Temporary Silicon-Tethered Ring-Closing Metathesis Approach to Polyketide Fragments: Asymmetric Synthesis of the C1-C30 Fragment of Amphidinol 3

Thesis submitted in accordance with the requirements of the University of Liverpool for the Doctor in Philosophy

By

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Abstract

The temporary silicon-tethered ring closing metathesis sequence represents an important cross-coupling reaction for the formation of medium-sized unsymmetrical silaketals. These cyclic silaketals are important class of compounds in the synthetic organic chemistry due to their propensity to undergo facile refunctionalization *via* protodesilylation, oxidation, silane group transfer or transmetallation. Particularly attractive utility of this methodology is an application in the synthesis of polyoxygenated motifs found in many biologically important natural products. We have investigated the merit of stereoselective electrophilic functionalization in the context of the synthetic approach toward complex polyketide motifs present in intriguing biological targets. Based on our preliminary results we decided to apply this fruitful methodology as approach toward construction of C1-C30 fragment of amphidinol 3.

Dedication

To my beautiful wife Anja and daughter Tanja,

and to the greatest parents in the world Ivica and Zorica

Acknowledgements

I would like to express a sincere gratitude to my advisor Prof. P. Andrew Evans for his support, encouragement and guidance through out my graduate career. I am also greatly indebted for the opportunity to work on exciting novel chemistry in the best environment known to graduate student.

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Contents

List of Schemes

Chapter 1 TETHERED RING-CLOSING METHATHESIS IN NATURAL PRODUCT SYNTHESIS

List of Tables

List of Figures

List of Abbreviations

Å	angstrom
Ac	acetate
APT	attached proton test
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
^{t}BHP	*tert*-butyl hyroperoxide
Bn	benzyl
BOC	*tert*-butoxycarbonyl
^{n}Bu	butyl
^{t}Bu	*tert*-butyl
Cat-Borane	catechol borane
CBS	Corey-Bakshi-Shibata
CI	chemical ionization
CO	carbon monoxide
COD	1,5-cyclooctadiene
COSY	^{1}H-^{1}H correlation spectroscopy
Cp	cyclopentadienyl
*m*CPBA	3-Chloroperbenzoic acid
DCM	methylene chloride
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide

ds	diastereoselectivity
EA	ethyl acetate
ee	enantiomeric excess
EI	electronic impact
ent	enantiomer
eq	equivalent
Et	ethyl
eV	electron volt
FCC	flash column chromatography
FTIR	Fourier transform infra-red
g	gram
GC	gas chromatography
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	infra-red
LDA	lithium diisopropyl amine
Ln	ligand set
M	molar
Me	methyl
mg	milligram
MHz	megahertz
mL	milliliter
mmol	milimole

MOM	methoxymethyl
N	normal
NBS	*N*-bromosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear overhauser effect spectroscopy
NOESY	nuclear overhauser effect 2D-spectroscopy
Pd	palladium
Ph	phenyl
Piv	pivoyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
^{i}Pr	*iso*-propyl
^{n}Pr	propyl
P-TLC	preparative thin layer chromatography
Rh	rhodium
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin layer chromatography
TMS	trimethylsilyl

Ts	toluenesulfonyl
UV	ultraviolet
μL	microliter

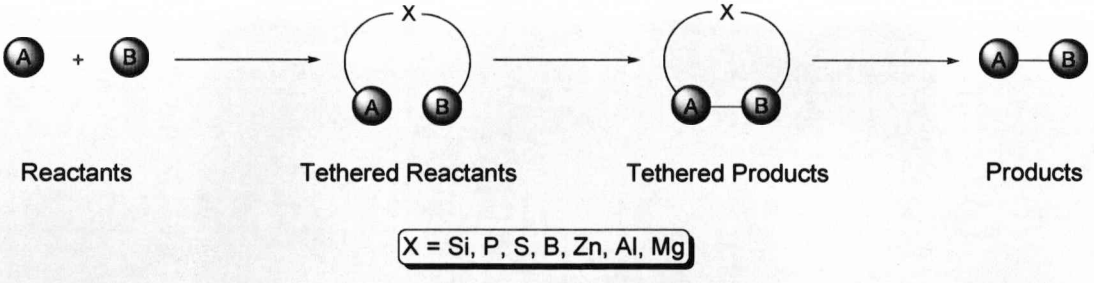
Chapter 1

Tethered Ring-Closing Metathesis in Natural Product Synthesis

1.1 Introduction

1.1.1 Temporary Silicon Tethers in Organic Chemistry

The proximity effect is an important parameter which describes the effectiveness of enzymatic biocatalytic transformations through their ability to attain and preserve a highly elevated concentration of reacting groups. Such effect can be achieved through a temporary intramolecular coupling of enzyme and specific substrate leading to the formation of enzyme-substrate complex. As the reaction proceeds, the product promptly migrates from the active site freeing the substrate from the enzyme, thus illustrating the temporary character of this process.[1] Well-documented advantages of intramolecular processes as opposed to intermolecular ones greatly contributed to the arrival of the concept of temporary tethers.[2] Temporary tethers were developed to transform an intermolecular reaction into the corresponding intramolecular variant through the sequential coupling of reacting partners. Optimal tethers allow for facile introduction of coupling partners, display a good stability toward reaction conditions and are readily removed or functionalized to provide the products not available *via* intermolecular version of a particular reaction (Scheme 1.1).



Scheme 1.1 *The Application of Temporary Tethers in Organic Synthesis*

In addition, tethering reaction partners decrease the entropic demands of a reaction, many times translating into higher reaction rates and milder reaction conditions. Transition states of temporarily tethered reactions also have fewer degrees of freedom which allows for greater selectivity in regio- and stereoselective reactions. Of the reported temporary tethers, silicon is used most frequently because it is readily accessible, it is stable to a multitude of reaction conditions and it is easily and selectively removed following the reaction.[3] Additionally, silicon readily undergoes refunctionalization *via* protodesilylation, oxidation, silane group transfer or transmetallation. Reactions contributing to the historical development of the temporary silicon tether concept are radical cyclizations[4a], allylations[4b], hydrosilylations[4c], [4+2] cycloadditions[4d,4e], [2+2] photocycloadditions[4f,4g], reductions[4h] and glycosylations.[4i] More recently, the utility of this concept has been expanded to transition metal catalyzed cycloisomerization[4j] and ring-closing metathesis reactions (*vide infra*). Furthermore, the temporary silicon tether concept is well established in the synthetic community particularly as it has been the subject of several comprehensive reviews.[5]

1.1.2 Olefin Metathesis Reactions in Organic Chemistry

The olefin metathesis reaction has emerged as a one of the most important carbon-carbon bond-forming reactions in modern synthetic chemistry. Construction of functionally diverse carbocycles and heterocycles *via* ring-closing metathesis (RCM) through metal mediated exchange of metal-alkylidine species and tethered dienes is primarily how this reaction has been utilized.[6] The stunning success of the ring-closing metathesis reaction can be largely attributed to the development of well-defined transition metal catalysts which displayed high activity and excellent

functional-group compatibility. Figure 1.1 depicts three of the most prominent olefin metathesis catalysts developed to date.

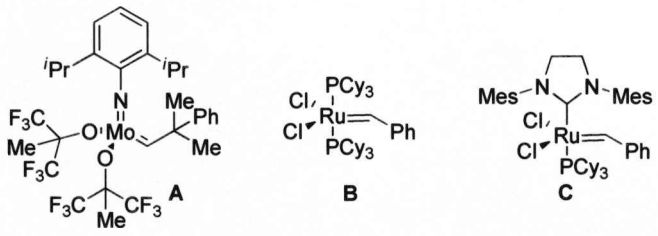


Figure 1.1 *The Most Prominent Olefin Metathesis Catalysts*

The molybdenum alkylidene catalyst **A,** initially developed by the Schrock group[7] revolutionized the modern metathesis reaction as well as catalyst development. Catalyst **A** displays extraordinary activity toward a variety of alkene substrates and is particularly well suited for the preparation of sterically congested systems. However, Schrock's catalyst is highly sensitive to air and moisture due to the electrophilic nature of the high-oxidation-state transition metal center. Subsequently, Grubbs and co-workers developed ruthenium carbene complex **B,** the so-called Grubbs' 1st generation catalyst.[8] Although less reactive then the molybdenum complex, Grubbs' catalyst displays a much broader functional group tolerance and provides opportunities for application of the ring-closing metathesis reaction toward the construction of complex natural products. Nevertheless, the search for new generation catalysts has continued to be the focus of much attention. Research efforts toward that end have been directed toward modifying ligands bound to the ruthenium center. Indeed, exchanging one of the phosphine ligands with an *N*-heterocyclic carbene ligand results in the formation of reactive complex **C**, which is, to some extent comparable to the activity of the complex **A**. This so-called, Grubbs' 2nd generation catalyst, as opposed to complex **A** displays exceptional thermal stability, functional group compatibility and resistance to

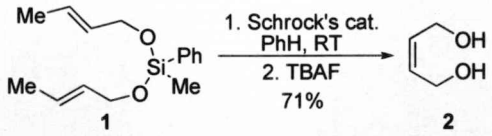
oxygen and moisture. In the last decade there has been an interesting development in the field of ring closing metathesis through the application of silicon tethers. The combination of a silicon-tether with ring closing metathesis provides a new strategy toward the construction of complex natural products and a variety of synthetically useful methodologies (*vide infra*).[5d,6j]

1.2 Temporary Silicon-Tethered Ring-Closing Metathesis Sequence and the Application in the Natural Product Synthesis

1.2.1 The Application of Silicon-Tether Bearing Two Oxygen Atoms (-O-Si-O-)

1.2.1.1 Alkene Ring-Closing Metathesis of Symmetrical Silaketals

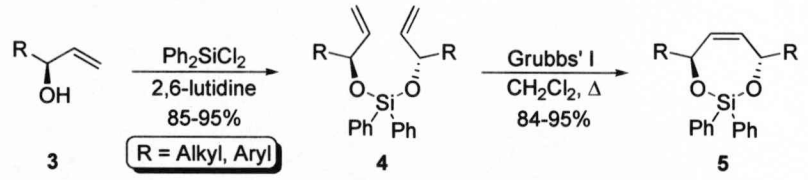
The temporary silicon-tethered ring-closing metathesis (TST-RCM) sequence was initially described by Grubbs and Fu, as a methodology for the construction of achiral 1,4-diols.[9] The key feature of this approach was the tolerance of the cyclization process to potentially sensitive *bis*-alkoxysilane functionality. However, due to sensitivity of the cyclic silaketal during purification, the crude material was treated with TBAF prior to isolation (Eq. 1.1).



(1.1)

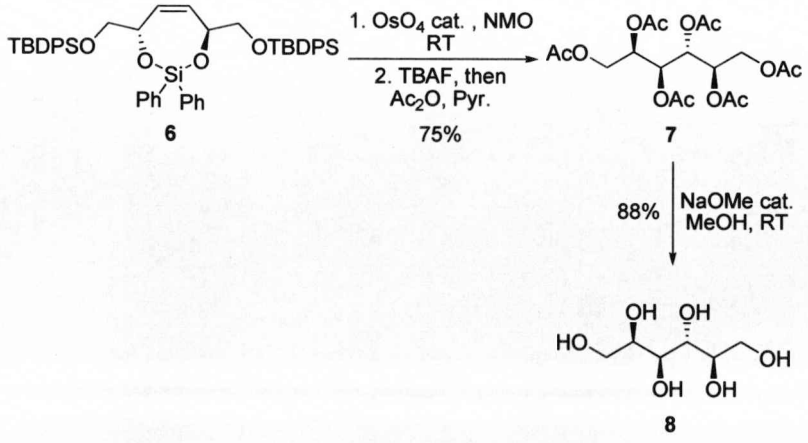
Evans and co-workers expanded the scope of the TST-RCM concept in construction of C_2-symmetric 1,4-diol intermediates (Scheme 1.2).[10] A series of enantiomerically enriched allylic alcohols, **3** were treated with diphenyldichloro-silane and 2,6-lutidine to furnish a variety of *bis*-alkoxysilane intermediates, **4** in excellent yield. The silaketal intermediates, **5** were then subjected to ring-closing metathesis utilizing Grubbs' 1st generation catalyst. The reaction proved to be

tolerant to a variety of secondary-substituted allyic alcohol substituents making the process fairly general for the construction of 1,4-diols.[10]



Scheme 1.2 *Synthesis of C_2-Symmetric Cyclic Silaketals*

Cyclic silaketals, **5** are masked C_2-symmetrical 1,4-diols which can be further elaborated into variety of other intermediates. The Evans' group applied this methodology toward the construction of carbohydrate *D*-altritol, **8** (Scheme 1.3).[10] Dihydroxylation of cyclic silaketal intermediate **6** with catalytic osmium tetroxide and NMO followed by silyl deprotection and subsequent peracetylation furnished peracetate, **7** in 75% overall yield. Saponification of **7** with sodium methoxide in methanol provided *D*-altritol **8** in 88% yield. This method is potentially applicable to solid-phase synthesis providing expeditious access to a library of carbohydrates.

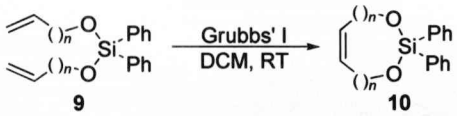


Scheme 1.3 *Asymmetric Synthesis of D-Altritol*

A year later, Hoye and Promo illustrated the utility of the TST-RCM reaction in preparation of cyclic *bis*-alkoxysilane intermediates.[11] They used diphenylsilane as a versatile linker substrate, which besides allowing for the formation of

symmetrical *bis*-alkoxysilanes allows for the preparation of unsymmetrical *bis*-alkoxysilanes through a sequential coupling of two different alcohols. RCM of silaketals was accomplished using Grubbs' 1st generation catalyst in refluxing DCM. When closing nine or eleven-membered silaketal rings, there was little conversion to the desired product, if the catalyst was added in a single portion, likely due to inactivation of the ruthenium catalyst. Bimolecular catalyst decomposition is even more evident when higher reaction concentrations were used. This event provides an access to a ruthenium hydride species which promotes the olefin isomerization as a competitive side-reaction. Hoye and Promo observed that slow addition of the catalyst as a solution in DCM *via* syringe pump increased the efficiency of the reaction. It is important to note that ring closing of the nine and eleven-membered silaketals afforded silacycles with satisfactory (*Z*)-olefin selectivity of 95:5 and 92:8, respectively (Table 1.1; entries 2-3).[11]

Table 1.1: *RCM Reaction of Symmetrical Silaketals*



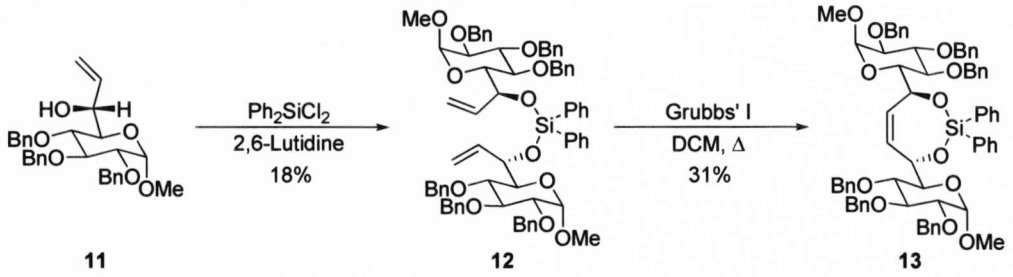
9 **10**

Entry	*n*	Temp.	Cat. Add. Time[a]	Reaction Time	Yield	*Z* : *E*[b]
1	1	25 °C	1 hr.	1 hr	84 %	97:3
2	2	25 °C	10 hr.	24 hr.	85 %	95:5
3	3	25 °C	10 hr.	10 hr.	78 %	92:8

[a] Catalyst was added slowly as a solution in DCM *via* syringe pump [b] GC-MS ratios

The TST-RCM cross-coupling reaction has rarely been used in carbohydrate chemistry. Köll and Lobbel adopted this strategy toward the construction of long chain-linked disaccharides.[12] Carbohydrate **11** was obtained from commercially available methyl *α-D*-glucopyranoside in five steps. Treatment of **11** with

diphenyldichlorosilane furnished C_2-symmetrical *bis*-alkoxysilane **12** in 18% isolated yield (Scheme 1.4). Ring closing metathesis of **12** utilizing Grubbs 1st generation catalyst provided the seven-membered cyclic diphenyl silaketal, **13** with flanking carbohydrate units in 31% yield. This approach has the potential to be used in iterative manner wherein homologation would provide long chain carbohydrate units with properties not yet explored.[12]



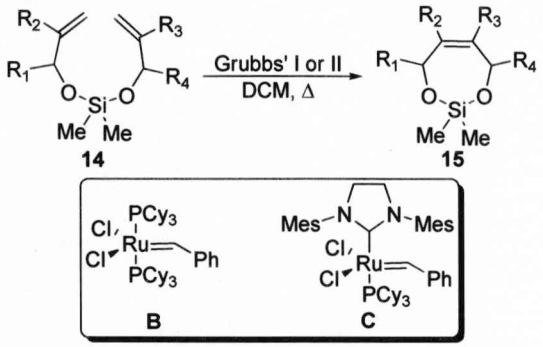
11 **12** **13**

Scheme 1.4 *Synthesis of Carbohydrate-Based Silacycle*

1.2.1.2 Alkene Ring-Closing Metathesis of Unsymmetrical Silaketals

Mioskowski and co-workers reported a comparative study in the preparation of various heterocycles through ring-closing metathesis employing Schrock's alkoxy imidomolybdenum, Grubbs' 1st and 2nd generation catalysts.[13] This study highlights further advances in the scope of RCM reaction, focusing on the ruthenium complex bearing the imidazolylidene ligand initially developed by Arduengo.[14] The now commercially available Grubbs' 2nd generation catalyst exhibits a greater functional group tolerance and is more stable to moisture and atmospheric oxygen than other RCM catalysts. Moreover, this catalyst displays greater thermal stability when compared to the 1st generation catalyst. Mioskowski and co-workers carried out a series of RCM experiments employing a variety of tethers such as phosphorus, nitrogen, oxygen and silicon. In nearly all examples, the ruthenium imidazolylidene emerged as a superior metathesis catalyst (Table 1.2; entries 2 and 4).[13] In the context of

Table 1.2: *RCM Reaction of Substituted Silaketals*



Entry	Cat.[a]	R_1	R_2	R_3	R_4	Yield	Time
1	**B**	Pr	H	H	Pr	57%	24 hr.
2	**C**	Pr	H	H	Pr	100%	2 hr.
3	**B**	H	Ph	H	Pr	0%	-
4	**C**	H	Ph	H	Pr	90%	24 hr.
5	**B**	H	Ph	Ph	H	0%	-
6	**C**	H	Ph	Ph	H	0%	-

[a] Reaction conditions: 0.02 M in refluxing DCM, 5-10 mol% of metathesis catalyst

closing seven-membered silaketals, acyclic precursors with substitution on both alkenes proved completely inactive to the RCM reaction (Table 1.2; entries 3, 5 and 6). In addition, substrates containing a nitrogen tether in the form of a secondary amine proved inactive, implying that molecules with the ability to strongly coordinate to the metal center inactivate the catalyst. BOC protection of the free amine provided a substrate that reacted smoothly in the RCM reaction providing the five-membered heterocycle in excellent yield.[13]

Heterocyclic ring systems are present in the "core" of many biologically active natural products which are of great importance in medicinal chemistry. In 1995, Witherup and co-workers isolated the novel bradykinin antagonists martinelline, **17** and martinellic acid, **16** from the root extract of the plant *Martinella*

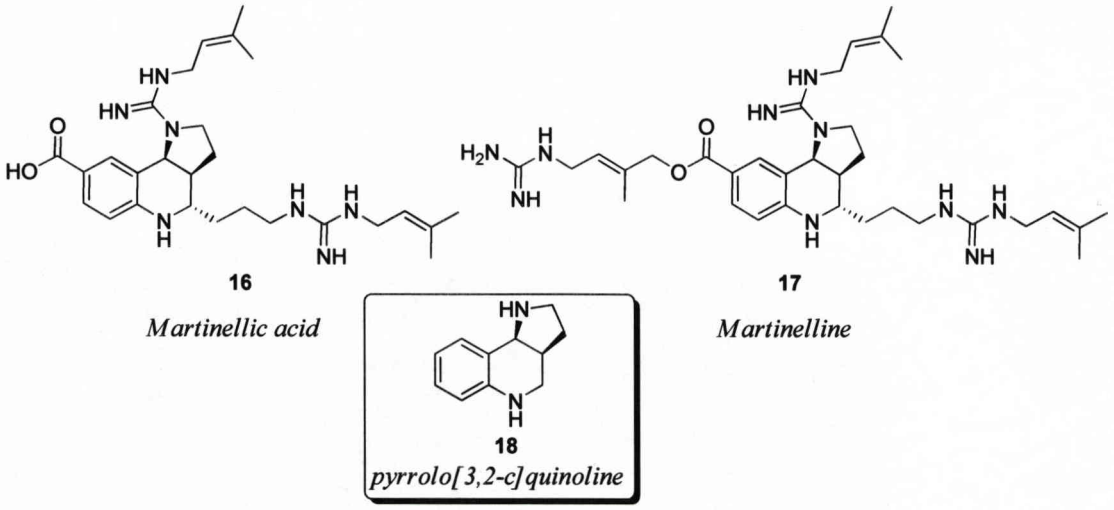
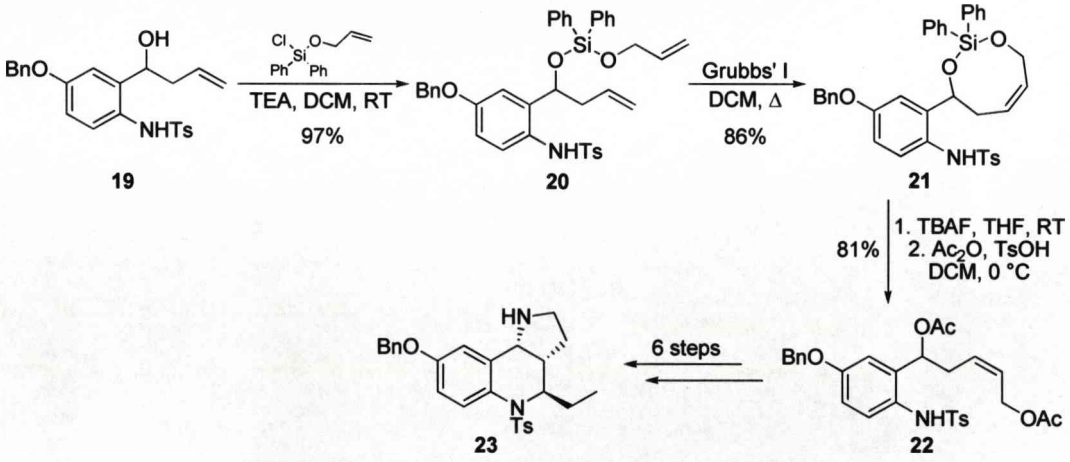


Figure 1.2 *Natural Products Containing The Pyrrolo[3,2-c]Quinoline Ring System*

iquitosensis.[15] The pyrrolo[3,2-*c*]quinoline, **18** (Figure 1.2) the central core of these alkaloids has garnered a significant amount of attention from the synthetic community.[16] Hara and co-workers described a method for the construction of the pyrroloquinoline framework using, as key steps, allylic substitution and TST-RCM

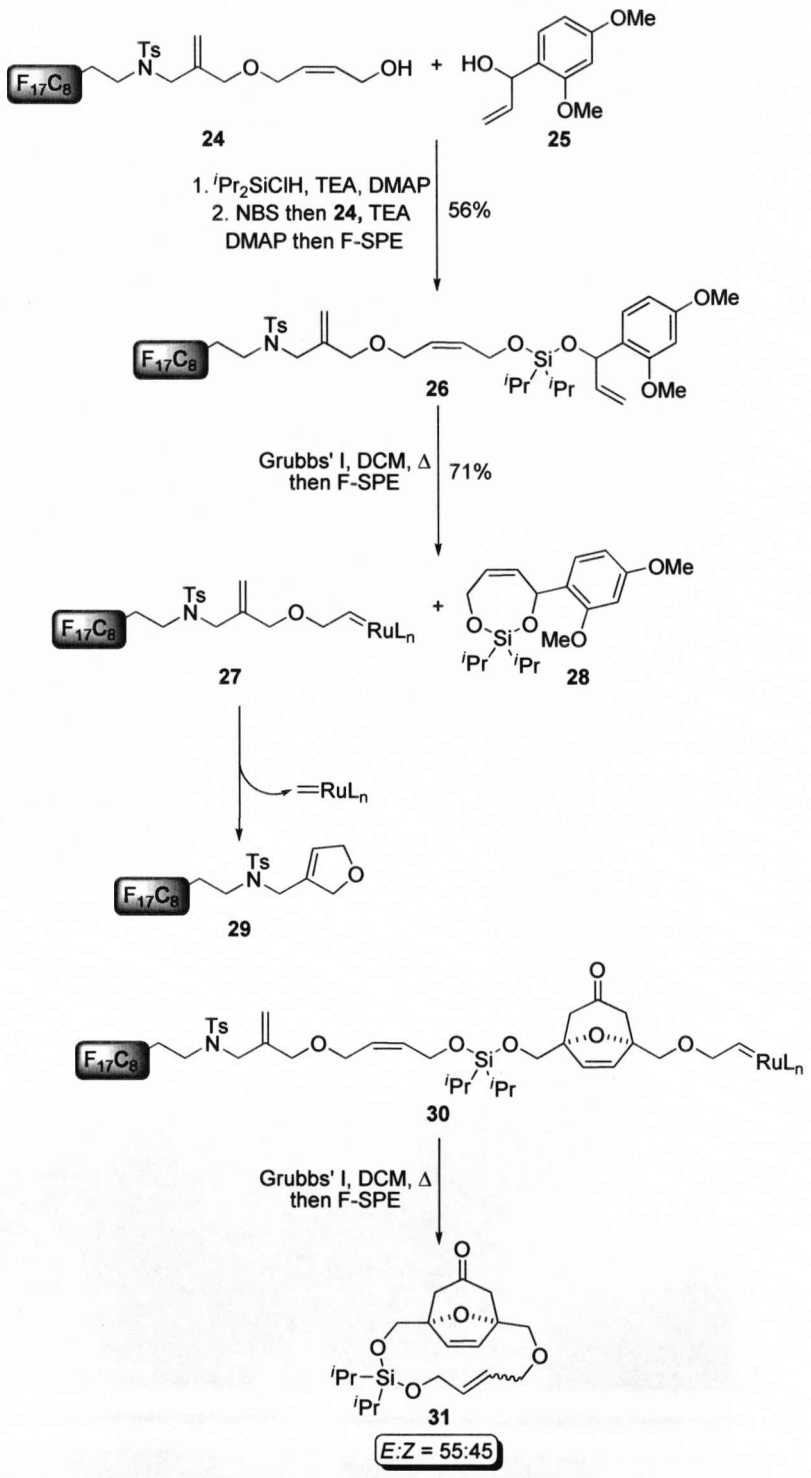


Scheme 1.5 *Synthesis of Pyrrolo[3,2-c]Quinoline Ring System*

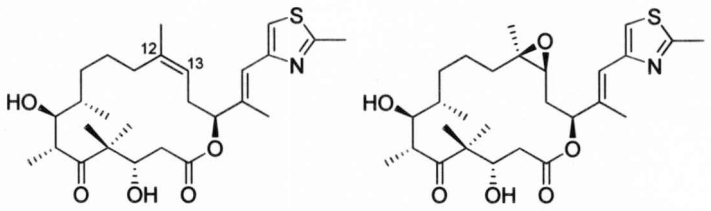
reactions.[16] Homoallylic alcohol **19** was successfully cross-coupled with *mono*-alkoxychlorodiphenylsilane to furnish *bis*-alkoxysilane intermediate **20** in excellent yield (Scheme 1.5). RCM of intermediate **20** afforded the eight-membered silacycle **21** which was further subjected to silyl deprotection followed by acetate formation

to furnish intermediate **22**. *Bis*-acetate **22** was elegantly elaborated into the pyrrolo-quinoline **23** over six steps highlighting a palladium mediated intramolecular allylic substitution reaction as a key step in the construction of the ring system.[16]

Nelson and co-workers reported an improved method for the construction of unsymmetrical silaketals used for fluorous-tagged metathesis substrates.[17] Substrates bearing a fluorous-tag can be easily purified using the fluorous-solid phase extraction method (F-SPE), making this method applicable to parallel synthesis. The silaketals in this study were constructed using a method originally developed in the Malacria laboratories.[18] Alcohol **25** was silylated with diisopropylchlorosilane (Scheme 1.6). Subsequent NBS activation of the silane provided the desired silyl bromide *in situ* which was immediately coupled to the fluorous-tagged alcohol, **24**. This protocol provided a wide range of fluorous-tagged silaketals with an uniformly high yield. The silyl activation using NBS exhibited a high degree of chemoselectivity, as functional groups which may be reactive toward NBS, such as alkenes, electron rich aromatics and alkyne remained intact. Fluorous-tagged silaketal **26** was then subjected to ring closing metathesis to provide the tag-free silacycle, **28** which was purified using the aforementioned F-SPE technique. Concomitant cyclization of **27** liberated the fluorous-tagged carbocycle, **29**. Chemoselective RCM of substrate **30** highlighted the utility of this concept. This cyclization furnished the fourteen-membered macrocycle **31** which was further elaborated into the corresponding diol by protodesilylation. Gratifyingly the competitive cyclization to form the six-membered ring was not observed, likely due to the reversible nature of this transformation.[17]



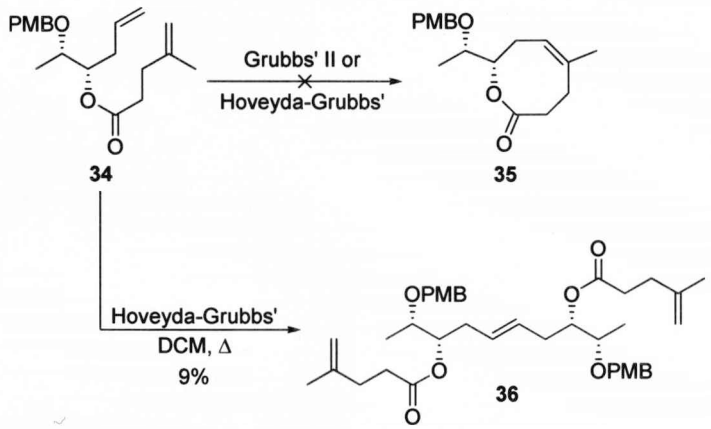
Scheme 1.6 *Fluorous-Tagged TST-RCM Reaction*



32 *Epothilone D* **33** *Epothilone B*

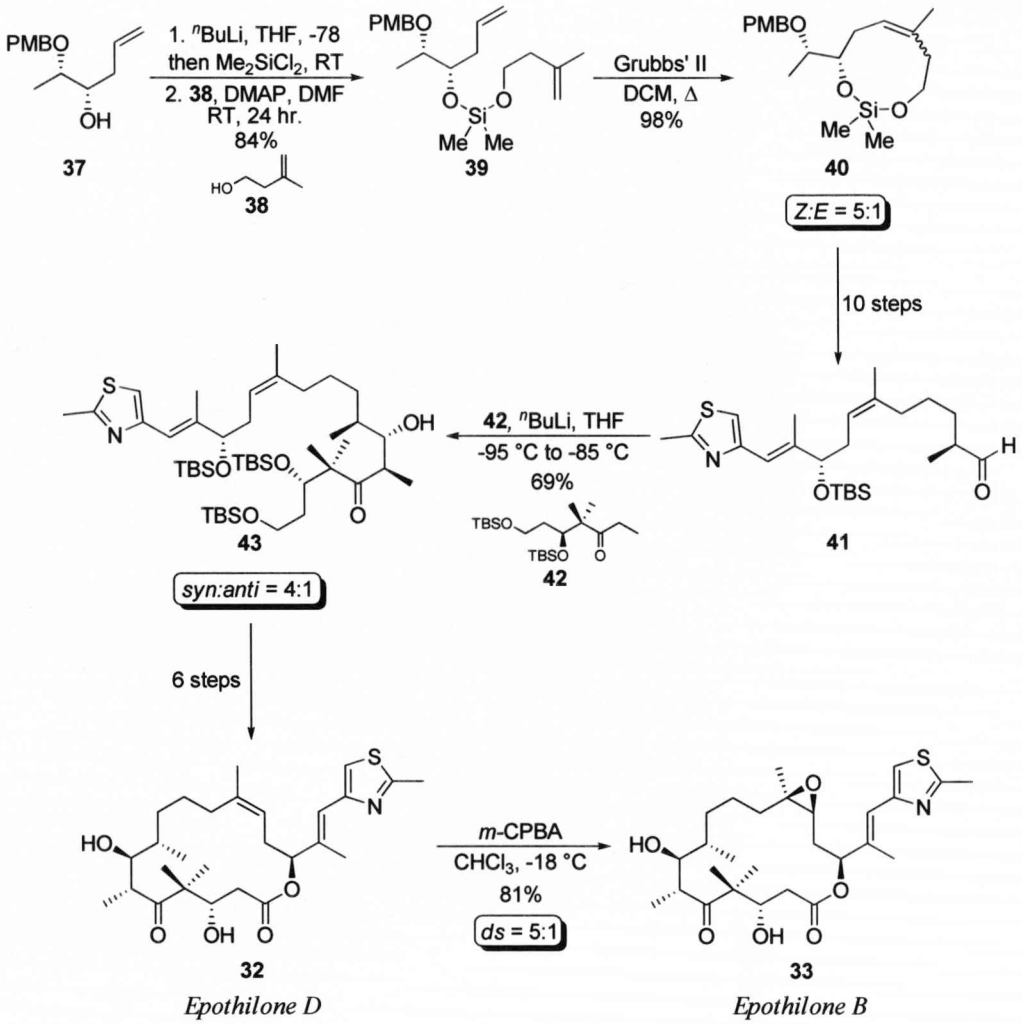
Figure 1.3 *Structures of Epothilone D and B*

Mulzer and co-workers utilized the TST-RCM strategy in the total synthesis of the complex natural products, epothilones B, **33** and its *deoxy*-precursor epothilone D, **32** (Figure 1.3).[19] Epothilone B **33** shows a remarkable affinity in microtubule binding and cytotoxicity against several standard and multiple drug res-



Scheme 1.7 *RCM Strategy for Construction of Eight-Membered Lactone* **35**

istant tumor cell lines. This secondary metabolite was isolated from the strain of myxobacteria *Sorangium cellulosum* by Höfle and co-workers in 1996.[20] Although epothilone B, **33** and natural products of the same class can be harvested efficiently from the fermentation broths, the possibility of discovering unnatural derivatives with greater potency has inspired many total synthetic efforts. One of the key synthetic issues in the total synthesis of epothilone D, **32** is the installation of the *cis*-olefin at the C12-C13 position. Mulzer and co-workers envisioned that the *Z*-olefin could be introduced through an RCM reaction of ester **34**. However, only the



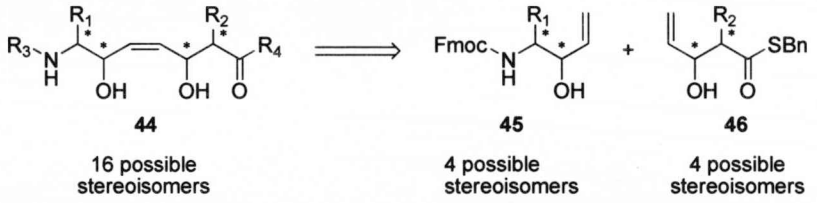
Scheme 1.8 *Total Synthesis of Epothilone D and B*

dimer **36** formation was observed in low yield (Scheme 1.7). This problem was circumvented utilizing a silicon tether as silicon is larger and is more polarizable, due to "soft" d-orbitals. This can lead to more facile bond angle distortion and weaker transannular interactions in medium ring silacycles as opposed to medium ring carbooxacycles. [19a]

The silicon-tethered RCM precursor, **39** was efficiently synthesized through the cross-coupling of **37** and **38** with dimethyldichlorosilane. Cyclization of **39** with Grubbs' 2nd generation catalyst proceeded smoothly favoring the *Z*-isomer. Silacycle **40** was then converted into advanced intermediate **41** over the course of ten steps,

setting the stage for the key aldol coupling. Union of aldehyde **41** and the enolate of **42** proceeded in good yield and modest diastereoselectivity favoring the *syn*-stereoisomer **43**. Aldol adduct **43** was further elaborated into the natural product **32** in six additional steps highlighting the Keck macrolactonization which allowed the closure of the sixteen-membered macrolactone in 69% yield. The natural product **33** was prepared by stereoselective epoxidation of the deoxygenated precursor **32** with modest level of diastereoselection (Scheme 1.8).[19]

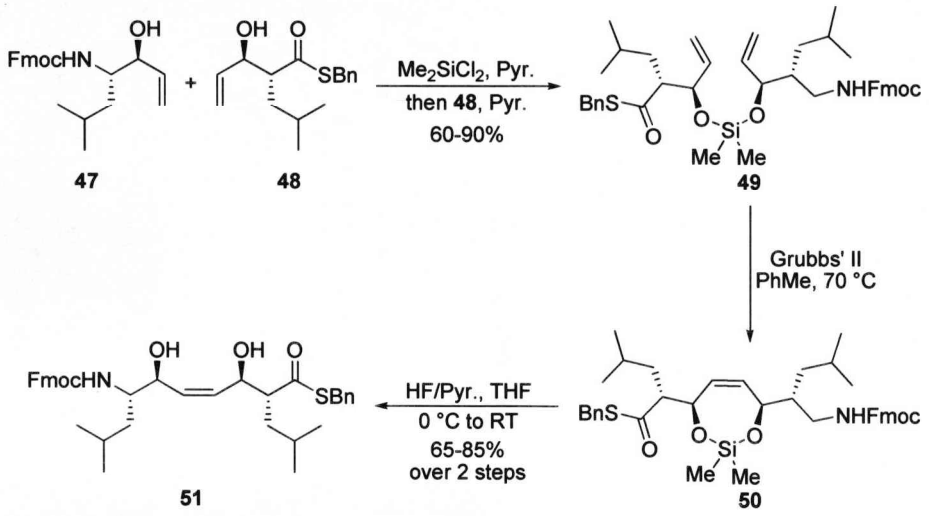
Verdine and co-workers reported an interesting modular approach toward stereodiversified natural product-like libraries using the TST-RCM reaction. The libraries were generated by union of amino monomer **45** with carboxy monomer **46** comprised of all possible stereoisomers connected by *cis*-olefin functionality installed through a silicon assisted RCM reaction (Eq. 1.2).[21] Groups R_1 and R_2 can



(1.2)

be varied to determine their affinity to interact with a receptor molecule through nonpolar and hydrogen-bonding interactions. Although this acyclic framework possesses some degree of conformational freedom, in reality, free rotation is restricted due to 1,3-allylic strain imposed by the *cis*-configured olefin and torsional strain between adjacent tertiary carbons. As a result, each of the 16 stereoisomers has a unique conformational preference. The entire library of conformers, in principle, covers a broad range of conformational space which increases the chance of matching the stereochemical requirement of a given receptor molecule. The amino and carboxylic acid functionalized termini of **44** allow installation of peptide

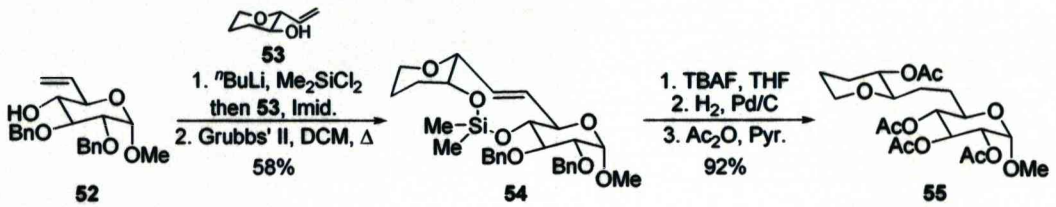
chains thus creating a chimerae type of polypeptide.[21] Allylic alcohol **47** was functionalized with Me_2SiCl_2 followed by a second coupling with allylic alcohol **48** provided the silaketal **49** in good overall yield (Scheme 1.9). RCM using Grubbs' 2nd generation catalyst required catalyst loadings between 5 and 10 mol% and furnished yields between 70 and 85% for *cis*-silaketal intermediates, **50**. *Trans*-silaketal rings required catalyst loadings between 10 and 15 mol% and furnished yields in the 65-70% ranges. Silyl deprotection afforded the 1,4-diol, **51** which can be further functionalized through standard solid phase peptide chemistry.[21]



Scheme 1.9 *Synthesis of Stereodefined Cis-1,4-Diol*

A year later, Verdine and Harrison expanded the scope of this modular approach to the stereodiversified libraries by utilizing the *cis*-1,5-enediol scaffold.[22a] The clear distinction between these two approaches is that the homoallylic alcohol version of monomer **47** was used. The four different stereoisomeric homoallylic alcohols were obtained through Brown enatioselective allylboration.[22b] The same three-step sequence as described above provided the access to all 16 stereoisomers of the *cis*-1,5-enediol fragment.[22a]

Metathesis chemistry has also received a significant amount of attention from the carbohydrate community over the past few years. Cross-metathesis between carbohydrate based olefins is generally inefficient and result in poor *E* to *Z* olefin geometry. To circumvent the selectivity problem, Postema and Piper envisioned that a TST-RCM approach would provide expeditious access to ethylene-linked disaccharides.[23]

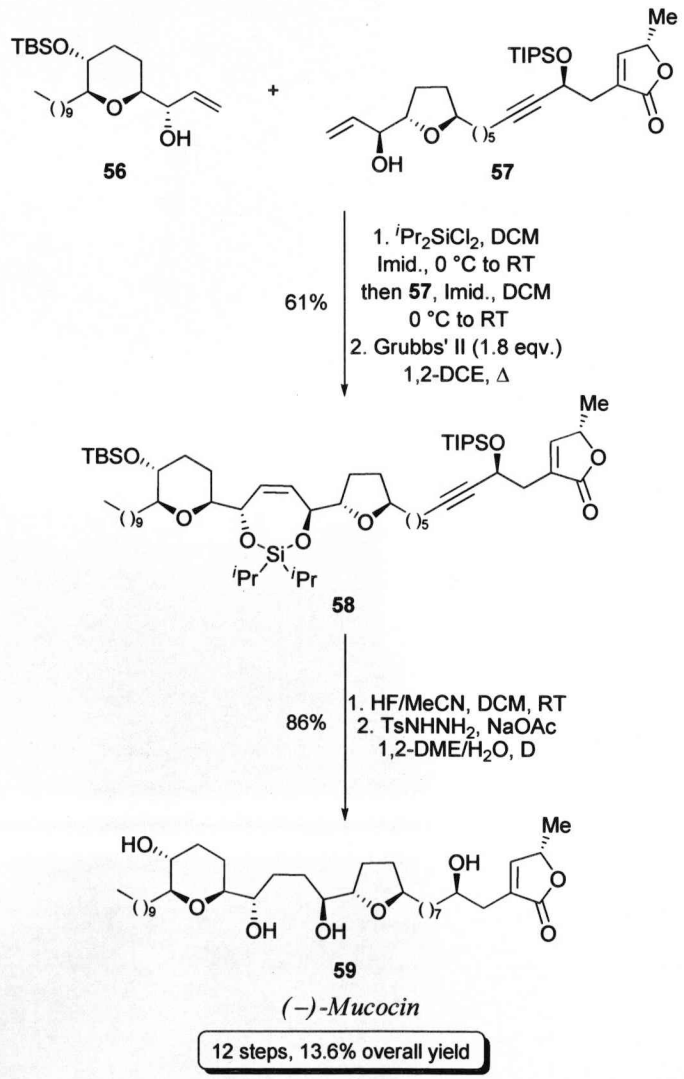


Scheme 1.10 *Cross-Coupling of Carbohydrate Units via TST-RCM*

Carbohydrates **52** and **53** were tethered using dimethyldichlorosilane (Scheme 1.10). Ring-closing metathesis using Grubbs 2nd generation catalyst provided nine-membered silacycle, **54** with exclusive (*E*)-olefin geometry. Silyl deprotection followed by double-bond reduction and peracetylation provided pyranoside **55** with excellent overall yield. Attempts to prepare more complex disaccharides proved troublesome as the reaction proceeded with low yields.[23]

Figure 1.4 *Rollinia mucosa*

Evans and co-workers further expanded the utility of the temporary silicon-tethered ring closing metathesis sequence in the total synthesis of the potent antitumor agent (−)-mucocin, **59**.[24] (−)-Mucocin was isolated by McLaughlin and co-workers in 1995 from the leaves of *Rollinia mucosa* (Figure1.4), a large tree native to the West Indies and Northern South America.[25] This annonaceous acetogenin displays an extraordinary activity against the A-549 and PACA-2 solid tumor cell lines with potency 10,000 times greater than adriamycin. [24] Allylic alcohol, **56** was treated with an excess of diisopropyldichlorosilane to afford the

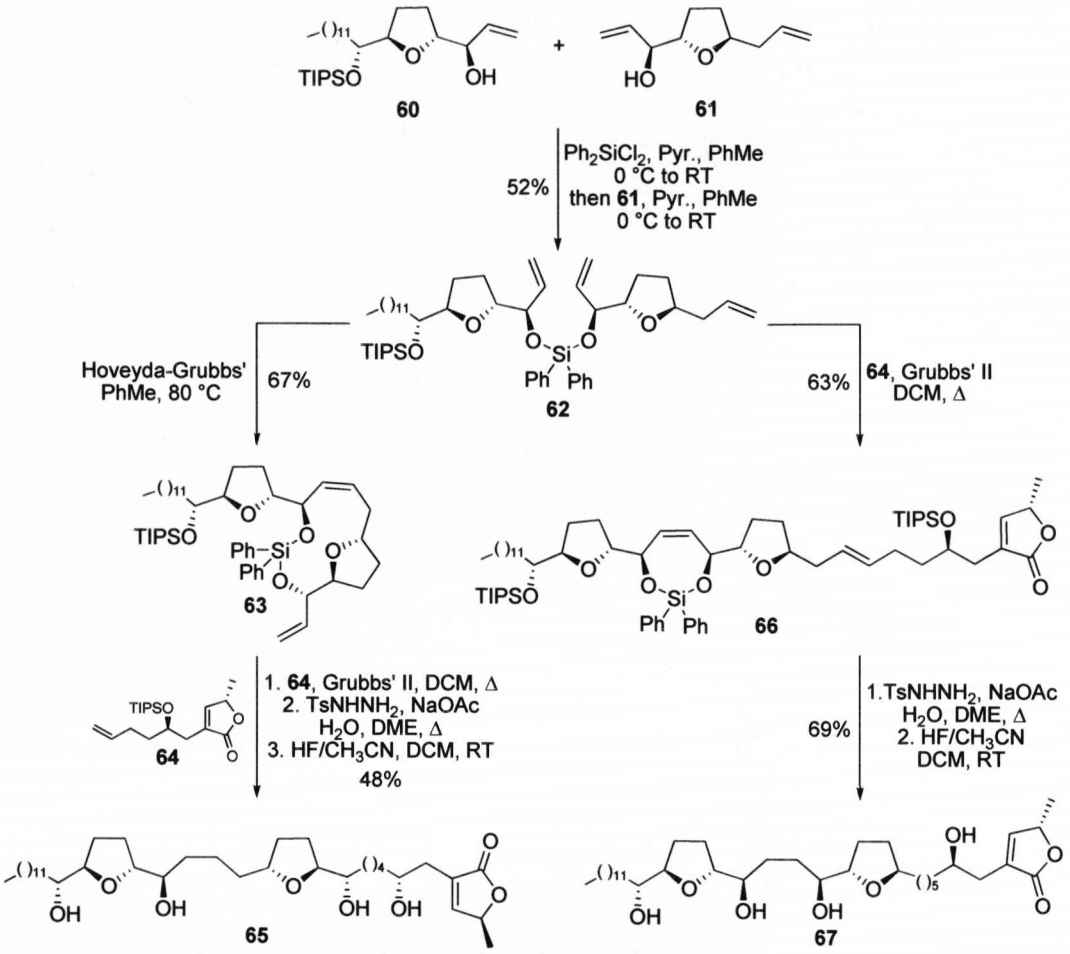


Scheme 1.11 *Total Synthesis of (−)-Mucocin*

corresponding *mono*-alkoxychlorosilane *in situ,* which was subjected to a second cross-coupling reaction with allylic alcohol, **57** (Scheme 1.11). The unsymmetrical *bis*-alkoxy silane intermediate was then treated with Grubbs' 2nd generation catalyst to furnish the cyclic silane, **58** in excellent overall yield (61% over three steps). Due to the increased steric demand of the diene a super-stoichiometric amount of ruthenium catalyst (1.8 equiv.) was required to complete this challenging transformation. Furthermore, slow addition the active carbene catalyst *via* syringe-pump was crucial for the suppression of unproductive dimerization and promotion of heterocoupling thus providing the silacycle, **58**. The synthesis was completed with a fluoride-mediated global silyl deprotection, followed by chemoselective diimide reduction of the alkyne and acyclic alkene in excellent overall yield. This triply convergent reaction sequence provided the potent antitumor natural product, **59** in twelve steps of the longest linear sequence and 13.6% overall yield.[24]

The TST-RCM reaction sequence has emerged as a prominent strategy toward the synthesis of annonaceous acetogenins.[24,26] Hoye and co-workers described an elegant and highly-convergent synthesis of (+)-gigantecin and its constitutional isomer (+)-14-deoxy-9-oxygigantecin. (+)-Gigantecin was isolated by McLaughlin and co-workers in 1990 from the bark of the Southeast Asian plant, *Goniothalamus giganteus*, and from the seeds of the Brazilian plant *Annona coriacea*.[27] Allylic alcohols **60** and **61** were sequentially coupled to diphenyldichlor-osilane to furnish *bis*-alkoxysilane **62** in modest yield. Silaketal **62** was subjected to ring-closing metathesis using Hoveyda-Grubbs' catalyst in an effort to furnish the predicted seven-membered cyclic silaketal intermediate, **66**. However, these conditions affected the formation of the eleven-membered silaketal, **63** through competitive cyclization with the distal alkene. Cross-metathesis with butenolide

fragment **64** followed by diimide reduction and global silyl deprotection gave 14-deoxy-9-oxygigantecin, **65** in 48% yield over three steps (Scheme 1.12).



Scheme 1.12 *Total Synthesis of 14-Deoxy-9-Oxygigantecin and (−)-Gigantecin*

It is important to note that result of this unexpected competitive ring closing metathesis was not discovered until the final product, **65** was compared to a sample of the real natural product (+)-gigantecin, spectroscopically. Hoye and co-workers overcame this problem by simply reversing the order of the metathesis reactions. Silaketal intermediate **62** was subjected to a one-pot cross-metathesis/RCM reaction with the butenolide fragment, **64** to afford the desired seven-membered silacycle product, **66** mixed with a small amount of the dimer of **62** which could be recycled by metathesis cleavage in the presence of ethylene.[28] Finally, diimide reduction and

subsequent silyl deprotection provided the natural product (+)-gigantecin, **67** in excellent overall yield (Scheme 1.12).[26]

Kozmin and Marjanovic reported an attractive display of the TST-RCM in the total synthesis of spirofungin A, **78**.[29] The natural product was isolated from *Streptomyces violaceusniger* Tü 4113 as a mixture of epimers in the spiroketal subunit. Spirofungin A displays a broad spectrum of biological activity against several human cancer cell lines with micromolar activity and selective inhibition of isoleucyl-*t*RNA synthetase in mammalian cells. The first synthesis of spirofungin A required chromatographic separation of the two spiroketal diasteromers.[29] Kozmin and Marjanovic developed the synthesis which overcomes this challenging spiroket-

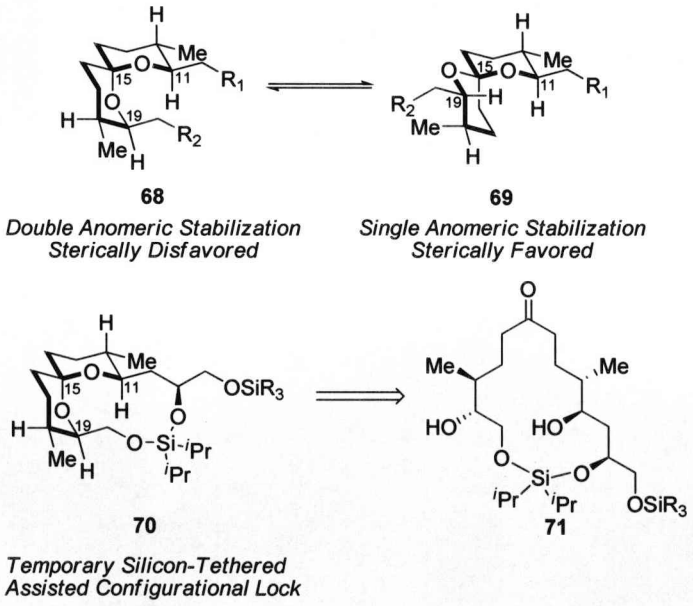
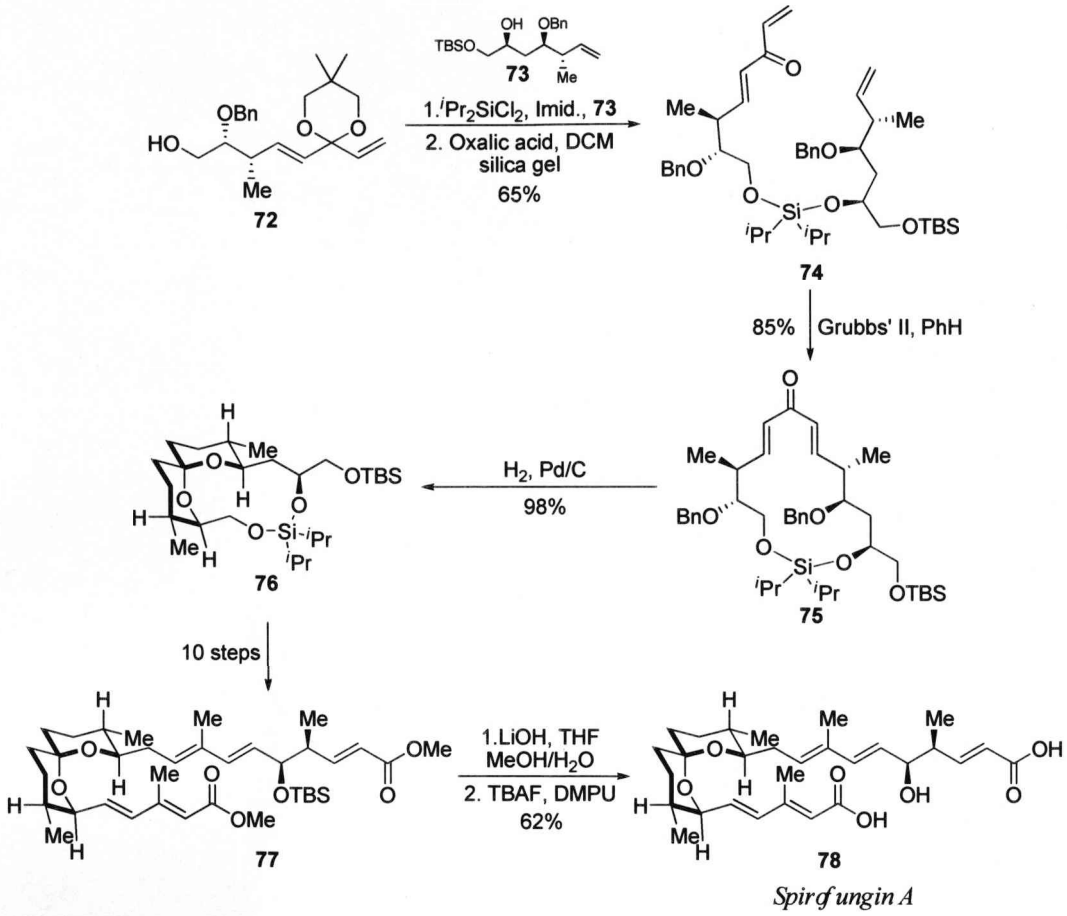


Figure 1.5 *Proposed Rationale for the Spiroketalization of Macrocycle* **71**

alization problem and provides a complete stereoselective access to spirofungin A. Desired spiroketal **68** is stereoelectronically favored by double anomeric stabilization; however, the axial substituent at C19 leads to significant steric interaction with C11. Furthermore, the undesired spiroketal, **69** while only displaying single anomeric stabilization lacks the steric congestion of **68**. As a

result, spontaneous spiroketalization leads to a mixture of the two spiroketals (Figure 1.5).[29] Kozmin and Marjanovic proposed that if the two structural side arms R_1 and R_2 were immobilized with a temporary silyl connection it would force the spiroketalization of macrosilacyclic ketone **71** to produce spirocycle **70** exclusively.

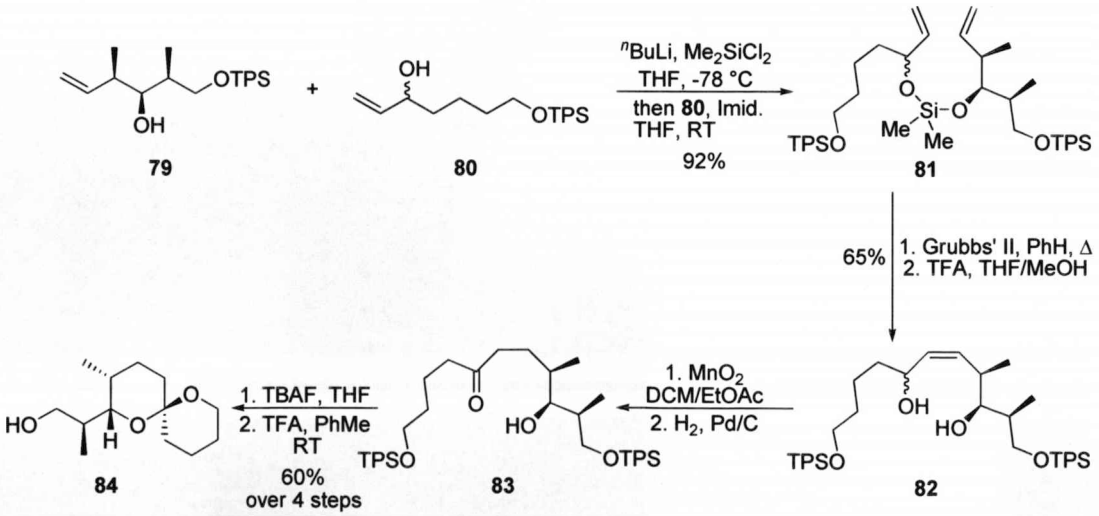


Scheme 1.13 *Total Synthesis of Spirofungin A*

Primary alcohol **72** was subjected to the sequential silicon tether cross-coupling utilizing secondary alcohol **73**, to furnish the *bis*-alkoxysilane intermediate (Scheme 1.13). Chemoselective removal of the 1,3-dioxane afforded tethered trienone, **74**. Ring closing metathesis utilizing Grubbs' 2nd generation catalyst delivered the fifteen-membered dienone, **75** in 85% yield. The reaction proceeded chemoselectively, promoting the cyclization at only the two terminal alkenes of trienone **74**. Hydrogenation of intermediate **75** followed by concomitant

deprotection of benzyl ether led to spontaneous cyclization to form the silicon tethered spiroketal, **76** as a single stereoisomer in a remarkable 98% yield. At this stage of the synthesis, intermediate **76** was elaborated into the advanced intermediate **77** over the course of ten steps. Finally, saponification of **77** followed by silyl deprotection delivered spirofungin A, **78** in a completely stereoselective manner in twenty longest linear steps.[29]

Eustache and co-workers reported an interesting approach to the spiro[5.5]ketal fragment of okadaic acid using the TST-RCM strategy.[30] The spiro[5.5]ketal systems are a common moiety found in numerous natural products. The most widely adopted protocol for spiroketalization is the acid catalyzed cyclization of dihydroxyketones. However, the preparation of the required dihydroxyketone precursors becomes increasingly more difficult as molecular complexity increases, which according to the hypothesis set forth by Eustache would be negated by the use of the TST-RCM sequence.[30]



Scheme 1.14 *Synthesis of Spiro[5.5]Ketal Unit*

Homoallylic alcohol **79** was treated with Me_2SiCl_2 at low temperatures followed by cross-coupling with the racemic allylic alcohol, **80** to furnish the unsymmetrical *bis-*

alkoxysilane, **81** as a mixture of diastereoisomers. RCM followed by selective silyl deprotection provided the desired 1,5-diol **82**. Intermediate **82** was then subjected to chemoselective oxidation and subsequent olefin reduction to provide hydroxyketone, **83**. With intermediate **83** in hand, the stage was set for the final spirocyclization. Exposure of **83** to TBAF followed by acid catalyzed spiroketalization provided the spiro[5.5]ketal moiety, **84** in excellent yield over four steps (Scheme 1.14).[30] The robustness of this approach for the synthesis of spiro[5.5]ketals was demonstrated unambiguously as it was utilized for the total synthesis of the spiroketal-containing natural product, attenol A.[31]

Temporary silicon-tethered ring-closing metathesis was the method of choice in the total synthesis of attenol A, **85** by Eustache and co-workers.[31] Attenols A, **85** and B, **86** were recently isolated from the Chinese bivalve *Pinna attenuata* and synthesized by Uemura.[32] Structural differentiation between the two metabolites is in the spiroketal region where attenol A contains [5.4] spiroketal unit and attenol B contains the dioxabicyclo[3.2.1]octane unit (Figure 1.6).

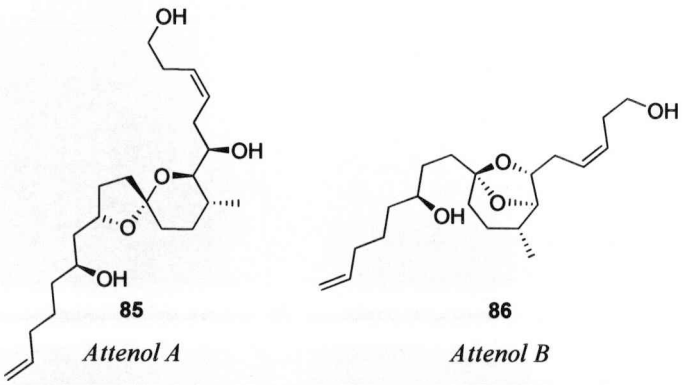
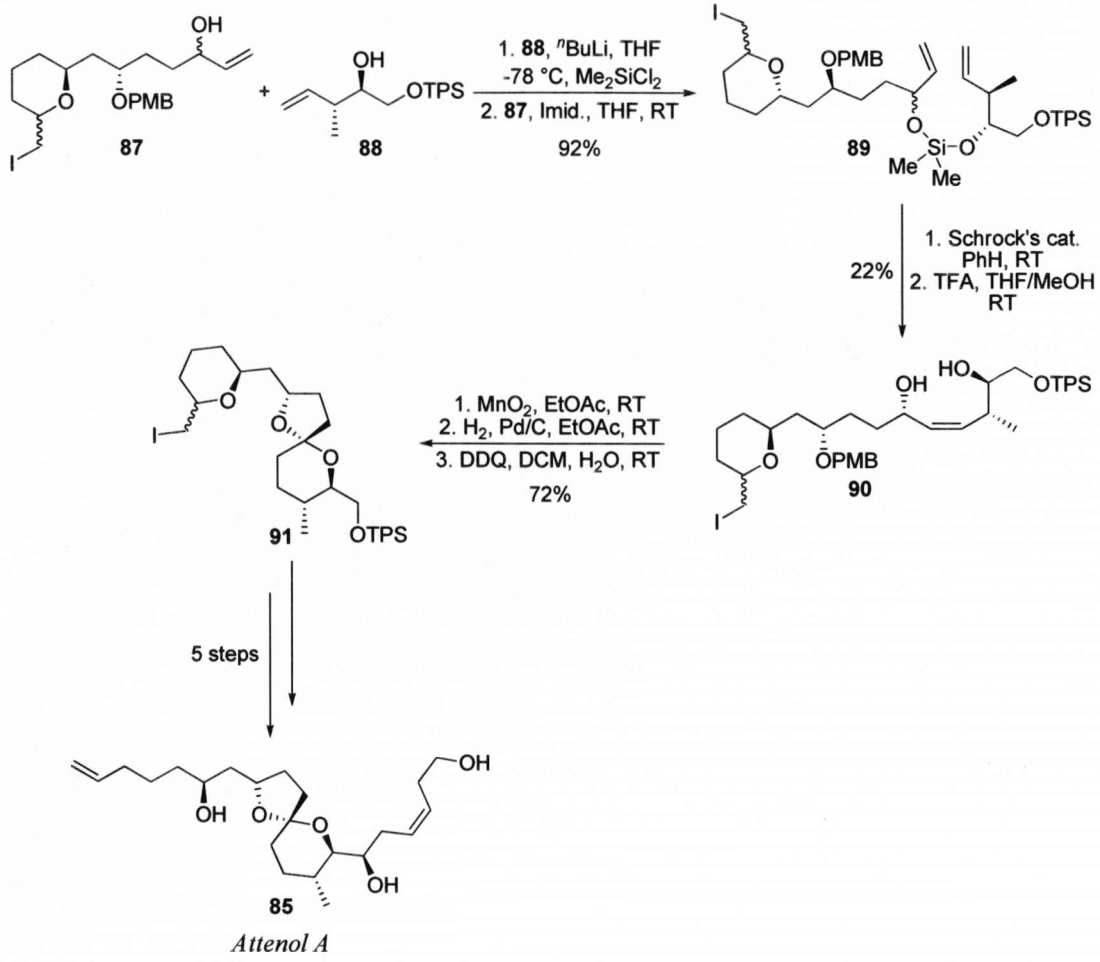


Figure 1.6 *Structures of Attenol A and B*

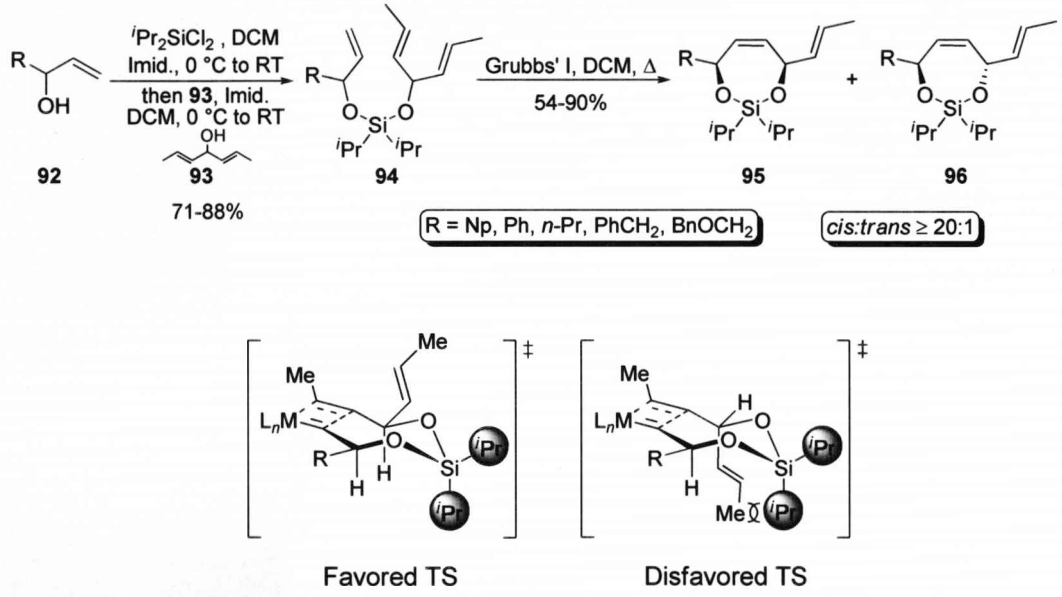
The key steps in this synthesis were silicon tethered cross-coupling followed by RCM for the union of the two central fragments. Of particular interest was the rare application of an iodoetherification as a means of protection of the 1,5-ene-ol



Scheme 1.15 *Total Synthesis of Attenol A*

moiety. Fragment **87** present as a diastereomeric mixture, was derived from iodoetherification and subsequent allylic oxidation of the C_2-symmetrical 1,3-diol. Sequential cross-coupling of intermediate **87** and homoallylic alcohol **88** furnished the *bis*-alkoxysilane intermediate **89** as an equimolar mixture of diastereomers in excellent yield over two steps. Exposure of the intermediate **89** to Schrock's metathesis catalyst resulted in only partial conversion affording the eight-membered silacylcle as a single diastereoisomer. NOE studies confirmed the *trans*-stereoisomer of the resultant silacycle. The recovered starting material, enriched with the opposite diastereoisomer could not be forced to completion by resubmitting it to the ring

closing metathesis conditions. It is likely that the conformational disposition of the unreacted isomer did not favor the ring closure so this transformation acted as a stereoisomeric resolution. Silyl deprotection furnished the diol intermediate **90** which was converted into the key spiroketal intermediate **91** by oxidation of the allylic alcohol, reduction of the conjugated alkene and oxidative removal of the PMB group with concomitant spiroketalization. Intermediate **91** was further elaborated into the natural product attenol A in five additional steps (Scheme 1.15).[31]



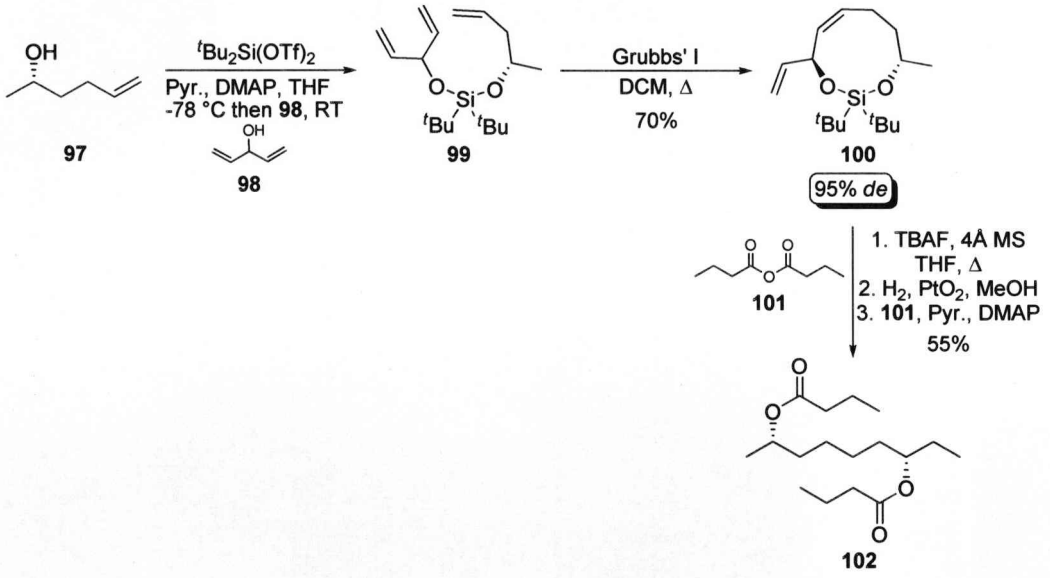
Scheme 1.16 *Application of TST-RCM in Long-Range Asymmetric Induction*

In an advancement in the field of long range asymmetric induction, Evans and co-workers described the use of the TST-RCM reaction toward the synthesis of 1,4-, 1,5- and 1,6-cyclic silaketals.[33] Towards this end, mixed *bis*-alkoxysilane, **94** was prepared through treatment of allylic alcohol **92** with diisopropyldichlorosilane followed by subsequent coupling with divinyl carbinol, **93**. Ring closing metathesis utilizing Grubbs' 1st generation catalyst provided the seven-membered cyclic silaketals, **95** with exquisite 1,4-diastereocontrol. Interestingly, Schrock's catalyst as

well as Grubbs' 2nd generation catalyst proved inferior for this transformation, both in yield and selectivity. The basis for this long-range stereoinduction is presumably the nonbonding interaction of the isopropyl group on the silicon tether with the *pseudo*-axial substituent on the forming ring; either the hydrogen, as seen in the favored transition state or the propenyl substituent as illustrated in the disfavored transition state (Scheme 1.16). This prompted an examination of the effect of the silicon tether substituent on the reaction and the diisopropylsilyl connection proved to be the best tether offering the highest level of diastereocontrol. This reaction was shown to be remarkably tolerant to a broad range of branched and linear alkyl substituents, as well as aryl, benzyloxymethyl and carboalkoxy substituents. Furthermore, this method of long range asymmetric induction was successfully employed for the formation of 1,5- and 1,6-cyclic silaketals. Remarkably, these reactions proceed with a reversal in diastereoselectivity favoring the *trans*-silaketal isomers.[33]

Organic synthesis plays an important role in crop protection. Standard measures for crop protection by controlling the pest population include the spraying of insecticides throughout the time of possible pest emergence. Because the infestation climax it is often difficult to determine, frequent insecticide treatments are necessary, which become an economical burden and detrimental to the environment. Sex pheromones, often attainable by means of organic synthesis, can be used effectively in trap monitoring of emerging adults of pest population to allow for the timing of effective spraying. The TST-RCM approach was used effectively in the synthesis of the sex pheromone (2*S*,7*S*)-dibutyroxynonane **102**, a sexual hormone of orange wheat blossom midge, *Sitodiplosis mosellana*. This pest causes serious damage to wheat crops all over the world by feeding on the wheat kernels,

decreasing the crop quality and promoting secondary fungal attack. Initial approaches in the synthesis involved enzymatic kinetic resolution and long-range asymmetric induction to selectively generate two stereogenic centers. However, the five-carbon distance between two stereogenic centers complicates the asymmetric induction of the second stereocenter. Pickett and co-workers envisioned that the long-range asymmetric induction necessary to accomplish this synthesis of (2*S*,7*S*)-dibutyroxynonane, **102** could be accomplished using TST-RCM.[34] Treatment of the enantiomerically enriched secondary alcohol **97** with one equivalent of $^{t}Bu_2Si(OTf)_2$ at low temperatures followed by addition of divinylcarbinol **98** with gradual warming afforded the *bis*-alkoxysilane intermediate **99**. Ring-closing metathesis rea-

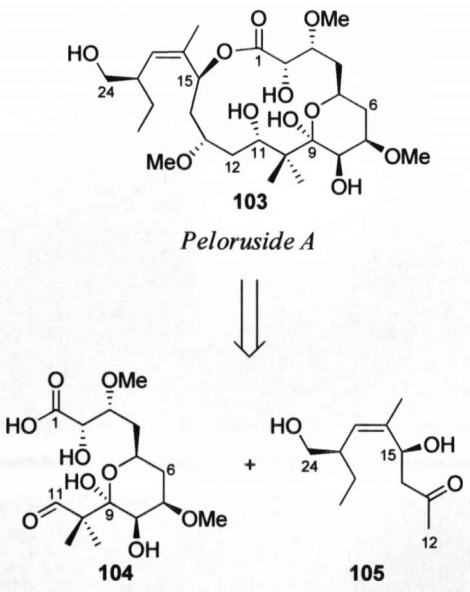


Scheme 1.17 *Total Synthesis of (2S,7S)-Dibutyroxynonane*

ction with Grubbs' 1st generation catalyst furnished the nine-membered silacycle **100** with excellent 1,6-diastereocontrol and overall yield. It is important to note that other temporary silicon tethers such as diphenylsilane and diisopropylsilane furnished the corresponding silacylcle with inferior diastereocontrol to that of the *tert*-butylsilyl derivative, due primarily to steric hindrance. However, the

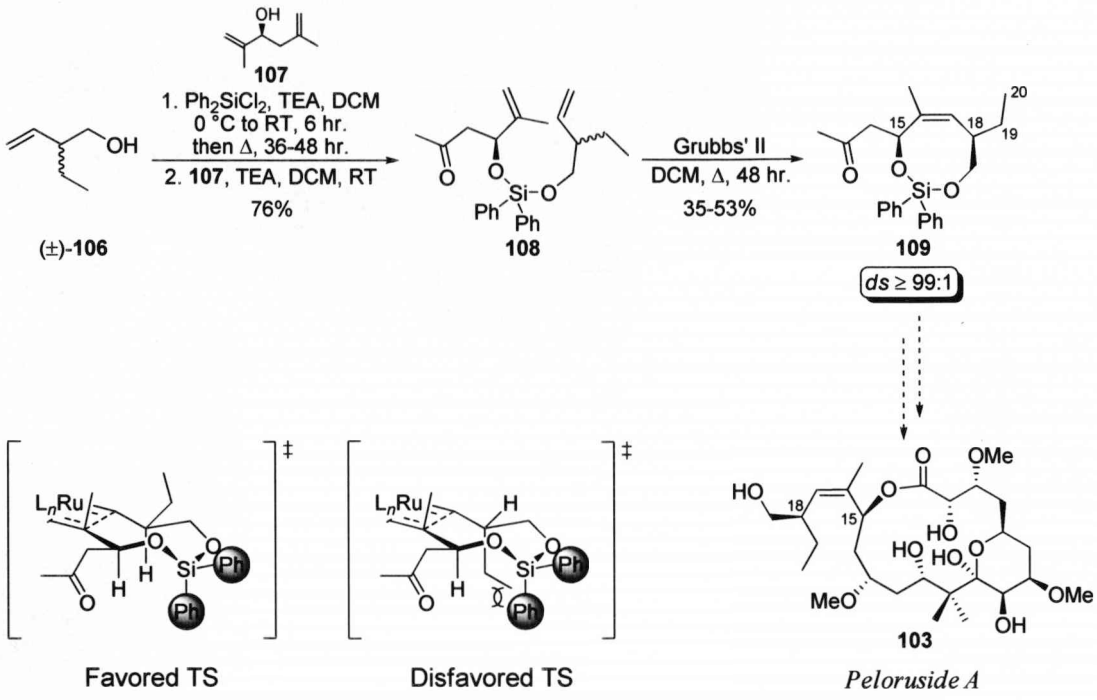
protodesilylation step is rather difficult, requiring overnight reflux using a ten fold excess of TBAF with molecular sieves. Peracylation of the diol furnished the sex pheromone (2*S*,7*S*)-dibutyroxynonane, **102** (22% overall yield, 99% *ee*, 94% *ds*) (Scheme 1.17). This approach provided a potential route for the commercial production of this pheromone.[34]

Recently, Harvey and co-workers described the utility of silicon-tethered ring-closing metathesis in the construction of C12-C24 fragment of peloruside A.[35] In 2000, Nortchote and co-workers reported an isolation of this potent cytotoxic macrolide from the marine sponge *Mycale hentscheli*.[36] Peloruside A, **103** displays a potent biological activity, featuring the microtubule stabilizing mode of action.[37] Pharmacological research revealed that the potency of peloruside A toward the cancer cells significantly increase when used in the combination with taxoid drugs[38] Such synergistic effect makes peloruside A **103** an attractive drug candidate.



Scheme 1.18 *Structure and Retrosynthetic Analysis of Peloruside A*

Harvey's efforts toward the synthesis of peloruside A **103** are based on the convergent strategy, which incorporates the union of the C1-C11 aldehyde **104** and C12-C24 methyl ketone **105** *via* aldol methodology (Scheme 1.18). The *Z*-olefin in



Scheme 1.19 *Synthesis of Eight-Membered Silacycle* **109** *via TST-RCM Reaction*

105 was installed stereoselectively through the one-pot silicon tether cross-coupling followed by subsequent ring-closing metathesis. Treatment of racemic homoallylic alcohol **106** with diphenyldichlorosilane and TEA provided a reactive *mono*-chloroalkoxysilane (Scheme 1.19). The reactive chlorosilane was then reacted with allylic alcohol **107** thus forming the *bis*-alkoxysilane **108** as a mixture of stereoisomers. With the compound **108** in hand the stage was set for the long range asymmetric induction.[30,31,33] Indeed, after an extensive optimization, the ring closing metathesis of **108** using the Grubbs' 2nd generation catalyst furnished the eight-membered *cis*-silacycle **109** with exquisite diastereocontrol thus illustrating the utility of 1,4-asymmetric induction.[33] The silacycle **109** represents a masked C12-

C24 diol, required for the synthesis of the peloruside A. The reminder of the material corresponds to the recovered starting diene and products of the cross-metathesis.

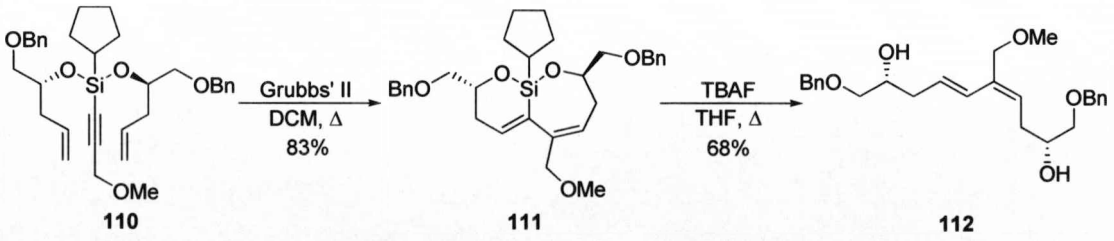
The stereoselectivity obtained in this reaction can be justified by the mechanistic rationale closely related to the one proposed by Evans and co-workers (Scheme 1.19).[33] The basis for the 1,4-stereoinduction lies in the assumption that the *pseudo*-axial phenyl group of the silicon tether would participate in nonbonding interactions with *pseudo*-axial ethyl group at C-18 as displayed in the disfavored transition state. Consequently, the ring-closing metathesis would proceed through the favored transition state with ethyl group in *pseudo*-equatorial position thus forming *cis*-1,4-silaketal **109**. The stereochemistry has been determined by a strong NOE correlation between H15 and H18 which is consistent with (15*S*, 18*R*) configuration as required in the natural product **103**.

