A HIGHLY CONVERGENT APPROACH TO BREVETOXIN A

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A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Chemistry.

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ABSTRACT

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(Under the direction of Michael T. Crimmins)

Through optimized, scaled-up routes to the G and J rings of brevetoxin A, a convergent strategy based upon a Horner-Wadsworth-Emmons coupling reaction completed the GHIJ fragment. Further studies toward an alternative protecting group strategy for the GHIJ fragment elucidated a shortened synthesis. The union of a GHIJ fragment aldehyde with a BCDE fragment phosphine oxide was accomplished using a Horner-Wittig reaction, and the resulting compound was taken on to the decacyclic core through a dithioketal cyclization/ reductive etherification sequence. The advanced intermediate thus obtained is expected to be a viable precursor to brevetoxin A.

ACKNOWLEDGEMENTS

"We take students who don't know which end of a 'sep funnel' is up, and turn them into well-trained organic chemists."

-Professor Michael Crimmins, on my visitation weekend

"The road to the PhD degree is not a sprint; it's a marathon."

-Professor Michel Gagne, in the ever-reliable Kenan elevator

The above two quotes describe a lot about my experiences at UNC-Chapel hill under the tutelage of Professor Crimmins. When I began work in his lab, I had to make the transition from the classroom, where I felt confident and comfortable, to the unfamiliar world of actual hands-on synthetic chemistry. While I had much to be taught and had plenty of learning experiences (i.e., errors), I remembered what Professor Crimmins had told me when I first met with him on my visitation weekend as a prospective graduate student. I can say that his statement was more accurate than he probably even knows. In all seriousness, I would like to thankfully acknowledge Professor Crimmins for his guidance, fairness, patience, scholarly advisement, and for creating a positive, up-beat working environment. Thank you, Mike, for equipping your students for success.

I would also like to express my gratitude to all of the talented scientists that I have had the pleasure of working with in the Crimmins laboratory for their helpfulness, advice, expertise, and most importantly, for their friendship. I never knew that so much of my graduate education would come from my peers, and I especially thank Dr. Pamela Cleary and Dr. Patrick McDougall for being "peer mentors." They are the ones who patiently worked with me one-on-one the most to get me up to speed on the technical aspects of organic chemistry. Also, my graduate experience was very much enriched by my teamwork with Dr. McDougall and Dr. Michael Ellis on the brevetoxin A project. My contributions to the project benefited greatly from my partnership with them, as well as the excellent foundational work set forth by Dr. Cleary and Dr. John Parrish. In addition, Dr. McDougall and Dr. Ellis were always there to bounce ideas off of, or just "talk chemistry," for which I am grateful.

Although my time in the Crimmins group was certainly a positive and enjoyable experience overall due to the atmosphere of camaraderie and thoughtful scientific inquiry, as the quote from Professor Gagne above alludes to, there are times when the road gets rough. I must thank those people that kept me going during the tough times when perseverance became key. To my darling wife Sandy: no matter how difficult a day was in lab, I always found a smile when I came home. Thank you for your love and steady support. To my parents and family: many thanks for just listening on the telephone, even when you didn't even really know what I was talking about, and for supporting me through a long educational journey. And perhaps more importantly, thank you for bringing me up the right way and enabling me to be who I am today.

Last but most important, I thank God for all the opportunities that I've been given, and for this wonderful chapter in my life in Chapel Hill.

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LIST OF ABBREVIATIONS

9-BBN	9-borabicyclo-[3.3.1]nonane
Ac	acetyl
acac	acetylacetonate ion
Bn	benzyl
Bu	butyl
Bz	benzoyl
CDI	1,1'-carbonyldiimidazole
COD	cyclooctadiene
COSY	correlation spectroscopy
Cy	cylcohexyl
DBU	1,8-Diazabicyclo-[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-*para*-benzoquinone
DIBALH	diisobutylaluminum hydride
DIEA	*N*-ethyldiisopropylamine
DMAP	*N,N*-dimethyl-4-aminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethylene
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
EE	1-(ethoxy)ethyl
ent	enantiomer (of)
Et	ethyl
G1	Grubbs catalyst, 1st generation
G2	Grubbs catalyst, 2nd generation
HMDS	hexamethyldisilizane
HWE	Horner-Wadsworth-Emmons
imid.	Imidazole
Ipc	isopinocampheyl
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LDBB	lithium di-*t*-butylbiphenyl
M	metal
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MOP	methoxy propyl
NaHMDS	sodium bis(trimethylsilyl)amide
NAP	napthyl

NMO	4-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidinone
NOESY	nuclear Overhauser effect spectroscopy
ox.	oxidation
P	protecting group
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
*p*TSA	*para*-toluenesulfonic acid
pyr	pyridine
RCM	ring-closing metathesis
SAE	Sharpless asymmetric epoxidation
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-piperidine 1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TfO	triflate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Tr	trityl
Xc	chiral auxiliary

CHAPTER 1

LADDER TOXINS AND STRATEGIES FOR THEIR SYNTHESIS

A. The Ladder Toxins: Introduction

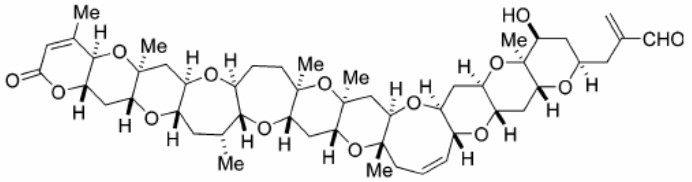
The chemical structure of natural products has intrigued the organic chemist over the course of the past two centuries. Since the first synthesis of urea in 1828 by Wöhler, the elucidation and chemical construction of Nature's molecular architecture has been a central endeavor in organic chemistry. Through the splendid efforts of many exceptional scientists whose work has spanned these many years, including Nobel Prize winners E. Fischer, H. Fischer, R. Robinson, R. B. Woodward, and E. J. Corey, synthetic organic chemistry has developed into a sophisticated science aimed at efficiently assembling even the most complex molecular frameworks through methods limited only by the imagination.

As much as ever, the modern synthetic organic chemist is inspired and challenged by the intricate structures found in Nature. One seemingly endless source of wonderfully complex and elegant structures is the oceanic environment. Among the plethora of molecular structural found in marine metabolites, medium ring ethers represent an interesting niche because of their challenge from a synthetic perspective. To date, three general classes of marine natural products are known to

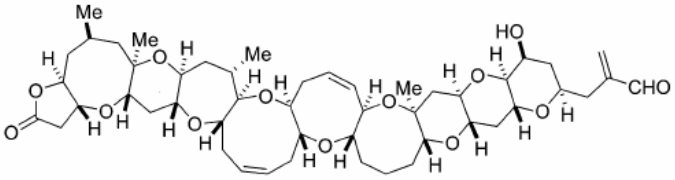
contain medium ring ethers: the C2,C11-cyclized cembranoids, the *Laurencia* metabolites, and the ladder toxins.[1]

The ladder toxins are distinguished by their ladder-like polycyclic ether core (Figure 1.1). The cyclic ethers are five- to nine-membered rings fused in a trans/syn/trans arrangement, and are decorated with intermittent hydroxyl and methyl groups. Brevetoxin B (**1**), isolated in 1981 from the marine dinoflagellate *Karenia breve*, was the first ladder toxin to be structurally defined.[2] Since that time, four other siblings of brevetoxin B have been isolated from the same organism: brevetoxin A (**2**),[3] hemibrevetoxin B (**3**),[4] and brevenal (**4**).[5]

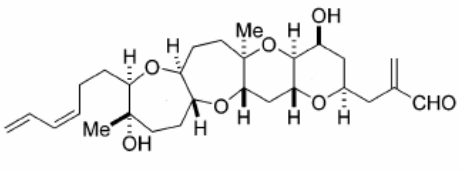
Figure 1.1. Ladder toxins isolated from *Karenia breve*.



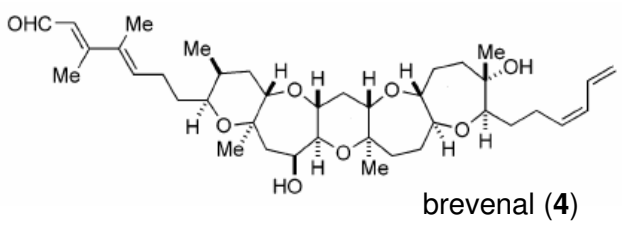
brevetoxin B (**1**)



brevetoxin A (**2**)



hemibrevetoxin B (**3**)



brevenal (**4**)

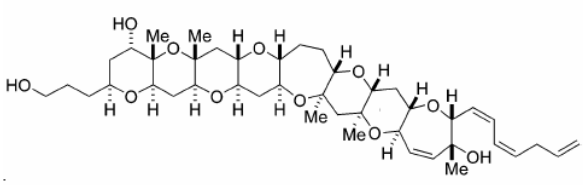
Additional ladder toxin molecules have been also been isolated from marine organisms other than *Karenia breve*. Gambierol (**5**),[6] ciguatoxin CTX3 (**6**),[7] gambieric acid (**7**),[8] and maitotoxin (**8**)[9] have all been isolated from *Gambierdiscus toxicus*, with maitotoxin being the largest non-polymeric natural product known (Figure 1.2). Gymnocin and yessotoxin (**9** and **10**, Figure 1.3) are two other interesting ladder toxins which have been isolated from *Gymnodinium mikimotoi* and *Protoceratium reticulatum*, respectively.[10,11]

The unicellular phytoplankton *Karenia breve* and the brevetoxins are infamous for their association with the destructive "red tide" phenomenon. *Karenia breve* phytoplankton are known to undergo rapid population growth spurts called algal blooms. These blooms impart a red coloration in the water due to the high concentration of the organism, which in some cases has stretched for miles of coastal waters. The red tide coincides with a significant increase in local concentrations of the brevetoxins derived from the organism, and has thereby caused massive fish kills as well as neurotoxic shellfish poisoning and respiratory irritation in humans.[12,13]

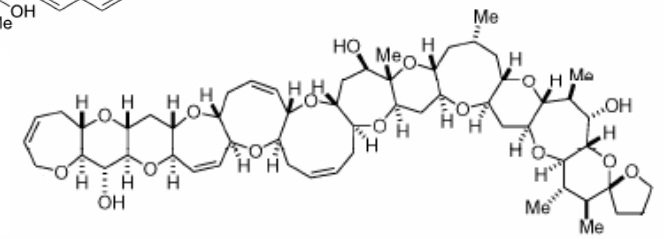
The mode of action for both the brevetoxins and ciguatoxins involves selective binding to site 5 of voltage-sensitive sodium channels (VSSCs). The binding causes open channel conformations to be stabilized, inhibition of inactivation, membrane depolarization, and neurotransmitter failure.[14,5] The symptomatic effects of the brevetoxins include paralysis and dyspnea, and can ultimately cause death due to respiratory paralysis.[15] The relative toxicity of these toxins are as follows: ciguatoxin (**6**, LD_{50}= 0.33 μg/kg, intraparitoneal injection) > brevetoxin A (**2**, LD_{50}=

100 μg/kg) > brevetoxin B (**1**, LD_{50}= 200 μg/kg) > hemibrevetoxin B (**3**).[14-17] Thus, it appears that molecular size (i.e., number of rings) and conformational flexibility (i.e., number of medium-sized rings, which have greater conformational freedom relative to common rings) are both important factors in the binding affinity to site 5 of the

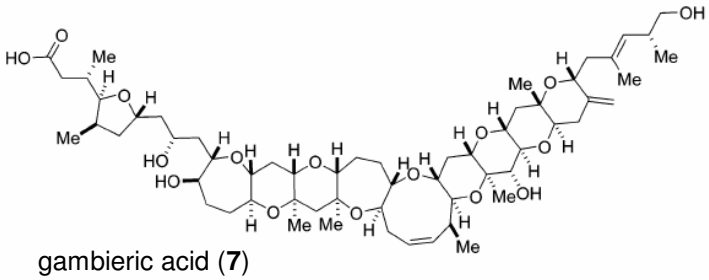
Figure 1.2 Ladder toxin molecules isolated from *Gambierdiscus toxicus*.



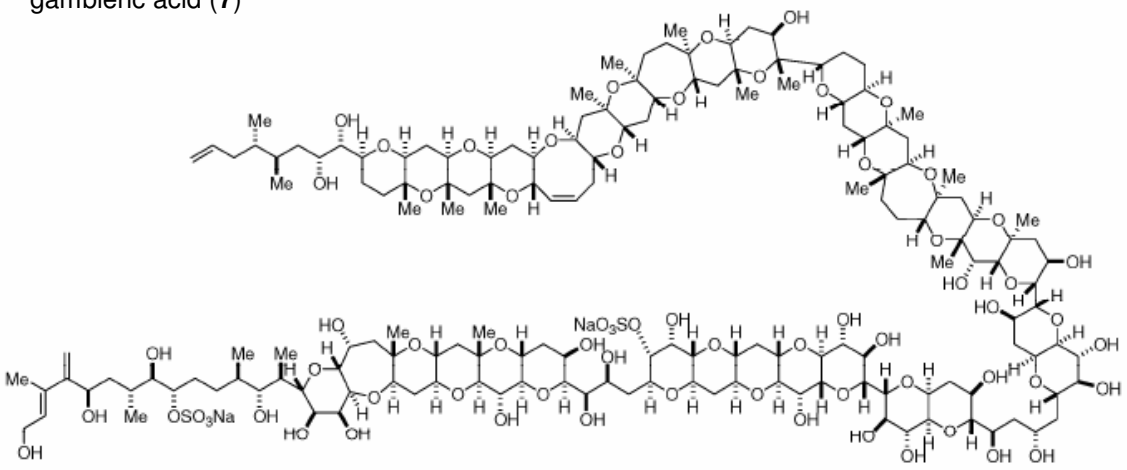
gambierol (**5**)



ciguatoxin CTX3 (**6**)



gambieric acid (**7**)

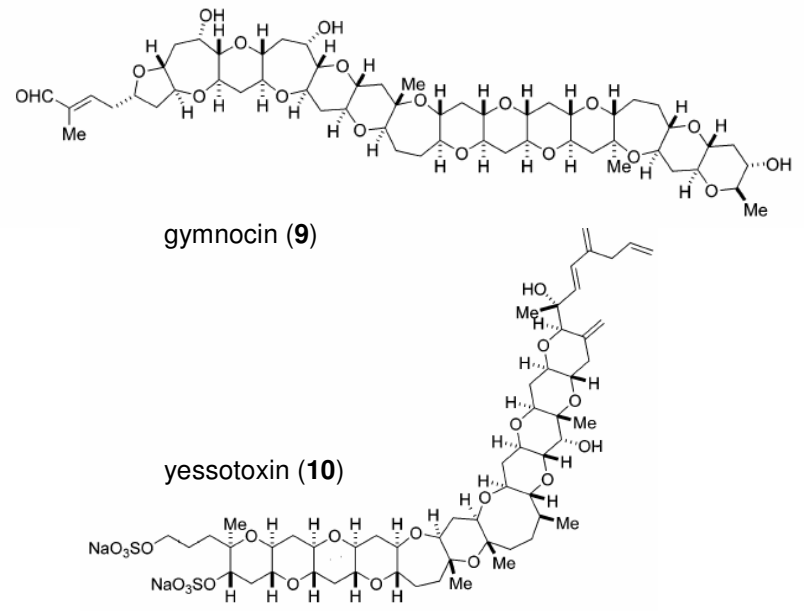


maitotoxin (**8**)

VSSCs. Furthermore, both the lactone carbonyl "head" and the aliphatic chain "tail" of brevetoxins A and B are important for binding, since chemical alteration of these

groups decreases binding affinity.[14] Interestingly, despite its structural similarity to the brevetoxins, brevenal (**4**) is actually non-toxic to fish and displaces the brevetoxins from their binding site in the VSSCs, thus counteracting their toxic effects.[5] The fact that the brevetoxins and brevenal both derive from the same organism is interesting from an evolutionary point of view.

Figure 1.3. Other ladder toxin molecules.



B. Synthetic Strategies for the Synthesis of Polycyclic Ethers

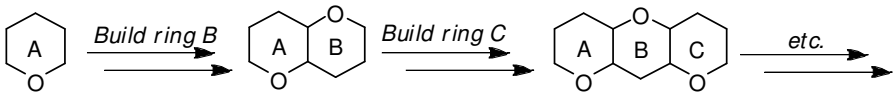
Since the elucidation of the structure of brevetoxin B in 1981, numerous synthetic strategies aimed at trans-fused polycyclic ethers have been developed. Some of these strategies have been successfully employed in the total synthesis of ladder toxin molecules, the ultimate test of their utility. Convergent strategies for polycyclic ether synthesis as well the total synthesis of ladder toxin natural products accomplished up to the year 2005 have been reviewed.[18,19] Therefore, the main

focus here will be on those strategies and syntheses published later than the most recent reviews.

1. Iterative (Linear) Strategies

The simplest strategy to envision for the assembly of a polycyclic ether array is the iterative addition of new rings onto existing ones (Scheme 1.1). Generically, ring B is built onto ring A; ring C is then built onto the AB bicycle; and so on. This type of strategy is most powerful when the ring-forming steps are highly efficient and the number of steps required per iteration is minimized. In practice, polycyclic ether arrays built through iterative strategies have generally been limited to four or five contiguous rings to avoid untenably lengthy linear sequences. If the natural product has additional rings to be built up, the tetra- or pentacyclic fragment is typically coupled with another (polycyclic) molecular fragment using a convergent coupling strategy, several of which are described below. Notable exceptions include iterative syntheses of a heptacyclic fragment of brevetoxin B (**1**) by Nicolaou[20] and Nakata.[21]

Scheme 1.1. Iterative approach to polycyclic ether synthesis.

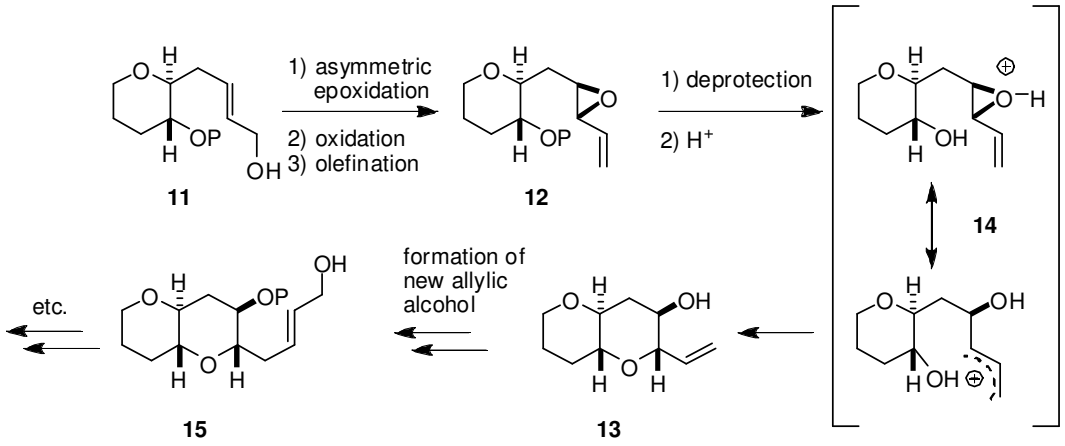


Hydroxy Vinylepoxide- Opening

The hydroxy vinylepoxide-opening strategy for the iterative assembly of cyclic ethers was originally designed by Nicolaou,[22] and has been regularly utilized in the appending of pyrans onto existing polycyclic arrays.[19] In this strategy, the allylic

alcohol moiety on a cyclic ether **11** is transformed to a vinyl epoxide **12** through a sequence consisting of asymmetric epoxidation, primary hydroxyl oxidation, and Wittig olefination (Scheme 1.2). The hydroxy vinylepoxide undergoes cyclization under acidic conditions to form a pyran ring **13** selectively due to π-stabilization of partial positive charge on intermediate **14**. The resulting vinyl group can be transformed into another allylic alcohol **15** to repeat the process.

Scheme 1.2. Generic depiction of the hydroxy vinylepoxide opening.



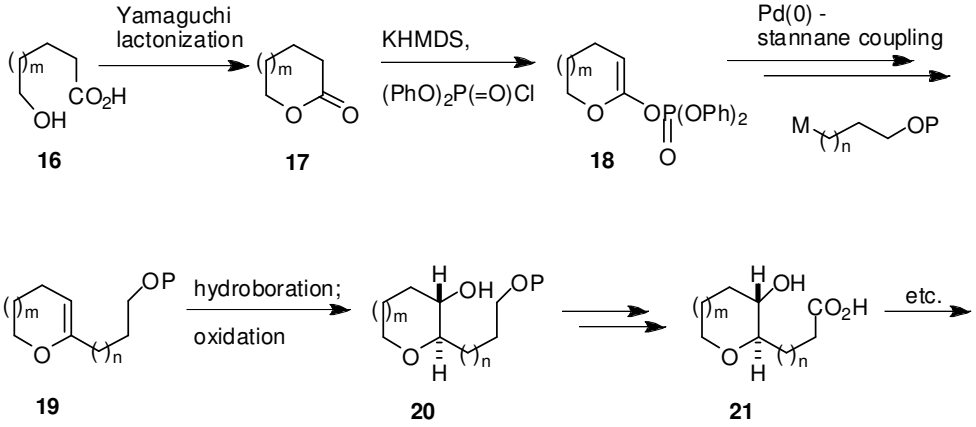
A concrete example of this strategy in the context of the total synthesis of brevetoxin A is described later in the chapter (section C).

Lactonization/Transition Metal-Mediated Enol Ether Formation

Another approach developed by Nicolaou[23] that is especially useful in the formation of medium-sized cyclic ethers involves lactonization of a hydroxy carboxylic acid **16** (Scheme 1.3) and subsequent exposure to KHMDS and $(PhO)_2P(=O)Cl$ to form the corresponding enol phosphate **18**. Enol phosphates are proven substrates for Pd(0)-catalyzed coupling with various stannanes to form enol

ethers **19**. Upon hydroboration, the resulting alcohol **20** can be taken on to another hydroxy carboxylic acid substrate **21** to repeat the process.

Scheme 1.3. Generic depiction of the lactonization/transition metal mediated enol ether formation. Note: n,m = 1-4.



16 **17** **18** **19** **20** **21**

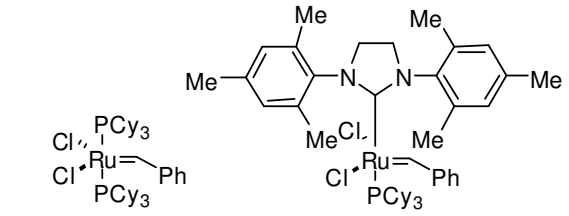
An example of this strategy in the context of the total synthesis of brevetoxin A is described later in the chapter (section C).

Enol Ether Formation/DMDO Epoxidation/Nucleophilic Addition

The enol ether formation/dimethyldioxirane (DMDO) epoxidation/nucleophilic addition strategy formulated by Rainier[24] has been recently employed in the synthesis of the A-E subunit of gambieric acid (**7**).[25] The C ring ester **22** was subjected first to the Takai-Utimoto procedure[26] for olefination of the ester carbonyl (Scheme 1.4), then to the second generation Grubbs catalyst (G2, Figure 1.4) for ring-closing metathesis (RCM)/enol ether formation. The enol ether **23** underwent epoxidation with DMDO and in situ reduction with DIBALH to complete the D ring of bicycle **24**. A second enol ether **25** was formed via transacetalization/elimination under acidic conditions, whereupon treatment with DMDO and CH_2=$CHCH_2MgCl$

allowed for epoxidation and in situ Grignard addition to procure the E ring **26** having appropriate functionality for further elaboration.

Figure 1.4. Grubbs catalysts



G1 = 1st generation catalyst

G2 = 2nd generation catalyst

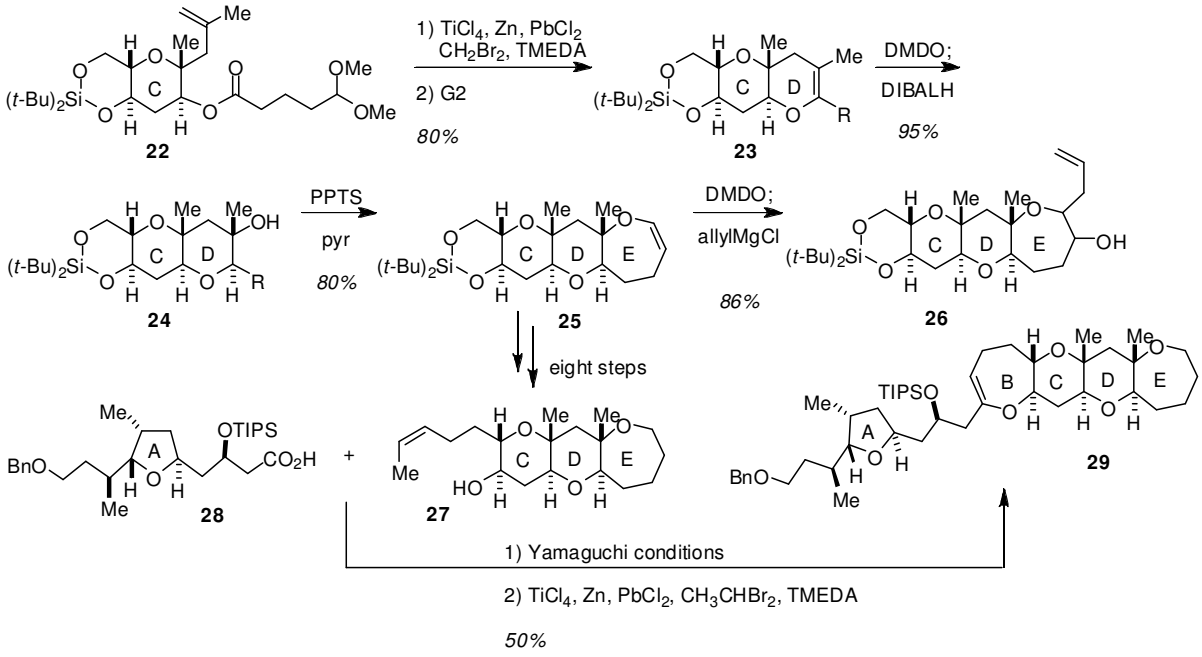
For the purposes of exploring completion of the A-E subunit, enol ether **25** was converted to alcohol **27** in eight steps and coupled with A ring carboxylic acid **28** under Yamaguchi conditions. Upon exposure of the resulting ester to the Takai-Utimoto procedure, a 50% yield of A-E subunit **29** was obtained directly. Importantly, the use of dibromoethane instead of dibromomethane favored the one-pot olefination/RCM reaction relative to undesirable oligomerization.

Trimethylsilyl-Assisted Biomimetic Cyclization

The proposal by Nakanishi in 1985 on the biogenesis of the ladder toxins[27] in which a polyepoxide is converted into a polycyclic ether through an epoxide-opening cascade has inspired several investigators to design biomimetic approaches for polycyclic ether synthesis.[28] The work by Jamison in this area has resulted in expedient access to polypyran subunits like those found in ladder toxins **5**, **7**, **9**, and **10**, and involves trimethylsilyl groups to direct regioselectivity in the key ring-forming

event.[29] Importantly, the silyl directing groups are removed during the cyclization cascade.

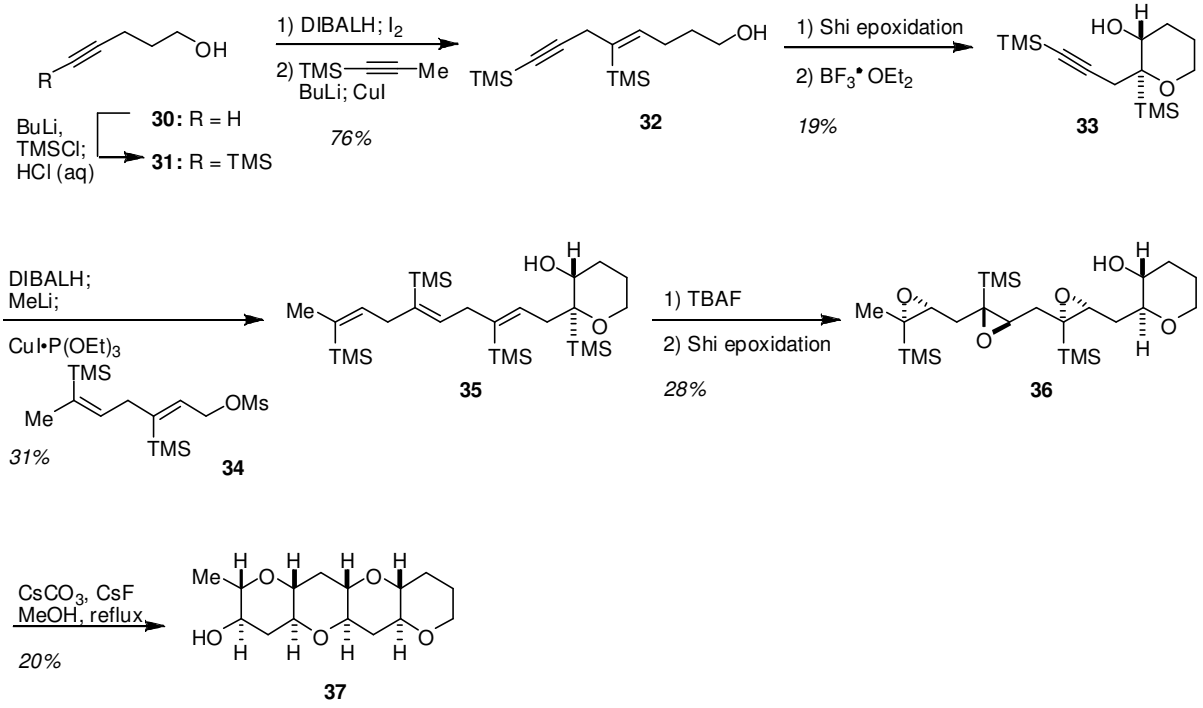
Scheme 1.4. Rainier's synthesis of the A-E subunit of gambieric acid.
Note: R = $-(CH_2)_3CH(OMe)_2$.



This strategy of Jamison was demonstrated in the synthesis of a pyran tetrad **37** (Scheme 1.5). Starting with alcohol **30**, a three step sequence involving protection, hydroalumination/iodination, and Cu(I)-mediated coupling with TMS-C≡C-CH_2Li produced alcohol **32**. The alcohol was exposed to Shi asymmetric epoxidation conditions, and the resultant epoxide was treated with BF_3•OEt_2 to bring about regioselective ring closure via an S_N2-like mechanism, albeit in 19% yield over two steps. Hydrometallation of pyran **33**, formation of the lithium ate complex, and Cu(I)-mediated coupling with mesylate **34** produced triene **35** in modest yield. After

treatment with TBAF to selectively remove the pyran TMS group, the triene was converted to the corresponding tris-epoxide diastereoselectively under Shi

Scheme 1.5. Synthesis of a pyran tetrad with a trimethylsilyl-assisted biomimetic cyclization.



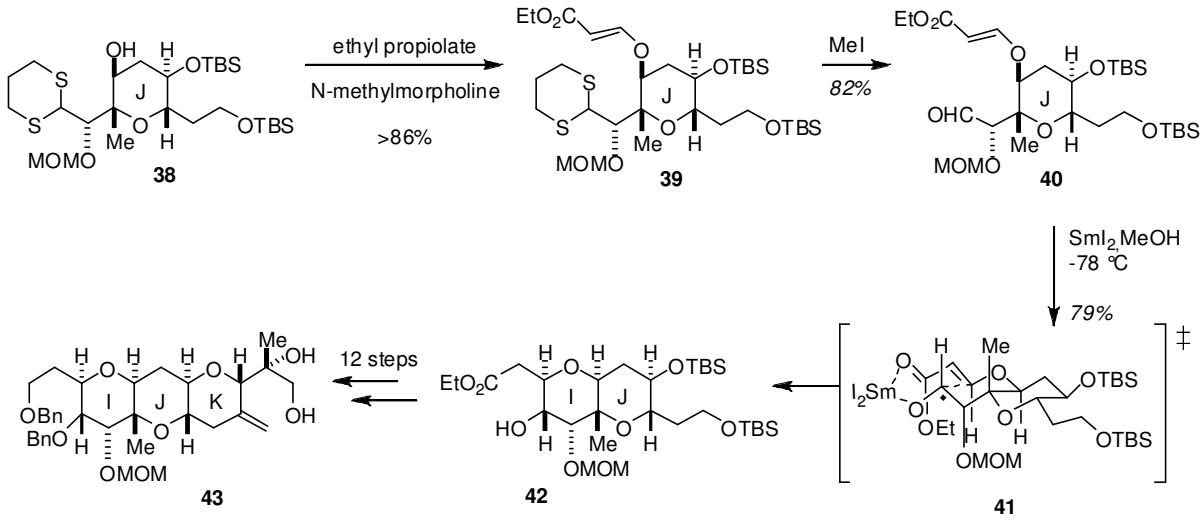
conditions. Tris-epoxide **36** then underwent an impressive epoxide-opening cascade in the presence of $CsCO_3$, CsF, and MeOH to afford pyran tetrad **37** in 20% yield. While this strategy allowed for very rapid access to a ladder toxin-like pyran tetrad (10 linear steps), improving the overall yield (ca. 0.2%) would make the approach even more attractive.

SmI_2-Promoted Enoate-Aldehyde Cyclization

Nakata has illuminated SmI_2 as an effective promoter of enoate-aldehyde cyclizations to form pyran or oxepane rings via a radical process.[30,31] Kadota and Yamamoto have recently employed Nakata's cyclization reaction in the synthesis of

the IJK fragment of yessotoxin (**10**).[32] The J ring alcohol **38** (Scheme 1.6) was reacted with ethyl propiolate under basic conditions to install the required enoate moiety. Dithiane **39** was then reacted with MeI to reveal aldehyde **40**, which was poised for cyclization in the presence of SmI_2. The cyclization involves formation of the ketyl radical and chelation of Sm(III) between the ketyl and ester carbonyl oxygen atoms, which helps to direct the stereoselectivity of the radical addition to the enoate through a chair-like transition state **41**. The resulting IJ bicycle **42** was taken on to IJK subunit **43** over 12 steps.

Scheme 1.6. SmI_2-promoted enoate-aldehyde cyclization of the I ring of yessotoxin (**10**).

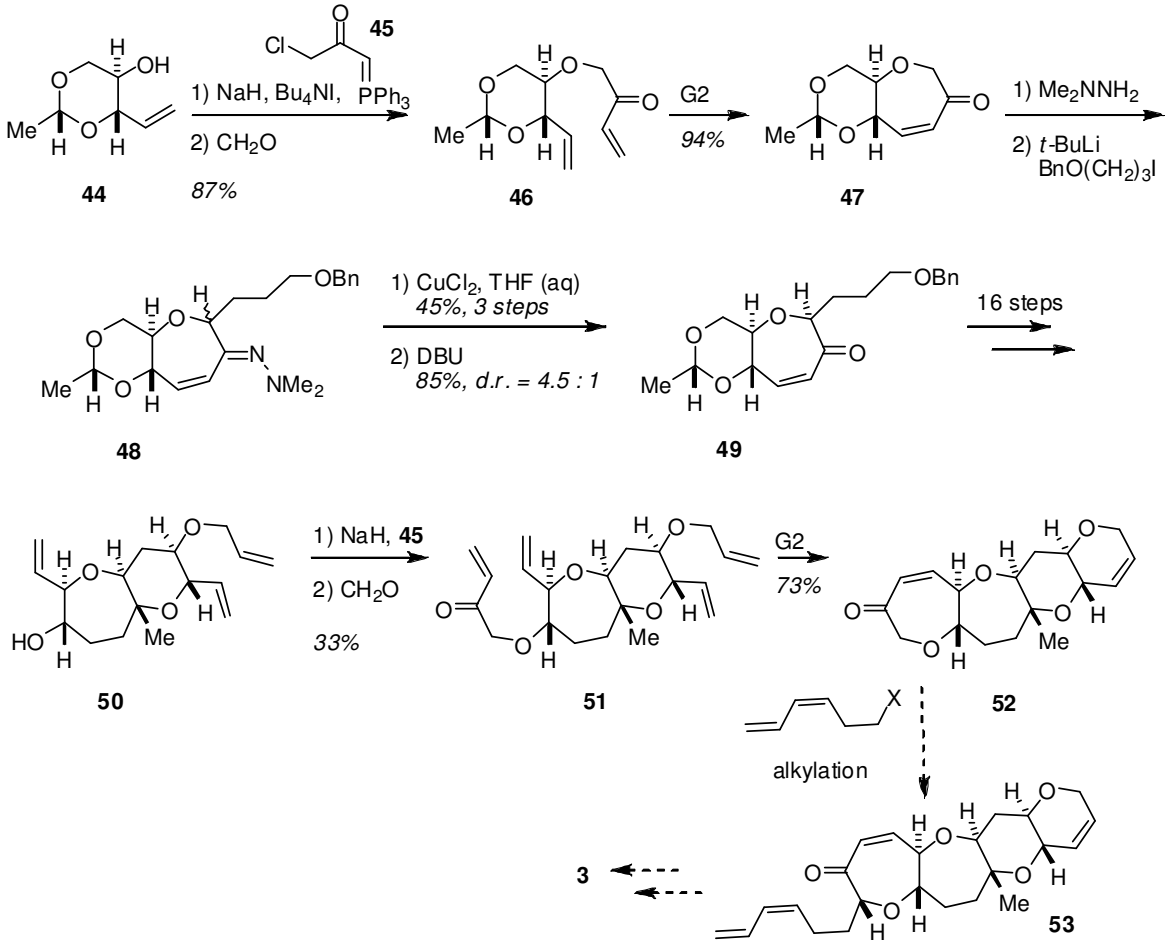


Wittig Olefination/RCM/Alkylation

A Wittig olefination/RCM/alkylation approach to polycyclic ethers has been applied by Clark toward the syntheses of ciguatoxin CTX3 (**6**)[33] and hemibrevetoxin B (**3**).[34] To prepare the tetracyclic core of hemibrevetoxin B, alcohol **44** (Scheme 1.7) was alkylated with the ylide-bearing α-chloroketone **45**, and subsequent Wittig olefination with formaldehyde yielded diene **46**. Ring-closing metathesis with G2 furnished

ketone **47**, which was converted to the *N,N*-dimethylhydrazone. Upon deprotonation with *t*-BuLi, the hydrazone was found to be a suitable substrate for alkylation with $BnO(CH_2)_3I$ to provide oxepene **48** as a mixture of diastereomers. Hydrolysis of the hydrazone with $CuCl_2$ and base-induced epimerization of the undesired

Scheme 1.7. Preparation of the tetracyclic core of hemibrevetoxin B (**3**) using a Wittig olefination/RCM/alkylation approach.



diastereomer with DBU provided ketone **49**, which was converted to alcohol **50** in 16 steps. Poised for another iteration, alcohol **50** underwent *O*-alkylation as before with ylide-bearing α-chloroketone **45**, Wittig olefination, and RCM to arrive at ketone **52**, the tetracyclic core of hemibrevetoxin B (**3**). To complete the iteration in future work, ketone **52** would be alkylated with an appropriate electrophile to install the diene-

bearing side chain of the natural product. This should lead to an intermediate which could ultimately be manipulated into the natural product.

Ru-Catalyzed Cycloisomerization

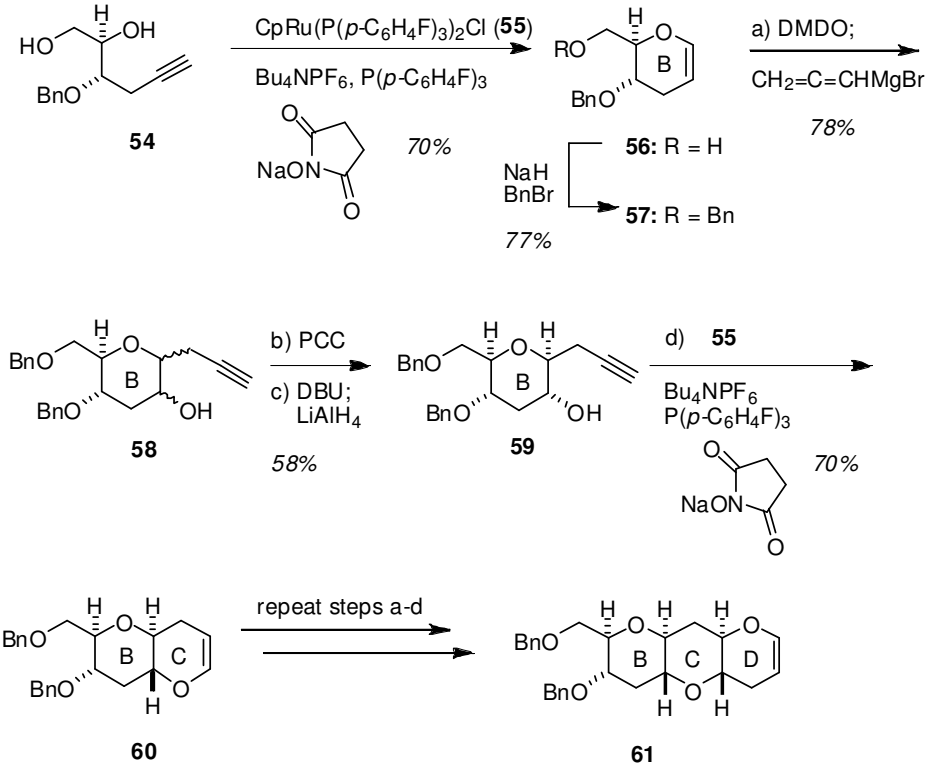
The Ru-catalyzed cycloisomerization reaction discovered by Trost has been featured in a rapid approach to the BCD subunit of yessotoxin (**10**).[35] Diol **54** underwent cycloisomerization to dihydropyran **56** in the presence of Ru catalyst **55** (Scheme 1.8), and after protection as the benzyl ether, the enol ether wasepoxidized with DMDO and reacted with allenylmagnesium bromide to provide bis-homopropargylic alcohol **58** as a mixture of diastereomers. The configurations of the newly formed stereocenters were corrected through oxidation to the ketone, followed by a one-pot isomerization/ketone reduction to produce pyran **59**. Exposure to the cycloisomerization conditions formed the corresponding enol ether **60** as before, which was taken through an additional iteration (steps a-d) to complete BCD subunit **61**.

2. [X + 1 + X] Convergent Strategies

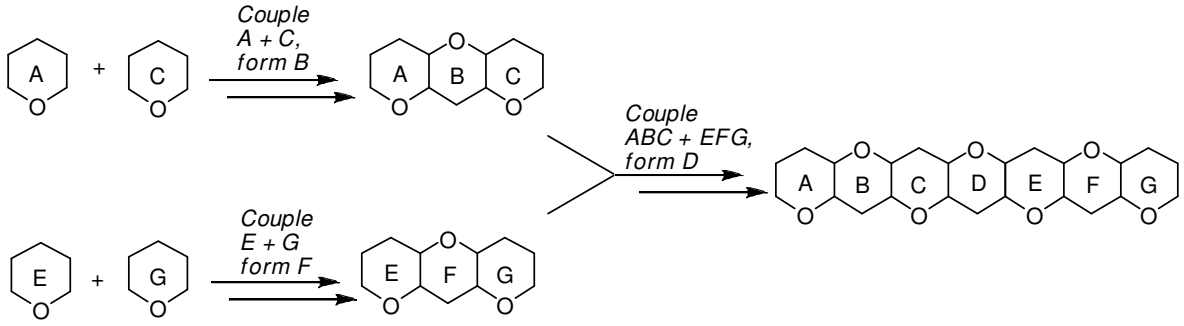
A convergent strategy for polycyclic ether synthesis in which two ring fragments are coupled and subsequently form one adjoining ring (Scheme 1.9) has been appropriately termed an [X + 1 +X] strategy by Inoue.[18] Generically, rings A and C are coupled, followed by further manipulations to form ring B in between them, resutling in a tricyclic array. Furthermore, the same approach could be used to bring

together two polycyclic fragments (e.g., ABC and EFG tricycles), with subsequent steps leading to D ring formation.

Scheme 1.8. A Ru-catalyzed cycloisomerization approach to the BCD fragment of yessotoxin (**10**).



Scheme 1.9. [X + 1 +X] approach to polycyclic ether synthesis.



