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Noah A. Setterholm Date

Investigations of *exo*-Mode Oxacyclizations for the Synthesis of Cyclic Ethers

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Doctor of Philosophy

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By

Noah A. Setterholm
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An abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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2017

Abstract

Investigations of *exo*-Mode Oxacyclizations for the Synthesis of Cyclic Ethers

By Noah A. Setterholm

The marine natural product brevenal behaves as a non-toxic inhibitor of the neurotoxin brevetoxin B_2. Our research has focused on the construction of the complex polycyclic core structures of brevenal and related compounds *via* diastereoselective *exo*-mode cycloetherifications. Strategies for closing the 7-membered brevenal D ring using *exo*-mode cyclizations of an epoxyalkene were investigated. Anhydrous benzenesulfonic acid in chloroform was found to catalyze the diastereoselective cyclization of epoxyalkenes to form 6-membered rings. NMR studies suggest the intermediacy of an allyl arene sulfonate generated from addition of the sulfonic acid to the alkene terminus of the epoxy alkene. Attempts to form 7-membered rings using benzenesulfonic acid were mostly unsuccessful, with the putative allyl arenesulfonate undergoing either hydration or elimination reactions. Also studied were palladium-catalyzed cycloisomerizations of epoxyalkenes. In the presence of triisopropyl phosphite, addition of a catalytic quantity of diphenylphosphinic acid activated the epoxyalkene for the addition of palladium. Subsequent displacement of the generated palladium π-allyl with a pendant alcohol allowed for the stereoselective synthesis of 6-membered rings. In some instances, replacing triisopropyl phosphite with trimethylolpropane phosphite enabled the formation of 7-membered rings, including the brevenal CD substructure, which was obtained in low yield after an extended reaction period. Efforts directed toward achieving *exo*-mode bicyclizations for the synthesis of 6,6-ring systems were met with limited success, the bis-allylic alcohol of the starting material being vulnerable to dehydration side reactions under the iodocyclization and oxymercuration conditions attempted.

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Dedication

To my wife Hannah
And to my friend Jessica
For all their support

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CHAPTER 1: The development of *exo*-mode oxacyclizations of epoxyalkenes

List of Illustrations

List of abbreviations

ABNO	9-azabicyclo[3.3.1] nonane *N*-oxyl
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app.	apparent
APT	attached proton test
biyp	bipyridine
CAL-B	*Candida antarctica* lipase
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
dba	dibenzylideneacetone
DET	diethyl tartrate
DIAD	diisopropyl azodicarboxylate
DIPT	diisopropyl tartrate
DMAP	4-*N,N*-dimethylaminopyridine
DMF	dimethylformamide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
er	enantiomeric ratio
Et	ethyl
EtCage	trimethylolpropane phosphite

h	hour(s)
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HPCL	high-performance liquid chromatography
HRMS	high resolution mass spectrometry
i-Pr	isopropyl
IR	infrared
Me	methyl
^{MeO}bipy	4,4′-dimethoxy-2,2′-bipyridine
min	minutes
MS	molecular sieves
n-Bu	*n*-butyl
NBS	*N*-bromosuccinimide
NMI	*N*-methylimidazole
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
NSI	nanospray ionization
PPh_3	triphenylphosphine
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
rt	room temperature

t-Bu	*tert*-butyl
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
Tf	triflyl, trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TOCSY	total correlation spectroscopy
Ts	tosyl, toluenesulfonyl

CHAPTER 1

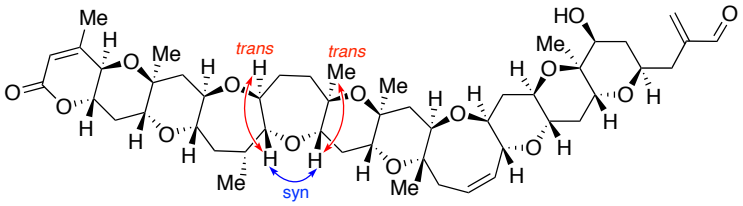
The development of exo-mode oxacyclizations of epoxyalkenes

1.1 Introduction

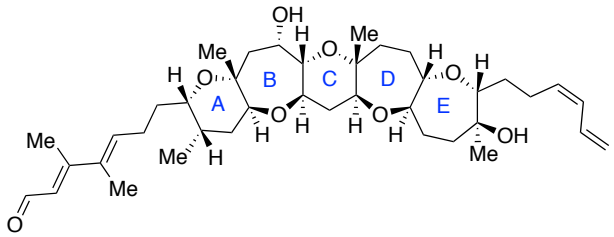
1.1.1 Brevetoxin & Brevenal

Brevetoxin B_2 (**1**), is a polycyclic ether marine natural product generated by the dinoflagellate *Karenia brevis* (Figure 1). It is one of the compounds responsible for the eco-toxicity of red tide events.[1] This toxicity arises when brevetoxin B_2 binds to voltage sensitive sodium ion channels,[2] inhibiting function and causing neurotoxic shellfish poisoning. Brevenal (**2**), a smaller compound produced by the same dinoflagellate, binds to the same sodium ion channels while exerting no toxic inhibitory effects. Thus, brevenal tempers brevetoxin's toxicity, making it a potential remedy for those exposed to brevetoxin. Furthermore, brevenal has been being investigated as a treatment for the symptoms of cystic fibrosis.[3]

Figure 1: Structures of brevetoxin B_2 and brevenal.



1
brevetoxin B_2



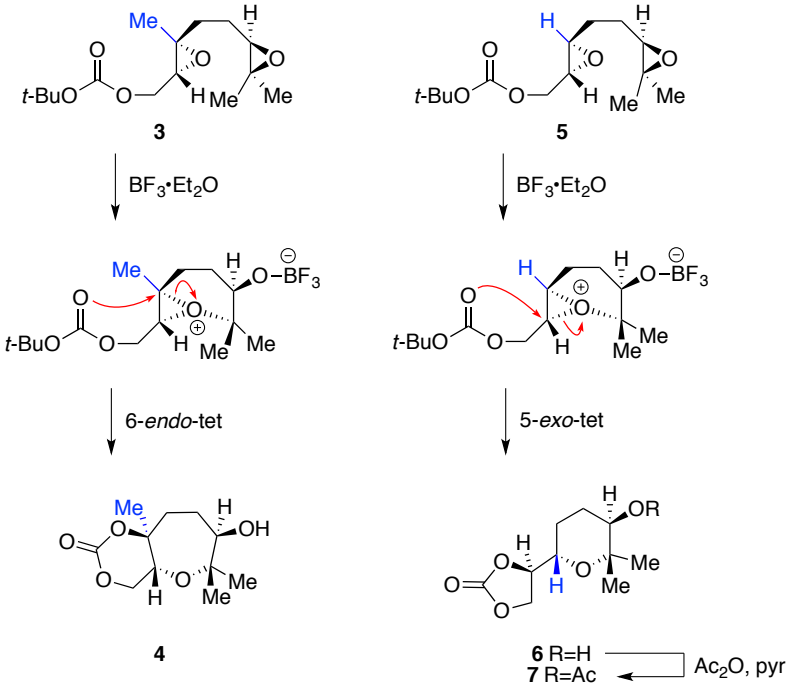
2
brevenal

While numerous total synthesis of brevetoxin,[4,5] brevenal[6–8] and other related compounds[9–11] have been reported, they typically require many chemical steps and functional group interconversions, usually generating only milligram quantities of the desired products. Isolation of brevenal from natural sources, although feasible for some applications, requires painstaking preparative HPLC to safely separate it from its toxic molecular cousins. Methods for the more efficient assembly of these complex *trans*-syn-*trans* (see compound **1**, Figure 1) polycyclic ether core structures are thus an area of active inquiry in the McDonald laboratory.[12,13]

1.1.2 Preparation of polycyclic ethers through endo-mode polyepoxide cascades

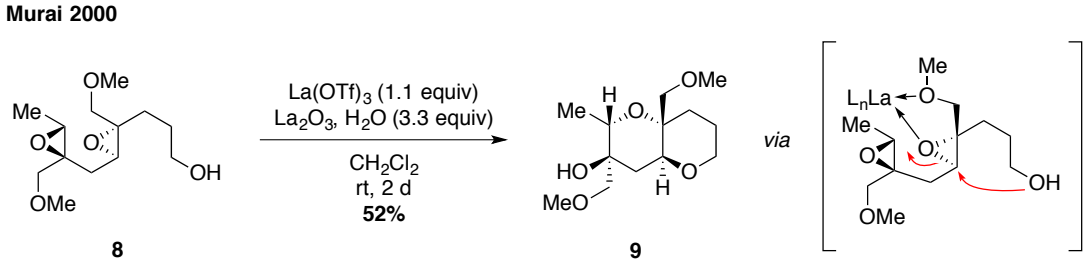
Early efforts in the McDonald laboratory sought to rapidly construct polycyclic ether frameworks containing six and seven-membered rings *via* cascade cyclizations of polyepoxides.[14–16] Although these cyclizations allow rapid access to complex polycyclic ether core structures, their utility has been limited to the preparation of certain substitution patterns in the desired product. For example, a simple methyl group in the desired product promotes the desired 6-*endo*-tet cyclization of **3** to **4** when subjected to BF_3•Et_2O (Scheme 1).[14] Replacing the methyl group with hydrogen, however, favors the undesired 5-*exo*-tet pathway, converting **5** to **6**, which was isolated as its acetate ester **7**.[17]

Scheme 1: The presence or absence of a methyl group changes the regioselectivity of bicyclization.



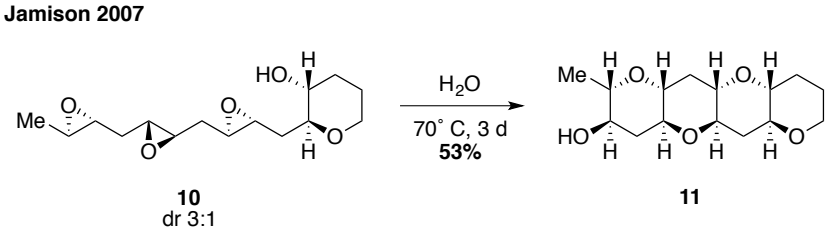
Several strategies have been developed in an attempt to circumvent these limitations. Murai and coworkers described the lanthanum triflate-mediated bicyclization of **8** (Scheme 2). They proposed that chelation of the lanthanum Lewis acid to the oxygens of the epoxide and a pendant methyl ether favored the desired 6-*endo* pathway to give **9**.[18] While these cyclizations were successful, the axial methyl methoxy ethers were not present in many polycyclic ether natural products and would be difficult to remove.

Scheme 2: Murai's lanthanum mediated *endo*-mode cycloetherification of methyl-methoxy-substituted polyepoxide substrates.



Jamison and coworkers have reported a different strategy for controlling the regiochemistry of poly-epoxide cyclization by incorporating a pre-formed pyran into the cyclization substrate (Scheme 3).[19] They proposed that the pre-formed pyran behaved as a template for further cyclizations. Thus **10** was heated in water for 3 days, giving tetracyclic **11** in 53% yield.

Scheme 3: Jamison's pyran-template polyepoxide cascade cyclization.

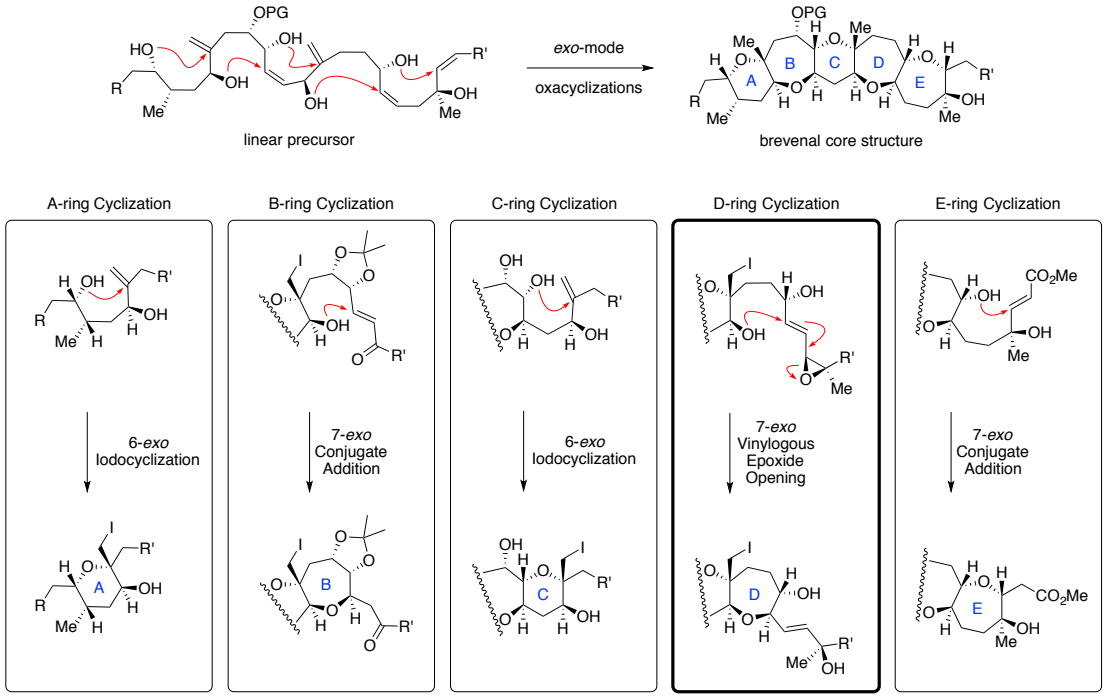


1.1.3 Focus on exo-mode cyclizations

Our current strategy in the McDonald laboratory is markedly different. Instead of attempting to effect polyepoxide cyclizations *via* endo-mode pathways, we propose to prepare polycyclic ether core structures using stereoselective *exo*-mode cyclizations of stereodefined allylic alcohols.

To this end, we have investigated various *exo*-mode oxacyclizations and have developed a strategy for the synthesis of the brevenal core structure. Thus a suitably protected linear precursor would undergo a sequence of diastereoselective *exo*-mode oxacyclizations to provide the desired pentacycle (Scheme 4).

Scheme 4: *Exo*-mode cyclization strategies for synthesis of brevenal core structure.



The 6-membered A and C rings may be formed through diastereoselective iodoetherefication reactions of 1,1 disubstituted allyl alcohols, as developed in our laboratory.[20] The 7-membered B and E rings would be constructed *via* 7-*exo* oxa-Michael reactions of secondary alcohols onto unsaturated carbonyls. For preparation of the D ring, we imagined leveraging the unique reactivity of epoxyalkenes[21] to affect a 7-*exo* vinylogous epoxide opening to give the D ring with concomitant formation of the tertiary alcohol present in the E ring.

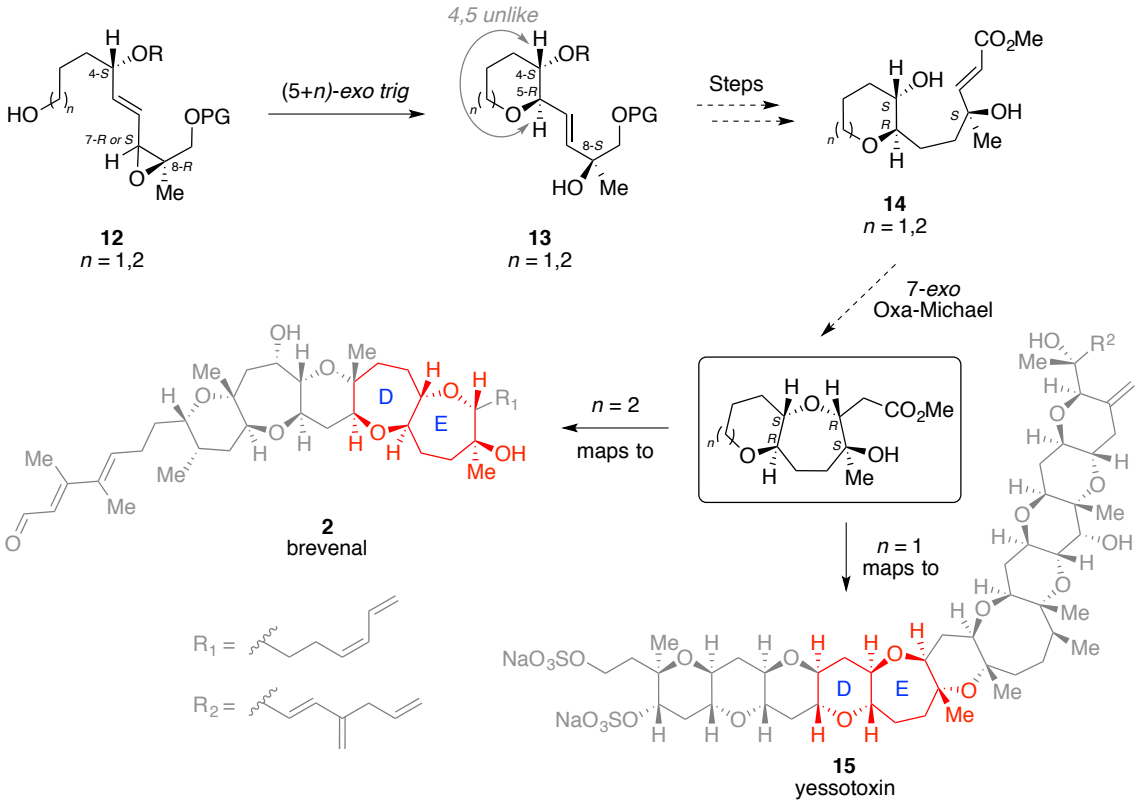
1.2 Design of test substrates

1.2.1 Planning a model system for exo-mode cyclization of epoxyalkenes

We envisioned a diastereoselective *exo*-trig oxacyclization of a pendant hydroxyl nucleophile onto the alkene terminus of an epoxy alkene **12**, with concomitant opening of the epoxide to give the needed stereochemistry of the distal tertiary alcohol at C-8 (Scheme 5). The newly formed stereocenter at C-5 in **13** would be controlled by the choice of the stereochemistry at C-7 in **12**. We choose to refer to the desired stereochemistry between the C-4 and C-5 of **13** as the *unlike* diastereomer, following the system proposed by Seebach and Prelog for unambiguous delineation of relative stereochemistry.[22] Briefly, when two stereocenters in a compound have the same configuration (*S*,*S* or *R*,*R*) their relationship is referred to as *like*; when the stereocenters bear different configurations (*S*,*R* or *R*,*S*), the relationship is described as *unlike*.

Compound **12** also bears a stereochemically defined allylic oxygen at C-4 that would serve as a nucleophile in a subsequent cyclization. Thus, following cyclization, compound **13** could be converted to ester **14** through a series of steps. This material could then undergo 7-*exo* oxa-Michael cyclization to give the bicyclic structures in compounds **2** or **15**. For n = 2, the 7,7 system corresponds to the DE bicyclic substructure of brevenal, **2**. The n = 1 compound maps onto the DE rings of yessotoxin,[23] **15**, as the enantiomer.

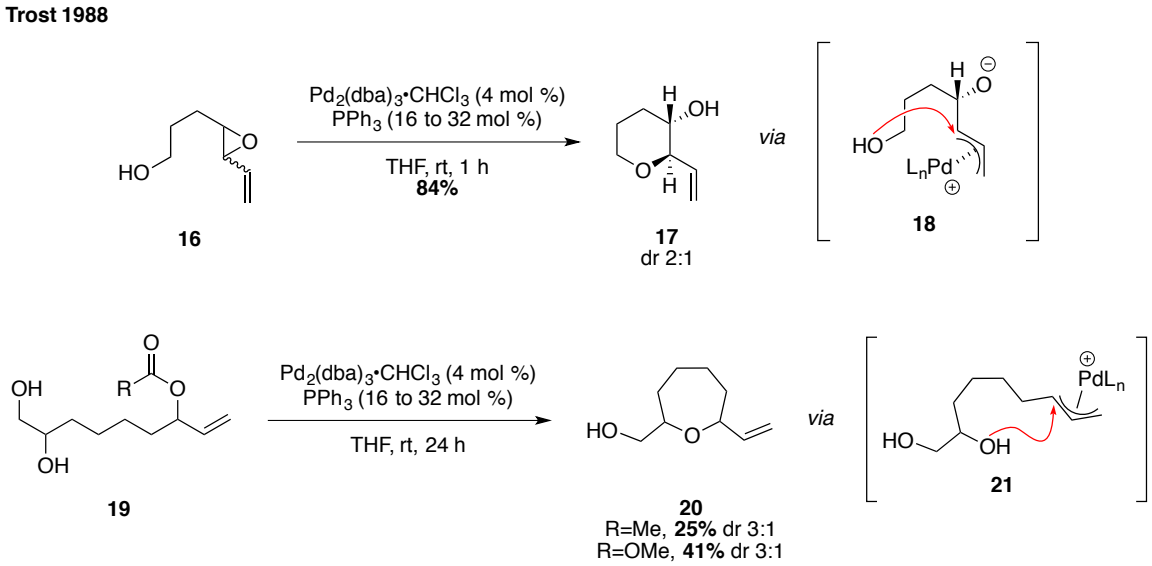
Scheme 5: Outline of investigation for *exo*-mode cyclizations of epoxyalkenes.



1.2.2 Precedent for cycloetherification with π-allyl intermediates

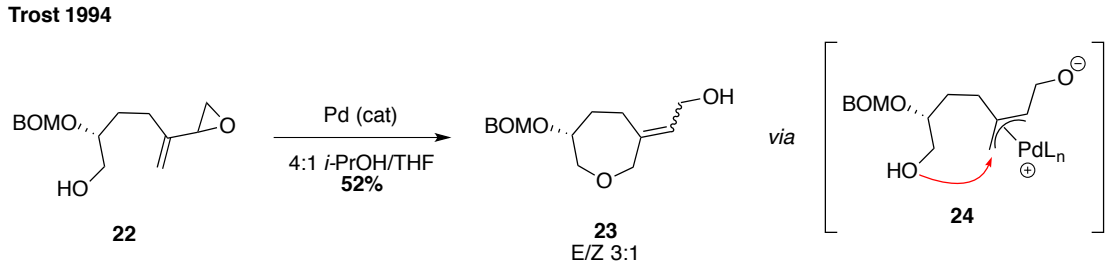
The addition of oxygen nucleophiles to Pd π-allyl complexes is precedented.[24] We were motivated to attempt our transformation in part because of work by Trost in the late 1980's demonstrating the ability of palladium catalysis to achieve 1,2 addition of a pendant hydroxyl group into the epoxyalkene **16**, giving pyran **17** through the intermediacy of Pd π-allyl complex **18** (Scheme 6).[25] The same publication also described palladium catalyzed cyclization of **19** to form oxepane **20**. The Pd π-allyl complex in this case generated from either the allylic acetate (**20**, R=Me) or the allylic carbonate (**20**, R=OMe).

Scheme 6: Palladium catalyzed cyclizations by Trost.



Later work by Trost and coworkers on a model system **22** toward the synthesis of zoapatanol illustrated the formal 1,4 addition of a pendant hydroxyl group onto an epoxyalkene to give oxepane **23**, proceeding through π-allyl **24** (Scheme 7).[26]

Scheme 7: Oxepane formation from an epoxyalkene.

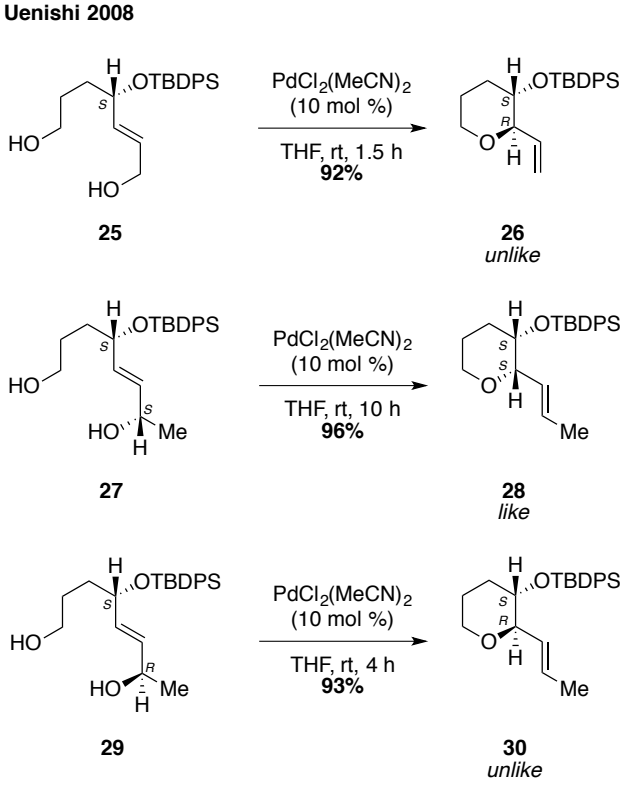


While work by Trost did show the addition of alcohols to π-allyl systems, generated from either epoxyalkenes or allylic ester derivatives, no examples described addition of an alcohol nucleophile to an alkene/π-allyl system that also contained an additional oxygen alpha to the alkene.

1.2.3 Dehydrative cyclizations by Uenishi

In 2008, Uenishi and coworkers described a palladium catalyzed dehydrative cyclization of allylic alcohols containing an additional allylic oxygen to give pyrans (Scheme 8).[27] In substrate **25**, where the allylic hydroxyl leaving group bears no stereochemistry, the allylic TBDPS group directed the formation of the *unlike* diastereomer **26**. For substrate **27**, the (*S*)-allylic alcohol directed dehydrative cyclization to occur to give the *like* diastereomer **28** after extended reaction times. For substrate **29**, bearing the (*R*)-allylic alcohol, the *unlike* diastereomer **30** was again favored during the dehydrative cyclization.

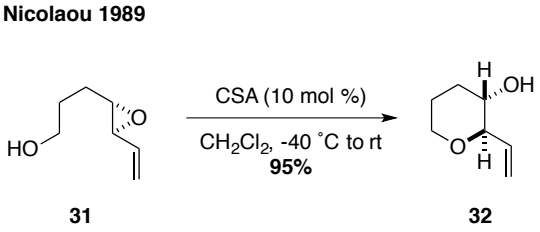
Scheme 8: Stereoselective dehydrative cyclizations by Uenishi.



1.2.4 Acid catalyzed cyclizations by Nicolaou

We also drew inspiration from some of Nicolaou's work with acid catalyzed cycloetherification of epoxyalkenes (Scheme 9).[28] It was demonstrated that regioselectivity of epoxide cyclizations could be altered by the presence of an attached vinyl group, with the pendant alcohol of **31** adding to the resonance-stabilized allylic carbocation to give **32** as the *unlike* diastereomer. We were aware that our proposed transformation placed the epoxide in a distal position relative to the epoxide. Nevertheless, we were open to the possibility that activation of the epoxide could lead to some vinylogous reactivity to produce our desired products.

Scheme 9: Acid-catalyzed cycloetherification of epoxyalkenes.

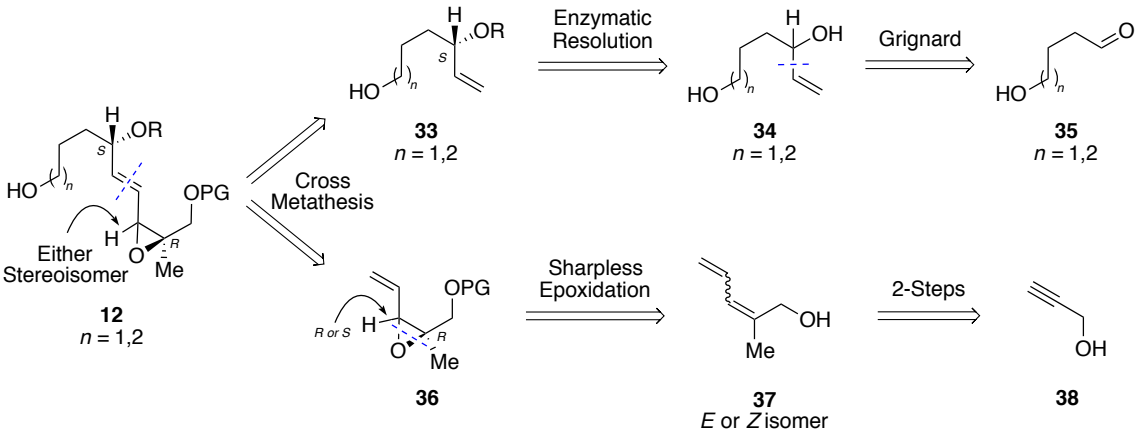


1.2.5 Retrosynthetic analysis of cyclization substrates

Retrosynthetically we considered that compound **12** could be disconnected across the *E*-alkene to reveal two type II olefins[29] that could be coupled using cross metathesis (Scheme 10). The chiral center of **33** would be derived from enzymatic resolution of **34**, arising from an addition of vinyl Grignard to the corresponding aldehyde **35**.

The epoxy alkene **36** would be made *via* a Sharpless asymmetric epoxidation of **37**, the *E* or *Z* configurations available in two steps from propargyl alcohol **38** and also ultimately controlling the stereoisomer at the allylic position of **36**.

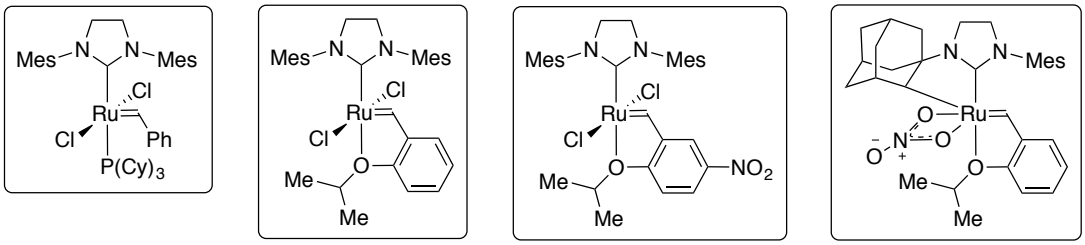
Scheme 10: Retrosynthetic analysis of cyclization substrates.



1.2.6 Olefin cross metathesis as an enabling strategy

For cross metathesis we were aware of many potential catalysts (Figure 2). The Grubbs 2nd generation catalyst,[30] **39**, is a common tool used for cross metathesis in many syntheses. For more difficult metathesis reactions, the 2nd generation Hoveyda-Grubbs catalyst, **40**, has proven effective.[31] Recently, Grela and coworkers described a modified version of the Hoveyda-Grubbs 2nd generation catalyst, **41**, containing a nitro group on the aromatic ring of the alkylidine, enhancing the initiation rate and showing greater efficiency for some metathesis reactions.[32] Also available was the Grubbs *Z* selective cross metathesis catalyst **42**,[33] which could be employed to prepare the *Z* isomers of the proposed epoxyalkene substrates.

Figure 2: Selected olefin metathesis catalysts.



39
Grubbs 2nd Generation Catalyst (Grubbs II)

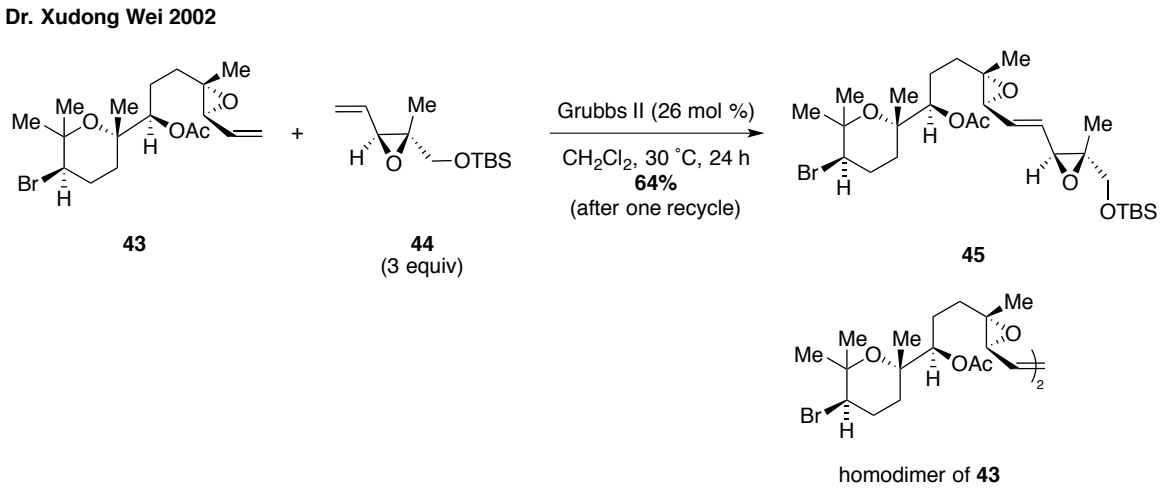
40
Hoveyda-Grubbs 2nd Generation Catalyst (HGII)

41
Nitro-Grela Metathesis Catayst (Nitro-Grela)

42
Grubbs Z Selective Catalyst (Grubbs Z)

We were confident in the prospect of using cross metathesis to forge the needed epoxy alkenes because of precedent from Dr. Xudong Wei, a postdoctoral associate in our laboratory in 2002. In the synthesis of the tris-tetrahydropyran sector of thyrsiferol venustatriol, it was necessary to couple the fragments **43** and **44** (Scheme 11).[34] Cross metathesis delivered the desired material **45** as the *E*-alkene stereoisomer. Resubjecting the isolated homodimer of **43** to cross metathesis with **44** allowed for the isolation of the desired product **45** in 64% overall yield.

Scheme 11: Work by Dr. Xudong Wei using olefin cross metathesis as a key carbon-carbon bond-forming step.

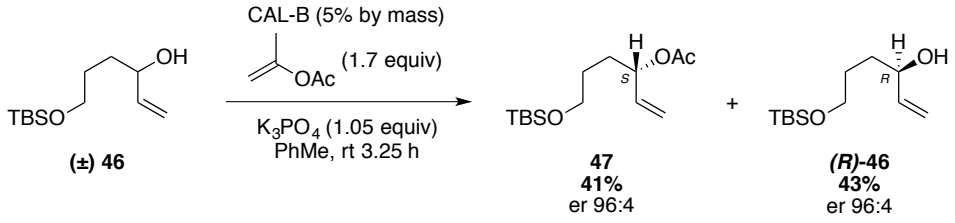


1.3 Synthesis of cyclization substrates

1.3.1 Preparation of allylic alcohol/ester metathesis coupling partner

To prepare the allylic alcohol metathesis coupling partner, racemic allyl alcohol **46**[35] was subjected to the action of *Candida antarctica* lipase in the presence of tribasic potassium phosphate, using isopropenyl acetate as the acylation source (Scheme 12).[36,37] The resolution was stopped after three and a quarter hours, after ^{1}H-NMR analysis of a removed aliquot showed approximately 50% conversion to the acetate product **47**. Chromatographic separation of the reaction mixture gave a 41% yield of (*S*)-acetate **47** as a 96:4 mixture of enantiomers as determined by Mosher ester analysis of the hydrolyzed material.[38] The non-acylated alcohol was recovered in 43% yield as the (*R*) enantiomer of **46** with an enantiomeric ratio of 96:4, also determined *via* Mosher ester analysis.

Scheme 12: Enzymatic resolution of alcohol **46** to give acetate **47**.



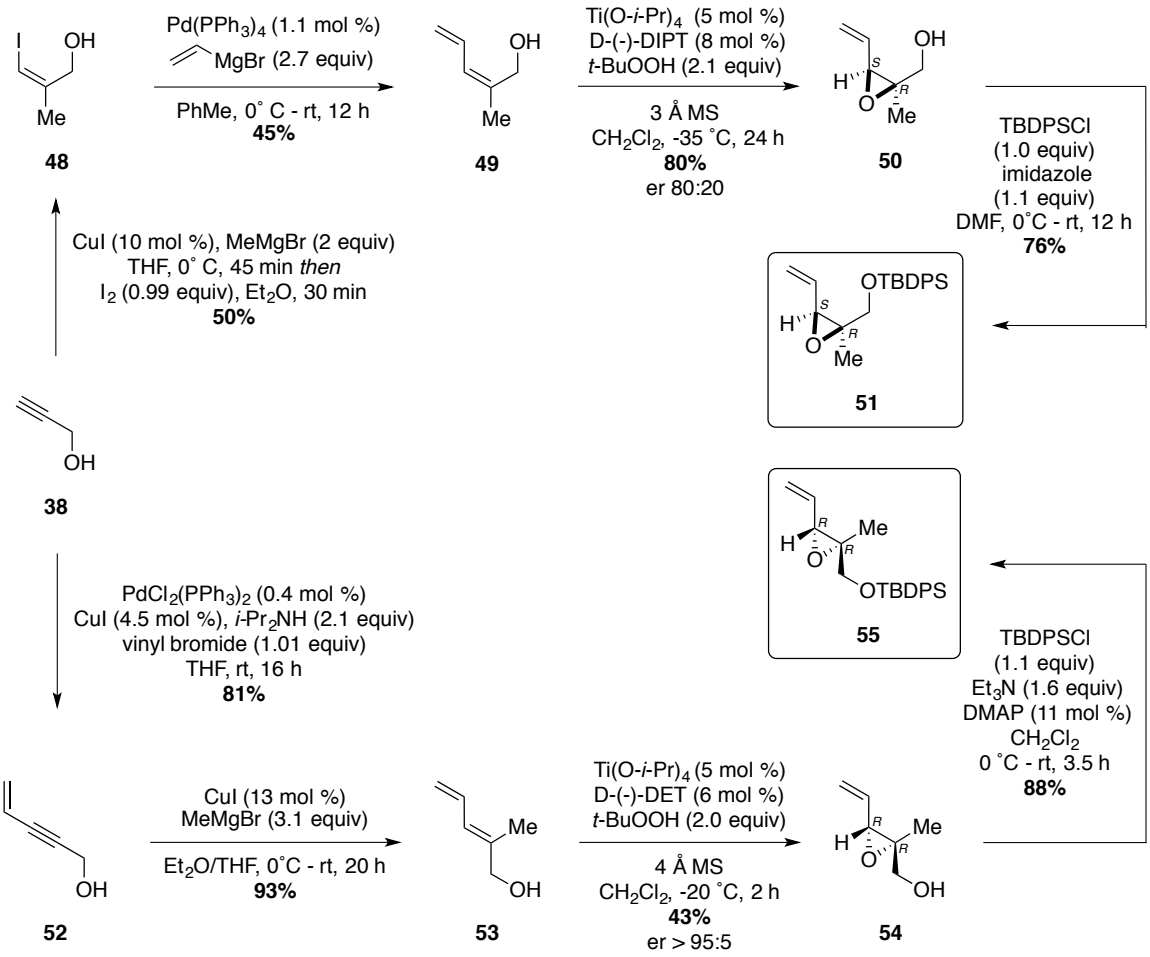
1.3.2 Synthesis of vinyl epoxide metathesis coupling partners

The synthesis of epoxy alkenes **51** and **55** is detailed in Scheme 13, both beginning from propargyl alcohol **38**. Compound **48** was derived from copper-mediated carbomagnesiation of **38** with methylmagnesium bromide followed by quenching with elemental iodine as described by Duboudin.[39] Kumada coupling[40] of vinyl iodide **48** with vinylmagnesium bromide then furnished *Z*-diene **49** which was then subjected to

Sharpless asymmetric epoxidation to give **50**. The poor enantioselectivity *Z*-alkenes is a known limitation with the Sharpless epoxidation.[41,42] Silylation of **50** with TBDPSCl then furnished **51**.

Compound **55** was prepared in a similar fashion. First, propargyl alcohol **38** underwent Sonogashira coupling with vinyl bromide to give enyne **52**.[43] Using conditions developed by Duboudin, copper-promoted carbomagnesiation of **52** with methylmagnesium bromide followed by a proton quench gave exclusively *E*-diene **53**.[44] Sharpless epoxidation of **53** gave **54** in moderate yield but with good enantioselectivity, which was then silylated with TBDPSCl to give epoxyalkene **55**.

Scheme 13: Synthesis of epoxyalkene coupling partners **51** & **55**.

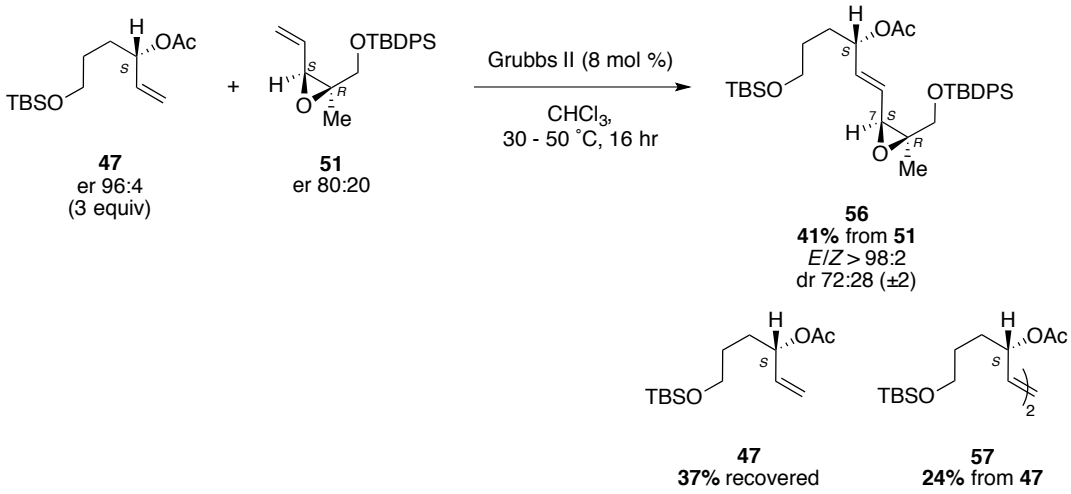


1.3.3 Early cross metathesis results

The initial metathesis experiment was performed using acetate **47** in threefold excess (it being the less valuable component of the reaction) with respect to epoxide **51** (Scheme 14). After heating the components overnight in the presence of Grubbs II catalyst **39**, the product **56** was obtained with good *E* selectivity in 41% yield with respect to the limiting reagent **51**. Acetate **47** was recovered in 37% yield in addition to a 24% yield (with respect to **47**) of its dimer **57**. The diastereomeric ratio of **56** was determined using the iNMR software package to manually fit Lorentzian functions to the overlapping doublets of the hydrogen at C-7.[45] The indicated uncertainty (±2%) signifies that the dr lies between 70:30 and 74:26, accounting for the level of precision in fitting the peak areas. For the sake of consistency, all diastereomeric ratios of epoxyalkenes were determined in this manner.

Statistically, by coupling components with enantiomeric ratios of 96:4 and 80:20, the *diastereomeric* ratio of the product is be expected to be 77.6:22.4. The obtained ratio is lower than expected, suggesting either a partial resolution during the cross metathesis, in this case in favor of the undesired minor diastereomer; or an undetectable depletion of the major diastereomer during column chromatography.

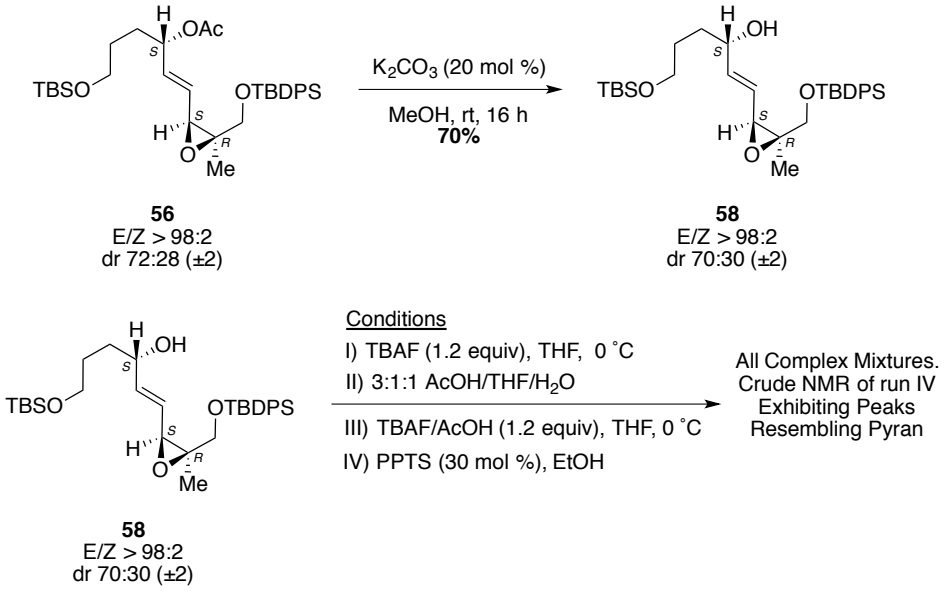
Scheme 14: First generation cross metathesis.



1.3.3.1 Problems with TBS deprotection of metathesis products

The acetate of **56** was easily removed with methanolic potassium carbonate to give alcohol **58** (Scheme 15). Subsequent selective deprotection of the TBS ether was more difficult that originally anticipated. Tetrabutylammonium fluoride (TBAF) showed no selectivity for cleavage of the TBS group of **58** over the TBDPS group. Using acetic acid/THF/water or buffering TBAF with acetic acid were likewise unsuccessful, producing complex mixtures. Attempts to deprotect the TBS group with ethanolic PPTS as described by Prakash[46] gave a complex mixture lacking the desired diol. Examination of the crude NMR of this reaction showed that allylic hydrogen resonance of the epoxide had disappeared and that olefinic hydrogens had shifted. Most intriguingly, there were resonances between 3.5 and 4.0 ppm that resembled diastereotopic hydrogens alpha to the oxygen of a pyran.

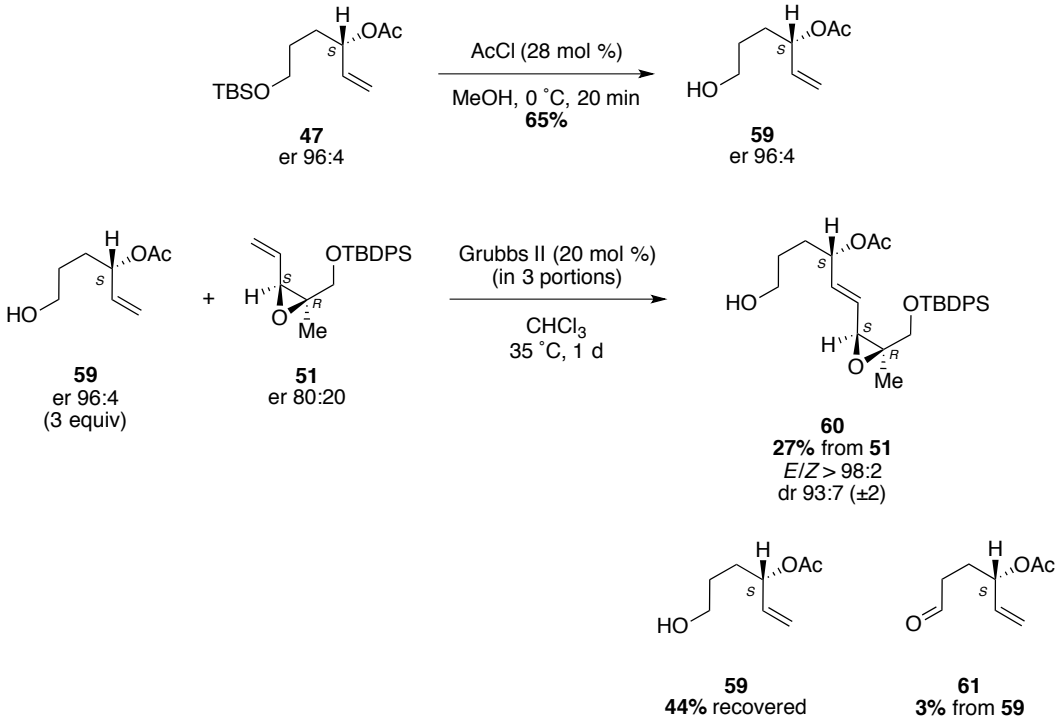
Scheme 15: Difficulties with selective TBS deprotection.



1.3.4 Cross metathesis with unprotected alcohol

In an attempt to circumvent difficulties with chemoselective deprotection of the TBS group in the presence of the TBDPS group, metathesis-coupling partner **47** was first desilylated with methanolic HCl to give the free alcohol **59** (Scheme 16). Engaging **59** in cross metathesis with epoxyalkene **51** gave a relatively low yield of the desired product **60**, along with a small amount of oxidized material **61.** Metathesis catalysts have been known to form ruthenium hydrides in the presence of alcohols, possibly explaining this observation.[47,48] Interestingly, the diastereomeric ratio of **60** was much higher than the statistically expected 77.6:22.4, again suggesting either a resolution during the metathesis reaction, or undetectable enrichment during chromatography, the two diastereomers being indistinguishable by TLC.

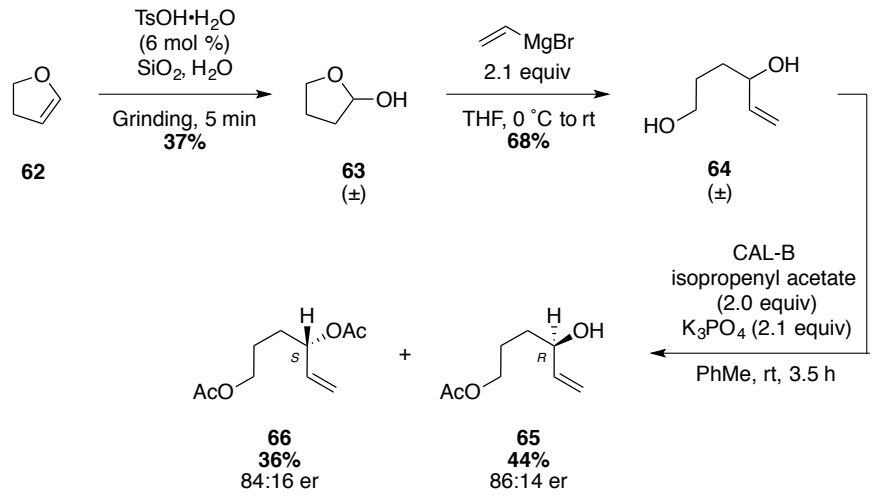
Scheme 16: Desilylation of **47** and cross metathesis with the free primary alcohol.



1.3.5 Synthesis of bisacetate metathesis coupling partner

In order to avoid the use of the free primary alcohol in the cross metathesis, we considered using the bisacetate. Since the TBS group was not judged to be necessary, an alternative synthesis was performed. Thus 2,3-dihydrofuran **62** was hydrated by grinding on wet silica, as reported by Dos Santos (Scheme 17).[49] This procedure allowed for the preparation of large amounts of lactol **63**, which furnished diol **64** upon exposure to excess vinylmagnesium bromide. Enzymatic acylation with *Candida antarctica* lipase using two equivalents of isopropenyl acetate first rapidly acylated all of the primary alcohols present (as observed by TLC). Prolonged exposure to the reaction conditions achieved enzymatic resolution of the secondary allylic alcohol. Bisacetate **66** was obtained in 36% yield, with an er of 84:16 by analysis of the Mosher esters of the hydrolyzed material. The (*R*) allylic alcohol **65** was also obtained in 44% yield with an er of 86:14.

Scheme 17: Preparation of bisacetate **66** using enzymatic resolution.



1.3.6 Metathesis of bisacetate with epoxyalkene and deprotection

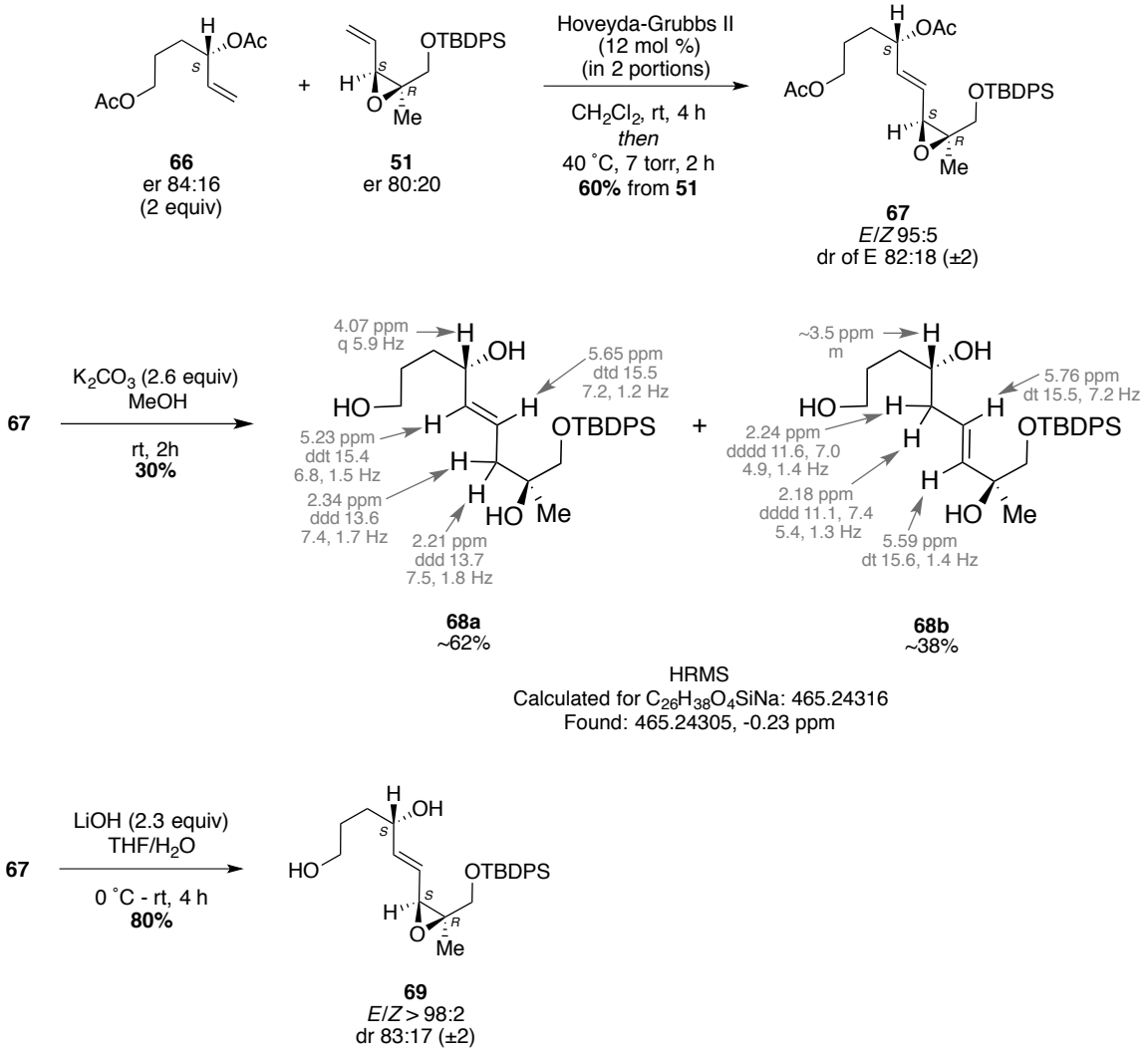
Although the er of **66** was inferior to that of **59** (84:16 vs. 96:4) we decided to study its cross metathesis and subsequent deprotection with the knowledge that if successful, **59** could be acylated to give **66** with an improved enantiomeric ratio. Thus, bisacetate **66** was subjected to cross metathesis with epoxyalkene **51** using Hoveyda Grubbs II to give the desired product **67** in 60% yield (Scheme 18). Interestingly, it was noted that concentration *in vacuo* at elevated temperature without solvent helped push the reaction to higher conversion, possibly because of continuous removal of the generated ethylene from the reaction headspace.

Purification of **67** was complicated by its co-elution with surviving Hoveyda-Grubbs II catalyst, as evidenced by the green color of the product oil. This caused difficulties during an attempt to deprotect both acetates using methanolic potassium carbonate, the isolated products having mass spectra indicating the addition of 2 hydrogen atoms. This was consistent with the NMR, consisting of regioisomers **68a** and **68b** arising from an apparent reductive ring opening of the epoxide. As noted before, metathesis catalysts are known to form ruthenium hydrides in the presence of

alcohols.[47,48] Ikariya and coworkers reported the reduction of epoxides to alcohols using a ruthenium hydride complex[50], so the residual metathesis catalyst may be responsible for the undesired production of **68a** and **68b**.

This deprotection difficulty was circumvented by using aqueous lithium hydroxide in THF, presumably because of destruction of remaining catalyst (as noted by decolorization of the reaction mixture), ultimately furnishing the desired diol **69**.

Scheme 18: Cross metathesis with bisacetate **66** and deprotection difficulties.

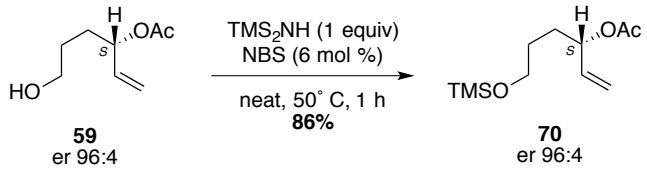


1.3.7 Switching to TMS group for protection of the primary hydroxyl

Although cross metathesis with either the free alcohol or the bisacetate did provide access to the desired materials, their disadvantages (low yields and difficult purifications) inspired further investigation.

A solution to the deprotection selectivity was found by using a TMS protective group on the primary position. Thus desilylation of **47** in methanolic HCl gave alcohol **59**, which was subjected to the trimethylsilylation conditions described by Shaterian to give silane **70** in 86% yield (Scheme 19).[51] Notably these silylation conditions do not require an aqueous workup.

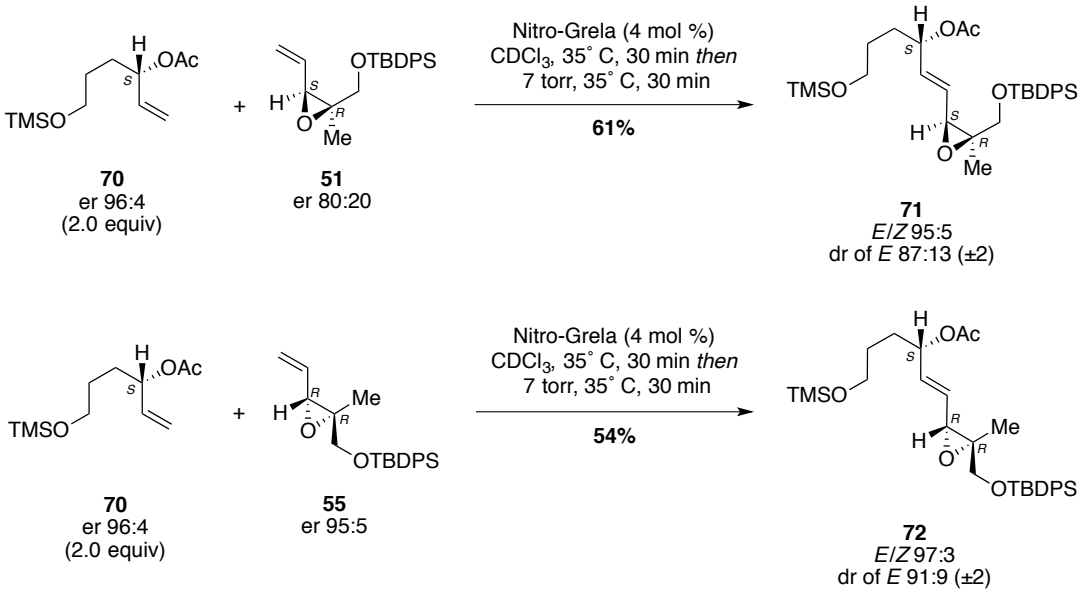
Scheme 19: Trimethylsilylation of **59**.



1.3.8 Cross metathesis using nitro-Grela catalyst

Experimentation using the nitro-Grela metathesis catalyst showed enhanced reactivity for the cross coupling of the alkene substrates by reducing the needed catalyst loading as well as shortening the reaction time. Thus a twofold excess of **70** was combined with epoxyalkene **51** in $CDCl_3$ (to facilitate facile reaction monitoring by NMR of aliquots) with 4 mol % of the nitro-Grela catalyst at 35 ˚C (Scheme 20). After 30 minutes, the reaction mixture was concentrated *in vacuo* at 35 ˚C and product **71** was isolated in 61% yield after purification. Similarly, **70** was combined with epoxide **55** to give the corresponding product **72** in 54% isolated yield.

