The Pennsylvania State University

The Graduate School

Department of Chemistry

PART 1. EXPLORATION OF BRAVERMAN DIRADICAL CYCLIZATIONS FOR ANGUCYCLINONE SYNTHESIS

PART 2. EFFORTS TOWARD THE SYNTHESIS OF LOMAIVITICINONE A

A Dissertation in

Chemistry

by

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ABSTRACT

Radical cyclization/addition reactions offer an efficient means to form rings within sterically congested systems. As a subset of radical-mediated closures, singlet diradical cyclizations have not been fully exploited for their potential in organic synthesis. The first part of this thesis focuses on the extension of Braverman diradical cyclizations of bis alkynyl sulfone substrates to the construction of the angucyclinone family of natural products, many of which display strong antibiotic properties. This diradical cyclization produced thiophene dioxide intermediates, which underwent formal [1,7]-hydride shifts to the more thermodynamically stable naphthalene derivatives in preference to the desired intramolecular Diels-Alder reaction with a tethered alkyne.

Lomaiviticins A and B have caught the attention of the synthesis community since their isolation in 2001 due to their interesting structural features coupled with promising anticancer activity. The second part of this thesis focuses on our efforts toward the construction of the core bicyclic structure of the lomaiviticins via several independent routes. Our approaches center around two-directional synthesis in which the key C-C linkage of the dimeric structure is formed early. The three independent routes covered in this thesis are categorized as follows: 1) stereoselective bis aldol reaction, 2) stereoselective Diels-Alder reaction between 1,3-butadiene and chirally substituted enediones, 3) double Ireland-Claisen reaction of PMB glycolates containing (*Z*)-alkenes, which is an unprecedented transformation. The lomaiviticinone A core was successfully synthesized enantioselectively in 11 steps from a known chiral propargylic alcohol utilizing the double Ireland-Claisen reaction route.

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I would also like to thank all my science teachers growing up and specifically Professor William Miles. Your sophomore organic class at Lafayette College greatly intrigued my interest in the subject. The opportunity to work in your laboratory over the summer doing synthetic work was an invaluable experience. This turned my luke-warm feelings for laboratory work into a newfound interest that has blossomed into a true love over the course of my graduate studies.

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PART I: EXPLORATION OF BRAVERMAN DIRADICAL CYCLIZATIONS FOR ANGUCYCLINONE SYNTHESIS

Chapter 1

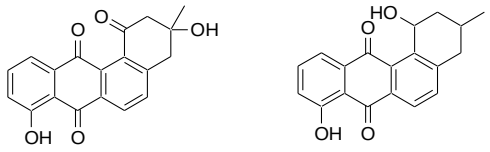
Braverman Diradical Cyclizations Towards Angucyclinones

1.1 Introduction

This first chapter focuses on the development of new methodology for the synthesis of polycyclic aromatic natural products of the angucyclinone family, a group of microbial isolates first reported in the 1960's. The new methodology focuses on singlet diradical generation from dipropargyl sulfones and the subsequent cyclization of those diyls as first described by Braverman. Our attempts to extend this methodology towards the angucyclinones will be presented.

1.2 Angucyclinone Background

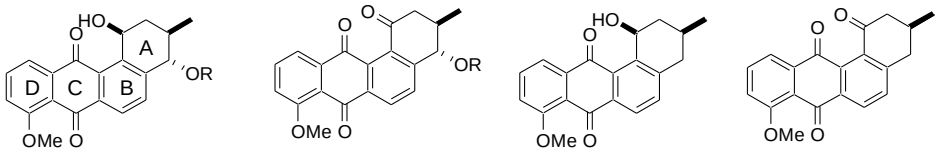
The angucyclinone family of natural products was first discovered in the 1960's as a result of extensive screening for novel antibacterial and antimicrobial compounds.[1] The first two angucyclinones described, tetrangomycin (**1**) and tetrangulol (**2**) (Figure **1**), were isolated by Kuntsmann and Mitscher in 1965 and 1966, respectively, from the fermentation broth of *Streptomyces rimosus*.[2,3] This family of natural products, characterized by their tetracyclic benz[a]anthracene structure, now contains hundreds of known compounds.[4,5,6]



(**1**) tetrangomycin (**2**) tetrangulol

Figure 1. Representative Angucyclinones

Further examples include the structurally related rubiginones, which were isolated in 1990 from *Streptomyces griseorubiginosus* contained in a soil sample from the Andhra Pradesh region of India.[7] (Figure 2) Vincristine-resistant Moser cells were rendered sensitive to vincristine upon treatment with the rubiginones. Likewise, rubiginone B_1 exhibited similar behaviour in vincristine-resistant P388 leukemia cells (IC_{50} = 0.007 μg/mL of vincristine at a concentration of 30 μg/mL rubiginone B_1 compared to the control IC_{50} = 0.59 μg/mL).



(**3**) rubiginone A_1 R = H
(**7**) rubiginone C_1 R = CO*i*-Pr

(**4**) rubiginone A_2 R = H
(**8**) rubiginone C_2 R = CO*i*-Pr

(**5**) rubiginone B_1

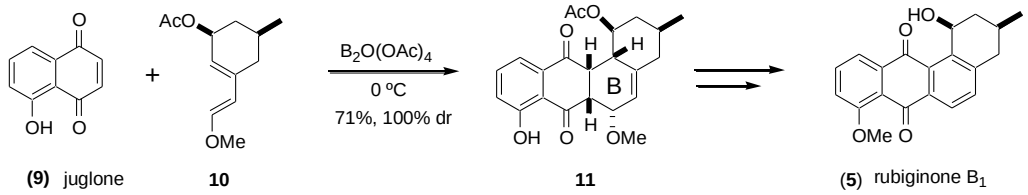
(**6**) rubiginone B_2

Figure 2. Rubiginone Family of Angucyclinones

There has been a plethora of total syntheses of various members of the angucylinone family during the last 50 years. A common approach in constructing these molecules is the use of Diels-Alder chemistry to rapidly access the B, C or D rings. As an example, Larsen's total synthesis of rubiginone B_1 utilized a boron-catalyzed Diels-Alder reaction between diene **10** and juglone (**9**) to construct the B ring of **11** (Scheme

1).[8] Rubiginone B_1 was synthesized in 7 steps from commercial materials in 30% overall yield by this chemistry.

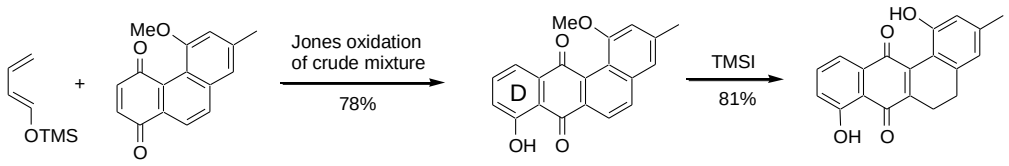
Scheme 1. B Ring-Forming Diels-Alder Approach to Rubiginone B_1 (**5**)



(9) juglone **10** **11** (**5**) rubiginone B_1

Alternatively, the D ring of the angucyclinone family also can be constructed with the Diels-Alder reaction. In 2001, Kraus *et al.* published the total synthesis of tetrangulol (**2**) using a Diels-Alder reaction between TMS dienol ether **12** and quinone **13** followed by Jones oxidation of the dihydroaromatic product to give quinone **14** (Scheme 2).[9] Demethylation of **14** afforded tetrangulol (**2**) in 81% yield, in a route totaling 6 steps with an 8% overall yield.

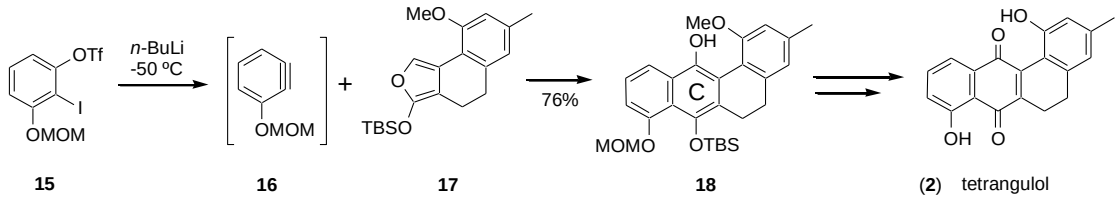
Scheme 2. D Ring-Forming Diels-Alder Approach to Tetrangulol (**2**)



12 **13** **14** (**2**) tetrangulol

Suzuki *et al.* performed a cycloaddition of furan **17** with *in situ* generated benzyne **16** to give tetracycle **18** (Scheme 3).[10] One benefit of this approach is the use of lower reaction temperatures compared to other Diels-Alder reactions used in angucyclinone synthesis.

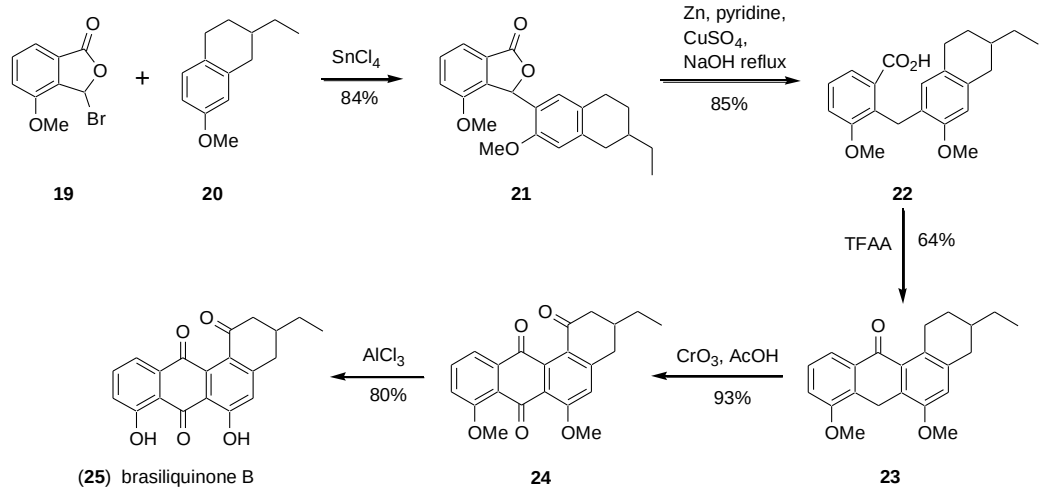
Scheme 3. C Ring-Cycloaddition Approach to Tetrangulol (**2**)



15 **16** **17** **18** (**2**) tetrangulol

A Friedel-Crafts approach was successful in the synthesis of brasiliquinone B (**25**) as described by Deshpande *et al.* in 2002.[11] A $SnCl_4$ promoted coupling of bromolactone **19** with aryl bicycle **20** gave **21** in 84% yield (Scheme 4). Zinc-mediated lactone cleavage followed by ring-closure of carboxylic acid **22** using trifluoroacetic anhydride (TFAA) afforded tetracycle **23**, which was subsequently elaborated through a series of oxidations and demethylations to give brasiliquinone B (**25**).

Scheme 4. Friedel-Crafts Approach to Brasiliquinone B (**25**)

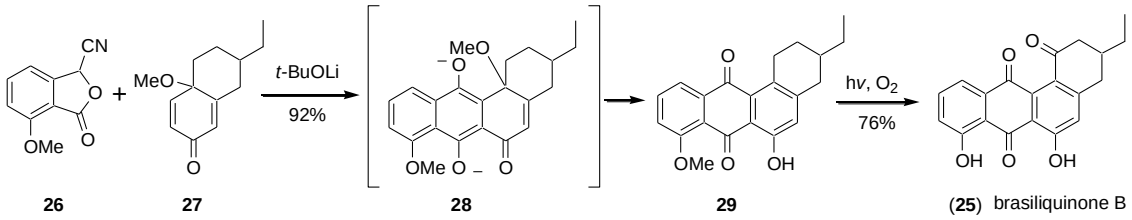


19 **20** **21** **22** **23** **24**

Brasiliquinone B (**25**) also was synthesized using an anionic annulation approach by Mal *et al.* in 1999.[12] Their key step involved a Michael addition of the anion derived from **26** with enone **27** to give an intermediate that cyclized to give dianion **28** (Scheme 5). Expulsion of the quaternary carbon's methoxy group and enolization of intermediate

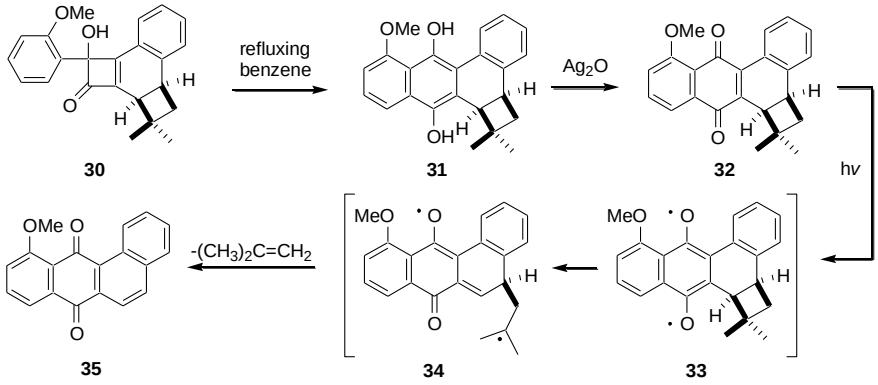
28 led to quinone **29**. A photochemical benzylic oxidation of **29** with O_2 afforded brasiliquinone B (**25**).

Scheme 5. Anionic Annulation Approach to Brasiliquinone B (**25**)



Another interesting approach to the angucyclinone framework was described by Moore *et al*. in 1998.[13] Formation of the C ring was accomplished by thermolysis of cyclobutenone **30** to form intermediate hydroquinone **31**, which was oxidized directly to quinone **32** with Ag_2O (Scheme 6). Photochemical degradation of the cyclobutane ring in **32** led to the angucyclinone tetracyclic core **35**.

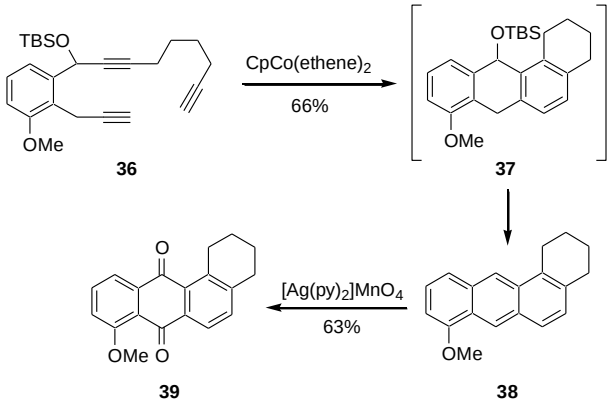
Scheme 6. Photochemical Cyclobutenone Rearrangement Approach



Groth *et al.* utilized a cobalt mediated [2+2+2]-cycloaddition to form the A, B, and C rings of the angucyclinone core in a succinct manner (Scheme 7).[14] Treatment of triyne **36** with $CpCo(ethene)_2$ formed intermediate tetracyclic ether **37**, which

subsequently eliminated the TBS ether to give anthracene derivative **38**. Oxidation of anthracene derivative **38** to the angucyclinone core quinone **39** was achieved with $[Ag(py)_2]MnO_4$.

Scheme 7. A,B,C Ring-Forming Cobalt-Mediated [2+2+2] Approach



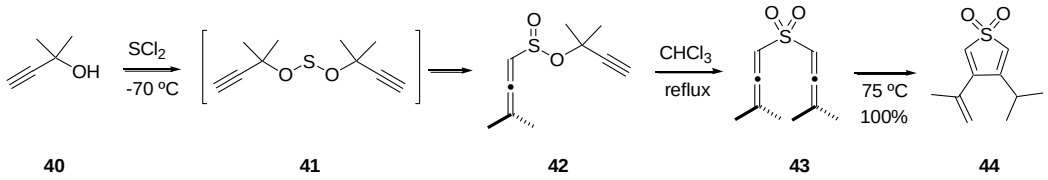
This brief survey of representative angucyclinone syntheses indicates that the simpler members of this family can be prepared in ≤ 10 steps from commercial starting materials. Thus, any subsequent synthesis efforts must proceed with these benchmarks in mind. A Braverman cyclization-based approach to these structures has the potential to challenge even the most efficient angucyclinone syntheses to date. Attempts to realize this potential are described in Chapter 2.

1.3 Introduction to Braverman Cyclizations

In 1974, Braverman *et al.* documented the [2,3]-sigmatropic rearrangement of dipropargylic sulfoxylic esters (Scheme 8).[15] They accessed dipropargylic sulfoxylic ester intermediate **41** by double chloride displacement on SCl_2 with 2 eq. of propargyl alcohol **40**. The first [2,3]-sigmatropic rearrangement afforded sulfoxide allene **42**,

whereas a second sigmatropic shift gave sulfone bis allene **43**. Upon continued heating, sulfone bis allene **43** cyclized to give thiophene dioxide **44** in quantitative yield. It is the seminal observation of **43** converting into **44** that forms the basis of our subsequent research in this area.

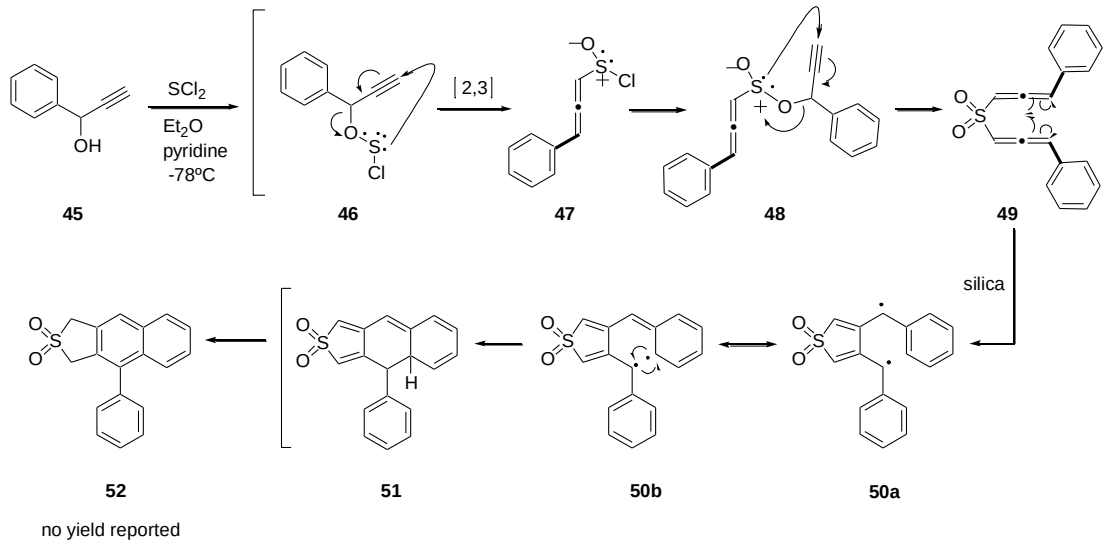
Scheme 8. Reaction of Propargyl Alcohol **40** With SCl_2 to Afford Thiophene Dioxide **44**



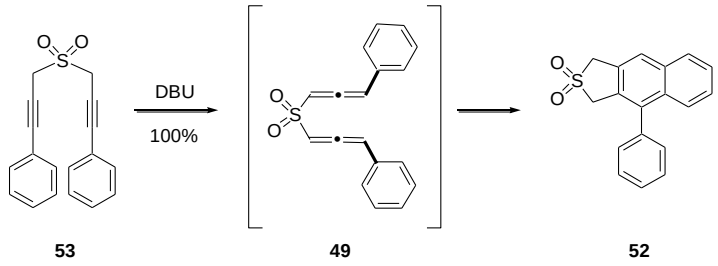
Another major advance in this area came in 2001 when Braverman *et al.* were able to utilize this reaction sequence with aromatic substrates to form naphthalene derivatives.[16] Their mechanistic speculation for the conversion of two molecules of **45** into **52** follows: the reaction of propargyl alcohol **45** with SCl_2 in the presence of pyridine first gave intermediate chlorosulfoxylic ester **46**, which underwent a [2,3]-sigmatropic rearrangement to form chlorosulfoxide allene **47** (Scheme 9). A displacement of the remaining chloride by a second equivalent of propargyl alcohol **45** afforded intermediate **48**. Another [2,3]-sigmatropic rearrangement within **48** furnished bis allene sulfone **49**, which cyclized to thiophene dioxide intermediate **50a** containing a singlet diradical. Presumably, the electron density of the diradical is spread throughout the highly conjugated intermediate. Cyclization of this diradical **50b** led to formation of a 6-membered ring within **51**. This system then underwent a facile formal [1,7]-hydride shift to restore aromaticity and arrive at naphthalene derivative **52** as the product. Braverman also was able to access the same bis allene intermediate **49**, and thus the same

naphthalene product **52**, in quantitative yield by the base-mediated isomerization of bis alkyne sulfone **53** (Scheme **10**). [16]

Scheme 9. Braverman Diradical Cyclization Cascade



Scheme 10. Braverman Diradical Cyclization of Sulfone **53**



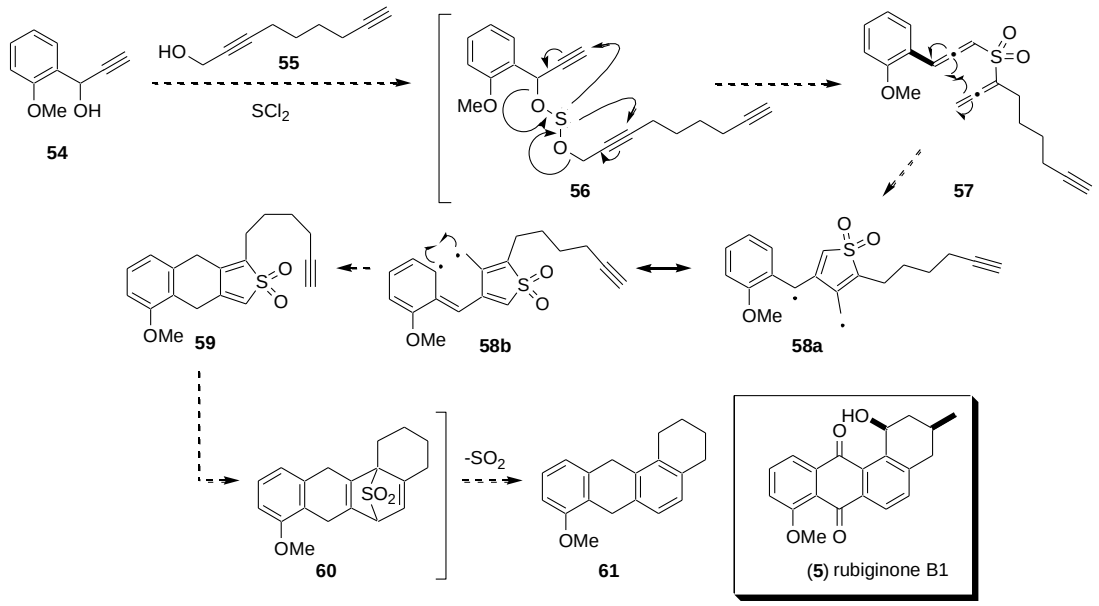
Chapter 2

Synthesis Efforts Towards Angucyclinones Utilizing Braverman Cyclizations

A succinct construction of the tetracyclic core of the angucyclinones could be envisioned from easily prepared precursors by utilizing Braverman's diradical cyclization cascade. In addition, a variety of angucyclinones could in theory be prepared efficiently by relatively simple alterations of the starting materials. Our efforts to achieve these goals were reported in 2010.[17]

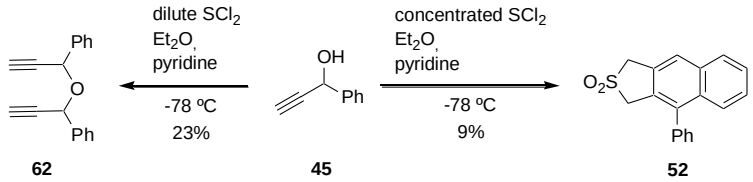
Our initial approach to the angucyclinone framework using Braverman chemistry involved sequentially coupling propargyl alcohols **54**[18] and **55**[19] with SCl_2 in the presence of base to form propargylic disulfoxylic ester **56** (Scheme 11) following Braverman's work. In the original version of the synthesis plan, sulfoxylic ester **56** should undergo a bis sigmatropic rearrangement to afford bis allenyl sulfone **57**, which would cyclize to the thiophene dioxide-stabilized diradical **58a**. Ring closure of diradical **58b** utilizing radical density within the aromatic ring system and the thiophene dioxide methylene would result in tricycle **59**. An intramolecular Diels-Alder reaction between the nascent thiophene dioxide unit and the pendant alkyne would give **60**. Chelatropic extrusion of sulfur dioxide from **60** would arrive at the tetracyclic core of the angucyclinones **61**. Diels-Alder reactions followed by chelatropic extrusions of SO_2 such as that described above are reported in the literature.[20,21] The partially saturated B ring could be oxidized easily to the quinone functionality found in this family of natural products. Thus, this approach to the angucyclinones has the potential to deliver the tetracyclic target in just a few discrete steps from simple precursors.

Scheme 11. Original Approach Towards the Angucyclinone Framework



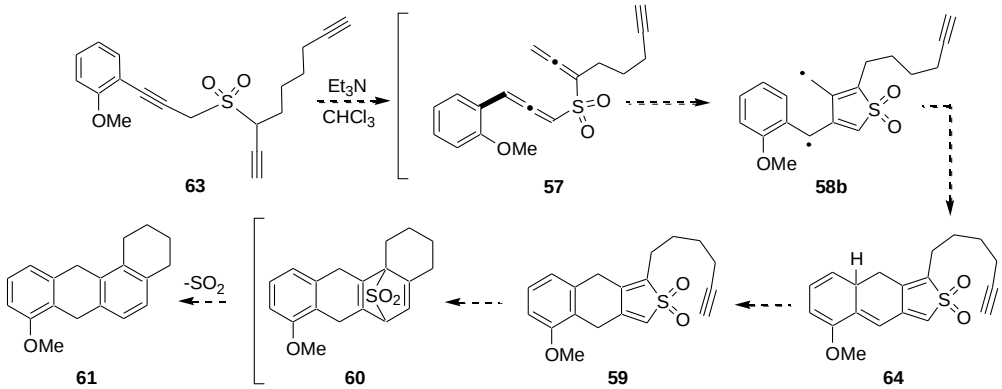
This synthesis plan was tested by reaction of propargyl alcohols **54** and **55** in the presence of SCl_2 and various bases, but only decomposition products were observed. A much simpler system then was examined to explore the feasibility of the reaction. Two equivalents of propargyl alcohol **45** were combined with SCl_2 in the presence of pyridine (Scheme 12). Interestingly, adding a more concentrated solution of SCl_2 afforded the desired naphthalene derivative **52** in 9% yield, whereas the addition of a more dilute solution of SCl_2 gave ether **62**. The formation of ether **62** presumably resulted from an S_N2-like displacement of an OSCl unit on an intermediate propargyl chlorosulfoxylic ester. Variations in base (pyridine, DBU, Et_3N, 2,6-lutidine, and NaH) temperature (-78 → 0 ºC), and solvents (Et_2O and toluene) never resulted in higher than 9% of the desired cyclization product **52**.

Scheme 12. Isolation of Ether **62** from SCl_2 Reaction

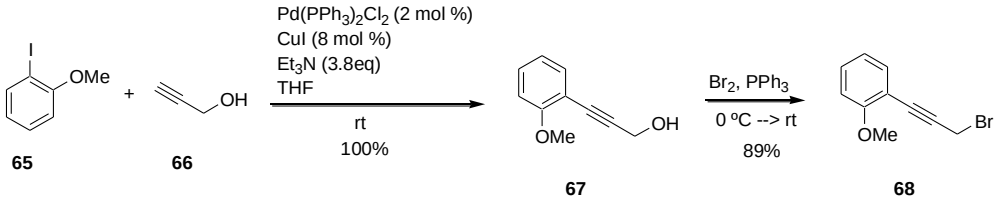


An alternative approach was devised due to the poor results attained utilizing Braverman's SCl_2 methodology. The desired bis allenyl sulfone intermediate **57** (Scheme 13) could be accessed by the addition of base to a bis β-alkynyl sulfone as previously shown by Braverman. For the particular goal at hand, addition of a base to sulfone **63** would give the same intermediate bis allenyl sulfone **57** that could lead to the tetracyclic core **61**. The sulfone **63** could be prepared from bromide **68** and thiol **75**. Construction of known bromide **68**[22] began by Sonogashira coupling of aryl iodide **65** and propargyl alcohol (**66**), followed by a Lee reaction on alcohol **67** with Br_2/PPh_3 (Scheme 14).

Scheme 13. Sulfone Approach Towards the Angucyclinone Framework

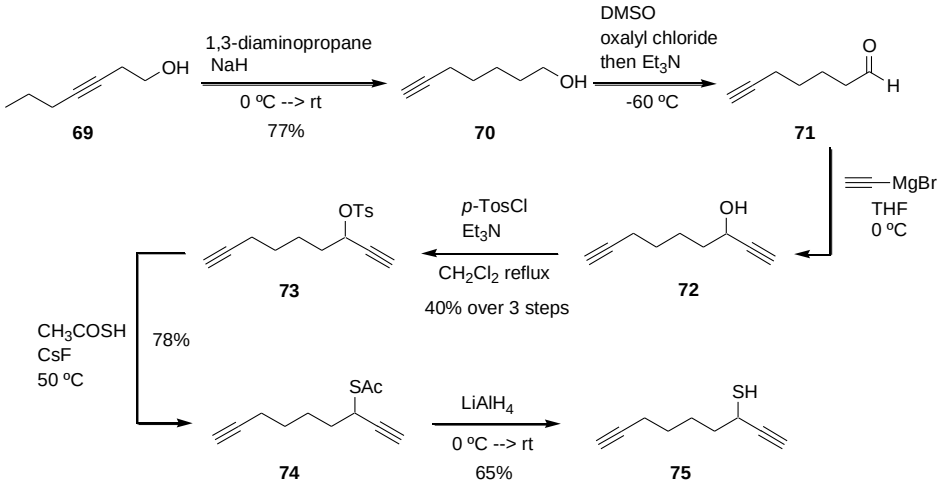


Scheme 14. Preparation of Coupling Partner **68**

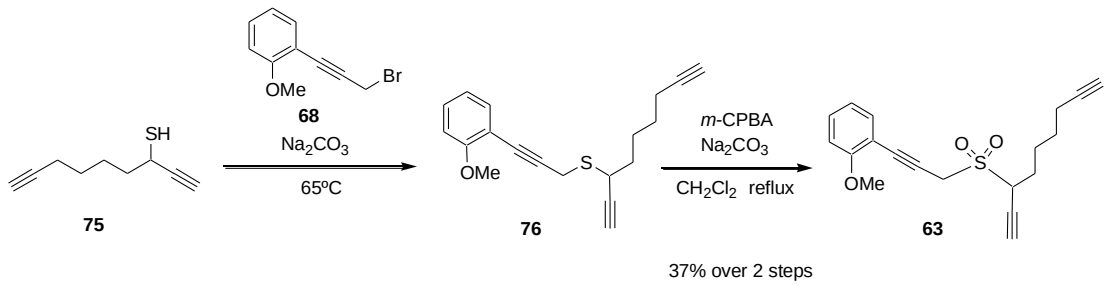


Preparation of thiol **75** commenced with an alkyne zipper reaction on internal alkyne **69** to give terminal alkyne **70** (Scheme 15).[23] Swern oxidation of the primary alcohol in **70** to aldehyde **71**,[24] followed by Grignard addition of ethynylmagnesium bromide to this aldehyde, afforded propargylic alcohol **72.** Tosylation of **72**, nucleophilic displacement of the tosyl group within **73** with thiolacetic acid,[25] and cleavage of the acetate in **74** with lithium aluminum hydride gave thiol **75**. Sulfone **63** was prepared by Na_2CO_3-mediated coupling of thiol **75** and propargylic bromide **68** followed by oxidation of the derived sulfide **76** with *m*-CPBA (Scheme 16).