Witting Coupling/Hydroxy Dithioketal Cyclization

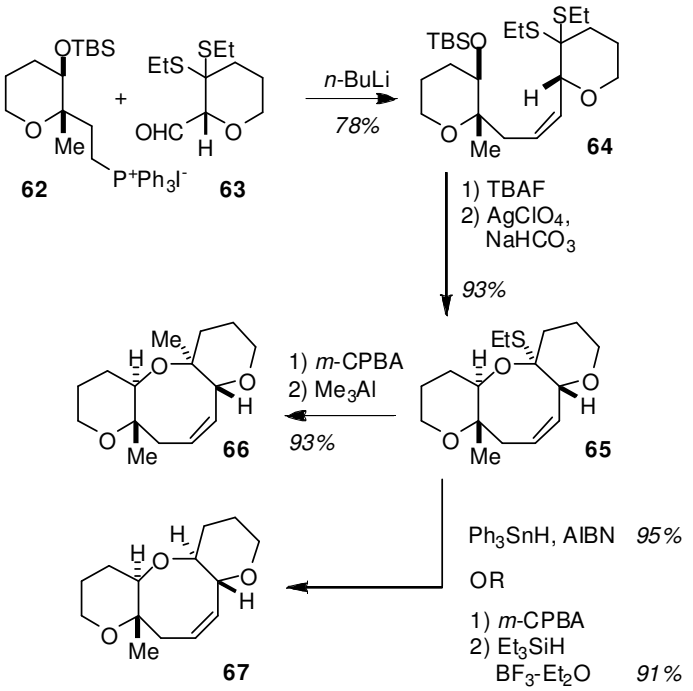
A convergent strategy for polycyclic ether synthesis developed early on by Nicolaou involves the Wittig coupling of two ring subunits, followed by a hydroxy dithioketal cyclization to form a new ring, particularly oxocenes.[36] For example, unstabilized ylide **62** and aldehyde **63** were coupled through a *Z*-selective Wittig olefination, and the resulting bispyran **64** was treated with TBAF to reveal the secondary hydroxyl needed for cyclization (Scheme 1.10). Under the action of $AgClO_4$, cyclization occurred to form the *S,O*-ketal **65**. The sulfur group underwent substitution by successive oxidization to the sulfone with *m*CPBA and exposure to Me_3Al to form oxocene **66**. Additionally, exchange of the sulfur group with hydrogen to form tricycle **67** was accomplished through a radical process using Ph_3SnH/AIBN, or through an oxidation-reduction sequence.

A concrete example of this strategy in the context of the total synthesis of brevetoxin A is described later in the chapter (section C).

Suzuki Coupling with Enol Phosphates

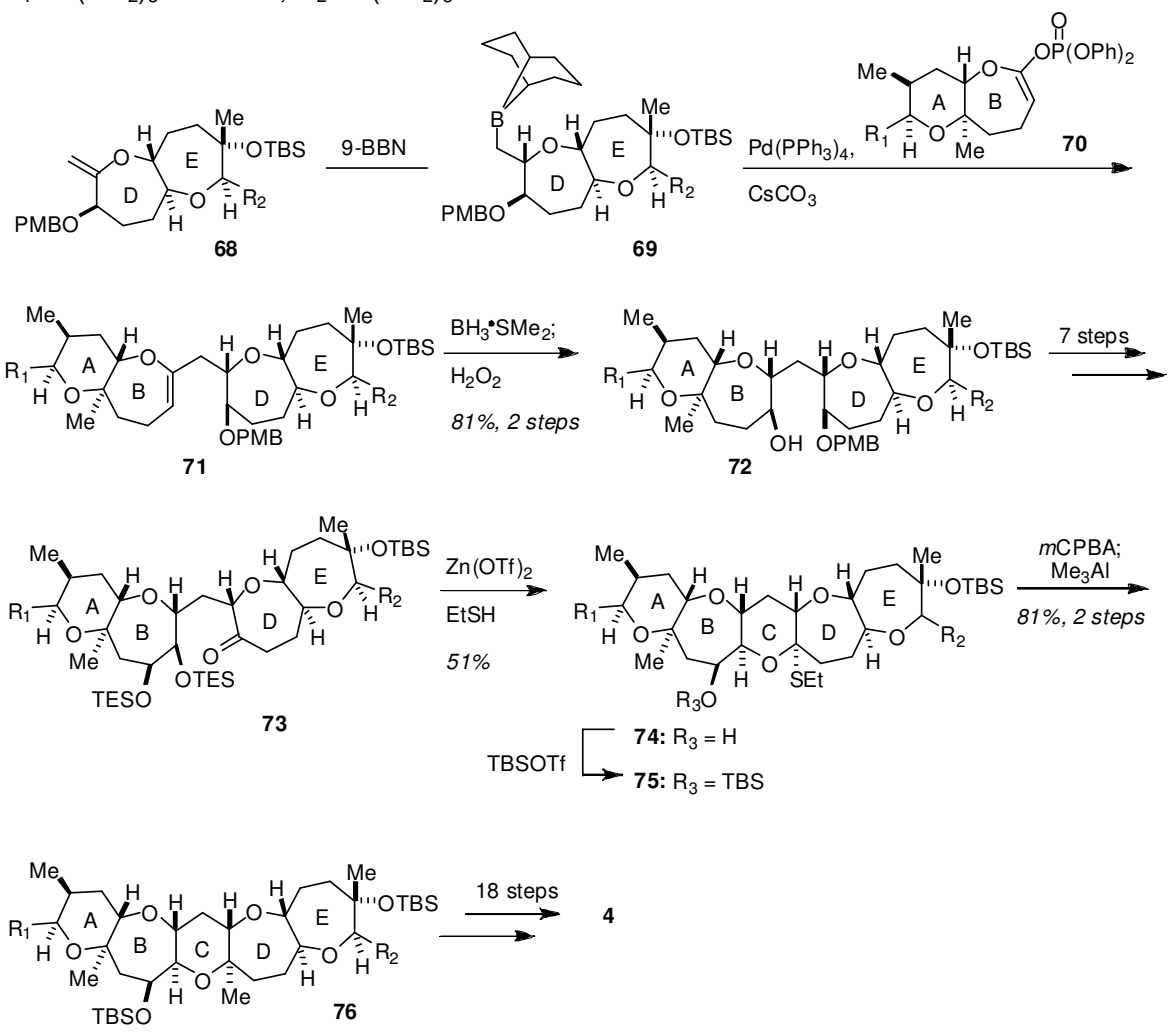
The Suzuki coupling of cyclic enol phosphates and *B*-alkyl coupling partners, followed by a reductive etherification sequence to form a new ring, has been shown by Sasaki to be an effective [X + 1 + X] strategy,[37] and was recently showcased in the total synthesis of brevenal (**4**).[38] The DE subunit **68** was subjected to a substrate-controlled diastereoselective hydroboration with 9-BBN (Scheme 1.11), leading to organoborane **69**. In the presence of catalytic Pd(0) and $CsCO_3$, the

Scheme 1.10. Nicolaou's Wittig coupling/hydroxy dithioketal cyclization approach.



organoborane was coupled with enol phosphate **70** to furnish enol ether **71**, which underwent further substrate-controlled hydroboration with $BH_3 \bullet SMe_2$ to produce tetracyclic fragment **72** in high yield. After seven additional manipulations, ketone **73** was exposed to $Zn(OTf)_2$ in EtSH, which served to remove both of the TES groups as well as form the *S,O*-ketal **74**. Upon re-protection of the remaining secondary hydroxyl with TBSOTf, the sulfur group was substituted with methyl by oxidizing to the sulfone with *m*CPBA, followed by reaction with Me_3Al. With the C ring completed, the brevenal pentacyclic core **76** was taken forward to the natural product in 18 additional steps.

Scheme 1.11. Sasaki's synthesis of brevenal (**4**) using a convergent Suzuki coupling. Note: R_1 = -$(CH_2)_3$OTBDPS, R_2 = -$(CH_2)_3$OBn.

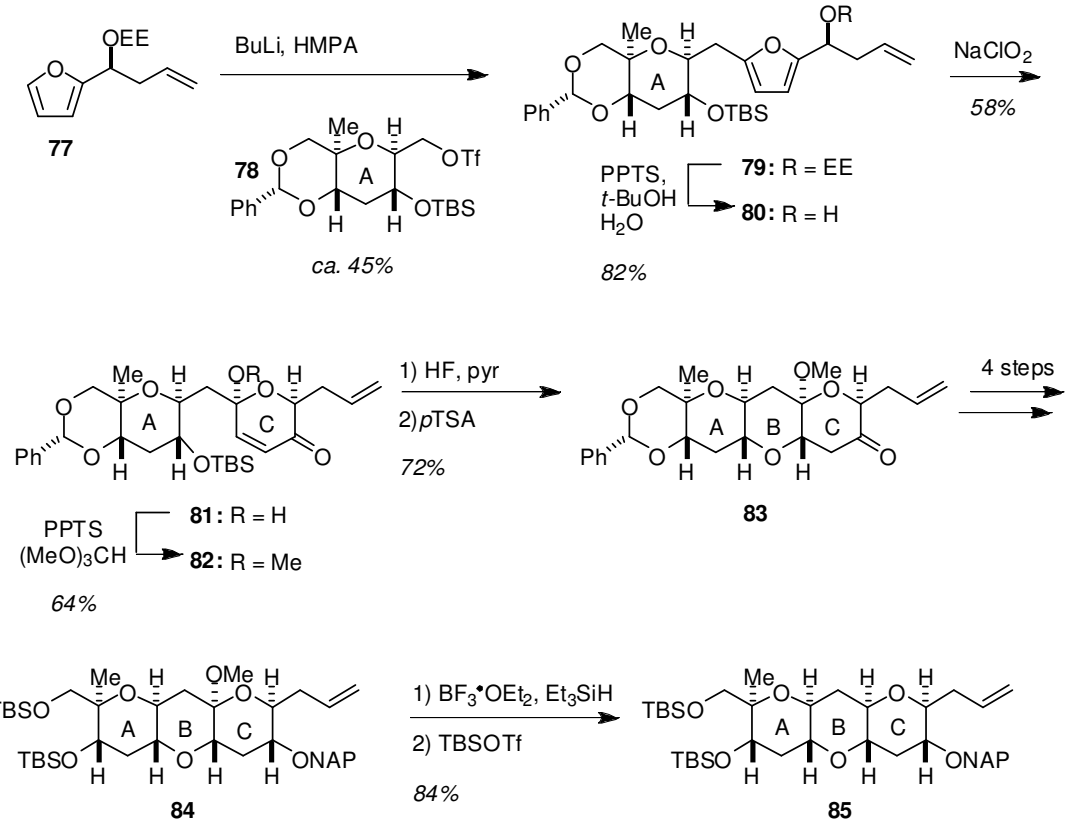


Lithiofuran-Triflate Coupling/Intramolecular Hetero-Michael Cyclization

Oishi has recently disclosed a novel [X + 1 + X] strategy for the ABC subunit of yessotoxin (**10**)[39] featuring lithiation of furan **77** and coupling with A ring triflate **78** (Scheme 1.12). After removal of the acid-labile EE protecting group, furan **80** was subjected to $NaClO_2$ to initiate an oxidative ring-expansion to produce C ring **81**. The $NaClO_2$ proved to be a superior reagent for this transformation relative to other conditions screened, including $VO(acac)_2$, NBS, or *m*CPBA. After converting the

hemi-ketal to the methoxy ketal **82** with PPTS and $(MeO)_3CH$ and removing the TBS group with HF, the B ring was closed through an intramolecular acid-promoted hetero-Michael addition to provide trispyran **83** without any unwanted spiroketalization. Interestingly, the acidic cyclization conditions favored the desired *trans*-fused stereoisomer, whereas basic conditions gave only the *cis*-fused diastereomer. Four additional steps led to ketal **84**, which underwent reductive etherification and silyl re-protection to complete ABC subunit **85**.

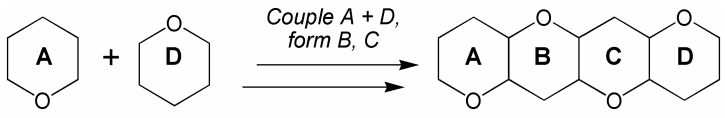
Scheme 1.12. Oishi's synthesis of the ABC fragment of yessotoxin (**10**).



3. [X + 2 + X] Convergent Strategies

The [X + 2 + X] strategies are those in which two ring fragments are coupled and subsequently form two new, adjoining rings (Scheme 1.13).[18] Generically, rings A and D are coupled, and further steps lead to formation of the central B and C rings.

Scheme 1.13. [X + 2 +X] approach to polycyclic ether synthesis.

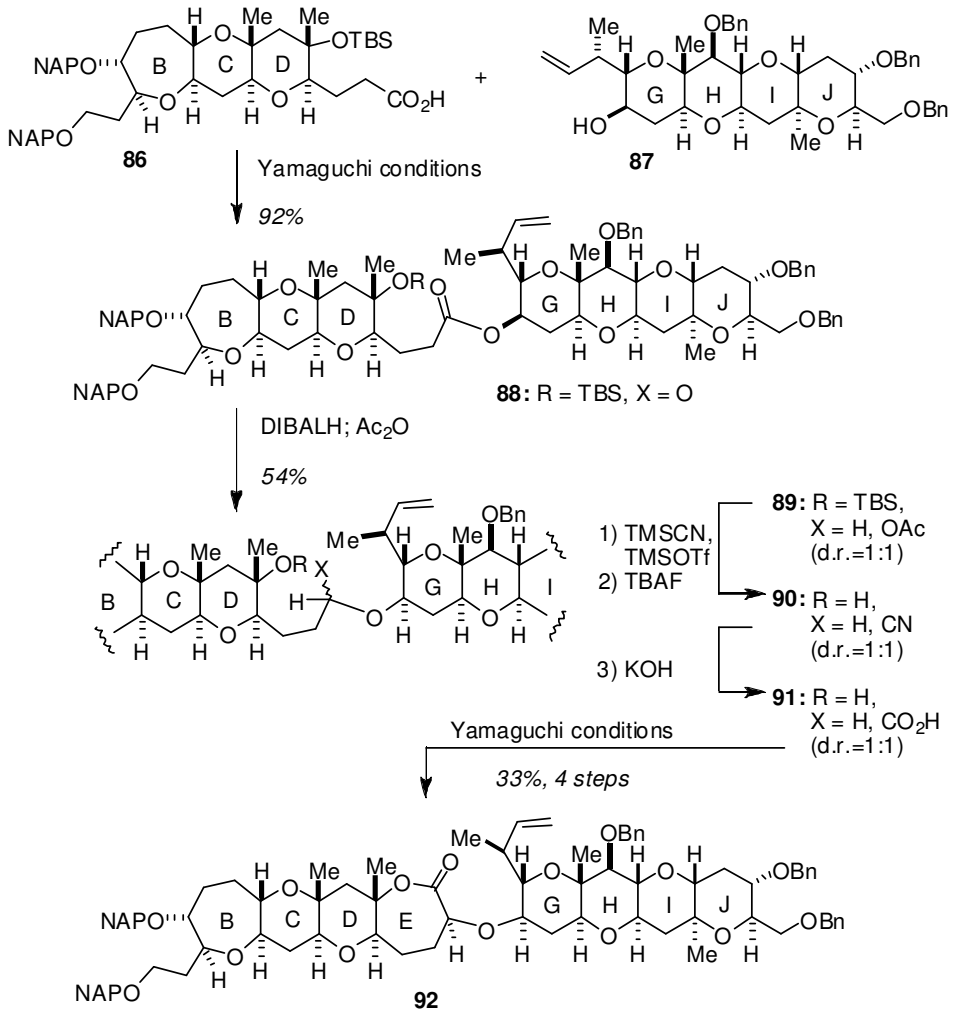


Esterification/Cyanation/Allylation/RCM

An approach to the nonacyclic core of gambieric acid (**7**) involving esterification, cyanation, allylation, and RCM events has been reported by Sasaki.[40] The BCD carboxylic acid **86** was joined with GHIJ alcohol **87** under Yamaguchi conditions (Scheme 1.14), efficiently providing ester **88**. The ester was converted to the α–acetoxy ether **89** using the Rychnovsky protocol in 54% yield, and the acetoxy group was substituted with a cyano group (1:1 mixture of diastereomers) through reaction with TMSCN and TMSOTf.[41] After removing the TBS group with TBAF, nitrile **90** was converted to the carboxylic acid **91** under the action of KOH. Yamaguchi lactonization then closed the E ring, providing the desired stereoisomer of lactone **92** in 33% yield over four steps.

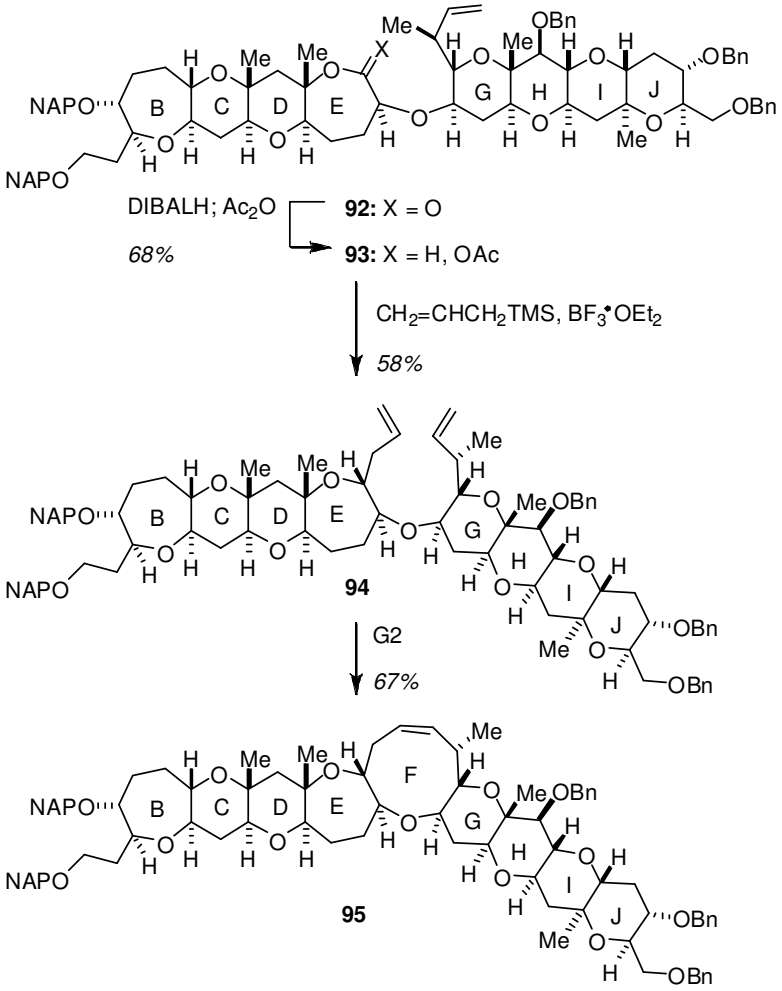
To close the F ring, lactone **92** was again subjected to the Rychnovsky protocol to form the α–acetoxy ether **93** (Scheme 1.15), which underwent a stereoselective

Scheme 1.14. Sasaki's [X + 2 +X] approach toward the synthesis of gambieric acid (**7**).



allylation reaction in the presence of BF_3•OEt_2 and CH_2=$CHCH_2TMS$. Ring-closing metathesis of the resulting diene **94** with G2 closed the F ring and completed the nonacyclic core **95** of gambieric acid. This strategy is clearly useful as a convergent strategy which creates medium-sized rings between two coupling partners, though the newly formed stereocenters therein require substrate control for reasonable stereoselectivity.

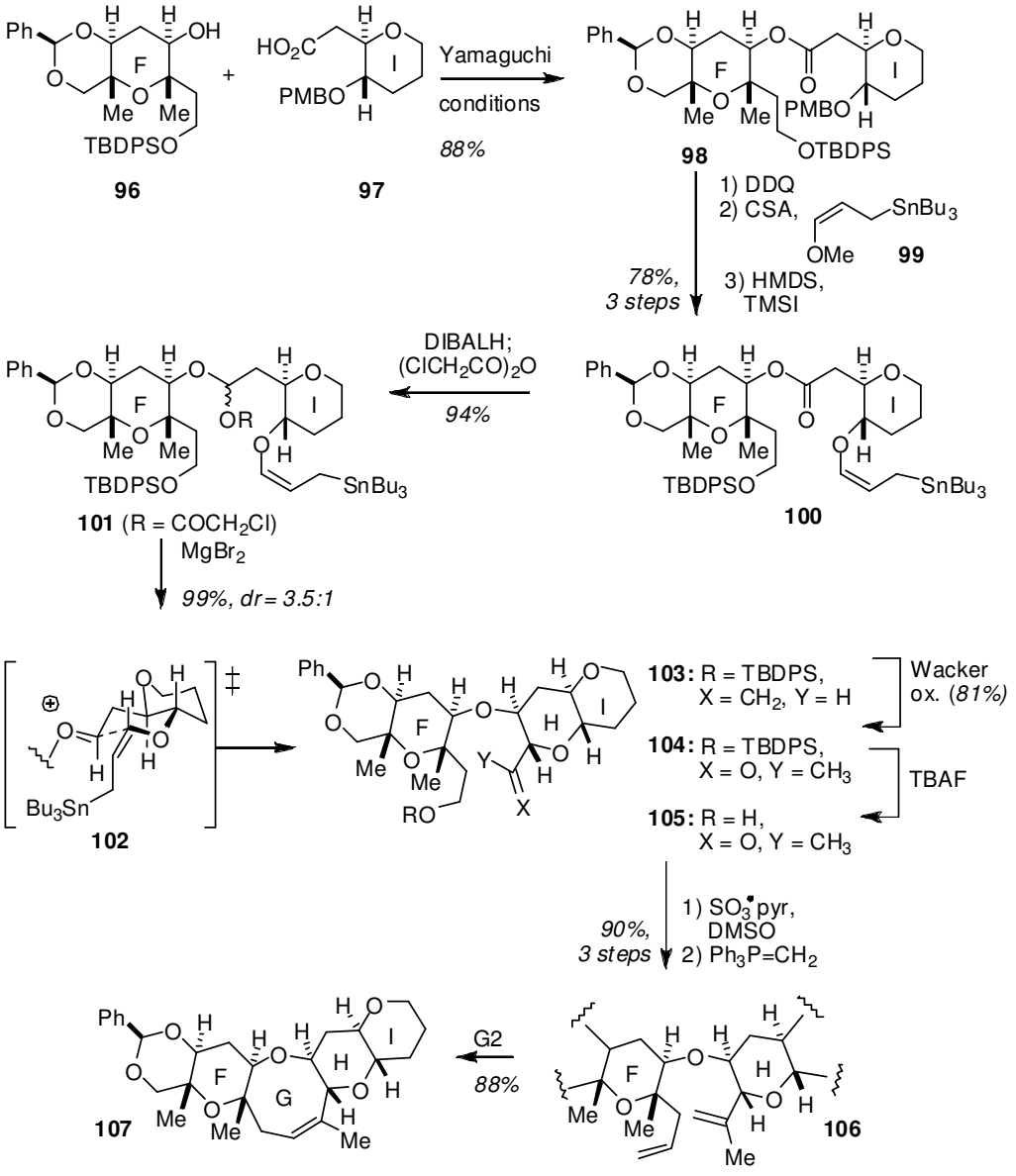
Scheme 1.15. Sasaki's completion of the nonacyclic core of gambieric acid (**7**).



Esterification/Intramolecular Allylation/RCM

Kadota and Yamamoto have recently applied their esterification/intramolecular allylation/RCM strategy for polycyclic ether synthesis[42] to the FGHI fragment of yessotoxin (**10**).[43] The F ring alcohol **96** (Scheme 1.16) and I ring carboxylic acid **97** were coupled under Yamaguchi conditions, assembling ester **98** in 88% yield. To install the allylstannane moiety for intramolecular allylation, the PMB group was oxidatively removed with DDQ, and the resultant alcohol was exposed to enol ether

Scheme 1.16. Preparation of the FGHI subunit of yessotoxin (**10**) with an esterification/intramolecular allylation/RCM strategy.



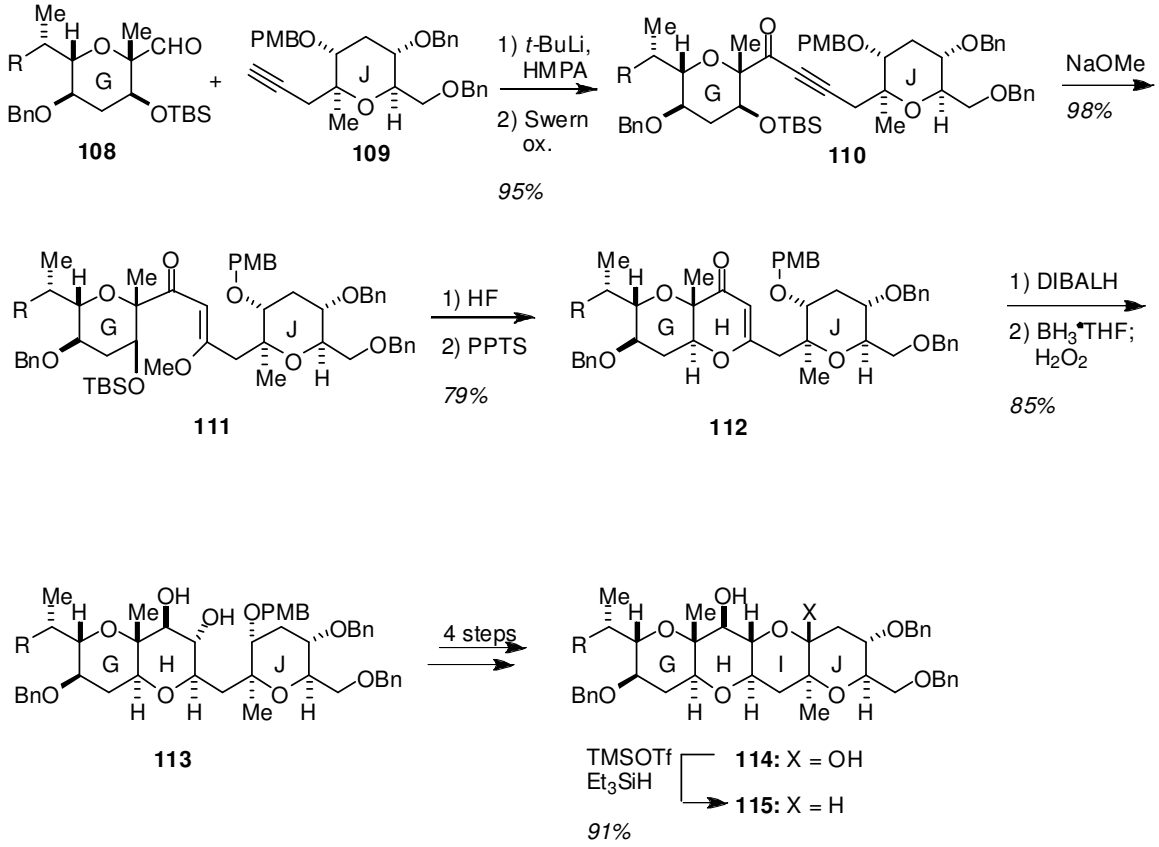
99 in the presence of CSA to form the mixed methoxy acetal; elimination of MeOTMS with HDMS and TMSI provided allylstannane **100** in high yield. The α-acetoxy ether **101** was formed using the Rychnovsky protocol,[41] and treatment with $MgBr_2$ initiated the intramolecular allylation through the favored transition state **102**

to provide trispyran **103** (d.r. = 3.5:1). Wacker oxidation of the terminal olefin produced ketone **104**, and removal of the TBDPS group with TBAF provided hydroxy ketone **105**. After Parikh-Doering oxidation, the keto aldehyde underwent double methylenation to furnish diene **106**, which set the stage for RCM to complete the FGHI tetracycle **107**. The fact that the G ring formed through RCM is eight-membered demonstrates the utility of this convergent strategy to create medium-sized rings between two coupling partners with useful levels of diastereoselectivity in the key intramolecular allylation event.

Acetylide-Aldehyde Coupling/Hetero-Michael Cyclization

An acetylide-aldehyde coupling/hetero-Michael cyclization strategy developed by Nakata in 2002 was shown to be particularly amenable to the synthesis of pyran units bearing a secondary hydroxyl, such as the I ring of yessotoxin (**10**).[44] This strategy was carried out by Sasaki in the synthesis of the GHIJ fragment of gambieric acid.[40] The J ring alkyne **109** (Scheme 1.17), upon lithiation, was added to G ring aldehyde **108**, and Swern oxidation of the resulting secondary alcohol produced ketone **110**. Intermolecular Michael addition of NaOMe into the ynone yielded vinylogous ester **111**. Removal of the TBS group with HF set the stage for an intramolecular hetero-Michael cyclization under acidic conditions to form tricycle **112** in good yield. Diastereoselective 1,2-reduction of the ketone with DIBALH and hydroboration of the enol ether with BH_3•THF led to diol **113**, which was taken on to hemiketal **114** in four steps. Reductive etherification with TMSOTf and Et_3SiH provided GHIJ tetracycle **115** in 91% yield.

Scheme 1.17. An acetylide-aldehyde coupling/hetero-Michael cyclization approach to the GHIJ fragment of gambieric acid (**7**). Note: R = $(CH_2)_2OBn$



C. Nicolaou's Synthesis of Brevetoxin A

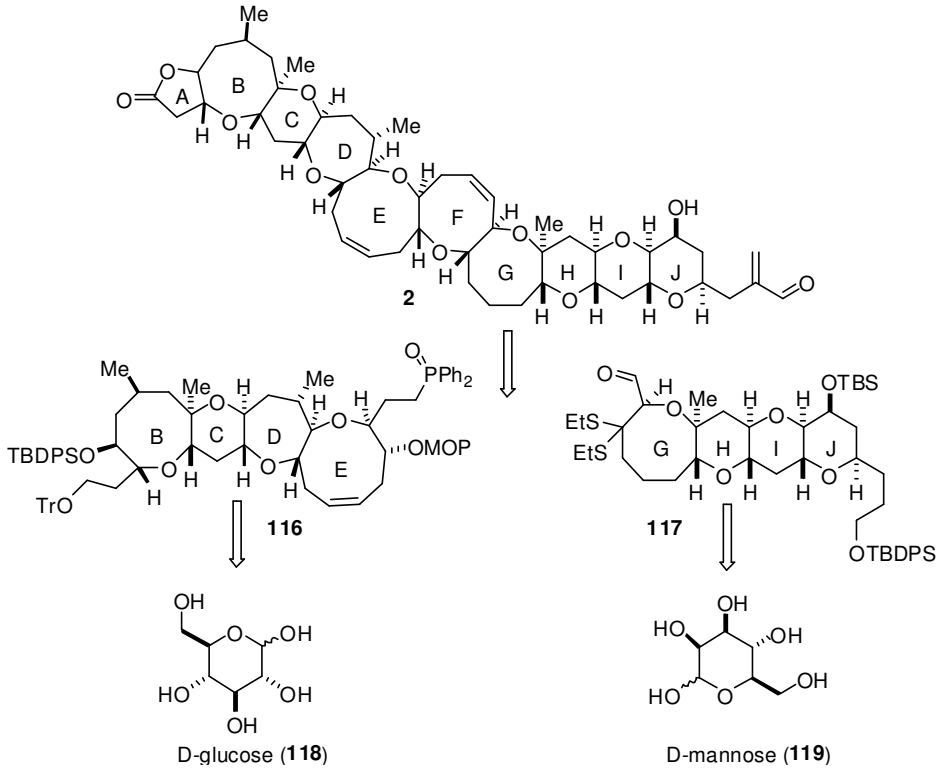
Brevetoxin A (**2**) is one of the more forbidding members of the ladder toxins from a synthetic perspective. The molecule contains five-, six-, seven-, eight-, and nine-membered rings (10 rings total), three C-C double bonds, and 22 stereocenters. Therefore, the synthesis of brevetoxin A by Nicolaou and co-workers in 1998 was a landmark achievement in the field of total synthesis,[45,46] and placed a capstone on their work on the total synthesis of ladder toxin natural products, which also included brevetoxin B[47] and hemibrevetoxin B.[48] Indeed, novel synthetic strategies and

methods which were successfully utilized in the synthesis of brevetoxin B and hemibrevetoxin B proved to be equally effective when brought to bear on brevetoxin A. Specifically, hydroxy vinylepoxide openings, Wittig coupling/hydroxy dithioketal cyclizations, and lactonization/transition metal mediated enol ether-forming reactions were key transformations in Nicolaou's ladder toxin syntheses, and are highlighted in the synthesis of brevetoxin A.

After significant exploration of first-generation strategies for the synthesis of brevetoxin A,[46a] an optimized retrosynthetic analysis was settled upon (Scheme 1.18). The molecule would be joined at a roughly central point through a Horner-Wittig reaction to couple BCDE fragment **116** and GHIJ fragment **117**, and a subsequent hydroxy dithioketal cyclization would form the F ring. The two tetracyclic fragments would ultimately be derived from simple carbohydrate starting materials (D-glucose **118** and D-mannose **119**, respectively).

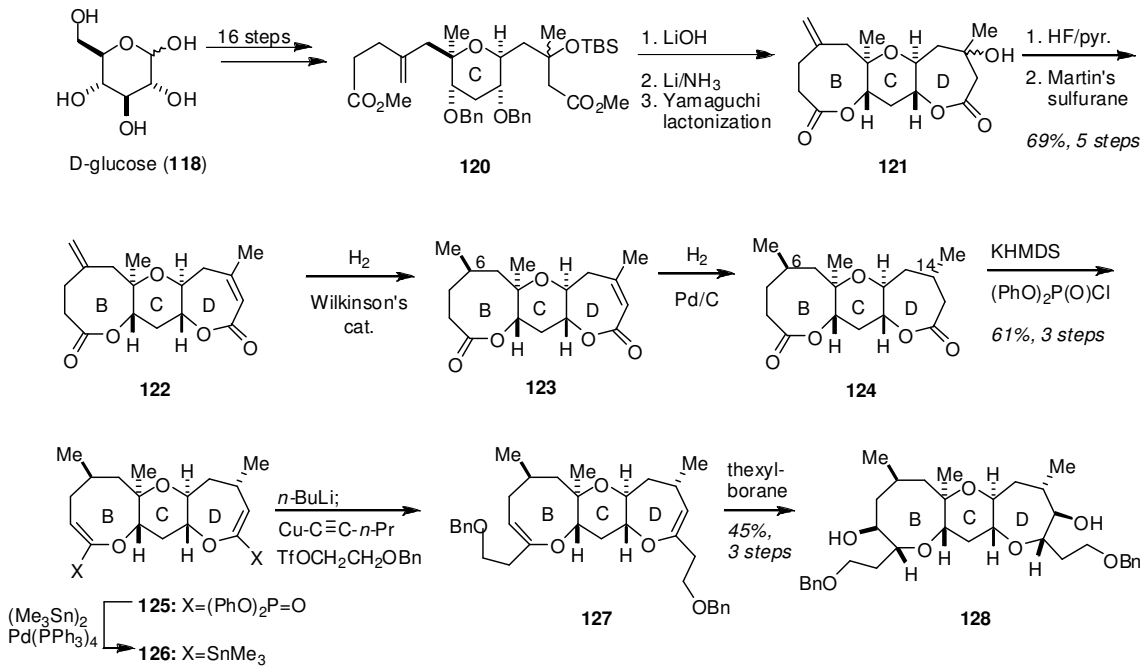
The synthesis of BCDE fragment **116** began with D-glucose **118**, which was manipulated to C ring pyran **120** in 16 steps (Scheme 1.19). With an eye toward efficiency, the B and D rings would be constructed simultaneously through a two-directional (double reaction) assembly using the lactonization/transition metal-mediated enol ether formation strategy. To this end, the C ring pyran **120** underwent saponification and debenzylation to yield a diacid for Yamaguchi lactonization to produce dilactone **121**. Removal of the TBS group and elimination of the resulting

Scheme 1.18. Nicolaou's retrosynthetic analysis of brevetoxin A (**2**).



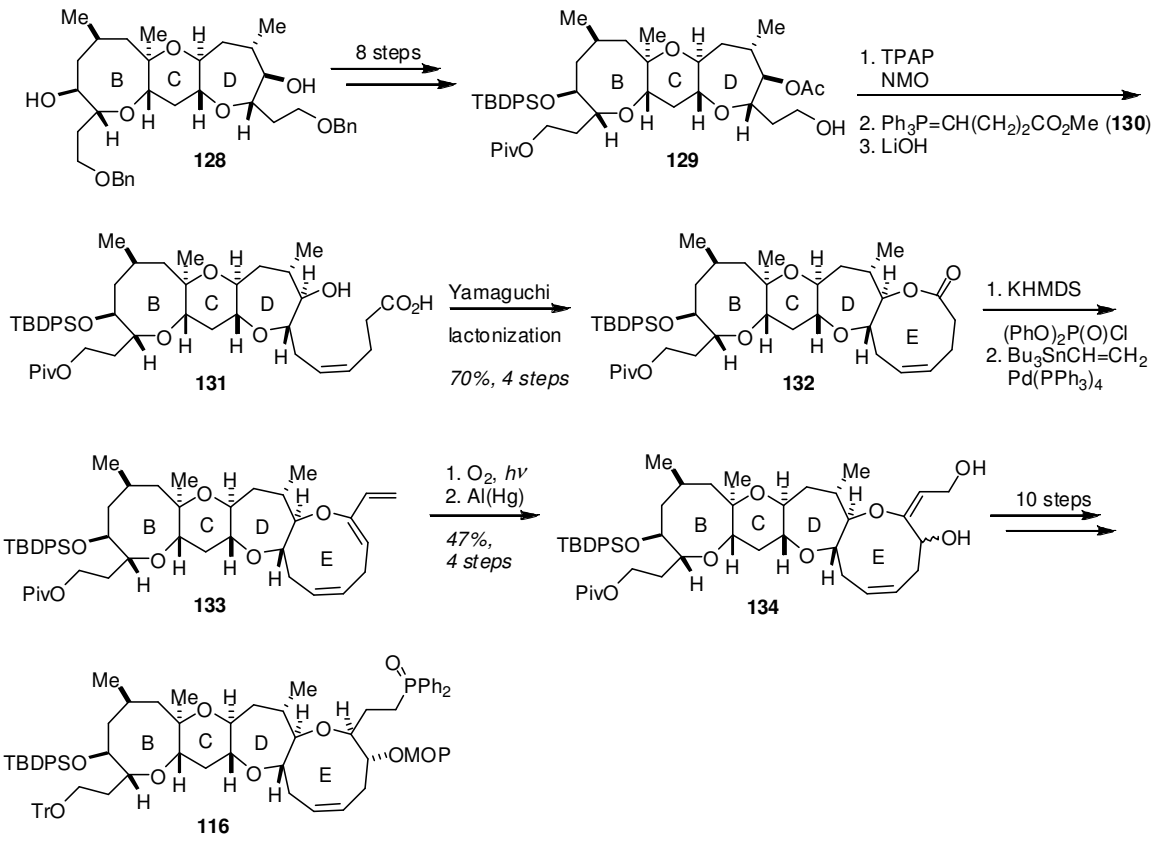
hydroxyl with Martin's sulfurane provided BCD fragment **122**. Hydrogenation of both of the olefins present in fragment **122** through successive use of Wilkinson's catalyst and Pd/C selectively set both the C6 and C14 stereocenters, thus furnishing dilactone **124**. A two-step procedure was then undertaken to form bis(vinylstannane) **126**, which then underwent a substitution reaction with $BnO(CH_2)_2OTf$ in the presence of BuLi and cuprous *n*-propylacetylide to yield cyclic enol ether **127**. Diastereoselective hydroboration of both enol ethers was accomplished with thexylborane, resulting in BCD subunit **128**.

Scheme 1.19. A two-directional assembly of BCD subunit **128.**



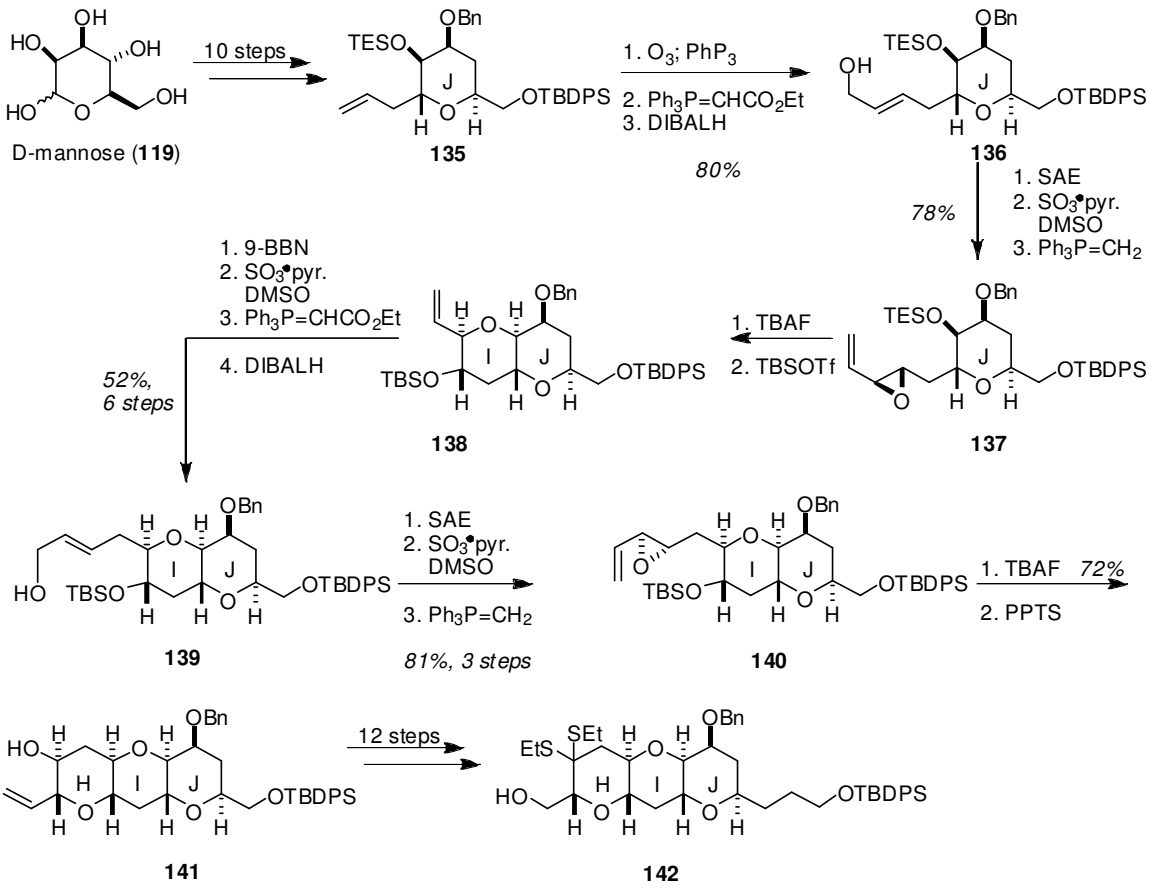
To append the E ring onto BCD subunit **128**, a series of protecting-group manipulations (eight steps) was undertaken to provide tricycle **129** (Scheme 1.20). This set the stage for another implementation of the lactonization/transition metal-mediated enol ether formation strategy to form the E ring. Specifically, the primary hydroxyl was oxidized to the aldehyde, and exposed to ylide **130** to produce the *Z*-olefin; subsequent saponification of the methyl ester then delivered acid **131**. Yamaguchi conditions once again affected lactonization, thus yielding BCDE lactone **132**. Formation of the enol phosphate allowed for Pd(0)-catalyzed coupling with $Bu_3SnCH{=}CH_2$ to furnish enol ether **133**. Oxidation with singlet oxygen and further manipulations (11 steps) then completed BCDE fragment **116**.

Scheme 1.20. Completion of BCDE fragment **116**.



