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Osmium Catalyzed Dihydroxylation And Oxidative Cleavage Of Vinyl Sulfone And Elucidation Of The Vinylsulfone Polypropionate Methodology For The Synthesis Of The C32 Des-Methyl C28-C34 Actin Binding Tail Of Aplyronine A

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For the degree of Doctor of Philosophy

Is approved by the final examining committee:

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OSMIUM CATALYZED DIHYDROXYLATION AND OXIDATIVE CLEAVAGE OF VINYL SULFONE AND ELUCIDATION OF THE VINYLSULFONE POLYPROPIONATE METHODOLOGY FOR THE SYNTHESIS OF THE C32 *DES*-METHYL C28-C34 ACTIN BINDING TAIL OF APLYRONINE A

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Thomas Paul Bobinski

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I would like to thank all of the great and influential chemists that have been responsible for molding me into the scientist I am today. First and foremost I would like to thank my truly visionary genius advisor and labmate Philip Lorenz Fuchs. Under his influence I have learned to be critical of scientific data and more importantly myself. I was shown how to think about organic synthesis without the typical limitations so common among organic chemists today. Thanks to him I was able to contribute to a synthetic methodology that will have a greater impact on natural product synthesis for years to come. Seeing him work in the hood sharpened my own skills. The positive impact of my association with Professor Harry Morrison can not be overstated. I was Professor Morrison's lecture TA from 2009-2012. I have never encountered a more precise communicator of the fundamental concepts of organic chemistry. Thanks to him, my understanding of physical organic concepts has increased exponentially due to my association with him. His continued mentorship and example he sets has inspired my scientific paradigm, not to mention he's really cool. I would be remiss if I did not recognize Dr. Jack Parson's of Starks Associates, my first principle investigator after getting my masters degree. I can unabashedly declare that the core of my laboratory skills is due to the delightfully harsh and, "nose to the

grindstone," style of mentorship of Dr. Parsons. It was Professor Fuchs and Dr. Parson's that made me one with the concept of, "all that matters is what you get in the bottle (vial)," everything else is window dressing. Mark Lipton's unrivalled understanding of mechanistic concepts contributed to the first paradigm shift I experienced upon my arrival to Purdue University. Subsequent candid discussions with Professor Lipton about electron pushing, hyperconjugation, and even the tetrahedral nature of sulfones and sulfuric acid compelled me to call on him to be the first member of my advisory committee. I would like to thank the rest of my committee members Professor Abu-Omar and Wenthold. I owe my understanding of reaction kinetics to Professor Wenthold. My understanding of organo-metallics rests on the concepts taught by Professor Abu-Omar.

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LIST OF ABBREVIATIONS

Ac	acetyl
Ar	aryl
b	broad
Bn	benzyl
°C	degrees Celsius
cat	catalytic/catalyst
CI	chemical ionization
CSA	camphor sulfonic acid
CBS	Corey-Bakshi-Shibata catalyst
δ	chemical shift
d	day(s)
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCAD	*di*-*p*-chlorobenzyl azodicarboxylate
de	diastereomeric excess
DCC	*N*,*N*-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine

DIPEA	*N,N*-diisopropylethylamine
DMDO	dimethyldioxirane
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	dimethylformamide
3,5-DMP	3,5-dimethylpyrazole
DMP	Dess-Martin periodinane
ee	enantiomeric excess
ent	enantiomer of
Et	ethyl
EtOAc	ethyl acetate
EI	electron impact
equiv	equivalent
Et	ethyl
g	gram(s)
h	hour(s)
Hex	hexanes
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IC_{50}	dose that is effective in 50% of test subjects
IR	Infrared
J	coupling constant

k	Kilo
L	liter(s)
LDA	lithium diisopropylamide
□	micro
m	milli
m	multiplet
M	moles per liter
m-CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MP	melting point
MS	mass spectrometry
MTM	methylthiomethyl
NHK	Nozaki-Hiyama-Kishi
NMA	*N*-methyl amino acid
NMR	nuclear magnetic resonance
Nu	Nucleophile
Oct	octyl
Ph	phenyl
P_3NO	4-(3-phenylpropyl)pyridine *N*-Oxide
ppm	parts per million
pyr	pyridine
q	quartet
R_f	retention factor

Rxn	reaction
s	singlet
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
S_N'	nucleophilic substitution with allylic rearrangement
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl, triflyl
OTf	trifluoromethansulfonate
THAM	tris(hydroxymethyl)aminomethane

ABSTRACT

Bobinski, Thomas Paul. Purdue University, December 2013. Osmium Catalyzed Dihydroxylation and Oxidative Cleavage of Vinyl Sulfone and Elucidation of the Vinylsulfone Polypropionate Methodology for the Synthesis of the C32 des-Methyl C28-C34 Actin Binding Tail of Aplyronine A. Major Professor: Philip L. Fuchs.

A general methodology for the generation of dipropionate functionalities using cyclic 7-membered vinylsulfones has been devised for the purpose of synthesizing polyketide natural products such as aplyronine A. Final oxidative cleavage via ozonolysis has been shown to be difficult providing variable yields. Furthermore, elegant synthesis of the C28-C34 segment of the aplyronine A actin binding tail has proved elusive. Utilization of OsO_4 and catalytic citric acid has led to a methodology whereby harsh ozonolysis procedures can be mostly avoided. A reengineering of the vinylsulfone polypropionate methodology in conjunction with osmylation has been found to provide the actin binding tail under mild high yielding conditions. These discoveries will be key in developing a methodology for providing highly complex large scale substrates for the synthesis of asymmetric natural products.

CHAPTER 1: RATIONALE

1.1: Biological Basis for Total Synthesis of Aplyronine

Regulative intervention of the mitotic process is experiencing intense study. The cytoskeleton must sustain a large number of chemically driven changes to successfully divide. Success in cancer chemotherapy using paclitaxel (Taxol™) to stabilize microtubules has elevated all three major polymeric constituents of the cytoskeleton (microfilaments, microtubules, and intermediate filaments) to be crucial targets for aggressive research. During cell division, the microtubule cytoskeleton forms a spindle apparatus between two microtubule-organizing centers, called centrosomes. During mitosis, chromosomes attach to microtubules and subsequently move to the spindle poles. A multiprotein complex called a kinetochore links chromosomes to microtubules and powers poleward movements.[10,11,17,18] During cytokinesis, the actin cytoskeleton and myosin motor molecules generate a contractile ring that cleaves the cytoplasm, forming two daughter cells. At the beginning of the 21st century the importance of centrosome amplification, aneuploidy and chromosomal instability were often heralded as *causes* for tumorigenic invasion and metastasis and are unquestionable markers of unfavorable treatment outcome. These observations strongly indicate the need for a more thorough understanding of the major

biochemical events that lead to disregulation of the centrosome. While cancer chemotherapy that targets DNA synthesis (with attendant interference of DNA metabolism) often leads to drug-resistant cells and secondary tumors, a treatment regime that effects *regulation of the centrosome* might eliminate proliferating cells while avoiding the issue of chromosomal instability.[17,22-27]There are similarities between DNA and centrosome duplication (initiated at G1, regulated by many of the same protein complexes).[28]However, while the mechanism of DNA replication is well known, understanding the detailed operation of the centrosome is a subject of tremendous interest. Both the microtubule and actin cytoskeleton are critical for proper cell division and are affected during tumorigenesis. The actin cytoskeleton regulates a number of cellular processes, including cytokinesis, cell migration, cell polarity, membrane trafficking and apoptosis. Monomeric or globular (G)-actin undergoes polymerization into filamentous (F)-actin (Fig. 1.3 and 1.4)[11,29-32] and represents the building block for a number of different F-actin subpopulations such as the contractile ring, filopodial bundles and lamellipodial networks. Actin organization and dynamics are regulated by a large number of actin binding proteins (ABPs).[16] Besides the microtubules, the actin cytoskeleton has become an interesting target for anti-cancer therapeutics,[33] since several actin-dependent processes become out of control during tumorigenesis, including proper alignment of the mitotic spindle.[34] An *actin-dependent* cell cycle checkpoint at the G2/M transition controls mitosis in primary mammalian cells, and the regulated polymerization of

a dendritic network of short filaments near the plasma membrane drives cell migration in normal and metastatic cells.[35-37]

Various marine organisms such as sponges and nudibranchs as well as fungi, algae and bacteria are known to produce natural products with high specificity to the actin cytoskeleton,[2,33,38,39] Several of these products, including cytochalasin B and D, phalloidin, and latrunculin A, (Figure 1.1) have emerged as essential tools for cell biologists to study the organization, dynamics and function of the actin cytoskeleton. Since actin is involved in numerous cellular processes that are affected during tumorigenesis, including cytokinesis, cell polarity, cell migration and apoptosis, these agents are of potential interest as anticancer drugs. Aplyronine A **1.6** is an *exceptionally scarce* macrolide originally isolated from the sea hare *Aplysia kurodai*.[7] It has actin binding and depolymerizing properties[3-5,7,40] as well as potent *in vivo* antitumor activity[4,5] However, the molecular and cellular mechanisms of how aplyronine A **1.6** mediates its actin depolymerizing, anti-tumor and cytotoxic activities are poorly understood.

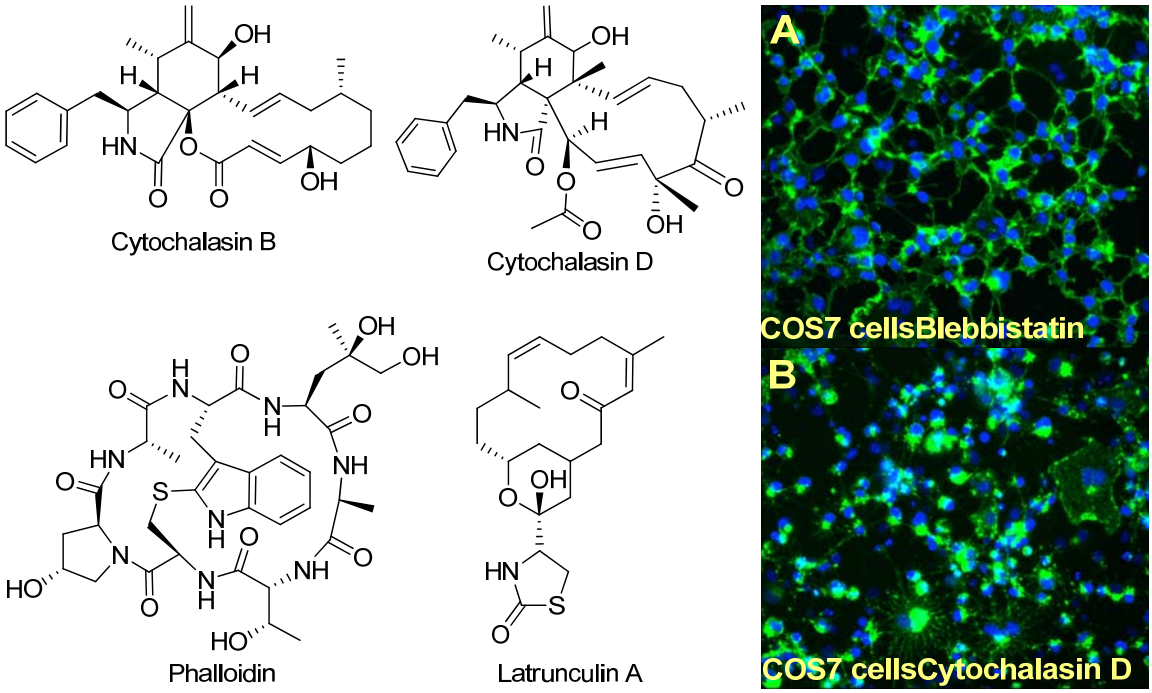

Figure 1.1: Chromophoric Bio-Visualization Substrates

*COS7 cells were treated with 50µM -(-)Blebbistatin **(A)** (not shown), control medium or 0.4µM Cytochalsin D **(B)** overnight. The cells were then fixed with 4% PFA and stained with phalloidin-FITC (green) to visualize the actin cytoskeleton and Hoechst (blue) for nuclei. Both Blebbistatin and Cytochalsin D caused drastic changes to the actin cytoskeleton as was expected.*

Scale bar = 70µm, 40X Images shown. Images courtesy of Genentech.

Aplysia kurodai

Location: Bethlehem, Maricaban Island, Anilao, Luzon; Date: 9 April, 2012

Natural products and their analogs have proven invaluable for probing the mechanism of action of actin dynamics in essential cellular processes. While it is beyond the scope of this chapter to fully review the entire collection, it is appropriate to indicate a set of macrocyclic *mono*- and *bis*-lactones bearing polar stereorich tail sequences that exhibit actin depolymerizing, monomer binding, filament capping, or severing activity. These include “single-tailed” mono-lactones ulapualide A[41] **1.1**, mycalolide B[42-44] **1.2**, kabiramide C **1.3**,

reidispongolide A[1,2] **1.4**, sphinxolide B **1.5**[45,46] and aplyronine A[3-5] **1.6**. A second set includes the "double-tailed" bis-lactones rhizopodin **1.8**,[9-11] misakinolide A (= bistheonellide A)[12-15,19,40,47,48] **1.9**, and swinholide A[20] **1.10** that bind monomers and sometimes sever filaments. Notably missing in this collection is the currently unknown aplyronine A bis-lactone **1.11**, an advanced target in this investigation (Fig. 1.2).

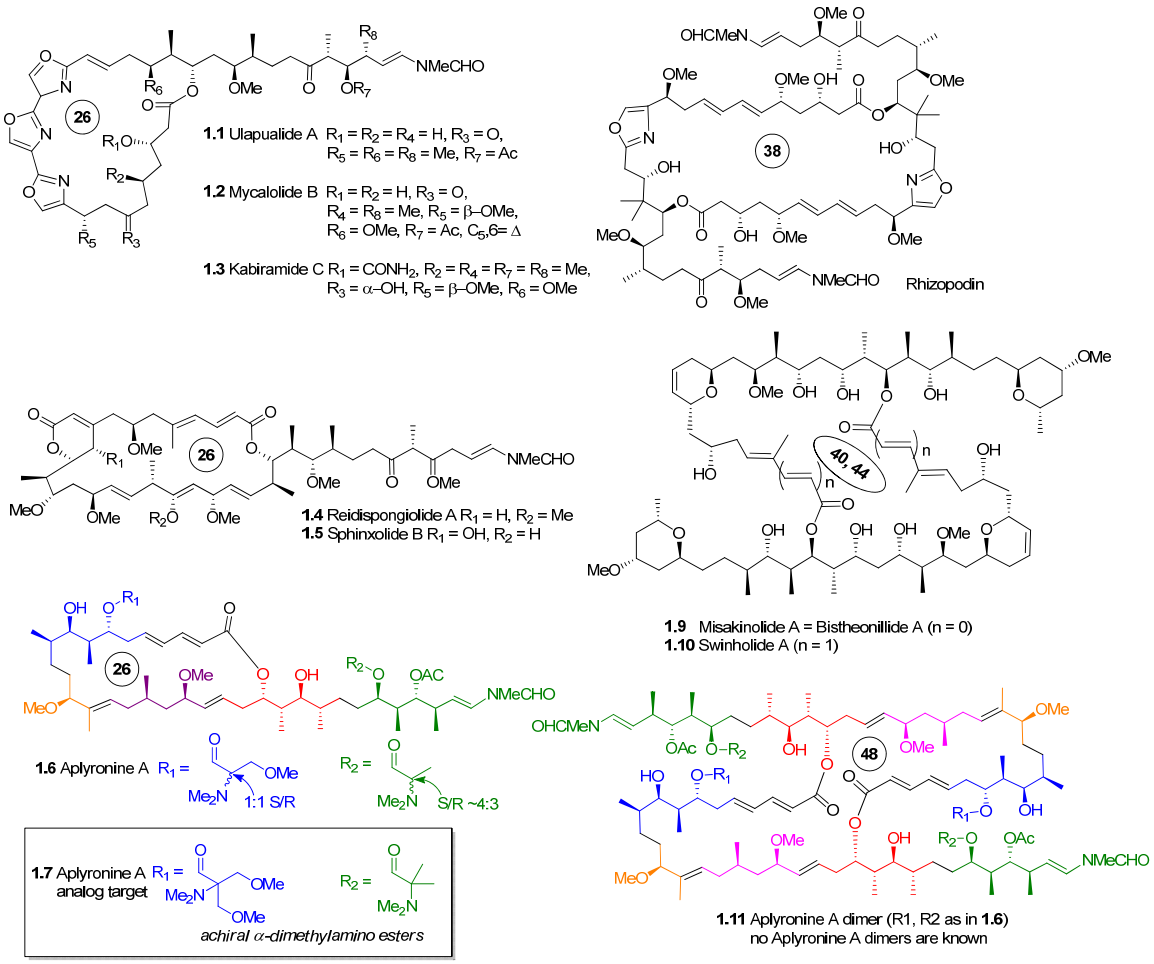

Figure 1.2: Natural Product Inhibitors Of Actin Polymerization.

Dimeric *bis*-lactones such as rhizopodin **1.8** sequester G-actin by forming an irreversible 2:1 actin-substrate complex **(Fig. 1.3)**,[9-11] whereas monolactones bind G-actin with 1:1 stoichiometry inhibiting polymerization and accelerating depolymerization. It has also been inferred that aplyronine A **1.6** is able to sever actin filaments (**Fig. 1.4**).[40] In his 1996 study, Saito first postulated that aplyronine A **1.6** and mycalolide A **1.2** form their 1:1 complexes with actin by binding to the *side chain*.[40] Understanding the interaction of actin with the above agents at the molecular level has been substantially aided by Ivan Rayment who has[46,49] used drug•actin x-ray structures to provide an *in silico* model of actin with many of the above macrocyclic mono-and bis-lactones.[21] The most significant general conclusion is that the binding of macrocyclic mono-lactones with a stereorich side chain that terminates in an enamide or oxazolidine heavily depends upon the side chain while accommodating the macrocyclic ring in a very forgiving fashion. C2 symmetric bis-lactones bearing a pair of sidechains bind *two monomers in an antiparallel orientation;* the macrocyclic ring serves as a backbone that allows the sidechain arms to snugly embrace identical binding sites on the individual actin units.

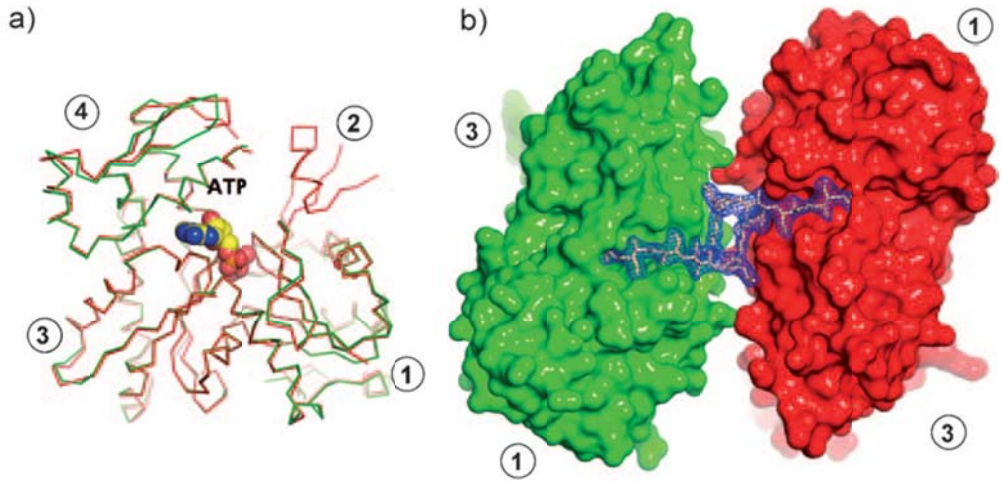

Figure 1.3: Antiparallel actin dimer bound to rhizopodin (X-ray).[9]

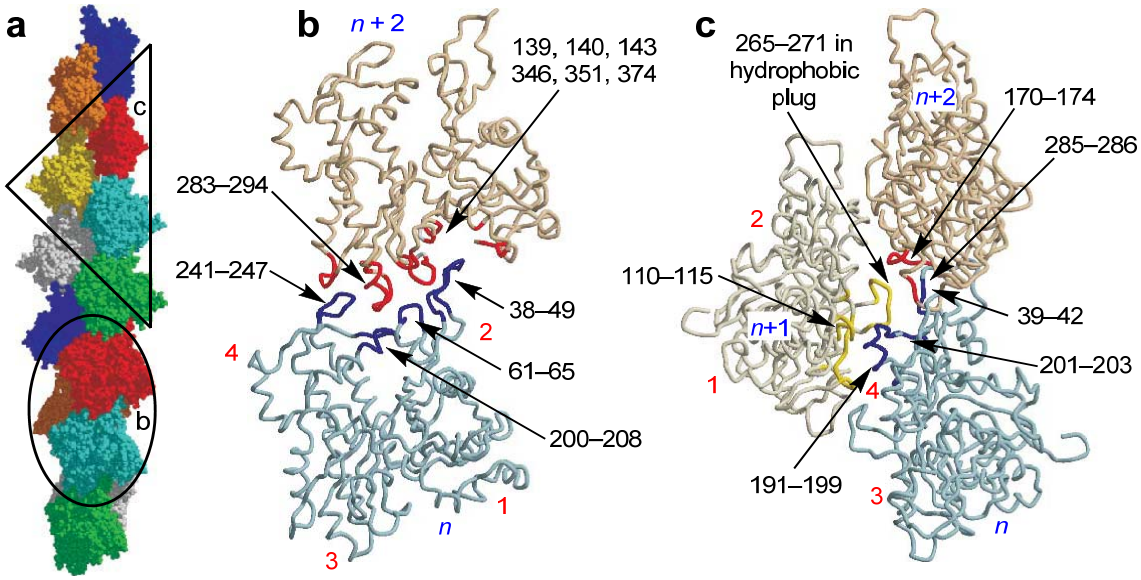

Figure 1.4 **a**. Oda Nature 2009 Actin filament with 13 subunits
b. Detail of red-blue section in oval.
c. Detail of red-yellow-blue triangle.[21]

Table 1.1: Natural Product Inhibitors of Actin Polymerization.

Drug *(X-ray +Actin Y/N)*[#]	Inhibits actin polym	Actin inhibitor mech	IC_{50}	ILS**	refs
Reidispongiolide A **1.4** (Y)	50nM	Cap&Sever F-actin G-actin binding	30nM (HT29)	NA	[1,2]
Aplyronine A **1.6** (Y)	31μM	Sever F-actin (?), 1:1 complex G-actin	0.4nM (HeLa)	545% P388	[3-8]
Rhizopodin **1.8** (Y)	100nM	2:1 G-actin/**1.8** complex	5nM	NA	[9-11]
Misakinolide A **1.9** (N)	10nM	(+) dimer cap; no sever	15nM (L1210)	140% P388	[12-16]
Swinholide A* **1.10** (Y)	.4nM-1μM	Sequester dimer; sever	20nM (12 lines)	115% P388	[19,20]

**The swinholide 22-membered ring monomeric lactone is devoid of antitumor activity; **ILS = Increase in lifespan (T/C) in cancer-bearing mice relative to untreated control; [#]actin-drug X-ray modeled in silico as small molecule mimics of gelsolin.*[10,18]

1.2: Retrosynthetic Analysis of Aplyronine Macrolactone Core

Aplyronine A is a 24-membered macrolactone with the lactone formed between carbonyl C1 and C23-OH. It has 34 carbons in the main skeleton, bears 5 olefins, 7 chiral centers **(1.6)**, and two α-aminoesters on the 7-OH and 29-OH groups. The stereocenters are comprised mainly of polypropionate, stereotetrads (alternating methyl and hydroxyl groups). Those polypropionates are C7-C10, C23-C26, and C29-C32 tetrads. The rest of the stereocenters include stereodiad C17-C19, an isolated stereocenter at C13, and the two α-aminoesters on hydroxyls 7 and 29 (Figure 1.6). After disconnection of the two α-aminoesters and replacing them with the appropriate aplyronine A analog esters, target molecule **1.7** is revealed as the desired aplyronine A core (Figure 1.6).

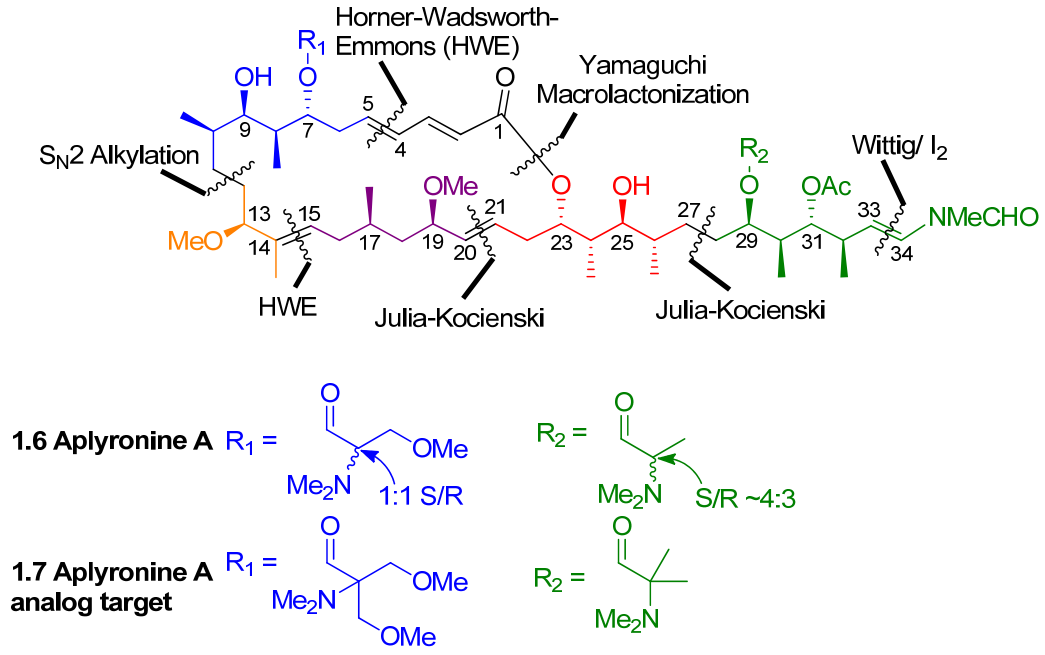

Figure 1.5: Retrosynthetic Analysis Of Aplyronine Core

Disconnection of aplyronine A analog **1.7** reveals 3 major stereotetrads as the potential aplyronine A precursors (Figure 1.7). The core lactone is formed via Yamaguchi macrolactonization between C1 and C23-OH while the *trans*-olefin between C4-C5 was formed via Horner-Wadsworth-Emmons (HWE) olefination. The C11-C12 bond is formed between a primary iodide on C11 and the α-position to a C13 carbonyl. The C11-C12 connection was presumed to take place via S_N2 attack of C12 anion on C11, which will be followed by Corey-Bakshi-Shibata (CBS) reduction of carbonyl C13 and subsequent methylation of the resultant 13-OH group. The *14E* olefin between C14-C15 was to be constructed via Massamune-Roush (HWE)[50] procedure. *20E* *trans*-olefin could be constructed via Julia-Kocienski olefination. The C27-C28 bond was to be formed

with a Julia-Kocienski or Wittig olefination followed by a Crabtree regioselective hydrogenation directed by the C29-OH. Finally *33E* olefin could be constructed employing Wittig olefination followed by iodine-equilibration in order to obtain the *trans*-olefin.

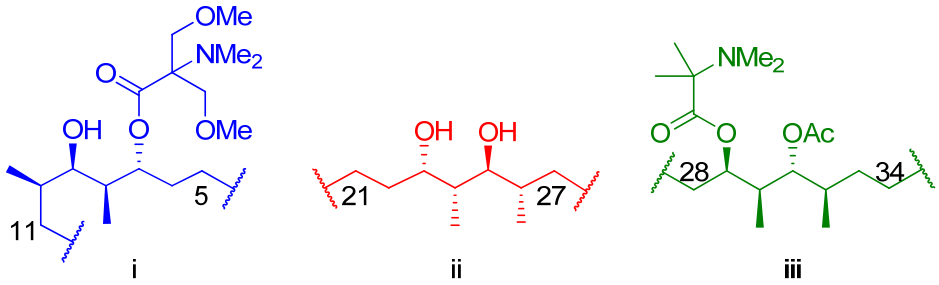

Figure 1.6: Aplyronine A Core Stereotetrads

The next level of synthetic specificity that must be addressed is the construction of the stereotetrads in Figure 1.7. A convergent strategy leading to the aplyronine core will require the use of tetrads i-iii. These stereotetrads require differentiated termini. Each stereotetrad has two hydroxyl groups that also must be set apart. C21-C27 fragment (ii) and C28-C34 fragment (iii) possess enantiomeric stereotetrads offset by one carbon. The position of the red and green stereotetrads on their respective backbones will be an important component of this investigation.

1.3: Polypropionate Generating Methodologies

The construction of polypropionates in organic synthesis has been a challenge that has been met with a growing number of methodologies through the years.[51-53] The Fuchs group has sought to add to, and improve the utility and scalability of polypropionate production.[54]

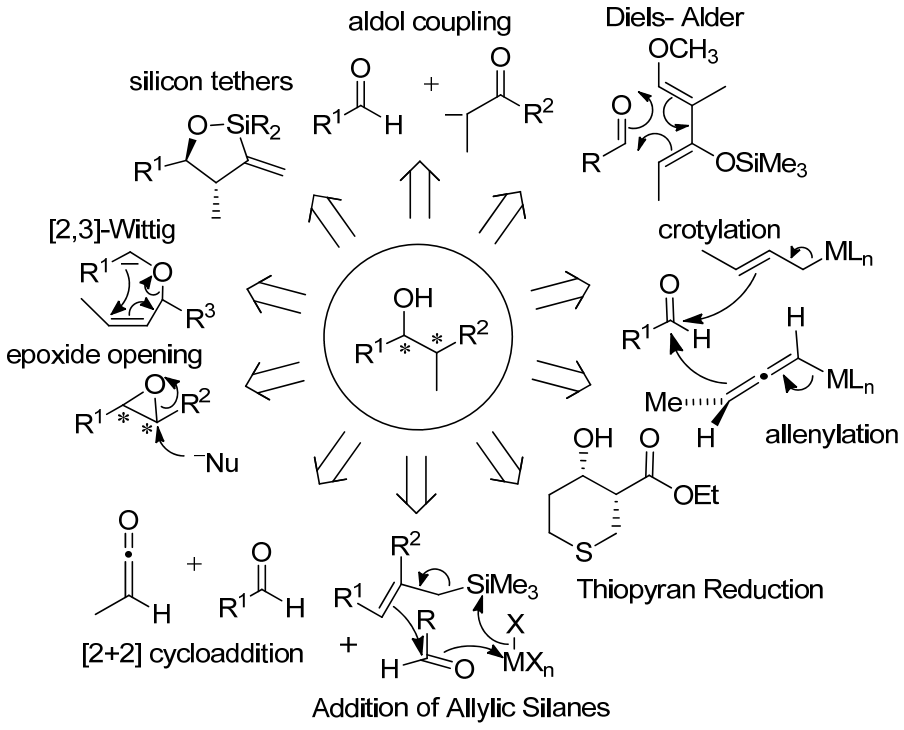

Figure 1.7: Polypropionate Methodologies

A key structural feature of polyketides in general, such as the macrolides aplyronine A **1.6** or misakinolide A **1.9** are the polypropionate segments. They are characterized by sequences of methyl- and hydroxy-bearing stereogenic centers, enabling large numbers of possible stereochemical permutations.[51]

Biosynthetically, these are derived by iterative condensations of propionyl subunits and subsequent reduction of the derived β-keto esters. Mimicking this biosynthetic pathway, the aldol reaction presents the most important method available for the stereocontrolled formation of propionates and many variants for regio-, stereo-, and enantioselective carbon–carbon bond formation have been reported.[55-58] Furthermore, alternative strategies are of increasingly high importance. To gain perspective as to the effectiveness of the vinylsulfone methodology, a survey of well-established as well as more recently developed methods for the stereoselective assembly of polypropionates is required, including propionate aldol reactions,[55] thiopyran reductions,[59-61] crotylations,[62-64] allenylations,[65-67] allylsilane addition,[68-72] silicon tethers,[73] epoxide openings,[74,75] rearrangements[76,77] and Diels-Alder cycloaddition[78-80] (Figure 1.7).

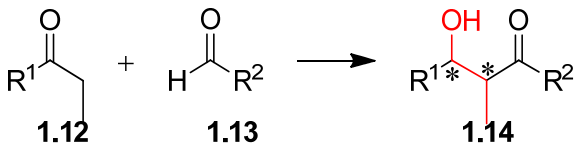

Figure 1.8: Aldol Condensation

The aldol addition reaction continues to be a highly versatile and widely used method for selective polypropionate synthesis.[55-57] The addition reaction involves the condensation of ethyl ketones (**1.12**), esters, or amides with aldehydes (**1.13**) to generate the required chiral β-hydroxycarbonyl adducts (**1.14**) in a direct fashion (Figure 1.8).

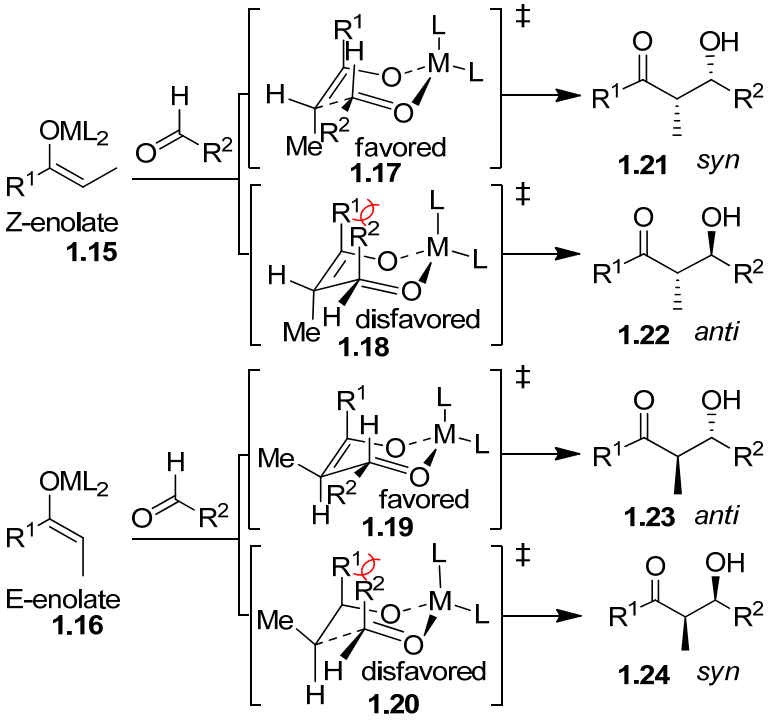

Figure 1.9: Aldol Condensation (Evans)

The relative configuration of the aldol adduct is usually determined by the geometry of the enolate intermediate, with *Z*-enolates (**1.15**) giving *syn* products (**1.21**) and *E*-enolates (**1.16**) *anti* products (**1.22**). As shown in **Figure 1.9**, this result has been rationalized by Zimmerman–Traxler transition states. Minimization of 1,3-diaxial interactions between R^1 and R^2 in the chair-like transition states **1.17** versus **1.18** and **1.19** versus **1.20** leads to the observed stereochemical outcome **(Scheme 3)**.[81]

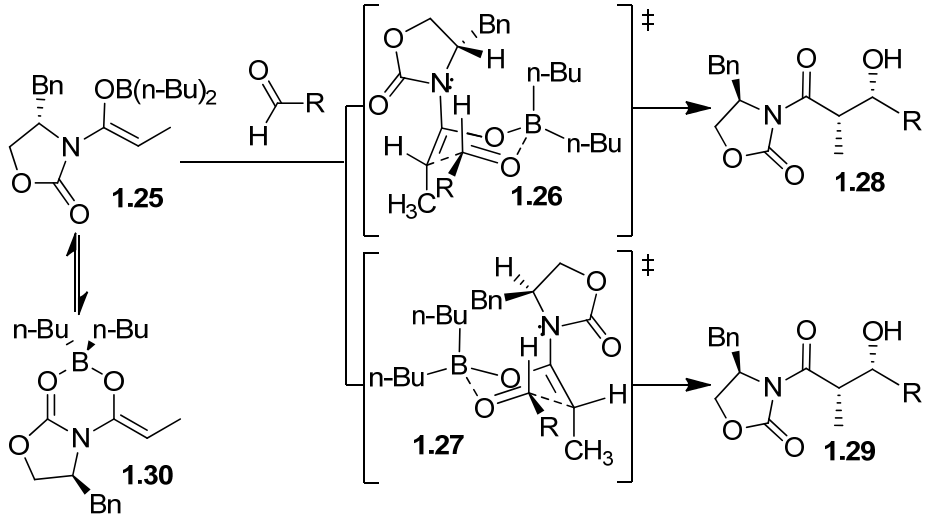

Figure 1.10: Evans Oxazolidinone Auxiliary

One of the most widely used methods of auxiliary-controlled diastereoselective aldol reactions employs the class of oxazolidinones[58] **(Figure 1.10)**, inititally developed by the Evans group for *syn*-aldol couplings.[55] The *syn*-aldol adducts are typically isolated in high diastereoisomeric purity (>250:1 dr) and yield. Enolization with dialkylboron triflates selectively affords Z-enolates **(1.30)**. The model proposed by Evans to account for the asymmetric induction of these chiral oxazolidinones is presented in **Figure 1.10**. It is based on minimization of carbonyl–carbonyl dipole interactions between the imide carbonyl and the aldehyde. For aldehyde addition, the reactive form **1.25** of enolate **1.30** has to be considered and two diastereomeric conformations **(1.26** and **1.27)** of the cyclic intermediate have to be taken into account. Due to steric interactions of the ligands on the boron and the chiral auxiliary, transition state **1.26** is favored,

consequently giving rise to ‘Evans syn’ product **1.28**, as opposed to **1.29**. Since its inception many permutations of this methodology have been developed.[82-88]

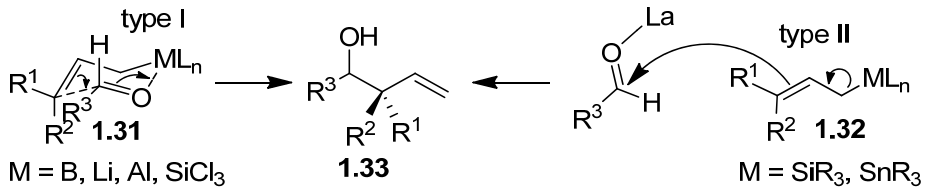

Figure 1.11: Crotylation (Brown, Denmark, Roush, Corey)

Asymmetric crotylation reactions have been studied extensively and used for the stereocontrolled assembly of polypropionates. One of the most intriguing features of these reactions is the predictable relationship between the configuration of the product and the geometry of the starting alkene. According to Denmark’s analysis,[89] they may be classified into three mechanistically distinct types. Type I reactions proceed via a rigid chair-like transition state **1.31** (Figure 1.11) which is characterized by coordination of the carbonyl to the metal atom. Consequently, the *syn/anti* diastereoselectivity of the product **1.33** reflects the *Z/E* ratio of the starting olefin geometry. Boron reagents are the most prominent representative of this type.[63,90-93] Type II reagents (**1.32**), exemplified by trialkylsilanes and stannanes usually proceed via an open transition state and require Lewis acid activation.[68-71,94-97] Type III reactants, not illustrated in Figure 1.11, also proceed via an open transition state. They provide the same diastereomeric product, independent of the starting double bond configuration.

Crotylation reactions may also be classified into stoichiometric and catalytic variants. The most widely used stoichiometric crotylation reactions belong to type I reactions, with Z-crotyl reagents giving *syn* isomers, and E-isomers the *anti* products. This simple stereoselectivity may be readily explained by Zimmerman–Traxler transition states.

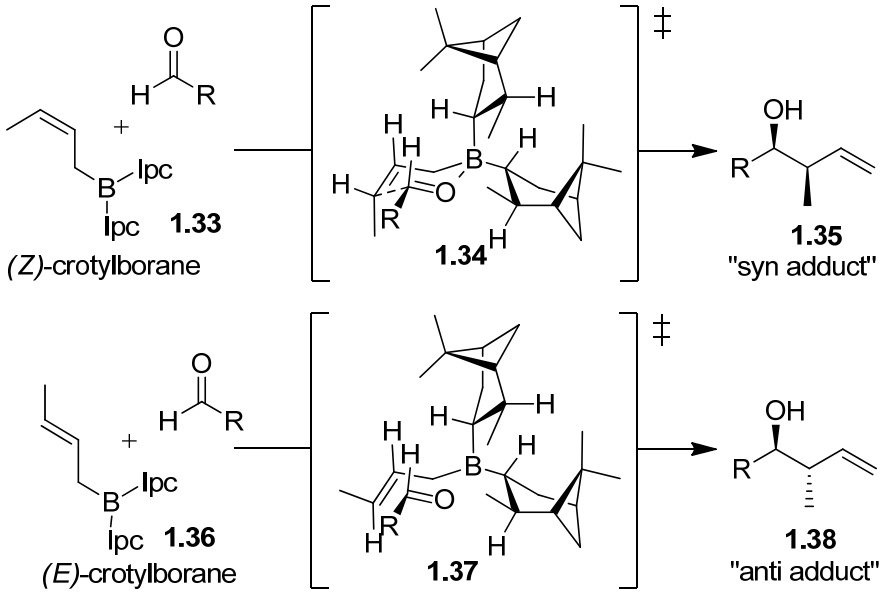

Figure 1.12: Crotylboration (Brown)

Chiral borane reagents have been developed by Hoffmann, Brown, Roush and others.[63,91,98,99] Hoffmann and Zeiss have shown that the reaction of (*E*)- or (*Z*)-crotylboronates with aldehydes results in the formation of *anti*- or *syn*-β–methyl homoallylic alcohols,[100] which may be explained by chairlike transitions states. Use of crotyl(diisopinocampheyl) boranes **1.33** and **1.36** was developed by Brown[63,91] (Figure 1.12). Owing to the good performance and commercial

availability of the chiral auxiliary, these have become the standard method for asymmetric crotylation. The high stereospecificity of these reactions may be explained by closed chair-like transition states **1.34** and **1.37**, where the boron is coordinated to the carbonyl oxygen. The aldehyde is oriented in such a manner that the R group is placed in an equatorial position of the chair to minimize steric interactions between the Ipc group on boron and the allyl unit.

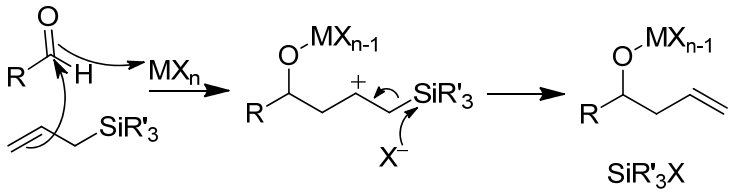

Figure 1.13: Crotylsilane Mechanism

In general, the addition of allylic silanes to electrophiles has been established to be a stepwise process.[101] Thus, initial addition of an allylic silane to an activated aldehyde forms a carbocation, which is stabilized by hyperconjugative overlap with the carbon-silicon bond (Figure. 1.14). Cleavage of the silyl electrofuge then provides the homoallylic alcohol product.

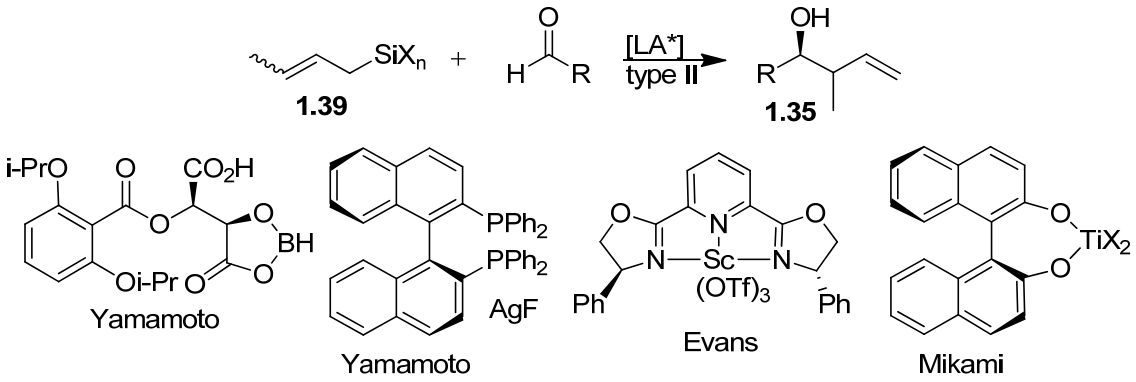

Figure 1.14: Chiral Lewis Acid Crotylation

Chiral Lewis acids have been widely employed as catalysts in the addition of crotyl organometallic reagents (1.39, Figure 1.14), mainly derived from Si, Sn and B. Usually, these reactions may be classified as type II reactions and predominantly the *syn* diastereomers **1.35** are obtained. Enantioselective Lewis acid catalyzed additions have been reported by Yamamoto,[102] Mikami,[103] Nishiyama,[104] Evans,[105] and Hall.[106,107]

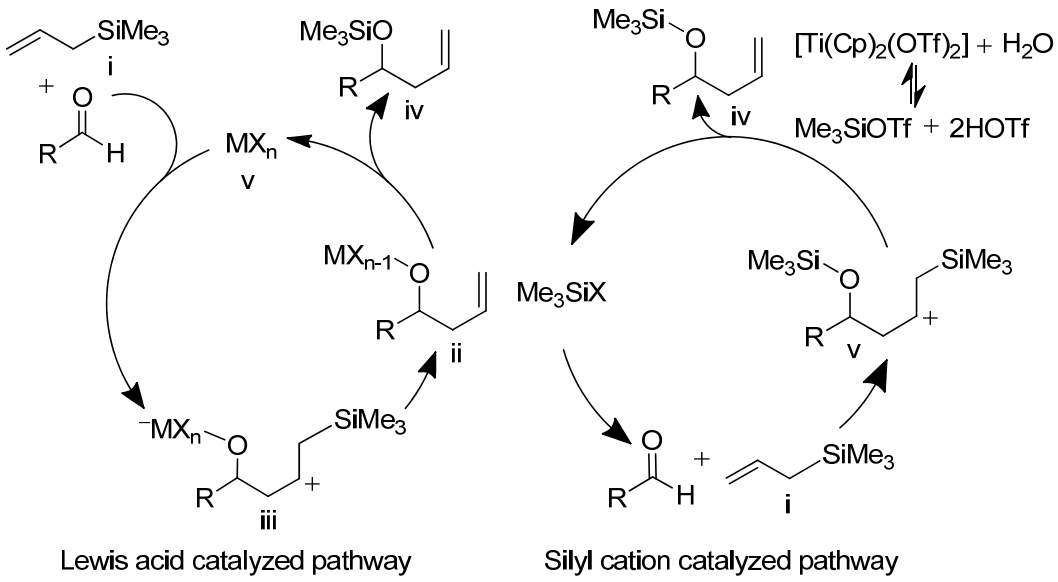

Figure 1.15: Catalytic Cycle of Lewis Acid Catalyzed Crotylation

In a mechanistic investigation on the addition of allyltrimethylsilane to aldehydes catalyzed by Lewis acids such as $[Ti(Cp)_2(OTf)_2]$, $Ph_3C^+OTf^-$, and $Ph_3C^+ClO_4^-$, it was found that the reactive species is actually the electrofugal trimethylsilyl cation.[108] This possibility was first discussed and eliminated in the Lewis acid-catalyzed aldol reaction with trialkylsilyl enolates.[109],[110] In the former study,[108] a trace amount of water in the reaction was shown to hydrolyze the Lewis acid to generate a Brønsted acid. The Brønsted acid then reacts with allyltrimethylsilane to produce Me_3SiOTf or $Me_3Si\text{-}ClO_4$, both of which are powerful catalysts for allylation. Furthermore, dehydration of the solvent or addition of a hindered base to quench the acid does not necessarily prevent the formation of these silyl catalysts. In the case of $[Ti(Cp)_2(OTf)_2]$, upon activation of the aldehyde and addition of ii, the metal alkoxide i and Me_3SiOTf are produced

(Figure 1.15). To achieve a catalytic process, the metal must dissociate from the complex assisted by the silylation of the adduct. However, the silylation does not occur, and instead Me_3SiOTf functions as highly reactive catalyst for the allylation. Thus, the reaction is actually a metal initiated, silyl cation-catalyzed process.

