Characterization and Synthetic Studies of Okundoperoxide and Synthetic Studies of Scyphostatin

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Abstract

The research presented in this thesis comprises two main projects: the structural characterization and synthetic studies of okundoperoxide (Chapter 4) and synthetic studies of scyphostatin (Chapter 3). In Chapter 4, I describe the characterization of a new antimalarial natural product. I also outline our biosynthetic hypothesis, which motivated us to launch a synthetic project to investigate these ideas. In Chapter 3, I describe work leading to a concise synthesis of the polar core of (+)-scyphostatin. This work included the study of a rare transformation, the vinylogous Payne rearrangement. Also, this rearrangement was found to be useful in a dynamic kinetic resolution to resolve a pair of pseudoenantiomers. Two smaller projects are discussed in the first two chapters. In Chapter 1, I discuss synthetic work directed towards preparation of an analog of kendomycin. In Chapter 2, I present reactions of various phenols with a nitrogen-based electrophile, N-phenyl-1,2,4-triazolinedione.

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List of Abbreviations

Ac	Acetyl
AcOH	Acetic acid
Ar	Aryl
BHT	Butylated hydroxy toluene
Bn	Benzyl ($C_6H_5CH_2$-)
BPS (TBDPS)	*tertiary*-Butyldiphenylsilyl
BPSCl (TBDPSCl)	*tertiary*-Butyldiphenylsilyl chloride
n-Bu or ^{n}Bu	normal-Butyl
t-Bu or ^{t}Bu	tertiary-Butyl
Calcd	Calculated
CAN	Cerric ammonium nitrate
CBz	Carbobenzyloxy
°C	degrees Celsius
CH_2Cl_2	Dichloromethane
COSY	Correlated spectroscopy
CSA	(+/-)-10-Camphorsulphonic acid
δ	Chemical shift, in NMR spectroscopy
d	Doublet, in NMR spectroscopy
DBU	1,8-Diazabicylco[5.4.0]undec-7-ene
DCC	*N*,*N*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	Diisobutylaluminum hydride

DIPEA	Diisopropylethylamine
DKR	Dynamic kinetic resolution
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMF	Dimthylformamide
DMP	Dess Martin Periodinane
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
EDCI	1-Ethyl-3-(3-Dimethylaminopropyl)carbodiimide
ESI	Electrospray Ionization
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
equiv	Equivalent
ee	Enantiomeric excess
er	Enantiomeric ratio
g	Gram(s)
G1	The first generation Grubbs initiator
G2	The second generation Grubbs initiator
GC-MS or GCMS	Capillary gas chromatography-mass spectrometry
HMBC	Hetero-nuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum correhence

HMPA	Hexamethylphosphoric triamide
HPLC	High pressure (or performance) liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz (cycles per second)
IC_{50}	50% of the concentration for complete inhibition of cellular viability
IR	Infrared
J	Coupling constant (NMR)
LC-MS or LCMS	Liquid chromatography-mass spectrometry
LDA	Lithium diisopropylamide
m	Multiplet, in NMR spectroscopy
*m*CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol
MHz	Megahertz
mol	Mole(s)
mmol	milliMole
MOM	Methoxymethyl
MOMCl	Methoxymethyl chloride
mp	Melting point
MPLC	Medium pressure liquid chromatography
4Å MS	4-angstrom molecular sieves
MTBE	Methyl *tertiary*-butyl ether

MTPA	α-Methoxytrifluoromethylphenylacetyl
NBS	*N*-bromosuccinimide
ND	not determined
NMR	Nuclear magnetic resonance
No-D	No deuterium
NOE	Nuclear Overhauser Effect/Enhancement
NR	no reaction
N-SMase	Neutral sphingomyelinase
p	pentet (NMR)
Ph	Phenyl
Ph_3P	Triphenylphosphine
PIDA	Phenyliodo(III)diacetate
PIFA	Phenyliodo(III)ditrifluoroacetate
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonic acid
PTAD	N-Phenyl-1,2,4-triazolinedione
*p*TsOH	*p*-Toluenesulfonic acid monohydrate
i-Pr or ^{i}Pr	Isopropyl
q	Quartet, in NMR spectroscopy
R	Rectus (configurational)
RCM	Ring-closing metathesis
R_f	Ratio to front
RT or rt	Room temperature

S	Sinister (configurational)
s	Singlet, in NMR spectroscopy
t	Triplet, in NMR spectroscopy
TBAF	Tetrabutylammonium fluoride
TBDPS (BPS)	*tertiary*-Butyldiphenylsilyl
TBDPSCl	*tertiary*-Butyldiphenylsilyl chloride
TBS	*tertiary*-Butyldimethylsilyl
TBSCl	*tertiary*-Butyldimethylsilyl chloride
TBSOTf	*tertiary*-Butyldimethylsilyl trifluoromethanesulfonate
TES	Triethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	tri*iso*propylsilyl
TIPSOTf	Tri*iso*propylsilyl trifluoromethanesulfonate
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
t_r	Retention time
Troc	Trichloroethyloxycarbonyl
Ts	para-Toluenesulfonyl

Chapter I. Synthetic Studies of a Kendomycin Analog

I.A. Introduction and Background

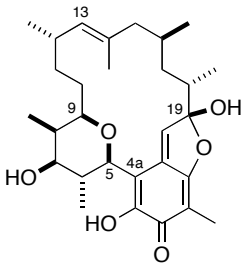
Although the primary focus of the majority of the projects within the Hoye group center around the usage of novel and efficient methods (many times biomimetic) to synthesize natural products, the kendomycin analog project described in this chapter also puts a great deal of emphasis on the structure of the final target itself. Since the aim of this project is to synthesize an analog of a natural product, it has a medicinal chemistry aspect to it. More specifically, we are interested in the biological activity of the simplified analog that we are attempting to construct. I will delve into both the specifics of the kendomycin analog structure and the inspiration for this approach in a later section. Even though this is a medicinal chemistry project, we are still staying true to our roots by proposing interesting and novel chemistry to synthesize the analog. We also propose a key transformation of a late-stage intermediate that relies on the inherent reactivity of the molecule, which is a theme that is similar to many of the biomimetic transformations proposed in other projects.

Kendomycin (**101**; Figure I-1) was isolated from *Streptomyces violaceoruber* in 1996 by Funahashi and co-workers.[1] Kendomycin was re-isolated in 2000 by Zeeck and co-workers from various strains of *Actinomycetes*, and it was this group that established the relative and absolute stereochemical features of kendomycin by single-crystal X-ray

[1] (a) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japan Patent 08231551 [A2960910], 1996; *Chem. Abstr.* **1997**, *126*, 6553. (b) Funahashi, Y.; Kawamura, N.; Ishimaru, T. Japan Patent 08231552, 1996; *Chem. Abstr.* **1996**, *125*, 326518.

analysis and modified Mosher ester analysis.[2] Kendomycin was initially found to have endothelin receptor antagonist activity and antiosteoporotic properties.[1,3] The Zeeck group later reported that kendomycin possessed potent cytotoxicity against various human tumor cell lines ($GI_{50} < 0.1$ μM for HMO2, HEP G2, MCF7) and antibacterial activity against a number of strains, including multi-resistant strains of *Staphylococcus aureus*.[2]

Figure I-1. Kendomycin (**101**), a Polyketide Macrocycle Isolated from *Streptomyces violaceoruber*.



kendomycin (***101***)

Kendomycin (**101**) has a number of unique structural features, which has made this a challenging target for synthetic chemists. The fully substituted tetrahydropyran ring (C5-C9) features five contiguous stereocenters. The all-carbon macrocyclic chain (C10-C18) of **101** contains three additional methyl stereocenters as well as a trisubstituted *(E)*-alkene (C13-C14). Finally, the quinone-methide-lactol chromophore (C4a-C19) of kendomycin is unprecedented among natural products. These unusual and challenging structural moieties motivated our group to devise a simplified analog of kendomycin that could possibly still contain significant biological properties. This structure will be discussed below in Section I.C.

[2] (a) "Structure and biosynthesis of kendomycin, a carbocyclic *ansa*-compound from *Streptomyces*," *J. Chem. Soc., Perkin Trans. 1* **2000**, 323-328. (b) "Biosynthesis of kendomycin: origin of the oxygen atoms and further investigations," *J. Chem. Soc., Perkin Trans. 1* **2000**, 2665-2670.

[3] Su, M. H.; Hosken, M. I.; Hotovec, B. J.; Johnston, T. L. U.S. Patent 5728727 [A 980317], 1998; *Chem. Abstr.* **1998**, *128*, 239489.

I.B. Previous Syntheses of Kendomycin

Due to the promising biological activity and challenging structural features of kendomycin (**101**), a number of research groups have attempted to synthesize this natural product. To date, there have been four total syntheses by the Lee group,[4] the Smith group,[5] the Panek group,[6] and the Mulzer group.[7] The Rychnovsky group reported a formal total synthesis,[8] and a number of other groups have reported synthetic studies toward kendomycin.[9] I will only highlight the Smith synthesis in this section because our synthetic strategy utilizes some of the chemistry they developed during this work. Also, I only ended up doing a limited amount of work on this project, so I don't feel it is worthwhile to go into great detail about the other syntheses and sythetic studies.

The Smith group reported the second total synthesis of kendomycin (**101**) in 2005,[5] and the retrosynthetic analysis is shown in Scheme I-1. Retrosynthetically, **101** could arise from **102** by TBS deprotection, hydrolysis of the vinylogous methyl ester

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[4] "Total Synthesis of Kendomycin: A Macro–*C*–Glycosidation Approach," Yuan, Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720–14721.

[5] "Total Synthesis of (–)-Kendomycin Exploiting a Petasis–Ferrier Rearrangement/Ring-Closing Olefin Metathesis Synthetic Strategy," Smith, A. B., III; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2005**, *127*, 6948–6949.

[6] "Total Synthesis of (–)-Kendomycin," Lowe, J. T.; Panek, J. S. *Org. Lett.* **2008**, *10*, 3813–3816.

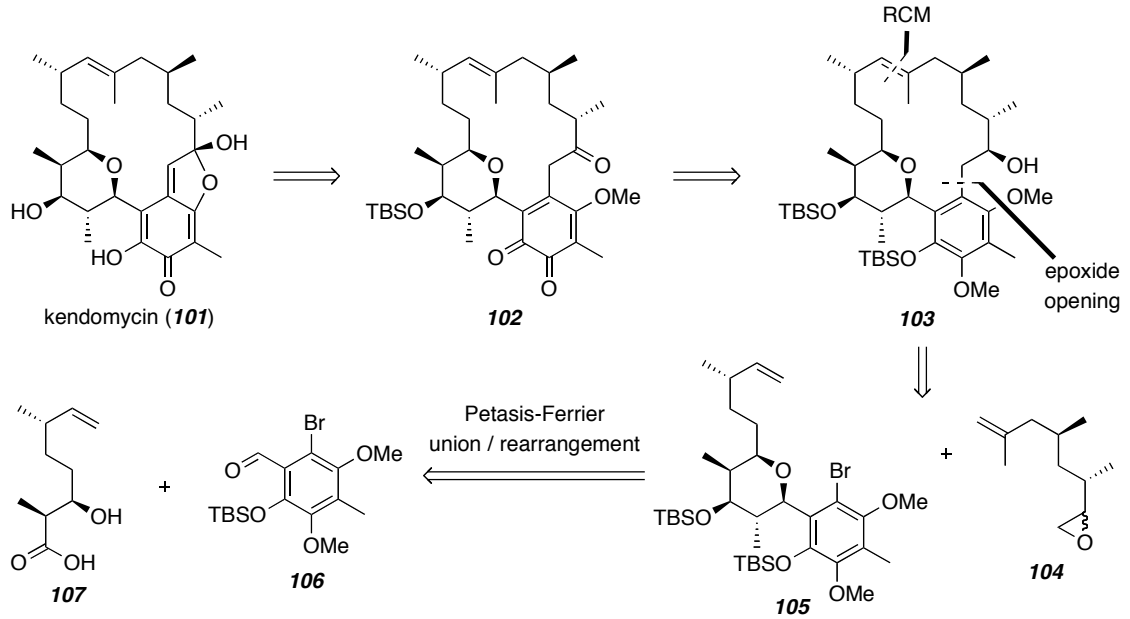
[7] "Total Synthesis of the Antibiotic Kendomycin by Macrocyclization using Photo-Fries Rearrangement and Ring-Closing Metathesis," Magauer, T.; Martin, H. J.; Mulzer, J. *Angew. Chem. Int. Ed.* **2009**, *Early View (published online)*.

[8] "Formal Synthesis of (–)-Kendomycin Featuring a Prins-Cyclization To Construct the Macrocycle," Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177–13181.

[9] (a) "Toward the synthesis of the carbacylic ansa antibiotic kendomycin," Mulzer, J.; Pichlmair, S.; Green, M. P.; Marques, M. M. B.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11980-11985. (b) "Ring-closing Metathesis Approach to a 16-Membered Macrocycle of Kendomycin," Sengoku, T.; Uemura, D.; Arimoto, H. *Chem. Lett.* **2007**, *36*, 726–727. (c) "Application of the Dötz Reaction to Construction of a Major Portion of the Ansa Macrocycle (–)-Kendomycin," White, J. D.; Smits, H. *Org. Lett.* **2005**, *7*, 235–238. (d) "Stereocontrolled [4+2]-Annulation Accessing Dihydropyrans: Synthesis of the C1a-C10 Fragment of Kendomycin," Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529–1532. (e) "Efforts toward the Total Synthesis of (–)-Kendomycin," Williams, D. R.; Shamim, K. *Org. Lett.* **2005**, *7*, 4161–4164.

followed by lactol formation, and tautomerization to the *para*-quinone methide. The alcohol **103** can be converted to the ketone-orthoquinone **102** by concomitant oxidation of the secondary alcohol and the phenol derived from selective TBS deprotection. Epoxide opening of **104** by the aryllithium species generated from **105** (lithium-halogen exchange) would furnish a diene, which could be cyclized by ring-closing metathesis (RCM) to give **103**. The Petasis-Ferrier union / rearrangement developed by the Smith group could be used to form the tetrahydropyran **105** from the aldehyde **106** and the β-hydroxy acid **107**.

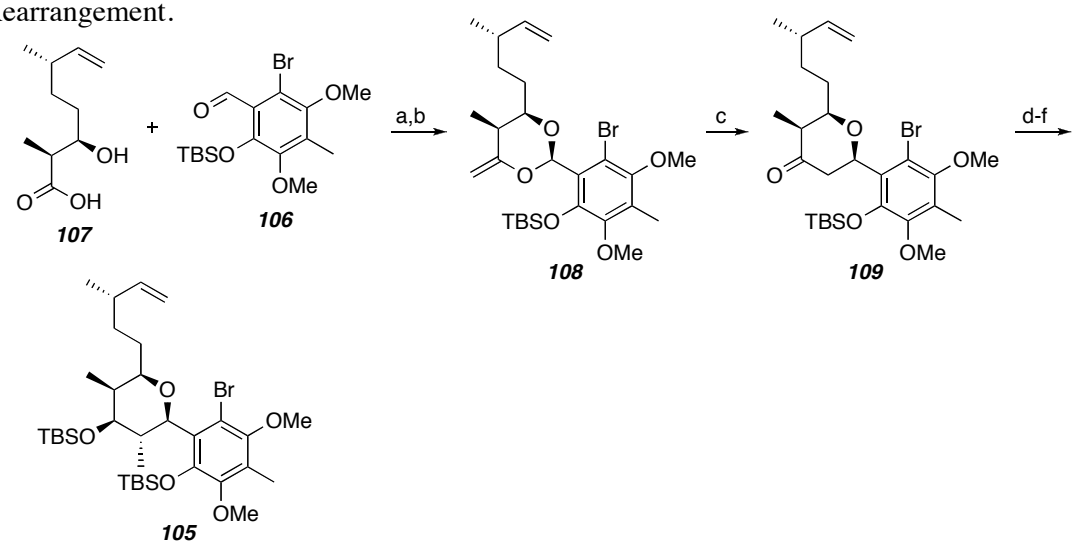
Scheme I-1. Smith Group's Kendomycin Retrosynthesis.



The synthesis of kendomycin (**101**) commenced (Scheme I-2) with the exposure of the β-hydroxy acid **107** (available in 3 steps from citronellene) and the aldehyde **106** (available in 5 steps from 2,4-dimethoxy-3-methylbenzaldehyde) to acidic conditions, which resulted in formation of a dioxanone that was subsequently methylenated using the Petasis reagent (Cp_2TiMe_2) to give the enol acetal **108**. The enol acetal **108** was treated with Me_2AlCl to effect the Ferrier rearrangement to yield the pyranone **109**.

Stereoselective methylation of **109** (LiHMDS, MeI) followed by $NaBH_4$ reduction (5:1 dr) of the ketone and subsequent TBS protection furnished the tetrahydropyran **105**.

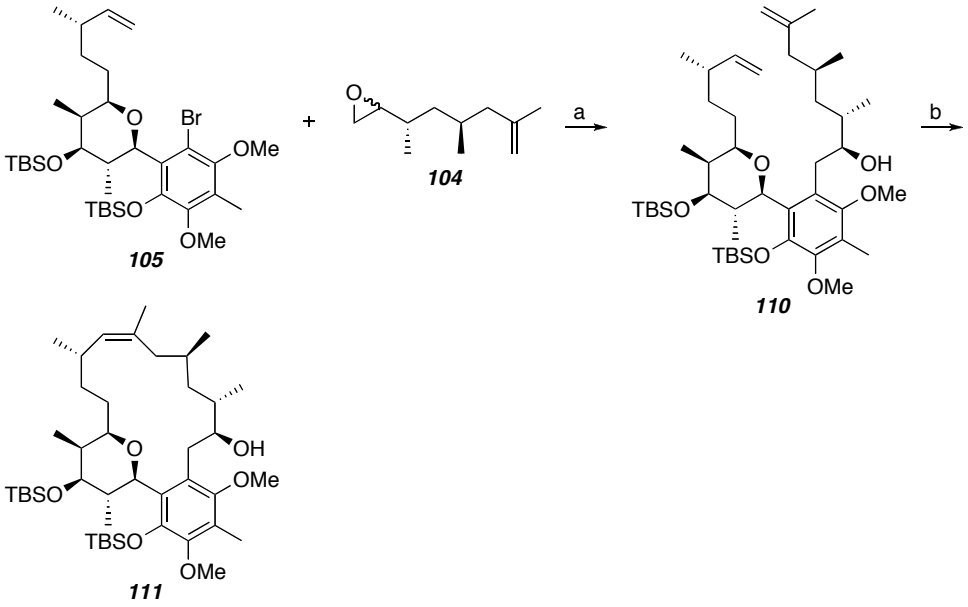
Scheme I-2. Synthesis of the Tetrahydropyran **105** using the Petasis-Ferrier Union / Rearrangement.



Reagents and Conditions: (a) *i*-PrOTMS, TMSOTf, CH_2Cl_2, -78 ºC, 77%; (b) Cp_2TiMe_2, THF, 63 ºC, 85%; (c) Me_2AlCl, CH_2Cl_2, -78 ºC, 85%; (d) LiHMDS, MeI, THF, -78 ºC, 70%; (e) $NaBH_4$, EtOH, -78 ºC, 97%, 5:1 dr; (f) TBSOTf, 2,6-lutidine, CH_2Cl_2, -10 ºC, 95%.

The diene required for the RCM was constructed next (Scheme I-3). This was achieved by treating the aryl bromide **105** with *t*-BuLi to give the aryllithium species, which was then exposed to the epoxide **104** in the presence of BF_3•OEt_2 to yield the alcohol **110** (2:1 dr). When **110** was oxidized to the ketone, this RCM substrate did not undergo any macrocyclization. However, when **110** was exposed to RCM conditions (Grubb's 2nd-generation catalyst [G2]), the major alcohol diastereomer (β-epimer) cyclized to **111**, but the α-epimer of **110** did not react. Unfortunately, the cyclization product, **111**, contained a (*Z*)-alkene (confirmed by X-ray analysis) instead of the desired (*E*)-alkene. Smith and co-workers decided to move ahead with **111**, knowing that they would have to find a way change the alkene configuration.

Scheme I-3. Synthesis of Macrocycle **111** via RCM.



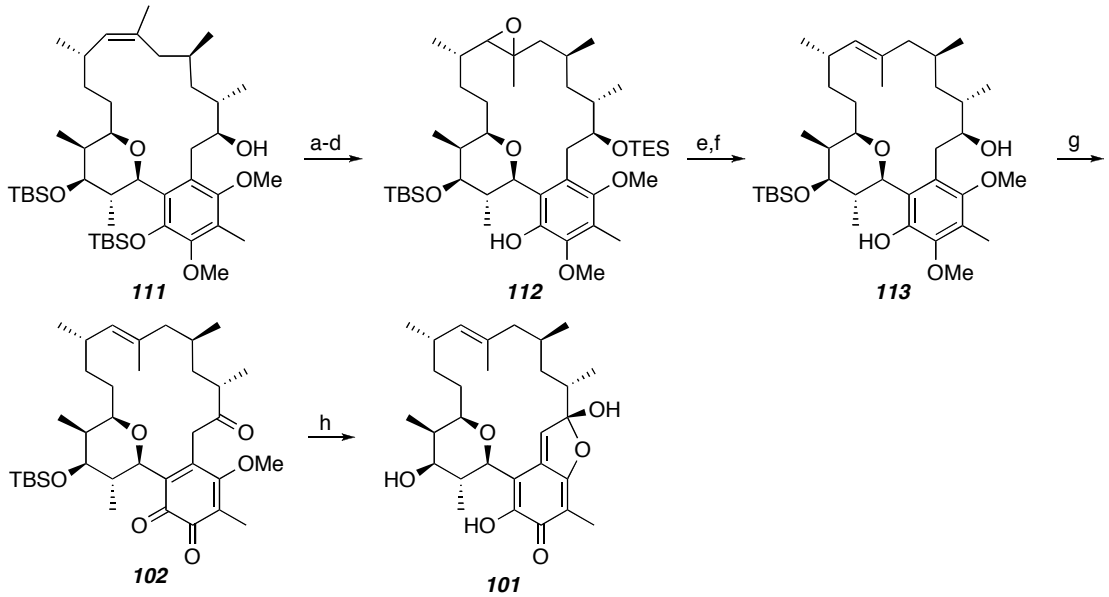
Reagents and Conditions: (a) *t*-BuLi, THF, -78 ºC; **104**, BF_3•OEt_2, THF, 60%, 2:1 dr; (b) **G2** (10 mol%), CH_2Cl_2, reflux, 57%.

The process of converting the *(Z)*-alkene of **111** to the *(E)*-alkene required six steps. This was accomplished (Scheme I-4) by protecting the alcohol of **111** with a TES group, followed by *cis* dihydroxylation (OsO_4) of the alkene, mesylation of the secondary alcohol, and base treatment ($BnNMe_3OH$) to yield the *trans* epoxide **112**. The phenolic TBS also was removed during the base treatment. The *(Z)*-alkene was then furnished by treatment of the *trans* epoxide **112** with a source of $[W^{4+}]$,[10] which results in deoxygenation with retention of configuration. Removal of the TES group with PPTS provided **113**. Exposure of **113** to Dess-Martin periodinane produced the ketone *ortho*-quinone **102**. Finally, treatment of **102** with aqueous HF resulted in TBS deprotection and hydrolysis of the vinylogous methyl ester, which allowed for formation of the lactol by attack of the ketone by the newly formed phenol. Tautomerization of the enone to the dienol resulted in the *para*-quinone methide **101**, which is kendomycin. This synthesis

[10] "Lower valent tungsten halides. New class of reagents for deoxygenation of organic molecules," Sharpless, K. B.; Umbreit, M. A.; Nieh, M. T.; Flood, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 6538–6540.

required 17 steps from the β-hydroxy acid **107** and the aldehyde **106** and was achieved in 1.1% overall yield.

Scheme I-4. Completion of Smith's Synthesis of Kendomycin (**101**).



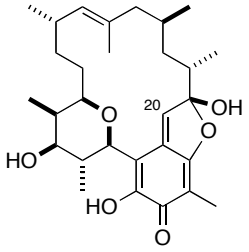
Reagents and Conditions: (a) TESOTf, DMAP, 2,6-lutidine, pyr, 0 ºC, 89%; (b) OsO_4, pyr, THF, 0 ºC, 78%; (c) MsCl, pyr, CH_2Cl_2, 0 ºC, 95%; (d) $BnNMe_3OH$, MeOH/THF, 0 ºC, 84%; (e) WCl_6, BuLi, THF, 0 ºC to rt, 71%; (f) PPTS, MeOH, 0 ºC, 95%; (g) Dess-Martin periodinane, pyr, CH_2Cl_2, 0 ºC to rt, 69%; (h) aq. HF, MeCN, rt, 40%.

I.C. An Analog of Kendomycin

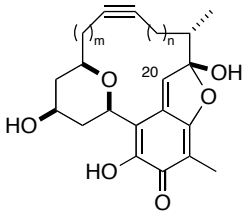
Structure **114 (**Figure I-2) represents a series of kendomycin analogs. It features an alkyne linker instead of the polyketide chain of **101**. This change simplifies the synthesis of **114** since 2 methyl stereocenters and the *(E)*-alkene, which presented a great challenge to the Smith group (Section I.B), have been removed from the structure. Also, an alkyne linker would allow for simple macrocyclization utilizing ring-closing alkyne metathesis (RCAM) in order to synthesize **114**. The number of methylene units (m, n = 1,2,3) could be changed on both sides of the alkyne to alter the macrocycle, which may affect both the efficiency of the RCAM macrocyclization and the biological activity of the analog **114**. Another feature of the analog **114** was removal of 2 methyl groups from the tetrahydropyran. This change would also simplify the synthesis of **114**, and we

believe that it would not greatly alter the 3 dimensional structure of **114** compared to kendomycin (**101**). Lastly, the *para*-quinone methide chromophore of **101** was left unchanged in the analog **114**. This moiety is believed to be the pharmacophore; specifically, conjugate addition to C20 has been implicated in the biological activity of kendomycin (**101**).[2] When **114** was modeled using Monte Carlo forcefield simulations, its 3-dimensional structure was shown to overlap favorably with that of kendomycin (**101**). Therefore, we believe we have devised an analog, **114**, that should require less effort to synthesize compared to **101** and that could mimic the biological activity of **101**.

Figure I-2. Structures of Kendomycin (**101**) and the Analog **114**.



101



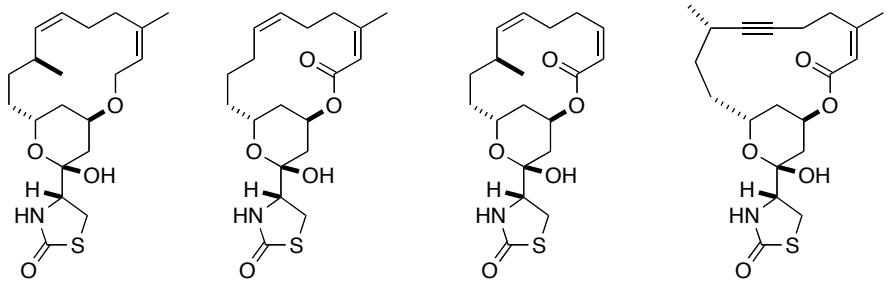
114

An example of a similar approach to generating analogs is Furstner and co-worker's synthesis of latrunculin B (**115**) and the analogs **116-118** (Figure I-3).[11] The analog **116** has an allylic methyl group removed from the macrocyclic tether, and the analog **117** is lacking a vinylic methyl group in the tether. The analog **118** contains an alkyne instead of the (*Z*)-alkene. A RCAM macrocyclization was used in the synthesis of all of these compounds, as well as other analogs that I have not shown here. This made it easy to generate a number of different analogs by simply attaching different alkyne containing chains to the heterocycle portion of latrunculin B, and then carrying out the

[11] "Diverted total synthesis: Preparation of a focused library of latrunculin analogues and evaluation of their actin-binding properties," Furstner, A.; Kirk, D.; Fenster, M. D. B.; Aissa, C.; De Souza, D.; Muller, O. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8103-8108.

macrocyclization using RCAM. Lindlar reduction of the alkyne then provided the (*Z*)-alkene when needed. The biological activity of these analogs turned out to be an interesting feature of this work. Specifically, the analogs **116** and **117** were found to have stronger actin-binding activity than latrunculin B (**115**)! Furstner and co-workers reasoned that the lack of methyl groups made the macrocycle more flexible, which allowed this portion to fit better into the greasy pocket of the enzyme.[11] The alkyne-containing analog **118** also had significant biological activity, but it was not as potent as latrunculin B (**115**).

Figure I-3. Structures of Latrunculin B (**115**) and Analogs **116-118**.



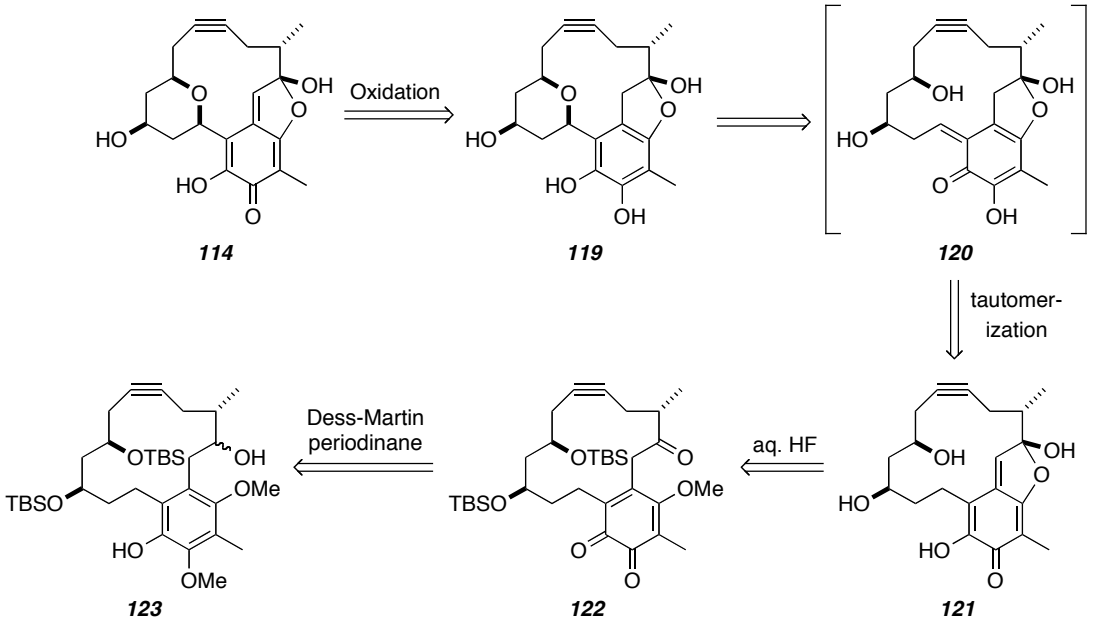
latrunculin B (***115***) ***116*** ***117*** ***118***

I.D. Synthetic Strategy of Kendomycin Analog

Our synthetic strategy to make the analog **114** is outlined in Scheme I-5. The *para*-quinone methide **114** could be accessed via selective oxidation of the catechol portion of **119**. If a selective oxidation could not be accomplished, then the secondary alcohol could be protected by a catechol protection-alcohol protection-catechol deprotection sequence. The key step of this strategy involved conjugate addition of the homopropargylic alcohol to the enone of the intermediate **120** to form the pyran in **119**. We believe that the enone of the *ortho*-quinone methide **120** could arise from the *para*-quinone methide **121** via tautomeric proton shifts. Therefore, **121** contains the inherent reactivity to form **119** spontaneously. The *para*-quinone methide **121** could be formed by

treatment of the *ortho*-quinone **122** with aqueous HF, which is an analogous step to what Smith and co-workers used to make kendomycin (**101**, Scheme I-4). The ketone *ortho*-quinone **122** could be accessed from **123** via oxidation with Dess-Martin periodinane, which is another step borrowed from the Smith kendomycin synthesis.

Scheme I-5. Retrosynthesis of the Kendomycin Analog **114**.

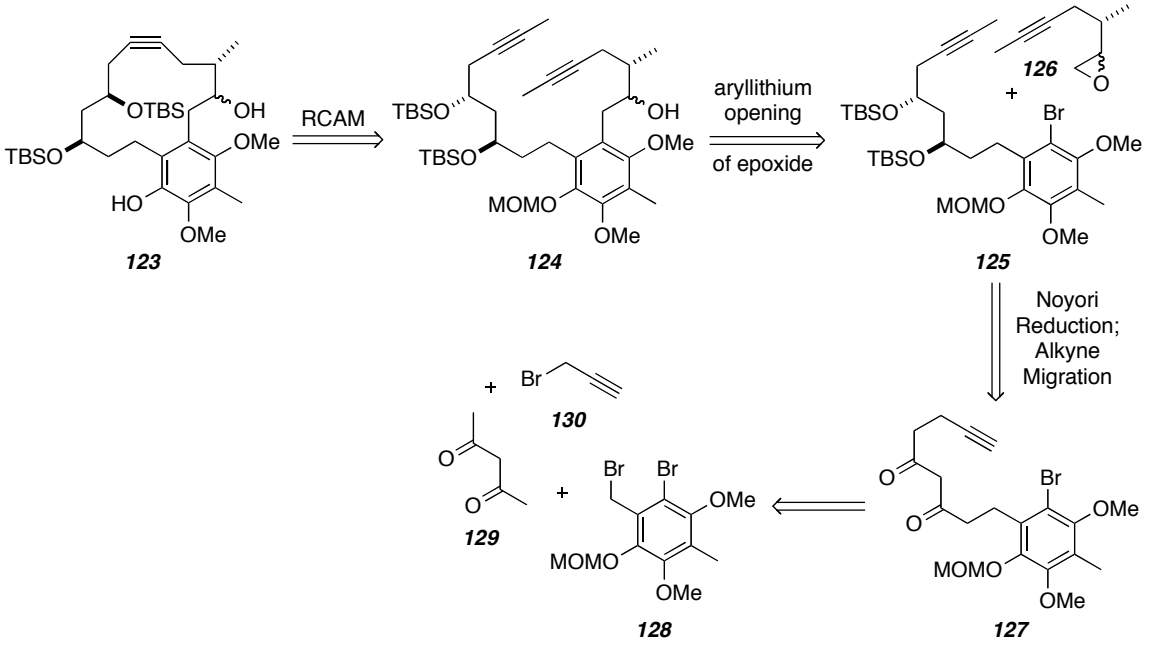


The other key step of our strategy is the use of RCAM (Scheme I-6) to form the macrocycle **123** from the diyne **124**. The diyne **124** could be furnished by epoxide opening of **126** with the aryllithium species generated from the lithium-halogen exchange of **125**. This type of transformation was also precedented in Smith's kendomycin synthesis (Scheme I-3). The alcohol stereocenters in **125** could be established by applying Noyori's asymmetric *anti*-reduction of 1,3-dicarbonyls to the diketone **127**.[12]

[12] "Homogeneous asymmetric hydrogenation of functionalized ketones," Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631.

Subsequent TBS-protection and alkyne migration would provide **125** from **127**.[13] The diketone **127** could be produced by consecutive alkylations of acetylacetone (**129**) with the benzylic bromide **128** and propargyl bromide (**130**). This strategy would allow for the synthesis of the kendomycin analog **114** in only 11 steps from **130**. Also, a number of other analogs could be made with this strategy by simply utilizing different alkynes, instead of **126** and **130**, in the synthetic sequence.

Scheme I-6. Retrosynthesis of the Macrocyclic Alkyne **123**.



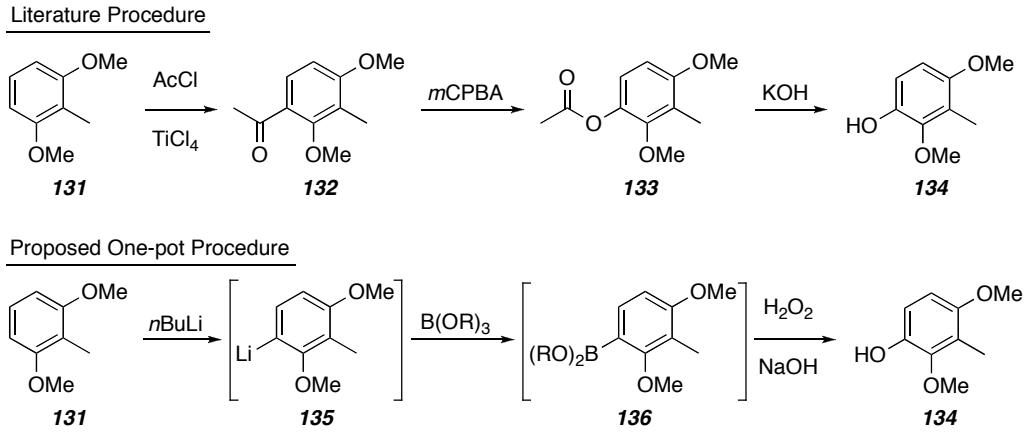
I.E. Results and Discussion

Initial efforts toward the synthesis of the kendomycin analog **114** involved the synthesis of the benzylic bromide **128** (Scheme I-6). Again, we intended to borrow from the Smith synthesis of kendomycin by using similar chemistry to make **128**.[5] We needed to first make the phenol **134** (Scheme I-7), and the Smith group turned to a 3-step literature protocol to convert commercially available 2,6-dimethoxytoluene (**131**) to

[13] "Ytterbium(II)-Aromatic Imine Dianion Complexes-Catalyzed Isomerization of Terminal Alkynes," Makioka, Y.; Saiki, A.; Takaki, K.; Taniguchi, Y.; Kitamura, T.; Fujiwara, Y. *Chem. Lett.* **1997**, *1*, 27-28.

134.[14] The 3-step protocol involved Friedel-Crafts acylation of **131** to give the ketone **132**, Baeyer-Villiger oxidation of **132** to yield the acetate **133**, and hydrolysis of **133** to provide the phenol **134**. This seemed to us like a lot of work to install one hydroxide. Instead, we wondered if treatment of **131** with *n*BuLi would cleanly give the lithiated species **135**, which could then be exposed to a trialkylborate to give the aryl borate **136**. Oxidation of **136** with H_2O_2 / NaOH would then directly provide the phenol **134**.

Scheme I-7. Proposed One-pot Synthesis of the Phenol **134**.



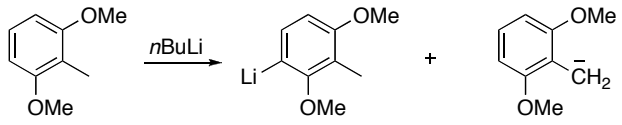
I decided that this transformation would be a good opportunity to use No-D NMR analysis, a technique that was recently studied in our group, to examine (Figure I-4) whether lithiation to give **135** or benzylic deprotonation to give **137** would be preferred.[15] This analysis would also allow me to quickly screen various conditions. Following treatment of **131** with *n*BuLi at -78 ºC, No-D NMR analysis (at room temperature) revealed that (Figure I-4; Entry 1) there was a slight preference for deprotonation to give **137** and that the conversion was poor (~40%). It was found that carrying out the reaction

[14] "Synthesis of 4, 7-Indolequinones. The Oxidative Demethylation of 4, 7-Dimethoxyindoles with Ceric Ammonium Nitrate," Kitahara, Y.; Nakahara, S.; Numata, R.; Kubo, A. *Chem. Pharm. Bull.* **1985**, *33*, 2122-2128.

[15] "No-D NMR (No-Deuterium Proton NMR) Spectroscopy: A Simple Yet Powerful Method for Analyzing Reaction and Reagent Solutions," Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. *Org. Lett.* **2004**, *6*, 953–956.

with TMEDA and excess *n*BuLi (1.5 equiv.) in Et_2O at 0 ºC resulted in preferential lithiation and much better conversion (Entry 4). The use of NaO*t*-Bu as an additive (Entry 5) resulted in preferential benzylic deprotonation and poor conversion. Altering the order of addition, temperature, concentration, and amount of *n*BuLi and TMEDA used (Entries 6-10) did not result in any significant changes to the reaction outcome. The reaction also gave a similar product distribution when using hexanes as a solvent (Entry11). I was never able to achieve full conversion for this reaction, even when excess reagents were used. The No-D analysis of this lithiation indicated a clean conversion to **135**, with **137** being the only observable side product.

Figure I-4. No-D NMR Study of Lithiation of **131**.



131 ***135*** ***137***

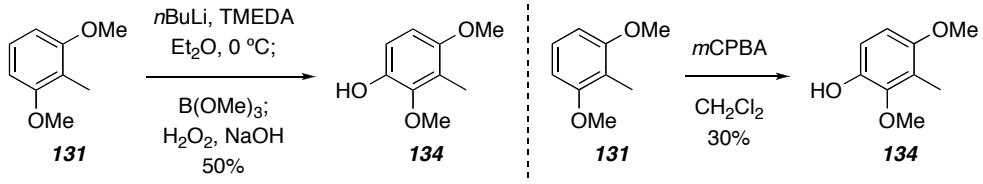
Entry	Solvent	Temp. (ºC)	Additive (Equiv.)	Equiv. *n*BuLi	**135** : **131** : **137**
1	THF	-78	none	1.1	18 : 57 : 25
2[a]	Et_2O	-40	TMEDA (1.0)	1.1	64 : 21 : 16
3	THF	-78	TMEDA (1.1)	1.1	23 : 68 : 9
4	Et_2O	0	TMEDA (1.1)	1.5	90 : 5 : 6
5	Et_2O	0	NaO*t*-Bu (1.2)	1.2	24 : 40 : 36
6	Et_2O	25	TMEDA (1.2)	1.2	82 : 14 : 4
7[b]	Et_2O	0	TMEDA (1.3)	1.3	87 : 6 : 6
8[c]	Et_2O	0	TMEDA (1.3)	1.3	89 : 5 : 6
9	Et_2O	0	TMEDA (2.6)	1.3	88 : 8 : 5
10	Et_2O	0	TMEDA (2.0)	2.0	93 : 3 : 4
11	hexanes	0	TMEDA (1.5)	1.5	86 : 10 : 4

Reactions were carried out on a 1 mmol scale via *n*BuLi addition to a 1.0 M solution of starting material and the other reagents. No-D NMR analysis done at room temp. (a) TMEDA added after reaction warmed to room temp. (b) More concentrated (2.0 M). (c) Reverse addition of starting material to a solution of nBuLi and the other reagents.

Now that conditions had been optimized for the lithiation of **131**, it was time to examine the 3-step one-pot procedure to make the phenol **134** (Scheme I-8). Unfortunately, even though the lithiation of **131** appeared clean by No-D NMR analysis as described above, the yield of the subsequent boration / oxidation product, **134**, was

only 50%. Use of freshly distilled $B(OMe)_3$ or $B(O\textit{i}\text{-}Pr)_3$ did not improve the yield of **134**, nor did extended reaction times after treatment with the borate. Attempts to observe the aryl borate interemediate **136** by No-D NMR were inconclusive due to broadened resonances in the spectrum, most likely due to the presence of various borate species. Attempts to achieve this oxidation directly with *m*CPBA did provide the phenol **134**, albeit in only 30% yield. I decided to move forward, with the one-pot lithiation / boration / oxidation protocol being the preferred method to make **134**.

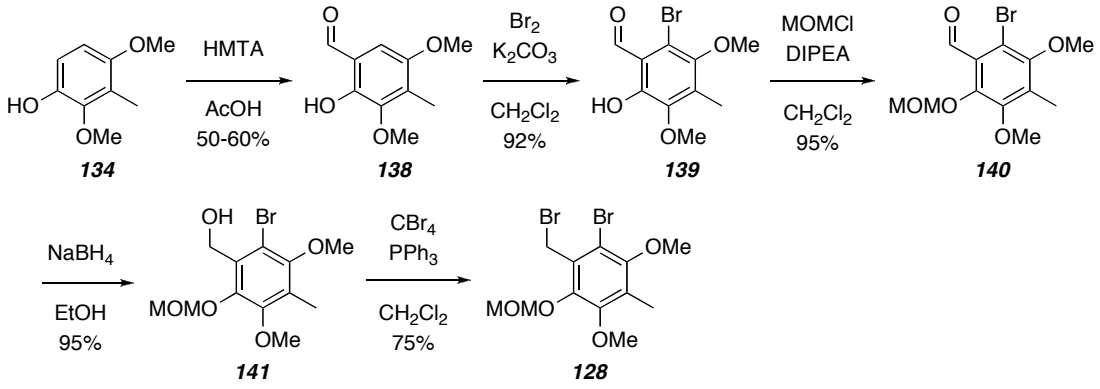
Scheme I-8. Synthesis of the Phenol **134**.



The remaining steps of the synthesis of the benzylic bromide **128** (Scheme I-9) were straightforward. The phenol **134** was formylated to give **138** by treating with hexamethylenetetramine (HMTA) in AcOH, which is known as the Duff reaction.[16] Subsequent bromination of **138** yielded the aryl bromide **139** in high yield. These first two steps were again precedented from Smith and co-worker's kendomycin synthesis.[5] The phenol **139** was protected as its MOM ether to yield **140**. The benzaldehyde **140** was reduced with $NaBH_4$ to provide the benzylic alcohol **141**. The benzylic bromide **128** was finally furnished by treatment of **141** with CBr_4 / PPh_3.

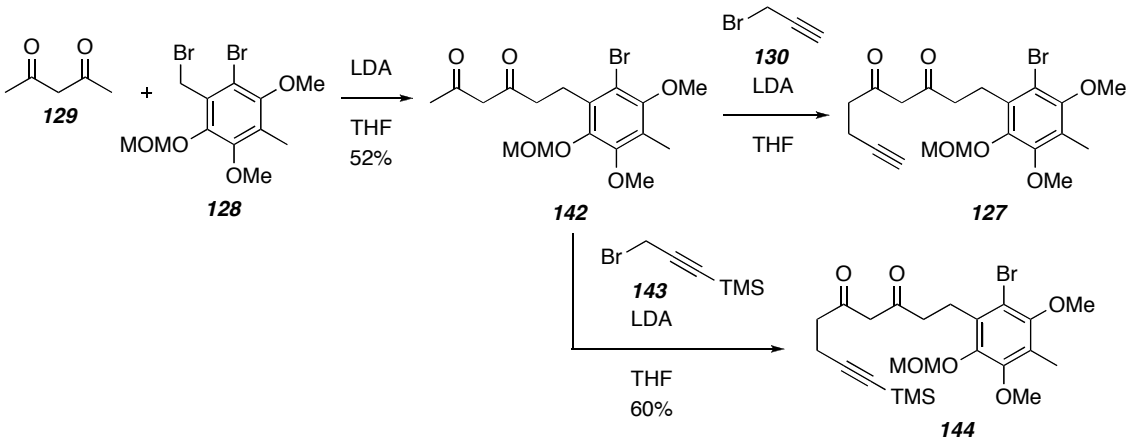
[16] "Reactions between hexamethylenetetramine and phenolic compounds. Part I. A new method for the preparation of 3- and 5-aldehydosalicylic acids," Duff, J. C.; Bills, E. J. *J. Chem. Soc.* **1932**, 1987.

Scheme I-9. Synthesis of the Benzylic Bromide **128**.



With the benzylic bromide **128** now in hand, it was time to explore the feasibility of the two consecutive alkylations required to make the diketone **127** (Scheme I-10). The first alkylation was carried out by exposing **128** to the dianion of acetylacetone (**129**), generated by treating **129** with 2.4 equivalents of LDA. This reaction gave the diketone **142** in 52% yield (65% brsm). The next alkylation was carried out in the same manner by treating propargyl bromide (**130**) with the dianion of **142**. However, this reaction resulted in mostly recovered starting material, but it looked as if a small amount of the desired product, **127**, may have been present as judged from the ^{1}H NMR spectrum of the crude material. I wondered if the dianion of **142** was deprotonating propargyl bromide (**130**), which would explain why mostly starting material was recovered. I decided to try alkylating **142** with the TMS alkyne **143** instead. This change proved to be benefical, because treating the dianion of **142** with the propargyl bromide **143** gave the diketone **144** in 60% yield. My efforts on this project ended at this point, as my focus turned to the okundoperoxide project (Chapter 4).

Scheme I-10. Attempted Synthesis of the Diketone **127**.

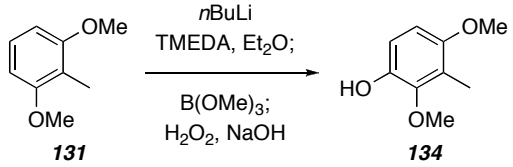


I.F. Conclusion

The first few steps of our proposed synthesis of the kendomycin analog **114** has been studied. A reliable synthesis of the benzylic bromide **128** was developed. Notably, a one-pot lithiation / boration / oxidation of 2,6-dimethoxytoluene (**131**) was developed to provide the phenol **134** in moderate yield (50%). At this point, no one has picked up this project again, but that possibility hasn't been ruled out.

I.G. Experimental Section

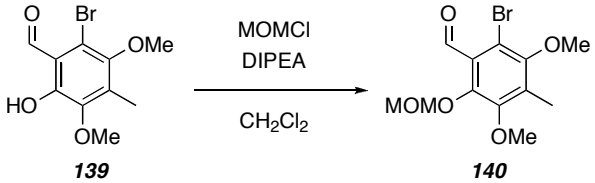
2,4-Dimethoxy-3-methyl-phenol (134)



To a solution of 2,6-dimethoxytoluene (**131**; 1.52 g, 10.0 mmol) and TMEDA (3.0 mL, 20 mmol) in Et_2O (10 mL) at 0 ºC was added *n*BuLi (2.15 M in hexanes, 9.3 mL, 20 mmol) dropwise. The solution was stirred an additional 1 h at 0 ºC, and $B(OMe)_3$ (2.2 mL, 20 mmol) was added dropwise. After stirring for 2 h at rt, the solution was diluted with Et_2O (180 mL). Aqueous NaOH (3 M, 30 mL) was added at rt, and the solution was cooled to 0 ºC. Aqueous H_2O_2 (30% w/w, 30 mL) was added to the solution over a 30 min period, and the solution was stirred overnight at rt. The solution was acidified to pH=1 with 6 M HCl. The solution was extracted with Et_2O (2x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by flash chromatography (6:1 hexanes:EtOAc) to give the phenol **134** (870 mg, 5.17 mmol, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[14]

2-Bromo-6-(methoxymethoxy)-3,5-dimethoxy-4-methyl-benzaldehyde (140)

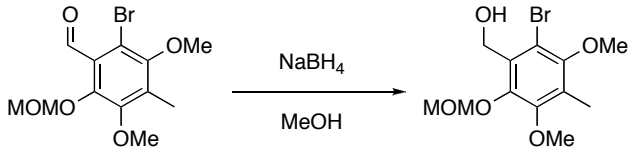


To a solution of the phenol **139 (**325 mg, 1.18 mmol) and DIPEA (330 μL, 1.89 mmol) in CH_2Cl_2 (2.4 mL) at 0 ºC was added a solution of MOMCl (45% w/w, density ~

1 mg/mL, 338 μL, 1.89 mmol) dropwise. The solution was stirred overnight at rt, and water was added to the solution. The mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (6:1 hexanes:EtOAc) to give the MOM ether **140** (363 mg, 1.14 mmol, 97% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 10.34 (s, 1H), 5.13 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 3.57 (s, 3H), and 2.31 (s, 3H).

2-Bromo-6-(methoxymethoxy)-3,5-dimethoxy-4-methyl-benzenemethanol (141)

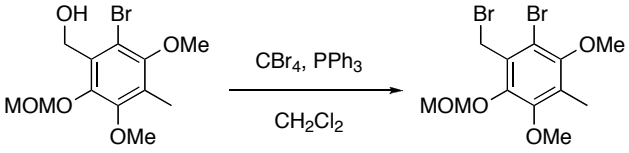


140 ***141***

To a solution of the benzaldehyde **140** (803 mg, 2.52 mmol) in MeOH (12.5 mL) at 0 ºC was added $NaBH_4$ (105 mg, 2.77 mmol) portionwise. The solution was allowed to warm to rt. After the reaction mixture was stirred at rt for 20 min, water was added to the mixture. NaCl was added to the mixture until the aqueous portion was saturated. The mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by flash chromatography (3:1 hexanes:EtOAc) to give the benzylic alcohol **141** (769 mg, 2.40 mmol, 95% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.09 (s, 2H), 4.83 (d, J = 7.1 Hz, 2H), 3.78 (s, 6H), 3.60 (s, 3H), 2.93 (t, J = 7.1 Hz, 1H), and 2.25 (s, 3H).

1-Bromo-2-(bromomethyl)-3-(methoxymethoxy)-4,6-dimethoxy-5-methyl-benzene (128)

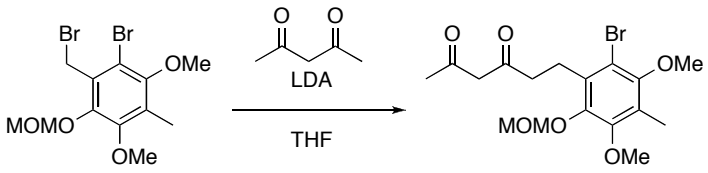


141 ***128***

To a solution of the benzylic alcohol **141** and CBr_4 in CH_2Cl_2 at 0 ºC was added PPh_3. The reaction mixture was stirred overnight at rt. The solution was concentrated to an oil. Silica gel and a small amount of CH_2Cl_2 was added to the oil, which was then concentrated again. This was repeated until a free flowing solid was produced upon concentrating, which was then dry loaded on top of a flash column. The flash column was eluted with hexanes to remove CBr_4 and $CHBr_3$. The column was then eluted with 9:1 hexanes:EtOAc to elute the benzylic bromide **128**, which gave a solid after concentration (458 mg, 1.19 mmol, 76% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.20 (s, 2H), 4.77 (s, 2H), 3.78 (s, 3H), 3.78 (s, 3H), 3.65 (s, 3H), and 2.25 (s, 3H).

6-(2-Bromo-6-(methoxymethoxy)-3,5-dimethoxy-4-methyl-phenyl)-2,4-hexanedione (142)



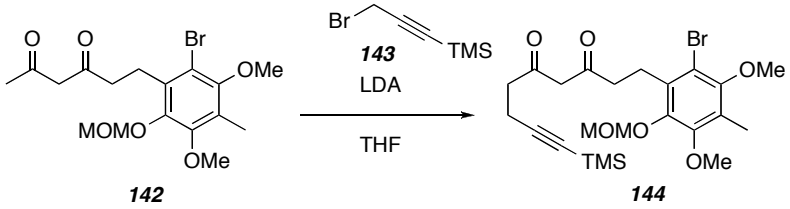
128 ***142***

To a solution of *i*-Pr_2NH (182 μL, 1.3 mmol) in THF (1.5 mL) was added *n*BuLi (2.2 M in hexanes, 570 μL, 1.25 mmol) at 0 ºC. After this solution was stirred for 15 min, acetylacetone (59 μL, 0.57 mmol) was added dropwise to the LDA solution. After the solution was stirred an additional 15 min at 0 ºC, a solution of the benzyl bromide **128** (200 mg, 0.52 mmol) in THF (0.6 mL) was added to the solution of the acetylacetone

dianion. This solution was stirred for 1 h at 0 ºC, and then allowed to warm to rt. Saturated aqueous NH_4Cl was added to the solution, which was then extracted with MTBE (2x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (4:1 hexanes:EtOAc) to provide the diketone **142** (109 mg, 0.27 mmol, 52% yield).

^{1}H NMR of enol tautomer (300 MHz, $CDCl_3$): δ 15.45 (s, 1H), 5.55 (s, 1H), 5.09 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.59 (s, 3H), 3.14 (m, 2H), 2.56 (m, 2H), 2.23 (s, 3H), and 2.07 (s, 3H).

9-(2-Bromo-6-(methoxymethoxy)-3,5-dimethoxy-4-methyl-phenyl)-1-(trimethylsilyl)-1-nonyne-5,7-dione (144)



To a solution of *i*-Pr_2NH (38 μL, 0.27 mmol) in THF (0.3 mL) was added *n*BuLi (2.1 M in hexanes, 124 μL, 0.26 mmol) at 0 ºC. After this solution was stirred for 15 min, a solution of the diketone **142** (50 mg, 0.12 mmol) in THF (0.32 mL) was added dropwise to the LDA solution. After the solution was stirred an additional 1 h at 0 ºC, the propargyl bromide **143** (19 μL, 0.13 mmol) was added to the solution of the **142** dianion. The solution was stirred for 30 min at 0 ºC and then stirred at rt for 30 min. Saturated aqueous NH_4Cl was added to the solution, which was then extracted with MTBE (4x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (9:1 hexanes:EtOAc) to provide the diketone **144** (38 mg, 0.074 mmol, 60% yield).

^{1}H NMR of enol tautomer (500 MHz, $CDCl_3$): δ 15.28 (s, 1H), 5.58 (s, 1H), 5.09 (s, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 3.59 (s, 3H), 3.14 (m, 2H), 2.57 (m, 2H), 2.53 (m, 4H), 2.23 (s, 3H), and 0.14 (s, 9H).

Chapter II. Reactivity of Phenols with N-Phenyltriazolinedione

II.A. Introduction

The development of new methodologies to prepare densely functionalized cores (scaffolds) is important in the field of medicinal chemistry. The preparation of new scaffolds allows for the analysis of unexplored chemical space, which could result in the discovery of new lead compounds exhibiting pharmacological activity. We were seeking to obtain preliminary results pertaining to this type of research prior to the submission of a grant application that focused on the development of new libraries. Specifically, we were looking to capitalize on our experience with reacting phenols like **201** with singlet oxygen ($^1O_2$) to give hydroperoxides like **202** (Scheme II-1), which will be discussed in Chapter 3. We wondered if an analogous transformation could be carried out with a nitrogen variant of $^1O_2$, namely azo compounds (RN=NR). The reaction of phenols like **201** with azo compounds would afford hydrazides like **203** and **204**. These products would allow for additional functionalization to give highly substituted cores. The reaction of electron-rich arenes with electron-deficient azo compounds has been previously reported, but this process has not been extensively studied. The examples all involve *para*-substitution of phenols with azodicarboxylates, which require some sort of activating reagent, or with N-phenyltriazolinedione (PTAD), which requires basic conditions.[17] Even though I only obtained a handful of preliminary results, the results proved to be quite interesting; therefore, I decided to include this work in my thesis.

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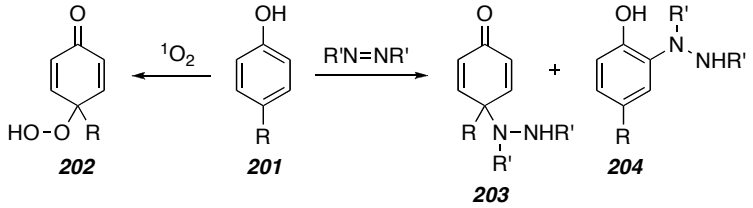
[17] (a) "Synthesis of aromatic amines from electron-rich arenes and bis(2,2,2-trichloroethyl) azodicarboxylate," Zaltsgendler, I.; Leblanc, Y.; Bernstein, M. A. *Tetrahedron Lett*. **1993**, *34*, 2441–2444. (b) "Electrophilic amination of 4-fluorophenol with diazenes: a complete removal of the fluorine atom," Bombek, S.; Pozgan, F.; Kocevar, M.; Polanc, S. *J. Org. Chem*. **2004**, *69*, 2224–2227. (c) "The condensation of dicarbonyl compounds with *N*-phenyltriazolinedione-dienone ylides derived from phenols:

Scheme II-1. Proposed Reaction of Phenols **201** with Azo Compounds (R'N=NR').



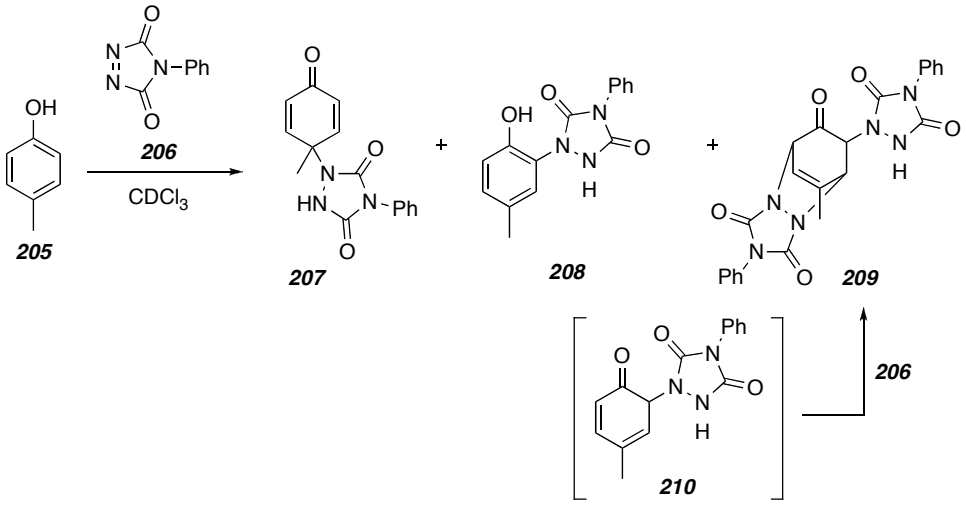
II.B. Results and Discussion

My first attempt at reacting a phenol with an azo compound involved combining *p*-cresol (**205**; Scheme II-2) and diisopropylazodicarboxylate (DIAD) in $CDCl_3$ in an NMR tube. No change was observed by ^1H NMR analysis, even after heating to reflux for an extended period of time. The reaction was carried out again in refluxing d_8-toluene in order to achieve a higher temperature, but no reaction was observed again. We concluded that DIAD was not reactive enough, so I decided to try a more reactive azo compound, PTAD (**206**). Upon mixing *p*-cresol (**205)** and 1.0 equivalent PTAD (**206)** in $CDCl_3$, the pink solution became colorless within one minute, which indicated the consumption of **206**. This was confirmed by ^1H NMR analysis, which also indicated an interesting product mixture. The dienone **207**, the *ortho*-substituted product **208**, and the bis-adduct **209** were observed in a ~1.5:1.3:1.0 ratio by ^1H NMR analysis. Subsequent MPLC purification and LC-MS analysis confirmed the structure of **209**. The structure of **209** could be explained mechanistically by an initial *ortho*-substitution to give the dienone **210**, which could undergo a [4+2]-cycloaddition with PTAD (**206**) prior to tautomerizing to **208**. The structure of **209** was interesting because it was a densely

the facile preparation of novel quinone methides," Wilson, R. M.; Chantarasiri, N. *J. Am. Chem. Soc.* **1991**, *113,* 2301-2302.

functionalized core with three new C-N bonds that was accessed in one step from simple precursors. The bis-adduct **209** could serve as a unique scaffold, which could be further derivatized in a number of ways. Specifically, the N-phenyltriazolidinedione rings of **209** could be opened with water[18] or alkoxide,[19] and the N-N bond of the ring-opened species could be reduced.[20] The ketone and alkene of **209** could also be functionalized in a number of ways.

Scheme II-2. Reaction of *p*-Cresol (**205**) with PTAD (**206**).



We wondered if blocking the *ortho*-postions of the phenol would allow for clean *para*-functionalization with PTAD (**206**). We used BHT (**211**) to test this hypothesis (Scheme II-3). Indeed, treatment of **211** with **206** cleanly afforded the dienone **212**.

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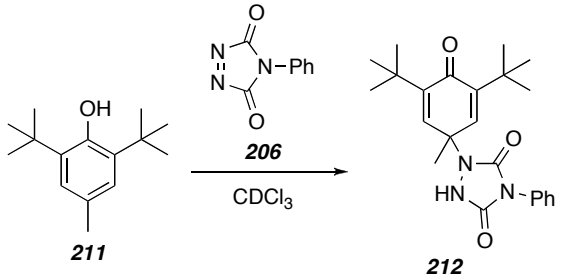
[18] (a) "*N*-Phenyltriazolinedione adducts of bicyclo[4.2.2]decatetraene and tricyclo[3.3.2.0^{2,8}]decatriene (bullvalene)," Joesel, R.; Schroeder, G. *Liebigs Ann. Chem.* **1980**, 1428–1437. (b) "Synthesis and properties of tricyclo[5.3.0.0^{2,8}]deca-3,5-dien-9-one. A new entry to the $C_{10}H_{10}$ manifold," Gleiter, R.; Zimmermann, H.; Sander, W.; Hauck, M. *J. Org. Chem.* **1987**, *52*, 2644–2653.