Scheme 15. Preparation of Coupling Partner **75**

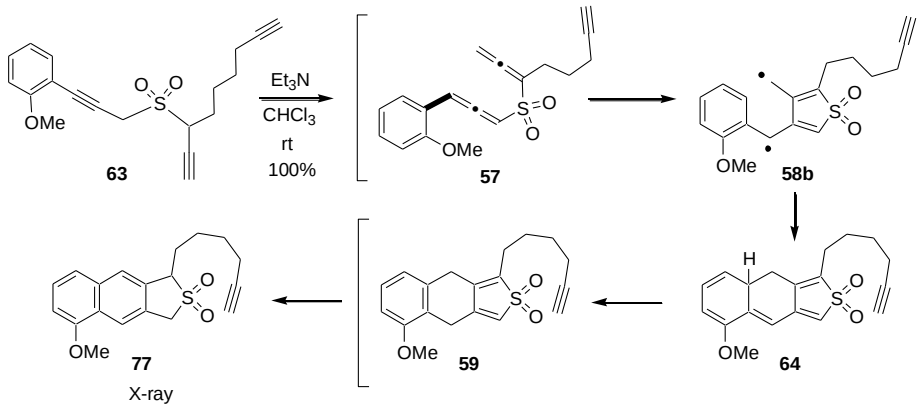


Scheme 16. Preparation of Sulfone **63**



Addition of triethylamine to sulfone **63** gave the undesired naphthalene derivative **77** as a single compound in quantitative yield (Scheme 17). The structure of naphthalene derivative **77** was verified by X-ray crystallography (Figure 3). Presumably, intermediate thiophene dioxide **59** does not persist long enough to undergo the desired Diels-Alder reaction with the pendant terminal alkyne. A survey of bases, solvents, and temperatures afforded cyclized product **77** as the only isolable compound in variable yields (Table **1**).

Scheme 17. Diradical Cyclization of Sulfone **63**



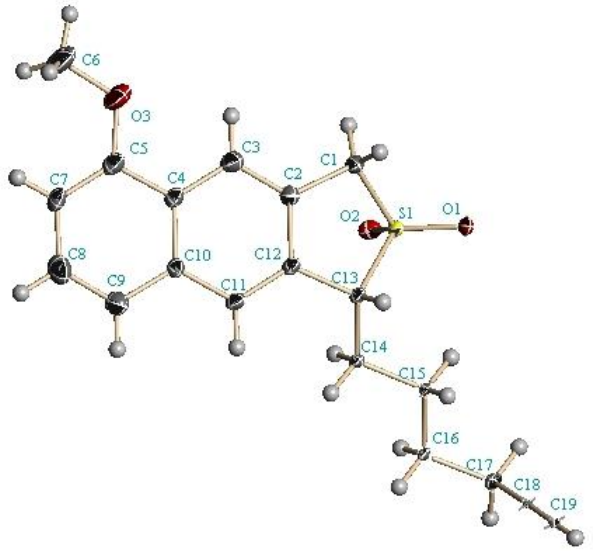


Figure 3. X-Ray Structure of Tricycle **77**

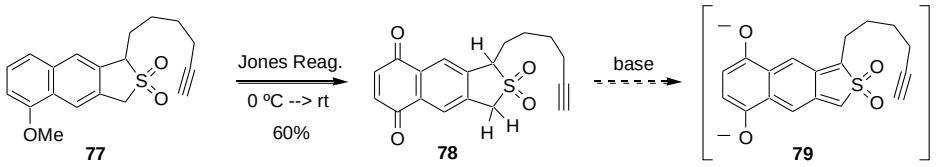
Table 1. Diradical Cyclization of Sulfone **63**

entry	base	solvent	temperature (°C)	yield 77 (%)
1	*t*-BuOK	THF	rt	--
2	*t*-BuOK	THF	110	--
3	*t*-BuOK	*t*-BuOH	rt	--
4	*t*-BuOK	toluene	105	--
5	DBU	$CHCl_3$	0	88
6	DBU	THF	0	13
7	DMAP	THF	rt	7
8	Et_3N	$CHCl_3$	rt	~100
9	Et_3N	toluene	110	~100
10	none	DMF	110	50

Naphthalene derivative **77** was oxidized with Jones reagent to give quinone **78** (Scheme 18). It was hoped that bis α-deprotonation of the sulfone would give hydroquinone intermediate **79**, which could undergo a Diels-Alder reaction with the pendant terminal alkyne. The goal here was to utilize the gain in stability in forming an

extended enolate (almost phenolic) anion to drive the formation of the unstable extended *o*-quinonemethide-thiophene dioxide **79**, a species that perhaps is more likely to engage the pendant alkyne in Diels-Alder cycloaddition than is the parent thiophene dioxide. However, addition of DBU to quinone **78** in THF at room temperature led to decomposition products, while Et_3N in refluxing THF returned the starting material. Further heating of **78** with Et_3N in THF in a sealed tube at 120 ºC led to partial decomposition.

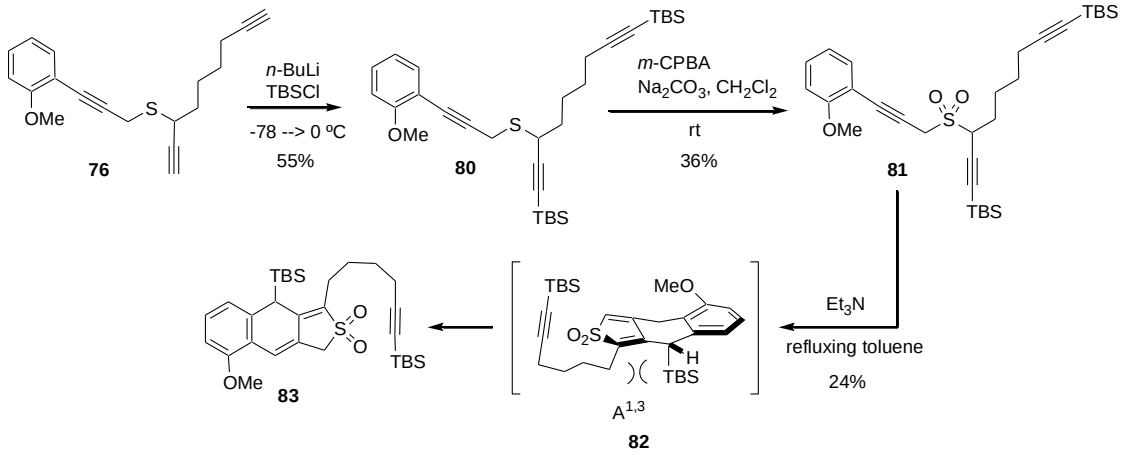
Scheme 18. Oxidation of **77** to Quinone **78**



As another possible solution, bis TBS protected sulfone **81** was synthesized (Scheme 19) in an attempt to suppress isomerization of the intermediate thiophene dioxide. We hoped that incorporation of a sterically bulky group such as TBS on the terminal alkyne would deliver a thiophene dioxide intermediate **82** in which the TBS group would project in an axial-like position in order to avoid an $A^{1,3}$ interaction with the tether (Scheme 19). With the adjacent hydrogen now in a pseudo-equatorial position, the facility for deprotonation should be diminished. For ease of initial exploration, a global TBS addition to the alkynes within sulfide **76** was conducted to give **80**. Oxidation of the sulfide **80** to sulfone **81** and treatment of this sulfone with triethylamine in refluxing toluene resulted in highly conjugated tricycle **83** via an isomerization of one of the

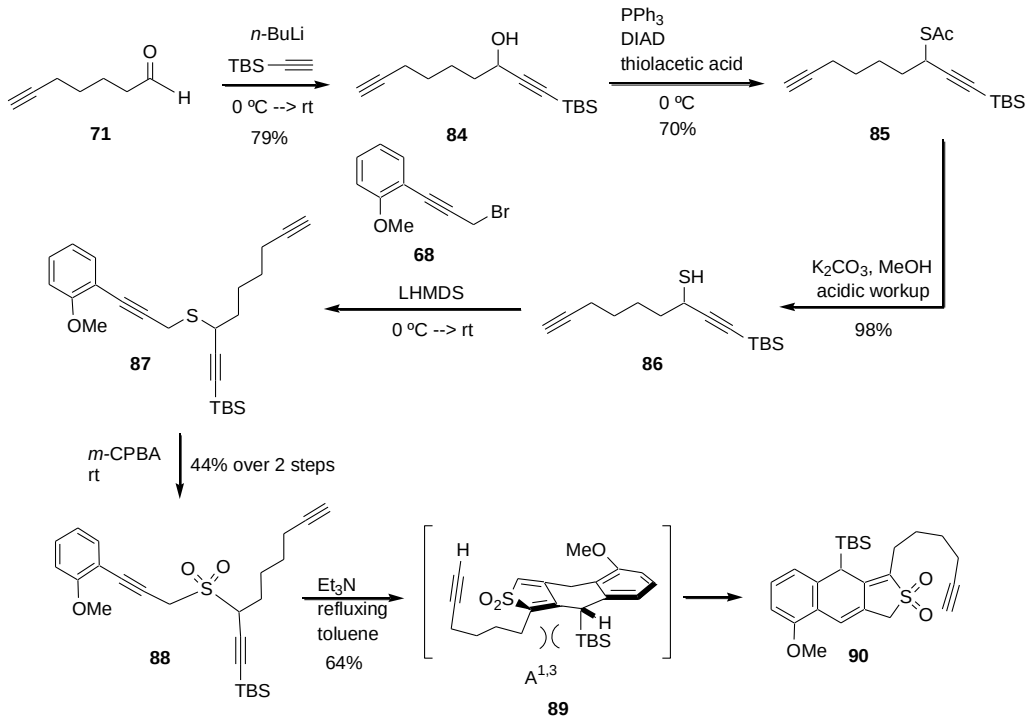
thiophene dioxide alkenes prior to any Diels-Alder reaction. Apparently the TBS steric block did its job, but the other α-proton did undergo isomerization.

Scheme 19. Construction and Diradical Cyclization of bis TBS **81**



In addition, cyclization precursor **88**, without a TBS group on the tether's terminal alkyne, was prepared (Scheme 20). Removal of the sterically bulky silicon group from the dienophile could possibly promote cyclization with the electron depleted thiophene dioxide, provided that the intermediate thiophene dioxide persisted long enough to react. Construction of the starting material began by the addition of lithium TBS acetylide to aldehyde **71**, followed by a Mitsunobu reaction on the resulting alcohol with thiolacetic acid as the nucleophile[26] to give thioacetate **85**. The acetate group of **85** was removed with methanolic K_2CO_3 to give thiol **86**, which was coupled with bromide **68** using LHMDS as base to afford sulfide **87**. Oxidation of sulfide **87** with *m*-CPBA gave sulfone **88**, which underwent diradical cyclization to deliver conjugated tricycle **90** upon treatment with Et_3N in refluxing toluene. Again, the thiophene dioxide intermediate **89** isomerized before a Diels-Alder reaction could take place.

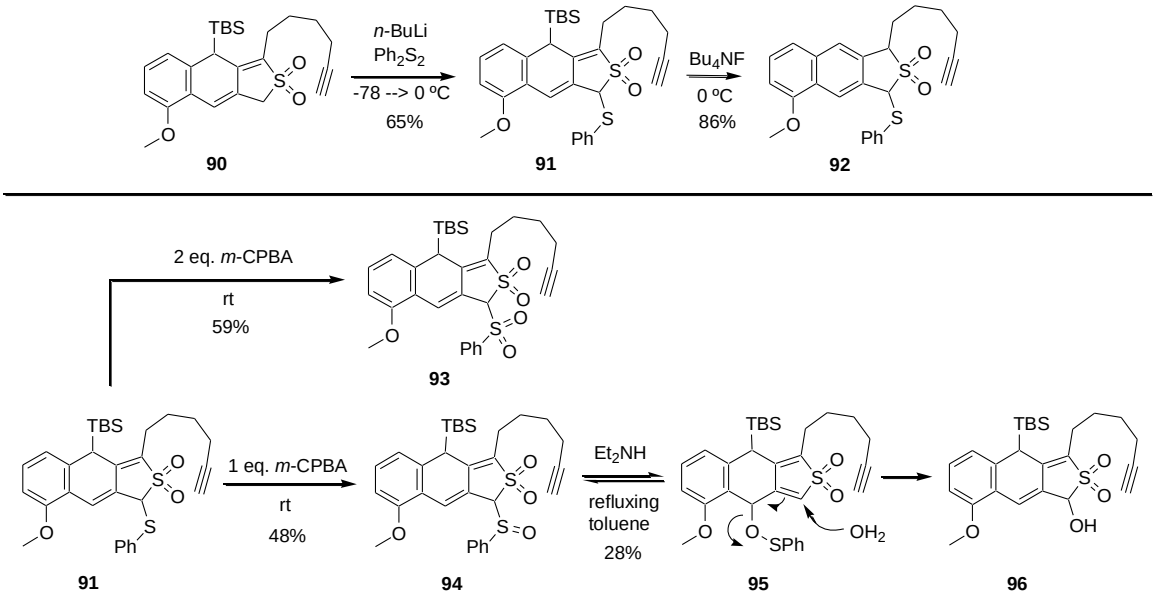
Scheme 20. Construction and Diradical Cyclization of Mono-TBS Alkyne **88**



A strategy for angucyclinone synthesis featuring post-cyclization modifications was formulated since the tendency for thiophene dioxide intermediates in this system to undergo isomerization upon cyclization could not be avoided. Perhaps a leaving group next to the sulfone on tricycle **90** could be eliminated, thus resulting in generation of the desired thiophene dioxide intermediate for a Diels-Alder reaction. The anion required to force this elimination could be prepared with base via deprotonation of a derivative of **90** or by a fluoride source via TBS removal. Initially, a thiophenyl group was attached to the ring using Ph_2S_2 and *n*-BuLi. Fluoride treatment of this resulting dihydrothiophene dioxide thioether **91** led to formation of naphthalene derivative **92** (Scheme 21). To increase its lability, the sulfide was oxidized to both sulfoxide **94** and sulfone **93**. After screening several fluoride sources and numerous bases, the only interesting result was the

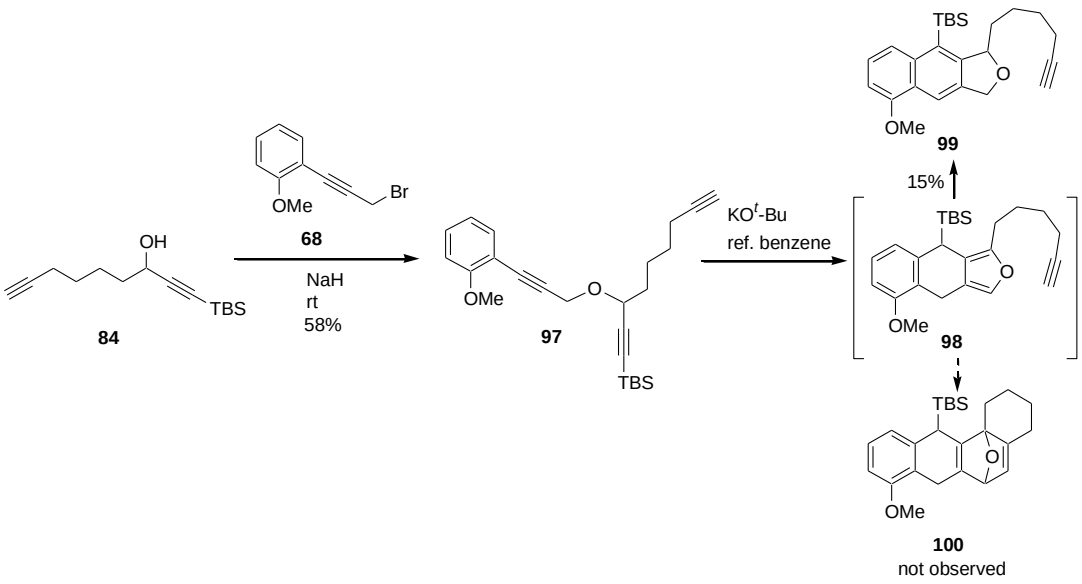
isolation of alcohol **96** presumably via a [2,3]-shift of the sulfoxide to **95** followed by addition of H_2O upon workup.

Scheme 21. Attempts to Access a Thiophene Dioxide Derivative from **90**



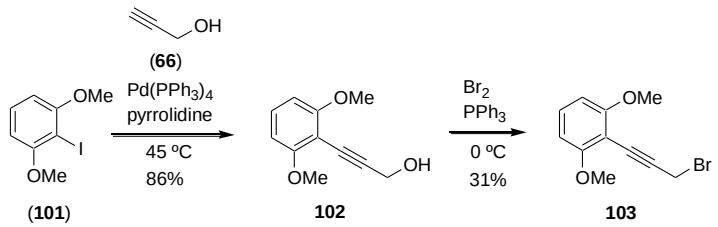
The diradical cyclization cascade was also examined with ether **97** (Scheme 22). This choice of substrate was predicated upon the expectation that an intermediate furan (analogous to the thiophene dioxide of **89**) would resist isomerization and thus be available for a Diels-Alder reaction, at least under forcing conditions, with the tethered alkyne. Nucleophilic displacement of bromide **68** with alcohol **84** afforded ether **97**. Addition of *t*-BuOK to **97** in refluxing benzene resulted in formation of naphthalene derivative **99** in low yield, with no sign of Diels-Alder adduct **100** that might have resulted from [4 +2] cycloaddition to an intermediate furan **98**.

Scheme 22. Construction and Diradical Cyclization of Ether **97**



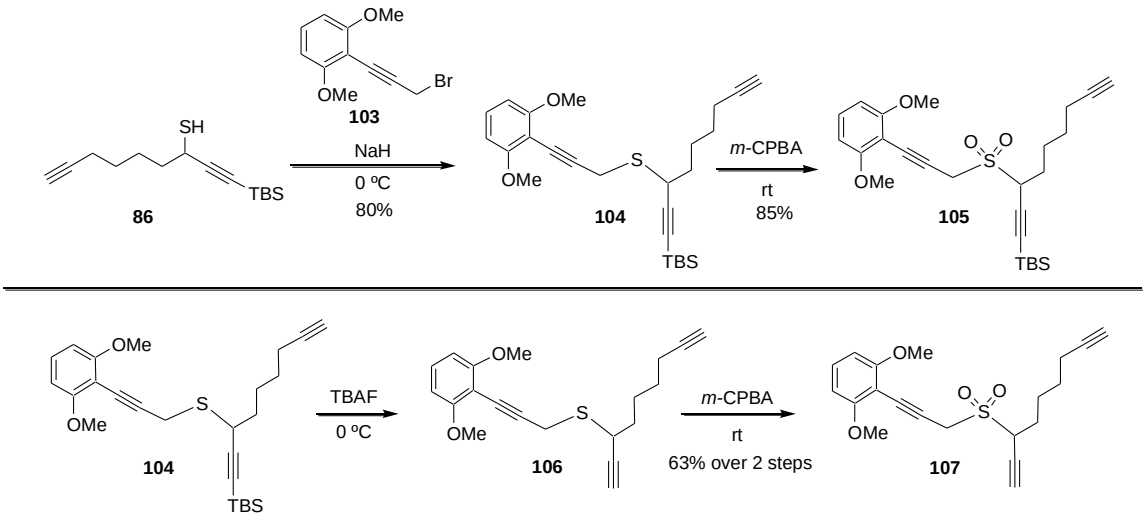
Substrates containing bis *o*-methoxy functionality on the aromatic ring were also constructed (Scheme 24). The plan was to use the ortho-substitution on the aromatic ring to block rearomatization of an intermediate diradical cyclization product. In this scenario, the intermediate thiophene dioxide might have a longer lifetime. Propargyl alcohol **102** was prepared from a Sonogashira reaction[27] of aryl iodide **101** with propargyl alcohol (**66**). The yield of the Sonogashira reaction was drastically increased from 11 to 86% by running the reaction with $Pd(PPh_3)_4$ and pyrrolidine[28] compared to a mixture of $PdCl_2$, CuI, Et_3N, and PPh_3. Bromide **103** was then accessed by a Lee reaction with Br_2/PPh_3.

Scheme 23. Preparation of Coupling Partner **103**



Sulfone **105** was prepared by coupling thiol **86** and bromide **103** using NaH as base to give an intermediate sulfide **104**, which subsequently was oxidized with *m*-CPBA (Scheme 24). Additionally, sulfone **107**, which did not contain a TBS group on the alkyne, was made by removal of the TBS group from sulfide **104** and oxidation of the resulting sufide **106** to sulfone **107** with *m*-CPBA. This inefficient sequence was utilized only because large quantities of thiol **86** were available at the time.

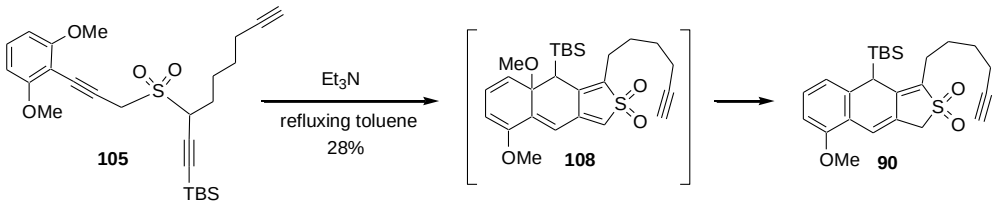
Scheme 24. Preparation of bis *o*-Methoxy Substituted Cyclization Precursors **105** and **107**



Diradical cyclization of sulfone **105** promoted by Et_3N in reluxing toluene again gave a familiar tricycle **90** in modest yield (Scheme 25). Rather than pausing at a highly conjugated system **108** containing a thiophene dioxide, apparently one of the methoxy

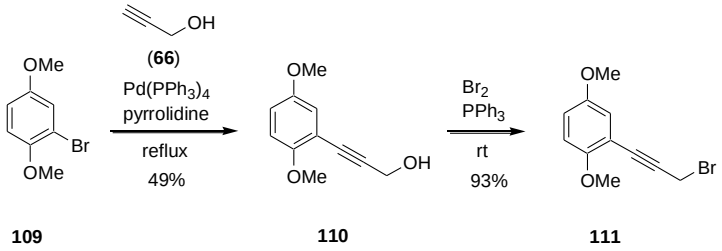
groups was eliminated post-cyclization, giving tetracycle **90**. It is evident that a formal reduction has occurred during this reaction, but the mechanism by which this process takes place is unclear.

Scheme 25. Diradical Cyclization of Sulfone **105**

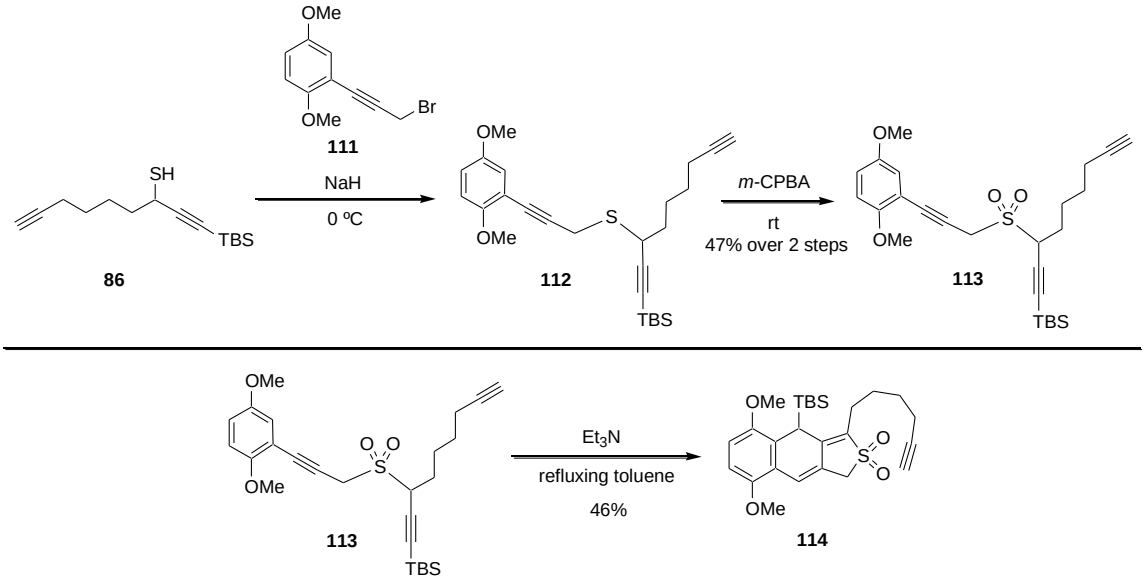


The deprotonation chemistry attempted with the napthoquinone **78** (Scheme 18) failed, but the basic idea of using a D-ring quinone to serve as an anion sink coupled with thiophene dioxide preservation was explored further with hydroquinone D-ring precursors. The idea in this case was to generate an extended anion containing a thiophene dioxide unit from a non-aromatic (non-naphthalene) precursor in the hope that such a species might be easier to make since there was no naphthalene aromaticity to overcome. A bis *p*-methoxy substrate was synthesized by first making bromide **111** (Scheme 26) by a similar protocol to that used for **103**. Coupling thiol **86** and bromide **111**, and oxidation of the sulfide product **112** with *m*-CPBA, gave sulfone **113** (Scheme 27). Cyclization of sulfone **113** with Et_3N in refluxing toluene predictably gave conjugated tricycle **114**.

Scheme 26. Construction of Bromide **111**



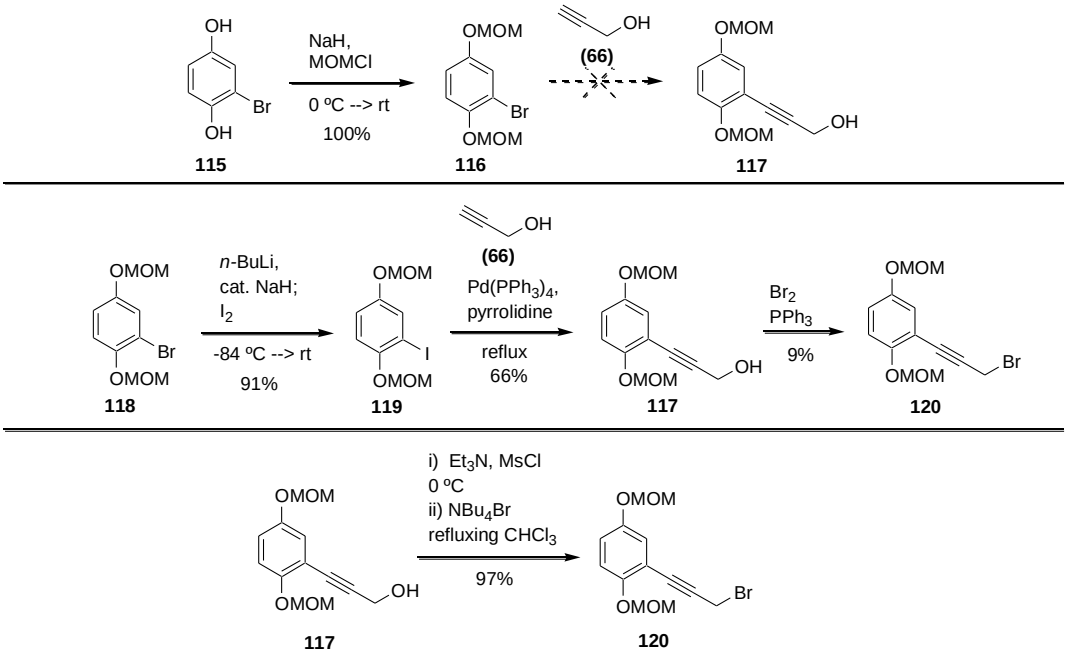
Scheme 27. Preparation and Diradical Cyclization of Sulfone **113**



In parallel with the *p*-methoxy series, a *p*-bis MOM ether functionalized aromatic ring also was prepared. This change in protecting groups was made in case removing the methyl ethers of **114** proved difficult. Initially, bis phenol **115** was protected as the bis-MOM ether to give bromide **116** (Scheme 28). Attempts at a Sonogashira coupling of bromide **116** with propargyl alcohol (**66**) led to no coupled product. Since the aromatic bromide was not reactive, the aryl iodide **119** was prepared via a lithium-halogen exchange reaction followed by addition of I_2. Aryl iodide **119** readily underwent Sonogashira coupling with propargyl alcohol (**66**) to afford **117**. The Lee reaction under

standard conditions with PPh_3/Br_2 proceeded to bromide product in very low yield. Instead, the alcohol was mesylated and then displaced with Br^- from Bu_4NBr[29] to arrive at bromide **120** in high yield.

Scheme 28. Preparation of Coupling Partner **120**



Coupling bromide **120** and thiol **86** mediated by NaH proceeded in very low yield, but deprotonation of **86** with LHMDS before the addition of **120** gave thiol **121** in moderate yield (Scheme 29). Oxidation of sulfide **121** with *m*-CPBA gave sulfone **122**. Addition of Et_3N to this cyclization precursor in refluxing benzene resulted predictably in a modest yield of conjugated tricycle **123**.

In a test of the "deprotonation" hypothesis, MOM deprotection of **123** with AcCl in MeOH[30] resulted in hydroquinone **124**, which was readily oxidized to quinone **125** with hypervalent iodine. Unfortunately, exposure of **125** to numerous bases only resulted in decomposition of the starting material (Table **2**). In addition, a thiophene dioxide

intermediate could not be accessed via TBS removal or trapping of the presumed hydroquinone intermediate as a bis acetate. Alternatively, TBS removal within MOM-protected tricycle **123** resulted in naphthalene derivative **127** (Scheme 30).

