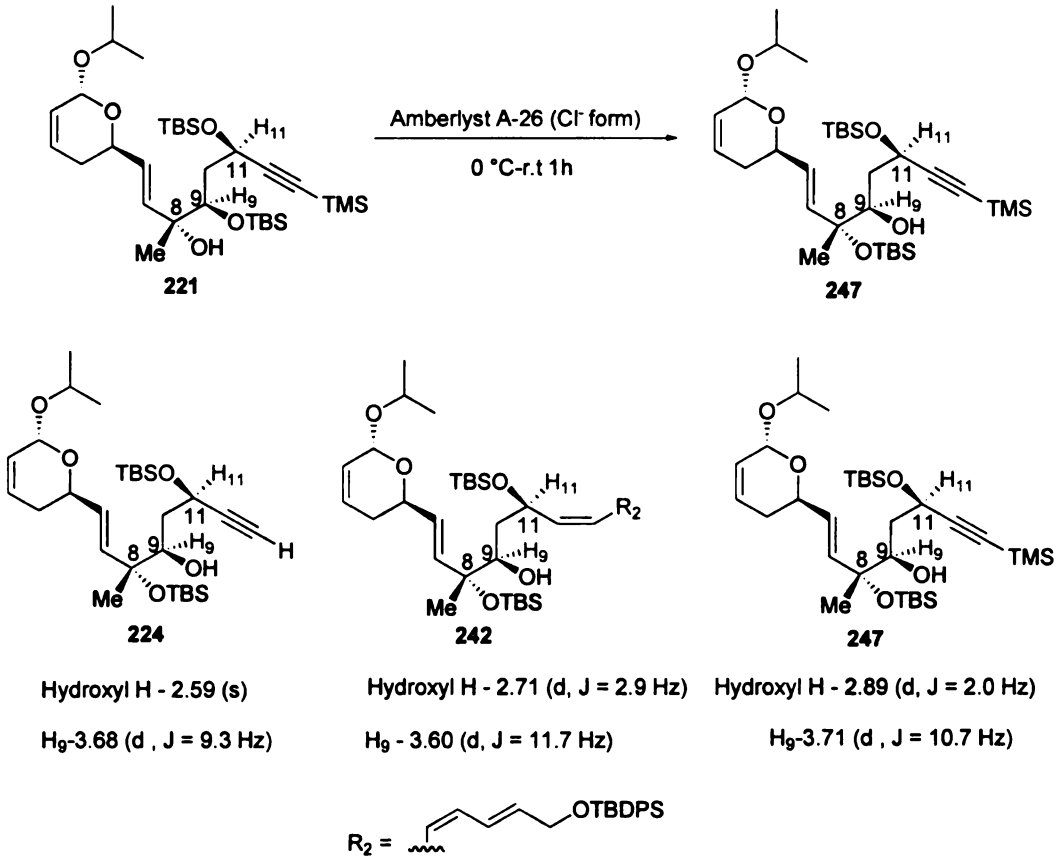
proton H_{11} had shifted downfield by 0.18 ppm. Refusing to believe that Boger isolated one thermodynamic product and our group another, more concrete information was sought. One breakthrough occurred when running a ^1H NMR of the minor isomer of alcohol **242** on the 500 MHz NMR instrument. On the 300 MHz NMR instrument, the unprotected hydroxyl group was a singlet but on the 500 MHz NMR, it was a doublet. This meant that homodecoupled experiment could now be accomplished to determine which proton (H_9 or H_{11}) was coupled to the unprotected hydroxyl. It was surprising but delightful to find that when the proton assigned as H_9 was irridated the *J* coupling of 2.9 Hz for the hydroxyl proton disappeared giving a broad singlet at 2.71 ppm. When the alcoholic peak was irradiated the H_9 doublet of doublets at 3.60 ppm with coupling constants of 11.7 and 2.9 Hz sharpened in appearance significantly, and coalesced to a doublet J = 11.7 Hz. This forced us to re-examine the previous assignment of compound **223**. When the ^1H NMR spectra of **223** was taken on the 500 MHz NMR instrument, instead of a doublet for the C_9 hydroxyl as in the case with acetal **242**, a singlet at 2.75 ppm was observed. Hence no homodecoupled experiment could be done.

Figure V-13 ^{1}H NMR of TBS Migrated Products 224 and 242



deprotection of the TMS from acetal **221** was quenched after 1 hour instead of allowing the reaction to run overnight. The ^{1}H NMR of **247** is very similar to that of the compound assigned **223**. Other than the hydroxyl shifts, only an extra nine protons at 0.12 ppm corresponding to the TMS and the disappearance of the terminal alkyne proton of **223** at 2.35 indicate any major differences. In addition a low resolution mass spectrum confirmed the molecular mass of **247** (see Chapter 5 experimental for details). A homodecoupled experiment performed on acetal **247** confirmed that indeed H_9 and the hydroxyl proton were coupled. When the doublet at $\delta = 2.89$ ($J = 2.0$ Hz) corresponding to the hydroxyl proton was irradiated the doublet at $\delta = 3.71$ ($J = 10.7$ Hz) corresponding to H_9 gave a sharper appearance. When the situation was reversed and H_9 was irradiated the doublet at 2.89 coalesced to a singlet. The proton H_{11} remained unchanged throughout these experiments and when it was irradiated the appearance of the hydroxyl proton or H_9 was unaffected. TBS migrated product **223** in chapter 4 was now reassigned as secondary alcohol **224** (Figure IV-12), based on the evidence suggested here.

Figure V-14 Comparing Secondary Alcohols 224, 247 and 242



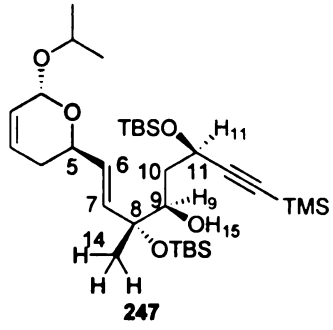
The assignment of compound **247** was also confirmed by HMBC and HMQC 2D experiments (Figure V-15). The results obtained from the HMBC only showed partial correlations but the evidence obtained was enough to confirm the structure of alkyne **247**. Identification of C_8 provided the most concrete evidence. This carbon is one of three quaternary carbons which do not appear on the HMQC spectrum, C_8, C_{12}, and C_{13}. Of these three carbons only C_8 can show an HMBC crosspeak to a vinylic proton (H_6), C_{12} and C_{13} are well out of the three bond coupling range. If the arrangement of alkyne **247** is as shown with the C_9 hydroxyl unprotected, then not only would H_6 couple to C_8 in the HMBC experiment but so would the hydroxyl proton H_{15}. When H_6 and H_{15} were

analyzed both showed correlation to a quaternary carbon at 77.30 ppm which was identified as C_8. The arrangement of silyl protecting groups seen in alkyne **248** (Figure V-15) does not allow for three bond coupling to any carbon around 77.30 ppm which will in turn be coupled to a vinylic hydrogen. Additional evidence to confirm the structure of alkyne **247** is provided by the methyl group C_{14} attached to C_8. The proton H_{14} is a singlet on the HMBC data shows crosspeaks to two carbons one at 76.60 ppm and the other at 134.86 ppm. The carbon at 134.86 ppm is C_7 corresponding to an sp^2 carbon which is three bonds away from H_{14}. Therefore a δ value of 76.60 ppm must correspond to C_9 (Figure V-15). The proton we assigned as H_9 in compound **247** is a doublet at 3.71 ppm and it was attached to a carbon at 76.60 ppm in the HMQC. Proton H_9 was important because it was shown by homodecoupling experiments to be coupled to the unprotected hydroxyl proton. These experiments are described in the previous paragraph. Since H_9 which is coupled to the free hydroxyl is attached to a carbon at 76.60 and this carbon shows a crosspeak by HMBC analysis to H_{14}, it can be safetly concluded that alcohol **247** (and not alcohol **248**) is the correct structure (Figure V-14). In addition, H_{14} showed no crosspeaks to C_5 at 66.50 ppm or C_{11} at 61.20 ppm which were the other two carbons seen in the HMQC that bore one hydroxyl.

Unfortunately H_5, H_9 and H_{11} showed no crosspeaks to any carbons in the HMBC experiment. Nevertheless the results that were obtained was enough to confirm the structure of **247**. The assignment of **247** also allows for the confirmation of the assignment of compound **X** (Figure IV-12) as alkyne **224** and triene **242** (Figure V-14) by correlation of proton chemical shifts and multiplicities.

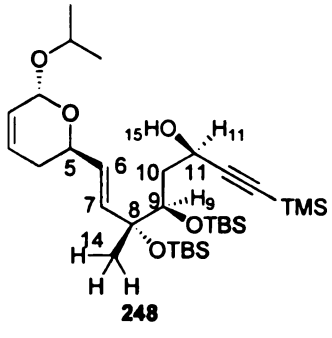
As was metioned earlier, TBS migration from a secondary to tertiary alcohol to give compounds such as alkyne **224** and triene **242** was suggested by Boger.[24] This migration was not accomplished before but was suggested because of an observation made by Boger on a related transformation in his synthetic investigations (Figure V-10).[24] Alcohol **246** could be protected selectively either at the C_8 or C_9 alcohol depending on the temperature at which the reaction was done (Figure V-10). At -78 °C hydroxyl protection at C_9 was favored but at -20 °C protection at C_8 was observed. As seen in Figure IV-10 a 1.5:1 ratio of compound **222** to compound **224** is observed when the TBS group migrates from the C_9 oxygen to C_{11} oxygen. If this migration is reversible and the products **222** and **224** are in equilibrium with a ratio of 1.5:1 respectively, then upon subjection of alkyne **224** to the migration protocol a similar outcome would be expected. In order to confirm Boger's hypothesis, alkyne **224** with TBS protected hydroxyls at C_8 and C_{11} was subjected to the migration conditions we developed earlier (Figure IV-10). As expected a 1.5:1 ratio of alkynes **222** to **224** was obtained, indicating that indeed the silyl migration is reversible and in this case that the alkynes **222** and **224** are in equilibrium.

Figure V-15 Partial HMBC and HMQC Analysis of Alkyne 247



247

Proton	HMQC Attached C	HMBC Correlation
H_5-4.38-4.48 ppm	C_5 -66.50 ppm	C_7 (134.86 ppm)
H_6-4.38-4.48 ppm	C_6 -128.06 ppm	C_8 (77.30 ppm)
H_7-5.64-5.84 ppm	C_7 -134.86 ppm	C_5 (66.50 ppm)
H_9-3.71 ppm	C_9 -76.60 ppm	———
H_{10}-1.72-1.84 ppm	C_{10} -39.40 ppm	C_{11} (61.5 ppm-2 bond coupling)
H_{14}-1.30 ppm	C_{14} -29.35 ppm	C_7 (134.9 ppm); C_9 (76.60 ppm)
H_{15}-2.90 ppm	———	C_8 (77.30 ppm); C_{10} (39.40 ppm)



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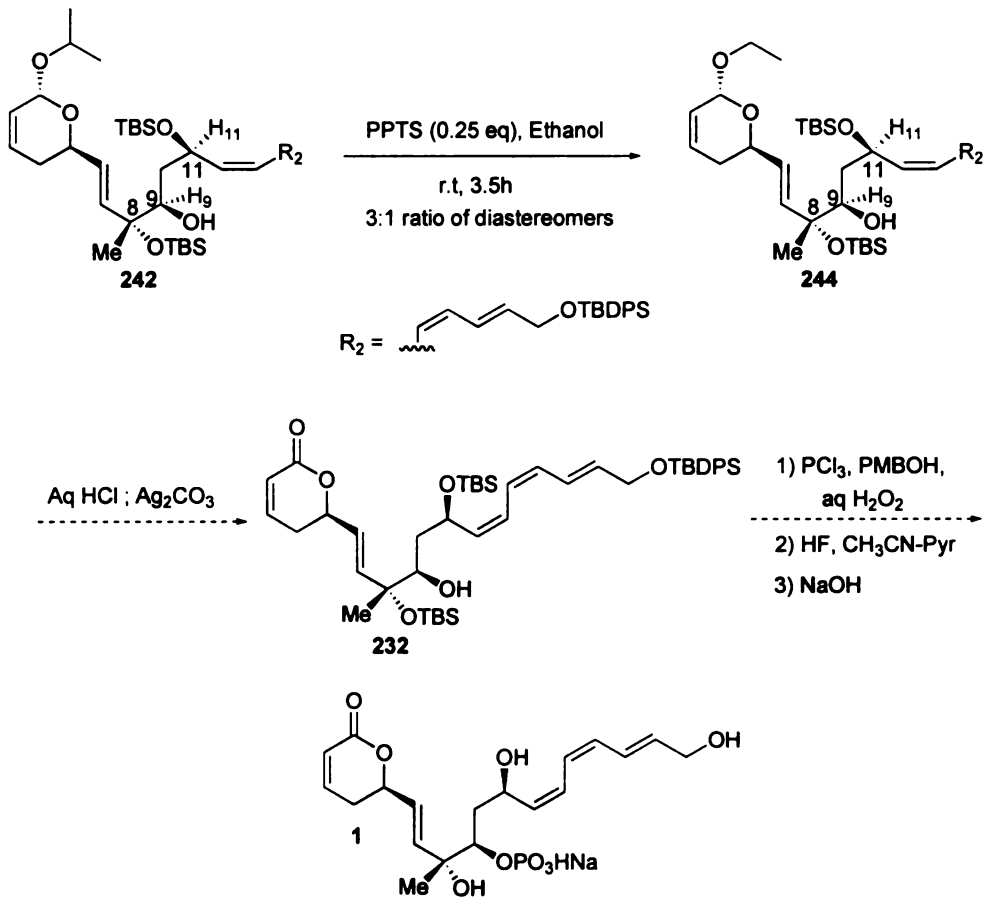
Formal Synthesis

With this newly found knowledge in hand the exchange of the isopropyl group in acetal **242** for ethyl groups in acetal **244** was attempted. Ethyl acetal **244** was prepared as a 3:1 mixture of diastereomers from the 3:1 mixture of diastereomers of isopropyl acetal **242** in 92% yield to provide a formal total synthesis of fostriecin (Figure V-16). The ^1H NMR and IR spectral data of **244** matched the spectra of an authentic sample (also a 3:1

mixture) provided by Boger. The remaining steps for the conversion of **244** to fostriecin as reported by Boger are shown in Figure V-16.

Figure V-16 Formal Synthesis of Fostriecin



Attempts to Prepare Lactone

During the synthesis of **244** it was realized that compounds containing the *Z,Z,E* triene intermediate are very unstable and decompose readily even when stored carefully under argon at cold temperatures. What seemed to be even more unstable were intermediates which also included the α,β- unsaturated lactone. When ethyl acetal **244** was hydrolyzed and oxidized to the lactone, the diastereomers could be separated but ^{1}H NMR showed the product with solvent peaks. When placed under vacuum (0.2 mmHg)

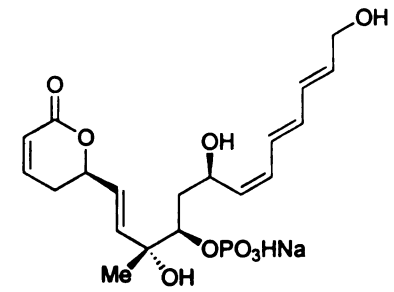
and carefully wrapped in foil overnight the ^{1}H NMR showed decomposition with new peaks at δ = 3.60 and 4.05 ppm as well as a messy olefinic region. These were all peaks that were not present a few hours earlier. Much care and precision needs to be taken when handling this intermediate.

This concern of stability made it very difficult to obtain clean carbon spectra for intermediates **232** and **244**. Other peaks began to develop while the ^{13}C NMRs were being taken. More material would need to be prepared in order to get clean ^{13}C NMR spectra carbons to complete the characterization of lactone **232** and ethyl acetal **244**.

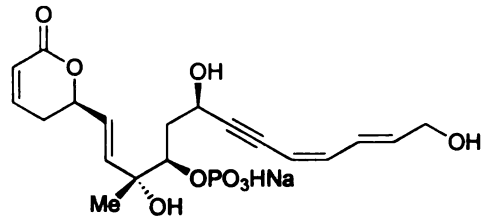
Conclusions

Our ultimate goal was not just the formal total synthesis or the synthesis of the natural product fostriecin itself, but also the synthesis of some closely related analogs. Fostriecin itself is somewhat unstable and when used in the clinic must be stored frozen in a buffer. Our experience in trying to make fostriecin indicates that the two main sources of instability are the α,β-unsaturated lactone and the *Z,Z,E* triene moiety. Boger's SAR studies discussed in Chapter 1 indicate that indeed the lactone is one of the most reactive fragments and is essential for such high protein phosphotase selectivity. The triene moeity, however, he assigns as just being a hydrophobic tail with not much significance in terms of the molecule's activity. For this reason we believe that intermediates of the type **234** and **243** are precursors to equally active analogs while at the same time would provide much less sensitive alternatives. A general scheme for these and other proposed intermediates is outlined in Figure V-17 below.

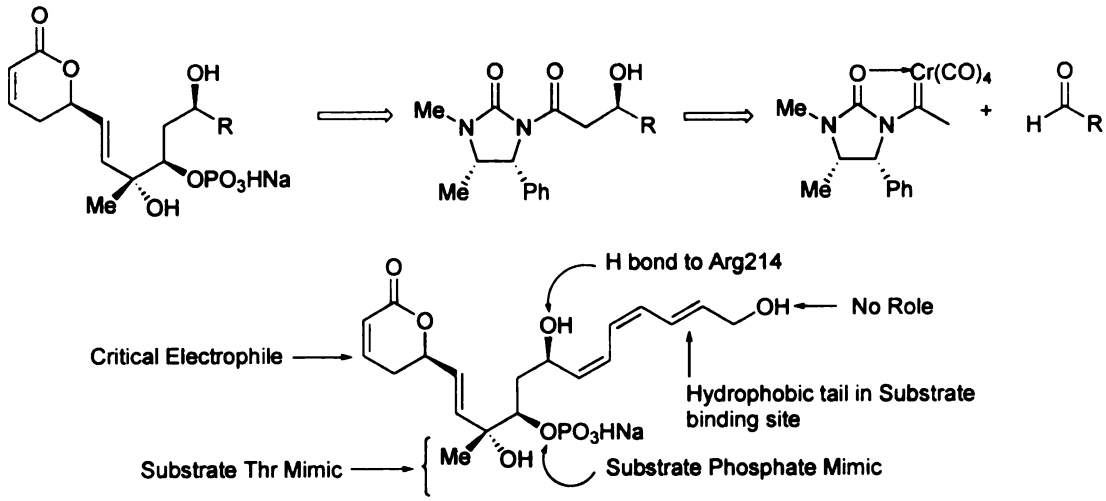
Figure V-17 Fostriecin Analogs



Derived from *Trans* -(*R,R,R,R*)-**243**



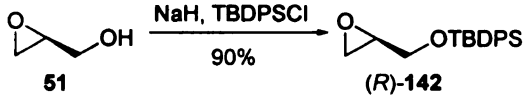
Derived fromDienyne (*R,R,R*)-**234**



CHAPTER 6

EXPERIMENTAL PROCEDURES

Experimental Data for Chapter 2

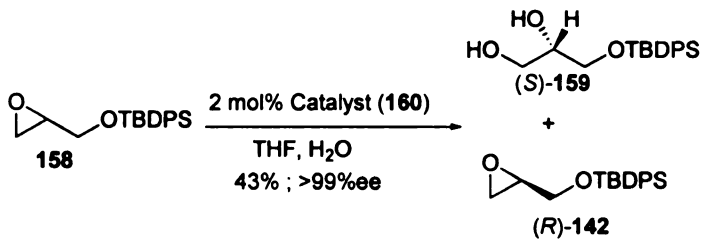


[a]**(*R*)-(Tert-butyldiphenylsilyl)glycidol 142.** A 500 mL round bottom flask was charged with *(S)*-glycidol (2.00 g, 27.0 mmol) and dissolved in 100 mL CH_2Cl_2. DMAP (132 mg, 1.08 mmol, 4 mol%) and triethylamine (3.00 g, 29.7 mmol, 4.13 mL), were added and the flask was placed under argon atmosphere. Tertbutyldiphenylsilyl chloride (8.9 g, 32.0 mmol, 8.42 mL), was added neat via syringe. The reaction turned cloudy after 1 hr, and was stirred for 24 hr.

The reaction was quenched by adding water (20 mL), poured into a separatory funnel, and the organic layer was washed with saturated NH_4Cl solution (2 x 20 mL), water (3 x 40 mL), and brine (1 x 40 mL) and then dried with $MgSO_4$, and concentrated to a pale yellow oil. The oil was purified by simple distillation (140-150 °C/0.2 torr) and chromatography on silica gel (9:1 pentane/ether, UV visualization – faint spots), which gave the product at R_f = 0.50 and TBDPS-OH at R_f = 0.2. The product (*R*)-(7.6 g, 0.051 mmol) was isolated in 90% yield as a thick colorless oil.

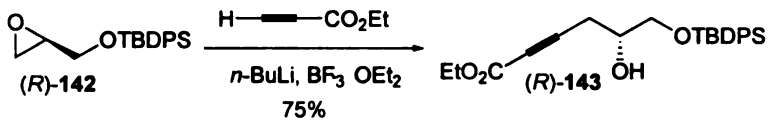
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (s, 9H), 2.61 (dd, 1H, *J* =2.7, 5.2 Hz), 2.74 (dd, 1H, *J* = 4.1, 2.4 Hz), 3.12 (m, 1H), 3.71 (dd, 1H, *J* = 4.8 11.8 Hz), 3.85 (dd, 1H, *J* =

3.2, 11.8 Hz), 7.37-7.43 (m, 6H), 7.67-7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.24, 26.75, 44.45, 52.26, 64.31, 127.71, 129.73, 133.30, 135.56, 135.62; IR (neat film on NaCl): 2959 (m), 2857 (m), 1428 (m), 1113 (s), 702 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 255 M^+ -57 (50), 225 (100), 211 (24), 183 (74), 177 (40), 135 (8), 117 (43), 105 (17), 91 (11), 77 (15); bp 140-150 °C/0.2 torr, R_f = 0.5 (9:1 pentane/ether), $[\alpha]_D$ -3.13 (*c* 1.05, $CHCl_3$).



Preparation of *R*-Gylcidol Silyl Ether by HKR-(*R*)-142[90]. Pre-catalyst (1*S*,2*S*)-(+)-1,2-cyclohexanediamino-N,N-bis-(3,5-di-t-butyl salicyclidene) Co (II) **160** (0.7 mg, 0.0012 mmol) and AcOH (0.32 mL, 0.0056 mmol) was added to neat racemic glycidol (17.46 g, 0.056 mol). The reaction flask was open to air, and after 10 mins the orange color turned to dark brown. The solution was cooled to 0 °C and 0.6 mL of THF and 0.55 mL (0.028 mol) of H_2O were added. A septum was then placed on the flask and a steady air-flow was maintained through the flask and out to a bubbler. The solution was warmed to ambient temperature over two hours and kept at that temperature for 30 h. All of the THF was removed via rotary evaporator and the H_2O was removed via short path distillation under vacuum (0.02 mmHg). The product was then distilled over at 150-158 °C under vacuum (0.02 mmHg). Column chromatography with 2% EtOAc in pentane of the

distilled product gave 43% of *R*-gylicdol silyl ether **142** with >99% ee. All the spectral data taken matched that reported above for (*R*)-**142**. The precatalyst may be recovered by dissolving the residue after distillation in CH_2Cl_2 and washing it multiple times (10 X 20 mL) with water. Some diol contaminant still remains but the recovered material can be reused to give a 43% yield of (*R*)-**142** which was > 96%ee. Chiracel OD, hexanes, 1mL/min, 254 nm, (*S*)-**142** (34.86 min), (*R*)-**142** (47.11 min).

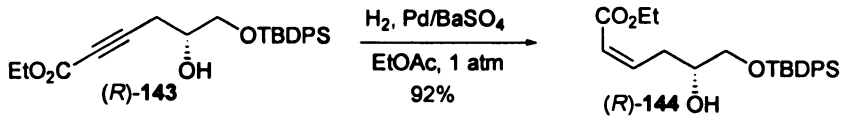


[a]**Alkynal Ester *R*)-143.** A 250 mL round bottom flask was charged with freshly distilled ethyl propiolate (0.76 g, 7.44 mmol, 0.75 mL), and dissolved in 60 mL THF at –78 °C. A solution of *n*-BuLi (2.5 M in hexane, 7.44 mmol, 3.08 mL), was added via syringe. The pale yellow reaction mixture was stirred for 10 minutes, then $BF_3.OEt_2$ (1.09 g, 7.44 mmol, 0.98 mL), was added neat via syringe. The yellow color persisted as the reaction was stirred for another 5 minutes, then protected glycidol (*R*)-**142** (2.187 g, 7.0 mmol) was added neat via syringe. The reaction mixture darkened slightly. The reaction was complete when checked by TLC after 1 h.

The reaction was quenched by adding saturated NH_4Cl at –78 °C, then allowing the mixture to warm to room temperature. The mixture was poured into a separatory funnel containing 30 mL water and 50 mL ether. The aqueous layer was back-extracted with 40 mL ether, and the combined organic layers were washed with water (2 x 50 mL)

and brine (1 x 50 mL), dried with $MgSO_4$ and concentrated to a yellow/orange oil. This oil was chromatographed on silica gel (5:1 hexane/EtOAc – $KMnO_4$). One fraction at R_f = 0.26 was collected and concentrated to give the product (*R*)-**143** (2.15 g, 5.24 mmol) in 75% yield as a pale yellow oil.

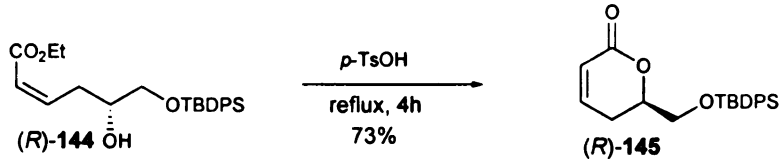
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.30 (t, 3H, *J* = 7.2 Hz), 2.60 (dd, 2H, *J* = 2.1, 6.4 Hz), 3.71 (dd, 2H, *J* = 4.2, 9.8 Hz), 3.90-3.98 (m, 1H), 4.21 (q, 2H, *J* = 7.1 Hz), 7.38-7.64 (m, 6H), 7.64-7.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.02, 19.25, 23.53, 26.82, 61.86, 66.19, 69.68, 84.98, 127.73, 127.86, 129.94, 132.76, 135.52, 153.45; IR (neat film on NaCl): 3700-3100 (w), 2958 (m), 2931 (m), 2858 (m), 2237 (m), 1711 (s), 1428 (m), 1253 (s), 1113 (s), 1073 (m), 702 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 365 M^+ -45 (18), 353 (26), 309 (15), 275 (91), 241 (84), 223 (26), 209 (65), 199 (95), 181 (100), 163 (58), 135 (30), 105 (26), 77 (20); R_f = 0.26 (5:1 hexane/EtOAc); $[\alpha]_D$ -6.40 (*c* 1.05, $CHCl_3$).



[a]Alkyne Reduction to Give (*R*)-144.[61] A 250 mL round bottom flask was charged with ester (*R*)-**143** (2.554 g, 6.22 mmol), and dissolved in 125 mL EtOAc at room temperature. Lindlar's catalyst (250 mg, 5% Pd on $CaCO_3$ poisoned with lead, Aldrich) and six drops of quinoline were added and the mixture was stirred briefly, then

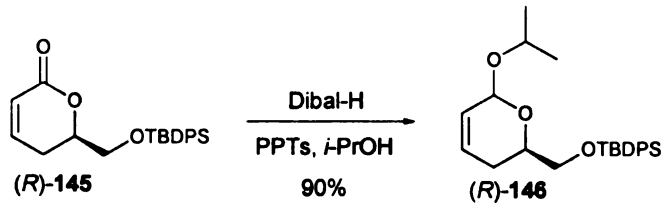
placed under hydrogen atmosphere via four evacuation/backfill cycles. The reaction was stirred for 2.5 h, then a small aliquot was removed, filtered, and checked by IR spectroscopy for complete disappearance of the C-C triple bond. The reaction was complete, so the catalyst was removed by filtration through Celite and the solution was concentrated to a pale yellow oil. The oil was chromatographed on silica gel (5:1 hexane/EtOAc – $KMnO_4$). One fraction at R_f = 0.37 was collected and concentrated to give 2.37 g (5.7 mmol) of the product (*R*)-**144** as a colorless oil in 92.3% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.26 (t, 3H, *J* = 7.2 Hz), 2.82 (m, 2H), 3.57 (m, 1H), 3.67 (dd, 1H, *J* = 4.2, 10.2 Hz), 3.85 (m, 1H), 4.14 (q, 2H, *J* = 7.2 Hz), 5.87 (dt, 1H, *J* = 11.6, 1.6 Hz), 6.34 (dt, 1H, *J* = 11.5, 7.5 Hz), 7.37-7.64 (m, 6H), 7.64-7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.22, 19.25, 26.85, 32.62, 60.02, 67.64, 71.40, 121.67, 127.78, 129.82, 133.12, 135.53, 145.59, 166.61; IR (neat film on NaCl): 3700-3400 (w), 2931 (m), 2858 (m), 1719 (s), 1427 (m), 1177 (m), 1113 (s), 702 (s); EI mass spectrum *m/z* (% rel intensity) 355 (M^+ -57) (22), 309 (100), 289 (7), 277 (16), 241 (58), 223 (29), 199 (78), 181 (22), 163 (61), 139 (23), 105 (18), 77 (13); R_f = 0.37 (5:1 hexane/EtOAc); $[\alpha]_D$ 1.33 (*c* 1.05, $CHCl_3$).