1.2.1.3 Enyne Ring-Closing Metathesis

Enyne metathesis is an exceptional reaction because it provides a product containing a 1,3-diene functionality clearly distinctive from the functionality of starting material.[39] Moreover, enyne metathesis can be used in tandem processes in combination with ring-closing metathesis or cross-metathesis to construct multiple carbon-carbon bonds in acyclic or cyclic substrates.[40] Unlike other metathesis reactions, however, enyne metathesis suffers from a lack of regio- and stereo-control. In the last few years, the focus of research concerning this reaction has been directed toward the development of methodology which would provide solutions to these shortcomings and transform this reaction into a general method for the construction of stereodefined dienes.[41] Temporary silicon-assisted enyne metathesis

offers new insights into the reactivity profile of tethered enyne intermediates through the stereoselective construction of silacyclic dienes (*vide infra*).[40]

Alkynyl silyl ethers are an important class of compounds which serve as precursors to stereochemically defined 1,3-dienes. They are prepared by successive silylation of primary, secondary or tertiary alcohols with di- or trialkynylsilanes under basic conditions.[40a] The reaction is fairly general and can be applied to the synthesis of *mono*-alkoxyalkynylsilanes, symmetrical *bis*-alkoxyalkynylsilanes and unsymmetrical *bis*-alkoxyalkynylsilanes. Lee and Grimm disclosed an alternative method for the preparation of alkynyl silyl ethers. Their use of the ring closing enyne metathesis further highlights the synthetic value of silyl ethers and silaketals in the formation of fused bicycles *via* a tandem process (Scheme 1.20).[40] Treatment of the symmetrical alkynyl silaketal, **110** with Grubbs' 2nd generation catalyst in refluxing DCM furnished the [5.4.0] bicyclic system, **111**. The removal of tether gave the corresponding diol, **112** in good yield.[40c]

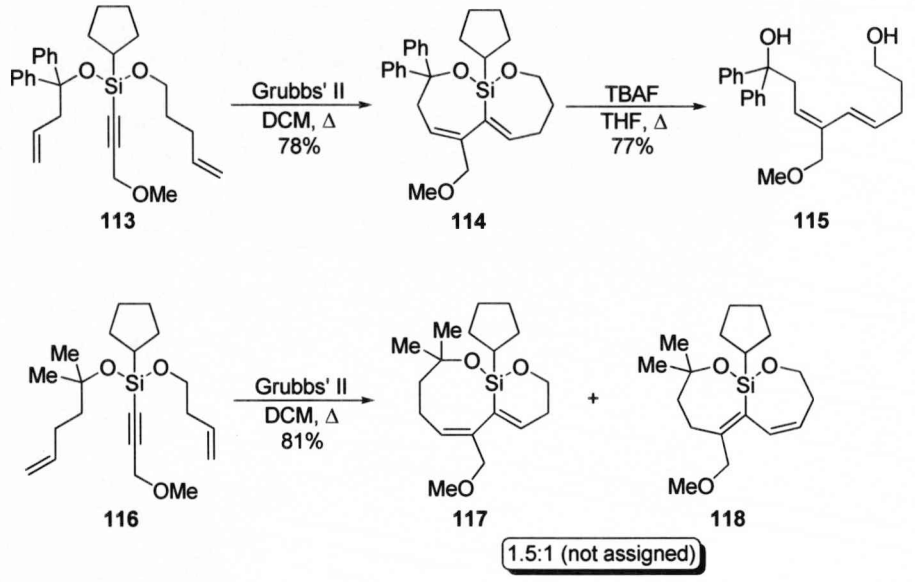


110 **111** **112**

Scheme 1.20 *Tandem Enyne RCM of Symmetrical Alkynylsilaketal*

When unsymmetrical alkynylsilaketals are subjected to the tandem enyne RCM, the product distribution depends on the length of the tether and its substitution. In alkynylsilaketal **113**, the steric differentiation of two pendant alkenes allows the initiation at the less hindered olefin (Scheme 1.21). Consequently, the tandem enyne metathesis furnished the bicyclic siloxane **114** as a single product. In

the silaketal **116**, the steric discrimination between the two initiation sites is insufficient which resulted in the formation of the mixture of two possible siloxanes **117** and **118** with 1.5:1 ratio (the identities of the major and minor products were not assigned).[40c]



Scheme 1.21 *Tandem Enyne RCM of Unsymmetrical Alkynylsilaketal*

In 1994, Höfle and co-workers isolated the structurally interesting boron-containing C_2-symmetrical macrodiolide tartrolon B, **119** from myxobacterium *Sorangium cellulosum* strain So ce678.[42] Tartrolon B is a boronate complex which is in equilibrium with the uncomplexed boron-free tartrolon A, **120** which exists as a

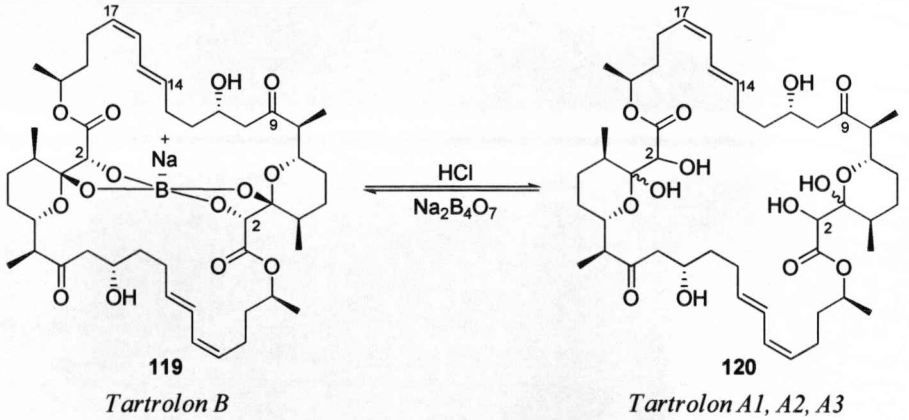
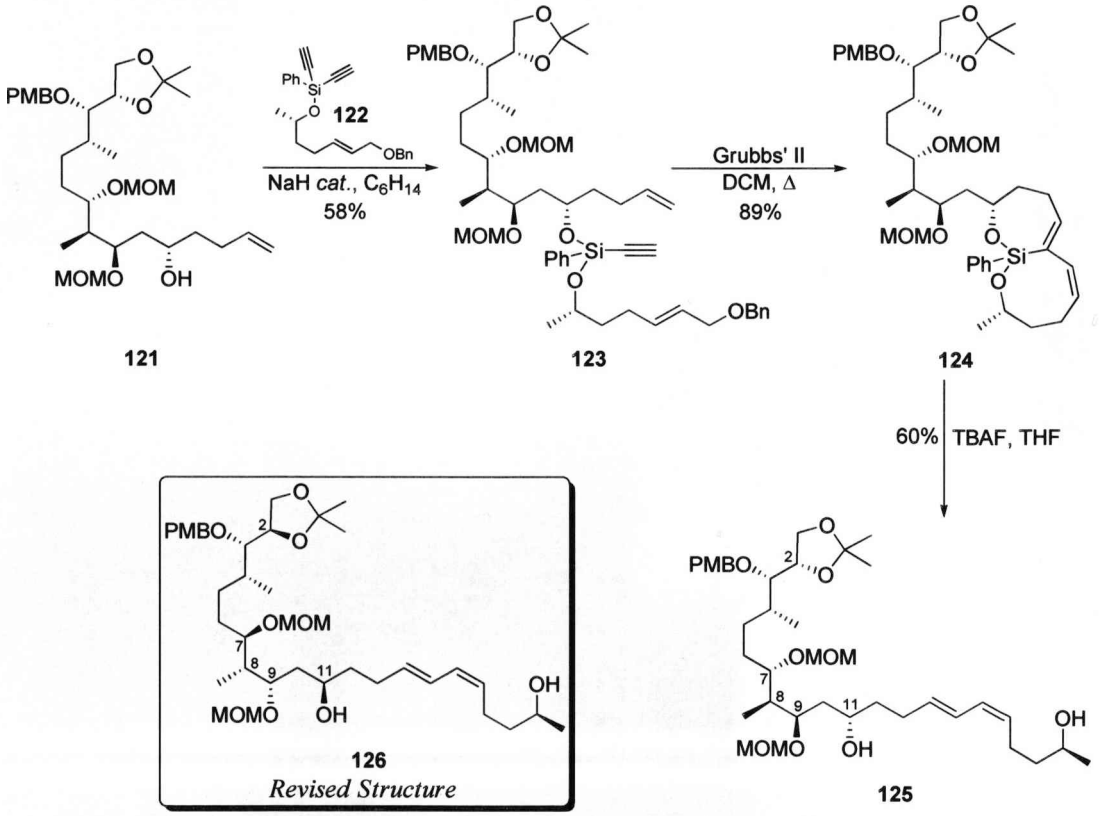


Figure 1.7 *Structures of Tartrolon B and A*

mixture of stereoisomers (Figure 1.7). Metabolite **119** belongs to the class of ion-carrier antibiotics and displays biological activity against Gram-positive bacteria with MIC values of 1 μg/ml. Both **119** and **120** are biologically active which indicates that the presence of boron is not required for its antibiotic activity.[43] A key structural feature of this metabolite is the C1-C7 segment which is also found in the structurally related boron-core antibiotics such as boromycin, aplasmomycin and borophycin.[44] Another key feature is the *E/Z* diene moiety at C14-C17. Lee and Kim envisioned that the diene motif could be installed utilizing a tandem temporary silicon-tethered ring-closing enyne metathesis.[44]



Scheme 1.22 *Synthesis of C1-C21 Fragment of Tartrolon B*

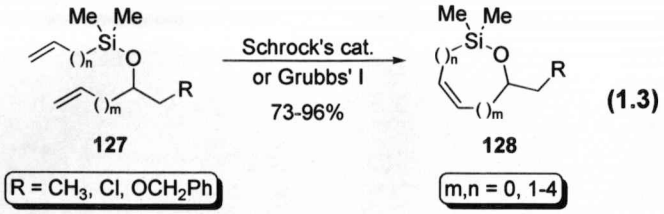
Advanced synthetic intermediate **121** was coupled smoothly with *mono*-alkoxysilane **122** to furnish the *bis*-alkoxysilane **123** as a diastereomeric mixture, due to newly formed asymmetric silicon center, in good yield (Scheme 1.22). Ring

closing metathesis delivered the bicyclic silacycle **124** which was subjected to silyl deprotection with TBAF to furnish the C1-C21 carbon framework of tartrolon B.[44] Unfortunately, Lee and Kim mistakenly used (−)-B-methoxydiisopinocampheyl-borane instead of the proposed (+)-B-methoxydiisopinocampheylborane in a stereo-defining step in the early stage of the synthesis.[45] Consequently, the absolute stereochemistry at C2, C7, C8, C9 and C11 in the structure **125** is wrong and should be inverted as illustrated in the fragment **126** (Scheme 1.22).

1.2.2 The Application of Silicon-Tether Bearing One Oxygen and One Carbon Atom (-C-Si-O-)

1.2.2.1 Alkene Ring-Closing Metathesis

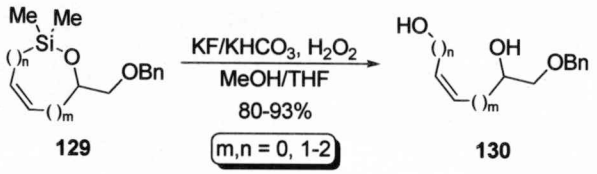
Grubbs and Chang developed a sequential TST-RCM and subsequent oxidative ring cleavage of *mono*-alkoxysilane dienes to prepare a series of *poly*-hydroxylated *cis*-olefin fragments.[46] Silacycle precursors, **127** were prepared over the course of three steps *via* benzyl protection of glycidol, epoxide opening with desired Grignard and cross-coupling with appropriate alkenyl chlorodimethylsilanes. Grubbs' 1st generation and Schrock's catalysts were employed depending on the nature of the dienes. Most silacycles examined formed efficiently at room temperature in good to excellent yields. In cases where eight and nine-membered silacycles were formed (m = 1, 2 and n = 0), Schrock's catalyst in benzene proved to



(1.3)

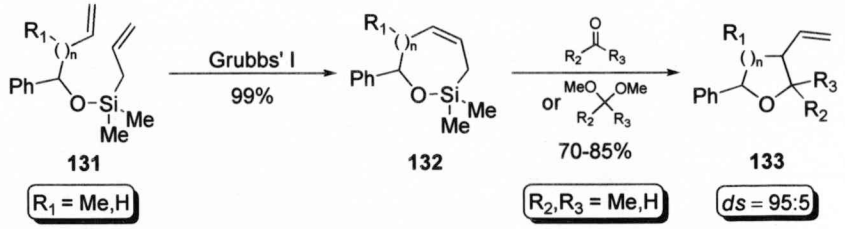
be more effective than the Grubbs' 1st generation catalyst. When n = 0, ring closure is sterically more demanding because the metalacycle formed is in proximity to the

bulky silicon linker and therefore requiring a catalyst which is less sensitive to steric bulk near the reaction center (Eq. 1.3).[46] Oxidative cleavage of corresponding silacycles, **129** developed by Tamao and Fleming, independently, furnished diol intermediates **130** with the *cis*-olefin geometry (Eq. 1.4). In the case where m = 1 and n = 0, the enol formed to afford hydroxyaldehyde in 80% yield.[46]



129 **130** **(1.4)**

At the same time Cossy and Meyer disclosed their results of the stereoselective transformation of allylalkoxysilanes into substituted oxygenated heterocycles, tetrahydrofurans and tetrahydropyrans through a tandem TST-RCM/Hosomi-Sakurai reaction.[47] Secondary alkenyl alcohols were derived from the addition of Grignard reagents to the benzaldehydes. A series of tethered allyldimethylalkoxysilanes, **131** were prepared by coupling of secondary alcohols to allylMe_2SiCl. RCM of **131** using Grubbs' 1st generation catalyst furnished the silacycles **132** in good to moderate yield. Formation of six, seven and eight-membered rings proceeded in good yield using similar conditions. When a methyl substituent is present at R_1 position, the ring closing metathesis resulted in substantially lower yield, indicating a sensitivity of the catalyst to the steric congestion. Silacycles, **132** containing allyl silane functionality were condensed using silyl modified Hosomi-Sakurai conditions with carbonyl compounds or their corresponding ketals in DCM at low temperatures utilizing a catalytic amount of trimethylsilyl triflate. The reaction provided the desired tetrahydrofurans and tetrah-

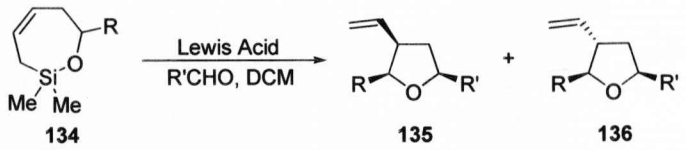


Scheme 1.23 *Stereoselective Synthesis of Tetrahydrofurans and Tetrahydropyrans*

ydropyrans, **133** in yields ranging from 70 to 85% and diastereoselectivities up to 95:5 (Scheme 1.23).[47] The reaction presumably proceeds through the formation of an oxocarbenium ion generated by Lewis acid assisted activation of the carbonyl or ketal compound which is trapped by intermolecular delivery of the allylsilane providing an oxygenated heterocycle simultaneously with the new Lewis acid species.[47]

Closely related work was reported by Marsden and co-workers.[48] They prepared a variety of seven-membered cyclic siloxanes, **134** from acyclic alkoxyallylsilanes using RCM conditions similar to those disclosed by the Cossy group. Silacylclic intermediates **134** were then subjected to Lewis acid promoted [3+2] annulation with desired aldehydes to furnish 2,3,5-trisubstituted tetrahydrofurans, **135** and **136**. Lewis acid and temperature screening which was performed on each set of conditions furnished the tetrahydrofurans, **135** and **136** in comparable yield albeit with variable stereoselectivity (Table 1.3). Boron trifluoride ethereate afforded tetrahydrofuran, **135** with the optimum diastereocontrol (Table 1.3; entries 1 and 4). Low reaction temperatures appeared to be a crucial factor for good diastereocontrol as complete erosion of stereoselectivity was observed when the reaction was performed at room temperature.[48]

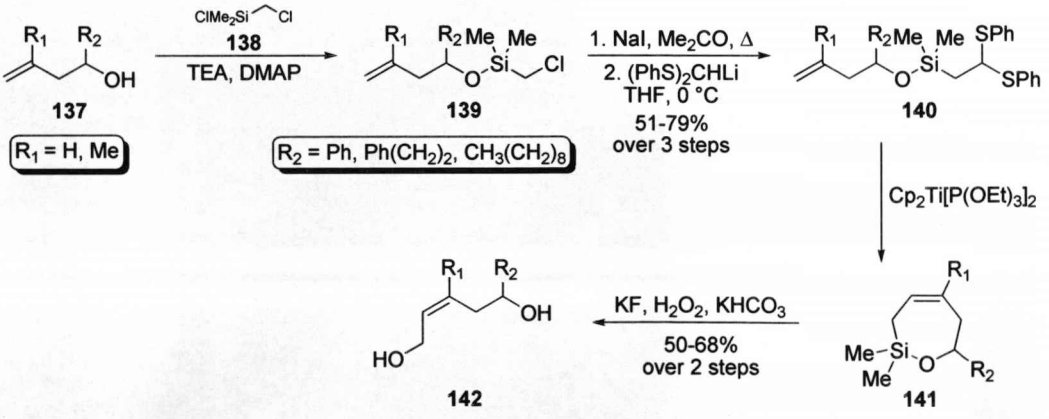
Table 1.3: *Tetrahydrofuran Formation from Allylsiloxane*



Entry	R	R'	L.A.	Temp.	Yield	*dr*(135:136)[a]
1	C_6H_{11}	Ph	$BF_3{\cdot}OEt$	-78°C	73%	92:8
2	C_6H_{11}	Ph	$TiCl_4$	-78°C	76%	75:25
3	C_6H_{11}	Ph	Et_2AlCl	-78°C	73%	90:10
4	C_6H_{11}	^{i}Pr	$BF_3{\cdot}OEt$	-78°C	84%	84:16
5	C_6H_{11}	^{i}Pr	$BF_3{\cdot}OEt$	RT	82%	52:48

[a]All ratios were determined by ^{1}H-NMR spectroscopy.

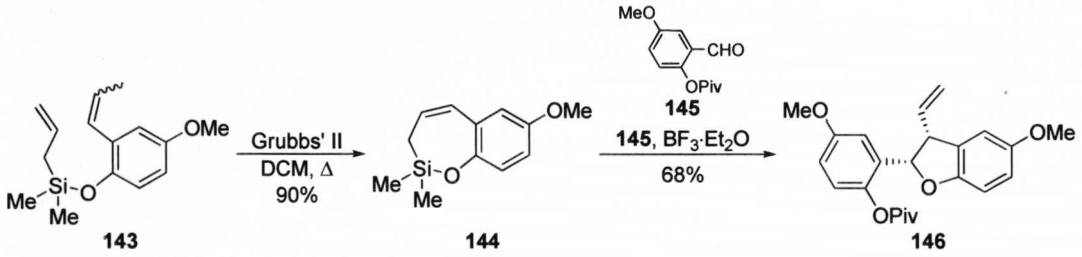
Takeda and co-workers reported a route toward the preparation of *Z*-alk-2-ene-1,5-diols utilizing the TST-RCM reaction promoted by a titanocene(II) complex with thioacetals which were subsequently cleaved by oxdation.[49] This method represents an alternative to the RCM reaction promoted by ruthenium and molybdenum catalysts. This reaction most likely proceeds *via* the initial formation of a titanium carbene complex formed by desulfurization of the thioacetal by the low-valent titanium(II) species. A series of homoallylic alcohols, **137** were treated



Scheme 1.24 *Stereoselective Synthesis of Z-Alk-2-Ene-1,5-Diols*

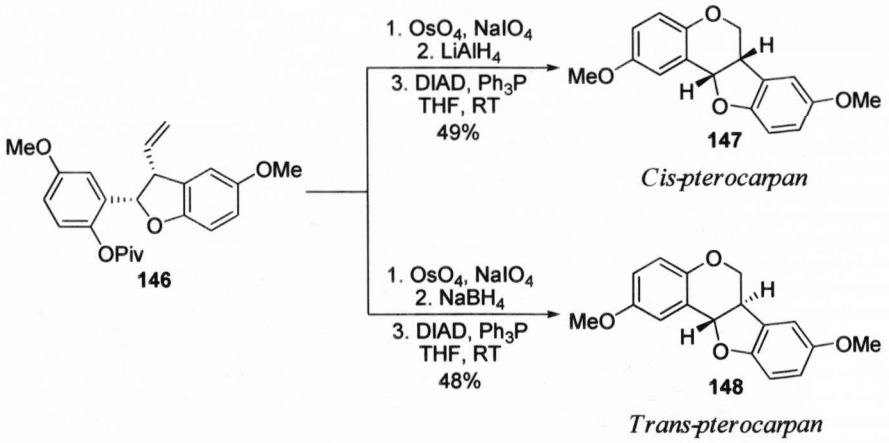
with chloro(chloromethyl)dimethylsilane, **138** to prepare *mono*-alkoxychloromethyl silanes, **139**. The Finklestein reaction of the alkoxychloromethylsilanes, **139**

followed by subsequent alkylation using *bis*(phenylthio)methyllithium furnished thioacetals in good overall yield. Ring-closing metathesis of **140** promoted by the phosphite modified titanocene(II) catalyst provided a series of silacycles, **141** in good to excellent yield, thus demonstrating that this metal center is a suitable alternative to ruthenium and molybdenum metathesis catalysts. Tamao oxidation provided olefinic diols, **142** with high *Z*-alkene selectivity (Scheme 1.24).[49] Interestingly, Takeda and co-workers found that it required a large quantity of hydrogen-peroxide (40 equiv.) and prolonged times as compared to Tamao's original protocol for complete oxidative cleavage.



Scheme 1.25 *Stereoselective Synthesis of Dihydrobenzofuran*

Recently Rodríguez-García and co-workers published a series of reports on synthesis of benzofuran containing natural products using the modified Hosomi-Sakurai condensation of aldehyde with benzoxasilepin.[50] Ring-closing metathesis of compound **143** furnished benzoxasilepin, **144** in excellent yield (Scheme 1.25). The modified Hosomi-Sakurai condensation of benzo-fused cyclic siloxane, **144** with the aldehyde **145** in the presence of $BF_3 \cdot Et_2O$ afforded the dihydrobenzofuran, **146** as a *cis*-stereoisomer exclusively. High levels of stereoselectivity in this transformation have been demonstrated previously in the synthesis of the trisubstituted tetrahydrofurans.[47,48].

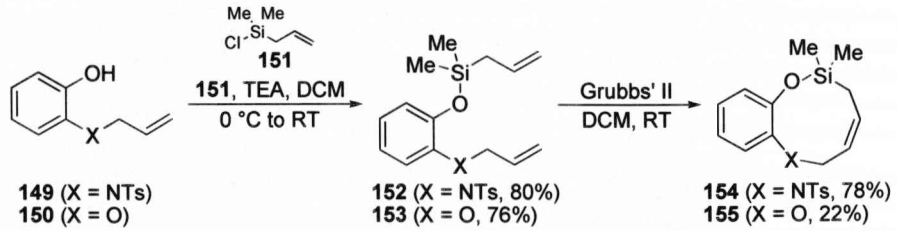


Scheme 1.26 *Stereoselective Synthesis of Cis- and Trans-Pterocarpans*

The synthesis of *cis*-pterocarpan, **147** was completed *via* annulation of the dihydrobenzopyran portion through the double bond degradation followed by Mitsunobu cyclization. However, column chromatography of product obtained upon oxidative cleavage of olefin functionality in **146** promoted partial isomerization to thermodynamically more stable *trans*-stereoisomer. The $LiAlH_4$ reduction of the crude mixture obtained after oxidative cleavage permitted the isolation of the primary alcohol without epimerization. Rodríguez-García and co-workers took advantage of this isomerization by treatment of crude mixture with $NaBH_4$. The reduction of the corresponding aldehyde with simultaneous epimerization furnished the primary alcohol which upon Mitsunobu cyclization provided the access to *trans*-pterocarpan, **148**.[50]

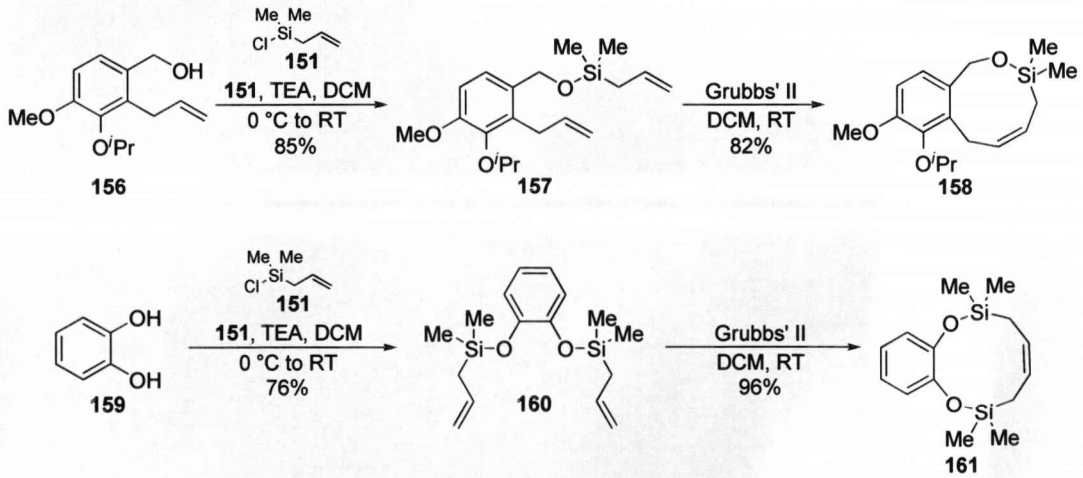
Benzo-fused heterocycles are an important class of compounds for the investigation of pharmaceutical scaffolds.[51] The possibility to introduce silicon atoms in their backbone makes them interesting candidates for the biological evaluation. Van Otterlo and co-workers have investigated the temporary silicon-tethered ring-closing metathesis approach toward the construction of silicon-containing benzo-fused heterocycles. Following the work described by Rodríguez-

García,[50] Van Otterlo and co-workers investigated the formation of silacycles containing nitrogen and oxygen atoms. Silylation of substituted phenol, **149** afforded



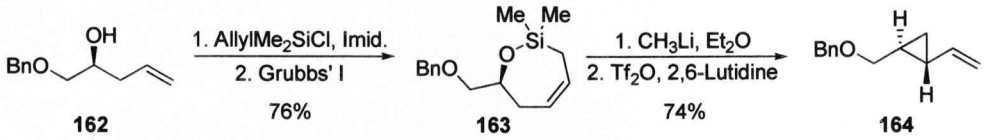
Scheme 1.27 *Synthesis of Benzo-Fused Silacycles A*

the *mono*-alkoxyallylsilane, **152** which upon treatment with Grubbs' 2nd generation catalyst furnished nine-membered benzoxazasilonine, **154** (Scheme 1.27). Silylation of phenol containing *o*-allyl ether, **150** provided the silyl ether **153** with comparable efficiency. However, ring-closing metathesis of **153** provided only 22% of cyclized product, **155**. A systematic search for other potential scaffolds for the RCM identified the substituted benzyl alcohol **156** and catechol **159** as practical starting materials. Benzyl alcohol **156** was readily converted into the silyl ether **157** (Scheme 1.28). Ring-closing metathesis furnished the silacycle, **158** in good yield. Silylation of catechol **159** furnished the *bis*-silylether, **160** which upon cyclization afforded the ten-membered benzo-fused silacycle, **161** in excellent yield.[51]



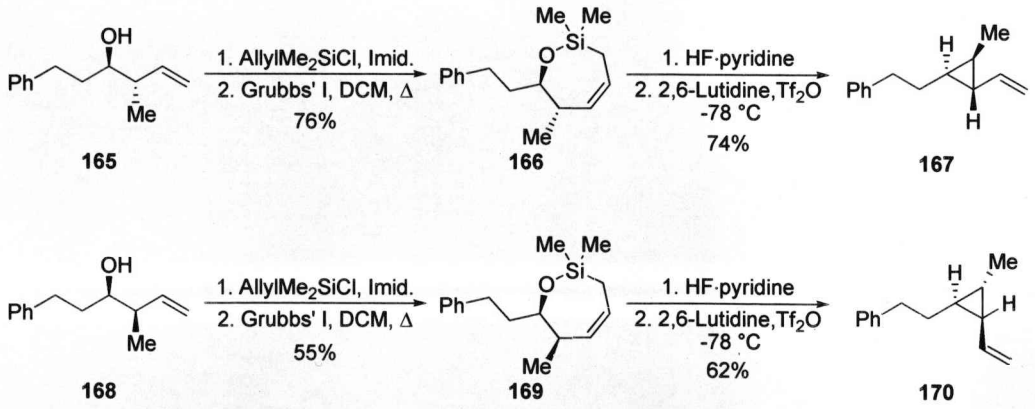
Scheme 1.28 *Synthesis of Benzo-Fused Silacycles B*

Between 1999 and 2001, Taylor and co-workers published a series of reports on the construction of structurally diverse cyclopropanes, *via* trapping of cyclopropylcarbinyl cationic intermediates.[52] The TST-RCM reaction was utilized to provide the cyclic allylsilane intermediates, **163**. The cyclopropanation protocol provided exclusively the *trans*-vinylcyclopropanes, **164** in good yield (Scheme 1.29).[52a]



Scheme 1.29 *Stereoselective Synthesis of Disubstituted Cyclopropanes*

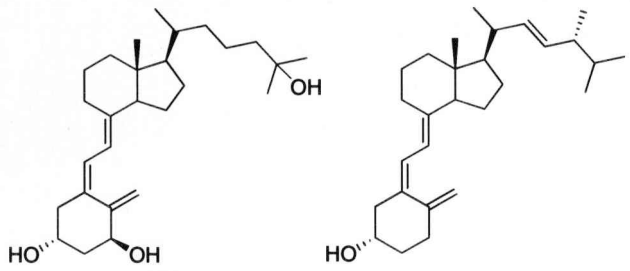
Taylor and co-workers rapidly expanded the scope of this cyclopropanation reaction, by using it to prepare a variety of 1,2,3-trisubstituted cyclopropanes as either the *cis*- or *trans*-stereoisomers.[52b,52c] *Anti*- and *syn*-homoallylic alcohols, **165** and **168** were derived from crotylation of hydrocinnamaldehyde using crotyl-bromide/$CrCl_2$ and crotylstannane/$BF_3 \cdot OEt_2$ reactions, respectively.[52c] Silyl protection with allyldimethylchlorosilane followed by subsequent ring-closing metathesis utilizing



Scheme 1.30 *Stereoselective Synthesis of Trisubstituted Cyclopropanes*

Grubbs' 1st generation catalyst furnished silacycles, **166** and **169** in good overall yield. Silyl deprotection using HF·pyridine followed by activation of the secondary

alcohol by triflic anhydride provided a rapid access to the racemic 1,2,3-trisubstituted cyclopropanes as single stereoisomers. Both cyclopropanation reactions are diastereospecific, thus providing *trans*-isomer **167** and *cis*-isomer **170** from alcohols **165** and **168** respectively (Scheme 1.30). These reactions proceed through overall inversion of the activated secondary alcohol. The stereochemical outcome is dependant on the relative stereochemistry between the activated alcohol and the vicinal methyl group (Scheme 1.30). This approach supplements the area of diastereoselective and enantioselective cyclopropanation reactions where most attention has been directed toward intramolecular carbenoid additions or intermolecular Simmons-Smith chemistry.[52c]



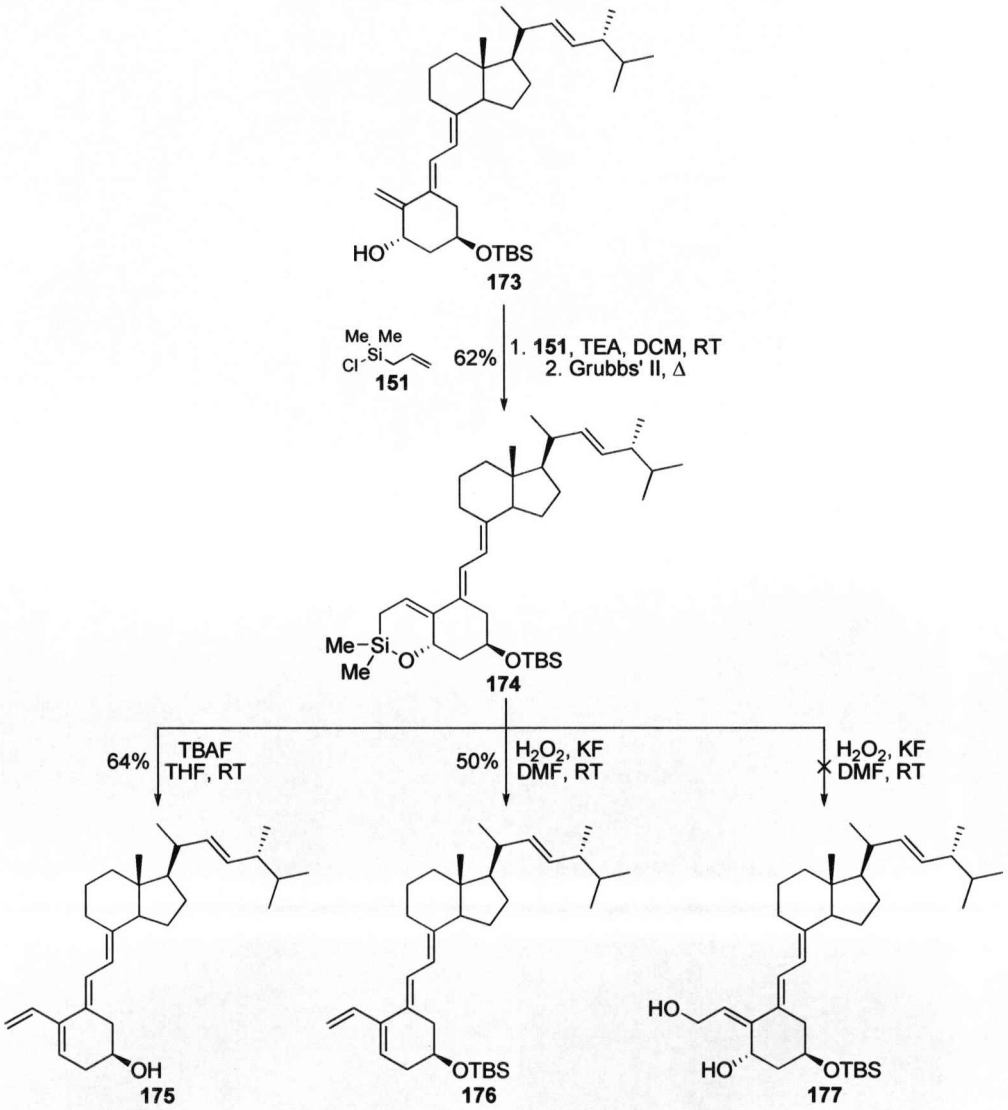
171 *1α,25-dihydroxyvitamin D_3*

172 *vitamin D_2*

Figure 1.8 *Structures of Dihydroxyvitamin D_3 and Vitamin D_2*

Recent studies revealed that the hormonally active form of vitamin D_3, **171** can promote the cell differentiation while inhibiting the tumor cell proliferation (Figure 1.8). Accordingly, it could be potentially used in the treatment of diseases such as leukemia and psoriasis.[53] However, therapeutically useful dosage often leads to a drug side effect such as hypercalcemia. Due to this therapeutic problem, the attention has been focused toward the synthesis of analogues, which would minimize the drug side effect and possibly augment the potency. Barrett and co-workers reported a synthesis of analogues of the easily accessible 1α-hydroxy-5,6-

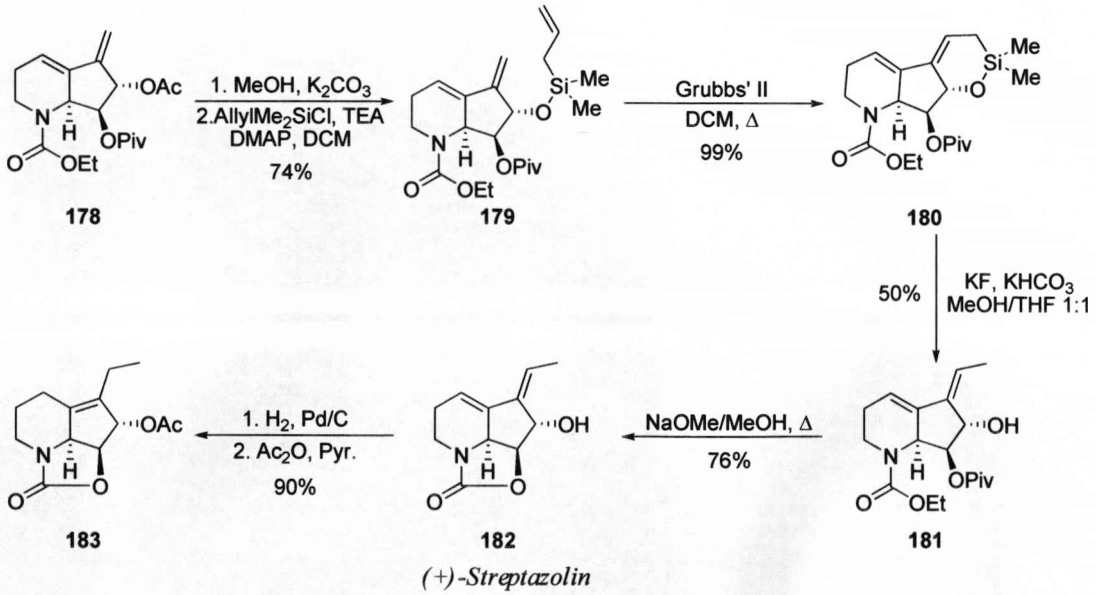
trans-vitamin D_2, **173** by using the TST-RCM strategy.[53] The treatment of alcohol **173** with dimethylallylchlorosilane, **151** furnished the silyl ether which upon ring-closing metathesis gave the desired silacycle **174** in 62% yield over two steps. Gratifyingly, the delicate triene system of the steroid core, survived the RCM reaction without any significant decomposition or rearrangement. When silacycle **174** was treated with hydrogen peroxide and potassium-fluoride none of the desired diol **177** was isolated (Scheme 1.31). Instead,



Scheme 1.31 *Synthesis of Vitamin D2 Analogues Via TST-RCM*

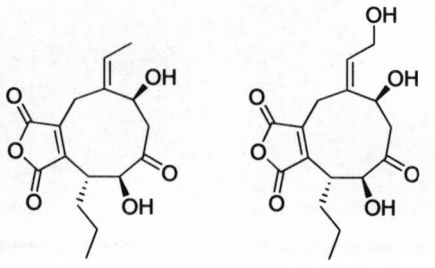
the tetraene **176** was formed presumably through the vinyloguous Peterson olefination. In agreement with this hypothesis, reaction of **174** with TBAF furnished the deprotected tetraene, **175**. The unexpected sideproduct **176** could still be used for the synthesis of derivatives *via* Diels-Alder reaction.[53]

Miller and Li, likewise, demonstrated the utility of TST-RCM reaction sequence in the total synthesis of the alkaloid (+)-streptazolin **182**.[54] Drautz and Zahner initially isolated this alkaloid from the cell cultures of *Streptomyces viridochromogenes* in 1981.[55] The same metabolite was rediscovered a decade later during the chemical screening of *Streptomyces luteogriseus.*[56] The natural product **182** has a fused tricyclic ring system featuring an urethane functionality and exocyclic olefin. Furthermore, a biological screening of this metabolite displayed an interesting antibiotic and antifungal activity. However, the isolation of (+)-streptazolin, hampered due to its ability to polymerize upon concentration, provided the impetus to prepare a more stable and more biologically active derivative. Previous synthetic attempts suffered from a lack of stereoselectivity during the insta-



Scheme 1.32 *Total Synthesis of (+)-Streptazolin*

llation of the ethylidine side chain. Miller and Li envisioned that the TST-RCM would be an effective way of controlling the (*Z*)-olefin geometry of alkylidine side chain. Initial results indicated that the internal urethane unit contributes to the instability of the molecule and should be installed at later stage of the synthesis. Silicon tether cross-coupling utilizing allyldimethyl-chlorosilane furnished the *mono*-alkoxysilane intermediate **179**. Ring closing metathesis using Grubbs' 2nd generation catalyst delivered the six-membered ring-fused silacycle **180** in quantitative yield. Protodesilylation of **180**, however, proved to be problematic. Treatment of **180** with potassium fluoride and $KHCO_3$ proved optimum, since it gave the desired product **181** in 50% yield. This reaction illustrates a rare occasion of protodesilylation of a conjugated and a fused allylic silane system. The synthesis was finalized by removal of pivaloate group followed by concomitant urethane formation to furnish (+)-streptazolin, **182** in excellent yield. Due to the partial decomposition upon isolation, the natural product, **182** was converted to the stable crystalline dihydroacetate **183** which thereby permits a comparison of spectroscopic data with the literature values (Scheme 1.32).[54]



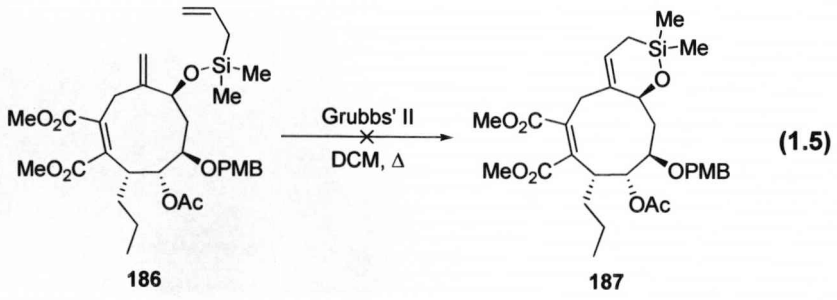
184 *Cornexistin*

185 *14-Hydroxycornexistin*

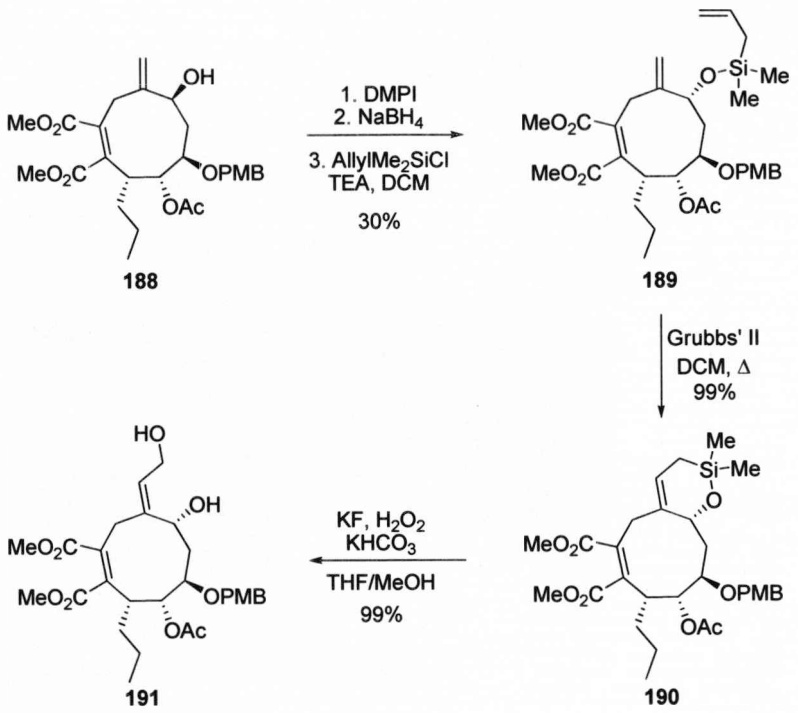
Figure 1.9 *Structures of Cornexistin and 14-Hydroxycornexistin*

Cornexistin, **184** is a fungal metabolite isolated in 1991 from *Paecilomyces variottii* SANK 21086 by scientists at Sankyo corporation.[57] The metabolite displays

a potent herbicidal activity against broadleaf weed species with a selective mode of action not affecting the maize plants. Simultaneously, a structurally comparable metabolite, 14-hydroxycornexistin, **185** was discovered displaying similar biological activity (Figure 1.9). The interesting structural features of both metabolites are nine-membered ring, maleic anhydride moiety and pendant alkyl groups. Taylor and co-workers devised a route toward the synthesis of cornexistin and its analog 14-hydroxycornexistin, **185** utilizing Diels-Alder cycloaddition and subsequent oxidative cleavage to furnish the highly functionalized nine-membered ring.[57] The TST-RCM approach was strategically applied to control the alkene geometry at the C12-C13 position. It was envisioned that a temporary silicon connection should direct ring-closing metathesis of **186** to afford the (*Z*)-alkene nonacycle, **187**. Unfortunately, only dimeric products were furnished, regardless catalyst employed. It was proposed that substrate **186** was in a conformational mismatch for the RCM reaction (Eq. 1.5). To impose a favorable conformational change the stereochemistry of allylic alcohol, **188** was inverted using a two step protocol; 1) Dess-Martin oxida-



186 **187** **(1.5)**

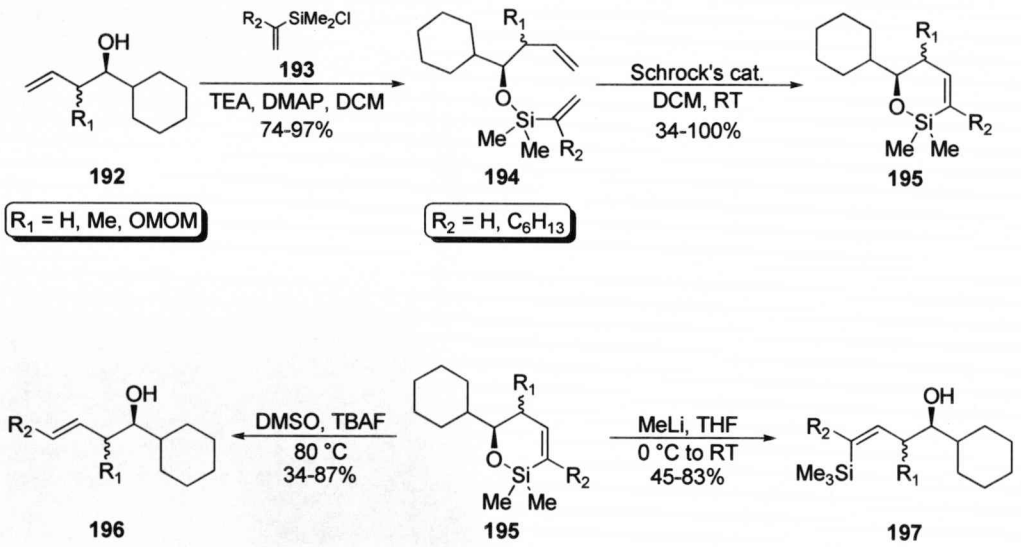


Scheme 1.33 *Stereoselective Synthesis of 14-Hydroxycornexistin Precursor*

tion and 2) $NaBH_4$ reduction. Reduction furnished the epimeric secondary alcohol in good yield but with only 4:1 diastereoselectivity. The Mitsunobu protocol was not successful, leading only to an elimination product. Silyl protection of inverted allylic alcohol delivered intermediate **189** in 50% yield. Ring closing metathesis finally delivered the 9,6-fused silacycle, **190** in quantitative yield. Taylor and co-workers further elaborated intermediate **190** through a Tamao-Fleming oxidation which provided the late stage intermediate **191** in excellent yield (Scheme 1.33).[57]

Barrett and co-workers utilized the TST-RCM reaction and subsequent oxidative cleavage/nucleophilic ring opening to prepare a variety of cross-coupled alkenes with full control of the olefin geometry.[58] A variety of enantiomerically enriched homoallylic alcohols, **192** derived from a Brown asymmetric allylation/crotylation sequence were coupled to either vinyldimethylchlorosilane or the *n*-hexyl derivative, **193** to furnish alkoxyvinylsilane intermediates, **194** in good

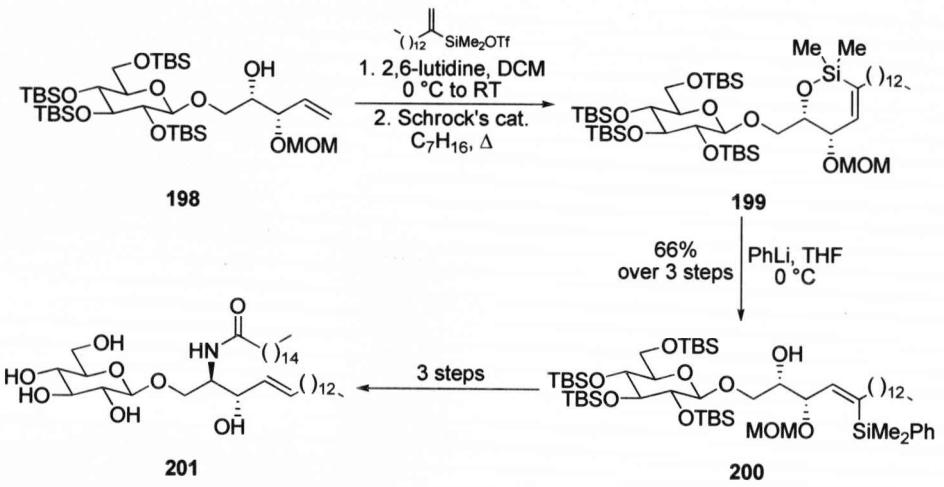
to excellent yield. Ring closing metathesis using Schrock's catalyst furnished silacycles, **195** in essentially quantitative yield. Owing to the intramolecular nature of TST-RCM reaction, the silacycles were formed as single geometric isomers. However, monitoring of the RCM reaction by ^{1}H-NMR revealed that the precursor, **194** (R_1=OMOM, R_2=C_6H_{13}) underwent an olefin isomerization with concomitant loss of the MOM protecting group thus accounting for the poor yield of the desired product, **195**. Further functionalization *via* protodesilylation or nucleophilic silacycle ring opening provided a series of "cross-coupled" desilylated homoallylic alcohols, **196** and ring-opened adducts bearing vinylsilane functionality, **197** respectively, in good to excellent yields (Scheme 1.34).[58]



Scheme 1.34 *Synthesis of "Cross-Coupled" Homoallylic Alcohols*

Barrett and co-workers developed a novel approach incorporating the TST-RCM strategy toward the synthesis of *D*, *L*-glucosylceramide, a member of the glycosphingolipids class of natural products.[59] Glycosphingolipids are important building blocks of various tissues and organs in biological systems. They have a central role in structural support *via* protein binding and they act as mediators of

important biological events such as intracellular communication, cell growth and cell death. Each of these events is triggered by specific glycosphingolipids which suggests that their analogues could be compelling new drug candidates.[59] Silylation of advanced intermediate **198** using the alkyldimethylsilyl triflate generated *in situ* from silver(I)-triflate and the corresponding silyl chloride, provided the RCM precursor (Scheme 1.35). Treatment of the tethered diene intermediate with Grubbs' 1st generation catalyst did not result in product formation. However, reoptimized conditions utilizing Schrock's catalyst furnished desired silacycle, **199** in quantitative yield.

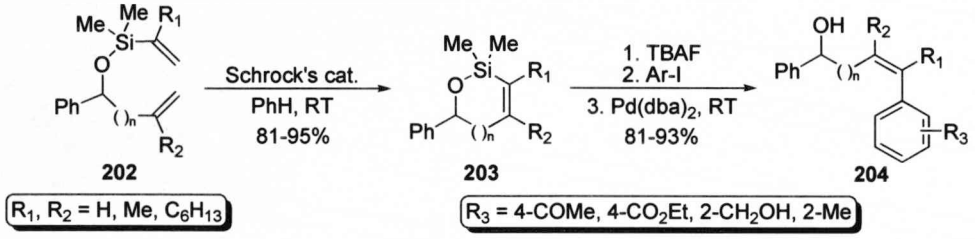


Scheme 1.35 *Stereoselective Synthesis of D,L-Glucosylaceramide*

Silacycle **199** was then treated with phenyl lithium to afford the stereochemically defined alkenylsilane, **200** in excellent yield. Due to the cyclic nature of precursor **199**, alkenylsilane, **200** was generated exclusively as the *cis*-stereoisomer. The intermediate **200** was elaborated into the natural product **201** in three additional steps.[59]

Denmark and Yang developed a sequential ring-closing metathesis followed by silicon-assisted cross-coupling.[60] Ring-closing metathesis using Schrock's alkoxy

imidomolybdenum catalyst effectively furnished cyclic alkenyl-siloxanes, **202** of various ring sizes (Scheme 1.36). These cyclic alkenylsiloxanes participate in the palladium assisted cross-coupling reaction between either aryl or alkenyl halides providing an easy access to styrenes and dienes, respectively, in high yield; high specificity and high functional group tolerance. Interestingly, initial RCM studies with substrate **202** where n = 1 and R_1,R_2 = H utilizing Grubbs' 1st and 2nd generation catalyst were unsuccessful. However, Schrock's molybdenum complex promoted the reaction of **202** and its derivatives in quantitative yield. This is yet another example of where the molybdenum complex catalyzes a reaction with equal

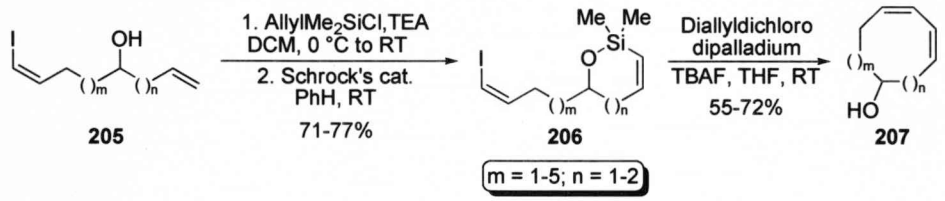


Scheme 1.36 *Palladium-Mediated Cross-Coupling of Vinylsiloxanes*

efficiency regardless of the steric bulk around the reactive centers. Palladium-catalyzed cross-coupling with aryl-iodides provided products, **204** in high yields. The reaction also tolerates diverse functional groups such as esters, ethers, nitro groups and free hydroxyls. Cross-coupling with *E*-bromostyrene proceeded equally efficient albeit with a slightly lower yield. The different silacycle ring sizes, n = 1,2 exhibited similar reactivity. Substitution at the R_1 position of the silacycle reduced the rate of the reaction, whereas, substitution at the R_2 position had little effect on the reaction (Scheme 1.36).[60]

In 2002, Denmark and Yang further contributed to the field of Pd-catalyzed silicon assisted intramolecular cross-coupling reactions with the development of a method to construct medium-sized rings bearing a 1,3-*cis*-*cis* diene functionality, as

illustrated in Scheme 1.37. This is an important reaction as the construction of medium-size rings with internal conjugated dienes is often problematic due to unfavorable enthalpic and entropic factors.[60b,61] Denmark's strategy included the preparation of cyclic *mono*-alkoxysilanes, **206** bearing a pendant side chain containing a remote vinyliodide functionality, by ring-closing metathesis. In a subsequent step, the vinyl iodide would then participate in a palladium-catalyzed intramolecular cross-coupling event with the transient and activated vinyl silane affecting the formation of carbocyclic alcohols, **207** containing a 1,3-*cis-cis* diene unit.[60b,61]

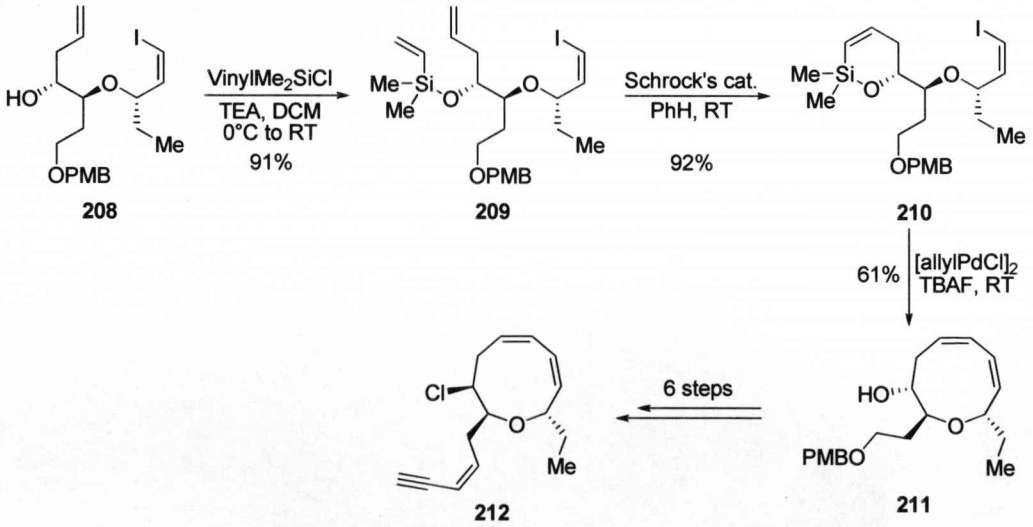


Scheme 1.37 *Intramolecular Palladium-Mediated Cross-Coupling of Vinylsiloxanes*

Silicon tether formation and subsequent ring-closing metathesis proceeded with uniform yields regardless of the length of pendant side chain. Initial cross-coupling attempts led to low conversion of **206** to **207** due to competitive *inter*molecular coupling. The reaction is general for the construction of 9-, 10-, 11- and 12-memberd cycloalkyldienes.[60b,61] This versatile and effective cross-coupling was utilized for the construction of the nine-membered cyclic core as the key step in the total synthesis of (+)-brasilenyne.[63]

In 1979, Fenical and co-workers reported the isolation of the structurally significant antifeedant brasilenyne, **212** from the digestive gland of the sea hare *Aplysia brasiliana*. It has been suggested that secondary metabolites like **212** are produced in high concentrations in the digestive gland to act as a chemical defense

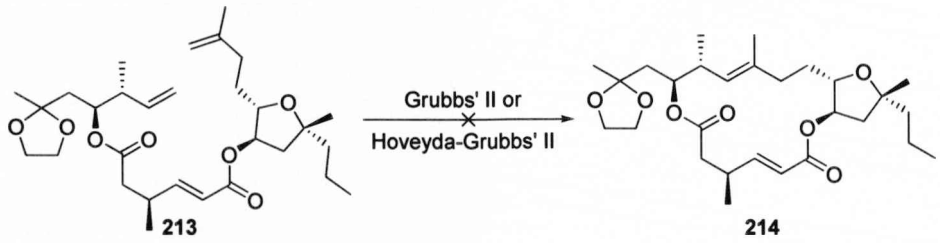
against predators. Brasilenyne contains a novel nine-membered cyclic ether skeleton containing a 1,3-*cis,cis*-diene unit which displays a significant level of structural complexity.[62] Denmark and Yang reported a total synthesis of this structurally important metabolite utilizing a TST-RCM strategy toward the construction of the 1,3-*cis,cis*-diene fragment.[63] Silylation of homoallylic alcohol **208** furnished the *mono*-alkoxysilane intermediate, **209** which was efficiently elaborated into the silacycle, **210** through a ring closing metathesis using Schrock's catalyst. The formation of the nine-membered cyclic ether **211** was accomplished utilizing an innovative palladium-catalyzed intramolecular cross-coupling utilizing TBAF as an activator of the silane. Intermediate **211** was elegantly elaborated into (+)-brasilenyne **212** in six additional steps (Scheme 1.38).[63]



Scheme 1.38 *Total Synthesis of (+)-Brasilenyne*

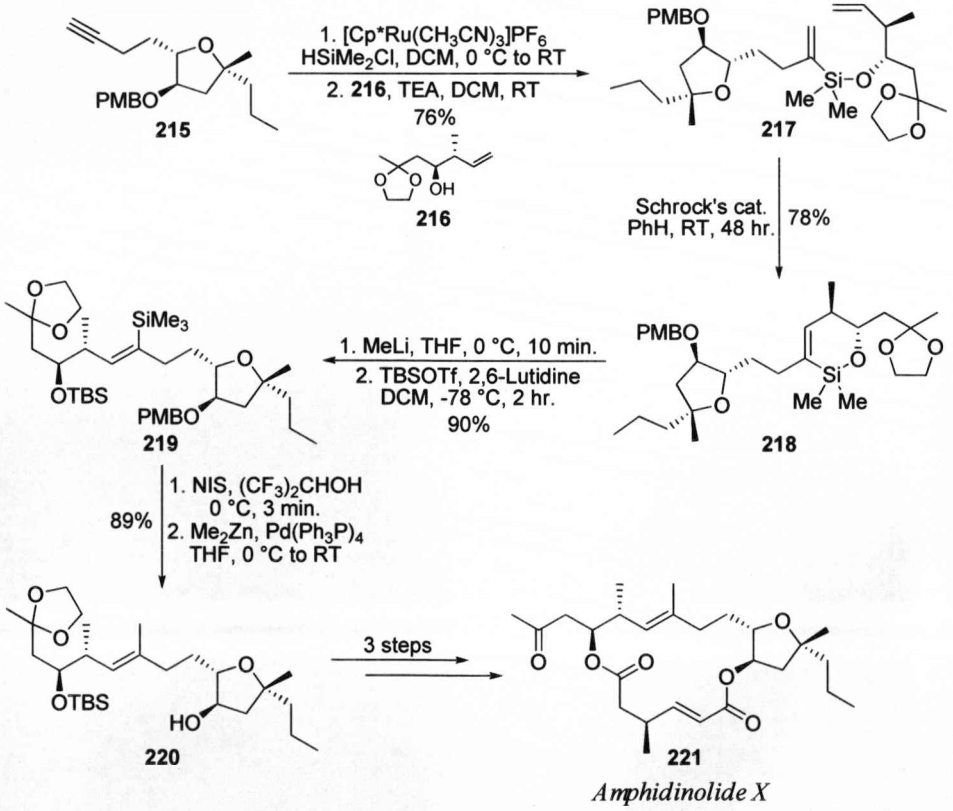
Vilarrasa and co-workers reported the application of temporary silicon-tethered ring closing metathesis reaction in the total synthesis of amphidinolide X.[64] This cytotoxic macrolide was isolated from *Amphidinium* dinoflagellate in 2003 by Kobayashi and co-workers.[65] Its unusual nonsymmetric diolide structure rapidly

captured a significant amount of the attention in the synthetic community.[66] Vilarrasa and co-workers initially envisioned the installation of the challenging trisubstituted C12-C13 olefin functionality in the late stage of the synthesis *via* ring-



(1.6)

closing metathesis.[64] Unfortunately, none of the cyclization attempts provided the desired sixteen-membered macrocycle **214** (Eq. 1.6). Faced with the failure in the final step of the synthesis, Vilarrasa's group considered an alternative strategy. They envisioned the olefin formation in the earlier stage of the synthesis *via* TST-RCM



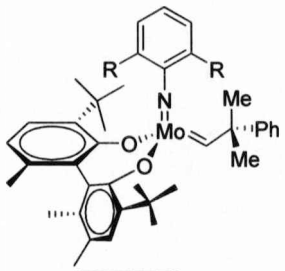
Scheme 1.39 *Total Synthesis of Amphidinolide X*

reaction methodology. The hydrosilylation of the alkyne **215** with the dimethylchlorosilane using Trost's catalyst,[67] gave the chlorosilane which was coupled *in situ* with the allylic alcohol **216** to provide the vinylalkoxysilane **217** (Scheme 1.39). Ring closing metathesis of the tethered diene in the presence of Schrock's catalyst furnished the six-membered silacycle **218** in 78% yield. A variety of conditions examined for the cleavage of the silicon tether to convert the C-Si bond into the C-Me bond did not furnish the desired compound. The tether was finally cleaved by addition of MeLi to provide the alkoxyvinylsilane, subsequently protected as TBS ether **219**. The vinyliodide formed by iododesilylation of the TMS group was subsequently methylated with Me_2Zn according to Negishi protocol to furnish the intermediate **220**.[68] Apparently, the use of hexafluoroisopropanol as a solvent was crucial to avoid the double bond isomerization during the iododesilylation step.[69] From the advanced intermediate **220**, the synthesis was completed in three additional steps highlighting the application of Yamaguchi[70] and Shiina[71] macrolactonization.

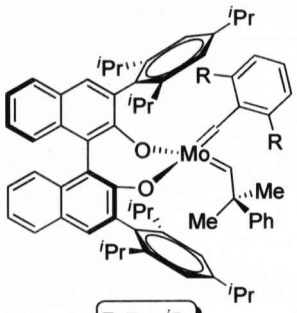
In the past decade, catalytic olefin metathesis has dramatically influenced the field of organic synthesis. The use of well-defined transition metal metathesis catalysts in the context of total synthesis of biologically significant molecules has been employed with such frequency that is now considered relatively routine. Research efforts have been directed toward the development of the chiral catalysts capable of promoting ring-closing, ring-opening or cross-metathesis to afford enantiomerically enriched materials. A few years ago, a new class of chiral Mo- and Ru-based complexes bearing functionalized chiral ligands emerged, as a result of continuous advances by Schrock, Hoveyda and Grubbs in the field of asymmetric ring-closing metathesis (ARCM).[72] These exceptionally efficient catalysts provide

an unique access to the materials of high enantiomeric purity that are otherwise difficult to access.

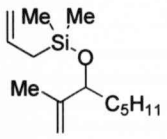
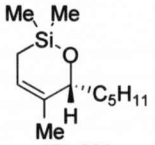
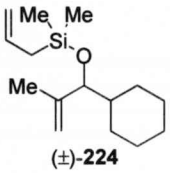
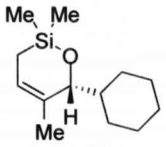
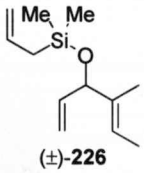
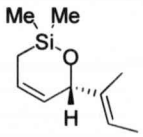
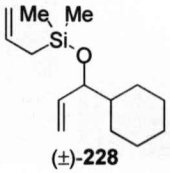
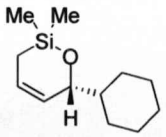
Table 1.4: *Enantioselective Synthesis of Silacycles by ARCM*



D, R = ^{i}Pr
E, R = Me



F, R = ^{i}Pr

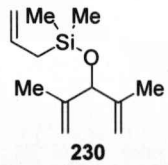
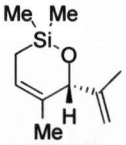
Entry	Substrate	Product	Cat.	Time	Conv.	Dimer	k_{rel}[a]
1			F	35 min.	53%	5%	>25
2			D	25 min.	58%	40%	1.9
3	(±)-**222**	(*R*)-**223**	E	20 min.	62%	19%	10
4			F	1 hr.	60%	8%	>25
5			D	1 hr.	54%	47%	1.1
6	(±)-**224**	(*R*)-**225**	E	1 hr.	58%	39%	14
7			F	5 min.	62%	<2%	1.9
8			D	3 min.	54%	<2%	21
9	(±)-**226**	(*R*)-**227**	E	1 min.	55%	<2%	1.4
10			F	5 min.	63%	<2%	3.0
11			D	2 min.	52%	<2%	>25
12	(±)-**228**	(*R*)-**229**	E	1 min.	70%	<2%	3.7

[a] Relative rates are based on recovered substrates

In 1999, Schrock and co-workers examined the ability of chiral molybdenum complexes **D**, **E** and **F** to catalyze an enatioselective formation of six-membered silacycles.[73] The results of Mo-catalyzed kinetic resolutions are presented in the Table 1.4. Racemic *mono*-alkoxysilane **222** was resolved efficiently during 35 min

with 5 mol% **F** (k_{rel} > 25) with less then 5% of dimeric species formed (Table 1.4; entry 1). Asymmetric RCM reaction promoted by catalyst **D** afforded a substantial amount of dimer and only marginal enantiodiscrimination (Table 1.4; entry 2). With catalyst **E**, the resolution efficiency is higher than that observed with **D** but significantly lower than that obtained with catalyst **F** (Table 1.4; entry 3). Comparable results were obtained when (±)-**224** was used as the substrate (Table 1.4; entries 4-6). Interestingly, when ARCM reaction furnished a silacycle containing the disubstituted olefin functionality, the efficiency and enantiodiscrimination of the catalysts are reversed (Table 1.4; entries 7-9 and 10-12). Accordingly, with two terminal olefins as reacting partners, **D** emerged as the superior catalyst. Despite producing only marginal levels of dimeric products, catalysts **F** and **E** are hardly stereodifferentiating (Table 1.4; entries 7, 9, k_{rel} < 2 and entries 10, 12, k_{rel} < 4).[73]

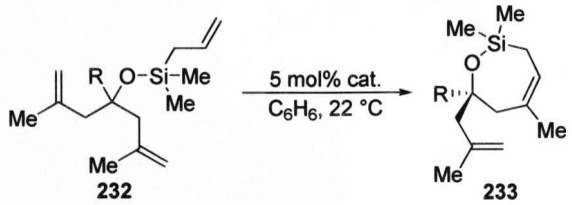
Table 1.5: *Enantioselective Synthesis of Six-Membered Silacycle by Mo-Catalyzed Desymmetrization*

Entry	Substrate	Product	Cat.	Time	Temp.	Conv.	Dimer	Yield	ee
1	 **230**	 (*R*)-**231**	**F**	3 h	60 °C	>99%	<2%	98%	>99%
2			**D**	24 h	RT	50%	32%	17%	65%
3			**E**	24 h	RT	51%	28%	20%	85%

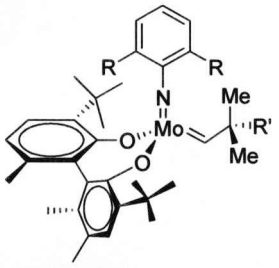
Schrock and co-workers further extended the concept of ARCM reaction through the catalytic desymmetrization of 1,7-dienes. Catalyst **F** readily promotes the desymmetrization of acyclic *mono*-alkoxysilane **230** into the six-membered siloxane, (*R*)-**231** within 3 h in >99% *ee* and 98% of isolated yield (Table 1.5; entry 1). Biphen-based catalysts **D** and **E** are significantly less effective. Even after prolonged time, the reaction displayed 50% of conversion accompanied by formation of significant amounts of dimer. Both catalysts promoted the reaction

where the silacycle (*R*)-**231** was obtained with substantially lower level of enantioselection (Table 1.5; entries 2 and 3).[73]

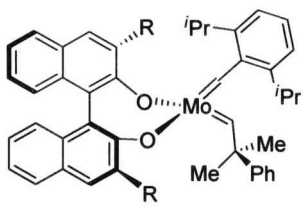
Table 1.6: *Mo-Catalyzed Asymmetric Synthesis of Seven-Membered Siloxanes*



Entry	R		Catalyst	Conv.	Yield[a]	ee
1	Ph	a	D	>98%	92%	93%
2	*p*-BrPh	b	G	>98%	98%	94%
3	Cy	c	D	>98%	91%	83%
4	^{i}Pr	d	D	>98%	92%	90%
5	^{n}Bu	e	E	>98%	87%	66%
6	Me	f	H	>98%	90%	47%



G, R = Cl R ' = Me

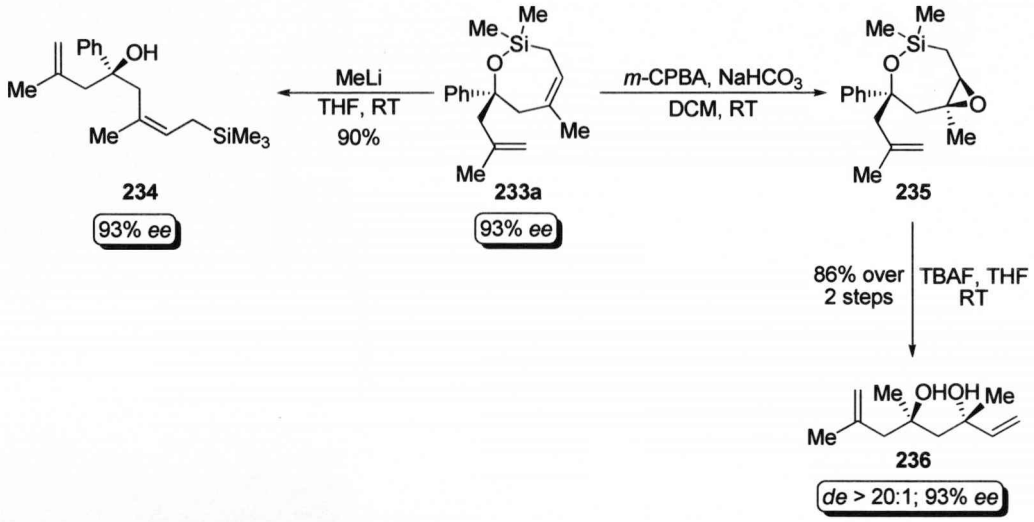


H, R = $CHPh_2$

In attempt to expand the generality of catalytic ARCM reaction, Schrock and co-workers carried out the synthesis of medium-ring heterocycles, tertiary ethers and tertiary alcohols.[74] Tertiary medium-ring siloxanes are particularly attractive since are readily available by ARCM and can be easily functionalized to provide the tertiary alcohols of high enantiopurity, often difficult to prepare by any other method.

The treatment of the triene **232a** with 5 mol% of catalyst **D**, at room temperature over 12 h furnished the seven-membered sialcycle **233a** in excellent

yield and enantioselectivity (Table 1.6; entry 1). The reaction of **232b** proceeded with equal level of efficiency thus forming the silacycle **233b** (Table 1.6; entry 2). Increasing the steric bulk around tertiary silyl ether in **232c** resulted in formation of **233c** in good yield albeit with reduced enantioselectivity (Table 1.6; entry 3). Cyclization of **232d** using 5 mol% of catalyst **D** preceded with same level of the efficiency as cyclization described in entries 1 and 2. However, when substrates **232e** and **232f** (entries 5 and 6) bearing sterically less encumbered substituents were used the reaction proceeded with 98% conversion albeit with erosion in enantioselectivity (66% and 47% *ee*, respectively).[74]

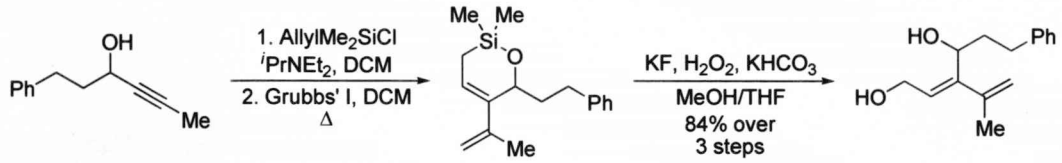


Scheme 1.40 *Functionalization of Enantiomerically Enriched Siloxane* **233a**

The Scheme 1.40 describes the functionalization of asymmetric siloxane to prepare a variety of tertiary alcohols. Treatment of corresponding siloxane, **233a** with MeLi in THF at ambient temperature resulted in the formation of tertiary alcohol **234** (93% *ee*), a compound difficult to prepare by any other method. Treatment of siloxane **233a** with *m*-CPBA resulted in stereoselective formation of the epoxide **235** with exquisite diastereocontrol (> 20:1). Fluoride mediated silyl deprotection furnished the 1,3-tertiary diol **236** in excellent yield over 2 steps.[74]

1.2.2.2 Enyne Ring-Closing Metathesis

Yao has showed that silicon-tethered enyne ring-closing metathesis has enormous potential toward the synthesis of stereodefined cyclic dienes.[75] Prior to his report, application of enyne metathesis in the synthesis of tri- and *tetra*-substituted acyclic dienes was not fully realized due to the lack of methods which control the chemo-, regio- and stereoselectivity. Application of the temporary tether in combination with enyne metathesis provided a much needed method to control these factors. Removal of a temporary tether would provide rapid access to stereodefined, highly substituted acyclic conjugated dienes. Propargylic alcohol **237** was silylated



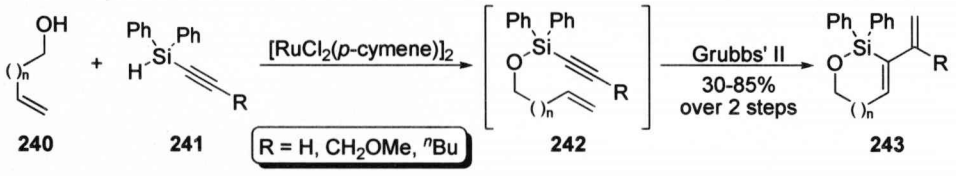
237 **238** **239**

Scheme 1.41 *Stereoselective Synthesis of Acyclic Conjugated Dienes A*

with allyldimethylchlorosilane and subjected to enyne ring-closing metathesis reaction which delivered the conjugated cyclic siladiene, **238**. Oxidative cleavage using Tamao protocol provided the diol **239** in excellent yield over three steps (Scheme 1.41). The reaction is fairly general in terms of different substitution patterns.[75]

Lee and co-workers recently developed a strategy for one-pot preparation of silaoxacycles, **243** from alkenyl alcohols, **240** and alkynilsilanes, **241** through tandem ruthenium catalyzed reactions.[76] This fruitful strategy was initiated by the preparation of the acyclic alkynylsilyl ether, **242** through a ruthenium catalyzed etherification reaction. However, the alkynylsilyl ether **242** was discovered to be difficult to isolate. To overcome this problem, Lee's group envisioned the possibility

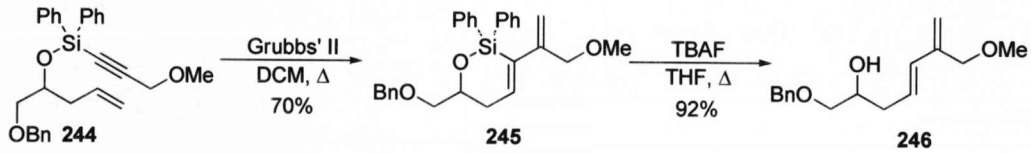
of performing a sequential etherification/ring closing metathesis reaction which would provide the desired product, **243** directly (Scheme 1.42).[76] A transition metal catalyzed etherification reaction was a great fit for one-pot sequence because it provided clean conversion of starting material and molecular hydrogen as the only byproduct. However, the functional group compatibility was a concern because of the distinct possibility of the system to facilitate the hydrogenation or hydrosilylation of certain substrates under the given conditions. After extensive screening of various catalytic systems, $[RuCl_2(p\text{-cymene})]_2$ was discovered as a suitable catalyst as it did not react with alkene and alkyne present in the starting materials or products.



Scheme 1.42 *One-Pot Synthesis of Vinylsiloxanes*

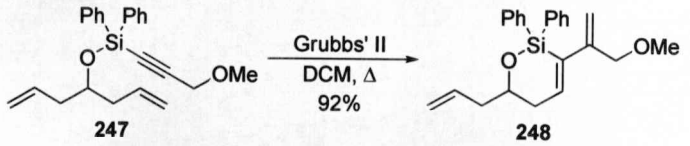
Ring-closing metathesis provided the desired silacycles in modest to good yield over two steps. The efficiency of the reaction is substantially greater when the catalyst from the first step is removed from the reaction by silica-plug filtration. Oxygen substitution off of the propargylic carbon has a positive impact on the etherification reaction by retarding the any observed hydrogenation of the triple bond. Moreover, an oxygen substituent has no influence on efficiency of ring-closing metathesis. Interestingly, the carbon analogues of the silicon tethered enynes, **242** were unreactive to the same reaction conditions. The difference is that the silicon center is also appended with two additional phenyl substituents, thus emphasizing the importance of the Thorpe-Ingold effect on this reaction.[76]

Alkynyl silyl ethers are an important class of compounds which serve as precursors to stereochemically defined 1,3-dienes. They are prepared by successive silylation of primary, secondary or tertiary alcohols with di- or trialkynylsilanes under basic conditions. The reaction is fairly general and can be applied to the synthesis of *mono*-alkoxyalkynylsilanes, symmetrical *bis*-alkoxyalkynylsilanes and unsymmetrical *bis*-alkoxyalkynylsilanes. Lee and Grimm disclosed an alternative method for the preparation of alkynyl silyl ethers.[77] Their use of the ring closing enyne metathesis further highlights the synthetic value of silyl ethers and silaketals in the formation of monocycles, **245** and fused bicycles (*vide supra*) *via* tandem process (Scheme 1.43).[77]



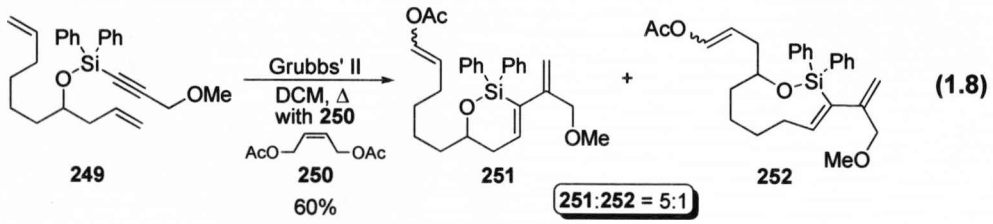
Scheme 1.43 *Stereoselective Synthesis of Acyclic Conjugated Dienes B*

Enyne metathesis is significantly more challenging when multiple pathways and products are accessible. Selectivity can be achieved through the modification of reacting partners using steric and stereoelectronic constraints. However, such modifications often require an additional synthetic manipulation. Lee and co-workers reported a study related to concentration-dependent selectivities.[78] Enyne metathesis of representative symmetrical alkoxysilane, **247** proceeded chemoselectively without interference from the competitive cyclization of the dienes, providing the cyclic 1,3-diene, **248** in excellent yield (Eq. 1.7).[78]



(1.7)

Alkoxysilanes bearing alkene chains of variable length are potentially problematic substrates for the enyne metathesis because they can lead to the competitive cyclization pathways, thus forming smaller and/or larger rings. Ring-closing enyne metathesis of intermediate **249** predominately furnished the smaller siloxacycle, **251** as a mixture of isomers. The external alkene, **250** was added to the reaction mixture to retard the unproductive dimerization of the products by capping the reactive terminal alkene after the initial enyne RCM. The selective formation of the smaller silaoxacycle is even more pronounced when the difference in tether length is greater. This observation is consistent with historical observation that smaller rings cyclize at faster rates than larger ones (Eq. 1.8).[78]

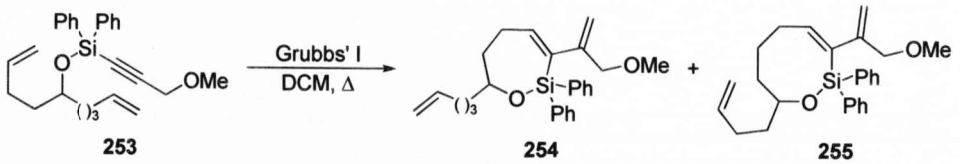


(1.8)

The selectivity of the enyne metathesis reaction drops to marginal level when the chain length of tethered dienes becomes more similar. This observation is probably due to similar rates of formation of both alkylidene intermediates followed by their cyclization prior to *pre*-equilibrium. Lee and co-workers envisioned that higher reaction concentration could intensify the selectivity as a result of more effective *pre*-equilibrium alkylidine exchange.[78] Such an exchange would help to discriminate between the two ring-closure pathways and therefore increase the selectivity of reaction. Indeed, the gradual increase of concentration was accompanied by a dramatic increase in selectivity, favoring the formation of the smaller silaoxacycle, **254**. Accordingly, the best ratio between seven and eight-membered

rings was obtained when a neat solution was employed (approx. 2.5 M) (Table 1.7, entry 5).[78]

Table 1.7: *Concentration Dependence on Dienyne RCM Selectivity*

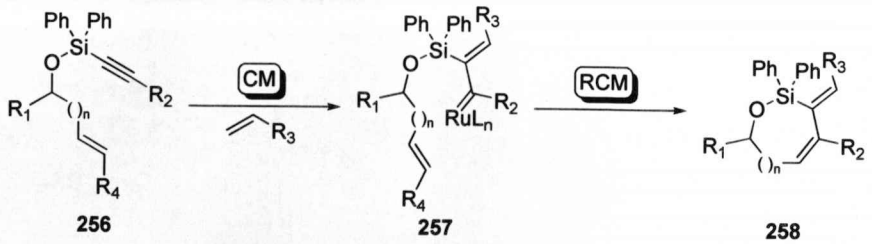


253 254 255

Entry	Conc.(M)	254:255	Yield(%)[b]
1	0.01	6.4:1	80
2	0.03	9:1	67
3	0.07	25:1	74
4	0.1	30:1	74
5	neat[a]	>50:1	79

[a] Reaction was heated for 15 minutes at 70 °C.
[b] Combined yield for **254**, **255**, homo- and heterodimers

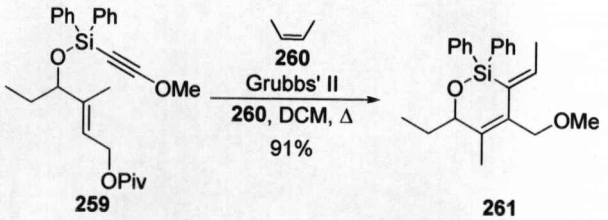
In 2005, Lee and co-workers reported a tandem cross-metathesis/ring-closing metathesis sequence as a route toward novel cyclic siloxanes.[79] One of the foremost challenges in the area of enyne cross-metathesis is the lack of regio- and diastereocontrol particularly for substrates with an internal alkyne and alkene functionality. While regio-controlled reactions of terminal alkynes are feasible, favorable *E* to *Z* ratios of the newly formed alkene functionality still remain a problem. Lee and co-workers envisioned that the reactivity and selectivity profiles of cross-metathesis and ring-closing metathesis could merge into a conceptually new



256 257 258

Scheme 1.44 *Synthesis of Conjugated Cyclic Siloxanes*

CM-RCM sequence. Based on the assumption that the double bond of fragment **256** is less reactive than the adjacent triple bond due to the R_4 substitution, a cross-metathesis reaction would provide the new alkylidine species, **257**. If the ring closure rate of **257** is significantly faster than intermolecular methylene transfer, the silaoxacycle, **258** would preferentially form. This type of cyclization represents a formal *endo*-mode closure which contains a 1,3-diene framework which is not accessible through a traditional RCM reaction (Scheme 1.44).[79] Based on this assumption Lee and co-workers defined an approach to the new connectivity precedent for silacyclic 1,3-dienes through fully stereo- and regioselective tandem cross-metathesis/ring-closing metathesis reaction utilizing both internal and terminal alkyne functionalities. Furthermore, the role of silicon in this transformation is much more than just a linker tethering two reactive entities. The geminal substituents of the silicon tether have a crucial role in reactivity profile of **256** due to the Thorpe-Ingold effect.[79,80] However, the internal alkynes with silyl substitution are generally less reactive then regular internal alkynes due to the steric hindrance. If an oxygen substituent is introduced in the propargylic position, the reactivity of the alkyne in the cross-metathesis reaction increases. Based on this observation, a propargylic methoxy group was used as the alkyne substitution. The yield of reaction largely depends on the choice of CM coupling partner and alkene substitution. A representative example of this tandem process can be seen in Equation 1.9.[79]



(1.9)

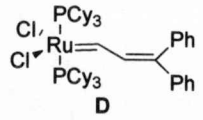
1.2.3 The Application of Silicon-Tether Bearing Two Carbon Atoms (-C-Si-C-)

1.2.3.1 Alkene Ring-Closing Metathesis

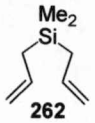
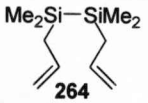
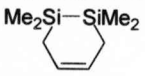
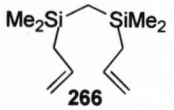
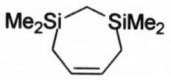
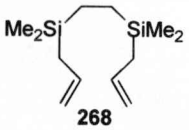
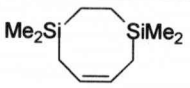
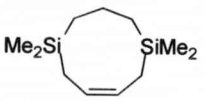
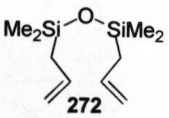
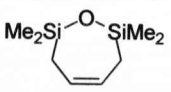
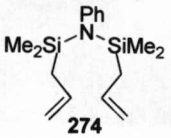
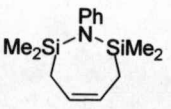
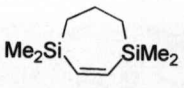
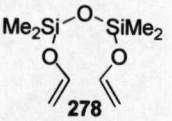
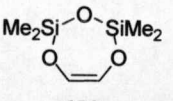
Silacycloalkanes are attractive class of compounds especially in the field of polymer chemistry. They are readily applied as monomers to the ring-opening metathesis polymerization (ROMP) to provide highly ordered, alternating copolymers. Sakurai and co-workers reported the ring-closing metathesis of α,ω-unsaturated silaalkadienes.[81] The cyclization feasibility of silaalkadienes was investigated based on the different substitution pattern and ring sizes. The initial studies are outlined in Table 1.8. The RCM of diallylsilane **262** and six-membered cyclization precursor, diallyldisilane **264** using 2 mol% of ruthenium complex **D** did not occur (Table 1.8; entries 1 and 2). In contrast, the cyclization of **266** furnished the seven-membered silacycle, **267** in respectable 87% yield under relatively mild conditions (Table 1.8; entry 3). The formation of eight-membered ring, **269** required larger amount of catalyst (11 mol%) and prolonged reaction time (Table 1.8; entry 4). The RCM become suppressed again, when attempt to form the nine-membered cyclic disilaalkene, **271** was made (Table 1.8; entry 5). Cyclization of 1,3-diallyl-1,1,2,2-tetramethyldisiloxane, **272** afforded the seven-membered oxacycle, **273** in respectable yield (Table 1.8; entry 6). The RCM of *N,N-bis*(allyldimethylsilyl)aniline, **274** furnished cyclic disilazane, **275** under mild conditions albeit in lower yield when compared to oxygen heterocycle **263** (Table 1.8; entry 7). Surprisingly, the cyclization of **276** and **278** showed no reactivity despite the possible formation of seven-membered ring (Table 1.8; entries 7 and 8). The RCM of **276** was suppressed presumably due to steric influence of methyl substituents on silicon in the close proximity to the reactive metallacycle. The cyclization of **278** failed most likely due

to electron donation from the oxygen through resonance effect, thus leading to the deactivation of the catalyst.[81]

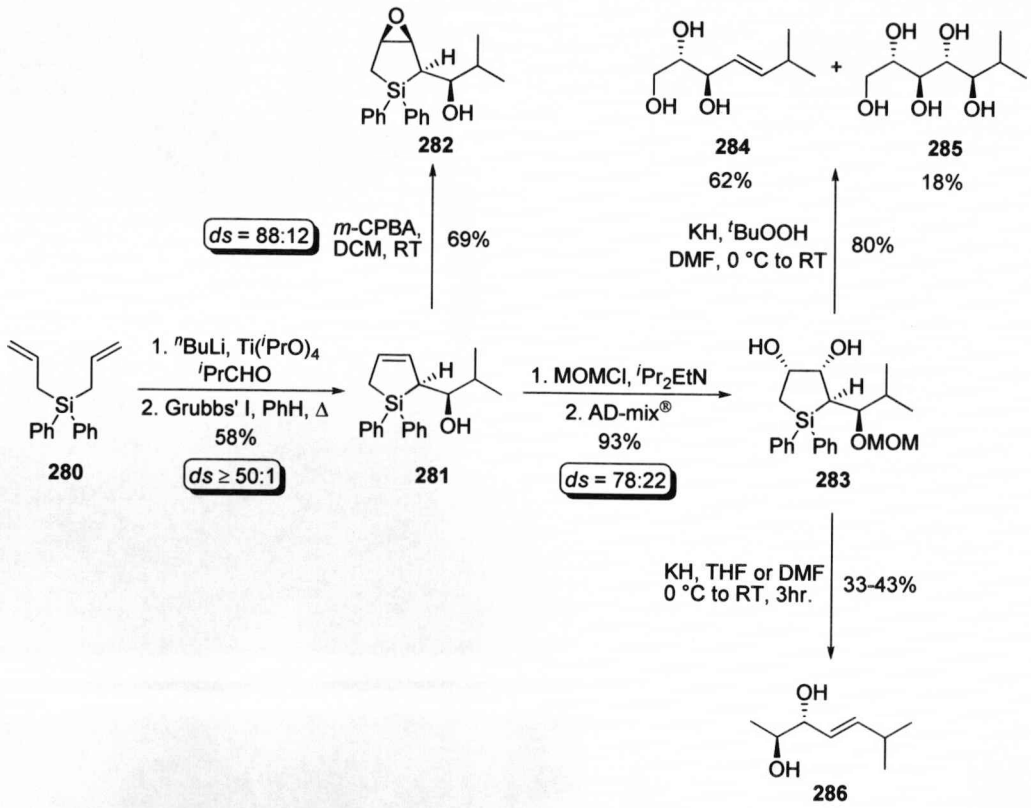
Table 1.8: *RCM Reaction of Unsaturated Silaalkadienes*



D

Entry	Substrate	Product	T/°C	Time	Yield
1	 **262**	 **263**	80	12 h	N.R.
2	 **264**	 **265**	80	12 h	N.R.
3	 **266**	 **267**	RT	2 h	87
4	 **268**	 **269**	65	21 h	51
5	 **270**	 **271**	RT	2 h	N.R.
6	 **272**	 **273**	RT	2 h	66%
7	 **274**	 **275**	RT	2 h	49%
8	 **276**	 **277**	RT	2 h	N.R.
9	 **278**	 **279**	RT	2 h	N.R.