In a similar vein to the BCDE fragment **116**, the synthesis of the GHIJ fragment **117** began with D-mannose (**119**), which was converted to J ring pyran **135** in 10 steps (Scheme 1.21). The J ring served as a scaffold for linear construction of the H and I rings using the hydroxy vinylepoxide opening strategy. Thus, ozonolysis of the terminal olefin of pyran **135**, Wittig olefination of the resultant aldehyde with $Ph_3P{=}CHCO_2Et$, and reduction of the ester with DIBALH provided allylic alcohol **136**. The allylic alcohol underwent Sharpless asymmetric epoxidation, and the alcohol

Scheme 1.21. Conversion of D-mannose to tricycle **142**.

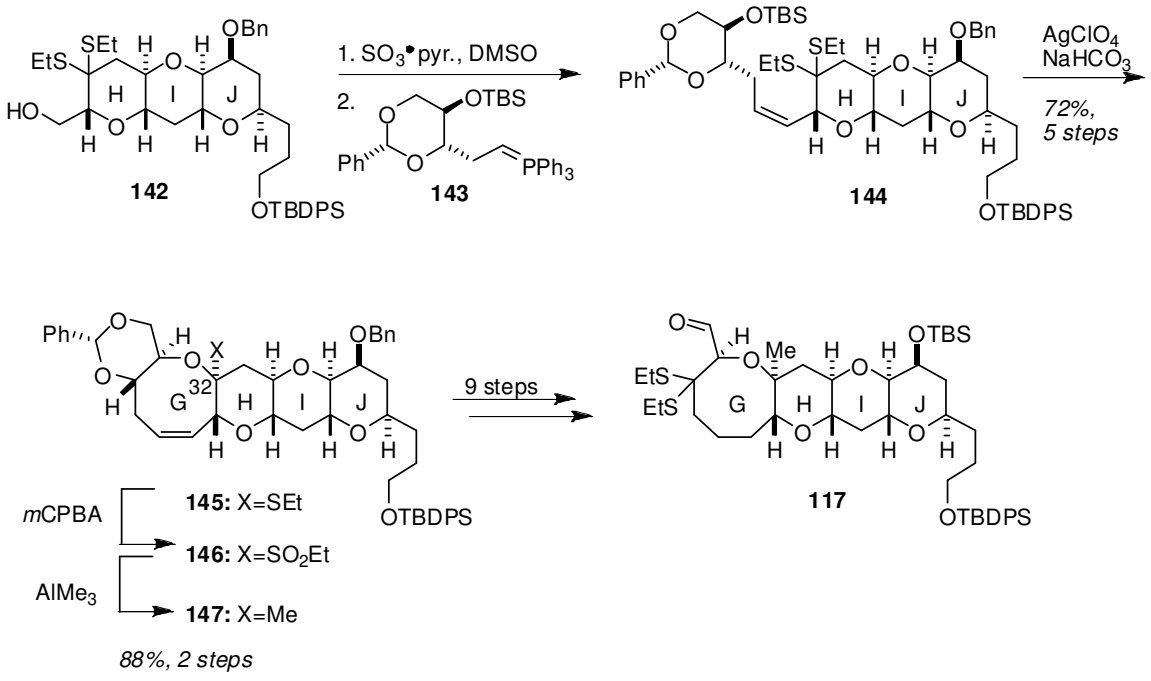


was then oxidized to the aldehyde and exposed to $Ph_3P{=}CH_2$ to form vinylepoxide **137**. Treatment with TBAF to remove the TES group followed by exposure to TBSOTf brought about an epoxide-opening cyclization reaction with concomitant protection as the TBS ether to give bicycle **138**. To set up a second hydroxy vinylepoxide opening, the terminal olefin underwent hydroboration, and the resulting alcohol was oxidized under Parikh-Doering conditions. Wittig olefination with $Ph_3P{=}CHCO_2Et$ followed by reduction of the ester with DIBALH produced another allylic alcohol **139**, which underwent the same three-step sequence as before to furnish a second vinylepoxide **140** poised for cyclization. In this case, treatment with

TBAF removed the TBS group, which allowed for cyclization of the exposed secondary hydroxyl into the vinylepoxide under acidic conditions. The resulting tricycle **141** was converted to hydroxy dithioketal **142** in 12 additional steps.

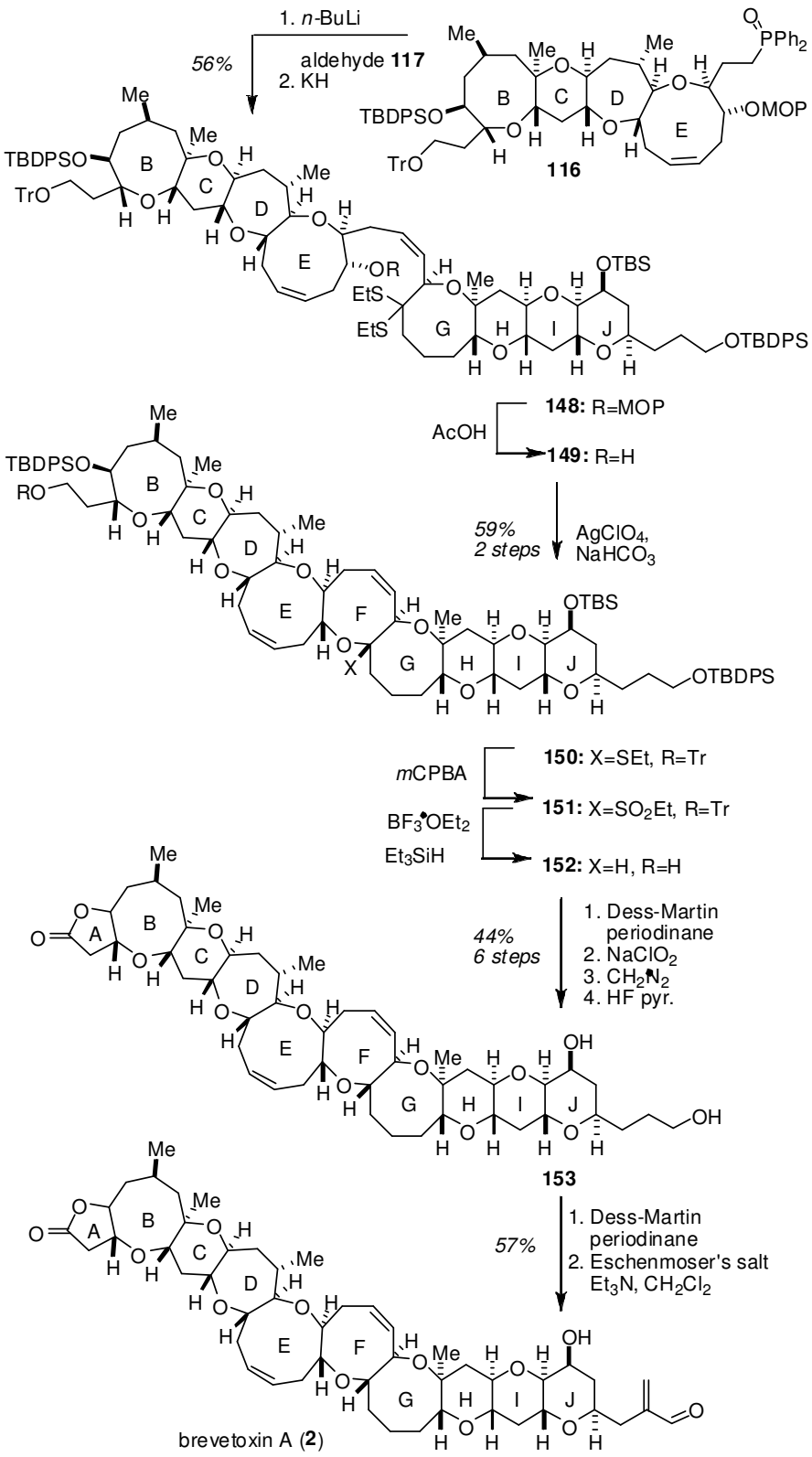
The G ring was then appended to tricycle **142** through the Wittig coupling/hydroxy dithioketal cyclization. First, the primary hydroxyl was oxidized to the aldehyde, and reacted with ylide **143** to produce olefin **144** with good selectivity for the *Z* isomer (Scheme 1.22). Under the action of $AgClO_4$, cyclization occurred to form the mixed *S,O*-ketal **145**. Selective oxidation of the sulfur atom with *m*CPBA and exposure to Me_3Al then installed the methyl-bearing stereocenter at C32. From the resulting intermediate **147**, the GHIJ tetracycle **117** was completed in 9 additional steps.

Scheme 1.22. Completion of GHIJ fragment **117**.



The penultimate coupling of fragments **116** and **117** and subsequent F ring formation was realized with the Wittig coupling/hydroxy dithioketal cyclization sequence (Scheme 1.23). Treatment of fragment **116** successively with BuLi and aldehyde **117**, followed by exposure of the Wittig adducts to KH, accomplished a Horner-Wittig coupling of the two tetracyclic fragments with high selectivity for the required *Z* isomer **148**. It was believed that the MOP protecting group was important for *Z*-selectivity due to its ability to coordinate to the lithium of the metalated phosphine oxide and thus form a chelated nucleophile. Removal of the MOP protecting group under acidic conditions preceded the hydroxy dithioketal cyclization reaction, which ensued smoothly in the presence of $AgClO_4$ and $NaHCO_3$ to produce *S,O*-ketal **150**. As before, selective oxidation of the sulfur atom with *m*CPBA and exposure to BF_3•OEt_2 and Et_3SiH brought about reduction of the *S,O*-ketal and concomitant removal of the trityl protecting group to form alcohol **152**. The unmasked primary alcohol was then oxidized to the acid under a two-step procedure, and subjected to CH_2N_2 to form the corresponding methyl ester. Treatment with HF•pyr then removed all silyl protecting groups and caused formation of the A ring lactone. The diol **153** thus formed was converted to brevetoxin A through selective oxidation of the primary hydroxyl to the aldehyde under Dess-Martin conditions, followed by reaction with Eschenmoser's salt. This completed the first total synthesis of brevetoxin A (**2**) in 66 steps (longest linear sequence).

Scheme 1.23. Nicolaou's endgame for brevetoxin A.



D. Summary

The ladder toxins are a remarkable group of natural products with structures which have inspired much synthetic investigation and led to the development of novel synthetic technology. While several of the ladder toxins have succumbed to total synthesis, as of this writing, gambieric acid (**7**), maitotoxin (**8**), yessotoxin (**10**), and others have remained synthetically elusive. The impetus for new and more efficient syntheses of the ladder toxins to bolster their biological study as well as spurn further improvements in chemical methodology drives continued research in this area of synthetic chemistry. In particular, convergent methods for the synthesis of polycyclic ethers possessing medium-sized rings through reliable, efficient, and selective bond-forming events remain as desirable goals.

CHAPTER 2

THE DEVELOPMENT OF A VIABLE ROUTE TO THE GHIJ FRAGMENT OF BREVETOXIN A

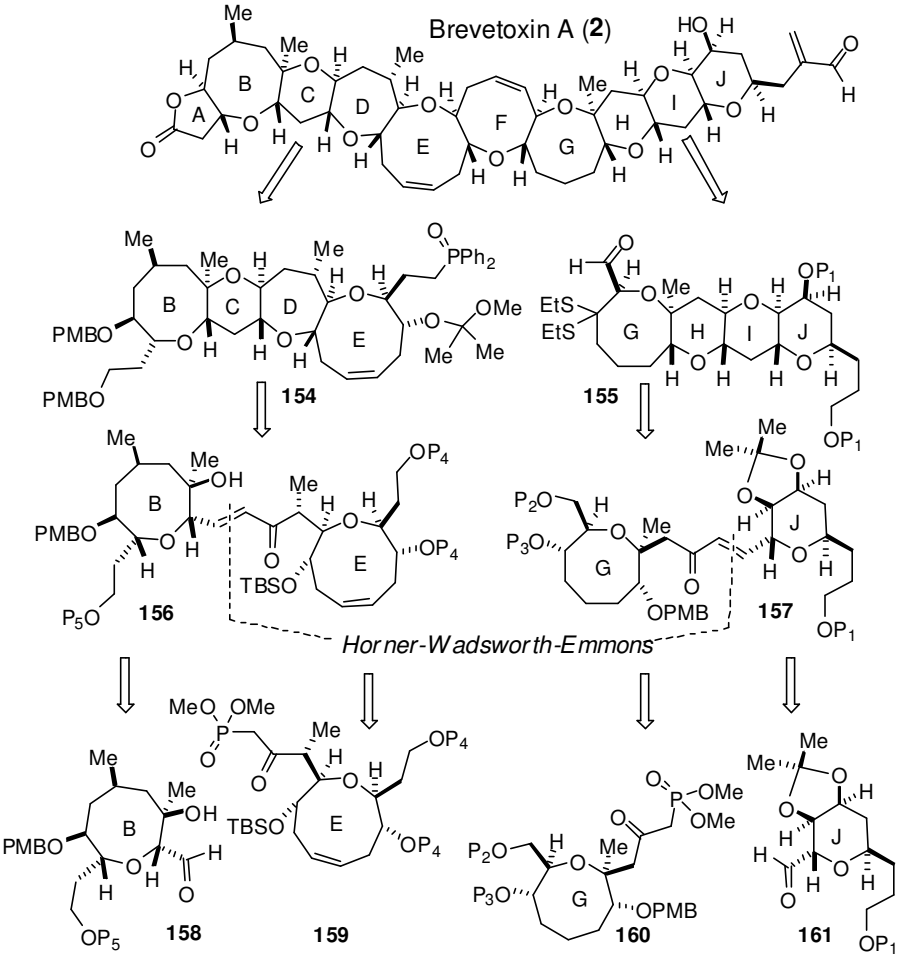
A. Synthetic Strategy For Brevetoxin A

The Crimmins laboratory became interested in the total synthesis of brevetoxin A because of its imposing synthetic challenge. As described in Chapter 1, the lone previous synthesis of this molecule required 66 linear steps,[46] and so the opportunity for a shortened, highly convergent, and efficient synthesis of brevetoxin A which incorporates methodology developed in the Crimmins laboratory in a powerful way was perceived. Like Nicolaou, it was believed that the most logical division point in the molecule was at the central F ring, leading to two tetracyclic fragments, BCDE phosphine oxide **154** and GHIJ aldehyde **155** (Scheme 2.1), which could be united through a Horner-Wittig olefination.[46]

Central to the overarching vision of synthetic convergence was the retrosynthetic analysis of the two tetracyclic fragments **154** and **155**, in which an [X+2+X] approach would be harnessed. For fragment **154**, this meant that the B ring **158** and E ring **159** would be joined together, followed by the formation of the internal C and D rings. Likewise, the fragment **155** would be assembled from the G and J rings **160** and **161**, followed by formation of the internal H and I rings. This would clearly be a highly convergent approach toward the two tetracyclic fragments, allowing for the

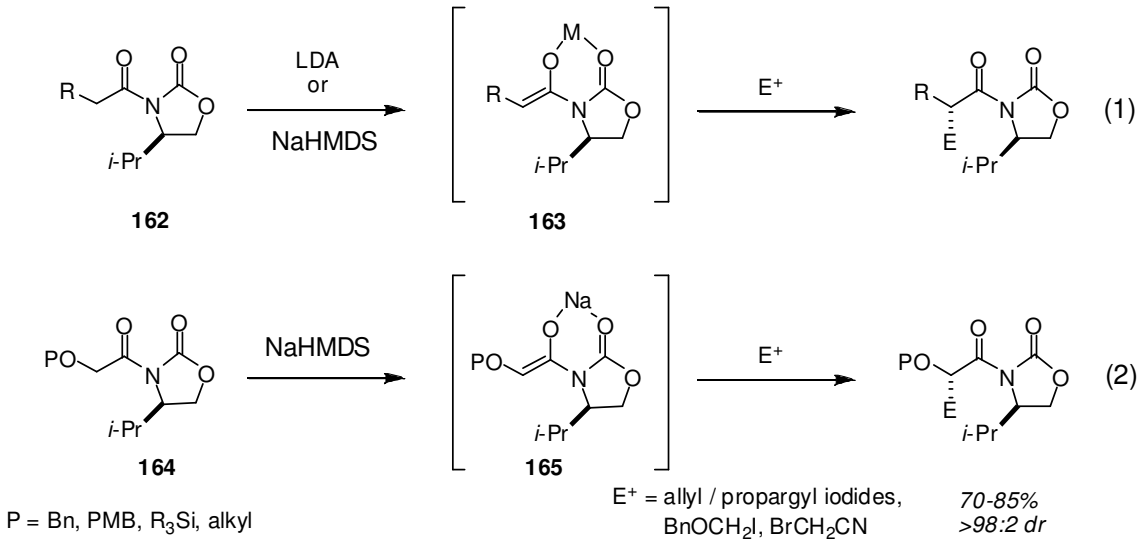
independent synthesis of the B, E, G, and J rings. This lends itself well to the strategic advances developed in the Crimmins laboratory for the construction of medium ring ethers. In particular, the RCM of diene intermediates assembled through chiral auxiliary-mediated aldol[49] and alkylation[50] reactions have been brought to bear on a variety of synthetic targets possessing medium ring ethers, including C2,C11-cyclized cembranoid diterpenes[51] and *Laurencia* metabolites.[52] Further application of these methods to the synthesis of the B, E, and G rings of brevetoxin A offered an excellent opportunity to expand their role in solving complex synthetic problems.

Scheme 2.1. Crimmins' retrosynthetic analysis of brevetoxin A.



As a key component of the asymmetric aldol/alkylation-RCM strategy for medium ring ethers, the asymmetric glycolate alkylation is a reaction that was optimized and expanded in scope by the Crimmins laboratory.[50] In fact, the asymmetric glycolate alkylation is an extension of the well-known methodology by Evans[53] which utilizes chiral oxazolidinone auxiliaries to impart diastereoselectivity on the alkylation of acyl moieties (Scheme 2.2, equation 1). In these reactions, treatment of the acyl oxazolidinone **162** with LDA or NaHMDS results in a *Z*-enolate which is chelated to Li or Na (enolate **163**). The chelation restricts free rotation of the auxiliary so that the *i*-Pr group blocks one face of enolate; thus, alkylation with an electrophile leads to products with high diastereoselectivity. For glycolyl oxazolidinones **164** (Scheme 2.2, equation 2), it was discovered that the corresponding enolate **165** was less reactive than those derived from simple acyl moieties. In turn, NaHMDS was

Scheme 2.2 Asymmetric alkylation using the Evans auxiliary.

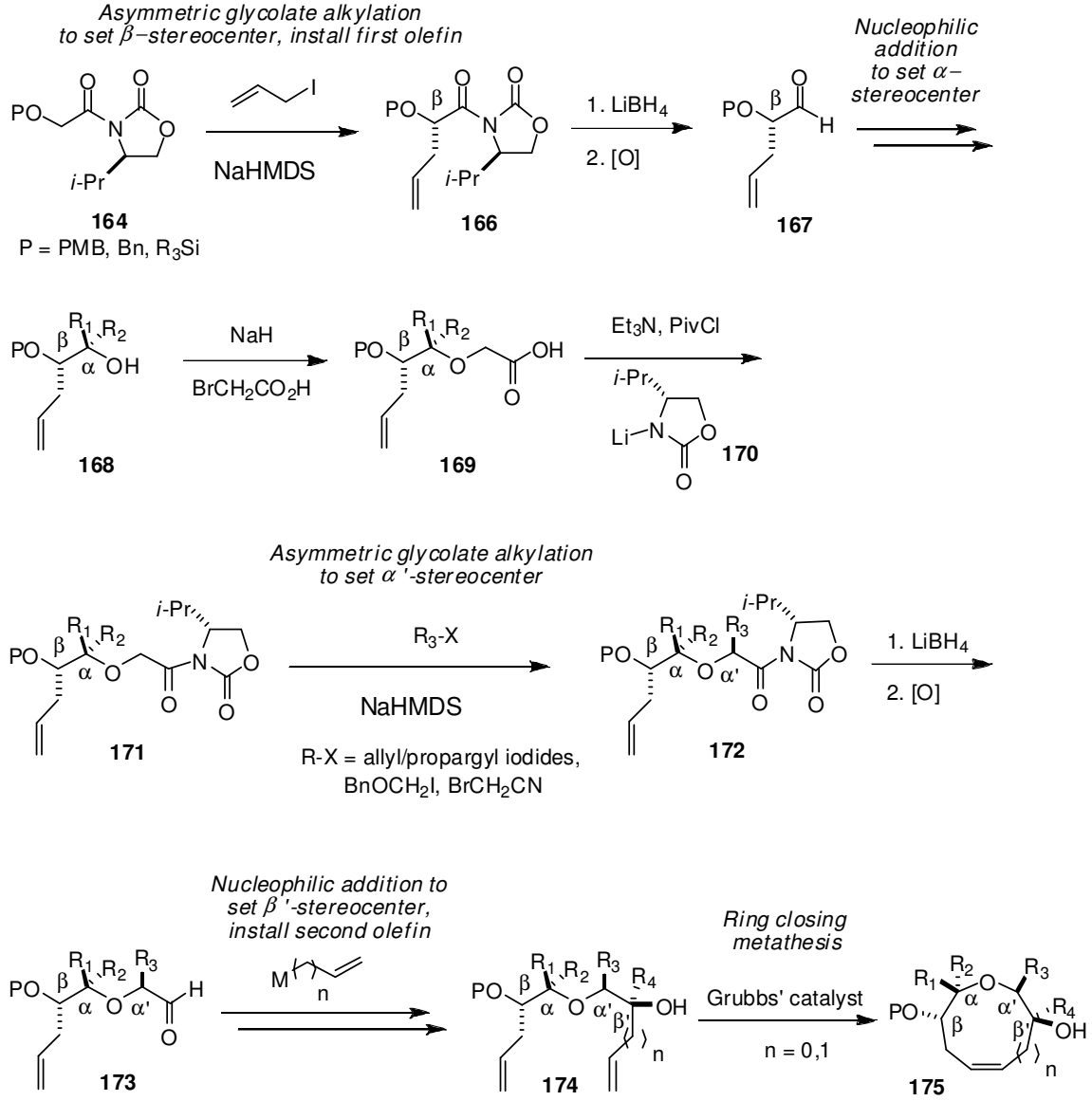


identified as the preferred base for deprotonation (over LDA, etc.) because the sodium enolates possessed enhanced reactivity toward electrophiles. Furthermore,

relatively activated electrophiles were shown to be required, such as allyl or propargyl iodides, $BnOCH_2I$, or $BrCH_2CN$. Under these conditions, the alkylation of glycolyl oxazolidinones proceeds in good yield and with excellent diastereoselectivity.

Drawing upon the asymmetric alkylation-RCM strategy, a generalized model (Scheme 2.3) for the synthesis of the medium ring ethers of brevetoxin A can be

Scheme 2.3. Generalized model for an alkylation/RCM approach to medium ring ethers.



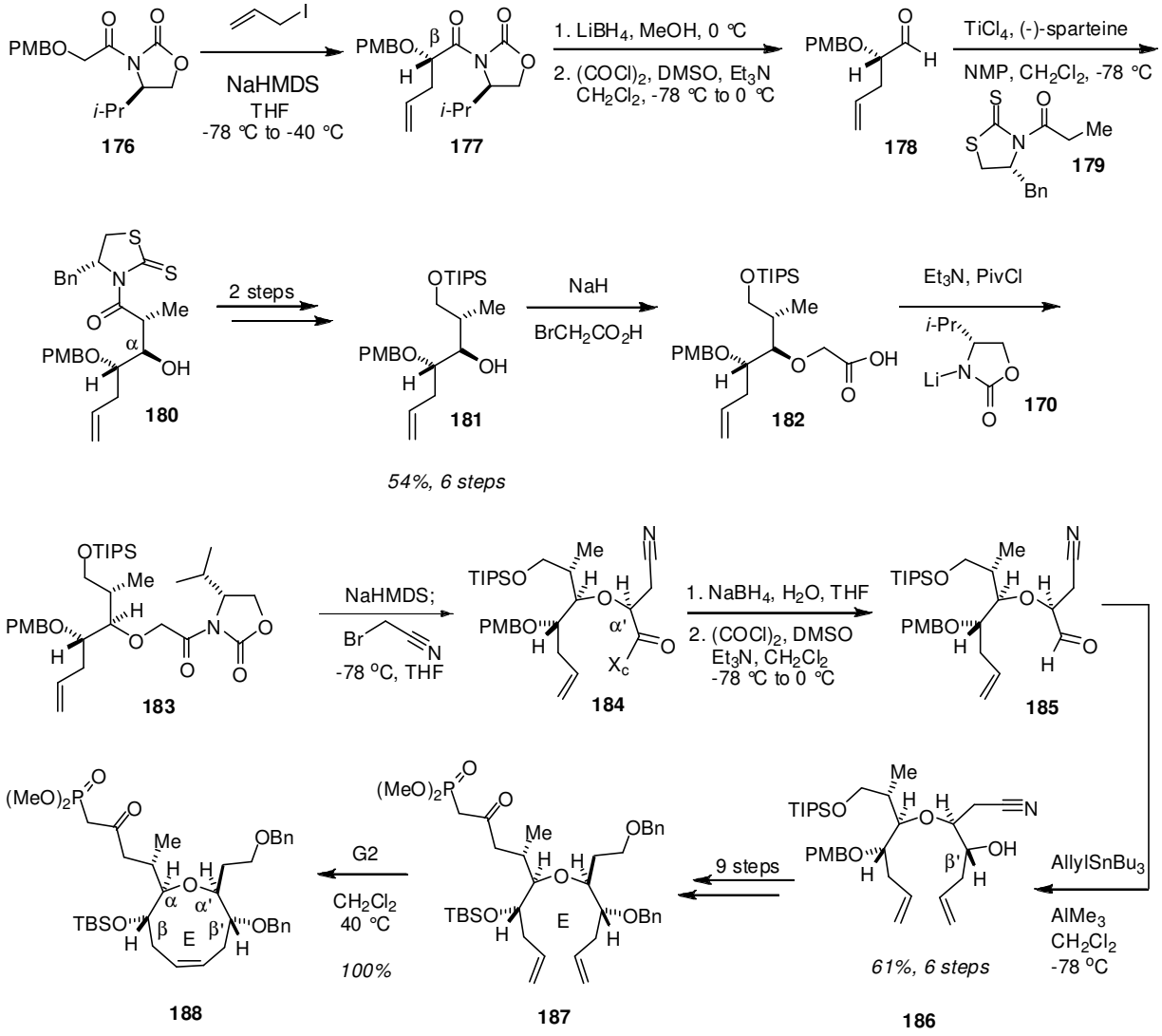
imagined in which a glycolyl oxazolidinone **164** undergoes asymmetric alkylation to install the β-stereocenter of the desired medium ring ether **175**. Reductive removal of the auxiliary and oxidation to access aldehyde **167** allows the introduction of the α-stereocenter through a nucleophilic addition (e.g., an asymmetric aldol reaction), and provides an alkoxy handle for installing another glycolyl oxazolidinone moiety through an *O*-alkylation/acylation sequence to arrive at imide **171**. A second asymmetric alkylation may ensue to install the α'-stereocenter, and subsequent removal of the auxiliary and oxidation to access aldehyde **173** allows for nucleophilic addition with a vinyl or allyl metal species to install the β'-stereocenter and the second required olefin. Finally, RCM completes the desired medium ring ether **175**.

This approach to the medium ring ethers of brevetoxin A has several advantages. First, it is predicated on reliable chiral auxiliary-mediated reactions which provide products with exquisite diastereoselectivity and reproducibly high yields. Secondly, the approach is flexible in terms of the configurations of the stereocenters present in the medium ring, since the chiral auxiliary dictates the stereochemical outcome of the asymmetric aldol or alkylation. Furthermore, the substituents on the ring (i.e. R_1, R_2, R_3, R_4, Scheme 2.3) can be varied based upon the choice of nucleophiles or electrophiles employed. Taken together, these factors amount to a viable approach for a variety of 8- or 9-membered cyclic ethers, including the B, E, and G rings of brevetoxin A.

Indeed, the efforts of Patrick McDougall and Kyle Emmitte led to the construction of the E ring of brevetoxin A through this approach (Scheme 2.4).[54,55] In this case, the β-stereocenter was set by asymmetric alkylation of imide **176** with allyl iodide,

while the α-stereocenter was installed via an asymmetric syn-aldol addition into aldehyde **178** with propionate **179**.[49b] After four additional steps, the α'-stereocenter

Scheme 2.4. Synthesis of the E ring of brevetoxin A.

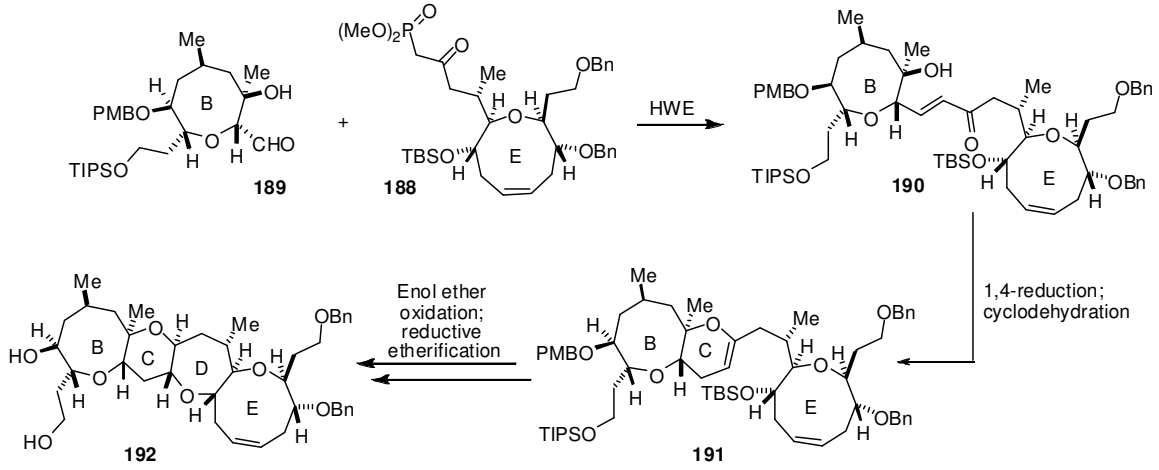


was set by asymmetric alkylation of imide **183** with bromoacetonitrile, and the β'-stereocenter was furnished through a substrate-controlled diastereoselective allylstannane addition into aldehyde **185**. Following nine additional steps, RCM revealed the completed E ring **188**. Likewise, the B ring of brevetoxin A was

synthesized by Patrick McDougall and J. Michael Ellis through an asymmetric alkylation-RCM strategy in line with the described model.[54]

Once the B and E rings were obtained, the next problem was the coupling of these two rings in a high-yielding manner to provide an intermediate well-suited for the closure of the internal C and D rings. This problem was addressed by Patrick McDougall in the discovery of a HWE coupling strategy involving E ring β-ketophosphonate **188** and B ring aldehyde **189** (Scheme 2.5). The resultant enone **190** underwent 1,4-reduction and *endo*-selective cyclodehydration to yield enol ether **191**. A subsequent enol ether oxidation/reductive etherification sequence then completed BCDE tetracycle **192**,[54] which could be taken on to phosphine oxide **154**.

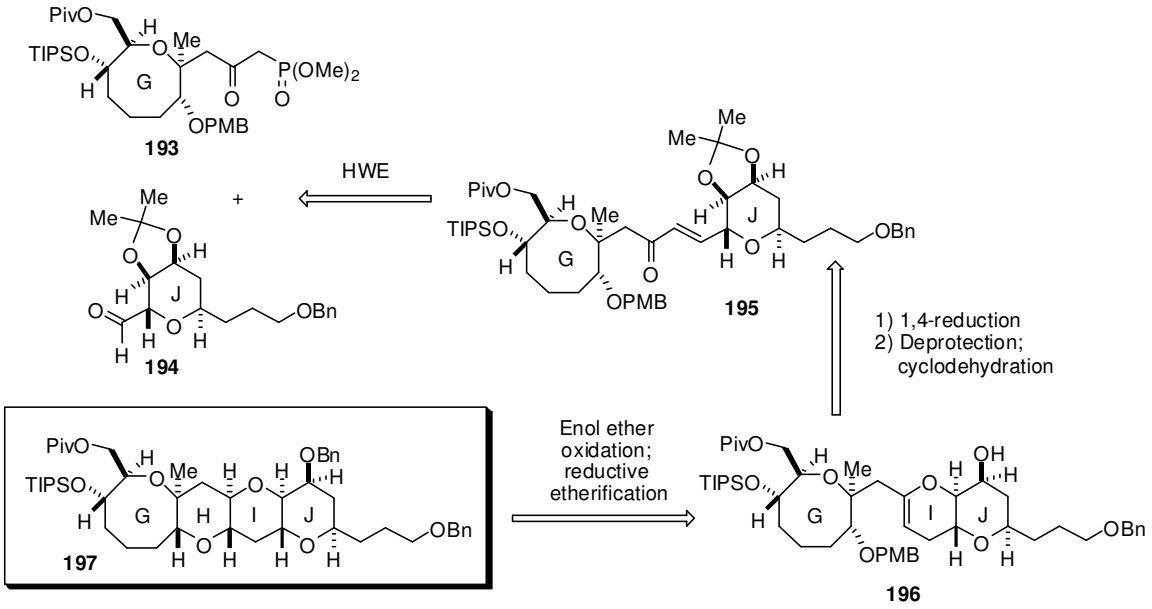
Scheme 2.5. A HWE coupling strategy for the synthesis of the BCDE fragment of brevetoxin A.



Thus, a strategy had been elucidated which effectively unites the synthetic methods for medium ring ethers developed in our laboratory with a convergent coupling strategy. Based upon the success of this approach, it was only logical to extend this strategy to the GHIJ fragment of brevetoxin A. Our vision of the GHIJ fragment synthesis involved the coupling of G ring β-ketophosphonate **193** with J

ring aldehyde **194** through a HWE reaction, which would produce enone intermediate **195**. (Scheme 2.6). Subsequent 1,4-reduction followed by *endo*-selective cyclodehydration would lead to enol ether **196**, which could then undergo an enol ether oxidation/reductive etherification sequence to the desired tetracyclic fragment **197**.

Scheme 2.6. Retrosynthetic analysis of the GHIJ fragment of brevetoxin A.



B. Improved, Scaled-Up Synthetic Routes to the G and J rings of Brevetoxin A

The goal of assembling the GHIJ fragment with the HWE coupling strategy had a clear starting point. Previous to publication of this convergent coupling strategy, considerable effort toward the G ring of brevetoxin A by Pamela Cleary had led to a useful route to advanced intermediate **205** (Scheme 2.7),[56] which could serve as a precursor to the requisite G ring β-ketophosphonate coupling partner **193**. However, optimized scale-up of this initial route to intermediate **205** and the remediation of inefficient or problematic steps therein were necessary for throughput of the

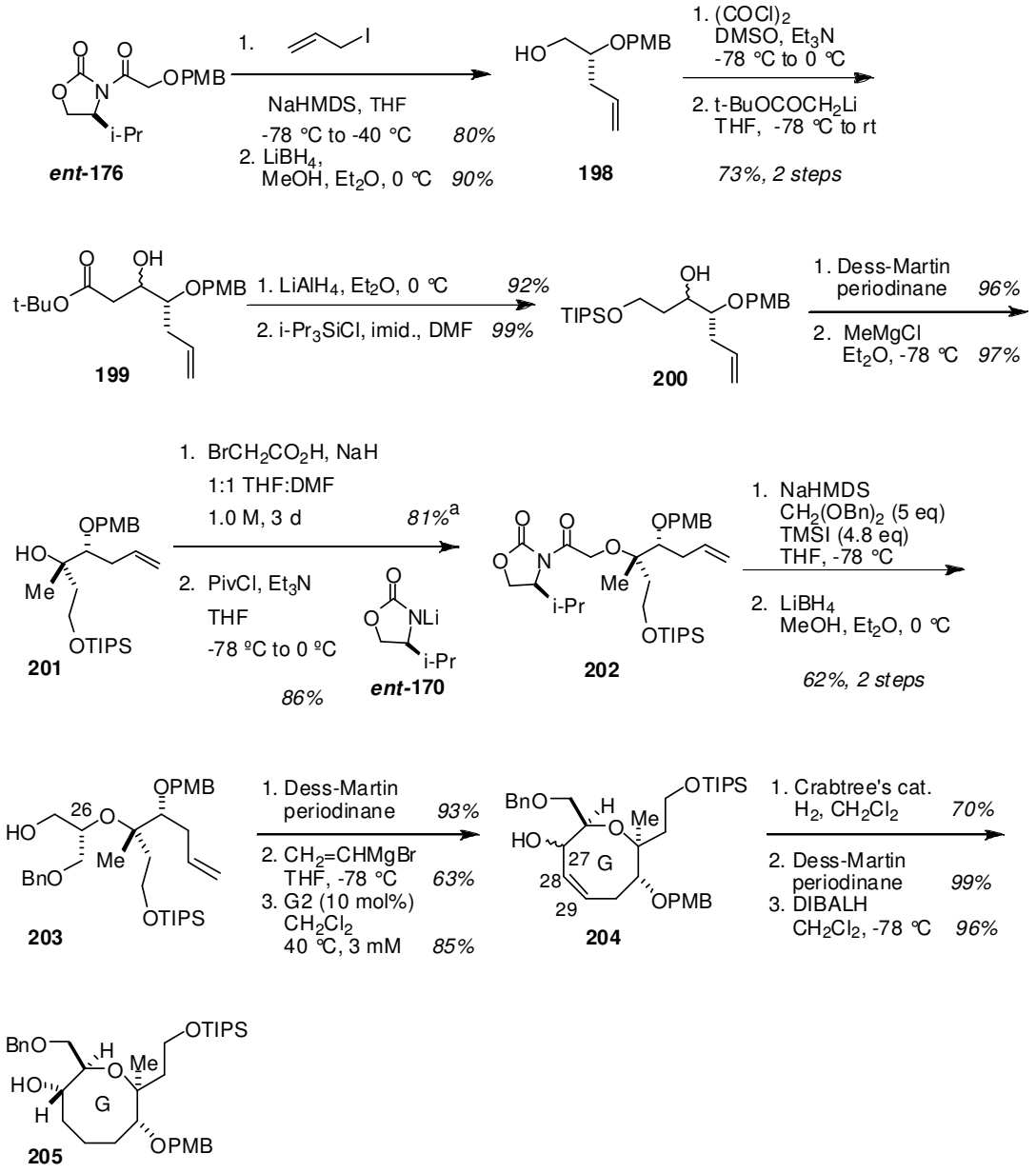
increased amount of material demanded by late-stage investigation. Furthermore, intermediate **205** needed to be converted to the β-ketophosphonate **193** in a straightforward manner, so that multigram quantities of the HWE coupling partner could be obtained.

The initial synthesis[56] of intermediate **205** commenced with an asymmetric alkylation of imide ***ent*-176** (Scheme 2.7) with allyl iodide, the product of which was treated with $LiBH_4$ for reductive removal of the auxiliary to produce alcohol **198**. The alcohol was oxidized under Swern conditions to the corresponding aldehyde, which underwent an unselective aldol addition with lithiated *t*-BuOAc to provide alcohol **199** as an inconsequential mixture of diastereomers. Exposure to $LiAlH_4$ and selective protection of the resulting primary alcohol as the triisopropylsilyl ether produced alcohol **200**. The diastereomers were then converged to a single compound by oxidation to the ketone under Dess-Martin conditions, and subsequent chelation-controlled addition of methylmagnesium chloride to the ketone afforded tertiary alcohol **201** as a single isomer in excellent yield.

To establish the C26 stereocenter, tertiary alcohol **201** was alkylated with sodium bromoacetate ($BrCH_2CO_2H$, NaH, 1:1 THF:DMF, 3 days), and the resulting acid was converted to the mixed anhydride with PivCl and treated with (*S)*-lithio-4-isopropyl-2-oxazolidinone ***ent*-170** to produce imide **202**. Alkylation of the sodium enolate of imide **202** with $BnOCH_2I$ (5 equivalents, prepared in situ from $(BnO)_2CH_2$ and TMSI) and immediate reductive removal of the chiral auxiliary with $LiBH_4$ afforded alcohol **203** as a single isomer in 62% yield over two steps. Setting the stage for ring

closing metathesis, alcohol **203** was oxidized to the aldehyde under Dess-Martin conditions, and then exposed to vinylmagnesium bromide at -78 °C to obtain the

Scheme 2.7. Initial route to intermediate **205**. (Yields reflect scaled-up conditions.)



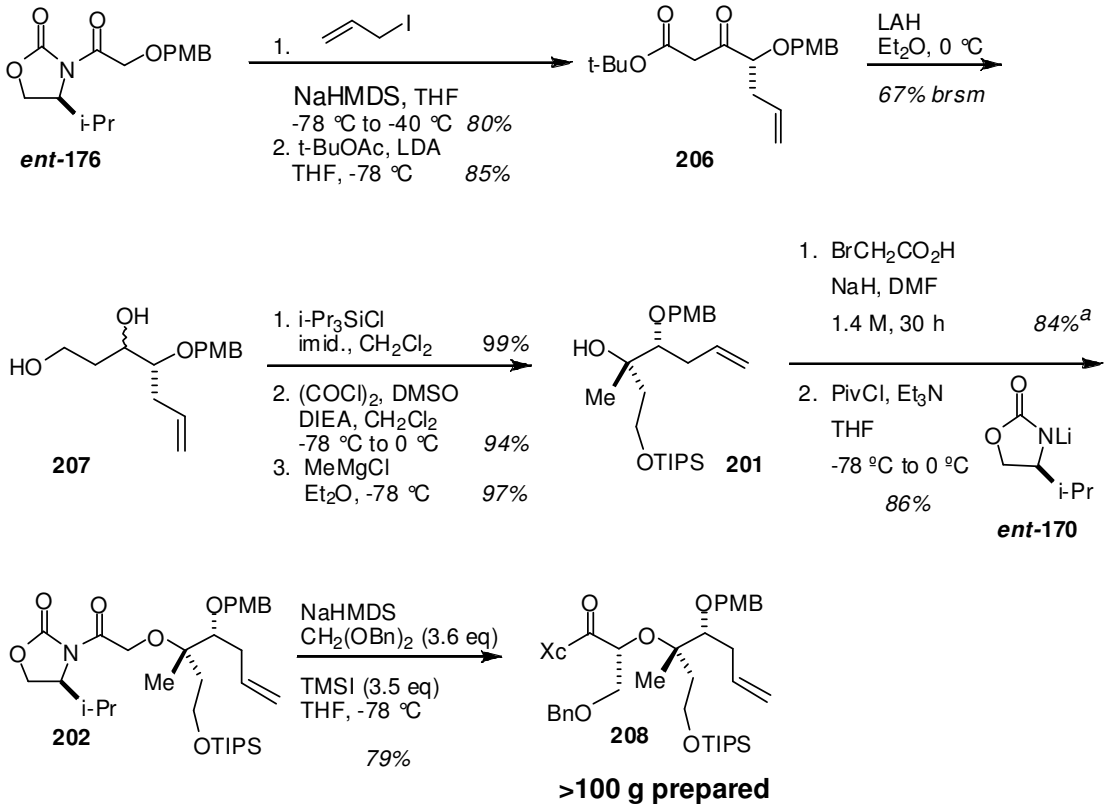
[a]Yield includes product obtained from one re-subjection of recovered starting material.

necessary diene intermediate as a mixture of C27 epimers. Ring closing metathesis was then accomplished smoothly with G2,[57] providing oxocene **204**. Using

$[PCy_3][COD][pyr]Ir^+PF_6^-$ (Crabtree's catalyst)[58] under H_2 atmosphere, the resulting C28-C29 double bond was hydrogenated to access the oxocane in 70% yield. At this point, the C27 epimers were converged by oxidizing to the ketone under Dess-Martin conditions, and exploiting the facial bias of the oxocane, reduction with DIBALH yielded intermediate **205** as a single isomer. Altogether, the synthesis of this intermediate required 18 linear steps with a 6.4% overall yield.

Toward the goal of reaching multigram quantities of β-ketophosphonate **193**, the optimized scale-up of the route to intermediate **205** commenced with the alkylation of imide ***ent*-176** on mole scale without loss of efficiency (Scheme 2.8). The alkylation product obtained was then subjected to a Claisen condensation with

Scheme 2.8. Optimized route to alkylation product **208**.