[a]**Lactone (*R*)-145**. A 250 mL round bottom flask was charged with reduced ester (*R*)-**144** (2.058 g, 5.0 mmol) and dissolved in 150 mL hexane (Optima grade, Fisher). Solid *p*-TsOH hydrate (47 mg, 0.25 mmol, 5 mol%) was added, and the reaction was heated to reflux for 24 h. The reaction was quenched with 20 mL $NaHCO_3$ solution, poured into a separatory funnel and washed with water (1 x 50 mL) and brine (1 x 50 mL), dried with $MgSO_4$ and concentrated to a yellow/orange oil. The oil was chromatographed on silica gel (5:1 hexane/EtOAc/$KMnO_4$) giving two fractions, one at R_f = 0.6 (presumed to be TBDPS-OH but not characterized) and the product (*R*)-**145** at R_f = 0.20, which was concentrated to a 73% yield of (*R*)-**145** (1.34 g, 3.65 mmol) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 9H), 2.45 (dt, 1H, *J* = 10.2, 1.2 Hz), 2.56 (ddt, 1H, *J* = 18.5, 11.0, 2.7 Hz), 3.84 (d, 2H, *J* = 4.9 Hz), 4.44-4.54 (m, 1H), 6.05 (dd, 1H, *J* = 1.1, 9.8 Hz), 6.83-6.91 (m, 1H), 7.40-7.44 (m, 6H), 7.64-7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.25, 26.77, 64.76, 77.56, 121.26, 127.80, 129.89, 132.96, 135.53, 135.60, 144.79, 163.75; IR (neat film on NaCl): 2957 (w), 2930 (m), 2858 (m), 1732 (s), 1427 (m), 1247 (m), 1247 (m), 1133 (m), 1113 (s), 1048 (m), 703 (s); EI mass spectrum *m/z* (% rel intensity) 309 M^+ -57 (100), 241 (55), 223 (22), 199 (21), 183 (13), 163 (58), 105 (13), 77 (7); R_f = 0.20 (5:1 hexane/EtOAc), $[\alpha]_D$ 38.3° (*c* 1.00, $CHCl_3$).

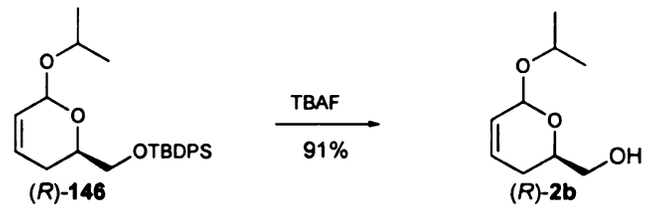


[a]Isopropyl Lactol (*R*)-146.[63,64] A 100 mL RB flask was charged with lactone (*R*)-**145** (0.366 g, 1.0 mmol) and dissolved in 10 mL CH_2Cl_2 at –78 °C under argon. A solution of DIBAL (1.0 M in hexane, 1.25 mL, 1.25 mmol), was added via syringe, and the reaction was monitored by TLC for disappearance of the starting material. After 2 h, the reaction was complete. The reaction was quenched at –78 °C with a 5 mL saturated aq NH_4Cl solution, then allowed to warm to room temperature. The reaction mixture was poured into a separatory funnel containing 10 mL of CH_2Cl_2 and 10 mL of aq NH_4Cl solution. The aqueous layer was back-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with NH_4Cl solution (1 x 20 mL) and brine (1 x 20 mL), dried with $MgSO_4$ and concentrated to a very sticky oil. The crude NMR and IR spectra were satisfactory.

The crude lactol was dissolved in 10 mL of isopropanol and PPTS (0.037 g, 0.15 mol%) were added to the solution. The reaction was stirred at room temperature while being monitored by TLC. The reaction was complete in 0.75 h. The reaction was quenched with 10 mL $NaHCO_3$ solution and poured into a separatory funnel. The aqueous layer was back-extracted with ether (2 x 10 mL). The combined organic layers were washed with water (2 x 20 mL) and brine (1 x 20 mL), dried over $MgSO_4$, and concentrated to a yellow oil. The oil was chromatographed on silica gel (10:1

hexane/EtOAc – $KMnO_4$), giving two compounds that were inseparable on TLC. The fractions containing the two compounds were concentrated to a colorless oil. The crude ^{1}HNMR spectra of this oil showed that two diastereomers of the product were present in a 9:1 ratio in 90% yield (0.369 g, 0.90 mmol). The ratio was determined by integration of the alcohol methine proton.

Characterization data for major isomer of (*R*)-146: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.17 (d, 3H, *J* = 6.1 Hz), 1.21 (d, 3H, *J* = 6.2 Hz), 1.98 (m, 2H), 3.63 (dd, 1H, *J* = 4.8, 10.6 Hz), 3.78 (dd, 1H, *J* = 4.5, 10.6 Hz), 4.03 (quintet, 1H, *J* = 4.2 Hz), 4.12 (m, 1H), 5.10 (s, 1H) (minor isomer has signal at 5.16 ppm), 5.72 (m, 1H), 6.00 (m, 1H), 7.37-7.42 (m, 6H), 7.68-7.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.21, 21.77, 23.90, 26.78, 27.10, 66.77, 67.01, 68.95, 92.58, 126.13, 127.62, 128.40, 129.60, 133.61, 135.62; IR (neat film on NaCl): 2966-2857 (m), 1472 (m), 1427 (m), 1183 (m), 1106 (s), 1020 (s), 823 (m), 701 (s) cm^{-1}; R_f = 0.52 (minor)/0.50 (major) (10:1 hexane/EtOAc).



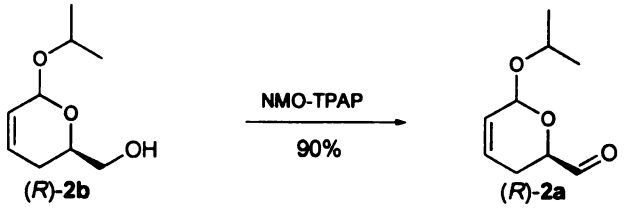
(*R*)-**146** (*R*)-**2b**

[a]Primary Alcohols 2b.[63,64] A solution of lactol (*R*)-**146** (740 mg, 1.87 mmol) was dissolved in 10 mL wet THF at room temperature. A solution of tetrabutylammonuim

fluoride (1.0 M in THF, 3.73 mmol, 2 equiv.) was added via syringe. The reaction was followed by TLC (10:1 hexane/EtOAc) to monitor disappearance of the starting material. The reaction was done after 1.5 h.

The reaction was quenched with aq $NaHCO_3$ solution (10 mL) and diluted with 10 mL ether. This mixture was poured into a separatory funnel, and the aqueous layer was back extracted with 20 mL ether. The combined organic layers were washed with water (2 x 10 mL) and brine (1 x 10 mL), dried with $MgSO_4$ and concentrated to a colorless oil. The oil was chromatographed on silica gel (gradient elution, 5:1 hexane/EtOAc followed by 2:1 hexane/EtOAc), giving a spot at $R_f = 0.52$ presumed to be TBDPS-OH (not characterized) and a spot at $R_f = 0.12$, which was concentrated to give the product alcohols (*R*)-**2b** (293 mg, 1.64 mmol) in 91% yield as a colorless oil.

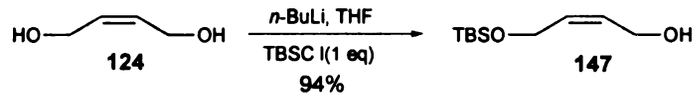
Characterization data (proton and carbon-13 NMR and IR) matched those reported by Crimmins et. al.[63] and Boger et. al.[24]



Oxidation to Aldehyde (*R*)-2a.[63,64] A solution of the 9:1 mixture of primary alcohols (*R*)-**2b** (50 mg, 0.29 mmol) and N-methylmorpholine *N*-oxide (51 mg, 0.44 mmol) in 5 mL of anhydrous CH_2Cl_2 was treated with activated 4 A° molecular sieves (0.75 g). After stirring at 25 °C for 1 h, TPAP (3.2 mg, 0.092 mmol) was added and the

reaction mixture was stirred at 25 °C for 30 min. Chromatography (SiO_2, 40% Et_2O-hexanes) provided (*R*)-**2a** (44.4 mg, 0.26 mmol) in 90% yield after careful evaporization. The aldehyde (*R*)-**2a** was produced as a 9:1 mixture of diastereomers that could be separated. The minor aldehyde is the *cis* isomer and has an R_f value of 0.48 and the major isomer is the *trans* isomer and has an R_f of 0.42. The *cis* and *trans* isomers were determined by a nOe experiment on acetal (*R*)-**146**. In that experiment only the acetal proton of the minor isomer showed a nOe to the methine proton at C_5.

Characterization data for the major isomer of (*R*)-2a (proton NMR) matched that reported by Crimmins et. al.[63] and also that reported by Boger et. al[24].

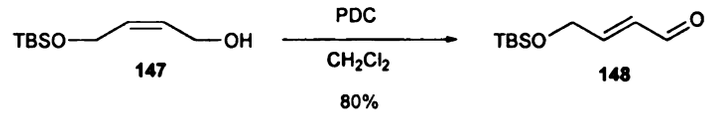


(*Z*)-4-(tert-butyldimethylsilyloxy)-2-buten-1-ol 147.[65] *Cis*-2-butene-1,4-diol (4.401 g, 4.11 mL, 50 mmol) was dissolved in 100 mL THF at 0 °C under argon. A solution of 2.5 M *n*-BuLi in hexane (20 mL, 50 mmol) was added via syringe. Insoluble yellow/white clumps of solid were formed upon addition of the *n*-BuLi, which were broken up to give a suspended white solid upon vigorous stirring. The reaction was stirred for 1 h at 0 °C, then tert-butyl dimethylsilyl chloride (7.54 g, 50 mmol) was added neat in one portion, and the cold bath was removed. The white suspension disappeared as the reaction progressed, leaving a transparent yellow solution. Stirring was continued for 3h, then the reaction was quenched by adding 50 mL saturated aqueous NH_4Cl solution.

The mixture was diluted with 100 mL ether, poured into a separatory funnel, and washed with 75 mL water and 50 mL brine and the dried over anhydrous $MgSO_4$, and

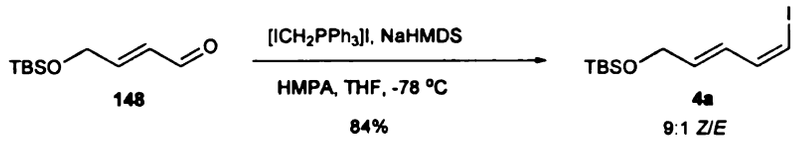
concentrated to a yellow oil. This oil was distilled under high vacuum (bp 82-88 °C/0.2 torr) to give **147** (9.54 g, 0.47 mmol) as a colorless oil in 94.3%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 2.32 (broad s, 1H), 4.17 (d, 2H, J = 5.1 Hz), 4.23 (d, 2H, J = 5.5 Hz), 5.56 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.30, 18.27, 25.84, 58.69, 59.51, 130.02, 131.15; IR (neat film on NaCl): 3350 (w), 2950-2850 (m), 1472 (m), 1254 (s), 1088 (s), 837 (m), 776 (m) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 145 M^+-57 (27), 127 (8), 99 (3), 75 (100).



[a]**(*E*)-4-(tert-butyldimethylsilyloxy)-2-butenal 148**. Alcohol **147** (2.02 g, 10 mmol) was dissolved in 150 mL dry CH_2Cl_2. Pyridinium dichromate (5.64, 15 mmol) was added, the reaction was placed under argon atmosphere and stirred for 20 h. The reaction was diluted with 150 mL ether and filtered through a 1 inch thick layer of silica gel to remove brown solids. The orange organic solution was washed with saturated aqueous $CuSO_4$ solution (2 x 50 mL), water (2 x 100 mL), and brine (1 x 100 mL) and then dried over $MgSO_4$, filtered through another 1 inch layer of silica gel, and concentrated to a pale yellow oil. The oil was chromatographed on silica gel (10:1 pentane/ether – UV/$KMnO_4$ visualization) to give **148** as a colorless oil in 80% yield (1.61 g, 0.81 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.094 (s, 6H), 0.93 (s, 9H), 4.46 (m, 2H), 6.40 (ddt, 1H, *J* = 15.4, 8.0, 2.1 Hz), 6.90 (dt, 1H, *J* = 15.5, 3.0 Hz), 9.61 (d, 1H, *J* = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.49, 18.28, 25.76, 62.21, 130.53, 156.46, 198.93; IR (neat film on NaCl): 2956-2857 (m), 1694 (s), 1255 (s), 1114 (s), 967 (m), 887 (m), 779 (m) cm^{-1}; R_f = 0.22 (10:1 pentane/ether).

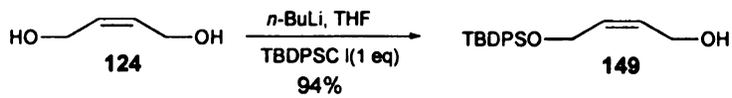


[a]**(*Z*,*E*)-Iododiene 4a.**[66] *Note: This compound is light-sensitive, and is best handled in a darkened room and used immediately.* A 250 mL round-bottom flask was charged with $ICH_2(PPh_3)I$ (8.80 g, 16.6 mmol) and suspended in 60 mL THF. The flask was wrapped with aluminium foil and cooled to –78 °C. A 1.0 M solution of sodium bis(trimethylsilyl)amide in THF (16.6 mL, 16.6 mmol) was added, and the solution was stirred for 15 min, then allowed to warm to room temperature. Freshly distilled HMPA (4 mL) was added and the reaction was briefly stirred, then cooled back down to –78 °C. A precooled (-78 °C) solution of aldehyde **148** (3.32 g, 16.6 mmol) in 10 mL THF was added via cannula, and the reaction was stirred for 15 min, then allowed to warm to room temperature while stirring for 1 hr.

The reaction was quenched by diluting with 50 mL ether, then adding saturated aqueous NH_4Cl solution. The mixture was poured into a separatory funnel, and the layers were separated. The aqueous layer was extracted with ether (2 x 80 mL), and the combined organic layers were washed with water (2 x 100 mL) and brine (1 x 80 mL)

and then dried over anhydrous $MgSO_4$ and concentrated to a dark brown oil. The oil was taken up in a mixture of 50 mL pentane and 1 mL ether, leading to formation of a brown solid precipitate. This precipitate ($Ph_3P=O$) was separated by filtration through a thin layer of silica gel and the resulting brown solution was chromatographed on silica gel (50:1 pentane/ether – UV visualization) and concentrated to give **4a** as a light orange liquid in 84% yield (4.12 g, 13.95 mmol). This material consisted of a 9:1 ratio of *cis/trans* isomers of **4a** as determined by integration of the vinylic proton doublet of triplets at 5.81 (minor) and doublet of triplets at 6.06 ppm in crude proton NMR spectrum.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 6H), 0.96 (s, 9H), 4.26 (d, 2H, J = 4.2 Hz), 6.06 (dt, 1H, J = 15.1, 4.6 Hz), 6.24 (d, 1H, J = 7.6 Hz), 6.42-6.56 (m, 1H), 6.75 (dd, 1H, J = 7.3, 10.2 Hz); R_f = 0.6 (50:1 pentane/ether).

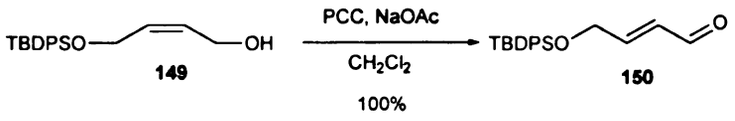


[a]**(*Z*)-4-(tert-butyldiphenylsilyloxy)-2-buten-1-ol 149.**[65] *Cis*-2-butene-1,4-diol (2.2 g, 4.11 mL, 25 mmol) was dissolved in 50 mL THF at 0 °C under argon. A solution of 2.5 M *n*-BuLi in hexane (10 mL, 25 mmol) was added via syringe. Insoluble yellow/white clumps of solid were formed upon addition of the *n*-BuLi, which were broken up to give a suspended white solid upon vigorous stirring. The reaction was stirred for 1 h at 0 °C, then tert-butyl diphenylsilyl chloride (6.5 mL, 25 mmol) was added neat in one portion, and the cold bath was removed. The white suspension

disappeared as the reaction progressed, leaving a transparent yellow solution. Stirring was continued for 15h, then the reaction was quenched by adding 25 mL saturated aqueous NH_4Cl solution.

The mixture was diluted with 50 mL ether, poured into a separatory funnel, and washed with 25 mL water and 25 mL brine and then dried over anhydrous $MgSO_4$, and concentrated to give **149** as a a colorless oil in 94% yield (7.66 g, 23.5 mmol). This oil was purified on a silica gel column (10:1 hexane:EtOAc) but compound **149** could also be purified by vacuum distillation (bp 244-254 °C/0.2 torr).

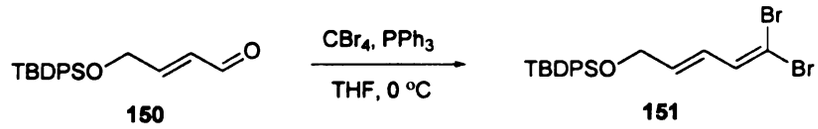
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 4.02 (d, 2H, J = 6.0 Hz), 4.29 (d, 2H, J = 5.8 Hz), 5.59-5.80 (m, 2H), 7.36-7.52 (m, 6H), 7.68-7.80 (m, 4H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.06, 26.72, 58.65, 60.18, 127.69, 129.74, 129.89, 130.85, 133.35, 135.57; IR (neat film on NaCl): 3352 (w), 3072 (s), 3049 (s), 3026 (s), 2999 (s), 2959 (s), 2932 (s), 2891 (s), 2858 (s), 1472 (s), 1427 (s), 1113 (s), 824 (s), cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) 327 (M^+ +1) (5), 309 (15), 269 (30), 199 (75), 152 (30), 122 (100), 93 (100), 75 (40), 57 (25); Anal calcd for $C_{20}H_{26}O_2Si$: C 73.57; H 8.03. Found: C 73.79; H 7.95.



[a]**(*E*)-4-(tert-butyldiphenylsilyloxy)-2-butenal 150.**[89] To a suspension of pyridinium chlorochromate (2.67 g, 12.4 mmol) and sodium acetate (2.7 g, 13.3 mmol) was added alcohol **149** (2.7 g, 8.3 mmol) dissolved in 20 mL dry CH_2Cl_2. The reaction was placed under argon atmosphere and stirred for 2 h. The reaction was diluted with 70 mL ether and filtered through a 1 inch thick layer of silica gel to remove the brown solids. The brown solids were washed twice with 70 mL of ether and the combined organic layers dried over $MgSO_4$. Aldehyde **150** was concentrated and dried, its crude NMR was satisfactory and the crude product was used for the next step. All of the following data was taken on unpurified material. Aldehyde **150** (2.69 g, 8.3 mmol) was obtained in 100% as a white solid. Characterization data (proton and carbon-13 NMR and IR) matched those reported by Evans et. al.[89]

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H), 4.42-4.46 (m, 2H), 6.56 (dd, 1H, J = 15.4, 8.0 Hz), 6.83 (dt, 1H, J = 15.7, 1.0 Hz), 7.35-7.48 (m, 6H), 7.64 (dd, 4H, J = 6.0, 1.7 Hz), 9.59 (d, 1H, J = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.17, 26.65, 62.90, 127.82, 129.93, 130.52, 132.66, 135.37, 155.93, 193.40; IR (neat film on NaCl): 3072 (s), 3052 (s), 2957 (s), 2919 (m), 2851 (m), 1694 (s), 1473 (s), 1429 (s), 1381 (s), 1113 (s), 968 (s), 824 (s) cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) 325 (M^+ +1) (21), 309 (30), 267 (20), 239 (35), 199 (98), 197.05 (95), 137 (95), 135 (100), 105 (60), 91 (60), 57

(55); Anal calcd for $C_{20}H_{24}O_2Si$: C 73.96; H 7.40. Found: C 73.87; H 7.75. R_f = 0.20 (10:1 pentane/ether).

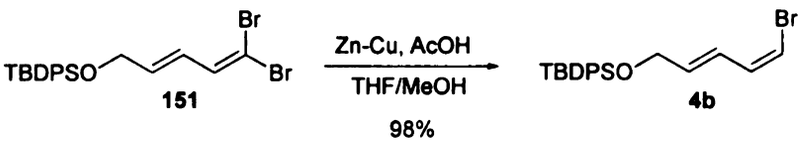


150 151

Dibromodiene 151. [38] To a solution of carbon tertrabromide at 0 °C (1.02 g, 3.08 mmol) in 15 mL of dry CH_2Cl_2 was added triphenyl phosphine (1.62 g, 6.16 mmol). After 5 mins, a solution of aldehyde **150** (500 mg, 1.54 mmol) in 7.5 mL of dry CH_2Cl_2 was added. The reaction mixture was stirred for 1.5 h, then diluted with 50 mL of hexanes. The diluted reaction mixture was then filtered through Celite and evaporated to give a beige solid. Flash chromatography on silica gel (20:1 pentane/ether) gave vinyl dibromide **151** in 91% (0.672 g, 1.40 mmol) as an off-white oil. R_f = 0.13 (20:1 pentane/ether).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 9H), 4.27 (dd, 2H, *J* = 4.3, 1.7 Hz), 5.97 (dt, 1H, *J* = 15.1, 4.1 Hz), 6.53 (tdd, 1H, *J* = 10.4, 4.7, 1.9 Hz), 6.99 (d, 1H, *J* = 10.1 Hz) 7.34-7.50 (m, 6H), 7.69-7.76 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.20, 26.77, 63.58, 90.62, 126.04, 127.73, 129.76, 133.24, 135.45, 136.29, 136.63; IR (neat film on NaCl): 3071 (s), 2932 (s), 2857 (s), 1472 (s), 1428 (s), 1113 (s), 968 (s), 826 (s) cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) 481 $(M-1)^+$ (2, ^{81}Br), 479 $(M-1)^+$ (4, ^{81}Br, ^{79}Br), 477 $(M-1)^+$ (2, ^{79}Br), 425 (6, ^{81}Br), 423 (12, ^{81}Br, ^{79}Br), 421 (6, ^{79}Br), 343 (2, ^{81}Br), 341 (2, ^{79}Br) 327 (7, ^{81}Br), 325 (5, ^{79}Br), 281 (9, ^{81}Br), 279 (9, ^{79}Br), 263 (30,

^{81}Br) 261 (30, ^{79}Br), 227 (10), 225 (20), 223 (10), 207 (20), 199 (48), 197 (50), 135 (100), 105 (30), 91 (30), 73 (60), 57 (37), 55 (40); Anal calcd for $C_{21}H_{24}OSiBr_2$: C 52.51; H 5.04. Found: C 52.16; H 5.13.

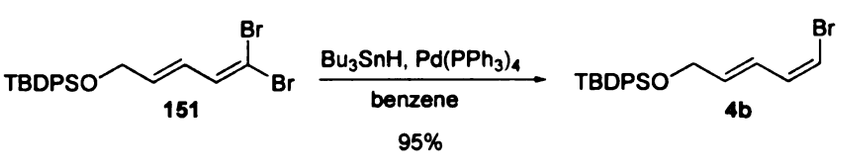


[a]**Activated Metal Reduction to Give diene 4b.**[68] A 250 mL flask was charged with zinc dust (25 g, 0.391 mol, 99.9%, 150-325 mesh, Alfa/Aesar) which was then suspended in 125 mL HPLC grade water and sparged with argon for 15 min. Anhydrous copper (II) acetate (2.5 g, 13.8 mmol) was added, the flask was capped with a rubber septum, and the slurry was stirred for 15 minutes. The black suspension of activated metal was isolated by filtration on a Buchner funnel followed by sequential washings with HPLC grade water and methanol.

Acetic acid (25 mL) followed by the black solid was immediately added to a solution of dibromide **151** (240 mg, 0.5 mmol) in 187.5 mL of a 2:1 mixture of THF/MeOH. The flask was placed under an argon atmosphere and stirred overnight at 0°C. The reaction mixture was filtered through Celite and the black metal filter cake was rinsed with 125 mL ether into a stirring solution of saturated sodium bicarbonate (50 mL). The resulting mixture was poured into a separatory funnel and the aqueous layer was extracted with ether (2 x 60 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous $MgSO_4$, and concentrated to a colorless oil. The oil was purified by chromatography on silica gel (100% hexane, UV/$KMnO_4$

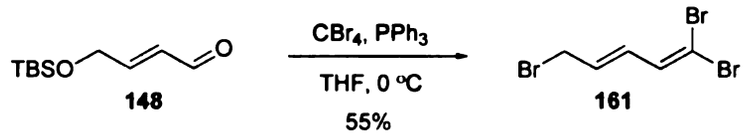
visualization) to give the product **4b** as an off-white oil in 98% yield (196 mg, 0.49 mmol). This oil was a single isomer by proton NMR. R_f = 0.10 (hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H), 4.24 (d, 2H, *J* = 13.8, 3.9 Hz), 5.93 (dt, 1H, *J* = 14.6, 5.8 Hz), 6.22 (d, 1H, *J* = 6.9 Hz), 6.58-6.78 (m, 2H) 7.32-7.44 (m, 6H), 7.62-7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.22, 26.77, 63.82, 107.62, 125.12, 127.59, 129.69, 132.01, 135.41, 135.52, 136.47; IR (neat film on NaCl): 3073 (s), 2959 (s), 2932 (s), 2857 (s), 1458 (s), 1428 (s), 1113 (s), 702 (s) cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) 402 M^+ (0.25, ^{81}Br), 400 M^+ (0.25, ^{79}Br), 372 (1.2, ^{81}Br), 370 (1.2, ^{79}Br), 345 (100, ^{81}Br), 343 (100, ^{79}Br), 315 (14, ^{81}Br), 313 (14, ^{79}Br), 265 (80), 263 (95), 261 (90), 199 (84), 187 (28), 181 (32), 143 (64), 135 (16), 77 (12), 65(12).



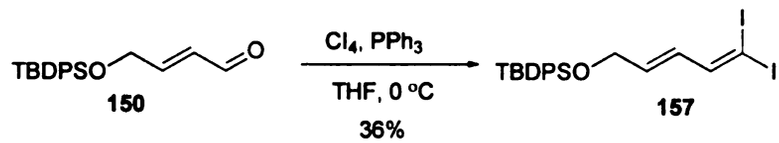
Bu_3SnH Reduction to Give diene 4b.[39] To a stirred solution of dibromide **151** (50 mg, 0.104 mmol) and $Pd(PPh_3)_4$ (4.6 mg, 0.004 mmol) in anhydrous benzene (0.7 mL) was added Bu_3SnH (0.032 mL, 0.12 mmol) in anhydrous benzene (0.3 mL) under an argon atmosphere and the mixture was stirred for 1h at room temperature. The mixture was diluted with hexane (0.7 mL) and washed with water (0.4 mL) and brine (0.4 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified on a silica gel column with hexanes as the eluent. A 95% (40 mg, 0.099 mmol)

yield of vinyl bromide **4b** was obtained an off-white oil. The ^{1}HNMR spectrum of **4b** matched that for **4b** obtained in the Zn/Cu reduction of **151** (see above) and it revealed that **4b** formed from this reaction was also formed as a single isomer.



[d]Tribromodiene 161.[38] To a solution of carbon tertrabromide at 0 °C (8.62 g, 26 mmol) in 120 mL of dry CH_2Cl_2 was added triphenyl phosphine (13.84 g, 52 mmol). After 15 mins, a solution of aldehyde **148** (2.6 g, 13 mmol) in 70 mL of dry CH_2Cl_2 was added. The reaction mixture was stirred for 1 h, then diluted with 150 mL of hexanes. The diluted reaction mixture was then filtered through Celite and evaporated to give a beige solid. Flash chromatography on silica gel (98:2 hexanes/EtOAc) gave 2.21 g (7.34 mmol) of an oil tentatively assigned as the vinyl tribromide **161** in 55% yield.

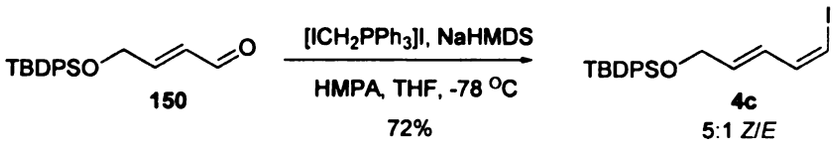
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.02 (dd, 2H, J = 7.8, 0.9 Hz), 6.03-6.15 (m, 1H), 6.36 (dd, 1H, J = 14.4, 10.8 Hz), 6.97 (d, 1H, J = 10.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.80, 93.63, 130.80, 132.14, 135.43.



Diiododiene 157. [38,67]*Note: This compound is light-sensitive, and is best handled in a darkened room and used immediately.* To a solution of carbon tertraiodide at 0 °C

(322 mg, 0.62 mmol) in 3 mL of dry CH_2Cl_2 was added triphenyl phosphine (325 mg, 1.24 mmol). After 5 mins, a solution of aldehyde **150** (100 mg, 0.31 mmol) in 1.5 ml of dry CH_2Cl_2 was added. The reaction mixture was stirred for 1.5 h, then diluted with 20 mL of hexanes. The diluted reaction mixture was then filtered through Celite and evaporated to give a beige solid. Flash chromatography on silica gel (20:1 pentane/ether) gave 36% (65.8 mg, 0.11 mmol) of colorless oil vinyl diiodide **157**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (s, 9H), 4.20 (dd, 2H, J = 4.1, 1.9 Hz), 5.99 (dt, 1H, J = 15.1, 4.1 Hz), 6.27 (ddt, 1H, J = 9.9, 5.2, 1.9 Hz), 7.30-7.46 (m, 6H), 7.49 (d, 1H, J = 9.9 Hz), 7.62-7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.21, 26.80, 63.44, 94.21, 127.74, 129.76, 131.57, 133.24, 135.48, 136.54, 149.52; IR (neat film on NaCl): 2963 (s), 2924 (s), 2851 (s), 2363 (s), 2336 (s), 1653 (s), 1262 (s), 1098 (s), 1020 (s) cm^{-1}.

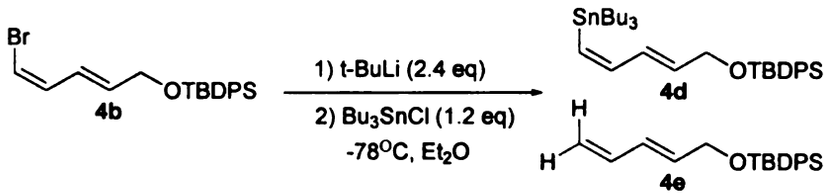


(*Z*,*E*)-Iododiene 4c.[66] *Note: This compound is light-sensitive, and is best handled in a darkened room and used immediately.* A 100 mL round-bottom flask was charged with $ICH_2(PPh_3)I$ (163.5 mg, 0.308 mmol) and suspended in 5 mL THF. The flask was wrapped with aluminium foil and cooled to –78 °C. A 1.0 M solution of sodium bis(trimethylsilyl)amide in THF (0.308 mL, 0.308 mmol) was added, and the solution

was stirred for 15 min, then allowed to warm to room temperature. Freshly distilled HMPA (0.31 mL) was added and the reaction was briefly stirred, then cooled back down to –78 °C. A precooled (-78 °C) solution of aldehyde **150** (100 mg, 0.308 mmol) in 1 mL THF was added via cannula, and the reaction was stirred for 15 min, then allowed to warm to room temperature while stirring for 1 hr.