Silacyclopent-3-enes are useful intermediates and are frequently used as polymer precursors. This attractive synthon has not found an extensive application in organic synthesis due to problems associated with its functionalization. Introduction of a substituent in the C2 position of a given silacyclopent-3-ene (See **281**, Scheme 1.45) is accomplished *via* metallation with a strong base followed by alkylation with an appropriate electrophile. Alkylation, however, is complicated by the propensity of silacyclopent-3-enes to polymerize upon exposure to strong bases, most likely due to nucleophilic attack of the base at the silicon center. Landais and co-workers published a series of reports on the preparation and functionalization of silacyclopent-3-enes.[82]

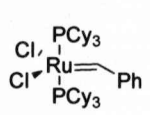


Scheme 1.45 *Functionalization of Silacyclopent-3-ene*

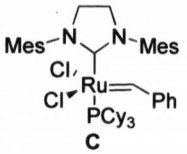
Their method included lithiation of the α-position of silacyclopentene precursor **280**, transmetallation with titanium and addition to an aldehyde to provide the acyclic β-hydroxysilane (Scheme 1.45). RCM of this tethered diene provided access to the β-hydroxysilacyclopentene **281** in modest yield and good diastereocontrol.[82a] Epoxidation of **281** proceeded with some degree of stereocontrol, providing the epoxyalcohol **282** in 69% yield. Alternatively, MOM protection of **281** followed by subsequent dihydroxylation provided diol **283** with modest stereocontrol.[82b] Landais further investigated these substrates by attempting oxidative cleavage of the C-Si bonds under various conditions. Initial investigations using Tamao[82c] and Fleming[82c] protocols were not successful. However, subjection of diol **283** to the Woerpel[82] conditions furnished the desired pentol, **285** in surprisingly low yield. Unexpected triol formation, as a result of Peterson elimination, was the major product, however, the presence of the (*E*)-olefin in the triol product, **284** was initially puzzling. Base promoted Peterson olefination is typically a *syn*-stereospecific process. The reaction most likely proceeds through a nucleophilic attack of the peroxide anion to the silicon centre, followed by *anti*-elimination and rearrangement to provide the observed triol. Exposure of **283** to a base provided the access to the diol **286** only in modest yield. The reaction is likely initiated by trace amounts of hydroxide ion present in the reaction, resulting in the elimination of the MOM group thus continuing the elimination process (Scheme 1.45).[82c]

Functional group tolerance in the RCM reaction has improved with advances in metal-alkylidine catalysts. However, the reaction is still substrate dependant as evidenced by an inability to employ sulfide tethers. This is attributed to the ability of sulfur to strongly coordinate the ruthenium center leading to catalyst inactivation. A standard solution to this problem is to increase the steric bulk around the sulfur functionality preventing coordination to the metal center. On the other hand, tuning of the electronic environment on the metal permits a certain level of catalysis.

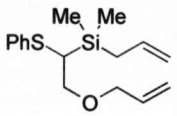
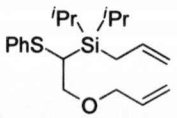
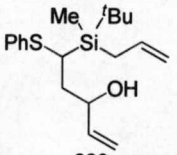
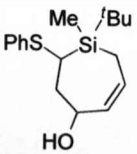
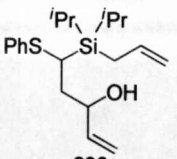
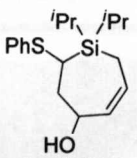
Table 1.9: *RCM Reaction of Sulfur Containing Dienes*



B

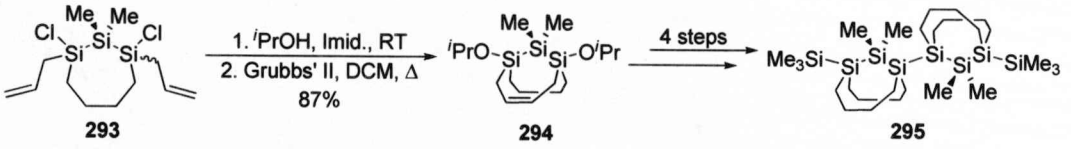


C

Entry	Substrate	Cat.	Mol.%	T/°C	Product	Yield/%
1		B	5	20		0
2		B	15	40		0
3		C	5	20		0
4	287	C	10	40		0
5		B	5	20		0
6		C	5	20		0
7	288	C	5	40		0
8		B	5	20		0
9		B	10	40		<20
10	289	C	5	20	291	76
11	 290	C	5	20	 292	77

Rowlands and Singleton attempted to prepare a series of acyclic silaketal intermediates with a pendant phenylsulfide functionality.[83] Unfortunately, most of

the sulfur-containing substrates were completely inactive in the metathesis reaction, regardless of ruthenium catalyst employed (Table 1.9; entries 1-8). A solution to this problem was discovered when a silicon-tethered substrate containing both the sulfide subunit and an allylic alcohol was used. The reaction proceeded to form the corresponding thioalcohol in good yield (Table 1.9; entries 10 and 11). It is evident from this result that the presence of the allylic alcohol functionality promotes the formation of transient metallacyclobutane *via* rapid and reversible ligand exchange or hydrogen bonding leading to a complex predisposed for cycloadditon.[83]



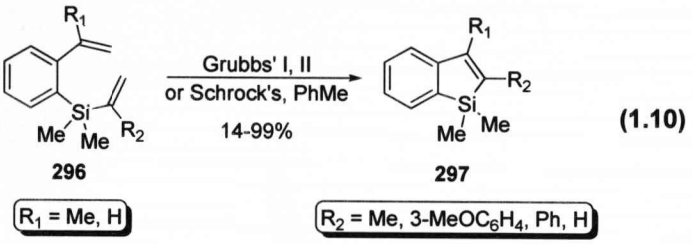
293 294 295

Scheme 1.46 *The Synthesis of All-Anti Octasilane* **295**

Tamao and co-workers have shown that the TST-RCM can be effectively applied toward the construction of linear polysilanes which are useful in the material sciences.[84] Structure control is very important for achieving desired physical properties of organic and organometallic polymers. Linear polysilanes are a representative class of one-dimensional polymers with extraordinary photophysical and electronic properties attributed to σ-electron delocalization over the silicon framework which is highly sensitive to the silicon backbone conformation. Preliminary studies have revealed that a polysilane chain has a random-coil structure due to unrestricted rotation around the Si-Si single bond. Additional studies have shown that the *anti*-orientation of a *tetra*-silane Si-Si-Si-Si, with a dihedral angle of 180°, is the optimal conformational disposition for an extensive σ-conjugation. A majority of efforts in this burgeoning field are now directed toward the construction of structural constraints to control silicon backbone conformation.[84] Tamao and co-

workers constructed a trimethylsilyl-capped dimer of a trisilane building block where the conformation of the silyl units is predominantly the *all-anti* orientation.[84]

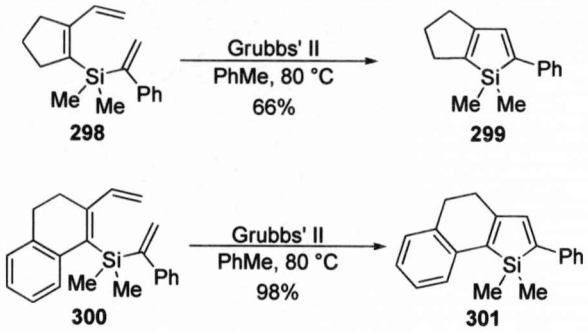
The synthetic route to octasilane **295** is described in the Scheme 1.46. Treatment of 1,3-diallyl-1,3-dichlorotrisilane with *iso*-propanol and imidazole furnished the isopropoxy-substituted trisilane. Ring-closing metathesis afforded the bicyclic *bis*-alkoxytrisilane, **294** which was elaborated into the desired octasilane, **295** in 4 additional steps. The spectroscopic data of octasilane **295** displayed an effective σ-delocalization over the silicon framework which clearly demonstrates the practical significance of the bicyclic trisilane unit as a powerful building block to attain *all-anti* polysilane as an ideal σ-conjugated system.[84]



(1.10)

Silacyclopentadiene intermediates, also known as siloles **297** are an important class of compounds in the area of material science due to their propensity to transfer electrons in organic light-emitting diodes (OLED). Murakami and co-workers reported a new strategy toward the construction of the silacyclopentadiene skeleton, **297** where the key cyclization step is accomplished through a ring-closing metathesis reaction.[85] The ability to cyclize several dimethyl(alkenyl)(2-alkenyl-phenyl)silanes, **296** bearing different substitution patterns was examined using Grubbs' 1st, 2nd generation and Schrock's catalysts. The reaction was quantitative using Grubbs' 2nd generation catalyst, where R_1 equals to Ph or 3-methoxyphenyl, yielding silacyclopentadiene intermediates **297** (Eq. 1.10).[85] On the contrary, when Schrock's catalyst was used on the substrate with the 3-methoxyphenyl substituent,

the reaction was completely ineffective, presumably due to oxygen coordination to the molybdenum center. Cyclization of the substrate, where $R_1 = R_2 = Me$, provided the *tetra*-substituted olefin albeit in poor yield. Ring-closing metathesis was equally productive when the *o*-phenylene silyl tether was replaced with the *cis*-1,2-vinylene silyl, providing bicyclic **299** and tricyclic **301** siloles in good to excellent yield (Scheme 1.47).[85]



Scheme 1.47 *Synthesis of Bicyclic and Tricyclic Siloles via RCM*

1.3 Conclusions and Outlook

Temporary silicon-tethered ring-closing metathesis is quickly emerging as modern and powerful cross-coupling reaction. Tremendous progress of this strategy is primarily due to advent of well-defined transition metal catalysts which displayed a high reactivity and functional group tolerance. Preparation of silicon-tethered rings of various sizes and their refunctionalization is being realized and numerous new aspects of this methodology have been discovered and applied in the total synthesis of complex natural products. The control of stereoselectivity in macrocyclizations and functional group incompatibility toward strongly coordinating heteroatoms are issues that need to be addressed in the future to make this strategy more valuable. Enantioselective ring-closing metathesis is a highly promising new strategy in asymmetric synthesis and its application will almost certainly gain great importance in the near future.

1.4 References

[1] (a) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York. 1969. (b) Knowles, J. R.; Parsons, C. A. *Nature* **1969**, *221*, 53-54. (c) Bruice, T. C. *Proximity Effects and Enzyme Catalysis; Enzymes, 3rd Ed.,* Academic: New York, 1970, 217-279.

[2] (a) Kirby, A. *J. Adv. Phys. Org. Chem.* **1980**, *17*, 183-278. (b) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. USA* **1971**, *68*, 1678-1683. (c) Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295-323. (d) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858-5865. (e) Bender, M. L.; Neveu, M. C. *J. Am. Chem. Soc.* **1958**, *80*, 5388-5391.

[3] For selective deprotection of silyl ethers see: (a) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, *9*, 1031-1069. (b) Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833-5871.

[4] For historical development of silicon tethered reactions see: (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298-2300. (b) Reetz, M.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889-3898. (c) Tamao, K.; Nakajima, T; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6090-6093. (d) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1990**, *31*, 6585-6588. (e) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578-7579. (f) Fleming, S. A.; Ward, S. C. *Tetrahedron Lett.* **1992**, *33*, 1013-1016. (g) Crimmins, M. T.; Guise, L. E. *Tetrahedron Lett.* **1994**, *35*, 1657-1660. (h) Anwar, S.; Davis, A. P. *J. Chem. Soc., Chem. Commun.* **1986**, 831-832. (i) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087-1088. (j) Evans, P. A.; Baum, E. W. *J. Am. Chem. Soc.* **2004**, *126*, 11150-11151.

[5] For review on disposable tethers see: (a) Gauthier, D. R. Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289-2338. For review on silicon tethers see: (b) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253-1277. (c) Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, 813-854. (d) Marciniec, B.; Pietraszuk, C. *Curr. Org. Chem.* **2003**, *7*, 691-735.

[6] For review on olefin metathesis see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. *Acc. Chem. Res.* **1995**, *28*, 446-452. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036-2056. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413-4449. (d) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371-388. (e) Blechert, S. *Pure and Appl. Chem.* **1999**, *71*, 1393-1399. (f) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75-89. (g) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012-3043. (h) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592-4633. (i) Deiters, A. Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199-2238. (j) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490-4527 and pertinent references therein.

[7] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886.

[8] Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974-3975.

[9] Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426-5427.

[10] Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768-6769.

[11] Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429-1432.

[12] Lobbel, M.; Köll P. *Tetrahedron: Asymmetry* **2000**, *11*, 393-396

[13] Briot, A.; Bujard, M.; Governeur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517-1519.

[14] Arduengo, A. J., III; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530-5534.

[15] Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682-6685.

[16] Hara, O.; Sugimoto, K.; Hamada, Y. *Tetrahedron* **2004**, *60*, 9381-9390 and pertinent references therein.

[17] Cordier, C.; Morton, D.; Leach, S.; Woodhall, T.; O'Leary-Steele, C.; Warriner, S.; Nelson, A. *Org. Biomol. Chem.* **2008**, *6*, 1734-1737.

[18] Pettit, M.; Chouraqui, G.; Aubert, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 2037-2040.

[19] (a) Mulzer, J.; Gaich, T. *Org. Lett.* **2005**, *7*, 1311-1313. (b) Mulzer, J.; Martin, H. J.; Karig, G.; Gaich, T. *Eur. J. Org. Chem.* **2006**, 3372-3394. (c) Mulzer, J.; Mantoulidis, A. *Tetrahedron Lett.* **1996**, *37*, 9179-9182. (d) Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456-7467 and pertinent references therein.

[20] Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1567-1569.

[21] Gierasch, T. M.; Chytil, M.; Didiuk, M. T.; Park, J. Y.; Urban, J. J.; Nolan, S. P.; Verdine, G. L. *Org. Lett.* **2000**, *2*, 3999-4002 and pertinent references therein

[22] (a) Harrison, B. A.; Verdine, G. L. *Org. Lett.* **2001**, *3*, 2157-2159. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401-404.

[23] Postema, M. H. D.; Piper, J. L. *Tetrahedron Lett.* **2002**, *43*, 7095-7099.

[24] Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H. -R. *J. Am. Chem. Soc.* **2003**, *125*, 14702-14703.

[25] Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z. -m.; Zhao, G. -x; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409-10410.

[26] Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. *Org. Lett.* **2006**, *8*, 3383-3386.

[27] (a) Alkofahi, A.; Rupprecht, J. K.; Liu, Y. M.; Chang, C. -J.; Smith, D. L.; McLaughlin, J. L. *Experientia* **1990**, *46*, 539-541. (b) Rupprecht, J. K.; Hui, Y. -H. McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237-278.

[28] For the cross-metathesis using ethylene gas see: (a) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082-6083. (b) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161-1163. (c) Ratnayake, A. S.; Hemscheidt, T. *Org. Lett.* **2002**, *4*, 4667-4669.

[29] Marjanovic, J.; Kozmin, S. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8854-8857 and pertinent references therein.

[30] Boiteau, J. -G.; Van de Weghe, P.; Eustache, J. *Tetrahedron Lett.* **2001**, *42*, 239-242.

[31] Van de Weghe, P.; Aoun, D.; Boiteau, J. -G.; Eustache, J. *Org. Lett.* **2002**, *4*, 4105-4108.

[32] (a) Takada, N.; Suenaga, K.; Yamada, K.; Zheng, S. –Z.; Chen, H. –S.; Uemura, D. *Chem. Lett.* **1999**, 1025-1026. (b) Suenaga, K.; Araki, K.; Sengoku, T.; Uemura, D. *Org. Lett.* **2001**, *3*, 527-529.

[33] Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734-1737.

[34] Hooper, A. M.; Dufour, S.; Willaert, S.; Pouvreau, S.; Pickett, J. A. *Tetrahedron Lett.* **2007**, *48*, 5991-5994.

[35] Casey, E. M.; Teesdale-Spittle, P.; Harvey, J. E. *Tetrahedron Lett.* **2008**, *49*, 7021-7023.

[36] West, L. M.; Northcote, P. T.; Battershill, C. N. *J. Org. Chem.* **2000**, *65*, 445-449.

[37] Hood, K. A.; West, L. M.; Rouwé, B.; Northcote, P. T.; Berridge, M. V.; Wakefield, S. J.; Miller, J. H. *Cancer Res.* **2002**, *62*, 3356-3360.

[38] (a) Gaitanos, T. N.; Buey, R. M.; Díaz, J. F.; Northcote, P. T.; Teesdale-Spittle, P.; Andreu, J. M.; Miller, J. H. *Cancer Res.* **2004**, *64*, 5063-5067. (b) Wilmes, A.; Bargh, K.; Kelly, C.; Northcote, P. T.; Miller, J. H. *Mol. Pharm.* **2007**, *4*, 269-280.

[39] (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317-1382. (b) Maifeld, S. V.; Lee, D. *Chem. Eur. J.* **2005**, *11*, 6118-6126. (c) Van de Weghe, P.; Bisseret, P.; Blanchard, N.; Eustache, J. *J. Organomet. Chem* **2006**, *691*, 5078-5108. (d) Chattopadhyay, S. K.; Karmakar, S.; Biswas, T.; Majumdar, K. C.; Rahaman, H.; Roy, B. *Tetrahedron* **2007**, *63*, 3919-3952.

[40] (a) Grimm, J. B.; Lee, D. *J. Org. Chem.* **2004**, *69*, 8967-8970. (b) Park, S.; Kim, M.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 9410-9415. (c) Grimm, J. B.; Otte, R. D.; Lee, D. *J. Organomet. Chem.* **2005**, *690*, 5508-5516.

[41] Hansen, E. C.; Lee, D. *Acc. Chem. Res.* **2006**, *39*, 509-519.

[42] (a) Schummer, D.; Irschik, H.; Reichenback, H.; Höfle, G. *Liebigs Ann. Chem.* **1994**, 283-289. (b) Schummer, D.; Schomburg, D.; Irschik, H.; Reichenbach, H.; Höfle, G. *Liebigs Ann. Chem.* **1996**, 965-969.

[43] Irschik, H.; Schummer, D.; Gerth, K.; Höfle, G.; Reichenbach, H. *J. Anibiot.* **1995**, *48*, 26-30.

[44] Lee, D.; Kim, Y. J. *Org. Lett.* **2006**, *8*, 5219-5222 and pertinent references therein.

[45] Lee, D.; Kim, Y. J. *Org. Lett.* **2007**, *9*, 3859.

[46] Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757-4760 and pertinent references therein.

[47] Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861-7864.

[48] Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 1411-1413.

[49] Fujiwara, T.; Yanai, K.; Shimane, K.; Takamori, M.; Takeda, T. *Eur. J. Org. Chem.* **2001**, 155-161.

[50] Jiménez-Gonzáles, L.; Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Commun.* **2005**, 2689-2691.

[51] Scalzullo, S. M.; Islam, R. U.; Morgans, G. L.; Michael, J. P.; van Otterlo, W. A. L. *Tetrahedron Lett.* **2008**, *49*, 7403-7405.

[52] (a) Taylor, R. E.; Engelhardt, F. C.; Yuan, H. *Org. Lett.* **1999**, *1*, 1257-1260. (b) Taylor, R. E.; Schmitt, M. J.; Yuan, H. *Org. Lett.* **2000**, *2*, 601-603. (c) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964-2969.

[53] Ahmed, M.; Atkinson, C. E.; Barrett, A. G. M.; Malagu, K.; Procopiou, P. A. *Org. Lett.* **2003**, *5*, 669-672 and pertinent references therein.

[54] Miller, M. J.; Li, F. *J. Org. Chem.* **2006**, *71*, 5221-5227.

[55] Drautz, H.; Zähner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752-1765.

[56] Grabley, S.; Hammann, P.; Kluge, H; Wink, J.; Kricke, P.; Zeek, A. *J. Antibiot.* **1991**, *44*, 797-800.

[57] Tung, J. C.; Chen, W.; Noll, B. C.; Taylor, R. E.; Fields, S. C.; Dent, W. H., III.; Green, F. R. *Synthesis*, **2007**, 2388-2396 and pertinent references therein.

[58] Ahmed, M.; Barret, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Procopiou, P. A.; Salter, M. M. *Tetrahedron* **1999**, *55*, 3219-3232.

[59] Barret, A. G. M.; Beall, J. C.; Braddock, D. C.; Flack, K.; Gibson, V. C.; Salter, M. M. *J. Org. Chem.* **2000**, *65*, 6508-6514 and pertinent references therein.

[60] (a) Denmark, S. E.; Yang, S. -M. *Org. Lett.* **2001**, *3*, 1749-1752. (b) Denmark, S. E.; Yang, S. -M. *Tetrahedron* **2004**, *60*, 9695-9708.

[61] Denmark, S. E.; Yang, S. -M. *J. Am. Chem. Soc.* **2002**, *124*, 2102-2103.

[62] (a) Kinnel, R. B.; Dieter, R. K.; Mienwald, J.; Engen, D. V.; Clardy, J.; Eisner, T.; Stallard, M. O.; Fenical, W. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3576-3579. (b) Fenical, W.; Sleeper, H. L.; Paul, V. J.; Stallard, M. O.; Sun, H. H. *Pure Appl. Chem.* **1979**, *51*, 1865-1874.

[63] (a) Denmark, S. E.; Yang, S. -M. *J. Am. Chem. Soc.* **2002**, *124*, 15196-15197. (b) Denmark, S. E.; Yang, S. -M. *J. Am. Chem. Soc.* **2004**, *126*, 12432-12440.

[64] Rodríguez-Escrich, C.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 5191-5194.

[65] Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Katsumata, K.; Horiguchi, T.; Kobayashi, J. *J. Org. Chem.* **2003**, *68*, 5339-5345.

[66] (a) Fürstner, A.; Kattnig, E.; Lepage, O.; *J. Am. Chem. Soc.* **2006**, *128*, 9194-9204. (b) Dai, W. -M.; Chen, Y.; Jin, J.; Wu, J.; Lou, J.; He, Q. *Synlett* **2008**, 1737-1741.

[67] (a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2001**, *123*, 12726-12727. (b) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644-17655.

[68] Review: Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichim. Acta* **2005**, *38*, 71-88.

[69] (a) Zakarian, A.; Batch, A.; Holton, R. A.; *J. Am. Chem. Soc.* **2003**, *125*, 7822-7824. (b) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727-1730.

[70] (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993 (b) Parenty, A.; Moreau, X.; Campagne, J. -M. *Chem. Rev.* **2006**, *106*, 911-939.

[71] (a) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822-1830. (b) Shiina, I.; Fukui, H.; Sasaki, A. *Nature Protocols* **2007**, *2*, 2312-2317.

[72] (a) Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041-4042. (b) La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720-9721. (c) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840-1846.

[73] Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251-8259.

[74] Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *12*, 2868-2869.

[75] Yao, Q. *Org. Lett.* **2001**, *3*, 2069-2072.

[76] Miller, R. L.; Maifield, S. V.; Lee, D. *Org. Lett.* **2004**, *6*, 2773-2776 and pertinent references therein.

[77] (a) Grimm, J. B.; Lee, D. *J. Org. Chem.* **2004**, *69*, 8967-8970. (b) Grimm, J. B.; Otte, R. D.; Lee, D. *J. Organomet. Chem.* **2005**, *690*, 5508-5516.

[78] Maifield, S. V.; Miller, R. L.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 12228-12229.

[79] Park, S.; Kim, M.; Lee, D. *J. Am. Chem. Soc.* **2005**, *127*, 9410-9415.

[80] Kim, Y. J.; Grimm, J. B.; Lee, D. *Tetrahedron Lett.* **2007**, *48*, 7961-7964.

[81] Hoshi, T.; Yasuda, H.; Sanji, T.; Sakurai, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 821-827.

[82] (a) Landais, Y.; Surange, S. S. *Tetrahedron Lett.* **2001**, *42*, 581-584. (b) Landais, Y.; Mahieux, C.; Schenk, K.; Surange, S. S. *J. Org. Chem.* **2003**, *68*, 2779-2789. (c) Landais, Y.; Mahieux, C. *Tetrahedron Lett.* **2005**, *46*, 675-679 and pertinent references therein.

[83] Rowlands, G. J.; Singleton, J. *J. Chem. Research* **2004**, 247-251.

[84] Fukazawa, A.; Tsuji, H.; Tamao, K. *J. Am. Chem. Soc.* **2006**, *128*, 6800-6801 and pertinent references therein.

[85] Takanori, M.; Yamaguchi, Y.; Murakami, M. *Synlett* **2008**, 561-564.

Chapter 2

Medium Ring Stereocontrol in the Construction of Silaketals

2.1. Introduction

2.1.1 Medium-Sized Rings in Synthetic Organic Chemistry

Structural complexity of medium-sized carbo- and heterocycles found in nature has captured the imagination of synthetic chemists ever since these structures began to be fully elucidated in the 1950's. Medium-sized macrocycles are defined as rings containing from eight to eleven atoms and many are incorporated within the structural core framework of biologically important natural products (Figure 2.1).[1]

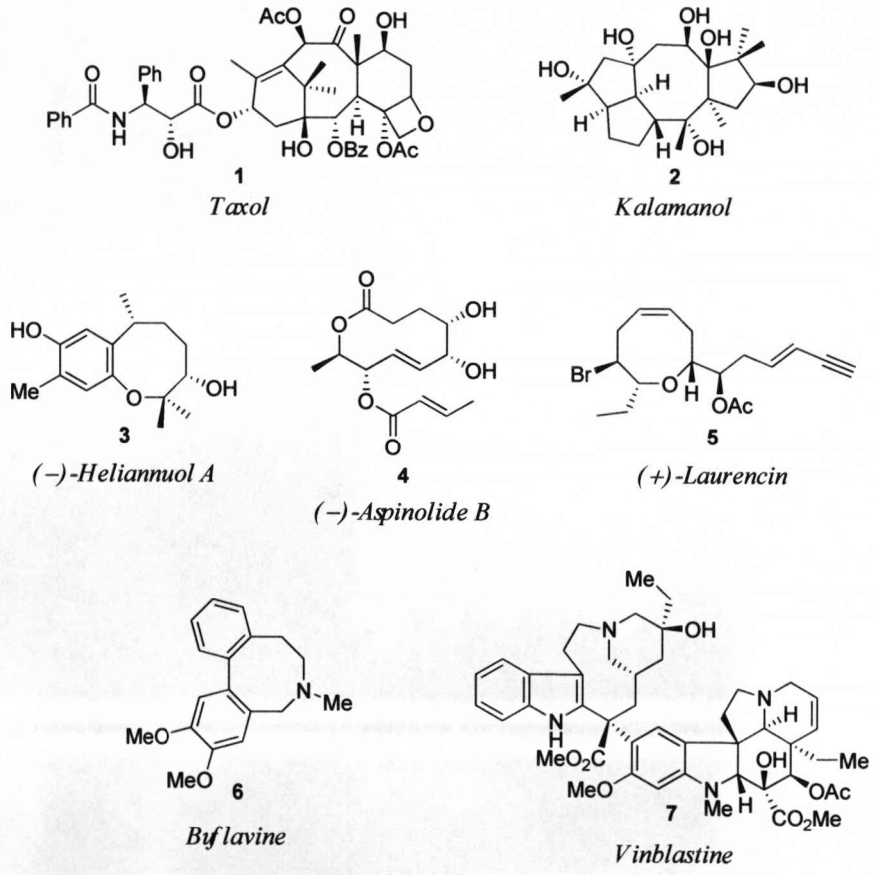
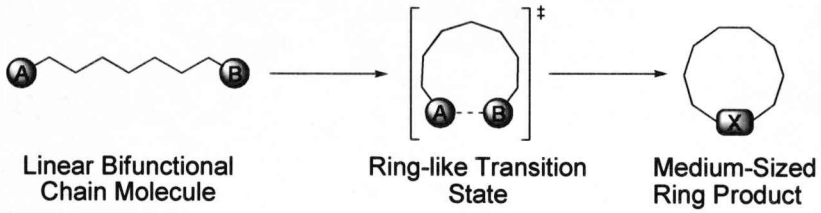


Figure 2.1 *Medium-Sized Ring Natural Products*

The groundbreaking work of Ruzicka[2] and Ziegler[3], inspired by the structural complexity of cyclic natural products, laid the foundations to modern

macrocyclization reaction. Following their studies, numerous cyclization approaches have been disclosed over the years to provide a methodology for the construction of these intriguing targets. Many of these approaches have been the subject of several comprehensive reviews.[4-9] However, the cyclization strategies to medium-sized rings are often complicated with a large enthalpic and entropic cost of ring formation as well as unfavorable transannular interactions.[10] These interactions are the dominant source of ring strain in medium-sized rings and thus cannot be avoided without adding a severe torsional and bond-angle distortion.



Scheme 2.1 *Intramolecular Ring-Forming Reaction and Transition State*

Intramolecular ring-forming reactions require a bifunctional substrate as a starting material (Scheme 2.1). Terminal functional groups **A** and **B** undergo ring closure reaction *via* ring-like transition state, thus forming a new functional group **X**. Due to the bifunctional disposition of starting material, the cyclization reaction suffers from the competitive polymerization through head-to-tail condensation. Low concentration conditions initially described by Ziegler[10] generally aid in suppressing the polymerization and promoting the cyclization. However, high dilution conditions suffer from two major shortcomings: 1) preparation of eight- and eleven-membered rings at high dilution still represents a formidable challenge due to unfavorable transannular interactions and 2) it significantly limits the preparative scale synthesis. Additionally, the structural complexity of the ring, formed in the cyclization reaction strongly affects the cyclization rate. Based on the transition state theory, the

cyclization rate depends on the structure of the open chain ground state and the transition state resembling the cyclic product (Scheme 2.1).[10]

The reactivity of the cyclization reaction can be defined in terms of activation energy and probability of end-to-end encounters. The activation energy of the medium ring reflects the strain energy, which is further dependent on the ring size.[11] Ring strain develops as a combination of a) bond opposition forces due to imperfect staggering (Pfitzer strain), b) bond angle distortion (Baeyer strain) and c) transannular repulsive orbital interactions of atoms across the ring forced in the close proximity. Another parameter, which has been used extensively over the past two decades to quantitatively assess the ease of ring closure is effective molarity (*EM*).[10,12,13] The effective molarity in respect to reaction rate is defined by Equation 2.1 wherein k_{intra} and k_{inter} are specific rates of analogous intra- and intermolecular reactions run under identical conditions. For purposes of equilibrium study, the Equation 2.2 defines the equilibrium *EM*. The *EM* is an essential parameter in physical organic chemistry and studies related to cyclization reactions. It represents an intramolecular reactivity that has been corrected for the inherent reactivity of the end groups.[10b]

$$EM = k_{intra}/k_{inter} \qquad \textbf{(2.1)}$$

$$EM = K_{intra}/K_{inter} \qquad \textbf{(2.2)}$$

Additionally, Thorpe-Ingold and heteroatom effects are equally important parameters, which also affect ring closure. Allinger and Zalkow[14] have demonstrated that ring closure of common rings is favored by the presence of the *gem*-dimethyl group incorporated within the structure due to a change in the number of gauche interactions evolving from the acyclic reactant to the cyclic transition state or product. However, in the formation of medium-sized rings, less favorable or

unfavorable enthalpy factors are present due to increasing ring strain and transannular interactions pertaining to methyl substitution. This effect subsides with the increase of the ring size.[10a]

The substitution of one or more methylene groups with heteroatoms such as O, N, S or Si can promote the rate of cyclization reaction. The manifestation of the heteroatom effect is clearly perceptible in the highly strained ring-like transition states, common for medium-sized rings. A faster cyclization rate is a consequence of reduced bond opposition forces and transannular interactions due to the installation of sterically less encumbered heteroatoms. Yet again, the effect seems to diminish when larger rings are formed.[10a]

2.1.2 Medium-Sized Ring Stereocontrol

Medium-sized rings are often capable of existence in a number of stable conformations albeit only a few of these conformers are low enough in energy to have a considerable population at room temperature. Well-defined conformational preferences can often provide the dominant controlling element regarding stereochemistry, for example in the preferential attack of reagent to more accessible face of prostereogenic carbon center. Substrate-directed stereocontrol has been extensively utilized in asymmetric synthesis.[15] However, the facial diastereocontrol on the medium-sized rings based exclusively on the conformational disposition of the substrate has not been extensively studied. It is partially due to difficulties associated with the prediction of the stereochemical course of their chemical reactions. Still and Galynker were first to use a computational models to predict the reactivity profile of the medium ring compounds.[16] The study focused on the reactions of simple, monosubstituted medium-sized and large ring carbocycles with the anticipation of conformationally controlled stereoselection. Medium-sized

carbocycles tend to exist in the conformations having as few transannular interactions and high-energy torsional arrangements as possible. A simple search of the cyclooctane conformational space disclosed a boat-chair conformation as the lowest energy conformer. The boat-chair conformation contains two eclipsed ethane linkages (darkened) as compared to the alternative chair-chair conformation with four such linkages or the boat-boat conformation, which has additional transannular repulsive interaction (Figure 2.2).[16]

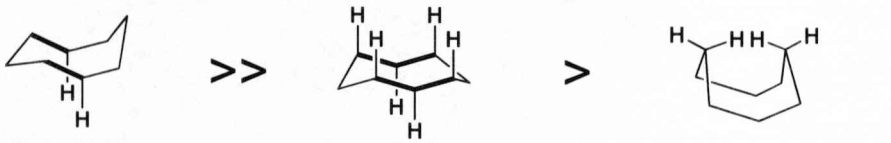


Figure 2.2 *The Cyclooctane Conformers*

Asymmetric induction on 6-membered unsaturated rings lacking bulky substituents often proceeds with poor diastereocontrol. This situation arises because two enantiotopic faces of the ring are not sufficiently different and most reactions do not tend to be stereospecific regarding to the particular conformation. However, the unsaturated medium-sized and large rings have 3-dimensional structures, which are considerably different from common rings because the sp^2 centers occupy the plane,

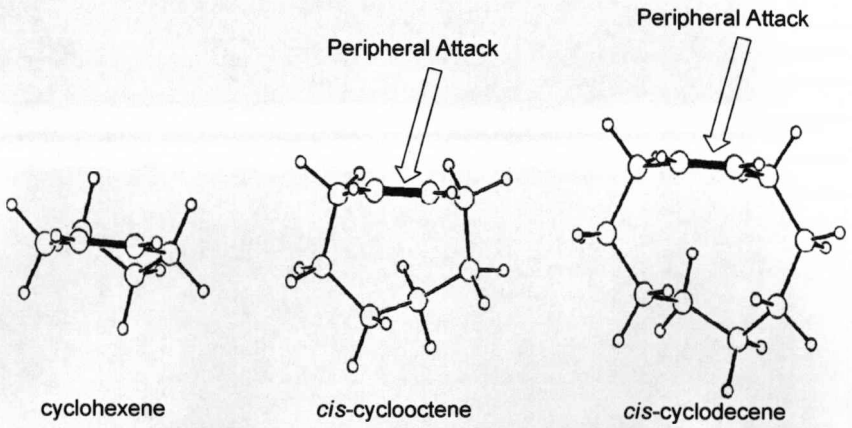
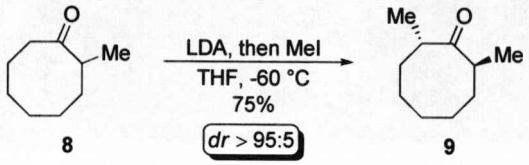


Figure 2.3 *Conformational Preference of Unsaturated Common and Medium Rings*

which is perpendicular to the plane of the ring. Such an arrangement is an outcome of minimized transannular nonbonding interactions.[16] From the Figure 2.3, it is evident that the olefin π-system in *cis*-cyclooctane and *cis*-cyclodecane are sterically very different. Since one face of the olefin is congested by the disposition of the allylic C-C bonds as well as by transannular methylene groups, it is expected that the particular reagent would approach the olefin from the less hindered, peripheral face (Figure 2.3).[16]

2.1.3 Diastereocontrol in Eight-Membered Rings

Still and Galynker investigated the propensity to attain the stereocontrol in eight-membered cyclic ketones through the kinetic enolate alkylation, conjugate addition and catalytic hydrogenation.[16] Substitution of one methylene unit with a carbonyl group could lead to five different boat-chair cyclooctanone conformers that are relatively close in energy. However, one conformer is particularly more stable than the others, so its energy corresponds to a global minimum. Molecular mechanics using the MM2 force field were employed to determine the minimum conformer, and thus predict the facial selectivity and distribution of products based on the starting material energies



8 9 **(2.3)**

(early transition state) or product energies (late transition state). Treatment of 2-methylcyclooctanone **8** with LDA at low temperatures afforded the kinetic enolate, which was alkylated with methyl iodide to furnish *trans*-dimethylcyclooctanone **9** with exquisite diastereocontrol (Eq. 2.3). In addition, 2,2-dimethycyclooctanone (15%) formed presumably through the alkylation of the thermodynamic enolate. The

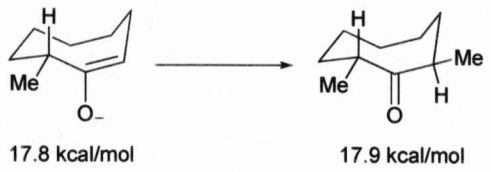
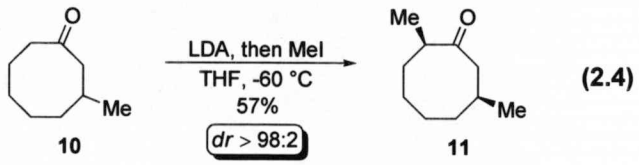


Figure 2.4 *The Boat-Chair Model of Enolate and Alkylated Product* **9**

boat-chair model provided an accurate prediction of the stereochemical outcome (Figure 2.4).[16] The alkylation of the kinetic enolate derived from the 3-methylcyclo-octanone **10** provided *syn*-dimethyl-cyclooctanone **11** with the same degree of stereocontrol (Eq. 2.4). In addition, this alkylation furnished 2,3-dimethylcycloocta-



none (33%) through the alkylation with the regioisomeric enolate.[16] Preference for the *syn*-stereoisomer is governed by the minimum energy enolate conformation where the methyl group at C_3 occupies a *pseudo*-equatorial position (Figure 2.5).

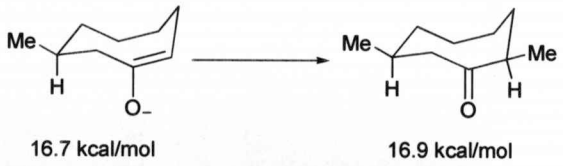
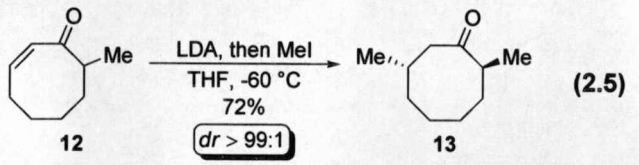


Figure 2.5 *The Boat-Chair Model of Enolate and Alkylated Product* **11**

In a related reaction, the addition of lithium dimethylcuprate to 8-methyl-cyclooct-2-en-1-one **12** provided the *trans*-1,4-adduct **13** with the highest degree of stereocontrol (Eq. 2.5). The stereochemical outcome of cuprate addition cannot be interpreted through the analysis of typical boat-chair conformation. The presence of



the enone changes the conformation so that C_1, C_2 and C_3 are coplanar with the methyl group in *pseudo*-equatorial position. Two of the lowest energy conformations are described in Figure 2.6. The *trans*-1,4-adduct is formed through the preferential attack of the cuprate reagent to the convex face of the molecule. Additional conformations having a *pseudo*-axial methyl group are destabilized by severe trans-

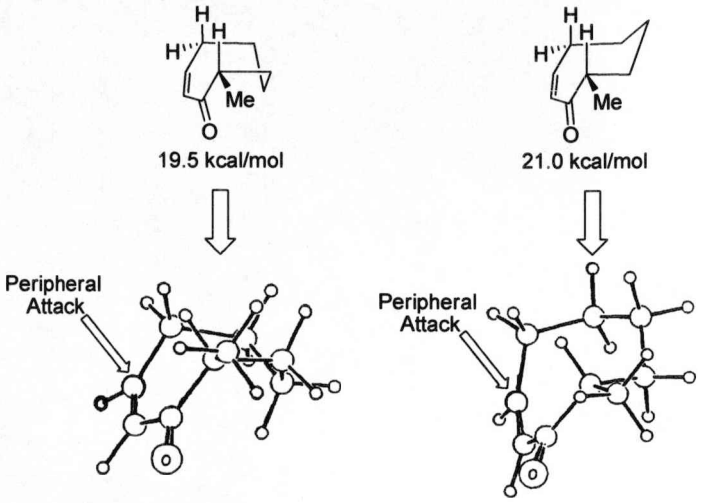
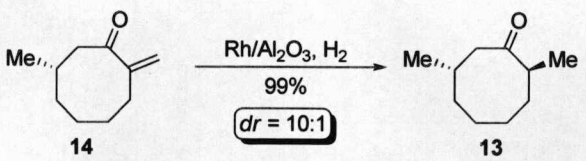


Figure 2.6 *Diastereoselectivity Models of 1,4-Addition to Enone* **12**

annular nonbonding interactions (>4 kcal/mol) and are excluded from the analysis.[16] The last reaction examined was the rhodium-catalyzed hydrogenation of α-methylenecyclooctanone **14**. The reaction proceeded almost quantitatively, with 10:1 diastereomeric ratio favoring *trans*-2,7-dimethylcyclooctanone **13** (Eq. 2.6).[16] The hydrogenation reaction provided a product identical to the one isolated from the cuprate addition (*vide supra*). The conformational analysis displayed four relevant conformations of **14** that were relatively close in energy (**A**-**D**). The hydrogenation



(2.6)

of conformers **C** and **D** through a peripheral approach of hydrogen would provide *syn*-2,7-dimethylcyclooctanone **13** but would suffer a severe transannular H-Me

interaction (Figure 2.7). The hydrogenation of conformers **A** and **B** would provide the product-like species with the methyl groups in the *pseudo*-axial position.[16] The erosion of selectivity when comparing with the cuprate addition, is probably due to a larger population of several conformers at room temperature as a result of relatively small barriers for *pseudo*-rotation and ring inversion.

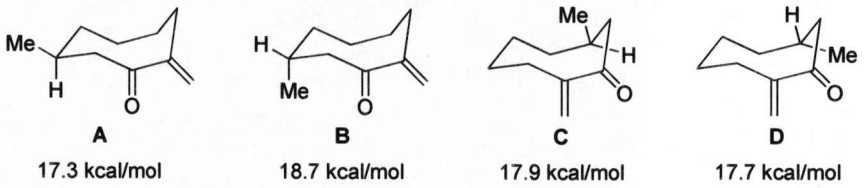
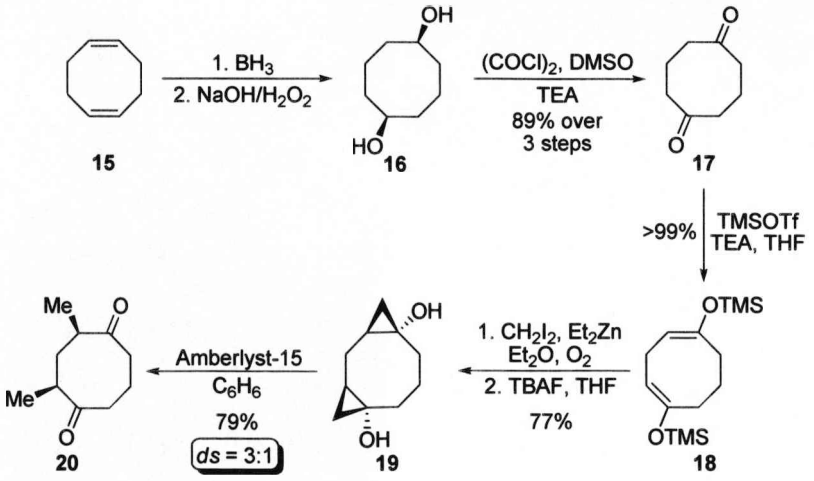


Figure 2.7 *Relevant Conformers of Enone* **14** *Relatively Close in Energy*

In related work, Schreiber and co-workers illustrated the utility of this principle with the stereocontrolled synthesis that relies on the conformational preferences of cyclooctyl systems.[17] Diastereoselective hydroboration of the 1,5-cyclooctadiene[18] **15** followed by oxidation to the dione[19] **17** provided an opportunity to examine the diastereocontrolled *bis*-cyclopropanation and ring opening (Scheme 2.2). Structural X-ray analysis indicated that 1,5-cyclooctanedione **17** exists in a boat-chair conformation, in which the carbonyl groups are located at flagpole positions in the boat-chair conformer, thus minimizing the transannular interactions across the ring. Schreiber and co-workers envisioned that *bis*-enolization would in fact occur stereoselectively from the same boat-chair conformation to produce *E,E*-1,4-*bis*-enolate. The most acidic protons in this system are the ones with the best orbital overlap with a carbonyl π-system (orthogonal to the carbonyl plane). Indeed, *bis*-silyl ether **18** was obtained as a single regio- and stereoisomer in quantitative yield when compound **17** was subjected to the enolate trapping conditions with TMSOTf. Subsequent alkylation utilizing various bases in the presence of methyl iodide resulted in poor regio- and stereoselectivity. The low selectivity is presuma-

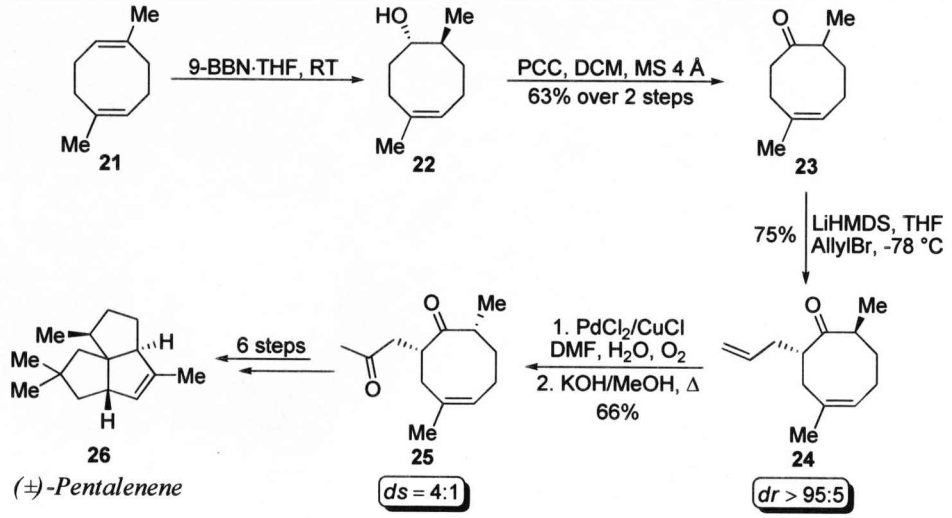


Scheme 2.2 *Stereoselective Synthesis of 2,4-Dimethyl-bis-Cyclooctanedione* **20**

bly due to the proton transfer causing an enolate isomerization between the monoalkylated intermediate and the dialkylated product. To circumvent this problem Schreiber and co-workers carried out the cyclopropanation of *bis*-silyl ether **18** using a modified Simmons–Smith protocol[20] followed by subsequent desilylation. This sequence furnished diol **19** as a single stereoisomer in good overall yield. The X-ray analysis determined that cyclopropanation occurred through the exo attack, which upon the ring opening with catalytic Amberlyst-15 in benzene at room temperature furnished the diketone **20** with poor stereocontrol (Scheme 2.2). Evidently, the ring opening process is accompanied with a competing epimerization. Pure 2,4-dimethyl-*bis*-cyclooctanedione **20** was obtained by HPLC separation and the structure was determined by X-ray analysis.[17]

Mehta and Rao reported a stereoselective enolate alkylation on eight-membered rings in studies related to the total synthesis of natural products (±)-pentalenene and (±)-*epi*-pentalenene.[21] The retrosynthetic analysis of (±)-pentalenene **26** identified 1,5-dimethyl-1,5-cyclooctadiene **21** as a viable synthetic precursor (Scheme 2.3). *En route* to (±)-pentalenene **26**, the stereoselective hydroboration of **21** furnished the cyclooctenol **22**, which upon PCC oxidation

afforded the cyclooctenone **23** in good overall yield. Kinetically controlled allylation of the corresponding enolate furnished the *trans*-intermediate **24** with excellent diastereocontrol as reported by Clark and Galynker.[16] Palladium-mediated Wacker oxidation provided an access to a *trans*-diketone intermediate. Subsequent epimerization using 2% KOH in methanol delivered the diketone **25** as 4:1 diastereomeric mixture favoring the *cis*-isomer. From this stage, the intermediate **25** was elaborated into (±)-pentalenene **26** over the course of 6 steps.[21]



Scheme 2.3 *Total Synthesis of (±)-Pentalene* **26**

Aggarwal and co-workers reported an expeditious route to (+)-anatoxin-a, **35** using a novel, highly enantioselective desymmetrization of eight-membered cyclic ketone as a key step.[22] Prior to this work, no such desymmetrization was reported

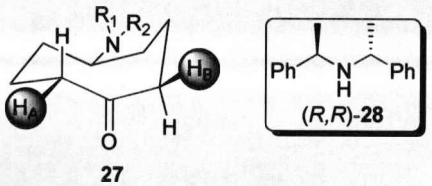
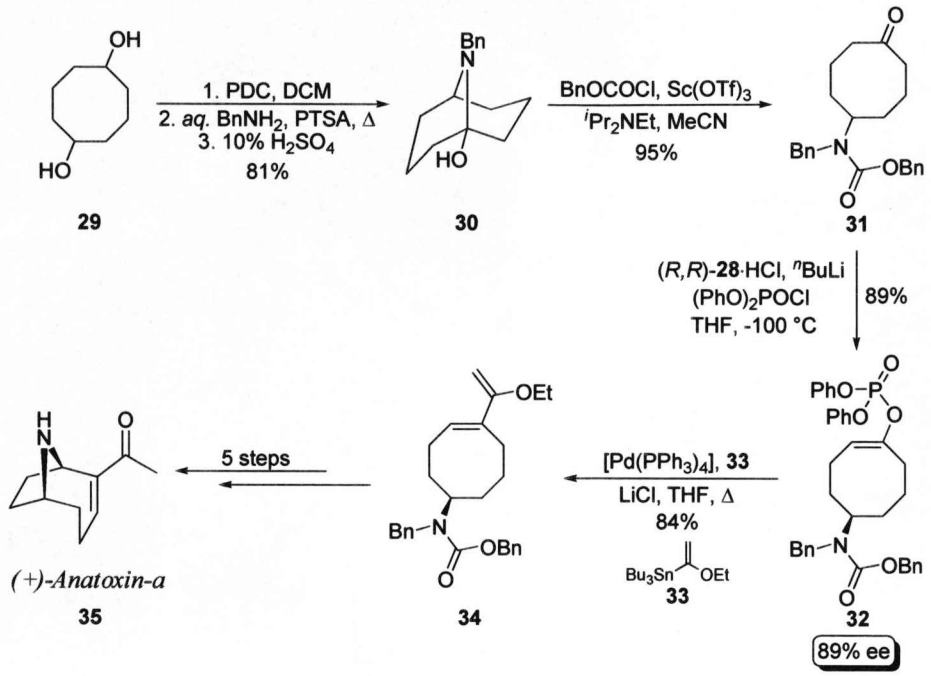


Figure 2.8 *Enolizable Protons in the Boat-Chair Conformation of Cyclooctanone* **27**

with the exception of one report of the enantioselective deprotonation of eight-membered rings.[23] The hypothesis was based on the earlier work by Still and

Allinger who demonstrated that cyclooctanones exist predominantly in low-energy boat-chair conformations.[16,24] The enolizable protons H_A and H_B in the low-energy boat-chair conformation of cyclooctanone **27** are portrayed in Figure 2.8. By correlating the sense of asymmetric induction with the Simpkins base[25] (*R,R*)-**28**,

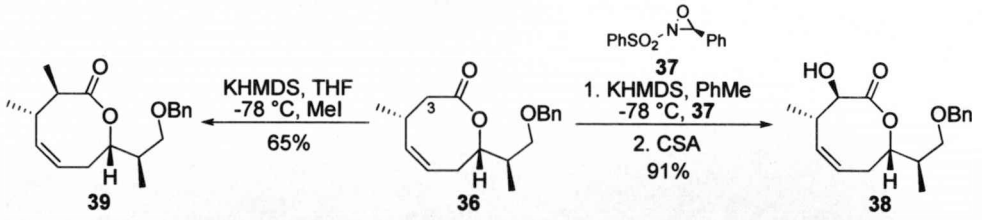


Scheme 2.4 *Total Synthesis of (+)-Anatoxin-a* **35**

Aggarwal and co-workers predicted the selective deprotonation of H_B, which would provide the enolate required for the completion of the synthesis of the natural product **35**.[22] The synthesis commenced from *cis*-1,5-cyclooctanediol **29** which was oxidized to provide the hemiacetal intermediate (Scheme 2.4). Treatment of this hemiacetal with hot aqueous benzylamine provided the mixture of hemiaminal and aminal. The mixture was converted to the desired hemiaminal **30** by subsequent treatment with sulfuric acid. Ring opening of hemiaminal **30** followed by *N*-acylation were accomplished using 5 mol% of $Sc(OTf)_3$ in excellent yield. The key desymmetrization step utilizing (*R,R*)-**28** with ^{n}BuLi and subsequent quenching with diphenyl chlorophosphate provided the enol phosphate **32** in high enantioselectivity.

Completion of intermediate **34** was realized through Stille cross-coupling of enol phosphate **32** and stannane **33** in the presence of $Pd(PPh_3)_4$ as a catalyst. From this stage of the synthesis intermediate **34** was elaborated into (+)-anatoxin-a **35** over the course of 5 steps.[22]

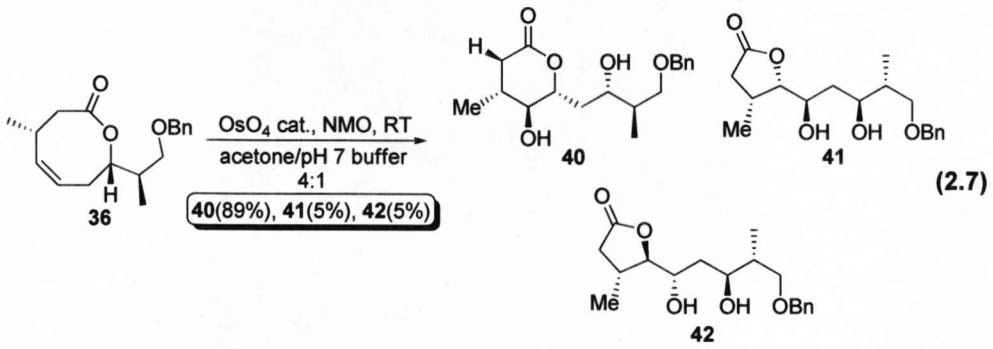
Holmes and co-workers demonstrated the regio- and stereoselective functionalization of medium ring lactams. The method permitted installation of amino substituents adjacent to the lactam carbonyl group with good stereocontrol.[26] Encouraged by these results, they reported the application of medium ring stereocontrol to unsaturated eight-membered cyclic lactones.[27] This method provides a rapid access to highly substituted polyketide fragments. Functionalization in position 3 is established through the enolate formation and subsequent alkylation with the appropriate electrophile (Scheme 2.5). Hydroxylation of the lactone **36** was accomplished using Davis' oxaziridine[28] which afforded the α-hydroxylactone **38** as



Scheme 2.5 *Stereoselective Functionalization of Eight-Membered Lactone* **36**

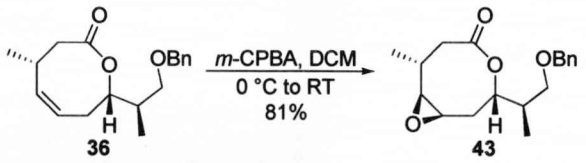
a single stereoisomer in excellent yield. Methylation of the same lactone using KHMDS and Methyl iodide furnished the methylated lactone **39** as a single stereoisomer albeit with lower yield.[27] The stereochemical outcome is in agreement with the MM2 calculations. Functionalization of the C5-C6 olefin was accomplished by treating the lactone **36** with a catalytic amount of osmium tetroxide and *N*-methylmorpholine-*N*-oxide in an acetone/pH 7 buffer solution (Eq. 2.7). However, the initial dihydroxylation product underwent *in situ* translactonization, to afford a

mixture of diols **40-42**. The diastereoselectivity was approximately 19:1 with ring-contracted, six-membered cyclic lactone **40** as the major product.[27] The relative configuration of lactones was confirmed by nOe studies. On the other hand the epoxidation of unsaturated lactone **36** with *m*-CPBA in DCM provided the epoxide



(2.7)

43 as a single stereoisomer in 81% yield (Eq. 2.8). The relative stereochemistry of the epoxide was in agreement with molecular modeling predictions.[27] This methodology provided a valuable insight into the functionalization of all available ring positions utilizing the conformational bias of the eight-membered lactones.

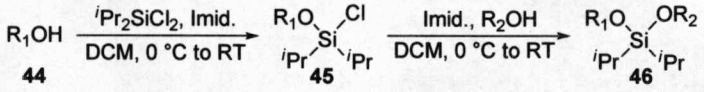


(2.8)

2.2 Preparation of Unsymmetrical Silaketals: Acyclic Precursors to Eight-Membered Cyclic Silaketals

Temporary tethers have become an immensely popular in the past decade, primarily due to their ability to transform an *inter*molecular reaction into its corresponding counterpart. The basis of this idea is to create a temporary intramolecular union, which overcomes entropically disfavored reactions and provide the products, which are not always available through intermolecular reaction. Facile removal of the tether in the final stage of the synthesis provides an

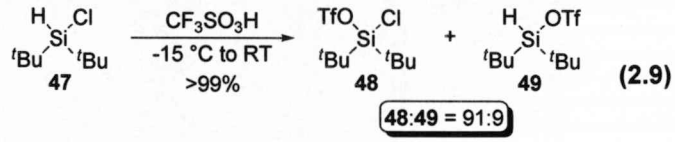
additional requirement. Need to introduce the silicon in this manifold *via* silicon tether has proven particularly popular and as described in the previous chapter fulfills all the key criteria. Hence, from a practical standpoint, the silicon-tether is introduced through silylation of alcohols to afford both symmetrical and asymmetrical silaketal intermediates. The silaketals are an important class of compounds in organic synthetic chemistry, and have been utilized extensively as starting materials for many different reactions (see Chapter 1). More recently, silaketals have been utilized in ring-closing metathesis in which the preparation of symmetrical silaketals does not require a sequential addition of coupling partners and therefore has the same complexity of standard silyl group protections.[29] The construction of unsymmetrical silaketals however, requires the carefully controlled sequential additions of two different alcohols. Furthermore, the synthesis is often hampered by the formation of undesired symmetrical silaketals. Scheme 2.6 outlines the typical sequential silylation procedure, which requires a syringe pump addition of an alcohol to a large excess of R_2SiCl_2 (R=Me, ^{i}Pr, Ph, ^{t}Bu) under dilute conditions to suppress the formation of the symmetrical silaketal. Subsequent removal of the remaining volatile silane leads to reactive *mono*-alkoxychlorosilane



Scheme 2.6 *Frye's Approach Toward the Unsymmetrical Silaketals*

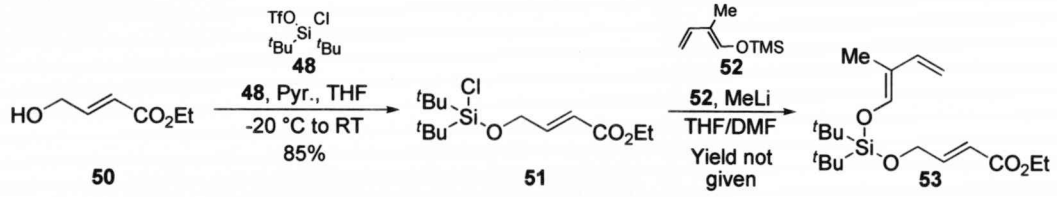
intermediate **45**, which is then subjected to the second cross-coupling reaction with different alcohol.[30] In order to make this procedure viable, the dichlorosilane reagent needs to be easily separable from the reactive *mono*-alkoxychlorosilane intermediate.

To circumvent these problems, Fortin and co-workers introduced the activated $^{t}Bu_2Si(OTf)Cl$ reagent **48** for sequential cross-coupling of alcohols. However, due to the bulky *tert*-butyl substituents, the second silylation is often quite problematic. Reagent **48** is prepared by treatment of di-*t*-butylchlorosilane **47** with triflic acid at low temperatures, providing chlorosilyl triflate **48** as a major product in quantitative yield (Eq. 2.9).[31] Selective monosubstitution was accomplished by



(2.9)

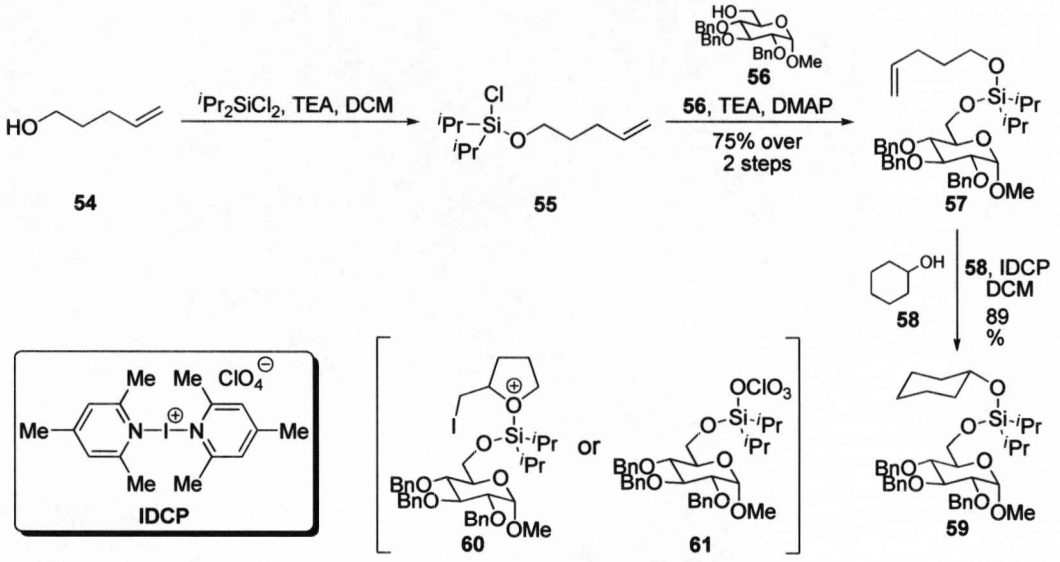
treatment of $^{t}Bu_2Si(OTf)Cl$ **48** with ethyl 4-hydroxycrotonate **50** at low temperatures. The reaction led to chromatographically stable alkoxychlorosilane **51** in excellent yield. The second cross-coupling reaction using the lithium enolate of **52** provided the requisite silaketal **53** (Scheme 2.7).[31]



Scheme 2.7 *Fortin's Approach Toward the Unsymmetrical Silaketals*

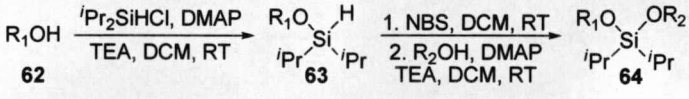
Skrydstrup and co-workers reported an interesting route toward the unsymmetrical silaketals through the activation of 4-pentenylsilyl ethers with iodonium dicollidine perchlorate (IDCP).[32] The method did not find the wide application since it was used only for glycosylations reaction and required the preparation of specific intermediate containing the 4-pentenyl silyl ether functionality. Carbohydrate intermediate **57** was prepared *via* standard sequential cross-coupling utilizing diisopropyldichlorosilane in good overall yield (Scheme 2.8). The second stage of the reaction required an activation of 4-pentenyl silyl ether

with the IDCP reagent to form an activated silyl oxocarbenium ion **60**. It is likely that activated species **60** may react with the IDCP perchlorate counterion through a substitution reaction to form silyl perchlorate **61**. However, the specific species directly responsible for the silylation to silaketal **59** has not been determined.[32]



Scheme 2.8 *Skrydstrup's Approach Toward the Unsymmetrical Silaketals*

In an alternative approach, Malacria described an efficient procedure for the preparation of unsymmetrical silaketals using a three-step protocol without the isolation of the intermediates (Scheme 2.9).[33] The basis of this method is the silylation of the first alcohol **62** with diisopropylmonochlorosilane in basic media. The resulting *mono*-alkoxysilane **63** is subsequently brominated *in situ* using stoichiometric amount of NBS, and the bromosilane subjected to the condensation reaction with the second coupling partner. A wide range of unsymmetrical silaketals of structure **64** were prepared bearing alkene and alkyne functional groups in high yield.[33]

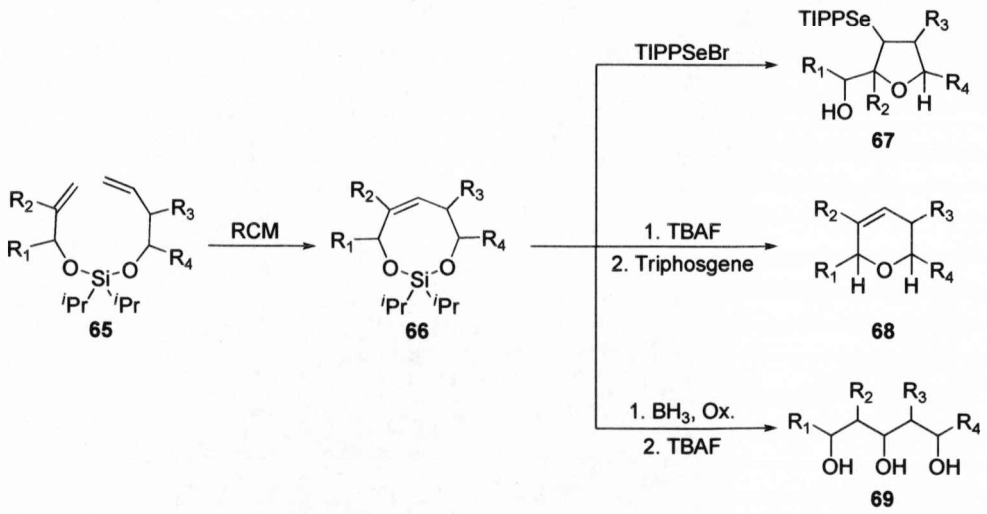


Scheme 2.9 *Malacria's Approach Toward the Unsymmetrical Silaketals*

2.3 Results and Discussion

2.3.1. Background and Hypothesis

Silacycles are important synthetic precursors due to their propensity to be readily functionalized into a variety of synthons using conventional procedures. The interest in these compounds has significantly increased since the advent of powerful temporary silicon-tethered ring-closing metathesis was reported. Despite well-developed asymmetric reactions on medium-sized carbocycles there are relatively few reports on diastereoselective functionalization of medium-sized silacycles. We envisioned that medium-sized silacycles would exist in energetically predefined conformations analogous to those of medium-sized carbocycles.[16] The medium-sized silacycles containing an endocyclic olefin would accordingly provide a general template for stereoselective electrophilic functionalization based on the conformational bias. We were interested in exploring the asymmetric induction on eight-membered rings in particular. Based on our hypothesis, highly functionalized cyclic silaketal **66** should be derived from the acyclic precursor **65** through a ring-closing metathesis reaction. The acyclic precursor is derived from silicon-tethered cross-coupling of enantiomerically enriched homoallylic and allylic alcohols that are readily available from the chiral pool intermediates according to conventional procedures. The versatile nature of silacycle **66** in a three-directional approach is described in the Scheme 2.10. When subjected to electrophilic functionalization with 2,4,6-Triisopropylphenylselenium bromide (TIPPSeBr) originally introduced by Lipshultz and Gross[34] the silacycle **66** would undergo a transannular cyclization to provide highly substituted tetrahydrofuran **67**. The stereochemical variability of the substitution pattern in **66** would provide a series of stereodivergent tetrahydrofurans.

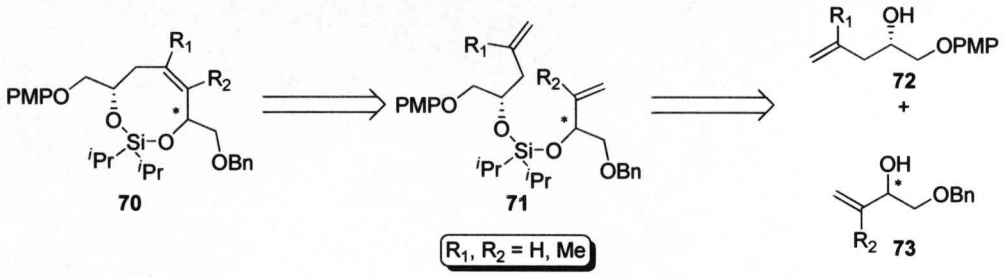


Scheme 2.10 *Silacycle as Versatile Intermediate in the Three-Directional Synthesis*

Silyl deprotection of **66** using TBAF followed by subsequent dehydrocyclization would provide an access to the highly substituted dihydropyrane **68**. Finally, the hydroboration of the endocyclic trisubstituted olefin in **66** followed by subsequent oxidation and silyl deprotection would furnish the polypropionate units such as **69**. All three motifs are often contained within the structural framework of many biologically important natural products.[35] Most of the attention in this study will be directed toward the stereoselective construction of polypropionate units. Various approaches have been reported for the construction of polypropionate units, notably the aldol condensation, which is a powerful and well-documented methodology. The development of new chiral auxiliaries and catalysts in addition to more classical ones have been extensively studied and the stereoselectivity profile of these reactions is now well established. However, the coupling of the advanced synthetic intermediates often occurs with diminished stereocontrol due to mismatched reactions. Our approach to polypropionate fragments stems from the ability to diastereoselectivly hydroborate the eight-membered silaketals, and thereby provide an alternative route to these important synthons.

2.3.2 Synthesis of Starting Materials

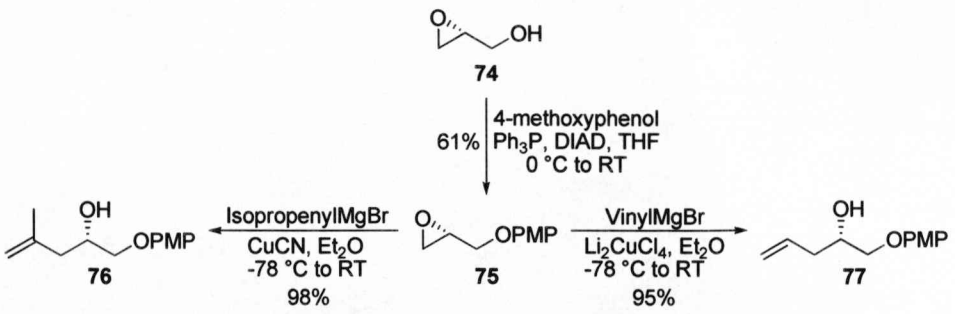
Scheme 2.11 displays the retrosynthetic analysis of the eight-membered cyclic silaketal **70**, which can be prepared from its acyclic precursor **71** *via* a ring-closing metathesis. Acyclic silaketal **71** will be derived from two relatively simple starting materials, namely the homoallylic alcohol **72** and the allylic alcohol **73**. The union of these two fragments using the tethering procedure originally developed by Malacria[33] will provide an access to silaketal **71**. We envisioned that the diisopropyl-



Scheme 2.11 *Retrosynthetic Analysis of the Eight-Membered Silacycle*

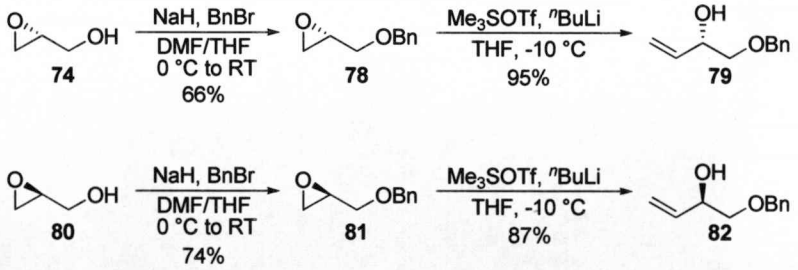
silyl tether would be the optimum linker due to its stability. Furthermore, the diisopropyl tether has been an important stereocontrolling factor in a study related to the long-range asymmetric induction recently developed in our group.[36]

The synthesis of enantiomerically enriched homoallylic alcohols commenced from the commercially available (*R*)-glycidol **74** (Scheme 2.12). Protection of the primary alcohol with 4-methoxyphenol under the standard Mitsunobu conditions furnished the PMP ether in 61% yield. Copper-mediated ring opening utilizing isopropenylmagnesium bromide furnished the homoallylic alcohol **76** in 98% yield, whereas the analogous reaction with vinylmagnesium bromide afforded an inseparable mixture of the homoallylic alcohol **77** and bromohydrin.



Scheme 2.12 *Synthesis of Homoallylic Alcohols via Epoxide Opening*

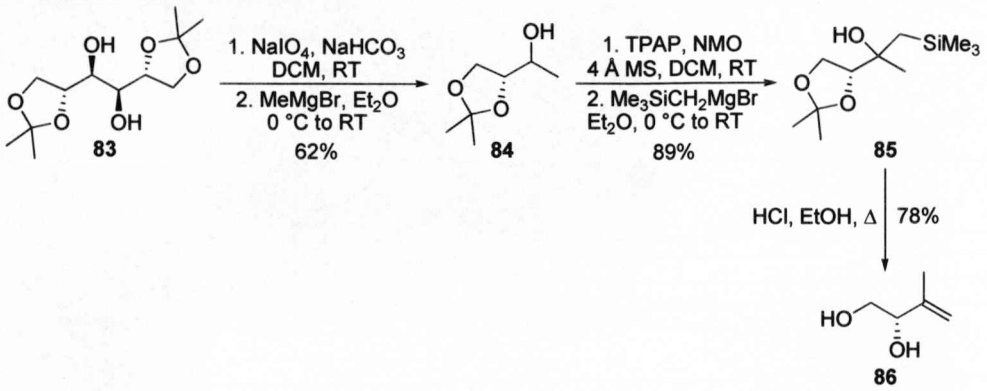
Fortunately, replacing the copper cyanide by commercially available dilithium tetrachlorocuprate(II) resulted in the clean formation of homoallylic alcohol **77** in 95% yield. The preparation of a series of allylic alcohols commenced from (*R*)- and (*S*)-glycidol **74** and **80** (Scheme 2.13). Benzyl protection of both enantiomers with benzyl bromide and sodium hydride resulted in the clean formation of benzyl ethers **78** and **81** in reasonable yield. Ring opening of the epoxide using the ylide derived form trimethylsulfonium triflate salt[37] furnished the allylic alcohols **79** and **82** in excellent yields.



Scheme 2.13 *Synthesis of Allylic Alcohols via Epoxide Opening*

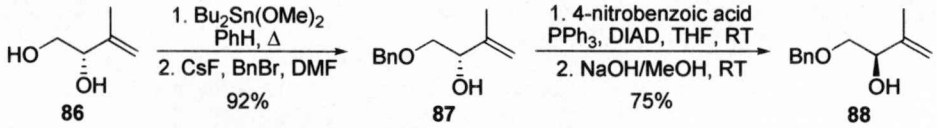
The enantiomerically enriched allylic diol **86** was prepared using the route described by Poulter and Leyes[38] (from commercial *D*-mannitol-*bis*-acetonide **83**) (Scheme 2.14). Glycol cleavage followed by the addition of methylmagnesium bromide to *D*-glyceraldehyde afforded the secondary alcohol **84** as a mixture of diastereoisomers. TPAP oxidation of the secondary alcohol[39] gave the ketone in excellent yield. Nucleophilic addition of (trimethylsilyl)methylmagnesium bromide

to the ketone furnished the Peterson adduct **85** in 89% overall yield as a mixture of stereoisomers. With adduct **85** in hand, the stage is set for Peterson olefination reaction. Treatment of tertiary alcohol **85** with HCl in refluxing ethanol provided the allylic diol **86** in 78% yield.



Scheme 2.14 *Synthesis of Allylic Diol from D-Mannitol-bis-Acetonide*

With diol **86** in hand the next step was the regioselective benzyl protection of the primary alcohol. Treatment of the diol **86** with sodium hydride and benzyl bromide in DMF at 0 °C afforded an inseparable mixture of regioisomers. Alternatively, we envisioned that the regioselective benzyl protection of diol **86** could be accomplished using Hanessian protocol which involves the preparation of the dibutyltin acetal intermediate.[40] This procedure has been successfully applied in carbohydrate chemistry for regioselective protection of primary hydroxyl groups.[41] Treatment of diol **86** with dibutyltin oxide in refluxing benzene, followed by the addition of benzyl bromide furnished the desired alcohol as a 5:1 mixture of regioisomers, albeit in a relatively poor yield of 56%. Ley and co-workers reported a modified procedure for the formation of tin acetals.[42] The method involves the reaction of diol with dibutyltin dimethoxide in benzene under Dean-Stark conditions. This method provided an access to a range of regioselectively monoprotected diol intermediates in excellent yield.[42]

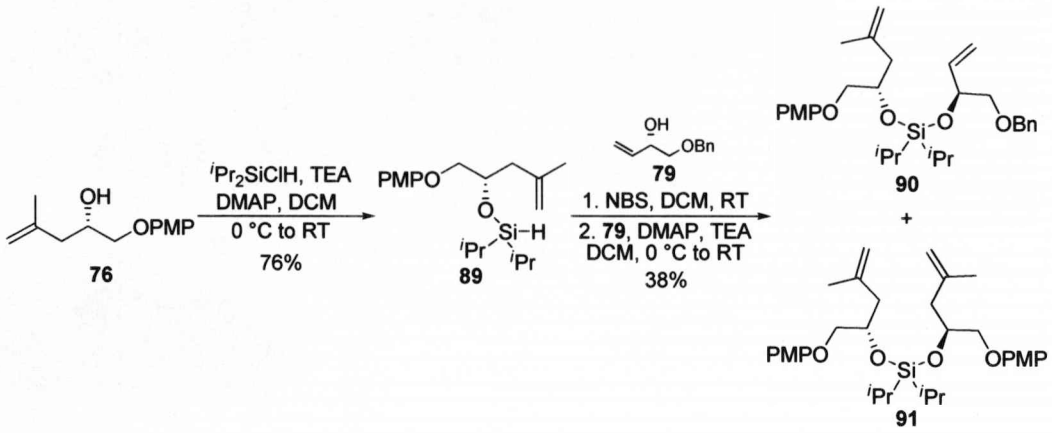


Scheme 2.15 *Regioselective Monobenzylation of Allylic Diol*

Gratifyingly, treatment of the diol **86** with dibutyltin dimethoxide in benzene followed by subsequent cleavage of tin acetal with concomitant benzyl protection furnished **87** as a major regioisomer with significantly improved yield (Scheme 2.15). The main disadvantage of this protocol is difficulty in removing the tin byproducts, which is particularly problematic on large scale. However, tin could be readily removed by treating the crude product with potassium fluoride at room temperature.[42] The separation of alcohol **87** and its regiosiomer, was accomplished by protection of crude mixture with triisopropylsilylchloride (TIPSCl), which led to the selective protection of primary alcohol thus leaving the unreacted secondary alcohol. This "nucleophilic scavenging effect" is well established in the solid-phase synthesis[43] wherein a polymer-supported tosyl chloride resin is used to immobilize a more reactive nucleophile. Simple resin wash and filtration provide the product, thus avoiding the chromatographic purification step. The opposite enantiomer **88** was obtained through the treatment of alcohol **87** under Martin's modified Mitsunobu procedure[44] using *p*-nitrobenzoic acid as a nucleophilic partner. Saponification of the aryl ester furnished the enantiomeric alcohol **88** in excellent yield over two steps with no loss of optical purity as described by chiral HPLC analysis.

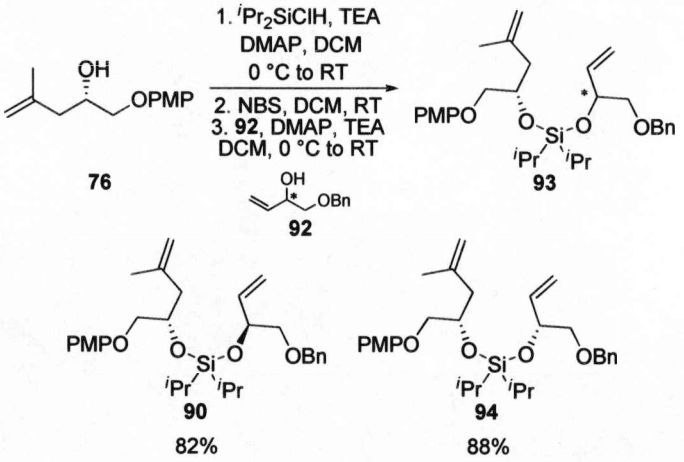
At this stage, the identification of the best route for the preparation of unsymmetrical silaketals turned out to be our primary concern. We have focused our attention toward the method originally developed by Malacria.[33] However, primary alcohols and phenols were the predominant coupling partners, with only one

example involving an enantiomerically enriched secondary alcohol.[33] Clearly the application of this protocol to our system would expand the scope of the preparation of unsymmetrical silaketals. Treatment of homoallylic alcohol **76** with diisopropylmonochlorosilane (1.0 equiv.) in relatively concentrated solution of DCM (1 M) in the presence of triethyl amine and catalytic DMAP resulted in incomplete transformation even after prolonged reaction time (Scheme 2.16). Proceeding to the second step of the reaction (*in situ* bromination) with a certain



Scheme 2.16 *Synthesis of Unsymmetrical Silaketal*

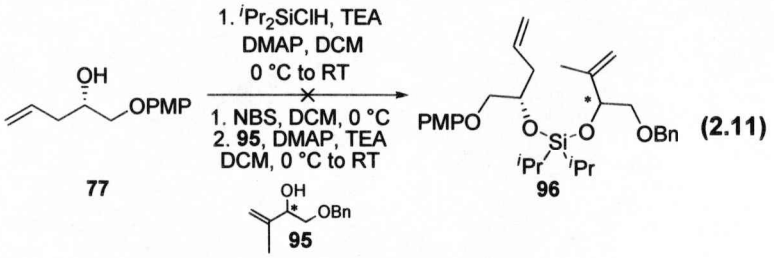
amount of unreacted alcohol **76** increases the probability of formation of symmetrical silaketal **91** so we decided to carry out the isolation of sensitive *mono*-alkoxysilane **89**. It is important to note that silane **89** partially decomposes on the silica-gel column, so a rapid purification is essential to obtain a good yield. Unfortunately, treatment of silane **89** through the portionwise addition of NBS at room temperature in DCM, led to deprotection of silyl tether thus providing the mixture of alkoxybromosilane and protodesilylated homoallylic alcohol. Silylation of such mixture by performing the second cross-coupling reaction with alcohol **79** led to poor yield of the desired silaketal **90** together with significant amount of **91**. In light of the problems, we elected to modify these reaction conditions.