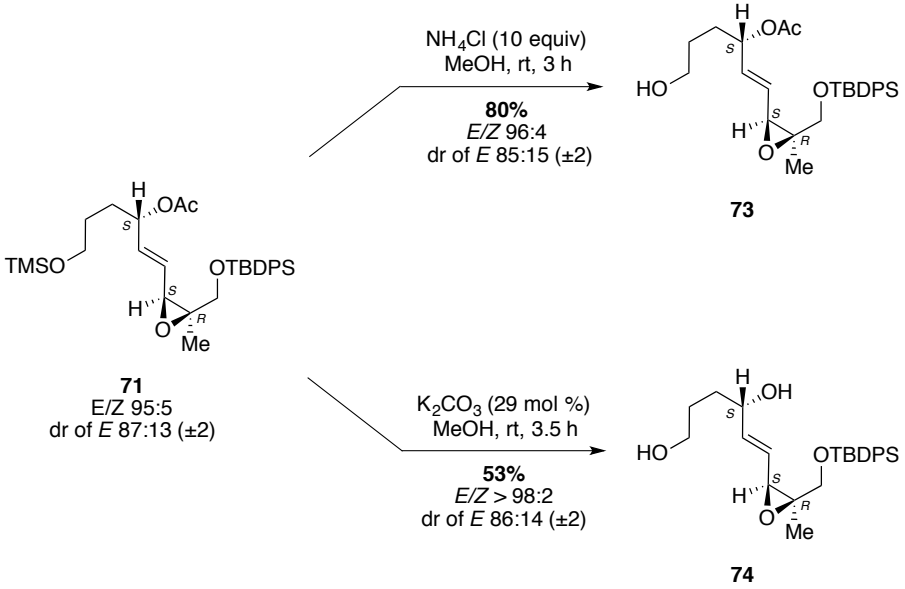
Scheme 20: Cross metathesis using the nitro-Grela catalyst.



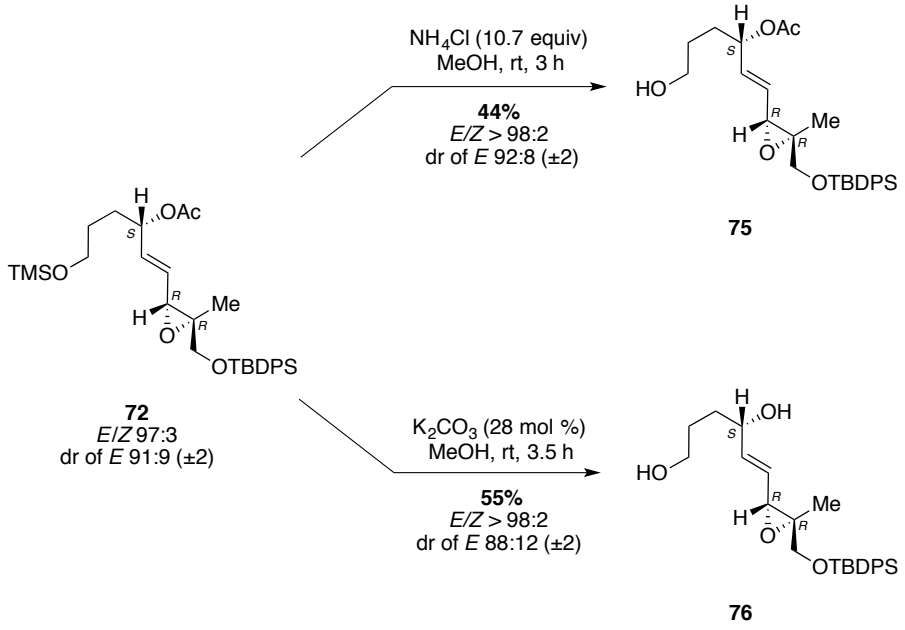
Following cross metathesis, alkenes **71** and **72** were divided into two portions. Treatment with an excess of solid ammonium chloride in methanol afforded exclusive hydrolysis of the primary trimethylsilyl protective group to furnish monoacetates **73** and **75** (Schemes 21 & 22). Alternatively, treatment with methanolic potassium carbonate resulted in hydrolysis of both the trimethylsilyl and acetate protective groups to give diols **74** and **76** (Schemes 21 & 22).

1.3.9 Chemoselective deprotection of cross-metathesis products

Scheme 21: Chemoselective divergent deprotection of **71**.



Scheme 22: Chemoselective divergent deprotection of **72**.

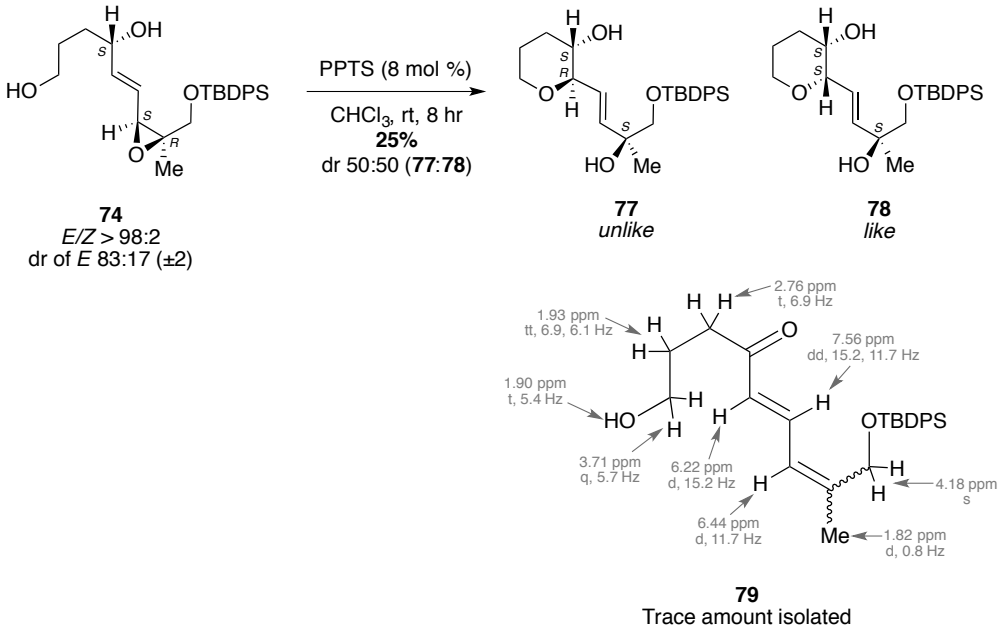


1.4 Brønsted acid catalyzed cyclizations

1.4.1 Cyclization of 6-membered rings with PPTS

To investigate the intriguing result of attempts to deprotect the TBS group of **58** with ethanolic PPTS, diol **74** was subjected to the action of PPTS in chloroform (Scheme 23). Pyrans **77** and **78** were subsequently isolated together as an approximately 50:50 mixture of diastereomers in 25% yield. Interestingly, a trace amount of dienone **79** was also isolated, presumably arising from an isomerization/dehydration sequence of **74**.

Scheme 23: Discovery of PPTS-mediated cycloetherification.

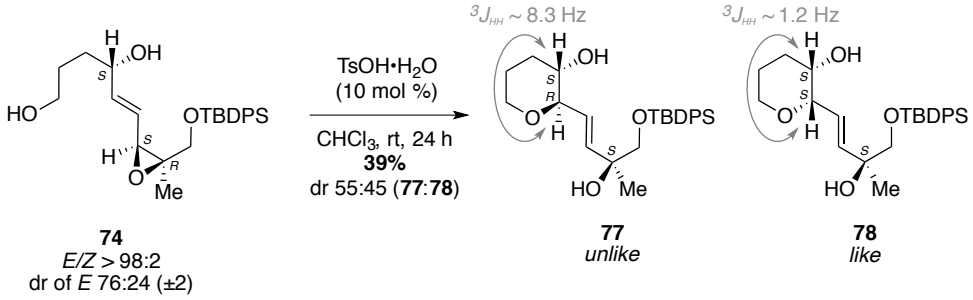


1.4.2 Cyclization of 6-membered rings with TsOH•H_2O

Subsequent experiments with diol **74** replaced PPTS with toluenesulfonic acid monohydrate. As Scheme 24 shows, the desired 1,2-*unlike* diastereomer **77** was produced in slight excess relative to the *like* diastereomer **78**. The identities of each diastereomer were established from the crude by the coupling constants between the hydrogens on the

pyran: J = 8.3 Hz for the *unlike* diastereomer **77** and J = 1.2 Hz for the *like* diastereomer **78**. Later experiments wherein **77** and **78** were separated confirmed these assignments (see pages 149 and 151).

Scheme 24: Cycloetherification with TsOH•H_2O.

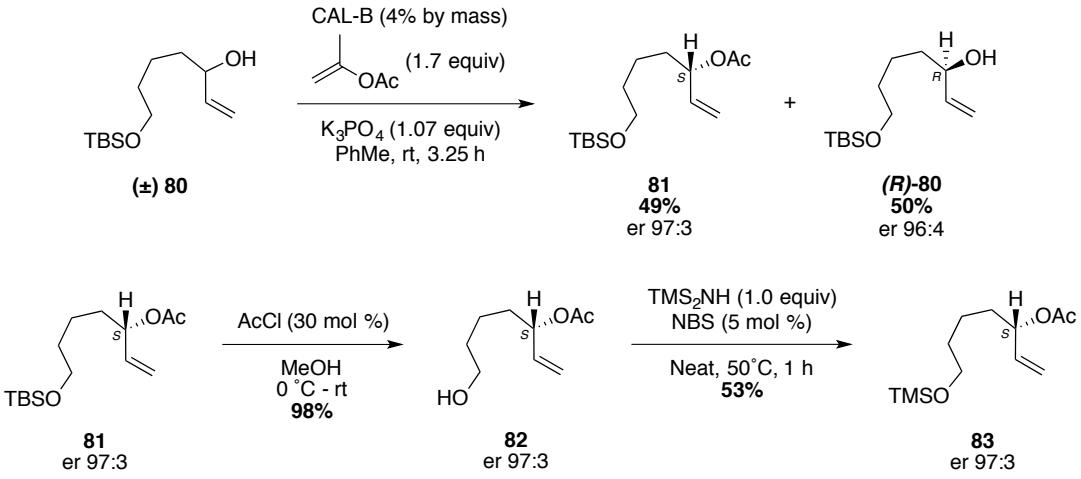


1.4.3 Synthesis of 7-membered ring cyclization substrate

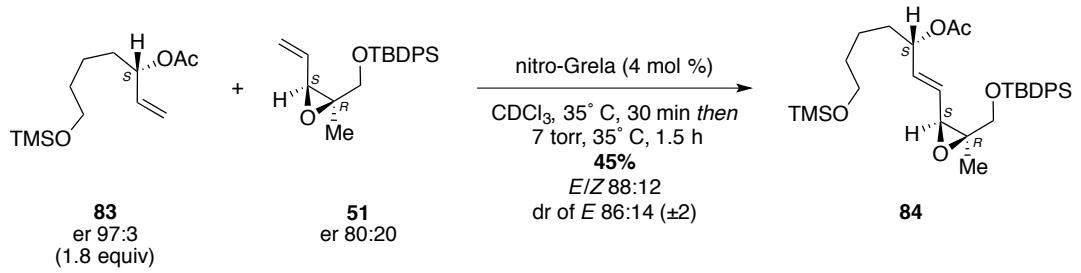
With the successful formation of pyrans using TsOH-H_2O, we were curious if the same conditions would enable the preparation of oxepanes. We thus set about preparing the analogous substrates.

Following the same enzymatic resolution procedure described for **46**, allyl alcohol **80**[35] was resolved with *Candida antarctica* lipase to give (*S*)-acetate **81** with an enantiomeric ratio of 97:3 (as determined by Mosher ester analysis following basic methanolysis of a small aliquot of the acetate). The TBS group of **81** was removed *via* the action of methanolic HCl to give alcohol **82**, which was subsequently protected as the TMS ether **83** using Shaterian's conditions[51] (Scheme 25). Cross metathesis of **83** with epoxyalkene **51** gave **84** in 45% yield (Scheme 26).

Scheme 25: Synthesis of allylic acetate **80.**

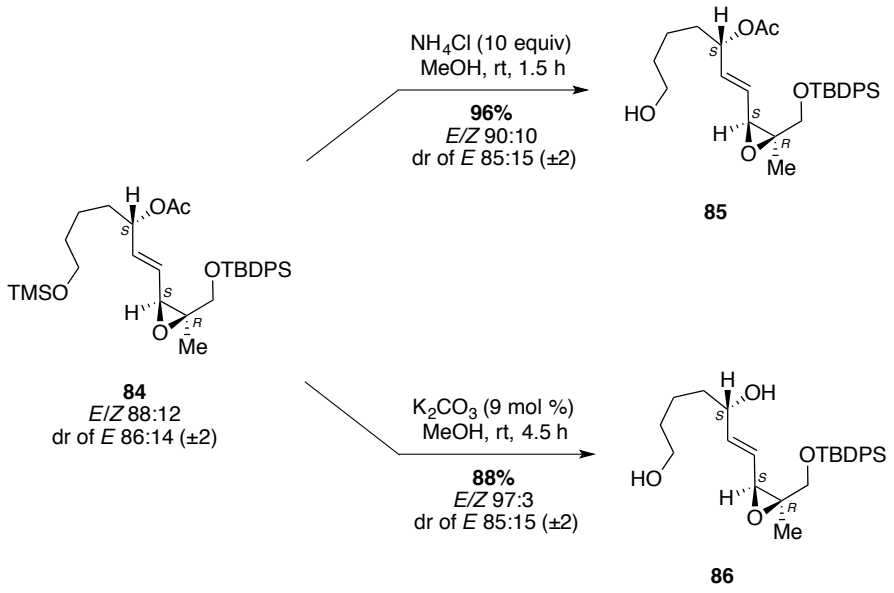


Scheme 26: Cross metathesis of **83** with **51**.



Substrate **84** was differentially deprotected as described in Scheme 27. Treatment with methanolic ammonium chloride delivered acetate **85** in 96% yield Methanolic potassium carbonate likewise gave diol **86** in 88%. For reasons that are unclear, the *E*/*Z* ratio noticeably increased during this transformation, conceivably from side reactions of the Z isomer.

Scheme 27: Differential deprotection of **84**.

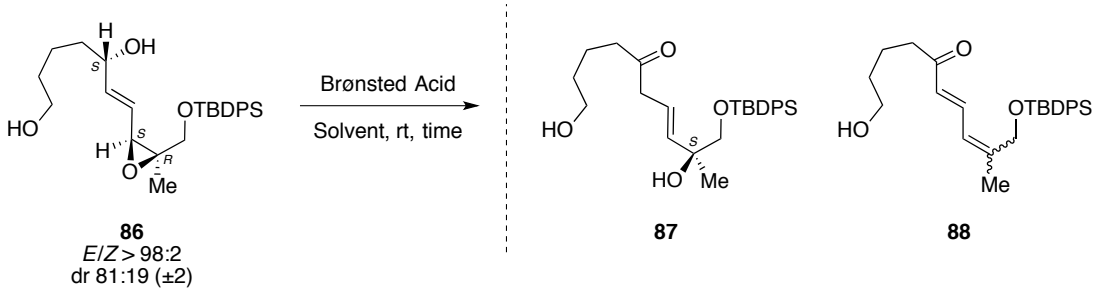


1.4.4 Attempts at oxepane formation via Brønsted acid catalysis

Diol **86** was subjected to toluenesulfonic acid in $CDCl_3$ and the reaction monitored by NMR. As Table 1 (Entry 1) indicates, mostly starting material was observed after 1 day, whereas after 4 days there was little evidence of cyclization. The major species present in the reaction mixture was identified as isomerization product **87** (NMR data for observed intermediates provided in experimental section). Next was tried camphorsulfonic acid (Entry 2), which likewise gave **87** after 1 day and its subsequent dehydration product **88** after 2 days. Subjecting **86** to toluenesulfonic acid in d_6-benzene (Entry 3) gave a complex mixture after only 2 hours, with trace amounts of **87** and **88** detected by NMR. Similarly, running the reaction in d_3-MeCN (Entry 4) showed some **87** after 2 hours, with a complex mixture by NMR observed after 15 hours. Lastly, the reaction was conducted in d_8-THF (Entry 5). After 2 hours, predominantly starting material **86** was observed by NMR. After 15 hours, a trace amount of **87** was seen, with

86 still being the predominant species. After 2 days, integration by NMR showed a 77:23 ratio of **86** to **87**.

Table 1: Investigation of various conditions for the cyclization of **86**.



86
E/*Z* > 98:2
dr 81:19 (±2)

87

88

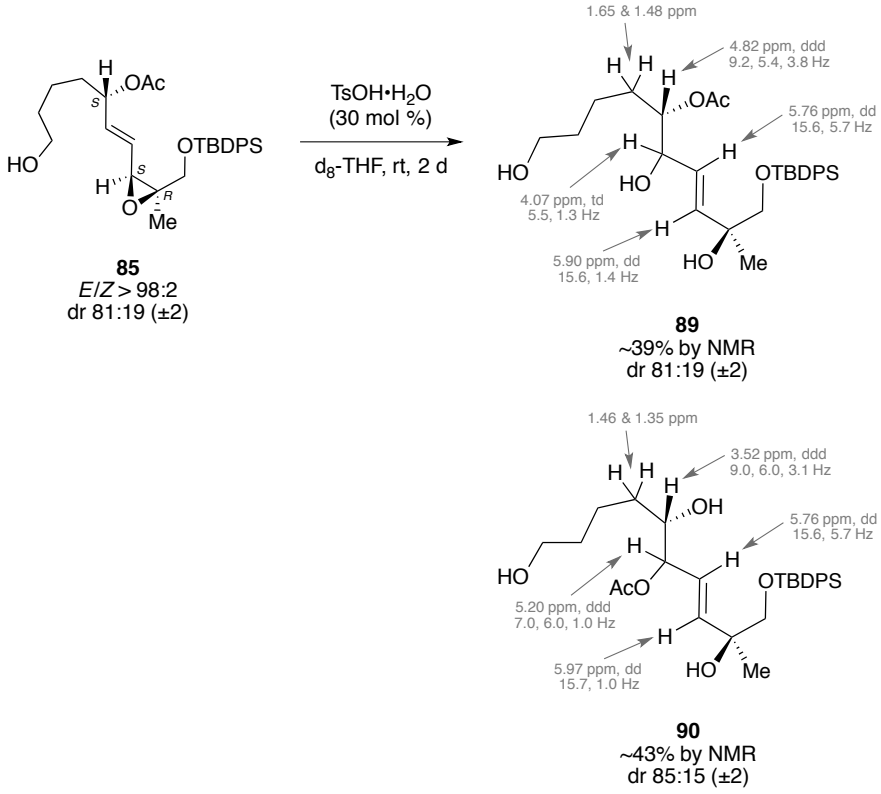
Entry	Solvent	Acid	Loading	Time	Product(s)
1	$CDCl_3$	TsOH•H_2O	~6 mol %	1 d	93:7 (**86**:**87**)
				4 d	33:67 (**86**:**87**) & unidentifiable products
2	$CDCl_3$	CSA	~4 mol %	1 d	38:62 (**86**:**87**)
				2 d	**88** & unidentifiable products
3	d_6-Benzene	TsOH•H_2O	~9 mol %	2 h	Complex mixture, trace **87**
4	d_3-MeCN	TsOH•H_2O	~10 mol %	2 h	75:25 (**86**:**87**)
				15 h	Complex Mixture
5	d_8-THF	TsOH•H_2O	~7 mol %	2 h	96:4 (**86**:**87**)
				15 h	93:7 (**86**:**87**)
				2 d	77:23 (**86**:**87**)

Although the experiment described in (Table 1, Entry 5) showed no signs of the desired cyclization, the relative disinclination toward the formation of **87** and **88** relative to the other conditions prompted the investigation of cyclizations of **85**, with the allylic hydroxyl protected as the acetate ester. This might presumably further inhibit this side reaction, with a potential added benefit of inductively withdrawing electron density away from the alkene, increasing its electrophilicity.

Thus, **85** was exposed to a total of 30 mol % of toluenesulfonic acid monohydrate over 2 days in d_8-THF (Scheme 28). Although the starting material was consumed over

time, both TLC and NMR data were inconsistent with the desired oxepane product. Following extensive analysis, we proposed that water present in the reaction mixture (either from the acid hydrate itself or from elsewhere) had added to the starting material to form triol **89**. In situ 1,2-acetate migration could then explain the observation of **90** by NMR. The facility of this interconversion was confirmed by 2D TLC, with the polar spots of **89** and **90** interconverting with gentle heating.

Scheme 28: Attempted cycloetherification of **85** giving only hydration products by ^{1}H-NMR.



85
E/*Z* > 98:2
dr 81:19 (±2)

89
~39% by NMR
dr 81:19 (±2)

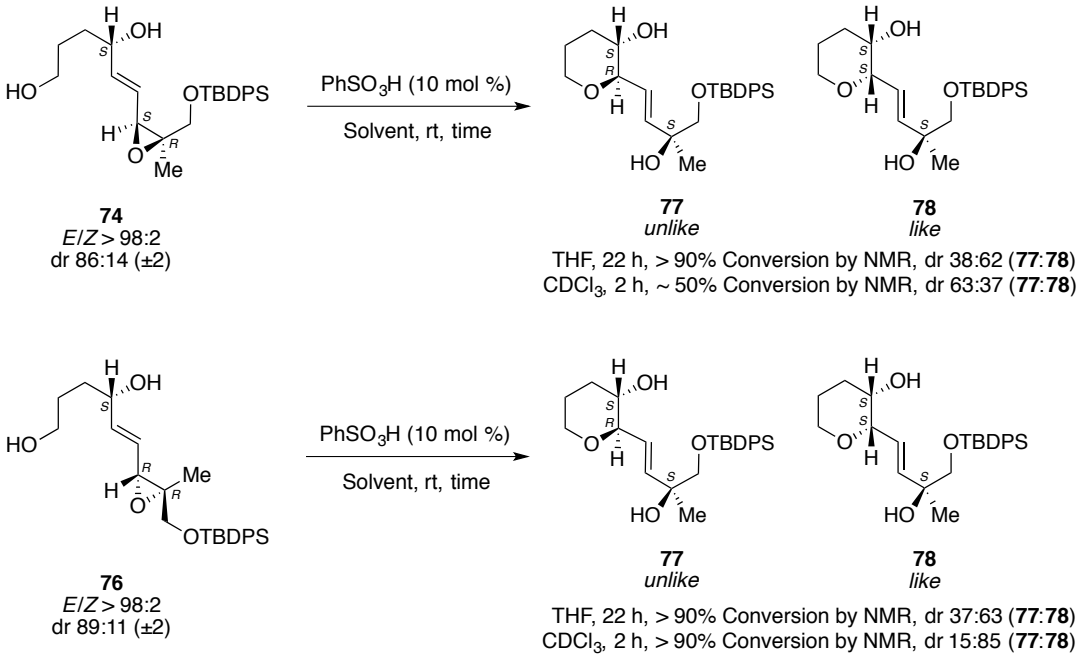
90
~43% by NMR
dr 85:15 (±2)

1.4.5 Cycloetherification of 6-membered rings with anhydrous benzenesulfonic acid

With the discovery of the participation of water from the toluenesulfonic acid monohydrate, an anhydrous alternative was sought. Interestingly, anhydrous toluenesulfonic acid was not commercially available, but the very similar anhydrous benzenesulfonic acid was.

Upon obtaining anhydrous benzenesulfonic acid, cyclizations were attempted on diols **74** and **76** in d_8-THF (Scheme 29). Interestingly, after 22 hours, both epoxide diastereomers favored formation of the *like* diastereomer **78**. As a control experiment, the same reactions were also conducted in $CDCl_3$. This solvent change exhibited some stereospecificity: the cyclization of **74** gave the *unlike* pyran **77** as the major diastereomer. Substrate **76** gave the *like* diastereomer **78** with enhanced selectivity relative to the reaction in THF.

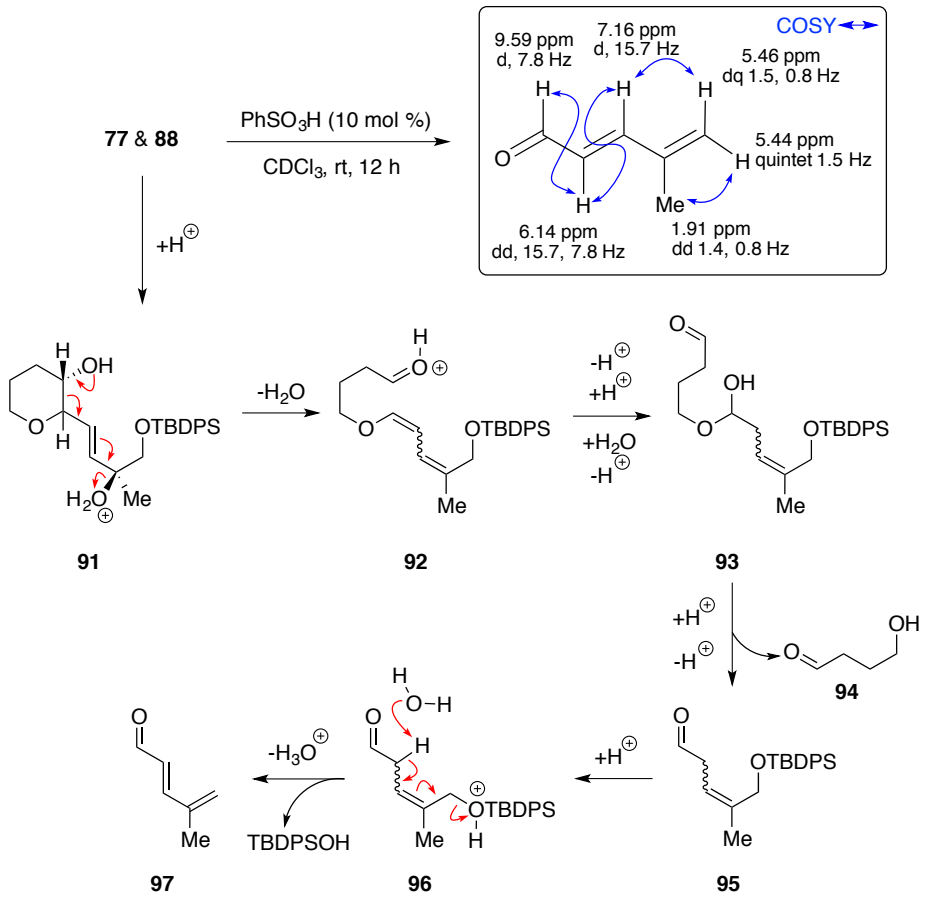
Scheme 29: Cycloetherification of diols **74** & **75** with anhydrous benzenesulfonic acid in THF and $CDCl_3$.



Prolonged exposure of the products **77** and **78** to the reaction conditions (Scheme 30) led to the formation of dienal **97**, identified by NMR and matching the literature data.[52] The formation of this product could be explained by the instability of the tertiary allylic alcohols of **77** and **78** to the acid conditions of the reaction. Thus, protonation of the tertiary allylic alcohol would give **91**, which could then undergo a Grob-type fragmentation[53,54] originating at the secondary alcohol of the pyran to give enol ether **92**. A series of proton transfers and hydration of the enol ether would then give hemiacetal **93**. Decomposition of the acetal would release aldehyde **94** (consistent with various alkyl aldehyde peaks in the NMR spectrum) and generate aldehyde **95**. Protonation of the silyl ether oxygen to give **96** could enable a 1,4 elimination of *tert*-butyldiphenylsilanol and generate dienal **97**.

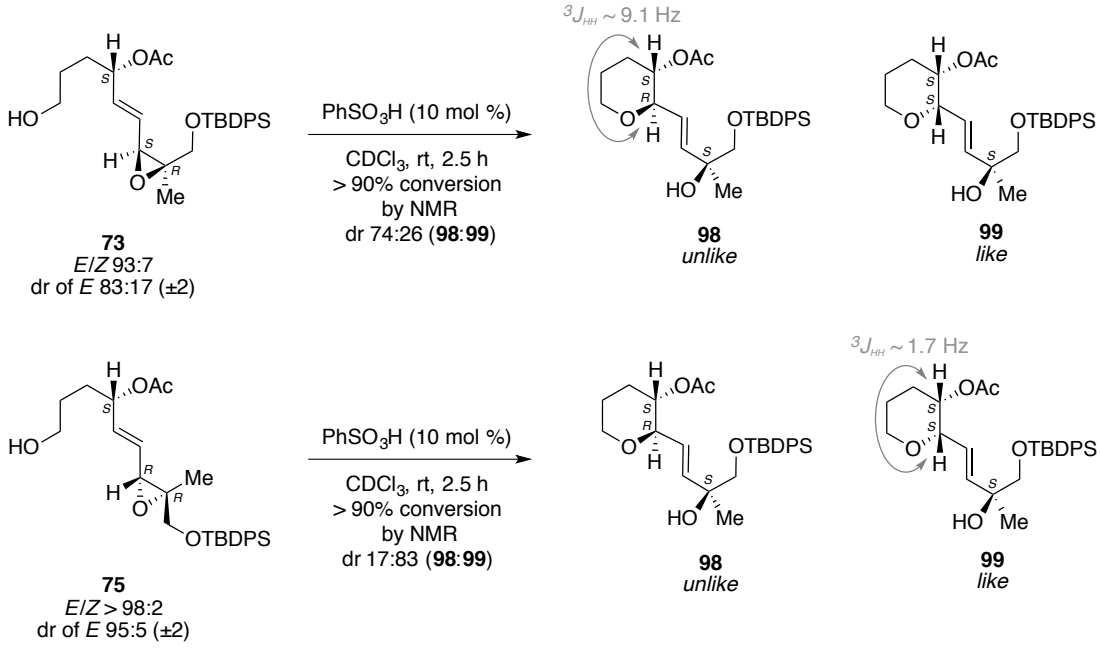
1.4.5.1 Decomposition products with prolonged reaction times

Scheme 30: Tentative mechanism for the generation of dienal **97** upon extended reaction times of **77** & **78** in $CDCl_3$.



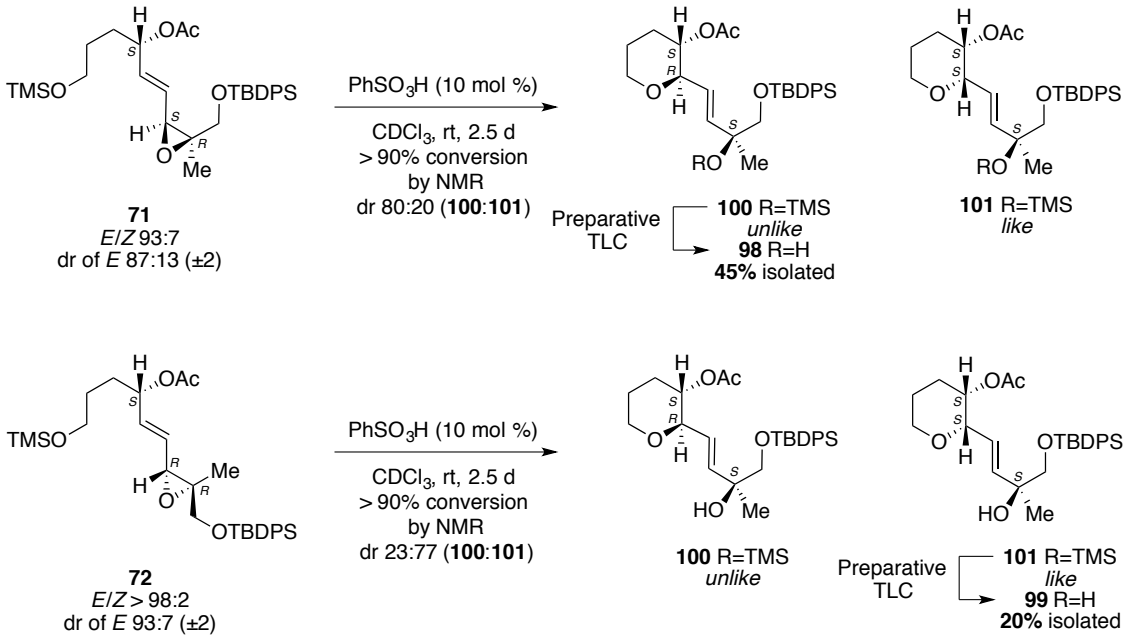
With the idea of potentially inhibiting the side reactions observed with diols **74** and **76**, the allylic acetates **73** and **75** were studied (Scheme 31). Thus alcohol **73** was exposed to benzenesulfonic acid in $CDCl_3$ to smoothly furnish pyran in 2.5 hours. The *unlike* configuration, **98**, was the major diastereomer, as evidenced by the 9.1 Hz coupling constant between the two relevant hydrogens. Alcohol **75** gave the corresponding *like* major diastereomer, **99**, with a coupling constant of 1.7 Hz.

Scheme 31: Acid-catalyzed cycloetherification of allylic acetates.



Interestingly, treatment of trimethylsilyl ethers **71** and **72** gave the same major diastereomer products, **101** and **102**, respectively, after prolonged reaction after 2.5 days (Scheme 32). Notable was the apparent stability of the products to the reaction conditions, possibly attributable to the trimethylsilyl group being transferred to the tertiary alcohol, although the isolated yields were still modest to low. This TMS group was present in the crude product NMRs of both reactions, but evidently hydrolyzed during chromatography.

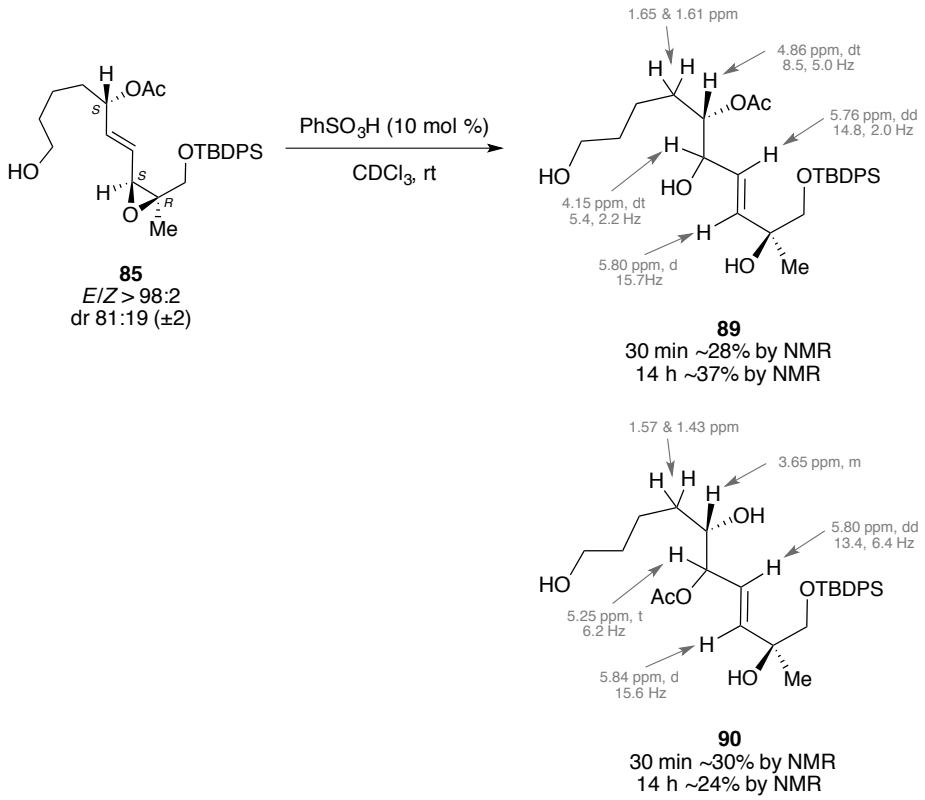
Scheme 32: Cyclizations of substrates with TMS protected primary alcohols.



1.5.6 Attempts at oxepane synthesis with anhydrous benzenesulfonic acid

Attempts to cyclize the 7-membered acetate **85** with benzenesulfonic acid in $CDCl_3$ unfortunately gave the same products as observed in d_8-THF, albeit much more rapidly (Scheme 33). After 30 minutes, approximately half of **85** was converted to **89** and **90** (the indicated percentages were calculated with respect to the TBDPS *tert*-butyl group). COSY correlations suggested the presence of several additional species, although their identities could not be ascertained. After 14 hours the NMR the concentrations of **89** and **90** had shifted, with **89** more prevalent. After 36 hours total decomposition was observed.

Scheme 33: Cyclization attempt with substrate **85** using anhydrous benzenesulfonic acid.



85
E/*Z* > 98:2
dr 81:19 (±2)

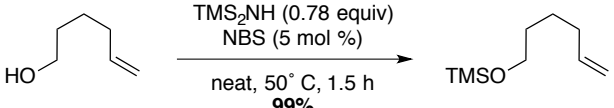
89
30 min ~28% by NMR
14 h ~37% by NMR

90
30 min ~30% by NMR
14 h ~24% by NMR

1.4.7 Preparation of substrates lacking an allylic oxygen

With some successful acid mediated cyclizations in hand, we were curious to investigate the effect of the oxygen substituent allylic to the epoxy alkene. Thus we went about preparing the corresponding de-hydroxylated substrates. Scheme 34 details a 50 mmol scale preparation of silane **103** using Shaterian's conditions[51], affording more than 8 grams of the silane in nearly quantitative yield with minimal purification.

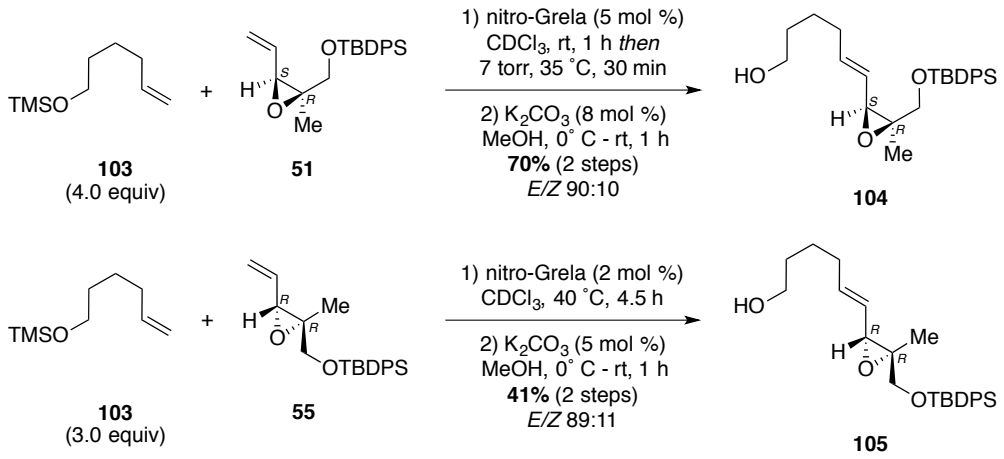
Scheme 34: Efficient trimethylsilylation of 4-pentene-1-ol.



102 **103**

Cross metathesis of **103** with epoxides **51** or **55** and subsequent deprotection with methanolic potassium carbonate gave alcohols **104** and **105** (Scheme 35).

Scheme 35: Cross metathesis of alkene **103** with epoxides **51** & **55** and subsequent desilylation.



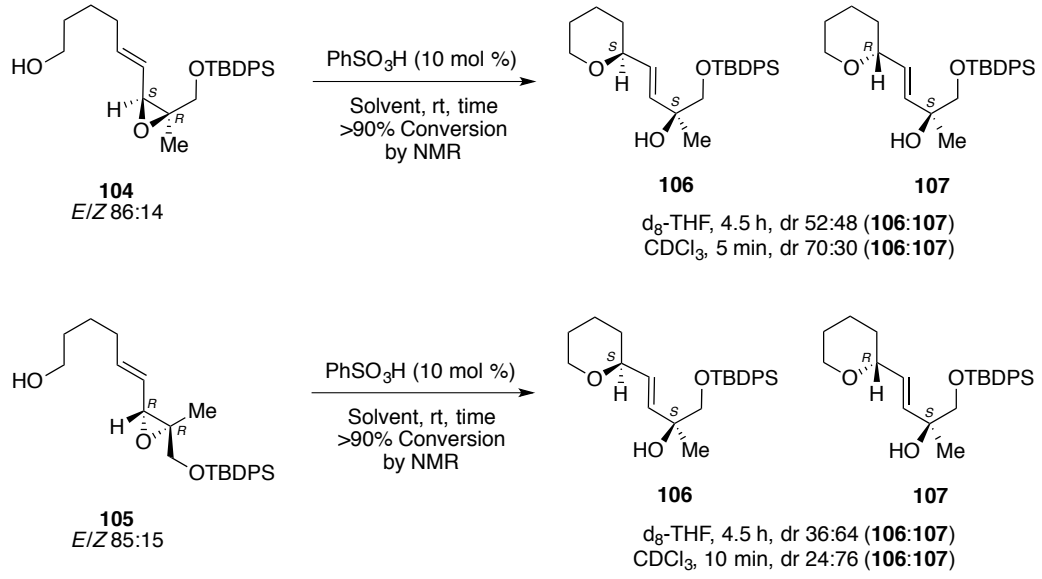
1.4.8 Benzenesulfonic acid mediated cyclization of epoxyalkenes lacking allylic oxygen substituents

Cyclization of substrates **104** and **105** (Scheme 36) was performed to give the corresponding pyrans. As with the diol cyclizations described in Section 1.5.5, the cyclizations proceeded slowly in THF, and with poor diastereoselectivity. Similarly, conducting the reaction in $CDCl_3$ afforded the product pyrans with better diastereoselectivity, in the case of alcohol **104**, forming the (*S*)-pyran diastereomer **106** preferentially. The epoxide diastereomer **105** gave the (*R*)-pyran diastereomer **107** as the major product. The notable diastereoselectivities of these reactions suggest that the allylic oxygen substituents may not substantially affect the cyclization diastereoselectivity. A

confounding variable is that **104** and **105** contain small amounts of the *Z*-alkene isomer, which may react differently.

At this point in our investigations we did not know the absolute configuration of the chiral centers of the pyrans **106** and **107**, but we could tell the two diastereomers apart spectroscopically. Later during our investigations with Pd-mediated cyclizations we were able to confirm the stereochemical assignments of **106** and **107**.

Scheme 36: $PhSO_3H$ Catalyzed Cycloetherification of **104** & **105**.

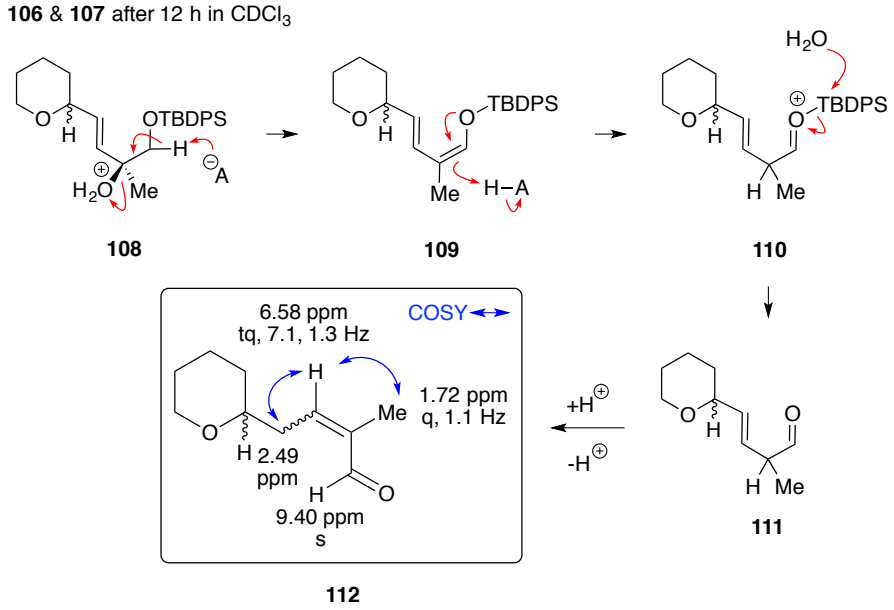


1.5.8.1 Decomposition of pyran products upon prolonged exposure to reaction conditions

Prolonged exposure of the product pyrans **106** and **107** in the $CDCl_3$ reactions produced compound **112** after 12 hours (Scheme 37). Similar to the decomposition described in Scheme 27, following protonation of the tertiary hydroxyl group, dehydration could occur to generate silyl enol ether **109**. Protonation of the enol ether then would give oxonium **110** which would then be desilylated with water generated

from the initial dehydration to give aldehyde **111**. Under the acidic conditions the β,γ–unsaturated aldehyde would then tautomerize to enal **112**.

Scheme 37: Decomposition of pyrans **106** & **107** upon prolonged exposure to reaction conditions.

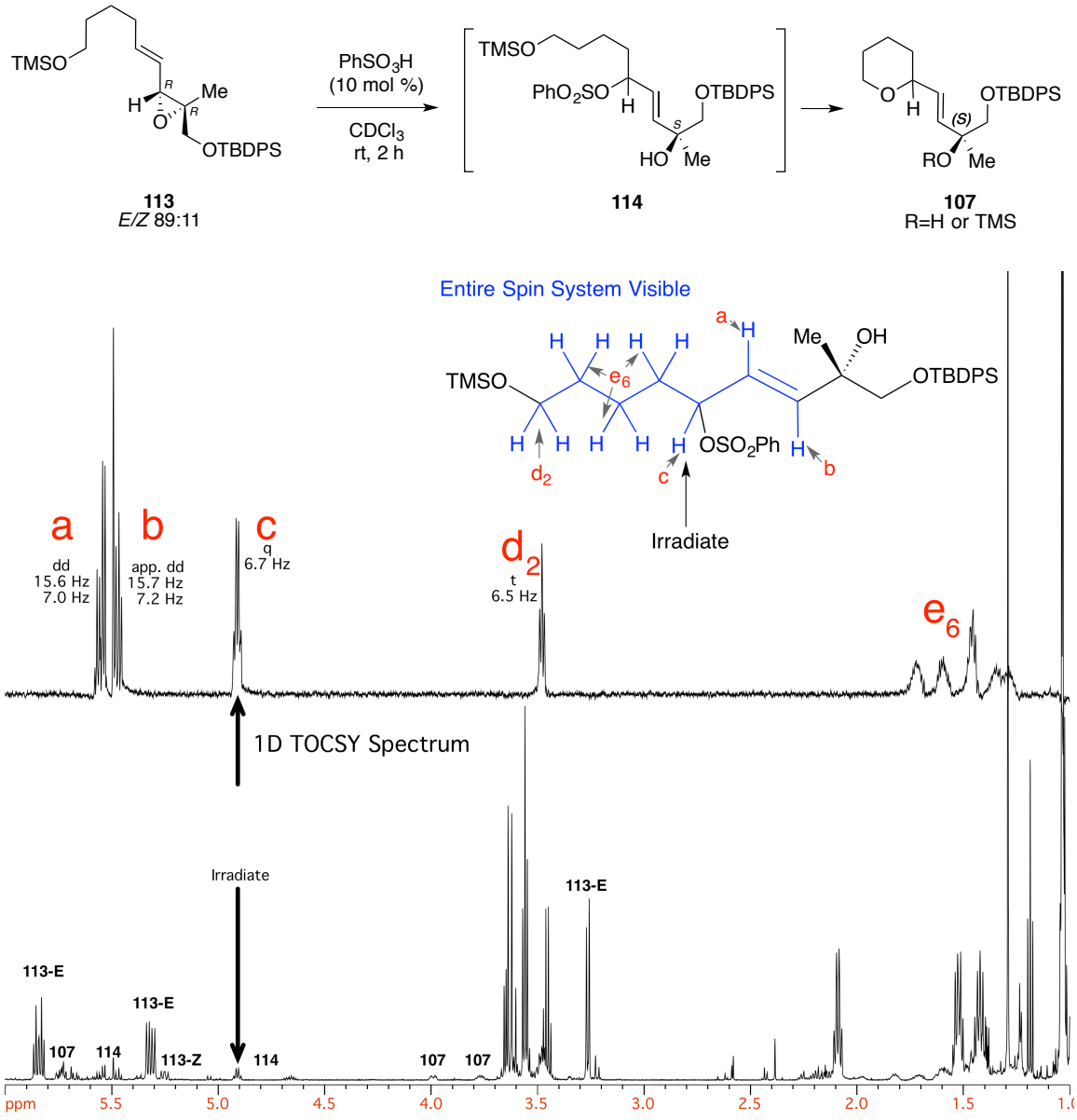


1.5.9 NMR investigation of sulfonic acid reaction mechanism

In an attempt to slow the cyclization to enable observation of the postulated intermediate, a cyclization of TMS protected compound **113** was conducted with the expectation that the presence of the hydrolytically labile trimethylsilyl group would slow down the cyclization step. Figure 3 shows two overlaid ^{1}H NMR spectra. The bottom half shows the NMR of the reaction mixture after 2 hours, with selected peaks indicated. Irradiation of the quartet at 4.9 ppm using a 1D-TOCSY[55] pulse sequence allowed for the acquisition of a sub-spectrum of the entire associated spin system. The top portion of Figure 3 shows this sub-spectrum, wherein two olefin hydrogens are revealed, along with

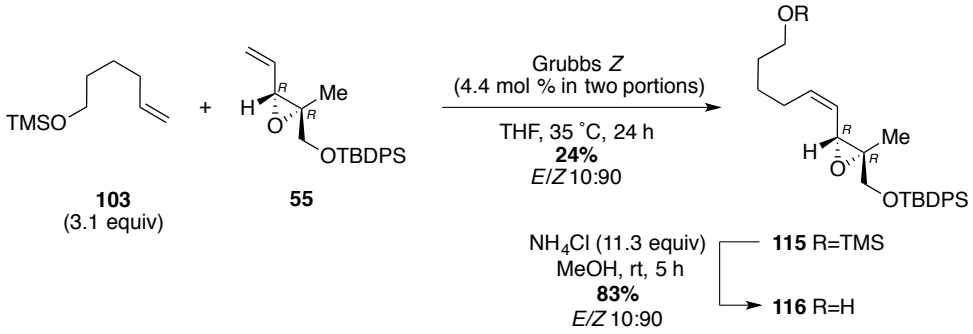
various methylene hydrogens as well as expected triplet of the carbinolic hydrogens adjacent to the trimethylsilyl ether. The chemical shift of 4.9 ppm for the hydrogen adjacent to the sulfonate is similar to the literature value for the methylene of allyl tosylate, 4.5 ppm.[56] Presumably **114** forms as a mixture of diastereomers, as evident by olefin signal b appearing to be a doublet of doublets.

Figure 3: NMR evidence for transient allyl benzenesulfonate intermediate.



In order to investigate the effect of the alkene stereochemistry on the cyclization, the corresponding *Z*-alkene was prepared *via* cross metathesis of **103** with epoxy alkene **55** in the presence of the *Z*-selective Grubbs catalyst[33] to give silylated cross product **115** in low yield, but with good *Z*-selectivity (Scheme 38). Desilylation of **115** with methanolic ammonium chloride afforded alcohol **116** in 83% yield.

Scheme 38: *Z*-selective cross metathesis between alkene **103** & epoxide **55**.



1.4.10 Comparison of acid-mediated cyclization of E and Z epoxyalkenes

With both alkene stereoisomers in hand, each was subjected to the reaction conditions using a lower acid loading (in an effort to slow the reaction down) and followed by ^{1}H-NMR. Notably, although the both compounds were derived from the same (*R*,*R*)-epoxide, they produced *different* major pyran diastereomers based on their alkene geometries (Scheme 39).

Scheme 39: Cyclization of *E*- and *Z*-isomers **105** & **116** with benzenesulfonic acid giving different product diastereomers.

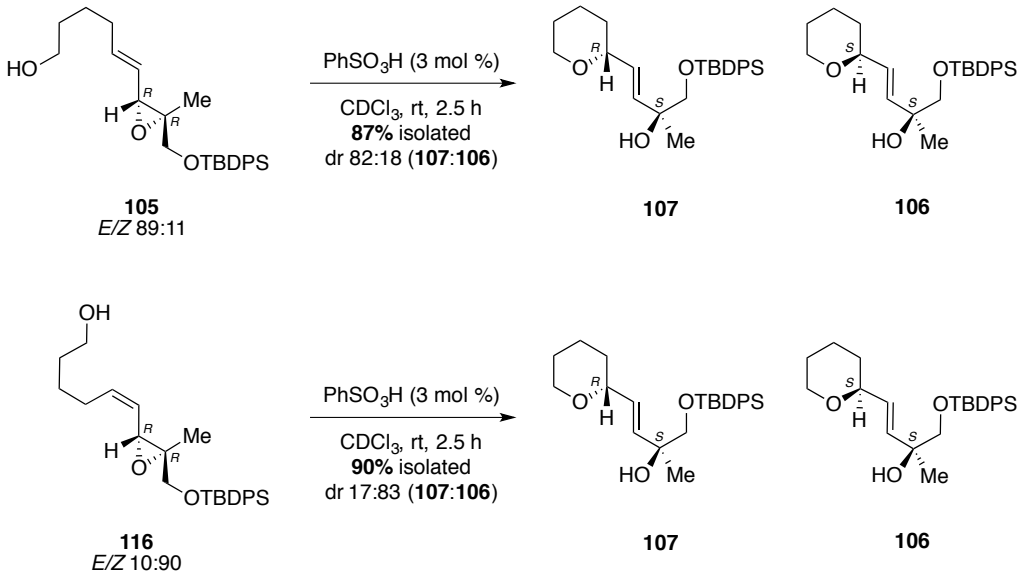
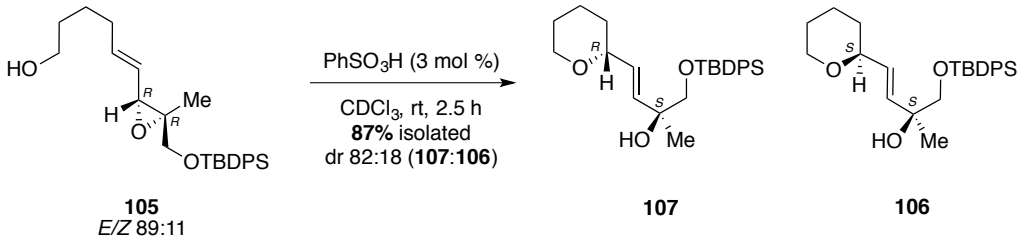


Figure 4 graphs the course of the cyclization of the *E*-alkene isomer **105** (using the TBDPS *tert*-butyl group for integral calibration between spectra). The reaction noticeably went to completion after 2.5 hours when using 3% catalyst loading. ^{1}H-NMR spectra of the reaction conducted at 5 minute intervals shows a nearly linear formation of the pyran product over time, along with a linear decrease of the concentration of the *E*-alkene (Figure 5). Interestingly the *Z*-alkene isomer **116** remained at a relatively constant concentration until all of the *E*-alkene had been consumed. Furthermore, the concentration of the putative allyl arenesulfonate intermediate remained fairly constant over time, suggesting that its formation is very rapid.

Figure 4: Normalized NMR conversion of species in cyclization of **105**.



105
E/Z 89:11

107

106

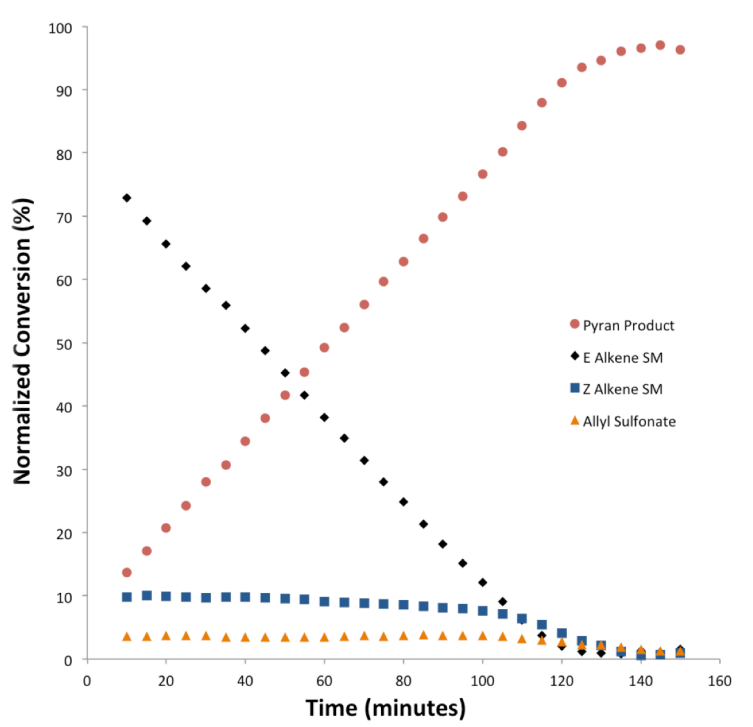


Figure 5: NMR time course, showing disappearance of **105** and appearance of product at five minute intervals.

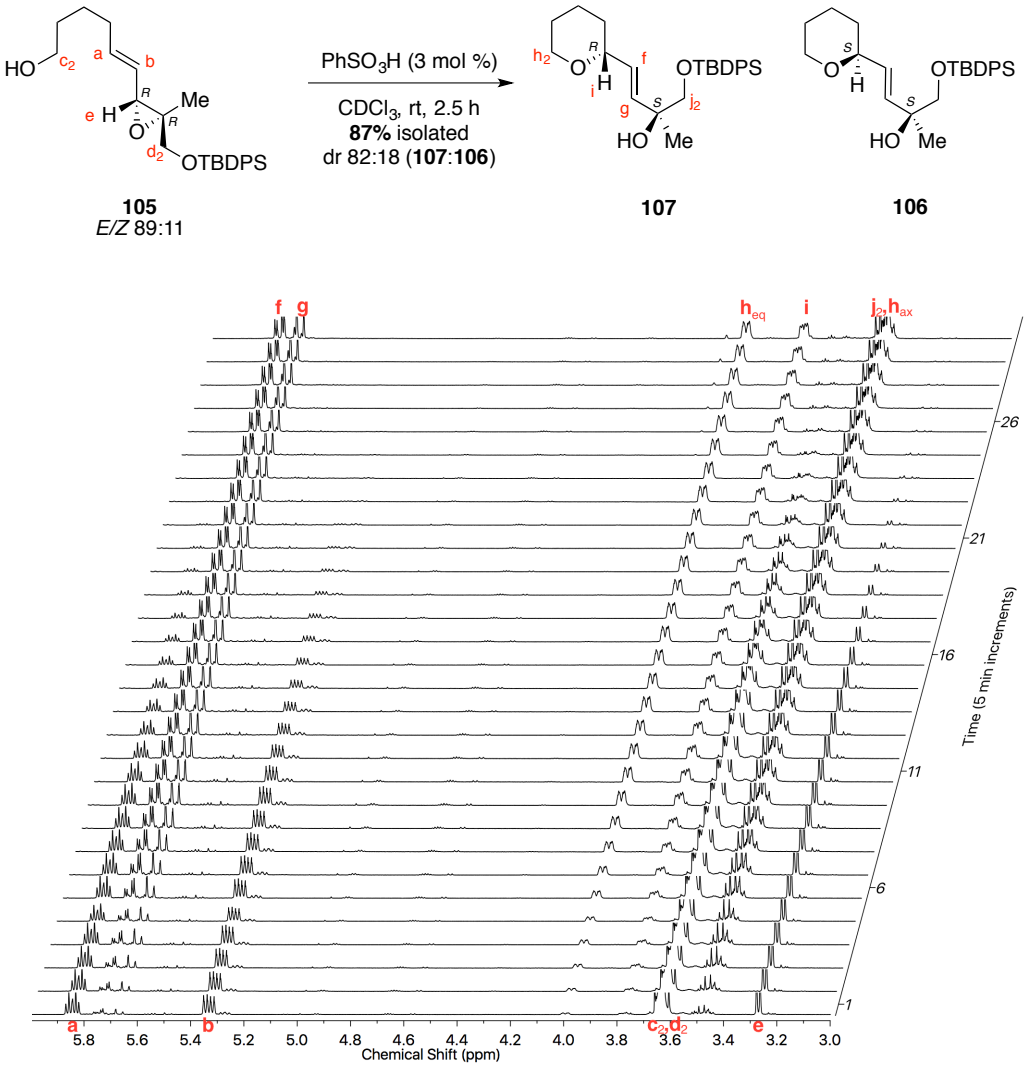
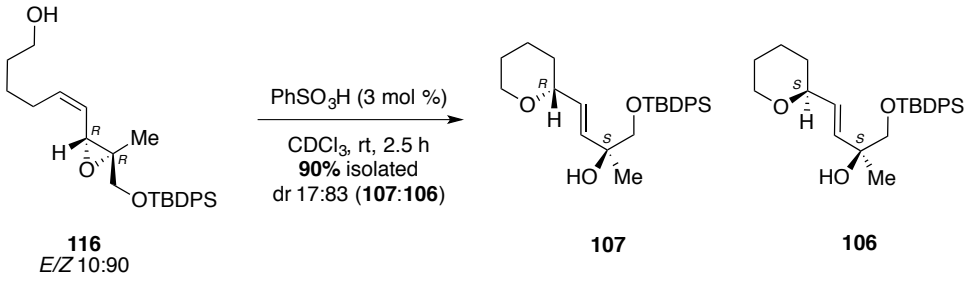


Figure 6 graphs the course of the cyclization of the *Z*-isomer **116** (also using the TBDPS *tert*-butyl group for integral normalization between spectra). Figure 7 shows an array of ^{1}H-NMR spectra during the course of the reaction. Notable is the early consumption of the small amount of *E*-isomer impurity, consistent with the observation that the *E*-isomer reacts faster. The cyclization reaction took 3.5 hours to go to completion, using the same 3 mol % benzenesulfonic acid loading as in the cyclization of

the *E*-isomer. Also visible in this reaction is the relatively constant amount of the allyl sulfonate intermediate, with a normalized concentration consistent with the acid catalyst loading (~ 3%).

