This is to certify that the

thesis entitled

Synthetic Studies Toward the Total Synthesis
of Fostriecin and Some Analogs

presented by

Glenn Phillips

has been accepted towards fulfillment
of the requirements for

M.S. degree in Chemistry

Major professor

Date 04/26/04

Synthetic Studies Toward The Total Synthesis of Fostriecin And Some Analogs

By

Glenn Walton Phillips

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Chemistry

2004

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, a diene, and a triol fragment.

All three fragments have been successfully prepared in high yields and the coupling of the lactone and triol fragment achieved. A model study investigating the coupling of the diene fragment to the lactone and triol unit has also proven to be a success. Three of the four stereocenters have been incorporated thus far and efftorts are on the way to determine the absolute stereochemistry of the fourth.

ACKNOWLEDGEMENTS

I would like to begin my acknowledgements by thanking God for the success which I have been granted with so far in my Graduate career and for the success to follow. I have been blessed to have a patient, encouraging and creative advisor who has guided me tremendously thus far. Thank you, Dr. Wulff, for not only being a source of inspiration, but a tennis partner and friend. I would also like that thank my committee members who have established high standards for me to ascertain as a chemist and are assisting me in reaching these standards. I would also like to thank my labmates of the Wulff group but in particular Manish Rawat, Huang Jie and Dr. Su Yu for helping me through my first year at MSU. Dr. Jones and Mr. Khun my undegrauate professors I also would like to thank for their encouragement. In addition I would also like to thank Mapitso Molefe, Chryssolua Vassiliou, Monsteratt Rabago-Smith and Edith Onyeozili for being great classmates and a source of encouragement.

In graduate school one quickly learns that you need a source of friends outside the chemistry community to keep you in the "real world"; my Bethel-church family have provided me with this and I thank them.

My Family in Barbados, aunty Verna, grand-grand, grand-daddy, Uncles Oliver and Rodney, I thank them for their financial support. Nanny, aunty G and her family for their occasional calls and food. Uncle Randall, aunty Pauline, Paul and Reesa for their food and hospitality during my vacation.

Finally I especially want to thank four very important people. My father and mother Walton and Karlene Phillips for their love encouragement prayers and support thus far; My brother Karl Phillips for being there whenever I needed him for anything and my girl-friend Alva Ferdinand for her support and TLC.

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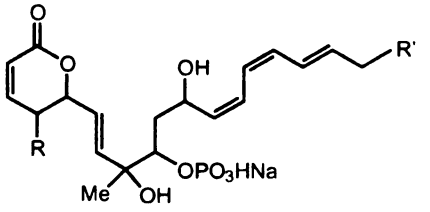
CHAPTER 1

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 insighted 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. 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.[9]

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).[10-16] 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.[12] This phenomenon is also known as G_2 arrest, and is the point in cell division

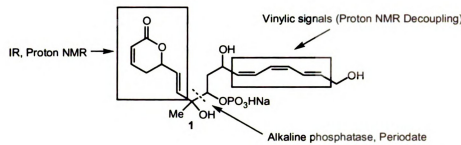
where damaged DNA is replaced or its synthesis is completed on entering mitosis.[17]

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.[18]

Structural and Stereochemical Determination

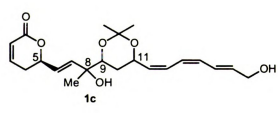
Although the 2-dimensional structure of fostriecin was first published in 1983, it would be fourteen years before the absolute configuration of all four stereocenters would be known. In 1985 Hokanson and French determined several stereochemical assignments of the molecule via proton and carbon-13 experiments, particularly the lactone and triene functionalities (Figure I-2).[19] 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.

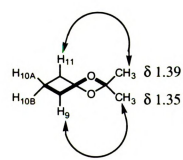
Figure I-2 Structural Determination from Spectral Data



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.[20] Extensive NMR, experiments and chemical degradation were the techniques they used to solve the absolute stereochemistry.

Figure I-3 Boger's Determination of the C_9 and C_{11} Stereochemistry



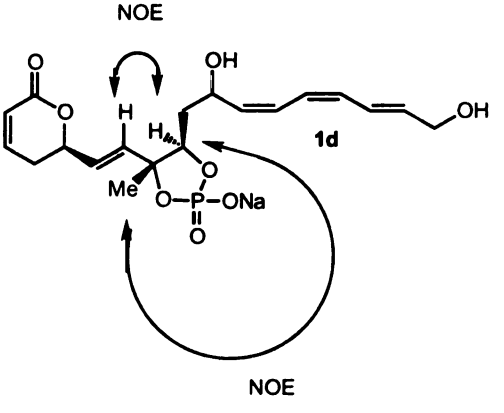


Proton	J (Hz)
9	10.5, 1.9
10A	10.5, 3.7
10B	9.6, 1.9
11	9.6, 3.7

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-3).[21]

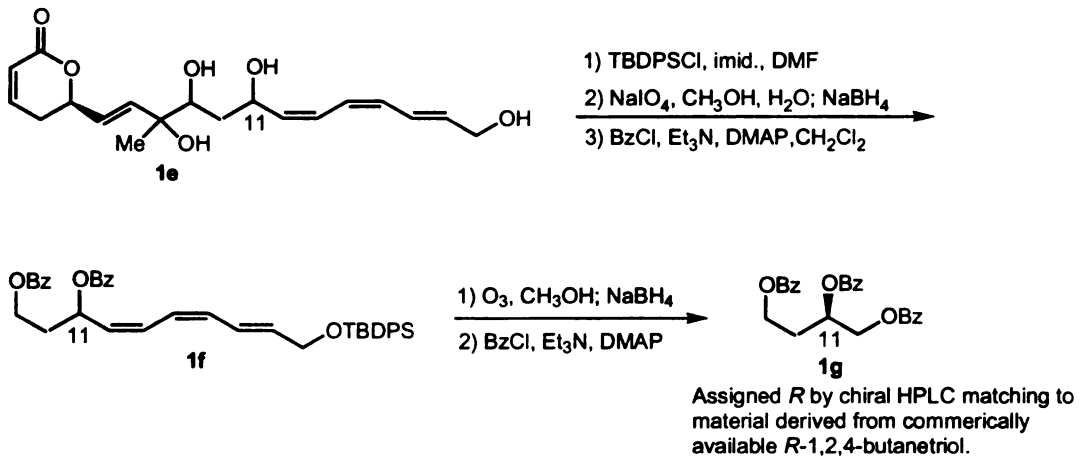
The relative stereochemistry of C_8 and C_9 was determined by converting fostriecin to a five-membered cyclic phosphate diester. ^{31}P NMR and 2D proton-proton ROESY NMR confirmed a 1,2-*syn* relationship (Figure I-4).

Figure I-4 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-5). This confirmed the C_{11} chiral center to be R and fostriecin 's complete stereochemical assignment to be 5*R*, 8*R*, 9*R*, 11*R*.

Figure I-5 Boger's Determination of C_{11} Absolute Stereochemistry



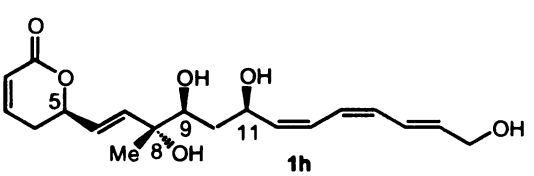
Introduction to the Synthetic Approaches to Fostriecin

With the knowledge of fostriecin's biological activity at hand, a profusion of syntheses and partial syntheses have been reported to date with the vast majority being published within the last two years. Thus far, there have been four total syntheses;[22-25] the synthesis of a dephosphorylated isomer of the natural product,[26] and two partial synthetic analyses reported.[27,28] Both classical and modern organic chemistry have been explored to a large extent. Some key reactions employed are Wittig and Horner-Wadsworth-Emmons olefinations, Sharpless asymmetric dihydroxylations, Felkin and non-Felkin additions, an asymmetric hetero-Diels-Alder reaction, asymmetric hydrogenation, Sonogashira, Stille, and Suzuki couplings, Grubb's metathesis, Swern, Dess-Martin and *N*-morphorline oxide-tetrapropylammonium peruthanate (NMO-TPAP) oxidations. In this chapter we shall explore briefly all seven approaches in a chronological fashion, and culminate with our retrosynthetic analysis.

Just's Synthetic Approach

The first attempt at the total synthesis of fostriecin was by Just and O'Connor in 1988.[26] It was attempted without knowledge of its absolute configuration, which would only be determined nine years later by Boger and co-workers. Of the eight possible diastereomers, they choose to prepare the 5*R*, 8*R*, 9*S*, 11*R* diastereomer (Figure I-6) and found it to be non-identical to the natural product. Their work narrowed the number of possibilities to just seven.

Figure I-6 Dephosphorylated Isomer of Fostriecin Synthesized by Just

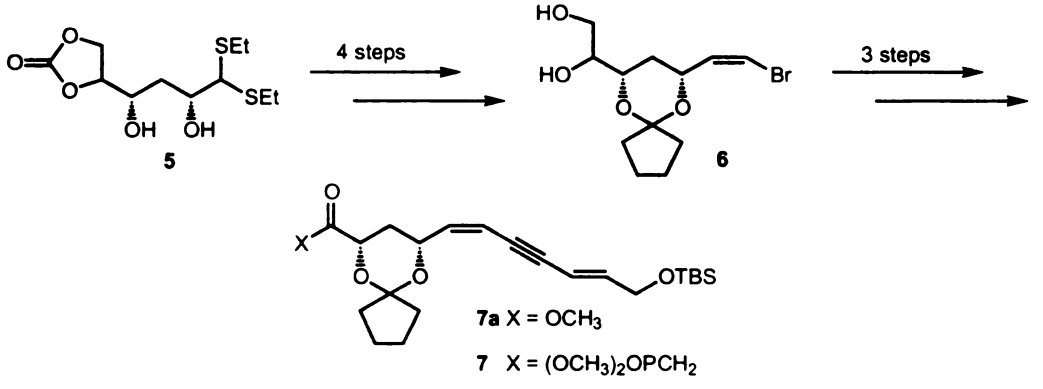


1h

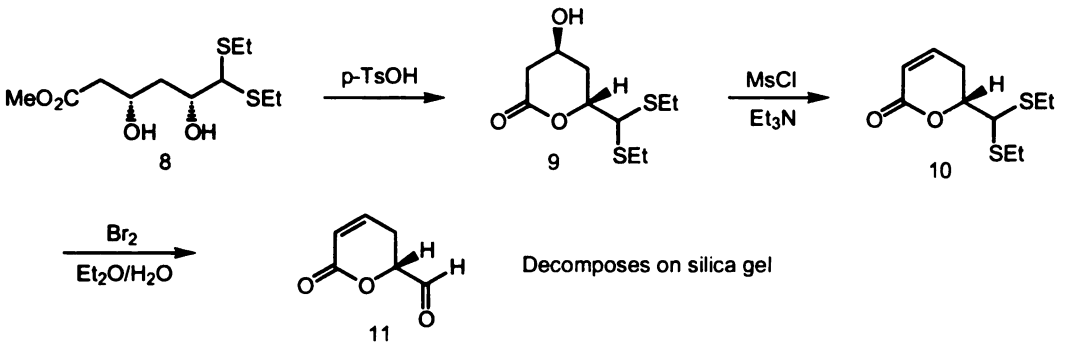
Their approach to this molecule utilized 1,2-O-isopropylidene-*D*-glucofuranose as a chiral starting reagent. The C_5, C_9, and C_{11} stereogenic centers were set in place by this choice of starting material. A few transformations led this synthetic team to a diethyl dithioacetal **5** and a very similar dithioacetal methyl ester **8**. The acetal **5** was used to make the central portion of the molecule, setting stereocenters C_9 and C_{11}, (Figure I-7) and the ester **8** was used to prepare the lactone **11** (Figure I-7) with the C_5 stereocenter. In the preparation of the lactone the acid catalyzed lactonization gave low yields and the lactone aldehyde proved to be very unstable on silica gel. A Horner-Wadsworth-Emmons (HWE) reaction between **7** and **11** connected the lactone to the rest of the molecule. The

triene unit was introduced in intermediate **7** by conversion of the dithioacetal **5** to a *cis* vinyl bromide by mercury deprotection of the thioacetal group and a Wittig reaction with bromomethylene triphenyl phosphorane. Sonogashira coupling of that bromide to a tertiary butyl silyl (TBS) protected enynol provided **7.** The last stereogenic center $C_{8,}$ was constructed by asymmetric methylation of the ketone **12**, which gave a 98:2 ratio of alcohol diastereomers in favor of the correct 8*R* isomer.

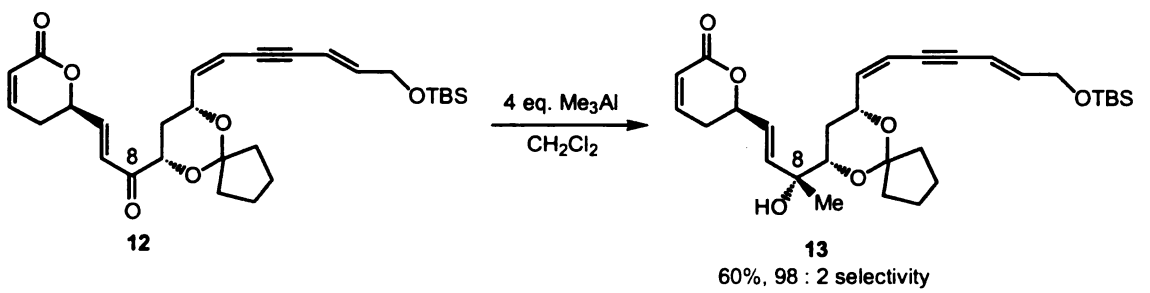
Figure I-7 Just Synthesis The Central Portion



The Lactone Aldehyde



The Methylation Step



A setback in the synthesis occurred at this point. When the hydrogenation of **13** using Lindlar's catalyst was attempted Just and O'Connor obtained a mixture of overreduced products. Having a low supply of compound **13**, Just and O'Connor decided to carry out this transformation at an earlier stage in the synthesis. Methyl ester **7a** 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.[17c] 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

Since the Boger group was the first group to tackle the stereochemical determination[20] and complete the total synthesis of natural fostriecin,[22] 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.

The 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-8). 5-Hexenoic acid was the starting material employed to make the lactone fragment. A Sharpless AD[29] on the olefin constructs the C_5 chiral center 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-9).

Figure I-8 Boger's Retrosynthetic Analysis

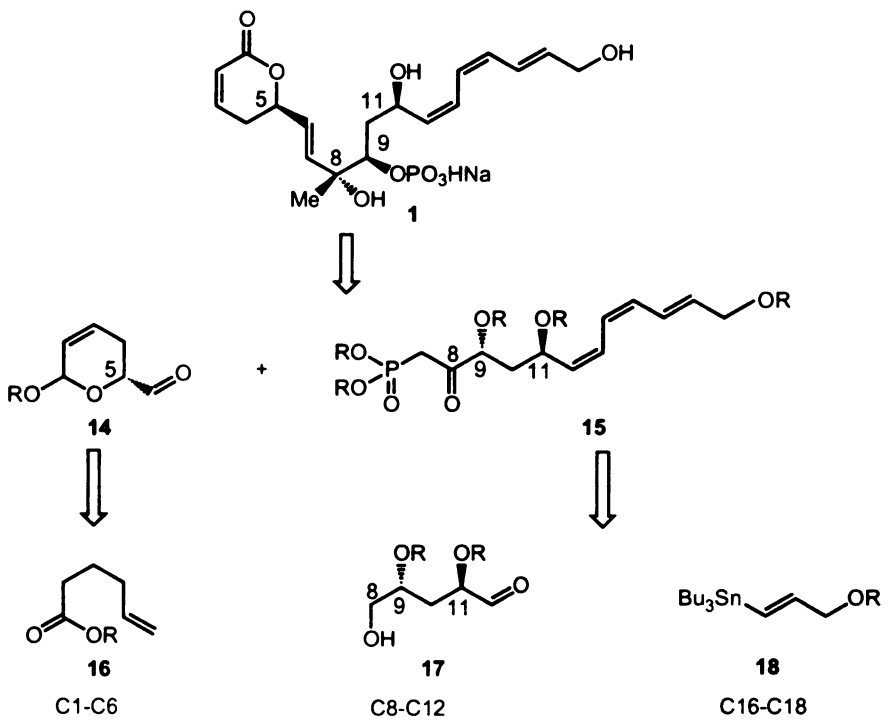
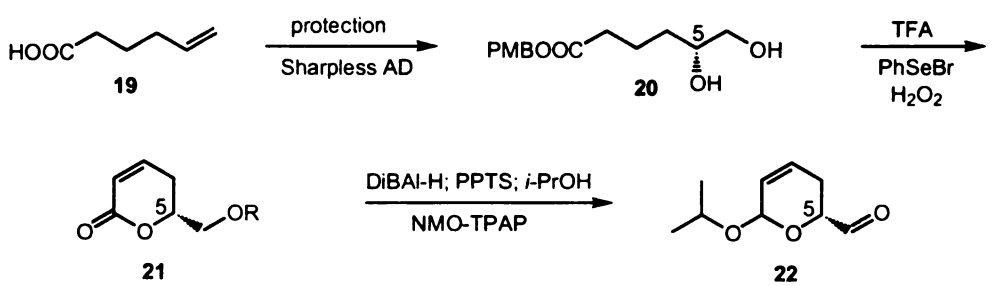


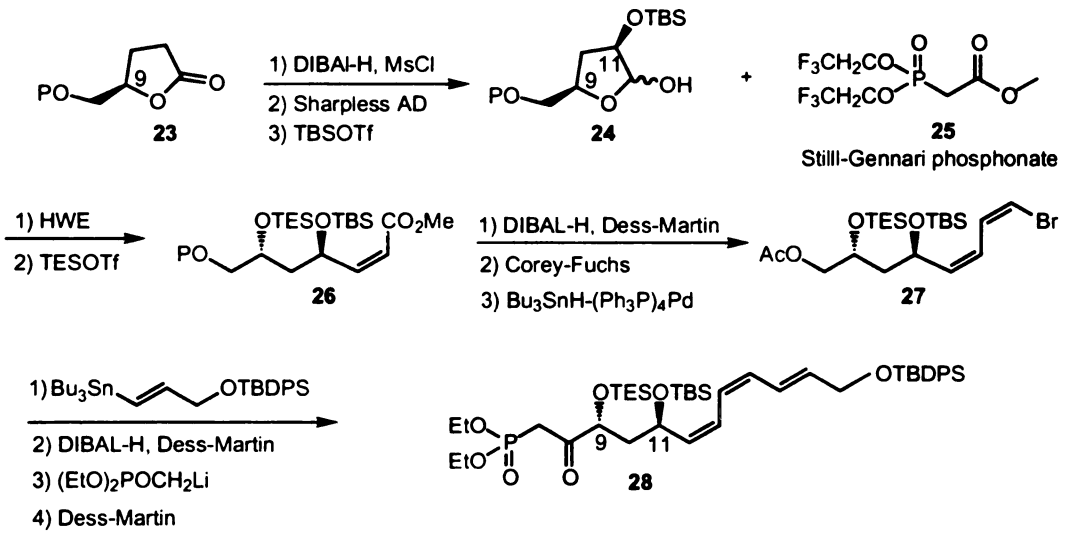
Figure I-9 Boger's Synthesis of the Lactone Fragment



Synthesis of the C_7-C_{18} fragment commenced with a two-step conversion of *D*-glutamic acid to an optically active lactone **23** incorporating the nescient C_9 chiral center (Figure I-10). 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 **24**. Boger then used a stepwise approach to assemble the sensitive *Z,Z,E*-triene. Condensation with a Still- Gennari phosphonate gave the methyl ester **26** and installed the first *Z* olefin.[30] 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-$Pd(PPh_3)_4$).[31,32] The last olefin would be constructed using a Stille coupling[33] of the vinyl bromide and the vinyl stannane **18**[34] shown in the retrosynthetic analysis.

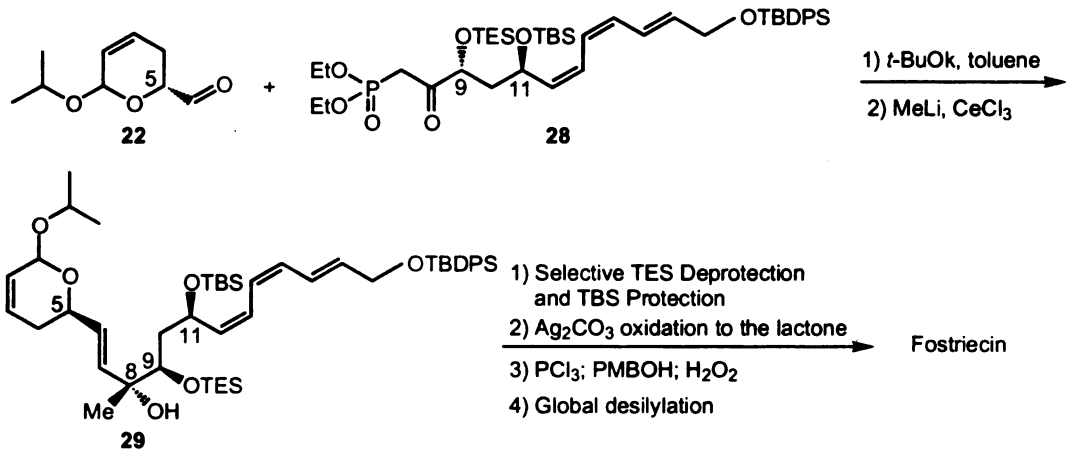
Figure I-10 Boger's Synthesis of the C_7-C_{18} Fragment



A Horner-Wadsworth-Emmons was used to couple the isopropyl lactol **22** 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.[35] 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.[36] Global desilylation was the last step (Figure I-11).

Figure I-11 Boger's Completetion of Fostriecin

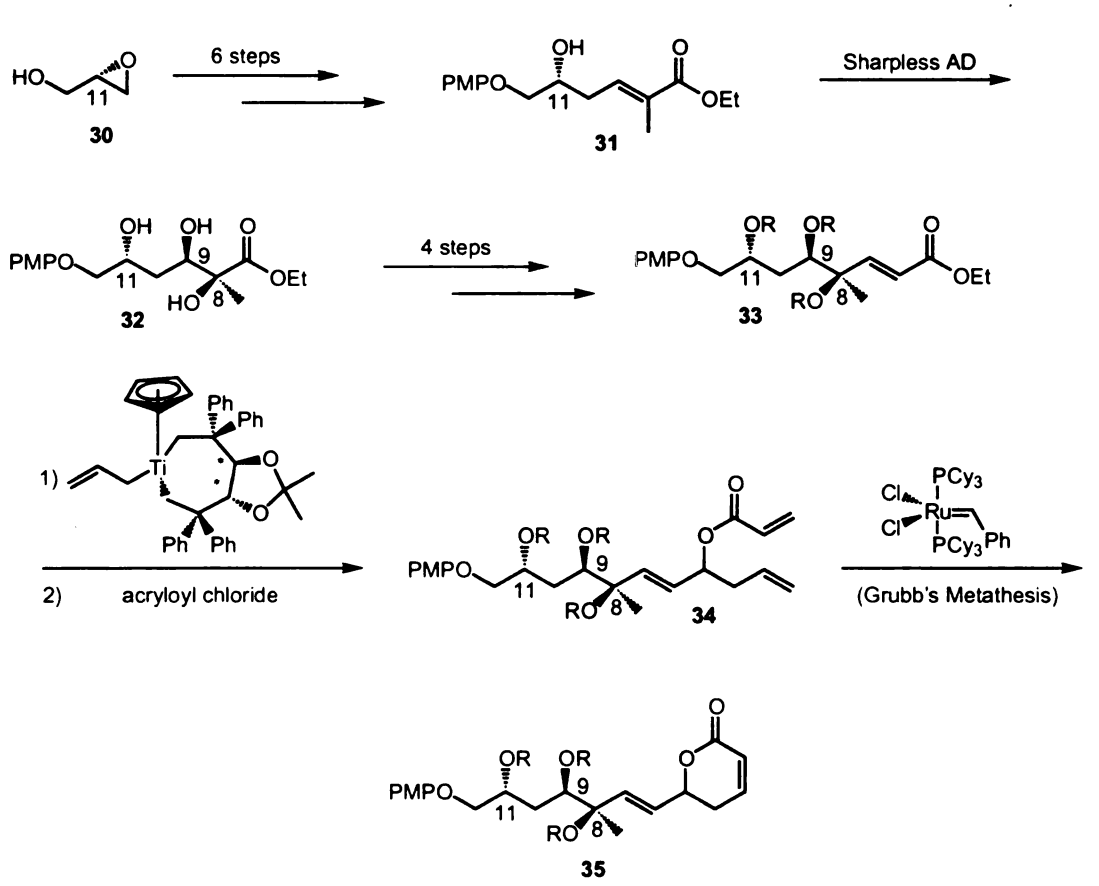


Cossy's Synthetic Approach

A partial synthesis of fostriecin was reported by Janine Cossy and co-workers at the Organic Chemistry Laboratory Association in Paris.[27] 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. 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 stereoisomers C_8 and C_9 simultaneously (Figure I-12).