(2.10)

The bromination of the silane using NBS provided the most challenging step during optimization. The key factor to consider was suppression of silyl deprotection during portionwise addition of solid NBS. Fortunately, this could be minimized at 0 °C under high dilution conditions (0.1 M) with the slow addition of NBS over the period of 6 hours. These optimizations of reaction conditions provided unsymmetrical silaketals **90** and **94** in 82 and 88% yields respectively (Eq. 2.10).

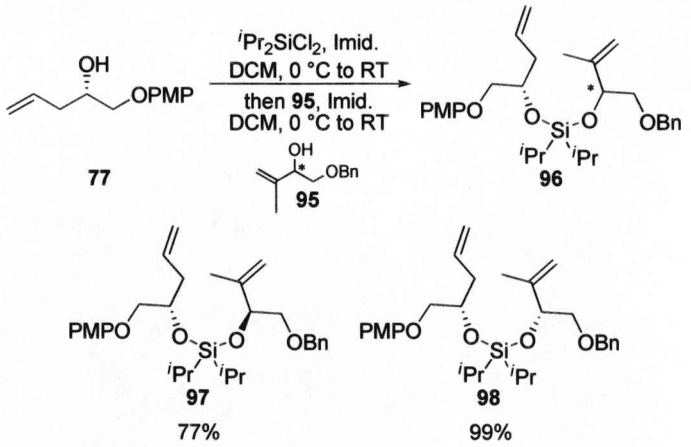
With **90** and **94** in our hands, we turned our attention toward the synthesis of regioisomeric silaketals **96** (Eq. 2.11). We assumed that the same reaction pathway would provide an access to this cyclization precursor, however, the NBS activation of alkoxysilane derived from alcohol **77** resulted in complete protodesilylation. Consequently, this protocol proved unworkable for these derivatives, in which the standard reaction parameters, such as concentration, temperature and the rate of addition did not lead to any notable improvement. Since NBS is a well known source of Br_2 and HBr we envisioned the acid was responsible for silyl ether cleavage. Consequently, silaketals bearing acid-sensitive functionalities are not well matched for the NBS mediated cross-coupling.



(2.11)

Based on these results we concluded that Malacria's procedure[33] was too substrate specific for this application. On several occasions, the preparation of unsymmetrical silaketal intermediates[29,30d,30e] has been accomplished using the Frye protocol.[30a] The method relies on the controlled monosilylation with an excess of imidazole and diisopropyldichlorosilane reagent, under high dilution conditions with the slow addition of the alcohol *via* syringe-pump, followed by the removal of unreacted dichlorosilane. The reactive monoalkoxychlorosilane intermediate then undergoes to smooth silylation with the second coupling partner, thus forming the desired unsymmetrical silaketal. The basic conditions of this reaction make it practical for the preparation of acid-sensitive silaketals.

Silaketals **97** and **98** were prepared in excellent yield as outlined in Equation 2.12. Slow addition (3 hours) of alcohol **77** to excess dichlorosilane and imidazole provided only the monoalkoxychlorosilane. Although a large excess (10 equiv) of the dichlorosilane is often required, [30d] in this system only a modest excess (1.5 equiv) was efficient (Eq. 2.12). The intermediate monoalkoxychlorosilane is very reactive and readily hydrolyzes, which requires the compound to be utilized without aqueous workup. The solvent (DCM) was removed *in vacuo* and residue triturated with anhydrous hexane under the atmosphere of argon. Careful removal of supernatant *via* syringe followed by transfer to the Schlenk flask provided a salt-free mixture of unreacted dichlorosilane and the desired monoalkoxychlorosilane.

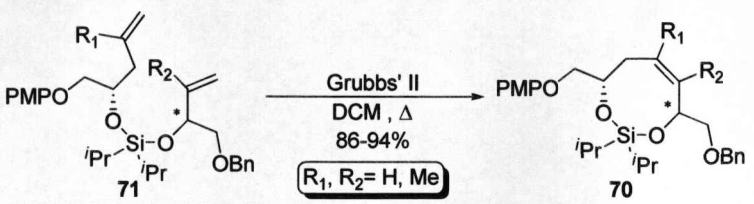


(2.12)

Removal of unreacted dichlorosilane was accomplished using a preheated oil bath (75 °C) for several hours under high vacuum (< 0.5 Torr). The crude reaction mixture was then dissolved in anhydrous DCM and treated with the alcohol **95** of desired configuration to afford the unsymmetrical silaketals **97** or **98** in good to excellent yield. Although this procedure is excellent on 1 mmol scale, there are practical problems on much larger scale due to difficulties associated with the removal of the diisopropyldichlorosilane.

2.3.3 Ring-Closing Metathesis

With four different acyclic silaketals **90**, **94**, **97** and **98** in hand we turned our attention toward the ring-closing metathesis reaction. Formation of medium-sized silacycles utilizing the metathesis catalysts is well documented (Chapter 1). Prior work in the group had demonstrated that Grubbs' 2nd generation catalyst was the optimum catalyst for the construction of eight-membered silaketals (Eq. 2.13).[45] Preliminary studies have provided the optimal solvent, concentration and catalyst loading. Dichloromethane emerged as a solvent of choice in which the concentration



(2.13)

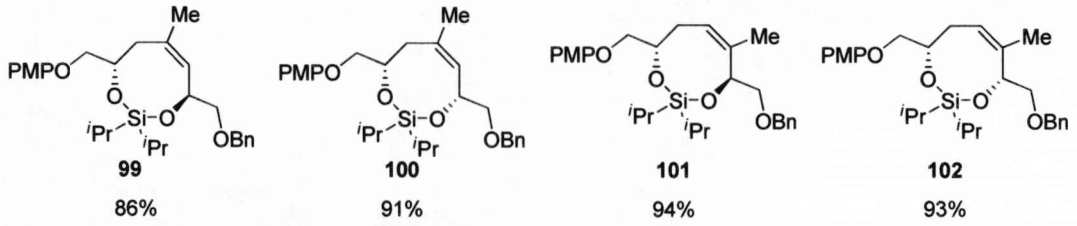
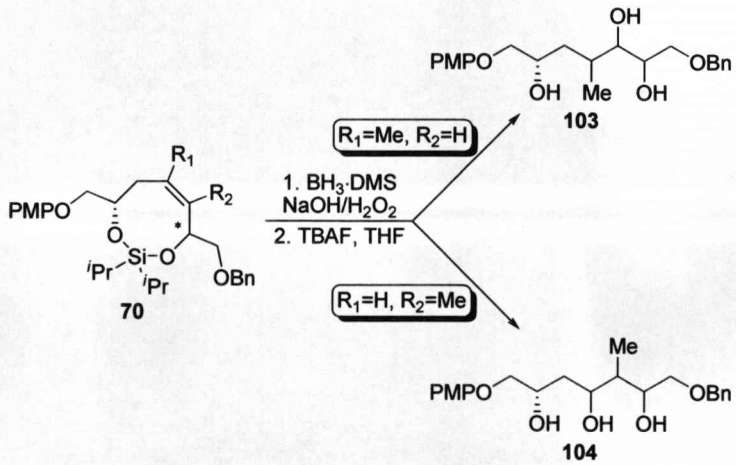


Figure 2.9 *Cyclic Unsaturated Silaketals Constructed via RCM Reaction*

proved to be a critical factor. Reactions that are more concentrated lead to intermolecular cross-coupling to form a dimeric species. Hence, a concentration of 10 mM using 10 mol% of Grubbs' 2nd generation catalyst under reflux conditions over a period of 12 hours provided silaketals **99-102** in excellent yield with exclusive *Z*-olefin geometry as confirmed by nOe studies (Figure 2.9). This result set the stage to explore the merit of diastereoselective hydroboration, dihydroxylation and epoxidations of eight-membered cyclic silaketals. Hydroboration of silaketals **99-102** should provide an array of stereochemical motifs found in many important natural products.[35d] In the case where R_1=Me and R_2=H, the hydroboration followed by silyl deprotection should provide a triol **103** with 1,4,5-triol arrangement of secondary hydroxyl groups. Alternatively, the hydroboration and protodesilylation of silaketal **70** (R_1=H and R_2=Me) should deliver the



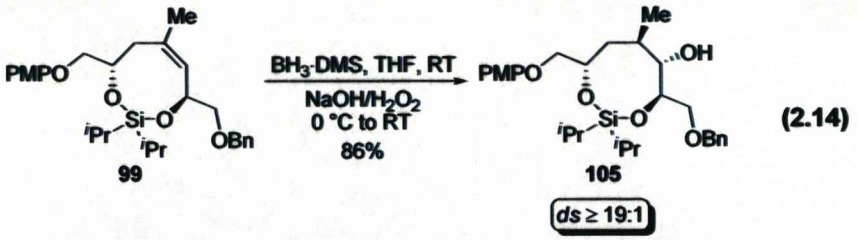
Scheme 2.17 *Hydroboration of the Unsaturated Silaketal*

"skipped" triol **104** with 1,3,5-triol arrangement (Scheme 2.17).

We envisioned that the stereochemical outcome of this reaction will largely depend on the conformational disposition of silaketal **70**, which will be governed by the configuration of two predefined stereogenic centers. We envisioned that the facial selectivity could be predicted using the molecular mechanics calculations in an analogous manner to the pioneering work of Still and Galynker.[16] Our major concern of the outset was the ability of the silaketal to survive the oxidative workup. The orthogonal protection of the primary alcohols in silaketal **70** would allow for selective deprotection and further functionalization, thereby providing the template that could be utilized in the synthesis of polyoxygenated natural products.

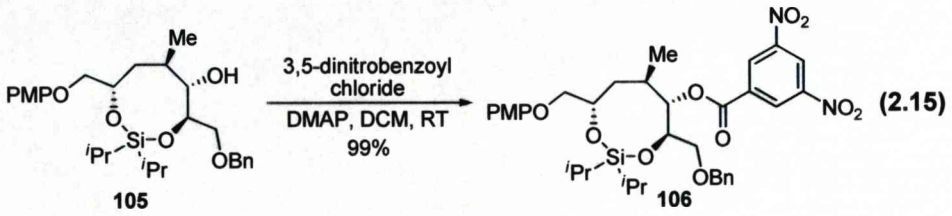
2.3.4 Diastereoselective Hydroboration

Inspired by the work of Holmes and co-workers on electrophilic functionalization of eight-membered lactones (section 2.1.3),[27] we decided to explore the merit of diastereoselective hydroboration on eight-membered silacycles. Although the hydroboration of unsaturated silacycles had been examined in the context of five- to seven-membered rings,[46,47,48] there is a lack of reports on eight-membered silacycles. Evans and Lawler initially demonstrated the diasteroselective hydroboration of eight-membered unsaturated silaketal, **100** where only one stereoisomer was isolated based on ^{1}H-NMR analysis in modest yield (<60%, unoptimized result).[45] Subsequent studies on the silaketal **99** using borane-dimethylsulfide complex followed by standard oxidative workup provided the secondary alcohol **105** in 55% yield as a single stereoisomer (^{1}H-NMR analysis). The modest yield was attributed to partial tether cleavage during the oxidative workup, which prompted further optimization. Treatment of *trans*-silaketal **99** with two equivalents of $BH_3 \cdot DMS$ at room temperature over the period of 2 hours, follo-

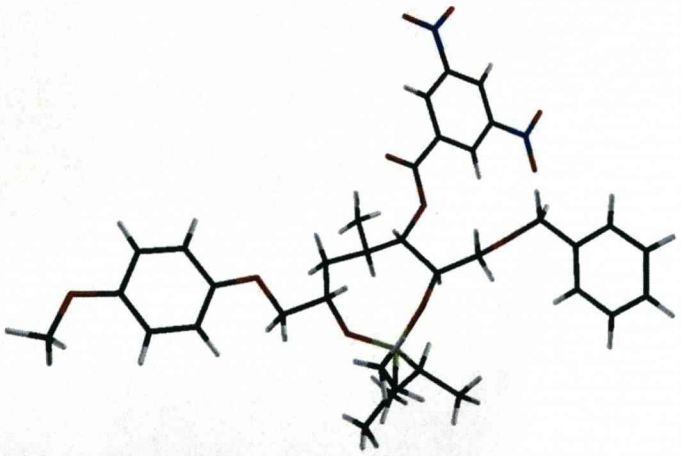


(2.14)

wed by the oxidation with a premixed equimolar solution of sodium hydroxide and hydrogen peroxide at 0 °C to RT over the period of 15 hours furnished the secondary alcohol **105** in 86% yield, with ≥ 19:1 diastereocontrol (Eq. 2.14).



(2.15)



Rendered image from
X-ray analysis of ester **106**

The absolute stereochemistry of this transformation was determined through the X-ray analysis of the ester derivative **106**.[49] Treatment of the alcohol **105** with 3,5-dinitrobenzoyl chloride in the presence of DMAP furnished the ester **106**, in nearly quantitative yield as a crystalline solid (Eq. 2.15), which was recrystallized from a DCM/hexane mixture by a slow diffusion method. Hence, the borane approaches from the bottom face of the olefin, opposite the allylic ring ether. The

absolute stereochemistry of secondary alcohol **105** was further confirmed through Mosher ester analysis.[50, 51]

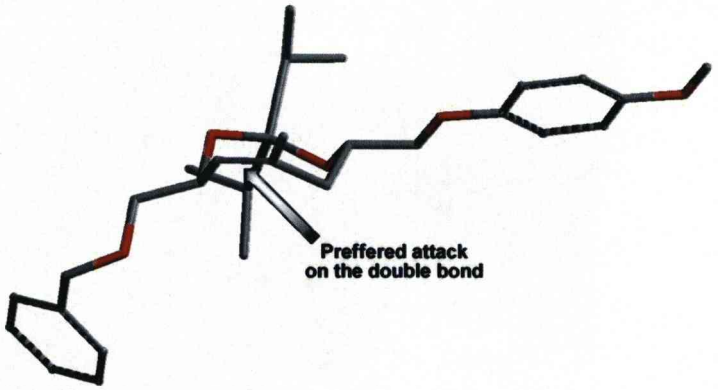
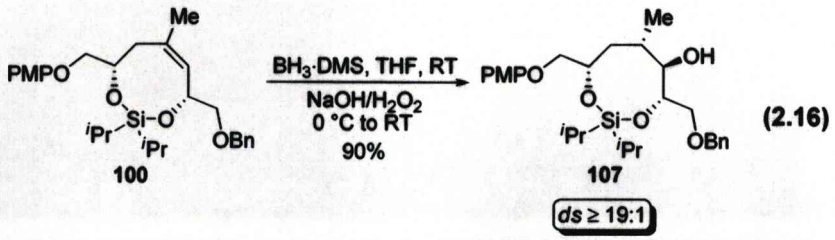


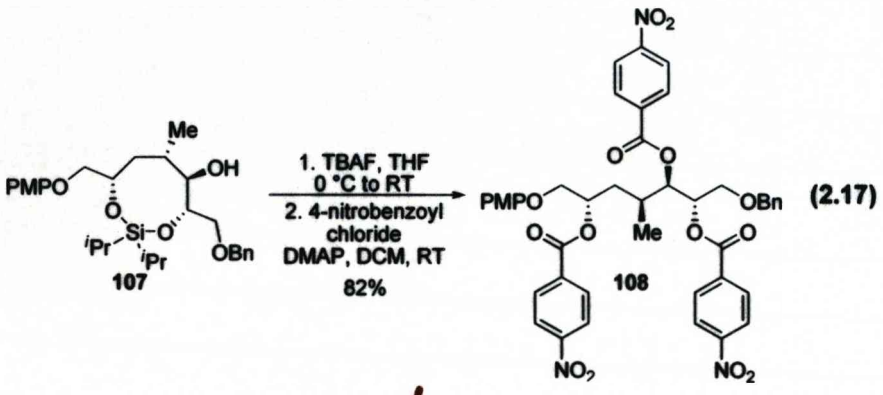
Figure 2.10 *The Stereoselectivity Model for the Hydroboration of Trans-Silaketal* **99**

The preferred conformation of unsaturated silaketal **99** was determined by a Monte Carlo conformational search using the MMFF force field in Spartan® 06. The global minimum of silaketal **99** clearly shows that the convex face of the olefin is more exposed owing to the boat-chair conformation with two bulky groups in *pseudo*-equatorial position. The borane will preferentially attack the bottom face, to avoid the steric interaction with the bulky isopropyl group in *pseudo*-axial position (Figure 2.10).

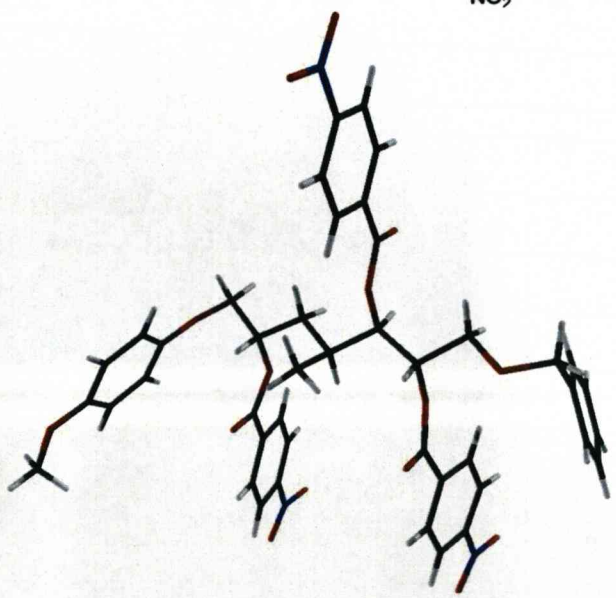


Treatment of *cis*-silaketal **100** under optimized hydroboration conditions led to the secondary alcohol **107** with the same efficiency (Eq. 2.16). This hydroboration product was isolated in 90% yield, with ≥ 19:1 diastereoslectivity (^{1}H-NMR analysis). The absolute stereochemistry was confirmed by X-ray crystallographic analysis of a crystalline derivative. Although, the previous example was readily

converted to a crystalline derivative suitable for the X-ray analysis, the alcohol **107** proved challenging in this regard. Hence, the temporary tether was removed with TBAF in THF providing the corresponding triol as a crystalline solid, which proved unsuitable for the X-ray analysis. Gratifyingly, the derivatization of the triol with 4-nitrobenzoyl chloride provided a triester **108** as a crystalline solid that proved suitable for X-ray analysis (Eq. 2.17).[52] The X-ray again indicated that the borane approached the olefin from the convex face, opposite from the adjacent stereogenic centre, analogous to the earlier study. The absolute stereochemistry of secondary alcohol **107** was further confirmed through Mosher ester analysis.[50,51]



(2.17)



Rendered image from
X-ray analysis of ester **108**

The molecular mechanics calculations involving an extensive conformational search provided a preferential conformation of unsaturated silaketal **100** as portrayed in Figure 2.11. The preferred conformation of this unsaturated eight-membered silaketal resembles the "cup-shape" as described earlier (Figure 2.6).

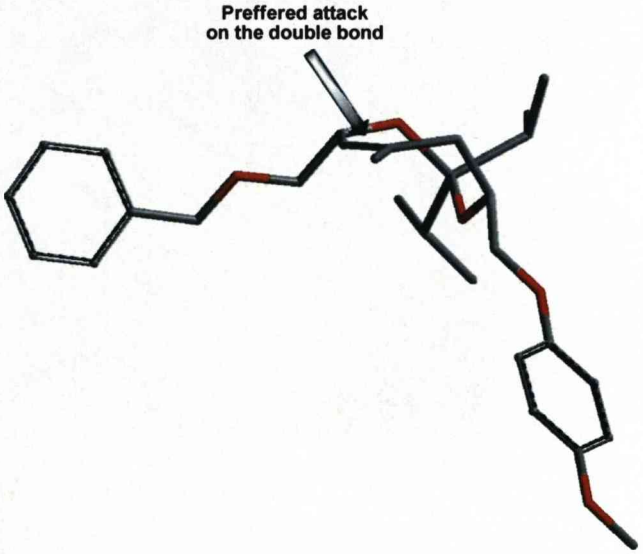


Figure 2.11 *The Stereoselectivity Model for the Hydroboration of Cis-Silaketal* **100**

At this junction, the analogous reaction of unsaturated silaketals **101** and **102**, whose functionalization should provide an access to skipped polyol units was examined. Treatment of silaketal **101** with $BH_3 \cdot DMS$ complex under the optimized conditions provided the secondary alcohol **114** and its regioisomeric tertiary alcohol

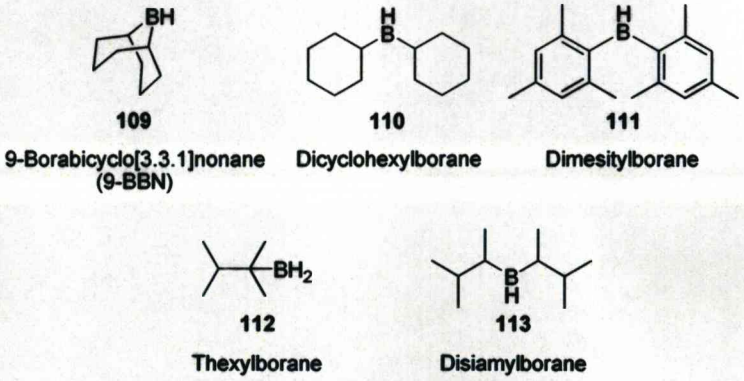
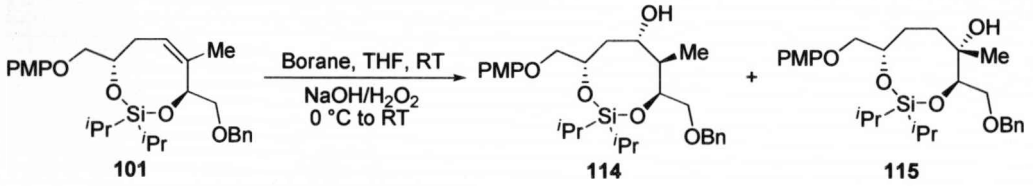


Figure 2.12 *Common Mono- and Dialkylborane Reagents*

115 in excellent yield (Table 2.1, entry 1). Although regioselectivity can often be a problem in the hydroboration reaction,[53] this result was somewhat surprising. Monoalkyl and dialkyl borane reagents[53d] (Figure 2.12) often provide the solution to these problems as outlined in Table 2.1.

Treatment of unsaturated silaketal **101** with 9-BBN **109** or dicyclohexyl-borane **110** furnished none of the desired secondary alcohol **114**, which was attributed to the steric bulk of the reagent (Table 2.1; entries 2 and 3). Gratifyingly, thexylborane **112**[54] furnished the corresponding secondary alcohol **114** in excellent yield with ≥ 19:1 diastereo- and regioselectivity (^{1}H-NMR analysis) (Table 2.1; entry 4).

Table 2.1: *Evaluation of Borane Reagents in the Hydroboration of Silaketal* **101**



101 **114** **115**

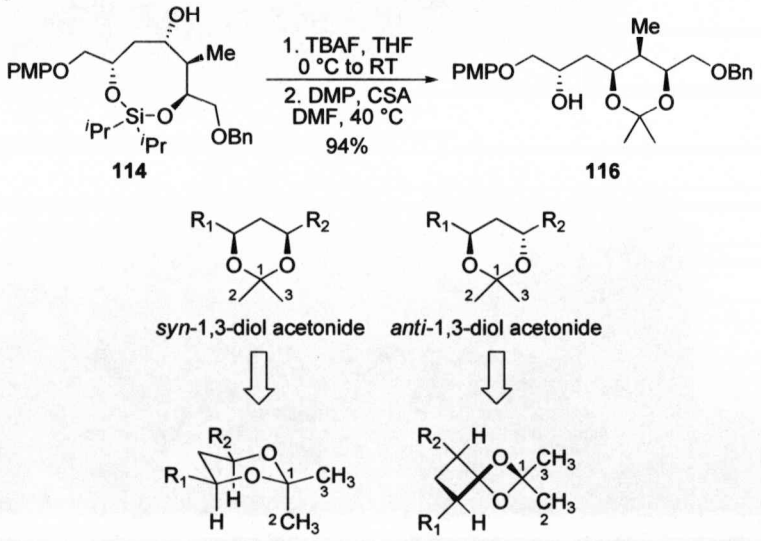
Entry	Borane	Yield[a]	*ds*[b]	114:115
1	BH_3·DMS	93%	14:1	2:1
2	9-BBN	0%	-	-
3	Cy_2BH	0%	-	-
4	Thexyl	90%	≥19:1	-

[a] Isolated yields; [b] Diastereoselectivity for **114**

We envisioned that derivatization of the secondary alcohol **114**, in a similar manner analogous to earlier derivatives should provide a crystalline derivative suitable for the X-ray analysis. However, since derivatization attempts failed to provide a crystalline material, the configuration of the secondary alcohol was determined by Mosher ester analysis. This analysis is the one of the most popular NMR-based methods for the determination of absolute configuration of various

substrates.[55] In our case, the method includes a derivatization of chiral secondary alcohol with both enatiomers of chiral derivatizing agent (so-called Mosher's acid chloride) thus forming the two diastereomeric esters that can be differentiated by NMR spectroscopy. The interpretation of the signs of $\Delta\delta$ values (chemical shift differences) using the certain empirical models provides the reliable information about the absolute configuration. However, Mosher ester method is entirely empirical; hence, the models represent no more than a practical way to correlate the experimental NMR data with the absolute configuration of the compounds examined. As the molecular complexity increases, the chemical shift differences are more influenced by adjacent stereogenic centers, which can transform a configurational assignment into a risky exercise.[55]

Table 2.2: *Determination of Relative Stereochemistry Based on ^{13}C-NMR Shift Correlation of Acetonides*



	^{13}C-NMR Shift Correlation For *syn*- and *anti*- Acetonides		
Carbon	*syn*	*anti*	**116**
1	98.5 ppm	100.6 ppm	99.0 ppm
2	19.6 ppm	24.6 ppm	19.7 ppm
3	30.0 ppm	24.6 ppm	29.9 ppm

In the case of configurational assignment of secondary alcohols, **114** and **117** we decided to provide the supporting evidence to the structural determination. As mentioned earlier, the alcohol **114** is a silyl-protected, skipped triol system. Silyl deprotection of **114** afforded the triol, which upon treatment with DMP and catalytic CSA delivered the thermodynamically more stable *syn*-acetonide **116**. Examination of ^{13}C-NMR acetonide shifts according to Rychnovsky's protocol confirmed the relative configuration as *syn*-acetonide (Table 2.2).[56] This approach provides an additional support for the stereochemical assignment. According to the stereochemical results, the borane approached the olefin in silaketal **101** from the bottom face in an analogous manner to the related derivatives (*vide supra*).

Conformational analysis determined the minimized conformer to be a boat-chair conformation with the *p*-methoxyphenyl and benzyl groups in *pseudo*-equatorial positions, which confirms the observed result (Figure 2.13).

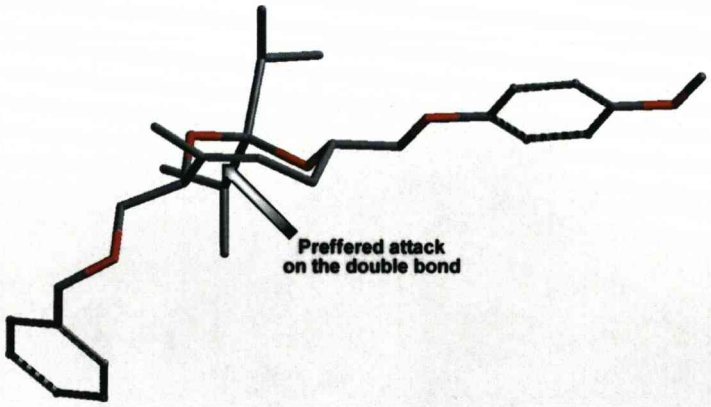
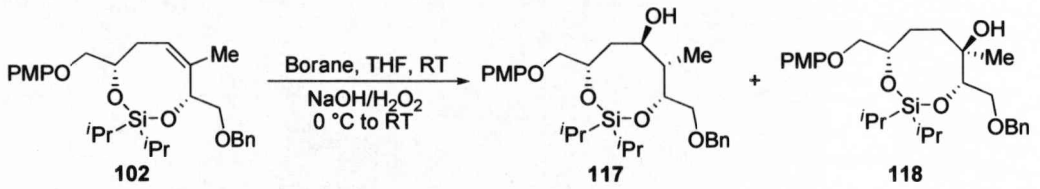


Figure 2.13 *The Stereoselectivity Model for the Hydroboration of Trans-Silaketal* **101**

Hydroboration of unsaturated silaketal **102** suffers from the same regiochemical problem as encountered before. Treatment of silaketal **102** under optimized conditions utilizing BH_3·DMS complex followed by oxidation provided a

secondary alcohol **117** and its regioisomer **118** in excellent yield, albeit with poor regiocontrol (Table 2.3, entry 1). Gratifyingly, treatment with thexylborane prepared *in situ*, provided the secondary alcohol **117** as a single regio- and stereoisomer (^{1}H-NMR analysis) (Table 2.3, entry 2).

Table 2.3: *Hydroboration of Silaketal* **102**



102 **117** **118**

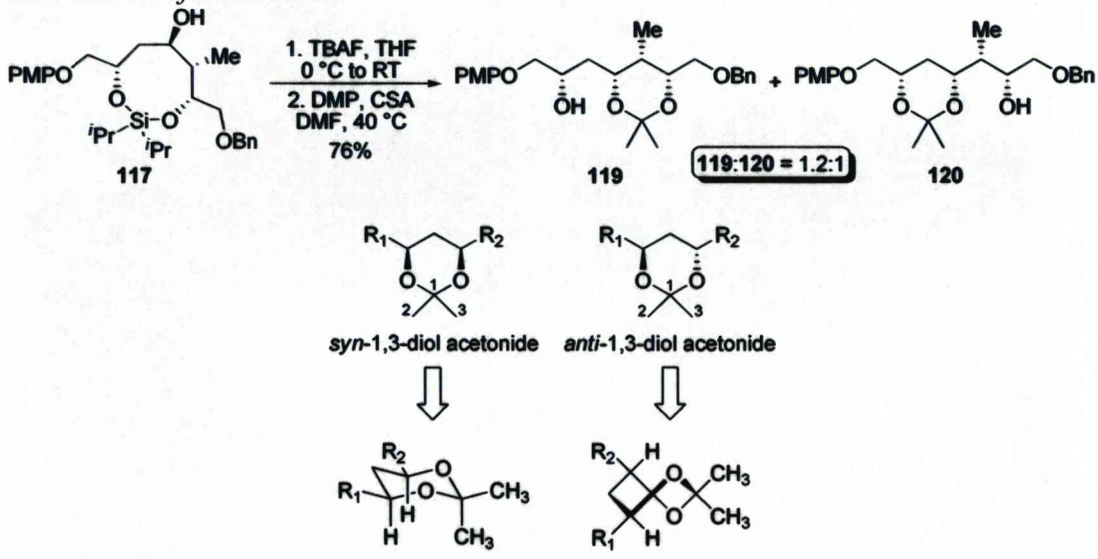
Entry	Borane	Yield[a]	*ds*[b]	117:118
1	BH_3·DMS	96%	12:1	2:1
2	Thexyl	90%	≥19:1	-

[a] Isolated yields; [b] Diastereoselectivity for **117**

The absolute configuration of the secondary alcohol was determined by Mosher ester analysis, since all attempts to prepare a crystalline derivative suitable for X-ray crystallographic analysis failed. The stereochemical outcome indicated an approach of thexylborane from the top face of the olefin, as previously described in detail for silaketal **100**. As described earlier, Mosher ester analysis is purely empirical method hence there is a probability of erroneous assignment of configuration as the stereochemical complexity of the compound increases.[55] Therefore, we decided to provide the supporting evidence to the structural determination of the alcohol **117**. The relative stereochemistry was assigned through the correlation of ^{13}C-NMR shifts of acetonide derived from the alcohol **117**. Deprotection of silaketal **117**, and treatment with DMP and catalytic CSA provided a mixture of acetonides **119** and **120**, favoring **119**. Following their isolation, each acetonide has been independently analyzed *via* ^{13}C-NMR spectroscopy.[56] Based on

the correlation data in Table 2.4, both intermediates, **119** and **120** correspond to *syn*-1,3-diol acetonide, which is further in agreement with the Mosher ester analysis.

Table 2.4: *Determination of Relative Stereochemistry Based on ^{13}C-NMR Shift Correlation of Acetonides*



	^{13}C-NMR Shift Correlation For *syn*- and *anti*- Acetonides			
Carbon	*syn*	*anti*	**119**	**120**
1	98.5 ppm	100.6 ppm	99.2 ppm	98.8 ppm
2	19.6 ppm	24.6 ppm	19.8 ppm	19.8 ppm
3	30.0 ppm	24.6 ppm	29.7 ppm	30.0 ppm

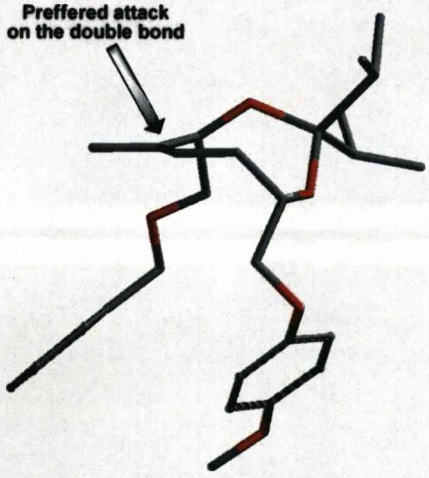


Figure 2.14 *The Stereoselectivity Model for the Hydroboration of Cis-Silaketal* **102**

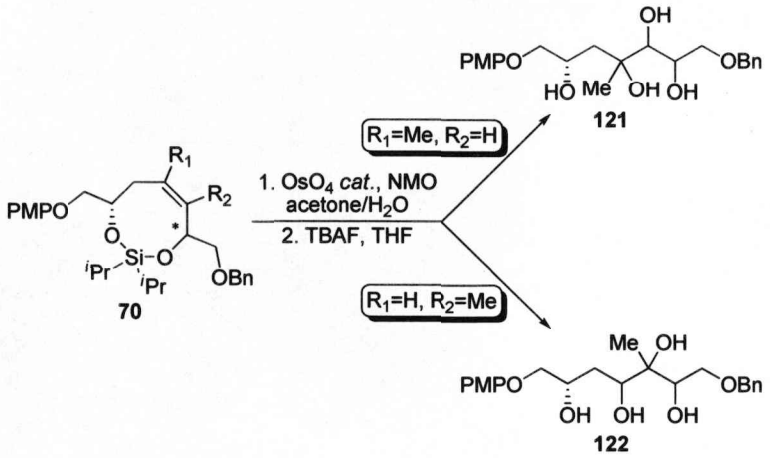
The molecular mechanics calculation provided the model based on the steric energy minimization. The model displays the preferential attack of borane reagent to the α-face of the olefin, which is in agreement with ^{13}C-acetonide and Mosher ester analysis (Figure 2.14).

2.3.5 Diastereoselective Dihydroxylation

Ever since the early pioneering work of Hoffmann[57] and Criegee,[58] the dihydroxylation reaction has emerged as the one of the most powerful transformations in organic chemistry. Initial studies used the stoichiometric amounts of osmium, making any industrial process uneconomical due to a high cost and toxicity of this metal. Over the last three decades, research has focused on the development of catalytic and asymmetric variants of this transformation.[59] The development of catalytic dihydroxylation utilized a combination of catalytic osmium tetroxide with relatively inexpensive oxidizing agents[59b,59c] for re-oxidation of osmium(VI) glycolate intermediate and completion of the catalytic cycle. In early 40's, Criegee reported a dramatic rate increase in the osmylation of alkenes due to the addition of tertiary amines.[60] This observation laid the foundation to the modern asymmetric dihydroxylation reactions for example, this prompted Sharpless and co-workers to employ a naturally occurring cinchona alkaloids as an effective source of chirality,[61] for the asymmetric dihydroxylation reaction.[59b,59c]

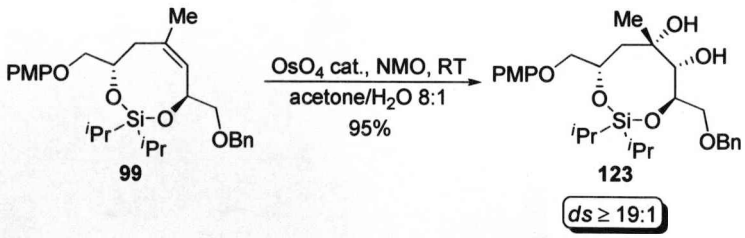
We envisioned that we could expand the scope of the stereoselective functionalization of unsaturated silaketals **99-102** through the dihydroxylation using catalytic osmium tetroxide with NMO as a co-oxidant (Upjohn process).[62] The excellent results from our diastereoselective hydroboration study on unsaturated silaketals **99-102** encouraged the application of the same principle (Scheme 2.18). The conformational bias of eight-membered silaketals should provide the analogous

facial selectivity, since the approach of the reagent had been determined (*vide supra*).



Scheme 2.18 *Dihydroxylation of Unsaturated Silaketal*

Treatment of silaketal **70** (R_1=Me, R_2=H or R_1=H, R_2=Me) with catalytic osmium tetroxide and NMO followed by deprotection should furnish a tetraol **121** and **122** respectively. The stereoselective installation of quaternary centers in **121** and **122** further highlights the utility of unsaturated silaketals **99-102** as versatile templates for asymmetric synthesis.

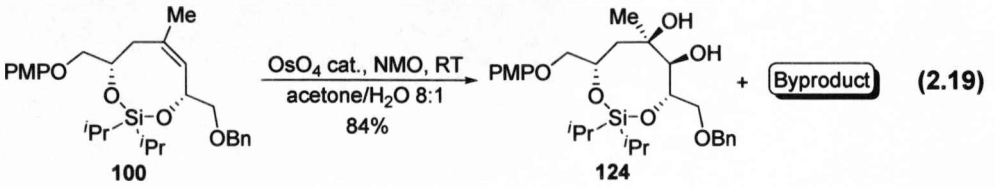


(2.18)

Treatment of silaketal **99** under standard dihydroxylation conditions furnished diol **123** in 95% yield, as a single stereoisomer (based on ^{1}H-NMR analysis) (Eq. 2.18). The absolute stereochemistry was determined through Mosher ester analysis of secondary alcohol by exploiting the difference in the reactivity of the two vicinal hydroxyl groups.[63] The analysis confirmed the approach of the osmium tetroxide reagent from the β-face of the olefin, which is consistent with the

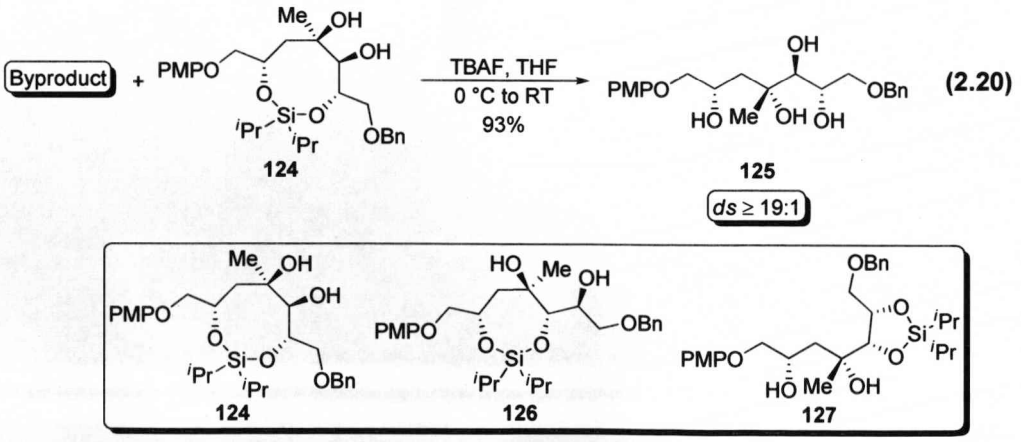
hydroboration reaction (*vide supra*). Unfortunately, at this stage we are unable to provide an additional evidence of configurational assignment for the diol **123** besides Mosher ester analysis.

Interestingly, the dihydroxylation of silaketal **100** provided a mixture of inseparable products (Eq. 2.19). Careful examination of ^{1}H- and ^{13}C-NMR shifts, suggested that a mixture of diastereomers was obtained with in a 1:1 ratio. Based on



(2.19)

the stereochemical analysis in the hydroboration, we concluded that the byproduct could not be a stereoisomer. Holmes and co-workers[27] have demonstrated that the dihydroxylation of unsaturated lactone **36** undergoes *in situ* translactonization (Eq. 2.7), which facilitated the ring contraction thus forming six-membered lactone **40** and five-membered lactones **41** and **42** with good facial selectivity. According to

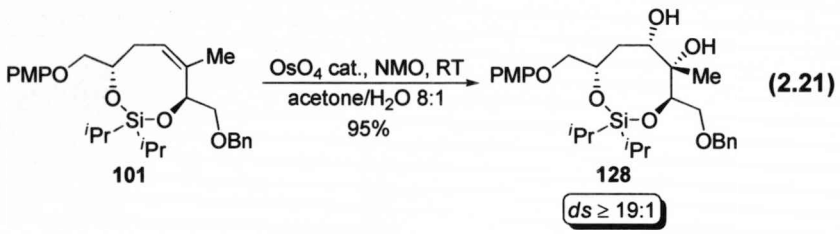


(2.20)

their observation, it appeared likely that the initial adduct undergoes *trans*-silyletherification with ring contraction. Deprotection with TBAF provided tetraol **125** in 93% yield, as a single stereoisomer (Eq. 2.20), thereby confirming this hypothesis. Although the various adducts were inseparable, Equation 2.20 displays

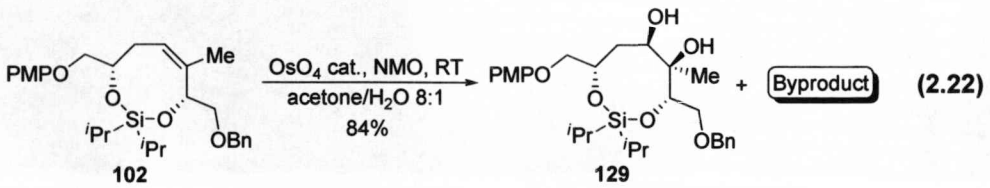
the reaction and possible ring-contraction intermediates **126** and **127**. Furthermore, only intermediates **126** and **127** were considered, since we assumed that the tertiary alcohol does not participate in the migration.

Additional studies explored the dihydroxylation reaction of the other unsaturated silaketals. Treatment of silaketal **101** under standard dihydroxylation conditions provided a single stereoisomer based on ^{1}H-NMR analysis in great yield, which is typical for *trans*-silaketals (Eq. 2.21). The absolute stereochemistry of diol **128** was determined through Mosher ester analysis of the more reactive secondary alcohol. Unfortunately, at this stage we are unable to provide an additional evidence of configurational assignment for the diol **128** besides Mosher ester analysis.



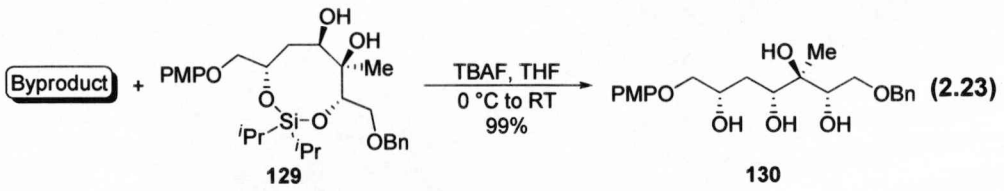
(2.21)

Treatment of *cis*-silaketal **102** with catalytic osmium tetroxide and NMO provided a mixture of products **129** in excellent yield (Eq. 2.22), which suffered from the same migration problem. Deprotection of the silaketals with TBAF provid-



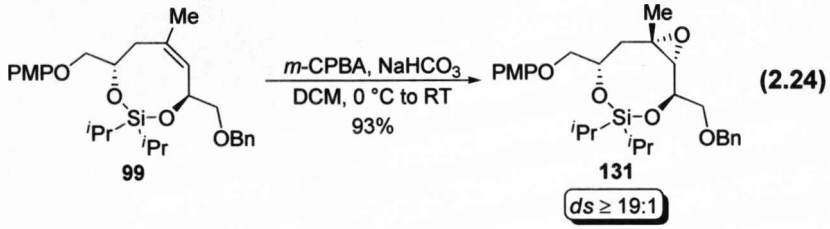
(2.22)

ed the tetraol **130** in 99% yield, as a single stereoisomer (based on ^{1}H-NMR analysis) (Eq. 2.23). The absolute stereochemistry of tetraol **130** was assigned by analogy with the previous examples.

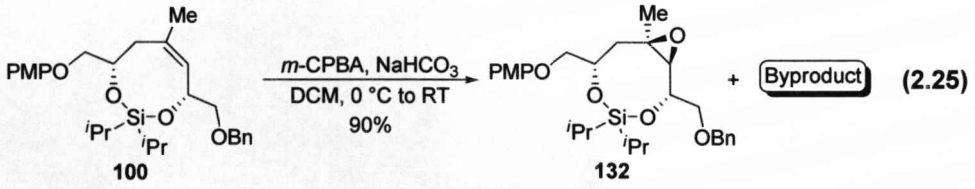


2.3.6 Diastereoselective Epoxidation

Having studied the two different types of electrophilic substitution of unsaturated silaketals **99-102**, we turned our attention to a stereoselective epoxidations. Treatment of silaketal **99** with a slight excess of *m*-CPBA in DCM in the presence of $NaHCO_3$ as a buffer, furnished an epoxide **131** in excellent yield, as

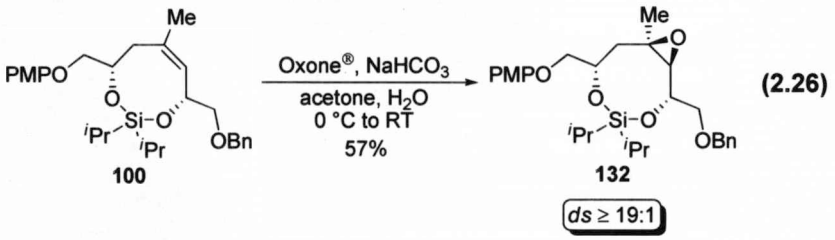


a single stereoisomer by ^{1}H-NMR analysis (Eq. 2.24). The stereochemistry was assigned based on the analogy with the hydroboration reaction. Unfortunately, at this stage, we are unable to provide the evidence for the stereochemical outcome of diastereoselective epoxidation.



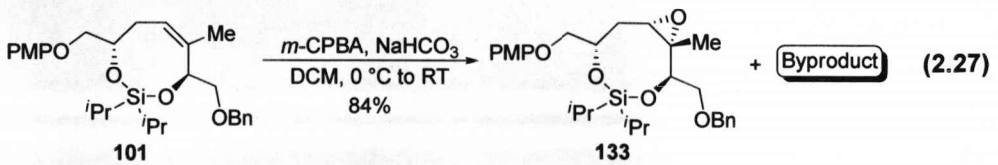
Treatment of silaketal **100** under the same epoxidation conditions provided a mixture of two chromatographically inseparable compounds, the epoxide **132** and the unidentified byproduct. Based on the ^{1}H and ^{13}C NMR analysis of the mixture, one product indeed corresponds to desired epoxide **132**, while the byproduct is probably a product of acid catalyzed epoxide rearrangement (Eq. 2.25). Since the epoxide **132**

and the undesired byproduct are not chromatographically separable, we could not provide a rationale toward this competitive side reaction nor identify the compound. It is strange that a competitive side reaction, which is presumably acid-catalyzed, occurs in a system that is buffered with $NaHCO_3$. Silyl deprotection of the reaction mixture with TBAF in THF still provided the mixture of products unlike in the dihydroxylation. Alternative methods of epoxidations, using dimethyloxirane prepared *in situ* from commercially available Oxone® were investigated.[64] Treatment



(2.26)

of acetone solution of silaketal **100** with an aqueous solution of Oxone® at ambient temperature provided a mixture of starting material **100** and epoxide **132** (Eq. 2.26). The reaction occurred without any indication of the side reaction observed during the epoxidation with *m*-CPBA. The epoxide **132** was isolated as a single stereoisomer albeit in a modest yield of 57%. Further work toward optimization of this reaction is required. This result indicates that the dimethyldioxirane epoxidation is more suitable to our silaketal system than *m*-CPBA conditions.

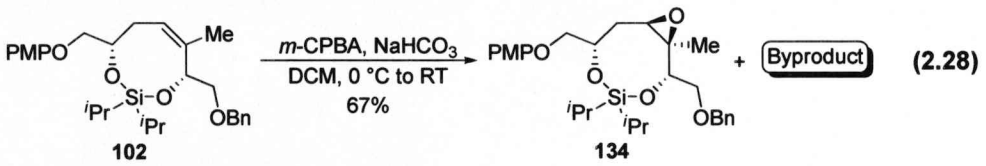


(2.27)

Interestingly, the epoxidation of silaketal **101** under *m*-CPBA conditions provided a mixture of products in 84% yield, favoring the epoxide **133** (Eq. 2.27). This result was curious owing to the fact that the epoxidation of regiosiomeric silaketal **99** provided only one stereoisomer in 93% yield (Eq. 2.24). Additional

studies on the epoxidation with *m*-CPBA and Oxone® are under way in order to delineate such discrepancy.

The epoxidation of unsaturated silaketal **102** using *m*-CPBA follows the same trend, thus forming a mixture of epoxide **134** and the unknown byproduct in modest yield (Eq. 2.28). Again, due to difficulties associated with chromatographic separation of the mixture, we were unable to isolate and characterize the byproduct and the epoxide **134**. Further studies are under way toward a solution to this problem. The most promising approach is the epoxidation using dimethyldioxirane reagent as outlined earlier.



102 **134** **(2.28)**

2.4 Conclusions

We have constructed an array of unsaturated, eight-membered silaketals **99-102** from enantiomerically enriched homoallylic and allylic alcohols using a powerful, temporary silicon-tethered ring-closing metathesis reaction. Furthermore, we have demonstrated the versatility of the eight-membered silacycles as synthons for asymmetric synthesis. Electrophilic functionalization of unsaturated silaketals through hydroboration, dihydroxylation and epoxidation provided the corresponding products with excellent diastereocontrol. The stereochemical outcome of this transformation has been determined with a combination of methods such as X-ray analysis, Mosher ester and other NMR techniques. The polyols obtained by diastereoselective substitution of silaketals can provide an easy access to fragments of the polypropionate moiety that are ubiquitous in nature and biologically relevant compounds. As an example of this, Chapter 3 will describe the application of above mentioned methodology in the approach to the asymmetric synthesis of the fully functionalized, C1-C30 polyol fragment of amphidinol 3.

2.5 Experimental

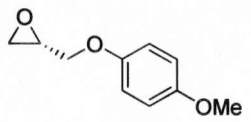
2.5.1 General

Analytical thin layer chromatography (TLC) was performed on either Merck 60 F_{254} or Whatman F_{254} precoated silica gel plates. Visualization was accomplished with a UV light and/or a $KMnO_4$ solution. Flash column chromatography (FCC) was performed using either Merck Silica Gel 60 (230-400 mesh) or Whatman Silica Gel Purasil® 60Å (230-400 mesh). Solvents for extraction and FCC were technical grade. Reported solvents mixtures for both TLC and FCC were volume/volume mixtures. Preparative thin layer chromatography (P-TLC) was performed on either Merck 60 F_{254} precoated glass silica gel plates or Whatman Partisil® K6F Silica Gel 60Å F_{254} precoated glass silica gel plates (250μm thickness). Visualization was accomplished with UV light. Reported solvent mixtures for P-TLC were volume/volume mixtures. ^1H NMR and ^{13}C NMR were recorded on either Varian Inova-400 MHz or Bruker AV 500 MHz NMR spectrometers in the indicated deuterated solvents. For ^1H NMR $CDCl_3$ was set to 7.24 ppm ($CDCl_3$ singlet) and for ^{13}C NMR to 77.16 ppm ($CDCl_3$ center of triplet). For ^1H NMR C_6D_6 was set to 7.15 ppm (C_6D_6 singlet) and for ^{13}C NMR to 128.06 ppm (C_6D_6 center of triplet). All values for ^1H NMR and ^{13}C NMR chemical shifts for deuterated solvents were obtained from Cambridge Isotope Labs. Data are reported in the following order: chemical shift in ppm (δ) (multiplicity, which are indicated by br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet)); assignment of 2^{nd} order pattern, if applicable; coupling constants (*J*, Hz); integration. All ^{13}C NMR spectra were reported using descriptor (*o*) and (*e*) refers to whether the peak is odd or even, respectively, and correlates to an attached proton test (ATP) experiment. Infrared

spectra (IR) were obtained on either Perkin-Elmer spectrum 1 or 100 series FTIR spectrophotometer. Peaks are reported in cm^{-1} with the following relative intensities: s (strong), m (medium) and w (weak). Mass spectra were performed by either the Indiana University Mass Spectroscopy center or the University of Liverpool Mass Spectrometry center. High-resolution electron-impact (EI, ionization voltages of 70 eV), chemical ionization (CI, reagent gas CH_4 or NH_3) were obtained on either a TermoFinnigan MAT 95 XP spectrometer or the VG 7070E double focusing magnetic sector mass spectrometer equipped with solid probe inlet. The electrospray (ESI) mass spectra were obtained either on either a TermoFinnigan MAT 95 XP spectrometer or a Waters micromass LCT mass spectrometer. All chromatographs were obtained using a Hewlett-Packard 1100 series HPLC equipped with a variable wavelength UV detector (set to 210 nm or 254 nm as appropriate). The instrument was fitted with CHIRALCEL^{TM} OD, AD, AD-H or AS column (Diacel, 4.6mm x 25cm).

Unless otherwise indicated, all reactions were carried out in flame-dried glassware and under an atmosphere of argon. Methylene chloride (CH_2Cl_2), ethyl ether (Et_2O) and tetrahydrofuran (THF) was dried over alumina column solvent system using the method of Grubbs. Dimethylsulfoxide (DMSO) was purchased from Fischer chemical company and used without further purification. All starting materials were purchased from Acros, Aldrich or Strem chemical companies and used without further purification unless otherwise noted.

2.5.2 Experimental Procedures



75

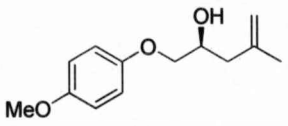
(*S*)-2-((4-Methoxyphenoxy)methyl)oxirane 75[65]

Experimental Procedure: (*R*)-Glycidol (4.760 g, 62.3 mmol) was dissolved in anhydrous tetrahydrofuran (312 mL) at room temperature under an atmosphere of argon. 4-Methoxyphenol (8.60 g, 68.6 mmol) and triphenylphosphine (20.64 g, 78.0 mmol) were added sequentially and the mixture was stirred until solid material dissolved and then cooled to 0 °C. Diisopropyl azodicarboxylate (15.47 mL, 74.8 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stir overnight (t.l.c. controlled). The resulting solution was concentrated *in vacuo* to afford the crude viscous yellow oil. Purification by flash chromatography (eluting with 5-20% ethyl acetate/hexanes) furnished epoxide **75** (6.79 g, 61% yield) as an off-white crystalline solid.

$[\alpha]_D^{25}$ +3.9 (c = 1.21, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87-6.79 (m, 4H), 4.15 (dd, A of ABX, J_{AB} = 11.0 Hz, J_{AX} = 3.2 Hz, 1H), 3.90 (dd, B of ABX, J_{AB} = 11.0 Hz, J_{BX} = 5.6 Hz, 1H), 3.75 (s, 3H), 3.33-3.29 (m, 1H), 2.87 (t, J = 4.5 Hz, 1H), 2.72 (dd, J = 4.9, 2.7 Hz, 1H).

IR ($CDCl_3$): 3057 (w), 3001 (m), 2932 (m), 2836 (m), 1592 (w), 1506 (s), 1231(s), 1042 (s), 827 (s) cm^{-1}.



76

(*S*)-1-(4-Methoxyphenoxy)-4-methylpent-4-en-2-ol 76

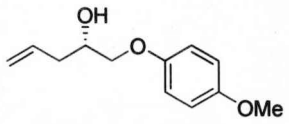
Experimental Procedure: Isopropenylmagnesium bromide (74.4 mL, 37.2 mmol, 0.5M solution in THF) was added dropwise to a suspension of copper(I) cyanide (0.22 g, 2.5 mmol) in anhydrous diethyl ether (116 mL) previously cooled to -78 °C under an atmosphere of argon. The orange suspension was stirred for *ca.* 15 minutes, before epoxide **75** (3.351g, 18.6 mmol) as a solution in anhydrous diethyl ether (30 mL + 10 mL + 10 mL rinse) was added *via* syringe. Solution was allowed to warm to room temperature with overnight stirring, after which the reaction's color changed to black. The reaction was slowly quenched by addition of aqueous NH_4Cl/NH_4OH (3:1) solution and partitioned between diethyl ether and aqueous NH_4Cl/NH_4OH (3:1) solution. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude yellow oil. Purification by flash chromatography (eluting with 10-30% ethyl acetate/hexanes) furnished alcohol **76** (4.03 g, 98% yield) as a colorless oil.

$[\alpha]_D^{27}$ +6.7 (c = 1.20, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86-6.74 (m, 4H), 4.88 (t, J =1.6 Hz, 1H), 4.82 (d, J = 1.0 Hz, 1H), 4.13 (dq, J = 6.7, 3.6 Hz, 1H), 3.92 (dd, A of ABX, J_{AB} = 9.4 Hz, J_{AX} = 3.7 Hz, 1H), 3.82 (dd, B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 6.8 Hz, 1H), 3.75 (s, 3H), 2.30 (d, J = 6.6 Hz, 2H), 1.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.23 (e), 152.91 (e), 141.95 (e), 115.74 (o), 114.80 (o), 113.74 (e), 72.64 (e), 68.01 (o), 55.84 (o), 41.99 (e), 22.64 (o).

IR (Neat): 3446 (br s), 3075 (m), 2935 (s), 2835 (m), 1652 (m), 1593 (w), 1506 (s), 1235 (s), 1043 (s), 825 (s), 751 (m) cm^{-1}.



77

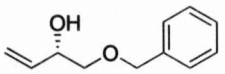
(*S*)-1-(4-Methoxyphenoxy)pent-4-en-2-ol 77[66]

Experimental Procedure: Vinyl magnesium bromide (57.2 mL, 57.2 mmol, 1.0 M in THF) was added to anhydrous diethyl ether (106 mL) at room temperature under an atmosphere of argon. The solution was cooled to -78 °C and Li_2CuCl_4 (19.1 mL, 1.91 mmol, 0.1M in THF) was added dropwise. The orange solution was stirred for *ca.* 15 minutes and epoxide **75** (3.439 g, 19.1 mmol) was added dropwise as a solution in diethyl ether (30 mL + 10 mL + 10 mL rinse). The reaction was allowed to warm to room temperature and stir overnight. The black mixture was quenched with the aqueous NH_4Cl/NaOH (3:1) solution and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude yellow oil. Purification by flash chromatography (eluting with 10-30 % ethyl acetate/hexanes) furnished the homoallylic alcohol **77** (3.776 g, 95% yield) as a yellow oil.

$[\alpha]_D^{25}$ +13.1 (c = 1.46, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85-6.80 (m, 4H), 5.91-5.81 (m, 1H), 5.18-5.11 (m, 2H), 4.06-4.00 (m, 1H), 3.92 (dd, A of ABX, J_{AB} = 9.4 Hz, J_{AX} = 3.3 Hz, 1H), 3.83-3.79 (m, 1H), 3.75 (s, 3H), 2.42-2.31 (m, 2H), 2.19 (br s, 1H).

IR (Neat): 3435 (br s), 3076 (m), 2933 (s), 2835 (m), 1642 (m), 1592 (w), 1506 (s), 1463 (s), 1234 (s), 1042 (s), 919 (m), 825 (s), 750 (m) cm^{-1}.



79

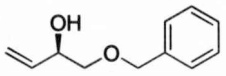
(*S*)-1-(Benzyloxy)but-3-en-2-ol 79[67]

Experimental Procedure: Trimethylsulfonium triflate (23.03 g, 101.8 mmol) was dissolved in anhydrous benzene (400 mL) at room temperature under an atmosphere of argon. The reaction mixture was refluxed for *ca.* 4 hours under Dean-Stark conditions. Solvent was removed *in vacuo* to afford white powder, which was suspended in anhydrous THF (275 mL). The suspension was cooled to -10 °C and ^{n}BuLi (40 mL, 99.8 mmol) was added dropwise. The reaction mixture was stirred for *ca.* 1 hour until most of the ylide was consumed. Epoxide **78** (3.4 g, 20.5 mmol) as a solution in anhydrous tetrahydrofuran (30 mL + 10 mL + 10 mL rinse) was added dropwise *via* syringe and solution was allowed to stir for an additional hour. The reaction was slowly quenched by addition of saturated aqueous NH_4Cl solution and partitioned between diethyl ether and saturated aqueous NH_4Cl solution. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude colorless oil. Purification by flash chromatography (eluting with 10-30% ethyl acetate/hexanes) furnished the allylic alcohol **79** (3.45 g, 95% yield) as a colorless oil.

$[\alpha]_D^{25}$ -0.9 (c = 1. 20, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 5.82 (ddd, J = 17.2, 10.6, 5.6 Hz, 1H), 5.34 (dt, J = 17.3, 1.5 Hz, 1H), 5.18 (dt, J = 10.6, 1.4 Hz, 1H), 4.56 (s, 2H), 4.36-4.31 (m, 1H), 3.53 (dd, A of ABX, J_{AB} = 9.6 Hz, J_{AX} = 3.3 Hz, 1H), 3.36 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 7.8 Hz, 1H), 2.11 (br s, 1H).

IR (Neat): 3433 (br s), 3063 (m), 3031 (m), 2984 (w), 2861 (s), 1646 (w) 1454 (s) 1105 (s), 928 (s), 738 (s), 701 (s) cm^{-1}.



82

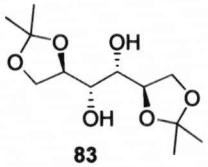
(*R*)-1-(Benzyloxy)but-3-en-2-ol 82[68]

Allylic alcohol **82** was prepared according to representative experimental procedure for the allylic alcohol **79**, starting with the epoxide **81** in 87 % isolated yield.

$[\alpha]_D^{28}$ +4.0 (c = 1.18, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) 7.36-7.26 (m, 5H), 5.82 (ddd, J = 17.0, 10.8, 5.9 Hz, 1H), 5.34 (dt, J = 17.3, 1.4 Hz, 1H), 5.18 (d, J = 10.6 Hz, 1H), 4.56 (s, 2H), 4.35-4.31 (m, 1H), 3.53 (dd, A of ABX, J_{AB} = 9.7 Hz, J_{AX} = 3.4 Hz, 1H), 3.36 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 7.8 Hz, 1H), 2.15 (br s, 1H).

IR (Neat): 3435 (br s), 3065 (m), 3031 (m), 2984 (w), 2861 (s), 1646 (w), 1454 (s), 1105 (s), 928 (s), 738 (s), 699 (s) cm^{-1}.



83

(1*S*,2*S*)-1,2-*bis*((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol 83[69]

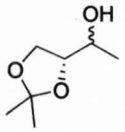
Experimental Procedure: D-Mannitol (146. g, 803 mmol) and CSA (3.86 g, 16.6 mmol) were dissolved in anhydrous DMF (480 mL) at room temperature under an atmosphere of argon. The reaction was heated to 40 °C and dimethoxy propane (200 mL, 1626 mmol) was added dropwise. The reaction mixture was stirred for *ca.* 5 hours, cooled to room temperature and partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The combined organic phases were washed twice with water, once with brine, dried ($MgSO_4$) and concentrated *in vacuo* to

afford a crude white solid. Purification by crystallization (from DCM/hexane mixture) furnished the diol **83** (105.6 g, 50 % yield) as a white solid.

$[\alpha]_D^{26}$ +2.2 (c = 2.40, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) 4.14 (dd, J = 12.3, 6.5 Hz, 1H), 4.08 (dd, A of ABX, J_{AB} = 8.5 Hz, J_{AX} = 6.3 Hz, 1H), 3.95 (dd, B of ABX, J_{AB} = 8.6 Hz, J_{BX} = 5.4 Hz, 1H), 3.71 (t, J = 6.2 Hz, 1H), 2.77 (d, J = 6.5 Hz, 1H), 1.38 (s, 3H), 1.32 (s, 3H).

IR (Neat): 3307 (br w), 2982 (w), 2940 (w), 2876 (w), 1387 (m), 1371 (m), 1205 (m), 1063 (s), 851 (m) cm $^{-1}$.



84

(*R*)-1-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethanol 84[38]

Experimental Procedure: Acetonide **83** (13.8 g, 52.4 mmol) was dissolved in anhydrous dichloromethane (120 mL) at room temperature. Saturated aqueous $NaHCO_3$ (6 mL) solution was added, followed by $NaIO_4$ (13.5 g, 62.9 mmol) in one portion. The reaction was vigorously stirred open to air with occasional breaking of the clumps for *ca.* 2.5 hours. $MgSO_4$ was added to scavenge the water and suspension was filtered. Precipitate was washed with two portions of dichloromethane and solvent was removed *in vacuo* to afford crude aldehyde, which was used without further purification.

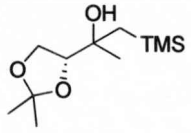
The crude aldehyde (*ca.* 105 mmol) was dissolved in anhydrous diethyl ether (150 mL) under an atmosphere of argon. Solution was cooled to 0 °C and methylmagnesiumbromide (43 mL, 129 mmol, 3M in pentane) was slowly added with stirring over period of *ca.* 70 minutes. The reaction was allowed to warm to room temperature and stir overnight. The reaction was quenched by pouring onto

ice-saturated NH_4Cl solution and partitioned between diethyl ether and saturated aqueous NH_4Cl solution. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 20% ethyl acetate/hexanes) furnished the alcohol **84** (9.52 g, 62% over two steps), as a colorless oil.

$[\alpha]_D^{26}$ +29.8 (c = 1.25, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01-3.85 (m, 3H), 2.00 (br s, 1H), 1.41 (s, 3H), 1.34 (s, 3H), 1.13 (d, *J*=6.4 Hz, 3H).

IR (Neat): 3435 (br s), 2986 (s), 2936 (s), 2888 (s), 1456 (m), 1372 (s), 1255 (s), 1067 (s), 908 (m), 855 (s) cm^{-1}.



85

2-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-(trimethylsilyl)propan-2-ol 85[38]

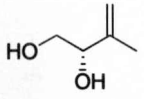
Experimental Procedure: N-Methylmorpholine oxide (NMO) (9.64 g, 82.3 mmol) was dissolved in DCM (375 ml) and treated with anhydrous $MgSO_4$ for 20 minutes The suspension was filtered and the filtrate allowed to stir with 4 Å MS and alcohol **84** (8.06 g, 55.2 mmol) for 15 minutes prior to the addition of tetra-n-propylammonium perruthenate (TPAP) (0.31 g, 0.88 mmol). The reaction was allowed to stir at ambient temperature for 8 hours. The brown suspension was filtered through the silica pad eluting with Et_2O. The eluent was washed with saturated solution of $CuSO_4$, brine and water. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo,* maintaining P ≥ 40 mm Hg to afford the ketone **84a** as crude colorless oil. The crude ketone **84a** was used for the next step without further purification.

Ketone **84a** (7.95 g, 55.2 mmol) was dissolved in anhydrous diethyl ether (390 mL) at room temperature under an atmosphere of argon and solution was cooled to -10 °C. (Trimethylsilyl)methylmagnesium chloride (5.2 mL, 5.2 mmol, 1M in diethyl ether) was added dropwise and solution was stirred overnight at ambient temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and partitioned between diethyl ether and saturated aqueous NH_4Cl solution. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude colorless oil. Purification by flash chromatography (eluting with 5-30% ethyl acetate/hexanes) furnished the alcohol **85** (10.68 g, 83% yield over two steps), as a colorless oil.

$[\alpha]_D^{27}$ +23.3 (c = 1.29, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94-3.90 (m, 2H), 3.78 (dt, J = 10.5, 1.5 Hz, 1H), 1.94 (d, J = 1.8 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H), 1.11 (s, 3H), 1.05 (d, A of AB, J_{AB} = 14.7 Hz, 1H), 0.90 (d, B of AB, J_{AB} = 14.7 Hz, 1H), 0.07 (s, 9H).

IR (Neat): 3494 (br m), 2986 (s), 2953 (s), 2896 (s), 1457 (w), 1380 (s), 1249 (s), 1071 (s), 844 (s), 689 (m) cm^{-1}.



86

(*S*)-3-Methylbut-3-ene-1,2-diol 86[38]

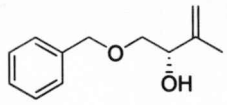
Experimental Procedure: The Peterson adduct **85** (5.05 g, 22.0 mmol) was dissolved in anhydrous ethanol (67 mL) at room temperature under an atmosphere of argon. 3N HCl (2 mL) was added and the reaction mixture was refluxed for *ca.* 2.5 hours. The reaction was cooled with stirring to room temperature. The acid was neutralized by slow addition of solid $NaHCO_3$ and $MgSO_4$ was added to remove residual water.

The suspension was filtered and solvent removed *in vacuo* to afford a crude viscous oil with some with some inorganic salts. Purification by flash chromatography (eluting with 30-50% ethyl acetate/hexanes) furnished the diol **86** (1.74 g, 78 % yield) as a colorless oil.

$[\alpha]_D^{25}$ +18.8 (c = 1.24, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) 5.03 (s, 1H), 4.93 (s, 1H), 4.15 (dd, J = 7.0, 2.7 Hz, 1H), 3.67 (dd, A of ABX, J_{AB} = 11.1 Hz, J_{AX} = 3.1 Hz, 1H), 3.53 (dd, B of ABX, J_{AB} = 11.1 Hz, J_{BX} = 7.4 Hz, 1H), 2.47 (br s, 2H), 1.72 (s, 3H).

IR (Neat): 3366 (br s), 2923 (s), 1652 (m), 1455 (m), 1069 (m), 901 (m) cm $^{-1}$.



87

(*S*)-1-(Benzyloxy)-3-methylbut-3-en-2-ol 87

Experimental Procedure: Diol **86** (0.82 g, 8.03 mmol) was dissolved in anhydrous benzene (320 mL) at room temperature under an atmosphere of argon Dibutyltin dimethoxide (2.03 mL, 8.83 mmol) was added and the mixture was refluxed until 160 mL of benzene was distilled off into the Dean-Stark trap. The tin acetal solution was allowed to cool to ambient temperature. The solvent was removed *in vacuo* to afford a white solid, which was dissolved in anhydrous DMF (160 mL). Cesium fluoride (1.48 g, 9.64 mmol) and benzyl bromide (1.1 mL, 8.83 mmol) were added sequentially and the resulting suspension was stirred at room temperature overnight. The reaction was quenched by addition of water and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash

chromatography (eluting with 2.5-10% ethyl acetate/hexanes) furnished the allylic alcohol **87** (1.42 g, 92% yield) as a colorless oil.

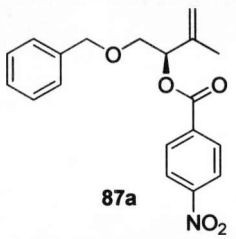
$[\alpha]_D^{28}$ +14.7 (c = 1.16, $CHCl_3$).

Chiral HPLC analysis (Diacel® AS column; 1% IPA/Hex, 1 ml/min at 25 °C; t_R**(87)** = 10.7 min, t_R**(88)** = 12.1 min) indicated *ee* = 99%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 5.05 (s, 1H), 4.91 (s, 1H), 4.56 (s, 2H), 4.27 (dd, *J* = 7.8, 2.5 Hz, 1H), 3.57 (dd, A of ABX, J_{AB} = 9.6 Hz, J_{AX} = 3.1 Hz, 1H), 3.41 (t, *J* = 8.8 Hz, 1H), 2.35 (br s, 1H), 1.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.93 (e), 137.98 (e), 128.62 (o), 127.96 (o), 127.91 (o), 112.17 (e), 74. 05 (o), 73.52 (e), 73.46 (e), 18.93 (o).

IR (Neat): 3445 (br s), 3065 (w), 3031 (m), 2916 (s), 2862 (s), 1653 (w), 1454 (s), 1114 (s), 903 (s), 738 (s), 698 (s) cm^{-1}.

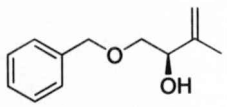


87a

(*R*)-1-(Benzyloxy)-3-methylbut-3-en-2-yl 4-nitrobenzoate 87a

Experimental Procedure: Allylic alcohol **87** (0.53 g, 2.75 mmol) was dissolved in anhydrous tetrahydrofuran (23 mL) at room temperature under an atmosphere of argon and solution was cooled to 0 °C. Triphenyl phosphine (0.80 g, 3.02 mmol), *p*-nitrobenzoic acid (0.51 g, 3.02 mmol) and diisopropyl azodicarboxylate (0.61 mL, 3.02 mmol) were added sequentially. Yellow solution was allowed to warm to room temperature and stir overnight. The solvent was removed *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 5-10% ethyl acetate/hexanes) furnished the ester **87a** (0.83 g, 89% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 8.3 Hz, 2H), 8.20 (d, J = 8.5 Hz, 2H), 7.32-7.26 (m, 5H), 5.64 (dd, J = 7.1, 3.8 Hz, 1H), 5.09 (s, 1H), 5.01 (s, 1H), 4.61 (d, A of AB, J_{AB} = 12.2 Hz, 1H), 4.54 (d, B of AB, J_{AB} = 12.2 Hz, 1H), 3.76 (dd, A of ABX, J_{AB} = 10.5 Hz, J_{AX} = 7.7 Hz, 1H), 3.69 (dd, B of ABX, J_{AB} = 10.6 Hz, J_{BX} = 3.6 Hz, 1H), 1.81 (s, 3H).



88

(*R*)-1-(Benzyloxy)-3-methylbut-3-en-2-ol 88

Experimental Procedure: To a neat **87a** was added 1% sodium hydroxide in methanol (150 mL) dropwise at room temperature under an atmosphere of argon. After stirring for *ca.* 30 minutes the reaction was neutralized by addition of saturated aqueous NH_4Cl solution until pH=7. Solution was diluted with diethyl ether and partitioned between diethyl ether and saturated aqueous NH_4Cl solution. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0-10% ethyl acetate/hexanes) furnished the allylic alcohol **88** (1.06 g, 94% yield) as a colorless oil.

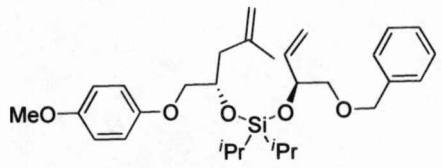
$[\alpha]_D^{27}$ -13.2 (c = 1.17, $CHCl_3$).

Chiral HPLC analysis (Diacel® AS column; 1% IPA/Hex, 1 ml/min at 25 °C; t_R**(87)** = 10.6 min, t_R**(88)** = 12.0 min) indicated *ee* = 98.8%

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 5.05 (s, 1H), 4.91 (s, 1H), 4.56 (s, 2H), 4.27 (dd, J = 8.2, 3.1 Hz, 1H), 3.57 (dd, A of ABX, J_{AB} = 9.6 Hz, J_{AX} = 3.3 Hz, 1H), 3.41 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 8.2 Hz, 1H), 2.27 (br s, 1H), 1.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 143.92 (e), 137.97 (e), 128.58 (o), 127.92 (o), 127.88 (o), 112.13 (e), 74. 02 (o), 73.47 (e), 73.45 (e), 18.90 (o).

IR (Neat): 3445 (br s), 3066 (w), 3031 (m), 2862 (s), 1652 (w), 1454 (s), 1114 (s), 903 (s), 738 (s), 698 (s) cm $^{-1}$.



90

(4*S*,8*S*)-6,6-Diisopropyl-8-((4-methoxyphenoxy)methyl)-10-methyl-1-phenyl-4-vinyl-2,5,7-trioxa-6-silaundec-10-ene 90

General Procedure for the Formation of Unsymmetrical Acyclic Silaketal (A): Alcohol **76** (0.952 g, 4.03 mmol) was dissolved in anhydrous dichloromethane (40 mL) at room temperature under an atmosphere of argon. DMAP (74.6 mg, 0.6 mmol) and TEA (0.48 mL, 6.04 mmol) were added sequentially and mixture was cooled to 0 °C. Diisopropylmonochlorosilane (0.69 mL, 4.03 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stir overnight. The solvent was removed *in vacuo via* dry ice trap. The solid residue was treated with hexane (2x10 mL) for *ca.* 10 minutes and then transferred *via* syringe into 50 mL Schlenck flask equipped with a stir bar. Crude oil was dried over the high vacuum line overnight. Crude oil was dissolved in anhydrous dichloromethane (40.3 mL) under an atmosphere of argon then cooled to 0 °C. NBS (0.78 g, 4.4 mmol) was slowly added from solid addition funnel over the period of *ca.* 6 hours. After addition the crude mixture was cannulated into the 100 mL round bottom flask containing alcohol **79** (0.34 g, 2.01 mmol), DMAP (0.25 g, 2.01 mmol) and TEA (2.81 mL, 20.15 mmol) as a solution in anhydrous dichloromethane (5 mL). The

mixture was stirred overnight at room temperature. Solution was filtered through the short silica pad (eluting with 30% ethyl acetate/hexanes) to afford the acyclic silaketal **90** (0.85 g, 82% yield) as a colorless oil.

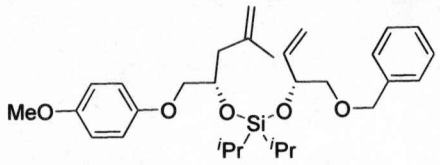
$[\alpha]_D^{25}$ -8.6 (c = 1.18, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.27-7.05 (m, 5H), 6.88-6.72 (m, 4H), 5.94 (ddd, *J* = 17.2, 10.5, 5.5 Hz, 1H), 5.38 (dt, *J* = 17.2, 1.7 Hz, 1H), 5.07 (dt, *J* = 10.6, 1.6 Hz, 1H), 4.87 (s, 1H), 4.84 (s, 1H), 4.74 (dq, *J* = 5.3, 1.1 Hz, 1H), 4.61-4.55 (m, 1H), 4.33 (s, 2H), 3.93 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 5.8 Hz, 1H), 3.89 (dd, B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 4.5 Hz, 1H), 3.54 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 6.4 Hz, 1H), 3.36 (dd, B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 5.3 Hz, 1H), 3.32 (s, 3H), 2.50-2.41 (m, 2H), 1.74 (s, 3H), 1.23-1.20 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.54 (e), 153.64 (e), 142.39 (e), 139.22 (o), 138.99 (e), 128.55 (o), 127.71 (o), 115.68 (o), 115.19 (e), 115.07 (o), 113.77 (e), 75.51 (e), 73.43 (e), 72.94 (o), 72.40 (e), 69.96 (o), 55.22 (o), 43.52 (e), 23.31 (o), 17.86 (o), 17.84 (o), 13.40 (o), 13.37 (o).

IR (Neat): 3072 (m), 3030 (m), 2944 (s), 2866 (s), 1646 (m), 1592 (w), 1508 (s), 1464 (s), 1232 (s), 1107 (s), 1039 (s), 886 (s), 824 (s), 735 (s), 697 (s) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{30}H_{44}O_5Si$ 512.2953, found 512.2955.



94

(4*R*,8*S*)-6,6-Diisopropyl-8-((4-methoxyphenoxy)methyl)-10-methyl-1-phenyl-4-vinyl-2,5,7-trioxa-6-silaundec-10-ene 94

Acyclic silaketal **94** was prepared according to the general procedure for the formation of unsymmetrical acyclic silaketal (A) in 88% yield as a colorless oil.

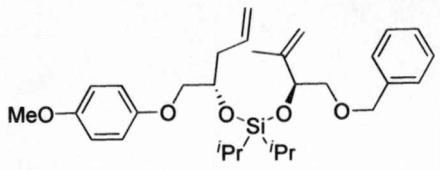
$[\alpha]_D^{28}$ +12.2 (c = 1.24, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.28-7.06 (m, 5H), 6.87-6.73 (m, 4H), 5.94 (ddd, J = 16.9, 10.8, 5.9 Hz, 1H), 5.39 (d, J = 17.2 Hz, 1H), 5.07 (d, J = 10.4 Hz, 1H), 4.87 (s, 1H), 4.85 (s, 1H), 4.74 (q, J = 5.4 Hz, 1H), 4.58 (quintet, J = 5.7 Hz, 1H), 4.34 (d, A of AB, J_{AB} = 12.3 Hz, 1H), 4.32 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 3.93 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.9 Hz, 1H), 3.88 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 4.6 Hz, 1H), 3.51 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 6.4 Hz, 1H), 3.37 (dd, B of ABX, J_{AB} = 9.3 Hz, J_{BX} = 5.1 Hz, 1H), 3.32 (s, 3H), 2.52-2.43 (m, 2H), 1.75 (s, 3H), 1.23-1.19 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.54 (e), 153.62 (e), 142.42 (e), 139.20 (o), 138.98 (e), 128.56 (o), 127.89 (o), 127.74 (o), 115.67 (o), 115.26 (e), 115.07 (o), 113.78 (e), 75.54 (e), 73.48 (e), 73.02 (o), 72.38 (e), 70.03 (o), 55.22 (o), 43.54 (e), 23.35 (o), 17.84 (o), 13.49 (o), 13.33 (o).

IR (Neat): 3072 (m), 3030 (m), 2944 (s), 2866 (s), 1646 (m), 1592 (w), 1507 (s), 1464 (s), 1232 (s), 1107 (s), 1039 (s), 886 (s), 824 (s), 735 (s), 697 (s) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{30}H_{44}O_5Si$ 512.2953, found 512.2957.



97

(4*S*,8*S*)-6,6-Diisopropyl-8-((4-methoxyphenoxy)methyl)-1-phenyl-4-(prop-1-en-2-yl)-2,5,7-trioxa-6-silaundec-10-ene 97

General Procedure for the Formation of Unsymmetrical Acyclic Silaketal (B): Imidazole (0.16 g, 2.33 mmol) was dissolved in anhydrous dichloromethane (50 ml) at room temperature under an atmosphere of argon. The solution was cooled to 0 °C, diisopropyldichlorosilane (0.295 mL, 1.63 mmol) was added dropwise, and the reaction mixture allowed to stir for *ca.* 10 minutes. Alcohol **77** (0.23 g, 1.1 mmol) was added as a solution in anhydrous dichloromethane (5 mL) *via* syringe pump over the period of *ca.* 3 hours. The reaction was allowed to warm to room temperature and stir overnight. Solvent was removed *in vacuo via* dry ice trap. The solid residue was treated with hexane (2x10 mL) for *ca.* 10 minutes then transferred *via* syringe into 50 mL Schlenck flask equipped with a stir bar. The hexane was removed *in vacuo* and oily residue was dipped in the oil bath preheated to 70 °C. After removal of unreacted dichlorosilane (*ca.* 3-4 hours), the residue was dissolved in anhydrous dichloromethane (5.0 mL) and cooled to 0 °C. Dichloromethane (2 mL) solution of imidazole (0.31 g, 4.60 mmol) was added dropwise and solution stirred for *ca.* 10 minutes. Dichloromethane (3 mL) solution of alcohol **87** (0.11 g, 0.55 mmol) was added dropwise and the reaction mixture allowed to warm to room temperature and stir overnight. Solution was filtered through the short silica pad (eluting with 30% ethyl acetate/hexanes). Solvent was removed *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0-4% ethyl

acetate/hexanes) furnished the acyclic silaketal **97** (0.22 g, 77% yield) as a colorless oil.

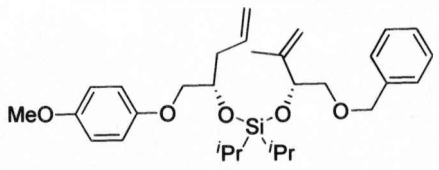
$[\alpha]_D^{27}$ +3.1 (c = 1.14, $CHCl_3$).

^{1}H NMR (300 MHz, C_6D_6): δ 7.28-7.04 (m, 5H), 6.88-6.72 (m, 4H), 5.95 (ddt, J = 17.2, 10.0, 7.1 Hz, 1H), 5.15-5.03 (m, 3H), 4.88 (t, J = 1.5 Hz, 1H), 4.70 (t, J = 5.7 Hz, 1H), 4.47 (quintet, J = 5.5 Hz, 1H), 4.37 (d, A of AB, J_{AB} = 12.1 Hz, 1H), 4.31 (d, B of AB, J_{AB} = 12.2 Hz, 1H), 3.94 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.9 Hz, 1H), 3.84 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 5.0 Hz, 1H), 3.55 (dd, A of ABX, J_{AB} = 9.5 Hz, J_{AX} = 6.5 Hz, 1H), 3.44 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 5.1 Hz, 1H), 3.32 (s, 3H), 2.56-2.40 (m, 2H), 1.72 (s, 3H), 1.22-1.17 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.54 (e), 153.65 (e), 145.74 (e), 139.01 (e), 134.72 (o), 128.55 (o), 128.36 (o), 127.71 (o), 117.59 (e), 115.71 (o), 115.05 (o), 112.56 (e), 75.93 (o), 74.65 (e), 73.40 (e), 72.16 (e), 70.76 (o), 55.21 (o), 39.65 (e), 18.21 (o), 17.84 (o), 13.31 (o).

IR (Neat): 3074 (m), 3031 (m), 2945 (s), 2867 (s), 1642 (w), 1593 (w), 1509 (s), 1464 (m), 1233 (s), 1106 (s), 1004 (s), 885 (m), 824 (m), 735 (m), 697 (m) cm $^{-1}$.

HRMS (EI, M^+): calcd for $C_{30}H_{44}O_5Si$ 512.2953, found 512.2951.



98

(4*R*,8*S*)-6,6-Diisopropyl-8-((4-methoxyphenoxy)methyl)-1-phenyl-4-(prop-1-en-2-yl)-2,5,7-trioxa-6-silaundec-10-ene 98

Acyclic silaketal **98** was prepared according to the general procedure for the formation of unsymmetrical acyclic silaketal (B) in 99% yield.