[19] "Bridgehead hydrazines. 2. Preparation and photolysis of 2-phenyl-s-triazolo[1,2-a]pyridazine-1,3-dione and of pyridazine[1,2-b]phthalazine-6,11-dione," Sheradsky, T.; Moshenberg, R. *J. Org. Chem.* **1985**, *50*, 5604–5608.

[20] "Chiral Ru-based complexes for asymmetric olefin metathesis: enhancement of catalyst activity through steric and electronic modifications," Veldhuizen, J. J. Van; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502–12508.

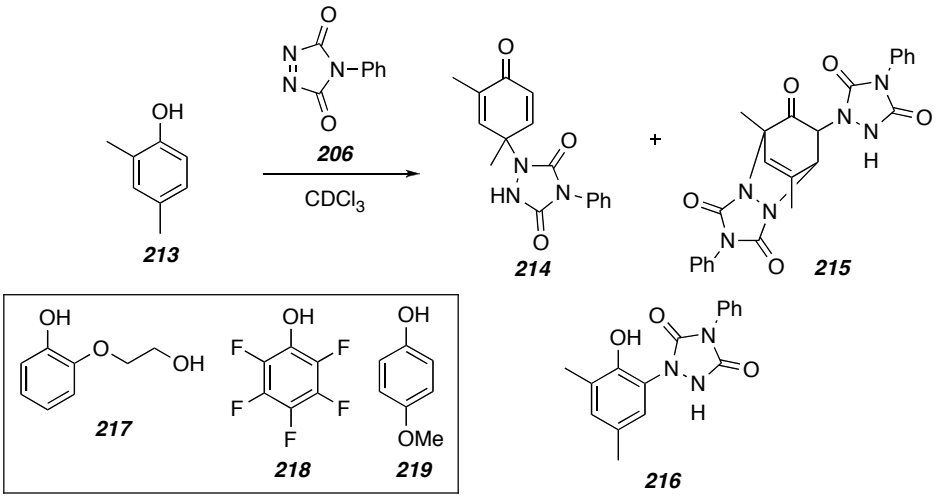
Thus, appropriate choice of the phenol could result in selective formation of *para*-substituted dienones.

Scheme II-3. Reaction of BHT (**211**) with PTAD (**206**).



Another phenolic substrate that gave an interesting result (Scheme II-4) upon treatment with PTAD (**206**) was 2,4-dimethyl-phenol (**213**). When **213** and **206** were combined in $CDCl_3$, ^1H NMR analysis of the reaction revealed three major components, the starting phenol **213**, the dienone **214**, and the bis-adduct **215**, in a ~1:1.6:1 ratio, respectively. It appears that most of the *ortho*-substituted phenol went on to form the bis-adduct **215** instead of tautomerizing to give **216**. It is not obvious why this substrate would preferentially give the bis-adduct **215** instead of **216**, but a study of other phenols could shed some light on this reactivity. Finally, a few additional phenols, **217**-**219**, were studied. ^1H NMR and LC-MS analysis of these reactions indicated the formation of mono- and bis-adducts, but these reactions did not give a clean product mixture. Therefore, the ratio and identity of the products were not as straightforward to analyze.

Scheme II-4. Reaction of 2,4-Dimethyl-phenol (**213**) with PTAD (**206**).

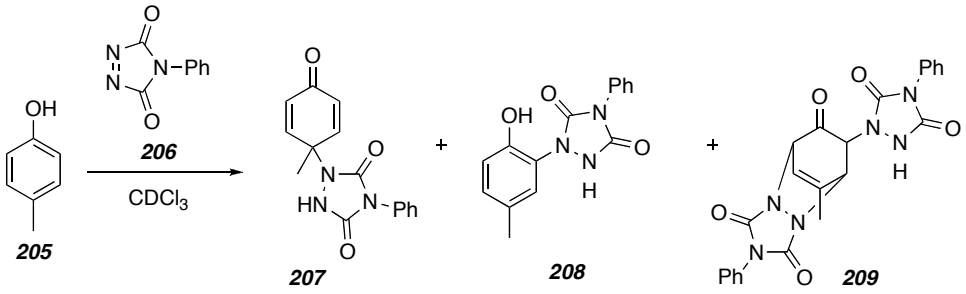


II.C. Conclusion

The reaction of various phenols with PTAD (**206**) resulted in the formation of an unexpected bis-adduct, which arose from *ortho*-substitution followed by a [4+2]-cycloaddition. The bis-adduct, as well as the expected *ortho*- and *para*-adducts, could serve as appropriate scaffolds for the development of pharmacological lead compounds. Each of these three classes of products would allow for a variety of additional functionalizations, which would make them suitable for the preparation of libraries of novel compounds.

II.D. Experimental Section

1-(1-Methyl-4-oxo-2,5-cyclohexadien-1-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione (207)



To a solution of *p*-cresol (**205**; 11.4 mg, 0.11 mmol) in $CDCl_3$ (0.7 mL) in an NMR tube was added PTAD (**206**; 18.4 mg, 0.11 mmol). The reaction progress was monitored by ^{1}H NMR spectroscopy, and no change in the spectra was observed after 10 min vs 1 h. The ratio of products was ~1.6:1.5:1.3:1.0 for **205**:**207**:**208**:**209**. The solution was diluted with EtOAc and washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the starting phenol **205** (3.8 mg, 0.035 mmol, 32% recovered), the *ortho*-substituted phenol **208** (3.7 mg, 0.013 mmol, 12% yield), and the bis-adduct **209** (5.6 mg, 0.012 mmol, 11% yield). The dienone **207** was lost during the workup, so its NMR data is reported as observed from the reaction mixture; therefore, minor changes in the chemical shift values of **207** would be expected if it were reported in its pure form.

207

^{1}H NMR from reaction mixture (500 MHz, $CDCl_3$): δ ? (m, 5H), 6.92 (d, J = 10.0 Hz, 2H), 6.28 (d, J = 10.2 Hz, 2H), and 1.67 (s, 3H).

208

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (m, 5H), 7.20 (d, *J* = 2.1 Hz, 1H), 7.05 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.01 (d, *J* = 8.3 Hz), and 2.31 (s, 3H).

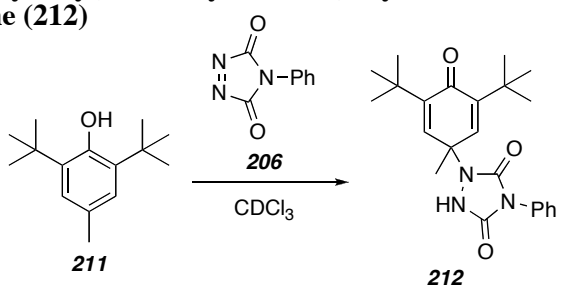
HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 284.0 $(M+H)^+$; t_r = 0.91 min.

209

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (m, 10H), 6.26 (ddq, *J* = 5.7, 1.8, 1.8 Hz, 1H), 5.19 (dd, *J* = 2.8, 2.2 Hz, 1H), 5.14 (d, *J* = 5.8 Hz, 1H), 4.86 (d, *J* = 2.9 Hz, 1H), and 2.11 (d, *J* = 1.8 Hz, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 459.0 $(M+H)^+$; t_r = 0.86 min.

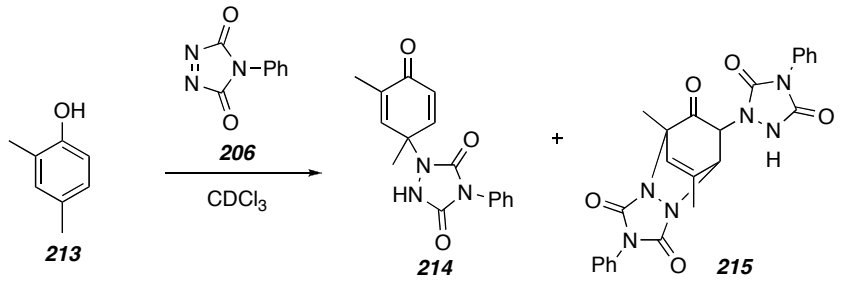
1-(3,5-Bis(1,1-dimethylethyl)-1-methyl-4-oxo-2,5-cyclohexadien-1-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione (212)



To a solution of BHT (**211**; 13.3 mg, 0.060 mmol) in $CDCl_3$ (0.7 mL) in an NMR tube was added PTAD (**206**; 11.6 mg, 0.066 mmol). One hour later, a ^{1}H NMR spectrum was collected, and this showed formation of the dienone **212** and no other products were observed. No purification was carried out, and the ^{1}H NMR data is reported from the reaction mixture.

^{1}H NMR from reaction mixture (500 MHz, $CDCl_3$): δ 9.20 (br s, 1H), 7.44 (m, 5H), 6.65 (s, 2H), 1.75 (s, 3H), and 1.17 (s, 18H).

1-(1,3-Dimethyl-4-oxo-2,5-cyclohexadien-1-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione (214)



To a solution of the phenol **213** (15.1 mg, 0.12 mmol) in $CDCl_3$ (0.7 mL) in an NMR tube was added PTAD (**206**; 22.8 mg, 0.13 mmol). One hour later, a ^1H NMR spectrum was collected, and this showed a mixture of the starting phenol **213**, the dienone **214**, and the bis-adduct **215** in a ~1:1.6:1 ratio, respectively. Other minor components are present in the reaction mixture. No purification was carried out, and the ^1H NMR data is reported from the reaction mixture.

214

^1H NMR from reaction mixture (500 MHz, $CDCl_3$): δ ? (m, 5H), 6.93 (dd, *J* = 10.0, 3.1 Hz, 1H), 6.70 (dq, *J* = 3.0, 1.5 Hz, 1H), 6.29 (d, *J* = 10.0 Hz, 1H), 2.04 (d, *J* = 1.8 Hz, 3H), and 1.93 (s, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 296.0 $(M-H)^-$; t_r = 4.85 min.

215

^1H NMR from reaction mixture (500 MHz, $CDCl_3$): δ ? (m, 10H), 5.97 (dq, *J* = 1.7, 1.7 Hz, 1H), 5.18 (dd, *J* = 2.6, 2.2 Hz, 1H), 4.84 (d, *J* = 2.7 Hz, 1H), 2.04 (d, *J* = 1.8 Hz, 3H), and 1.93 (s, 3H).

Chapter III. Scyphostatin

III.A. Introduction and Background

The field of synthetic organic chemistry involves attempting to synthesize a complex target molecule (often a natural product) from simpler precursors through a number of chemical steps. The focus of research programs can usually be generalized into two main groups: those concerned with 'what' they are making and those concerned with 'how' they are making their target. Those in a 'what' group are motivated by getting their hands on the target molecule as quickly as possible, and in a manner that allows them to make the required amounts for some sort of testing (usually testing the biological activity of a natural product or natural product analog). This group is not as concerned with elegance or creativity of the science, instead their main focus is on the practicality and reliability of their synthesis to achieve the target. Those in a 'how' group, on the other hand, are motivated by the novelty and efficiency of the processes they are developing. Therefore, the approaches taken in this work are typically more risky, and result in more 'failed' experiments, while trying to uncover unprecedented chemistry. Even though those in a 'how' group usually require more time to achieve their goal, when they are successful in discovering novel chemistry, it usually results in an improved synthesis of the natural product and / or a greater understanding of new chemical processes.

The Hoye group falls into the category of focusing on the 'how' of organic synthesis. Scyphostatin is a complex natural product that presents a challenge for which we believe new chemistry could be developed to improve on the current syntheses of the

polar core of this natural product.[21] More specifically, we envision that a vinylogous-Payne rearrangement, a relatively unknown process, could open the door for a dynamic kinetic resolution (DKR) that would generate the necessary stereochemical features of the polar core of scyphostatin. Also, the chemistry preceding the DKR process to be studied should be straightforward and require relatively few steps.

In this chapter, I will begin by discussing the isolation, characterization,[21,22] and biological activity[23] of scyphostatin. I then will review the previously published syntheses of scyphostatin[24,25,26] (and a scyphostatin analog)[27] carried out by other research groups. It will become apparent in this section that the polar core of scyphostatin has been quite challenging for other synthetic organic research groups, as well. Then I will summarize the previous work done on scyphostatin within the Hoye

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[21] "Structural Elucidation of Scyphostatin, an Inhibitor of Membrane-Bound Neutral Sphingomyelinase," Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita T. *J. Am. Chem. Soc.* **1997**, *119*, 7871–7872.

[22] (a) "Absolute Configuration of Scyphostatin," Saito, S.; Tanaka, N.; Fujimoto, K; Kogen, H. *Org. Lett.* **2000**, *2*, 505–506. (b) "Synthesis (and Alternative Proof of Configuration) of the Scyphostatin C(1')–C(20') Trienoyl Fragment," Hoye, T. R.; Tennakoon, M. A. *Org. Lett.* **2000**, *2*, 1481–1483.

[23] (a) "Scyphostatin, a neutral sphingomyelinase inhibitor from a discomycete, Trichopeziza mollissima: taxonomy of the producing organism, fermentation, isolation, and physico-chemical properties," Nara, F.; Tanaka, M.; Hosoya, T.; Suzuki-Konagai, K.; Ogita, T. *J. Antibiot.* **1999**, *52*, 525-530. (b) "Biological activities of scyphostatin, a neutral sphingomyelinase inhibitor from a discomycete, Trichopeziza mollissima," Nara, F.; Tanaka, M.; Masuda-Inoue, S.; Yamasato, Y.; Doi-Yoshioka, H.; Suzuki-Konagai, K.; Kumakura, S.; Ogita, T. *J. Antibiot.* **1999**, *52*, 531-535.

[24] "Total Synthesis of (+)-Scyphostatin, a Potent and Specific Inhibitor of Neutral Sphingomyelinase," Inoue, M.; Yokota, W.; Murugesh, M. G.; Izuhara, T.; Katoh, T. *Angew. Chem. Int. Ed.* **2004**, *116*, 4303-4305.

[25] "Stereoselective total synthesis of (+)-Scyphostatin via a pi-facially selective Diels-Alder reaction," Takagi, R.; Miyanaga, W.; Tojo, K.; Tsuyumine, S.; Ohkata, K. *J. Org. Chem.* **2007**, *72*, 4117-4125.

[26] "Concise Asymmetric Total Synthesis of Scyphostatin, a Potent Inhibitor of Neutral Sphingomyelinase," Fujioka, H.; Sawama, Y.; Kotoku, N.; Ohnaka, T.; Okitsu, T.; Murata, N.; Kubo, O.; Li, R.; Kita, Y. *Chem. Eur. J.* **2007**, *13*, 10225-10238.

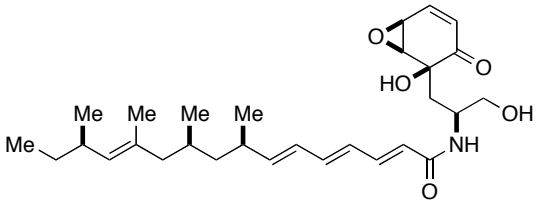
[27] "Short and Efficient Route to the Fully Functionalized Polar Core of Scyphostatin," Pitsinos, E. M.; Cruz, A. *Org. Lett.* **2005**, *7*, 2245-2248.

group, while also introducing the central hypothesis driving this project. Finally, I will discuss my efforts toward a concise synthesis of the polar core of scyphostatin.

III.B. Isolation, Characterization, and Biological Activity of Scyphostatin

Scyphostatin (**301**, Figure III-1) is regarded as the most specific and potent inhibitor (IC_{50}=1.0 μM)[23] of neutral sphingomyelinase (N-SMase), an encouraging pharmacological target for treating inflammation, AIDS, and immunological and neurological disorders.[28] It was isolated in 1997 by Ogita and co-workers from the culture broth of *Dasyscyphus mollisimus* SANK-13892, and further studies by this group allowed

Figure III-1. Scyphostatin (**301**), a specific and potent inhibitor of N-SMase.



scyphostatin (**301**)

for elucidation of the absolute configuration of the polar core of scyphostatin.[21,22] As can be seen by its structure (Figure III-1), scyphostatin features two principal moieties: a densely functionalized epoxy cyclohexenone polar core and an unsaturated fatty acid side chain. The unique structure and potent biological activity of scyphostatin has motivated many in the field of synthetic organic chemistry to launch synthetic efforts to make this natural product, which will be illustrated below.[24,25,26,27]

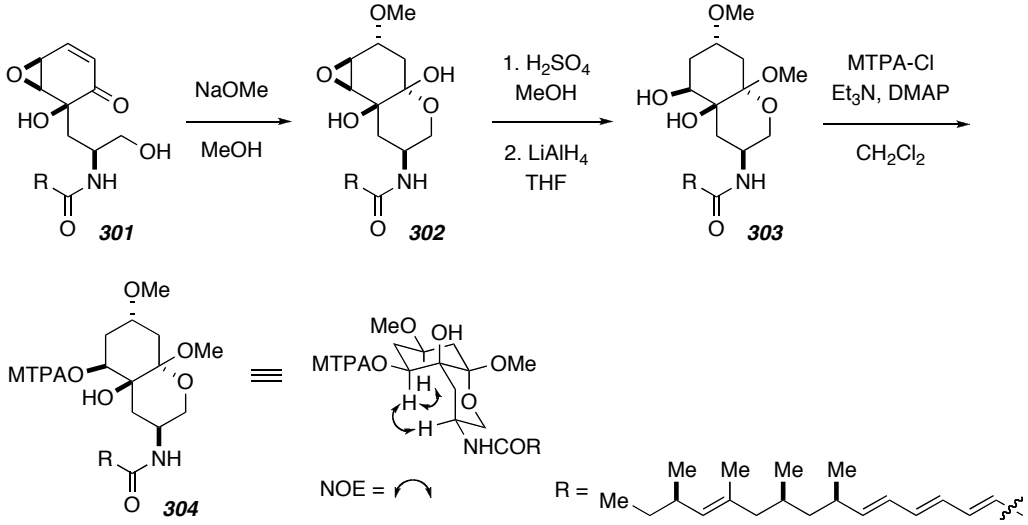
Scyphostatin has an interesting biological mode of activity, which will briefly be discussed here. N-SMase is an enzyme that catalyzes the hydrolysis of sphingomyelin to

[28] "Neutral Sphingomyelinase: Past, Present, and Future," Chatterjee, S. *Chem. Phys. Lipids* **1999**, *102*, 79-96.

form ceramide. Therefore, N-SMase inhibitors (such as scyphostatin) could be used to regulate ceramide levels in a variety of mammalian cell types. It is believed that ceramide is an intracellular lipid second messenger that plays a critical role in apoptosis, cellular proliferation and differentiation, and inflammation.[29] Since N-SMase is a new pharmacological target, there is much excitement about the novel types of therapies that could result from greater understanding of how to modulate its activity.

The structure of scyphostatin was determined by Ogita and co-workers on the basis of ^{1}H and ^{13}C NMR spectroscopy data, using both 1D and 2D (COSY and HMBC) data sets.[21] The relative and absolute configuration of the polar core was established utilizing an elegant degradation study (Scheme III-1) of scyphostatin.[21] More specifically, scyphostatin (**301**) was treated with NaOMe, which resulted in methanol addition followed by hemiketalization to give the hemiketal **302**. The diol **303** was then formed in two steps by first exposing the hemiketal **302** to acidic methanol to effect

Scheme III-1. Degradation of Scyphostatin (**301**) to Elucidate Absolute Configuration.



[29] (a) "Functions of Ceramide in Coordinating Cellular Responses to Stress," Hannun, Y. A. *Science* **1996**, *274*, 1855-1859. (b) "Enzymes of Sphingolipid Metabolism: From Modular to Integrative Signaling," Hannun, Y. A.; Luberto, C.; Argraves, K. M. *Biochemistry* **2001**, *40*, 4893-4903.

ketalization, followed by $LiAlH_4$ reduction to regioselectively open the epoxide. The secondary alcohol of the diol **303** could then be derivatized with (*R*)- and (*S*)-Mosher acid chlorides to yield the (*S*)- and (*R*)-Mosher esters **304**, respectively. This indicated an (*S*) configuration at the carbinol center upon modified Mosher analysis.[30] Relative configuration was also established from the indicated NOE enhancements (Scheme III-1) of the ester **304**, thus allowing assignment of the all configurations of the polar core of scyphostatin (**301**).

The relative and absolute configuration of the scyphostatin side chain was also deduced from degradation studies, work that was carried out by Kogen and co-workers.[22(a)] They were able to establish the absolute configuration by synthetically producing (from starting materials with known stereocenters) the same compounds as those prepared from degradation of natural scyphostatin, and then comparing their physical properties (optical rotation, IR, ^1H and ^{13}C NMR spectroscopy) to the degradation products derived from the natural material. Hoye and Tennakoon also confirmed this assignment via the synthesis of a variety of relevant diastereomers of the fatty acid side chain, and subsequent comparison of their ^1H NMR data to the natural material.[22(b)]

III.C. Previous Syntheses and Synthetic Studies of Scyphostatin

Three total syntheses of scyphostatin have been reported, as well as numerous additional reports on synthetic studies of scyphostatin and its analogs.[31] Upon reviewing

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[30] "Mosher ester analysis for the determination of absolute configuration of stereogenic (chiral) carbinol carbons," Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols*, **2007**, *2*, 2451-2458.

[31] (a) "Enantiocontrolled synthesis of (4*S*,5*S*,6*S*)-6-benzyl-4,5-epoxy-6-hydroxy-2-cyclohexen-1-one, a model compound for the epoxycyclohexenone moiety of scyphostatin," Izuhara, T.; Katoh, T. *Tetrahedron Lett*. **2000**, *41*, 7651-7655. (b) "Studies toward the Total Synthesis of Scyphostatin: First Entry to the Highly Functionalized Cyclohexenone Segment," Izuhara, T.; Katoh, T. *Org*. *Lett*. **2001**, *3*, 1653-1656. (c)

this work, I will focus on the details of how the polar core of scyphostatin was made. I will cover the three total syntheses and one analog synthesis.

III.C.1. Katoh's Synthesis of Scyphostatin

The first total synthesis of scyphostatin was reported by the Katoh group in 2004, and it was achieved in 22 steps (longest linear sequence) from the alcohol **305**, a protected form of D-arabinose, in 0.75% overall yield.[24] Synthesis of the polar core of scyphostatin commenced (Scheme III-2) with PMB protection of the alcohol **305**, followed by debenzylation and Wittig methylenation to give the alcohol **306**. The alcohol **306** was converted to the methyl ester **307** by a two-step oxidation to the acid and subsequent methylation with diazomethane. The ester **307** was efficiently coupled to Garner's aldehyde (**308**, 1.1 equiv) using NaHMDS to give the alcohol **309** as a single diastereomer (Felkin-Anh addition). This stereocenter, however, was of no consequence because the alcohol was removed by Barton-McCombie deoxygenation (xanthate ester formation followed by radical deoxygenation). Next, DIBAL reduction of the ester at -100 ºC followed by vinyl Grignard addition to the resulting aldehyde yielded the diene

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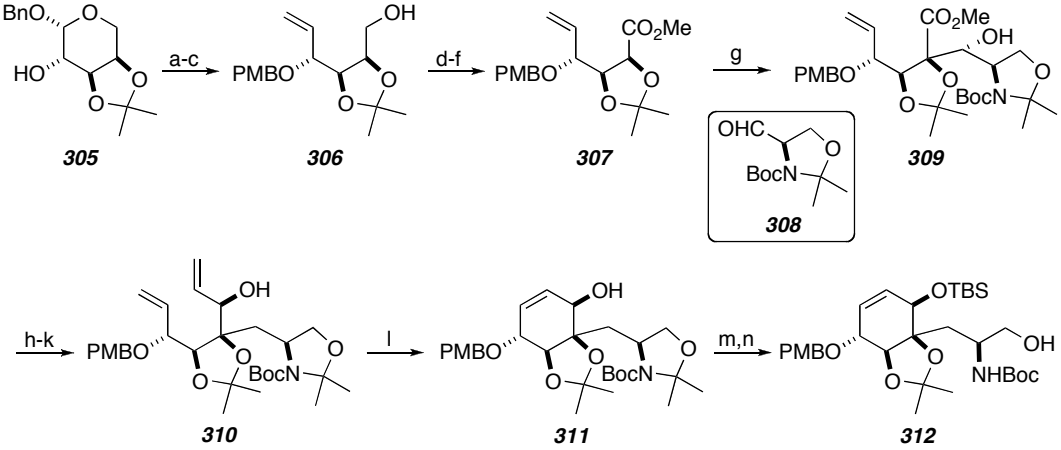
"Towards the Synthesis of Scyphostatin," Gurjar, M. K.; Hotha, S. *Heterocycles* **2000**, *53*, 1885-1889. (d) "Stereoselective Reactions of a (–)-Quinic Acid-Derived Enone: Application to the Synthesis of the Core of Scyphostatin," Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943-1946. (e) "Enantiocontrolled synthesis of the epoxycyclohexenone moieties of scyphostatin, a potent and specific inhibitor of neutral sphingomyelinase," Katoh, T.; Izuhara, T.; Yokota, W.; Inoue, M.; Watanabe, K.; Nobeyama, A.; Suzuki, T. *Tetrahedron* **2006**, *62*, 1590-1608. (f) "A Short and Efficient Route to Novel Scyphostatin Analogues," Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237-3239. (g) "Efficient synthesis of a 4,5-epoxy-2-cyclohexen-1-one derivative bearing a spirolactone *via* a Diels–Alder reaction with high -facial selectivity: a synthetic study towards scyphostatin," Takagi, R.; Miyanaga, W.; Tamura, Y.; Ohkata, K. *Chem. Commun.* **2002**, 2096-2097. (h) "Synthesis of a 4,5-epoxy-2-cyclohexen-1-one derivative *via* epoxide ring opening, 1,3-carbonyl transposition and epoxide ring regeneration: a synthetic study on a scyphostatin analogue," Takagi, R.; Tojo, K. Iwata, M.; Ohkata, K. *Org. Biomol. Chem.* **2005**, *3*, 2031-2036. (i) "Furan Diels-Alder Cycloaddition Approach to the Highly Oxygenated Core of Scyphostatin," Stevenson, N. G.; Savi, C. D.; Harrity, J. P. *Synlett* **2006**, 2272-2274. (j) "Synthesis and Evaluation of Three Novel Scyphostatin Analogues as Neutral Sphingomyelinase Inhibitors," Pitsinos, E. N.; Wascholowski, V.; Karaliota, S.; Rigou, C.; Couladouros, E. A.; Giannis, A. *ChemBioChem* **2003**, *4*, 1223-1225. (k) "Synthesis and Antiapoptotic Activity of a Novel Analogue of the Neutral Sphingomyelinase Inhibitor Scyphostatin," Claus, R. A.; Wustholz, A.; Muller, S.; Bockmeyer, C. L.; Riedel, N. H.; Kinscherf, R, Deigner, H-P. *ChemBioChem* **2005**, *6*, 726-727.

310. This diene allowed for the formation of the cyclohexene **311** by RCM, which was successfully carried out in high yield by treatment with Grubbs first-generation catalyst (G1) in refluxing CH_2Cl_2. The synthesis of the cyclohexene **312** was completed by TBS-protection of the allylic alcohol and selective removal of the *N*,*O*-acetonide with PPTS.

Scheme III-2. Synthesis of the Cyclohexene **312** from the Alcohol **305**.



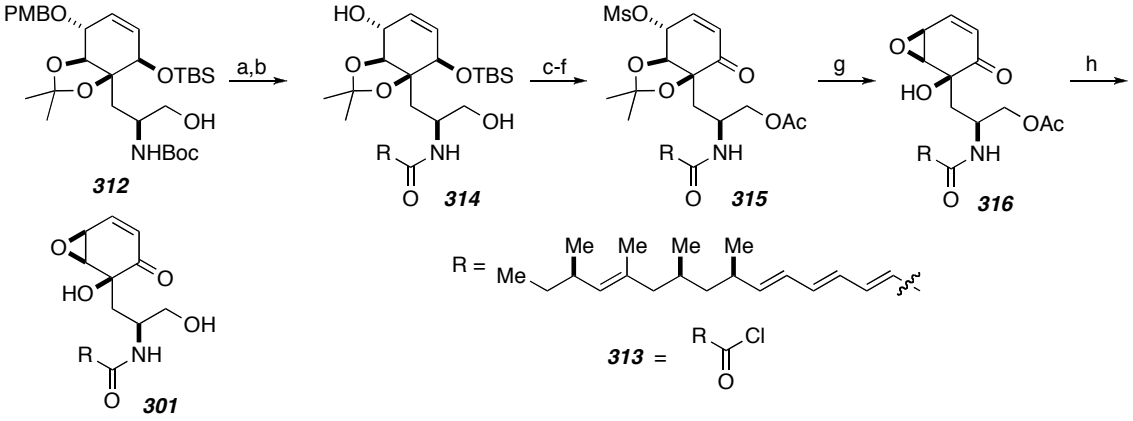
305 306 307 308 309 310 311 312

Reagents and Conditions: (a) PMBCl, NaH, DMSO, rt, 70%; (b) H_2, Raney Ni, EtOH, rt, 86%; (c) $Ph_3P^+CH_3Br^-$, *t*BuOK, PhH, reflux, 86%; (d) Swern oxidation, 95%; (e) $NaClO_2$, NaH_2PO_4, DMSO/H_2O, rt; (f) CH_2N_2, Et_2O/MeOH, 0 ºC, 78% (2 steps); (g) NaHMDS, THF, -78 ºC;Garner's aldehyde (**308**), -78 ºC, 69%; (h) NaHMDS, THF, 0 ºC; CS_2; MeI, 0 ºC to rt; (i)*n*Bu_3SnH, AIBN, $PhCH_3$, reflux, 53% (2 steps); (j) DIBAL, CH_2Cl_2, -100 ºC, 88%; (k) vinylmagnesium bromide, THF, 0 ºC, 93%; (l) $(Cy_3P)_2RuCl_2$(=CHPh) (10 mol%), CH_2Cl_2, reflux, 96%; (m) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 93%; (n) PPTS, EtOH, 60 ºC, 57%.

The synthesis of scyphostatin continued (Scheme III-3) by treatment of the Boc-amine **312** with TMSOTf, which affected not only Boc removal, but also PMB deprotection. Immediate exposure of this free amine to the acid chloride **313** provided the amide **314**. At this point, the carbon skeleton of scyphostatin was in place, and only functional group manipulation of the cyclohexene ring was needed in order to form the required epoxy cyclohexenone. To achieve this, the primary alcohol of the amide diol **314** was acetylated, followed by mesylation of the secondary alcohol. The TBS group of the orthogonally protected pentaol was selectively removed with TBAF, and oxidation of the free allylic alcohol with Dess-Martin periodinane furnished the cyclohexenone **315**.

The acetonide was then removed with trichloroacetic acid, and subsequent treatment with NaOH gave the epoxide **316** via intramolecular mesylate displacement. Finally, mild deacetylation was accomplished with lipase PS in aqueous media to deliver (+)-scyphostatin (**301**).

Scheme III-3. Completion of Katoh's Synthesis of Scyphostatin.



Reagents and Conditions: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, rt; MeOH; (b) **313**, Et_3N, CH_2Cl_2, rt; AcOH (aq.) 73% (2 steps); (c) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 72%; (d) MsCl, Et_3N, CH_2Cl_2, rt, 93%; (e) TBAF, THF, rt; (f) Dess-Martin periodinane, CH_2Cl_2, rt, 98% (2 steps); (g) CCl_3CO_2H, CH_2Cl_2/H_2O, reflux; NaOH (2M), rt, 45%; (h) lipase PS, pH=7 phosphate buffer/acetone, rt, 60%.

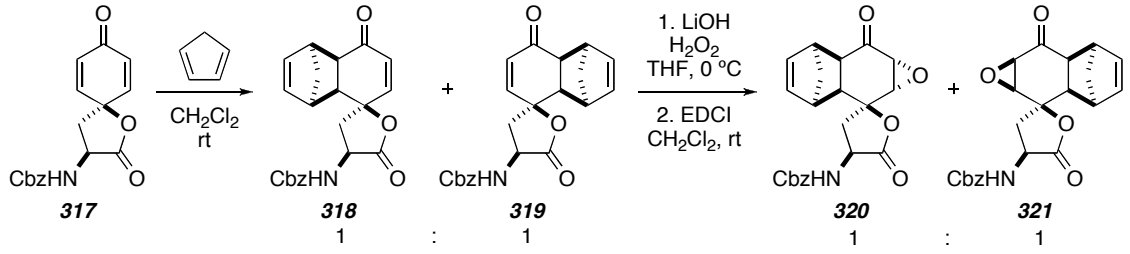
III.C.2. Takagi's Synthesis of Scyphostatin

The second total synthesis of scyphostatin was reported by the Takagi group in 2007.[25] Takagi's synthesis of the polar core started (Scheme III-4) with the Diels-Alder reaction of cyclopentadiene and the spirolactone **317** (available in 2 steps from L-tyrosine).[32] This produced the two *endo* Diels-Alder adducts, **318** and **319**, in a 1:1 mixture. Epoxidation of this mixture of enones with LiOH / H_2O_2, followed by treatment with EDCI to reform the lactone, gave the epoxides **320** and **321**. The configuration of the *exo*-epoxide **320** and the *endo*-epoxide **321**, which curiously resulted from opposite facial selectivity, was determined by ^{1}H NMR dif-NOE experiments. These products

[32] "Studies on the synthesis of *Stemona* alkaloids; stereoselective preparation of the hydroindole ring system by oxidative cyclization of tyrosine," Wipf, P.; Kim, Y. *Tetrahedron Lett*. **1992**, *33*, 5477-5480.

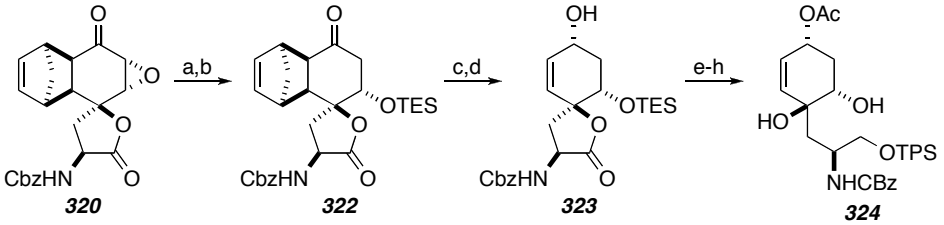
were separated by column chromatography, and only the desired epoxide **320** was carried forward.

Scheme III-4. Diels-Alder Reaction of the Dienone **317** followed by Epoxidation.



The epoxide **320** was further elaborated (Scheme III-5) by SmI_2-induced reductive cleavage of the C-O bond α to the ketone, followed by TES-protection of the alcohol to give the ketone **322**. Next, the cyclohexenone double bond was revealed by a retro-Diels-Alder reaction, which was achieved quantitatively by heating **322** to 230 ºC in the presence of maleic anhydride. The enone was reduced in a 1,2-fashion utilizing Luche's conditions to yield the allylic alcohol **323** as a single diastereomer. The diol **324** was obtained in a straightforward manner from the allylic alcohol **323** by acetylation, $NaBH_4$-reduction of the lactone to the diol, TES-deprotection with TBAF, and TPS-protection of the primary alcohol with TPSOTf.

Scheme III-5. Synthesis of the Diol **324** from the Epoxide **320**.

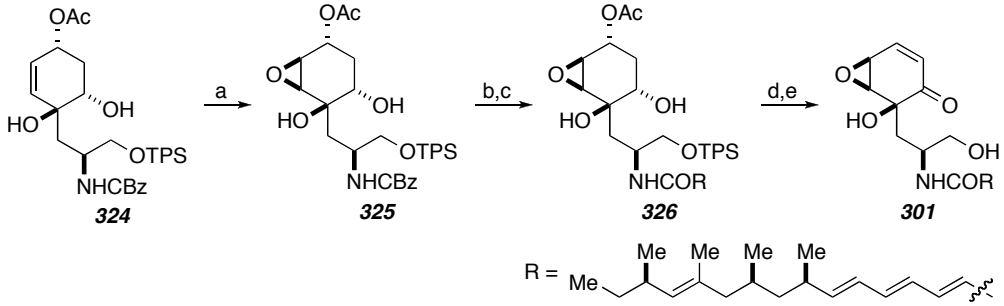


Reagents and conditions: (a) SmI_2, MeOH, THF, -78 ºC; (b) TESCl, imidazole, CH_2Cl_2, rt, 83% (2 steps); (c) maleic anhydride, Ph_2O, 230 ºC, 100%; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, THF, *i*-PrOH, 0 ºC, 95%; (e) Ac_2O, pyr, CH_2Cl_2, 0 ºC, 99%; (f) $NaBH_4$, EtOH, 0 ºC, 94%; (g) TBAF, THF, rt, 94%; (h) TPSOTf, 2,6-lutidine, CH_2Cl_2, 0 ºC, 83%.

The final steps (Scheme III-6) of Takagi's synthesis of scyphostatin began with a directed epoxidation of the allylic alcohol **324** with *m*CPBA to produce the epoxide **325**

as a single diastereomer. Next, hydrogenolysis of the CBz-group was accomplished with $Pd(OH)_2/C$ in the presence of AcOH, and the free amine was immediately exposed to amide coupling conditions (EDCI) to provide the amide **326**. Swern oxidation of **326** also resulted in β-elimination of acetate to give the required cyclohexenone moiety. (+)-Scyphostatin (**301**) was finally generated when TPS-deprotection occurred upon exposure to TBAF under acidic conditions (AcOH). To summarize, this synthesis was achieved in 16 steps (longest linear sequence) from the spirolactone **317** (available from L-tyrosine in 2 steps) in 2.2% overall yield.

Scheme III-6. Completion of Takagi's Synthesis of Scyphostatin.



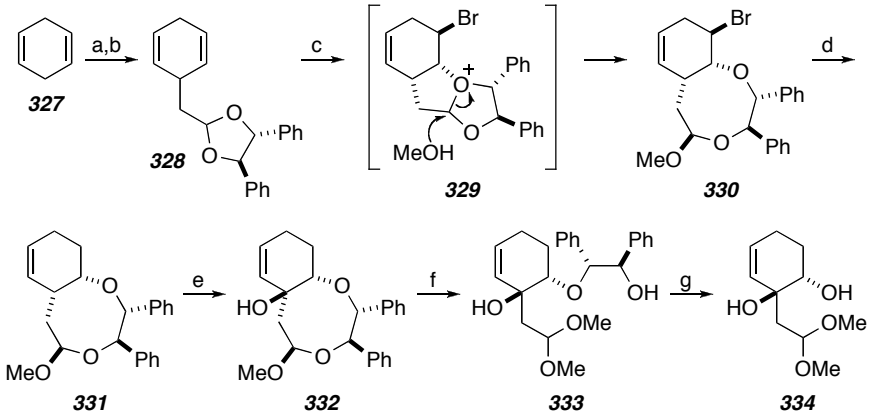
Reagents and Conditions: (a) *m*CPBA, CH_2Cl_2, 0 ºC, 84%; (b) $Pd(OH)_2/C$, H_2, AcOH, MeOH, rt; (c) RCO_2H, EDCI, DIPEA, DMF, 0 ºC, 65% (2 steps); (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ºC, 49% (72% brsm); (e) TBAF, AcOH, THF 0 ºC, 61%.

III.C.3. Kita's Synthesis of Scyphostatin

The only other total synthesis of scyphostatin disclosed to date was reported by Kita's group in 2007.[26] This synthesis was completed in 17 steps from 1,4-cyclohexadiene (**327**) in 0.4% overall yield. The synthesis was initiated by lithiation of 1,4-cyclohexadiene, which was alkylated with bromoacetaldehyde diethyl acetal. Subsequent treatment with (*R,R*)-hydrobenzoin under acidic conditions (*p*TsOH) yielded the transacetalized product, the acetal **328**. Exposure of the acetal **328** to NBS allowed for the formation of an intermediate oxonium species, **329**, which underwent ring-

expansion upon MeOH attack to give the bromide **330**. Next, debromination was effected under radical conditions (AIBN, Bu_3SnH) to produce the ether **331**. The allylic alcohol **332** was formed by regio- and stereoselective oxidation with SeO_2, and the cyclic acetal was opened with acidic MeOH to give the dimethyl acetal **333**. Finally, the diol **334** was obtained by cleaving the benzylic ether bond using dissolving metal reduction conditions.

Scheme III-7. Synthesis of the Diol **334** from 1,4-cyclohexadiene (**327**).

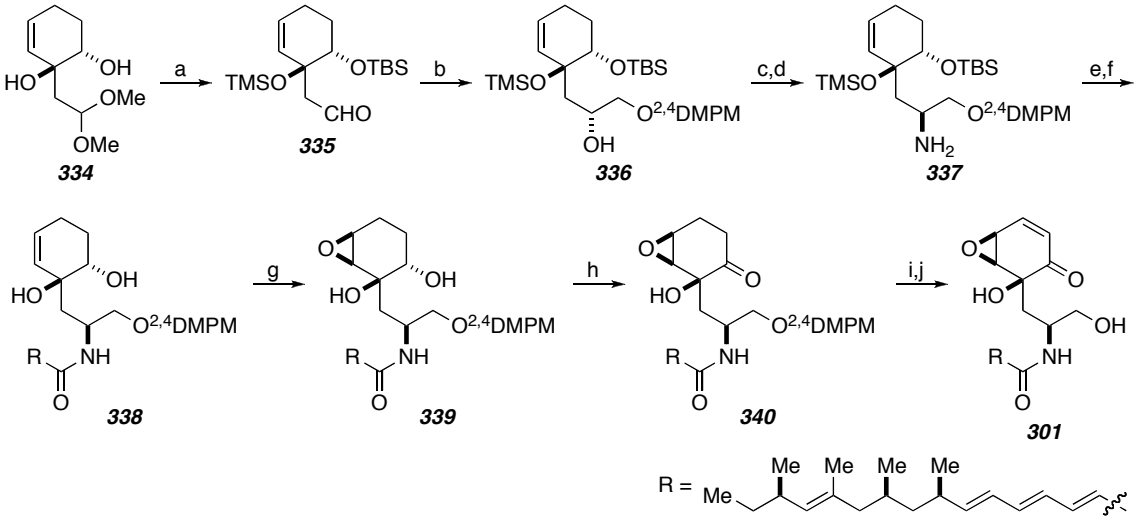


Reagents and Conditions: (a) *sec*-BuLi, TMEDA, THF, -78 ºC, then $BrCH_2CH(OEt)_2$, 75%; (b) (*R,R*)-hydrobenzoin, *p*TsOH, $PhCH_3$, 50 ºC, quant.; (c) NBS, MeOH, CH_3CN, -40 ºC to rt, 64%; (d) Bu_3SnH, AIBN, PhH, reflux, 89%; (e) SeO_2, pyridine, dioxane, 70 ºC, 42% (58% brsm); (f) PPTS, MeOH, rt, 91%; (g) Ca, EtOH, liq. NH_3, -40 ºC, 91%.

Kita's synthesis resumed (Scheme III-8) with a sequential, selective TBS- and TMS-protection of the diol **334**, followed by hydrolysis of the dimethyl acetal, all of which were carried out in one pot to provide the aldehyde **335**. Treatment of this aldehyde with the alkyllithium species derived from the transmetalation of 2,4-dimethoxyphenylmethyloxymethyl (^{2,4}DMPM) tributyl stannane with *n*BuLi furnished the *R*-alcohol **336** with modest stereoselectivity (~2:1 *R*-alcohol:*S*-alcohol, separated by column chromatography). Mitsunobu displacement of the alcohol with azide, followed by reduction with $LiAlH_4$ resulted in the inverted amine **337**. The amide **338** was then obtained via amide coupling (DCC) with the required acid, followed by silyl-deprotection

(TBAF). Tertiary alcohol-directed epoxidation with TBHP and [$VO(acac)_2$] yielded the epoxide **339** as a single diastereomer. The ketone **340** was then obtained upon Dess-Martin oxidation. (+)-Scyphostatin (**301**) was finally produced after the lithium enolate was treated with *N-tert*-butylphenylsulfinimidoyl chloride to form the enone, followed by mild deprotection of the ^{2,4}DMPM-protected alcohol with trityl tetrafluoroborate.

Scheme III-8. Completion of Kita's Synthesis of Scyphostatin.



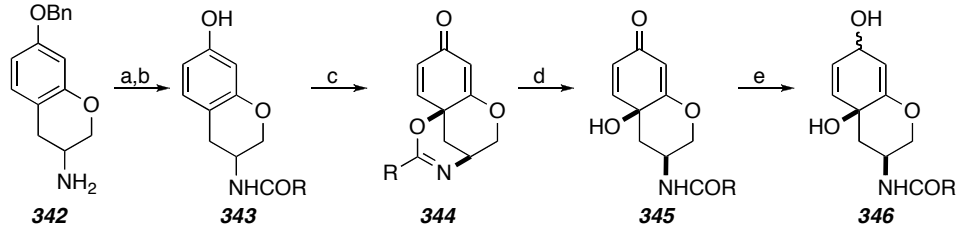
Reagents and Conditions: (a) TBSOTf, 2,4,6-collidine, CH_2Cl_2, -78 ºC; TMSOTf; H_2O, 94%; (b) $^{2,4}DMPMOCH_2SnBu_3$, *n*BuLi, THF, -78 ºC, 56%; (c) DPPA, PPh_3, DEAD, THF, rt, 75%; (d) $LiAlH_4$, THF, 0 ºC to rt; (e) RCO_2H, DCC, DMAP, CH_2Cl_2, rt; (f) TBAF, THF, rt, 59% (3 steps); (g) TBHP, [$VO(acac)_2$], $PhCH_3$, 0 ºC, 73%; (h) Dess-Martin periodinane, CH_2Cl_2, 40 ºC, 69% (78% brsm); (i) Ph(Cl)S=N*t*Bu, LDA, [15]crown-5, THF, -78 ºC, 35% (82% brsm); (j) $Ph_3C^+BF_4^-$, CH_2Cl_2, 0 ºC, 66%.

III.C.4. Pitsinos' Synthetic Studies of the Polar Core of Scyphostatin

The Pitsinos group carried out an efficient synthesis of the palmitoyl side-chain scyphostatin analog **341** (Scheme III-10), the same analog I was aiming to make.[27] Their synthesis of the scyphostatin analog **341** in its racemic form was achieved in 9 steps from

the amine **342**.[33] In a more recent report, Pitsinos discloses a synthesis of the enantiomerically pure amine **342**.[34] The synthesis began (Scheme III-9) with the amide coupling (EDCI) of palmitic acid to the amine **342**, followed by debenzylation to give the amide **343**. Next, oxidative dearomatization (PIFA) was carried out in the presence of trifluoroethanol, a non-nucleophilic solvent, to allow intramolecular attack from the amide oxygen to give the oxazine **344**. Hydrolysis of this oxazine resulted in the amide **345** as one diastereomer (oxidative dearomatization in the presence of CH_3CN/H_2O resulted in poor diastereoselectivity, which is why this two-step process was employed to make the amide **345**). Luche reduction of the dienone **345** yielded the allylic alcohol **346** as a 2:1 mixture of diastereomers.

Scheme III-9. Synthesis of the Amide **III-8e** from the Amine **342**.



342 ***343*** ***344*** ***345*** ***346***

R = $CH_2(CH_2)_{13}CH_3$

Reagents and Conditions: (a) Palmitic acid, EDCI, HOBT, DIPEA, CH_2Cl_2/DMF, 0 ºC to rt, 85%; (b) H_2, 10% Pd/C, EtOH/THF, 98%; (c) PIFA, CF_3CH_3OH; (d) PPTS, THF/H_2O; K_2CO_3, 37% (2 steps); (e) $NaBH_4$, $CeCl_3$, MeOH, 0 ºC, 98%.

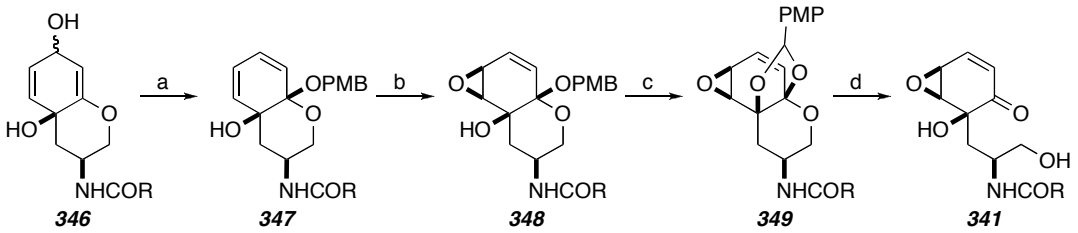
The final steps of Pitsinos' synthesis (Scheme III-10) of the scyphostatin analog **341** started with acidic dehydration of the alcohol **346** in the presence of PMBOH to give the ketal **347**. Then, regio- and stereoselective epoxidation (*m*CPBA) of the diene **347** furnished the epoxide **348** as one diastereomer. The acetal **349** was formed upon

[33] "*N,N*-Disubstituted Aminomethyl Benzofuran Derivatives: Synthesis and Preliminary Binding Evaluation," Boye, S.; Pfei, B.; Renard, P.; Rettori, M.-C.; Guillaumet, G.; Viaud, M.-C. *Bioorg. Med. Chem.* **1999**, *7*, 335-341.

[34] "Synthesis of enantiopure (*S*)-7-hydroxy-3-amino-3,4-dihydro-2*H*-1-benzopyran en route to (+)-scyphostatin," Pitsinos, E. N.; Moutsos, V. I.; Vageli, O. *Tetrahedron Lett.* **2007**, *48*, 1523-1526.

treatment with DDQ, and subsequent exposure to montmorillonite K10 finally resulted in the (±)-scyphostatin analog **341**. This synthesis of the racemic analog **341** was achieved in 9 steps from the amine **342** in 6.6% overall yield.

Scheme III-10. Completion of Pitsinos' Synthesis of the Scyphostatin Analog **341**.

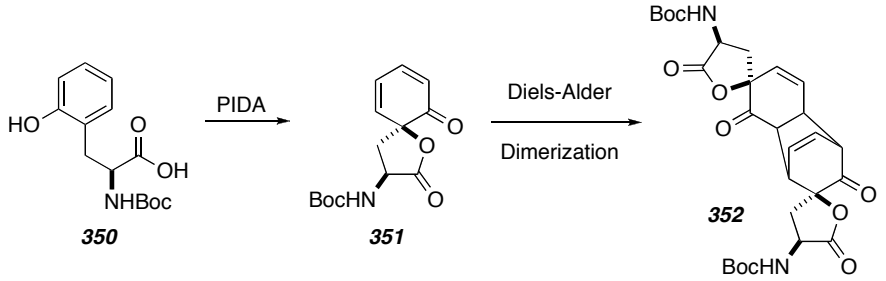


Reagents and Conditions: (a) PPTS, PMBOH, THF, 4Å MS, 63%; (b) *m*CPBA, Na_2HPO_4, CH_2Cl_2, 0 ºC, 89%; (c) DDQ, CH_2Cl_2, 71%; (d) Montmorillonite K10, CH_2Cl_2, 55%.

III.D.1. Previous Hoye Group Synthetic Efforts Towards Scyphostatin

Initial efforts toward scyphostatin began shortly after the structure was reported in 1997. Oxidative dearomatization (Scheme III-11) of the Boc-protected *o*-tyrosine **350** gave the desired dienone spirolactone **351**. Further studies of epoxidizing the dienone **351** could not be carried out, however, due to the propensity of the dienone to dimerize via a Diels-Alder reaction to form the adduct **352** as a mixture of diastereomers.[35]

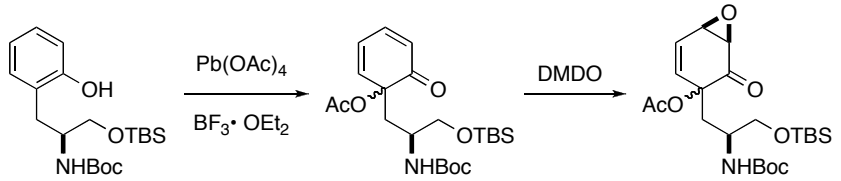
Scheme III-11. Hoye Group's Initial Approach to the Scyphostatin Polar Core



[35] "Reactive Dienes: Intramolecular Aromatic Oxidation of 3-(2-Hydroxyphenyl)-propionic Acids," Drutu, I.; Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2002**, *4*, 493-496.

A former Hoye group member, Manomi Tennakoon, was able to solve the dimerization issue by treating (Scheme III-12) the *o*-tyrosine derivative **353** with $Pb(OAc)_4$ in the presence of BF_3•OEt_2 to produce the less reactive dienone **354**, which was less susceptible to Diels-Alder dimerization.[36] Epoxidation of the dienone **354**, however, only led to the undesired epoxide **355**. All attempts to convert the epoxide **355** into the polar core of scyphostatin were unsuccessful; therefore, this approach was deserted.

Scheme III-12. Tennakoon's Approach toward the Scyphostatin Polar Core



353 ***354*** ***355***

III.D.2. A Revised Strategy to the Polar Core of Scyphostatin

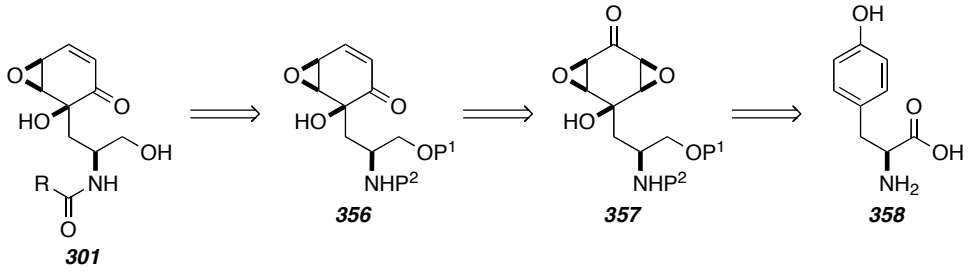
The scyphostatin project had laid dormant in the Hoye group for a number of years, but in 2006 work on this project was restored due to a new strategy devised by Hoye and Jeffrey.[37] This novel approach (Scheme III-13) would again require an oxidative dearomatization of an intermediate derived from L-tyrosine (**358**), followed by an epoxidation to produce the diepoxide **357**. The key transformations of this approach would rely upon desymmetrizing the pseudo-symmetric diepoxide **357** to give the epoxycyclohexenone **356** in a quite efficient manner. Schyphostatin **301** could then be achieved in a few steps via amide coupling and deprotection. The process of desymmetrization, if realized in this project, would allow for a substantial reduction in

[36] Tennakoon, M., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2001**.

[37] Jeffrey, C. S., Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2007**.

the number of steps needed to synthesize the polar core of (+)-scyphostatin compared to the prior syntheses discussed above (Section III.C). The synthesis under this revised strategy could be completed in 10 or fewer steps from an inexpensive and commercially available starting material, L-tyrosine (**358**). The previous syntheses all required about twice as many steps.[24,25,26]

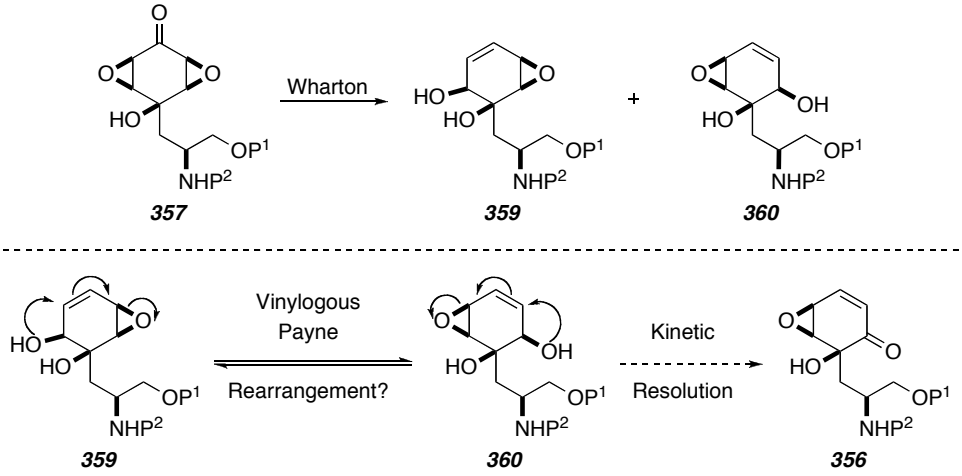
Scheme III-13. Retrosynthesis of Revised Strategy to Scyphostatin Polar Core



As stated above, the desymmetrization of the pseudo-symmetric diexpoxide **357** is the critical element of this strategy, and it would be accomplished (Scheme III-14) by a Wharton rearrangement followed by a kinetic resolution of the diastereomeric epoxy allylic alcohols **359** and **360**. It was anticipated that the Wharton rearrangement would result in an ~1:1 product ratio of the epoxy allylic alcohols **359** and **360**, with the allylic alcohol **360** being the desired diastereomer that would only need to be oxidized to the enone **356** to give the polar core of (+)-scyphostatin. It was believed that **359** and **360** could possibly interconvert (Scheme III-14, bottom) under acid or base catalysis by an intramolecular S_N2' opening of the epoxide, a process referred to as a vinylogous Payne rearrangement.[38]

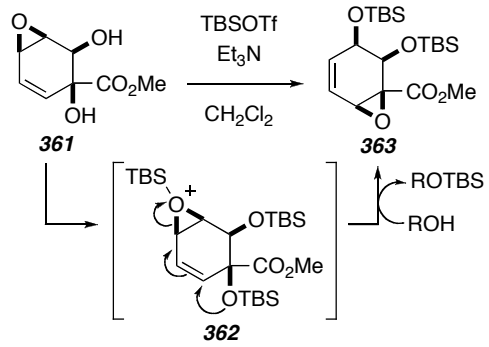
[38] "Control of Secondary Metabolite Congener Distributions via Modulation of the Dissolved Oxygen Tension," Frykman, S. A.; Tsuruta, H.; Starks, C. M.; Regentin, R.; Carney, J. R.; Licari, P. J. *Biotechnol. Prog.* **2002**, *18*, 913-920.

Scheme III-14. Wharton Reaction Followed by a Possible Vinylogous Payne Rearrangement



Myers had reported on a similar reaction occurring under silylative conditions (Scheme III-15), which further strengthened Hoye and Jeffrey's hypothesis.[39] The Myers result involved treatment of the epoxy diol **361** with TBSOTf to give the rearranged epoxide **363**. The reaction was believed to have occurred via the cationic intermediate **362**, which was poised to undergo a vinylogous Payne rearrangement. Subsequent intermolecular silyl transfer furnished the epoxide **363**.

Scheme III-15. Myers' Silylative Vinylogous Payne Rearrangement



[39] "Synthesis of a Broad Array of Highly Functionalized, Enantiomerically Pure Cyclohexanecarboxylic Acid Derivatives by Microbial Dihydroxylation of Benzoic Acid and Subsequent Oxidative and Rearrangement Reactions," Myers, A. G.; Siegel, D. R.; Buzard, D. J.; Charest, M. G. *Org. Lett.* **2001**, *3*, 2923-2926.

There are two main ways to take advantage of an equilibration of the epoxides **359** and **360** (Scheme III-14) via a vinylogous Payne rearrangement. The first scenario would only be relevant if the epoxides **359** and **360** could be separated by chromatography. If this were the case, then the undesired diastereomer, the epoxide **359**, could be separated from the epoxide **360** and reequilibrated to a 1:1 mixture of the epoxides **359** and **360**. Multiple iterations of this process would allow for the mixture of diastereomers to be completely converted to the desired diastereomer, the epoxide **360**.

The second and far more appealing scenario (Scheme 14, bottom) would involve a dynamic kinetic resolution (DKR), in which the 1:1 mixture of the expoxides **359** and **360** could be directly converted to the enone **356**.[40] This oxidative DKR could be realized if a couple of criteria could be met. First, a chiral oxidant would be needed that would *selectively* oxidize the desired diastereomer, the epoxide **360**, while being unreactive (or oxidize at a negligible rate) towards the undesired diastereomer, the epoxide **359**. The second criteria would be that the epoxides **359** and **360** could equilibrate under these oxidative conditions, allowing complete conversion to the enone **356**. A DKR is one of the most elegant and efficient of chemical processes, and it would be the capstone of this project if it could be pulled off.

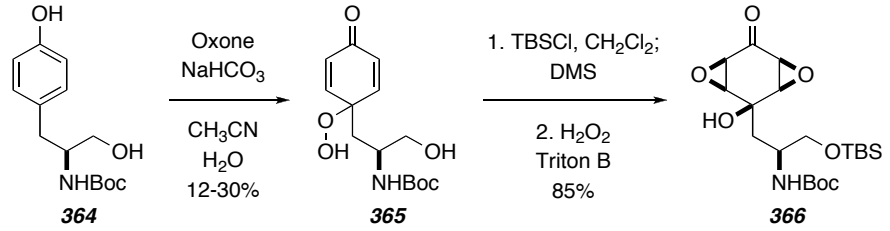
III.D.3. Chris Jeffrey's Efforts Toward the Polar Core of Scyphostatin

The revised strategy was investigated by Chris Jeffrey by first analyzing the oxidative dearomatization / epoxidation / Wharton rearrangement sequence with a simplified model system.[37] The model study proved to be successful, so Jeffrey turned his focus to making the actual (+)-scyphostatin polar core by first employing a Boc-TBS

[40] "Dynamic Kinetic Resolution," Pellissier, H. *Tetrahedron* **2003**, *59*, 8291-8327.

protection strategy of the amino alcohol (Scheme III-16). Oxidative dearomatization of the known phenol **364** was executed using Oxone® under aqueous basic conditions (these conditions chemically generate singlet oxygen and were used successfully [65% yield] in the model system) to give the hydroperoxide **365** in low yield.[41,42] The primary alcohol was protected as its TBS-ether, followed by reduction of the hydroperoxide with dimethyl sulfide (Jeffrey found that reversing the order of these two steps resulted in a much lower yield). Subsequent epoxidation with basic H_2O_2 gave the diepoxide **366** as a single diastereomer. The directing effect of the tertiary alcohol in this basic epoxidation to give the all *syn* configuration of the five contiguous stereocenters in the diepoxide **366** is a critical component of this synthesis since it gives the relative configuration that is required for the polar core of scyphostatin.[43] Furthermore, I will speculate in the next section (Section III.E, Synthetic Efforts Toward the Polar Core of Scyphostatin) that this stereochemical relationship ended up being an essential feature that permitted the vinylogous Payne rearrangement to take place under relatively mild conditions.

Scheme III-16. Jeffrey's Synthesis of the Diepoxide **366**.



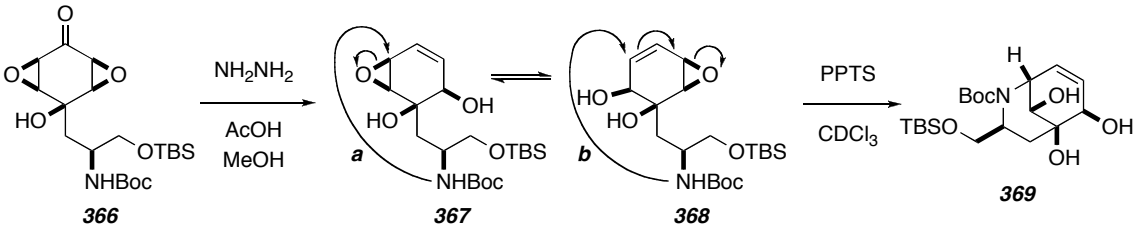
[41] "Efficient Procedure for the Reduction of α-Amino Acids to Enantiomerically Pure α-Methylamines," Quagliato, D. A.; Andrae, P. M.; Matelan, E. M. *J. Org. Chem.* **2000**, *65*, 5037–5042

[42] "Oxidative De-Aromatization of Para-Alkyl Phenols in Para-Peroxyquinols and Para-Quinols Mediated by Oxone as a Source of Singlet Oxygen," Carreno, M. C.; Gonzalez-Lopez, M.; Urbano, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 2737-2741.