The reaction was quenched by diluting with 10 mL ether and then adding saturated aqueous NH_4Cl solution. The mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was extracted with ether (2 x 8 mL), and the combined organic layers were washed with water (2 x 10 mL) and brine (1 x 8 mL), dried over anhydrous $MgSO_4$ and then concentrated to a dark brown oil. The oil was taken up in 50 mL : 1 mL pentane/ether leading to formation of a brown solid precipitate. This precipitate ($Ph_3P=O$) was removed by filtration through a thin layer of silica gel and the brown filtrate was stripped of solvent. The crude product was purified by chromatography on silica gel (50:1 pentane/ether – UV visualization) to give **4c** a light yellow oil in 72% yield (0.100 g, 0.223 mmol). This material had a 5:1 ratio of *cis/trans* isomers as determined by integration of the vinylic protons at 5.78 (minor) and 6.02 ppm (major) in crude proton NMR spectrum.

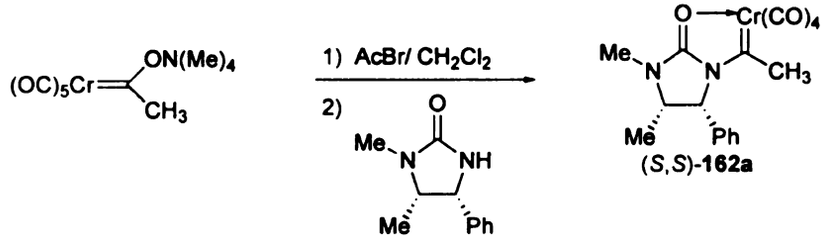
^1H NMR (300 MHz, $CDCl_3$): δ 1.07 (s, 9H), 4.24 (dd, 2H, J = 4.6, 1.7 Hz), 6.02 (dt, 1H, J = 14.9, 4.7 Hz), 6.22 (d, 1H, J = 7.3 Hz), 6.52-6.65 (m, 1H), 6.72 (dd, 1H, J = 10.0, 7.3 Hz), 7.36-7.48 (m, 6H), 7.64-7.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.19, 26.78, 63.70, 81.75, 100.25, 127.66, 129.66, 133.35, 135.49, 137.13, 137.75.



Preparation of Vinyl Stannane 4d:[28] To a solution of vinyl bromide **4b** (72 mg, 0.186 mmol) in 3 mL of ether at –78 °C was added *t*-BuLi (1.7 M in pentane, 263 μL, 0.446 mmol). This solution was stirred for 2h after which time Bu_3SnCl (60 μL, 0.223 mmol) was added and stirred for an additional 2h. The reaction was quenched with water (4 mL) and diluted with EtOAc (8 mL). The organic layer was washed with brine (10 mL), dried over Na_2SO_4 and concentrated. Column chromatography in pure pentane revealed the presence of two compounds which were separated and identified as **4d** and **4e** (both colorless oils) which were obtained in 62% (70.6 mg, 0.12 mmol) and 31% (18.6 mg, 0.058 mmol) of yields respectively.

Vinyl Stannane 4d [28]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, 9H, J = 7.5 Hz), 0.95 (dd, 6H, J = 7.8, 8.4 Hz), 1.08 (s, 9H), 1.29 (6H, dq, 6H, J = 14.4, 7.2 Hz), 1.45-1.55 (m, 6H), 4.27 (dd, 2H, J = 1.7, 4.5 Hz), 5.80 (dd, 1H, J = 15.0, 4.5 Hz), 6.06 (d + dd, 1H, $J^1_{H\text{-}H}$ = 12.9 Hz, $J^2_{Sn\text{-}H}$ = 63.9 H), 6.29-6.38 (m, 1H), 7.09 (dd, 1H, J = 10.8, 12.6 Hz), 7.35-7.46 (m, 6H), 7.69 (dd, 4H, J = 2.0, 8.7 Hz); R_f = 0.22 (pentane). This ^{1}H NMR matches that reported previously for this compound.

Side Product 4e: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H), 4.22 (d, 2H, *J* = 4.7 Hz), 5.04 (d, 1H, *J* = 10.2 Hz), 5.15 (d, 1H, *J* = 15.9 Hz), 5.76 (dt, 1H, *J* = 14.3, 4.7 Hz), 6.22-6.40 (m, 2H), 7.28-7.40 (m, 6H), 7.65 (dd, 4H, *J* = 1.9, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.25, 26.81, 63.97, 116.58, 127.65, 129.63, 130.31, 132.80, 133.64, 135.54, 136.61; R_f = 0.17 (pentane); IR (neat film on NaCl): 3073 (s), 2957 (s), 2930 (s), 2857 (s), 1472 (s), 1428 (s), 1113 (s), 1053 (s), 1005 (s), 823 (s), 741 (s) cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) 321 $(M-1)^+$ (20), 307 (15), 265 (68), 199 (76), 197 (48), 187 (36), 137 (62), 136 (50), 135 (100), 121 (20), 105 (20), 91 (20), 75 (20), 67 (52), 57 (8); Anal calcd for $C_{21}H_{26}OSi$: C 78.21; H 8.13. Found C 78.54; 8.59.



[b]Methyl [(4*S*, 5*S*) -1,5-dimethyl-4-phenyl-2-imidazolidinone] methylene tetracarbonyl chromium (0) 162a and its Enantiomer 162b.[69]

Tetramethylammonium(1-hydroxyethylidene)pentacarbonylchromium (0)[69] (3.0 g, 9.7 mmol) was dissolved in 45 mL CH_2Cl_2 under an atmosphere of argon and cooled to -78 °C. Freshly distilled acetyl bromide (0.72 mL, 9.7 mmol) was then added dropwise and the remaining solution was stirred for an additional 60 minutes after which (4*S*, 5*S*)-1,5-dimethyl-4-phenyl-2-imidazolidinone[69] (1.84 g, 9.7 mmol) was added neat to the

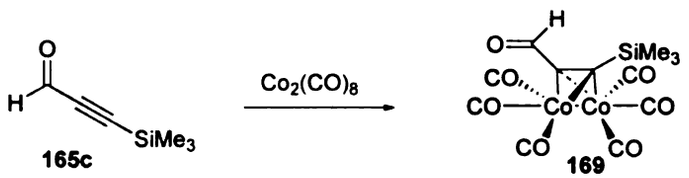
solution. The mixture was gradually warmed to -55 °C over a 15 minute period and was stirred at this temperature for 18 hr. The mixture was quickly warmed to room temperature, washed with $NaHCO_3$ (3 x 75 mL), dried with $MgSO_4$ and concentrated on a rotary evaporator to remove two-thirds of the solvent. The resulting reddish-brown solution was loaded onto a silica gel column and the product was eluted with CH_2Cl_2 (R_f = 0.63) to give complex **162a** (2.40 g, 6.31 mmol) as a deep-red solid in 65% yield.

Spectral data for **162a**: mp 117 °C (dec.); ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, 3H, *J* = 6.7 Hz), 2.78 (s, 3H), 2.94 (s, 3H), 4.40-4.48 (m, 1H), 5.35 (d, 1H, *J* = 8.5 Hz), 7.08 (br s, 2H), 7.41 (t, 3H, *J* = 5.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.84, 28.43, 34.35, 59.98, 61.79, 126.36, 128.35, 129.24, 133.85, 162.32, 215.21, 215.49, 231.62 (2C), 320.87; IR (neat) 2007 (s), 1982 (shoulder, s), 1900 (vs), 1827 (s), 1711 (s), 1355 (m), 1148 (m) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 380 M^+ (10), 244 (25), 230 (15), 220 (100), 203 (40), 132 (40), 118 (30), 108 (95), 80 (100); Anal calcd for $C_{17}H_{16}O_5N_2Cr$: C, 53.68; H, 4.24; N, 7.37. Found: C, 53.31; H, 4.24; N, 7.20.

Carbene complex **162b**, the enantiomer of complex **162a**, was synthesized according to the above procedure by using the (4*S*, 5*R*)-1,5-dimethyl-4-phenyl-2-imidazolidinone as the chiral auxiliary.

[a]**Preparation of 2-alkynals. Illustrated with the Preparation of Trimethylsilylpropynal 165c.**[91] A solution of (trimethylsilyl)acetylene (15.72 g, 22.6 mL, 0.16 mol) in 120 mL ether was cooled to –78 °C. A solution of methyl lithium (1.6 M in ether, 100 mL, 0.16 mol) was added via cannula. *Note: for the preparation of volatile aldehydes, solutions of n-BuLi in hexane should not be used.* The reaction was stirred for 20 min, then anhydrous dimethylformamide (14.04 g, 14.9 mL, 0.192 mol) was added neat via syringe. The cold bath was removed and the reaction was stirred for 3h while warming to room temperature. The reaction was quenched and hydrolyzed by pouring the ether solution into a solution of excess dilute aqueous hydrochloric acid at 0 °C (2.5 eq., 0.4 mol, 33 mL 12 M concentrated HCl). The mixture was neutalized to pH 6 by adding saturated aqueous $NaHCO_3$ solution, and poured into a 1 L separatory funnel. The aqueous layer was back-extracted with ether (4 x 100 mL). The combined organic layers were dried with $MgSO_4$, filtered through a 2" plug of silica gel to remove red material, and concentrated on the rotary evaporator without vacuum and the water bath at 40 °C. The remaining ether was removed via short-path distillation at atmospheric pressure by heating in an oil bath at 65 °C. The product **165c** an acrid-smelling liquid was purified by vacuum transfer (0.2 mm Hg) into a flask cooled to –78 °C in 66.5% yield (13.4 g, 0.11 mol). The following ^{1}HNMR data matches that reported for this compound.[91]

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.260 (s, 9H), 9.16 (s, 1H).



[c]**Cobalt protected Alkyne 169**. To a solution of $Co_2(CO)_8$ (8.75g, 25 mmol) in 100 mL of ether was added aldehyde **165c** (3.0 g, 23.8 mmol) in 20 mL of ether at room temperature. There was an immediate effervescence and the solution turned dark red. The solution was concentrated and first chromatographed with hexanes to remove any inorganic compounds then with CH_2Cl_2 to obtain the desired product **169** in 94% yield (9.7 g, 23.6 mmol) a deep red solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.32 (s, 9H), 10.28 (s, 1H).

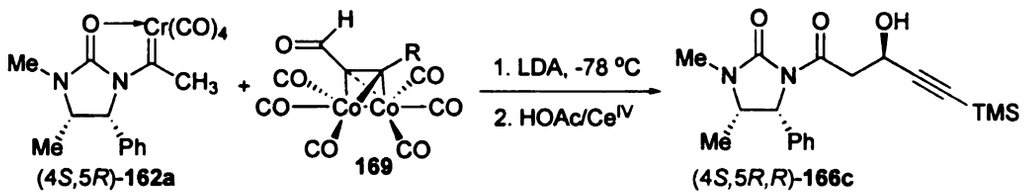
a- Data obtained from Mark Parisi's Thesis;[56]

b- Data obtained from Yan Shi's Thesis;[71]

c- Data obtained from the unpublished results of Kenneth Wilson and W. D. Wulff.[58]

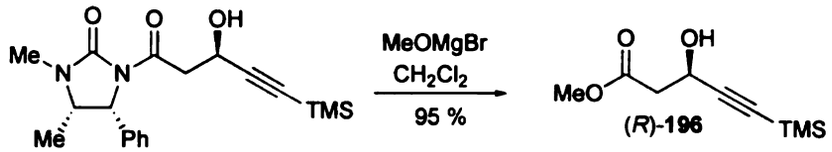
d- Data obtained from the unpublished results of XueLui Jun and W. D. Wulff.[76]

Experimental data for Chapter 3.



[b](4*S*,5*R*)-1-((*R*)-3-hydroxy-5-(trimethylsilyl)pent-4-ynoyl)-3,4-dimethyl-5-phenylimidazolidin-2-one. A solution of LDA was prepared by adding 3.67 mL of *n*-BuLi (1.6 M in hexanes, 4.5 mmol) to a solution of freshly distilled diisopropylamine (0.66 mL, 4.74 mmol) in 20 mL of THF at room temperature and stirring for 15 minutes. A solution of 1.64 g (5.0 mmol) of carbene complex (4*S*,5*S*)-**162a** in 20 mL THF was added dropwise to the solution of LDA at –78 °C. The resultant yellow-orange solution was stirred for 5 minutes at –78 °C. A precooled solution (–78 °C) of dicobalt hexacarbonyl complexed (trimethylsilyl) propynal **169** (2.13 g, 5.16 mmol) in 15 mL THF was added dropwise via syringe. The dark red reaction mixture was allowed to stir for 3 h, then quenched by adding acetic acid (0.271 mL, 4.74 mmol) and stirring for 5 minutes. A freshly prepared solution of ceric ammonium nitrate (37.72g, 68.8 mmol) in 20 mL of H_2O : MeOH (2 : 1) was added in 4 equal portions, and the cold bath was removed. Stirring was continued for 15 minutes, and the reaction mixture was extracted with ether (3 x 30 mL). The combined organic layers were washed with $NaHCO_3$ solution (30 mL), H_2O (50 mL), and brine (50 mL), dried with $MgSO_4$ and concentrated on the rotary evaporator. Purification of the crude product by flash chromatography on silica gel (1:1 hexanes/EtOAc) affored aldol adduct (4*S*,5*S*,*R*)-**166c** (1.43 g, 4.0 mmol) as a viscous pale yellow oil in a 99.5:0.5 diastereomeric ratio in 80% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 9H), 0.75 (d, 3H, J = 6.6 Hz), 2.78 (s, 3H), 3.28 (dd, 1H, J = 17.4, 3.3 Hz), 3.48 (s, 1H), 3.51 (dd, 1H, J = 17.4, 9.0 Hz), 3.81-3.92 (m, 1H), 4.68-4.74 (m, 1H), 5.25 (d, 1H, J = 8.7 Hz), 7.07-7.10 (m, 2H), 7.25-7.28 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.03, 15.09, 28.29, 43.29, 54.22, 59.43, 59.49, 89.42, 104.82, 126.91, 128.40, 128.74, 136.12, 155.70, 171.02; IR (neat film on NaCl): 3414 (m), 2957 (m), 2169 (w), 1727 (s), 1634 (m), 1413 (m), 1381 (m), 1243 (m), 1056 (m) cm $^{-1}$; CI mass spectrum m/z (% rel intensity) 358 M^+ (62), 343 (35), 285 (63), 189 (100), 175 (48), 132 (46); R_f = 0.36 (1:1 hexane/EtOAc); $[\alpha]_D$ -22.81°, (c 0.79, $CHCl_3$).

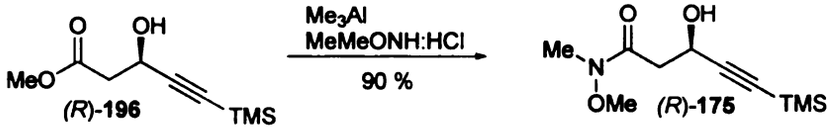


(*S,S,R*)-**166c** (*R*)-**196**

[a]**Methyl Ester (*R*)-196**. Anhydrous methanol (1.50 g, 1.90 mL, 4.7 mmol) was added to 60 mL CH_2Cl_2 at 0 °C. A 3.0 M solution of MeMgBr in ether (1.72 mL, 5.2 mmol) was added dropwise via syringe, resulting in the formation of a white precipitate and vigorous evolution of methane. A solution of aldol adduct (4*S*,5*S*,*R*)-**166c** (1.68 g, 4.7 mmol) in 40 mL CH_2Cl_2 at 0 °C was added via cannula, and the reaction was stirred for 1 hr, at which time the white precipitate had disappeared, and TLC of the reaction showed no remaining starting material.

The reaction was quenched by adding 30 mL saturated aqueous $NaHCO_3$ and stirring. The mixture was poured into a separatory funnel, and the aqueous layer was extracted with 30 mL CH_2Cl_2. The combined organic layers were washed with 40 mL water and 40 mL brine, dried with $MgSO_4$, and concentrated to a sticky yellow solid. The solid was washed with 5:1 hexane/EtOAc. The insoluble white solid was carefully filtered off, and the yellow liquid was chormatographed on silica gel (5:1 hexane/EtOAc, $KMnO_4$ visualization) to give the product (*R*)-196 as a yellow oil in 62.3% yield (584 mg, 2.93 mmol). The insoluble white solid is the imidizolidinone chiral auxiliary, which was recovered in 66% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.17 (s, 9H), 2.75 (d, 2H, *J* = 6.1 Hz), 2.99 (m, 1H), 3.73 (s, 3H), 4.77 (q, 1H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.27, 41.81, 51.93, 59.11, 85.26, 104.26, 171.61; IR (neat film on NaCl): 3500-3400 (m), 2959 (w), 2176 (w), 1742 (w), 1251 (m), 1060 (m), 844 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 199 M^+ - 1 (11), 185 (100), 153 (36), 143 (83), 127 (47), 111 (76), 99 (55), 89 (73), 75 (68); R_f = 0.26 (5:1 hexane/EtOAc);

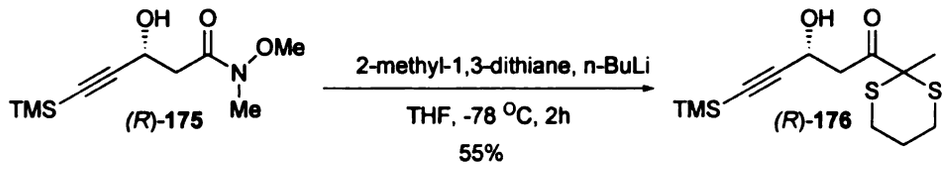


[a]**Weinreb amide (*R*)-175**. The aluminium amide reagent was prepared by adding trimethylaluminum (2.0 M in hexane, 5.25 mL, 10.5 mmol) dropwise via syringe to a

stirring suspension of N, O-dimethyl hydroxylamine in 30 mL CH_2Cl_2 at 0 °C. The colorless solution was stirred for 45 minutes, then added via cannula to a solution of ester (*R*)-**196** (957 mg, 4.78 mmol) in 20 mL CH_2Cl_2. The cold bath was removed and the reaction allowed to stir overnight (16 h) at room temperature, during which time the reaction color turned slightly yellow.

The reaction was quenched with excess aq. NH_4Cl solution, added slowly to avoid excessively rapid gas evolution, and poured into a separatory funnel. The organic layer was washed with water (2 x 30 mL) and brine (1 x 30 mL), dried over $MgSO_4$, and concentrated to a pale yellow oil. The oil was chromatographed on silica gel (2:1 hexane/EtOAc), giving one fraction at R_f = 0.29 which was collected and concentrated to (*R*)-175 as a colorless oil in 90% yield (986 mg, 4.3 mmol).

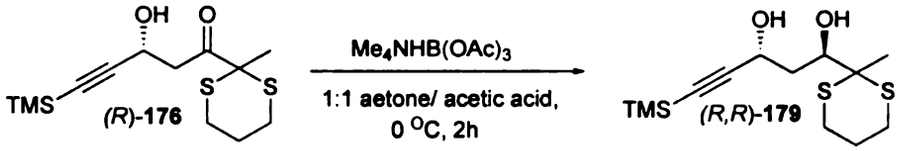
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 9H), 2.83-2.90 (m, 2H), 3.21 (s, 3H), 3.72 (s, 3H), 4.81 (d, 1H, *J* = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.32, 31.73, 38.65, 59.22, 61.35, 89.35, 104.91, 172.34; IR (neat film on NaCl): 3600-3200 (m), 2962 (m), 2174 (w), 1645 (s), 1436 (w), 1389 (m), 1250 (s), 1055 (m), 843 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 230 M^+ + 1 (12), 214 (30), 151 (62), 127 (100), 111 (17), 99 (95), 75 (80), 61 (70); R_f = 0.29 (2:1 hexane/EtOAc – $KMnO_4$); $[\alpha]_D$ 24.0° (*c* 1, $CHCl_3$); colorless oil. Yield: 986 mg (90%).



[a]**Dithiane (*R*)-176**. 2-Methyl-1,3-dithiane (2.66 g, 2.37 mL, 19.8 mmol, 2.1 equiv.) was dissolved in 50 mL THF at –78 °C. A solution of *n*-BuLi (2.5 M in hexane, 7.92 mL, 19.8 mmol, 2.1 equiv.) was added via syringe. The reaction flask was put into a 0 °C cold bath and stirred for 30 minutes. The solution was then added via cannula to a solution of Weinreb amide (*R*)-**175** (2.16 g, 9.4 mmol) in 50 mL THF at 0 °C. The reaction was monitored by TLC and done when checked after 1 h. The reaction was quenched by adding acetic acid (1.13 mL, 19.8 mmol, 2.1 equiv.) neat via syringe and briefly stirred. The mixture was poured into a separatory funnel containing 80 mL ether and 80 mL water. The aqueous layer was back-extracted with ether (2 x 30 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (1 x 50 mL), dried with $MgSO_4$, and concentrated to a dark brown oil. This oil was chromatographed on silica gel (5:1 hexane/EtOAc), giving unreacted/excess 2-methyl-1,3-dithiane at R_f = 0.65 and the product at R_f = 0.31, which was collected and concentrated to (*R*)-176 as a pale yellow oil in 55.2% yield (1.57 g, 5.2 mmol).

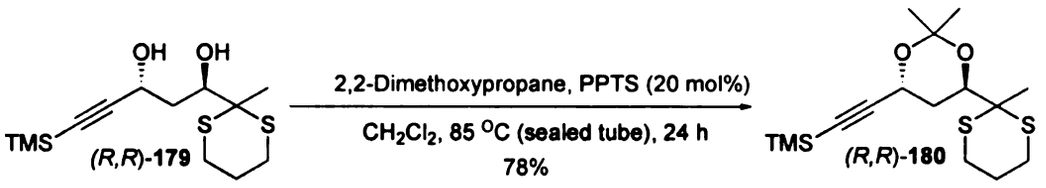
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.16 (s, 9H), 1.65 (s, 3H), 1.82 (m, 1H), 2.17 (m, 1H), 2.62 (m, 2H), 2.97 (dd, 1H, *J* = 3.8, 17.3 Hz), 3.06 (tt, 2H, J = 2.7, 14.0 Hz), 3.42 (dd, 1H, *J* = 7.8, 17.3 Hz), 4.82 (dd, 1H, *J* = 3.8, 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.23, 23.92, 24.45, 27.90, 28.01, 42.67, 54.66, 59.53, 89.72, 104.82; IR (neat film on

NaCl): 3600-3200 (m), 2959 (m), 2900 (m), 2173 (w), 1707 (m), 1416 (w), 1250 (m), 844, (s), 760 (m) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 302 M^+ (1), 269 (1), 195 (0.6), 176 (0.8), 133 (100), 111 (12), 59 (22); R_f = 0.31 (5:1 hexane/EtOAc); $[\alpha]_D$ 11.6° (*c* 1, $CHCl_3$).



[a]**Diol (*R,R*)-179 by Evans Reduction.** See preparation of diol (*R,R*)-**192** for the procedure. This reaction was run on a 2.71 mmol scale. The product (*R,R*)-**179** was isolated as fibrous white needles in 91% yield (741 mg, 2.44 mmol) as a single diastereomer.

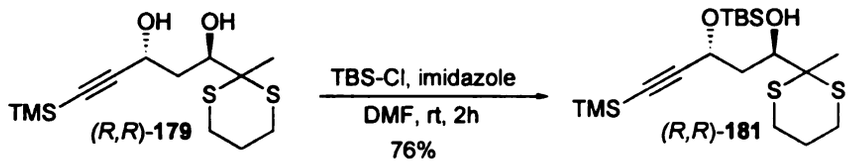
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 9H), 1.37 (s, 3H), 1.83 (m, 2H), 2.12 (m, 1H), 2.41 (m, 1H), 2.59 (m, 2H), 3.09 (m, 2H), 4.67-4.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.06, 21.29, 24.13, 25.59, 25.79, 35.93, 52.74, 61.82, 68.34, 89.32, 106.65; IR (neat film on NaCl): 3600-3100 (m), 2895 (w), 2173 (w), 1249 (m), 1058 (m), 842 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 304 M^+ (3), 164 (3), 133 (100), 99 (4), 73 (9), 59 (14); mp 112-113 °C; R_f = 0.28 (3:1 hexane/EtOAc); $[\alpha]_D$ 32.9° (*c* 1, $CHCl_3$). Anal calcd for $C_{13}H_{24}O_2S_2Si$: C 51.27, H 7.94. Found: C 51.32, H 8.05.



[a]**Acetal (*R*,*R*)-180**. A solution of diol (*R*,*R*)-**179** (32 mg, 0.105 mmol), freshly distilled 2,2-dimethoxypropane (55 mg, 0.65 mL, 0.52 mmol), and PPTS (5.2 mg, 0.02 mmol) was dissolved in 1 mL dry CH_2Cl_2 and stirred under argon at room temperature. The reaction was followed by TLC, but the reaction did not appear to be proceeding after 48 h. The reaction mixture was transferred into a Schlenk flask, which was sealed and heated to 85 °C for another 24 h. When checked by TLC after this period of heating, the reaction had gone to completion. The reaction was diluted with 5 mL CH_2Cl_2, washed with $NaHCO_3$ (1 x 5 mL), water (1 x 5 mL, and brine (1 x 5 mL), dried with $MgSO_4$ and concentrated to a yellow oil. The crude product was chromatographed on silical gel (using a 9" disposable pipet as the column) to give the product a pale yellow oil in 78% yield (28 mg, 0.082 mmol).

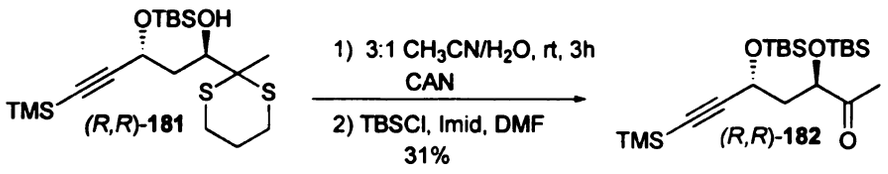
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.41 (s, 3H), 1.46 (s, 3H), 1.58 (s, 3H), 1.93 (m, 1H), 2.00-2.05 (m, 2H), 2.23 (ddd, 1H, *J* = 4.2, 2.7, 10.2 Hz), 2.70 (m, 2H), 3.15 (m, 2H), 4.35 (dd, 1H, *J* = 4.7, 10.2 Hz), 4.70 (t, 1H, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.21, 23.50, 23.81, 24.89, 26.81, 27.24, 34.05, 50.19, 61.82, 68.32, 74.16, 90.77, 101.26, 106.63; IR (neat film on NaCl): 2936 (m), 2169 (w), 1380 (m), 1249 (s), 1157 (w), 1106 (m), 1064 (w), 908 (m), 855 (s), 843 (s), 760 (m); EI mass

spectrum *m/z* (% rel intensity) 344 M^+ (3), 286 (5), 271 (9), 211 (23), 153 (40), 133 (100), 109 (15), 73 (36), 59 (26); R_f = 0.55 (10:1 hexane/EtOAc).



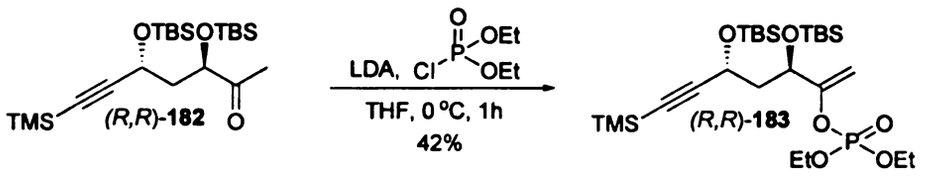
[a]**Protected Diol (*R,R*)-181**. See preparation of (*R,R*)-**202** for procedure. Reaction was run on a 1.13 mmol scale. The product (*R,R*)-**181** was isolated as a white solid in 76% yield (359 mg, 0.86 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 0.19 (s, 6H), 0.88 (s, 9H), 1.39 (s, 3H), 1.69 (m, 1H), 1.87 (m, 1H), 2.09 (m, 1H), 2.41 (m, 1H), 2.60 (m, 2H), 3.03 (m, 2H), 4.35 (d, 1H, *J* = 10.1 Hz), 4.68 (d, 1H, *J* = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.08, -4.54, -0.21, 18.21, 21.65, 24.37, 25.77, 25.82, 25.89, 38.70, 52.87, 61.21, 67.24, 88.85, 107.31; IR (neat film on NaCl): 2955 (m), 2930 (m), 2856 (w), 2173 (w), 1472 (w), 1250 (m), 1063 (m), 841 (s), 779 (m) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 418 M^+ (8), 361 (6), 285 (22), 255 (16), 201 (16), 153 (22), 133 (100), 107 (8), 73 (72); mp 66-68 °C; R_f = 0.18 (50:1 hexane/EtOAc); $[\alpha]_D$ 80.82° (*c* 1.05 in $CHCl_3$).



[a]**Ketone (*R,R*)-182.** The dithiane (*R,R*)-**181** (1.67 g, 3.12 mmol) was suspended in a solution of 60 mL acetonitrile and 20 mL water. Solid cerium (IV) ammonium nitrate (6.85 g, 12.5 mmol), was added in one portion, and the reaction was stirred for 5 minutes, at which time the solid white suspension of dithiane had completely disappeared. The reaction was diluted with 20 mL water and 50 mL ether and poured into a separatory funnel. The aqueous layer was back-extracted with ether (2 x 25 mL), and the combined organic layers were washed with $NaHCO_3$ (1 x 50 mL), water (2 x 50 mL), and brine (1 x 30 mL), dried with $MgSO_4$ and concentrated to a pale yellow oil. The crude reaction mixture was chromatographed on silica gel (50:1 hexane/EtOAc) to give the product (*R,R*)-**182** as a pale yellow oil in 31% yield (429 mg, 0.97 mmol).