Figure 6: Normalized NMR conversion of species in cyclization of **116**.



116
E/*Z* 10:90

107

106

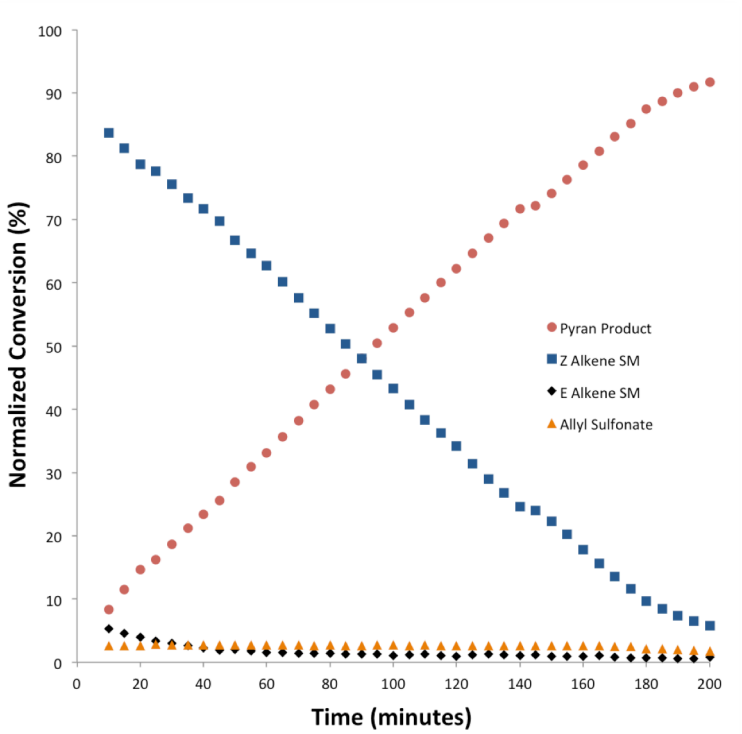


Figure 7: NMR time course, showing disappearance of **116** and appearance of product at five minute intervals.

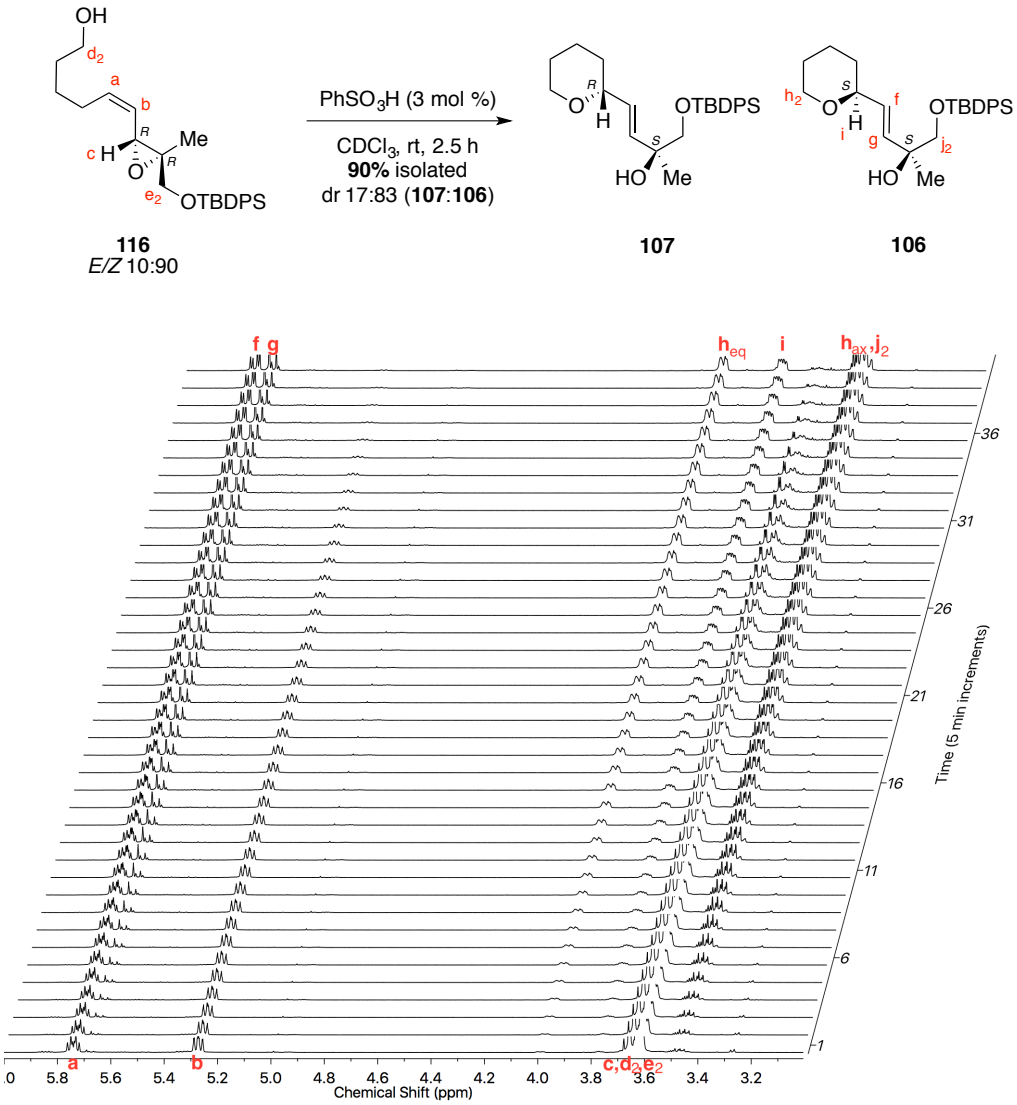
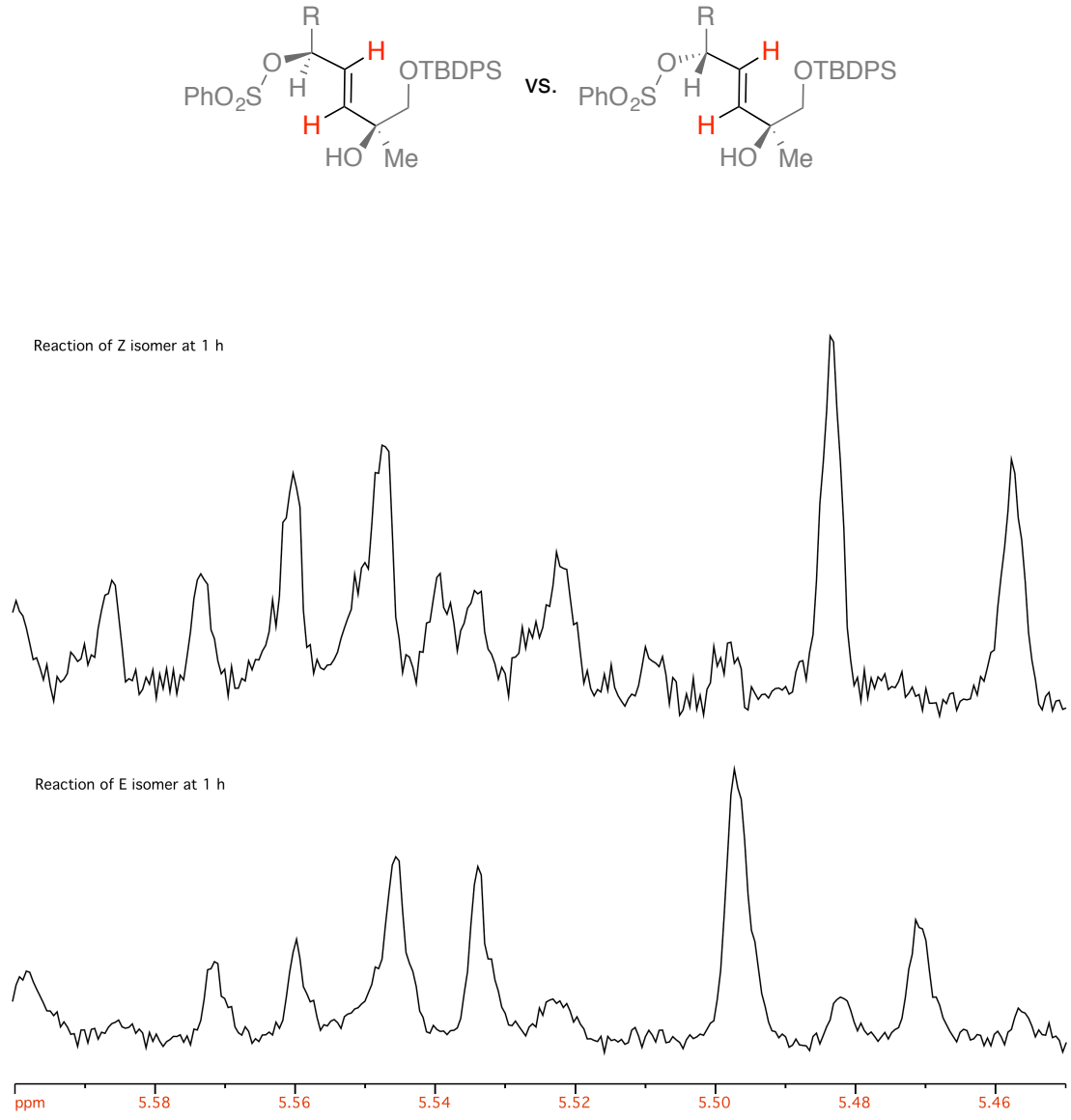


Figure 8 compares the spectra of what are likely the alkene protons of the aryl benzenesulfonate intermediate. Clearly the intermediates are different species, likely just the epimeric diastereomers of the allyl benzenesulfonate.

Figure 8: Spectra of intermediate allyl arenesulfonate alkene protons at 1 h in both the *E* and *Z* reactions.



1.4.11 Proposal for explanation of observed pyran stereochemistry

Scheme 40 describes a proposed model for the observed diastereoselectivity observed in the cycloetherification reactions. Informing this proposal are several important details. Firstly, diastereoselectivities drop off sharply in THF solvent. The

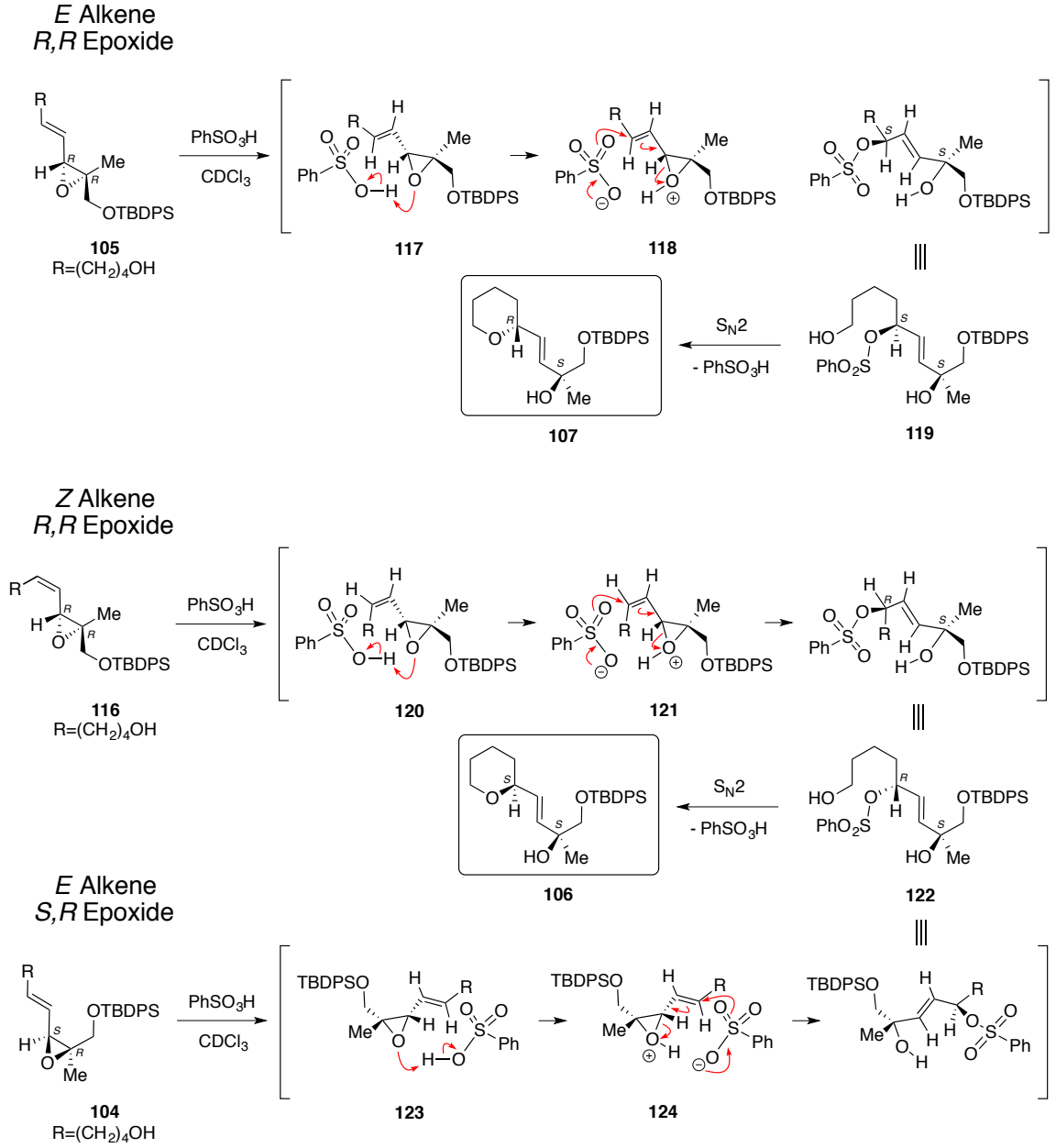
leveling effect may account for this observation – with protonated solvent being the active catalyst. If a key step of the reaction involves direct proton transfer from the benzenesulfonic acid to the substrate then the presence of oxygenated solvent could disrupt this step. The early use of hydrated toluenesulfonic acid may also have encountered similar problems – with hydronium being the active acid instead of the sulfonic acid itself.

A mechanism is thus proposed wherein the first step involves direct protonation of the epoxide with the sulfonic acid. Thus, in the case of **105**, **118** is generated as an ion pair. In the absence of significant solvent stabilization, the sulfonate may then add to the distal position of the vinyl epoxide, the facial selectivity being derived from pre-organization (to minimize sterics) prior to protonation. This generates the (*S*)-diastereomer of the allyl sulfonate **119**, which then undergoes subsequent S_N2 displacement with the pendant alcohol to give the (*R*)-pyran diastereomer **107**.

In the case of the *Z*-alkene **116** all the same steps are followed, except that the R group of the alkyl chain is pointed down in the key step because of the alkene geometry. Thus the (*R*)-diastereomer of the allyl sulfonate is generated, producing the (*S*)-pyran upon ring closure.

A similar case can be made for the *E*-alkene of the (*S*,*R*)-epoxide stereoisomer **104**. Pre-organization minimizing steric interactions within the substrate would give **124** after protonation. Prompt addition of the sulfonate to the alkene terminus then also gives the (*R*)-diastereomer of allyl sulfonate **122**, again furnishing the (*S*)-pyran **106** after ring closure and regeneration of the acid catalyst.

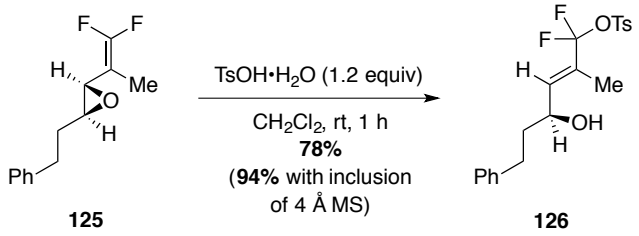
Scheme 40: Possible mechanistic explanation to account for the observed diastereoselectivities in cycloetherification.



1.4.12 Precedent for 1,4 addition of sulfonic acids to epoxy alkenes

This type of transformation of an epoxyalkene with a sulfonic acid is largely unprecedented in the literature. The closest similar transformation that could be found was that described by Kitazume *et al*.: during their investigations of the regiochemistry of the additions of nucleophiles to fluorinated epoxyalkenes, they found that treatment of **125** with a slight excess of $TsOH•H_2O$ in CH_2Cl_2 furnished allyl tosylate **126** (Scheme 41).[57] Notably, when molecular sieves were employed to generate anhydrous TsOH the reaction yield improved from 78% to 94%.

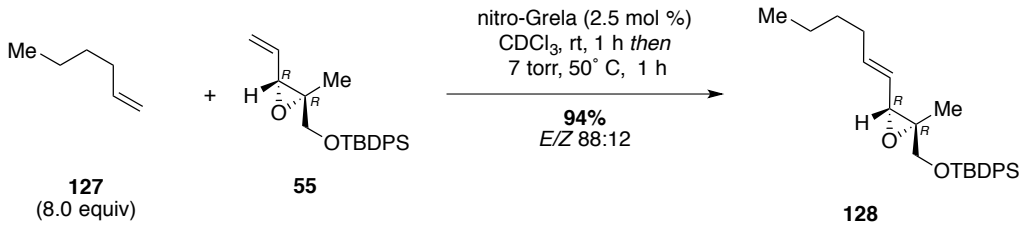
Scheme 41: Precedent for addition of arenesulfonic acids across epoxy alkenes.



1.4.13 Preparation of substrate for investigation of reaction intermediate

While the 1D TOCSY data from Figure 3 suggested the intermediacy of an allylic arenesulfonate, its identity could not be unambiguously established. Thus in order to further study the nature of the intermediate in the sulfonic acid mediated cyclizations, substrate **128** was prepared, lacking the terminal hydroxyl group and thus incapable of cyclization. Epoxy alkene **55** was reacted with excess 1-hexene, **127**, using the nitro-Grela catalyst to give **128** in 94% yield (Scheme 42).

Scheme 42: Cross metathesis of **55** with 1-hexene to make **128**, incapable of cyclization.



127
(8.0 equiv)

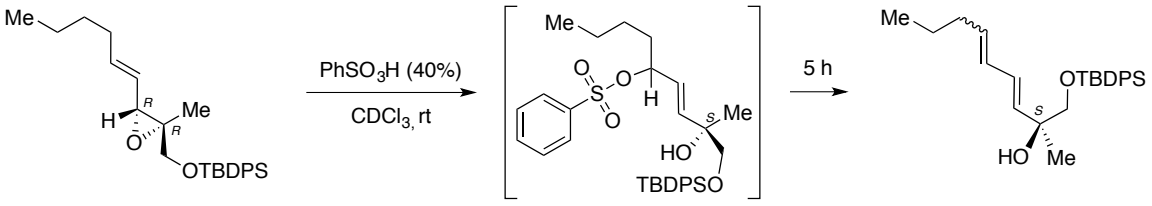
55

128

1.4.14 Direct NMR evidence for allyl arenesulfonate intermediate

After some experimentation, it was found that exposure of **128** to a large, but sub-stoichiometric, amount of acid was optimal for obtaining a high concentration of intermediate in solution (Scheme 43). If a stoichiometric amount was used, the products quickly decomposed; if too little was used, insufficient **129** was generated. Because of the high rate of reaction observed between benzenesulfonic acid and epoxy alkenes such as **128**, any acid present in solution will immediately react with it. Decomposition of the intermediate **129** will release the acid back into solution, which will quickly react with another equivalent of **128**. Thus, a steady amount of **129** is generated for NMR analysis over several hours of spectrometer time. Attempts to quench and isolate **129** were frustrated by rapid degradation during NMR acquisition.

Scheme 43: Reaction of **128** with benzenesulfonic acid, allowing for NMR analysis of intermediate **129**.



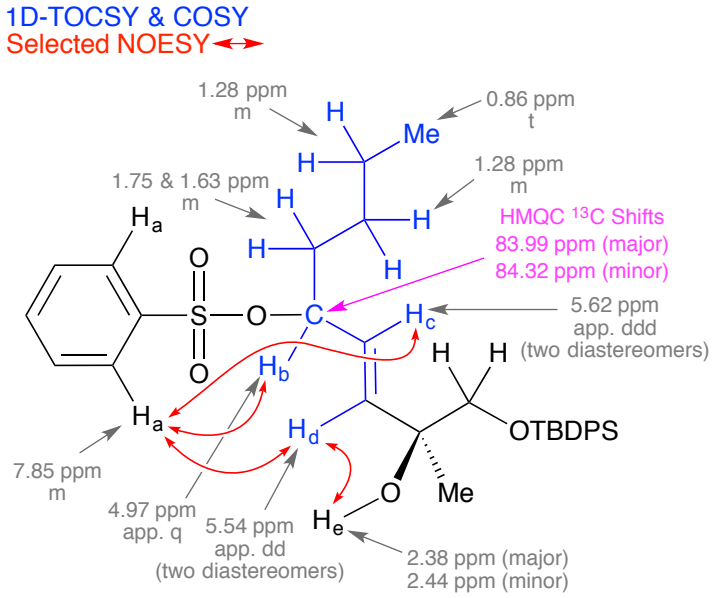
128
E/Z 88:12

129
dr ~ 65:35

130
E,E/Z,E ~ 65:35

We observed that the intermediate **129** was produced as a mixture of diastereomers (Figure 9). 1D-TOCSY and COSY experiments confirmed the spin system was analogous to that observed in Figure 3. Heteronuclear correlation experiments showed that the proton resonance at 4.97 ppm was correlated to two carbons around 84 ppm, presumably representing both diastereomers. Attempts at observing a long range heteronuclear coupling between H_b and the *ipso* carbon of the benzenesulfonate were unsuccessful. However, the large concentration of **129** in solution allowed for NOE correlations to be measured, revealing correlations between H_a on the benzenesulfonate with H_b, H_c and H_d. These NOE correlations provide strong evidence for the identity of **129** as the allyl arenesulfonate.

Figure 9: NMR evidence for the formation of allyl sulfonate **129**.



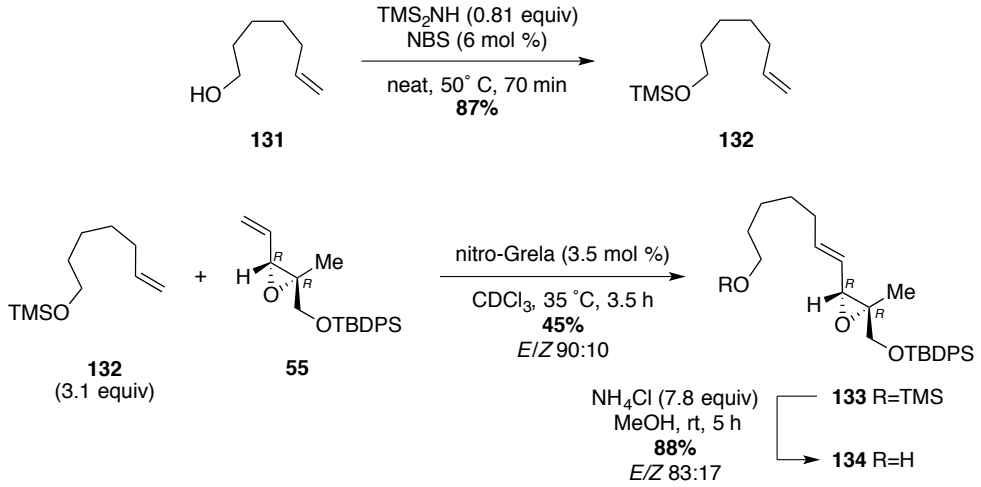
Notably the byproduct observed, **130**, is the diene that one would expect from elimination of the arenesulfonate. Interestingly, the ratio of *E*,*E*:*Z*,*E*-dienes is 65:35, the same as the diastereomeric ratio of **129**. The dr observed in **129** is diminished with

respect to the diastereomeric ratios of the pyran products described in section 1.4.10. The high acid loading (40% vs. 3%) may account for this discrepancy, possibly facilitating equilibration between allyl arenesulfonate diastereomers.

1.4.15 Preparation of 7-membered cyclization substrate lacking allylic oxygen

Having established the nature of the reaction intermediate as the allyl arenesulfonate, an attempt was made at oxepane formation without an oxygen allylic to the epoxyalkene. Thus compound **134** was prepared *via* cross metathesis of silane **132** (prepared *via* silylation of **131**) and epoxyalkene **55** to give **133** followed by mild desilylation (Scheme 44).

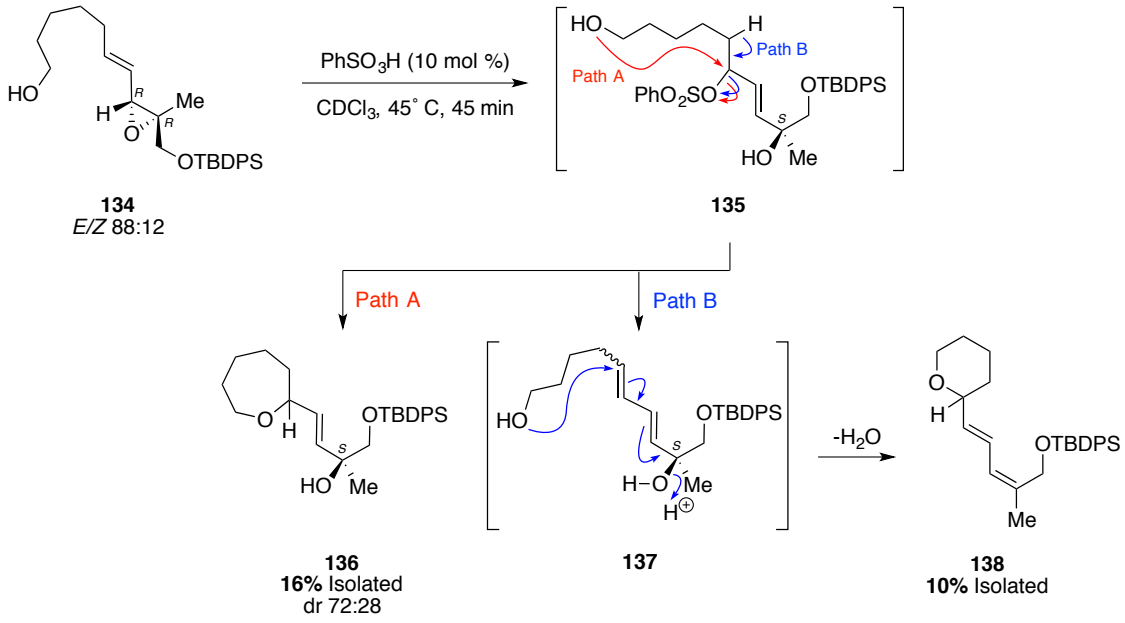
Scheme 44: Cross metathesis of silane **132** with epoxide **55** and deprotection to give alcohol **134**.



1.4.16 Cyclization attempt for 7-membered ring not bearing an allylic oxygen

Subjecting **134** to the reaction conditions in $CDCl_3$ showed the slow formation of **135** by NMR (Scheme 45). Gentle heating of the NMR sample furnished desired oxepane **136**, albeit in 16 % isolated yield. The other major product isolated was pyranyl diene **138** in 10% yield. Whereas **136** likely arose from nucleophilic displacement of the allyl sulfonate (Path A), **138** may have arisen from elimination of the allyl sulfonate to give **137** (Path B). Protonation of the allylic tertiary hydroxyl group would then enable a vinylogous dehydrative etherification to give **138**.

Scheme 45: Attempted cyclization of **134** with benzenesulfonic acid.



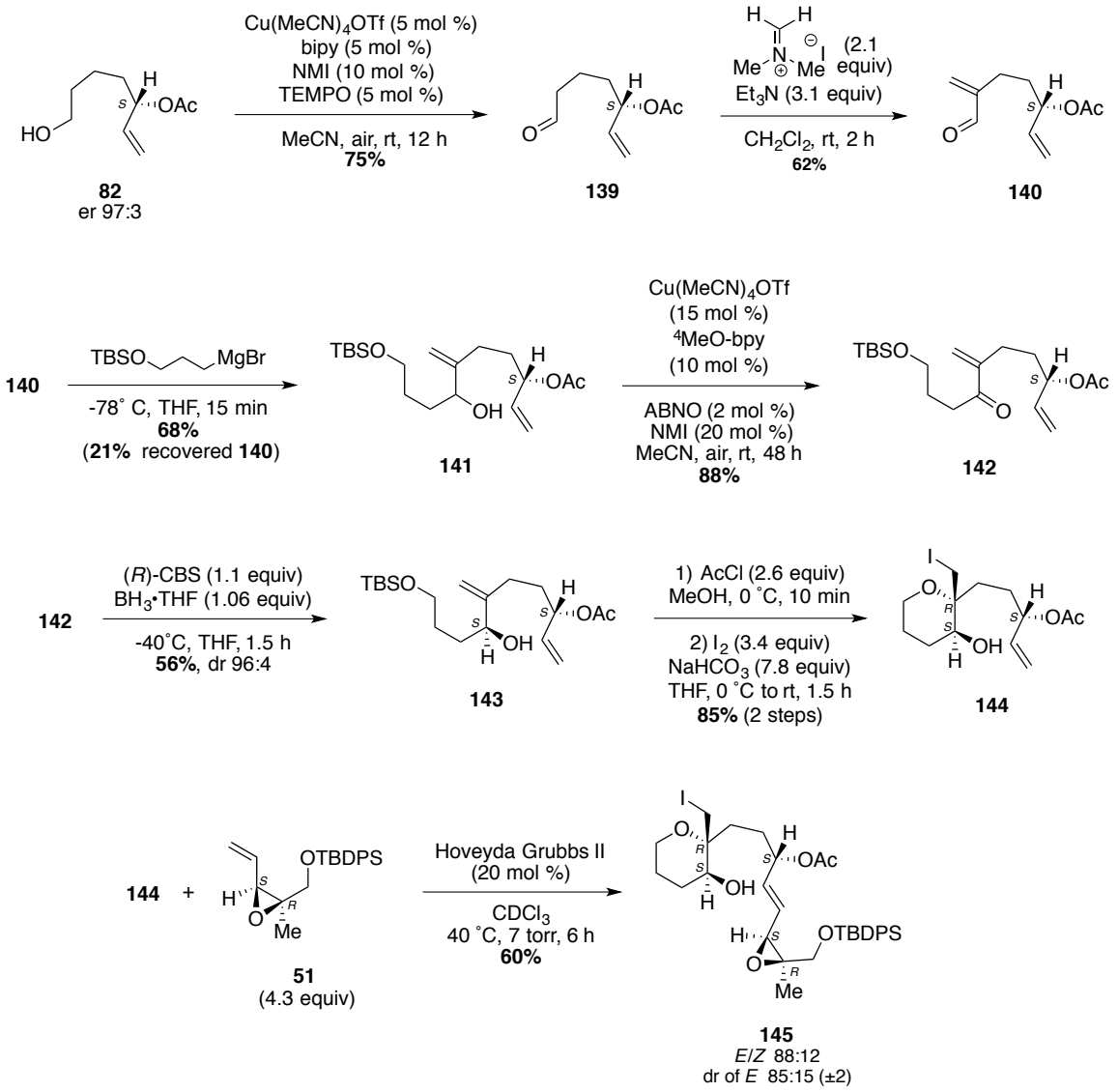
1.4.17 Synthesis of C-ring appended 7-exo cyclization substrate

Motivated by our limited success with cycloetherifications using benzenesulfonic acid, we next aimed to attempt to prepare the D ring oxepane of brevenal using this

strategy. We reasoned that perhaps the structural rigidity of an appended C ring would accelerate the ring closing reaction enough to compete with the various side reactions.

Alcohol **82** was first oxidized to aldehyde **139** using Stahl's aerobic primary alcohol oxidation conditions (Scheme 46).[58] Subsequent alpha methylenation of the aldehyde with Eschenmoser's salt[59] in the presence of triethylamine gave enal **140**. Addition of (3-((*tert*-butyldimethylsilyl)oxy)propyl)magnesium bromide to a solution of **140** at -78˚ C followed by rapid quenching gave alcohol **141** in 68% yield with 21% of the aldehyde recovered. Oxidation of **141** to the enone was achieved using a modified version of Stahl's aerobic oxidation of secondary alcohols using a higher loading of copper to give **142** in 88% yield.[60] Corey-Bakshi-Shibata reduction[61] of enone **142** using stoichiometric *R*-CBS reagent and borane-THF gave *S*-alcohol **143** as a 96:4 mixture of diastereomers as determined by Mosher ester analysis. Desilylation of **143** under acidic conditions followed by subsequent diastereoselective iodoetherefication[20] furnished pyran **144** in 85% yield over two steps. Cross metathesis of **144** with 4.3 equivalents of epoxyalkene **51** using a high loading of Hoveyda-Grubbs II catalyst under 7 torr vacuum gave cross metathesis product **145** in 60% yield.

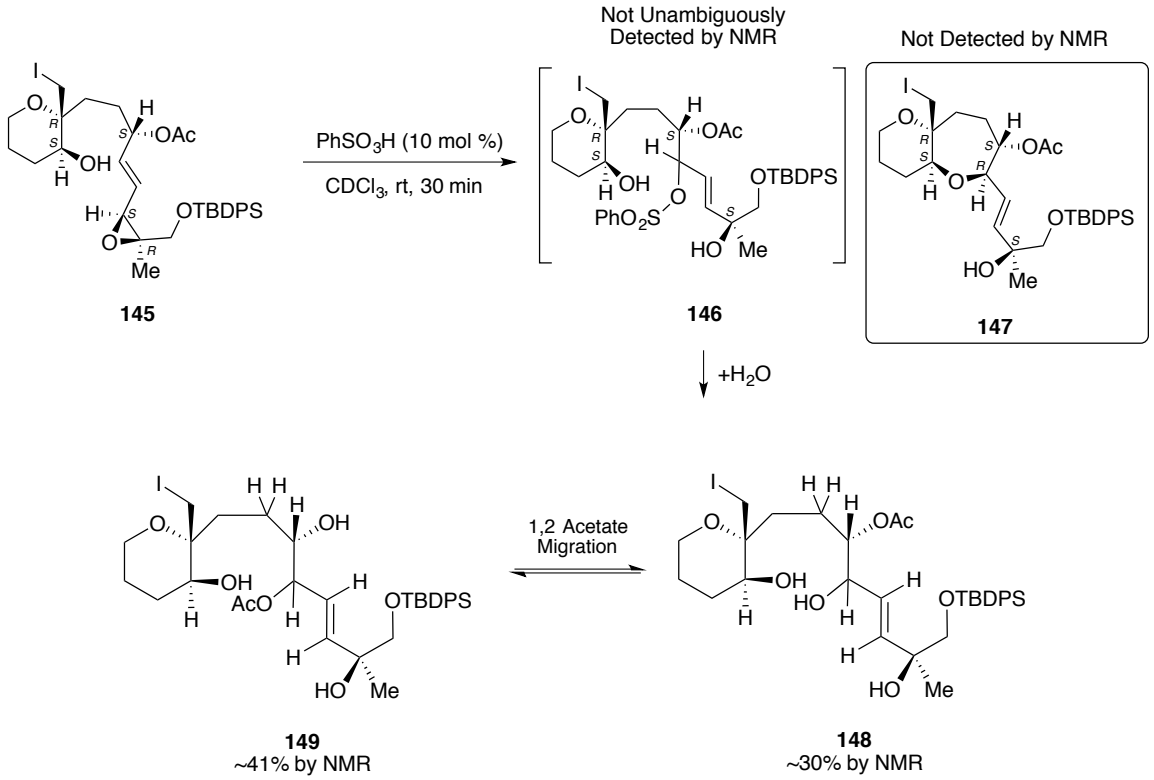
Scheme 46: Preparation of C-ring appended cyclization substrate.



1.4.18 Cyclization attempts of C-ring appended 7-exo substrate with benzenesulfonic acid

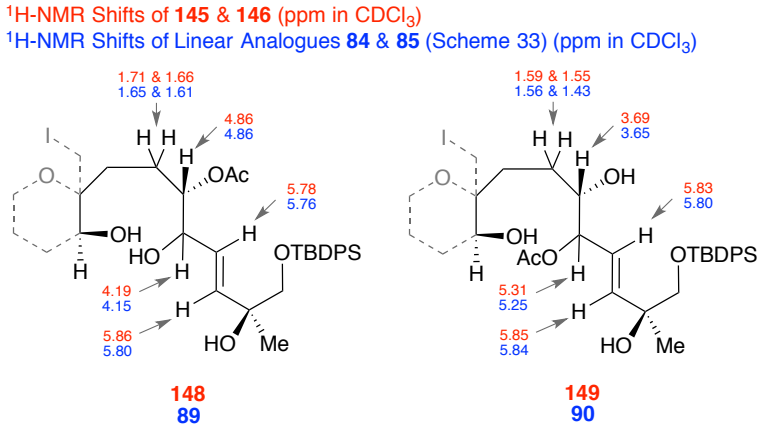
Subjecting substrate **145** to the action of benzenesulfonic acid did not produce the desired 6,7 ring system (Scheme 47). Despite rigorous attempts to exclude water, hydration of the substrate was observed, presumably from direct nucleophilic displacement of water onto the unobserved allyl benzenesulfonate to give **148**. As with the linear analogue, the hydrate underwent 1,2 acetate migration to give **149**.

Scheme 47: Attempts to form the D ring with a C-ring containing precursor.



Scheme 48 shows the similarities in chemical shift of the undesired hydrate byproducts to those from the linear analogue in Scheme 33.

Scheme 48: Chemical shift comparisons of **148**/**149** with linear analogs **89**/**90**.



1.4.19 Conclusions about Brønsted acid cyclizations of epoxyalkenes

The ability for benzenesulfonic acid to catalyze the cyclization of epoxy alkenes has been demonstrated. Important factors include the exclusion of water and use of chloroform as the solvent. NMR studies show that the reaction proceeds through a transient allyl-sulfonate intermediate that generated diastereoselectivity from the epoxy alkene. Cyclizations to form 7-membered rings have been largely unsuccessful, with hydration of the substrate often observed, followed by subsequent elimination reactions. Although the sulfonic acid conditions have been shown to be successful for pyran formation, great care must be taken to isolate the products immediately upon the completion of the reaction; otherwise acid mediated decomposition will occur as described in Schemes 30 and 37.

1.5 Palladium catalyzed cyclizations

1.5.1 Exploration of added acid to Pd-catalyzed cyclizations

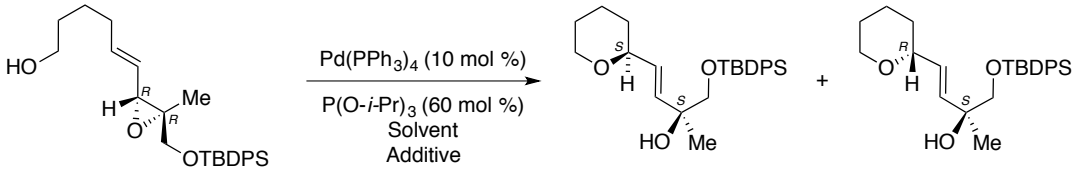
Concurrent with our investigations of the acid-catalyzed cyclizations of epoxy alkenes were studies toward performing the same transformation with palladium catalysis. Initial attempts to cyclize simple substrates **104** and **105** using $Pd_2(dba)_3$•$CHCl_3$ or $Pd(PPh_3)_4$ gave no reaction, with only starting material recovered, even when triisopropyl phosphite ($P(O\text{-}i\text{-}Pr)_3$) was added, an additive described by Trost as helpful for activation of epoxyalkenes.[62,63]

Our success with anhydrous benzenesulfonic acid alone led us to consider that perhaps the addition of a Brønsted acid or Lewis acid might activate the vinyl epoxide for addition of palladium.

We investigated the cyclization of substrate **105** with $Pd(PPh_3)_4$ and $P(O\text{-}i\text{-}Pr)_3$, in the presence of various Lewis and Brønsted acids (Table 2). Both zinc and copper(I) triflates produced the pyran products **106** and **107** with low diastereoselectivities (Entries 2,3). Prolonged exposure of the products to the reaction conditions gave spiroketal byproducts. Titanium(IV) additives exhibited improved diastereoselectivities favoring pyran **107**, although the reaction with titanium(IV) tetraisopropoxide was much slower than with chlorotitanium(IV) triisopropoxide (Entries 4,5). Diphenylphosphinic acid was the best additive for these cyclizations, rapidly furnishing the pyran product **107** with good diastereoselectivity (Entry 6) (Subsequent experiments showed that diphenylphosphinic acid also promoted the reaction in catalytic quantities). No reaction was observed upon addition of only water or isopropanol[26] (Entries 7,8). With excess acetic acid, the desired product **107** was formed with good diastereoselectivity, but

accompanied by acetate addition adduct (Entry 9). Hexafluoroisopropanol (HFIP) as a cosolvent also yielded pyran **107**, but unidentified side-products were also generated (Entry 10).

Table 2: Screening various additives for activation of the epoxide.



105 *E/Z* 89:11 **106** **107**

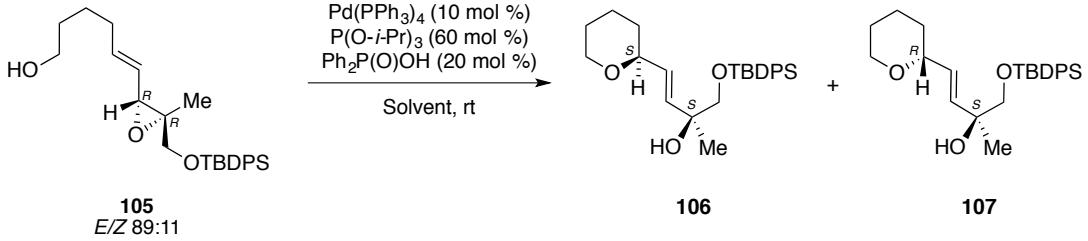
Entry	Additive	Equiv	Solvent	Time	Conversion[a]	dr (106:107)[b]
1	(none)	-	$CDCl_3$	3 h	no reaction	-
2	$Zn(OTf)_2$	1.1	$CDCl_3$	3 h	80%[c]	36:64
				6 d	52%[d]	37:63
3	$Cu(OTf)•(MeCN)_4$	1.3	$CDCl_3$	3 h	86%[c]	42:58
				6 d	50%[d]	ND[e]
4	$Ti(O\text{-}i\text{-}Pr)_4$	0.9	$CDCl_3$	6 d	38%[c]	23:77
				15 d	>95%	20:80
5	$ClTi(O\text{-}i\text{-}Pr)_3$	1.0	$CDCl_3$	17 h	>95%	20:80
6	$Ph_2P(O)OH$	0.9	$CDCl_3$	1 h	>95%	17:83
7	H_2O	260	THF	24 h	no reaction	-
8	*i*-PrOH	42	THF	24 h	no reaction	-
9	AcOH	82	THF	24 h	76%[f]	15:85
10	HFIP	45	THF	24 h	69%[g]	15:85

[a]Determined by NMR integration with resepect to the tert-butyl group of the TBDPS. [b]The diastereomer ratio was determined by integration of distinct alkene resonances of the product diastereomers **106** and **107**. [c]The remainder is vinyl epoxide **105**. [d]All of the starting material was consumed; the remaining material was identified as a spiroketal derived from the pyran products. [e]The diastereomer ratio could not be determined because of line broadening induced by paramagnetic copper species. [f]The remaining 24% was converted into the product of acetic acid addition instead of cyclization. [g]The remaining 31% was consumed to generate unidentified species.

1.5.2 Solvent screening of Pd cyclizations with added diphenylphosphinic acid

With the discovery that diphenylphosphinic acid promotes the desired cyclization of **107** in $CDCl_3$, we attempted the reaction in CH_2Cl_2 and THF as well (Table 3). Remarkably, except for a slightly slower reaction rate (by TLC) for the reaction in THF, all 3 solvents gave complete conversion to the product within 15 minutes, all with identical diastereomeric ratios.

Table 3: Solvent Screening for Pd-catalyzed cyclizations.



105 *E/Z* 89:11 **106** **107**

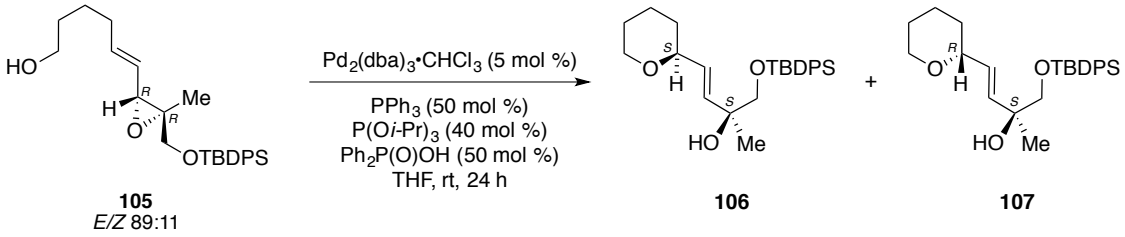
Entry	Solvent	Conversion (15 min)	Product dr (106:107)
1	$CDCl_3$	100%	15:85
2	CH_2Cl_2	100%	15:85
3	THF	100%	15:85

1.5.3 Investigation of different Pd ligands

Next we investigated the effects of omitting or replacing various ligands in the system (Table 4). Exclusion of diphenylphosphinic acid gave no desired product (Entry 2). Exclusion of either triisopropyl phosphite or triphenylphosphine gave only trace quantities of the desired pyran by NMR (Entries 3,4). Omitting both triisopropyl phosphite and triphenylphosphine produced no detectable product, showing that palladium with diphenylphosphinic acid alone does not catalyze the reaction (Entry 5). Removal of triphenylphosphine and doubling of triisopropyl phosphite gave a 92% conversion to the pyran, with a comparable dr (Entry 6). The fact that this reaction did

not proceed to completion suggests a positive effect of the triphenylphosphine. Replacing triphenylphosphine with tricyclohexylphosphine gave the desired product in 78% yield after 24 hours (Entry 7). Similarly replacing triphenylphosphine with bidentate dppp gave the pyran product in only 44% yield, with a slight erosion in the diastereomeric ratio.

Table 4: Ligand investigations of Pd-catalyzed cyclizations.

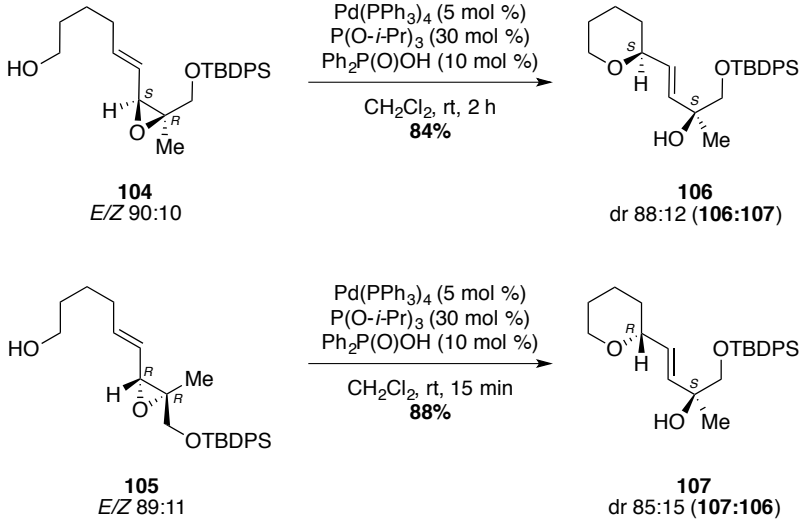


Entry	Change	NMR Conversion	dr (106:107)
1	none	100 %	15:85
2	$Ph_2P(O)OH$ excluded	None	-
3	$P(O\text{-}i\text{-}Pr)_3$ excluded	Trace	-
4	PPh_3 excluded	Trace	-
5	PPh_3 and $P(O\text{-}i\text{-}Pr)_3$ excluded	None	-
6	PPh_3 excluded, $P(O\text{-}i\text{-}Pr)_3$ doubled (80 mol % total)	92 %	17:83
7	PPh_3 replaced with PCy_3 (50 mol %)	78 %	15:85
8	PPh_3 replaced with dppp (25 mol %)	44 %	19:81

1.5.4 Cyclization with optimized Pd conditions

Having established the need for both triphenylphosphine and triisopropyl phosphite we set about optimizing the reaction conditions. We found that we could lower the Pd loading to 5% as well as halving the phosphite and acid loading, with no effect on reactivity or selectivity (Scheme 49). Thus we cyclized **104** to **106** in 84% isolated yield with a dr of 88:12. Compound **105** likewise gave **107** in 88% yield with a dr of 85:15.

Scheme 49: Pd-catalyzed cyclization of compounds **104** & **105.**

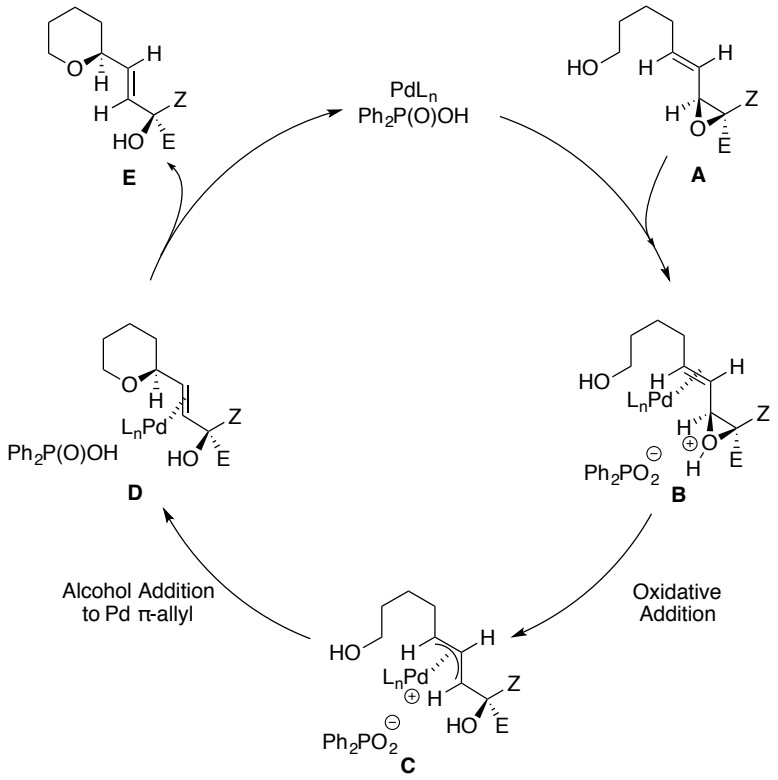


1.5.5 Proposed catalytic cycle for Pd/phosphinic acid cycloetherification

Scheme 50 details our proposed catalytic cycle for these cyclization reactions. Thus the epoxide of **A** is protonated with contemporaneous coordination of palladium to the alkene to give **B.** The protonation of the epoxide then facilitates oxidative addition of the palladium to the backside of the epoxide to give π-allyl complex **C**. Nucleophilic addition of the pendant alcohol to the top face of the π-allyl complex then gives **D**,

regenerating the diphenylphosphinic acid after proton transfer. Dissociation of the palladium complex then gives pyran **E** and regenerates both catalysts.

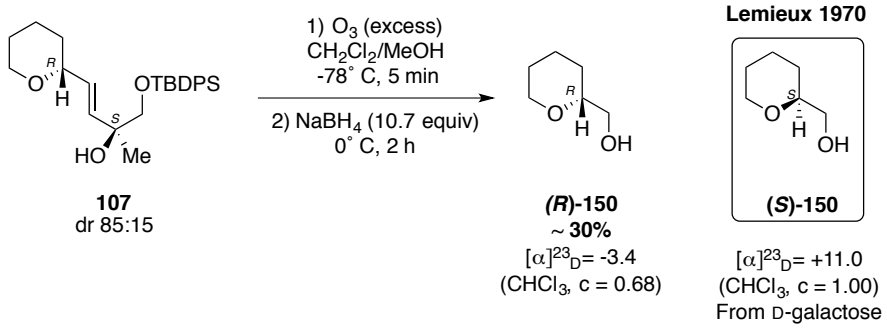
Scheme 50: Proposed catalytic cycle for Pd-catalyzed cyclization.



1.5.6 Determination of the absolute stereochemistry of pyran centers

We set out confirm the stereochemistry of the chiral center on the pyrans. Following the protocol described by Aponick, pyran **107** was subjected to ozonolysis with a reductive quench. Measurement of the optical rotation of the resulting tetrahydropyran methanol[64] **150** allowed for assignment of *R* as the major diastereomer of **107** (Scheme 51).[65] This stereochemistry is consistent with that expected from a double inversion of stereochemistry *via* a Pd π-allyl intermediate as proposed in our catalytic cycle. Furthermore, this verified the stereochemistry of the pyrans **106** and **107** obtained from sulfonic acid mediated cyclization. Several factors may contribute to the lower observed magnitude of the optical rotation when compared with that of the enantiomer described by Lemieux.[65] Compound **107** was derived from **105**, which was prepared by cross metathesis from epoxy alkene **55**, having had an er of greater than 95:5. Thus the tertiary alcohol of **107** should be predominantly (*S*), with the pyran center being *ca*. 85:15 (*R*):(*S*). Thus, upon cleavage, pyran **(*R*)-150** would be expected to have an er of *ca*. 85:15, an enantiomeric excess of 70%, which would decrease the observed rotation. During the reductive quench of the ozonide, the aldehyde of **150** could facilitate epimerization of the pyran stereocenter prior to being reduced to the alcohol.

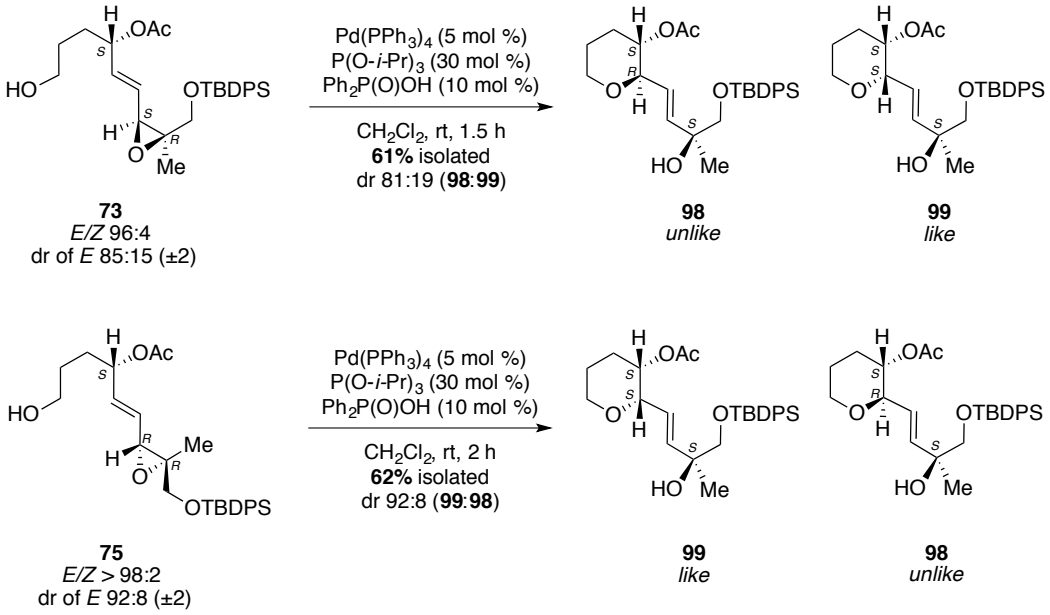
Scheme 51: Determination of pyran stereochemistry.



1.5.7 Pd cyclization of substrates bearing allylic oxygen substituents

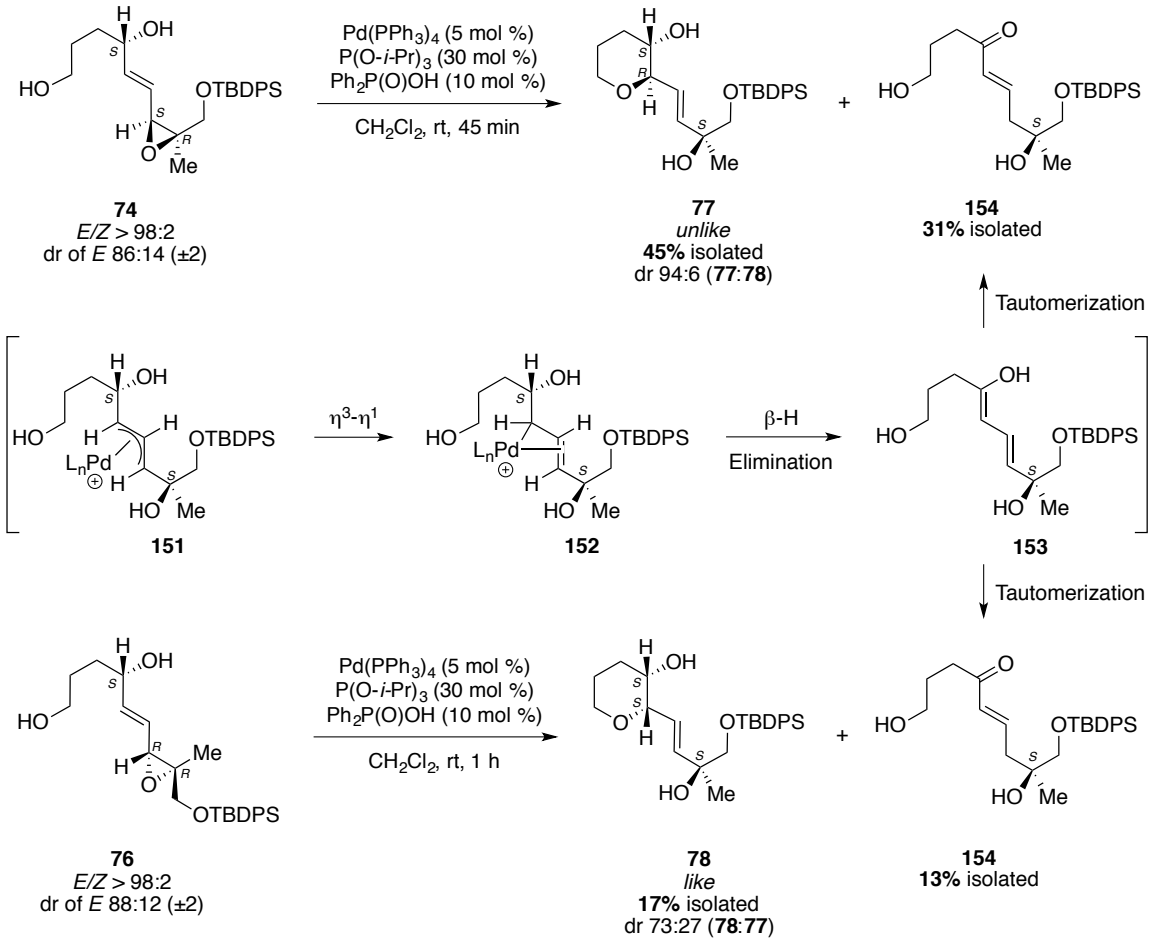
We harbored some concern in attempting a Pd mediated cyclization in the presence of an allylic acetate, fearing competitive π-allyl formation. Fortunately, these fears were unfounded. Both substrates **73** and **75** furnished their corresponding *unlike* and *like* pyrans, respectively, in high conversion (>90% by NMR with respect to the *tert*-butyl group of the TBDPS) and in moderate isolated yields (Scheme 52).