$[\alpha]_D^{26}$ +3.6 (c = 1.11, $CHCl_3$).

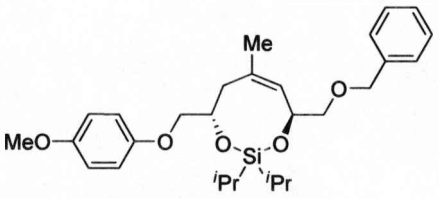
^{1}H NMR (400 MHz, C_6D_6): δ 7.28-7.05 (m, 5H), 6.86-6.72 (m, 4H), 5.97 (ddt, J = 17.2, 10.1, 7.1 Hz, 1H), 5.14-5.04 (m, 3H), 4.87 (t, J = 1.5 Hz, 1H), 4.68 (t, J=5.7 Hz, 1H), 4.46 (quintet, J = 5.5 Hz, 1H), 4.37 (d, A of AB, J_{AB} = 11.9 Hz, 1H), 4.31 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 3.92 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 6.0 Hz, 1H), 3.81 (dd, B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 5.1 Hz, 1H), 3.51 (dd, A of ABX, J_{AB} = 9.6 Hz, J_{AX} = 6.6 Hz, 1H), 3.44 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 4.9 Hz, 1H), 3.32 (s, 3H), 2.57-2.43 (m, 2H), 1.71 (s, 3H), 1.22-1.14 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.59 (e), 153.67 (e), 145.75 (e), 139.01 (e), 134.79 (o), 128.58 (o), 128.35 (e), 128.11 (e), 127.83 (e), 127.76 (o), 117.63 (e), 115.72 (o), 115.08 (o), 112.58 (e), 76.00 (o), 74.75 (e), 73.48 (e), 72.16 (e), 70.80 (o), 55.25 (o), 39.71 (e), 18.28 (o), 17.85 (o), 13.44 (o), 13.25 (o).

IR (Neat): 3074 (m), 3031 (m), 2944 (s), 2866 (s), 1643 (w), 1592 (w), 1506 (s), 1455 (s), 1232 (s), 1106 (s), 1004 (s), 885 (m), 824 (m), 735 (m), 697 (m) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{30}H_{44}O_5Si$ 512.2953, found 512.2945.

HRMS (CI, M-$C_3H_7^+$): calcd for $C_{27}H_{37}O_5Si$ 469.2405, found 469.2415.



99

(4*S*,8*S*,*Z*)-8-(Benzyloxymethyl)-2,2-diisopropyl-4-((4-methoxyphenoxy)methyl)-6-methyl-5,8-dihydro-4H-1,3,2-dioxasilocine 99

General Procedure for the Ring-Closing Metathesis of Eight-Membered Unsaturated Silaketals: The Grubbs' 2nd generation catalyst (68.8 mg, 0.081 mmol) was dissolved in anhydrous dichloromethane (81 ml) at room temperature under an atmosphere of argon. Acyclic silaketal **90** (0.41 g, 0.81 mmol) was added and the mixture was stirred under reflux condition for *ca.* 12 hours. The reaction mixture was cooled to room temperature, silica gel was added (10 eq by weight of the catalyst) and mixture was stirred for an additional 10 minutes. The suspension was filtered through the short silica pad (eluting with 15-30% ethyl acetate/hexanes). The solvent was removed *in vacuo* to afford a crude brownish oil, which was diluted with anhydrous dichloromethane (8.1 ml) and stirred with DMSO (50 eq relative to catalyst) for *ca.* 12 hours. The solvent was removed *in vacuo* to afford a crude brownish oil. Purification by flash chromatography (eluting with 0-3% ethyl acetate/hexanes) furnished the cyclic silaketal **99** (0.34 g, 86 % yield) as a pale yellow oil.

$[\alpha]_D^{29}$ +1.4 (c = 1.11, $CHCl_3$).

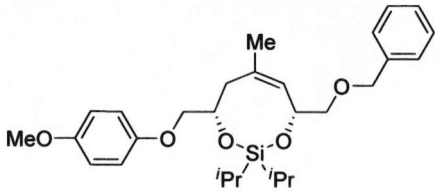
^{1}H NMR (400 MHz, C_6D_6): δ 7.34-7.06 (m, 5H), 6.83-6.74 (m, 4H), 5.63 (d, J = 8.8 Hz, 1H), 4.73 (dt, J = 11.2, 5.6 Hz, 1H), 4.46 (s, 2H), 4.10 (dt, J = 8.9, 6.1 Hz, 1H), 3.92 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.5 Hz, 1H), 3.66 (dt, J = 9.5, 6.2 Hz, 2H),

3.53 (dd, B of ABX, J_{AB} = 9.8 Hz, J_{BX} = 5.5 Hz, 1H), 3.33 (s, 3H), 2.47 (dd, J = 13.7, 9.4 Hz, 1H), 2.09 (d, J = 13.1 Hz, 1H), 1.61 (d, J = 1.4 Hz, 3H), 1.25-1.00 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.70 (e), 153.50 (e), 139.37 (e), 138.53 (e), 129.52 (o), 128.55 (o), 127.64 (o), 115.96 (o), 115.07 (o), 74.82 (e), 73.53 (e), 73.09 (e), 72.19 (o), 68.41 (o), 55.24 (o), 38.59 (e), 25.17 (o), 17.91 (o), 17.82 (o), 17.71 (o), 13.61 (o), 13.05 (o).

IR (Neat): 3064 (m), 3031 (m), 2943 (s), 2865 (s), 1667 (w), 1592 (w), 1506 (s), 1455 (s), 1179 (s), 885 (s), 824 (s), 733 (s), 697 (s) cm $^{-1}$.

HRMS (CI, M-H$^+$): calcd for $C_{28}H_{39}O_5Si$ 483.2561, found 483.2545.



100

(4*S*,8*R*,*Z*)-8-(Benzyloxymethyl)-2,2-diisopropyl-4-((4-methoxyphenoxy)methyl)-6-methyl-5,8-dihydro-4H-1,3,2-dioxasilocine 100

Cyclic silaketal **100** was prepared according to the general procedure for the ring-closing metathesis of eight-membered unsaturated silaketals in 91% yield, as a pale yellow oil.

$[\alpha]_D^{26}$ -1.13 (c = 1.24, $CHCl_3$).

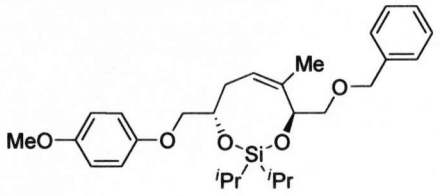
^{1}H NMR (400 MHz, C_6D_6): δ 7.31-7.04 (m, 5H), 6.79-6.68 (m, 4H), 5.52 (d, J = 5.9 Hz, 1H), 4.64 (dd, J = 11.0, 6.0 Hz, 1H), 4.48-4.37 (m, 3H), 3.88 (dd, A of ABX, J_{AB} = 9.1 Hz, J_{AX} = 5.6 Hz, 1H), 3.68 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 7.0 Hz, 1H), 3.54 (dd, A of ABX, J_{AB} = 9.8 Hz, J_{AX} = 6.4 Hz, 1H), 3.44 (dd, B of ABX, J_{AB} = 9.7 Hz, J_{BX} = 5.0 Hz, 1H), 3.30 (s, 3H), 2.70 (dd, A of ABX, J_{AB} = 14.0 Hz, J_{AX} = 7.3 Hz,

1H), 2.30 (dd, B of ABX, J_{AB} = 14.0 Hz, J_{BX} = 3.6 Hz, 1H), 1.61 (s, 3H), 1.20-0.98 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.68 (e), 153.37 (e), 139.39 (e), 137.03 (e), 129.21 (o), 128.57 (o), 127.73 (o), 127.66 (o), 115.84 (o), 115.10 (o), 75.07 (e), 73.48 (e), 72.67 (e), 71.96 (o), 70.40 (o), 55.23 (o), 37.58 (e), 25.88 (o), 17.96 (o), 17.94 (o), 17.92 (o), 17.80 (o), 13.88 (o), 13.50 (o).

IR (Neat): 3030 (w), 2943 (s), 2866 (s), 1663 (w), 1592 (w), 1508 (s), 1464 (m), 1233 (s), 1050 (s), 886 (m), 824 (m), 734 (m), 698 (m) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{28}H_{40}O_5Si$ 484.2640, found 484.2626.



101

(4*S*,8*S*,*Z*)-8-(Benzyloxymethyl)-2,2-diisopropyl-4-((4-methoxyphenoxy)methyl)-7-methyl-5,8-dihydro-4H-1,3,2-dioxasilocine 101

Cyclic silaketal **101** was prepared according to the general procedure for the ring-closing metathesis of eight-membered unsaturated silaketals in 94 % yield, as a pale yellow oil.

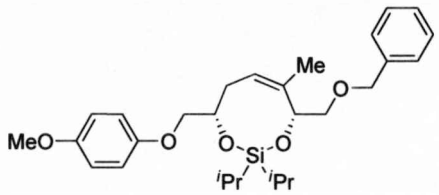
$[\alpha]_D^{24}$ -34.9 (c = 1.11, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.31-7.06 (m, 5H), 6.82-6.74 (m, 4H), 5.33 (t, *J* = 8.3Hz, 1H), 4.88 (t, *J* = 6.3 Hz, 1H), 4.44 (d, A of AB, J_{AB} = 12.1 Hz, 1H), 4.37 (d, B of AB, J_{AB} = 12.3 Hz, 1H), 4.15 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.88 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.7 Hz, 1H), 3.66 (dt, *J* = 12.4, 6.8 Hz, 2H), 3.58 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 6.1 Hz, 1H), 3.33 (s, 3H), 2.51 (t, *J* = 10.8Hz, 1H), 2.35-2.28 (m, 1H), 1.71 (s, 3H), 1.21-1.01 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.63 (e), 153.62 (e), 140.87 (e), 139.22 (e), 128.57 (o), 127.78 (o), 127.69 (o), 125.14 (o), 115.89 (o), 115.06 (o), 73.53 (e), 73.31 (o), 72.88 (e), 72.24 (e), 55.26 (o), 32.04 (e), 19.98 (o), 17.75 (o), 17.71 (o), 13.27 (o), 13.00 (o).

IR (Neat): 3031 (m), 2943 (s), 1593 (w), 1506 (s), 1456 (s), 1234 (s), 1106 (s), 885 (m), 823 (m), 732 (m), 697 (m) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{28}H_{40}O_5Si$ 484.2640, found 484.2644.



102

(4*S*,8*R*,*Z*)-8-(Benzyloxymethyl)-2,2-diisopropyl-4-((4-methoxyphenoxy)methyl)-7-methyl-5,8-dihydro-4H-1,3,2-dioxasilocine 102

Cyclic silaketal **102** was prepared according to the general procedure for the ring-closing metathesis of eight-membered unsaturated silaketals in 93% yield, as a pale yellow oil.

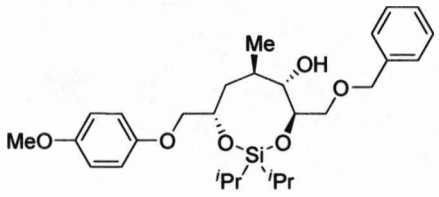
$[\alpha]_D^{24}$ +10.7 (c = 1.08, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.34-7.06 (m, 5H), 6.84-6.71 (m, 4H), 5.31 (t, J = 8.9Hz, 1H), 4.62 (dd, J = 6.4, 4.9 Hz, 1H), 4.49 (d, A of AB, J_{AB} = 12.3 Hz, 1H), 4.44 (d, B of AB, J_{AB} = 12.3 Hz, 1H), 4.27-4.21 (m, 1H), 3.91 (dd, A of ABX, J_{AB} = 9.1 Hz, J_{AX} = 5.0 Hz, 1H), 3.74 (dd, B of ABX, J_{AB} = 9.0 Hz, J_{BX} = 6.8 Hz, 1H), 3.62 (dd, A of ABX, J_{AB} = 9.9 Hz, J_{AX} = 6.5 Hz, 1H), 3.55 (dd, B of ABX, J_{AB} = 9.9 Hz, J_{BX} = 4.8 Hz, 1H), 3.32 (s, 3H), 2.91 (dt, J = 13.6, 9.5 Hz, 1H), 2.21 (ddd, J = 13.5, 8.0, 1.6 Hz, 1H), 1.66 (s, 3H), 1.22-1.05 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.61 (e), 153.49 (e), 140.68 (e), 139.31 (e), 128.57 (o), 127.64 (o), 125.06 (o), 115.86 (o), 115.05 (o), 74.95 (o), 73.98 (e), 73.66 (o), 73.46 (e), 72.75 (e), 55.21 (o), 32.88 (e), 22.71 (o), 18.01 (o), 17.90 (o), 17.71 (o), 13.84 (o), 13.58 (o).

IR (Neat): 3031 (m), 2866 (s), 1592 (w), 1506 (s), 1464 (s), 1180 (s), 1134 (s), 886 (m), 824 (m), 698 (s) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{28}H_{40}O_5Si$ 484.2640, found 484.2625.



105

(4*R*,5*S*,6*R*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocan-5-ol 105

General Procedure for the Hydroboration of Eight-Membered Cyclic Silaketals A: Cyclic silaketal **99** (48.4 mg, 0.1 mmol) was dissolved in anhydrous tetrahydrofuran (1.0 ml) at room temperature under an atmosphere of argon. BH_3·DMS complex (20.5 µl, 0.2 mmol) was added and reaction mixture was stirred for *ca.* 2 hours. The reaction mixture was then cooled to 0 °C and premixed 3M NaOH/30 wt % H_2O_2 (0.33 ml/0.11 ml, 1 mmol/1 mmol) solution was slowly added *via* pipette. The reaction was allowed to warm to room temperature and stir for an additional 12 hours. Reaction mixture was diluted with ethyl acetate and partitioned between ethyl acetate and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0-15% ethyl acetate/hexanes) furnished the alcohol **105** (86 % yield) as a colorless oil.

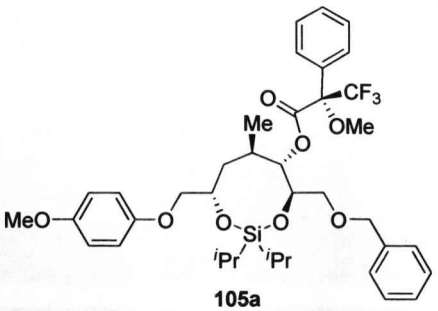
$[\alpha]_D^{25}$ +14.7 (c = 1.11, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.22-7.07 (m, 5H), 6.84-6.73 (m, 4H), 4.41 (dt, *J* = 10.9, 5.5 Hz, 1H), 4.32 (d, A of AB, J_{AB} = 11.7 Hz, 1H), 4.25 (d, B of AB, J_{AB} = 11.7 Hz, 1H), 4.01 (d, *J* = 9.2 Hz, 1H), 3.92 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 5.8 Hz, 1H), 3.82-3.76 (m, 1H), 3.70 (dd, A of ABX, J_{AB} = 9.0, J_{AX} = 2.9 Hz, 1H), 3.61 (ddd, *J* = 13.6, 9.1, 5.9 Hz, 2H), 3.32 (s, 3H), 2.62-2.59 (m, 1H), 2.32 (d, *J* = 5.3 Hz, 1H), 1.85 (dd, A of ABX, J_{AB} = 14.4, J_{AX} = 4.8 Hz, 1H), 1.55 (ddd, *J* = 14.3, 10.7, 3.3 Hz, 1H), 1.16-0.96 (m, 17H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.53 (e), 153.73 (e), 138.52 (e), 128.66 (o), 128.18 (o), 127.98 (o), 115.87 (o), 115.00 (o), 76.96 (o), 73.70 (e), 73.59 (e), 72.51 (e), 71.13 (o), 68.11 (o), 55.24 (o), 41.66 (e), 31.84 (o), 17.89 (o), 17.72 (o), 12.92 (o), 12.80 (o), 10.66 (o).

IR (Neat): 3477 (br m), 3031 (m), 2929 (s), 1592 (w), 1506 (s), 1465 (s), 1235 (s), 1067 (s), 886 (s), 825 (s), 741 (s), 697 (s) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{28}H_{42}O_6Si$ 502.2745, found 502.2745.



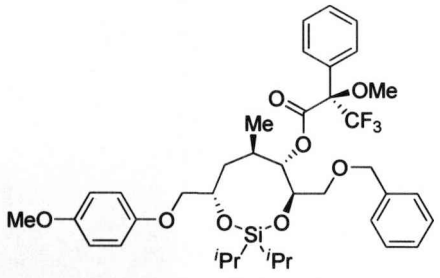
105a

(*S*)-((4*R*,5*S*,6*R*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocan-5-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 105a

General Procedure for the Formation of Mosher Ester Derivatives: Alcohol **105** (20.1 mg, 0.04 mmol) was dissolved in anhydrous dichloromethane (2.0 ml) at room

temperature under an atmosphere of argon. The reaction was cooled to 0 °C and DMAP (0.8 mg, 6.0 μmol), TEA (8.4 μl, 0.06 mmol) and (*R*)-(−)-MTPA-Cl (8.4 μl 0.044 mmol) were added sequentially. The reaction mixture was allowed to warm to room temperature and stir for *ca.* 12 hours. The solvent was removed *in vacuo* to afford the crude oil. Purification by flash chromatography (eluting with 0-20% ethyl acetate/hexanes) furnished the (*S*)-MTPA ester **105a** in 95% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.82-7.80 (m, 2H), 7.25-7.02 (m, 8H), 6.78-6.72 (m, 4H), 5.45 (ddd, J = 9.3, 5.6, 2.3 Hz, 1H), 4.31-4.25 (m, 1H), 4.27 (s, 2H), 4.20 (d, J = 9.4 Hz, 1H), 3.87 (dd, A of ABX, J_{AB} = 10.7 Hz, J_{AX} = 2.3 Hz, 1H), 3.81 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.7 Hz, 1H), 3.74 (dd, B of ABX, J_{AB} = 10.7 Hz, J_{BX} = 5.5 Hz, 1H), 3.58 (s, 3H), 3.50 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 6.1 Hz, 1H), 3.32 (s, 3H), 1.80-1.79 (m, 1H), 1.59 (dd, J = 14.7, 4.7 Hz, 1H), 1.23 (ddd, J = 14.4, 10.8, 3.1 Hz, 1H), 1.13-0.87 (m, 6H), 1.06-0.99 (m, 8H), 0.95 (d, J = 7.0 Hz, 3H).



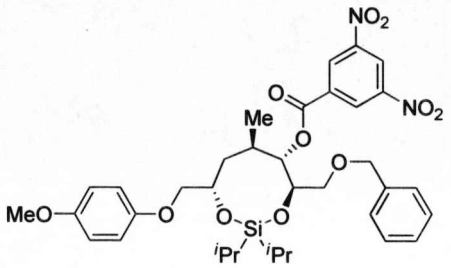
105b

(*R*)-((4*R*,5*S*,6*R*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)-methyl)-6-methyl-1,3,2-dioxasilocan-5-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 105b

(*R*)-MTPA ester **105b** was prepared according to the general procedure for the formation of Mosher ester derivatives in 81% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.76 (d, J = 7.0 Hz, 2H), 7.17-7.02 (m, 8H), 6.82-6.74 (m, 4H), 5.50 (ddd, J = 8.9, 5.7, 2.9 Hz, 1H), 4.35-4.29 (m, 2H), 4.21 (s, 2H), 3.87

(dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.7 Hz 1H), 3.77 (dd, A of ABX, J_{AB} = 10.7 Hz, J_{AX} = 2.5 Hz, 1H), 3.71 (dd, B of ABX, J_{AB} = 10.7 Hz, J_{BX} = 5.5 Hz, 1H), 3.57 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 6.3 Hz, 1H), 3.42 (s, 3H), 3.32 (s, 3H), 2.15-2.13 (m, 1H), 1.72 (dd, J = 14.6, 4.8 Hz, 1H), 1.36 (ddd, J = 14.4, 10.6, 3.4 Hz, 1H), 1.12 (d, J = 6.8 Hz, 6H), 1.06-1.01 (m, 8H).



106

((4*R*,5*S*,6*R*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocan-5-yl-3,5-dinitrobenzoate 106

Experimental Procedure: Alcohol **105** (0.06 g, 0.12 mmol) was dissolved in anhydrous dichloromethane (1.5 mL) at room temperature under an atmosphere of argon. DMAP (0.022 g, 0.18 mmol) and 3,5-dinitrobenzoyl chloride (0.042 g, 0.18 mmol) were added sequentially and the mixture was stirred for *ca.* 4 hours. The reaction was concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 5-15% ethyl acetate/hexanes) furnished the ester **106** (0.083 g, 99% yield), as a yellow crystalline solid.

mp = 101-104 °C.

$[\alpha]_D^{25}$ -4.6 (c = 1.08, $CHCl_3$).

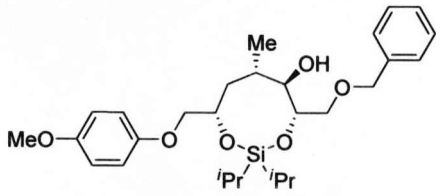
^{1}H NMR (400 MHz, C_6D_6): δ 8.72 (d, J = 2.1 Hz, 2H), 8.46 (d, J = 2.1 Hz, 1H), 6.95-6.91 (m, 2H), 6.86-6.75 (m, 7H), 5.30 (t, J = 8.7 Hz, 1H), 4.42 (dt, J = 10.8, 5.4 Hz, 1H), 4.22 (dt, J = 9.1, 4.5 Hz, 1H), 4.12 (s, 2H), 3.91 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.7 Hz 1H), 3.71 (dd, B of ABX, J_{AB} = 9.3 Hz, J_{BX} = 6.9 Hz 1H), 3.61-3.54

(m, 2H), 3.32 (s, 3H), 2.35-2.29 (m, 1H), 2.19 (ddd, J = 14.7, 6.3, 4.3 Hz, 1H), 1.71 (ddd, J = 14.8, 5.1, 3.0 Hz, 1H), 1.20-1.08 (m, 14H), 0.99 (d, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, C_6D_6): δ 162.19 (e), 154.77 (e), 153.40 (e), 148.34 (e), 137.93 (e), 133.52 (e), 128.78 (o), 128.41 (e), 127.76 (o), 122.05 (o), 115.82 (o), 115.13 (o), 79.34 (o), 75.08 (o), 74.27 (e), 73.83 (e), 71.24 (e), 69.45 (o), 55.26 (o), 37.89 (e), 31.76 (o), 19.40 (o), 17.84 (o), 17.83 (o), 17.76 (o), 17.68 (o), 12.86 (o), 12.51 (o).

IR (Neat): 3104 (m), 3031 (w), 2944 (s), 2868 (s), 1732 (s), 1629 (m), 1547 (s), 1508 (s), 1463 (s), 1275 (s), 1073 (s), 825 (m), 731 (s), 698 (m) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{35}H_{44}N_2O_{11}Si$ 696.2709, found 696.2719.



107

(4*S*,5*R*,6*S*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocan-5-ol 107

Alcohol **107** was prepared according to the general procedure for the hydroboration of eight-membered cyclic silaketals A in 90% yield, as a pale yellow oil.

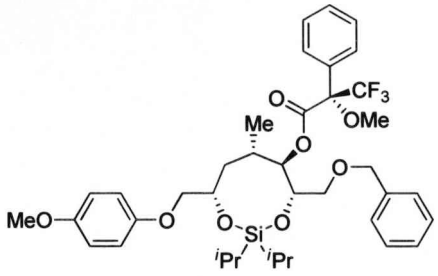
$[\alpha]_D^{26}$ -2.9 (c = 1.12, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.22-7.07 (m, 5H), 6.84-6.73 (m, 4H), 4.33 (d, A of AB, J_{AB} = 11.7 Hz, 1H), 4.25 (d, B of AB, J_{AB} = 11.5 Hz, 1H), 4.19 (quintet, J = 5.0 Hz, 1H), 4.12 (dd, J = 9.1, 3.2 Hz, 1H), 3.96-3.88 (m, 1H), 3.80 (dd, A of ABX, J_{AB} = 9.1 Hz, J_{AX} = 4.6 Hz, 1H), 3.73 (dd, A of ABX, J_{AB} = 9.0 Hz, J_{AX} = 2.9 Hz, 1H), 3.66 (dd, B of ABX, J_{AB} = 9.1 Hz, J_{BX} = 6.2 Hz, 1H), 3.60 (dd, B of ABX, J_{AB} = 9.0 Hz, J_{BX} = 6.1 Hz, 1H), 3.33 (s, 3H), 2.29-2.21 (m, 2H), 1.93 (dd, J = 14.8, 6.0 Hz, 1H), 1.64 (dt, J = 15.0, 10.3 Hz, 1H), 1.17-0.99 (m, 17H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.57 (e), 153.70 (e), 138.48 (e), 128.68 (o), 128.17 (o), 128.01 (o), 115.84 (o), 115.04 (o), 73.62 (e), 73.56 (o), 73.51 (e), 72.73 (e), 72.14 (o), 71.25 (o), 55.24 (o), 39.11 (e), 34.24 (o), 17.86 (o), 17.76 (o), 17.62 (o), 15.43 (o), 13.73 (o), 13.56 (o).

IR (Neat): 3480 (br w), 2943 (m), 2866 (m), 1509 (s), 1465 (m), 1233 (s), 1110 (m), 1052 (m), 886 (m), 825 (m), 736 (m), 698 (m) cm $^{-1}$.

HRMS (EI, M^+): calcd for $C_{28}H_{42}O_6Si$ 502.2745, found 502.2732.

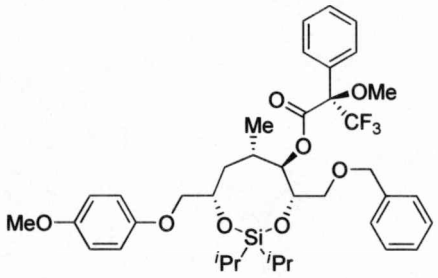


107a

(*S*)-((4*S*,5*R*,6*S*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocan-5-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 107a

(*S*)-MTPA ester **107a** was prepared according to the general procedure for the formation of Mosher ester derivatives in 90% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.86-7.84 (m, 2H), 7.27-7.03 (m, 8H), 6.75 (s, 4H), 5.50 (ddd, J = 8.8, 5.4, 2.6 Hz, 1H), 4.41 (dd, J = 9.2, 2.9 Hz, 1H), 4.28 (s, 2H), 3.90 (dd, A of ABX, J_{AB} = 10.9 Hz, J_{AX} = 2.5 Hz, 1H), 3.85 (dq, J = 9.8, 4.9 Hz, 1H), 3.78 (dd, B of ABX, J_{AB} = 10.9 Hz, J_{BX} = 5.3 Hz, 1H), 3.60 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 4.3 Hz, 1H), 3.58 (s, 3H), 3.54 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 5.7 Hz, 1H), 3.32 (s, 3H), 1.78-1.66 (m, 2H), 1.49 (dt, J = 14.8, 9.9 Hz, 1H), 1.15-0.97 (m, 14H), 0.87 (d, J = 6.5 Hz, 3H).

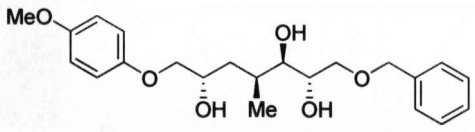


107b

(*R*)-((4*S*,5*R*,6*S*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocan-5-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 107b

(*R*)-MTPA ester **107b** was prepared according to the general procedure for the formation of Mosher ester derivatives in 62% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.80 (d, J = 7.2 Hz, 2H), 7.16-7.02 (m, 8H), 6.81-6.74 (m, 4H), 5.59 (ddd, J = 8.6, 5.6, 2.8 Hz, 1H), 4.46 (dd, J = 8.6, 3.1 Hz, 1H), 4.21 (s, 2H), 3.96 (dq, J = 10.1, 5.0 Hz, 1H), 3.77 (dd, A of ABX, J_{AB} = 10.8 Hz, J_{AX} = 2.8 Hz, 1H), 3.72-3.68 (m, 2H), 3.59 (dd, B of ABX, J_{AB} = 9.0 Hz, J_{BX} = 6.3 Hz, 1H), 3.43 (s, 3H), 3.33 (s, 3H), 2.02-1.92 (m, 1H), 1.83 (dd, J = 15.0, 6.4 Hz, 1H), 1.55 (dt, J = 15.2, 10.2 Hz, 1H), 1.51-0.99 (m, 14H), 0.96 (d, J = 6.6 Hz, 3H).



107c

(2*S*,3*R*,4*S*,6*S*)-1-(Benzyloxy)-7-(4-methoxyphenoxy)-4-methylheptane-2,3,6-triol 107c

Experimental Procedure: Silaketal **107** (0.071 g, 0.139 mmol) was dissolved in anhydrous tetrahydrofuran (8.5 mL) under an atmosphere of argon and solution was cooled to 0 °C. TBAF (0.56 mL, 0.56 mmol, 1M in THF) was added dropwise. The reaction mixture was allowed to warm to room temperature and stir overnight. The

reaction was quenched with saturated aqueous NH_4Cl solution and partitioned between ethyl acetate and saturated aqueous NH_4Cl solution. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 50-80% ethyl acetate/hexanes) furnished the triol **107c** (0.049 g, 90 % yield), as a white crystalline solid.

mp = 105-108 °C.

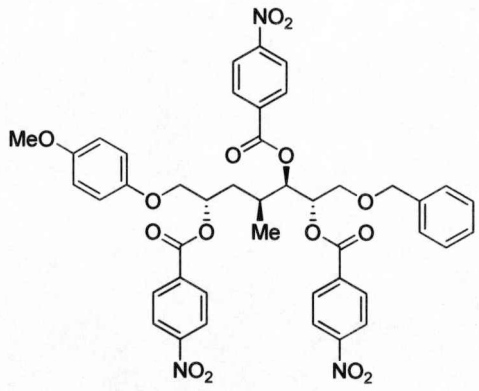
$[\alpha]_D^{26}$ +1.4 (c = 1.13, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H), 6.80 (s, 4H), 4.55 (d, A of AB, J_{AB} = 11.7 Hz, 1H), 4.51 (d, B of AB, J_{AB} = 11.7 Hz, 1H), 4.07-4.02 (m, 1H), 3.84 (dd, J = 9.2, 3.1 Hz, 1H), 3.82-3.77 (m, 1H), 3.76-3.70 (m, 5H), 3.63 (dd, J = 9.3, 6.0 Hz, 2H), 2.77 (br s, 3H), 2.13-2.02 (m, 1H), 1.55 (ddd, J = 14.2, 9.7, 6.3 Hz, 1H), 1.41 (ddd, J = 14.0, 8.3, 2.2 Hz, 1H), 2.19 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.26 (e), 152.74 (e), 137.89 (e), 128.62 (o), 128.01 (o), 127.95 (o), 115.72 (o), 114.82 (o), 74.93 (o), 73.68 (e), 73.58 (e), 72.37 (e), 70.54 (o), 68.71 (o), 55.83 (o), 36.69 (e), 32.12 (o), 13.98 (o).

IR (Neat): 3572 (w), 3353 (br m), 2917 (m), 1592 (w), 1509 (s), 1453 (m), 1239 (s), 1065 (s), 984 (s), 827 (s), 697 (m) cm^{-1}.

HRMS (CI, M^+): calcd for $C_{22}H_{30}O_6$ 390.2037, found 390.2035.



108

(2*S*,3*R*,4*S*,6*S*)-1-(Benzyloxy)-7-(4-methoxyphenoxy)-4-methyl-6-(4-nitrobenzoyloxy)heptane-2,3-diyl *bis*(4-nitrobenzoate) 108

Experimental Procedure: Triol **107c** (0.049 g, 0.125 mmol) was dissolved in anhydrous dichloromethane (4 mL) at room temperature under an atmosphere of argon. DMAP (0.01 g, 0.082 mmol), TEA (0.11 mL, 0.82 mmol) and 4-nitrobenzoyl chloride (0.142 g, 0.75 mmol) were added sequentially and the mixture was stirred for *ca.* 4 hours. The solvent was removed *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-30% ethyl acetate/hexanes) furnished the triester **108** (0.095 g, 91% yield), as a yellow solid.

$[\alpha]_D^{26}$ -14.9 (c = 1.23, $CHCl_3$).

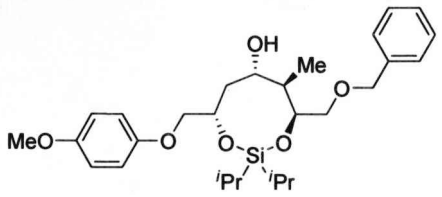
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.23 (m, 2H), 8.17-8.08 (m, 8H), 8.05-8.02 (m, 2H), 7.19-7.13 (m, 5H), 6.78-6.73 (m, 4H), 5.67-5.57 (m, 3H), 4.43 (d, A of AB, J_{AB} = 11.9 Hz, 1H), 4.38 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 4.09 (d, J = 4.7 Hz, 2H), 3.79 (dd, A of ABX, J_{AB} = 10.7 Hz, J_{AX} = 3.5 Hz, 1H), 3.71 (s, 3H), 3.70 (dd, B of ABX, J_{AB} = 10.6 Hz, J_{BX} = 4.9 Hz, 1H), 2.26-2.18 (m, 2H), 1.75 (ddd, J = 14.8, 10.6, 3.7 Hz, 1H), 1.13 (d, J = 6.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.34 (e), 163.99 (e), 163.81 (e), 154.43 (e), 152.50 (e), 150.87 (e), 150.78 (e), 150.71 (e), 137.23 (e), 135.16 (e), 134.90 (e),

134.82 (e), 130.92 (o), 130.87 (o), 128.48 (o), 127.99 (o), 127.75 (o), 123.81 (o), 123.63 (o), 123.58 (o), 115.81 (o), 114.76 (o), 76.11 (o), 73.53 (e), 72.58 (o), 72.10 (o), 69.99 (e), 68.16 (e), 55.76 (o), 35.17 (e), 30.86 (o), 14.41 (o).

IR (Neat): 3112 (w), 3056 (w), 2933 (m), 2870 (m), 1728 (s), 1606 (m), 1531 (s), 1508 (s), 1455 (m), 1350 (s), 1320 (s), 1263 (s), 1102 (s), 873 (m), 841 (m), 719 (s) cm^{-1}.

HRMS (CI, M^+): calcd for $C_{43}H_{39}N_3O_{15}$ 837.2376, found 837.2386.



114

(4*S*,5*R*,6*S*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocan-6-ol 114

General Procedure for the Hydroboration of Eight-Membered Cyclic Silaketals B: 2,3-Dimethyl-2-butene (36.4 µl, 0.3 mmol) was added dropwise to BH_3·THF solution (0.3 ml, 0.3 mmol, 1M solution) previously cooled to 0 °C under an atmosphere of argon. The mixture was allowed to stir for *ca.* 1 hour. Tetrahydrofuran (0.5 mL + 0.5 mL rinse) solution of cyclic silaketal **101** (48.4 mg, 0.1 mmol) was added dropwise and reaction was allowed to warm to room temperature with stirring for an additional 2 hours (t.l.c. control). The reaction mixture was cooled back to 0 °C and premixed 3M NaOH/30 wt % H_2O_2 (0.50 ml/0.17 ml, 1.5 mmol/1.5 mmol) solution was slowly added *via* pipette. The reaction was allowed to warm to room temperature and stir for an additional *ca.* 12 hours. Reaction was diluted with ethyl acetate and partitioned between ethyl acetate and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and

concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0-15% ethyl acetate/hexanes) furnished the alcohol **114** (90 % yield) as a colorless oil.

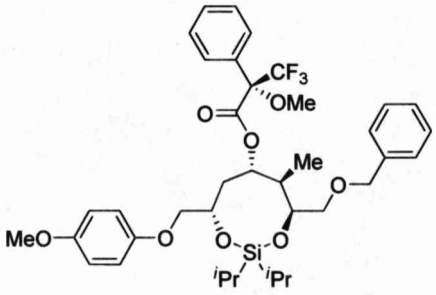
$[\alpha]_D^{26}$ -25.5 (c = 1.10, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.27-7.06 (m, 5H), 6.84-6.73 (m, 4H), 4.50 (dt, J = 6.3, 2.5 Hz, 1H), 4.34 (d, A of AB, J_{AB} = 12.1 Hz, 1H), 4.28 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 4.26-4.22 (m, 1H), 3.87 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 5.8 Hz, 1H), 3.63 (dd, B of ABX, J_{AB} = 9.3 Hz, J_{BX} = 6.2 Hz, 1H), 3.56-3.51 (m, 2H), 3.42 (dd, B of ABX, J_{AB} = 9.2, J_{BX} = 6.3 Hz, 1H), 3.33 (s, 3H), 1.97-1.84 (m, 2H), 1.74-1.66 (m, 1H), 1.33 (br s, 1H), 1.16-1.03 (m, 17H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.62 (e), 153.63 (e), 138.92 (e), 128.58 (o), 127.97 (o), 115.95 (o), 115.05 (o), 75.60 (o), 73.57 (e), 73.37 (e), 73.11 (o), 72.96 (e), 70.06 (o), 55.27 (o), 43.78 (o), 42.10 (e), 18.05 (o), 17.75 (o), 17.54 (o), 13.31 (o), 12.41 (o), 10.57 (o).

IR (Neat): 3419 (br m), 3031 (m), 2866 (s), 1592 (w), 1506 (s), 1464 (s), 1234 (s), 1127 (s), 886 (m), 824 (m), 736 (m), 698 (m) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{28}H_{42}O_6Si$ 502.2745, found 502.2746.

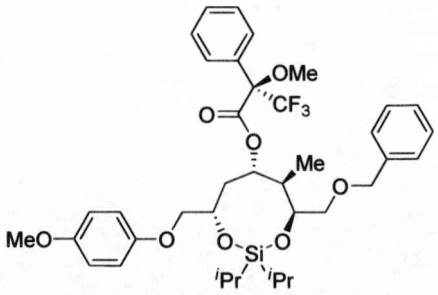


114a

(*S*)-((4*S*,5*R*,6*S*,8*S*)-4-(benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocan-6-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 114a

(*S*)-MTPA ester **114a** was prepared according to the general procedure for the formation of Mosher ester derivatives in 94% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.77 (d, J = 7.8 Hz, 2H), 7.23-6.98 (m, 8H), 6.85-6.81 (m, 2H), 6.77-6.73 (m, 2H), 5.22 (dd, J = 10.5, 6.7 Hz, 1H), 4.80-4.75 (m, 1H), 4.44 (dt, J = 6.5, 2.5 Hz, 1H), 4.31 (d, A of AB, J_{AB} = 11.9 Hz, 1H), 4.23 (d, B of AB, J_{AB} = 11.9 Hz, 1H), 3.88 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.1 Hz, 1H), 3.62 (dd, B of ABX, J_{AB} = 9.1 Hz, J_{BX} = 7.1 Hz, 1H), 3.49 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 6.3 Hz, 1H), 3.45 (s, 3H), 3.37 (dd, B of ABX, J_{AB} = 9.2, J_{BX} = 6.8 Hz, 1H), 3.33 (s, 3H), 2.01 (d, J = 15.8 Hz, 1H), 1.96-1.91 (m, 1H), 1.75 (ddd, J = 16.3, 9.8, 6.8 Hz, 1H), 1.18-1.01 (m, 17H).

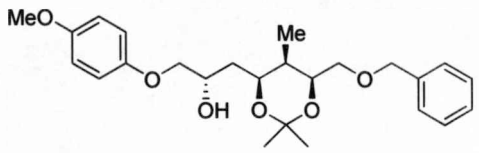


114b

(*R*)-((4*S*,5*R*,6*S*,8*S*)-4-(benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocan-6-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 114b

(*R*)-MTPA ester **114b** was prepared according to the general procedure for the formation of Mosher ester derivatives in 97% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.74 (d, J = 7.8 Hz, 2H), 7.22-7.02 (m, 8H), 6.80-6.77 (m, 2H), 6.76-6.73 (m, 2H), 5.23 (dd, J = 10.6, 6.8 Hz, 1H), 4.78-4.72 (m, 1H), 4.49 (dt, J = 6.4, 2.4 Hz, 1H), 4.30 (d, A of AB, J_{AB} = 12.1 Hz, 1H), 4.22 (d, B of AB, J_{AB} = 11.9 Hz, 1H), 3.88 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 5.2 Hz, 1H), 3.62 (dd, B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 6.8 Hz, 1H), 3.48 (dd, A of ABX, J_{AB} = 8.9 Hz, J_{AX} = 6.2 Hz, 1H), 3.46 (s, 3H), 3.34 (dd, B of ABX, J_{AB} = 9.4, J_{BX} = 6.6 Hz, 1H), 3.32 (s, 3H), 2.14 (d, J = 15.6 Hz, 1H), 1.99-1.89 (m, 2H), 1.18-1.01 (m, 14H), 0.93 (d, J = 6.6 Hz, 3H).



116

(*S*)-1-((4*S*,5*R*,6*S*)-6-(Benzyloxymethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-3-(4-methoxyphenoxy)propan-2-ol 116

General Procedure for the Formation of Acetonides: Alcohol **114** (70.4 mg, 0.14 mmol) was dissolved in anhydrous THF (8.4 ml) under an atmosphere of argon and solution cooled to 0 °C. TBAF (0.56 ml, 0.56 mmol, 1 M in THF) was added dropwise and mixture allowed to stir overnight at ambient temperature. The reaction was quenched with saturated solution of NH_4Cl and partitioned between ethyl acetate and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude oil. Purification by flash chromatography (eluting with 60-90% ethyl acetate/hexanes) furnished the triol **114a** (95% yield) as a colorless oil. Purified material was used immediately for the next step.

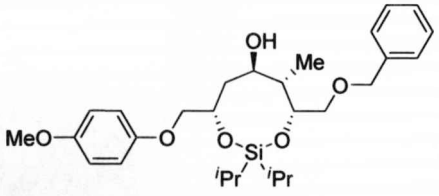
Triol **114a** (50.8 mg, 0.13 mmol) was dissolved in anhydrous DMF (2 mL) at room temperature under an atmosphere of argon. CSA (0.6 mg, 2.6 μmol) was added and mixture was heated to 40 °C. Dimethoxy propane (32.0 μl, 0.26 mmol) was added dropwise and mixture was stirred overnight. After cooling to room temperature, the reaction was quenched with TEA and partitioned between ethyl acetate and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the crude oil. Purification by flash chromatography (eluting with 10-30% ethyl acetate/hexanes) furnished the acetonide **116** (94% yield, over two steps), as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.25 (m, 5H), 6.82 (s, 4H), 4.60 (d, A of AB, J_{AB} = 12.1 Hz, 1H), 4.47 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 4.28 (dd, A of ABX, J_{AB} = 10.2 Hz, J_{AX} = 2.0 Hz, 1H), 4.20 (dt, J = 6.2, 2.2 Hz, 1H), 4.15-4.12 (m, 1H), 3.94 (dd, B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 3.8 Hz, 1H), 3.79 (dd, A of ABX, J_{AB} = 9.4 Hz, J_{AX} = 7.8 Hz, 1H) 3.50-3.46 (m, 1H), 3.40 (dd, B of ABX, J_{AB} = 9.7 Hz, J_{AX} = 6.0 Hz, 1H), 2.58 (br s, 1H), 1.76 (ddd, J = 13.9, 10.4, 3.5 Hz, 1H), 1.55-1.50 (m, 1H), 1.47 (s, 3H), 1.39 (s, 3H), 0.84 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.02 (e), 152.70 (e), 138.15 (e), 128.33 (o), 127.66 (o), 127.68 (o), 115.46 (o), 114.64 (o), 99.07 (e), 73.39 (e), 73.33 (e), 73.27 (e), 72.83 (e), 72.23 (o), 70.84 (e), 69.37 (o), 67.30 (o), 55.67 (o), 36.17 (e), 33.60 (o), 29.86 (o), 19.68 (o), 5.17 (o).

IR (Neat): 3460 (br m), 3064 (w), 3030 (w), 2990 (m), 2916 (m), 1592 (w), 1509 (s), 1456 (m), 1232 (s), 1107 (s), 1044 (s), 825 (m), 699 (m) cm^{-1}.

HRMS (CI, M^+): calcd for $C_{25}H_{34}O_6$ 430.2350, found 430.2340.



117

(4*R*,5*S*,6*R*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocan-6-ol 117

Alcohol **117** was prepared according to the general procedure for the hydroboration of eight-membered cyclic silaketals B in 90% yield, as colorless oil.

$[\alpha]_D^{25}$ +0.46 (c = 1.09, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.30-7.07 (m, 5H), 6.85-6.73 (m, 4H), 4.60-4.55 (m, 2H), 4.39 (d, A of AB, J_{AB} = 12.1 Hz, 1H), 4.33 (d, B of AB, J_{AB} = 12.1 Hz, 1H),

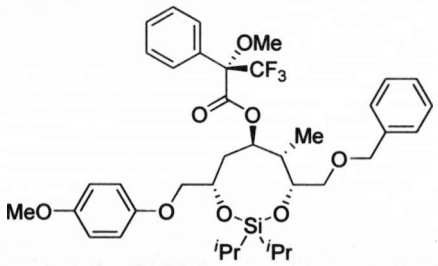
3.83 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 6.2 Hz, 1H), 3.76 (t, J = 6.7 Hz, 1H), 3.64 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 5.3 Hz, 1H), 3.49 (dd, A of ABX, J_{AB} = 9.4 Hz, J_{AX} = 6.1 Hz, 1H), 3.39 (dd, B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 6.4 Hz, 1H), 3.33 (s, 3H), 1.98-1.90 (m, 2H), 1.80 (ddd, J = 14.9, 8.0, 3.2 Hz, 1H), 1.34-1.03 (m, 18H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.59 (e), 153.69 (e), 139.01 (e), 128.63 (o), 127.91 (o), 115.86 (o), 115.06 (o), 74.19 (e), 73.54 (e), 73.48 (e), 70.61 (o), 69.58 (o), 67.20 (o), 55.25 (o), 42.46 (o), 38.55 (e), 17.90 (o), 17.83 (o), 17.80 (o), 17.74 (o), 12.34 (o), 11.94 (o), 11.11 (o).

IR (Neat): 3441 (br m), 3065 (m), 3031 (m), 2942 (s), 2866 (s), 1592 (w), 1506 (s), 1464 (s), 1233 (s), 1107 (m), 885 (m), 824 (m), 741 (m), 700 (m) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{28}H_{42}O_6Si$ 502.2745, found 502.2744.

HRMS (CI, MH^+): calcd for $C_{28}H_{43}O_6Si$ 503.2823, found 502.2823.



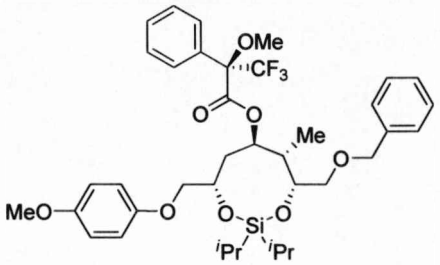
117a

(*S*)-((4*R*,5*S*,6*R*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocan-6-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 117a

(*S*)-MTPA ester **117a** was prepared according to the general procedure for the formation of Mosher ester derivatives in 99% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.75 (d, J = 7.8 Hz, 2H), 7.27-7.00 (m, 8H), 6.77-6.72 (m, 4H), 5.50 (br s, 1H), 4.50 (quintet, J = 5.8 Hz, 1H), 4.35-4.32 (m, 1H), 4.31 (d, A of AB, J_{AB} = 12.5 Hz, 1H), 4.26 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 3.84 (dd, A of

ABX, J_{AB} = 9.1 Hz, J_{AX} = 5.8 Hz, 1H), 3.60 (dd, B of ABX, J_{AB} = 9.0 Hz, J_{BX} = 6.4 Hz, 1H), 3.47 (s, 3H), 3.39 (dd, A of ABX, J_{AB} = 9.4 Hz, J_{AX} = 5.9 Hz, 1H), 3.33 (s, 3H), 3.24 (dd, B of ABX, J_{AB} = 9.3 Hz, J_{BX} = 6.2 Hz, 1H), 2.29 (quintet, J = 6.9 Hz, 1H), 2.06 (t, J = 5.0 Hz, 2H), 1.20-1.01 (m, 14H), 0.86 (d, J = 6.8 Hz, 3H).

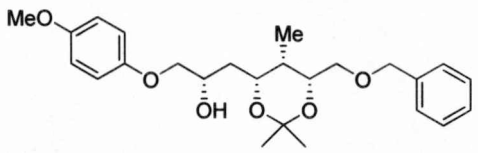


117b

(*R*)-((4*R*,5*S*,6*R*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocan-6-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 117b

(*R*)-MTPA ester **117b** was prepared according to the general procedure for the formation of Mosher ester derivatives in 99% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.74 (d, J = 7.6 Hz, 2H), 7.24-6.98 (m, 8H), 6.78-6.73 (m, 4H), 5.40 (s, 1H), 4.44 (t, J = 5.9 Hz, 1H), 4.32 (d, A of AB, J_{AB} = 12.1 Hz, 1H), 4.27 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 4.27-4.24 (m, 1H), 3.73 (dd, A of ABX, J_{AB} = 9.0 Hz, J_{AX} = 6.1 Hz, 1H), 3.50 (dd, A of ABX, J_{AB} = 9.1 Hz, J_{AX} = 6.0 Hz, 1H), 3.46 (s, 3H), 3.42 (dd, B of ABX, J_{AB} = 9.3 Hz, J_{BX} = 5.6 Hz, 1H), 3.33 (s, 3H), 3.30 (dd, B of ABX, J_{AB} = 9.1 Hz, J_{BX} = 6.9 Hz, 1H), 2.33 (quintet, J = 6.8 Hz, 1H), 2.07 (dd, J = 13.7, 7.4 Hz, 1H), 1.95 (dd, J = 15.1, 8.3 Hz, 1H), 1.18-1.00 (m, 14H), 0.94 (d, J = 7.0 Hz, 3H).



119

(*S*)-1-((4*R*,5*S*,6*R*)-6-(Benzyloxymethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)-3-(4-methoxyphenoxy)propan-2-ol 119

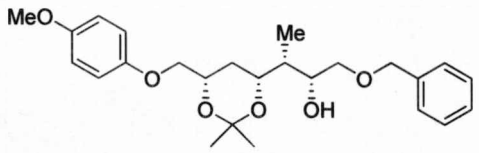
Acetonide **119** was prepared according to the general procedure for the formation of acetonides as a colorless oil as a major component of the mixture of regioisomers (1.2:1) in 72% yield over two steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 6.85-6.79 (m, 4H), 4.60 (d, A of AB, J_{AB} = 12.1 Hz, 1H), 4.47 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 4.25 (dt, J = 9.7, 2.5 Hz, 1H), 4.20 (dt, J = 6.2, 2.1 Hz, 1H), 4.16-4.12 (m, 1H), 3.90 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 6.0 Hz, 1H), 3.80 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 5.3 Hz, 1H), 3.75 (s, 3H), 3.48 (dd, A of ABX, J_{AB} = 9.6 Hz, J_{AX} = 6.4 Hz, 1H), 3.40 (dd, B of ABX, J_{AB} = 9.8 Hz, J_{BX} = 6.1 Hz, 1H), 3.37 (br s, 1H), 1.82 (dt, J = 14.3, 9.5 Hz, 1H), 1.66 (dt, J = 14.4, 2.7 Hz, 1H), 1.58-1.52 (m, 1H), 1.49 (s, 3H), 1.39 (s, 3H), 0.85 (d, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.97 (e), 152.85 (e), 138.10 (e), 128.38 (o), 127.73 (o), 127.69 (o), 115.42 (o), 114.65 (o), 99.24 (e), 73.44 (e), 73.29 (o), 72.28 (e), 72.16 (o), 70.70 (e), 69.96 (o), 55.71 (o), 36.17 (e), 33.21 (o), 29.88 (o), 19.79 (o), 5.23 (o).

IR (Neat): 3494 (br m), 3030 (w), 2990 (m), 2920 (m), 1592 (w), 1509 (s), 1456 (m), 1233 (s), 1107 (s), 1043 (s), 825 (m), 699 (m) cm^{-1}.

HRMS (EI, M^+): calcd for $C_{25}H_{34}O_6$ 430.2350, found 430.2347.



120

(2*R*,3*R*)-1-(Benzyloxy)-3-((4*R*,6*S*)-6-((4-methoxyphenoxy)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)butan-2-ol 120

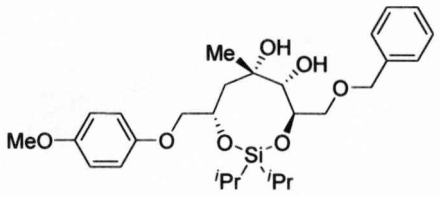
Acetonide **120** was prepared according to the general procedure for the formation of acetonides as a colorless oil as a minor component of the mixture of regioisomers (1.2:1) in 72% yield over two steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 6.84-6.78 (m, 4H), 4.54 (s, 2H), 4.21 (ddt, J = 11.1, 5.5, 2.6 Hz, 1H), 4.05 (dt, J = 11.8, 3.2 Hz, 1H), 4.02-3.99 (m, 1H), 3.96 (dd, A of ABX, J_{AB} = 9.6 Hz, J_{AX} = 5.5 Hz, 1H), 3.77 (dd, B of ABX, J_{AB} = 9.8 Hz, J_{BX} = 5.7 Hz, 1H), 3.74 (s, 3H), 3.56-3.43 (m, 2H), 2.73 (br s, 1H), 1.72-1.65 (m, 1H), 1.58 (dt, J = 12.7, 2.6 Hz, 1H), 1.52-1.46 (m, 1H), 1.44 (s, 3H), 1.38 (s, 3H), 0.94 (d, J = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.98 (e), 152.92 (e), 138.06 (e), 128.43 (o), 127.78 (o), 127.75 (o), 115.72 (o), 114.58 (o), 98.78 (e), 73.37 (e), 72.60 (o), 72.39 (e), 72.16 (e), 71.80 (o), 68.03 (o), 55.70 (o), 39.30 (o), 30.96 (e), 30.00 (o), 19.80 (o), 7.65 (o).

IR (Neat): 3502 (br w), 3030 (w), 2991 (m), 2923 (m), 1592 (w), 1509 (s), 1455 (m), 1233 (s), 1107 (m), 1043 (m), 825 (m), 700 (m) cm^{-1}.

HRMS (EI, M^+): calcd for $C_{25}H_{34}O_6$ 430.2350, found 430.2349.



123

(4*R*,5*R*,6*S*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocane-5,6-diol 123

General Procedure for the Dihydroxylation of Eight-Membered Cyclic Silaketals: Cyclic silaketal **99** (49.6 mg, 0.1 mmol) was dissolved in acetone-water (8:1) (1.0 ml) solution at room temperature under an atmosphere of argon. NMO (38.6 mg, 0.32 mmol) and OsO_4 (54.0 µl, 0.0043 mmol, 2.5 wt % solution in ^tBuOH) were added sequentially and the reaction allowed to stir for *ca.* 16 hours. The reaction was quenched with saturated aqueous Na_2SO_3 solution and partitioned between diethyl ether and saturated aqueous solution of Na_2SO_3. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0-20% ethyl acetate/hexanes) furnished the diol **123** (50.4 mg, 95 % yield) as a colorless oil.

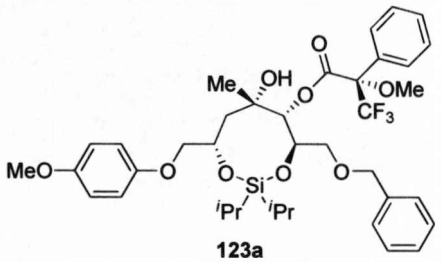
$[\alpha]_D^{26}$ -12.78 (c = 1.33, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.20-7.05 (m, 5H), 6.81-6.72 (m, 4H), 4.30 (dt, J = 8.8, 4.7 Hz, 1H), 4.30 (d, A of AB, J_{AB} = 11.9 Hz, 1H), 4.34-4.27 (m, 1H), 4.23 (d, B of AB, J_{AB} = 11.9 Hz, 1H), 3.89 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 6.3 Hz, 1H), 3.77 (dd, B of ABX, J_{AB} = 7.7 Hz, J_{BX} = 2.8 Hz, 1H), 3.69-3.59 (m, 3H), 3.55 (br s, 1H), 3.32 (s, 3H), 2.60 (br s, 1H), 2.34 (dd, A of ABX, J_{AB} = 15.2 Hz, J_{AX} = 8.4 Hz, 1H), 1.99 (dd, B of ABX, J_{AB} = 15.2 Hz, J_{BX} = 1.8 Hz, 1H), 1.45 (s, 3H), 1.16-1.01 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.61 (e), 153.50 (e), 138.25 (e), 128.71 (o), 127.97 (o), 115.88 (o), 115.03 (o), 79.04 (o), 74.64 (e), 73.87 (e), 73.70 (e), 73.57 (e), 71.62 (o), 69.23 (o), 55.26 (o), 43.25 (e), 26.62 (o), 17.81 (o), 17.75 (o), 17.70 (o), 17.62 (o), 13.59 (o), 13.10 (o).

IR (Neat): 3445 (br s), 3031 (m), 2920 (s), 1593 (w), 1505 (m), 1471 (m), 1238 (m), 887 (w), 823 (w), 741 (w), 698 (w) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{28}H_{42}O_7Si$ 518.2694, found 518.2694.

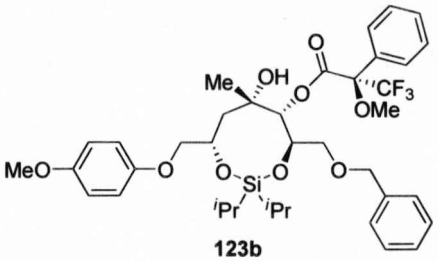


123a

(*S*)-((4*R*,5*R*,6*S*,8*S*)-4-(benzyloxymethyl)-6-hydroxy-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocan-5-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 123a

(*S*)-MTPA ester **123a** was prepared according to the general procedure for the formation of Mosher ester derivatives in 81% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.73 (d, J = 7.4 Hz, 2H), 7.31-7.00 (m, 8H), 6.77-6.72 (m, 4H), 5.58 (d, J = 7.0 Hz, 1H), 4.65-4.61 (m, 1H), 4.40 (d, A of AB, J_{AB} = 12.3 Hz, 1H), 4.36 (d, B of AB, J_{AB} = 12.3 Hz, 1H), 4.28 (q, J = 6.5 Hz, 1H), 3.81 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 6.1 Hz, 1H), 3.64 (dd, A of ABX, J_{AB} = 10.1 Hz, J_{AX} = 5.4 Hz, 1H), 3.60-3.40 (m, 2H), 3.38 (s, 3H), 3.32 (s, 3H), 2.21 (dd, J = 15.4, 8.8 Hz, 1H), 1.92-1.87 (m, 2H), 1.26 (s, 3H), 1.17-1.10 (m, 14H).

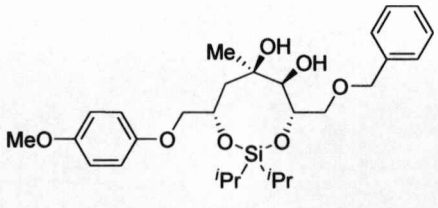


123b

(*R*)-((4*R*,5*R*,6*S*,8*S*)-4-(benzyloxymethyl)-6-hydroxy-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocan-5-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 123b

(*R*)-MTPA ester **123b** was prepared according to the general procedure for the formation of Mosher ester derivatives in 81% yield, as a colorless oil.

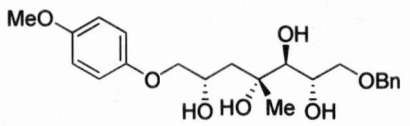
^{1}H NMR (400 MHz, C_6D_6): δ 7.82 (d, J = 7.6 Hz, 2H), 7.29-7.00 (m, 8H), 6.78-6.72 (m, 4H), 5.53 (d, J = 7.2 Hz, 1H), 4.39-4.36 (m, 1H), 4.32 (d, A of AB, J_{AB} = 12.3 Hz, 1H), 4.27 (d, B of AB, J_{AB} = 12.1 Hz, 1H), 4.28-4.24 (m, 1H), 3.83 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 6.1 Hz, 1H), 3.61-3.57 (m, 1H), 3.59 (s, 3H), 3.39 (dd, A of ABX, J_{AB} = 10.2 Hz, J_{AX} = 5.1 Hz, 1H), 3.34-3.31 (m, 1H), 3.32 (s, 3H), 2.30 (dd, J = 15.3, 9.1 Hz, 1H), 1.95-1.85 (m, 2H), 1.32 (s, 3H), 1.15-0.88 (m, 14H).



124

(4*S*,5*S*,6*R*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-6-methyl-1,3,2-dioxasilocane-5,6-diol 124

Diol **124** was prepared according to the general procedure for the dihydroxylation of eight-membered cyclic silaketals in 84 % yield, as a colorless oil.



125

(2*S*,3*S*,4*R*,6*S*)-1-(benzyloxy)-7-(4-methoxyphenoxy)-4-methylheptane-2,3,4,6-tetraol 125

General Procedure for the Deprotection of Eight-Membered Cyclic Silaketals: Crude cyclic silaketal **124** (0.054 g, 0.105 mmol) was dissolved in anhydrous tetrahydrofuran (6.6 mL) at room temperature under an atmosphere of argon. Reaction mixture was cooled to 0° C and solution of TBAF (0.42 mL, 0.42 mmol, 1M in THF) was added dropwise. The reaction was allowed to warm to room temperature and stir overnight. Solvent was removed *in vacuo* to afford a crude brown oil. Purification by flash chromatography (eluting with 30-70% ethyl acetate/hexanes) furnished the tetraol **125** (0.04g, 93 % yield) as a colorless oil.

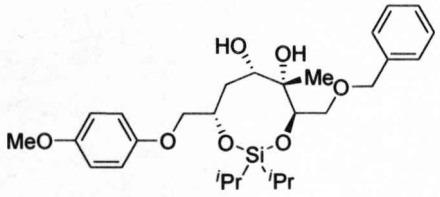
$[\alpha]_D^{20}$ +10.7 (c = 1.98, $CHCl_3$).

^{1}H NMR (500 MHz, C_6D_6): δ 7.20 (d, J = 7.0 Hz, 2H), 7.17-7.06 (m, 3H), 6.74 (s, 4H), 4.44-4.40 (m, 1H), 4.31 (d, A of AB, J_{AB}= 11.9 Hz, 1H), 4.27 (d, B of AB, J_{AB}= 11.9 Hz, 1H), 4.08 (ddd, J = 9.7, 6.4, 3.3 Hz, 1H), 3.81 (dd, A of ABX, J_{AB} = 9.5 Hz, J_{AX} = 3.5 Hz, 1H), 3.73 (d, J = 9.3Hz, 1H), 3.62 (dd, B of ABX, J_{AB} = 9.5 Hz, J_{BX} = 6.6 Hz, 1H), 3.56-3.49 (m, 2H), 3.35 (s, 3H), 1.79 (dd, A of ABX, J_{AB} = 14.7 Hz, J_{AX} = 10.0 Hz, 1H), 1.64-1.59 (m, 1H), 1.44 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6): δ 154.72 (e), 153.14 (e), 138.43 (e), 128.72 (o), 128.35 (o), 128.08 (o), 128.02 (o), 115.99 (o), 115.01 (o), 75.33 (e), 74.65 (o), 73.58 (e), 73.48 (e), 71.81 (o), 67.10 (o), 55.28 (o), 41.84 (e), 23.24 (o).

IR (Neat): 3390 (br w), 2922 (w), 2866 (w), 1592 (w), 1508 (s), 1455 (m), 1229 (s), 1041 (s), 825 (m), 745 (m), 699 (m) cm $^{-1}$.

HRMS (CI, M^+): We were unable to obtain a high resolution mass spectrum.



128

(4*R*,5*S*,6*S*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocane-5,6-diol 128

Diol **128** was prepared according to the general procedure for the dihydroxylation of eight-membered cyclic silaketals in 95 % yield, as colorless oil.

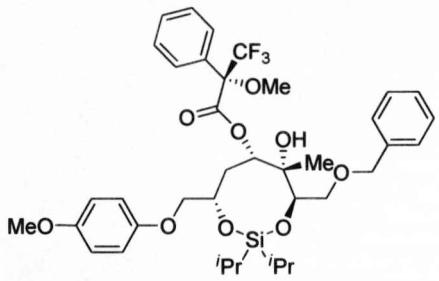
$[\alpha]_D^{27}$ -35.6 (c = 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ 7.16-7.04 (m, 5H), 6.81-6.73 (m, 4H), 4.36 (t, J = 6.6 Hz, 1H), 4.28 (dt, J = 10.5, 5.1 Hz, 1H), 4.18 (s, 2H), 3.84 (dd, A of ABX, J_{AB} = 9.4 Hz, J_{AX} = 5.9 Hz, 1H), 3.77 (br s, 1H), 3.72 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 7.2 Hz, 1H), 3.62 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 5.9 Hz, 1H), 3.57 (dd, B of ABX, J_{AB} = 9.1 Hz, J_{BX} = 6.2 Hz, 1H), 3.33 (s, 3H), 3.27 (s, 1H), 2.52 (br s, 1H), 2.42 (ddd, J = 16.1, 9.8, 6.8 Hz, 1H), 1.92 (d, J = 15.6 Hz, 1H), 1.42 (s, 3H), 1.12-0.94 (m, 14H).

^{13}C NMR (100 MHz, C_6D_6): δ 154.57 (e), 153.65 (e), 137.94 (e), 128.69 (o), 128.11 (o), 115.97 (o), 115.01 (o), 76.40 (o), 76.37 (e), 73.78 (e), 73.39 (e), 73.23 (o), 72.29 (e), 71.42 (o), 55.25 (o), 39.08 (e), 19.02 (o), 17.95 (o), 17.68 (o), 17.62 (o), 17.44 (o), 13.21 (o), 12.19 (o).

IR (Neat): 3479 (br s), 3032 (m), 2923 (s), 1592 (w), 1505 (s), 1456 (s), 1372 (s), 1234 (s), 1128 (s), 886 (m), 824 (m), 735 (m), 697 (m) cm $^{-1}$.

HRMS (CI, M^+): calcd for $C_{28}H_{42}O_7Si$ 518.2694, found 518.2690.

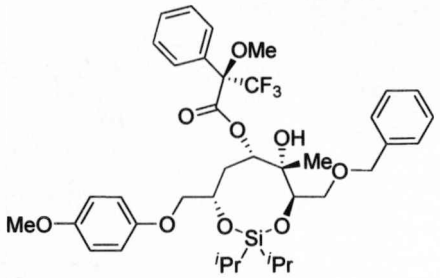


128a

(*S*)-((4*R*,5*S*,6*S*,8*S*)-4-(benzyloxymethyl)-5-hydroxy-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocan-6-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate128a

(*S*)-MTPA ester **128a** was prepared according to the general procedure for the formation of Mosher ester derivatives in 91% yield, as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6): δ 7.75 (d, J = 7.8 Hz, 2H), 7.17-6.98 (m, 8H), 6.80-6.72 (m, 4H), 5.49 (d, J = 5.9 Hz, 1H), 4.85 (dt, J = 9.3, 6.2 Hz, 1H), 4.39 (t, J = 6.1 Hz, 1H), 4.20 (d, A of AB, J_{AB} = 12.3 Hz, 1H), 4.17 (d, B of AB, J_{AB} = 13.3 Hz, 1H), 3.88 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.3 Hz, 1H), 3.71 (dd, A of ABX, J_{AB} = 9.2 Hz, J_{AX} = 5.9 Hz, 1H), 3.63 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 7.0 Hz, 1H), 3.54 (dd, B of ABX, J_{AB} = 9.2 Hz, J_{BX} = 6.5 Hz, 1H), 3.45 (s, 3H), 3.32 (s, 3H), 2.63-2.52 (m, 2H), 1.96 (d, J = 16.4 Hz, 1H), 1.31 (s, 3H), 1.20-1.08 (m, 14H).

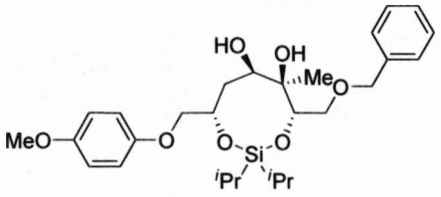


128b

(*R*)-((4*R*,5*S*,6*S*,8*S*)-4-(benzyloxymethyl)-5-hydroxy-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocan-6-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 128b

(*R*)-MTPA ester **128b** was prepared according to the general procedure for the formation of Mosher ester derivatives in 94% yield, as a colorless oil.

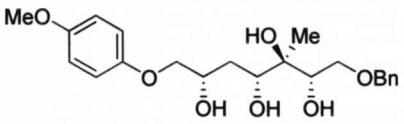
^{1}H NMR (400 MHz, C_6D_6): δ 7.75 (d, J = 7.6 Hz, 2H), 7.13-6.99 (m, 8H), 6.77-6.71 (m, 4H), 5.45 (d, J = 6.1 Hz, 1H), 4.84 (dt, J = 9.7, 5.9 Hz, 1H), 4.41 (t, J = 6.1 Hz, 1H), 4.18 (d, A of AB, J_{AB} = 11.9 Hz, 1H), 4.14 (d, B of AB, J_{AB} = 11.9 Hz, 1H), 3.88 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 5.2 Hz, 1H), 3.67 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 5.8 Hz, 1H), 3.64 (dd, B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 6.6 Hz, 1H), 3.53-3.50 (m, 1H), 3.50 (s, 3H), 3.32 (s, 3H), 2.69 (ddd, J = 16.4, 10.0, 6.4 Hz, 1H), 2.58 (s, 1H), 2.07 (d, J = 16.2 Hz, 1H), 1.20 (s, 3H), 1.16-1.08 (m, 14H).



129

(4*S*,5*R*,6*R*,8*S*)-4-(Benzyloxymethyl)-2,2-diisopropyl-8-((4-methoxyphenoxy)methyl)-5-methyl-1,3,2-dioxasilocane-5,6-diol 129

Diol **129** was prepared according to the general procedure for the dihydroxylation of eight-membered cyclic silaketals as a mixture of products in 84 % yield, as a colorless oil.



130

(2*S*,3*R*,4*R*,6*S*)-1-(benzyloxy)-7-(4-methoxyphenoxy)-3-methylheptane-2,3,4,6-tetraol 130

Tetraol **130** was prepared according to the general procedure for the deprotection of eight-membered cyclic silaketals in 99 % yield, as a colorless oil.

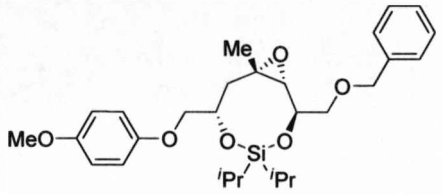
$[\alpha]_D^{20}$ +7.0 (c = 2.05, $CHCl_3$).

^{1}H NMR (500 MHz, C_6D_6): δ 7.18-7.12 (m, 4H), 7.08-7.03 (m, 1H), 6.74 (s, 4H), 4.24 (d, A of AB, J_{AB}= 11.9 Hz, 1H), 4.21 (d, B of AB, J_{AB}= 11.9 Hz, 1H), 4.07-4.02 (m, 2H), 3.96 (dd, J= 9.9, 1.4 Hz, 1H), 3.77 (dd, A of ABX, J_{AB} = 9.6 Hz, J_{AX} = 4.5 Hz, 1H), 3.69 (dd, B of ABX, J_{AB} = 9.6 Hz, J_{BX} = 6.2 Hz, 1H), 3.59 (dd, A of ABX, J_{AB} = 9.3 Hz, J_{AX} = 7.2 Hz, 1H), 3.53 (dd, B of ABX, J_{AB} = 9.4 Hz, J_{BX} = 3.9 Hz, 1H), 3.34 (s, 3H), 2.02 (dd, A of ABX, J_{AB} = 12.3 Hz, J_{AX} = 1.9 Hz, 1H), 1.65 (dt, J = 12.7, 10.1 Hz, 1H), 1.37 (s, 1H), 1.35 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6): δ 154.73 (e), 153.16 (e), 138.15 (e), 128.75 (o), 128.35 (o), 128.11 (o), 115.98 (o), 115.01 (o), 77.23 (o), 75.05 (e), 74.33 (o), 73.69 (e), 73.13 (e), 71.91 (o), 71.80 (e), 55.28 (o), 33.28 (e), 18.00 (o).

IR (Neat): 3415 (br w), 2928 (w), 2871 (w), 2830 (w), 1592 (w), 1508 (s), 1455 (m), 1229 (s), 1039 (s), 824 (m), 745 (m), 699 (m) cm $^{-1}$.

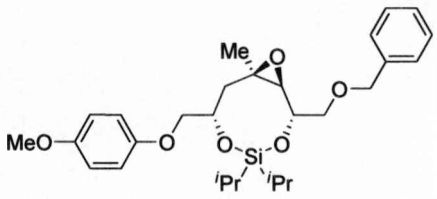
HRMS (CI, M^+): We were unable to obtain a high resolution mass spectrum.



131

(1*R*,2*R*,6*S*,8*S*)-2-(Benzyloxymethyl)-4,4-diisopropyl-6-((4-methoxyphenoxy)methyl)-8-methyl-3,5,9-trioxa-4-silabicyclo[6.1.0]nonane 131

General Procedure for the Epoxidation of Eight-Membered Cyclic Silaketals: Cyclic silaketal **99** (48.4 mg, 0.1 mmol) was dissolved in anhydrous dichloromethane (2.0 ml) at room temperature under an atmosphere of argon. Solid sodium bicarbonate was added (16.8 mg, 0.2 mmol) and suspension was cooled to 0 °C. *m*-CPBA (37.0 mg, 0.15 mmol) was added over period of *ca.* 2 hours *via* solid addition funnel. The reaction was allowed to warm to room temperature and stirred overnight (t.l.c. control). Reaction mixture was filtered through alumina pad (eluting with 30% ethyl acetate/hexanes) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0-10% ethyl acetate/hexanes) furnished the epoxide **131** (93 % yield) as a colorless oil.



132

(1*S*,2*S*,6*S*,8*R*)-2-(Benzyloxymethyl)-4,4-diisopropyl-6-((4-methoxyphenoxy)methyl)-8-methyl-3,5,9-trioxa-4-silabicyclo[6.1.0]nonane 132

Experimental Procedure: Cyclic silaketal **100** (24 mg, 0.05 mmol) was dissolved in acetone (0.6 ml) at room temperature under an atmospher of argon. Solid $NaHCO_3$ (51 mg, 0.61 mmol) was added in a single portion followed by addition of water (0.36 ml). Oxone® (0.118 g, 0.35 mmol) was added in the single portion and suspension allowed to stir for *ca.* 4 hours at ambient temperature. The reaction mixture was quenched with water and partitioned between water and ether. Combined organic phase was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford a yellow crude oil. Purification by flash chromatography (eluting with 5-20% ethyl acetate/hexanes) furnished the epoxide **132** (57 % yield) as a colorless oil.

$[\alpha]_D^{20}$ -40.0 (c = 1.43, $CHCl_3$).

^{1}H NMR (500 MHz, C_6D_6): δ 7.36 (d, J = 7.6 Hz, 2H), 7.21-7.08 (m, 3H), 6.80-6.75 (m, 4H), 4.42 (d, A of AB, J_{AB} = 12.4 Hz, 1H),), 4.42 (d, B of AB, J_{AB} = 12.4 Hz, 1H), 4.30 (dq, J = 6.7, 2.3 Hz, 1H), 3.89 (dd, A of AB, J_{AB} = 9.3 Hz, J_{AX} = 7.0 Hz, 1H), 3.85 (ddd, J = 9.1, 6.3, 2.8 Hz, 1H), 3.71 (dd, A of AB, J_{AB} = 10.2 Hz, J_{AX} = 2.8 Hz, 1H), 3.65-3.62 (m, 2H), 3.33 (s, 3H), 2.82 (d, J = 9.1 Hz, 1H), 2.14 (dd, J = 15.1, 2.4 Hz, 1H), 1.87 (dd, J = 15.1, 8.1 Hz, 1H), 1.28 (s, 3H), 1.20-1.13 (m, 9H), 1.10-1.01 (m, 5H).

^{13}C NMR (125 MHz, C_6D_6): δ 154.72 (e), 153.34 (e), 139.25 (e), 128.56 (o), 127.63 (o), 127.62 (o), 115.87 (o), 115.06 (o), 73.74 (e), 73.50 (e), 72.52 (e), 72.30 (o), 68.11 (o), 62.34 (o), 57.99 (e), 55.24 (o), 36.42 (e), 25.26 (o), 17.67 (o), 17.62 (o), 17.58 (o), 17.51 (o), 12.43 (o), 11.61 (o).

IR (Neat): 2928 (m), 2865 (m), 1507 (s), 1463 (m), 1378 (w), 1230 (s), 1091 (s), 1053 (s), 994 (m), 968 (m), 884 (m), 823 (m) 746 (s), 698 (s) cm $^{-1}$.

HRMS (CI, M^+): We were unable to obtain a high resolution mass spectrum.

2.6 References

[1] (a) Holton, R. A.; Somoza, C.; Kim, H. -B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598. (b) Nicolaou, K. C.; Ueno, H.; Liu, J. -J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653-659. (c) Borrelly, S.; Paquette, L. *J. Am. Chem. Soc.* **1996**, *118*, 727-740. (d) Kishuku, H.; Shindo, M.; Shishido, K. *Chem. Commun.* **2003**, 350-351. (e) Pilli, R. A.; Victor, M. M.; de Meijere, A. *J. Org. Chem.* **2000**, *65*, 5910-5916. (f) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029-2032. (g) Hoarau, C.; Couture A.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2002**, *67*, 5846-5849.(h) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137-2319.

[2] Ruzicka, L.; Stoll, M.; Schinz, *H. Helv. Chim. Acta* **1926**, *9*, 249-264.

[3] Ziegler, K.; Eberle, H.; Ohlinger, H. *Liebigs Ann. Chem.* **1933**, *504*, 94-130.

[4] For a review on metal-mediated ring constructions see: Yet, L. *Chem. Rev.* **2000**, *100*, 2963-3007.

[5] For a review on eight-membered ring carbocycles construction see: (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757-5821. (b) Mehta, G.; Singh, *V. Chem. Rev.* **1999**, *99*, 881-930.

[6] For a review on medium-sized ring expansions see: (a) Roxburg, C. J. *Tetrahedron* **1993**, *49*, 10749-10784. (b) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777-2849.

[7] For a review on medium-ring nitrogen heterocycles see: Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131-9166.

[8] For a review on free radical in the synthesis of medium-sized rings see: Yet, L. *Tetrahedron* **1999**, *55*, 9349-9403.

[9] For a review on seven-membered oxacycles see: Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631-12670.

[10] (a) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95-102. (b) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117-3125 and pertinent references therein.

[11] Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311-365.

[12] Mandolini, L *Adv. Phys. Org. Chem.* **1986**, *22*, 1-111.

[13] Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183-278.

[14] Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701-704.

[15] Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

[16] Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981-3996.

[17] Schreiber, S. L.; Smith, D. B.; Schulte, G. *J. Org. Chem.* **1989**, *54*, 5994-5996.

[18] Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5280-5281.

[19] Lyttle, M. H.; Streitwieser, A.; Miller, M. J. *J. Org. Chem.* **1989**, *54*, 2331-2335.

[20] Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53-58.

[21] Mehta, G.; Rao, K. W. *J. Am. Chem. Soc.* **1986**, *108*, 8015-8021.

[22] Aggarwal, V. K.; Humphries, P. S.; Fenwick, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1985-1986.

[23] Berkowitz, W. F.; Wu, Y. *J. Org. Chem.* **1997**, *62*, 1536-1539.

[24] Allinger, N. L.; Tribble, M. T.; Miller, M. A. *Tetrahedron* **1972**, *28*, 1173-1190.

[25] Cain, C. M.; Cousins, R. P. C.; Coubarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523-544.

[26] Evans, P. A.; Collins, I.; Hamley, P.; Holmes, A. B.; Raithby, P. R. *Tetrahedron Lett.* **1992**, *33*, 6859-6862.

[27] Anderson, E. A.; Holmes, A. B.; Collins, I. *Tetrahedron Lett.* **2000**, *41*, 117-121.

[28] Davis, F. A.; Chen, B. -C. *Chem. Rev.* **1992**, *92*, 919-934.

[29] Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768-6769.

[30] For preparation of unsymmetrical silaketals using dialkyldichlorosilane method see: (a) Chu, H. K.; Johnson, M. D.; Frye, C. L. *J. Organomet. Chem.* **1984**, *271*, 327-336. (b) Bradford, C. L.; Fleming, S. A.; Ward, S. C. *Tetrahedron Lett.* **1995**, *36*, 4189-4192. (c) Hutchinson, J. H.; Daynard, T. S.; Gillard, J. W. *Tetrahedron Lett.* **1991**, *32*, 573-576. (d) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H. -R. *J. Am. Chem. Soc.* **2003**, *125*, 14702-14703. (e) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734-1737.

[31] (a) Gillard, J. W.; Fortin, R.; Morton, H. E.; Yoakim, C.; Quesnelle, C. A.; Daignault, S.; Guindon, Y. *J. Org. Chem.* **1988**, *53*, 2602-2608. (b) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstain, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145-1148.

[32] Colombier, C.; Skrydstrup, T.; Beau, J. M. *Tetrahedron Lett.* **1994**, *35*, 8167-8170.

[33] Petit, M.; Chouraqui, G.; Aubert, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 2037-2040.

[34] Lipshutz, B. H.; Gross, T. *J. Org. Chem.* **1995**, *60*, 3572-3573.

[35] (a) Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z. -m.; Zhao, G. -x; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409-10410. (b) Rupprecht, J. K.; Hui, Y. -H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237-278. (c) Hui, Y. -H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. L.; Chang, C. J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463-477. (d) Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870-871.

[36] Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734-1737.

[37] Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410-6424.

[38] Leyes, A. E.; Poulter, C. D. *Org. Lett.* **1999**, *1*, 1067-1070.

[39] Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625-1627.

[40] Gauthier, D. R., Jr.; Szumigala, R. H., Jr.; Armstrong, J. D., III.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 7011-7014.

[41] David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643-663.

[42] Boons, G. -J.; Castle, G. H.; Clase, J. A.; Grice, P.; Ley, S. V.; Pinel, C. *Synlett* **1993**, 913-914.

[43] (a) Marsh, A.; Carlisle, S. J.; Smith, S. C. *Tetrahedron Lett.* **2001**, *42*, 493-496. (b) Moore, J. D.; Herpel, R. H.; Lichtsinn, J. R.; Flynn, D. L.; Hanson, P. R. *Org. Lett.* **2003**, *5*, 105-107 and pertinent references therein.

[44] Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017-3020.

[45] Evans, P. A.; Lawler, M. J. *Unpublished Results.*

[46] Araki, T.; Ternuma, D.; Kato, F.; Kaneda, H.; Iino, A. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 644-646.

[47] Soderquist, J. A.; Negron, A. *Tetrahedron Lett.* **1998**, *39*, 9397-9400.

[48] Brook, A. G.; Kuchera, H. W.; MacRae, D. M. *Can. J. Chem.* **1970**, *48*, 818-823.

[49] The crystallographic details of X-ray analysis for ester **106** *and* **108** are described in the apendix B.

[50] The details of Mosher ester analysis for alcohols **105**, **107**, **114**, **117** can be found in appendix A.

[51] (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, 95, 512-519. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-2147. (d) Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17-117. (e) Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256-270.

[52] Evans, P. A.; Lawler, M. J.; Cusak, A. *Unpublished Results.*

[53] (a) Brown, H. C. *Boranes in Organic Chemistry*; Cornell Univ. Press: Ithaca, N. Y., **1972**. (b) Brown, H. C. *Organic Syntheses via Boranes*; Wiley-Interscience, New York, N. Y., **1975**. (c) Brown, H. C. *Hydroboration*; Benjamin W. A. Inc.: New York, **1962**. (d) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, U.K., **1988**.

[54] Negishi, E.; Brown, H. C. *Synthesis* **1974**, 77-89.

[55] Seco, J. M.; Quio, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17-118.

[56] (a) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511-3515. (b) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948. (c) Rychnovsky, S. D.; Richardson, T. I.; Rogers, B. N. *J. Org. Chem.* **1997**, *62*, 2925-2934.

[57] (a) Hofmann, K. A. *Chem. Ber.* **1912**, *45*, 3329-3336. (b) Hofmann, K. A.; Ehrhart, O.; Schneider, O. *Chem. Ber.* **1913**, *46*, 1657-1668.

[58] Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75-96.

[59] (a) Schröder, M. *Chem. Rev.* **1980**, *80*, 187-213. (b) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317-1349. (c) Kolb, H. C.; VanNiuewenhze, M. C.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. (d) Donohoe, T. J. *Synlett* **2002**, 1223-1232. and pertinent references therein.

[60] Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99-133.

[61] Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263-4265.

[62] (a) Schneider, W. P.; McIntosh, A. V. *U. S. Patent 2,769,824* Nov. 6, **1956**. (b) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973-1976.

[63] The details of Mosher ester analysis for diols **124** and **129** can be found in appendix A.

[64] (a) Ferraz, H. M. C.; Muzzi, R. M.; Viera, T. de O.; Viertler, H. *Tetrahedron Lett.* **2000**, *41*, 5021-5023. (b) de Sousa, S. E.; O'Brien, P.; Pilgram, C. D.; Roder, D.; Towers, T. D. *Tetrahedron Lett.* **1999**, *40*, 391-392. (c) Yang, D.; Jiao, G. -S.; Yip, Y. -C.; Wong, M. -K. *J. Org. Chem.* **1999**, *64*, 1635-1639. (d) Denmark, S. E.; Wu, Z. *J. Org. Chem.* **1997**, *62*, 8964-8965. (e) Denmark, S. E.; Forbes, D. C.; Hays, D.

S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391-1407. (f) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288-8289.

[65] Kamal, A.; Sandbhor, M.; Shaik, A. A.; Malik, M. S. *Tetrahedron: Asymmetry* **2005**, *16*, 1855-1859.