Another interesting application was the use of an allyltitanium complex to construct the C_5 stereogenic center.[37] This reaction not only accomplishes this, but leads to the lactone in only two additional steps. Protecting the alcohol resulting from that transformation with acryoyl chloride, set up two terminal olefins for a Grubbs' metathesis reaction,[38] which proceeded with an 86% yield. This was the first example of this type of lactonization used on route to fostriecin.

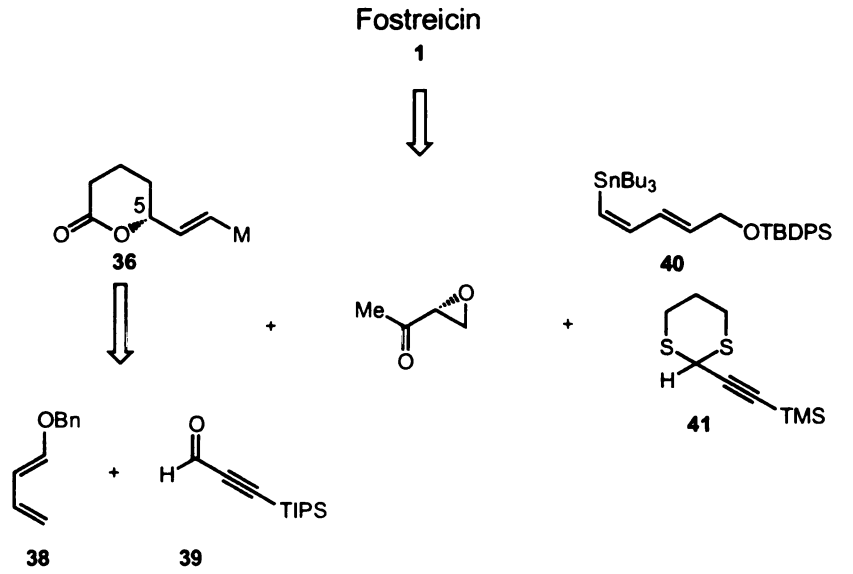
Figure I-12 Cossy Synthesis of the C_1-C_{12} Fragment



Jacobsen's Synthetic Approach

Shortly after Boger's and Cossy's publications, Jacobsen and Chavez achieved a second total synthesis of fostriecin.[23] 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-13 Jacobsen's Retrosynthetic Analysis



The C_5 stereocenter was established via an asymmetric hetero-Diels-Alder reaction catalyzed by a chromium complex developed in the Jacobsen laboratory.[39] High yields, enantiomeric excess (ee's) and diastereomeric ratios (dr) were obtained (Figure I-15). The acetylene unit on the protected lactol after hydrozirconation\transmetalation[40] 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-16). The C_9 stereogenic center was also prepared uniquely. 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-14).[41]

The last chiral center was constructed using Noyori's transfer hydrogenation methodology.[42] The reaction proceeded with a 25:1 diastereomeric ratio. The sensitive triene unit was completed by a Stille[43] coupling of a vinyl iodide **49** to the *Z,E*-stannane **40** (Figure I-13) 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-14 Jacobsen Hydrolytic Kinetic Resolution of Epoxyketone

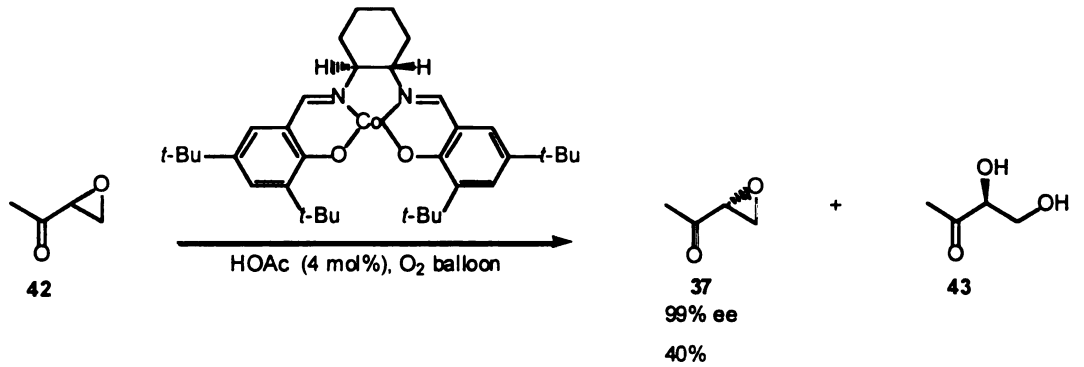


Figure I-15 Jacobsen Asymmetric Hetero-Diels-Alder Reaction

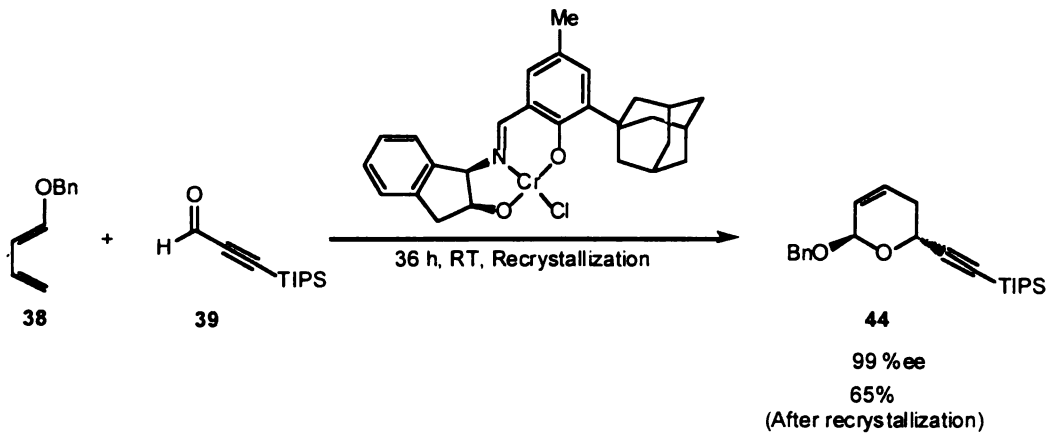
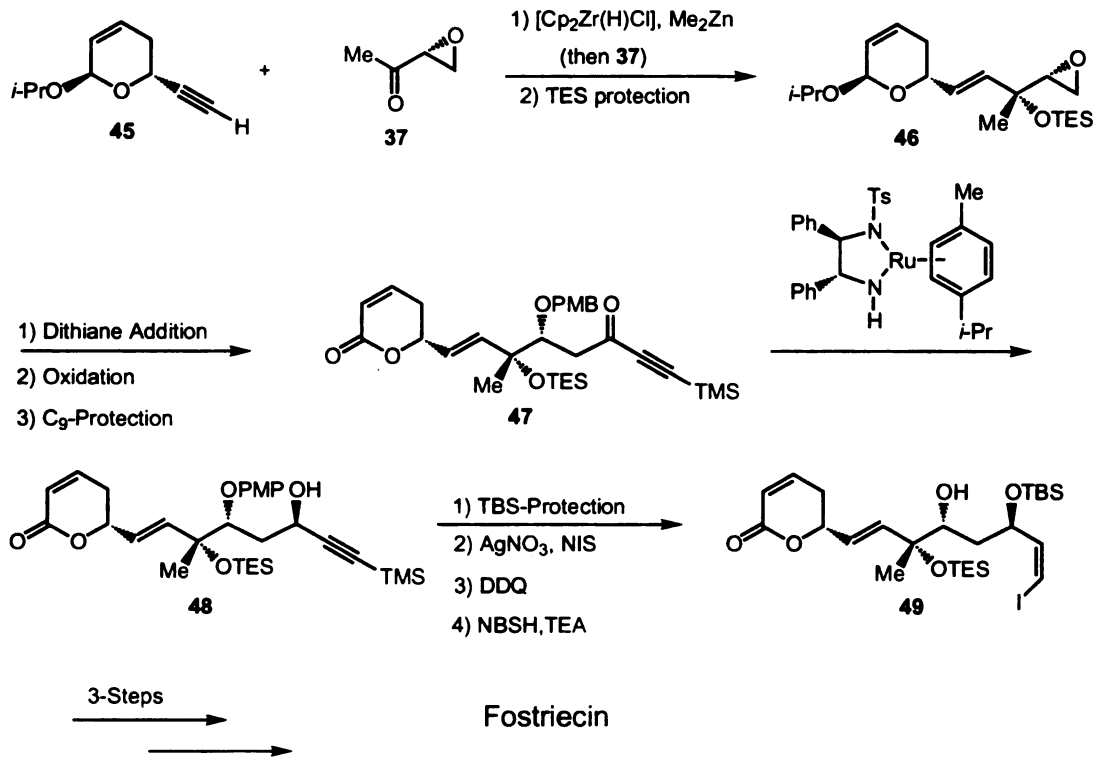


Figure I-16 Jacobsen Synthetic Analysis Continued



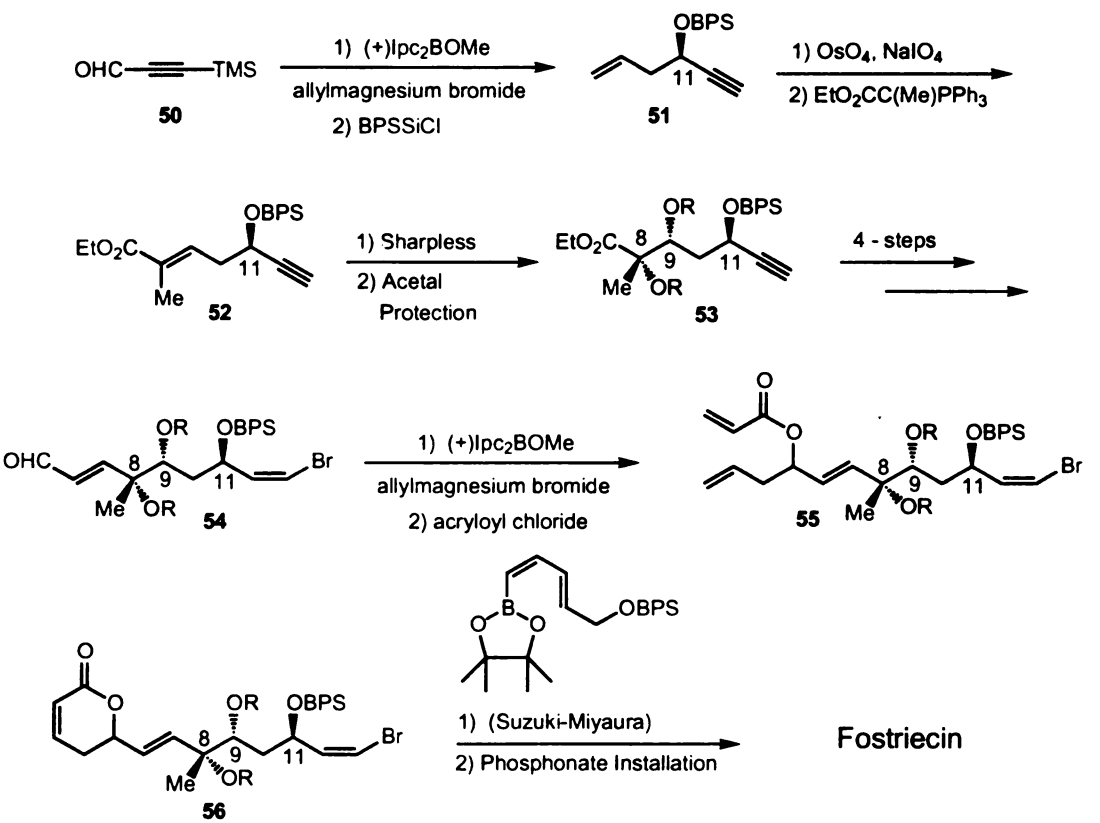
Falck's Synthetic Approach

Reddy and Falck reported the third complete synthesis which had very few steps that would render their strategy unique.[24] Two of their key steps are identical to Cossy's approach, and another uses the same approach but a different catalyst. The latter strategy is in their very first step. Allylation with (+)-β–methoxydiisopinocamphenyl borane and allyl magnesium bromide of the aldehyde **50** sets the C_{11} stereocenter with approximately 98 % ee (Figure I-17).[44] Later the same method was used to generate the C_5 chiral center with the same ee, which was comparable to Cossy's allyl titanium complex. 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. The other two chiral centers were also generated as seen before by Cossy and co-workers, via a Sharpless AD of intermediate **52**.

A Suzuki-Miyaura cross coupling[45] was the strategy utilized by this group, to construct the *Z,E,E-* triene moiety, completing the synthesis of the fostriecin core.

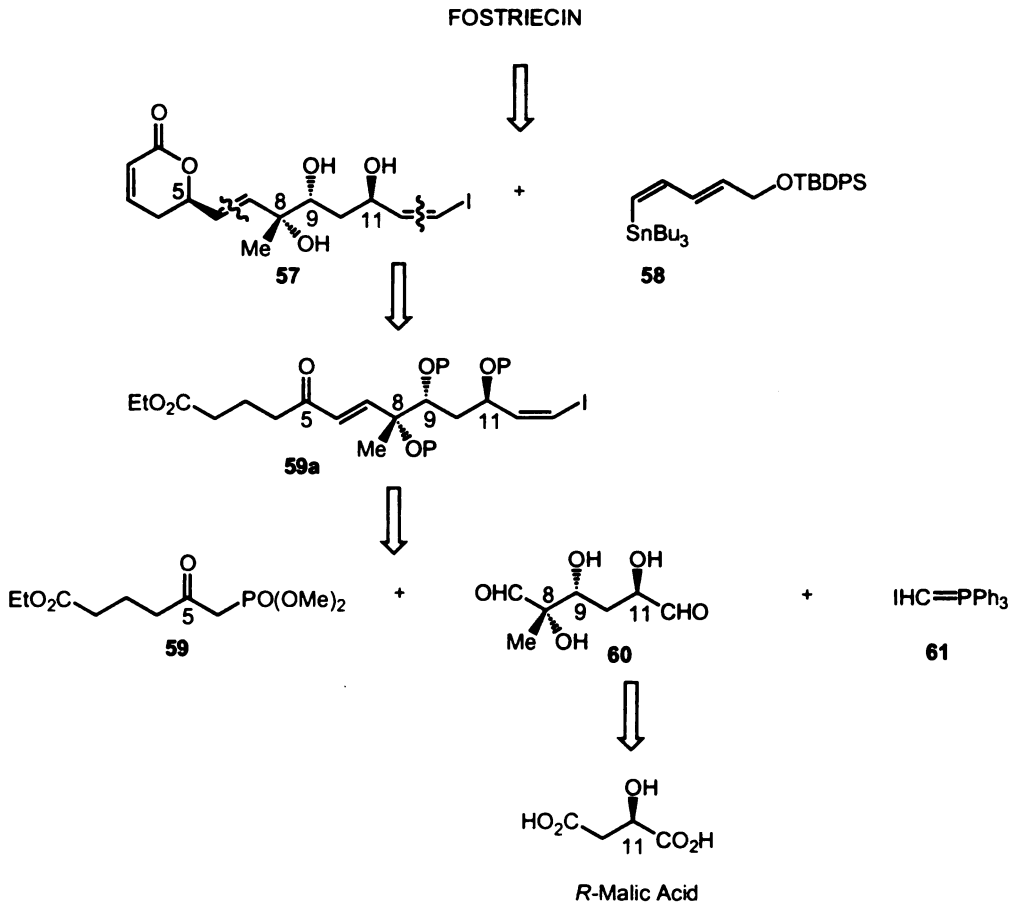
Figure I-17 Falck Synthetic Analysis



Imanishi Synthetic Approach

The last total synthesis of fostriecin (CI-920) seen to date was published by Imanishi in March of this year,[25] sixteen days after Falck's publication. Like Falck's synthesis many steps are reminiscent of those seen in previous syntheses (Figure I-18). A Horner-Wadsworth-Emmons 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 coupling of a *cis* vinyl iodide to a *Z,E*-stannane. The C_8 and C_9 stereocenters were prepared via a Sharpless AD. A *R*-Binapthol aluminum hydride (BINAl-H) reduction[46] of **59a** 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 the earlier synthetic approaches.

Figure I-18 Imanishi's Retrosynthetic Analysis of Fostriecin



Kobayashi's Synthetic Approach

In the most recent publication concerning fostriecin's synthesis, Kobayashi synthesized the C_3-C_{12} fragment of fostriecin.[28] This focused on the asymmetric dihydroxylation of several dienes prepared by cross coupling reactions (Figures I-19 and 20). Suzuki, Stille and Sonogashira[47] were utilized, all techniques seen previously. 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

used for these studies as a mixture of epimers. 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-19 Kobayashi's Retrosynthetic Analysis

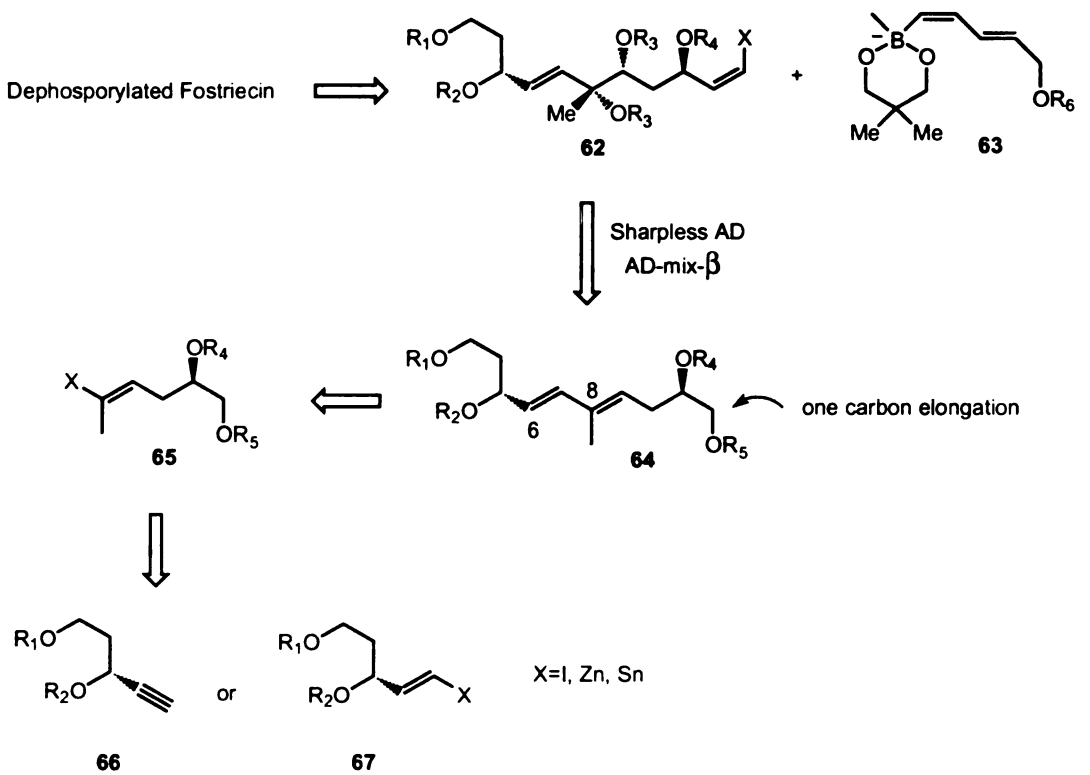
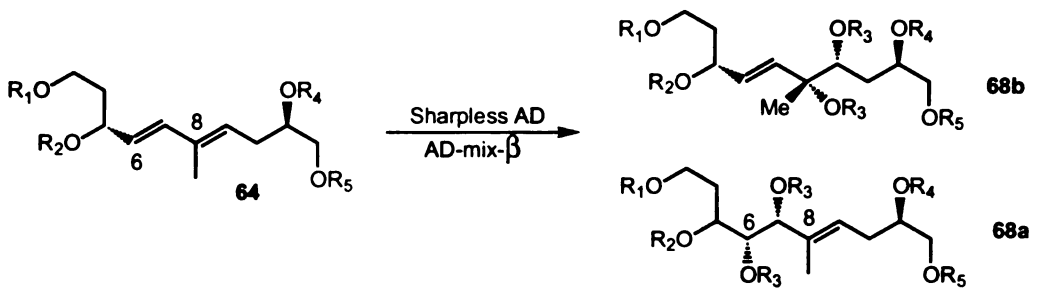


Figure I-20 Optimizing Conditions for the Sharpless AD Reaction



Entry	R_1	R_2	R_4	R_5	ratio (**68a:68b**)	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.

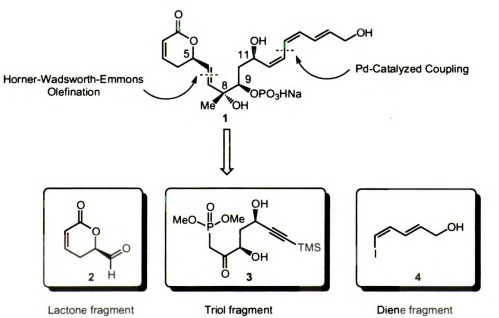
Our Retrosynthetic Analysis

At the time our synthetic strategy was planned, only Just and O'Connor's synthesis of the dephosphorylated fostriecin isomer had been published. 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 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 model approach were encured, but the basic model 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-21). High *E*-selectivity may be achieved from the Horner-Wadsworth-Emmons olefination between **2** and **3**, while the Sonogashira coupling of the deprotected acetylene to the vinyl iodide should complete the fostriecin core. A detailed examination of each fragment and their assembly will be given in the following chapters.

Figure I-21 Our Retrosynthetic Analysis of Fostriecin

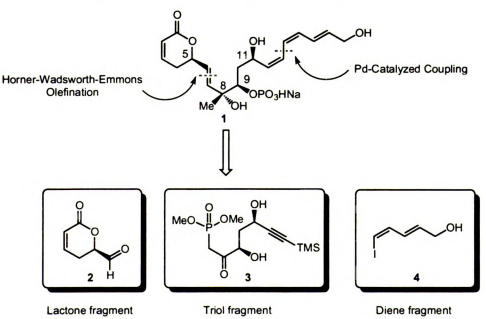


CHAPTER 2

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 diol 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 and then modified by Su Yu.[60,81] 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]

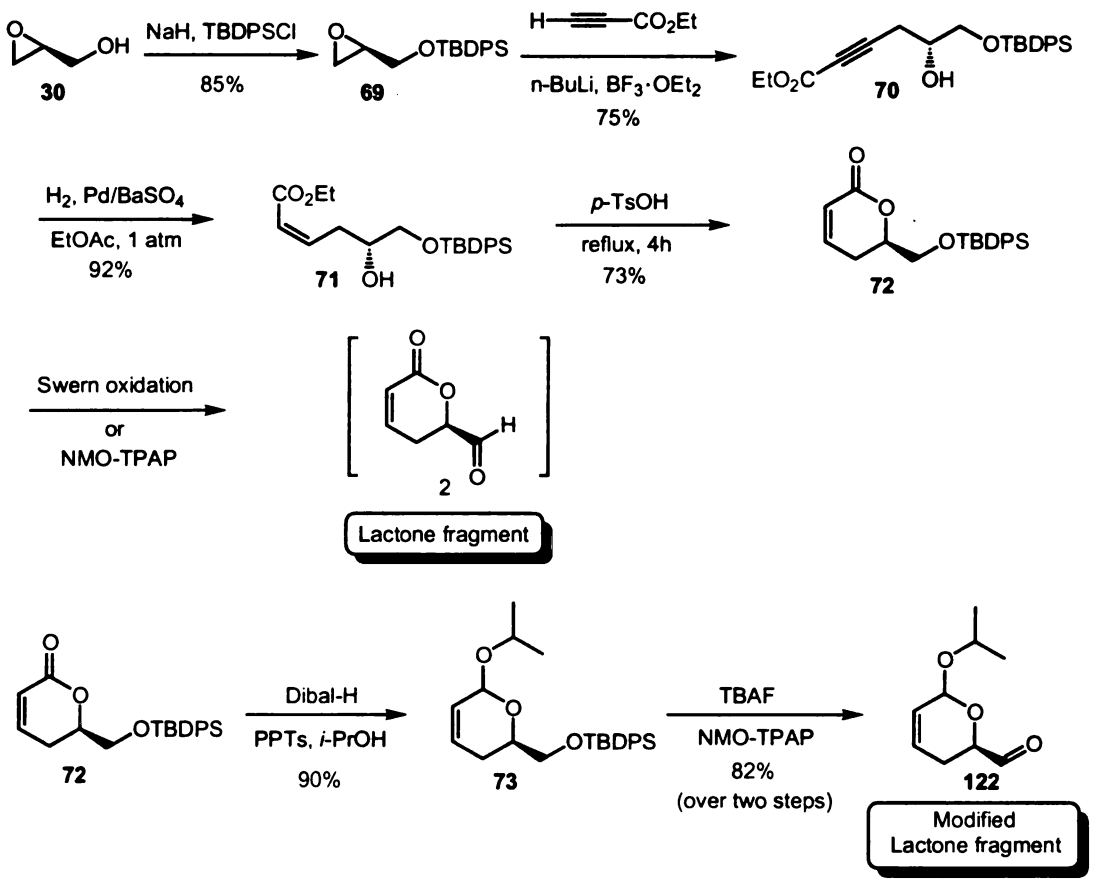
Figure II-1 Our Retrosynthetic Analysis of Fostriecin



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)[48] initiated the six-step sequence shown in Figure II-2. Nucleophilic ring opening of epoxide **69** with the anion of ethyl propiolate gave alcohol **70** in 75% yield.[49] The anion of ethyl propiolate is not stable above –78 ^{o}C and this is the first time that it has been alkylated with an epoxide. This alkynol was then reduced to the *cis*-alkene **71**,[50] and the six-membered ring lactone formed by acid catalysis in an overall yield of 42% for the five steps.[51] 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.[20] 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.[52,53] This methodology was adopted and the isopropyl lactol was obtained in 74% yield over the three steps as our unoptimized result.