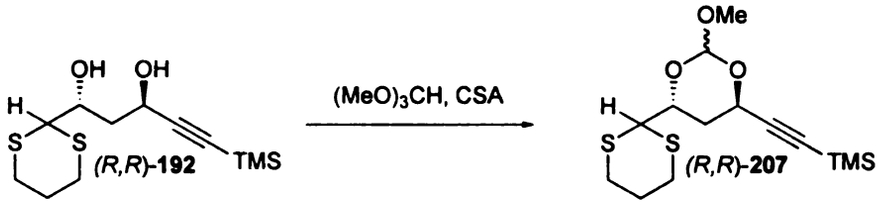
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.14 (s, 3H), 0.16 (s, 12H), 0.17 (s, 3H), 0.90 (s, 9H), 0.92 (s, 9H), 1.94 (m, 2H), 2.16 (s, 3H), 4.18 (dd, 1H, J = 5.3, 7.0 Hz), 4.52 (dd, 1H, J = 5.4, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ -4.86, -4.82, -4.77, -4.54, -0.36, 18.10, 18.21, 25.39, 25.75, 25.83, 43.90, 59.48, 75.55, 89.95, 106.91, 210.68; IR (neat film on NaCl): 2957 (m), 2930 (m), 2858 (m), 2173 (w), 1720 (m), 1472 (m), 1257 (s), 1092 (s), 889 (s), 778 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 427 M^+-15 (2), 385 (28), 311 (3), 259 (49), 253 (43), 241 (80), 221 (9), 147 (31), 133 (11), 115 (14), 73 (100); R_f = 0.24 (50:1 hexane/EtOAc); $[\alpha]_D$ 65.0° (*c* 1, $CHCl_3$).



[a]**Phosphonate (*R,R*)-183.** A solution of LDA was prepared by adding *n*-BuLi (2.5 M solution in hexane, 0.4 mL, 1.0 mmol) to a solution of diisopropylamine (0.15 mL, 1.05 mmol, 1.05 equiv.) in 5 mL THF at -78 °C, then warming the reaction to room temperature for 15 minutes then cooling back down to -78 °C. This solution was added to a precooled (-78 °C) solution of ketone (*R,R*)-**182** (420 mg, 0.95 mmol) in 5 mL THF. The reaction was stirred at -78 °C for 5 minutes, then warmed to 0 °C for 15 minutes and cooled back down to -78 °C. Diethylchlorophosphonate (0.28 mL, 331 mg, 1.92 mmol), was added neat via syringe, and the reaction was monitored by TLC for disappearance of starting material. No reaction was observed after 15 minutes, so the reaction was allowed to warm to room temperature. It was complete after 45 minutes.

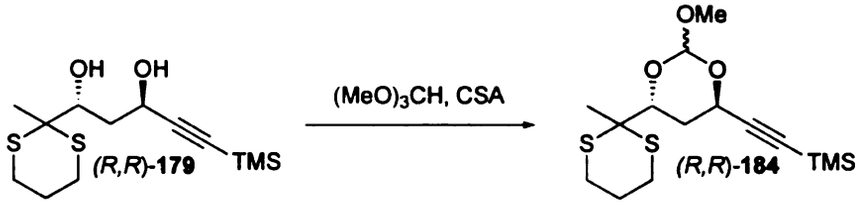
The reaction was quenched with aq. NH_4Cl solution and diluted with 10 mL water and 20 mL ether. The reaction was poured into a separatory funnel and the aqueous layer was back-extracted with ether (2 x 10 mL). The combined organic layers were washed with water (2 x 20 mL) and brine (1 x 20 mL), dried with $MgSO_4$ and concentrated to a pale yellow oil. The oil was purified by chromatography on silica gel (10:1 hexane/EtOAc – $KMnO_4$). One fraction at $R_f = 0.12$ was isolated and concentrated to a colorless oil in 42% yield (230 mg, 0.40 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.14-0.17 (15 H, overlapping TMS and TBS singlets), 0.89 (s, 9H), 0.91 (s, 9H), 1.37 (t, 6H, J = 6.5 Hz), 1.87 (m, 1H), 2.04 (m, 1H), 4.17 (m, 4H), 4.22 (m, 1H), 4.46 (m, 1H), 4.75 (t, 1H, J = 1.6 Hz), 4.98 (t, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.00, -4.59, -4.37, -3.71, -0.28, 16.03, 18.11, 25.81, 25.87, 45.33, 59.84, 64.34, 69.42, 89.52, 96.19, 107.35, 156.26; IR (neat film on NaCl): 2958 (m), 2930 (m), 2858 (m), 2172 (w), 1659 (w), 1472 (m), 1276 (w), 1251 (m), 1098 (s), 1034 (s), 838 (s), 778 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 563 M^+-15 (6), 521 (95), 424 (4), 397 (13), 367 (12), 315 (9), 267 (7), 211 (27), 183 (11), 155 (35), 109 (6), 75 (100); R_f = 0.12 (10:1 hexane/EtOAc); $[\alpha]_D$ 22.5° (*c* 1.5, $CHCl_3$).



[d]Trimethyl Ortho Ester Derived (*R*,*R*)-207 (from (*R*,*R*)-192). To a solution of compound (*R*,*R*)-**192** (286 mg, 0.98 mmol) in 2 ml of CH_2Cl_2 was added camphor sulfonic acid (CSA, 5 mg) in one portion, 10 mg of 4A° molecular sieves and trimethyl ortho ester (208 mg, 2 mmol) dropwise. The reaction was stirred for 48 h at room temperature. After separation by flash chromatography (10% EtOAc in hexanes), compound (*R*,*R*)-**207** was isolated as a colorless oil 98% yield (319.4 mg, 0.96 mmol) in a 6:1 diastereomeric ratio. Major isomer of (*R*,*R*)-**207**:

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.18 (s, 9H), 1.74 (dt, 1H, *J* = 2.10, 13.19, Hz), 1.86-2.04 (m, 1H), 2.04-2.30 (m, 2H), 2.74-2.89 (m, 2H), 2.89-3.02 (m, 2H), 3.48 (s, 3H), 4.08 (d, 1H, *J* = 5.77 Hz), 4.38 (ddd, 1H, *J* = 2.20, 5.77, 8.24 Hz), 4.96 (dd, 1H, *J* = 1.37, 5.49 Hz), 5.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.33, 25.73, 29.16, 29.26, 32.50, 49.61, 52.32, 63.74, 74.51, 93.71, 101.27, 108.34. R_f = 0.50 (20% EtOAc in hexanes).

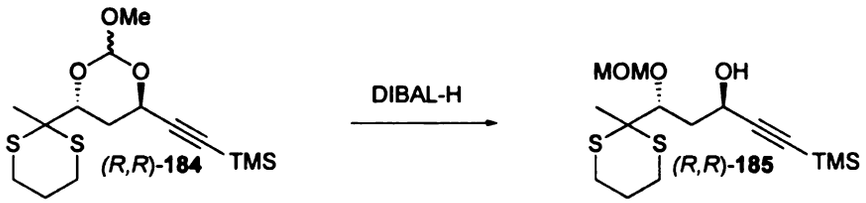


[e]**Trimethyl Ortho Ester (*R,R*)-184.** Procedure same as above, data not reported.

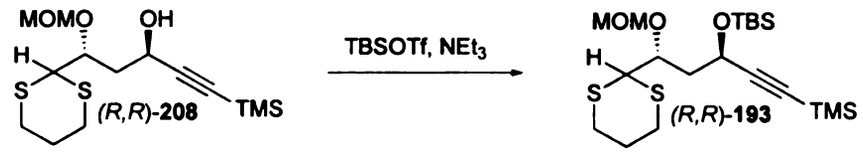
[d]**DIBAl Reduction Precursor to (*R,R*)-208.** To a solution of the ortho ester derivative (*R,R*)-**207** (473 mg, 1.42 mmol) in 12 mL of CH_2Cl_2 was added 7.1 mL of 1 M DIBAL-H (7.1 mmol in hexanes) at –78 °C. After stirring for 1 hour at –78 °C, the reaction warm up to 0 °C for 10 min. The reaction was quenched by aq. HCl (1N). The reaction mixture was filtered through Celite and washed with methylene chloride (4 x 100 mL). The combined organic layers were washed aq. NH_4Cl, and brine (200 mL), dried over $MgSO_4$ and concentrated on the rotary evaporator. Purification of the crude

product by flash chromatography on silica gel (1:1 hexanes/EtOAc) afforded 445 mg (1.32 mmol) of MOM mono-protected product (*R,R*)-**208** as a colorless oil in 93% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 9H), 1.85 (m, 1H), 2.08 (m, 3H), 2.86 (m, 4H), 3.07 (d, 1H, *J* = 6.6 Hz), 3.44 (s, 3H), 4.11 (dt, 1H, *J* = 4.3, 9.1 Hz), 4.36 (d, 1H, *J* = 4.4 Hz), 4.54 (m, 1H), 4.72 (d, 1H, *J* = 6.9 Hz), 4.78 (d, 1H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.28, 29.98, 30.15, 30.36, 39.77, 52.51, 56.25, 59.35, 77.15, 89.20, 97.19, 105.96. R_f = 0.14 (20% EtOAc in hexanes).



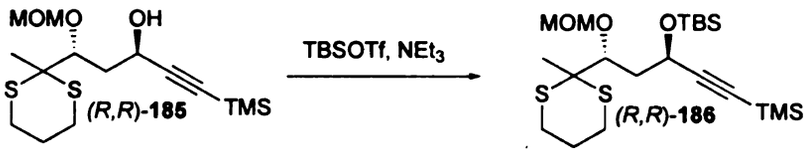
[e]**(*R,R*)-185 by DIBAl Reduction of (*R,R*)-184.** Procedure same as above, data not reported.



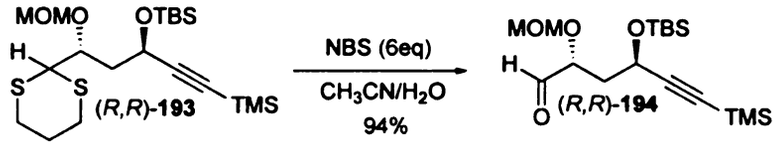
[d]**TBS Protection (*R,R*)-193.** To a solution of (*R,R*)-**208** (212 mg, 0.63 mmol) in 3 mL CH_2Cl_2 at room temperature, NEt_3 (0.263 mL, 1.89 mmol) was dropwise added and then TBSOTf (0.433 mL, 1.89 mmol) also dropwise added. The reaction mixture has been stirred for 10 min and quenched with brine (100 ml). After extraction with CH_2Cl_2 (3 x 30 ml) of reaction mixture, the combined organic layers were concentrated in vacuo.

Flash chromatography on silical gel with 10% EtOAc in hexanes gave 274.2 mg (0.61 mmol) of product (*R,R*)-**193** as colorless oil in 97% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.15 (s, 9H), 0.18 (s, 3H), 0.91 (s, 9H), 1.80-2.20 (m, 4H), 2.89 (m, 4H), 3.45 (s, 3H), 3.99 (dt, 1H, *J* = 3.6, 8.8 Hz), 4.47 (d, 1H, *J* = 3.6 Hz), 4.52 (dd, 1H, *J* = 3.3, 9.9 Hz), 4.73 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.86, -4.04, -0.30, 18.10, 25.81, 26.26, 30.44, 30.73, 41.41, 53.32, 56.06, 59.76, 77.12, 89.16, 96.97, 107.02. R_f = 0.34 (10% EtOAc in hexanes).



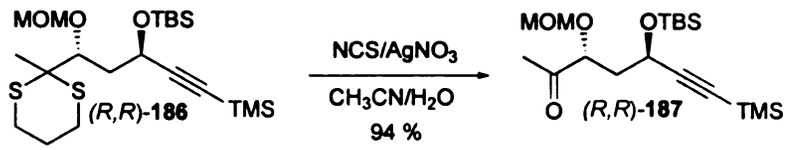
[e]**TBS Protection (*R,R*)-186.** Procedure same as above, data not reported.



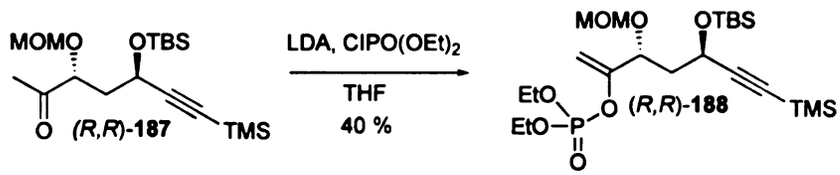
[d]**Aldehyde (*R,R*)-194.** A solution of 200 mg (0.448 mmol) of compound (*R,R*)-**193** in 5 mL acetonitrile was added to a solution of NBS (476 mg, 2.68 mmol) in aqueous 80% acetonitrile at 0 °C, and was stirred for 10 min. The red reaction solution quickly turned to an orange color. After quenching with saturated aqueous sodium sulfite, the reaction mixture was extracted with 1:1 hexane-CH_2Cl_2. The organic phase was washed

with saturated aqueous NaCl solution. Chromatography on silica gel (20% EtOAc in hexanes) provided aldehyde (*R,R*)-**194** (145.8 mg, 0.41 mmol) as a colorless oil in 91% yield.

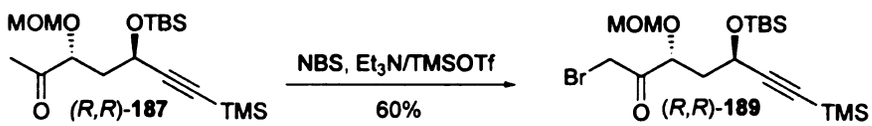
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.17 (s, 9H), 0.18 (s, 3H), 0.92 (s, 9H), 1.95 (ddd, 1H, *J* = 3.9, 9.1, 14.3 Hz), 2.09 (ddd, 1H, *J* = 3.9, 9.3, 14.3 Hz), 3.44 (s, 3H), 4.12 (ddd, 1H, *J* = 1.7, 3.9, 16.7 Hz), 4.58 (dd, 1H, *J* = 3.9, 9.1 Hz), 4.71 (d, 1H, *J* = 6.9 Hz), 4.74 (d, 1H, *J* = 6.9 Hz), 9.86 (d, 1H, *J* = 1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.92, -4.22, -0.35, 18.15, 25.78, 39.05, 56.12, 59.02, 79.72, 89.93, 97.23, 106.56, 202.11. R_f = 0.30 (20% EtOAc in hexanes).



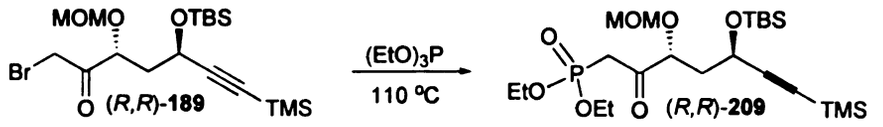
[e]**Ketone (*R,R*)-187.** Data not reported.



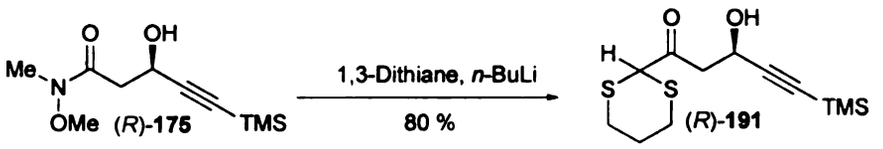
[d]**Phosphonate (*R,R*)-188.** Proceedure same as for (*R,R*)-**103**. Data not reported.



[d]**Acyl Bromide (*R,R*)-189.** Data not reported.



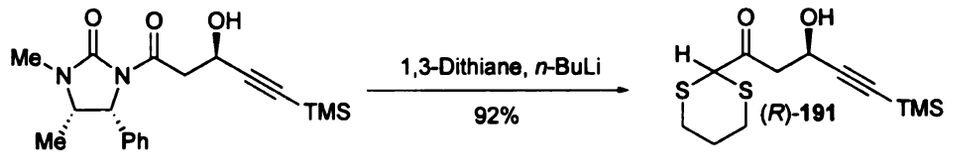
[d]**Phosphonate (*R,R*)-209**. Data not reported.



[d]**Dithiane (*R,R*)-191 from Weinreb's Amide (*R,R*)-175**. To a solution of 1,3-dithiane (48 mg, 0.40 mmol) in 50 mL THF was added *n*-BuLi (250 μL, 0.40 mmol) at –78 °C. The reaction mixture was warmed up to 0 °C and stirred for 30 minutes, and then the solution of adduct (*R,R*)-**175** (50 mg, 0.14 mmol) in 30 ml THF was added dropwise. The reaction was stirred for 30 min and quenched with acetic acid (1 eq). The solution was diluted with ether (50 mL), washed with aq. $NaHCO_3$ (1 x 20 mL), extracted with CH_2Cl_2 and subjected to column chromatography. Product (*R,R*)-**191** was obtained in 79% yield (31.7 mg, 0.11 mmol) as a colorless oil after silica gel chromatography (R_f = 0.40, 1:4 EtOAc/hexanes).

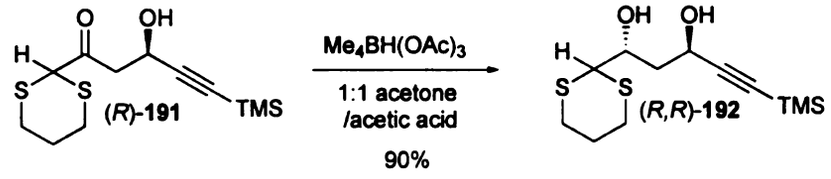
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.94-2.20 (m, 2H), 2.57 (ddd, 1H, *J* = 2.7, 2.7, 5.2 Hz), 2.61 (ddd, 1H, *J* = 2.74, 2.74, 5.22 Hz), 3.05 (dd, 1 H, *J* = 4.1, 16.8 Hz), 3.17 (dd, 1 H, *J* = 7.7, 16.8 Hz), 3.20 (ddd, 1H, *J* = 3.0, 4.9, 11.3 Hz), 3.25 (ddd, 1H, *J* = 3.0, 4.9, 11.3 Hz), 4.23 (s, 1H), 4.83 (dd, 1H, *J* = 4.1, 7.7 Hz); ^{13}C NMR (75 MHz,

$CDCl_3$): δ -0.30, 24.96, 25.84, 25.88, 46.83, 59.14, 90.01, 104.45, 200.65; ^{13}C DEPT NMR (75 MHz, $CDCl_3$): δ -0.30 (CH_3), 24.96 (CH_2), 25.84 (CH_2), 25.88 (CH_2), 46.83 (CH and CH_2), 59.14 (CH), 90.01 (C), 104.45 (C), 200.65 (C). R_f = 0.40 (1:4 EtOAc/hexanes); Anal calcd for $C_{12}H_{20}O_2S_2Si$: C 49.96, H 6.99. Found: C 49.85, H 6.96.



(4S,5R,R)-166c

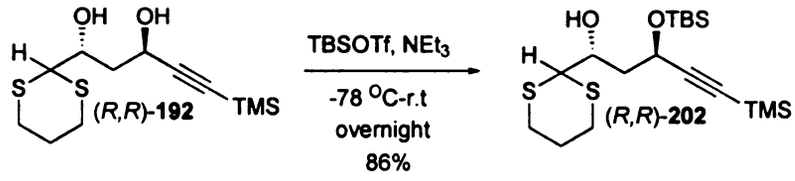
[d]**Dithiane (*R*,*R*)-191 from Imidazolidinone.** To a solution of 1,3-dithiane (535 mg, 4.47 mmol) in 50 mL THF was added *n*-BuLi (2.5 M in hexanes, 1.79 mL, 4.47 mmol) at –78 °C. The reaction mixture was warmed to 0 °C and stirred for 1 h. A solution of imidazolinone adduct (4*S*,5*R*,*R*)-**166c** (550 mg, 1.54 mmol) in 30 mL THF was added dropwise. The reaction mixture was immediately re-cooled to –78 °C, stirred overnight and quenched with acetic acid (3.98 mL, 2.65 mmol). The solution was diluted with ether (50 mL), washed with aq. $NaHCO_3$ (1 x 20 mL), extracted with CH_2Cl_2 and subjected to column chromatography on silica gel (R_f = 0.40, 1:4 EtOAc/hexanes). The product (*R*,*R*)-**191** was obtained in 92% yield (402 mg, 1.42 mmol) as a colorless oil. Spectral data for the product from this reaction matched that for (*R*,*R*)-**191** reported above.



[d]Diol (*R*,*R*)-192 from Evan's Reduction[75]. Tetramethylammonium triacetoxyborohydride (3.32 g, 12.61 mmol) was dissolved in 10 mL acetone and 20 mL acetic acid at 0 °C and stirred for 30 min. A solution of compound (*R*)-**191** (562 mg, 1.94 mmol) in 10 mL acetone was added. The reaction mixture was stirred for 1 h, quenched with excess saturated aqueous sodium potassium tartrate solution and diluted with 50 mL ether. The aqueous layer was neutralized with solid K_2CO_3 and the reaction mixture was extracted with ether (3 x 50 mL). The combined organic layers were washed with aq. $NaHCO_3$ solution (50 mL), H_2O (50 mL), and brine (50 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator to give a white solid. Purification of the crude product by flash chromatography on silica gel (1:1 hexanes/EtOAc) affored 90% yield (506.34 mg, 1.75 mmol) of diol product (*R*,*R*)-**192** (20:1 ratio of *anti*:*syn* diastereomers) as a white solid.

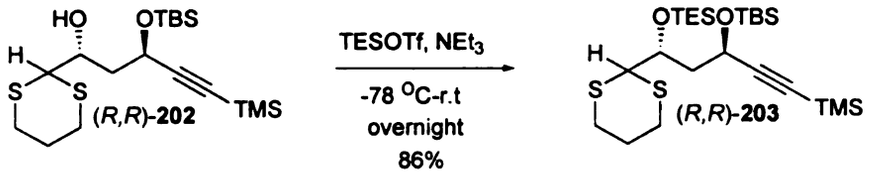
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.19 (s, 9H), 1.92-2.16 (m, 3H), 2.31 (ddd, 1H, *J* = 2.2, 6.5, 14.3 Hz), 2.71 (ddd, 1H, *J* = 3.3, 8.0, 14.0 Hz), 2.92-3.02 (m, 2H), 3.80 (d, 1H, *J* = 7.4 Hz), 3.90 (d, 1H, *J* = 6.4 Hz distinguishable proton), 4.45 (ddd, 1H, *J* = 2.2, 7.4, 9.8 Hz), 4.72 (dd, 1H, *J* = 3.3, 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.16, 25.40, 26.95, 27.34, 40.21, 50.88, 60.87, 68.94, 89.67, 106.00; IR (neat film on NaCl): 3150-3610 (w), 2957 (s), 2924 (s), 2901 (s), 2172 (s), 1423 (s), 1277 (s), 1250 (s), 1064 (s),

843 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 290 M^+ (8), 149 (10), 121 (17), 120 (36), 119 (100), 106 (8), 84 (10), 75 (13), 73 (15); R_f = 0.26 (40% EtOAc in hexanes).



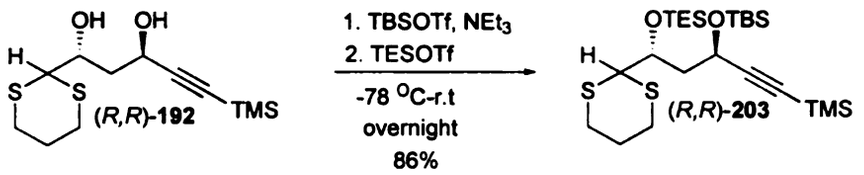
(*R*,*R*)-202 : TBS-Monoprotection of Diol (*R*,*R*)-192. To a cooled solution (–78 °C) of diol (*R*,*R*)-**192** (110 mg, 0.38 mmol) in 3.5 mL of CH_2Cl_2 was added NEt_3 (191 μL, 1.36 mmol) and TBSOTf (87.3 μL, 0.38 mmol). The solution was stirred overnight at this temperature and allowed to warm to ambient temperature prior to quenching with $NaHCO_3$. The organic phase was extracted with CH_2Cl_2 and dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (1:9 EtOAc/hexanes, R_f = 0.24) gave (*R*,*R*)-**192** as a colorless oil in 86% yield (132.6 mg, 0.33 mmol).

^1H NMR (300 MHz, $CDCl_3$): δ 0.13 (m, 15H), 0.88 (s, 9H), 1.84-2.14 (m, 4H), 2.70-2.80 (m, 2H), 2.80- 2.98 (m, 2H), 3.27 (broad s, 1H), 3.93 (d, 1H, *J* = 6.3 Hz), 4.28 (t, 1H, *J* = 7.8 Hz), 4.69 (dd, 1H, *J* = 6.9, 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.52, -0.46, 0.00, 18.2, 26.12, 26.20, 28.61, 28.98, 42.12, 53.53, 61.98, 69.97, 90.20, 106.59; IR (neat film on NaCl): 3340 -3580 (w), 2955 (s), 2928 (s), 2349 (s), 1259 (s), 1095 (s), 841 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 404 M^+ (15), 386 (13), 285 (18), 255 (14), 241 (28), 221 (13), 201 (42), 179 (10), 147 (49), 133 (28), 119 (69), 84 (30), 73 (100), 59 (20), 47 (13). R_f = 0.24 (1:9 EtOAc/hexanes).

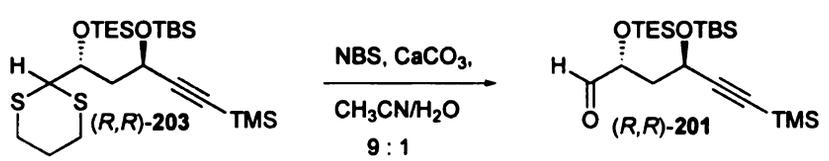


(*R*,*R*)-203: TES Protection of Alcohol (*R*,*R*)-202. To a cooled solution (–78 °C) of mono protected diol (*R*,*R*)-**202** (100 mg, 0.25 mmol) in 5 mL of CH_2Cl_2 was added NEt_3 (70 μL, 0.5 mmol) and TESOTf (79 μL, 0.35 mmol). The solution was stirred overnight at this temperature and allowed to warm up to ambient temperature prior to quenching with aq. $NaHCO_3$. The organic phase was extracted with CH_2Cl_2 and dried on $MgSO_4$ and concentrated. Flash chromatography on silica gel (R_f = 0.57, 1:9 EtOAc/hexanes) provided (*R*,*R*)-**203** as a colorless oil in 86% yield (113.4 mg, 0.22 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.09-0.16 (m, 15H), 0.64 (dq, 6H, *J* = 4.15, *J* = 0.7 Hz), 0.87 (s, 9H), 0.97 (t, 9H, *J* = 4.9 Hz), 1.60-1.93 (m, 2H), 2.00-2.17 (m, 2H), 2.72-2.92 (m, 4H), 4.10 (quintet, 1H, *J* = 3.9 Hz), 4.19 (d, 1H, *J* = 3.4 Hz), 4.46 (dd, 1H, *J* = 4.4, 4.9 Hz). IR (neat film on NaCl): 2957 (s), 2930 (s), 2897 (m), 2857 (s), 1250 (s), 1093(s), 839 (s) cm^{-1}; EI mass spectrum *m*/*z* (% rel intensity) 518 M^+ (5), 365 (4), 262 (16), 241 (100), 207 (4), 181 (6), 147 (16), 115 (14), 87 (15), 73 (42), 59 (12). R_f = 0.57 (1:9 EtOAc/hexanes); Anal calcd for $C_{24}H_{50}O_2S_2Si_3$: C 55.60, H 9.65. Found: C 55.31, H 10.0.



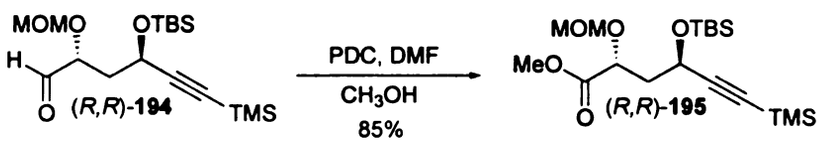
(*R*,*R*)-203: One-Pot Protection of Diol (*R*,*R*)-192. To a cooled solution (–78 °C) of diol (*R*,*R*)-**192** (37 mg, 0.127 mmol) in 5 mL of CH_2Cl_2 was added NEt_3 (89.1 μL, 0.635 mmol) and TBSOTf (29.2 μL, 0.127 mmol). After all the starting material was consumed as indicated by TLC, TESOTf (40.2 μL, 0.178 mmol) was added to the solution. The solution was stirred overnight at this temperature and allowed to warm up to ambient temperature prior to quenching with aq. $NaHCO_3$. The organic phase was extracted with CH_2Cl_2 and dried on $MgSO_4$ and concentrated. Flash chromatography on silica gel (R_f = 0.57, 1:9 EtOAc/Hexanes) gave (*R*,*R*)-**203** as a colorless oil in 100% yield (66.8 mg, 0.127 mmol). Spectral data for the product from this reaction matched that for (*R*,*R*)-**203** reported above.



Aldehyde (*R*,*R*)-201. A solution of protected diol (*R*,*R*)-**203** (54 mg, 0.104 mmol) in 1 mL of acetone was added to a solution of NBS (111.3 mg, 0.625 mmol) and $CaCO_3$ (416 mg, 4.16 mmol) in 90% aqueous acetonitrile at 0 °C, and was stirred for 10 min. The white suspension quickly acquired a yellow coloration. After quenching with saturated

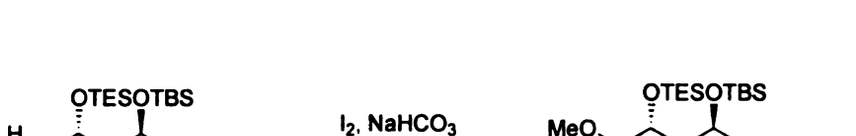
aqueous sodium sulfite, the reaction mixture was extracted ether. The organic phase was washed with saturated aq. NaCl solution. Chromatography on silica gel (20% EtOAc in hexanes) provided the aldehyde (*R,R*)-**201** as a colorless oil in 91% yield (40.4 mg, 0.095 mmol). A crude ^{1}H NMR indicated that the material was satisfactory and could be used for the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.11 (s, 3H), 0.13 (s, 9H), 0.14 (s, 3H), 0.61 (q, 6H, *J* = 7.8 Hz), 0.87 (s, 9H), 0.94 (t, 9H, *J* = 7.8 Hz), 1.86-1.95 (m, 1H), 1.99-2.11 (m, 1H), 4.18 (dt, 1H, *J* = 5.1, 1.5 Hz), 4.55 (dd, 1H, *J* = 5.1, 3.0 Hz), 9.61 (dd, 1H, *J* = 1.2, 0.5 Hz). R_f = 0.68 (1:4 EtOAc/hexanes).



[d]**Methyl Ester (*R,R*)-195**. To a solution of aldehyde (*R,R*)-**194** (150 mg, 0.42 mmol) in methanol (100 μL, 25 mmol) and dry dimethylformamide (5 mL) at room temperature was added pyridinium dichromate (950 mg, 25 mmol) and the reaction mixture stirred for 40 h. The solution was poured into hexanes (200 mL)/water (50 mL), filtered over Celite and then the water layer was extracted with hexanes (3 x 50 mL). The combined hexanes extracts were dried over magnesium sulfate. Removal of the solvent on a rotary evaporator gave the methyl ester (*R,R*)-**195** as colorless oil in in 85% yield (139 mg, 0.36 mmol). The crude product was used for the next step.