[a]Yield includes product obtained from one re-subjection of recovered starting material.

lithiated *t*-BuOAc to yield β-ketoester **206**, thus avoiding the lengthier reduction-oxidation-aldol addition sequence that was previously employed.[54] Reduction with $LiAlH_4$ then yielded diol **207**, although the presence of enol tautomers of β-ketoester **206** also led to enolate intermediates resistant to reduction in the presence of $LiAlH_4$. In effect, starting material (ca. 20%) was routinely recovered from this reaction; nonetheless, a 67% yield of diol **207** based on recovered starting material was reproducible.

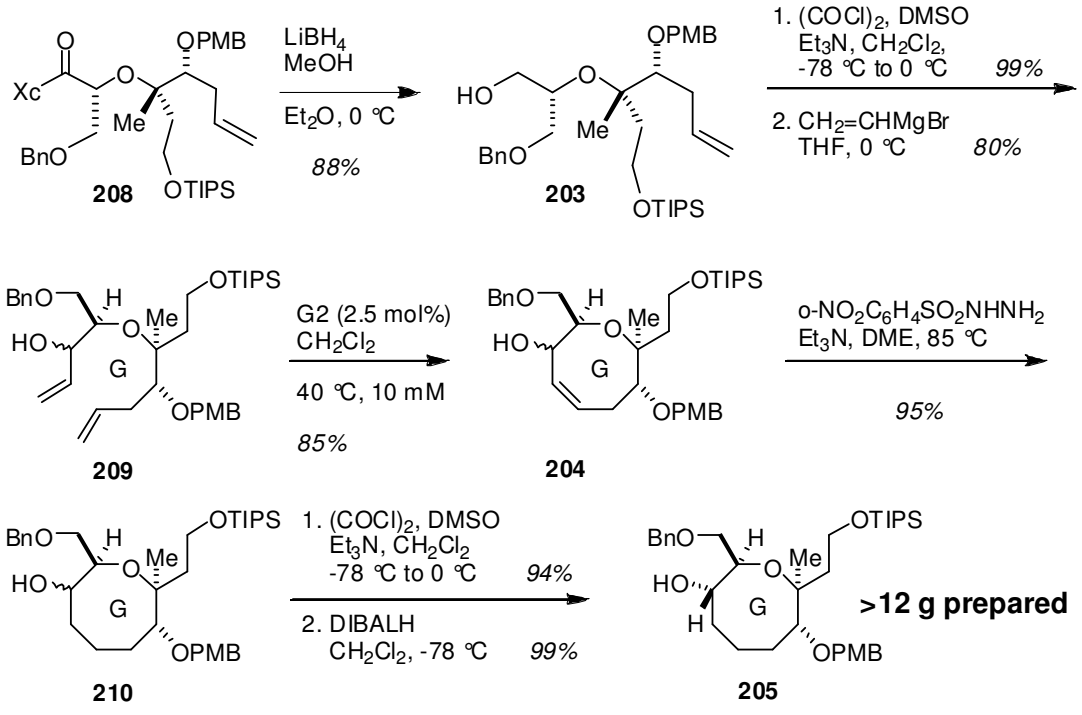
As before, the primary alcohol was selectively protected as the triisopropylsilyl ether, though as a minor point, it was shown that this reaction could be conducted in CH_2Cl_2 instead of the more costly and toxic DMF with an identical yield. At this point, alternative conditions for the oxidation to the corresponding ketone were considered, since the Dess-Martin periodinane is costly and potentially unsafe in large-scale applications. Pleasingly, oxidation under Swern conditions with DIEA as the base occurred smoothly without any measurable epimerization of the α-stereocenter. The resulting ketone then underwent chelation-controlled addition of MeMgCl as before.

Conditions for improving the rate of *O*-alkylation of tertiary alcohol **201** were investigated, since previously employed conditions required 3 days for maximum conversion of the starting material. By increasing the concentration of this bimolecular reaction to 1.4 M and using pure DMF as the solvent, the reaction time was reduced to about 30 h, with a slight increase in yield. Formation of imide **202** then set the stage for asymmetric alkylation. Under typical conditions,[50,56] the $BnOCH_2I$ alkylating reagent is generated from the reaction of 5 equivalents each of $(BnO)_2CH_2$ and TMSI. The excessive use of these reagents was undesirable from a

scale perspective due to costliness of TMSI, and because of the large amount of BnOH byproduct which makes purification of the alkylation product difficult. Fortunately, it was found that the alkylation proceeded to completion with 3.5 equivalents of the alkylation reagents, ameliorating the cost and purification difficulties. Furthermore, the yield was observed to be more reproducible by an improved work-up procedure in which product degradation via reactive iodide species is avoided by a $Na_2S_2O_3$ quench. Notably, over 100 g of alkylation product **208** has been procured.

Subsequent reductive removal of the chiral auxiliary from product **208** provided alcohol **203** (Scheme 2.9) and oxidation to the aldehyde under the more scalable Swern conditions proceeded in excellent yield. Minor procedural optimization of the subsequent vinylmagnesium bromide addition, including increasing the reaction temperature to 0 °C, realized an enhanced yield of diene **209**. The RCM reaction of

Scheme 2.9. Optimized route to G ring intermediate **205**.



diene **209** was improved from a cost and practicality perspective by increasing the concentration to 10 mM, greatly reducing the amount of solvent required for reaction, and by decreasing the catalyst loading of G2 to 2.5 mol%. These changes did not cause any loss in yield.

The endocyclic olefin of oxocene **204** then needed to be hydrogenated without affecting the hydroxyl protecting groups. While use of Crabtree's catalyst under H_2 atmosphere accomplished this result with fair success, it was observed that significant amounts of unwanted byproducts arose from this reaction. In particular, loss of the PMB protecting group and epimerization at C26 via alkene isomerization accounted for undesirable portions of the mass balance. However, transfer hydrogenation with *o*-$NO_2C_6H_4SO_2NHNH_2$[59] and Et_3N was found to cleanly afford the oxocane **210** in 96% yield without any significant side reactions. Finally, oxidation to the ketone under Swern conditions followed by treatment with DIBALH completed a scaled-up synthesis of intermediate **205** in 16 steps, with an overall yield of 12%. To date, over 12 g of intermediate **205** have been prepared.

The stereochemical assignment of *S* for the C27 stereocenter was based upon comparison to the stereochemical outcome of an analogous reaction in which B ring intermediate **211**, a constitutional isomer of intermediate **213** with identical relative stereochemistry (Scheme 2.10), underwent nucleophilic addition syn to the neighboring benzyloxy substituent.[54] It was reasoned that addition of hydride and methyl should both be governed by the facial bias imparted from the conformations of the oxocane substrate. To confirm this assignment, a derivative of intermediate **213** was prepared in two steps: the benzyl group was removed by treatment with

LDBB, and the resulting diol was exposed to benzaldehyde dimethyl acetal under acidic conditions to access dioxane **214.**[60] The dioxane derivative possessed the conformational rigidity needed for NOESY NMR analysis (Figure 2.1), which elucidated the expected 1,3-diaxial proton interactions. Together with the observed coupling constants between neighboring equatorial and axial protons, the configuration of C27 was verified.

Scheme 2.10. Confirmation of the configuration of C27.

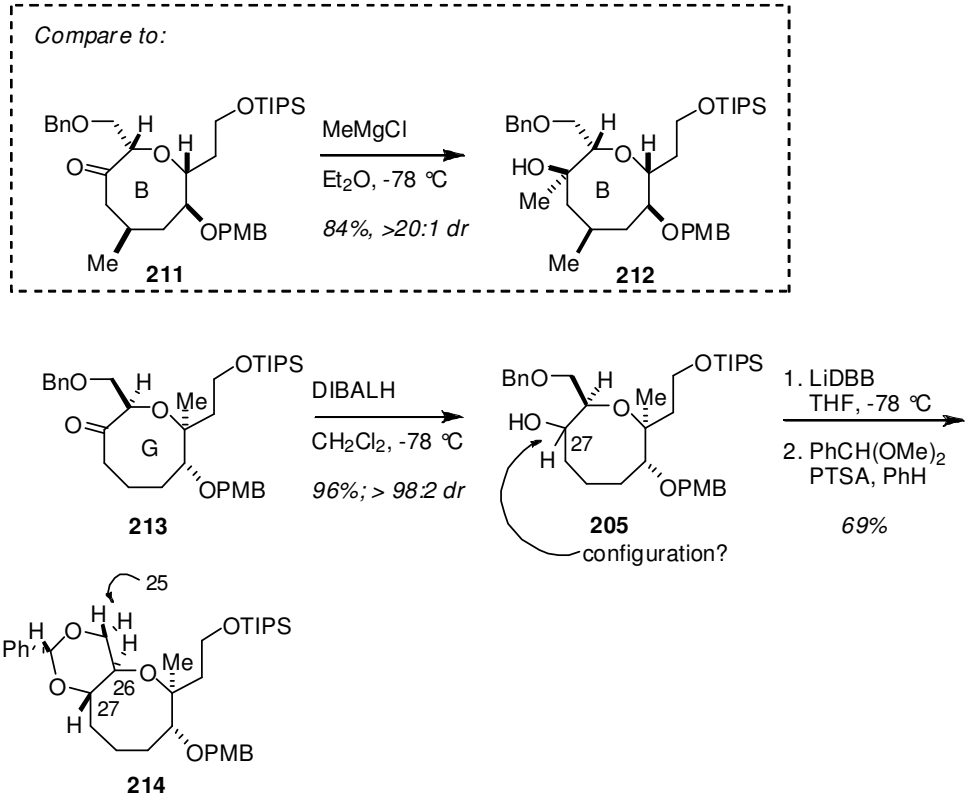
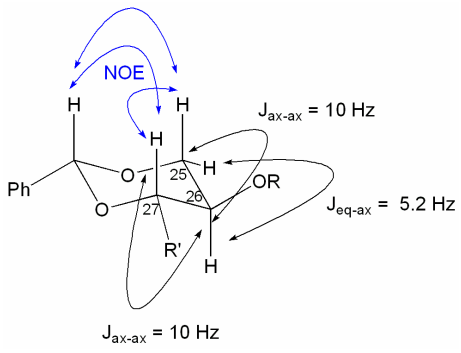
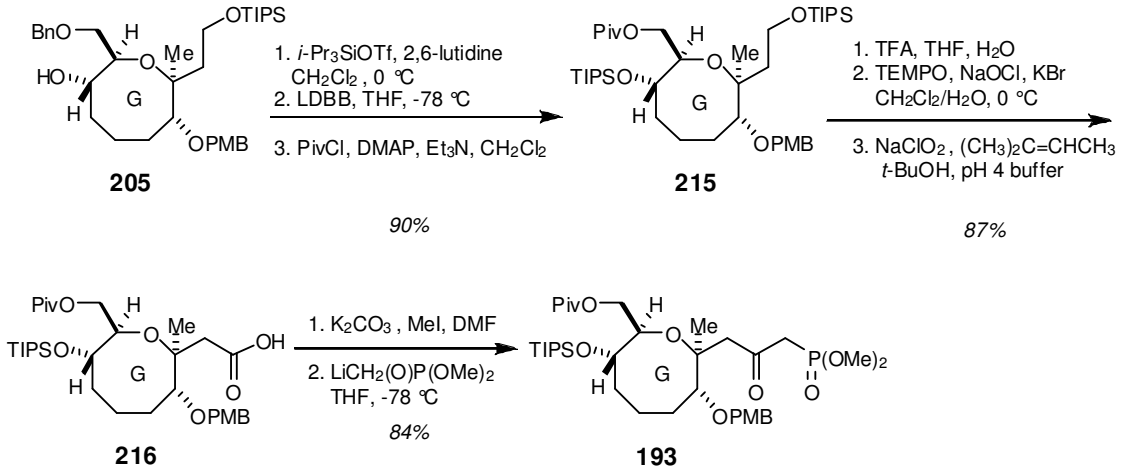


Figure 2.1. NOESY interactions and coupling constants observed for dioxane **214**.



With an optimized route to intermediate **205**, the task of converting this intermediate to the β-ketophosphonate G ring coupling partner **193** was pursued. To this end, the secondary hydroxyl of intermediate **205** was protected as the triisopropylsilyl ether (Scheme 2.11), and the benzyl protecting group was exchanged for a pivaloyl ester to retain orthogonality with the J ring (vide infra), revealing ester **215**. Selective removal of the primary triisopropylsilyl protecting group under acidic conditions followed by a two-step oxidation process provided carboxylic acid **216** in high yield. Exposure to K_2CO_3 and MeI in DMF revealed the methyl ester, which underwent a Claisen condensation with lithiated dimethyl methylphosphonate at -78 °C to furnish the desired β-ketophosphonate **193** in 84% yield over two steps.[61]

Scheme 2.11. Conversion of intermediate **205** to β-ketophosphonate **193**.

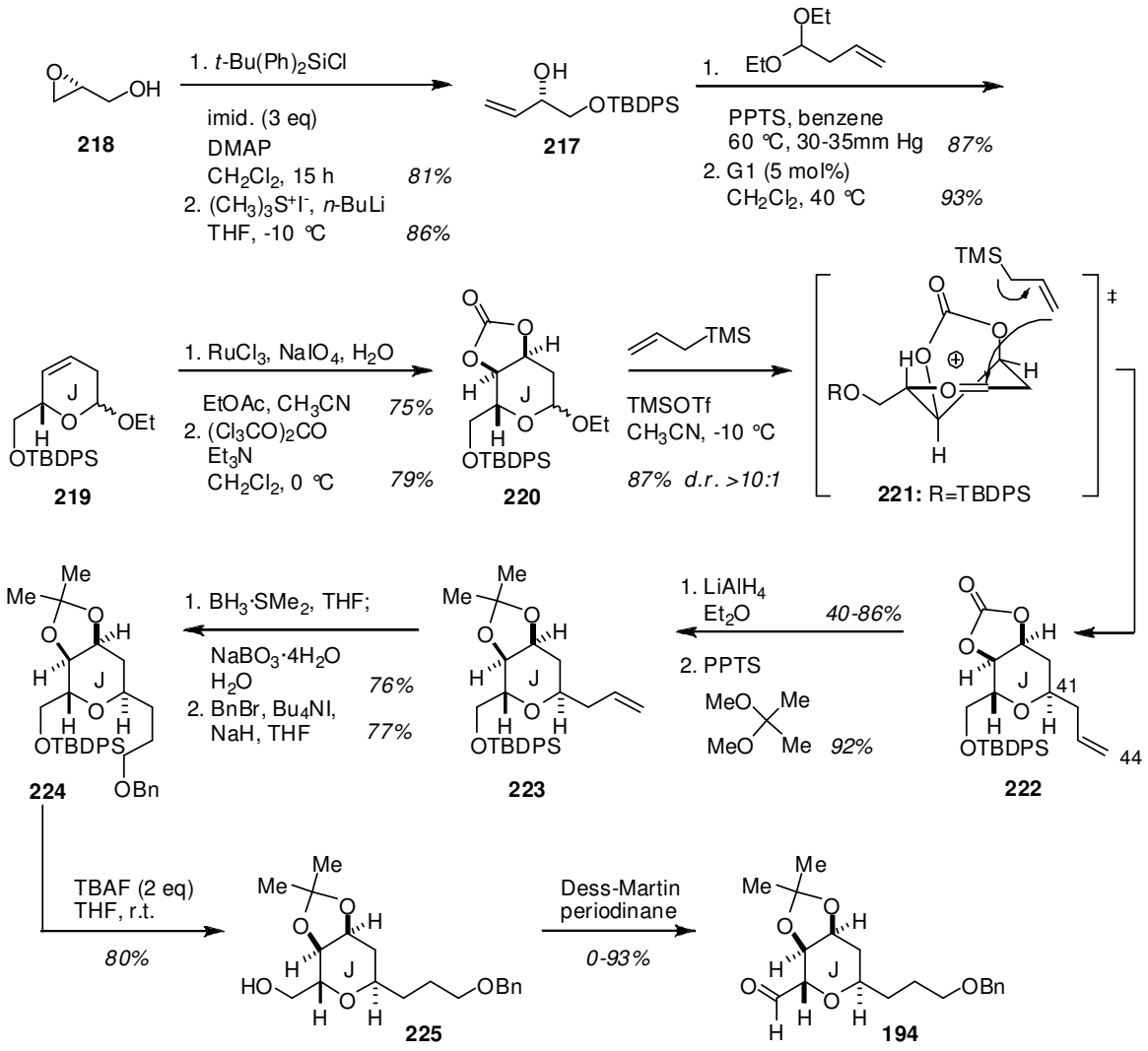


Like the G ring, valuable work by Pamela Cleary and John Parrish previous to publication of the HWE coupling strategy had led to a short synthetic sequence to J ring aldehyde **194**,[60] which could be used directly as a coupling partner with G ring

β-ketophosphonate **193**. As before, improvement of this initial route to the J ring—i.e., addressing inefficient or problematic steps, improving overall yields, and optimizing scale-up—was necessary to make this route efficient for throughput purposes.

The synthesis of the J ring aldehyde coupling partner **194** commenced with the preparation of known alcohol **217**[62] from (*R)*-glycidol **218** (Scheme 2.12) through protection of the alcohol as the TBDPS ether, and exposure to trimethylsulfonium iodide in the presence of *n*-BuLi (Scheme 2.12).[63] Alcohol **217** was then converted to the mixed acetal under transacetalization conditions, and RCM with the first generation Grubbs catalyst (G1, Figure 1.4)[64] delivered dihydropyran **219**. Dihydroxylation with $RuCl_3/NaIO_4$ produced the desired diol in 75% isolated yield, which was protected as the carbonate **220** using triphosgene in 79% yield. A key Hosomi-Sakurai reaction[65] which proceeded via favored transition state **221** then afforded oxane **222** in high yield, thus installing the C42 – C44 side-chain and setting the C41 stereocenter (d.r. > 10:1). The carbonate group was then removed with $LiAlH_4$ in varying yield, and the resulting diol was reprotected with 2,2-dimethoxypropane under acidic conditions to produce acetonide **223**. Hydroboration of the terminal olefin with $BH_3•SMe_2$ gave the primary alcohol in 76% yield, which was protected as the benzyl ether to afford pyran **224**. Removal of the TBDPS group with TBAF at room temperature revealed alcohol **225** in 80%. Thus, alcohol **225** was obtained in approximately 8% over 12 steps. Oxidation under Dess-Martin conditions then completed aldehyde **194**, albeit in irreproducible yield.

Scheme 2.12. Initial route to the J ring of brevetoxin A.



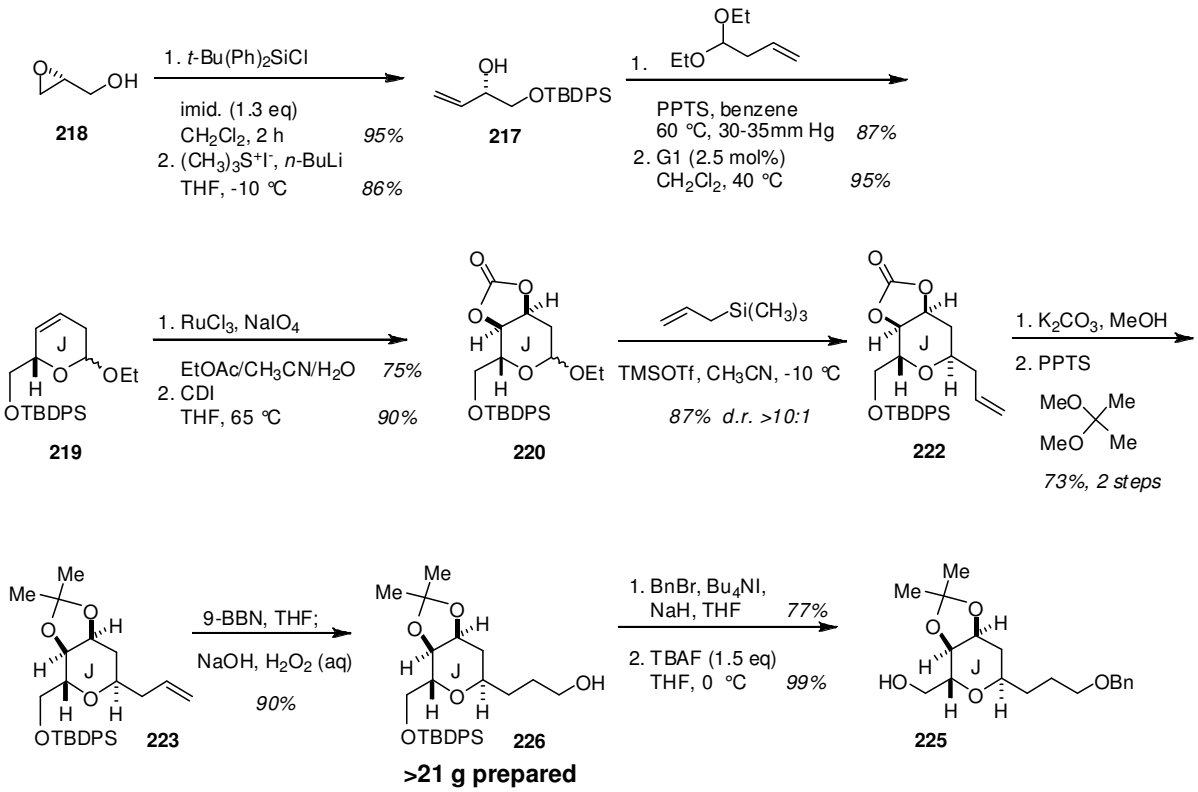
Optimization of the route to J ring aldehyde **194** for scale-up purposes (Scheme 2.13) began with a small adjustment to the protocol for protecting (*R*)-glycidol **218**. By excluding DMAP from the reaction and purifying the silyl ether product immediately upon its complete formation, an additional 14% yield was observed. Upon delivery of alcohol **217** through exposure to trimethylsulfonium iodide in the presence of *n*-BuLi, subsequent transacetalization set the stage for RCM, which was

accomplished with a catalyst loading of only 2.5 mol%. As before, dihydroxylation of the resulting dihydropyran **219** afford the diol in good yield.

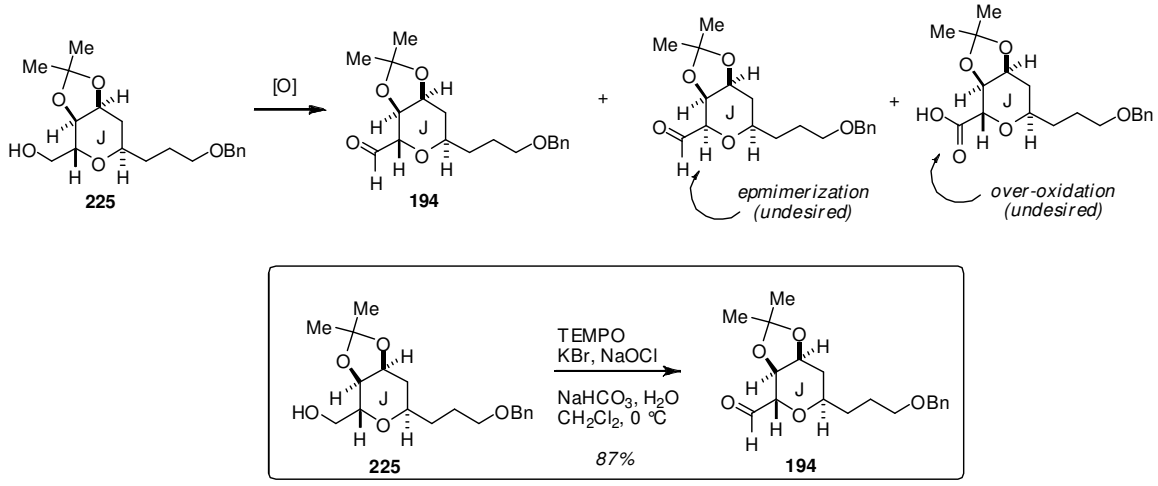
It was discovered that 1,1'-carbonyldiimidazole was a superior reagent for formation of carbonate **220**, routinely providing a high yield. After the Hosomi-Sakurai reaction, the carbonate group was removed reproducibly with K_2CO_3 in MeOH. The resulting diol was protected as the acetonide as before to produce oxane **223**. It was reasoned that the use of a hydroboration reagent with exquisite regioselectivity would improve the yield of alcohol **226**, and in the event, subjection to 9-BBN with sonication led to a 14% increase in yield relative to that obtained from BH_3•SMe_2. It should be noted that over 21 g of alcohol **226** was prepared in this way. Subsequent protection as the benzyl ether and exposure to TBAF at 0 °C furnished alcohol **225** in 20% yield over 12 steps.

To complete the desired aldehyde coupling partner efficiently, the oxidation of alcohol **225** needed to be improved, since the use of Dess-Martin periodinane typically led to extensive decomposition, including epimerization and over-oxidation to the carboxylic acid (Scheme 2.14). While most oxidants screened failed to give acceptable results, it was pleasing to find that the use of catalytic TEMPO in the presence of excess bleach at 0 °C completed aldehyde **194** in 87% yield with minimal over-oxidation.

Scheme 2.13. Optimized route to J ring alcohol **225**.



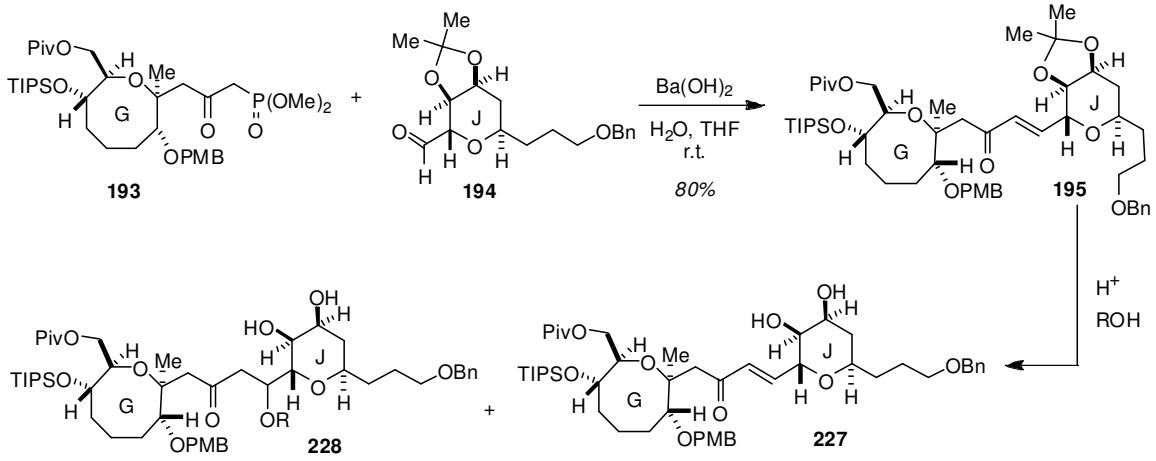
Scheme 2.14. Oxidation of alcohol **225** to aldehyde **194**.



C. Completion of the GHIJ Fragment

With both the G ring β-ketophosphonate **193** and J ring aldehyde **194** coupling partners in hand in multigram quantities, efforts toward realizing the convergent HWE/cyclodehydration coupling strategy were undertaken. While the conditions described by Meyers[66] for HWE olefination involving lithium hexafluoroisopropoxide led to a sluggish reaction, the protocol described by Ibarra[67] and Paterson[68] using $Ba(OH)_2$ reliably coupled the G and J rings at room temperature to provide enone **195** in good yield (Scheme 2.15). The next task was to remove the acetonide protecting group and accomplish 1,4-reduction of the enone. First, enone **195** was treated with a range of acids in various alcoholic solvents with the intention of removing the acetonide. While these conditions did remove the protecting group to provide diol **227**, undesired 1,4-addition of the alcoholic solvent into the enone (byproduct **228**) was also observed in all cases. Thus, it was determined that the 1,4-reduction needed to take place before acetonide removal.

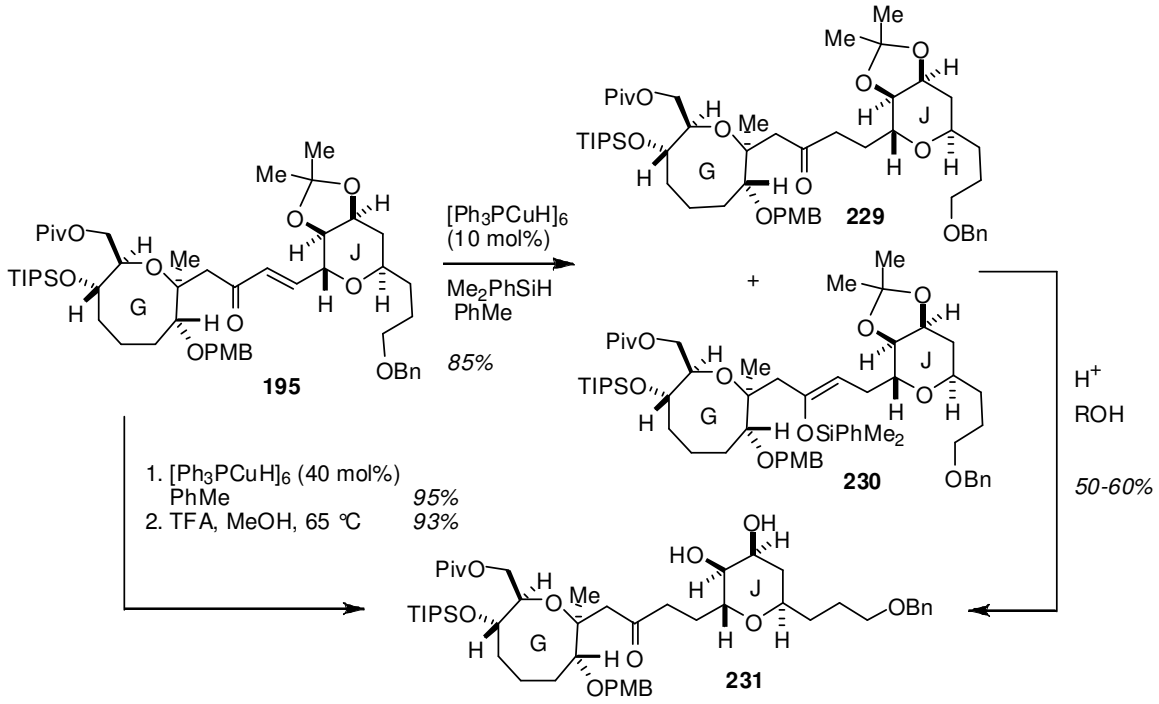
Scheme 2.15. HWE coupling followed by acetonide deprotection.



To this end, enone **195** was subjected to a catalytic amount of $[Ph_3PCuH]_6$ (Stryker's reagent) in the presence of excess Me_2PhSiH according to the procedure described by Lipshutz[69] (Scheme 2.16). While seemingly convenient in that only 10 mol% of Stryker's reagent would be required, the Lipshutz procedure led to a mixture of the desired ketone **229** and the corresponding silyl enol ether **230**. Treatment of the resulting mixture with alcoholic solvents under acidic conditions then removed both the acetonide and silane moieties, revealing ketodiol **231**, though in moderate yield. It appeared that compounds **229** and **230** were somewhat acid-sensitive. To circumvent this problem, enone **195** was simply treated with a larger amount of Stryker's reagent in the absence of organosilane. Under optimized conditions, 40 mol% of Stryker's reagent was found to completely reduce the enone to the ketone in high yield. Conditions were then screened for the swift removal of the acetonide. Acid-sensitivity was again observed during screening experiments, but ultimately the use of TFA in refluxing MeOH was found to give the best balance of acid strength and reaction time, removing the acetonide cleanly in 30 minutes without significant degradation of ketodiol **231**.

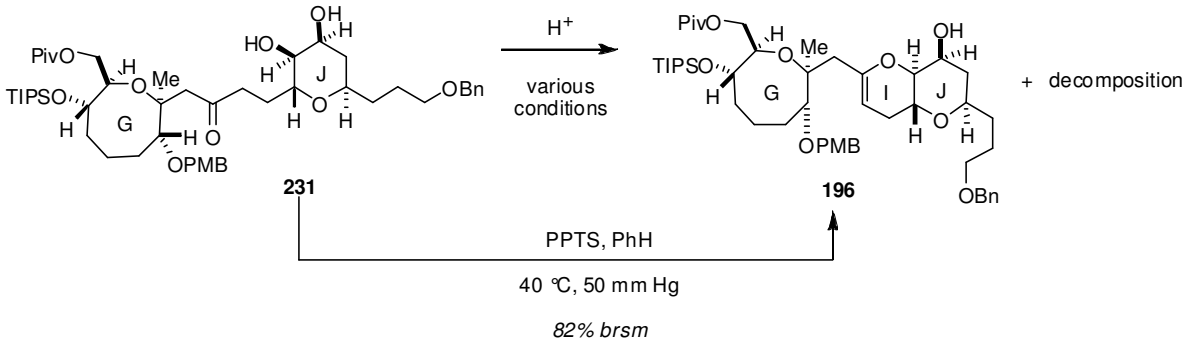
The cyclodehydration of ketodiol **231** to form the I ring was met with considerable resistance, as the acid-sensitivity of this compound was problematic (Scheme 2.17). Under a variety of acidic conditions, both the desired product **196** and the starting material were observed to degrade into a complex mixture of intractable products, particularly upon heating. Furthermore, conversion of the starting material was often sluggish, indicating the need for rigorous removal of water. It was hoped that the reaction would proceed at room temperature in the presence of strong acid and

Scheme 2.16. HWE coupling followed by 1,4-reduction.



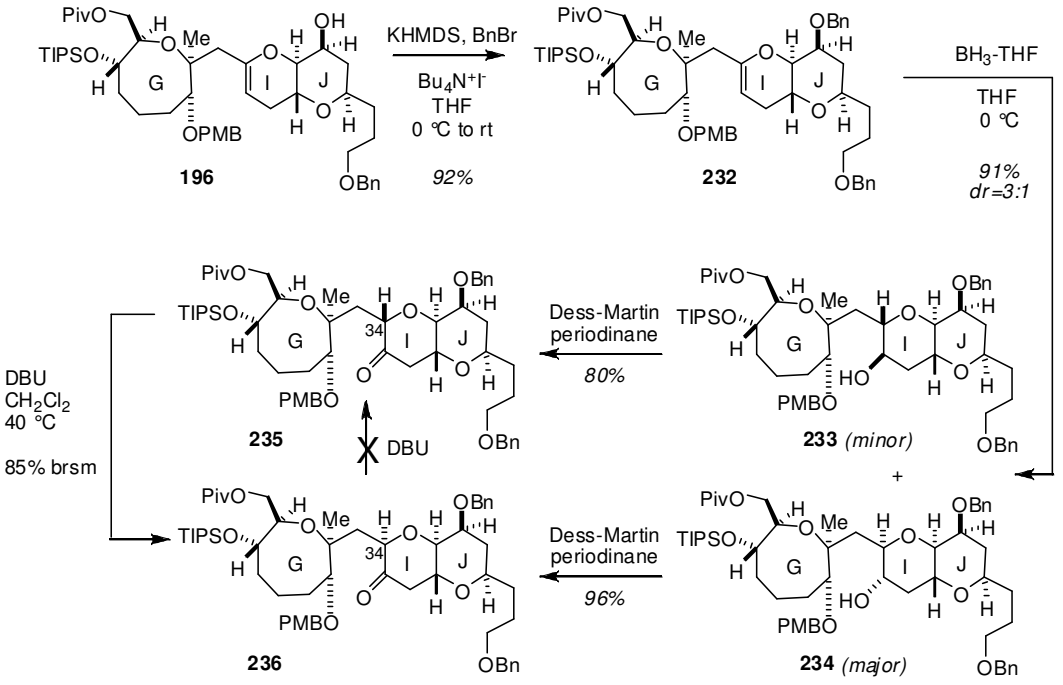
molecular sieves, but in practice, the activation barrier for reaction required elevated temperature. Surprisingly, even heating ketodiol **231** in dry CH_2Cl_2 at 40 °C with PPTS led to low mass recovery and unacceptable conversion. Fortunately it was found that reaction with PPTS in benzene at 40 °C under reduced pressure with azeotropic removal of water smoothly produced the desired endocyclic enol ether **196** in good yield with minimal decomposition.

Scheme 2.17. The cyclodehydration of ketodiol **231**.



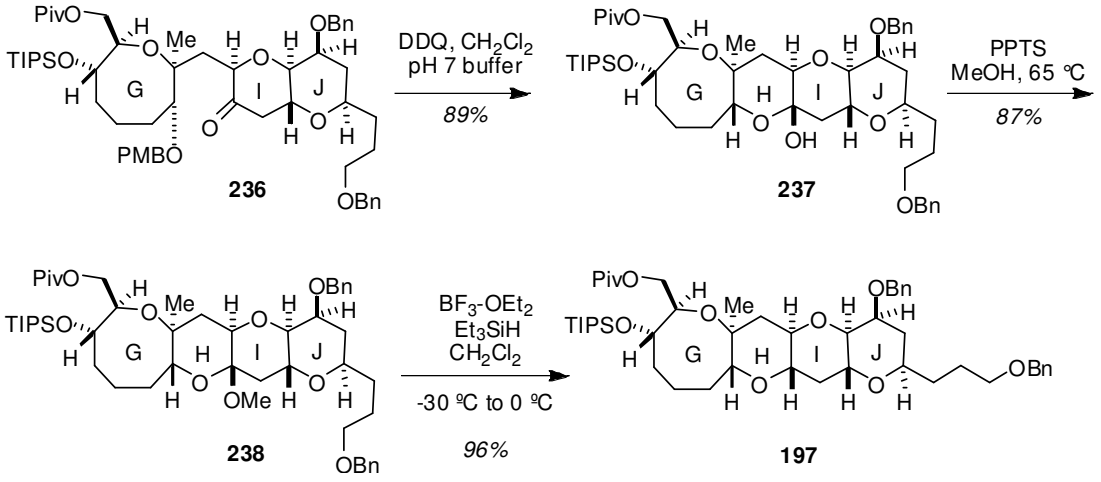
Benzyl protection of the remaining hydroxyl of tricycle **196** yielded ether **232**, which set the stage for the critical oxidation of the enol ether (Scheme 2.18). While BH_3•DMS was unsatisfactory, BH_3•THF[46,70,71] allowed for a 91% yield of a 3:1 mixture of separable diastereomers **233** and **234** after alkaline peroxide work-up. Both isomers were separately oxidized to the corresponding ketones **235** and **236** with Dess-Martin periodinane. The minor epimer **235** was isomerized to the major epimer **236** with DBU at 40 °C in reasonable yield. Conversely, the major epimer **236** could not be isomerized to the minor epimer **235** under identical conditions, confirming that the major epimer **236** was indeed more thermodynamically stable than the minor epimer. The major isomer was reasoned to have the desired configuration at C34, since having the G ring substituent in an equatorial position on the I ring should be more favorable.

Scheme 2.18. Oxidation of the enol ether.



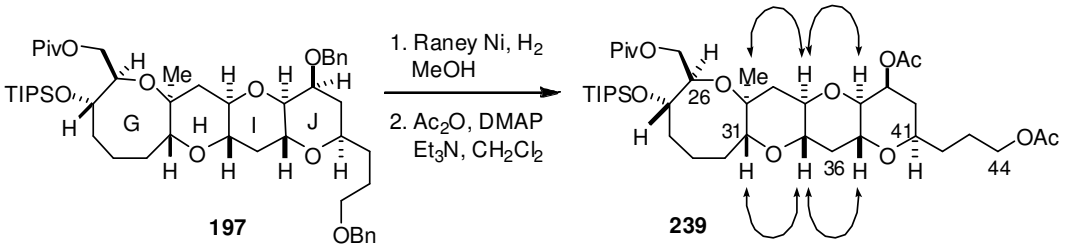
To complete the GHIJ fragment, the PMB protecting group of ketone **236** was oxidatively removed with DDQ (Scheme 2.19), and the resulting hemiketal **237** was treated with PPTS in MeOH to form mixed methoxy ketal **238**. Reductive etherification mediated by BF_3•Et_2O and Et_3SiH then completed GHIJ tetracycle **197** in excellent yield as a single isomer.

Scheme 2.19. Completion of the GHIJ fragment.



Further structural verification of the GHIJ fragment **197** through 2-D NMR spectral analysis was desirable, but was not directly possible due to poor resolution of key ^1H signals in the NMR spectrum. However, diacetate derivative **239**, prepared in two steps from tetracycle **197** (Scheme 2.20), provided NMR spectra with sufficient resolution for structural verification through gradient COSY and NOESY analysis. Key NOESY interactions were observed between the axial protons at C31, C35, and C37, as well as between the C32 methyl, C34 proton, and C38 proton.

Scheme 2.20. Structural verification of the GHIJ fragment. (Observed key NOESY interactions are indicated by arrows.)



D. Summary

Existing routes to the G and J ring intermediates of brevetoxin A, which drew upon methods for medium ring ether synthesis developed in the Crimmins laboratory, were optimized for throughput in order to access multigram quantities of G and J ring coupling partners. These coupling partners were united via HWE coupling, and subsequent cyclodehydration formed the I ring, paving the way for completion of the GHIJ tetracycle **197** through oxidation and reductive etherification processes. The success of this novel [X + 2 + X] convergent coupling strategy demonstrated in this endeavor, which stands along side the previous synthesis of the BCDE fragment in which the HWE coupling strategy was also invoked, testifies to the power of this approach to polycyclic ether fragments. In particular, the reliably high yields, flexibility to incorporate various ring sizes, and overall straightforwardness are all noteworthy advantages of the strategy.

CHAPTER 3

THE SUCCESSFUL COUPLING OF THE BCDE AND GHIJ FRAGMENTS OF BREVETOXIN A

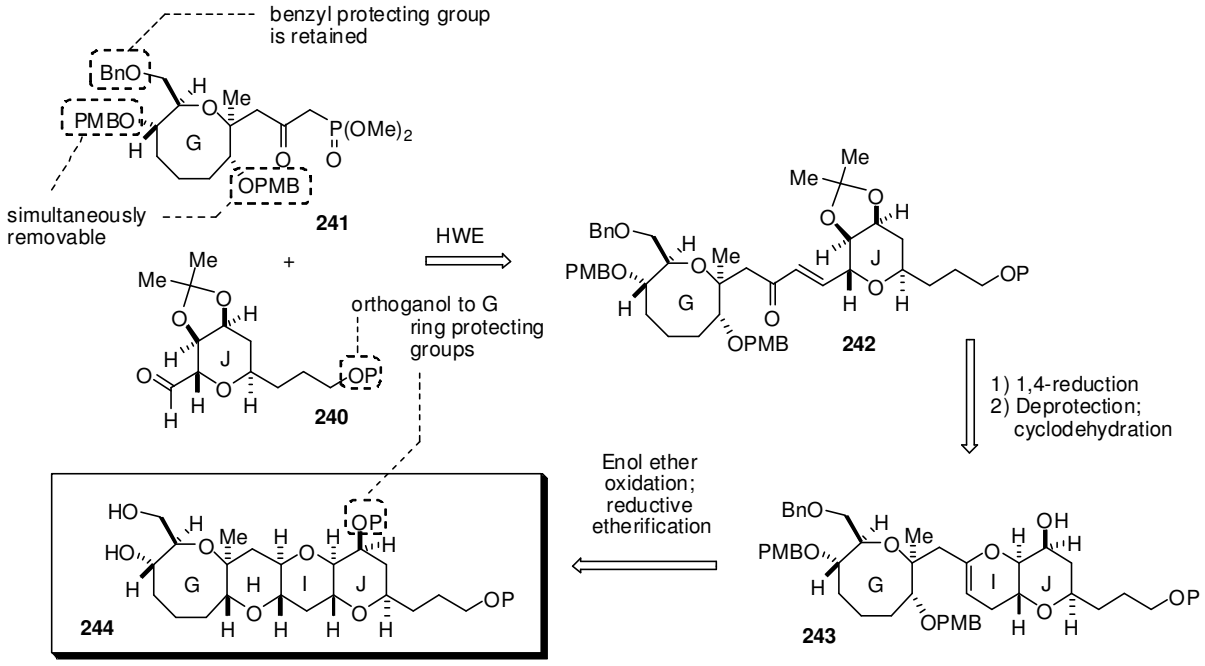
A. An Alternative Route to the GHIJ Fragment

Despite procuring a working synthetic route to the GHIJ fragment of brevetoxin A, it was felt that additional improvement on this route could be made. In particular, we wished to alter our protecting group strategy with the intention of shortening the GHIJ fragment synthesis, as well as replacing the benzyl protecting groups on the J ring with either silyl or benzoyl groups, both of which would have multiple options for removal (**240**, Scheme 3.1). In turn, this obviated the need to exchange the benzyl group for a pivaloyl group on the G ring **241** for orthogonality reasons. Furthermore, it was envisaged that the use of a second PMB group in place of a TIPS group on the G ring would allow for up to three simultaneous deprotections at a later stage. Overall, it was felt that these protecting group changes would make the synthesis more efficient without a significant change to the basic chemistry to follow, thus expediting access to a suitable GHIJ intermediate **244**.