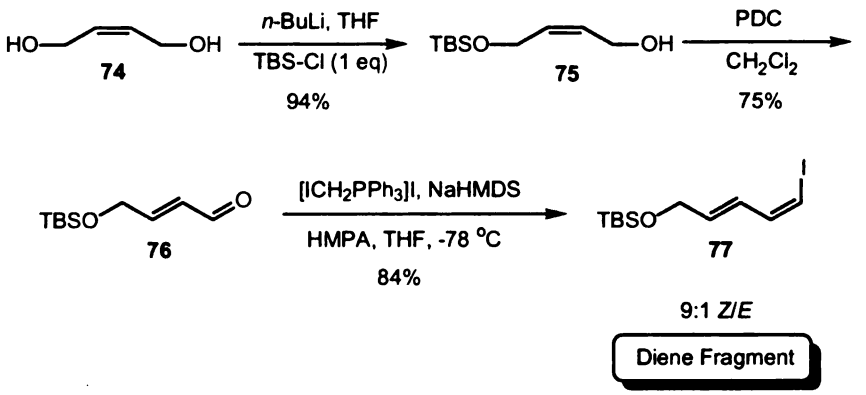
Figure II-2 Synthesis of the Lactone Fragment



The Diene Fragment

This fragment was the least difficult to prepare but as reported in chapter one, it is also the part of the molecule responsible for its instability. Coupling the acetylene of the triol fragment **3** to the *Z*,*E*-iododiene **4** prepared as outlined in the following scheme, minimizes the exposure of this sensitive portion to many transformations that would result if a linear approach was to be used where this portion of the molecule is formed early.[60]

Figure II-3 Synthesis of the Diene Fragment

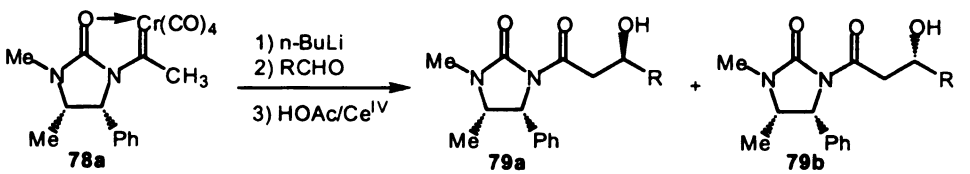


Our synthesis of this fragment commences with the tertiary butyl silyl (TBS) monoprotection of *cis*-2-butene-1,4-diol using Marshall's protocol.[54] The unprotected alcohol was then oxidized with pyridinium dichromate (PDC) to form the α,β–unsaturated aldehyde **76** with complete isomerization of the double bond to the desired *trans* stereochemistry. The final step was achieved using Stork's procedure for the synthesis of *cis* iodo-alkenes.[55] A 9:1 ratio of separable isomers was obtained. The overall yield for these three steps was 59%. It is important to note that this compound is prepared immediately before use and not stored as the vinyl iodide, since it is light sensitive.

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-4 Asymmetric Aldol Reactions Using a Chiral Imidazolidinone Fischer Carbene Complex

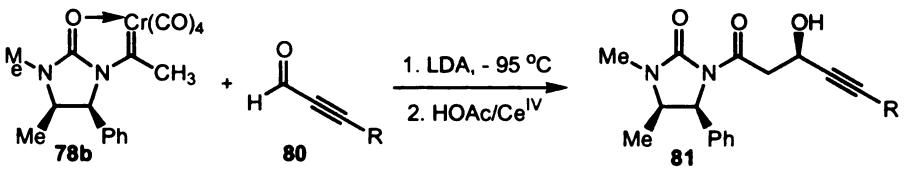


R	temperature (°C)	time (min)	ratio (*anti*:*syn*)	yield (%)
n-Pr	-10	2	91:9	83
	-30	30	89:11	87
	-30	30	87:13	85 *
i-Pr	-10	10	91:9	83
	-30	30	95:5	88
Ph	-78 to -30	30	98:2	60

* 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.[56] As can be seen in Figure II-4, excellent yields and diastereoselectivities were observed when the enolate anion of complex **78a** was reacted with a variety of alkyl and aryl aldehydes. These encouraging results prompted Dr. Wilson to expand the scope of this reaction to 2-alkynals.[57] He found that the desired propargylic alcohols were prepared in good yields and diastereoselectivities, however the stereoinduction observed in these products was reversed. This observation was confirmed by X-ray crystallography.[58]

Figure II-5 Asymmetric Aldol Reactions of 2-Alkynals Using a Chiral Imidazolidinone Fischer Carbene Complex



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

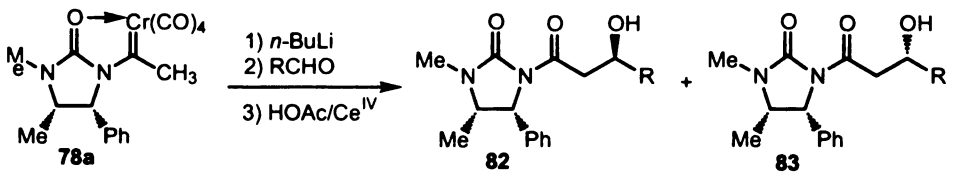
Before one can attempt to explain this anomaly a clear understanding of the original mechanism involved is essential. The carbene chiral auxillary has three main features that ensure high diastereoselectivity. First the phenyl and methyl groups on the imidazolidinone provides facial selectivity by steric 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. The larger group on the incoming aldehyde and the carbonyl itself will avoid interaction with these ligands increasing the selectivity (Figure II-10, transition state I).

Both these features would likely not be nearly as effective if there was free rotation around the nitrogen-carbene carbon bond. In other oxazolidinone and imidazolidinone chiral auxiliaries there is free rotation around the amide bond. In these systems, this rotation is prevented by

adding a Lewis acid or chelating transition metal to the system. These set the orientation of the chiral auxiliary spacially. In our version, the oxygen from the imidazolidinone coordinates to the chromium directly accomplishing the same type of orientation intramolecularly. This last element ensures the efficiency of the other two factors making this chiral auxiliary a very effective one.

So why is the diastereoselectivity reversed for 2-alkynals? There are many factors which may lead to the reversal observed between 2-alkynals and the alkyl and aryl aldehydes, but all possible explanations fall under two main catergories: steric interaction and aggregation. Yan Shi performed a series of asymmetric aldol reactions with aryl, α–branched aliphatic and α–unbranched aliphatic aldehydes.[59] Entries 1,2 and 3 of Figure II-6 shows an improvement in diastereoselectivity with increasing steric bulk on the α– carbon of the aldehyde. The larger the substituent on the α– carbon the more the *anti* product will be favored.

Figure II-6 The Effects of α–Substituents on the Asymmetric Aldol Reaction

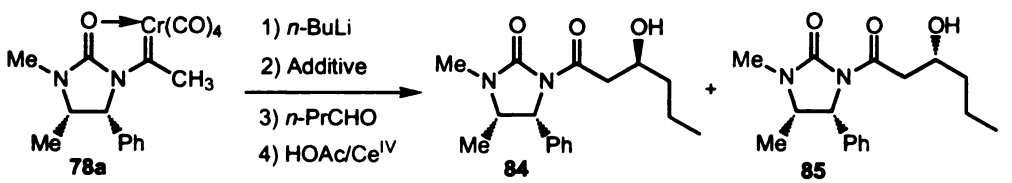


Entry	R	temperature (°C)	ratio (*anti*:*syn*)	yield (%)
1	Me	-30	53:47	81
2	n-Pr	-30	89:11	87
3	i-Pr	- 30	95:5	88
4	Ph	-35	98:2	60

The effects of additives were also studied by Wulff and Shi and some data are shown in Figure II-7. It is known that lithium aggregates maybe disrupted using amine bases such as hexamethylphosphoramine (HMPA) or tetramethylethylenediamine (TMEDA).[83]

In the reaction with *n*-butanal, extensive studies were carried out to determine if aggregates were involved in this asymmetric aldol reaction. Figure II-7 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. At -30 °C, however very little change in diastereoselectivity is observed.

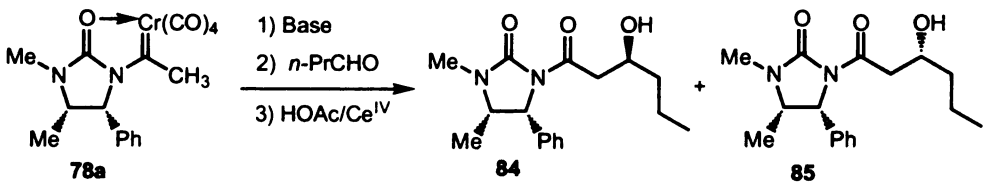
Figure II-7 The Effects of Additives on the Asymmetric Aldol Reaction



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

Figure II-8 entries 2 and 3 also show that using sodium or potassium instead of lithium changes the selectivities dramatically. However because the sodium and potassium ions are bigger and softer cations, it is difficult to compare its results since these ions may be able to form aggregates at higher temperatures than can lithium. Repeating these reactions at –78 °C would provide a broader and a more accurate scope for analysis but these reactions have not yet been performed.

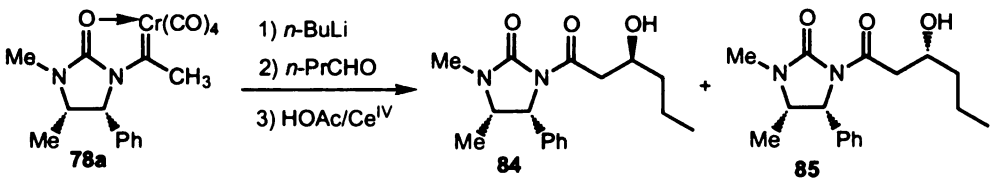
Figure II-8 The Effects of Other Cations on the Asymmetric Aldol Reaction



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 results from Figure II-9, entries 1 and 3 are also consistent with the presence of aggregates at the lower temperatures. Entries 1 - 3 show an erosion of diastereoselectivity as the temperature moves from –10 °C to –78 °C and a reversal in selectivity at –95 °C. A 10 fold decrease in the concentration (entries 3 vs 4) also results in a change in selectivity, favoring the *anti* product. These data are consistent with the formation of aggregates at lower temperatures and high concentration which give the *syn* diastereomer.

Figure II-9 The Effects of Temperature and Concentration on the Asymmetric Aldol Reaction



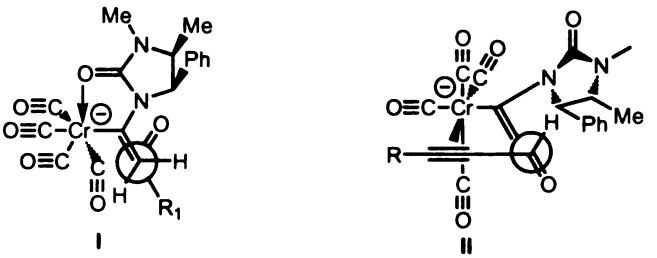
Entry	R	temperature (°C)	ratio (*anti*:*syn*)	yield (%)
1	*n*-Pr	-10	93:7	83
2	*n*-Pr	-50	84:16	83
3	*n*-Pr	- 78	55:45	85
4	*n*-Pr[a]	-78	73:27	85
5	*n*-Pr	-95	28:72	60

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

Only aldehydes that can not 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-7 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.[59,60,82] While the mechanism of the reaction is not known in detail, the stereoselectivity appears 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-10). 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-10 Hypothesized Transition States of Aldol Reactions

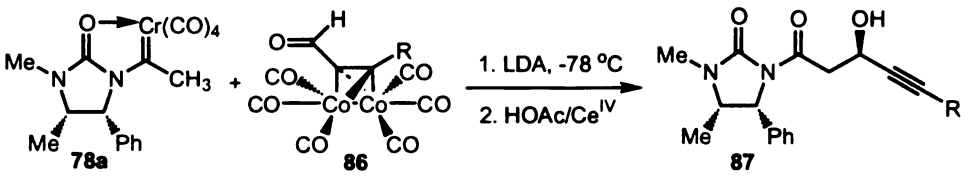


I Monomeric Enolate

II Co-ordinated Alkyne enolate

High selectivities are obtained when the reactions are carried out using a dicobalt hexacarbonyl complexed 2-alkynal (Figure II-11).[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-11 Asymmetric Aldol Reactions of 2-Alkynal Cobal Complexes with a Chiral Imidazolidinone Fischer Carbene Complex



78a 86 87

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 this transformation is still unknown. There is however some evidence 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

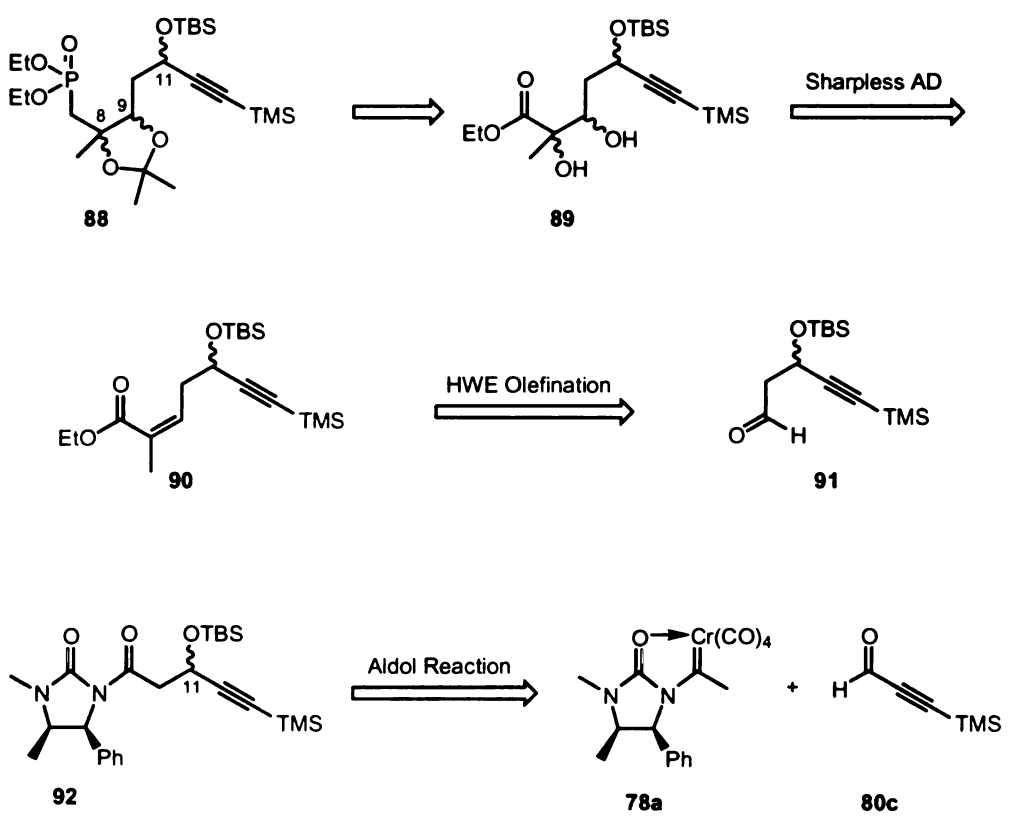
The initial synthetic strategy of the triol fragment dates back to 1994 and the discovery of the asymmetric aldol reactions of imidazolindinone carbene complexes.[60] At this point the absolute configuration of fostriecin was unknown and as a result the initial and final strategies differ significantly 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 and a 2-alkynal to construct the C_{11} stereogenic center; a Horner-Wadswoth-Emmons (HWE)[61] olefination to construct either the *E* or *Z* isomer of a trisubstituted alkene; and a Sharpless asymmetric dihydroxylation 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 and Sharpless AD could access any of the eight permutations possible.

This synthetic route was abandoned because of disappointing diastereoselectivities observed in the Sharpless AD 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 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

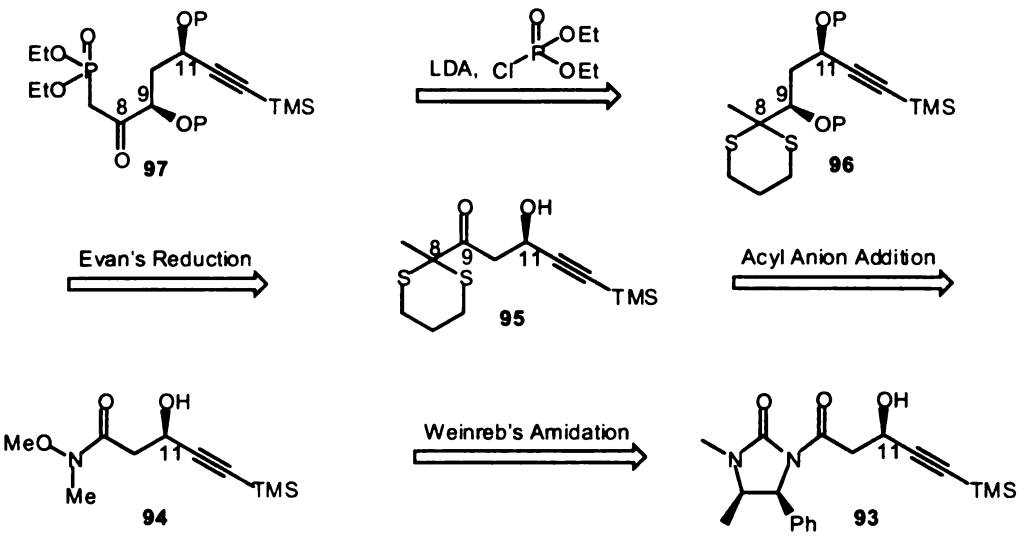


Second Generation Synthesis of the Triol Fragment

In 1997, Boger and co-workers published the absolute stereochemistry of fostriecin. 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 and Sharpless AD would be replaced by an acyl anion addition and an Evan's 1,3-*anti* reduction as key reaction steps as outlined in Figure III-2.[62]

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 of the β- keto alcohol 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 **94** to the dithiane adduct **95** was planned utilizing the previous work of Leibeskind who demonstrated that Weinreb's amide could be directly alkylated with 2-lithio-1,3-dithiane.[63] The one-step conversion of **93** to **95** by addition of 2-lithio-1,3-dithiane to **93** failed. In addition the direct conversion of **93** to **94** failed. The synthesis of **95** was achieved by initial conversion of **93** to the methyl ester and then transformed to **95** via **94**.

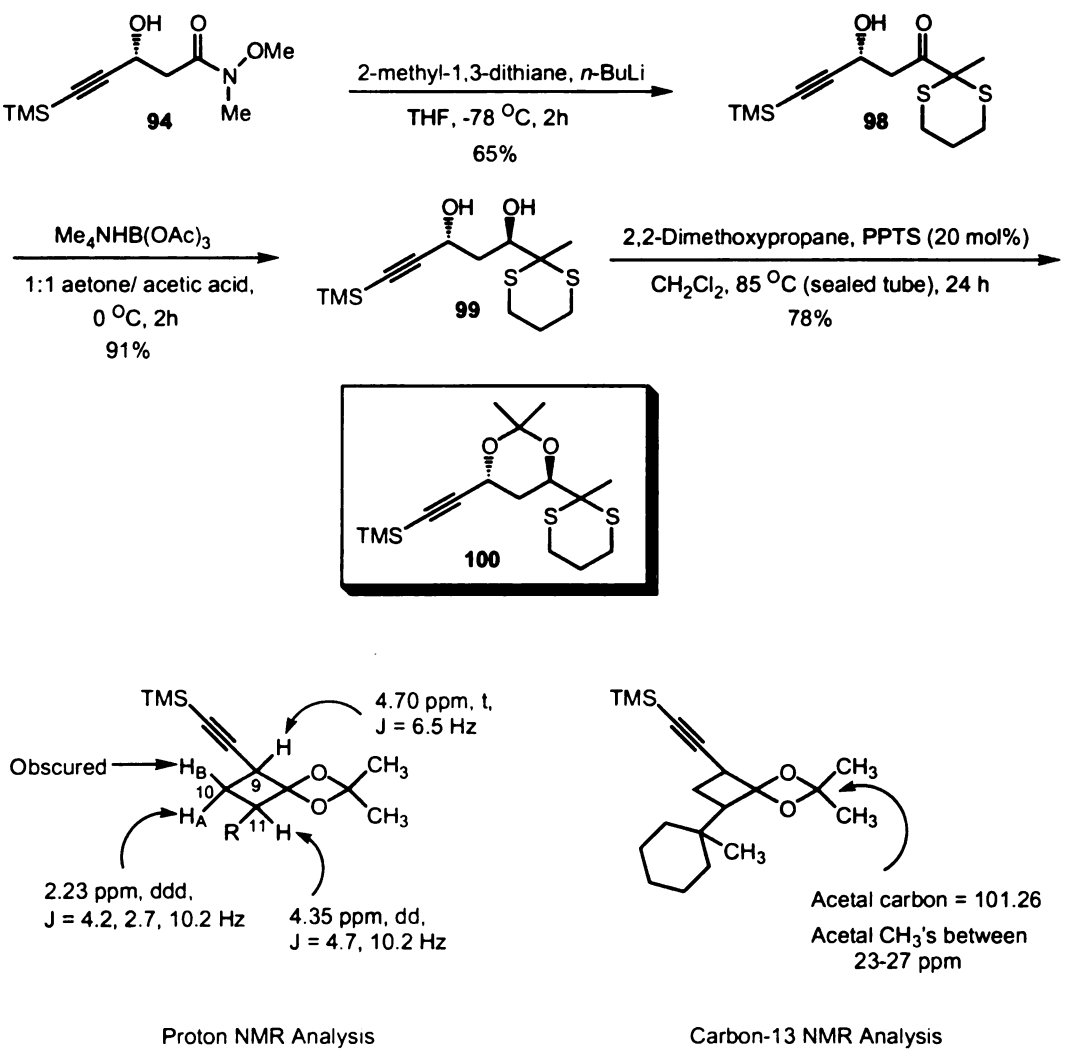
Figure III-2 Second Generation Retrosynthesis of Triol Fragment



As shown in Figure III-3, the reduction of **98** with Evan's procedure gave a single diastereomer by proton NMR, which was presumed to be the *anti*-diol **99**. The *anti*-stereochemistry was confirmed by Mark Parisi upon derivatization of diol **99** with 2,2-dimethoxypropane and subsequent proton and carbon-13 studies.[60] 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 in Figure III-3 provided additional verification of the relative stereochemistry of the two alcohols.[21,66] The chemical shift of the acetal carbon is 101.26 ppm, within the range

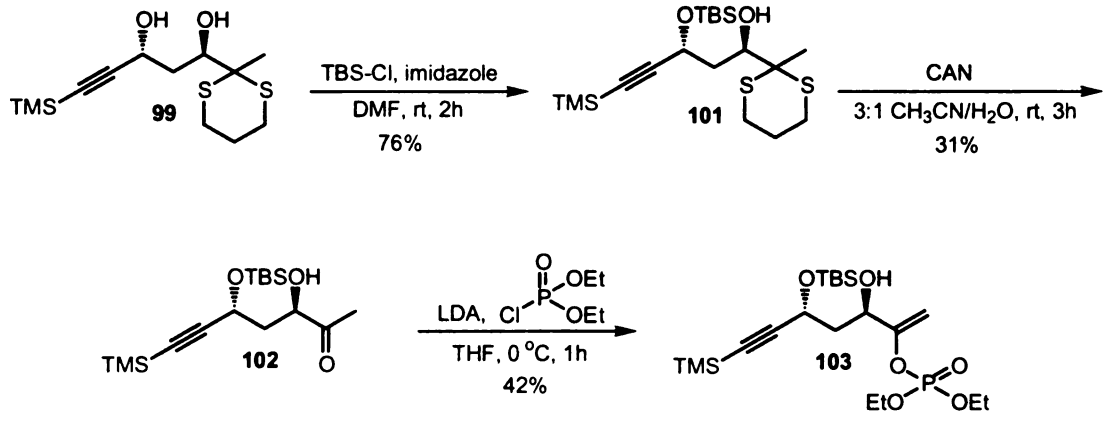
reported by Rychnovsky[66] for *anti* diol acetonides (*syn* acetonides usually have chemical shifts near 99.0 ppm), and well outside the 99.5-100.5 ppm range where and assignment could be ambiguous. The methyl groups on the acetonide are located between 21 and 27 ppm, also well within the range reported by Rychnovsky 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



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 and cerium ammonium nitrate (CAN) oxidation afforded the ketone **102** in moderate yields.[67] The product expected from the TBS protection of **99** was the bis silyl ether. This was shown by Su Yu to be the mono-silyl ether **101** correcting an error that had been made in Mark Parisi's thesis. Oxidative cleavage of the dithiane in **101** gave the ketone **102**. Alkylation of the enolate of **102** with diethyl chloro phosphonate was found to give the O-alkylated product **103** and not the desired C-alkylated product.