Scheme 52: Pd-catalyzed cyclization of allylic acetate-substituted epoxyalkenes.



We likewise tried our optimized conditions on diol substrates **74** and **76** (Scheme 53). While in both cases, some of the desired pyran was formed; both reactions were met with the generation of enone **154** as a byproduct. This could be explained by positing an η^3-η^1 slip of π-allyl **151** to compound **152**, which could undergo β-hydride elimination to give enol **153**. Keto-enol tautomerization would then give enone **154.**

Scheme 53: Pd-catalyzed cyclization of allylic alcohol-substituted epoxyalkenes.

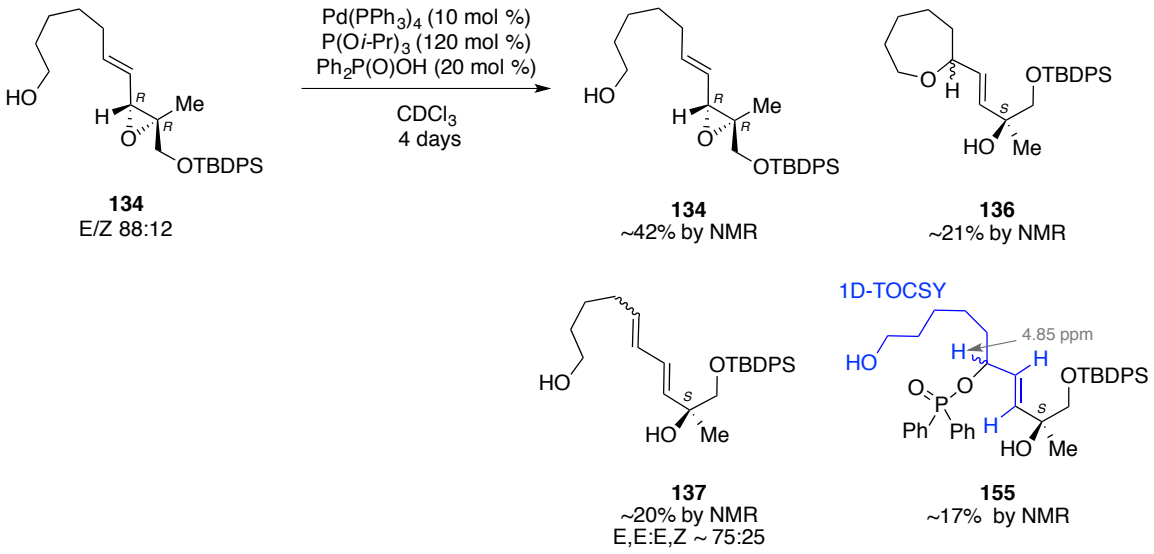


1.5.8 Attempts at oxepane formation with Pd/phosphinic acid conditions

Scheme 54 details attempts to apply the diphenylphosphinic acid mediated conditions to the cyclization of **134**. After multiple days, a low conversion to oxepane **136** was detected by NMR. Also detected was diene **137**, possibly arising from a β-hydride elimination of the Pd π-allyl complex, something that has been observed before by Spilling *et al*.[66] Compound **155** was detected *via* 1D-TOCSY irradiation of an apparent quintet at 4.85 ppm. The resulting spectrum bears a great resemblance to that of the allyl sulfonate **114** (Figure 3). The apparent quintet of the hydrogen at 4.85 suggests

possible $^{3}J_{H\text{-}P}$ coupling, however this was not proven. With these results, it was clear that even with the Pd catalyzed conditions, 7-membered ring formation was still very slow.

Scheme 54: Attempts at oxepane formation.

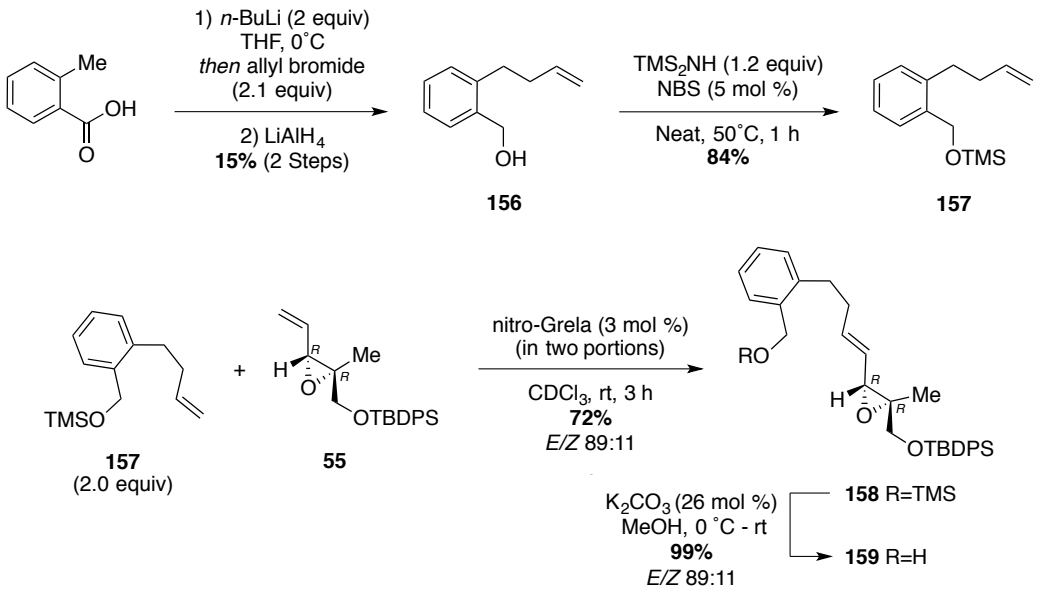


1.5.9 Preparation of 7-exo cyclization substrate with an aromatic group in the tether

In order to investigate the hypothesis that the slower ring closing kinetics were hindering the formation of the desired oxepane, substrate **159** was conceived, bearing an aromatic ring in the tether, with the idea that it might promote cyclization by constraining the available conformations. Thus, in a procedure modified from Li and coworkers,[67] *o*-toluic acid **155** was subjected to two equivalents of *n*-BuLi, deprotonating both the carboxylic acid as well as the benzylic methyl group. Quenching this cherry-red dianion with excess allyl bromide, followed by $LiAlH_4$ reduction of the resulting ester gave benzyl alcohol **156** in low yield (Scheme 55). Silylation, again using Shaterian's[51] conditions gave **157**, which was then subjected to cross metathesis with epoxyalkene **55**

to give cross product **158** in 72% yield. Deprotection of **158** in methanolic K_2CO_3 gave a nearly quantitative amount of compound **159**.

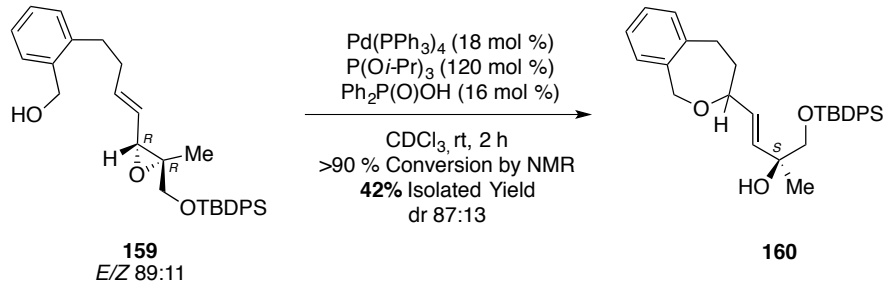
Scheme 55: Preparation of benzyl alcohol **159**.



1.5.10 Successful cyclization to give a benzooxepane

Upon exposure to the reaction conditions, benzooxepane **160** was formed within 2 hours with high conversion by NMR (with respect to the *tert*-butyl group of the TBDPS) (Scheme 56). The diastereoselectivity was also high. The ring stereocenter of the major diastereomer cannot be rigorously identified, although we expect that it is (*R*) by analogy to other systems.

Scheme 56: Cyclization of **159** to give benzooxepane **160**.



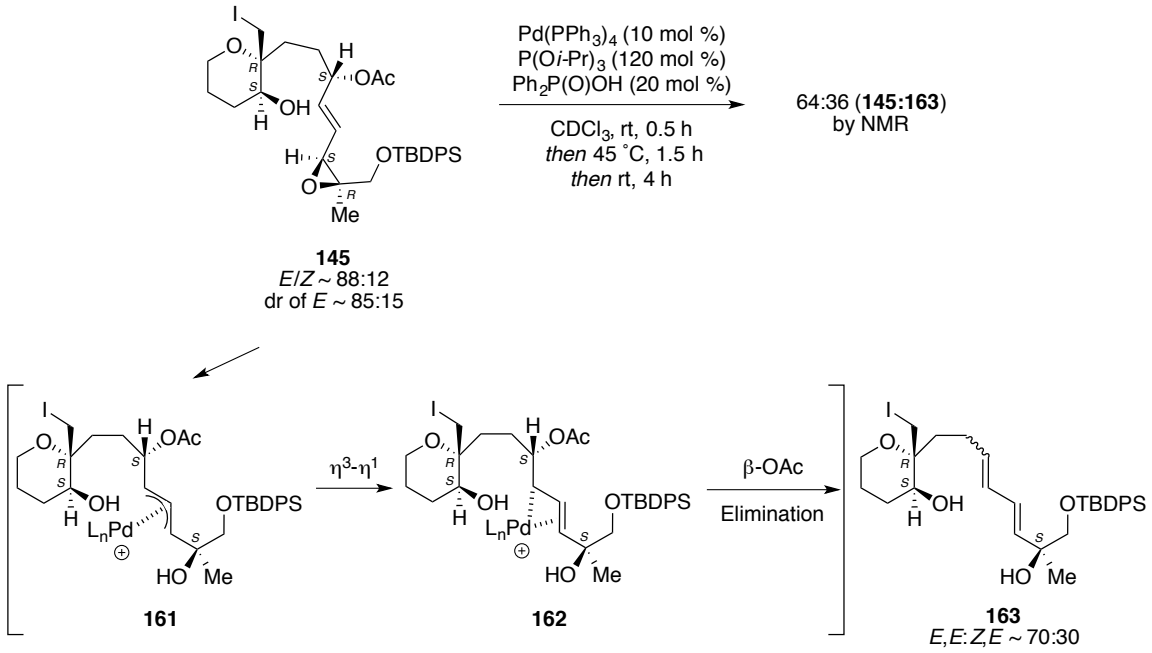
159
E/Z 89:11

160

1.5.11 Investigation of the cyclization of C-ring appended substrate using Pd/phosphinic acid conditions

Having shown that it was possible to form an oxepane with our Pd conditions when the substrate is conformationally restricted, we were optimistic about cyclizing our C-ring appended substrate **145**. Treatment of **145** with Pd at room temperature showed no reaction by NMR (Scheme 57). Gently heating the reaction mixture showed the formation of diene **163**, as identified by 1D TOCSY (a spectroscopically identical species was later isolated and characterized in the experiment described in Scheme 60). No desired oxepane was observed. The generation of **163** may arise from a η^3-η^1 slip of π-allyl complex **161** to **162**. Subsequent β-acetoxy elimination would then give diene **163**. Such an elimination would be a formal reduction of the substrate, with concomitant oxidation of Pd(0) to Pd(II). Trost has reported the β-elimination of carbonates from Pd π-allyl species, with triisopropyl phosphite being capable of reducing Pd(II) back to Pd(0).[68]

Scheme 57: Attempts to form the CD rings using phosphinic acid promoted Pd catalysis.



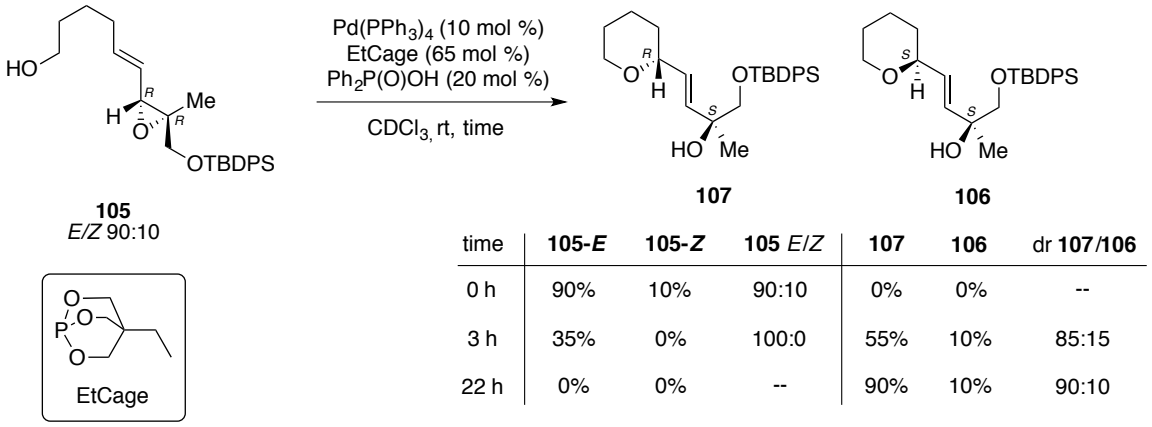
1.5.12 Investigations replacing triisopropyl phosphite with trimethylolpropane phosphite (EtCage)

Disappointed with the limitations of our catalytic system for the closure of 7-membered rings we looked to the literature for possible alternatives. Our attention was caught by work by Trost toward carbocyclizations of epoxy alkenes using alternative phosphites to triisopropyl phosphite. Trost describes numerous examples wherein trimethylolpropane phosphite (EtCage) gives superior reaction rate along with diminished side product formation.[69]

Thus we subjected substrate **105** to our cyclization conditions, replacing triisopropyl phosphate with EtCage. By NMR the reaction proceeded, although noticeably slower than with triisopropyl phosphate, with only 65% conversion after 3 h (Scheme 58). At the 3 hour point, no *Z*-alkene starting material was observed by NMR, and the dr of the

products formed was 85:15. Remarkably, NMR of the reaction mixture after 22 h revealed complete conversion to the pyrans, now with a diastereomeric ratio exactly matching the *E*/*Z* ratio of the starting alkene isomer. This enhancement of the dr is consistent with conversion of the remaining *E* isomer at 3 h into exclusively the (*R*)-pyran diastereomer **107**, suggesting that with EtCage the reaction is highly stereospecific.

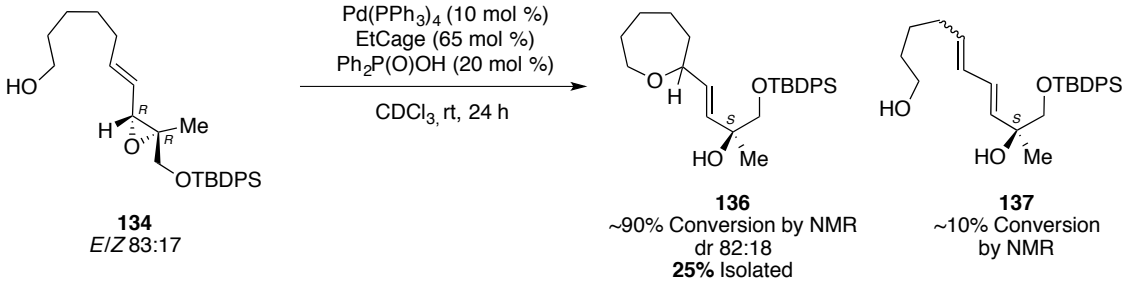
Scheme 58: EtCage gives product dr that matches starting material *E*/*Z* ratio.



time	**105-*E***	**105-*Z***	**105** *E*/*Z*	**107**	**106**	dr **107**/**106**
0 h	90%	10%	90:10	0%	0%	--
3 h	35%	0%	100:0	55%	10%	85:15
22 h	0%	0%	--	90%	10%	90:10

With successful cyclization to form a pyran using EtCage, we attempted the cyclization of **134** as well (Scheme 59). Excitingly, after 24 hours, **134** was successful cyclized to form oxepane **136** in greater than 90% conversion by NMR. The remaining material (~10%) was identified as diene **137**. Unfortunately, only a 25% isolated yield of **136** was obtained, possibly from incomplete extraction of the silica gel following preparative TLC (although multiple extractions with EtOAc did not increase the recovered mass). Like the pyran example in Scheme 58, the product dr of **136** is close to the *E*/*Z* ratio of the starting material. Although the oxepane stereocenter was not established, we expect it to be (*R*) by analogy to the pyran cyclizations.

Scheme 59: Replacement of triisopropyl phosphite with EtCage enables oxepane formation.



The success of the reaction may attributable the reduced cone-angle of the EtCage ligand (cone angle 101˚) with respect to triisopropyl phosphite (cone angle 130˚).[70] This size reduction may enable more facile nucleophilic addition of the pendant alcohol. Interestingly, the ^{31}P chemical shift of the phosphorus in EtCage is -90.1 ppm, whereas in triisopropyl phosphite it is -137.5 ppm.[70] Thus, the phosphorus in EtCage is more deshielded than in triisopropyl phosphite, suggesting that the beneficial effect may be more than just more facile nucleophilic addition to the epoxyalkene.

1.5.13 Successful preparation of the brevenal CD substructure using Pd catalysis with EtCage

With the successful cyclization to give oxepane **136**, we decided to apply these EtCage conditions to the cyclization of compound **145** to make the D ring (Scheme 60). Thus, in an NMR tube, **145** was exposed to 10 mol % $Pd(PPh_3)_4$, 65 mol % EtCage and 18 mol % $Ph_2P(O)OH$ in $CDCl_3$. Again using the *tert*-butyl peak of the TBDPS allowed for estimation of the relative abundance of molecules present. After the reaction had aged for 5 minutes, only the starting material was observed by NMR. After 18 h, mostly starting material was observed, with several new species having appeared, including a

small amount of what was later determined to be the desired bicycle **147**. The most recognizable byproduct at 18 hours was diene **163**, presumably from β-acetoxy elimination analogous to Scheme 57. Also forming present at 18 hours was bisacetate **164**, presumably arising from addition of acetate (generated from β-acetoxy elimination to give **163**) addition to the activated species. After 6 days the relative amount of **145** dropped to 29%, with increases in **147**, **163** and **164**. NMR of the reaction mixture after 21 days strongly suggested the presence of the desired bicyclic product **147**, representing approximately 18% of the conversion. Preparative TLC allowed for the isolation of **147** in 8% isolated yield and enabled thorough determination of its structure. Also isolated was diene **163** in 25% yield and bisacetate **164** in 29% yield.

Scheme 60: Successful preparation of CD ring system and reaction byproducts.

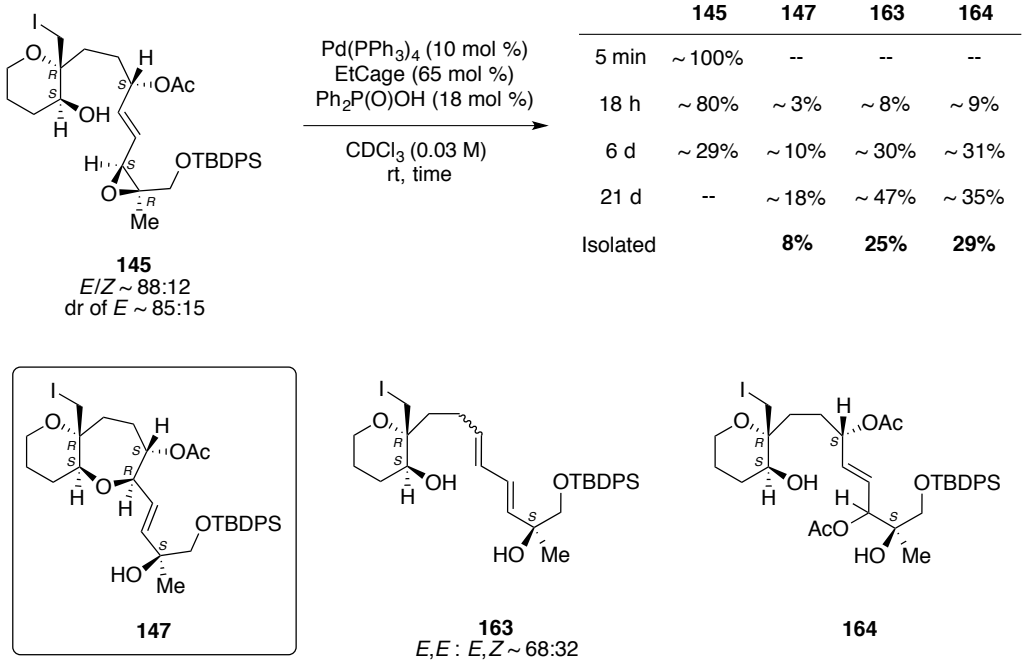
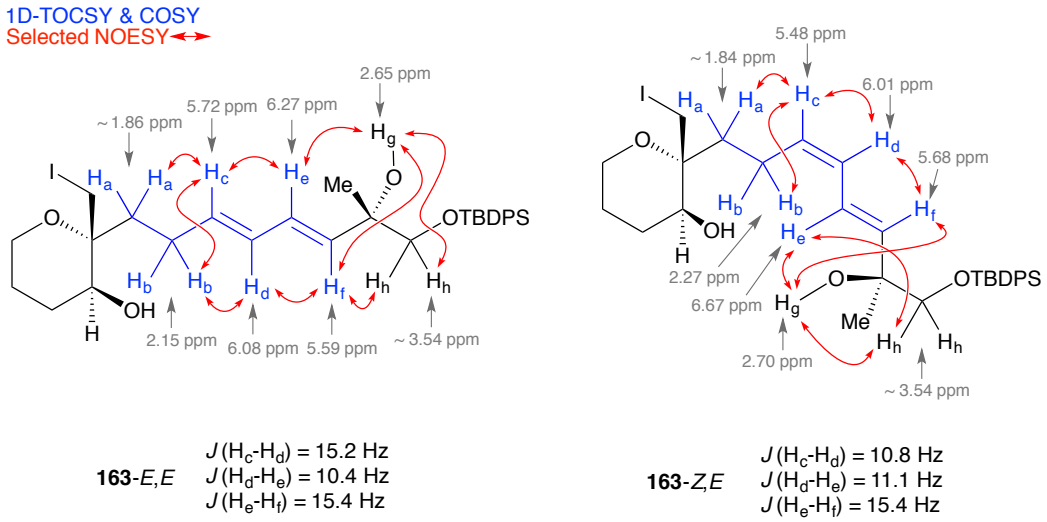


Figure 10 shows the NMR characterization data for the diene byproducts **163**-*E*,*E* and **163**-*E*,*Z* obtained in the reaction. Notably numerous NOE correlations were observed between the alkenyl protons with the hydrogen on the tertiary alcohols.

Figure 10: NMR characterization of diene byproducts **163**.

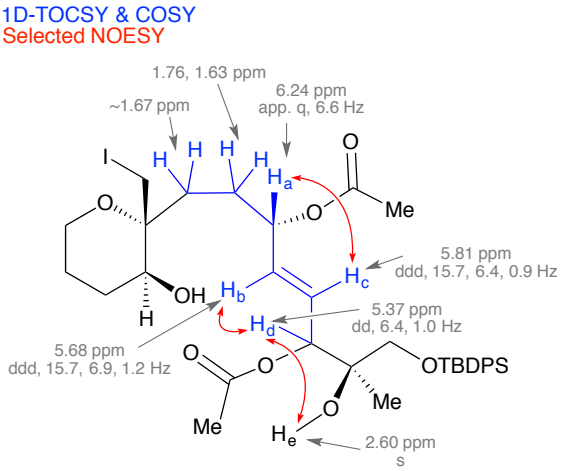


163-*E*,*E* $J(H_c\text{-}H_d) = 15.2$ Hz, $J(H_d\text{-}H_e) = 10.4$ Hz, $J(H_e\text{-}H_f) = 15.4$ Hz

163-*Z*,*E* $J(H_c\text{-}H_d) = 10.8$ Hz, $J(H_d\text{-}H_e) = 11.1$ Hz, $J(H_e\text{-}H_f) = 15.4$ Hz

Figure 11 shows selected NMR data for the isolated bisacetate **164**. Not indicated in the figure is a direct COSY correlation observed between H_a and H_d. A $^5J_{HH}$ coupling is precedented,[71] especially when there is an intervening double bond, although it was not observed in the 1-D ^{1}H-NMR spectrum.

Figure 11: NMR characterization of bisacetate byproduct **164**.



164

Tables 5 and 6 list the proton and carbon assignments and correlations of **147**. COSY and 1D-TOCSY analysis of **147** showed the presence of two large, independent spin systems, represented by the green and blue coloring in Figure 12. NOE correlations confirmed the 1,3-syn relationship of the H_i and H_g protons of the oxepane, in addition to identifying the hydrogen of the tertiary alcohol as H_o. The coupling constant between H_g and H_f was measured to be approximately 1.3-1.5 Hz, indicating that the major conformation in solution does not orient them anti to each other. Instead, the small coupling constant suggests a dihedral angle between them that is close to ~90˚. The fact that there is an NOE correlation between H_f and H_g, in addition to the high chemical shift of H_f (5.02 ppm) are consistent with a conformation that places H_f in a pseudo-equatorial orientation.

Figure 13 shows selected long-range heteronuclear correlations measured after an 8 hour HMBC acquisition on a sample of 1.2 mg. Figure 13 shows the correlations most important for structure verification; notably $\mathbf{C_H}$-H_i, supporting ring-closing to the

oxepane, $\mathbf{C_A}$-H_f, verifying the location of the acetate group and all correlations of $\mathbf{C_L}$, particularly $\mathbf{C_L}$-H_O, confirming the presence and location of the tertiary alcohol.

Table 5: Tabulation of ^{1}H shifts and homonuclear correlations of compound **145**.

^{1}H-NMR Label	**Shift (ppm)**	**Multiplicity**	**Couplings (Hz)**	**COSY Correlations**	**NOESY Correlations**
a_4	7.68-7.65	m	-	H_{c4}	H_{c4}, H_l, H_m, H_{y9}
b_2	7.48-7.45	m	-	H_{c4}	H_{c4}
c_4	7.43-7.40	m	-	H_{a4}, H_{b2}	H_{a4}, H_{b2}
d	5.83	dd	15.7, 1.6	H_e, H_g	H_f, H_g, H_l
e	5.74	dd	15.7, 4.8	H_d, H_g	H_f, H_g, H_l, H_o
f	5.02	dt	7.0, 1.3	H_r, H_g, H_w	H_d, H_e, H_g, H_r, H_w
g	4.23	dt	4.8, 1.5	H_e, H_d, H_f	H_d, H_e, H_f, H_i
h	3.81	dd	11.8, 2.2	**H_k**, H_v (**W coupling**)	H_k, H_v, H_n
i	3.73	dd	11.7, 5.0	H_u, H_s	H_g, H_s, H_{t2}
j	3.66	ddd	12.3, 4.5, 1.5	H_n, H_{t2}	H_n, H_{t2}, H_h, H_k
k	3.58	d	11.9	H_h	H_n, H_h, H_w
l	3.53	d	9.7	H_m	H_d, H_e, H_o, H_m
m	3.51	d	9.6	H_l	H_d, H_e, H_o, H_l
n	3.38	td	11.9, 3.3	H_j, H_{t2}	H_j, H_k, H_h, H_{t2}
o	2.63	s	-	none	H_l, H_e, H_2O
p_3	2.14	s	-	none	not observed
q	1.99	dd	13.3, 5.2	H_v, H_r, H_w	H_v, H_h, H_k
r	1.87	td	13.2, 6.4	H_w, H_f, H_q	H_f, H_w
s	1.84	dd	13.1, 4.0	H_u, H_i, H_{t2}	H_i, H_u, H_{t2}
t_2	1.75-1.55	m	-	H_n, H_j, H_s	H_i, H_j
u	1.65-1.57	m	-	H_s, H_i, H_{t2}	H_h
v	1.62-1.58	m	-	H_q, H_w, H_r	H_h
w	1.54-1.49	m	-	H_r, H_q, H_f, H_v	H_f, H_k
x_3	1.46	s	-	none	not observed
y_9	1.09	s	-	none	H_{a4}

Table 6: Tabulation of ^{13}C shifts and heteronuclear correlations of compound **145**.

^{13}C-NMR Label	Shift (ppm)	HMQC Correlations	HMBC Correlations
A	170.05	none	H_f
B_2	135.56	H_{a4}	H_{a4}, H_{b2}, H_{c4}
B'_2	135.61	H_{a4}	H_{a4}, H_{b2}, H_{c4}
C	135.25	H_d	H_o, H_e, H_g, H_l, H_m
D	132.86	none	H_{a4}, H_{c4}
D'	132.97	none	H_{a4}, H_{c4}
E_2	129.86	H_{b2}	H_{a4}, H_{c4}
F_4	127.8	H_{c4}	H_{a4}, H_{b2}, H_{c4}
G	127.44	H_e	H_g, H_d
H	82.01	H_g	H_e, H_r, H_d, H_i, H_f
I	76.97	H_f	H_v, H_r
J	76.08	H_i	not observed
K	75.44	none	H_h, H_v, H_r
L	72.86	none	H_d, H_o, H_l, H_m, H_e
M	70.93	H_l, H_m	not observed
N	60.35	H_n, H_j	not observed
O	32.84	H_v, H_q	H_f, H_h, H_r
P	30.32	H_{x3}	not observed
Q_3	26.83	H_{y9}	not observed
R	26.76	H_w, H_r	not observed
S	25.13	H_{t2}	not observed
T	21.96	H_u, H_s	H_t
U	21.35	H_{p3}	not observed
V	19.33	none	not observed
W	10.19	H_n, H_k	H_v, H_q

Figure 12: Homonuclear correlations of bicyclic compound **147**.

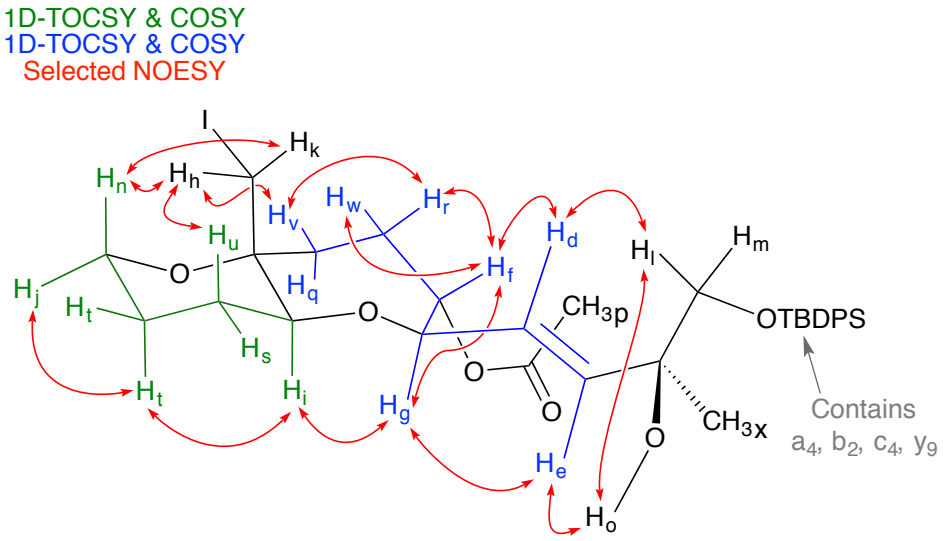
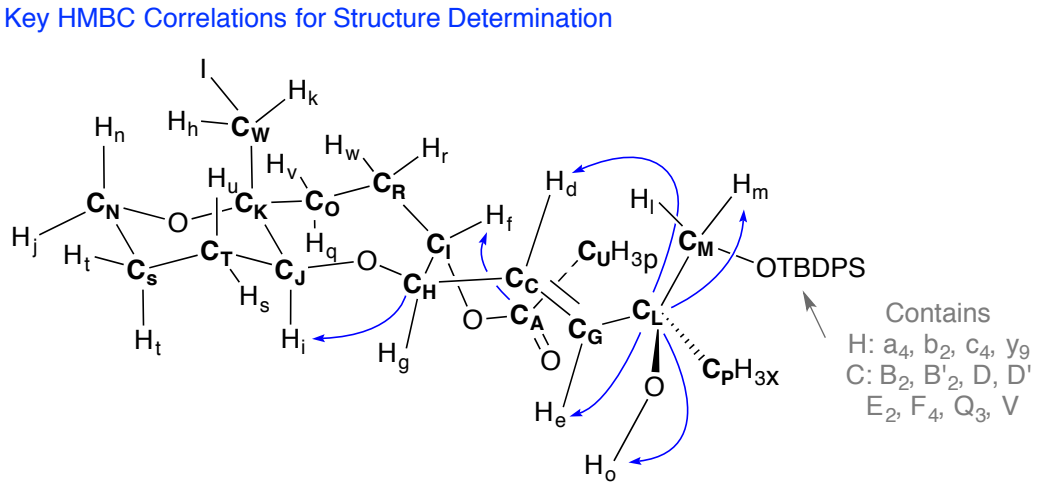


Figure 13: Key heteronuclear correlations of bicyclic compound **147**.



1.6.16 Conclusions about Pd-catalyzed cyclizations

Pd-catalyzed cycloisomerizations allow for the preparation of stereodefined pyrans, with the stereo-control arising from the stereochemistry of the epoxide and not being directed by an endocyclic allyl alcohol. Addition of a catalytic amount of phosphinic acid promotes epoxyalkene activation and enabling the reaction. Switching the added phosphite from triisopropyl phosphite to EtCage enables cyclization of 6-membered rings with higher diastereoselectivity (matching the starting material *E*/*Z* ratio)

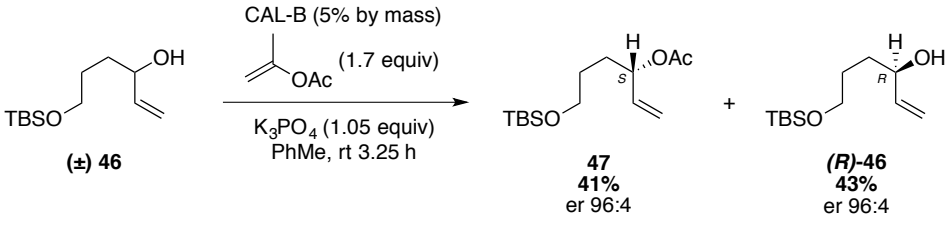
as well as for the formation of 7 membered rings. Use of EtCage also enabled the preparation of the brevenal CD ring system **147** by promoting D ring formation, albeit in very low yield and with very long reaction times. Future work will strive to increase the cyclization reaction rate, which may also affect a reduction in the amount of diene side products produced. Upon obtaining larger quantities of the CD bicyclic product, the substrate may be homologated to an unsaturated ester for study of the closure of the E ring.

1.6 Experimental Details

General information: Proton and carbon NMR spectra were recorded on an MERCURY 300 (300 MHz), NOVA-400 (400 MHz), VNMRS 400 (400 MHz), INOVA-500 (500 MHz), INOVA-600 (600 MHz), Unity-600 (600 MHz) or BRUKER 600 (600 MHz) equipped with cryogen probe. NMR spectra were recorded in solutions of deuterated chloroform ($CDCl_3$) with the residual chloroform (7.27 ppm for ^{1}H NMR and 77.23 ppm for ^{13}C NMR) taken as the internal standard, deuterated methanol (CD_3OD) with residual methanol (3.31 ppm for ^{1}H-NMR and 49.3 ppm for ^{13}C-NMR) taken as the internal standard, or deuterated benzene with residual benzene (7.16 ppm for ^{1}H NMR and 128.23 ppm for ^{13}C NMR) taken as the internal standard, and were reported in parts per million (ppm). With the exception of the diastereomeric ratios of the epoxyalkene cross metathesis products (Section 1.3.3), all drs, ers (of Mosher esters) and *E*/*Z* ratios were determined by NMR integration of isolated peaks with an uncertainty of ±2%. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; m, multiplet. IR spectra were collected on a Nicolet iS10 from Thermo Scientific and reported in units of cm^{-1}. Mass spectra (high resolution ESI and APCI) were recorded on

a Finnigan LTQ FTMS Mass spectrometer. Optical rotations were measured using a Perkin-Elmer 341 polarimeter (concentration in g/100mL). Thin layer chromatography (TLC) was performed on pre-coated glass-backed plates purchased from Whatman (silica gel 60F254; 0.25mm thickness). Preparative TLC was performed on pre-coated glass-backed plates purchased from Analtech (20 x 20 cm, Silica gel GF UV254, 1.0 mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from Silicycle. All reactions were carried out with anhydrous solvents in oven dried or flame dried and argon-charged glassware unless otherwise specified. All anhydrous solvents were dried with 4Å molecular sieves purchased from Sigma-Aldrich and tested for trace water content with Coulometric KF titrator from Denver instruments. All solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification. All metathesis catalysts were purchased from Sigma Aldrich, with the exception of the nitro-Grela catalyst, which was purchased from Strem Chemical.

Compound 47



Racemic alcohol **46**35 (22.2 g, 96.3 mmol) was dissolved in PhMe (250 mL) and powdered K_3PO_4 (22.4 g, 100.7 mmol), CAL-B resin (980 mg) and isopropenyl acetate (18 mL, 163 mmol) were added. The mixture was stirred for 3.25 hours (NMR showed ~50% conversion), filtered through Celite with Et_2O and the eluant concentrated *in vacuo* to give an orange oil. Column chromatography of the crude eluting with 20/80

Et_2O/Hexanes -> 50/50 Et_2O/Hexanes gave the acetate **47** (10.71 g, 41%, er 96:4 by analysis of the Mosher ester of the hydrolyzed acetate) as a clear oil and the alcohol (9.46 g, 43%, er 96:4 by analysis of the Mosher ester) as a yellow oil. The spectra and sign of the optical rotation of **47** matched that reported in the literature.[36]

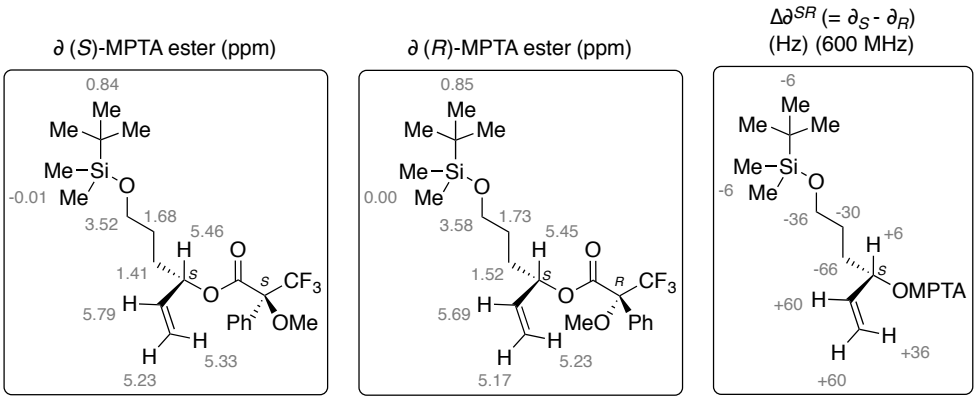
Data for 47

^{1}H-NMR (600 MHz; $CDCl_3$): δ 5.78 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H), 5.27-5.22 (m, 2H), 5.17 (dt, *J* = 10.5, 1.2 Hz, 1H), 3.65-3.59 (m, 2H), 2.07 (s, 3H), 1.68 (q, *J* = 7.3 Hz, 2H), 1.61-1.50 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H).

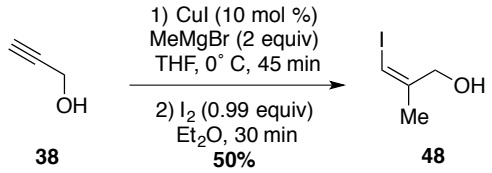
IR (CH_2Cl_2) 2930, 2954, 2858, 1742, 1472, 1371, 1239, 1099, 835, 776 cm^{-1}.

$[\alpha]_D^{20}$ = -3.2 (CH_2Cl_2, *c* = 0.69). Literature value **$[\alpha]_D^{29}$** = -2.7 (MeOH, *c* = 1.00)[36]

Mosher Ester Data[38]

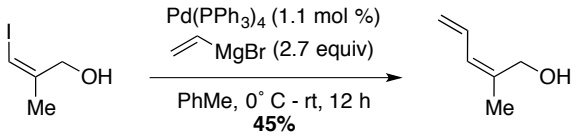


Compound 48



CuI (2.77 g, 14.5 mmol) was suspended in THF (150 mL) at 0˚ C and MeMgBr (100 mL, 300 mmol, 3 M in Et_2O) was added by cannula. To this solution was added slowly (Caution! vigorous gas evolution) propargyl alcohol **38** (9.0 mL, 8.55 g, 152.5 mmol). The mixture was stirred at 0˚ C for 45 minutes whereupon a solution of I_2 (38.3 g, 150.9 mmol) in Et_2O (250 mL) was added slowly. The mixture was removed from the cooling bath, stirred for 30 more minutes and poured directly into a separatory funnel charged with sat. NH_4Cl (150 mL) and brine (150 mL). Solid $Na_2S_2O_3$ was added in portions to remove unreacted iodine from the organic layer (turning it from brown to yellow). The layers were separated and the blue (likely due to formation of copper ammine) aqueous layer extracted with Et_2O (3 x 250 mL). The combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to give a yellow oil (15.95 g). Crude NMR showed the oil to be 93.5% **48** by weight (14.91 g, 75.3 mmol, 50%), the remaining mass being 2-methyl-2-propen-1-ol. The oil of this experiment was carried on directly to the next step, but may be purified *via* short path distillation (bp 72 ˚C, 7 torr) if desired. Spectral data matched that reported in the literature.[72]

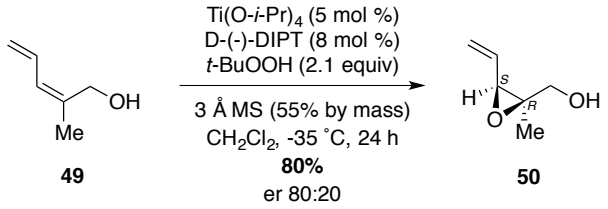
Compound 49



48 **49**

A solution of vinyl iodide **48** (15.95 g, 93.5% by weight, 75.3 mmol) in PhMe (250 mL) was degassed with argon for 20 minutes and cooled to 0 ˚C. $Pd(PPh_3)_4$ (1.00 g, 0.86 mmol) was added and the solution aged for 20 minutes whereupon a solution of vinylmagnesium bromide (200 mL, 200 mmol, 1 M in THF) was added slowly (Caution! Vigorous gas evolution) *via* addition funnel over 10 minutes. The reaction mixture was allowed to warm to room temperature overnight and quenched with saturated NH_4Cl (200 mL). The solution was further diluted with water (200 mL), the layers separated and the aqueous layer extracted with Et_2O (3 x 300 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* (the water bath temperature was kept between 10 and 20 ˚C) to give an orange oil with some red solids. The oil was filtered though a small pad of cotton with Et_2O and distilled under reduced pressure to give diene **49** (3.35 g, 34.1 mmol, 45%, bp 49–51 ˚C at 7 torr) as a clear liquid. Spectral data matched that reported in the literature.[73]

Compound 50



To a suspension of ground activated 3Å molecular sieves (1.86 g) in CH_2Cl_2 (150 mL) at -20 ˚C was added titanium isopropoxide (0.50 mL, 1.7 mmol), D-(-)-diisopropyl tartrate (0.55 mL, 2.6 mmol). To the mixture was then added *tert*-butyl hydroperoxide (5.5 M in decane, 13.0 mL, 71.5 mmol) over 5 minutes and the reaction aged for 30 minutes. After cooling to -35 ˚C a solution of allyl alcohol **49** (3.35 g, 34 mmol) in CH_2Cl_2 (30 mL) was added slowly. The reaction mixture was stirred at -35 ˚C for 24 hours and then warmed to -20 ˚C whereupon it was quenched via addition of a 10% NaOH solution in saturated NaCl (2.7 mL). After adding Et_2O (20 mL) the mixture was allowed to warm to 10 ˚C over 2 hours whereupon $MgSO_4$ (2.7 g) and Celite (380 mg) were added and the mixture stirred for 10 minutes before being filtered through a pad of Celite with Et_2O (~500 mL). The eluant was concentrated *in vacuo* and the resulting oil was purified by column chromatography eluting with 30/70 EtOAc/Hexanes to give epoxide **50** (3.12 g, 80%, 80:20 er by analysis of the corresponding Mosher esters) as a clear liquid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.85 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.50 (ddd, *J* = 17.2, 1.4, 0.9 Hz, 1H), 5.38 (ddd, *J* = 10.5, 1.4, 0.8 Hz, 1H), 3.69 (d, *J* = 6.1 Hz, 2H), 3.35 (d, *J* = 7.2 Hz, 1H), 1.60 (t, *J* = 5.2 Hz, 1H), 1.45 (s, 3H).

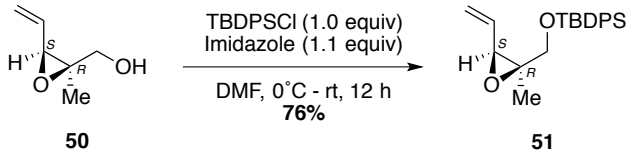
^{13}C-NMR (101 MHz; $CDCl_3$): δ 132.5, 121.1, 64.64, 64.56, 64.0, 20.02, 19.97.

IR (neat) 3418, 2974, 2935, 1740, 1640, 1448, 1377, 1044, 1027 cm^{-1}.

HRMS (NSI) calculated for $C_6H_{10}O_2Na^+$ $[M+Na]^+$ 137.05730, found 137.05721.

$[\alpha]_D^{20}$ = +7.0 (CH_2Cl_2, *c* = 0.91).

Compound 51



To a solution of epoxy alcohol **50** (2.31 g, 20.3 mmol) and imidazole (1.51 g, 22.1 mmol) in dry DMF (20 mL) was added TBDPSCl (5.20 mL, 5.51 g, 20.3 mmol) at 0˚ C. The reaction mixture was allowed to warm to rt overnight, diluted with water (100 mL) and extracted with Et_2O (5 x 50 mL). The combined organics were back-extracted with water (5 x 50 mL), washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was subjected to column chromatography eluting with 5/95 Et_2O/Hexanes to give silyl ether **51** (5.47 g, 15.5 mmol, 76%) as a white, amorphous, waxy solid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.71-7.66 (m, 4H), 7.47-7.37 (m, 6H), 5.60 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.37 (ddd, *J* = 17.1, 1.5, 0.8 Hz, 1H), 5.22 (ddd, *J* = 10.5, 1.5, 0.7 Hz, 1H), 3.68 (dd, *J* = 17.2, 10.9 Hz, 2H), 3.29 (d, *J* = 6.9 Hz, 1H), 1.51 (s, 3H), 1.08 (s, 9H).

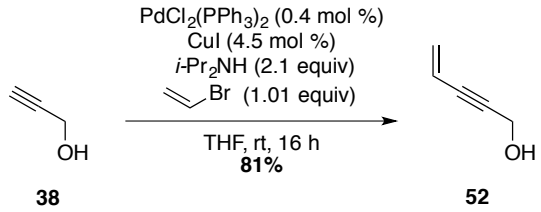
^{13}C-NMR (101 MHz; $CDCl_3$): δ 135.85, 135.80, 133.5, 133.3, 132.6, 129.9, 127.9, 120.2, 65.2, 64.09, 64.07, 63.0, 27.0, 20.1, 19.5. IR (neat) 3071, 2960, 2931, 2858, 1590, 1472, 1428, 1112, 702 cm^{-1}.

IR (CH_2Cl_2): 3071, 3049, 2959, 2931, 2891, 2858, 1589, 1487, 1428, 1111, 823, 701cm^{-1}.

HRMS (NSI) calculated for $C_{22}H_{28}O_2NaSi^+$ $[M+Na]^+$ 375.17508, found 375.17486.

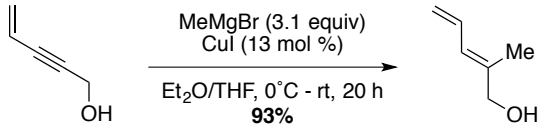
$[\alpha]_D^{20}$ = +10.7 (CH_2Cl_2, *c* = 0.65).

Compound 52



To a 1 M solution of vinyl bromide (84 mL, 84 mmol) in THF was added CuI (728 mg, 3.8 mmol), $PdCl_2(PPh_3)_2$ (247 mg, 0.35 mmol) and iPr_2NH (25 mL, 178 mmol). The mixture was cooled to 0˚ C and propargyl alcohol **38** (4.8 mL, 83 mmol) was added dropwise over 5 minutes, whereupon the cooling bath was removed. After aging for 20 h at rt, the reaction mixture was poured into a mixture of saturated aqueous NH_4Cl (100 mL) and Et_2O (50 mL). The layers were separated and the aqueous layer extracted with Et_2O (3 x 50 mL) (for the last extraction, the aqueous layer was diluted with 20 mL water). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* in a fume hood to give enyne **52** as a dark red oil (5.55 g, 81 %). Spectral data matched that reported in the literature.[74]

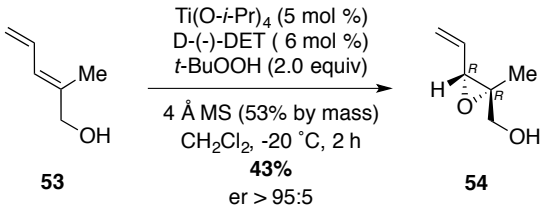
Compound 53



52 **53**

To a 0˚ C suspension of CuI (1.68 g, 8.8 mmol) in THF (20 mL) was added MeMgBr (3 M in Et_2O, 70 mL, 210 mmol). To the yellow suspension was added dropwise a solution of enyne **52** (5.55 g, 67.6 mmol) in THF (20 mL) over 10 minutes (**caution!** vigorous CH_4 evolution). The reaction mixture was allowed to warm to rt over 20 h and then quenched slowly at 0˚ C *via* addition of a 1:1 mixture of water:saturated NH_4Cl (100 mL). The mixture was further diluted with water (200 mL) and extracted with Et_2O (3 x 100 mL). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* (the water bath temp was kept < 20 ˚C) to afford diene **53** (6.18 g, 93%) as a red-orange oil. Spectral data matched that reported in the literature.[75]

Compound 54



53 **54**

To a cooled (-20 ˚C) suspension of powdered 4 Å molecular sieves (3.27 g) in CH_2Cl_2 (200 mL) was added Ti(O*i*-Pr)$_4$ (0.93 mL, 3.1 mmol) and D-(-)-diethyl tartrate (0.68 mL, 3.9 mmol). Over the course of 5 minutes was added dropwise *t*-BuOOH (5.5 M in decane, 23 mL, 127 mmol). After aging for 45 minutes at -20 ˚C a solution of alcohol **53** (6.18 g, 63 mmol) in CH_2Cl_2 (15 mL) was added portionwise over 15 minutes.

After 2 hours, the reaction was quenched via addition of a 10% NaOH solution in saturated NaCl (8 mL). After allowing the mixture to warm to 0˚C over 30 minutes Et_2O (40 mL) was added followed by $MgSO_4$ (5.5 g) and Celite (0.76 g) and the mixture allowed to warm to 10 ˚C over a further 30 minutes. Filtration of the solution through a pad of Celite and concentration of the crude gave a yellow oil whose NMR showed it to be approximately 2:1 epoxide:diene. The crude oil was purified via flash column chromatography to give epoxide **54** (2.97 g, 41% yield, 54% brsm, er> 95:5 by analysis of the corresponding Mosher esters) as a colorless oil. Some of the starting diene **53** (1.37 g, 22%) was also recovered.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.77 (ddd, *J* = 17.2, 10.5, 7.3 Hz, 1H), 5.50 (ddd, *J* = 17.2, 1.5, 0.8 Hz, 1H), 5.40 (ddd, *J* = 10.5, 1.5, 0.8 Hz, 1H), 3.74 (dd, *J* = 12.4, 4.3 Hz, 1H), 3.65 (dd, *J* = 12.4, 8.9 Hz, 1H), 3.57 (d, *J* = 7.3 Hz, 1H), 1.83 (dd, *J* = 8.9, 4.3 Hz, 1H), 1.30 (s, 3H).

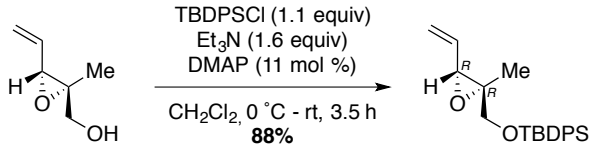
^{13}C-NMR (101 MHz; $CDCl_3$): δ 132.6, 121.2, 64.9, 62.9, 60.2, 14.4.

IR (neat) 3408, 2932, 1638, 1451, 1384, 1067, 986, 924, 871, 805, 696, 649 cm^{-1}.

HRMS (NSI) calculated for $C_6H_{10}O_2Na^+$ $[M+Na]^+$ 115.07536, found 115.07533.

$[\alpha]_D^{20}$ = +9.4 (CH_2Cl_2, *c* = 0.60).

Compound 55



54 **55**

To a 0 ˚C solution of epoxy alcohol **54** (2.64 g, 23.2 mmol) in CH_2Cl_2 (80 mL) was added Et_3N (5 mL, 36 mmol) followed by TBDPSCl (6.5 mL, 25 mmol) and DMAP (311 mg, 2.5 mmol). The mixture was allowed to warm to rt over 3.5 h and quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), the combined organics washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was purified via column chromatography eluting with 5/95 Et_2O/Hexanes to give silyl ether **55** as a clear oil (7.18 g, 88%).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.71-7.68 (m, 4H), 7.47-7.37 (m, 6H), 5.75 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.44 (ddd, *J* = 17.2, 1.6, 0.8 Hz, 1H), 5.36 (ddd, *J* = 10.5, 1.6, 0.7 Hz, 1H), 3.72-3.65 (dd, *J* = 16.1, 11.3 Hz, 2H), 3.35 (d, *J* = 7.2 Hz, 1H), 1.32 (s, 3H), 1.07 (s, 9H).

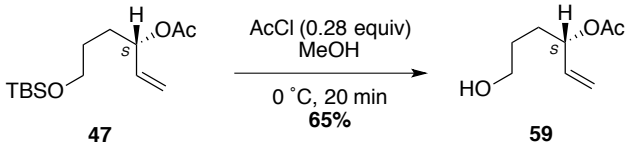
^{13}C-NMR (151 MHz, $CDCl_3$): δ 135.89, 135.80, 133.55, 133.49, 133.18, 129.95, 127.94, 127.93, 120.49, 77.44, 77.23, 77.02, 67.95, 62.97, 61.15, 27.01, 19.52, 14.52.

IR (neat) 3071, 2959, 2931, 2858, 1589, 1471, 1427, 1113, 702 cm^{-1}.

HRMS (NSI) calculated for $C_{22}H_{28}NaO_2Si^+$ $[M+Na]^+$ 375.17508, found 375.17436.

$[\alpha]_D^{20}$ = -3.8 (CH_2Cl_2, *c* = 0.95).

Compound 59



47 **59**

To a stirred solution of silane **47** (4.0 g, 17.3 mmol) in MeOH (30 mL) at 0˚ C was added AcCl (0.35 mL, 4.9 mmol) dropwise. After 20 minutes saturated aqueous $NaHCO_3$ (10 mL) was added, and the resulting suspension concentrated *in vacuo* to remove the MeOH. The remaining solution was extracted with Et_2O (3 x 20 mL), the combined organics washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a pale yellow oil. The oil was purified via column chromatography eluting with 70/30 Et_2O/Hexanes to give alcohol **59** (1.77 g, 65%) as a pale yellow oil.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.78 (ddd, *J* = 17.1, 10.6, 6.5 Hz, 1H), 5.29-5.24 (m, 2H), 5.18 (dt, *J* = 10.5, 1.1 Hz, 1H), 3.67 (q, *J* = 5.1 Hz, 2H), 2.07 (s, 3H), 1.77-1.54 (m, 5H).

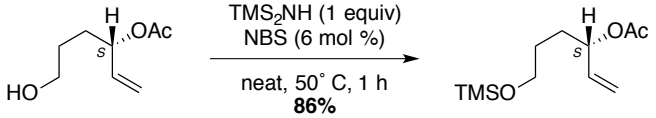
^{13}C-NMR (101 MHz; $CDCl_3$): δ 170.7, 136.4, 117.1, 74.7, 62.6, 30.7, 28.3, 21.5.

IR (neat) 3398, 2945, 2871, 1736, 1647, 1373, 1242 cm^{-1}.

HRMS (NSI) calculated for $C_8H_{14}O_3Na^+$ $[M+Na]^+$ 181.08352, found 181.08329.

$[\alpha]_D^{20}$ = -11.3 (CH_2Cl_2, *c* = 0.78).

Compound 70



59 **70**

To a neat mixture of alcohol **59** (646 mg, 4.1 mmol) and hexamethyldisilazane (0.85 mL, 4.1 mmol) was added NBS (44 mg, 0.25 mmol).[51] The mixture was heated to 50 ˚C for 1 h, diluted with pentane and filtered through a pad of SiO_2 (10 g) with 5/95 Et_2O/pentane (100 mL). The eluant was concentrated *in vacuo* to give silane **70** (813 mg, 86%) as a colorless oil.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 5.78 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H), 5.28-5.23 (m, 2H), 5.18 (dt, *J* = 10.5, 1.2 Hz, 1H), 3.61-3.57 (m, 2H), 2.07 (s, 3H), 1.68-1.66 (m, 2H), 1.59-1.54 (m, 2H), 0.11 (s, 9H).

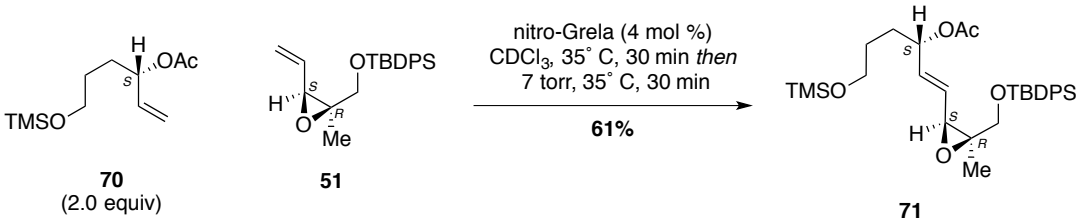
^{13}C-NMR (125 MHz; $CDCl_3$): δ 170.6, 136.7, 116.9, 74.8, 62.3, 30.8, 28.4, 21.5, -0.3.

IR (neat) 2956, 1741, 1371, 1249, 1095, 841 cm^{-1}.

HRMS (NSI) calculated for $C_{11}H_{22}O_3NaSi^+$ $[M+Na]^+$ 253.12304, found 253.12243.

$[\alpha]_D^{20}$ = -2.8 (CH_2Cl_2, *c* = 0.58).

Compound 71



70 (2.0 equiv) **51** **71**

To a solution of epoxide **51** (350 mg, 0.99 mmol) and the alkene **70** (464 mg, 2.01 mmol) in $CDCl_3$ (2 mL) was added nitro-Grela catalyst (24.3 mg, 0.036 mmol). The solution was stirred at 35 ˚C for 0.5 h, then concentrated *in vacuo* (~ 7 torr) at 35 ˚C for another 0.5 hours. The crude oil was chromatographed on SiO_2 eluting with 20/80 Et_2O/Hexanes to furnish the product **71** (335 mg, 0.60 mmol, 61%).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.46-7.38 (m, 6H), 5.75 (ddd, *J* = 15.6, 6.7, 0.9 Hz, 1H), 5.49 (ddd, *J* = 15.6, 6.8, 1.1 Hz, 1H), 5.22 (q, *J* = 6.3 Hz, 1H), 3.66-3.62 (m, 2H), 3.53-3.48 (m, 2H), 3.27 (d, *J* = 6.7 Hz, 1H), 2.00 (s, 3H), 1.61-1.43 (m, 7H), 1.07 (s, 9H), 0.10 (s, 9H).