[43] "Organometallic additions to protected quinone bis-epoxides and quinone monoacetals: synthesis of the aranorosin nucleus," McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Chem. Commun.* **1992**, 1589–1591.

Jeffrey was now able to study the Wharton rearrangement (Scheme III-17) of the diepoxide **366**. Exposure of this diepoxy ketone to hydrazine and acetic acid gave an ~1:1 ratio of the epoxy allylic alcohols **367** and **368**, according to crude ^{1}H NMR analysis. He was unable to isolate these products, however, by silica gel chromatography. Instead, he isolated a more polar compound, which proved to be the diastereomerically pure azabicycle **369**. Since the azabicycle **369** formed as a single diastereomer, there must be a mechanism that allows both the epoxy allylic alcohols **367** and **368** to converge to a single product. Jeffrey envisioned that this could occur in one of two ways. Either, the N-Boc nitrogen in **367** could directly attack the epoxide (Scheme III-17, arrow *a*) to give the azabicycle **369**, or the same nucleophile in **368** could attack in an S_N2' manner (Scheme III-17, arrow *b*) to also give the same product. The other mechanism that would result in convergence to a single product would involve equilibration of **367** and **368** via a vinylogous Payne rearrangement, while product formation would occur exclusively through one or the other of the two processes shown in Scheme III-17. Jeffrey speculated that the acidity of silica gel induced the cyclization to the azabicycle **369**; thus, he was able to recreate this reaction by treating **366** with acid (PPTS) in $CDCl_3$. He monitored the cyclization by ^{1}H NMR spectroscopy and observed that the epoxides **367** and **368** were being consumed at essentially the same rate. This would not be expected if the operative mechanism required both S_N2 and S_N2' pathways, since the rate of these two processes would be expected to be noticeably different. This observation is more consistent with one or the other of paths *a* vs *b* coupled with more rapid equilibration of **367** and **368**, thereby providing support for the feasibility of a vinylogous Payne rearrangement in this system.

Scheme III-17. Wharton Rearrangement Followed by Undesired Epoxide Opening



A modified protecting group strategy was then employed to keep the amine from interfering. A Boc-acetonide protecting group pair was used, starting with the known phenol **370**.[44] The singlet oxygen conditions used above (Oxone® / aq. $NaHCO_3$) proved to be even less effective with this substrate. Jeffrey then turned to more standard oxidative dearomatization conditions using hypervalent iodine species (PIDA or PIFA) in aqueous solvent combinations, but all of these attempts also gave very low yields. Next, he explored conditions using photochemically generated singlet oxygen (irradiation in the presence of oxygen and a sensitizer). The use of photochemically generated singlet oxygen to effect oxidative dearomatization in a natural product synthetic study has rarely been reported, and Jeffrey found it to work well for him in this case.[45] He found that basic conditions (pH=10 buffer) were needed in order for the reaction to proceed at a reasonable rate.[46] Photooxygenation (O_2, Rose Bengal [RB], $MeOH/H_2O$[pH=10]) of the phenol **370**, followed by reduction of the hydroperoxide with dimethyl sulfide gave the

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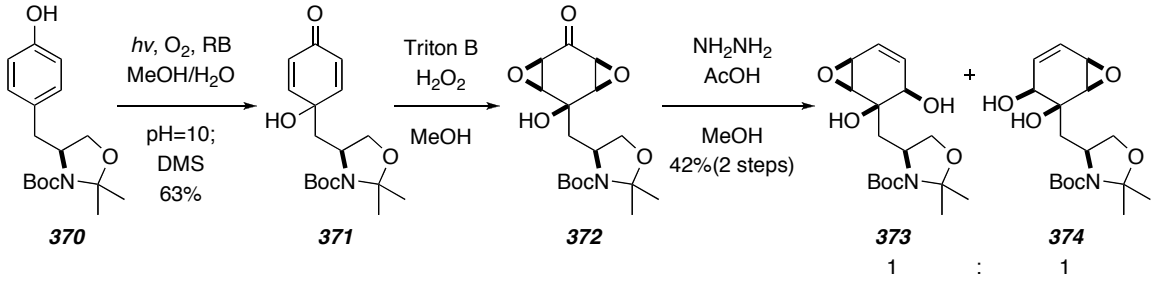
[44] "The Total Synthesis of the Diepoxycyclohexanone Antibiotic Aranorosin and Novel Synthetic Analogs," McKillop, A.; McLaren, L.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1385-1393.

[45] (a) "Diastereotopic Group Selective Intramolecular Conjugate Addition of 4-(2-Hydroxyethyl)-p-Quinol Derivatives: Synthesis of the Optically Pure cis-7-0xabicyclo[4.3.0]non-2-en-4-one Skeleton," Fujioka, H.; Kitagaki, S.; Ohno, N.; Kitagawa, H.; Kita, H. *Tetrahedron: Asymmetry* **1994**, *5*, 333-336. (b) "Biogenesis-like transformation of salidroside to rengyol and its related cyclohexyletanoids of *Forsythia suspensa*," Endo, K.; Seya, K.; Hikino, H. *Tetrahedron* **1989**, *45*, 3673-3682.

[46] "Quenching of Singlet Oxygen by Trolox C, Ascorbate, and Amino Acids: Effects of pH and Temperature," Bisby, R. H.; Morgan, C. G.; Hamblett, I.; Gorman, A. A. *J. Phys. Chem. A* **1999**, *103*, 7454-7459.

dienone **371** in a good yield. Epoxidation of the dienone produced the diepoxide **372**, which was subsequently exposed to the Wharton rearrangement conditions to yield the diastereomeric epoxides **373** and **374** as a 1:1 mixture. Gratifyingly, Jeffrey was able to separate these diastereomers by normal phase HPLC. Spectroscopic analysis of the epoxides **373** and **374**, however, was complicated by broadening of the ^{1}H NMR peaks due to the Boc rotamers. It also became known around this time that the Boc protecting group could not be removed in the presence of the epoxy cyclohexenone core of scyphostatin.[37] Therefore, the Boc protecting group approach was abandoned.

Scheme III-18. Wharton Rearrangement of the Boc-Acetonide **372**.

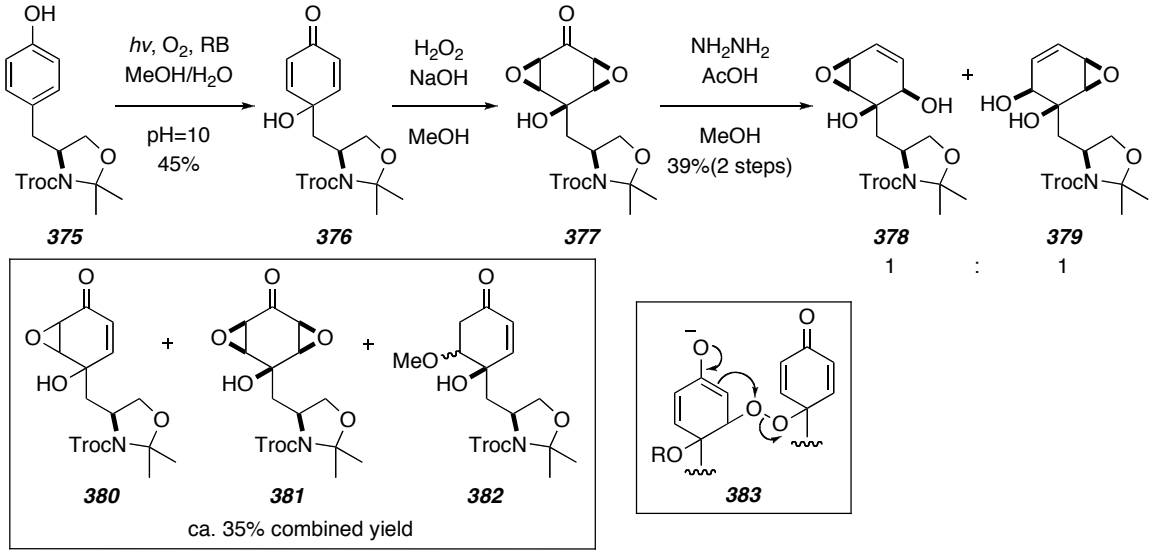


The carbamate protecting group was changed to Troc because it can be removed under mild conditions, and it has been known to be removed in the presence of epoxides and enones.[47] The Troc-acetonide **375** (available in 3 steps from L-tyrosine)[37] gave a different product mixture than the Boc-acetonide **370** in the photooxygenation reaction. It resulted in direct formation of the hydoxy dienone **376** (45% yield) without any of the corresponding hydroperoxide being isolated. This was accompanied by isolation of the monoepoxide **380** (2 diastereomers), the diepoxide **381**, and the methanol adduct **382** in a combined 35% yield. Jeffrey reasoned that the epoxides **380** and **381** could have resulted

[47] "Synthesis of Vinca Alkaloids and Related Compounds. 100. Stereoselective Oxidation Reactions of Compounds with the Aspidospermane and Quebrachamine Ring System. First Synthesis of Some Alkaloids Containing the Epoxy Ring," Éles, J.; Kalaus, G.; Greiner, I.; Kajtár-Peredy, M.; Szabó, P.; Keserû, G. M.; Szabó, L.; Szántay, C. *J. Org. Chem.* **2002**, *67*, 7255–7260.

from enone epoxidation through an intermediate like **383**, in which the initially formed hydroperoxide acts as the oxidant. This would also explain why the hydroperoxide wasn't isolated, because it was all reduced to the alcohol **376**. The yield of the dienone **376** in this reaction was still reasonable, so Jeffrey moved forward. Dienone epoxidation resulted in the diepoxide **377**, which was then treated with hydrazine and acetic acid to give the epoxy allylic alcohols **378** and **379** as a 1:1 mixture. These diastereomers, the epoxides **378** and **379**, could also be separated by normal phase HPLC.

Scheme III-19. Synthesis of the Troc-Acetonide Epoxy Allylic Alcohols **378** and **379**.



At this point, Jeffrey's efforts on the scyphostatin project ended due to completion of his Ph.D. studies. He was successful in demonstrating the feasibility of the oxidative dearomatizion / epoxidation / Wharton rearrangement sequence. He also showed that it was desirable to protect all of the open valencies of the amine. Finally, he was able to provide evidence that supports that a vinylogous rearrengement could be occurring in this system. My job upon taking over this project was to try to optimize these early steps, further investigate the vinylogous Payne rearrangement, develop a DKR that would

provide the stereochemical features of (+)-scyphostatin, and to finish the synthesis of the polar core of (+)-scyphostatin.

III.E. Synthetic Efforts Toward the Polar Core of (+)-Scyphostatin

My work on the synthesis of the polar core of (+)-scyphostatin will be discussed in this section. I will start by describing my efforts to improve the oxidative dearomatization of the Troc-acetonide tyrosinol **375**. Then, I will discuss the synthesis of the vinylogous Payne rearrangement substrates, followed by studies of this rearrangement. Next, my efforts to achieve a DKR will be covered. The end game studies (oxidation to enone and deprotection) will conclude this section.

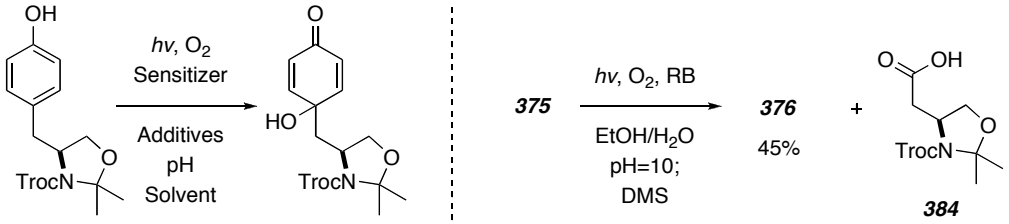
III.E.1. Oxidative Dearomatization Studies ($^1O_2$ vs. PIDA)

The first order of business when I picked up this project was to study the photooxygenation of the phenol **375**. As discussed above (Scheme III-19), Jeffrey's synthesis of dienone **376** was accompanied by side products: the monoepoxide **380**, the diepoxide **381**, and the methanol adduct **382**. In an effort to eliminate these side products I screened (Scheme III-20) various conditions by changing sensitizers (RB, methylene blue [MB], tetraphenylporphyrin [TPP]), using additives / bases (K_2CO_3, NaO*t*Bu, TBAF, cyclohexenone), changing pH (10,9,7), and changing solvents (MeOH, EtOH, *i*PrOH, *t*BuOH, $CHCl_3$; with or without H_2O). In all, 23 different conditions were screened. I will highlight some of the observations from this study, rather than discuss the outcome of each reaction.

Cyclohexenone was used in varying amounts as a sacrificial enone in order to reduce the amount of the epoxide byproducts **380** and **381** produced via the speculated intermediate **383**. Even though this tactic seemed to reduce these byproducts by crude ^1H

NMR spectroscopy, a complicated product mixture was still produced, and the isolated yield was not improved. Changing the sensitizers from RB to MB and TPP resulted in slower reaction rates. The base additives (K_2CO_3 and NaO*t*Bu) only led to greater decomposition. The use of TBAF with TPP in $CHCl_3$ was effective in increasing the rate of the reaction in this sensitizer/solvent combination, but it was still slower than using RB in an aqueous alcohol solvent.[48]

Scheme III-20. Screening of Photooxygenation Conditions to make the Dienone **376**.



The one change that did show a dramatic effect (Scheme III-20) was using a more hindered alcohol, like EtOH and *i*PrOH. None of the epoxide and alcohol adduct byproducts were observed when using an EtOH/H_2O (pH=10) solvent system. In my hands, I isolated the hydroperoxide product along with the alcohol **376**, so DMS was used to reduce the hydroperoxide. Although a cleaner product mixture was achieved with these conditions, a newly isolated byproduct, the acid **384**, proved to be problematic. The formation of carboxylic acids from para-phenols has been observed before under oxidative conditions.[49] (sentence or two explaining the literature precedent of this oxidation) The amount of the acid **384** in the product mixture increases over time, which

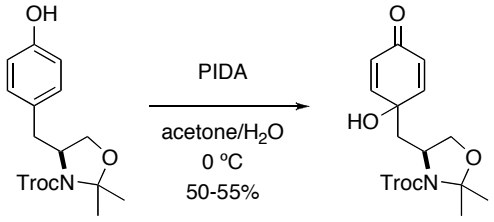
[48] "Fluoride-promoted, dye-sensitized photooxidation of enols," Wasserman, H. H.; Pickett, J. E. *J. Am. Chem. Soc.* **1982**, *104*, 4695-4696.

[49] (a) "Concise Synthesis of All Stereoisomers of β-Methoxytyrosine and Determination of the Absolute Configuration of the Residue in Callipeltin A," Zampella, A.; D'Orsi, R.; Sepe, V.; Casapullo, A.; Monti, M. C.; D'Auria, M. V. *Org. Lett.* **2005**, *7*, 3585–3588. (b) "Complete Stereochemistry of Neamphamide A and Absolute Configuration of the β-Methoxytyrosine Residue in Papuamide B," Oku, N.; Krishnamoorthy, R.; Benson, A. G.; Ferguson, R. L.; Lipton, M. A.; Phillips, L. R.; Gustafson, K. R.; McMahon, J. B. *J. Org. Chem.* **2005**, *70*, 6842–6847.

was unfortunate because extended reaction times (6-7 hours) were needed to achieve full conversion. Therefore, even though I was able to find conditions that did not produce the epoxide and alcohol adduct byproducts, the isolated yield of the dienone **376** was the same as in Jeffrey's case.

I decided to revisit more traditional oxidative dearomatization conditions using hypervalent iodine species. After screening a few different reagents (PIDA and PIFA) and solvent systems (CH_3CN/H_2O and acetone/H_2O), it became evident that the choice of solvent was important with this substrate. Upon examining the crude reaction profiles by ^1H NMR spectroscopy, the reaction of the phenol **375** with PIDA was much cleaner in acetone/H_2O than in CH_3CN/H_2O. Further optimization of the amount of PIDA (1.8 equiv) and the reaction temperature (0 ºC) resulted in the oxidation of the phenol **375** to the dienone **376** in 50-55% yield (Scheme III-21). Although the improvement in yield was modest, this reaction was more reproducible and easier to carry out; therefore, it became the desired method to make the dienone **376** moving forward.

Scheme III-21. Oxidative Dearomatization of the Phenol **375** with PIDA.



375 ***376***

III.E.2. Synthesis of Vinylogous Payne Rearrangement Substrates

When Jeffrey passed this work on to me, the preferred method to epoxidize the dienone **376** was to treat with LiOH and H_2O_2 (30% w/w in H_2O) in THF. In my hands, this protocol did not work very well, so I turned to a literature procedure of a

diepoxidation of another cyclohexadienone.[50] Epoxidation of the dienone **376** with NaOH and H_2O_2 in MeOH (Scheme III-22) gave the diepoxide **377** in 95% crude yield. The diepoxide **377** could not be purified by silica gel chromatography due to its streaky behavior on TLC. This was of little consequence, however, because the crude diepoxide **377** was quite pure by ^{1}H NMR analysis.

My attention then turned to making the vinylogous Payne rearrangement substrates, the epoxy allylic alcohols **378** and **379**, via the Wharton rearrangement of the diepoxide **377** (Scheme III-22). Treatment of a methanolic solution of the diepoxide **377** at room temp with AcOH (5 equiv) followed by $NH_2NH_2 \bullet H_2O$ (5 equiv) gave a 1:1 mixture of the allylic alcohols **378** and **379** in 30-40% over two steps. The equivalents of AcOH and $NH_2NH_2 \bullet H_2O$ could be reduced to a slight excess (1.5 equiv), and no change was observed in the yield. However, all attempts to optimize this reaction (0.1 equiv AcOH, lower reaction temps, 4Å MS, $NH_2NH_2 \bullet HCl$ / Et_3N, reverse order of addition) resulted in similar or lower yields. This reaction was also complicated by instability of the allylic alcohols **378** and **379** to silica gel chromatography. Purification by flash chromatography (also when doping with Et_3N) resulted in complete decomposition, and usage of MPLC to purify gave nearly complete decomposition (impure fractions containing some of the allylic alcohols **378** and **379** were isolated). Fortunately, normal phase HPLC purification (as well as flushing through a pipet of silica gel) resulted in only minimal, if any, decomposition. HPLC purification proved to be essential in analyzing the vinylogous Payne rearrangement, which I will discuss next.

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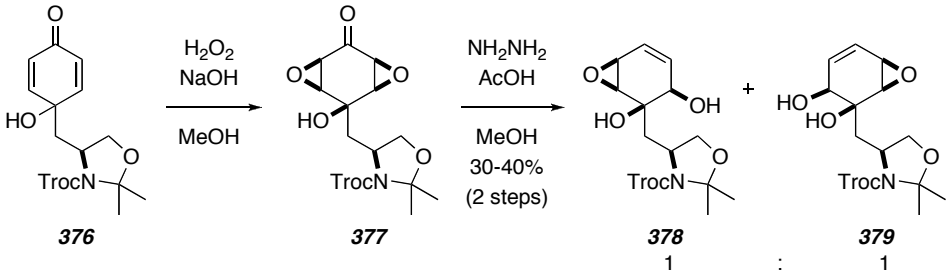
[50] "From *p*-benzoquinone to cyclohexane chirons: first asymmetric synthesis of (+)-rengyolone and (+)- and (–)-menisdaurilide," Busque, F.; Canto, M.; de March, P.; Figueredo, M.; Font, J.; Rodriguez, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2021-2032.

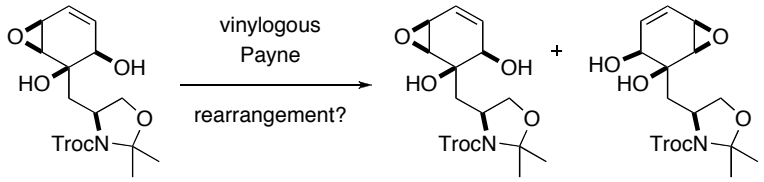
Scheme III-22. Synthesis of the Vinylogous Payne Rearrangement Substrates **378** and **379**.



III.E.3. Vinylogous Payne Rearrangement Studies

Now that I was able to make the vinylogous Payne rearrangement substrates **378** and **379**, it was time to study this rearrangement in greater detail. The approach I took to analyze this process was to separate the allylic alcohols **378** and **379** by HPLC, and then explore conditions that might convert the isolated diastereomer **378** (or **379**) back to a 1:1 mixture of the diastereomers **378** and **379** via a vinylogous Payne rearrangement. This equilibration would be directly observable by ^{1}H NMR, since the allylic alcohols **378** and **379** are diastereomeric and therefore distinguishable by ^{1}H NMR analysis.

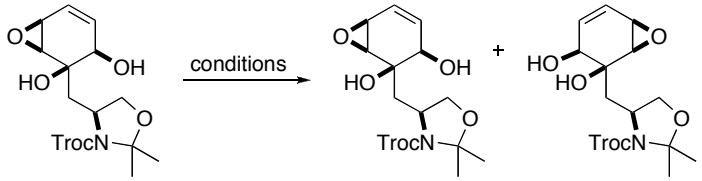
Scheme III-23. Approach to Studying the Vinylogous Payne Rearrangement



As was noted above in the discussion of Jeffrey's work, the diastereomers **378** and **379** could be separated by normal phase HPLC. After separating the diastereomers, the first condition I explored was to heat them in $CDCl_3$ and observe by ^{1}H NMR spectroscopy (Scheme III-24). The heat was incrementally increased, and after heating each of the separated diastereomers **378** and **379** at 70 ºC (sealed NMR tube) for 6 hours, a ~95:5 ratio of diastereomers was observed by ^{1}H NMR. This was the first direct

evidence of a vinylogous Payne rearrangement in this system! Extended heating at 80 ºC eventually resulted in a ~1:1 mixture of the diastereomers **378** and **379** after 3 days. A few other thermal equilibration conditions were studied. Heating in d_6-DMSO (80 ºC) resulted in complete equilibration after 2 days, but this was accompanied with significant decomposition. Heating in d_6-acetone (80 ºC) gave complete equilibration after 3 days. Unfortunately, heating in d_8-THF and in d_6-acetone containing AcOH primarily resulted in decomposition.

Scheme III-24. Thermal Vinylogous Payne Rearrangement Studies

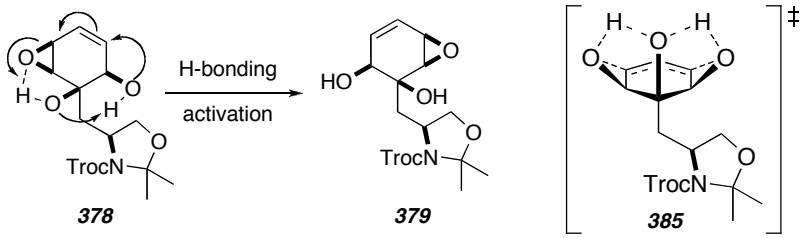


378 ***378*** : ***379***
1 1

Conditions	Results
$CDCl_3$, 80 ºC	~1:1 **378:379** after 3 days
d_6-DMSO, 80 ºC	~1:1 **378:379** after 2 days (significant decomposition)
d_6-acetone, 80 ºC	~1:1 **378:379** after 3 days
d_8-THF, 80 ºC	mostly decomposition
d_6-acetone, AcOH, 80 ºC	mostly decomposition

We were somewhat surprised that the vinylogous Payne rearrangement could occur under such mild conditions (without acid or base). Therefore, we wondered if the tertiary alcohol in the rearrangement substrate **378** could be acting as an intramolecular H-bond donor towards the epoxide (Scheme III-25), thus activating it to rearrange to **379**. We would envision a transition state geometry for this rearrangement looking like **385**, in which the hydrogens are shuttled within the molecule. The *syn* relationship of the cyclohexene oxygen substituents in **378** and **379** (discussed above, Section III.D.3) make it possible for this hydrogen shuttling to occur.

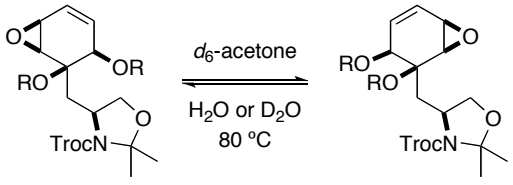
Scheme III-25. H-Bonding Activation of Vinylogous Payne Rearrangement.



378 ***379*** ***385***

We probed this possible mechanism by comparing the rate of the rearrangement between **378** and **379** when spiking the d_6-acetone with H_2O vs D_2O (which would cause deuterium exchange of the alcohols in **378**). If the mechanism we propose were correct, the D_2O spiked sample would be expected to rearrange at a slower rate. Indeed, this was observed, with the D_2O sample rearranging at about half the rate of the H_2O sample. Also, deuterium exchange was observed by ^{1}H NMR analysis of the sample treated with D_2O, confirming that **386** had been formed. The data (collected by ^{1}H NMR spectroscopy) of the ratio of the diol **378** to the diol **379** and of the deuterium-exchanged diol **386** to the diol **387** is reported below (Scheme III-26) at various time points. Therefore, this result *supports* our proposed mechanism, but, of course, it does not *prove* that this mechanism is occurring.

Scheme III-26. Rate of Rearrangement of **378** vs. **386** (deuterium exchange).



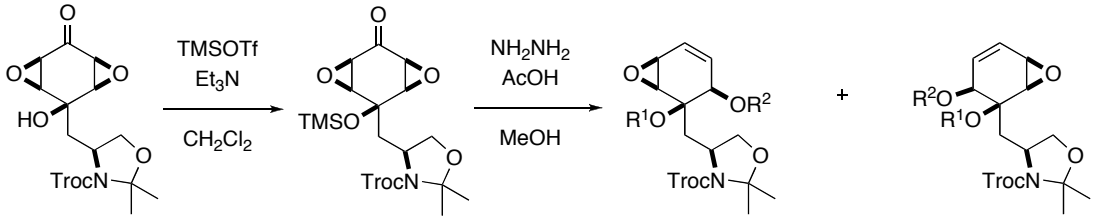
378 (R=H)
386 (R=D)

379
387

Reaction Time	Ratio of **378 : 379** (R=H)	Ratio of **386 : 387** (R=D)
19 h	1 : 0.34	1 : 0.17
45 h	1 : 0.86	1 : 0.34
73 h	1 : 1	1 : 0.43

Another way to probe this mechanism would be to protect the tertiary alcohol of the epoxy diol **377**, which would prevent it from acting as a H-bond donor, and, therefore, slow down the rearrangement. The synthesis of the TMS-protected rearrangement substrates **389** and **390** was accomplished (Scheme III-27) by first treating the hydoxy diepoxide **377** with TMSOTf to give the TMS-protected hydroxy diepoxide **388**. Then, the Wharton rearrangement resulted in the desired allylic alcohols **389** and **390**, but these were minor components of the product mixture. The major products were the silyl-migrated alcohols **391** and **392**, and this silyl migration would prove to complicate the thermal equilibration studies. The allylic alcohols **389** and **390** were separable by normal phase HPLC, which permitted the thermal equilibration studies to still be carried out.

Scheme III-27. Synthesis of the TMS-protected Rearrangement Substrates **389** and **390**.

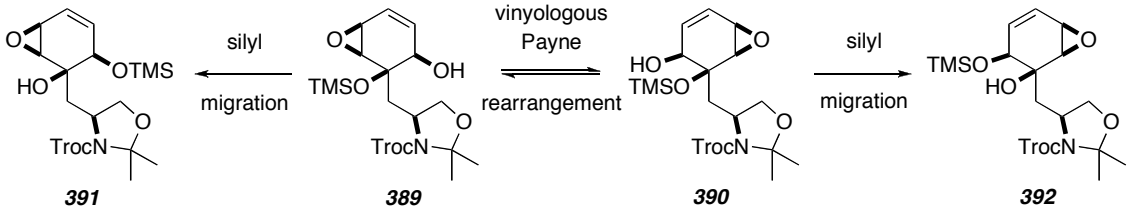


377 ***388*** ***389*** (R^1=TMS, R^2=H) ***391*** (R^1=H, R^2=TMS) + ***390*** (R^1=TMS, R^2=H) ***392*** (R^1=H, R^2=TMS)

The thermal equilibration of the TMS-protected alcohols **389** and **390** provided some interesting results (Scheme III-28), but, unfortunately, these studies did not give any further insight into the mechanism of the vinylogous Payne rearrangement. Thermal equilibration (overnight) of the less polar diastereomer **389** (the structure of this diastereomer depicted in Scheme III-28 is arbitrarily assigned) resulted in complete conversion to the silyl-migrated product **391** instead of yielding the vinylogous Payne rearrangement product **390**. Thermal equilibration (overnight) of the more polar

diastereomer **390** (again, arbitrarily assigned), however, resulted in a product mixture of the rearranged product **389** and the silyl-migrated products **391** and **392**. It was interesting that the two diastereomers, **389** and **390**, behaved differently, and I briefly became excited at the possibility of a thermodynamic resolution resulting in complete conversion to the alcohol **391**. This would require that **391** be lower in energy than **392**, and silyl migration of **390** to **392** would have to be reversible. Heating the alcohol **392** in d_8-toluene at 120 ºC (after first trying d_6-acetone at 80 ºC), however, did not effect silyl migration.

Scheme III-28. Thermal Equilibration of the TMS-Protected Substrates **389** and **390**.



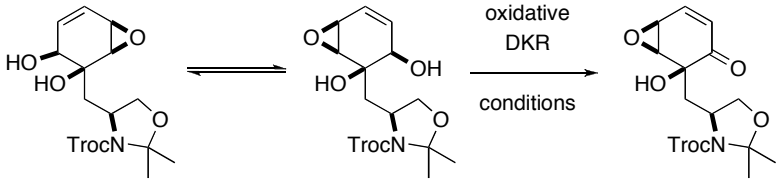
III.E.4. Dynamic Kinetic Resolution (DKR) Studies

Now that I had direct evidence of the allylic alcohols **378** and **379** interconverting via a vinylogous Payne rearrangement, it was time to explore oxidative DKR conditions (Scheme III-29) that could possibly give the epoxy cyclohexenone **393** as one diastereomer. The first condition I explored was Noyori's hydrogen transfer oxidation[51] (Scheme III-29, conditions *a*) using the catalyst **395**. The reaction gave no conversion to

[51] "Kinetic Resolution of Racemic Secondary Alcohols by Ru^{II}-Catalyzed Hydrogen Transfer," Hashiguchi, S.; Fujii, S.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1997**, *36*, 288-290.

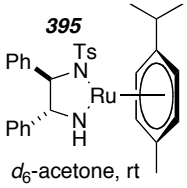
the enone **393** at rt, and gave only decomposition upon heating. In order to verify that I had made the active catalyst **395**, the model allylic alcohol **394** was successfully oxidized under these conditions (conditions *b* and *c* were also successfully tested in this manner). Furthermore, when the alcohol **394** was added to a reaction mixture of the alcohols **378** and **379** under conditions *a*, no oxidation of the model alcohol **394** was observed; therefore, the substrates **378** and **379** must be poisoning the catalyst, **395**. I also tried to oxidize the TMS-protected alcohols **389** and **390** under these conditions, but no conversion was observed. Sigman's conditions[52] (Scheme III-29, conditions *b*) using (-)-sparteine as the chiral reagent also resulted only in decomposition. Finally, conditions that utilize Jacobsen's Mn-salen catalyst as the chiral reagent (Scheme III-29, conditions *c*) did not yield the oxidized product **393**, but only showed decomposition.[53]

Scheme III-29. Oxidative DKR Studies.



Oxidative DKR Conditions

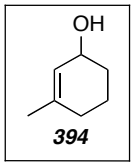
a) **395**



d_6-acetone, rt

b) Pd[(-)-sparteine]Cl_2
(-)-sparteine
3A MS, O_2
*t*BuOH, 65 °C

c) Jacobsen's (*R*,*R*)-
Mn-salen catalyst
PIDA, KBr
DCM / H_2O



394

[52] "Palladium-Catalyzed Enantioselective Oxidations of Alcohols Using Molecular Oxygen," Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476.

[53] "Chiral-Mn(Salen)-Complex-Catalyzed Kinetic Resolution of Secondary Alcohols in Water," Sun, W.; Wang, H.; Xia, C.; Li, J.; Zhao, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1042-1044.

The next DKR option that was explored involved using lipase to selectively acetylate the secondary alcohol of one of the pseudo-enantiomers, **378** or **379**.[54] After screening a few initial conditions, I found that treating the allylic alcohols **378** and **379** with Amano PS, vinyl acetate, and 4Å MS in $PhCH_3$ at rt for 5 days resulted in 25% conversion to the acetate **396** (Scheme III-30) as a single diastereomer! I was extremely encouraged by this exciting result and went on to screen over 30 conditions in order to improve this outcome. The variables that were screened included type of lipase (Novozyme, Amano PS, Amano AK), acetate or benzoate source (isopropenyl acetate, vinyl acetate, vinyl benzoate), base additive (Et_3N, Na_2CO_3), solvent (CH_2Cl_2, $PhCH_3$, THF, hexanes, vinyl acetate), and temperature. The best conditions (Scheme III-30) used hexanes as a solvent and gave near full conversion (>95%) after 14 days at rt. The rate of the reaction was quite slow, but carrying out the reaction at elevated temps resulted in a fair amount of decomposition products along with the acetate **396**. Even though ^1H NMR analysis of the crude product mixture seemed to indicate that a DKR was occurring, this could not be confirmed by an isolated yield (>50% would indicate a DKR) of the acetate **396** due to decomposition upon silica gel purification. Also, the structure of the acetate **396** (which is the desired diastereomer needed to synthesize (+)-scyphostatin) was loosely assigned based on models of lipase reactivity.[54] Therefore, I would need more definitive proof of the structure of **396**. I also sought to find another way to determine whether or not a DKR was occurring.

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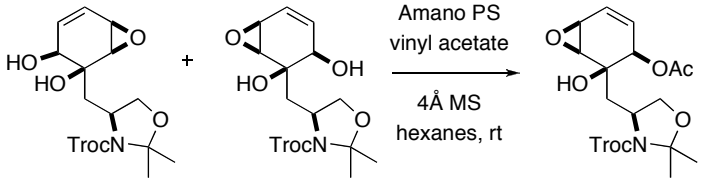
[54] "Lipase-mediated chiral resolution of racemates in organic solvents," Ghanem, A.; Aboul-Enein, H. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3331-3351.

Scheme III-30. Amano PS Lipase Acetylation.



The first step toward determining the structure of the acetate from the Amano PS acetylation was to acetylate (Scheme III-31) each of the separated diastereomers, **378** and **379**, and then determine which product, **396** or **397**, matches the structure of the acetate from the Amano PS acetylation. The product of the less polar starting allylic alcohol, the acetate **396**, gave the same ^{1}H NMR spectrum as the acetate from the Amano PS acetylation. Next, Mosher ester analysis of one of the allylic alcohols would allow for assignment of configuration of the secondary alcohol, which would in turn allow for complete assignment of all configurations of both the allylic alcohols **378** and **379**. This analysis was achieved via conversion of the more polar allylic alcohol **379** (chosen because I had a larger amount of this diastereomer in hand) to the (*S*)-Mosher ester **398** and the (*R*)-Mosher ester **399** by treating with the (*R*)- and (*S*)-Mosher acid chlorides, respectively.[55] Modified Mosher ester analysis (Figure III-2) allowed the configuration of the secondary alcohol of **379** to be assigned as (*S*).[30] This was good news, since it meant that the structure of the acetate **396** from the Amano PS reaction had the same epoxide and tertiary alcohol configurations as (+)-scyphostatin, which was also in agreement with the lipase model of reactivity.

[55] "A simple method for the microscale preparation of mosher's acid chloride," Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165-7166.

Scheme III-31. Structure Determination of the Amano PS Acetylation Reaction Product.

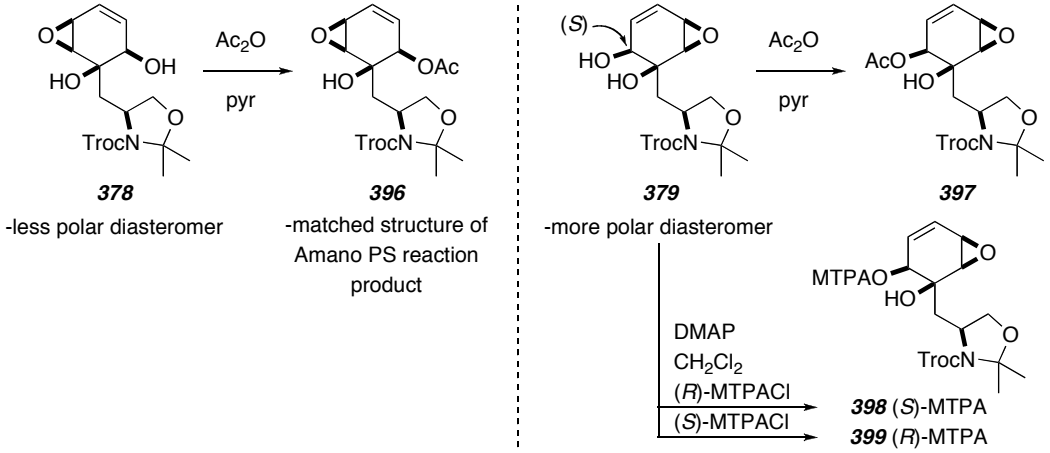
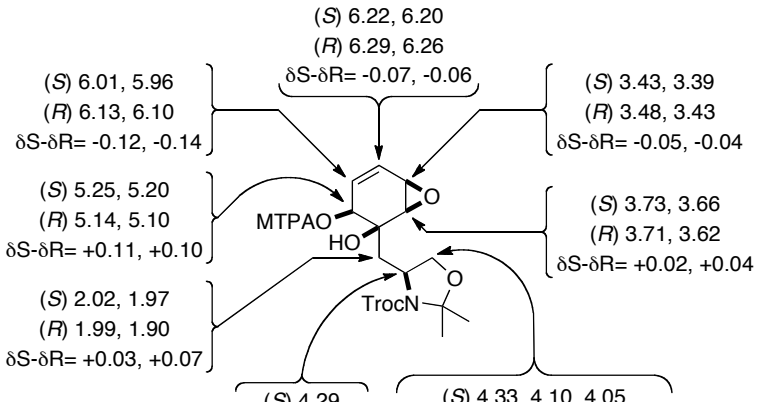


Figure III-2. Modified Mosher Ester Analysis (δS-δR) of the More Polar Diastereomer **379**.



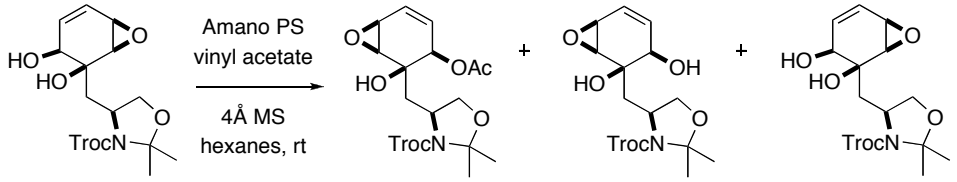
*There are two sets of chemical shifts for most protons because each of the carbamate rotamers is observed by ^{1}H NMR spectroscopy

One proton of this methylene pair has two signals and the other proton has one signal

In an effort to determine whether or not the Amano PS acetylation conditions were resulting in a DKR, the unreactive diastereomer, **379**, was exposed to the optimized conditions (Scheme III-32). The only way that acetylation could occur would be for starting allylic alcohol **379** to undergo the vinylogous Payne rearrangement followed by reaction with Amano PS / vinyl acetate. Gratifyingly, exposure of allylic alcohol **379** to these conditions for 14 days resulted in formation of the acetate **396**, confirming that a DKR is operative under these conditions! Also, a 1:1 mixture of **378** and **379** was

observed in the crude product mixture. This led me to believe that perhaps the Amano PS conditions became inactive at some point; thus, portionwise treatment with these reagents (Amano PS, vinyl acetate, 4Å MS) might permit full conversion in a shorter time period. At this juncture, no further optimization of the Amano PS DKR conditions or studies of converting acetate **396** to the polar core of (+)-scyphostatin were implemented because it had become apparent that a new protecting group strategy would be required. The details of this will be provided in the following sections.

Scheme III-32. Definitive Evidence of a DKR.



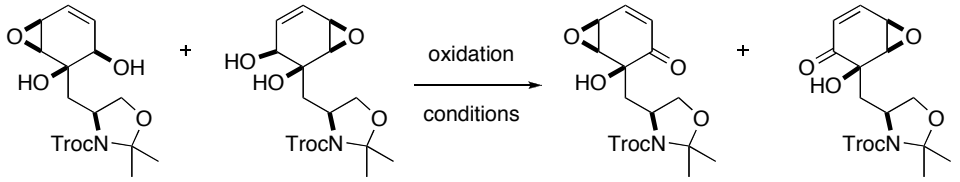
III.E.5. Oxidation to Cyclohexenone and Deprotection Studies

Studies of the end game chemistry were ongoing at the same time of the vinylogous Payne rearrangement and DKR studies. The end game studies included oxidation of the allylic alcohol to the cyclohexenone (which was required since I was unable to develop an oxidative resolution) as well as deprotection studies of the Troc-acetonide protecting groups. I also intended to study the amide coupling as part of the end game studies, but problems with the deprotection chemistry did not give me access to the appropriate amide coupling intermediates.

The oxidation studies (Scheme III-33) were carried out on the 1:1 mixture of the allylic alcohols **378** and **379**. Oxidation with Dess-Martin periodinane (DMP) gave the enones **393** and **400** in low yield. Exposure to the mild MnO_2 conditions gave full conversion, but these conditions did not give the enones **393** and **400**. The Parikh-

Doering conditions (SO_3•pyr, Et_3N, DMSO) produced the enones **393** and **400** in moderate yield.[56] As in the case of the DKR studies, no further optimization of the oxidation conditions were carried out at this point since a different protecting group strategy would need to be devised. However, I was delighted that I was able to produce the epoxy cyclohexenone polar core of scyphostatin.

Scheme III-33. Oxidation of the Allylic Alcohols **378** and **379**.



378 + ***379*** → ***393*** + ***400***

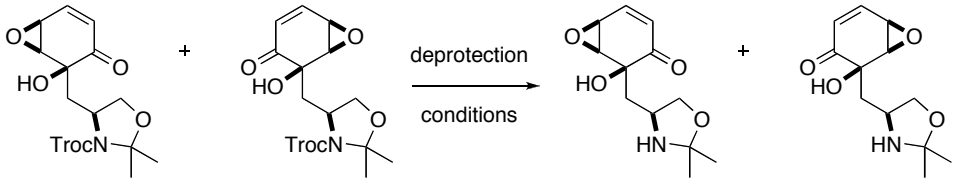
Conditions	Results
DMP, $CDCl_3$	20% yield
MnO_2, CH_2Cl_2	full conversion, but **393** and **400** not isolated
SO_3•pyr, Et_3N, DMSO	50% yield

The deprotection strategy for the Troc-acetonide protected enones **393** and **400** was to selectively remove the Troc group to provide the *N*,*O*-acetonides **301a** and **302a**. Then, all that would remain to complete the synthesis of scyphostatin (or its analogs) would be to carry out an amide coupling of the amine **301a** with the fatty acid side chain (or analogs thereof) followed by acetonide deprotection. The selective Troc deprotection was first attempted using the standard Zn dust / AcOH conditions (Scheme III-34), but this resulted in decomposition. Crude ^1H NMR analysis revealed that perhaps a trace amount of the desired enones **301a** and **302a** could be present in this complicated product mixture. The most obvious decomposition pathways would involve the amine of **301a** and **302a** engaging the epoxide in a similar manner that Jeffrey observed (Scheme III-

[56] "Facile Syntheses of All Possible Diastereomers of Conduritol and Various Derivatives of Inositol Stereoisomers in High Enantiopurity from *myo*-Inositol," Kwon, Y-U.; Lee, C.; Chung, S-K. *J. Org. Chem.* **2002**, *67*, 3327–3338.

17); the other decomposition pathway would be that the acetonide was also removed, which would produce a free amine that could engage the ketone. Basic conditions were also attempted (aq. NaOH), but that also resulted in decomposition with no evidence of an enone signal in the crude ^{1}H NMR spectrum.

Scheme III-34. Troc-Deprotection of the Enones **393** and **400**.

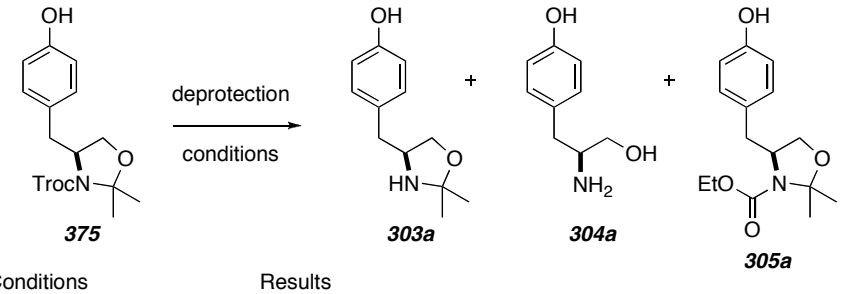


393 ***400*** ***301a*** ***302a***

Conditions	Results
Zn dust, AcOH, THF/H_2O	Mostly decomposition, possibly a trace of desired products
NaOH, THF/H_2O, 50 ºC	Only decomposition, no product

Deprotection of the simpler Troc-acetonide **375** was attempted next so that the product mixture would be easier to analyze. Treatment with Zn / AcOH resulted in mostly Troc and acetonide deprotection to yield amino alcohol **304a**, as was indicated by LC-MS analysis. A small amount (<5%) of the acetonide **303a** was also isolated. Deprotection under basic conditions (LiOH, EtOH, H_2O) only provided the ethyl carbamate **305a**. Since selective Troc removal was problematic even with this simpler substrate, I decided a different protecting group strategy would be needed, as was alluded to above.

Scheme III-35. Troc-Deprotection of the Troc-acetonide **375**.

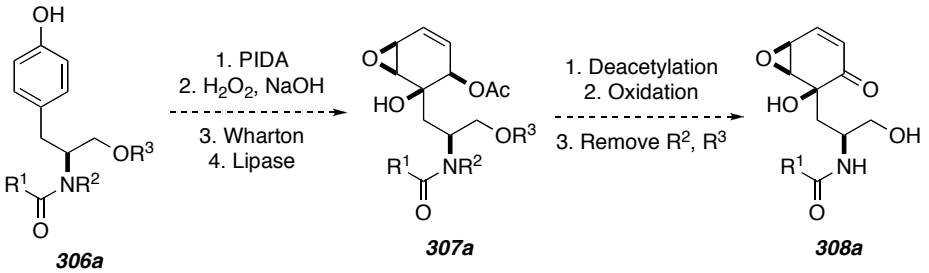


Conditions	Results
Zn dust, AcOH, THF/H_2O	Mostly complete deprotection to the amino alcohol **304a** (MS data), isolated a small amount (<5%) of the acetonide **303a**
LiOH, EtOH/H_2O, 80 ºC	Partial conversion to the ethyl carbamate **305a**, none of the desired acetonide **303a** isolated

III.F. New Synthetic Strategy Toward the Polar Core of Scyphostatin

A new approach to the scyphostatin polar core (Scheme III-36) was devised in which the fatty acid amide is formed early in the synthetic sequence. Therefore, this strategy would first require synthesizing the amide **306a** with an amide (R^2) and an alcohol (R^3) protecting group. Our side chain analog would either be the sorboyl or palmitoyl (the latter the same as Pitsinos's analog; section III.C.4) amide; both were examined. Various R^2 / R^3 protecting group strategies will be discussed in this section. The protected amide **306a** would then be carried through the steps previously developed (oxidative dearomatization, epoxidation, Wharton rearrangement, lipase acetylation; discussed above in section III-3.E.) to produce the allylic acetate **307a**. Then, the scyphostatin analog **308a** perhaps could be produced via deacetylation, oxidation, and R^2 / R^3 deprotection. This approach would minimize the number of steps required after formation of the unstable epoxy cyclohexenone core.

Scheme III-36. New Synthetic Strategy Toward the Polar Core of Scyphostatin.



306a

R^1 = sorbyl ($CH=CH-CH=CH-CH_3$)
palmityl ($(CH_2)_{14}CH_3$)

307a

308a

III.F.1. *N,O*-Acetonide Protecting Group Strategy

A simple protecting group approach would be to make the amide-acetonide **311a**, which is closely related to the carbamate-acetonide substrates discussed in the previous section.[57] The approach was studied by initially coupling sorbic acid to the known amine salt **309a** using EDCI (Scheme III-37) to provide the amide **310a**.[58] Acetonide protection of the amide yielded the amide-acetonide **311a**. Oxidative dearomatization of the phenol **311a** with PIDA, however, resulted in complete decomposition. ^{1}H NMR analysis of the crude and purified fractions (MPLC) revealed that the acetonide did not survive these conditions. The alternative singlet oxygen oxidative dearomatization conditions were not attempted because the diene in the side chain would also be reactive with singlet oxygen.[57] Since the amide-acetonide protecting group proved to not be very robust, this approach was quickly abandoned.

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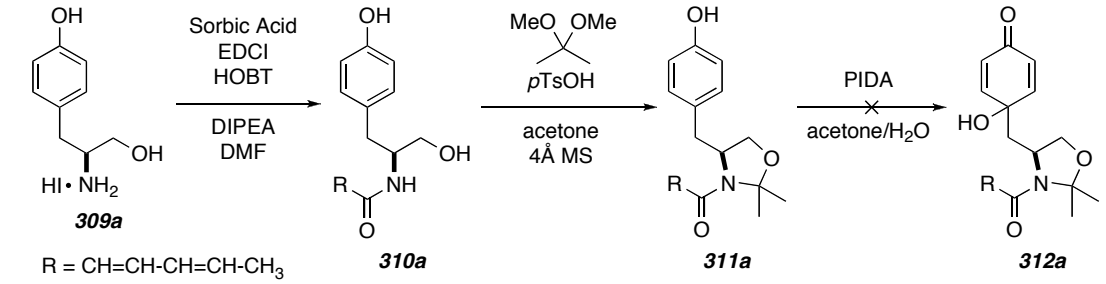
[57] "Chiral-Auxiliary-Induced Diastereoselectivity in the [4 + 2] Cycloadditions of Optically Active 2,2-Dimethyloxazolidine Derivatives of Sorbic Acid: A Model Study with Singlet Oxygen as the Smallest Dienophile," Adam, W.; Güthlein, M.; Peters, E.-M.; Peters, K.; Wirth, T. *J. Am. Chem. Soc.* **1998**, *120*, 4091–4093.

[58] "A convenient reduction of amino acids and their derivatives," McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568–3571.

Scheme III-37. *N*,*O*-Acetonide Protecting Group Strategy of the Sorboyl Amide **310a**.



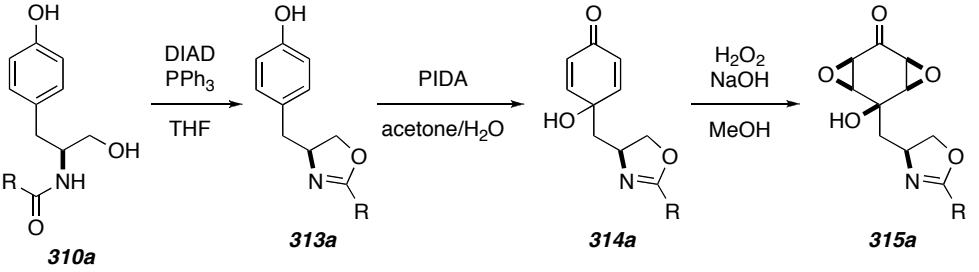
III.F.2. Oxazoline Protecting Group Strategy

We realized that instead of introducing an external protecting group we could convert the amide alcohol into an oxazoline since the oxygen and nitrogen have a vicinal relationship to each other. Then, after the epoxy cyclohexenone of scyphostatin was completed, the amide alcohol **308a** (Scheme III-36) could be revealed via hydrolysis of the oxazoline. This study was initiated (Scheme III-38) by exposing the sorboyl amide **310a** to Mitsunobu conditions (DIAD, PPh_3) to cleanly furnish the oxazoline **313a** via intramolecular displacement.[59] Oxidative dearomatization of the phenol **313a** gave the dienone **314a** in a yield (50%) similar to what was reported with the Troc-acetonide **376** (50-55%) in the previous section. Subsequent epoxidation of the dienone **314a** seemed to give smooth conversion (by LC-MS analysis) to the diepoxide **315a**, but a complicated product mixture was isolated, which could not be cleaned up by column chromatography due to the streaky nature of the diepoxide **315a** on TLC (it was assumed that the broad TLC spot was from the diepoxide, since the diepoxide **377** from the previous section also had similar TLC behavior). The product mixture was not carried forward; instead, it was decided around this time to target the palmitoyl amide analog **308a** [$R^1 = (CH_2)_{14}CH_3$] since it had the same length as the actual scyphostatin fatty acid side chain, and this

[59] "Total Synthesis of (-)-Thiangazole and Structurally Related Polyazoles," Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1995**, *60*, 7224–7229.

substituent would also reduce the polarity of these intermediates, which I thought would make them easier to handle. Furthermore, Pitsinos synthesized the palmitoyl analog **341**, so I could compare the data of the completed scyphostatin analog to his data.[27] Thus, the isolation issue of the diepoxide **315a** would be resolved in the palmitoyl series.

Scheme III-38. Oxazoline as Protecting Group of the Amide Alcohol **310a**.

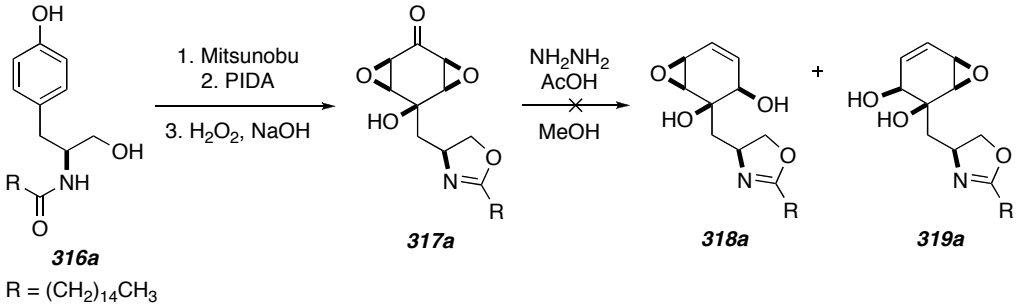


310a ***313a*** ***314a*** ***315a***

R = CH=CH-CH=CH-CH_3

The palmitoyl amide **316a** (Scheme III-39; made by EDCI coupling of **309a** with palmitic acid) was taken through the same series of steps (Mitsunobu, oxidative dearomatization, and epoxidation) to provide the diepoxide **317a**. The diepoxide was isolable, and the only change during the workup was to quench the epoxidation reaction with sat'd aq. $NaHCO_3$ instead of H_2O. Unfortunately, the diepoxide **317a** did not yield the allylic alcohols **318a** and **319a** upon exposure to the Wharton rearrangement conditions, but gave complete decomposition instead. In order to test the stability of the oxazoline moiety to AcOH, the phenol oxazoline derived from Mitsunobu reaction of **316a** was treated with aq. AcOH in THF at rt. The oxazoline had completely hydrolyzed by the next day. The facile nature of this hydrolysis surprised us. Also, these oxazoline intermediates were much less stable than the Troc-acetonide series of compounds, and had to be stored at cold temperatures. Therefore, no more studies were carried out on these oxazoline compounds.

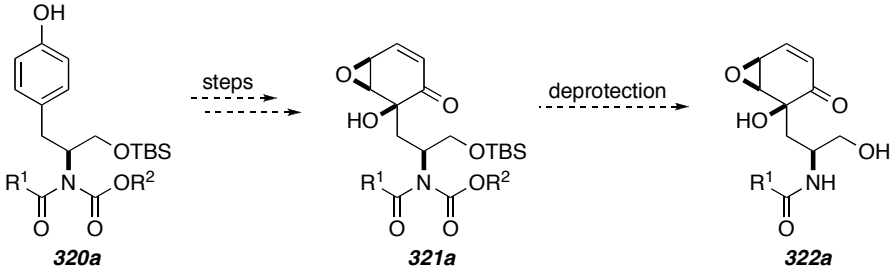
Scheme III-39. Oxazoline as Protecting Group of Palmitoyl Analog Series.



III.F.3. Amide-Carbamate / Alcohol-TBS Protection Strategy

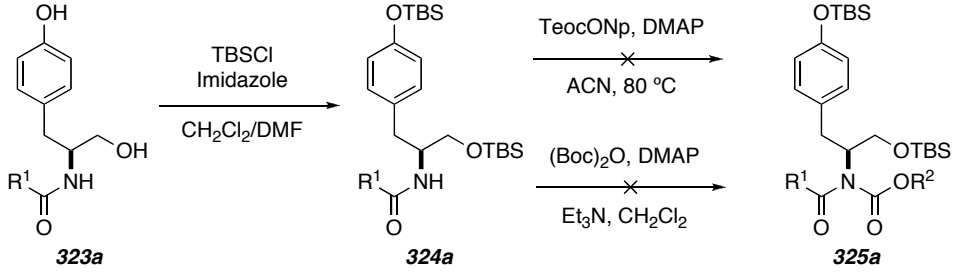
Another protecting group strategy that I studied involved using two separate protecting groups for the amide (carbamate protection) and the alcohol (silyl ether protection). Two different carbamates, Boc (R^2=*t*Bu) and Teoc (R^2=CH_2CH_2TMS), were used, and the alcohol was protected as its TBS-ether. The TBS-carbamate **320a** could then be carried through the steps to achieve the epoxy cyclohexenone **321a** (same steps as in Scheme III-36). Finally, carbamate / TBS deprotection would furnish the scyphostatin analog **322a**. Simultaneous carbamate and TBS deprotection could possibly be carried out in one step whether the Boc group (acidic conditions) or the Teoc group (F^- conditions) was used. I will discuss different approaches to making the carbamates **320a**, which proved to be more challenging than expected. Then I will discuss how the carbamates **320a** fared in the subsequent steps.

Scheme III-40. Amide-Carbamate / TBS-Alcohol Protection Strategy.



One of my first approaches to make the TBS-carbamate **325a** started with TBS protection of the diol **323a** to provide the bis-TBS ether **324a.** Treatment of the amide **324a** with 2-trimethylsilylethyl *p*-nitrophenyl carbonate failed to give the Teoc amide **325a** (R^2=CH_2CH_2TMS).[60] Also, the Boc amide **325a** (R^2=*t*Bu) was not furnished upon exposure to $(Boc)_2O$. I had found literature precedent for these transformations, but perhaps this amide was too hindered to react under these conditions.[61] The next approach would be to first introduce the carbamate protecting group, followed by amide formation.

Scheme III-41. Attempts to Protect the Amide **324a**.



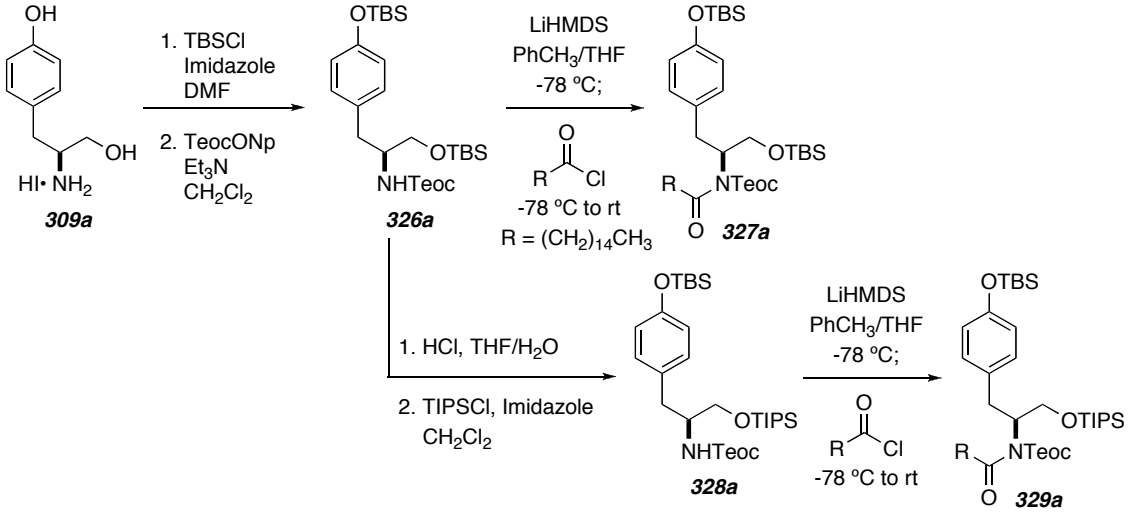
The revised approach, carbamate formation followed by amide coupling, was initiated by synthesis of the Teoc amine **326a** (Scheme III-42). It was made by treating the diol **309a** with TBSCl followed by 2-trimethylsilylethyl *p*-nitrophenyl carbonate (Teoc-protection of the diol **309a** did not proceed cleanly; therefore, these steps [TBS protection / carbamate protection] were reversed compared to the approach used to make the Boc amine **335a**, discussed below in Scheme III-45). The amide coupling (LiHMDS; palmitic acid chloride) of the Teoc amine **326a** furnished the corresponding amide **327a**

[60] "N.omega.-Alkoxycarbonylation of .alpha.,.omega.-diamino acids with 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate," Rosowsky, A.; Wright, J. E. *J. Org. Chem.* **1983**, *48*, 1539–1541.

[61] (a) "Incorporation of 5-hydroxytryptophan in oligopeptides," Lescrinier, T.; Busson, R.; Rozenski, J.; Janssen, G.; Van Aerschot, A.; Herdewijn, P. *Tetrahedron* **1996**, *52*, 6965-6972. (b) "Easy access to orthogonally protected α-alkyl aspartic acid and α-alkyl asparagine derivatives by controlled opening of β-lactams," Gerona-Navarro, G.; Garcia-López, T.; González-Muñiz, R. *Tetrahedron Lett.* **2003**, *44*, 6145-6148.

in low yield due to poor conversion. The use of different bases (NaHMDS and *n*BuLi) or DMAP did not improve the rate of the amide coupling with the Teoc amine **326a**. We hypothesized that the rate of this reaction could be slow because the lithium anion of the amine might form an N-bound silicate with the silicon of the primary alcohol TBS, rendering it less reactive to external electrophiles. I tested this idea by changing the TBS-ether to a TIPS-ether, which would be less disposed toward silicate formation. This was accomplished by selectively deprotecting the bis-TBS ether **326a** with aq. HCl in THF, and then treating with TIPSCl to give the TIPS-ether **328a**.[62] The TIPS-ether **328a**, however, also reacted slowly under the same amide coupling conditions to give the Teoc-amide **329a**; therefore, our hypothesis appeared to be incorrect.

Scheme III-42. Synthesis of the Teoc Amides **327a** and **329a**.

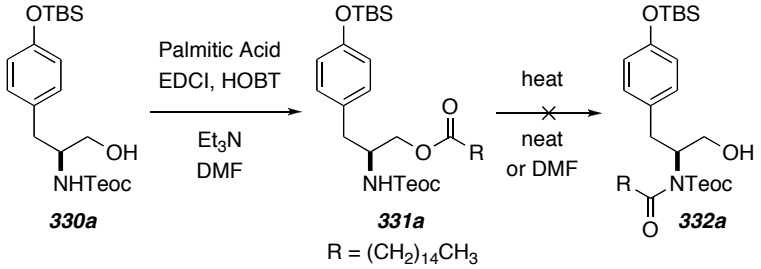


Another approach to effect amide coupling of the Teoc amine would be to form the palmitic ester **331a**, which could possibly undergo acyl transfer from oxygen to nitrogen to give the Teoc amide **332a** (Scheme III-43). The literature precedence for this

[62] "Synthetic Studies toward Ecteinascidin 743," Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397–4408.

process indicates that it may even occur immediately after ester formation at room temperature.[63] The alcohol **330a** (made as described in Scheme III-42 by treating **326a** with HCl) was esterified to the palmitic ester **331a** with EDCI and palmitic acid. None of the acyl transfer product **332a** was observed in this product mixture. Unfortunately, heating the ester neat (160 ºC) or in DMF (140 ºC) provided none of the acyl transfer product **332a**.