Figure III-4 Protection, Oxidation and Phosphonate Addition



In addition to the above problem of O-alkylation, 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 dithiane. So again another strategy was sought at this point.

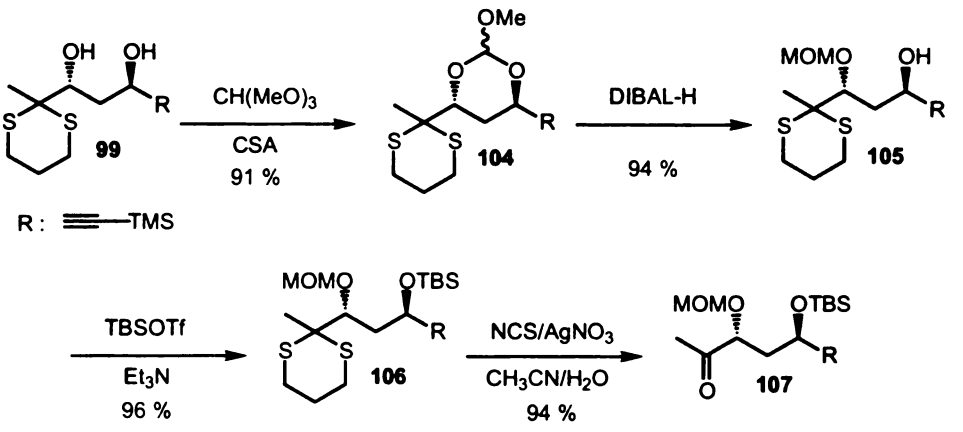
Third Generation Synthesis of the Triol Fragment

Fortunately, the third route sought would retain the same key steps. A change of one protective 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 **99** 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.

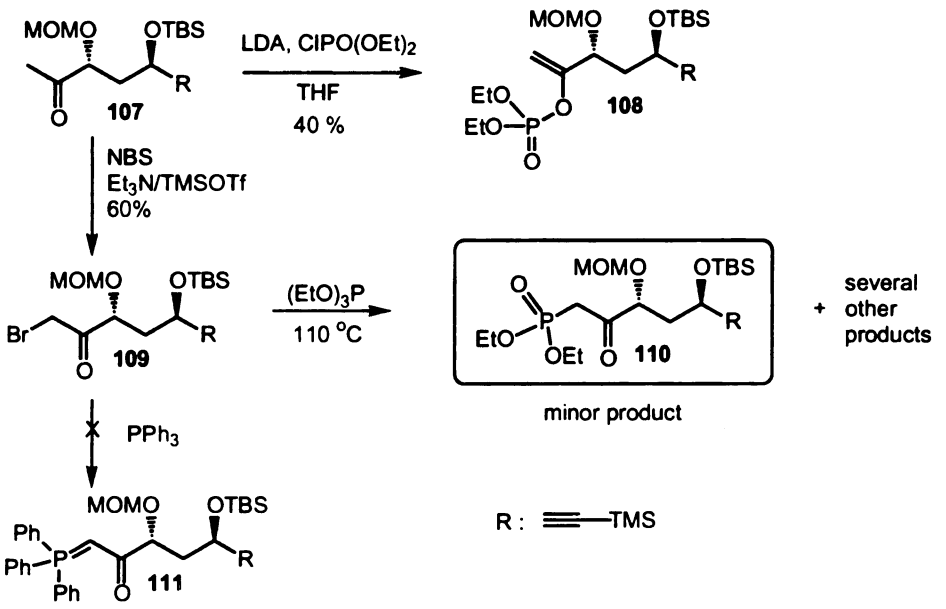
Su Yu, a post doctoral fellow in the Wulff group, utilized a trimethyl ortho ester formation and its reductive cleavage as a solution to this problem (Figure III-5).[68,69] Reductive cleavage with DIBAl-H placed the MOM group on the more hindered C_9 alcohol, and a subsequent TBS protection of the C_{11} 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



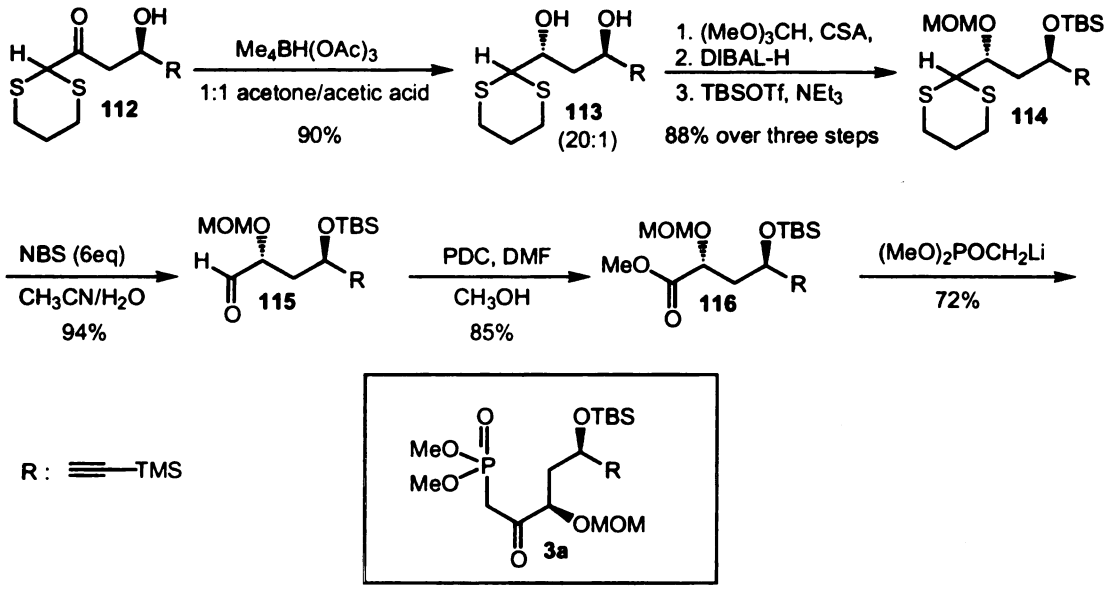
With the problem of selective protection of C_9 vs C_{11} solved attention was turned to the problem of C vs O phosphorylation. It was envisioned that *O*-phosphorylation could be reduced if the ketone **107** was converted to an alpha bromo ketone and the Arbuzov's reaction perfomed. Xuejun Lui in our group found that the reaction of the bromo ketone **109** with triethyl phosphite gave several products with the desired phosphonate **110** as a minor product. Conversion to the triphenyl phosphine **111** derivative from the alpha bromo ketone **109** also failed. The reaction gave primarily reduction to **107**.

Figure III-6 Preparation of Phosphonate



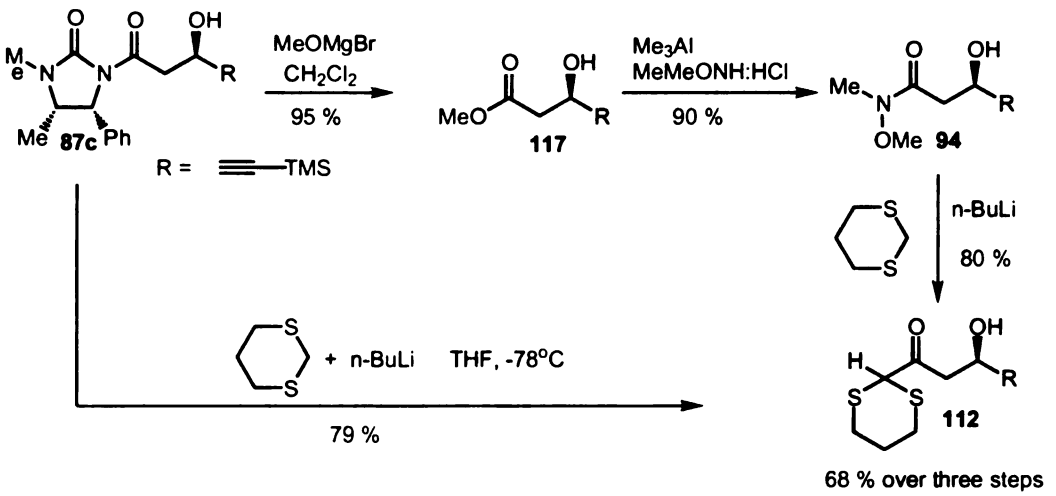
In 2001 Xuejun Lui suggested that the methylene unit alpha to the phosphonate in the triol fragment could be installed via nucleophilic addition of a phosphonate enolate to a methyl ester (Figure III-7). This meant that instead of using 2-methyl-1,3-dithiane as an acyl anion equivalent 1,3-dithiane would have to be used. This reaction sequenced worked smoothly to produce the desired phosphonate **3a** in a 7.6% yield over 15 steps.

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 **93** to the dithiane derivative **95** (Figure III-2). Xuejun successfully achieved this transformation of **87c** to **112** in 79% yield as shown in Figure III-8. This removed two steps in the preparation of **3a** to provide a 13 step synthesis in 8.8% overall yield. This step was later optimized to 92% increasing the overall yield of this fragment to 10.2%.

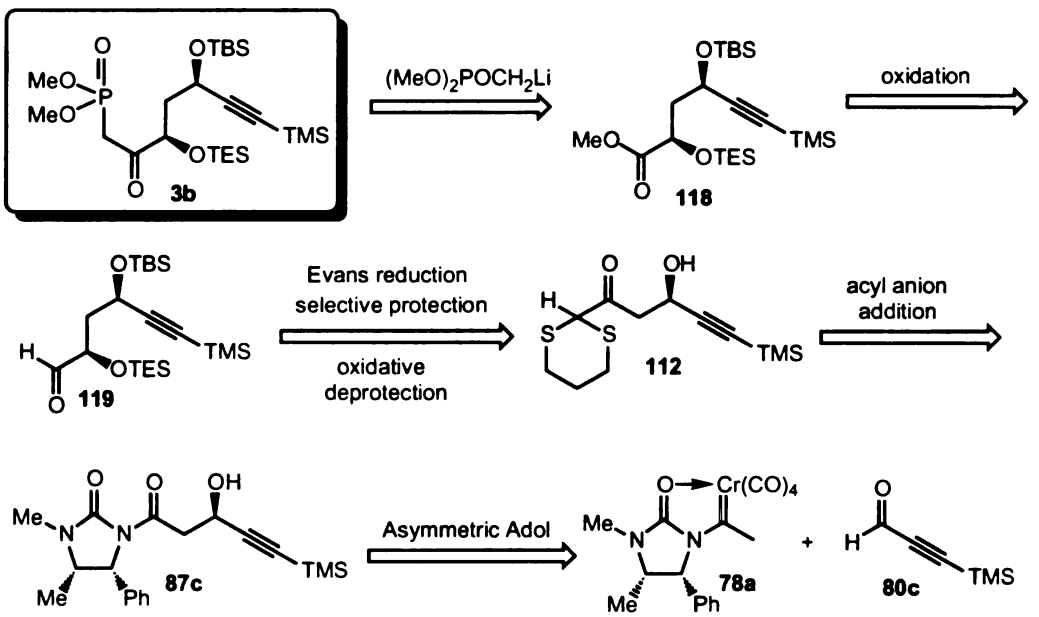
Figure III-8 Improved Acyl Anion Equivalent Addition



Final Synthetic Strategy of the Triol Fragment

The first total synthesis of fostiecin (CI-920) was achieved by Boger and co-workers around the same time our triol fragment was completed and being scaled up. Boger had employed similar approaches to the coupling of the lactone fragment to the rest of the molecule and the methylation of the C_8 carbonyl. 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. He achieved this using MeLi-$CeCl_3$ mixture resulting in a 3:1 diastereomeric ratio, with a 20:1 ratio of 1,2 versus 1,4 addition products. 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. The protecting group used in Boger's synthesis was a triethyl silyl group which is known to promote non-chelation controlled additions. This meant our synthetic approach had to be modified to avoid this problem (Figure III-9).

Figure III-9 Final Retrosynthetic Analysis of the Fostriecin Triol Fragment



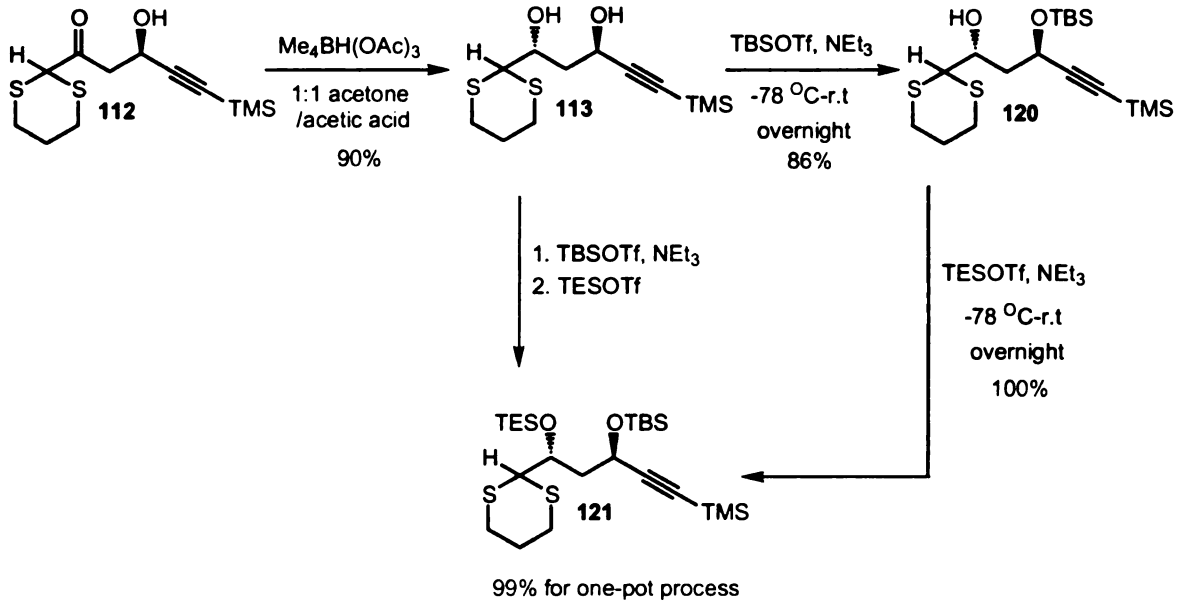
Problems Encountered in Modification

At first glance it may seem like a trivial task to change the protecting groups at the C_9 position, however many challenges were encountered mainly due to the lability of the TES group.

Since there was a ready supply of the MOM protected intermediate **114**, the most efficient approach to **121** (Figure III-10) would be to develop a protocol for the removal of this MOM group from **114** and then reprotection with a TES group.[70] The product obtained, however was a mixture of undesired compounds. Better luck was obtained when the trimethyl ortho ester of **113** was reduced back to the diol **113** using boron triflouride etherate ($BF_3.OEt_2$) in mercaptoethanol.[71] 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 **113** was modified. With the change from substituted dithiane **99** (Figure III-5) to the monosubstituted dithiane **113** (Figure III-10) it was thought that the slightly less hindered environment at C_9 may make the required stepwise selective protection feasible. Using this change to our advantage we protected the C_{11} alcohol with TBS and subsequently were in fact able to protect the C_9 alcohol with the TES group. The results were encouraging with an overall yield of 86% for the two steps. As can be seen from Figure III-10, the conditions required for protection of C_9 and C_{11} were identical, 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 the result, almost quantitative.

Figure III-10 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 **115** (Figure III-7, see experimental for details).[72] However, repeating this protocol with the TES protected **121** 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 an acetonitrile with a propionitrile solvent system. This also gave only 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 screening reactions were set up as seen in Table III-1. Two of the five reactions screened gave a clean crude proton

NMR of the desired product.[73] In entry 5, one can see that using the same conditions developed before for the MOM derivative **114**, and with addition of $CaCO_3$ gave a good result. Based on this observation, it was hypothesized that a buffer 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 at that concentration would leave 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.

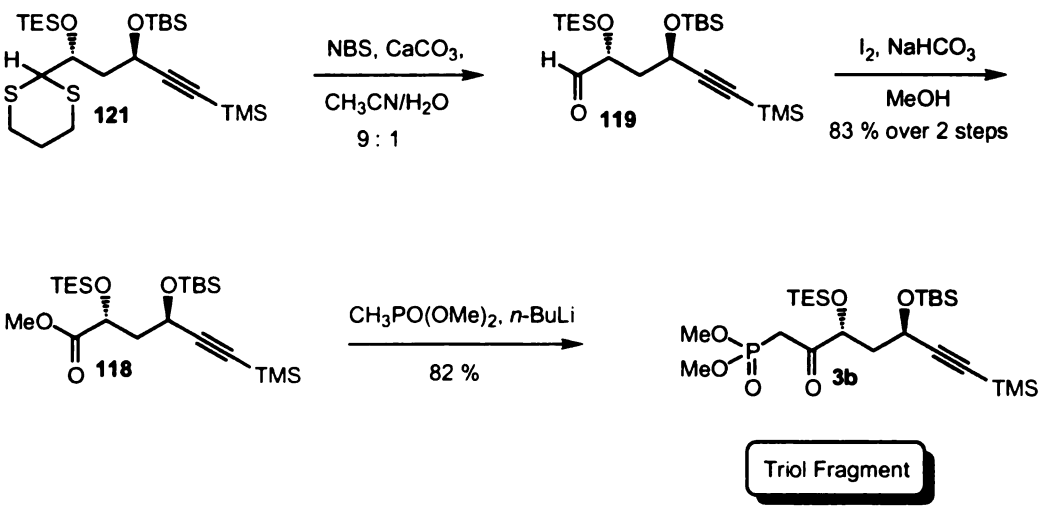
Preparation of the Methyl Ester

Having overcome one major set back, the synthesis was continued as planned. A pyridinium dichromate (PDC) oxidation in methanol (MeOH) and dimethyl formamide (DMF) proved successful in the conversion of the alsehyde **115** to ester **116** (Figure III-7).[74] Again problems were encountered when this procedure was apllied to the TES protected aldehyde **119** since only a 44% yield of the methyl ester **118** was obtained which had lost its TES protecting group.

The solution to this predicament came via a *Leibegs Ann. Chemistry* 1992 publication by the König group.[75] In their strategy an iodine (I_2) oxidation in MeOH in the presence of sodium bicarbonate ($NaHCO_3$) was reported as 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 **121** to the methyl ester **118** was attempted and found to work. It was found that purification of the aldehyde via chromatography was unnecessary to obtain good yields. A simple work-up with a saturated solution 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 a yield of 83%.

Figure III-11 Oxidative Deprotection and Triol Fragment Completion



Preparation of Phosponate 3b

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 **116** to **3a** (Figure III-7) were attempted on ester **118**.[76] The reaction was however not complete after 48h. This was suprising since the MOM protected derivative **116** only required 2h. Increasing the reaction temperature to 25 ^{o}C overnight gave **3b** in an 82% yield of the final triol fragment **3b** for a total of 14.2% yield over 10 steps.

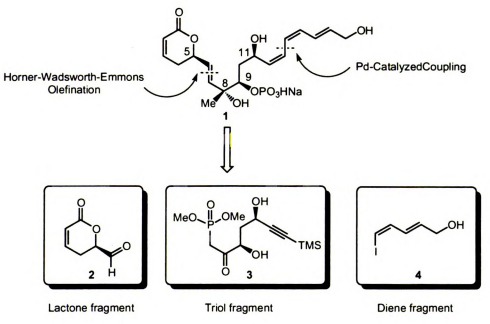
While repeating the sequence in Figure III-11, other problems were incurred that were not seen in the first time through. The *n*-butyl lithium used must have an accurate titer otherwise the TES group is lost. In addition when performing silica gel chromatography on the intermediates a solvent system containing 0.5-1% triethyl amine should be used a precautionary measure to avoid any loss of the TES group.

CHAPTER 4

FINAL ASSEMBLY OF FRAGMENTS AND PLAN FOR COMPLETION

With the three fragments in hand, it was planned that the lactone and triol first would be assembled first, by utilizing a Horner-Wadworths-Emmons (HWE) reaction. After methyl addition to the ketone at C_8 and deprotection of the acetylene, a palladium cross coupling to the diene fragment 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 at C_{12} versus a triple bond at C_{12} in our compound (Figure IV-3, Figure IV-8). In addition the silyl groups on the C_{18} primary alcohol differ, a TBS group in our fostriecin core versus a TBDPS group in Boger's .