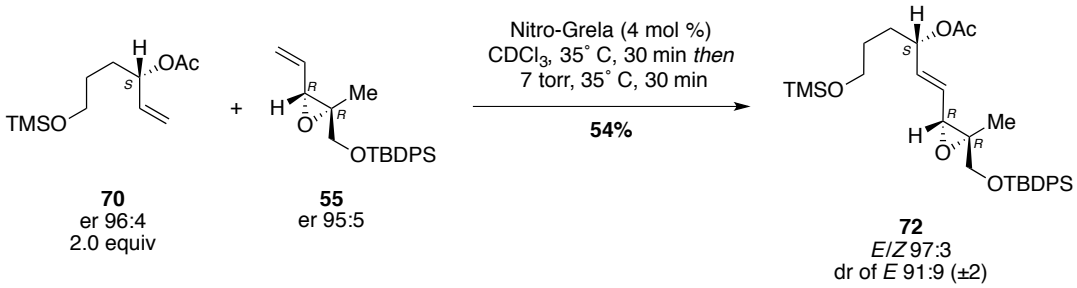
^{13}C-NMR (151 MHz; $CDCl_3$): δ 170.3, 135.85, 135.78, 134.4, 133.5, 133.3, 130.0, 127.93, 127.91, 126.9, 73.5, 65.2, 63.16, 63.14, 62.2, 30.9, 28.3, 27.0, 21.4, 20.1, 19.5, -0.3.

IR (neat) 2956, 2859, 1740, 1473, 1428, 1373, 1239, 1110, 841, 703 cm^{-1}.

HRMS (NSI) calculated for $C_{31}H_{47}O_5Si_2^+$ $[M+H]^+$ 555.29565, found 555.29546.

$[\alpha]_D^{20}$ = +0.1 (CH_2Cl_2, *c* = 0.48).

Compound 72



To a solution of epoxide **55** (260 mg, 0.74 mmol) and the alkene **70** (341 mg, 1.48 mmol) in $CDCl_3$ (2 mL) was added nitro-Grela catalyst (18.7 mg, 0.028 mmol). The solution was stirred at 35 ˚C for 0.5 h, then concentrated *in vacuo* (~ 7 torr) at 35 ˚C for another 0.5 hours. NMR of the crude mixture showed complete consumption of the epoxide. The crude oil was chromatographed on SiO_2 eluting with 20/80 Et_2O/Hexanes to furnish the product **72** (223 mg, 0.40 mmol, 54%).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m,4H), 5.80 (ddd, *J* = 15.6, 6.6, 0.8 Hz, 1H), 5.61 (ddd, *J* = 15.6, 6.9, 1.1 Hz, 1H), 5.32 (q, *J* = 6.3 Hz, 1H), 3.68 (dd, *J* = 16.9, 11.4 Hz, 2H), 3.60 (td, *J* = 6.4, 1.6 Hz, 2H), 3.36 (d, *J* = 6.9 Hz, 1H), 2.07 (s, 3H), 1.72-1.68 (m, 2H), 1.64-1.50 (m, 2H), 1.27 (s, 3H), 1.06 (s, 9H), 0.12 (s, 9H).

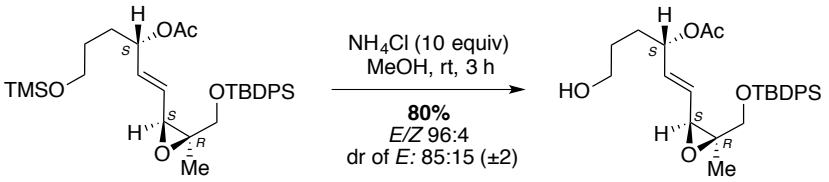
^{13}C-NMR (151 MHz; $CDCl_3$): δ 170.4, 135.88, 135.78, 134.3, 133.48, 133.39, 130.0, 127.94, 127.93, 127.5, 73.7, 67.5, 63.2, 62.3, 59.9, 31.8, 31.0, 28.4, 27.0, 21.4, 19.5, -0.3.

IR (neat) 2956, 2859, 1740, 1473, 1429, 1372, 1239 cm^{-1}.

HRMS (NSI) calculated for $C_{31}H_{47}O_5Si_2^+$ $[M+H]^+$ 555.29565, found 555.29594.

$[\alpha]_D^{20}$ = -9.7 (CH_2Cl_2, *c* = 0.59).

Compound 73



71 **73**

To a stirred solution of **71** (208 mg, 0.37 mmol) in MeOH (3.7 mL) at rt was added solid NH_4Cl (200 mg, 3.7 mmol). The mixture was stirred for 3 h and then the solvent removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g). The resulting eluant was concentrated *in vacuo* and the resulting oil purified by preparatory thin layer chromatography eluting with Et_2O to give **73** (143 mg, 0.296 mmol, 80%, *E*/*Z* 96:4, dr of *E* 85:15 (±2)) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.71-7.65 (m, 4H), 7.46-7.39 (m, 6H), 5.73 (ddd, *J* = 15.6, 6.8, 0.9 Hz, 1H), 5.52 (ddd, *J* = 15.6, 6.5, 1.1 Hz, 1H), 5.21 (q, *J* = 6.4 Hz, 1H), 3.65 (d, *J* = 1.8 Hz, 2H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.28 (d, *J* = 6.4 Hz, 1H), 2.01 (s, 3H), 1.64-1.58 (m, 1H), 1.56-1.51 (m, 1H), 1.49 (s, 3H), 1.48-1.40 (m, 2H), 1.07 (s, 9H).

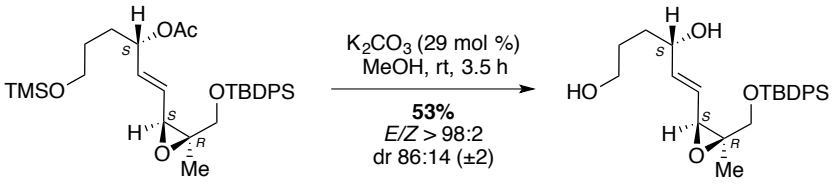
^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.37, 135.84, 135.75, 133.97, 133.52, 133.28, 129.96, 129.95, 127.92, 127.90, 127.16, 73.54, 65.15, 63.18, 62.98, 62.46, 30.75, 28.28, 26.94, 21.37, 20.04, 19.46.

IR (CH_2Cl_2): 3449, 3071, 2931, 2858, 1737, 1428, 1373, 1239, 1111, 704 cm^{-1}

HRMS (NSI, negative ion mode) calculated for $C_{28}H_{37}O_5Si^-$ $[M-H]^-$ 481.24157, found 481.24207.

$[\alpha]_D^{20}$ = -1.8 (CH_2Cl_2, *c* = 0.998).

Compound 74



71 **74**

To a stirred solution of **71** (92 mg, 0.16 mmol) in MeOH (2 mL) was added K_2CO_3 (6.4 mg, 0.046 mmol). The reaction was stirred at rt for 3.5 h and concentrated *in vacuo* to give a residue which was dissolved in Et_2O (5 mL). The resulting solution was washed with water (2 x 5 mL), brine (5 mL) and dried over Na_2SO_4. Concentration of the Et_2O solution gave a crude oil which was purified by preparatory thin layer chromatography eluting with 5/95 MeOH/CH_2Cl_2 to give diol **74** (37.1 mg, 0.084 mmol, 53%, *E*/*Z* > 98:2, dr 86:14 (±2)) as a viscous oil.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.44 (ddt, *J* = 9.4, 5.2, 1.8 Hz, 2H), 7.42-7.38 (m, 4H), 5.81 (ddd, *J* = 15.5, 6.2, 0.9 Hz, 1H), 5.43 (ddd, *J* = 15.5, 6.9, 1.3 Hz, 1H), 4.08-4.03 (m, 1H), 3.71-3.57 (m, 4H), 3.28 (d, *J* = 6.8 Hz, 1H), 2.21-1.92 (m, 2H), 1.64-1.52 (m, 4H), 1.51 (s, 3H), 1.06 (s, 9H).

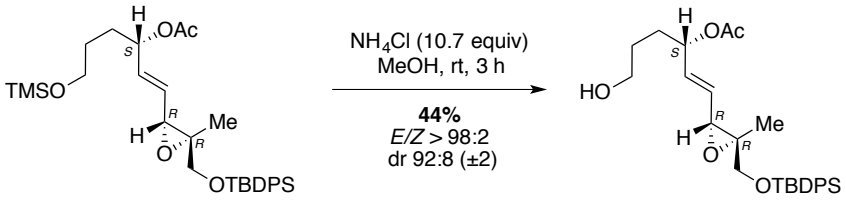
^{13}C-NMR (125 MHz; $CDCl_3$): δ 139.4, 135.88, 135.79, 133.50, 133.42, 130.0, 127.94, 127.93, 125.3, 72.1, 67.8, 66.1, 63.16, 63.09, 60.3, 34.4, 28.9, 27.0, 19.5, 15.5, 14.7.

IR (CH_2Cl_2) 3365, 3071, 2931, 2858, 1471, 1428, 1111, 703 cm^{-1}.

HRMS (NSI, negative ion mode) calculated for $C_{26}H_{35}O_4Si^-$ $[M-H]^-$ 439.23101, found 439.23144.

$[\alpha]_D^{20}$= +10.2 (CH_2Cl_2, *c* = 1.005).

Compound 75



72 **75**

To a stirred solution of **72** (78 mg, 0.14 mmol) in MeOH (1.4 mL) at rt was added solid NH_4Cl (80 mg, 1.5 mmol). The mixture was stirred for 3 h and then the solvent removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g) (NOTE: for this run some of the material was irretrievably spilled). The resulting eluant was concentrated *in vacuo* and the resulting oil purified by preparatory thin layer chromatography eluting with Et_2O to give **76** (29.9 mg, 0.296 mmol, 44%, *E*/*Z* >98:2, dr 92:8 (±2)) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m,4H), 5.81 (ddd, *J* = 15.6, 6.5, 0.8 Hz, 1H), 5.63 (ddd, *J* = 15.6, 6.8, 1.2 Hz, 1H), 5.34 (q, *J* = 6.7 Hz, 1H), 3.69-3.68 (m, 4H), 3.36 (d, *J* = 6.8 Hz, 1H), 2.07 (s, 3H), 1.78-1.70 (m, 2H), 1.66-1.59 (m, 2H), 1.42 (m, 1H), 1.28 (s, 3H), 1.07 (s, 9H).

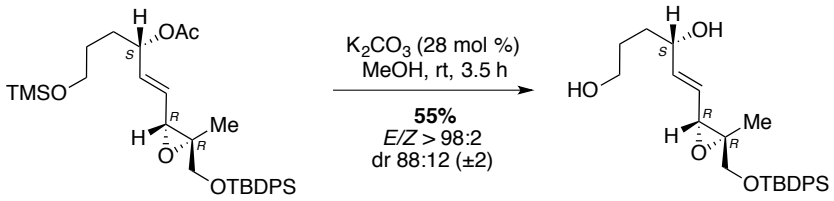
^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.48, 135.87, 135.77, 134.09, 133.49, 133.40, 129.96, 127.94, 127.93, 127.67, 73.61, 67.57, 63.19, 62.61, 59.81, 30.85, 28.39, 26.99, 21.41, 19.50, 14.47.

IR (CH_2Cl_2): 3425, 3071, 2931, 2858, 1737, 1427, 1239, 1112, 704 cm^{-1}.

HRMS (NSI) calculated for $C_{28}H_{39}O_5Si^+$ $[M+H]^+$ 483.25613, found 483.25649.

$[\alpha]_D^{20}$= -13.3 (CH_2Cl_2, *c* = 1.005).

Compound 76



72 **76**

To a stirred solution of **72** (97 mg, 0.17 mmol) in MeOH (2 mL) was added K_2CO_3 (6.5 mg, 0.047 mmol). The reaction was stirred at rt for 3.5 h and concentrated *in vacuo* to give a residue which was dissolved in Et_2O (5 mL). The resulting solution was washed with water (2 x 5 mL), brine (5 mL) and dried over Na_2SO_4. Concentration of the Et_2O solution gave a crude oil which was purified by preparatory thin layer chromatography eluting with Et_2O to give diol **76** (41.0 mg, 0.093 mmol, 55%, *E*/*Z* >98:2, dr 88:12 (±2)) as a viscous oil.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m,4H), 5.93 (ddd, *J* = 15.6, 5.9, 0.6 Hz, 1H), 5.62 (ddd, *J* = 15.5, 7.5, 1.3 Hz, 1H), 4.27-4.24 (m, 1H), 3.73-3.65 (m, 4H), 3.36 (d, *J* = 7.5 Hz, 1H), 2.34-2.33 (m, 1H), 2.02-1.89 (m, 1H), 1.77-1.63 (m, 4H), 1.32 (s, 3H), 1.07 (s, 9H).

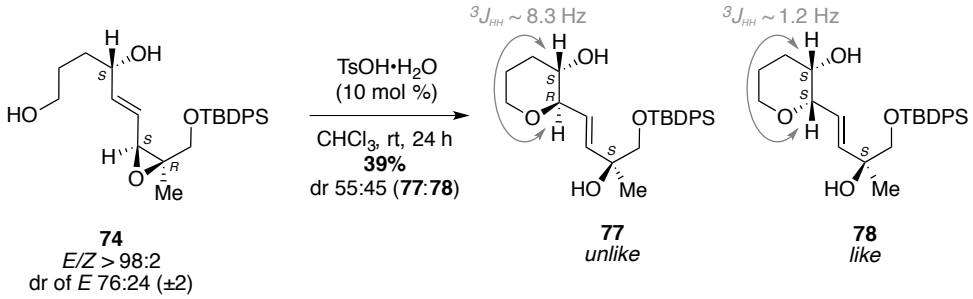
^{13}C-NMR (125 MHz; $CDCl_3$): δ 139.4, 135.88, 135.79, 133.50, 133.42, 130.0, 127.94, 127.93, 125.3, 72.1, 67.8, 66.1, 63.16, 63.09, 60.3, 34.4, 28.9, 27.0, 19.5, 15.5, 14.7.

IR (CH_2Cl_2) 3365, 3071, 2930, 2857, 1471, 1428, 1112, 703 cm^{-1}.

HRMS (NSI, negative ion mode) calculated for $C_{26}H_{35}O_4Si^-$ $[M-H]^-$ 439.23101, found 439.23146.

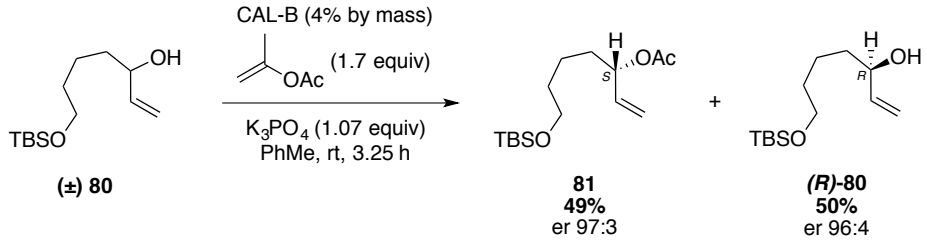
$[\alpha]_D^{20}$= +8.0 (CH_2Cl_2, *c* = 0.993).

Cyclization of 74 with TsOH•H_2O in $CHCl_3$



To a solution of diol **74** (39.5 mg, 0.090 mmol) in $CHCl_3$ (5 mL) was added a solution of TsOH•H_2O (1.4 mg, 0.007 mmol) in $CHCl_3$ (1 mL) at rt. The solution was stirred for 24 h and then concentrated *in vacuo*. NMR of the crude reaction mixture showed the presence of the *unlike* and *like* pyran diastereomers **77** and **78** in a ratio of 55:45. Column chromatography eluting with 50:50 EtOAc/hexanes gave a mixture of both diastereomers (15.5 mg, 0.035 mmol, 39%) as a colorless film. The identity of both products match those isolated from later palladium cyclization reactions (see pages 149 and 151).

Compound 81



To a solution of allyl alcohol **80**35 (17.3 g, 70.8 mmol) in toluene (175 mL) was added K_3PO_4 (16.9 g, 76 mmol), isopropenyl acetate (12 mL, 120 mmol) and CAL-B resin (733 mg). The mixture was stirred at rt for 3.25 h (whereupon an NMR aliquot showed ~50% conversion to the acetate) and filtered through a pad of Celite with Et_2O.

The solution was concentrated in vacuo and chromatographed eluting with 5/95 EtOAc/hexanes – 20/80 EtOAc/hexanes – EtOAc to give the (*S*)-acetate **81** (9.87 g, 34.5 mmol, 49%, er 97:3 by analysis of the Mosher esters following acetate removal) as a clear oil and (*R*)-alcohol **80** (8.62 g, 35.3 mmol, 50%, er 96:4 by analysis of the Mosher esters) as a yellow oil. The spectra and optical rotation of **81** match that described in the literature.[76]

^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.78 (ddd, *J* = 17.3, 10.6, 6.4 Hz, 1H), 5.25-5.22 (m,2H), 5.17 (dt, *J* = 10.5, 1.2 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.07 (s, 3H), 1.70-1.57 (m, 2H), 1.56-1.50 (m, 2H), 1.43-1.33 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H).

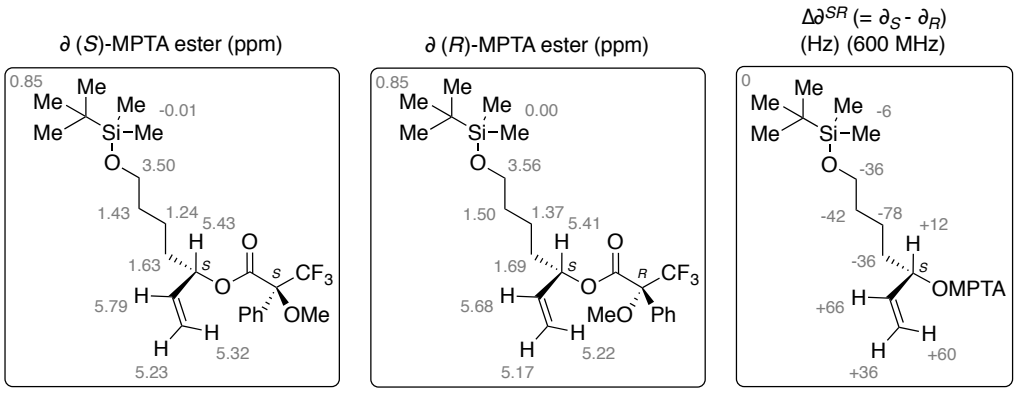
^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.56, 136.76, 116.80, 75.02, 63.10, 34.17, 32.72, 26.17, 21.66, 21.46, 18.56, -5.07.

HRMS (NSI) calculated for $C_{15}H_{31}O_3Si^+$ $[M+H]^+$ 287.20370, found 287.20405.

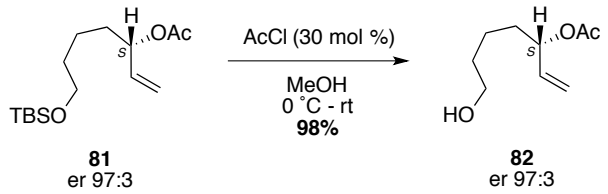
IR (CH_2Cl_2): 2951, 2930, 2858, 1741, 1472, 1371, 1238, 1099, 835, 775 cm^{-1}.

$[\alpha]_D^{20}$ = -2.6 (CH_2Cl_2, *c* = 1.3).

Mosher Ester Data[38]



Compound 81



81
er 97:3

82
er 97:3

To a cooled (0 ˚C) solution of crude **81** (7.91 g, 27.6 mmol) in MeOH (100 mL) was added AcCl (0.6 mL, 8.4 mmol). After 20 min the starting material was gone by TLC so saturated $NaHCO_3$ (20 mL) was added. The solution was concentrated *in vacuo* to remove the methanol. The aqueous layer was then extracted with Et_2O (5 x 50 mL). The combined organics were washed with brine (50 mL) dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. Flash chromatography eluting with 50/50 Et_2O/hexanes -> 75/25 Et_2O/hexanes -> Et_2O delivered alcohol **82** (4.67 g, 27.2 mmol, 98%, yellow oil).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 5.78 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H), 5.27-5.23 (m,2H), 5.18 (dt, *J* = 10.5, 1.2 Hz, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.07 (s, 3H), 1.72-1.56 (m, 4H), 1.46-1.38 (m, 2H), 1.29 (s, 1H).

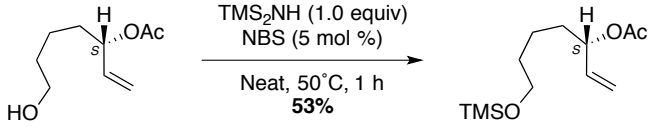
^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.61, 136.64, 116.96, 74.88, 62.93, 34.17, 32.63, 21.58, 21.47.

HRMS (NSI) calculated for $C_9H_{17}O_3^+$ $[M+H]^+$ 173.11722 found 173.11714.

IR (CH_2Cl_2): 3412, 3088, 2939, 2865, 1736, 1647, 1373, 1240, 1021 cm^{-1}.

$[\alpha]_D^{20}$ = -8.3 (CH_2Cl_2, *c* =1.00).

Compound 83



82
er 97:3

83
er 97:3

To a neat mixture of alcohol **82** (659 mg, 3.8 mmol) and hexamethyldisilazane (0.8 mL, 3.8 mmol) was added NBS (32 mg, 0.18 mmol).[51] The mixture was heated to 50 ˚C for 1 h, diluted with pentane (20 mL) and filtered through a pad of SiO_2 (10 g) with 5/95 Et_2O/pentane (100 mL) and then 10/90 Et_2O/pentane (100 mL). The eluant was concentrated *in vacuo* to give silane **83** (488 mg, 2.0 mmol, 53%) as colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.78 (ddd, *J* = 17.3, 10.5, 6.4 Hz, 1H), 5.26-5.22 (m,2H), 5.17 (dt, *J* = 10.5, 1.2 Hz, 1H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.07 (s, 3H), 1.70-1.59 (m, 2H), 1.58-1.52 (m, 2H), 1.42-1.32 (m, 2H), 0.11 (s, 9H).

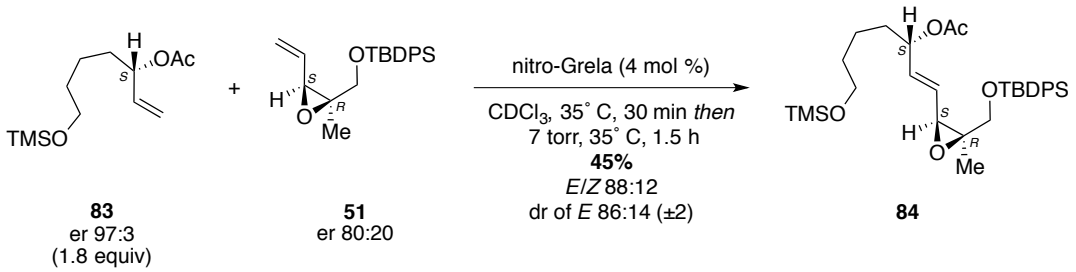
^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.55, 136.73, 116.84, 75.00, 62.56, 34.19, 32.61, 21.69, 21.46, -0.26.

HRMS (NSI) calculated for $C_{12}H_{25}O_3Si^+$ $[M+H]^+$ 245.15675, found 245.15647.

IR (CH_2Cl_2): 3088, 2953, 2863, 1741, 1648, 1371, 1240, 1097, 841 cm^{-1}.

$[\alpha]_D^{20}$ = -3.4 (CH_2Cl_2, *c* = 0.73).

Compound 84



83
er 97:3
(1.8 equiv)

51
er 80:20

84

To a solution of epoxide **51** (360 mg, 1.02 mmol) and the alkene **83** (455 mg, 1.86 mmol) in $CDCl_3$ (2 mL) was added nitro-Grela catalyst (29.4 mg, 0.044 mmol). The solution was stirred at 35 ˚C for 0.5 h, then concentrated *in vacuo* (~ 7 torr) at 35 ˚C for another 1.5 h. The crude oil was chromatographed on SiO_2 eluting with 10/90 to 20/80 Et_2O/Hexanes to furnish the product **84** (260 mg, 0.46 mmol, 45%, *E*/*Z* 88:12, dr of *E* 86:14 (±2)) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.46-7.42 (m, 2H), 7.42-7.38 (m, 4H), 5.74 (ddd, *J* = 15.6, 6.7, 0.9 Hz, 1H), 5.49 (ddd, *J* = 15.6, 6.8, 1.1 Hz, 1H), 5.19 (q, *J* = 6.4 Hz, 1H), 3.66-3.63 (m, 2H), 3.52 (td, *J* = 6.7, 1.4 Hz, 2H), 3.27 (d, *J* = 7.2 Hz, 1H), 2.00 (s, 3H), 1.59-1.41 (m, 7H), 1.33-1.21 (m, 2H), 1.07 (s, 9H), 0.10 (s, 9H).

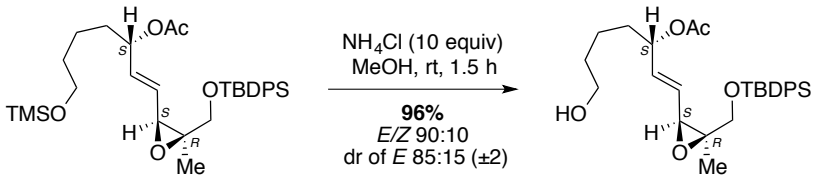
^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.33, 135.87, 135.79, 134.46, 133.54, 129.97, 127.94, 127.92, 126.86, 73.77, 65.22, 63.16, 63.14, 62.48, 34.30, 32.56, 26.99, 21.63, 21.40, 20.10, 19.51, -0.25.

HRMS (NSI) calculated for $C_{32}H_{49}O_5Si_2^+$ $[M+H]^+$ 569.31130, found 569.30923.

IR (CH_2Cl_2): 3072, 3050, 2955, 2932, 2859, 1740, 1676, 1589, 1463, 1372, 1239, 1111, 841, 703 cm^{-1}.

$[\alpha]_D^{20}$ = +0.2 (CH_2Cl_2, *c* = 0.77).

Compound 85



84
E/*Z* 88:12
dr of *E* 86:14 (±2)

85

To a stirred solution of **84** (157 mg, 0.28 mmol) in MeOH (2.8 mL) at rt was added solid NH_4Cl (148 mg, 2.8 mmol). The mixture was stirred for 1.5 h and then the solvent removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g). The resulting eluant was concentrated *in vacuo* give **85** (134 mg, 0.27 mmol, 96%, *E*/*Z* 90:10, dr of *E* 85:15 (±2)) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.46-7.43 (m, 2H), 7.42-7.39 (m, 4H), 5.73 (ddd, *J* = 15.6, 6.8, 0.9 Hz, 1H), 5.51 (ddd, *J* = 15.6, 6.6, 1.1 Hz, 1H), 5.19 (q, *J* = 6.9 Hz, 1H), 3.67-3.63 (m, 2H), 3.56 (t, *J* = 6.4 Hz, 2H), 3.27 (d, *J* = 7.1 Hz, 1H), 2.01 (s, 3H), 1.60-1.42 (m, 7H), 1.37-1.23 (m, 2H), 1.21-1.15 (m, 1H), 1.07 (s, 9H).

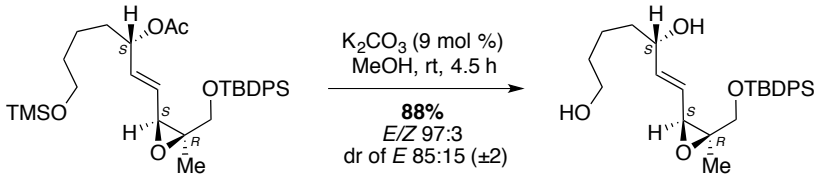
^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.39, 135.87, 135.79, 134.22, 133.56, 133.32, 129.97, 127.94, 127.02, 73.70, 65.20, 63.21, 63.06, 62.81, 34.23, 32.53, 26.97, 21.50, 21.41, 20.08, 19.50.

HRMS (NSI) calculated for $C_{29}H_{41}O_5Si^+$ $[M+H]^+$ 497.27178, found 497.27179.

IR (CH_2Cl_2): 3438, 3071, 3049, 2931, 2858, 1737, 1672, 1589, 1463, 1428, 1373, 1237, 1112, 824, 703 cm^{-1}.

$[\alpha]_D^{20}$ = -0.4 (CH_2Cl_2, *c* = 0.68).

Compound 86



84
E/*Z* 88:12
dr of *E* 86:14 (±2)

86

To a stirred solution of **84** (87 mg, 0.15 mmol) in MeOH (0.3 mL) was added K_2CO_3 (2 mg, 0.014 mmol). The reaction was stirred at rt for 4.5 h and the solvent removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g). The resulting eluant was concentrated *in vacuo* give **86** (60 mg, 0.132 mmol, 88%, *E*/*Z* 97:3, dr of *E* 85:15 (±2)) as a viscous, colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.73-7.65 (m, 4H), 7.46-7.43 (m, 2H), 7.43-7.38 (m, 4H), 5.80 (ddd, *J* = 15.5, 6.3, 0.8 Hz, 1H), 5.42 (ddd, *J* = 15.5, 7.0, 1.2 Hz, 1H), 4.00 (q, *J* = 6.3 Hz, 1H), 3.70 (d, *J* = 11.0 Hz, 1H), 3.66 (d, *J* = 11.0 Hz, 1H), 3.58 (t, *J* = 6.5 Hz, 2H), 3.28 (d, *J* = 7.0 Hz, 1H), 1.62-1.27 (m, 11H), 1.07 (s, 9H).

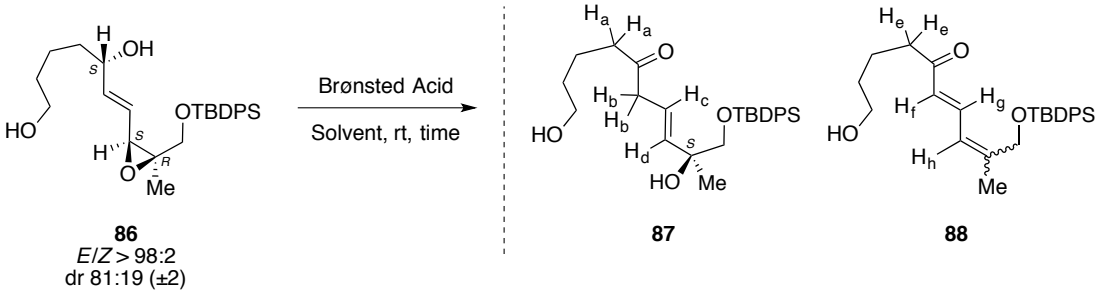
^{13}C-NMR (151 MHz, $CDCl_3$): δ 139.18, 135.86, 135.78, 133.65, 133.27, 129.98, 129.96, 127.92, 127.90, 124.85, 72.05, 65.27, 63.34, 63.13, 62.79, 36.71, 32.56, 26.96, 20.08, 19.49.

HRMS (NSI) calculated for $C_{27}H_{39}O_4Si^+$ $[M+H]^+$ 455.26121, found 455.26037.

IR (CH_2Cl_2): 3368, 3071, 3049, 2931, 2858, 1589, 1462, 1473, 1112, 824, 703 cm^{-1}.

$[\alpha]_D^{20}$ = +10.3 (CH_2Cl_2, *c* =1.09).

Details for Experiments Described in Table 1



86
E/*Z* > 98:2
dr 81:19 (±2)

87

88

Hydrogen	Solvent	Shift (ppm)	Multiplicity	Couplings (Hz)
Compound **87**				
H_a	$CDCl_3$	2.48	t	7.1
	d_6-Benzene	2.00	t	7.3
	d_3-MeCN	2.44	t	7.2
	d_8-THF	2.43	t	7.3
H_b	$CDCl_3$	3.14	dt	6.9, 1.6
	d_6-Benzene	2.77	d	6.7
	d_3-MeCN	3.12	dd	7.1, 1.3
	d_8-THF	3.10	dd	7.0, 1.2
H_c	$CDCl_3$	5.86	dt	15.6, 7.1
	d_6-Benzene	--	not resolvable	--
	d_3-MeCN	5.78	dt	15.7, 7.1
	d_8-THF	--	not resolvable	--
H_d	$CDCl_3$	5.60	dt	15.6, 1.4
	d_6-Benzene	--	not resolvable	--
	d_3-MeCN	5.63	dt	15.7, 1.4
	d_8-THF	5.71	dt	15.7, 1.4
Compound **88**				
H_e	$CDCl_3$	2.64	t	7.1
H_f	$CDCl_3$	6.21	d	15.3
H_g	$CDCl_3$	7.54	dd	15.2, 11.8
H_h	$CDCl_3$	6.43	d	10.8

$CDCl_3$/TsOH•H_2O (Table 1, entry 1)

To a solution of diol **86** (22.4 mg, 0.049 mmol) in $CDCl_3$ (0.7 mL) in a clean NMR tube was added a solution of TsOH•H_2O (0.58 mg, 0.0030 mmol) in $CDCl_3$ (0.1 mL). The reaction was monitored periodically by NMR, with ketone **87** being the major constituent after 4 d.

$CDCl_3$/(±)-CSA (Table 1, entry 2)

To a solution of diol **86** (20.2 mg, 0.044 mmol) in $CDCl_3$ (0.6 mL) in a clean NMR tube was added a solution of (±)-CSA (0.44 mg, 0.0018 mmol) in $CDCl_3$ (0.1 mL). The reaction was monitored periodically by NMR, with dienone **88** being the major species after 2 d.

d_6-Benzene/TsOH•H_2O (Table 1, entry 3)

A solution of diol **86** (16.2 mg, 0.036 mmol) in d_6-benzene (0.75 mL) was added to a vial charged with TsOH•H_2O (0.6 mg, 0.0031 mmol). The solution was gently swirled (the acid did not dissolve well) and transferred to a clean NMR tube. The reaction was monitored by NMR, with a complex mixture being observed after 2 h.

d_3-MeCN/TsOH•H_2O (Table 1, entry 4)

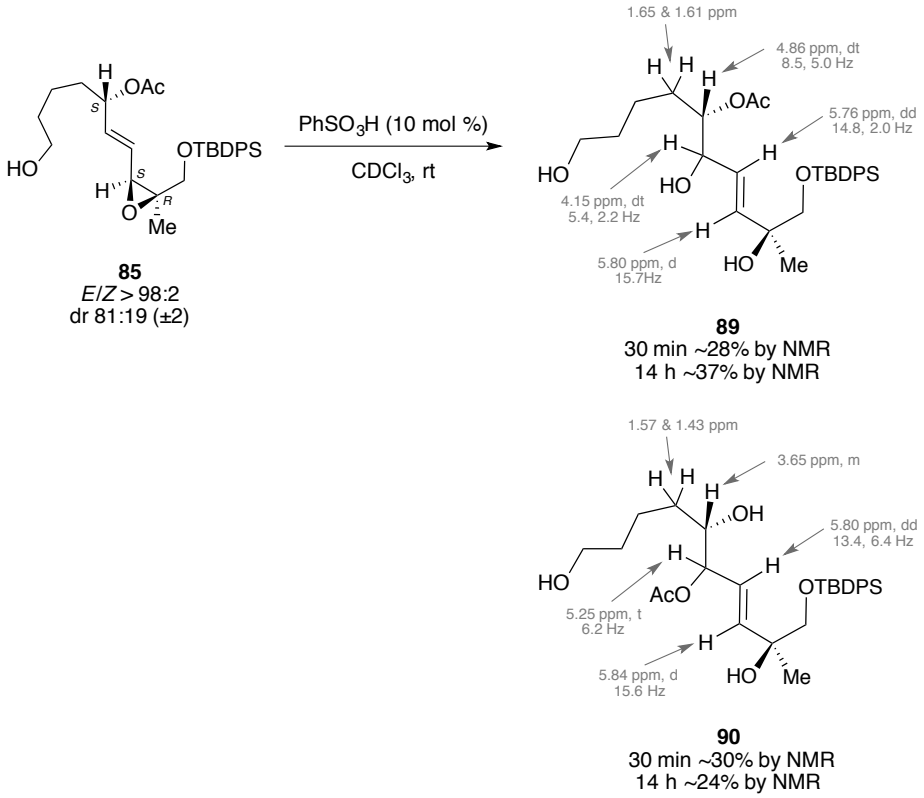
A solution of diol **86** (17.4 mg, 0.038 mmol) in d_3-MeCN (0.75 mL) was added to a vial charged with TsOH•H_2O (0.7 mg, 0.0037 mmol). The solution was shaken and transferred to a clean NMR tube. The reaction was monitored periodically by NMR, with some ketone **87** being detected after 2 h, and a intractable complex mixture seen after 15 h.

d_8-THF/TsOH•H_2O (Table 1, entry 5)

A solution of diol **86** (17.3 mg, 0.038 mmol) in d_8-THF (0.75 mL) was added to a vial charged with TsOH•H_2O (0.5 mg, 0.0026 mmol). The solution was shaken and transferred to a clean NMR tube. The reaction was monitored by NMR, with only small

amounts of **87** being detected after 2 h and 15 h. After 2 d, most of the starting material **86** was still present, with an elevated amount of **87**.

Reaction of 85 with TsOH•H_2O in d_8-THF (Scheme 33)



85
E/*Z* > 98:2
dr 81:19 (±2)

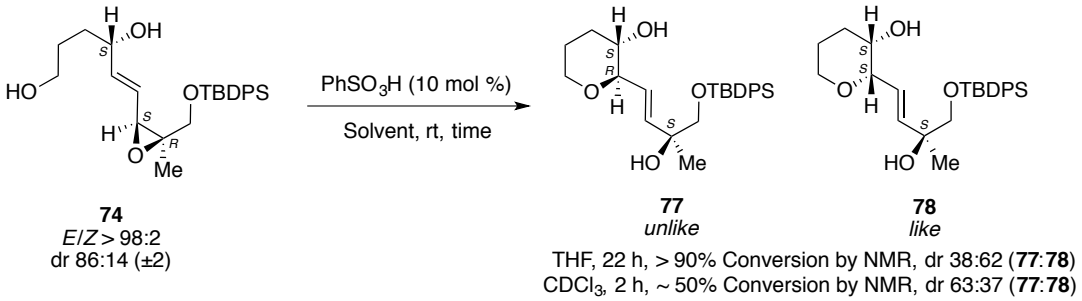
89
30 min ~28% by NMR
14 h ~37% by NMR

90
30 min ~30% by NMR
14 h ~24% by NMR

A solution of acetate **85** (10.4 mg, 0.022 mmol) in d_8-THF (0.75 mL) was added to a vial charged with TsOH•H_2O (1.2 mg, 0.0063 mmol). The solution was shaken and transferred to a clean NMR tube. The reaction monitored by NMR, with acetates **89** and **90** being observed after 2 d, their concentration being estimated using the *tert*-butyl group of the TBDPS as an internal standard. The diastereomeric ratios of **89** and **90** were obtained by fitting the olefinic signals at 5.9 and 5.97 ppm, respectively. Two-dimensional TLC (70:30 EtOAc/hexanes) of the reaction mixture (with heating between

dimensions) showed interconversion between two spots with R_f=0.28 and 0.2, consistent with intramolecular transacylation of triols **89** and **90**.

Cyclization of 74 with $PhSO_3H$ in THF & $CDCl_3$ (Scheme 29)



Reaction conducted in THF

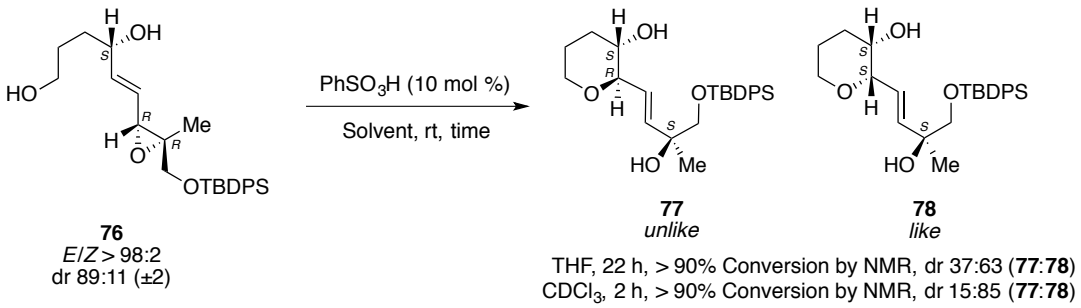
A solution of diol **74** (13.7 mg, 0.031 mmol) in THF (0.5 mL) was added to a flask charged with anhydrous $PhSO_3H$ (0.5 mg, 0.0032 mmol). The solution was stirred at rt for 22 h whereupon TLC showed complete consumption of **74**. The mixture was concentrated *in vacuo* and analyzed by NMR. The diastereomeric ratio was determined by integration and the identity of both products match those isolated from later palladium cyclization reactions (see pages 149 and 151).

Reaction conducted in $CDCl_3$

To a solution of diol **74** (10.3 mg, 0.023 mmol) in $CDCl_3$ (0.8 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.36 mg, 0.0023 mmol) in $CDCl_3$ (0.1 mL). The reaction was monitored by NMR. After 2 h the reaction had gone to ~50% completion. The diastereomeric ratio was determined by integration and the identity of

both products match those isolated from later palladium cyclization reactions see pages 149 and 151. Prolonged reaction gave dienal **97** as described in Scheme 30.

Cyclization of 76 with $PhSO_3H$ in THF & $CDCl_3$ (Scheme 29)



Reaction conducted in THF

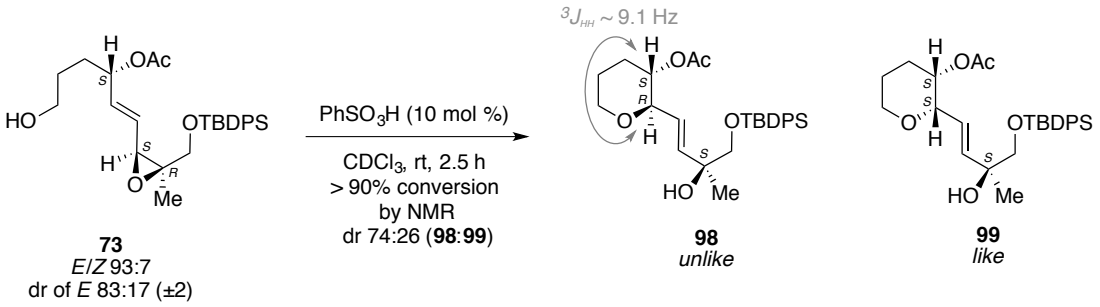
A solution of diol **76** (10.5 mg, 0.024 mmol) in THF (0.4 mL) was added to a flask charged with anhydrous $PhSO_3H$ (0.4 mg, 0.0025 mmol). The solution was stirred at rt for 22 h whereupon TLC showed total consumption of **76**. The mixture was concentrated *in vacuo* and analyzed by NMR. The diastereomeric ratio was determined by integration and the identity of both products match those isolated from later palladium cyclization reactions (see pages 149 and 151).

Reaction conducted in $CDCl_3$

To a solution of diol **76** (12.9 mg, 0.029 mmol) in $CDCl_3$ (0.8 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.46 mg, 0.0029 mmol) in $CDCl_3$ (0.1 mL). The reaction was monitored by NMR. After 2 h the reaction had gone to >90% completion (by integration with respect to the TBDPS *tert*-butyl group). The diastereomeric ratio was determined by integration and the identity of both products

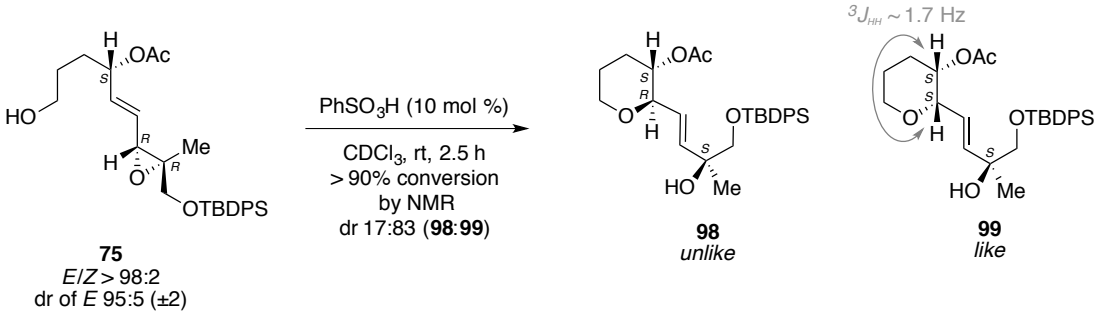
match those isolated from later palladium cyclization reactions (see pages 149 and 151). Prolonged reaction gave dienal **97** as described in Scheme 30.

Cyclization of 73 with $PhSO_3H$ in $CDCl_3$ (Scheme 31)



To a solution of acetate **73** (14.0 mg, 0.029 mmol) in $CDCl_3$ (0.5 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.44 mg, 0.0028 mmol) in $CDCl_3$ (0.2 mL). The reaction was monitored by NMR. After 2.5 h the reaction had gone to >90% completion (by integration with respect to the TBDPS *tert*-butyl group). The diastereomeric ratio was determined by integration and the identity of both products match those isolated from later palladium cyclization reactions (see pages 143 and 146).

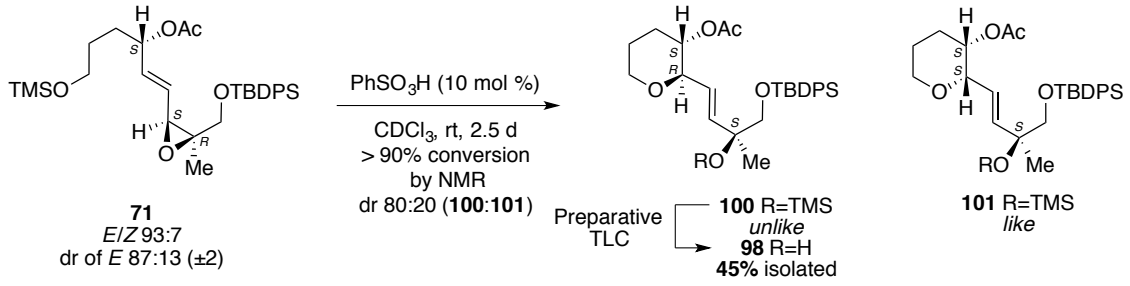
Cyclization of 75 with $PhSO_3H$ in $CDCl_3$ (Scheme 31)



To a solution of acetate **75** (13.2 mg, 0.027 mmol) in $CDCl_3$ (0.5 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.44 mg, 0.0028 mmol) in $CDCl_3$ (0.2 mL).

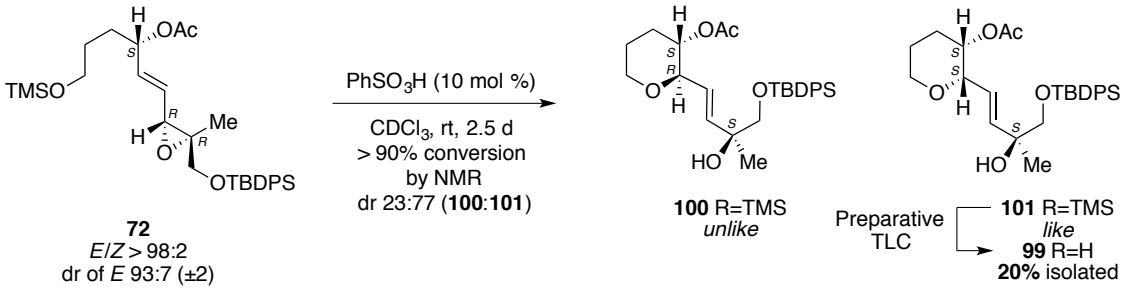
The reaction was monitored by NMR. After 2.5 h the reaction had gone to >90% completion (by integration with respect to the TBDPS *tert*-butyl group). The diastereomeric ratio was determined by integration and the identity of both products match those isolated from later palladium cyclization reactions (see pages 143 and 146).

Cyclization of 71 with $PhSO_3H$ in $CDCl_3$ (Scheme 32)



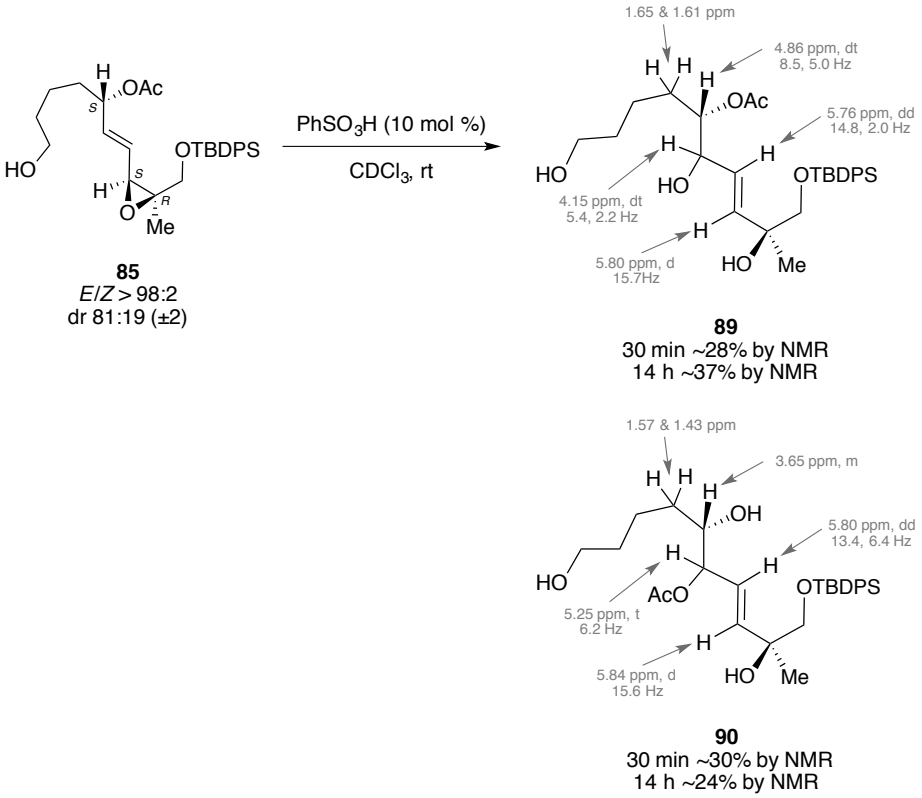
To a solution of **71** (12.6 mg, 0.023 mmol) in $CDCl_3$ (0.5 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.36 mg, 0.0023 mmol) in $CDCl_3$ (0.3 mL). The reaction was monitored by NMR. After 2.5 d the reaction had gone to >90% completion (by integration with respect to the TBDPS *tert*-butyl group). The diastereomeric ratio was determined by integration. The crude was purified *via* column chromatography eluting with Et_2O to give TMS-desilylated *unlike* **98** (5.7 mg, 0.010 mmol, 45%) as a colorless oil. The spectrum of *unlike* **98** matches that isolated from a later palladium cyclization reaction (see page 143).

Cyclization of 72 with $PhSO_3H$ in $CDCl_3$ (Scheme 32)



To a solution of **72** (12.8 mg, 0.023 mmol) in $CDCl_3$ (0.5 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.36 mg, 0.0023 mmol) in $CDCl_3$ (0.3 mL). The reaction was monitored by NMR. After 2.5 d the reaction had gone to >90% completion (by integration with respect to the TBDPS *tert*-butyl group). The crude was purified *via* column chromatography eluting with Et_2O to give TMS-desilylated *like* **99** (2.6 mg, 0.0047 mmol, 20%) as a colorless oil. The spectrum of *like* **99** matches that obtained from a later palladium cyclization reaction (see page 146).

Reaction of 83 with $PhSO_3H$ in $CDCl_3$ (Scheme 33)



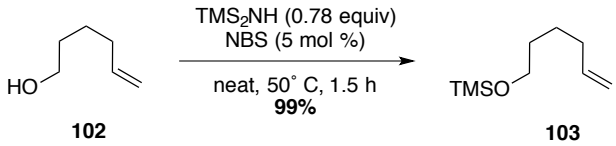
85
E/*Z* > 98:2
dr 81:19 (±2)

89
30 min ~28% by NMR
14 h ~37% by NMR

90
30 min ~30% by NMR
14 h ~24% by NMR

To a solution of **85** (7.7 mg, 0.016 mmol) in $CDCl_3$ (0.5 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.24 mg, 0.0015 mmol) in $CDCl_3$ (0.1 mL). The reaction monitored by NMR, with acetates **89** and **90** being observed after only 30 min, their concentration again being estimated using the *tert*-butyl group of the TBDPS as an internal standard. After 14 h both species were still present, with **89** present in higher concentration. The diastereomeric ratios could not be determined in $CDCl_3$, unlike when the reaction was performed in d_8-THF.

Compound 103



To a neat mixture of alcohol **102** (7.0 mL, 52 mmol) and hexamethyldisilazane (8.5 mL, 40.7 mmol) was added NBS (461 mg, 2.6 mmol).[51] The mixture was heated to 50 ˚C for 1.5 h, diluted with pentane and filtered through a pad of SiO_2 (20 g) with pentane (200 mL). The eluant was concentrated in vacuo at 20 ˚C to give silane **103** (8.89 g, 51.6 mmol, 99%) as colorless liquid.

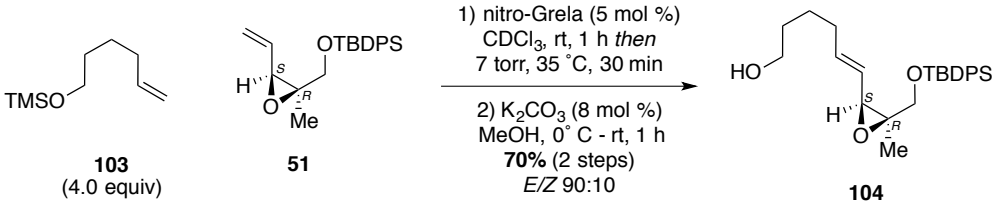
^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.01 (ddt, *J* = 17.1, 2.1, 1.6 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.08 (q, *J* = 7.1 Hz, 2H), 1.58-1.53 (m, 2H), 1.46-1.41 (m, 2H), 0.12 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 139.08, 114.63, 62.71, 33.76, 32.39, 25.39, -0.24.

IR (neat): 3078, 2934, 2861, 1641, 1439, 1386, 1250, 1095, 835 cm^{-1}.

HRMS (APCI) calculated for $C_9H_{21}OSi^+$ $[M+H]^+$ 173.13562, found 173.13528.

Compound 104



To a solution of epoxide **51** (349 mg, 0.99 mmol) and the alkene **103** (683 mg, 3.96 mmol) in $CDCl_3$ (2 mL) was added nitro Grela catalyst (21 mg, 0.051 mmol). The solution was stirred at rt under active argon flow for 1 h, then concentrated *in vacuo* at 35

˚C for 0.5 hours. The resulting oil was chromatographed on SiO_2 eluting with 5/95 Et_2O/Hexanes to furnish the trimethylsilyl-protected cross product (361 mg, 0.73 mmol). The oil was dissolved in MeOH (1.4 mL) and cooled to 0 ˚C whereupon K_2CO_3 (11.2 mg, 0.081 mmol) was added. After 1 h, the reaction mixture was concentrated *in vacuo*, diluted with Et_2O and filtered through a small pipette containing SiO_2 (~1 g). The resulting solution was concentrated *in vacuo* to give **104** (293 mg, 70 % yield over 2 steps, *E*/*Z* 90:10) as a clear oil.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.70-7.66 (m, 4H), 7.46-7.37 (m, 6H), 5.82 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.21 (ddt, *J* = 15.4, 7.5, 1.4 Hz, 1H), 3.67 (dd, *J* = 26.7, 10.9 Hz, 2H), 3.60 (q, *J* = 5.7 Hz, 2H), 3.25 (d, *J* = 7.4 Hz, 1H), 2.03 (q, *J* = 7.3 Hz, 2H), 1.54-1.50 (m, 2H), 1.41-1.35 (m, 2H), 1.19-1.17 (m, 1H), 1.07 (s, 9H).

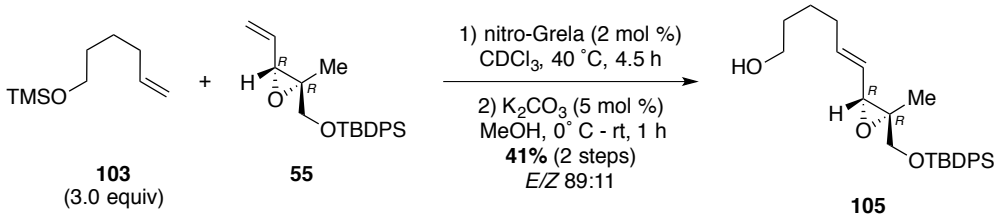
^{13}C-NMR (101 MHz; $CDCl_3$): δ 137.3, 135.86, 135.79, 133.6, 133.4, 129.92, 129.91, 127.90, 127.87, 124.6, 65.5, 64.1, 62.93, 62.86, 32.4, 27.0, 25.2, 20.2, 19.5.

IR (neat) 3419, 3070, 2932, 2858, 1472, 1428, 1111, 703 cm^{-1}.

HRMS (NSI) calculated for $C_{26}H_{36}NaO_3Si^+$ $[M+Na]^+$ 447.23259, found 447.23192.

$[\alpha]_D^{20}$ = +10.6 (CH_2Cl_2, *c* = 0.53).

Compound 101



103 (3.0 equiv) **55** **105**

To a solution of epoxide **55** (1.72 g, 4.9 mmol) and the alkene **103** (2.52 g, 14.6 mmol) in $CDCl_3$ (10 mL) was added nitro-Grela catalyst (34 mg, 0.051 mmol). The solution was heated to 40 ˚C for 1 h, whereupon NMR of a small aliquot indicated 60% conversion to the desired product. At 1.5 hours, a solution of additional nitro Grela catalyst (36 mg, 0.054 mmol) in $CDCl_3$ was added. At 3.5 hours, NMR of an aliquot showed the presence of ethylene (singlet ca. 5.4 ppm) dissolved in the reaction mixture. Argon was then bubbled through the reaction mixture to displace the ethylene, with an aliquot at 4.5 h showing *ca*. 67% conversion to the desired product. The reaction mixture was thus concentrated *in vacuo* and the resulting oil chromatographed eluting with 5/95 Et_2O/Hexanes to furnish the trimethylsilyl-protected cross product (996 mg, 2.0 mmol). This product was immediately dissolved in MeOH (4 mL) and cooled to 0 ˚C whereupon K_2CO_3 (32 mg, 0.23 mmol) was added. After 1 h, the reaction mixture was concentrated *in vacuo*, diluted with Et_2O and filtered through a small pipette containing SiO_2 (~1 g). The resulting solution was concentrated *in vacuo* to give **105** (879 mg, 41% yield over 2 steps, *E*/*Z* 89:11) as a clear oil.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.69-7.68 (m, 4H), 7.45-7.38 (m,6H), 5.88 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.36 (dd, *J* = 15.4, 7.9 Hz, 1H), 3.69-3.63 (m, 4H), 3.30 (d, *J* = 7.8 Hz, 1H),

2.15 (q, *J* = 7.2 Hz, 2H), 1.63-1.58 (m, 2H), 1.53-1.47 (m, 2H), 1.33 (s, 3H), 1.25-1.22 (m, 1H), 1.07 (s, 9H).