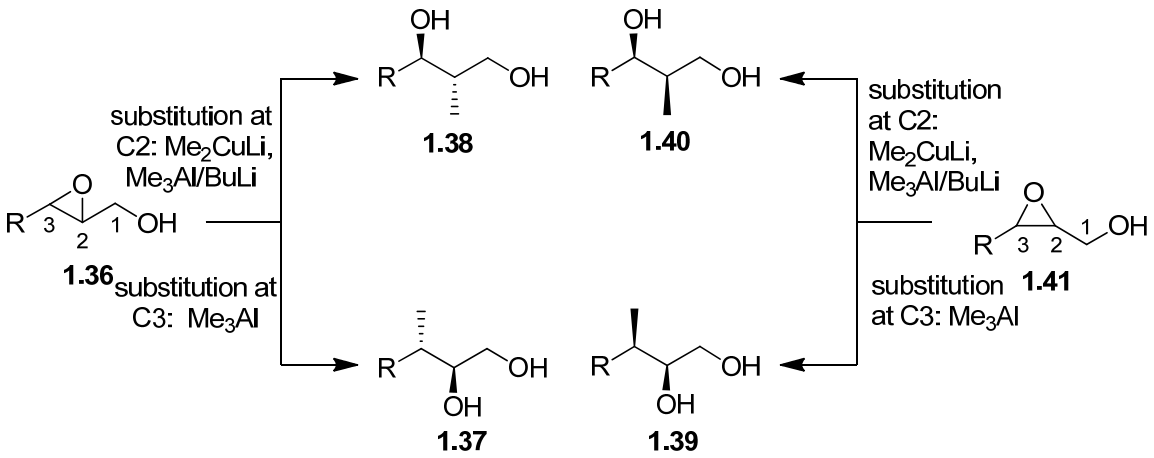

Figure 1.16: Epoxide Opening (Posner, Lipshutz, Trost, Kishi, Miyashita**)**

Stereoselective epoxide-opening reactions have been recognized as an important transformation in organic synthesis and are widely used as key steps in natural product syntheses.[111] Nucleophilic substitution reactions of *trans* or *cis*-configured epoxy-ols **1.36** and **1.41** with organometallic reagents, including organocuprates and organoaluminum complexes, provide an efficient method for the stereoselective construction of propionate frameworks.[111] Regioselective openings with lithium dimethyl cuprate[112] or trimethylaluminum and butyllithium[113]

preferentially lead to 2-methyl-1,3-diols **1.38** and **1.40**, while trimethylaluminum[114] reacts at C3 to give the 3-methyl-1,2-diols **1.37** and **1.39** (Figure 1.16).

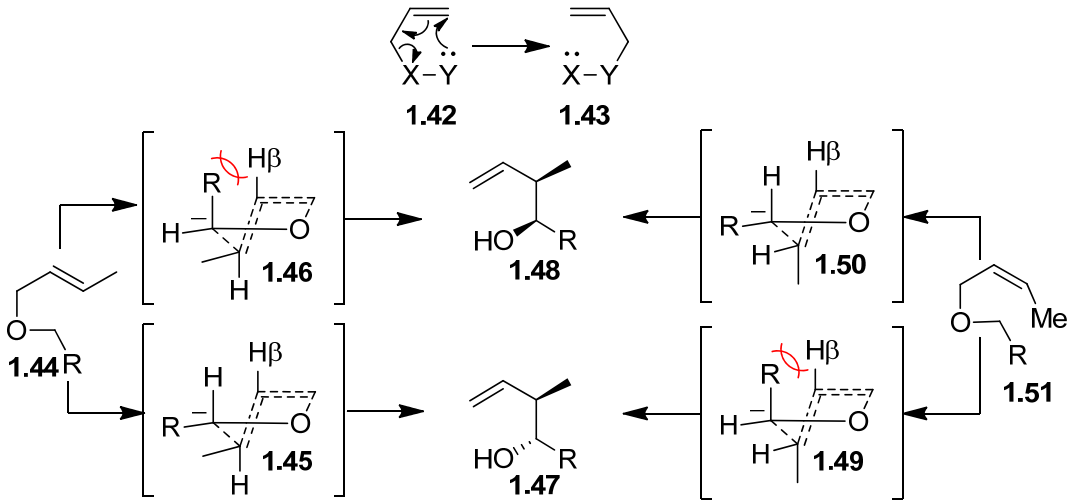

Figure 1.17: [2,3]-Wittig Rearrangement (Mikami and Nakai)

[2,3]-Sigmatropic rearrangements constitute a versatile type of bond reorganization with many applications in organic synthesis. This reaction may be generalized as shown in Figure 1.17 for structures **1.42** and **1.43**. It is defined as a thermal isomerization that proceeds through a six-electron, five-membered cyclic transition state.[76,77] Mikami and Nakai have studied the diastereoselectivity of a broad range of [2,3]-Wittig rearrangements and proposed transition states **1.45**, **1.46**, **1.49** and **1.50** to explain the results (Figure 1.17). In general, *E*-configured substrates **(1.44)** give *anti* products **(1.47)** while the *Z*-congeners **(1.51)** give *syn* isomers **(1.48)**. This may be explained in terms of pseudo-1,3-

diaxial interactions of R with H_β in **1.46** and **1.49**. Accordingly, **1.50** should be sterically favored, thus leading to *syn*-selectivity. The order of selectivity is correlated with an increase in 1,3-repulsion. A marked dependence of the *anti*-selectivity on the size of the substituent R is best explained by additional steric gauche interactions between R and Me in the preferred transition state **1.45**, hence the *anti* selectivity decreases with an increase of this gauche interaction.[77]

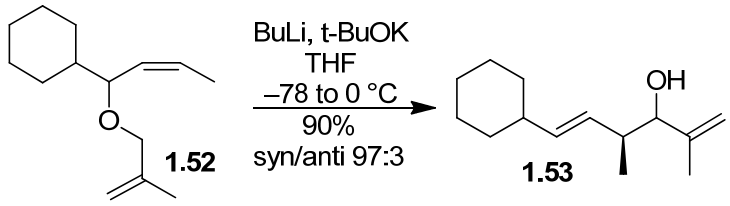

Figure 1.18: Wittig Rearrangement

Application of the [2,3]-Wittig rearrangement reactions of (*Z*)-allylic ether **1.52**, a cyclohexanecarboxaldehyde-derived intermediate for the synthesis of *syn* stereodiad **1.53**, was described by Parker (Figure 1.18).[115,116] This product was converted into (*syn*,*anti*)-polypropionate building blocks.[115]

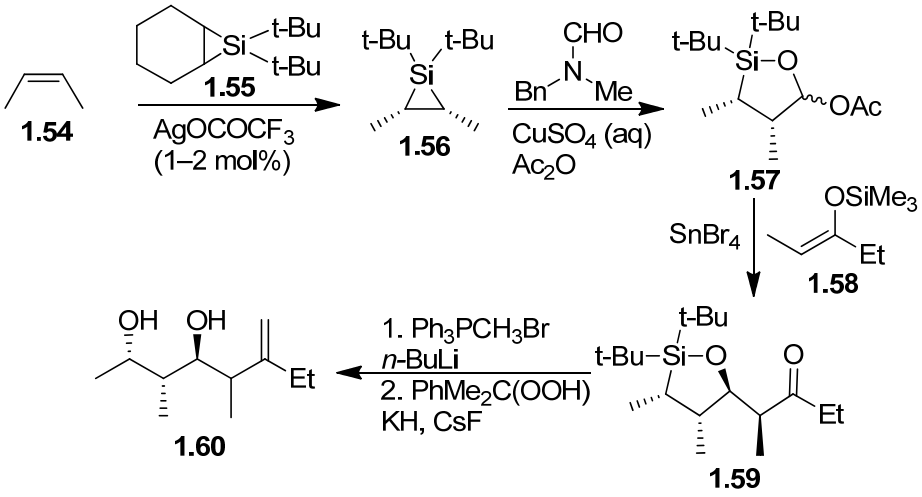

Figure 1.19: Silicon Tether (Phillips)

Silacyclopropanes such as **1.56** are strained silanes that undergo carbon–carbon bond-forming reactions with various carbonyl compounds.[117] Carbonyl insertions proceed with high stereo-, regio-, and chemoselectivity to afford oxasilacyclopentane adducts **(1.57)** under mild, metal catalyzed conditions (Figure 1.20).[118] Woerpel has developed a silver-catalyzed silylene transfer as a mild and efficient method for the synthesis of silacyclopropanes **1.56**;[117-123] the process uses a stereospecific silylene transfer from cyclohexene silacyclopropane **1.55** to alkene **1.54** (Figure 1.1). Treatment of intermediate **1.56** *in situ* with *N*-methyl-*N*-benzylformamide and catalytic amounts of copper iodide resulted in an N,O-acetal, which may be hydrolyzed and acetylated to provide oxasilacyclopentane **1.57** in high yield. Nucleophilic substitution with silyl enol ether **1.58** produced ketone **1.59** in high yield and diastereoselectivity. Wittig

methylenation followed by carbon–silicon bond oxidation afforded diol **1.60,** a key fragment for the synthesis of 1‘-*epi*-stegobinone.[124]

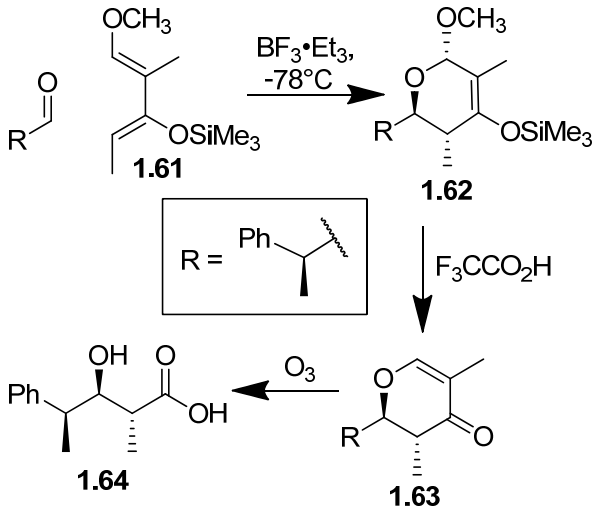

Figure 1.20: Diels-Alder (Danishefsky)

The cycloaddition of Danishefsky's diene to aldehydes corresponds to an aldol addition. The Cram product **1.63** (Figure 1.20) was formed with a normal diastereoselectivity of 4.3 : 1 and, after refunctionalization, gave the carboxylic acid **1.64** (stereotriad C).[80] Upon changing the solvent stereotriad A could be obtained with a selectivity of up to 10 : 1.[78,80] It remains to be clarified whether or not high diastereoselectivities can be generally obtained with reagent **1.61** on addition to chiral aldehydes.

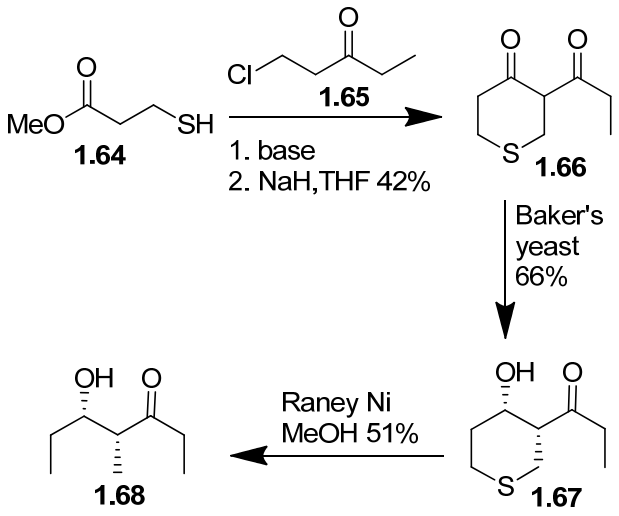

Figure 1.21: Thiopyran Reduction (Fujisawa)

One of the most intriguing non-traditional methodologies for obtaining polypropionates is by way of thiopyrans. An exhaustive review by Ward[59] elucidates the flexibility of this methodology. By way of example Fujisawa et al.[125] employed enantioselective reduction of **1.66** as the key step in a synthesis of sitophilure **(1.68)**, an aggregation pheromone of Sitophilus weevils (Figure 1.21).[126] The preparation of **1.66** involved alkylation of **1.64** with **1.65** followed by intramolecular Claisen reaction to yield the 1,3-diketone **1.66** in moderate yield. Baker's yeast reduction of **1.66** gave **1.67** with excellent stereoselectivity. Although the reaction was not completely regioselective, the ketol products resulting from reduction of the exocyclic ketone were lost during the work up, presumably due to decomposition via a retro-aldol reaction. Raney™ nickel desulfurization of **1.67** gave sitophilure **(1.68)** in moderate yield.

The goal of this project is to better characterize the effects of aplyronine A **1.6** on both the actin cytoskeleton and other potential cellular targets. In pursuit of this goal, a greater understanding of the vinylsulfone polypropionate strategy is sought. This knowledge is essential for potential future application of aplyronine A-type compounds as anticancer drugs. Since the proposed experiments would require unobtainable amounts of *Aplysia* in order to purify significant quantities of aplyronine A **1.6** it was decided to synthesize a highly similar aplyronine analog **1.7**, mono-lactone and bis-lactone aplyronine A analog **1.11** which is intended for use in collaborative biochemical and cellular studies. (Figure 1.2)

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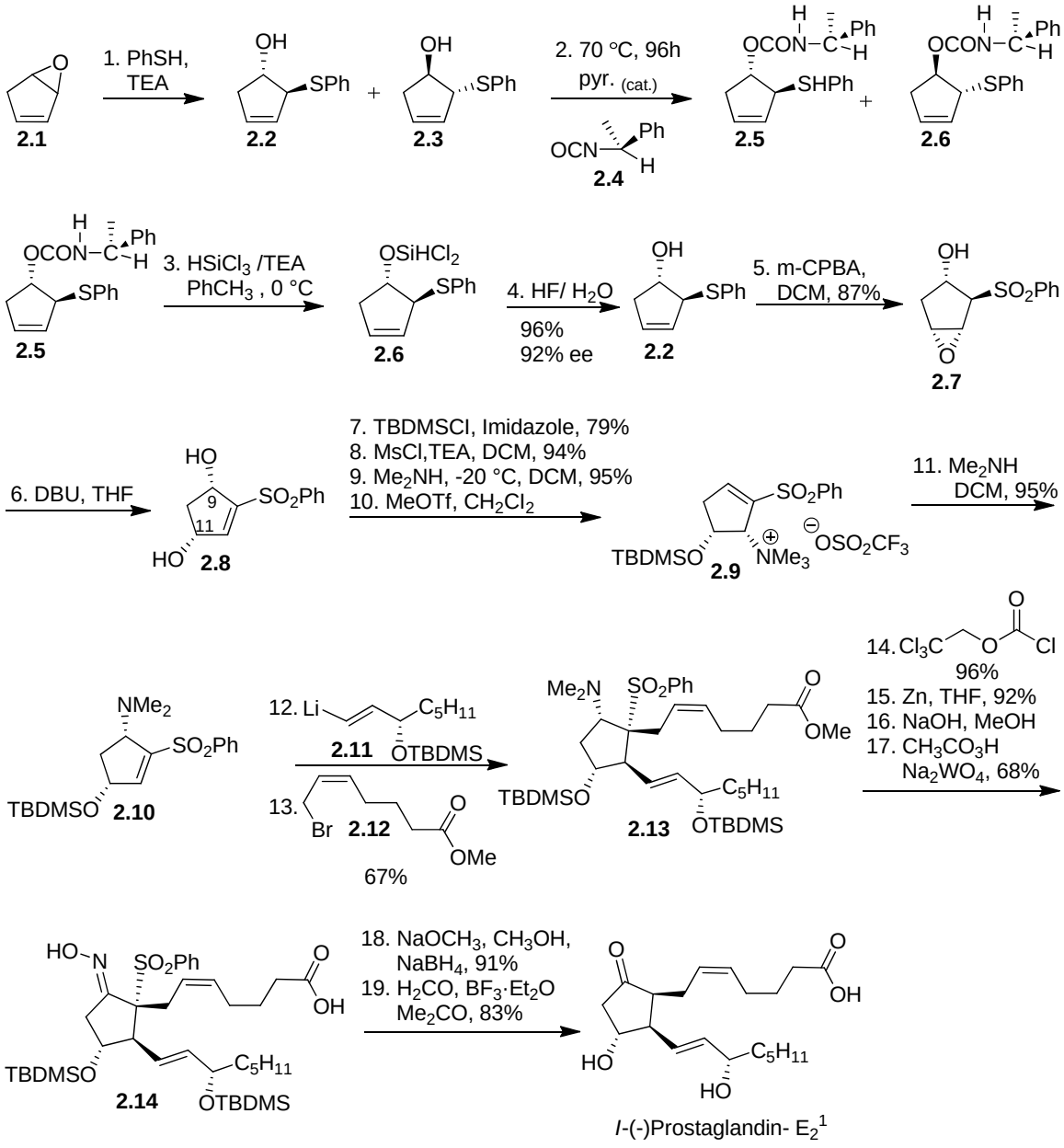
CHAPTER 2: THE VINYL SULFONE MOIETY AS A POLYPROPIONATE FACILITATOR

2.1: Use of Carbocyclic Scaffold in the Vinylsulfone Polypropionate Strategy

Work accomplished by Saddler and Donaldson in the Fuchs group[1] utilized application of the vinylsulfone moiety as a facilitator of asymmetry in the total synthesis of *I*-(-)-Prostaglandin E_2 (Scheme 2.1**)**. *I*-(-)Prostaglandin E_2 has a β-hydroxy cyclopentanone core containing three contiguous chiral centers consisting of a *cis*-fatty acid, *trans*-allyl alcohol, and the keto-cyclopentanol. Treatment of the racemic cyclopentene epoxide **(2.1)** with thiophenol yields **2.2** & **2.3**. Racemic sulfide alcohols (**2.2** & **2.3**) were resolved on the mole scale by treatment with 1 equivalent of *S*-(-)-(α-methylbenzyl)isocyanate (**2.4**) to give a mixture of diastereomeric urethanes **2.5** and **2.6**. Crystallization of this mixture from methanol gives pure **2.5**. Cleavage of urethane **2.5** with trichlorosilane allows for greater than 90% recovery of chiral **2.4** for recycle. The resulting silyl ether **2.6** is then hydrolyzed (without isolation) with dilute aqueous hydrofluoric acid to optically active sulfide **2.2** (92% ee). Reaction of **2.2** with 2 equivalents of peracetic acid gives hydroxysulfone (not shown), which is generally not purified, but directly treated with 1.1 equivalents of *m*-chloroperoxybenzoic acid (MCPBA) to produce highly crystalline epoxysulfone (**2.7**) 88%, 97% de. On small scale it was convenient to simply use 3 equivalents of MCPBA to directly obtain

epoxysulfone (**2.7**) (97% de). Purification of the mother liquors (plug on silica gel) afforded 3% of the relatively unstable epoxy sulfone diastereomer **epi-2.7**. Treatment of epoxysulfone (**2.7**) with catalytic DBU (to produce the dihydroxy vinylsulfone **2.8**) followed by *in situ* silylation of less hindered alcohol with t-$BuMe_2SiCl$ and imidazole in THF; (use of less bulky chlorosilanes, e.g., *i*-$PrMe_2SiCl$, gives no selectivity between C-9 and C-11) gives crystalline monosilyl ether, (79%).



Scheme 2.1: Prostaglandin-E_2 Via Vinylsulfone Polypropionate Strategy

Purification of the mother liquors gives 9% disilyl ether which can be hydrolyzed to diol **2.8** (CF_3CO_2H, THF, H_2O) in near quantitative yield and recycled in the silylation step. Treatment of **2.8** with mesylchloride and

triethylamine in methylene chloride results in the formation of the sensitive mesylate (94%), which is not routinely isolated but rather treated directly with dimethylamine at -20 ºC (<5min) to give amino vinylsulfone (95%). An expedient preparation of **2.9** from aminovinylsulfone involves quaternization of the amine with methylfluorosulfonate (1.1 equivalents, CH_2Cl_2, 25 ºC, 2 h) to give the crystalline ammonium salt **2.9**, which is not normally isolated but rather directly treated with dimethylamine at -20 ºC (5 min) to give **2.10** (95%). Treatment of amino vinyl sulfone **2.10** with optically active vinyllithium reagent **2.11** (THF/hexane, -60 ºC; the reaction is slow below -70 ºC) followed by quenching with water provides a separable 92%:5% mixture of the *cis* : *trans* adducts **2.13** and **epi-2.13** (not shown). The treatment of **2.13** with 2,2,2-trichloroethylchloroformate (2 equivalents, neat, 25 ºC, 72 h) in the presence of solid sodium bicarbonate to give urethane (96%) as an oil after excess 2,2,2-trichloroethylchloroformate, is removed with a silica gel plug. Treatment of urethane with activated zinc in THF at reflux for 6 h affords a 92% yield of desired secondary amine. These reactions have been easily run on ~40g scale. Ester hydrolysis of with sodium hydroxide (3 equivalents) in 2% aqueous methanol (48 h) yields the carboxylic acid (99%), which is oxidized with 40% peracetic acid (6 equivalents) in wet methanol containing solid sodium carbonate (15 equivalents) and a catalytic amount of sodium tungstate (0.1 equivalent) to deliver oxime (**2.14**). Desulfonylation of oximino acid **2.14** is accomplished by treatment with sodium methoxide and sodium borohydride in methanol to give

91% of the oxime. Hydrolysis of this oxime (boron trifluoride, paraformaldehyde, aqueous acetone) furnishes *I*-(-)-PGE_2 (83%).

The *I*-(-)-PGE_2 was obtained as an oil (6.69 g, 80%) after column chromatography on silica gel to remove a small amount of PGA_2. The efficacy of the cyclic 5-membered vinylsulfone is demonstrated in Scheme 2.1.[2-5]

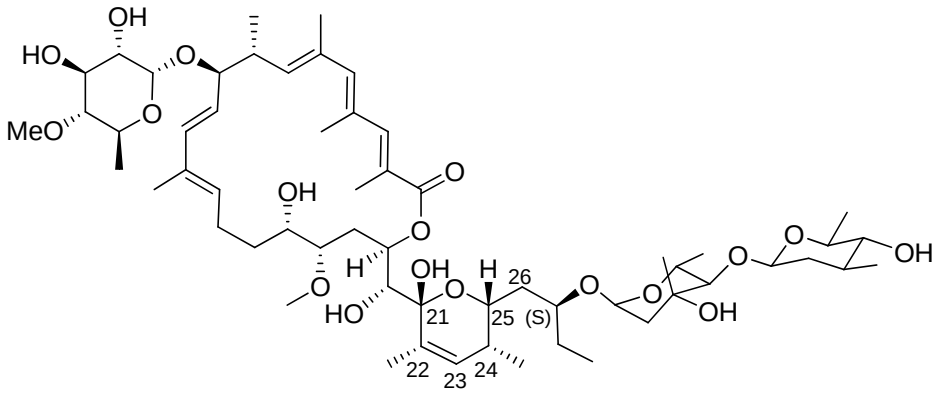
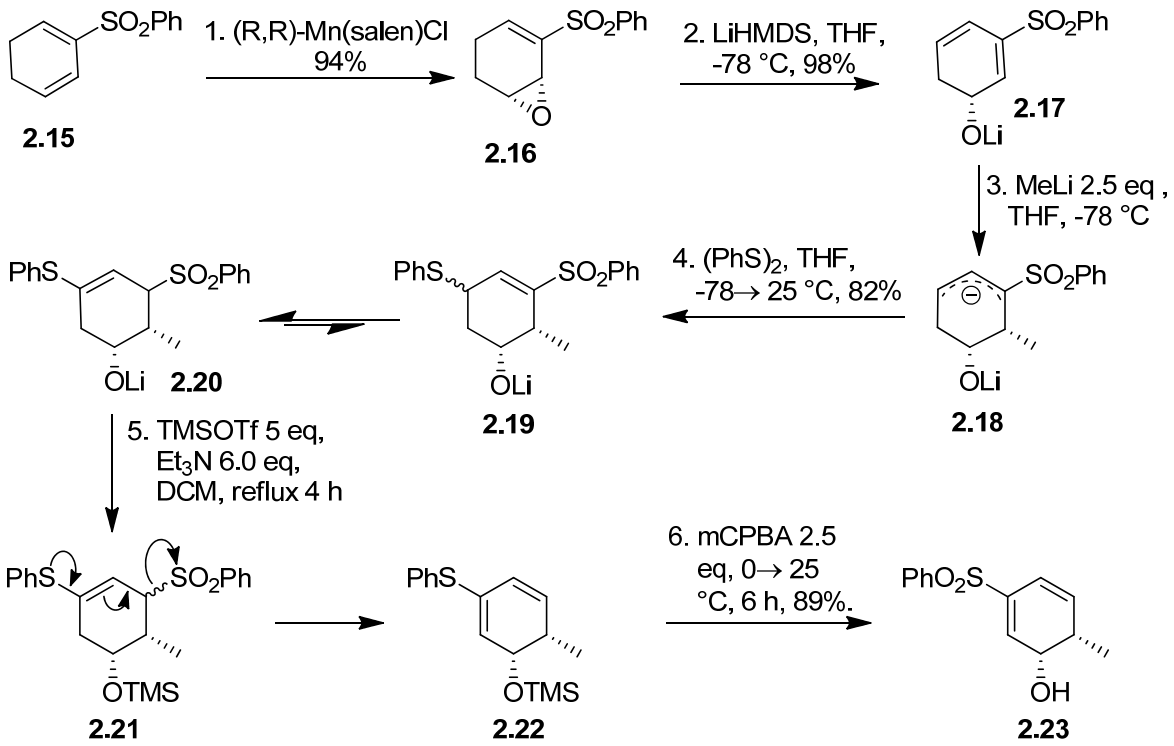


Figure 2.1: Apoptolidine

A utilization of the six membered vinylsulfone by Chen, Y.; Evarts, J. B., Jr. & Torres, E. was employed in efforts to assemble the C21-C26 fragment of Apoptolidine **(Figure 2.1)**. Starting from dienylsulfone **(2.15)** Jacobsen asymmetric epoxidation yields the enantiopure epoxide **2.16** (94%). Addition of 1.1 equiv of LiHMDS to the epoxy vinylsulfone to furnish oxido diene **2.17** followed by 2.5 equiv of MeLi generates dianion **2.18**. Further addition of $(PhS)_2$ results in regiospecific capture of the allyl sulfonyl anion to produce vinyl sulfide

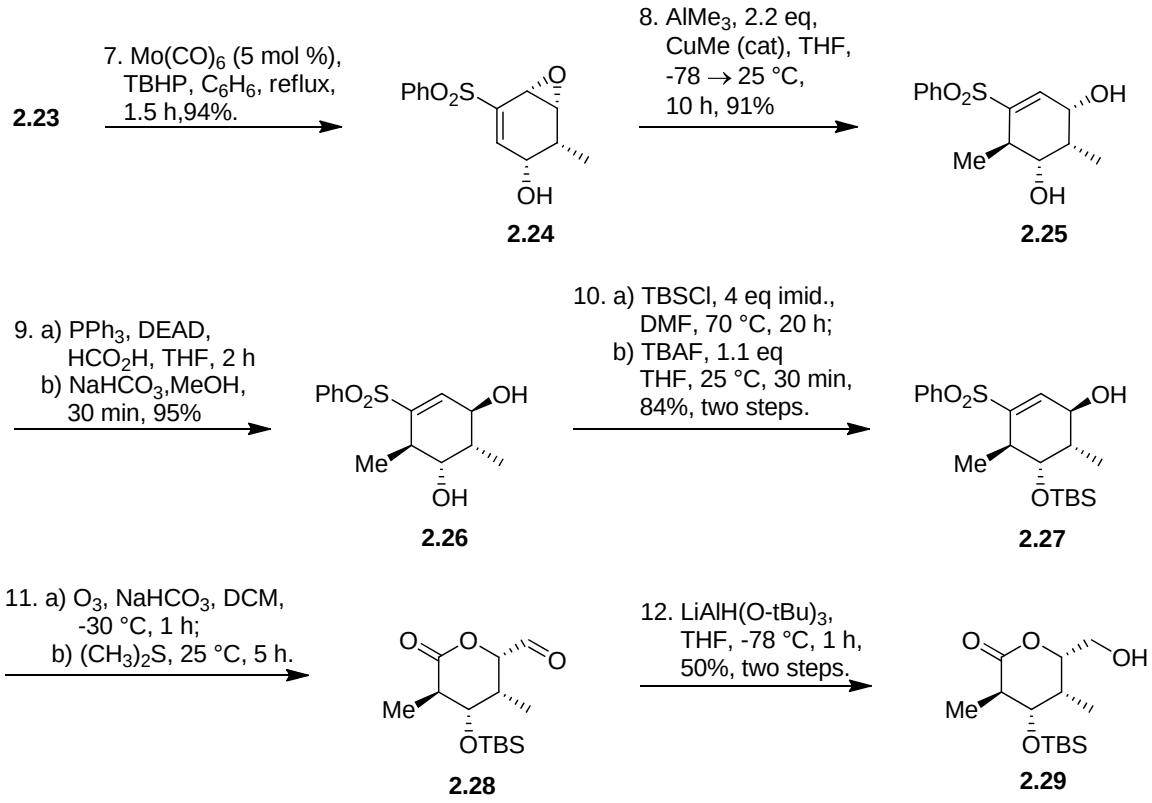
2.20 (isolated as the alcohol) in 82% yield after stirring for 8 h at 25 °C. As has been shown in the 7-membered ring series, formation of intermediate **2.19** proceeds via conjugate addition of methyllithium followed by γ-sulfenylation. The unusual γ-regiochemistry of this process appears to result from the interplay of the weak sulfenylation reagent in concert with the high steric demand imposed by the proximally methylated *R*-sulfonyl center. TMS triflate-promoted, lone-pair assisted elimination of the crude diastereomeric mixture **2.19** and **2.20** to dienyl sulfide **2.22** was readily accomplished in 94% yield by heating **2.21** with 5.0 equivalents of TMSOTf



Scheme 2.2: Apoptolidine C21-C26 Via Vinylsulfone Polypropionate Strategy

and 6.0 equivalents of Et_3N in methylene chloride at reflux for 4 h. The reaction mixture was cooled to 0 °C, and 2.5 equivalents of *m*-CPBA was added in portions; the mixture was stirred for 6 h at 25 °C to afford dienylsulfone **2.23** (Scheme 2.2).

Directed catalytic epoxidation of alcohol **2.23** with $Mo(CO)_6$ (5 mol %) and TBHP in benzene at reflux for 1 h smoothly gave **2.24** as a single diastereomer in 94% yield. Treatment of alcohol **2.24** with trimethylaluminum in the presence of a catalytic amount of methylcopper affords **2.25** in 91% yield. The nucleophilic methylation reaction has the potential of both 1,2- and 1,4-addition modes. In this instance, any competitive 1,2-*trans*-addition results in formation of the enantiomer of **2.25**, an especially serious consequence. Fortunately, chiral HPLC demonstrates that the enantiomeric excess of **2.25** is >98%, which indicates a 1,4-/1,2-selectivity ratio of >49:1 in the methylation process. The allylic hydroxyl of diol **2.25** can be selectively inverted using the Mitsunobu reaction to give **2.26** in 95% yield.



Scheme 2.3: C21- C26 Apoptolidine Fragment Assembly

Sequential treatment of **2.26** with excess *tert*-butyldimethylsilyl chloride, followed by cleavage of the less hindered silyl ether with 1 equivalent of TBAF delivers **2.27** in 84% yield. Finally, ozonolysis of **2.27** in methylene chloride gives aldehyde **2.28**. For long-term storage, **2.28** is reduced with LiAlH(O-*t*-Bu)$_3$ to afford alcohol **2.29** in 50% overall yield from **2.28** (Scheme 2.3).

With the previous exploration of the synthetic utility of the 5 and 6-membered vinylsulfone rings having been suitably illustrated, the strategic implications of this moiety will be addressed in the following sections. Much of the chemistry discussed up to this point applies to the 5, 6 and 7- membered dienylsulfone rings. In the following examination, the chemistry that applies to the

cycloheptadienyl sulfone ring, a key Aplyronine A intermediate, will be highlighted.

2.2: Dienylsulfone Asymmetry

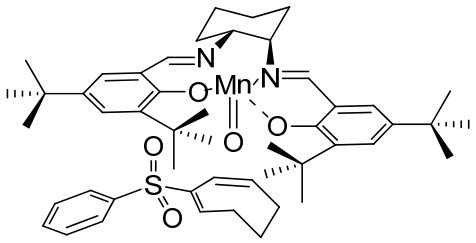
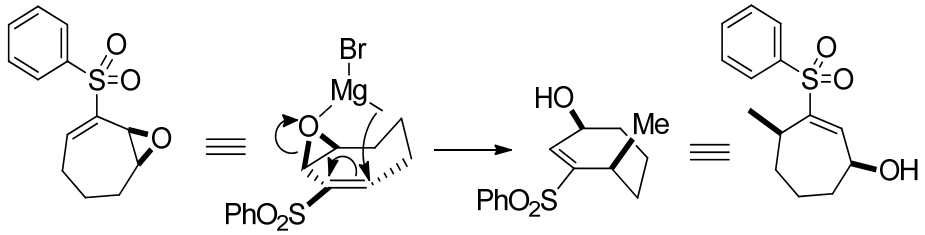


Figure 2.2: Jacobsen Catalyst & Dienyl Sulfone

The implicit asymmetry of the vinylsulfone functional group contributes greatly to its ability to facilitate asymmetric epoxidation adjacent olefinic stereocenters.[6-8] As is shown in Figure 2.2 the interaction between the adjacent *Z*-olefin of the dienylsulfone ring and the salen ligand defines alignment of the sulfone moiety and the equatorial side of the salen ligand, where the catalyst and substrate interact in an *exo*-manner. Such steric interactions allow the oxygen to be delivered selectively to only one side of the olefin adjacent to the vinylsulfone moiety (Figure 2.2).

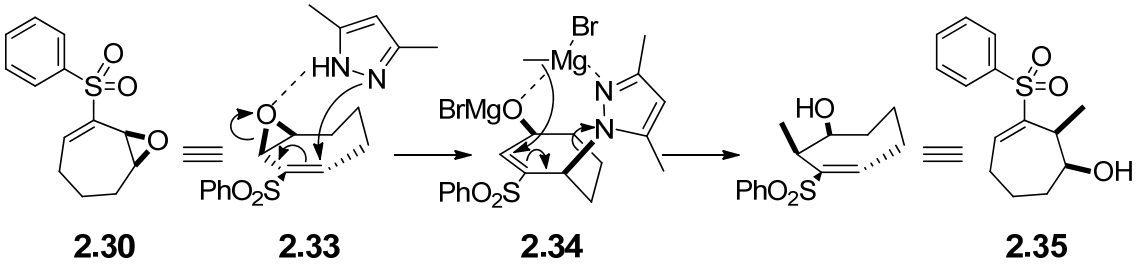
2.3: Epoxide Directed Asymmetry



2.30 **2.31** **2.32**

Figure 2.3: Asymmetric Nucleophilic Addition to the Vinylsulfone

The enantiopure epoxyvinylsulfone **(2.30)** has directs further asymmetry on the molecule *via* the Lawton strategy.[9] The basicity of the epoxide oxygen allows for coordination with Lewis acidic metals bearing nucleophiles to be either delivered to the vinylsulfone in a syn manner **(2.31),** or directly to the epoxide in *anti* fashion. As can be seen in Figure 2.3 the Grignard reagent coordinates to the epoxide, forcing addition to the vinylsulfone *cis* to the epoxide **(2.31)**. The strong inductive property of the sulfone in combination with the ability of the epoxide to be cleaved by olefin activation yields two chiral centers proximal to the vinylsulfone **(2.32)**. [10-12]



2.30 **2.33** **2.34** **2.35**

Figure 2.4: Syn Nucleophilic Addition to Epoxyvinylsulfones

The Lawton strategy can be used in an iterant manner to assemble the *syn*-diad. As can be seen in Figure 2.4 the pyrazole N-H coordinates with the epoxide, facilitating *cis* addition to the epoxy vinylsulfone **(2.33)**. With the *syn* motif established between the alcohol and the 3,5-dimethylpyrazole moieties, the Lewis acidic coordinated Grignard reagent directs *syn* Sn2' addition **(2.34)** to deliver the *syn* diad **(2.35)**.

2.4: Aluminoxane as a Nucleophilic Methylation Species

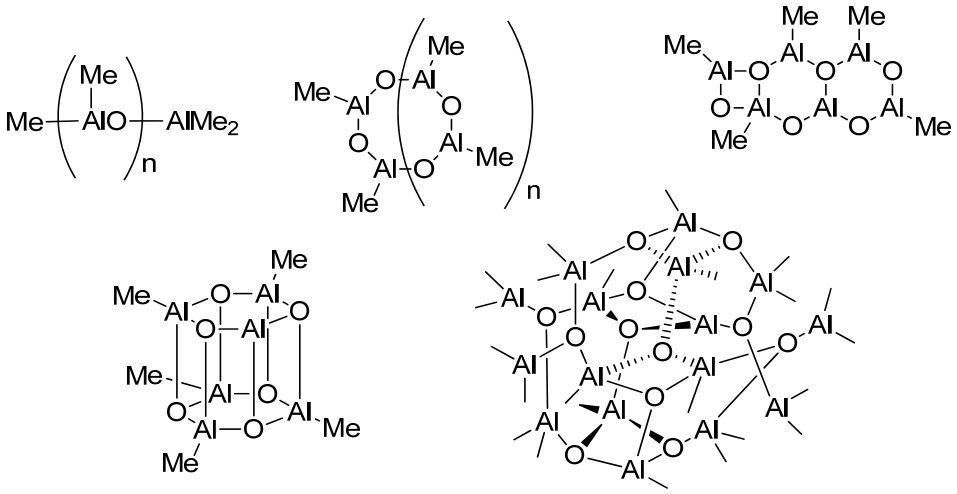


Figure 2.5: Proposed Aluminoxane Structural Architectures

Trimethylaluminoxane (Figure 2.5 is a sterically hindered aggregated species with the ability to activate carbonyls and epoxides via a bidendate coordination of two aluminum atoms to the oxygen **(2.36)**.[13] Maruoka and coworkers showed that the methyl cleaves the epoxide proximal to the olefin on γ,δ-epoxy acrylates. A methyl nucleophile from either a second equivalent of aluminoxane or the aggregate associated with the epoxide then undergoes addition to the activated epoxide in an *anti*-manner to deliver the *anti*-diad **(2.37).** (Figure 2.6)

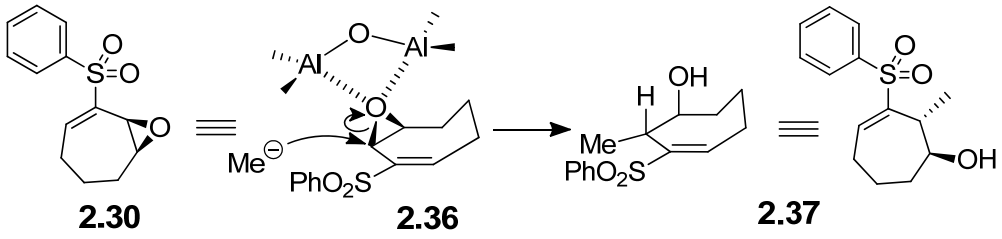


Figure 2.6: Epoxide Directed Methylation via Aluminoxane Species

2.5: Differentiation of Termini Post Oxidative Cleavage

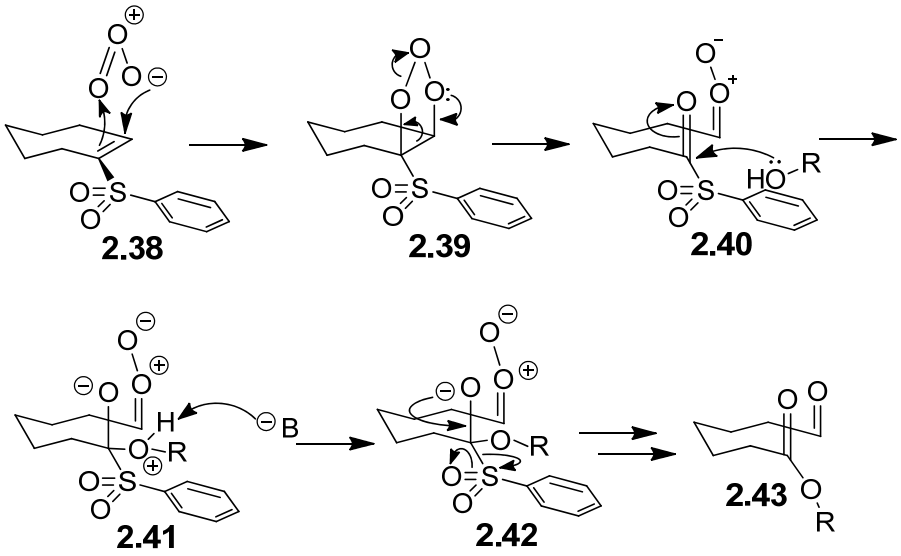


Figure 2.7: Cleavage of Vinylsulfone via Ozonolysis

The sulfone moiety also differentiates the two terminal carbons upon oxidative cleavage of the vinylsulfone. Addition across the vinyl sulfone olefin by

the nucleophilic ozone forms the highly reactive molzonide **(2.39)**. Decomposition of the molzonide **(2.39)** delivers a species with an acylsulfone end and a carbonyl oxide terminus **(2.40)**. Alcohol attacks the acylsulfone to form the terminal ester **(2.43)**. The additional advantage of this methodology is that the sulfone is disposed of in the oxidative process, as very few desirable biologically active target molecules possess the sulfone functionality (Figure 2.7).

2.6: Formation of the β, γ-Unsaturated Sulfone

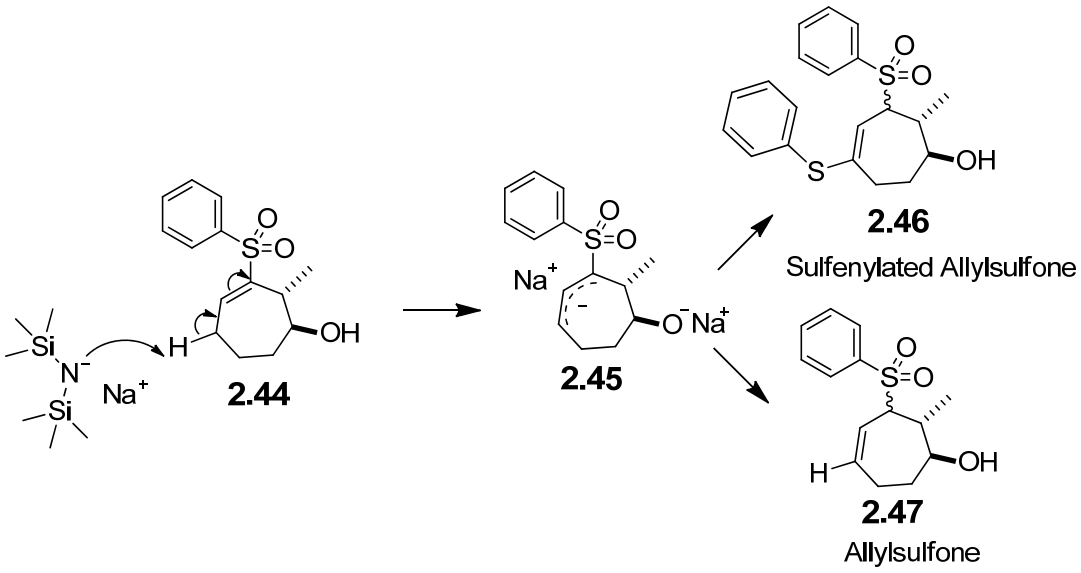


Figure 2.8: Allylsulfone Formation

Due to vinylogy, the γ-position of the sulfone is highly acidic and when treated with base **(2.44)** easily forms the allyl anion **(2.45)**. The allyl anion when quenched with a proton source yields allylsulfone **(2.47)**. This reactive property of

the vinylsulfone can be used with great utility to form the electron rich vinylsulfide **(2.46)** from quenching the anion with diphenyl disulfide. The vinylsulfide formed will be the platform from which greater intricacy can be introduced (Figure 2.8).

2.7: 1,4-Elimination of Sulfone with Trimethylaluminum

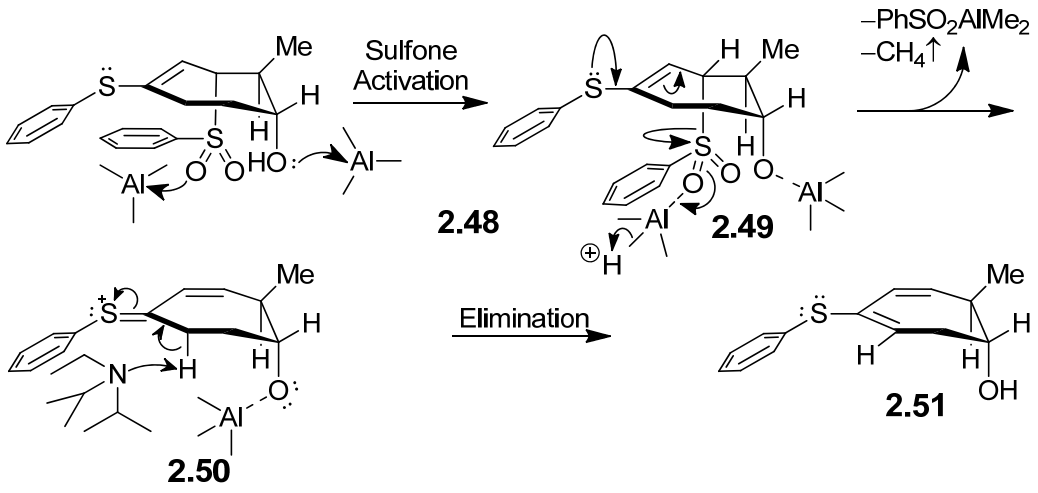


Figure 2.9: 1,4- Elimination of Sulfinic Acid with $AlMe_3$

Sulfenylation product **(2.46)**, has the perfect electronic motif for activation of the sulfone by a Lewis acid and subsequent elimination of sulfinic acid. The desulfonylation takes place through binding of trimethylaluminum to the sulfone oxygen(s), and the free –OH groups (if present) to create aluminate complex **(2.48)**. Subsequent elimination of trimethylaluminumsulfinate occurs with the aid of the Hünig's base in a vinylogous E_2 elimination **(2.49)**. Alternatively, the

weakening of the C-S bond leads to complete expulsion of the trimethylaluminum sulfinate (with the assistance of the sulfur lone pair) to create thionium ion **(2.50)**. Further abstraction of the β-proton by the base leads to desired dienylsuflide **(2.51)** in an E_1-like fashion **(Figure 2.9)**.[8,14]

2.8 References

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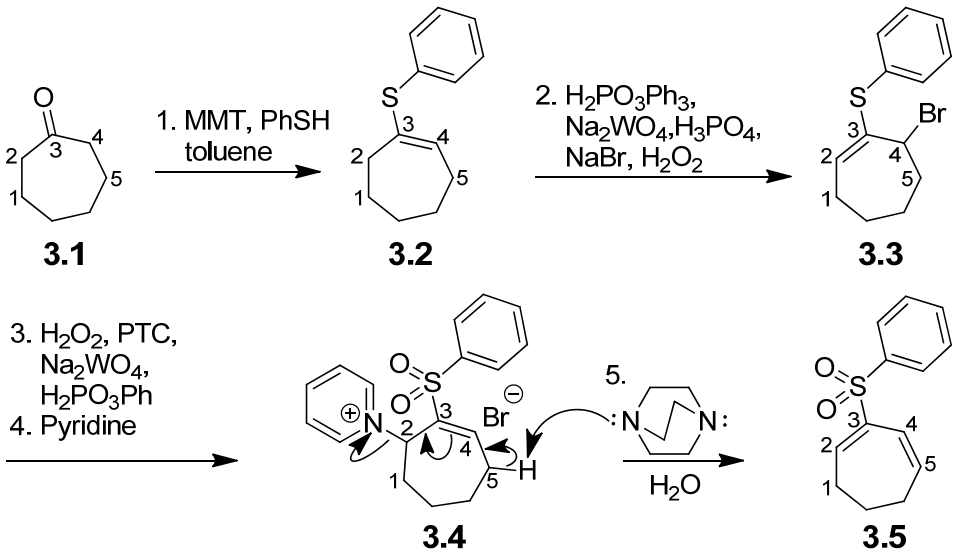
CHAPTER 3: DEVELOPMENT AND APPLICATION OF THE VINYLSULFONE POLYPROPIONATE METHODOLOGY

3.1: Large Scale Generation of Dienylsulfone

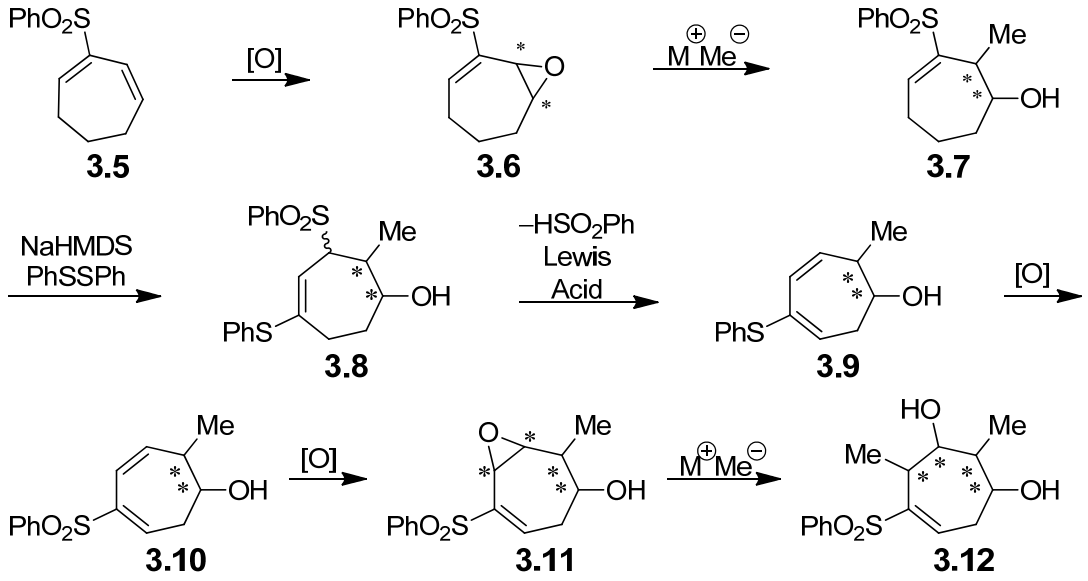


Scheme 3.1: Large Scale Generation of Dienylsulfone

With the synthetic versatility of the vinylsulfone functional group being apparent, an efficient strategy for polypropionate assembly was devised. Efficacious methodologies employ large quantities of affordable and robust starting materials. The 7-membered cross-conjugated dienylsulfone **(3.5)** is obtained by a process requiring no purification. Cycloheptanone **(3.1)** and

thiophenol are treated with the acidic clay Montmorillonite using a Dean-Stark trap[1,2] to afford the vinyl sulfide **(3.2).** Oxidation of vinylsulfide **(3.2)** by the *in situ* generation of Br_2 from Sodium Bromide, H_2O_2[3,4] and buffered Sodium Tungstate provides access to **3.3** without the danger of manipulating 10 moles of liquid Br_2. The sulfide is oxidized to the sulfone using economic Noyori conditions[5,6] H_2O_2, methyltrioctylammonium hydrogen sulfate as a phase transfer catalyst (PTC), Na_2WO_4 & H_2PO_3Ph buffer (this would be the first example of using a 1% catalytic buffer—Phosphinic acid provides a ligand on the tungstate that gives better solubility and therefore reactivity). Treatment of the resulting bromo sulfone with stoichiometric pyridine provides the pyridinium bromide salt (**3.4)** precipitate which is isolated by vacuum filtration. The filter-cake is suspended in diethyl ether and recollected via vacuum filtration to give a flocculent solid of extremely high purity. 1,4 elim starting with the gamma allylic hydrogen. of the pyridinium salt using 1,4-diazabicyclo[2.2.2]octane (DABCO), in aqueous conditions yields the desired 7-membered cross-conjugated dienylsulfone **(3.5)** precipitate (>98% pure) collected via vacuum filtration and air dried to furnish 65% yield over 5 steps.[4] With the starting material obtainable in Kg amounts with relative ease of operation, a polypropionate strategy based on the 7-membered dienylsulfone is well positioned to exert a high degree of synthetic utility.