[66] Jiang, B.; Chen, Z. -L.; Shen, M.; Wang, Z. -M.; Shi, M. *Chin. J. Chem.* **2003**, *21*, 789-792.

[67] Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264-10266.

[68] Ghosh, A. K.; Leshchenko, S.; Noetzel, M. *J. Org. Chem.* **2004**, *69*, 7822-7829.

[69] Huang, J. -M.; Xu, K. -C.; Loh, T. -P. *Synthesis* **2003**, 755-764.

Chapter 3

Approach to the Asymmetric Synthesis of C1-C30 Fragment of Amphidinol 3

3.1 Introduction

3.1.1 Amphidinol 3

Marine dinoflagellates are a valuable source of biologically significant and structurally distinctive secondary metabolites.[1] The amphidinols were isolated from the dinoflagellate *Amphidinium Klebsii* and many members of this family display potent antifungal and hemolytic activity.[2] Eight congeners bearing a significant structural resemblance have been reported to date,[2a,2b,3] in which amphidinol 3 **1** has emerged as the most potent antifungal agent of its class (*MEC* = 6.0 μg/disc against *Aspergillus niger*). However, despite this activity it also displays a potent toxicity against human erythrocytes (EC_{50} = 0.4 μM) which significantly limits its application for the medicinal purposes.[4] The recent studies implied that activity of amphidinol 3, **1** is mainly due to the formation of pores/lesions in the lipid bilayer,

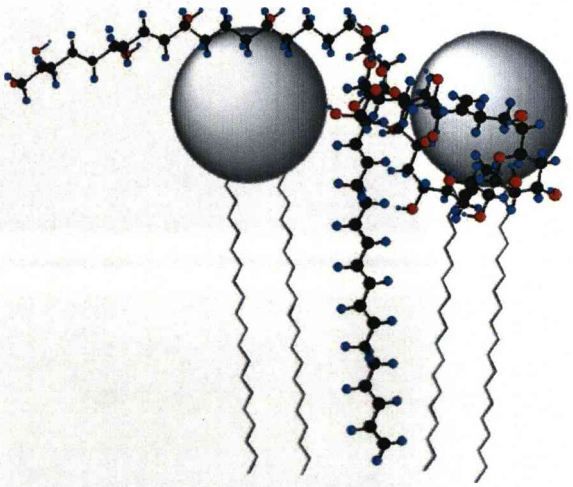


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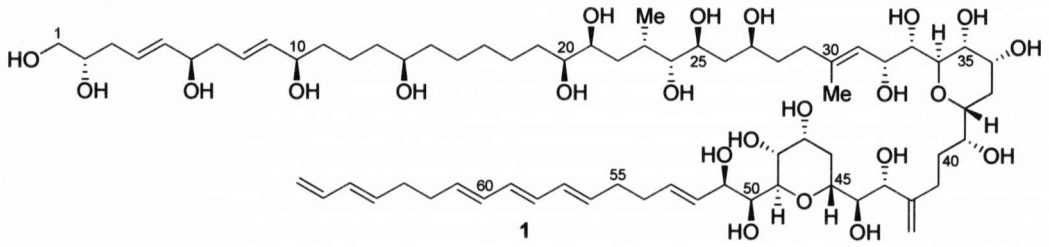
Figure 3.1 *Hypothetical Model of Insertion in to the Lipid Bilayer*

which strongly affect the membrane permeabilizing activity (Figure 3.1).[3,5] The pores/lesions formed by amphidinol 3 are supposed to induce the passage of the small molecules which is presumably responsible for its antifungal activity. Amphidinol 3, **1** consists of a hydrophobic polyene unit and the hydrophilic region comprising an acyclic polyol unit and densely functionalized tetrahydropyran rings (Figure 3.2). The absolute configuration of this metabolite was elucidated *via* an extensive NMR analysis based on the JBCA method,[6] modified Mosher method[7] and



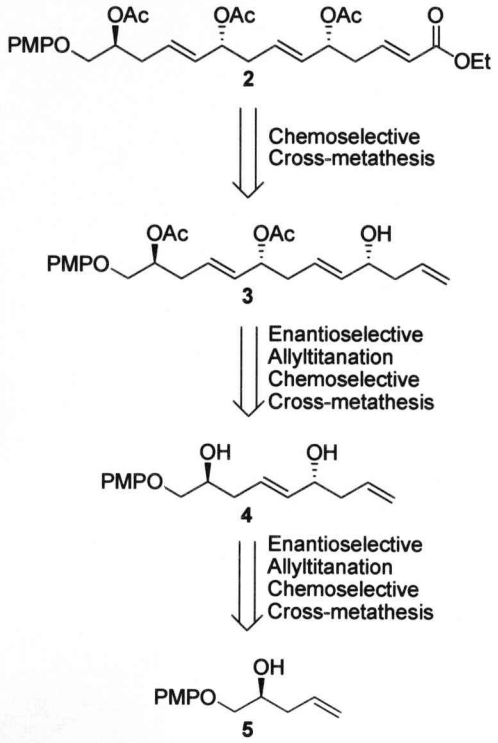
Amphidinol 3

Figure 3.2 *Amphidinol 3*

HPLC analysis of the degradation products.[8] The structural complexity of amphidinol 3 has captured the imagination of the synthetic community and a number of synthetic studies have been reported by Cossy,[9] Roush,[10] Rychnovsky,[11] Paquette,[12] Markó[13]and Murata[14] groups. Although, the total synthesis of amphidinol 3 has not been disclosed, Rychnovsky, Paquette and Roush independently provided the routes toward the advanced synthetic intermediates. Our study will primarily focus on the construction of C1-C30 fragment of amphidinol 3, therefore only approaches describing the syntheses of the sequence of allylic and homoallylic 1,5-diols will be discussed in the following section.[9a,10a,11c,12a,14]

3.1.2 Cossy's Approach to the C1-C14 Fragment of Amphidinol 3

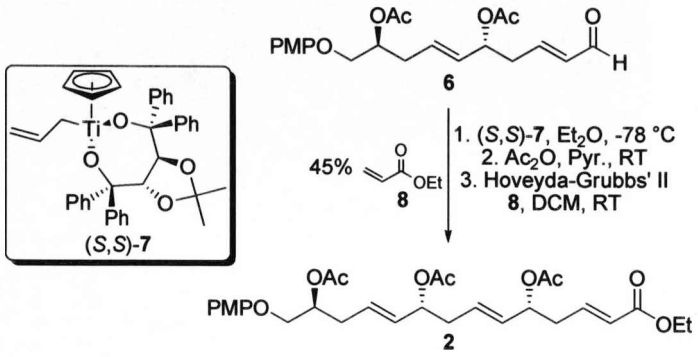
In 2001, Cossy and BouzBouz reported a diastereoselective synthesis of 1,5-diols which resulted in expeditious construction of C1-C14 fragment of amphidinol 3.[9a] Their synthesis is outlined retrosynthetically in Scheme 3.1. The final fragment **2** was prepared from intermediate **3** *via* acetylation and subsequent cross-metathesis with ethyl acrylate. The triol **3** was obtained from the diol **4** through cross-metathe-



Scheme 3.1 *Retrosynthetic Analysis of Cossy's Synthesis*

sis and subsequent allyltitanation. The installation of the final stereogenic center in triol **3** was accomplished with high diastereoselectivity (*ds* > 95:5). The 1,5-*anti*-diol **4** was readily available from homoallylic alcohol **5** using the same iterative sequence. All cross-metathesis reactions of homoallylic acetates with acrolein or ethyl acrylate provided the products favoring *E*-olefin geometry with selectivities >50:1. The homoallylic alcohol **5** was readily available from the commercially available (*R*)-glycidol in 2 steps.[9a] This synthesis highlighted the application of

iterative sequence of enantioselective allyltitanations[15,16] and chemoselective cross-metathesis reaction[17] of homoallylic acetates (Eq. 3.1). The chemoselective cross-metathesis presumably occurs due to steric protection of the allylic double bond. Cossy and BouzBouz completed the C1-C14 fragment of amphidinol 3 in seven steps starting from homoallylic alcohol **5** with an overall yield of 17.5%.

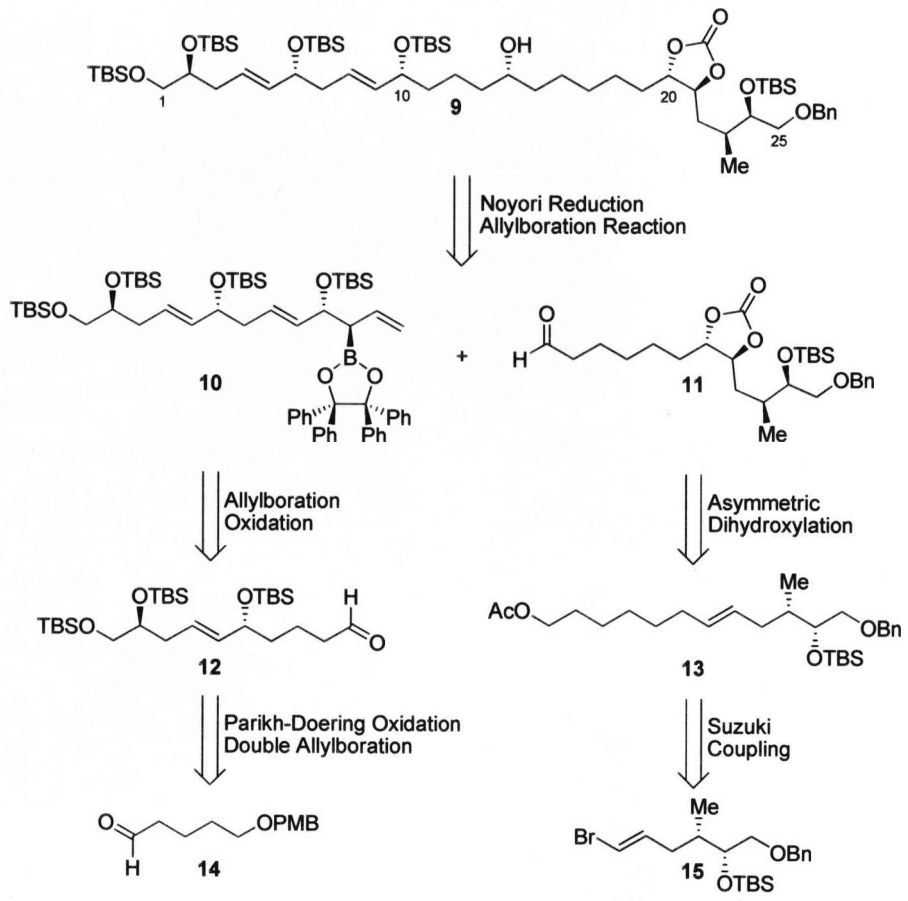


(3.1)

3.1.3 Roush's Approach to the C1-C25 Fragment of Amphidinol 3

Prior studies by Roush and Flamme reported the stereoselective synthesis of C1-C25 fragment of amphidinol 3.[10a] The retrosynthetic analysis of their synthesis is outlined in Scheme 3.2. The fragment **9** was constructed *via* stereoselective addition of β-hydroxy-substituted allylborane reagent **10** to the aldehyde **11** thereby setting the stage for a highly chemoselective hydroxyl-directed reduction of the C11-C12 olefin.[19,20] The allylboronate **10** was prepared stereoselectivly from the aldehyde **12** through the enol ether formation[21] and concomitant oxidation to α,β-unsaturated aldehyde,[22] followed by allylboration reaction. The aldehyde **12** is easily accessible from the simple aldehyde **14** *via* one-pot double allylboration sequence, which installed two stereogenic centers with high enantioselectivity (94% *ee*). The diol precursor was elaborated into the aldehyde **12** by standard protection/deprotection sequence and subsequent Parikh-Doering oxidation.[23] Sharpless asymmetric

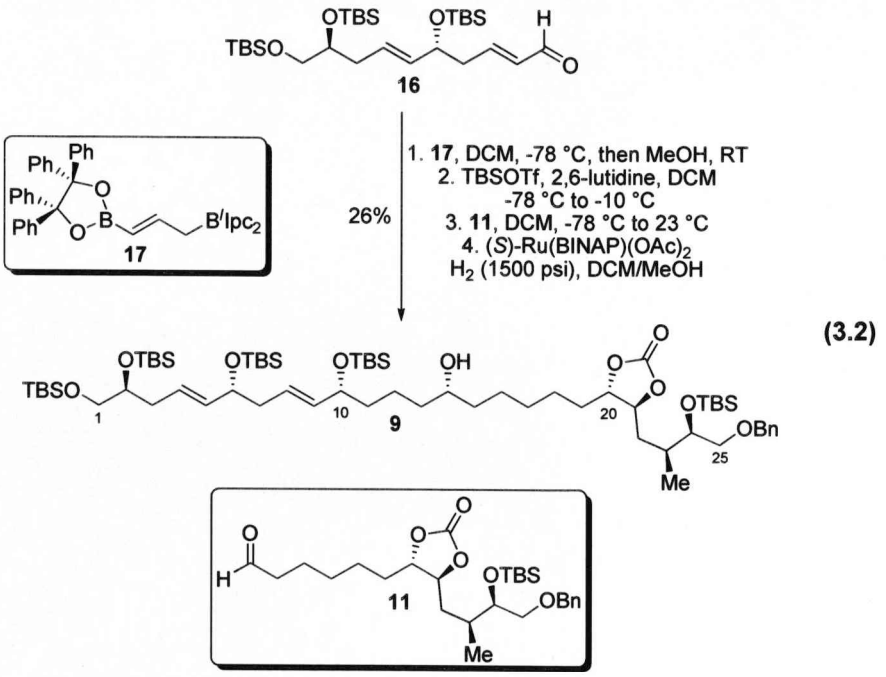
dihydroxylation[24] of the olefin **13** furnished the 1,2-diol as a mixture of stereoisomers with *ds* = 15:1. Protection with triphosgene gave the cyclic carbonate,



Scheme 3.2 *Retrosynthetic Analysis of Roush's Synthesis*

which allowed the simple chromatographic separation of the minor stereoisomer. The access to the aldehyde **11** was secured *via* the primary acetate deprotection and subsequent oxidation. The olefin **13** was efficiently constructed from vinylbromide **15** and corresponding dialkylborane using the palladium-mediated Suzuki cross-coupling reaction.

The synthesis highlighted the application of double allylboration reaction methodology in the highly selective construction of 1,5-diol units (Eq. 3.2).[18] The allylboration reaction, which was recently developed in this group for the synthesis of secondary 1,5-diols appeared to be an ideal transformation for the construction of

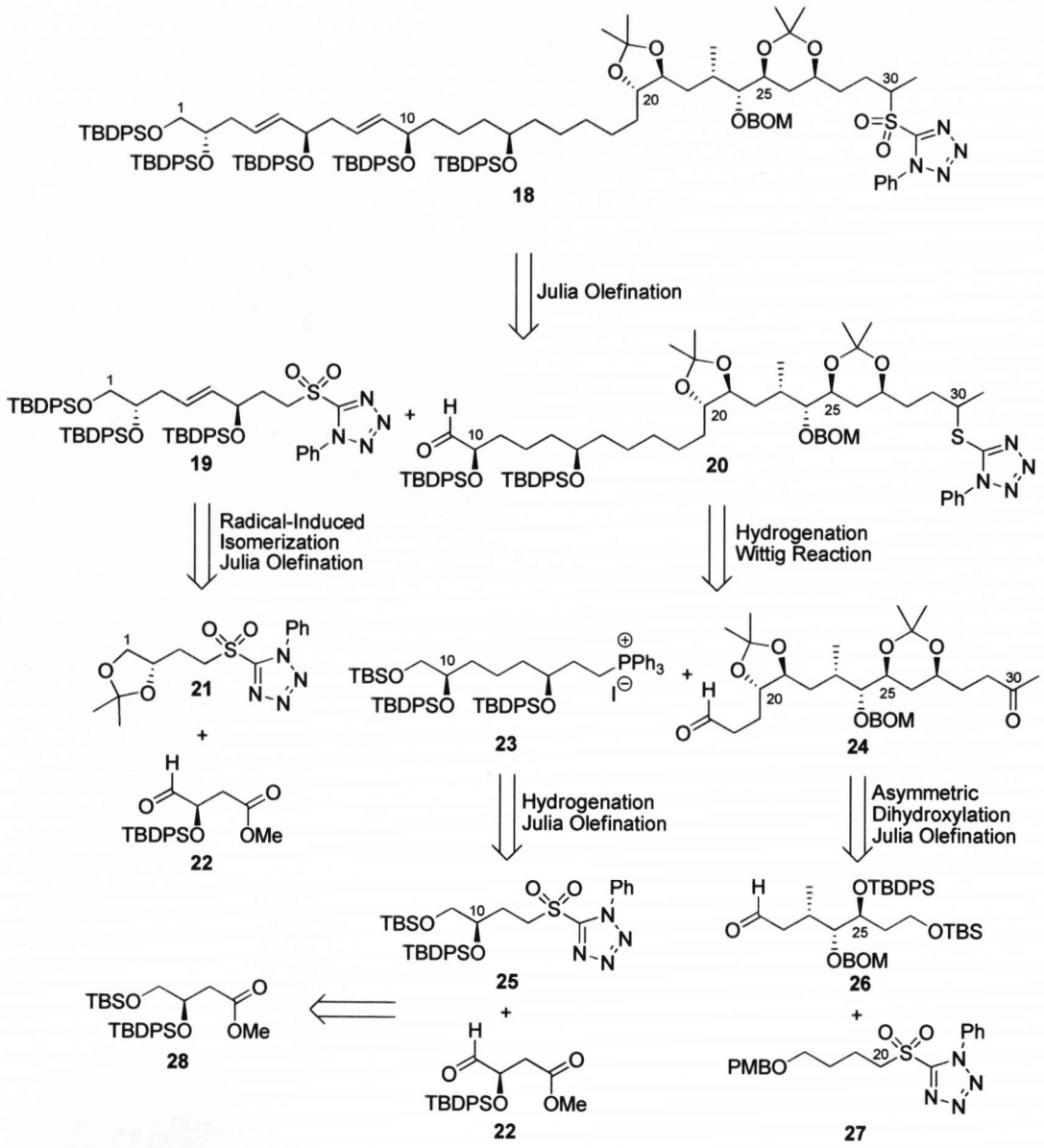


(3.2)

the polyoxygenated fragment of amphidinol 3. In addition, this method enables the reaction of organoborane **17** prepared *in situ* with the appropriate carbonyl in the iterative manner, which allows a rapid assembly of complex polyol fragments. The synthesis of the C1-C25 fragment of the amphidinol 3 was accomplished in 11 steps of the longest linear sequence with the overall yield of 18.8%.

3.1.4 Paquette's Approach to the C1-C30 Fragment of Amphidinol 3

Later studies by Paquette and Chang reported a stereoselective synthesis of C1-C30 polyol domain in the protected form.[12a] The synthesis incorporated 10 out of the 25 stereogenic centers through the asymmetric pathway that is based on the efficient union of three independently prepared subunits. This highly convergent route highlighted a repeated application of Kocienski modification[27] of Julia olefination reaction.[28] The retrosynthetic analysis of Paquette's synthesis is outlined in the Scheme 3.3. Julia-Kocienski cross-coupling furnished the target molecule **18** as *E/Z* mixture of stereoisomers at C8-C9 position favoring the *E*-stereoismer with

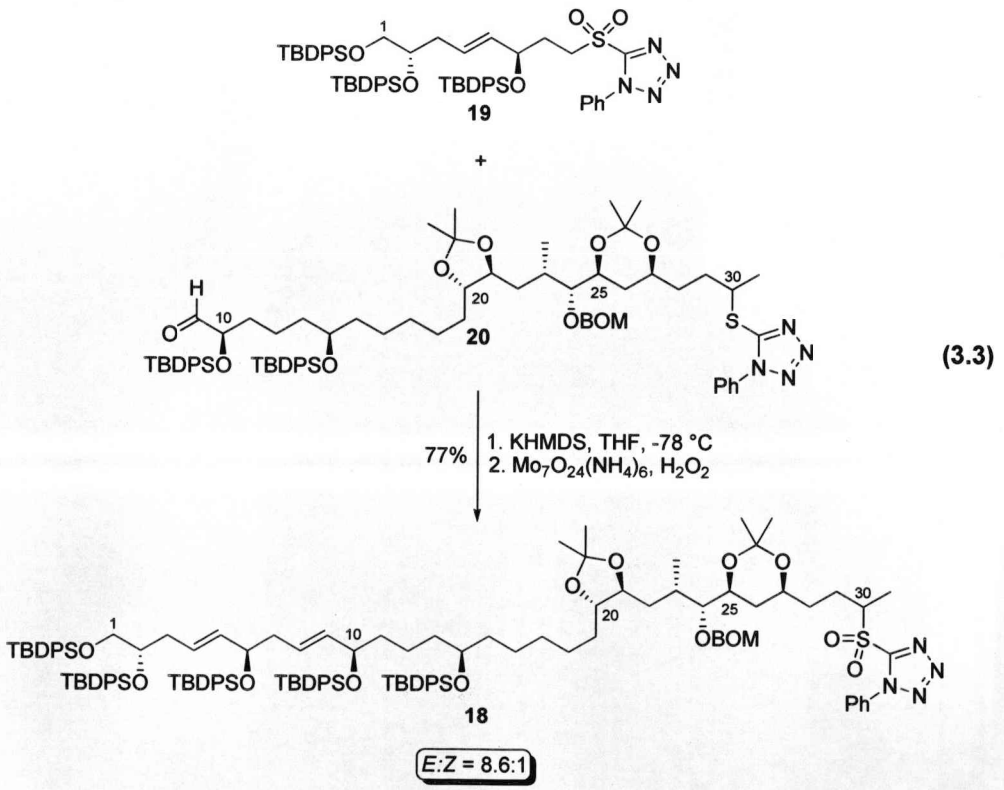


Scheme 3.3 *Retrosynthetic Analysis of Paquette's Synthesis*

the ratio of 8.6:1. The carbon backbone of the corresponding sulfone **19** was prepared *via* Julia-Kocienski cross-coupling using the fragments **21** and **22**. The standard reaction conditions furnished the corresponding olefin with poor stereo-control of 3:1 favoring the *E*-stereoisomer. The exposure of the olefin mixture to the radical-induced isomerization involving the tiophenol and AIBN improved the *E/Z* ratio (12:1) through the formation of thermodynamically more stable product.[12a,29]

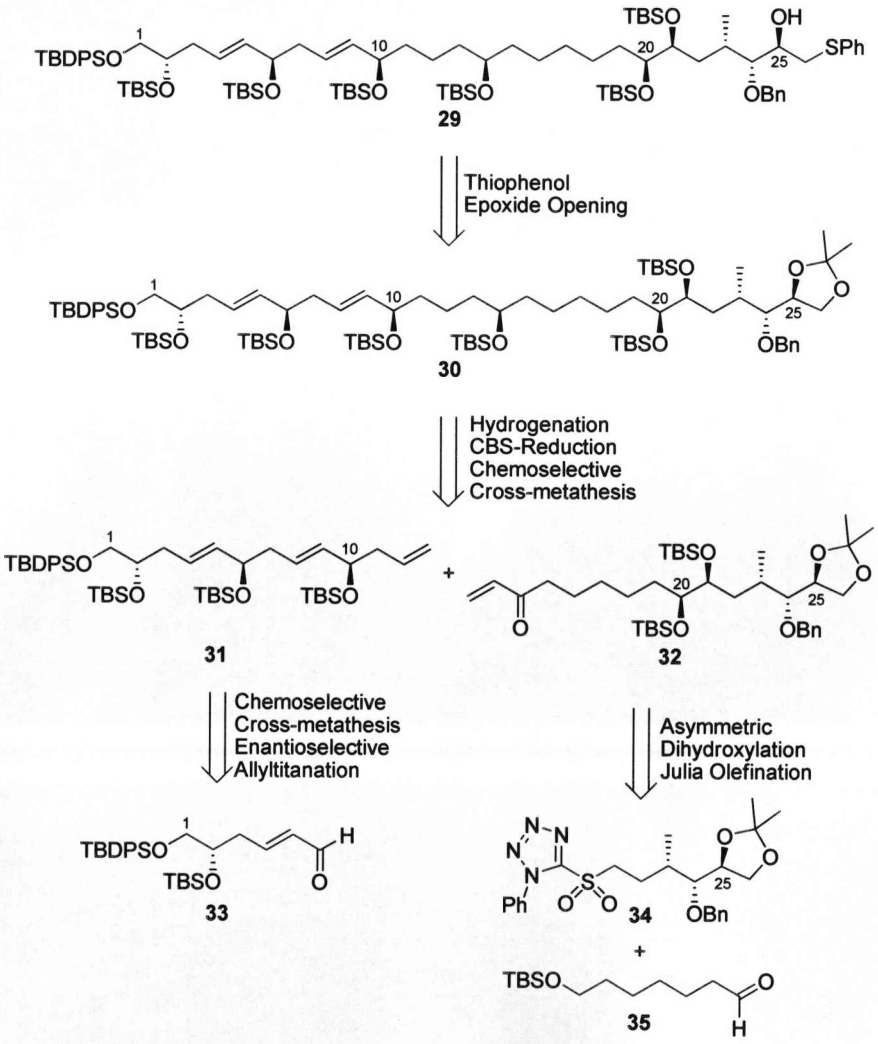
The sulfone **21** was prepared from the commercially available dimethyl (*S*)-malate.[30] Aldehyde **22** was derived from the readily available *D*-malic acid.

The C9-C30 carbon framework was constructed *via* Wittig olefination between the phosphonium salt **23** and ketoaldehyde **24**. The olefination reaction provided the *Z*-olefin selectively based on the ^{1}H-NMR analysis. Subsequent catalytic hydrogenation gave the saturated subunit, which was elaborated into the aldehyde **20** over the course of 4 steps. The phosphonium salt precursor was prepared from the ester **25** and aldehyde **22** *via* Julia-Kocienski olefination reaction and subsequent hydrogenation. The phosphonium salt **23** was obtainable from corresponding precursor through a simple functional group interconversion. Compounds **25** and **22** stem from the identical ester intermediate **28**, which was derived from the *D*-malic acid. The differential protecting groups in ester **28** facilitated the construction of structurally differentiated fragments **25** and **22** thus



(3.3)

illustrating the bifurcative nature of this process. The Julia-Kociensky cross-coupling of fragments **26** and **27** furnished the precursor to ketoaldehyde **24** thus introducing the olefin at C20-C21 position. Sharpless asymmetric dihydroxylation, followed by standard functional group manipulation provided the access to the ketoaldehyde **24**. Equation 3.3 outlines the key cross-coupling between the sulfone **19** and the aldehyde **20** *via* Julia-Kocienski olefination[27] thus providing **18**, the fully protected C1-C30 fragment of amphidinol 3. The construction of this fragment required 23 steps of the longest linear sequence with the overall yield of 13.5%.



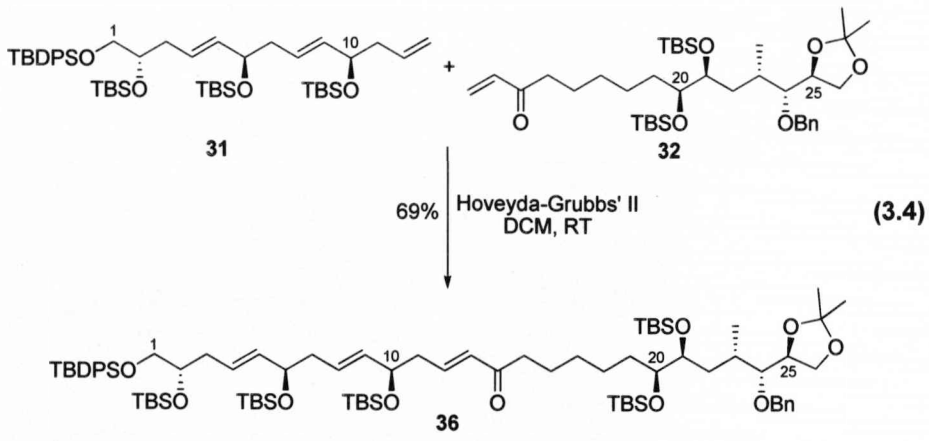
Scheme 3.4 *Retrosynthetic Analysis of Rychnovsky's Synthesis*

3.1.5 Rychnovsky's Approach to the C1-C26 Fragment of Amphidinol 3

In 2007, Rychnovsky and co-workers reported an asymmetric synthesis of the C1-C26 polyol unit *en route* to the C1-C52 fragment of amphidinol 3.[11c] The retrosynthetic analysis of Rychnovsky's synthesis is described in the Scheme 3.4. The target molecule **29** was constructed from the precursor **30** *via* deprotection and standard functional group interconversion. The carbon framework of intermediate **30** was constructed using the pivotal chemoselective cross-metathesis reaction.[17] The CBS-reduction[31] of the corresponding enone provided the allylic alcohol with 17:1 diastereomeric ratio. Following Roush's literature precedent,[10a] hydroxyl directed reduction[19] of the C12-C13 olefin using Noyori's catalyst[20] and subsequent silyl protection provided the access to the intermediate **30**. The silyl protected homoallylic triol **31** was efficiently prepared from the enone **33** *via* sequential allyltitanation and cross-metathesis reaction as previously described by Cossy and BouzBouz.[9a] The enone **32** was derived from the sulfone **34** and the aliphatic aldehyde **35** by using the powerful Julia-Kocienski olefination method.[28] The exposure of the corresponding olefin to Sharpless asymmetric dihydroxylation[24] led to stereoisomerically pure diol, which was elaborated into the enone **32** using the standard protecting group manipulation.

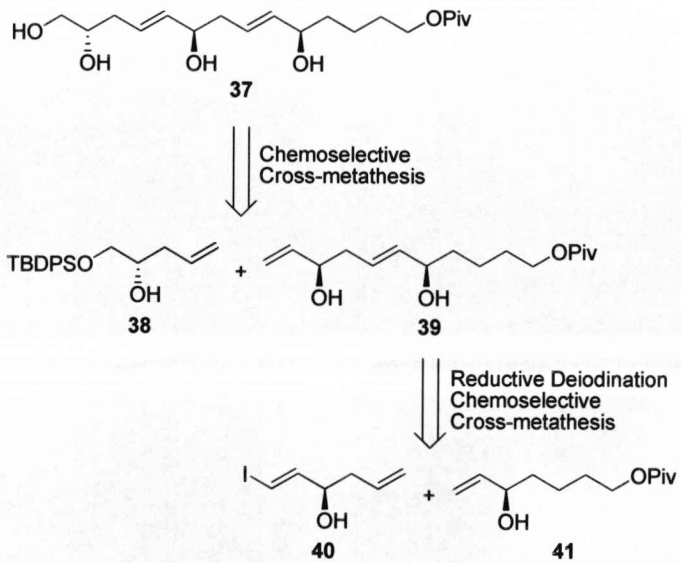
This synthesis highlighted the application of stereoselective cross-metathesis reaction[17] in the union of the C1-C12 and C13-C26 fragments. The construction of the C1-C52 fragment was finalized by utilizing a cross-coupling between the unusual β-alkoxy alkyllithium reagent and Weinreb amide. The product of this reaction represents one of the most advanced synthetic intermediate reported to date in the construction of amphidinol 3. Equation 3.4 illustrates the key step in the construction of the C1-C26 fragment. The Rychnovsky's synthesis of the C1-C26

fragment of amphidinol 3 **29** was accomplished in 22 steps of the longest linear sequence with the overall yield of 5.5%.



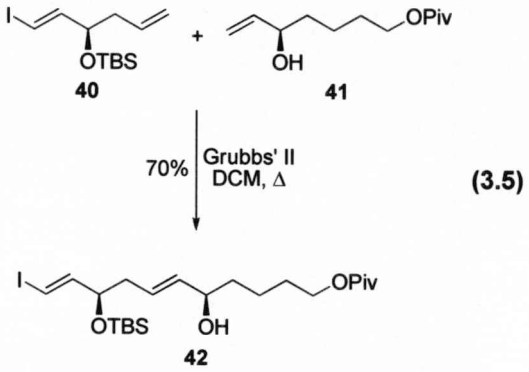
3.1.6 Murata's Approach to the C1-C14 Fragment of Amphidinol 3

Recently, Murata and co-workers reported a combinatorial synthesis approach to the 1,5-polyol system based on the chemoselective cross-metathesis.[14] The group made an effort to investigate weather the absolute configuration of the acyclic polyol domain of amphidinol 3 has an effect on the biological activity. The



Scheme 3.5 *Retrosynthetic Analysis of Murata's Synthesis*

asymmetric construction of the C1-C14 moiety of amphidinol 3 and its diastereomers *via* pivotal cross-metathesis step[17] resulted in the structure revision of natural product (*vide infra*). The retrosynthetic analysis of Murata's synthesis is described in the Scheme 3.5. Since alcohols **40** and **41** were obtained in enantiopure form *via* lipase-catalyzed kinetic resolution from corresponding racemates,[32] Murata and co-workers could carry out the synthesis of all possible stereoisomers of C1-C14 fragment **37** by simply choosing the correct enantiomer.



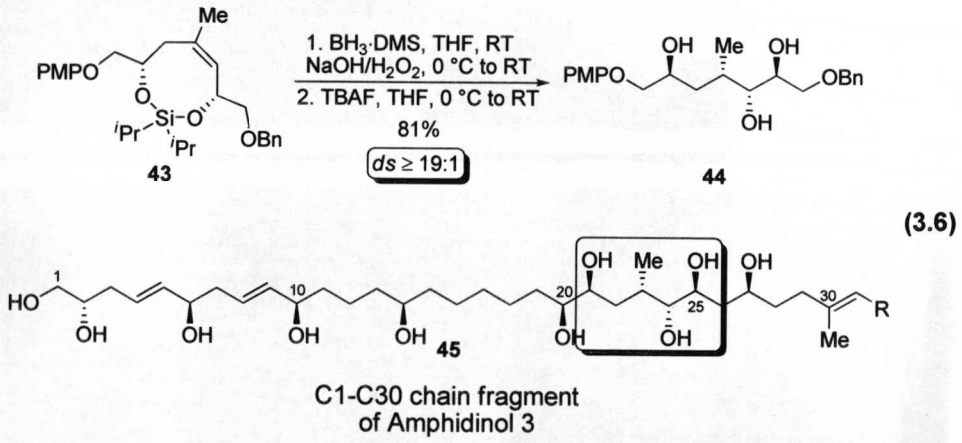
(3.5)

The Equation 3.5 describes the key intermediate in which the iodoolefin **40** is regarded as a protected terminal olefin for the chemoselective cross-metathesis with intermediate **41**. The iodoolefin moiety was converted to a terminal olefin *via* reductive removal of the iodide using *n*-Bu_3SnH and $Pd(PPh_3)_4$ conditions. The stage was set for the subsequent cross-metathesis with homoallylic alcohol **38**. The spectral data analysis that led to the controversy regarding the originally proposed structure of amphidinol 3 will be discussed later in this chapter.

3.2 Results and Discussion

3.2.1 Background and Hypothesis

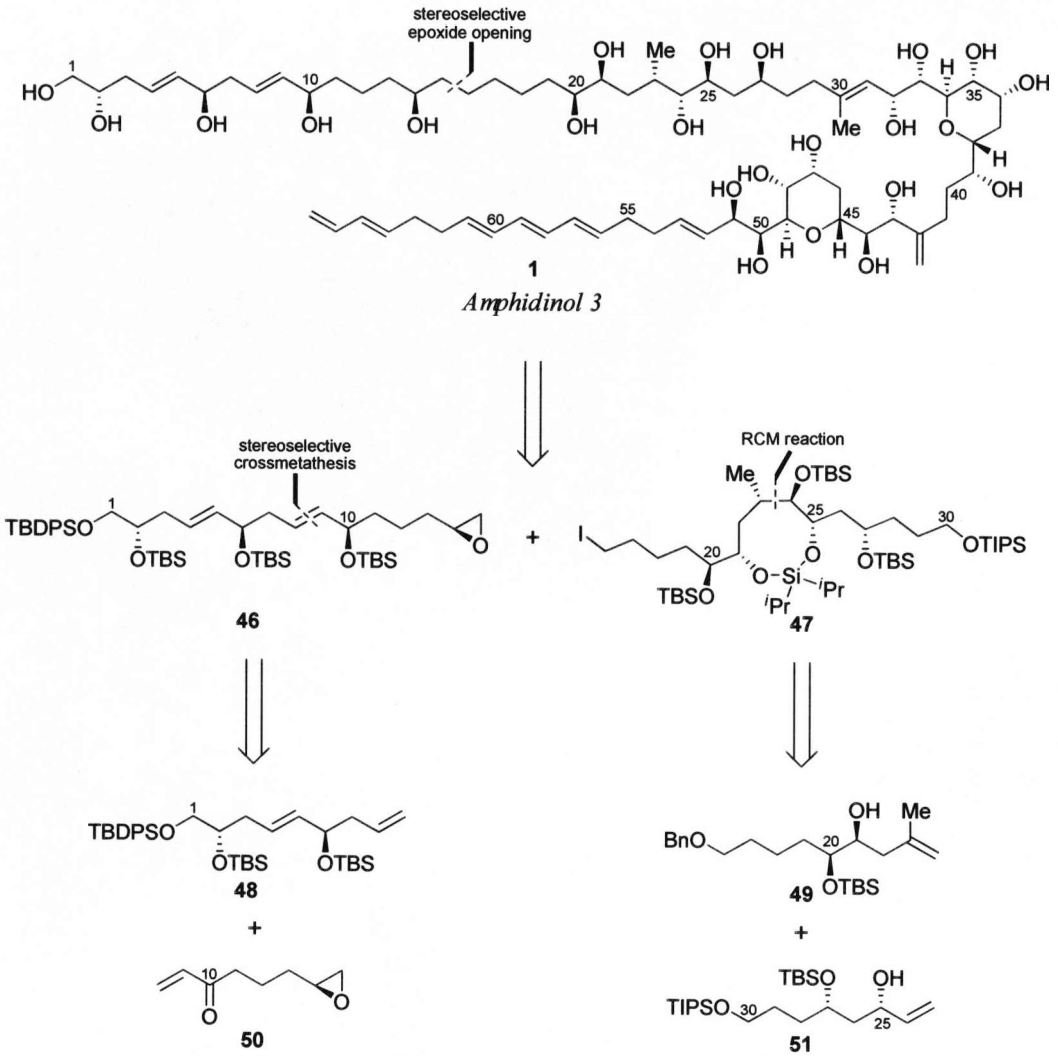
Although the total synthesis of amphidinol 3, **1** has not been completed, the attention of the synthetic community has been focused to the three main sections: a) C1-C30 linear chain fragment rich in polyol units, b) C31-C51 fragment with two densely functionalized *trans*-tetrahydropyrans and c) C51-C67 polyene chain (Figure 3.2). Intriguing structural complexity of the C1-C30 linear chain containing the polyol units in 1,5-, 1,3- and 1,2- stereochemical arrangement have captured the imagination of several synthetic groups (*vide supra*).[9-14] Based on previously described stereoselective functionalization of unsaturated eight-membered silaketals, we envisioned the installation of the C23-C24 propionate unit utilizing the stereoselective hydroboration. This approach will focus on the asymmetric construction of the C16-C30 chain fragment of amphidinol 3. Based on the model studies (*vide supra*), the hydroboration and subsequent silyl deprotection of the unsaturated silaketal **43** provided the access to the triol **44** which stereochemically corresponds to the C21-C25 chain fragment of amphidinol 3 (Eq. 3.6). The stereoselective hydroboration will be a key step toward the asymmetric construction



of the C16-C30 portion. *En route* to the C1-C15 chain fragment **46**, we envisioned that the key coupling would establish the *E*-olefin functionality between C8 and C9 through stereoselective cross-metathesis reaction.[17] The final coupling between the two fragments should construct the new C-C bond between C15 and C16, *via* stereoselective epoxide opening utilizing *in situ* prepared organocuprate reagent (Scheme 3.6).

3.2.2 Retrosynthetic Analysis

Our synthetic plan hinges on the disconnection of the C15-C16 bond as described in Scheme 3.6. Such retrosynthetic modification provides two pivotal fragments, epoxide **46** and iodosilaketal **47**. This approach capitalizes on the lithium-iodide exchange[33] together with a subsequent transmetallation to copper, which thereby should permit the formation of the organocuprate reagent capable of stereoselective epoxide opening[34] thus forging the C15-C16 bond. This transformation will install the concluding hydroxyl group at C14. We further envisioned that the C8-C9 olefin could be formed *via* stereoselective *cross*-metathesis between alkene **48** and epoxyenone **50**.[11c,17] Elaboration to the fragment **46** would require the CBS-reduction[11c,31] followed by subsequent TBS protection.[11c] Further disconnection at C23-C24 retrosynthetically transforms the iodosilaketal **47** into the *homo*-allylic alcohol **49** and its coupling partner, the allylic alcohol **51**. The eight-membered silaketal framework could be constructed utilizing the temporary silicon-tethered ring-closing metathesis reaction recently developed in our laboratories. The key hydroboration step should permit the installation of two stereogenic centers at the C23-C24 according to our initial model studies. Following the hydroboration, the construction of the iodosilaketal **47** should be completed utilizing

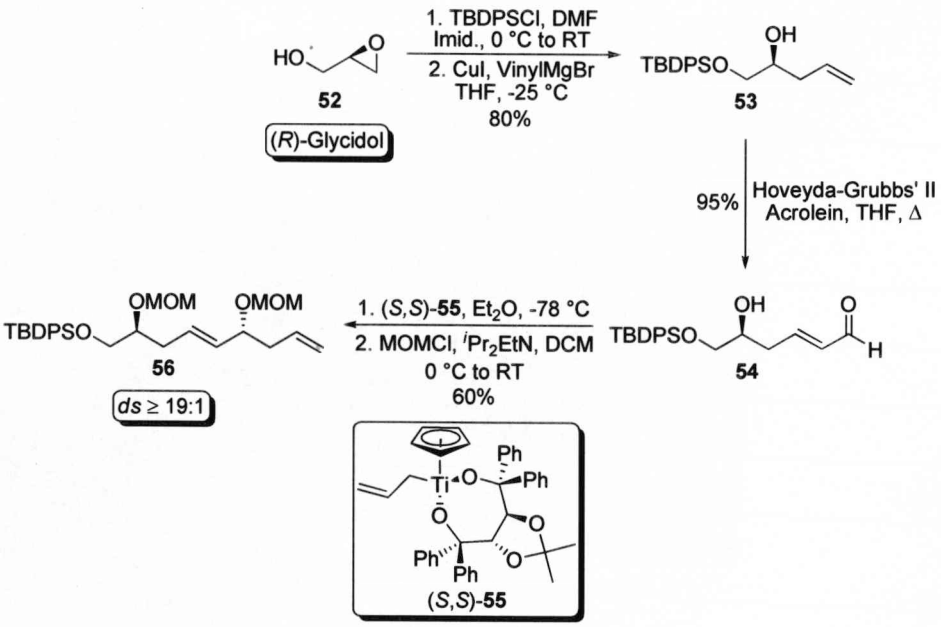


Scheme 3.6 *Retrosynthetic Analysis of C1-C30 Fragment of Amphidinol 3*

a series of standard synthetic manipulations such as protection, deprotection and functional group interconversion.

3.2.3 Asymmetric Construction of C1-C15 Fragment of Amphidinol 3

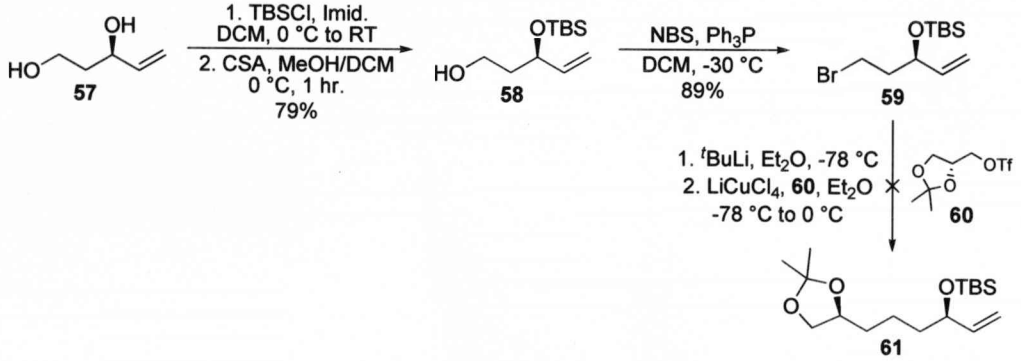
According to our retrosynthetic plan, the synthesis of C1-C15 fragment commenced from commercially available (*R*)-glycidol **52** as described in the Scheme 3.7. Selective protection of the primary alcohol **52** followed by subsequent copper-mediated epoxide opening furnished the *homo*-allylic alcohol **53** in excellent overall yield.[11c] *Cross*-metathesis[17] of **53** utilizing 5 mol% of the Hoveyda-Grubbs' 2nd generation catalyst together with five equivalents of acrolein in refluxing THF



Scheme 3.7 *Asymmetric Construction of C1-C8 Fragment*

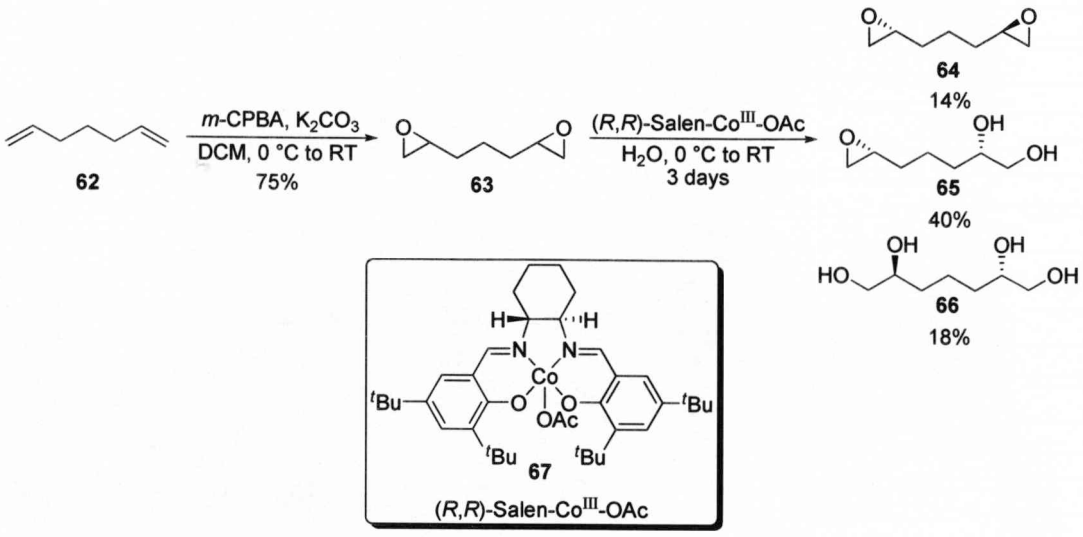
provided the adduct **54**, with exclusive *E*-olefin geometry in excellent yield. In 2001, Cossy and BouzBouz reported the chemoselective *cross*-metathesis approach toward the synthesis of the C1-C14 fragment of amphidinol 3.[9a] However, the application of their original *cross*-metathesis conditions[35] provided an enal **54** albeit with inferior yield and poor conversion. Having secured the access to **54**, the stage was set for the enantioselective allyltitanation reaction using *in situ* prepared Duthaler-Hafner's reagent, (*S*,*S*)-**55**.[15] Organotitanium regents were introduced to the synthetic community in early 80's, mainly through the work of Seebach[36] and Reetz[37]. Their popularity rapidly expanded as they opened the new prospective to chemo-, regio- and stereoselectivity in asymmetric synthesis. Titanium is readily available, nontoxic and easily susceptible to transmetallation reaction with organolithium or Grignard reagents. Furthermore, the structural variability in the organotitanium reagents allows the adjustment of the reactivity profile. Last decade, the organotitanium reagents have been used extensively in the asymmetric synthesis of biologically important natural products.[9a,16]

We envisioned that stereoselective allylation of enal **54** using the asymmetric organotitanium reagent (*S*,*S*)-**55** should provide an access to 1,5-*anti*-diol.[9a,11c] The titanium reagent is easily prepared from $CpTiCl_3$ and (*S*,*S*)-TADDOL ligand derived from (*S*,*S*)-diethyl tartarate.[15] The advantage of allyltitanation is that hydroxyl group of the enal **54** does not need to be protected. Indeed, treatment of **54** with (*S*,*S*)-**55** at low temperatures followed by a MOM protection delivered a *bis*-MOM ether **56** in good overall yield and great stereoselectivity. With the satisfactory amount of the C1-C8 fragment in hand, we turned our attention toward the construction of the C9-C15 fragment.



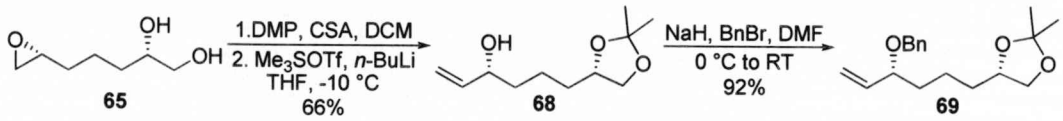
Scheme 3.8 *Synthesis of C9-C15 Fragment of Amphidinol 3*

The synthesis of C9-C15 fragment commenced with the allylic diol **57**.[38] *Bis*-silyl protection followed by selective desilylation of primary silyl ether with catalytic CSA in MeOH/DCM afforded a primary alcohol **58** (Scheme 3.8). The alcohol was converted into the bromide **59** through the combination of NBS and triphenylphosphine. The lithium-bromide exchange followed by the transmetallation to copper provided the organometallic reagent required for the primary triflate displacement.[39] Unfortunately, after several conditions examined, the organocopper reagent failed to provide a substitution product **61** presumably due to the stabilizing effect of β-oxygen.[40]



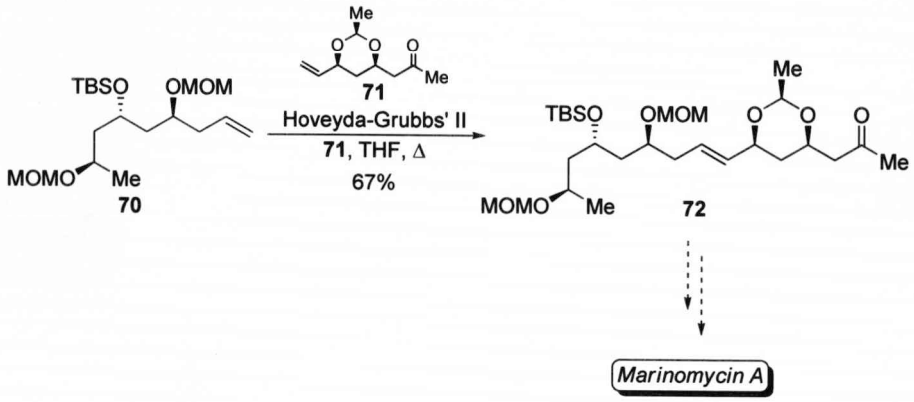
Scheme 3.9 *Hydrolitic Kinetic Resolution of Terminal Bis-Epoxide*

In a search for the alternative route, we were intrigued by the application of Jacobsen's hydrolytic kinetic resolution[41] of the *bis*-epoxides in the synthesis of the insect pheromones.[42,43] Epoxides are very important and versatile building blocks in the organic synthesis. Terminal epoxides emerged as the most important subclass of these compounds. However, there is a lack of the general method, which would permit the construction of these compounds in highly enantiomeric form. Furthermore, terminal epoxides are generally inexpensive as a racemic mixture or readily accessible by standard preparative synthesis. Jacobsen's hydrolytic kinetic resolution[41a] is an attractive strategy for the production of the optically active epoxides due to the economical and operational simplicity. We decided to carry out the preparation of epoxydiol **65** using the procedure reported by Kitching and co-workers.[43] Treatment of commercially available 1,6-heptadiene **62** with *m*-CPBA at 0 °C to ambient temperature afforded the *bis*-epoxide **63** (Scheme 3.9). The hydrolytic kinetic resolution of **63** after three days furnished enantiomerically enriched C_2-symmetrical *bis*-epoxide **64**, C_2-symmetrical tetraol **66** and the major product, epoxydiol **65**. Protection of the diol moiety[42] followed by epoxide opening



Scheme 3.10 *Synthesis of Benzyl-Protected Allylic Alcohol*

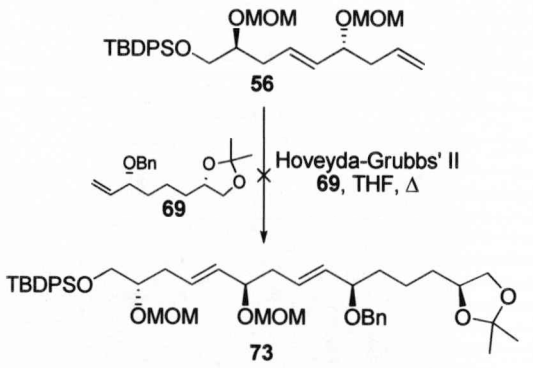
using Me_3SOTf salt[44] furnished an allylic alcohol **68** in good overall yield (Scheme 3.10). The benzyl protection using NaH and benzyl bromide provided the access to **69** as a fully protected C9-C15 fragment of amphidinol 3. With *bis*-MOM ether **56** and benzyl protected allylic alcohol **69** the stage was set for the cross-coupling reaction *via* stereoselective cross-metathesis.[17]



Scheme 3.11 *Recent Advances in the Total Synthesis of Marinomycin A*

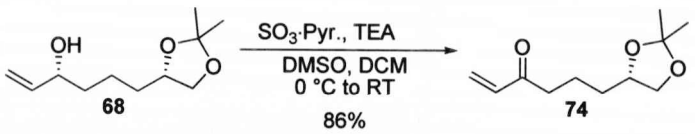
In the recent studies related to the total synthesis of marinomycin A,[45] Evans and Lawler[46] have demonstrated a remarkable transformation between the alkene fragments **70** and **71** using a cross-metathesis reaction (Scheme 3.11). This cross-coupling provided an alkene **72** as a single *E*-olefin stereoisomer based on the ^{1}H-NMR analysis. The yield of 67% for this transformation is impressive knowing that the alkenes **70** and **71** were reacted in the equimolar ratios. Inspired by this result, we decided to apply the same principle in the cross-coupling of alkenes **56** and **69** which would finalize the construction of C1-C15 fragment of amphidinol 3. Unfortunately, the exposure of alkenes **56** and **69** to Hoveyda-Grubbs' 2nd

generation catalyst in refluxing THF provided a complex mixture of products albeit none of the desired alkene **73** (Eq. 3.7).



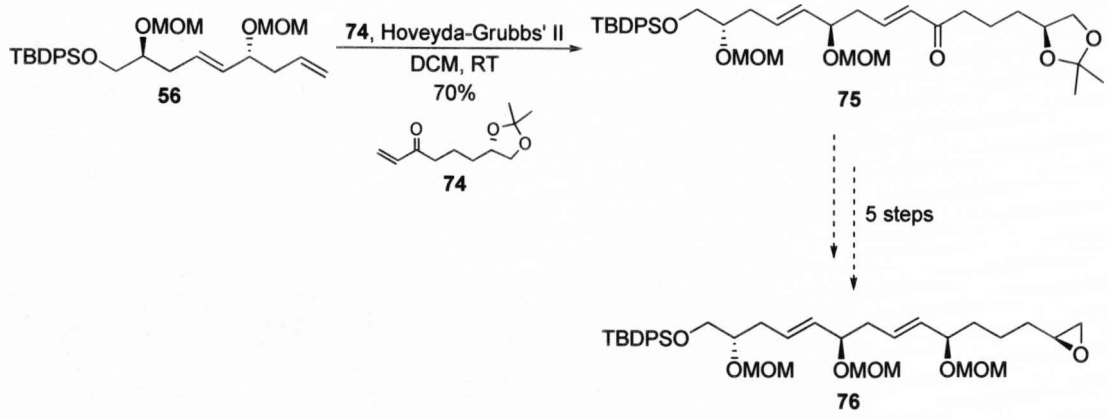
(3.7)

In 2007, Rychnovsky and co-workers demonstrated a successful cross-metathesis reaction using an equimolar amount a silyl protected homoallylic alcohol **31** and an enone **32** (Eq. 3.4).[11c] The reaction provided the C1-C26 fragment of amphidinol 3 in excellent yield of 69%. Accordingly, we decided to modify the precursor of the allylic benzyl ether **69** through the oxidation reaction (Eq. 3.8). A suitable enone **74** was generated by Parikh-Doering oxidation[23] of the allylic alcohol



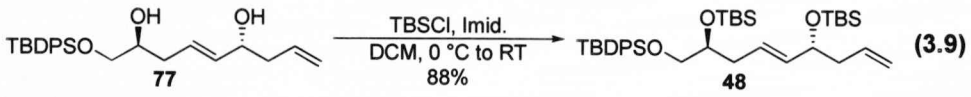
(3.8)

68 using SO_3·Pyridine complex with DMSO and TEA. Gratifyingly, the exposure of **56** and **74** in equimolar ratio to the Hoveyda-Grubbs' 2nd generation catalyst furnished the cross-coupling adduct **75** in 70% yield as a single *E*-stereoisomer based on the geometry of the olefin (Scheme 3.12). From this stage on, the fragment **75** is away from the fully functionalized C1-C15 fragment of amphidinol 3, **76** by a sequence of five steps.[11c]

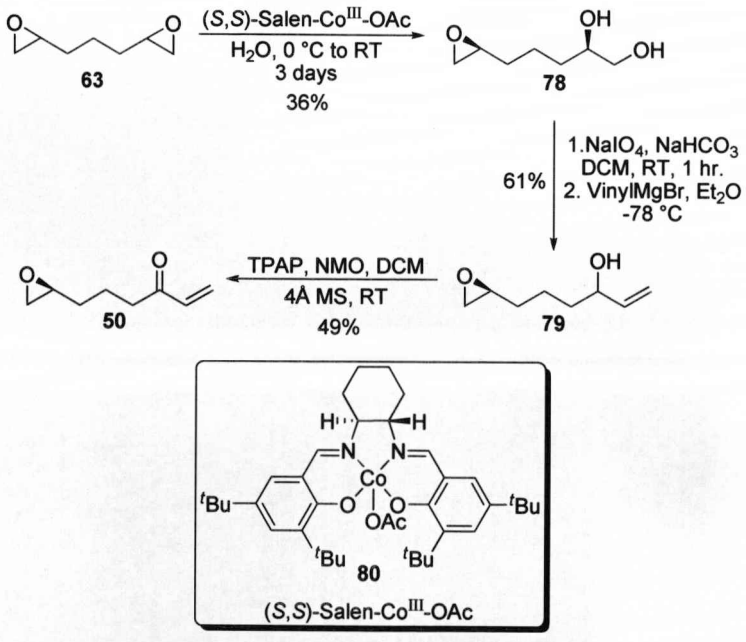


Scheme 3.12 *Synthesis of the C1-C15 Framework of Amphidinol 3*

We also envisioned a slightly shorter and more efficient route to the same fragment. Treatment of the 1,5-homoallylic diol **77** prepared by allyltitanation[11c]

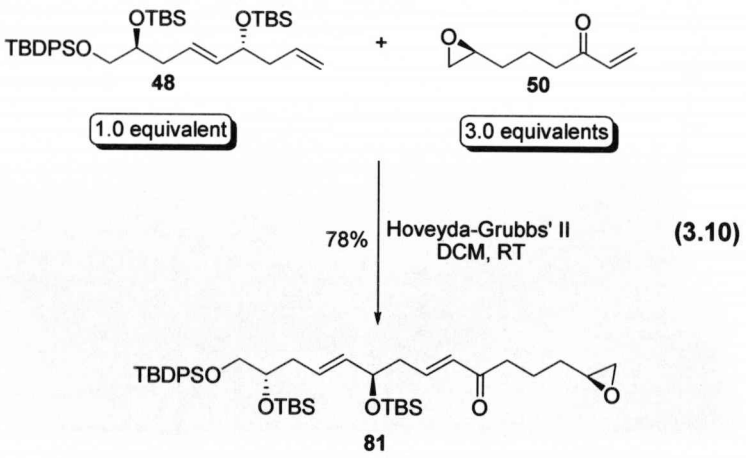


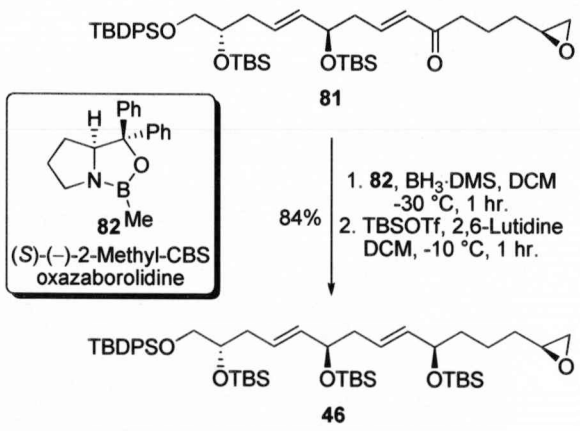
with TBSCl and imidazole furnished the silylether **48** (Eq. 3.9). We also decided to revisit a hydrolytic kinetic resolution[41] of *bis*-epoxides[42,43] as a viable route for the preparation of epoxyenone **50** (*vide supra*). Hydrolitic kinetic resolution of *bis*-



Scheme 3.13 *Synthesis of Epoxyenone* **50**

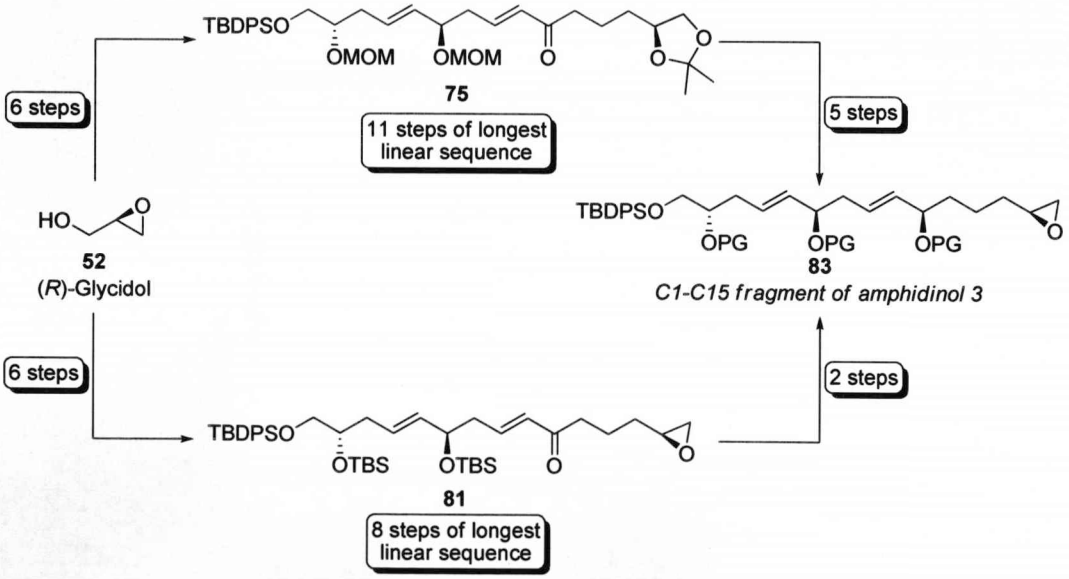
epoxide **63** using (*S*,*S*)-Salen-Co^{III}-OAc catalyst **80** furnished after 3 days of stirring at ambient temperature an epoxydiol **78** as a major product in 36% yield. The compound **78** is an enantiomer of epoxy diol **65**. With the required epoxide functionality already in place, a simple refunctionalization of the diol moiety should provide an access to the desired fragment **50** as described in Scheme 3.13. Indeed, the glycol cleavage of the diol **78** followed by a chemoselective addition of vinylmagnesium bromide to the corresponding aldehyde provided the allylic alcohol **79** as a diastereomeric mixture in good yield. Oxidation[47] of the allyic alcohol **79** using a catalytic TPAP and NMO furnished the desired epoxyenone **50** in the modest yield. Treatment of the homoallylic silyl ether **48** with excess of epoxyenone **50** under the standard cross-metathesis condition furnished the cross-coupling adduct **81** in 78% yield (Eq. 3.10). Enantioselective reduction of the enone **81** with commercially available (*S*)-(−)-2-Methyl-CBS-oxazaborolidine **82** as 1 molar





(3.11)

solution in toluene afforded an allylic alcohol as a single stereoisomer (based on the ^{1}H-NMR analysis), which was protected to afford the epoxide **46**, which represents the fully functionalized C1-C15 fragment of amphidinol 3 (Eq. 3.11). Hence, we have accomplished an efficient synthesis of fully functionalized C1-C15 chain frag-



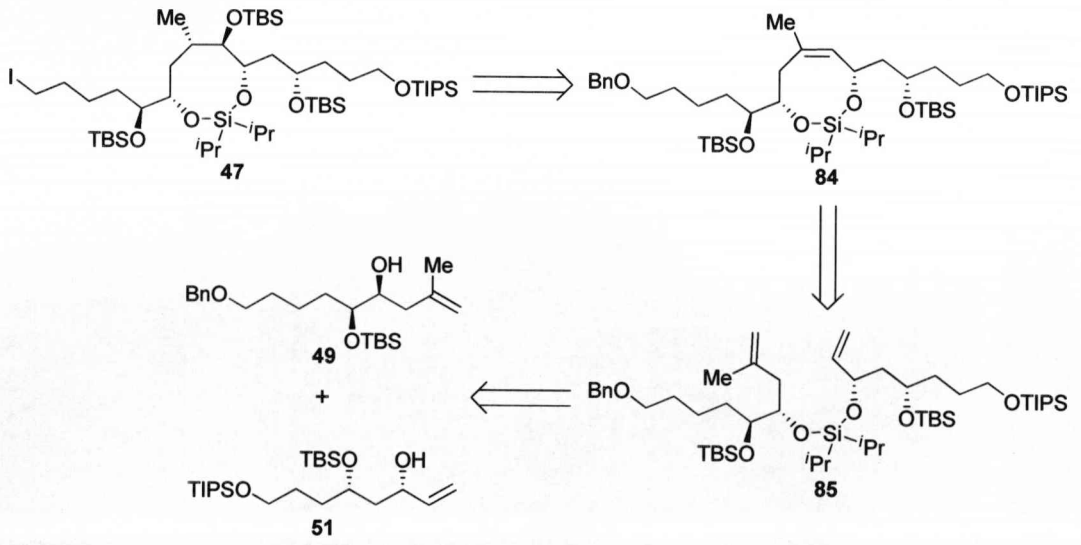
Scheme 3.14 *The Comparison of Synthetic Efficiency from Intermediates* **75** *and* **81**

ment of amphidinol 3, **46** by highlighting the utility of Jacobsen's hydrolityc kinetic resolution.[41] The stereoselective cross-metathesis[11c,17] followed by CBS-reduction[11c,31] represented the valuable strategy in the construction of this fragment. Scheme 3.14 illustrates the comparison of synthetic efficiency of two different pathways invoking the advanced intermediates **75** and **81**. Both advanced

intermediates are obtainable from commercially available (*R*)-glycidol **52** in 6 steps of longest linear sequence. According to the Scheme 3.14, the synthesis of the fully protected C1-C15 epoxide **83** from the advanced intermediate **75** would require 5 additional steps. Alternatively, the route starting from the intermediate **81** provided the C1-C15 fragment **83** in only 2 steps thus saving the synthetic manipulation required for the preparation of the epoxide functionality.

3.2.4 Asymmetric Construction of C16-C30 Fragment of Amphidinol 3

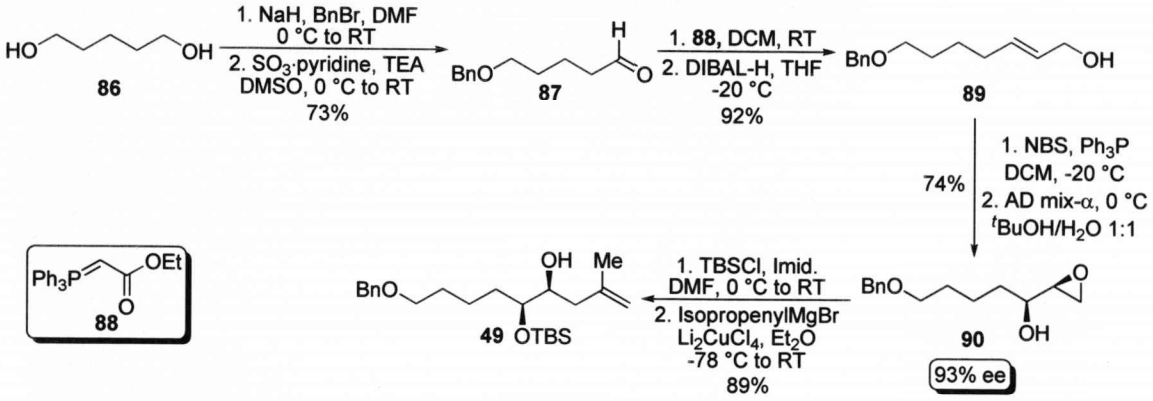
Having accomplished the synthesis of the C1-C15 fragment, attention turned to the synthesis of the C16-C30 fragment of the amphidinol 3, which required the iodide **47** that is derived from the unsaturated silaketal **84**. This intermediate will be prepared by powerful temporary silicon-tethered ring-closing metathesis reaction followed by stereoselective hydroboration and then conversion of benzyl ether to the



Scheme 3.15 *Retrosynthetic Analysis of the C16-C30 Fragment of Amphidinol 3*

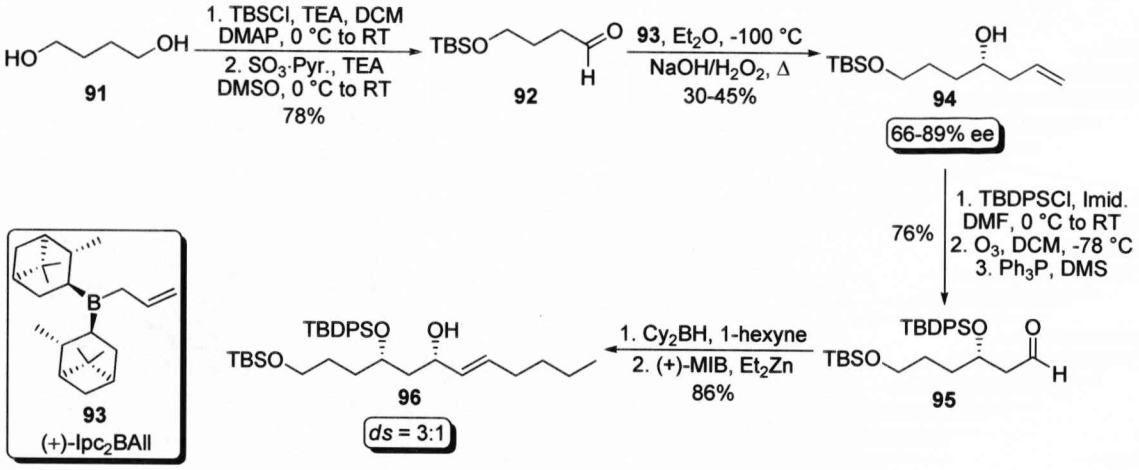
primary iodide **47** (Scheme 3.15). Acyclic silaketal **85** is retrosynthetically modified to the starting materials of reasonable simplicity. The homoallylic alcohol **49** and allylic alcohol **51** are readily available from the aldehyde **87** and epoxide **112** respectively (*vide infra*).

Our synthetic endeavor to the homoallylic alcohol **49** commenced with a simple, commercially available 1,5-pentanediol **86** (Scheme 3.16). *Mono*-benzyl protection of the diol **86** using benzyl bromide and sodium hydride conditions followed by Parikh-Doering oxidation[23] afforded an aldehyde **87** in good overall yield. The stabilized Wittig homologation[48] using the stabilized ylide **88** afforded the *E*-stereoisomer predominantly, which was subjected to DIBAL-H reduction to prov-



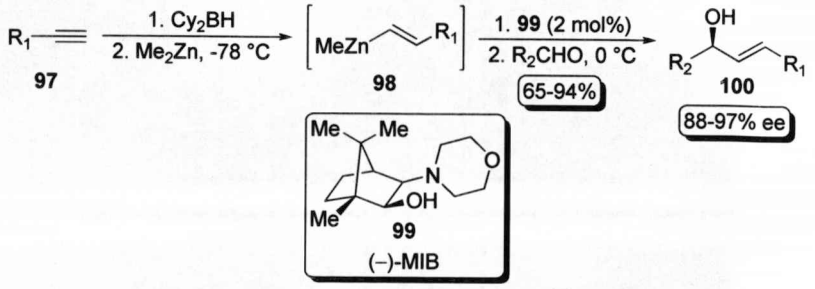
Scheme 3.16 *Synthesis of Homoallylic Alcohol* **49**

ide the allylic alcohol **89**. The treatment of the alcohol **89** with NBS and triphenylphosphine afforded the allylic bromide, which was further subjected to Sharpless asymmetric dihyroxylation using AD mix-α reagent.[24] The asymmetric dihydroxylation and concomitant intramolecular epoxidation gratifyingly delivered epoxyalcohol **90** in 93% of enantiomeric excess as determined by chiral HPLC analysis. Protection of the secondary alcohol **90** as the *tert*-butyldimethylsilyl ether followed by copper mediated epoxide opening using the isopropenylmagnesium bromide furnished a homoallylic alcohol **49** in excellent overall yield. The absolute stereochemistry of secondary alcohol was confirmed through Mosher ester analysis. This stereoselective sequence provided the access to the multigram quantities of the homoallyic alcohol **49**.



Scheme 3.17 *Synthesis of Allylic Alcohol* **96**

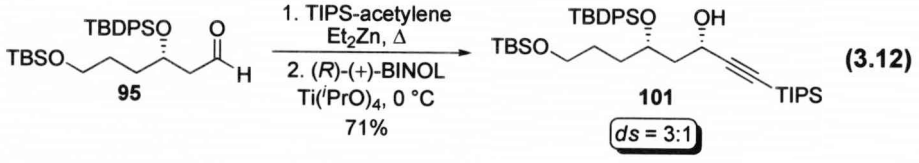
The synthesis of the allylic alcohol **96** started with monoprotection of simple 1,4-butanediol **91** using *tert*-butyldimethylsilyl chloride (Scheme 3.17). Subsequent oxidation of primary alcohol furnished the aldehyde **92**, which was subjected to Brown enantioselective allylboration under the salt-free conditions.[49] The (+)-Ipc_2B-All reagent, **93** prepared from (−)-α-pinene according to the procedure reported by Racherla and Brown,[49] afforded the homoallylic alcohol **94** albeit in modest yield and variable enantioselectivity. The absolute configuration of the secondary alcohol **94** was determined through Mosher ester analysis.



Scheme 3.18 *Preparation of Allylic Alcohols through Alkenyl Zinc Addition*

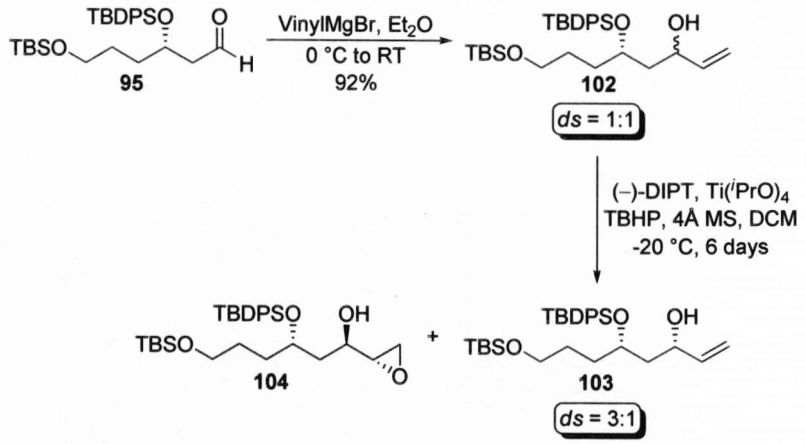
The silyl protection of the secondary alcohol **94** followed by the ozonolysis of the terminal olefin provided the access to the aldehyde **95** in good overall yield. At this stage of the synthesis, we envisioned a vinylzinc addition to the aldehyde **95**

with the aim to construct the *mono*-protected 1,3-*syn*-diol functionality. The methodology developed by Walsh and co-workers looked promising for our application (Scheme 3.18).[50] This reaction consists of the several different stages. The first stage is the *in situ* preparation of dicyclohexylborane. The hydroboration of the alkyne **97** followed by the transmetallation to zinc provides *in situ* alkenylzinc species **98**, which upon addition of catalytic amount of chiral morpholinoisoborneol ligand (MIB)[51] **99** undergoes to smooth addition to variety of aldehydes to form an allylic alcohols **100** with high levels of enantioselectivity. Unfortunately, treatment of aldehyde **95** with *in situ* formed alkenyl zinc reagent afforded the allylic alcohol **96** in good yield albeit with only marginal level of stereoselectivity (Scheme 3.17). The corresponding allylic alcohol is available *via* cross-metathesis reaction under the atmosphere of ethylene gas.[52] However, due to the poor stereocontrol obtained in this reaction, we decided to examine the alternative routes.



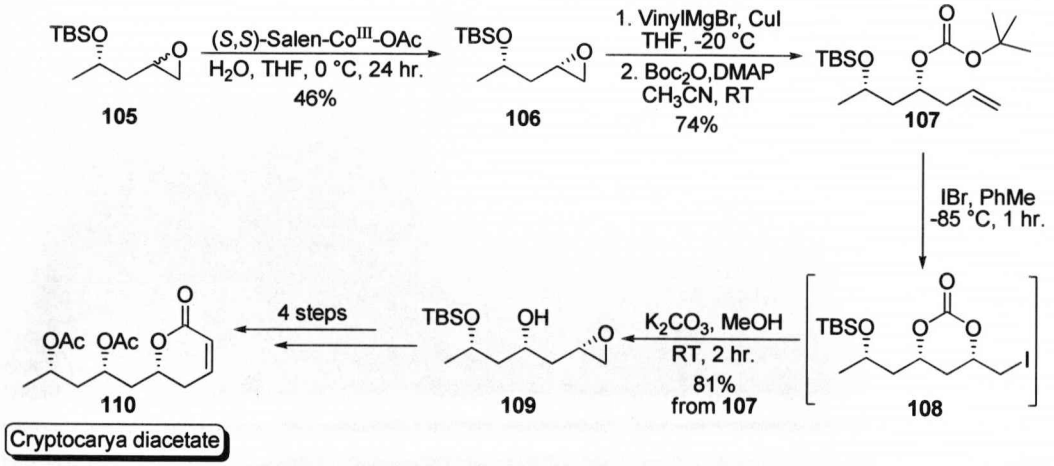
(3.12)

Pu and co-workers developed methodology based on the formation of zinc acetylide species *in situ* from the higher boiling acetylenes (TIPS-acetylene) and neat diethylzinc. The newly formed organozinc reagent is added to the aldehyde enantioselectively with assistance of Ti(^{i}PrO)$_4$ Lewis acid having (*R*)- or (*S*)-BINOL chiral ligand. Treatment of aldehyde **95** with zinc acetylide in the presence of Ti(^{i}PrO)$_4$ and (*R*)-(+)-BINOL furnished the propargylic alcohol **101** in 71% yield but poor diastereoselectivity (Eq. 3.12). Although, the extensive modification of this reaction had proven more fruitful in a related transformation,[54] this approach did not afford any significant improvement in terms of diastereoselectivity.



Scheme 3.19 *Sharpless Kinetic Resolution of Diastereomeric Allylic Alcohol* ***102***

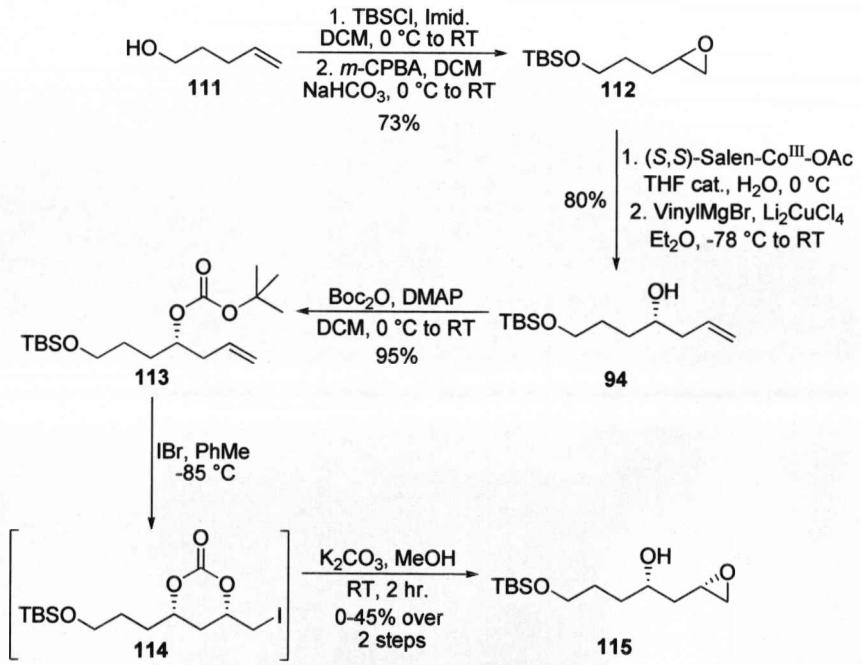
Additional studies examined a Sharpless kinetic resolution of the epimeric allylic alcohol.[55] Treatment of aldehyde **95** with vinylmagnesium bromide provided the allylic alcohol **102** as 1:1 mixture of diastereomers (Scheme 3.19). Treatment of allylic alcohol **102** under standard resolution conditions using (−)-diisopropyl-tartarate, Ti(^{i}PrO)$_4$ and ^{t}BHP at -20 °C after 6 days provided an allylic alcohol **103** in 3:1 diastereomeric ratio based on the ^{1}H-NMR-analysis.



Scheme 3.20 *Total Synthesis of Cryptocarya Diacetate* **110**

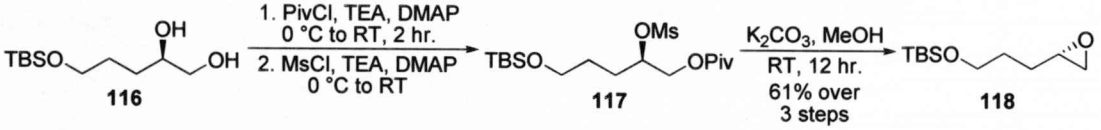
Recently, Kumar and co-workers reported an efficient approach to 1,3-polyols in the synthesis of cryptocarya diacetate **110**, a natural product with the broad range of biological activity (Scheme 3.20).[56] Their approach was based on the

iterative Jacobsen's hydrolytic kinetic resolution[41], diastereoselective iodine-induced electrophilic cyclization[57,58] and the ring-closing metathesis. The Jacobsen's resolution of the *bis*-epoxides[42,43] has already been used in our synthesis for the construction of epoxydiols with high diastereoisomeric purity *en route* to the C1-C15 fragment of amhidinol 3. Particularly interesting part of the Kumar's synthesis was the application of the IBr reagent for the preparation of cyclic iodocarbonate **108**.[56,57,58] Treatment of the iodocarbonate **108** with 3 equivalents of K_2CO_3 in methanol furnished the epoxyalcohol **109** as a single stereoisomer in 81% yield from the BOC protected homoallylic alcohol **107**. From the intermediate **109**, the desired allylic alcohol functionality in the intermediate **51** would be accessible through silyl protection of the secondary alcohol and subsequent epoxide opening using the Me_3SOTf salt.[44] Cyclic iodocarbonates such as **108** are versatile intermediates in the organic synthesis. They can be readily converted into the variety of synthetically useful intermediates.[57]



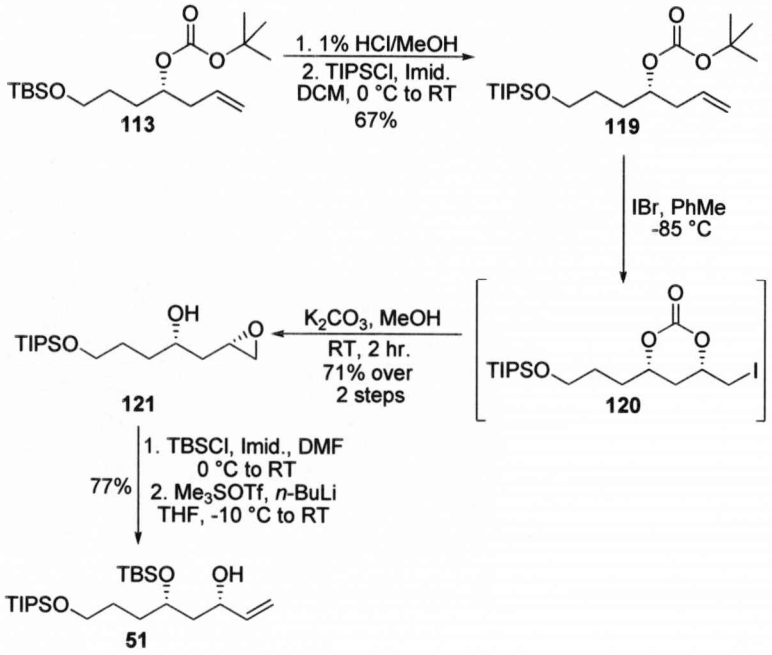
Scheme 3.21 *The Synthesis of Epoxy Alcohol **115***

Protection of the alcohol **111** (Scheme 3.21) followed by epoxidation with *m*-CPBA afforded the racemic epoxide **112**. Treatment of the reacemic epoxide **112** with the (*S*,*S*)-Salen-Co-OAc catalyst and 0.55 equivalents of water gave the enantiomerically pure epoxide **118** and a diol **116** with an opposite absolute stereochemistry. Copper catalyzed epoxide opening of **118** with vinylmagnesium bromide provided the access to the homoallylic alcohol **94**. The absolute configuration of this alcohol was confirmed *via* Mosher ester analysis (Appendix A).