Scheme III-43. Attempts to Acyl-transfer from O to N.



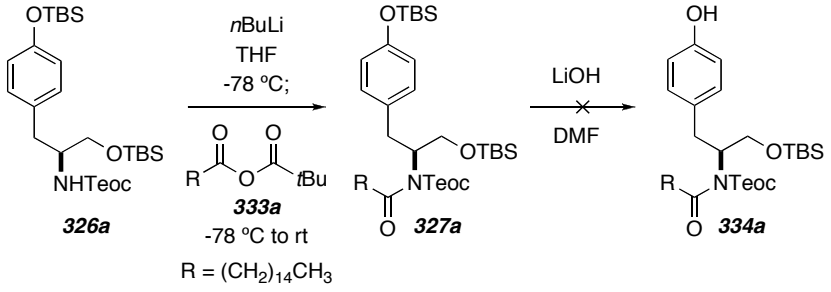
A variant of the previous LiHMDS / palmitic acid chloride amide coupling conditions (Scheme III-42) resulted in improved yield and conversion. These conditions (Scheme III-44) utilized *n*BuLi and the palmitoyl mixed anhydride **333a** to produce the Teoc amide **327a** in 30-50% yield (70% brsm).[64] Full conversion was still not achieved, but this procedure would allow for sufficient mass throughput to be considered a viable option. Unfortunately, the selective phenolic-TBS deprotection conditions (LiOH, DMF; conditions that selectively deprotected the Boc substrate **336a**, discussed below in

[63] (a) "Disruption of Amyloid-Derived Peptide Assemblies through the Controlled Induction of a -Sheet to -Helix Transformation: Application of the Switch Concept," Mimna, R.; Camus, M.-S.; Schmid, A.; Tuchscherer, G.; Lashuel, H. A.; Mutter, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 2681-2684. (b) "Carboxylic fused furans for amino acid fluorescent labeling," Piloto, A. M.; Fonseca, A. S. C.; Costa, S. P. G.; Gonçalves, M. S. T. *Tetrahedron*, **2006**, *62*, 9258-9267.

[64] "The synthesis of novel matrix metalloproteinase inhibitors employing the Ireland-Claisen rearrangement," Pratt, L. M.; Beckett, R. P.; Bellamy, C. L.; Corkill, D. J.; Cossins, J.; Courtney, P. F.; Davies, S. J.; Davidson, A. H.; Drummond, A. H.; Helfrich, K.; Lewis, C. N.; Mangan, M.; Martin, F. M.; Miller, K.; Nayee, P.; Ricketts, M. L.; Thomas, W.; Todd, R. S.; Whittaker, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1359-1364.

Scheme III-45) did not convert the Teoc amide **327a** to the phenol **334a**.[65] The lack of solubility of **327a** in DMF seemed to be the problem, but the use of cosolvents (or aq. LiOH in THF) to dissolve **327a** resulted in complete insolubility of LiOH. I also tried to achieve selective deprotection with TBAF, but was unsuccessful.

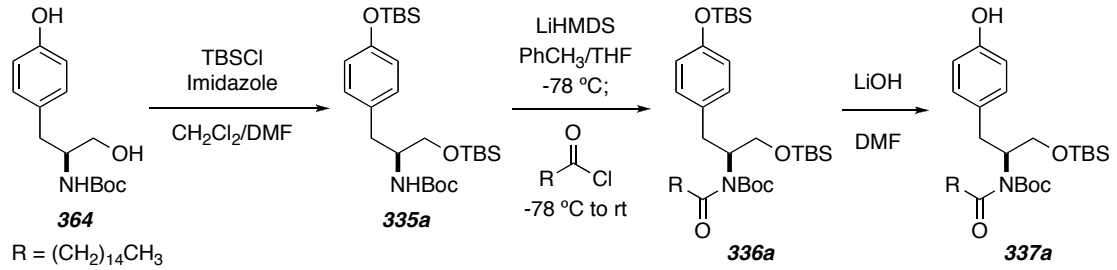
Scheme III-44. Improved Amide Coupling Conditions.



The Boc amine protection strategy was explored (Scheme III-45) by TBS protection of the diol **364** to produce the bis-TBS ether **335a**.[41] The first few attempts to couple the Boc amine **335a** failed to provide the Boc amide **336a**. These conditions include: palmitic acid, EDCI, HOBT, Et_3N, DMF; (R=Me) acetyl chloride, DMAP, $CDCl_3$; and palmitic acid chloride, DMAP, Et_3N. Finally, formation of the lithium anion of the Boc amine **335a** followed by exposure to palmitic acid chloride resulted in formation of the Boc amide **336a**, albeit in low yield (10-31%). The low yield was due to poor conversion (as was the case above with the Teoc amine **326a**), which could not be overcome via extended reaction times (3 days at rt) or use of excess LiHMDS (3 equiv). Selective phenolic-TBS deprotection of the bis-TBS ether **336a** was achieved cleanly by treatment with LiOH in DMF to provide the phenol **337a**.[65]

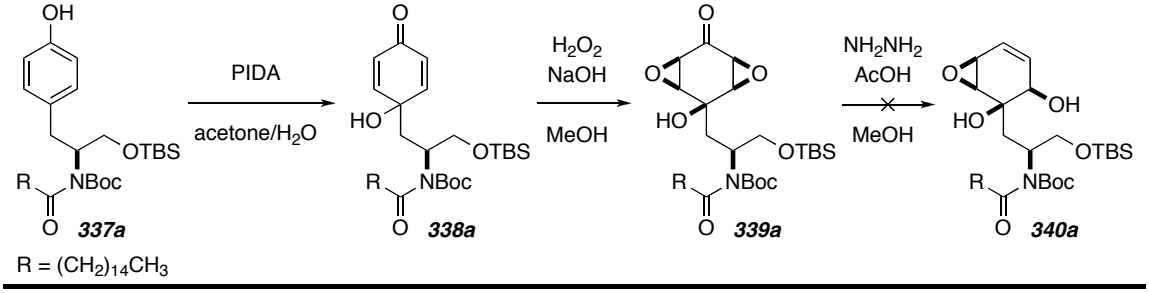
[65] "Selective deprotection of either alkyl or aryl silyl ethers from aryl, alkyl bis-silyl ethers," Ankala, S. V.; Fenteany, G. *Tetrahedron Lett*. **2002**, *43*, 4729-4732.

Scheme III-45. Synthesis of the Boc Amide **337a**.



Since I was able to successfully carry out this deprotection on the Boc substrate to give the phenol **337a**, it was finally time to explore (Scheme III-46) the chemistry that would elaborate the phenol **337a** to the epoxy cyclohexenone of scyphostatin (**301**). The oxidative dearomatization of the phenol **337a** with PIDA gave the dienone **338a**, but this reaction was low yielding (16%). The epoxidation of the dienone **338a** also did not work as well as it did for the Troc-acetonide **376**, giving a 59% crude yield of the diepoxide **339a** compared to a 95% crude yield for the Troc-acetonide **377** (Scheme III-22). The Wharton reaction of the diepoxide **339a** was also disappointing since it resulted in mostly decomposition. Perhaps a small amount of the allylic alcohol **340a** was observed by crude ^{1}H NMR and LC-MS data. After a great deal of effort was put into the carbamate-protected amide strategy, I decided that there were too many questionable steps at this point to consider this a viable path, especially since the Wharton rearrangement worked so poorly.

Scheme III-46. Elaboration of the Phenol **337a** to the Diepoxide **340a**.



III.F.4. *N*,*O*-Benzylidene Acetal Protecting Group Strategy

I decided to revisit the *N*,*O*-acetonide protecting group approach (Section III.F.1) by exploring a more robust variant of this protecting group, the *N*,*O*-benzylidene acetal protecting group.[66] This type of protecting group is extremely appealing because it can protect the amide nitrogen and primary alcohol in one step, and deprotection after the epoxy cyclohexene core is completed would lead directly to the scyphostatin analog **308a** (R^1 = palmityl; Scheme III-36), since the amide side chain was in place from the beginning. Installation of the *N*,*O*-benzylidene acetal was accomplished by treating the amide **323a** with benzaldehyde dimethyl acetal in the presence of acid (*p*TsOH) to furnish the benzylidene acetal **341a** (Scheme III-47). Oxidative dearomatization of the phenol **341a** with PIDA gave the dienone **342a** in a reasonable yield (46%). Epoxidation of the dienone **342a** provided the diepoxide **343a**, although the crude yield was a little low (69%) compared to the Troc-acetonide **377** (95%; Scheme III-22). The Wharton rearrangement of the diepoxide **343a** resulted in the formation of the allylic alcohols **344a** and **345a** in ~40% crude yield, as indicated by crude ^{1}H NMR and LC-MS analysis. I was not able to get my hands on a pure sample of **344a** and **345a** by MPLC purification. The lipase acetylation (Amano PS, vinyl acetate) was attempted on the crude allylic alcohols **344a** and **345a**, and partial conversion was observed after one week. ESI-MS and crude NMR analysis indicated the presence of the allylic acetate product **346a**, but silica gel purification resulted in mostly decomposition. This is where my work ended on this project. Even though I have one short section remaining, this chapter is not completely in chronological order. The Wharton rearrangement and lipase acetylation

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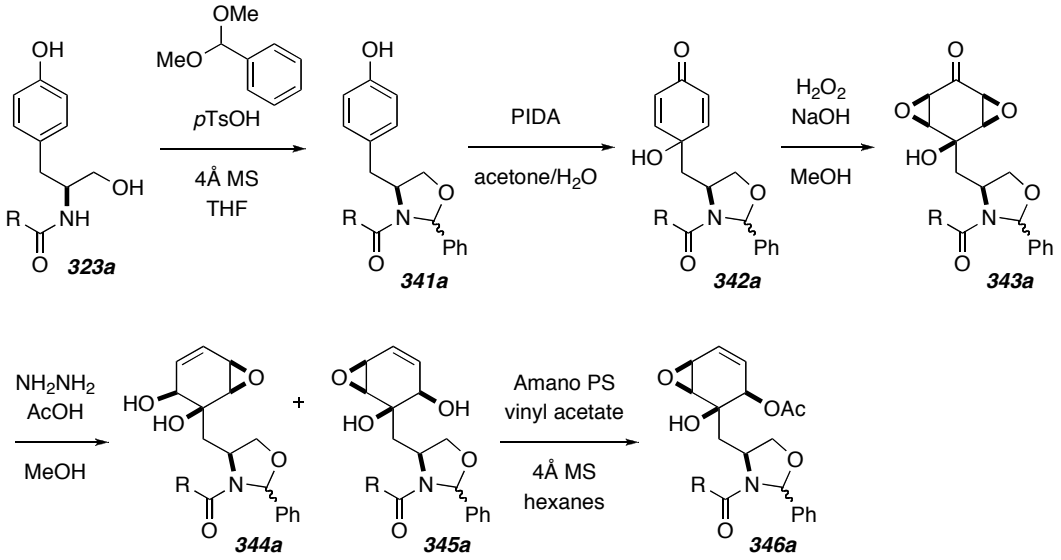
[66] "Design and Synthesis of a Conformationally Restricted Cysteine Protease Inhibitor," Cheng, H.; Keitz, P.; Jones, J. B. *J. Org. Chem.* **1994**, *59*, 7671–7676.

need to be revisited, and HPLC (normal and reverse phase) should be utilized to purify the products of these reactions in order to get a better handle on these results. Then, after assessing these steps, a decision can be made whether or not to further investigate this protecting group strategy.

Scheme III-47. *N*,*O*-Benzylidine Acetal Protection Strategy.



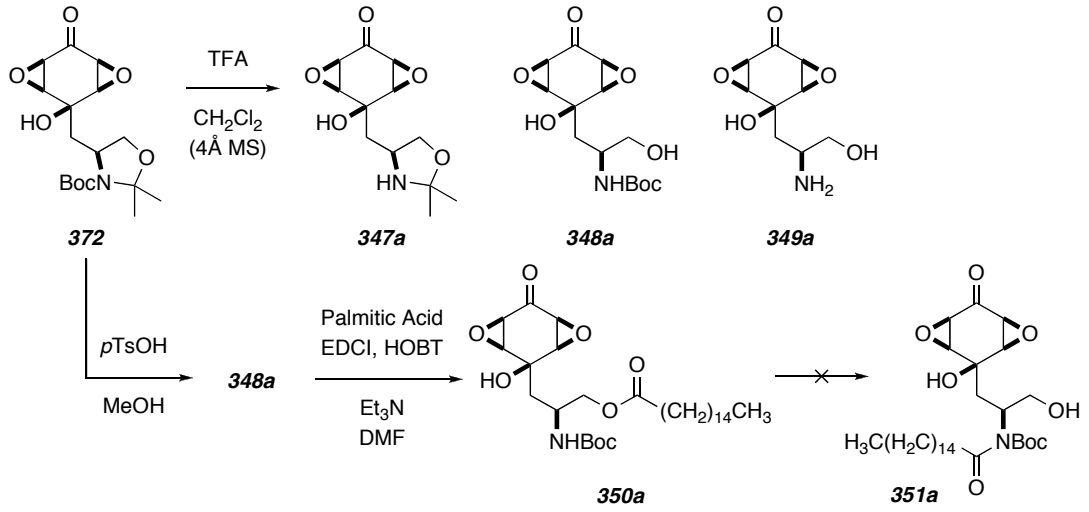
III.G. Miscellaneous Strategies

The remaining synthetic work I did on the scyphostatin polar core was not appropriate for the earlier sections, so I will discuss it in this final section. The work I will discuss in this section was not the final studies I carried out, so it is taken out of chronological order. One of these studies involved efforts to selectively deprotect (Scheme III-48) the Boc-acetonide **372** to give the amine **347a**, which would then be able to undergo amide coupling with the analog side chain.[67] In an attempt to selectively remove the Boc group, the diepoxide **372** was treated with TFA. LC-MS analysis showed the corresponding molecular weights for the amine **347a**, the acetonide-

[67] "An easy access to the optically active azocine derivatives," Torisawa, Y.; Motohashi, Y. Ma, J.; Hino, T.; Nakagawa, M. *Tetrahedron Lett*. **1995**, *36*, 5579-5580.

deprotected product **348a**, and the completely deprotected amine **349a**; therefore, selective deprotection was not achieved, and only the Boc amine **348a** was isolated. Various attempts were made at this selective deprotection using 4Å MS and various workups, but the primary isolated product was always the Boc amine **348a**. Therefore, I thought perhaps I could capitalize on my ability to selectively remove the acetonide. The best conditions to effect acetonide removal were to treat **372** with *p*TsOH in MeOH. With the Boc amine **348a** in hand, I tried to form the amide bond via an oxygen-to-nitrogen acyl transfer.[63] Formation of the ester **350a** was accomplished with palmitic acid and EDCI, but none of the Boc amide **351a** was formed via an acyl transfer.

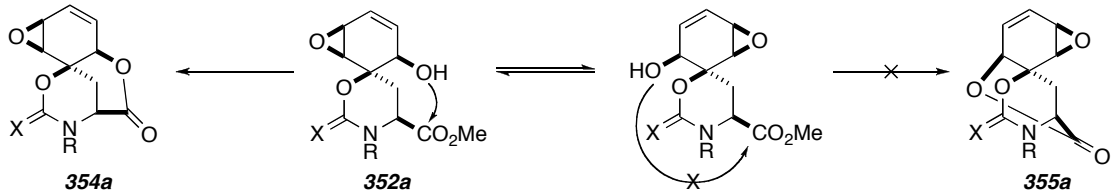
Scheme III-48. Attempts to Selectively Deprotect the Boc-Acetonide **372**.



The other miscellaneous approach involved my attempts to make an intermediate in which the tertiary alcohol and amine were used to make a six-membered ring (Scheme III-49) by making an *N*,*O*-acetonide (X=Me,Me) or a cyclic carbamate (X=O). If this could be achieved, the allylic alcohol **352a** could form the lactone **354a** upon attacking the ester (or alternatively, if the ester was reduced to an alcohol, this alcohol could be used to form an eight-membered acetonide or carbonate). This approach could allow for

a DKR, however, since the L-tyrosine amine stereocenter would only permit lactonization of the desired vinylogous Payne rearrangement isomer **352a**. The alcohol of the other Payne isomer, **353a**, would be unlikely to engage the ester and form lactone **355a**. Therefore, if lactonization conditions also permitted vinylogous Payne equilibration of **352a** and **353a**, complete conversion to the lactone **354a** (which has the stereochemical configuration needed to make (+)-scyphostatin) could be achieved via a DKR.

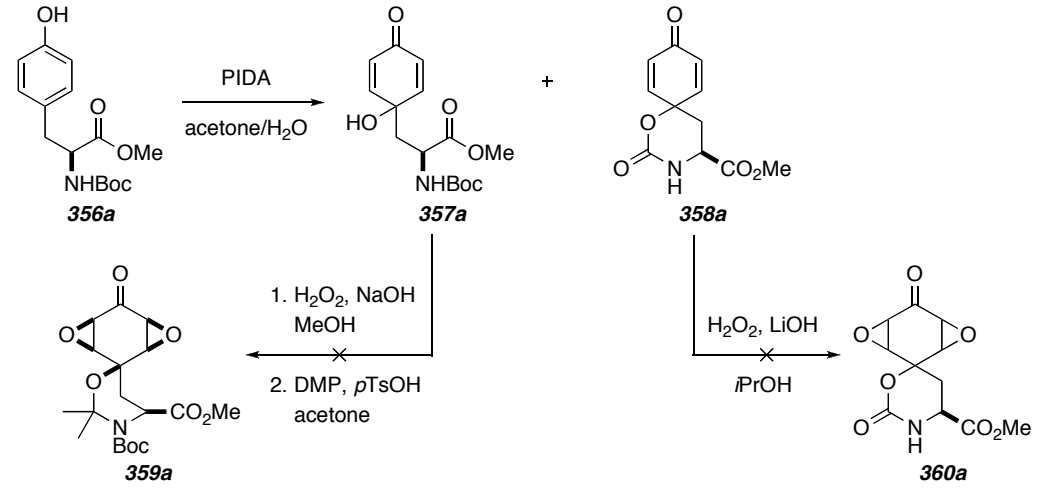
Scheme III-49. DKR via Lactonization.



354a ***352a*** ***353a*** ***355a***

I initially set out to make the *N*,*O*-acetonides **352a** and **353a** (X=Me,Me) by exposing the phenol **356a** to oxidative dearomatization conditions to give the dienone **357a**, along with the unexpected side product carbamate **358a**. This serendipitous formation of the side product **358a** allowed me to attempt to make carbamates **352a** and **353a** (X=O). The dienone **357a** was epoxidized under the standard conditions, and this crude material was subsequently exposed to the acetonide formation conditions. However, none of the acetonide **359a** was isolated from this complex product mixture. Meanwhile, the epoxidation (LiOH, H_2O_2; conditions known to epoxidize a similar spirocycle) of the spirocycle **358a** did not yield any of the diepoxide **360a**. Most likely, saponification of the ester could have led to undesired products. Since this idea was a diversion from the main focus of the project, no more work was done to produce the allylic alcohols **352a** and **353a**.

Scheme III-50. Attempts to Make Lactonization-DKR Intermediates.

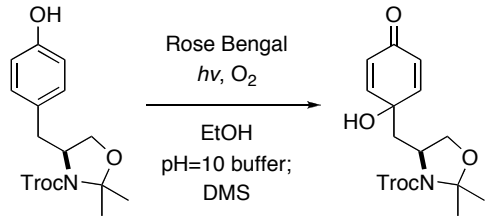


III.H. Conclusion

In summary, progress has been made toward the synthesis of the (+)-scyphostatin polar core. Most importantly, I have been able to show that a vinylogous Payne rearrangement can occur in this system, and it can be used to carry out a DKR that provides an intermediate with the stereochemical features required to make (+)-scyphostatin. Also, various protecting group strategies were explored, providing insight into the reactivity of a number of intermediates.

III.I. Experimental Section

(*S*)-3-Oxazolidinecarboxylic acid, 4-[(1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (376)



375 ***376***

To a solution of the phenol **375** (62.7 mg, 0.164 mmol) in EtOH (12.3 mL) and aqueous buffer (4.1 mL; pH=10, 0.025 M carbonate buffer) was added Rose Bengal (16.7 mg, 0.0164 mmol). The solution was cooled to 0 ºC for 5 min using a tube fitted with a cold finger. Air was bubbled into the cold solution as it was irradiated (175W mercury vapor lamp) for 3 h. Dimethyl sulfide (1 mL) was added to the solution, which was warmed to rt. After the solution was stirred for 30 min, aqueous buffer (16 mL; pH=7, 0.05 M phosphate buffer) was added, and the solution was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (2:1 hexanes:EtOAc) to give the dienone **376** (29.5 mg, 0.074 mmol, 45% yield).

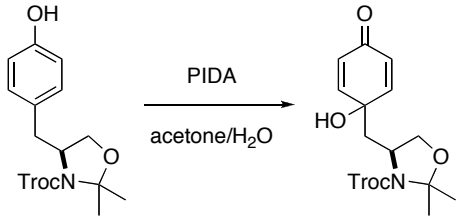
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (dd, *J* = 10.1, 3.2 Hz, 0.5H), 6.94 (dd, *J* = 10.0, 3.1 Hz, 0.5H), 6.90 (dd, *J* = 10.1, 3.0 Hz, 0.5H), 6.89 (dd, *J* = 10.6, 2.9 Hz, 0.5H), 6.23 (dd, *J* = 10.0, 2.0 Hz, 0.5H), 6.21 (m, 1H), 6.20 (dd, *J* = 10.1, 2.0 Hz, 0.5H), 4.82 (d, *J* = 11.9 Hz, 0.5H), 4.79 (d, *J* = 11.9 Hz, 0.5H), 4.77 (d, *J* = 12.1 Hz, 0.5H), 4.71 (d, *J* = 12.1 Hz, 0.5H), 4.12 (m, 1H), 4.07 (d, *J* = 9.7 Hz, 0.5H), 4.05 (ddd, *J* = 9.2, 5.2, 1.0 Hz, 0.5H), 3.98 (ddd, *J* = 9.3, 5.2, 1.7 Hz, 0.5H), 3.87 (dd, *J* = 9.1, 1.3 Hz, 0.5H), 2.24 (dd, *J* = 13.7,

11.0 Hz, 0.5H), 2.17 (dd, *J* = 14.1, 3.2 Hz, 0.5H), 2.12 (d, *J* = 14.2 Hz, 0.5H), 2.10 (dd, *J* = 14.1, 8.1 Hz, 0.5H), 1.66 (s, 1.5H), 1.62 (s, 1.5H), 1.55 (s, 1.5H), and 1.51 (s, 1.5H).

^{13}C NMR (125 MHz, $CDCl_3$): 185.2, 185.1, 154.9, 153.4 150.8, 150.6, 150.5, 149.8, 128.7, 128.6 (x2), 128.2, 114.7, 113.6, 94.4$^+$, 94.4$^-$, 75.4, 74.9, 69.2, 68.8, 68.7+, 68.7-, 54.8, 54.1, 44.3, 42.9, 27.7, 26.6, 24.7, and 23.0.

ESI-HRMS: calcd for $C_{15}H_{18}Cl_3NO_5$ $(M+Na)^+$ 420.0143, found 420.0142.

(*S*)-3-Oxazolidinecarboxylic acid, 4-[(1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (376)

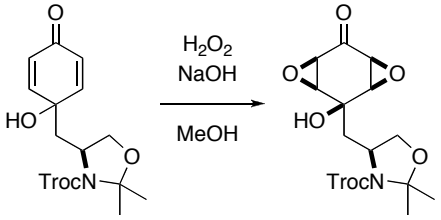


375 ***376***

To a solution of the phenol **375** (100 mg, 0.261 mmol) in acetone (19 mL) and H_2O (2 mL) at 0 ºC was added PIDA (151 mg, 0.47 mmol), and the solution was stirred for 1 h. After warming the solution to rt, H_2O (15 mL) was added and the solution was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (2:1 hexanes:EtOAc) to give the dienone **376** (53.9 mg, 0.135 mmol, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$): Matches data reported above.

(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(2-hydroxy-6-oxo-4,8-dioxatricyclo[5.1.0.03,5]oct-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (377)



376 ***377***

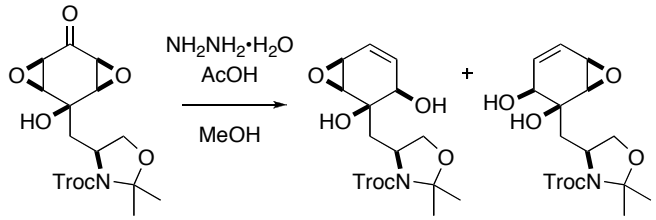
To a solution of the dienone **376** (481 mg, 1.21 mmol) in MeOH (63 mL) was added H_2O_2 (4.3 mL, 42 mmol; 30% w/w aqueous solution) and aqueous NaOH (3.0 mL, 0.18 mmol; 0.06 M). The solution was stirred for 16 h at rt. Aqueous buffer (9 mL; pH=7, 0.05 M phosphate buffer) was added to the solution, which was subsequently extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid (471 mg, 1.09 mmol, 90% crude yield). The crude diepoxide **377** was taken directly onto the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.81 (d, *J* = 11.9 Hz, 0.5H), 4.78 (d, *J* = 12.0 Hz, 0.5H), 4.74 (d, *J* = 11.9 Hz, 0.5H), 4.68 (d, *J* = 12.1 Hz, 0.5H), 4.31 (d, *J* = 9.1 Hz, 0.5H), 4.29 (m, 1H), 4.11 (m, 1.5H), 3.86 (app t, *J* = 3.7 Hz, 0.5H), 3.80 (app t, *J* = 3.7 Hz, 0.5H), 3.52 (dd, *J* = 4.0, 2.5 Hz, 0.5H), 3.49 (m, 2.5H), 3.03 (br s, 0.5H), 2.89 (br s, 0.5H), 2.22 (dd, *J* = 14.2, 11.2 Hz, 0.5H), 2.16 (dd, *J* = 14.2, 9.5 Hz, 0.5H), 2.09 (br d, *J* = 13.6 Hz, 1H), 1.67 (s, 1.5H), 1.65 (s, 1.5H), 1.59 (s, 1.5H), and 1.55 (s, 1.5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.4, 198.1, 150.9, 149.8, 113.03, 113.00, 94.3, 94.0, 75.1, 74.8, 69.1, 68.7, 68.2, 68.1, 64.8, 64.7, 62.80, 62.78, 57.4, 56.91, 56.85, 56.8, 54.2, 53.4, 38.3, 37.8, 27.5, 26.5, 24.3, and 22.7.

ESI-HRMS: calcd for $C_{15}H_{18}Cl_3NO_7$ $(M+Na+MeOH)^+$ 484.0303, found 484.0306.

(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(1*S,2*R**,3*R**,6*S**)-(2,3-dihydroxy-7-oxabicyclo[4.1.0]hept-4-en-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (378, 379)**



377 ***378*** ***379***

To a solution of the diepoxide **377** (100 mg, 0.23 mmol) in MeOH (2.3 mL) was added AcOH (14.3 μL, 0.25 mmol) and $NH_2NH_2•H_2O$ (12.1 μL, 0.25 mmol). After the solution was stirred at rt for 15 min, saturated aqueous $NaHCO_3$ (0.5 mL) was added and the solution was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by normal phase HPLC (3:2 hexanes:EtOAc) to give the allylic alcohols **378** and **379** (33.2 mg, 0.080 mmol, 35% yield).

<u>378 (less polar diastereomer)</u>

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.37 (ddd, *J* = 9.6, 6.6, 2.0 Hz, 0.5H), 6.29 (ddd, *J* = 9.6, 6.4, 2.0 Hz, 0.5H), 6.18 (ddd, *J* = 9.4, 5.4, 3.9 Hz, 1H), 5.02 (d, *J* = 12.2 Hz, 0.5H), 4.81 (d, *J* = 11.9 Hz, 0.5H), 4.70 (d, *J* = 11.9 Hz, 0.5H), 4.50 (d, *J* = 12.2 Hz, 0.5H), 4.27 (dd, *J* = 9.2, 0.9 Hz, 0.5H), 4.16 (ddd, *J* = 11.9, 6.6, 2.9 Hz, 0.5 H), 4.15 (d, *J* = 7.5 Hz, 0.5H), 4.08 (m, 3H), 3.68 (ddd, *J* = 2.0, 2.0, 3.9 Hz, 1H), 3.49 (ddd, *J* = 4.0, 4.0, 2.0 Hz, 0.5H), 3.48 (ddd, *J* = 4.0, 4.0, 2.0 Hz, 0.5H), 3.41 (dd, *J* = 4.2, 2.8 Hz, 0.5H), 3.39 (dd, *J* = 4.2, 2.8 Hz, 0.5H), 2.28 (dd, *J* = 11.8, 7.7 Hz, 0.5H), 2.27 (dd, *J* = 11.8, 8.3 Hz, 0.5H), 1.98 (dd, *J* = 14.2, 11.0 Hz, 0.5H), 1.91 (dd, *J* = 14.1, 10.0 Hz, 0.5H), 1.63 (s, 1.5H), 1.61 (s, 1.5H), 1.56 (s, 1.5H), and 1.52 (s, 1.5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.5, 149.9, 135.3, 134.9, 127.8, 127.3, 113.1 (x2), 94.0, 93.6, 75.0, 74.3, 71.0, 70.7, 69.4, 69.3, 68.1, 68.0, 62.3, 62.2, 54.9, 53.9, 50.7, 50.6, 36.2, 35.6, 27.5, 26.5, 24.4 and 22.7.

ESI-HRMS: calcd for $C_{15}H_{20}Cl_3NO_6$ $(M+Na)^+$ 438.0248, found 438.0259.

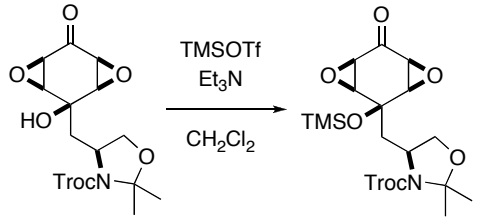
379 (more polar diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.25 (ddd, 9.6, 6.1, 1.6 Hz, 0.5H), 6.24 (ddd, *J* = 9.7, 5.9, 1.7 Hz, 0.5H), 6.19 (dd, *J* = 9.6, 3.7 Hz, 0.5H), 6.16 (dd, *J* = 9.6, 3.8 Hz, 0.5H), 4.82 (d, *J* = 11.9 Hz, 0.5H), 4.76 (d, *J* = 12.1 Hz, 0.5H), 4.71 (d, *J* = 12.0 Hz, 0.5H), 4.70 (d, *J* = 11.9 Hz, 0.5H), 4.41 (d, *J* = 9.2 Hz, 0.5H), 4.34 (dd, *J* = 11.7, 5.7 Hz, 0.5H), 4.30 (dd, *J* = 10.9, 5.7 Hz, 0.5H), 4.21 (d, *J* = 9.2 Hz, 0.5H), 4.06 (m, 2H), 3.78 (dd, *J* = 4.2, 2.7 Hz, 0.5H), 3.70 (m, 2H), 3.64 (br d, *J* = 4.8 Hz, 0.5H), 3.57 (ddd, *J* = 4.0, 4.0, 1.9 Hz, 0.5H), 3.51 (ddd, *J* = 4.0, 4.0, 1.7 Hz, 0.5H), 2.37 (dd, *J* = 11.9, 4.5 Hz, 0.5H), 2.32 (dd, *J* = 11.8, 5.4 Hz, 0.5H), 1.96 (d, *J* = 13.8 Hz, 0.5H), 1.91 (d, *J* = 13.8 Hz, 0.5H), 1.81 (dd, *J* = 14.0, 11.4 Hz, 0.5H), 1.75 (dd, *J* = 13.8, 10.6 Hz, 0.5H), 1.63 (s, 1.5H), 1.61 (s, 1.5H), 1.57 (s, 1.5H), and 1.53 (s, 1.5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.7, 150.0, 135.0 (x2), 127.9, 127.8, 113.0 (x2), 94.0, 93.7, 75.0, 74.7, 71.8 (x2), 71.0, 70.7, 68.7, 68.5, 60.8, 60.6, 54.6, 53.8, 51.1, 50.9, 38.4, 38.2, 27.5, 26.5, 24.5, and 22.8.

ESI-HRMS: calcd for $C_{15}H_{20}Cl_3NO_6$ $(M+Na)^+$ 438.0248, found 438.0236.

(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(2-[(trimethylsilyl)oxy]-6-oxo-4,8-dioxatricyclo[5.1.0.03,5]oct-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (388)

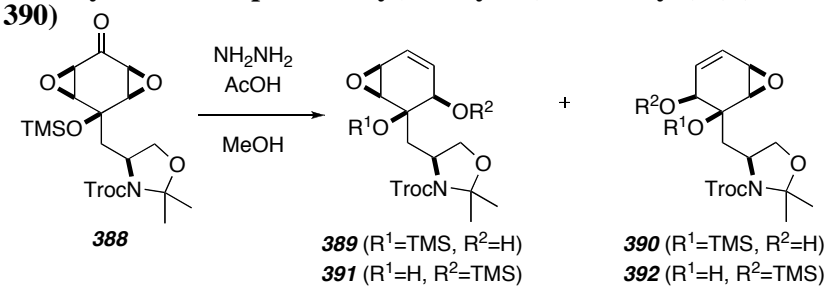


377 ***388***

To a solution of the diepoxide **377** (166 mg, 0.39 mmol) and Et_3N (80 μL, 0.59 mmol) in CH_2Cl_2 (2 mL) at 0 ºC was added TMSOTf (100 μL, 0.55 mmol) dropwise. The reaction mixture was stirred at 0 ºC for 30 min and then warmed to rt and stirred for an additional 2 h. The reaction was quenched with MeOH (100 μL). H_2O was added to the mixture, which was then extracted with CH_2Cl_2 (3x). The combined organic layers were washed with saturated aq. $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the TMS-ether **388** (131 mg, 0.26 mmol, 67% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.84 (d, *J* = 11.9 Hz, 0.5H), 4.81 (d, *J* = 12.2 Hz, 0.5H), 4.67 (d, *J* = 11.9 Hz, 0.5H), 4.66 (d, *J* = 12.2 Hz, 0.5H), 4.26 (d, *J* = 9.4 Hz, 0.5H), 4.23 (ddt, *J* = 11.4, 5.7, 1.4 Hz, 0.5H), 4.19 (ddt, *J* = 10.4, 5.2, 1.4 Hz, 0.5H), 4.07 (m, 1.5H), 3.83 (t, *J* = 4.0 Hz, 0.5H), 3.74 (t, *J* = 3.8 Hz, 0.5H), 3.48 (dd, *J* = 4.1, 2.6 Hz, 0.5H), 3.45 (m, 1.5H), 3.39 (t, *J* = 4.0 Hz, 0.5H), 3.38 (t, *J* = 4.0, 0.5 Hz, 0.5H), 2.15 (dd, *J* = 14.0, 11.0 Hz, 0.5H), 2.09 (dd, *J* = 13.9, 10.3 Hz, 0.5H), 1.894 (d, *J* = 13.9 Hz, 0.5H), 1.891 (d, *J* = 13.9 Hz, 0.5H), 1.65 (s, 1.5H), 1.63 (s, 1.5H), 1.58 (s, 1.5H), 1.54 (s, 1.5H), 0.29 (s, 4.5H), and 0.29 (s, 4.5H).

(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(1*S,2*R**,3*R**,6*S**)-(2-[(trimethylsilyl)oxy]-3-hydroxy-7-oxabicyclo[4.1.0]hept-4-en-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (389, 390)**



388

389 (R^1=TMS, R^2=H)
391 (R^1=H, R^2=TMS)

390 (R^1=TMS, R^2=H)
392 (R^1=H, R^2=TMS)

To a solution of the diepoxide **388** (27.5 mg, 0.055 mmol) in MeOH (0.6 mL) was added AcOH (4.8 μL, 0.083 mmol) and $NH_2NH_2 \cdot H_2O$ (4.0 μL, 0.083 mmol). After the solution was stirred at rt for 15 min, saturated aqueous $NaHCO_3$ (0.2 mL) was added and the solution was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by normal phase HPLC to give the allylic alcohols **389** and **390** (*less polar diastereomer*: 0.9 mg, 0.0018 mmol, 3.3 % yield; *more polar diastereomer*: 1.4 mg, 0.0029 mmol, 5.3% yield) and the allylic TMS ethers **391** and **392** (*combined*: 5.5 mg, 0.011 mmol, 20% yield).

<u>389 and 390 (less polar diastereomer)</u>

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.40 (ddd, *J* = 9.0, 6.4, 2.0 Hz, 0.5H), 6.31 (ddd, *J* = 9.1, 6.3, 2.1 Hz, 0.5H), 6.09 (dd, *J* = 9.5, 3.9 Hz, 0.5H), 6.06 (dd, *J* = 9.6, 3.9 Hz, 0.5H), 5.12 (d, *J* = 12.2 Hz, 0.5H), 4.81 (d, *J* = 11.9 Hz, 0.5H), 4.69 (d, *J* = 11.9 Hz, 0.5H), 4.41 (d, *J* = 12.2 Hz, 0.5H), 4.19 (d, *J* = 8.4 Hz, 0.5H), 4.08 (m, 2.5H), 3.47 (ddd, *J* = 6.2, 4.2, 2.0 Hz, 0.5H), 3.46 (ddd, *J* = 6.1, 4.1, 2.1 Hz, 0.5H), 3.39 (dd, *J* = 4.3, 2.9 Hz, 0.5H), 3.36 (dd, *J* = 4.3, 2.8 Hz, 0.5H), 2.43 (d, *J* = 2.0 Hz, 0.5H), 2.41 (d, *J* = 2.0 Hz, 0.5H), 1.90 (dd, *J* = 14.1, 10.6 Hz, 0.5H), 1.82 (dd, *J* = 13.9, 10.2 Hz, 0.5H), 1.70 (d, *J* = 13.9 Hz, 1H), 1.62 (s, 1.5H), 1.60 (s, 1.5H), 1.56 (s, 1.5H), 1.51 (s, 1.5H), and 0.21 (s, 9H).

389 and 390 (more polar diastereomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.29 (m, 1H), 6.11 (dd, *J* = 9.5, 3.9 Hz, 0.5H), 6.07 (dd, *J* = 9.5, 4.0 Hz, 0.5H), 4.90 (d, *J* = 12.1 Hz, 0.5H), 4.83 (d, *J* = 11.9 Hz, 0.5H), 4.68 (*J* = 11.9 Hz, 0.5H), 4.59 (d, *J* = 12.1 Hz, 0.5H), 4.29 (d, *J* = 9.1 Hz, 0.5H), 4.25 (m, 1H), 4.12 (m, 0.5H), 4.07 (ddd, *J* = 9.2, 5.6, 1.4 Hz, 0.5H), 4.03 (m, 0.5H), 3.76 (dd, *J* = 4.3, 2.8 Hz, 0.5H), 3.70 (dd, *J* = 4.3, 2.9 Hz, 0.5H), 3.57 (ddd, *J* = 4.3, 4.3, 2.1 Hz, 0.5H), 3.51 (ddd, *J* = 4.0, 4.0, 2.1 Hz, 0.5H), 1.94 (d, *J* = 13.8 Hz, 0.5H), 1.88 (d, *J* = 13.7 Hz, 0.5H), 1.73 (dd, *J* = 13.9, 11.3 Hz, 0.5H), 1.67 (dd, *J* = 13.7, 10.8 Hz, 0.5H), 1.62 (s, 1.5H), 1.60 (s, 1.5H), 1.57 (s, 1.5H), 1.52 (s, 1.5H), and 0.22 (s, 9H).

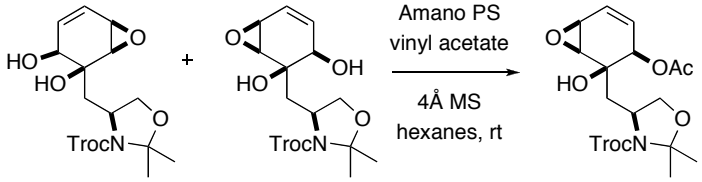
391 and 392 (both diastereomers)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.13 (ddd, *J* = 9.7, 3.9, 3.9 Hz, 1H), 6.05 (m, 1H), 6.02 (ddd, *J* = 9.8, 6.0, 1.9 Hz, 0.5H), 5.95 (ddd, *J* = 9.8, 6.0, 1.8 Hz, 0.5H), 5.88 (ddd, *J* = 9.8, 4.6, 1.5 Hz, 0.5H), 5.87 (ddd, *J* = 9.8, 4.4, 1.4 Hz, 0.5H), 4.90 (d, *J* = 12.2 Hz, 0.5H), 4.82 (d, *J* = 11.9 Hz, 0.5H), 4.79 (d, *J* = 11.9 Hz, 0.5H), 4.78 (d, *J* = 12.1 Hz, 0.5H), 4.74 (d, *J* = 11.9 Hz, 0.5H), 4.73 (d, *J* = 12.2 Hz, 1H), 4.60 (d, *J* = 12.2 Hz, 0.5H), 4.40 (d, *J* = 9.2 Hz, 0.5H), 4.39 (dd, *J* = 6.1, 2.5 Hz, 0.5H), 4.35 (d, *J* = 9.3 Hz, 0.5H), 4.32 (m, 0.5H), 4.27 (m, 0.5H), 4.25 (dd, *J* = 6.0, 2.4 Hz, 0.5H), 4.21 (dd, *J* = 9.2, 1.6 Hz, 0.5H), 4.16 (br s, 0.5H), 4.14 (br s, 0.5H), 4.08 (m, ?H), 4.00 (d, *J* = 4.3 Hz, 0.5H), 3.94 (d, *J* = 4.6 Hz, 0.5H), 3.74 (dd, *J* = 4.2, 1.3 Hz, 0.5H), 3.65 (dd, *J* = 4.1, 1.6 Hz, 0.5H), 3.45 (d, *J* = 1.7 Hz, 0.5H), 3.41 (d, *J* = 1.9 Hz, 0.5H), 3.36 (ddd, *J* = 4.4, 3.3, 1.4 Hz, 0.5H), 3.33 (m, 1.0H), 3.28 (dd, *J* = 4.1, 2.5 Hz, 0.5H), 3.27 (dd, *J* = 4.1, 2.3 Hz, 0.5H), 3.24 (d, *J* = 1.5 Hz, 0.5H), 3.16 (d, *J* = 1.7 Hz, 0.5H), 2.008 (dd, *J* = 13.8, 10.5 Hz, 0.5H), 2.000 (dd, *J* = 13.9, 11.1 Hz, 0.5H), 1.98 (dd, *J* = 14.2, 11.0 Hz, 1H), 1.94 (dd, *J* = 14.2, 10.3 Hz,

1H), 1.90 (d, *J* = 13.7, 1H), 1.65 (s, 1.5H), 1.64 (s, 1.5H), 1.63 (s, 3H), 1.58 (s, 1.5H), 1.57 (s, 1.5H), 1.54 (s, 1.5H), 1.53 (s, 1.5H), 0.18 (s, 4.5H), 0.16 (s, 9H), and 0.14 (s, 4.5H).

ESI-MS: low res for $C_{18}H_{28}Cl_3NO_6Si$ $(M+Na)^+$ 510.06, found 509.95.

(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(1*S*,2*R*,3*R*,6*S*)-(2-hydroxy-3-acetyloxy-7-oxabicyclo[4.1.0]hept-4-en-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (396)



379 ***378*** ***396***

To a solution of the allylic alcohols **378** and **379** (48 mg, 0.115 mmol) in hexanes (1.2 mL) in a sealed tube was added vinyl acetate (53 μL, 0.58 mmol), Amano PS (48 mg), and 4Å MS (480 mg). The tube was wrapped with Teflon tape, and the mixture was stirred at rt for 14 days. The mixture was filtered through a silica plug with EtOAc, and the solvent was removed under reduced pressure to give an oil. The crude oil was purified by MPLC (2:1 hexanes:EtOAc) to give the acetate **396** (6.6 mg, 0.014 mmol, 12% yield).

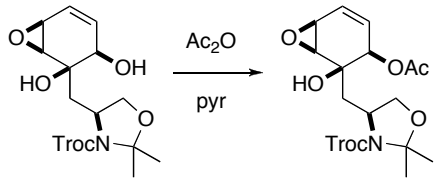
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.239 (dd, *J* = 9.7, 3.8 Hz, 0.5H), 6.236 (dd, *J* = 9.7, 3.9 Hz, 0.5H), 6.13 (ddd, *J* = 9.7, 6.3, 1.9 Hz, 0.5H), 6.11 (ddd, *J* = 9.7, 6.1, 1.9 Hz, 0.5H), 5.51 (dd, *J* = 6.3, 2.4 Hz, 0.5H), 5.37 (dd, *J* = 6.2, 2.4 Hz, 0.5H), 4.99 (d, *J* = 12.0 Hz, 0.5H), 4.83 (d, *J* = 11.9 Hz, 0.5H), 4.72 (d, *J* = 11.9, 0.5H), 4.55 (d, *J* = 12.1 Hz, 0.5H), 4.28 (d, *J* = 9.6 Hz, 0.5H), 4.23 (m, 1H), 4.08 (br s, 0.5H), 4.07 (br s, 0.5H), 4.04 (ddd, *J* = 9.3, 5.3, 1.6 Hz, 0.5 H), 3.42 (ddd, *J* = 3.8, 3.8, 1.9 Hz, 0.5H), 3.41 (ddd, *J* = 3.9, 3.9, 1.9 Hz, 0.5H), 3.34 (dd, *J* = 3.2, 2.4 Hz, 0.5H), 3.33 (dd, *J* = 3.2, 2.4 Hz, 0.5H), 2.93 (d, *J* = 1.8 Hz, 0.5H), 2.76 (d, *J* = 2.0 Hz, 0.5H), 2.11 (s, 1.5H), 2.09 (s, 1.5H), 2.03 (dd, *J* =

14.3, 11.1 Hz, 0.5H), 1.95 (dd, *J* = 14.2, 9.6 Hz, 0.5H), 1.81 (d, *J* = 14.2 Hz, 0.5H), 1.72 (d, *J* = 14.2 Hz, 0.5H), 1.65 (s, 1.5H), 1.63 (s, 1.5H), 1.57 (s, 1.5H), and 1.52 (s, 1.5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.5, 170.3, 150.7, 150.0, 130.2, 129.9, 129.4, 129.1, 113.2, 113.1, 94.0, 93.8, 75.1, 74.4, 71.3, 71.0, 69.2, 69.1, 68.7, 68.4, 61.0, 60.9, 54.7, 53.9, 48.9 (x2), 37.1, 36.9, 27.5, 26.5, 24.4, 22.7, 21.12, and 21.06.

ESI-HRMS: calcd for $C_{17}H_{22}Cl_3NO_7$ $(M+Na)^+$ 480.0354, found 480.0353.

(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(1*S*,2*R*,3*R*,6*S*)-(2-hydroxy-3-acetyloxy-7-oxabicyclo[4.1.0]hept-4-en-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (396)

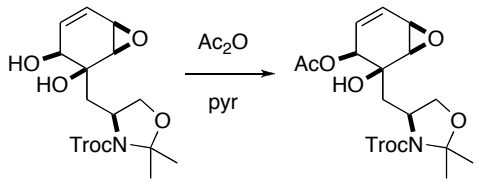


378 ***396***

To a solution of the allylic alcohol **378** (5 mg, 0.012 mmol) in pyridine (0.2 mL) was added Ac_2O (0.1 mL). The solution was stirred overnight at rt. The solvent was removed under reduced pressure to give an oil. The crude oil was purified by MPLC (2:1 hexanes:EtOAc) to give the allylic acetate **396** (1.2 mg, 0.0026 mmol, 22% yield).

^{1}H NMR (500 MHz, $CDCl_3$): Matched data reported above.

(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(1*R*,2*S*,3*S*,6*R*)-(2-hydroxy-3-acetyloxy-7-oxabicyclo[4.1.0]hept-4-en-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (397)



379 ***397***

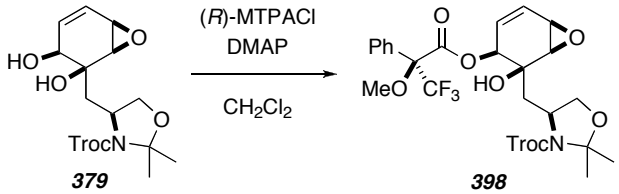
To a solution of the allylic alcohol **379** (5 mg, 0.012 mmol) in pyridine (0.2 mL) was added Ac_2O (0.1 mL). The solution was stirred overnight at rt. The solvent was

removed under reduced pressure to give an oil. The crude oil was purified by MPLC (2:1 hexanes:EtOAc) to give the allylic acetate **397** (2.0 mg, 0.0044 mmol, 37% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.15 (ddd, *J* = 9.5, 5.9, 3.3 Hz, 1H), 5.95 (ddd, *J* = 9.7, 4.6, 1.5 Hz, 0.5H), 5.91 (ddd, *J* = 9.7, 4.3, 1.4 Hz, 0.5H), 5.15 (dt, *J* = 4.3, 1.3 Hz, 0.5H), 5.10 (dt, *J* = 4.7, 1.2 Hz, 0.5H), 4.82 (d, *J* = 11.9 Hz, 0.5H), 4.77 (d, *J* = 11.9 Hz, 0.5H), 4.74 (d, *J* = 12.1 Hz, 0.5H), 4.73 (d, *J* = 11.9 Hz, 0.5H), 4.33 (d, *J* = 9.0 Hz, 0.5H), 4.28 (m, 2H), 4.13 (br s, 0.5H), 4.12 (br s, 0.5H), 4.07 (ddd, *J* = 9.2, 5.4, 1.5 Hz, 0.5H), 3.82 (dd, *J* = 4.2, 1.4 Hz, 0.5H), 3.73 (dd, *J* = 4.2, 1.6 Hz, 0.5H), 3.44 (ddd, *J* = 4.5, 3.5, 1.4 Hz, 0.5H), 3.40 (ddd, *J* = 4.3, 3.5, 1.6 Hz, 0.5H), 2.94 (d, *J* = 1.5 Hz, 0.5H), 2.78 (d, *J* = 1.7 Hz, 0.5H), 2.15 (s, 1.5H), 2.14 (s, 1.5H), 2.06 (dd, *J* = 14.2, 11.2 Hz, 0.5H), 2.02 (dd, *J* = 14.2, 9.4 Hz, 0.5H), 1.97 (d, *J* = 14.2 Hz, 0.5H), 1.96 (d, *J* = 14.2 Hz, 0.5H), 1.65 (s, 1.5H), 1.62 (s, 1.5H), 1.58 (s, 1.5H), and 1.53 (s, 1.5H).

ESI-HRMS: calcd for $C_{17}H_{22}Cl_3NO_7$ $(M+Na)^+$ 480.0354, found 480.0356.

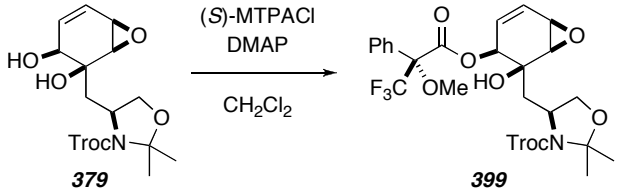
(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(1*R*,2*S*,3*S*,6*R*)-(2-hydroxy-3-[(α*S*)-α-methoxy-α-(trifluoromethyl)benzeneacetate]-7-oxabicyclo[4.1.0]hept-4-en-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (398)



To a solution of (*S*)-MTPA (28 mg, 0.12 mmol) and DMF (9.5 μL, 0.12 mmol) in hexanes (5 mL) was added oxalyl chloride (50 μL, 0.57 mmol) at rt. After the reaction mixture was stirred for 1 h at rt, it was filtered through a cotton plug and concentrated under reduced pressure to give the (*R*)-MTPACl as an oil. A solution of the allylic alcohol **379** (10 mg, 0.024 mmol) in CH_2Cl_2 (1 mL) was added to the (*R*)-MTPACl oil,

and DMAP (14.7 mg, 0.12 mmol) was then added to this solution. After the reaction mixture was stirred at rt for 1 h, saturated aq. $NaHCO_3$ was added to the mixture. The layers were separated, and the aqueous layer was extracted once more with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (3:1 hexanes:EtOAc) to give the (*S*)-MTPA ester **398** (1.8 mg, 0.0028 mmol, 12% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.54 (m, 2H), 7.42 (m, 3H), 6.22 (dd, *J* = 9.8, 3.4 Hz, 0.5H), 6.20 (dd, *J* = 9.8, 3.5 Hz, 0.5H), 6.01 (ddd, *J* = 9.7, 5.0, 1.6 Hz, 0.5H), 5.96 (ddd, *J* = 9.7, 4.8, 1.6 Hz, 0.5H), 5.25 (br d, *J* = 4.8 Hz, 0.5H), 5.20 (dd, *J* = 5.0, 1.8 Hz, 0.5H), 4.83 (d, *J* = 11.9 Hz, 0.5H), 4.75 (s, 1H), 4.72 (d, *J* = 11.9 Hz, 0.5H), 4.33 (d, *J* = 9.2 Hz, 0.5H), 4.29 (m, 1H), 4.11 (br s, 0.5H), 4.10 (br s, 0.5H), 4.05 (ddd, *J* = 9.3, 5.4, 1.4 Hz, 0.5H), 3.73 (dd, *J* = 4.1, 1.6 Hz, 0.5H), 3.66 (dd, *J* = 4.1, 1.7 Hz, 0.5H), 3.55 (s, 1.5H), 3.52 (s, 1.5H), 3.43 (ddd, *J* = 3.8, 3.8, 1.6 Hz, 0.5H), 3.39 (ddd, *J* = 3.8, 3.8, 1.6 Hz, 0.5H), 2.90 (d, *J* = 1.5 Hz, 0.5H), 2.68 (d, *J* = 1.7 Hz, 0.5H), 2.05 (dd, *J* = 14.2, 10.4 Hz, 0.5H), 2.02 (br d, *J* = 14.0 Hz, 1H), 1.97 (dd, *J* = 14.1, 9.3 Hz, 0.5H), 1.64 (s, 1.5H), 1.61 (s, 1.5H), 1.58 (s, 1.5H), and 1.53 (s, 1.5H).

(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(1*R*,2*S*,3*S*,6*R*)-(2-hydroxy-3-[(α*R*)-α-methoxy-α-(trifluoromethyl)benzeneacetate]-7-oxabicyclo[4.1.0]hept-4-en-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (399)

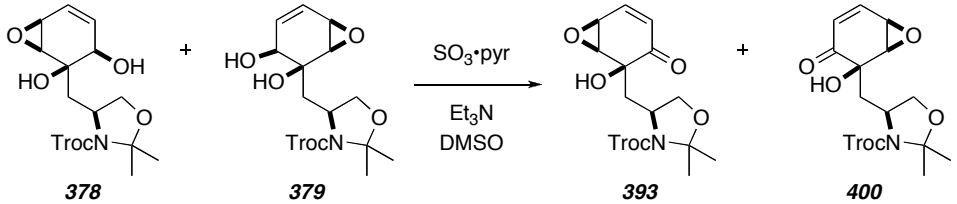


379 ***399***

To a solution of (*R*)-MTPA (28 mg, 0.12 mmol) and DMF (9.5 μL, 0.12 mmol) in hexanes (5 mL) was added oxalyl chloride (50 μL, 0.57 mmol) at rt. After the reaction

mixture was stirred for 1 h at rt, it was filtered through a cotton plug and concentrated under reduced pressure to give the (*S*)-MTPACl as an oil. A solution of the allylic alcohol **379** (10 mg, 0.024 mmol) in CH_2Cl_2 (1 mL) was added to the (*S*)-MTPACl oil, and DMAP (14.7 mg, 0.12 mmol) was then added to this solution. After the reaction mixture was stirred at rt for 1 h, saturated aq. $NaHCO_3$ was added to the mixture. The layers were separated, and the aqueous layer was extracted once more with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (3:1 hexanes:EtOAc) to give the (*R*)-MTPA ester **399** (2.9 mg, 0.0046 mmol, 19% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.56 (m, 2H), 7.41 (m, 3H), 6.29 (dd, *J* = 9.7, 3.6 Hz, 0.5H), 6.26 (dd, *J* = 9.7, 3.6 Hz, 0.5H), 6.13 (ddd, *J* = 9.7, 5.5, 1.7 Hz, 0.5H), 6.10 (ddd, *J* = 9.7, 5.2, 1.7 Hz, 0.5H), 5.14 (dd, *J* = 5.2, 1.9 Hz, 0.5H), 5.10 (dd, *J* = 5.4, 1.9 Hz, 0.5H), 4.82 (d, *J* = 11.9 Hz, 0.5H), 4.76 (d, *J* = 12.1 Hz, 0.5H), 4.73 (d, *J* = 12.1 Hz, 0.5H), 4.71 (d, *J* = 11.9 Hz, 0.5H), 4.30 (dd, *J* = 9.3, 1.1 Hz, 0.5H), 4.27 (m, 1H), 4.07 (m, 1H), 4.01 (dd, *J* = 9.4, 5.2 Hz, 0.5H), 3.71 (dd, *J* = 4.1, 1.8 Hz, 0.5H), 3.62 (dd, *J* = 4.1, 1.9 Hz, 0.5H), 3.582 (s, 1.5H), 3.577 (s, 1.5H), 3.48 (ddd, *J* = 3.8, 3.8, 1.6 Hz, 0.5H), 3.43 (ddd, *J* = 3.8, 3.8, 1.7 Hz, 0.5H), 2.62 (d, *J* = 2.0 Hz, 0.5H), 2.52 (s, 0.5H), 2.00 (d, *J* = 14.0 Hz, 0.5H), 1.97 (m, 1H), 1.90 (dd, *J* = 14.0, 10.2 Hz, 0.5H), 1.63 (s, 1.5H), 1.61 (s, 1.5H), 1.57 (s, 1.5H), and 1.52 (1.5H).

(4*S*)-3-Oxazolidinecarboxylic acid, 4-[(1*S,2*S**,6*S**)-(2-hydroxy-3-oxo-7-oxabicyclo[4.1.0]hept-4-en-2-yl)methyl]-2,2-dimethyl-, 2,2,2-trichloroethyl ester (393, 400)**



378 ***379*** ***393*** ***400***

To a solution of the allylic alcohols **378** and **379** (13 mg, 0.031 mmol) and Et_3N (47 μL) in DMSO (0.1 mL) at 0 ºC was added a solution of SO_3•pyr (50% w/w; 35 mg, 0.109 mmol) in DMSO (50 μL). The solution was allowed to warm to rt and stirred for an additional 4h. H_2O was added to the reaction mixture, which was then extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (2:1 hexanes:EtOAc) to give the enones **393** and **400** (6.5 mg, 0.016 mmol, 52% yield).

^{1}H NMR of both diastereomers (500 MHz, $CDCl_3$): δ 7.23 (dd, *J* = 9.7, 3.8 Hz, 0.5H), 7.20 (dd, *J* = 9.5, 3.6 Hz, 0.5H), 7.18 (dd, *J* = 9.5, 3.8 Hz, 0.5H), 7.15 (dd, *J* = 9.7, 3.8 Hz, 0.5H), 6.33 (dd, *J* = 9.9, 1.8 Hz, 0.5H), 6.25 (dd, *J* = 9.9, 1.7 Hz, 0.5H), 6.22 (dd, *J* = 9.8, 1.7 Hz, 0.5H), 6.20 (dd, *J* = 9.8, 1.7 Hz, 0.5H), 4.87 (d, *J* = 12.1 Hz, 0.5H), 4.83 (d, *J* = 12.1 Hz, 0.5H), 4.82 (d, *J* = 11.9 Hz, 0.5H), 4.77 (d, *J* = 11.9 Hz, 0.5H), 4.73 (d, *J* = 11.9 Hz, 0.5H), 4.70 (d, *J* = 12.1 Hz, 0.5H), 4.69 (d, *J* = 11.9 Hz, 0.5H), 4.53 (d, *J* = 12.1 Hz, 0.5H), 4.41 (dt, *J* = 4.9, 1.5 Hz, 0.5H), 4.39 (dt, *J* = 4.1, 1.5 Hz, 0.5H), 4.38 (dt, *J* = 3.9, 1.74 Hz, 0.5H), 4.36 (dt, *J* = 5.5, 1.6 Hz, 0.5H), 4.30 (dd, *J* = 9.2, 0.8 Hz, 0.5H), 4.15 (dd, *J* = 9.2, 1.6 Hz, 1H), 4.10 (dd, *J* = 5.5, 1.5 Hz, 0.5H), 4.08 (dd, *J* = 5.5, 1.5 Hz, 0.5H), 4.06 (dd, *J* = 3.2, 1.2 Hz, 0.5H), 4.04 (br s, 0.5H), 4.03 (dd, *J* = 5.5, 1.4 Hz, 0.5H), 4.02 (dd, *J* = 5.2 Hz, 1.6 Hz, 0.5H), 4.00 (dd, *J* = 5.2, 1.8 Hz, 0.5H), 3.98 (br s, 0.5H), 3.98 (br s, 0.5 H), 3.97 (dd, *J* = 9.5, 1.6 Hz, 1H), 3.87 (d, *J* = 3.9 Hz, 1H), 3.79 (dt, *J* = 5.6, 1.8 Hz, 0.5H), 3.77 (dt, *J* = 5.6, 1.8 Hz, 0.5 H), 3.69 (d, *J* = 3.8 Hz, 0.5H), 3.67 (d, *J* = 3.9 Hz, 1H), 3.67 (ddd, *J* = 4.0, 4.0, 1.7 Hz, 0.5H), 3.63 (ddd, *J* = 4.0, 4.0, 1.7 Hz, 0.5H), 3.62 (d, *J* = 3.5 Hz, 0.5H), 3.60 (ddd, *J* = 4.0, 4.0, 1.8 Hz, 0.5H), 3.60 (ddd, *J* =

3.9, 3.9, 1.7 Hz, 0.5H), 2.18 (dd, *J* = 14.2, 11.1 Hz, 1H) 2.14 (dd, *J* = 14.0, 10.0 Hz, 1H),1.86 (dd, *J* = 13.9, 11.2 Hz, 1H), 1.82 (dd, *J* = 13.9, 10.2 Hz, 1H), 1.62 (s, 1.5H), 1.61 (s, 1.5H), 1.58 (s, 1.5H), 1.57 (s, 1.5H), 1.57 (s, 1.5H), 1.53 (s, 1.5H), 1.52 (s, 1.5H), and 1.50 (s, 1.5H).

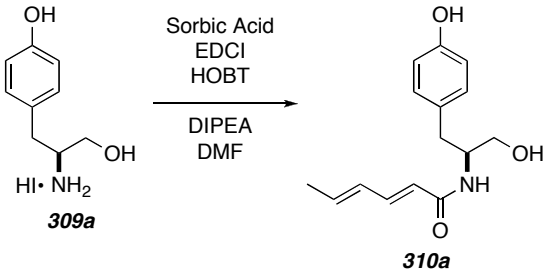
^{13}C NMR of 393 (125 MHz, $CDCl_3$): δ 197.7, 197.2, 150.5, 149.9, 145.2, 144.2, 130.5, 130.2, 113.2 (x2), 94.0, 93.6, 75.0, 74.3, 68.5 (x2), 68.3, 67.8, 56.7, 56.4, 54.1, 53.3, 48.0, 47.9, 38.3, 37.8, 27.4, 26.4, 24.4, and 22.7.

ESI-HRMS of 393: calcd for $C_{15}H_{18}Cl_3NO_6$ $(M+Na)^+$ 436.0092, found 436.0104.