Figure IV-1 Our Retrosynthetic Analysis of Fostriecin

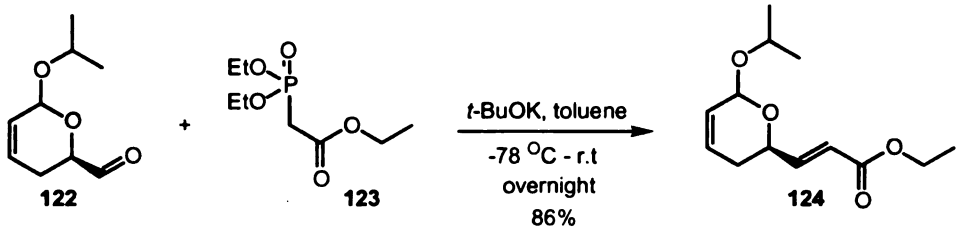


The Horner-Wadsworth-Emmons Reaction

The retrosynthesis shown in Figure IV-1 like the synthesis by Boger and the synthesis by Just and O'Connor employs a Horner-Wadsworth-Emmons reaction as a key reaction necessary to obtain the *E*-configuration at C_5-C_6 double bond. Attempts to repeat Bogers' protocol for the Horner-Wadsworth-Emmons reaction gave a disappointing 12% yield as the best result (Figure IV-2). In order to test whether the substrate **3b** was sensitive to these conditions, the reaction was repeated with the simple substrate **123** and the *E*-olefin **124** was obtained in 86% yield. Thus it is likely that the TMS-protected acetylene unit in **3b**, which is not present in Boger's phosphonate 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]

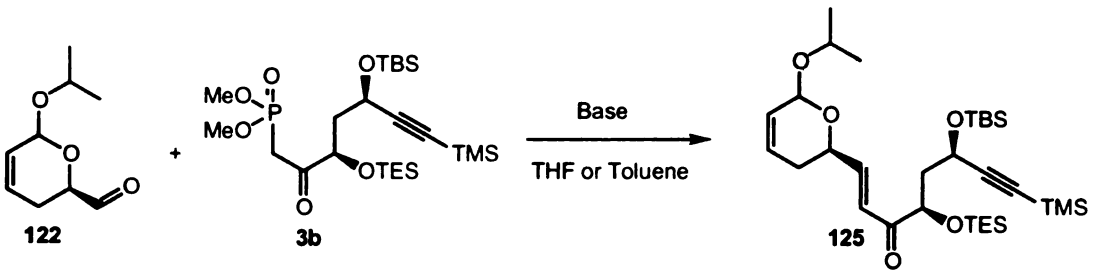
Figure IV-2 Attempts at Horner-Wadsworth-Emmons Coupling

Model Reaction



122 123 124

Screening Reactions and Conditions



122 3b 125

	Conditions	Yield (%)
1)	*t*-BuOK, toluene, -78 °C - r.t, overnight	12
2)	LDA, THF, **3b**, -78 °C, 45 min, ii) then aldehyde, -78 °C, 45 min, r.t, 2h	45
3)	LiCl, THF, **3b**, 5 min, ii) 0 OC; Et3N, warm to r.t, 30 min iii) 0 OC, aldehyde, warm to r.t, 24 h	94

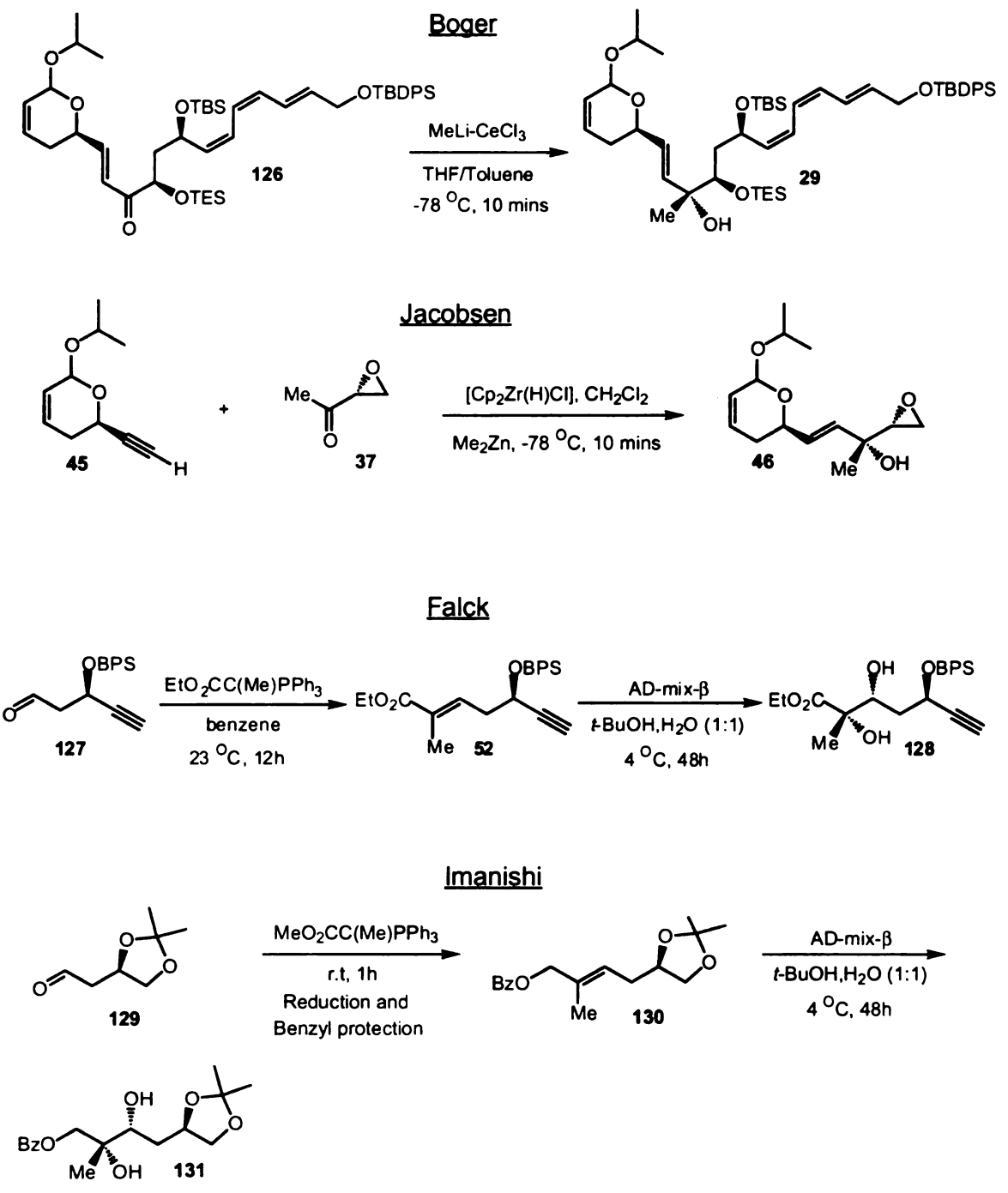
The Methylation Step

Of the many total syntheses and synthetic strategies towards fostriecin that have been published, there are only three fundamental methods used to establish the proper stereochemical relationship between the chiral centers at the C_8 and C_9 carbons. These three methods are the addition of a vinyl organometallic reagent to the ketone **37**, the addition of a methyl organo-

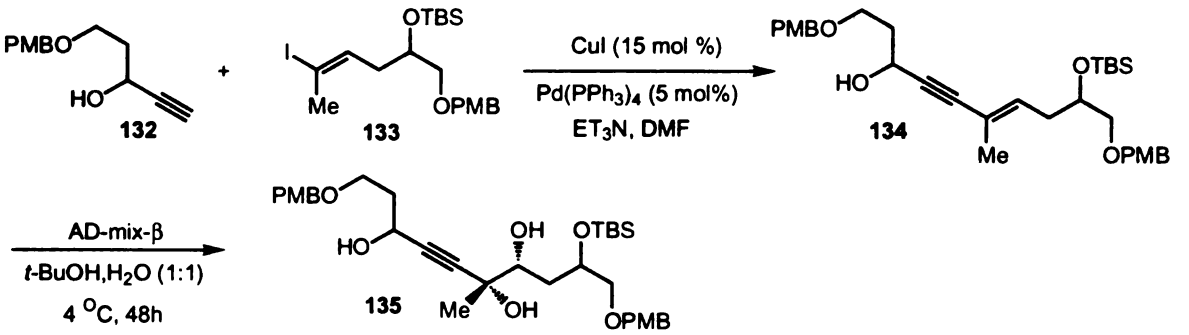
metallic reagent to the ketone **126** and the Sharpless AD of the substrates of the type **52**, **130** or **134**. Boger's and Jacobsen's synthesis both involved the addition of organometallic reagents to set the relative stereochemistry at C_8 and C_9. These approaches are also complimentary in regard to whether the bond being made is part of the carbon backbone or not. The approach taken here is similar to Boger's since the carbon backbone is already present in the ketone to be alkylated.

The best result Boger obtained was the addition of a methyl cerium reagent to the ketone **126** to give a 98% yield of a 3:1 diastereomeric ratio of C_8 epimers with a 20:1 ratio of 1,2 to 1,4 addition products (Figure IV-3). This reagent was prepared by the addition of 15.2 equivalents of MeLi to 15.8 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 ^{o}C-90 ^{o}C for 2 h, then at 130 ^{o}C-140 ^{o}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). Impassioned to improve upon this selectivity it was decided to try a more bulky methylating agent. Addition of methyl titanium tris(isopropoxide) to ketone **125** resulted in an 80% recovery of starting material. This outcome was not too discouraging because we knew beforehand that Boger had also been unsuccessful at his attempt with this less reactive reagent. An attempt to reduce the steric bulk by using dimethyl titanium bis(isopropoxide) was considered since it is an inherently a more reactive nucleophile. However, this reaction also resulted in only recovery of starting material (Figure IV-4).

Figure IV-3 Strategies Used for Constructing the C_8 Chiral Center

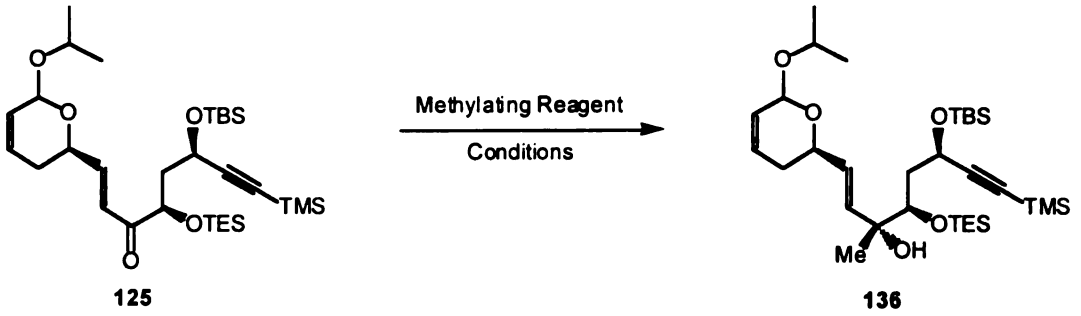


Kobayashi



Given the unreactivity of the methyl titanium reagents, attention was turned to the methyl cerium reagent prepared according to his procedure. The ketone **125** under his conditions only resulted in the recovery of the starting material in 57% yield. The failure of the addition of methyl cerium reagent to ketone **125** was perplexing because the ketone used by the Boger group differed from ours only in the side chain attached to C_{11} which is far away from the active site. The side chain contained the necessary *Z,Z,E*-trienol protected by tertiary butyl diphenyl silyl (TBDPS) in their substrate **126** the ketone **125** contained a TMS protected acetylene at the side chain. At this point a model system was devised using α-tetralone as the substrate. This reaction probably also failed due to the inadequate preparation of dry $CeCl_3$.

Figure IV-4 Attempts at Methylation

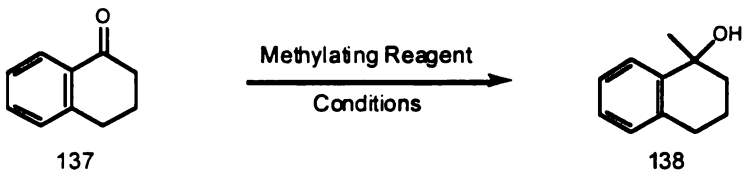


125 136

Entry	Methylating Reagent	Conditions	Results
1	$ClTi(i\text{-}PrO)_3$, MeLi(1eq)	-40 ^{O}C,1.5 h, add **125**, warm to r.t, 3 days	90 % starting material recovered
2	$ClTi(i\text{-}PrO)_3$, MeLi(2eq)	-30 ^{O}C,10 mins,add **125** warm to r.t, 3 days	83 % starting material without TES recovered
3	MeLi-$CeCl_3$	-78 ^{O}C, MeLi, 10 mins, 0 ^{O}C, 10 mins, -78 ^{O}C, add **125**, r.t	57% starting material recovered

There is one other example of a stereoselective methyl addition to a ketone at C_8 in a synthesis of a Fostriecin diastereomer and this was from the work of Just in 1988 (Figure I-7).[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 **13** was obtained in 60% yield. The problem was that they obtained the chelation controlled product using this reagent. Their C_9 and C_{11} alcohol groups in their ketone **12** were protected with an acetonide which promotes this type of stereocontrol. The C_9-*S* stereogenic center of compound **12** (Figure I-7) gave the correct C_8 stereochemistry. It was hypothesized that in order to maintain the correct stereochemistry at C_8, while using C_9-*R* chiral center, a non-chelation controlled approach would be necessary.

Figure IV-5 Model Methylation Reactions

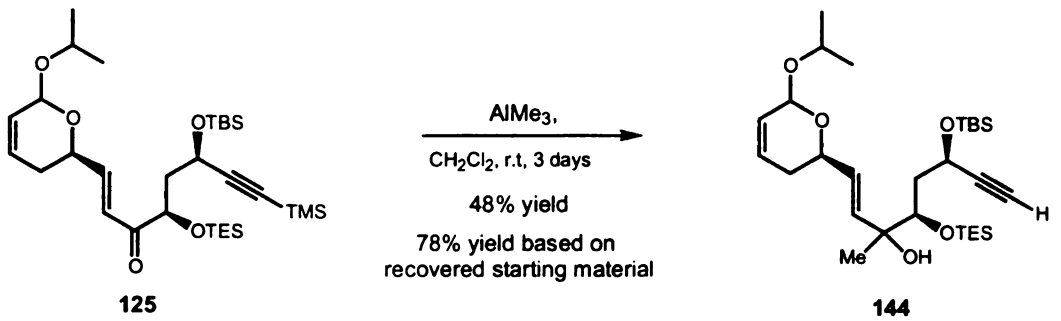


137 138

Entry	Methylating Reagent	Conditions	Results
1	MeLi-$CeCl_3$	-78^{O}C, MeLi, 10 mins, 0 ^{O}C, 10 mins, -78 ^{O}C, add **137**, r.t	No reaction
2	$AlClMe_2$	-15 ^{O}C, add **137** warm to r.t, 3 days	No reaction
3	$AlMe_3$	-15 ^{O}C, add **137** warm to r.t, 3 h	99 % **138**

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. The reaction with $AlClMe_2$ was disappointing since after three days there was no reaction. In contrast the reaction with $AlMe_3$ was quite facile giving a 99% yield of **138** in three hours. When this methodology was applied to our desired substrate **125** a 48% yield of methylated product **144** was obtained. This reaction is rather sluggish by comparison to the model study using α-tetralone **137**. It required three days for a 60 % conversion to **144** (Figure IV-6).

Figure IV-6 Methylation of Ketone 125 with $AlMe_3$



125 144

There were at least three other advantages to using $AlMe_3$ as a methylating reagent. First, no 1,4 addition product was observed as reported by Boger.[22] 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-7), in which compound **12** gave a 98:2 ratio of C_8 epimers with no 1,4 addition product being reported.

Secondly, there only appears to be one diastereomer of compound **144**. The TES protecting group on C_9 in **125** (Figure IV-6) 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 **12** (Figure I-7). This difference in size may prevent chelation and lead to the correct stereochemistry at C-8.

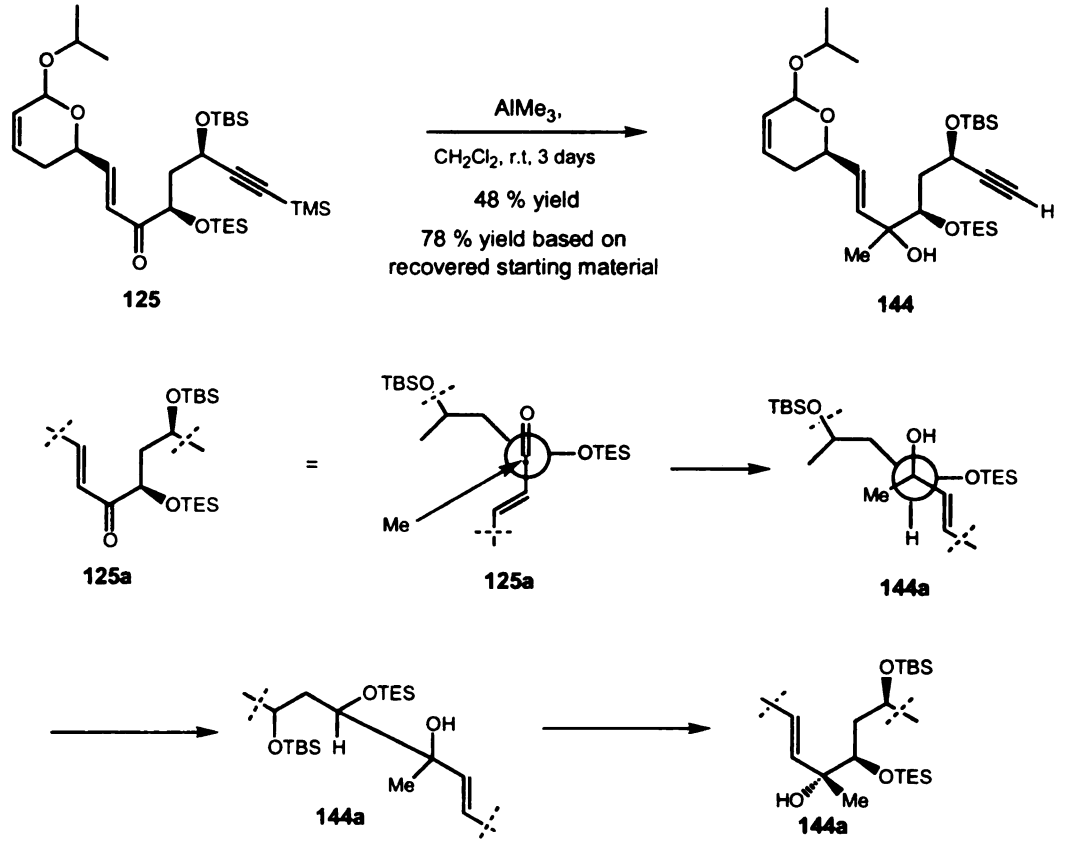
The last but certainly not the least advantage was that the TMS group on acetylene **125** was cleaved during this reaction (Figure IV-6). The product of this reaction was expected to retain the TMS protection of the acetylene in **125**. A selective deprotection of TMS would have been required prior to the palladium cross coupling reaction seen in Figure IV-8. This result evades that step. The loss of the TMS group was confirmed by the appearance of an acetylenic proton at 2.16 ppm in the proton NMR and the

disappearance of the nine trimethyl protons of TMS at 0.04 ppm. We are currently trying to optimize these reaction conditions and determine the relative stereochemistry of this molecule.

Determining the Stereochemistry at C_8

One of the advantages of using $AlMe_3$ as a methylation reagent mentioned above was that only one diastereomer is obtained, which is confirmed by NMR. According to Figure IV-7 the non-chelation controlled Felkin product is predicted. The bulky TES protecting group should prevent chelation control and give the desired stereoisomer. Boger obtained a 3:1 mixture of diastereomers for this step, with the Felkin model (Figure IV-7) as the major isomer. Since Boger's compound (Figure IV-3) has the identical environment around C_8 to compound **125** (Figure IV-6), we intend to compare the coupling constants of diastereomers **144** (Figure IV-3) to **29** (Figure IV-6) to confirm which isomer has been made.

Figure IV-7 Predicted Model for C_8 Methylation



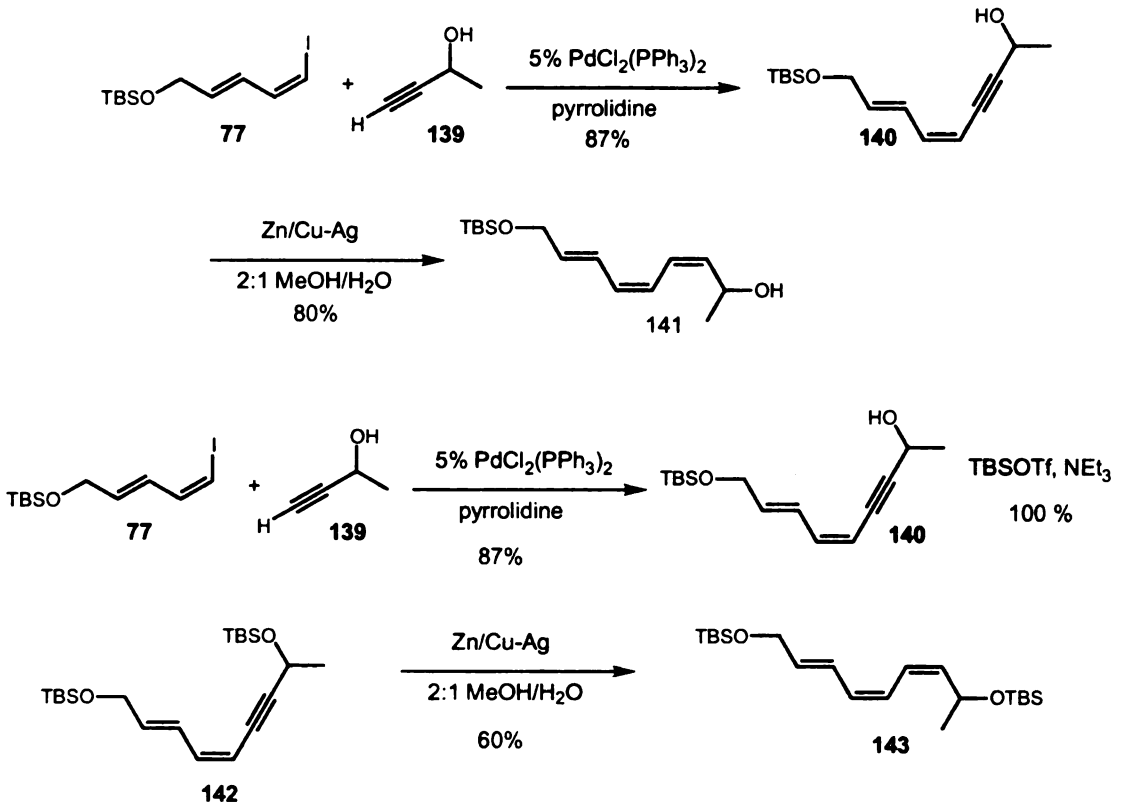
Palladium Cross Coupling

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. Subjecting the aldehyde **76** to Stork's protocol for synthesis of *cis* iodo-alkenes, the *Z,E*-iododiene was obtained in 84% yield with a 9:1 ratio of separable isomers (Chapter 2 Figure II-3). Due to its light sensitivity and its instability in solution, the desired *Z,E*-isomer of **77** was immediately used after purification in the model study shown in Figure IV-

7. Using 1-butyne-3-ol as the model acetylene, the palladium cross coupling gave an 87% yield of dieyne **140**.[79] The subsequent reduction[80] proceeded cleanly to give the *Z*,*Z*,*E*-triene **141** with no evidence of over reduced products or starting material as indicated by the carbon-13 spectrum.

It is known that the Zn/Cu-Ag reduction of acetylenes is influenced by the environment around the acetylene.[80] The model compound **140** possesses a free propargyl alcohol (Figure IV-8), this is different from the desired substrate compound **144** (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 **140** was protected with TBS giving the TBS protected dienyne **142** in quantitative yield. The reduction was successful giving an unoptimized yield of 60% for the conversion of dienyne **142** to the *Z*,*Z*,*E*-triene **143**.

Figure IV-8 Model Study for Diene Triol Coupling



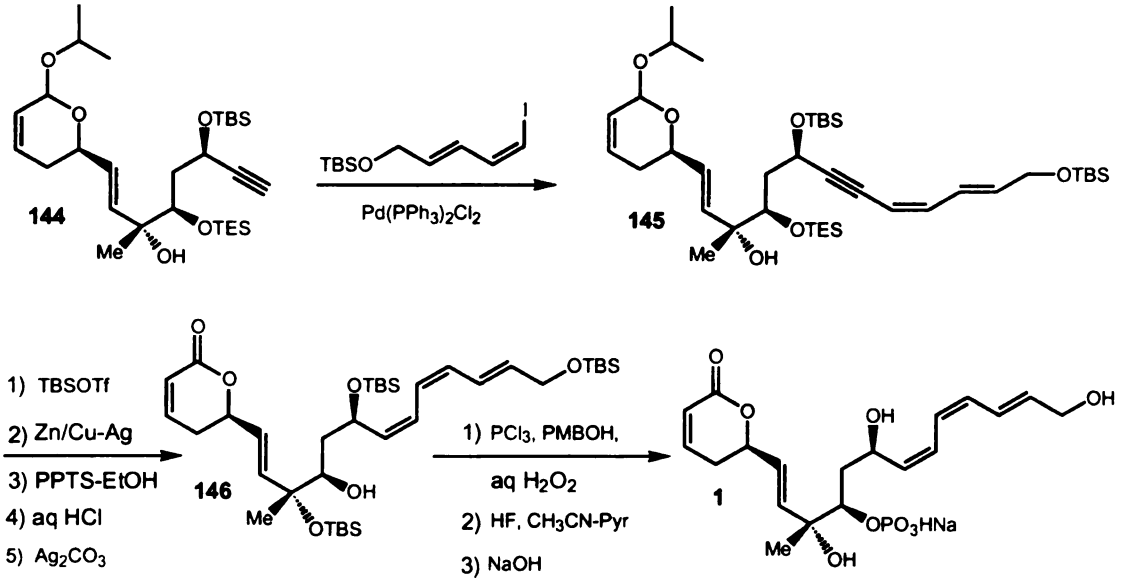
Plan for Completion

This successful model study is encouraging and gives confidence that these steps can be extended to the actual substrate **144** in high yields. Upon coupling and reduction of the alkyne, the fostriecin core would be in hand and all that is required is the conversion of the acetal to the lactone, a couple of protecting and deprotecting steps and installation of the phosphate group on C_9 (Figure IV-9).