To this end, G ring intermediate **205** (Scheme 3.2) was protected as the bis-PMB ether by reacting with freshly prepared PMBBr. Rapid removal of the triisopropylsilyl group with H_2SiF_6 and oxidation of the resultant alcohol to the

aldehyde with catalytic TEMPO revealed aldehyde **245** in 87% yield over three steps. To shorten the installation of the phosphonate moiety by one step, the

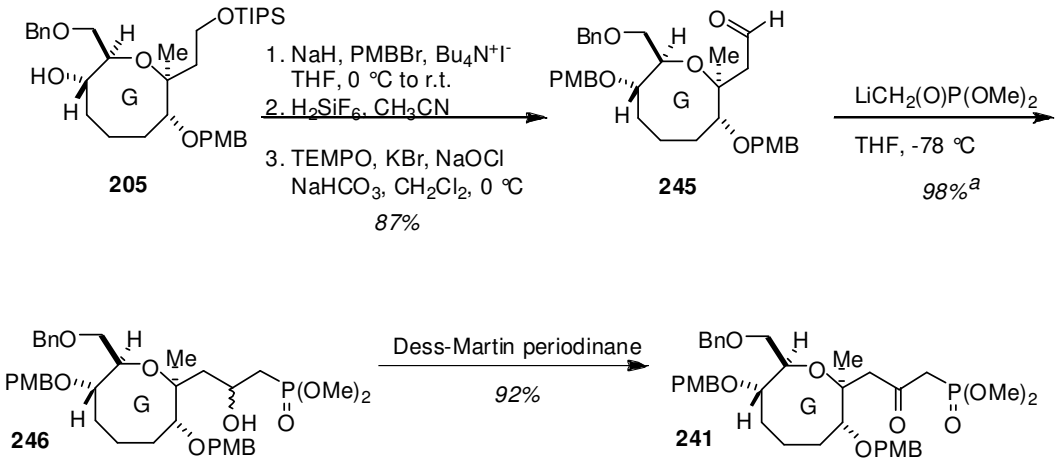
Scheme 3.1. Revised protecting group strategy: retrosynthetic analysis.



Note: P = silyl or benzoyl protecting group

aldehyde was reacted directly with lithiated dimethyl methylphosphonate to provide β–hydroxyphosphonate **246** in excellent yield, and oxidation under Dess-Martin conditions afforded the revised G ring coupling partner **241**. These changes rendered the coupling partner available in three less steps, and in 13% additional yield.

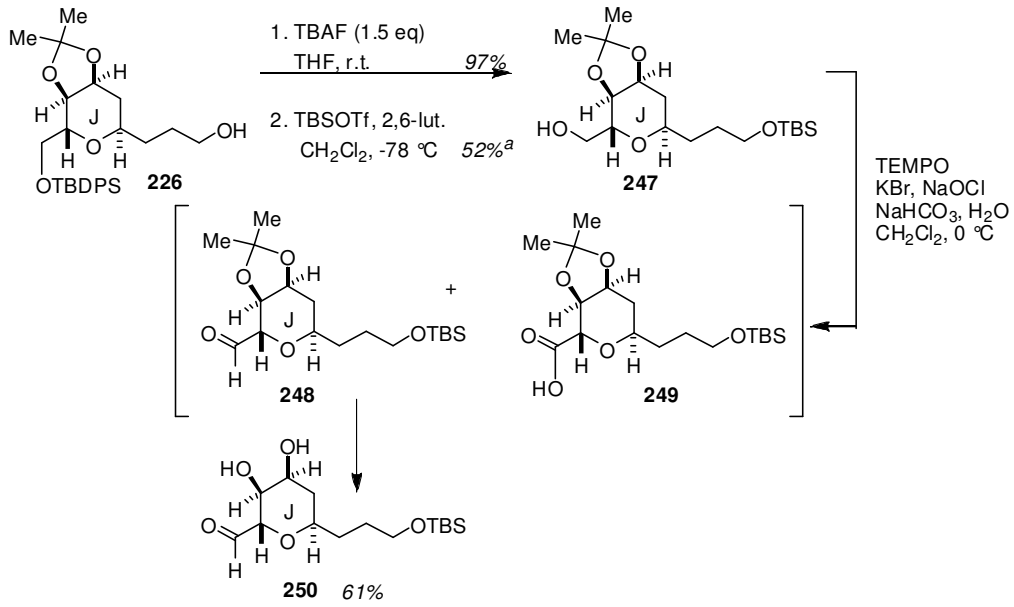
Scheme 3.2. Synthesis of revised G ring β–ketophosphonate.



[a]Yield includes product obtained from one re-subjection of recovered starting material.

The first protecting group chosen to replace the benzyl groups on the J ring was the TBS group, given its ease of manipulation. Thus, J ring alcohol **226** was deprotected with TBAF (Scheme 3.3), and the resulting diol was protected with TBSOTf at -78 °C to access alcohol **247** in modest yield, although the starting material, the regioisomeric TBS ether, and the bis-protected silyl ether were also recovered and could be recycled. Upon reaction with TEMPO, oxidation to aldehyde **248** was accompanied by over-oxidation to carboxylic acid **249**, resulting in acidic conditions which led to deprotected dihydroxy aldehyde **250** as the major product.

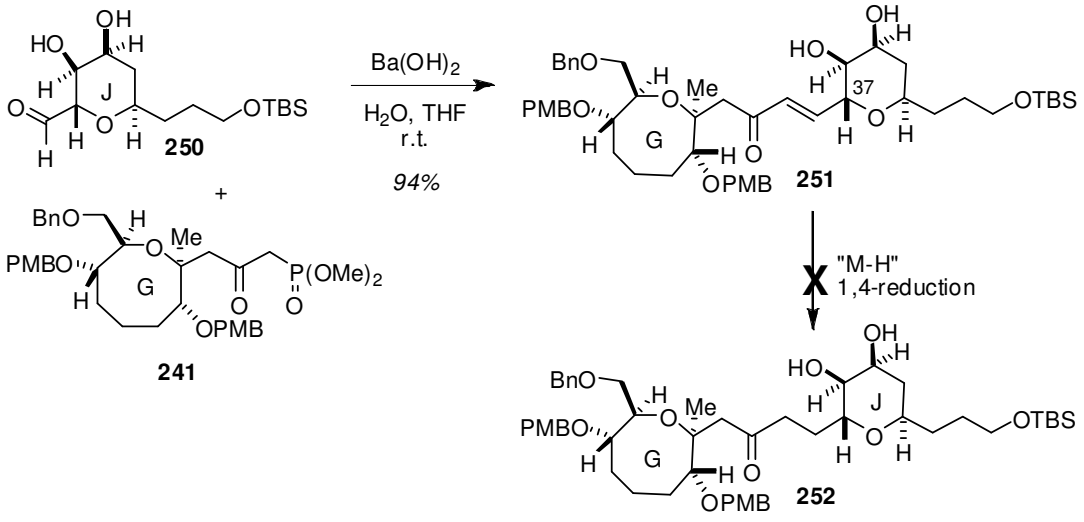
Scheme 3.3. An unexpected coupling partner.



[a]Starting material, regioisomer, and bis-silyl ether were also recovered.

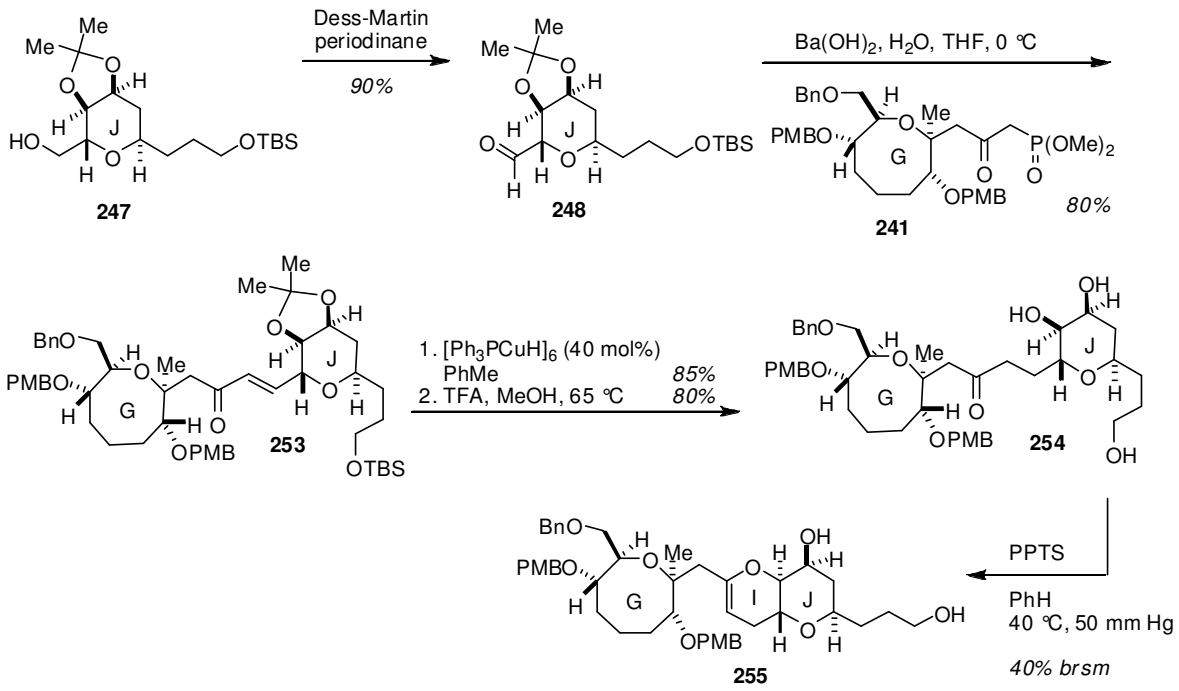
This unexpected product was used in the HWE reaction nonetheless, since it would bring the advantage of not needing an additional deprotection step for acetonide removal after coupling. In fact, the union of dihydroxy aldehyde **250** with β–ketophosphonate **241** proceeded in higher yield than previously observed (Scheme 3.4). Unfortunately, attempts at 1,4-reduction of the resulting dihydroxy enone **251** were unsuccessful, due in part to epimerization at C37 (perhaps via proximal metal alkoxide groups formed in the reaction).

Scheme 3.4. Attempted coupling and 1,4-reduction with dihydroxy aldehyde **250.**



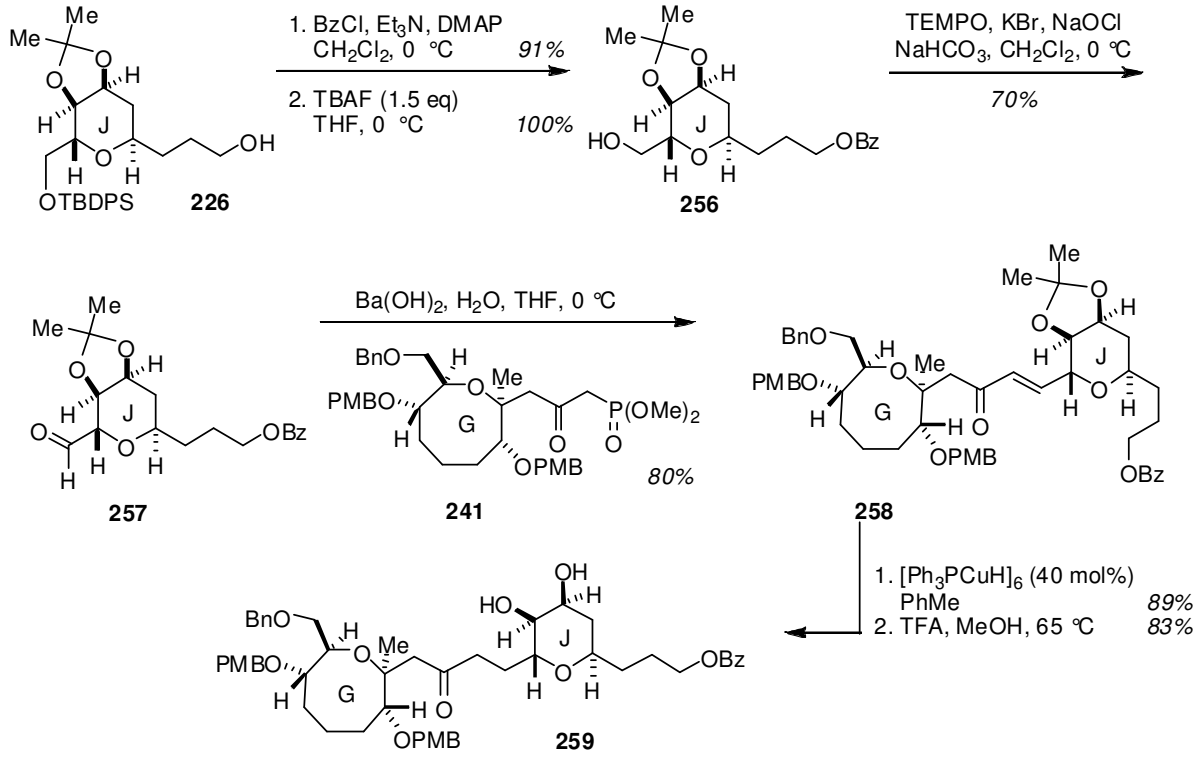
Faced with this roadblock, various conditions for the oxidation of alcohol **247** were reexamined, and it was found that for this particular substrate, Dess-Martin periodinane performed agreeably without concomitant over-oxidation to deliver aldehyde **248** (Scheme 3.5). Subsequent HWE coupling with β–ketophosphonate **241** furnished enone **253** in good yield, and 1,4-reduction with Stryker's reagent worked adequately as before. Treatment with TFA in methanol then removed both the acetonide and TBS protecting groups at similar rates to afford triol **254**. However, difficulty was encountered in the following cyclodehydration step. As with substrate **231** described in Chapter 2, triol **254** proved sensitive to conditions involving acid and heat, particularly above 40 °C. Even with conditions that proved satisfactory for substrate **231**, yields around 40% based on recovered starting material were typically obtained for dihydroxy enol ether **255**.

Scheme 3.5. HWE coupling with acetonide-protected aldehyde **248**.



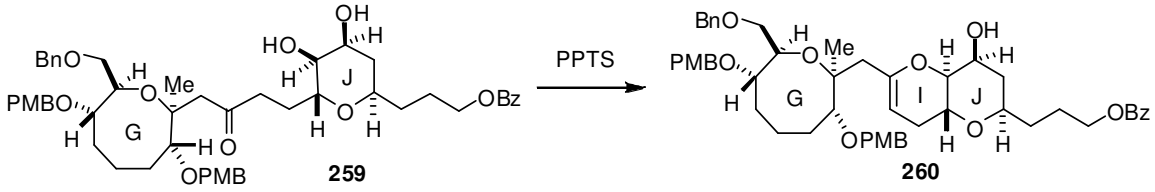
Due to the lability of the TBS group and the resistance of triol **254** toward cyclodehydration, the J ring protecting groups were reconsidered. It was reasoned that the benzoyl group would be well-suited because of its robustness toward the acidic conditions used at various points in GHIJ fragment synthesis. Therefore J ring alcohol **226** was protected with BzCl in the presence of DMAP to provide the benzoate ester (Scheme 3.6), which was subjected to TBAF to access alcohol **256** in 91% over two steps. Once again, TEMPO proved to be the oxidant of choice for formation of the sensitive aldehyde **257**. Coupling of the aldehyde with β–ketophosphonate **241**, 1,4-reduction, and acetonide removal proceeded smoothly as before, leading to diol **259**.

Scheme 3.6. HWE coupling with benzoyl-protected aldehyde **257**.



Conditions involving PPTS in benzene under reduced pressure for cyclodehydration were once again examined for ketodiol **259** (Table 3.1). On small scale, increasing the temperature from 40 °C to 53 °C and adding pyridine to buffer the reaction improved the yield (up to 46%, entry 4); however, yields and conversion levels fluctuated greatly, and tended to be significantly lowered to unacceptable levels upon increasing the reaction scale (entries 2 and 5).

Table 3.1. Cyclodehydration of ketodiol **259** with PPTS in benzene at 50 mm Hg.

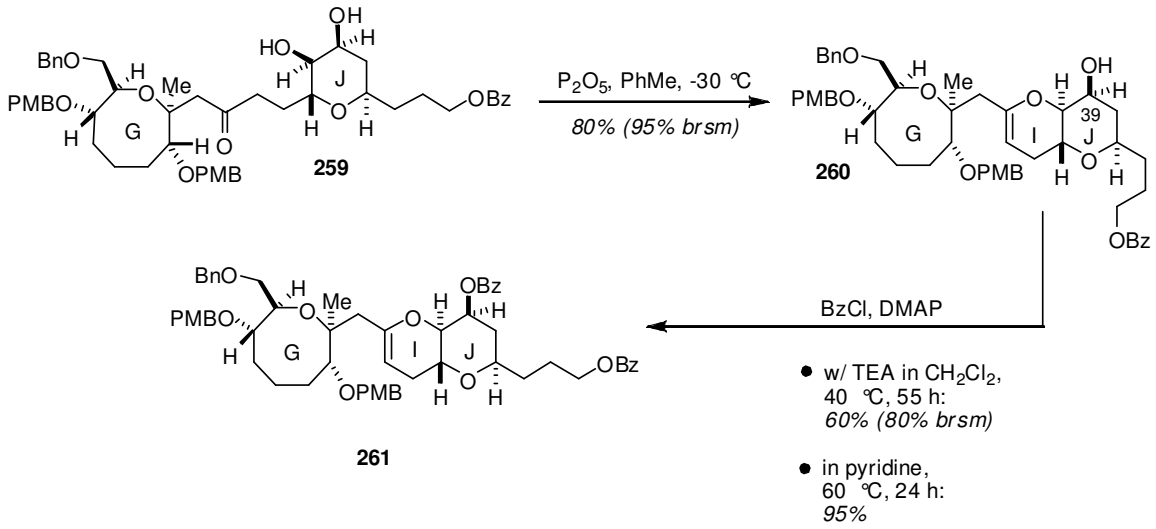


259 **260**

Entry	Pyr. Buffer	Temp. (deg. C)	Scale (mg)	Yield
1	N	40	25	28% (98% brsm @ 29% conv.)
2	N	40	218	21% (85% brsm @ 25% conv.)
3	N	53	25	37% (73% brsm @ 50% conv.)
4	Y	53	25	46% (89% brsm @ 52% conv.)
5	Y	53	330	23% (69% brsm @ 33% conv.)

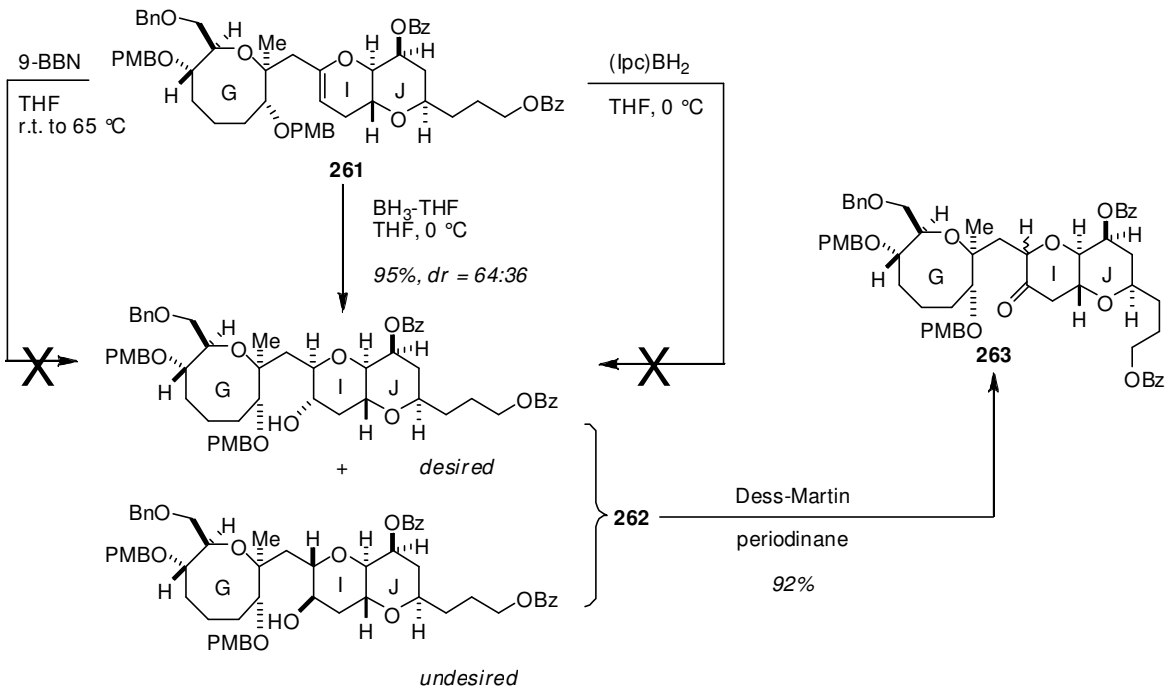
Upon searching for alternative conditions for cyclization, it was found that treatment with of ketodiol **259** with P_2O_5 very rapidly formed the desired enol ether **260** with complete conversion, even at sub-ambient temperature. Gratifyingly, conducting the cyclodehydration with P_2O_5 in toluene at -30 °C delivered the endocyclic enol ether **260** in excellent yield (Scheme 3.7). Not surprisingly, acylation of the C39 hydroxyl with BzCl and DMAP in CH_2Cl_2 at 40 °C was sluggish, leading to a 60% yield of dibenzoate **261** after 55 h. However, switching to pyridine as the solvent and heating to 60 °C improved the yield to 95% after 24 h.

Scheme 3.7. Cyclodehydration of ketodiol **259** with P_2O_5 and subsequent protection.



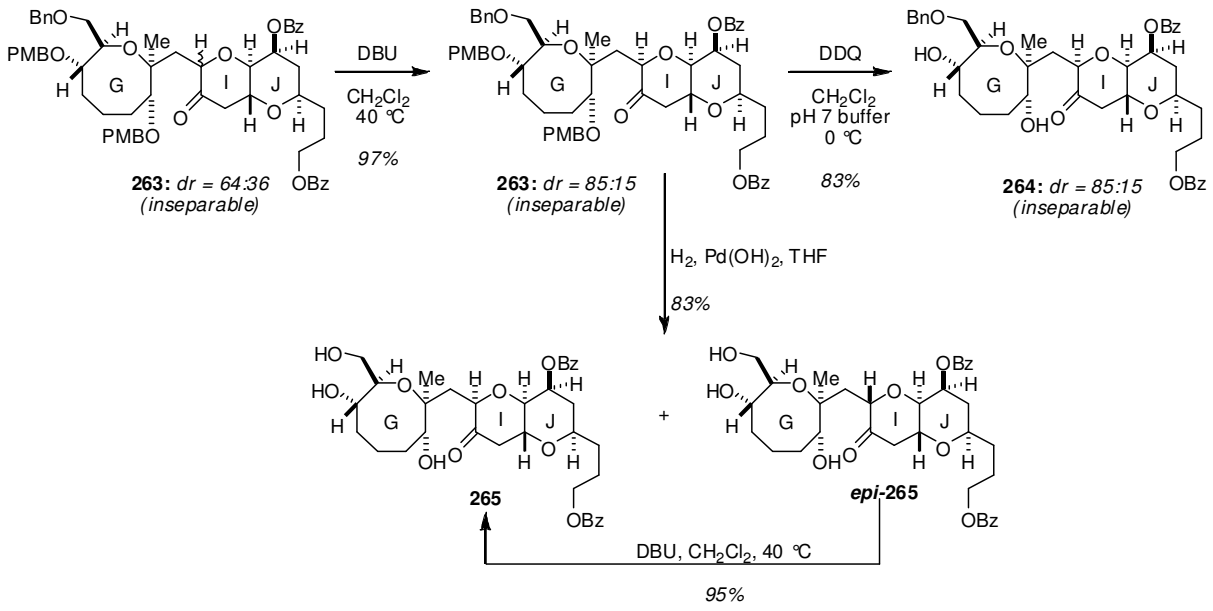
At this point, hydroboration of enol ether **261** was investigated. Similar to before, BH_3•THF performed this operation effectively (95% yield), but the product **262** was obtained as an inseparable 64:36 mixture of diastereomers (Scheme 3.8). Other reagents for hydroboration, including 9-BBN and enantiopure $(Ipc)BH_2$,[72] were probed with the intention of increasing the diastereoselectivity of the reaction, but inferior results were obtained. Thus, the 64:36 mixture of diastereomers was oxidized to ketone **263** (64:36 mixture of inseparable epimers) with Dess-Martin periodinane.

Scheme 3.8. Enol ether oxidation.



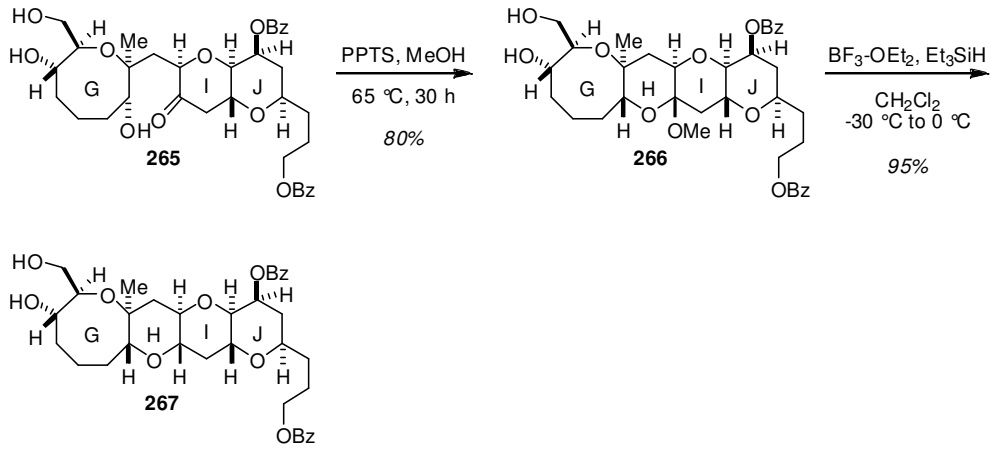
Exposure of the epimeric mixture of ketones **263** to DBU then increased the diastereomeric ratio to 85:15 (Scheme 3.9). At this point, it was postulated that removal of one or more hydroxyl protecting groups might allow for separation of the epimers. Treatment with DDQ removed both PMB groups, but the resulting diol **264** was still an inseparable mixture. Fortunately, hydrogenolysis of both PMB groups and the benzyl group using Pearlman's catalyst lead to triol **265**, from which the minor, undesired isomer *epi*-**265** was easily removed via chromatography and re-subjected to DBU to further bolster the overall yield of desired isomer **265**.

Scheme 3.9. Isomerization of the undesired isomer and hydrogenolysis.



Ketalization with PPTS in MeOH lead to mixed methoxy ketal **266** after 30 h (Scheme 3.10), and reductive etherification under conditions used before accomplished a more efficient synthesis of the GHIJ fragment **267** in excellent yield.

Scheme 3.10. Completion of the alternative GHIJ synthesis.



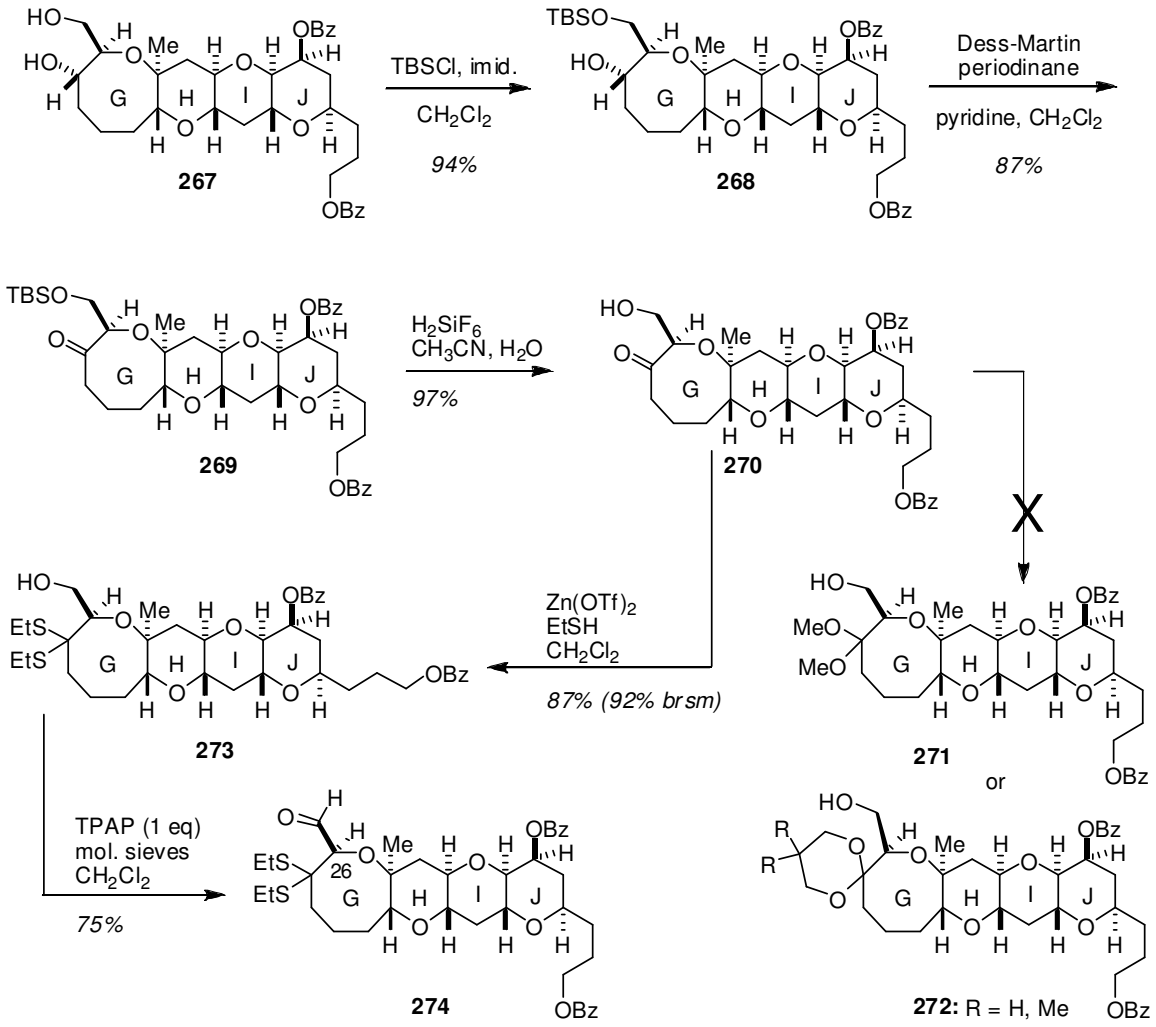
B. Attempted Coupling of BCDE and GHIJ Fragments

With sufficient quantities of tetracycle **267** available, attention was then focused on preparing a suitable coupling partner for the BCDE fragment. As mentioned in Chapter 2, the late-stage strategy for coupling the BCDE and GHIJ fragments called for a Horner-Wittig olefination involving an aldehyde derivative of the GHIJ fragment (Scheme 2.1). To this end, the primary hydroxyl of tetracycle **267** was selectively protected as the TBS ether (Scheme 3.11), and the remaining secondary hydroxyl was oxidized under buffered Dess-Martin conditions to afford ketone **269**. Removal of the silyl protecting group with H_2SiF_6[73] provided hydroxy ketone **270** in excellent yield, which was probed as a substrate for ketalization. Though the observed acid-sensitivity of hydroxy ketone **270** prevented the formation of a dimethoxy ketal **271** or dioxane **272** derivative, exposure to $Zn(OTf)_2$ in 1:1 EtSH:CH_2Cl_2 reliably furnished dithioketal **273**. While a variety of conditions proved ineffective or inconsistent for the clean oxidation of dithioketal **273** to the aldehyde due to epimerization at C26 and unwanted oxidation of sulfur, reaction with one equivalent of TPAP reliably delivered aldehyde **274** in good yield.

With aldehyde **274** in hand, coupling with phosphine oxide **154** (efficiently prepared in eight steps from BCDE diol **192** by J. Michael Ellis)[74] was set to be attempted (Scheme 3.12). It was quickly observed that LDA could be used in excess to improve the longevity of the metallated phosphine oxide, especially on small scale. Furthermore, it was hoped that the sterically hindered nature of LDA would slow unwanted side reactions with aldehyde **274** (e.g., epimerization)

relative to the rate of Wittig adduct formation. In the event, phosphine oxide **154** and aldehyde **274** reacted completely in the presence of three equivalents of LDA. The desired Wittig adduct **275** was obtained in 28% yield, along with an

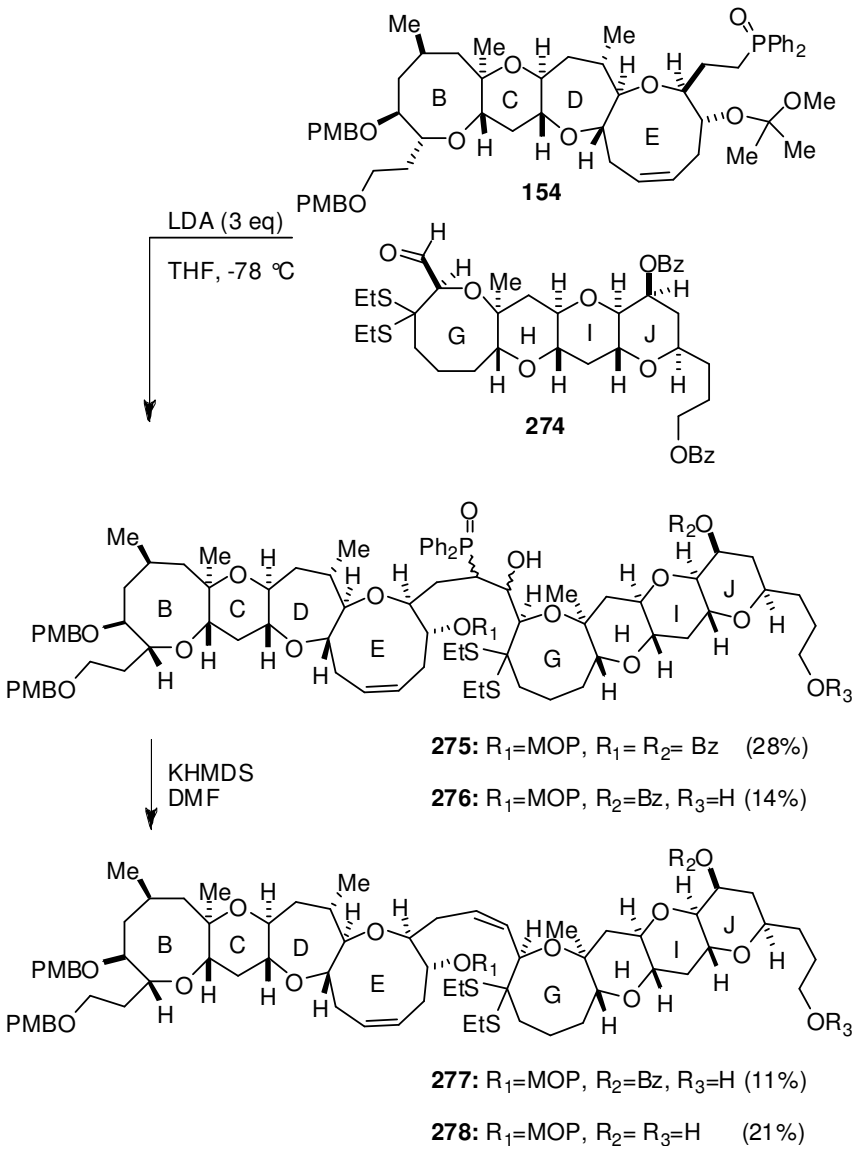
Scheme 3.11. Preparation of a GHIJ coupling partner of the BCDE fragment.



additional 14% of adduct in which a benzoate protecting group had been lost (product **276**). These adducts were tentatively designated as single isomers based upon their ^{1}H NMR spectra. The remainder of the mass balance from this reaction could not be definitively identified. Treatment of adducts **275** and **276** with KHMDS in DMF at ambient temperature lead to elimination of the phosphine

oxide moiety and olefin formation, but the reaction was complicated by the further loss of benzoate protecting groups. Thus, products **277** and **278** were both

Scheme 3.12. Attempted coupling of the BCDE and GHIJ fragments.



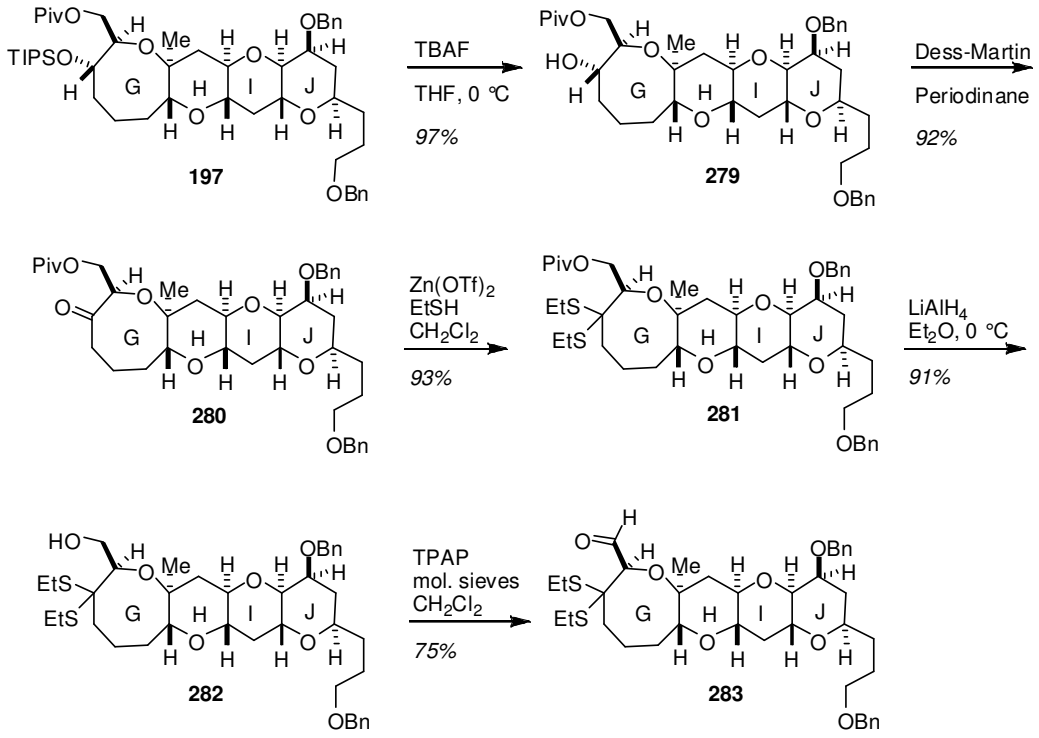
observed in the reaction, along with unidentified byproducts. Under prolonged reaction times, complete loss of benzoate groups did occur, but this was accompanied by significant product decomposition. Further attempts to identify

cleaner elimination conditions by altering the base, solvent, and temperature were unsuccessful. In the end, the overall yield of desired products from the Horner-Wittig/elimination sequence was unacceptable.

C. Coupling of BCDE and GHIJ Fragments: The Original Route Revisited

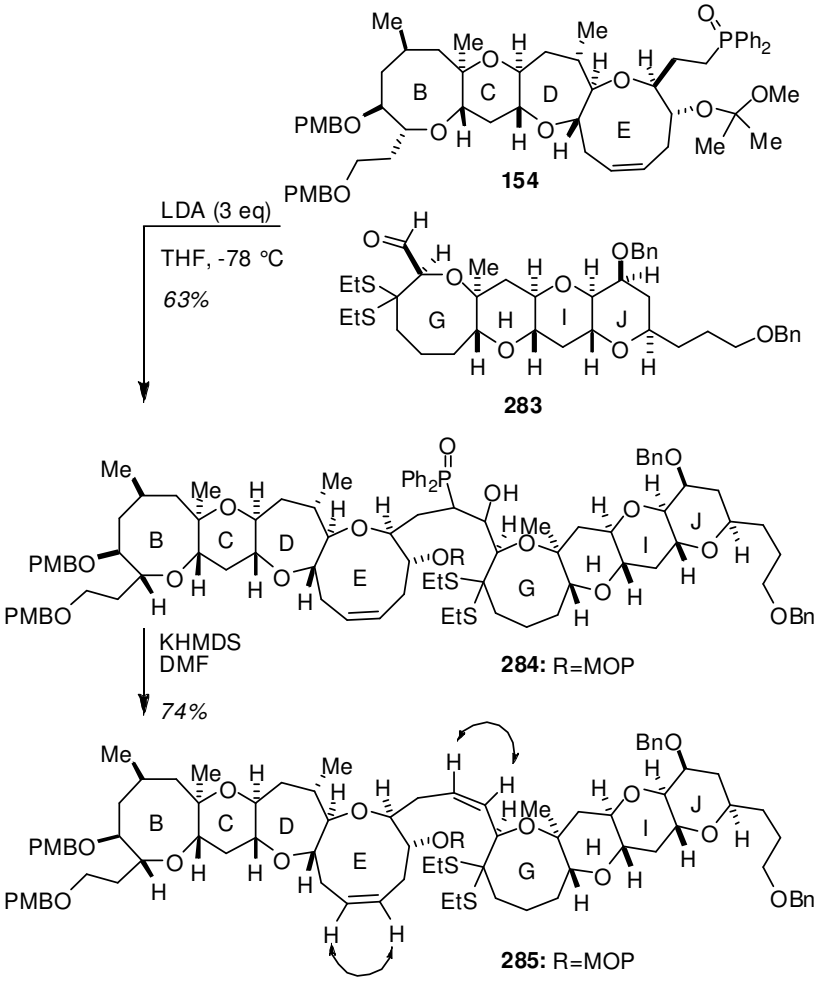
Because the benzoate protecting groups of aldehyde **274** were problematic in the coupling with phosphine oxide **154**, it was decided that the orignial route to GHIJ fragment **197** could be a useful alternative. The benzyl groups of aldehyde **283** (Scheme 3.13) were predicted to be more well-suited for the Horner-Wittig conditions to be employed for the coupling reaction. To test this hypothesis, GHIJ fragment **197** was treated with TBAF to remove the TIPS protecting group, and the resulting secondary alcohol **279** was oxidized to the ketone **280** under Dess-Martin conditions in excellent yield. Conversion to the dithioketal **281** as before and reductive removal of the pivaloyl group with $LiAlH_4$ provided alcohol **282**, which was cleanly oxidized to the aldehyde **283** using TPAP.

Scheme 3.13. Conversion of intermediate **197** to aldehyde **283**.



The Horner-Wittig coupling was then attempted once again using aldehyde **283** and phosphine oxide **154** in the presence of excess LDA (Scheme 3.14). The major product from this reaction was obtained as a single adduct isomer **284** in 50% yield, and exposure to KHMDS in DMF at room temperature promptly initiated elimination of diphenylphosphinic acid to form the desired olefin **285** in good yield. The *Z* geometry of the newly formed alkene was confirmed through NOESY analysis.