Scheme 29. Construction and Diradical Cyclization of Sulfone **122**

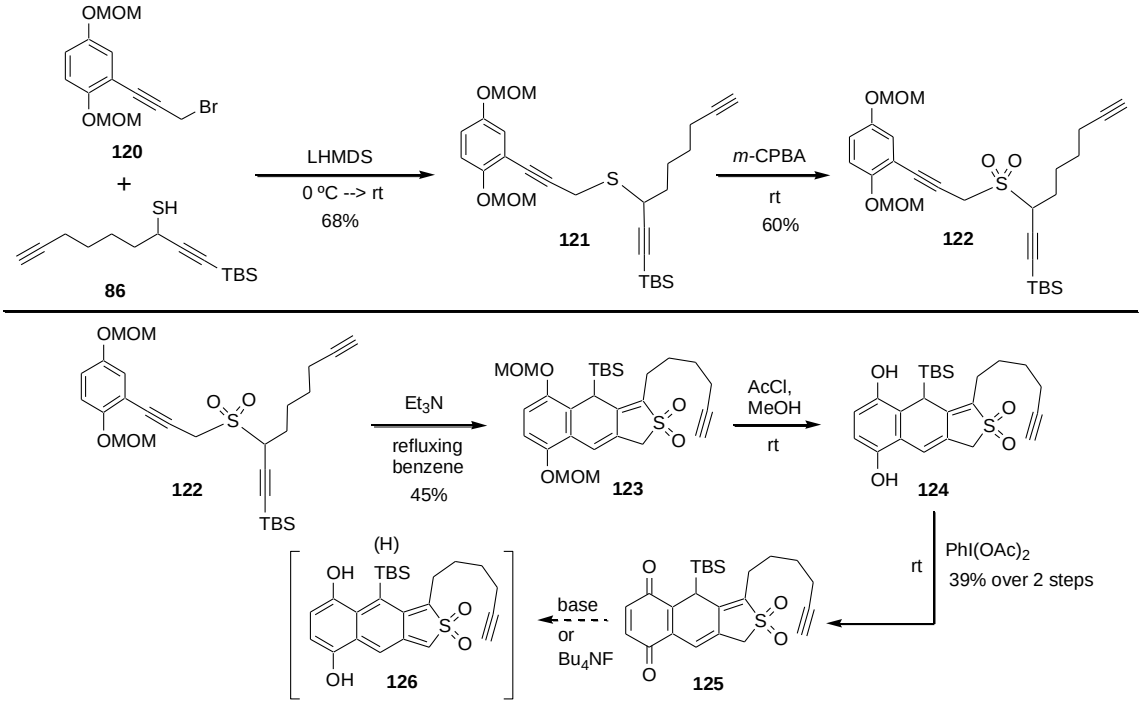
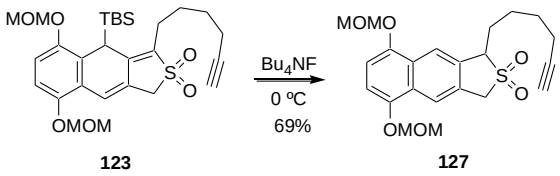


Table 2. Base/Fluoride Source or Additive Addition to Quinone **125**

entry	base/fluoride source or additive	solvent	temperature (°C)	outcome
1	Et_3N	toluene	<200	no reaction
2	Et_3N	toluene	>200	decomposition
3	Et_3N/Bu_4NF	benzene	rt	decomposition
4	2 eq. Bu_4NF	benzene	rt	decomposition
5	2 eq. Bu_4NF	DMF	0 --> rt	decomposition
6	2 eq. Bu_4NF	THF	-78	decomposition
7	*t*-BuOK	THF	-78	decomposition
8	DBU	THF	-78	decomposition
9	DBU/Bu_4NF	benzene	rt	decomposition
10	DBU/acetyl chloride	CH_2Cl_2	-78 --> rt	decomposition
11	DBU/acetyl chloride	THF	-78 --> rt	decomposition
12	HMPA	*t*-BuOH	110	decomposition

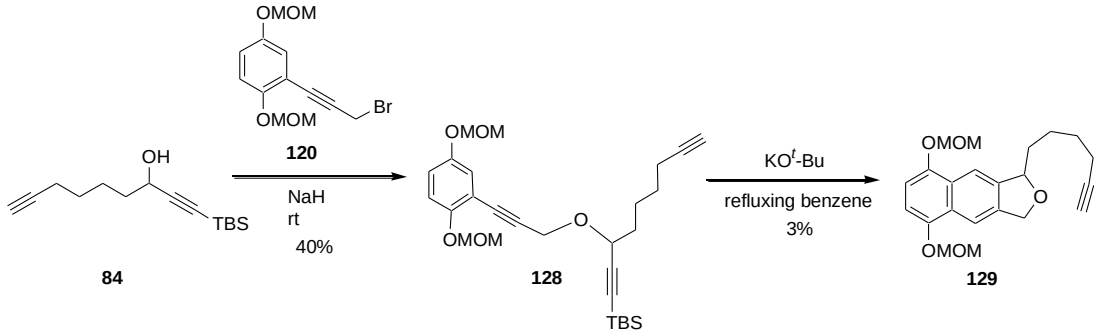
Scheme 30. TBS Removal From bis MOM Cyclization Product **123**



123 **127**

Dipropargyl ethers were examined in this series as well, since the sulfone to thiophene dioxide chemistry uniformLy failed. Bis MOM protected ether **128** was prepared by the displacement of bromide **120** by alcohol **84** in an analogous fashion to sulfide **112** (Scheme 31). Cyclization of **128** with *t*-BuOK in refluxing benzene afforded naphthalene tricycle **129** in very low yield. Milder bases such as Et_3N in refluxing benzene returned the starting material.

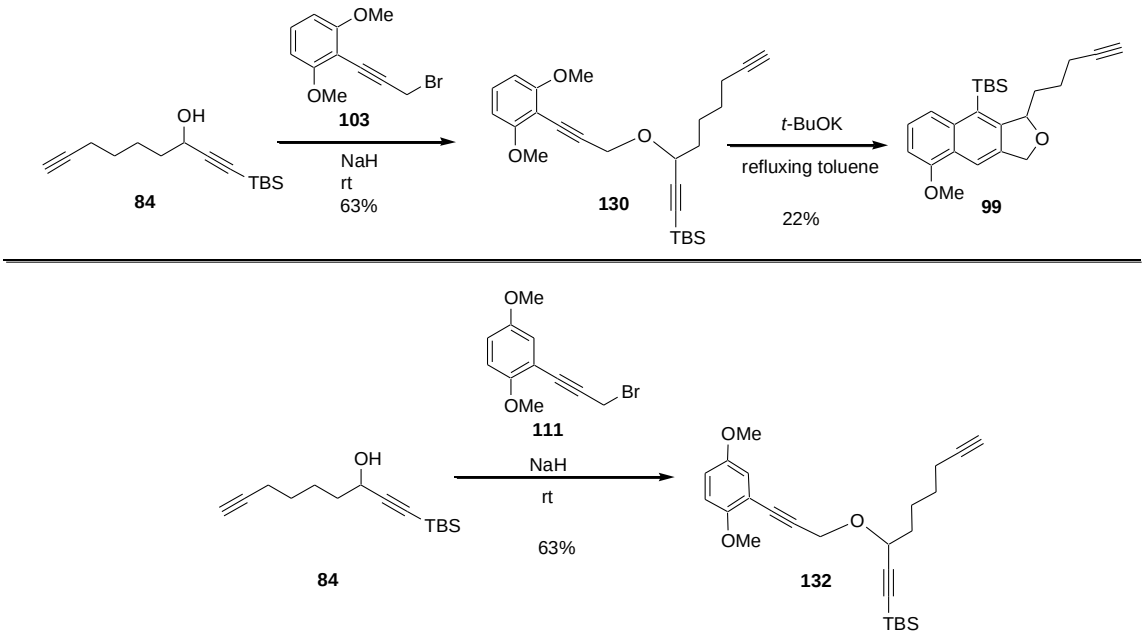
Scheme 31. Preparation and Diradical Cyclization of Ether **128**



84 **128** **129**

o- and *p*-Substituted bis methoxy ethers **130** and **132** were prepared from alcohol **84** and bromides **103** and **111**, respectively, in addition to bis MOM protected ether **128** (Scheme 32). Cyclization of *o*-bis methoxy substrate **130** with *t*-BuOK in refluxing toluene led to undesired naphthalene derivative **99** in low yield, whereas attempts to cyclize *p*-substituted bis methoxy substrate **132** were unsuccessful. Once again, an unanticipated formal reduction accompanied formation of **99**.

Scheme 32. Preparation of bis Methoxy Ethers **130** and **132**



Structure-energy calculations on relevant tricycles in this series were conducted since numerous cyclizations afforded either the naphthalene tricycles or conjugated systems in the case of TBS protected alkyne substrates, without any sign of a persistent thiophene dioxide intermediate. Using simplified structures **133**, **134**, and **135** (Figure 4), B3LYP 631G* density functional calculations were done with Spartan 2004. Napthalene derivative **133** was calculated to be 18 kcal/mol more thermodynamically favorable than conjugated species **134** and 30 kcal/mol more energetically favorable than thiophene dioxide **135**.

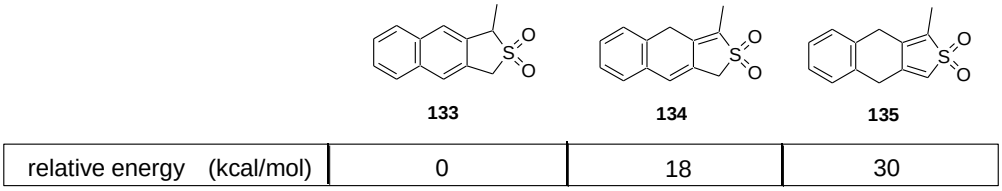


Figure 4. Density Functional Calculations of Diradical Cyclization Product Isomers

Conclusions

Braverman diradical cyclization chemistry is an interesting means to construct naphthalene derivatives, but was unproductive for accessing thiophene dioxide intermediates for a subsequent Diels-Alder reaction with a pendant alkyne. Proton shifts rapidly isomerize the thiophene dioxide intermediate's alkenes into the central ring, creating naphthalene derivatives, which are thermodynamic sinks on the order of 18-30 kcal/mol more energetically favorable. Therefore, the commonly utilized Diels-Alder reactions using juglone and other similar quinones still remain as the most efficient means to construct the angucyclinone family of natural products.

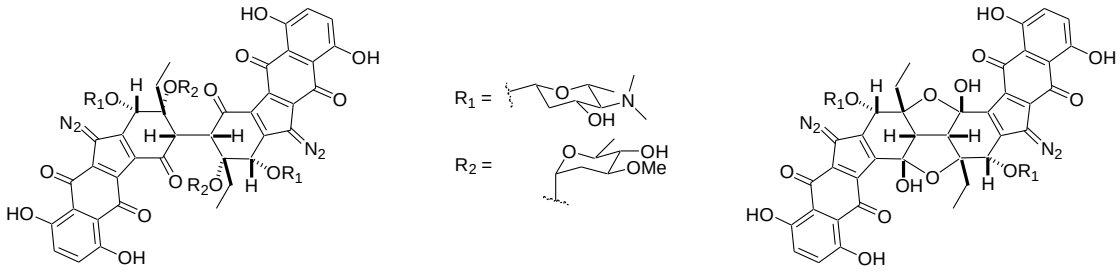
PART II: EFFORTS TOWARD THE SYNTHESIS OF LOMAIVITICINONE A

Chapter 1

Introduction and Background For the Lomaiviticins

2.1 Isolation and Structural Characterization of the Lomaiviticins

Lomaiviticins A (**136**) and B (**137**) were isolated in 2001 by He *et al.* from the fermentation broth of *Micromonospora lomaivitiensis*, a strain of actinomycetes isolated from the marine ascidian *Polysyncraton lithostrotum*[31] (Figure 5). Both lomaiviticins contain the reactive diazoparaquinone functionality present in the kinamycin family of natural products. In addition, both lomaiviticins contain unique stereochemical complexity. Lomaiviticn A contains 6 contiguous stereogenic centers within its dimeric structure. Lomaiviticin B has 8 contiguous stereogenic centers within a strained 6, 5, 5, 6 ring system core that could result from cyclization of the lomaiviticin A aglycone after removal of R_2 (Figure 5). It is also important to note that only the relative stereochemistry of the cores of each of these molecules has been established. Neither the absolute stereochemistry nor the relative stereochemical relationship between the core and the pendant sugars have been determined. Herzon has recently published a review of the lomaiviticins and kinamycins.[32]



(**136**) lomaiviticin A

(**137**) lomaiviticin B

Figure 5. Lomaiviticins A and B

2.1.2 Pharmacology of the Lomaiviticins

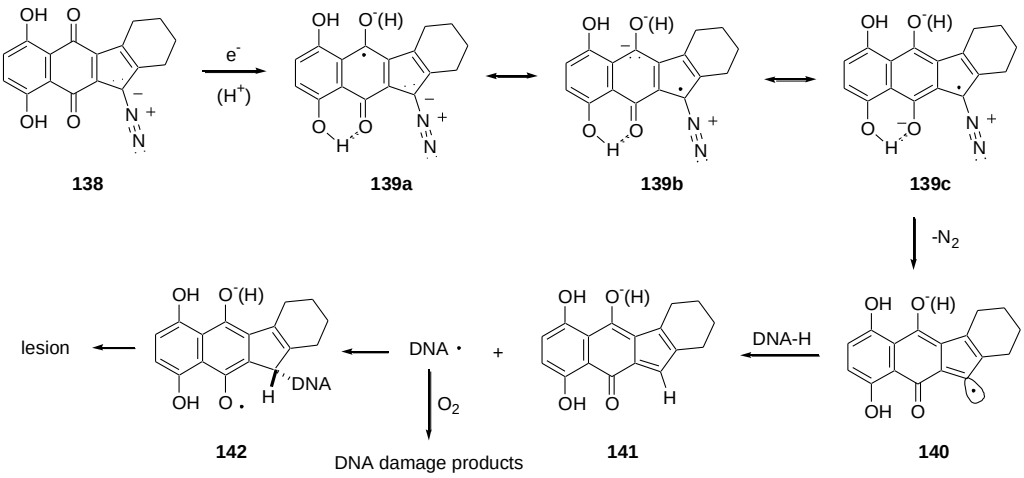
The lomaiviticins are potent antibiotics against gram positive bacteria (*ie. S. aureus*). They also exhibit DNA damaging properties.[31] Lomaiviticin A demonstrated cytotoxicity against 24 cancer cell lines (leukemia, prostate, melanoma, lung, brain, colon, and ovarian), inducing cancer cell death at IC_{50} values ranging from 0.01 to 98 ng/mL.[31]

2.1.3 Proposed Biomechanism of Action of the Lomaiviticins

It has been proposed that the unique diazoparaquinone functionality confers a potent pathway to cancer cell death that is unique to this family of molecules.[33] He's isolation paper stated that under "reducing conditions", lomaiviticin A cleaved double stranded DNA. Direct investigation of the biological properties of these natural products has been hampered by their limited availability via isolation or synthesis. However, a number of studies on diazoparaquinone model systems have been conducted, as described below.

Feldman and Eastman have proposed a mechanism-of-action[34] for the diazoparaquinones based on He's observation and previous work on the interactions of sp^2 radicals with DNA (Scheme 33).[35,36,37] They proposed a single electron reduction of paraquinone **138** to give the "3-electron" species **139a**, which is a resonance form of **139b** and **139c**. After a β-elimination of N_2 affording sp^2 radical **140**, H-abstraction from proximal DNA then might form orthoquinonemethide **141** and a DNA radical. Orthoquinonemethide **141** could be attacked by either (1) DNA●, or (2) by a guanosine nitrogen from a neighboring section of DNA, thus leading to DNA destruction (*i.e.*, lesion formation).

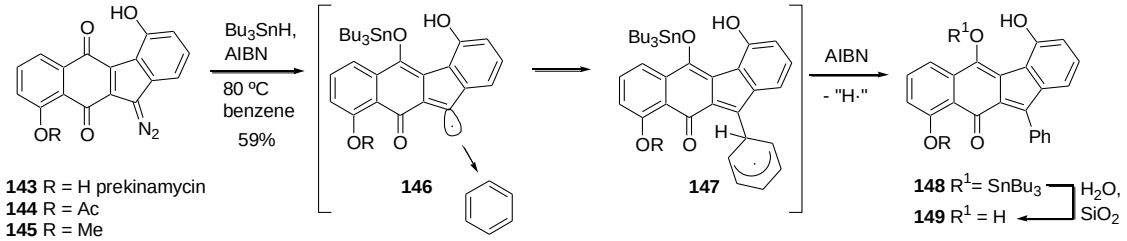
Scheme 33. Feldman and Eastman's Proposed Mechanism of Action for Diazoparaquinones



Feldman and Eastman tested this hypothesis by subjecting known prekinamycin (**143**)[38] to non-biological radical generating conditions (Bu_3SnH and AIBN in benzene). An intermediate enone radical **146** apparently was formed, which added to benzene (solvent), resulting in intermediate **147** (Scheme 34).[39] A subsequent AIBN-mediated

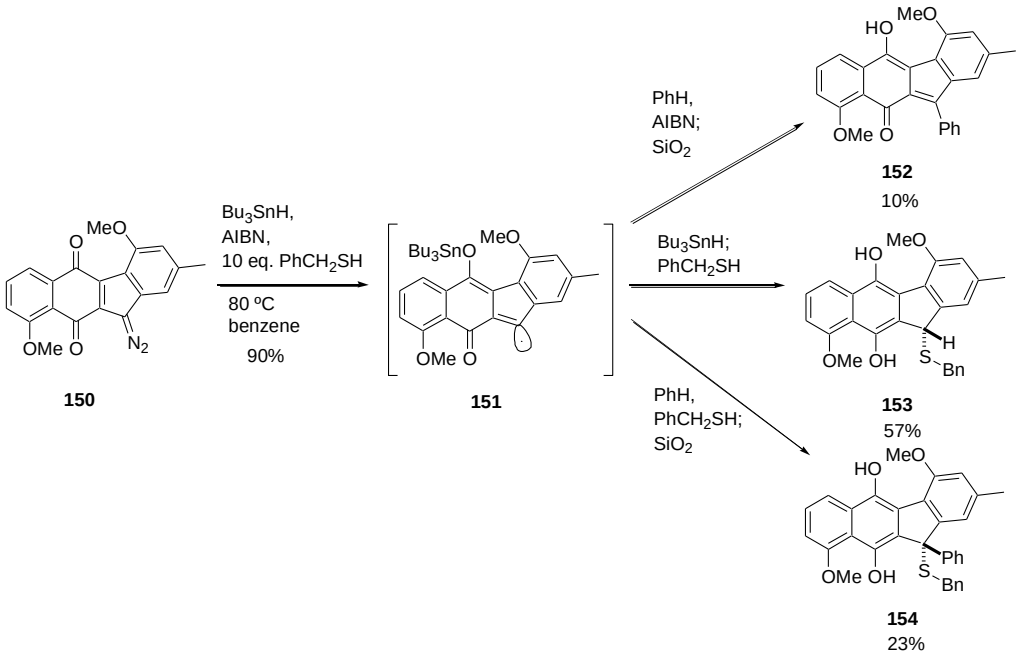
oxidation of **148** afforded **149** in 59% yield. This reaction was successful with electron rich and electron deficient substituted benzenes.

Scheme 34. Feldman and Eastman's Experimental Probe of Prekinamycin Under Reducing Conditions

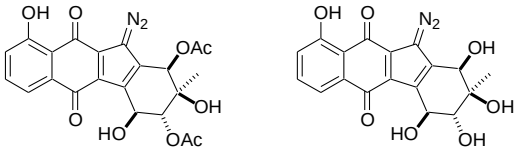


Feldman *et al.* also conducted a study to probe the participation of thiols, as a biologically relevant test nucleophile, under their *o*-quinonemethide-forming conditions (Scheme 35). The inclusion of 10 eq. of $PhCH_2SH$ in their previously established reducing conditions led to a mixture of products with the highest proportion (57% yield) being sulfide **153** resulting from the nucleophilic addition of $PhCH_2SH$ to the intermediate orthoquinonemethide **151** derived from H-atom abstraction by a precursor radical. In addition, sulfide **154**, which was formed by initial sp^2 radical trapping by benzene to form an intermediate orthoquinonemethide followed by addition of $PhCH_2SH$, was isolated in 23% yield.

Scheme 35. Feldman and Eastman's Experimental Probe of Prekinamycin Derivative **150** Under Reducing Conditions With $PhCH_2SH$



An alternative but closely related mechanism was proposed by Melander,[40] and independently by Skibo,[41] who investigated the interactions of the naturally occurring diazoparaquinone kinamycin D (Figure 6) with DNA. Melander found that moderate DNA damage occurred at room temperature *in vitro* upon the addition of low concentrations of kinamycin D in the presence of the common non-biological $2e^-$ reductant dithiothreitol (DTT). Inclusion of the common bioreductant glutathione (GSH) did not result in DNA cleavage. These studies, conducted at the biologically relevant temperature of 37 ºC, led to significant DNA damage in a reducing environment. These results raise the possibility that the mode of action for diazoparaquinones involves an initial 2-electron reduction process rather than the 1-electron reduction cited by Feldman.

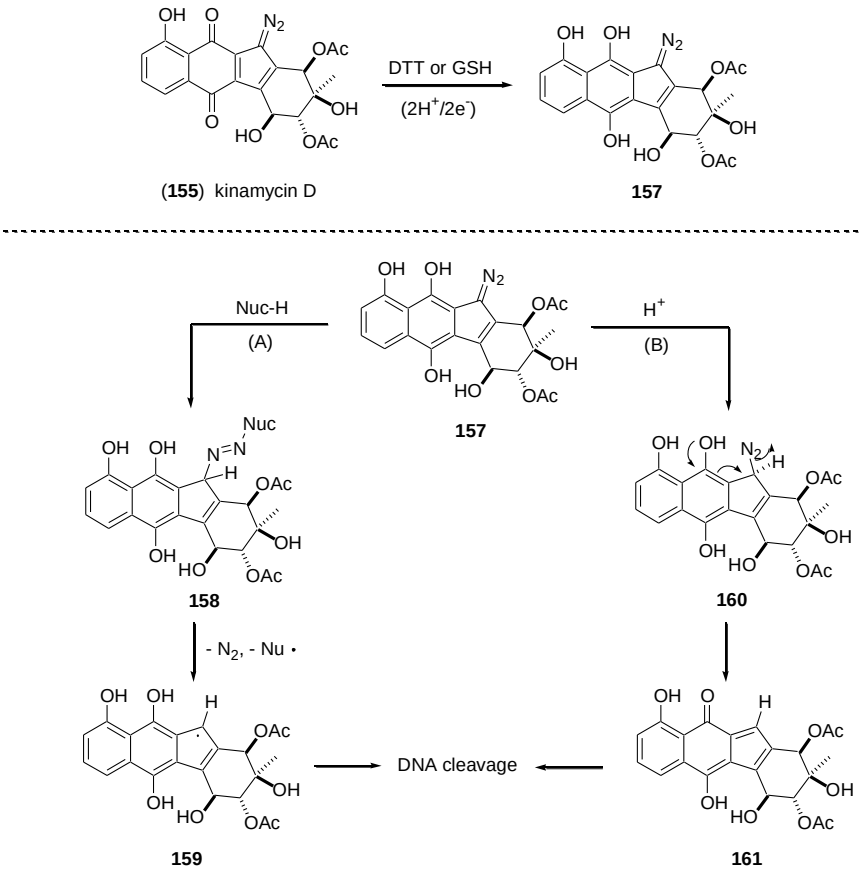


(**155**) kinamycin D (**156**) kinamycin F

Figure 6. Kinamycin D and F

Melander has proposed two different pathways for DNA destruction stemming from the hypothetical 2-electron reduced hydroquinone intermediate **157** (Scheme 36). In path A, nucleophilic addition to the diazo moiety is followed by homolytic cleavage of the C-N bond to afford radical species **159**, which is cited as a DNA damaging radical. Alternatively, protonation of the diazofunction in **157** (pathway B) followed by N_2 expulsion would result in orthoquinonemethide **161**, which could alkylate DNA and eventually cause strand scission. Melander's orthoquinonemethide **161** generated in pathway B is the same type of reactive intermediate proposed earlier by Feldman (Scheme 33). Additional experiments would have to be conducted to differentiate between Melander's two proposed mechanisms. However, it seems unlikely that the intermediate radical **159** would participate in H-atom abstraction since it is stabilized by extensive resonance throughout the aromatic system.

Scheme 36. Melander's Biomechanistic Proposal for Kinamycin D



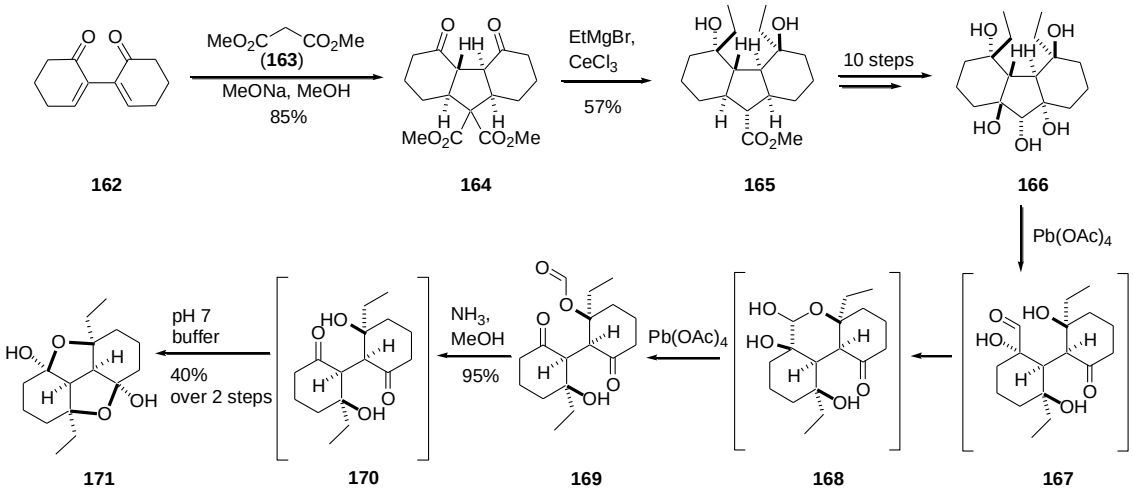
2.2 Previous Synthesis Approaches Towards the Lomaiviticins

2.2.1 Nicolaou's Synthesis Efforts Towards the Lomaiviticins

Nicolaou and colleagues synthesized the core of lomaiviticin B in 2006 (Scheme 37).[42] The route commenced with the stereoselective double Michael addition reaction of dimethyl malonate (**163**) with the known bicyclic enone **162**[43] to prepare tricycle **164**. The double ethylation of bis ketone **164** with ethylmagnesium bromide in the presence of cerium trichloride was accompanied by concomitant decarboxylation of the 1,3-diester moiety to give diol **165** as a single diastereomer. Transformation of ester **165** to pentaol

166 required an additional 10 steps. Tricycle **166** then was converted to the lomaiviticinone B core **171** in a two-step sequence (Scheme 37). Thus, oxidative cleaveage of a cyclopentane C-C bond within **166** with $Pb(OAc)_4$ gave hemiacetal **168**. Further oxidative cleavage of the diol function in transient intermediate **168** mediated by $Pb(OAc)_4$ delivered formate ester **169**. Treatment of this ester **169** with methanolic ammonia provided the lomaiviticinone B core **171**. Unfortunately, the core structure **171** lacked sufficient functionality to complete the synthesis of lomaiviticin B.

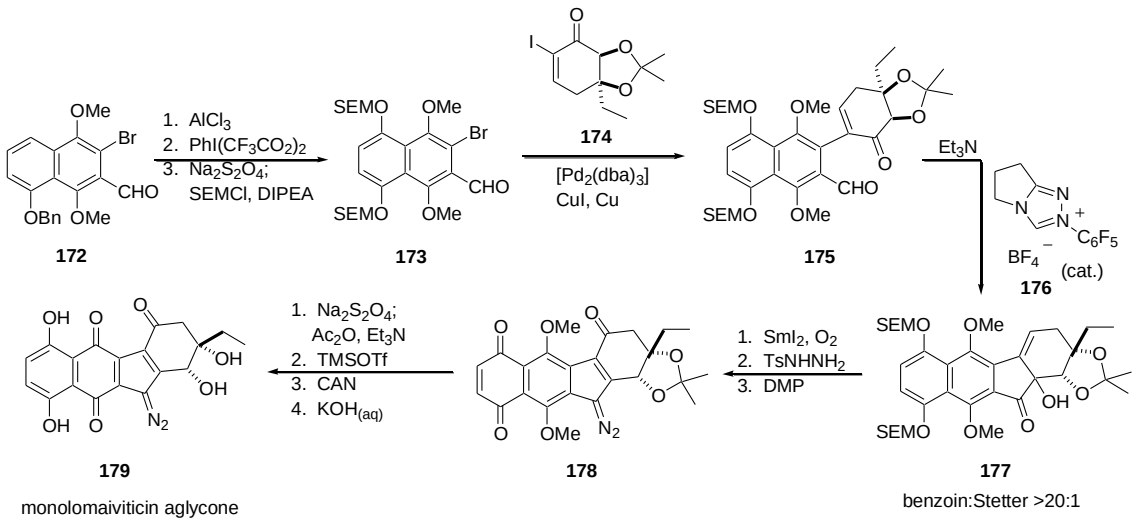
Scheme 37. Nicolaou's Construction of the Lomaiviticinone B Core



Nicolaou published a synthesis of the lomaiviticin monomer (**179**) in 2009 (Scheme 38).[44] The route began with bromide **172**, a species prepared in 8 steps en route to kinamycins C, F, and J.[45] Benzyl deprotection of the naphthalene derivative and oxidation of the resulting phenol with hypervalent iodine gave a quinone that was reduced to the hydroquinone and subsequently double SEM-protected to yield **173**. An intermolecular Ullmann cross coupling of α-iodo enone **174** and aryl bromide **173** afforded enone **175**. Treatment of aldehyde **175** with Rovis catalyst **176** in the presence

of Et_3N afforded benzoin product **177** in a 3:1 dr. Allylic alcohol transposition within **177** under radical conditions in an O_2 atmosphere afforded a γ-hydroxy enone intermediate. The azide moiety was incorporated into this intermediate through initial formation of the hydazone by addition of $TsNHNH_2$ to the cyclopentenone. Under the acidic conditions utilized for hydrazone formation, the SEM protecting groups were removed to afford the hydroquinone. Treatment of this species with Dess Martin periodinane (DMP) led to an α-elimination from the tosyl hydrazone along with concommittant oxidation of both the secondary alcohol on the cylcohexene ring and the hydroquinone to afford quinone **178**. Reduction of the quinone moiety in **178** and acetate protection of the resulting hydroquinone was followed by acetal removal. A CAN-mediated oxidation of the bis methoxy aromatic ring and subsequent acetate removal from the A-ring hydroquinone under basic conditions afforded the monolomaiviticin aglycone **179**.

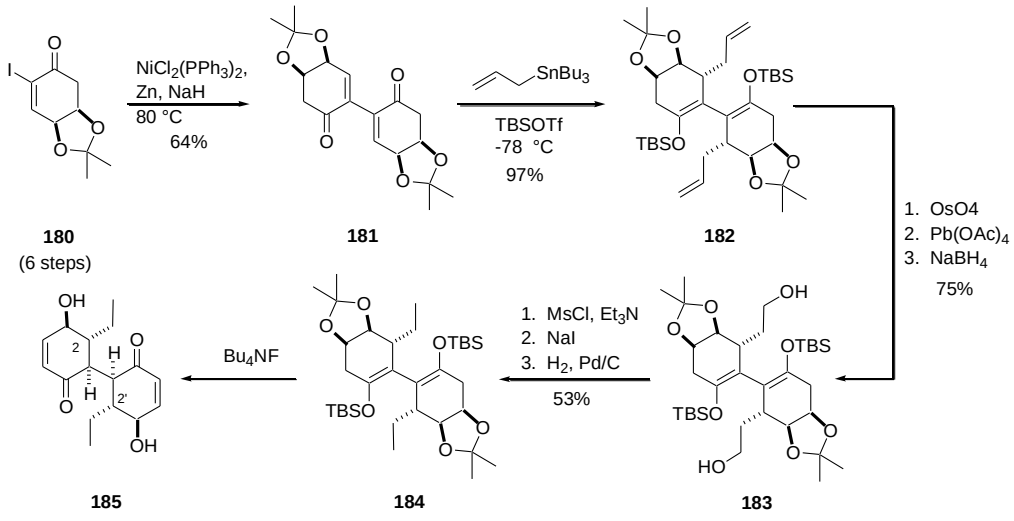
Scheme 38. Nicolaou's Efforts Towards a Lomaiviticin Aglycone



2.2.2 Sulikowski's Efforts Towards the Lomaiviticins

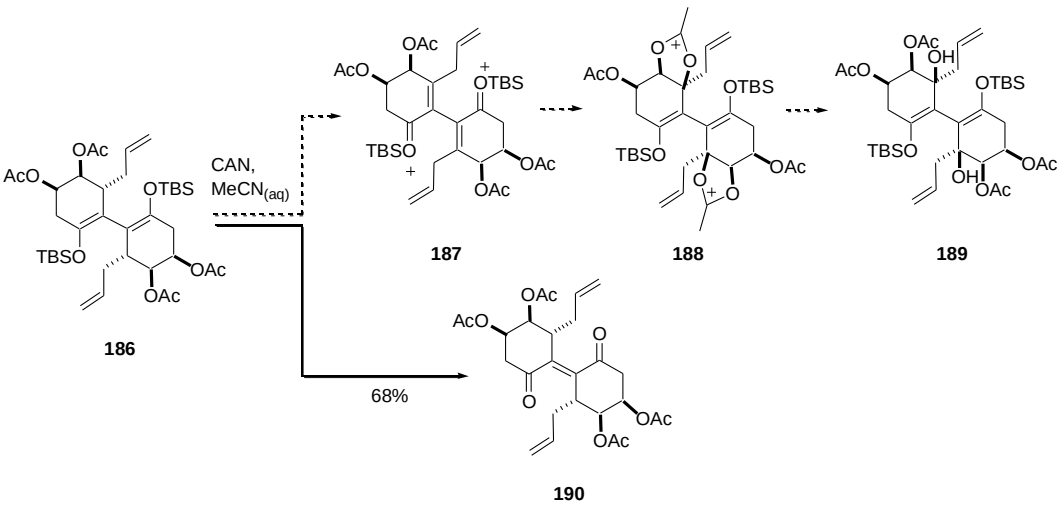
Sulikowski's approach to the lomaiviticins involved the dimerization of α-iodo enone **180** to give tetracycle **181** (Scheme 39).[46] Stereoselective 1,4 allyl addition to each enone function followed by trapping of the bis enolate with TBSOTf afforded bis allyl dienolsilyl ether **182**. Dihydroxylation of the terminal olefins followed by a $Pb(OAc)_4$-mediated oxidative cleavage of the resulting tetraol and then $NaBH_4$ reduction of the derived bis aldehyde accessed diol **183**. Mesylation of diol **183** followed by iodide displacement of the mesylates, and reductive cleaveage of the resultant bis iodide, afforded diethyl species **184**. Double TBS deprotection of **184** gave bis γ-hydroxyenone **185** following elimination of the β ether moiety. However, Sulikowski's most advanced bicycle **185** lacked the necessary tertiary hydroxyl groups at C(2)/C(2') for construction of the lomaiviticins.