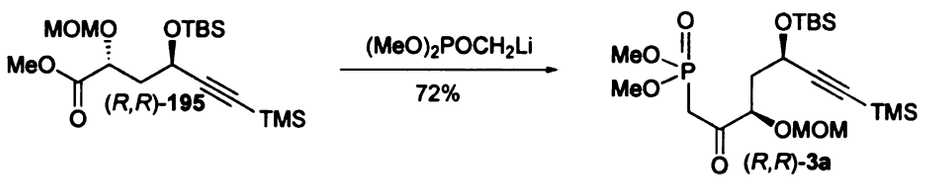
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.16 (s, 9H), 0.19 (s, 3H), 0.92 (s, 9H), 2.05-2.12 (m, 2H), 3.40 (s, 3H), 3.75 (s, 3H), 4.26 (dd, 1H, J = 3.8, 9.2 Hz), 4.58 (dd, 1H, J = 3.8, 9.2 Hz), 4.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.86, -4.11, -0.33, 18.13, 25.78, 41.96, 51.96, 56.28, 59.15, 72.77, 89.49, 96.90, 106.61, 173.10. R_f = 0.45 (10% EtOAc in hexanes).



Methyl Ester (*R,R*)-200. To a solution of aldehyde (*R,R*)-**201** (22.4 mg, 0.053 mmol) in methanol (1 mL) was added $NaHCO_3$ (17.4 mg, 0.21 mmol) and I_2 (39.5 mg 0.312 mmol). The reaction was stirred for 36 h at room temperature and then quenched slowly with aq. NaS_2O_4 at 0 °C slowly. The organic phase was extracted with EtOAc (3 × 10 mL), washed once with aq. NaS_2O_4 and (3 × 10 mL) with brine. The combined organic layers was dried on Na_2SO_4 and concentrated. The crude product (*R,R*)-**200** was isolated in 91% yield (21.8 mg, 0.048 mmol) as a colorless oil and was used for the next step without any further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.06 (s, 3H), 0.12 (s, 9H), 0.62 (q, 6H, J = 7.4), 0.88 (s, 9H), 0.93 (t, 9H, J = 2.75 Hz), 1.80-2.00 (m, 1H), 2.00-2.14 (m, 1H), 3.69 (s, 3H), 4.37 (dd, 1H, J = 8.5, 4.4 Hz), 4.53 (dd, 1H, J = 9.1, 4.7 Hz); ^{13}C NMR

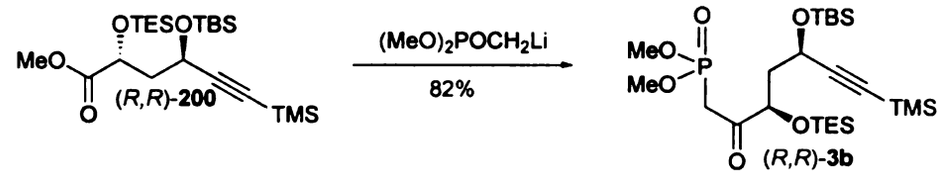
(75 MHz, $CDCl_3$): δ -4.3, -3.8, -0.33, 5.0, 7.0, 18.6, 26.2, 44.8, 54.0, 59.8, 68.9, 89.9, 108.2, 174.5; EI mass spectrum *m/z* (% rel intensity) 458 M^+ (2), 443 (4), 401 (64), 269 (23), 241 (50), 227 (56), 215 (9), 189 (24), 147 (40), 89 (38), 73 (100).



[d]**Triol Fragment (*R*,*R*)-3a**. To a solution of dimethyl methyl phosphonate (37.6 μL, 0.347 mmol) in 2 mL of THF at –78 °C was added *n*-BuLi (0.23 mL, 0.368 mmol). After 1 h, a solution of ester (*R*,*R*)-**195** (73 mg, 0.16 mmol) in 2 mL of THF was added and the reaction mixture allowed to warm to ambient temperature. After another hour at this temperature, the solution was quenched with 5 mL of saturated aq. NH_4Cl and diluted with CH_2Cl_2 (30 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 30 mL) dried on $MgSO_4$, then concentrated down to a yellow oil. Column chromatography on silica gel with 1:2:17 CH_3OH/EtOAc/hexanes gave (*R*,*R*)-**3a** as a yellow oil in 72% yield (79.2 mg, 0.115 mmol).

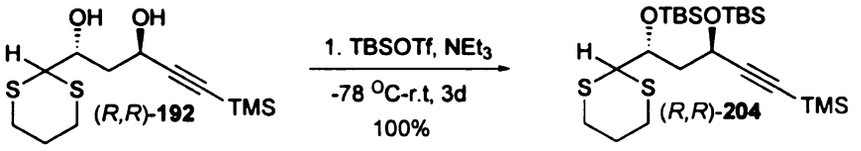
^1H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.15 (d, 9H, *J* = 0.6 Hz), 0.18 (s, 3H), 0.92 (d, 9H, *J* = 0.6 Hz), 1.98 (m, 2H), 3.24 (m, 2H), 3.37 (d, 3H, *J* = 0.6 Hz), 3.78 (m, 3H), 3.82 (m, 3H), 4.31 (dd, 1H, *J* = 9.07, 3.02 Hz), 4.54 (dd, 1H, *J* = 9.1, 3.6), 4.65 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.97, -4.20, -0.37, 18.10, 25.75, 36.84 (d, *J* =

132.8 Hz), 40.39, 52.98 (m), 56.14, 59.24, 79.50 (d, J = 0.4 Hz), 89.85, 97.02, 106.40, 202.15. R_f = 0.76. (1:2:17 CH_3OH/EtOAc/hexanes).



Triol Fragment (*R,R*)-3b. To a solution of dimethyl methyl phosphonate (87.4 μL, 0.81 mmol) in 2 mL of THF at –78 °C was added *n*-BuLi (0.531 mL, 0.85 mmol). After 1 h, a solution of ester (*R,R*)-**200** (170 mg, 0.37 mmol) in 2 mL of THF was added and the reaction mixture allowed to warm to ambient temperature. The reaction was held overnight at room temperature. The work-up procedure was identical to that given above for (*R,R*)-**3a**. Phosphonate (*R,R*)-**3b** was isolated as a yellow oil in 82% yield (166.6 mg, 0.30 mmol).

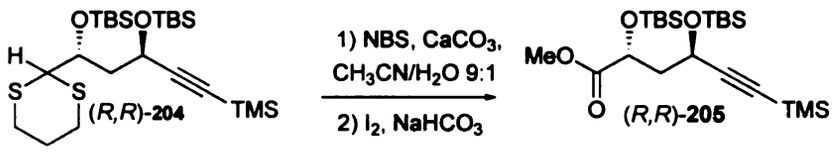
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (m, 15H), 0.62 (q, 6H, J = 8.3 Hz), 0.93 (m, 18H), 1.80- 1.92 (m, 1H), 1.95-2.50 (m, 1H), 3.11 (dd, 1H, J = 14.9, 7.1 Hz), 3.33 (dd, 1H, J = 14.9, 7.08 Hz), 3.75 (s, 3H), 3.78 (s, 3H), 4.33 (dd, 1H, J = 5.4, 1.5 Hz), 4.48 (dd, 1H, J = 5.6, 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.2, -3.8, 0.0, 5.0, 7.0, 18.6, 26.0, 35.7 (d, J = 115.5 Hz), 43.8, 56.5, 59.9, 75.8, 90.4, 106.9, 204.0. IR (neat film on NaCl): 2957 (s), 2918 (s), 2851 (s), 1726 (s), 1462 (s), 1521 (s), 1035 (s), 841 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 535 M^+ -15 (10), 521 (20), 421 (15), 389 (70), 367 (35), 333 (18), 309 (13), 287 (19), 241 (72), 181 (27), 147 (30), 129 (25), 87 (52), 73 (100), 57 (31); R_f = 0.85 (5:2 pentane/ether).



(*R*,*R*)-204 : Di-TBS Protection of Diol (*R*,*R*)-192. To a cooled solution (–78 °C) of diol (*R*,*R*)-**192** (77 mg, 0.27 mmol) in 2.0 mL of CH_2Cl_2 was added NEt_3 (151.6 μL, 1.08 mmol) and TBSOTf (170 μL, 0.74 mmol). The solution was stirred at this temperature for 3 days while being allowed to warm up to ambient temperature. After three days the reaction was quenched with $NaHCO_3$. The organic phase was extracted with CH_2Cl_2 and dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (R_f = 0.80, 5:19 EtOAc/hexanes) gave the protected diol (*R*,*R*)-**204** in 100% yield (140 mg, 0.27 mmol) as a colorless oil.

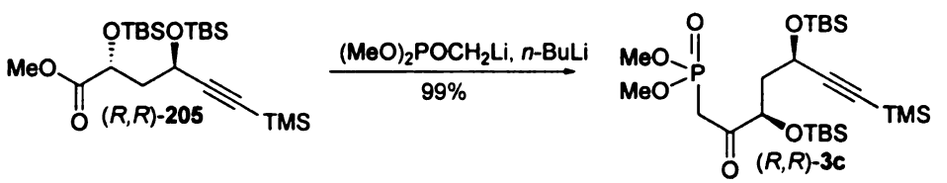
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.06 (s, 3H), 0.10-0.14 (s, 12H), 0.16 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.74-1.94 (m, 2H), 1.96-2.15 (m, 2H), 2.72-2.90 (m, 4H), 4.04-4.12 (m, 1H), 4.20 (d, 1H, *J* = 3.3 Hz), 4.45 (dd, 1H, *J* = 9.2, 4.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.86, -4.75, -3.93, -3.31, -0.61, 17.83, 25.50, 25.57, 26.14, 30.10, 30.48, 43.41, 55.09, 59.59, 70.95, 89.17, 106.92, (1 Sp^3 C not located); IR (neat film on NaCl): 2957 (s), 2930 (s), 2897 (s), 2856 (s), 1251 (s), 1093 (s), 839 (s), 777 (s); EI mass spectrum *m/z* (% rel intensity) 518 (4), 503 (3), 461 (5), 397 (2), 387 (9), 355 (3), 263 (25), 241 (50), 147 (50), 133 (20), 73 (100), 59 (15). R_f = 0.80 (5:19

EtOAc/hexanes); $[\alpha]_D$ 41.0°, (*c* 2.0, acetone). Anal calcd for $C_{24}H_{50}O_2S_2Si_3$: C 55.54, H 9.71. Found: C 55.93, H 9.35.



Dithiane Removal To Give (*R,R*)-205. A solution of protected diol (*R,R*)-**204** (200 mg, 0.386 mmol) in 1 mL of acetone was added to a solution of NBS (417 mg, 2.32 mmol) and $CaCO_3$ (1.54 g, 15.4 mol) in aqueous 90% acetonitrile at 0 °C, and was stirred for 10 mins. The white suspension quickly turned to a yellow coloration. After quenching with saturated aqueous sodium sulfite, the reaction mixture was extracted ether. The organic phase was washed with saturated NaCl solution. The crude aldehyde was dissolved in methanol (8 mL) and then $NaHCO_3$ (129 mg, 1.54 mmol) and I_2 (294 mg, 2.32 mmol) were added. The reaction was stirred for 36 h at room temperature and then quenched with aq. NaS_2O_4 at 0 °C slowly. The organic phase was extracted with EtOAc (3 × 10 mL), washed once with NaS_2O_4 and (3 × 10 mL) with brine. The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product (*R,R*)-**205** was isolated as a colorless oil in 95% yield (168 mg, 0.367 mmol) and used in the next step without any further purification.

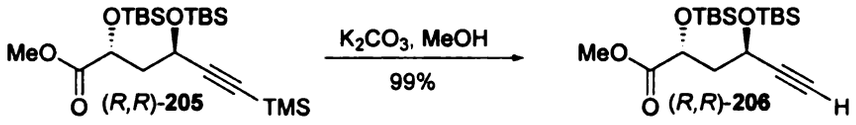
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.05 (s, 3H), 0.12 (s, 3H), 0.13 (s, 9H), 0.15 (s, 3H), 0.88 (s, 18H), 1.90-2.16 (m, 2H), 3.68 (s, 3H), 4.41 (dd, 1H, J = 8.5, 3.8 Hz), 4.53 (dd, 1H, J = 8.9, 4.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.23, -4.82, -4.44, -3.74, -0.31, 18.17, 18.23, 25.75, 25.87, 44.57, 51.76, 59.41, 68.73, 89.16, 106.96, 173.98; FAB mass spectrum *m/z* (% rel intensity) 459 M^+ +1 (3), 443 (1), 401 (3), 369 (4), 327 (5), 277 (12), 241 (5), 185 (100), 93 (70), 73 (15), 57 (5). Anal calcd for $C_{22}H_{46}O_4Si_3$: C 57.59, H 10.10. Found: C 57.68, H 10.11.



Triol Fragment (*R,R*)-3c. To a solution of dimethyl methyl phosphonate (76 μL, 0.70 mmol) in 10 mL of THF at –78 °C was added *n*-BuLi (0.416 mL, 0.67 mmol). After 1 h a solution of ester (*R,R*)-**205** (160 mg, 0.35 mmol) in 2 mL of THF was added and the reaction mixture allowed to warm to ambient temperature. The reaction was held overnight at room temperature. The work-up procedure was identical to that described above for (*R,R*)-**3a**. After purification on silica gel (R_f = 0.81, 5:2 pentane/ether) phosphonate (*R,R*)-**3c** was isolated as a yellow oil in 99% yield (190.5 mg, 0.347 mmol).

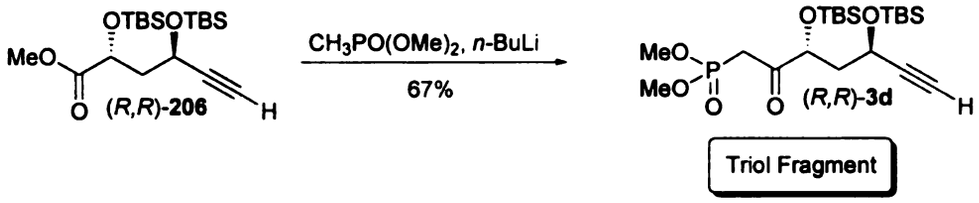
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.15 (s, 3H), 0.16 (s, 9H), 0.18 (s, 3H), 0.91 (s, 9H), 0.93 (s, 9H), 1.84-2.10 (m, 2H), 3.13 (dd, 1H, J = 22.0, 15.1 Hz), 3.35

(dd, 1H, J = 21.2, 15.4 Hz), 3.78 (s, 3H), 3.82 (s, 3H), 4.35 (dt, 1H, J = 5.2, 1.7 Hz), 4.52 (dt, 1H, J = 5.5, 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.62, -4.60, -4.29, -3.69, -0.09, 18.43, 26.04, 26.11, 35.29 (d, J = 80.1 Hz), 43.67, 53.14, 59.78, 75.80, 90.44, 107.04, 203.50, (1 Sp^3 C not located); FAB mass spectrum m/z (% rel intensity) 551 (M + H) (8), 535 (8), 493 (15), 419 (28), 361 (10), 295 (15), 287 (22), 241 (12), 73 (100); R_f = 0.81 (5:2 pentane/ether).



Methyl Ester (*R,R*)-206: To a solution of alkyne *(R,R)*-**205** (40 mg, 0.088 mmol) in MeOH (2.5 mL) at 0 °C was added K_2CO_3 (24 mg, 0.176 mmol). The mixture was stirred 2 h at 0 °C and then filtered through a sintered glass funnel lined with Celite. The Celite bed was washed with 3 x 10 mL of EtOAc and then the combined organic layers were concentrated. The crude (*R,R*)-**206** was isolated as a white solid in 99% yield (33.6 mg, 0.087 mmol) and was used in the next step without any further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.06 (s, 3H), 0.11 (s, 3H), 0.15 (s, 3H), 0.88 (s, 18H), 2.01 (ddd, 1H, J = 13.5, 8.0, 4.8 Hz), 2.12 (ddd, 1H, J = 13.7, 8.3, 4.4 Hz), 2.39 (d, 1H, J = 2.2 Hz), 3.69 (s, 3H), 4.37 (dd, 1H, J = 7.8, 4.3 Hz), 4.56 (ddd, 1H, J = 8.0, 4.9, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.60, -5.13, -5.10, -4.32, 17.80, 17.89, 25.39, 25.47, 44.20, 51.42, 58.45, 68.42, 72.79, 84.63, 173.74.



Triol Fragment 3d. To a solution of dimethyl methyl phosphonate (28.6 μL, 0.264 mmol) in 5 mL of THF at –78 °C was added *n*-BuLi (151 μL, 0.242 mmol, 1.6 M). After 1 h, a solution of ester (*R,R*)-**206** (34 mg, 0.088 mmol) in 5 mL of THF was added and the reaction mixture stirred at –78 °C for an additional 2 hours. The reaction was quenched with 10 mL of saturated aq. NH_4Cl and then diluted with CH_2Cl_2 (30 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 30 mL) dried on $MgSO_4$, then concentrated to an oil. Column chromatography on silica gel with 6:4 pentane/EtOAc gave (*R,R*)-**3d** a colorless oil in 67% yield (28.2 mg, 0.059 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.11 (s, 3H), 0.14 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.78-2.20 (m, 2H), 2.42 (d, 1H, J = 2.2 Hz), 3.12 (dd, 1H, J = 22.0, 15.1 Hz), 3.35 (dd, 1H, J = 21.2, 14.8 Hz), 3.74 (s, 3H), 3.78 (s, 3H), 4.33 (t, 1H, J = 6.0 Hz), 4.50 (dt, 1H, J = 8.0, 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.64, -4.50, -3.85, 18.34, 18.42, 26.02, 26.06, 26.11, 35.40 (d, J = 80.6 Hz), 43.54, 53.20, 59.14, 74.04, 75.64, 84.96, 203.70, (1 Sp^3 C not located). R_f = 0.45 6:4 pentane/EtOAc).

a- Data obtained from Mark Parisi's Thesis;[56]

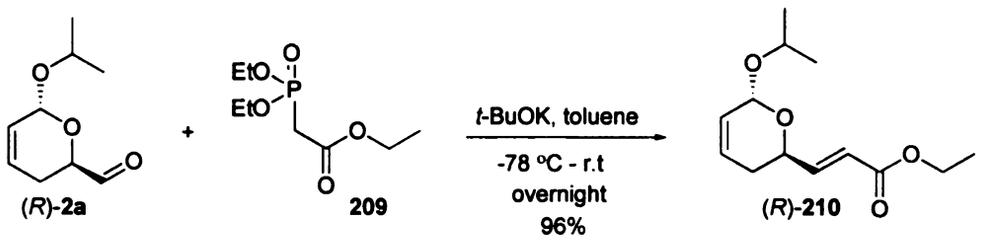
b- Data obtained from Yan Shi's Thesis;[71]

c- Data obtained from unpublished results of Kenneth Wilson and W.D. Wulff;[58]

d- Data obtained from unpublished results of Xuejun Lui and W.D. Wulff;[88]

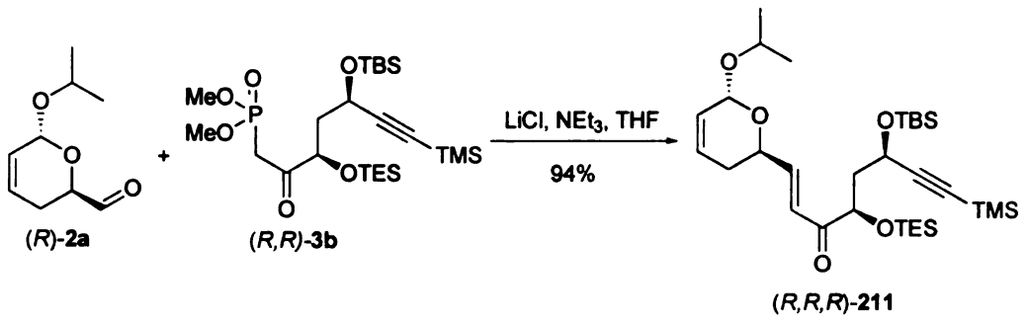
e- Data obtained from unpublished results of Su Yu and W.D. Wulff.[57]

Experimental data for Chapter 4.



HWE Olefination (*R*)-210. A solution of phosphonate **209** (23.2 mg, 0.104 mmol) and the purified major isomer of aldehyde (*R*)-**2a** (30 mg, 0.177 mmol) in 10 mL of anhydrous toluene at –78 °C was treated dropwise with *t*-BuOK (0.152 mL, 0.152 mmol, 1.0 M in THF). The reaction mixture was allowed to warm up to 0 °C slowly and stirred at 0 °C overnight. The reaction was mixture was quenched by addition of 10 mL of saturated aqueous $NaCHO_3$. The organic layers were combined, dried with Na_2SO_4, concentrated and chromatographed with pentane/ether (4:1). Ethyl ester (*R*)-**210** was obtained as a colorless oil in 96 % yield (24.2 mg, 0.101 mmol).

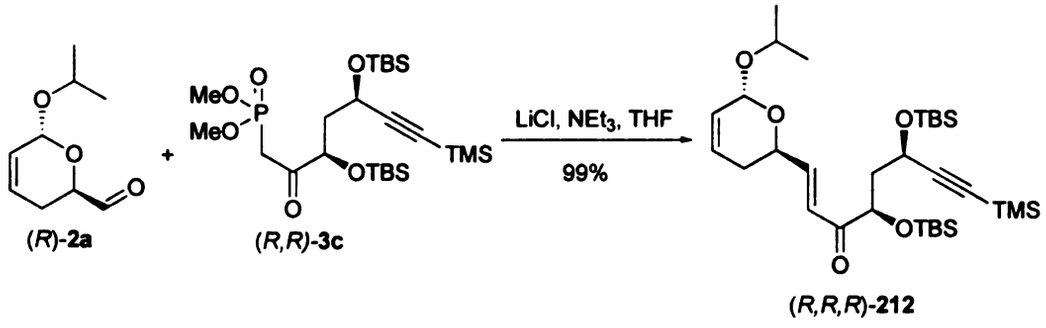
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07 (dd, 6H, J = 6.0, 1.7 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.04-2.10 (m, 2H), 3.96 (sept, 1H, J = 6.3 Hz), 4.18 (q, 2H, J = 7.2 Hz), 4.58-4.66 (m, 1H), 5.12 (d, 1H, J = 2.5 Hz), 5.68-5.79 (m, 1H), 5.95-6.05 (m, 1H), 6.08 (dd, 1H, J = 15.9, 1.9 Hz), 6.95 (dd, 1H, J = 15.7, 4.1 Hz); IR (neat film on NaCl): 2916 (m), 2849 (m), 2363 (m), 2338 (m), 1718 (m), 1653 (s), 1558 (s), 1458 (s), 1030 (m); R_f = 0.46 (4:1 pentane/ether).



HWE Olefination (*R*)-211. A solution of LiCl (3.35 mg, 0.0797 mmol) in 0.5 mL of THF was added to a solution of phosphonate (*R,R*)-**3b** (40.4 mg, 0.0736 mmol) in 3 mL of THF at room temperature and stirred for 5 minutes. The solution was then cooled to 0 °C and Et_3N (10.30 μL, 0.0736 mmol) was added and the solution stirred for 30 minutes at ambient temperature. At this point, the solution was re-cooled to 0 °C and the purified major isomer of aldehyde (*R*)-**2a** (12.5 mg, 0.0736 mmol) was added dropwise in 1 mL of THF. The solution was stirred for 24 h at ambient temperature before being quenched with H_2O (5 mL) and extracted with ether (10 mL). The organic layer was washed with brine and dried over $MgSO_4$. Column chromatography on silica gel (2:5 ether/pentane) provided ketone (*R,R,R*)-**211** in 94 % yield (41.1 mg, 0.069 mmol) as a colorless oil.

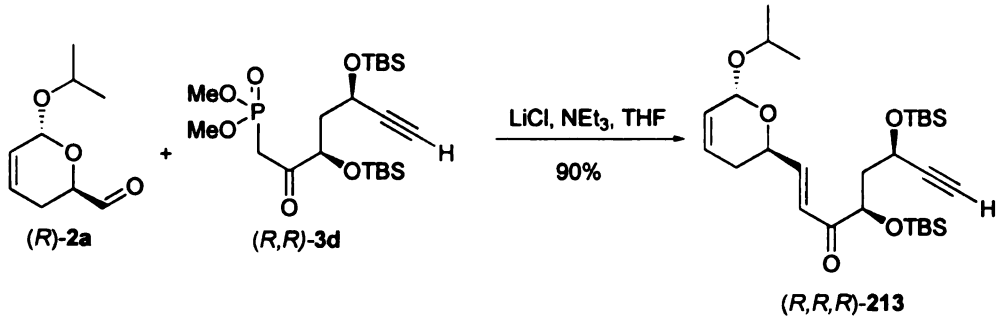
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 9H), 0.13 (s, 6H), 0.58 (q, 6H, *J* = 8.0 Hz), 0.80-0.96 (m, 18H), 1.16 (d, 3H, *J* = 6.1 Hz), 1.18 (d, 3H, *J* = 6.1 Hz), 1.85 (ddd, 1H, *J* = 4.4, 8.8, 13.6 Hz), 1.96-2.10 (m, 3H), 3.98 (sept, 1H, *J* = 6.1 Hz), 4.44 (dd, 1H, *J* = 3.9, 8.3 Hz), 4.52 (dd, 1H, *J* = 8.8, 4.4 Hz), 4.58-4.66 (m, 1H), 5.13 (broad s, 1H), 5.70-5.79 (m, 1H), 5.96-6.04 (m, 1H), 6.67 (dd, 1H, *J* = 13.9, 1.7 Hz), 6.95 (dd, 1H, *J* = 11.7, 3.9); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.36, -3.62, 1.24, 5.15, 7.03, 18.45, 22.30,

24.00, 26.10, 30.13, 44.41, 59.88, 65.53, 70.10, 74.78, 89.96, 93.41, 107.25, 123.60, 126.57, 128.19, 146.27, 200.80; IR (neat film on NaCl): 3045 (s), 2959 (m), 2928 (m), 2857 (s), 2174 (m), 1703 (m), 1632 (s), 1462 (m), 1259 (m), 1096 (m), 1032 (m), 841 (s), 802 (s); EI mass spectrum *m/z* (% rel intensity) 594 M^+ (1), 565 (1), 537 (2), 505 (1), 477 (2.5), 461 (1), 433 (2), 425 (2), 411(5), 403 (2), 271 (9), 241 (100), 161 (7), 87 (15), 73 (39), 59 (6). R_f = 0.85 (5:2 pentane/ether).



HWE Olefination-Ketone (*R,R,R*)-212: A solution of LiCl (16.8 mg, 0.4 mmol) in 2 mL of THF was added to a solution of phosphonate (*R,R*)-**3c** (87 mg, 0.182 mmol) in 5 mL of THF at room temperature and stirred for 5 minutes. The solution was then cooled to 0 °C, Et_3N (35.5 μL, 0.255 mmol) was added and the solution stirred for 30 minutes at ambient temperature. At this point, the solution was re-cooled to 0 °C and the purified major isomer of aldehyde (*R*)-**2a** (37.2 mg, 0.218 mmol) was added dropwise in 1 mL of THF. The solution was stirred for 24 h at ambient temperature before being quenched with H_2O (5 mL) and extracted with ether (20 mL). The organic layer was washed with brine and dried on $MgSO_4$. Column chromatography on silica gel (2:5 ether/pentane) gave ketone (*R,R,R*)-**212** in 99 % yield (107.0 mg, 0.180 mmol) as a colorless oil.

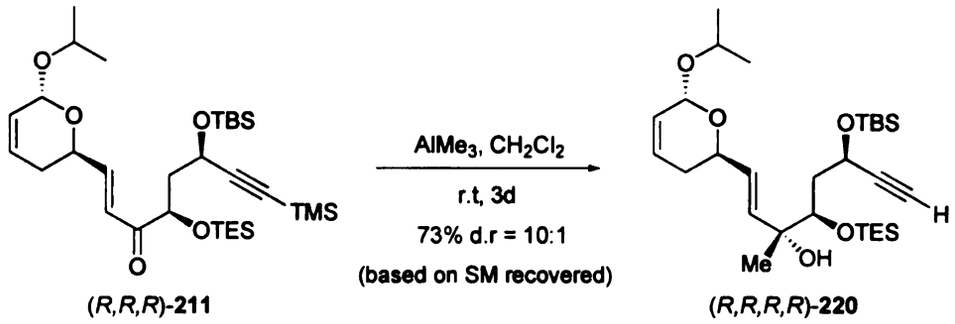
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.12 (s, 12H) 0.16 (s, 3H) 0.88 (s, 18H), 1.15 (d, 3H, J = 6.1 Hz), 1.17 (d, 3H, J = 6.1 Hz), 1.80-1.92 (m, 1H), 1.92-2.18 (m, 3H), 3.97 (sept, 1H, J = 6.3 Hz), 4.38 (dd, 1H, J = 8.2, 4.1 Hz), 4.52 (dd, 1H, J = 8.8, 4.4 Hz), 4.52-4.68 (m, 1H), 5.12 (broad s, 1H), 5.73 (d, 1H, J = 10.4 Hz), 5.94-6.04 (m, 1H), 6.68 (d, 1H, J = 15.7 Hz), 6.94 (dd, 1H, J = 15.5, 4.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.86, -4.56, -4.45, -3.74, -0.31, 18.17, 22.00, 23.81, 25.81, 25.90, 29.83, 44.17, 59.53, 65.33, 69.78, 74.71, 89.81, 93.04, 107.02, 123.40, 126.31, 127.92, 145.95, 200.62, (1 sp^3 C not located); IR (neat film on NaCl): 3045 (s), 2961 (s), 2928 (s), 2857 (s), 2174 (s), 1700 (s), 1636 (s), 1464 (s), 1401 (s), 1362 (s), 1318 (s), 1260 (s), 1096 (s), 1032 (s), 839 (s), 802 (s), cm^{-1}; EI mass spectrum m/z (% rel intensity) 595 (M^++1) (3), 537 (3), 477 (2), 461 (4), 419 (3), 411 (2), 405 (3), 403 (6), 397 (2), 377 (2) 363 (2), 331 (2), 271 (5), 241 (100), 227 (5), 147 (30), 73 (90); R_f = 0.82 (5:2 pentane/ether), $[\alpha]_D$ +6.6° (c 1.0, C_5H_{12}). Anal calcd for $C_{31}H_{58}O_5Si_3$: C 62.57; H 9.82. Found: C 62.23; H 9.50.