^{13}C NMR of 400 (125 MHz, $CDCl_3$): δ 197.8 (x2), 150.7, 149.9, 146.1, 145.9, 129.6 (x2), 112.9 (x2), 94.1, 93.8, 75.0, 74.6, 68.6, 68.1, 67.64, 67.56, 55.6, 55.5, 54.0, 53.1, 48.2, 48.0, 39.6, 39.3, 27.4, 26.4, 24.4, and 22.7.

ESI-HRMS of 400: calcd for $C_{15}H_{18}Cl_3NO_6$ $(M+Na)^+$ 436.0092, found 436.0088.

(2*E*,4*E*)-N-[(1*S*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl]-2,4-hexadienamide (310a)



309a ***310a***

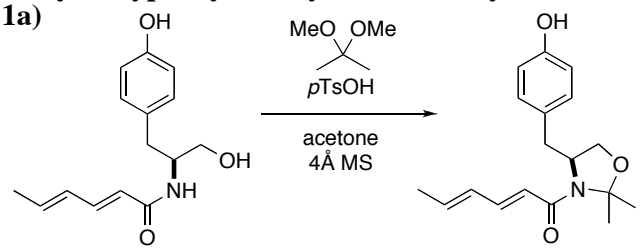
To a solution of (*S*)-tyrosinol•HI (**309a**; 4 g, 13.6 mmol) in DMF (54 mL) was added sorbic acid (1.83 g, 16.3 mmol), HOBT (2.03 g, 15.0 mmol), DIPEA (7.6 mL, 43.5 mmol), and EDCI (2.88g, 15.0 mmol) at rt. The reaction mixture was stirred overnight at rt. H_2O was added to the reaction mixture, which was then extracted with EtOAc (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil

was purified by flash chromatography (EtOAc) to give the amide **310a** (2.46 g, 9.41 mmol, 69% yield).

^{1}H NMR (500 MHz, acetone-d_6): δ 8.12 (s, 1H), 7.07 (d, J = 8.5 Hz, 2H), 7.06 (dd, J = 15.2, 10.7 Hz, 1H), 7.01 (br d, J = 7.7 Hz, 1H), 6.73 (d, J = 8.5 Hz, 2H), 6.18 (ddqd, J = 15.1, 10.9, 1.7, 0.6 Hz, 1H), 6.05 (dqt, J = 15.4, 6.7, 0.7 Hz, 1H), 5.95 (dq, J = 15.1, 0.7 Hz, 1H), 4.09 (dddt, J = 8.2, 7.2, 7.2, 4.9 Hz, 1H), 4.00 (t, J = 5.5 Hz, 1H), 3.52 (t, J = 5.2 Jz, 2H), 2.83 (dd, J = 13.7, 6.9 Hz, 1H), 2.72 (dd, J = 13.8, 7.3 Hz, 1H), and 1.79 (dd, J = 6.7, 1.6 Hz, 3H).

ESI-HRMS: calcd for $C_{15}H_{19}NO_3$ $(M+Na)^+$ 284.1257, found 284.1260.

(2*E*,4*E*)-1-[(4*S*)-4-[(4-Hydroxyphenyl)methyl]-2,2-dimethyl-3-oxazolidinyl]-2,4-hexadien-1-one (311a)



310a ***311a***

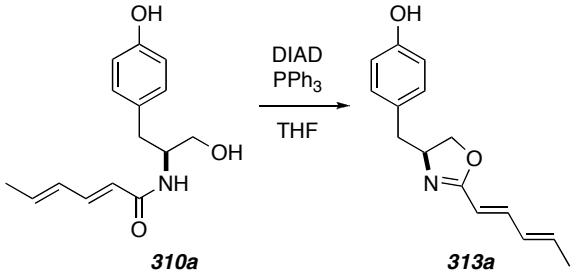
To a solution of the amide **310a** (41 mg, 0.157 mmol) in acetone (0.5 mL) was added dimethoxypropane (194 μL, 1.57 mmol), *p*TsOH•H_2O (1 mg, 0.005 mmol), and 4Å MS (200 mg) at rt. The reaction mixture was stirred overnight at rt. H_2O was added to the reaction mixture, which was then extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the phenol **311a** (14.5 mg, 0.048 mmol, 31% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (dd, J = 14.7, 10.8 Hz, 1H), 7.05 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 6.63 (br s, 1H), 6.19 (ddqd, J = 15.0, 10.7, 1.6, 0.6 Hz,

1H), 6.08 (dq, *J* = 15.2, 6.6 Hz, 1H), 6.01 (d, *J* = 14.7 Hz, 1H), 4.07 (m, 1H), 3.89 (d, *J* = 2.6 Hz, 2H), 2.92 (dd, *J* = 13.9, 4.7 Hz, 1H), 2.81 (dd, *J* = 13.8, 9.8 Hz, 1H), 1.85 (d, *J* = 6.6 Hz, 3H), 1.75 (s, 3H), and 1.59 (s, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 302.3 $(M+H)^+$; t_r = 5.54 min.

[*S*-(*E*,*E*)]-4,5-Dihydro-2-(1,3-pentadienyl)-4-[(4-hydroxyphenyl)methyl]-oxazole (313a)



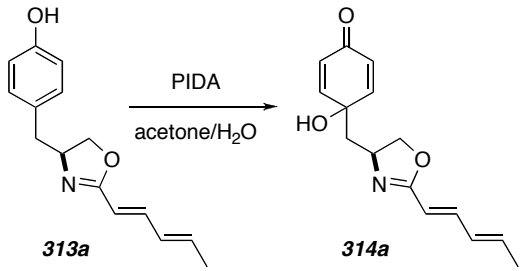
310a ***313a***

To a solution of the amide **310a** (500 mg, 1.91 mmol) and PPh_3 (600 mg, 2.29 mmol) in THF (7.6 mL) was added DIAD (450 μL, 2.29 mmol) at 0 ºC. The reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction mixture was concentrated to an oil under reduced pressure. The crude oil was purified by flash chromatography (1:1 hexanes:EtOAc) to give the oxazoline **313a** (306 mg, 1.26 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (br s, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.94 (ddd, *J* = 15.3, 10.8, 0.7 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 2H), 6.16 (ddqd, *J* = 14.9, 10.9, 1.8, 0.7 Hz, 1H), 6.01 (dqt, *J* = 15.1, 6.8, 0.7 Hz, 1H), 5.98 (d, *J* = 15.3 Hz, 1H), 4.46 (dddd, *J* = 9.4, 7.2, 7.2, 7.2 Hz, 1H), 4.33 (dd, *J* = 9.3, 8.4 Hz, 1H), 4.04 (dd, *J* = 8.4, 7.3 Hz, 1H), 2.87 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.70 (dd, *J* = 13.8, 7.1 Hz, 1H), and 1.82 (dd, *J* = 6.6, 1.6 Hz, 3H).

ESI-MS: low res for $C_{15}H_{19}NO_3$ $(M+H)^+$ 244.13, found 244.03.

[*S*-(*E*,*E*)]-4,5-Dihydro-2-(1,3-pentadienyl)-4-[(1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl)methyl]-oxazole (314a)

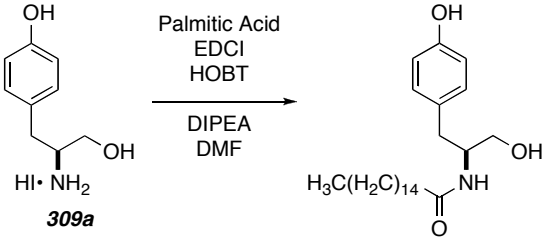


To a solution of the phenol **313a** (50 mg, 0.206 mmol) in acetone (14.8 mL) and H_2O (1.7 mL) at 0 ºC was added PIDA (120 mg, 0.371 mmol), and the solution was stirred for 1 h. After warming the solution to rt, H_2O was added, and the solution was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (1:1 hexanes:EtOAc) to give the dienone **314a** (27.1 mg, 0.105 mmol, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 10.2, 3.0 Hz, 1H), 7.00 (dd, *J* = 15.6, 10.8 Hz, 1H), 6.87 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.19 (ddqd, *J* = 14.8, 11.0, 1.5, 0.7 Hz, 1H), 6.19 (dd, *J* = 10.2, 2.0 Hz, 1H), 6.14 (dd, *J* = 10.1, 2.0 Hz, 1H), 6.07 (dqt, *J* = 15.3, 6.8, 0.7 Hz, 1H), 5.92 (d, *J* = 15.7 Hz, 1H), 4.50 (m, 2H), 3.84 (t, *J* = 7.6 Hz, 1H), 2.03 (dd, 14.0, 10.7 Hz, 1H), 1.86 (dd, *J* = 6.8 Hz, 1.6 Hz, 3H), and 1.81 (dd, *J* = 13.7, 4.1 Hz, 1H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m*/*z* = 260.0 $(M+H)^+$; t_r = 4.41 min.

N-[(1*S*)-2-Hydroxy-1-[(4-hydroxyphenyl)methyl]ethyl]-hexadecanamide (316a)

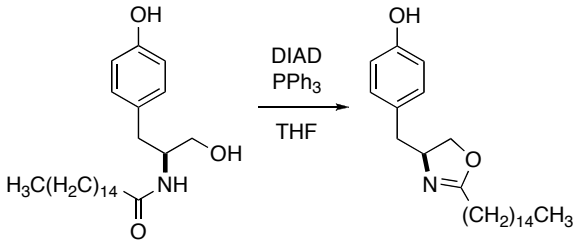


To a solution of (*S*)-tyrosinol•HI (**309a**; 4.2 g, 14.2 mmol) in DMF (57 mL) was added palmitic acid (90% w/w; 4.84 g, 17.0 mmol), HOBT (2.11 g, 15.6 mmol), DIPEA (7.9 mL, 45.4 mmol), and EDCI (2.99g, 15.6 mmol) at rt. The reaction mixture was stirred overnight at rt. H_2O was added to the reaction mixture, which was then extracted with EtOAc (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by flash chromatography (1:2 hexanes:EtOAc) to give the amide **316a** (1.50 g, 3.70 mmol, 26% yield).

^{1}H NMR (500 MHz, acetone-d_6): δ 8.14 (s, 1H), 7.07 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 7.9 Hz, 1H), 6.73 (d, J = 8.6 Hz, 2H), 4.02 (m, 1H), 3.95 (t, J = 5.5 Hz, 1H), 3.49 (t, J = 5.2 Hz, 2H), 2.81 (dd, J = 13.7, 6.7 Hz, 1H), 2.67 (dd, J = 13.7, 7.6 Hz, 1H), 2.11 (t, J = 7.6 Hz, 2H), 1.52, (m, 2H), 1.28 (m, 24H), and 0.87 (t, J = 6.6 Hz, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 406.2 $(M+H)^+$; t_r = 11.17 min.

[*S*-(*E*,*E*)]-4,5-Dihydro-2-pentadecyl-4-[(4-hydroxyphenyl)methyl]-oxazole (316b)

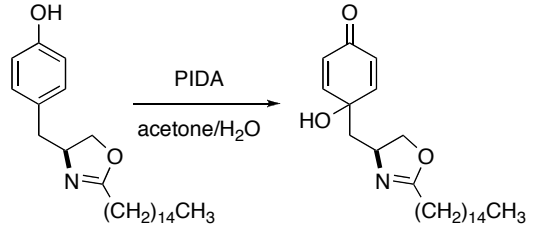


316a ***316b***

To a solution of the amide **316a** (1.21 g, 2.98 mmol) and PPh_3 (939 mg, 3.58 mmol) in THF (12 mL) was added DIAD (705 μL, 3.58 mmol) at 0 ºC. The reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction mixture was concentrated to an oil under reduced pressure. The crude oil was purified by flash chromatography (2:1 hexanes:EtOAc) to give the oxazoline **316b** (656 mg, 1.69 mmol, 57% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 4.35 (dddd, *J* = 9.5, 7.0, 7.0, 7.0 Hz, 1H), 4.25 (dd, *J* = 9.6, 8.2 Hz, 1H), 3.97 (dd, *J* = 8.5, 7.0 Hz, 1H), 2.84 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.66 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.29 (t, *J* = 7.7 Hz, 2H), 1.61 (p, *J* = 7.6 Hz, 2H), 1.25 (m, 24H), and 0.88 (t, *J* = 6.9 Hz, 3H).

[*S*-(*E*,*E*)]-4,5-Dihydro-2-pentadecyl-4-[(1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl)methyl]-oxazole (316c)



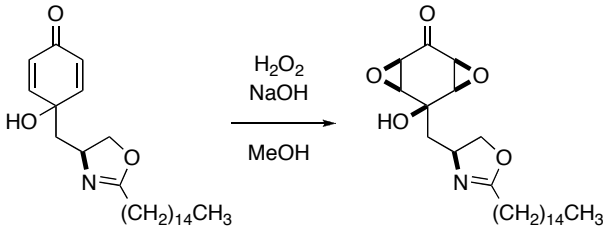
316b ***316c***

To a solution of the phenol **316b** (185 mg, 0.477 mmol) in acetone (34.2 mL) and H_2O (3.8 mL) at 0 ºC was added PIDA (277 mg, 0.859 mmol), and the solution was stirred for 1 h. After warming the solution to rt, H_2O was added, and the solution was

extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (2:1 hexanes:EtOAc) to give the dienone **316c** (70 mg, 0.173 mmol, 36% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.86 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.19 (dd, *J* = 10.1, 2.0 Hz, 1H), 6.15 (dd, 10.0, 2.2 Hz, 1H), 4.42 (m, 2H), 3.79 (m, 1H), 2.29 (t, *J* = 7.7 Hz, 2H), 1.98 (m, 1H), 1.78 (m, 1H), 1.63 (p, *J* = 7.2 Hz, 2H), 1.26 (m, 24H), and 0.88 (t, *J* = 6.5 Hz, 3H).

[*S*-(*E*,*E*)]-4,5-Dihydro-2-pentadecyl-4-[(2-hydroxy-6-oxo-4,8-dioxatricyclo[5.1.0.03,5]oct-2-yl)methyl]-oxazole (317a)



316c ***317a***

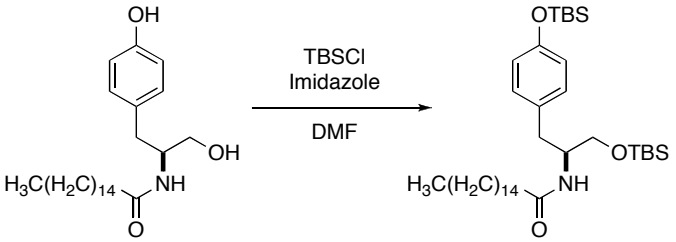
To a solution of the dienone **316c** (70 mg, 0.173 mmol) in MeOH (9 mL) was added H_2O_2 (0.62 mL, 6 mmol; 30% w/w aqueous solution) and aqueous NaOH (0.43 mL, 0.026 mmol; 0.06 M). The solution was stirred overnight at rt. Aqueous buffer (1.3 mL; pH=7, 0.05 M phosphate buffer) was added to the solution, which was subsequently extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid (73.1 mg, 0.168 mmol, 97% crude yield). The crude diepoxide **317a** was taken directly onto the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.41 (m, 2H), 3.84 (t, *J* = 6.1 Hz, 1H), 3.66 (t, *J* = 3.7 Hz, 1H), 3.60 (t, *J* = 3.7 Hz, 1H), 3.48 (m, 2H), 2.23 (t, *J* = 7.6 Hz, 2H), 2.00 (dd, *J* = 14.0,

4.4 Hz, 1H), 1.91 (dd, *J* = 14.1, 9.8 Hz, 1H), 1.59 (p, *J* = 7.2 Hz, 2H), 1.25 (m, 24H), and 0.88 (t, *J* = 6.7 Hz, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 436.3 $(M+H)^+$; t_r = 11.8 min.

N-[(1*S*)-2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-[(4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl)methyl]ethyl]-hexadecanamide (324a)



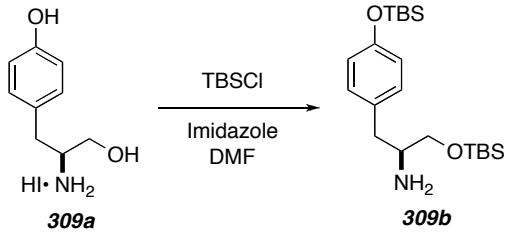
323a ***324a***

To a solution of the phenol **323a** (285 mg, 0.70 mmol) and imidazole (381 mg, 5.6 mmol) in DMF (7 mL) was added TBSCl (422 mg, 2.8 mmol) at rt. The reaction mixture was stirred for 3 h at rt. H_2O was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (429 mg, 0.68 mmol, 97% crude yield). The crude bis-TBS ether **324a** was taken directly onto the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): 7.06 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.65 (d, *J* = 8.6 Hz, 1H), 4.15 (m, 1H), 3.49 (m, 2H), 2.79 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.74 (dd, *J* = 13.5, 8.6 Hz, 1H), 2.13 (t, *J* = 7.7 Hz, 2H), 1.58 (m, 2H), 1.25 (m, 24H), 0.97 (s, 9H), 0.92 (s, 9H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.18 (s, 6H), 0.05 (s, 3H), and 0.03 (s, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 634.3 $(M+H)^+$; t_r = 16.25 min.

(αS)-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-α-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-benzeneethanamine (309b)



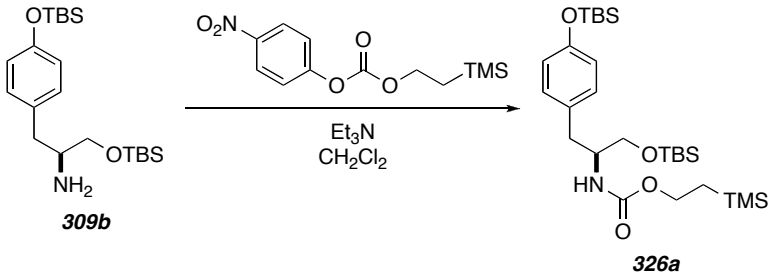
309a ***309b***

To a solution of the phenol **309a** (100 mg, 0.34 mmol) and imidazole (138 mg, 2.0 mmol) in DMF (7 mL) was added TBSCl (154 mg, 1.0 mmol) at rt. The reaction mixture was stirred for 4 h at rt. H_2O was added to the mixture, which was then extracted with EtOAc (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (132 mg, 0.33 mmol, 97% crude yield). The crude bis-TBS ether **309b** was taken directly onto the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): 7.05 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 3.57 (dd, J = 9.8, 4.2 Hz, 1H), 3.42 (dd, J = 9.8, 6.6 Hz, 1H), 3.06 (m, 1H), 2.70 (dd, J = 13.5, 5.8 Hz, 1H), 2.49 (dd, J = 13.5, 8.1 Hz, 1H), 0.98 (s, 9H), 0.90 (s, 9H), 0.18 (s, 6H), and 0.10 (s, 6H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 396.3 $(M+H)^+$; t_r = 13.72 min.

Carbamic acid, N-[(1S)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[(4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl)methyl]ethyl]-, 2-(trimethylsilyl)ethyl ester (326a)



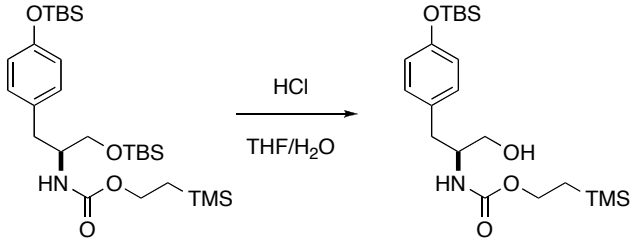
309b ***326a***

To a solution of the bis-TBS ether **309b** and Et_3N in CH_2Cl_2 was added 2-trimethylsilylethyl *p*-nitrophenyl carbonate at rt. The reaction mixture was stirred for an overnight period. H_2O was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the TEOC amine **326a** (23 mg, 0.043 mmol, 13 % yield over 2 steps, a different 136 mg fraction contained **326a** but was contaminated with 2-trimethylsilylethyl *p*-nitrophenyl carbonate).

^{1}H NMR (500 MHz, $CDCl_3$): 7.06 (d, J = 8.3 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 4.84 (d, J = 8.6 Hz, 1H), 4.13 (m, 2H), 3.83 (br s, 1H), 3.49 (d, J = 3.6 Hz, 2H), 2.76 (m, 2H), 0.973 (s, 9H), 0.972 (m, 2H), 0.92 (s, 9H), 0.18 (s, 6H), 0.04 (s, 3H), 0.034 (s, 3H), and 0.031 (s, 9H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 540.3 $(M+H)^+$; t_r = 13.32 min.

Carbamic acid, N-[(1*S*)-2-hydroxy-1-[(4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl)methyl]ethyl]-, 2-(trimethylsilyl)ethyl ester (330a)



326a ***330a***

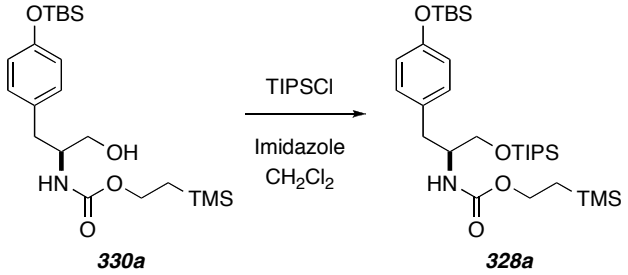
To a solution of the bis-TBS ether **326a** (337 mg, 0.62 mmol) in THF (12 mL) was added 6M aq. HCl (240 μL). The reaction mixture was stirred at rt for 2 h. Saturated aq. $NaHCO_3$ was added to the mixture, which was then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered,

and concentrated under reduced pressure to give an oil (280 mg, 0.66 mmol, quantitative crude yield). The crude alcohol **330a** was taken directly onto the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 7.05 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.3 Hz, 2H), 4.78 (br d, *J* = 7.3 Hz, 1H), 4.13 (m, 2H), 3.87 (m, 1H), 3.68 (d, *J* = 9.2 Hz, 1H), 3.56 (dd, *J* = 10.7, 5.2 Hz, 1H), 2.77 (d, *J* = 7.2 Hz, 2H), 0.98 (s, 9H), 0.95 (m, 2H), 0.18 (s, 6H), and 0.03 (s, 9H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 448.0 $(M+Na)^+$; t_r = 11.26 min.

Carbamic acid, N-[(1*S*)-2-[[tris(1-methylethyl)silyl]oxy]-1-[(4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl)methyl]ethyl]-, 2-(trimethylsilyl)ethyl ester (328a)



330a ***328a***

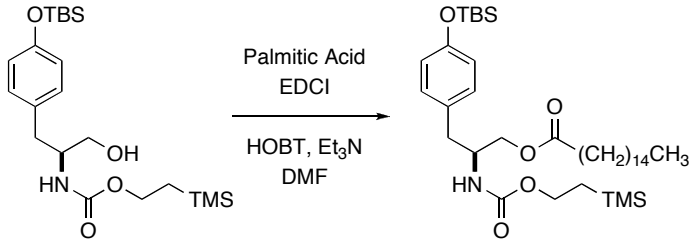
To a solution of the alcohol **330a** (162 mg, 0.38 mmol) and imidazole (78 mg, 1.14 mmol) in CH_2Cl_2 (4 mL) was added TIPSCl (122 μL, 0.57 mmol) at rt. The reaction mixture was stirred at rt for an overnight period. H_2O was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (218 mg, 0.37 mmol, 97% crude yield). The crude TIPS ether **328a** was taken directly onto the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): 7.07 (d, *J* = 8.3 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.87 (br d, *J* = 8.6 Hz, 1H), 4.12 (m, 2H), 3.85 (m, 1H), 3.60 (d, *J* = 3.7 Hz, 2H), 2.81 (d, *J* = 7.0

Hz, 2H), 1.08 (m, 3H), 1.06 (d, *J* = 3.9 Hz, 27H), 0.97 (s, 9H), 0.95 (m, 2H), 0.18 (s, 6H), and (s, 9H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 582.3 $(M+H)^+$; t_r = 14.30 min.

(2*S*)-3-(4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]phenyl)-2-[[[2-(trimethylsilyl)ethoxy]carbonyl]amino]propyl ester hexadecanoic acid (331a)



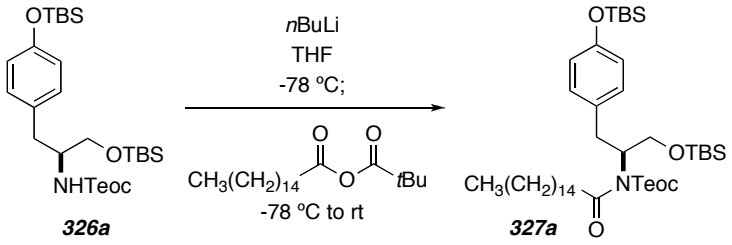
330a ***331a***

To a solution of the alcohol **330a** (100 g, 0.24 mmol) in DMF (1 mL) was added palmitic acid (90% w/w; 73 mg, 0.26 mmol), HOBT (32 mg, 0.24 mmol), Et_3N (72 μL, 0.52 mmol), and EDCI (45 mg, 0.24 mmol) at rt. The reaction mixture was stirred at rt for an overnight period. H_2O was added to the reaction mixture, which was then extracted with EtOAc (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the ester **331a** (69 mg, 0.10 mmol, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 7.02 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 4.71 (br d, *J* = 7.6 Hz, 1H), 4.12 (m, 2H), 4.02 (m, 2H), 2.81 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.73 (dd, *J* = 13.7, 7.5 Hz, 1H), 2.33 (t, *J* = 7.6 Hz, 2H), 1.63 (p, *J* = 7.4 Hz, 2H), 1.25 (m, 24H), 0.97 (s, 9H), 0.96 (m, 2H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.18 (s, 6H), and 0.03 (s, 9H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 664.2 $(M+H)^+$; t_r = 15.31 min.

Carbamic acid, N-[(1*S*)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[(4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl)methyl]ethyl]-N-(1-oxohexadecyl)-, 2-(trimethylsilyl)ethyl ester (327a)

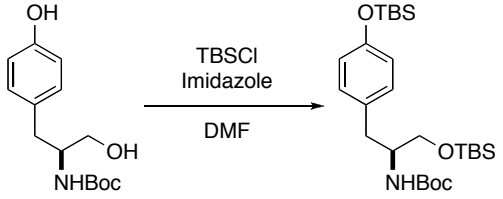


To a solution of palmitic acid (90% w/w; 57.7 mg, 0.204 mmol) and Et_3N (32 μL, 0.231 mmol) in THF (1 mL) at -78 ºC was added pivaloyl chloride (25 μL, 0.204 mmol). After the reaction mixture was stirred for 10 min at -78 ºC, it was warmed to 0 ºC and stirred for an additional 45 min. In a separate flask, *n*BuLi (2.5 M in hexanes, 78 μL, 0.194 mmol) was added to a -78 ºC solution of the Teoc amine **326a** (100 mg, 0.185 mmol) in THF (1 mL). The slurry of the *t*-butyl-palmitoyl mixed anhydride was cooled to -78 ºC. The -78 ºC solution of the Li anion of **326a** was cannulated into the mixed anhydride solution. The reaction mixture was stirred at -78 ºC for an additional 30 min, and then allowed to warm to rt and stirred for an overnight period. H_2O was added to the reaction mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the Teoc amide **327a** (73 mg, 0.094 mmol, 51% yield, 70% brsm).

^{1}H NMR (500 MHz, $CDCl_3$): 6.98 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 4.85 (m, 1H), 4.16 (m, 2H), 3.97 (t, J = 9.1 Hz, 1H), 3.76 (dd, J = 10.0, 6.1 Hz, 1H), 2.98 (dd, J = 13.8, 9.7 Hz, 1H), 2.89 (dd, J = 13.8, 6.3 Hz, 1H), 2.44 (t, J = 7.5 Hz, 2H), 1.65 (p, J =

7.4 Hz, 2H), 1.25 (m, 24H), 0.96 (s, 9H), 0.95 (m, 2H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.85 (s, 9H), 0.16 (s, 6H), 0.06 (s, 9H), 0.01 (s, 3H) and 0.00 (s, 3H).

Carbamic acid, [(1S)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]methyl]ethyl]-, 1,1-dimethylethyl ester (335a)



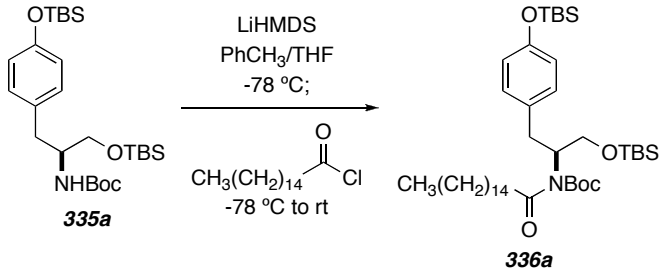
364 ***335a***

To a solution of the phenol **364** (190 mg, 0.71 mmol) and imidazole (388 mg, 5.7 mmol) in DMF (7 mL) was added TBSCl (422 mg, 2.8 mmol) at rt. The reaction mixture was stirred at rt for an overnight period. H_2O was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the bis-TBS ether **335a** (235 mg, 0.47 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 7.06 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 4.73 (br d, *J* = 8.5 Hz, 1H), 3.78 (br s, 1H), 3.50 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.46 (dd, *J* = 10.0, 3.2 Hz, 1H), 2.76 (m, 2H), 1.43 (s, 9H), 0.97 (s, 9H), 0.92 (s, 9H), 0.18 (s, 6H), and 0.04 (s, 6H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 496.3 $(M+H)^+$; t_r = 12.84 min.

Carbamic acid, N-[(1*S*)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[(4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl)methyl]ethyl]-N-(1-oxohexadecyl)-, 1,1-dimethylethyl ester (336a)

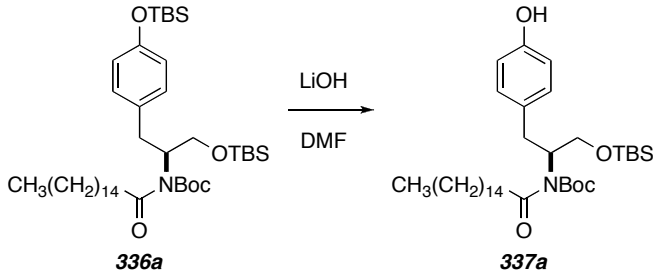


To a solution of the Boc amine **335a** (99 mg, 0.20 mmol) in THF (2 mL) at -78 ºC was added LiHMDS (1.0 M in THF; 240 μL, 0.24 mmol), and the reaction mixture was stirred for 30 min at the same temp. A solution of palmitoyl chloride (55 mg, 0.20 mmol) dissolved in $PhCH_3$ (1 mL) was added to the solution of the Li anion of **335a**. The reaction mixture was stirred an additional 30 min at -78 ºC and then allowed to warm to rt. After stirring at rt for 3 days, a saturated solution of aq. $NaHCO_3$ was added to the reaction mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the Boc amide **336a** (45.3 mg, 0.062, 31% yield).

^{1}H NMR (300 MHz, $CDCl_3$): 6.99 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.3 Hz, 2H), 4.80 (br s, 1H), 3.96 (app t, J = 9.0 Hz, 1H), 3.73 (dd, J = 10.0, 6.2 Hz, 1H), 2.97 (dd, J = 13.9, 9.7 Hz, 1H), 2.85 (dd, J = 13.9, 6.3 Hz, 1H), 2.55 (t, J = 7.6 Hz, 2H), 1.48 (m, 2H), 1.45 (s, 9H), 1.24 (m, 24H), 0.95 (s, 9H), 0.87 (t, J = 6.5 Hz, 3H), 0.85 (s, 9H), 0.15 (s, 6H), and -0.01 (s, 6H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 756.3 $(M+Na)^+$; t_r = 20.85 min.

Carbamic acid, N-[(1*S*)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[(4-hydroxyphenyl)methyl]ethyl]-N-(1-oxohexadecyl)-, 1,1-dimethylethyl ester (337a)



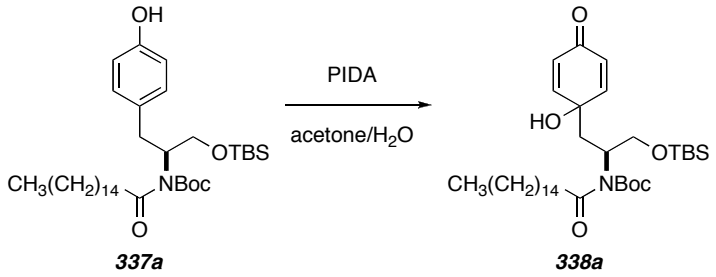
336a ***337a***

To a solution of the Boc amide **336a** (45.3 mg, 0.062 mmol) in DMF (0.6 mL) at rt was added LiOH•H_2O (8.0 mg, 0.19 mmol). After the reaction mixture was stirred for an overnight period, saturated aq. $NaHCO_3$ was added to the mixture, which was then extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (34.7 mg, 0.056 mmol, 90% crude yield). The crude phenol **337a** was taken directly onto the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): 7.00 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 4.77 (br s, 1H), 3.95 (dd, J = 10.0, 8.1 Hz, 1H), 3.74 (dd, J = 10.0, 6.2 Hz, 1H), 2.97 (dd, J = 13.9, 9.9 Hz, 1H), 2.84 (dd, J = 13.9, 5.5 Hz, 1H), 2.56 (t, J = 7.5 Hz, 2H), 1.44 (s, 9H), 1.42 (m, 2H), 1.24 (m, 24H), 0.87 (t, J = 6.5 Hz, 3H), 0.84 (s, 9H) and -0.01 (s, 6H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 642.3 $(M+Na)^+$; t_r = 15.08 min.

Carbamic acid, N-[(1*S*)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[(1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl)methyl]ethyl]-N-(1-oxohexadecyl)-, 1,1-dimethylethyl ester (338a)



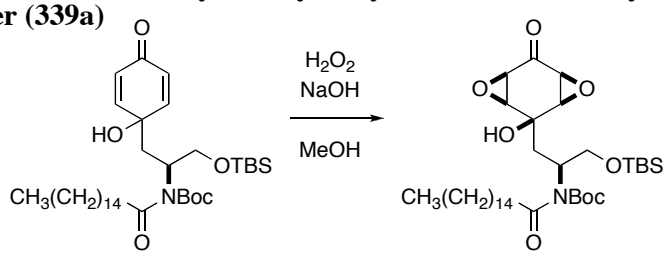
337a ***338a***

To a solution of the phenol **337a** (34.7 mg, 0.056 mmol) in acetone (4.9 mL) and H_2O (0.5 mL) at 0 ºC was added PIDA (39 mg, 0.12 mmol), and the solution was stirred for 1 h. After warming the solution to rt, H_2O was added, and the solution was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the dienone **338a** in ~ 90% purity (6.1 mg, 0.0096 mmol, 15% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): 6.92 (dd, J = 10.4, 3.0 Hz, 1H), 6.85 (dd, J = 10.3, 3.1 Hz, 1H), 6.15 (dd, J = 10.4, 1.9 Hz, 1H), 6.13 (dd, J = 10.2, 1.9 Hz, 1H), 4.81 (m, 1H), 3.80 (dd, J = 9.6, 7.5 Hz, 1H), 3.75 (dd, J = 9.5, 6.8 Hz, 1H), 2.35 (t, J = 7.6 Hz, 2H), 2.15 (m, 2H), 1.61 (p, J = 7.5 Hz, 2H), 1.52 (s, 9H), 1.25 (m, 24H), 0.883 (s, 9H), 0.880 (t, J = 7.0 Hz, 3H), and 0.06 (s, 6H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 658.3 $(M+Na)^+$; t_r = 14.57 min.

Carbamic acid, N-[(1*S*)-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-[(2-hydroxy-6-oxo-4,8-dioxatricyclo[5.1.0.03,5]oct-2-yl)methyl]ethyl]-N-(1-oxohexadecyl)-, 1,1-dimethylethyl ester (339a)



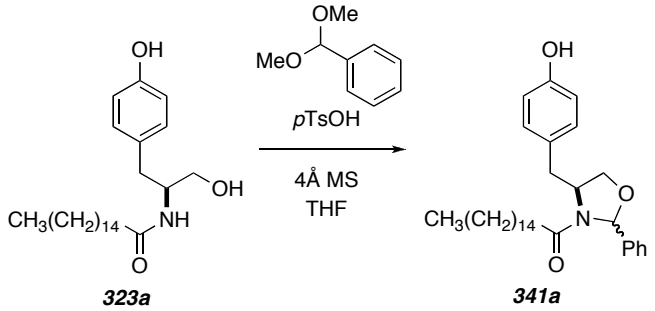
338a ***339a***

To a solution of the dienone **338a** (6.1 mg, 0.0096 mmol) in MeOH (0.6 mL) was added H_2O_2 (123 μL, 1.2 mmol; 30% w/w aqueous solution) and aqueous NaOH (28 μL, 0.005 mmol; 0.18 M). The solution was stirred for 16 h at rt. Aqueous buffer (100 μL; pH=7, 0.05 M phosphate buffer) was added to the solution, which was subsequently extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid (3.5 mg, 0.0052 mmol, 54% crude yield). The crude diepoxide **339a** was taken directly onto the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): 4.80 (br d, J = 9.7 Hz, 1H), 3.63 (d, J = 3.9 Hz, 2H), 3.60 (app t, J = 3.6 Hz, 1H), 3.53 (app t, J = 3.7 Hz, 1H), 3.50 (dd, J = 3.9, 2.5 Hz, 1H), 3.44 (dd, J = 3.8, 2.4 Hz, 1H), 2.34 (t, J = 7.5 Hz, 2H), 2.01 (m, 2H), 1.63 (p, J = 7.4 Hz, 2H), 1.43 (s, 9H), 1.25 (m, 24H), 0.90 (s, 9H), 0.88 (t, J = 6.9 Hz, 3H), and 0.07 (s, 6H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 690.3 $(M+Na)^+$; t_r = 13.60 min.

1-Hexadecanone, (4*S*)-1-(4-[(4-hydroxyphenyl)methyl]-2-phenyl-3-oxazolidinyl)- (341a)



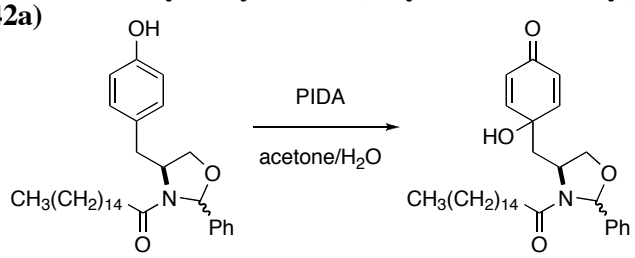
323a ***341a***

To a solution of the amide **323a** (2.54 g, 6.26 mmol) in THF (63 mL) at rt was added benzaldehyde dimethylacetal (9.4 mL, 63 mmol), *p*TsOH (120 mg, 0.63 mmol), and 4Å MS (3g). The reaction mixture was refluxed for an overnight period. The mixture was filtered through a cotton plug to remove the sieves. Saturated aq. $NaHCO_3$ was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by flash chromatography (3:1 hexanes:EtOAc) to give the benzylidene acetal **341a** (1.11 g, 2.25 mmol, 36% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 7.38 (m, 3H), 7.29 (m, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 6.16 (s, 1H), 4.52 (dddd, J = 10.0, 5.0, 2.5, 2.5 Hz, 1H), 3.85 (dd, J = 9.3, 2.0 Hz, 1H), 3.82 (dd, J = 9.5, 5.1 Hz, 1H), 3.39 (dd, J = 13.2, 3.0 Hz, 1H), 2.66 (dd, J = 13.2, 10.0 Hz, 1H), 2.02 (ddd, J = 15.2, 8.8, 6.3 Hz, 1H), 1.85 (ddd, J = 15.1, 8.7, 6.2 Hz, 1H), 1.57 (m, 1H), 1.46 (m, 1H), 1.25 (m, 24H), and 0.88 (t, J = 7.0 Hz, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 494.3 $(M+H)^+$; t_r = 12.35 min.

1-Hexadecanone, (4*S*)-1-(4-[(1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl)methyl]-2-phenyl-3-oxazolidinyl)- (342a)

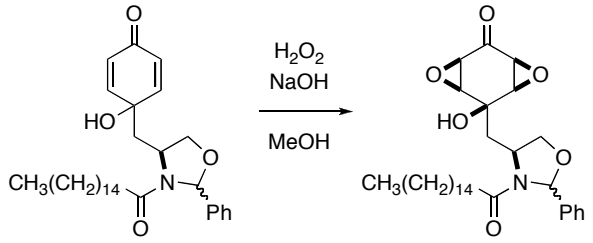


To a solution of the phenol **341a** (544 mg, 1.1 mmol) in acetone (79 mL) and H_2O (9 mL) at rt was added PIDA (531 mg, 1.65 mmol), and the solution was stirred for 1 h. H_2O was added the reaction mixture, which was then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by flash chromatography (3:2 hexanes:EtOAc) to give the dienone **342a** (258 mg, 0.51 mmol, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 7.42 (m, 3H), 7.29 (m, 2H), 6.98 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.95 (dd, *J* = 10.0, 3.1 Hz, 1H), 6.23 (dd, *J* = 10.0, 1.9 Hz, 1H), 6.20 (s, 1H), 6.18 (dd, *J* = 10.0 2.0 Hz, 1H), 4.51 (br t, *J* = 6.5 Hz, 1H), 4.04 (dd, *J* = 9.3, 5.8 Hz, 1H), 3.81 (dd, *J* = 9.3, 1.4 Hz, 1H), 2.42 (dd, *J* = 14.3, 2.4 Hz, 1H), 2.00 (m, 2H), 1.85 (ddd, *J* = 15.2, 8.8, 6.2 Hz, 1H), 1.53 (m, 1H), 1.44 (m, 1H), 1.25 (m, 24H), and 0.88 (t, *J* = 7.0 Hz, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m*/*z* = 510.3 $(M+H)^+$; t_r = 12.13 min.

1-Hexadecanone, (4*S*)-1-(4-[(2-hydroxy-6-oxo-4,8-dioxatricyclo[5.1.0.03,5]oct-2-yl)methyl]-2-phenyl-3-oxazolidinyl)- (343a)

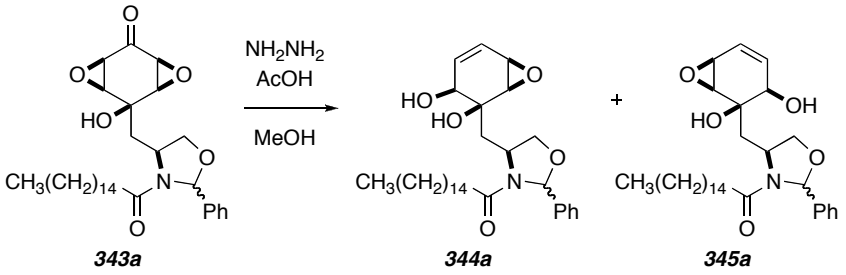


To a solution of the dienone **342a** (258 mg, 0.51 mmol) in MeOH (26 mL) was added H_2O_2 (5.5 mL, 54 mmol; 30% w/w aqueous solution) and aqueous NaOH (1.3 mL, 0.23 mmol; 0.18 M). The solution was stirred for at rt for an overnight period. Aqueous buffer (3.7 mL; pH=7, 0.05 M phosphate buffer) was added to the solution, which was subsequently extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a solid (188 mg, 0.35 mmol, 69% crude yield). The crude diepoxide **343a** was taken directly onto the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): 7.42 (m, 3H), 7.30 (m, 2H), 6.20 (s, 1H), 4.61 (m, 1H), 4.08 (m, 2H), 3.98 (app t, J = 3.5 Hz, 1H), 3.56 (dd, J = 4.0, 2.2 Hz, 1H), 3.49 (m, 2H), 2.35 (d, J = 13.7 Hz, 1H), 2.08 (dd, J = 14.1, 9.2 Hz, 1H), 1.99 (ddd, J = 15.3, 8.9, 6.1 Hz, 1H), 1.85 (ddd, J = 15.3, 8.9, 6.4 Hz, 1H), 1.49 (m, 1H), 1.40 (m, 1H), 1.25 (m, 24H), and 0.88 (t, J = 7.0 Hz, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 542.3 $(M+H)^+$; t_r = 12.00 min.

1-Hexadecanone, (4*S*)-1-(4-[(1*S,2*R**,3*R**,6*S**)-(2,3-dihydroxy-7-oxabicyclo[4.1.0]hept-4-en-2-yl)methyl]-2-phenyl-3-oxazolidinyl)- (344a, 345a)**

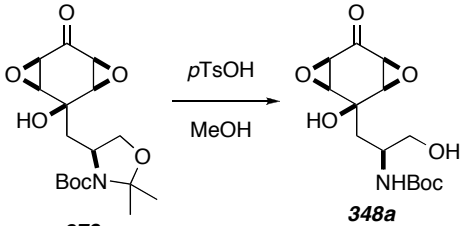


343a ***344a*** ***345a***

To a solution of the diepoxide **343a** (58 mg, 0.11 mmol) in MeOH (1.1 mL) was added AcOH (3.4 μL, 0.06 mmol) and NH_2NH_2•H_2O (8.2 μL, 0.17 mmol). After the solution was stirred at rt for 15 min, saturated aqueous $NaHCO_3$ was added and the solution was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (25.2 mg, 0.048 mmol, 44% crude yield).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 528.3 $(M+H)^+$; t_r = 12.29 min.

Carbamic acid, N-[(1*S*)-2-hydroxy-1-[(2-hydroxy-6-oxo-4,8-dioxatricyclo[5.1.0.03,5]oct-2-yl)methyl]ethyl]-, 1,1-dimethylethyl ester (348a)



372 ***348a***

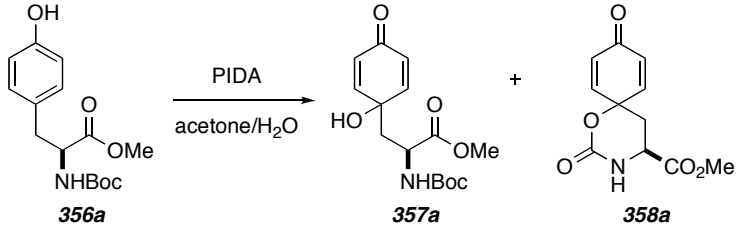
To a solution of the diepoxide **372** (190 mg, 0.53 mmol) in MeOH (5.3 mL) at rt was added *p*TsOH (10 mg, 0.05 mmol). The solution was stirred at rt for an overnight period. Saturated aq. $NaHCO_3$ was added to the reaction mixture, which was then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (73.8 mg,

0.24 mmol, 45% crude yield). The crude diepoxide **348a** was taken directly onto the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): 5.06 (br d, *J* = 7.8 Hz, 1H), 3.97 (m, 1H), 3.72 (m, 2H), 3.61 (app t, *J* = 3.7 Hz, 1H), 3.56 (app t, *J* = 3.7 Hz, 1H), 3.50 (app t, *J* = 3.2 Hz, 1H), 3.46 (app t, *J* = 3.1 Hz, 1H), 2.44 (br s, 1H), 2.06 (dd, *J* = 14.9, 5.0 Hz, 1H), 2.00 (dd, *J* = 15.1, 8.8 Hz, 1H), and 1.44 (s, 9H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 316.0 $(M+H)^+$; t_r = 1.37 min.

Propanoic acid, 2-[[(1,1-dimethylethoxy)carbonyl]amino]-3-(1-hydroxy-4-oxo-2,5-cyclohexadien-1-yl), methyl ester, (2*S*)- (357a)



356a ***357a*** ***358a***

To a solution of the phenol **356a** (220 mg, 0.75 mmol) in acetone (54 mL) and H_2O (6 mL) at rt was added PIDA (288 mg, 0.89 mmol), and the solution was stirred for 1 h. H_2O was added the reaction mixture, which was then extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (1:1 hexanes:EtOAc) to give the dienone **357a** (72 mg, 0.23 mmol, 34% yield) and the dienone **358a** (16 mg, 0.067 mmol, 10% yield).

357a

^{1}H NMR (500 MHz, $CDCl_3$): 6.96 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.88 (dd, *J* = 10.2, 3.1 Hz, 1H), 6.18 (d, *J* = 10.2 Hz, 2H), 5.39 (br d, *J* = 7.0 Hz, 1H), 4.53 (m, 1H), 3.76 (s, 3H),

3.48 (br s, 1H), 2.29 (dd, *J* = 14.4, 3.9 Hz, 1H), 2.00 (dd, *J* = 14.4, 8.7 Hz, 1H), and 1.45 (s, 9H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 334.0 $(M+Na)^+$; t_r = 1.74 min.

358a

^{1}H NMR (500 MHz, $CDCl_3$): 7.00 (dd, *J* = 10.2, 3.2 Hz, 1H), 6.82 (dd, *J* = 10.1, 3.2 Hz, 1H), 6.35 (dd, *J* = 10.2, 2.0 Hz, 1H), 6.31 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.31 (dd, *J* = 10.7, 5.5 Hz, 1H), 3.84 (s, 3H), 2.37 (dd, *J* = 14.2, 5.4 Hz, 1H), and 2.26 (dd, *J* = 14.0, 10.7 Hz, 1H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 238.0 $(M+H)^+$; t_r = 1.13 min.

Chapter IV. Okundoperoxide

IV.A. Introduction and Background

Natural products provide the synthetic chemistry community with endless targets that have interesting structural features and biological activities. It is the biological activity of these new molecules that often primarily motivates the natural product chemist to explore new chemicals derived from natural sources. Despite significant efforts by humans to design chemicals that have a specific biological function, nature provides us with the majority of pharmaceutical agents to this day. Therefore, it is imperative that chemists continue to mine natural sources for new chemicals that could potentially have an incredible impact on the health of humans in the future, as well as impacting various disciplines within the scientific community.

We have collaborated with Professor Simon Efange (University of Buea, Cameroon; formerly a professor at the University of Minnesota) to elucidate the structure of a new natural product, okundoperoxide (**401**, Figure IV-1). Okundoperoxide possesses moderate antiplasmodial (antimalarial) activity and has a unique bicyclofarnesyl sesquiterpene endoperoxide structure. Endoperoxides have been known to exhibit antimalarial activity, which became better understood when the mode of activity of artemisinin (**402**, Figure IV-1) was deciphered.[68] Endoperoxides have also been shown to have antifungal, cytotoxic, antiviral, and antitrypanosomal activities.[69] Initially, there was some confusion regarding the structure of okundoperoxide, but we helped deduce the

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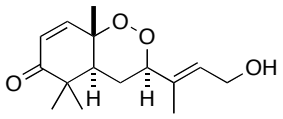
[68] (a) "Peroxy Natural Products," Casteel, D. A. *Nat. Prod. Rep.* **1992**, *9*, 289–312. (b) "Peroxidic Antimalarials," Dong, Y.; Vennerstrom, J. L. *Exp. Opin. Therap. Pat.* **2001**, *11*, 1753–1760.

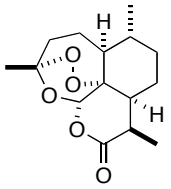
[69] "Naturally Occurring Peroxides with Biological Activities," Jung, M.; Kim, H.; Lee, K.; Park, M. *Mini-Rev. Med. Chem.* **2003**, *3*, 159-165.

correct structure. The details of the characterization of okundoperoxide will be discussed below.[70]

Figure IV-1. Okundoperoxide and another Endoperoxide Antimalarial, Artemisinin.



okundoperoxide (**401**)



artemisinin (**402**)

The structure of certain natural products provides an opportunity to discover new chemistry by asking the question, 'how did nature make that(?)'. Unusual structural features of some natural products can provoke the consideration of novel chemistry to explain how the plant assembled the structure. Often chemists assume that the biosynthetic machinery of the plant (or another natural source) could account for the construction of these unusual features, even though the biosynthetic details may not be understood yet. Those in the Hoye group have hypothesized for a number of natural products that spontaneous (non-enzymatic) reactivity of a simpler biosynthetic intermediate can account for much of the structural complexity of these natural products. The spontaneous reactivity will many times utilize a novel chemical process. Along these lines, the unique endoperoxide motif of okundoperoxide (**401**) piqued our interest from a biosynthetic point of view, and I will explain our biosynthetic hypothesis in one of the sections below. The majority of this chapter will focus on my synthetic efforts to study this biosynthetic hypothesis.

[70] "Okundoperoxide, a Bicyclic Cyclofarnesylsesquiterpene Endoperoxide from *Scleria striatinux* with Antiplasmodial Activity," Efange, S. M. N.; Brun, R.; Wittlin, S.; Connolly, J. D.; Hoye, T. R.; McAkam, T.; Makolo, F. L.; Mbah, J. A.; Nelson, D. P.; Nyongbela, K. D.; Wirmum, C. K. *J. Nat. Prod.* **2009**, *72*, 280–283.

Our collaborator, Professor Simon Efange, specifically set out to discover new antimalarial natural products, a venture that resulted in the isolation of okundoperoxide (**401**).[70] Malaria is a devastating disease that causes the death of 1.5 to 2.7 million people annually, mostly infants and the elderly in Africa.[71] Malaria has become resistant to many of the drugs (e.g., chloroquine) traditionally used to treat it, so there is a critical need to develop new antimalarial agents.[69] Natural products hold promise in discovering new antimalarial treatments, since previous antimalarial drugs (quinine, quinidine, and their analogs) were discovered from natural product leads. My synthetic studies may not only offer insight into the biosynthesis of okundoperoxide, but this work could also aid others who may want to synthesize analogs of okundoperoxide and examine their biological properties.

IV.B. Isolation and Biological Activity

Dr. Efange and coworkers at Buea isolated okundoperoxide **(401)** from the roots of *Scleria striatinux* (a plant that they believe was unstudied), which was harvested in Oku in the Northwest Province of Cameroon (hence the name of this endoperoxide natural product, okundoperoxide).[70] The plant was identified with the help of botanists from the Limbe Botanical and Zoological Gardens and the Cameroon National Herbarium, Yaounde, Cameroon. *S. striatinux* is used as a spice in parts of Cameroon, and its roots are also used to make an herbal tea for fevers. Further study of this plant was prompted by the moderate activity of the crude CH_2Cl_2/MeOH extract against chloroquine-sensitive and -resistant strains of *Plasmodium falciparum*.

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[71] "Gaps in the Childhood Malaria Burden in Africa: Cerebral Malaria, Neurological Sequelae, Anemia, Respitory Distress, Hypoglycemia, and Complications of Pregnancy," Murphy, S. C.; Breman, J. G. *Am. J. Trop. Med. Hyg.* **2001**, *64*, 57–67.

The isolation was carried out by air drying the roots and grinding to a powder (10 kg), which was then macerated with CH_2Cl_2/MeOH (1:1) for 6 days.[70] After decanting the extract, the process was repeated. Evaporation of the solvent gave 450 g of crude extract. Gradient chromatography of the crude material with silica gel followed by size exclusion chromatography (Sephadex LH-20) of the 3:2 hexanes/EtOAc fraction resulted in isolation of 1 gram of okundoperoxide (**401**; ~90% pure by NMR analysis). Biological testing was carried out on this sample. A minor component that comprises the remaining ~10% of the okundoperoxide sample was subsequently isolated in pure form and shown to have no antiplasmodial activity in the same assay. I carried out further purification of okundoperoxide by normal-phase HPLC (2:1 hexanes/EtOAc) to provide pure material. I collected all of the spectroscopic data (HR-ESIMS, IR, ^{1}H NMR [1D, NOE, COSY, HMQC, and HMBC], and ^{13}C NMR) with this material.

The antiplasmodial activity (data collected at the Walter Reed Army Institute of Research [WRAIR; Washington, DC] and at the Swiss Tropical Institute [STI; Basel, Switzerland] using the [^{3}H]hypoxanthine incorporation assay developed by Desjardins et. al.) of the crude *S. striatinux* extract and of okundoperoxide is reported in Table IV-1.[70,72] Okundoperoxide was shown to have moderate activity (483 ng/mL) against the chloroquine-sensitive (D6) strain and (470 ng/mL) against the chloroquine-resistant (W2) strain. Weaker antiplasmodial activity was observed against the strains tested at the STI (1498 ng/mL for K1 and 1308 ng/mL for NF54). As expected, okundoperoxide exhibited stronger antiplasmodial activity than the crude *S. striatinux* extract, but this does not mean that okundoperoxide would be the only antiplasmodial agent in the crude extract.

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[72] "Quantitative assessment of antimalarial activity in vitro by a semiautomated microdilution technique," Desjardins, R. E.; Canfield, C. J.; Haynes, J. D.; Chulay, J. D. *Antimicrob. Agents Chemother.* **1979**, *16*, 710–718.

Dr. Efange and coworkers have continued to work on isolating other possible antimalarials from *S. striatinux*. Also, okundoperoxide has negligible cytotoxicity compared to the podophyllotoxin control.

Table IV-1. Antiplasmodial Activity of Crude *S. striatinux* and Okundoperoxide.

Sample	**IC_{50} (ng/mL)**				
	W2[a]	**D6**[a]	**K1**[b]	**NF54**[b]	Cytotoxicity
S. striatinux (crude extract)	804	894	NT[c]	NT[c]	NT[c]
Okundoperoxide (**401**)	470	483	1498	1308	22,700
Chloroquine (control)	84	3	62[d]	5.1[d]	NT[c]
Podophyllotoxin	-	-	-	-	7

[a] Results obtained from WRAIR; W2 is a chloroquine-resistant and D6 a chloroquine-sensitive strain of *Plasmodium falciparum*. [b] Results obtained from STI. K1 is a chloroquine- and pyrimethamine-resistant strain of *Plasmodium falciparum* from Thailand. NF54 is a drug sensitive airport strain of unknown origin. Results presented as mean of 2-3 determinations. Individual measurements generally differed by less than 50%. [c]NT, not tested. [d]See ref. 73.

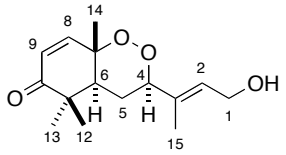
IV.C. Characterization and Derivatization of Okundoperoxide

Much of this characterization section is an excerpt (indicated by quotations, although the structure and figure numberings have been changed to be consistent for insertion into this thesis) from our *Journal of Natural Products* publication on the isolation and structure elucidation of okundoperoxide (**401**).[70] I became involved in this project when Dr. Efange approached me with a sample of okundoperoxide, which he wanted to analyze by GC-MS. I was in charge of maintaining the GC-MS in our group; therefore, to my good fortune, it was because of this that I became involved in the

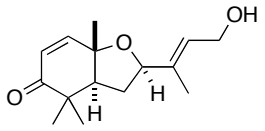
[73] "Identification of an antimalarial synthetic trioxolane drug development candidate," Vennerstrom, J. L.; Arbe-Barnes, S.; Brun, R.; Charman, S. A.; Chiu, F. C. K.; Chollet, J.; Dong, Y.; Dorn, A.; Hunziker, D.; Matile, H.; McIntosh, K.; Padmanilayam, M.; Tomas, J. S.; Scheurer, C.; Scorneaux, B.; Tang, Y.; Urwyler, H.; Wittlin, S.; Charman, W. N. *Nature* **2004**, *430*, 900–904.

okundoperoxide project. Dr. Efange and coworkers had originally assigned the structure of this newly isolated natural product as the tetrahydrofuran **403** (Figure IV-2), but GC-MS analysis of this pure sample (by ^{1}H NMR analysis) resulted in a number of peaks in the GC chromatogram. Importantly, none of the masses of the corresponding peaks indicated the correct molecular weight of the tetrahydrofuran **403**. Perplexed by this result, I analyzed the sample by high resolution ESI-MS and observed a mass of 289.1402. This mass turned out to be the sodiated parent ion of the molecular formula $C_{15}H_{22}O_4$ (calculated mass of 289.1410), which indicated that an additional oxygen was present in the molecule. The antimalarial properties of this natural product lead us to consider the presence of an endoperoxide subunit in lieu of the initially proposed tetrahydrofuran ring.[68] The following observations and data analysis allowed us to confirm that the endoperoxide **401** was indeed the correct structure.

Figure IV-2. Okundoperoxide (**401**, with numbering) and the Initially Assigned Structure **403**.



okundoperoxide (**401**)



403

"With the intent of reducing the peroxide bond in **401** with Ph_3P via an intermediate like **408** (Scheme IV-1), we treated a sample of **401** with Ph_3P in $CDCl_3$ and monitored the subsequent events by ^{1}H NMR spectroscopy. Somewhat surprisingly, there was no observable change at ambient temperature. Moreover, when the reaction solution was heated in a 65 °C bath, the major product formed was the furan **404**, which has the same overall oxidation state as **401** and is the result of a net dehydration reaction. We suspect that enone **405** is an intermediate in this transformation. Zwitterion **408**, if

formed, could preferentially undergo intramolecular elimination of phosphine (see arrows in **408**) rather than, for example, cyclization to a fused tetrahydrofuran derivative via displacement of triphenylphosphine oxide. Alternatively, the hindered nature of the dialkylperoxide in **401** may have induced a different reaction course from the outset. Namely, the phosphine may have functioned preferentially as a base rather than as a reductant to effect an eliminative opening via loss of H-4 and cleavage of the peroxide O-O bond (see arrows in **401**) to give the enone **405**. (*E*)-γ-Hydroxy-α,β-enones similar to **405** are known to undergo spontaneous isomerization and dehydration reactions to give furans.[74] Enone (*E*)- to (*Z*)-isomerization to convert **405** to **406** could involve a reversibly formed, rotatable intermediate epoxide (cf. **409a**) or triphenylphosphine adduct (cf. **409b**). There are many reported examples of dehydration of (*Z*)-γ-hydroxy-α,β-enones like **406** under mild conditions to give the corresponding furans, likely via hemiketals like **407**.[75] It is notable that among the many thermal decomposition products observed upon GC-MS analysis of okundoperoxide (**401**), the furan **404** was the most abundant."[76] I also attempted to convert okundoperoxide to the furan **404** by heating in

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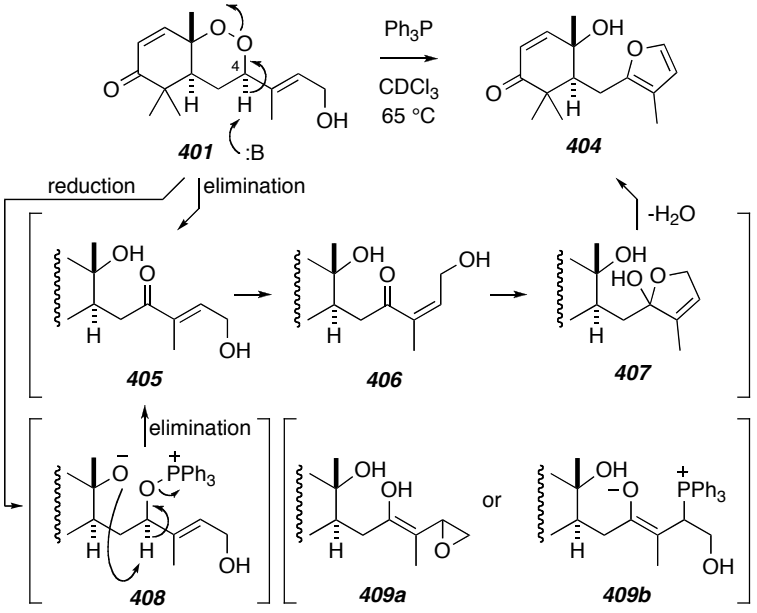
[74] (a) "A New Route to Diastereomerically Pure Cyclopropanes Utilizing Stabilized Phosphorus Ylides and γ-Hydroxy Enones Derived from 1,2-Dioxines: Mechanistic Investigations and Scope of Reaction," Avery, T. D.; Taylor, D. K.; Tiekink, E. R. T. *J. Org. Chem.* **2000**, *65*, 5531–5546. (b) "Preparation of 2,5-Disubstituted Furans from Terminal Ynones and Aldehydes with $CrCl_2$, Me_3SiCl, and H_2O," Takai, K.; Morita, R.; Sakamoto, S. *Synlett.* **2001**, *10*, 1614–1616.