3.2: VinylsulfonePolypropionate Algorithm



Scheme 3.2: Vinylsulfone Polypropionate Algorithm

When developing a polypropionate synthetic strategy, it is essential to have an iterative process for generating the contiguous chiral centers. Much of the fundamental chemistry had been established on the 5 and 6 membered vinylsulfone scaffolds.[7-9] Exploiting the prochiral nature of the dienylsulfone **(3.5)**, the Jacobsen Salen catalyst affords the chiral epoxide **(3.6)** in high enantiomeric excess.[10,11] Epoxyvinylsulfone **(3.6)** is directly methylated *via* nucleophilic attack or indirectly by Lawton S_N2' [12,13] substitution to give the dipropionate **(3.7)**. Base generates the dianion. Quenching of the dianion with diphenyl disulfide gives the sulfenylated allylsulfone **(3.8)** which bears extremely favorable electronics for 1,4-elimination *via* activation of the sulfone with Lewis acid to afford the

dienylsulfide diad **(3.9)**.[11] The acid labile dienylsulfide diad is immediately oxidized to dienylsulfone diad **(3.10)**. Asymmetric Jacobsen epoxidation begins the second application of the algorithm. Direct or indirect cleavage of the chiral epoxide **(3.11)** with methyl anion will depend on whether syn or anti configuration is desired. The final epoxide substitution yields the vinylsulfone stereotetrad **(3.12)**, comprising the vinylsulfone polypropionate strategy.

3.3: Application of Vinylsulfone Polypropionate Methodology. The C5-C11 *syn, anti, syn* Blue Fragment **(3.13)**

The first introduction of asymmetry on the target was achieved using methodology developed by Du Jardin, by the Jacobsen epoxidation using Salen catalyst with hydrogen peroxide, ammonium tetrafluoroborate, and sodium phosphate.[14-21]

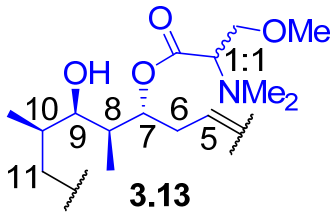
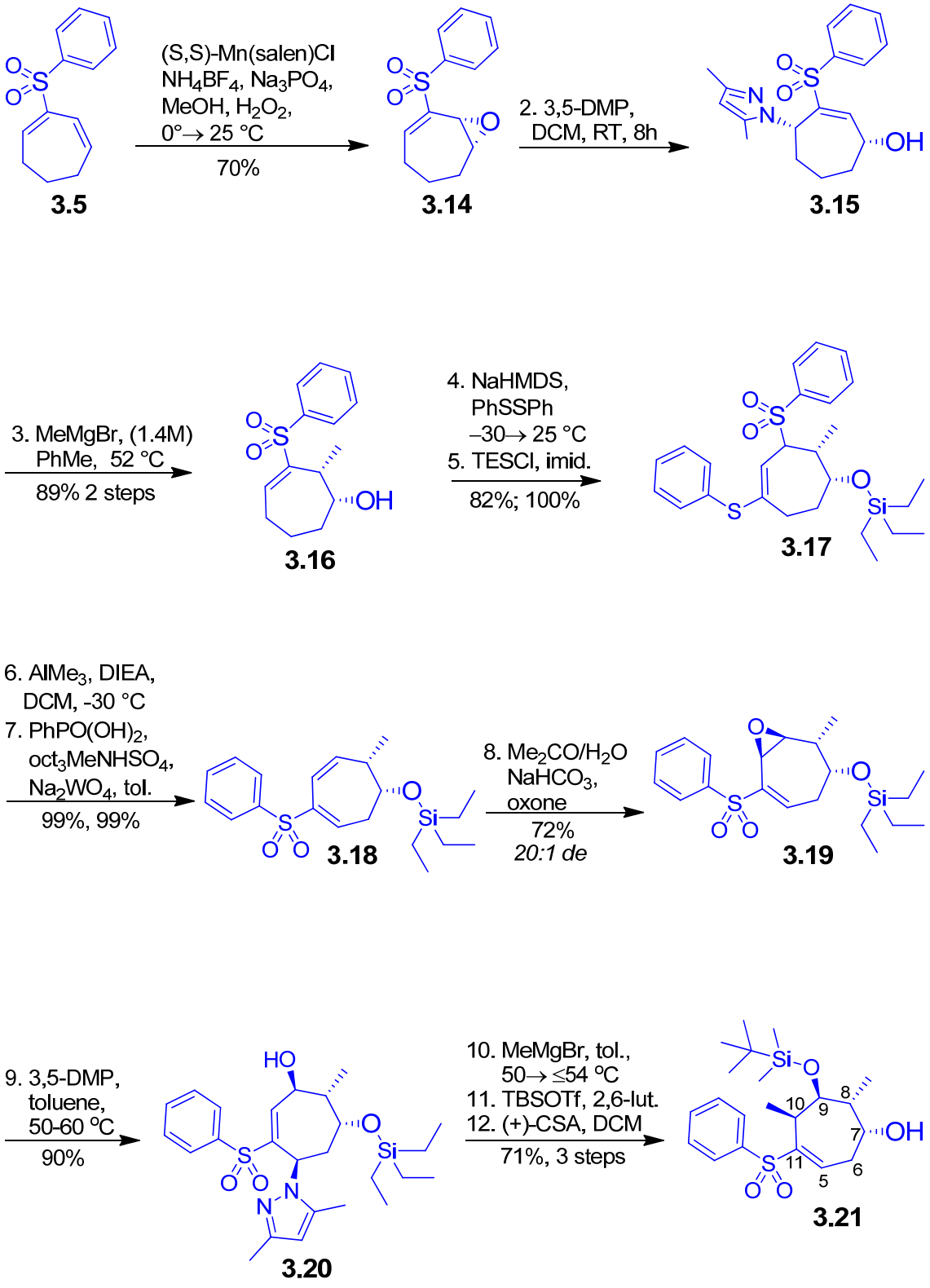


Figure 3.1: C5-C11

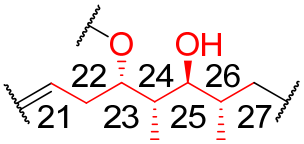
Hong utilized Lawton S_N2' addition to the epoxyvinylsulfone **(3.14)** by 3,5-dimethylpyrazole (3,5-DMP) to afford the allyl alcohol **(3.15)**.[12,13,22] The pyrazole and hydroxy moieties direct the methyl Grignard in a second irreversible S_N2' addition to the vinylsulfone to form the vinylsulfone monopropionate **(3.16)** with a *syn* landscape. From this point Noshi-optimized methodology, allowed multigram quantities of the stereotetrad to be obtained with relative ease. Sodium hexamethyldisilazide (3.3 eq.) forms the dianion which is quenched with diphenyldisulfide to give an allylsulfone protected with TES-Cl & imidazole in methylene chloride to furnish **(3.17)**.[23] **3.17** is eliminated with

trimethylaluminum and Hünig's base to provide the dienylsulfide[11] which is oxidized under Noyori conditions to the dienylsulfone diad **(3.18)**.[24] The dienylsulfone is then epoxidzed using the achiral reagent dimethyldioxirane (DMDO)[25,26] to provide the asymmetric epoxide **(3.19)** 20 : 1 de in a *trans* relationship to the methyl group. S_N2' addition by 3,5-dimethylpyrazole to the epoxy vinylsulfone forms 3,5-DMP adduct **(3.20)**.[11,13] Pyrazole-alcohol directed methyl Grignard addition to the vinylsulfone and subsequent 3,5-dimethylpyrazole (3,5-DMP) displacement provides the 7-membered vinylsulfone dipropionate. *t*-Butyl dimethylsilyl (TBDMS) ether formation using TBDMS triflate gives the disilyl ether. (+)-Camphor sulfonic acid selectively cleaved the less hindered, more labile triethylsilyl ether (TES) to give **3.21**.[27-31] With the cyclic vinylsulfone stereotetrad **(3.21)** now in hand, oxidative cleavage of the vinylsulfone olefin was examined to determine the most efficacious way to obtain the termini-differentiated dipropionate fragment.



Scheme 3.3: Vinylsulfone Polypropionate Strategy C5-C11 (Noshi, Hong)

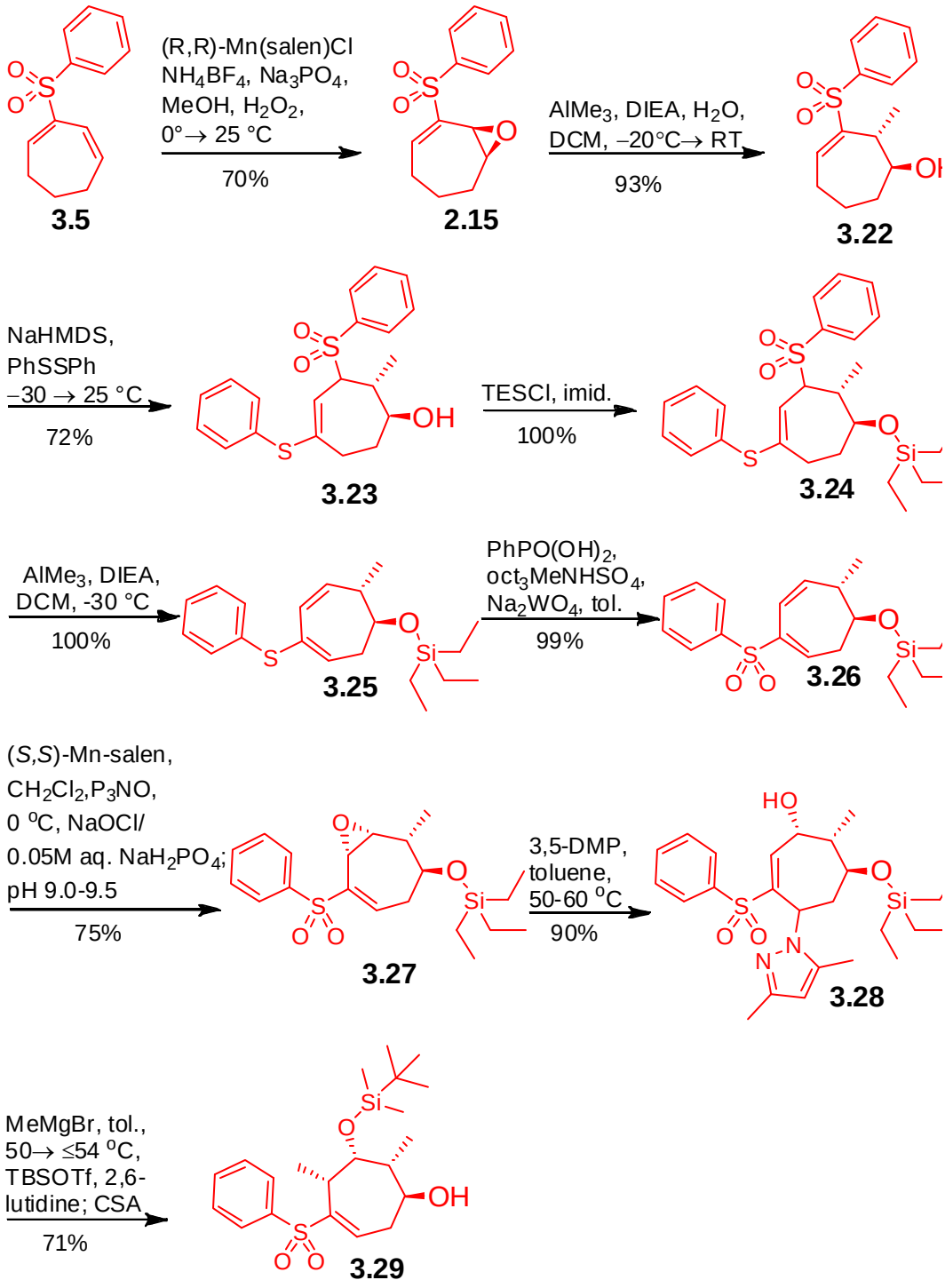
3.4: Application of Vinylsulfone Polypropionate Methodology C21-C27 Red, C28-C34 Green Fragments *syn, anti, syn*



3.22

Figure 3.2: C21-C27

Since a *syn, syn, anti* relationship was required for aplyronine A fragments C21-C27 and C28-C34, a methodology providing the *anti*-monopropionate relationship *via* epoxide modification was required. Epoxidation of the starting cross-conjugated dienylsulfone **(3.5)** was effected under established DuJardin Jacobsen conditions.[14,32-34] All subsequent operations optimized by Noshi were used. The epoxide **(2.15)** was cleaved using the trimethylaluminum-aluminoxane complex to provide the *anti*-monopropionate **(3.22)**.[11,24] The dianion formed with sodium hexamethyldisilazide was quenched with diphenyldisulfide to give the allylsulfonyl vinylsulfide **(3.23)**.[11,35-39] The free hydroxyl was silylated with TES-Cl to provide the silylether **(3.24)**. 1,4-Elimination[11,36] via trimethylaluminum and Hünig's base yielded the cross-conjugated dienylsulfide **(3.25)** that is immediately oxidized to sulfone **(3.26)** with hydrogen peroxide, PTC & sodium tungstate.[5,6,40] The dienylsulfone diad was epoxidized using the *(S,S)*-Mn-Salen catalyst, 4-(3-phenylpropyl)pyridine N-oxide (P_3NO) and sodium hypochlorite to give the *cis*-epoxide **(3.27)**.[41,42] S_N2' addition to the vinylsulfone functionalizes the epoxide in a 1,4-fashion to give the DMP adduct.[11] Directed Grignard[13] methylation delivers the *syn, syn, anti* landscape. TBDMS triflate forms the more robust silylether at C23 to give the diprotected stereotetrad



Scheme 3.4: Vinylsulfone Polyproprionate Strategy C21-C27

that was selectively deprotected by using *(+)*-CSA[28-31,43] to cleave the triethylsilyl ether at what will become C25. The original plan for the green fragment (C28-C34) utilized the enantiomer of the red fragment (C21-C27), therefore employing identical chemistry. The standard polypropionate algorithm intended for producing the green fragment, while sufficient in yielding the desired chiral motif, was incapable of giving the desired spacing on the carbon backbone. An alternate variant of the vinylsulfone polypropionate methodology was explored to obviate this issue. Finding a solution to the difficulties presented by the green fragment, C28-C34 is central this thesis as will be made clear in the ensuing chapter.

3.5 References

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CHAPTER 4: IN DEPTH EXAMINATION OF THE APLYRONINE ACTIN BINDING TAIL REGION

4.1: Introduction

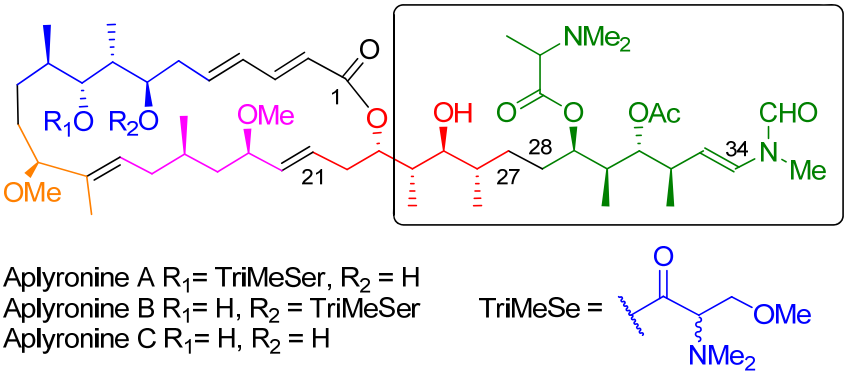
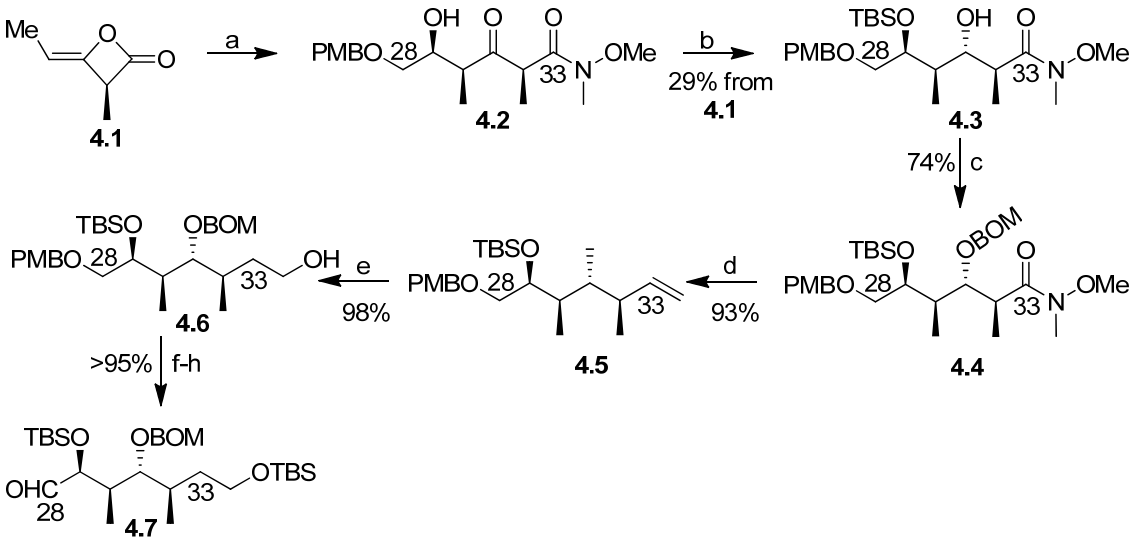


Figure 4.1: The Actin Binding Tail Region C23-C34

As can be seen in Figure 4.1, the structure of the actin binding tail (C24-C34) is conserved in aplyronines A-C. An effective route to deliver the C24-C34 architecture would make these rare polyketide molecules more available for further study. The current synthetic strategy for assemblage of the C21-C27 stereotetrad has been previously reviewed (Chapter 3, Scheme 3.4). The "vinylsulfone polypropionate strategy" has proven its effectiveness with fragments C5-C11 and C21-C27.[1-3] The actin binding tail C28-C34 of aplyronine A proved very resistant to the vinylsulfone polypropionate methodology. As will be seen, a

key to this methodology is having the vinylsulfone properly substituted pre-oxidative cleavage (O_3, OsO_4) as shown in **Figure 2.7**. To better gain an understanding of the synthetic challenges the actin binding tail presents, efforts by other synthetic groups will be surveyed.

Calter and Guo used a strategy based on derivatives of asymmetric ketene dimers constructed from cinchona alkaloid catalysis[4] to assemble the C28-C34 aplyronine A fragment.

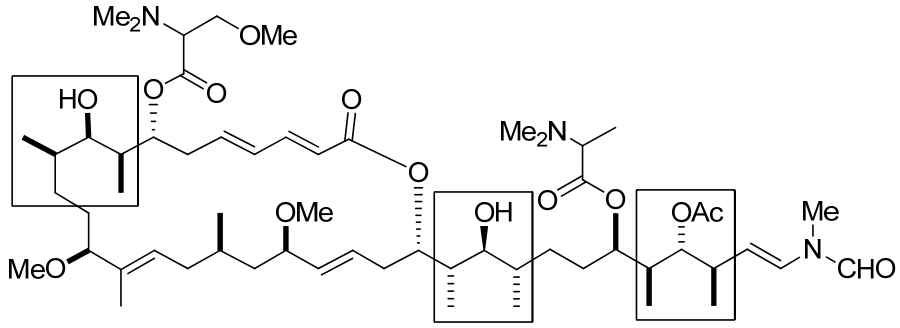


(a) (i) LiN(OMe)Me; (ii) a-(p-methoxybenzyloxy)acetaldehyde THF, -78 °C (b) (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C; (ii) $KBEt_3H$, Et_2O, -78°C. (c) BOMCl, i-Pr_2NEt, CH_2Cl_2, (d) (i) DIBAL-H, THF,-78 °C; (ii) $(Ph_3PCH_3)\cdot Br$, NaHMDS, Et_2O, 0°C. (e) (i) 9-BBN, THF, 0 °C; (ii) H_2O_2, NaOH, THF, 0 °C, (f) TBSOTf, 2,6-lutidine, CH_2Cl_2,-78 °C, (g) DDQ, CH_2Cl_2, H_2O. (h) Dess–Martin periodinane, pyridine, CH_2Cl_2.

Figure 4.2: Synthesis of the C28-C34 Fragment (Calter)

Calter and Guo began with the aldol adduct **4.2** prepared by the reaction of the enolate derived from ketene dimer **4.1** with α-(*p*-methoxybenzyloxy) acetaldehyde (Figure 4.2) as an inseparable mixture of diastereomers in a 6:1

ratio. After silylation of the mixture, the diastereomers were still inseparable. Treatment of this mixture of diastereomers with lithium triethylborohydride ($LiBEt_3H$) reduced the major diastereomer without affecting the minor compound, allowing isolation of **4.3** as a diastereomerically pure compound. Protection of the C31-hydroxyl as a benzyloxymethyl (BOM) ether afforded **4.4**. Homologation was required to fully elaborate the C28-C34 fragment. Reduction of **4.4** to the aldehyde, followed by Wittig reaction yielded monosubstituted olefin **4.5**. Hydroboration gave primary alcohol **4.6** which was silylated followed by removal of the PMB group. Dess–Martin oxidation yielded aldehyde **4.7**. It is worthy of note that a homologation was required to realize the C28-C34 fragment.



The Marshall Stereotriad Strategy

Marshall and co-workers developed a strategy focusing on the central stereotriads and using the chiral alcohol moieties as points of coupling **(Figure 4.3)**. Using a very well developed methodology[5-10] involving enantioselective additions of chiral allenylindium reagents to chiral aldehydes, the Marshall group was able to effect a number of complex natural product syntheses.[10]

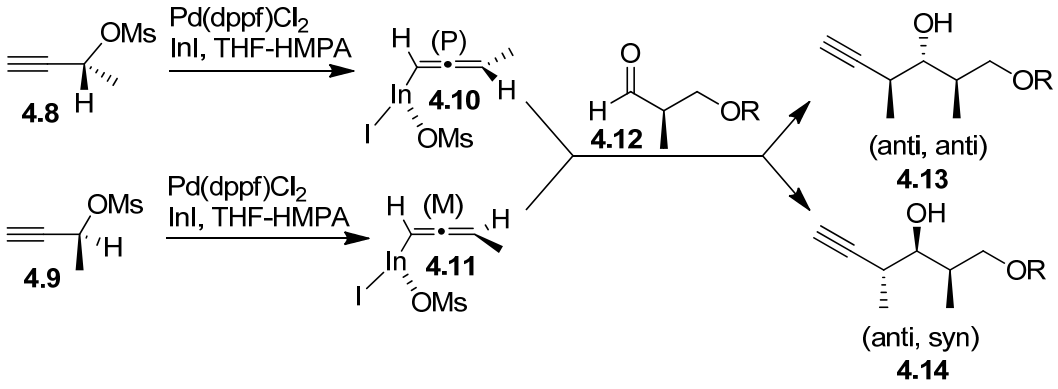
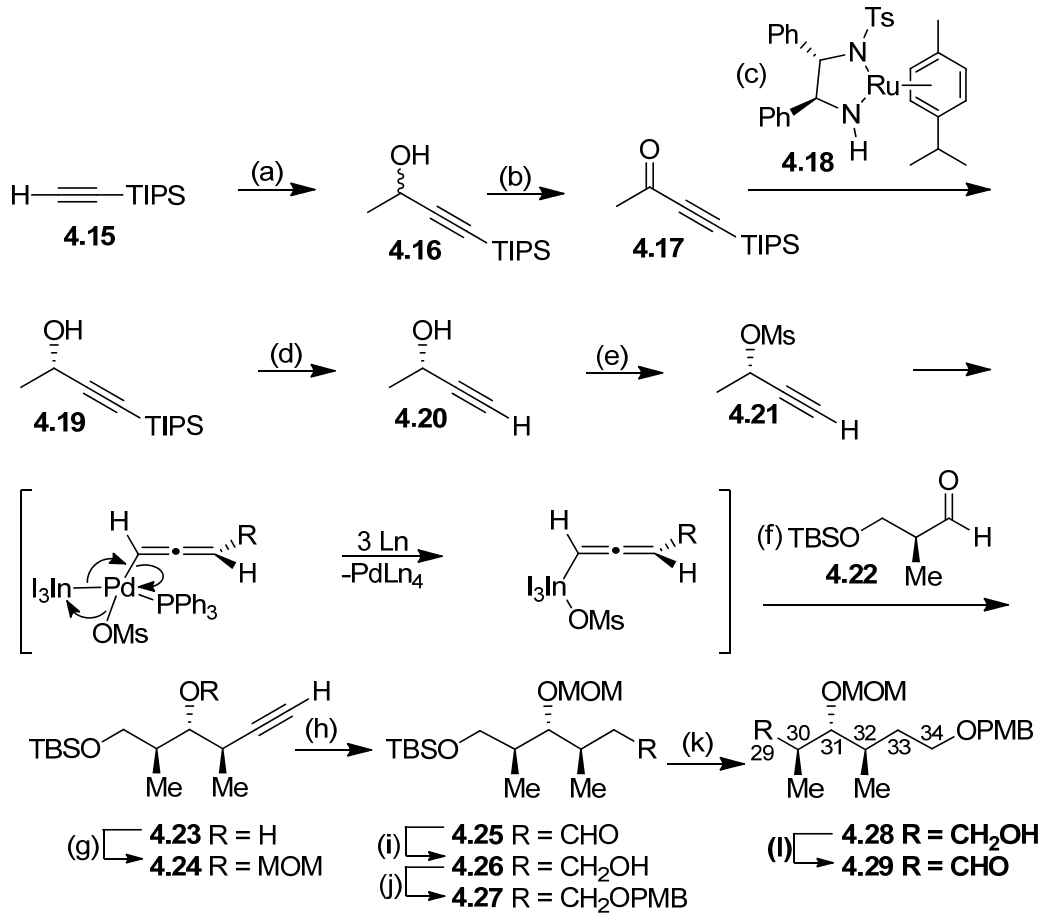


Figure 4.3: Allenyl Indium Generation of Stereotriads

Figure 4.3 highlights the allenylindium **(4.10, 4.11)** formation from the chiral propargyl mesylates **(4.8, 4.9)**. Though indium is shown here, a number of different metals have been successfully utilized.[10] Chiral aldehyde **4.12** was obtained using the Roush variant of the Brown crotylboration.[11]The synthesis of the C29-C34 fragment (Scheme 4.4) begins with attack by lithium acetylide on acetaldehyde to deliver propargyl alcohol **(4.16)**. MnO_2 oxidation of the alcohol gives 4-TIPS-3-butyn-2-one **(4.17)**. The reduction of 4-TIPS-3-butyn-2-one **(4.17)** with ca. 1 mol % of the Noyori chiral Ru catalyst **(4.18)** in isopropyl alcohol proceeds rapidly to afford (*S*)-TIPS-3-butyn-2-ol **(4.19)** in >95% yield and >95% enantiomeric purity. The corresponding mesylate **(4.21)** is converted *in situ* to chiral allenylindium reagent, which reacts with aldehyde **(4.22)**[11] to form homopropargylic alcohol **(4.23)** with high diastereo- and enantioselectivity. Hydroboration-oxidation of the derived alkyne **4.24** led to a separable 85:15 mixture of aldehyde **4.25** and alcohol **4.26**.



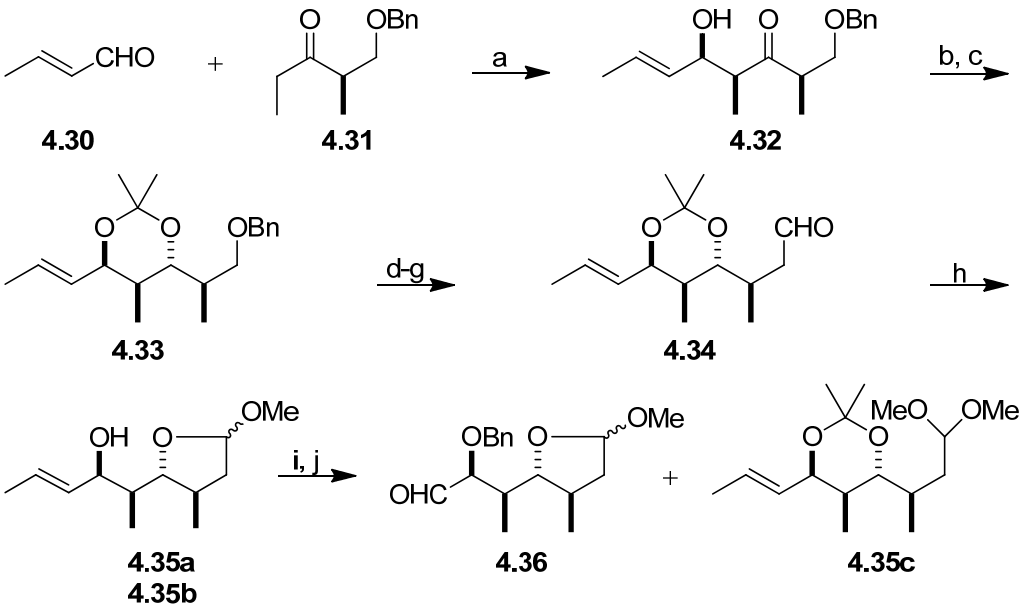
(a) (i) t-BuLi, THF -40 °C, 30 min (ii) CH_3CHO, -40 °C, 20 min (95%) (b) MnO_2, CH_2Cl_2 rt, 30 min (87-89%) (c) KOH, CH_2Cl_2, H_2O, rt, 10 min (85% 3 steps) (d) $Bu_4N^+ F^-$ or $Bu_4N^+ OH^-$ THF (quant.) (e) MsCl, Et_3N (96%) (f) Pd(dppf)Cl_2,InI, HMPA-THF (79%) (g) MOMCl, Bu_4NI, i-Pr_2NEt, CH_2Cl_2 (96%) (h) (i) c-$C_6H_{11}BH$ (ii) H_2O_2, NaOH (i) DIBAL-H (84%); (j) NaH, p-$MeOC_6H_4CH_2Cl$, Bu_4NI, 15-Crown-5, THF (90%) (k) TBAF (71 %) (l) Dess-Martin (99%)

Figure 4.4: Synthesis Of The C29- C34 Fragment (Marshall)

Aldehyde **4.25** was reduced with DIBAL-H, and the combined alcohol product **4.26** was protected as PMB ether **4.27**. The use of dicyclohexylborane in DME for this hydroboration gave a significantly higher yield of the aldehyde/alcohol mixture than BH_3•THF or catecholborane. The formation of the

alcohol byproduct **4.26** may result from *in situ* reduction of the intermediate aldehyde by borohydride species, $R_2B^+(H)OH^-$, produced during the basic oxidation procedure. However, in the case at hand, this side reaction is of no consequence. TBS ether cleavage of **4.27** and oxidation of the alcohol **4.28** gave the aldehyde **4.29** representing C29-C34 of the targeted subunit.

Kigoshi, Suenaga and co-workers assembled the C28-C34 stereotetrad by utilizing an asymmetric aldol strategy. The synthesis of C29–C35 segment **4.36** is shown in Figure 4.5.



(a) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, –78 °C→–60 °C, 85%; (b) $Me_4NBH(OAc)_3$, AcOH, MeCN, -25 °C; (c) $(MeO)_2CMe_2$, PPTS, acetone, rt, 84% (two steps); (d) Ca, liq. NH_3, i-PrOH, THF, –78 °C, 98%; (e) p-TsCl, pyridine, 0 °C, 100%; (f) NaCN, DMSO, 50 °C, 98%; (g) DIBAL, CH_2Cl_2, hexane, –78 °C, 93%; (h) PPTS, MeOH, rt, 82%; (i) BnBr, NaH, DMF, rt, 93%; (j) OsO_4, NMO,H_2O, acetone, rt; then $NaIO_4$, rt, 99%

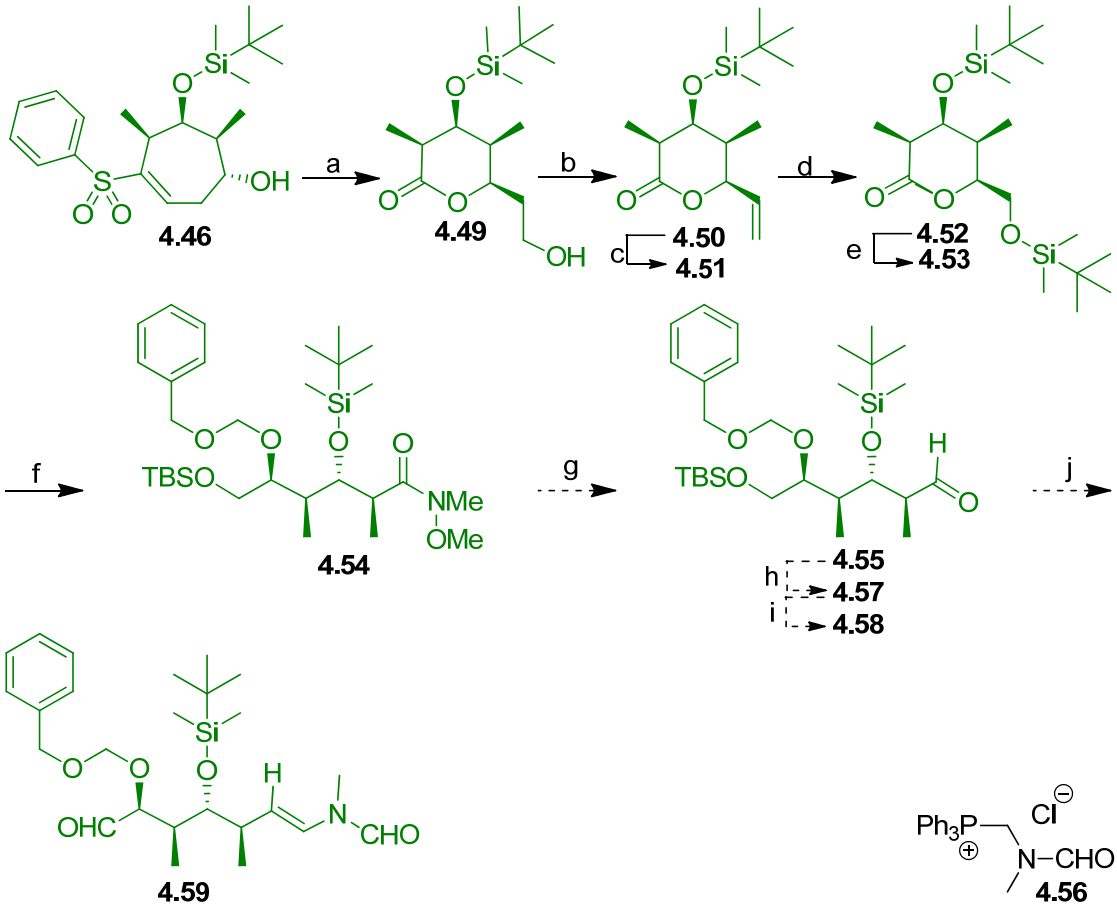
Figure 4.5: C28-C34 via Asymmetric Aldol Coupling (Kigoshi).

Compound **4.36**, with four contiguous *syn, anti, anti*-stereocenters, was previously prepared by using the Evans aldol reaction and Sharpless epoxidation as the key steps,[12,13] the improved synthesis of **4.36** used the Paterson aldol reaction[14,15] as the key step. Thus, the Paterson aldol reaction between ethyl ketone **4.31** and crotonaldehyde **4.30** gave the hydroxy ketone **4.32**. Stereoselective reduction of **4.32** with tetramethylammonium triacetoxyborohydride afforded an *anti*-1,3-diol, which was transformed into acetonide **4.33**. Conversion of **4.33** into the aldehyde **4.34** was effected by a four-step sequence of reactions. Aldehyde **4.34** was treated with pyridinium p-toluenesulfonate (PPTS) in methanol to provide a separable mixture of diastereomeric acetals, **4.35a** and **4.35b**, and the dimethyl acetal **4.35c**. The stereochemistry at C34 of acetals **4.35a** and **4.35b** was not determined. After chromatographic separation, two minor products, **4.35b** and **4.35c**, were subjected to equilibration (PPTS in methanol) to afford a mixture of **4.35a**, **4.35b**, and **4.35c**, from which the major acetal **4.35a** was again obtained. By repeating this procedure, **4.35b** and **4.35c** could be transformed into **4.35a**. Protection of the hydroxy group in **4.35a** followed by oxidative cleavage of the double bond provided the C29–C35 segment **4.36** (48% from **4.31**).

As can be seen, while the above examples are elegant, they each suffer drawbacks. The Calter ketene dimer methodology gives low yields and mixtures of diastereomers that must be carried multiple steps before they can be separated. These drawbacks waste reagents making large-scale endeavors costly. The Marshall allenylinduim strategy has great potential. The main

drawback being that the triisopropylsilyl acetylene is needed for greatest facial selectivity and the price makes large-scale projects less attractive. The Kigoshi aldol strategy is excellent in that it produces the full stereotetrad. It doesn’t suffer from the need for a stoichiometric amount of chiral auxiliary like the traditional Evans methodology. The main drawback is equilibration of the lactols and dimethyl ketal. On a large scale (> 250 g) a re-equilibration can prove onerous. It was the hope of the Fuchs lab that many of the limitations inherent in other methodologies could be remedied with the vinylsulfone polypropionate methodology.

4.2: C28-C34 Green Fragment Backbone Strategy 1st Generation



(a) (i) O_3, $NaHCO_3$, DCM; (**ii**) Me_2S, BH_3•t-$BuNH_2$; (b) (i) ArSeCN, Bu_3P (ii) H_2O_2 76%; (c) (**i**) O_3, $NaHCO_3$ (**ii**) Me_2S, BH_3•$ButNH_2$; (d) TBSCl, Imidazole 85% (3 steps); (e) MeONHMe.HCl *i*-PrMgCl 90% (f) 3,4-dimethoxybenzyl chloride (DMBOMCl) i-Pr_2NEt, DCM (yield not reported); *(g) DIBAl-H (h) (i)* ***4.56****, THF, -78°C, LiHMDS, 2h (ii) DCM,* I_2 *dark, 48 h; (i) TBAF (1 eq.); (j) Dess-Martin*

Scheme 4.1: Original Fuchs group approach to C28-C34

The first attempt by El-Awa to solve the structural deficiencies of tetrad **4.46** involved a desperate oxidative cleavage of a carbon at one terminus and subsequent installation of the methylformamide via the Wittig olefination at the

opposite end. Ozonolysis of **4.46** with $NaHCO_3$, methylene chloride and reductive work-up with Me_2S, and *t*-$BuNH_2$ gave the stereotetrad lactone core ethyl alcohol **(4.49)**. Selenylation of the terminal alcohol with ArSeCN, Bu_3P and H_2O_2, followed by oxidative elimination affords terminal olefin **(4.50),** which is then amputated by ozonolysis and reductive work-up (Me_2S, *t*-$BuNH_2$•BH_3) to provide the terminal alcohol **4.51**, which is then protected as the TBDMS silyl ether **(4.52)**. The magnesium methoxymethyl amide cleaves the lactone to produce the terminal Weinreb amide **4.53** while the free hydroxyl was protected as the BOM ether **4.54**. It was at this point that El-Awa stopped the sequence. The plan was to effect reduction of the Weinreb amide to aldehyde **4.55** with DIBAL-H, with subsequent olefination by the dimethyl formamide ylide **4.56**, then I_2 catalyzed olefin isomerization[16] to **4.57.** Deprotecton of the C28 TBDMS-silylether **(4.58)** followed by a Dess-Martin oxidation would supposedly give the properly functionalized green fragment **4.59** in roughly 13 operations post oxidative cleavage of the 7-membered vinylsulfone tetrad **(4.46)**. The inelegance of this synthetic strategy ultimately led to a cessation of inquiry into the cleavage strategy (Scheme 4.1) for furnishing C28-C34 aplyronine A polypropionate fragment.

4.3: C28-C34 Green Fragment Backbone Strategy 2nd Generation

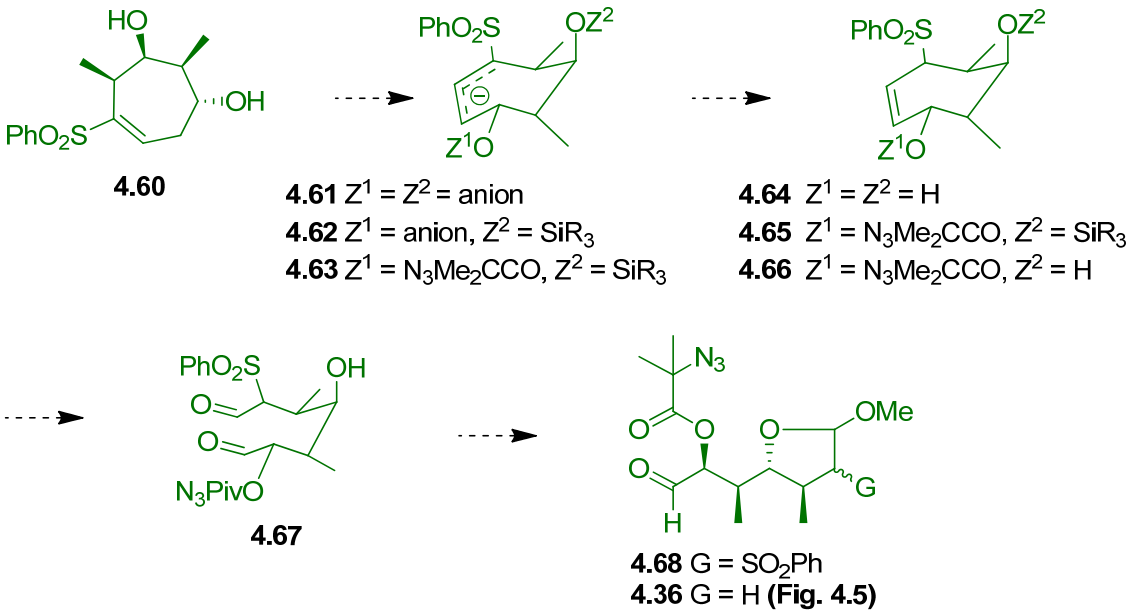


Figure 4.6: A Proposed Improved Route to Green Segment 4.**36**

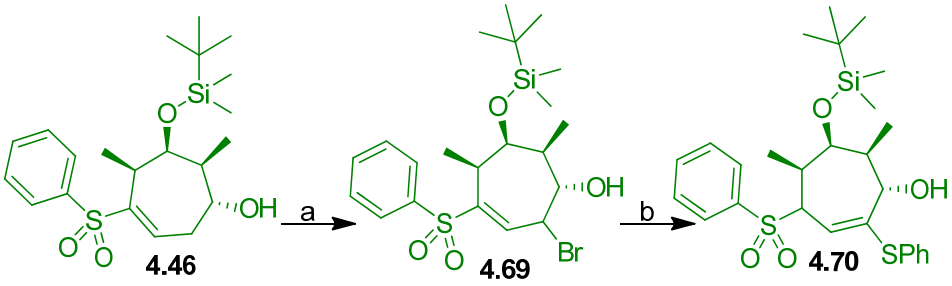
The above synthesis of the green segment deletes then later reintroduces a carbon atom to the backbone **(Section 4.2)**, a tactic that is conceptually avoidable. The intention was to subject dihydroxy vinylsulfone **4.60** (or its mono and diprotected variants) to the various reagents (phosphazene bases, Li, Na, K amide anions) known to effect thermodynamic isomerization[17] to the more stable allyl sulfones **4.64-4.66** via intermediate allylic anions **4.61-4.63 (Fig. 4.6**). The Z^1O group in the δ–position is equatorial, which should provide a measure of protection from β–elimination, even with the prized azidopivalate ester **4.63**. As can be appreciated, while the concept is easily stated, the number of

experimental variants is potentially large. For example, treatment of **4.60** with DBU in various solvents returns the starting material.[17] It now appears that polyanion experiments involving **4.61** and **4.62** followed by kinetic quench in the α–position will be required. Once having obtained **4.66**, ozonolysis to hydroxy dialdehyde **4.67** can be undertaken. In such a case direct double bond differentiation would likely be sacrificed as the sulfinic acid leaving group would no longer be part in the oxidative cleavage. This pseudo-symmetrical intermediate can provide lactol products from alcohol attack at *either aldehyde*. While the α–sulfonylaldehyde should be more reactive[18] and 5-ring α–pivaloxyaldehydes may suffer ring opening,[19] to allow thermodynamic equilibration of the two lactols to a mixture rich in **4.68**. Desulfonylation prior to ozonolysis and adjusting the timing of azidopivalate addition are additional options. In the final analysis, the brevity of this approach to **C28-C34** underwent careful evaluation. Ultimate introduction of the N-formyl enamine moiety was to directly follow the Yamada precedent using the 5-ring methoxyacetal, which has since been improved by other syntheses[18,20-23] introducing this important recognition element from a terminal aldehyde. Since the goal is to provide aplyronine A analogs and biotools, the plan will exploit the successes by Yamada and Paterson in their syntheses.[12,24]

Subsequent experimentation illustrated the inefficacy of such an approach. Isomerization and equilibration of the vinylsulfone to the allylsulfone cannot be executed, possibly due to the steric encumbrances imposed by the four stereocenters on the tetrad.[25] It is necessary for the orbitals on the α, β and

γ–sulfone carbons to align in the same plane to deliver the allylsulfone from the vinylsulfone. The impasse for the vinyl to allyl sulfone equilibration effectively eliminates this strategy as a viable option.