Scheme 39. Sulikowski's Efforts Towards the Lomaiviticin Aglycone



Sulikowski's plan was to install the required hydroxyl groups at an earlier stage utilizing methodology developed by Magnus.[47] He proposed that treatment of bis TBS enol ether **186** with CAN in $MeCN_{(aq)}$ would provide enone **187**, which would be poised for internal nucleophilic addition of acetate to give diol **189** following hydrolysis (Scheme 40). Diol **189** theoretically could be isolated and pressed forward in an analogous fashion to the sequence **183** to **185** (Scheme 39). However, treatment of silyl enol ether **186** with CAN led exclusively to the undesired enedione **190** in good yield (68%).

Scheme 40. Sulikowski's Failed Hydroxylation

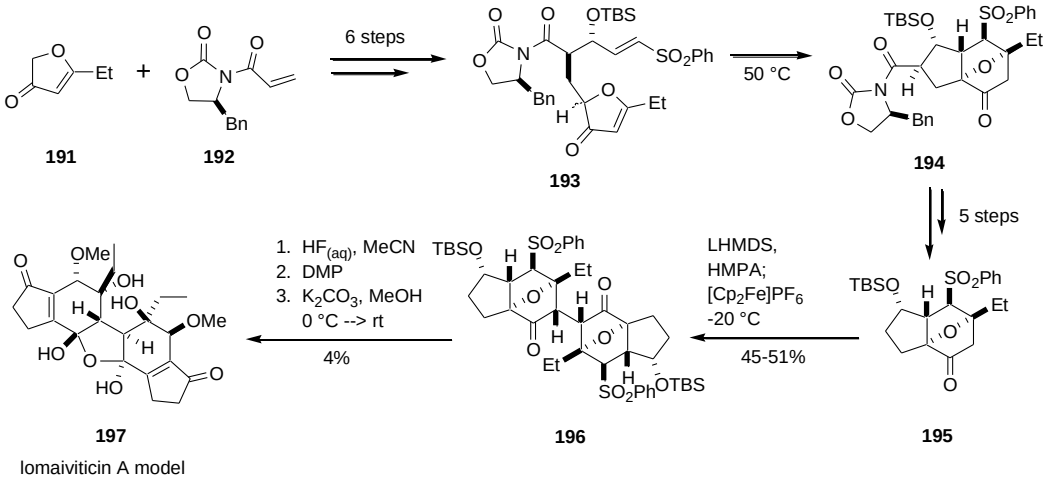


2.2.3 Shair's Synthesis Efforts Towards Lomaiviticin A

Shair published his synthesis work on a lomaiviticin A model system in 2008.[48] This synthesis effort began with the stereoselective coupling of furanone **191** and Evan's chiral auxiliary-functionalized acrylate **192** (Scheme 41). After five additional functional group manipulations, chiral furanone **193** underwent enolization upon heating and then a

Diels-Alder cycloaddition led to endocyclic product **194** as the major component of a 3:1 mixture of diastereomers. It was presumed that the typical *exo* product was the minor species since this particular Diels-Alder reaction is essentially irreversible, as shown by subjection of the minor *exo* product to the reaction conditions, which returned only starting material. The chiral auxiliary was removed, and after another 5 steps, a Barton reductive decarboxylation afforded **195**. The key convergent dimerization/coupling was achieved by treatment of the lithium enolate of ketone **195** with the strong oxidant $[Cp_2Fe]PF_6$ to give dimer **196** as a single diastereomer. TBS deprotection within this dimer **196** followed by Dess Martin oxidation of the resulting alcohols afforded tetraol **197** as a lomaiviticin A aglycone model in low yield following a complex series of transformations.

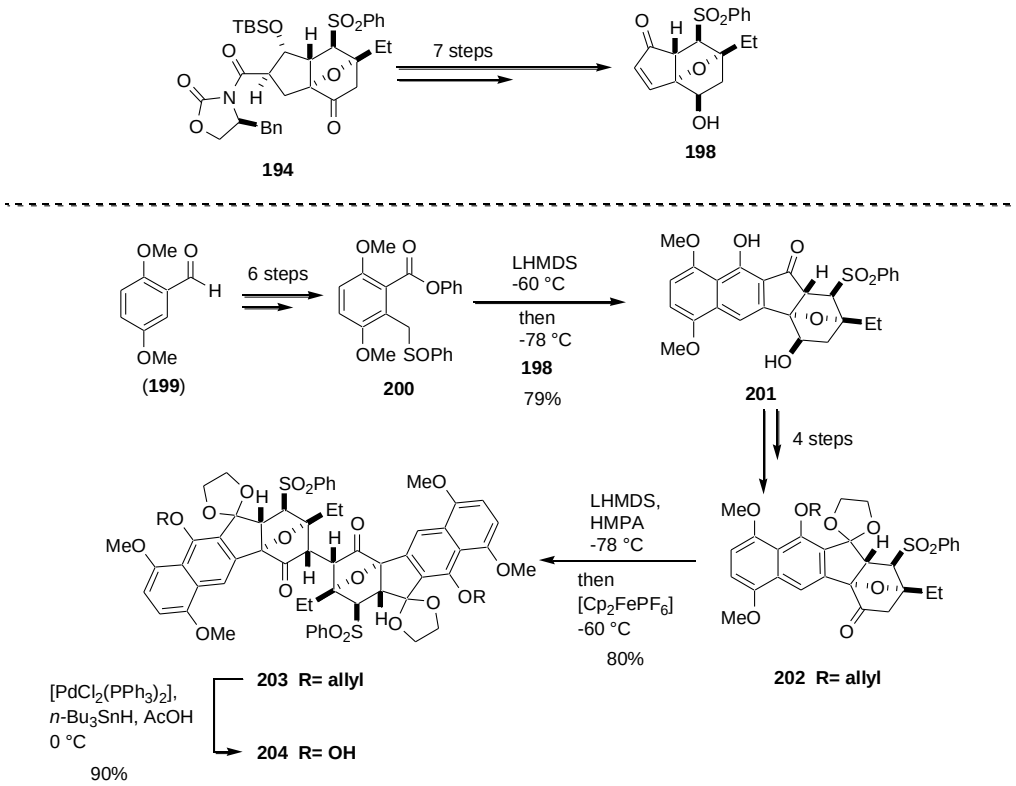
Scheme 41. Shair's Synthesis of a Lomaiviticin A-Type Model



Shair published the synthesis of a more advanced intermediate containing the full carbon skeleton of the lomaiviticin aglycone in 2010.[49] By utilizing his previously published oxazolidinone **194** (Scheme 41), enone **198** was synthesized in an additional 7

steps (Scheme 42). Hauser-type sulfoxide **200** was prepared in 6 steps from commercially available 2,5-(dimethoxy)benzaldehyde (**199**). Hauser annulation product **201** was prepared by the addition of the anion of sulfoxide **200** to enone **198**. Oxidative dimerization of **202** proceeded in high yield by the addition of LHMDS and HMPA to **202** followed by the oxidant [Cp_2FePF_6] to form **203**. Removal of the allyl protecting groups afforded **204** as Shair's most advanced lomaiviticin intermediate, which contains the full aglycone carbon skeleton.

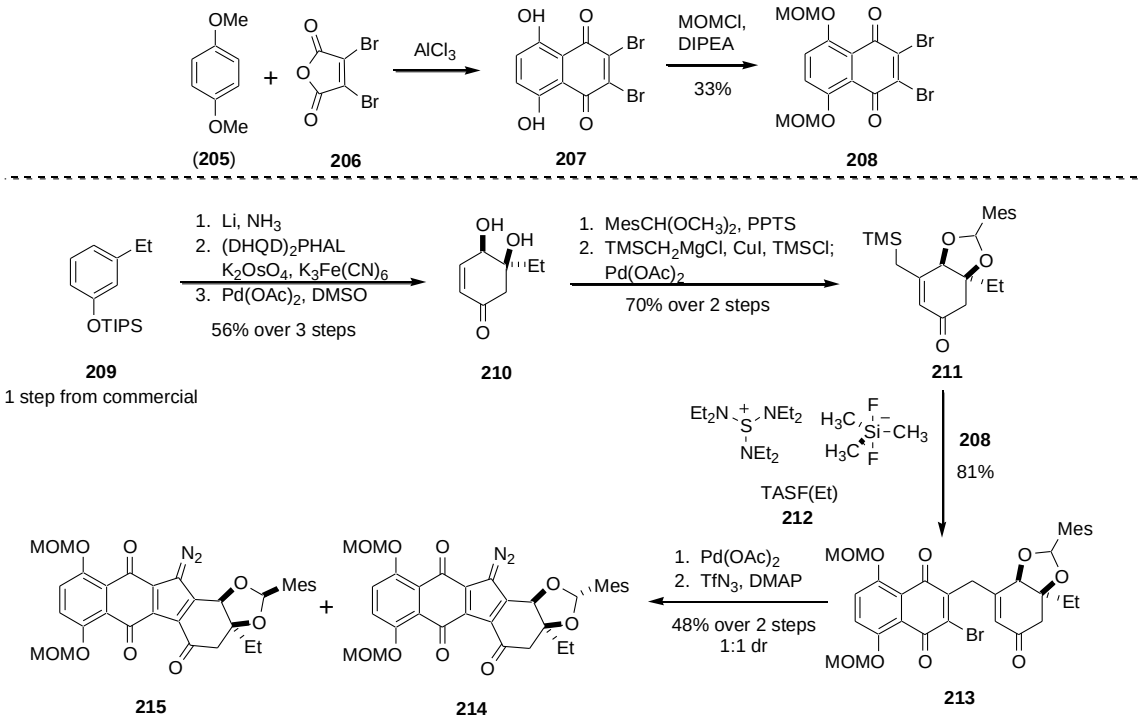
Scheme 42. Shair's Synthesis of the Lomaiviticin Aglycone Carbon Skeleton



2.2.4 Herzon's Lomaiviticinone B Total Synthesis

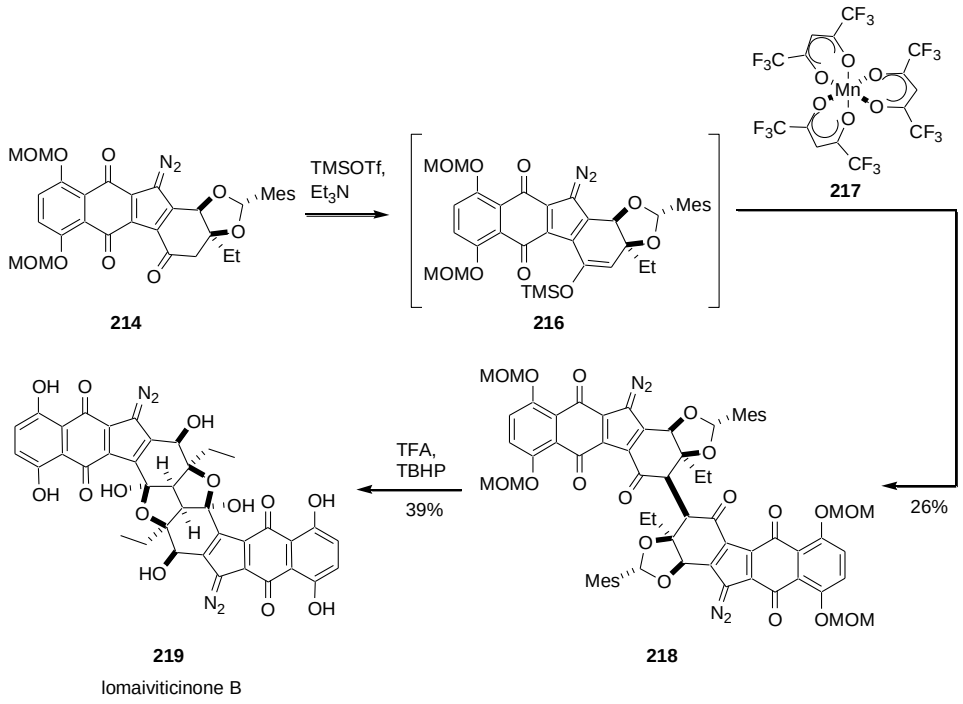
Herzon disclosed the first enantioselective total synthesis of lomaiviticinone B in 2011[50] by building off of his synthesis of the related natural product kinamycin F (Scheme 43).[51] The synthesis commenced with a Birch reduction of TIPS ether **209**, prepared in one step from the commercially available phenol, to give the corresponding 1,4-cyclohexadiene. Enantioselective dihydroxylation of the more accessible olefin in this diene was followed by Saegusa oxidation of the silylenol ether function to give enone **210**. The diol in **210** then was protected as its mesitylaldehyde acetal as a 1:1 mixture of diastereomers that were homologated to the β-TMSMe-α,β-unsaturated ketone by 1,4-addition of $TMSCH_2MgCl$, trapping of the derived enolate with TMSCl, and oxidation of the resulting silyl enol ether with $Pd(OAc)_2$ to give coupling partner **211**. The complementary dibromoquinone coupling partner **208** was prepared in two steps from a Friedel-Crafts condensation of *p*-dimethoxybenzene (**205**) and dibromomaleic anhydride **206** to give dibromo-dihydroxy napthoquinone **207**, which was subsequently protected as its bis MOM ether. An addition/elimination sequence between dibromide **208** and **211** was accomplished using TASF(Et) **212** (Scheme 43) to give **213**. Intramolecular Heck-type coupling of the remaining bromide and the enone promoted by $Pd(OAc_2)$, Ag_2CO_3, and polymer supported PPh_3, followed by diazo transfer to the cyclized product, gave diazo diastereomers **214** and **215** (1:1 ratio).

Scheme 43. Commencement of Herzon's Synthesis of Lomaiviticinone B



Addition of Et_3N followed by TMSOTf to ketone **214** resulted in formation of intermediate TMS enol ether **216**, which was directly dimerized with manganese tris(hexafluoroacetylacetonate) **217** to give the desired diastereomer **218** in 26% yield along with the undesired diastereomer in 12% yield (Scheme 44). Treatment of the desired stereoisomer **218** with a solution of *t*-butyl hydroperoxide (TBHP) and trifluoroacetic acid (TFA) resulted in deprotection of the diol and cyclization of the resulting tetraol into lomaiviticinone B **219** in a total of 11 steps from silyl ether **209**.

Scheme 44. Herzon's Total Synthesis of Lomaiviticinone B



2.3.1 Conclusions

Several groups have worked towards the syntheses of lomaiviticins A and B since their isolation over a decade ago. Nicolaou has constructed core model systems for both lomaiviticins, with his lomaiviticinone B core construction taking 15 steps, whereas Sulikowski's 22-step approach lacked the required hydroxyl groups. Shair has published a lomaiviticin B model system that resulted from an undesired cyclization event, in addition to the synthesis of a dimeric species containing the full carbon skeleton of lomaiviticin A. Herzon has efficiently synthesized lomaiviticinone B enantioselectively in 11 steps. This work stands out as the only successful synthesis to date.

Chapter 2

Synthesis Efforts Toward Lomaiviticinone A

2.2.1 Introduction

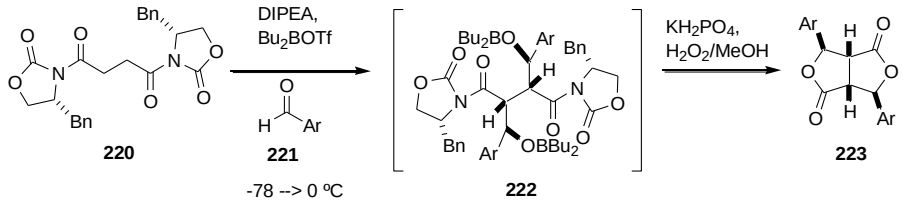
The dimeric nature of the lomaiviticin target naturally suggests two diametrically opposing strategies for chemical synthesis; (1) a monomer dimerization strategy as explored by Herzon and by Shair, and (2) a divergent two-directional growth strategy as initiated by Nicolaou and by Sulikowski. Clearly, the dimerization strategy has yielded fruit in the work of Herzon, whose efficient 11-step synthesis demonstrates the advantages of this approach. However, stereochemical control was lacking in the dimerization and in earlier steps, and so there is room for improvement. In fact, a divergent two-directional approach may provide a concise solution to the stereochemical issues raised by the Herzon chemistry, if executed correctly. In this vein, several routes have been explored for the construction of lomaiviticinone A. The routes included in this section involve (1) a double aldol approach, (2) a Diels-Alder approach, and finally (3) a double Ireland-Claisen rearrangement approach, which also includes a mono Ireland-Claisen rearrangement model system and a double Ireland-Claisen rearrangement model system.

2.2.2 Double Aldol Approach

2.2.2a Retrosynthetic Analysis

Park *et al.* developed an enantioselective double aldol reaction between Evans' chiral auxiliary succinic acid derivative **220** and strictly aromatic aldehydes leading to bis lactone substrates **223** upon oxidative workup (Scheme 45).[52] This methodology efficiently establishes the 4 stereogenic centers found in lactone **223** in a dr greater than 95:5. If this chemistry can be extended to functionalized aliphatic aldehydes, an efficient and stereoselective approach to the lomaiviticin core can be envisioned.

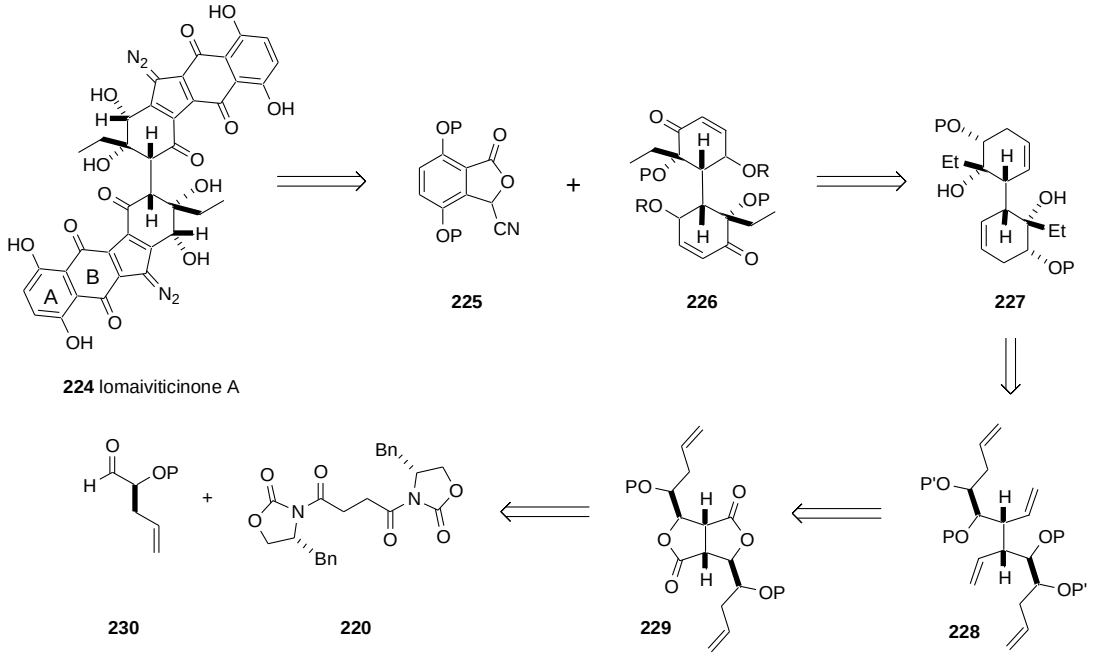
Scheme 45. Enantioselective Bis Aldol Using Succinic Acid Derivative **220**



A retrosynthesis of lomaiviticinone A featuring this chemistry is shown in Scheme 46. This approach relies on a two-directional annulation strategy between the bicyclic core **226** and the A/B ring synthon **225**. This Hauser annulation approach, utilized by the Feldman group during attempts towards kinamycin F,[53] represents an efficient sequence to build molecular complexity quickly. Construction of bis enone **226** then forms the first goal, and its synthesis will rely on the Park double aldol chemistry. This species could be formed from bicycle **227** through a short series of modifications. The bis cyclohexene **227** could be made via ring closing metathesis of tetraene **228**. Tetraene **228** could be prepared by a double Wittig methylenation of the bis lactol

derived from bis lactone **229**, a species that could be synthesized via a stereoselective double aldol reaction utilizing succinic acid derivative **220** and chiral aldehyde **230**.

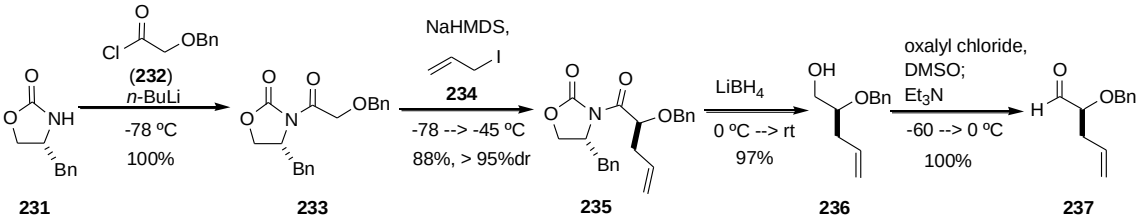
Scheme 46. Double Aldol Retrosynthesis



2.2.2b Results and Discussion

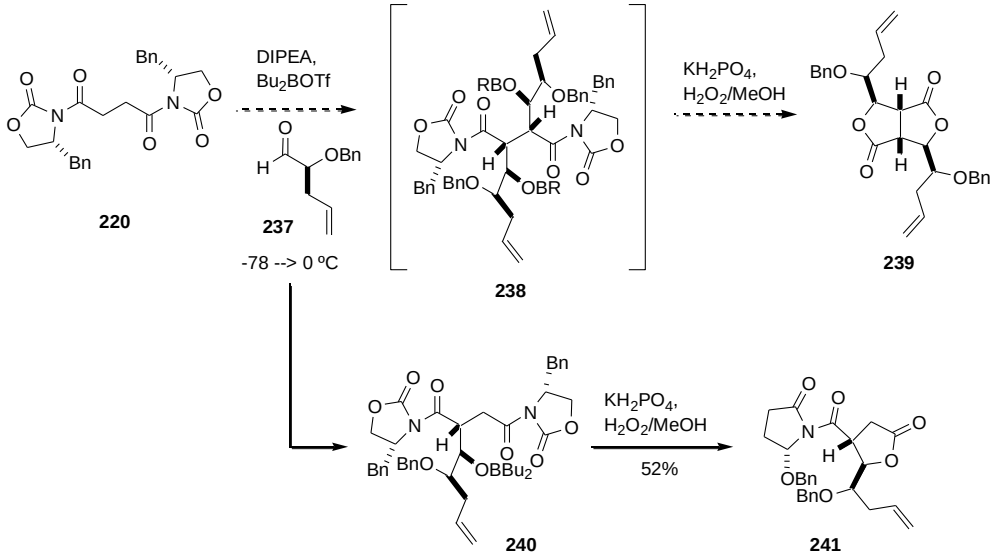
Construction of chiral aldehyde **237** began by coupling Evans' chiral auxiliary **231** and benzyloxyacetyl chloride (**232**) to give **233** in high yield (Scheme 47). Stereoselective allylation of **233** followed by chiral auxiliary removal/reduction with $LiBH_4$ afforded alcohol **236**. Swern oxidation of alcohol **236** readily afforded aldehyde **237**.

Scheme 47. Construction of Chiral Aldehyde **237**



The aldol reaction with succinic acid derivative **220**[52] and aldehyde **237** resulted in mono addition, giving **241** as the only isolable compound (Scheme 48). Intermediate **240** (as its boron enolate) was presumably too sterically encumbered to participate in a second aldol reaction.

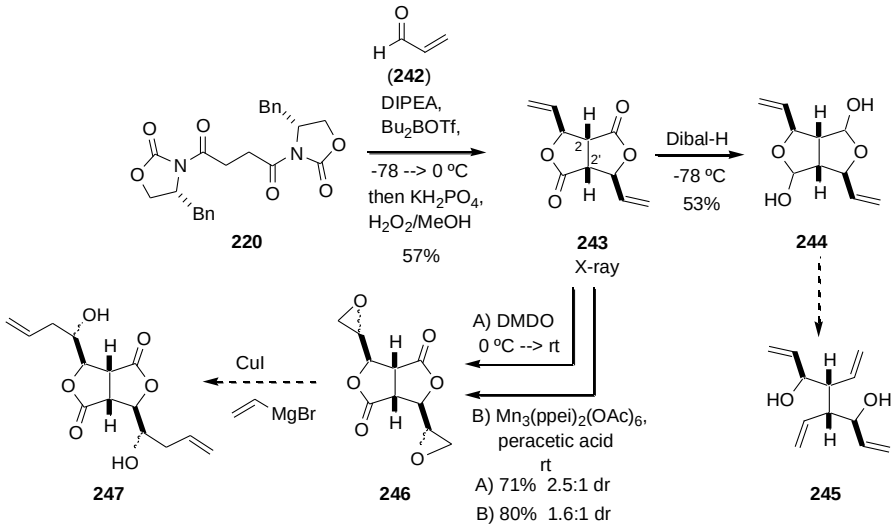
Scheme 48. Double Aldol With Functionalized Aldehyde **237**



The attempted double aldol reaction of **220** and branched aliphatic aldehyde **237** was quite distant from the Park precedent. In order to increase the chance of success, a more conservative approach using the simpler aldehyde acrolein was pursued next. The stereoselective double aldol reaction was performed with acrolein (**242**) to give bis lactone **243** (Scheme 49) as a single compound whose relative stereochemistry was

confirmed by single crystal X-ray diffraction (Figure 7). This transformation represented the first example of a Park double aldol with a non-aromatic aldehyde. Partial reduction of bis lactone **243** with Dibal-H afforded bis lactol **244**, which was subjected to a number of olefination conditions in an attempt to access tetraene **245** directly (Table 3). All of these attempts failed. Stereoselective bis epoxidation of the diene **243** to give **246** was achieved with DMDO in a modest 2.5:1 dr, whereas $Mn_3(ppei)_2(OAc)_6$ and peracetic acid[54] produced **246** in slightly better yield but even lower dr (1.6:1). Unfortunately, all attempts at vinyl cuprate addition to bis epoxide **246** led to decomposition products.

Scheme 49. Double Aldol With Acrolein (**242**)



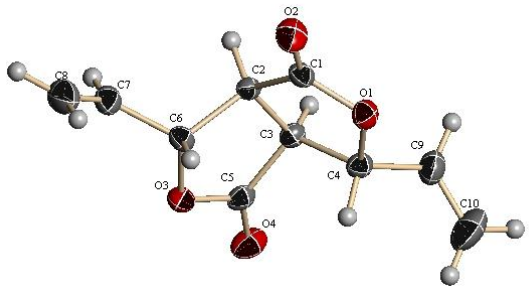


Figure 7. X-Ray Structure of Double Aldol Product **243**

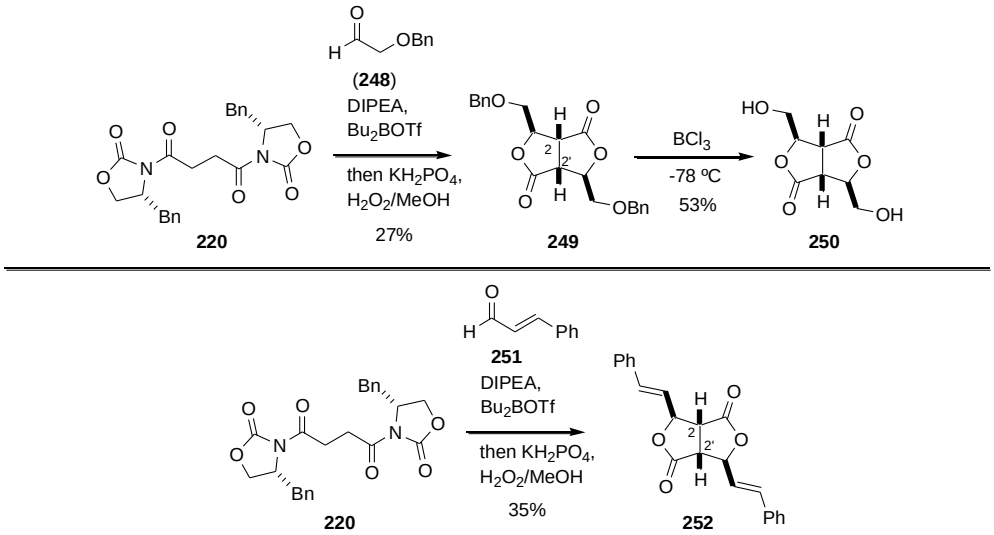
Table 3. Failed Olefination Attempts on Lactol **244**

Entry	Base	Ylide Precursor	Solvent	Temperature (°C)
1	NaH	Ph_3PCH_3Br	THF	0 to reflux
2	NaH	Ph_3PCH_3Br	DMSO	70
3	*n*-BuLi	Ph_3PCH_3Br	THF	0 to reflux
4	*t*-BuOK	Ph_3PCH_3I	THF	-78 to rt
5	*n*-BuLi	Ph_3PCH_3Br	tol	0 to 80

The double aldol reaction with succinic acid derivative **220** also was successful with other aliphatic aldehyde substrates. Benzyloxyacetaldehyde (**248**) and **220** led to bis lactone **249** in 27% yield, whereas trans-cinnamaldehyde (**251**) gave bis lactone **252** in a slightly better yield of 35%. The stereochemical assignments of **249** and **252** were made by a comparison of their ^{1}H NMR spectra with that of bis lactone **243**, whose stereochemistry was established by single crystal X-ray analysis (*vide supra*). The ^{1}H NMR signals for the protons located on C(2)/C(2') of bis lactones **243**, **249**, and **252** were each singlets, verifying their anti-relationship with the neighboring non-equivalent proton.

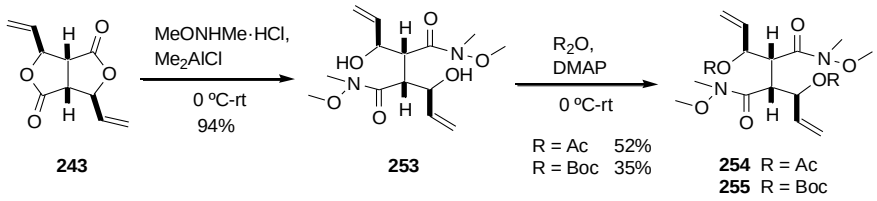
Bis lactone **249** contains an ether functionality, which was envisioned to serve as a starting point to introduce a bis acid chloride or bis aldehyde en route to a bis allyl species. Bis lactone **252** was envisioned to serve the same role as bis lactone **243** through ozonolysis of the alkenes to afford a bis aldehyde. Benzyl deprotection of **249** with BCl_3 afforded diol **250**, but the low yield of the **220** → **249** transformation dissuaded further work on this substrate.