[75] (a) "Studies of vitamin D oxidation. 3. Dye-sensitized photooxidation of vitamin D and chemical behavior of vitamin D 6,19-epidioxides," Yamada, S.; Nakayama, K.; Takayama, H.; Itai, A.; Iitaka, Y. *J. Org. Chem.* **1983**, *48*, 3477–3483. (b) "Quantitative rearrangement of monocyclic endoperoxides to furans catalyzed by cobalt(II)," O'Shea, K. E.; Foote, C. S. *J. Org. Chem.* **1989**, *54*, 3475–3477. (c) "Synthesis of furans by silver(I)-promoted cyclization of allenyl ketones and aldehydes," Marshall, J. A.; Wang, X. J. *J. Org. Chem.* **1991**, *56*, 960–969.

[76] "A Chemical Study of Burley Tobacco Flavour (Nicotiana tabacum L.). III. Structure Determination and Synthesis of 5-(4-Methyl-2-furyl)-6-methylheptan-2-one (Solanofuran) and of 3,4,7-Trimethyl-1,6- dioxa-spiro[4.5]dec-3-en-2-one (Spiroxabovolide), Two New Flavour Components of Burley Tobacco," Demole, E.; Demole, C.; Berthet, D. *Helv. Chim. Acta* **1973**, *56*, 265– 271.

$CDCl_3$ and also by heating with Et_3N (in $CDCl_3$), but furan formation was not observed in either instance.

Scheme IV-1. Conversion of Okundoperoxide (**401**) to the Furan **404**.



"Key ^1H and ^{13}C NMR data are reported in Table IV-2. All 15 carbon and 22 (first-order) proton resonances were identified. The ^{13}C NMR spectrum contained resonances for one ketone and four olefinic carbons. The ^1H NMR spectrum suggested the presence of four methyl groups (one allylic with only long-range coupling and three aliphatic singlets) and three olefinic, one oxymethine, and one pair of oxymethylene protons. The HMQC spectrum clearly showed one-bond correlations that are the primary basis for the assignments of carbon chemical shifts listed in Table IV-2."

Table IV-2: ^{13}C and ^{1}H NMR Spectral Data for Okundoperoxide ($CDCl_3$, 75 and 500 MHz).

Atom number	Carbon	Proton			COSY	HMBC
	δ_C	δ_H	mult	*J* [Hz]	(to ^{1}H-#)	(from $^{1}H \rightarrow {}^{13}C$-#)
1	59.0	4.26	br dd	5.5, 5.5	H-2, H-15	C-2, C-3
2	128.3	5.75	tdq	6.4, 1.3, 1.3	H-1, H-15	C-1, C-4, C-15
3	135.0					
4	86.6	4.56	br dd	11.2, 2.7	H-5a, H-5b	C-2, C-3, C-15
5ax	24.7	1.96	ddd	13.0, 13.0, 11.2	H-4, H-5b, H-6	C-3, C-4, C-6, C-7
5eq		1.70	dddd	13.2, 3.0, 2.5, 0.8	H-4, H-5a, H-6	C-6, C-7
6	49.3	2.45	dd	12.9, 3.3	H-5a, H-5b	C-5, C-7, C-11, C-12, C-13
7	79.4					
8	150.3	6.73	dd	10.2, 0.8	H-9	C-6, C-10
9	127.9	5.94	d	10.2	H-8	C-7, C-11
10	203.2					
11	43.5					
12	20.5	1.09	s			C-6, C-10, C-11, C-13
13	26.0	1.19	s			C-6, C-10, C-11, C-12
14	21.1	1.59	s			C-6, C-7, C-8
15	13.8	1.76	dt	1, 1	H-1, H-2	C-2, C-3, C-4
OH		1.36	br t	5.3		

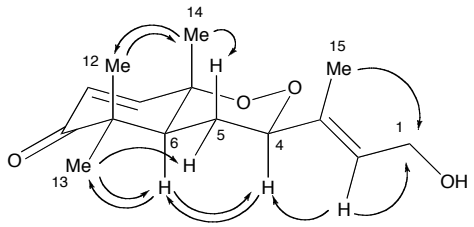
"The IR spectrum showed characteristic absorption bands for hydroxyl (3477 cm^{-1}) and carbonyl (1674 cm^{-1}) groups. The former was consistent with a one-proton resonance at δ 1.36 ppm, which disappeared in a deuterium exchange experiment. The carbonyl absorption was suggestive of a conjugated enone, which was supported in the NMR spectrum by the chemical shifts of olefinic proton (δ 6.73 and 5.94) and carbon (δ 150.3 and 127.9) signals and of the carbonyl carbon resonance (δ 203.2). These data,

together with the doublets of the olefinic proton resonances (J = 10.2 Hz), pointed to a 4,4-disubstituted *Z*-enone moiety."

"The ^{1}H-^{1}H COSY spectrum indicated an isolated four-spin system that included the proton at δ 1.96, having three large coupling constants (13.0, 13.0, 11.2 Hz). This was indicative of an axial-like methylene proton in a six-membered ring, flanked by two vicinal, *trans* methine protons (-CHC$\underline{H}_{ax}H_{eq}$CH-). A COSY correlation between resonances for the olefinic proton at δ 5.75 and the methylene pair centered at δ 4.26 indicated a trisubstituted olefin bearing an oxymethylene group. The connectivity pattern deduced from the HMBC spectrum integrated the above subunits, along with the four methyl groups, into a common constitution. Specifically, structure **401** was consistent with all of the COSY and HMBC correlation data. "

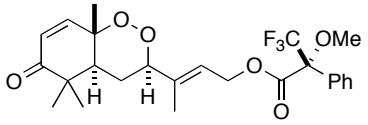
"In addition to the 1,3-diaxial nature of H-4 and H-6 deduced from the coupling constant analysis, the remaining relative configurations shown in **401** were assigned largely on the basis of NOE observations (Figure IV-3). The acyclic (*E*)-olefin geometry is indicated by the enhancement of H-1 by H-15. Mutual enhancements of H-4 and H-6 reaffirm their *cis* relationship. The *trans* nature of the ring fusion was deduced from the sets of NOEs among H-5_{ax}/H-12/H-14 and H-4/H-5_{eq}/H-6/H-13."

Figure IV-3. The Most Relevant NOE Correlations in Okundoperoxide (**401**).

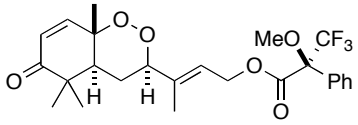


"Finally, the (*R*)- and the (*S*)-Mosher ester (methoxytrifluoromethylphenylacetyl, MTPA) derivatives of the alcohol **401** (**410R** and **410S**, respectively, in Figure IV-4) were prepared using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) and the (*R*)- and (*S*)-Mosher acid (MTPA-OH), respectively.[30] The ^{1}H NMR data for these esters do not allow us to deduce the absolute configuration of **401** because of the large distance between the MTPA and substrate stereogenic centers. However, the spectra of these diastereomers are distinguishable, which should be helpful for later assignment of absolute configuration upon synthesis of one enantiomer of **401**."

Figure IV-4. Mosher Esters of Okundoperoxide.



(*R*)-Mosher Ester ***410R***



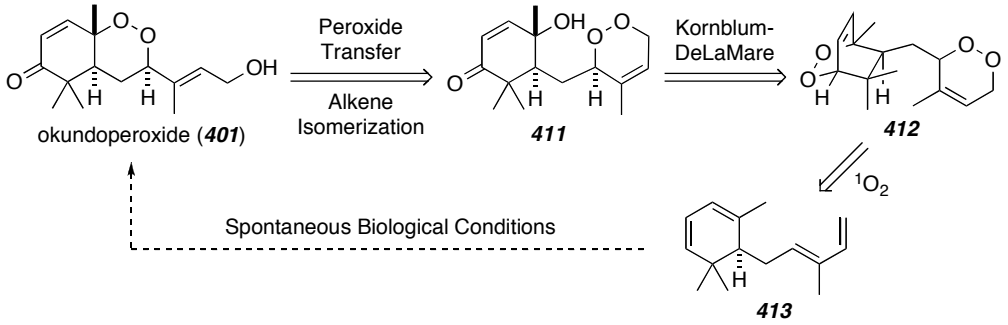
(*S*)-Mosher Ester ***410S***

IV.D. Biosynthetic Hypothesis

Our interest in synthesizing okundoperoxide (**401**) was driven by the biosynthetic hypothesis we devised. As I stated above, the spontaneous (non-enzymatic) reactivity of simple biosynthetic intermediates to give much more complex natural products is a theme of a number of projects in the Hoye group, including the okundoperoxide project. I will present our hypothesis, and then discuss each of the steps in greater detail. The

hypothesis is shown retrosynthetically in Scheme IV-2. Specifically, we speculate that okundoperoxide (**401**) could arise via a spontaneous sequence of reactions under biologically relevant conditions from the simple tetraene hydrocarbon **413**. The required steps involve a $^1O_2$ [4+2] reaction at each of the conjugated dienes of the tetraene **413** to give the bis-endoperoxide **412**. Base-induced opening of the more strained endoperoxide (Kornblum-DeLaMare reaction) in the bis-endoperoxide **412** would lead to the hydroxy-enone **411**.[77] Finally, the key step of our proposal is a peroxide transfer (metathesis) in which the tertiary alcohol of the hydroxy-enone **411** opens the endoperoxide and forms a new endoperoxide to give the *(Z)*-alkene isomer of **401**. This is an unknown transformation and would most likely occur via radical chemistry. Therefore, the resulting allylic oxy-centered radical could easily undergo alkene isomerization to give, via an oxiranyl carbinyl radical, the more stable *(E)*-alkene. These steps would result in the formation of okundoperoxide (**401**).

Scheme IV-2. Okundoperoxide Biosynthetic Hypothesis.



The tetraene **413** has not been isolated as a natural product, but very similar compounds have been isolated. The most notable is α-snyderol **414** (Scheme IV-3),

[77] (a) "The Base Catalyzed Decomposition of a Dialkyl Peroxide," Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880-881. (b) "Asymmetric induction in the rearrangement of monocyclic endoperoxides into γ-hydroxy-α,β-unsaturated aldehydes," Hagenbuch, J. P.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1980**, 1062-1063.

which is just two eliminations removed from the tetraene **413**.[78] As stated above, the tetraene would need to undergo two [4+2] reactions with $^1O_2$ to produce the bis-endoperoxide **412**. However, this would not be expected to be the sole product upon exposure of the tetraene **413** to $^1O_2$, since $^1O_2$ is known to react with alkenes in a number of ways (e.g., ene reaction and [2+2] in addition to [4+2]).[79] The facial selectivity of the [4+2] reaction is another variable that needs to be considered. It is reasonable to anticipate that the [4+2] reaction with the cyclic diene of **413** would preferentially occur by $^1O_2$ approaching from the α-face of the cyclic diene due to steric accessibility, which would yield the endoperoxide with the relative configuration shown in **412**. This relative configuration would lead to the *trans* ring junction of okundoperoxide (**401**). Little facial selectivity would be expected for the reaction of $^1O_2$ with the acyclic diene of **413**; only the [4+2] product resulting from the β-face approach of $^1O_2$ would give the relative configuration of okundoperoxide. The Kornblum-DeLaMare reaction would occur by selective deprotonation (see arrows in **412**; Scheme IV-3) of the more strained bicylic endoperoxide to give the hydroxy enone **411**.

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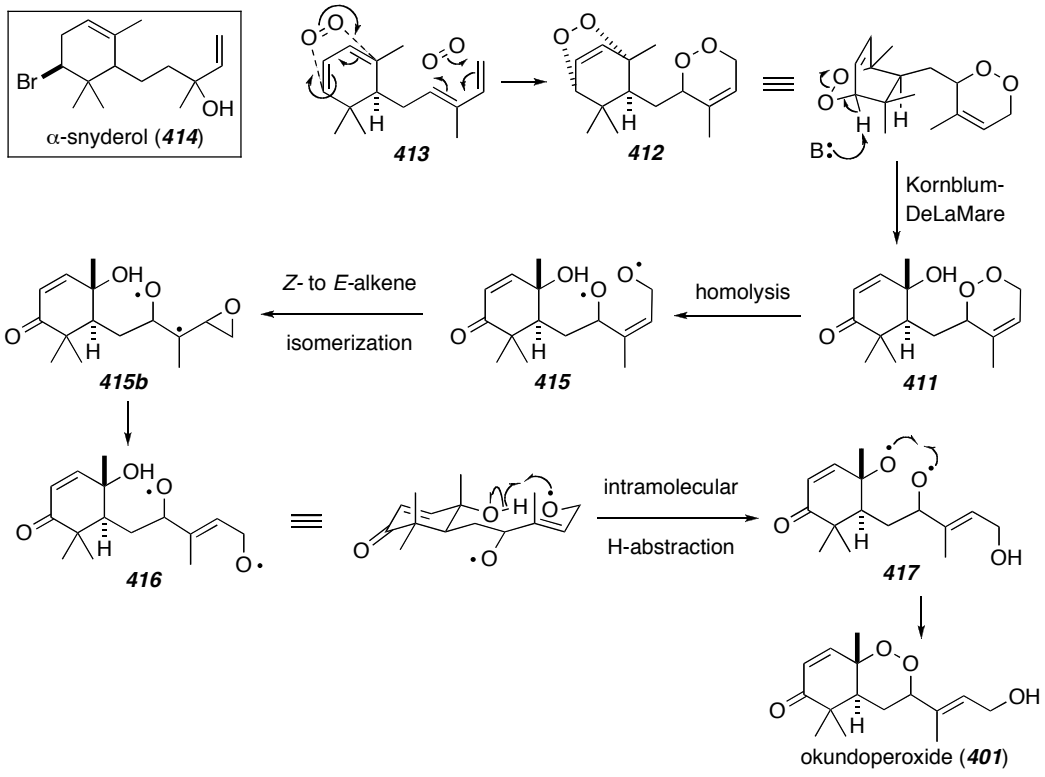
[78] "α- and β-Snyderol; New Bromo-Monocyclic Sesquiterpenes from the Seaweed *Laurencia*," Howard, B. M.; Fenical, W. *Tetrahedron Lett.* **1976**, *17*, 41-44.

[79] "Singlet oxygen in organic synthesis," Wasserman, H. H.; Ives, J. L. *Tetrahedron* **1981**, *37*, 1825-1852.

Scheme IV-3. Mechanistic Details of Biosynthetic Hypothesis.



To complete the formation of okundoperoxide (**401**) from the tetraene **413**, the hydroxy enone **411** would need to undergo peroxide transfer and alkene isomerization. The details of how this might occur are shown in Scheme IV-3, but since this is an unknown process, these details are speculative. The conversion of the hydroxy enone **411** to okundoperoxide (**401**) could begin by homolysis of the endoperoxide O-O bond to give the diradical **415**. Facile isomerization of the *(Z)*-alkene **415** to the *(E)*-alkene **416** could occur via the epoxide **415b**. Next, the primary oxy-centered radical of **416** could abstract the hydrogen of the tertiary alcohol (see arrows in **416**; Scheme IV-3) to provide the diradical **417**, which is poised for the completion of the peroxide transfer. Finally, formation of the endoperoxide (see arrows in **417**; Scheme IV-3) would produce okundoperoxide (**401**). We realize that since there are a number of steps in our

biosynthetic hypothesis to convert the tetratene **413** to okundoperoxide, this is not likely to be an efficient process. Our aim is to show that this process is biosynthetically feasible (as opposed to being synthetically useful), while also possibly discovering an unknown chemical process, the peroxide transfer (or metathesis). Undoubtedly, it would be a remarkable feat to carry out the direct conversion of the tetraene **413** to okundoperoxide.

A recently reported group of natural products isolated from the Formosan soft coral *Sinilaria* sp., sinularioperoxides A-D (**418-421**, Figure IV-5), have the same allylic alcohol-endoperoxide moiety as okundoperoxide (**401**).[80] Therefore, we would propose that the sinularioperoxides could also be biosynthetically produced by a similar peroxide transfer (or metathesis) step similar to that presented above. Upon inspecting the sinularioperoxides A-D (**418-421**), a couple of interesting structural relationships were noticed. First, it appears that if a peroxide transfer was used to make the endoperoxide in these natural products (in a manner similar to the conversion of **411** to **401**, Scheme IV-2), then both tertiary alcohol epimers underwent a peroxide transfer with a single endoperoxide epimer (**418, 419** vs. **420, 421**). The other interesting structural feature is that the allylic alcohol of sinularioperoxide B (**419**) is a *(Z)*-alkene; therefore, an alkene isomerization would not be required in the biosynthesis of this compound, and peroxide transfer would directly provide **419**. Sinularioperoxides A-D did not show any activity against a number of cancer cell lines, and the antiplasmodial activity was not tested.

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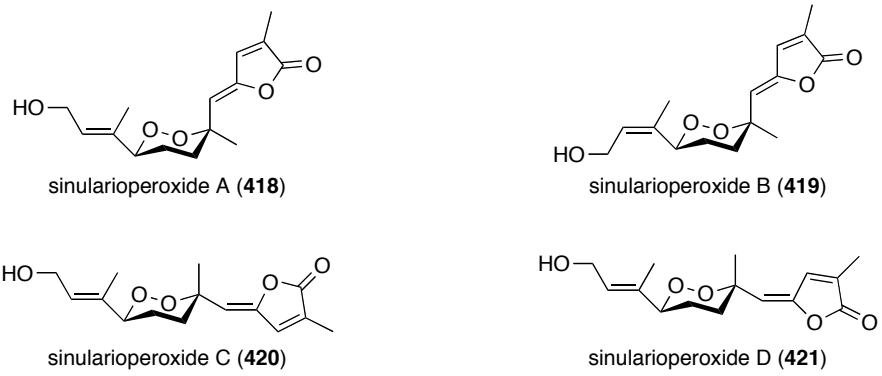
[80] "Novel cyclic sesquiterpene peroxides from the Formosan soft coral *Sinularia* sp.," Chao, C.-H.; Hsieh, C.-H.; Chen, S.-P.; Lu, C.-K.; Dai, C.-F.; Wu, Y.-C. Sheu, J.-Y. *Tetrahedron Lett*. **2006**, *47*, 2175-2178.

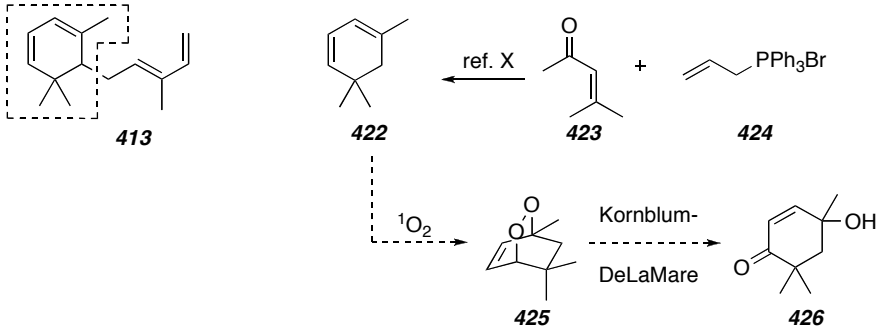
Figure IV-5. Sinularioperoxides A-D (**418-421**).



IV.E. Synthesis and $^1O_2$ Reactivity of Model System Dienes

My efforts to study the biosynthetic hypothesis began with the analysis of model dienes that would give insight into the reactivity of each of the conjugated dienes in the tetraene **413**. I first examined a model of the cyclic diene (Scheme IV-4), specifically the trimethyl cyclohexadiene **422**. This known model compound was available in one step from mesityl oxide (**423**) and allyltriphenylphosphonium bromide (**424**).[81] The cyclic diene **422** would be used to investigate the $^1O_2$-[4+2] reaction and the subsequent Kornblum DeLaMare reaction of the corresponding endoperoxide **425** to provide the enone **426**.

Scheme IV-4. Cyclic Diene Model System.



[81] "Synthetic Potential of the Reaction of Allylic Phosphonium Ylides with α,β-Unsaturated Carbonyl Compounds," Schneider, D. F.; Venter, A. C. *Syn. Comm.* **1999**, *29*, 1303-1315.

The [4+2] reaction of the diene **422** and $^1O_2$ was first attempted with chemically generated $^1O_2$ (Oxone®, aq. $NaHCO_3$, Scheme IV-5) to give the endoperoxide **425** as the major product, even though it was only isolated in 20% yield. I was also able to make the endoperoxide **425** using photochemical conditions (rose bengal, O_2, MeOH/H_2O or methylene blue, O_2, EtOH/H_2O), but the yield for these reactions was also ~20%. The minor side products of these reactions were the ene products **429** and **430**. Various basic conditions were screened to examine the Kornblum DeLaMare reaction. Treating the endoperoxide **425** with triethylamine in $CDCl_3$ showed no conversion at room temperature (no observable conversion by NMR after a few hours), but complete conversion was observed after heating (70 ºC, sealed NMR tube) overnight. A 1 to 6 ratio of the enone **426** to the diepoxide **427** was produced, but the diepoxide was an unexpected product. Closer inspection of the literature revealed many examples of the thermal rearrangement of endoperoxides to diepoxides.[82] Thus, I anticipated that repeating this reaction without triethylamine may also induce this rearrangement, but no change was observed when heating the endoperoxide **425** in $CDCl_3$ to 70 ºC for 24 h. The triethylamine must be playing a role in this rearrangement. Exposure of the endoperoxide **425** to methanolic KOH resulted in complete conversion after 3 hours, and a 1 to 2.4 ratio of the enone **426** to the methanol adduct **428** was observed. Finally, clean conversion of the endoperoxide **425** to the enone **426** was achieved using DBU in $CDCl_3$ at room temperature. The rate of this reaction, however, was very slow (~95% conversion after 7 days).

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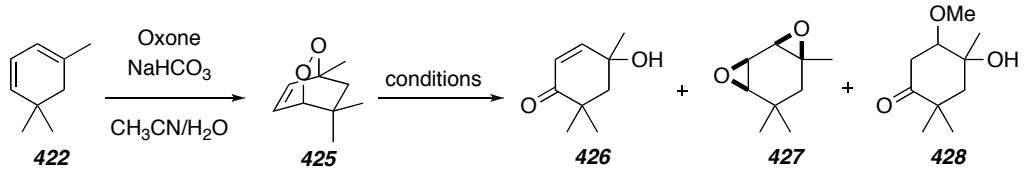
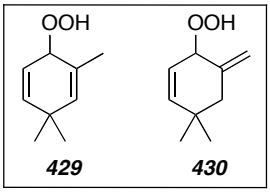
[82] Frimer, A. A., *Singlet O_2: Volume II: Reaction Modes and Products*. CRC Press: Boca Raton, 1985; 140 pp.

Scheme IV-5. Analysis of $^1O_2$-[4+2] and Kornblum DeLaMare Reactions.





Conditions	Results
Et_3N, $CDCl_3$, 70 ºC	1:6 ratio of **426**:**427**
$CDCl_3$, 70 ºC	no change
KOH, MeOH, rt	1:2.4 ratio of **426**:**428**
DBU, $CDCl_3$, rt	clean formation of **426** (very slow)

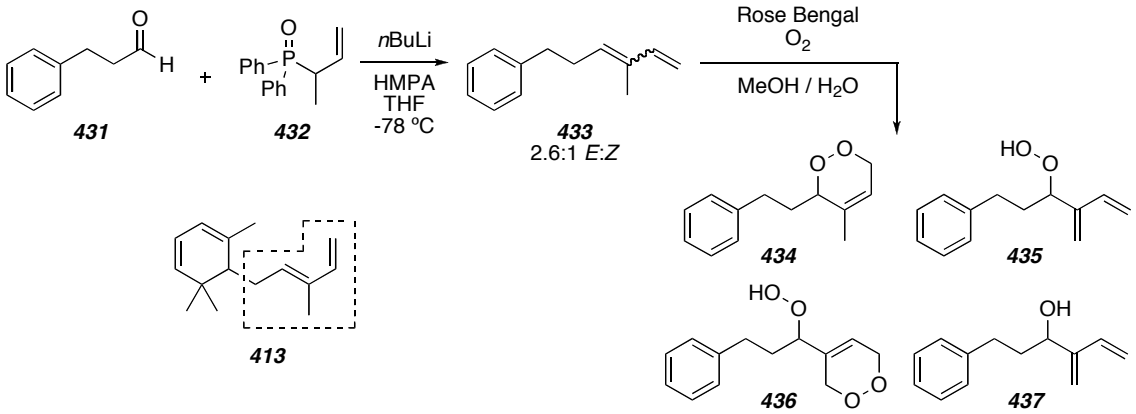
The model system of the acyclic diene portion of the tetraene **413** was the diene **433** (Scheme IV-6). This diene was synthesized via the olefination of hydrocinnamaldehyde (**431**) with the phosphine oxide **432** (available in one step from crotyl alcohol and chlorodiphenylphosphine).[83] The diene **433** was produced in 74% yield as a 2.6 to 1 ratio of the (*E*)- to (*Z*)-alkenes using this method.[84] With the model diene in hand, the $^1O_2$ reactivity of this compound was investigated. Upon exposure of the diene **433** to rose bengal and O_2 in MeOH/H_2O, a ~1:1:0.5 ratio (by crude NMR analysis) of the endoperoxide **434**, the hydroperoxide **435** (ene product), and the endoperoxide **436** (ene followed by [4+2] product) was observed, respectively. However, the endoperoxide **434** was only isolated in 8% yield, while the hydroperoxide **435** was isolated in 19% yield. Also, the alcohol **437**, which is the product of reduction (possibly during workup or purification) of **435**, was isolated in 7% yield. Therefore, the crude ratio of products

[83] "A new route for the conversion of carvone into eudesmane sesquiterpenes," Caine, D.; Stanhope, B. *Tetrahedron* **1987**, *43*, 5545-5555.

[84] "α-Haloenol Acetates: Versatile Reactants for Oxetan-2-one, Azetidin-2-one and Isoxazolidin-5-one Synthesis," Bejot, R.; Anjaiah, S.; Falck, J. R.; Mioskowski, C. *Eur. J. Org. Chem.* **2007**, 101–107.

observed by NMR analysis does not correlate to the isolated yields, possibly due to the instability of the endoperoxide **434**.

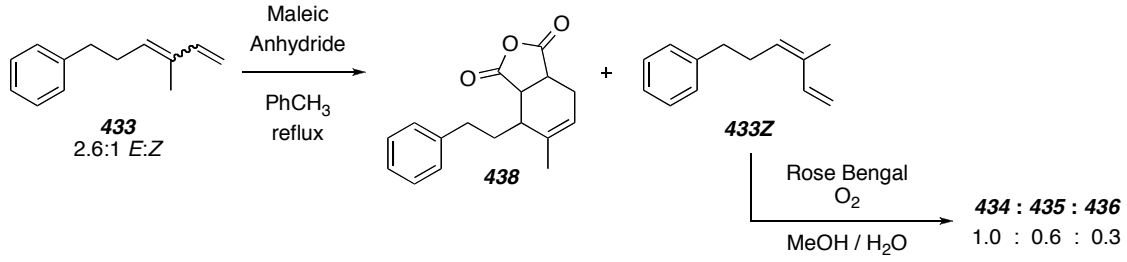
Scheme IV-6. Synthesis of the Acyclic Model Diene **433** and Its Reactivity with $^1O_2$.



We were curious how each of the alkene isomers of the diene **433** would behave in the [4+2] reaction, thinking that if I could find a way to make **433** with a higher *(E)*-alkene content, then maybe the yield of the endoperoxide **434** could be improved. I tried to improve the (*E*) to (*Z*) ratio of **433** utilizing equilibration conditions (I_2 and *hv*), but no change was observed. We did, however, think that we could easily get our hands on the pure (*Z*)-alkene **433Z** by carrying out a Diels-Alder reaction with maleic anhydride, which would selectively consume the *E* alkene **433E**. Separation of the Diels-Alder adduct **438** and **433Z** by chromatography should allow for isolation of the pure *Z* alkene **433Z**. This was successfully carried out (Scheme IV-7), and the alkene geometry of **433Z** was assigned based on comparison to the ^{1}H NMR data of the known compound.[84] Surprisingly, when the (*Z*)-alkene **433Z** was reacted with $^1O_2$ under the same conditions as above, the endoperoxide **434** comprised a larger portion (53% vs. 40%) of the product ratio (1:0.6:0.3 ratio of **434**:**435**:**436**) derived from the crude NMR analysis! Although

this seems counterintuitive, it actually makes sense upon closer inspection of the mechanism of this reaction.

Scheme IV-7. Singlet Oxygen Reactivity of the *Z* alkene **433Z**.



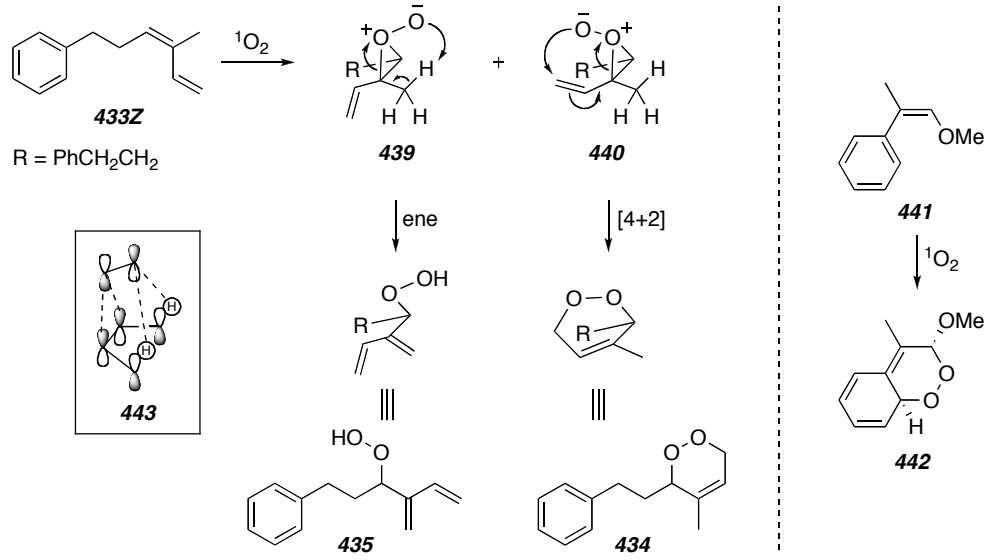
The [4+2] reaction of a diene with $^1O_2$ is not believed to proceed through a concerted process analogous to the Diels-Alder reaction.[85] Instead, it has been proposed to occur via a stepwise process (Scheme IV-8) that passes through a pair of stereoisomeric perepoxide intermediates, **439** or **440**.[86] The perepoxide **439** can rearrange (see arrows in **439**) to the ene product **435**, while the other perepoxide stereoisomer **440** can rearrange (see arrows in **440**) to give the endoperoxide **434**. The perepoxide intermediate is not believed to be formed reversibly; therefore, any factor that influences which stereoisomeric perepoxide forms, **439** or **440**, would in turn affect the product distribution. When trisubstituted alkenes are reacted with $^1O_2$, the product distribution favors the ene products in which the newly formed double bond resides on the more substituted side of the double bond of the trisubstituted alkene starting material. The phenomenon is known as the '*cis* effect', and a dramatic example of this effect pertaining to the $^1O_2$-[4+2] reaction is the conversion of the enol ether **441** to the

[85] (a) "Chemistry of singlet oxygen. 51. Zwitterionic intermediates from 2,4-hexadienes," O'Shea, K. E.; Foote, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 7167–7170. (b) "Chemistry of singlet oxygen. 52. Reaction with trans-stilbene," Kwon, B. M.; Foote, C. S.; Khan, S. I. *J. Org. Chem.* **1989**, *54*, 3378–3382.

[86] "Unusual Facial Selectivity in the Cycloaddition of Singlet Oxygen to a Simple Cyclic Diene," Davis, K. M.; Carpenter, B. K. *J. Org. Chem.* **1996**, *61*, 4617–4622.

endoperoxide **442**.[87] None of the ene product was observed in this reaction, which exemplifies the remarkable selectivity in this instance relative to the poor level of selectivity typically observed with $^1O_2$. One explanation of the '*cis* effect' states that as the oxygen approaches the alkene, the trailing oxygen atom of the approaching O_2 molecule can undergo favorable HOMO-LUMO interactions with the allylic hydrogens, and these interactions are maximized on the more substituted side (disubstituted side vs. monosubstituted side) of the alkene.[87a,b] This interaction is illustrated by the structure **443** (Scheme IV-8).

Scheme IV-8. Mechanistic Aspects of $^1O_2$-[4+2] Reaction.

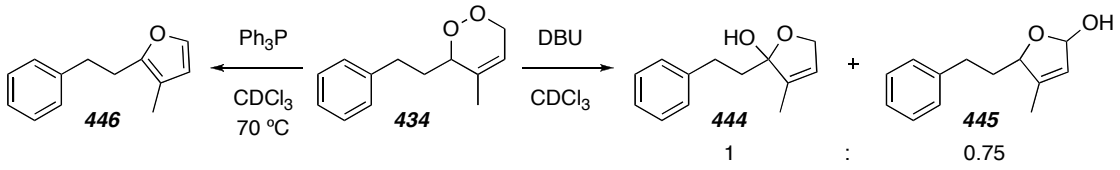


With the endoperoxide **434** now in hand, I was able to investigate its reactivity with DBU and Ph_3P. Treatment of the endoperoxide **434** with DBU in $CDCl_3$ resulted in formation of the hemiketal **444** and the hemiacetal **445** in a 1.0:0.75 ratio, respectively.

[87] (a) "The Selection of $O_2(^1\Delta_g)$-Olefin Reaction Courses. Intermolecular Nonbonded Attraction and π Bond Polarity of Olefins," Inagaki, S.; Fujimoto, H.; Fukui, K. *Chem. Lett.* **1976**, 749-752. (b) "The Mechanism of the Singlet Oxygen Ene Reaction," Stephenson, L. M. *Tetrahedron Lett.* **1980**, *21*, 1005-1008. (c) "Conformational control of reactivity and regioselectivity in singlet oxygen ene reactions: relationship to the rotational barriers of acyclic alkylethylenes," Houk, K. N.; Williams Jr., J. C.; Mitchell, P. A.; Yamaguchi, K. *J. Am Chem. Soc.* **1981**, *103*, 949-951.

The rate of this reaction, ~95% conversion at 20 hours, was much faster than the rate of the DBU reaction with the bicyclic model endoperoxide **425** (Scheme IV-5) discussed above (95% conversion at 7 days). This is in disagreement with our hypothesis that the more strained bicyclic endoperoxide of **412** (Scheme IV-3) would react faster than the monocyclic endoperoxide of **412**. This is most likely due to the steric accessibility of the proton being removed. Also, the endoperoxide **434** can undergo the Kornblum DeLaMare reaction via deprotonation of three different protons, while the same reaction with the endoperoxide **425** can only occur by the removal of one proton. The steric nature of the base is likely to influence the relative rates of these reactions. Another interesting note is that the Kornblum DeLaMare reaction of **434** slightly favored the formation **444**, which is the result of deprotonation of the most hindered of the three available protons. Treatment of the endoperoxide **434** with Ph_3P in $CDCl_3$ at 70 ºC resulted in the furan **446** being formed as the major product. This is reminiscent of, although not the same as, the conversion of okundoperoxide (**401**) to the furan **404** (Scheme IV-1).

Scheme IV-9. Reactivity of the Endoperoxide **434**.



IV.F. Synthetic Study of Possible Biosynthetic Intermediates

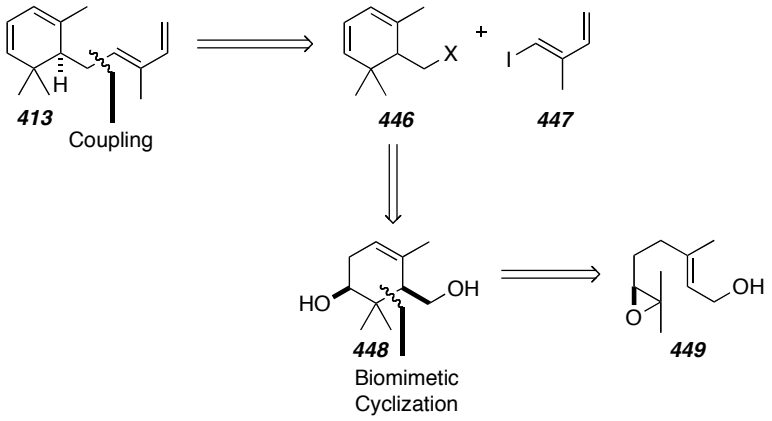
The rest of this chapter will focus on my efforts to synthesize various intermediates that would allow me to study our biosynthetic hypothesis (Scheme IV-2). I will first discuss the synthesis of the tetraene **413**, and a number of different approaches to make this compound. I will then explain my work on two different syntheses of a

precursor to the hydroxy enone **411**. Finally, the studies of the peroxide transfer (or metathesis) will be discussed.

IV.F.1. Initial Approaches Toward the Synthesis of the Tetraene

The first approach I investigated to synthesize the tetraene **413** is outlined retrosynthetically in Scheme IV-10. I envisioned a cross coupling disconnection to bring the two diene portions together from the alkyl halide **446** and the vinyl iodide **447**. The alkyl halide could arise from the diol **448** via conversion of the primary alcohol to the halide and an elimination of the secondary alcohol to form the diene. The diol **448** could be furnished by a $ZrCl_4$-mediated biomimetic cyclization of geraniol epoxide **449**.[88]

Scheme IV-10. Retrosynthesis of the Tetraene **413**.



Geraniol epoxide **449** can be made (Scheme IV-11) in two different ways from commercially available geranyl acetate (**450**). It can be made in a stereoselective manner by chemoselective Sharpless asymmetric dihydroxylation (AD), subsequent mesylation of the secondary alcohol, and treatment with K_2CO_3/MeOH to effect epoxide closure and

[88] "A Simple and Efficient Highly Enantioselective Synthesis of α-Ionone and α-Damascone," Bovolenta, M.; Castronovo, F.; Vadal, A.; Zanoni, G.; Vidari G. *J. Org. Chem.* **2004**, *69*, 8959-8962.

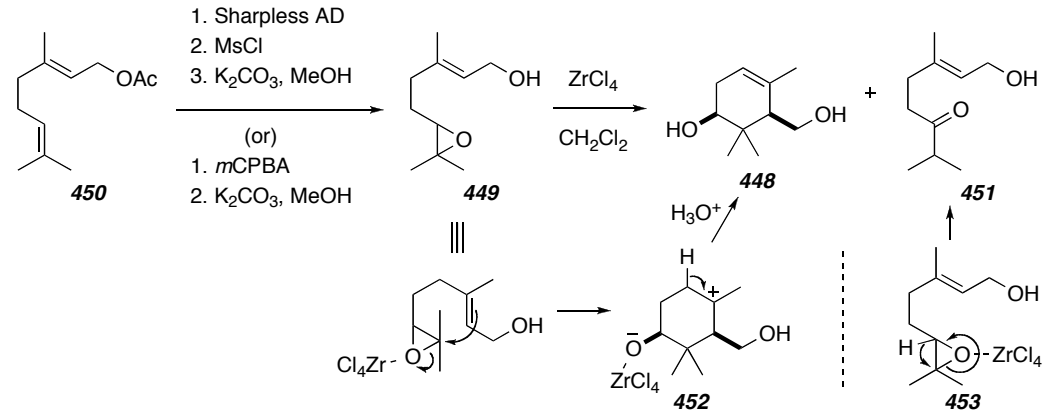
deacetylation.[89] Geraniol epoxide **449** can also be made in racemic form from **450** by epoxidation (*m*CPBA) followed by deacetylation. I utilized both of these procedures to make **449**, but on a large scale I used the nonstereoselective protocol since it did not require expensive reagents and involved fewer steps. Also, at this stage of the project it was not deemed necessary to make enantiomerically pure material, especially since the absolute configuration of okundoperoxide (**401**) was unknown. However, if we were able to devise a plausible route to make okundoperoxide, we could then turn to the Sharpless AD route to make enantiomerically pure material. This would allow us to determine the absolute configuration of okundoperoxide by making the Mosher esters **410R** and **410S** (Figure IV-4) described above (Section IV.C), which are distinguishable by ^{1}H NMR analysis.

The epoxide **449** was then cyclized (Scheme IV-11, see arrows in **449**) by treating with $ZrCl_4$ (3 equiv) in CH_2Cl_2 to give the diol **448**.[88] These conditions resulted in regioselective alkene formation (see arrows in **452**), and neither of the other two possible alkene isomers (exocyclic or tetrasubstituted) was observed. The primary side product isolated was the ketone **451**, which is formed via a hydride shift (see arrows in **453**). I observed a 3:1 ratio of **448** to **451** by crude ^{1}H NMR analysis using the literature conditions for this cyclization (room temperature). In my hands, these conditions resulted in a 45-50% yield of the diol **448** (literature yield was 53%). When I carried out this reaction at 0 ºC, however, I observed an improved ratio of **448** to **451** (4:1). This ratio was not further improved when I cooled the reaction to -40 ºC. Also, I noticed slightly higher yields when I stirred for an extended period of time upon quenching the

[89] "A short and convergent enantioselective synthesis of (*3S*)-2,3-oxidosqualene," Corey, E. J.; Noe, M. C.; Shieh, W.-C. *Tetrahedron Lett*. **1993**, *34*, 5995-5998.

reaction with aqueous HCl. As a result of these changes, I was achieving slightly better yields (55-65%).

Scheme IV-11. $ZrCl_4$-Mediated Biomimetic Cyclization.

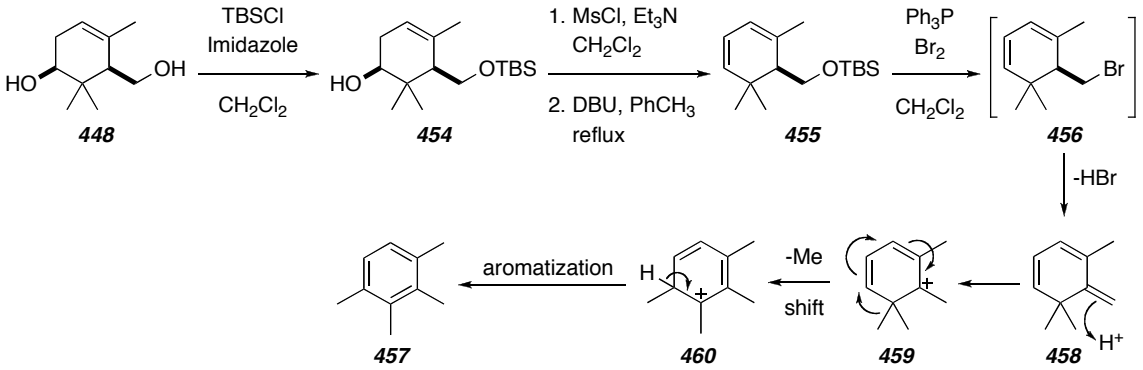


The diol **448** was elaborated by selective TBS protection of the primary alcohol to provide the TBS ether **454**. Mesylation of the secondary alcohol of **454** followed by elimination (DBU) produced the diene **455**. The yield across these three steps was low (26%), which was mostly due to the elimination step (33% crude yield). Next, I attempted to directly convert the TBS ether **455** to the alkyl bromide **456**. A one step protocol (Ph_3P, Br_2) for this transformation that doesn't require a separate deprotection step had previously been reported.[90] Even though the reaction seemed to proceed smoothly, I was not able to isolate the alkyl bromide **456**. Instead, the tetramethyl benzene **457** was observed by GC-MS and ^{1}H NMR analysis. I believe this side product was arising by a pathway involving an initial elimination of HBr from **456** to give **458**. Protonation (see arrows in **458**) would then provide the tertiary carbocation **459**, which could undergo a methyl shift (see arrows in **459**) to give another tertiary carbocation **460**.

[90] "Reagents and synthetic methods. 61. Reaction of hindered trialkylsilyl esters and trialkylsilyl ethers with triphenylphosphine dibromide: preparation of carboxylic acid bromides and alkyl bromides under mild neutral conditions," Aizpurua, J. M.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941–4943.

Finally, deprotonation (see arrows in **460**) would allow for aromatization and formation of the tetramethyl benzene **457**. Upon observing this reaction by ^{1}H NMR analysis in CD_2Cl_2, an intermediate, which I believed to be **456**, was forming, but then was further converted to **457**. Therefore, although it seemed that **456** was being produced, it was not a stable compound and would not be synthetically useful. Any other substrate with a leaving group at the same position would most likely be unstable also; therefore, this route to make the tetraene **413** was abandoned.

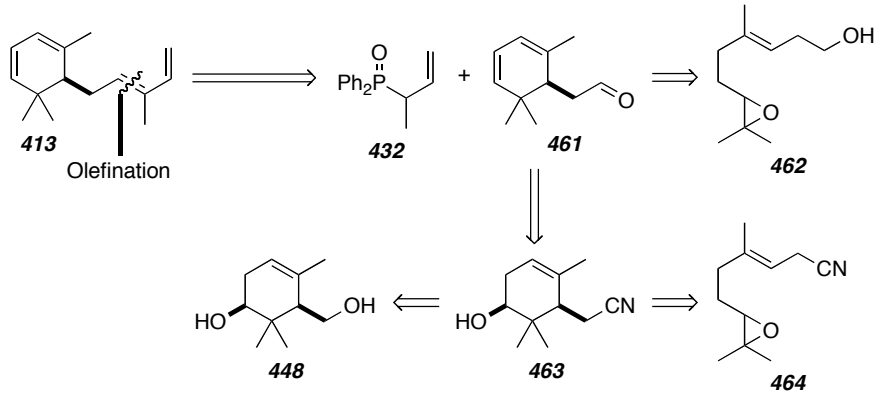
Scheme IV-12. Elaboration of the Diol **448**.



A new approach for constructing the tetraene **413** (Scheme IV-13) was devised in which an olefination disconnection would be used to form the acyclic trisubstituted alkene. This olefination could be achieved by treating the aldehyde **461** with the anion of the previously described (Section IV.E) phosphine oxide **432**.[83] Therefore, the new synthetic target would become the aldehyde **461**. I envisioned that **461** could be made in a number of different ways using the $ZrCl_4$-mediated cyclization described earlier in this section. The first two approaches would capitalize on a one-carbon homologation prior to cyclization. One way to do this would involve the cyclization of the homogeraniol epoxide **462** (or an alcohol protected variant), which would yield the aldehyde **461** after an elimination to form the diene and oxidation of the primary alcohol. The second one-

carbon homologation approach would rely upon the cyclization of the nitrile **464** to give the alcohol **463**. The aldehyde **461** could then be formed from **463** by subsequent elimination to form the diene and reduction (DIBAL) of the nitrile to the aldehyde. The previously synthesized diol **448** could also be used to make **463** by converting the primary alcohol to a leaving group and then displacing with cyanide.

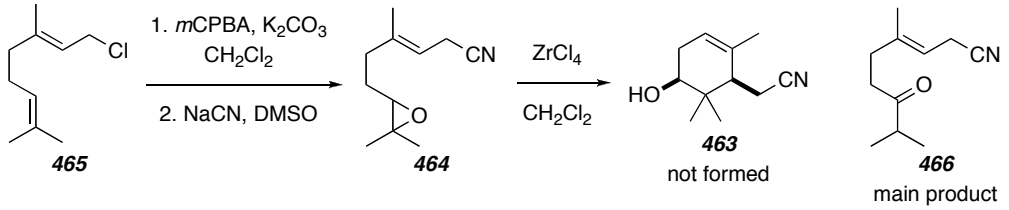
Scheme IV-13. Retrosynthesis of Olefination Strategy to Synthesize Tetraene **413**.



The cyclization of the nitrile **464** was the first approach investigated in an effort to synthesize the aldehyde **461**. The nitrile **464** was furnished (Scheme IV-14) via the regioselective epoxidation of geranyl chloride **465** followed by cyanide displacement (NaCN, DMSO).[91] Exposure of the nitrile **464** to $ZrCl_4$, however, did not produce any of the desired alcohol **463**. Instead, the ketone **466** was the main product of this reaction. We wondered if an alcohol was required in this reaction in order to produce HCl upon reacting with $ZrCl_4$, and perhaps HCl was inducing the cyclization. This hypothesis was tested by spiking the reaction with an equivalent of EtOH, but the same result was observed.

[91] "Chemo-enzymatic enantio-convergent asymmetric synthesis of (*R*)-(+)-Marmin," Edegger, K.; Mayer, S. F.; Steinreiber, A.; Faber, K. *Tetrahedron* **2004**, *60*, 583-588.

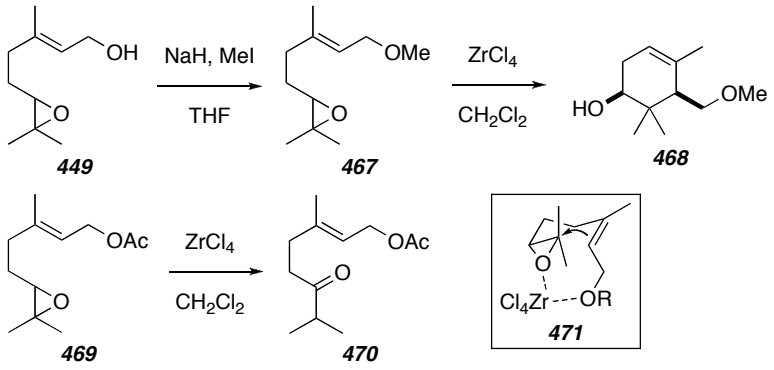
Scheme IV-14. Attempt to Cyclize the Nitrile **464**.



465 ***464*** ***463*** not formed ***466*** main product

In light of the previous result and in an effort to better understand the cyclization, we were curious if the methyl ether **467** or the acetate **469** would cyclize upon treatment with $ZrCl_4$ (Scheme IV-15). The methylation of geraniol epoxide **449** was carried out by deprotonation with NaH and subsequent exposure to MeI to provide the methyl ether **467**. Exposure of the methyl ether **467** to $ZrCl_4$ resulted in cyclization to the alcohol **468** (10:1 ratio of **468**:**470**). This further supported that a free alcohol was not required to carry out this cyclization, and maybe the alcohol could be protected with other protecting groups prior to cyclization. When the acetate **469** was treated to $ZrCl_4$, however, the ketone **470** was produced exclusively. The acetate of **469** may have rendered the alkene less nucleophilic, or maybe it prevented some sort of preorganized intermediate like **471** from forming which would bring the epoxide and alkene near each other.

Scheme IV-15. Further Investigation of $ZrCl_4$ Cyclization.



449 ***467*** ***468*** ***469*** ***470*** ***471***

The last set of cyclization substrates I analyzed (Scheme IV-16) were homogeraniol epoxide **462**, the TPS ether **476**, and the acetate **477**. Homogeraniol epoxide **462** had the same functional groups as geraniol epoxide **449**, so I was optimistic that **462** could cyclize in a similar manner as **449** upon treatment with $ZrCl_4$. Homogeraniol epoxide **462** was made by epoxidizing homogeraniol (**472**, available in three steps from geraniol [MnO_2 oxidation, Wittig methylenation, and hydroboration-oxidation]), although the isolated yield of **472** was low (20%) due to no regioselectivity and challenging chromatographic separation.[92] A better alternative to make **462**, which was demonstrated by undergraduate researcher Chris Tervo, was to carry geraniol epoxide **449** through the one-carbon homologation protocol (oxidation, methylenation, and hydroboration-oxidation). When homogeraniol epoxide was treated with $ZrCl_4$, however, the alcohol **473** was not produced. Instead, the main product was the alkene isomer **474**, which was identified by matching to the literature reported ^{1}H NMR spectrum.[93] The tetrahydrofuran **475** was also believed to be in the crude product mixture by comparing the ^{1}H NMR data with similar compounds reported in the literature. Next, the TPS ether **476** and the acetate **477** were made by treating **462** with TPSCl and Ac_2O, respectively. Exposure of the TPS ether **476** to $ZrCl_4$ resulted in the alkene isomer **480** being formed as well, while there was no evidence for the desired product **478**. The same result, production of **481** and no observable **479**, occurred when treating the acetate **477** with $ZrCl_4$. The alcohol **481** was formed in a relatively clean manner in 61% crude yield, and this reaction could be useful for the synthesis of other

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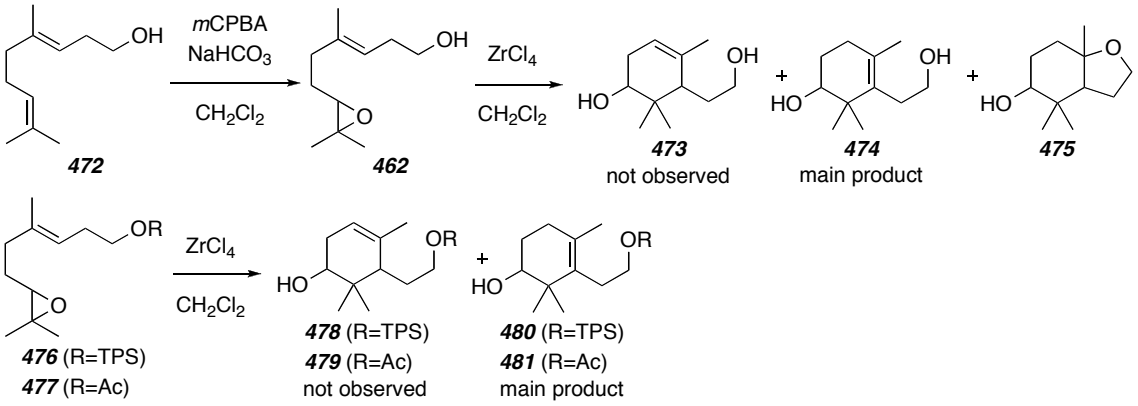
[92] "Selective Hydroboration of a 1,3,7-Triene: Homogeraniol," Leopold, E. J. *Organic Syntheses* **1986**, *64*, 164-170.

terpene natural products that contain this type of cyclohexene moiety. The one-carbon homologation followed by cyclization strategy was abandoned, since none of these reactions provided any of the desired cyclohexene product.

Scheme IV-16. Cyclization of Homogeraniol Epoxide **462**.

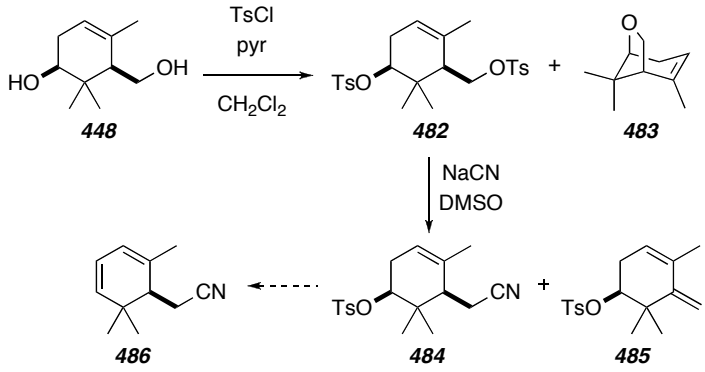


My attention now turned to finding a way to convert the diol **448** to the aldehyde **461**. The first strategy I envisioned (Scheme IV-17) to accomplish this would be to make the ditosylate **482**,which could undergo displacement with cyanide at the more reactive primary tosylate to give **484**. Subsequent elimination of the secondary tosylate would furnish the diene **486**. Treatment of the diol **448** with TsCl and pyridine in CH_2Cl_2 provided the ditosylate **482** in only 21% yield. The major product was the ether **483**, which was the result of primary tosylate formation followed by displacement with the secondary alcohol. Lowering the temperature, increasing the equivalents of TsCl, or utilizing a slow addition of the diol **448** did not result in an improved yield for this reaction. Conversion of **482** to the nitrile **484** was investigated with different cyanide sources (NaCN and KCN) and solvents (DMSO, DMF, THF/H_2O). The best conditions (NaCN, DMSO) resulted in a moderate yield (40%) of the nitrile **484**, along with

[93] "Microbial synthesis of optically pure (R)-2,4,4-trimethyl-3-(2′-hydroxyethyl)-cyclohex-2-en-1-ol, a new and versatile chiral building block for terpene synthesis," Aranda, G.; Azerad, M. B. R.; Maurs, M. *Tetrahedron: Asymmetry* **1995**, *6*, 675-678.

production of the diene side product **485** (23% yield). This seemingly straightforward approach was abandoned since both of these steps were low yielding.

Scheme IV-17. Synthesis of the Ditosylate **482** and Its Reactivity with Cyanide.

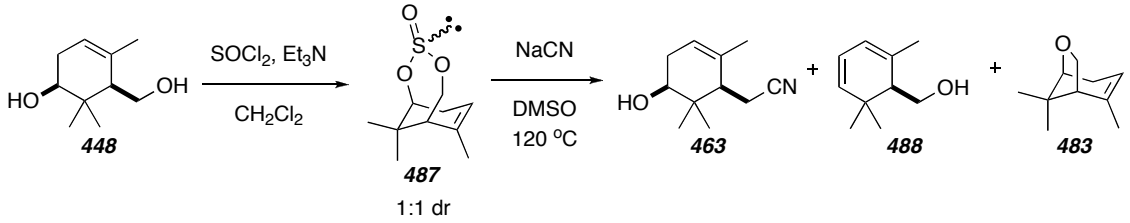


IV.F.2. Synthesis of the Tetraene

A new strategy to utilize the diol **448** capitalized on the close proximity of the two alcohols. Specifically, **448** would be converted (Scheme IV-18) to the cyclic sulfite **487**, which may in turn be a suitable electrophile for cyanide. This idea was realized by treating the diol **448** with thionyl chloride at 0 ºC to cleanly yield the cyclic sulfite **487** as a ca. 1:1 mixture of diastereomers, as indicated by GC-MS and crude ^{1}H NMR analysis. The cyclic sulfite was not stable enough to survive silica gel chromatography, but the reaction resulted in a high crude yield (~95%) and was very clean by analysis of the ^{1}H NMR spectrum of the crude reaction mixture. Attempts to oxidize ($RuCl_3 \bullet 3H_2O$, $NaIO_4$) the cyclic sulfite **487** to the corresponding sulfate only lead to decomposition. The cyclic sulfite **487** was exposed to a number of cyanide displacement conditions (KCN, DMSO; KCN, 18-C-6, DMSO; KCN, DMF; NaCN, DMF; NaCN, DMSO; NaCN, ethylene glycol; NaCN, TBABr, DMSO; NaCN, TBAI, DMSO; KCN, 18-C-6, TMSCN, CH_2Cl_2; BrCN, CH_2Cl_2; $BF_3 \bullet OEt_2$, TMSCN, CH_2Cl_2; and acetone cyanohydrin, DBU, CH_3CN), and the best conditions proved to be NaCN in DMSO at 120 ºC. These conditions

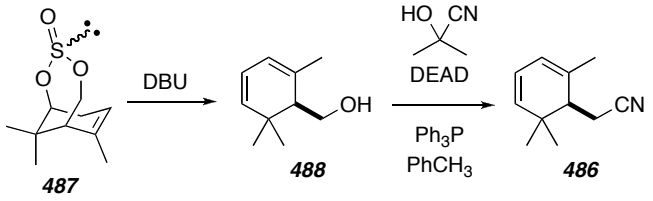
produced the nitrile **463** in low yield (20-30%, 2 steps), and the alcohol **488** (~20%) and the cylic ether **483** (~15%) were also isolated in significant amounts. It was discovered later that when the formation of the cyclic sulfite **487** was carried out at room temperature a 2:1 ratio of diastereomers was formed (compared to a 1:1 dr at 0 ºC). Exposing this mixture of diastereomers to the cyanation conditions resulted in a higher yield (30-40%, 2 steps) of **463**. This became the desired protocol moving forward.

Scheme IV-18. Synthesis of the Cyclic Sulfite **487**, and Its Reactivity with Cyanide.



Since the cyanide displacement of **487** gave moderate yields, I wanted to try to selectively convert **487** to the dienol **488** by treating with base (Scheme IV-19) hoping that this elimination may be a cleaner transformation. Subsequent Mitsunobu reaction of the dienol **488** with a nucleophilic cyanide source could provide the nitrile **486**. Treatment of **487** with *n*BuLi in various solvents ($PhCH_3$, THF, Et_2O, hexanes) or with LDA in THF did not give the dienol **488**, but instead resulted in formation of the parent diol **448**. The elimination did occur, however, upon exposure of **487** to DBU (neat or in $PhCH_3$), but the best conditions (neat DBU) resulted in crude material that was ~65% pure and a crude yield of ~35%. The conversion of **488** to the nitrile **486** utilizing Mitsunobu conditions gave a complicated product mixture, and **486** was only a minor component of this mixture. Since this was not a viable approach, my efforts returned to how to move forward with the nitrile **463**.

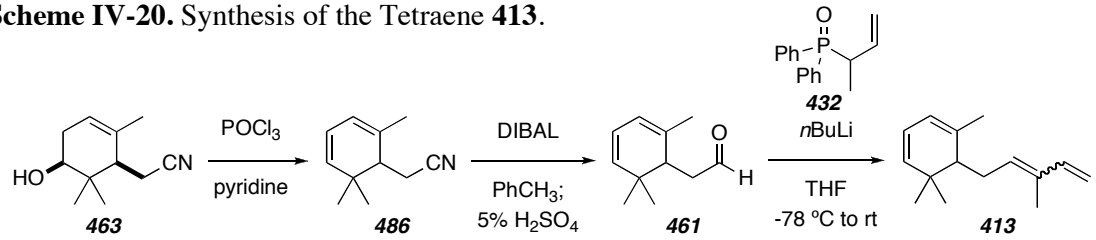
Scheme IV-19. Selective Elimination of the Cyclic Sulfite **487** to the Dienol **488**.



487 ***488*** ***486***

The synthesis of the tetraene **413** (Scheme IV-20) was finally completed via elaboration of the nitrile **463**. This was achieved by treating **463** with $POCl_3$ in pyridine to effect elimination to the diene **486** (83% crude yield). The nitrile **486** was converted to the aldehyde **461** by treating with DIBAL followed by exposure to aqueous H_2SO_4 (56% crude yield, 2 steps). The critical olefination step was realized by adding the aldehyde **461** to a solution of the anion of the phosphine oxide **432** (3 equiv) at -78 ºC and then allowing the solution to warm to room temperature. The tetraene **413** (4:1 *E*:*Z*) was isolated in 58% yield from the crude aldehyde **461** (32% yield, 3 steps). This olefination was carried out multiple times, and the (*E*) : (*Z*) ratio varied from 4 :1 to 5 : 1. The olefination could also be carried out with HMPA as an additive, but the yield of **413** was not improved. The (*E*) : (*Z*) ratio of **413** was 3 to 1 when using HMPA. The (*E*)- and (*Z*)-alkenes of **413** could not be separated by HPLC (normal or reverse phase). The yield of this olefination could not be improved by using more equivalents of the phosphine oxide **432** or by extending the reaction time (room temperature overnight).

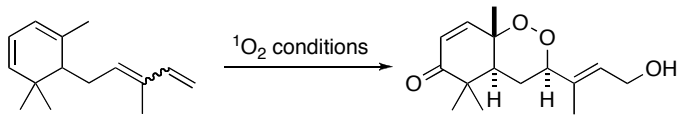
Scheme IV-20. Synthesis of the Tetraene **413**.



463 ***486*** ***461*** ***432*** ***413*** 4:1 *E*:*Z*

With the tetraene **413** now in hand, it was time to investigate its reactivity with $^1O_2$ (Scheme IV-21). The chemically generated $^1O_2$ conditions (Oxone® / aqueous $NaHCO_3$) were first examined.[42] The tetraene **413** gave poor conversion with these conditions, and the product mixture did not show any distinguishable compounds by crude ^1H NMR analysis; therefore, no further purification was carried out. Photochemically generated $^1O_2$ turned out to give better results. Irradiation of the tetraene **413** with Rose Bengal in an O_2 saturated $MeOH/H_2O$ solution provided a much more tractable product mixture. The mixture was purified by MPLC to yield fractions that contained some discreet compounds; however, okundoperoxide (**401**) was not observed by ^1H NMR analysis in any of these fractions, nor was it indicated by the observation of the furan **404** during GC-MS analysis. These photochemical conditions were repeated with KOH in order to promote the Kornblum DeLaMare reaction. The crude ^1H NMR profile was different than the previous reaction without base, and more enone containing compounds were observed. MPLC purification once again did not provide okundoperoxide (**401**), however. At this time, I decided to target a more advanced intermediate in our biosynthetic hypothesis so I could investigate the peroxide transfer step.