4.4: Surrogate Methodologies En Route to the C28-C34 Fragment



(a) NBS, AIBN, CCl_4, 50 °C (65%); (b) NaH, PhSH, THF, 25 °C

Figure 4.7: Isomerization via Allylic Oxidation

Due to the apparent inability of the stereotetrad to form the allylanion, an allyl radical pathway was investigated (Figure 4.7). The initial strategy attempted entails an oxidation at the γ–position on **4.46**. Many conditions to effect an allylic oxidation were examined.[25] Treating **4.46** CCl_4, azobisisobutyronitrile (AIBN), and N-Bromosuccinimide (NBS) gives yields of bromide **(4.69)** ranging from 50% to 65%, while alternate conditions[26] enabled no improvement.

The free radical bromination yielded multiple spots on chromatography plates. The reaction generates a stoichiometric amount of HBr, which is problematic for silyl ethers. This fact coupled with the apparent ketone **(iii)** formation due to hydrogen abstraction during the course of the reaction made for an inefficient conversion (Figure 4.8). Due to lack of viable alternatives, the allyl bromide **(4.69)** was further utilized.

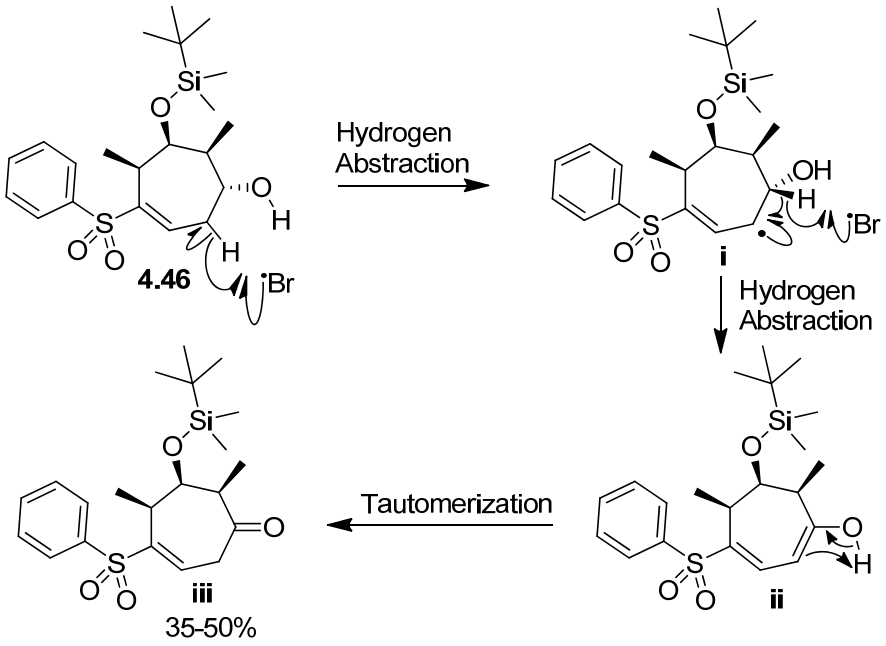
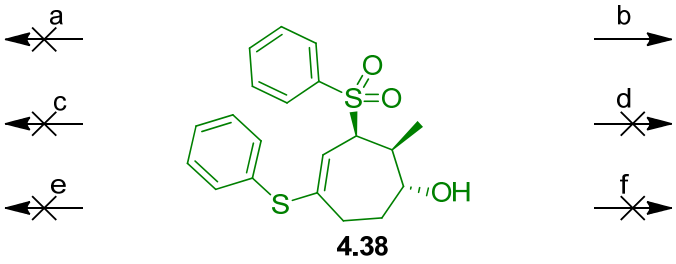


Figure 4.8: Radical Bromination Ketone Formation

Bromide **4.69** was treated with sodium phenylmercaptide (3-10 eq.) to provide **4.70**. With vinylsulfide **4.70** in hand the electronic configuration favorable to elimination of the sulfone was established. Unfortunately the previously used 1,4-elimination was ineffecive (Figure 2.9). Due to limited supply of **4.46** model studies were undertaken; **4.38** was deemed an acceptable proxy for **4.46**.



4.38

(a) Raney Ni, EtOH, Δ; (b) NaHg,Na_2HPO_4 (quant); (c) Bu_3SnH,AIBN, PhMe; (d) Naphthalene, Li, THF, -60°; (e) SmI_2, MeOH, THF, DMPU; (f) Indium, THF:H_2O, 25 °C, 24 hr

Figure 4.9: Desulfonylation Ventures

Reductive cleavage of the allylsulfone with Raney nickel[27] at reflux in ethanol returned starting material. Sodium-Mercury amalgam with phosphate buffer was successful but deemed substandard for anticipated large-scale operations. Attempted reductive cleavage of the allylsulfone by tributyltin hydride and AIBN[28] also returned of starting material. A continuation of the reductive cleavage concept making use of lithuim metal and naphthalene[29] likewise returned starting material. A more effective electron transfer reagent samarium iodide, DMPU, methanol, and THF[30] again yielded starting material. Indium[31] likewise led to fruitless results. Such observations brought into doubt the efficacy of the established polypropionate strategy for use in the assembly of the C28-C34 green fragment. Success with White conditions

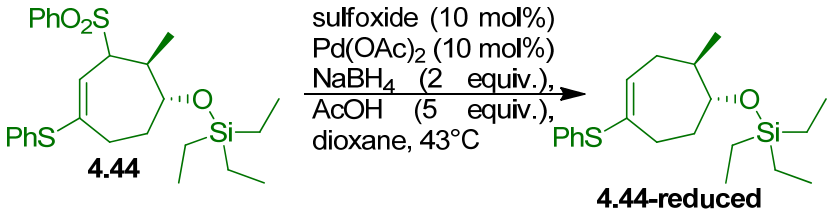
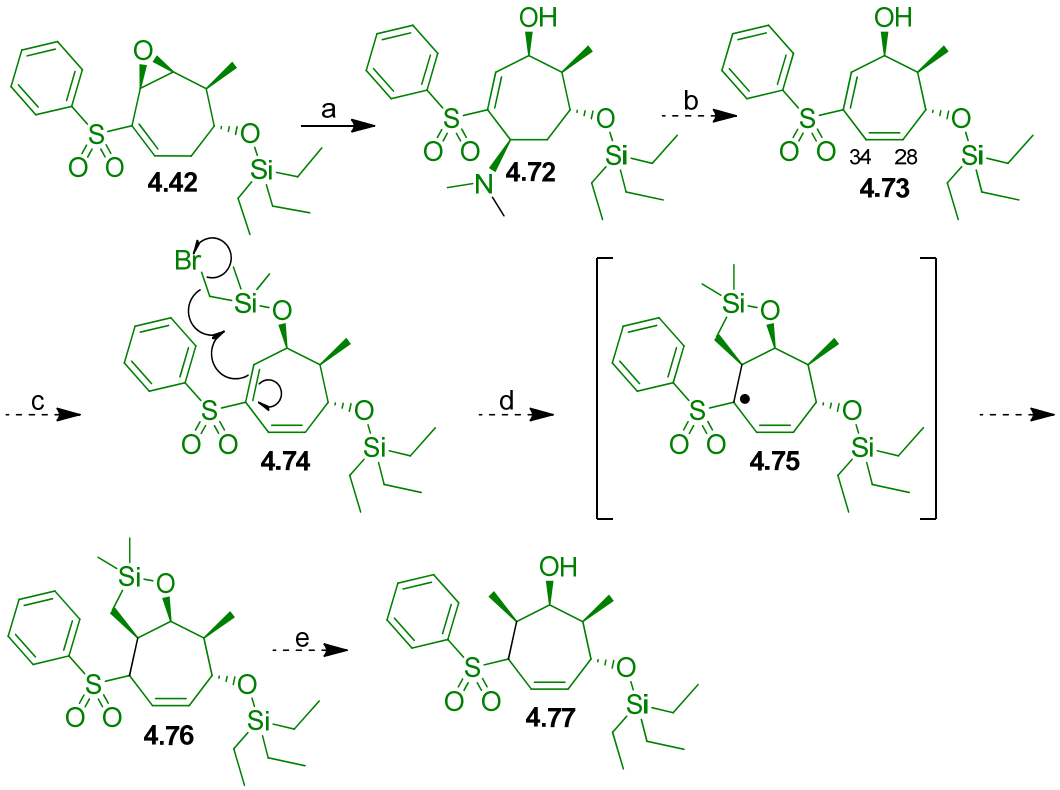


Figure 4.10: White Conditions

$Pd(OAc)_2$, DMSO, and 1,3-Bis(diphenylphosphino)propane[32] met on the dipropionate model but coupled with the fact that green tetrad was limited and the bottleneck caused by considerable degradation in yield of the *n*-bromosuccinimide (NBS) oxidation this methodology was abandoned.

4.5:The Stork-Sophia Strategy

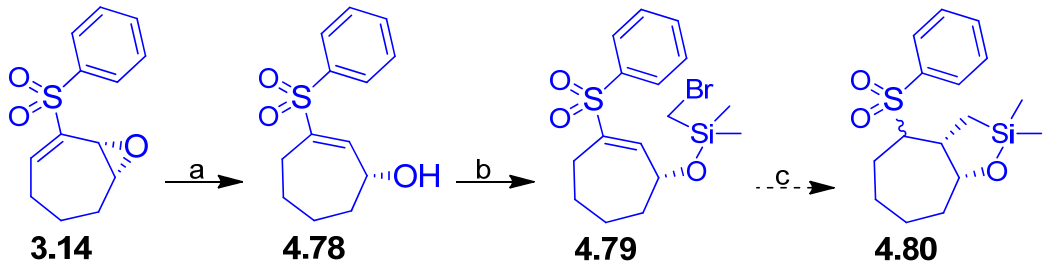


(a) Me_2NH, H_2O, DCM, 100%; (b) (i) xs CH_3I; (ii) Ag_2I, H_2O (iii) heat; (c) Me_2CH_2SiCl, Et_3N
(d) nBu_3SnH, AIBN, Δ, 4 h, C_6H_6, Bu_3SnH (e) Bu_4NF on SiO_2, DMF, 60 °C

Figure 4.11: Stork Sophia Route to Green Tetrad

Dimethylamine is well established in the Fuchs group as an excellent S_N2' Lawton nucleophile for epoxyvinylsulfone **4.42**.[1] Hoffmann conditions[33] on **4.42** would furnish dienylsulfone **4.73** with the β,γ–olefin at C28-C34. Bromomethyldimethylchlorosilane, and excess triethylamine delivers silylether **4.74**. Radical initiation with azobisisobutylonitrile (AIBN), heat or light with tri-*n*-butyltin hydride provides siloxane [34-40] **4.76** which would be hydrolyzed to **4.77**[41]

(Figure 4.11).This synthetic scheme would allow exploration of the chemistry proposed in Figure 4.7.



(a) DBU (cat.), MeOH; (b) Me_2CH_2SiCl (2.5 eq), Et_3N (10 eq) (100%); (c) **Table 4.1**

Entry	Conditions (c)	Result
1	t-BuLi, THF, -78 °C	Deprotecton
2	tris(pyridin-2-ylmethyl)amine AIBN, Bu_3SnH, Bz, 80 °C	Bromine Reduction
3	tris(pyridin-2-ylmethyl)amine, AIBN, Cu(II)Br, tol. 110°C	Bromine Reduction
4	In, THF:H_2O (5:2) 25 °C, 24 hrs.	Recovery of Starting Material
5	1-Naphthylamine, N,N-dimethyl-, Li, THF, -55 → -40 °C	Recovery of Starting Material

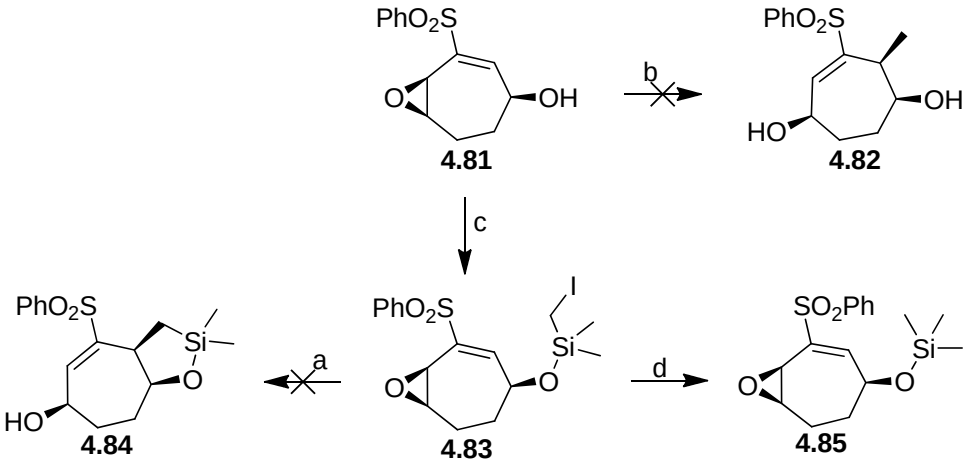
Figure 4.12: Stork Sophia on Vinylsulfone

Due to the scarcity and value of epoxide **4.42** and lack of precedent of this methodology on γ–hydroxy vinylsulfones, **4.79** was utilized as the model substrate. Unfortunately silylether **4.79** proved extremely acid labile and storage in a Teflon vessel was necessary. Metallation of the bromomethyl moiety with *t*-

butyllithium led to deprotection (Entry 1). Unfortunately attempts at forming the radical with AIBN under any conditions (Entries 2 and 3) simply afforded the direct reduction product, the TMS ether. Reduction by single electron transfer using Indium, or Lithium metals (Entries 4 and 5) led to recovery of starting material, and deprotecton of the silylether respectively.

The Stork-Sophia free radical cyclization is a methodology that has been long anticipated as becoming a facet of the vinylsulfone polypropionate methodology and it was therefore necessary to review the group literature to see if any insights could be gleaned from past exploration.

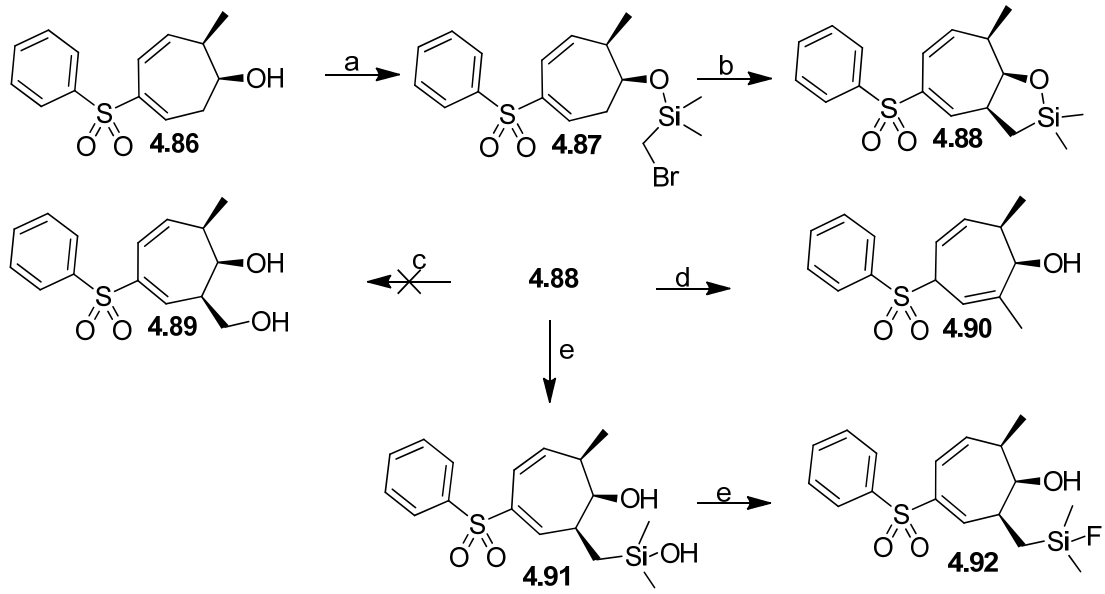
A reexamination of the work of Inchul Kim[42] proved to have exceptional value. In an effort to expand the scope of the vinylsulfone polypropionate strategy, Kim investigated intra/ inter-molecular, S_N2' Lawton anionic cyclization



(a) *t*-BuLi (b) 2 eq. MeLi (c) Me_2CH_2SiCl, Et_3N (d) *t*-BuLi

Figure 4.13: Syn Methylation Lawton Strategy (Kim)

The construction of *syn*-relationship was tried previously with 6-epoxy-3-hydroxy-vinylsulfone **4.81** by using the hydroxyl group as a silicon tether. A trial with methyllithium expecting a directing effect of lithium alkoxy group did not afford any *syn*-addition product **4.82**. Treatment of **4.83** with *tert*-butyllithium did not give siloxane **4.84** but only give the protonated compound **4.85** (Figure 4.13).



(a) $BrCH_2(Me)_2SiCl$, Py, CH_2Cl_2, rt, 1 h 95%; (b) LiHMDS, THF, -78 °C, ~10 min. 83%; (c) H_2O_2, KF; (d) TBAF, DMF, 70 °C (<30%); (e) H_2O work up; (f) TBAF, DMF, 70 °C

Figure 4.14: Kim Probe of Stork-Sophia Photocyclization

The diad **4.86** was converted to bromomethyldimethylsilyl ether **4.87.** Intramolecular alkylation of this material was effected by low temperature treatment of LiHMDS, which provided annulated siloxane **4.88**. While the literature has several examples of anionic cyclizations that occur via initial intra-molecular attack at the silyl moiety followed by rearrangement,[43] this is

apparently the first example of anionic formation of a siloxane from the familiar Stork halomethylsilyl ether functionality.[36] The success of this reaction with the avoidance of 1,3-elimination presumably is partially due to the delocalized soft nature of the sulfone stabilized pentadienyl anion. For the siloxane cleavage, protiodesilylation was attempted using the Hoveyda method.[44] However, even though TBAF in DMF seemed to effect partial cleavage of the siloxane, the fluoride anion was basic enough to deprotonate the allylic proton of the desilylated **4.88** resulting in small amounts of vinyl sulfone **4.90** together with unknown side products. Aqueous workup afforded the siloxane-opened silanol **4.91**, which was also subjected to the above condition. However, it only yielded a fluorinated mixture. The Kumada-Fleming-Tamao oxidation was also applied to siloxane **4.88** anticipating conversion to hydroxymethyl compound **4.89**. Under these conditions, the olefin in the starting material was reactive enough to result in multiple side products (Figure 4.14).

From the data provided by this work some key insights could be extrapolated. Operating on the homoallylic alcohol rather than the allyl alcohol is far more effective. Finding a way to alter current methodology to allow exploitation of the homoallyl rather than allyl alcohol had to be deduced. Pursuit of a design alteration allowing for utilization of the homoallylic alcohol paved the way for a profound increased understanding of the capability and versatility of the vinylsulfone polyproprionate methodology.

4.6: C28-C34 Green Fragment via a “Pivot Strategy”

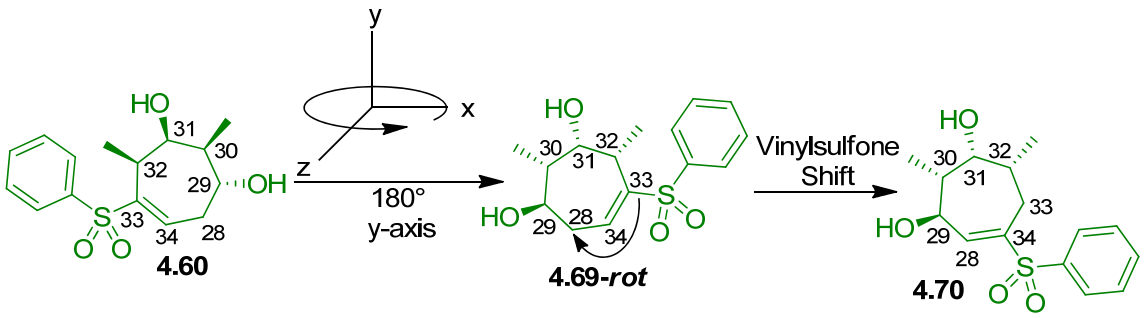
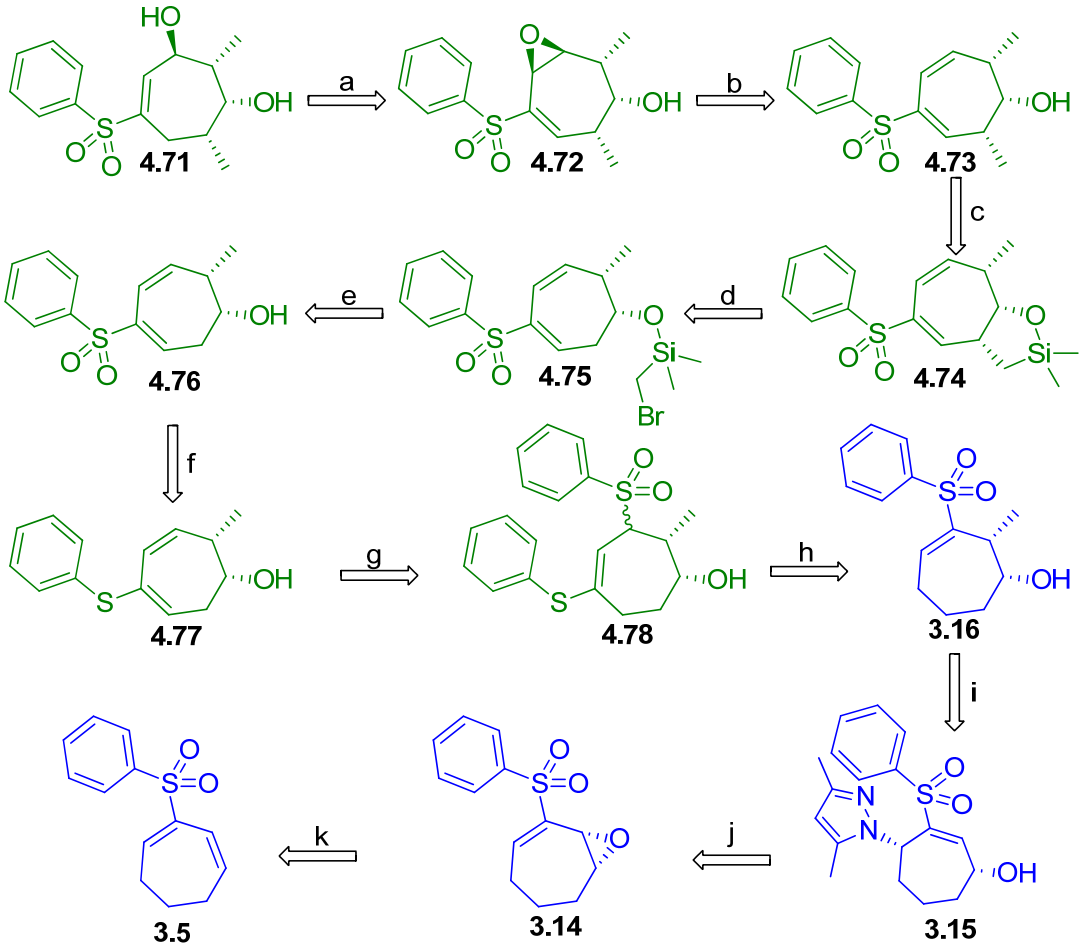


Figure 4.15: Vinylsulfone Transposition Strategy

Pursuant to obtaining the C28-C34 stereotetrad with the transposed vinylsulfone **(4.70)** a new perspective was sought. Rotating Fragment **(4.60)** on the y-axis through the x,z-plane gives the perspective of inverted chiral centers **(4.69-*rot*)**. Transposition of the vinylsulfone from C33-C34 to C34-C28 furnishes **4.70**, a target that meets strategic structural needs (Figure 4.15).

Based on the Kim success with the allylanion of **4.87** a stepwise retrosynthetic analysis was designed that utilized the siloxane annulation. S_N2' on epoxide **4.72** with sodium borohydride should yield tetrad **4.71**. Epoxidation with dimethyldioxirane (DMDO) from stereotriad **4.73** should furnish the penultimate epoxide **4.72**. Treatment of **4.74** with $Bu4N^{+}\bullet F^{-}$, SiO_2, in DMF provides **4.73**.[41] Intramolecular annulation of sulfone **4.75** allylanion with LiHMDS should provide the fused siloxane ring **4.74**. Bromomethylsilylether **4.75** is obtained from dienyl alcohol **4.76**.[36] Noyori conditions on sulfide **4.77** delivers

sulfone **4.76**. Activation of sulfone **4.78** followed by 1,4-elimination using trimethylaluminum and Hünig's base affords the acid sensitive dienylsulfide **4.77**.

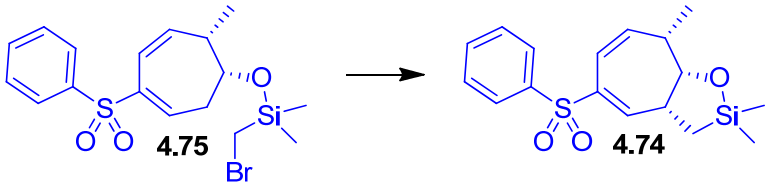


(a) $NaBH_4$, MeOH; (b) Oxone™, acetone; (c) $Bu_4N^+F^-$, SiO_2, DMF; (d) LiHMDS, THF, -78 °C; (e) $Me_2CH_2BrSiCl$, pyr., DCM; (f) $PhPO_3H_2$, $oct_3MeNHSO_4$, Na_2WO_4, PhMe; (g) $AlMe_3$, DIEA, DCM; (h) NaHMDS, THF, -30→ 10°C ; (i) MeMgBr, PhMe; (j) 3, 5-DMP, PhMe, Δ; (k) *(S, S)*-Mn-salen, H_2O_2, NH_4OAc

Scheme 4.2: Retrosynthesis of the Vinylsulfone Transposition Target

Dianion formation with phenyldisulfide quench of **3.16** affords **4.78**. Retrosynthetic steps i-k are identical to methodology in Scheme **3.3** steps **1-4**. All of the chemistry in this analysis has been well established-save that of the siloxane ring formation and subsequent oxidation, so steps c and d in Scheme 4.2 provide the most compelling points of investigation.

Fortunately previous to his departure, Wan Pyo Hong, provided a significant amount (~40 g) of Blue allylsulfone intermediate **4.78** triethylsilyl ether.



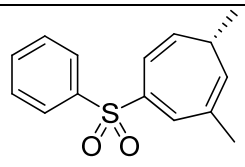
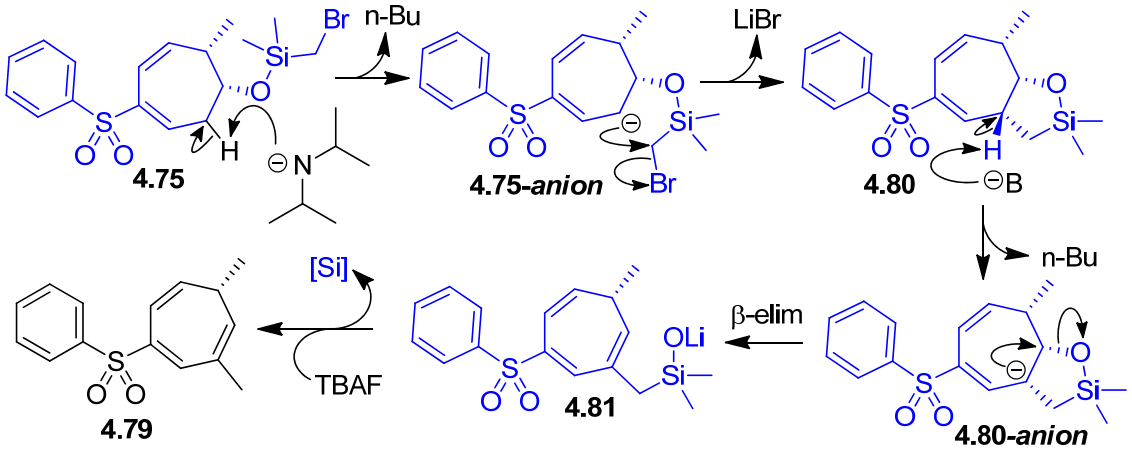
Entry	Conditions	Result
1	LDA, THF, 0.1 M, −78 °C⟶ −20 °C, 30 m	Decomposed on Silica
2	n-BuLi, THF, 0.1 M, −78 °C⟶ −20 °C, 30 m	TMS Ether Recovery
3	LDA, THF, 0.1 M, HMPA, −78 °C⟶ −20 °C, 30 m	 **4.79**

Figure 4.16: Anionic 5-exo-tet Siloxane Cyclization

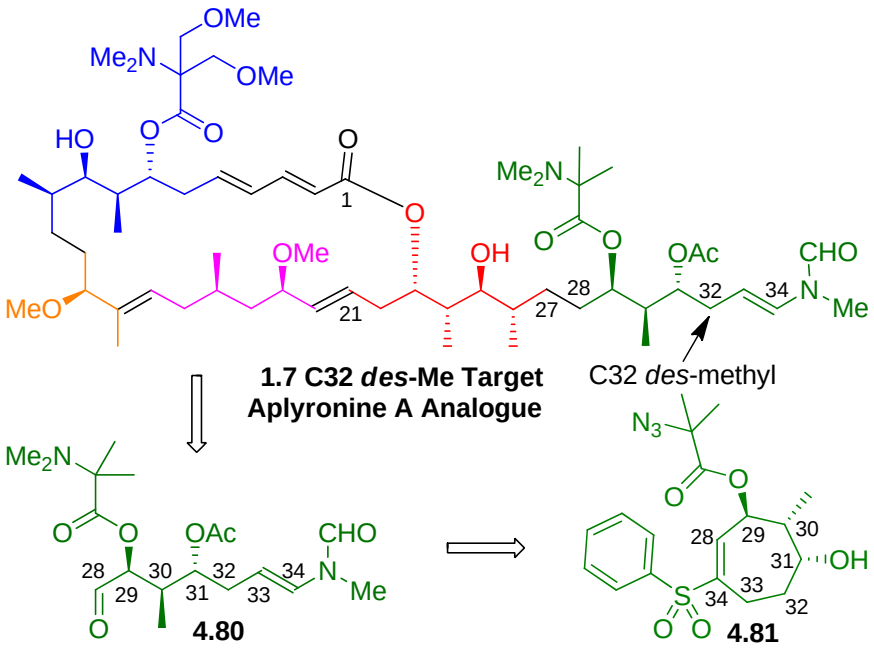
Unfortunately other than concept, Kim left little in the way of spectra (one very crude NMR) or detailed methodology with which to work with. This did however present the opportunity to re-explore the cyclization methodology

virtually from scratch. A brief cross-section of reaction attempts is shown in the above table. Traditional LDA conditions provided a repeatedly non-isolable spot on TLC (Entry 1). *N*-Butyllithuim in THF allowed for recovery of TMS ether (Entry 2) but HMPA, in standard LDA conditions gave the triene **4.79** in quantitative yield.



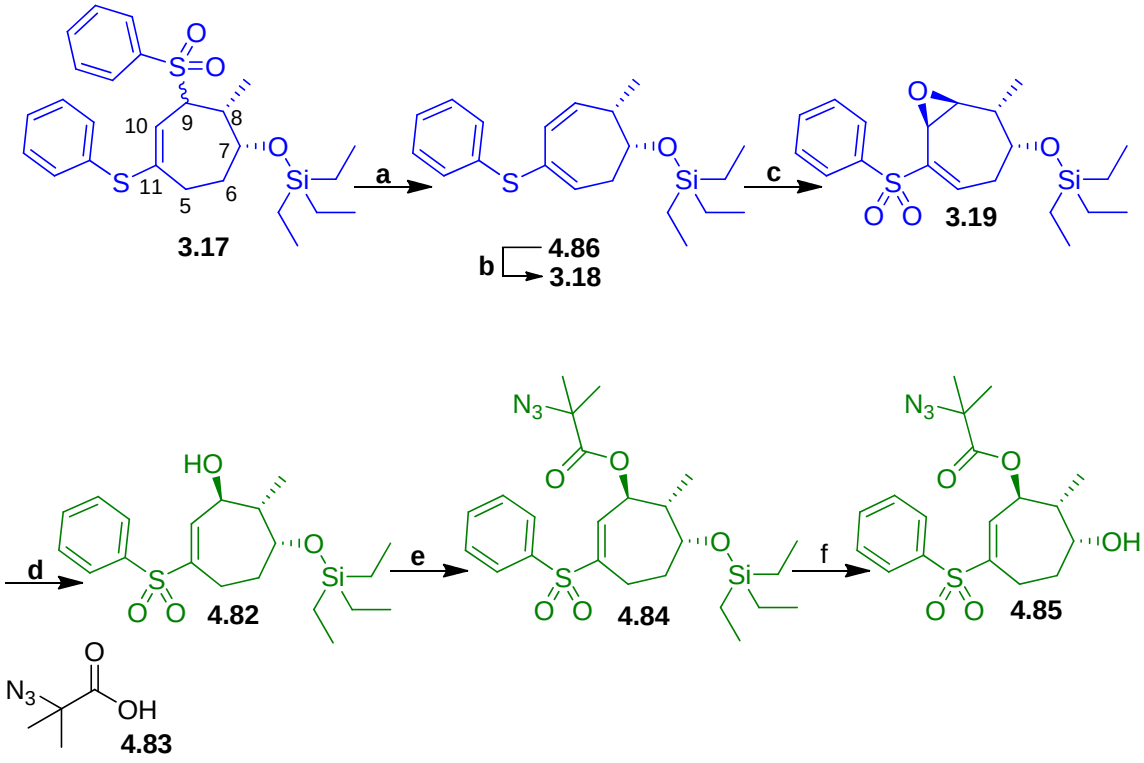
Scheme 4.3: Triene 4.79 Formation Mechanism

Formation of triene **4.79** starts with proton abstraction of **4.75** to furnish the allylanion. Nucleophilic attack of the allylanion on the bromomethyl silyl ether moiety delivers siloxane **4.80**. Additional base induces β-elimination causing an opening of the siloxane ring to afford triene **4.81**. Tetrabutyl ammonium fluoride (TBAF) gives 4.79 in quantitative yields.



Scheme 4.4: C32 des-Methyl Aplyronine A Analogue Target

Time constraints dictated that the siloxane formation step be delayed until a later time. This development facilitated **C32 des-methyl of aplyronine A analog 1.7** as the new target. Fragment **4.80** would be the working target for this new synthetic investigation. Stereotriad **4.81** is the ultimate cyclic vinylsulfone target for the C28-C34 fragment (Scheme 4.4).



(a) DIEA, $AlMe_3$ (b) $PhPO(OH)_2$, $oct_3MeNHSO_4$, Na_2WO_4, tol.95% 2 steps (c) *(R,R)*-Mn salen, NH_4OAc, urea·H_2O_2 88% (d) $NaBH_4$, MeOH 82% (e) **4.83,** $(COCl)_2$, DMF, DMAP,TEA 75% (f) (1S)-(+)-10-Camphorsulfonic acid, MeOH or $CeCl_3$, MeOH 78%

Scheme 4.5: Green Triad Transposed Vinylsulfone

Fortunately the new scheme was implemented with little difficulty. Allylsulfone **3.17** smoothly converts to dienylsulfide **4.86** upon treatment with trimethylaluminium and Hunig's base. Noyori Oxidation of **3.17-sulfide** delivers sulfone **3.18**. Jacobsen Epoxidation of diene **3.18** with the anhydrous H_2O_2 source urea hydrogen peroxide, provides epoxide **3.19**. Sodium borohydride reduction of **3.19** provides alcohol **4.82** in acceptable yield. Azido acid **4.83** forms the in situ acid chloride with oxalyl chloride, dimethylformamide (DMF), dimethylaminopyridine (DMAP), and triethylamine (TEA). Esterification of **4.82** to

azido ester **4.84** occurs smoothly. Cleavage of the silylether on **4.84** with camphorsulfonic acid or cerium chloride yields target **4.85**. With the Green Triad in hand oxidative cleavage of the vinylsulfone was next explored.

4.7 References

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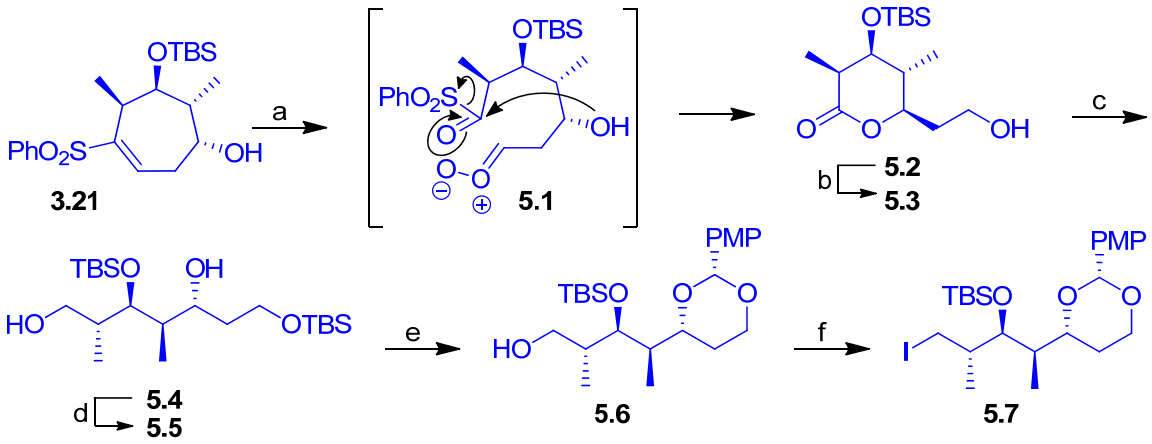
CHAPTER 5: OXIDATIVE CLEAVAGE OF CYCLIC VINYLSULFONES

5.1: Oxidative Cleavage of Cyclic Vinylsulfone Stereotetrads

Oxidative cleavage of cyclic vinylsulfone stereotetrads via ozonolysis has been investigated extensively by Noshi.[1,2] Subsequent exploration of the ozonolysis methodology by Hong[3,4] has established sound methodology for the C5-C11 & C21-C27 linear fragments. An encapsulation of the methodology achived by Noshi & Hong starts with an examination of the C5-C11 fragment.



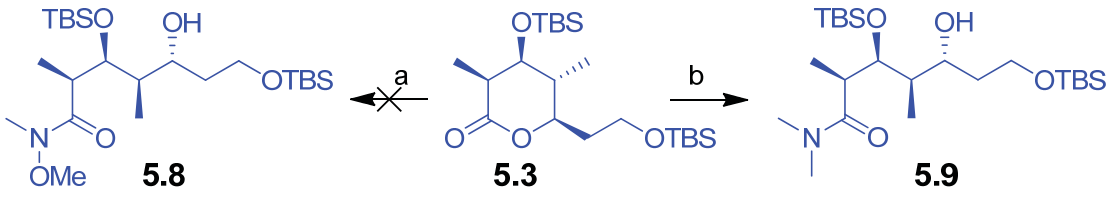
(a) (i) O_3, $NaHCO_3$ (ii) $BH_3{}^tBuNH_2$ 70%, 2 steps; (b) TBSOTf (c) $LiBH_4$ 78%, 2 steps; (d) CSA; (e) $MeO(C_6H_4)CH(OMe)_2$, CSA 90%; (f) TsCl, pyridine (g) NaI, acetone

Scheme 5.1: Synthesis of the C5-C11 Segment (Noshi, Hong)

Ozonolysis of **3.21** provided lactone **5.2** via intermediate **5.1** in good yield (70%). Protection of the alcohol **5.2** as TBS ether **5.3,** followed by lithium

borohydride ($LiBH_4$) induced lactone cleavage, afforded the linear fragment **5.4**. **5.4** was converted to triol **5.5** and then protected as *p*-methoxybenzylidene acetal **5.6** as a single diastereomer. Tosylation of primary alcohol **5.6** followed by iodination furnished fragment **5.7** (Scheme 5.1).

It is advantageous to open lactones with methoxymethylamine anion to give Weinreb amides[5-7] as termini-differentiated linear fragments. Exploration by Noshi elucidates the lactone opening by metallated amides on the C5-C11 fragment.

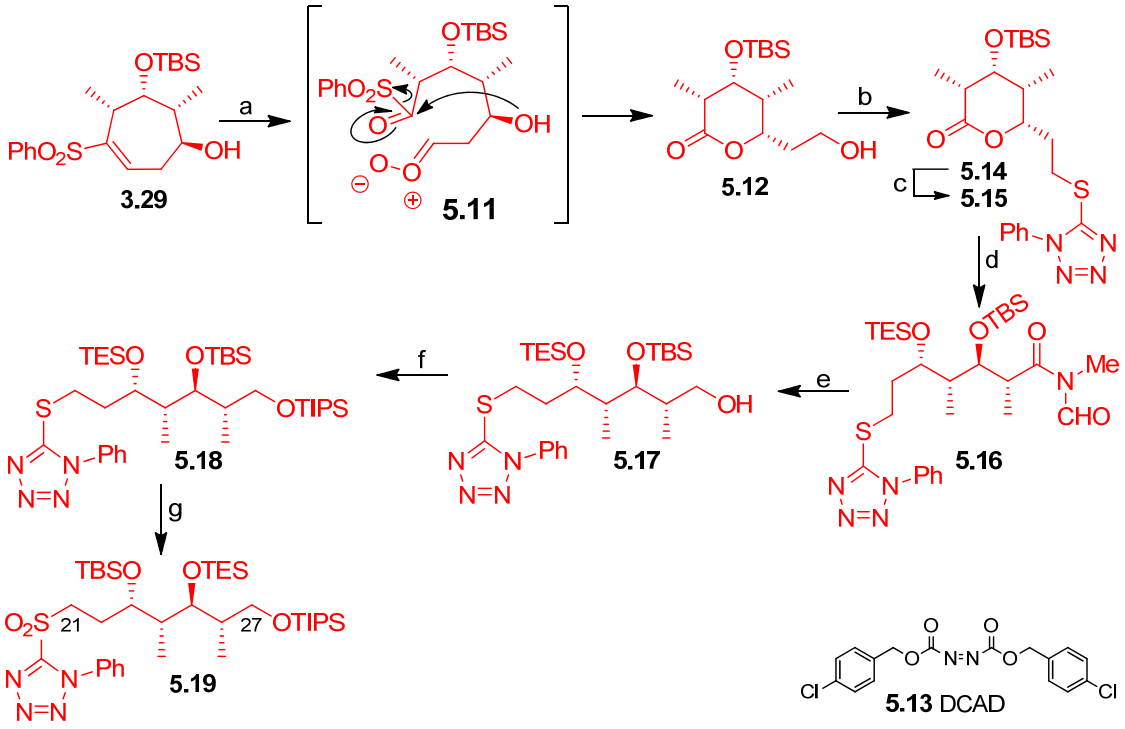


(a) MeNH(OMe)·HCl/*i*PrMgCl, THF, -10 ºCl; (b) Me_2NH·HCl/*i*PrMgCl, THF, -10 ºC 83%

Scheme 5.2: Amine Cleavage of Lactone (Noshi)

Opening of lactone **5.3** *via* Weinreb amine·HCl/ *i*-PrMgCl is not successful even when 10 equivalents of nucleophile were added at 25 ºC instead of -10 ºC. In all attempts, starting **5.3** was recovered quantitatively without any linear fragment **5.8** in evidence. Lactone **5.3** however was smoothly opened employing dimethylamine·HCl/*i*-PrMgCl on scales 3-4 g to afford dimethyl amide **5.9**[1] (Scheme 5.2). Ultimately, as can be seen in Scheme **5.1**, $LiBH_4$ was ultimately chosen for opening of lactone **5.3** to diol **5.4**.

As will be seen, control of the termini differentiation of the C21-C27 fragment is absolutely critical to the attainment of the aplyronine A analog. Inquiry by Noshi and elucidation by Hong established a solid foundation for the acquisition of the linear C21-C27 fragment.



(a) (i) O_3, $NaHCO_3$, EtOAc (ii) BH_3, *t*-$BuNH_2$ 65%, 2 steps; (b) DCAD, PPh_3 1-phenyltetrazole-5-thiol 84%; (c) MeONHMe, *i*PrMgCl, 80%; (d) TESOTf, quant; (e) (i) DIBAL (ii) BH_3 *t*-$BuNH_2$ 90%; (f) TIPSOTf, 2,6-lutidine 88%; (g) MCPBA, $NaHCO_3$ 71%

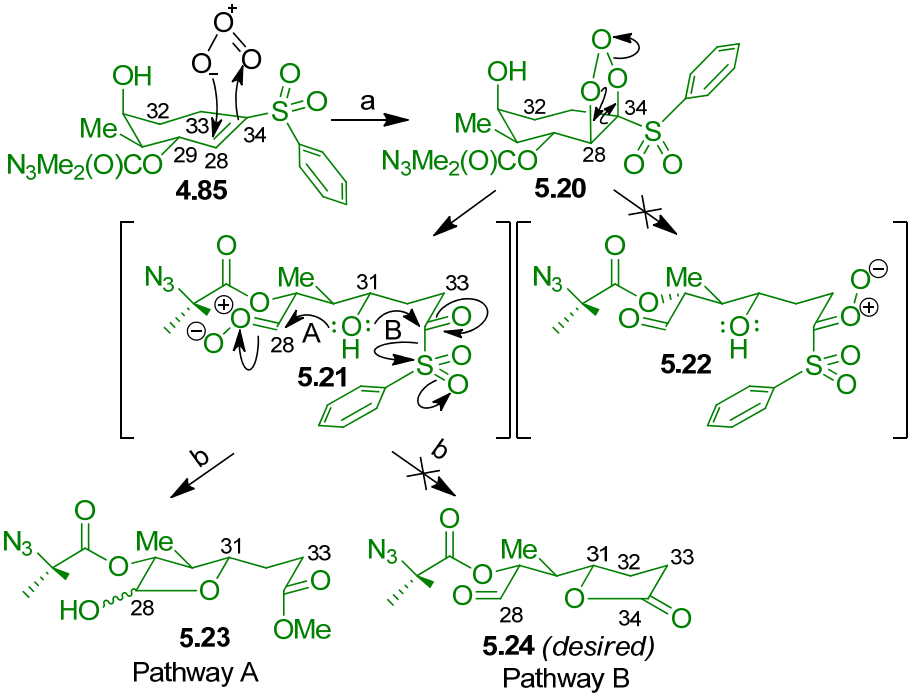
Scheme 5.3: Synthesis of the C21-C27 Segment

The synthesis of C21-C27 intermediate **5.19** commences with ozonolysis of **3.29** followed by reduction to afford lactone-alcohol **5.12** via intermediate **5.11**. DCAD **(5.13)** Mitsunobu coupling of **5.12** delivers **5.14** followed by lactone opening generated Weinreb amide[5] **5.15.** Treatment of **5.15** with *t*-

butyldimethylsilyl triflate (TBSOTf) gives disilylether **5.16**, which was transformed to terminal alcohol **5.17** via the intermediate aldehyde. TIPS protection was successful using TIPSOTf/2,6-lutidine at -78°C giving **5.18** in 88% yield. Oxidation with *m*-chloroperoxybenzoic acid (MCPBA) provided the C21-C27 linear Julia-Kocienski[8,9] sulfone intermediate **5.19**.

The studies of Noshi & Hong on linear fragments C5-C11 & C21-C27 gives clear vision as to how the C32 des-methyl cyclic stereotriad **4.85** can be utilized.

5.2: Oxidative Cleavage of the Vinyl Sulfone – Ozonolysis



(a) O_3, $NaHCO_3$, -78 °C, DCM: MeOH (5:1); (b) Me_2S

Figure 5.1: Ozonolysis of Green Vinylsulfone Stereotriad

Ozonolysis of C28-C34 stereotriad **4.85** has considerations beyond those of stereotetrads **3.21** & **3.29**. Ozonolysis of **4.85** in methylene chloride / methanol (4:1) likely passes through molozonide **5.20**. Decomposition of **5.20** presumably exclusively yields Criegee zwitterion **5.21** due to the instability of **5.22**. Secondary ozonide formation is arrested by an intramolecular attack **(5.21)**. The free alcohol of **5.21** is five atoms away from both electron-deficient terminii. C31 alcohol could either add to the acylsulfone delivering **5.24** (Pathway B) or add to the carbonyl

oxide to give lactol **5.23** (Pathway A) shown in Figure 5.1. Unlike the C5-C11 fragment **(3.21)** and C21-C27 fragment **(3.29)**, which have a free hydroxyl positioned 4 atoms from the carbonyl oxide and 6 atoms from the acylsulfone. This arrangement leads stereotetrads **3.21** & **3.29** exclusively forming 6-membered lactones upon ozonolysis. The reactivity of the carbonyl oxide however is greater than that of the acylsulfone, and 5-membered lactol **5.23** was furnished as a ~3:1 NMR ratio of the two possible diastereomers. The 5-membered lactol was however very resistant to coupling efforts.