HWE Olefination-Ketone (*R,R,R*)-213: A solution of LiCl (3.2 mg, 0.076 mmol) in 0.5 mL of THF was added to a solution of phosphonate (*R,R*)-**3d** (18 mg, 0.038 mmol) in 1 mL of THF at room temperature and stirred for 5 minutes. The solution was

then cooled to 0 °C, Et_3N (7.4 μL, 0.053 mmol) was added and the solution stirred for 30 minutes at ambient temperature. At this point, the solution was re-cooled to 0 °C and the purified major isomer of aldehyde (*R*)-**2a** (7.7 mg, 0.045 mmol) was added dropwise in 0.5 mL of THF. The solution was stirred for 24 h at ambient temperature before being quenched with H_2O (1 mL) and extracted with ether (5 mL). The organic layer was washed with brine and dried over $MgSO_4$. Column chromatography on silica gel (2:5 ether/pentane) gave ketone (*R,R,R*)-**213** in 90% yield (17.7 mg, 0.034 mmol) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.12 (s, 3H) 0.16 (s, 3H) 0.88 (s, 9H), 0.89 (s, 9H), 1.16 (d, 3H, *J* = 5.7 Hz), 1.18 (d, 3H, *J* = 5.8 Hz), 1.85-2.16 (m, 4H), 2.41 (dd, 1H, *J* = 0.8, 1.4 Hz), 3.97 (sept, 1H, *J* = 6.6 Hz), 4.38 (dd, 1H, *J* = 8.0, 4.4 Hz), 4.53 (td, 1H, *J* = 6.9, 2.2 Hz), 4.57-4.64 (m, 1H), 5.12 (d, 1H, *J* = 2.2 Hz), 5.72 (dd, 1H, *J* = 9.9, 1.9 Hz), 5.94-6.04 (m, 1H), 6.69 (d, 1H, *J* = 16.8 Hz), 6.95 (dd, 1H, *J* = 15.7, 4.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.85, -4.69, -4.53, -3.95, 18.18, 22.03, 23.82, 25.80, 25.85, 29.85, 44.21, 59.00, 63.35, 69.84, 73.39, 74.73, 85.05, 93.09, 123.38, 126.33, 127.92, 146.07, 200.59, (1 sp^3 C not located); IR (neat film on NaCl): 3312 (s), 2963 (s), 2926 (s), 2855 (s), 1738 (s), 1373 (s), 1260 (s), 1094 (s), 1022 (s), 800 (s), cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) 523 (M^+ +1) (7), 463 (7), 423 (2), 405 (3), 391 (2), 349 (3), 331 (7), 327 (7), 325 (6), 251 (10), 193 (10), 169 (60), 147 (15), 73 (100); HRMS calcd for $C_{28}H_{50}O_5Si_2$ *m/z* 523.3275, meas 523.3276. R_f = 0.75. (5:2 pentane/ether).



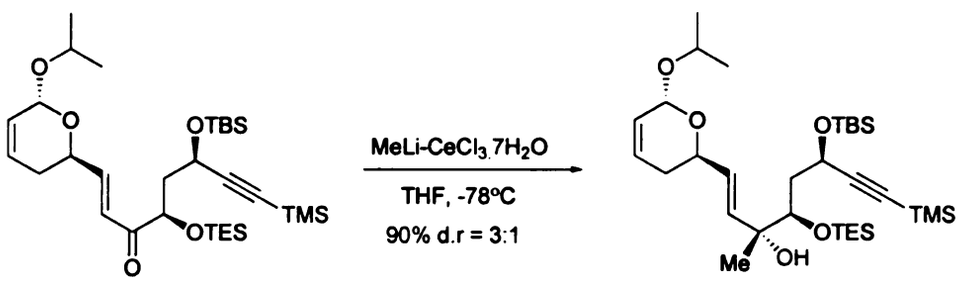
(*R,R,R*)-**211** (*R,R,R,R*)-**220**

Tertiary Alcohol (*R,R,R,R*)-220: To a solution of ketone (*R,R,R*)-**211** (8 mg, 0.014 mmol) in CH_2Cl_2 (3 mL) was added at –15 °C, $AlMe_3$ (2.0 M, 0.056 mmol). The reaction mixture was warmed to 0 °C and stirred at that temperature for 3 h. After no change in TLC occurred, the reaction mixture was raised to ambient temperature and stirred for 3 days. The flask was then recooled to 0 °C and 2 mL of H_2O was added slowly. The organic portion was extracted with CH_2Cl_2 (3 x 5 mL), dried over $MgSO_4$ and concentrated. Column chromatography on silica gel gave (*R,R,R,R*)-**220** in 48% yield (3.6 mg, 0.0067 mmol) as a colorless film. The starting material ketone (*R,R,R*)-**211** was recovered in 40% yield (3.2 mg, 0.0057 mmol). The yield of (*R,R,R,R*)-**220** based on starting material recovered is 73%. Tertiary alcohol (*R,R,R,R*)-**220** was isolated as a 10:1 inseparable mixture of diastereomers. The ratio was determined by intergration of the hydroxyl proton (δ = 2.23 ppm major, δ = 2.26 ppm minor). The stereochemistry of the major diastereomer was assumed to be the $C_8(R)$ epimer based on the stereochemistry observed by Just[32] and Boger[24] in a similar addition to a related molecule.

The following spectral data was taken on a 10:1 mixture of diastereomers.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 6H), 0.63 (q, 6H, *J* = 8.0 Hz), 0.83-1.04 (m, 18H), 1.14 (d, 3H, *J* = 6.0 Hz), 1.19 (d, 3H, *J* = 6.3 Hz), 1.23 (s, 3H), 1.58-1.70 (m, 1H), 1.92-2.10 (m, 3H), 2.23 (s, 1H), 2.41 (d, 1H, *J* = 2.2 Hz), 3.67 (t, 1H, *J* = 5.5 Hz), 3.98 (sept, 1H, J = 6.3 Hz), 4.38-4.54 (m, 2H), 5.09 (s, 1H), 5.69 (d, 1H, J = 10.4 Hz), 5.74-5.86 (m, 2H), 5.92-6.00 (m, 1H). R_f = 0.60 (4 :1 pentane/ether).

Minor isomer: δ = 2.26 (s, 1H) only distinguishable proton.



(*R,R,R*)-**211** (*R,R,R,R*)-**217**

Tertiary Alcohol (*R,R,R,R*)-217: $CeCl_3.7H_2O$ (892 mg, 1.7 mmol) was heated from room temperature to 100 °C overnight under vacuum (0.2 mmHg). At 70 °C to 100 °C heating was allowed to proceed slowly. The temperature was then raised to 140 °C and kept there for 12 h. At this point the reaction flask was allowed to cool to room temperature under argon and 2 mL of THF was added to a grayish-white solid and stirred for 10 h. The solution was then cooled to -78 °C and MeLi (1.49 mL, 1.69 mmol) was added. This reaction was stirred for 10 min at –78 °C and 10 min at room temperature. The reaction mixture was beige/orange in color. The flask was then re-cooled to -78 °C and a single epimer at C_1 of ketone (*R,R,R*)-**211** (18 mg, 0.032 mmol) was added in 1 mL

of dry THF and stirred at the same temperature for 10 mins. A saturated solution of $NaHCO_3$ (2 mL) was used to quench the reaction, which was extracted with CH_2Cl_2 (3 X 5 mL) and chromatographed (4:1 pentane/ether) on silica gel. Alcohol (*R,R,R,R*)-**217** was obtained in 90 % (17.5 mg, 0.029 mmol) as a colorless oil. Tertiary alcohol (*R,R,R,R*)-**217** was isolated as a 3:1 inseparable mixture of diastereomers. The ratio was determined by intergration of the hydroxyl proton (δ = 2.31 ppm major, δ = 2.36 ppm minor). The stereochemistry of the major diastereomer was assumed to be the C_8(*R*) epimer based on the stereochemistry observed by Just[32] and Boger[24] in a similar addition to a related molecule.

The following spectral data was collected on a 3:1 mixture of diastereomers. The ^{1}H NMR and ^{13}C NMR data for the major isomer were extracted from the spectrum of the mixture.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 9H), 0.10-0.14, (m, 6H), 0.63 (q, 6H, *J* = 7.8 Hz), 0.87 (s, 9H), 0.94 (dt, 9H, *J* = 2.7, 7.8 Hz), 1.15 (d, 3H, *J* = 6.0 Hz), 1.18-1.26 (m, 6H), 1.58-1.68 (m, 1H), 1.92-2.13 (m, 3H), 2.31 (d, 1H, *J* = 7.0 Hz), 3.64-3.73 (m, 1H), 3.99 (sept, 1H, *J* = 5.7 Hz), 4.41-4.48 (m, 2H), 5.10 (broad s, 1H), 5.74 (d, 1H, *J* = 10.1 Hz), 5.76-5.82 (m, 2H), 5.95-6.02 (m, 1H).

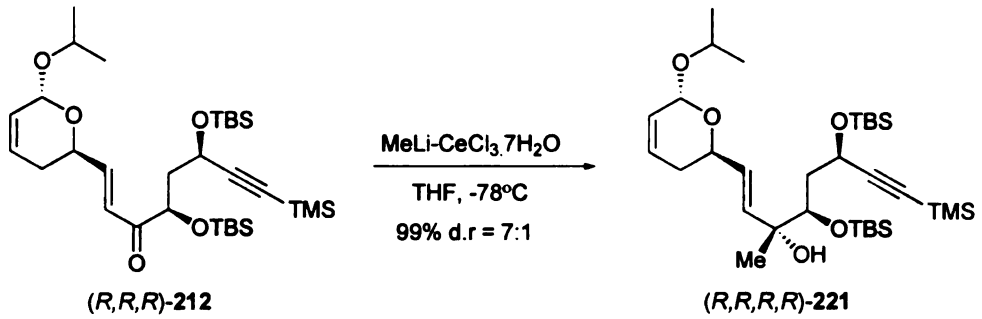
Minor isomer: δ = 2.36 (d, 1H, *J* = 6.7 Hz), only distinguishable proton.

^{13}C NMR (75 MHz, $CDCl_3$): δ -4.38, -3.68, -0.27, 5.38, 6.95, 18.14, 21.97, 23.90, 25.87, 25.98, 29.68, 30.75, 43.10, 60.88, 69.40, 74.89, 75.57, 89.50, 93.03, 107.48, 126.12, 128.51, 129.53, 135.11; IR (neat film on NaCl): 3474 (w), 3045 (s), 2959 (s),

2930 (s), 2901 (s), 2858 (s), 2174 (s), 1464 (s), 1383 (s), 1260 (s), 1096 (s), 1030 (s), 839 (s), 806 (s), 777 (s) cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) (M^+-17) 593 (0.7), 551 (0.4), 493 (0.5), 486 (0.6), 485 (0.6), 461 (0.7), 419 (2), 401 (1), 399 (1), 385 (0.6), 366 (1), 341 (1), 327 (3), 325 (4), 311 (1), 309 (1), 295 (1), 281 (7), 267 (4), 241 (70), 147 (30), 73 (100); HRMS calcd for $C_{32}H_{61}O_4Si_3$ *m/z* 593.38778, meas 593.3874. R_f = 0.56 (4:1 pentane/ether).

The ^1H NMR spectrum of ***(R,R,R,R)*-217** was also taken in CD_3CN to compare to Boger's tertiary alcohol *(R,R,R,R)*-**50**. Major isomer: ^{1}HNMR (300 MHz, CD_3CN): δ -0.03-0.16 (m, 15H), 0.32 (dq, 6H, *J* = 7.8, 4.4 Hz), 0.54 (s, 9H), 0.62 (t, 9H, *J* = 7.8 Hz), 0.76 (d, 3H, J = 5.9 Hz), 0.82 (d, 3H, J = 6.1 Hz), 0.86 (s, 3H), 1.12-1.23 (m, 1H), 1.45-1.59 (m, 3H), 2.83 (d, 1H, *J* = 2.4 Hz), 3.63-3.72 (m, 1H), 3.89-3.97 (m, 1H), 4.37 (m, 1H), 4.47-4.59 (m, 1H), 5.07 (broad s, 1H), 5.63-5.68 (m, 1H), 5.69-5.90 (m, 2H), 5.92-5.99 (m, 1H).

Minor isomer: δ = 2.79 (d, 1H, *J* = 10 Hz), only distinguishable proton.



(*R,R,R*)-**212** (*R,R,R,R*)-**221**

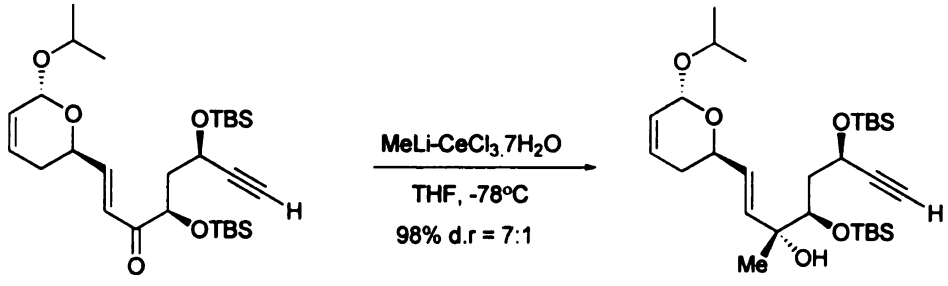
Tertiary Alcohol (*R,R,R,R*)-221: $CeCl_3.7H_2O$ (892 mg, 1.7 mmol) was heated from room temperature to 100 °C overnight under vacuum (0.2 mmHg). At 70 °C to 100 °C heating was allowed to proceed slowly. The temperature was then raised to 140 °C and kept there for 12 h. At this point the reaction flask was allowed to cool to room temperature under argon and 2 mL of THF was added to a grayish-white solid and stirred for 10 h. The solution was then cooled to -78 °C and MeLi (1.49 mL, 1.69 mmol) was added. This reaction mixture was stirred for 10 min at –78 °C and 10 min at room temperature. The solution was beige/orange at this point and was then re-cooled to -78 °C and a single epimer at C_1 of ketone (*R,R,R*)-**212** (50 mg, 0.09 mmol) was added in 2 mL of dry THF and stirred at -78 °C for 10 min. A saturated solution of $NaHCO_3$ (2 mL) was used to quench the reaction, which was extracted with CH_2Cl_2 (3 X 5 mL) and chromatographed (4:1 pentane/ether) on silica gel. Alcohol (*R,R,R,R*)-**221** was obtained in 99 % (54.4 mg, 0.089 mmol) as a colorless oil. Tertiary alcohol (*R,R,R,R*)-**221** was isolated as a 7:1 inseparable mixture of diastereomers. The ratio was determined by intergration of the hydroxyl proton (δ = 2.29 ppm major, δ = 2.35 ppm minor). The stereochemistry of the major diastereomer was assumed to be the C_8(*R*) epimer based on

the stereochemistry observed by Just[32] and Boger[24] in a similar addition to a related molecule.

Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03-0.15 (m, 21H), 0.86 (s, 18H), 1.14 (d, 3H, *J* = 6.3 Hz), 1.16-1.24 (m, 6H), 1.52-1.70 (m, 1H), 1.92-2.14 (m, 3H), 2.29 (s, 1H), 3.67 (t, 1H, *J* = 5.2 Hz), 3.98 (sept, 1H, *J* = 6.0 Hz), 4.36-4.50 (m, 2H), 5.08 (broad s, 1H), 5.69 (d, 1H, *J* = 7.3 Hz), 5.76-5.82 (m, 2H), 5.92-6.02 (m, 1H).

Minor isomer: δ = 2.35 (s, 1H) only distinguishable proton.

^{13}C NMR (75 MHz, $CDCl_3$): δ -4.38, -4.37, -3.85, -3.75, -0.29, 18.18, 18.19, 21.97, 23.89, 25.87, 25.98, 29.67, 30.75, 43.10, 60.87, 66.07, 69.06, 74.96, 75.48, 89.51, 93.02, 107.48, 126.13, 128.49, 129.52, 135.09; IR (neat film on NaCl): 3466 (w), 2963 (s), 2930 (s), 2901 (s), 2859 (s), 2174 (s), 1201 (s), 1095 (s), 1022 (s), 839 (s), 800 (s), cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) (M^+-1) 609 (0.1) 593 (0.7), 551 (0.4), 493 (0.5), 461 (1), 419 (2), 397 (1), 349 (1), 327 (2), 325 (1), 309 (1), 241 (100), 147 (30), 73 (95); R_f = 0.50 (4:1 pentane/ether).



(*R,R,R*)-**213** (*R,R,R,R*)-**222**

Tertiary Alcohol (*R,R,R,R*)-222: $CeCl_3.7H_2O$ (132.4 mg, 0.36 mmol) was heated from room temperature to 100 °C overnight under vacuum (0.2 mmHg). At 70 °C

to 100 °C heating was allowed to proceed slowly. The temperature was then raised to 140 °C and kept there for 12 h. At this point the reaction flask was allowed to cool to room temperature under argon and 1 mL of THF was added to a grayish-white solid and stirred for 10 h. The solution was then cooled to -78 °C and MeLi (0.216 mL, 0.346 mmol) was added. This reaction was stirred for 10 min at –78 °C and 10 min at room temperature. The solution was beige/orange at this point and was then re-cooled to -78 °C and a single epimer at C_1 of ketone (*R,R,R*)-**213** (10.0 mg, 0.019 mmol) was added in 1 mL of dry THF and stirred at -78 °C for 10 min. A saturated solution of $NaHCO_3$ (1 mL) was used to quench the reaction, which was extracted with CH_2Cl_2 (3 X 5 mL) and chromatographed (4:1 pentane/ether) on silica gel. Alcohol (*R,R,R,R*)-**222** was obtained in 98 % (10.0 mg, 0.018 mmol) as a colorless oil. Tertiary alcohol (*R,R,R,R*)-**222** was isolated as a 7:1 inseparable mixture of diastereomers. The ratio was determined by intergration of the hydroxyl proton (δ = 2.23 ppm major, δ = 2.30 ppm minor). The stereochemistry of the major diastereomer was assumed to be the C_8(*R*) epimer based on the stereochemistry observed by Just[32] and Boger[24] in a similar addition to a related molecule.

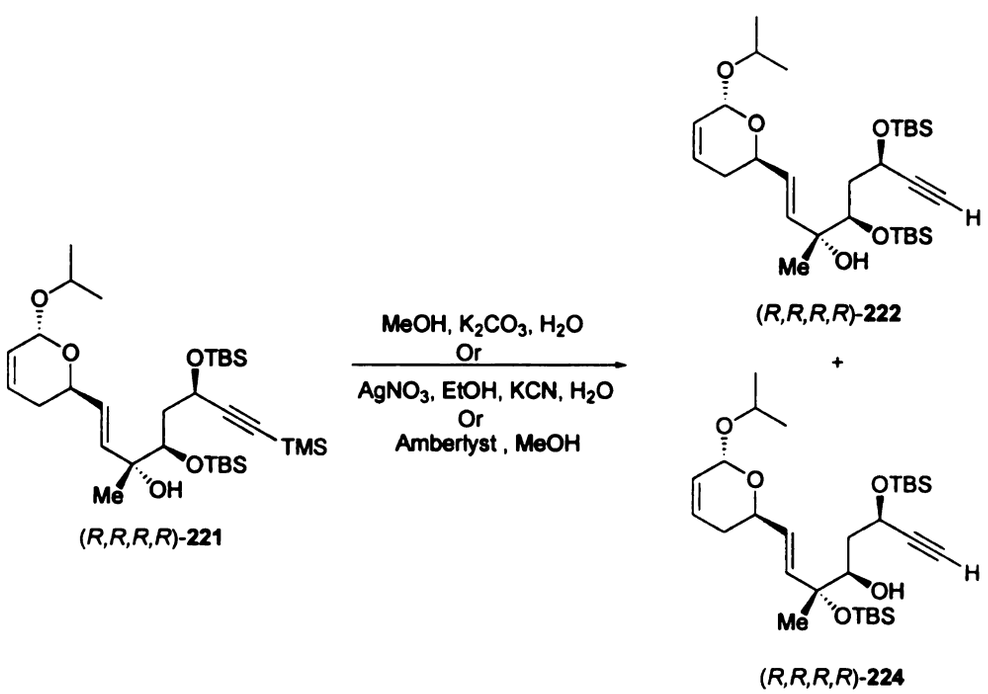
Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.11 (s, 3H), 0.13 (s, 3H), 0.15 (s, 3H), 0.88 (s, 18H), 1.15 (d, 3H, *J* = 6.2 Hz), 1.21 (d, 3H, *J* = 6.0 Hz), 1.24 (s, 3H), 1.58-1.70 (m, 1H), 1.95-2.08 (m, 3H), 2.23 (s, 1H), 2.41 (d, 1H, *J* = 2.7 Hz) 3.68

(t, 1H, J = 4.6 Hz), 3.99 (sept, 1H, J = 6.0 Hz), 4.40-4.52 (m, 2H), 5.09 (broad s, 1H), 5.70 (d, 1H, J = 7.3 Hz), 5.76-5.84 (m, 2H), 5.94-6.02 (m, 1H).

Minor isomer: δ = 2.30 (s, 1H) only distinguishable proton.

^{13}C NMR (75 MHz, $CDCl_3$): δ -4.59, -4.30, -3.95, -3.91, 18.14, 21.97, 23.88, 25.83, 25.95, 29.67, 30.78, 43.34, 60.30, 66.04, 69.42, 73.02, 75.01, 75.54, 85.50, 93.03, 126.15, 128.48, 129.61, 134.93, (1 sp^3 C not located); IR (neat film on NaCl): 3467 (w), 3312 (s), 2957 (s), 2928 (s), 2857 (s), 1258 (s), 1099 (s), 1022 (s), 839 (s), 800 (s), cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) (M^+-17) 521 (10), 479 (6), 461 (5), 421 (8), 389 (8), 347 (12), 327 (59), 267 (15), 169 (100), 147 (30), 129 (22), 115 (60), 97 (25), 75 (70), 73 (99); R_f = 0.34 (4 :1 pentane/ether).

Trimethyl silyl Deprotection of (*R,R,R,R*)-221



(*R,R,R,R*)-**221**

(*R,R,R,R*)-**222**

(*R,R,R,R*)-**224**

Methanol and Potassium Carbonate: To a solution of a 7:1 diastereomeric mixture of alkyne (*R,R,R,R*)-**221** (10 mg, 0.018 mmol) in MeOH (1 mL) at 0 °C, was added K_2CO_3 (5.0 mg, 0.036 mmol) and H_2O (0.125 mL). The mixture was stirred 3 h after which it was quenched with H_2O (1 mL), extracted with EtOAc (3 X 5 mL) and dried on $MgSO_4$. The solution was concentrated on the rotary evaporator and chromatograghed on silica gel with EtOAc/pentane 1:20. Compound (*R,R,R,R*)-**224** was obtained in 40% yield (3.8 mg, 0.007 mmol) in a 7:1 ratio as a colorless oil and compound (*R,R,R,R*)-**222** was obtained in 60% yield (5.8 mg, 0.011 mmol) in a 7:1 ratio as a colorless oil. Compounds (*R,R,R,R*)-**224** and (*R,R,R,R*)-**222** were isolated in a 2:3 ratio and had an R_f values of 0.30 and 0.34 respectively in 20% ether in pentane. The spectral data for compound (*R,R,R,R*)-**222** matches that reported above from the methyl addition to (*R,R,R*)-**213**. Compound (*R,R,R,R*)-**224** was assigned as the compound having the C_8 and C_{11} hydroxyls protected with TBS based on HMQC and HMBC data of a related compound, (*R,R,R,R*)-**247**. Secondary alcohol (*R,R,R,R*)-**224** was isolated as a 7:1 inseparable mixture of diastereomers. The ratio was determined by intergration of the hydroxyl proton (δ = 2.75 ppm major, δ = 2.59 ppm minor). The stereochemistry of the major diastereomer was assumed to be the C_8(*R*) epimer based on the stereochemistry observed by Just[32] and Boger[24] in a similar addition to a related molecule.

Silver Nitrate, Ethanol and Potassium Cyanide: To a solution of alkyne (*R,R,R*)-**221** (10 mg, 0.018 mmol) in EtOH (1 mL) at 0 °C, was added dropwise a solution of $AgNO_3$ (7 mg, 0.041 mmol) dissolved in H_2O (0.3 mL) and EtOH (0.7 mL). Stirring was

continued for 1 h and KCN (12 mg, 0.18 mmol) was added neat. The mixture was stirred for 2.5 h, diluted with ether, washed with H_2O (10 mL) and brine (10 mL), and dried on $MgSO_4$. The solution was concentrated on the rotary evaporator and and the crude oil chromatographed on silica gel as described above. The yield and ratio of (*R,R,R,R*)-**222** and (*R,R,R,R*)-**224** were the same as listed above in the preparation using MeOH, K_2CO_3 and H_2O. Secondary alcohol (*R,R,R,R*)-**224** was isolated as a 7:1 inseparable mixture of diastereomers. The ratio was determined by intergration of the hydroxyl proton (δ = 2.75 ppm major, δ = 2.59 ppm minor). The stereochemistry of the major diastereomer was assumed to be the C_8(*R*) epimer based on the stereochemistry observed by Just[32] and Boger[24] in a similar addition to a related molecule.

Amberlyst A-26 (Chloride Ion Form) in Methanol: To a solution of alkyne (*R,R,R*)-**221** (10 mg, 0.018 mmol) in MeOH (1 mL) was added amberlyst resin A-26 (Cl ion form, 8.0 mg) which was prewashed with MeOH. The reaction was run overnight and then filtered and washed sequentially with MeOH (5 mL), Et_2O (5 mL) and CH_2Cl_2 (5 mL). The combined rinses were concentrated *in vacuo* and the crude oil chromatographed on silica gel as described above. The yield and ratio of (*R,R,R,R*)-**222** and (*R,R,R,R*)-**224** were the same as listed above in the preparation using MeOH, K_2CO_3 and H_2O. Secondary alcohol (*R,R,R,R*)-**224** was isolated as a 7:1 inseparable mixture of diastereomers. The ratio was determined by intergration of the hydroxyl proton (δ = 2.75 ppm major, δ = 2.59 ppm minor). The stereochemistry of the major diastereomer was

assumed to be the $C_8(R)$ epimer based on the stereochemistry observed by Just[32] and Boger[24] in a similar addition to a related molecule.

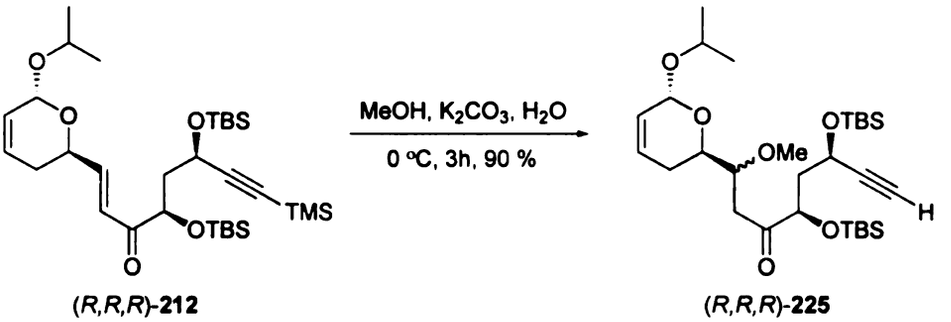
Characterization of (R,R,R,R)-222 and (R,R,R,R)-224.

^{1}H NMR spectrum obtained for tertiary alkynol (*R,R,R,R*)-**222** matches that reported above from the methyl addition to (*R,R,R*)-**213**.

Major isomer: ^{1}H NMR for tertiary alkynol (*R,R,R,R*)-**224:** δ 0.04 (s, 3H), 0.06 (s, 3H), 0.10 (s, 3H), 0.12 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 1.15 (d, 3H, J = 6.0 Hz), 1.20 (d, 3H, J = 6.6 Hz), 1.23 (s, 3H), 1.75-1.89 (m, 1H), 1.98-2.10 (m, 3H), 2.35 (s, 1H), 2.75 (broad s, 1H) 3.68 (d, 1H, J = 9.4 Hz), 3.97 (sept, 1H, J = 6.0 Hz), 4.38-4.48 (m, 1H), 4.55-4.64 (m, 1H), 5.08 (broad s, 1H), 5.65-5.84 (m, 3H), 5.94-6.04 (m, 1H).

Minor isomer: δ = 2.59 (s, 1H) only distinguishable proton.

^{13}C NMR (75 MHz, $CDCl_3$): δ -5.18, -4.44, -1.98, -1.89, 18.35, 18.43, 22.41, 24.13, 25.93, 26.10, 29.92, 30.84, 39.67, 60.72, 66.42, 70.03, 72.36, 74.93, 85.68, 93.54, 126.48, 128.63, 130.81, 134.82, (1 sp^3 C not located); IR (neat film on NaCl): 3468 (w), 3312 (s), 2957 (s), 2930 (s), 2859 (s), 1385 (s), 1254 (s), 1090 (s), 1032 (s), 1005 (s), 838 (s), 800 (s), 777 (s) cm^{-1}; R_f = 0.30 (4 :1 pentane/ether).

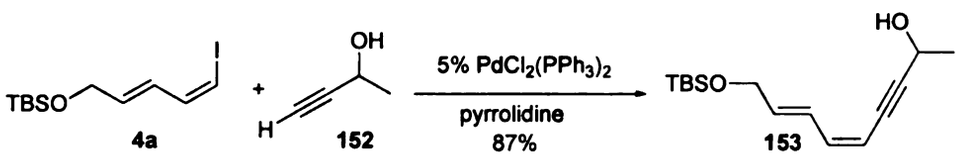


(*R,R,R*)-**212** (*R,R,R*)-**225**

Ketone (*R,R,R*-225): To a solution of alkyne (*R,R,R*)-**212** (10 mg, 0.018 mmol) in MeOH (0.5 mL) at 0 °C, was added K_2CO_3 (5.02 mg, 0.036 mmol) and H_2O (0.125 mL). The mixture was stirred 3 h after which it was quenched with H_2O (1 mL), extracted with EtOAc (5 mL) and dried over $MgSO_4$. The solution was concentrated on the rotary evaporator and chromatograghed on silica gel with EtOAc/pentane 2:5. Ketone (*R,R,R*)-**225** was obtained as a 2:1 ratio of diastereomers in 90% (9.0 mg, 0.016 mmol) as a colorless oil. It is assumed that the ratio of Michael products at C_6 is the only unknown stereogenic center since ^1H NMR shows no epimerization at C_9. Ketone (*R,R,R,R*)-**225** was isolated as a 2:1 inseparable mixture of diastereomers. The ratio was determined by intergration of the acetal proton (δ = 5.04 ppm major, δ = 5.08 ppm minor). The stereochemistry of the major diastereomer was not determined.