Scheme 50. Double Aldols With Alternative Aldehydes



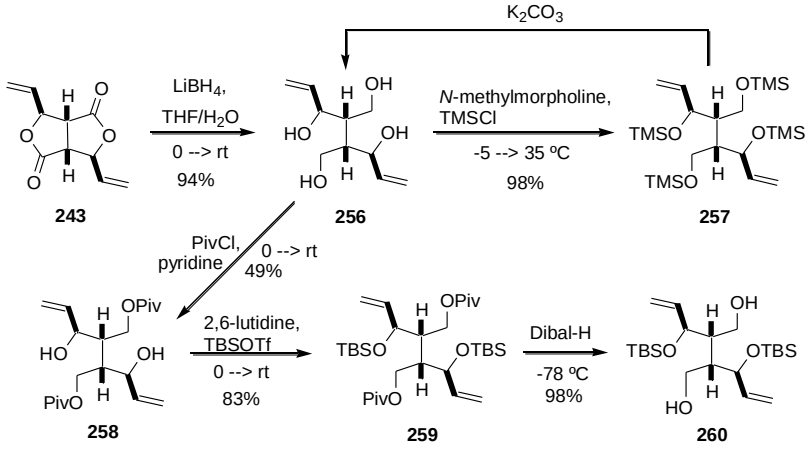
Efforts were refocused on functionalizing bis lactone **243** due to the low yields of the aforementioned double aldol reactions. Bis Weinreb amide **253** was prepared in high yield by treating bis lactone **243** with the *N,O*-dimethoxyhydroxyl amine HCl salt and Me_2AlCl[55] (Scheme 51). Attempts to protect the diols in **253** as their TBS or MOM ethers were unsuccessful, but the acetate and Boc-protected species **254** and **255**, respectively, were prepared. Attempted Sharpless epoxidation of diol **253** surprisingly led to no reaction whereas attempts to convert bis Weinreb amides **254** and **255** to their respective bis aldehydes also were unsuccessful.

Scheme 51. Preparation of Bis Weinreb Amides **254** and **255**



A longer but more productive route to incorporate the desired methylene groups then was pursued. Bis lactone **243** was reduced to tetraol **256** with $LiBH_4$ (Scheme 52). Subsequent global alcohol protection as the tetra-TMS ether gave **257**. It was hoped that a regioselective desilylation would remove the primary TMS groups while leaving the secondary TMS groups untouched, but this selectivity proved impossible to achieve, as tetraol **256** was formed each time. Instead, the primary alcohols of **256** were protected as their pivalate esters to give **258**, followed by TBS protection of the secondary alcohols to give bis silyl ether **259**. The pivalates were cleaved with Dibal-H to give diol **260** in near quantitative yield.

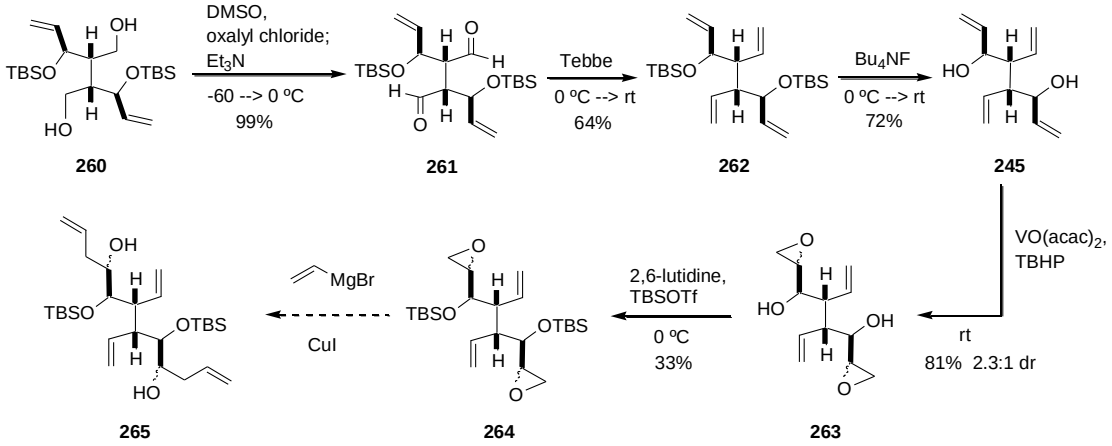
Scheme 52. Preparation of Diol **260**



Bis Swern oxidation of the diol gave bis aldehyde **261**, which was olefinated with Tebbe's reagent to furnish tetraene **262** (Scheme 53). Removal of the silyl ethers in **262** afforded bis allylic diol **245**, which was epoxidized with *t*-butyl hydroperoxide (TBHP) and $VO(acac)_2$ to give bis epoxide **263** in a modest 2.3:1 dr. Protection of diol **263** as the bis TBS ether gave epoxide **264**. All attempts at vinyl cuprate addition to epoxide **264**

again met with failure. Ultimately, this route was too inefficient for the synthesis of **245** and so new efforts were focused on potentially more efficient approaches.

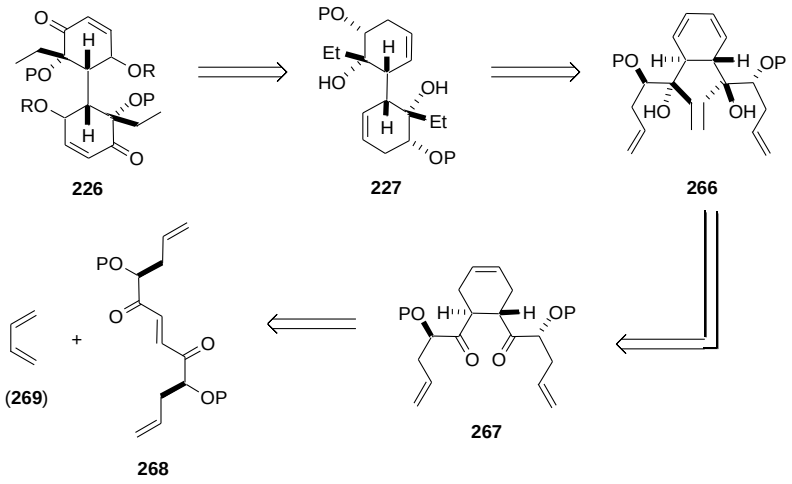
Scheme 53. Preparation of Diol **245**



2.2.3 Diels-Alder Reaction Approach

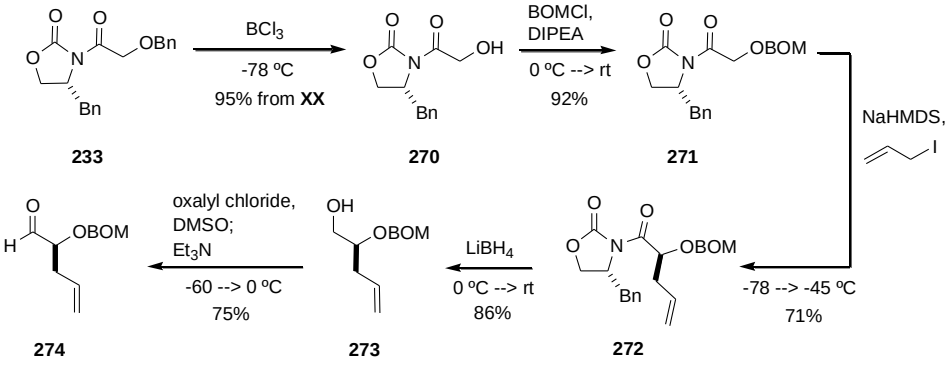
Another route to the lomaiviticin A bicyclic core **226** utilized a stereoselective Diels-Alder reaction between 1,3-butadiene (**269**) and chiral enedione **268** as the key step (Scheme 54). Some of the preliminary work for this route was performed by Dr. Daljit Matharu, a postdoctoral researcher in the Feldman laboratory. The lomaiviticinone A core could arise from a short series of transformations on bicycle **227**, which could be made from double ring-closing metathesis of tetraene **266** (Scheme 54). Tetraene **266** could arise from diketone **267**, which could be constructed from a Diels-Alder reaction between butadiene (**269**) and enedione **268**.

Scheme 54. Diels-Alder Reaction-Based Retrosynthesis



The preparation of homo-chiral enediones **284** and **285** (Scheme 56) began with the previously utilized benzyloxy substrate **233** (Scheme 47). Benzyl deprotection of **233** with BCl_3 followed by BOM reprotection of the liberated alcohol led to BOM ether **271** (Scheme 55). Stereoselective allylation of **271**, followed by reductive cleaveage of the chiral auxiliary with $LiBH_4$, afforded alcohol **273**, which was readily oxidized to aldehyde **274** under Swern conditions.

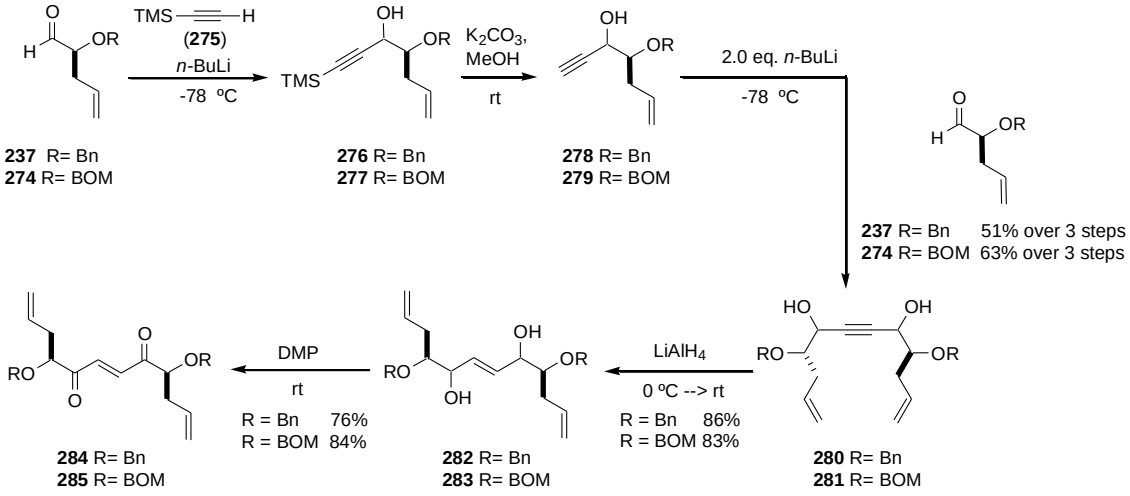
Scheme 55. Construction of Aldehyde **274**



Addition of the lithiate of TMS acetylene to aldehydes **237** and **274** and subsequent TMS removal with K_2CO_3/MeOH afforded propargylic alcohols **278** and **279**,

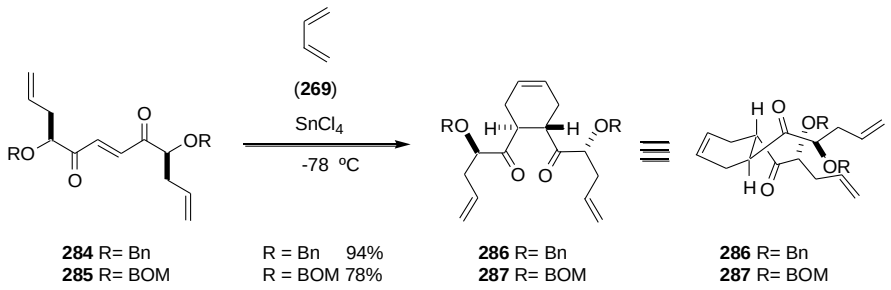
respectively (Scheme 56). Addition of the dianions of **278** and **279** to aldehydes **237** and **275** provided the desired diols **280** and **281**, respectively. Enediones **284** and **285** were prepared by a stereoselective reduction of the alkynes in **280** and **281** with $LiAlH_4$ to furnish the *trans*-substituted alkenes **282** and **283**, respectively. Dess Martin periodinane (DMP) oxidations of the intermediate enediols **282** and **283** led to the enediones **284** and **285**, respectively.

Scheme 56. Preparation of Ene-diones **284** and **285**

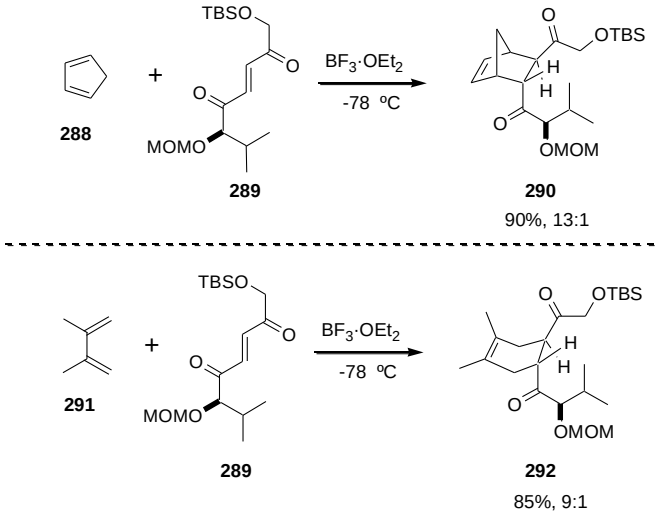


Diels-Alder cycloaddition between butadiene (**269**) and enediones **284** and **285** in the presence of a catalytic amount of $SnCl_4$ afforded diketones **286** and **287**, respectively, in high yields as single isomers (Scheme 57). The stereochemical assignments were suggested by ^1H NMR spectral data comparison with similar Diels-Alder reaction products synthesized by Kobayashi *et al.*[56] (Scheme 58) and by nOe studies of a downstream intermediate (*vide infra).*

Scheme 57. Diels-Alder Reaction of Dienophiles **284** and **285** with Butadiene (**269**)



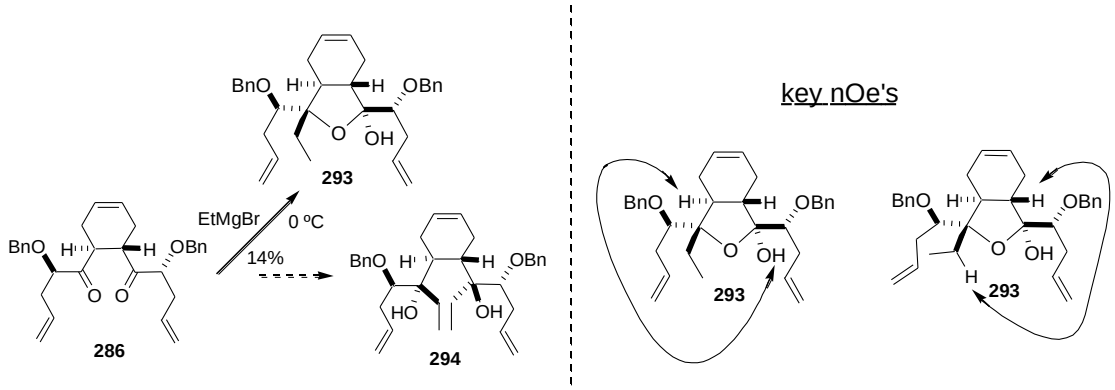
Scheme 58. Kobayashi's Diels-Alder Reactions Employing Site-Recognition of Alkoxy Carbonyls



Attempted addition of EtMgBr to diketone **286** resulted in monoaddition with the resulting alcohol cyclizing into the remaining ketone to give hemiacetal **293**, whose stereochemical assignment was made through nOe studies (Scheme 59), as the only isolable compound. Alternatively, the addition of EtLi, which may have less propensity to chelate the diketone, did not afford the desired diol **294**, surprisingly returning only diketone **286**. The addition of $MgBr_2 \cdot Et_2O$ with EtMgBr was shown to avoid this type of hemiketal-forming cyclization problem in a similar system,[57] but this reagent combination did not solve the unwanted cyclization problem with our substrate. The

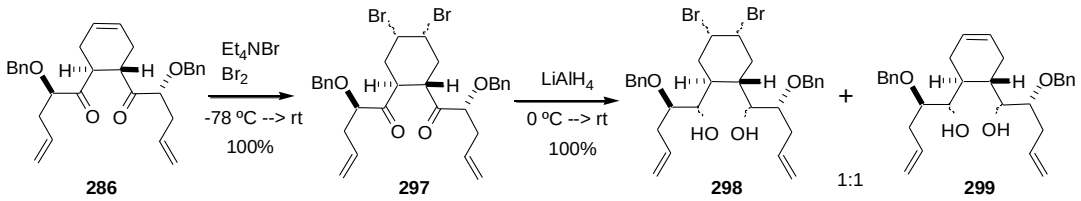
required ethyl units would have to be incorporated at a later stage since double ethyl addition to diketone **286** led to undesired hemiacetal **293**.

Scheme 59. Ethyl Addition to Diketone **286**



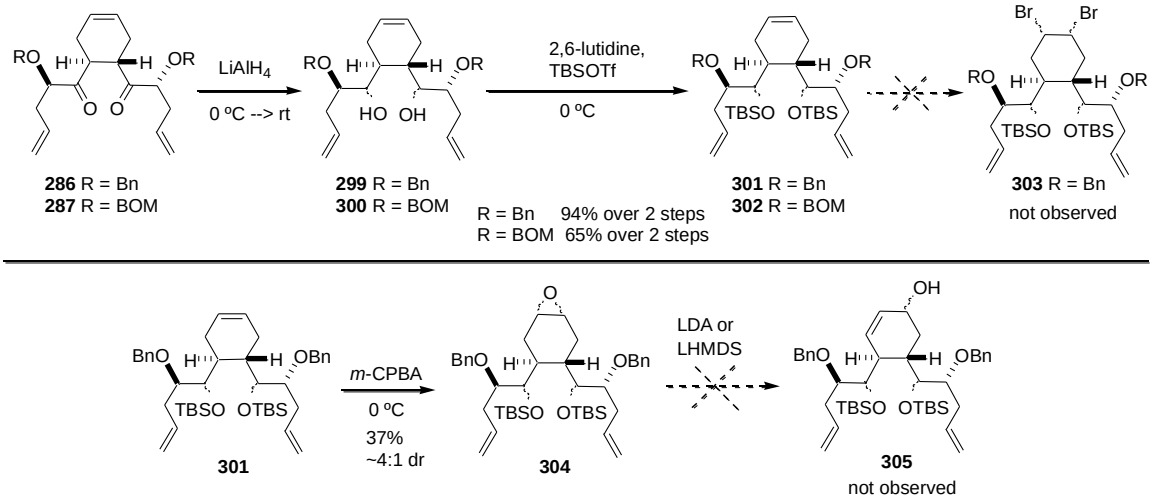
The cyclohexenyl alkene in **286** would have to be transformed into a diene such as in **266** (Scheme 54) in order to set up a ring-closing metathesis with the terminal olefins of **286** to form the desired bicycle **227**. Towards this goal, bromination of the cyclic alkene within **286** afforded dibromide **297** as a mixture of isomers (Scheme 60). Elimination of the dibromide likely would have resulted in an isomerization of the double bonds into conjugation with the ketones. To prevent this isomerization, the ketone moieties of **297** first were reduced with $LiAlH_4$. Unfortunately, this reduction resulted in the formation of undesired elimination product **299** in addition to the desired diol **298**.

Scheme 60. Accessing Diol **298**



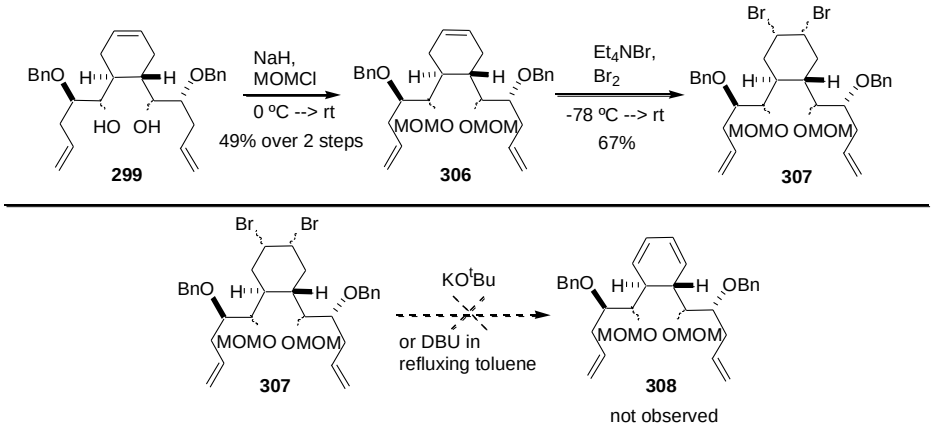
A reduction of the diketones in **286** and **287** was performed before bromination to circumvent the elimination problem as seen with dibromide **298**. TBS ethers **301** and **302** were synthesized by reduction of diketones **286** and **287** with $LiAlH_4$ followed by protection of the resulting mixture of isomeric alcohols with TBSOTf (Scheme 61). Bromination attempts on benzyl ether **301** (pyridinium tribromide, Et_4NBr with Br_2, and *N*-bromosuccinimide (NBS)) were unsuccessful, but epoxidation of the cyclic alkene with *m*-CPBA afforded epoxide **304** as roughly a 4:1 mixture of diastereomers. Attempts to open this epoxide with either LDA or LHMDS in order to yield allylic alcohol **305** failed.

Scheme 61. Preparation of TBS Ethers **301** and **302** and Epoxide **304**



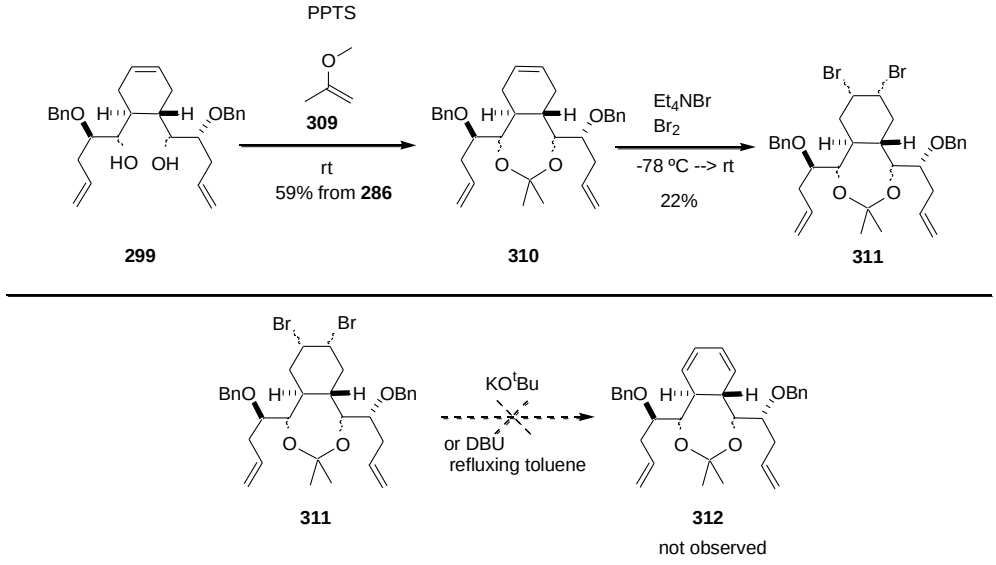
In addition, diol **299** was bis MOM ether protected and subsequently brominated to afford dibromide **307** (Scheme 62). Unfortunately, all attempts at base promoted elimination of 2HBr from dibromide **307** resulted in either decomposition or no reaction.

Scheme 62. Preparation of MOM-Protected Ether **306** and Failed Bromide Elimination



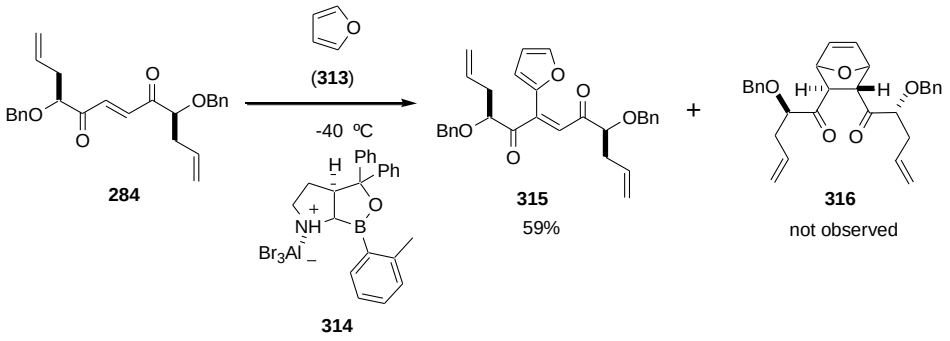
As an alternative, cyclic acetonide **310** was prepared from diol **299** (Scheme 63). Bromination of **310** proceeded in poor yield to give dibromide **311**. Attempted elimination of the bromines with strong bases again did not give desired tetraene **312**, but only complete destruction of **311** was observed.

Scheme 63. Preparation of Cyclic Ketal **311** and Subsequent Failed Bromide Elimination

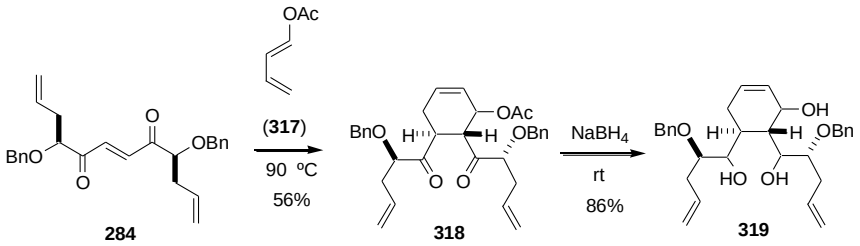


A number of alternative dienes were also examined in the Diels-Alder reaction with enedione **284**. Attempted oxazaborolidine(**314**)-catalyzed Diels-Alder reaction between furan (**313**) and enedione **284** exclusively afforded a 1,4-addition product **315** (Scheme 64). Diels-Alder reaction with 1-acetoxybutadiene (**317**) and enedione **284** was successful upon heating at 90 ºC (Scheme 65). Attempted double ethyl addition to diketone **318** with EtMgBr surprisingly only returned starting material, whereas reduction of **318** with $NaBH_4$ afforded triol **319**. Since differentiation of the ring and sidechain secondary alcohols in a protection/elimination sequence seemed exceedingly cumbersome if not impossible, this approach to lomaiviticinone A was abandoned.

Scheme 64. Failed Diels-Alder Reaction with Furan



Scheme 65. Diels-Alder Reaction with 1-Acetoxy Butadiene (**317**)

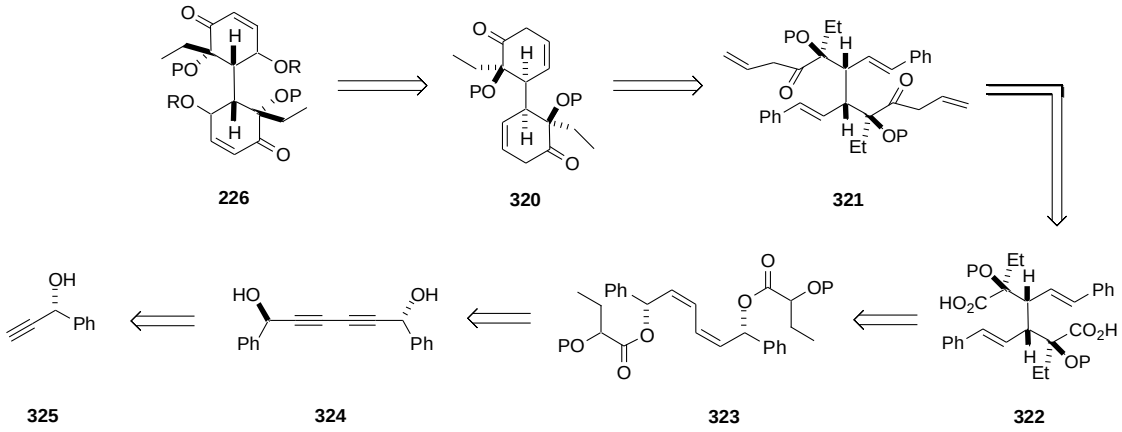


2.2.4 Double Ireland-Claisen Rearrangement Route

A double Ireland-Claisen rearrangement was envisioned to be an efficient alternative means to assemble the bicyclic lomaiviticin A core with stereochemical control. Elaborating on this idea, the lomaiviticinone A core **226** could be constructed from β,γ-unsaturated enone bicycle **320**, which itself could be formed via ring closing metathesis of tetraene **321** (Scheme 66). The bis allyl portion of **321** could arise from dicarboxylic acid **322**, which could be made stereoselectively from a double Ireland-Claisen rearrangement of glycolate derivative **323**. Ireland-Claisen substrate **323** could arise from diyne diol **324**, which could be prepared from enantiomerically pure propargyl alcohol **325** via a Glaser coupling.

The Ireland-Claisen reaction is a [3,3]-sigmatropic rearrangement that was first described in 1972 by Ireland.[58] Most notably, contiguous stereogenic centers can be formed with high diastereoselectivity. The stereochemical outcome of the rearrangement is dictated by the geometries of both the intermediate silylketene acetal and allylic alkene, along with the transition state topology (*vide infra*). The reaction has been utilized often in the construction of numerous natural products[59,60] and thoroughly examined in the context of synthesis methodology development.[61,62,63] However, a double rearrangement of a diene diester system like **323** has never been reported. At issue is the expectation that both rearrangements will proceed as planned without unfavorably influencing each other.

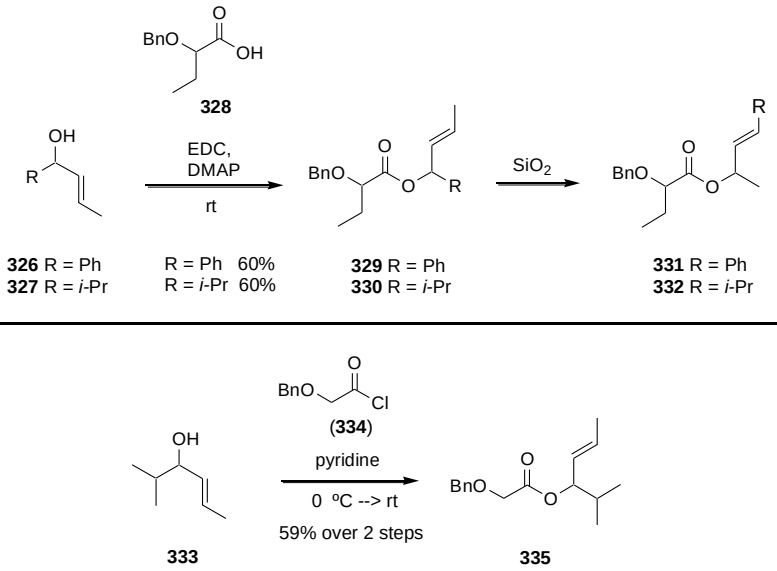
Scheme 66. Retrosynthesis Utilizing a Double Ireland-Claisen Rearrangement



2.2.5 Model System for the Ireland-Claisen Rearrangement Route

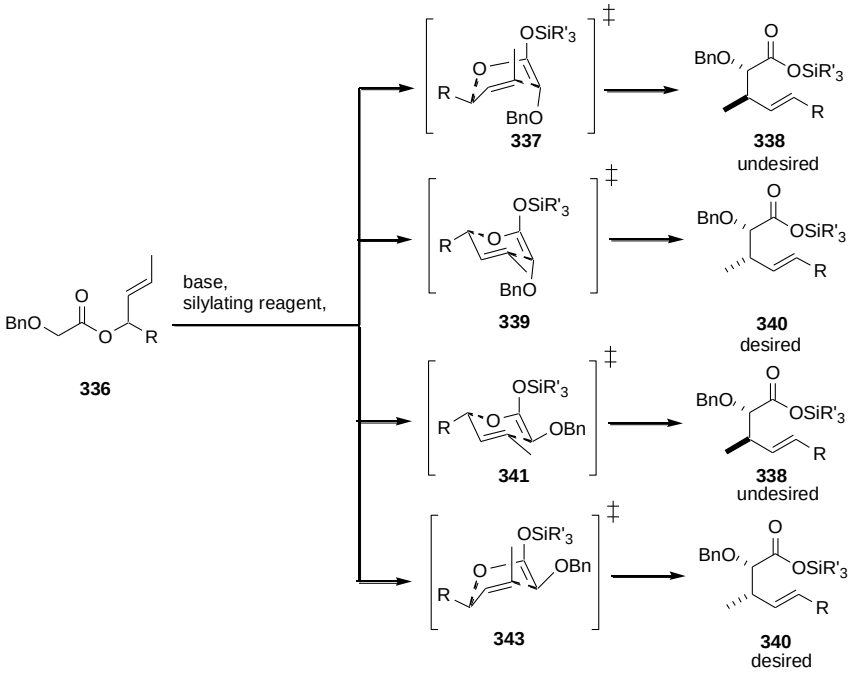
A monomeric model system, which was published in 2012,[64] was explored to develop optimal Ireland-Claisen rearrangement conditions for this diene diester system. Benzyloxyglycolates **329** and **330** were prepared by the EDC coupling of the known alcohols **326**[65] and **327**, respectively, with carboxylic acid **328** (Scheme 67). These substrates were acid sensitive, undergoing allylic rearrangements to **331** and **332**, respectively, upon SiO_2 chromatography, although these unwanted rearrangements could be suppressed by purification on Et_3N-deactivated-SiO_2. In addition, a simpler model system **335**, lacking the α-ethyl moiety found on substrates **329** and **330**, was prepared from known allylic alcohol **333**[64] and benzyloxyacetyl chloride (**334**) (Scheme 67).