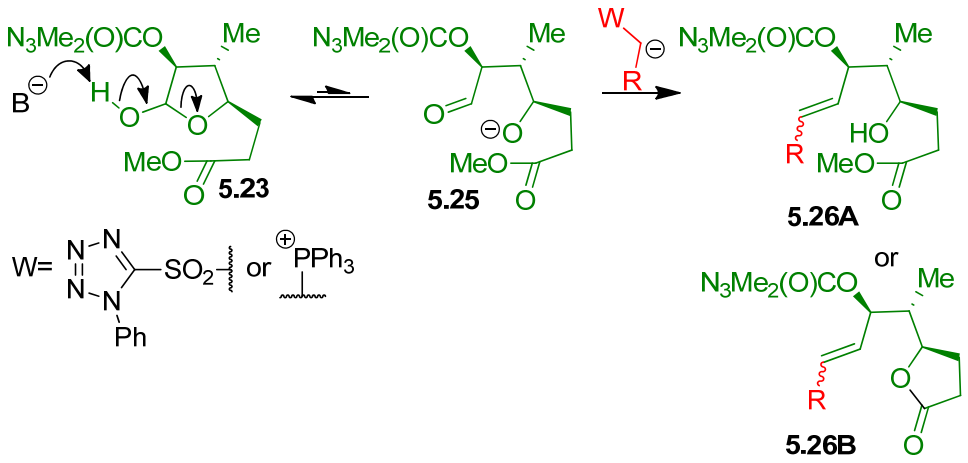
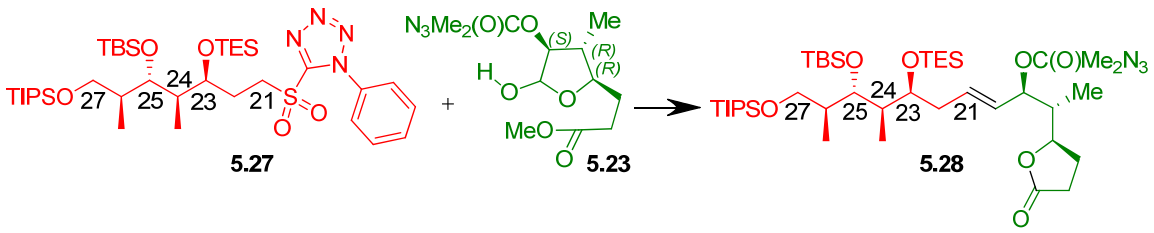


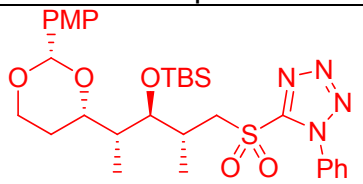
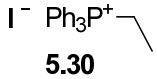
Figure 5.2: In *Situ* Aldehyde Generation From Lactol

Expectations of lactol **5.23** were initially very optimistic. Deprotonation of lactol **5.23** would, under ideal circumstances lead to an equilibrium with δ–alkoxy aldehyde **5.25**. An irreversible olefination (Wittig or Julia-Kocienski) would trap the aldehyde driving equilibrium to completion. For example, Boger condensed a similar lactol with the Still-Gennari phosphonate ($(CF_3CH_2O)_2P(O)CH_2CO_2Me$,

KHMDS, 18-crown-6, THF, -78 °C) to afford the first cis olefin of a sensitive Z,Z,E-triene (88%, Z:E 29:1) in his total synthesis of fostriecin (CI-920).[10] Fernandez de la Pradilla examined the Wittig reaction on a similar unprotected lactol that cleanly led to an unsaturated ester (67:33, E/Z mixture) and the smooth base-catalyzed cyclization of led to a 75:25 mixture of epimers that are key intermediates in the formal synthesis of kumausyne and kumausallene.[11] After olefination, the δ−alkoxide would be either quenched on work up delivering linear ester or form a cyclic 5-membered lactone Figure 5.2.



Conditions: LiHMDS (1.2 eq), THF: HMPA (5:1),–78→ 0 °C, 30 min 22%

Entry	Conditions	Nucleophile	Result
1	LiHMDS (1.2 eq), THF: HMPA (5:1), -78→0 °C, 30 min	 **5.29**	N/R
2	LiHMDS (1.2 eq), THF:DMF:HMPA (3:9:1) -78→0 °C, 30 min	**5.29**	N/R
3	NaH (50 eq), THF -78→0 °C, 30 min	**5.29**	N/R
4	n-BuLi, THF, - 42 °C→25 °C 20 hr	 **5.30**	N/R

Scheme 5.4: Julia-Kocienski Coupling C21-C27

Entry	Conditions	Nucleophile	Result
5	DBU, THF -40 °C→25 °C 30 min	**5.30**	N/R
6	NaHMDS, THF 0 °C→25 °C, 45 min	**5.30**	N/R

Scheme 5.4, contd.

Lithium hexamethyldisilazide with HMPA and THF at -78- 0 °C, with 3 eq of **5.27** effected olefination at the C21 end of the red fragment **(5.28)** in low but promising yield (Scheme 5.4). Ultimately using either of the information-rich polypropionate segments in excess would be an inefficient and untenable strategy. Pursuing a 1:1 substrate ratio with the rare C21-C23 *p*-methoxybenzylidine **5.29** under the same conditions shows the lactol to possess robustness beyond expectations, returning starting material. LiHMDS (1.2 eq), THF:DMF:HMPA (3:9:1), -78→0 °C, 30 min, similarly returned starting material. Using the stronger irreversible base NaH (50 eq), THF, -78→0 °C, 30 min, returned a faint light blue spot upon para-anisaldehyde staining. NMR of the crude material revealed no signals in the olefinic region possessing the requisite AB splitting patterns. *n*-BuLi, THF, -42 →25 °C, 20 hr, with commercially available **5.30**, likewise furnished no desired product. In an attempt to see what an amidine base could achieve, **5.30** was treated with DBU, THF, -40 °C→25 °C, 30 min but to no avail. As a last-ditch effort, NaHMDS, THF, 0 °C→25 °C, 45 min, was attempted on substrate **5.30** but the weaker base did not affect the desired transformation. It was readily apparent that the lactol functionality was not

synthetically compliant. Revisiting past efforts in the Fuchs group revealed a possibly more promising methodology for obtaining desired lactone **5.24**. Dihydroxylation of the vinylsulfone was next explored.

5.3: Dihydroxylation Via Established Methodology

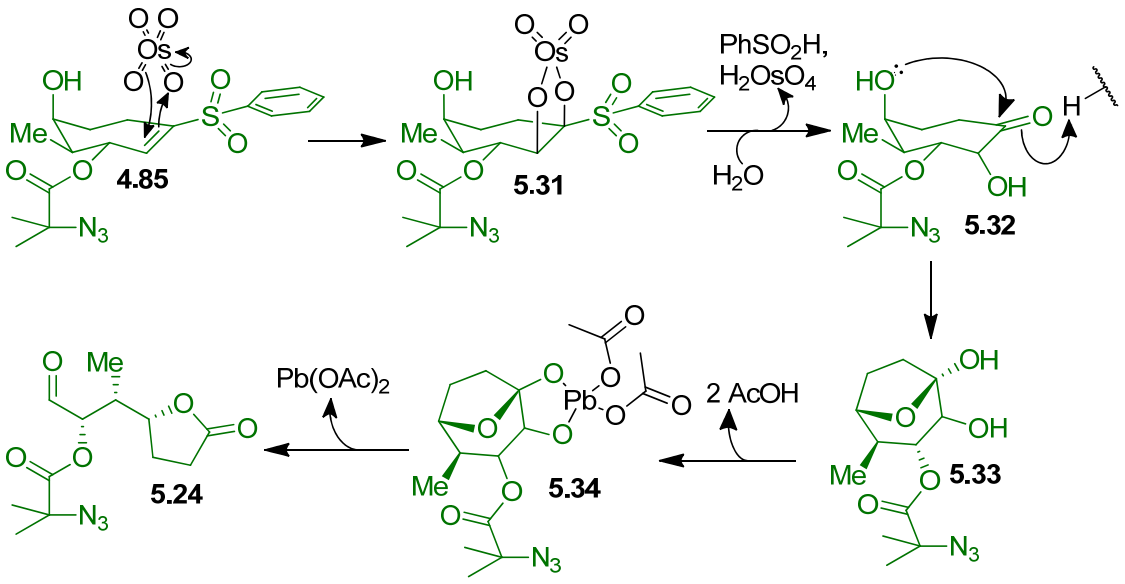
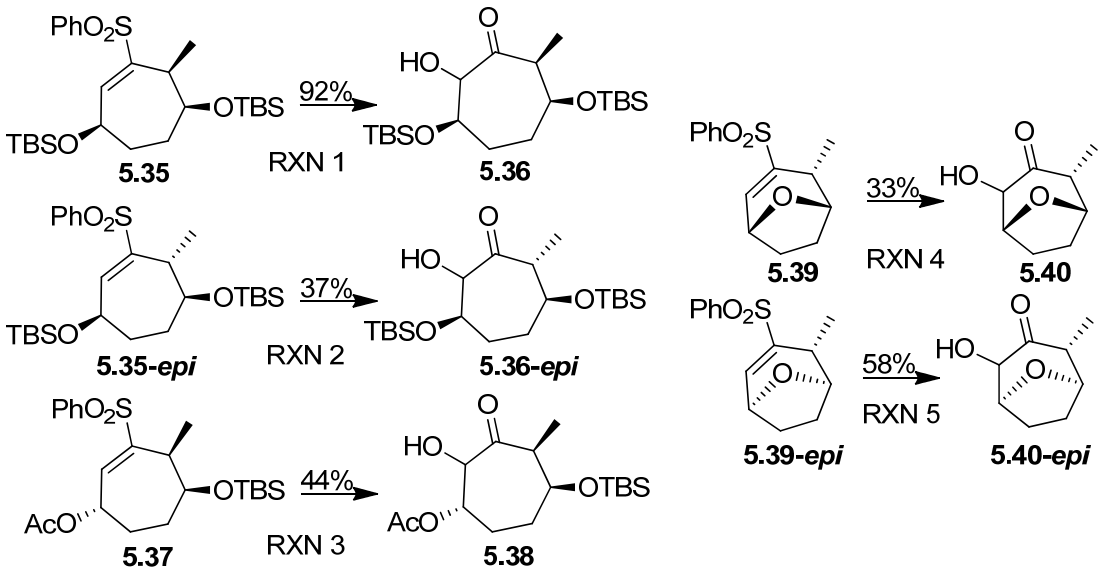


Figure 5.3: Vinylsulfone Dihydroxylation Strategy

Reproducible dihydroxylation of vinylsulfones has been an elusive methodology for oxidative cleavage of cyclic vinylsulfones. Ideally dihydroxylation *via* osmylation (Figure 5.3) would have osmium (VIII) oxide add to vinylsulfone **5.24** to provide osmate **5.31**. Hydrolysis of osmate **5.31** ejects the sulfinic acid to deliver acyloin **5.32**. Intramolecular addition by the free alcohol gives α-hydroxy lactol **5.33**. Cleavage of diol **5.33** by lead (IV) acetate would furnish lactone **5.24** via intermediate **5.34.**

Previous work by Jiang[12] focused primarily on the ability of Os(Vlll) and Ru(Vlll) species to effect dihydroxylation of the electron deficient vinylsulfones. While limited success with osmylation was indeed achieved using Bäckvall

methodology,[13] satisfactory results over a diverse cross section of multi-functional vinylsulfones was lacking.

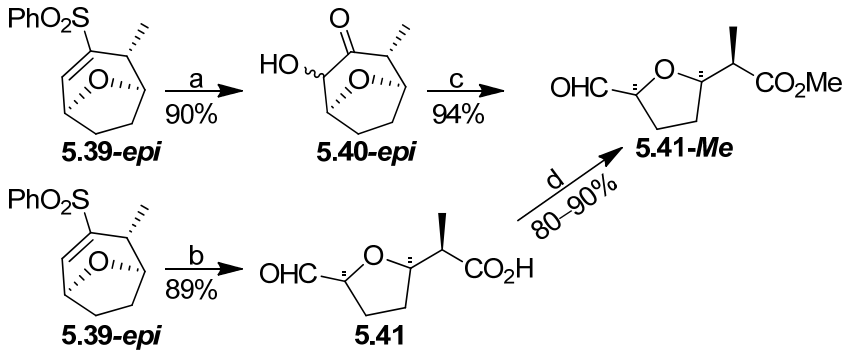


Dihydroxylation ConditionsOsO_4 0.05 equiv., NMO 3 equiv., Me_2CO:H_2O (2:1) 23°C, 10h

Figure 5.4 Osmylation Study of Non-Contiguous Stereotetrads (Jiang)

Jiang employed the Bäckvall methodology for the conversion of vinyl sulfone substrates to α-hydroxyketones. Only one of several substrates **(5.35)** gave a high yield of the desired α-hydroxyketone (**5.36** in RXN 1). The rest of the cases examined gave either low yields or low conversion (Figure 5.4).

It was theorized that the low yield/conversion was due to steric hindrance in vinylsulfones **5.35-*epi***, **5.37**, **5.39** & **5.39-*epi***. This problem was addressed by using Sharpless methodology by treatment with catalytic ruthenium dioxide and sodium periodate.[14]

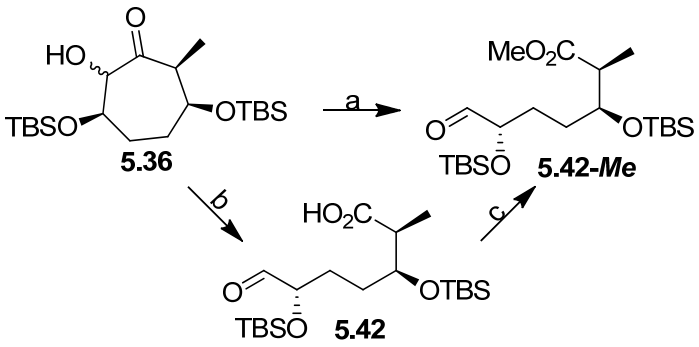


(a) RuO_2 0.03 eq., $NaIO_4$ 3 × 1 eq., CCl_4:CH_3CN:H_2O(1:1:1.5), pH = 5.0, 23°C, 30 min; (b) RuO_2 0.03 eq., $NaIO_4$ 3 eq., CCl_4:CH_3CN:H_2O(1:1:1.5), pH = 5.0, 23°C, 30 min; (c) $Pb(OAc)_4$, MeOH; (d) CyNHC(OMe)=NCy or CH_2N_2

Scheme 5.5: Oxidative Cleavage via RuO_4-$NaIO_4$/ $Pb(OAc)_4$ (Jiang)

Treatment of vinylsulfone **5.39-*epi*** with 0.03 equivalents of ruthenium dioxide and 2 equivalents of sodium periodate added in 3 portions was shown to avoid or minimize the α-hydroxyketone cleavage reaction. Treatment of **5.40-*epi*** with lead tetraacetate in methanol provided aldehyde-methyl ester **5.41-*Me*** in 94% yield. Alternatively, use of 3 equiv. of sodium periodate in the ruthenium dioxide reaction of oxabicyclic sulfone **5.39-*epi*** directly gave aldehyde-carboxylic acid **5.41** in 89% yield. Esterification of carboxylic acid **5.41** with methylisourea or *in situ* diazomethane delivered aldehyde-methyl ester **5.41-*Me*** (Scheme 5.5).

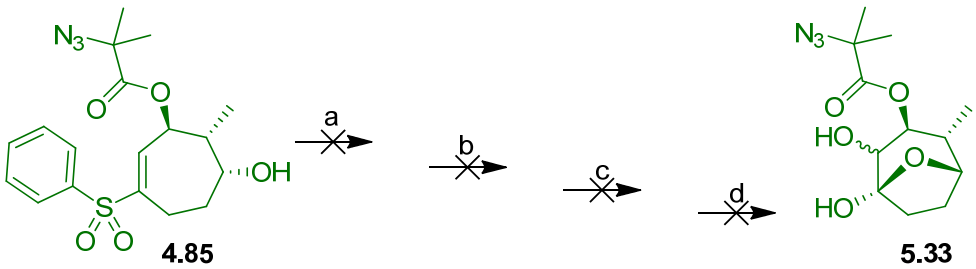
Oxidative cleavage of **5.36** with sodium periodate followed by esterification of carboxylic acid **5.42** with methylisourea or *in situ* diazomethane gave aldehyde-methyl ester **5.42-*Me*** without difficulty. Application of the lead tetraacetate/ methanol procedure again obviated the necessity to isolate carboxylic acid **5.42** (Scheme 5.6).



(a) $Pb(OAc)_4$, MeOH 23°C,1.5h 91%; (b) $NaIO_4$, t-BuOH/H_2O 23°C, 8-10h >90%;(c) CyNHC(OMe)=NCy or CH_2N_2 80-90%

Scheme 5.6: Oxidative Cleavage of Acyloin Stereotetrad

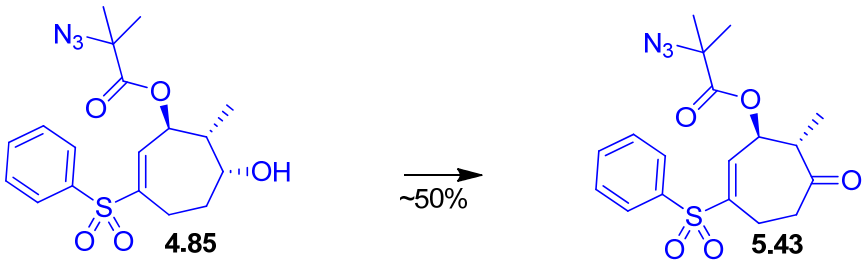
Based on the work of Kim[15] exploration of the osmium dihydroxylation methodology was investigated. Stereotriad **4.85** was treated with NMO (N-Methyl morpholine N-oxide), followed by an aqueous solution of osmium tetroxide (4 wt% in water) in a mixture of acetone and water and stirred at 0 °C→25 ºC for 6 hours returned starting material (method a, Figure 5.5).



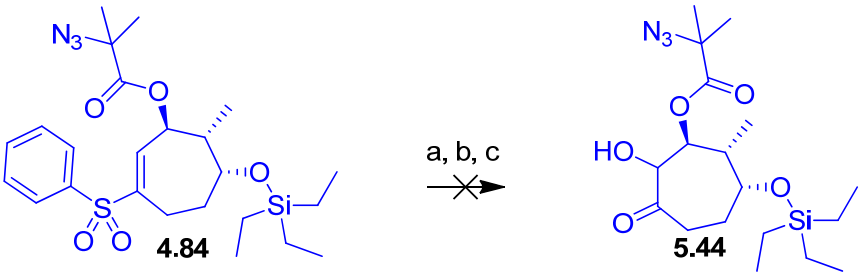
(a) NMO 2eq., OsO_4 (4% H_2O) 7 mol %, Acetone: Water 4:1, 0 → 25 °C, 6 hr, Na_2SO_3 10 eq. wk-up (b) NMO 2.1eq., OsO_4 (4% H_2O) 0.010 eq., THF: Water 5:1, 20 °C, 50 min, Na_2SO_3 10 eq. wk-up (c) NMO 2 eq., OsO_4 (2.5% t-BuOH) 0.020 eq., BuOH:THF:Water 3:1:1, 0→ 25 °C, 18 hr; (d) NMO 3 eq., OsO_4 (2.5% in H_2O) 0.025 eq.; Acetone: Water 2:1, 25 °C, 24 hr;

Figure 5.5: Osmylation Initial Exploration

The solvent was changed to THF:water (method b) likewise returning starting material. Switching to osmium tetroxide 2.5 wt% in t-BuOH, 4-methyl morpholine *N*-oxide in *t*-BuOH:THF:water (method c) showed no reaction after 18 hours. Changing to the Kim conditions (method d) of **Scheme 5.4** showed no reaction, which apparently eliminated osmylation as an option for oxidative cleavage of stereotriad **4.85** (Figure 5.5).



Conditions: $RuCl_3{\cdot}H_2O$ 0.03 eq., $NaIO_4$ 3 eq., CCl_4:CH_3CN:H_2O(1:1:1.5), pH = 5.0, 23°C, 30 min;



Conditions: (a) $RuCl_3{\cdot}H_2O$ 0.03 eq., $NaIO_4$ 3 eq., MeCN:EtOAc:Water 1:1:1.5 (biphasic), 25 °C, 3hr (b) $RuCl_3{\cdot}H_2O_2$ 0.03 eq, $NaIO_4$ 3 eq., CCl_4:CH_3CN:H_2O(1:1:1.5), pH = 5.0, 23°C, 30 min; (c) RuO_2 0.03 eq, $NaIO_4$ 2 eq., CCl_4:CH_3CN:H_2O(1:1:1.5), pH = 5.0, 23°C, 30 min

Figure 5.6: Ruthenium Catalyzed Dihydroxylation

Initially ruthenium catalyzed oxidative cleavage of the vinylsulfone using sodium periodate was avoided, due to the need to esterify the terminal carboxylic acid (Scheme 5.4). The ineffectiveness of osmium methodologies however

necessitated investigation of the ruthenium approach. It is worthy of note that none of the Kim substrates **5.35**, **5.37**, or **5.39** possessed any free alcohols. Treatment of free alcohol **4.85** with catalytic $RuCl_3 \bullet H_2O$ and stoichiometric $NaIO_4$ in CCl_4:CH_3CN:H_2O (1:1:1.5), phosphate buffer pH 5, provided ketone **5.43** in roughly 50% yield (Figure 5.6). Lack of literature precedent for the preservation of the secondary alcohol under these conditions demanded examination of silylether **4.84**. Application of the aforementioned conditions but with a biphasic solvent system returned starting material (a). Changing back to the single solvent system (b) also yielded starting material. Kim conditions of RuO_2, $NaIO_4$ in CCl_4:CH_3CN:H_2O (1:1:1.5), pH 5 (c) similarly returned starting material **(Figure 5.6)**. At this point it seemed ozonolysis with both hydroxyl groups protected was the only remaining option.

5.4: Citric Acid Catalyzed Dihydroxylation

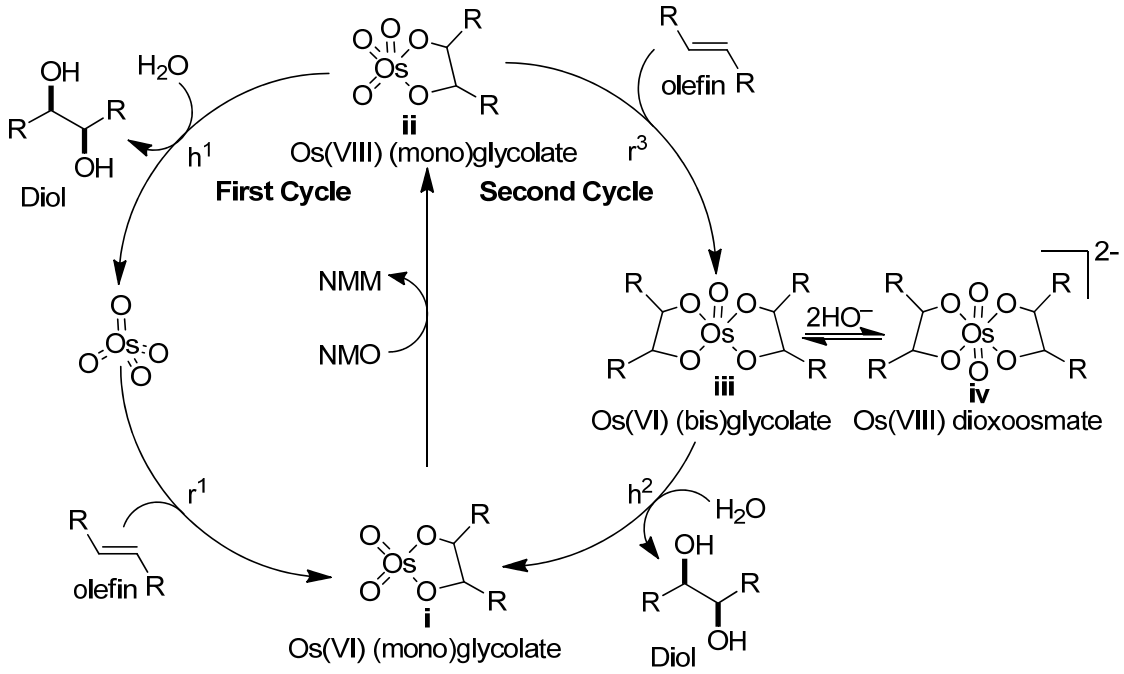


Figure 5.7: *cis*-Dihydroxylation of Alkenes

The proposed mechanism of osmium tetroxide (OsO_4) dihydroxylation (Figure 5.7) suggested that the rate is sacrificed if (mono)glycosylate **ii** is hydrolyzed to regenerate diol and osmium tetroxide perpetuating the First Cycle.[16] The Second Cycle is favored over the First Cycle all things being equal. Since the rate of hydrolysis (h^1) is much slower than the reduction (r^3), the osmium(VI) bis(glycolate) **iii** builds up as the reaction progresses, generating diol via hydrolysis of (bis)glycolate **iii**. To exploit the Second Cycle when using chiral ligand, a slow addition technique was recommended to suppress the second cycle pathway during asymmetric dihydroxylation (AD).[16] However, if high reactivity is required, the second cycle gives a clear advantage over the first

cycle. Citric acid improves the rates and the yields of *cis*-dihydroxylations of various electron-deficient alkenes. In addition to acting as a pH buffer thereby preventing formation of insoluble Os(VIII) dioxoosmate **iv**, a species, that inhibits the second cycle, citric acid strongly binds to OsO_4 and maintains the reaction in the second cycle.[17]

Addition of citric acid to improve the catalytic asymmetric osmylation system led to a greater understanding of the catalytic cycle that the vinylsulfone substrate undergoes. During the course of Sharpless' investigation to improve upon the Upjohn protocol, it was found that the osmylation catalytic cycle can, as has already been stated, progress via two alternate avenues where the rate limiting step is hydrolysis of the monoglycolate **(i)** in the case of the first cycle and bisglycolate **(ii)** in the case of the faster second cycle Figure 5.7. When the osmylation is undertaken in homogeneous conditions the co-oxidant (NMO) has access to the intermediates over the entire catalytic cycle. Since the **Second Cycle** is faster, the reaction gets locked into the second cycle (bis)glycolate **(ii)** hydrolysis furnishes Os(VI) species **iii**. The Sharpless group postulated that acids assist catalyst turnover by preventing formation of the catalytically dormant dioxoosmate dianion species **iv**, which is formed upon deprotonation of the hydrated (bis)glycolate **iii** at higher pH.

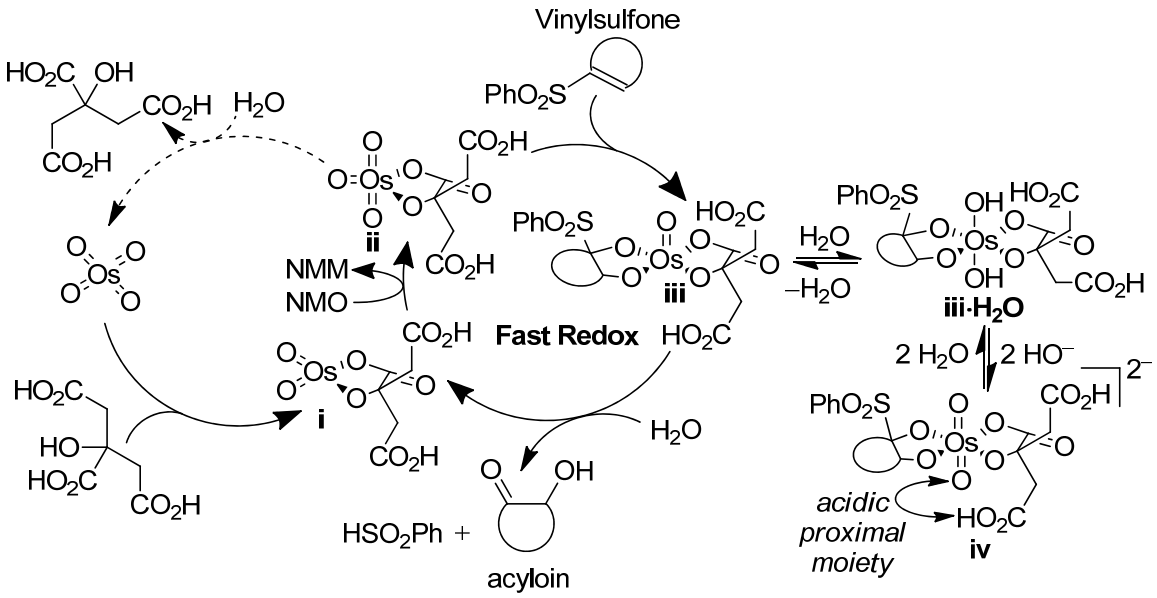


Figure 5.8: Citric Acid Catalyzed cis-Dihydroxyltion of Vinylsulfones

The strong electron withdrawing ability of the sulfone contributes to the acidity of the hydrated bis(glycolate) species **iii•H_2O** thus increasing the concentration of the dioxoosmate **iv** and crippling the cycle. The Sharpless group then discovered, based on the aforementioned hypotheses that the dioxoosmate **iv** is especially stable and resistant to substitutions of any kind under basic conditions including hydrolysis irrespective of the presence co-oxidant. According to Sharpless, all acidic mixtures remain green indicating the presence of neutral bis(glycolate) (**ii**) whereas basic mixtures took on a reddish brown color indicating the presence of dioxoosmate dianion species **iv.** Adding citric acid however arrests the formation of osmium tetroxide (OsO_4) in favor of species **iii** thereby impeding the First Cycle (Figure 5.8). With proximal acidic moieties acting as a buffer in hydrated (bis)glycolate **iii•H_2O** and dioxoosmate **iv** the

equilibrium leans strongly in favor of bis(glycolate) **ii** which can then be hydrolyzed back to species **i** so the cycle may continue (Figure 5.8).

Methodology elucidated by Sharpless,[18-20] involving dihydroxylation of election deficient olefins by osmium, catalyzed by citric acid was explored on green stereotriad **4.85**. Rationale for the efficacy of the osmium/citric acid methodology is derived from the proposed catalytic cycle in Figure 5.8.

It is noteworthy that olefins such as diethyl maleate show the greatest benefit from performing the dihydroxylation at lower pH.[18] The hydrated osmium(VI) bis(glycolates) like species **iii•H_2O** formed from such electron-poor olefins would be expected to be much more acidic and correspondingly more likely to get trapped as the unwanted dioxoosmate dianion **iv**, even in the presence of a relatively weak base like 4-methylmorpholine. Citric acid however not only coordinates to the osmium, but coordinates the acidic moieties proximal to the oxygens of the hydrated (bis)glycolate **iii** so buildup of dioxoosmate **iv** will not terminate the catalytic cycle.

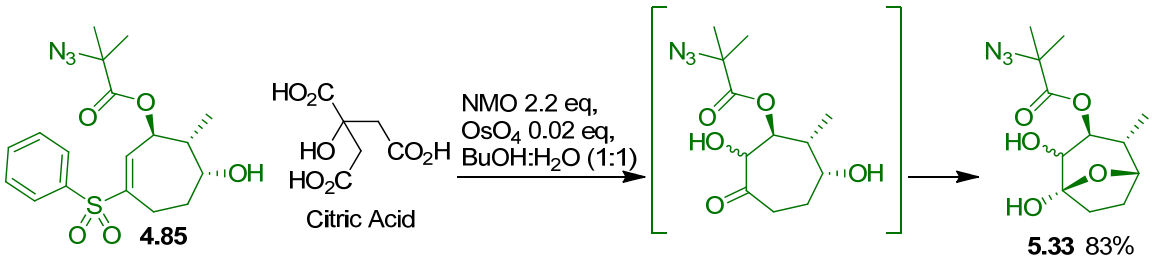


Figure 5.9: Citric Acid Catalyzed Osmylation of Green Stereotriad C28-C34

With a sound rationale for catalytic dihydroxylation of the electron deficient vinylsulfone, further inquiry was made into the efficacy of this new osmylation methodology on the vinylsulfone stereotriad. Under these conditions, the osmylation smoothly provided α-hydroxy lactol (83%; ~3:1 epimeric NMR ratio) (Figure 5.9).

Lead tetraacetate instantaneously cleaves both α-hydroxy lactol epimers to the lactone-aldehyde (Figure 5.10).

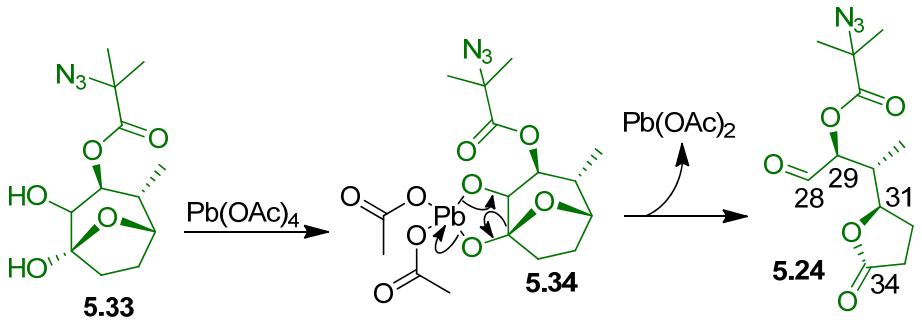


Figure 5.10: $Pb(OAc)_4$ Glycolytic Cleavage

With the proper C28-C34 chiral motif in hand, it is now possible to couple the green fragment. Due to the ester at C29, the olefin coupling must entail the aldehyde being attacked by the nucleophile rather than the nucleophile being on C28 as the danger of beta elimination is too great.

5.5 References

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CHAPTER 6: C28-C34 STEREOTRIAD SYNTHETIC RAMIFICATIONS

6.1: Assembly of Aplyronine A Backbone

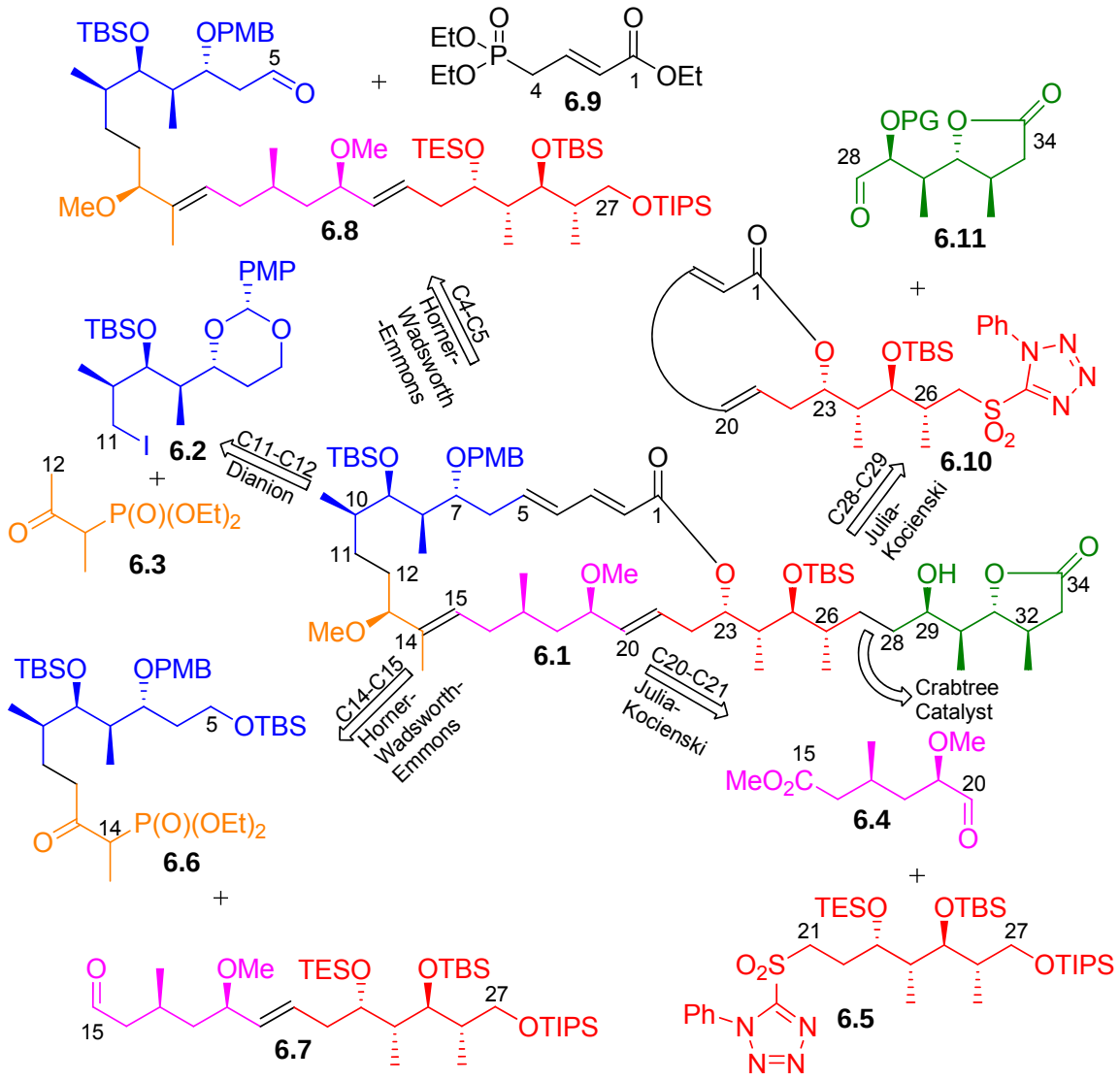
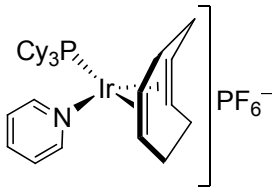


Figure 6.1: Aplyronine Core Assembly (Fuchs)

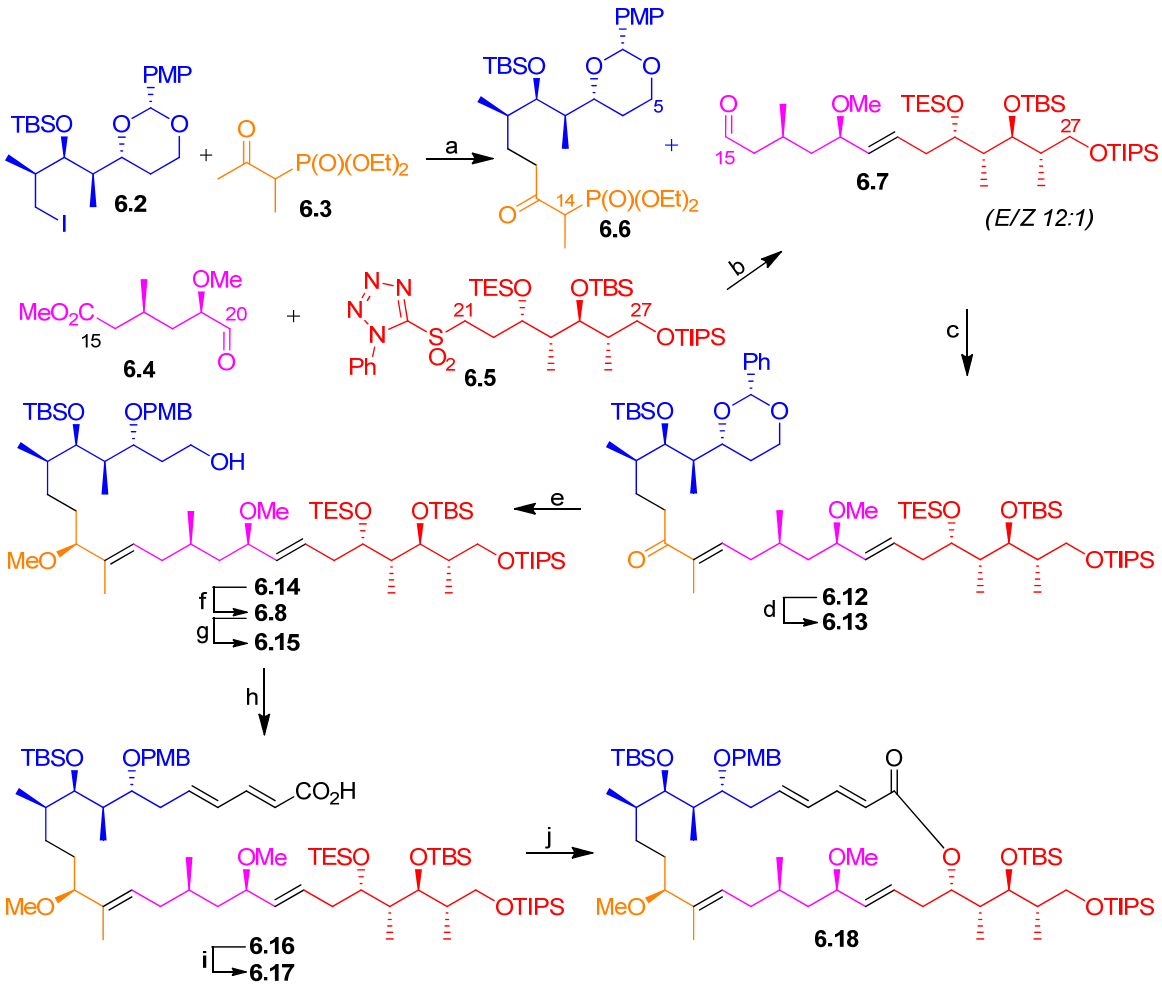
With an iterative way to access polypropionate motifs from cyclic vinylsulfones,[1] a working, sequential and convergent strategy was devised to assemble an aplyronine core.

Previous work done in the Fuchs group by El-Awa, Noshi and Hong achieved synthesis of the C1-C27 segment of aplyronine A.[2-4] Macrocyclic lactone **6.1** (C1-C27 segment) was desired as a key fragment of the aplyronines. As outlined in **Figure 6.1**, the synthetic approach is based on disconnection of macrocyclic core **6.1**. Core **6.1** is accessed from building blocks **6.6**, **6.9** and **6.7**. Fragments **6.2**, **6.4** and **6.5** are derived by vinylsulfone strategies creating stereodefined polypropionate fragments. Side Chain **6.11** was originally to be constructed as previously described in **Schemes 4.2 & 4.3**. Ozonolysis was the designated methodology to access the desired acyclic segments. Fragment **6.2**, possessing the stereotetrad, (C7-C10 dipropionate portion) can be obtained from cyclic vinylsulfone **3.21**. Similarly, fragment **6.5** with a C23-C26 dipropionate portion can be prepared from cyclic vinylsulfone **3.29**. Fragment **6.4** was chosen to introduce the C15-C20 array.[3,5] As reported,[6] β-ketophosphonate **6.3** was adopted for connecting iodide **6.2** and aldehyde **6.7**. Macrolactone **6.10** was to have been joined to lactone **6.11** via a Julia-Kocienski olefination followed by deprotection. Selective reduction with Crabtree's catalyst at the C27-C28 position would deliver aplyronine A core



Crabtree's Catalyst

6.1. The anticipated use of Crabtree's catalyst to selectively reduce the C27-C28 allylic alcohol from coupling of **6.10** to **6.11** is key to the plan proposed in Figure 6.1.

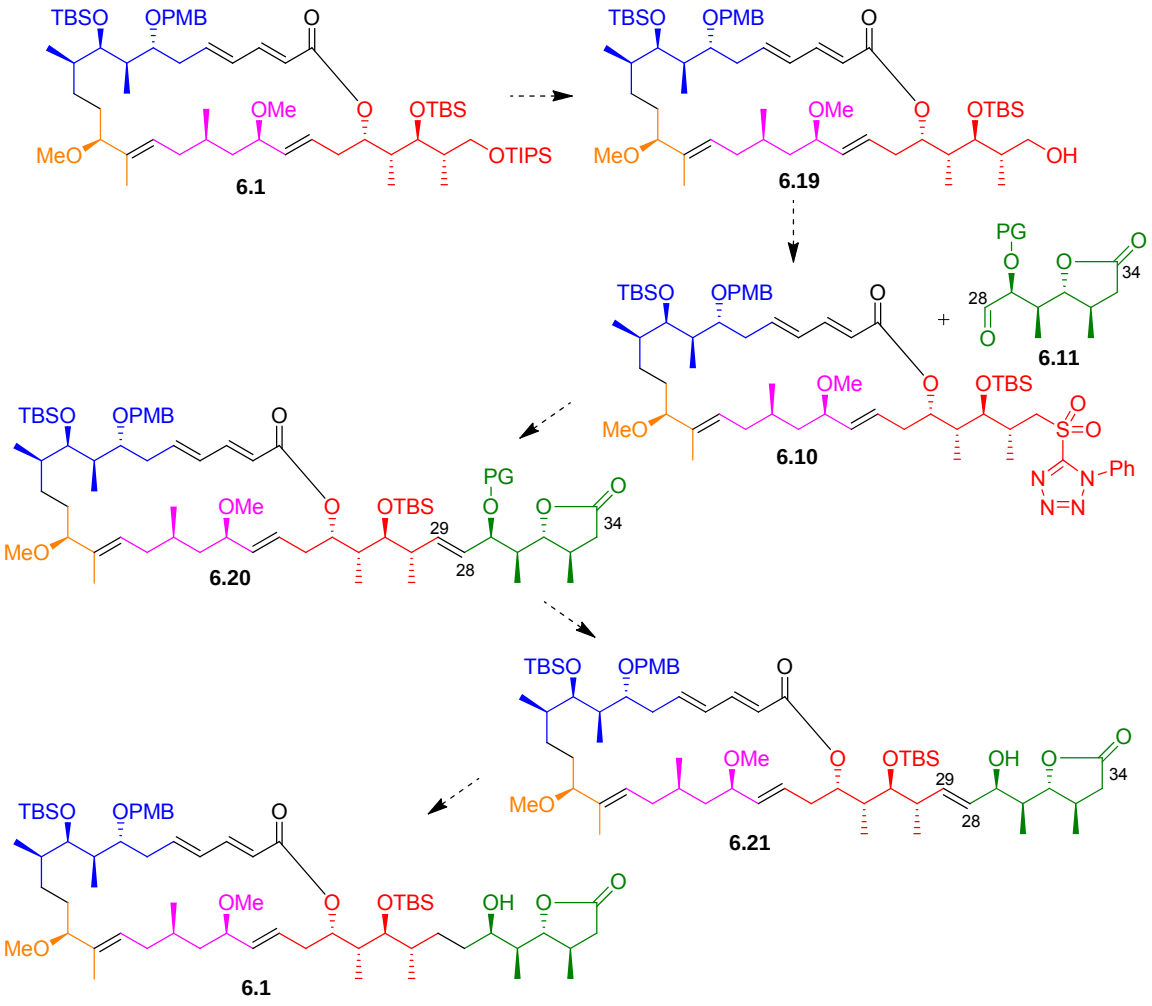


(a) NaH, BuLi 88%; (b) (i) LiHMDS (1M THF), DMF/ HMPA (4:1) 60% (83% brsm) 12:1 (ii) DIBAL-H, PhMe, -78 °C, 45 min; (c) (i) $Ba(OH)_2$, THF:H_2O (40:1), rt, 36 h, 84% (d) (R)-MeCBS, BH_3 SMe_2, THF, -10 °C; NaH, MeI, THF, rt, 84%; (e) DIBAL, PhMe, 88% (f) pyridine, Dess-Martin periodinane, rt, 80%; (g) $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$, LiHMDS, THF, 72%; (h) 1N KOH, EtOH, THF, 88%; (i) CSA (0.2 eq), MeOH, 74%; (j) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, PhMe, rt, 36 h, 66%

Scheme 6.1: Assembly of Aplyronine Macrolactone Core (Hong)

Preparation of **6.4** was elaborated by Noshi[3,5] and **6.5** (Scheme 5.3), was discussed in Chapter 5. Substrates **6.4** and **6.5** were linked using a Julia-Kocienski olefination,[7-9] where Jacobsen's solvent combination (DMF/HMPA)[10,11] gave the best selectivity (E:Z = 12:1) in 60% yield, 83% based upon recovered starting material. Epimerization of C19 methoxy group was not observed in the crude product unless the base was added to the mixture of **6.4** and **6.5**. Reduction of C15 methyl ester with DIBAL-H afforded the desired aldehyde **6.7**. Addition of the dianion of β-ketophosphonate **6.3** to iodide **6.2** furnished a 1:1 mixture of diastereomeric C14 methyl groups in fragment **6.6**. A $Ba(OH)_2$ mediated Horner-Wadsworth-Emmons olefination between C5−C14 β-ketophosphonate **6.6** and the C15−C27 aldehyde **6.7** supplied the desired C5-C27 segment **6.12** (70% yield) as an inseparable 12:1 mixture of (14E, 20E) and (14E, 20Z), resulting from Julia-Kocienski product **6.7**. The minor product (14E, 20Z) could be separated at a later stage of the synthesis.[12] Chemo- and stereoselective reduction of enone **6.12** gave the secondary alcohol in 84% yield, which was treated with methyl iodide to afford methyl ether **6.13**. The regioselective ring opening of the *p*-methoxybenzylidene acetal with DIBAL-H at 0 ºC afforded intermediate **6.14** which was oxidized using Dess-Martin Periodane to give aldehyde **6.8**, which was immediately used in crude form for the next reaction. Horner-Wadsworth-Emmons conditions coupled **6.8** with $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$ **6.9** delivers dienoate **6.15** in 72% yield. Treatment of dienoate **6.15** with 1N KOH gave carboxylic acid **6.16** in 88% yield. Selective deprotection with 0.2 equivalents of (1S)-(+)-10-Camphorsulfonic acid exclusively

furnished **6.17** (74%). The *seco*-acid **6.17** was then subjected to macrolactonization by using the Yamaguchi procedure to provide macrolactone **6.18**.