Scheme IV-21. Singlet Oxygen Reactivity of the Tetraene **413**.



413

okundoperoxide (**401**)
not observed

$^1O_2$ Conditions	Results
Oxone, $NaHCO_3$, CH_3CN/H_2O	Poor conversion, product mixture does not show distinguishable peaks by crude ^1H NMR analysis
Rose Bengal, O_2, $MeOH/H_2O$	More tractable product mixture by crude ^1H NMR analysis, **401** not observed
Rose Bengal, KOH, O_2, $MeOH/H_2O$	Also more tractable mixture, more enone containing products observed, **401** not observed

IV.F.3. First Generation Synthesis of the Diol-Diene 489

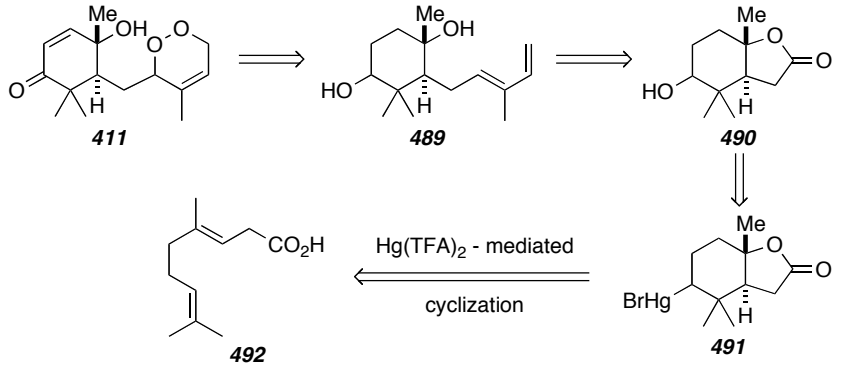
The new synthetic target was the diol diene **489** (Scheme IV-22), which is a precursor to the peroxide transfer substrate **411**. The enone endoperoxide **411** could be produced from the diol diene **489** via oxidation of the alcohol to the enone and $^1O_2$-[4+2] of the diene. I believed that the diol diene **489** could be accessed from the known lactone **490** by olefination of its corresponding lactol with the phosphine oxide **432** described above (Scheme IV-20). The alcohol **490** can be made by oxidizing the mercuric bromide **491**, as reported by Crich.[94] The mercuric bromide **491** can arise via cyclization of the acid **492** using $Hg(TFA)_2$ followed by treatment with KBr.[95] This cyclization reaction was developed by the Hoye group almost thirty years ago, and our collaborator, Dr. Efange, was aware of this chemistry, which is why he approached our research group with this project. However, this chemistry would be more relevant for synthesizing Dr.

[94] "Synthesis of the taxol AB-system by olefination of an A-ring C1 ketone and direct B-ring closure," Crich, D.; Natarajan, S.; Crich, J. Z. *Tetrahedron* **1997**, *53*, 7139-7158.

[95] "Mercuric Trifluoroacetate Mediated Brominative Cyclizations of Dienes. Total Synthesis of *dl*-3β-Bromo-8-epicaparrapi Oxide," Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1979**, *44*, 3461-3467.

Efange's originally assigned structure of the natural product, the tetrahydrofuran **403** (Figure IV-2).

Scheme IV-22. Retrosynthesis of the First Generation Synthesis of the Diol Diene **489**.

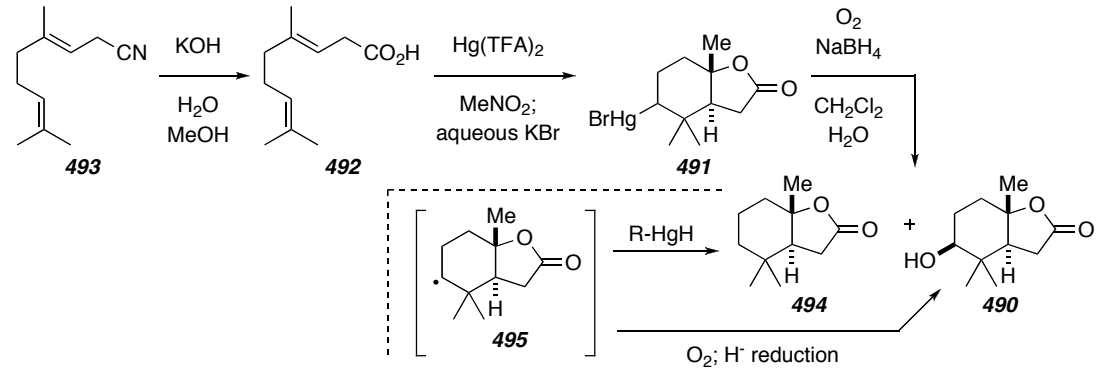


The synthesis of the lactone **490** (Scheme IV-23) commenced with the hydrolysis of the nitrile **493** (available in two steps [PBr_3; NaCN] from geraniol) to provide the acid **492**.[96] Although the hydrolysis gave a yield similar to what was reported in the literature (80%) on a moderate scale (4 g), on a large scale (25 g) this reaction resulted in a much lower yield. The cyclization of **492** with $Hg(TFA)_2$ was achieved to give the mercuric trifluoroacetate product, which was converted to the mercuric bromide **491** upon treatment with aqueous KBr. On a multi-gram scale (4-8 g) this transformation gave variable yields in my hands. The conversion of the mercuric bromide **491** to the alcohol **490** was accomplished by slowly adding an aqueous solution of $NaBH_4$ to an O_2-saturated solution of **491** in CH_2Cl_2.[94] This reaction worked very well on a moderate scale (1-3 g), but on a large scale (15 g) a significant amount of the reduction product **494** was isolated. We believe that the reduction to form **494** occurred because it was difficult to maintain a high enough O_2 concentration in a large solution (1.5 L). As a result, the proposed intermediate radical **495** (formed from the breakdown of the mercuric hydride

[96] "Brominative cyclizations of geranyl derivatives," Hoye, T. R.; Kurth, M. J. *J. Org. Chem.* **1978**, *43*, 3693-3697.

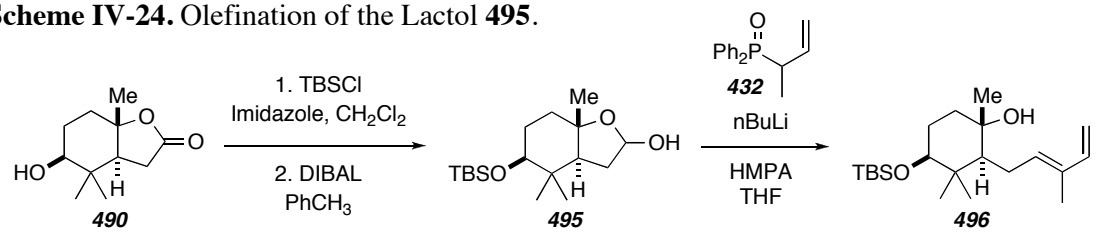
derived from **491**) could competitively react with the mercuric hydride to give **494** instead of reacting with triplet O_2 to give the hydroperoxy precursor to alcohol **490**. Also, a slower rate of addition of $NaBH_4$ would most likely increase the ratio of **490** to **494**. Despite the problems associated with scaling up these reactions, I was able to access sufficient quantities of **490** to move forward.

Scheme IV-23. Synthesis of the Lactone **490**.



In order to olefinate the lactol of **490** (Scheme IV-24), I thought it would be necessary to protect the alcohol. The alcohol **490** was protected as its TBS ether, and subsequent DIBAL reduction furnished the lactol **495**. The olefination of **495** with the phosphine oxide **432** was attempted a few times, but only a 5-10% yield of the diene **496** could be achieved. Full conversion could be accomplished upon stirring overnight at room temperature, but no side products could be isolated cleanly that would indicate why this reaction was not working better. LC-MS analysis suggested that the olefination halted at some intermediate species that could not go on to product, because masses corresponding to the lactol **495** plus the phosphine oxide **432** were observed.

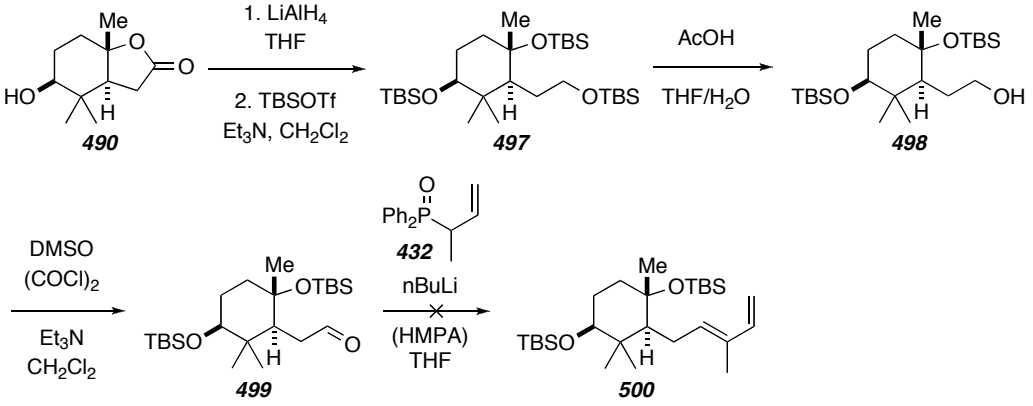
Scheme IV-24. Olefination of the Lactol **495**.



490 ***495*** ***432*** ***496***

Since the lactol **495** gave a poor yield in the olefination reaction, I decided to target the aldehyde **499** (Scheme IV-25), hoping that it would be a better substrate for olefination. The synthesis of **499** began with exhaustive reduction ($LiAlH_4$) of the lactone **490** to the corresponding triol, and subsequent global TBS protection provided **497**. In my first attempt to selectively deprotect the primary TBS ether of **497**, I used CSA in $MeOH/CH_2Cl_2$. However, these conditions resulted in deprotection of both the primary and secondary TBS ethers of **497**. Therefore, I turned to milder conditions ($AcOH/THF/H_2O$), which successfully provided the alcohol **498**. Finally, Swern oxidation of **498** produced the aldehyde **499**. Disappointingly, exposure of **499** to the olefination conditions (with or without HMPA) with the phosphine oxide **432** did not give any of the diene **500**. We speculated that **499** was too sterically encumbered to react with a bulky nucleophile like **432**. Although **499** does not appear very hindered since the aldehyde is neighbored by a methylene carbon, closer inspection reveals that it is flanked by two quaternary centers that are three carbons removed from the aldehyde. We decided the next approach should involve the elaboration of the aldehyde **499** with a smaller nucleophile in an effort to overcome these steric issues.

Scheme IV-25. Synthesis and Efforts to Olefinate the Aldehyde **499**.

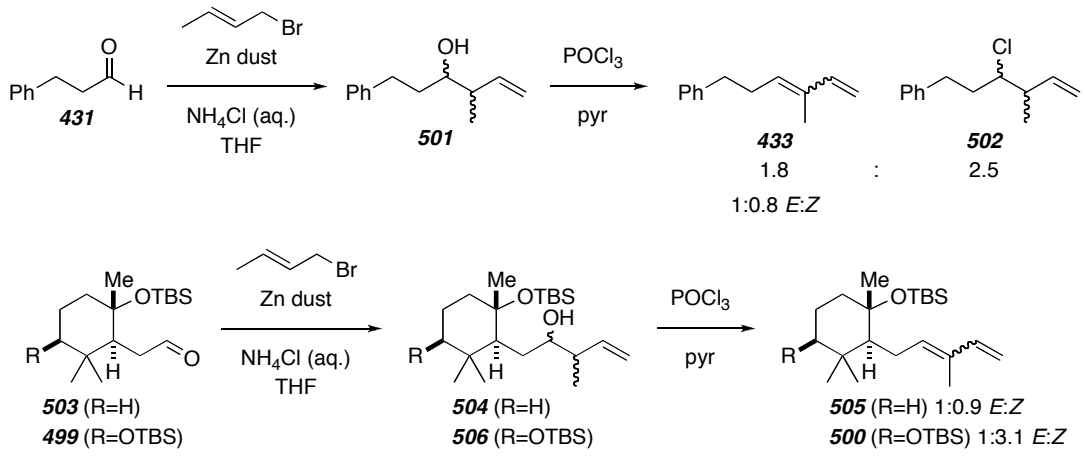


We chose to carry out a two-step sequence (Scheme IV-26), crotylation followed by elimination, to make the diene **500**. We believed that this nucleophile would be slender enough to attack the hindered aldehyde **499**. These steps were first analyzed with a model aldehyde, hydrocinnamaldehyde (**431**). When **431** was exposed to the crotylation conditions developed by Luche (Zn dust, crotyl bromide, aqueous NH_4Cl, THF), the alcohol **501** was provided cleanly as a mixture of diastereromers.[97] Elimination of **501** with $POCl_3$ in pyridine yielded the diene **433** (1:0.8 *E*:*Z*) as well as the chloride **502**. Since I had a significant amount of the reduced side product **494** (~1g) from the attempted oxidation described above (Scheme IV-23), I used it to make the model aldehyde **503** in four steps ($LiAlH_4$; TBSOTf; CSA; Swern oxidation). The aldehyde **503** worked well in the crotylation reaction to provide the alcohol **504**, which underwent complete conversion to the diene **505** (1:0.9 *E*:*Z*) after stirring overnight with $POCl_3$ in pyridine. Since the model system proved successful (93% yield, 2 steps) using the crotylation / elimination protocol, the aldehyde **499** was carried through these steps. The diene **500** (1:3.1 *E*:*Z*) was furnished from the aldehyde **499**, via the alcohol

[97] "Selective tin and zinc mediated allylations of carbonyl compounds in aqueous media," Petrier, C. Einhorn, C. Luche, J.-L. *Tetrahedron Lett*. **1985**, *26*, 1449-1452.

intermediate **506** in a moderate yield (64% crude yield, 2 steps). However, the crude diene **500** underwent significant decomposition (indicated by ^{1}H NMR analysis) upon sitting overnight before purification, which resulted in a much lower isolated yield than expected (13% yield, 2 steps). The reversal of the *E*/*Z* selectivity from **505** to **500** was an interesting result. The presence of the secondary TBS ether in **499** must have significantly altered its conformation, resulting in a change of the preferred nucleophilic approach angle to the aldehyde. All that remained to complete the synthesis of the diol diene **489** was to deprotect the TBS ethers of **500**.

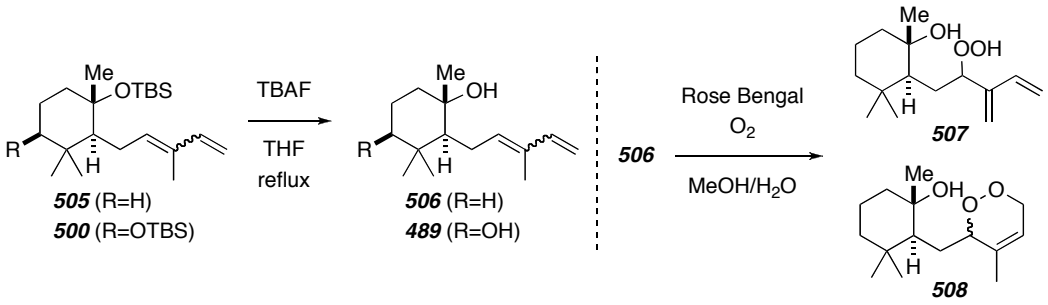
Scheme IV-26. Crotylation / Elimination Strategy to Synthesize the Diene **500**.



The deprotection of the TBS ethers **500** and **505** was accomplished (Scheme IV-27) under refluxing TBAF conditions to give **489** and **506**, respectively. Therefore, the synthesis of the target diol diene **489** had been achieved. However, I was only able to make a relatively small amount of **489** (33 mg), because of the poor scalability of some of the earlier steps in this synthesis and because of the decomposition of the crude diene **500**. Also, this synthesis required 12 steps from geraniol. I would prefer to develop a shorter synthesis in order to allow for a greater mass throughput. Therefore, I decided to move on to a different approach to synthesize the diol diene **489**, but I would end up

turning to some of the chemistry developed in this route in the new approach. Before moving on I attempted to carry out the $^1O_2$-[4+2] with the model diene **506**. Treating **506** with Rose Bengal and O_2 in a MeOH/H_2O solution resulted in the production of the ene product **507** as the main product, but I was also able to isolate the endoperoxide (**508**; dr=1.6:1) in 13% yield. No evidence for the peroxide transfer was observed by ^1H NMR analysis of the crude material or the isolated fractions from MPLC.

Scheme IV-27. TBS Deprotection and $^1O_2$ Reactivity of the Model Diene **506**.



IV.F.4. Second Generation Synthesis of the Diol-Diene

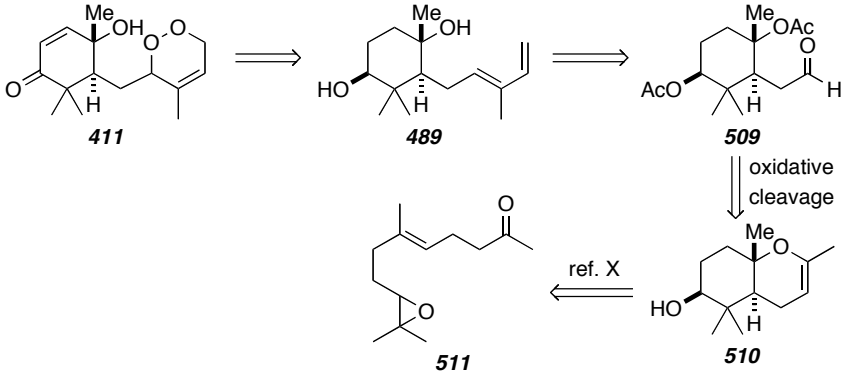
The second generation approach to the synthesis of the diol diene **489** was inspired by the recently reported cyclization of geranyl acetone epoxide **511** to the cyclic enol ether **510**.[98] I found precedence in the literature for the oxidative cleavage of a cyclic enol ether like **510** to directly give an aldehyde acetate like **509** (if the acetate derivative of **510** was used).[99] The diene diol **489** could then be made from **509** using the crotylation / elimination protocol described above (Scheme IV-26) followed by deacetylation. If this approach proved to be feasible, then the diol diene **489** could be accessed in 8 steps from commercially available geranylacetone (**512**, Scheme IV-29),

[98] "Selective Monocyclization of Epoxy Terpenoids Promoted by Zeolite NaY. A Short Biomimetic Synthesis of Elegansidiol and Farnesiferols B–D," Tsangarakis, C.; Arkoudis, E.; Raptis, C.; Stratakis, M. *Org. Lett.* **2007**, *9*, 583–586.

[99] "The synthesis of (–)-Ambrox® starting from labdanolic acid," Bolster, M. G.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2001**, *57*, 5657-5662.

while **489** was made in 12 steps from commercially available geraniol using the previous approach (Section IV.F.3).

Scheme IV-28. Retrosynthesis of the Second Generation Synthesis of the Diol Diene **489**.

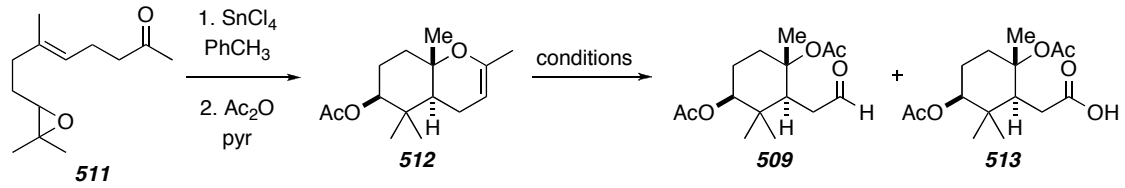


The second generation approach to **489** began with geranyl acetone epoxide **511** (Scheme IV-29), which was available in two steps (NBS, THF/H_2O; K_2CO_3, MeOH) from geranyl acetone. The cyclization of **511** with $SnCl_4$ in $PhCH_3$ was carried out according to the literature procedure, and subsequent acetate protection (Ac_2O, pyridine) furnished the cyclic enol ether **512**.[98] The oxidative cleavage of **512** was then optimized by screening a few conditions, which were all known to effect a similar transformation of a precursor to pumiloxide, another terpenoid natural product.[100] Ozonolysis of **512** to the aldehyde **509** proved to be low yielding (~10%). I tried different solvent combinations (MeOH, CH_2Cl_2, $MeOH/CH_2Cl_2$), base additives ($NaHCO_3$, pyridine, no base), and reductants (DMS, Ph_3P), but no improvement in yield was achieved. I next tried using the Jones reagent (CrO_3, H_2SO_4, H_2O) to carry out this oxidative cleavage of **512**.[101] This resulted in the production of **509** in 25% yield, but it was accompanied with the

[100] "New diterpenoid components of the oleoresin of *Pinus pumila*," Raldugin, V. A.; Demenkova, L. I.; Pentegova, V. A. *Chem. Nat. Prod.* **1978**, *14*, 286-289.
[101] "A Synthesis of (-)-12,lS-Epoxylabda-8(17),12,14-trien-16-yl Acetate and (-)-Pumiloxide," Cambie, R. C.; Moratti, S. C.; Rutledge, R. S.; Weston, R. J.; Woodgate, P. D. *Aust. J. Chem.* **1990**, *43*, 1151-1162.

overoxidized acid **513**. I screened conditions in an effort to reduce the amount of the undesired acid **513** formed, which should in turn improve the yield of **509**. When I reduced the amount of Jones reagent to 0.7 equivalents, I still observed a large amount of the undesired acid (1.5:1 **509**:**513**). Also, the yield of **509** was not improved when either quenching at -40 ºC or adding a sacrificial aldehyde (hydrocinnamaldehyde) at -40 ºC before warming to 0 ºC. Finally, the best results were achieved using the Johnson-Lemieux oxidative conditions (OsO_4, $NaIO_4$).[102] Overnight exposure of **512** to these conditions (0 ºC to room temperature) resulted in a 2:1 ratio of **509**:**513**. However, when the reaction was carried out at room temperature (7 hours), **509** was formed cleanly with only a trace of **513** observed. The crude material appeared rather clean by ^{1}H NMR analysis, but the isolated yield of **509** was lower than expected (50%). This was still a significant improvement compared to the ozonolysis, and the Johnson-Lemieux conditions were the preferred method to make the aldehyde **509**.

Scheme IV-29. Synthesis of the Aldehyde **509**.



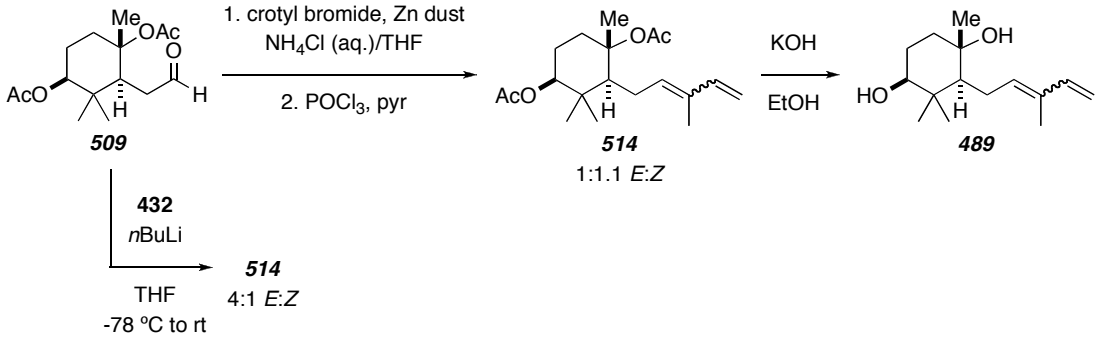
511 ***512*** ***509*** ***513***

Conditions	Results
O_3, pyr, MeOH; DMS	Complicated product mixture, **509** isolated in 10-15% yield
CrO_3, H_2SO_4, H_2O, acetone, -40 ºC to 0 ºC	Observed ~1:1 ratio of **509**:**513**, **509** isolated in 25% yield
OsO_4, $NaIO_4$, THF/H_2O	Clean formation of **509** with trace of **513**, **509** isolated in 50%

[102] "Synthesis of Ambrox® from (–)-sclareol and (+)-*cis*-abienol," Barrero, A. F.; Alvarez-Manzaneda, E. J.; Altarejos, J.; Salido, S. Ramos, J. M. *Tetrahedron* **1993**, *49*, 10405-10412.

Only a few steps remained to complete the second generation synthesis of **489**. The crotylation / elimination protocol was investigated with **509** to make sure that the diacetate protected version of this aldehyde would fare well in these steps. Exposure of **509** to the same crotylation and subsequent elimination steps described above (Scheme IV-26) cleanly furnished the diene **514** (1:1.1 *E*:*Z*). Deacetylation of **514** was accomplished by treatment with ethanolic KOH to finally yield the diol diene **489**. The yield over these three steps was 61% on a small scale, but was lower (30%) on a large scale. The olefination of **509** was also attempted using the same phosphine oxide **432** as above (Scheme IV-20). This procedure did provide the diene **514**, albeit in low yield (20%, 4:1 *E*:*Z*). The second generation synthesis of **489** highlighted in this section proved to be superior to the first generation approach (Section IV.F.3) in both the reliability and number of steps. This synthesis allowed for the production of greater amounts of **489** (~200 mg, much more [~400 mg] could have been made, but ~1 g of the enol ether **512** decomposed upon storage at room temperature) compared to the previous approach (~30 mg). Therefore, a more exhaustive evaluation of the subsequent chemistry could be carried out, which will be discussed in the following sections.

Scheme IV-30. Completion of the Second Generation Synthesis of **489**.



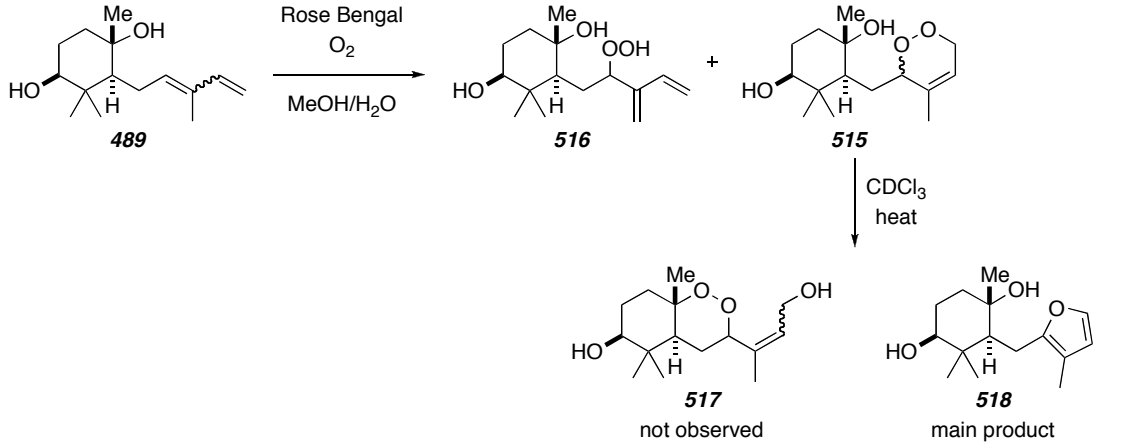
IV.F.5. $^1O_2$-[4+2] Reaction with the Diol Diene and Reactivity of the Endoperoxide

With the diol diene **489** now in hand, I was able to study the $^1O_2$-[4+2] reaction (Scheme IV-31) with this diene to give the endoperoxide **515**. A study of the reactivity of the endoperoxide **515** would then reveal whether or not the peroxide transfer would be a feasible step to form the okundoperoxide-like endoperoxide **517**. In the next section I will discuss my efforts to convert the diol **489** to the hydroxy enone **521** (Scheme IV-33), which would lead to okundoperoxide (**401**) upon $^1O_2$-[4+2], peroxide transfer, and alkene isomerization.

The diol diene **489** was exposed (Scheme IV-31) to photochemically generated $^1O_2$ (Rose Bengal, O_2, MeOH/H_2O) at 0 ºC. The main product of this reaction was the ene product **516**, but the endoperoxide **515** (1:0.8 dr) was isolated in low yield (~10%). Similar results were observed when different solvent systems (CH_2Cl_2/MeOH or MeOH) were used. When the reaction was carried out at an elevated temperature (warmed by the lamp), the crude ^1H NMR spectrum seemed to show a slightly higher proportion of the endoperoxide **515** in the product mixture; however, the isolated yield of **515** was still ~10%. The endoperoxide **515** was isolated by MPLC purification and subsequent normal phase HPLC purification of the MPLC fraction containing **515**. The thermal reactivity of **515** was then studied by heating in $CDCl_3$ in a sealed NMR tube. After heating **515** for 3 hours at 65 ºC, no change was observed by ^1H NMR analysis. Further heating overnight at 80 ºC resulted in complete conversion to the furan **518**, and the peroxide transfer product **517** was not observed. The conversion of endoperoxides to furans is known in the literature, but it requires higher temperatures than what I observed for the

transformation of **515** to **518**;[103] thus, we were curious whether the tertiary alcohol of **515** plays a role in the formation of **518**, possibly via a peroxide transfer pathway. If this reaction could be stopped at partial conversion to **518**, perhaps intermediates could be isolated that would implicate the peroxide transfer mechanism. Also, we wondered if furan formation would occur if the tertiary alcohol of **515** was protected, rendering the tertiary alcohol incapable of direct participation.

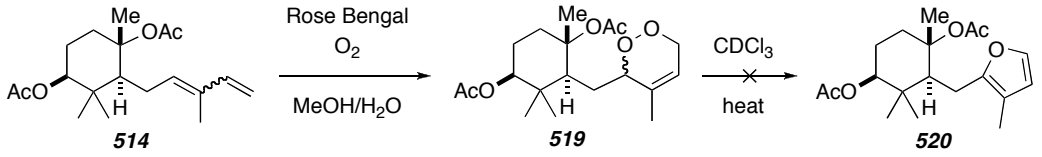
Scheme IV-31. $^1O_2$-[4+2] Reaction of the Diene **489** and Reactivity of the Endoperoxide **515**.



I decided to use the acetate-protected version of **515** since it could be accessed from an intermediate that I had already made, the diacetate **514**. Therefore, **514** was exposed (Scheme IV-32) to the same $^1O_2$ conditions used above to give the endoperoxide **519**. When the endoperoxide **519** was heated to 80 ºC in $CDCl_3$ for an overnight period, no change was observed by ^1H NMR analysis. This result supports our notion that the tertiary alcohol is playing a role in the thermal conversion of **515** to **518** (Scheme IV-31). However, more evidence would be needed to suggest that a peroxide transfer is operative under these conditions. Since my supply of **489** was exhausted at this point, no more studies of the peroxide transfer with this substrate were carried out.

[103] "Fonctionnalisation des γ- et δ-pyronènes. Synthèse et étude de la réactivité des composés peroxydiques," Campagnole, M.; Bourgeois, M.-J.; Montaudon, E. *Tetrahedron* **2002**, *58*, 1165-1172.

Scheme IV-32. $^1O_2$-[4+2] Reaction of the Diene **514** and Reactivity of the Endoperoxide **519**.



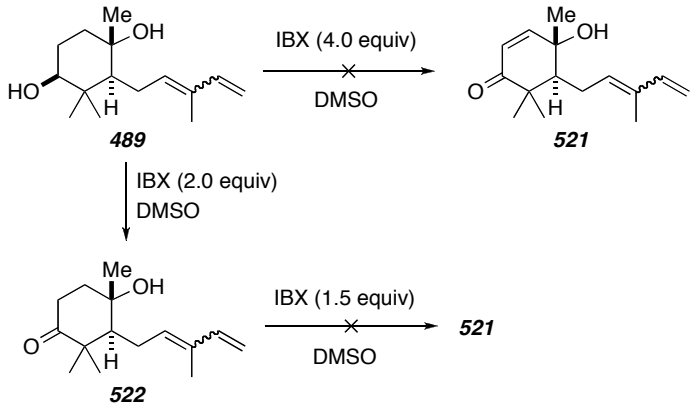
IV.F.6. Efforts to Convert the Diol to the Hydroxy Enone

With the diol diene **489** in hand, I was also able to study (Scheme IV-33) its conversion to the enone **521**, which would allow for the synthesis of okundoperoxide (**401**) upon $^1O_2$-[4+2], peroxide transfer, and alkene isomerization (Scheme IV-3). When the diol **489** was exposed to IBX (4.0 equiv) in DMSO at 85 ºC, a complicated product mixture was generated and none of the hydroxy enone **521** was seen by ^{1}H NMR analysis of the crude material.[104] This experiment was repeated and monitored closely by LC-MS analysis, which indicated clean ketone formation immediately after warming to 85 ºC. Extended heating resulted in the appearance of many new peaks by LC-MS analysis. Even though the mass of the enone **521** was observed by LC-MS analysis, the reaction was not clean and **521** was never isolated. This reaction was also attempted in the presence of *p*TsOH, which is known to accelerate similar oxidations, but the same result was obtained.[104] Treatment of **489** with 2.0 equivalents of IBX resulted in clean formation of the ketone **522**. Subsequent treatment of purified **522** with 1.5 equivalents of IBX again resulted in a complicated product mixture. Closer inspection of the ^{1}H NMR spectra of these crude reaction mixtures revealed that the NMR signals corresponding to the diene of **489** were no longer present and that an aldehyde NMR signal was observed; therefore, perhaps one decomposition pathway could involve

[104] "Iodine(V) Reagents in Organic Synthesis. Part 4. *o*-Iodoxybenzoic Acid as a Chemospecific Tool for Single Electron Transfer-Based Oxidation Processes," Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.

oxidation of the vinylic methyl group of **489**. Due to the exhaustion of my supply of **489** from this study and the work discussed above (Section IV.F.5), no further studies of the conversion of **489** to **521** were carried out.

Scheme IV-33. Attempts to Convert the Diol **489** to the Hydroxy Enone **521**.

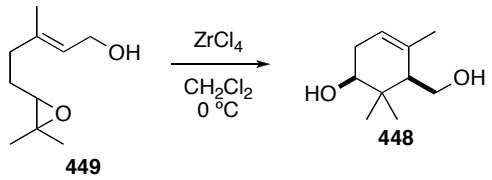


IV.G. Conclusion

The isolation and characterization of okundoperoxide (**401**) has been described. I explained the biosynthetic hypothesis that we had devised for the formation of **401**, and described my synthetic efforts to explore this hypothesis. I was able to synthesize the tetraene **413**, but this proposed biosynthetic precursor did not form okundoperoxide (**401**) upon exposure to $^1O_2$. I was also able to synthesize the diol diene **489**, but exposure of this intermediate to $^1O_2$ did not show any evidence of the proposed peroxide transfer transformation.

IV.H. Experimental Section

(±)-(1R*,5S*)-5-(Hydroxymethyl)-4,6,6-trimethylcyclohex-3-enol (448)



449 **448**

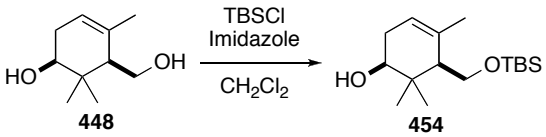
The procedure from Vidari et al[88] was slightly modified. To a mixture of (*E*)-5-(3,3-dimethyloxiran-2-yl)-3-methylpent-2-en-1-ol (**449**, 208 mg, 1.22 mmol) in CH_2Cl_2 (180 mL) at 0 ºC was added solid $ZrCl_4$ (853 mg, 3.66 mmol). The reaction mixture was stirred for 1 h at 0 ºC, and then allowed to warm to rt. Aqueous 1.2 M HCl (30 mL) was added to the mixture, which was then stirred vigorously until the organic layer was homogeneous. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (1:1 hexanes:EtOAc) to give the diol **448** (133 mg, 0.78 mmol, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[88]

TLC: (1:1 hex:EtOAc): $R_f = 0.3$

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): m/z = 193.0 $(M+Na)^+$; t_r = 10.50 min.

(±)-(1R*,5S*)-5-((tert-Butyldimethylsilyloxy)methyl)-4,6,6-trimethylcyclohex-3-enol (454)



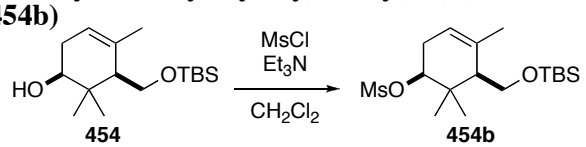
448 **454**

To a mixture of diol **448** (123 mg, 0.72 mmol) and imidazole (98 mg, 1.44 mmol) in CH_2Cl_2 (1.5 mL) was added TBSCl (115 mg, 0.76 mmol). After being stirred at rt for 30 min, the heterogeneous mixture was filtered, and the filtrate was diluted with water. The mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (168 mg, 0.59 mmol, 82% crude yield). The crude TBS-ether **454** was taken directly into the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): 5.42 (m, 1H, C=C*H*CH_2), 4.79 (d, *J* = 11.1 Hz, 1H, CHO*H*), 3.81 (dd, *J* = 10.7, 3.3 Hz, 1H, C*H*$_a$H$_b$OTBS), 3.76 (dd, *J* = 10.7, 1.6 Hz, 1H, CH$_a$*H*$_b$OTBS), 3.24 (dd, *J* = 11.0, 4.9, Hz, 1H, C*H*OH), 2.33 (ddq, *J* = 18.3, 5.0, 2.5 Hz, 1H, C=CHC*H*$_a$H$_b$), 2.14 (dd, *J* = 18.3, 4.3 Hz, 1H, C=CHCH$_a$*H*$_b$), 1.70 (m, 3H, C=CC*H*$_3$), 1.67 (m, 1H, C=CC*H*C(Me)$_2$), 1.12 (s, 3H, C(C*H*$_3$)(CH$_3$)), 0.95 (s, 3H, C(CH$_3$)(C*H*$_3$)), 0.89 (s, 9H, OSi(Me)$_2$C(C*H*$_3$)$_3$), 0.09 (s, 3H, OSi(C*H*$_3$)(CH$_3$)*t*Bu), and 0.08 (s, 3H, OSi(CH$_3$)(C*H*$_3$)*t*Bu).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m*/*z* = 285.2 $(M+H)^+$; t_r = 12.82 min.

(±)-(1R*,5S*)-5-((tert-Butyldimethylsilyloxy)methyl)-4,6,6-trimethylcyclohex-3-enyl methanesulfonate (454b)



454 **454b**

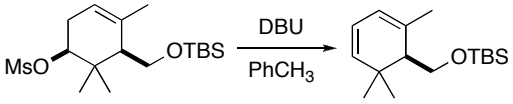
To a mixture of TBS-ether **454** (168 mg, 0.59 mmol) and Et_3N (164 μL, 1.18 mmol) in CH_2Cl_2 (3 mL) at 0 ºC was added MsCl (69 μL, 0.89 mmol). After being stirred at 0 ºC for 45 min, MeOH (200 μL) was added to the mixture, which was then diluted with CH_2Cl_2 and washed with aq. 1M HCl to neutrality. The organic layer was

washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (206 mg, 0.57 mmol, 96% crude yield). The crude mesylate **454b** was taken directly into the next step without further purification.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.29 (m, 1H), 4.52 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.84 (dd, *J* = 10.7, 4.6 Hz, 1H), 3.71 (dd, *J* = 10.6, 4.7 Hz, 1H), 3.00 (s, 3H), 2.45 (m, 1H), 2.35 (m, 1H), 1.75 (s, 3H), 1.74 (m, 1H), 1.10 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), and 0.05 (s, 6H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 385.1 $(M+Na)^+$; t_r = 14.81 min.

(±)-tert-Butyldimethyl((2,6,6-trimethylcyclohexa-2,4-dienyl)methoxy)silane (455)

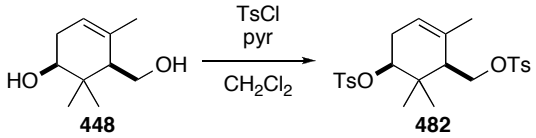


454b **455**

To a mixture of the mesylate **454b** (295 mg, 0.81 mmol) in $PhCH_3$ (8.1 mL) was added DBU (485 μL, 3.24 mmol). The mixture was heated at reflux for 8 h and then cooled to rt. Water was added to the mixture, which was extracted with hexanes (3x). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (19:1 hexanes:EtOAc) to give the diene **455** (73 mg, 0.27 mmol, 33 % yield from crude mesylate, 26% yield over 3 steps).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.69 (dd, *J* = 9.4, 5.1 Hz, 1H), 5.59 (m, 1H), 5.24 (d, *J* = 9.3 Hz, 1H), 3.71 (dd, *J* = 10.1, 6.3 Hz, 1H), 3.53 (dd, 10.1, 6.4 Hz, 1H), 1.84 (br s, 3H), 1.80 (t, *J* = 6.3 Hz, 1H), 1.05 (s, 3H), 0.99 (s, 3H), 0.88 (s, 9H), 0.019 (s, 3H) and 0.013 (s, 3H).

(±)-(1R*,5S*)-2,6,6-Trimethyl-5-(tosyloxy)cyclohex-2-enyl)methyl 4-methylbenzenesulfonate (482)

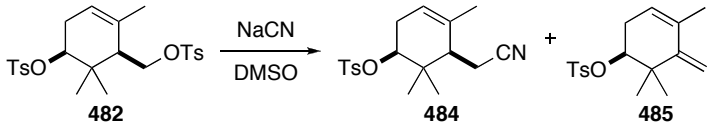


448 **482**

To a mixture of the diol **448** (141 mg, 0.83 mmol) and pyridine (267 μL, 3.3 mmol) in CH_2Cl_2 (0.8 mL) at 0 ºC was added TsCl (475 mg, 2.5 mmol). The mixture was allowed to warm to rt and stirred for 2 h. Water was added to the mixture, which was then extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (3:1 hexanes:EtOAc) to give the ditosylate **482** (84 mg, 0.18 mmol, 21% yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76 (d, *J* = 8.3 Hz, 2 H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 5.24 (m, 1H), 4.30 (t, *J* = 5.5 Hz, 1H), 4.25 (dd, *J* = 10.5, 4.8 Hz, 1H), 3.99 (dd, *J* = 10.5, 4.5 Hz), 2.46 (s, 3H), 2.45 (s, 3H), 2.21 (m, 2H), 2.04 (m, 1H), 1.64 (m, 3H), 0.84 (s, 3H), and 0.80 (s, 3H).

(1S,5R)-5-(cyanomethyl)-4,6,6-trimethylcyclohex-3-enyl 4-methylbenzenesulfonate (484)



482 **484** **485**

To a mixture of the ditosylate **482** (20 mg, 0.042 mmol) in DMSO (0.17 mL) was added NaCN (3.1 mg, 0.063 mmol) and the mixture was stirred overnight at rt. Water was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (3:1 hexanes:EtOAc) to give the diene **485** (2.9 mg, 0.0095 mmol, 23% yield,

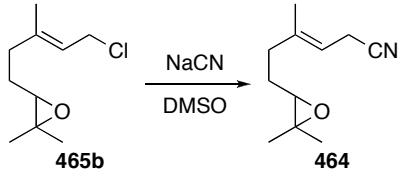
27% brsm), nitrile **484** (5.6 mg, 0.017 mmol, 40% yield, 47% brsm), and recovered starting material **482** (2.9 mg, 0.006 mmol, 14% recovered).

Diene 485 ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 5.39 (m, 1H), 5.02 (d, *J* = 0.8 Hz, 1H), 5.01 (m, 1H), 4.41 (dd, *J* = 6.9, 5.1 Hz, 1H), 2.45 (s, 3H), 2.43 (m, 1H), 2.34 (m, 1H), 1.80 (m, 3H), and 0.99 (s, 6H).

Nitrile 484 ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.33 (m, 1H), 4.39 (t, *J* = 5.5 Hz, 1H), 2.64 (dd, *J* = 17.6, 5.9 Hz, 1H), 2.36 (dd, *J* = 17.6, 5.7 Hz, 1H), 2.26 (m, 2H), 2.12 (m, 1H), 1.80 (m, 3H), 0.97 (s, 3H), and 0.92 (s, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 356.0 $(M+Na)^+$; t_r = 3.30 min.

(*E*)-6-(3,3-dimethyloxiran-2-yl)-4-methylhex-3-enenitrile (464)



465b **464**

To a mixture of the chloride[105] **465b** (143 mg, 0.76 mmol) in DMSO (2.3 mL) was added NaCN (41 mg, 0.84 mmol), and the mixture was stirred overnight at rt. Water was added to the solution, which was extracted with MTBE (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (122 mg, 0.68 mmol, 90% crude yield). The crude nitrile **464** was taken on directly to the next step without further purification.

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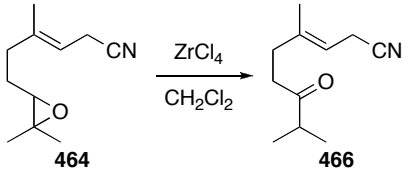
[105] "Chemo-enzymatic enantio-convergent asymmetric synthesis of (*R*)-(+)-Marmin," Edegger, K.; Mayer, S. F.; Steinreiber, A.; Faber, K. *Tetrahedron* **2004**, *60*, 583-588.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.23 (tq, *J* = 7.0, 1.4 Hz, 1H), 3.06 (d, *J* = 7.0 Hz, 2H), 2.70 (t, *J* = 6.2 Hz, 1H), 2.20 (m, 2H), 1.71 (m, 3H), 1.66 (m, 2H), 1.32 (s, 3H), and 1.27 (s, 3H).

HPLC-MS (Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm, APCI/ESI, 50-100% MeOH:H_2O + 0.05% NH_4OAc): *m/z* = 202.1 $(M+Na)^+$; t_r = 3.30 min.

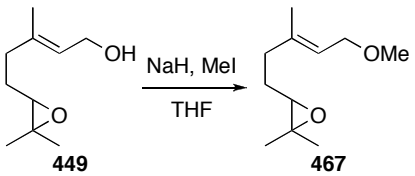
(*E*)-4,8-dimethyl-7-oxonon-3-enenitrile (466)



To a mixture of the crude nitrile **464** (22.3 mg, 0.124 mmol) in CH_2Cl_2 (19 mL) was added solid $ZrCl_4$ (87 mg, 0.37 mmol). The reaction was stirred for 30 min at rt. Aqueous 1.2 M HCl (3 mL) was added to the mixture, which was then stirred vigorously until the organic layer was homogeneous. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with saturated aq. $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to cleanly give the crude ketone **466** (20.9 mg, 0.117 mmol, 94% crude yield), instead of cyclization to the cyclohexene.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.18 (ttq, *J* = 6.9, 1.4, 1.4 Hz, 1H), 3.04 (dtq, *J* = 7.0, 0.9, 0.9 Hz, 2H), 2.61 (sept, *J* = 6.9 Hz, 1H), 2.58 (t, *J* = 7.9 Hz, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 1.69 (m, 3H), and 1.11 (d, *J* = 7.0 Hz, 6H).

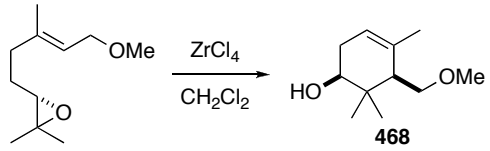
(S,*E*)-3-(5-methoxy-3-methylpent-3-enyl)-2,2-dimethyloxirane (467)



To a mixture of the alcohol[88] **449** (50 mg, 0.294 mmol) in THF (1.2 mL) at 0 ºC was added NaH (60% in mineral oil, 17.6 mg, 0.44 mmol). After stirring for 15 min, MeI (55 μL, 0.88 mmol) was added to the mixture. After stirring for 1 h at 0 ºC, the mixture was allowed to warm to rt. Water was added to the mixture, and then the THF was removed under reduced pressure. The mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude methyl ether **467** (53 mg, 0.288 mmol, 98% crude yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.39 (ttq, J = 6.8, 1.3, 1.3 Hz, 1H), 3.94 (dq, J = 6.8, 0.8 Hz, 2H), 3.33 (s, 3H), 2.72 (t, J = 6.2 Hz, 1H), 2.18 (m, 2H), 1.70 (m, 3H), 1.66 (m, 2H), 1.31 (s, 3H), and 1.26 (s, 3H).

(1S,5R)-5-(methoxymethyl)-4,6,6-trimethylcyclohex-3-enol (468)

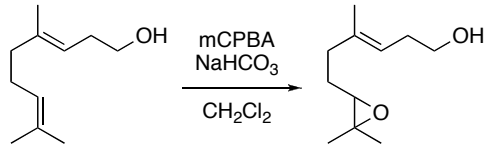


467 **468**

To a mixture of the crude ether **467** (11.8 mg, 0.064 mmol) in CH_2Cl_2 (9.6 mL) was added solid $ZrCl_4$ (44.7 mg, 0.192 mmol). The reaction was stirred for 15 min at rt. Aqueous 1.2 M HCl (1.5 mL) was added to the mixture, which was then stirred vigorously until the organic layer was homogeneous. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with saturated aq. $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude alcohol **468** (7.1 mg, 0.039 mmol, 61% crude yield).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.44 (m, 1H), 4.58 (d, *J* = 10.7 Hz, 1H), 3.64 (dd, *J* = 9.9, 3.5 Hz, 1H), 3.49 (dd, *J* = 9.9, 2.0 Hz, 1H), 3.37 (s, 3H), 3.27 (dd, *J* = 10.7, 5.1 Hz, 1H), 2.33 (m, 1H), 2.14 (m, 1H), 1.74 (m, 3H), 1.74 (m, 1H), 1.09 (s, 3H), and 0.96 (s, 3H).

(*E*)-6-(3,3-Dimethyloxiran-2-yl)-4-methylhex-3-en-1-ol (462)

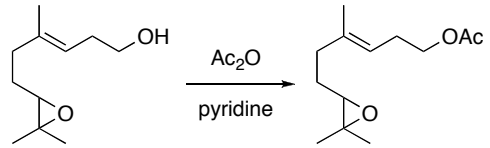


472 **462**

To a mixture of homogeraniol[106] **472** (127 mg, 0.75 mmol) and $NaHCO_3$ (60.4 mg, 0.72 mmol) in CH_2Cl_2 at 0 ºC was added mCPBA (80% w/w, 155 mg, 0.72 mmol). After stirring at 0 ºC for 1 h, the mixture was warmed to rt. Water was added to the mixture, which was then extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with saturated aq. $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (3:2 hexanes:EtOAc) to give the epoxide **462** (26.8 mg, 0.15 mmol, 20% yield).

^{1}H NMR (CDCl3, 500 MHz): δ 5.21 (ttq, *J* = 7.5, 1.4, 1.4 Hz, 1H), 3.64 (t, *J* = 6.3 Hz, 2H), 2.71 (dd, *J* = 7.0, 5.2 Hz, 1H), 2.29 (m, 2H), 2.19 (m, 2H), 1.67 (br s, 3H), 1.67 (m, 2H), 1.30 (s, 3H), and 1.26 (s, 3H).

(*E*)-6-(3,3-Dimethyloxiran-2-yl)-4-methylhex-3-enyl ethanoate (477)



462 **477**

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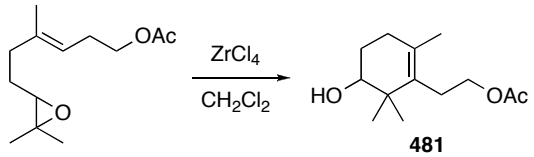
[106] "Selective Hydroboration of a 1,3,7-Triene: Homogeraniol," Leopold, E. J. *Organic Syntheses* **1986**, *64*, 164-174.

To a mixture of the alcohol **462** (5 mg, 0.027 mmol) in pyridine (100 μL) was added Ac_2O (50 μL). After stirring for 1 h at rt, the mixture was diluted with Et_2O. The mixture was washed with saturated aq. $CuSO_4$ (2x), washed with saturated aq. $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude acetate **477** (3.6 mg, 0.016 mmol, 59% crude yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (m, 1H), 4.14 (t, J = 7.0 Hz, 2H), 2.71 (t, J = 6.2 Hz, 1H), 2.34 (br q, J = 7.0 Hz, 2H), 2.17 (m, 2H), 2.05 (s, 3H), 1.65 (br s, 3H), 1.62 (m, 2H), 1.31 (s, 3H), and 1.27 (s, 3H).

2-(5-hydroxy-2,6,6-trimethylcyclohex-1-enyl)ethyl ethanoate (481)



477 **481**

To a mixture of the crude acetate **477** (3.6 mg, 0.016 mmol) in CH_2Cl_2 (2.4 mL) was added solid $ZrCl_4$ (11.2 mg, 0.048 mmol). The reaction was stirred for 45 min at rt. Aqueous 1.2 M HCl was added to the mixture, which was then stirred vigorously until the organic layer was homogeneous. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with saturated aq. $NaHCO_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude alcohol **481** (2.2 mg, 0.0097 mmol, 61% crude yield).

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[107]

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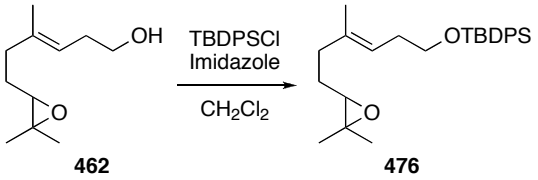
[107] "Fermentation of Fragrances: Biotransformation of β-Ionone by *Lasiodiplodia theobromae*," Krasnobajew, V.; Helmlinger, D. *Helv. Chim. Acta* **1982**, *65* 1590-1601.

(*E*)-*tert*-Butyl(6-(3,3-dimethyloxiran-2-yl)-4-methylhex-3-enyloxy)diphenylsilane (476)

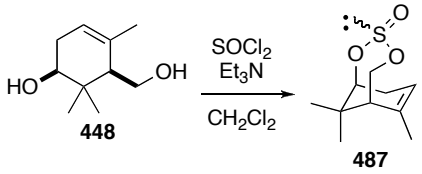


462 **476**

To a mixture of alcohol **462** (4.2 mg, 0.023 mmol) and imidazole (3.3 mg, 0.048 mmol) in CH_2Cl_2 (0.1 mL) was added TBDPSCl (6.6 mg, 0.024 mmol). After stirring for 1 h at rt, the mixture was concentrated under reduced pressure. The residue was filtered through a glass pipet silica plug (hexanes, then 1:1 hexanes:EtOAc), and the filtrate was concentrated under reduced pressure to give the crude TBDPS-ether **476** (9.7 mg, 0.023 mmol, 100% crude yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (m, 4H), 7.40 (m, 6H), 5.17 (ttq, *J* = 7.3, 1.4, 1.4 Hz, 1H), 3.63 (t, *J* = 7.0 Hz, 2H), 2.68 (t, *J* = 6.3 Hz, 1H), 2.27 (app q, *J* = 7.1 Hz, 2H), 2.13 (m, 2H), 1.61 (m, 2H), 1.57 (d, *J* = 1.3 Hz, 3H), 1.27 (s, 3H), 1.23 (s, 3H), and 1.04 (s, 9H).

Cyclic Sulfite (487)



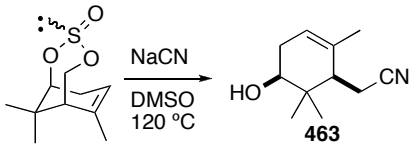
448 **487**

To a mixture of diol **448** (500 mg, 2.94 mmol) and Et_3N (1.35 mL, 9.70 mmol) in CH_2Cl_2 (22 mL) was added $SOCl_2$ (280 μL, 3.82 mmol) dropwise at rt. After stirring for 30 min, water (50 mL) was added, and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (621 mg, 2.87 mmol, 98% crude yield). The crude NMR of the cyclic sulfites (two diastereomers) was clean, and GC-MS

analysis showed a ~2:1 ratio of diastereomers. The crude cyclic sulfite **487** was taken on directly to the next step without further purification.

^{1}H NMR of both diastereomers (500 MHz, $CDCl_3$): δ 5.51 (m, 1H), 5.49 (m, 1H), 4.66 (dd, *J* = 12.3, 1.9 Hz, 1H), 4.34 (d, *J* = 13.0 Hz, 1H), 4.29 (dd, *J* = 6.9, 1.1 Hz, 1H), 4.15 (dd, *J* = 4.9, 2.5 Hz, 1H), 4.06 (dd, *J* = 12.2, 3.4 Hz, 1H), 4.02 (dd, *J* = 13.0, 3.5 Hz, 1H), 3.03 (br d, *J* = 20.2 Hz, 1H), 2.60 (br s, 2H), 2.49 (br d, *J* = 20.2 Hz, 1H), 1.89 (br s, 1H), 1.87 (br s, 1H), 1.80 (app q, *J* = 2.0 Hz, 6H), 1.32 (s, 3H), 1.24 (s, 3H), and 1.00 (s, 6H).

2-((1R*,5S*)-5-Hydroxy-2,6,6-trimethylcyclohex-2-enyl)ethanenitrile (463)

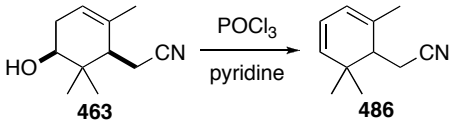


487 **463**

To a mixture of the crude cyclic sulfites **487** (2.94 mmol, from above) in DMSO (11.8 mL) in a sealed tube was added NaCN (433 mg, 8.82 mmol). The mixture was heated to 120 ºC and stirred for 3 h. After cooling to rt, water (50 mL) was added to the mixture, which was then extracted with Et_2O (3 x 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (3:1 hexanes:EtOAc) to give the nitrile **463** (176 mg, 0.98 mmol, 33% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.42 (tdq, *J* = 3.0, 3.0, 1.5 Hz, 1H), 3.53 (t, *J* = 5.5 Hz, 1H), 2.81 (dd, *J* = 17.5, 6.0 Hz, 1H), 2.43 (dd, *J* = 17.5, 5.5 Hz), 2.32 (ddddq, *J* = 18.0, 7.0, 2.0, 2.0, 2.0 Hz, 1H), 2.12 (br t, *J* = 6.0 Hz, 1H), 2.04 (br d, *J* = 18.0 Hz, 1H), 1.82 (m, 3H), 1.03 (s, 3H), and 1.00 (s, 3H).

2-(2,6,6-Trimethylcyclohexa-2,4-dienyl)ethanenitrile (486)

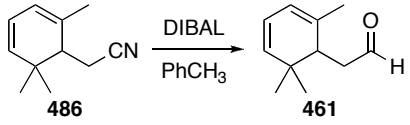


463 **486**

To a mixture of the alcohol **463** (353 mg, 1.97 mmol) in pyridine (9.9 mL) was added $POCl_3$ (1.8 mL, 19.7 mmol). The mixture was heated to 50 ºC for 3 h. After cooling to rt, wet Et_2O was added slowly until the remaining $POCl_3$ was quenched. Water was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with saturated aq. $CuSO_4$, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (262 mg, 1.63 mmol, 83% crude yield). The crude nitrile **486** was taken on directly to the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 (ddq, *J* = 9.3, 5.2, 0.6 Hz, 1H), 5.72 (dqd, *J* = 5.2, 1.7, 0.9 Hz, 1H), 5.30 (dddq, *J* = 9.3, 1.7, 0.8, 0.8 Hz, 1H), 2.42 (dd, *J* = 16.7, 6.3 Hz, 1H), 2.32 (dd, *J* = 16.7, 7.3 Hz, 1H), 1.98 (ddd, *J* = 7.5, 6.3, 1.4 Hz, 1H), 1.93 (br d, *J* = 1.7 Hz, 1H), 1.10 (s, 3H), and 1.02 (s, 3H).

2-(2,6,6-trimethylcyclohexa-2,4-dienyl)ethanal (461)



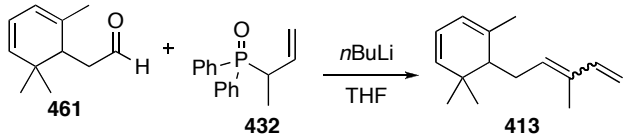
486 **461**

To a mixture of the crude nitrile **486** (1.63 mmol) in $PhCH_3$ (16.3 mL) at -78 ºC was added DIBAL (1.4 M in $PhCH_3$, 1.5 mL, 2.12 mmol). After stirring at -78 ºC for 30 min, the mixture was warmed to rt and stirred an additional 2.5 h. Saturated aq. NH_4Cl (8.1 mL) was added to the mixture, and it was stirred for 30 min. Aqueous 5% H_2SO_4 (5.4 mL) was added to the mixture, and it was stirred for 1 h. The mixture was diluted

with water and extracted with Et_2O (3x). The combined organic layers were washed with saturated aq. Rochelle's salt, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (180 mg, 1.1 mmol, 56% crude yield over 2 steps). The crude aldehyde **461** was taken on directly to the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (t, *J* = 2.6 Hz, 1H), 5.77 (ddq, *J* = 9.4, 5.2, 0.6 Hz, 1H), 5.69 (dqd, *J* = 5.2, 1.7, 0.7 Hz, 1H), 5.31 (dq, *J* = 9.4, 0.9 Hz, 1H), 2.56 (ddd, *J* = 15.8, 6.2, 2.4 Hz, 1H), 2.28 (ddd, *J* = 15.8, 5.2, 2.8 Hz, 1H), 2.21 (t, *J* = 5.7 Hz, 1H), 1.81 (br d, *J* = 1.7 Hz, 3H), 1.02 (s, 3H), and 0.99 (s, 3H).

1,5,5-Trimethyl-6-(3-methylpenta-2,4-dienyl)cyclohexa-1,3-diene (413)

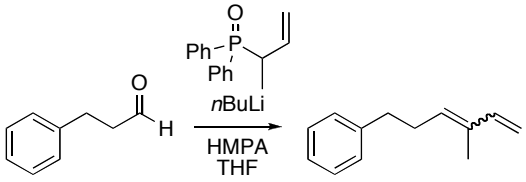


To a mixture of phosphine oxide **432**[83] (646 mg, 2.52 mmol) in THF (8.4 mL) at -78 ºC was added *n*BuLi (2.09 M in hexanes, 1.2 mL, 2.52 mmol). After stirring for 20 min at -78 ºC, the aldehyde **461** (137 mg dissolved in 1 mL of THF, 0.84 mmol) was added dropwise to this mixture. After stirring the mixture for 2 h at -78 ºC, it was warmed to 0 ºC and stirred an additional 10 min. Water was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was filtered through a silica plug (4:1 hexanes:EtOAc) to remove the polar byproducts, and then purified by MPLC (hexanes) to give the tetraene **413** (98.9 mg, 0.49 mmol, 58% yield from crude aldehyde, 32% over three steps, 4:1 *E*:*Z*).

^{1}H NMR of XXE (500 MHz, $CDCl_3$): δ 6.35 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.73 (dd, *J* = 9.4, 5.1 Hz, 1H), 5.57 (m, 2H), 5.27 (d, *J* = 9.4 Hz, 1H), 5.04 (d, *J* = 17.2 Hz, 1H), 4.89 (d, *J* = 10.7 Hz, 1H), 2.28 (m, 2H), 1.78 (m, 1H), 1.76 (d, *J* = 1.7 Hz, 3H), 1.70 (d, *J* = 1.0 Hz, 3H), 1.02 (s, 3H), and 0.98 (s, 3H).

^{1}H NMR of XXZ (500 MHz, $CDCl_3$): δ 6.74 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.73 (dd, *J* = 9.4, 5.1 Hz, 1H), 5.58 (m, 1H), 5.44 (br t, *J* = 7.2 Hz, 1H), 5.27 (d, *J* = 9.4 Hz, 1H), 5.15 (d, *J* = 17.1 Hz, 1H), 5.03 (d, *J* = 11.1 Hz, 1H), 2.28 (m, 2H), 1.78 (m, 1H), 1.75 (s, 3H), 1.70 (d, *J* = 1.0 Hz, 3H), 1.02 (s, 3H), and 0.98 (s, 3H).