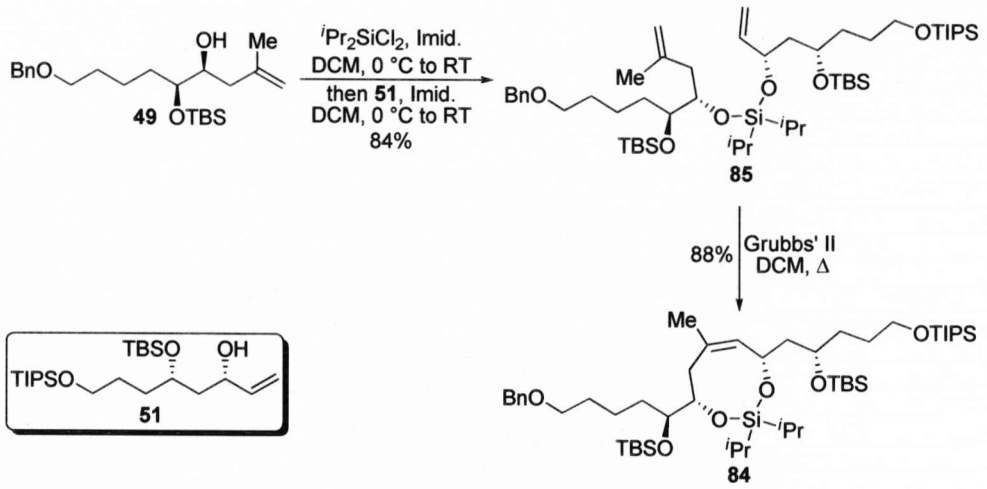
Scheme 3.22 *The conversion of diol* **116** *to the epoxide* **118**

When comparing two procedures used for the preparation of alcohol **94**, the hydrolytic kinetic resolution[41] offers a several advantages over the Brown allylation.[49] The resolved alcohol **94** was obtained as a single enantiomer, while allylation rarely provided the product with the enantioselectivity higher than 85% *ee*. The resolution was effectively performed on 50-gram scale at 0 °C over the period of 24 hours. Furthermore, the diol byproduct **116** is effectively converted back into the epoxide **118** using the three-step sequence outlined in Scheme 3.22. Treatment of alcohol **94** with BOC anhydride and DMAP gave the carbonate **113**, which upon exposure to iodinemonobromide in toluene at -85 °C resulted in clean conversion to the cyclic iodocarbonate **114**. Unfortunately, the iodocarbonate **114** is unstable to aqueous workup and concentration, which prompted carbonate deprotection with the concomitant cyclization with K_2CO_3 in methanol to afford the epoxy alcohol **115** in 45% yield (Scheme 3.21). We concluded that the primary TBS group in **113** was too labile, which prompted us to change the protecting group.



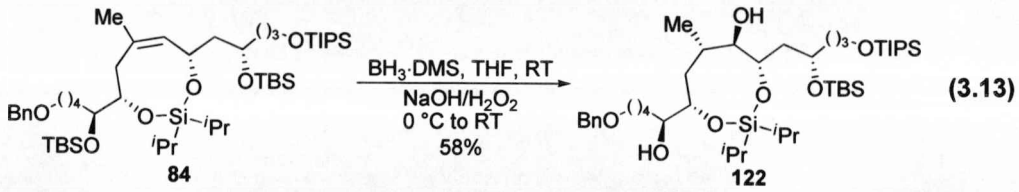
Scheme 3.23 *Synthesis of Allylic Alcohol* ***51***

Treatment of the homoallylic carbonate, **113** with 1% HCl in methanol, gave the primary alcohol which was protected as the TIPS ether **119** in 67% overall yield (Scheme 3.23). Treatment of **119** with IBr at -85 °C followed by carbonate deprotection and concomitant cyclization using the standardized procedure[56] afforded the desired epoxyalcohol **121** as a single stereoisomer in 71% overall yield. The improved stability of the TIPS ether enabled the workup without the decomposition thus allowing a high reproducibility of this reaction. The standard silyl protection of the secondary alcohol **121** followed by epoxide opening using Me_3SOTf salt[44] finally provided the access to the allylic alcohol **51**. Now the stage was set to examine the TST-RCM coupling.



Scheme 3.24 *The Synthesis of Cyclic Silaketal* ***84***

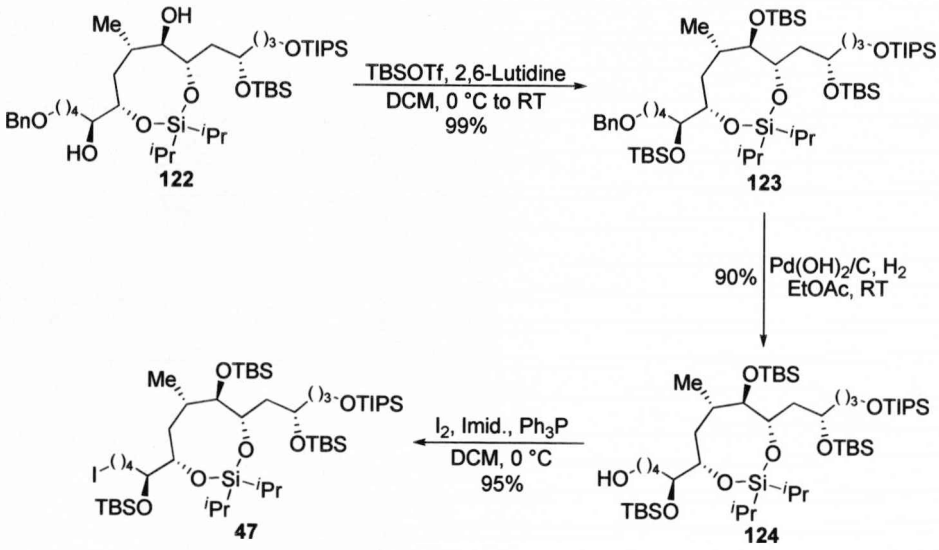
The initial optimization studies related to the silicon tether reaction indicated that the selective monosilylation of the alcohol **49** required 4.5 equivalents of the diisopropyldichlorosilane, to minimize problems associated with the formation of the symmetrical silaketal. The controlled monosilylation of **49** was established through the slow addition *via* syringe pump, followed by removal of excess diisopropyldichlorosilane, prior to the introduction of the allylic alcohol to provide the desired silaketal **85** in 84% yield (Scheme 3.24). Treatment of the acyclic silaketal **85** with the catalytic amount of the Grubbs' 2nd generation catalyst in refluxing DCM furnished the silacycle **84** in 88% yield, in addition to a trace amount of the dimerized product. Treatment of silacycle **84** with BH_3·DMS complex at the



(3.13)

ambient temperature for 2 hours followed by an overnight oxidation furnished a partially desilylated product **122** in 58% yield as a single stereoisomer (Eq. 3.13). However, since the next step in the synthesis of fully functionalized C16-C30

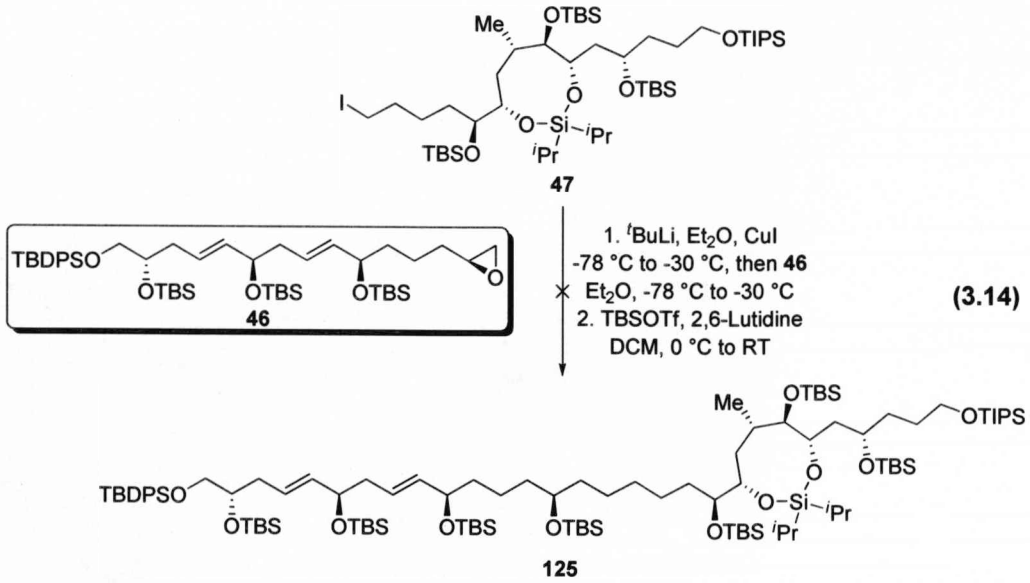
fragment is the TBS protection of the secondary alcohol installed through the hydroboration reaction, crude hydroboration mixture was treated with TBSOTf and 2,6-lutidine to provide the compound **123** in 92% yield over two steps. Deprotection



Scheme 3.25 *The Synthesis of Primary Iodide* ***47***

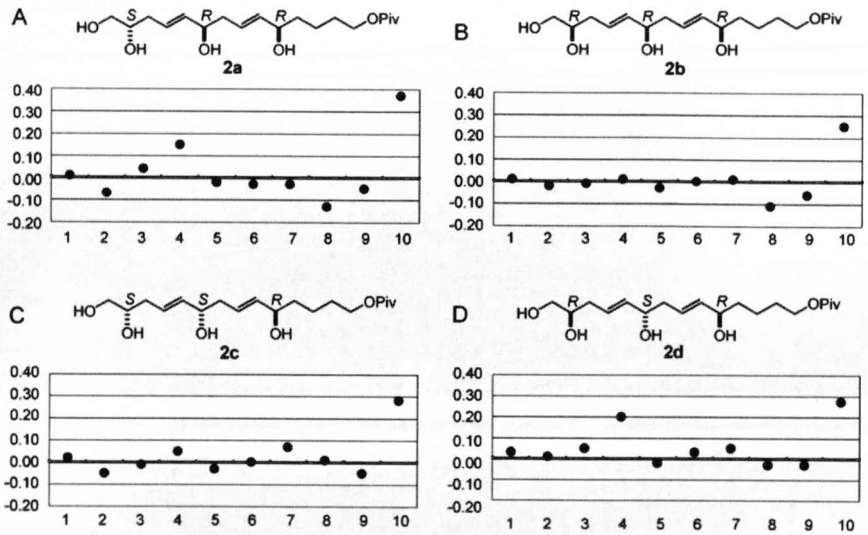
of the benzyl ether in the compound **123** gave the primary alcohol **124** in 90% yield. Finally, the iodination of the primary alcohol **124** using the procedure described by Zakarian and Stivala[59] furnished the primary iodide **47** in the 95% yield (Scheme 3.25). This reaction finalizes the synthesis of the C16-C30 fragment of amphidinol 3.

Hence, with the two fragments in hand the final coupling could be examined. Treatment of the primary iodide **47** with 2.2 equivalents of ^{t}BuLi in Et_2O at -78 °C, followed by transmetallation with CuI or CuCN to provide the cuprate, followed by the addition of the epoxide failed to afford the ring-opening product (Eq. 3.14). The analysis of reaction mixture indicated that iodide **47** did not undergo to substantial lithium-iodide exchange.



3.3 Structure Revision of Amphidinol 3

In 2008, Murata and co-workers reported the combinatorial synthesis of the C1-C14 polyol fragment of amphidinol 3 highlighting the application of the chemoselective cross-metathesis (*vide supra*).[14] The methodology allowed the synthesis of the all-possible stereoisomers corresponding to the C1-C14 moiety.



Reproduced from: *Org. Lett.* **2008**, *10*, 5203-5206.

Figure 3.3 *Differences in* ^{13}*C-NMR Chemical Shifts Between Amphidinol 3 and Synthetic Fragments* ***(2a-2d)***

NMR spectra of synthetic C1-C14 fragments were compared with those of amphidinol 3. The ^{1}H-NMR data among the diastereomers were virtually indistinguishable based on either chemical shifts or *J*-coupling values. The chemical shift differences in ^{13}C-NMR (125 MHz, 1:2 C_5D_5N/CD_3OD) were also inconsequential and within 0.2 ppm as described in the Figure 3.3. However, the discrepancies at C4 of the 2,6-*syn* stereoisomers (**2b**, **2c**) appeared to be lower than those of the 2,6-*anti* stereoisomers (**2a**, **2d**). During the structural elucidation of amphidinol 3, Murata and co-workers have determined the absolute configuration at C6 and C10 unambiguously *via* modified Mosher method, however the stereochemistry at C2 position was assigned by chemical degradation studies in combination with the partial synthesis. However, Murata and co-workers decided to

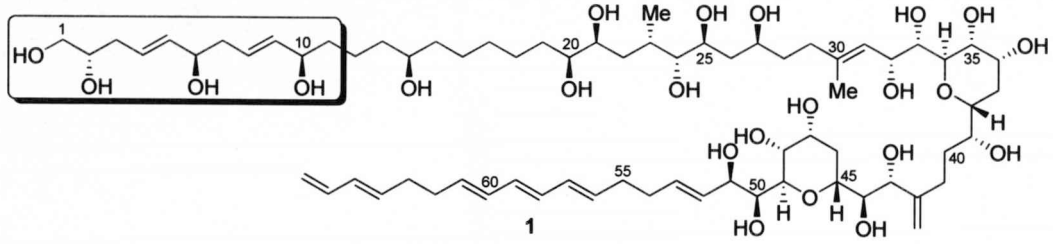


Figure 3.4 *Originally Proposed and Revised Structure of Amphidinol 3*

reconfirm the absolute configuration at C2 position. The degradation of the amphidinol 3 was accomplished in a single step *via* olefin metathesis under the

atmosphere of ethylene due to the limited availability of the natural product. The comparison of the degradation fragments and authentic samples *via* GC-MS instrument equipped with a chiral capillary column indicated indeed that the absolute configuration at C2 is *R* (Figure 3.4). The reason for the missassignment in the original structure is unclear, therefore a further investigation is required.

In our synthetic approach toward the C1-C30 fragment, the missassigned stereocenter is contained within the epoxide **46**. The synthesis of this C1-C15 fragment commenced with the (*R*)-glycidol. In order to install the correct stereochemistry at C2 position the synthesis has to begin from (*S*)-glycidol.

3.4 Conclusions

We have developed an efficient stereoselective synthesis of the C16-C30 polyol fragment of amphidinol 3 utilizing a highly convergent 11 step longest linear sequence in 23.7% overall yield. The synthesis highlighted the development and the first application of the temporary silicon-tethered ring-closing metathesis and diastereoselective hydroboration reaction in the construction of polyol domain of the amphidinol 3. The synthesis further described the utility of cyclic iodocarbonates as a versatile synthons for the construction of 1,3-*syn*-diols. In addition, we have developed the asymmetric synthesis of C1-C15 fragment, which highlights the application of chemoselective cross-metathesis and enantioselective allyltitanation reactions. Both advanced synthetic fragments were utilized for the key cross-coupling reaction to establish the synthesis of entire C1-C30 polyol domain through the stereoselective epoxide opening *via* organocopper reagent. However, at this stage, the final coupling was not successfully realized. Further studies are under way toward the solution of this problem and completion of the synthesis.

3.5 Experimental

3.5.1 General

Analytical thin layer chromatography (TLC) was performed on Whatman F_{254} precoated silica gel plates (250 μm thickness). Visualization was accomplished with a UV light and/or a $KMnO_4$ solution. Flash column chromatography (FCC) was performed using Whatman Silica Gel Purasil® 60Å (230-400 mesh). Solvents for extraction and FCC were technical grade. Reported solvents mixtures for both TLC and FCC were volume/volume mixtures.

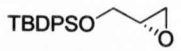
^1H NMR and ^{13}C NMR were recorded on Bruker AV 500 MHz NMR spectrometers in the indicated deuterated solvents. For ^1H NMR $CDCl_3$ was set to 7.24 ppm ($CDCl_3$ singlet) and for ^{13}C NMR to 77.16 ppm ($CDCl_3$ center of triplet). For ^1H NMR C_6D_6 was set to 7.15 ppm (C_6D_6 singlet) and for ^{13}C NMR to 128.0 ppm (C_6D_6 center of triplet). All values for ^1H NMR and ^{13}C NMR chemical shifts for deuterated solvents were obtained from Cambridge Isotope Labs. Data are reported in the following order: chemical shift in ppm (δ) (multiplicity, which are indicated by br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet)); assignment of 2^{nd} order pattern, if applicable; coupling constants (*J*, Hz); integration. All ^{13}C NMR spectra were reported using descriptor (*o*) and (*e*) referring to whether the peak is odd or even, respectively, and correlates to an attached proton test (ATP) experiment. Infrared spectra (IR) were obtained on a Perkin-Elmer Spectrum 100 series FTIR spectrophotometer. Peaks are reported in cm^{-1} with the following relative intensities: s (strong), m (medium) and w (weak). Mass spectra were performed by the University of Liverpool Mass Spectrometry center. High resolution electron impact (EI, ionization voltages of 70 eV) and

chemical ionization (CI, reagent gas NH_3) were obtained on the VG 7070E double focusing magnetic sector mass spectrometer equipped with solid probe inlet. Electrospray ionization (ESI) mass spectra by direct infusion using a syringe pump were obtained on a Waters micromass LCT mass spectrometer.

Unless otherwise indicated, all reactions were carried out in flame dried round bottom flasks and under an atmosphere of argon. Syringes and needles were oven-dried (125 °C) and cooled in a desiccator. Benzene (PhH) was dried over an alumina column solvent system using the method of Grubbs.[66] Ethanol (EtOH) was purchased from Aldrich chemical company and used without further purification.

All high-pressure liquid chromatographs were obtained using an Agilent Technologies 1200 series liquid chromatograph. With wavelength of diode array detector set at either 210 or 254nm. HPLC grade solvents were used as eluents. The instrument was fitted with a chiral AD-H or AS-H Daicel Chemical Industries Ltd. column (0.46cm x 25 cm) for separation of enantiomers. All starting materials were purchased from Acros, Aldrich, Alfa Aesar or Strem chemical companies and used without further purification unless otherwise noted.

3.5.2 Experimental Procedures



52a

(*S*)-*tert*-Butyl(oxiran-2-ylmethoxy)diphenylsilane 52a[11c]

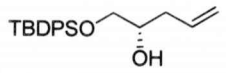
Experimental Procedure: To a solution of (*R*)-glycidol **52** (5.05 g, 66.2 mmol) in anhydrous DMF (97 mL) was added imidazole (5.86 g, 86. mmol) and the mixture was cooled with stirring to 0 °C under an atmosphere of argon. *tert*-Butyl(chloro)diphenylsilane (21.08 mL, 79 mmol) was added dropwise and the mixture was allowed to warm to room temperature and stirred for *ca.* 3 hours. The

reaction was quenched with water, diluted with diethyl ether, and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 3% diethyl ether/hexanes) furnished epoxide **52a** (17.55 g, 85% yield) as a colorless oil.

$[\alpha]_D^{23}$ -2.9 (c = 2.02, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.44-7.36 (m, 6H), 3.84 (dd, A of ABX, J_{AB} = 11.8 Hz, J_{AX} = 3.2 Hz, 1H), 3.70 (dd, B of ABX, J_{AB} = 11.9 Hz, J_{BX} = 4.7 Hz, 1H), 3.13-3.10 (m, 1H), 2.73 (dd, J = 4.9, 4.4 Hz, 1H), 2.60 (dd, J = 5.2, 2.7 Hz, 1H), 1.05 (s, 9H).

IR (Neat): 3071 (w), 3050 (w), 2999 (w), 2958 (w), 2931 (w), 2894 (w), 2858 (w), 1590 (w), 1472 (w), 1428 (m), 1111 (m), 1090 (m), 823 (m), 739 (m), 700 (s) cm^{-1}.



53

(*S*)-1-(*tert*-Butyldiphenylsilyloxy)pent-4-en-2-ol 53[11c]

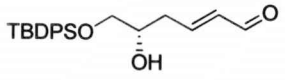
Experimental Procedure: To a suspension of copper iodide (0.015 g, 0.077 mmol) in anhydrous tetrahydrofuran (4.02 mL) previously cooled to -25 °C was added vinyl magnesium bromide (3.22 mL, 3.22 mmol, 1.0M in THF) under an atmosphere of argon at such rate that the internal temperature never rose above -22 °C. The mixture was stirred for *ca.* 30 minutes, then epoxide **52a** (0.25 g, 0.8 mmol) as a solution in anhydrous tetrahydrofuran (3 mL) was added at such rate that the internal temperature never rose above -22 °C. The reaction mixture was stirred for an additional hour, then quenched with saturated aqueous NH_4Cl solution and filtered through Celite. The mixture was diluted with diethyl ether and water and partitioned

between diethyl ether and water. The combined organic phases were washed twice with water, once with brine. The combined aqueous phases were back extracted twice with diethyl ether, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 2-5% ethyl acetate/hexanes) furnished homoallylic alcohol **53** (0.27 g, 99% yield) as a colorless oil.

$[\alpha]_D^{22}$ -3.4 (c = 1.21, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (t, J = 1.4 Hz, 2H), 7.64 (t, J = 1.4 Hz, 2H), 7.44-7.36 (m, 6H), 5.78 (ddt, J = 17.2, 10.2, 7.0 Hz, 1H), 5.08 (dd, J = 3.3, 1.5 Hz, 1H), 5.05-5.03 (m, 1H), 3.80-3.74 (m, 1H), 3.65 (dd, A of ABX, J_{AB} = 10.2 Hz, J_{AX} = 3.8 Hz, 1H), 3.53 (dd, B of ABX, J_{AB} = 10.2 Hz, J_{BX} = 6.9 Hz, 1H), 2.45 (d, J = 4.0 Hz, 1H), 2.23 (dt, J = 6.7, 1.1 Hz, 2H), 1.05 (s, 9H).

IR (Neat): 3445 (br w), 3072 (w), 3050 (w), 2931 (w), 2858 (w), 1642 (w), 1590 (w), 1472 (w), 1428 (m), 1111 (s), 823 (m), 739 (m), 700 (s) cm^{-1}.



54

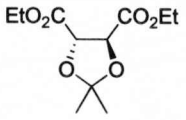
(*S*,*E*)-6-(*tert*-Butyldiphenylsilyloxy)-5-hydroxyhex-2-enal 54[11c]

Experimental Procedure: To a solution of homoallylic alcohol **53** (3.865 g, 11.4 mmol) in anhydrous tetrahydrofuran (95 mL) was added acrolein (4.21 mL, 56.7 mmol) at room temperature under an atmosphere of argon. To the mixture was added the Hoveyda-Grubbs' 2nd generation catalyst (0.356 g, 0.567 mmol) and the mixture was heated under reflux for *ca.* 12 hours. The mixture was concentrated *in vacuo* to afford the dark brown crude oil. Purification by flash chromatography (eluting with 25% ethyl acetate/hexanes) furnished aldehyde **54** (3.597 g, 86% yield) as a yellow oil.

$[\alpha]_D^{24}$ -13.3 (c = 1.21, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 1.4 Hz, 2H), 7.62 (d, *J* = 1.5 Hz, 2H), 7.45-7.37 (m, 6H), 6.83 (dt, *J* = 15.7, 7.1 Hz, 1H), 6.12 (ddt, *J* = 15.7, 7.9, 1.4 Hz, 1H), 3.90-3.85 (m, 1H), 3.67 (dd, A of ABX, J_{AB} = 10.3 Hz, J_{AX} = 3.8 Hz, 1H), 3.54 (dd, B of ABX, J_{AB} = 10.3 Hz, J_{BX} = 6.6 Hz, 1H), 2.53 (d, *J* = 4.4 Hz, 1H), 2.48-2.45 (m, 2H), 1.06 (s, 9H).

IR (Neat): 3450 (br w), 3071 (w), 3049 (w), 2931 (w), 2858 (w), 2739 (w), 1687 (s), 1589 (w), 1428 (m), 1111 (s), 823 (m), 741 (m), 702 (s) cm^{-1}.



55a

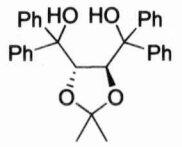
(4*S*,5*S*)-diethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 55a[67]

Experimental Procedure: (−)-Diethyl-D-tartarate (3.34 ml, 17.8 mmol) was dissolved in anhydrous benzene (9.7 ml) at ambient temperature under an atmosphere of argon. 2,2-Dimethoxypropane (17.89 ml, 143 mmol) was added dropwise followed by addition of CSA (0.21 g, 0.89 mmol) in one portion. The reaction mixture was refluxed under Dean-Stark trap for 90 min. The reaction mixture was allowed to cool to ambient temperature after which was neutralized with triethylamine. The solvent was removed *in vacuo* to afford a colorless crude oil. Purification by flash chromatography (eluting with 5-20% ethyl acetate/hexanes) furnished the diester **55a** (4.12 g, 94% yield) as a colorless oil.

$[\alpha]_D^{24}$ + 37.1 (c = 18.0, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 4H), 1.48 (s, 6H), 1.30 (t, *J* = 7.2 Hz, 6H).

IR (Neat): 2988 (w), 2941 (w), 1736 (s), 1448 (w), 1373 (m), 1203 (s), 1106 (s), 1023 (s), 854 (m) cm^{-1}.



55b

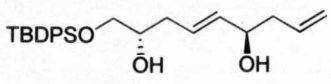
((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)*bis*(diphenylmethanol) 55b[68]

Experimental Procedure: Phenylmagnesium bromide (15.0 ml, 15.0 mmol, 1 M in diethyl ether) was added to anhydrous diethyl ether (28.4 ml) at ambient temperature under an atmosphere of argon. The solution was cooled to 0 °C and diester **55a** (0.68 g, 2.77 mmol) was added dropwise as a solution in diethyl ether (20 ml). Reaction mixture was allowed to stir overnight at ambient temperature. Reaction was quenched with saturated aqueous of NH_4Cl and partitioned between diethyl ether and water. Combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to afford the crude crystalline solid. Purification by flash chromatography (eluting with 10-30% diethyl ether/hexanes) furnished the diol **55b** (0.97 g, 75% yield) as a white crystalline solid

$[\alpha]_D^{19}$ +67.0 (c = 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52-7.50 (m, 4H), 7.35-7.29 (m, 10H), 7.28-7.20 (m, 6H), 4.58 (s, 2H), 4.07 (s, 2H), 1.02 (s, 6H).

IR (Neat): 3297 (br w), 3058 (w), 2985 (w), 2897 (w), 1600 (w), 1495 (m), 1447 (m), 1167 (m), 1048 (m), 885 (m), 739 (s), 700 (s) cm^{-1}.



77

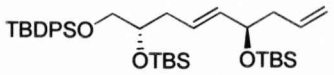
(2*S*,6*R*,*E*)-1-(*tert*-Butyldiphenylsilyloxy)nona-4,8-diene-2,6-diol 77[11c]

Experimental Procedure: To a solution of Duthaler-Hafner titanium complex (*S*, *S*)-**55** (1.039 g, 1.695 mmol) in anhydrous diethyl ether (21.3 mL) cooled at 0 °C, was added allyl magnesium bromide (1.47 mL, 1.47 mmol, 1.0 M in diethyl ether) under an atmosphere of argon over the period of *ca.* 15 minutes. The mixture was stirred for *ca.* 1.5 hours, and then cooled to -78 °C. A solution of aldehyde **54** (0.39 g, 1.06 mmol) in anhydrous diethyl ether (5.7 mL) was added over period of *ca.* 15 minutes. The reaction was stirred at -78 °C for an additional 4 hour, then quenched with water and allowed to warm to room temperature and stirred vigorously for *ca.* 14 hours. The mixture was filtered through Celite and partitioned between diethyl ether and water. The combined organic phases were washed twice with water, once with brine. The combined aqueous phases were back extracted twice with ethyl acetate, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-30 % ethyl acetate/hexanes) furnished diol **77** (0.29 g, 68% yield) as a yellow oil.

$[\alpha]_D^{26}$ +3.6 (c = 1.04, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 1.7 Hz, 2H), 7.63 (d, J = 1.8 Hz, 2H), 7.44-7.36 (m, 6H), 5.74 (ddt, J = 17.2, 10.3, 7.1 Hz, 1H), 5.65-5.59 (m, 1H), 5.51 (dd, J = 15.5, 6.4 Hz, 1H), 5.11-5.06 (m, 2H), 4.08 (q, J = 6.1 Hz, 1H), 3.77-3.72 (m, 1H), 3.63 (dd, A of ABX, J_{AB} = 10.2 Hz, J_{AX} = 3.8 Hz, 1H), 3.52 (dd, B of ABX, J_{AB} = 10.2 Hz, J_{BX} = 6.9 Hz, 1H), 2.44 (d, J = 3.5 Hz, 1H), 2.29-2.18 (m, 4H), 1.61 (br s, 1H), 1.05 (s, 9H).

IR (Neat): 3378 (br w), 3072 (w), 2930 (w), 2858 (w), 1641 (w), 1590 (w), 1428 (m), 1111 (s), 823 (m), 740 (m), 701 (s) cm^{-1}.



48

(5*R*,9*S*,*E*)-5-Allyl-9-(*tert*-butyldimethylsilyloxy)-2,2,3,3,13,13-hexamethyl-12,12-diphenyl-4,11-dioxa-3,12-disilatetradec-6-ene 48

Experimental Procedure: To a solution of a diol **77** (0.216 g, 0.53 mmol) in anhydrous dichloromethane (5.3 mL) at room temperature under an atmosphere of argon was added imidazole (0.214 g, 3.15 mmol). The reaction mixture was cooled to 0 °C and to the mixture was added *tert*-butyl(chloro)dimethylsilane (0.237 g, 1.574 mmol) dropwise in anhydrous dichloromethane (1 mL). The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 0-8 % diethyl ether/hexanes) furnished protected diol **48** (0.294 g, 88% yield) as a yellow oil.

$[\alpha]_D^{23}$ +3.4 (c = 1.42, $CHCl_3$).

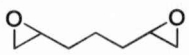
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.63 (m, 4H), 7.42-7.33 (m, 6H), 5.75 (ddt, J = 17.3, 10.2, 7.1 Hz, 1H), 5.60-5.54 (m, 1H), 5.45 (dd, J = 15.4, 6.2 Hz, 1H), 5.01-5.00 (m, 1H), 4.98-4.95 (m, 1H), 4.05 (q, J = 6.1 Hz, 1H), 3.73 (quintet, J = 5.3 Hz, 1H), 3.50 (dd, A of ABX, J_{AB} = 10.0 Hz, J_{AX} = 5.3 Hz, 1H), 3.45 (dd, B of ABX, J_{AB} = 10.1 Hz, J_{BX} = 6.7 Hz, 1H), 2.39-2.34 (m, 1H), 2.26-2.14 (m, 3H), 1.02 (s, 9H), 0.86 (s, 9H), 0.82 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H), -0.03 (s, 3H), -0.08 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.73 (o), 135.62 (o), 135.45 (o), 133.82 (e), 133.78 (e), 129.74 (o), 127.79 (o), 126.14 (o), 116.74 (e), 73.30 (o), 72.83 (o), 67.04

(e), 43.28 (e), 37.29 (e), 26.99 (o), 26.07 (o), 26.01 (o), 19.35 (e), 18.41 (e), 18.22 (e), -4.09 (o), -4.38 (o), -4.60 (o), -4.65 (o).

IR (Neat): 3073 (w), 2955 (m), 2929 (m), 2894 (w), 2857 (m), 1641 (w), 1428 (m), 1253 (m), 1111 (s), 1073 (s), 974 (m), 834 (s), 775 (s), 701 (s) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{37}H_{62}O_3NaSi_3$ 661.3905, found 661.3932.



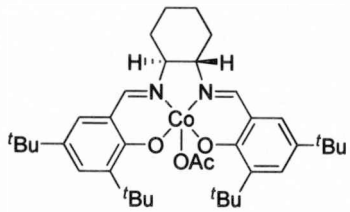
63

1,3-Di(oxiran-2-yl)propane 63[42,43]

Experimental Procedure: To a solution of 1,6-heptadiene (7 mL, 51.5 mmol) in anhydrous dichloromethane (99 mL) cooled to 0 °C was added *m*-CPBA (39 g, 113 mmol) in portions over the period of *ca.* 30 minutes, followed by potassium carbonate (1.16 g, 8.39 mmol) under an atmosphere of argon,. The reaction mixture was stirred for *ca.* 30 minutes, then was allowed to warm to room temperature and stirred for an additional 4 hours. The reaction mixture was filtered and precipitate was washed with cold dichloromethane. The combined filtrates were washed once with 5% aqueous solution of Na_2SO_3, three times with saturated aqueous $NaHCO_3$ solution and once with brine. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0-50 % diethyl ether/petroleum ether) furnished *bis*-epoxide **63** (6.53 g, 99% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.92-2.88 (m, 1H), 2.74 (t, J = 4.4 Hz, 1H), 2.46 (dt, J = 5.1, 3.0 Hz, 1H), 1.66-1.50 (m, 3H).

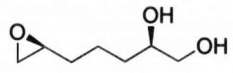
IR (Neat): 3049 (w), 2985 (w), 2925 (m), 2863 (w), 1483 (w), 1410 (m), 1259 (m), 1133 (w), 913 (m), 831 (s) cm^{-1}.



80

(*S*,*S*)-Salen-Co^{III}-OAc 80[41b]

Experimental Procedure: (*S*,*S*)-Salen cobalt(II) (0.319 g, 0.529 mmol) was dissolved in anhydrous toluene (6.61 mL) at room temperature under an atmosphere of argon. The acetic acid (0.32 mL, 5.55 mmol) was added dropwise and the reaction was stirred open to air for *ca.* 30 minutes. Toluene and acetic acid were removed *in vacuo*, and crude brown solid was dried *in vacuo* overnight. The crude catalyst **80** was used for next step without further purification (0.35 g, 100% yield).



78

(*R*)-5-((*S*)-Oxiran-2-yl)pentane-1,2-diol 78

Experimental Procedure: The Jacobsen catalyst **80** (0.341 g, 0.515 mmol) was dissolved in *bis*-epoxide **63** (6.6 g, 51.5 mmol) and solution was cooled to 0 °C. Water (0.94 mL, 52.2 mmol) was added dropwise and reaction mixture was allowed to warm to room temperature and stirred for *ca.* 3 days. The crude oil was dissolved in dichloromethane and was dry-packed on silica gel *in vacuo*. Purification by flash chromatography (eluting with 50-90 % ethyl acetate/petroleum ether) afforded epoxy diol **78** (3.76 g, 68% yield) as a yellow oil.

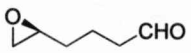
$[\alpha]_D^{24}$ -12.1 (c = 1.15, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (br s, 1H), 3.61 (d, J = 10.6 Hz, 1H), 3.40 (t, J = 9.3Hz, 1H), 2.94 (br s, 1H), 2.92-2.89 (m, 1H), 2.81 (br s, 1H), 2.73 (dd, J = 4.9, 4.1 Hz, 1H), 2.46 (dd, J = 4.9, 2.8 Hz, 1H), 1.65-1.59 (m, 2H), 1.50-1.43 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 71.98 (o), 66.56 (e), 52.39 (o), 47.10 (e), 32.65 (e), 32.25 (e), 22.09 (e).

IR (Neat): 3378 (br s), 2927 (s), 2865 (m), 1649 (w), 1459 (m), 1411 (m), 1261 (m), 1067 (s), 1038 (s), 913 (m), 829 (s) cm^{-1}.

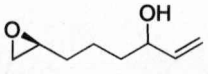
HRMS (CI, MNH_4^+): calcd for $C_7H_{18}O_3N$ 164.12867, found 164.12799.



78a

(*S*)-4-(Oxiran-2-yl)butanal 78a

Experimental Procedure: Epoxy diol **78** (2.56 g, 17.52 mmol) was dissolved in dichloromethane/water mixture (25 mL, 1:1) at room temperature. Sodium periodate (7.57 g, 35.0 mmol) was added in portions and biphasic mixture was allowed to stir for *ca.* 1 hour. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and partition between dichloromethane and water. The combined organic phases were washed twice with 10% aqueous Na_2SO_3 solution, once with brine, dried ($MgSO_4$) and concentrated *in vacuo* (not below 60 Torrs) to afford a crude aldehyde **78a**, which was used for the next step without further purification.



79

6-((*S*)-Oxiran-2-yl)hex-1-en-3-ol 79

Experimental Procedure: Crude aldehyde **78a** (*ca.* 17.52 mmol) was dissolved in anhydrous diethyl ether (175 mL) and the solution was cooled to -78 °C under an atmosphere of argon. Vinyl magnesium bromide (35 mL, 35 mmol, 1M in THF) was added dropwise. The reaction was stirred for *ca.* 1 hour, then quenched with saturated aqueous NH_4Cl solution and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and

concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 30-50 % diethyl ether/petroleum ether) furnished the allylic alcohol **79** (1.513 g, 61% yield) as a yellow oil.

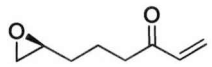
$[\alpha]_D^{23}$ -9.8 (c = 1.19, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dddd, *J* = 17.2, 10.4, 6.3, 1.1 Hz, 1H), 5.20 (dq, *J* = 17.4, 1.1 Hz, 1H), 5.09 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.09 (d, *J* = 4.7 Hz, 1H), 2.91-2.87 (m, 1H), 2.73 (t, *J* = 4.5 Hz, 1H), 2.46-2.44 (m, 1H), 1.69 (d, *J* = 11.5 Hz, 1H), 1.60-1.45 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 141.15 (o), 141.12 (o), 114.66 (e), 114.65 (e), 72.85 (o), 72.83 (o), 52.37 (o), 52.33 (o), 47.13 (e), 47.10 (e), 36.60 (e), 36.55 (e), 32.28 (e), 32.25 (e), 21.90 (e), 21.77 (e).

IR (Neat): 3414 (br m), 2924 (m), 2860 (m), 1644 (w), 1458 (m), 1410 (m), 1260 (m), 1133 (m), 991 (m), 918 (s), 831 (m) cm^{-1}.

HRMS (CI, MNH_4^+): calcd for $C_8H_{18}O_2N$ 160.13375, found 160.13311.



50

(*S*)-6-(Oxiran-2-yl)hex-1-en-3-one 50

Experimental Procedure: *N*-Methyl morpholine *N*-oxide monohydrate (7.32 g, 52.5 mmol) was dissolved in anhydrous dichloromethane (72.1 mL) and treated with excess $MgSO_4$ for 20 minutes at room temperature with vigorous stirring. The drying agent was filtered, and filtrate was stirred with activated molecular sieves (4 Å). Allylic alcohol **79** (1.51 g, 10.64 mmol) was added as a solution in anhydrous dichloromethane (5 mL). The mixture was stirred for *ca.* 20 minutes prior to addition of the catalyst. TPAP (0.1 g, 0.28 mmol) was added in one portion and

suspension was stirred overnight. The brown suspension was filtered through silica pad, eluting with diethyl ether. The combined organic phases were washed with saturated aqueous $CuSO_4$ solution, brine, water, then brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 20-40 % diethyl ether/petroleum ether) furnished epoxy enone **50** (0.753 g, 49% yield) as a yellow oil.

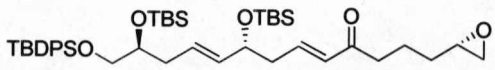
$[\alpha]_D^{23}$ -11.5 (c = 1.16, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (dd, *J* = 17.7, 10.5 Hz, 1H), 6.20 (dd, *J* = 17.7, 1.0 Hz, 1H), 5.81 (dd, *J* = 10.5, 1.0 Hz, 1H), 2.91-2.87 (m, 1H), 2.72 (t, *J* = 4.5 Hz, 1H), 2.64 (dt, *J* = 7.1, 1.7 Hz, 2H), 2.44 (dd, *J* = 5.0, 2.7 Hz, 1H), 1.81-1.75 (m, 2H), 1.66-1.59 (m, 1H), 1.50-1.43 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 200.27 (e), 136.49 (o), 128.17 (e), 52.01 (o), 46.80 (e), 38.92 (e), 31.79 (e), 20.30 (e).

IR (Neat): 2936 (w), 1698 (m), 1678 (s), 1615 (m), 1403 (m), 1187 (w), 965 (m), 921 (m), 835 (m) cm^{-1}.

HRMS (CI, MH^+): calcd for $C_8H_{13}O_2$ 141.09155, found 141.09141.



81

(5*E*,8*R*,9*E*,12*S*)-8,12-*bis*(*tert*-Butyldimethylsilyloxy)-13-(*tert*-butyldiphenylsilyloxy)-1-((*S*)-oxiran-2-yl)trideca-5,9-dien-4-one 81

Experimental Procedure: To *bis*-protected diol **48** (0.107 g, 0.167 mmol) was added epoxy enone **50** (0.07 g, 0.502 mmol) as a solution in anhydrous dichloromethane (1.7 mL) at room temperature under an atmosphere of argon. The Hoveyda-Grubbs' 2nd generation catalyst (10.5 mg, 0.017 mmol) was added and solution was stirred

for *ca.* 48 hours. The solvent was removed *in vacuo* to afford the dark brown oil. Purification by flash chromatography (eluting with 0-30 % diethyl ether/petroleum ether) furnished epoxide **81** (0.098 g, 78% yield) as a yellow oil.

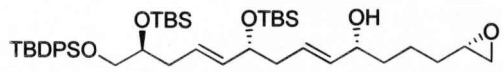
$[\alpha]_D^{23}$ +3.1 (c = 1.12, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65-7.62 (m, 4H), 7.42-7.34 (m, 6H), 6.80 (dt, *J* = 15.7, 7.5 Hz, 1H), 6.06 (d, *J* = 16.0 Hz, 1H), 5.64-5.58 (m, 1H), 5.44 (dd, *J* = 15.4, 6.2 Hz, 1H), 4.14 (q, *J* = 6.1 Hz, 1H), 3.72 (quintet, *J* = 5.2 Hz, 1H), 3.50 (dd, A of ABX, J_{AB} = 10.1 Hz, J_{AX} = 5.2 Hz, 1H), 3.45 (dd, B of ABX, J_{AB} = 11.1 Hz, J_{BX} = 7.0 Hz, 1H), 2.90-2.87 (m, 1H), 2.72 (t, *J* = 4.5 Hz, 1H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.44 (dd, *J* = 5.0, 2.7 Hz, 1H), 2.40-2.31 (m, 3H), 2.25-2.20 (m, 1H), 1.79-1.72 (m, 2H), 1.60-1.53 (m, 1H), 1.48 (quintet, *J* = 7.2 Hz, 1H), 1.02 (s, 9H), 0.85 (s, 9H), 0.81 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H), -0.04 (s, 3H), -0.09 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 199.86 (e), 144.16 (o), 135.66 (o), 135.01 (o), 133.67 (e), 133.65 (e), 132.37 (o), 129.74 (o), 127.76 (o), 126.91 (o), 72.56 (o), 72.44 (o), 66.89 (e), 52.09 (o), 46.93 (e), 41.79 (e), 39.13 (e), 37.15 (e), 31.99 (e), 26.94 (o), 25.94 (o), 20.57 (e), 19.29 (e). 18.26 (e), 18.16 (e), -4.08 (o), -4.43 (o), -4.71 (o), -4.74 (o).

IR (Neat): 2954 (m), 2929 (m), 2857 (m), 1698 (w), 1675 (w), 1631 (w), 1472 (w), 1252 (m), 1112 (s), 1071 (m), 834 (s), 775 (s), 701 (s) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{43}H_{70}O_5NaSi_3$ 773.4429, found 773.4439.



81a

(4*R*,5*E*,8*R*,9*E*,12S)-8,12-*bis*(*tert*-Butyldimethylsilyloxy)-13-(*tert*-butyldiphenyl-silyloxy)-1-((*S*)-oxiran-2-yl)trideca-5,9-dien-4-ol 81a

Experimental Procedure: To a solution of epoxide **81** (0.098 g, 0.131 mmol) in anhydrous tetrahydrofuran (0.65 mL) cooled to -30 °C was added (*S*)-2-methyl-CBS-oxazaborolidine **82** (0.393 mL, 0.393 mmol, 1M in toluene) dropwise under an atmosphere of argon. $BH_3 \cdot DMS$ complex (0.093 mL, 0.917 mmol) was added slowly over period of *ca.* 10 minutes. The reaction mixture was stirred for 1 hour, then slowly quenched with methanol (0.32 mL) over the period of 1 hour. After majority of gas evolution subsided, the reaction was quenched with saturated aqueous NH_4Cl solution and partitioned between diethyl ether and water. The combined organic phases were washed twice with water, once with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 5-20 % ethyl acetate/hexanes) furnished the epoxy alcohol **81a** (0.094 g, 95% yield) as a yellow oil.

$[\alpha]_D^{24}$ +2.7 (c = 1.14, $CHCl_3$).

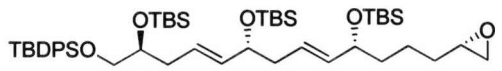
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66-7.64 (m, 2H), 7.64 (dd, J = 3.1, 1.5 Hz, 2H), 7.42-7.34 (m, 6H), 5.64-5.54 (m, 2H), 5.48-5.52 (m, 2H), 4.04 (q, J = 6.2 Hz, 1H), 4.01 (q, J = 6.4 Hz, 1H), 3.73 (quintet, J = 5.5 Hz, 1H), 3.50 (dd, A of ABX, J_{AB} = 10.0 Hz, J_{AX} = 5.2 Hz, 1H), 3.44 (dd, B of ABX, J_{AB} = 10.0 Hz, J_{BX} = 6.9 Hz, 1H), 2.90-2.87 (m, 1H), 2.72 (dd, J = 4.9, 4.0 Hz, 1H), 2.45 (dd, J = 5.0, 2.7 Hz, 1H), 2.39-2.34 (m, 1H), 2.25-2.11 (m, 3H), 1.59-1.49 (m, 6H), 1.28-1.23 (m, 1H), 1.02 (s,

9H), 0.86 (s, 9H), 0.82 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H), -0.03 (s, 3H), -0.08 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.70 (o), 135.53 (o), 135.13 (o), 133.76 (e), 133.74 (e), 129.74 (o), 128.79 (o), 127.78 (o), 126.22 (o), 73.28 (o), 73.07 (o), 72.74 (o), 66.97 (e), 52.34 (o), 47.21 (e), 41.55 (e), 37.23 (e), 36.92 (e), 32.47 (e), 26.97 (o), 26.04 (o), 25.99 (o), 22.08 (e), 19.33 (e). 18.38 (e), 18.21 (e), -4.06 (o), -4.39 (o), -4.61 (o), -4.65 (o).

IR (Neat): 3433 (br w), 2952 (m), 2929 (m), 2886 (m), 2857 (m), 1472 (m), 1428 (m), 1252 (m), 1112 (s), 1072 (s), 971 (m), 834 (s), 775 (s), 702 (s) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{43}H_{72}O_5NaSi_3$ 775.4585, found 775.4592.



46

(5*R*,6*E*,9*R*,10*E*,13*S*)-9,13-*bis*(*tert*-Butyldimethylsilyloxy)-2,2,3,3,17,17-hexamethyl-5-(3-((*S*)-oxiran-2-yl)propyl)-16,16-diphenyl-4,15-dioxa-3,16-disilaoctadeca-6,10-diene 46

Experimental Procedure: To a solution of epoxy alcohol **81a** (0.027 g, 0.036 mmol) in anhydrous dichloromethane (0.725 mL) at room temperature under an atmosphere of argon was added 2,6-lutidine (0.017 mL, 0.141 mmol) and solution was cooled to 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.011 mL, 0.047 mmol) was added dropwise. The reaction was stirred for *ca.* 1 hour then quenched with saturated aqueous $NaHCO_3$ solution and partitioned between dichloromethane and water. The combined organic phases were washed twice with water, once with brine. The combined aqueous phases were extracted twice with dichloromethane. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a

crude yellow oil. Purification by flash chromatography (eluting with 0-15 % diethyl ether/hexanes) furnished the epoxide **46** (0.028 g, 88% yield) as a yellow oil.

$[\alpha]_D^{22}$ -0.4 (c = 1.01, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (t, J = 1.8 Hz, 2H), 7.64 (t, J = 1.9 Hz, 2H), 7.42-7.33 (m, 6H), 5.60-5.36 (m, 4H), 4.04 (q, J = 6.1 Hz, 1H), 4.00 (q, J = 6.1 Hz, 1H), 3.72 (quintet, J = 5.6 Hz, 1H), 3.50 (dd, A of ABX, J_{AB} = 10.0 Hz, J_{AX} = 5.2 Hz, 1H), 3.45 (dd, B of ABX, J_{AB} = 10.0 Hz, J_{BX} = 6.7 Hz, 1H), 2.88-2.85 (m, 1H), 2.72 (t, J = 4.5 Hz, 1H), 2.43 (dd, J = 5.0, 2.7 Hz, 1H), 2.39-2.34 (m, 3H), 2.23-2.11 (m, 6H), 1.54-1.43 (m, 1H), 1.03 (s, 9H), 0.86 (s, 9H), 0.86 (s, 9H), 0.82 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H), -0.02 (s, 3H), -0.03 (s, 3H), -0.09 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.83 (o), 135.73 (o), 135.52 (o), 133.81 (e), 133.78 (e), 129.74 (o), 127.79 (o), 126.67 (o), 126.20 (o), 73.68 (o), 73.41 (o), 72.83 (o), 67.10 (e), 52.44 (o), 47.28 (e), 41.65 (e), 38.29 (e), 37.38 (e), 32.61 (e), 30.46 (o), 26.99 (o), 26.07 (o), 26.01 (o), 21.95 (e), 19.35 (e). 18.38 (e), 18.22 (e), -3.94 (o), -4.11 (o), -4.36 (o), -4.59 (o), -4.65 (o).

IR (Neat): 2954 (m), 2929 (m), 2857 (m), 1472 (w), 1428 (w), 1251 (m), 1112 (m), 1072 (m), 971 (m), 834 (s), 774 (s), 701 (s) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{49}H_{86}O_5NaSi_4$ 889.5450, found 889.5452.

86a

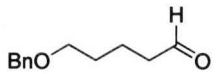
5-(Benzyloxy)pentan-1-ol 86a[69]

Experimental Procedure: To a suspension of sodium hydride (6 g, 150 mmol) in anhydrous DMF (500 mL) previously cooled to 0 °C, was added 1,5-pentanediol **86** (31.43 mL, 300 mmol) dropwise under an atmosphere of argon. The reaction was stirred for 15 minutes, after which time it was allowed to warm to room temperature

and stirred for an additional 1 hour. The suspension was cooled back to 0 °C and benzyl bromide (12.1 mL, 100 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude colorless oil. Purification by flash chromatography (eluting with 10-50% ethyl acetate/hexanes) furnished alcohol **86a** (17.0 g, 88% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 4.48 (s, 2H), 3.62 (t, J = 6.4 Hz, 2H), 3.46 (t, J = 6.4 Hz, 2H), 1.67-1.54 (m, 4H), 1.47-1.39 (m, 2H), 1.32 (br s, 1H).

IR (Neat): 3391 (br s), 3088 (m), 3064 (m), 3031 (m), 2937 (s), 2862 (s), 1604 (w), 1455 (m), 1099 (s), 1029 (m), 736 (m), 698 (m) cm^{-1}.



87

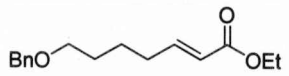
5-(Benzyloxy)pentanal 87[71]

Experimental Procedure: Alcohol **86a** (1.59 g, 8.20 mmol) was dissolved in anhydrous DCM (23 ml) at ambient temperature under an atmosphere of argon. The solution was cooled to 0 °C and triethylamine (8.0 ml, 57.4 mmol) followed by dimethylsulfoxide (5.6 ml, 78.3 mmol) was added dropwise. The solution was allowed to stir at 0 °C for 15 minutes. SO_3·pyridine complex (4.0 g, 24.6 mmol) was added in one portion and reaction allowed to stir for 4 hours at ambient temperature. The reaction mixture was diluted with DCM and washed with 5% HCl in water (v/v), saturated aqueous solution of $NaHCO_3$ and brine. Organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow crude oil. Purification by

flash chromatography (eluting with 5-20% ethyl acetate/hexanes) afforded the aldehyde **87** (1.31 g, 83% yield) as yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (t, J = 1.5 Hz, 1H), 7.38-7.25 (m, 5H), 4.49 (s, 2H), 3.48 (t, J = 6.0 Hz, 2H), 2.44 (dt, J = 7.1, 1.4 Hz, 2H), 1.81-1.58 (m, 4H).

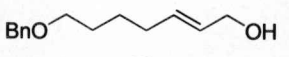
IR (Neat): 3030 (m), 2940 (s), 2865 (s), 2740 (w), 1725 (s), 1455 (m), 1365 (w), 1205 (w), 1100 (s), 740 (m), 700 (m) cm^{-1}.



87a

(*E*)-Ethyl-7-(benzyloxy)hept-2-enoate 87a

Experimental Procedure: (Carbetoxymethylene)triphenylphosph-orane (3.79 g, 10.9 mmol) was dissolved in anhydrous DCM (96 ml) at room temperature under an atmosphere of argon. Aldehyde **87** (1.31 g, 6.81 mmol) was added as a solution in DCM (10 ml + 10 ml rinse) and mixture allowed to stir overnight at ambient temperature. The reaction mixture was diluted with water and partitioned between water and ethyl acetate. Combined organic phases were washed with brine, dried (MgSO4) and concentrated *in vacuo* to afford the colorless crude oil. Purification by flash chromatography (eluting with 5-20% ethyl acetate/hexanes) furnished ester 87a (1.73 g, 97% yield) as a colorless oil.



89

(*E*)-7-(Benzyloxy)hept-2-en-1-ol 89

Experimental Procedure: DIBAL-H solution (14.5 mL, 14.5 mmol, 1.0 M in hexanes) was added dropwise to solution of ester **87a** (1.72 g, 6.58 mmol) in an anhydrous tetrahydrofuran (27 mL) previously cooled to -20 °C, under an atmosphere of argon. The reaction was stirred for 3 hours then quenched slowly with

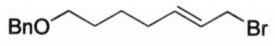
Rochelle salts, followed by addition of glycerol. The complex was stirred at room temperature overnight. The reaction was partitioned between ethyl acetate and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude colorless oil. Purification by flash chromatography (eluting with 10-50% ethyl acetate/hexanes) furnished allylic alcohol **89** (1.37 g, 95% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 5.71-5.55 (m, 2H), 4.47 (s, 2H), 4.05 (t, J = 5.3 Hz, 2H), 3.44 (t, J = 6.5 Hz, 2H), 2.04 (q, J = 6.7 Hz, 2H), 1.64-1.56 (m, 2H), 1.49-1.41 (m, 2H), 1.24 (t, J = 5.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.61 (e), 132.78 (o), 129.37 (o), 128.40 (o), 127.67 (o), 127.57 (o), 72.92 (e), 70.23 (e), 63.62 (e), 32.00 (e), 29.26 (e), 25.75 (e).

IR (Neat): 3390 (br m), 3088 (w), 3064 (w), 3030 (m), 2934 (s), 2858 (s), 1670 (w), 1496 (m), 1455 (m), 1101 (s), 971 (s), 736 (s), 698 (m) cm^{-1}.

HRMS (CI, M-OH^+): calcd for $C_{14}H_{19}O$ 203.1430, found 203.1430.



89a

(*E*)-((7-Bromohept-5-enyloxy)methyl)benzene 89a

Experimental Procedure: The allylic alcohol **89** (1.37 g, 6.22 mmol) was dissolved in anhydrous dichloromethane (20 mL) at room temperature under an atmosphere of argon. Triphenyl phosphine (1.97 g, 7.46 mmol) was added in one portion and the reaction was cooled to -30 °C. *N*-bromosuccinamide (1.33 g, 7.46 mmol) was added in portions. The reaction was stirred for *ca.* 3 hours then quenched with water and partitioned between dichloromethane and water. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude colorless oil. Purification

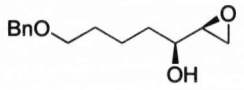
by flash chromatography (eluting with 1-10% ethyl acetate/hexanes) furnished allylic bromide **89a** (1.48 g, 84% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 5H), 5.78-5.63 (m, 2H), 4.48 (s, 2H), 3.92 (d, J = 7.0 Hz, 2H), 3.45 (t, J = 6.4 Hz, 2H), 2.07 (q, J = 6.9 Hz, 2H), 1.64-1.57 (m, 2H), 1.52-1.43 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.68 (e), 136.32 (o), 128.43 (o), 127.67 (o), 127.57 (o), 126.67 (o), 72.96 (e), 70.14 (e), 33.55 (e), 31.89 (e), 29.27 (e), 25.52 (e).

IR (Neat): 3063 (w), 3030 (m), 2936 (s), 2857 (s), 1660 (w), 1496 (m), 1454 (m), 1205 (s), 1105 (s), 967 (m), 736 (s), 698 (s) cm^{-1}.

HRMS (CI, M-H^+): calcd for $C_{14}H_{18}OBr$ 281.0536, found 281.0528.



90

(*S*)-5-(Benzyloxy)-1-((*S*)-oxiran-2-yl)pentan-1-ol 90

Experimental Procedure: $(DHQ)_2PHAL$ (28.7 mg, 0.035 mmol), $K_2Fe(CN)_6$ (3.49 g, 10.5 mmol), potassium carbonate (1.45 g, 10.5 mmol), $MeSO_2NH_2$ (0.34 g, 3.5 mmol) and $K_2OsO_2(OH)_4$ (10.31 mg, 0.028 mmol) were dissolved in *tert*-butanol (21.6 mL) and water (21.6 mL) at room temperature. The reaction was cooled to 0 °C and allylic bromide **89a** (0.99 g, 3.5 mmol) was added dropwise. The reaction was stirred for 12 hours. The reaction was quenched with saturated aqueous Na_2SO_3 solution and the solution was stirred for 1 hour at room temperature. The reaction was partitioned between ethyl acetate and water. The combined organic phases were washed twice with 3N KOH, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 10-30% ethyl acetate/hexanes) furnished epoxy alcohol **90** (0.72 g, 83% yield) as a yellow oil.

Chiral HPLC analysis (Diacel® AD-H column; 7% IPA/Hex, 1 ml/min at 25 °C; t_R(**(*R*,*R*)-90**) = 16.6 min, t_R(**(*S*,*S*)-90**) = 19.9 min) indicated *ee* = 93%

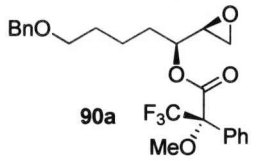
$[\alpha]_D^{25}$ +3.0 (c = 1.42, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 4.48 (s, 2H), 3.47 (t, *J* = 6.3 Hz, 2H), 3.44-3.41 (m, 1H), 2.96 (dt, *J* = 4.5, 2.8 Hz, 1H), 2.79 (t, *J* = 4.5 Hz, 1H), 2.69 (dd, *J* = 5.1, 2.7 Hz, 1H), 1.82 (br s, 1H), 1.70-1.42 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.59 (e), 128.40 (o), 127.70 (o), 127.58 (o), 72.95 (e), 71.71 (o), 70.15 (e), 55.50 (o), 45.20 (e), 34.09 (e), 29.68 (e), 22.11 (e).

IR (Neat): 3434 (br s), 3062 (m), 3031 (m), 2938 (s), 2862 (s), 1604 (w), 1496 (m), 1455 (m), 1099 (s), 738 (m), 699 (m) cm^{-1}.

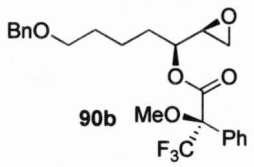
HRMS (CI, MH^+): calcd for $C_{14}H_{21}O_3$ 237.1485, found 237.1475.



(*S*)-((*S*)-5-(benzyloxy)-1-((*S*)-oxiran-2-yl)pentyl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 90a

General Procedure for The Formation of Mosher Ester Derivatives: Allylic alcohol **90** (12.7 mg, 0.054 mmol) was dissolved in anhydrous dichloromethane (2 mL) at room temperature under an atmosphere of argon. The reaction was cooled to 0 °C and DMAP (1.5 mg, 0.012 mmol), triethylamine (11.3 μL, 0.081 mmol) and (*R*)-MTPA-Cl (11.2 μL, 0.096 mmol) were added sequentially. The reaction was allowed to warm to room temperature and stirred for *ca.* 12 hours. The solvent was removed *in vacuo* to afford the crude oil. Purification by flash chromatography (eluting with 0-10% ethyl acetate/hexanes) furnished (*S*)-MTPA ester **90a** (18.4 mg, 76% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (t, J = 3.6 Hz, 2H), 7.38-7.25 (m, 8H), 4.81 (dd, J = 13.4, 7.3 Hz, 1H), 4.46 (s, 2H), 3.58 (d, J = 1.0 Hz, 3H), 3.39 (t, J = 6.4 Hz, 2H), 3.08 (ddd, J = 6.9, 4.2, 2.7 Hz, 1H), 2.85 (t, J = 4.5 Hz, 1H), 2.66 (dd, J = 4.8, 2.6 Hz, 1H), 1.76-1.50 (m, 4 H), 1.49-1.31 (m, 2H).

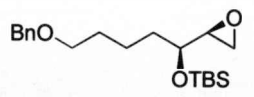


90b

(*R*)-((*S*)-5-(benzyloxy)-1-((*S*)-oxiran-2-yl)pentyl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 90b

(*R*)-MTPA ester **90b** was prepared according to the general procedure for the formation of Mosher ester derivatives in 81% yield, as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.53 (m, 2H), 7.38-7.25 (m, 8H), 4.88 (q, J = 6.7 Hz, 1H), 4.47 (s, 2H), 3.53 (d, J = 1.0 Hz, 3H), 3.44 (t, J = 6.3 Hz, 2H), 3.04 (ddd, J = 6.6, 4.1, 2.5 Hz, 1H), 2.76 (t, J = 4.5 Hz, 1H), 2.56 (dd, J = 4.9, 2.5 Hz, 1H), 1.82-1.71 (m, 2 H), 1.69-1.59 (m, 2H), 1.52-1.42 (m, 2H).



90c

((*S*)-5-(Benzyloxy)-1-((*S*)-oxiran-2-yl)pentyloxy)(*tert*-butyl)dimethylsilane 90c

Experimental Procedure: Epoxy alcohol **90** (0.60 g, 2.56 mmol) was dissolved in anhydrous DMF (10.2 mL) at room temperature under an atmosphere of argon. Imidazole (0.52 g, 7.68 mmol) was added in single portion and solution was cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (0.59 g, 3.84 mmol) was added in a single portion. The reaction was warmed to room temperature and stirred for *ca.* 8 hours. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and partitioned between diethyl ether and water. The combined organic phases were

washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 2-10% ethyl acetate/hexanes) furnished epoxide **90c** (0.78 g, 87% yield) as a yellow oil.

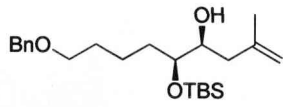
$[\alpha]_D^{26}$ -5.2 (c = 1.24, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 4.48 (s, 2H), 3.45 (t, J = 6.3 Hz, 2H), 3.28-3.21 (m, 1H), 2.89 (ddd, J = 6.6, 4.0, 2.6 Hz, 1H), 2.75 (t, J = 4.5 Hz, 1H), 2.51 (dd, J = 4.9, 2.7 Hz, 1H), 1.66-1.34 (m, 6H), 0.89 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.73 (e), 128.46 (o), 127.71 (o), 127.61 (o), 74.69 (o), 73.02 (e), 70.28 (e), 56.03 (o), 44.98 (e), 34.66 (e), 29.90 (e), 25.99 (o), 22.17 (e), 18.29 (e), -4.24 (o), -4.87 (o).

IR (Neat): 3088 (w), 3032 (w), 2929 (s), 2857 (s), 1472 (m), 1462 (m), 1256 (m), 1107 (s), 838 (s), 778 (s), 698 (m) cm^{-1}.

HRMS (CI, MH^+): calcd for $C_{20}H_{35}O_3Si$ 351.2350, found 351.2353.



49

(4*S*,5*S*)-9-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2-methylnon-1-en-4-ol 49

Experimental Procedure: Isopropenyl magnesium bromide (14.2 mL, 7.08 mmol, 0.5M in THF) was added to anhydrous diethyl ether (114 mL) at room temperature under an atmosphere of argon. The solution was cooled to -78 °C and Li_2CuCl_4 (2.36 mL, 0.236 mmol, 0.1M in THF) was added dropwise. The orange solution was stirred for *ca.* 15 minutes and epoxide **90a** (0.82 g, 2.36 mmol) was added dropwise as a solution in diethyl ether (10 mL). The reaction was allowed to warm to room temperature and stirred overnight. The black mixture was quenched with the

aqueous NH_4Cl/NaOH (3:1) solution and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0-10 % ethyl acetate/hexanes) furnished homoallylic alcohol **49** (0.78 g, 91% yield) as a yellow oil.

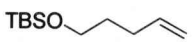
$[\alpha]_D^{27}$ -1.6 (c = 1.06, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.23 (m, 5H), 4.82 (s, 1H), 4.75 (s, 1H), 4.48 (s, 2H), 3.67-3.61 (m, 1H), 3.58-3.55 (m, 1H), 3.45 (dt, *J* = 6.4, 1.3 Hz, 2H), 2.19-2.09 (m, 3H), 1.74 (s, 3H), 1.69-1.55 (m, 3H), 1.46-1.34 (m, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.10 (e), 138.74 (e), 128.46 (o), 127.72 (o), 127.61 (o), 112.81 (e), 74.57 (o), 73.02 (e), 70.51 (o), 70.35 (e), 42.21 (e), 33.34 (e), 30.11 (e), 26.03 (o), 22.62 (o), 22.14 (e), 18.23 (e), -3.99 (o), -4.39 (o).

IR (Neat): 3472 (br w), 3071 (w), 3031 (w), 2930 (s), 2857 (s), 1647 (w), 1472 (m), 1455 (m), 1256 (m), 1102 (s), 836 (s), 776 (s), 697 (m) cm^{-1}.

HRMS (CI, MH^+): calcd for $C_{23}H_{41}O_3Si$ 393.2819, found 393.2820.



111a

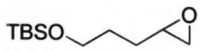
***tert*-Butyldimethyl(pent-4-enyloxy)silane 111a**[70]

Experimental Procedure: 4-Pentene-1-ol **111** (26.5 mL, 250 mmol) was dissolved in anhydrous dichloromethane (1250 mL) at room temperature under an atmosphere of argon. Imidazole (25.6 g, 375 mmol) was added and solution was cooled to 0 °C. *tert*-Butyl(chloro)dimethylsilane (45.22 g, 300 mmol) as a solution in anhydrous dichloromethane was cannulated over and reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated

aqueous NH_4Cl solution and partitioned between dichloromethane and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 0-5 % diethyl ether/petroleum ether) furnished silyl protected primary alcohol **111a** (48.34 g, 94% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (ddt, J = 16.9, 10.3, 6.7 Hz, 1H), 5.00 (dd, J = 17.1, 1.5 Hz, 1H), 4.93 (d, J = 10.2 Hz, 1H), 3.60 (t, J = 6.5 Hz, 2H), 2.08 (q, J = 7.2 Hz, 2H), 1.59 (quintet, J = 7.0 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H).

IR (Neat): 3080 (w), 2952 (w), 2930 (m), 2886 (w), 2858 (m), 1642 (w), 1472 (w), 1463 (w), 1254 (m), 1098 (s), 834 (s), 774 (s) cm^{-1}.



112

***tert*-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane 112**

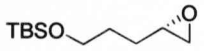
Experimental Procedure: Silyl protected primary alcohol **111a** (10.483 g, 52.3 mmol) was dissolved in anhydrous dichloromethane (1000 mL) at room temperature under an atmosphere of argon. $NaHCO_3$ (13.18 g, 156.9 mmol) was added and solution was cooled to 0 °C. *m*-CPBA (23.5 g, 104.6 mmol) was added in few portions and reaction mixture was allowed to warm to room temperature and stirred over 12 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and partitioned between dichloromethane and water. The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 5-10 % diethyl ether/petroleum ether) furnished epoxide **112** (8.274 g, 73% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68-3.59 (m, 2H), 2.94-2.91 (m, 1H), 2.73 (t, J = 4.5 Hz, 1H), 2.46 (dd, J = 4.9, 2.8 Hz, 1H), 1.72-1.51 (m, 4H), 0.87 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 62.77 (e), 52.30 (o), 47.25 (e), 29.26 (e), 29.17 (e), 26.06 (o), 18.44 (e), -5.19 (o).

IR (Neat): 2953 (m), 2929 (m), 2857 (m), 1473 (w), 1254 (m), 1096 (s), 832 (s), 774 (s) cm^{-1}.

HRMS (CI, MH^+): calcd for $C_{11}H_{25}O_2Si$ 217.16238, found 217.16192.



118

(*S*)-*tert*-Butyldimethyl(3-(oxiran-2-yl)propoxy)silane 118

Experimental Procedure: (*S*,*S*)-Salen-Co^{III}-OAc **80** (0.618 g, 0.932 mmol) was dissolved in racemic epoxide **112** (34.65 g, 160 mmol) and anhydrous tetrahydrofuran (2.1 mL) was added at room temperature under an atmosphere of argon. The solution was cooled to 0 °C and water (1.59 mL, 88 mmol) was added dropwise. The reaction was stirred for *ca.* 3 days then concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 5-30 % diethyl ether/petroleum ether) furnished epoxide **118** (15.532 g, 90% yield) as a yellow oil.

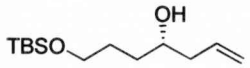
$[\alpha]_D^{23}$ -3.9 (c = 1.79, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68-3.59 (m, 2H), 2.94-2.91 (m, 1H), 2.73 (t, J = 4.5 Hz, 1H), 2.46 (dd, J = 5.0, 2.7 Hz, 1H), 1.72-1.51 (m, 4H), 0.87 (s, 9H), 0.03 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 62.70 (e), 52.24 (o), 47.18 (e), 29.22 (e), 29.12 (e), 26.01 (o), 18.38 (e), -5.25 (o).

IR (Neat): 2953 (m), 2929 (m), 2886 (w), 2857 (m), 1472 (w), 1254 (m), 1097 (s), 833 (s), 775 (s) cm^{-1}.

HRMS (CI, MH^+): calcd for $C_{11}H_{25}O_2Si$ 217.16238, found 217.16192.



94

(*S*)-7-(*tert*-Butyldimethylsilyloxy)hept-1-en-4-ol 94

Experimental Procedure: Vinyl magnesium bromide (61.5 mL, 61.5 mmol, 1M in THF) was added to anhydrous diethyl ether (114 mL) at room temperature under an atmosphere of argon. The cloudy suspension was cooled to -78 °C and Li_2CuCl_4 (20.49 mL, 2.049 mmol, 0.1M in THF) was added dropwise. The orange solution was stirred for *ca.* 15 minutes and epoxide **112** (4.43 g, 20.49 mmol) as a solution in diethyl ether (30 mL) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The black reaction mixture was quenched with the aqueous NH_4Cl/NaOH (3:1) solution and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 5-20 % ethyl acetate/hexanes) furnished homoallylic alcohol **94** (4.55 g, 91% yield) as a yellow oil.

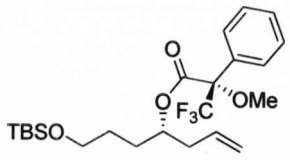
$[\alpha]_D^{25}$ -7.4 (c = 1.41, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.4, 10.3, 7.1 Hz, 1H), 5.11-5.07 (m, 2H), 3.68-3.61 (m, 3H), 2.61 (d, *J* = 3.8 Hz, 1H), 2.28-2.16 (m, 2H), 1.66-1.59 (m, 3H), 1.49-1.40 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.24 (o), 117.56 (e), 70.65 (o), 63.54 (e), 42.02 (e), 33.98 (e), 29.23 (e), 26.05 (o), 18.38 (e), -5.30 (o).

IR (Neat): 3369 (br w), 2929 (m), 2858 (m), 1642 (w), 1472 (w), 1254 (m), 1095 (m), 832 (s), 773 (s) cm^{-1}.

HRMS (CI, MH^+): calcd for $C_{13}H_{29}O_2Si$ 245.19368, found 245.19426.



94a

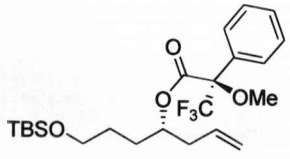
(*S*)-((*S*)-7-(*tert*-Butyldimethylsilyloxy)hept-1-en-4-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 94a

(*S*)-MTPA ester **94a** was prepared according to the general procedure for the formation of Mosher ester derivatives in 98% yield, as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H), 7.37-7.36 (m, 3H), 5.74 (ddt, J = 17.0, 10.2, 6.9 Hz, 1H), 5.17 (quintet, J = 6.1 Hz, 1H), 5.11-4.98 (m, 2H), 3.53 (s, 3H), 3.53-3.50 (m, 2H), 2.41 (t, J = 6.5 Hz, 2H), 1.72-1.58 (m, 2H), 1.54-1.31 (m, 2H), 0.85 (s, 9H), 0.00 (s, 6H).

IR (Neat): 3079 (w), 2955 (s), 2930 (s), 2858 (s), 1747 (s), 1645 (w), 1464 (m), 1472 (m), 1258 (s), 1170 (s), 835 (s), 777 (s), 697 (m) cm^{-1}.

HRMS (CI, MH^+): calcd for $C_{23}H_{36}O_4F_3Si$ 461.2329, found 461.2346.



94b

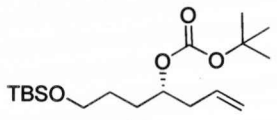
(*R*)-((*S*)-7-(*tert*-Butyldimethylsilyloxy)hept-1-en-4-yl)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 94b

(*R*)-MTPA ester **94b** was prepared according to the general procedure for the formation of Mosher ester derivatives in 85% yield, as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.51 (m, 2H), 7.38-7.35 (m, 3H), 5.67-5.57 (m, 1H), 5.15 (quintet, J = 6.1 Hz, 1H), 5.02-4.98 (m, 2H), 3.58 (dt, J = 6.1, 1.7 Hz, 2H), 3.52 (s, 3H), 2.34 (t, J = 6.4 Hz, 2H), 1.75-1.63 (m, 2H), 1.60-1.46 (m, 2H), 0.86 (s, 9H), 0.01 (s, 6H).

IR (Neat): 3079 (w), 2954 (s), 2931 (s), 2858 (s), 1747 (s), 1645 (w), 1464 (m), 1472 (m), 1258 (s), 1170 (s), 836 (s), 777 (s), 697 (m) cm^{-1}.

HRMS (CI, MH^+): calcd for $C_{23}H_{36}O_4F_3Si$ 461.2329, found 461.2332.



113

(*S*)-*tert*-Butyl 7-(*tert*-butyldimethylsilyloxy)hept-1-en-4-yl carbonate 113

Experimental Procedure: Homoallylic alcohol **94** (4.55 g, 18.6 mmol) was dissolved in anhydrous dichloromethane (186 mL) at room temperature under an atmosphere of argon. DMAP (6.88 g, 55.8 mmol) was added in one portion and solution was cooled to 0 °C. BOC-anhydride (11.3 mL, 46.5 mmol) was added dropwise as a solution in dichloromethane (30 mL) and reaction was allowed to warm to room temperature and stirred for *ca.* 12 hours. The mixture was quenched with the saturated aqueous NH_4Cl solution and partitioned between diethyl ether and water. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 0-10 % ethyl acetate/hexanes) furnished homoallylic carbonate **113** (5.75 g, 90% yield) as a colorless oil.

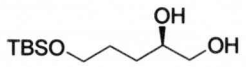
$[\alpha]_D^{25}$ -14.1 (c = 1.12, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.10-5.03 (m, 2H), 4.76-4.66 (m, 1H), 3.62-3.54 (m, 2H), 2.33 (t, J = 6.5 Hz, 2H), 1.69-1.50 (m, 4H), 1.45 (d, J = 1.6 Hz, 9H), 0.86 (s, 9H), 0.01 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.51 (e), 133.67 (o), 117.92 (e), 81.76 (e), 76.49 (o), 62.84 (e), 38.93 (e), 30.14 (e), 28.68 (e), 27.93 (o), 26.07 (o), 18.44 (e), -5.19 (o).

IR (Neat): 2955 (w), 2930 (w), 2858 (w), 1737 (s), 1644 (w), 1473 (w), 1368 (w), 1277 (s), 1252 (s), 1165 (m), 1092 (s), 833 (s), 774 (m) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{18}H_{36}O_4NaSi$ 367.2281, found 367.2296.



116

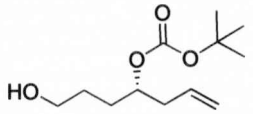
(*R*)-5-(*tert*-Butyldimethylsilyloxy)pentane-1,2-diol 116

Experimental Procedure: (*S*, *S*)-Salen-Co^{III}-OAc **80** (0.618 g, 0.932 mmol) was dissolved in racemic epoxide **112** (34.65 g, 160 mmol) and anhydrous tetrahydrofuran (2.1 mL) was added at room temperature under an atmosphere of argon. The solution was cooled to 0 °C and water (1.59 mL, 88 mmol) was added. The reaction was stirred for *ca.* 3 days then was concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 30-70% ethyl acetate/hexanes) furnished diol **116** (15.532 g, 90% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72-3.67 (m, 2H), 3.65-3.56 (m, 3H), 3.44 (ddd, J = 11.5, 7.4, 4.3 Hz, 1H), 2.17 (br s, 1H), 1.73-1.57 (m, 3H), 1.51-4.13 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 72.08 (o), 66.89 (e), 63.60 (e), 30.67 (e), 29.15 (e), 26.01 (o), 18.41 (e), -5.29 (o), -5.31 (o).

IR (Neat): 3356 (br w), 2929 (m), 2857 (m), 1472 (w), 1463 (w), 1253 (m), 1094 (m), 832 (s), 773 (s) cm^{-1}.



113a

(*S*)-*tert*-Butyl 7-hydroxyhept-1-en-4-yl carbonate 113a

Experimental Procedure: The homoallylic carbonate **113** (0.26 g, 0.75 mmol) was dissolved in anhydrous MeOH/DCM mixture (7.5 mL, 2:1) at room temperature under an atmosphere of argon. The solution was cooled to 0 °C and CSA (0.018 g, 0.079 mmol) was added in one portion. The reaction was stirred for *ca.* 1 hour then quenched with the triethylamine (1.056 mL). The solution was filtered through silica pad eluting with 30% ethyl acetate/hexanes. Solvent was removed *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 20-30 % ethyl acetate/hexanes) furnished primary alcohol **113a** (0.13 g, 74% yield) as a yellow oil.

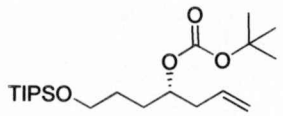
$[\alpha]_D^{20}$ -22.8 (c = 1.05, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.09 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.07-5.04 (m, 1H), 4.70 (quintet, *J* = 6.0 Hz, 1H), 3.63 (s, 2H), 2.38-2.30 (m, 2H), 1.71-1.52 (m, 4H), 1.45 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.51 (e), 133.47 (o), 118.03 (e), 81.95 (e), 76.35 (o), 62.48 (e), 38.87 (e), 30.06 (e), 28.47 (e), 27.86 (o).

IR (Neat): 3365 (br w), 2980 (w), 2935 (w), 1735 (s), 1644 (w), 1477 (w), 1457 (w), 1368 (m), 1276 (s), 1252 (s), 1159 (s), 791 (m) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{12}H_{22}O_4Na$ 253.1416, found 253.1407.



119

(*S*)-*tert*-Butyl 7-(triisopropylsilyloxy)hept-1-en-4-yl carbonate 119

Experimental Procedure: The primary alcohol **113a** (2.95 g, 12.82 mmol) was dissolved in anhydrous dichloromethane (64 mL) at room temperature under an atmosphere of argon. Imidazole (1.48 g, 21.8 mmol) was added in a single portion. The reaction was cooled to 0 °C and chlorotriisopropylsilane (4.2 mL, 19.23 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The mixture was quenched with the saturated aqueous NH_4Cl solution and partitioned between dichloromethane and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 0-10 % ethyl acetate/hexanes) furnished homoallylic carbonate **119** (4.47 g, 90% yield) as a yellow oil.

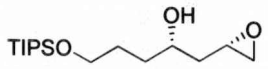
$[\alpha]_D^{26}$ -10.1 (c = 1.15, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.08 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 4.69 (quintet, *J* = 6.1 Hz, 1H), 3.70-3.62 (m, 2H), 2.34 (t, *J* = 6.6 Hz, 2H), 1.73-1.65 (m, 1H), 1.64-1.54 (m, 3H), 1.45 (s, 9H), 1.08-1.00 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.50 (e), 133.67 (o), 117.88 (e), 81.71 (e), 76.56 (o), 63.05 (e), 38.91 (e), 30.14 (e), 28.84 (e), 27.90 (o), 18.12 (o), 12.07 (o).

IR (Neat): 2943 (m), 2867 (m), 1737 (s), 1644 (w), 1463 (w), 1368 (m), 1276 (s), 1253 (s), 1165 (s), 1095 (s), 881 (m), 679 (m) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{16}H_{34}O_2NaSi$ 309.2226, found 309.2212.



121

(*S*)-1-((*S*)-Oxiran-2-yl)-5-(triisopropylsilyloxy)pentan-2-ol 121

Experimental Procedure: Homoallylic carbonate **119** (3.46 g, 8.95 mmol) was dissolved in anhydrous toluene (90 mL) and solution was cooled to -85 °C under an atmosphere of argon. The solution of iodine monobromide (13.43 mL, 13.43 mmol, 1M in DCM) was added slowly. The reaction mixture was stirred for *ca.* 1 hour, then quenched with the mixture of aqueous 20% $Na_2S_2O_3$/5% $NaHCO_3$ (1:1) solution and diluted with diethyl ether. The reaction was partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 30-70 % diethyl ether/petroleum ether) furnished cyclic iodocarbonate **120**.

Iodocarbonate **120** (8.95 mmol) was dissolved in anhydrous methanol (35.8 mL) at room temperature under an atmosphere of argon. The potassium carbonate (3.74 g, 27.0 mmol) was added in a single portion and suspension was stirred for *ca.* 2 hours. The reaction was diluted with diethyl ether and quenched with the saturated aqueous $Na_2S_2O_3$/$NaHCO_3$ (1:1) solution. The reaction was partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 5-40 % ethyl acetate/hexanes) furnished epoxy alcohol **121** (1.92 g, 71% yield) as a yellow oil.

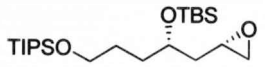
$[\alpha]_D^{24}$ -5.70 (c = 1.35, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89-3.84 (m, 1H), 3.78-3.70 (m, 2H), 3.22 (d, J = 3.3 Hz, 1H), 3.09 (ddt, J = 6.9, 4.2, 2.5 Hz, 1H), 2.76 (t, J = 4.5 Hz, 1H), 2.50 (dd, J = 5.0, 2.8 Hz, 1H), 1.77-1.53 (m, 6H), 1.09-1.02 (m, 21H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 69.86 (o), 63.82 (e), 50.45 (o), 46.84 (e), 39.93 (e), 35.00 (e), 29.41 (e), 18.07 (o), 12.02 (o).

IR (Neat): 3426 (br w), 2942 (s), 2865 (s), 1463 (m), 1383 (w), 1257 (w), 1099 (s), 882 (s), 679 (s) cm^{-1}.

HRMS (CI, MH^+): calcd for $C_{16}H_{35}O_3Si$ 303.23555, found 303.23515.



121a

(*S*)-10,10-Diisopropyl-2,2,3,3,11-pentamethyl-5-((*S*)-oxiran-2-ylmethyl)-4,9-dioxa-3,10-disiladodecane 121a

Experimental Procedure: Epoxy alcohol **121** (1.08 g, 3.58 mmol) was dissolved in anhydrous DMF (143 mL) at room temperature under an atmosphere of argon. Imidazole (0.74 g, 10.75 mmol) was added in one portion and solution was cooled to 0 °C. *tert*-Butyl(chloro)dimethylsilane (1.38 g, 8.96 mmol) was added dropwise as a solution in DMF (2 mL). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 0-8 % diethyl ether/hexanes) furnished epoxide **121a** (1.14 g, 77% yield) as a yellow oil.

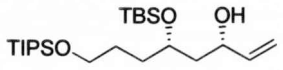
$[\alpha]_D^{22}$ -2.0 (c = 1.40, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (quintet, J = 5.6 Hz, 1H), 3.69-3.64 (m, 2H), 3.03-2.99 (m, 1H), 2.73 (t, J = 4.5 Hz, 1H), 2.44 (dd, J = 5.1, 2.8 Hz, 1H), 1.75 (dt, J = 13.9, 5.9 Hz, 1H), 1.63-1.51 (m, 5H), 1.09-1.02 (m, 21H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 70.39 (o), 63.54 (e), 49.71 (o), 47.01 (e), 40.22 (e), 33.63 (e), 29.02 (e), 25.94 (o), 18.15 (o), 12.10 (o), -4.41 (o), -4.48 (o).

IR (Neat): 2942 (m), 2892 (w), 2865 (m), 1463 (m), 1388 (w), 1254 (m), 1099 (s), 1067 (s), 834 (s), 773 (s), 679 (m) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{22}H_{48}O_3NaSi_2$ 439.3040, found 439.3024.



51

(3*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-8-(triisopropylsilyloxy)oct-1-en-3-ol 51

Experimental Procedure: Trimethylsulfonium triflate (3.81 g, 16.85 mmol) was dried under Dean-Stark conditions for *ca.* 3 hours in refluxing benzene. The solvent was removed *in vacuo* and salt was suspended in anhydrous tetrahydrofuran (44.3 mL) at room temperature under an atmosphere of argon. The suspension was cooled to -10 °C and ^{n}BuLi (6.61 mL, 16.52 mmol, 2.5M in hexanes) was added dropwise. The reaction mixture was stirred for *ca.* 1 hour before addition of epoxide **121a** (0.70 g, 1.68 mmol as a solution in anhydrous tetrahydrofuran (3 mL). The reaction was stirred for an additional hour, after which was allowed to warm to room temperature and stir overnight. The reaction was quenched with saturated aqueous NH_4Cl solution and partitioned between diethyl ether and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford crude yellow oil. Purification by flash chromatography (eluting with 0-10 %

ethyl acetate/hexanes) furnished allylic alcohol **51** (0.599 g, 82% yield) as a yellow oil.