Scheme 6.2: Final Assembly of Aplyronine Core

The sequence elucidated in Scheme 6.1 was devised to prepare the C28-C34 fragment. The working hypothesis (Scheme 6.2), however, required deprotection of the primary triisopropylsilyl ether at C27 of macrolactone **6.18** to primary alcohol **6.19**. Mitsunobu reaction followed by oxidation would likely furnish phenyltetrazole sulfone **6.10**. A Julia-Kocienski olefination between sulfone **6.10** and lactone **6.11** would afford triene **6.20**. Selective deprotection to allyl alcohol **6.21** followed by hydrogenation in the presence of Crabtree's catalyst[13] would deliver aplyronine core **6.1**. It should be emphasized that **Scheme 6.2** could not be explored due to a lack of a substrate possessing the C28-C34 landscape. The strategy illustrated in Scheme 6.2, as will be seen, had deep implications for the unification of lactone triad **5.48**.

6.2: Implications of C32 *des*-Methyl Stereotriad

The synthetic sequence elucidated in Scheme 6.2 hinges on formation of allylic alcohol **6.21**. This key intermediate **(6.21)** contains olefins at *14E*, *20E* & *27E*. Crabtree's catalyst allows for selective reduction of *27E* while leaving *14E* & *20E* intact. Coupling of stereotriad **5.48** to macrolactone **6.10** would afford triene **6.22**. Triene **6.22** has an azidopivalate ester at the C29 position. The azidopivalate is the precursor to the desired dimethylamino pivalate **6.23**. Unfortunately the presence of the azido ester eliminates the option of selective hydrogenation with Crabtree's catalyst. These facts eliminate Scheme 6.1 as a viable option.

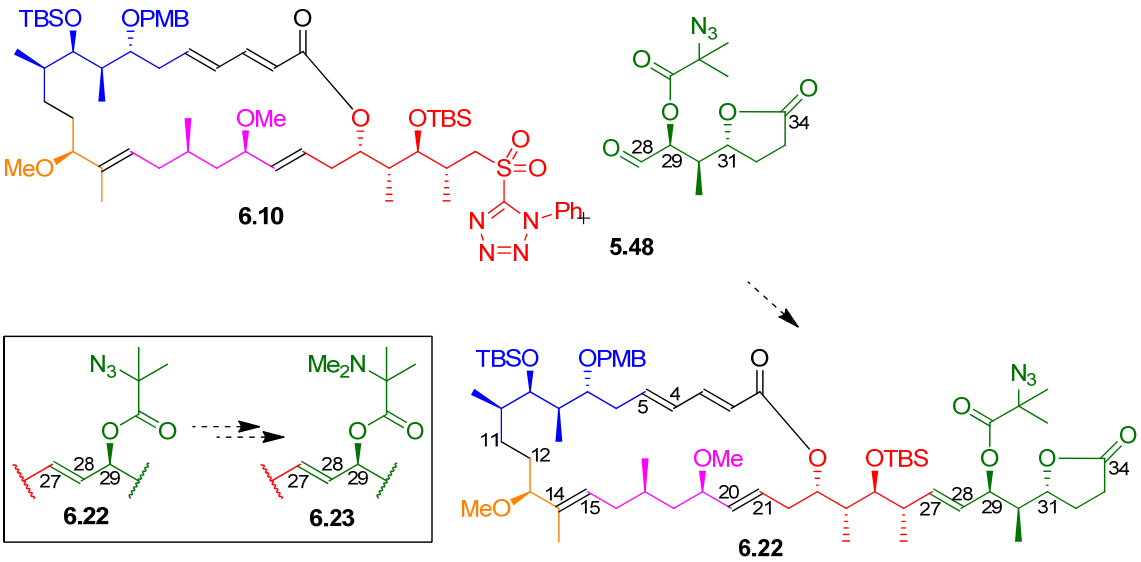


Figure 6.2: Repercussions of C29 Azidopivalate Stereotriad.

Constructing the C21-C34 Fragment

As previously discussed, the fulcrum of synthetic rationale for the entire coupling order of the aplyronine core target hinged upon there being an alcohol available at the allylic position (C29) to allow for a directed iridium catalyzed Crabtree hydrogenation in the presence of olefins at *14E* & *20E* to furnish the single bond at C27-C28 without disturbing the spectator olefins **(6.22)**. Previously discussed limitations with the green C28-C34 fragment ultimately didn't allow for the Crabtree favorable landscape to be put into place. The most expedient remedy would involve coupling red C21-C27 fragment **6.24** to C28-C34 green stereotriad **5.48** by way of traditional olefination methodologies followed by hydrogenation of the resulting olefin **6.26**.

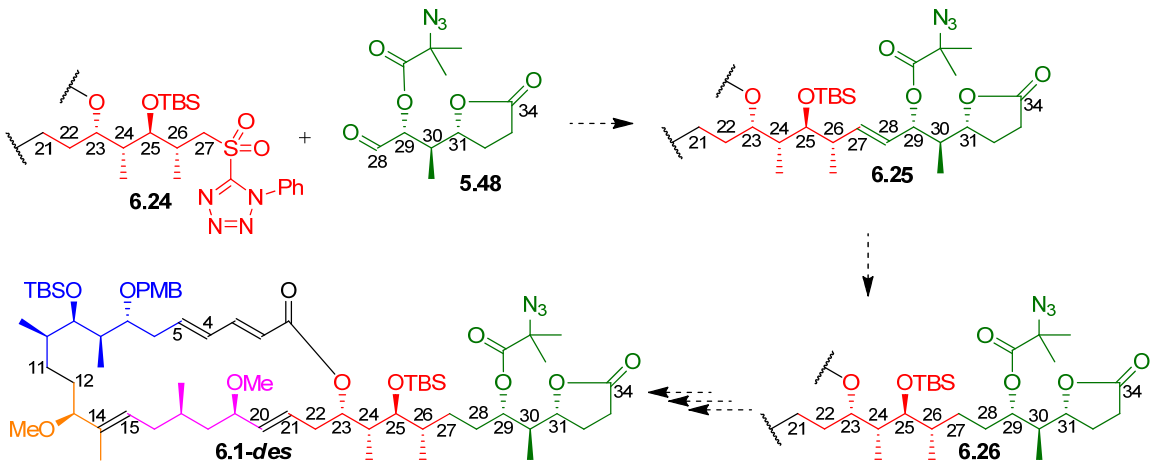
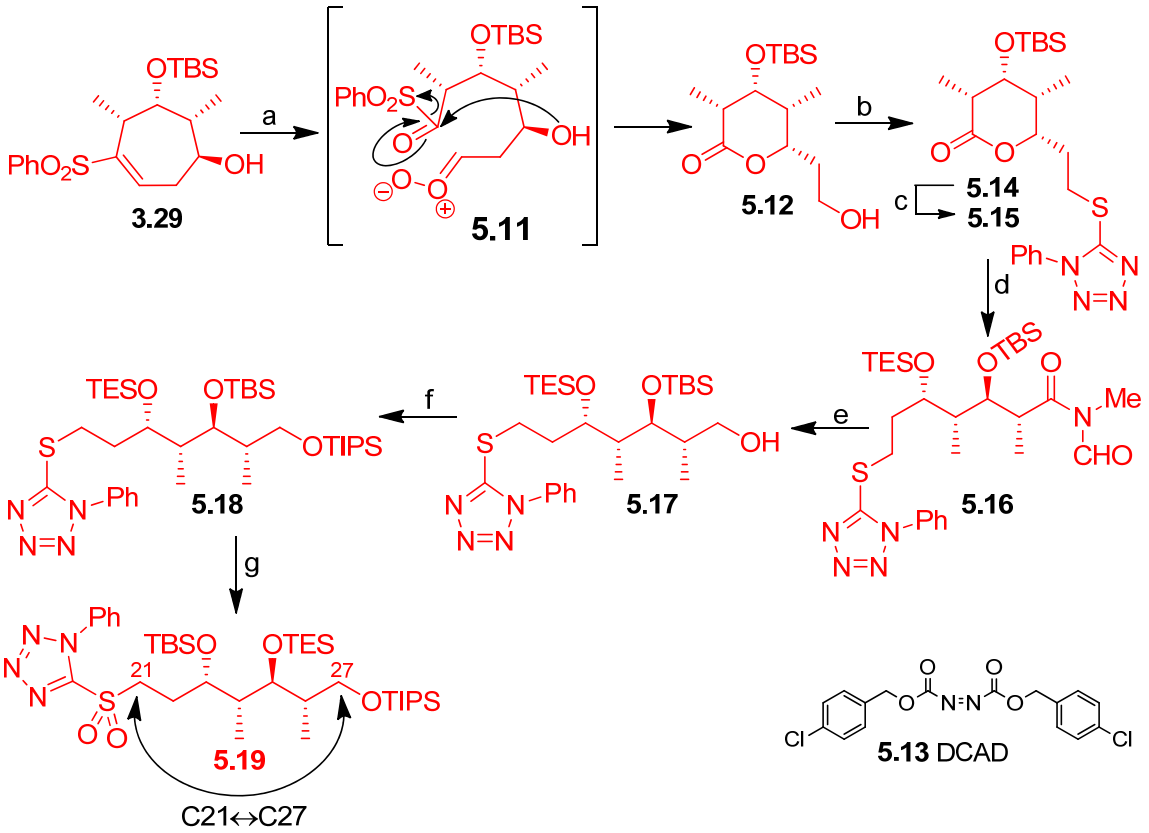


Figure 6.3: Constructing the C21-C34 Fragment

Utilization of the vinylsulfone polypropionate methodology to assemble the aplyronine core reveals the importance of red C21-C27 fragment **6.24** as the key to accessing macrolactone **6.1-*des***. Fragment **6.24** is undefined at C21 and the

C23 oxygen. To complete construction of the aplyronine core the C21 & C23 positions of **6.24** must be defined in such a way so as to allow olefination/reduction at the C27 position prior to installation of the C21 olefin. The prevailing methodology used to construct the linear red stereotetrad **5.19** (Schemes 3.4 & 6.3) does not allow this (Figure 6.3).



(a) (i) O_3, $NaHCO_3$, EtOAc (ii) BH_3, t-$BuNH_2$ 65%, 2 steps; (b) DCAD, PPh_3,1-phenyltetrazole-5-thiol 84%; (c) MeONHMe, iPrMgCl, 80%; (d) TESOTf, quant; (e) (i) DIBAL (ii) BH_3 t-$BuNH_2$ 90%; (f) TIPSOTf, 2,6-lutidine 88%; (g) MCPBA, $NaHCO_3$ 71%

Scheme 6.3 (= 5.3): Synthesis of the C21-C27 Segment

A cursory examination of **5.19** shows that the nature of the functional groups on C21 & C27 must be inverted to allow the C27-C28 olefin to be formed **(6.25)** and reduced **(6.26)** prior to construction of the aplyronine core.. Compounds **3.29**, **5.12**, & **5.17** can be important intermediates for the achievement of a fully functionalized **6.24** fragment. An analysis and exploration of efforts to construct a favorable linear C21-C27 fragment follows.

6.3: A Reexamination of the C21-C27 Fragment

Re-examination of the red fragment began with consideration of the existing inventory of red stereotetrad linear intermediates (Figure 6.4). The Hong archive contained intermediates directed towards linear stereotetrad **5.19**. The available compounds offered flexibility with respect to the construction of **6.24**.

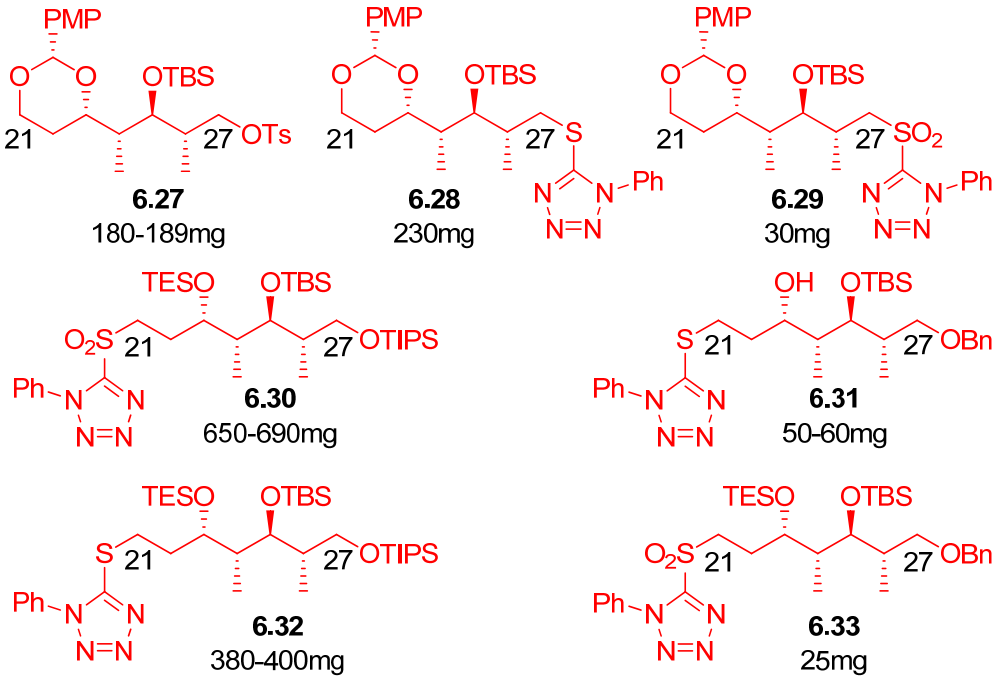
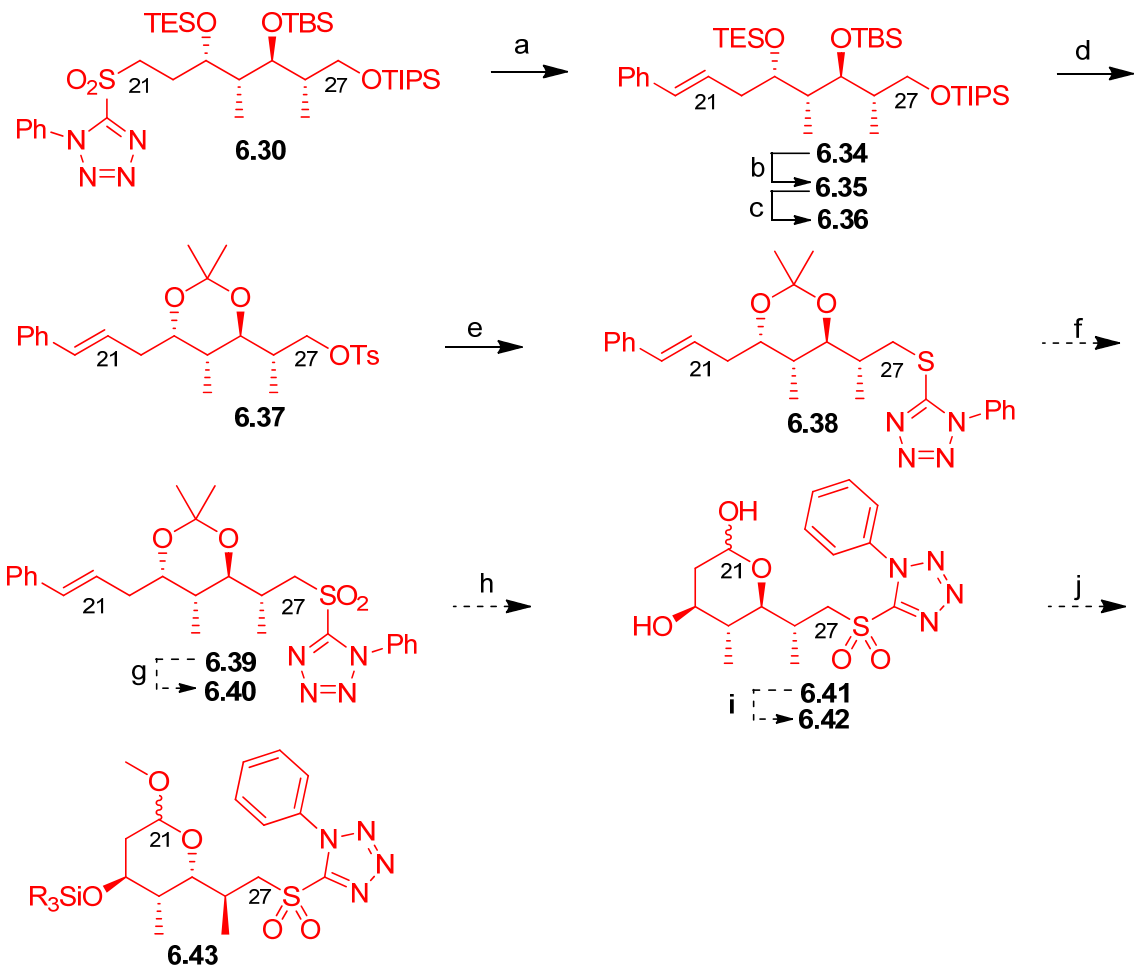


Figure 6.4: Linear C21-C27 Stereotetrad Intermediates

The structures shown in **Figure 6.4** show a definite bias in favor of Julia-Kocienski precursors. **6.28** and **6.29** contain phenyltetrazole (PT) sulfide and phenyltetrazole (PT) sulfone respectively at the favored C27 position. **6.30** and **6.33** have phenyltetrazole (PT) sulfone functionalities at C21, which is very unfavorable. **6.31** and **6.32** have phenyltetrazole (PT) functionalities at C21 which may act as both olefination activators as well as transient protecting groups. C21 and C23 of substrates **6.28**, **6.29** and **6.30** are protected as *para*-methoxybenzylidine, providing the possibility of differentiation between C21 and C23 upon deprotection. C27 of **6.30** and **6.32** are capped with a triisopropyl silyl ether, utilized to differentiate existing *t*-butyldimethyl and triethylsilyl ethers. Initial

investigation explored the efficacy of the intermediates in **Figure 6.4** for obtaining a practical linear C21-C27 stereotetrad.

The value of the compounds of **Figure 6.4** is self-evident. Therefore the first probe into procuring a useable C21-C27 linear section **(Scheme 6.3)** made use of the most abundant compound of the inventory, **6.30**. A model Julia-Kocienski reaction with benzaldehyde delivered styrene **6.34**. Global deprotection with catalytic *p*-toluenesulfonic acid (*p*-TsOH) afforded triol **6.35**. The crude triol was selectively tosylated at the C27 primary alcohol with 1.1 equivalents of tosyl chloride **(6.36)**. Treatment of **6.36** with *p*-TsOH in acetone delivers acetonide **6.37** in quantitative yield. Reaction of **6.37** with 1-phenyl-5-mercaptotetrazole in acetone at reflux delivered PT sulfide **6.38** in quantitative yield. Multiple attempts at oxidation of sulfide **6.38** with ammonium molybdate simply returned starting material. Time constraints, the small quantity of **6.30**, and possible need for optimization, contributed to the abandonment of this pathway. Compound **6.39** was to be oxidized to sulfone **6.40**, and after treatment with *p*-TsOH to give diol **6.40**. Ozonolysis of **6.40** would likely have delivered lactol **6.41**. Formation of ketal **6.42**, should be effected with catalytic sulfuric acid in methanol followed by silylether formation to have given **6.43**.

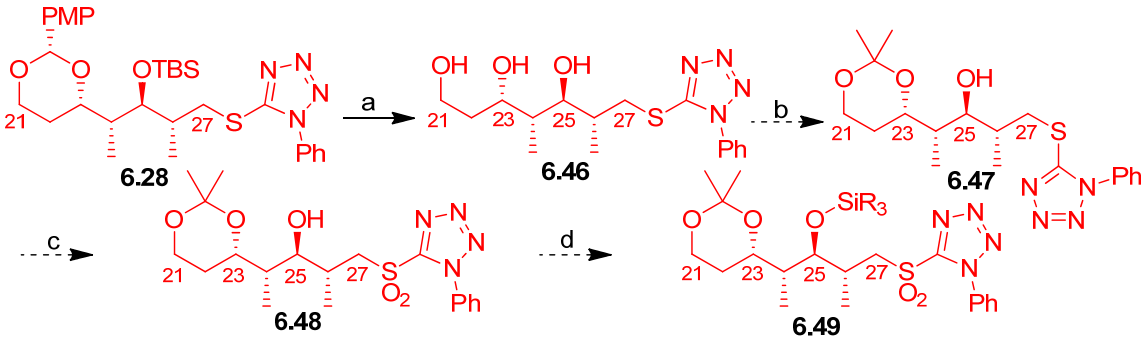


(a) PhCHO, NaHMDS, -78 °C,THF, 4hr, 71.7 %; (b) p-toluenesulfonic acid, MeOH, 86%; (c) tosyl chloride (1.1 eq), pyr, 18 hrs, rt, 87%; (d) p-toluenesulfonic acid, Acetone, 100%; (e) 1-Phenyl-5-mercaptotetrazole, K_2CO_3, acetone, reflux , 100%; (f) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, rt; (g) p-toluenesulfonic acid (2 eq), 4h, THF: H_2O, reflux; (h) O_3, DCM, MeOH, $NaHCO_3$, -78 °C; (i) H_2SO_4 (0.01%), MeOH; (j) R_3Si, 1H-Imidizole, DMAP (cat), DMF, rt→0 °C

Scheme 6.4: Transmutation of C21 Phenyltetrazole Sulfide 6.30

Compound **6.28** was a promising intermediate for the stated goals. C27 possesses the desired sulfide, and C21 is incorporated in the benzylidine. Cerium ammonium nitrate (CAN) gives triol **6.46**. Acetone with *p*-TsOH would deliver acetonide **6.47**. Ammonium molybdate oxidation should afford sulfone

6.48 followed by silylether formation **(6.49)** to protect the C25 hydroxyl. Unfortunately there was only 230 mg of **6.28** remaining in inventory and subjecting such a small amount of valuable material to a 4-step sequence was deemed impractical due to time constraints (Scheme 6.4).

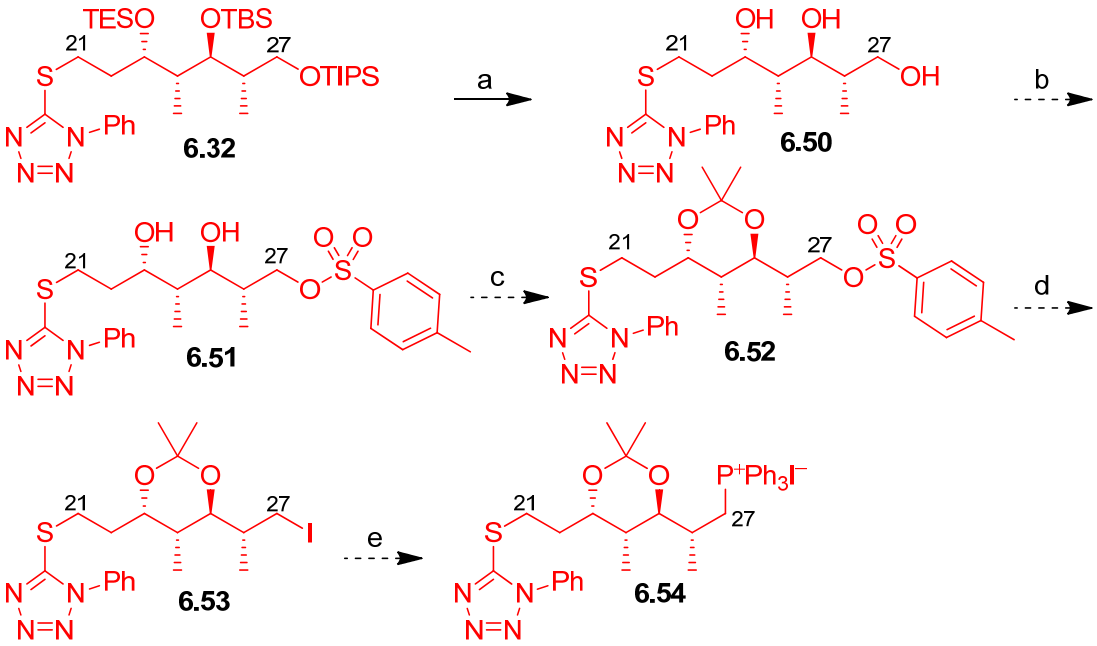


(a) $(\underline{NH_4})_2Ce(NO_3)_6$, MeCN:$H_2O$ (9:1), rt; (b) $MePhSO_3H$, Acetone (c) $(NH_4)_6Mo_7O_{24}$, H_2O_2, EtOH, rt; (d) R_3SiCl, NR_3, DCM, rt

Figure 6.5: Expediency of Sulfide 6.28

Sulfide **6.32** (Figure 6.6) offers a unique opportunity to achieve a viable C21-C27 linear vinylsulfone fragment. The phenyltetrazole sulfide may act as a dormant functional group while the C27 can be transformed into a useable cross-coupling moiety. It is also a natural intermediate with respect to the prevailing methodology (Schemes 3.4 and 5.3) so examination would provide valuable information. It is worthy of note that triisopropylsilyl (TIPS) ether was very resilient to cleavage. A global deprotection to triol **(6.50)** was required to remove it, thus its use would have to be avoided in the future. Selective tosylation of 1° alcohol at the C27 position would afford **6.51**. Acetone and *p*-TsOH should yield

acetonide **6.52.** Finkelstein conditions would produce iodide **6.53**. Phosphonium iodide **6.54** can then undergo the Wittig olefination with **5.48** to obtain a C21-C34 *27Z* olefin.

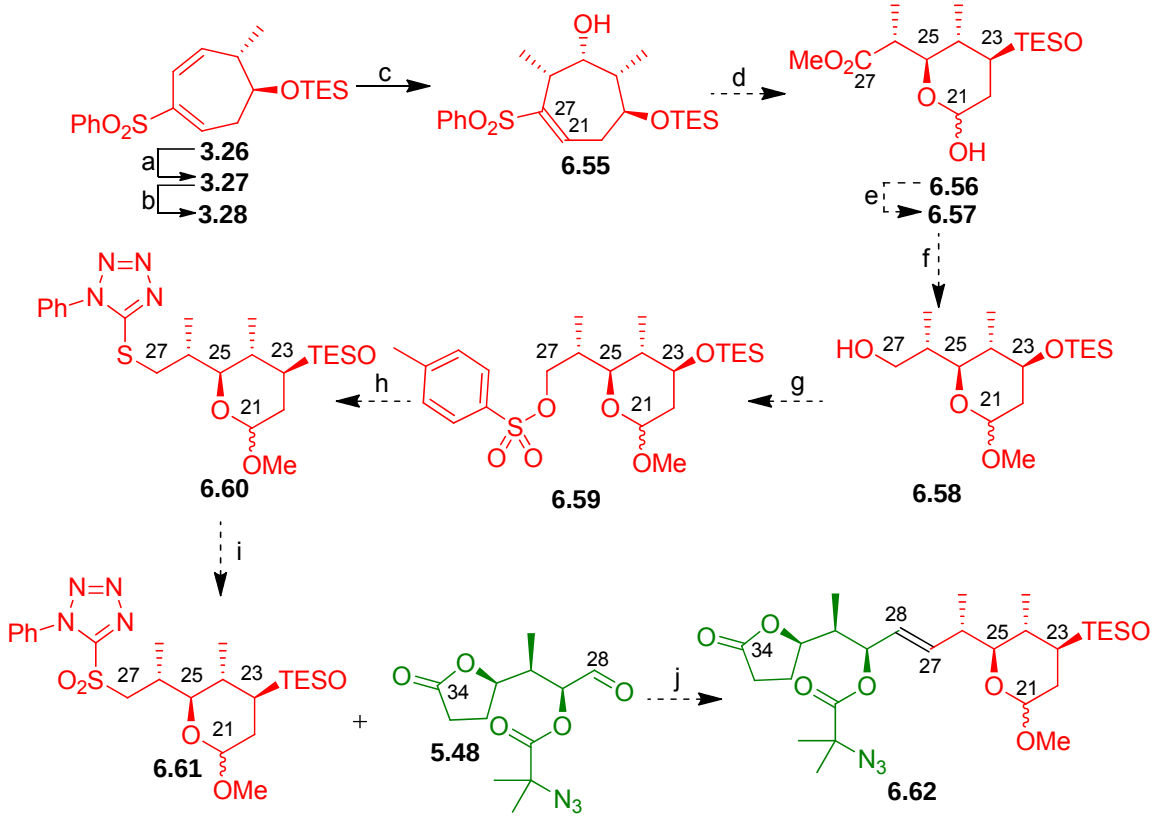


(a) *p*-TsOH, MeOH; (b) tosyl chloride , C_5H_5N; (c) acetone, *p*-TsOH; (d) NaI, acetone, reflux → rt; (e) $NaHCO_3$, MeCN, PPh_3, 8 h, reflux

Figure 6.6: Versatility of Sulfide 6.32

While the highly intricate fragments provided by Hong were not themselves utilized to provide the desired C21-C27 motif, they provided direction to future investigation, and proffered information as to the limitations of the prevailing methodology.

6.4: Further Evaluation Of C21-C27 Strategies



(a) *(S, S)*-Jacobsen, 4-PPPy, $NaClO_3$, NaH_2PO_3, pH=9; (b) 3,5-DMP, 50→ -60 °C, PhMe, 1hr; (c) MeMgBr, Tol. 50 °C→ 52 °C; (d) O_3, $NaHCO_3$, DCM, MeOH, -78 °C, 10 m; (e) KHMDS, 18-Crown-6, MeI, THF, -78°C; (f) $LiAlH_4$, Et_2O or DiBAL-H; (g) TsCl, pyr., rt, 24 hrs; (h) PTS, K_2CO_3, Me_2CO, reflux; (i) Ox, TBA (j) NaHMDS, THF

Scheme 6.5: Protecting Group Inversion Strategy

The Hong archive contained 14 grams of dienyl diad **3.26**. Cyclic vinylsulfone stereotetrad **6.55** was prepared as described in Scheme 3.4 without treatment with *t*-butyldimethylsilyl triflate and camphor sulfonic acid in the final

steps. Ozonolysis of **6.55** would produce lactone **6.56** and on subsequent treatment with potassium hexamethyldisilazide and methyl iodide generate ketal **6.57**. The methyl ester of **6.57** can be reduced to alcohol **6.58** and upon treatment with tosyl chloride in pyridine provide tosylate **6.59**. Displacement of the **6.59** tosylate with phenyltetrazole thione affords sulfide **6.60;** oxidation to sulfone would give sulfone **6.61**. Finally a Julia-Kocienski olefination between **6.61** and **5.48** would give the valuable C21-C34 olefin **6.62**. The overall strategy illustrated in Scheme 6.5 has become a working foundation for obtaining the C21-C34 fragment.

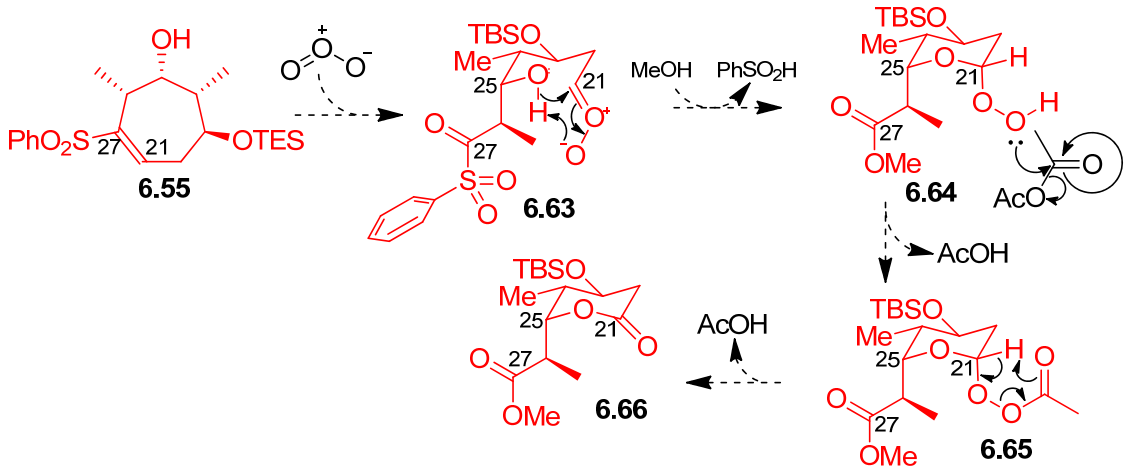


Figure 6.7: Schreiber Ozonolysis Strategy

A variant of the traditional route could involve the innovation by Schreiber[14,15] of using acetic anhydride in the workup of the termini differentiated ozonolysis intermediates. Decomposition of the molozide of **6.55** delivers

Criegee zwitterion[16] **6.63** which is reduced to hydroperoxide **6.64**. Treatment of **6.64** with acetic anhydride affords lactone **6.66** *via* perester **6.65**. This tactic would install the functionality at C27 needed to enable the coupling of C21-C27 and C28-C34 fragments.

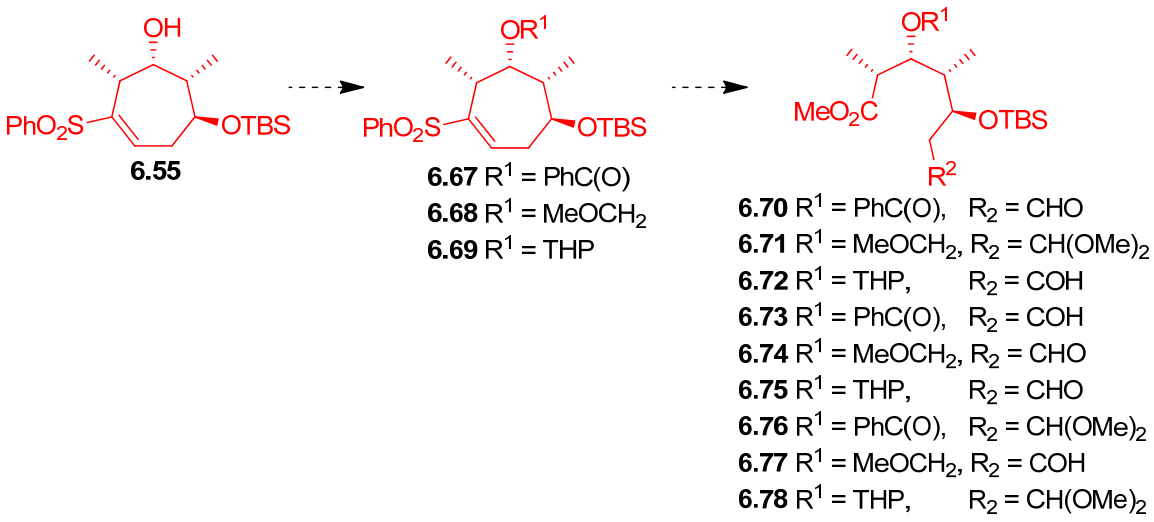
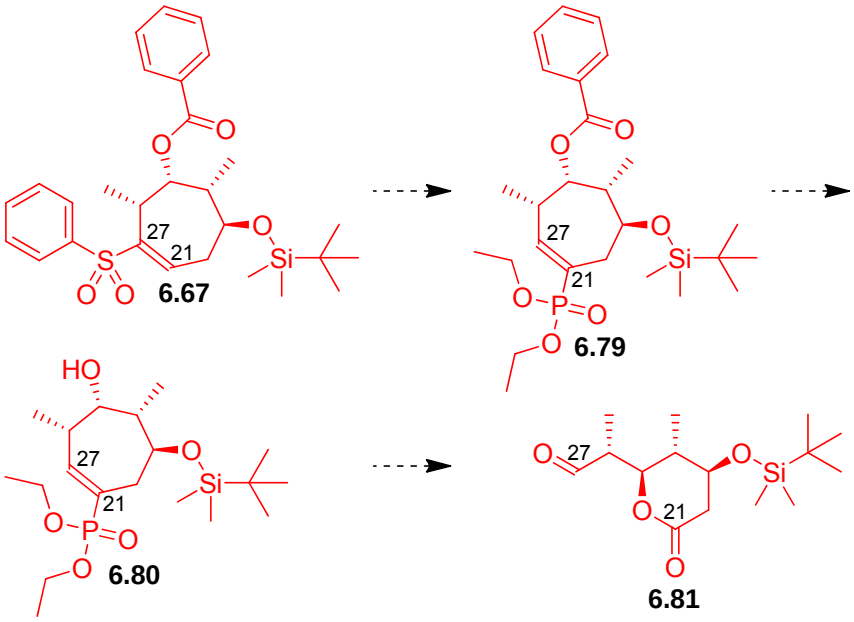


Figure 6.8: Ozonolysis Of Diprotected Cyclic Vinylsulfone

A little explored strategy, is ozonolysis of the diprotected cyclic vinylsulfone stereotetrads. From a strategic standpoint, the C23 and C25 hydroxy groups must be differentiated so the desired macrolactone core can be constructed. Under established methodology **5.19** achieved differentiation with a triethylsilyl ether on C23 and t-butyldimethylsilyl ether on C25, **5.19** is formed via lactone **5.12**. Protection of C23 as the benzylester **(6.67)**, methoxymethyl ether **(6.68)**, or THP **(6.69)** should prevent interference of the multifunctional substrate

with the ozonolysis. Work-up with BH_3•t–$BuNH_2$ procures alcohols **6.72**, **6.73**, and **6.77**. Dimethylsulfide work-up, should give aldehydes **6.70**, **6.74**, and **6.75**. Treatment of these aldehydes with *p*-TsOH, in methanol would deliver ketals **6.71**, **6.76** and **6.78**. These post-ozonolysis termini differentiated fragments could provide a solid foundation from which to achieve coupling of C21-C27 and C28-C34 fragments that allow differentiation between the C23 and C25 alcohols.

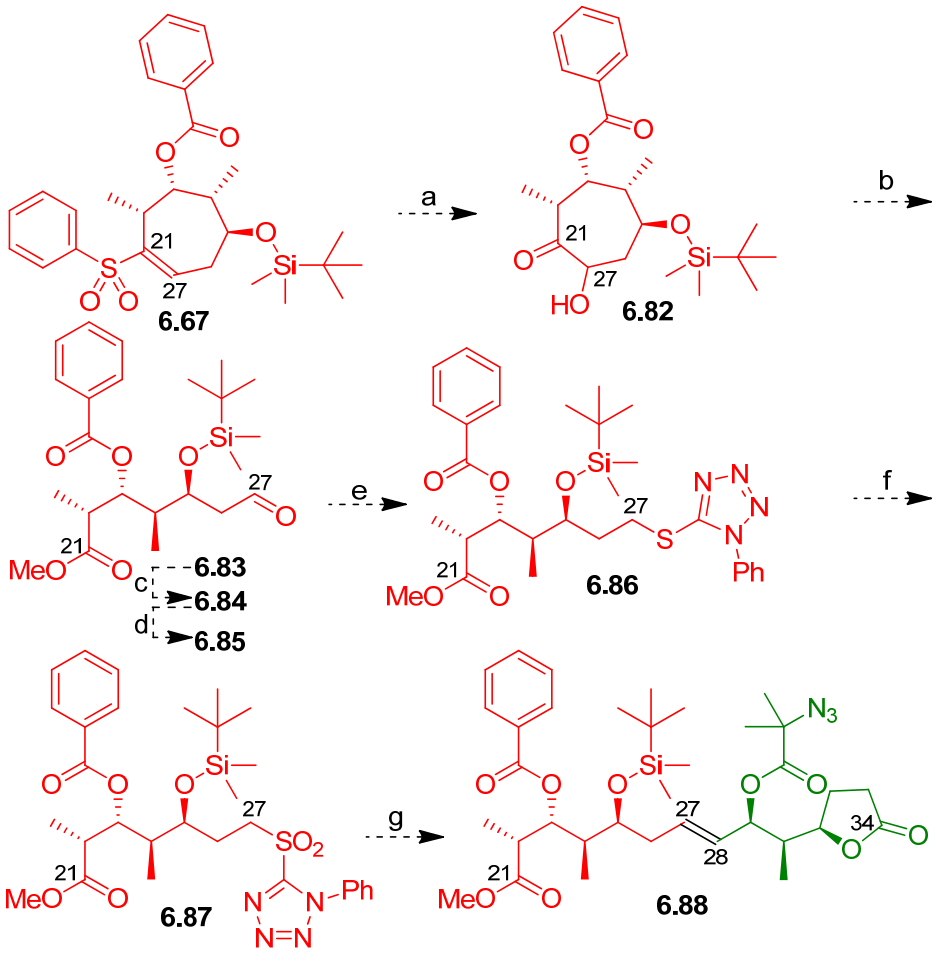


(a) NaHMDS, $((EtO)_2HPO)$, THF; (b) NH_3, MeOH, 24 hr, rt; (c) (i) O_3, AcOEt, $NaHCO_3$; (ii) MeOH; (iii) Me_2S.

Figure 6.8: Transposed Vinyl Phosphate Strategy

Transposition of the vinylsulfone to the vinyphosphonate was optimized by Noshi,[3,5] and ozonolysis of the vinyphosphonate explored by DuJardin.[17] The diprotected cyclic stereotetrad **6.67** is subjected to NaHMDS, $((EtO)_2HPO)$, THF

to obtain transposed vinyphosphonate **6.79**. Cleavage of the benzylester using a solution of methanol saturated with ammonia,[18] would give alcohol **6.80**. Ozonolysis of **6.80** can then furnish desired lactone **6.81**.



(a) NMO, 1.1 eq.,OsO_4 cat., H_2O/t-BuOH, 1:1,citric acid, 25 mol %; (b) (i) $Pb(OAc)_4$, MeOH (ii) $NaHCO_3$, Me_2CO, 14 h, reflux; (c) DiBAL-H; (d) TsCl, pyr., rt, 24 hrs; (e) PhTezSH, K_2CO_3, Me_2CO, reflux; (f) Oxone, MeOH, 2 d, rt; (g) **5.48**, NaHMDS, THF

Figure 6.10: Osmylation And Acyloin Cleavage Strategy

Diprotected cyclic vinylsulfone **6.67** could also be subjected to Sharpless osmylation conditions.[19] Acyloin **6.82** can then undergo oxidative cleavage on

exposure to lead (IV) acetate in methanol to potentially furnish linear termini differentiated C21-C27 fragment **6.83**.

Reduction of **6.83** to terminal alcohol **6.84** followed by tosylation to **6.85** allows installation of terminal phenyltetrazole sulfide **6.86**. Oxidation of **6.86** to sulfone **6.87**[20] now allows for coupling via Julia-Kocienski conditions[8] to afford C21-C34 27Z olefin **6.88**.

Of great interest was the concept of a self-immolating protecting group. The azidopivalate utilized as a precursor for the dimethylamino ester at C32 shows potential self-immolative potential.

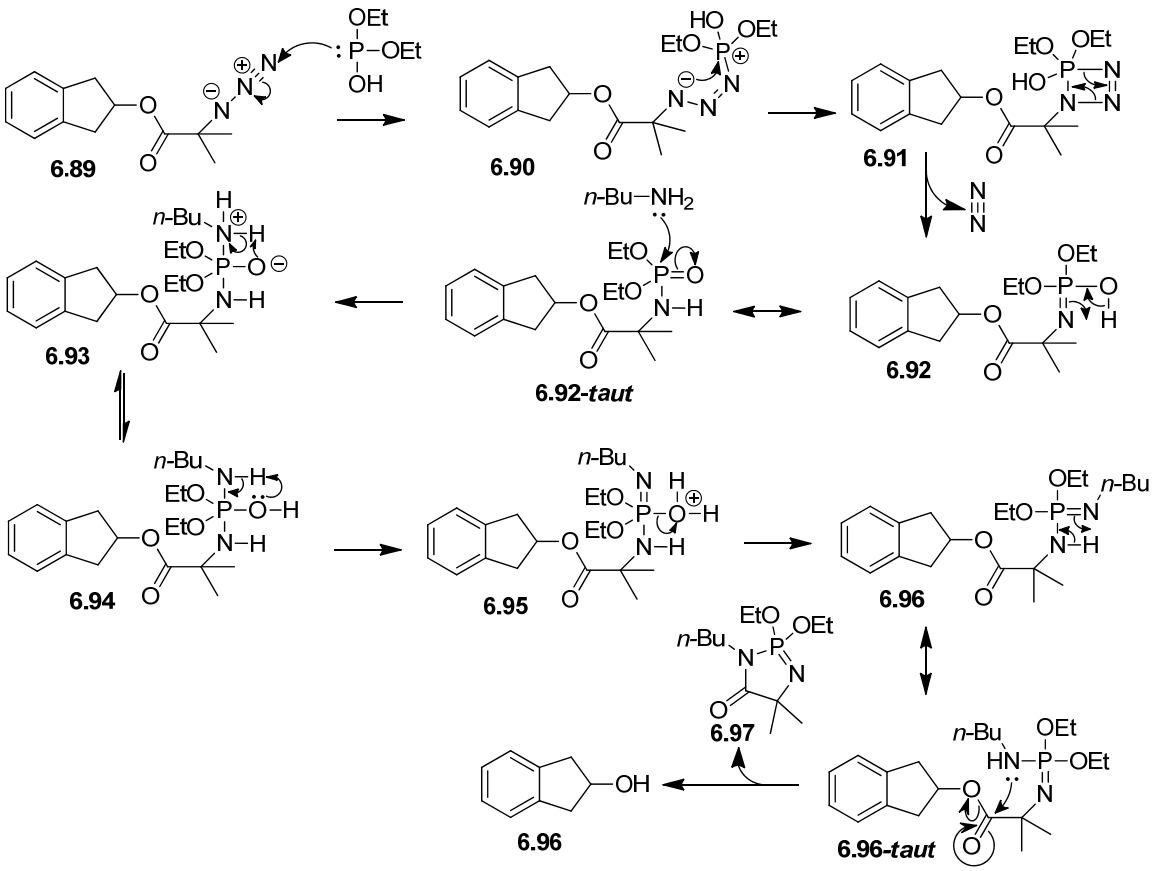
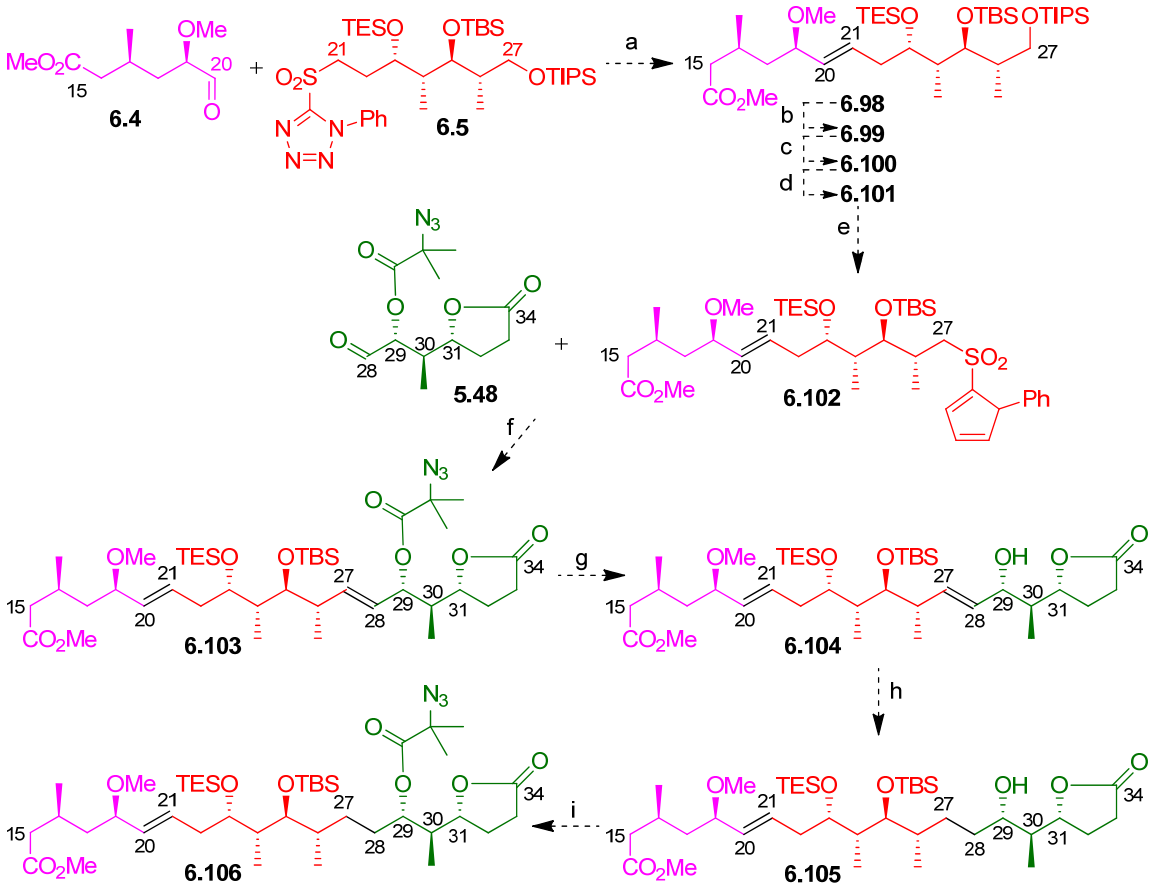


Figure 6.11: Azidopivalate As A Self-Immolating Protecting Group

This concept was initially explored on indane azidopivalate ester **6.89** (Figure 6.11). Using Staudinger conditions with diethylphosphite, rather than the traditional triphenylphosphine. Reduction of azide **6.89** by diethylphosphite leads to intermediate **6.91** via **6.90**. Cyclic intermediate **6.91** decomposes to nitrogen and **6.92**. The tautomer of **6.92** (**6.92-*taut***) undergoes addition with *n*-butylamine to afford **6.96**; via **6.93**, **6.94** and **6.95**. Tautomerization of **6.96** to **6.96-*taut*** would be expected to decompose to alcohol **6.96** and **6.97**.