(4-methylhexa-3,5-dienyl)benzene (433)

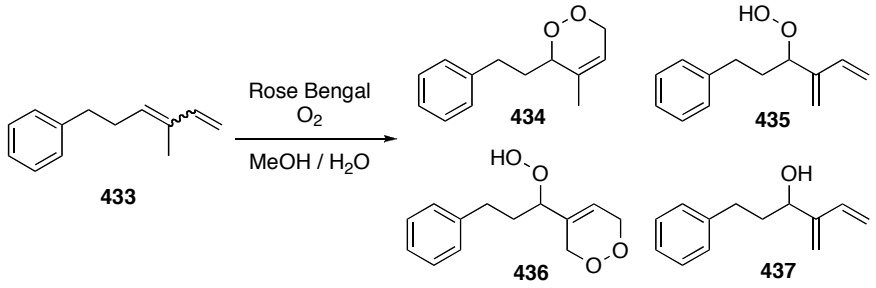


431 **433**

To a mixture of the phosphine oxide (333 mg, 1.3 mmol) and HMPA (452 µL, 2.6 mmol) in THF (10 mL) at -78 ºC was added *n*BuLi (2.09 M in hexanes, 622 µL, 1.3 mmol). After stirring for 20 min at -78 ºC, the aldehyde **431** (dissolved in 1 mL of THF, 121 mg, 0.9 mmol) was added dropwise to this mixture. After stirring for 1 h at -78 ºC, the mixture was warmed to 0 ºC and quenched with water. The mixture was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The oil was filtered through a glass pipet silica plug with pentane, and the filtrate was concentrated to give the diene **433** (115 mg, 0.67 mmol, 74% yield, 2.6:1 *E*:*Z*).

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[84]

4-Methyl-3-phenethyl-3,6-dihydro-1,2-dioxine (434)



To a mixture of the diene **433** (52.3 mg, 0.30 mmol, 2.6:1 *E*:*Z*) in MeOH / H_2O (4:1, 3 mL) in a screw-cap culture tube was added rose bengal (6 mg, 0.006 mmol). The mixture was saturated with O_2 by bubbling with O_2 for one minute. Then, the headspace was flushed with O_2, and the cap was immediately screwed on. The cap was sealed by wrapping it with Teflon tape. The mixture was irradiated (175W mercury vapor lamp) for 1 h and allowed to be warmed by the light source. After cooling to rt, another portion of rose bengal (6 mg, 0.006 mmol) was added, and the mixture was saturated with O_2 again (as above). The mixture was irradiated for 1 h, and then allowed to cool back to rt. Water was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give (from least polar to most polar) endoperoxide **434** (4.9 mg, 0.024 mmol, 8% yield), hydroperoxide **435** (11.7 mg, 0.057 mmol, 19% yield), alcohol **437** (3.6 mg, 0.019 mmol, 6% yield), and hydroperoxide **436** (5.0 mg, 0.021 mmol, 7% yield).

Endoperoxide **434**

^{1}H NMR (500 MHz, $CDCl_3$): 7.29 (m, 2H), 7.20, (m, 3H), 5.63 (m, 1H), 4.60 (ddq, *J* = 16.0, 4.3, 2.1 Hz, 1H), 4.45 (ddq, *J* = 16.0, 5.5, 2.0 Hz, 1H), 4.27 (br d, *J* = 9.6 Hz, 1H), 2.86 (ddd, *J* = 14.3, 10.0, 4.9 Hz, 1H), 2.70 (ddd, *J* = 13.8, 9.8, 7.2 Hz, 1H), 2.04 (dddd, *J*

= 14.3, 9.5, 9.5, 4.8 Hz, 1H), 1.96 (dddd, *J* = 14.4, 10.1, 7.3, 3.0 Hz, 1H), and 1.70 (app q, *J* = 2.0 Hz, 3H).

Hydroperoxide **435**

^{1}H NMR (500 MHz, $CDCl_3$): 7.89 (s, 1H), 7.29 (m, 2H), 7.20 (m, 3H), 6.37 (ddd, *J* = 17.8, 11.2, 0.8 Hz, 1H), 5.32 (dd, *J* = 17.8, 0.8 Hz, 1H), 5.31 (app t, *J* = 1.0 Hz, 1H), 5.27 (app q, *J* = 1.1 Hz, 1H), 5.12 (dddd, *J* = 11.2, 0.9, 0.9, 0.9 Hz, 1H), 4.71 (ddd, *J* = 7.8, 5.4, 0.7 Hz, 1H), 2.76 (ddd, *J* = 13.9, 9.4, 6.2 Hz, 1H), 2.69 (ddd, *J* = 14.0, 9.2, 7.5 Hz, 1H), and 1.95 (m, 2H).

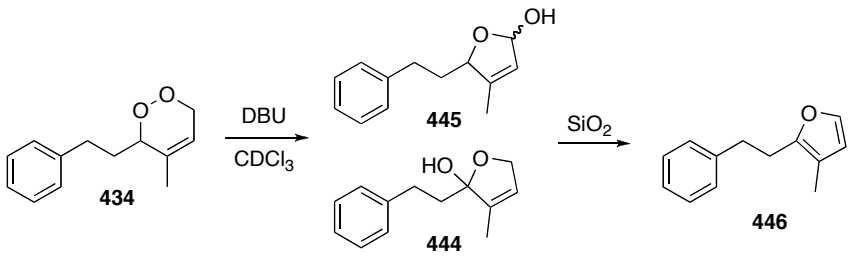
Alcohol **437**

^{1}H NMR (500 MHz, $CDCl_3$): 7.29 (m, 2H), 7.20 (m, 3H), 6.34 (ddd, *J* = 17.8, 11.2, 0.9 Hz, 1H), 5.28 (app q, *J* = 1.3 Hz, 1H), 5.21 (dd, *J* = 17.8, 0.9 Hz, 1H), 5.17 (dt, *J* = 1.3, 0.7 Hz, 1H), 5.08 (dddd, *J* = 11.2, 0.9, 0.9, 0.9 Hz, 1H), 4.44 (ddd, *J* = 7.5, 3.4, 3.4 Hz, 1H), 2.80 (ddd, *J* = 14.4, 9.7, 5.4 Hz, 1H), 2.71 (ddd, *J* = 13.7, 9.5, 6.9 Hz, 1H), 2.01 (dddd, *J* = 13.9, 9.8, 7.0, 4.1 Hz, 1H), and 1.88 (dddd, *J* = 13.8, 9.5, 8.2, 5.4 Hz, 1H).

Endoperoxide-Hydroperoxide **436**

^{1}H NMR (500 MHz, $CDCl_3$): 7.92 (s, 1H), 7.30 (m, 2H), 7.20 (m, 3H), 5.99 (m, 1H), 4.70 (m, 1H), 4.66 (m, 1H), 4.62 (m, 1H), 4.58 (m, 1H), 4.41 (m, 1H), 2.73 (m, 1H), 2.02 (dddd, *J* = 14.2, 9.1, 8.0, 6.3 Hz, 1H), and 1.83 (dddd, *J* = 14.0, 9.3, 6.3, 6.3 Hz, 1H).

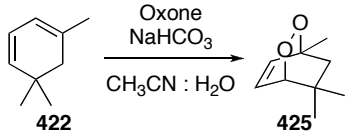
3-Methyl-2-phenethylfuran (446)



To a mixture of the endoperoxide (3.2 mg, 0.016 mmol) **434** in $CDCl_3$ (0.7 mL) was added DBU (2.7 μL, 0.018 mmol). The reaction was monitored by NMR. NMR showed that furanols **444** and **445** were formed cleanly. After 2 days the mixture was concentrated to an oil under reduced pressure. The crude oil was purified by MPLC to give the furan **446** (0.7 mg, 0.004 mmol, 25% yield).

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[108]

1,8,8-Trimethyl-2,3-dioxabicyclo[2.2.2]oct-5-ene (425)



Oxone® (6.15 g, 10 mmol) and $NaHCO_3$ (2.6 g, 31 mmol) were combined and ground together using a mortar and pestle. To a mixture of diene **422** (122 mg, 1.0 mmol) in CH_3CN:H_2O (4:3, 35 mL) was slowly added this Oxone® / $NaHCO_3$ mixture over 1 min. The flask was sealed with a septum which had a balloon attached to it (this probably wasn't necessary, but the original protocol called for this). After stirring at rt for 1 h, another portion of Oxone® / $NaHCO_3$ (same amount as before) was added. This was stirred for 1 h. Water was added to the mixture, which was then extracted with MTBE (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (10:1 pentane:MTBE) to give the endoperoxide **425** (31.2 mg, 0.20 mmol, 20% yield).

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[109]

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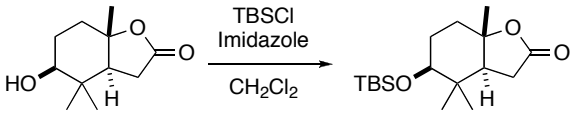
[108] "(E)-1-Bromo-3,3-diethoxy-1-propene (diethyl acetal of 3-bromoacrolein). A versatile synthon for the synthesis of furans, butenolides, and (Z)-allyl alcohols," Meyers, A. I.; Spohn, R. F. *J. Org. Chem.* **1985**, *50*, 4872–4877.

(3S*,5S*,7S*)-5-(*tert*-Butyldimethylsilyloxy)-4,4,7a-trimethylhexahydrobenzofuran-2(3H)-one (490b)

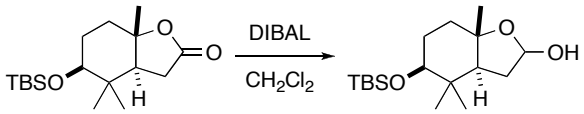


490 **490b**

To a mixture of alcohol **490**[94] (350 mg, 1.77 mmol) and imidazole (241 mg, 3.54 mmol) in CH_2Cl_2 (3.5 mL) was added TBSCl (401 mg, 2.66 mmol) at rt. After stirring overnight, the heterogeneous mixture was filtered, and the filtrate was diluted with water. The mixture was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the TBS ether **490b** as a crude oil (743 mg), which was carried on directly to the next step.

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[110]

(3S*,5S*,7S*)-5-(*tert*-Butyldimethylsilyloxy)-4,4,7a-trimethyloctahydrobenzofuran-2-ol (495)



490b **495**

To a mixture of lactone **490b** (70.7 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) at -78 ºC was added DIBAL (1.4 M in $PhCH_3$, 180 µL, 0.25 mmol) dropwise over 5 min. After 30 min, MeOH was added to quench the reaction, and the mixture was allowed to warm to 0 ºC. The mixture was diluted with Et_2O and brine, and then shaken to give an emulsion. After adding 10% HCl, the layers were separated. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with saturated aq. $NaHCO_3$,

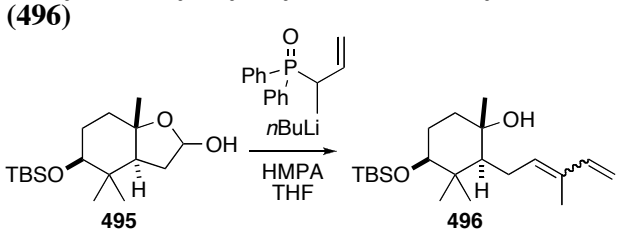
[109] "Ruthenium(II)-catalyzed reactions of 1,4-epiperoxides," Suzuki, M.; Ohtake, H.; Kameya, Y.; Hamanaka, N.; Noyori, R. *J. Org. Chem.* **1989**, *54*, 5292–5302.

[110] "Synthesis of mono- and sesquiterpenoids, XIX. Synthesis of the enantiomers of ancistrofuran, a defensive compound from *Ancistrotermes cavithorax*," Mori, K.; Suzuki, N. *Liebigs Annalen*. **1990**, 287-292.

washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the lactol **495** as an oil (53.1 mg, 0.17 mmol, 74% crude yield).

^{1}H NMR (500 MHz, $CDCl_3$): 9.76 (dd, *J* = 2.9, 1.4 Hz, 0.5H), 5.53 (dd, *J* = 5.7, 3.7 Hz, 0.5H), 5.50 (d, *J* = 5.2 Hz, 0.5H), 3.39 (dd, *J* = 10.9, 4.7 Hz, 0.5H), 3.31 (dd, *J* = 11.0, 4.9 Hz, 0.5H), 2.81 (d, *J* = 3.8 Hz, 0.5H), 2.57 (m, 0.5H), 2.14 (ddd, *J* = 18.8, 6.2, 6.2 Hz, 0.5H), 2.02 (m, 0.5H), 1.86-1.67 (m, 4H), 1.57-1.46 (m, 2H), 1.32 (s, 1.5H), 1.13 (s, 1.5H), 0.96 (s, 1.5H), 0.92 (s, 1.5H), 0.89 (s, 9H), 0.82 (s, 1.5H), 0.78 (s, 1.5H), and 0.05 (s, 6H).

(1S*,2S*,4S*)-4-(*tert*-Butyldimethylsilyloxy)-1,3,3-trimethyl-2-(3-methylpenta-2,4-dienyl)cyclohexanol (496)



To a mixture of the phosphine oxide (62 mg, 0.24 mmol) and HMPA (86 µL, 0.48 mmol) in THF (1 mL) at -78 ºC was added *n*BuLi (2.09 M in hexanes, 110 µL, 0.24 mmol). After stirring for 20 min at -78 ºC, the lactol **495** (dissolved in 0.5 mL of THF, 15 mg, 0.048 mmol) was added dropwise to this mixture. After stirring for 1 h at -78 ºC, the mixture was warmed to 0 ºC and stirred overnight, warming to rt as the ice bath melted. The reaction was quenched with water, and the mixture was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give diene **496** (1.9 mg, 0.0054 mmol, 11% yield from crude lactol, 8% yield over 2 steps 1.3:1 *E*:*Z*).

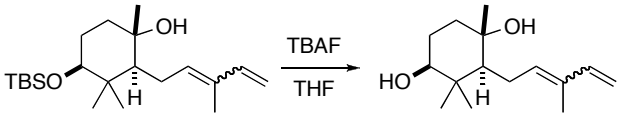
496E

^{1}H NMR (500 MHz, $CDCl_3$): 6.35 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.62 (t, *J* = 7.2 Hz, 1H), 5.08 (d, *J* = 17.4 Hz, 1H), 4.93 (d, *J* = 10.7 Hz, 1H), 3.29 (m, 1H), 2.40 (ddd, *J* = 15.6, 7.8, 7.8 Hz, 1H), 2.28 (ddd, *J* = 15.8, 5.6, 5.6 Hz, 1H), 1.81 (s, 3H), 1.70 (m, 1H), 1.60 (m, 1H), 1.48 (m, 2H), 1.41 (m, 1H), 1.21 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.80 (s, 3H), 0.05 (s, 3H), and 0.04 (s, 3H).

496Z

^{1}H NMR (500 MHz, $CDCl_3$): 6.88 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.52 (t, *J* = 7.6 Hz, 1H), 5.23 (d, *J* = 17.3 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 3.29 (m, 1H), 2.48 (ddd, *J* = 15.8, 7.9, 7.9 Hz, 1H), 2.28 (ddd, *J* = 15.8, 5.6, 5.6 Hz, 1H), 1.81 (s, 3H), 1.70 (m, 1H), 1.60 (m, 1H), 1.48 (m, 2H), 1.41 (m, 1H), 1.21 (s, 3H), 0.97 (s, 3H), 0.89 (s, 9H), 0.79 (s, 3H), 0.05 (s, 3H), and 0.04 (s, 3H).

(1S*,2S*,4S*)-1,3,3-Trimethyl-2-(3-methylpenta-2,4-dienyl)cyclohexane-1,4-diol (496b)



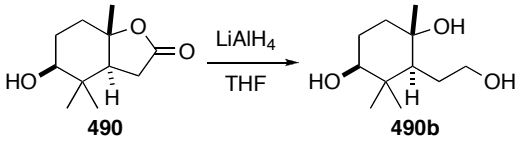
496 **496b**

To a mixture of diene **496** (1.9 mg, 0.0054 mmol) in THF (0.1 mL) was added TBAF (1.0 M in THF, 11 μL, 0.011 mmol) at rt. After stirring overnight, the mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the diol **496b** as an oil (1.4 mg, 0.0059 mmol, 104% crude yield).

^{1}H NMR of both diastereomers (500 MHz, $CDCl_3$): 6.88 (ddd, *J* = 17.3, 10.9, 0.9 Hz, 1H), 6.36 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.62 (t, *J* = 7.4 Hz, 1H), 5.52 (t, *J* = 7.5 Hz, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.15 (dt, *J* = 10.8, 1.7 Hz, 1H), 5.09 (d, *J* = 17.4 Hz, 1H), 4.93 (d, *J* = 10.7 Hz, 1H), 3.36 (br s, 1H), 3.34 (br s, 1H), 2.50 (ddd, *J* = 15.9, 8.1, 8.1 Hz,

1H), 2.42 (ddd, *J* = 15.6, 7.8, 7.8 Hz, 1H), 2.29 (dt, *J* = 15.8, 5.4 Hz, 2H), 1.81 (s, 6H), 1.74 (m, 4H), 1.51 (m, 4H), 1.44 (ddd, *J* = 7.4, 7.4, 4.4 Hz, 2H), 1.22 (s, 6H), 1.06 (s, 3H), 1.05 (s, 3H), 0.833 (s, 3H), and 0.826 (s, 3H).

(1S*,2S*,4S*)-2-(2-Hydroxyethyl)-1,3,3-trimethylcyclohexane-1,4-diol (490b)

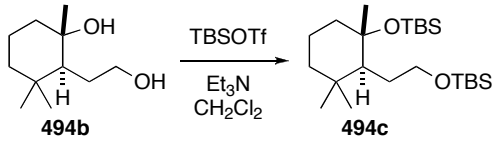


490 **490b**

To a mixture of lactone **490** (1.15 g, 5.8 mmol) in THF (29 mL) at 0 ºC was added $LiAlH_4$ (1.1 g, 29 mmol). After stirring overnight at rt, the reaction was quenched by adding water (2 mL), then 3M NaOH (2 mL), and then more water (4 mL). The mixture was filtered through a pad of celite, and EtOAc was used to rinse. The filtrate was concentrated under reduced pressure to give the triol **490b** as an oil (601 mg, 3.0 mmol, 52% crude yield).

^{1}H NMR (500 MHz, $CDCl_3$): 3.83 (ddd, *J* = 10.4, 4.5, 4.5 Hz, 1H), 3.55 (ddd, *J* = 10.4, 9.2, 3.5 Hz, 1H), 3.43 (m, 1H), 1.93 (ddd, *J* = 13.2, 13.2, 4.0 Hz, 1H), 1.87-1.62 (m, 5H), 1.59 (ddd, *J* = 12.4, 3.4, 3.4 Hz, 1H), 1.24 (s, 3H), 1.02 (s, 3H), and 0.84 (s, 3H).

***tert*-Butyl(2-((1S*,2S*)-2-(*tert*-butyldimethylsilyloxy)-2,6,6-trimethylcyclohexyl)ethoxy)dimethylsilane (494c)**



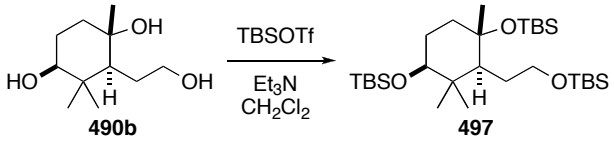
494b **494c**

To a mixture of diol **494b**[95] (792 mg, 4.25 mmol) and Et_3N (1.83 mL, 13.1 mmol) in CH_2Cl_2 (22 mmol) at 0 ºC was added TBSOTf (2.93 mL, 12.8 mmol) dropwise. After stirring for overnight at rt, methanol (small amount to quench excess TBSOTf) and then water were added to the mixture, which was then extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and

concentrated under reduced pressure to give the bis-TBS ether **494c** as an oil (1.96 g). This crude material was taken on directly to the next step.

^{1}H NMR (500 MHz, $CDCl_3$): 3.71 (ddd, *J* = 10.8, 9.4, 5.8 Hz, 1H), 3.53 (ddd, *J* = 11.0, 9.3, 5.5 Hz, 1H), 1.82-1.75 (m, 3H), 1.53-1.32 (m, 6H), 1.19 (s, 3H), 1.01 (t, *J* = 4.6 Hz, 1H), 0.89 (s, 9H), 0.864 (s, 3H), 0.860 (s, 9H), 0.81 (s, 3H), 0.07 (s, 6H), 0.05 (s, 3H), and 0.04 (s, 3H).

((1S*,2S*,4S*)-2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-1,3,3-trimethylcyclohexane-1,4-diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (497)

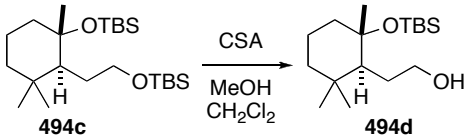


490b **497**

To a mixture of triol **490b** (178 mg, 0.88 mmol) and Et_3N (455 µL, 3.26 mmol) in CH_2Cl_2 (4.4 mmol) at 0 ºC was added TBSOTf (728 µL, 3.17 mmol) dropwise. After stirring for overnight at rt, methanol (small amount to quench excess TBSOTf) and then water were added to the mixture, which was then extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the tris-TBS ether **497** as an oil (419 mg, 0.77 mmol, 88% crude yield).

^{1}H NMR (500 MHz, $CDCl_3$): 3.70 (ddd, *J* = 10.7, 9.4, 5.9 Hz, 1H), 3.51 (ddd, *J* = 11.2, 9.4, 5.5 Hz, 1H), 3.30 (t, *J* = 3.0 Hz, 1H), 2.01 (m, 1H), 1.77 (dddd, *J* = 13.2, 10.8, 5.9, 4.7 Hz, 1H), 1.66 (m, 1H), 1.54 (m, 1H), 1.48 (m, 2H), 1.41 (m, 1H), 1.18 (d, *J* = 0.9 Hz, 3H), 0.92 (s. 3H), 0.91 (s, 9H), 0.89 (s, 12H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.044 (s, 3H), 0.042 (s, 3H), 0.033 (s, 3H), and 0.030 (s, 3H).

2-((1S*,2S*)-2-(*tert*-Butyldimethylsilyloxy)-2,6,6-trimethylcyclohexyl)ethanol (494d)

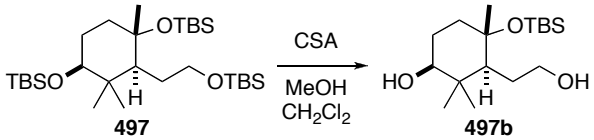


494c **494d**

To a mixture of crude bis-TBS ether **494c** (4.25 mmol) in CH_2Cl_2 (28 mL) was added CSA (198 mg, 0.85 mmol, dissolved in 14 mL of MeOH) at rt. After stirring for 3 h, saturated aq. $NaHCO_3$ was added to the mixture, which was then extracted with CH_2Cl_2 (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give alcohol **494d** (121 mg, 0.40 mmol, 9% yield over two steps, other impure MPLC fractions contained some of the alcohol **494d**).

^{1}H NMR (500 MHz, $CDCl_3$): 3.66 (ddd, *J* = 10.1, 10.1, 5.9 Hz, 1H), 3.58 (ddd, *J* = 10.2, 10.2, 6.9 Hz, 1H), 1.85 (dddd, *J* = 14.5, 9.9, 6.0, 4.7 Hz, 1H), 1.79-1.70 (m, 2H), 1.56 (dddd, *J* = 14.5, 9.9, 6.6, 3.1 Hz, 1H), 1.40 (dddd, *J* = 12.9, 3.1, 3.1, 1.9 Hz, 1H), 1.33 (m, 1H), 1.27 (m, 1H), 1.19 (s, 3H), 1.13 (ddd, *J* = 13.2, 13.2, 3.5 Hz, 1H), 0.96 (s, 3H), 0.89 (s, 9H), 0.84 (s, 3H), 0.71 (dd, *J* = 4.7, 3.0 Hz, 1H), 0.104 (s, 3H), and 0.100 (s, 3H).

(1S*,3S*,4S*)-4-(*tert*-Butyldimethylsilyloxy)-3-(2-hydroxyethyl)-2,2,4-trimethylcyclohexanol (497b)



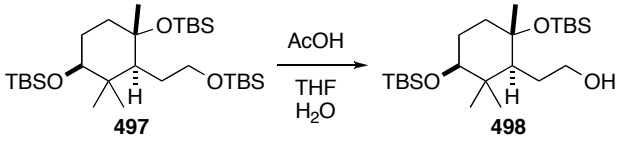
497 **497b**

To a mixture of crude tris-TBS ether **497** (0.88 mmol) in CH_2Cl_2 (6 mL) was added CSA (21 mg, 0.09 mmol) dissolved in 3 mL of MeOH) at rt. After stirring for 3 h, saturated aq. $NaHCO_3$ was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by

MPLC to give diol **497b** (114 mg, 0.36 mmol, 41% yield from crude tris-TBS ether, 27% yield over three steps).

^{1}H NMR (500 MHz, $CDCl_3$): 3.80 (ddd, *J* = 10.5, 4.6, 4.6 Hz, 1H), 3.53 (ddd, *J* = 10.4, 9.3, 3.8 Hz, 1H), 3.35 (dd, *J* = 3.4, 2.0 Hz, 1H), 1.97 (m, 1H), 1.77-1.49 (m, 6H), 1.23 (s, 3H), 0.91 (s, 12H), 0.80 (s, 3H), 0.05 (s, 3H), and 0.04 (s, 3H).

2-((1S*,3S*,6S*)-3,6-Bis(*tert*-butyldimethylsilyloxy)-2,2,6-trimethylcyclohexyl)ethanol (498)

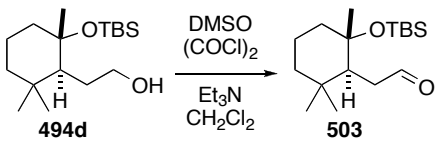


497 **498**

To a mixture of tris-TBS ether **497** (117 mg, 0.215 mmol) in THF (4.4 mL) and H_2O (1.1 mL) was added AcOH (1.1 mL) at rt. After stirring for 4 days, the mixture was diluted with water and then extracted with Et_2O (3x). The combined organic layers were washed with saturated aq. $NaHCO_3$, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (9:1 hexanes:EtOAc) to give alcohol **498** (61.6 mg, 0.143 mmol, 67% yield, 79% yield brsm).

^{1}H NMR (500 MHz, $CDCl_3$): 3.66 (m, 1H), 3.58 (m, 1H), 3.32 (dd, *J* = 3.5, 1.9 Hz, 1H), 2.09 (m, 1H), 1.77-1.65 (m, 3H), 1.57-1.48 (m, 3H), 1.22 (s, 3H), 0.91 (s, 9H), 0.883 (s, 3H), 0.877 (s, 9H), 0.81 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), and 0.03 (s, 3H).

2-((1S*,2S*)-2-(*tert*-Butyldimethylsilyloxy)-2,6,6-trimethylcyclohexyl)ethanal (503)



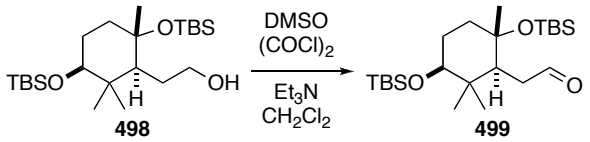
494d **503**

To a mixture of $(COCl)_2$ (19 μL, 0.22 mmol) in CH_2Cl_2 (0.6 mL) at – 78 ºC was added DMSO (36 μL, 0.50 mmol dissolved in 0.15 mL of CH_2Cl_2). After 20 min,

alcohol **494d** (57 mg, 0.19 mmol dissolved in 0.25 mL of CH_2Cl_2) was added dropwise to the reaction mixture. After 30 min, Et_3N (132 μL, 0.95 mmol) was added to the mixture, which was then allowed to warm to rt. After 1 h, the mixture was diluted with CH_2Cl_2, and then washed with water, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (30:1 hexanes:EtOAc) to give aldehyde **503** (40 mg, 0.13 mmol, 68% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 9.84 (dd, *J* = 2.0, 1.2 Hz, 1H), 2.77 (ddd, *J* = 18.9, 6.0, 2.0 Hz, 1H), 2.39 (ddd, *J* = 18.9, 3.3, 1.2 Hz, 1H), 1.77 (m, 1H), 1.72 (m, 1H), 1.44 (dddd, *J* = 12.9, 3.0, 3.0, 1.9 Hz, 1H), 1.38 (m, 2H), 1.23 (m, 2H), 1.07 (s, 3H), 0.94 (s, 3H), 0.89 (s, 9H), 0.79 (s, 3H), 0.104 (s, 3H), and 0.097 (s, 3H).

2-((1S*,3S*,6S*)-3,6-Bis(*tert*-butyldimethylsilyloxy)-2,2,6-trimethylcyclohexyl)ethanal (499)



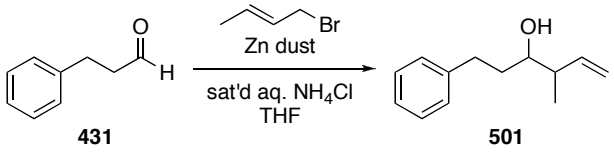
498 **499**

To a mixture of $(COCl)_2$ (244 μL, 2.88 mmol) in CH_2Cl_2 (4.8 mL) at – 78 ºC was added DMSO (470 μL, 6.62 mmol dissolved in 1.2 mL of CH_2Cl_2). After 20 min, alcohol **498** (829 mg, 1.92 mmol dissolved in 2 mL of CH_2Cl_2) was added dropwise to the reaction mixture. After 30 min, Et_3N (1.8 mL, 12.7 mmol) was added to the mixture, which was then allowed to warm to rt. After 1 h, the mixture was diluted with CH_2Cl_2 and then washed with water, washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (30:1 hexanes:EtOAc) to give aldehyde **499** (552 mg, 1.29 mmol, 67% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 9.62 (t, *J* = 2.9 Hz, 1H), 3.36 (dd, *J* = 3.6, 2.0 Hz, 1H), 2.56 (ddd, *J* = 15.8, 6.4, 2.9 Hz, 1H), 2.47 (t, *J* = 2.5 Hz, 1H), 2.23 (ddd, *J* = 15.8, 6.1, 3.0

Hz, 1H), 2.13 (m, 1H), 1.70 (dddd, J = 15.0, 15.0, 4.2, 1.9 Hz, 1H), 1.55 (m, 2H), 1.17 (s, 3H), 0.93 (s, 9H), 0.841 (s, 3H), 0.836 (s, 9H), 0.81 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.050 (s, 3H), and 0.045 (s, 3H).

4-Methyl-1-phenylhex-5-en-3-ol (501)

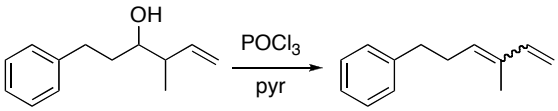


431 **501**

To a mixture of aldehyde **431** (134 mg, 1.0 mmol) in THF (10 mL) at 0 ºC was added Zn dust (327 mg, 5.0 mmol) and crotyl bromide (80% w/w, 258 μL, 2.0 mmol). Then, saturated aq. NH_4Cl (5 mL) was added slowly to the mixture over 10 min. After stirring at 0 ºC for 2 h, the mixture was allowed to warm to rt and then filtered through a pad of celite and rinsed with EtOAc. The filtrate was diluted with EtOAc and washed with aq. 2N HCl, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give alcohol **501** as an oil (194 mg, 1.0 mmol, 100% crude yield).

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[111]

(4-Methylhexa-3,5-dienyl)benzene (433)



501 **433**

To a mixture of alcohol **501** (194 mg, 1.0 mmol) in pyridine (5 mL) was added $POCl_3$ (458 μL, 5.0 mmol) at rt. After stirring overnight, the remaining $POCl_3$ was quenched by slowly adding wet Et_2O. The mixture was diluted with Et_2O and washed with water, washed with saturated aq. $CuSO_4$ (2x), washed with brine, dried over

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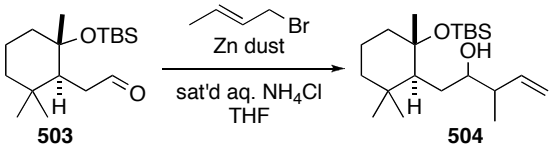
[111] "New and Stereoselective Synthesis of 1,4-Disubstituted Buten-4-ols (Homoallylic Alcohol α-Adducts) from the Corresponding γ-Isomers (3,4-Disubstituted Buten-4-ols) via an Acid-Catalyzed Allyl-Transfer Reaction with Aldehydes," Sumida, S.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310–1313.

Na_2SO_4, filtered, and concentrated under reduced pressure to give the diene **433** as an oil (124 mg, 0.72 mmol, 72% crude yield, 1:0.8 *E*:*Z*).

^{1}H NMR (500 MHz, $CDCl_3$): Matched reported data.[84]

1-((1S*,2S*)-2-(*tert*-Butyldimethylsilyloxy)-2,6,6-trimethylcyclohexyl)-3-methylpent-4-en-2-ol (504)

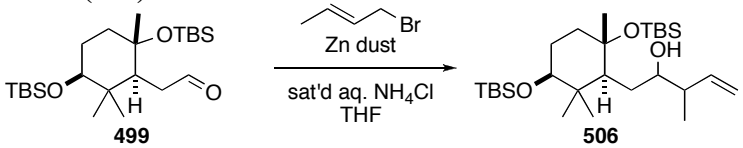


503 **504**

To a mixture of aldehyde **503** (26.3 mg, 0.088 mmol) in THF (2 mL) at 0 ºC was added Zn dust (29 mg, 0.44 mmol) and crotyl bromide (80% w/w, 23 μL, 0.18 mmol). Then, saturated aq. NH_4Cl (1 mL) was added slowly to the mixture over 10 min. After stirring at 0 ºC for 2 h, the mixture was allowed to warm to rt and then filtered through a pad of celite and rinsed with EtOAc. The filtrate was diluted with EtOAc and washed with aq. 2N HCl, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the alcohol **504** as an oil (32 mg, 0.090 mmol, 102% crude yield).

^{1}H NMR of all 4 diastereomers (500 MHz, $CDCl_3$): 5.86-5.75 (m, 1H), 5.15-5.07 (m, 2H), 3.55-3.43 (m, 1H), 2.36-2.19 (m, 1H), 1.96-1.89 (m, 0.65H), 1.80-1.69 (m, 2.35H), 1.58-1.54 (m, 1H), 1.42-1.31 (m, 3H), 1.29-1.24 (m, 2H), 1.22 (s, 1H), 1.19 (s, 1H), 1.18 (s, 1H), 1.09 (d, J = 2.7 Hz, 1H), 1.08 (d, J = 3.5 Hz, 1H), 1.06 (d, J = 3.5 Hz, 1H), 0.91 (s, 1H), 0.90 (s, 1H), 0.89 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.86 (s, 1H), 0.85 (s, 1H), 0.835 (s, 1H), 0.830 (s, 1H), 0.101 (s, 1H), 0.097 (s, 1H), and 0.09 (s, 4H).

1-((1S*,3S*,6S*)-3,6-Bis(*tert*-butyldimethylsilyloxy)-2,2,6-trimethylcyclohexyl)-3-methylpent-4-en-2-ol (506)

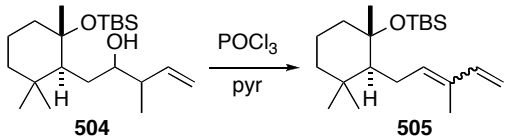


499 **506**

To a mixture of the aldehyde **499** (545 mg, 1.27 mmol) in THF (20 mL) at 0 ºC was added Zn dust (598 mg, 9.15 mmol) and crotyl bromide (80% w/w, 471 μL, 3.66 mmol). Then, saturated aq. NH_4Cl (10 mL) was added slowly to the mixture over 10 min. After stirring at 0 ºC for 2 h, the mixture was allowed to warm to rt and then filtered through a pad of celite and rinsed with EtOAc. The filtrate was diluted with EtOAc and washed with aq. 2N HCl, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the alcohol **506** as an oil (577 mg, 1.19 mmol, 94% crude yield).

^{1}H NMR of all 4 diastereomers (500 MHz, $CDCl_3$): 5.92-5.77 (m, 1H), 5.07-4.99 (m, 2H), 3.85-3.76 (m, 1H), 3.31 (m, 1H), 2.32-2.08 (m, 2H), 2.02-1.94 (m, 1H), 1.73-1.29 (m, 4H), 1.27 (s, 3H), 1.08-1.05 (m, 3H), 0.93-0.86 (m, 21 H), 0.78 (m, 3H), 0.15 (s, 1.5H), 0.09 (s, 1.5H), and 0.03 (s, 3H).

***tert*-Butyldimethyl((1S*,2S*)-1,3,3-trimethyl-2-(3-methylpenta-2,4-dienyl)cyclohexyloxy)silane (505)**



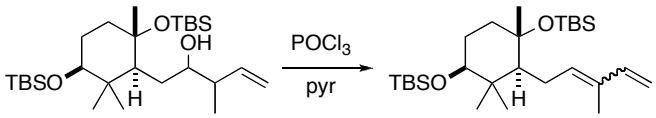
504 **505**

To a mixture of the crude alcohol **504** (0.088 mmol) in pyridine (0.5 mL) was added $POCl_3$ (40 μL, 0.44 mmol) at rt. After stirring overnight, the remaining $POCl_3$ was quenched by slowly adding wet Et_2O. The mixture was diluted with Et_2O and washed with water, washed with saturated aq. $CuSO_4$ (2x), washed with brine, dried over

Na_2SO_4, filtered, and concentrated under reduced pressure to give the diene **505** as an oil (27.5 mg, 0.082 mmol, 93% crude yield over 2 steps, 1:0.9 *E*:*Z*).

^{1}H NMR of both *E* and *Z* isomers (500 MHz, $CDCl_3$): 6.87 (dd, *J* = 17.3, 10.8 Hz, 1H), 6.35 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.49 (t, *J* = 7.3 Hz, 1H), 5.37 (t, *J* = 7.2 Hz, 1H), 5.17 (d, *J* = 17.3 Hz, 1H), 5.08 (d, *J* = 11.1 Hz, 1H), 5.05 (d, *J* = 18.1 Hz, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 2.50 (m, 2H), 2.13 (m, 2H), 1.79 (s, 3H), 1.77 (s, 3H), 1.76-1.70 (m, 4H), 1.42-1.25 (m, 10H), 1.16 (s, 3H), 1.15 (s, 3H), 0.96 (s, 6H), 0.91 (s, 18H), 0.85 (s, 6H), and 0.10 (s, 6H).

((1S*,2S*,4S*)-1,3,3-Trimethyl-2-(3-methylpenta-2,4-dienyl)cyclohexane-1,4-diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (500)



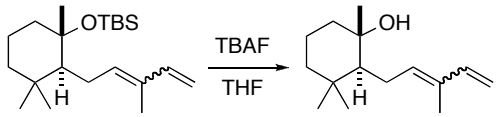
506 **500**

To a mixture of the alcohol **506** (590 mg, 1.22 mmol) in pyridine (6.1 mL) was added $POCl_3$ (560 μL, 6.1 mmol) at rt. After stirring overnight, the remaining $POCl_3$ was quenched by slowly adding wet Et_2O. The mixture was diluted with Et_2O and washed with water, washed with saturated aq. $CuSO_4$ (2x), washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil (387 mg, 0.83 mmol, 68% crude yield, NMR has decent purity (~75%), 1:3.1 *E*:*Z*). The crude oil was purified by MPLC to give the diene **500** (73.3 mg, 0.16 mmol, 13% yield, the yield is low due to significant decomposition believed to have occurred as the crude oil sat overnight, perhaps trace acid remained).

^{1}H NMR of both *E* and *Z* isomers (500 MHz, $CDCl_3$): 6.86 (dd, *J* = 17.3, 10.8 Hz, 1H), 6.35 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.51 (dd, *J* = 8.4, 5.6 Hz, 1H), 5.40 (t, *J* = 7.0 Hz, 1H), 5.14 (d, *J* = 17.3 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 5.00 (d, *J* = 17.4 Hz, 1H), 4.85 (d, *J*

= 10.7 Hz, 1H), 3.27 (m, 2H), 2.43 (br d, *J* = 16.1 Hz, 2H), 2.26 (ddd, *J* = 16.4, 8.2, 8.2 Hz, 2H), 2.08 (ddd, *J* = 14.6, 14.6, 5.0 Hz, 2H), 1.89 (dd, *J* = 7.9, 2.7 Hz, 1H), 1.86 (dd, *J* = 7.8, 3.0 Hz, 1H), 1.77 (s, 3H), 1.75 (s, 3H), 1.67 (m, 2H), 1.52-1.44 (m, 4H), 1.15 (s, 6H), 0.92 (s, 9H), 0.90 (s, 3H), 0.833 (s, 9H), 0.829 (s, 3H), 0.82 (s, 3H), 0.80 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), and 0.02 (s, 3H).

(1S*,2S*)-1,3,3-Trimethyl-2-(3-methylpenta-2,4-dienyl)cyclohexanol (506)

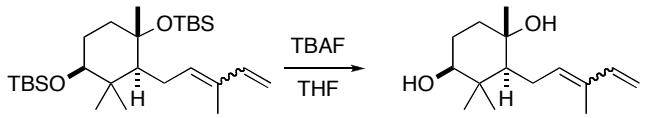


505 **506**

To a mixture of the crude diene **505** (0.088 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 176 μL, 0.176 mmol), and the mixture was heated to reflux. After stirring overnight, the mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (9:1 hexanes:EtOAc) to give the alcohol **506** (11.3 mg, 0.051 mmol, 58% yield over 3 steps, other impure MPLC fractions contained some alcohol **XX**).

^{1}H NMR of both *E* and *Z* isomers (500 MHz, $CDCl_3$): 6.88 (dd, *J* = 17.3, 10.8 Hz, 1H), 6.35 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.49 (t, *J* = 7.0 Hz, 1H), 5.38 (t, *J* = 7.2 Hz, 1H), 5.19 (d, *J* = 17.3 Hz, 1H), 5.10 (d, *J* = 11.1 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 4.91 (d, *J* = 10.7 Hz, 1H), 2.51-2.38 (m, 2H), 2.25-2.16 (m, 2H), 1.80 (s, 3H), 1.79 (s, 3H), 1.73 (m, 2H), 1.62 (m, 2H), 1.45-1.35 (m, 6H), 1.20 (m, 2H), 1.14 (s, 3H), 1.13 (s, 3H), 1.10 (m, 2H), 0.994 (s, 3H), 0.988 (s, 3H), and 0.89 (s, 6H).

(1S*,2S*,4S*)-1,3,3-Trimethyl-2-(3-methylpenta-2,4-dienyl)cyclohexane-1,4-diol (489)

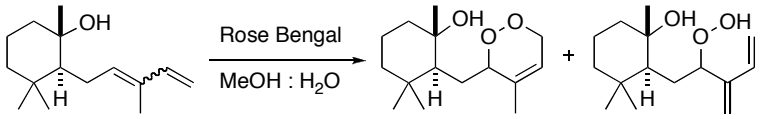


500 **489**

To a mixture of the diene **500** (46.6 mg, 0.10 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 300 μL, 0.30 mmol), and the mixture was heated to reflux. After stirring for 2 h, the mixture was diluted with water and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the diol **489** (17.5 mg, 0.073 mmol, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$): Reported above.

(1S*,2S*)-1,3,3-Trimethyl-2-((4-methyl-3,6-dihydro-1,2-dioxin-3-yl)methyl)cyclohexanol (508)



506 **508** **507**

To a mixture of the diene **506** (10 mg, 0.045 mmol) in MeOH / H_2O (4:1, 0.5 mL) in a screw-cap culture tube was added rose bengal (5 mg, 0.005 mmol). The mixture was saturated with O_2 by bubbling with O_2 for one minute. Then, the headspace was flushed with O_2, and the cap was immediately screwed on. The cap was sealed by wrapping it with Teflon tape. The mixture was irradiated (175W mercury vapor lamp) for 1 h and allowed to be warmed by the light source. After cooling to rt, water was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (4:1 hexanes:EtOAc) to give various mixed fractions. The third fraction (other fractions contained products, but this one

contained the endoperoxide, so it was further purified) was repurified by MPLC (5:1 hexanes:EtOAc) to give endoperoxide **508** (1.5 mg, 0.0059 mmol, 13% yield) and diene **507** (1.6 mg, 0.0063 mmol, 14% yield).

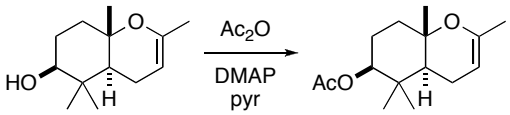
Endoperoxide **508**

^{1}H NMR (500 MHz, $CDCl_3$): 5.60 (m, 1H), 4.66 (dq, *J* = 16.0, 2.0 Hz, 1H), 4.33 (br d, *J* = 16.3 Hz, 1H), 4.14 (br d, *J* = 7.8 Hz, 1H), 1.93 (m, 1H), 1.81 (s, 3H), 1.78-1.60 (m, 2H), 1.49-1.39 (m, 2H), 1.36-1.20 (m, 2H), 1.29 (s, 3H), 1.06 (s, 3H), 0.92-0.85 (m, 2H), and 0.91 (s, 3H).

Hydroperoxide **507**

^{1}H NMR (500 MHz, $CDCl_3$): 7.84 (s, 1H), 6.38 (dd, *J* = 17.8, 11.3 Hz, 1H), 5.57 (d, *J* = 17.7 Hz, 1H), 5.30 (br s, 1H), 5.25 (br s, 1H), 5.19 (d, *J* = 11.2 Hz, 1H), 4.70 (dd, *J* = 10.2, 3.8 Hz, 1H), 1.85 (ddd, *J* = 15.9, 6.0, 3.8 Hz, 1H), 1.76-1.69 (m, 1H), 1.64-1.57 (m, 2H), 1.47-1.40 (m, 3H), 1.34 (dd, *J* = 6.1, 2.3 Hz, 1H), 1.21 (s, 3H), 0.929 (s, 3H), 0.925 (s, 3H), and 0.89-0.83 (m, 1H).

(4S*,6S*,8S*)-2,5,5,8a-Tetramethyl-4a,5,6,7,8,8a-hexahydro-4H-chromen-6-yl ethanoate (512)



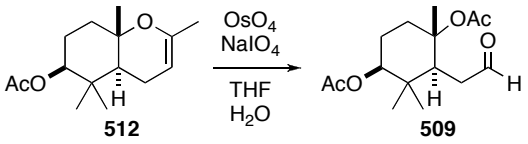
511b **512**

To a mixture of alcohol **511b** (87 mg, 0.41 mmol) and DMAP (5 mg, 0.041 mmol) in pyridine (2.1 mL) was added Ac_2O (59 μL, 0.62 mmol) at rt. After stirring overnight, water was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with saturated aq. $CuSO_4$ (2x), washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The

crude oil was purified by MPLC (9:1 hexanes:EtOAc) to give acetate **512** (89 mg, 0.35 mmol, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$): 4.59 (dd, *J* = 11.6, 4.2 Hz, 1H), 4.46 (ddq, *J* = 5.2, 2.2, 1.1 Hz, 1H), 2.06 (s, 3H), 1.87 (m, 4H), 1.69 (dt, *J* = 1.1, 1.1 Hz, 3H), 1.65 (m, 1H), 1.56 (m, 1H), 1.51 (dd, *J* = 11.8, 5.6 Hz, 1H), 1.19 (d, *J* = 0.9 Hz, 3H), 0.90 (s, 3H), and 0.86 (s, 3H).

(1S*,2S*,4S*)-1,3,3-Trimethyl-2-(2-oxoethyl)cyclohexane-1,4-diyl diethanoate (509)

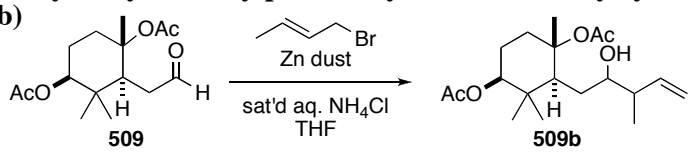


512 **509**

To a solution of the acetate **512** (108 mg, 0.43 mmol) in THF (2.2 mL) and H_2O (0.55 mL) was added $NaIO_4$ (471 mg, 2.2 mmol) and OsO_4 (0.2% w/w solution in H_2O, 0.55 mL, 0.0043 mmol) at rt. After stirring for 7 h, the mixture was filtered through a cotton plug and diluted with Et_2O. The filtrate was washed with H_2O (3x), washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (6:1 hexanes:EtOAc) to give the aldehyde **509** (58 mg, 0.20 mmol, 47% yield, there may have been some decomposition during MPLC because the crude mass and purity by NMR indicated the yield should have been ~80-90%).

^{1}H NMR (500 MHz, $CDCl_3$): 9.67 (dd, *J* = 4.0, 1.2 Hz, 1H), 4.67 (dd, *J* = 11.5, 4.2 Hz, 1H), 2.76 (ddd, *J* = 13.2, 3.5, 3.5 Hz, 1H), 2.53 (ddd, *J* = 16.3, 8.3, 4.0 Hz, 1H), 2.43 (ddd, *J* = 16.4, 3.9, 1.3 Hz, 1H), 2.35 (dd, *J* = 8.2, 4.0 Hz, 1H), 2.07 (s, 3H), 1.90 (s, 3H), 1.86 (dq, *J* = 13.4, 4.1 Hz, 1H), 1.76 (tdd, *J* = 13.5, 4.0, 0.9 Hz, 1H), 1.54 (d, *J* = 0.8 Hz, 3H), 1.53 (ddd, *J* = 13.6, 3.6, 2.1 Hz, 1H), 0.95 (s, 3H), and 0.91 (s, 3H).

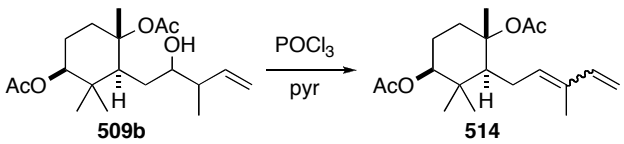
(1S*,2S*,4S*)-2-(2-Hydroxy-3-methylpent-4-enyl)-1,3,3-trimethylcyclohexane-1,4-diyl diethanoate (509b)



To a mixture of the aldehyde **509** (512 mg, 1.8 mmol) in THF (36 mL) at 0 ºC was added Zn dust (589 mg, 9.0 mmol) and crotyl bromide (80% w/w, 436 μL, 3.6 mmol). Then, saturated aq. NH_4Cl (18 mL) was added slowly to the mixture over 20 min. After stirring at 0 ºC for 3 h, the mixture was allowed to warm to rt and then filtered through a pad of celite and rinsed with EtOAc. The filtrate was diluted with EtOAc and washed with aq. 2N HCl, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the alcohol **509b** as an oil (514 mg, 1.5 mmol, 83% crude yield).

^{1}H NMR of all 4 diastereomers (500 MHz, $CDCl_3$): 5.81 (m, 1H), 5.11 (m, 2H), 4.63 (m, 1H), 3.70 (ddd, *J* = 10.1, 5.5, 2.8 Hz, 0.3H), 3.66 (ddd, *J* = 10.3, 5.6, 2.6 Hz, 0.3H), 3.50 (ddd, *J* = 10.4, 3.9, 2.4 Hz, 0.2H), 3.42 (dd, *J* = 10.1, 5.4 Hz, 0.2H), 2.79 (m, 1H), 2.50 (m, 1H), 2.28 (m, 1H), 2.10 (s, 0.6H), 2.08 (s, 0.6H), 2.06 (s, 0.9H), 2.05 (s, 0.9H), 2.00 (s, 1.2H), 1.96 (s, 0.9H), 1.95 (s, 0.9H), 1.92-1.47 (m, 5H), 1.564 (s, 0.9H), 1.555 (s, 0.9H), 1.53 (s, 1.2H), 1.10 (d, *J* = 3.8 Hz, 0.6H), 1.09 (d, *J* = 1.7 Hz, 0.9H), 1.08 (d, *J* = 1.9 Hz, 0.6H), 1.07 (d, *J* = 1.9 Hz, 0.9H), 0.973 (s, 0.6H), 0.967 (s, 0.9H), 0.96 (s, 1.5H), 0.91 (s, 0.6H), 0.90 (s, 0.6H), and 0.88 (s, 1.8H).

(1S*,2S*,4S*)-1,3,3-Trimethyl-2-(3-methylpenta-2,4-dienyl)cyclohexane-1,4-diyl diethanoate (514)



To a mixture of the crude alcohol **509b** (1.5 mmol) in pyridine (18 mL) was added $POCl_3$ (824 μL, 9.0 mmol) at rt. After stirring overnight, the remaining $POCl_3$ was quenched by slowly adding wet Et_2O. The mixture was diluted with Et_2O and washed with water, washed with saturated aq. $CuSO_4$ (2x), washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the diene **514** as an oil (291 mg, 0.90 mmol, 50% crude yield over 2 steps, 1:1 *E*:*Z*).

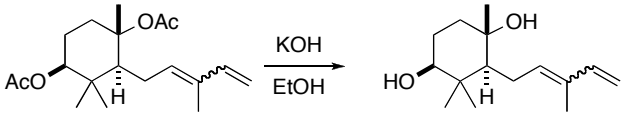
514E

^{1}H NMR (500 MHz, $CDCl_3$): 6.35 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.53 (t, *J* = 7.1 Hz, 1H), 5.06 (d, *J* = 17.6 Hz, 1H), 4.91 (d, *J* = 10.7 Hz, 1H), 4.61 (ddd, *J* = 11.4, 4.1, 3.2 Hz, 1H), 2.52 (dt, *J* = 13.2, 3.8 Hz, 1H), 2.34 (m, 2H), 2.05 (s, 3H), 1.96 (t, *J* = 5.4 Hz, 1H), 1.88 (s, 3H), 1.81 (m, 2H), 1.77 (q, *J* = 1.1 Hz, 3H), 1.56 (m, 1H), 1.51 (d, *J* = 0.9 Hz, 3H), and 0.94 (s, 6H).

514Z

^{1}H NMR (500 MHz, $CDCl_3$): 6.84 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.42 (t, *J* = 7.5 Hz, 1H), 5.20 (d, *J* = 17.3 Hz, 1H), 5.09 (d, *J* = 11.5 Hz, 1H), 4.65 (dd, *J* = 11.6, 4.9 Hz, 1H), 2.52 (m, 1H), 2.34 (m, 2H), 2.08 (s, 3H), 1.96 (m, 1H), 1.90 (s, 3H), 1.81 (m, 2H), 1.80 (q, *J* = 1.4 Hz, 3H), 1.56 (m, 1H), 1.51 (s, 3H), 0.97 (s, 3H), and 0.96 (s, 3H).

(1S*,2S*,4S*)-1,3,3-Trimethyl-2-(3-methylpenta-2,4-dienyl)cyclohexane-1,4-diol (489)



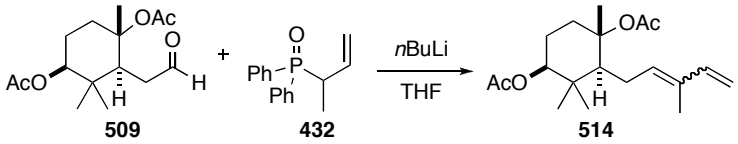
514 **489**

To a mixture of the crude diacetate **514** (0.90 mmol) in EtOH (9 mL) was added KOH (898 mg, 16 mmol) at rt. After stirring overnight, saturated aq. $NaHCO_3$ was added to the mixture, which was then extracted with EtOAc (3x). The combined organic layers

were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (2:1 hexanes:EtOAc) to give the diol **489** (122 mg, 0.51 mmol, 28% yield over 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$): Reported above.

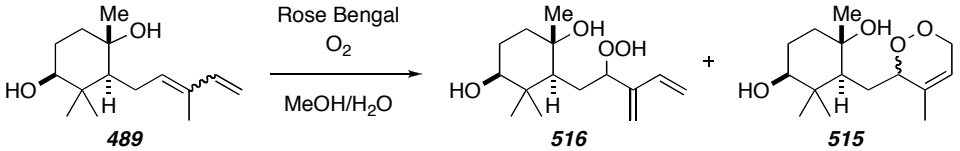
(1S*,2S*,4S*)-1,3,3-Trimethyl-2-(3-methylpenta-2,4-dienyl)cyclohexane-1,4-diyl diethanoate (514)



To a mixture of phosphine oxide **432**[83] (154 mg, 0.60 mmol) in THF (4 mL) at -78 ºC was added *n*BuLi (2.5 M in hexanes, 0.24 mL, 0.60 mmol). After stirring for 20 min at -78 ºC, the aldehyde **509** (57.7 mg dissolved in 0.5 mL of THF, 0.20 mmol) was added dropwise to this mixture. After stirring the mixture for 2 h at -78 ºC, it was warmed to 0 ºC and stirred an additional 2 h. Water was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (30:1 hexanes:EtOAc) to give the diene **514** (12.7 mg, 0.039 mmol, 20% yield, 22% brsm, 4.5:1 *E*:*Z*).

^{1}H NMR (500 MHz, $CDCl_3$): Reported above.

(1*S*,2*S*,4*S*)-1,3,3-trimethyl-2-((4-methyl-3,6-dihydro-1,2-dioxin-3-yl)methyl)cyclohexane-1,4-diol (515)

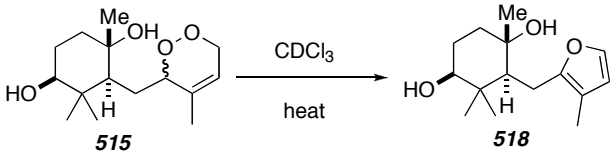


To a mixture of the diene **489** (30 mg, 0.126 mmol) in MeOH / H_2O (4:1, 2.5 mL) in a screw-cap culture tube was added rose bengal (12.3 mg, 0.012 mmol). The mixture

was saturated with O_2 by bubbling with O_2 for one minute. Then, the headspace was flushed with O_2, and the cap was immediately screwed on. The cap was sealed by wrapping it with Teflon tape. The mixture was irradiated (175W mercury vapor lamp) for 1 h and allowed to be warmed by the light source. After cooling to rt, water was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (1:2 hexanes:EtOAc) to give endoperoxide **515** (3.0 mg, 0.011 mmol, 9% yield).

^{1}H NMR (500 MHz, $CDCl_3$, 1:0.7 ratio of diastereomers): 5.62 (br s, 1H major), 5.58 (br s, 1H minor), 4.71 (dq, *J* = 16.1, 2.0 Hz, 1H major), 4.69 (dq, *J* = 15.9, 2.0 Hz, 1H minor), 4.65 (br d, *J* = 10.2 Hz, 1H minor), 4.36 (br d, *J* = 15.9 Hz, 1H major), 4.30 (br d, *J* = 16.0 Hz, 1H minor), 4.09 (br d, *J* = 10.0 Hz, 1H major), 3.42-3.36 (m, 1H major and minor), 2.82 (s, 1H major), 2.18 (s, 1H minor), 1.97 (m, 1H major and minor), 1.87-1.76 (m, 3H major and minor), 1.81 (br s, 3H major), 1.79 (br s, 3H minor), 1.65 (dd, *J* = 8.4, 2.0 Hz, 1H major), 1.56-1.50 (m, 4H major and minor), 1.25 (s, 3H minor), 1.17 (s, 3H major), 1.11 (s, 3H minor), 1.05 (s, 3H major), 0.84 (s, 3H major), and 0.77 (s, 3H minor).

(1*S,2*S**,4*S**)-1,3,3-Trimethyl-2-((3-methylfuran-2-yl)methyl)cyclohexane-1,4-diol (518)**

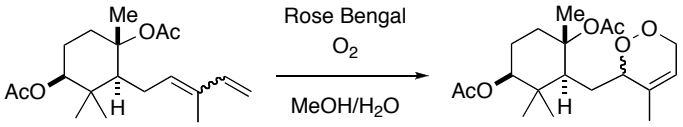


515 ***518***

A solution of the endoperoxide **515** (3.0 mg, 0.011 mmol) in $CDCl_3$ was heated to 80 ºC in a sealed NMR tube. After the solution was heated overnight, ^{1}H NMR analysis revealed that the furan **518** had been cleanly formed. No purification was carried out.

^{1}H NMR (500 MHz, $CDCl_3$): 7.24 (d, *J* = 1.8 Hz, 1H), 6.15 (d, *J* = 1.8 Hz, 1H), 3.38-3.34 (m, 1H), 2.78 (dd, *J* = 15.6, 7.1 Hz, 1H), 2.72 (dd, *J* = 15.6, 5.1 Hz, 1H), 2.01 (s, 3H), 1.81-1.73 (m, 4H), 1.53 (m, 1H), 1.28 (s, 3H), 1.01 (s, 3H), and 0.88 (s, 3H).

(1*S*,2*S*,4*S*)-1,3,3-trimethyl-2-((4-methyl-3,6-dihydro-1,2-dioxin-3-yl)methyl)cyclohexane-1,4-diyl diethanoate (519)



514 ***519***

To a mixture of the diene **514** (6.8 mg, 0.021 mmol) in MeOH / H_2O (4:1, 0.5 mL) in a screw-cap culture tube was added rose bengal (2 mg, 0.002 mmol). The mixture was saturated with O_2 by bubbling with O_2 for one minute. Then, the headspace was flushed with O_2, and the cap was immediately screwed on. The cap was sealed by wrapping it with Teflon tape. The mixture was irradiated (175W mercury vapor lamp) for 1 h and allowed to be warmed by the light source. After cooling to rt, water was added to the mixture, which was then extracted with Et_2O (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC (1:1 hexanes:EtOAc) to give endoperoxide **519** (1.0 mg, 0.003 mmol, 14% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ~1:1 ratio of diastereomers): 5.62 (br s, 2H one for each diastereomer), 4.74-4.67 (m, 2H), 4.67-4.59 (m, 2H), 4.39 (br d, *J* = 10.5 Hz, 1H), 4.31-4.24 (m, 2H), 4.16 (br d, *J* = 10.2 Hz, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.98-1.82 (m, 10H), 1.94 (s, 3H), 1.80 (br s, 3H), 1.78 (br s, 3H), 1.61 (s, 3H), 1.47 (s, 3H), 1.03 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), and 0.90 (s, 3H).

(3*S,4*S**)-4-Hydroxy-2,2,4-trimethyl-3-(3-methylpenta-2,4-dienyl)cyclohexanone (522)**

489 ***522***

To a solution of the diol **489** (25 mg, 0.105 mmol) in DMSO (0.7 mL) was added IBX (59 mg, 0.21 mmol). The solution was briefly warmed in a 80 ºC oil bath to dissolve the IBX, and then cooled back to rt. After the solution was stirred an additional 10 min, it was diluted with Et_2O and washed with saturated aq. $NaHCO_3$ (3x), H_2O, and brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure to give an oil. The crude oil was purified by MPLC to give the ketone **522** (9.2 mg, 0.039 mmol, 37% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ~1:1 ratio of *E* and *Z* isomers): 6.84 (ddd, *J* = 17.3, 10.8, 0.9 Hz, 1H), 6.36 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.59 (br t, *J* = 7.3 Hz, 1H), 5.48 (br t, *J* = 7.5 Hz, 1H), 5.28 (br d, *J* = 17.2 Hz, 1H), 5.18 (dt, *J* = 10.9, 1.6 Hz, 1H), 5.12 (br d, *J* = 17.4 Hz, 1H), 4.97 (br d, *J* = 10.7 Hz, 1H), 2.60-2.53 (m, 1H), 2.52-2.46 (m, 5H), 2.34-2.27 (m, 2H), 1.97 (dq, *J* = 13.6, 5.9 Hz, 2H), 1.92-1.85 (m, 4H), 1.83 (br s, 3H), 1.82 (br s, 3H), 1.39 (s, 6H), 1.189 (s, 3H), 1.187 (s, 3H), 1.071 (s, 3H), and 1.066 (s, 3H).

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