Scheme 67. Preparation of Benzyloxyglycolate Derivatives



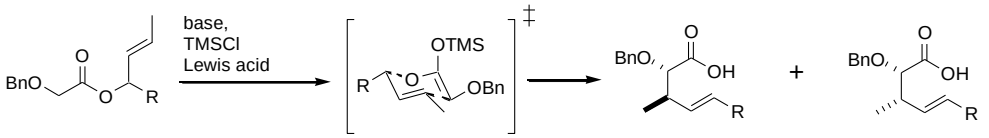
The possible Ireland-Claisen reaction transition states for benzyloxyglycolate substrate **336**, assuming the equatorial positioning of R, are shown in Scheme 68. The silylketene acetal formed can exist in either a (Z) or (*E*) configuration and the transition state can proceed through a chair or a boat. The choice of an (*E*)-alkene-containing allylic alcohol would require formation of an (*E*)-silylketene acetal, assuming a chair-like transition state such as **339**, in order to arrive at silyl ester **340**, which contains the correct relative stereochemistry for the lomaiviticin core (Scheme 68). The same stereochemical outcome could also be achieved with formation of a (*Z*)-silylketene acetal in a boat-like transition state such as **343**. Much evidence suggests that, in fact, enolization of glycolates typically proceeds to give the alternative (*Z*)-silylketene acetal, which most often reacts through a chair-like transition state.[66] Nevertheless, the more conveniently available (*E*)-allyl alcohol was used at this initial juncture since the goal of these studies was just yield optimization as a function of reaction conditions.

Scheme 68. Possible Chair and Boat Transition States for Ireland-Claisen Rearrangement of Benzyloxyglycolate Derivatives **336**



Substrates **345** and **346** were subjected to numerous Ireland-Claisen rearrangement conditions by altering the solvent, silylating reagent, base, and temperature to optimize the diastereoselectivies and yield (Scheme 69). Additionally, the effect of Lewis acids was examined when using THF as a solvent and TMSCl as the silylating agent (-78 ºC warmed to room temperature) (Table 4). The most notable result from these studies was the superiority of LHMDS as a base as compared to KHMDS and NaHMDS for Ireland-Claisen rearrangements of substrates **345** and **346**. Additionally, Lewis acids had a very minor impact on yield and diastereoselectivity. Small increases in yield and diastereoselectivity could result simply from removal of trace amounts of moisture by these acids. More pronounced increases in diastereoselectivity with Lewis acid additives have been reported for other systems.[67]

Scheme 69. Ireland-Claisen Rearrangement of Benzyloxyglycolate Derivatives **345** and **346**



345 R = Ph
346 R = *i*-Pr

347 R = Ph
348 R = *i*-Pr

349 R = Ph
353 R = *i*-Pr

350 R = Ph
354 R = *i*-Pr

Table 4. Ireland-Claisen Rearrangement of **345** and **346** Examining Lewis-Acid Catalysis

Entry	Substrate	Base (1.5 equiv.)	Additive (mol %)	Yield (%)	% 349 or 353
1	**345**	**LHMDS**	**$SnCl_4$ (2)**	**100**	**94**
2	**345**	LHMDS	$TiCl_4$ (2)	94	92
3	**345**	LHMDS	$BF_3{\cdot}OEt_2$ (20)	99	91
4	**345**	LHMDS	Ti(*i*-OPr)$_4$ (5)	69	93
5	**345**	LHMDS	$ZnCl_2$	45	92
6	**345**	LHMDS	none	94	88
7	**345**	KHMDS	none	7	>95:5[a]
8	**345**	NaHMDS	none	--	--
9	**346**	**LHMDS**	**$ZnCl_2$ (5)**	**99**	**>95:5[a]**
10	**346**	LHMDS	$SnCl_4$ (2)	93	>95:5[a]
11	**346**	LHMDS	$BF_3{\cdot}OEt_2$ (20)	92	>95:5[a]
12	**346**	LHMDS	Ti(*i*-OPr)$_4$ (5)	92	>95:5[a]
13	**346**	LHMDS	$TiCl_4$ (2)	84	>95:5[a]
14	**346**	LHMDS	none	83	>95:5[a]
15	**346**	KHMDS	none	27	84
16	**346**	NaHMDS	none	--	--
	[a] ^{1}H NMR detection limit				

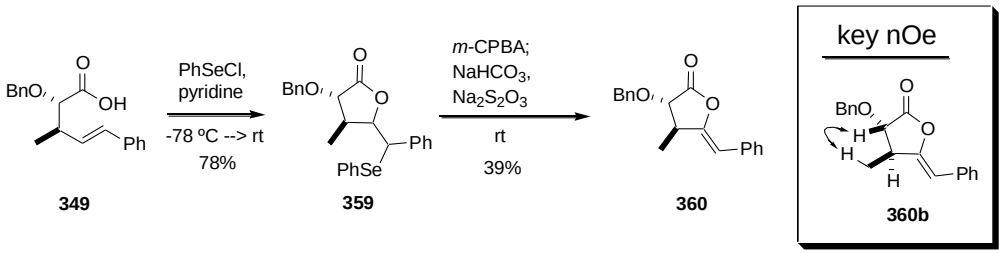
Increasing the quantity of base used from 1.5 eq. to 3.0 equiv. in the deprotonation of the esters **345** and **346** led to higher yields when using TMSCl as the silylating reagent and THF as solvent (-78 ºC warmed to room temperature) (Table 5). In addition, diastereoselectivities were greatly increased when using the sodium and potassium salts of the base under these excess base conditions.

Table 5. Ireland-Claisen Rearrangement of **345** and **346** Using Increased Base

Entry	Substrate	Base (3 equiv.)	Yield (%)	% 349 or 353
1	**345**	**NaHMDS**	**64**	**>95:5**[a]
2	**345**	LHMDS	78	76
3	**345**	KHMDS	12	60
4	**346**	**NaHMDS**	**83**	**>95:5**[a]
5	**346**	LHMDS	80	82
6	**346**	KHMDS	46	90
	[a] ^{1}H NMR detection limit			

2D NMR techniques were utilized to verify the relative stereochemistry of **349** since X-ray quality crystals of this species or its carboxylic acid derivatives could not be obtained. Lactonization of carboxylic acid **349** with PhSeCl and pyridine gave selenide **359**, which was oxidized and eliminated to give lactone **360** (Scheme 70). The key nOe's verified that the benzyloxy and methyl groups of **360** were *anti*-disposed as shown.

Scheme 70. Determination of **349** Relative Stereochemistry



349 **359** **360** **360b**

Lewis acid, base, and silylating reagent variation (Table 6) were also examined for the Ireland-Claisen rearrangement of *ethyl*-substituted benzyloxyglycolates **329** and **330** (Scheme 71). These reactions create a new quaternary stereogenic center with high diastereoselectivity. By passing through a (*Z*)-silylketene acetal (*vide infra*) in a chair conformation, phenyl-bearing substrate **329** is transformed into carboxylic acid **362** in

modest yield and acceptable diastereoselectivity without the need of a Lewis acid. Overall, the highest yields were achieved when using the bulkier TIPS group instead of TMS.

The addition of select Lewis acids did, however, marginally improve the diastereoselectivity for the *i*-Pr bearing substrate **330** (Table 6, entries 9-12). When using LHMDS, the dr achieved in the conversion of **330** to **368** was increased by the addition of a catalytic amount of $SnCl_4$. This same level of diastereoselectivity was achieved with KHMDS without the need for a Lewis acid and with the added benefit of an increase in yield. Again, using TIPSOTf instead of TMSCl as the electrophilic silylating agent afforded the highest yield and diastereoselectivity (Table 6, entries 7 and 15). On a more interesting note, NaHMDS reversed the diastereoselectivity of the reaction (Table 6, entry 16). It isn't entirely clear why switching to a sodium counterion should have this profound of an effect.

Scheme 71. Ireland-Claisen Rearrangement of α-Ethyl Benzyloxyglycolate Derivatives

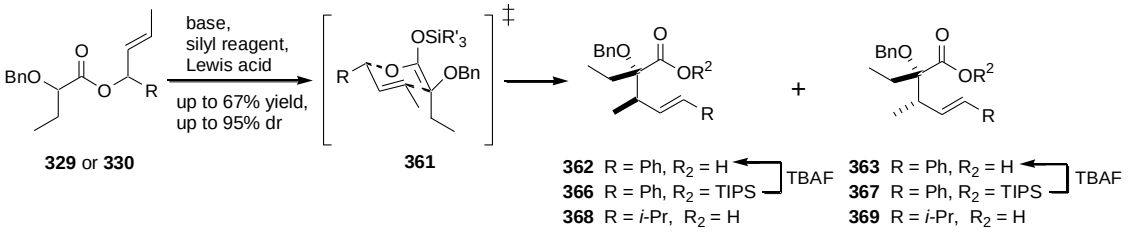


Table 6. Lewis Acid and Base Survey Comparison of **329** and **330** Using 1.5 equiv. of TMSCl or TIPSOTf and THF as Solvent

Entry	Substrate	Base (1.5 equiv.)	Additive (mol %)	Yield	% 362 or 368
1	**329**	**LHMDS**	**none**	**48**	**84**
2	**329**	LHMDS	$TiCl_4$ (2)	36	82
3	**329**	LHMDS	$SnCl_4$ (2)	44	84
4	**329**	LHMDS	Ti(*i*-OPr)$_4$ (5)	20	60
5	**329**	LHMDS	$ZnCl_2$ (5)	13	75
6	**329**	KHMDS	none	--	--
7[b]	**329**	KHMDS	none	67	93
8	**329**	NaHMDS	none	16	65
9	**330**	**LHMDS**	**$SnCl_4$ (2)**	**43**	**>95:5[a]**
10	**330**	LHMDS	$TiCl_4$ (2)	34	>95:5[a]
11	**330**	LHMDS	Ti(*i*-OPr)$_4$ (5)	42	93
12	**330**	LHMDS	$ZnCl_2$ (5)	47	87
13	**330**	LHMDS	none	40	88
14	**330**	**KHMDS**	**none**	**53**	**>95:5[a]**
15[b]	**330**	**KHMDS**	**none**	**57**	**>95:5[a]**
16	**330**	**NaHMDS**	**none**	**22**	**41**

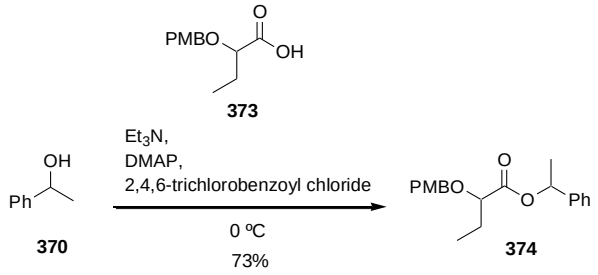
[a] ^{1}H NMR detection

[b] ^{1}H Entries 7 and 15 utilized TIPSOTf as the silylating agent, 1:1 THF/toluene as the solvent, and a final Bu_4NF treatment to form the acid product

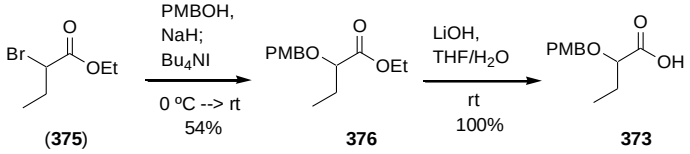
Model substrate **374** was prepared in order to verify the geometry of the enolate formed during the Ireland-Claisen reactions (Scheme 72). *p*-Methoxybenzyl substrate **374** was prepared by coupling known alcohol **370** with *p*-methoxybenzyl carboxylic acid **373**. Synthesizing *p*-methoxybenzyl carboxylic acid **373** began with the displacement of the bromide within **375** by sodium *p*-methoxybenzyl alcoholate to give **376** (Scheme 73). This reaction proceeded slowly without the addition of Bu_4NI. Hydrolysis of the ethyl ester in **376** with LiOH afforded PMB 2-(ethyl)glycolate **373**. Addition of KHMDS

and TIPSOTf to glycolate **374** resulted in a *Z*-silylketene acetal (Scheme 74) whose geometry was determined by nOe difference experiments.

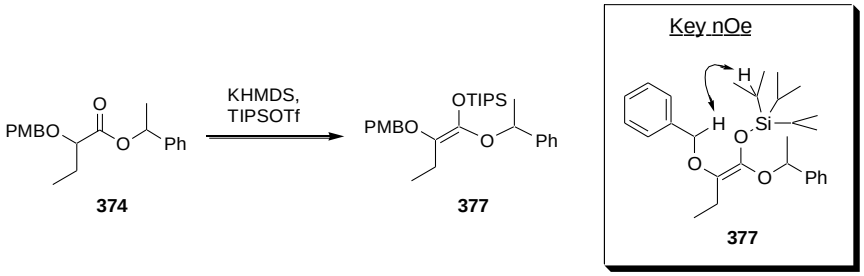
Scheme 72. Preparation of PMB Glycolates **374**



Scheme 73. Preparation of PMB 2-(Ethyl)glycolate **373**



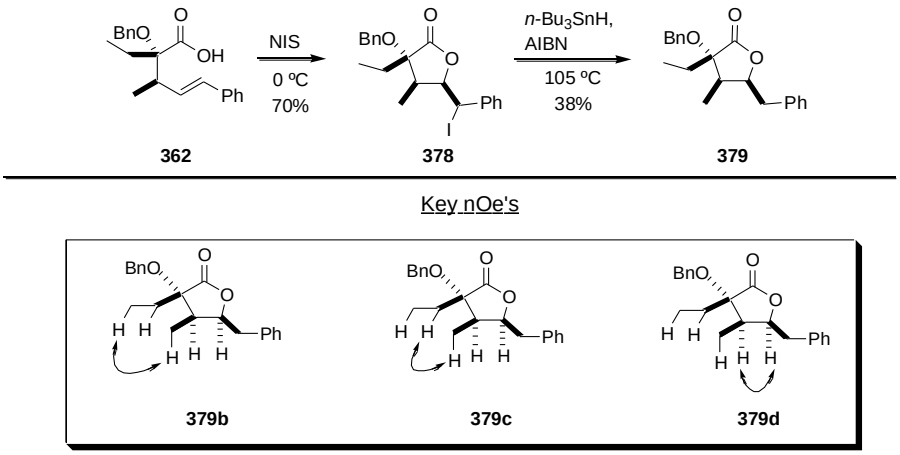
Scheme 74. Evidence for a (*Z*)-Silylketene Acetal Intermediate via an nOe Experiment



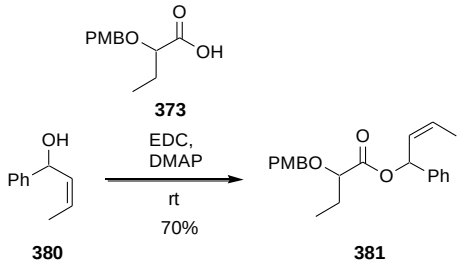
Determination of the relative stereochemistry of Ireland-Claisen rearrangement product benzyloxy carboxylic acid **362** was accomplished via 2D NMR nOe experiments on lactone **379**, which was prepared by iodolactonization of **362** followed by radical dehalogenation of the intermediate iodide **378** (Scheme 75). The key nOe's verify that the ethyl and methyl groups are on the same face of the molecule. As anticipated, this compound bore the undesired stereochemical relationship with regards to lomaiviticin A.

Since the silyl ketene acetal formed from **329** is most assuredly (*Z*) (cf. **377** above), the stereochemical results obtained verify the intermediacy of the (expected) chair-like transition state. Given this chair-like transition state, obtaining the correct (for lomaiviticinone A) relative stereochemistry should be no more complicated than substituting a (*Z*)-allylic alcohol for the (*E*)-allylic alcohol used above. (*Z*)-Alkene glycolate derivative **381** was synthesized by EDC coupling of alcohol **380** containing a (*Z*)-substituted alkene with carboxylic acid **373** (Scheme 76).

Scheme 75. Determination of **362** Relative Stereochemistry



Scheme 76. Preparation of (*Z*)-Alkene Glycolate Derivative **381**



An investigational study of the ethyl substituted PMB glycolate **381** containing a (*Z*)-allylic alkene as the Ireland-Claisen substrate then was conducted (Scheme 77 and

Table 7). As anticipated, the diastereoselectivity of the Ireland-Claisen rearrangement for phenyl containing (*Z*)-alkene substrate **381** was reversed compared to the (*E*)-alkene series (**329**/**330**) (Scheme 71). Addition of ester **381** to a mixture of base and silylating reagent led to the Ireland-Claisen rearrangement presumably through an intermediate (*Z)*-silylketene acetal **382** in a chair-like transition state to give silyl ester **387**. Treatment of the isolable silyl ester with Bu_4NF afforded carboxylic acid **383** in good yield and with high diastereoselectivity (Table 7).

Previous work done on the ethyl containing *benzyl*oxyglycolates revealed the superiority of the silyl triflates to the silyl chlorides (Table **6**), a result which extended to the PMB series. Both TIPSOTf and TESOTf greatly increased the yield and diastereoselectivity of the **381** to **383**/**384** transformation (Table 7, entries 1 and 8). These bulkier silylating reagents may have an impact on the Ireland-Claisen rearrangement at several key points in the reaction: a) their increased electrophilicity compared to the corresponding chlorides may provide faster enolate trapping, thus reducing competitive side reactions and increasing the yield of **387**, b) the larger silyl groups (compared to TMS) may make alternative transition states to **387** more energetically penalizing, and c) the added stability of the bulkier silyl esters may aid in initial silyl ester isolation without decomposition.

A short survey of bases showed KHMDS to be a superior choice when using TIPSOTf as the silylating agent (Table 7, entry 6). In addition, it was found that using a mixed solvent system of toluene and THF led to higher diastereoselectivities (Table 7, entry 2).

Scheme 77. Ireland-Claisen of Rearrangement of PMB Glycolate with (*Z*)-Alkene **381**

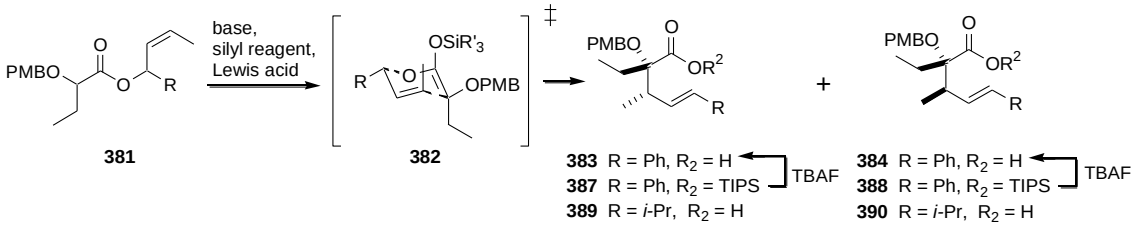
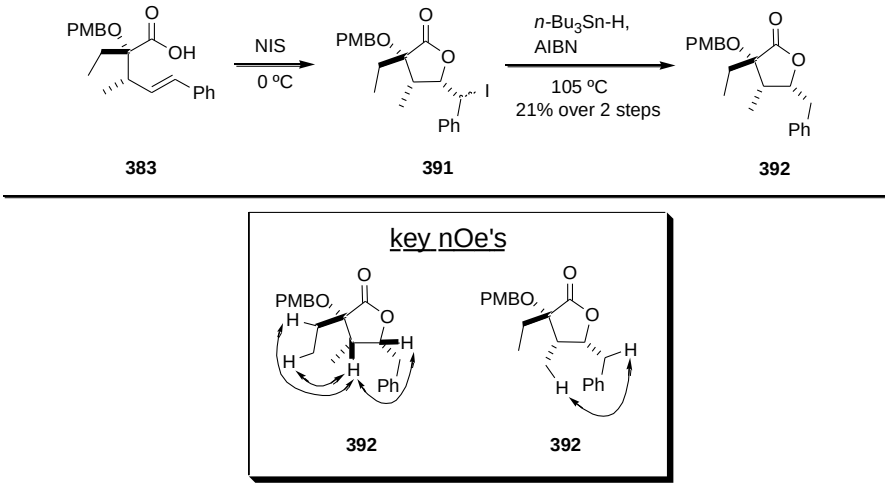


Table 7. Effects of Silylating Reagent and Solvent in the Ireland-Claisen Rearrangement of **381** into **383** and **384**

Entry	Base (3.0 equiv.)	Solvent	Silyl Reagent (3.0 equiv.)	additive (mol %)	yield (%)	% 383
1	**KHMDS**	**toluene/THF**	**TIPSOTf**	**$TiCl_4$ (10)**	**73**	**95**
2	KHMDS	toluene/THF	TIPSOTf	--	36	>95:5[a]
3	KHMDS	THF	TIPSOTf	--	44	>95:5[a]
4	LHMDS	THF	TIPSOTf	--	50	93
5	NaHMDS	THF	TIPSOTf	--	--	--
6	KHMDS	toluene	TIPSOTf	--	71	87
7	KHMDS	toluene	TIPSCl	--	61	75
8	**KHMDS**	**toluene**	**TESOTf**	--	**75**	**92**
9	KHMDS	toluene	TMSOTf	--	--	--
10	KHMDS	toluene	TMSCl	Et_3N	71	87
11	KHMDS	toluene	TMSCl	--	13	78
[a] ^{1}H NMR detection limit						

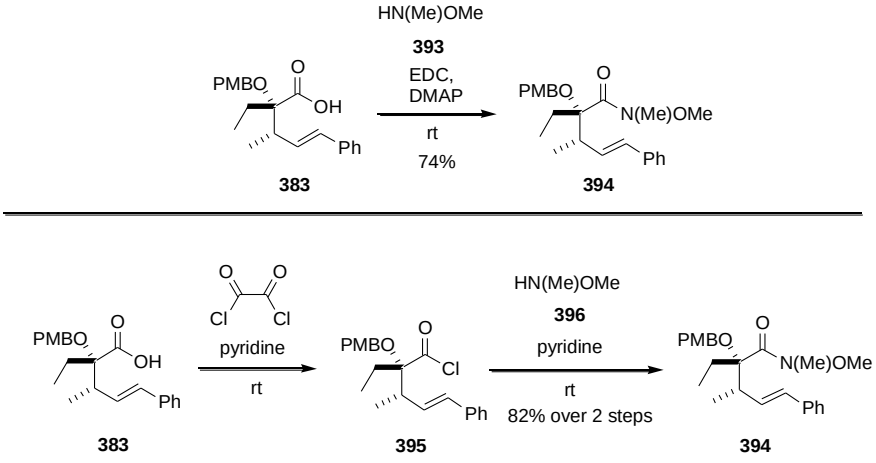
The relative stereochemistry of the major diastereomer **283** was established using 2D NMR nOe experiments on a derivative. Iodolactonization of carboxylic acid **283** gave iodide **391** (Scheme 78). Radical dehalogenation afforded lactone **392**. The ethyl and methyl units were determined to be on opposite faces of the molecule by difference nOe experiments.

Scheme 78. Relative Stereochemistry Determination for **383**



Installation of the Weinreb amide on carboxylic acid **383** was successful utilizing EDC coupling with amine **393** (Scheme 79). As an alternative, a sequence proceeding through acid chloride **395** worked as well.

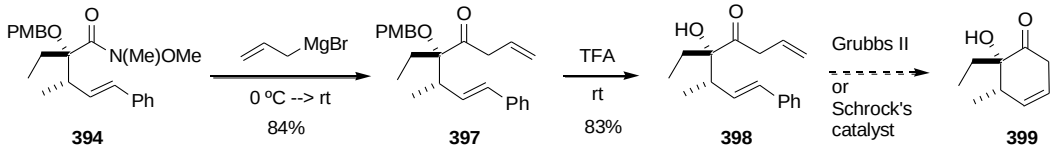
Scheme 79. Preparation of Weinreb Amide **394**



Allylation of Weinreb amide **394** was performed with allylmagnesium bromide (Scheme 80). Removal of the PMB protecting group with TFA gave rise to ring-closing metathesis precursor **398**. Ring-closing metathesis (RCM) using either Grubbs 2nd

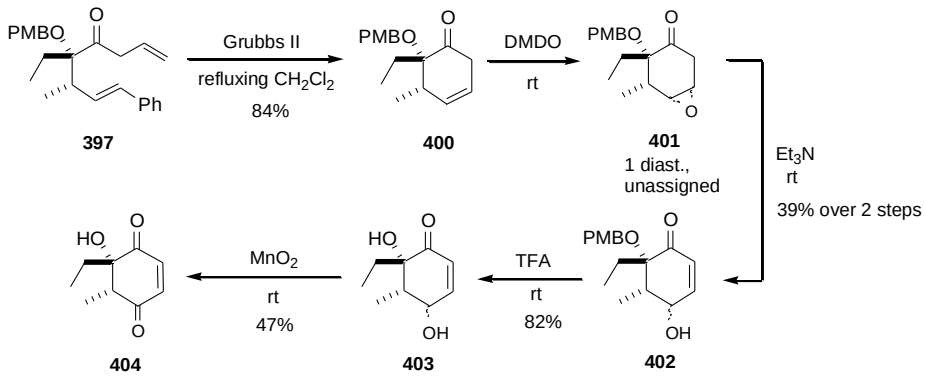
generation catalyst or Schrock's catalyst each led to decomposition products without any of the desired cyclization product **399**. To test if the free alcohol diverted the reaction, similar chemistry was explored with PMB ether **397**.

Scheme 80. Attempted Ring-Closing Metathesis of **398**



Ring-closing metathesis of **397** was performed with Grubbs II catalyst in refluxing CH_2Cl_2, leading to β,γ-unsaturated cyclic enone **400** in good yield (Scheme 81). Stereoselective epoxidation of the alkene within **400** with DMDO gave epoxide **401**, whereas *m*-CPBA treatment just decomposed the alkene substrate. A base-promoted opening of the epoxide in **401** with Et_3N followed by removal of the PMB protecting group with TFA gave diol **403**. Oxidation of the resulting allylic alcohol with MnO_2 afforded enedione **404**.

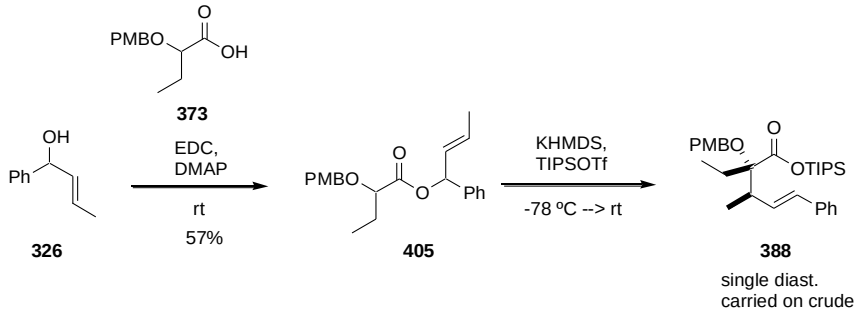
Scheme 81. Completion of the Model System



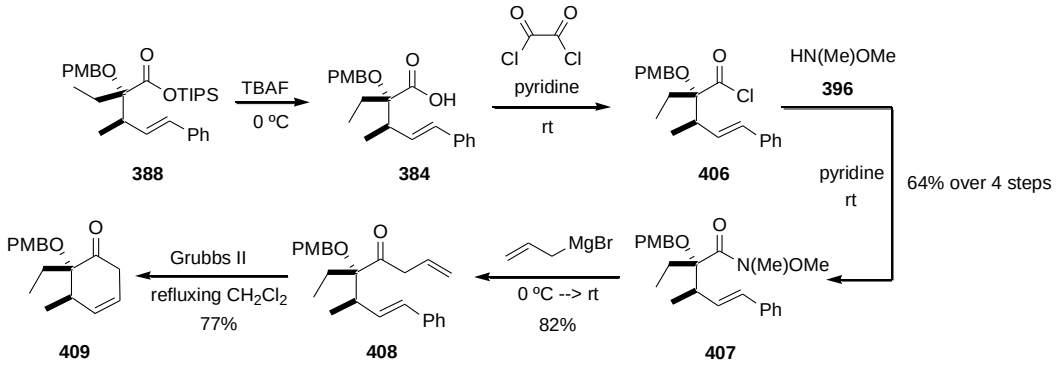
Exploratory studies of transformations required for lomaiviticinone A core synthesis would benefit from ready access to large amounts of model acid **383**.

Unfortunately, low yields in making the known *Z*-allylic alcohol **380** hampered this goal. Thus, the diastereomeric acid, made from the more readily available (*E*)-alkene allylic alcohol **326**, was chosen as a model system for these investigations. (*E*)-alkene Ireland-Claisen substrate **405** was prepared from an EDC coupling of alcohol **326** and carboxylic acid **373** (Scheme 82). An Ireland-Claisen reaction using KHMDS and TIPSOTf afforded **388**, which was carried on crude for further chemistry. Significant quantities of silyl ester **388** could be readily accessed with this procedure. This silyl ester was carried on to **409** in an analogous fashion to **387** → **400** (Scheme 83).

Scheme 82. Ireland-Claisen Rearrangement of PMB Glycolate with (*E*)-Alkene **405**



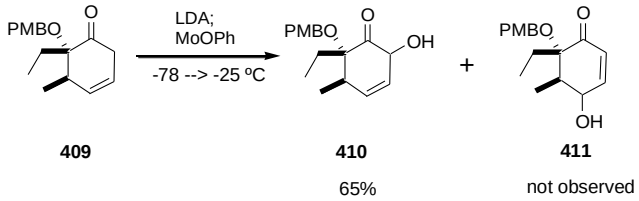
Scheme 83. Construction of Alternative Diastereomer **409**



Direct allylic oxidation of β,γ-unsaturated enone **409** to alcohol **410** was explored in an attempt to shorten the route (Scheme 84). Treatment of ketone **409** with LDA and

then Vedejs' reagent afforded α-hydroxyketone **410** with no formation of the desired isomer **411**.