(a) LiHMDS (1M THF), DMF/ HMPA (4:1) 60% (83% brsm) 12:1; (b) $Bu_4N^+ \cdot F^-$, THF, AcOH (c) TsCl, pyr., rt, 24 hrs; (d) PhTezSH, K_2CO_3, Me_2CO, reflux; (e) Oxone, MeOH, 2 d, rt; (f) NaHMDS, THF (g) $HP(OEt)_2$, n-$BuNH_2$, base (h) $[Ir(cod)(PCy_3)(py)]PF_6$, H_2, CH_2Cl_2, 18 h, rt; (i) **4.83**, $(COCl)_2$, DMF, DMAP,TEA

Figure 6.12: Self-Immolative Azidopivalate Ester Strategy

The self-immolative potential of the C32 azidopivalate moiety could be exploited so as to allow utilization of the original aplyronine core assembly strategy (Scheme 6.1). Coupling fragments **6.4** and **6.5** with Julia-Kocienski conditions was shown by Hong[4] to give olefin **6.98**. Selective deprotection[21] of the primary triisopropylsilyl ether may furnish primary alcohol **6.99**. Tosylation **(6.100)**, sulfide formation **(6.101)**, then oxidation would give sulfone **6.102**. A

second Julia-Kocienski coupling with **5.48** can deliver C15-C34 diolefin fragment **6.103** which could undergo self-immolation at the C32 azidopivalate to give allylic alcohol **6.104**. Regioselective hydrogenation using Crabtree's $[Ir(cod)(PCy_3)(py)]PF_6$ catalyst would give mono-olefin **6.105**. Re-esterification of **6.105** with the *in situ* acid chloride of azido acid would produce the target olefin azidopivalate **6.106**.

Application of the vinylsulfone polypropionate methodology to the construction of the aplyronine defined its limitations. An illustration of this is shown in the osmylation of the vinylsulfone. The addition of citric acid to the Upjohn osmylation conditions, increased the versatility of vinylsulfone methodology. The structure of the aplyronine core allows the question of synthetic strategy to be answered. This was illustrated in the difficulty of dealing with the order of coupling between the C15-C20, C21-C27 and C28-C34 linear fragments. The structural requirements of the aplyronine core, lend themselves to a number of synthetic strategies for assembling the C15-C34 fragment. The richly-functionalized nature of the desired fragments forces analysis from multiple angles, as seen with C28-C34 stereotriad **5.48** and illustrated in Figure 4.5. Exploration of vinylsulfone chemistry was begun by the Fuchs research group in 1978[22-25] and after 35 years of investigation, vinylsulfone methodologies continue to evolve.

6.5 References

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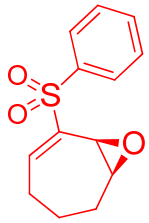
APPENDICES

Appendix A: Experimental

General Procedures

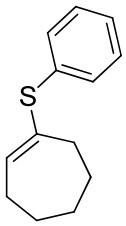
All reagents purchased were used as received. Tetrahydrofuran (THF) and diethyl ether were distilled from benzophenone ketyl. Benzene, toluene, and methylene chloride (CH_2Cl_2) were distilled from calcium hydride. Acetonitrile (CH_3CN) and methanol were spectra-grade. Sodium sulfate (Na_2SO_4) was anhydrous. All recrystallization, chromatographic, and workup solvents were reagent grade. Progress of reactions was monitored by thin layer chromatography (TLC) using silica gel 60 F-254 plates (EM reagents, 0.25 mm). The TLC plates were visualized with a UV lamp (254 nm) and/or with TLC visualizing solutions activated with heat. The two commonly employed TLC visualizing solutions were: (i) *p*-anisaldehyde solution (1350 mL absolute ethanol, 50 mL concentrated H_2SO_4, 37 mL *p*-anisaldehyde), and (ii) permanganate solution (weight percents of 1% $KMnO_4$ and 2% Na_2CO_3 in water). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Inova 300 (300 MHz), Bruker DRX 500 (500 MHz), Varian Inova 600 (600 MHz), Bruker AV 800 (800 MHz). NMR spectra were determined in chloroform-d_1 ($CDCl_3$), dimethylsulfoxide (DMSO-d_6), benzene-d_6 (C_6D_6) or acetone-d_6 solution and reported in parts per million (ppm) from the residual chloroform (7.27 ppm and 77.0 ppm), DMSO (2.50ppm and 39.52ppm), benzene (7.16 ppm and 128.0 ppm) and acetone (2.05 ppm and 29.9/ 206.7 ppm) standard respectively. Peak multiplicities in ^{1}H-NMR spectra, when reported, are abbreviated as s (singlet), d (doublet), t (triplet), q (quartet), p

(quintet), m (multiplet), ap (apparent), and br (broad). *Mass spectra were determined by the Purdue University campus wide mass spectrometry facility.*



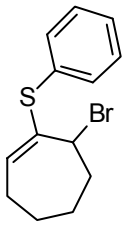
2.15 To a cooled 0 °C solution of 2-(phenylsulfonyl)cyclohepta-1,3-diene **3.5** (40 g, 171 mmol), Ammonium acetate (2.63 g, 34.1 mmol), and (R,R)-(-)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (1.627 g, 2.56 mmol) in MeOH (Ratio: 1.000, Volume: 285 mL) : DCM (Ratio: 1.000, Volume: 285 mL) was added pre-cooled aqueous hydrogen peroxide 30% (17.44 mL, 171 mmol) in four portions during 40 minutes. The mixture was stirred at 0 ºC and the reaction was monitored by TLC. After the reaction had reached completion, the mixture was diluted with ether and extra H_2O_2 was added to decompose any remaining catalyst, and transferred into a separatory funnel containing water. The organic layer was washed with water and brine. The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude material was used in the next step w/o further purification. The residue was analyzed by ^{1}H NMR and found to be highly pure, yielding (1S,7S)-2-(phenylsulfonyl)-8-oxabicyclo[5.1.0]oct-2-ene (38.0 g, 152 mmol, 89 % yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 – 7.86 (m, 2H), 7.64 – 7.55 (m, 1H), 7.55 – 7.49 (m, 2H), 7.37 (ddd, *J* = 7.5, 3.3, 1.3 Hz, 1H), 3.67 (dd,

J = 4.4, 1.3 Hz, 1H), 3.41 (td, *J* = 4.3, 2.6 Hz, 1H), 2.58 – 2.47 (m, 1H), 2.24 (ddt, *J* = 19.0, 9.4, 3.7 Hz, 1H), 2.15 – 1.97 (m, 2H), 1.67 – 1.54 (m, 2H).



3.2

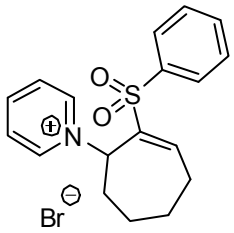
2-(Phenylsulfonyl)-1,3-cycloheptadiene (2.2): To a 12-L 3-neck round bottom flask equipped with a mechanical stirrer, heating mantle, Dean-Stark trap and condenser, were added cycloheptanone (1.0 kg, 8.92 mol), 1.05 equivalents benzenethiol (1.06 kg), and 10 wt% Montmorillonite KSF (100 g) in toluene (2.2 L) and refluxed for 24 hours. After the reaction, the resulting vinyl sulfide mixture was cooled to room temperature and then filtered through a Celite® (100 g) pad and the pad was washed with toluene (2.2 L). A sample of the toluene mixture was dried via spin-evaporation to an amber syrup. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.33 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.30 (dd, *J* = 8.6, 6.7 Hz, 2H), 7.22 – 7.19 (m, 1H), 6.17 (t, *J* = 6.6 Hz, 1H), 2.39 – 2.34 (m, 3H), 2.24 – 2.18 (m, 3H), 1.79 – 1.72 (m, 3H), 1.59 – 1.53 (m, 6H).



3.3

The solution was transferred to a 22-L 3-neck round bottom flask equipped with a mechanical stirrer, addition funnel, thermometer, and water bath, 1.0 equiv sodium bromide (918 g), 1.0 equiv 2 M H_3PO_4 solution (4.46 L), 0.01 equiv 1M aqueous $Na_2WO_4 \cdot 2H_2O$ (89 mL), and 0.01 equiv 1M aqueous $PhPO(OH)_2$ (89 mL) were added and stirred in the water bath for 30 minutes. With vigorous stirring, 1.0 equiv 30 wt% H_2O_2 (857 mL) was slowly added with the addition funnel for 3 hours. The reaction temperature was below 25 $^\circ$C and the bath temperature was in the range of 15 to

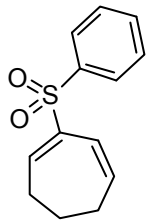
18 °C. After one more hour of stirring, the aqueous layer was removed, and the organic layer was washed with 2 M Na_2SO_3 (1 L) and 2 M H_3PO_4 (1 L) to give a crude mixture of **3.3**. To the solution of **3.3** was added 0.01 equiv 1M aqueous $Na_2WO_4 \cdot 2H_2O$ (89 mL), 0.01 equiv 1M aqueous $PhPO(OH)_2$ (89 mL), 0.01equiv PTC (0.5M solution in toluene, 180 mL) and stirred in the water bath for 30 minutes. 2.0 equiv 30 wt% H_2O_2 (1.7 L) was added slowly with an addition funnel for 2.5 hours. After stirring vigorously in the water bath for 15 hours, brine (1 L) was added and stirred for 1 minute. The aqueous layer was removed. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.49 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 3H), 7.30 (td, *J* = 7.5, 5.6 Hz, 3H), 7.22 (td, *J* = 7.0, 1.9 Hz, 1H), 6.42 (ddd, *J* = 8.2, 5.0, 1.2 Hz, 1H), 4.77 – 4.71 (m, 1H), 2.53 – 2.43 (m, 1H), 2.37 (dtd, *J* = 17.7, 7.7, 2.4 Hz, 1H), 2.29 (dddd, *J* = 16.1, 11.4, 4.9, 2.5 Hz, 1H), 2.17 – 2.06 (m, 2H), 1.97 (ddq, *J* = 13.1, 6.5, 3.2 Hz, 1H), 1.87 (ddd, *J* = 13.9, 6.8, 3.5 Hz, 1H), 1.82 (ddt, *J* = 14.8, 12.1, 3.0 Hz, 1H), 1.71 (qd, *J* = 5.7, 4.8, 1.9 Hz, 1H), 1.48 (dtt, *J* = 13.5, 10.8, 2.6 Hz, 1H).



3.4

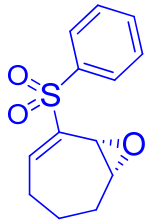
To the toluene solution of **3.3** were added 0.8 equivalents pyridine (580 mL) and water (8.92 L) and with stirring, heated from room temperature to 60 °C for 2 hours. After removal of the organic layer, the aqueous layer was washed with ethyl acetate (2 x 1 L) and then hexane (1 L) while the solution temperature maintained about 60 °C. To remove the insoluble solid, the warm aqueous layer was filtered through a small glass filter into a 22-L 3-neck round bottom flask, equipped with a mechanical stirrer. Cooling to room temperature gave a white

solid suspension of **3.4**. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.50 (d, *J* = 6.1 Hz, 2H), 8.40 (t, *J* = 7.7 Hz, 1H), 8.05 (t, *J* = 7.0 Hz, 2H), 7.91 (dd, *J* = 7.4, 5.4 Hz, 1H), 7.87 – 7.82 (m, 2H), 2.91 (ddt, *J* = 15.3, 10.0, 4.9 Hz, 1H), 2.84 – 2.70 (m, 2H), 2.28 (ddt, *J* = 14.7, 11.3, 3.4 Hz, 1H), 1.85 (dq, *J* = 12.7, 6.9, 5.6 Hz, 1H), 1.80 – 1.64 (m, 2H), 1.45 (ddd, *J* = 19.6, 8.7, 5.3 Hz, 1H).

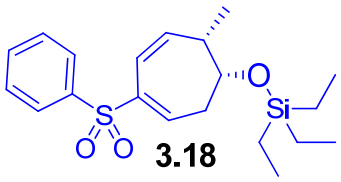


3.5

To the white solid suspension of **3.4** were added 0.1 wt% of seed crystals of **3.5** (1 g) and 0.7 equiv 1,4-diazabicyclo[2.2.2]octane (Dabco^{TM}, 701 g). After stirring for 36 hours at room temperature, 2 N HCl (4.0 L) was added, filtered through a large glass filter and rinsed with water (5 L). It was dried to content weight in a dying oven under vacuum at 40 °C to give a pure and white solid (**3.5**, 1.11 kg, 53% yield over 5 steps from cycloheptanone, 98% purity by HPLC). mp: 61-62 °C (lit. 57-58 °C); ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.92 – 7.87 (m, 2H), 7.66 – 7.60 (m, 1H), 7.55 (td, *J* = 7.7, 7.3, 1.4 Hz, 2H), 7.33 – 7.30 (m, 1H), 6.10 – 6.02 (m, 2H), 2.62 – 2.57 (m, 2H), 2.35 (qd, *J* = 5.1, 2.3 Hz, 2H), 1.92 – 1.85 (m, 2H).

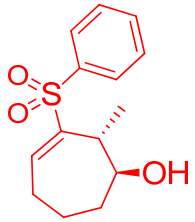


3.14 To a cooled 0 °C solution of 2-(phenylsulfonyl)cyclohepta-1,3-diene **3.5** (58 g, 248 mmol), Ammonium acetate (3.82 g, 49.5 mmol), and (S,S)-(+)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (3.93 g, 6.19 mmol) in MeOH (Ratio: 1.000, Volume: 413 mL) : DCM (Ratio: 1.000, Volume: 413 mL) was added pre-cooled aqueous hydrogen peroxide 30% (25.3 mL, 248 mmol) in four portions during 40 minutes. The mixture was stirred at 0 ºC and the reaction was monitored by TLC. After the reaction had reached completion, the mixture was diluted with DCM (Ratio: 1.000, Volume: 413 mL) and transferred into a separatory funnel containing water. The organic layer was washed with water and brine. The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude material was used in the next step without further purification. The residue was analyzed by ^{1}H NMR and found to be highly pure, yielding (1R,7R)-2-(phenylsulfonyl)-8-oxabicyclo[5.1.0]oct-2-ene (62.0 g, 248 mmol, 100 % yield) ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.93 – 7.88 (m, 2H), 7.62 (t, *J* = 7.4 Hz, 3H), 7.54 (t, *J* = 7.7 Hz, 2H), 7.41 – 7.37 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 1H), 3.69 (d, *J* = 4.3 Hz, 1H), 3.43 (td, *J* = 4.3, 2.4 Hz, 1H), 2.59 – 2.49 (m, 1H), 2.26 (ddt, *J* = 18.9, 9.9, 3.6 Hz, 1H), 2.12 (dddd, *J* = 14.9, 6.7, 4.1, 1.8 Hz, 3H), 2.08 – 2.00 (m, 2H), 1.61 (dtt, *J* = 14.7, 10.7, 3.6 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 1H).



3.18

A solution of crude triethyl((1R,2S)-2-methyl-5-(phenylthio)cyclohepta-3,5-dienyloxy)silane (5.38 g, 15.52 mmol) in toluene, (155 mL) was stirred under air to give a brown solution. Sequential addition of Sodium tungstate dihydrate (0.310 mL, 0.310 mmol), phenylphosphonic acid (0.310 mL, 0.310 mmol), methyltrioctylammonium hydrogen sulfate (0.621 mL, 0.310 mmol), and hydrogen peroxide 30% (3.17 mL, 31.0 mmol), was followed by vigorous stirring at 25 °C. After 4 hr the reaction was judged complete by TLC and the mixture was transferred to a separatory funnel, brine (200 mL) was added. The aqueous layer was extracted with ether (2×100 mL) and the combined organic layers were washed with saturated Na_2SO_3 solution, dried over Na_2SO_4 and concentrated via rotary evaporation to give triethyl((1R,2S)-2-methyl-5-(phenylsulfonyl)cyclohepta-3,5-dienyloxy)silane (4.93 g, 13.0 mmol, 84 % yield) as a light yellow viscous oil Use appropriate number of sig figs throughout. This material was used in the next step w/o further purification. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.85 – 7.82 (m, 2H), 7.60 – 7.56 (m, 1H), 7.50 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.07 (ddd, *J* = 6.4, 4.9, 1.4 Hz, 1H), 6.00 (d, *J* = 11.8 Hz, 1H), 5.90 (dd, *J* = 11.8, 6.5 Hz, 1H), 4.05 (ddd, *J* = 8.8, 4.3, 3.1 Hz, 1H), 3.40 (dt, *J* = 11.0, 3.3 Hz, 0H), 2.69 – 2.55 (m, 3H), 2.42 (qd, *J* = 7.9, 5.5 Hz, 1H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.55 (q, *J* = 7.9 Hz, 6H).

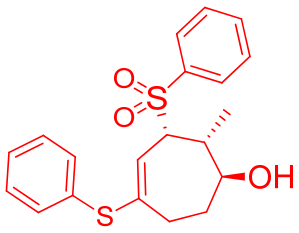


3.22

A solution of trimethylaluminum 25% in hexanes (40.3 mL, 101 mmol) in dry methylene chloride (105 mL) was cooled to -20 ^{o}C for 30 minutes then water (0.311 mL, 17.28 mmol) was very carefully added dropwise over 30 minutes. The dry ice bath was removed and the reaction stirred for 1h. Solid (1S,7S)-2-(phenylsulfonyl)-8-oxabicyclo[5.1.0]oct-2-ene **(2.5)** (7.21 g, 28.8 mmol) was added in portions and the reaction was stirred at 25 °C for 40 minutes. Reaction was checked for completion using TLC (50% ethyl acetate/hexanes) then the reaction mixture was cooled again to -40 °C for 30 minutes. Upon completion the contents were carefully poured into excess HCl $_{(aq)}$/ crushed ice mixture and allowed to warm to room temperature. The organic phase was separated, washed with brine (1 L), dried over Na_2SO_4, and then was concentrated via rotary evaporation to afford crude yellowish oil (*dr* 10:1). Purification by flash column chromatography (20% ethyl acetate/hexanes) afforded (1S,2R)-2-methyl-3-(phenylsulfonyl)cyclohept-3-enol (7.59 g, 27.1 mmol, 94 % yield) as a colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.90 – 7.84 (m, 2H), 7.62 – 7.57 (m, 1H), 7.55 – 7.49 (m, 2H), 7.34 (ddd, *J* = 9.6, 4.1, 1.3 Hz, 1H), 3.79 (qd, *J* = 4.9, 1.9 Hz, 1H), 2.94 – 2.84 (m, 1H), 2.50 – 2.40 (m, 1H), 2.24 (dddd, *J* = 15.7, 12.8, 4.2, 2.7 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.87 – 1.78 (m, 1H), 1.75 – 1.65 (m, 1H), 1.57 – 1.46 (m, 2H), 1.22 (d, *J* = 13.8 Hz, 1H), 0.88

(d, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.96, 142.26, 138.70, 133.18, 128.99, 128.33, 69.38, 39.70, 31.33, 27.33, 18.20, 15.37.

show stereo of sulfone below

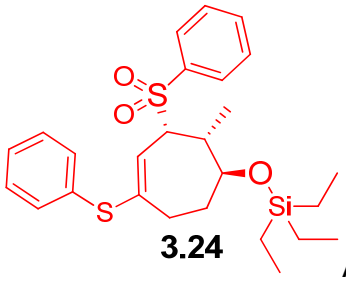


3.23

A solution of (1S,2R)-2-methyl-3-(phenylsulfonyl)cyclohept-3-enol (10.07 g, 37.8 mmol) in THF (95 mL) was cooled to -78 °C for 30 min then sodium bis(trimethylsilyl)amide, (60.5 mL, 121 mmol) was added dropwise over 10 minutes to give a clear yellow solution that eventually turns into deep red clear solution. The dry ice bath was removed and the mixture was stirred at 25 °C for 4 hr to give a bright orange suspension. Reaction is checked for complete dianion formation using TLC (50% ethyl acetate/hexane). Phenyl disulfide (8.25 g, 37.8 mmol) was added as a solid at 25 °C to the reaction mixture where the orange suspension dissolves and reforms immediately. After stirring for 1 hr, reaction was quenched with aqueous hydrochloric acid (182 mL, 250 mmol) and diluted with ether (182 mL, 1750 mmol). After discarding aqueous phase, hydrochloric acid (182 mL, 250 mmol) was added and the mixture was stirred for 1 hr. After discarding aqueous phase the organic phase was separated, washed with brine, and dried over Na_2SO_4 for 2h. Concentration of the organic phase via rotary evaporation afforded (1S,2R)-2-methyl-3-(phenylsulfonyl)-5-

(phenylthio)cyclohept-4-enol (14.16 g, 37.8 mmol, 100 % yield) as a brown oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 7.7 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.34 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.27 (dd, *J* = 6.7, 2.7 Hz, 2H), 5.31 (d, *J* = 6.1 Hz, 1H), 4.52 (d, *J* = 6.1 Hz, 1H), 3.93 (q, *J* = 3.6 Hz, 1H), 2.77 (dd, *J* = 15.8, 12.8 Hz, 1H), 2.69 – 2.61 (m, 1H), 1.78 – 1.69 (m, 2H), 1.59 (dt, *J* = 14.9, 5.0 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.79, 138.64, 133.81, 133.42, 131.66, 129.30, 129.00, 128.56, 128.42, 116.68, 72.49, 62.45, 35.59, 26.52, 26.29, 12.75.

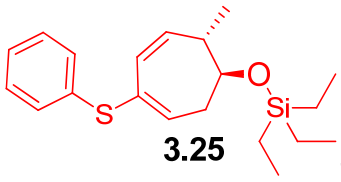
stereo of sulfone?



3.24

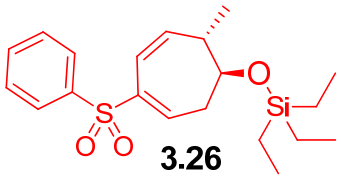
A 3-neck 1 liter flask was flame dried under dry N_2 atmosphere then was charged with a solution of thoroughly dried (1S,2R)-2-methyl-3-(phenylsulfonyl)-5-(phenylthio)cyclohept-4-enol (11.39 g, 30.4 mmol) in anhydrous dichloroethane, (Volume: 76 mL) at 25 °C. The reaction was cooled to 0 °C then solid imidazole (4.55 mL, 33.5 mmol) was added followed slow stream addition of chlorotriethylsilane (5.67 mL, 33.5 mmol) over 10 minutes. After the reaction shows yellowish precipitation of imidazolium hydrochloride, stirring was continued for 1-2 hours at 0 to 25 °C. The reaction was checked for completion by TLC (50% ethyl acetate/hexane) then was filtered over a celite pad under

vacuum. The pad was washed with DCE (2 x 100 mL), and the combined organic phases were concentrated via rotary evaporation to afford crude triethyl (((1S,2R)-2-methyl-3-(phenylsulfonyl)-5-(phenylthio)cyclohept-4-en-1-yl)oxy)silane (14.56 g, 29.8 mmol, 98 % yield) as an amber oil that did not require further purification. An analytical sample was obtained via FCC (10% ethyl acetate/hexane) as a clear yellow oil. TLC (50% ethyl acetate/hexane) R_f 0.9; ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.72 (d, *J* = 7.7 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.30 (m, 5H), 5.53 (d, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 6.0 Hz, 1H), 3.87 – 3.79 (m, 1H), 2.82 (dd, *J* = 15.4, 12.7 Hz, 1H), 2.47 (dt, *J* = 11.5, 5.8 Hz, 1H), 2.04 (d, *J* = 11.6 Hz, 0H), 1.77 – 1.65 (m, 2H), 1.43 (dt, *J* = 14.8, 5.5 Hz, 1H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.89 (t, *J* = 7.9 Hz, 9H), 0.51 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.4, 138.8, 133.5, 133.3, 132.1, 129.3, 129.0, 128.5, 128.3, 117.4, 72.8, 62.6, 36.3, 27.5, 26.4, 12.6, 6.8, 4.7.



3.25 triethyl(((1S,2R)-2-methyl-3-(phenylsulfonyl)-5-(phenylthio)cyclohept-4-en-1-yl)oxy)silane (14.56 g, 29.8 mmol) and N,N-diisopropylethylamine (18.21 mL, 104 mmol) was dissolved in dry methylene chloride (149 mL) then was transferred to a 3-neck 1 L flask under Ar atmosphere. The flask was cooled to -78 °C until the internal temperature became at least -72 °C then was added trimethylaluminum 25% in Hexanes (27.4 mL, 68.5 mmol). The acetone/ dry ice bath was removed, and the reaction was allowed to warm to 25 ºC then stirring was continued for at least 2 hours.

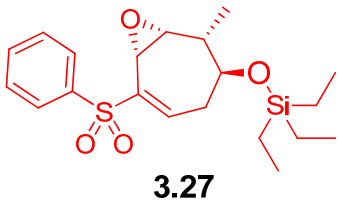
The reaction was checked for completion via TLC (20% ethyl acetate/ hexane) then the reaction contents were transferred to a suspension of 5%$_{(aq)}$ HCl (1.3 L, 10 eq) / crushed ice. The mixture is added to a separatory funnel and washed with deionized water. Methylene chloride was removed via spin-evaporation and the remaining aqueous mixture was extracted with toluene (150 mL). The wet toluene layer was filtered through a celite pad to provide a filtrate of triethyl(((1S,2S)-2-methyl-5-(phenylthio)cyclohepta-3,5-dien-1-yl)oxy)silane (10.32 g, 29.8 mmol, 100 % yield). The crude filtrate was subjected to the Noyori oxidation without further purification.



3.26

A solution of triethyl(((1S,2S)-2-methyl-5-(phenylthio)cyclohepta-3,5-dien-1-yl)oxy)silane (10.32 g, 29.8 mmol) in toluene (298 mL), was stirred under air to give a brown solution. The solution was treated with sequential addition of aqueous sodium tungstate dihydrate (0.595 mL, 0.595 mmol), aqueous phenylphosphonic acid (0.595 mL, 0.595 mmol), aqueous methyltrioctylammonium hydrogen sulfate (1.191 mL, 0.595 mmol), and hydrogen peroxide 30% (6.08 mL, 59.5 mmol), was followed by vigorous stirring at 25 °C. After 4 hr the reaction was judged complete by TLC and the mixture was transferred to a separatory funnel, brine (200 mL) was added. The aqueous layer was extracted with ether (2×100 mL) and the combined organic layers were washed with saturated Na_2SO_3 solution, dried over Na_2SO_4 and concentrated via rotary evaporation to give triethyl(((1S,2S)-2-methyl-5-

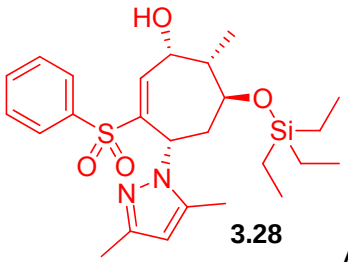
(phenylsulfonyl)cyclohepta-3,5-dien-1-yl)oxy)silane (11.27 g, 29.8 mmol, 100 % yield) as an orange oil triethyl(((1S,2S)-2-methyl-5-(phenylsulfonyl)cyclohepta-3,5-dien-1-yl)oxy)silane (11.27 g, 29.8 mmol, 100 % yield) as a light yellow viscous oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.89 – 7.85 (m, 2H), 7.62 – 7.57 (m, 1H), 7.52 (ddd, *J* = 8.1, 6.7, 1.2 Hz, 2H), 7.21 (ddd, *J* = 7.0, 5.6, 1.5 Hz, 1H), 6.05 (dt, *J* = 11.7, 1.6 Hz, 1H), 5.85 (dd, *J* = 11.8, 5.2 Hz, 1H), 3.83 (ddd, *J* = 7.2, 6.2, 3.2 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.53 (ddd, *J* = 16.6, 5.7, 3.1 Hz, 1H), 2.34 – 2.26 (m, 1H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.61 – 0.54 (m, 6H). This material was used in the next step without further purification.



3.27

A 3-neck 3 L flask was equipped with an overhead mechanical stirrer, a thermometer, and an argon inlet triethyl(((1S,2S)-2-methyl-5-(phenylsulfonyl)cyclohepta-3,5-dien-1-yl)oxy)silane (3.000 g, 7.92 mmol) was dissolved in acid-free methylene chloride (60 mL) then was transferred to the flask, and cooled to 0 °C, 0.132 M. After stirring for 10 minutes, (*S,S*)-(+)-N,N'-*bis*(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (0.252 g, 0.400 mmol), 4-(3-Phenylpropyl)pyridine *N*-oxide (0.510 g, 2.38 mmol) were sequentially added. Cold sodium hypochlorite 10.8% (15.49 mL, 20.60 mmol) was freshly mixed with cold 0.05 M sodium dihydrogen phosphate$_{(aq)}$ (37 mL, 1.86 mmol), and the mixture was poured as a slow but continuous stream to the cold reaction. After 2 hours at 0 °C, the reaction progress was checked via

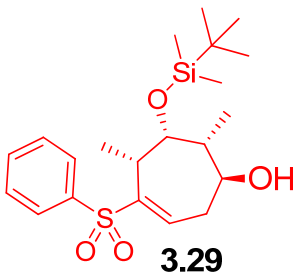
TLC (30% ethyl acetate/hexane). It is noted that the stirring needs to be stopped until phase separation occurs, then the TLC sample must be withdrawn from the bottom organic layer via a Pasteur pipette. After completion, hexane (3x 60 mL) was added to the reaction, and stirring was continued for 1-2 hours at 25 ^{o}C. Ideally, Mn-salen catalyst precipitates as brown aggregates leaving a clear pale yellow solution above. If necessary, additional 10% aq. NaOCl (0.5 equiv.) is added at 25 ^{o}C in order to create a minor exotherm thereby destroying the residual Mn-salen catalyst, and preparing it for precipitation. Filtration over Whatman 1 filter paper provides a clear yellow solution. Removal of solvents via rotary evaporation afforded triethyl(((1R,2S,3S,7R)-2-methyl-6-(phenylsulfonyl)-8-oxabicyclo[5.1.0]oct-5-en-3-yl)oxy)silane (3.2 g, 8.11 mmol, 100 % yield) as a dark brown oil that was sufficiently pure as judged by NMR for the next synthetic step. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 – 7.88 (m, 2H), 7.66 – 7.61 (m, 1H), 7.58 – 7.52 (m, 2H), 7.31 (ddd, *J* = 8.8, 3.8, 1.3 Hz, 1H), 3.69 (dd, *J* = 4.2, 1.2 Hz, 1H), 3.33 (td, *J* = 9.2, 2.0 Hz, 1H), 3.26 (dd, *J* = 4.2, 2.9 Hz, 1H), 2.56 (ddd, *J* = 17.1, 8.8, 2.0 Hz, 1H), 2.44 (ddd, *J* = 17.2, 9.2, 3.9 Hz, 1H), 2.25 – 2.14 (m, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.61 – 0.53 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.20, 139.92, 139.37, 133.48, 129.17, 127.96, 70.83, 60.41, 52.18, 42.13, 38.13, 16.51, 6.74, 4.71.



3.28

A 3-neck 1L flask was fit with an overhead reflux condenser, and two septa. Crude triethyl(((1R,2S,3S,7R)-2-methyl-6-(phenylsulfonyl)-8-oxabicyclo[5.1.0]oct-5-en-3-yl)oxy)silane **(3.27)** (7.08 g, 17.94 mmol) was dissolved in dry toluene (90 mL), then was transferred to the reaction flask. 3,5-dimethylpyrazole (1.90 g, 19.74 mmol) was added, then the reaction was heated at 50-60 ^{o}C for 1 hour and/ or until TLC shows consumption of starting material. The reaction was cooled to 25 ^{o}C then washed with crushed ice/ brine (150 mL)/ 5% aqueous HCl (39 mL, 0.8 equiv.). The aqueous phase was discarded, and then the organic phase was washed with brine, and dried over Na_2SO_4 for 3 hours. The toluene was removed via spin-evaporation to provide a crude semi-solid. The semi-solid was purified by silica-gel chromatography (9:1 toluene : tetrahydrofuran) to furnish (1R,4S,6S,7S)-4-(3,5-dimethyl-1H-pyrazol-1-yl)-7-methyl-3-(phenylsulfonyl)-6-((triethylsilyl)oxy)cyclohept-2-enol (6.69 g, 13.64 mmol, 76 % yield) ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.80 (dd, *J* = 8.7, 0.9 Hz, 1H), 7.58 (dt, *J* = 8.5, 1.1 Hz, 2H), 7.48 – 7.44 (m, 1H), 7.33 (tt, *J* = 7.4, 0.9 Hz, 2H), 7.01 – 6.96 (m, 1H), 5.50 (s, 1H), 5.37 (dd, *J* = 5.3, 2.9 Hz, 1H), 4.40 (ddd, *J* = 10.9, 8.7, 2.0 Hz, 1H), 4.00 (td, *J* = 10.5, 2.4 Hz, 1H), 2.36 (t, *J* = 0.8 Hz, 1H), 2.14 (ddd, *J* = 14.4, 5.3, 2.5 Hz, 1H), 2.09 (d, *J* = 0.8 Hz, 3H), 2.09 – 2.03 (m, 2H), 1.98 (d, *J* = 0.9 Hz, 3H), 1.83 – 1.75 (m, 1H), 1.66 (s, 1H), 1.25 (dd, *J* = 6.9, 0.9 Hz, 3H), 1.02 (td, *J* = 8.0,

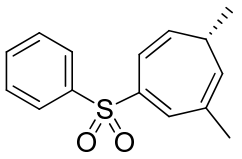
0.9 Hz, 2H), 0.82 (td, *J* = 8.0, 0.9 Hz, 9H), 0.41 (qdd, *J* = 8.1, 3.6, 1.0 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.94, 146.28, 140.07, 138.79, 138.48, 132.83, 128.43, 126.98, 105.22, 68.71, 67.22, 50.43, 45.80, 44.17, 16.42, 12.71, 10.44, 6.59, 4.59.



3.29

A dry 100 mL RB flask was charged with a solution of (1R,2R,6S,7S)-2,7-dimethyl-3-(phenylsulfonyl)-6-((triethylsilyl)oxy)cyclohept-3-enol (0.360 g, 0.877 mmol) in dry methylene chloride (10 mL), then the solution was cooled to 0 °C. After 15 min, 2,6-lutidine (0.102 mL, 0.877 mmol) was added dropwise, then *t*-butyldimethylsilyl trifluoromethansulfonate (0.202 mL, 0.877 mmol) was added dropwise via syringe. The reaction was stirred at 0 °C for 30-60 minutes, then methanol (0.177 mL, 4.38 mmol) was added dropwise, and stirring was continued for another 30 minutes. The reaction was diluted with 5% $HCl_{(aq)}$, washed, then the aqueous layer was discarded after neutralization. The organic layer was transferred to another flask, cooled to 0 °C, and then camphorsulfonic acid (0.102 g, 0.438 mmol) was added. After stirring at 0 °C for 2 hours, the reaction was neutralized carefully with sat aq. $NaHCO_3$, and then washed with saturated $NaHCO_{3(aq)}$. The organic layer was then washed with brine, and then dried over Na_2SO_4 for 6 hours. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.88 – 7.83 (m, 2H), 7.62 – 7.57 (m, 1H), 7.56 – 7.49 (m, 3H), 7.13 (t, *J* = 6.2

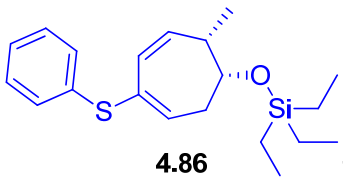
Hz, 1H), 3.88 (ddd, *J* = 8.3, 6.5, 2.0 Hz, 1H), 3.76 (dd, *J* = 5.6, 3.6 Hz, 1H), 2.74 (ddd, *J* = 16.8, 6.1, 2.1 Hz, 1H), 2.66 – 2.58 (m, 1H), 2.56 – 2.50 (m, 1H), 2.11 – 2.02 (m, 1H), 2.00 (d, *J* = 0.6 Hz, 1H), 1.19 (d, *J* = 7.5 Hz, 3H), 1.11 (d, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 2H), 0.78 (s, 9H), 0.63 – 0.55 (m, 2H), -0.20 (s, 3H), -0.36 (s, 3H).



4.79

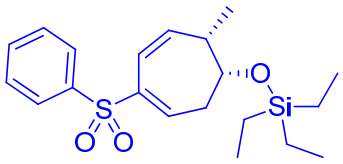
To a solution of diisopropylamine (0.031 mL, 0.218 mmol) in anhydrous tetrahydrofuran and hexamethylphosphoramide (HMPA) (5:2) at - 20 °C a commercially available *n*-butyllithium solution (0.091 mL, 0.228 mmol) was added under an argon atmosphere at which point the diphenyl-2-pyridylmethane indicator turned red remained that way briefly and faded back to pale yellow. Additional *n*-butyllithuim (0.0455 mL, 0.114 mol) was added and the indicator remained red. The resulting solution was stirred for ca. 30 min and then a solution of (bromomethyl)dimethyl((1R,2S)-2-methyl-5-(phenylsulfonyl) cyclohept-3,5-dienyloxy)silane (0.0411 g, 0.099 mmol) in THF (4.12 mL) was added with a syringe. An orange color was observed. At -35 °C the indicator turned red and a TLC indicated no starting material remaining. The THF was removed *via* spin-evaporation and the HMPA concentrate was partitioned between ethyl acetate (100 mL) and aqueous HCl (100 mL). The ethyl acetate portion was washed with HCl (2 × 100 mL), deionized water (1×100 mL) and brine (1×100 mL). The ethyl acetate was removed by spin evaporation. The

crude oil was purified via flash chromatography (4:1 hexanes: ethyl acetate) to yield (S)-2,7-dimethyl-4-(phenylsulfonyl)cyclohepta-1,3,5-triene (0.020 g, 0.077 mmol 78 %) as a white semi-solid. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.89 – 7.83 (m, 2H), 7.68 (s, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 6.38 (d, *J* = 9.5 Hz, 1H), 5.31 (dd, *J* = 9.5, 5.5 Hz, 1H), 5.09 (d, *J* = 5.3 Hz, 1H), 1.98 (d, *J* = 1.5 Hz, 3H), 1.58 (q, *J* = 6.5 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H).

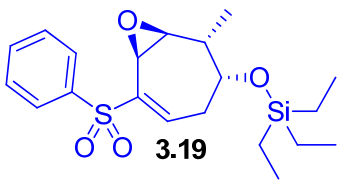


4.86 Triethyl((1R,2R)-2-methyl-3-(phenylsulfonyl)-5-(phenylthio)cyclohept-4-enyloxy)silane (3.77 g, 7.70 mmol) and N,N-diisopropylethylamine (4.71 mL, 26.9 mmol) was dissolved in dry methylene chloride (77 mL) then was transferred to a 3-neck 1 L flask under Ar atmosphere. The flask was cooled at -78 °C until the internal temperature became at least -72 °C. Trimethylaluminum 25% in Hexanes (7.08 mL, 17.71 mmol) was added via cannula as a continuous stream over 15 minutes. The acetone/ dry ice bath was removed, and the reaction was allowed to warm to 25 ºC then stirring was continued for at least 2 hours. The mixture is added to a separatory funnel and washed with deionized water. Methylene chloride was removed via spin-evaporation and the remaining aqueous mixture was extracted with toluene (150 mL). The wet toluene layer was filtered through a celite pad to provide filtrate with an assumed quantitative yield of triethyl((1R,2S)-2-methyl-5-(phenylthio)cyclohepta-3,5-dienyloxy)silane (2.67 g, 7.70 mmol, 100 % yield).

The crude filtrate was subjected to the Noyori oxidation without further purification.

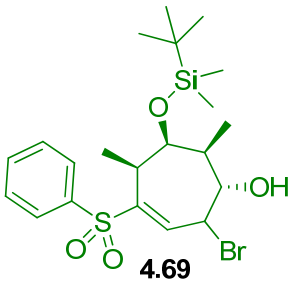


A solution of crude triethyl((1R,2S)-2-methyl-5-(phenylthio)cyclohepta-3,5-dienyloxy)silane (2.670 g, 7.70 mmol) in toluene, (35.0 mL) is stirred under air to give a brown solution. Sequential addition of sodium tungstate dihydrate (0.154 mL, 0.154 mmol), phenylphosphonic acid (0.154 mL, 0.154 mmol), methyltrioctylammonium hydrogen sulfate (0.308 mL, 0.154 mmol), and hydrogen peroxide 30% (1.57 mL, 15.4 mmol), was followed by vigorous stirring at 25 °C. After 4 hr the reaction was judged complete by TLC and the mixture was transferred to a separatory funnel, brine (200 mL) was added. The aqueous layer was extracted with ether (2×100 mL) and the combined organic layers were washed with saturated Na_2SO_3 solution, dried over Na_2SO_4 and concentrated via rotary evaporation to give triethyl((1R,2S)-2-methyl-5-(phenylsulfonyl)cyclohepta-3,5-dienyloxy)silane (2.79 g, 7.4 mmol, 96 % yield) as an orange oil TLC (50% ethyl acetate/hexanes) R_f 0.39. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.85 – 7.82 (m, 2H), 7.60 – 7.56 (m, 1H), 7.51 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.11 – 7.04 (m, 1H), 6.00 (d, *J* = 11.8 Hz, 1H), 5.91 (dd, *J* = 11.8, 6.5 Hz, 1H), 4.08 – 4.01 (m, 1H), 2.71 – 2.55 (m, 2H), 2.43 (ddd, *J* = 14.7, 7.2, 3.6 Hz, 1H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.55 (q, *J* = 7.9 Hz, 6H). This material was used in the next step without further purification.



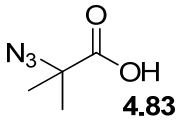
3.19

A solution of triethyl((1R,2S)-2-methyl-5-(phenylsulfonyl)cyclohepta-3,5-dienyloxy)silane (0.106 g, 0.280 mmol) and urea hydrogen peroxide (UHP) (0.100 g, 1.021 mmol) in DCM : MeOH (0.470 mL: 0.466 mL) in the presence of ammonium acetate (4.31 mg, 0.056 mmol) and (*S,S*)-(+)-*N,N'*-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride (8.88 mg, 0.014 mmol) at 0 °C. After completion of the reaction, catalyst was destroyed at room temp with hydrogen peroxide, turning the reaction mixture from dark brown to golden yellow, the method was spun off and the aqueous-layer was diluted with methylene chloride: hexanes 1:10 and the mixture was stirred and the layer allowed to settle. The catalyst was separated from the epoxide by precipitating it with hexane. Enantiomeric excess for the product epoxide was determined NMR integration. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.63 – 7.57 (m, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.15 (dd, *J* = 3.8, 1.8 Hz, 1H), 4.64 (dd, *J* = 10.0, 3.7 Hz, 1H), 3.96 (dt, *J* = 6.2, 2.1 Hz, 1H), 2.58 (dddt, *J* = 13.6, 11.9, 2.8, 1.6 Hz, 1H), 2.22 – 2.14 (m, 1H), 1.77 (dtd, *J* = 16.5, 6.9, 2.0 Hz, 1H), 1.64 (dtd, *J* = 13.9, 6.7, 1.9 Hz, 1H), 1.31 (ddt, *J* = 14.4, 12.0, 2.4 Hz, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 8.0 Hz, 9H), 0.55 (q, *J* = 8.0 Hz, 6H).

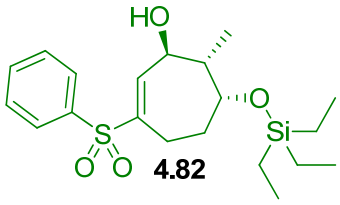


4.69

To a fire-dried 5 mL 3-neck round-bottom flask under argon was added (1R,5S,6S,7S)-6-(tert-butyldimethylsilyloxy)-5,7-dimethyl-4-(phenylsulfonyl)cyclohept-3-enol (50 mg, 0.122 mmol) and 2,2'-Azobisisobutyronitrile (1.000 mg, 6.09 µmol). The solids were dissolved in Carbon tetrachloride (1.218 mL) with stirring and the reaction was heated to 50 °C. The reaction was monitored by TLC (2:1 Hexanes: Ethyl Acetate; *p*-anisaldehyde-UV/vis) and when no remaining starting material was observed, the reaction was quenched with saturated sodium thiosulfate solution, the organic layer dried over sodium sulfate, and the solvent removed via rotary evaporation. The crude product was purified by silica gel flash chromatography, 3:1 hexanes: ethyl acetate, and the product was dried under high vacuum to yield (1S,2S,5S,6S,7S)-2-bromo-6-(tert-butyldimethylsilyloxy)-5,7-dimethyl-4-(phenylsulfonyl)cyclohept-3-enol (15 mg, 0.031 mmol, 25.2 % yield). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.87 – 7.82 (m, 2H), 7.64 – 7.58 (m, 1H), 7.54 (dd, *J* = 8.5, 7.1 Hz, 2H), 7.22 (d, *J* = 6.9 Hz, 1H), 5.04 (s, 1H), 3.93 (d, *J* = 9.5 Hz, 1H), 3.64 (d, *J* = 41.3 Hz, 1H), 2.52 (qd, *J* = 7.4, 3.0 Hz, 1H), 1.53 (d, *J* = 3.1 Hz, 1H), 1.31 – 1.24 (m, 3H), 1.24 – 1.13 (m, 3H), 0.75 (s, 9H), -0.20 (s, 3H), -0.43 (s, 3H).

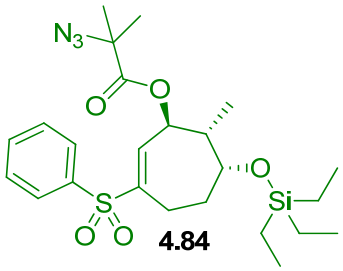


4.83 2-bromo-2-methylpropanoic acid (10 g, 59.9 mmol) and sodium azide (5.84 g, 90 mmol) were mixed in dry dimethylformamide (DMF) (130 mL) and stirred at 20 °C. The reaction was monitored after 2 days, then partitioned between 5% LiCl solution (2 × 1L), Washed with 0.1 M HCl solution (2 × 1L) , then brine, dried over $MgSO_4$, filtered, spin-evaporated and dried to constant weight (3.212 g, 0.91 mmol, 55 % yield) under hi-vac. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 11.12 (s, 1H), 1.52 (s, 6H).



4.82 triethyl(((1S,2S,3R,7S)-2-methyl-6-(phenylsulfonyl)-8-oxabicyclo[5.1.0]oct-5-en-3-yl)oxy)silane (1.205 g, 3.05 mmol) was stirred in MeOH (30.5 mL) cooled to 0 °C with an ice bath. Powdered sodium borohydride (0.127 g, 3.36 mmol) was added and the ice bath removed. After 20 min H_2O was carefully added and the methanol was removed wide rotary evaporation. The remaining aqueous layer was extracted with dichloromethane (2 x 50 mL). The crude mixture was purified by flash chromatography. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.87 – 7.84 (m, 2H), 7.62 – 7.57 (m, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.15 (dd, *J* = 3.8, 1.8 Hz, 1H), 4.68 – 4.61 (m, 1H), 3.96 (dt, *J* = 6.3, 2.1 Hz, 1H), 2.58 (ddq, *J* = 15.2, 11.7, 1.7 Hz, 1H), 2.22 – 2.14 (m, 1H), 1.82 – 1.72 (m, 1H),

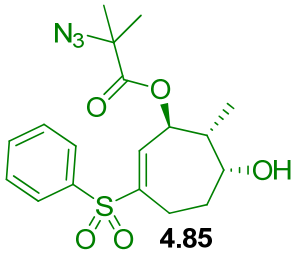
1.68 – 1.58 (m, 1H), 1.31 (ddt, *J* = 14.1, 11.9, 2.2 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 8.0 Hz, 9H), 0.54 (q, *J* = 7.9 Hz, 6H).