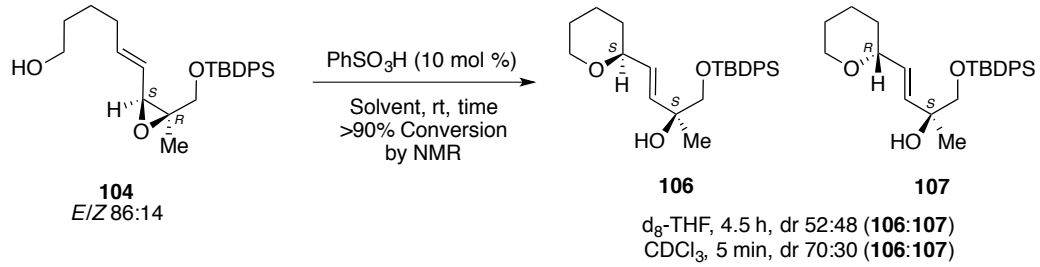
^{13}C-NMR (101 MHz; $CDCl_3$): δ 137.7, 135.88, 135.79, 133.54, 133.50, 129.9, 127.92, 127.90, 125.1, 68.0, 62.99, 62.86, 61.1, 32.51, 32.40, 27.0, 25.4, 19.5, 14.7.

IR (neat) 3392, 3071, 2931, 2858, 1590, 1472, 1427, 1112, 703 cm^{-1}.

HRMS (NSI) calculated for $C_{26}H_{36}NaO_3Si$ $[M+Na]^+$ 447.23259, found 447.23194.

$[\alpha]_D^{20}$ = +5.4 (CH_2Cl_2, *c* = 0.65).

Cyclization of 100 with $PhSO_3H$ in THF & in $CDCl_3$ (Scheme 36)



104
E/*Z* 86:14

106 **107**

d_8-THF, 4.5 h, dr 52:48 (**106**:**107**)
$CDCl_3$, 5 min, dr 70:30 (**106**:**107**)

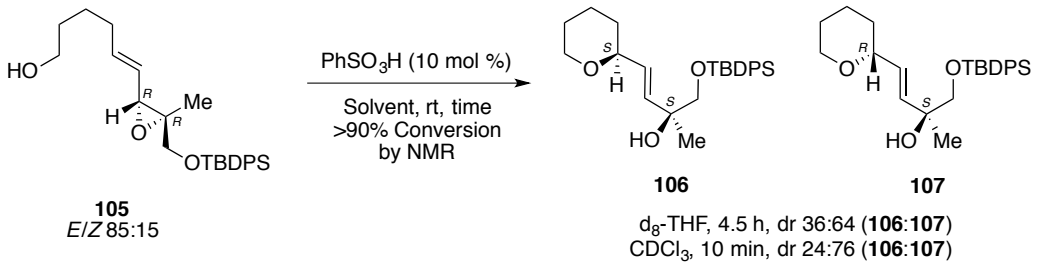
Reaction conducted in THF

To a flask charged with alkene **104** (11.4 mg, 0.027 mmol) was added a solution of anhydrous $PhSO_3H$ (0.47 mg, 0.0030 mmol) in THF (0.25 mL). The solution was stirred at rt for 4.5 h whereupon TLC showed total consumption of **104**. The mixture was concentrated *in vacuo* and analyzed by NMR. The diastereomeric ratio was determined by integration and the identity of both products match those isolated from later palladium cyclization reactions (see pages 138 and 139).

Reaction conducted in $CDCl_3$

To a solution of alkene **104** (10.8 mg, 0.025 mmol) in $CDCl_3$ (0.5 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.40 mg, 0.0025 mmol) in $CDCl_3$ (0.18 mL). The reaction was monitored by NMR. After 5 min the reaction had gone to >90% completion (by integration with respect to the TBDPS *tert*-butyl group). The diastereomeric ratio was determined by integration and the identity of both products match those isolated from later palladium cyclization reactions (see pages 138 and 139). Prolonged exposure to the reaction conditions resulted in formation of enal **112** as described in section 1.5.8.1.

Cyclization of 101 with $PhSO_3H$ in THF & $CDCl_3$ (Scheme 36)



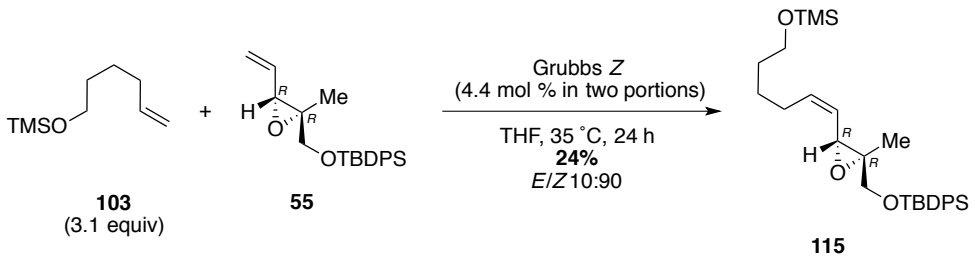
Reaction conducted in THF

To a flask charged with alkene **105** (8.8 mg, 0.022 mmol) was added a solution of anhydrous $PhSO_3H$ (0.38 mg, 0.0024 mmol) in THF (0.20 mL). The solution was stirred at rt for 4.5 h whereupon TLC showed complete consumption of **105**. The mixture was concentrated *in vacuo* and analyzed by NMR. The diastereomeric ratio was determined by integration and the identity of both products match those isolated from later palladium cyclization reactions (see pages 138 and 139).

Reaction conducted in $CDCl_3$

To a solution of alkene **105** (8.3 mg, 0.020 mmol) in $CDCl_3$ (0.5 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.31 mg, 0.0020 mmol) in $CDCl_3$ (0.14 mL). The reaction was monitored by NMR. After 10 min the reaction had gone to >90% completion (by integration with respect to the TBDPS *tert*-butyl group). The diastereomeric ratio was determined by integration and the identity of both products match those isolated from later palladium cyclization reactions (see pages 138 and 139). Prolonged exposure to the reaction conditions resulted in formation of enal **112** as described in Scheme 37.

Compound 115



103 (3.1 equiv) **55** **115**

To a stirred solution of epoxide **55** (366 mg, 1.04 mmol) and alkene **103** (550 mg, 3.2 mmol) in THF (2 mL) was added Grubbs Z Catalyst[33] ([2-(1-Methylethoxy-*O*)phenylmethyl-*C*](nitrato-*O,O'*){*rel*-(2*R*,5*R*,7*S*)-tricyclo[3.3.1.13,7]decane-2,1-diyl[3-(2,4,6-trimethylphenyl)-1-imidazolidinyl-2-ylidene]}ruthenium) (15.4 mg, 0.024 mmol). The solution was heated at 35 ˚C for 5 h whereupon a solution of Grubbs Z (13.6 mg, 0.021 mmol) in THF (1 mL) was added. The solution was stirred at 35 ˚C for another 19 h and then concentrated in vacuo. Chromatography of the resulting oil eluting with 5/95 Et_2O/hexanes gave alkene **115** (124 mg, 0.25 mmol, 24%, *E*/*Z* 90:10) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.70-7.66 (m, 4H), 7.46-7.42 (m, 2H), 7.42-7.38 (m, 4H), 5.77 (dtd, *J* = 11.1, 7.6, 1.0 Hz, 1H), 5.29 (ddt, *J* = 11.2, 8.2, 1.5 Hz, 1H), 3.71-3.67 (m, 2H), 3.65 (dd, *J* = 8.1, 0.9 Hz, 1H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.27-2.14 (m, 2H), 1.59-1.54 (m, 2H), 1.50-1.43 (m, 2H), 1.33 (s, 3H), 1.08 (s, 9H), 0.11 (s, 9H).

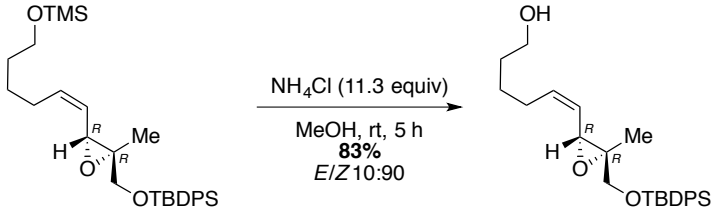
^{13}C-NMR (151 MHz, $CDCl_3$): δ 137.22, 135.86, 135.80, 133.56, 133.48, 129.93, 127.93, 127.92, 124.65, 68.03, 62.69, 62.62, 56.69, 32.50, 27.90, 27.00, 26.08, 19.53, 15.05, -0.24.

HRMS (NSI) calculated for $C_{29}H_{45}O_3Si_2^+$ $[M+H]^+$ 497.29017, found 497.28976.

IR (CH_2Cl_2): 3071, 3049, 2999, 2931, 2896, 2858, 1590, 1473, 1428, 1250, 1113, 841, 702 cm^{-1}.

$[\alpha]_D^{20}$ = -10.5 (CH_2Cl_2, *c* = 0.84).

Compound 116



115 **116**

To a stirred solution of **115** (83 mg, 0.16 mmol) in MeOH (2 mL) at rt was added solid NH_4Cl (97 mg, 1.8 mmol). The mixture was stirred for 5 h and then the solvent removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g). The resulting eluant was

concentrated *in vacuo* and then chromatographed eluting with 50/50 Et_2O/hexanes to 75/25 Et_2O/hexanes to give **116** (56 mg, 0.13 mmol, 83%, *E*/*Z* 10:90) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.70-7.68 (m, 4H), 7.46-7.43 (m, 2H), 7.42-7.38 (m, 4H), 5.78 (dtd, *J* = 11.1, 7.6, 0.9 Hz, 1H), 5.31 (ddt, *J* = 11.1, 8.1, 1.5 Hz, 1H), 3.72-3.67 (m, 2H), 3.67-3.64 (m, 3H), 2.29-2.16 (m, 2H), 1.63-1.57 (m, 2H), 1.53-1.48 (m, 2H),1.33 (s, 3H), 1.30 (s, 1H), 1.08 (s, 9H).

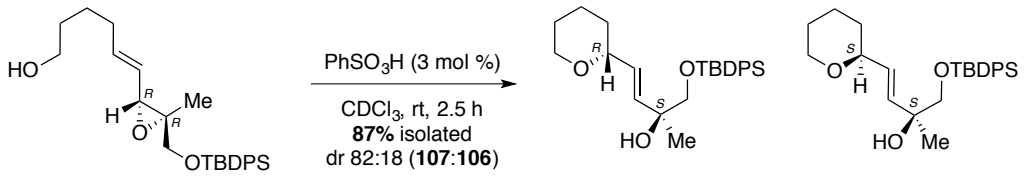
^{13}C-NMR (151 MHz, $CDCl_3$): δ 137.00, 135.85, 135.78, 133.54, 133.46, 129.94, 127.93, 127.91, 124.84, 67.97, 62.91, 62.70, 56.69, 32.41, 27.80, 26.99, 25.87, 19.53, 15.06.

HRMS (NSI) calculated for $C_{26}H_{37}O_3Si^+$ $[M+H]^+$ 425.25065, found 425.25095.

IR (CH_2Cl_2): 3405,3071, 2048, 2998, 2931, 2858, 1589, 1462, 1428, 1113, 823, 702 cm^{-1}.

$[\alpha]_D^{20}$ = -13.4 (CH_2Cl_2, *c* = 1.19).

NMR Study of the Cyclization of 105 with $PhSO_3H$ in $CDCl_3$ (Scheme 39)

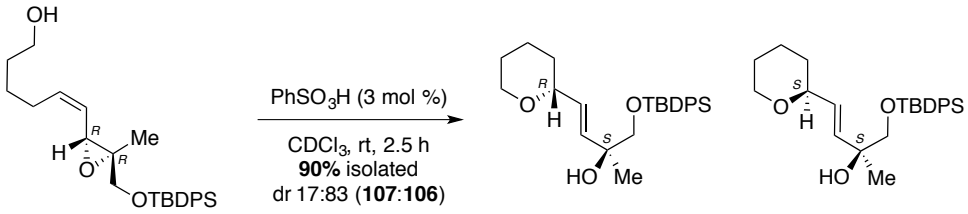


105 *E/Z* 89:11 **107** **106**

To a solution of alkene **105** (10.3 mg, 0.025 mmol) in $CDCl_3$ (0.6 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.12 mg, 0.00075 mmol) in $CDCl_3$ (0.1 mL). The reaction was monitored by NMR every 5 minutes over 2.5 h whereupon the starting material **101** was fully consumed. The reaction was poured over solid $NaHCO_3$ (~50 mg) and filtered through a small plug of SiO_2 eluting with Et_2O to give the pyrans

106 and **107** as a mixture of diastereomers (8.9 mg, 0.022 mmol, 87%) as a colorless film. The identity of both products match those isolated from later palladium cyclization reactions (see pages 138 and 139).

NMR Study of the Cyclization of 116 with $PhSO_3H$ in $CDCl_3$ (Scheme 39)



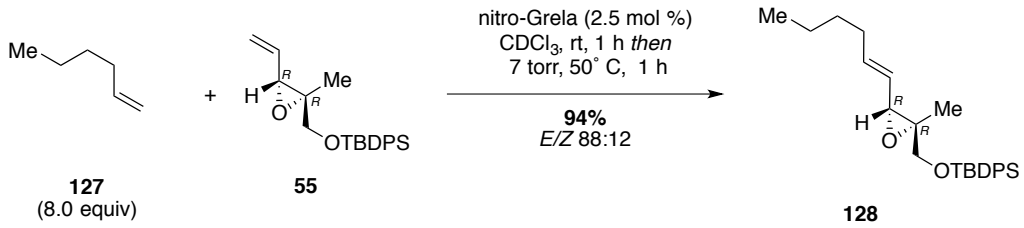
116
E/Z 10:90

107

106

To a solution of alkene **116** (10.3 mg, 0.025 mmol) in $CDCl_3$ (0.6 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.12 mg, 0.00075 mmol) in $CDCl_3$ (0.1 mL). The reaction was monitored by NMR every 5 minutes over 3.5 hours whereupon the starting material **116** was consumed. The reaction was poured over solid $NaHCO_3$ (~50 mg) and filtered through a small plug of SiO_2 eluting with Et_2O to give the pyrans **106** and **107** as a mixture of diastereomers (9.3 mg, 0.023 mmol, 90%) as a colorless film. The identity of both products match those isolated from later palladium cyclization reactions (see pages 138 and 139).

Compound 128



To a solution of epoxide **55** (352 mg, 1.0 mmol) and 1-hexene **127** (1.00 mL, 8.0 mmol) in $CDCl_3$ (1 mL) was added nitro-Grela catalyst (17.2 mg, 0.026 mmol). The solution was concentrated *in vacuo* (~7 torr) at 50 ˚C for 1 h. The resulting oil was passed through a plug of SiO_2 (10 g) eluting with 5/95 Et_2O/hexanes (100 mL) and the eluent concentrated *in vacuo* to give alkene **128** as a thick oil (385 mg, 0.94 mmol, 94%, *E*/*Z* 88:12).

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.71-7.66 (m, 4H), 7.46-7.42 (m, 2H), 7.42-7.38 (m, 4H), 5.88 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.34 (ddt, *J* = 15.4, 7.9, 1.5 Hz, 1H), 3.67 (app. q, *J* = 11.2 Hz, 2H), 3.30 (d, *J* = 7.9 Hz, 1H), 2.11 (qd, *J* = 7.3, 1.2 Hz, 2H), 1.43-1.31 (m, 7H), 1.07 (s, 9H), 0.92 (t, *J* = 7.2 Hz, 3H).

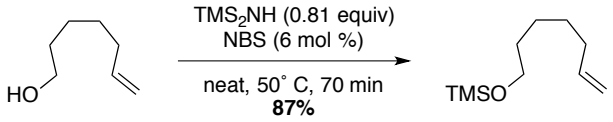
^{13}C-NMR (151 MHz, $CDCl_3$): δ 138.08, 135.68, 135.60, 133.39, 133.35, 129.69, 127.70, 127.68, 124.36, 67.95, 62.59, 61.05, 32.29, 31.16, 26.80, 22.19, 19.31, 14.52, 13.91.

HRMS (NSI) calculated for $C_{26}H_{37}O_2Si^+$ $[M+H]^+$ 409.25683, found 409.25592.

IR (CH_2Cl_2): 2071, 2049, 2998, 2957, 2929, 2857, 1665, 1589, 1472, 1428, 1112, 823, 701 cm^{-1}.

$[\alpha]_D^{20}$ = +6.5 (CH_2Cl_2, *c* = 1.03).

Compound 132



131 **132**

To a neat mixture of alcohol **131** (1.71 g, 14.9 mmol) and hexamethyldisilazane (2.5 mL, 12.0 mmol) was added NBS (158 mg, 0.9 mmol).[51] The mixture was heated to 50 ˚C for 70 min, diluted with pentane and filtered through a pad of SiO_2 (10 g) with pentane (200 mL). The eluant was concentrated in vacuo at 20 ˚C to give silane **132** (2.42 g, 13.0 mmol, 87%) as colorless liquid.

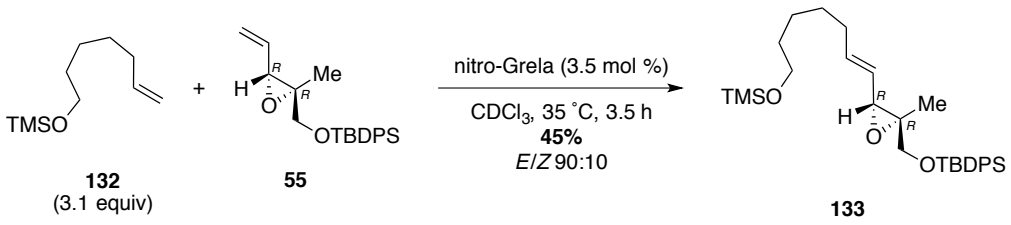
^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.01 (ddt, *J* = 17.1, 2.1, 1.6 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H), 3.58 (t, *J* = 6.7 Hz, 2H), 2.06 (q, *J* = 7.3 Hz, 2H), 1.55 (dt, *J* = 14.6, 7.1 Hz, 2H), 1.44-1.38 (m, 2H), 1.37-1.32 (m, 2H), 0.12 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 139.22, 114.48, 62.87, 33.99, 32.81, 28.96, 25.57, -0.23.

HRMS (APCI) calculated for $C_{10}H_{23}OSi^+$ $[M+H]^+$ 187.15127, found 187.15092.

IR (neat): 3078, 2931, 2859, 1641, 1437, 1387, 1250, 1095, 836 cm^{-1}.

Compound 133



To a solution of epoxide **55** (379 mg, 1.07 mmol) and the alkene **127** (611 mg, 3.3 mmol) in $CDCl_3$ (3 mL) was added nitro-Grela catalyst (14.9 mg, 0.022 mmol). The solution was heated to 35 ˚C for 2 h, whereupon NMR of a small aliquot indicated ~ 60% conversion to the desired product. Additional metathesis catalyst (10.3 mg, 0.054 mmol) was then added and the reaction aged another 1.5 h at 35 ˚C. The reaction mixture was then concentrated *in vacuo* and the resulting oil chromatographed eluting with 5/95 Et_2O/Hexanes to furnish silane **133** (247 mg, 0.48 mmol, 45%, *E*/*Z* 90:10) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.69-7.68 (m, 4H), 7.45-7.42 (m, 2H), 7.41-7.37 (m, 4H), 5.87 (dtd, *J* = 15.4, 6.9, 0.5 Hz, 1H), 5.34 (ddt, *J* = 15.4, 7.8, 1.5 Hz, 1H), 3.67 (app. q, *J* = 10.8 Hz, 2H), 3.58 (t, *J* = 6.7 Hz, 2H), 3.30 (d, *J* = 7.8 Hz, 1H), 2.11 (q, *J* = 6.8 Hz,2H), 1.57-1.52 (m, 2H), 1.46-1.40 (m, 2H), 1.38-1.33 (m, 2H), 1.33 (s, 3H), 1.07 (s, 9H), 0.12 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 138.06, 135.90, 135.81, 133.61, 133.56, 129.91, 127.92, 127.90, 124.74, 68.14, 62.83, 62.81, 61.21, 32.79, 32.77, 29.05, 27.02, 25.60, 19.53, 14.74, -0.23.

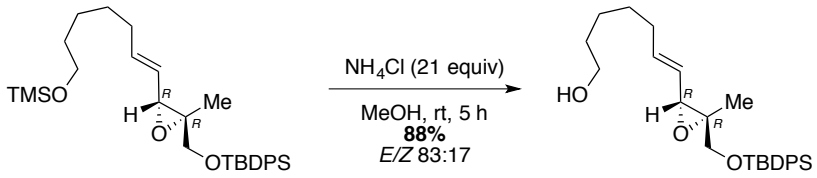
HRMS (NSI) calculated for $C_{30}H_{47}O_3Si_2^+$ $[M+H]^+$ 511.30582, found 511.30542.

IR (CH_2Cl_2): 3071, 3049, 2998, 2956, 2931, 2858, 1590, 1473, 1250, 1106, 840, 702

cm^{-1}.

$[\alpha]_D^{20}$ = +7.4 (CH_2Cl_2, *c* =0.49).

Compound 134



133 **134**

To a stirred solution of **133** (191 mg, 0.37 mmol) in MeOH (3.8 mL) at rt was added solid NH_4Cl (417 mg, 7.8 mmol). The mixture was stirred for 5 h and then the solvent removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g). The resulting eluant was concentrated *in vacuo* and then chromatographed eluting with 50/50 Et_2O/hexanes to 75/25 Et_2O/hexanes to give **134** (144 mg, 0.33 mmol, 88%, *E*/*Z* 83:17) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.70-7.67 (m, 4H), 7.45-7.42 (m, 2H), 7.41-7.38 (m, 4H), 5.87 (dtd, *J* = 15.4, 6.9, 0.5 Hz, 1H), 5.35 (ddt, *J* = 15.4, 7.8, 1.5 Hz, 1H), 3.69-3.62 (m, 4H), 3.30 (d, *J* = 7.8 Hz, 1H), 2.12 (qd, *J* = 7.2, 1.2 Hz, 2H), 1.62-1.57 (m, 2H), 1.47-1.38 (m, 4H), 1.33 (s, 3H), 1.22 (s, 1H), 1.07 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 137.91, 135.90, 135.81, 133.60, 133.56, 129.92, 127.92, 127.90, 124.88, 68.13, 63.16, 62.85, 61.17, 32.82, 32.75, 29.01, 27.02, 25.48, 19.53, 14.74.

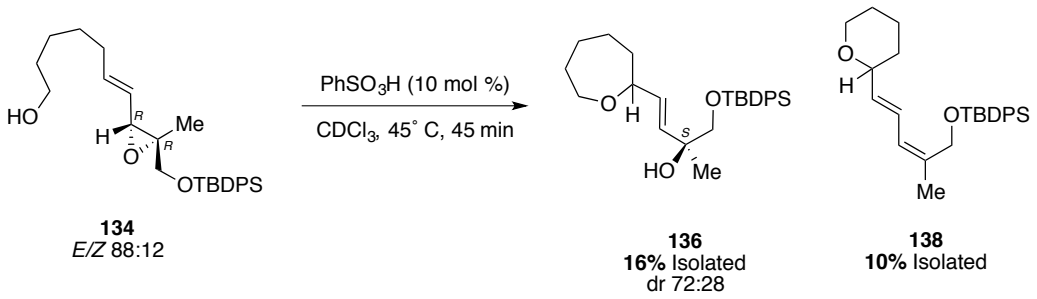
HRMS (NSI) calculated for $C_{27}H_{39}O_3Si^+$ $[M+H]^+$ 439.26630, found 439.26673.

IR (CH_2Cl_2): 3370, 3070, 3049, 2998, 2931, 2857, 1665, 1589, 1428, 1113, 824, 702

cm^{-1}.

$[\alpha]_D^{20}$ = +5.1 (CH_2Cl_2, *c* =0.35).

Cyclization of 134 with $PhSO_3H$ in $CDCl_3$ (Scheme 45)



134
E/Z 88:12

136
16% Isolated
dr 72:28

138
10% Isolated

To a solution of alkene **134** (16.1 mg, 0.037 mmol) in $CDCl_3$ (0.6 mL) in a clean NMR tube was added a solution of $PhSO_3H$ (0.63 mg, 0.0040 mmol) in $CDCl_3$ (0.2 mL). The reaction was monitored by NMR at rt for 15 min, whereupon the NMR sample was heated to 45 ˚C with FIDs being acquired every minute. After 25 min at 45 ˚C, alkene **134** had been consumed. The sample was removed from the NMR and poured over solid $NaHCO_3$ (~50 mg). The mixture was diluted with Et_2O, filtered and concentrated in vacuo. The resulting residue was purified by preparatory thin layer chromatography to give oxepane **136** (2.6 mg, 0.006 mmol, 16%, dr 72:28) and pyranyl diene **138** (1.8 mg. 0.037 mmol, 10%) as colorless oils. The spectral data for oxepane **136** match the oxepane isolated from later palladium cyclization reactions (see page 151).

Data for Compound 138:

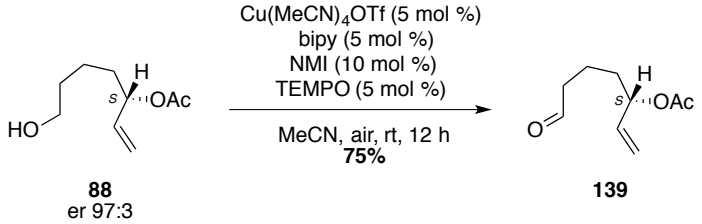
^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.70-7.67 (m, 4H), 7.45-7.37 (m,6H), 6.51 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.17 (d, *J* = 11.1 Hz, 1H), 5.67 (dd, *J* = 15.3, 6.1 Hz, 1H), 4.10 (s, 2H), 4.05 (ddt, *J* = 11.4, 4.0, 2.0 Hz, 1H), 3.89 (dd, *J* = 10.6, 6.2 Hz, 1H), 3.52 (td, *J* = 11.5,

2.2 Hz, 1H), 1.88-1.85 (m, 1H), 1.71 (s, 3H), 1.71-1.67 (m, 1H), 1.56 (s, 3H), 1.47-1.40 (m, 1H), 1.06 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 137.35, 135.75, 133.92, 133.88, 133.71, 129.81, 127.87, 126.32, 123.26, 78.32, 68.59, 68.58, 32.47, 27.03, 19.54, 14.19.

IR (CH_2Cl_2): 3070, 3048, 2998, 2930, 2855, 1736 (weak) 1664, 1462, 1428, 1361, 1146, 1112, 824, 740, 702 cm^{-1}.

Compound 139



To a solution of alcohol **88** (4.69 g, 27.2 mmol) in MeCN (150 mL) was added Stahl 1˚ Alcohol Solution (7 mL, 0.2 M in TEMPO, 0.2 M in bpy and 0.4 M in NMI, all in MeCN) followed by $Cu(MeCN)_4OTf$ (512 mg, 1.4 mmol). The resulting red solution was stirred vigorously while open to air for 12 h whereupon it turned green, indicating completion. The mixture was concentrated *in vacuo*, the resulting oil filtered through a plug of SiO_2 with Et_2O and the eluant concentrated to give the aldehyde **139** as an orange oil (3.50 g, 20.6 mmol, 75%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ 9.77 (t, *J* = 1.5 Hz,1H), 5.78 (ddd, *J* = 17.2, 10.7, 6.4 Hz, 1H), 5.28-5.23 (m, 2H), 5.19 (dt, *J* = 10.5, 1.1 Hz, 1H), 2.48 (tdd, *J* = 6.7, 3.1, 1.5 Hz, 2H), 2.08 (s, 3H), 1.72-1.62 (m, 4H).

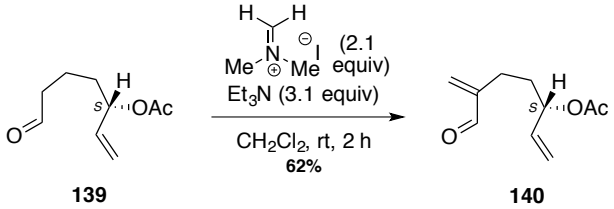
^{13}C-NMR (151 MHz, $CDCl_3$): δ 202.06, 170.50, 136.24, 117.26, 74.40, 43.64, 33.64, 21.41, 17.81.

HRMS (NSI) calculated for $C_9H_{15}O_3^+$ $[M+H]^+$ 171.10157, found 171.10153.

IR (CH_2Cl_2): 3087, 2940, 2725, 1732, 1646, 1372, 1237, 1020 cm^{-1}.

$[\alpha]_D^{20}$ = -7.1 (CH_2Cl_2, *c* =1.13).

Compound 140



To a solution of aldehyde **137** (3.33 g, 19.6 mmol) in CH_2Cl_2 (70 mL) at rt was added Et_3N (8.5 mL, 61 mmol) followed by *N*,*N*-dimethylmethyleneiminium iodide (7.51 g, 40.6 mmol). The reaction was stirred for 2 h whereupon the starting aldehyde was gone by TLC. The mixture was quenched with sat. $NaHCO_3$ (50 mL), the aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography eluting with 25/75 Et_2O/Hexanes gave the enal **140** (2.2 g, 12.1 mmol, 62%) as a pale yellow oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 9.55 (s, 1H), 6.29 (t, *J* = 1.4 Hz, 1H), 6.04 (s, 1H), 5.78 (ddd, *J* = 17.1, 10.6, 6.4 Hz, 1H), 5.26 (d, *J* = 17.2 Hz, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 5.20 (d, *J* = 10.6 Hz, 1H), 2.37-2.23 (m, 2H), 2.08 (s, 3H), 1.86-1.74 (m, 2H).

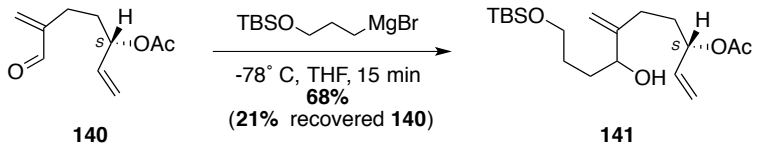
^{13}C-NMR (151 MHz, $CDCl_3$): δ 194.55, 170.48, 149.45, 136.15, 134.58, 117.39, 74.20, 32.20, 23.82, 21.41.

HRMS (NSI) calculated for $C_{10}H_{15}O_3^+$ $[M+H]^+$ 183.10157, found 183.10144.

IR (CH_2Cl_2): 3088, 2933, 2821, 2702, 1735, 1688, 1647, 1629, 1431, 1372, 1236, 1022, 958 cm^{-1}.

$[\alpha]_D^{20}$ = -1.7 (CH_2Cl_2, *c* =1.14).

Compound 139



140 **141**

To an oven dried 100 mL round bottomed flask equipped with a new stir bar was added Mg turnings (788 mg, 32.4 mmol) (note, Mg turnings should be shiny, no black MgO on the surface, it is advisable to clean them with HCl prior to use). The flask was purged with argon (x 3) whereupon THF (30 mL) was added, followed by 1 M DIBAL in hexanes (0.15 mL, 0.15 mmol). (Note, the DIBAL serves both to dry the THF and to help activate the Mg surface).[77] The reaction mixture was stirred at rt for 20 minutes whereupon 1,2-dibromoethane was added (0.05 mL) followed by the dropwise addition of TBS protected 3-bromopropan-1-ol (3.2 mL, 13.8 mmol) over 25 minutes (the surface of the flask not exceeding 34 ˚C as observed by thermal camera (SeekThermal™ Thermal Camera for iPhone). After aging for 2 h, the solution was black. Removal of a small (0.1 mL) aliquot of the solution, quenching it with CD_3OD and NMR analysis showed the solution to be ~33% Grignard (the rest of the material being dimerized bromide or elimination products).

Separately, a solution of the aldehyde **140** (846 mg, 4.6 mmol) in THF (20 mL) was cooled to -78 ˚C. The entire Grignard solution (30 mL) was slowly added down the side of the flask via syringe. After 5 minutes, TLC showed almost complete conversion

to the alcohol product. After 15 minutes, the reaction mixture was quenched at -78 ˚C with the addition of sat. NH_4Cl (10 mL) by syringe. After warming to rt, more sat. NH_4Cl (40 mL) was added. The aqueous layer was extracted with Et_2O (3 x 50 mL), the combined organics washed with water (10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography eluting with 1/100 MeOH CH_2Cl_2 to 3/100 MeOH/CH_2Cl_2 gave product **141** as a clear oil (1.12 g, 3.1 mmol, 68%). Also recovered was aldehyde **140** (180 mg, 0.98 mmol, 21%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ 5.79 (app, dddd, *J* = 17.2, 10.6, 6.5, 0.9 Hz, 1H (0.9 Hz because of two diastereomers), 5.29-5.24 (m, 2H), 5.19 (dq, *J* = 10.5, 1.2 Hz, 1H), 5.08 (tt, *J* = 2.2, 1.1 Hz, 1H), 4.86 (quintet, *J* = 1.4 Hz, 1H), 4.10-4.08 (m, 1H), 3.67 (t, *J* = 5.8 Hz, 2H), 2.64 (s, 1H), 2.14 (tdd, *J* = 16.1, 10.6, 5.7 Hz, 1H), 2.08 (app. d, *J* = 0.7 Hz, 3H (both diastereomers)), 2.02 (tdd, *J* = 16.8, 10.7, 6.2 Hz, 1H), 1.89-1.74 (m, 2H), 1.75-1.68 (m, 1H), 1.65-1.54 (m, 3H), 0.91 (s, 9H), 0.07 (s, 6H).

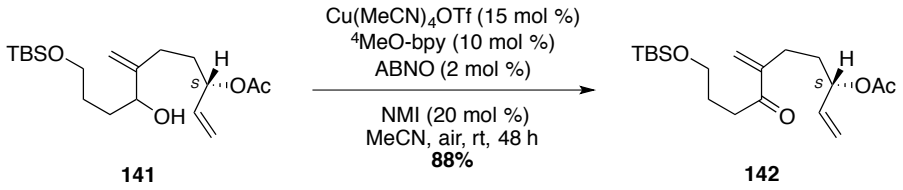
^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.60, 170.55, 151.09, 150.98, 136.53, 136.50, 117.17, 117.13, 110.10, 109.94, 75.28, 75.09, 74.78, 74.69, 63.55, 33.11, 33.02, 32.71, 32.69, 29.19, 27.21, 26.93, 26.16, 25.87, 21.47, 18.55, -5.15. (Many peaks are very close together because of the presence of two diastereomers).

HRMS (NSI) calculated for $C_{19}H_{37}O_4Si^+$ $[M+H]^+$ 357.24556, found 357.24498.

IR (CH_2Cl_2): 3446, 3084, 2952, 2929, 2885, 2857, 1740, 1645, 1472, 1372, 1239, 1098, 1023, 835, 775 cm^{-1}.

$[\alpha]_D^{20}$ = -1.3 (CH_2Cl_2, *c* =0.88).

Compound 142



141 **142**

To a solution of alcohol **141** (349 mg, 0.98 mmol) in MeCN (5 mL) was added 2° Stahl solution (15 mL, 0.002 M in ABNO, 0.01 M in ^{MeO}bipy and 0.02 M in NMI, all in MeCN) followed by $Cu(MeCN)_4OTf$ (68 mg, 0.18 mmol). The reaction was stirred open to air for 2 days, and concentrated *in vacuo*. The resulting residue was filtered through a plug of SiO_2 with Et_2O and the eluant concentrated *in vacuo* to give nearly pure **142** (305 mg, 0.86 mmol, 88%).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 6.06 (s, 1H), 5.79 (ddd, *J* = 17.4, 10.8, 6.7 Hz, 1H), 5.76 (t, *J* = 1.8 Hz, 1H), 5.25 (d, *J* = 17.3 Hz, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 5.19 (d, *J* = 10.6 Hz, 1H), 3.64 (t, *J* = 6.1 Hz, 2H), 2.78 (t, *J* = 7.3 Hz, 2H), 2.36-2.27 (m, 2H), 2.08 (s,3H), 1.83 (dt, *J* = 13.7, 6.7 Hz, 2H), 1.79-1.69 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

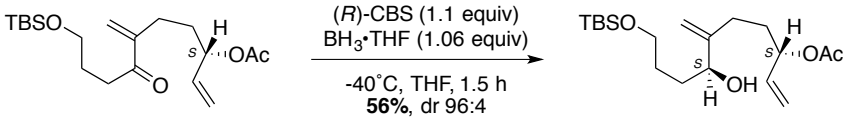
^{13}C-NMR (151 MHz, $CDCl_3$): δ 201.80, 170.53, 148.07, 136.35, 124.53, 117.17, 74.42, 62.37, 34.19, 33.04, 27.69, 26.84, 26.14, 25.86, 21.44, -5.12.

HRMS (NSI) calculated for $C_{19}H_{35}O_4Si^+$ $[M+H]^+$ 355.22991, found 355.22970.

IR (CH_2Cl_2): 3090, 2953, 2929, 2857, 1737, 1678, 1472, 1372, 1236, 1097, 1021, 836, 776 cm^{-1}.

$[\alpha]_D^{20}$ = +1.6 (CH_2Cl_2, *c* = 1.13).

Compound 141

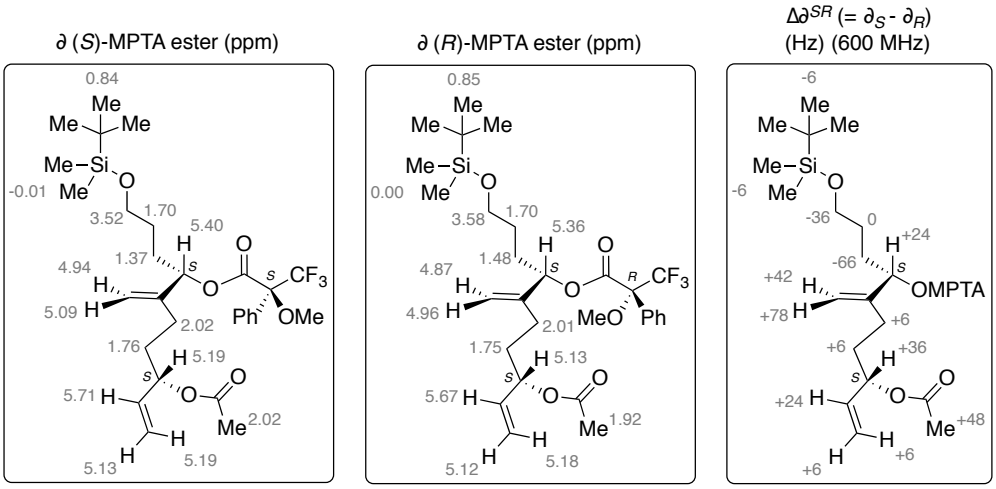


142 **143**

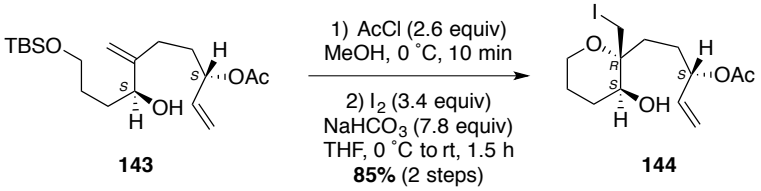
To a flask charged with THF (5 mL) was added *R*-CBS (0.53 mL, 1 M in PhMe, 0.53 mmol) followed by BH_3•THF (0.51 mL, 1 M in THF, 0.51 mmol). The mixture was stirred at rt for 1 before cooling to -40 ˚C. A solution of enone **140** (174 mg, 0.48 mmol) in THF (5 mL) was added dropwise. After 1.5 h the reaction was done by TLC and quenched with the addition of MeOH (0.4 mL). Following concentration, the resulting residue was chromatographed to give **141** (96 mg, 0.27 mmol, 56%). The newly reduced allyl alcohol stereocenter was determined to be *S* by analysis of the corresponding Mosher Esters, which also revealed a dr of 96:4.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 5.80 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H), 5.28 (q, *J* = 6.6 Hz, 1H), 5.26 (dt, *J* = 17.3, 1.2 Hz, 1H), 5.19 (dt, *J* = 10.6, 1.2 Hz, 1H), 5.08 (quintet, *J* = 1.0 Hz, 1H), 4.86 (q, *J* = 1.4 Hz, 1H), 4.10 (dd, *J* = 7.3, 3.2 Hz, 1H), 3.67 (t, *J* = 5.8 Hz, 2H), 2.67 (d, *J* = 3.6 Hz, 1H), 2.13 (ddd, *J* = 15.8, 10.1, 5.8 Hz, 1H), 2.08 (s, 3H), 2.03 (ddd, *J* = 15.9, 10.5, 5.6 Hz, 1H), 1.88-1.77 (m, 2H), 1.74-1.69 (m, 1H), 1.64-1.56 (m, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

Mosher Ester Data[38]



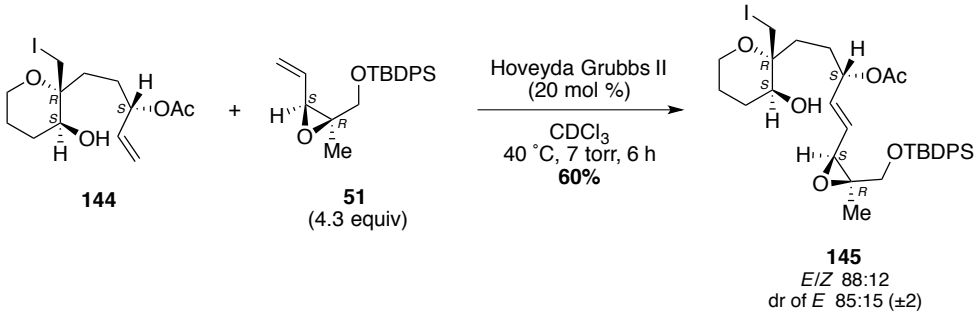
Compound 144



To a cooled (0 ˚C) solution of **143** (96 mg, 0.27 mmol) in MeOH (3 mL) was added a few drops (3-5, ~0.05 mL, ~0.7 mmol) of AcCl. The reaction was stirred for 10 minutes and then quenched with solid $NaHCO_3$ (47 mg). Filtration and concentration *in vacuo* gave the diol (TBS removed) which was carried on to the next step without further purification. To a 0 ˚C solution of the diol in THF (5 mL) was added $NaHCO_3$ (180 mg, 2.1 mmol) followed by I_2 (235 mg, 0.93 mmol). After 1.5 h the reaction was done by TLC and thus quenched with sat $Na_2S_2O_3$ (2 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics dried over $MgSO_4$ and concentrated to give pyran **144** (93 mg, 0.25 mmol, 93%, 2 Steps).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 5.80 (ddd, *J* = 17.2, 10.7, 6.4 Hz, 1H), 5.30-5.24 (m,2H), 5.21 (d, *J* = 10.5 Hz, 1H), 3.79 (ddd, *J* = 7.7, 5.9, 4.0 Hz, 1H), 3.61 (ddd, *J* = 11.6, 6.8, 4.5 Hz, 1H), 3.53 (ddd, *J* = 11.8, 7.8, 4.0 Hz, 1H), 3.47 (d, *J* = 10.9 Hz, 1H), 3.40 (d, *J* = 10.9 Hz, 1H), 2.10 (s, 3H), 1.91 (ddt, *J* = 12.8, 8.2, 4.3 Hz, 1H), 1.83 (d, *J* = 6.1 Hz, 1H), 1.80-1.63 (m, 6H), 1.54-1.47 (m, 1H).

Compound 145



To a solution of **142** (93 mg, 0.25 mmol) and epoxide **51** (385 mg, 1.1 mmol) in $CDCl_3$ (5 mL) was added Hoveyda Grubbs II catalyst (10 mg, 0.016 mmol). The mixture was concentrated *in vacuo* at 50 ˚C for 2 hours, whereupon another portion of catalyst (10 mg) was added with $CDCl_3$ (5 mL). After concentrating *in vacuo* for another 2 hours an additional portion of catalyst (10 mg) was added with $CDCl_3$. After a final 2 hours (6 total), NMR of an aliquot of the reaction mixture showed high conversion to the desired cross metathesis product **145**. Column chromatography of the resulting oil eluting with 60/40 Et_2O/Hexanes gave product **145** (104 mg, 0.15 mmol, 60%, *E*/*Z* 88:12, dr of *E* 85:15 (±2)) as brown oil.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.71-7.65 (m, 4H), 7.46-7.38 (m, 6H), 5.78 (ddd, *J* = 15.6, 6.5, 0.9 Hz, 1H), 5.53 (ddd, *J* = 15.6, 6.9, 1.1 Hz, 1H), 5.23 (q, *J* = 6.0 Hz, 1H),

3.72-3.39 (m, 6H), 3.32 (d, J = 10.9 Hz, 1H), 3.28 (d, J = 6.7 Hz, 1H), 2.03 (s, 3H), 1.93-1.43 (m, 11H), 1.26 (s, 1H), 1.07 (s, 9H).

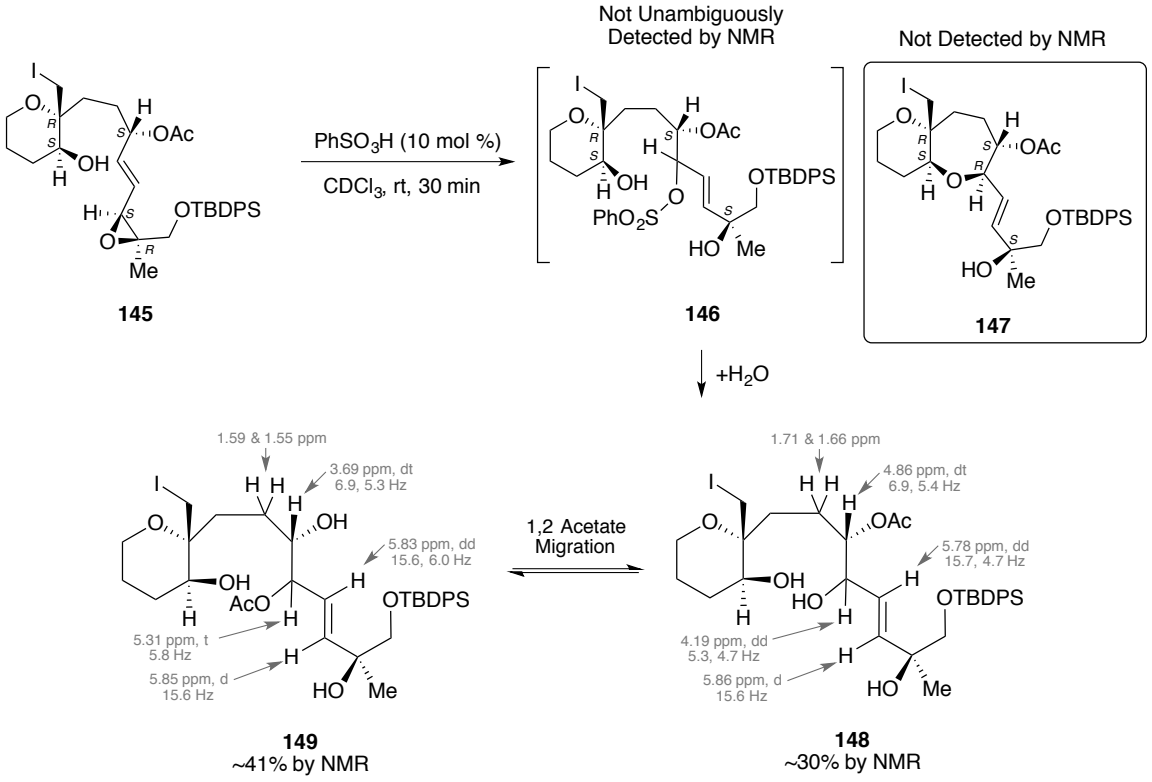
^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.49, 135.87, 135.78, 134.21, 133.54, 133.33, 129.98, 129.97, 127.98, 127.94, 127.18, 75.54, 73.60, 68.05, 65.26, 63.26, 63.12, 61.54, 29.57, 27.64, 27.32, 26.98, 22.68, 21.44, 20.08, 19.50, 10.85.

IR (CH_2Cl_2) 3459, 3070, 3048, 2931, 2858, 1736, 1471, 1428, 1372, 1237, 1112, 1085, 1020, 824, 742, 703 cm^{-1}.

HRMS (APCI) calculated for $C_{33}H_{46}IO_6Si^+$ $[M+H]^+$ 693.21029, found 693.20889.

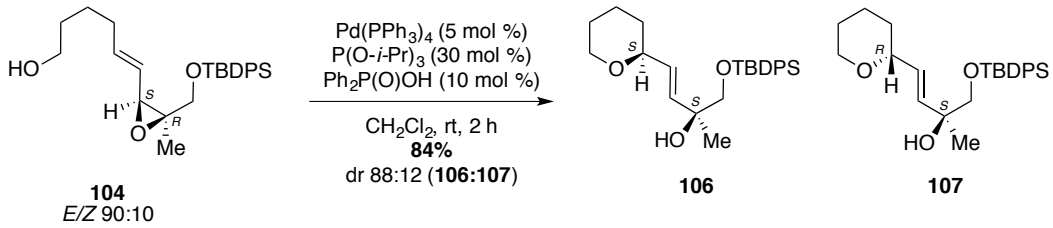
$[\alpha]_D^{20}$= -0.8 (CH_2Cl_2, c = 0.883).

NMR Study of the Reaction of 145 with $PhSO_3H$ in $CDCl_3$ (Scheme 47)



A solution of **145** (4.5 mg, 0.0065 mmol) in $CDCl_3$ (1 mL) was stirred with activated 4 Å molecular sieves at rt for 3 h under Ar. The solution was transferred to a dry NMR tube whereupon a solution of $PhSO_3H$ (0.10 mg, 0.00075 mmol) in $CDCl_3$ (0.1 mL) was added. The reaction mixture was monitored by NMR, with acetates **148** and **149** being observed after within 30 min, their concentration being estimated using the *tert*-butyl group of the TBDPS as an internal standard. Attempts to isolate either product were unsuccessful.

Compound 106



104
E/Z 90:10

106

107

To a solution of **104** (182 mg, 0.43 mmol) in CH_2Cl_2 (4 mL) was added $Ph_2P(O)OH$ (10.5 mg, 0.048 mmol), $P(O\text{-}i\text{-}Pr)_3$ (32 μL, 0.131 mmol) followed by $Pd(PPh_3)_4$ (25.3 mg, 0.022 mmol) at rt. After 2 hr, saturated aqueous $NaHCO_3$ (1 mL) was added, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 1 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to give an orange oil. NMR of the crude showed no residual starting material and that the dr was 88:12 (**106**:**107**). Chromatography of the crude on SiO_2 eluting with 50/50 Et_2O/hexanes furnished **106** (153 mg, 0.36 mmol, 84%) as a colorless oil.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.68-7.64 (m, 4H), 7.46-7.43 (m,2H), 7.41-7.37 (m, 4H), 5.78 (dd, *J* = 15.8, 5.4 Hz, 1H), 5.72 (dd, *J* = 15.8, 1.1 Hz, 1H), 4.03 (ddt, *J* = 11.5, 4.0,

1.9 Hz, 1H), 3.80 (dddd, *J* = 11.0, 5.4, 2.2, 1.0 Hz, 1H), 3.55-3.46 (m, 3H), 2.62 (s, 1H), 1.88-1.83 (m, 1H), 1.66 (dtt, *J* = 13.5, 2.9, 2.1 Hz, 1H), 1.63-1.49 (m, 3H), 1.39 (tdd, *J* = 12.6, 11.1, 3.7 Hz, 1H), 1.27 (s, 3H), 1.08-1.07 (m, 9H).

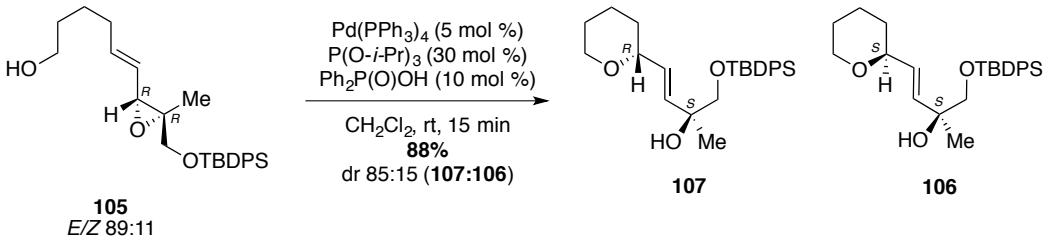
^{13}C-NMR (125 MHz; $CDCl_3$): δ 135.85, 135.80, 134.5, 133.27, 133.21, 130.9, 130.0, 127.95, 127.93, 77.9, 73.0, 71.3, 68.6, 32.4, 27.1, 26.1, 24.4, 23.6, 19.6.

IR (neat) 3429, 3071, 2932, 2857, 1589, 1472, 1428, 1362, 1203, 1110, 1084, 702 cm^{-1}.

HRMS (NSI) calculated for $C_{26}H_{36}NaO_3Si^+$ $[M+Na]^+$ 447.23259, found 447.23277.

$[\alpha]_D^{20}$ = -15.5 (CH_2Cl_2, *c* = 0.78).

Compound 107



To a solution of **105** (131 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) was added $Ph_2P(O)OH$ (7.5 mg, 0.034 mmol), $P(O\text{-}i\text{-}Pr)_3$ (23 μL, 0.094 mmol) followed by $Pd(PPh_3)_4$ (18.8 mg, 0.016 mmol) at rt. TLC showed the reaction to be complete after 15 minutes. Saturated aqueous $NaHCO_3$ (1 mL) was then added, the layers separated and the aqueous layer extracted with CH_2Cl_2 (3 x 1 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to give an orange oil. NMR of the crude showed no residual starting material and that the dr was 85:15 (**107**:**106**). Chromatography of the crude on SiO_2 eluting with 50/50 Et_2O/hexanes furnished **107** (115 mg, 0.27 mmol, 88%) as a colorless oil.

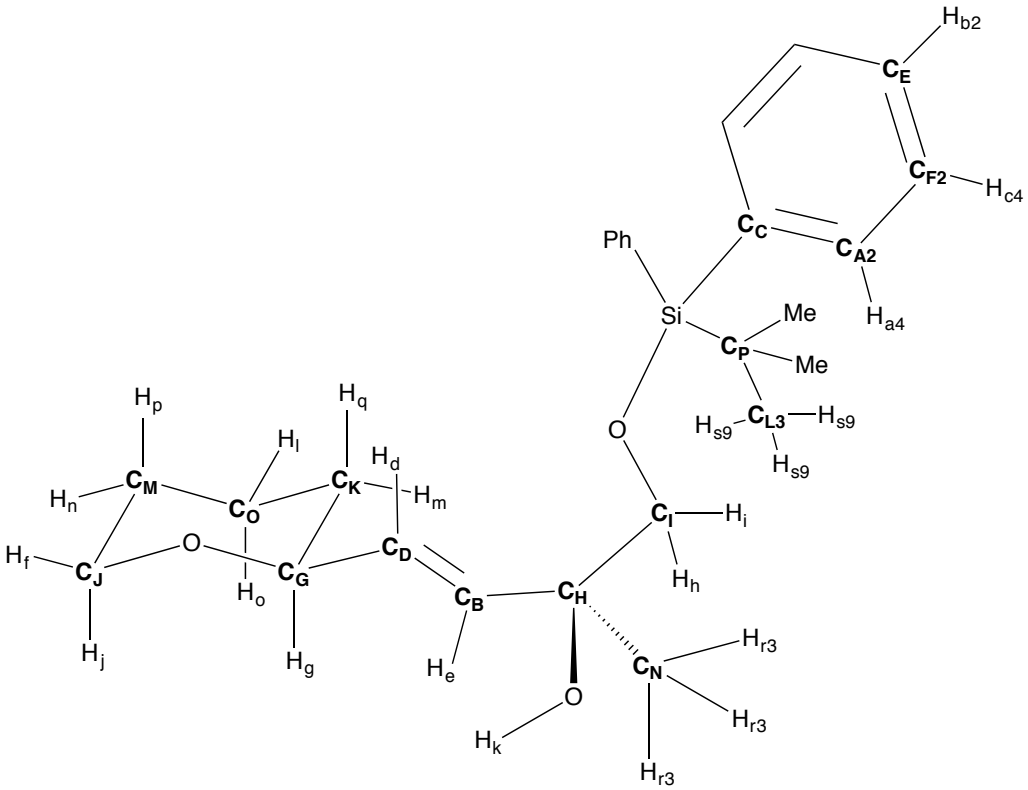
^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.68-7.65 (m,4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m, 4H), 5.79 (dd, *J* = 15.8, 5.1 Hz, 1H), 5.71 (dd, *J* = 15.8, 1.3 Hz, 1H), 4.03 (ddt, *J* = 11.5, 4.0, 1.9 Hz, 1H), 3.82 (dddd, *J* = 11.0, 5.1, 2.2, 1.3 Hz, 1H), 3.55-3.47 (m, 3H), 2.63 (s, 1H), 1.87-1.83 (m, 1H), 1.65 (dddt, *J* = 12.3, 4.3, 2.3, 2.0 Hz, 1H), 1.62-1.49 (m, 3H), 1.40-1.32 (m, 1H), 1.27 (s, 3H), 1.08 (s, 9H).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 135.88, 135.81, 134.1, 133.28, 133.20, 130.8, 130.0, 127.95, 127.93, 77.7, 73.0, 71.2, 68.6, 32.3, 27.1, 26.1, 24.5, 23.7, 19.5**.**

IR (neat) 3442, 3071, 2932, 2857, 1590 1472, 1428, 1361, 1110, 1084, 702 cm^{-1}.

HRMS (NSI) calculated for $C_{26}H_{36}NaO_3Si^+$ $[M+Na]^+$ 447.23259, found 447.23315.

$[\alpha]_D^{20}$ = -17.8 (CH_2Cl_2, *c* = 0.72).