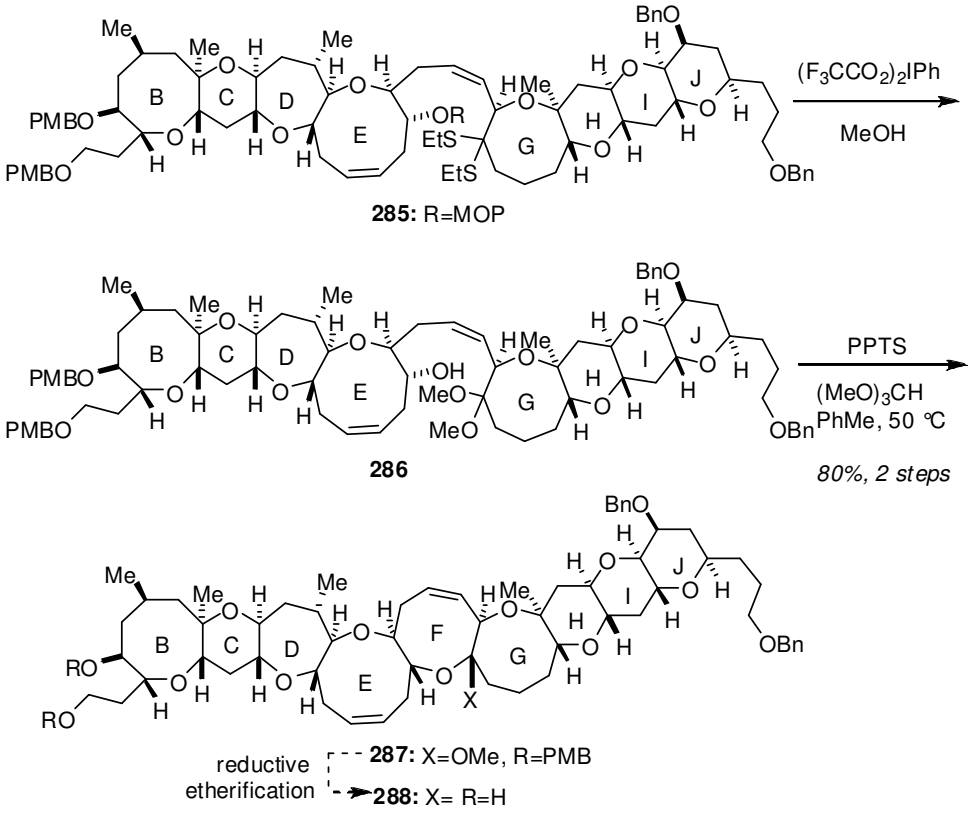
Scheme 3.14. Successful coupling of the BCDE and GHIJ fragments. Observed (non-aryl) NOE interactions between vinyl protons are indicated by arrows.

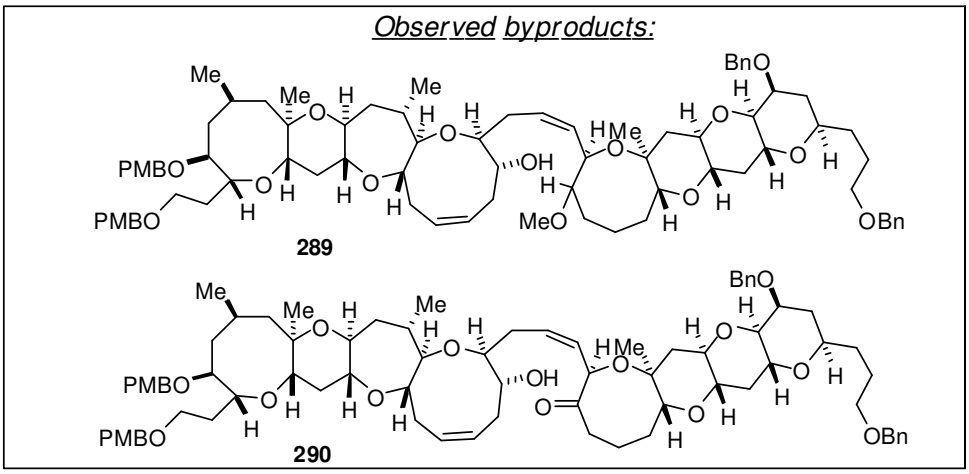


D. Proposed Completion of Brevetoxin A

In results obtained by J. Michael Ellis, the first endgame strategy for the completed total synthesis of brevetoxin A involved conversion of olefin **285** to dimethoxy ketal **286** (Scheme 3.15). This was accomplished through exposure to $(CF_3CO_2)_2IPh$ in MeOH, with concomitant loss of the MOP protecting group. Upon heating in the presence of PPTS and $(MeO)_3CH$ in benzene, the dimethoxy ketal can be converted to the mixed methoxy ketal **287**, which was

Scheme 3.15. Attempted closure of the F ring .



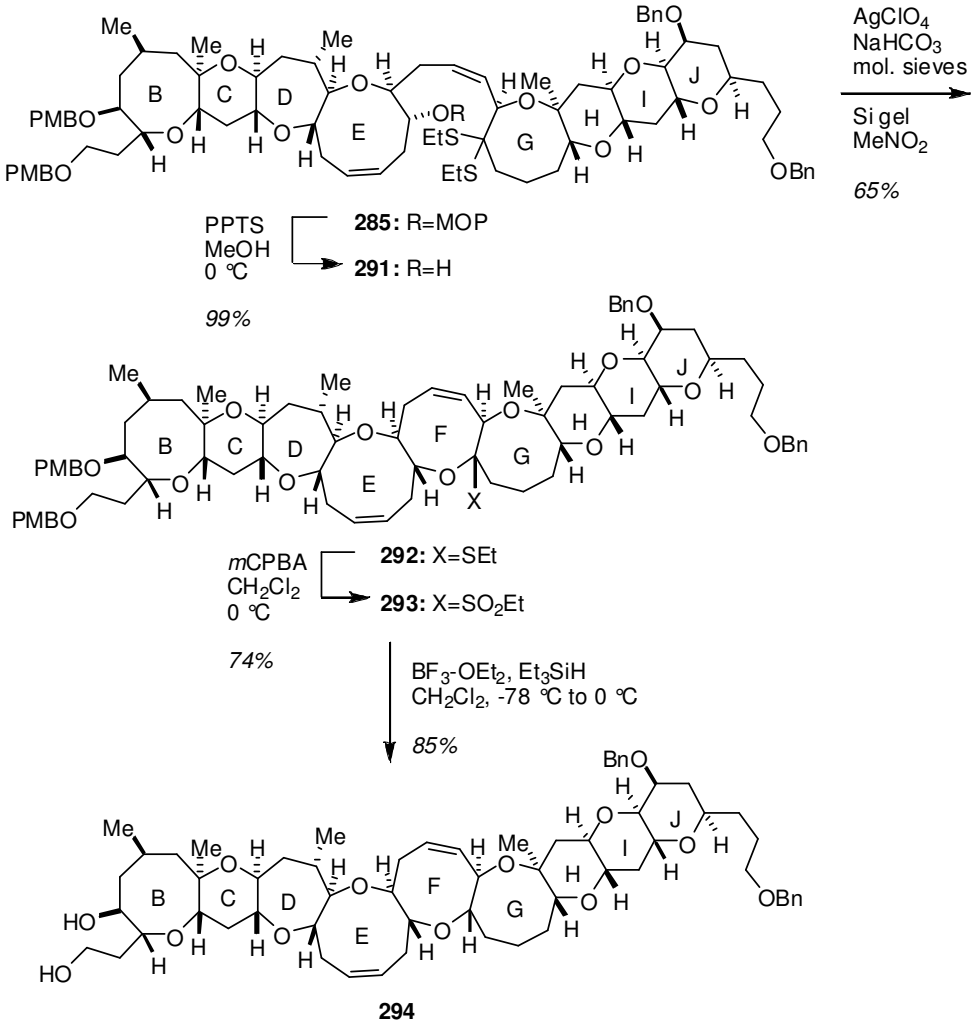


anticipated to be a suitable substrate for reductive etherification to complete the F ring. However, all reaction conditions examined for this transformation failed to produce the desired nonacycle **288**. Among byproducts observed in these

reactions were methyl ether **289** (from reductive cleavage of the F ring C-O bond) and hydroxy ketone **290** (hydrolysis of the ketal).

Attention was then turned toward an endgame mimicking the F ring assembly featured in the Nicolaou synthesis.[45,46] To this end, the MOP protecting group was removed from olefin **285** with PPTS in MeOH (Scheme 3.16), and the resulting hydroxy dithioketal **291** underwent cyclization to the mixed *S,O*-ketal **292** in the presence of $AgClO_4$ and $NaHCO_3$ in 65% yield. Oxidation of sulfur to

Scheme 3.16. Closure of the F ring via dithioketal cyclization/reductive etherification.



the sulfone with *m*CPBA at 0 °C provided sulfone **293**, and reductive etherification proceeded smoothly upon exposure to BF_3-OEt_2 and Et_3SiH, with concomitant loss of the PMB protecting groups, to afford diol **294**.

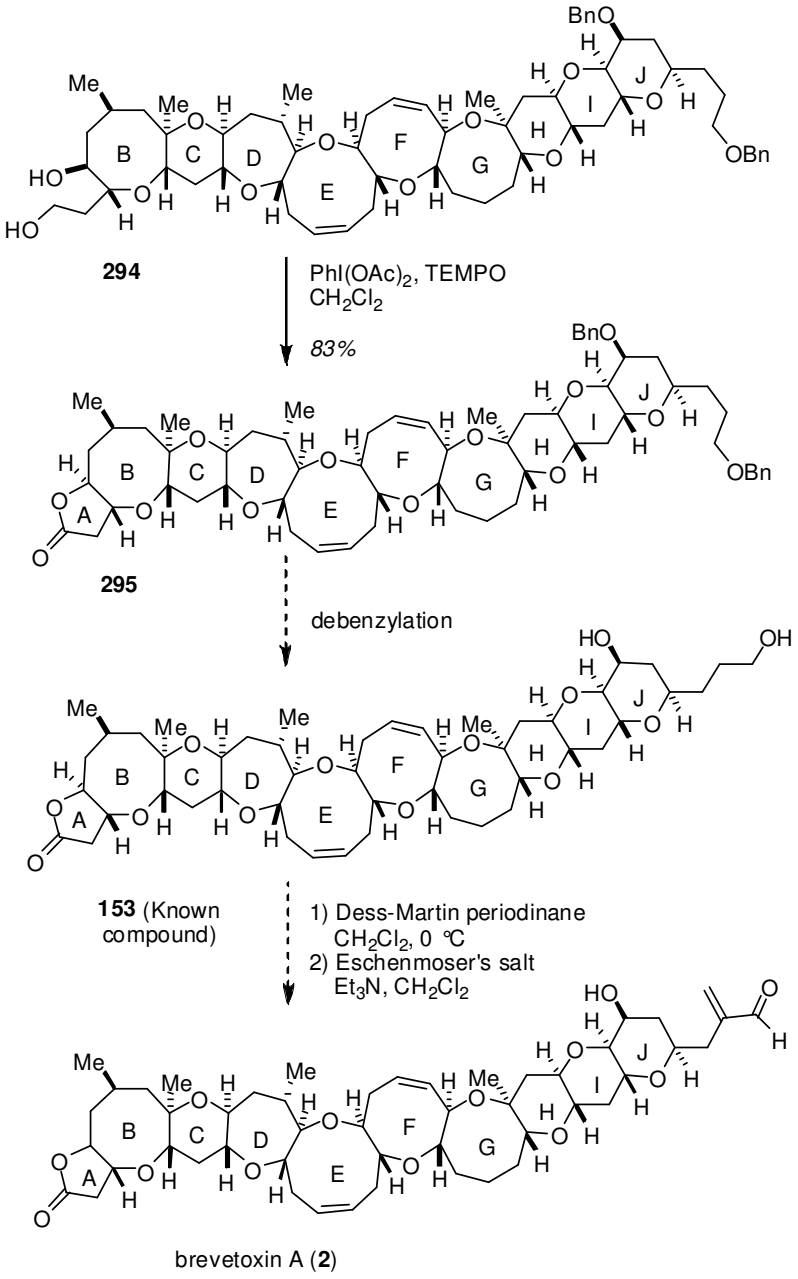
To furnish the A ring lactone, diol **294** was reacted with $(AcO)_2IPh$ and catalytic TEMPO,[75] providing decacycle **295** in 83% yield (Scheme 3.17). Currently, the debenzylation of decacycle **295** stands as the only obstacle to the completed total synthesis of brevetoxin A, since diol **153** is a known compound from the Nicolaou synthesis,[45,46] and requires only oxidation and methylenation to be converted to the natural product.

E. Summary

An alternative route to the GHIJ ring fragment was completed by altering the protecting group strategy of the original route. The alternative strategy provided improved access to a G ring HWE coupling partner (β–ketophosphonate **241**), and led to an efficient synthesis of aldehyde **274** in 36 linear steps. While aldehyde **274** proved to be unsuitable for the Horner-Wittig conditions used for coupling with BCDE fragment **154**, an intermediate on route to aldehyde **274** such as diol **267** could be obtained with a somewhat lower step count (32 linear steps) and prove to be useful in alternative endgame strategies to be explored in the future. On the other hand, the original route to GHIJ fragment **197** was shown to effectively lead to a proper substrate for union with BCDE fragment **154**. The olefin **285** thus obtained was converted to the decacyclic core **295** of

brevetoxin A through a dithioketal cyclization/reductive etherification process. The final steps of the total synthesis continue to be explored.

Scheme 3.17. Proposed completion of the total synthesis of brevetoxin A.



CHAPTER 4

EXPERIMENTAL

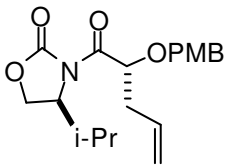
A. Materials and Methods

Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Nuclear magnetic resonance (^{1}H, ^{13}C, COSY, NOESY) spectra were recorded on Bruker model Avance 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz) and Bruker model Avance 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz) instruments. Optical rotations were determined using a Jasco P1010 polarimeter. Mass spectra were obtained using a Micromass Quattro II (triple quad) with nano-electrospray ionization. Thin layer chromatography (TLC) was conducted on silica gel F_{254} TLC plates purchased from EMD Chemicals Inc. Flash column chromatography was carried out using Ultra Pure Silica Gel Silia-P (40 to 63 μm) purchased from SiliCycle Inc. Diethyl ether (Et_2O), tetrahydrofuran (THF), and dichloromethane (CH_2Cl_2) were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines, benzene, and toluene were distilled from calcium hydride immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under reduced pressure and stored over 4 Å molecular sieves. Anhydrous *N,N*-dimethylformamide (DMF) was purchased from Aldrich chemical company in 1L Sure/Seal^{TM} bottles. Pivaloyl chloride was distilled and stored over 4

Å molecular sieves. Allyl iodide was distilled and stored over copper wire at -20 ℃. Stryker's reagent was prepared according to literature procedures and stored in a glove box. Dess-Martin periodinane was prepared according to literature procedures and stored at -20 ºC. Sodium bis(trimethylsilyl)amide was prepared according to literature procedures and stored under a blanket of argon. All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were preformed in flasks flame dried under positive flow of argon and conducted under an argon atmosphere.

B. Experimental

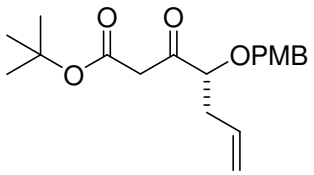
1. Optimized Synthesis of G Ring Intermediate **205**



Alkylation product of *ent*-176.

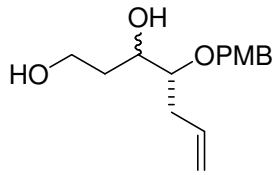
A 5 L flask equipped with a mechanical stirrer, addition funnel and a low temperature thermometer containing a solution of freshly prepared sodium bis(trimethylsilyl)amide (745 mL, 0.580 mol; 0.78 M in toluene/THF) and 1.1 L THF under an argon atmosphere was cooled to -78 ºC. The PMB glycolate[50] (118.78 g, 0.386 mol) dissolved in 0.49 L THF was added dropwise over 40 min, maintaining a temperature < –65 ºC. The resulting solution was stirred at -78 ºC for an additional

30 minutes. Allyl iodide (176 mL, 1.92 mol) was added to the solution over 30 min, and the solution was then warmed to –40 ºC over 35 minutes and maintained at that temperature for 1.5 h. The reaction was quenched using aqueous NH_4Cl (saturated). The organic layer was separated and the aqueous layer extracted twice with EtOAc. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography gave 107 g (80%) of the desired product as a single diastereomer (judged by NMR analysis). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.14 (band, 2H), 6.75-6.71 (band, 2H), 5.79 (dddd, *J* = 17.2, 10.0, 7.2, 7.2 Hz, 1H), 5.09-4.96 (band, 3H), 4.34 (AB, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 40.1 Hz, 2H), 4.28 (ddd, *J* = 7.6, 3.6, 3.6 Hz, 1H), 4.10-4.02 (band, 2H), 3.64 (s, 3H), 2.50 (ddd, *J* = 14.0, 6.4, 4.8 Hz, 1H), 2.40 (ddd, *J* = 14.4, 7.2, 7.2 Hz, 1H), 2.14 (ds, *J* = 6.8, 3.6Hz, 1H), 0.75 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 158.9, 153.1, 132.7, 129.4, 129.2, 117.5, 113.2, 75.9, 71.6, 63.5, 57.7, 54.7, 37.0, 28.0, 17.3, 14.3; IR (film) 2964, 1779, 1709, 1613, 1513, 1388, 1301, 1247, 1206, 1104, 1033 cm^{-1}; $[\alpha]^{23}_D$ = -97 (*c* 7.7, CH_2Cl_2), MS (ESI) for $C_{19}H_{25}NO_5$ [M + Na] calc 370.2, found 370.2.



β-Ketoester 206.

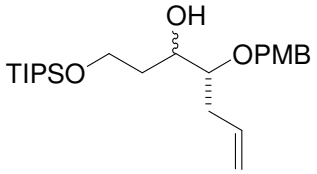
To a stirred solution of diisopropylamine (1.21 mL, 8.63 mmol) in 11.5 mL THF at -78 °C was added BuLi (2.5 M in hexanes, 3.45 mL, 8.6 mmol) dropwise. After 30 min, *t*-BuOAc was added dropwise. After 1 h, alkylation product of ***ent*-176** in 8 mL THF was added dropwise over 30 min. After an addition 10 min, the reaction was quenched by the addition of aqueous NH_4Cl (saturated), and the resulting mixture was warmed to room temperature. The aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (12% EtOAc in hexanes) afforded 0.976 g (85%, mixture of keto and enol tautomers) of β-ketoester **206** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{13}C NMR (100 MHz, $CDCl_3$) δ IR (film) $[\alpha]^{23}_D$ = +26.9 (c 0.078, CH_2Cl_2); MS (ESI) for $C_{19}H_{26}O_5$ [M + Na] calc 334.2, found 334.2.



Diols 207.

To a stirred solution of $LiAlH_4$ (0.22 g, 5.5 mmol) in 21 mL Et_2O at 0 °C was added β-ketoester **206** (0.922 g, 2.76 mmol) in 7 mL THF dropwise. After 1 h, the reaction was quenched by addition of 0.22 mL H_2O, 0.22 mL 10% NaOH, and 0.66 mL H_2O. The heterogenous mixture was filtered, and the filter cake was washed with Et_2O. The filtrate was concentrated in vacuo, and purification by flash chromatography (14%→80% EtOAc in hexanes→100% EtOAc) provided 0.204 g of recovered β-ketoester **206** and 0.383 g (52%, 67% brsm) of diols **207** as a mixture of

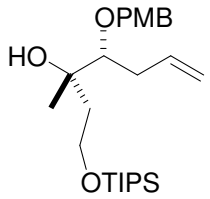
epimers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 d, *J* = 8.7 Hz, 2H), [6.87 (d, *J* = 8.8 Hz), 6.86 (d, *J* = 8.7 Hz), 2H], 5.92-5.80 (m, 1H), 5.15-5.06 (m, 2H), 4.64-4.40 (m, 2H), 3.93-3.89 (m, 1H), [3.791 (s), 3.788 (s), 3H], 3.83-3.74 (m, 2H), [3.44-3.40 (m), 3.34 (q, *J* = 5.6 Hz), 1H], 3.04 (s, 1H), 2.98 (s, 1H), 2.50-2.23 (m, 2H), 1.75-1.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.2, 134.9, 134.0, 130.2, 130.0, 129.5, 129.4, 117.6, 117.1, 113.8, 113.7, 81.3, 81.2, 72.2, 72.0, 71.9, 71.7, 61.1, 61.0, 55.2, 34.7, 34.5, 34.1, 33.7;IR (film) 3398, 3075, 2936, 1640, 1613, 1586, 1514, 1440, 1301, 1248, 1174, 1058, 917, 823, 454 cm^{-1}; $[\alpha]^{23}_D$ = -13.2 (c 0.040, CH_2Cl_2); MS (ESI) for $C_{15}H_{22}O_4$ [M + Na] calc 289.1, found 289.3.



Silyl ethers 200.

To a stirred solution of diols **207** (54.93 g, 0.2062 mol) in CH_2Cl_2 (690 mL) was added imidazole (42.1 g, 0.618 mol). The resulting solution was cooled to 0 °C, and triisopropylsilyl chloride (45.9 mL, 0.208 mol) was added. The reaction was warmed to room temperature and allowed to stir for 12 hours. The solution was poured into aqueous NH_4Cl (saturated), and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (10%→15%→20% EtOAc in hexanes) provided 87.2 g (100%, dr = 2:1) of alcohols **200** as a mixture of epimers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 d, *J* = 8.2 Hz, 4H), [6.86 (d, *J* = 8.6 Hz), 6.85 (d, *J* = 8.6 Hz), 2H], 5.96-5.81 (m, 1H), 5.16-5.04 (m, 2H), 4.61-4.43 (m, 2H),

3.98-3.81 (m, 2H), [3.782 (s), 3.780 (s), 3H], 3.44-3.36 (m, 2H), [3.45 (d, J = 3.1 Hz), 3.02 (d, J = 3.5 Hz), 1H], [2.51-2.44 (m), 2.34-2.27 (m), 1H], 2.42-2.38 (m, 1H), 1.86-1.79 (m, 1H), 1.77-1.66 (m, 1H), [1.062 (s), 1.056 (s), 21H]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 159.1, 135.0, 134.9, 130.7, 130.5, 129.4, 129.3, 117.0, 116.9, 113.7, 113.6, 81.2, 81.1, 72.6, 71.9, 71.8, 71.1, 55.2, 35.0, 34.5, 34.4, 34.1, 17.9, 11.7; IR (film) 3492, 3075, 2943, 2866, 1640, 1613, 1586, 1514, 1464, 1387, 1302, 1249, 1173, 1087, 1038, 996, 915, 882, 822, 739, 682, 659, 425, 412 cm^{-1}; $[\alpha]^{23}_D$ = -5.0 (c 0.049, CH_2Cl_2); MS (ESI) for $C_{24}H_{42}O_4Si$ [M + Na] calc 445.3, found 445.5.



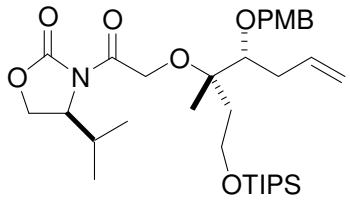
Tertiary alcohol 201.

In a 5 L flask was added 640 mL CH_2Cl_2 and $(COCl)_2$ (2.0 M in CH_2Cl_2, 155 mL, 0.310 mol), and the resulting solution was cooled to -78 °C. DMSO was then added (29.3 mL, 0.413 mol) in 320 mL CH_2Cl_2 dropwise at such a rate that the temperature remained below -65 °C. Silyl ethers **200** (87.16 g, 0.2062 mol) were then added in 320 mL CH_2Cl_2 dropwise at such a rate that the temperature remained below -65 °C. After an additional hour at -78 °C, DIEA (180 mL, 1.03 mol) was added dropwise, and the solution was warmed to 0 °C over 25 min. After an additional 30 min at 0 °C, the reaction was quenched by the addition of H_2O, and the organic layer was washed successively with cold 1 M HCl (aq), aqueous $NaHCO_3$ (saturated), H_2O, and brine, and dried over Na_2SO_4. Concentration in vacuo and purification by flash

column chromatography (10% EtOAc in hexanes) delivered 81.5 g (94%) of the ketone as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.82-5.72 (m, 1H), 5.11-5.03 (m, 2H), 4.45 (AB, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 58.4 Hz, 2H), 2.75-2.70 (m, 2H), 2.42 (t, *J* = 6.65 Hz, 2H), 1.03 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 159.4, 133.2, 129. 6, 129.5, 117.8, 113.8, 84.2, 72.0, 58.5, 55.2, 41.2, 36.1, 17.9, 11.9; IR (film) 2942, 2865, 1718, 1613, 1514, 1464, 1389, 1303, 1250, 1173, 1097, 1038, 918, 883, 822, 745, 682 cm^{-1}; $[\alpha]^{23}_D$ = +6.7 (*c* 0.38, CH_2Cl_2); MS (ESI) for $C_{24}H_{40}O_4Si$ [M + Na] calc 443.3, found 443.3.

To a stirred solution of the ketone obtained as above (79.04 g, 0.188 mol) in Et_2O (1.5 L) at -78 °C was added methylmagnesium chloride (3.0M in THF, 188 mL, 0.564 mol) in Et_2O (200 mL) dropwise. After 25 min, the reaction was quenched by the addition of aqueous NH_4Cl (saturated) and allowed to warm to room temperature. The aqueous layer was extracted twice with 2:1 hexanes:EtOAc, and the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography (15%→20% EtOAc in hexanes) provided 79.6 g (97%) of tertiary alcohol **201**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.05-5.95 (m, 1H), 5.18-5.04 (m, 2H), 4.59 (AB, J_{AB} = 11.0 Hz, $\Delta\nu_{AB}$ = 59.4 Hz, 2H), 4.08 (s, 1H), 3.99-3.89 (m, 2H), 3.80 (s, 3H), 3.40 (dd, *J* = 3.1, 8.8 Hz, 1H), 2.60-2.54 (m, 1H), 2.34-2.27 (m, 1H), 1.96-1.90 (m, 1H), 1.76-1.70 (m, 1H), 1.21 (s, 3H), 26.1 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 137.2, 131.0, 129.3, 116.2, 113.6, 84.9, 75.3, 73.4, 61.0, 55.2, 38.6, 35.0, 22.7, 17.9, 11.7; IR (film) 3486, 3074, 2943, 2867, 1639, 1613, 1586, 1514, 1464,

1389, 1339, 1302, 1248, 1173, 1091, 1038, 995, 910, 883, 822, 737, 683 cm^{-1}; $[\alpha]^{23}_D$ = -26.6 (*c* 0.33, CH_2Cl_2); MS (ESI) for $C_{25}H_{44}O_4Si$ [M + Na] calc 459.3, found 459.4.



Imide 202.

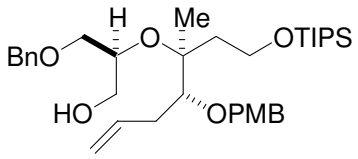
To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 27.8 g, 0.695 mmol, pre-washed with pentanes) in DMF (75 mL) at 0 °C was added bromoacetic acid (32.25 g, 0.232 mol) in 75 mL DMF dropwise. After 10 min, neat tertiary alcohol **201** (101.3 g, 0.232 mol) was added dropwise via syringe, and the syringe was rinsed with 20 mL DMF. The reaction was warmed to room temperature and stirred for 30 h. The heterogeneous mixture was then cooled to 0 °C and *carefully* quenched by the slow addition of water, followed by Et_2O (200 mL). The pH of the aqueous layer was adjusted to 3 by the addition of conc. H_2SO_4, and then extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes→99:1 EtOAc:AcOH) provided 27 g of recovered starting material **201** and 74 g of the acid; re-subjection of the recovered starting material once to the same reaction/purification conditions provided a total of 96 g (84%) of the acid : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 5.98-5.88 (m, 1H), 5.15-5.05 (m, 2H), 4.50 (AB, J_{AB} = 11.0, $\Delta\nu_{AB}$ = 76.8 Hz, 2H), 4.09 (d, J = 5.1 Hz, 2H), 3.78 (s, 3H), 3.80-3.77 (m, 2H), 4.41 (dd, J

= 7.6, 4.2 Hz, 1H), 2.51-2.44 (m, 1H), 2.40-2.33 (m, 1H), 1.98-1.91 (m, 1H), 1.75-1.68 (m, 1H), 1.26 (s, 3H), 1.04 (s, 21H); ^{13}C NMR (100MHz, $CDCl_3$) δ 172.2, 159.4, 135.9, 129.9, 129.5, 116.8, 113.8, 83.2, 81.3, 73.4, 61.1, 59.3, 55.2, 39.2, 34.8, 19.2, 11.9; IR (film) 2943, 2866, 1734, 1609, 1514, 1464, 1249, 1092, 882, 825, 679, 426 cm^{-1}; $[\alpha]^{23}_D$ = -21.0 (*c* 0.40, CH_2Cl_2); MS (ESI) for $C_{27}H_{46}O_6Si$ [M + Na] calc 517.3, found 517.3.

To a stirred solution of the acid obtained as above (56.5 g, 114 mmol) and triethylamine (17.5 mL, 126 mmol) in THF (700 mL) at -78 °C was added pivaloyl chloride (15.5 mL, 126 mmol) dropwise over 20 min. The resulting cloudy solution was then warmed to 0 °C, and after 1 h, re-cooled to -78 °C.

To a separate stirred solution of (*S*)-4-isopropyl-2-oxazolidinone (19.16 g, 148 mmol) in THF (430 mL) at -78 °C was added BuLi (2.35 M in hexanes, 63.0 mL, 148 mmol) dropwise. After 30 minutes, the lithiated oxazolidinone was cannulated into the mixed anhydride solution. The resulting mixture was warmed to 0 °C over 45 min, and stirred an additional 1.5 h at 0 °C. The reaction was then quenched with aqueous NH_4Cl (saturated). The aqueous layer was extracted once with EtOAc, and the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography (20%→25%→40% EtOAc in hexanes→100% EtOAc) afforded 59.2 g (86%) of imide **202**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.01-5.91 (m, 1H), 5.13-4.99 (m, 2H), 4.68 (AB, J_{AB}= 17.9, $\Delta\nu_{AB}$ = 43.1 Hz, 2H), 4.52 (AB, J_{AB} = 11.1, $\Delta\nu_{AB}$ = 40.4 Hz, 2H), 4.40-4.36 (m, 1H), 4.26 (t, *J* = 8.6 Hz, 1H), 4.20 (dd, *J* = 3.3, 8.8 Hz, 1H), 3.81 (t, *J* = 7.3 Hz, 2H), 3.77, (s, 3H), 3.46 (dd, *J* = 3.3, 8.4 Hz, 1H),

2.60-2.54 (m, 1H), 2.43-2.29 (m, 1H), 2.05-1.97 (m, 1H), 1.88-1.81 (m, 1H), 1.22 (s, 3H), 1.03 (s, 21H), 0.86 (dd, J = 7.0, 19.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 159.0, 153.9, 136.9, 130.9, 129.1, 116.3, 113.6, 83.2, 80.2, 73.5, 64.1, 63.0, 59.2, 58.2, 55.2, 39.0, 35.2, 28.2, 19.1, 18.0, 17.8, 14.5, 11.9; IR (film) 1782, 1718, 1636, 1514, 1458, 1389, 1249, 1209, 1092 cm^{-1}; $[\alpha]^{23}_D$ = +16.7 (*c* 0.46, CH_2Cl_2); MS (ESI) for $C_{33}H_{55}NO_7Si$ [M + Na] calc 628.4, found 628.4.



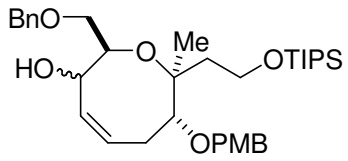
Alcohol 203.

To a stirred solution of NaHMDS (0.74 M in PhMe/THF, 130 mL, 96.2 mmol) in THF (320 mL) at -78 °C in darkness was added imide **202** (38.85 g, 64.12 mmol) in THF (320 mL) dropwise such that the temperature of the solution remained below -65 °C. After 30 min, $BnOCH_2I$ [224 mmol, generated immediately prior to addition by stirring a mixture of $(BnO)_2CH_2$ (49.4 mL, 231 mmol) and TMSI (31.9 mL, 224 mmol) for 30 min at 0 °C in darkness] was added via cannula over 4 min. After 30 min, the reaction was quenched by addition of half-saturated NH_4Cl (aq), and the resulting mixture was warmed to ~10 °C, at which point the organic layer was immediately washed with aqueous $Na_2S_2O_3$, and the combined aqueous layers were extracted once with 1:1 EtOAc/hexanes. The combined organic layers were washed with brine and dried over Na_2SO_4; concentration in vacuo and purification by flash chromatography (5%→10%→15%→20%→25% EtOAc in hexanes) afforded 36.8 g (86%) of imide **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.19 (m, 7H), 6.80 (d, J = 8.6

Hz, 2H), 5.96-5.86 (m, 1H), 5.78 (dd, J = 3.9, 6.4 Hz, 1H), 5.12-4.97 (m, 2H), 4.51 (AB, J_{AB} = 12.3, $\Delta\nu_{AB}$ = 31.2 Hz, 2H), 4. 4.40 (AB, J_{AB} = 11.0, $\Delta\nu_{AB}$ = 34.4 Hz, 2H), 4.22-4.18 (m, 1H), 3.95 (dd, J = 3.1, 13.2 Hz, 1H), 3.80-3.70 (m, 3H), 3.75 (s, 1H), 3.54 (dd, J = 4.1, 10.0 Hz, 1H), 3.27 (dd, J = 3.5, 8.4 Hz, 1H), 2.66-2.59 (m, 1H), 2.47-2.40 (m, 1H), 2.24-2.16 (m, 1H), 1.94-1.87 (m, 1H), 1.75-1.67 (m, 1H), 1.20 (s, 3H), 0.98 (s, 21H), 0.75 (d, J = 7.0 Hz, 3H), 0.64 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 159.1, 153.7, 138.1, 137.5, 130.8, 129.5, 128.2, 127.5, 127.4, 116.2, 113.6, 84.3, 80.5, 73.9, 73.2, 72.0, 70.4, 63.3, 59.3, 58.1, 55.3, 40.5, 34.8, 27.9, 19.5, 18.0, 17.8, 14.4, 11.9; IR (film) 3789, 3661, 1778, 1722, 1658, 1612, 1549, 1514, 1463, 1389, 1249, 1095, 440 cm^{-1}; $[\alpha]^{23}_D$ = +29.7 (*c* 0.32, CH_2Cl_2); MS (ESI) for $C_{41}H_{63}NO_8Si$ [M + Na] calc 748.4, found 748.5.

To a stirred solution of the benzyl ether obtained as above (46.4 g, 64.0 mmol) and MeOH (8.3 mL, 205 mmol) in Et_2O (340 mL) at 0 ºC was added lithium boroyhydride (2.0 M in THF, 102 mL, 204 mmol) dropwise. After 1 hour, the reaction was quenched by addition of aqueous K^+/Na^+ tartrate (saturated), and the resulting turbid mixture was warmed to ambient temperature and stirred vigorously for an additional 3 h, at which time both layers were clear. The aqueous layer was extracted twice with 1:1 EtOAc/hexanes, and the combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography (25%→30% EtOAc in hexanes →50% EtOAc in CH_2Cl_2) provided 33.9 g (88%) of alcohol **203**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 7H), 6.84 (d, J = 8.8 Hz, 2H), 5.99-5.88 (m, 1H), 5.12 (dd, J = 1.8, 17.0 Hz, 1H), 5.02 (d, J = 10.2 Hz, 1H), 4.48 (AB, J_{AB} = 10.6, $\Delta\nu_{AB}$ = 88.0 Hz, 2H), 4.47 (s, 2H), 3.95-

3.90 (m, 1H), 3.77 (s, 3H), 3.74 (t, *J* = 7.0 Hz, 2H), 3.64 (dd, *J* = 3.5, 11.2 Hz, 1H), 3.54 (dd, *J* = 5.9, 11.0 Hz, 1H), 3.43 (dd, *J* = 5.1, 9.6 Hz, 1H), 3.39-3.34 (m, 2H), 2.53-2.40 (m, 2H), 1.93-1.86 (m, 1H), 1.78-1.71 (m, 1H), 1.27 (s, 3H), 1.03 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.0, 136.7, 130.2, 129.3, 128.3, 127.6, 127.5, 116.4, 113.7, 84.1, 79.9, 73.4, 73.3, 71.7, 71.2, 64.5, 59.5, 55.2; IR (film) 3433, 2941, 2865, 1515, 1457, 1249, 1092, 882, 822, 742, 677 cm^{-1}; $[\alpha]^{23}_D$ = -26.6 (*c* 0.17, CH_2Cl_2); MS (ESI) for $C_{35}H_{56}O_6Si$ [M + H] calc 601.4, found 601.4.



Oxocene 204.

To a stirred solution of $(COCl)_2$ (2.0 M in CH_2Cl_2, 23.0 mL, 46.0 mmol) in CH_2Cl_2 (100 mL) at -78 °C was added DMSO (4.40 mL, 62.0 mmol) in 50 mL CH_2Cl_2 dropwise at such a rate that the temperature remained below -65 °C. After 10 min, alcohol **203** (18.45 g, 30.7 mmol) in 50 mL CH_2Cl_2 was added dropwise at such a rate that the temperature remained below -65 °C. After an additional hour at -78 °C, Et_3N (21.4 mL, 154 mmol) was added dropwise, and the solution was warmed to ambient temperature. Water was then added, and the organic layer was diluted with Et_2O and washed successively with aqueous $NaHCO_3$ (saturated) and brine, and dried over $MgSO_4$. Concentration in vacuo and purification through a short silica plug (product eluted with Et_2O) delivered 18.2 g (99%) of aldehyde, which was used immediately in the next reaction: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 1.6 Hz, 1H), 7.32-7.23 (m, 5H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6, 2H), 5.99-5.89 (m,

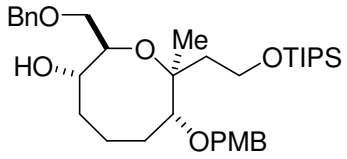
1H), 5.14-5.01 (m, 2H), 4.48 (AB, J_{AB} = 11.0, $\Delta\nu_{AB}$ = 85.2 Hz, 2H), 4.49 (s, 3H), 4.23 (td, *J* = 2.0, 5.0 Hz, 1H), 3.79 (t, *J* = 7.8 Hz, 2H), 3.77 (s, 3H), 3.64-3.56 (m, 2H), 3.38 (dd, *J* = 3.5, 8.0 Hz, 1H), 2.65-2.58 (m, 1H), 2.44-2.36 (m, 1H), 1.99-1.92 (m, 1H), 1.79-1.72 (m, 1H), 1.18 (s, 3H), 1.02 (s, 21H).

Into a 500 mL flask fitted with a cold-finger condenser, addition funnel, and argon inlet was added magnesium (6.75 g, 278 mmol), an iodine crystal, and 25 mL THF. Small aliquots of a solution of vinyl bromide (22 mL, 305 mmol) in THF (25 mL) were added to the magnesium via addition funnel until initiation was observed, at which point the remainder of the vinyl bromide solution was added at a rate such that refluxing of the magnesium/THF mixture was continuous. The resulting darkly-colored mixture was stirred vigorously for an additional 30 min, and then diluted with THF (135 mL) to produce a 1.5 M solution of vinylmagnesium bromide. One hundred milliliters of this solution (150 mmol) was then immediately added to 130 mL THF in a separate flask, and the diluted solution of Grignard reagent was cooled to 0 °C. The aldehyde obtained as above (18 g, 31 mmol) in THF (70 mL) was then added dropwise. After 5 min, the resulting solution was quenched by the addition of aqueous NH_4Cl (saturated), and the resulting mixture was warmed to ambient temperature. After adding additional water and stirring vigorously to dissolve precipitated solids, the aqueous layer was extracted twice with petroleum ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (13%→16%→19% EtOAc in hexanes) yielded 15 g (80%, dr = 1.5:1) of the diene as a mixture of epimers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 7H), 6.85-6.82 (m, 2H), 5.99-

5.80 (m, 2H), 5.33-5.00 (m, 4H), 4.62-4.37 (m, 4H), 4.19-4.11 (m, 1H), 4.04-4.00 (m, 1H), [3.87 (d, *J* = 7.3 Hz), 3.63 (d, *J* = 5.5Hz), 1H] 3.77 (s, 3H), [3.73 (t, *J* = 7.1 Hz), 3.72 (t, *J* = 7.0 Hz), 2H], 3.53-3.43 (m, 1H), 3.40-3.34 (m, 2H), 2.53-2.39 (m, 2H), 1.99-1.71 (m, 2H), [1.30 (s), 1.25 (s), 3H], 1.03 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 159.1, 138.2, 138.0, 137.9, 137.2, 136.9, 136.8, 130.6, 130.2, 129.4, 129.2, 128.4, 128.3, 127.66, 127.65, 127.56, 127.52, 116.5, 116.3, 116.1, 115.9, 113.8, 113.7, 84.8, 83.9, 80.4, 80.0, 74.4, 73.9, 73.8, 73.6, 73.5, 73.4, 73.3, 73.2, 71.8, 71.7, 59.6, 59.5, 55.23, 55.21, 41.8, 41.1, 34.9, 34.8, 20.3, 20.1, 18.1, 12.0; IR (film) 2945, 2865, 1612, 1514, 1463, 1249, 1091 cm^{-1}; $[\alpha]^{23}_D$ = -4.6 (*c* 0.018, CH_2Cl_2); MS (ESI) for $C_{37}H_{58}O_6Si$ [M + Na] calc 649.4, found 649.7.

To a stirred solution of the diene obtained as above (14.6 g, 23.3 mmol) in CH_2Cl_2 (2.33 L, degassed) was added tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene] [benzylidine]ruthenium(IV)dichloride (494 mg, 0.58 mmol). The resulting brown solution was heated to reflux and stirred for 1 h, then cooled to ambient temperature and sparged with air 2 h. Concentrated in vacuo and purification by flash chromatography (20%→25% EtOAc in hexanes) provided 11.8 g (85%, dr = 1.5:1) of oxocene **204** as a mixture of epimers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.18 (m, 5H), [7.15 (d, *J* = 8.6 Hz), 7.14 (d, *J* = 9.0 Hz), 2H], 6.77 (d, *J* = 8.2 Hz, 2H), 5.69-5.47 (m, 2H), 4.53-4.40 (m, 3H), 4.33-.421 (m, 2H), [4.17-4.12 (m), 4.07-3.96 (m), 1H], 3.73-3.65 (m, 5H), 3.62-3.46 (m, 2H), 3.41-3.36 (m, 1H), 3.14-3.08 (m, 1H), 2.53-2.38 (m, 1H), [2.34-2.14 (m), 2.08-1.95 (m), 1H], [1.87-1.82 (m), 1.74-1.65 (m), 1H], 1.56 (m, 1H), [1.22 (s), 1.21 (s), 3H], [0.97 (s), 0.96 (s), 21H]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.9, 137.8, 137.6, 133.9, 132.6, 130.5,

130.2, 129.2, 129.0, 128.4, 128.3, 127.7, 127.6, 127.2, 125.9, 113.6, 113.5, 85.2, 83.8, 79.6, 78.4, 73.9, 73.6, 71.9, 71.2, 71.1, 71.0, 70.9, 69.6, 59.3, 59.1, 55.1, 45.7, 44.5, 27.4, 27.0, 18.0, 17.2, 15.4, 11.9, 11.8; IR (film) 3445, 2941, 2864, 1613, 1514, 1464, 1387, 1302, 1249, 1092, 883, 822, 736, 682, 454 cm^{-1}; $[\alpha]^{23}_{D}$ = -17.8 (*c* 0.037, CH_2Cl_2); MS (ESI) for $C_{35}H_{54}O_6Si$ [M + Na] calc 621.4, found 621.6.



Alcohol 205.