After the palladium cross coupling to give **145** the tertiary alcohol on C_8 will be protected with a TBS group and the *cis* reduction of the alkyne will follow. All the remaining steps have been accomplished in Boger's synthesis of fostriecin on an almost identical compound.[22] A selective

deprotection of TES with pyridinium para toluene sulfonate (PPTS) and ethanol also transforms the isopropyl group to the ethyl group on that oxygen. A silver carbonate oxidation restores the ethyl acetal to the lactone which when treated with phosphorous trichloride (PCl_3), para methoxy benyzl alcohol (PMBOH) and aqueous hydrogen peroxide (H_2O_2) installs the phosphonate. Global deprotection of this compound and sodium salt formation should afford the natural product.

Figure IV-9 Plan for Completition of the Total Synthesis of Fostriecin

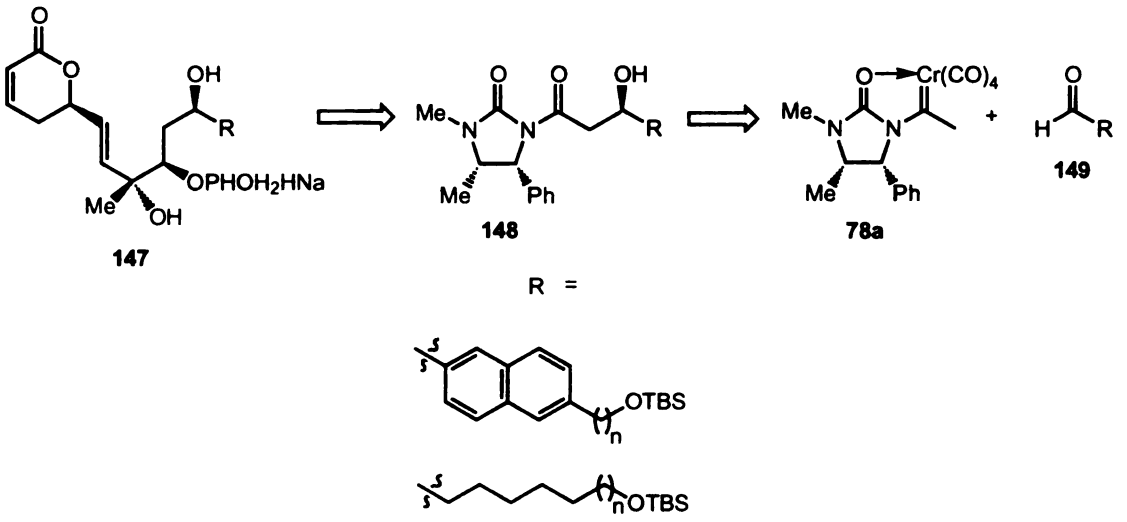


Synthetic Studies of Closely Related Analogs

Our ultimate goal is not just the total synthesis of the natural product itself, but also the synthesis of some closely related analogs. Fostriecin is somewhat unstable and when used in the clinic must be stored frozen in a buffer. It is suspected that the source of instability the triene-diol moiety. To test this, it is planned to utilize the general synthetic strategy developed to

prepare a number of derivatives that hopefully will still be active and at the same time be much less sensitive compounds. These analogs and their retrosynthetic analyses are shown in Figure IV-10.

Figure IV-10 Retrosynthetic Anaylsis of Fostriecin Analogs

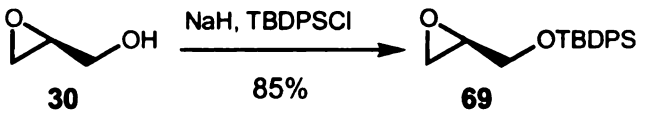


Our synthetic strategy for the synthesis of fostriecin has been planned to allow for significant molecular diversity with a minimum of modification of the retrosynthesis as indicated in Figure IV-10. This will be attempted by employing different aldehydes as substrates in the asymmetric aldol reaction to establish the C_{11} streocenter. These derivatives are anticipated to have a greater chemical stability than the natural product itself.

CHAPTER 5

Experimental

Experimental Data for Chapter 2

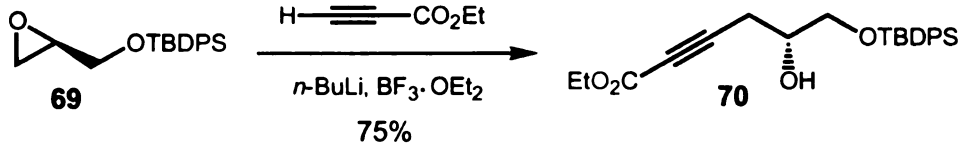


30 69

[a]**(*S*)-(Tert-butyldiphenylsilyl)glycidol 69.** A 500 mL round bottom flask was charged with *(S)*-glycidol (5.00g, 67.5 mmol) and dissolved in 200 mL CH_2Cl_2. DMAP (330 mg, 4 mol%) and triethylamine (7.518g, 10.35 mL), were added and the flask was placed under argon atmosphere. Tertbutyldiphenylsilyl chloride (20.41 g, 19.3 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 (50 mL), poured into a sep funnel, and the organic layer was washed with saturated NH_4Cl solution (2 x 50 mL), water (3 x 100 mL), and brine (1 x 100 mL), 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 was isolated 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, 4.2 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 spec. *m/z*: 255 (50), 225 (100), 211 (24), 183 (74), 177 (40), 135 (8), 117 (43), 105 (17), 91 (11), 77 (15); bp140-150 °C/0.2 torr, R_f = 0.5 (9:1 pentane/ether), $[\alpha]_D$ = -3.13° (c = 1.05, $CHCl_3$), colorless oil. Yield: 17.92g (85%).



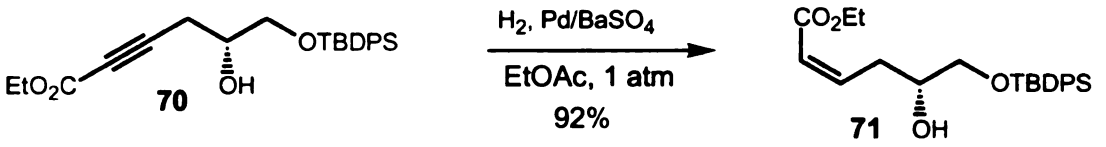
[a]**Alkynal Ester 70.** A 250 mL round bottom flask was charged with freshly distilled ethyl propiolate (0.76 g, 0.75 mL), and dissolved in 60 mL THF at –78 °C. A solution of *n*-BuLi (2.5 M in hexane, 3.08 mL), was added via syringe. The pale yellow reaction mixture was stirred for 10 minutes, then BF_3:OEt_2 (1.09 g, 0.98 mL), was added neat via syringe. The yellow color persisted as the reaction was stirred for another 5 minutes, then protected glycidol **69** (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 spot at R_f = 0.26 was collected and concentrated to give the product as a pale yellow oil.

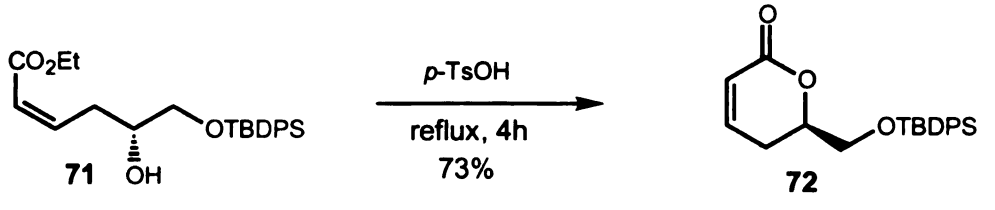
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.30 (t, 3H, J = 7.2 Hz), 2.60 (dd, 2H, J = 2.1, 6.4 Hz), 3.71 (dq, 2H, J = 4.2, 9.8 Hz), 3.93 (quintet, 1H, J = 5.1 Hz), 4.21 (q, 2H, J = 7.1 Hz), 7.38-7.64 (m, 6H), 7.64-7.66 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.02, 19.25, 23.53, 26.82, 61.86, 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 spec. *m/z*: 365 (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, $CHCl_3$), pale yellow oil. Yield: 2.15 g (75%).



[a]**Alkyne Reduction to Give 71**. A 250 mL round bottom flask was charged with ester **70** (2.554 g, 6.22 mmol), and dissolved in 125 mL EtOAc at room temperature. Lindlar 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 spot at R_f = 0.37 was collected and concentrated to give the product as a colorless oil.

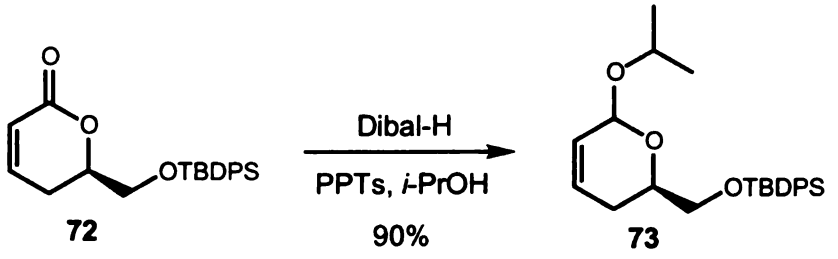
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 9H), 1.26 (t, 3H, J = 7.2 Hz), 2.82 (m, 2H), 3.57 (m, 1H), 3.67 (dd, 1H, J = 4.2, 10.2 Hz), 3.85 (m, 1H), 4.14 (q, 2H, J = 7.2 Hz), 5.87 (td, 1H, J = 1.6, 11.6 Hz), 6.34 (dt, 1H, J = 7.5, 11.5 Hz), 7.37-7.64 (m, 6H), 7.64-7.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.22, 19.25, 26.85, 32.62, 60.02, 67.64, 71.40, 121.67, 127.78, 129.82, 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 spec. *m/z*: 355 (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, $CHCl_3$); colorless oil. Yield: 2.367g (92.3%).



[a]**Lactone 72**. A 250 mL round bottom flask was charted with reduced ester **71** (2.058g, 5.0 mmol) and dissolved in 150 mL hexane (Optima grade, Fisher). Solid *p*-TsOH hydrate (47 mg, 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 spots, one at R_f = 0.6 (presumed to be TBDPS-OH but not characterized) and the product at R_f = 0.20, which was concentrated to a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 9H), 2.45 (dt, 1H, J = 1.2, 10.2 Hz), 2.56 (ddt, 1H, J = 2.7, 11.0, 18.5 Hz), 3.84 (d, 2H, J = 4.9 Hz), 4.51 (m, 1H), 6.05 (dd, 1H, J = 1.1, 9.8 Hz), 6.90 (m, 1H), 7.40-7.44 (m, 6H), 7.64-7.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.25, 25.95, 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 spec. *m/z*: 309 (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, $CHCl_3$), colorless oil. Yield: 1.506 g (73%).

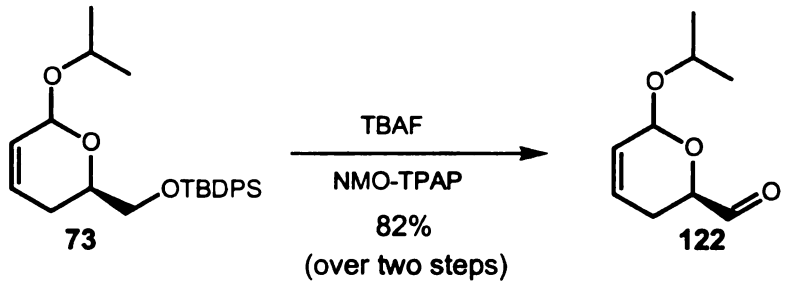


[a]Isopropyl Lactol 73. A 100 mL RB flask was charged with lactone **72** (0.366 g, 1.0 mmol) and dissolved in 10 mL CH_2Cl_2 at –78 °C under argon. A solution of DIBAl (1.0 M in hexane, 1.25 mL), was added via syringe, and the reaction was monitored by TLC for disappearance of the starting material. After 2 h, the reaction was complete. The reaction was quenched at –78 °C with 5 mL saturated NH_4Cl solution, then allowed to warm to room temperature. The reaction mixture was poured into a separatory funnel containing 10 mL CH_2Cl_2 and 10 mL 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 oil redissolved in 10 mL benzene, and isopropanol (0.23 mL, 3.0 mmol, 3 equiv.) and PPTS (0.125 g, 50 mol%) were added to the solution. The reaction was stirred at room temperature while being monitored by TLC. The reaction was complete in 2 h. The reaction was quenched with 10

mL $NaHCO_3$ solution and poured into a separatory funnel. The aqueous layer was back-extracted with benzene (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 spots which co-eluted on TLC. These fractions were concentrated to a colorless oil. The NMR spectra of this oil showed that two diastereomers of the product were present in an 8:1 ratio, by integration of the alcohol methane proton.

Characterization data for major isomer: ^1H 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, 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 = 0.52/0.50 (10:1 hexane/EtOAc); colorless oil.

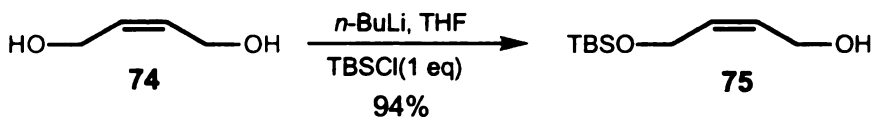


[a]**Deprotected Lactol Precursor to 122.** A solution of lactol **73** (740 mg, 1.87 mmol) was dissolved in 10 mL wet THF at room temperature. A solution of tetrabutylammonuim fluoride (1.0 M in THF, 3.73 mmol, 2 equiv.) was added via syringe. The reaction was followed by TLC (10:1 hexane/EtOAc) to monitor disappearance of the starting material. The reaction was done after 1.5 h.

The reaction was quenched with $NaHCO_3$ solution (10 mL) a 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 as a colorless oil. Yield: 178 mg (91 %).

Characterization data (proton and carbon-13 NMR and IR) matched those reported by Crimmins et. al. in the supplementary material to reference 52 in Chapter 2.

Oxidation to Aldehyde 122. See Chapter 4 experimental section. Characterization data (proton NMR) matched that reported by Crimmins et. al. in the supplementary material to reference 52 in Chapter 2.

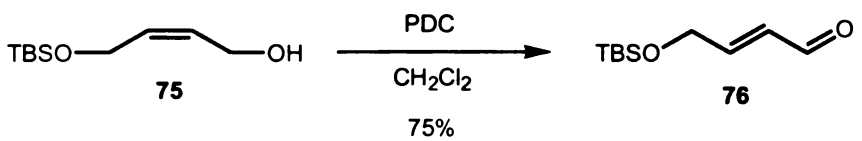


[a]**(*Z*)-4-(tert-butyldimethylsilyloxy)-2-buten-1-ol 75.** *Cis*-2-butene-1,4-diol (4.401 g, 4.11 mL, 50 mmol) was dissolved in 100 mL THF at 0 °C under argon. A solution of 2.5 M *n*-BuLi in hexane (20 mL, 50 mmol) was added via syringe. Insoluble yellow/white clumps of solid were formed upon addition of the *n*-BuLi, which were broken up to 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, 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 a colorless oil.

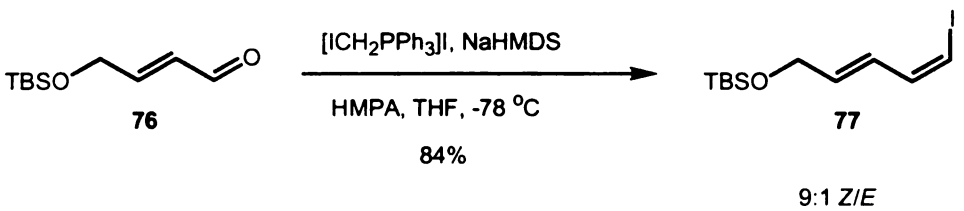
^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 6H), 0.89 (s, 9H), 2.32 (m, 1H), 4.17 (d, 2H, J = 5.1 Hz), 4.23 (d, 2H, J = 5.5 Hz), 5.56 (m, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.30, 18.27, 25.84, 58.69, 59.51, 130.02, 131.15; IR (neat film on NaCl): 3350 (w), 2950-2850 (m), 1472 (m), 1254 (s), 1088 (s), 837 (m), 776 (m) cm^{-1}; EI mass spec. *m/z*: 145 (27), 127 (8), 99 (3), 75 (100); bp 82-88 °C/0.2 torr; colorless oil. Yield: 9.54 g (94.3%).



[a]**(*E*)-4-(tert-butyldimethylsilyloxy)-2-butenal 76**. Alcohol **75** (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), 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 a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 6H), 0.93 (s, 9H), 4.46 (m, 2H), 6.40 (ddt, J = 15.4, 8.0, 2.1 Hz), 6.90 (dt, J = 15.5, 3.0 Hz), 9.61 (d, 1H, J = 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.49, 1.34, 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); colorless oil. Yield: 1.61 g 75%.



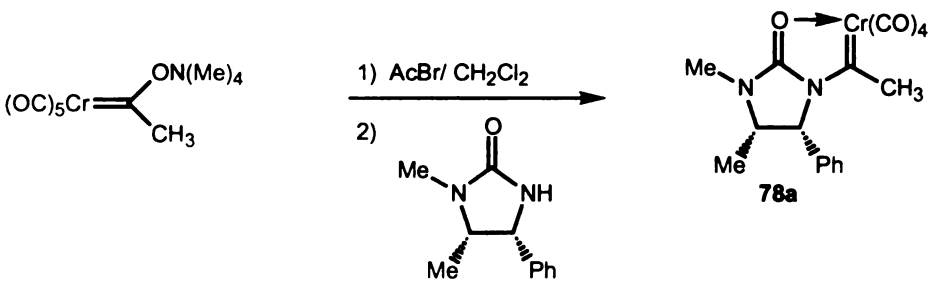
[a]**(*Z*,*E*)-Iododiene 77**. *Note: This compound is light-sensitive, and is best handled in a darkened room and used immediately.* A 250 mL round-

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 1.0M 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 **76** 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), dried over anhydrous $MgSO_4$ and concentrated to a dark brown oil. The oil was taken up in 50:1 pentane/ether, leading to formation of a brown solid precipitate. This precipitate ($Ph_3P=O$) was filtered off through a thin layer of silica gel, and the brown solution was chromatographed on silican gel (50:1 pentane/ether – UV visualization) and concentrated to a light orange liquid. This material had a 9:1 ratio of

cis/trans isomers by integration of the vinylic protons at 6.0 and 6.2 ppm in crude proton NMR spectrum.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 6H), 0.94 (s, 9H), 4.22 (s, 2H), 5.98 (m, 1H), 6.17 (d, 1H, J = 7.4 Hz), 6.42 (t, 1H, J = 10.3 Hz), 6.68 (t, 1H, J = 8.3 Hz); R_f = 0.6 (50:1 pentane/ether); light orange oil; Yield: 4.12 g (84%).



[b]Methyl [(4R, 5S) -1,5-dimethyl-4-phenyl-2-imidazolidinone] methylene tetracarbonyl chromium (0) 78a and its Enantiomer 78b.

Tetramethylammonium(1-hydroxyethylidene)pentacarbonylchromium (0) (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*R*, 5*S*)-1,5-dimethyl-4-phenyl-2-imidazolidinone (1.84 g, 9.7 mmol) was added neat to the solution. The

mixture was gradually warmed to -55 ^{o}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 residue was chromatographed on silica gel with CH_2Cl_2 (Rf = 0.63) to give complex **78a** as a deep-red solid.

Spectral data for **78a**: mp 117 $^{\circ}$C (dec.); ^{1}H 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 (300 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 spec *m/z*: 380 (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. Yield : 65%.

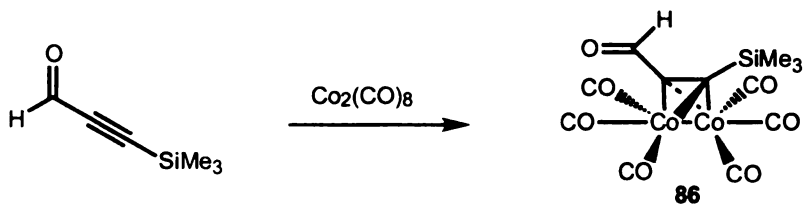
Carbene complex **78b**, the enantiomer of complex **78a**, was synthesized according to the above procedure by using the (4*S*, 5*R*)-1,5-dimethyl-4-phenyl-2-imidazolidinone as the chiral auxiliary.

[a]Preparation of 2-alkynals. Illustrated with the Preparation of Trimethylsilylpropynal 80.

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 methllithium (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 was purified by vacuum transfer (0.2 mm Hg) into a flask cooled to –78 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.260 (s, 9H), 9.16(s, 1H); a colorless acrid-smelling liquid; Yield: 13.4 g (66.5%)



86

[c]Cobalt protected Alkyne 86. To a solution of $Co_2(CO)_8$ (8.75g, 25 mmol) in 100 mL of ether was added aldehyde **80** (3.0g, 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.

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.321 (s, 9H), 10.28 (s, 1H).

a- Data obtained from Mark Parisi's Thesis;[60]

b- Data obtained from Yan Shi's Thesis;[59]

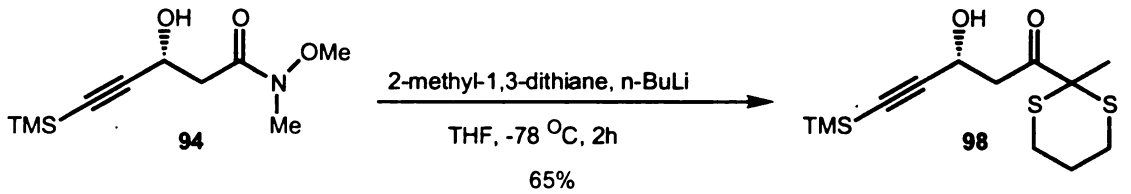
c- Data obtained from the unpublished results of Kenneth Wilson and W. D. Wulff.[58]

Experimental data for Chapter 3.

[a]**Weinreb amide 94.** 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_2C_{12} at 0 °C. The colorless solution was stirred for 45 minutes, then added via cannula to a solution of ester **117** (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 NH_4Cl solution, added slowly to avoid excessively rapid gas evolution, and poured into 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 spot at R_f = 0.29 which was collected and concentrated to a colorless oil.

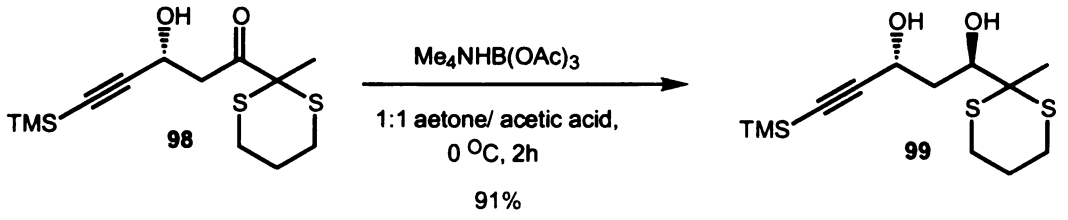
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (s, 9H), 2.83-2.90 (m, 2H), 3.21 (s, 3H), 3.72 (s, 3H), 4.81 (d, 1H, J = 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.32, 31.73, 38.65, 59.22, 61.35, 89.35, 104.91, 172.34; IR (neat film on NaCl): 3600-3200 (m), 2962 (m), 2174 (w), 1645 (s), 1436 (w), 1389 (m), 1250 (s), 1055 (m), 843 (s) cm^{-1}; EI mass spec. *m/z*: 230 (M^+ + H, 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 98. 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 **94** 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

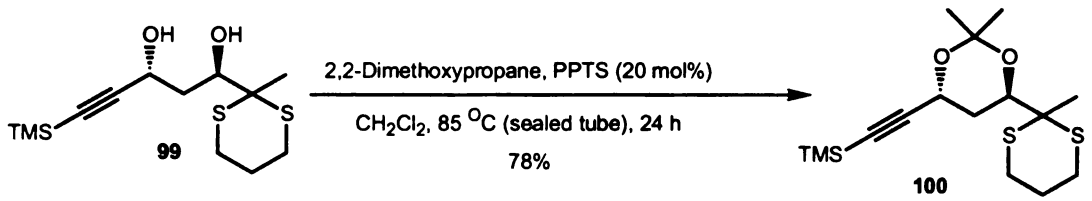
mL, 19.8 mmol, 2.1 equiv.) neat via syringe and briefly stirred. The mixture was poured into a separatory funnel containing 80 mL ether and 80 mL water. The aqueous layer was back-extracted with ether (2 x 30 mL). The combined organic layers were washed with water (2 x 50 mL) and brine (1 x 50 mL), dried 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 a pale yellow oil.