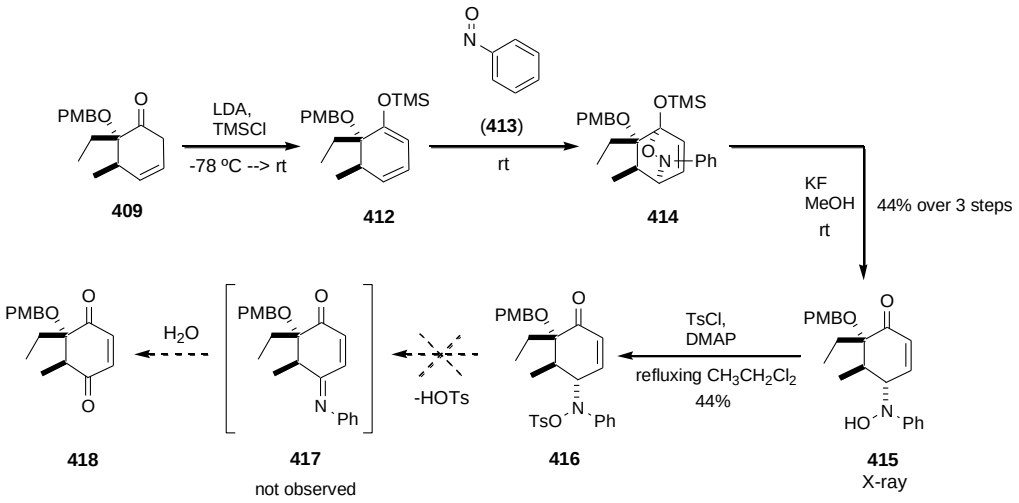
Scheme 84. Attempt to Prepare Allylic Alcohol **411** Directly from **409**



409 **410** 65% **411** not observed

The epoxidation/oxirane opening chemistry of β,γ-unsaturated enone **400** that accessed the γ-hydroxyenone moiety of **402** did not translate to bicyclic structures as would be required for lomaiviticinone core synthesis (*vide infra*). Therefore, alternative methods had to be developed, and model system **409** was used as the platform for these studies. TMS dienol ether **412** was prepared from **409** with LDA and TMSCl (Scheme 85). Diels-Alder reaction of dienol ether **412** with nitrosobenzene (**413**) afforded nitroso adduct **414**. Removal of the TMS group with KF in MeOH opened the alkylhydroxylamine bridge to give hydroxylamine **415** as a single compound whose relative stereochemistry was confirmed by X-ray diffraction (Figure 8). Tosylation of the hydroxyl moiety in **415** proceeded successfully to afford **416**, but a subsequent attempt at elimination of TsOH (DBU or KOH) to give an intermediate imine **417** failed.

Scheme 85. Preparation of Hydroxyl Amine **415** via TMS Dienol Ether Diels-Alder with Nitrosobenzene



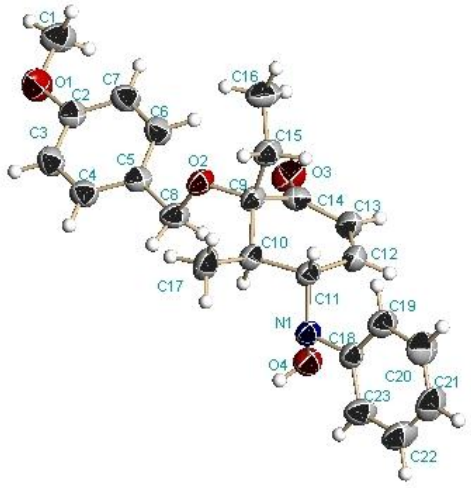
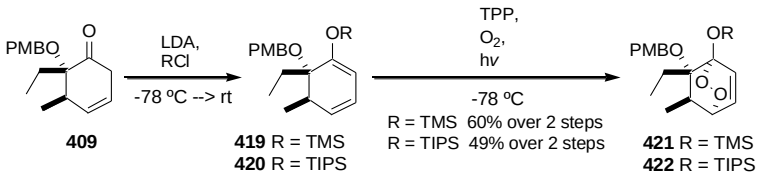


Figure 8. X-Ray Structure of Hydroxylamine **415**

In a similar fashion, Diels-Alder reactions were performed on both TMS dienol ether **419** and TIPS dienol ether **420** with singlet molecular oxygen to give endoperoxides **421** and **422**, respectively (Scheme 86). The TMS ether **421** was unstable to SiO_2 chromatography, and so the larger silicon protecting groups TIPS and TBS were used in subsequent transformations. The relative stereochemistries of **421** and **422** were

tentatively assigned based on the precedent of the Diels-Alder reaction of **412** with nitrosobenzene (**413**) (*vide supra*).

Scheme 86. Preparation of Endoperoxides **421**and **422** via Diels-Alder Reaction with singlet O_2

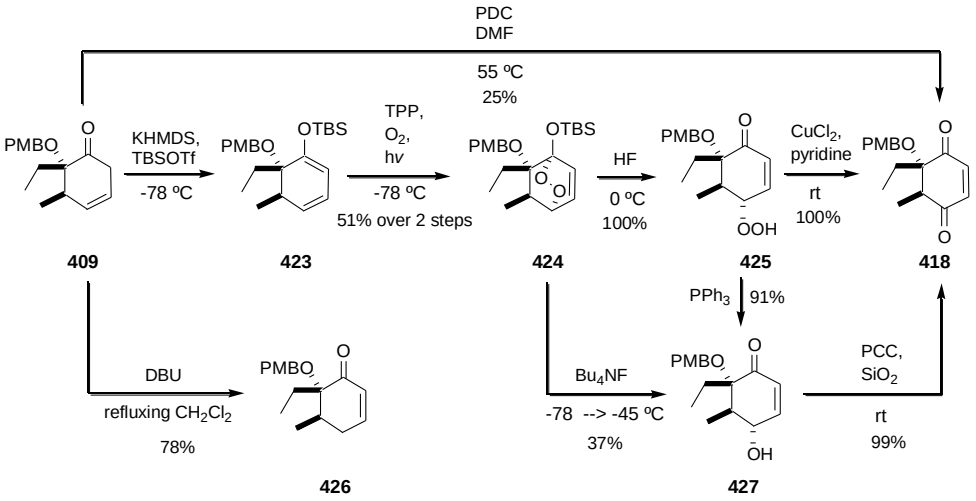


The Diels-Alder reaction of **423** with singlet O_2 also was successful using KHMDS and TBSOTf for deprotonation/silylation of the starting enone **409** (Scheme 87). TBS removal from the derived endoperoxide **424** with aqueous HF proceeded in quantitative yield to give peroxide **425**. Alternatively, Bu_4NF deprotection of **424** resulted in a low yield of keto alcohol **427**. The source of the reducing agent in this step is not known. Peroxide **425** was directly transformed into enedione **418** with $CuCl_2$ and pyridine. The peroxide **425** could be reduced to the keto alcohol **427** in quantitative yield by treatment with PPh_3. Mild PCC oxidation of alcohol **427** delivered enedione **418**. In addition, treatment of β,γ-unsaturated enone **409** with PDC afforded enedione **418** directly in low yield.

Thus, these model studies with the monomeric system illustrated that a γ-hydroxy enone or enedione could be prepared, each containing useful functional handles for further advancement towards lomaiviticinone A. As an aside, β,γ-unsaturated enone **409** was isomerized to enone **426** with DBU in an attempt to explore direct γ-oxidation. All trials at an allylic oxidation of enone **426** met with failure. In addition, attempts to directly access **427** by cleaving the O-O bond in **424** (Me_2S, thiourea, and PPh_3) also

were unsuccessful. In summary, these model system studies on the monomeric enone system **409** identified useful chemistry for comparable downstream efforts on the authentic bicyclic core of lomaiviticinone A.

Scheme 87. Preparation of Diketone **418** via Endoperoxide **424**

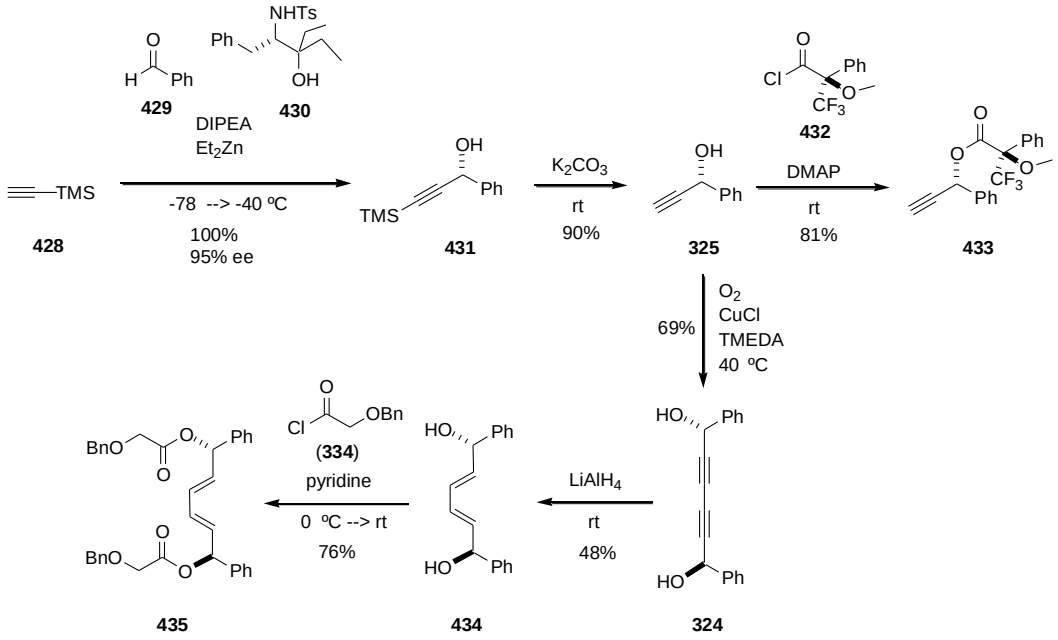


2.2.6 Model System for the Double Ireland-Claisen Rearrangement

An initial model system for the double Ireland-Claisen rearrangement, which lacked the α-ethyl unit and contained (*E*)-alkenes, was prepared as another step towards achieving a double Ireland-Claisen rearrangement on the fully substituted system (Scheme 88). The route began by preparation of known enantiomerically pure alcohol **431**[68] and subsequent removal of the TMS moiety to give known chiral propargyl alcohol **325**[69]. The enantiomeric purity of **325** was assayed by preparation and ^{1}H NMR analysis of the Mosher ester **433**. Glaser coupling[70] of alcohol **325** gave diol diyne **324**, which was reduced to bis (*E*)-alkene **434** with $LiAlH_4$. Coupling benzyloxyacetyl chloride (**334**) with this diol gave double Ireland-Claisen precursor **435**. Note that in forming the C-C

bond of the Glaser coupling product **435**, the two "halves" of the dimeric lomaiviticinone structure are joined. Thus, this most challenging central C-C bond in the target is formed quite early in the route, and in good yield. Exploiting this strategic gain by divergent two-directional synthesis occupies the remainder of the effort.

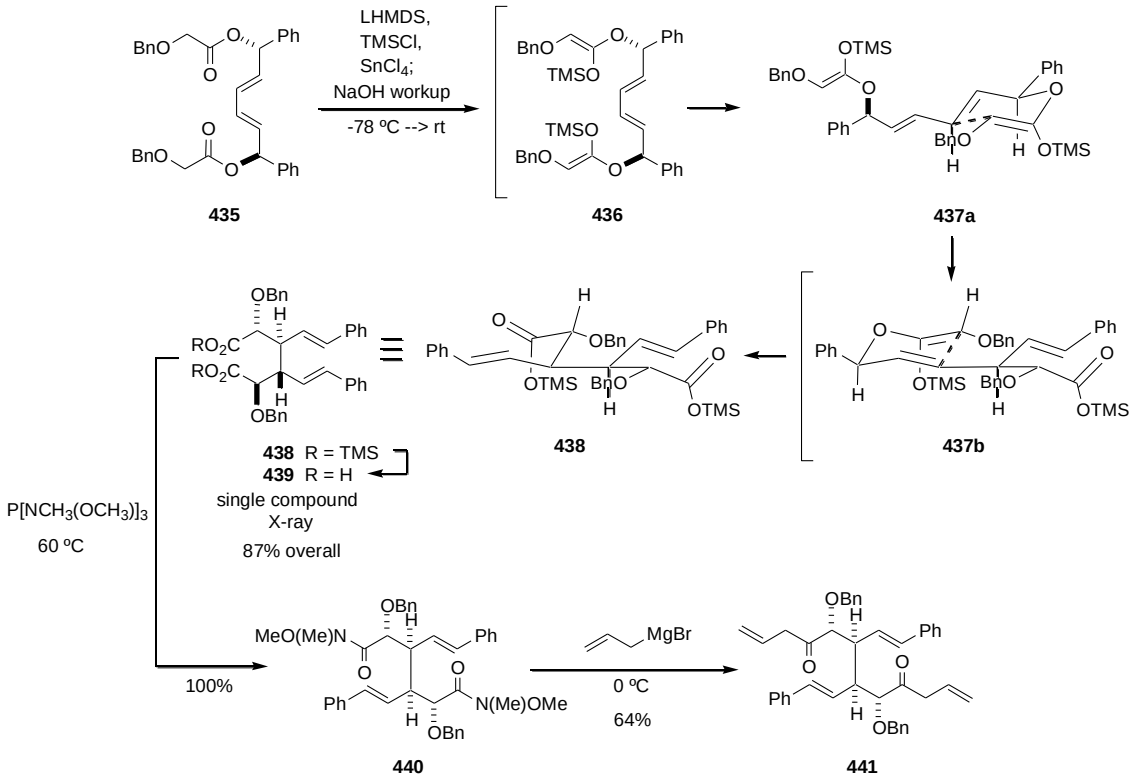
Scheme 88. Preparation of Bis Benzyloxyglycolate **435** Containing (*E*)-Alkenes



The double Ireland-Claisen rearrangement of bis (*E*)-alkene **435** (Scheme 89) using LHMDS, TMSCl, and a catalytic amount of $SnCl_4$ presumably proceeded through (*Z*)-silyl ketene acetals **436** in sequential chair transition states **437a** and **437b** to give the bis TMS ester **438**. The TMS esters were readily hydrolyzed upon basic workup to give dicarboxylic acid **439** as a single diastereomerically pure compound in excellent yield. The relative stereochemistry of diacid **439** was confirmed by X-ray diffraction (Figure 9). Bis Weinreb amide **440** was prepared in quantitative yield from diacid **439** using

$P[NCH_3(OCH_3)]_3$[71] and subsequent treatment of this bis amide with allylmagnesium bromide gave bis allyl ketone **441**.

Scheme 89. Double Ireland-Claisen Rearrangement of **435** Containing (*E*)-Alkenes and Construction of **441**



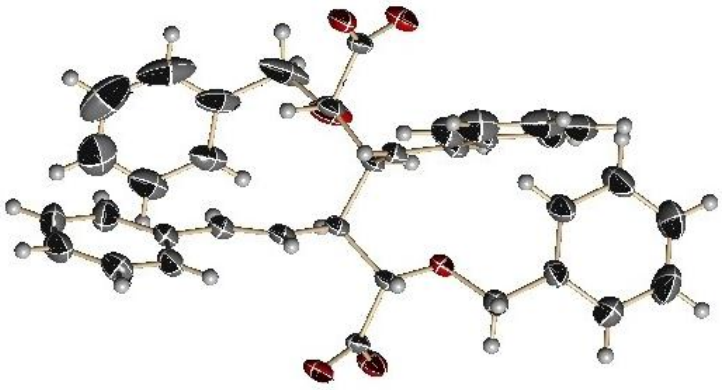
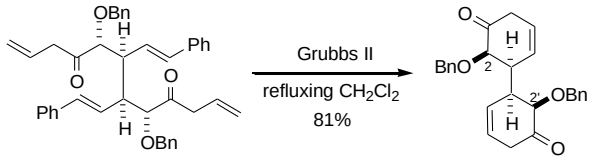


Figure 9. X-Ray Structure of Double Ireland-Claisen Product **439**

Ring-closing metathesis of tetraene **441** with Grubbs 2nd generation catalyst in refluxing CH_2Cl_2 afforded the desired bicycle **442** (Scheme 90). Transformation of **442** to lomaiviticinone A would require numerous steps to install the required ethyl units at C(2)/C(2'). Therefore, these model studies were terminated in favor of work on the "real" system containing the ethyl moieties. Nevertheless, this simple model system did demonstrate that (1) a double Ireland-Claisen rearrangement is feasible, (2) a diacid substrate could be converted to a bis allyl substrate, and (3) ring-closing metathesis can be used to arrive at the desired bicyclic species.

Scheme 90. Ring-Closing Metathesis to Make Bicycle **442**



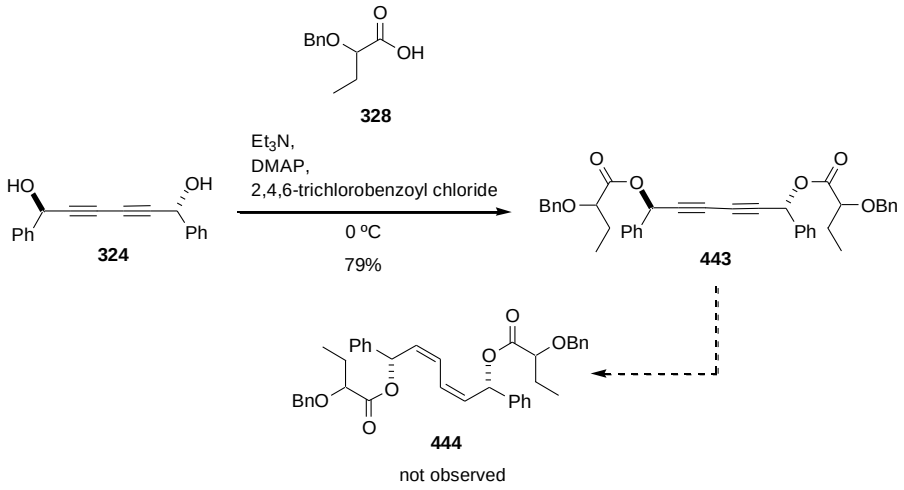
441 **442**

2.2.7 Progress Towards the Lomaiviticinone A Core Utilizing the Double Ireland-Claisen Rearrangement

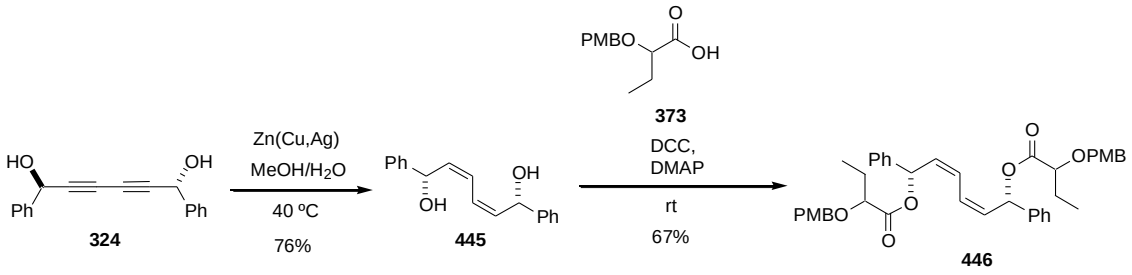
The fully ethyl-substituted esters **444** and **446** were explored by building off of the success of the model Ireland-Claisen rearrangement of ester **435** (Scheme 92). The initial attempt at the preparation of bis (*Z*)-alkene Ireland-Claisen substrate **444** involved coupling diol **324** with carboxylic acid **328** to give diester **443** (Scheme 91). Partial reduction of diyne **324** was unsuccessful with the traditional Lindlar catalyst/H_2 method. However, diyne **324** was reduced with Zn(Cu, Ag) amalgam[72] in MeOH/H_2O to afford bis (*Z*)-alkene diol **445** in good yield (Scheme 92). *p*-Methoxybenzyl protected bis (*Z*)-

alkene Ireland-Claisen substrate **446** was prepared by DCC coupling of this diol with **373**.

Scheme 91. Failed Preparation of α-Ethyl Benzyloxyglycolate **444** Containing (*Z*)-Alkenes



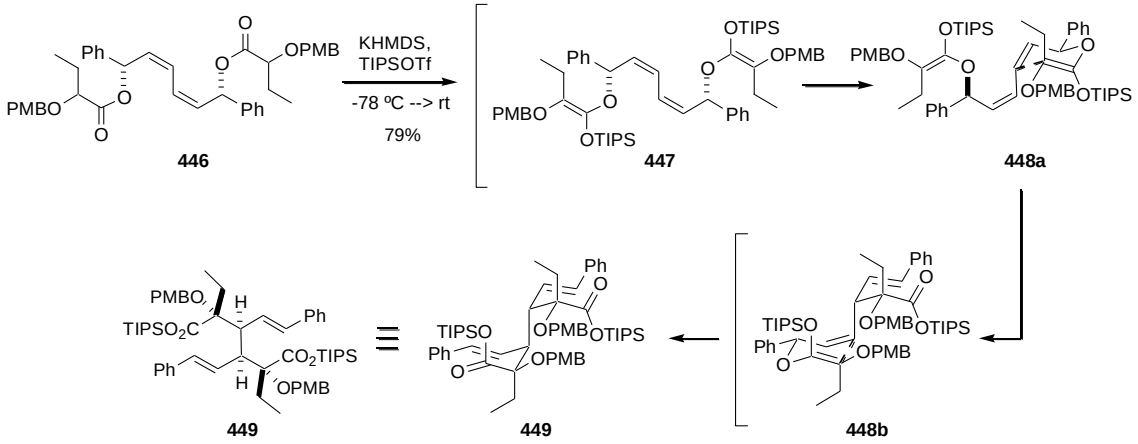
Scheme 92. Preparation of 2-(Ethyl)glycolate **446** Containing (*Z*)-Alkenes



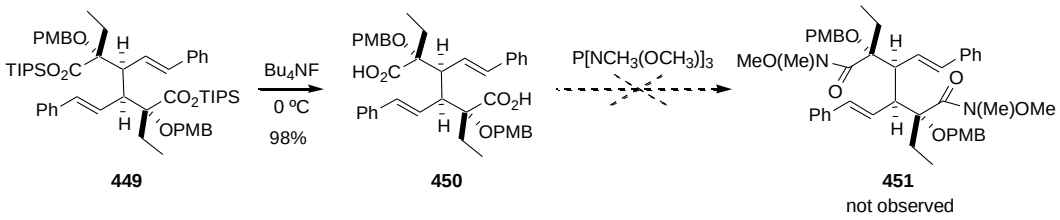
Addition of bis (*Z*)-alkene substrate **446** in Et_2O to a solution of KHMDS in toluene/Et_2O followed by the addition of TIPSOTf presumably afforded intermediate bis (*Z*)-silylketene acetal **447** (Scheme 93). Intermediate **447** underwent double (sequential) 3,3-sigmatropic (Ireland-Claisen) rearrangements to arrive at bis TIPS ester **449** in good yield (Scheme 93). The bis TIPS ester of **449** was deprotected with Bu_4NF to give dicarboxylic acid **450** (Scheme 94). Dicarboxylic acid **450** was treated with

$P[NCH_3(OCH_3)]_3$ in an attempt to access bis Weinreb amide **451** in the same fashion as model Weinreb amide **440** (Scheme 89), but that chemistry failed on the more sterically hindered diacid system **450**.

Scheme 93. Double Ireland-Claisen Rearrangement of **446**

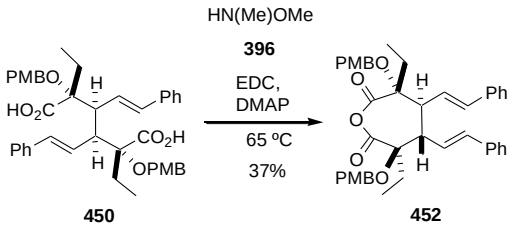


Scheme 94. Attempted Preparation of Bis Weinreb Amide **451**



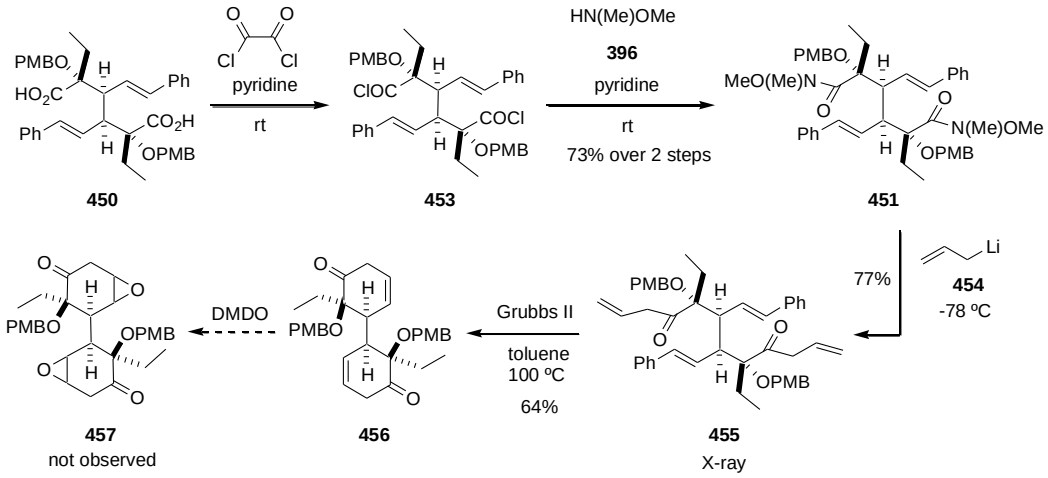
Alternatively, attempted EDC coupling of free amine **396** with dicarboxylic acid **450** led to cyclic anhydride **452** (Scheme 95). This undesired cyclization most likely resulted from the displacement of the activated EDC-anhydride on one acid by the remaining carboxylic acid.

Scheme 95. Undesired Cyclization of Diacid **450** While Trying to Access Bis Weinreb Amide **451**



Instead, bis Weinreb amide **451** was prepared by first making the bis acid chloride **453** with oxalyl chloride and pyridine, followed by addition of the free amine **396** (Scheme 96). Allylation attempts with allylmagnesium bromide failed to give double addition products. Examination of the crude reaction product suggested that mono allylation had occurred. It turned out that allyllithium did not suffer this same fate, and bis allyl ketone **455** could be prepared from **451** in good yield. The relative stereochemistry of bis allyl ketone **455** was verified by single crystal X-ray diffraction (Figure **10**). Initial attempts at ring-closing metathesis of tetraene **455** were unsuccessful, with only trace amounts of desired bicycle **456** being detected (Table 8). Reproducible but moderate yields of bicycle **456** were achieved at 100 ºC in a sealed tube at a substrate concentration of 0.02 M in freeze-pump thawed toluene with Grubbs II catalyst (40 mol%). The purity of the starting material tetraene **455** was of utmost importance for success of this transformation. It was necessary to remove oily residues from tetraene **455** by pentane rinses prior to subjection to the ring-closing metathesis conditions. Unfortunately, treatment of β,γ-unsaturated enone **456** with DMDO resulted in only decomposition products.

Scheme 96. Preparation of Bicycle **456** and Subsequent Failed Epoxidation



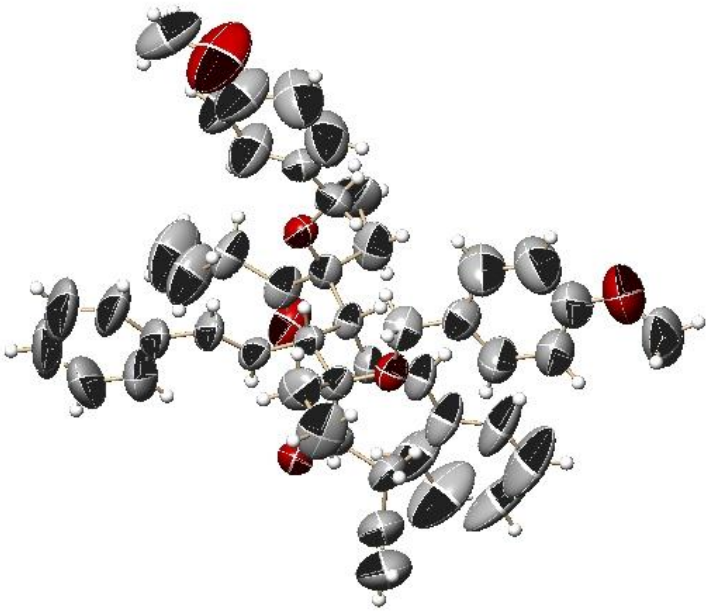


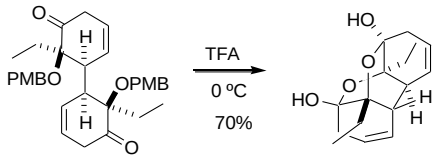
Figure 10. X-Ray Structure of Bis Allyl Ketone **455**

Table 8. Failed bis Ring-Closing Metathesis of Tetraene **455**

catalyst	solvent	temperature (ºC)	concentration (M)
Grubbs I	CH_2Cl_2	reflux	0.004
Grubbs I	$CH_3CH_2Cl_2$	reflux	0.03
Schrock's	benzene	rt	0.007
Grubbs II	toluene	80	0.002
Grubbs II	toluene	microwave 85	0.002
Grubbs II	toluene	90	0.006
Grubbs II	CH_2Cl_2 then toluene	reflux	0.005
Grubbs II	$CH_3CH_2Cl_2$	reflux	0.009
Grubbs II under $H_2C{=}CH_2$	toluene	110	0.003
Grubbs II under $H_2C{=}CH_2$	toluene	80	0.01

The order of operations was changed to remove the PMB protecting group before epoxidation in an effort to exploit hydroxyl-directed oxirane formation (Scheme 97). Unfortunately, treatment of bicycle **456** with TFA led to an undesired cyclization of the liberated alcohols into the opposing rings' ketones to afford bis hemiketal **458**.

Scheme 97. Undesired Cyclization Upon PMB Removal from **456**

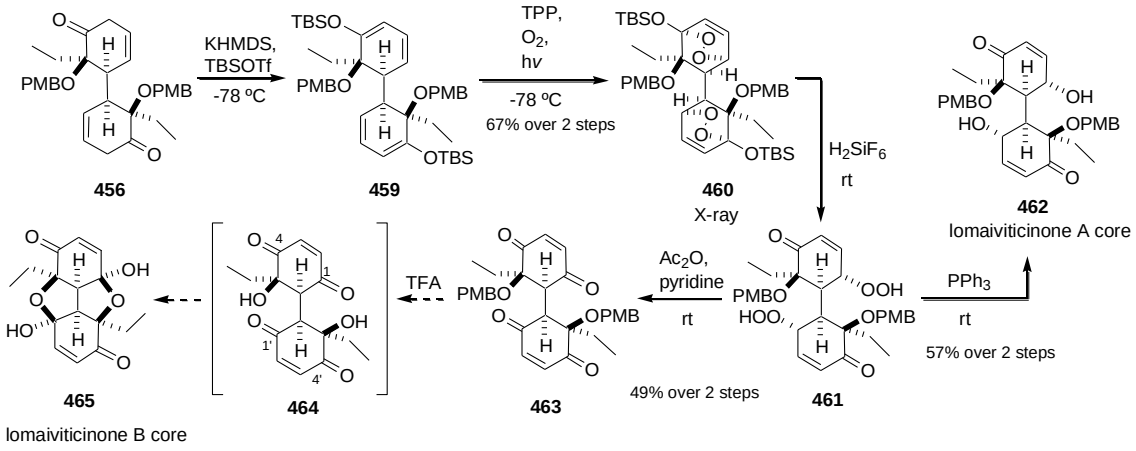


456 **458**

An alternative route to access hydroxyenone **462** was necessary since epoxidation of bis β,γ-unsaturated enone **456** proved problematic (Scheme 98). The oxygenation chemistry worked out on model system **409** proved invaluable in this regard. Bis endoperoxide **460** was prepared by first making bis TBS dienol ether **459** with KHMDS and TBSOTf and combining it in a Diels-Alder reaction with singlet molecular oxygen generated with tetraphenyl porphine (TPP) as a photosensitizer. The relative

stereochemistry of the endoperoxides was verified by single crystal X-ray analysis (Figure 11). Only a single diastereomer of bis endo-peroxide **460** was formed in this transformation (^{1}H NMR level of analysis). The addition of singlet oxygen occurred on the least sterically hindered faces of the bicycle, away from the large PMB group. Double TBS removal from **460** with concomitant endoperoxide opening initially was achieved with $HF_{(aq)}$ in MeCN to give bis peroxide **461**. Reproducibility problems with this reaction led to use of the alternative fluoride source H_2SiF_6, which was much more reliable.[73] Bis peroxide **461** was treated with PPh_3 to give lomaiviticinone A core **462**. In addition, the bis peroxide **461** could be converted into the bis enedione **463** by simple treatment with acetic anhydride. PMB removal from **463** was anticipated to initiate a double cyclization to form bis hemi ketal **465**, the core structure of lomaiviticin B. However, exposing **463** to TFA led to complete destruction of the material. Given the limited amount of **463** available, further deprotection methods were not explored. However, the ready cyclization of **456** into **458** (Scheme 97) raises some concerns about the **463** → **465** transformation. Specifically, an alternative OH → C(4') ketone cyclization is possible, and the relative energies of the two processes (OH → C(4'), undesired vs OH → C(1'), desired) became a topic of great interest.