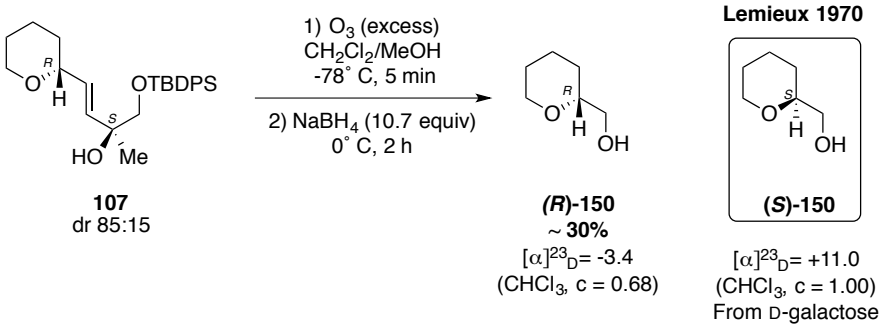


^{1}H-NMR Label	Shift (ppm)	Multiplicity	Couplings (Hz)	COSY Correlations	NOESY Correlations
a_4	7.68-7.65	m	-	H_{c4}	H_{c4}, H_e, H_h, H_i, H_k, H_{s9}
b_2	7.46-7.43	m	-	H_{c4}	H_{c4}
c_4	7.41-7.38	m	-	H_{a4}, H_{b2}	H_{a4}, H_{b2}
d	5.78	dd	15.8, 5.0	H_e, H_g	H_f, H_k, H_m, H_q, H_{r3}
e	5.71	dd	15.8, 1.3	H_d, H_g	H_f, H_h, H_i, H_k, H_m, H_q, H_{r3}
f	4.03	ddt	11.5, 4.0, 1.9	H_j, H_n, H_p, **H_l (W coupling)**	H_j, H_n, H_p
g	3.81	dddd	11.0, 5.1, 2.2, 1.3	H_q, H_d, H_m, H_e	H_d, H_e, H_j, H_q, H_m
h	3.54	d	9.7	H_i	H_d, H_e, H_k, H_{a4}, H_{r3}, H_{s9}
i	3.5	d	9.7	H_h	H_d, H_e, H_k, H_{a4}, H_{r3}, H_{s9}
j	3.52-3.47	m	-	H_f, H_p, H_n	H_f, H_g, H_n, H_o, H_p
k	2.61	s	-	none	H_{a4}, H_d, H_e, H_h, H_i, H_2O, H_{r3}
l	1.87-1.83	m	-	H_o, H_m, H_q, H_p, H_n, **H_f (W Coupling)**	H_m, H_o, H_p, H_n, H_q
m	1.65	ddq	12.3, 4.4, 2.3	H_q, H_o, H_l, H_g, **H_n (W Coupling)**	H_l, H_g, H_q
n	1.60-1.57	m	-	H_p, H_f, H_j, H_o, H_l, **H_m (W Coupling)**	H_l, H_f, H_j
o	1.56-1.53	m	-	H_l, H_p, H_q, H_n, H_m	H_j, H_g, H_l
p	1.52-1.49	m	-	H_n, H_j, H_f, H_o, H_l	H_l, H_f, H_q
q	1.39-1.32	m	-	H_m, H_g, H_o, H_l	H_p, H_d, H_g, H_l, H_m
r_3	1.26	s	-	none	H_{a4}, H_d, H_e, H_h, H_i, H_k
s_9	1.08	s	-	none	H_{a4}, H_k

^{13}C-NMR Label	Shift (ppm)	APT Phase	HMQC Correlations	HMBC Correlations
A_2	135.9	+	H_{a4}	H_{a4}, H_{b2}, H_{c4}
A'_2	135.83	+	H_{a4}	H_{a4}, H_{b2}, H_{c4}
B	134.1	+	H_e	H_d, H_h, H_i, H_k, H_{r3}
C	133.33	-	none	H_{a4}, H_{c4}
C'	133.25	-	none	H_{a4}, H_{c4}
D	130.8	+	H_d	H_e, H_g
E_2	130.01	+	H_{b2}	H_{a4}, H_{c4}
F_2	127.97	+	H_{c4}	H_{a4}, H_{c4}
F'_2	127.95	+	H_{c4}	H_{a4}, H_{c4}
G	77.68	+	H_g	H_d, H_e, H_f, H_j, H_l, H_q
H	73.04	-	none	H_h, H_i, H_k, H_{r3}
I	71.29	-	H_h, H_i	H_k, H_{r3}
J	68.61	-	H_f, H_j	H_l, H_n

K	32.36	-	H_m, H_q	H_d, H_o, H_p
L_3	27.11	+	H_{s9}	H_{s9}
M	26.13	-	H_n, H_p	H_f, H_m, H_o, H_q
N	24.53	+	H_{r3}	H_e, H_h, H_i, H_k
O	23.68	-	H_l, H_o	H_f, H_j, H_m, H_n, H_o, H_p, H_q
P	19.57	-	none	H_{s9}

Determination of absolute stereochemistry of pyran center (Scheme 51)



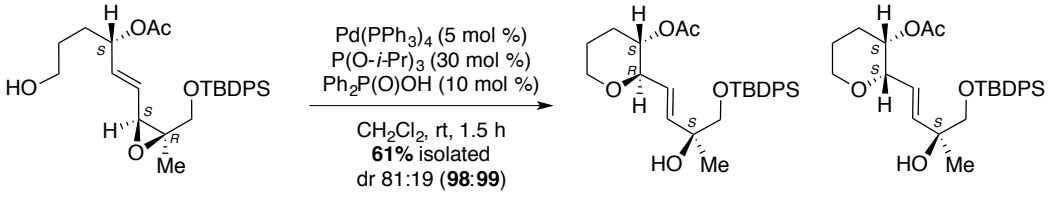
Pyran **107** (97 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (3 mL) and MeOH (3 mL) and the solution cooled to -78 ˚C. Ozone was bubbled through the solution for 5 min, whereupon the solution turned blue. O_2 was then bubbled through the solution until it decolorized (5 min). After warming to 0 ˚C, $NaBH_4$ (93 mg, 2.46 mmol) was added to the solution slowly in portions. The mixture was stirred for 2 h whereupon water (5 mL) was added. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 3 mL). The combined organics were dried over anhydrous KCl and concentrated *in vacuo*. The resulting residue was purified by preparatory thin layer chromatography eluting with Et_2O to furnish pyran **150** (8 mg, 0.069 mmol, 30%). Spectra matched those reported in the literature.[64] The sign of the optical rotation was opposite that described by Lemieux for the enantiomer,[65] allowing for the assignment of the pyran center of **107** as (*R*).

$[\alpha]_D^{20}$= -3.4 ($CHCl_3$, *c* = 0.68).

Standard Pd Cyclization Procedure (Used for compounds 98, 99, 77 & 78)

$Pd(PPh_3)_4$ (29 mg, 0.025 mmol) was dissolved in dry CH_2Cl_2 (5 mL). To this solution was added P(O-*i*-Pr)$_3$ (37 μL, 0.15 mmol) followed by $Ph_2P(O)OH$ (11 mg, 0.05 mmol). The yellow-orange solution was then agitated in a sonicator (Note: the phosphinic acid does not all dissolve, thus is important to homogenize the solution as much as possible prior to removing an aliquot).

Compound 98



73
E/Z 96:4
dr of *E* 85:15 (±2)

98
unlike

99
like

To a vial charged with **73** (37 mg, 0.077 mmol) was added catalyst solution (0.75 mL). The reaction was stirred at rt for 1.5 h (complete by TLC) and then concentrated *in vacuo*. NMR of the crude showed >90% conversion to product respect to the TBDPS *tert*-butyl group. Preparative thin layer chromatography of the crude eluting with Et_2O gave *unlike*-**98** (18.3 mg, 0.038 mmol, 49%) and *like*-**99** (4.3 mg, 0.009 mmol, 12%) for a combined 61% yield.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.65 (dd, *J* = 6.7, 0.8 Hz, 4H), 7.46-7.42 (m, 2H), 7.41-7.38 (m, 4H), 5.83 (dd, *J* = 15.8, 0.9 Hz, 1H), 5.73 (dd, *J* = 15.8, 6.2 Hz, 1H), 4.57 (ddd, *J* = 10.5, 9.1, 4.6 Hz, 1H), 3.96 (ddt, *J* = 11.3, 4.1, 2.0 Hz, 1H), 3.70 (ddd, *J* = 9.1, 6.3, 0.8 Hz, 1H), 3.50 (q, *J* = 10.2 Hz, 2H), 3.42 (td, *J* = 11.3, 3.2 Hz, 1H), 2.57 (s, 1H), 2.17

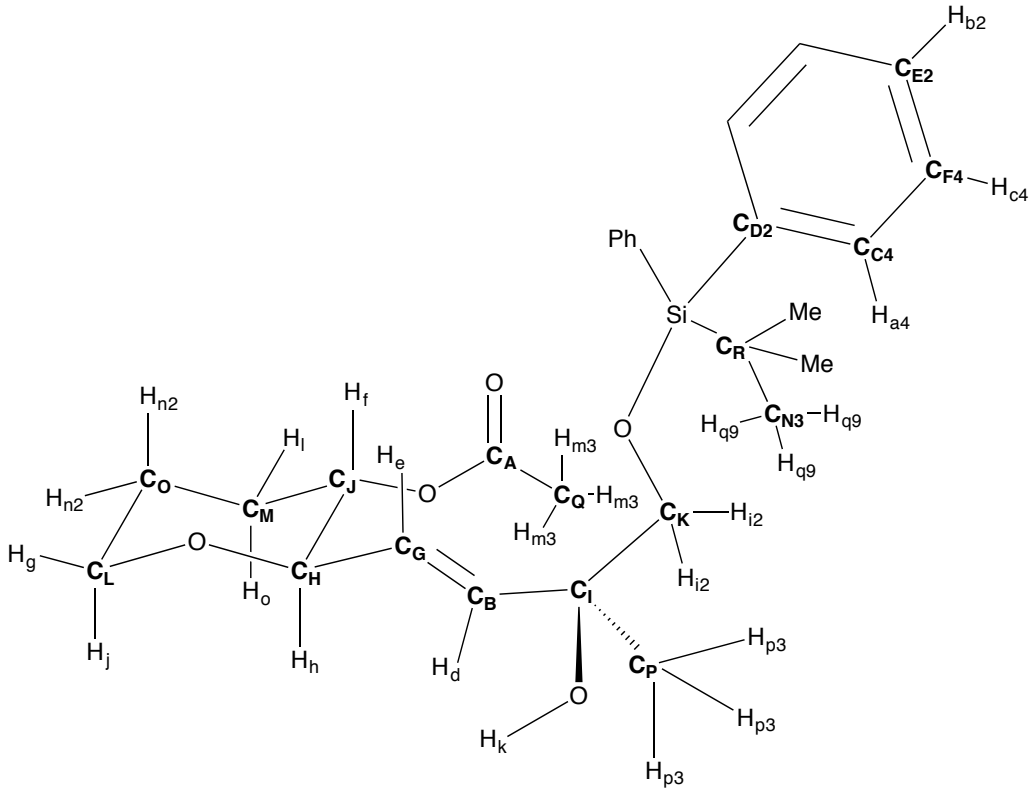
(dqd, *J* = 12.5, 4.1, 1.2 Hz, 1H), 1.94 (s, 3H), 1.79-1.69 (m, 2H), 1.51 (tdd, *J* = 12.3, 10.7, 4.9 Hz, 1H), 1.27 (s, 3H), 1.08 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.29, 137.65, 135.84, 135.80, 133.24, 133.16, 130.04, 130.03, 127.98, 127.96, 126.65, 80.02, 72.99, 71.76, 71.21, 67.50, 29.31, 27.10, 25.13, 24.43, 21.36, 19.56.

IR (CH_2Cl_2) 3466, 3071, 2931, 2857, 1740, 1472, 1428, 1239, 1106, 1082, 703 cm^{-1}.

HRMS (NSI) calculated for $C_{28}H_{38}NaO_5Si^+$ $[M+Na]^+$ 505.23807, found 505.23730.

$[\alpha]_D^{20}$ = -2.6 (CH_2Cl_2, *c* = 0.983).

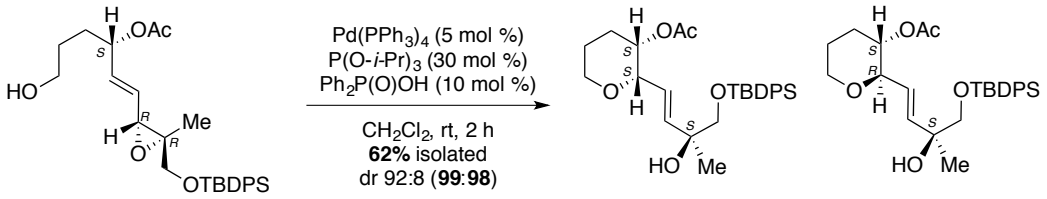


^{1}H-NMR Label	Shift (ppm)	Multiplicity	Couplings (Hz)	COSY Correlations	NOESY Correlations
a_4	7.65	dd	6.7, 0.8	H_{c4}, H_{b2}	H_{c4}, H_{i2}, H_k, H_{q9}
b_2	7.46-7.42	m	-	H_{c4}, H_{a4}	H_{c4}
c_4	7.41-7.38	m	-	H_{a4}, H_{b2}	H_{a4}, H_{b2}
d	5.83	dd	15.8, 0.9	H_e, H_h	H_h, H_{i2}, H_k, H_{p3}
e	5.73	dd	15.8, 6.2	H_d, H_h	H_f, H_i, H_k, H_{p3}
f	4.57	ddd	10.5, 9.1, 4.6	H_o, H_h, H_l	H_e, H_h, H_l, H_{n2}
g	3.96	ddt	11.3, 4.1, 2.0	H_j, H_{n2}, H_{n2}, **H_l (W coupling)**	H_j, H_{n2}
h	3.7	ddd	9.1, 6.3, 0.8	H_f, H_e, H_d	H_d, H_e, H_f, H_j, H_o
i_2	3.5	app. q	10.2	none	H_{a4}, H_d, H_e, H_k, H_{p3}
j	3.42	td	11.3, 3.2	H_g, H_{n2}, H_{n2}	H_g, H_h, H_{n2}, H_o
k	2.57	s	-	none	H_d, H_e, H_{i2}, H_2O, H_{p3}
l	2.17	dqd	12.5, 4.1, 1.2	H_o, H_f, H_{n2}, H_{n2}, **H_g (W coupling)**	H_f, H_{n2}, H_o
m_3	1.94	s	-	none	none
n_2	1.79-1.69	m	-	H_l, H_o, H_g, H_j	H_f, H_g, H_j, H_l, H_o
o	1.51	tdd	12.3, 10.7, 4.9	H_l, H_f, H_{n2}, H_{n2}	H_f, H_h, H_j, H_l, H_{n2}
p_3	1.27	s	-	none	H_d, H_e, H_{i2}, H_k
q_9	1.08	s	-	none	H_{a4}

^{13}C-NMR Label	Shift (ppm)	APT Phase	HMQC Correlations	HMBC Correlations
A	170.29	-	none	H_{m3}, H_f
B	137.65	+	H_d	H_{i2}, H_e, H_k, H_h, H_{p3}
C2	135.84	+	H_{a4}	H_{a4}, H_{b2}, H_{c4}
C'2	135.8	+	H_{a4}	H_{a4}, H_{b2}, H_{c4}
D	133.24	-	none	H_{a4}, H_{c4}
D'	133.16	-	none	H_{a4}, H_{c4}
E	130.04	+	H_{b2}	H_{a4}, H_{c4}
E'	130.03	+	H_{b2}	H_{a4}, H_{c4}
F2	127.98	+	H_{c4}	H_{a4}, H_{b2}, H_{c4}
F'2	127.96	+	H_{c4}	H_{a4}, H_{b2}, H_{c4}
G	126.65	+	H_e	H_f, H_h, H_d
H	80.02	+	H_h	H_f, H_l, H_j, H_g, H_d, H_e
I	72.99	-	none	H_{i2}, H_e, H_d, H_k, H_{p3}
J	71.76	+	H_f	H_l, H_{n2}, H_h
K	71.21	-	H_{i2}	H_{p3}, H_k
L	67.5	-	H_g, H_j	H_h, H_l, H_{n2}
M	29.31	-	H_l, H_o	H_j, H_g, H_h, H_{n2}
N3	27.1	+	H_{q9}	H_{q9}
O	25.13	-	H_{n2}	H_o, H_g, H_l

P	24.43	+	H_{p3}	H_{i2}, H_k
Q	21.36	+	H_{m3}	none
R	19.56	-	none	H_{q9}

Compound 99



75
E/Z > 98:2
dr of *E* 92:8 (±2)

99
like

98
unlike

To a vial charged with **75** (18.8 mg, 0.039 mmol) was added catalyst solution (0.38 mL). The reaction was stirred at rt for 2 h (complete by TLC) and then concentrated *in vacuo*. NMR of the crude showed >90% conversion to product with respect to the TBDPS *tert*-butyl group. Preparative thin layer chromatography of the crude eluting with Et_2O gave *unlike*-**98** (1 mg, 0.002 mmol, 5%) and *like*-**99** (10.7 mg, 0.022 mmol, 57%) for a combined 62% yield.

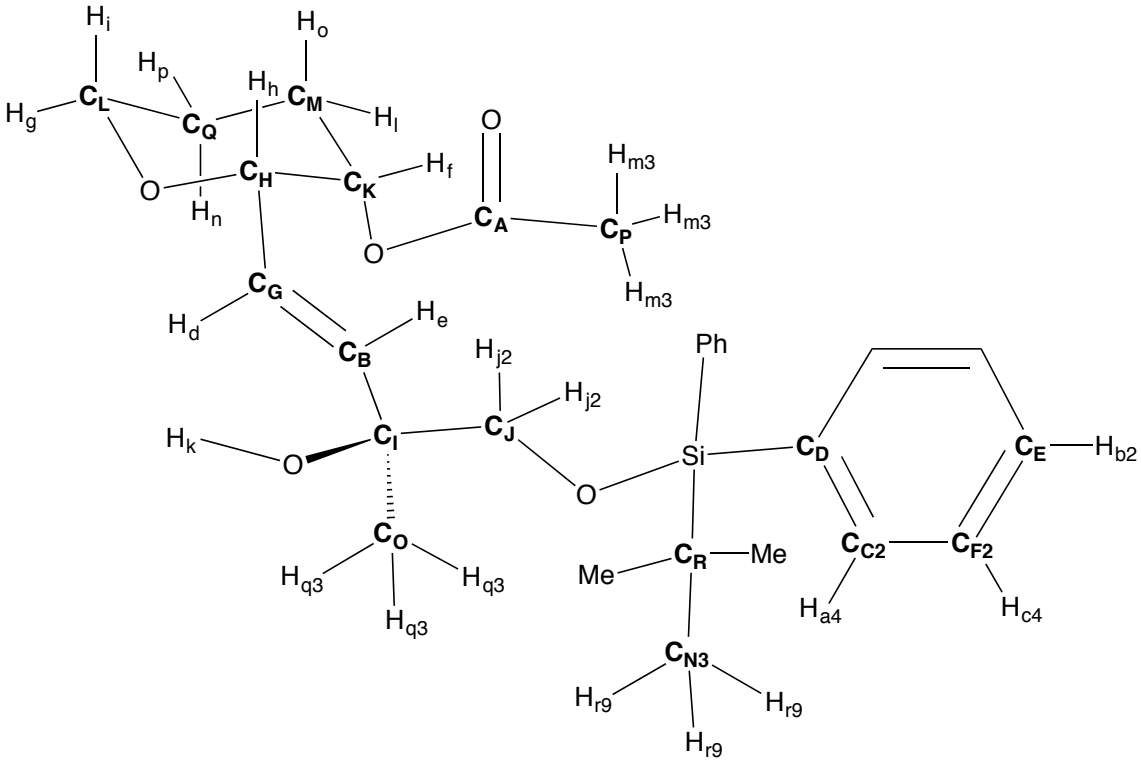
^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 8.0, 1.4 Hz, 4H), 7.46-7.42 (m, 2H), 7.40-7.37 (m, 4H), 5.75 (d, *J* = 15.8 Hz, 1H), 5.72 (dd, *J* = 15.9, 3.5 Hz, 1H), 4.91-4.89 (q, *J* = 2.8 Hz, 1H), 4.07 (ddt, *J* = 11.5, 4.3, 2.0 Hz, 1H), 3.99 (dd, *J* = 3.5, 1.7 Hz, 1H), 3.55 (td, *J* = 11.8, 2.4 Hz, 1H), 3.50-3.46 (m, 2H), 2.56 (s, 1H), 2.01 (ddq, *J* = 13.6, 3.9, 2.5 Hz, 1H), 1.95 (s, 3H), 1.90 (qt, *J* = 13.2, 4.3 Hz, 1H), 1.75 (tdd, *J* = 13.7, 4.3, 3.1 Hz, 1H), 1.44 (dtt, *J* = 12.3, 3.5, 2.4 Hz, 1H), 1.26 (s, 3H), 1.08 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.77, 136.00, 135.85, 135.82, 133.25, 133.22, 130.02, 127.97, 127.96, 126.68, 78.21, 73.06, 71.34, 69.41, 67.97, 27.90, 27.12, 24.62, 21.23, 20.90, 19.56.

IR (CH_2Cl_2) 3467, 3070, 3953, 2930, 2857, 1736, 1241, 1087, 704 cm^{-1}.

HRMS (NSI) calculated for $C_{28}H_{38}NaO_5Si^+$ $[M+Na]^+$ 505.23807, found 505.23735.

$[\alpha]_D^{20}$= -16.2 (CH_2Cl_2, *c* = 0.925).

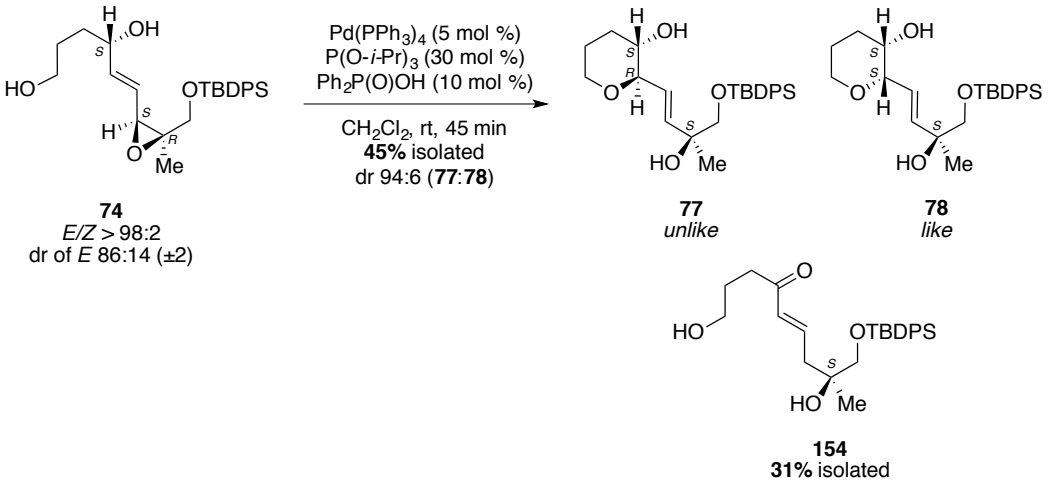


^{1}H-NMR Label	Shift (ppm)	Multiplicity	Couplings (Hz)	COSY Correlations	NOESY Correlations
a_4	7.65	dd	8.0, 1.4	Hc_4	H_{c4}, H_{j2}, H_k, H_{r3}
b_2	7.46-7.42	m	-	Hc_4	H_{c4}
c_4	7.40-7.37	m	-	H_{a4}, H_{b2}	H_{a4}, H_{b2}
d	5.75	d	15.8	H_e, H_h	H_f, H_h, H_{j2}, H_i, H_{q3}
e	5.72	dd	15.9, 3.5	H_d, H_h	H_f, H_h, H_{j2}, H_i, H_{q3}
f	4.91-4.89	q	2.8	H_l, H_o, H_h	H_d, H_h, H_o, H_l
g	4.07	ddt	11.5, 4.3, 2.0	H_i, H_o, H_p, **H_l (W Coupling)**	H_i, H_n, H_p

h	3.99	dd	3.5, 1.7	H_d, H_e, H_f	H_d, H_e, H_f, H_o
i	3.55	td	11.8, 2.4	H_g, H_n, H_p	H_g, H_h, H_n, H_p, H_o
j_2	3.50-3.46	m	-	none	H_{a4}, H_d, H_e, H_k, H_{q3}
k	2.56	s	-	none	H_d, H_e, H_2O
l	2.01	ddq	13.6, 3.9, 2.5	H_o, H_n, H_f, H_p, **H_g (W coupling)**	H_f, H_o, H_p
m_3	1.95	s	-	none	none detected
n	1.9	qt	13.2, 4.3	H_p, H_g, H_o, H_i, H_l	H_g, H_i, H_o
o	1.75	tdd	13.7, 4.3, 3.1	H_l, H_n, H_p, H_f	H_f, H_l, H_h, H_i, H_p
p	1.44	dtt	12.3, 3.5, 2.4	H_n, H_o, H_l, H_i, H_g	H_n, H_i, H_g, H_o
q_3	1.26	s	-	none	H_e
r_9	1.08	s	-	none	Ha_4

^{13}C-NMR Label	**Shift (ppm)**	**APT Phase**	**HMQC Correlations**	**HMBC Correlations**
A	170.56	-	none	H_{m3}, H_f
B	135.79	+	H_e	H_k, H_h, H_{q3}, H_{j2}, H_d
C_2	135.64	+	H_{a4}	H_{a4}, H_{b2}, H_{c4}
C'_2	135.60	+	H_{a4}	H_{a4}, H_{b2}, H_{c4}
D	133.04	-	none	H_{a4}, H_{c4}
D'	133.00	-	none	H_{a4}, H_{c4}
E_2	129.81	+	H_{b2}	H_{a4}, H_{c4}
F_2	127.76	+	H_{c4}	H_{a4}, H_{b2}, H_{c4}
F'_2	127.74	+	H_{c4}	H_{a4}, H_{b2}, H_{c4}
G	126.47	+	H_d	H_h, H_e
H	78.00	+	H_h	H_d, H_f, H_i
I	72.84	-	none	H_d, H_{j2}, H_{q3}, H_k
J	71.12	-	H_{j2}	H_k, H_{q3}, H_e
K	69.20	+	H_f	H_l, H_h, H_o, H_d
L	67.76	-	H_i, H_g	H_n, H_h
M	27.69	-	H_o, H_l	H_f, H_i, H_o, H_g, H_p
N_3	26.91	+	H_{r9}	H_{r3}
O	24.41	+	H_{q3}	H_k, H_{j2}
P	21.02	+	H_{m3}	none detected
Q	20.68	-	H_p, H_n	H_o, H_f, H_l
R	19.35	-	none	H_{r9}

Compound 77



To a vial charged with **74** (19.1 mg, 0.043 mmol) was added catalyst solution (0.45 mL). The reaction was stirred at rt for 0.75 h (complete by TLC) and then concentrated *in vacuo*. NMR of the crude showed trace of starting material. Preparative thin layer chromatography of the crude eluting with 5/95 MeOH/CH_2Cl_2 gave *unlike*-**77** (8.6 mg, 0.019 mmol, 45%) and enone **154** (6.1 mg, 0.013 mmol, 31%) for a combined 76% yield.

Data for compound 77:

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.68-7.64 (m, 4H), 7.47-7.38 (m, 6H), 5.89 (d, *J* = 15.8 Hz, 1H), 5.84 (dd, *J* = 15.7, 6.5 Hz, 1H), 3.95 (ddt, *J* = 11.2, 4.0, 1.9 Hz, 1H), 3.56-3.47 (m, 5H), 3.39 (td, *J* = 11.1, 3.6 Hz, 1H), 3.30 (dddd, *J* = 11.2, 8.3, 5.0, 3.1 Hz, 1H), 2.68 (s, 1H), 2.15 (dqd, *J* = 12.4, 4.1, 1.3 Hz, 1H), 1.86 (d, *J* = 3.2 Hz,1H), 1.45 (tdd, *J* = 12.4, 10.6, 5.3 Hz, 1H), 1.28 (s, 3H), 1.08 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 138.77, 135.82, 135.80, 133.10, 133.05, 130.11, 130.10, 128.03, 127.38, 83.41, 73.13, 71.26, 69.97, 67.68, 31.62, 27.13, 25.61, 24.30, 19.54.

IR (CH_2Cl_2) 3374, 3052, 2930, 2856, 1462, 1437, 1112, 1090, 701, 541 cm^{-1}.

HRMS (NSI) calculated for $C_{26}H_{36}NaO_4Si^+$ $[M+Na]^+$ 463.22751, found 463.22723.

$[\alpha]_D^{20}$= -4.6 (CH_2Cl_2, *c* = 0.683).

Data for compound 154:

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.66-7.65 (m, 4H), 7.47-7.45 (m, 2H), 7.42-7.39 (m, 4H), 6.88 (ddd, *J* = 15.9, 8.1, 7.1 Hz, 1H), 6.13 (dt, *J* = 15.9, 1.3 Hz, 1H), 3.67 (q, *J* = 4.5 Hz, 2H), 3.48 (s, 2H), 2.68 (td, *J* = 6.9, 1.3 Hz, 2H), 2.53 (ddd, *J* = 14.1, 7.0, 1.4 Hz, 1H), 2.49 (s, 1H), 2.36 (ddd, *J* = 14.1, 8.1, 1.2 Hz, 1H), 1.88 (tt, *J* = 6.9, 6.1 Hz, 2H), 1.84-1.80 (m, 1H), 1.16 (s, 3H), 1.10 (s, 9H).

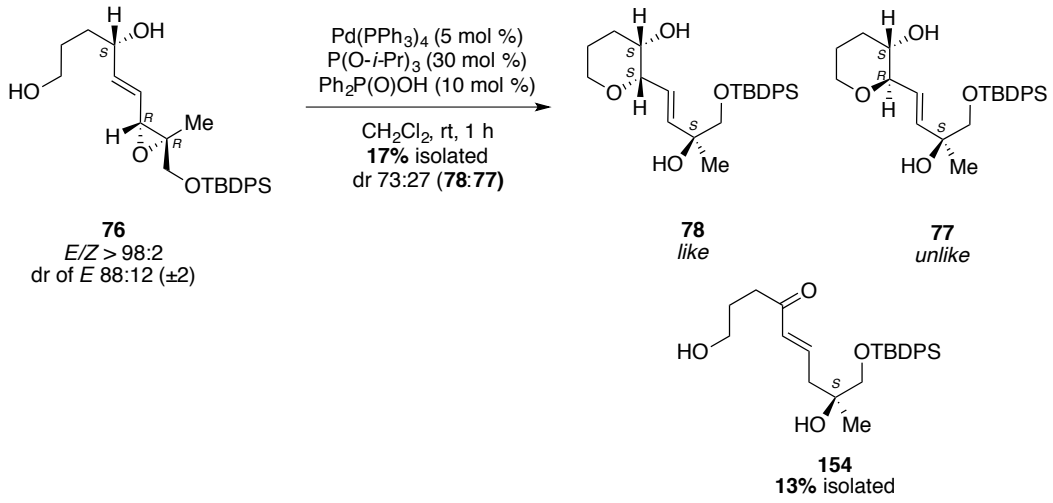
^{13}C-NMR (151 MHz, $CDCl_3$): δ 200.72, 143.30, 135.79, 133.38, 132.97, 132.94, 130.20, 130.18, 128.08, 72.85, 70.80, 62.56, 42.10, 36.77, 27.13, 27.03, 23.74, 19.55.

IR (CH_2Cl_2) 3413, 3071, 2958, 2030, 2857, 1663, 1828, 1427, 1110, 821, 703 cm^{-1}.

HRMS (NSI) calculated for $C_{26}H_{36}NaO_4Si^+$ $[M+Na]^+$ 463.22751, found 463.22730.

$[\alpha]_D^{20}$= -9.1 (CH_2Cl_2, *c* = 0.550).

Compound 78



To a vial charged with **76** (34.6 mg, 0.078 mmol) was added catalyst solution (0.78 mL). The reaction was stirred at rt for 1 h (complete by TLC) and then concentrated *in vacuo*. NMR of the crude showed no remaining starting material. Preparative thin layer chromatography of the crude eluting with Et_2O gave *like*-**78** (5.8 mg, 0.013 mmol, 17%) and enone **77** (4.8 mg, 0.011 mmol, 13%) for a combined 30% yield.

Data for compound 78:

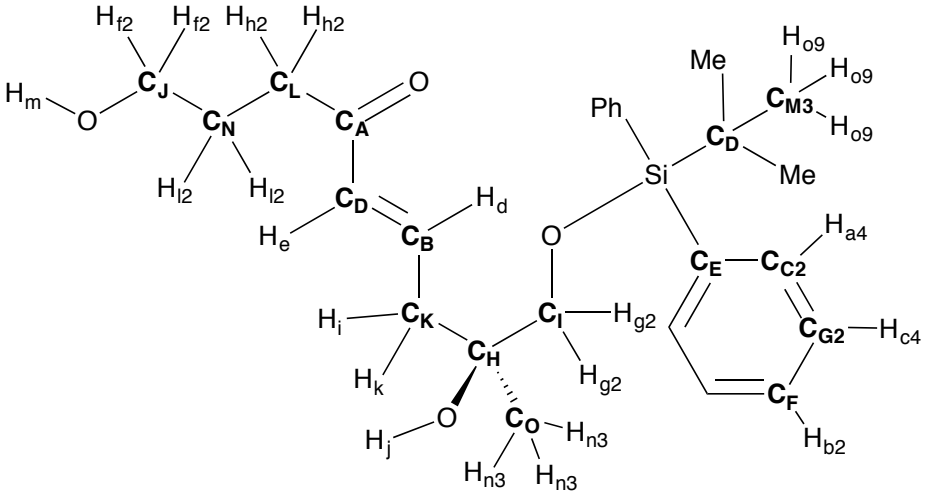
^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.67-7.64 (m, 4H), 7.44 (ddt, *J* = 8.4, 6.2, 1.8 Hz, 2H), 7.41-7.38 (m, 4H), 5.86 (dd, *J* = 15.8, 1.3 Hz, 1H), 5.80 (dd, *J* = 15.8, 4.2 Hz, 1H), 4.04 (ddt, *J* = 11.3, 4.4, 2.1 Hz, 1H), 3.95 (dt, *J* = 4.1, 1.2 Hz, 1H), 3.70 (m, 1H), 3.56-3.51 (m,3H), 2.62 (s, 1H), 2.04-1.93 (m, 2H), 1.86 (d, *J* = 5.7 Hz, 1H), 1.69 (tdd, *J* = 13.2, 4.4, 2.5 Hz, 1H), 1.39 (ddt, *J* = 13.6, 4.5, 2.3 Hz, 1H), 1.27 (d, *J* = 4.2 Hz, 3H), 1.08 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 136.74, 135.85, 135.84, 133.18, 133.16, 130.06, 128.00, 127.10, 79.49, 73.25, 71.29, 68.57, 66.84, 30.12, 27.12, 24.62, 20.23, 19.53.

IR (CH_2Cl_2) 3411, 2929, 2855, 1464, 1427, 1107, 703 cm^{-1}.

HRMS (NSI) calculated for $C_{26}H_{36}NaO_4Si^+$ $[M+Na]^+$ 463.22751, found 463.22683.

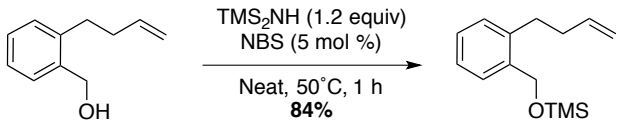
$[\alpha]_D^{20}$= -12.0 (CH_2Cl_2, *c* = 0.508).



^{1}H-NMR Label	Shift (ppm)	Multiplicity	Couplings (Hz)	COSY Correlations
a_4	7.66-7.65	m	-	H_{c4}
b_2	7.47-7.45	m	-	H_{c4}
c_4	7.42-7.39	m	-	H_{a4}, H_{b2}
d	6.88	ddd	15.9, 8.1, 7.1	H_e, H_k, H_i
e	6.13	dt	15.9, 1.3	H_d, H_k, H_i
f_2	3.67	q	4.5	H_{l2}, H_m
g_2	3.48	s	-	none
h_2	2.68	td	6.9, 1.3	H_{l2}
i	2.53	ddd	14.1, 7.0, 1.4	H_k, H_d, H_e
j	2.49	s		none
k	2.36	ddd	14.1, 8.1, 1.2	H_i, H_d, H_e
l_2	1.88	tt	6.9, 6.1	H_{f2}, H_m
m	1.84-1.80	m	-	H_{f2}, H_{l2}
n_3	1.16	s	-	none
o_9	1.1	s	-	none

^{13}C-NMR Label	Shift (ppm)	APT Phase	HMQC Correlations	HMBC Correlations
A	200.72	-	none	H_d, H_e, H_{h2}, H_{l2}
B	143.3	+	H_d	H_i, H_k
C_2	135.79	+	H_{a4}	H_{a4}, H_{b2}, H_{c4}
D	133.38	+	H_e	H_i, H_k
E	132.97	-	H_{c4}	H_{a4}, H_{c4}
E'	132.94	-	H_{c4}	H_{a4}, H_{c4}
F	130.2	+	H_{b2}	H_{a4}, H_{c4}
F'	130.18	+	H_{b2}	H_{a4}, H_{c4}
G_2	128.08	+	none	H_{a4}, H_{b2}, H_{c4}
H	72.85	-	none	H_{g2}, H_i, H_k, H_{n3}
I	70.8	-	H_{g2}	H_i, H_k, H_{n3}
J	62.56	-	H_{f2}	H_{h2}, H_{l2}
K	42.1	-	H_i, H_k	H_d, H_e, Hg_2, H_j, H_{n3}
L	36.77	-	H_{h2}	H_e, H_{l2}
M_3	27.13	+	H_{o9}	H_{o9}
N	27.03	-	H_{l2}	H_{h2}
O	23.74	+	H_{n3}	H_{f2}, H_i, H_k, H_j
P	19.55	-	none	H_{o9}

Compound 157



156 **157**

To a neat mixture of alcohol **156** (prepared from o-toluic acid in 2 steps[67]) (168 mg, 1.03 mmol) and hexamethyldisilazane (0.25 mL, 1.2 mmol) was added NBS (9 mg, 0.05 mmol).[51] The mixture was heated to 50 ˚C for 1 h, diluted with hexanes and filtered through a pad of SiO_2 with hexanes. The eluant was concentrated in vacuo to give silane **157** (204 mg, 0.87 mmol, 84%) as colorless oil.

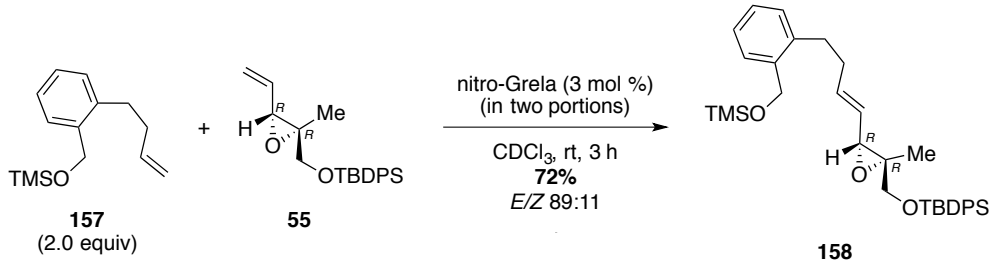
^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.0 Hz, 1H), 7.24-7.18 (m, 3H), 5.91 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.08 (dquintet, *J* = 17.1, 1.7 Hz, 1H), 5.01 (dquintet, *J* = 10.2, 1.3 Hz, 1H), 4.72 (s, 2H), 2.73 (dd, *J* = 8.6, 7.4 Hz, 2H), 2.37 (q, *J* = 7.4 Hz, 2H), 0.17 (s, 9H).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 139.62, 138.46, 138.43, 129.24, 127.90, 127.56, 126.24, 115.08, 62.86, 35.21, 31.81, -0.19.

HRMS (NSI) calculated for $C_{14}H_{23}OSi^+$ $[M+H]^+$ 235.15127, found 235.15120.

IR (CH_2Cl_2): 3078, 3021, 2956, 2871, 1640, 1605, 1490, 1454, 1379, 1251, 1068, 878, 840, 753 cm^{-1}.

Compound 158



To a solution of epoxide **55** (151 mg, 0.43 mmol) and alkene **157** (197 mg, 0.84 mmol) in $CDCl_3$ (1 mL) was added nitro-Grela catalyst (3.9 mg, 0.0058 mmol). The solution was stirred for 1 h whereupon NMR of a small aliquot indicated ~60% conversion to the desired product. An additional amount of nitro-Grela catalyst (4.9 mg, 0.0073 mmol) was then added and the reaction stirred at rt for another 2 h. NMR of the crude reaction mixture then showed high (>90%) conversion to the desired cross metathesis product. The reaction mixture was concentrated *in vacuo* and the resulting oil

chromatographed eluting with 5/95 Et_2O/hexanes to give silane **158** (173 mg, 0.31 mmol, 72%, *E*/*Z* 89:11) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.70-7.67 (m, 4H), 7.46-7.42 (m, 2H), 7.42-7.37 (m, 5H), 7.24-7.19 (m, 2H), 7.18-7.16 (m, 1H), 5.95 (dtd, *J* = 15.4, 6.8, 0.5 Hz, 1H), 5.40 (ddt, *J* = 15.4, 7.8, 1.5 Hz, 1H), 4.71 (s, 2H), 3.69 (d, *J* = 11.2 Hz, 1H), 3.65 (d, *J* = 11.3 Hz, 1H), 3.30 (d, *J* = 7.8 Hz, 1H), 2.80-2.70 (m, 2H), 2.44-2.39 (m, 2H), 1.32 (s, 3H), 1.07 (s, 9H), 0.17 (s, 9H).

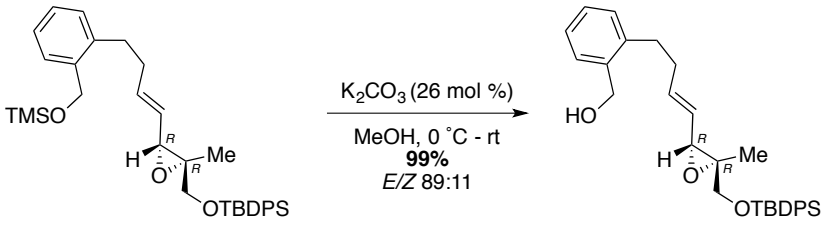
^{13}C-NMR (151 MHz, $CDCl_3$): δ 139.38, 138.46, 137.13, 135.90, 135.82, 133.58, 133.55, 129.93, 129.26, 128.07, 127.93, 127.91, 127.66, 126.35, 125.39, 68.13, 62.93, 62.88, 61.09, 34.03, 31.92, 27.02, 19.53, 14.73, -0.16.

HRMS (NSI) calculated for $C_{34}H_{47}O_3Si_2^+$ $[M+H]^+$ 559.30582, found 559.30268.

IR (CH_2Cl_2): 3071, 3049, 3021, 2957, 2931, 2896, 2858, 1737 (weak), 1589, 1487, 1428, 1251, 1113, 1074, 873, 841, 742, 702 cm^{-1}.

$[\alpha]_D^{20}$ = +5.1 (CH_2Cl_2, *c* = 0.48).

Compound 159



158 **159**

To a solution of silane **158** (164 mg, 0.29 mmol) in MeOH (1 mL) at 0˚ C was added K_2CO_3 (10.3 mg, 0.075 mmol). After 1 h, the reaction mixture was concentrated

in vacuo, triturated with Et_2O and the triturate filtered through a small pipette containing SiO_2 (~1 g) eluting with Et_2O. The resulting solution was concentrated *in vacuo* to give alcohol **159** (140 mg, 0.28 mmol, 99% , *E*/*Z* 89:11) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.46-7.42 (m, 2H), 7.42-7.37 (m, 5H), 7.28-7.19 (m, 3H), 5.94 (dt, *J* = 15.4, 6.8 Hz, 1H), 5.39 (ddt, *J* = 15.5, 7.8, 1.4 Hz, 1H), 4.74 (d, *J* = 5.8 Hz, 2H), 3.69 (d, *J* = 11.2 Hz, 1H), 3.64 (d, *J* = 11.3 Hz, 1H), 3.30 (d, *J* = 7.8 Hz, 1H), 2.81 (dd, *J* = 8.8, 7.3 Hz, 2H), 2.45-2.41 (m, 2H), 1.54 (t, *J* = 5.8 Hz, 1H), 1.31 (s, 3H), 1.08 (s, 9H).

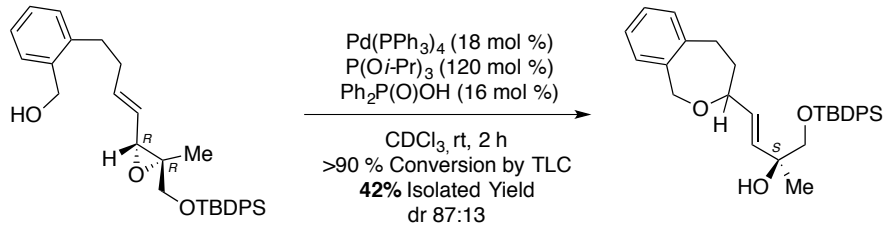
^{13}C-NMR (151 MHz, $CDCl_3$): δ 139.90, 138.50, 136.88, 135.89, 135.81, 133.57, 133.54, 129.93, 129.65, 128.58, 128.28, 127.93, 127.91, 126.62, 125.58, 68.12, 63.43, 62.91, 61.05, 34.28, 31.99, 27.02, 19.53, 14.72.

HRMS (NSI) calculated for $C_{31}H_{39}O_3Si^+$ $[M+H]^+$ 487.26739, found 487.26603.

IR (CH_2Cl_2): 3402, 3070, 3049, 3027, 2998, 2957, 2930, 2892, 2857, 1589, 1428, 1112, 702 cm^{-1}.

$[\alpha]_D^{20}$ = +10.6 (CH_2Cl_2, *c* = 0.60).

Compound 160



159
E/*Z* 89:11

160

To a solution of **159** (13.7 mg, 0.028 mmol) in $CDCl_3$ (0.7 mL) was added $Ph_2P(O)OH$ (1 mg, 0.004 mmol), P(O-*i*-Pr)$_3$ (8 μL, 0.033 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol) at rt. NMR after 35 min showed a ratio of starting material to cyclization product of (22:78). TLC after 2 h showed complete disappearance of starting alcohol **159**. The reaction mixture was purified by preparatory thin layer chromatography eluting with 50/50 Et_2O/hexanes to give **160** (5.8 mg, 0.012 mmol, 42%, dr of 87:13) as a colorless oil.

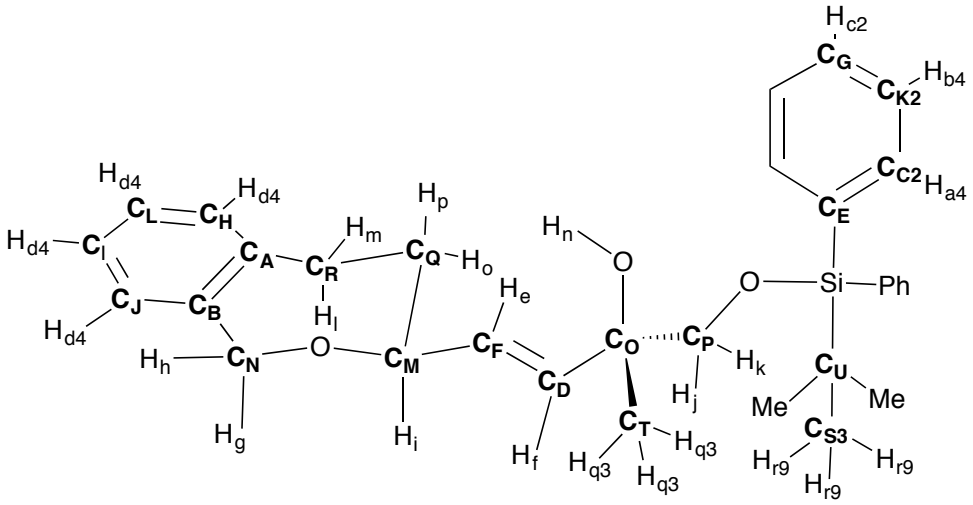
^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.67-7.63 (m, 4H), 7.45-7.36 (m, 4H), 7.35-7.32 (m, 2H), 7.22-7.15 (m, 4H), 5.83 (dd, *J* = 15.8, 5.1 Hz, 1H), 5.74 (dd, *J* = 15.8, 1.3 Hz, 1H), 4.74 (d, *J* = 13.7 Hz, 1H), 4.73 (d, *J* = 13.8 Hz, 1H), 4.28 (dddd, *J* = 10.3, 5.1, 2.2, 1.4 Hz,1H), 3.52 (d, *J* = 9.8 Hz, 1H), 3.50 (d, *J* = 9.7 Hz, 1H), 3.11 (ddd, *J* = 14.5, 12.4, 1.8 Hz, 1H), 2.91 (ddd, *J* = 14.9, 7.0, 1.7 Hz, 1H), 2.61 (s, 1H), 1.97 (ddt, *J* = 14.2, 7.0, 2.1 Hz, 1H), 1.64 (dddd, *J* = 14.1, 12.2, 10.3, 1.8 Hz, 1H), 1.26 (s, 3H), 1.07 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 142.27, 140.04, 135.86, 135.82, 134.30, 133.28, 133.19, 130.74, 130.01, 129.99, 129.27, 128.57, 128.08, 127.96, 127.92, 126.36, 84.48, 73.44, 73.02, 71.27, 35.24, 34.23, 27.10, 24.53, 19.55.

HRMS (NSI) calculated for $C_{31}H_{39}O_3Si^+$ $[M+H]^+$ 487.26739, found 487.26598.

IR (CH_2Cl_2): 3565, 3450, 3070, 3047, 3019, 2998, 2930, 2856, 1671, 1428, 1374, 1112, 1082, 823, 702 cm^{-1}.

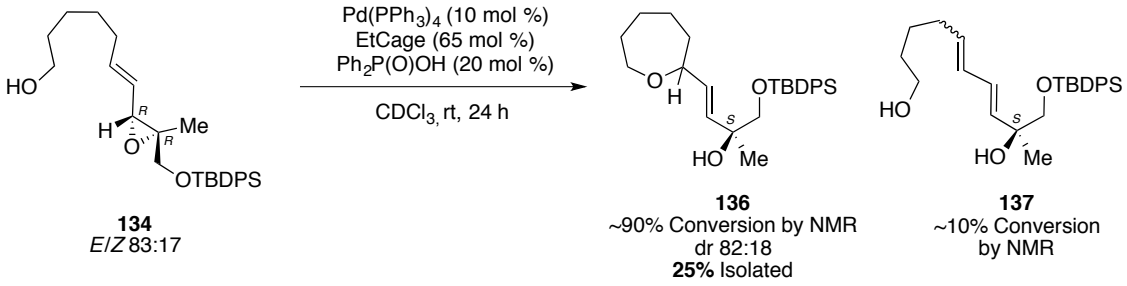
$[\alpha]_D^{20}$ = -8.8 (CH_2Cl_2, *c* = 0.42).



^{1}H-NMR Label	Shift (ppm)	Multiplicity	Couplings (Hz)	COSY Correlations	NOESY Correlations
a_4	7.67-7.63	m	-	H_{b4}, H_{c2}	H_{b4}, H_f, H_j, H_k, H_{r9}
b_4	7.45-7.36	m	-	H_{a4}, H_{c2}	H_{a4}, H_{c2}
c_2	7.35-7.32	m	-	H_{a4}, H_{b4}	H_{b4}
d_4	7.22-7.15	m	-	H_g, H_h, H_l (weak)	H_g, H_h, H_l, H_m
e	5.83	dd	15.8, 5.1	H_f, H_i	H_i, H_j, H_k, H_n, H_o, H_p
f	5.74	dd	15.8, 1.3	H_e, H_i	H_{a4}, H_i, H_j, H_k, H_o, H_p
g	4.74	d	13.7	H_h	H_{d4}, H_i, H_l
h	4.73	d	13.8	H_g	H_{d4}, H_i, H_l
i	4.28	dddd	10.3, 5.1, 2.2, 1.4	H_p, H_e, H_p, H_f	H_e, H_f, H_g/H_h, H_l, H_o
j	3.52	d	9.8	H_k	H_{a4}, H_e, H_f, H_n, H_{q3}
k	3.5	d	9.7	H_j	H_{a4}, H_e, H_f, H_n, H_{q3}
l	3.11	ddd	14.5, 12.4, 1.8	H_m, H_p, H_o	H_g/H_h, H_i, H_m, H_o, H_p
m	2.91	ddd	14.9, 7.0, 1.7	H_l, H_p, H_o	H_{d4}, H_l, H_o, H_p
n	2.61	s	-	none	H_j/H_k, H_2O
o	1.97	ddt	14.2, 7.0, 2.1	H_p, H_m, H_l, H_i	H_e, H_f, H_i, H_l, H_m, H_p
p	1.64	dddd	14.1, 12.2, 10.3, 1.8	H_o, H_l, H_i, H_m	H_e, H_f, H_i, H_l, H_m, H_o
q_3	1.26	s	-	none	H_e, H_f, H_j/H_k
r_9	1.07	s	-	none	H_{a4}, H_j/H_k

^{13}C-NMR Label	Shift (ppm)	APT Phase	HMQC Correlations	HMBC Correlations
A	142.27	-	none	H_{d4}, H_g, H_l, H_m, H_o
B	140.04	-	none	H_{d4}, H_g, H_m
C_2	135.86	+	H_{a4}	H_{a4}, H_{b4}
C'_2	135.82	+	H_{a4}	H_{a4}, H_{b4}
D	134.30	+	H_f	H_e, H_j, H_{q3}
E	133.28	-	none	H_{a4}, H_{b4}, H_{c2}
E'	133.19	-	none	H_{a4}, H_{b4}, H_{c2}
F	130.74	+	H_e	H_f
G	130.01	+	H_{b4}	H_{a4}
G'	129.99	+	H_{b4}	H_{a4}
H	129.27	+	H_{d4}	H_{d4}, H_m, H_l
I	128.57	+	H_{d4}	H_{d4},
J	128.08	+	H_{d4}	H_{d4}, H_g
K_2	127.96	+	H_{c2}	H_{a4}, H_{b4}, H_{c2}
K'_2	127.92	+	H_{c2}	H_{a4}, H_{b4}, H_{c2}
L	126.36	+	H_{d4}	H_{d4}
M	84.48	-	H_i	H_e, H_f, H_g, H_l, H_m, H_q
N	73.44	-	H_g, H_h	H_{d4}
O	73.02	-	none	H_e, H_f, H_j, H_{q3}
P	71.27	-	H_j, H_k	H_f, H_{q3}
Q	35.24	-	H_o, H_p	H_l, H_m
R	34.23	-	H_l, H_m	H_{d4}, H_o
S_3	27.1	+	H_{r9}	H_{r9}
T	24.53	+	H_{q3}	H_j
U	19.55	-	none	H_{r9}

Compound 131



134
E/*Z* 83:17

136
~90% Conversion by NMR
dr 82:18
25% Isolated

137
~10% Conversion
by NMR

To a solution of **134** (18.7 mg, 0.043 mmol) in $CDCl_3$ (0.7 mL) was added a solution of $Ph_2P(O)OH$ (1.9 mg, 0.009 mmol), trimethylolpropane phosphite (EtCage)

(4.5 mg, 0.028 mmol) and $Pd(PPh_3)_4$ (4.9 mg, 0.004 mmol) at rt. After 24 hours, **136** was observed greater than 90% conversion by NMR (with respect to the *tert*-butyl group of the TBDPS). The remaining material (~10%) was identified as diene **137**. The reaction mixture was purified by preparatory thin layer chromatography eluting with 50/50 Et_2O/hexanes to give **136** (4.7 mg, 0.011 mmol, 25%, dr of 82:18) as a colorless oil.

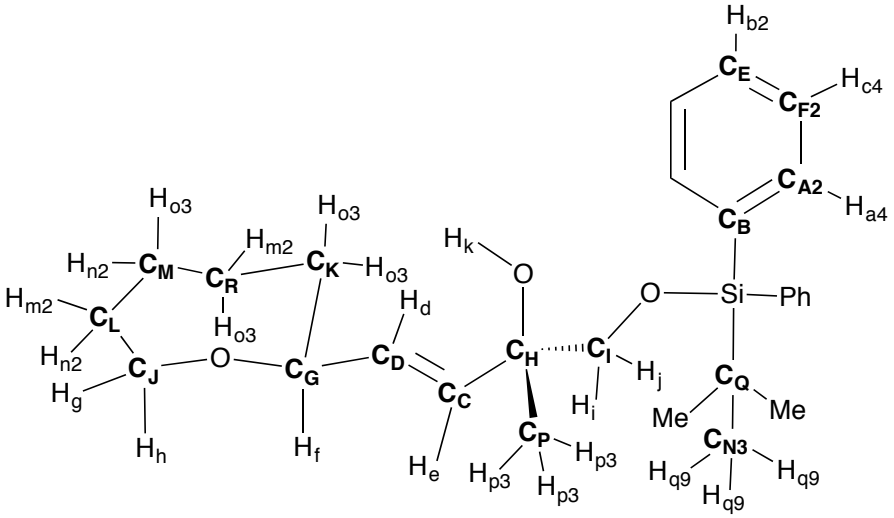
^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m, 4H), 5.78 (dd, *J* = 15.7, 5.0 Hz, 1H), 5.69 (dd, *J* = 15.7, 1.4 Hz, 1H), 4.07 (dtd, *J* = 9.0, 4.5, 1.3 Hz, 1H), 3.83 (ddd, *J* = 12.4, 6.8, 4.0 Hz, 1H), 3.60 (ddd, *J* = 12.3, 7.6, 3.9 Hz, 1H), 3.54 (d, *J* = 9.7 Hz, 1H), 3.50 (d, *J* = 9.7 Hz, 1H), 2.61 (s, 1H), 1.86 (dddd, *J* = 11.5, 7.1, 4.5, 2.4 Hz, 1H), 1.80-1.71 (m, 2H), 1.70-1.63 (m, 2H), 1.60-1.51 (m, 3H), 1.26 (s, 3H), 1.08 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 135.89, 135.82, 133.35, 133.31, 133.26, 131.45, 130.00, 127.97, 127.95, 79.05, 73.04, 71.35, 67.89, 36.05, 31.39, 27.43, 27.10, 25.56, 24.55, 19.56.

HRMS (NSI) calculated for $C_{27}H_{39}O_3Si^+$ $[M+H]^+$ 439.26630, found 439.26729.

IR (CH_2Cl_2): 3424, 3071, 3050, 2998, 2929, 2857, 1671, 1590, 1472, 1112, 823, 702 cm^{-1}.

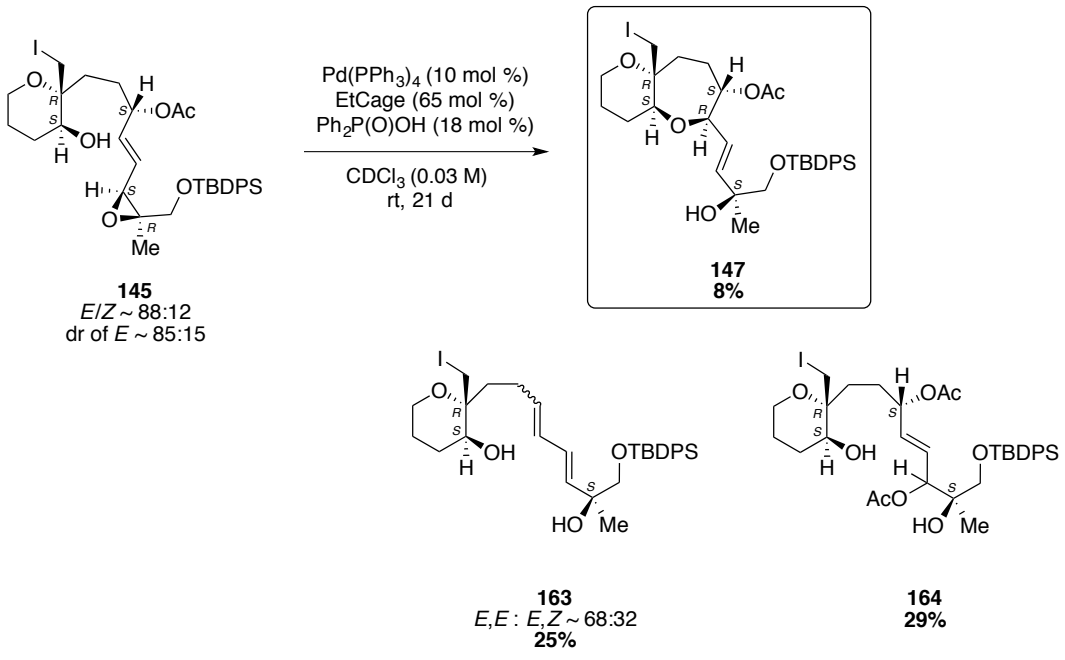
$[\alpha]_D^{20}$ = -18.7 (CH_2Cl_2, *c* =0.35).