A stirred solution of oxocene **204** (7.140 g, 11.92 mmol), *o*-nitrobenzenesulfonylhydrazide[59] (12.9 g, 59.4 mmol), Et_3N (12.5 mL, 89.7 mmol), and DME (60 mL) in a 250 mL flask equipped with reflux condenser and Ar inlet was gently heated. As refluxing temperature was approached, the Ar inlet and septum were removed, opening the reaction apparatus to air. The red solution was then heated at reflux for 30 min, at which point two layers were visible. The mixture was cooled to ambient temperature and washed with 1 M $NaHSO_4$ (aq) twice. The aqueous layer was extracted twice with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. **(Note: Due to the release of heat and N_2 during this reaction, higher dilution is recommended to avoid a runaway reaction and eruption of solvent.)** Purification with flash chromatography (25% EtOAc in hexanes) gave 6.8 g (95%) of the oxocane as a mixture of epimers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.20 (m, 5H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.56-4.46 (m, 3H), [4.34-4.30

(m), 4.18-4.13 (m), 1H], 4.24-4.20 (m, 1H), 3.82-3.69 (m, 6H), 3.60-3.50 (m, 1H), 3.43-3.38 (m, 1H), 3.35-3.31 (m, 1H), [3.11 (s), 2.35 (d, J = 7.8 Hz), 1H], 2.06-1.46 (m, 8H), [1.23 (s), 1.22 (s), 3H], [1.03 (s), 1.02 (s), 21H]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 130.7, 130.6, 129.2, 129.1, 128.4, 128.3, 127.7, 127.6, 113.6, 85.3, 83.6, 79.2, 79.1, 74.8, 74.5, 73.5, 73.4, 71.7, 71.6, 71.5, 71.4, 71.3, 69.9, 59.6, 55.2, 43.5, 34.7, 32.8, 27.4, 19.5, 18.7, 18.04, 18.02, 17.5, 16.0, 11.93, 11.91; IR (film) 3434, 2940, 2864, 2281, 1612, 1513, 1462, 1248, 1090, 882, 821, 736 cm^{-1}; $[\alpha]^{23}_{D}$ = -27.5 (*c* 0.022, CH_2Cl_2); MS (ESI) for $C_{35}H_{56}O_6Si$ [M + Na] calc 623.4, found 623.7.

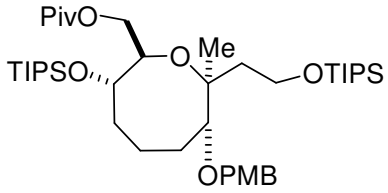
To a stirred solution of $(COCl)_2$ (2.0 M in CH_2Cl_2, 15.2 mL, 30.4 mmol) in CH_2Cl_2 (63 mL) at -78 °C was added DMSO (2.85 mL, 40.2 mmol) in 30 mL CH_2Cl_2 dropwise at such a rate that the temperature remained below -65 °C. After 10 min, the oxocane obtained as above (11.77 g, 19.59 mmol) in 30 mL CH_2Cl_2 was added dropwise at such a rate that the temperature remained below -65 °C. After an additional hour at -78 °C, Et_3N (13.7 mL, 98.3 mmol) was added dropwise, and the solution was warmed to 0 °C. After 20 min, water was then added, and the organic layer was washed successively with cold 1 M $NaHSO_4$, aqueous $NaHCO_3$ (saturated), and H_2O. The combined aqueous layers were extracted once with Et_2O, and the combined organic layers were washed with brine and dried over $MgSO_4$. Concentration in vacuo and purification with flash chromatography (30%→40% Et_2O in hexanes) delivered 11.17 g (94%) of the ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.23 (m, 5H), 7.16 (d, J = 8.6, 2H), 6.84 (d, J = 8.6, 2H), 4.47 (AB, J_{AB} = 12.5, $\Delta\nu_{AB}$ = 22.8 Hz, 2H), 4.33 (AB, J_{AB} = 11.5, $\Delta\nu_{AB}$ = 150.8 Hz, 2H), 4.32 (dd, J = 2.7, 5.6 Hz, 1H), 3.87-3.76 (m, 2H), 3.78 (s, 3H), 3.59 (dd, J = 5.9, 10.0 Hz, 1H), 3.49

(dd, J = 3.1, 10.0 Hz, 1H), 2.99 (td, J = 11.4, 2.2 Hz, 1H), 2.22-2.17 (m, 1H), 2.00-1.89 (m, 4H), 1.83-1.76 (m, 1H), 1.73-1.65 (m, 1H), 1.22, (s, 3H), 1.03 (s, 21H); ^{13}C NMR (100MHz, $CDCl_3$) δ 217.0, 159.0, 138.3, 130.0, 129.1, 128.2, 127.3, 127.2, 113.6, 81.3, 79.7, 79.1, 73.3, 71.7, 59.6, 55.2, 42.9, 40.8, 25.8, 21.5, 18.5, 18.0, 11.9; IR (film) 3853, 3734, 2064, 1647, 1558, 1541, 1515, 1457, 1248, 1098 cm^{-1}; $[\alpha]^{24}_D$ = +6.4 (*c* 0.47, CH_2Cl_2); MS (ESI) for $C_{35}H_{54}O_6Si$ [M + H] calc 599.4, found 599.4.

To a stirred solution of the ketone obtained as above (11.17 g, 18.65 mmol) in CH_2Cl_2 (375 mL) at -78 °C was added diisobutylaluminum hydride (1.0 M in hexanes, 56 mL, 56 mmol) dropwise. After 1 h, the reaction was quenched by addition of aqueous K^+/Na^+ tartrate (saturated), and the resulting mixture was warmed to ambient temperature and stirred vigorously for 15 h. The aqueous layer was extracted twice with 1:1 EtOAc:hexanes, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (25% EtOAc in hexanes) gave 11.09 g (99%) of alcohol **205** as a single diastereomer: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.31-7.22 (m, 7H), 6.83 (d, J = 8.8 Hz, 2H), 7.37 (AB, J_{AB} = 11.3, $\Delta\nu_{AB}$ = 132.8 Hz, 2H), 4.49 (d, J = 2.6 Hz, 1H), 4.16-4.11 (m, 1H), 3.76 (s, 3H), 3.76-3.74 (m, 1H), 3.69 (t, J = 7.0 Hz, 2H), 3.56 (dd, J = 4.6, 8.8 Hz, 1H), 3.38 (d, J = 6.6 Hz, 1H), 3.32 (t, J = 8.1 Hz, 1H), 3.08 (s, 1H), 2.04-1.96 (m, 1H), 1.93-1.78 (m, 3H), 1.72-1.61 (m, 3H), 1.52-1.44 (m, 1H), 1.20 (s, 3H), 1.00 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 137.9, 130.7, 129.2, 128.4, 127.7, 127.6, 113.7, 83.7, 79.2, 74.9, 74.5, 73.6, 71.9, 71.4, 59.7, 55.3, 43.6, 32.9, 27.5, 19.5, 18.0, 16.2, 12.0; IR (film) 3434, 2940, 2864, 2281, 1612, 1513, 1462,

1248, 1090, 882, 821, 736 cm^{-1}; $[\alpha]^{23}_D$ = -47.8 (*c* 0.32, CH_2Cl_2); MS (ESI) for $C_{35}H_{56}O_6Si$ [M + Na] calc 623.4, found 623.4.

2. Synthesis of β-Keto phosphonate **193**



Oxocane 14.

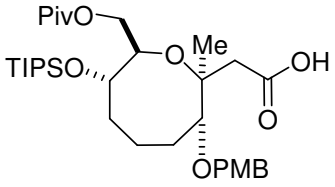
To a stirred solution of alcohol **215** (3.27 g, 5.43 mmol) in CH_2Cl_2 (54 mL) at 0 °C was added 2,6-lutidine (3.2 mL, 27 mmol) and TIPSOTf (2.15 mL, 8.00 mmol). After 1.5 h, the reaction was quenched with saturated, aqueous $NaHCO_3$ and warmed to ambient temperature. The aqueous layer was diluted with NH_4Cl (aq) and extracted with 1:1 EtOAc/hexanes four times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (3% → 5% → 10% EtOAc in hexanes) 4.01 g (98%) of the silyl ether: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.23 (m, 7H), 6.83 (d, *J* = 8.7 Hz; 2H), 4.50 (AB, J_{AB} = 12.5 Hz, $\Delta\nu_{AB}$ = 22.6 Hz, 2H), 4.37 (AB, J_{AB} = 11.9 Hz, $\Delta\nu_{AB}$ = 130.5 Hz, 2H), 4.08 (m, 2H), 3.86-3.77 (m, 5H), 3.49 (m, 2H), 3.40 (d, *J* = 7.2 Hz, 1H), 2.09-1.66 (m, 7H), 1.41 (m, 1H), 1.24 (s, 3H), 1.03 (m, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 138.9, 131.2, 128.8, 128.1, 127.6, 127.2, 113.6, 84.2, 79.0, 74.7, 73.2, 72.6, 71.4, 71.0, 59.9, 55.2, 43.9, 33.5, 27.4, 19.5, 18.2, 18.14, 18.06, 12.8, 12.0; IR (film) 3068, 2944, 2867, 1742, 1615, 1515, 1465, 1374, 1245, 1096, 884, 679, 565 cm^{-1};

$[\alpha]^{23}_D$ = -9.8 (c 0.010, CH_2Cl_2); MS (ESI) for $C_{44}H_{76}O_6Si_2$ [M + H] calc 757.5, found 757.6.

To a solution of the silyl ether obtained as above (4.00 g, 5.28 mmol) in THF (53 mL) at -78 °C, stirred with a glass stir bar, was added LDBB (1 M in THF, freshly prepared by sonicating a mixture of Li (0.500 g, 72 mmol) and di-*t*-butylbiphenyl (20.14 g, 75.6 mmol) in THF (72 mL) at 0 °C for 3 h) in 6 mL aliquots until the starting material was consumed (about 36 mL total LDBB solution added). The green solution was then quenched with H_2O and warmed to ambient temperature. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (2%→8% EtOAc in hexanes) afforded 3.32 g of the primary alcohol (95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.37 (AB, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 134.3 Hz, 2H), 4.02 (m, 2H), 3.82-3.70 (m, 5H), 3.64-3.52 (m, 2H), 3.36 (d, J = 6.8 Hz, 1H), 2.27 (dd, J = 3.6, 8.9 Hz, 1H), 2.07-1.88 (m, 2H), 1.83-1.66 (m, 5H), 1.43 (m, 1H), 1.29 (s, 3H), 1.05 (s, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 130.9, 128.9, 113.6, 83.9, 79.3, 74.7, 71.6, 70.9, 64.0, 59.7, 55.2, 43.4, 34.0, 27.5, 19.6, 18.2, 18.1, 18.0, 12.8, 11.9; IR (film) 3475, 2940, 1613, 1514, 1464, 1389, 1249, 1090, 883, 740, 680 cm^{-1}; $[\alpha]^{23}_D$ = -6.5 (c 0.009, CH_2Cl_2); MS (ESI) for $C_{37}H_{70}O_6Si_2$ [M + Na] calc 689.5, found 689.6.

To a stirred solution of the primary alcohol obtained as above (3.32 g, 4.98 mmol) in CH_2Cl_2 (50 mL) was added TEA (7.0 mL, 50 mmol), DMAP (610 mg, 5.0 mmol), and PivCl (2.56 mL, 20.8 mmol). After 28 h, the reaction was quenched with

saturated, aqueous $NaHCO_3$, and the aqueous layer diluted with NH_4Cl (aq) and extracted with EtOAc three times. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (4.5% EtOAc in hexanes) afforded 3.64 g oxocane **215** (97%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.38 (dd, J = 2.2, 11.5 Hz, 1H), 4.37 (AB, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 134.8 Hz, 2H), 4.18 (m, 1H), 4.01 (dt, J = 3.5, 8.9 Hz, 1H), 3.88 (dd, J = 3.1, 11.6 Hz, 1H), 3.78 (s, 3H), 3.73 (m, 2H), 3.38 (d, J = 6.7 Hz, 1H), 2.04 (m, 1H), 1.91 (m, 1H), 1.85-1.74 (m, 3H), 1.72-1.59 (m, 2H), 1.43 (m, 1H), 1.28 (s, 3H), 1.16 (s, 9H), 1.03 (s, 42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 158.9, 131.0, 128.7, 113.6, 84.2, 79.0, 73.2, 71.2, 71.1, 65.9, 59.7, 55.2, 43.6, 38.8, 33.9, 27.4, 27.2, 19.6, 18.2, 18.1, 18.0, 12.8, 12.0; IR (film) 2943, 2867, 1731, 1514, 1464, 1249, 1094, 883, 740 cm^{-1}; $[\alpha]^{23}_D$ = -1.9 (c 0.010, CH_2Cl_2); MS (ESI) for $C_{42}H_{78}O_7Si_2$ [M + Na] calc 773.5, found 773.4.



Carboxylic acid 216.

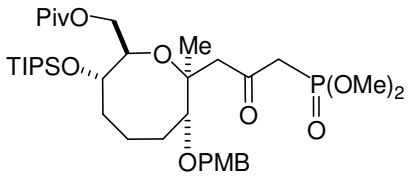
To a stirred mixture of oxocane **215** (3.64 g, 4.85 mmol), THF (60 mL), and water (60 mL) was added TFA (5.4 mL, 73 mmol). After 8.5 h, the mixture was quenched with saturated, aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography

(20%→30%→40% EtOAc in hexanes) afforded 2.77 g of the alcohol (96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.37 (AB, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 144.8 Hz, 2H), 4.28 (dd, J = 2.5, 11.7 Hz, 1H), 4.21 (m, 1H), 4.10-4.02 (m, 2H), 3.85 (m, 1H), 3.78 (s, 3H), 3.58 (m, 1H), 3.33 (dd, J = 2.2, 8.9 Hz, 1H), 3.27 (d, J = 7.0 Hz, 1H), 2.07 (m, 1H), 2.02-1.91 (m, 2H), 1.91-1.80 (m, 2H), 1.75 (ddd, J = 2.3, 9.1, 15.1 Hz, 1H), 1.45 (m, 1H), 1.37-1.30 (m, 4H), 1.18 (s, 9H), 1.01 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 159.0, 130.5, 128.9, 113.7, 83.8, 82.5, 73.6, 71.0, 70.5, 65.3, 59.3, 55.2, 44.1, 38.9, 33.8, 27.2, 27.1, 19.0, 18.14, 18.07, 12.8; IR (film) 3510, 2946, 1729, 1514, 1464, 1248, 1101, 910, 735, 680 cm^{-1}; $[\alpha]^{23}_D$ = -4.6 (c 0.024, CH_2Cl_2); MS (ESI) for $C_{33}H_{58}O_7Si$ [M + Na] calc 617.4, found 617.4.

To a stirred solution of the alcohol obtained as above (1.626 g, 2.733 mmol) in CH_2Cl_2 at 0 °C was added KBr (0.1 M in H_2O, 2.7 mL, 0.27 mmol), TEMPO (21 mg, 0.13 mmol), and bleach (1:1 bleach (5% aqueous solution) : saturated, aqueous $NaHCO_3$, 9.2 mL, 3.3 mmol). After 2 h, the mixture was quenched with saturated, aqueous Na_2SO_3 and warmed to ambient temperature. The mixture was diluted with EtOAc, and the organic layer was washed with water. The combined aqueous layers were extracted with EtOAc, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (12% EtOAc in hexanes) afforded 1.550 g of the aldehyde (95%) as a light brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (dd, J = 2.4, 3.1 Hz, 1H), 7.25 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.55 (m, 2H), 4.22 (d, J = 11.2 Hz, 1H), 4.16-4.03 (m, 2H), 3.90 (dd, J = 3.4, 11.6 Hz, 1H), 3.82 (s, 3H), 3.31 (d, J = 7.7 Hz,

1H), 2.54 (dd, *J* = 2.4, 14.9 Hz, 1H), 2.30 (dd, *J* = 3.1 Hz, 14.9 Hz, 1H), 2.09-1.94 (m, 2H), 1.91-1.78 (m, 2H), 1.71 (m, 1H), 1.51-1.43 (m, 4H), 1.20 (s, 9H), 1.07 (s, 21H).

To a stirred solution of the aldehyde obtained as above (1.550 g, 2.614 mmol) in *t*-BuOH (50 mL) was added *trans*-2-methyl-2-butene (6.8 mL, 64 mmol). Sodium chlorite (2.79 g in 50 mL pH 4 buffer solution, 31 mmol) was then added via addition funnel. After 10 min, the mixture was diluted with EtOAc. The organic and aqueous layers were separated, and the aqueous layer was cooled to 0 ℃ and adjusted to pH 3 with conc. sulfuric acid. The cooled aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (25% EtOAc→48% EtOAc, 2% AcOH in hexanes) afforded 1.592 g carboxylic acid **216** (100%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 4.56 (d, *J* = 11.1 Hz, 1H), 4.35 (d, *J* = 9.0 Hz, 1H), 4.22 (d, *J* = 11.1 Hz, 1H), 4.21-4.10 (m, 3H), 3.78 (s, 3H), 3.30 (d, *J* = 7.3 Hz, 1H), 2.70 (d, *J* = 15.3 Hz, 1H), 2.30 (d, *J* = 15.3 Hz, 1H), 2.11 (dt, *J* = 7.5, 15.3 Hz, 1H), 2.10-1.87 (m, 2H), 1.81 (m, 1H), 1.62 (dd, *J* = 6.2, 9.4 Hz, 1H), 1.48 (dt, *J* = 7.8, 15.2 Hz, 1H), 1.41 (s, 3H), 1.17 (s, 9H), 1.01 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ178.4, 171.2, 159.2, 129.7, 129.2, 113.8, 82.5, 79.7, 74.4, 71.3, 70.1, 64.9, 55.2, 45.5, 38.9, 33.9, 27.5, 27.2, 19.4, 18.1, 18.0, 12.7; IR (film) 3158 (br), 2945, 2868, 1727, 1515, 1464, 1248, 1162, 1106, 909, 738, 679 cm^{-1}; $[\alpha]^{23}_{D}$ = -18.5 (c 0.011, CH_2Cl_2); MS (ESI) for $C_{33}H_{56}O_8Si$ [M + H] calc 609.4, found 609.4.



β-Keto phosphonate 193.

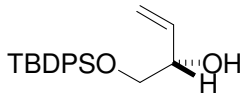
To a stirred solution of carboxylic acid **216** (2.03 g, 3.33 mmol) in DMF (33 mL) was added K_2CO_3 (1.15 g, 8.3 mmol), and the resulting mixture was cooled to 0 °C. Methyl iodide (1.05 mL, 16.8 mmol) was added dropwise, and after 20 min, the cloudy reaction mixture was warmed to ambient temperature. After an additional 20 min, the yellow mixture was diluted with half-saturated aqueous NH_4Cl and Et_2O. The aqueous layer was extracted with Et_2O three times, and the combined organic layers were washed with saturated $Na_2S_2O_3$ (aq) to remove the yellow coloration. The $Na_2S_2O_3$ aqueous layer was extracted with Et_2O twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (13% EtOAc in hexanes) afforded 1.99 g of the ester (96%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.40 (dd, J = 2.0, 12.5 Hz, 1H), 4.39 (AB, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 104.3 Hz, 2H), 4.08 (m, 1H), 3.96 (m, 1H), 3.85 (dd, J = 4.0, 7.5 Hz, 1H), 3.78 (s, 3H), 3.63 (d, J = 7.3 Hz, 1H), 3.56 (s, 3H), 2.48 (AB, J_{AB} = 13.9 Hz, $\Delta\nu_{AB}$ = 12.3 Hz, 2H), 2.04-1.84 (m, 3H), 1.79-1.66 (m, 2H), 1.49-1.39 (m, 4H), 1.17 (s, 9H), 1.02 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 171.2, 158.9, 130.8, 128.9, 113.6, 82.1, 78.8, 73.9, 71.4, 71.0, 66.1, 55.2, 51.3, 45.4, 38.8, 33.0, 27.4, 27.2, 19.1, 18.2, 18.1, 12.8; IR (film) 2946, 2867, 1733, 1514, 1464, 1286, 1248, 1162,

1102, 739, 681 cm^{-1}; $[\alpha]^{23}_D$ = +6.6 (c 0.007, CH_2Cl_2); MS (ESI) for $C_{34}H_{58}O_8Si$ [M + Na] calc 645.4, found 645.4.

To a stirred solution of dimethyl methylphosphonate (0.620 mL, 5.62 mmol) in THF (5.6 mL) at -78 °C was added BuLi (2.5 M in hexanes, 2.14 mL, 5.34 mmol). This solution was stirred 1 h. A separate 3-neck, 100 mL flask equipped with a jacketed addition funnel was charged with the ester obtained as above (270 mg, 0.433 mmol) and THF (19 mL). This flask and addition funnel were cooled to -78 °C, and the lithiated phosphonate solution was added *via* cannula to the cooled addition funnel. An aliquot (about 1 mL) of the lithiated phosphonate solution was then added dropwise to the solution of ester. After 5 min, the reaction was checked by TLC, and additional aliquots were added until the reaction was judged complete by TLC. Once complete, the reaction was quenched with saturated, aqueous NH_4Cl and warmed to ambient temperature. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (80% EtOAc in hexanes →100% EtOAc) afforded 269 mg phosphonate **1** (87%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.39 (AB, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 100.1 Hz, 2H), 4.25 (dd, J = 2.1, 11.7 Hz, 1H), 4.14 (m, 1H), 3.98 (dt, J = 3.6, 8.7 Hz, 1H), 3.94 (dd, J = 4.0, 11.8 Hz, 1H), 3.78 (s, 3H), 3.75 (d, J = 2.4 Hz, 3H), 3.72 (d, J = 2.4 Hz, 3H), 3.42 (d, J = 7.5 Hz, 1H), 3.39 (dd, J = 13.6, 22.6 Hz, 1H), 3.01 (dd, J = 13.6, 22.3 Hz, 1H), 2.97 (d, J = 12.7 Hz, 1H), 2.45 (d, J = 12.7 Hz, 1H), 2.07-1.87 (m, 2H), 1.87-1.77 (m, 2H), 1.68 (m, 1H), 1.43 (m, 1H), 1.33 (s, 3H), 1.17 (s, 9H), 1.02 (s, 21H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (d, J = 7.0 Hz),

178.4, 159.0, 130.5, 128.9, 113.6, 82.7, 80.0, 73.9, 71.04, 70.99, 66.3, 55.2, 53.3, 52.9 (d, *J* = 6.6 Hz), 52.7 (d, *J* = 6.4 Hz), 43.5 (d, *J* = 126.3 Hz), 38.7, 32.7, 27.2, 19.3, 18.10, 18.05, 12.7; IR (film) 3439, 2952, 1728, 1613, 1514, 1464, 1382, 1143, 882, 822, 680, 445 cm^{-1}; $[\alpha]^{23}_D$ = -20.7 (c 0.017, CH_2Cl_2); MS (ESI) for $C_{36}H_{63}O_{10}PSi$ [M + H] calc 715.4, found 715.3.

3. Optimized Synthesis of the J Ring

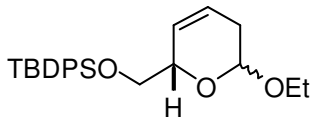


Preparation of known alcohol **217:**

To a stirred solution of (*R*)-glycidol (20 g, 0.262 mol) in CH_2Cl_2 (1 L) at 0 °C was added imidazole (23.89 g, 0.351 mol). After 15 min, *t*-butyldiphenylsilylchloride (70.2 mL, 0.270mol) was added in CH_2Cl_2 (80 mL) *via* addition funnel. The reaction was warmed to room temperature and stirred for 2 h. The salty mixture was then diluted with water, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography through a silica plug (3%→8% EtOAc in hexanes) afforded 77.7 g (95%) of (*S*)-*tert*-butyl-oxiranylmethoxydiphenylsilane.

A 500 mL flask fitted with an addition funnel was charged with 170 mL of THF and trimethylsulfonium iodide (31 g, 149 mmol) and cooled to -10 °C. *n*-Butyllithium (1.6M in hexanes, 92 mL, 147 mmol) was added dropwise via addition funnel. After stirring for 30 minutes at -10 °C, (*S*)-*tert*-butyl-oxiranylmethoxydiphenylsilane (15.6 g, 50 mmol) in 40 mL THF was added *via* cannula into the ylide. The reaction was

warmed to 0 °C and then room temperature for 2 hours. The reaction was quenched by addition of water, and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (5%→6% EtOAc in hexanes) afforded 16 g (86%) of known alcohol **217**.[63]

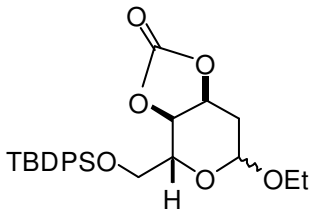


Dihydropyran 219.

A 1 L flask was charged with benzene (240 mL), alcohol **217** (28.73 g, 87.99 mmol), pyridium-*p*-toluenesulfonate (2.2 g, 8.8 mmol), and 3-butenal diethylacetal (45 mL, 264 mmol), and heated to 50 °C. After mixing the reaction for 10 min, about 90% of the solvent removed in vacuo. Addition of fresh benzene (~200 mL) and 3-butenal diethylacetal (15 mL, 88 mmol), mixing at 50 °C, and concentration in vacuo was repeated until the starting material was consumed as much as possible. The concentrated mixture was then diluted with EtOAc and saturated, aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (10%→50% EtOAc in hexanes) afforded 3.49 g starting material **217** and 30.7 g of the mixed acetal (82%, 93% brsm) as a colorless oil (mixture of epimers, 2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.64 (m, 4H), 7.41-7.33 (m, 6H), 5.84-5.66 (m, 2H), 5.27-5.00 (m, 4H), [4.66 (t, *J* = 5.7 Hz), 4.58 (t, *J* = 5.9 Hz), 1H], [4.17 (dd, *J* = 6.2, 12.8 Hz), 4.10 (dd, *J* = 7.0, 12.0 Hz), 1H], 3.76-3.49 (m, 3H), 3.48-3.39 (m, 1H), 2.41-2.34 (m, 2H), 1.14-1.10 (m, 3H), 1.03 (s,

9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 136.2, 135.9, 135.7, 133.6, 133.5, 129.69, 129.67, 129.6, 127.7, 118.3, 117.3, 116.9, 102.6, 99.8, 78.6, 77.7, 67.0, 66.7, 60.8, 59.2, 39.0, 38.7, 26.8, 19.3, 19.2, 15.3, 15.2; IR (film) 3072, 1643, 1472, 1428, 1390, 1113, 918, 823, 741, 702, 613 cm^{-1}; $[\alpha]^{23}_D$ = +2.7 (*c* 0.005, CH_2Cl_2); MS (ESI) for $C_{26}H_{36}O_3Si$ [M + Na] calc 447.2, found 447.3.

To a stirred, degassed solution of the mixed acetal obtained as above (32.59 g, 76.75 mmol) in CH_2Cl_2 (1.53 L) was added bis(tricyclohexylphosphine)benzylidine-ruthenium(IV)dichloride (1.58 g, 1.92 mmol). The purple solution was heated to reflux. After 2.5 h, the solution was cooled to ambient temperature, and DMSO (6.8 mL, 96 mmol) was added. This solution was opened to air and stirred overnight. Concentration in vacuo and flash column chromatography (5%→8% EtOAc in hexanes) afforded 28.26 g of dihydropyran **219** (93%) as a light brown oil (mixture of epimers, 1.2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H), 7.42-7.33 (m, 6H), 5.80-5.71 (m, 2H), [4.97 (d, *J* = 4.4 Hz), 4.68 (dd, *J* = 4.5, 6.4 Hz), 1H], [4.32(s), 4.23 (s) 1H], 3.94-3.74 (m, 2H), 3.69-3.61 (m, 1H), 3.53-3.45 (m, 1H), [2.43-2.35 (m), 2.07-2.01 (m), 1H], 2.20-2.16 (m, 1H), 1.23-1.17 (m, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.6, 133.73, 133.72, 129.6, 127.6, 127.1, 126.4, 123.7, 122.5, 98.2, 95.6, 75.0, 68.8, 66.6, 63.9, 62.9, 31.3, 30.3, 26.8, 19.3, 15.2, 15.1; IR (film) 3072, 2930, 2858, 1589, 1472, 1428, 1376, 1216, 1113, 1028, 941, 823, 741, 702, 613 cm^{-1}; $[\alpha]^{23}_D$ = -0.7 (*c* 0.009, CH_2Cl_2); MS (ESI) for $C_{24}H_{32}O_3Si$ [M + Na] calc 419.2, found 419.4.

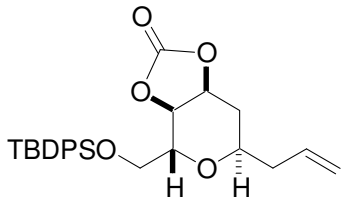


Carbonate 220.

Sodium periodate (15.08 g, 70.5 mmol) and $RuCl_3 \cdot 7H_2O$ (0.682 g, 3.29 mmol) were stirred vigorously in water (128 mL) at 0 °C for 30 min. The dark colored mixture was added to a stirred solution of dihydropyran **219** (18.66 g, 47.0 mmol) in EtOAc (315 mL) and CH_3CN (315 mL) at 0 °C. After 1 minute, the reaction was quenched with saturated, aqueous sodium thiosulfate, and the resulting mixture was warmed to ambient temperature. The organic layer was washed with fresh saturated, aqueous sodium thiosulfate, and the combined aqueous layers were extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography provided 15.18 g (75%) of the desired diastereomers of the diol as a light brown oil (mixture of anomers, 1.3:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.64 (m, 4H), 7.45-7.33 (m, 6H), [4.93, (d, *J* = 3.7 Hz), 4.82 (dd, *J* = 2.2 Hz), 1H], [4.12 (dd, *J* = 3.3, 6.2 Hz), 3.99 (dd, *J* = 2.6, 10.8 Hz), 1H], 3.98-3.66 (m, 6H), [3.55 (d, *J* = 9.9 Hz), 3.49-3.40, (m), 2H], [2.65 (d, *J* = 1.1 Hz), 2.55 (d, *J* = 9.9 Hz), 1H], 2.16-2.08 (m, 1H), [1.86 (ddd, *J* = 3.5, 3.5, 14.6 Hz), 1.67-1.60 (m), 1H], [1.20 (t, *J* = 7.0 Hz), 1.15 (t, *J* = 7.1 Hz), 3H], [1.06 (s), 1.05 (s), 9H]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.6, 135.5, 133.7, 133.6, 132.3, 132.2, 130.1, 129.63, 129.60, 127.9, 127.6, 97.7, 96.7, 72.3, 70.5, 69.5, 67.6, 67.49, 67.47, 67.0, 64.6, 67.5, 63.1, 36.4, 35.0, 26.8, 19.3, 19.1, 15.2, 15.0; IR (film) 3433, 2930, 1467, 1428, 1113, 1072,

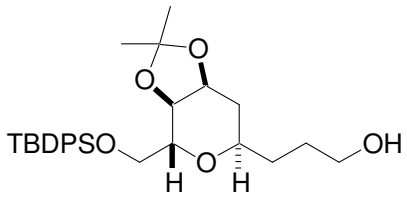
1007, 822, 740, 703 cm^{-1}; $[\alpha]^{23}_D$ = +33.3 (*c* 0.006, CH_2Cl_2); MS (ESI) for $C_{24}H_{34}O_5Si$ [M + Na] calc 453.2, found 453.3.

To a stirred solution of the diol obtained as above (15.18 g, 35.25 mmol) in THF (440 mL) was added 1,1'-carbonyldiimidazole (8.57 g, 52.88 mmol), and this solution was heated to reflux. After 2.5 h, the solution was cooled to ambient temperature, and saturated, aqueous NH_4Cl was added. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with saturated, aqueous $NaHCO_3$. The basic aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatrography (25% EtOAc in hexanes) gave 14.44 g (90%) of carbonate **220** as a colorless oil (mixture of epimers, 1.3:1): ^1H NMR (400 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.45-7.35 (m, 6H), 4.99-4.92 (m, 1H), [4.82-4.76 (m), 4.69 (t, *J* = 7.8 Hz), 2H], [3.99-3.93 (m), 3.92-3.82 (m), 3H], [3.74 (dd, *J* = 7.0, 10.0 Hz), 3.67-3.63 (m), 1H], 3.53-3.40 (m, 1H), 2.35-2.25 (m, 1H), 2.16-2.03 (m, 1H), 1.20-1.15 (m, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 154.2, 135.6, 135.5, 133.0, 132.93, 132.89, 129.9, 129.8, 127.8, 127.74, 127.73, 96.7, 94.7, 74.3, 73.9, 72.3, 71.3, 70.9, 68.0, 64.2, 63.6, 63.3, 63.0, 31.7, 30.8, 26.7, 19.3, 15.1, 14.9; IR (film) 1813, 1641, 1428, 1360, 1113, 1070, 741, 703 cm^{-1}; $[\alpha]^{23}_D$ = +43.2 (*c* 0.089, CH_2Cl_2); MS (ESI) for $C_{25}H_{32}O_6Si$ [M + Na] calc 479.2, found 479.4.



Oxane 222.

To a stirred solution of carbonate **220** (7 g, 15.3 mmol) in acetonitrile (320 mL) and allyltrimethylsilane (49 mL, 306 mmol) at -10 °C was added trimethylsilyl triflate (2.3 mL, 7.7 mmol) dropwise *via* syringe. After 6 hours, the reaction was quenched by addition of saturated, aqueous $NaHCO_3$. The aqueous layer was extracted twice with ether, and the combined organic extracts were dried over sodium sulfate and concentrated in vacuo. Purification by flash chromatography (15%→25% EtOAc in hexanes) gave 6.94 g (87%, dr > 10:1, minor diastereomer removed after the subsequent reaction/purification) of oxane **222**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (td, *J* = 1.6, 8.0 Hz, 4H), 7.44-7.36 (m, 6H), 5.82-5.72 (m, 1H), 5.13-5.08 (m, 2H), 4.91-4.85 (m, 1H), 4.67 (dd, *J* = 4.7, 7.2 Hz, 1H), 5.05 (dd, *J* = 4.5, 8.0 Hz, 1H), 4.01-3.94 (m, 1H), 3.88 (dd, *J* = 3.1, 11.6 Hz, 1H), 3.79 (dd, *J* = 4.3, 11.2 Hz, 1H), 2.39-2.31 (m, 1H), 2.27-2.21 (m, 1H), 2.20-2.13 (m, 1H), 1.74-1.65 (m, 1H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 135.6, 135.5, 133.3, 132.5, 132.4, 130.04, 130.02, 127.90, 127.87, 118.1, 73.4, 73.2, 71.9, 69.4, 65.2, 39.8, 31.3, 26.8, 19.1; IR (film) 1807, 1642, 1428, 1113, 1040, 741, 703; $[\alpha]^{22}_D$ = -4.0 (*c* 0.14, CH_2Cl_2); MS (ESI) for $C_{26}H_{32}O_5Si$ [M + Na] calc 475.2, found 475.3.



Alcohol 226.

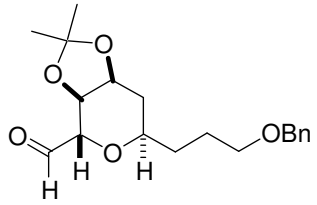
To a stirred solution of oxane **222** (16.75 g, 37.0 mmol) in MeOH (670 mL) was added K_2CO_3 (25.6 g, 185 mmol). After 30 min, the reaction was diluted with EtOAc and saturated, aqueous NH_4Cl. The aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (45%→60% EtOAc in hexanes) afforded 12.06 g (76%) of isomerically pure diol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.62 (m, 4H), 7.46-7.36 (m, 6H), 5.78-5.67 (m, 1H), 5.06-4.98 (m, 2H), 3.98-3.90 (m, 2H), 3.83-3.65 (m, 4H), 2.98 (d, J = 3.7 Hz, 1H), 2.56-2.48 (m, 1H), 2.35 (d, J = 4.8 Hz, 1H), 2.29-2.22 (m, 1H), 1.78 (ddd, J = 4.4, 4.4, 13.9 Hz, 1H), 1.70-1.63 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.5, 134.9, 132.7, 132.6, 130.0, 127.8, 116.9, 73.0, 70.8, 70.3, 66.4, 64.7, 39.1, 33.4, 26.8, 19.1; IR (film) 3398, 3077, 2929, 1428, 1112, 915, 804, 737, 702 cm^{-1}; $[\alpha]^{23}_D$ = -5.4 (*c* 0.17, CH_2Cl_2); MS (ESI) for $C_{25}H_{34}O_4Si$ [M + Na] calc 449.2, found 449.3.

To a stirred solution of the diol obtained as above (10.08 g, 23.63 mmol) in 2,2-dimethoxypropane (170 mL) was added PPTS (0.594 g, 2.36 mmol). After 18 h, the reaction was poured into saturated, aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash

chromatography (10% EtOAc in hexanes) afforded 10.55 g (96%) of the acetonide as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.7 Hz, 4H), 7.35-7.44 (m, 6H), 5.91-5.81 (m, 1H), 5.12-5.05 (m, 2H), 4.33-4.28 (m, 1H), 4.02 (t, J = 5.9 Hz, 1H), 3.92-3.76 (m, 4H), 2.49-2.41 (m, 1H), 2.29-2.22 (m, 1H), 1.98 (ddd, J = 4.0, 5.8, 13.6 Hz, 1H), 1.68-1.60 (m, 1H), 1.47 (m, 3H), 1.32 (m, 3H), 1.07 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.68, 135.66, 134.6, 133.4, 129.6, 127.6, 117.0, 108.3, 73.1, 72.2, 71.9, 70.1, 65.4, 39.7, 32.6, 27.9, 26.8, 25.6, 19.2; IR (film) 1641, 1429, 1376, 1218, 1113, 1060, 822, 702, 453 cm^{-1}; $[\alpha]^{22}_D$ = +8.5 (*c* 0.48, CH_2Cl_2); MS (ESI) for $C_{28}H_{38}O_4Si$ [M + Na] calc 489.2, found 489.3.

To a stirred solution of the acetonide obtained as above (9.24 g, 19.8 mmol) in THF (102 mL) at 0 °C was added 9-BBN (0.5 M in THF, 79 mL, 39.5 mmol). This solution was sonicated for 30 min, after which the reaction was allowed to warm to ambient temperature. After sonicating for an additional 17 h, sonication was discontinued, and the reaction was cooled to 0 °C. Water (2.5 mL) was added, followed by NaOH (3 M in H_2O, 28 mL, 84 mmol) and hydrogen peroxide (30% in H_2O, 56 mL, 490 mmol). After 1.5 h, the mixture was warmed to ambient temperature. After another 4 h, saturated, aqueous NH_4Cl was added. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with saturated, aqueous Na_2SO_3. The aqueous Na_2SO_3 layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (50% EtOAc in hexanes) afforded 8.6 g (90%) of alcohol **226** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.56 (m, 4H), 7.43-7.34 (m, 6H),

4.31-4.25 (m, 1H), 3.95 (t, *J* = 6.0 Hz, 1H), 3.88-3.72 (m, 4H), 3.63 (t, *J* = 5.5 Hz, 2H), 1.96 (ddd, *J* = 4.0, 5.9, 13.4 Hz, 1H), 1.80-1.58 (m, 5H), 1.44, (s, 3H), 1.29 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ135.71, 135.67, 133.41, 133.37, 129.71, 129.68, 127.68, 108.47, 72.9, 72.2, 71.8, 70.5, 65.4, 62.7, 33.4, 31.7, 29.3, 28.0, 26.8, 25.7, 19.2; IR (film) 3420, 2931, 1428, 1380, 1217, 1113, 1052, 823, 741, 703 cm^{-1}; $[\alpha]^{23}_D$ = -18.9 (*c* 0.15, CH_2Cl_2); MS (ESI) for $C_{28}H_{40}O_5Si$ [M + Na] calc 507.3, found 507.3.



Aldehyde 194.

To a stirred solution of primary alcohol **226** (49 mg, 0.10 mmol) and TBAI (4 mg, 0.01 mmol) in THF (1.0 mL) at 0 °C was added KH (30% in mineral oil, 40 mg, 0.30 mmol). After 10 min, BnBr (18 μL, 0.15 mmol) was added. After 3 h, the reaction was quenched with saturated, aqueous NH_4Cl, and the mixture was warmed to ambient temperature. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (10%→15% EtOAc in hexanes) afforded 50 mg (88%) of the benzyl ether as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.66 (d, *J* = 6.3 Hz, 4H), 7.42-7.29 (m, 11H), 4.46 (s, 2H), 4.29-4.24 (m, 1H), 3.97 (t, *J* = 5.9 Hz, 1H), 3.87-3.72 (m, 4H), 3.52-3.42 (m, 2H), 1.96 (ddd, *J* = 4.1, 6.2, 13.6, 1H), 1.85-1.49 (m, 5H), 1.43 (s, 3H), 1.30 (s, 3H), 1.04 (s,

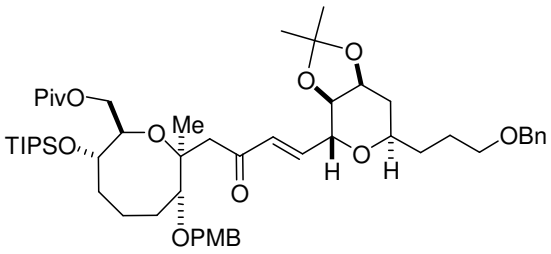
9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 135.7, 135.6, 133.40, 133.39, 129.65, 129.63, 128.3, 127.64, 127.58, 127.4, 108.4, 72.8, 72.7, 72.2, 71.9, 70.2, 65.4, 33.2, 31.8, 28.0, 26.8, 25.9, 25.7, 19.2; IR (film) 1647, 1428, 1362, 1204, 1112, 1060, 821, 739, 701; $[\alpha]^{22}_D$ = +9.1 (*c* 0.56, CH_2Cl_2); MS (ESI) for $C_{35}H_{46}O_5Si$ [M + Na] calc 597.3, found 597.3.

To a stirred solution of the benzyl ether obtained as above (3.03 g, 5.27 mmol) in THF (55 mL) at 0 °C was added TBAF (1.0 M in THF, 7.9 mL, 7.9 mmol) dropwise. After 4.5 h, saturated, aqueous NH_4Cl was added, and the mixture was warmed to ambient temperature. After diluting with water and EtOAc, the aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (60%→75% EtOAc in hexanes) afforded 1.755 g (99%) of the alcohol as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 4.32-4.27 (m, 1H), 3.96 (t, *J* = 6.6 Hz, 1H), 3.73-3.71 (m, 2H), 3.69-3.60 (m, 2H), 3.52-3.43 (m, 2H), 2.06-2.00 (m, 1H), 1.85-1.51 (m, 6H), 1.45 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 128.4, 127.7, 127.5, 108.9, 72.9, 72.1, 71.8, 71.3, 70.2, 70.1, 63.1, 32.4, 31.6, 27.8, 25.9, 25.4; IR (film) 3435, 2984, 2933, 2866, 1646, 1454, 1369, 1216, 1164, 1055, 861, 738, 698, 439 cm^{-1}; $[\alpha]^{24}_D$ = +28.8 (*c* 0.49, CH_2Cl_2); MS (ESI) for $C_{19}H_{28}O_5$ [M + Na] calc 359.2, found 359.2.

To a stirred solution of the alcohol obtained as above (131 mg, 0.389 mmol) in CH_2Cl_2 at 0 °C was added KBr (0.1 M in H_2O, 390 μL, 0.039mmol), TEMPO (3 mg, 0.02 mmol), and bleach (1:1 bleach (5% aqueous solution) : saturated, aqueous $NaHCO_3$, 1.3 mL, 0.467 mmol). After 1 h, additional KBr, TEMPO, and bleach

(same amounts as before) were added to the reaction. Again, after 1 h, additional KBr, TEMPO, and bleach (same amounts as before) were added. After 20 min, the mixture was quenched with saturated, aqueous Na_2SO_3 and warmed to ambient temperature. The mixture was diluted with EtOAc, and the organic layer was washed with water, then brine, then dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography through a silica plug (30%→60% EtOAc in hexanes) afforded 113 mg aldehyde **194** (87%) as a colorless oil, which was used immediately in the next reaction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.34-7.31 (m, 5H), 4.48 (s, 2H), 4.44 (d, *J* = 3.1 Hz, 1H), 4.35 (dd, *J* = 3.1, 5.6 Hz, 1H), 4.16-4.11 (m, 1H), 3.52-3.36 (m, 3H), 1.90-1.47 (m, 6H), 1.51 (s, 3H), 1.35 (s, 3H).

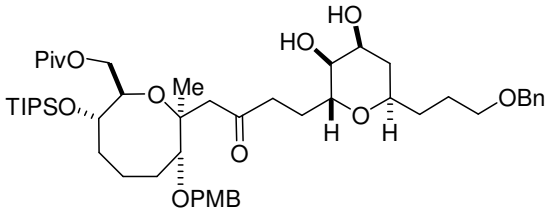
4. Synthesis of GHIJ Fragment **197**



Enone 195.