(Spectra was obtained as a 2:1 mixture): ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.11 (s, 3H), 0.15 (s, 3H), 0.88 (m, 9H), 0.89 (s, 9H), 1.13-1.24 (m, 6H), 1.80-2.15 (m, 4H), 2.40-2.42 (m, 1H), 2.58 (ddd, 1H *J* = 28.4, 17.2, 3.0 Hz), 2.90 (ddd, 1H, *J* = 32.3, 17.3, 9.1 Hz), 3.37 (s, 3H), 3.75-3.88 (m, 1H), 3.90-4.04 (m, 2H), 4.26 (dd, 1H, J = 7.3, 5.2 Hz), 4.45-4.58 (m, 1H), 5.04 (s, 1H), 5.58-5.74 (m, 1H), 5.92-6.04 (m, 1H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ -4.72, -4.03, 1.00, 18.15, 21.67, 23.84, 25.79, 25.82, 29.69, 39.60, 43.46, 58.93, 67.51, 68.91, 73.43, 74.71, 75.78, 78.80, 84.95, 92.50, 126.00, 128.28, 210.26, (2 sp^3 C not located); IR (neat film on NaCl): 3312 (s), 2957 (s), 2930 (s), 2858 (s), 1727 (s), 1472 (s), 1385 (s), 1258 (s), 1098 (s), 1018 (s), 839 (s) cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) (M^+-1) 553 (1), 495 (12), 463 (5), 461 (5), 437 (3), 405 (6), 385 (3), 363 (15), 353 (4), 331 (15), 169 (99), 147 (30), 136 (18), 115 (60), 73 (100); HRMS calcd for $C_{30}H_{56}O_5Si_2$ *m/z* 553.3745, meas 553.3749. R_f = 0.67 (5:2 pentane/ether).

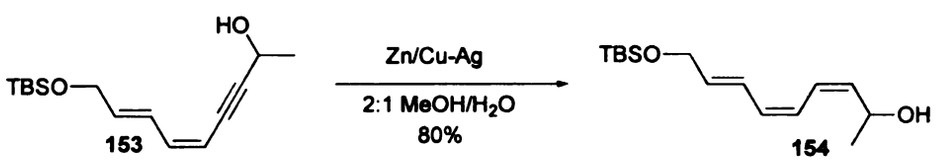


[a]**Dienyne 153**. A 100 mL round-bottom flask was charged with $PdCl_2(PPh_3)_2$ (702 mg, 1.0 mmol) and dissolved in 30 mL freshly distilled pyrrolidene under argon. The flask was wrapped with aluminium foil, and iododiene **4a** (6.49 g, 20 mmol) as the pure *E,Z*-isomer was added neat via cannula. The solution darkened slightly, and was briefly stirred before 3-butyn-2-ol (1.402 g, 1.57 mL, 20 mmol) was added in one portion via syringe. The reaction was stirred at room temperature and followed by TLC until the starting material had disappeared.

The reaction was quenched by adding excess saturated NH_4Cl solution at 0 °C, and then the mixture was further diluted with 150 mL ether. The mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was extracted with

ether (2 x 60 mL). The combined organic layers were washed with saturated NH_4Cl (1 x 150 mL), saturated $Na_2S_2O_3$ (1 x 100 mL), water (2 x 100 mL), and brine (1 x 80 mL), dried over anhydrous $MgSO_4$, and concentrated to a thick brown oil. The oil was taken up in approximately 30 mL of ether and stored at –40 °C overnight, giving an orange solution containing a precipitated orange solid. The solid was filtered off through Celite, and the orange solution was concentrated to an orange oil. This oil was purified by chromatography on silica gel (4:1 pentane/ether – UV visualization) to give the product **153** in 87% yield (4.66 g, 17.5 mmol) as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.88 (s, 9H), 1.50 (d, 3H, J = 6.5 Hz), 4.29 (d, 2H, J = 4.3 Hz), 4.68 (dq, 1H, J = 1.7, 6.6 Hz), 5.42 (d, 1H, J = 10.4 Hz), 5.95 (dt, 1H, J = 15.3, 4.6 Hz), 6.40 (t, 1H, J = 10.9 Hz), 6.78 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.84, 18.79, 24.83, 26.05, 59.36, 63.51, 81.44, 97.35, 108.20, 126.70, 137.04, 140.20; IR (neat film on NaCl): 3360 (m), 2980-2850 (m), 1463 (s), 1362 (m), 1256 (m), 1073 (s), 837 (m), 777 (m) cm^{-1}; R_f = 0.38 (4 :1 pentane/ether).



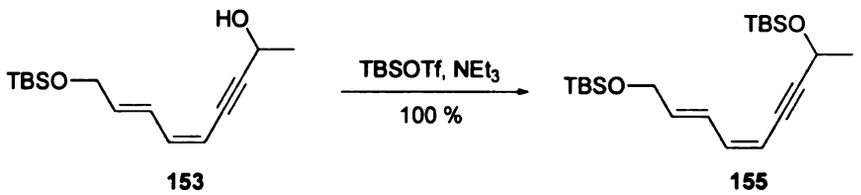
[a]**Activated Metal Reduction to Give Triene 154.** A 100 mL flask was charged with zinc dust (10 g, 0.154 mol, 99.9%, 150-325 mesh, Alfa/Aesar), suspended in 50 mL HPLC grade water and sparged with argon for 15 min. Anhydrous copper (II) acetate (1.0

g, 0.006 mol) was added, the flask was capped with a rubber septum, and the slurry was stirred for 15 minutes. Silver nitrate (1.0 g, 0.006 mol) was then added and the flask warmed noticeably while stirring was continued for 30 minutes. The black suspension of activated metal was isolated by filtration on a Buchner funnel followed by sequential washings with HPLC grade water, methanol, acetone, and ether.

The black solid was immediately added to a solution of dienyne **153** (133 mg, 0.5 mmol) in 15 mL of 2:1 methanol/water. The contents of the flask was placed under an argon atmosphere and stirred for 20 h. The reaction mixture was filtered through Celite and the black metal filter cake was rinsed with 50 mL ether. The liquid was poured into a separatory funnel and the aqueous layer was extracted with ether (2 x 30 mL). The combined organic layers were washed with brine (1 x 50 mL), dried over anhydrous $MgSO_4$, and concentrated to a yellow oil. The oil was purified by chromatography on silica gel (5:1 hexane/EtOAc, UV/$KMnO_4$ visualization) to give the product triene **154** (100 mg, 0.37 mmol) in 74.6% yield as a pale yellow oil. TLC showed only one spot at R_f = 0.28 (5:1 hexanes/EtOAc). No over reduced products were isolated or observed.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.93 (s, 9H), 1.29 (d, 3H, *J* = 6.3 Hz), 4.27 (d, 2H, *J* = 1.35 Hz), 4.82 (m, 1H), 5.52 (t, 1H, *J* = 10.1 Hz), 5.81 (dt, 1H, *J* = 15.0, 4.9 Hz), 6.07 (t, 1H, *J* = 10.9 Hz), 6.18 (t, 1H, *J* = 11.5 Hz), 6.40 (t, 1H, *J* = 11.4 Hz), 6.67 (t, 1H, *J* = 11.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.37, 14.66, 23.35, 25.84, 63.40, 63.83, 122.92, 123.99, 124.27, 130.63, 135.23, 135.56; IR (neat film on NaCl): 3370 (w), 2959 (m), 2855 (m), 1426 (w), 1253 (m), 1121 (m), 1056 (m), 835 (s), 775 (m)

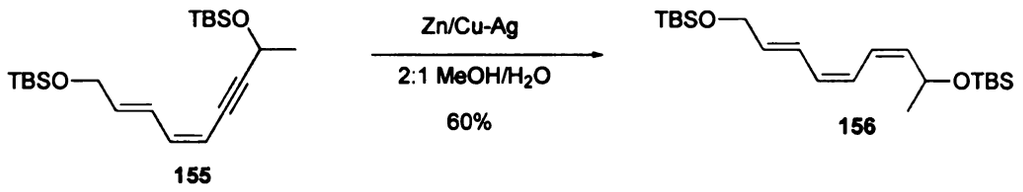
cm^{-1}; EI mass spectrum *m/z* (% rel intensity) (M^+-29) 239 (2), 226 (2), 211 (3), 197 (6), 183 (5), 169 (7), 145 (7), 117 (43), 89 (46), 75 (100), 59 (23); R_f = 0.28 (5 : 1 hexane/EtOAc); Anal calcd for $C_{15}H_{28}O_2Si$: C 67.11, H 10.51. Found: C 67.13, H 10.46.



153 155

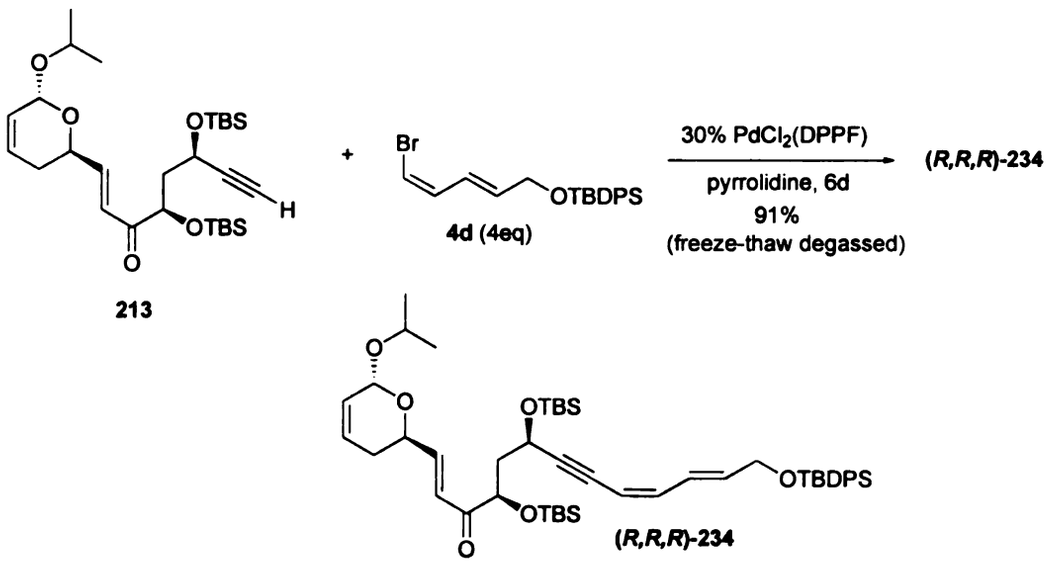
Dienyne 229. The proceedure was the same as that for compound **202** and was run on a 0.188 mmol scale. Dienyne **229** (71.4 mg, 0.188 mmol) was obtained as a colorless oil in 100% yield.

^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.11 (d, 6H, *J* = 3.0 Hz), 0.89 (s, 9H), 0.90 (s, 9H), 1.42 (d, 3H, *J* = 6.6 Hz), 4.59 (d, 2H, *J* = 3.3 Hz), 4.67 (dq, 1H, *J* = 1.9, 6.6 Hz), 5.4 (d, 1H, *J* = 10.7 Hz), 5.88 (dt, 1H, *J* = 15.1, 5.2 Hz), 6.33 (t, 1H, *J* = 11.0 Hz), 6.68-6.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.31, -4.99, -4.60, 18.17, 18.31, 25.43, 25.76, 25.88, 59.48, 63.29, 80.20, 97.83, 108.43, 126.72, 136.02, 139.11, (1 Sp^3 C not located). R_f = 0.2 (100:1 hexane/EtOAc).



Activated Metal Reduction to Give Triene 156. The procedure was the same as that for compound **154**, and was run on a 0.0635 mmol scale. Triene **156** (14.5 mg, 0.038 mmol) was obtained as a colorless oil in 60% yield. TLC showed only one spot at R_f = 0.36 (99:1 pentane/EtO_2). No over reduced products were isolated or observed.

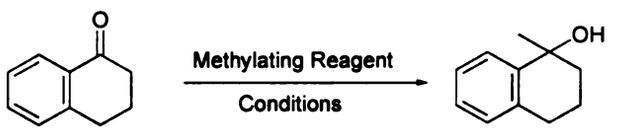
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.85 (s, 9H), 0.90 (s, 9H), 1.19 (d, 3H, *J* = 6.3 Hz), 4.24 (d, 1H, *J* = 4.9 Hz), 4.76 (quintet, 1H, *J* = 7.4 Hz), 5.48 (t, 1H, *J* = 10.4 Hz), 5.81 (dt, 1H, *J* = 14.8, 5.0 Hz), 6.04 (t, 1H, *J* = 11.3 Hz), 6.14 (t, 1H, *J* = 11.3 Hz), 6.30 (t, 1H, *J* = 11.3 Hz), 6.68 (dd, 1H, *J* = 14.8, 11.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.95, -4.47, -4.20, 18.45, 24.91, 24.99, 26.11, 63.74, 65.25, 121.62, 123.59, 124.76, 129.81, 134.81, 137.69, (1 sp^3 C not located); IR (neat film on NaCl): 2957 (m), 2928 (m), 2857 (m), 2363 (m), 2336 (m), 1653 (s), 1474 (s), 1458 (s), 1256 (s), 1123 (m), 1078 (m), 1005 (m), 835 (m), 775 (m); EI mass spectrum *m/z* (% rel intensity) 382 M^+ (18), 325 (18), 250 (38), 237 (45), 189 (18), 147 (100), 119 (34), 91 (25), 73 (98); Yield: 14.5 mg (60%).



Alkyne (*R,R,R*)-234: To a solution of pure *E,Z*-bromide **4d** (45 mg, 0.116 mmol) in 1.5 mL of freshly distilled pyrrolidine, was added $Pd(dppf)_2Cl_2$ (7 mg, 0.0087 mmol) and pure ketone **213** (15 mg, 0.029 mmol) in 1 mL of pyrrolidine. The reaction was freeze-thaw degassed (3 cycles) and left under an argon atmosphere for 6 days at ambient temperature. The reaction was quenched with saturated NH_4Cl (2 mL), diluted with ether (5 mL) and the water layer extracted three times with ether (5 mL each). The combined organic layers were washed with water (5 mL) and brine (5 mL) and dried over $MgSO_4$. Column chromatography on silica gel with 20:1 pentane to ether gave 91% of fostriecin core **234** (22 mg, 0.026 mmol) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.05 (s, 3H), 0.13 (s, 3H), 0.16 (s, 3H), 0.90 (s, 9H), 0.91 (s, 9H), 1.06 (s, 9H), 1.16 (d, 3H, J = 6.2 Hz), 1.18 (d, 3H, J = 6.2 Hz), 1.88-1.98 (m, 1H), 1.98-2.15 (m, 3H), 3.97 (sept, 1H, J = 6.2 Hz), 4.29 (d, 2H, J = 4.6 Hz), 4.42 (dd, 1H, J = 8.2, 3.3 Hz), 4.54-4.66 (m, 1H), 4.70-4.88 (m, 1H), 5.12 (broad s, 1H), 5.40 (d, 1H, J = 10.6 Hz), 5.74 (d, 1H, J = 10.2 Hz), 5.93 (dt, 1H, J = 15.2, 4.9

Hz), 5.96-6.04 (m, 1H), 6.36 (t, 1H, J = 10.8 Hz), 6.69 (dd, 1H, J = 15.8, 1.8 Hz), 6.72-6.84 (m, 1H), 6.94 (dd, 1H, J = 17.2, 4.2 Hz), 7.33-7.47 (m, 6H), 7.64-7.69 (m, 4H); R_f = 0.69 (10:1 pentane/ether).

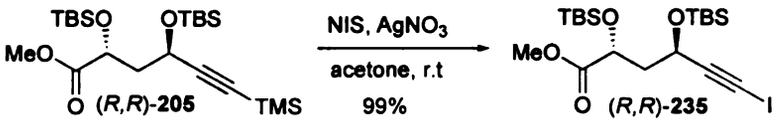


218 **219**

219 from Methylation of 218. The procedure was the same as that for (*R,R,R,R*)-**220** and run on a 0.0075 mmol scale. Yield (99%, 0.0074 mmol).[106]

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 3H), 1.76-1.97 (m, 4H), 2.70-2.88 (m, 2H), 7.04-7.09 (m, 1H), 7.13-7.24 (m, 2H), 7.58 (dd, 1H, J = 7.5, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.37, 29.89, 30.69, 39.71, 70.55, 126.29, 126.31, 127.03, 128.76, 136.20, 142.83; white solid.

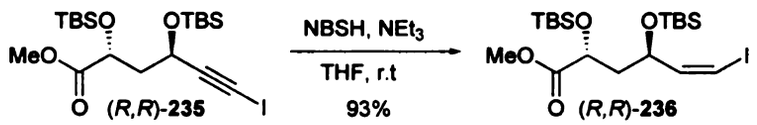
Experimental data for Chapter 5.



Iodoacetylene (*R,R*)-235: To a solution of TMS protected alkyne (*R,R*)-**205** (30 mg, 0.066 mmol) in 4 mL of acetone was added $AgNO_3$ (12.3 mg, 0.072 mmol) and NIS (17.8 mg, 0.079 mmol). The solution was stirred for 3 hours then cooled to 0 °C and diluted with 5 mL of EtOAc. The reaction was quenched with 5 mL of H_2O. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the organic layers combined and dried over Na_2SO_4. The solution was concentrated on the rotary evaporator and chromatographed on silica gel (pentane/EtOAc 10:1). Iodoacetylene (*R,R*)-**235** was obtained as a colorless oil in 99% yield (33 mg, 0.065 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.06 (s, 3H), 0.10 (s, 3H), 0.13 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.90-2.16 (m, 2H), 3.70 (s, 3H), 4.34 (dd, 1H, J = 8.0, 4.1 Hz), 4.69 (dd, 1H, J = 8.4, 4.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.26, -4.80, -4.68, -4.03, 18.19, 18.24, 25.75, 25.82, 44.52, 51.90, 60.05, 68.64, 95.49, 173.71 (1sp C not located); IR (neat film on NaCl): 2957 (s), 2930 (s), 2859 (s), 1759 (s), 1472 (s), 1385 (s), 1252 (s), 1094 (s), 837 (s), 779 (s), 667 (s) cm^{-1}; EI mass spectrum *m/z* (% rel intensity) 497 M^+ -15 (1), 455 (7), 369 (1), 323 (3), 295 (7), 291 (8), 229 (4), 189 (5), 147 (12), 115

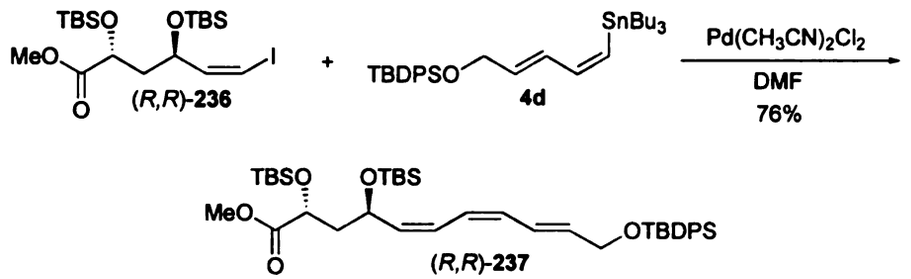
(5), 89 (40), 73 (100), 57 (25). Anal calcd for $C_{19}H_{37}IO_4Si_2$: C 44.52, H 7.28. Found: C 44.41, H 7.49. R_f = 0.60 (10:1 pentane/EtOAc) $[\alpha]_D$ 44.4° (*c* 1.0, acetone).



Vinyl Iodide (*R,R*)-236: To a solution of iodoacetylene (*R,R*)-**235** (26 mg, 0.051 mmol) in 0.5 mL of THF and 0.5 mL of ^{i}PrOH was added Et_3N (11 μL, 0.076 mmol) and NBSH[100] (22 mg, 0.102 mmol). The mixture was stirred for 14 hours then quenched with 2 mL of saturated $NaHCO_3$ and diluted with 4 mL of EtOAc. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the organic layers combined and dried over Na_2SO_4. The solution was concentrated on the rotary evaporator and chromatographed on silica gel (Pentane/EtOAc 10:1). Vinyl iodide (*R,R*)-**236** was obtained as a colorless oil in 93% yield (24.3 mg, 0.047 mmol).

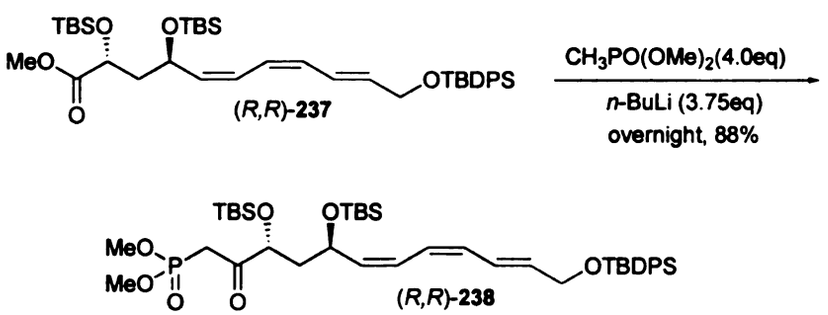
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.07 (s, 6H), 0.08 (s, 3H), 0.86 (s, 9H), 0.92 (s, 9H), 1.74 (ddd, 1H, *J* = 13.7, 8.2, 3.3 Hz), 1.93 (ddd, 1H, *J* = 13.8, 7.1, 3.6 Hz), 3.68 (s, 3H), 4.35 (dd, 1H, *J* = 8.2, 3.3 Hz), 4.57 (ddd, 1H, *J* = 8.8, 7.1, 3.6 Hz), 6.12-6.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.10, -4.68, -4.51, -3.57, 17.98, 18.23, 25.83, 44.80, 51.71, 68.69, 72.32, 80.54, 143.69, 174.11, (1 sp^3 C not located); IR (neat film on NaCl): 2955 (s), 2930 (s), 2859 (s), 1757 (s), 1472 (s), 1362 (s), 1258 (s), 1134 (s), 1092 (s), 1005 (s), 837 (s) cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) 515 M^+ +1

(10), 499 (10), 457 (69), 383 (30), 325 (20), 297 (50), 283 (18), 251 (15), 229 (20), 203 (30), 154 (20), 147 (25), 136 (30), 115 (20), 89 (35), 73 (100), 59 (15). Anal calcd for $C_{19}H_{39}IO_4Si_2$: C 44.35, H 7.64. Found: C 44.31, H 8.02. R_f = 0.56 (10:1 pentane/EtOAc) $[\alpha]_D$ 33.2° (*c* 1.0, ether).



Triene (*R,R*)-237: To a solution of vinyl iodide (*R,R*)-**236** (10 mg, 0.0195 mmol) and stannane **4d** (47 mg, 0.078 mmol) in dry DMF in a Schlenk flask was added $Pd(CH_3CN)_2Cl_2$ (0.5 mg, 0.002 mmol). The solution was freeze-thaw degassed (3 cycles) and sealed under an argon atmosphere. The Schlenk flask was wrapped in foil and the solution stirred at 0 °C for 24 h. The reaction mixture was diluted with 4 mL of Et_2O and quenched with 2 mL of saturated $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the organic layers combined and dried over Na_2SO_4. The solution was concentrated on the rotary evaporator and chromatographed on silica gel (pentane/EtOAc 10:1). Triene (*R,R*)-**237** was obtained as a yellow oil in 76% yield (10.5 mg, 0.0148 mmol).

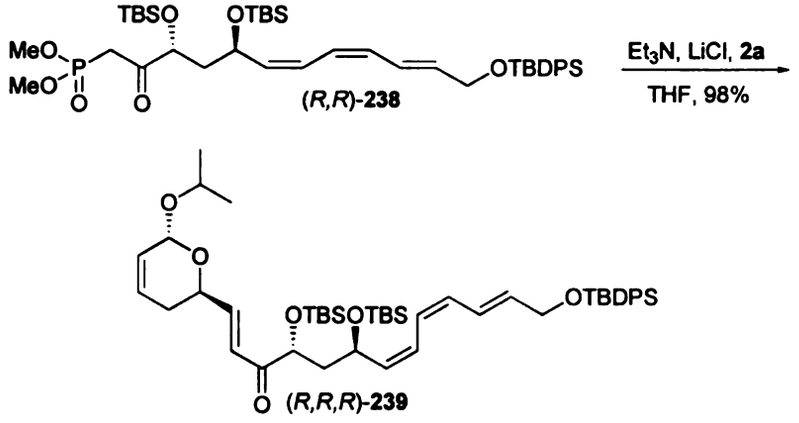
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.017 (s, 3H), 0.021 (s, 3H), 0.05 (s, 3H), 0.06 (s, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 1.05 (s, 9H), 1.75 (ddd, 1H, *J* = 13.3, 8.2, 3.3 Hz), 1.93 (ddd, 1H, *J* = 13.3, 7.1, 3.6 Hz), 3.66 (s, 3H), 4.26 (d, 2H, *J* = 4.7 Hz), 4.33 (dd, 1H, *J* = 3.9 Hz), 4.76-4.88 (m, 1H), 5.40 (t, 1H *J* = 9.9 Hz), 5.80 (dt, 1H, *J* = 15.1, 4.9 Hz), 6.03 (t, 1H, *J* = 10.8 Hz), 6.16 (t, 1H, *J* = 12.1 Hz), 6.33 (t, 1H, *J* = 11.0 Hz), 6.72 (dd, 1H, *J* = 12.6, 13.5 Hz), 7.30-7.44 (m, 6H), 7.65 (dd, 4H, *J* = 6.6, 0.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.09, -4.62, -4.60, -3.51, 18.17, 18.28, 19.28, 25.82, 25.97, 26.86, 44.48, 51.70, 64.22, 65.08, 69.24, 123.11, 123.31, 124.52, 127.71, 129.71, 130.18, 133.60, 134.33, 135.04, 135.59, 174.29; IR (neat film on NaCl): 2957 (s), 2924 (s), 2853 (s), 1755 (s), 1620 (s), 1462 (s), 1260 (s), 1094 (s), 801 (s), 702 (s) cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) 708 M^+ (1), 693 (1), 651(6), 577 (5), 519 (6), 491 (4), 452 (5), 327 (6), 321 (11), 229 (15), 197 (60), 147 (40), 135 (99), 89 (40), 73 (100), 59 (22); HRMS calcd for $C_{40}H_{64}O_5Si_3$ *m/z* 708.4065, meas 708.4062. R_f = 0.56 (10:1 pentane/EtOAc). $[\alpha]_D$ 3.6° (*c* 1.0, ether).



Phosphonate (*R*,*R*)-238. To a solution of dimethyl methyl phosphonate (24.5 μL, 0.226 mmol) in 2 mL of dry toluene at –78 °C was added *n*-BuLi (1.6 M, 132.4 μL, 0.212 mmol). After 1 h, a solution of ester (*R*,*R*)-**237** (40 mg, 0.057 mmol) in 1 mL of dry toluene was added and the reaction mixture stirred at –78 °C for 30 min. The reaction mixture was quenched with 2 mL of saturated $NaHCO_3$ and diluted with CH_2Cl_2 (8 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 5 mL) and the organic layers combined and dried over Na_2SO_4. The solution was concentrated and the product was purified by column chromatography (1:1 pentane/EtOAc) to give (*R*,*R*)-**238** as a yellow oil in 88% yield (40.1 mg, 0.05 mmol).

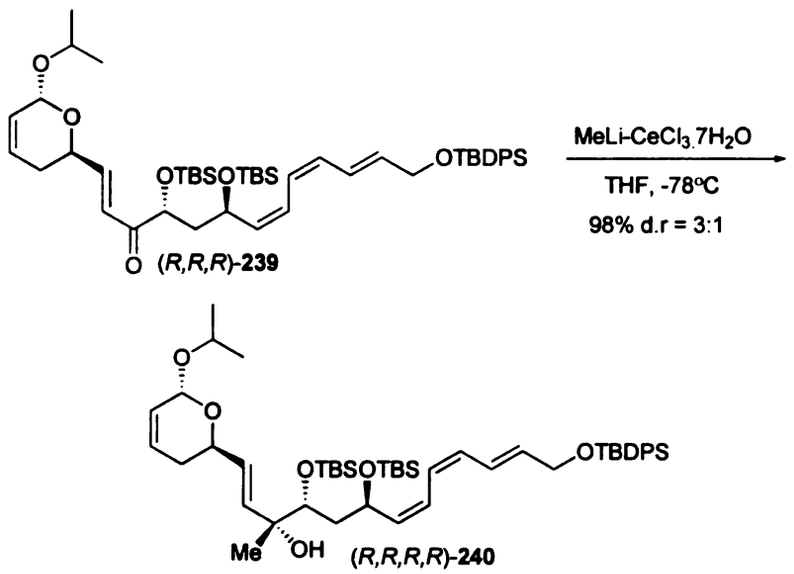
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.02 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 1.05 (s, 9H), 1.62-1.75 (m, 1H), 1.83-2.00 (m, 1H), 3.10 (dd, 1H, *J* = 22.4, 15.1 Hz), 3.22 (dd, 1H, *J* = 21.2, 15.4 Hz), 3.73 (d, 3H, *J* = 2.5 Hz), 3.76 (d, 3H, *J* = 2.5 Hz), 4.26 (d, 2H, *J* = 4.4 Hz), 4.26-4.30 (m, 1H), 4.74-4.85 (m, 1H), 5.37 (t, 1H *J* = 10.2 Hz), 5.81 (dt, 1H, *J* = 15.1, 4.9 Hz), 6.04 (t, 1H, *J* = 10.4 Hz), 6.16 (t, 1H, *J* = 10.7 Hz), 6.34 (t, 1H, *J* = 11.5 Hz), 6.74 (dd, 1H, *J* = 15.6, 11.3 Hz), 7.31-7.42 (m, 6H), 7.65 (d, 4H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.85, -4.70, -4.69, -3.66, 18.09, 19.22, 25.79, 25.89, 26.80, 35.43 (d, *J* = 134.1 Hz), 43.23, 52.88, 64.14, 65.12, 75.82, 123.03, 123.48, 124.34, 127.67, 129.68, 130.54, 133.49, 134.57, 134.69, 135.52, 203.96, (1 sp^3 C not located); FAB mass spectrum *m/z* (% rel intensity) 807 M^+ +7 (4), 743 (2), 537 (2), 469 (2), 461 (2), 413 (6), 401 (5), 355 (6), 341 (6), 327 (8), 325 (8), 281 (16), 252 (100), 221 (20), 207 (24), 147 (55), 123 (75), 106 (20), 73 (99), 59

(22); Anal calcd for $C_{42}H_{69}O_7PSi_3$ C 62.96, H 8.68. Found: C 62.60, H 8.26. R_f = 0.79 (1:1 pentane/EtOAc).