^{1}H-NMR Label	Shift (ppm)	Multiplicity	Couplings (Hz)	COSY Correlations	NOESY Correlations
a_4	7.68-7.65	m	-	H_{c4}	H_{c4}, H_i, H_j, H_k, H_{q9}
b_2	7.46-7.43	m	-	H_{c4}	H_{c4}
c_4	7.41-7.38	m	-	H_{a4}, H_{b2}	H_{a4}
d	5.78	dd	15.7, 5.0	H_e, H_f	H_f, H_i, H_j, H_k, H_{p3}
e	5.69	dd	15.7, 1.4	H_d, H_f	H_f, H_i, H_j, H_k, H_{p3}
f	4.07	dtd	9.0, 4.5, 1.3	H_{o3}, H_l, H_d, H_e	H_d, H_e, H_h, H_l, H_{o3}
g	3.83	ddd	12.4, 6.8, 4.0	H_h, H_{m2}, H_{n2}	H_h, H_{m2}, H_{n2}
h	3.6	ddd	12.3, 7.6, 3.9	H_g, H_{n2}, H_{m2}	H_k, H_g, H_{m2}, H_{n2}
i	3.54	d	9.7	H_j	H_j, H_d, H_e, H_k, H_{p3}, H_{q9}
j	3.50	d	9.7	H_i	H_i, H_d, H_e, H_k, H_{p3}, H_{q9}
k	2.61	s	-	none	H_d, H_j, H_i, H_2O
l	1.86	dddd	11.5, 7.1, 4.5, 2.4	H_{o3}, H_{m2}, H_f, H_{n2}	H_d, H_k, H_{n2}, H_{m2}, H_{o3}
m_2	1.80-1.71	m	-	H_{n2}, H_g, H_h, H_l, H_{o3}	H_{n2}, H_{o3}
n_2	1.70-1.63	m	-	H_{m2}, H_{o3}, H_g, H_h	H_{m2}, H_{o3}, H_g, H_h
o_3	1.60-1.51	m	-	H_{n2}, H_{m2}, H_f	H_d, H_f, H_h, H_{m2}, H_{n2}, H_l
p_3	1.26	s	-	none	H_{a4}, H_d, H_e, H_i, H_j, H_k
q_9	1.08	s	-	none	H_{a4}, H_i, H_j

^{13}C-NMR Label	Shift (ppm)	APT Phase	HMQC Correlations	HMBC Correlations
A_2	135.89	+	H_{a4}	H_{a4}, H_{b2}, H_{c4}
A'_2	135.82	+	H_{a4}	H_{a4}, H_{b2}, H_{c4}
B	133.35	-	none	H_{a4}, H_{c4}
C	133.31	+	H_e	H_d, H_i, H_j
B'	133.26	-	none	H_{a4}, H_{c4}, H_k
D	131.45	+	H_d	H_e
E	130.00	+	H_{b2}	H_{a4}
F_2	127.97	+	H_{c4}	H_{a4}, H_{b2}, H_{c4}
F'_2	127.95	+	H_{c4}	H_{a4}, H_{b2}, H_{c4}
G	79.05	+	H_f	H_d, H_e, H_g, H_{m2}
H	73.04	-	none	H_d, H_e, H_i, H_j, H_k, H_{p3}
I	71.35	-	H_i, H_j	H_k, H_{p3}
J	67.89	-	H_g, H_h	none observed
K	36.05	-	H_{o3}, H_l	H_{m2}, H_{n2}
L	31.39	-	H_{m2}, H_{n2}	H_{m2}
M	27.43	-	H_{o3}, H_{n2}	none observed
N_3	27.10	+	H_{q9}	H_{q9}
O	25.56	-	H_{m2}, H_{o3}	H_l, H_{o3}
P	24.55	+	H_{p3}	H_i, H_j, H_k
Q	19.56	-	none	H_{q9}

Compound 147



Epoxy alkene **145** (15.3 mg, 0.022 mmol) was combined with $Pd(PPh_3)_4$ (2.8 mg, 0.0025 mmol), trimethylolpropane phosphite (EtCage) (2.5 mg, 0.016 mmol) and diphenylphosphinic acid (0.9 mg, 0.004 mmol) in $CDCl_3$ (0.7 mL) in a clean NMR tube. The solution was monitored by NMR at several time points, with extensive 2-dimmensional analysis after 21 days indicating the presence of the desired bicycle **147**. Preparative thin layer chromatography (eluting with Et_2O) allowed for the isolation of **147** (1.2 mg, 0.0017 mmol, 8%), **163** (3.5 mg, 0.0055 mmol, 25%), and **164** (4.8 mg, 0.0064, 29%) as colorless films.

Data for 147 (See Tables 5 & 6 for NMR assignments and correlations):

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.68-7.65 (m,4H), 7.48-7.45 (m, 2H), 7.43-7.40 (m, 4H), 5.83 (dd, *J* = 15.7, 1.6 Hz, 1H), 5.74 (dd, *J* = 15.7, 4.8 Hz, 1H), 5.02 (dt, *J* = 7.0, 1.3 Hz, 1H), 4.23 (dt, *J* = 4.8, 1.5 Hz, 1H), 3.81 (dd, *J* = 11.8, 2.2 Hz, 1H), 3.73 (dd, *J* = 11.7, 5.0 Hz, 1H), 3.66 (ddd, *J* = 12.3, 4.5, 1.5 Hz, 1H), 3.58 (d, *J* = 11.9 Hz, 1H), 3.53 (d, *J* = 9.7 Hz, 1H), 3.51 (d, *J* = 9.6 Hz, 2H), 3.38 (td, *J* = 11.9, 3.3 Hz, 1H), 2.63 (s, 1H), 2.14 (s, 3H), 1.99 (dd, *J* = 13.3, 5.2 Hz, 1H), 1.87 (td, *J* = 13.2, 6.4 Hz, 1H), 1.84 (dd, *J* = 13.1, 4.0 Hz, 1H), 1.75-1.55 (m, 2H), 1.65-1.57 (m, 1H), 1.62-1.58 (m, 1H), 1.54-1.49 (m, 1H), 1.46 (s, 1H), 1.09 (s, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 170.05, 135.56, 135.61, 135.25, 132.86, 132.97, 129.86, 127.8, 127.44, 82.01, 76.97, 76.08, 75.44, 72.86, 70.93, 60.35, 32.84, 30.32, 26.83, 26.76, 25.13, 21.96, 21.35, 19.33, 10.19.

IR (CH_2Cl_2) 3361, 3312, 2952, 2921, 1737, 1659, 1633, 1468, 1390, 1260, 1088, 1019, 800, 702 cm^{-1}.

HRMS (APCI, negative ion mode) calculated for $[M-H]^- C_{33}H_{44}IO_6Si^-$ 691.19573, found 691.19320.

$[\alpha]_D^{20}$ = -4.0 (CH_2Cl_2, *c* = 0.100).

Data for compound 163:

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.69-7.64 (m, 4H), 7.47-7.43 (m, 2H), 7.42-7.38 (m,4H), 6.64 (ddd, *J* = 15.4, 11.1, 1.1 Hz, 1H, (*Z*,*E*)), 6.27 (dd, *J* = 15.4, 10.4 Hz, 1H, (*E*,*E*)), 6.07 (dd, *J* = 15.2, 10.4 Hz, 1H, (*E*,*E*)), 6.00 (t, *J* = 10.9 Hz, 1H, (*Z*,*E*)), 5.71 (dt, *J* = 14.8, 7.2 Hz, 1H, (*E*,*E*)), 5.67 (d, *J* = 15.3 Hz, 1H, (*Z*,*E*)), 5.57 (d, *J* = 15.5 Hz,1H, (*E*,*E*)), 5.46 (dt, *J* = 10.7, 7.5 Hz, 1H, (*Z*,*E*)), 3.82 (ddd, *J* = 7.4, 6.5, 3.8 Hz, 1H), 3.66-3.62 (m, 1H), 3.57-3.54 (m, 1H), 3.53-3.46 (m, 3H), 3.41 (app. dd, *J* = 10.9, 1.1 Hz, 1H), 2.69 (s, 1H, (*Z*,*E*)), 2.64 (s, 1H, (*E*,*E*)), 2.31-2.08 (m, 2H), 1.96-1.66 (m, 5H), 1.54-1.47 (m,1H), 1.27 (app. d, *J* = 3.2 Hz, 3H), 1.07 (app. d, *J* = 0.8 Hz, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 137.91, 137.88, 135.90, 135.83, 135.55, 135.47, 134.03, 133.96, 133.33, 133.22, 131.44, 130.40, 130.07, 130.04, 129.32, 128.82, 128.02, 127.99, 127.98, 127.96, 124.40, 124.39, 73.46, 73.20, 71.36, 71.34, 68.04, 61.67, 61.64, 29.92, 29.89, 27.61, 27.57, 27.11, 27.05, 25.69, 24.51, 22.58, 22.48, 20.98, 20.92, 19.56, 10.99, 10.90 (note: many double peaks due to presence of both *E*,*E* and *Z*,*E* stereoisomers).

HRMS (NSI) calculated for $C_{31}H_{42}IO_3Si^+$ $[M-OH]^+$ 617.19424, found 617.19670.

IR (CH_2Cl_2): 3423, 3071, 3048, 2929, 2857, 1735 (weak), 1691, 1671, 1472, 1428, 1112, 1085, 823, 741, 702 cm^{-1}.

Data for compound 164:

^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.66-7.62 (m, 4H), 7.48-7.44 (m, 2H), 7.43-7.38 (m,4H), 5.80 (ddd, *J* = 15.7, 6.4, 0.9 Hz, 1H), 5.66 (ddd, *J* = 15.7, 6.9, 1.2 Hz, 1H), 5.36 (dd, *J* = 6.4, 1.0 Hz, 1H), 5.23 (q, *J* = 6.6 Hz, 1H), 3.76 (dt, *J* = 8.8, 4.6 Hz, 1H), 3.61-3.58 (m, 1H), 3.58 (d, *J* = 10.1 Hz, 1H), 3.52 (d, *J* = 11.0 Hz, 1H), 3.51-3.45 (m, 1H), 3.46 (d, *J* = 10.1 Hz, 1H), 3.35 (d, *J* = 11.0 Hz, 1H), 2.59 (s, 1H), 2.30 (d, *J* = 6.0 Hz, 1H), 2.04 (s, 3H), 2.00 (s, 3H), 1.89 (dt, *J* = 12.7, 6.1 Hz, 1H), 1.80-1.71 (m, 3H), 1.70-1.59 (m, 2H), 1.55-1.48 (m, 2H), 1.12 (s, 3H), 1.08 (s, 9H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 170.45, 170.25, 135.88, 135.81, 133.07, 132.89, 132.84, 130.17, 130.16, 128.07, 128.04, 127.77, 75.97, 75.70, 73.94, 73.80, 67.91, 67.67, 61.49, 29.93, 27.57, 27.51, 27.11, 23.12, 21.53, 21.38, 19.99, 19.47, 11.57.

HRMS (NSI) calculated for $C_{35}H_{48}IO_7Si^+$ $[M\text{-}OH]^+$ 735.22085, found 735.22098.

IR (CH_2Cl_2): 3468, 3071, 3049, 2929, 2857, 1737, 1665, 1428, 1371, 1234, 1085, 1022, 973, 824, 741, 703 cm^{-1}.

CHAPTER 2

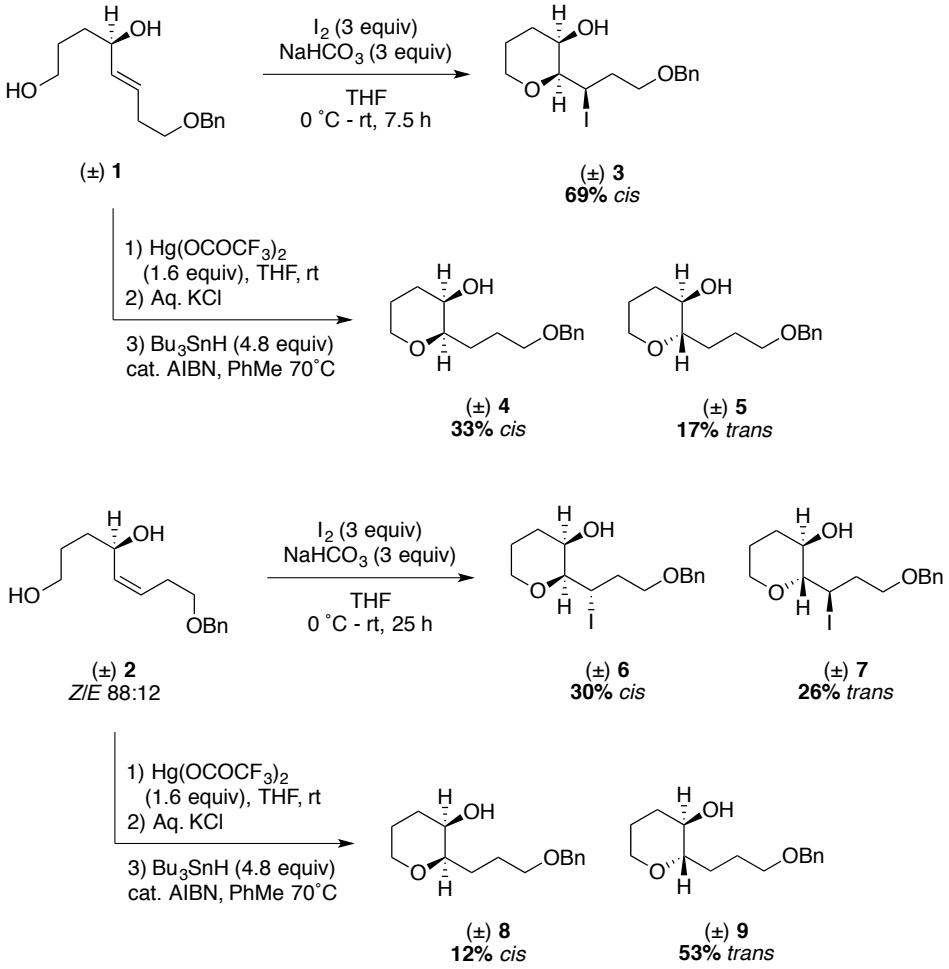
Investigations of exo-mode bicyclizations

2.1 Introduction

2.1.1 Exo-mode oxacyclizations in the McDonald laboratory

As part of our interest in *exo*-mode oxacyclizations to form cyclic ethers we were interested in investigating the effect of an allyl alcohol on the stereoselectivity of electrophile promoted cyclizations. Dr. Kento Ishida, a postdoctoral fellow in our lab, prepared diol substrates **1** and **2** and investigated their cyclization outcomes.[20]

Scheme 1: McDonald laboratory *exo*-mode oxacyclization precedent.



Dr. Ishida found that exposure of *trans*-alkene **1** to an excess of iodine and sodium bicarbonate in THF furnished the *cis* pyran **3** (in this case the *unlike* stereoisomer) as a single diastereomer in 69% yield. Treatment of the same diol **1** with mercuric trifluoroacetate, followed by exchange of the trifluoroacetate for chloride with the addition of KCl, and subsequent free radical demercuration with tributyltin hydride gave the desired pyran as a mixture of diastereomers. As with the iodine cyclization, the *cis* pyran was **4** formed preferentially in 33% yield. However, unlike the iodine cyclization, the *trans* diastereomer **5** was also isolated, albeit in lower yield.

Iodine promoted cyclization of the *cis*-alkene **2** (note the 88:12 *Z*/*E* ratio) gave the *cis* pyran **6** as the major diastereomer in 30% isolated yield. Notably, the alkene stereoisomer of the starting material is reflected the stereochemistry of the iodine atom in the pyran product, thus the iodine of **6** is epimeric to that of **3**. The *trans*-pyran diastereomer **7** was also isolated in 26% yield.

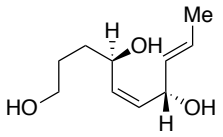
Subjection of **2** to the same sequence of oxymercuration, anion exchange and free-radical demetalation gave the desired *trans* pyran **9** as the major diastereomer in 53% yield. The *cis*-diastereomer **8** was also isolated in 12% yield.

2.2 Preparation of bicyclization substrate

2.2.1 Bicyclization substrate design

Hoping to expand this work, our attention then turned toward the idea of effecting an iodine or mercury mediate bicyclization to form a 6,6-fused pyran. To prepare the type of substrate necessary for this reaction (such as **10**, Figure 1), we drew inspiration from both the work of Andrew Evans and Gregory Verdine.[78,79]

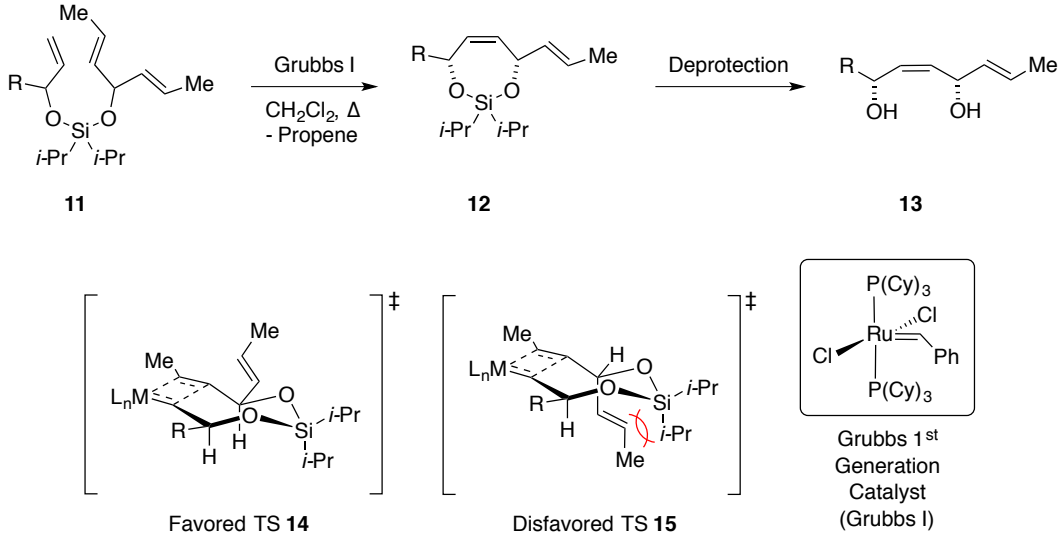
Figure 1: Proposed bicyclization substrate **10**.



(±) **10**

We envisaged that **10** could be prepared rapidly using diastereoselective ring closing metathesis of a silaketal to give the syn 1,4-diol after desilylation as shown by Evans.[78] Evans proposed that transition state **14** is favored during the final 2+2 cyclization in the ring closing metathesis. The alternative transition state **15** is disfavored because the axial propenyl group experiences unfavorable crowding interactions from the isopropyl groups in the silaketal (Scheme 2).

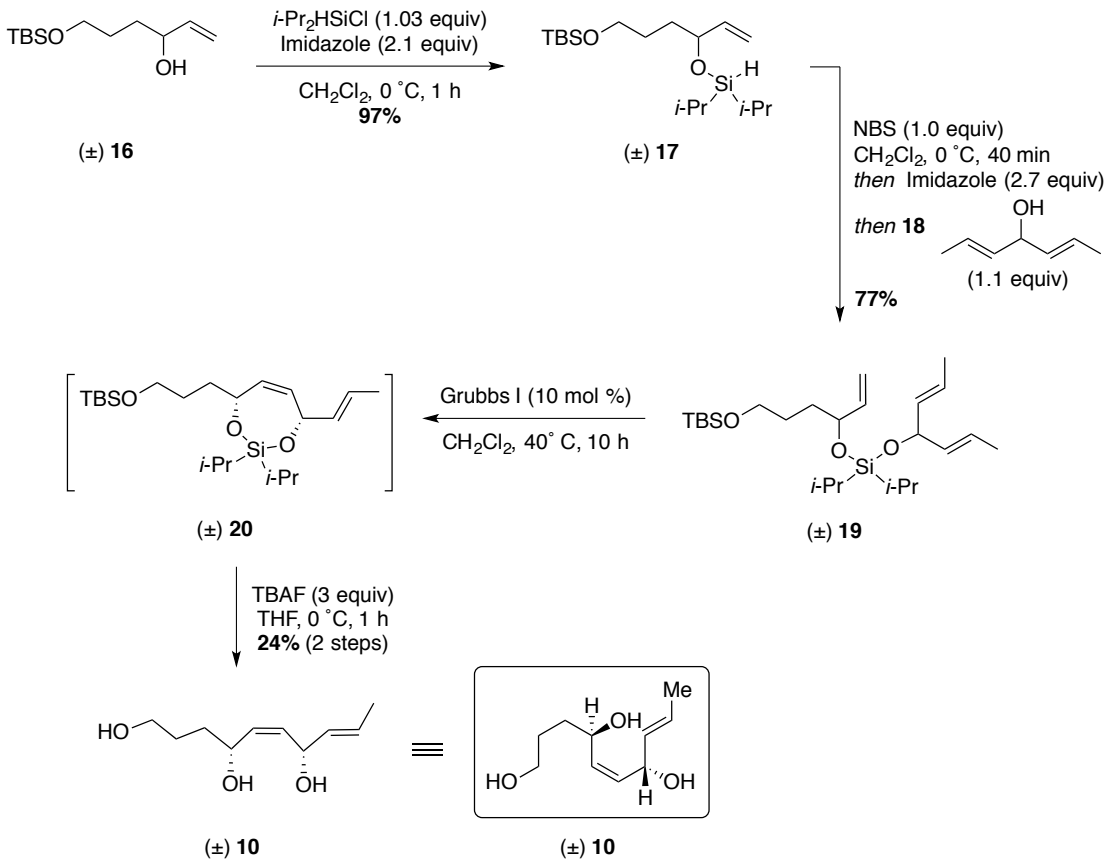
Scheme 2: The synthesis of 1,4-syn diols *via* ring closing metathesis.



2.2.2 Synthesis of bicyclization substrate

Thus, using the silaketal synthesis strategy described by Aubert and Malacria,[80] the allyl alcohol **16** was silylated with chlorodiisopropylsilane to give silane **17** (Scheme 3). Oxidation of the silane with *N*-bromosuccinimide generated the silyl bromide *in situ*, which was then trapped *via* the addition to divinyl alcohol **18**[81] to give silaketal **19**. Ring closing metathesis with Grubbs 1st generation catalyst gave diene **20**, which was subsequently deprotected using excess TBAF to give diol **10**.

Scheme 3: Synthesis of syn-1,4 diol cyclization substrate **10**.

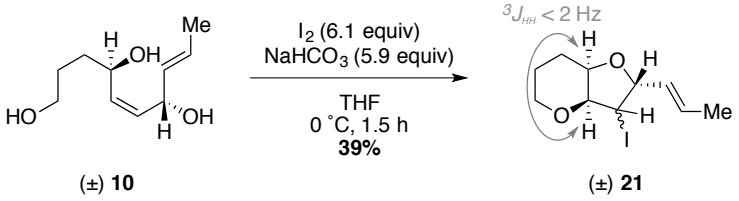


2.3 Bicyclization studies

2.3.1 Bicyclizations with iodine

Scheme 4 details the first attempt at iodine polycyclization. Thus **10** was subjected to 6 equivalents of iodine with sodium bicarbonate. After 1.5 hours, bicycle **21** was isolated in 39% yield. Measurement of the small coupling constant across the pyran strongly suggested that the pyran was *cis*-fused. Close examination of the reaction conditions showed that a there was a slight paucity of sodium bicarbonate relative to iodine. This suggested that HI could have been generated to cause undesired dehydrative cyclizations.

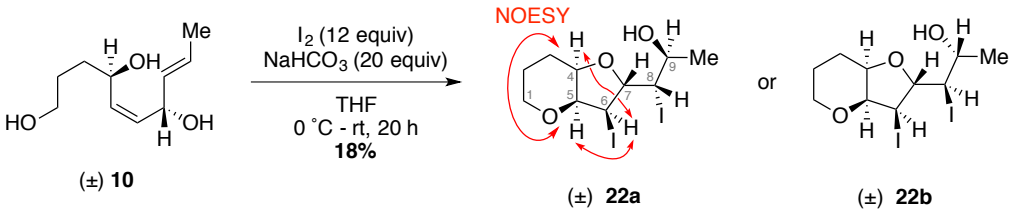
Scheme 4: Use of excess of iodine gives a 6,5 bicycle **21**.



(±) **10** (±) **21**

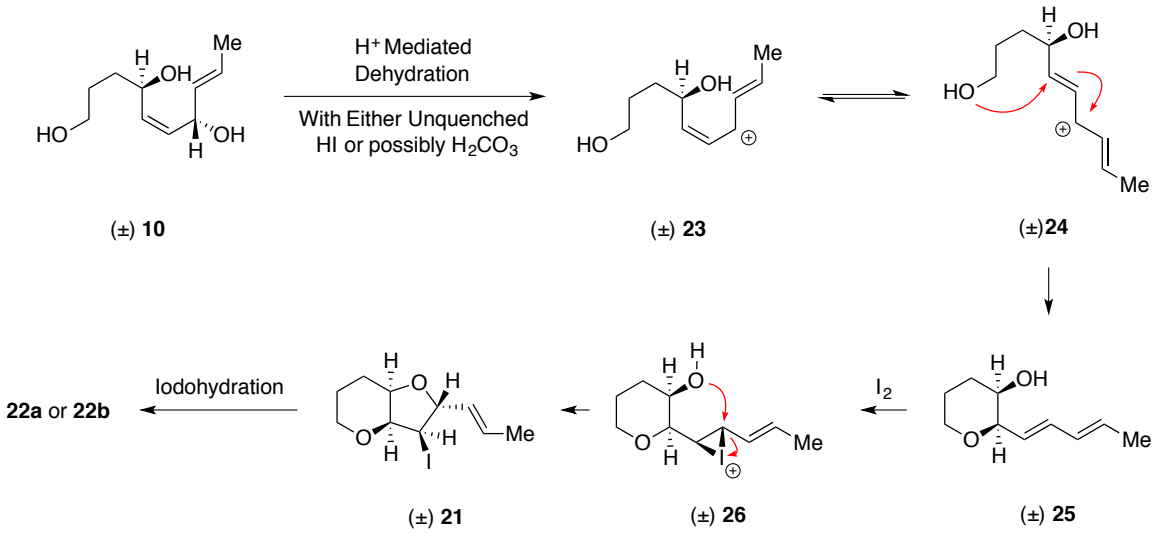
Bicyclization was attempted again, this time using a large excess of sodium bicarbonate (Scheme 5). After 24 hours, compound **23** was isolated as a 6,5 iodohydrin **22a** or **22b**. Only one diastereomer was isolated and it is not clear what the stereochemistry of the iodohydrin sector is. It is suspected to be **22a** based on the small coupling constant between the iodohydrin hydrogen on C-8 and its vicinal hydrogen on the C-7. If the hydroxyl group on C-9 is able to hydrogen bond to the tetrahydrofuran oxygen, then **22a** is more consistent with the observed coupling constants (see experimental for full NMR data).

Scheme 5: Iodocyclization attempt of **10** with excess sodium bicarbonate relative to iodine.



NOE correlations revealed the stereochemistry of the iodine in the tetrahydrofuran ring as well as confirming the *cis*-stereochemistry of the pyran. It became clear that **22** was likely derived from iodohydration of **21**. The observed syn stereochemistry between the hydrogens on C-5 and C-6 was inconsistent with that obtained from iodocyclizations of *cis*-alkenes described in Scheme 1. Scheme 6 details a possible mechanistic explanation for the observed product. Compound **10** could undergo dehydrative ionization to give pentadienyl cation **23**, either through the action of unquenched HI or possibly even from undissociated carbonic acid (pk_a~3.5).[82] Cation **23** could then undergo isomerization to give **24**, which would then cyclization to give diene **25**. The diene could then undergo iodocyclization to give **21** with the observed stereochemistry. Subsequent iodohydration with the water generated in the first step would then give the observed product **22**.

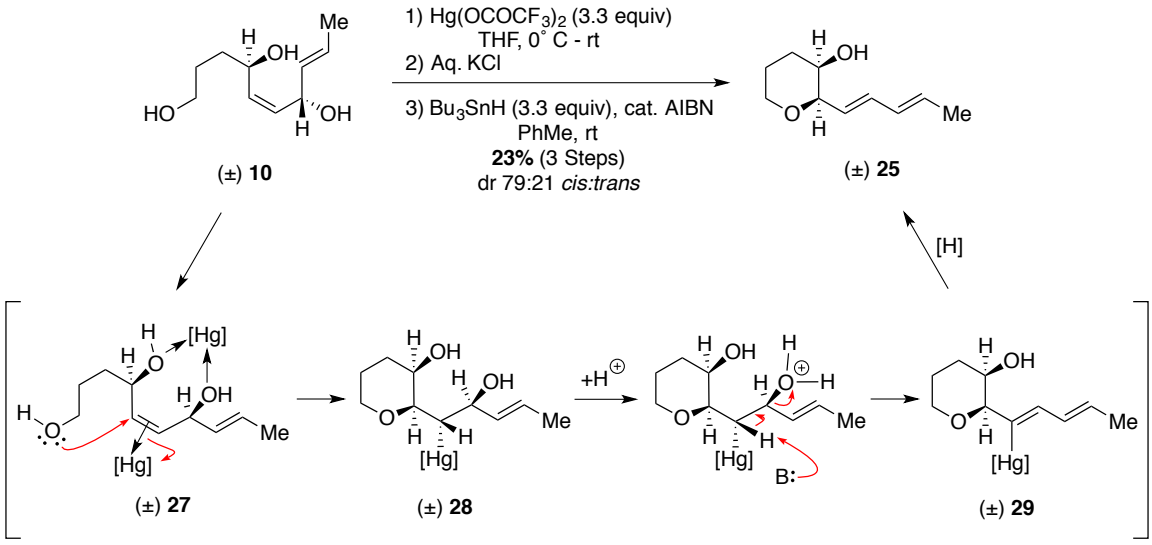
Scheme 6: Possible mechanism for the formation of iodohydrin **22**.



2.3.2 Bicyclization with mercury trifluoroacetate

Disappointment with the results of attempted iodocyclizations of **10** we made an attempt with mercuric trifluoroacetate. Thus, treatment of **10** with an excess of $Hg(OCOCF_3)_2$, followed by anion exchange with KCl and radical demercuration gave diene **28** as the only identifiable product.

Scheme 7: Attempted bicyclization with mercury trifluoroacetate giving pyranyl diene **25**.



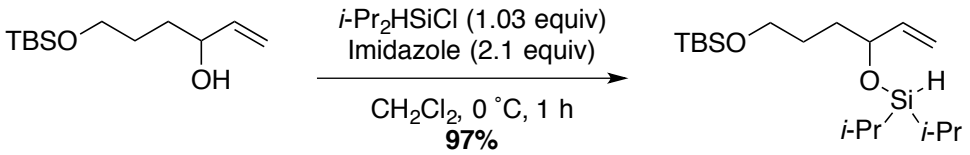
It is not immediately apparent how this came about. It may be possible that one equivalent of mercury coordinated both allylic alcohols to give chelated **29**. Oxymercuration could then give *cis*-fused **30**. The trifluoroacetic acid present would promote elimination to diene **31**, which gave **28** upon radical demetalation. More simply, compound **10** could have undergone dehydration with in situ generated TFA, and then directly cyclized to give **25**, as postulated for the iodocyclization in scheme 6.

2.3.3 Conclusions

Our laboratory has had success with iodine and mercury mediated monocyclizations of allylic alcohols. Unfortunately, these successes did not extent to the cyclization of **10**, with *cis*-pyrans being the only major products with the conditions tested. Particularly challenging are the vulnerabilities of the bis allylic alcohol to undergo dehydration and isomerization under the tested reaction conditions.

2.4 Experimental details

Compound 17



(±) **16** (±) **17**

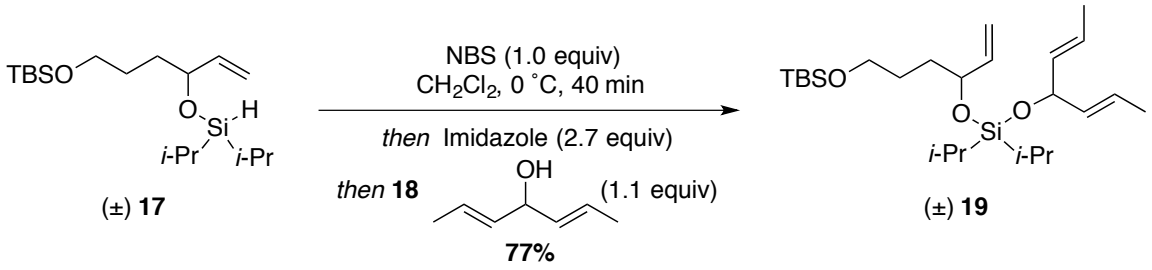
To a solution of the alcohol **16**35 (3.38 g, 14.7 mmol) in CH_2Cl_2 (35 mL) was added imidazole (2.10 g, 31 mmol). The solution was cooled to 0 ˚C and chlorodiisopropylsilane (2.6 mL, 2.3 g, 15.2 mmol) was added dropwise. The mixture was added for 1 h, concentrated under reduced pressure and the resulting oil was filtered through a plug of silica gel (10 g) with an excess of 5/95 Et_2O/Hexanes. The eluant was concentrated under reduced pressure to give the silane **17** (4.93 g, 14.3 mmol, 97%) as a yellow oil.

^{1}H-NMR (300 MHz; $CDCl_3$): δ 5.80 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H), 5.17 (d, *J* = 17.1 Hz, 1H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.18 (s, 1H), 4.14 (q, *J* = 6.0 Hz, 1H), 3.62 (t, *J* = 5.5 Hz, 2H), 1.62-1.52 (m, 6H), 1.02 (m, 12H), 0.90 (s, 9H), 0.05 (s, 6H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 141.06, 114.49, 76.22, 63.38, 34.29, 28.61, 26.19, 26.17, 18.57, 17.80, 17.68, 17.59, 17.54, 17.48, 17.34, 13.47, 12.86, 12.70, -5.05.

IR (CH_2Cl_2) 2950, 2893, 2864, 2094 (Si-H), 1743 (weak), 1463, 1384, 1361, 1255, 1097, 1002. 921. 835, 775 cm^{-1}.

Compound 19



To a solution of the silane **17** (4.93 g, 14.3 mmol) in CH_2Cl_2 (50 mL) at 0 ˚C was added freshly recrystallized *N*-bromosuccinimide (2.55 g, 14.3 mmol). The reaction mixture was stirred at 0 ˚C for 40 minutes whereupon imidazole (2.50 g, 38 mmol) was added followed by a solution of the bis-allyl alcohol **18** (1.75 g, 15.6 mmol) in CH_2Cl_2 (10 mL) at 0 ˚C. The reaction mixture was allowed to warm to rt over 6 h, concentrated under reduced pressure and the resulting oil filtered through silica gel (20 g) with 3/97 Et_2O/Hexanes (200 mL). The eluant was concentrated under reduced pressure to give the silaketal **19** (5.0 g, 11 mmol, 77%) as a yellow oil.

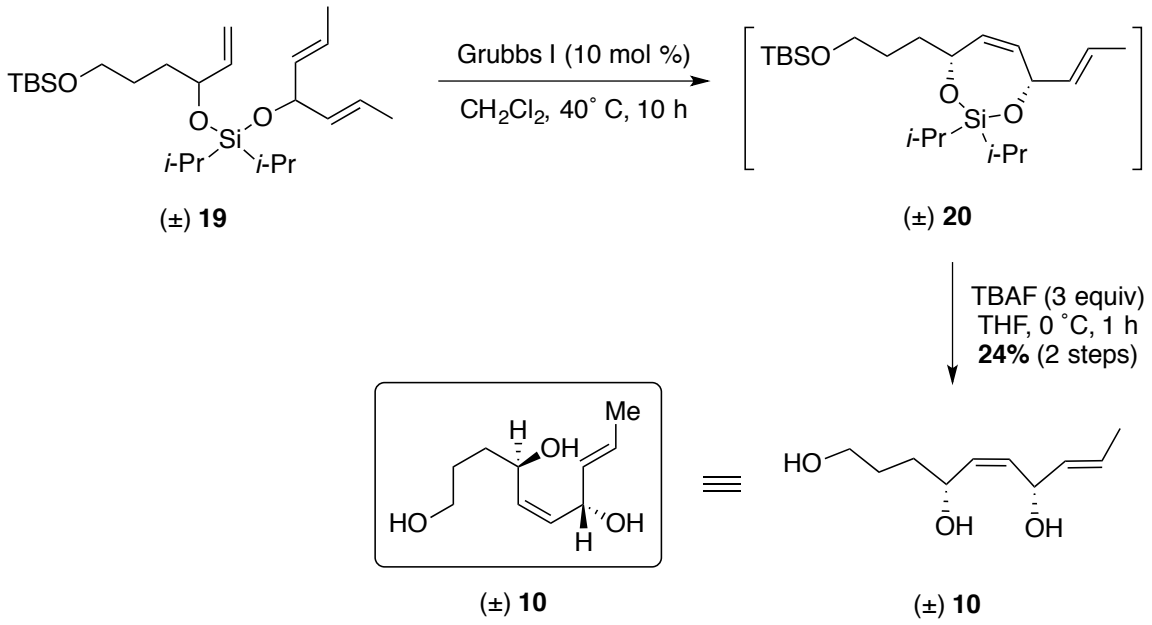
^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.81 (ddd, *J* = 17.0, 10.6, 6.3 Hz, 1H), 5.66-5.54 (m, 2H), 5.50-5.42 (m, 2H), 5.16 (d, *J* = 17.2 Hz, 1H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.69 (t, *J* = 6.1 Hz, 1H), 4.33 (q, *J* = 4.9 Hz, 1H), 3.61 (t, *J* = 6.0 Hz, 2H), 1.69 (d, *J* = 6.4 Hz, 6H), 1.65-1.51 (m, 6H), 1.08-1.01 (m, 12H), 0.88 (s, 9H), 0.05 (s, 6H).

^{13}C-NMR (101 MHz; $CDCl_3$): δ 141.4, 134.10, 134.06, 124.89, 124.88, 114.1, 73.7, 73.3, 63.6, 34.4, 28.2, 26.2, 17.84, 17.83, 17.63, 17.60, 12.96, 12.94, -5.1.

IR (CH_2Cl_2) 3065, 3029, 2947, 2928, 2893, 2864, 1741 (weak), 1644, 1463, 1361, 1252, 1093, 1057, 1030, 922, 884, 834, 775, 696 cm^{-1}

HRMS (APCI) calculated for $C_{25}H_{49}O_3Si_2^+$ $[M-H]^+$ 453.32147, found 453.32150.

Compound 10



(±) **19** (±) **20** (±) **10** (±) **10**

A solution of Grubbs' first generation catalyst (256 mg, 0.31 mmol) in degassed CH_2Cl_2 (10 mL) was added *via* syringe pump over 10 hours to a refluxing solution of silaketal **19** (1.41 g, 3.1 mmol) in degassed CH_2Cl_2 (20 mL). Upon complete addition of the catalyst, the reaction mixture was refluxed for a further 10 hours. After cooling to rt the mixture was diluted with Et_2O, filtered through a pad of silica gel and concentrated under reduced pressure to give a black oil. The oil was dissolved in THF (10 mL), cooled to 0 ˚C and TBAF solution (9.5 mL, 9.5 mmol, 1M in THF) was added slowly. The reaction mixture was stirred at 0 ˚C for 1 h whereupon sat. aq. NH_4Cl (10 mL) was added followed by water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 x 20 mL). The combined organics were washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give a black oil. Column chromatography of the oil (1/99 MeOH/EtOAc) gave the triol **10** (141 mg, 0.76 mmol) as a black oil in 24% yield over two steps.

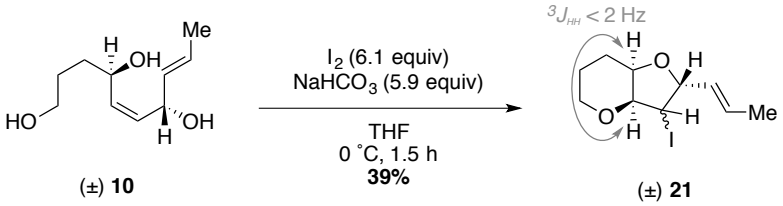
^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.65 (dq, *J* = 15.3, 6.4 Hz, 1H), 5.50-5.44 (m, 3H), 4.88 (t, *J* = 6.2 Hz, 1H), 4.47 (q, *J* = 5.2 Hz, 1H), 3.65-3.54 (m, 2H), 1.67 (d, *J* = 6.4 Hz, 3H), 1.64-1.52 (m, 4H).

^{13}C-NMR (101 MHz; $CDCl_3$): δ 133.8, 132.8, 132.4, 127.5, 68.4, 67.4, 62.6, 34.5, 29.0, 18.0.

IR (CH_2Cl_2) 3344, 3012, 2932, 2856, 1726, 1670, 1447, 1378, 1261, 1056, 1005, 968, 751 cm^{-1}

HRMS (APCI) calculated for $C_{10}H_{18}O_3Na^+$ $[M+Na]^+$ 209.11482, found 209.11542.

Compound 21



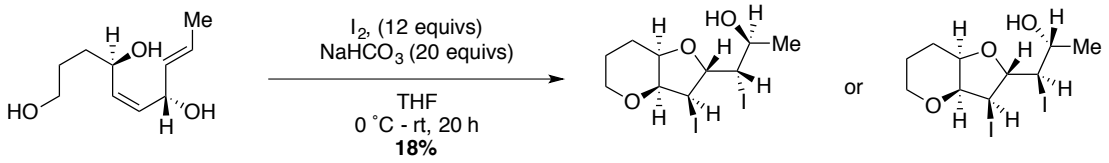
To a solution of the triol **10** (35 mg, 0.19 mmol) in 2 mL THF at 0 ˚C was added $NaHCO_3$ (94 mg, 1.12 mmol) followed by I_2 (294 mg, 1.16 mmol). The reaction mixture was stirred at 0 ˚C for 1.5 hours and quenched with sat. aq. $Na_2S_2O_3$ (5 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography of the crude product eluting with 5/95 EtOAc/Hexanes gave the *cis*-fused dehydrative cyclization product **21** (21 mg, 0.072 mmol, 39%) as a clear oil.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 5.85 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.50 (ddd, *J* = 17.2, 1.4, 0.9 Hz, 1H), 5.38 (ddd, *J* = 10.5, 1.4, 0.8 Hz, 1H), 3.69 (d, *J* = 6.1 Hz, 2H), 3.35 (d, *J* = 7.2 Hz, 1H), 1.60 (t, *J* = 5.2 Hz, 1H), 1.45 (s, 3H).

^{13}C-NMR (101 MHz; $CDCl_3$): δ 132.3, 128.1, 86.7, 73.98, 73.95, 67.2, 30.8, 26.3, 20.0, 18.1.

HRMS (APCI) calculated for $C_{10}H_{16}O_2I^+$ $[M+H]^+$ 295.01895, found 295.01908.

Compound 22



(±) **10** (±) **22a** (±) **22b**

To a solution of the triol **10** (28.7 mg, 0.154 mmol) in 2 mL THF at 0 ˚C was added $NaHCO_3$ (260 mg, 3.09 mmol) followed by I_2 (471 mg, 1.85 mmol). The reaction mixture was allowed to warm to rt over 20 h and quenched with sat. aq. $Na_2S_2O_3$ (8 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 x 5 mL). The combined organics were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography of the crude product eluting with 20/80 EtOAc/Hexanes –> 100% EtOAc gave **22** (12 mg, 0.028 mmol, 18%) as a clear oil.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 4.58 (dd, *J* = 5.1, 1.4 Hz, 1H), 4.26 (dd, *J* = 9.7, 3.4 Hz, 1H), 4.25 (q, *J* = 2.1 Hz, 1H), 4.04 (ddt, *J* = 11.4, 4.0, 1.9 Hz,1H), 3.98 (dqd, *J* = 7.5, 6.3, 5.2 Hz, 1H), 3.91 (dd, *J* = 9.8, 1.2 Hz, 1H), 3.82 (dd, *J* = 3.4, 1.8 Hz, 1H), 3.43 (ddd, *J* = 12.3, 11.6, 1.9 Hz, 1H), 2.48 (d, *J* = 7.7 Hz, 1H), 2.09 (ddq, *J* = 14.7, 4.1, 2.1 Hz, 1H),

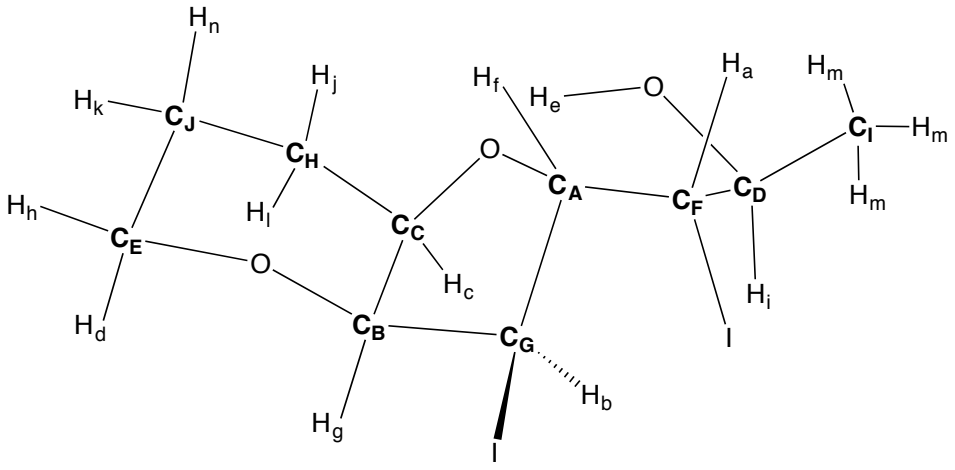
1.83 (qt, *J* = 12.9, 4.1 Hz, 1H), 1.72 (dddd, *J* = 14.6, 13.3, 4.7, 3.4 Hz, 1H), 1.45 (d, *J* = 6.4 Hz, 3H), 1.38 (ddt, *J* = 13.4, 6.7, 2.1 Hz, 1H).

^{1}H-NMR (600 MHz, C_6D_6): δ 4.46 (dd, *J* = 6.1, 1.3 Hz, 1H), 4.13 (dd, *J* = 9.8, 3.4 Hz, 1H), 4.03 (dd, *J* = 9.7, 1.2 Hz, 1H), 3.76 (q, *J* = 2.2 Hz, 1H), 3.74 (q, *J* = 6.5 Hz, 1H), 3.61 (ddt, *J* = 11.4, 4.2, 2.0 Hz, 1H), 3.10 (dd, *J* = 3.3, 1.9 Hz, 1H), 2.80 (ddd, *J* = 12.4, 11.4, 1.8 Hz, 1H), 1.74 (d, *J* = 7.2 Hz, 1H), 1.65 (dtt, *J* = 14.8, 4.0, 2.0 Hz, 1H), 1.55 (tdt, *J* = 13.2, 13.1, 4.3 Hz, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.98 (dddd, *J* = 14.7, 13.2, 5.0, 3.4 Hz, 1H), 0.70 (ddq, *J* = 13.9, 4.6, 2.2 Hz, 1H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 83.82, 76.47, 75.62, 72.13, 67.21, 46.92, 31.48, 26.00, 22.96, 20.04.

IR (CH_2Cl_2): 3370, 2924, 2854, 1658, 1279, 1132, 11015, 801 cm^{-1}.

HRMS (APCI) calculated for $C_{10}H_{17}O_3I_2$ $[M+H]^+$ 438.92616, found 438.92731.



$CDCl_3$

^{1}H-NMR Label	Shift (ppm)	Multiplicity	Couplings (Hz)	COSY Correlations	NOESY Correlations
a	4.58	dd	5.1, 1.4	H_e, H_f	H_e, H_f, H_{m3}
b	4.26	dd	9.7, 3.4	H_f, H_g	large overlaps
c	4.25	q	2.1	H_l, H_j, H_g	large overlaps
d	4.04	ddt	11.4, 4.0, 1.9	H_h, H_k, H_n, **H_j (W Coupling)**	H_h, H_n, H_k
e	3.98	dqd	7.5, 6.3, 5.2	H_i, H_{m3}, H_a	H_a, H_{m3}, H_i
f	3.91	dd	9.8, 1.2	H_b, H_a	H_a
g	3.82	dd	3.4, 1.8	H_b, H_c	H_l, H_g
h	3.43	ddd	12.3, 11.6, 1.9	H_d, H_k, H_n	H_d, H_g, H_n, H_k
i	2.48	d	7.7	H_e	H_e
j	2.09	ddq	14.7, 4.1, 2.1	H_l, H_k, H_n, H_c, **H_d (W Coupling)**	H_l, H_k
k	1.83	qt	12.9, 4.1	H_n, H_h, H_j, H_l, H_d	H_n, H_h, H_d
l	1.72	dddd	14.6, 13.3, 4.7, 3.4	H_j, H_n, H_c, H_k	H_j, H_h, H_g
m_3	1.45	d	6.4	H_e	H_e, H_a
n	1.38	ddt	13.4, 6.7, 2.1	H_k, H_h, H_d, H_j, H_l	H_k, H_h, H_d

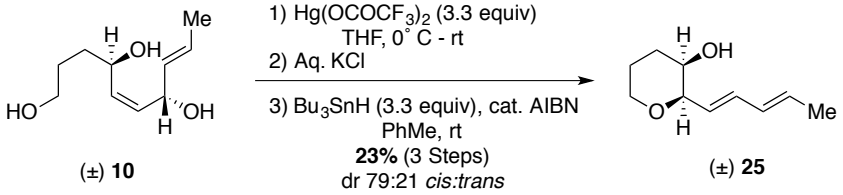
C_6D_6

^{1}H-NMR Label	Shift (ppm)	Multiplicity	Couplings (Hz)	COSY Correlations	NOESY Correlations
a	4.46	dd	6.1, 1.3	H_e, H_f	H_b, H_e, H_f, H_{m3}
b	4.13	dd	9.8, 3.4	H_f, H_g	H_a, H_c, H_g
c	3.76	q	2.2	H_l, H_j, H_g	large overlaps
d	3.61	ddt	11.4, 4.2, 2.0	H_h, H_k	H_h, H_k, H_n
e	3.74	app. q	6.5	H_i, H_{m3}, H_a	large overlaps
f	4.03	dd	9.7, 1.2	H_b, H_a	H_a
g	3.1	dd	3.3, 1.9	H_b, H_c	H_b, H_c, H_l
h	2.8	ddd	12.4, 11.4, 1.8	H_d, H_k	H_d, H_g, H_k, H_l
i	1.74	d	7.2	H_e	H_e
j	1.65	dtt	14.8, 4.0, 2.0	H_l, H_k	H_c, H_l, H_n
k	1.55	tdt	13.2, 13.1, 4.3	H_n, H_h, H_j, H_l, H_d	H_d, H_h, H_l, H_n
l	0.98	dddd	14.7, 13.2, 5.0, 3.4	H_j, H_k, H_c, H_n	H_c, H_g, H_h, H_j
m_3	1.17	d	6.3	H_e	H_a, H_f, H_e
n	0.7	ddq	13.9, 4.6, 2.2	H_k, H_h, H_d, H_j, H_l	H_k, H_d, H_h, H_j, H_l

$CDCl_3$

^{13}C-NMR Label	Shift (ppm)	APT Phase	HMQC Couplings	HMBC Couplings
A	83.82	+	H_f	H_b, H_e, H_g
B	76.47	+	H_g	H_d, H_h, H_b
C	75.62	+	H_c	H_g, H_n, H_j
D	72.13	+	H_e	H_a, H_f, H_i, H_{m3}
E	67.21	-	H_d, H_h	H_k
F	46.92	+	H_a	H_b, H_f, H_i, H_{m3}
G	31.48	+	H_b	H_f, H_a
H	26.00	-	H_j, H_l	H_d, H_h, H_k, H_n
I	22.96	+	H_{m3}	H_a, H_e, h_i
J	20.04	-	H_k, H_n	H_c, H_h, H_j, H_l

Compound 25



(±) **10** (±) **25**

To a solution of the triol **10** (52.9 mg, 0.280 mmol) in THF (3 mL) at 0 ˚C was added a solution of $Hg(TFA)_2$ (387 mg, 0.91 mmol) in THF (4 mL). The reaction mixture was stirred at 0˚ C for 1 h 20 min and then allowed to warm to rt over 2 h whereupon sat. aq. KCl (0.4 mL) was added. The reaction mixture was diluted with EtOAc (5 mL), washed with water (2 x 5 mL), brine (5 mL) and the organics dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in PhMe (10 mL) and a single crystal of AIBN added followed by Bu_3SnH (0.25 mL, 0.93 mmol) whereupon the reaction mixture immediately turned grey, suggesting elemental Hg precipitation. The reaction was stirred for another 12 hours, whereupon sat. aq. KF (10 mL) was added and the mixture stirred for 2 h. The mixture was extracted with EtOAc (2 x 5 mL), the combined organics dried over $MgSO_4$ and concentrated under *in*

vacuo. Chromatography of the crude material with using 10% KF wt/wt in silica gel and eluting with 20/80 EtOAc/Hexanes gave the pyranyl diene **25** (10.7 mg, 0.064 mmol, 23%, dr 79:21 *cis*/*trans*) as a colorless film.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.31 (dd, *J* = 15.4, 11.0 Hz, 1H), 6.07 (ddq, *J* = 14.7, 10.9, 1.7 Hz, 1H), 5.73 (dd, *J* = 15.0, 6.9 Hz, 1H), 5.58 (dd, *J* = 15.6, 5.1 Hz, 1H), 4.04 (ddt, *J* = 11.4, 4.4, 2.1 Hz, 1H), 3.96 (t, *J* = 4.5 Hz, 1H), 3.74-3.71 (dt, *J* = 6.6, 3.2 Hz, 1H), 3.53 (td, *J* = 11.8, 2.4 Hz, 1H), 2.03-1.93 (m, 2H), 1.76 (d, *J* = 6.6 Hz, 3H), 1.73-1.69 (m, 1H), 1.42-1.37 (m, 1H).

^{13}C-NMR (151 MHz, $CDCl_3$): δ 132.63, 131.04, 130.55, 127.66, 79.86, 68.52, 67.28, 30.17, 20.23, 18.34.

3.1 References

(1) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.

(2) Bourdelais, A. J.; Campbell, S.; Jacocks, H.; Naar, J.; Wright, J. L. C.; Carsi, J.; Baden, D. G. *Cell. Mol. Neurobiol.* **2004**, *24*, 553.

(3) Potera, C. *Science.* **2007**, *316*, 1561.

(4) Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374.

(5) Nicolaou, K. C. *Angew. Chem., Int. Ed.* **1996**, *35*, 588.

(6) Zhang, Y.; Rohanna, J.; Zhou, J.; Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2011**, *133*, 3208.

(7) Fuwa, H.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 9648.

(8) Takamura, H.; Kikuchi, S.; Nakamura, Y.; Yamagami, Y.; Kishi, T.; Kadota, I.; Yamamoto, Y. *Org. Lett.* **2009**, *11*, 2531.

(9) Sakai, T.; Matsushita, S.; Arakawa, S.; Mori, K.; Tanimoto, M.; Tokumasu, A.; Yoshida, T.; Mori, Y. *J. Am. Chem. Soc.* **2015**, *137*, 14513.

(10) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983.

(11) Hirama, M. *Science.* **2001**, *294*, 1904.

(12) McDonald, F. E.; Valentine, J. C. *Synlett*. **2006**, *12*, 1816.

(13) McDonald, F. E.; Tong, R.; Valentine, J. C.; Bravo, F. *Pure Appl. Chem.* **2007**, *79*, 281.

(14) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515.

(15) Bravo, F.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *Org. Lett.* **2004**, *6*, 4487.

(16) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917.

(17) Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586.

(18) Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett*. **2000**, *3*, 335.

(19) Vilotijevic, I.; Jamison, T. F. *Science*. **2007**, *317*, 1189.

(20) McDonald, F. E.; Ishida, K.; Hurtak, J. A. *Tetrahedron*. **2013**, *69*, 7746.

(21) He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, 8037.

(22) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed*. **1982**, *21*, 654.

(23) Murata, M.; Kumagai, M.; Lee, J. S.; Yasumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5869.

(24) Muzart, J. *J. Mol. Catal. A Chem.* **2010**, *319*, 1.

(25) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927.

(26) Trost, B. M.; Greenspan, P. D.; Geissler, H.; Kim, J. H.; Greeves, N. *Angew. Chemie., Int. Ed.* **1994**, *33*, 2182.

(27) Uenishi, J.; Vikhe, Y. S.; Kawai, N. *Chem. - An Asian J.* **2008**, *3*, 473.

(28) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(29) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(30) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(31) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973.

(32) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318.

(33) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2012**, *134*, 693.

(34) McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593.

(35) Ascic, E.; Ohm, R. G.; Petersen, R.; Hansen, M. R.; Hansen, C. L.; Madsen, D.; Tanner, D.; Nielsen, T. E. *Chem. - A Eur. J.* **2014**, *20*, 3297.

(36) Jana, N.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2622.

(37) Kim, N.; Ko, S.; Kwon, M. S.; Kim, M.; Park, J. *Org. Lett.* **2005**, *7*, 4523.

(38) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat Protoc*. **2007**, *2*, 2451.

(39) Duboudin, J. G.; Jousseaume, B.; Bonakdar, A.; Saux, A. *J. Organomet. Chem.* **1979**, *168*, 227.

(40) Xiao, Q.; Young, K.; Zakarian, A. *Org. Lett.* **2013**, *15*, 3314.

(41) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(42) Katsuki, T.; Martin, V. *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, **1995**, *48*, 1.

(43) Hamze, A.; Provot, O.; Brion, J.-D.; Alami, M. *J. Org. Chem.* **2007**, *72*, 3868.

(44) Duboudin, J. G.; Jousseaume, B.; Saux, A. *J. Organomet. Chem.* **1979**, *168*, 1.

(45) *iNMR*, version 5.5.7; software for NMR spectra analysis and diastereomeric ratio fitting; Mestrelab Research: Molfetta, Italy **2016**.

(46) Prakash, C.; Saleh, S.; Blair, I. A. *Tetrahedron Lett*. **1989**, *30,* 19.

(47) Schmidt, B. *Eur. J. Org. Chem.* **2004**, *2004*, 1865.

(48) Dinger, M. B.; Mol, J. C. *Organometallics* **2003**, *22*, 1089.

(49) Dos Santos, A. A.; Brito Jr., G. A.; Archilha, M. V. L.; Bele, T. G. A.; Dos Santos, G. P.; Mello, M. B. M. de. *J. Braz. Chem. Soc.* **2009**, *20*, 42.

(50) Ito, M.; Hirakawa, M.; Osaku, A.; Ikariya, T. *Organometallics* **2003**, *22*, 4190.

(51) Shaterian, H. R.; Doostmohammadi, R.; Ghashang, M. *Chin. J. Chem.* **2008**, *26*, 1709.

(52) Spangler, C. W.; McCoy, R. K.; Karavakis, A. A. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1203.

(53) Grob, C. A.; Baumann, W. *Helv. Chim. Acta* **1955**, *38*, 594.

(54) Prantz, K.; Mulzer, J. *Chem. Rev.* **2010**, *110*, 3741.

(55) Davis, D. G.; Bax, A. *J. Am. Chem. Soc.* **1985**, *107*, 7197.

(56) Rössle, M.; Del Valle, D. J.; Krische, M. J. *Org. Lett.* **2011**, *13*, 1482.

(57) Ueki, H.; Kitazume, T. *J. Org. Chem.* **2005**, *70*, 9354.

(58) Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 16901.

(59) Kleinman, E. F. "Dimethyl(methylene)ammonium Iodide" *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd: Chichester, UK, 2001.

(60) Steves, J. E.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 15742.

(61) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

(62) Trost, B. M.; Ito, N.; Greenspan, P. D. *Tetrahedron Lett.* **1993**, *34*, 1421.

(63) Trost, B. M.; Vos, B. A.; Brzezowski, C. M.; Martina, D. P. *Tetrahedron Lett.* **1992**, *33*, 717.

(64) Aponick, A.; Biannic, B. *Org. Lett.* **2011**, *13*, 1330.

(65) Lemieux, R. U.; Martin, J. C. *Carbohydr. Res.* **1970**, *13*, 139.

(66) He, A.; Sutivisedsak, N.; Spilling, C. D. *Org. Lett.* **2009**, *11*, 3124.

(67) Li, Y.; Jardine, K. J.; Tan, R.; Song, D.; Dong, V. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9690.

(68) Trost, B. M.; Tometzki, G. B. *J. Org. Chem.* **1988**, *53*, 915.

(69) Trost, B. M.; Vos, B. A.; Brzezowski, C. M.; Martina, D. P. *Tetrahedron Lett.* **1992**, *33*, 717.

(70) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

(71) Garbisch, E. W.; Griffith, M. G. *J. Am. Chem. Soc.* **1968**, *90*, 3590.

(72) Del Valle, D. J.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 10986.

(73) Steinhardt, S. E.; Silverston, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 7560.

(74) Park, J.; Kim, S. H.; Lee, P. H. *Org. Lett.* **2008**, *10*, 5067.

(75) Hatakeyama, S.; Ishihara, J.; Tokuda, O.; Shiraishi, K.; Nishino, Y.; Takahashi, K. *Heterocycles* **2010**, *80*, 1067.

(76) Enders, D.; Nguyen, D. *Synthesis.* **2000**, *2000*, 2092.

(77) Tilstam, U.; Weinmann, H. *Org. Process Res. Dev*. **2002**, *6*, 906.

(78) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1734.

(79) Harrison, B. A.; Verdine, G. L. *Org. Lett.* **2001**, *3*, 2157.

(80) Petit, M.; Chouraqui, G.; Aubert, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 2037.

(81) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7591.

(82) Pines, D.; Ditkovich, J.; Mukra, T.; Miller, Y.; Kiefer, P. M.; Daschakraborty, S.; Hynes, J. T.; Pines, E. *J. Phys. Chem. B.* **2016**, *120*, 2440.