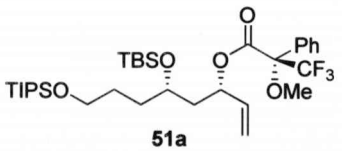
$[\alpha]_D^{24}$ +23.3 (c = 1.00, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 16.7, 10.5, 6.0 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 4.27-4.24 (m, 1H), 4.00-3.95 (m, 1H), 3.70-3.61 (m, 2H), 3.23 (d, *J* = 1.7 Hz, 1H), 1.69-1.46 (m, 6H), 1.09-1.02 (m, 21H), 0.88 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.95 (o), 114.18 (e), 72.93 (o), 72.19 (o), 63.49 (e), 43.05 (e), 34.51 (e), 28.22 (e), 25.97 (o), 18.16 (o), 18.16 (e), 12.08 (o), -3.83 (o), -4.58 (o).

IR (Neat): 3434 (br w), 2942 (s), 2865 (s), 1463 (m), 1383 (w), 1254 (m), 1097 (s), 1067 (s), 835 (s), 774 (s), 680 (m) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{23}H_{50}O_3NaSi_2$ 453.3196, found 453.3188.



51a

(*S*)-((3*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-8-(triisopropylsilyloxy)oct-1-en-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 51a

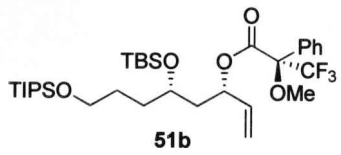
(*S*)-MTPA ester **51a** was prepared according to the general procedure for the formation of Mosher ester derivatives in 100% yield, as yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.48 (m, 2H), 7.38-7.36 (m, 3H), 5.80 (ddd, *J* = 17.5, 10.3, 7.3 Hz, 1H), 5.52 (q, *J* = 7.1 Hz, 1H), 5.38 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 3.63-3.61 (m, 2H), 3.57-3.55 (m, 1H), 3.52 (s, 3H), 1.84 (ddd, *J* = 14.0, 7.7, 6.4 Hz, 1H), 1.69 (quintet, *J* = 6.7 Hz, 1H), 1.50-1.41 (m, 4H), 1.09-1.02 (m, 21H), 0.84 (s, 9H), -0.06 (s, 3H), -0.07 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.79 (e), 135.39 (o), 132.62 (e), 129.68 (o), 128.50 (o), 127.39 (o), 123.50 (e), 122.36 (e), 119.62 (e), 75.28 (o), 68.46 (o), 63.56 (e), 55.61 (o), 41.40 (e), 32.99 (e), 28.43 (e), 25.97 (o), 18.18 (o), 18.18 (e), 12.12 (o), -4.28 (o), -4.57 (o).

IR (Neat): 2945 (m), 2891 (w), 2865 (m), 1749 (s), 1463 (m), 1383 (w), 1251 (s), 1169 (s), 1103 (s), 994 (s), 835 (s), 774 (s), 680 (m) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{33}H_{57}O_5F_3NaSi_2$ 669.3594, found 669.3620.



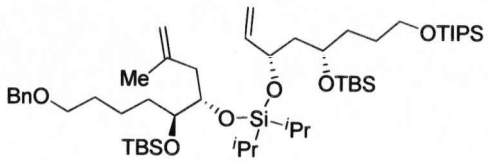
51b

(*R*)-((3*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)-8-(triisopropylsilyloxy)oct-1-en-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 51b

(*R*)-MTPA ester **51b** was prepared according to the general procedure for the formation of Mosher ester derivatives in 100% yield, as yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.47 (m, 2H), 7.39-7.36 (m, 3H), 5.71 (ddd, J = 17.4, 10.4, 7.0 Hz, 1H), 5.52 (q, J = 7.1 Hz, 1H), 5.29 (d, J = 17.2 Hz, 1H), 5.22 (d, J = 10.5 Hz, 1H), 3.72-3.69 (m, 1H), 3.66-3.61 (m, 2H), 3.51 (d, J = 0.9 Hz, 3H), 1.90 (quintet, J = 6.9 Hz, 1H), 1.76 (ddd, J = 13.3, 6.9, 6.2 Hz, 1H), 1.56-1.49 (m, 4H), 1.09-1.02 (m, 21H), 0.86 (s, 9H), 0.00 (s, 6H).

IR (Neat): 2945 (m), 2891 (w), 2865 (m), 1749 (m), 1463 (w), 1383 (w), 1252 (s), 1170 (s), 1103 (s), 835 (s), 774 (s), 680 (m) cm^{-1}.



85

(5*S*,6*S*,10*S*,12*S*)-5-(4-(Benzyloxy)butyl)-12-(*tert*-butyldimethylsilyloxy)-8,8,17,17-tetraisopropyl-2,2,3,3,18-pentamethyl-6-(2-methylallyl)-10-vinyl-4,7,9,16-tetraoxa-3,8,17-trisilanonadecane 85

Experimental Procedure: Imidazole (0.084 g, 1.23 mmol) was dissolved in anhydrous dichloromethane (4.7 mL) at room temperature under an atmosphere of argon and solution was cooled to 0 °C. Diisopropyldichlorosilane (0.157 mL, 0.844 mmol) was added dropwise and the reaction was stirred for *ca.* 10 minutes. Homoallylic alcohol **49** (0.074 g, 0.187 mmol) was added as a solution in anhydrous dichloromethane (2 mL) *via* syringe pump over period of *ca.* 3 hours. The reaction was allowed to warm to room temperature and stirred overnight. Solvent was removed *in vacuo via* dry ice trap. The solid residue was treated with anhydrous hexane (2x5 mL) for *ca.* 10 minutes and then transferred *via* syringe into 50 mL Schlenk flask equipped with a stir bar. Solvent was removed *in vacuo* and flask with oily residue was dipped in oil bath preheated to 75 °C. After removal of unreacted diisopropyldichlorosilane, the residue was dissolved in anhydrous dichloromethane (2 mL) and cooled to 0 °C. Dichloromethane (0.5 mL) solution of imidazole (0.061 g, 0.89 mmol) was added dropwise and solution allowed to stir for *ca.* 10 minutes. Dichloromethane (0.5 mL) solution of allylic alcohol **51** (0.041 g, 0.096 mmol) was added dropwise and mixture was allowed to warm to room temperature and stir overnight. The reaction mixture was filtered through short silica pad (eluting with 30% ethyl acetate/hexanes). Solvent was removed *in vacuo* to afford a crude oil.

Purification by flash chromatography (eluting with 0-4% ethyl acetate/hexanes) furnished acyclic silaketal **85** (0.0756 g, 84% yield) as a colorless oil.

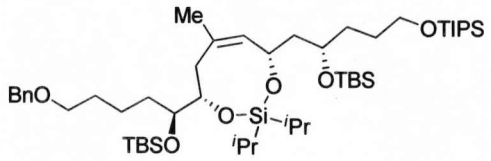
$[\alpha]_D^{25}$ -0.5 (c = 1.12, $CHCl_3$).

^{1}H NMR (500 MHz, C_6D_6) δ 7.33 (d, *J* = 7.5 Hz, 2H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 5.95 (ddd, *J* = 17.3, 10.3, 6.9 Hz, 1H), 5.32 (d, *J* = 17.2 Hz, 1H), 5.11 (d, *J* = 10.3 Hz, 1H), 5.04 (s, 1H), 4.96 (s, 1H), 4.68-4.64 (m, 1H), 4.38 (d, A of AB, J_{AB} = 12.2 Hz, 1H), 4.34 (d, B of AB, J_{AB} = 12.2 Hz, 1H), 4.26 (ddd, *J* = 9.4, 4.0, 2.2 Hz, 1H), 4.04-4.02 (m, 1H), 3.87-3.85 (m, 1H), 3.69-3.64 (m, 2H), 3.41 (t, *J* = 6.1 Hz, 2H), 2.65 (d, *J* = 13.5 Hz, 1H), 2.29 (dd, A of ABX, J_{AB} = 13.6 Hz, J_{AX} = 9.5 Hz, 1H), 2.15 (ddd, *J* = 13.4, 8.9, 4.5 Hz, 1H), 1.98-1.92 (m, 1H), 1.89 (s, 3H), 1.85-1.75 (m, 3H), 1.70-1.61 (m, 5H), 1.58-1.48 (m, 2H), 1.27-1.22 (m, 14H), 1.14-1.10 (m, 21H), 1.03 (s, 9H), 1.02 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H), 0.14 (s, 3H), 0.12 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 143.71 (e), 141.67 (o), 139.64 (e), 128.52 (o), 127.65 (o), 127.53 (o), 115.16 (e), 113.41 (e), 75.50 (o), 74.13 (o), 72.97 (e), 72.02 (o), 70.55 (e), 69.58 (o), 63.82 (e), 46.30 (e), 39.66 (e), 34.83 (e), 30.71 (e) , 30.36 (e), 28.60 (e), 26.22 (o), 24.11 (e), 23.36 (o), 18.36 (o), 18.33 (e), 18.13 (o), 18.04 (o), 17.95 (o), 17.90 (o), 13.72 (o), 13.50 (o), 12.37 (o), -3.50 (o), -3.67 (o), -4.09 (o), -4.12 (o).

IR (Neat): 2928 (m), 2865 (m), 1648 (w), 1463 (m), 1361 (w), 1252 (m), 1199 (s), 834 (s), 773 (s), 680 (m) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{52}H_{102}O_6NaSi_4$ 957.6651, found 957.6656.



84

(4*S*,8*S*,*Z*)-4-((*S*)-5-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)pentyl)-8-((*S*)-2-(*tert*-butyldimethylsilyloxy)-5-(triisopropylsilyloxy)pentyl)-2,2-diisopropyl-6-methyl-5,8-dihydro-4H-1,3,2-dioxasilocine 84

Experimental Procedure: The acyclic silaketal **85** (0.295 g, 0.315 mmol) was dissolved in anhydrous dichloromethane (31.5 mL) at room temperature and under an atmosphere of argon. The Grubbs' 2nd generation catalyst (0.0574 g, 0.068 mmol) was added in one portion and mixture was stirred under reflux condition for *ca.* 24 hours. The reaction mixture was cooled to room temperature, silica gel was added (600 mg), and mixture was stirred for an additional 10 minutes. The suspension was then filtered through short silica pad (eluting with 10% ethyl acetate/hexanes). The solvent was removed *in vacuo* to afford a crude brownish oil, which was diluted in dichloromethane (3.15 mL) and stirred with DMSO (0.241 mL) for *ca.* 12 hours. The solvent was removed *in vacuo* to afford a crude brownish oil. Purification by flash chromatography (eluting with 0-7% ethyl acetate/hexanes) furnished cyclic silaketal which was further purified by preparative t.l.c (eluting 1-2 % ethyl acetate/hexanes) affording the cyclic silaketal **84** (0.252 g, 88% yield) as a yellow oil.

$[\alpha]_D^{24}$ +3.7 (c = 1.11, $CHCl_3$).

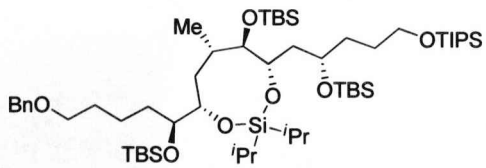
^{1}H NMR (500 MHz, C_6D_6) δ 7.32 (d, J = 7.4 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.4 Hz, 1H), 5.57 (d, J = 5.1 Hz, 1H), 4.62 (quintet, J = 4.9 Hz, 1H), 4.37 (d, A of AB, J_{AB} = 12.3 Hz, 1H), 4.34 (d, B of AB, J_{AB} = 12.3 Hz, 1H), 4.24-4.18 (m,

1H), 4.13 (dd, J = 8.5, 3.4 Hz, 1H), 3.79 (quintet, J = 3.8 Hz, 1H), 3.74 (t, J = 5.8 Hz, 2H), 3.42-3.36 (m, 2H), 3.11 (dd, A of ABX, J_{AB} = 13.4 Hz, J_{AX} = 9.8 Hz, 1H), 2.18 (ddd, J = 13.9, 9.3, 4.5 Hz, 1H), 2.14 (d, J = 12.7 Hz, 1H), 2.03-1.98 (m, 1H), 1.92-1.76 (m, 8H), 1.72 (s, 3H), 1.59-1.48 (m, 2H), 1.29-1.17 (m, 14H), 1.16-1.10 (m, 21H), 1.04 (s, 9H), 1.01 (s, 9H), 0.22 (s, 3H), 0.20 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 139.58 (e), 136.59 (e), 131.69 (o), 128.53 (o), 127.69 (o), 127.55 (o), 76.23 (o), 76.12 (o), 73.02 (e), 70.43 (e), 70.15 (o), 69.35 (o), 64.09 (e), 46.31 (e), 35.80 (e), 33.09 (e), 31.99 (e) , 31.66 (e), 30.63 (e), 30.47 (o), 30.24 (e), 29.42 (e), 26.24 (o), 26.21 (o), 25.65 (o), 23.54 (e) 18.40 (o), 18.29 (o), 18.18 (o), 18.06 (o), 18.03 (o), 14.04 (o), 13.69 (o), 12.41 (o), -3.98 (o), -4.04 (o), -4.18 (o), -4.34 (o).

IR (Neat): 2928 (m), 2864 (m), 1463 (m), 1361 (w), 1252 (m), 1099 (s), 834 (s), 773 (s) cm^{-1}.

HRMS (ESI, MNa$^+$): calcd for $C_{50}H_{98}O_6NaSi_4$ 929.6338, found 929.6368.



123

(4*S*,5*R*,6*S*,8*S*)-8-((*S*)-5-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)pentyl)-5-(*tert*-butyldimethylsilyloxy)-4-((*S*)-2-(*tert*-butyldimethylsilyloxy)-5-(triisopropylsilyl-oxy)pentyl)-2,2-diisopropyl-6-methyl-1,3,2-dioxasilocane 123

Experimental Procedure: The cyclic silaketal **84** (0.046 g, 0.051mmol) was dissolved in anhydrous tetrahydrofuran (2.0 mL) at room temperature under an atmosphere of argon. BH_3·DMS complex (10.44 μL, 0.10 mmol) was added and

reaction mixture was stirred for 2 hours. The reaction mixture was then cooled to 0 °C and premixed solution of 3M NaOH (0.34 mL, 1.02 mmol)/30 wt % H_2O_2 (0.104 mL, 1.02 mmol) was slowly added *via* pipette. The reaction was allowed to warm to room temperature and stir for *ca.* 12 hours. Reaction was diluted with ethyl acetate and partitioned between ethyl acetate and water. The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil. Crude alcohol **122** was used without further purification in the next step.

Crude alcohol **122** (*ca.* 0.051 mmol) was dissolved in anhydrous dichloromethane (2.0 mL) at room temperature under an atmosphere of argon. 2,6-Lutidine (0.071 mL, 0.612 mmol) was added dropwise and solution was cooled to 0 °C. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (0.057 mL, 0.245 mmol) was added and the reaction was warmed to room temperature and stirred for *ca.* 24 hours. The reaction was quenched with the mixture of saturated aqueous $NaHCO_3$ solution and partitioned between dichloromethane and water. The combined organic phases were washed with water, brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 0-2% ethyl acetate/hexanes) furnished silyl protected alcohol **123** (0.049 g, 92 % yield) as a yellow oil.

$[\alpha]_D^{24}$ -5.5 (c = 1.05, $CHCl_3$).

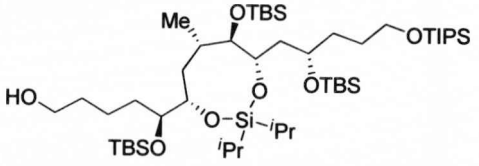
^{1}H NMR (500 MHz, C_6D_6) δ 7.32 (d, J = 7.1 Hz, 2H), 7.20 (t, J = 7.6 Hz, 2H), 7.11 (t, J = 7.4 Hz, 1H), 4.36 (d, A of AB, J_{AB} = 12.4 Hz, 1H), 4.33 (d, B of AB, J_{AB} = 12.4 Hz, 1H), 4.27-4.25 (m, 1H), 4.21 (dd, J = 5.6, 3.2 Hz, 1H), 4.16 (dd, A of ABX, J_{AB} = 9.8 Hz, J_{AX} = 3.8 Hz, 1H), 4.11 (q, J = 5.7 Hz, 1H), 3.73-3.67 (m, 3H), 3.40-3.34 (m, 2H), 2.21-2.15 (m, 1H), 2.11 (quintet, J = 7.0 Hz, 2H), 1.99 (ddd, J =

13.7, 7.0, 5.2 Hz, 1H), 1.90-1.84 (m, 3H), 1.82-1.76 (m, 2H), 1.71-1.63 (m, 5H), 1.60-1.49 (m, 3H), 1.46-1.40 (m, 1H), 1.26-1.21 (m, 14H), 1.17-1.13 (m, 21H), 1.07 (s, 9H), 1.04 (s, 9H), 1.00 (s, 9H), 0.26 (s, 3H), 0.25 (s, 3H), 0.25 (s, 3H), 0.22 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 139.580 (e), 128.54 (o), 127.69 (o), 127.56 (o), 77.96 (o), 76.17 (o), 75.47 (o), 72.98 (e), 71.82 (o), 70.45 (e), 70.14 (o), 64.12 (e), 43.92 (e), 37.05 (e), 34.75 (o), 33.90 (e) , 31.36 (e), 30.61 (e), 30.26 (e), 28.62 (e), 26.32 (o), 26.30 (o), 26.18 (o), 23.48 (e) 18.45 (e), 18.43 (e), 18.37 (o), 18.14 (o), 18.09 (o), 17.77 (o), 17.70 (o), 16.38 (o), 14.16 (o), 13.79 (o), 12.36 (o), -3.53 (o), -3.56 (o), -3.67 (o), -4.07 (o), -4.25 (o).

IR (Neat): 2928 (m), 2859 (m), 1463 (m), 1380 (w), 1251 (m), 1101 (s), 1072 (s), 834 (s), 773 (s) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{56}H_{114}O_7NaSi_5$ 1061.7309, found 1061.7281.



124

(*S*)-5-(*tert*-Butyldimethylsilyloxy)-5-((4*S*,6*S*,7*R*,8S)-7-(*tert*-butyldimethylsilyl-oxy)-8-((*S*)-2-(*tert*-butyldimethylsilyloxy)-5-(triisopropylsilyloxy)pentyl)-2,2-diisopropyl-6-methyl-1,3,2-dioxasilocan-4-yl)pentan-1-ol 124

Experimental Procedure: The benzyl ether **123** (15.0 mg, 0.014 mmol) as a solution in anhydrous ethyl acetate (1 mL) was added to a suspension of palladium(II) hydroxide on charcoal (16 mg, 0.003 mmol) in anhydrous ethyl acetate (1 mL) at room temperature under an atmosphere of hydrogen. The reaction was stirred for *ca.* 16 hours (t.l.c. control). The suspension was filtered over silica gel pad (eluting with

30% ethyl acetate/hexane). The filtrate was concentrated *in vacuo* to afford a crude oil. Purification by flash chromatography (eluting with 5-20% ethyl acetate/hexanes) furnished primary alcohol **124** (12.3 mg, 90 % yield) as a yellow oil.

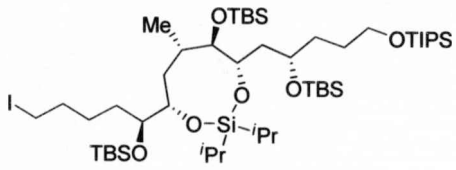
$[\alpha]_D^{24}$ -2.4 (c = 1.24, $CHCl_3$).

^{1}H NMR (500 MHz, C_6D_6) δ 4.29-4.24 (m, 1H), 4.22 (dd, *J* = 5.5, 3.2 Hz, 1H), 4.16 (dd, *J* = 9.8, 3.7 Hz, 1H), 4.11 (q, *J* = 5.7 Hz, 1H), 3.74-3.69 (m, 3H), 3.40 (t, *J* = 6.4 Hz, 2H), 2.22-2.17 (m, 1H), 2.14-2.08 (m, 2H), 2.00 (ddd, *J* = 13.7, 6.6, 5.4 Hz, 1H), 1.92-1.77 (m, 4H), 1.26-1.22 (m, 13H), 1.14-1.11 (m, 32H), 1.07 (s, 9H), 1.04 (s, 9H), 1.00 (s, 9H), 0.26 (s, 3H), 0.25 (s, 6H), 0.22 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 78.00 (o), 76.18 (o), 75.46 (o), 71.85 (o), 70.17 (o), 64.15 (e), 62.64 (e), 43.93 (e), 37.08 (e), 34.76 (o), 33.92 (e), 33.42 (e), 31.32 (e), 30.48 (o), 30.25 (e), 28.63 (e), 26.32 (o), 26.30 (o), 26.18 (o), 22.90 (e) 18.45 (e), 18.44 (e), 18.37 (o), 18.14 (o), 18.09 (o), 17.76 (o), 17.70 (o), 16.40 (o), 14.16 (o), 13.80 (o), 12.38 (o), -3.52 (o), -3.55 (o), -3.67 (o), -4.05 (o), -4.25 (o).

IR (Neat): 3332 (br w), 2928 (m), 2891 (w), 2859 (m), 1463 (m), 1387 (w), 1252 (m), 1100 (m), 1068 (m), 833 (s), 773 (s) cm^{-1}.

HRMS (ESI, MNa^+): calcd for $C_{49}H_{108}O_7NaSi_5$ 971.6839, found 971.6876.



47

(4*S*,5*R*,6*S*,8*S*)-5-(*tert*-Butyldimethylsilyloxy)-4-((*S*)-2-(*tert*-butyldimethylsilyl-oxy)-5-(triisopropylsilyloxy)pentyl)-8-((*S*)-1-(*tert*-butyldimethylsilyloxy)-5-iodopentyl)-2,2-diisopropyl-6-methyl-1,3,2-dioxasilocane 47

Experimental Procedure: Primary alcohol **124** (24.8 mg, 0.023 mmol), imidazole (17 mg, 0.25 mmol) and triphenylphosphine (21 mg, 0.08 mmol) were dissolved in anhydrous dichloromethane (0.52 mL) at room temperature under an atmosphere of argon. Iodine (21 mg, 0.08 mmol) was added in a single portion and reaction was stirred for *ca.* 2 hours. The reaction was quenched with water, washed with water and 1:1 mixture of saturated aqueous $NaHCO_3/Na_2S_2O_3$ solution. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil. Purification by flash chromatography (eluting with 0-5% ethyl acetate/hexanes) furnished primary iodide **47** (22.1 mg, 80 % yield) as a yellow oil.

$[\alpha]_D^{24}$ We were unable to obtain the specific rotation.

^{1}H NMR (500 MHz, C_6D_6) δ 4.24-4.23 (m, 1H), 4.18 (dd, J = 5.5, 3.2 Hz, 1H), 4.11 (dd, A of ABX, J_{AB} = 9.7, J_{AX} = 3.9 Hz, 1H), 4.08 (q, J = 6.0 Hz, 1H), 3.71 (t, J = 4.9 Hz, 2H), 3.62 (dt, J = 8.0, 4.0 Hz, 1H), 2.83-2.75 (m, 2H), 2.19-2.14 (m, 1H), 2.12-2.03 (m, 2H), 1.97 (ddd, J = 13.8, 6.9, 5.1 Hz, 1H), 1.89-1.62 (m, 5H), 1.57-1.42 (m, 4H), 1.37-1.29 (m, 5H), 1.23-1.19 (m, 14H), 1.14-1.10 (m, 21H), 1.05 (s, 9H), 1.03 (s, 9H), 0.98 (s, 9H), 0.24 (s, 3H), 0.24 (s, 3H), 0.23 (s, 3H), 0.20 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6) δ 77.97 (o), 75.92 (o), 75.36 (o), 71.80 (o), 70.15 (o), 64.13 (e), 43.88 (e), 36.96 (e), 34.72 (o), 33.90 (e), 33.85 (e), 30.28 (e), 28.62 (e), 27.56 (e), 26.32 (o), 26.31 (o), 26.17 (o), 18.45 (e), 18.44 (e), 18.37 (o), 18.13 (o), 18.08 (o), 17.78 (o), 17.69 (o), 16.41 (o), 14.11 (o), 13.71 (o), 12.38 (o), 6.78 (e), -3.53 (o), -3.56 (o), -3.68 (o), -4.05 (o), -4.23 (o).

IR (Neat): 2928 (m), 2891 (w), 2860 (m), 1463 (m), 1387 (w), 1251 (m), 1097 (s), 1074 (s), 833 (s), 773 (s) cm^{-1}.

HRMS (ESI, MNa^+): We were unable to obtain a high resolution mass spectrum.

3.6 References

[1] (a) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685-1698. (b) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897-1909.

[2] Amphidinols: (a) Satake, M.; Murata, Yasumoto, T.; Fujita, T.; Naoki, H. *J. Am. Chem. Soc.* **1991**, *113*, 9859-9861. (b) Paul, G. K.; Matsumori, N.; Murata, M.; Tachibana, K. *Tatrahedron Lett.* **1995**, *36*, 6279-6282. (c) Morsy, N.; Matsuoka, S.; Houdai, T.; Matsumori, N.; Adachi, S.; Murata, M.; Iwashita, T.; Fujita, T. *Tetrahedron* **2005**, *61*, 8606-8610. (d) Echigoya, R.; Rhodes, L.; Oshima, Y.; Satake, M. *Harmful Algae* **2005**, *4*, 383-389. (e) Morsy, N.; Houdai, T.; Matsuoka, S.; Matsumori, N.; Adachi, S.; Oishi, T.; Murata, M.; Iwashita, T.; Fujita, T. *Bioorg. Med. Chem.* **2006**, *14*, 6548-6554.

[3] Paul, G. K.; Matsumori, N.; Konoki, K.; Murata, M.; Tachibana, K. *J. Mar. Biotechnol.* **1997**, *5*, 124-128.

[4] Morsy, N.; Konoki, K.; Houdai, T.; Matsumori, N.; Oishi, T.; Murata, M.; Aimoto, S. *Biochim. Biophys. Acta* **2008**, *1778*, 1453-1459.

[5] (a) Morsy, N.; Houdai, T.; Konoki, K.; Matsumori, N.; Oishi, T.; Murata, M. *Bioorg. Med. Chem.* **2008**, *16*, 3084-3090. (b) Houdai, T.; Matsumori, N.; Murata, M. *Org. Lett.* **2008**, *10*, 4191-4194.

[6] Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866-867.

[7] Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.

[8] Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870-871.

[9] (a) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451-1454. (b) Cossy, J.; Tsuchiya, T.; Ferrie, L.; Reymond, S.; Kreuzer, T.; Colobert, F.; Jourdain, P.; Markó, I. E. *Synlett* **2007**, 2286-2288. (c) Colobert, F.; Kreuzer, T.; Cossy, J.; Reymond, S.; Tsuchiya, T.; Ferrie, L.; Markó, I. E.; Jourdain, P. *Synlett* **2007**, 2351-2354.

[10] (a) Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 1411-1414. (b) Hicks, J. D.; Flamme, E. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 5509-5512. (c) Hicks, J. D.; Roush, W. R. *Org. Lett.* **2008**, *10*, 681-684.

[11] (a) de Vicente, J.; Betzemeier, B.; Rychnovsky, S. D.; *Org. Lett.* **2005**, *7*, 1853-1856. (b) de Vicente, J.; Huckins, J. R.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7258-7262. (c) Huckins, J. R.; de Vicente, J.; Rychnovsky, S. D. *Org. Lett.* **2007**, *9*, 4757-4760.

[12] (a) Paquette, L. A.; Chang, S. -K. *Org. Lett.* **2005**, *7*, 3111-3114. (b) Chang, S. -K.; Paquette, L. A. *Synlett* **2005**, 2915-2918. (c) Bedore, M. W.; Chang, S. -K.; Paquette, L. A. *Org. Lett.* **2007**, *9*, 513-516.

[13] Dubost, C.; Markó, I. E.; Bryans, J. *Tetrahedron Lett.* **2005**, *46*, 4005-4009.

[14] Oishi, T.; Kanemoto, M.; Swasono, R.; Matsumori, N.; Murata, M. *Org. Lett.* **2008**, *10*, 5203-5206.

[15] Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321-2336.

[16] For use of organotitanium reagents in asymmetric synthesis see: (a) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807-832. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2*, 3975-3977. (c) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2*, 501-504. (d) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *Synlett* **2000**, 1461-1463. (e) Cossy, J.; Willis, C.; Bellosta, V.; BouzBouz, S. *J. Org. Chem.* **2002**, *67*, 1982-1992. (f) Cossy, J.; Willis, C.; Bellosta, V.; Saint-Jalmes, L. *Synthesis* **2002**, 951-957. (g) Cossy, J.; BouzBouz, S.; Preadaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595-1606. (h) BouzBouz, S.; Cossy, J. *Org. Lett.* **2003**, *5*, 3029-3031.

[17] For alkene *cross*-metathesis see: (a) Gibson, S.; Keen, S. P. *Top. Organomet. Chem.* **1998**, *1*, 155-181. (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900-1923. (c) Vernall, A. J.; Abell, A. D. *Aldrichim. Acta* **2003**, *36*, 93-105. (d) Prunet, J. *Curr. Top. Med. Chem.* **2005**, *5*, 1559-1577. (e) Netscher, T. J. *J. Organomet. Chem.* **2006**, *691*, 5148-5154. (f) Waetzig, J. D.; Hanson, P. R. *Chemtracts* **2006**, *19*, 157-167. (g) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243-251. (h) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427-7430. (i) O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 1091-1094. (j) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751-1753. (k) Toste, F. D.; Chatterjee, A. K.; Grubbs, R. H. *Pure Appl. Chem.* **2002**, *74*, 7-10. (l) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939-1942. (m) Chatterjee, A. K.; Choi, T. -L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370. (n) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591-7595. (o) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441-444.

[18] Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644-13645.

[19] For hydroxyl-directed hydrogenation reaction see: (a) Brown, J. M. *Angew. Chem., Int. Ed.* **1987**, *26*, 190-203. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

[20] For Noyori's ruthenium catalyst, (*S*)-Ru(BINAP)$(OAc)_2$ see: (a) Takaya, H.; Ohta, T.; Sayo, N.; Kumboyashi, H.; Akutagawa, S.; Inoue, S. -I.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596-1597. (b) Imperiali, B.; Zimmerman, J. W. *Tetrahedron Lett.* **1988**, *29*, 5343-5344.

[21] Tanabe, Y.; Misaki, T.; Kurihara, M.; Iida, A.; Nishii, Y. *J. Chem. Soc., Chem. Commun.* **2002**, 1628-1629.

[22] Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011-1013.

[23] Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

[24] (a) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263-4265. (b) Kolb, H. C.; VanNiuewenhze, M. C.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483-2547. (c) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317-1349.

[25] Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314-321.

[26] Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544-4568.

[27] Julia, M.; Paris, J. -M. *Tetrahedron Lett.* **1973**, *14*, 4833-4836.

[28] Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26-28.

[29] Schwartz, M.; Graminski, G. F.; Waters, R. M. *J. Org. Chem.* **1986**, *51*, 260-263.

[30] Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067-4086.

[31] For CBS reduction see: (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. -P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861-2863. (d) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209-1216. (e) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1988**, *37*, 1986-2012.

[32] (a) Ghanem, A.; Aboul-Enein, H. Y. *Chirality* **2005**, *17*, 1-15. (b) Ghanem, A.; Aboul-Enein, H. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3331-3351.

[33] For lithium-halide exchange see: (a) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1997**, *119*, 12031-12040. (b) Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1986**, *52*, 473-475. (c) Myers, A. G.; Goldberg, S. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2732-2735. (d) Bogenstatter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206-12207. (e) Bailey, W. F.; Khanolkar, A. D. *Tetrahedron* **1991**, *47*, 7727-7738. (f) Wu, Y.; Gao, J. *Org. Lett.* **2008**, *10*, 1533-1536.

[34] For copper-mediated stereoselective epoxide opening see: (a) Takahashi, S.; Hosoya, M.; Koshino, H.; Nakata, T. *Org. Lett.* **2003**, *5*, 1555-1558. (b) Lawhorn, B. G.; Boga, S. B.; Wolkenberg, S. E.; Colby, D. A.; Gauss, C. -M.; Swingle, M. R.; Amable, L.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 16720-16732. (c) La Cruz, T. E.; Rychnovsky, S. D. *J. Org. Chem.* **2007**, *72*, 2602-2611.

[35] Original conditions for the *cross*-metathesis of PMP protected *homo*-allylic alcohol include 2.5 mol% of 2nd generation Hoveyda-Grubbs' catalyst and 3 equivalents of acrolein with stirring for 36 hours in DCM at room temperature.

[36] Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed.* **1983**, *22*, 31-41.

[37] Reetz, M. T. *Pure Appl. Chem.* **1985**, *57*, 1781-1788.

[38] González-García, E.; Helaine, V.; Klein, G.; Schuermann, M.; Sprenger, G. A.; Fessner, W. -D.; Reymond, J. -L. *Chem. Eur. J.* **2003**, *9*, 893-899.

[39] Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1989**, *30*, 1281-1284.

[40] (a) Streitwieser, A. *Solvolytic Displacement Reactions*; McGraw-Hill Book Co.: New York, **1962**. (b) Francisco, C. G.; Freire, R.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett.* **1995**, *36*, 2141-2144. (c) Barton, D. H. R.; Hartwig, W.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1982**, 447-448. (d) Jenkins, I. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1227-1228.

[41] For Jacobsen's hydrolytic kinetic resolution see: (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936-938. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315. (c) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5-26.

[42] Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 779-793.

[43] Chow, S.; Koenig, W. A.; Kitching, W. *Eur. J. Org. Chem.* **2004**, 1198-1201.

[44] Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410-6424.

[45] For marinomycin A see: (a) Kwon, H. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **2006**, *128*, 1622-1632. (b) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6527-6532. (c) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc.* **2007**, *129*, 1760-1768.

[46] Lawler, M. J. *The Development of New Rhodium-Catalyzed Allylic Alkylation Reactions and Their Application Towards the Total Synthesis of Marinomycin A;* Indiana University: Bloomington, 2008.

[47] Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625-1627.

[48] Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863-927.

[49] Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401-404.

[50] (a) Garcia, C.; Libra, E. R.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 3210-3211. (b) Lurain, A. E.; Carrol, P. J.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 1262-1268. (c) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355-8361. (d) Jeon, S. -J.; Chen, Y. K.; Walsh, P. J. *Org. Lett.* **2005**, *7*, 1729-1732.

[51] Chen, Y. K.; Jeon, S. -J.; Walsh, P. J.; Nugent, W. A. *Org. Synth.* **2005**, *82*, 87-90.

[52] For the cross-metathesis using ethylene gas see: (a) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082-6083. (b) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, *3*, 1161-1163. (c) Ratnayake, A. S.; Hemscheidt, T. *Org. Lett.* **2002**, *4*, 4667-4669.

[53] For Lin Pu alkylation see: (a) Gao, G.; Moore, D.; Xie, R. -G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143-4146. (b) Moore, D.; Pu, L. *Org. Lett.* **2002**, *4*, 1855-1857. (c) Li, Z. -B.; Pu, L. *Org. Lett.* **2004**, *6*, 1065-1068. (d) Liu, L.; Pu, L. *Tetrahedron* **2004**, *60*, 7427-7430. (e) Qin, Y. -C.; Liu, L.; Sabat, M.; Pu, L. *Tetrahedron* **2006**, *62*, 9335-9348. (f) Gao, G.; Wang, Q.; Yu, X. -Q.; Xie, R. -G.; Pu, L. *Angew. Chem., Int. Ed.* **2006**, *45*, 122-125. (g) Li, Z. -B.; Liu, T. -D.; Pu, L. *J. Org. Chem.* **2007**, *72*, 4340-4343. (h) Wang, Q.; Chen, S. -Y.; Yu, X. -Q.; Pu, L. *Tetrahedron* **2007**, *63*, 4422-4428.

[54] Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H. -R. *J. Am. Chem. Soc.* **2003**, *125*, 14702-14703.

[55] Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240.

[56] Kumar, P.; Gupta, P.; Naidu, S. V. *Chem. Eur. J.* **2006**, *12*, 1397-1402.

[57] Duan, J. J. -W.; Sprengeler, P. A.; Smith, A. B., III. *Tetrahedron Lett.* **1992**, *33*, 6439-6442.

[58] Duan, J. J. -W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703-3711.

[59] Stivala, C. E.; Zakarian, A. *J. Am. Chem. Soc.* **2008**, *130*, 3774-3776.

[60] Wittig, G.; Pockels, U.; Droge, H. *Chem. Ber.* **1938**, *71*, 1903-1912.

[61] Gilman, H.; Langham, W.; Jacoby, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 106-109.

[62] Applequist, D. E.; O'Brien, D. F. *J. Am. Chem. Soc.* **1963**, *85*, 743-748.

[63] Bailey, W. F.; Punzalan, E. R. *J. Org. Chem.* **1990**, *55*, 5404-5406 and pertinent references therein.

[64] Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, 352, 1-46.

[65] Yang, X.; Knochel, P. *Synthesis* **2006**, 2618-2623.

[66] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

[67] Yeager, A. R.; Finney, N. S. *Bioorg. Med. Chem.* **2004**, *12*, 6451-6460.

[68] Canova, S.; Bellosta, V.; Mignani, S.; Bigot, A.; Cossy, J. *Org. Lett.* **2006**, *8*, 2091-2094.

[69] Tompson, A. M.; Delaney, A. M.; Hamby, J. M.; Schroeder, M. C.; Spoon, T. A.; Crean, S. M.; Showalter, H. D.; Hollis, D. W. A. *J. Med. Chem.* **2005**, *48*, 4628-4653.

[70] Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A.; *J. Am. Chem. Soc.* **2007**, *129*, 9592-9593.

[71] Osterkamp, F.; Ziemer, B.; Koert, U.; Wiesner, M.; Raddatz, P.; Goodman, S. L. *Chem. Eur. J.* **2000**, *6*, 666-683.

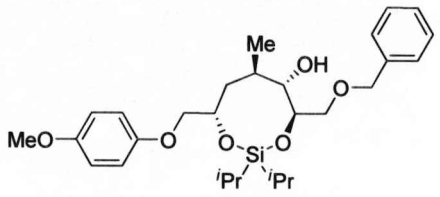
[72] Nishizawa, M.; Hirakawa, H.; Nakagava, Y.; Yamamoto, H.; Namba, K.; Imagawa, H. *Org. Lett.* **2007**, *9*, 5577-5580.

Chapter 4

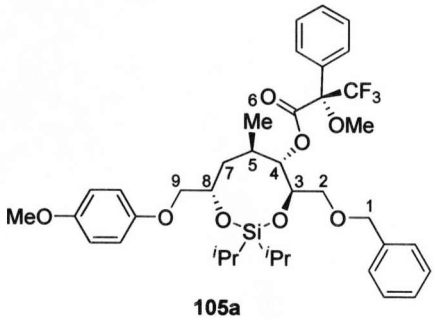
APPENDIX

4.1 Appendix A

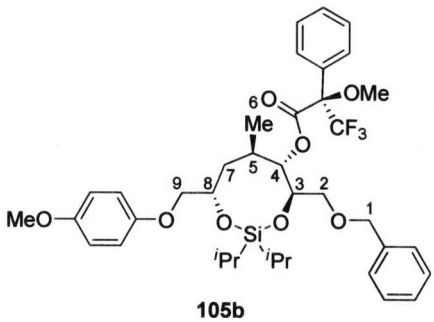
Table 4.1: *Comparative analysis of the ^1H NMR data of each of the two diastereomeric MTPA esters for alcohol* **105** *(Chapter 2)*



105



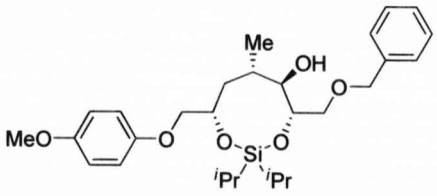
105a



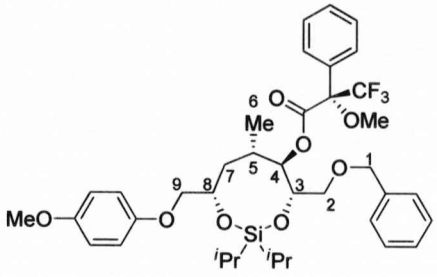
105b

	δ *S*-ester, **105a** **(4S)** (ppm)	δ *R*-ester, **105b** **(4R)** (ppm)	$\Delta\delta = \delta_S - \delta_R$	
			ppm	Hz (400 MHz)
1	4.27	4.21	+0.06	+24
2a	3.87	3.77	+0.04	+16
2b	3.74	3.71	+0.03	+12
3			-0.05	-20
5	1.80-1.79 (1.80)	2.15-2.13 (2.14)	-0.34	-136
6	1.13-0.87	1.12		
7a	1.59	1.72	-0.13	-52
7b	1.23	1.36	-0.13	-52
9a	3.81	3.87	-0.06	-24
9b	3.50	3.57	-0.07	-28

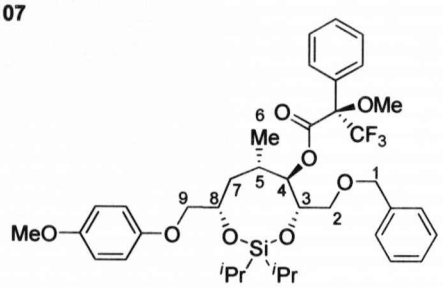
Table 4.2: *Comparative analysis of the ^1H NMR data of each of the two diastereomeric MTPA esters for alcohol* **107** *(Chapter 2)*



107



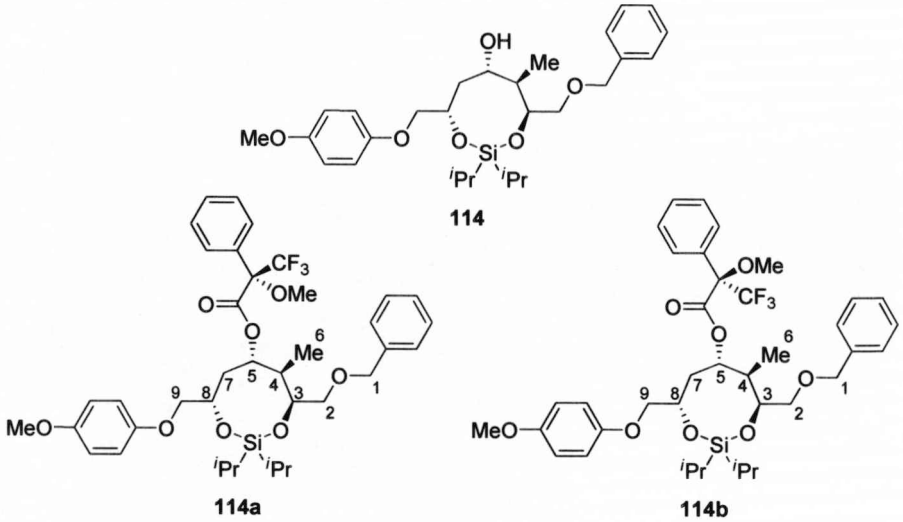
107a



107b

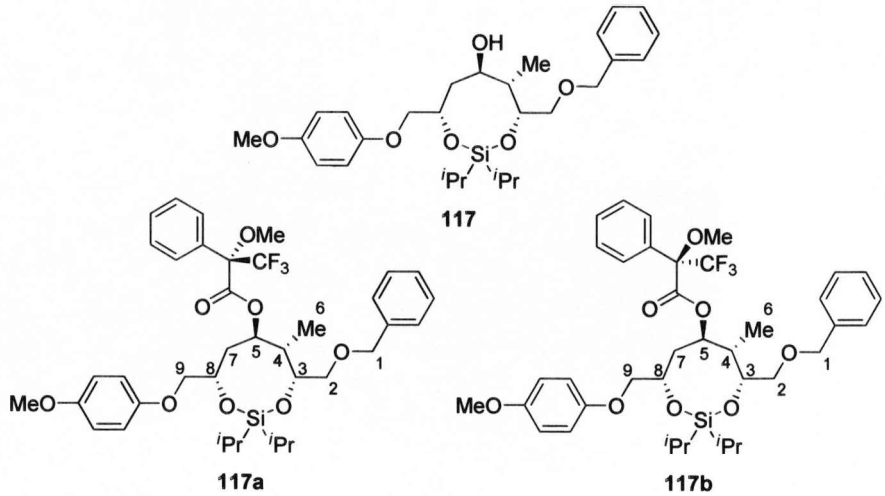
	δ *S*-ester, **107a** **(4S)** (ppm)	δ *R*-ester, **107b** **(4R)** (ppm)	$\Delta\delta = \delta_S - \delta_R$	
			ppm	Hz (400 MHz)
1	4.28	4.21	+0.07	+28
2a	3.90	3.77	+0.13	+52
2b	3.78			
3	5.50	5.59	-0.09	-36
5		2.02-1.92 (1.97)		
6	0.87	0.96	-0.09	-36
7a		1.83		
7b	1.49	1.55	-0.06	-24
8	3.85	3.96	-0.11	-44
9a	3.60			
9b	3.54	3.59	-0.05	-20

Table 4.3: *Comparative analysis of the ^1H NMR data of each of the two diastereomeric MTPA esters for alcohol* **114** *(Chapter 2)*



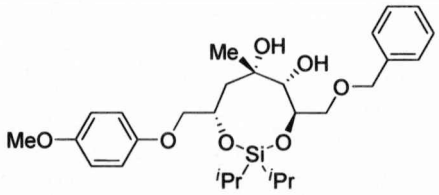
	δ *S*-ester, **114a** **(5S)** (ppm)	δ *R*-ester, **114b** **(5R)** (ppm)	$\Delta\delta = \delta_S - \delta_R$	
			ppm	Hz (400 MHz)
1a	4.31	4.30	+0.01	+4
1b	4.23	4.22	+0.01	+4
2a	3.49	3.48	+0.01	+4
2b	3.37	3.34	+0.03	+4
3	4.44	4.49	-0.05	-20
4	1.96-1.95			
6		0.93		
7a	2.01	2.14	-0.13	-52
7b	1.75			
8	4.80-4.75 (4.78)	4.78-4.72 (4.75)	+0.03	+12
9a	3.88	3.88	0.00	0
9b	3.62	3.62	0.00	0

Table 4.4: *Comparative analysis of the ^1H NMR data of each of the two diastereomeric MTPA esters for alcohol* **117** *(Chapter 2)*

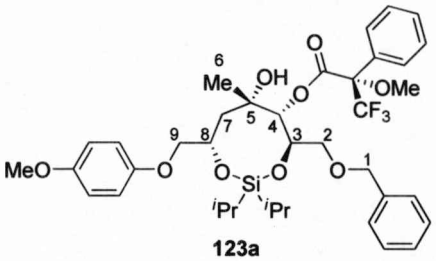


	δ *S*-ester, **117a** **(5S)** (ppm)	δ *R*-ester, **117b** **(5R)** (ppm)	$\Delta\delta = \delta_S - \delta_R$	
			ppm	Hz (400 MHz)
1a	4.31	4.32	-0.01	-4
1b	4.26	4.27	-0.01	-4
2a	3.47	3.50	-0.03	-12
2b	3.39	3.42	-0.03	-12
3	4.35-4.32 (4.34)	4.27-4.24 (4.26)	+0.08	+32
4	2.29	2.33	-0.04	-16
6	0.86	0.94	-0.08	-32
7a	2.06	2.07	-0.01	-4
7b	2.06	1.95	+0.11	+44
8	4.50	4.44	+0.06	+24
9a	3.84	3.73	+0.11	+44
9b	3.60	3.30	+0.30	+120

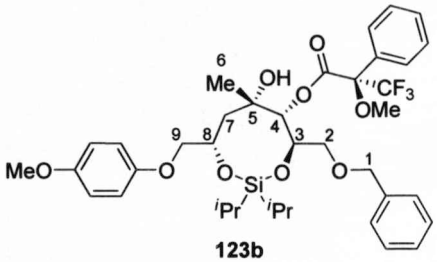
Table 4.5: *Comparative analysis of the ^1H NMR data of each of the two diastereomeric MTPA esters for diol* **123** *(Chapter 2)*



123



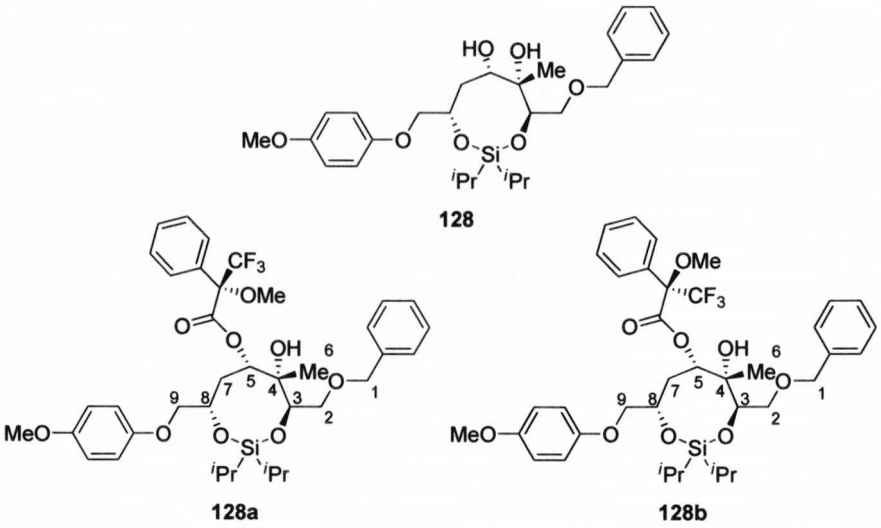
123a



123b

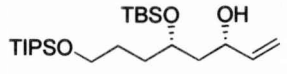
	δ *S*-ester, **123a** **(4S)** (ppm)	δ *R*-ester, **123b** **(4R)** (ppm)	$\Delta\delta = \delta_S - \delta_R$	
			ppm	Hz (400 MHz)
1a	4.40	4.32	+0.08	+32
1b	4.36	4.27	+0.09	+36
2a	3.64	3.39	+0.25	+100
2b				
3	4.65-4.61 (4.63)	4.39-4.36 (4.38)	+0.26	+104
6	1.26	1.32	-0.06	-24
7a	2.21	2.30	-0.09	-36
7b	1.92-1.87 (1.90)	1.95-1.85 (1.90)	0.00	0
8	4.28	4.28-4.24 (4.26)	+0.02	+8
9a	3.81	3.83	-0.02	-8
9b				

Table 4.6: *Comparative analysis of the ^1H NMR data of each of the two diastereomeric MTPA esters for diol* **128** *(Chapter 2)*

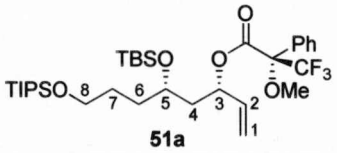


	δ *S*-ester, **128a** **(5S)** (ppm)	δ *R*-ester, **128b** **(5R)** (ppm)	$\Delta\delta = \delta_S - \delta_R$	
			ppm	Hz (400 MHz)
1a	4.20	4.18	+0.02	+8
1b	4.17	4.14	+0.03	+12
2a	3.71	3.67	+0.04	+16
2b	3.54	3.53-3.50 (3.52)	+0.02	+8
3	4.39	4.41	-0.02	-8
6	1.31	1.20	+0.11	+44
7a	2.63-2.52 (2.58)	2.69	-0.11	-44
7b	1.96	2.07	-0.11	-44
8	4.85	4.84	+0.01	+4
9a	3.88	3.88	0.00	0
9b	3.63	3.63	0.00	0

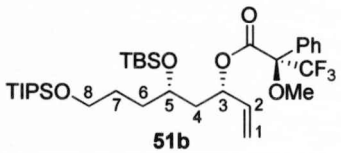
Table 4.7: *Comparative analysis of the ^1H NMR data of each of the two diastereomeric MTPA esters for alcohol* **51** *(Chapter 3)*



51



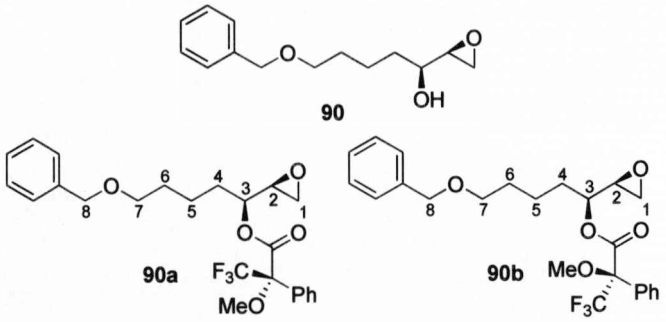
51a



51b

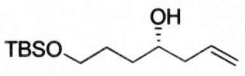
	δ *S*-ester, **51a** **(3S)** (ppm)	δ *R*-ester, **51b** **(3R)** (ppm)	$\Delta\delta = \delta_S - \delta_R$	
			ppm	Hz (500 MHz)
1a	5.38	5.29	+0.09	+45
1b	5.27	5.22	+0.05	+25
2	5.80	5.71	+0.09	+45
4a	1.84	1.90	-0.06	+30
4b	1.69	1.76	-0.07	-35
5	3.57-3.55 (3.56)	3.72-3.69 (3.71)	-0.15	-75
6/7	1.50-1.41 (1.46)	1.56-1.49 (1.53)	-0.07	-35
8	3.63-3.61 (3.62)	3.66-3.61 (3.64)	-0.02	-10

Table 4.8: *Comparative analysis of the ^1H NMR data of each of the two diastereomeric MTPA esters for alcohol* **90** *(Chapter 3)*

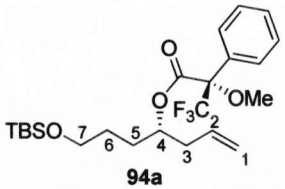


	δ *S*-ester, **90a** **(3S)** (ppm)	δ *R*-ester, **90b** **(3R)** (ppm)	$\Delta\delta = \delta_S - \delta_R$	
			ppm	Hz (400 MHz)
1a	2.85	2.76	+0.09	+36
1b	2.66	2.56	+0.10	+40
2	3.08	3.04	+0.04	+16
4/6	1.76-1.50 (1.63)	1.82-1.59 (1.71)	-0.08	-32
5	1.49-1.31 (1.40)	1.52-1.42 (1.47)	-0.07	-28
7	3.39	3.44	-0.05	-20
8	4.46	4.47	-0.01	-4

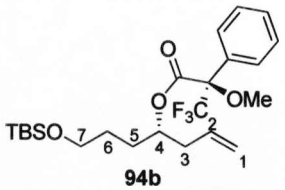
Table 4.9: *Comparative analysis of the ^1H NMR data of each of the two diastereomeric MTPA esters for alcohol* **94** *(Chapter 3)*



94



94a



94b

	δ *S*-ester, **94a** **(4S)** (ppm)	δ *R*-ester, **94b** **(4R)** (ppm)	$\Delta\delta = \delta_S - \delta_R$	
			ppm	Hz (400 MHz)
1	5.11-4.98 (5.05)	5.02-4.98 (5.0)	+0.05	+20
2	5.74	5.67-5.57 (5.62)	+0.12	+48
3	2.41	2.34	+0.07	+28
5	1.72-1.58 (1.65)	1.75-1.63 (1.69)	-0.04	-16
6	1.54-1.31 (1.43)	1.60-1.46 (1.53)	-0.10	-40
7	3.53-3.50 (3.52)	3.58	-0.06	-24

4.2 Appendix B

Table 4.10: *Crystal Data and Structure Refinements for* **106** *(Chapter 2)*

Empirical Formula:	$C_{35}H_{44}N_2O_{11}Si$
Color of Crystal:	yellow
Crystal Dimensions were:	0.30 x 0.20 x 0.04 mm.
Space Group:	P2(1)2(1)2(1)

Cell Dimensions (at 123(2) K; 999 reflections)

a =	6.6527(13)
b =	16.830(5)
c =	31.052(13)
alpha =	90
beta =	90
gamma =	90

Z (Molecules/cell):	4
Volume:	3476.8(19)
Calculated Density:	1.331
Wavelength:	0.71073
Molecular Weight:	696.81
F(000):	1480
Linear Absorption Coefficient:	0.131

Notes:

Data were collected on a Bruker SMART 6000 sealed-tube system comprising a three-circle platform goniostat, an HOG crystal monochromator, a four kilopixel by four kilopixel single-chip CCD-based detector, a K761 high voltage generator, and a PC interface running Bruker's SMART software.

Detector to sample distance =	5.0 cm.
Take off angle =	6.0 deg.

Data collected by the omega scan technique according to the following parameters:

frame width =	0.3 deg.
time per frame =	30.0 sec.

Data processing statistics for 27.6 degrees maximum theta:

Total number of intensities integrated =	13036
Number of unique intensities =	7740
Number with F > 4sigma(F) =	4711
R for averaging =	0.073

Refinement results:

Final residuals are:

R(F) (observed data) =	0.0593
Rw(F2) (refinement data) =	0.1331

Final Goodness of Fit =	0.857
Maximum delta/sigma for the last cycle =	2.17

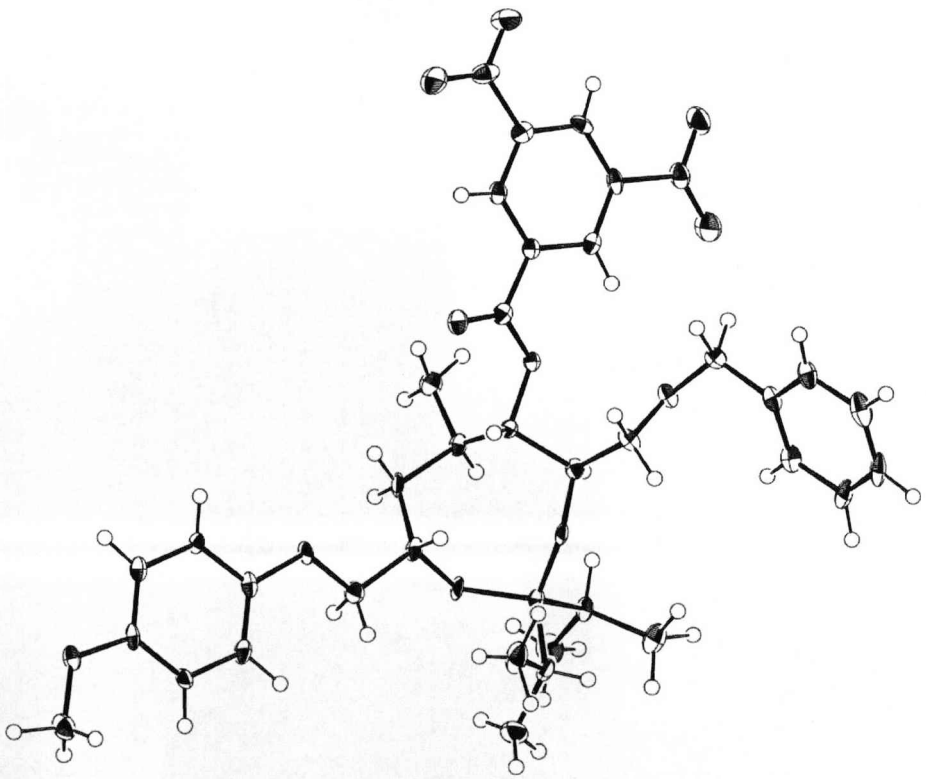


Table 4.11: *Crystal Data and Structure Refinements for* **108** *(Chapter 2)*

Empirical Formula	$C_{43}H_{39}N_3O_{15}$
Color of Crystal:	yellow
Crystal Dimensions were:	0.25 x 0.20 x 0.20 mm.
Space Group:	P1

Cell Dimensions (at 126(2) K; 1070 reflections)

a =	7.0018(13)
b =	10.728(2)
c =	26.931(5)
alpha =	89.714(5)
beta =	84.549(5)
gamma =	84.198(5)

Z (Molecules/cell):	2
Volume:	2003.5(7)
Calculated Density:	1.389
Wavelength:	0.71073
Molecular Weight:	837.77
F(000):	876

Linear Absorption Coefficient: 0.106

Notes:

Data were collected on a Bruker SMART 6000 sealed-tube system comprising a three-circle platform goniostat, an HOG crystal monochromator, a four kilopixel by four kilopixel single-chip CCD-based detector, a K761 high voltage generator, and a PC interface running Bruker's SMART software.

Detector to sample distance =	5.0 cm.
Take off angle =	6.0 deg.

Data collected by the omega scan technique according to the following parameters:

frame width =	0.3 deg.
time per frame =	30.0 sec.

Data processing statistics for 27.6 degrees maximum theta:

Total number of intensities integrated =	15714
Number of unique intensities =	12236
Number with F > 4sigma(F) =	4519

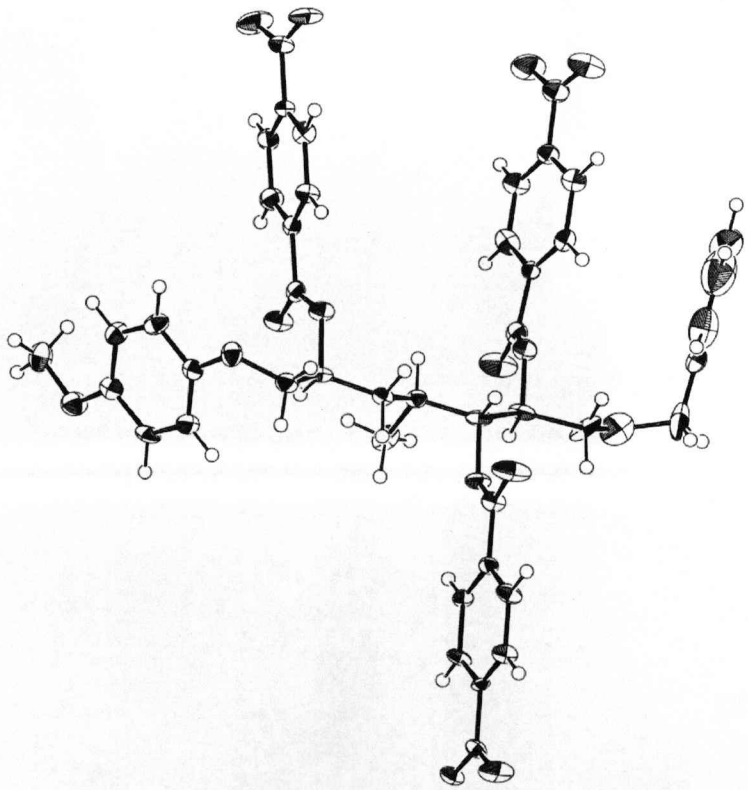
R for averaging =	0.061

Refinement results:

Final residuals are:

R(F) (observed data) =	0.0533
Rw(F2) (refinement data) =	0.1108

Final Goodness of Fit =	0.693
Maximum delta/sigma for the last cycle =	0.00



4.3 Appendix C

2D NMR Data: Chapter 2 and 3

Figure 4.1 *COSY Spectrum of Structure* **46**

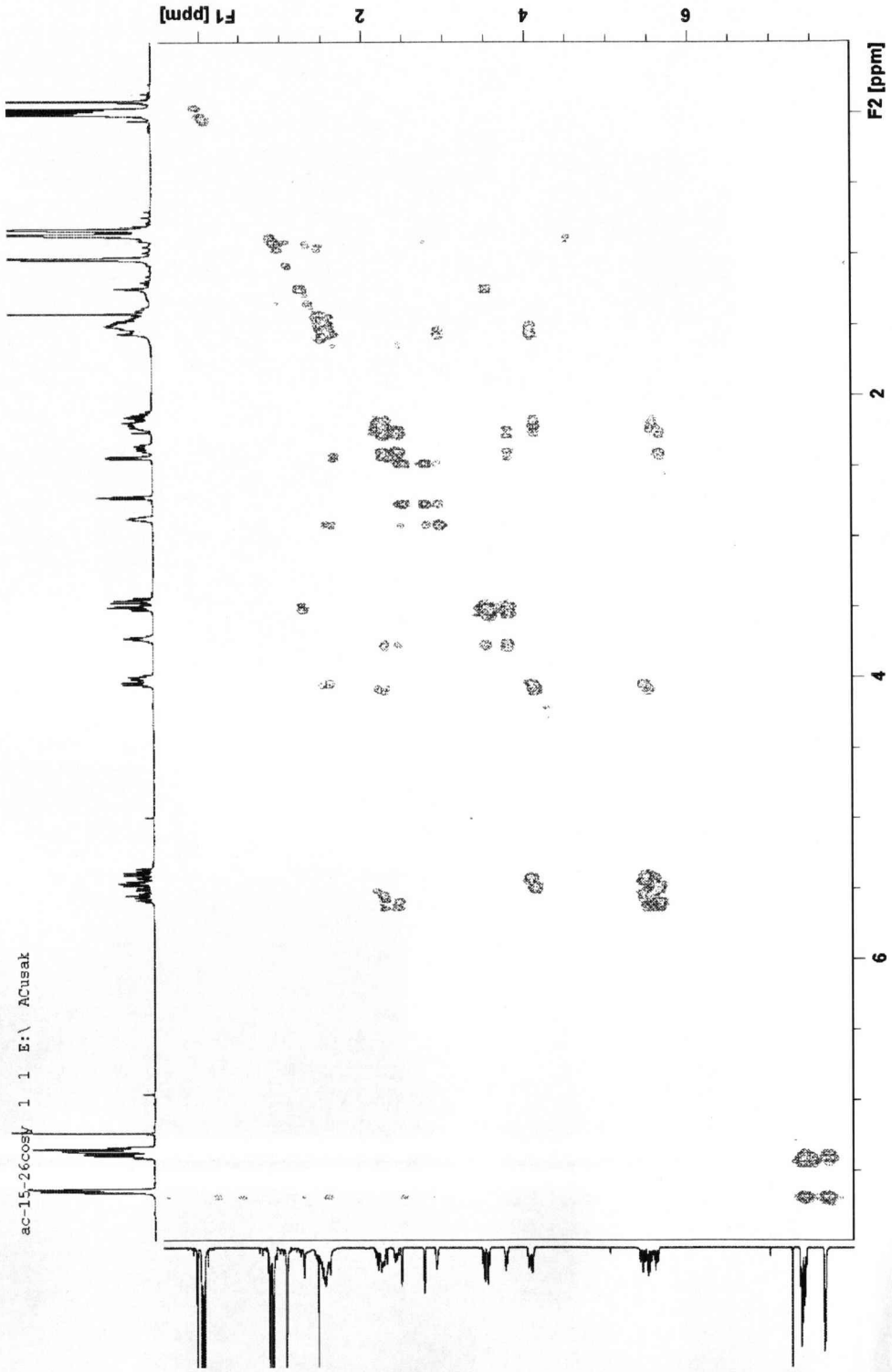


Figure 4.2 *HMBC Spectrum of Structure* **46**

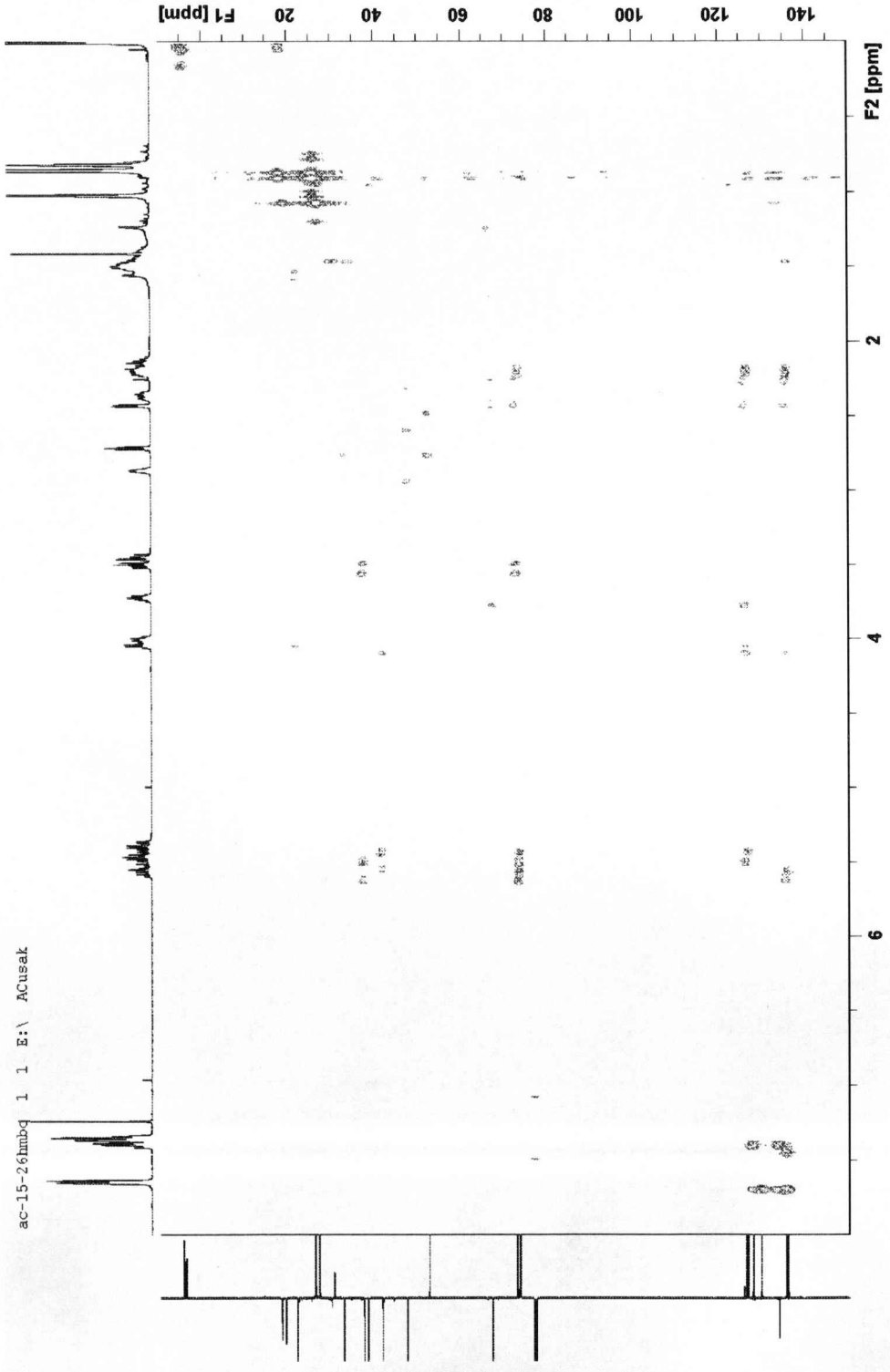


Figure 4.3 *HSQC Spectrum of Structure* **46**

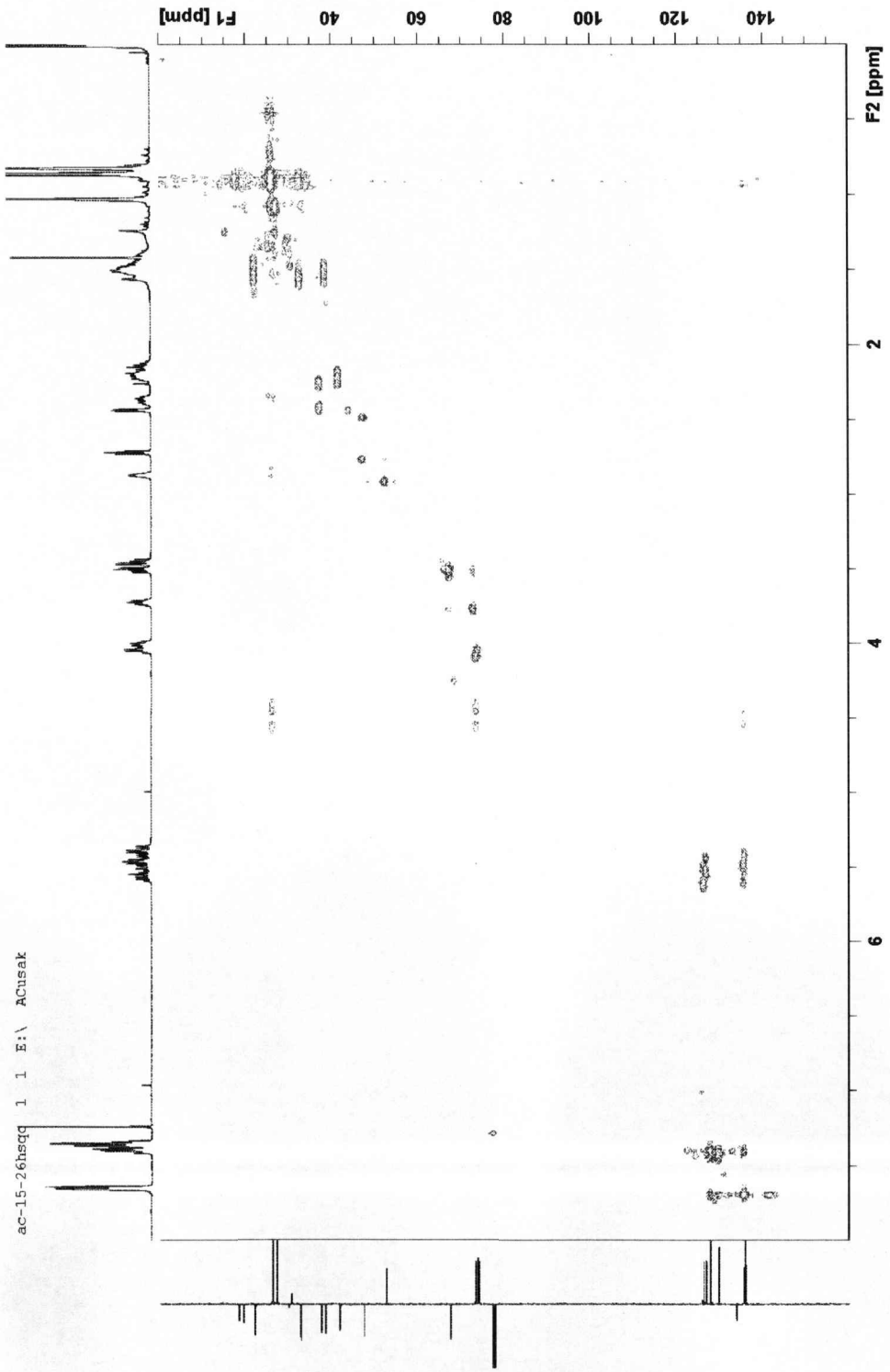


Figure 4.4 *COSY Spectrum of Structure* **123**

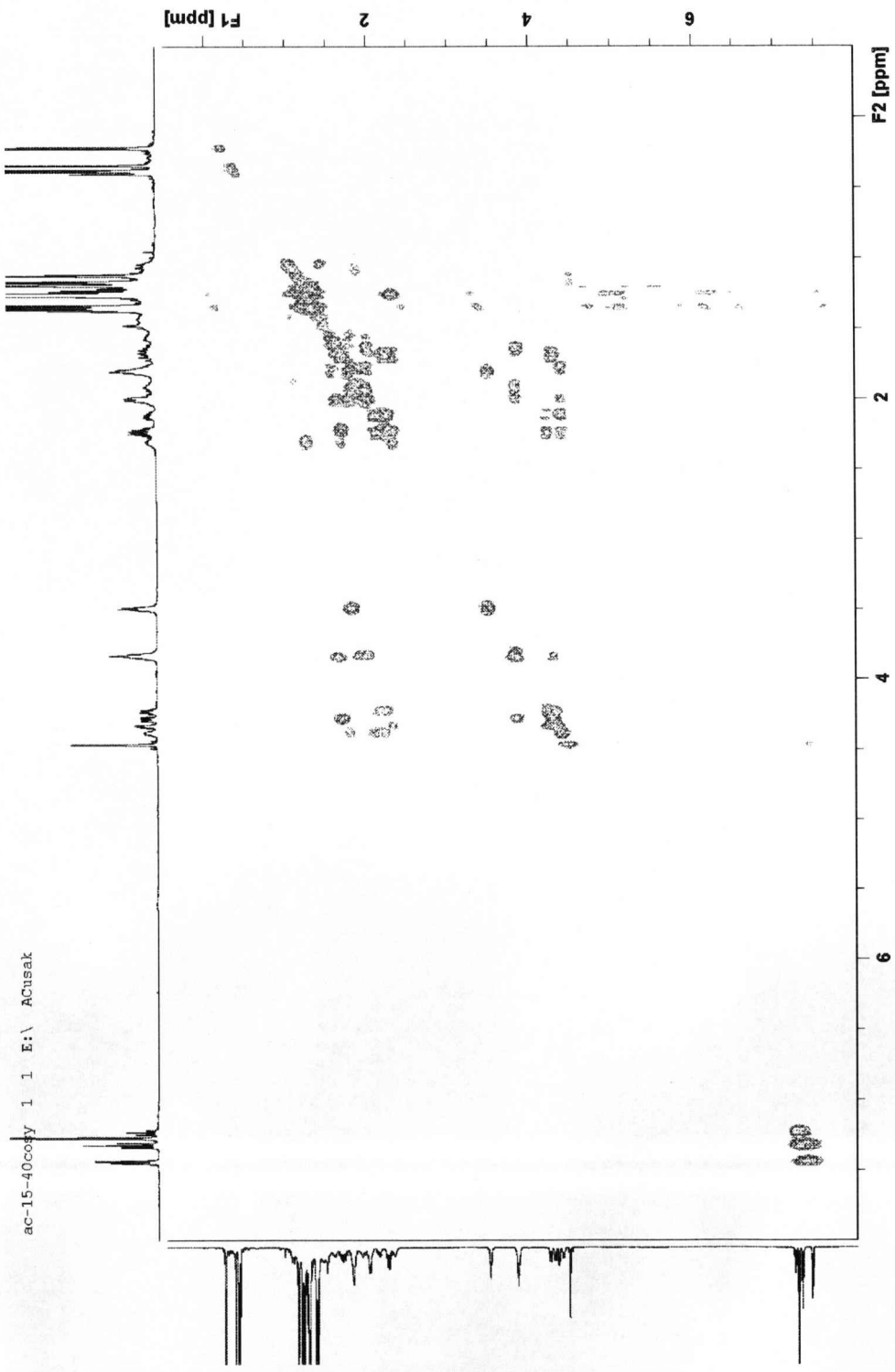


Figure 4.5 *HMBC Spectrum of Structure* **123**

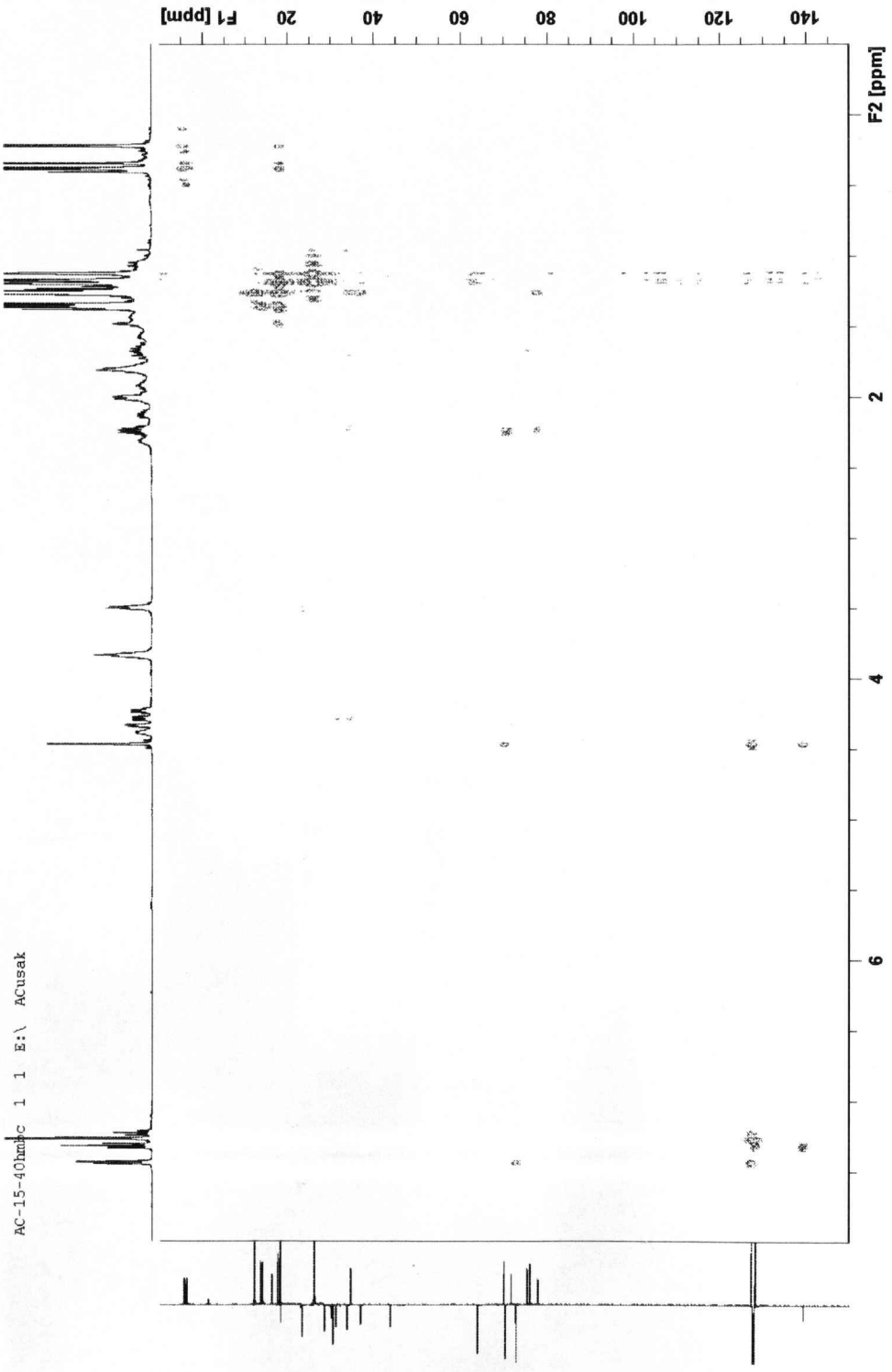


Figure 4.6 *HSQC Spectrum of Structure* **123**

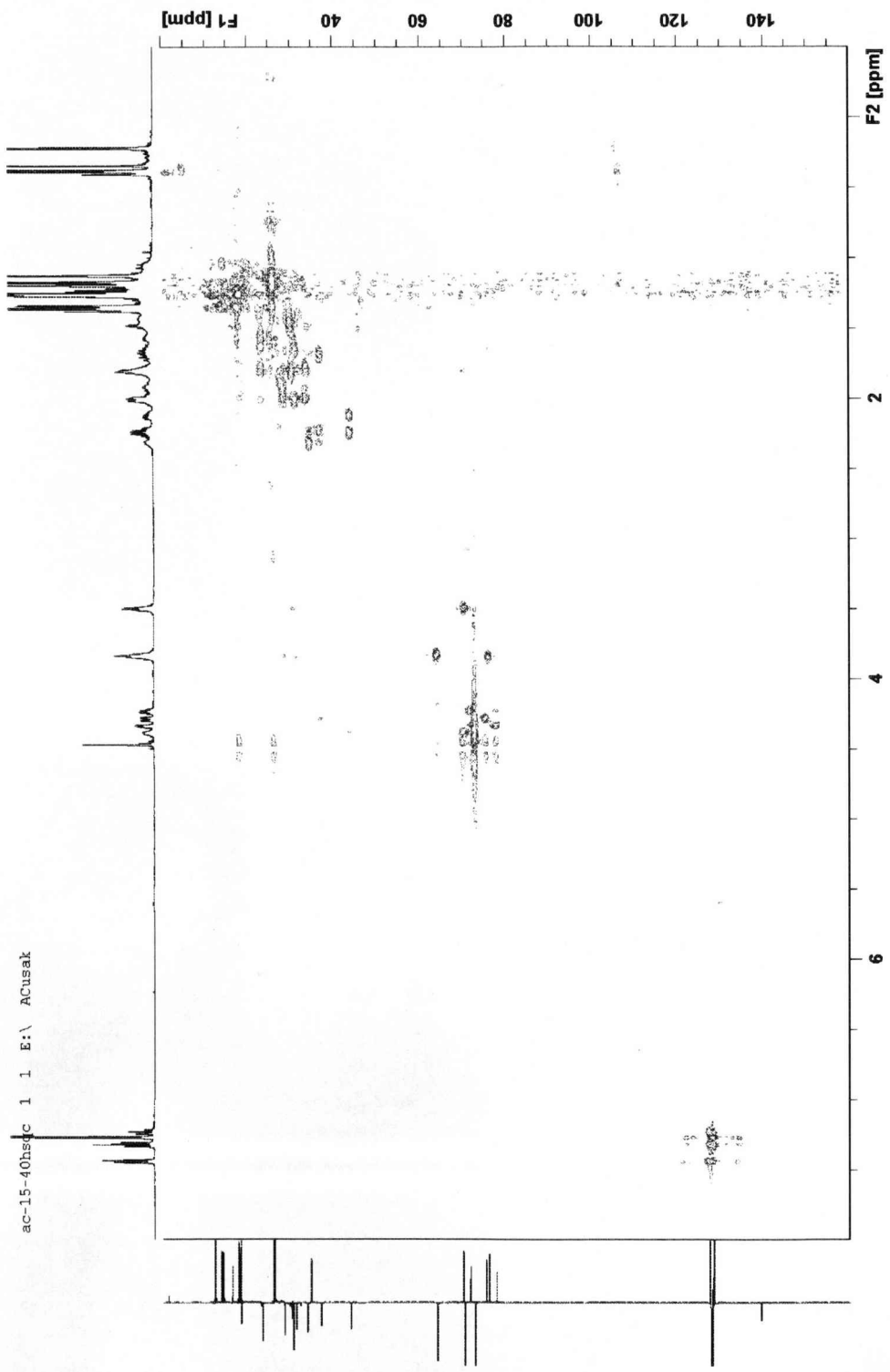


Figure 4.7 *NOESY Spectrum of Structure* **123**