HWE Olefination-Ketone (*R,R,R*)-239. A solution of LiCl (3.0 mg, 0.070 mmol) in 3 mL of THF was added to a solution of phosphonate (*R,R*)-**238** (40 mg, 0.050 mmol) in 1 mL of THF at room temperature and stirred for 5 minutes. The solution was then cooled to 0 °C and Et_3N (9.76 μL, 0.070 mmol) was added and the solution stirred for 30 minutes at ambient temperature. At this point, the solution was re-cooled to 0 °C and the purified major isomer of aldehyde (*R*)-**2a** (25.5 mg, 0.150 mmol) was added dropwise. The flask was wrapped in foil and the solution was stirred overnight at ambient temperature. The solution was then quenched with H_2O (5 mL) and extracted with ether (10 mL). The organic layer was washed with brine and dried over $MgSO_4$. Column chromatography (2:5 ether/pentane) gave the purified ketone (*R,R,R*)-**239** in 98 % yield (40.1 mg, 0.048 mmol) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 1.05 (s, 9H), 1.15 (d, 3H, *J* = 6.4 Hz), 1.17 (d, 3H, *J* = 6.4 Hz) 1.67 (ddd, 1H, *J* = 4.4, 7.6, 13.7 Hz), 1.87 (ddd, 1H, *J* = 4.4, 8.2, 13.4 Hz), 2.01-2.09 (m, 2H), 3.97 (sept, 1H, *J* = 6.4 Hz), 4.26 (d, 2H, *J* = 4.4 Hz), 4.34 (dd, 1H, *J* = 8.3, 3.9 Hz), 4.57 (dd, 1H, *J* = 9.5, 5.8 Hz), 4.81 (td, 1H, *J* = 8.3, 4.4 Hz), 5.11 (s, 1H), 5.40 (t, 1H *J* = 9.8 Hz), 5.72 (d, 1H, *J* = 7.3 Hz), 5.82 (dt, 1H, *J* = 15.1, 5.4 Hz), 5.94-6.01 (m, 1H), 6.04 (t, 1H, *J* = 11.2 Hz), 6.19 (t, 1H, *J* = 11.2 Hz), 6.32 (t, 1H, *J* = 11.2 Hz), 6.65 (ddd, 1H, *J* = 16.1, 4.8, 2.0 Hz), 6.64-6.75 (m, 1H), 6.91 (dd, 1H, *J* = 15.6, 4.4 Hz), 7.33-7.43 (m, 6H), 7.65 (dd, 4H, *J* = 6.3, 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.80, -4.64, -4.38, -3.49, 18.16, 18.23, 19.28, 22.07, 23.86, 25.86, 25.98, 26.85, 29.88, 44.13, 64.19, 65.29, 69.84, 75.18, 77.25, 93.09, 123.18, 123.23, 123.65, 124.44, 126.31, 127.71, 128.02, 129.71, 130.31, 133.56, 134.46, 135.13, 135.57, 145.69, 201.12; IR (neat film on NaCl): 2959 (s), 2922 (s), 2851 (s), 1653 (s), 1559 (s), 1462 (s), 1260 (s), 1094 (s), 1022 (s), 801 (s) cm^{-1}; FAB mass spectrum *m/z* (% rel intensity) 844 M^+ (0.5), 785 (0.5), 713 (0.9), 653 (0.8), 517 (1.2), 505 (3.9), 491 (2.3), 457 (1.6), 373 (2.5), 340 (2.8), 301 (2.5), 239 (8), 223 (6), 209 (8), 197 (40), 171 (14), 147 (16), 135 (76), 73 (100); HRMS calcd for $C_{49}H_{76}O_6Si_3$ *m/z* 844.4955, meas 844.4950. R_f = 0.40 (10:1 pentane/EtOAc). $[\alpha]_D$ 13.8° (*c* 1.0, ether).

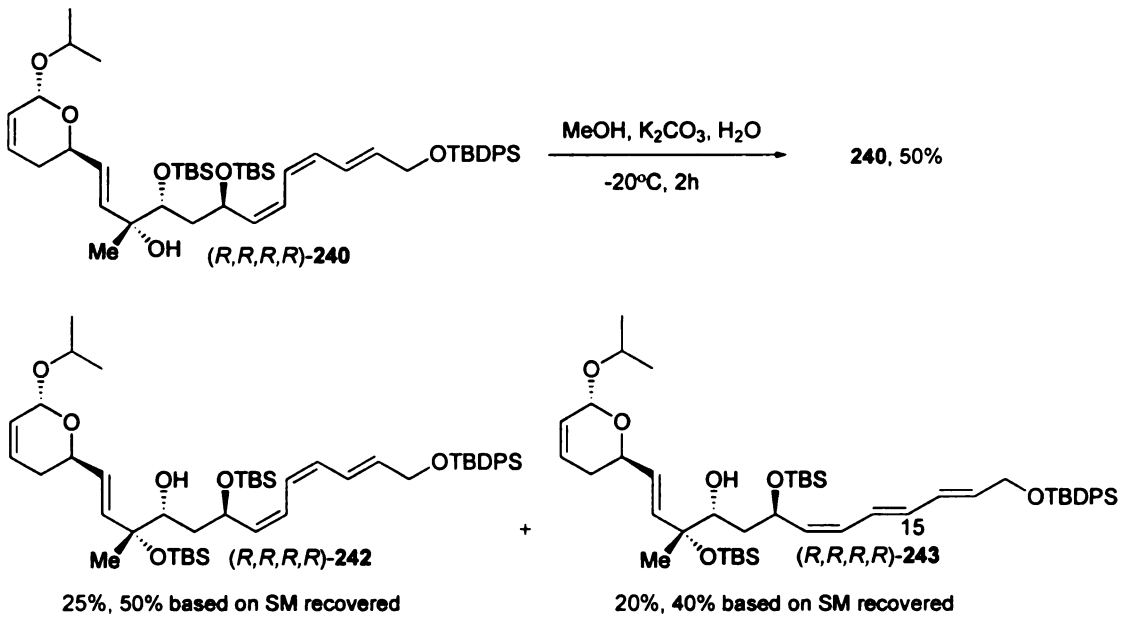


Tertiary Alcohol (*R,R,R,R*)-240: $CeCl_3.7H_2O$ (121.2 mg, 0.326 mmol) was heated under vacuum (0.2 mmHg) at 70 °C. The temperature was raised from 70 °C to 100 °C slowly over three hours and then allowed to stay at 100 °C overnight. The temperature was then raised to 140 °C and kept there for 12 h. At this point the reaction flask was allowed to cool to room temperature under argon and 2 mL of THF was added to a grayish-white solid and stirred for 10 h. The solution was then cooled to -78 °C and MeLi (1.5 M, 212 μL, 0.32 mmol) was added. This reaction mixture was stirred for 10 min at –78 °C and 10 min at room temperature. The beige/orange solution was then re-cooled to -78 °C and ketone (*R,R,R*)-**239** (7 mg, 0.0087 mmol) was added in 0.5 mL of dry THF. A saturated solution of $NaHCO_3$ (1 mL) was used to quench the reaction, which was extracted with CH_2Cl_2 (3 X 5 mL) and chromatographed (4:1 pentane/ether) on silica gel (pretreated with 5% Et_3N in hexanes). Alcohol (*R,R,R,R*)-**240** was obtained in 98% (7.3 mg, 0.085 mmol) as a 3:1 ratio of diastereomers of a colorless oil. Pure major isomer of **240** was obtained when Preparative TLC was carried out on a silica gel plate (20 x 20

cm, 250 μm) pre-treated with 5% Et_3N/hexanes and eluted with 1% Et_3N, 5% EtOAc and 94% hexanes. Alcohol **240** was used immediately for the next step as a mixture of 3:1 diastereomers in hopes that an easier separation would be achieved when lactone **232** is prepared. Boger achieved an easier separation on lactone **232** (Chapter 5, Figure V-11).[24] However for the purpose of characterization, on one occasion alcohol **240** was separated into its major and minor isomers.

Tertiary Alcohol (*R,R,R,R*)-240 (major isomer): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.86 (s, 9H), 0.88 (s, 9H), 1.05 (s, 9H), 1.15 (d, 3H, *J* = 6.3 Hz), 1.20 (d, 3H, *J* = 6.4 Hz) 1.23 (s, 3H), 1.91 (ddd, 1H, *J* = 4.9, 9.8, 14.6 Hz), 2.01-2.14 (m, 3H), 2.72 (s, 1H), 3.64 (t, 1H, *J* = 4.6 Hz), 3.98 (sept, 1H, *J* = 6.0 Hz), 4.27 (d, 2H, *J* = 3.6 Hz), 4.41-4.46 (m, 1H), 4.72 (td, 1H, *J* = 9.1, 3.6 Hz), 5.10 (s, 1H), 5.38 (t, 1H, *J* = 11.3 Hz), 5.69 (d, 1H, *J* = 9.9 Hz), 5.80-5.92 (m, 3H), 5.96-6.02 (m, 1H), 6.04 (t, 1H, *J* = 10.9 Hz), 6.13 (t, 1H, *J* = 10.9 Hz), 6.34 (t, 1H, *J* = 11.3 Hz), 6.74 (dd, 1H, *J* = 14.4, 11.4 Hz), 7.34-7.44 (m, 6H), 7.65 (dd, 4H, *J* = 6.3, 1.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.45, -4.34, -3.72, -3.49, 18.15, 19.25, 22.09, 23.89, 25.93, 26.80, 29.69, 30.76, 42.87, 64.14, 66.07, 67.06, 69.55, 74.95, 75.90, 93.18, 122.76, 123.02, 124.36, 126.10, 127.68, 128.67, 129.34, 129.69, 130.35, 133.50, 134.55, 134.94, 135.39, 135.54, (2 sp^3 C not located); FAB mass spectrum *m/z* (% rel intensity) 860 M^+ (0.2), 843 (0.2), 801 (0.3), 669 (1), 589 (4), 491 (5), 461 (2), 401 (3), 327 (5), 325 (3), 239 (6), 221 (6), 207 (10), 197 (25), 171 (15), 147 (25), 121 (10), 107 (18), 91 (25), 73 (100), 55 (20); R_f = 0.31 (10:1 pentane/EtOAc).

Tertiary Alcohol (*R,R,R,R*)-240 (minor isomer): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.12 (s, 3H), 0.86 (s, 9H), 0.88 (s, 9H), 1.06 (s, 9H), 1.15 (d, 1H, *J* = 6.0 Hz), 1.20 (d, 1H, *J* = 6.1 Hz) 1.23 (s, 3H), 1.91-2.14 (m, 4H), 2.69 (s, 1H), 3.68 (t, 1H, *J* = 4.0 Hz), 3.98 (sept, 1H, *J* = 6.1 Hz), 4.27 (d, 2H, *J* = 3.8 Hz), 4.40-4.48 (m, 1H), 4.72 (td, 1H, *J* = 9.1, 3.6 Hz), 5.08 (s, 1H), 5.38 (t, 1H, *J* = 10.4 Hz), 5.69 (d, 1H, *J* = 8.8 Hz), 5.80-5.92 (m, 3H), 5.96-6.02 (m, 1H), 6.04 (t, 1H, *J* = 11.2 Hz), 6.13 (t, 1H, *J* = 10.9 Hz), 6.34 (t, 1H, *J* = 11.3 Hz), 6.74 (dd, 1H, *J* = 14.9, 12.1 Hz), 7.34-7.44 (m, 6H), 7.65 (d, 4H, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.42, -3.50, 1.01, 18.09, 19.24, 19.72, 22.07, 23.88, 25.92, 26.80, 29.79, 31.91, 37.08, 64.12, 66.13, 66.74, 69.47, 74.71, 80.62, 93.11, 122.79, 123.03, 124.32, 126.09, 127.67, 128.28, 128.55, 129.68, 130.35, 133.48, 134.54, 135.15, 135.39, 135.52, (2 Sp^3 C not located); R_f = 0.31 (10:1 pentane/EtOAc).



Secondary Alcohol (*R,R,R,R*)-242: To a solution of alkyne (*R,R,R,R*)-**240** a 3:1 mixture of C_8 diastereomers (10 mg, 0.012 mmol) in MeOH (1 mL) at -20 °C, was added K_2CO_3 (4.2 mg, 0.03 mmol) and H_2O (0.125 mL). The mixture was stirred for 2 h after which it was quenched with H_2O (1 mL), extracted with EtOAc (3 X 5 mL) and dried over $MgSO_4$. The solution was concentrated on the rotary evaporator and chromatograghed with Et_3N/EtOAc/hexane (1:5:144) on a preparatory thin layer chromatography (PTLC) silica gel plate (20 x 20 cm, 250 μm) that was pre-treated with Et_3N/EtOAc/hexane (5:12:83).

Compound (*R,R,R,R*)-**243** (C_{15}-*trans*-isomer) was obtained in 20% yield (2.0 mg, 0.0024 mmol) as an inseparable 3:1 diastereomeric mixture as a colorless oil. The ratio was determined by intergration of the hydroxyl proton (δ = 2.87 ppm major, δ = 2.69 ppm minor). The stereochemistry of the major diastereomer was assumed to be the C_8(*R*)

epimer based on the starting alcohol (*R,R,R,R*)-**240** from which it was derived. Compound (*R,R,R,R*)-**242** was obtained in 25% yield (2.5 mg, 0.003 mmol) as a colorless oil as a separable 3:1 diastereomeric mixture. Alcohol (*R,R,R,R*)-**240** was recovered in 50% yield (5 mg, 0.006 mmol). The order of elution is as listed above with *trans*-(*R,R,R,R*)-**243** first followed by compound (*R,R,R,R*)-**242** and the starting material alcohol (*R,R,R,R*)-**240** last.

Alcohol **242** was used immediately for the next step as a mixture of 3:1 diastereomers in hopes that an easier separation would be achieved when lactone **232** is prepared. Boger achieved an easier separation on lactone **232** (Chapter 5, Figure V-11).[24] However for the purpose of characterization on one occasion alcohol **242** was separated into its major and minor isomers.

Secondary Alcohol (*R,R,R,R*)-242 (major isomer): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.05 (s, 6H), 0.06 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 1.06 (s, 9H), 1.17 (d, 3H, J = 5.9 Hz), 1.22 (d, 3H, J = 5.9 Hz) 1.24 (s, 3H), 1.94-2.16 (m, 4H), 2.83 (d, 1H, J = 1.5 Hz), 3.66 (d, 1H, J = 10.2 Hz), 3.98 (sept, 1H, J = 6.3 Hz), 4.27 (d, 2H, J = 4.4 Hz), 4.41-4.48 (m, 1H), 4.88 (t, 1H, J = 8.1 Hz), 5.09 (s, 1H), 5.47 (t, 1H, J = 9.8 Hz), 5.62-5.86 (m, 4H), 5.94-6.08 (m, 2H), 6.17 (t, 1H, J = 10.9 Hz), 6.30 (t, 1H, J = 11.2 Hz), 6.74 (dd, 1H, J = 14.2, 12.4 Hz), 7.34-7.44 (m, 6H), 7.65 (dd, 4H, J = 6.6, 1.7 Hz); R_f = 0.48 (10:1 Pentane/EtOAc).

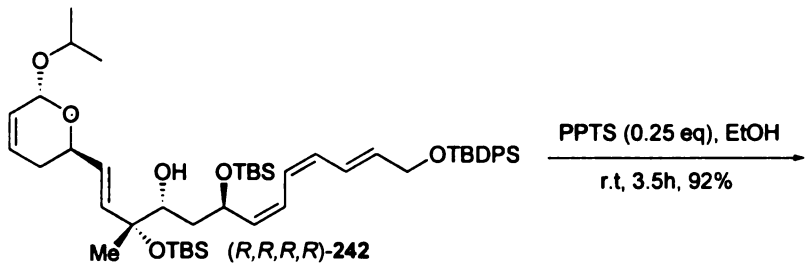
Secondary Alcohol (*R,R,R,R*)-242 (minor isomer): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.05 (s, 6H), 0.08 (s, 3H), 0.86 (s, 9H), 0.87 (s, 9H), 1.06 (s, 9H), 1.15 (d, 3H, *J* = 6.4 Hz), 1.18 (d, 3H, *J* = 6.3 Hz) 1.24 (s, 3H), 1.95-2.16 (m, 4H), 2.71 (d, 1H, *J* = 2.9 Hz), 3.60 (d, 1H, *J* = 11.7 Hz), 3.97 (sept, 1H, *J* = 6.1 Hz), 4.27 (d, 2H, *J* = 4.9 Hz), 4.40-4.52 (m, 1H), 4.87 (t, 1H, *J* = 7.8 Hz), 5.08 (s, 1H), 5.48 (t, 1H, *J* = 10.0 Hz), 5.64 (dd, 1H, *J* = 16.0, 6.1 Hz), 5.70-5.76 (m, 1H), 5.75-5.86 (m, 2H), 5.94-6.05 (m, 2H), 6.17 (t, 1H, *J* = 11.2 Hz), 6.30 (t, 1H, *J* = 10.5 Hz), 6.74 (dd, 1H, *J* = 13.4, 13.4 Hz), 7.34-7.44 (m, 6H), 7.66 (d, 4H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.10, -4.34, -2.22, 18.12, 19.22, 19.71, 22.09, 23.85, 25.81, 25.83, 26.79, 29.69, 31.92, 37.07, 64.14, 66.27, 66.62, 69.56, 74.99, 77.52, 93.12, 121.95, 123.35, 124.49, 126.06, 127.66, 128.51, 129.66, 130.15, 133.51, 134.04, 135.13, 135.52, 136.06, (1 sp^3 and 1 sp^2 C not located); R_f = 0.48 (10:1 pentane/EtOAc).

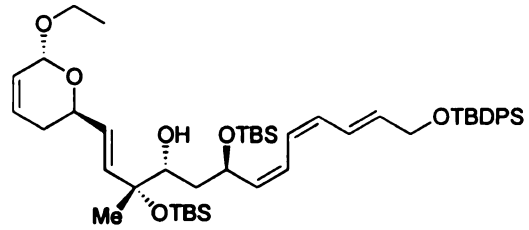
The following spectral data was taken on a 3:1 mixture of diastereomers.

***Trans*-Triene-(*R,R,R,R*)-243 (major isomer):** ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03-0.10 (m, 12H), 0.83 (s, 9H), 0.84 (s, 9H), 1.05 (s, 9H), 1.15 (d, 3H, *J* = 6.3 Hz), 1.20 (d, 3H, *J* = 6.0 Hz) 1.28 (s, 3H), 1.90-2.10 (m, 4H), 2.87 (s, 1H), 3.66 (t, 1H, *J* = 10.2 Hz), 3.98 (sept, 1H, *J* = 6.0 Hz), 4.23 (d, 2H, *J* = 4.6 Hz), 4.30-4.50 (m, 1H), 4.88 (t, 1H, *J* = 8.2 Hz), 5.08 (s, 1H), 5.39 (t, 1H, *J* = 8.5 Hz), 5.60-5.80 (m, 4H), 5.90 (t, 1H, *J* = 11.2 Hz), 5.94-6.01 (m, 1H), 6.17 (dd, 1H, *J* = 14.1, 10.9 Hz), 6.30 (dd, 1H, *J* = 15.0, 11.2 Hz), 6.40 (dd, 1H, *J* = 14.0, 12.1 Hz), 7.34-7.44 (m, 6H), 7.65 (d, 4H, *J* = 6.6 Hz);

^{13}C NMR (125 MHz, $CDCl_3$): δ -5.12, -4.29, -2.21, -2.14, 18.20, 19.25, 21.25, 22.25, 23.93, 25.86, 26.85, 30.66, 39.16, 64.24, 66.36, 66.86, 69.90, 74.79, 77.54, 93.39, 126.28, 127.09, 127.39, 127.66, 128.40, 129.64, 129.86, 130.50, 130.35, 133.20, 133.65, 134.99, 135.15, 135.56, (2 Sp^3 C not located); FAB mass spectrum *m/z* (% rel intensity) 859 M^+-1 (0.2), 800 (0.3), 728 (1.3), 711 (0.3), 685 (0.3), 669 (1.5), 651 (0.6), 611 (1.0), 559 (1.2), 491 (4), 413 (4), 403 (2), 373 (3), 325 (11), 267 (10), 239 (15), 197 (60), 185 (50), 135 (99), 91 (15), 75 (70), 73 (100), 59 (18); HRMS calcd for $C_{50}H_{84}NO_6Si_3$ *m/z* (M + $NH_4)^+$ 878.5643, meas 878.5643. R_f = 0.7 (10:1 pentane/EtOAc).

Minor isomer: δ = 2.69 (d, 1H, *J* = 2.5 Hz) only distinguishable proton.





(*R,R,R,R*)-**244 (Boger's Intermediate)**

Ethyl Acetal (Boger's Intermediate) (*R,R,R,R*)-244 : To a solution of isopropyl acetal (*R,R,R,R*)-**242** (5.5 mg, 0.0067 mmol) in 1 mL of EtOH was added PPTS (0.4 mg, 0.0017 mmol) at room temperature. The reaction was stirred for 3.5 h then diluted with

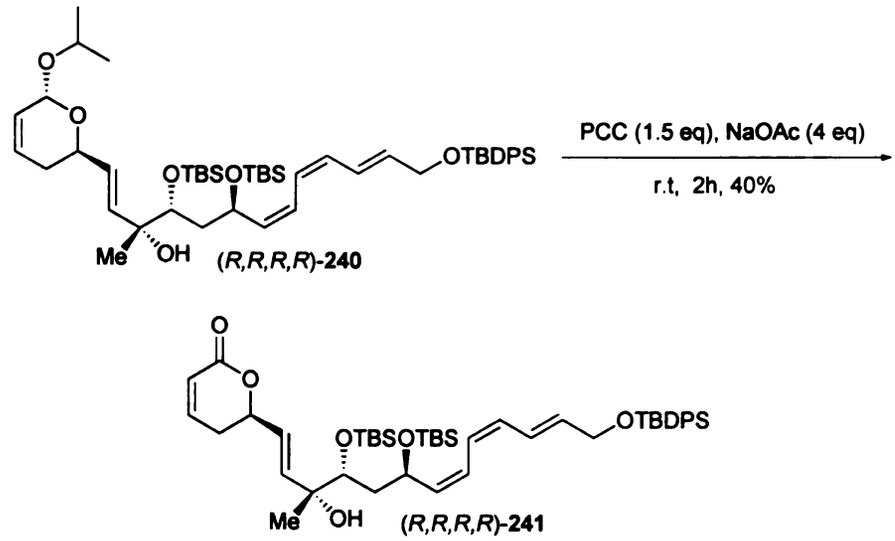
2.5 mL of CH_2Cl_2 and quenched with 1 mL of $NaHCO_3$. The layers were separated and the aqueous layer extracted twice with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. Preparative TLC was carried out on a silica gel plate (20 x 20 cm, 250 μm) pre-treated with 5% Et_3N/hexanes and chromatographed 28% EtOAc/hexanes. Ethyl acetal (*R,R,R,R*)-**244** was isolated as a colorless oil in 92% yield (5.2 mg, 0.0062 mmol) as an inseparable 3:1 mixture of diastereomers. The ratio was determined by intergration of the hydroxyl proton (δ = 2.98 ppm major, δ = 2.87 ppm minor). The stereochemistry of the major diastereomer was assumed to be the C_8(*R*) epimer based on the spectral data provided by Boger.[24] The ^{1}H NMR spectrum and IR spectrum matched those of an authentic sample. These spectra were kindly provided by professor Boger (also a 3:1 mixture of epimers at C_8). Copies of these spectra as well as those of **244** can be found below.

The following spectral data was taken on a 3:1 mixture of diastereomers.

^{1}H NMR (500 MHz, CD_3CN) major isomer: δ 0.01 (s, 3H), 0.07-0.09 (m, 9H), 0.88 (s, 9H), 0.89 (s, 9H), 1.06 (s, 9H), 1.12-1.20 (m, 3H), 1.28-1.32 (m, 3H) 1.66-1.75 (m, 1H), 1.98-2.10 (m, 2H), 2.10-2.20 (m, 1H), 2.98 (d, 1H, *J* = 4.4 Hz), 3.46-3.56 (m, 1H), 3.61(dd, 1H, *J* = 10.0, 3.9 Hz), 3.71-3.78 (m, 1H), 4.27-4.38 (m, 3H), 4.88-4.93 (m, 1H), 4.98 (broad s, 1H), 5.48-5.54 (m, 1H), 5.65-5.82 (m, 3H), 5.88 (dt, 1H, *J* = 15.1, 4.9 Hz), 5.95-6.02 (m, 1H), 6.08 (t, 1H, *J* = 10.7 Hz), 6.23 (t, 1H, *J* = 11.7 Hz), 6.32 (t, 1H, *J* = 11.2 Hz), 6.74 (dd, 1H, *J* = 14.4, 12.2 Hz), 7.39-7.48 (m, 6H), 7.67 (d, 4H, *J* = 6.8). IR

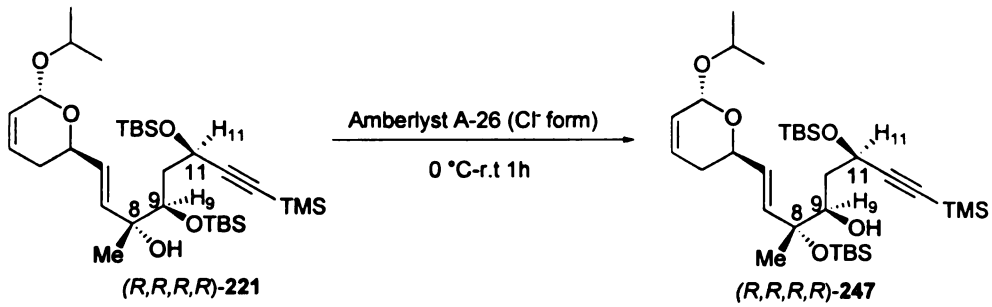
(neat film on NaCl): 3422 (w), 2957 (s), 2928 (s), 2857 (s), 1472 (s), 1462 (s), 1429 (s), 1385 (s), 1363 (s), 1260 (s), 1105 (s), 1022 (s), 837 (s), 802 (s), 777 (s), 702 (s) cm^{-1}; R_f = 0.65 (10:1 pentane/EtOAc).

Minor isomer: δ = 2.87 (d, 1H, J = 4.8 Hz) only distinguishable proton.



Lactone (*R,R,R,R*)-241 To a flamed dried flask cooled under argon was added PCC (1.6 mg, 0.007 mmol) and NaOAc (1.6 mg, 0.020 mmol) followed by 2 mL of CH_2Cl_2. The suspension was stirred for 15 minutes before rapidly adding the acetal (4 mg, 0.005 mmol). After 2.5 hours the suspension was filtered through a small silica gel pad and rinsed eight times with ether. The solution was concentrated in *vacuo* and purification on a Preparative TLC plate (silica gel, 20 x 20 cm, 250 μm) gave lactone (*R,R,R,R*)-**241** as a colorless oil in 40% yield (1.5 mg, 0.002 mmol).

(Spectra was obtained as a 1:1 mixture) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03-0.09 (m, 12H), 0.86 (s, 9H), 0.87 (s, 9H), 1.05 (s, 9H), 1.23 (s, 3H), 1.80-2.04 (m, 1H), 2.20-2.49 (m, 3H), 2.87 (s, 1H), 3.50-3.75 (m, 1H), 4.26 (d, 2H, J = 4.4 Hz), 4.34 (d, 1H, J = 4.0 Hz), 4.64-4.78 (m, 1H), 4.87-4.98 (m, 1H), 5.65-6.22 (m, 4H), 6.22-6.50 (m, 2H), 6.64-6.90 (m, 2H), 7.32-7.43 (m, 6H), 7.65 (d, 4H, J = 6.0 Hz); R_f = 0.33 (CH_2Cl_2).



Alkyne (*R,R,R,R*)-247: To a solution of alkyne (*R,R,R*)-**221** (20 mg, 0.036 mmol) with a 7:1 mixture at C_8 in MeOH (1 mL) was added amberlyst resin A-26 (Cl ion form, 16.0 mg) which was prewashed with MeOH. The reaction was run for 1 h and then filtered and washed sequentially with MeOH (5 mL), Et_2O (5 mL) and CH_2Cl_2 (5 mL). The combined rinses were concentrated *in vacuo* and the crude oil chromatographed on silica gel with EtOAc/Pentane 1:20. Alkyne (*R,R,R,R*)-**247** was isolated as a colorless oil in 23% yield (4 mg, 0.076 mmol) and 44% (8.8 mg, 0.014 mmol) of starting alcohol (*R,R,R,R*)-**221** was recovered. Compound (*R,R,R,R*)-**247** was assigned as the compound having the C_8 and C_{11} hydroxyls protected with TBS based on incomplete HMQC and HMBC data collected. Secondary alcohol (*R,R,R,R*)-**247** was isolated as a 7:1 inseparable mixture of diastereomers. The ratio was determined by intergration of the hydroxyl proton (δ = 2.90 ppm major, δ = 2.66 ppm minor). The stereochemistry of the major diastereomer was assumed to be the C_8(*R*) epimer based on the starting material **221**. Compound's **221** preparation is outlined in chapter 4 experimental.

Major isomer: ^{1}H NMR for secondary alkyne (*R,R,R,R*)-**247:** δ 0.04 (s, 3H), 0.06 (s, 3H), 0.09 (s, 3H), 0.12 (s, 3H), 0.13 (s, 9H), 0.85 (s, 9H), 0.86 (s, 9H), 1.14 (d, 3H, *J* =

6.0 Hz), 1.20 (d, 3H, J = 6.3 Hz), 1.31 (s, 3H), 1.75-1.86 (m, 1H), 1.98-2.10 (m, 3H), 2.90 (s, 1H), 3.71 (d, 1H, J = 13.9 Hz), 3.97 (sept, 1H, J = 6.0 Hz), 4.38-4.48 (m, 1H), 4.65 (dd, 1H, J = 7.9, 3.2 Hz), 5.08 (broad s, 1H), 5.65-5.84 (m, 3H), 5.94-6.04 (m, 1H). FAB mass spectrum m/z (% rel intensity) (M^+-1) 609 (0.2), 591 (0.2), 493 (1), 477 (0.8), 463 (0.8), 419 (6), 361 (1.5), 325 (12), 267 (25), 241 (30), 185 (15), 157 (15), 147 (15), 135 (20), 73 (100); R_f = 0.4 (4:1 pentane/ether).

Minor isomer: δ = 2.66 (s, 1H) only distinguishable proton.

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