To a stirred solution of phosphonate **193** (2.10 g, 2.94 mmol) in THF (24 mL) was added $Ba(OH)_2 \cdot 8\ H_2O$ (742 mg, 2.35 mmol, activated at 100 °C for 2 h). After 30 min, aldehyde **194** (1.16 g, 3.47 mmol) in THF/H_2O (40:1, 20 mL) was added dropwise via cannula. After 30 min, the reaction was quenched with saturated, aqueous NH_4Cl, and diluted with EtOAc/hexanes. The aqueous layer was extracted

with EtOAc twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (19%→24% EtOAc in hexanes) afforded 2.19 g enone **195** (81%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.15 (m, 7H), 6.77 (d, J = 8.7 Hz, 2H), 6.72 (dd, J = 4.0, 16.0 Hz, 1H), 6.31 (dd, J = 1.8, 16.0 Hz, 1H), 4.41 (s, 2H), 4.33 (AB, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 93.8 Hz, 2H), 4.31 (dd, J = 1.7, 11.5 Hz, 1H), 4.21 (m, 2H), 4.08 (m, 1H), 3.86 (m, 1H), 3.81-3.73 (m, 2H), 3.70 (s, 3H), 3.66 (m, 1H), 3.56 (d, J = 7.4 Hz, 1H), 3.41 (m, 2H), 2.74 (d, J = 13.8 Hz, 1H), 2.53 (d, J = 13.8 Hz, 1H), 2.01-1.46 (m, 12H), 1.41 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 1.11 (s, 9H), 0.97 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 178.3, 158.8, 142.9, 138.4, 131.0, 130.7, 128.7, 128.2, 127.43, 127.36, 113.5, 108.9, 82.2, 79.7, 75.0, 73.8, 72.7, 71.6, 70.9, 70.2, 70.1, 69.8, 66.4, 55.1, 50.5, 38.6, 32.2, 31.4, 27.7, 27.3, 27.1, 25.8, 25.3, 19.5, 18.04, 17.98, 12.6; IR (film) 3067, 2940, 1728, 1691, 1614, 1514, 1462, 1368, 1247, 1101, 883, 822, 739, 680, 447 cm^{-1}; $[\alpha]^{23}_D$ = +31.9 (c 0.015, CH_2Cl_2); MS (ESI) for $C_{53}H_{82}O_{11}Si$ [M + Na] calc 945.6, found 945.5.



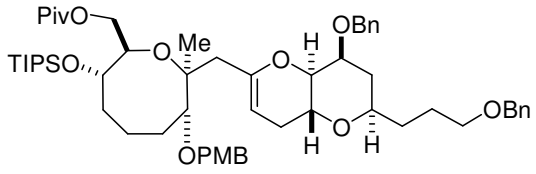
Diol 231.

To a stirred, red solution of Stryker's reagent (2.3 g, 1.2 mmol) in toluene (15 mL, degassed) was added enone **195** (2.19 g, 2.37 mmol) in toluene (30 mL, degassed) via cannula, whereupon the solution immediately turned deep red to black in color.

After 5 min, H_2O (140 μL, degassed) was added. After 1 h, the reaction was opened to air for 1 h, and then concentrated in vacuo. Flash column chromatography (25%→30%→40% EtOAc in hexanes) afforded 2.08 g of the ketone (95%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.14 (m, 7H), 6.76 (d, J = 8.6 Hz, 2H), 4.41 (s, 2H), 4.32 (AB, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 119.1 Hz, 2H), 4.26 (d, J = 11.6 Hz, 1H), 4.22-4.15 (m, 1H), 4.08 (m, 1H), 3.87 (m, 1H), 3.80 (dd, J = 4.4, 11.7 Hz, 1H), 3.74-3.68 (m, 4H), 3.56-3.48 (m, 3H), 3.43-3.35 (m, 2H), 2.60 (d, J = 13.7 Hz, 1H), 2.53 (m, 1H), 2.42 (m, 1H), 2.36 (d, J = 13.7 Hz, 1H), 1.97-1.81 (m, 3H), 1.81-1.71 (m, 3H), 1.67-1.50 (m, 7H), 1.45 (m, 1H), 1.37 (s, 3H), 1.29 (s, 3H), 1.24 (s, 3H), 1.10 (s, 9H), 0.96 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 178.4, 158.9, 138.5, 130.8, 129.8, 128.8, 128.3, 127.6, 127.5, 113.6, 108.6, 82.4, 79.5, 77.2, 76.1, 73.8, 72.8, 71.7, 71.4, 71.1, 70.4, 70.1, 69.3, 66.5, 55.2, 52.5, 41.1, 38.8, 32.8, 31.7, 27.8, 27.4, 27.3, 26.8, 26.0, 25.5, 18.2, 18.1, 12.8; IR (film) 3064, 2939, 1729, 1613, 1514, 1462, 1367, 1248, 1099, 882, 741, 679, 438 cm^{-1}; $[\alpha]^{23}_D$ = +9.4 (c 0.015, CH_2Cl_2); MS (ESI) for $C_{53}H_{84}O_{11}Si$ [M + Na] calc 947.6, found 947.6.

To a stirred solution of the ketone obtained as above (141 mg, 0.152 mmol) in MeOH (42 mL) was added TFA (0.34 mL, 4.57 mmol). This solution was heated to reflux, and then cooled to ambient temperature after 30 min. Saturated, aqueous $NaHCO_3$ and EtOAc/hexanes were added, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (50%→80% EtOAc in hexanes) afforded 126 mg diol **231** (93%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.13 (m, 7H), 6.77 (d, J = 8.6 Hz, 2H), 4.40 (s,

2H), 4.31 (AB, J_{AB} = 11.2 Hz, $\Delta\nu_{AB}$ = 102.1 Hz, 2H), 4.19 (d, J = 11.3 Hz, 1H), 4.04 (m, 1H), 3.87-3.76 (m, 3H), 3.74-3.69 (m, 4H), 3.46-3.34 (m, 5H), 2.60 (d, J = 13.2 Hz, 1H), 2.53-2.38 (m, 3H), 2.34 (d, J = 13.2 Hz, 1H), 2.26 (d, J = 6.1 Hz, 1H), 1.97-1.32 (m, 14H), 1.28 (s, 3H), 1.10 (s, 9H), 0.96 (s, 21H); ^{13}C NMR (100 MHz, C_6D_6) δ 208.5, 178.0, 159.6, 139.4, 131.1, 129.3, 128.5, 127.7, 127.6, 114.0, 82.6, 79.9, 75.8, 74.4, 72.9, 72.1, 71.4, 71.2, 70.6, 69.2, 66.7, 66.6, 54.8, 52.7, 41.6, 38.9, 35.4, 33.4, 32.5, 27.6, 27.5, 26.7, 23.3, 19.8, 18.41, 18.36, 13.1; IR (film) 3434, 2942, 1728, 1613, 1514, 1463, 1365, 1285, 1248, 1099, 883, 822, 737, 698, 679, 452 cm^{-1}; $[\alpha]^{23}_D$ = +6.3 (c 0.012, CH_2Cl_2); MS (ESI) for $C_{50}H_{80}O_{11}Si$ [M + Na] calc 907.5, found 907.5.



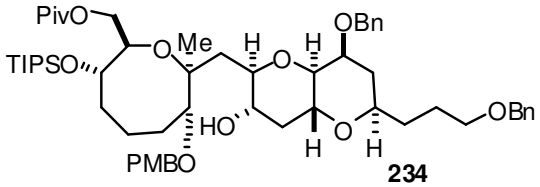
Tricycle 232.

A 300 mL flask equipped with a short path distillation head and argon inlet was charged with diol **231** (410 mg, 0.463 mmol), benzene (dry, 40 mL), and PPTS (80 mg, 0.32 mmol). The mixture was heated to 40 °C, and after 15 min, the reaction mixture was concentrated to about 1 mL *via* aspirator vacuum (~50 mmHg). Argon atmosphere (1 atm) was then re-established, and additional benzene (dry, 40 mL) was added. After another 15 min, the reaction mixture was again concentrated, and this process was repeated five times. Saturated, aqueous $NaHCO_3$ was then added, and the aqueous layer was extracted with EtOAc twice. The combined organic

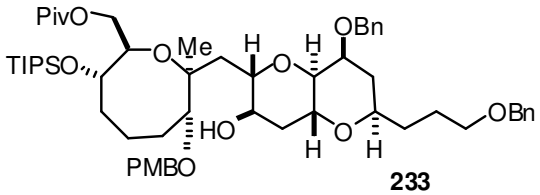
layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Flash column chromatography (10%→30%→85% EtOAc in hexanes) afforded 36 mg starting material **231** and 301 mg of the enol ether **196** (75%, 82% brsm) as a light yellow oil: ^{1}H NMR (400 MHz, C_6D_6) δ 7.28 (d, J = 7.0 Hz, 2H), 7.19-7.05 (m, 5H), 6.76 (d, J = 8.6 Hz, 2H), 4.87 (d, J = 11.5 Hz, 1H), 4.43 (m, 1H), 4.33 (s, 2H), 4.29 (d, J = 3.4 Hz, 1H), 4.23 (m, 1H), 4.21 (AB, J_{AB} = 11.6 Hz, $\Delta\nu_{AB}$ = 145.5 Hz, 2H), 4.12 (m, 1H), 3.99-3.88 (m, 2H), 3.72 (m, 1H), 3.47 (d, J = 6.8 Hz, 1H), 3.41-3.34 (m, 5H), 3.06 (dd, J = 2.7, 9.7 Hz, 1H), 2.45 (m, 1H), 2.29 (s, 2H), 2.15-2.04 (m, 3H), 2.04-1.92 (m, 4H), 1.83-1.56 (m, 7H), 1.44 (s, 3H), 1.22 (s, 9H), 1.09 (s, 21H); ^{13}C NMR (100 MHz, C_6D_6) δ 177.7, 159.6, 151.2, 139.5, 130.6, 129.8, 128.53, 128.46, 127.7, 127.5, 113.9, 98.3, 80.9, 80.2, 77.0, 73.9, 72.9, 72.3, 71.9, 70.5, 70.4, 65.7, 65.6, 59.8, 54.7, 45.4, 39.0, 34.9, 33.7, 29.8, 28.2, 27.7, 27.6, 27.5, 21.5, 18.5, 18.4, 13.2; IR (film) 3586, 3503, 3068, 2941, 1730, 1672, 1612, 1513, 1462, 1365, 1285, 1248, 1097, 946, 883, 821, 741, 678, 463 cm^{-1}; $[\alpha]^{23}_D$ = -0.30 (c 0.013, CH_2Cl_2); MS (ESI) for $C_{50}H_{78}O_{10}Si$ [M + Na] calc 889.5, found 889.4.

To a stirred solution of the enol ether obtained as above (485 mg, 0.559 mmol) and TBAI (40 mg, 0.11 mmol) in THF (11.2 mL) at 0 °C was added KHMDS (0.5 M in toluene, 3.4 mL, 1.7 mmol) and BnBr (460 μL, 3.9 mmol). The reaction was warmed to ambient temperature, and after 2.5 h, the reaction was quenched with water. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (20%→25% EtOAc in hexanes) afforded 491 mg (92%) of tricycle **232** as a light yellow oil: ^{1}H NMR (400 MHz, CD_3CN) δ 7.35-

7.16 (m, 12H), 6.81 (d, J = 8.7 Hz, 2H), 4.61 (AB, J_{AB} = 12.2 Hz, □□$_{AB}$ = 20.0 Hz, 2H), 4.45-4.39 (m, 4H), 4.19 (AB, J_{AB} = 11.4 Hz, $\Delta\nu_{AB}$ = 137.9 Hz, 2H), 4.18 (m, 1H), 4.02 (m, 1H), 3.91 (td, J = 6.5, 9.5 Hz, 1H), 3.87-3.82 (m, 2H), 3.78 (m, 1H), 3.71 (s, 3H), 3.49-3.43 (m, 3H), 3.24 (dd, J = 3.2, 9.9 Hz, 1H), 2.28 (m, 1H), 2.19-1.98 (m, 5H), 1.89-1.78 (m, 5H), 1.68-1.50 (m, 4H), 1.42 (m, 1H), 1.24 (s, 3H), 1.13 (m, 9H), 1.04 (s, 21H); ^{13}C NMR (100 MHz, C_6D_6) δ 177.6, 159.6, 151.4, 139.6, 139.5, 131.0, 129.6, 128.6, 127.7, 127.54, 127.47, 127.46, 113.8, 97.7, 81.5, 80.4, 77.6, 73.9, 73.00, 72.95, 72.8, 72.3, 72.0, 70.7, 70.4, 65.7, 60.0, 54.7, 45.7, 39.0, 35.0, 32.7, 29.6, 28.4, 27.8, 27.7, 27.5, 21.7, 18.5, 18.4, 13.2; IR (film) 3089, 3033, 2934, 1730, 1673, 1612, 1586, 1513, 1456, 1364, 1285, 1248, 1065, 883, 737, 676, 453 cm^{-1}; $[\alpha]^{23}_D$ = -17.3 (c 0.013, CH_2Cl_2); MS (ESI) for $C_{57}H_{84}O_{10}Si$ [M + Na] calc 979.6, found 979.4.



234



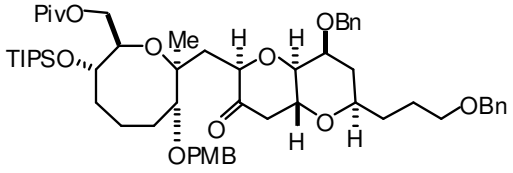
233

Alcohols 22 and 23.

To a stirred solution of tricycle **232** (579 mg, 0.605 mmol) in THF (5.9 mL) at 0 °C was slowly added BH_3·THF (1.0 M in THF, 3.6 mL, 3.6 mmol) dropwise. After 2.5 h,

the reaction was carefully quenched with a THF/H_2O mixture (9:1, 5 mL), followed by addition of 3 M NaOH (4.1 mL, 12.3 mmol), and 30% H_2O_2 (8.2 mL, 72 mmol). The reaction was warmed to ambient temperature, and after 1.5 h, was neutralized with NH_4Cl (0.5 g). The aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with saturated, aqueous Na_2SO_3. The aqueous Na_2SO_3 layer was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (35%→40%→50% EtOAc in hexanes) afforded 397 mg alcohol **234** and 137 mg of the undesired diastereomer **233** (91% overall yield, dr = 3:1) as colorless oils. Major isomer **234**: ^{1}H NMR (400 MHz, C_6D_6) δ 7.39 (d, *J* = 7.1 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 2H), 7.24-7.14 (m, 6H), 7.09 (m, 2H), 6.77 (d, *J* = 8.7 Hz, 2H), 4.68 (dd, *J* = 1.8, 11.6 Hz, 1H), 4.65 (AB, J_{AB} = 12.6 Hz, $\Delta\nu_{AB}$ = 90.6 Hz, 2H), 4.36 (m, 1H), 4.31 (s, 2H), 4.27 (AB, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 112.1 Hz, 2H), 4.20 (m, 2H), 4.00 (m, 1H), 3.75 (m, 1H), 3.71 (d, *J* = 2.7 Hz, 1H), 3.57-3.45 (m, 2H), 3.41-3.30 (m, 5H), 3.25 (m, 1H), 3.06 (s, 1H), 2.94 (dd, *J* = 2.6, 9.5 Hz, 1H), 2.49-2.41 (m, 2H), 2.16-1.91 (m, 5H), 1.86 (m, 1H), 1.79-1.59 (m, 7H), 1.52-1.40 (m, 4H), 1.26 (s, 9H), 1.18 (s, 21H); ^{13}C NMR (100 MHz, C_6D_6) δ178.0, 159.7, 140.0, 139.5. 131.0, 129.5, 128.5, 127.7, 127.5, 127.4, 114.0, 82.5, 81.5, 80.9, 80.4, 74.4, 73.7, 72.9, 72.1, 71.7, 71.1, 70.4, 69.2, 66.0, 62.7, 54.7, 43.8, 39.8, 39.1, 34.0, 33.5, 29.7, 27.7, 27.6, 27.5, 20.8, 18.43, 18.38, 13.1; IR (film) 3438, 3031, 2942, 2866, 1728, 1612, 1514, 1456, 1364, 1248, 1158, 1102, 1038, 888, 822, 737, 698, 436 cm^{-1}; $[\alpha]^{23}_D$ = +28.1 (c 0.009, CH_2Cl_2); MS (ESI) for $C_{57}H_{86}O_{11}Si$ [M + Na] calc 997.6, found 997.6.

Minor isomer **233**: ^{1}H NMR (400 MHz, C_6D_6) δ 7.46 (d, *J* = 7.4 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 2H), 7.25-7.07 (m, 8H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.73 (AB, J_{AB} = 12.5 Hz, $\Delta\nu_{AB}$ = 80.5 Hz, 2H), 4.54 (m, 1H), 4.34-4.27 (m, 4H), 4.22 (AB, J_{AB} = 11.3 Hz, $\Delta\nu_{AB}$ = 140.7 Hz, 2H), 4.20 (m, 1H), 4.13 (dd, *J* = 2.9, 11.6 Hz, 1H), 3.81 (m, 1H), 3.75-3.67 (m, 2H), 3.40-3.29 (m, 6H), 3.18 (d, *J* = 7.2 Hz, 1H), 2.51 (m, 1H), 2.32 (s, 1H), 2.23 (m, 1H), 2.06 (m, 1H), 1.98-1.77 (m, 5H), 1.76-1.64 (m, 5H), 1.57-1.37 (m, 6H), 1.25 (s, 9H), 1.09 (s, 21H); ^{13}C NMR (100 MHz, C_6D_6) δ 178.1, 159.8, 140.1, 139.6, 130.9, 129.4, 128.54, 128.47, 127.7, 127.6, 127.43, 127.42, 114.1, 84.4, 79.8, 75.9, 74.6, 74.3, 74.0, 73.0, 72.9, 72.6, 71.6, 71.33, 71.28, 70.4, 65.8, 60.2, 54.8, 39.5, 39.1, 34.1, 33.2, 29.8, 27.7, 27.4, 18.43, 18.38, 13.2; IR (film) 3462, 3062, 2942, 1727, 1613, 1514, 1455, 1364, 1285, 1248, 1098, 948, 883, 822, 736, 680, 451cm^{-1}; $[\alpha]^{23}_D$ = +14.5 (c 0.015, CH_2Cl_2); MS (ESI) for $C_{57}H_{86}O_{11}Si$ [M + Na] calc 997.6, found 997.6.



Ketone 236.

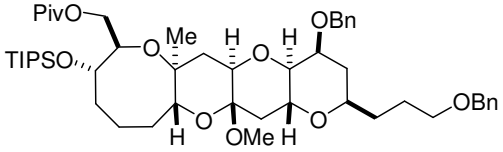
From alcohol **234**: To a stirred solution of alcohol **234** (162 mg, 0.166 mmol) in CH_2Cl_2 (1.7 mL) was added Dess-Martin periodinane (141 mg, 0.332 mmol). After 45 min, the cloudy solution was diluted with hexanes and a 5:1 mixture of saturated, aqueous $Na_2S_2O_3$ / $NaHCO_3$ solutions. The aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over

sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (30% EtOAc in hexanes) gave 155 mg (96%) of ketone **236** as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 7.33 (d, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.21-7.08 (m, 8H), 6.76 (d, *J* = 8.6 Hz, 2H), 4.74 (d, *J* = 11.1 Hz, 1H), 4.58 (AB, J_{AB} = 12.3 Hz, $\Delta\nu_{AB}$ = 93.5 Hz, 2H), 4.33-4.28 (m, 3H), 4.22 (AB, J_{AB} = 11.1 Hz, $\Delta\nu_{AB}$ = 148.8 Hz, 2H), 4.18-4.00 (m, 4H), 3.76 (d, *J* = 2.6 Hz, 1H), 3.69 (m, 1H), 3.37-3.25 (m, 7H), 2.83 (dd, *J* = 5.6, 14.6 Hz, 1H), 2.53 (d, *J* = 11.9 Hz, 1H), 2.38 (dd, *J* = 11.7, 14.4 Hz, 1H), 2.27 (m, 1H), 2.06-1.83 (m, 5H), 1.70-1.48 (m, 6H), 1.46-1.37 (m, 4H), 1.20 (s, 9H), 1.08 (s, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 203.8177.7, 159.5, 139.5, 139.4, 131.0, 129.3, 128.5, 128.2, 128.0, 127.8, 127.7, 127.50, 127.48, 113.9, 83.7, 80.9, 80.4, 79.1, 74.2, 73.4, 72.93, 72.89, 72.1, 71.9, 71.2, 70.2, 65.8, 64.2, 54.8, 45.8, 40.0, 38.9, 34.2, 33.0, 29.5, 27.52, 27.47, 20.4; IR (film) 3064, 2942, 1727, 1612, 1514, 1455, 1284, 1248, 1101, 882, 822, 736, 697, 437 cm^{-1}; $[\alpha]^{23}_D$ = +34.0 (c 0.008, CH_2Cl_2); MS (ESI) for $C_{57}H_{84}O_{11}Si$ [M + Na] calc 995.6, found 995.6.

From alcohol **233**: To a stirred solution of alcohol **233** (137 mg, 0.140 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (119 mg, 0.28 mmol). After 40 min, the cloudy solution was diluted with hexanes and a 5:1 mixture of saturated, aqueous $Na_2S_2O_3$ / $NaHCO_3$ solutions. The aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (30% EtOAc in hexanes) gave 110 mg (80%) of the ketone as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 7.50 (d, *J* = 7.3 Hz, 2H), 7.33-7.08 (m, 10H), 6.84 (d, *J* =

8.6 Hz, 2H), 4.84 (dd, J = 2.0, 11.6 Hz, 1H), 4.75 (AB, J_{AB} = 12.6 Hz, $\Delta\nu_{AB}$ = 100.4 Hz, 2H), 4.74 (dd, J = 2.6, 9.1 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.37-4.32 (m, 3H), 4.28-4.16 (m, 2H), 4.14 (dd, J = 2.8, 11.6 Hz, 1H), 4.06 (d, J = 11.2 Hz, 1H), 3.73 (m, 2H), 3.41-3.29 (m, 6H), 3.21 (d, J = 7.3 Hz, 1H), 2.82 (dd, J = 5.7, 15.8 Hz, 1H), 2.41-2.31 (m, 2H), 2.12-1.82 (m, 4H), 1.80-1.55 (m, 8H), 1.52 (s, 3H), 1.44 (m, 1H), 1.25 (s, 9H), 1.13 (s, 21H); ^{13}C NMR (100 MHz, C_6D_6) δ 206.9, 177.8, 159.8, 139.9, 139.5, 131.0, 129.3, 128.6, 128.5, 127.59, 127.56, 127.53, 114.1, 84.3, 79.2, 79.1, 74.2, 73.5, 73.4, 73.0, 72.3, 71.7, 71.3, 70.2, 63.1, 54.7, 44.1, 39.0, 33.6, 27.5, 18.44, 18.38, 13.2; IR (film) 3054, 2943, 1725, 1612, 1514, 1460, 1365, 1265, 1096, 883, 822, 737, 457cm^{-1}; $[\alpha]^{23}_D$ = +2.5 (c 0.017, CH_2Cl_2); MS (ESI) for $C_{57}H_{84}O_{11}Si$ [M + Na] calc 995.6, found 995.6.

To a stirred solution of the ketone obtained as above (71 mg, 0.073 mmol) in CH_2Cl_2 (5.3 mL) was added DBU (24 μL, 0.16 mmol). This solution was heated to reflux, and after 20 h, the reaction was cooled to ambient temperature and poured into 1 M $NaHSO_4$. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (27% EtOAc in hexanes) afforded 12 mg ketone starting material and 50 mg (70%, 85% brsm) of ketone **236**.

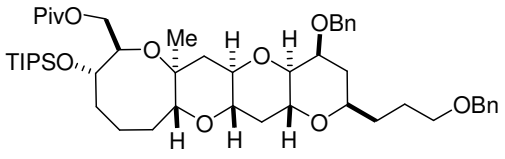


Mixed methoxy ketal 238.

To a stirred mixture of ketone **236** (424 mg, 0.436 mmol) in CH_2Cl_2 (6 mL) and pH 7 buffer solution (0.7 mL) at 0 °C was added DDQ (148 mg, 0.652 mmol). After 50 min, additional DDQ (8 mg, 0.04 mmol) was added, and after and additional 10 min, the red mixture was poured into saturated, aqueous $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (10% EtOAc in CH_2Cl_2→30% EtOAc in hexanes) afforded 331 mg (89%) of the hemiketal as a viscous, slightly yellow oil: ^{1}H NMR (400 MHz, C_6D_6) δ 7.43 (d, *J* = 7.9 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.28-7.21 (m, 4H), 7.15 (m, 2H), 4.84 (d, *J* = 10.7 Hz, 1H), 4.70 (AB, J_{AB} = 12.4 Hz, $\Delta\nu_{AB}$ = 72.0 Hz, 2H), 4.46 (m, 1H), 4.39 (s, 2H), 4.33 (dd, *J* = 1.9, 9.1 Hz, 1H), 4.13 (m, 1H), 3.98 (s, 2H), 3.83 (m, 2H), 3.43-3.34 (m, 3H), 3.10 (dd, *J* = 2.4, 9.7 Hz, 1H), 3.00 (s, 1H), 2.57-2.46 (m, 2H), 2.28 (t, *J* = 12.2 Hz, 1H), 2.20-2.12 (m, 2H), 2.00-1.50 (m, 11H), 1.35 (s, 3H), 1.28 (s, 9H), 1.18-1.13 (m, 21H); ^{13}C NMR (100 MHz, C_6D_6) δ 177.8, 139.9,139.4, 128.50, 128.49, 127.73, 127.67, 127.51, 127.45, 93.8, 82.7, 78.3, 76.5, 73.7, 73.4, 72.9, 72.6, 72.5, 70.2, 66.7, 63.0, 42.5, 40.5, 38.9, 33.5, 29.6, 27.6, 27.5, 18.40, 18.36, 16.2, 13.1; IR (film) 3448, 3059, 2944, 2868, 1737, 1455, 1373, 1244, 1099, 1046, 739, 700, 453 cm^{-1}; $[\alpha]^{23}_D$ = +73.3 (c 0.011, CH_2Cl_2); MS (ESI) for $C_{49}H_{76}O_{10}Si$ [M + Na] calc 875.5, found 875.8.

To a solution of the hemiketal obtained as above (107 mg, 0.125 mmol) in MeOH (6.2 mL) was added PPTS (63 mg, 0.25 mmol). This solution was heated to reflux and stirred for 12 hours. The reaction was cooled to ambient temperature and

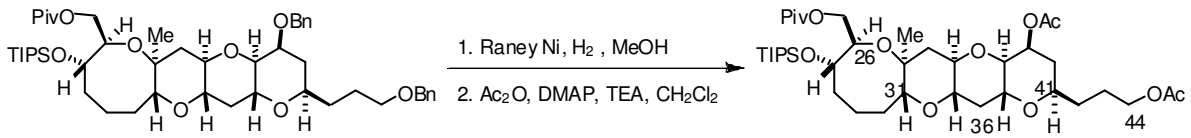
poured into a mixture of EtOAc, hexanes, and saturated, aqueous $NaHCO_3$. The aqueous layer was extracted with a hexanes/EtOAc mixture (1:1) twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (30%→35% EtOAc in hexanes) afforded 7 mg of hemiketal starting material and 92 mg (84%, 90% brsm) of mixed methoxy ketal **25** as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 7.41 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.20-7.14 (m, 4H), 7.11-7.06 (m, 2H), 5.04 (d, *J* = 12.2 Hz, 1H), 4.77 (d, *J* = 10.4 Hz, 1H), 4.64 (d, *J* = 12.2 Hz, 1H), 4.31 (s, 2H), 4.26 (ddd, *J* = 4.8, 9.7, 11.5 Hz, 1H), 4.04 (m, 1H), 3.88 (s, 2H), 3.83-3.73 (m, 3H), 3.40-3.31 (m, 3H), 3.08 (dd, *J* = 2.4, 9.6 Hz, 1H) 3.04 (s, 3H), 2.61 (dd, *J* = 4.8, 12.7 Hz, 1H), 2.56 (m, 1H), 2.48 (t, *J* = 12.2 Hz, 1H), 2.09 (dd, *J* = 4.4, 11.6 Hz, 1H), 2.03 (d, *J* = 13.3 Hz, 1H), 1.95-1.60 (m, 8H), 1.59-1.37 (m, 3H), 1.28 (s, 3H), 1.19 (s, 9H), 1.12-1.02 (m, 21H); ^{13}C NMR (100 MHz, C_6D_6) δ 177.8, 140.2, 139.6, 128.5, 128.4, 127.9, 127.6, 127.4, 96.5, 83.0, 78.9, 76.6, 73.9, 73.8, 73.5, 73.2, 72.9, 72.7, 72.5, 70.4, 66.7, 62.1, 46.8, 40.5, 38.8, 36.0, 34.2, 29.7, 28.4, 27.7, 27.5, 19.8, 18.39, 18.36, 16.4, 13.1; IR (film) 3030, 2944, 2867, 2279, 1731, 1455, 1364, 1330, 1283, 1205, 1161, 1101, 1030, 883, 813, 735, 697, 680, 499 cm^{-1}; $[\alpha]^{23}_D$ = +64.0 (c 0.010, CH_2Cl_2); MS (ESI) for $C_{50}H_{78}O_{10}Si$ [M+H] calc 867.5, found 867.5.



GHIJ fragment 197.

To a stirred solution of mixed methoxy ketal **238** (81 mg, 0.093 mmol) and Et_3SiH (222 μL, 1.39 mmol) in CH_2Cl_2 (1.9 mL) at -30 °C was added $BF_3{\cdot}OEt_2$ (118 μL, 0.93 mmol) dropwise. After 30 minutes, the reaction temperature was allowed to rise to 0 °C over 30 min. After 20 minutes at 0 °C, the reaction was quenched with saturated, aqueous $NaHCO_3$, and the resulting mixture was warmed to ambient temperature. The aqueous layer was extracted with EtOAc three times, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (10%→20% EtOAc in CH_2Cl_2) afforded 75 mg (96%) of GHIJ fragment **197** as a colorless oil: ^1H NMR (400 MHz, C_6D_6) δ 7.38 (d, *J* = 7.3 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.22-7.13 (m, 4H), 7.11-7.05 (m, 2H), 4.74 (dd, *J* = 1.7, 11.1 Hz, 1H), 4.64 (AB, J_{AB} = 12.4 Hz, $\Delta\nu_{AB}$ = 87.8 Hz, 2H), 4.33 (s, 2H), 4.05 (dd, *J* = 5.6, 11.2 Hz, 1H), 4.00 (m, 1H), 3.95-3.86 (m, 2H), 3.74 (m, 2H), 3.38 (m, 2H), 3.23 (dd, *J* = 1.9, 8.5 Hz, 1H), 3.10 (ddd, *J* = 4.5, 9.2, 11.8 Hz, 1H), 2.96 (dd, *J* = 2.6, 9.5 Hz, 1H), 2.84 (ddd, *J* = 3.8, 11.7, 15.2 Hz, 1H), 2.51 (m, 1H), 2.42-2.31 (m, 2H), 2.06 (m, 1H), 1.96-1.73 (m, 5H), 1.70-1.43 (m, 7H), 1.25 (s, 3H), 1.21 (s, 9H), 1.13-0.97 (m, 21H); ^{13}C NMR (100 MHz, C_6D_6) δ 177.8, 140.0, 139.5, 128.48, 128.45, 127.7, 127.5, 127.4, 83.6, 81.8, 78.5, 77.7, 76.4, 73.8, 72.9, 72.5, 72.2, 70.3, 66.7, 63.1, 45.7, 38.9, 36.6, 33.7, 29.7, 28.7, 27.7, 27.5, 19.6, 18.39, 18.35, 16.8, 13.1; IR (film) 3031, 2944, 2869, 1737, 1457, 1374, 1241, 1142, 1100, 1048, 735, 699, 543 cm^{-1}; $[\alpha]^{23}_D$ = +64.8 (c 0.010, CH_2Cl_2); MS (ESI) for $C_{49}H_{76}O_9Si$ [M+Na] calc 859.5, found 859.5.

5. Stereochemical Characterization of GHIJ fragment **197**



197 **239**

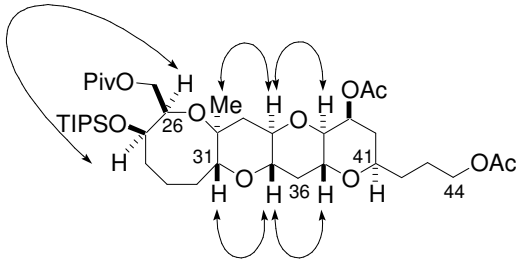
Preparation of diacetate derivative 239.

To a stirred solution of GHIJ fragment **197** (4 mg, 5 μmol) in MeOH (1.5 mL) was added Raney Nickel 2800 (ca. 100 mg), and a hydrogen atmosphere was established. After 20 h, the heterogeneous mixture was filtered through a frit, rinsing with MeOH. The filtrate was diluted with benzene and concentrated in vacuo to azeotropically remove the water. Purification through a short silica plug (80% EtOAc in hexanes) afforded 2 mg of the diol, which was used immediately in the next reaction: ^{1}H NMR (500 MHz, C_6D_6) δ 4.80 (dd, *J* = 2.2, 11.3 Hz, 1H), 4.08 (dd, *J* = 5.6, 11.3 Hz, 1H), 3.99-3.93 (m, 2H), 3.89 (m, 1H), 3.79 (m, 1H), 3.67 (m, 1H), 3.47 (m, 2H), 3.28 (d, *J* = 9.2 Hz, 1H), 3.14 (ddd, *J* = 4.5, 9.3, 11.9 Hz, 1H), 2.84-2.77 (m, 2H), 2.45-2.36 (m, 2H), 2.30 (dd, *J* = 4.4, 11.8 Hz, 1H), 2.11 (m, 1H), 1.98-1.73 (m, 5H), 1.65-1.40 (m, 9H), 1.25 (s, 3H), 1.23 (s, 9H), 1.10 (s, 21H).

To a stirred solution of the diol obtained as above (2 mg, 3 μmol) in CH_2Cl_2 (150 μL) was added DMAP (4 mg, 33 μmol), TEA (20 μL, 140 μmol), and Ac_2O (7 μL, 74 μmol). After 3 h, the solution was diluted with saturated, aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc twice, and the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo. Purification by flash chromatography (35% EtOAc in hexanes) provided 2 mg of the diacetate derivative **239**: ^{1}H NMR (500 MHz, C_6D_6) δ 5.37 (m, *H*39, 1H), 4.76 (d,

*H*26, *J* = 11.0 Hz, 1H), 4.07-3.96 (m, C*H*$_2$OPiv, *H*27, 3H), 3.94-3.86 (m, *H*44, 2H), 3.83 (m, *H*37, 1H), 3.54 (m, *H*41, 1H), 3.27 (d, *H*31, *J* = 7.8 Hz, 1H), 3.11 (ddd, *H*34, *J* = 4.6, 9.4, 12.1 Hz, 1H), 2.98 (m, *H*35, 1H), 2.83 (dd, *H*38, *J* = 3.0, 9.6 Hz, 1H), 2.42 (m, H_{eq}36, 1H), 2.36 (dd, H_{eq}33, *J* = 4.4, 11.9 Hz, 1H), 2.11-2.00 (m, 2H), 1.95-1.76 (m, includes H_{ax}33, 4H), 1.74-1.53 (m, 11H), 1.51-1.34 (m, 3H), 1.27 (s, C*H*$_3$, 3H), 1.19 (s, C=OC(C*H*$_3$)$_3$ 9H), 0.99 (s, Si(C$_3$*H*$_7$)$_3$, 21H); ^{13}C NMR (125 MHz, C_6D_6) δ 177.8, 170.1, 169.5, 83.9, 78.5, 78.4, 77.8, 76.3, 73.8, 72.4, 71.5, 68.1, 66.4, 64.1, 63.4, 45.5, 38.8, 36.5, 32.6, 30.2, 29.0, 28.8, 26.4, 20.9, 20.5, 18.4, 18.3, 16.7, 13.0; . MS (ESI) for $C_{39}H_{68}O_{11}Si$ [M + Na] calc 763.4, found 763.4.

Observed key NOESY interactions:



REFERENCES

1. Faulkner, J. D. *Nat. Prod. Rep.* **2002**, *19*, 1.

2. Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc*. **1981**, *103*, 6773.

3. Shimizu, Y.; Chou, H.-N.; Bando, H.; Van Duyne, G.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514.

4. Prasad, A. V. K.; Shimizu, Y. *J. Am. Chem. Soc*. **1989**, *111*, 6476.

5. Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, P. M. Jr.; Baden, D. G. *J. Nat. Prod.* **2005,** *68,* 2.

6. Satake, M.; Murata, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 361.

7. Murata, M.; Legrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc*. **1989**, *111*, 8929.

8. Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem*. **1992**, *57*, 5448.

9. Zheng, W.; DeMattei, J. A.; Wu, J.-P.; Duan, J.-W.; Cook, L. R.; Oinuma, H.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 7946 and references therein.

10. Satake, M.; Shoji, M.; Oshima, Y.; Naoki, H.; Fujita, T.; Yasumoto, T. *Tetrahedron Lett.* **2002**, *43*, 5829.

11. Takahashi, H.; Kusumi, T.; Kan, Y.; Satake, M.; Yasumoto, T. *Tetrahedron Lett.* **1996**, *37*, 7087 and references therein.

12. Okaichi, T.; Anderson, D. M.; Nemoto, T. *Red Tides. Biology, Enviromental Science, and Toxicology*; Elsevier: New York, 1989.

13. Fleming, L.E.; Backer, L. C.; Baden, D. G. *Environmental Health Perspectives* **2005,** *113*, 618.

14. Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Re*v. **1995**, *95*, 1953.

15. Baden, D. G. *FASEB J*. **1989**, *3*, 1807.

16. Gawley, R. E.; Rein, K. S.; Kinoshita, M.; Baden, D. G. *Toxicon* **1992**, *30,* 780.

17. Dechraoui, M.-Y.; Naar, J.; Pauillac, S.; Legrand, A.-M. *Toxicon* **1999**, *37*, 125.

18. Inoue, M. *Chem. Rev.* **2005,** *105,* 4379.

19. Nakata, T. *Chem. Rev.* **2005,** *105,* 4314.

20. Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 10252.

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

22. Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K.; *J. Am. Chem. Soc*. **1989**, *111*, 5330.

23. K. C. Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997,** *119,* 5467.

24. Allwein, S. P.; Cox, J. M.; Howard, B. E.; Johnson, H. W. B.; Rainier, J. D. *Tetrahedron* **2002**, *58,* 1997.

25. Roberts, S. W.; Rainier, J. D. *Org. Lett.* **2007**, *9*, 2227.

26. Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.

27. Nakanishi, K. *Toxicon* **1985**, *23*, 473.

28. Valentine, J. C.; McDonald, F. E.; Neiwert, W. A.; Hardcastle, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 4586 and references therein.

29. Graham L. Simpson, G. L..; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056.

30. Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett*. **1999**, *40*, 2811.

31. Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett*. **1999**, *1*, 1099–1101.

32. Kadota, I.; Abe, T.; Sato, Y.; Kabuto, C.; Yamamoto, Y. *Tetrahedron Lett.* **2006**, *47*, 6545.

33. Clark, S. J.; Joanne Conroy, J.; Blake, A. J. *Org. Lett*., **2007**, *9*, 2091.

34. Clark, S. J.; Grainger, D. M.; Ehkirch, A. A-C.; Blake, A. J.; Wilson, C. *Org. Lett*., **2007**, *9*, 1033.

35. Barry M. Trost, B. M.; Rhee, Y. H. *Org. Lett.* **2006***, 4,* 2311.

36. Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc*. **1989**, *111*, 5321 and references therein.

37. Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075.

38. Fuwa, H.; Ebine,M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc*. **2006**, *128*, 16989.

39. Oishi, T.; Miho Suzuki, M.; Watanabe, K.; Murata, M. *Tetrahedron Lett*. **2006**, *47,* 3975.

40. Sato, K.; Sasaki, M. *Angew. Chem. Int. Ed*. **2007**, *46*, 2518.

41. Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem*. **2000**, *65*, 191.

42. Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc*. **2002**, *124*, 3562.

43. Kadota, I.; Ueno, H.; Sato, Y.; Yamamoto, Y.; *Tetrahedron Lett.* **2006**, *47,* 89.

44. Suzuki, K.; Nakata, T. *Org. Lett.* **2002**, *4*, 2739.

45. Nicolaou, K. C.; Yang, Z.; Shi, G.-Q.; Gunzner, J. L.; Agrios, K. A.; Gartner, P. *Nature* **1998**, *392*, 264.

46. (a) Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J*. **1999**, *5*, 599. (b) Nicolaou, K. C.; Wallace, P. A.; Shi, S.; Ouellette, M. A.; Bunnage, M. E.; Gunzner, J. L.; Agrios, K. A.; Shi, G.-q.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 618. (c) Nicolaou, K. C.; Shi, G.-q.; Gunzner, J. L.; Gärtner, P.; Wallace, P. A.; Ouellette, M. A.; Shi, S.; Bunnage, M. E.; Agrios, K. A.; Veale, C. A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C. V. C.; Ogilvie, W. W.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 628. (d) Nicolaou, K. C. Gunzner, J. L.; Shi, G.-q.; Agrios, K. A.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 646.

47. Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 588.

48. Nicolaou, K. C.; Reddy, K. R.; Skototas, G.; Sato, F.; Xiao, K.-Y. *J. Am. Chem. Soc.* **1992**, *114*, 7935.

49. (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997,** *119*, 7883. (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000,** *2*, 775. (c) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001,** *66*, 894. (d) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003,** *5*, 591. (e) Crimmins, M. T.; She, J. *Synlett* **2004,** *8*, 1371. (f) Crimmins, M. T.; Shamszad, M. *Org. Lett.* **2007,** *9*, 149.

50. Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165.

51. (a) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004,** *126*, 10264. (b) Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005,** *127*, 17200. (c) Crimmins, M. T.; Brown, B. H.; Plake, H. R. *J. Am. Chem. Soc.* **2006,** *128*, 1371.

52. (a) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548. (b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (c) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029. (d) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473. (e) Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817. (f) Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592. (g) Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2003**, *5*, 3009.

53. Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

54. Crimmins, M. T.; McDougall, P. J.; Ellis, J. M. *Org. Lett.* **2006**, *8*, 4079.

55. Crimmins, M. T.; McDougall, P. J.; Emmitte, K. A. *Org. Lett.* **2005**, *7*, 4033.

56. Crimmins, M. T.; Cleary, P. A. *Heterocycles* 2003, *61*, 87.

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

58. Crabtree, R. H.; Felkin, H.; Fillebeen-Khan, T.; Morris, G. E. *J. Organomet. Chem.* **1979**, *168*, 183.

59. Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62,* 7507.

60. Cleary, P. A. Ph. D. Thesis. University of North Carolina at Chapel Hill, Chapel Hill, 2003.

61. Crimmins, M. T.; Zuccarello, J. L.; Cleary, P. A.; Parrish, J. D. *Org. Lett.* **2006**, *8*, 15.

62. Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852.

63. Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449.

64. Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.

65. Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett*. **1984**, *25*, 2383.

66. Blasde, L. K.; Myers, A. G. *Org. Lett.* **2005**, *7*, 4281.

67. Alvarez-Ibarra, C.; Arias, S.; Banon, G.; Fernandez, M. J.; Rodriguez, M.; Sinisterra, V. *J. Chem. Soc., Chem. Comm.* **1987**, 1509.

68. Paterson, I.; Yeung, K.-S.; Smaill, J. B. *Synlett* **1993**, 774.

69. Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627.

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

71. Tsukano, C.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4326.

72. Brown, H. C.; Mandal, A. K.; Yoon, N. M.; Singaram, B.; Schwier, J. R.; Jadhav, P. *J. Org. Chem.* **1982**, *47*, 5069.

73. Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1993**, *58*, 5130.

74. Ellis, J. M. Ph. D. Thesis, University of North Carolina at Chapel Hill, Chapel Hill, 2007.

75. Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J. H.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett*. **2003**, *44*, 57.