4.84

Oxalyl chloride (0.212 mL, 2.420 mmol) was added at 0 °C to a solution of 2-azido-2-methylpropanoic acid (0.391 g, 3.03 mmol), DMF (0.023 mL, 0.303 mmol) in $PhCH_3$, (10 mL). The mixture was stirred for 1 h at 25 °C. In a separate reaction vessel dimethylaminopyridine DMAP (0.037 g, 0.303 mmol) was added to a solution of triethylamine (TEA) (0.84 mL, 6.05 mmol) and alcohol (1S,6R,7S)-7-methyl-3-(phenylsulfonyl)-6-((triethylsilyl)oxy)cyclohept-2-enol (0.400 g, 1.009 mmol) in methylene chloride (10.00 mL) at 25 °C. The alcohol solution was then transferred to the acid chloride solution at 0 °C and the mixture was stirred for 1 hr at 0 °C. Phosphate buffer (3 mL, 0.05 M, pH = 7) was added and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic extracts were washed with brine (3 mL), dried (Na_2SO_4), filtered, the solvent was removed under reduced pressure, and purified by column chromatography (SiO_2, 5-10% EtOAc/hexanes) to furnish the (1S,6R,7S)-7-methyl-3-(phenylsulfonyl)-6-((triethylsilyl)oxy)cyclohept-2-en-1-yl 2-azido-2-methylpropanoate (0.461 g, 0.91 mmol, 90 % yield) as a yellow oil. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.86 – 7.83 (m, 2H), 7.64 – 7.60 (m, 1H), 7.54

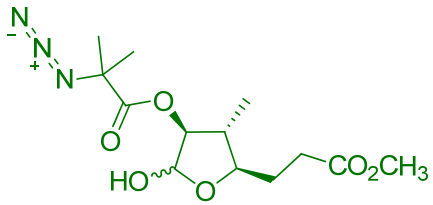
(t, *J* = 7.7 Hz, 2H), 6.98 – 6.94 (m, 1H), 5.80 (dd, *J* = 10.1, 4.1 Hz, 1H), 4.00 (dt, *J* = 6.5, 2.1 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.22 – 2.14 (m, 1H), 2.03 (dtd, *J* = 16.3, 6.8, 1.9 Hz, 1H), 1.75 – 1.66 (m, 1H), 1.50 (d, *J* = 7.2 Hz, 6H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.56 (q, *J* = 7.9 Hz, 6H).



4.85

A dry 250 mL round-bottomed flask was charged with a solution of (1S,6R,7S)-7-methyl-3-(phenylsulfonyl)-6-((triethylsilyl)oxy)cyclohept-2-en-1-yl 2-azido-2-methylpropanoate (0.626 g, 1.23 mmol) in methylene chloride (12.3 mL) then the solution was cooled to 0 °C, then (1R,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-sulfonic acid (0.32 g, 1.48 mmol) was added. After 24 hours the reaction was not completely done so additional (1R,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-sulfonic acid (0.323 g, 1.480 mmol) was added and the reaction was monitored by TLC (35% EtOAc: Hexanes; UV/ PAA vis) there was starting material left, so an additional aliquant of (1R,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-sulfonic acid (0.323 g, 1.480 mmol) was added TLC monitoring (see above) showed. The reaction mixture was washed with sodium bicarbonate solution, deionized water, and brine. The isolated organic layer was dried over sodium sulfate clarified by gravity filtration, spin-evaporated down to oil, and dried to constant weight under hi vac. The crude oil was partitioned between acetonitrile and hexanes to remove the silicon oil from the desired

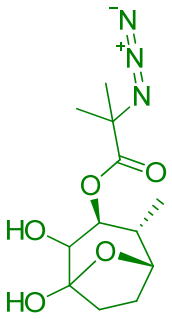
product. The acetonitrile layer was isolated and washed twice more with an equal volume of hexanes. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.86 – 7.82 (m, 2H), 7.64 – 7.60 (m, 1H), 7.54 (t, *J* = 7.7 Hz, 2H), 6.97 (dd, *J* = 4.1, 1.4 Hz, 1H), 5.77 (dd, *J* = 10.0, 4.2 Hz, 1H), 4.03 (dt, *J* = 6.6, 2.5 Hz, 1H), 2.62 (ddd, *J* = 16.0, 11.4, 2.0 Hz, 1H), 2.21 (ddd, *J* = 16.0, 7.7, 2.2 Hz, 1H), 2.16 (s, 1H), 2.14 (s, 1H), 1.80 – 1.74 (m, 1H), 1.60 – 1.54 (m, 1H), 1.49 (d, *J* = 3.2 Hz, 6H), 1.03 (d, *J* = 7.0 Hz, 3H).



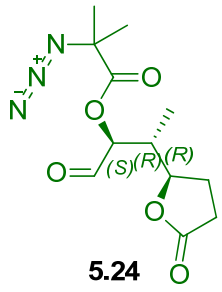
5.23

To a stirred clear colorless solution of (1S,6R,7R)-6-hydroxy-7-methyl-3-(phenylsulfonyl)cyclohept-2-en-1-yl-2-azido-2-methylpropanoate (1.0525 g, 2.68 mmol) in methylene chloride (15 ml) and methanol (3.75 ml) was added sodium bicarbonate (2.25 g, 0.03 mol) followed by cooling to -78 °C and bubbling of ozone for 15 min followed by addition of dimethyl sulfide (2.0 ml, 0.03 mol). The above mixture was stirred at room temperature for 4 hr then quenched by addition of 5% HCl (12 mL). The quenched reaction mixture was transferred to a separatory funnel and extracted with Et_2O (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated by rotary evaporation to give a colorless oil. The crude oil was purified by flash column chromatography (Hexanes:EtOAc = 1:1) to give (3S,4R,5R)-2-hydroxy-5-(3-methoxy-3-oxopropyl)-

4-methyltetrahydrofuran-3-yl 2-azido-2-methylpropanoate (0.700 g, 2.220 mmol, 83 % yield) as a colorless oil.

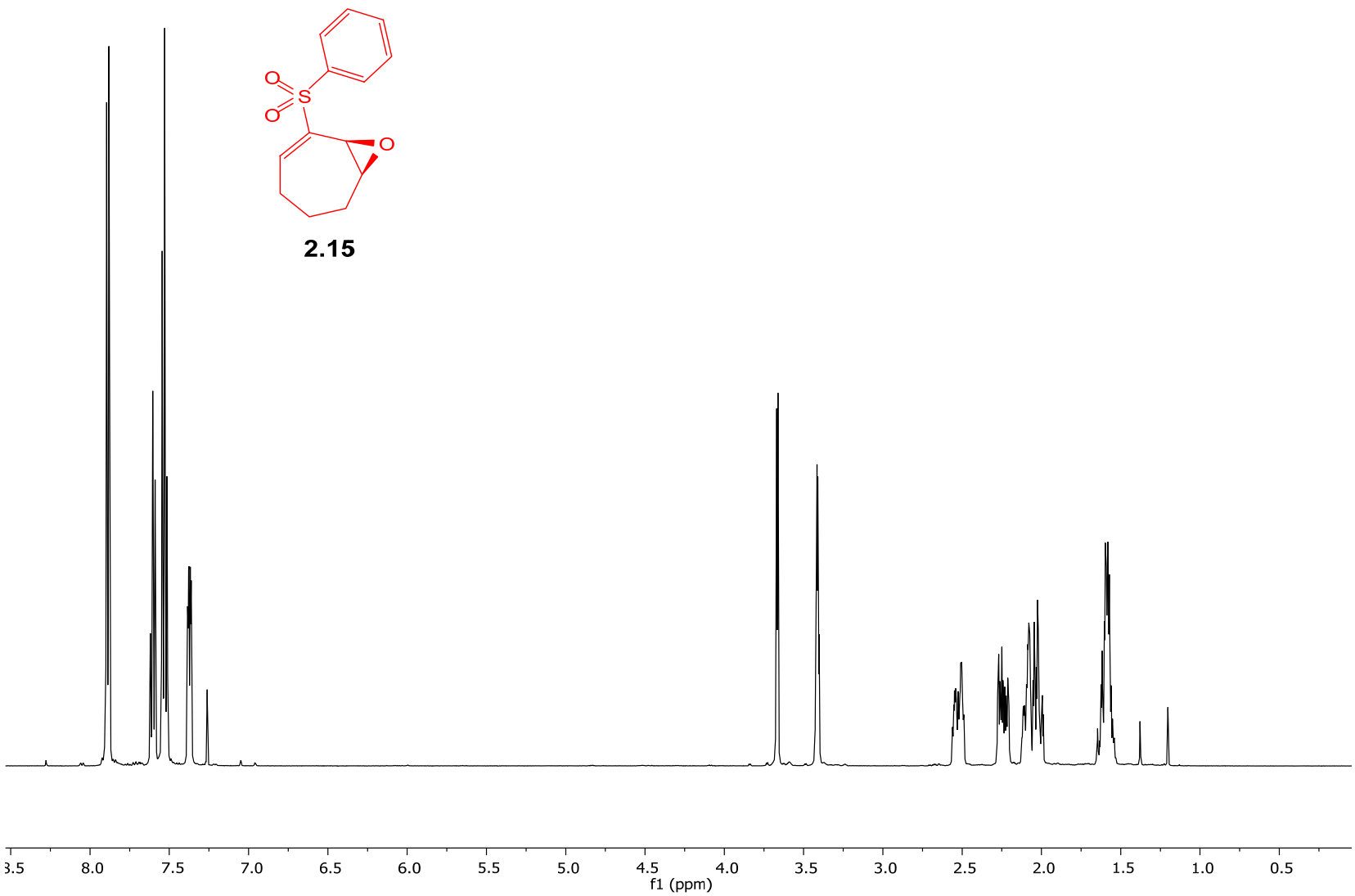


5.33 To a solution of (1S,6R,7R)-6-hydroxy-7-methyl-3-(phenylsulfonyl)cyclohept-2-en-1-yl 2-azido-2-methylpropanoate (0.133 g, 0.338 mmol) in 1:1 BuOH (2.414 mL) : water (2.414 mL) was added N-methylmorpholine-N-oxide (NMO) (0.087 g, 0.744 mmol) (50% wt in H_2O, 2 eq), citric acid (0.016 g, 0.085 mmol), and osmium tetroxide (0.085 mL, 6.76 µmol). After 24 h, The TLC (1:1; Hex:EtOAC) indicated disappearance of starting material so the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ and stirred for 30 min. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to furnish (1S,3S,4R,5R)-1,2-dihydroxy-4-methyl-8-oxabicyclo[3.2.1]octan-3-yl 2-azido-2-methylpropanoate (80 mg, 0.280 mmol, 83 % yield) as a clear resin. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.20 (dt, *J* = 5.2, 1.2 Hz, 1H), 4.19 (d, *J* = 8.1 Hz, 1H), 3.99 (dd, *J* = 5.3, 2.0 Hz, 1H), 2.65 – 2.57 (m, 1H), 2.30 (tdd, *J* = 12.9, 8.1, 4.8 Hz, 1H), 2.02 – 1.94 (m, 1H), 1.88 (q, *J* = 7.2 Hz, 1H), 1.61 (tdd, *J* = 13.1, 4.8, 2.2 Hz, 1H), 1.54 (d, *J* = 4.3 Hz, 5H), 1.43 (d, *J* = 5.9 Hz, 1H), 1.28 (dd, *J* = 4.1, 3.0 Hz, 2H), 1.23 (d, *J* = 7.5 Hz, 3H).



5.24

To a stirred solution of the (1S,3S,4R,5R)-1,2-dihydroxy-4-methyl-8-oxabicyclo[3.2.1]octan-3-yl 2-azido-2-methylpropanoate (0.020 g, 0.070 mmol) in 1:2 MeOH (0.467 mL) and benzene (0.935 mL) was added lead tetraacetate (0.042 g, 0.095 mmol) in portions over a period of 30 min at room temperature. After the mixture stirred for the required time, dilute $NaHCO_3$ was added and extracted with ethyl acetate. The combined organic layer was washed once with brine and dried over anhydrous Na_2SO_4. Concentration followed by silica gel chromatography of the crude yielded (2S,3R)-1-oxo-3-((R)-5-oxotetrahydrofuran-2-yl)butan-2-yl 2-azido-2-methylpropanoate (17 mg, 0.060 mmol, 86 % yield).^{1}H NMR (600 MHz, Chloroform-*d*) δ 9.56 (d, *J* = 1.1 Hz, 1H), 5.51 (t, *J* = 1.7 Hz, 1H), 4.42 (td, *J* = 9.2, 6.4 Hz, 1H), 2.65 (ddd, *J* = 10.1, 5.9, 1.7 Hz, 3H, 1.61 (d, *J* = 1.2 Hz, 3H), 1.57 (s, 3H), 1.11 (dd, *J* = 7.0, 1.9 Hz, 1H), 1.04 (dd, *J* = 7.0, 1.1 Hz, 3H).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O
O
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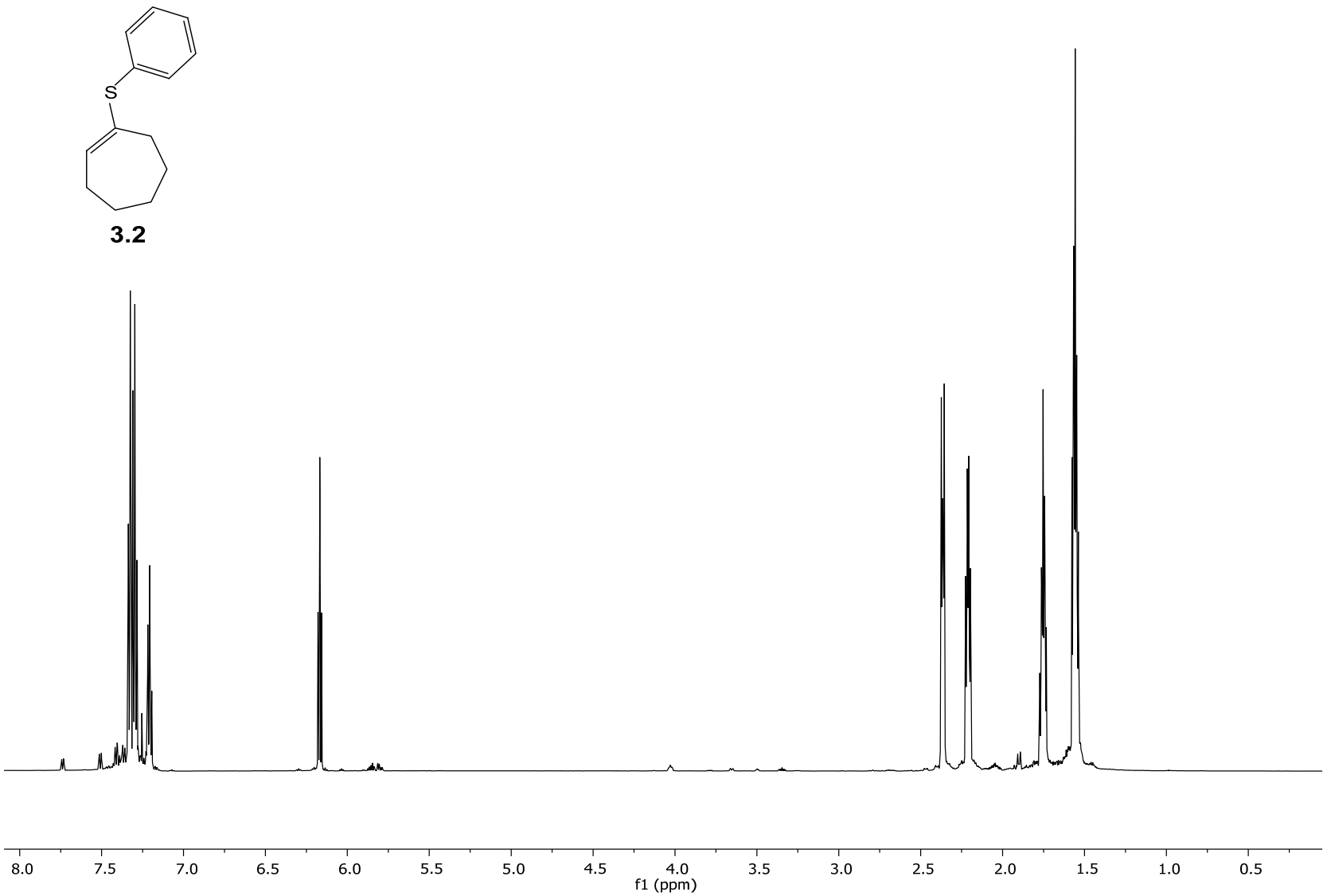
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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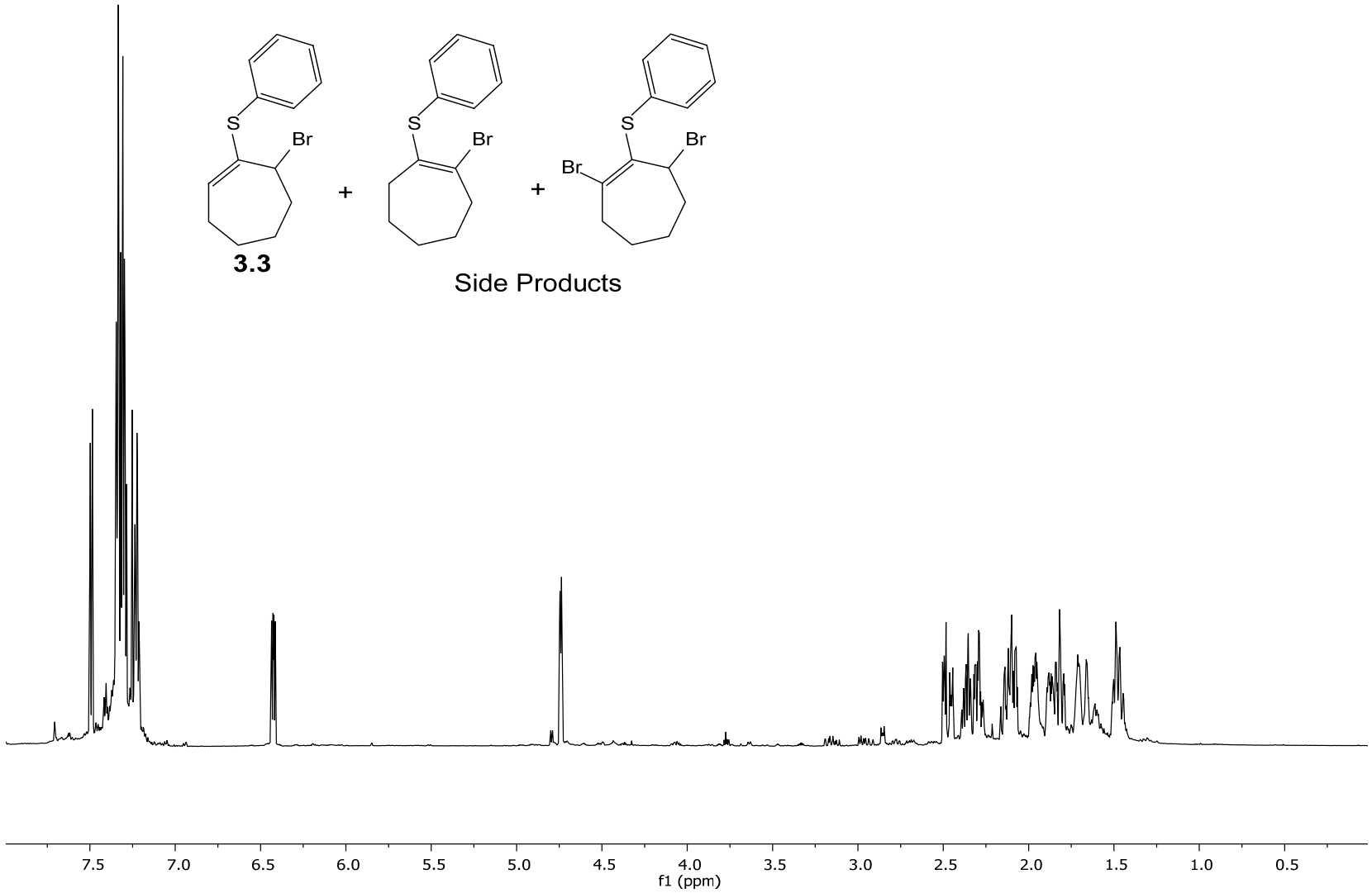
1.0
0.5
f1 (ppm)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Br
+
S
Br
+
S
Br
Br
3.3
Side Products
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6.5
6.0
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4.0
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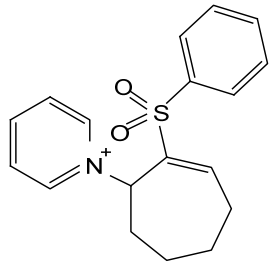
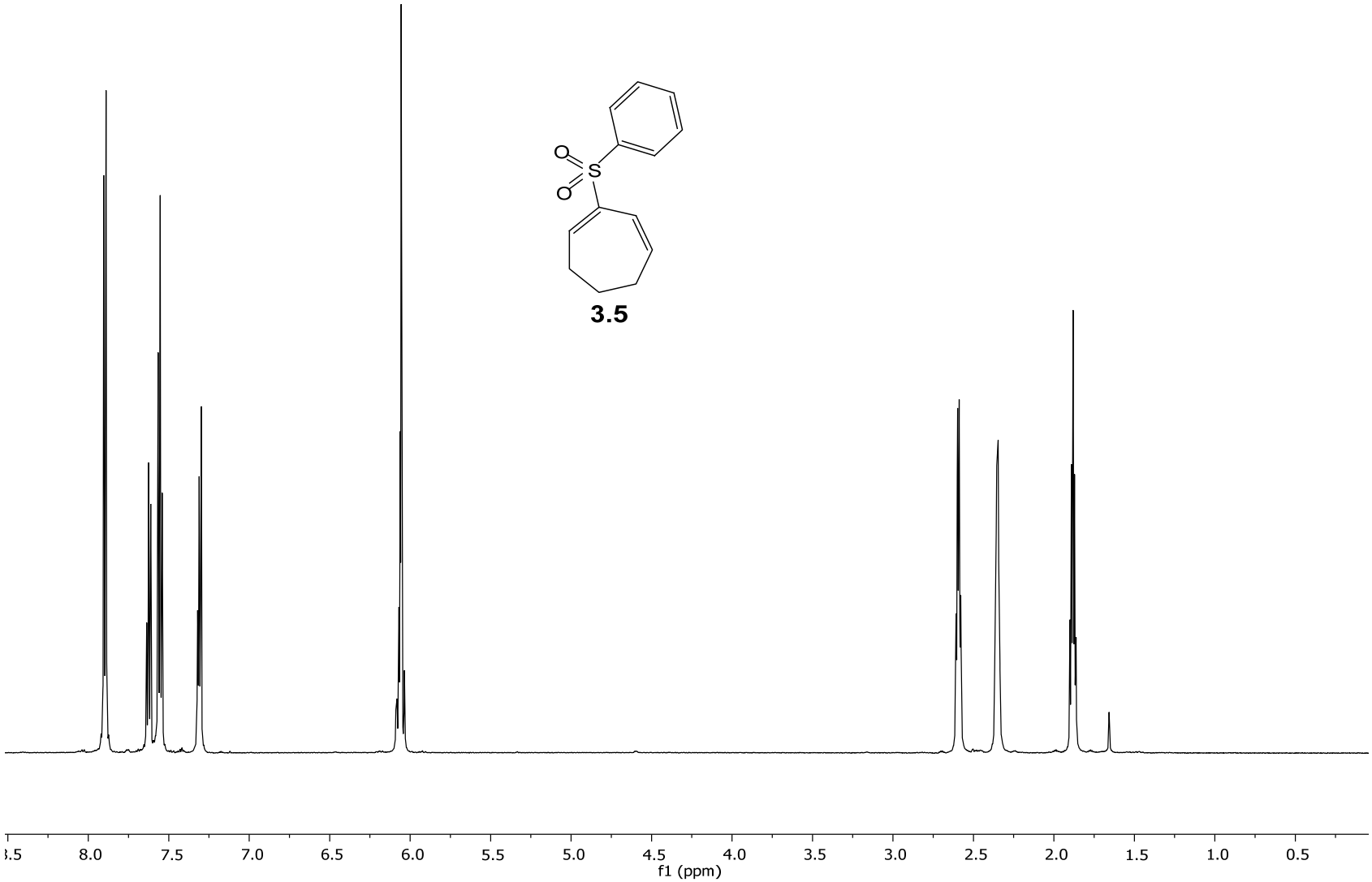
1.0
0.5
f1 (ppm)



3.4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S
O
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
3.5
3.0
2.5
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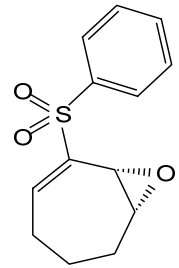
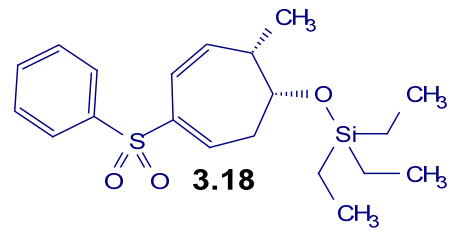
1.5
1.0
0.5
f1 (ppm)



3.14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CH3
Si
S
CH3
O
O
CH3

3.18

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7.0
6.5
6.0
5.5
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1.5
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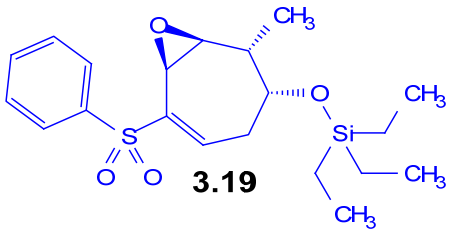
0.5
f1 (ppm)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CH3
S
Si
O
O
CH3
CH3

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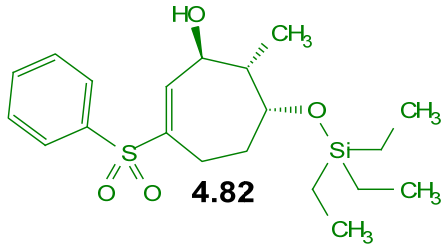
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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CH3
S
Si
O
O
CH3
CH3

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6.0
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3.0
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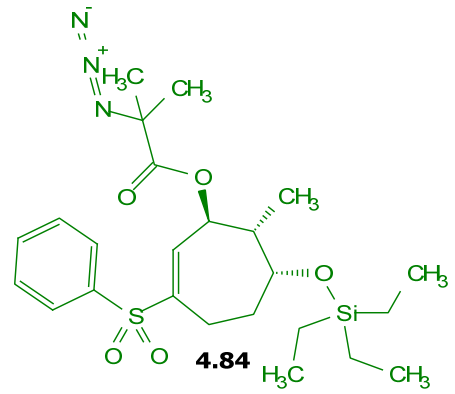
2.0
1.5
1.0
0.5
f1 (ppm)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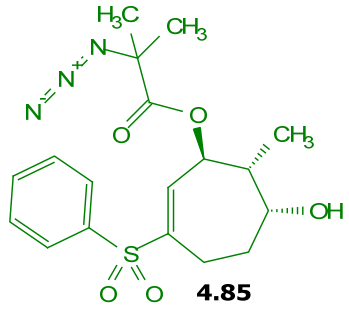
1.0
0.5
f1 (ppm)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N
N
O
O
CH3
OH
S
O
O

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6.5
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2.0
1.5
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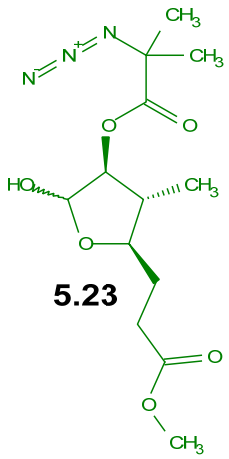
0.5
f1 (ppm)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4.0
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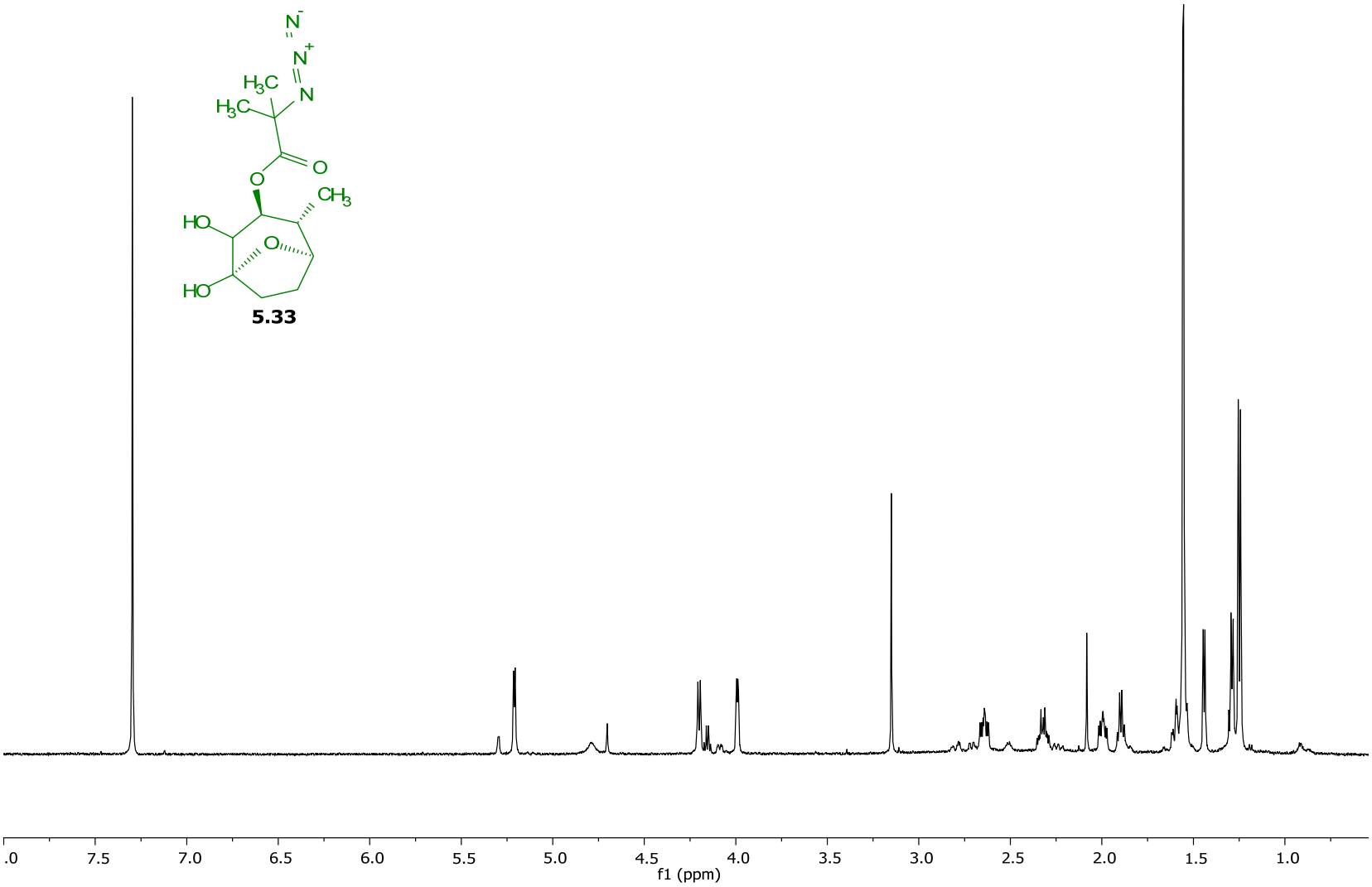
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


N
N
H3C
H3C
N
O
O
CH3
HO
O
HO
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.0
7.5
7.0
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2.0
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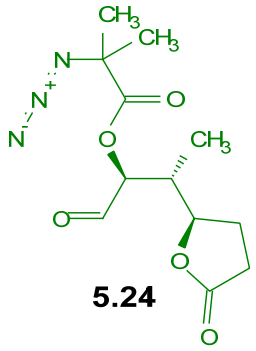
1.0
f1 (ppm)


CH3
CH3
N
N+
N-
O
O
O
CH3
O
O
O

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9.0
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8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

VITA

VITA

Thomas Paul Bobinski was born on August 9th, 1972 in Buffalo, NY. In 1999 he enrolled in the combined BS/MS combined degree in Medicinal Chemistry at the State University of New York at Buffalo. During that period he worked on pp60 *c-src* tyrosine kinase inhibitors for anti-cancer applications. In 2004, he received a BS/ MS combined degree in Medicinal Chemistry. In 2004, he was employed at Starks Associates in Buffalo, NY in process research. In 2007 he enrolled at Purdue University, and joined Professor P. L. Fuchs' group. He worked on the methodology for the synthesis of stereotetrads and towards the total synthesis of Aplyronine A. He received the Doctor of Philosophy degree in December 2013.

PUBLICATION

Citric Acid Buffered Osmylation of Cyclic Enantiopure Vinylsulfones and Vinyphosphonates with Sequential Oxidative Cleavage with Lead Tetraacetate

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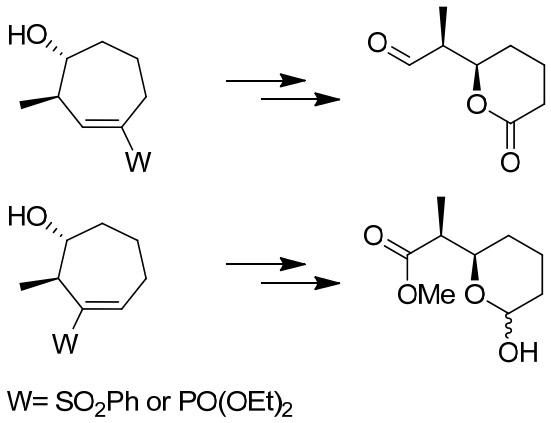
pfuchs@purdue.edu

Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



Cyclic asymmetric vinylsulfones and vinyphosphonates have been used towards the synthesis of aplyronine A and discodermolide respectively. Oxidative cleavage of these highly deactivated olefins to furnish linear fragments has been accomplished under harsh ozonolysis conditions. Osmylation of these substrates can now be accomplished with the addition of citric acid. The resulting acyloins and lactols can be smoothly cleaved with lead tetraacetate.

Catalytic osmylation of olefins is a well-established protocol developed by chemists at Upjohn.[1] While the Sharpless' group has provided the state-of-the-art osmylation in organic synthesis.[2345] Highly electron deficient olefins proved to be unreactive to traditional osmium catalyzed dihydroxylation procedures. Due to the mildness and general application of osmylation methodology, it is greatly preferred over ozonolysis.

[1] V. Vanrheenen, R. C. Kelly, and D. Y. Cha *Tetrahedron Lett.* **1976**, 1973-76.
[2] S. G. Hentges and K. B. Sharpless *J. Am. Chem. Soc.* **1980**, *102*, 4263-65.
[3] E. N. Jacobsen et al. *J. Am. Chem. Soc.* **1988**, *110*, 1968-70.
[4] C. J. Burns, C. A. Martin, and K. B. Sharpless *J. Org. Chem.* **1989**, *54*, 2826-34.
[5] J. S. M. Wai et al. *J. Am. Chem. Soc.* **1989**, *111*, 1123-25.

Use of cyclic asymmetric vinylsulfones has formed the backbone of a polypropionate strategy developed by the Fuchs group.[6] This methodology has been used for the successful synthesis of L-(-)-prostaglandin E_2,[78] dl-morphine,[91011] and 19-nor-Vitamin D-3.[12] This methodology has been used to generate the dipropionate fragments C5-C12, C21-C27 and *des*-methyl C28-C34 of aplyronine A.[131415] This investigation examines the effects of citric acid buffered osmium catalyzed dihydroxylation on cyclic vinylsulfones and vinyphosphonates.

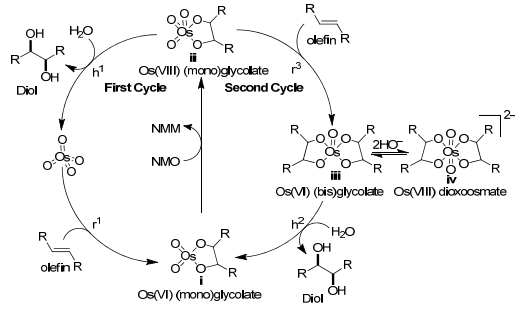


Figure 1. Caption

The proposed mechanism of osmium tetroxide (OsO4) dihydroxylation **(Figure 1)** suggested that the rate is sacrificed if (mono)glycosylate **ii** is hydrolyzed to regenerate diol and osmium tetroxide perpetuating the First Cycle.[16] The Second Cycle is favored over the First Cycle all things being equal. Since the rate of hydrolysis (h1) is much slower than the reduction (r3), the osmium(VI) bis(glycolate) **iii** builds up as the reaction progresses, generating diol via hydrolysis of (bis)glycolate **iii**. To exploit the Second Cycle when using chiral ligand, a slow addition technique was recommended to suppress the second cycle pathway during asymmetric dihydroxylation (AD).[17] However, if high reactivity is required, the second cycle gives a clear advantage over the first cycle. Citric acid improves the rates and the yields of cis-dihydroxylations of various electron-deficient alkenes. In addition to acting as a pH buffer thereby preventing formation of insoluble Os(VIII) dioxoosmate **iv**, a species, that inhibits the second cycle, citric acid strongly binds to OsO4 and maintains the reaction in the second cycle.[18]

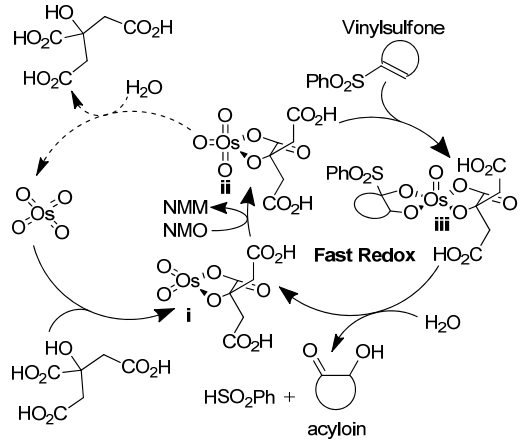


Figure 2. Citric Acid Catalyzed cis-Dihydroxyltion of Vinylsulfones

Addition of citric acid to improve the catalytic asymmetric osmylation system led to a greater understanding of the catalytic cycle that the vinylsulfone substrate undergoes (**Figure 2**). During the course of Sharpless' investigation to improve upon the Upjohn protocol, it was found that the osmylation catalytic cycle can, as previously stated, progress via two alternate avenues where the rate limiting step is hydrolysis of the monoglycolate **(i)** in the case of the first cycle and bisglycolate **(ii)** in the case of the faster second cycle **Figure 2**. When the osmylation is undertaken in homogeneous conditions the co-oxidant *N*-methylmorpholine *N*-oxide (NMO) has access to the intermediates over the entire catalytic cycle. Since the **Second Cycle** is faster, with the addition of citric acid, the reaction gets locked into the second cycle (bis)glycolate **(ii)** hydrolysis furnishes Os(VI) species **iii**.

The Sharpless group postulated that acids assist catalyst turnover by preventing formation of the catalytically dormant dioxoosmate dianion species **iv**, which is formed upon deprotonation of the hydrated (bis)glycolate **iii** at higher pH (**Figure 3**).

The strong electron withdrawing ability of the sulfone contributes to the acidity of the hydrated bis(glycolate) species **iii•H_2O** thus increasing the concentration of the dioxoosmate **iv** and crippling the cycle. The Sharpless group then discovered, based on the

[6] A. El-Awa et al. *Chem. Rev.* **2009**, *109*, 2315-49.
[7] R. E. Donaldson and P. L. Fuchs *J. Am. Chem. Soc.* **1981**, *103*, 2108-10.
[8] R. E. Donaldson et al. *J. Org. Chem.* **1983**, *48*, 2167-88.
[9] J. E. Toth and P. L. Fuchs *J. Org. Chem.* **1987**, *52*, 473-75.
[10] J. E. Toth, P. R. Hamann, and P. L. Fuchs *J. Org. Chem.* **1988**, *53*, 4694-708.
[11] ——— *J. Org. Chem.* **1988**, *53*, 4694-708.
[12] V. Sikervar, J. C. Fleet, and P. L. Fuchs *Chem. Commun.* **2012**, *48*, 9077-79.
[13] A. El-Awa, X. M. du Jourdin, and P. L. Fuchs *J. Am. Chem. Soc.* **2007**, *129*, 9086-93.
[14] M. N. Noshi, A. El-Awa, and P. L. Fuchs *J. Org. Chem.* **2008**, *73*, 3274-77.
[15] W. P. Hong et al. *Org. Lett.* **2011**, *13*, 6342-45.
[16] Wai et al.
[17] Ibid.

[18] Yun Gao and Young Cheun, "Osmium Tetroxide–N-Methylmorpholine N-Oxide," in *Encyclopedia of Reagents for Organic Synthesis* (John Wiley & Sons, Ltd, 2001).

aforementioned hypotheses that the dioxoosmate **iv** is especially stable and resistant to substitutions of any kind under basic conditions including hydrolysis irrespective of the presence co-oxidant. According to Sharpless, all acidic mixtures remain green indicating the presence of neutral bis(glycolate) (**ii**) whereas basic mixtures took on a reddish brown color indicating the presence of dioxoosmate dianion species **iv.** Adding citric acid however arrests the formation of osmium tetroxide (OsO_4) in favor of species **iii** thereby impeding the **First Cycle (Figure 2)**. With proximal acidic moieties acting as a buffer in hydrated (bis)glycolate **iii•H_2O** and dioxoosmate **iv** the equilibrium leans strongly in favor of bis(glycolate) **ii** which can then be hydrolyzed back to species **i** so the cycle may continue **(Figure 3)**.

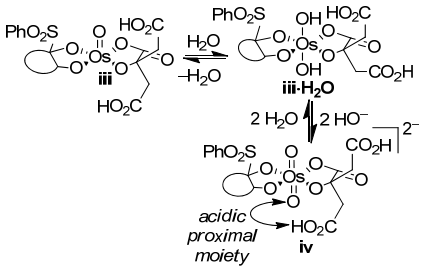


Figure 3. Effect of Citric Acid on Dioxoosmate Formation

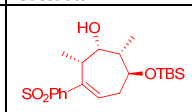
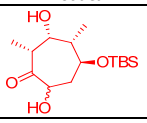
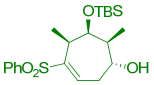
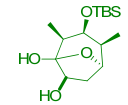
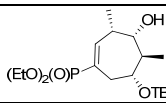
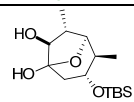
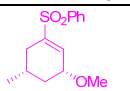
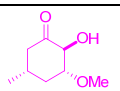
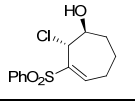
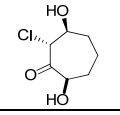
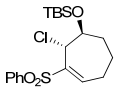
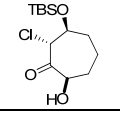
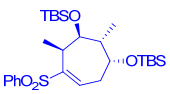
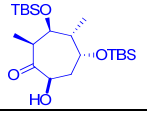
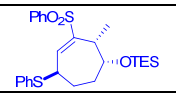
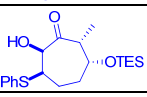
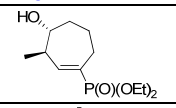
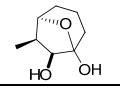
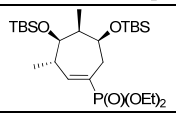
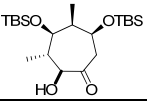
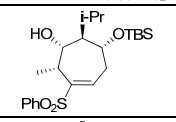
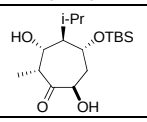
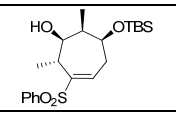
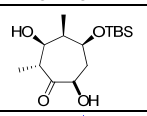
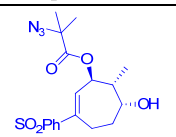
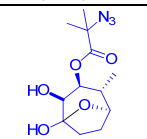
It is noteworthy that olefins such as diethyl maleate show the greatest benefit from performing the dihydroxylation at lower pH.[19] The hydrated osmium(VI) bis(glycolates) like species **iii•H_2O** formed from such electron-poor olefins would be expected to be much more acidic and correspondingly more likely to get trapped as the unwanted dioxoosmate dianion **iv**, even in the presence of a relatively weak base like 4-methylmorpholine. Citric acid however not only coordinates to the osmium, but coordinates the acidic moieties proximal to the oxygens of the hydrated (bis)glycolate **iii** so buildup of dioxoosmate **iv** will not terminate the catalytic cycle.

Methodology elucidated by Sharpless,[20][21][22] involving dihydroxylation of election deficient olefins by osmium, catalyzed by citric acid was explored on stereotriad entry 13. Rationale for the efficacy of the osmium/citric acid methodology is derived from the proposed catalytic cycle in **Figure 2**.

With a solid foundation for osmium catalyzed dihydroxylation of olefin deficient olefins being in evidence, investigation of this methodology on advanced vinylsulfones and vinyphosphonates was undertaken.

[19] Philippe Dupau et al. *Adv. Synth. Catal.* **2002**, *344*, 421-33.
[20] Ibid.
[21] Timothy J. Donohoe et al. *J. Org. Chem.* **2006**, *71*, 4481-89.
[22] Timothy J Donohoe et al. *Angew. Chem.* **2008**, *120*, 2914-17.

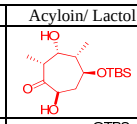
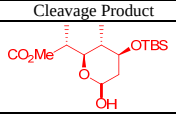
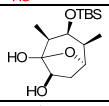
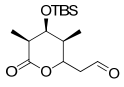
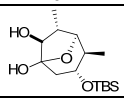
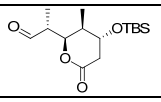
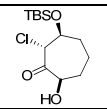
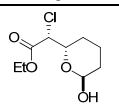
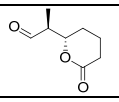
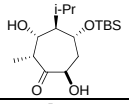
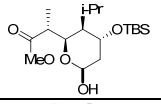
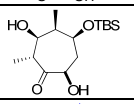
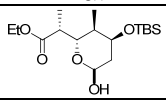
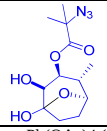
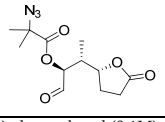
Table 1. Osmium Catalyzed Dihydroxylation of Vinyl Sulfones and Phosphonates

Entry	Substrate	Product	Yield
1			100%[a]
2			79%[a]
3			100%[b]
4			NR [a,b]
5			59%[b]
6			NR[a]
7			NR[a,b]
8			NR [b]
9			68%[b]
10			NR[a]
11			45%[b]
12			62%[b]
13			89%[b]

a. Conditions: 0.1M, citric acid (20 mol%), NMO (1.5 eq.), K_2OsO_4 (5 mol %), MeCN: H_2O (4:1), 50 ºC, 24 hrs *b.* Conditions: 0.1M, NMO (1.5 eq.), K_2OsO_4 (5 mol %), MeCN: H_2O (4:1), 25 ºC, 24 hrs

The data obtained by the examination represented by **Table 1** indicates that bulky stereotetrads such as those represented in entries 1 and 2 required heating at 50 °C to effect dihydroxylation. Entries 3, 5, 9, 12 and 13 however dihydroxylated smoothly at room temperature. Entry 3 is a bulky vinyphosphonate, and entry 9 is an unhindered vinyphosphonate. Yields would indicate that entry 3 is in a more favorable conformation to form the α-hydroxy lactol than is entry 9. In contrast entry 10 recovered starting material under the stated conditions. Entry 10 does not however have the possibility of forming α-hydroxy lactol as it is *di*-protected. Entry 11 also reacted at room temperature but in low yield probably due to the presence of isopropyl and TBS moieties. Entries 4, 6, 7, 8, & 10 did not react under the stated conditions. Entry 4 is a 6-membered ring which may have less flexibility. Entry has a chloro and TBS silylether which may contribute negative steric and electronic effects. Entries 7 & 10 have the added bulk of 2 TBS groups.

Table 2. Pb(IV)OAc Cleavage

Entry	Acyloin/ Lactol	Cleavage Product	Yield
1			100%
2			100%
3			100%
4			100%
5			100%
6			100%
7			100%
8			89%

a. Conditions: Pb(OAc)4 (1.5 eq.), dry methanol (0.1M), room temperature, 24 hrs.

All acyloins and α-hydroxy lactols underwent complete conversion to their respective cleavage products in ~24 hours under the stated conditions (**Table 2**).

Overall, we have described a general mild oxidative cleavage methodology for vinylsulfones and vinyphosphonates that provides acceptable yields over a considerable range of diverse substrates. Our preliminary studies have defined (1) a general methodology for the osmium catalyzed dihydroxylation of vinylsulfones and vinyphosphonates, which are valuable intermediates in the synthesis of polyketide natural products. (2) the impact of stereochemistry and and steric bulk on the dihydroxylation process. As such, this method is anticipated to greatly facilitate the efficient synthesis of linear complex polyketidederived targets from vinylsulfone derived polypropionate substrates. Progress along these lines, will be reported in due course.