^{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, 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 spec. *m/z*: 302 (1), 269 (1), 195 (0.6), 176 (0.8), 133 (100), 111 (12), 59 (22); $R_f = 0.31$ (5:1 hexane/EtOAc); $[\alpha]_D = 11.6^\circ$ (c = 1, $CHCl_3$); pale yellow oil. Yield: 1.57 g (55.2%).



[a]Diol 99 by Evans Reduction. See Chapter 4 for the Procedure, reaction was ran at a 2.71 mmol scale.

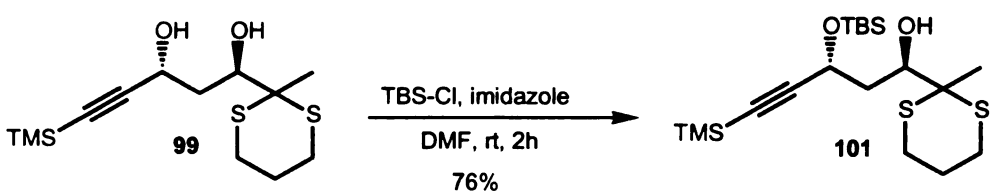
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 ((s, 9H), 1.37 (s, 3H), 1.83 (m, 2H), 2.12 (m, 1H), 2.41 (m, 1H), 2.59 (m, 2H), 3.09 (m, 2H), 4.67-4.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ -0.06, 21.29, 24.13, 25.59, 25.79, 35.93, 52.74, 61.82, 68.34, 89.32, 106.65; IR (neat film on NaCl): 3600-3100 (m), 2895 (w), 2173 (w), 1249 (m), 1058 (m), 842 (s) cm^{-1}; EI mass spec. *m/z*: 304 (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, $CHCl_3$); white fibrous needles; Yield: (91%).



[a]**Acetal 100**. A solution of diol **99** (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 one-neck Kontes 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.

^{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,

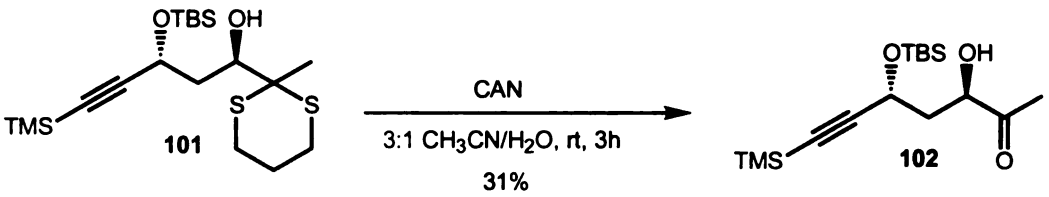
24.89, 26.81, 27.24, 34.05, 50.19, 61.82, 68.32, 74.16, 90.77, 101.26, 106.63; IR (neat film on NaCl): 2936 (m), 2169 (w), 1380 (m), 1249 (s), 1157 (w), 1106 (m), 1064 (w), 908 (m), 855 (s), 843 (s), 760 (m); EI mass spec, *m/z*: 344 (3), 286 (5), 271 (9), 211 (23), 153 (40), 133 (100), 109 (15), 73 (36), 59 (26); R_f = 0.55 (10:1 hexane/EtOAc), pale yellow oil. Yield: 28 mg (77.8%).



[a]**Protected Diol 101**. See preparation of 113 for procedure. Reaction was ran on a 1.13mmol scale.

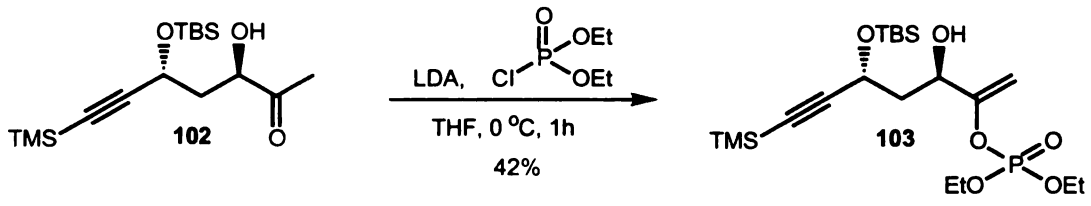
^{1}H NMR (400 MHz, $CDCl_3$): δ 0.17 (s, 9H), 0.19 (s, 6H), 0.88 (s, 9H), 1.39 (s, 3H), 1.69 (m, 1H), 1.87 (m, 1H), 2.09 (m, 1H), 2.41 (m, 1H), 2.60 (m, 2H), 3.03 (m, 2H), 4.35 (d, 1H, J = 10.1 Hz), 4.68 (d, 1H, J = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.08, -4.54, -0.21, 18.21, 21.65, 24.37, 25.77, 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 spec. *m/z*: 418 (8), 361 (6), 285 (22), 255 (16), 201 (16), 153 (22), 133 (100), 107 (8), 73 (72); mp 66-68 ^{o}C; R_f = 0.18 (50:1 hexane/EtOAc); [α]D = 80.82° (c = 1.05 in $CHCl_3$, white solid. Yield: (76.4%).



Ketone 102. The dithiane **101** (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 reaction was chromatographed on silica gel (50:1 hexane/EtOAc) to give the product as a pale yellow oil.

^{1}H NMR (400 MHz, CDCl3): δ 0.07 (s, 6H), 0.16 (s, 9H), 0.90 (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); 13C NMR (100 MHz, CDCl3): δ -4.82, -4.77, -4.54, -0.36, -0.27, 18.21, 25.39, 25.75, 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 spec. m/z: 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); [α]D = 65.0° (c = 1, $CHCl_3$); pale yellow oil. Yield: 429 mg (31.1%).



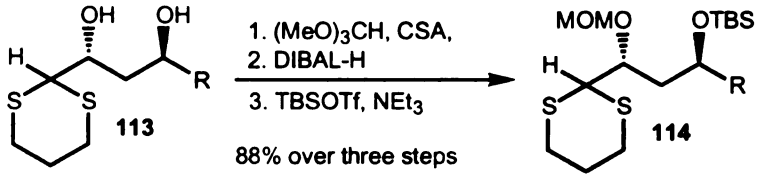
Phosphonate 103. A solution of LDA was prepared by adding *n*-BuLi (2.5 M solution in hexane, 0.4 mL, 1.0 mmol) to a solution of diisopropylamine (0.15 mL, 1.05 mmol, 1.05 equiv.) in 5 mL THF at –78 °C, then warming the reaction to room temperature for 15 minutes then cooling back down to -78 °C. This solution was added to a precooled (-78 °C) solution of ketone **102** 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 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.

^{1}H NMR (400 MHz, CDCl3): δ 0.09 (s, 3H), 0.14-0.17 (12 H, overlapping TMS and TBS singlets), 0.89 (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); 13C NMR (100 MHz, CDCl3): δ-5.00, -4.59, -4.37, -3.71, -0.28, 16.03, 18.11, 25.81, 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 spec. *m/z*: 563 (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, $CHCl_3$); colorless oil; Yield: 230 mg (41.4%).



[d]**Trimethyl Ortho Ester Derived from 113**. To a solution of compound **99** (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 (208mg, 2 mmol) dropwise. The reaction was stirred for 48 h at room temperature. After the separation of flash chromatography (10% EtOAc in hexanes), compound **104** was isolated as a colorless oil. Major isomer of **104**:

^{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); colorless oil; Yield: 319.4 mg (98%).

[c]**Trimethyl Ortho Ester 104.** Procedure same as above, data not reported.

[d]**DIBAl Reduction Precursor to 114**. To a solution of the ortho ester derivative (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 HCl (1N). The reaction mixture is 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) affored 445 mg of Mom mono-protected product **105** as colorless oil.

^{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 = 6.59 Hz), 3.44 (s, 3H), 4.11 (dt, 1H, J = 4.28, 9.07 Hz), 4.36 (d, 1 H, J = 4.39 Hz), 4.54 (m, 1H), 4.72 (d, 1H, J = 6.87 Hz), 4.78 (d, 1H, J = 6.87 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). Yield: 445 mg (93%)

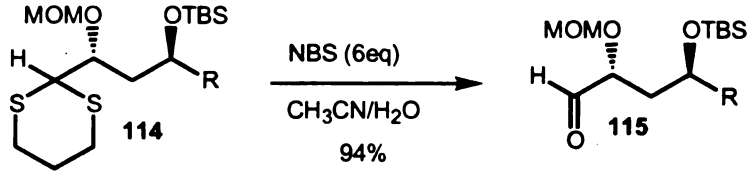
[e]**105 by DIBAl Reduction of 104**. Procedure same as above, data not reported.

[d]**TBS Protection 114**. To a solution of alcohol derived from **113** (212 mg, 0.63 mmol) in 3 mL CH_2Cl_2 at room temperature, NEt_3 was dropwise added and TBSOTf 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. The flash chromatography on silical gel with 10% EtOAc in hexanes gave 274.2 mg product **112** as colorless oil.

^{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 =

3.57, 8.79 Hz), 4.47 (d, J = 3.57 Hz), 4.52 (dd, 1 H, J = 3.30, 9.89 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). Yield: 274.2 mg (97%).

[c]**TBS Protection 106**. Procedure same as above, data not reported.



[d]**Aldehyde 115.** A solution of 200 mg compound **114** 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 orange color. After quenching with sat. aq. Sodium sulfite, the reaction mixture was extracted with 1:1 hexane-CH_2Cl_2. The organic phase was washed with sat. NaCl solution. The chromatography on silica gel (20% EtOAc in hexanes) provided 145.8 mg of product **115** as colorless oil.

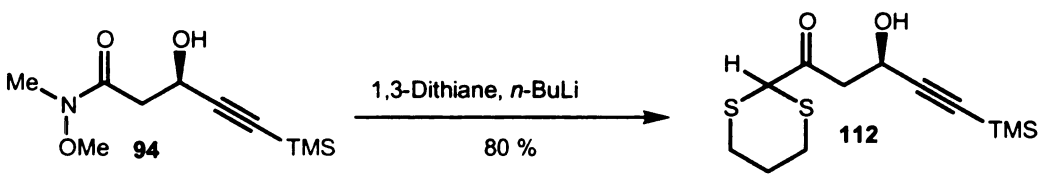
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.17 (s, 9H), 0.18 (s, 3H), 0.92 (s, 9H), 1.95 (ddd, 1H, J = 3.85, 9.07, 14.28 Hz), 2.09 (ddd, 1H, J = 3.85, 9.34, 14.28 Hz), 3.44 (s, 3H), 4.12 (ddd, 1H, J = 1.65, 3.85, 1.65 Hz), 4.58 (dd, J = 3.85, 9.07 Hz), 4.71 (d, 1H, J = 6.87 Hz), 4.74 (d, 1H, J = 6.87 Hz), 9.86 (d, 1H, J = 1.65 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). Yield: 145.8 mg (91%).

[c]**Ketone 107.** Data not reported.

[d]**Phosphonate 108**. Proceedure same as for 103. Data not reported.

[d]**Acyl Bromide 109**. Data not reported.

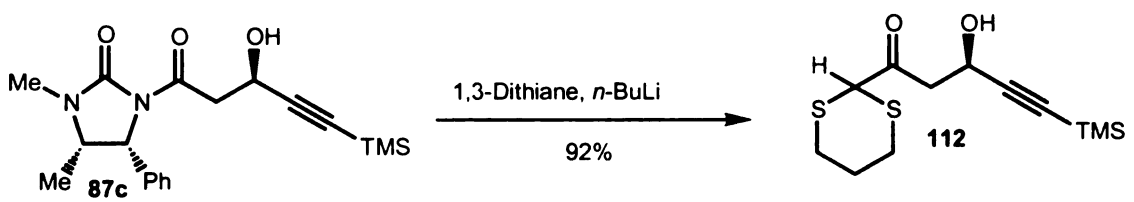
[d]**Phosphonate 110**. Data not reported.



[d]**Dithiane 112 from Weinreb's Amide**. 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

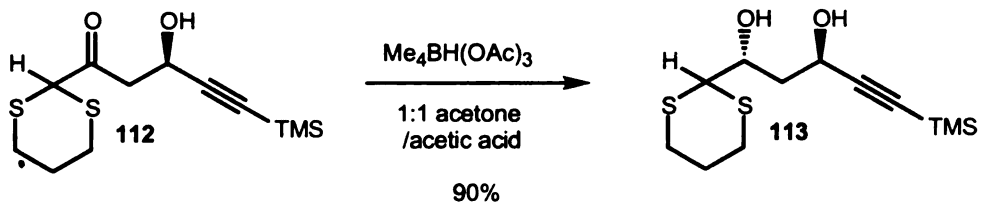
minutes, and then the solution of adduct **94** (50 mg, 0.14 mmol) in 30 ml THF was added dropwise. The reaction was stirred for 30 min and quenched with acetic acid (1 eq). The solution was diluted with ether (50 mL), washed with $NaHCO_3$ (1 x 20 mL), extracted with CH_2Cl_2 and subjected to column chromatography. Product **112** was obtained as a colorless oil by the chromatography.

^1H NMR (300 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.94-2.20 (m, 2H), 2.57 (ddd, 1H, *J* = 2.74, 2.74, 5.22 Hz), 2.61 (ddd, 1H, *J* = 2.74, 2.74, 5.22 Hz), 3.05 (dd, 1 H, *J* = 4.12, 16.76 Hz), 3.17 (dd, 1 H, *J* = 7.69, 16.75 Hz), 3.20 (ddd, 1H, *J* = 3.02, 4.93, 11.26 Hz), 3.25 (ddd, 1H, *J* = 3.02, 4.94, 11.26 Hz), 4.23 (s, 1H), 4.83 (dd, 1H, *J* = 4.12, 7.69 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). Elemental analysis calculated for $C_{12}H_{20}O_2S_2Si$: C 49.96, H 6.99, found: C 49.85, H 6.96. R_f = 0.40 (1:4 EtOAc/hexanes); Yield: 31.7 mg (79%).



[d]Dithiane 112 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 up to 0 °C and stirred for 1 h. A solution of imidazolinone adduct (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 $NaHCO_3$ (1 x 20 mL), extracted with CH_2Cl_2 and subjected to column chromatography.

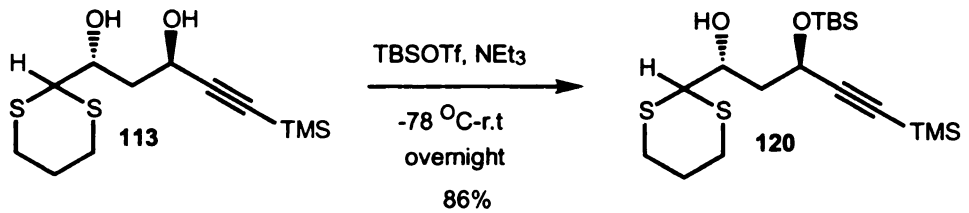
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.17 (s, 9H), 1.94-2.20 (m, 2H), 2.57 (ddd, 1H, J = 2.74, 2.74, 5.22 Hz), 2.61 (ddd, 1H, J = 2.74, 2.74, 5.22 Hz) 3.05 (dd, 1 H, J = 4.12, 16.76 Hz), 3.17 (dd, 1 H, J = 7.69, 16.75 Hz), 3.20 (ddd, 1H, J = 3.02, 4.93, 11.26 Hz), 3.25 (ddd, 1H, J = 3.02, 4.94, 11.26 Hz) 4.23 (s, 1H), 4.83 (dd, 1H, J = 4.12, 7.69 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). R_f = 0.40 (1:5 EtOAc/Hexanes); a colorless oil; Yield: 408 mg (92%).



[d]**Diol 113 from Evan's Reduction.** 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 **112** (562 mg, 1.94 mmol) in 10 mL acetone was added previous solution. The reaction mixture was stirred for 1 h, quenched with excess saturated aqueous sodium potassium tartrate solution and diluted with 50 mL ether. 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 $NaHCO_3$ solution (50 mL), H_2O (50 mL), and brine (50 mL), dried over $MgSO_4$ and concentrated on a rotary evaporator to white solid. Purification of the crude product by flash chromatography on silica gel (1:1 hexanes/EtOAc) affored mg of diol product **113** (20:1 ratio of *anti*:*syn* diastereomers).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.19 (s, 9H), 1.92-2.16 (m, 3H), 2.31 (ddd, 1H, J = 2.20, 6.49, 14.29 Hz), 2.71 (ddd, 1H, J = 3.30, 7.97, 14.01),

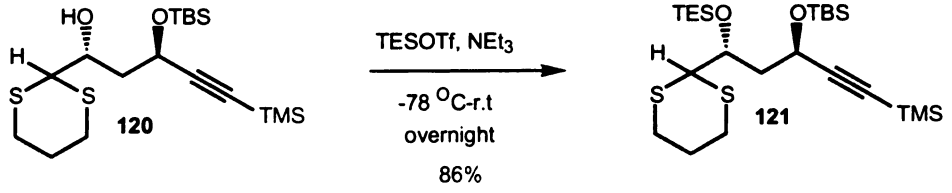
2.92-3.02 (m, 2 H), 3.80 (d, 1 H, J = 7.41 Hz), 3.90 (d, 1 H, J = 6.4 Hz distinguishable proton), 4.45 (ddd, 1H, J = 2.20, 7.41, 9.78 Hz), 4.72 (dd, 1H, J = 3.30, 6.87 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.14, 25.46, 26.83, 27.25, 40.20, 50.74, 60.97, 68.94, 89.73, 105.99; IR (neat film on NaCl): 3150.00-3610.00 (w), 2957.25 (m), 2924.46 (m), 2901.31 (m), 2172.12 (m), 1423.65 (m), 1277.04 (m), 1250.03 (s), 1064.84 (m), 843.00 (m); EI mass spec. *m/z*: 290 (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). Yield: 506.34mg (90%)



120 : TBS-MonoProtection of Diol 113. To a cooled solution (–78 °C) of diol **113** (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 up 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 revealed a colorless oil. R_f = 0.24 (10% EtOAc in hexanes).

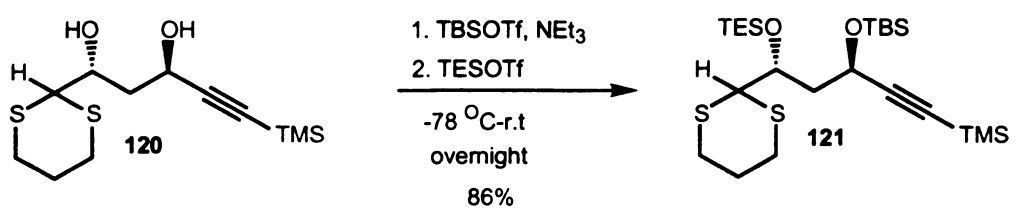
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (m, 15H), 0.882 (s, 9H), 1.84-2.14 (m, 4H), 2.7-2.8 (m, 2H), 2.8- 2.98 (m, 2H), 3.265 (broad s, 1H), 3.93 (d, 1H, J = 6.3 Hz), 4.28 (t, 1H, J = 7.8 Hz), 4.69 (dd, 1H, J = 6.91, 3.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -0.52, -0.46, 0.00, 18.2, 26.12, 28.61, 28.98, 42.12, 53.53, 61.98, 69.97, 90.20, 106.59; IR (neat film on NaCl): 3340.00-3580.00 (w), 2955.32 (m), 2928.32 (m), 2349.60 (m), 1259 (m), 1095.71 (m), 841.07 (m); EI mass spec. *m/z*: 404 (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); colorless oil; Yield: 132.6 mg (86.4 %).



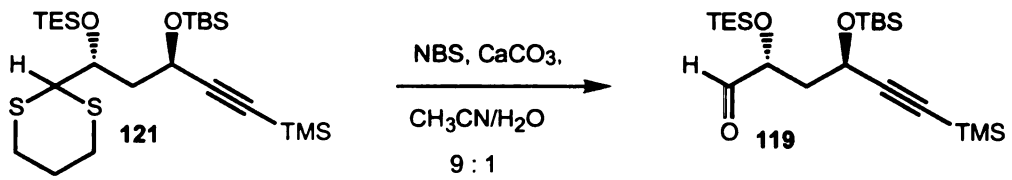
121 : TES Protection of Alcohol 120. To a cooled solution (–78 °C) of mono protected diol **120** (100 mg, 0.25 mmol) in 5 mL of CH_2Cl_2 was

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 $NaHCO_3$. The organic phase was extracted with CH_2Cl_2 and dried on $MgSO_4$ and concentrated. Flash chromatography revealed a colorless oil.

^1H NMR (300 MHz, $CDCl_3$): δ 0.09-0.16 (m, 15H), 0.639 (dq, 6H, J = 4.15, J = 0.732 Hz), 0.873 (s, 9H), 0.965 (t, 9H, J = 4.88 Hz), 1.6-1.93 (m, 2H), 2.0-2.17 (m, 2H), 2.72-2.92 (m, 4H), 4.10 (quintet, 1H, J = 3.91 Hz), 4.19 (d, 1H, J = 3.42 Hz), 4.46 (dd, 1H, J = 4.39, J = 4.88 Hz). IR (neat film on NaCl): 2957 (s), 2930 (s), 2897 (m), 2857 (s), 1250 (s), 1093(s), 839 (s) cm^{-1}; Elemental analysis calculated for $C_{24}H_{50}O_2S_2Si_3$: C 55.60, H 9.65, found: C 55.31, H 10.0; EI mass spec. *m/z*: 518 (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); Yield: 129.5 mg (100%).



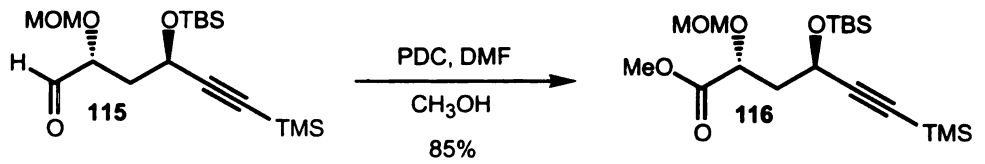
121 : One-Pot Protection of Diol 113. To a cooled solution (–78 °C) of diol **120** (37 mg, 0.127 mmol) in 5 mL of CH_2Cl_2 was added NEt_3 (89.1 μL, 0.635 mmol) and TBSOTf (29.2 μL, 0.127 mmol). After all the starting material was consumed as indicated by TLC, TESOTf (40.2 μL, 0.178 mmol) was added to the solution. The solution was stirred overnight at this temperature and allowed to warm up to ambient temperature prior to quenching with $NaHCO_3$. The organic phase was extracted with CH_2Cl_2 and dried on $MgSO_4$ and concentrated. Flash chromatography revealed a colorless oil.



Dithiane Removal 119. A solution of protected diol (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 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. Chromatography on silica gel (20% EtOAc in hexanes) provided the aldehyde as a colorless oil.

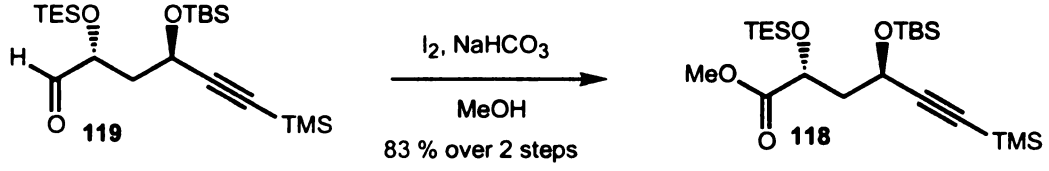
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.10-0.18 (m, 15H), 0.61 (q, 6H, J = 7.8 Hz), 0.939 (t, 9H, J = 7.8 Hz), 1.86-1.95 (m, 2H), 1.99-2.11 (m, 2H), 4.18 (dt, 1H, J = 5.13, 1.47 Hz), 4,55 (dd, 1H, J = 5.13, 2.93 Hz), 9.61 (dd, 1H, J = 1.22, J = 0.49 Hz). R_f= 0.68 (1:4 EtOAc/hexanes); Yield: 40.4 mg (91%). A crude product was satisfactory for the next step.



[d]**Methyl Ester 116**. To a solution of aldehyde **115** (150 mg, 0.42 mmol) in methanol (100 μL, 25 mmol), and dry dimethylformamide (5 mL), at room temperature , was added pyridinium dichlomate (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, the water layer extracted with hexanes (3 x 50 mL) and the combined hexanes extracts dried over magnesium sulfate. Removal of the solvent on the rotary evaporator,

gave the methyl ester as colorless oil. The crude product was used for the next step.

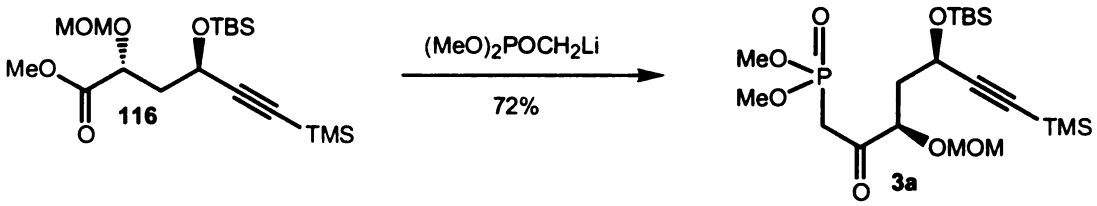
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.16 (s, 9H), 0.19 (s, 3H), 0.92 (s, 9H), 2.05-2.12 (m, 2H), 3.40 (s, 3H), 3.75 (s, 3H), 4.26 (dd, 1H, J = 3.84, 9.20 Hz), 4.58 (dd, J = 3.84, 9.20 Hz), 4.69 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.86, -4.11, -0.33, 18.13, 25.78, 41.96, 51.96, 56.28, 59.15, 72.77, 89.49, 96.90, 106.61, 173.10. R_f = 0.45 (10% EtOAc in hexanes). Yield: 139 mg (85%).



Methyl Ester 118. To a solution of aldehyde **119** (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 with 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 was dried on Na_2SO_4 and concentrated. The crude product was used for the next step.

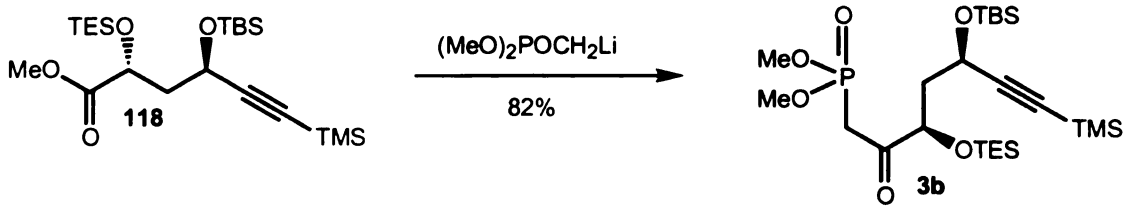
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.1-0.18 (m, 15H), 0.624 (q, 6H, J = 7.4), 0.881 (s, 9H), 0.928 (t, 9H, J = 2.75 Hz), 1.8-2.0 (m, 2H), 2.0-2.14 (m, 2H), 3.69 (s, 3H), 4.529 (dd, 1H, J = 9.10, 4.67 Hz), 4.37 (dd, 1H, J = 8.5, 4.40 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.3, -3.8, 0.33, 5.0, 7.0, 18.6, 26.2, 44.8, 54.0, 59.8, 68.9, 96.90, 89.9, 108.2, 174.5; EI mass spec *m/z* : 458 (2), 443 (4), 401 (64), 269 (23), 241 (50), 227 (56), 215 (9), 189 (24), 147 (40), 89 (38), 73 (100). Yield 21.8 mg (91%).



[d]**Triol Fragment 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 **116** (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 NH_4Cl and diluted with CH_2Cl_2 (30mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 30 mL) dried on $MgSO_4$, then concentrated down to a yellow oil.

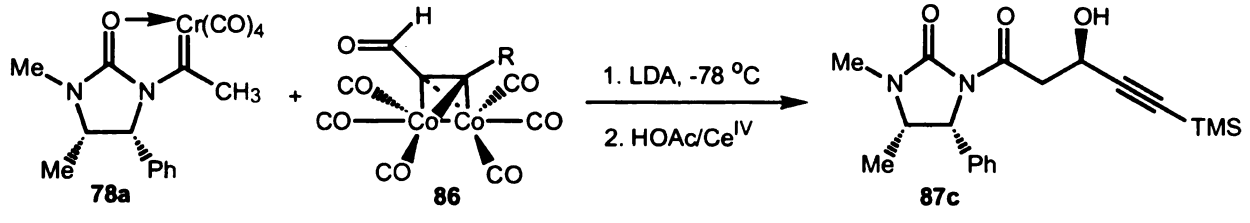
^1H NMR (300 MHz, $CDCl_3$): δ 0.14 (s, 3H), 0.15 (d, 9H, J = 0.55 Hz), 0.18 (s, 3H), 0.92 (d, 9H, J = 0.55 Hz), 1.98 (m, 2H), 3.24 (m, 2H), 3.37 (d, 3H, J = 0.55 Hz), 3.78 (m, 3H), 3.82 (m, 3H), 4.31 (dd, 1H, J = 9.07, 3.02 Hz), 4.54 (dd, 1H, J = 9.07, 3.57), 4.65 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.97, -4.20, -0.37, 18.10, 25.75, 36.84 (d, J = 132.84 Hz), 40.39, 52.98 (m), 56.14, 59.24, 79.50 (d, J = 0.44 Hz), 89.85, 97.02, 106.40, 202.15 (d, J = 6.87 Hz). R_f = 0.76. (1:2:17 CH_3OH/EtOAc/Hexanes). Yield 79.2 mg (72%).



Triol Fragment 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 **118** (170 mg, 0.37 mmol) in 2

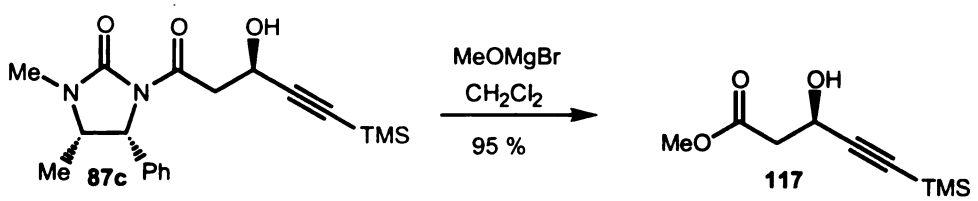
mL of THF was added and the reaction mixture allowed to warm to ambient temperature. The reaction was held overnight at room temperature. The work-up procedure was identical to that of **3a**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.126 (m, 15H), 0.62 (q, 6H, J = 8.3 Hz), 0.934 (m, 18H), 1.80- 1.92 (m, 1H), 1.95-2.5 (m, 1H), 3.04-3.17 (dd, 1H, J = 14.9, 7.08 Hz), 3.26-3.39 (dd, 1H, J = 14.9, 7.08 Hz), 3.75 (s, 3H), 3.78 (s, 3H), 4.33 (dd, 1H, J = 5.4, 1.46 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): 2957.25 (s), 2918.67 (s), 2851.15 (s), 1726.51 (s), 1462.23 (s), 1521.96 (s), 1035.91 (s), 841.07 (s) cm^{-1}; EI mass spec *m/z* : 550 (0), 535 (M^+ -15, 10), 521 (20), 421 (15), 389 9700, 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); yellow oil; Yield: 166.6 mg (82%).



[b]**Aldol Adduct 87c.** 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. The solution of 1.64 g (5.0 mmol) of carbene complex **78a** 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 **86** (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 1.23g of aldol adduct **87c** as a viscous pale yellow oil.

^{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); (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 spec *m/z* : 358 (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, $CHCl_3$). Yield: 1.23 g (80%).



[a]Methyl Ester 117. Anhydrous methanol (1.50 g, 1.90 mL, 47 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 **87c** (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 as a yellow oil. 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), 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 spec. *m/z*: 199 (M^+ - H, 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); pale yellow oil; Yield: 584 mg (62.3%).

a- Data obtained from Mark Parisi's Thesis;[60]

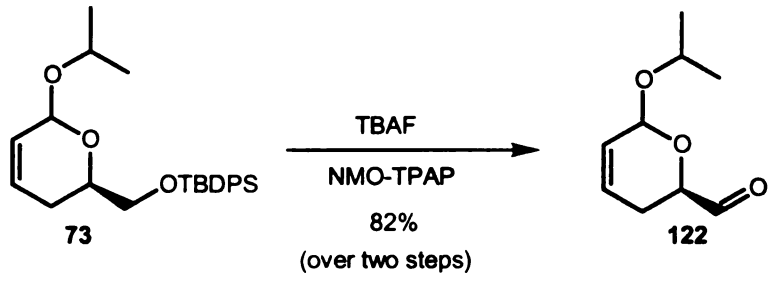
b- Data obtained from Yan Shi's Thesis;[59]

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;[84]

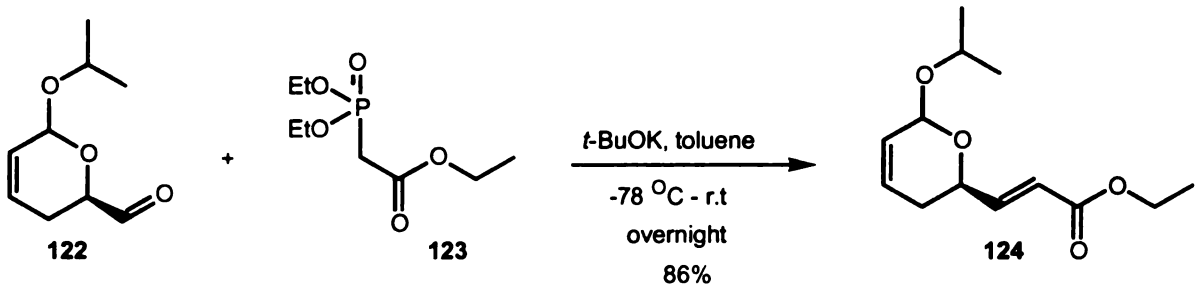
e- Data obtained from unpublished results of Su Yu and W.D. Wulff.[81]

Experimental data for Chapter 4



Aldehyde 122. To a solution of alcohol (100 mg, 0.58 mmol) and N-methylmorpoline N-oxide (102 mg, 0.870 mmol) in 5 mL of anhydrous CH_2Cl_2 was treated 1.5 g of activated molecular sieves. After stirring mixture at 25 °C for 1 h, 6.4 mg of TPAP was added and the reaction mixture was stirred at 25 °C for 30 minutes. At this point another portion of TPAP was added and the reaction allowed to stir for another 30 minutes. The residue was filtered and washed with CH_2Cl_2, concentrated carefully, then separated. $R_f = 0.33$ (4 :1 pentane/ether). Yield (90%).

Characterization data (proton NMR) matched that reported by Crimmins et. al. in the supplementary material to reference 52 in Chapter 2.

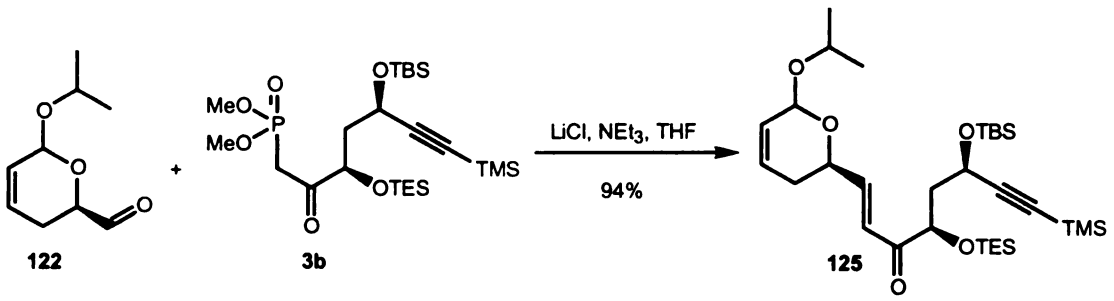


122 123 124

HWE Olefination 124. A solution of phosphonate **123** (23.2 mg, 0.117 mmol) and aldehyde **122** (30mg, 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 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 (Na_2SO_4), concentrated and chromatographed.

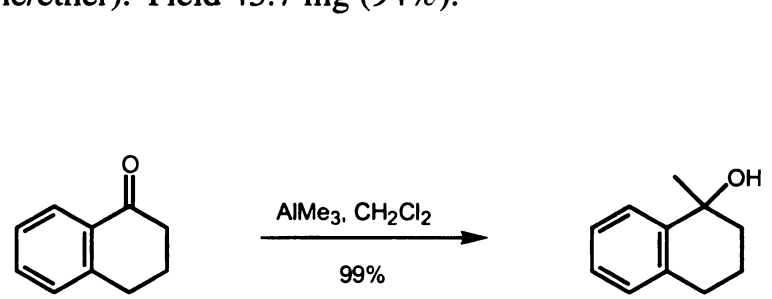
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.7 (dd, 6H, J = 6.0, 1.65 Hz), 1.28 (t, 3H, J = 7.14 Hz), 2.04-2.10 (m, 2H), 3.96 (sept, 1H, J = 6.3 Hz), 4.18 (q, 2H, J = 7.15 Hz), 4.58-4.66 (m, 1H), 5.12 (d, 1H, J = 2.5 Hz), 5.68-5.79 (m, 1H), 5.95-6.05 (m, 1H), 6.90-6.99 (dd, 1H, J = 11.5, 4.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.16, 21.96, 23.76, 29.63, 60.38, 64.92, 69.82, 93.05, 94.18, 120.30, 126.22, 127.89, 146.92. IR (neat film on NaCl): 2916.07 (m), 2849.22 (m), 2363.10 (m), 2338.02 (m), 1718 (m), 1653.21 (s), 1558.68 (s),

1458.37 (s), 1030.12 (m); R_f = 0.46 (4 :1 pentane/ether). Yield 24.2 mg 86%.



HWE Olefination 125. A solution of LiCl (3.35 mg, 0.0797 mmol) in 0.5 mL of THF was added to a solution of phosphonate (40.4mg, 0.0736 mmol) in 3 mL of THF at room temperature and stirred for 5 minutes. The solution was then cooled to 0 °C, 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 aldehyde (12.5 mg, 0.0736 mmol) was added dropwise. 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 on $MgSO_4$. Column chromatography (2:5 ether/pentane) revealed a colorless oil.

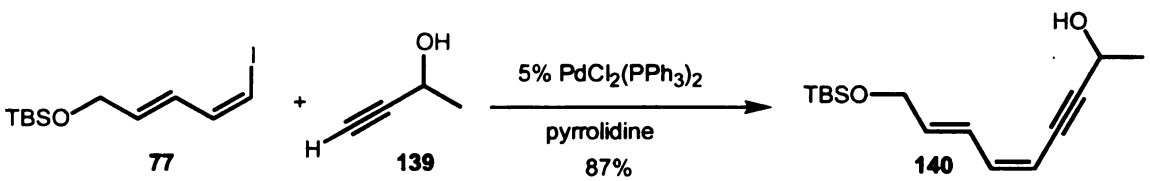
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.04 (s, 9H), 0.12 (s, 6H) 0.58 (q, 1H, J = 8.0 Hz) 0.8-0.96 (m, 18H), 1.17 (apparent t, 6H, J = 6.1 hz), 1.80-1.89 (m, 1H), 1.96-2.10 (m, 1H), 3.98 (sept, 1H, J = 6.1 Hz), 4.441 (dd, 1H, J = 3.9, 8.3 Hz), 4.52 (dd, 1H, J = 8.8, 4.4 Hz), 4.58-4.66 (m, 1H), 5.13 (broad 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 -4.2, -3.5, 0.0, 1.2, 5.2, 7.1, 18.5, 26.2, 30.1, 44.2, 59.9, 65.8, 70.2, 74.8, 90.0, 93.5, 107.2, 123.7, 126.5, 128.2, 146.2, 200.8; IR (neat film on NaCl): 2955.32 (m), 2918.67 (m), 2851.15 (s), 2363.10 (m), 2336.09 (m), 1701.43 (m), 1458.37 (m) 1377.35 (m), 1251.96 (m), 1099.56 (m), 1030.12 (m); EI mass spec. *m/z*: 594 (1), 565 (1), 537 (2), 505 (1), 477 (2.5), 453 (1), 433 (2), 425 (2), 411(5), 271 (9), 241 (100), 161 (7), 115 (15), 87 (15), 73 (39), 59 (6). R_f = 0.85 (5:2 pentane/ether). Yield 43.7 mg (94%).



137 138

138 from Methylation of 137. Procedure same as for **144** and ran on a .0075 mmol scale.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.59 (s, 3H), 1.78-2.80 (m, 2H), 2.82 (q, 2H, J = Hz), 7.11 (d, 1H, J = 6.9 Hz), 7.17-7.32 (m, 2H), 7.62 9dd, 1H, J = 7.7, 1.6 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; Yield (99%).

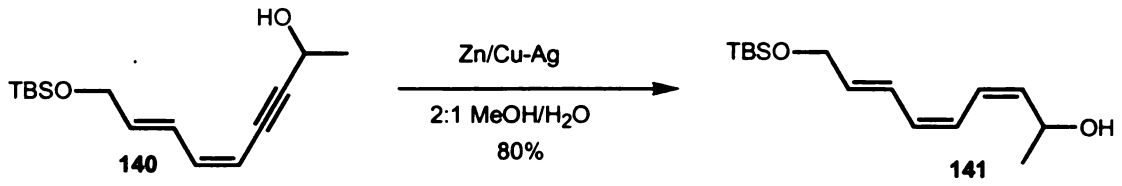


[a]**Dienyne 140**. A 100 mL round-bottom flask was charged with (702 mg, 1.0 mmol) of $PdCl_2(PPh_3)_2$ and dissolved in 30 mL freshly distilled pyrrolidene under argon. The flask was wrapped with aluminium foil, and iododiene **77** (6.49 g, 20 mmol) was added neat via cannula. The solution darkened 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 spot had disappeared after 24 h.

The reaction was quenched by adding excess 0 °C saturated NH_4Cl solution, and 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 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 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, 1 H, J = 6.6, 1.7 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); orange oil. Yield: 4.66 g (87.4%).

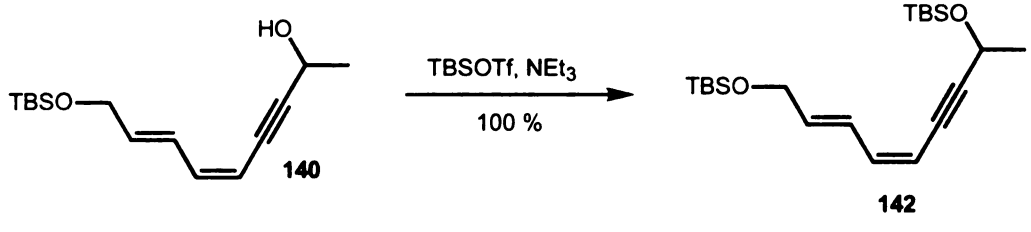


[a]**Activated Metal Reduction to Give Triene 141.** A 100 mL flask was charged with zinc dust (10 g, 99.9%, 150-325 mesh, Alfa/Aesar), suspended in 50 mL HPLC grade water and sparged with argon for 15 min. Anhydrous copper (II) acetate (1.0 g) was added, the flask was capped with a rubber septum, and the slurry was stirred for 15 minutes. Silver nitrate (1.0 g) 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 **140** (133 mg, 0.5 mmol) in 15 mL 2:1 methanol/water. The flask was placed under 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

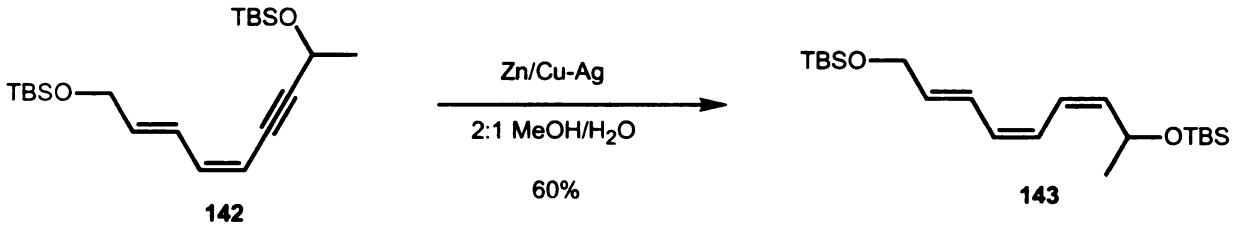
concentrated to a yellow oil. The oil was purified by chromatography on silica gel (5:1 hexane/EtOAc, UV/$KMnO_4$ visualization) to give the product as a colorless oil.

^{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 = 4.9, 15.0 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 spec. *m/z*: 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); Elemental analysis calculated for $C_{15}H_{28}O_2Si$: C 67.11 %, H 10.51 %, found: C 67.13 %, H 10.46 %; pale yellow oil; Yield: 100 mg (74.6%).



Dienyne 142. Proceedure same as for compound **120** and was ran on a 0.188 mmol scale.

^{1}H 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 = 6.6, 1.9 Hz), 5.4 (d, 1H, J = 10.7 Hz), 5.88 (td, 1H, J = 15.1, 5.2 Hz), 6.33 (t, 1H, J = 11), 6.68-6.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3, -5.0, -4.6, 18.2, 18.03, 25.4, 59.5, 63.3, 80.2, 97.8, 108.4, 126.7, 136.0, 139.1. Yield 100 % R_f = 0.2 (100 : 1 hexane/EtOAc).

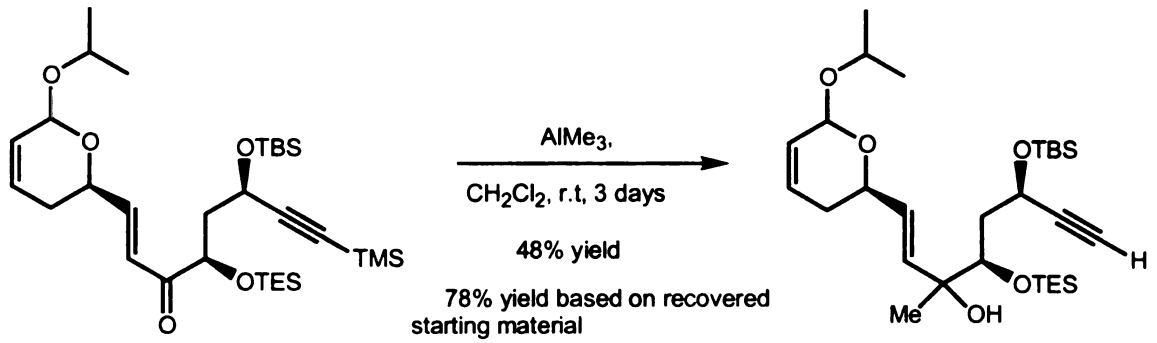


142 143

Activated Metal Reduction to Give Triene 143. Proceedure same as for compound **141,** and was ran on a 0.0635 mmol scale.

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.02 (d, 6H, J = 4.7 Hz) 0.06 (s, 6H), 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 (td, 1H, J =

14.83, 5.0 Hz), 6.04 (t, 1H, J = 11.26 Hz), 6.14 (t, 1H, J = 11.26 Hz), 6.30 (t, 1H, J = 11.26 Hz), 6.68 (apparent dd, 1H, J = 14.8 Hz, other coupling is obscured); ^{13}C NMR (75 MHz, $CDCl_3$): δ -4.95, -4.47, -4.20, 18.45, 24.94, 26.11, 63.74, 65.25, 121.62, 123.59, 124.76, 129.81, 134.81, 137.69; IR (neat film on NaCl): 2957.25 (m), 2928.32 (m), 2856.94 (m), 2363.10 (m), 2336.09 (m), 1653.21 (s), 1473.99 (s), 1458.37 (s), 1255.82 (s), 1122.71 (m), 1078.35 (m), 1005.04 (m), 835.28 (m), 775.48 (m); EI mass spec. *m/z*: 382 (18), 325 (18), 250 (38), 237 (45), 189 (18), 147 (100), 119 (34), 91 (25), 73 (98); Yield: 14.5 mg (60%).



125 144

144 from Methylation of 125. To a solution of ketone **125** (8 mg, 0.014 mmol) in CH_2Cl_2 (3 mL) was added at –15 °C, $AlCl_3$ (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 on $MgSO_4$ and concentrated. Column chromatography revealed a colorless film.

^{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), 1.14-1.36 (m, 11H), 1.92-2.10 (m, 2H), 2.16 (s, 1H), 3.71 (dd, 1H, 6.0, 4.1 Hz), 3.98 (sept, 1H, J = 6.3 Hz), 4.38-4.46 (m, 1H), 5.10 (s, 1H), 5.71 (d, 1H, J = 10.4 Hz), 5.96-6.06 (m, 1H). R_f = 0.60 (4 :1 pentane/ether). Yield 78% based on starting material recovered.

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