Scheme 98. Preparation of Enedione **463** and Lomaiviticinone A Core **462**



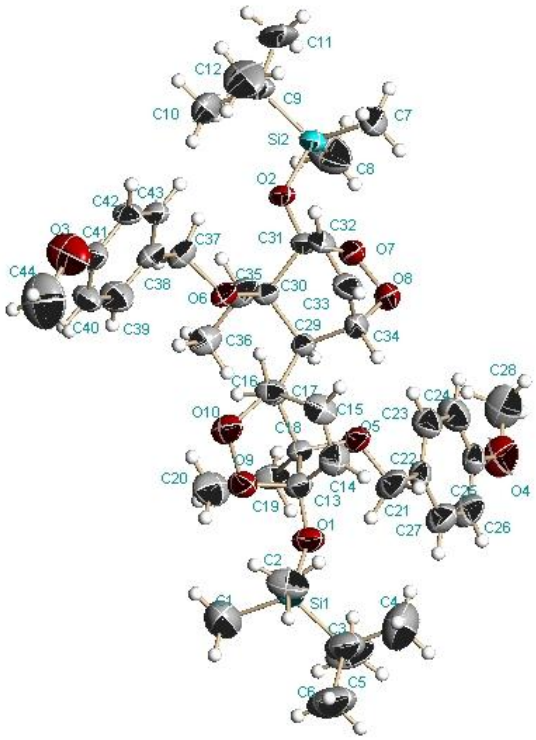
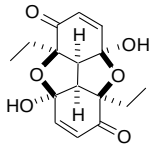
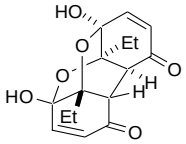
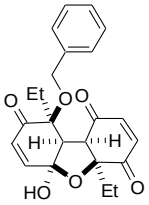
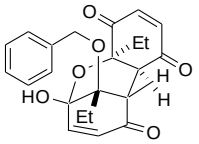
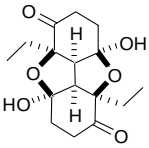
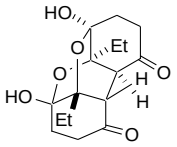


Figure 11. X-Ray Structure of Bis Endoperoxide **460**

Density functional calculations (B3LYP/6-31**) were performed to determine the relative energies of the lowest energy conformers of various cyclized species that might arise from **464** (Table 9). The lomaiviticinone B core **465** is calculated to be 8.3 kcal/mol

higher in energy than the undesired cyclization product **466** that results from addition of the alcohols into the C(4) ketones. With only one PMB group removed, the difference in energy between desired cyclization product **467** and undesired species **468** is only 0.5 kcal/mol. In addition, a calculation was performed on the reduced species **465b** and **469**; the desired cyclization product **465b** still remains 3.9 kcal/mol higher in energy than the undesired product **469**. Thus, these calculations suggest that a double cyclization in the transformation of intermediate enedione **464** to the lomaiviticinone B core **465** is very unlikely to occur as desired.

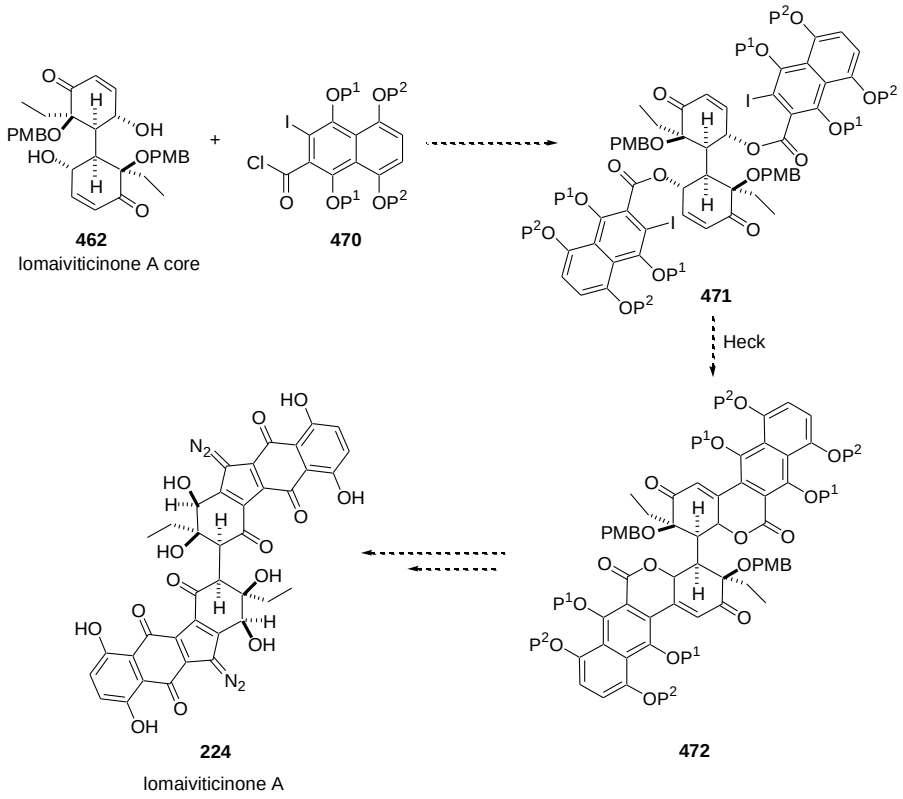
Table 9. Density Functional Calculation-Based Conformational Analysis

	 **465**	 **466**
rel E (kcal/mol)	8.3	0.0
	 **467**	 **468**
rel E (kcal/mol)	0.5	0.0
	 **465b**	 **469**
rel E (kcal/mol)	3.9	0.0

2.2.8 Study to Attach the Aromatic Portion of Lomaiviticinone A to the Bicyclic Core Structure

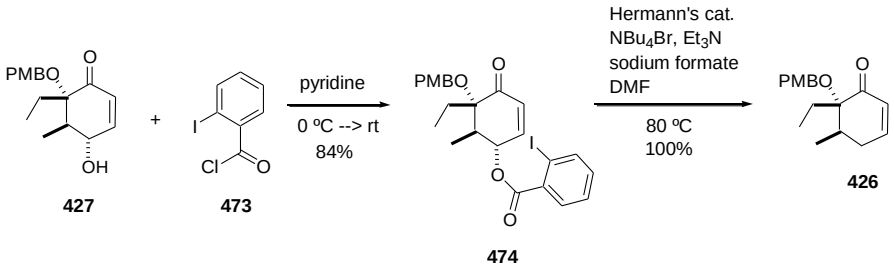
A few scouting experiments were performed in order to assess an approach to coupling the aromatic portions of lomaiviticinone A to the core structure in hand. One means to incorporate the aromatic portion of lomaiviticinone A would be to couple the core's alcohols within **462** with an aromatic acid chloride such as **470** to afford diester **471** (Scheme 99). An intramolecular Heck reaction then could provide the desired C-C linkage between the core structure and the aromatic portion as illustrated in **472**, which could ultimately be transformed into lomaiviticinone A.

Scheme 99. Construction of Model Substrate **471** for Heck Cyclization



An investigation of the Heck reaction for solving this problem was conducted using the model enone **427** (Scheme 100). γ-Hydroxyenone **427** was coupled with known acid chloride **473**[74] to give ester **474** containing an aryl iodide. Numerous Heck reaction conditions (Table 10) were screened initially with minimal success. The use of Hermann's catalyst under reductive conditions led to enone **426**, presumably via a π-allyl complex that resulted in the expulsion of the entire ester portion of the molecule. A successful 6-*exo* trig Heck cyclization ultimately was achieved to afford lactone **475** (Scheme 101), where the double bond had isomerized. Luckily, the loss of stereochemistry at the lactone is not important, as that carbon is destined for oxidation later in the route.

Scheme 100. Construction of Model Substrate **474** for Heck Cyclization



Scheme 101. Successful 6-*Exo* Trig Heck Cyclization on Model Substrate **474**

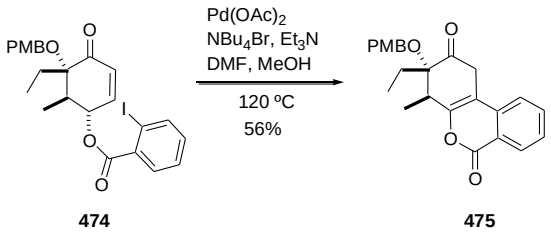


Table 10. Heck Cyclization Conditions for Transformation of **474** to **475**

Pd source	Additives	Solvent	Temp. (ºC)	Outcome
$Pd_2(dba)_3$	P(*o*-tol)$_3$, Et_3N	MeCN	reflux	mainly decomp. small amount of starting material recovered
$Pd_2(dba)_3$	Et_3N	DMA	140	decomp.
$Pd_2(dba)_3.CHCl_3$	K_2CO_3, NEt_4Br, PPh_3	DMF	120	decomp.
$Pd(OAc)_2$	$NaHCO_3$, Bu_4NCl	DMF	60	decomp.
$Pd(OAc)_2$	Ag_2CO_3, PPh_3	MeCN	60	no reaction
$Pd(OAc)_2$	Ag_2CO_3, PPh_3	THF	70	mainly starting material
$Pd(OAc)_2$	Ag_2CO_3, PPh_3	toluene	120	decomp
$Pd(OAc)_2$	**Et_3N, Bu_4NBr**	**DMF/MeOH**	**120 microwave**	**56% 475**
Hermann's cat.	**Et_3N, Bu_4NBr, sod. Formate**	**DMF**	**80**	**100% 426**
$Pd(PPh_3)_4$	K_2CO_3	MeCN	reflux	no reaction
$Pd(PPh_3)_4$	K_2CO_3	MeCN	90	no reaction
$Pd(PPh_3)_4$	Et_3N	MeCN	100	no reaction
$Pd(PPh_3)_4$	K_2CO_3	MeCN	110	complex mixture
$Pd(PPh_3)_4$	K_2CO_3	toluene	110	mainly decomposition
$Pd(PPh_3)_4$	K_2CO_3	MeCN	150	PMB came off

2.2.9 Conclusions

The lomaiviticinone A core **462** was constructed in 11 steps from chiral alkynol **325** with complete control of both absolute and relative stereochemistry. This route included an unprecedented double Ireland-Claisen rearrangement, which succinctly established the desired relative stereochemistry between the C-C linkage region and neighboring quaternary carbon of the dimeric target. Another key C-C bond was formed by a bis ring-closing metathesis of tetraene **455** to form bicycle **456**. Transformation of bicycle **456** to lomaiviticinone A core **462** was achieved via formation of bis

endoperoxide **460** followed by TBS removal and cleaveage of the resultant peroxide. This lomaiviticin A core contains useful functional handles to attach the aryl portion of the natural product.

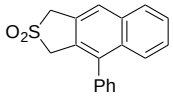
Chapter 3

Experimentals

2.3.1 General Experimental

Moisture- and oxygen-sensitive reactions were carried out in flame-dried glassware under an inert nitrogen atmosphere. Dry ether (Et_2O), toluene, acetonitrile (MeCN), dichloromethane (CH_2Cl_2), methanol (MeOH), tetrahydrofuran (THF) and dimethylformamide (DMF) were purified by passing these solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification unless otherwise stated. Reactions were monitored by thin layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV visualization and PMA staining. Purification of products via flash chromatography was performed with 40-63 μm silica gel and the solvent system indicated. Melting points are uncorrected.

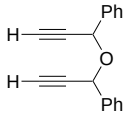
2.3.2 Braverman Diradical Cyclization Experimentals



52

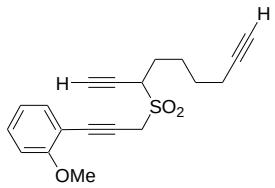
4-Phenyl-1,3-dihydronaphtho[2,3-*c*]thiophene 2,2-Dioxide (52). A stirring solution of alkyne **45** (50 mg, 0.39 mmol) in 5 mL of Et_2O was treated with pyridine (35 μL, 0.44 mmol). After 1 h, the reaction mixture was cooled to -78 °C and freshly distilled SCl_2 (13 μL, 0.94 mmol) was added dropwise. After 1 h at -78 °C, saturated

$NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 25% Et_2O/hexanes → 50% Et_2O/hexanes as eluent) gave tetracycle **52** (4.9 mg, 9%) as a light yellow oil. Spectral data matched those reported by Braverman.[16]



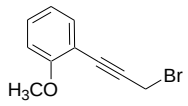
62

1,1'-(Oxydi-2-propyn-1-ylidene)bisbenzene (62). To a stirring solution of alkyne **45**[75] (0.100 g, 0.774 mmol) in 10 mL of Et_2O was added pyridine (70 μL, 0.87 mmol). After 1 h, the reaction mixture was cooled to -78 °C and a solution of freshly distilled SCl_2 (26 μL, 0.39 mmol) in 330 μL of CH_2Cl_2 was added to the reaction solution. After 1 h at -78 °C, saturated $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 10% Et_2O/hexanes → Et_2O as eluent) gave bis propargylic ether **62** (21.7 mg, 23%) as a colorless oil. Spectral data matched those reported by Bustelo.[76]



63

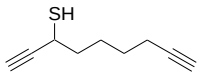
1-Methoxy-2-[3-(nona-1,8-diyne-3-sulfonyl)-prop-1-ynyl]benzene (63). A stirring suspension of crude sulfide **76** and Na_2CO_3 (1.07 g, 10.1 mmol) in 65 mL of CH_2Cl_2 was treated with 70% *m*-CPBA (0.917 g, 5.04 mmol). The reaction mixture was heated at reflux for 12 h, cooled to room temperature, and then saturated $NaHCO_3$ (70 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic fractions were sequentially washed with 1 M H_3PO_4 (200 mL) and brine (200 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (5% Et_2O/hexanes, then CH_2Cl_2 as eluent) gave sulfone **63** (0.343 g, 37% over 2 steps) as a light yellow oil. IR (thin film) 3272, 2359 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 1H), 7.31 (tdd, *J* = 8.0, 1.7, 1.0 Hz, 1H), 6.88 (tt, *J* = 7.5, 1.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.55 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.44-4.39 (m, 1H), 4.13 (d, *J* = *1*7.0 Hz, 1H), 3.84 (s, 3H), 2.60 (d, *J* = 2.5 Hz, 1H), 2.20 (td, *J* = 6.1, 2.0 Hz, 2H), 2.13-2.07 (m, 1H), 2.01-1.92 (m, 1H), 1.93 (t, *J* = *2*.6 Hz, 1H), 1.85-1.79 (m, 1H), 1.60-1.53 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 133.5, 130.6 (2), 120.4, 110.6, 84.5, 83.7, 79.9, 75.8, 68.7 (2), 55.7, 44.3, 44.2, 27.7, 25.8, 25.7, 18.1; LRMS (ESI) *m/z* (relative intensity) 346.2 (50%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{19}H_{24}NO_3S]^+$, 346.1477, found 346.1474.



68

1-(3-Bromo-prop-1-ynyl)-2-(methoxy)benzene (68). To a stirring solution of 2-iodoanisole (**65**) (13.9 mL, 107 mmol) in 350 mL of THF was sequentially added propargyl alcohol (**66**) (21.6 mL, 371 mmol), $Pd(PPh_3)_2Cl_2$ (1.09 g, 1.40 mmol), Et_3N (40.5 mL, 291 mmol), and CuI (1.08 g, 5.67 mmol). After 14 h, the reaction mixture was poured into H_2O (400 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 250 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (50% EtOAc/hexanes as eluent) propargylic alcohol **67** (17.3 g, 100%) as a light yellow solid. Spectral data matched those reported by Franks.[77]

A stirring solution of PPh_3 (18.0 g, 68.7 mmol) in 200 mL of CH_2Cl_2 was cooled to 0 ºC and Br_2 (3.51 mL, 68.7 mmol) was added dropwise to the reaction mixture. A solution of propargylic alcohol **67** (11.1 g, 68.4 mmol) in 50 mL of CH_2Cl_2 was added dropwise to the reaction mixture and solution was stirred for an additional 4 h at 0 ºC. The reaction mixture was warmed to room temperature and concentrated *in vacuo* to give a light yellow oil. Purification of the oil by SiO_2 flash column chromatography (10% benzene/hexanes) gave bromide **68** (13.7 g, 89%) as a colorless oil whose spectral data matched those reported by Dai.[78]



75

Nona-1,8-diyne-3-thiol (75). To a stirring solution of hept-6-ynal (**71**)[79] (1.01 g, 9.14 mmol) in 75 mL of THF at 0 °C was added a solution of ethynylmagnesium bromide in THF (0.5M, 21.9 mL, 11.0 mmol). The reaction mixture was stirred at 0 °C for 2 h and then saturated NH_4Cl (100 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic fractions were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford alcohol **72** (0.717 g, 58%) as a colorless oil. A yield of 90% was obtained on a 32 mg scale. IR (thin film) 3950, 3500, 2115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (qd, *J* = 6.1, 2.0 Hz, 1H), 2.49 (br s, 1H), 2.43 (d, *J* = 2.1 Hz, 1H), 2.19-2.13 (m, 2H), 1.91 (t, *J* = 2.6, 1H), 1.71-1.64 (m, 2H), 1.57-1.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.8, 84.2, 72.9, 68.4, 65.8, 61.9, 36.9, 27.9, 24.1, 18.2; GC-MS (EI) *m/z* (relative intensity) 136.2 (5%, M^+).

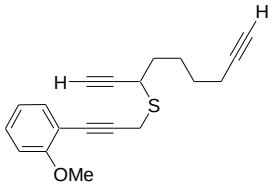
To a stirring solution of alcohol **72** (0.668 g, 4.88 mmol) in 1.55 mL CH_2Cl_2 at 0 °C was added *p*-toluenesulfonyl chloride (0.998 g, 5.23 mmol). The reaction mixture was stirred for 3 h and then H_2O (25 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic fractions were washed with 1 M HCl (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of the oil by SiO_2 flash column chromatography (5 % EtOAc/hexanes as eluent) gave tosyl ether (**73**) (0.988 g, 70%) as a yellow oil. IR (thin film) 3292, 2123 cm^-

^{1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 5.00 (td, *J* = 6.5, 2.1 Hz, 1H), 2.39 (s, 3H), 2.38 (s, 1H), 2.11 (td, *J* = 6.6, 2.6 Hz, 2H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.83-1.73 (m, 2H), 1.56-1.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 133.5, 129.6, 127.9, 83.7, 79.4, 76.2, 70.7, 68.6, 34.9, 27.4, 23.5, 21.5, 18.0; LRMS (ESI) *m/z* (relative intensity) 308.1 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{16}H_{22}NO_3S]^+$, 308.1320, found 308.1316.

To a stirring solution of CsF (0.44 g, 2.9 mmol) in 10 mL of DMF was added thiolacetic acid (274 μL, 3.89 mmol). The reaction mixture was stirred for 20 min, and then a solution of tosyl ether **73** (0.832 g, 2.87 mmol) in 5 mL of DMF was added. The reaction mixture was stirred for 20 h at 50 °C and then H_2O (10 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic fractions were sequentially washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude yellow oil. Purification of the oil by SiO_2 flash column chromatography (10% Et_2O/hexanes as eluent) afforded thiolacetate **74** (0.433 g, 78%) as a yellow oil. IR (thin film) 3294, 1695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (td, *J* = 6.8, 2.5 Hz, 1H), 2.31 (s, 3H), 2.26 (d, *J* = 2.6 Hz, 1H), 2.20-2.13 (m, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.77-1.70 (m, 2H), 1.62-1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 84.0, 82.2, 71.6, 68.5, 34.9, 33.3, 30.2, 27.7, 26.0, 18.2; GC-MS (EI) *m/z* (relative intensity) 194.0 (5%, M^+).

To a stirring solution of $LiAlH_4$ (49.1 mg, 1.29 mmol) in 10 mL of Et_2O at 0 °C was added a solution of thiolacetate **74** (346 mg, 1.78 mmol) in 5 mL of Et_2O. The reaction mixture was warmed to room temperature, stirred for 14 h, and poured into ice-

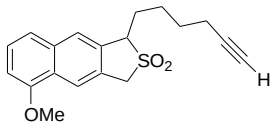
cold H_2O. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic fractions were sequentially washed with 1 M H_3PO_4 (60 mL) and then brine (60 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by passing through a thin pad of SiO_2 (33% Et_2O/hexanes as eluent) gave thiol **75** (125 mg, 46%) as a yellow oil. A yield of 60% was obtained on a 2.12 g scale. IR (thin film) 3293 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53-3.51 (m, 1H), 3.26 (s, 1H), 2.17-2.14 (m, 3H), 1.93 (d, J = 2.4 Hz, 1H), 1.76-1.73 (m, 2H), 1.59-1.49 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.0, 84.0, 71.4, 68.5, 38.5, 28.3, 27.6, 26.1, 18.2; GC-MS (EI) *m/z* (relative intensity) 152.0 (100%, M^+).



76

1-[3-(1-Ethynylhept-6-ynylsulfanyl)-prop-1-ynyl]-2-(methoxy)benzene (76). To a stirring suspension of K_2CO_3 (0.254 g, 1.84 mmol) in 7 mL of MeCN was added a solution of thiol **75** (0.432 g, 2.83 mmol) in 3 mL of MeCN. The reaction mixture was stirred for 10 min and then bromide **68** (404 μL, 2.83 mmol) was added. The reaction mixture was heated at 60 °C for 14 h, cooled to room temperature, and then 1 M phosphoric acid (10 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give sulfide **76** as a yellow oil, which was carried on

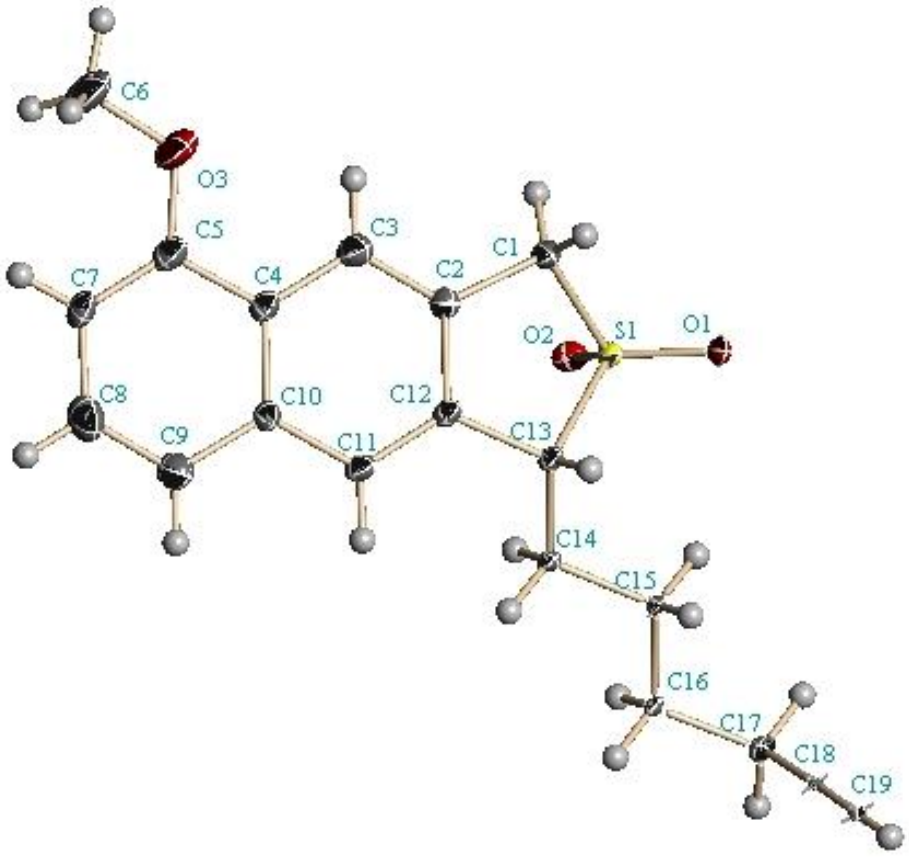
without further purification. IR (thin film) 3284, 2214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.26 (td, *J* = 7.9, 1.7 Hz, 1H), 6.87 (td, *J* = 7.5, 1.0 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.92-3.86 (m, 1H), 3.85 (s, 3H), 3.81 (d, *J* = 16.8 Hz, 1H), 3.62 (d, *J* = 16.8 Hz, 1H), 2.39 (d, *J* = 2.4 Hz, 1H), 2.19 (td, *J* = 6.9, 2.6 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.82 (t, *J* = 7.0 Hz, 2H), 1.69-1.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 133.3, 129.6, 120.2, 111.9, 110.4, 89.3, 83.9, 82.8, 79.5, 72.1, 68.4, 55.5, 34.0, 33.7, 27.7, 26.2, 20.1, 18.1; LRMS (ESI) *m/z* (relative intensity) 297.1 (60%, M + H^+).



77

1-Hex-5-ynyl-5-methoxy-1,3-dihydronaphtho[2,3-c]thiophene 2,2-Dioxide (77). A stirring solution of sulfone **63** (209 mg, 0.635 mmol) in 20 mL of $CHCl_3$ was treated with Et_3N (136 μL, 0.953 mmol). The reaction mixture was stirred for 3 d and concentrated *in vacuo* to give tricycle **77** (209 mg, 100%) as a yellow solid. A sample of this solid was recrystallized using $MeCN/CH_2Cl_2$ to obtain X-ray quality crystals. mp 141-143 ºC; IR (thin film) 3284, 1308, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.68 (s, 1H), 7.44-7.39 (m, 2H), 6.84 (d, *J* = 6.8 Hz, 1H), 4.43 (s, 2H), 4.29 (t, *J* = 7.1 Hz, 1H), 3.99 (s, 3H), 2.27 (td, *J* = 7.0, 2.1 Hz, 2H), 2.25-2.04 (m, 2H), 1.98 (t, *J* = 2.2 Hz, 1H), 1.88-1.76 (m, 2H), 1.75-1.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 134.3, 134.0, 127.05, 127.02, 125.1, 124.1, 120.0, 119.8, 104.6, 83.9, 68.7, 64.9, 55.6, 55.2, 29.0, 28.2, 25.6, 18.1; LRMS (ESI) *m/z* (relative intensity) 346.1 (100%, M + NH_4^+).

X-ray Data for Tricycle 77 (CCD# 713998)

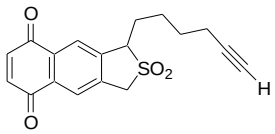


A colorless block shaped crystal of tricycle **77** (C19 H20 O3 S) with approximate dimensions 0.16 x 0.20 x 0.25 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 123(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600

watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

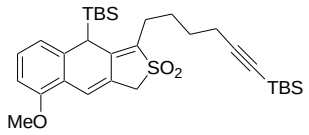
A total of 1850 frames were collected with a scan width of 0.3º in ω and an exposure time of 5 seconds/frame. The total data collection time was about 6 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Triclinic unit cell yielded a total of 15455 reflections to a maximum θ angle of 28.32° (0.90 Å resolution), of which 7788 were independent, completeness = 97.4%, R_{int} = 0.0209, R_{sig} = 0.0310 and 6960 were greater than 2σ(I). The final cell constants: a = 10.9938(18)Å, b = 11.2801(18)Å, c = 15.065(2)Å, α = 97.803(3)°, β = 97.670(3)°, γ = 117.288(2)°, volume = 1603.8(4)$Å^3$, are based upon the refinement of the XYZ-centroids of 7859 reflections above 20σ(I) with 2.280° <θ < 28.320° . Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.8484.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P-1, with Z = 4 for the formula unit, C19 H20 O3 S. The final anisotropic full-matrix least-squares refinement on F^2 with 417 variables converged at R1 = 4.04%, for the observed data and wR2 = 11.26% for all data. The goodness-of-fit was 0.608. The largest peak on the final difference map was 0.631 $e^-/Å^3$ and the largest hole was -0.334 $e^-/Å^3$. Based on the final model, the calculated density of the crystal is 1.360 g/cm^3 and F(000) amounts to 696 electrons.



78

1-Hex-5-ynyl-2,2-dioxo-2,3-dihydro-1*H*-2λ^6-naphtho[2,3-c]thiophene-5,8-dione (78). A stirring solution of sulfone **77** (0.209 g, 0.635 mmol) in 15 mL of acetone was treated with Jones reagent (695 μL, 2.54 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 14 h after which time additional Jones reagent (695 μL, 2.54 mmol) was added. The reaction mixture was stirred for 1 h at room temperature and then isopropanol (15 mL) and H_2O (15 mL) were added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic fractions were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this yellow oil by SiO_2 flash column chromatography (15:4:1 hexanes/Et_2O/CH_2Cl_2, then 13:5:2 hexanes/Et_2O/CH_2Cl_2 as eluent) gave quinone **78** (126 mg, 60%) as a yellow oil. IR (thin film) 3272, 1666, 1314, 1132 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (app d, *J* = 5.1 Hz, 2H), 7.01 (s, 2H), 7.68 (s, 1H), 4.41 (app s, 2H), 4.29 (dd, *J* = 8.4, 6.0 Hz, 1H), 2.25 (td, *J* = 6.8, 2.6 Hz, 2H), 2.19-2.11 (m, 2H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.84-1.76 (m, 2H), 1.67 (q, *J* = 4.4 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 183.9, 183.8, 142.4, 138.7 (2), 136.6, 132.0, 131.8, 124.2, 123.5, 83.6, 69.0, 65.3, 55.3, 28.7, 28.0, 25.6, 18.1; LRMS (ESI) *m/z* (relative intensity) 351.2 (100%, M + Na$^+$).



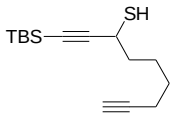
83

4-(*tert*-Butyl(dimethyl)silanyl)-3-[6-(*tert*-butyl(dimethyl)silanyl)-hex-5-ynyl]-8-methoxy-1,4-dihydronaphtho[2,3-c]thiophene 2,2-Dioxide (83). To a stirring solution of sulfide **76** (0.479 g, 1.62 mmol) in 32 mL of THF at -78 °C was added *n*-BuLi (2.5 M in hexanes, 1.31 mL, 3.24 mmol) dropwise. After 1 h, a solution of TBSCl (0.504 g, 3.24 mmol) in 5 mL of THF was added. After stirring for 5 min, the solution was allowed to warm to 0 °C, stirred for 2 h, and then warmed to rt. After stirring the mixture for 30 min, saturated NH_4Cl (50 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (99:1 hexanes/Et_2O as eluent) gave sulfide **80** (0.471 g, 55%) as a yellow oil.

To a stirring solution of this sulfide **80** (0.282 g, 0.537 mmol) and Na_2CO_3 (0.404 g, 3.81 mmol) in 8 mL of CH_2Cl_2 was added 70-75% *m*-CPBA (0.359 g, 2.50 mmol). The reaction mixture was stirred for 3 d and then treated with saturated $NaHCO_3$ (10 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The organic fractions were washed with 1 M phosphoric acid (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography

(5:1 hexanes/Et_2O → 5:1 hexanes/EtOAc as eluent) gave sulfone **81** (0.066 g, 22%) as a yellow oil. A yield of 36% was obtained on a 526 mg scale

A stirring solution of this sulfone **81** (0.055 g, 0.099 mmol) in 3.7 mL of toluene was treated with Et_3N (22 μL, 0.158 mmol) in 1.8 mL of toluene in a sealed tube. The reaction mixture was heated to 140 °C, stirred for 15 h, and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (89:10:1 hexanes/Et_2O/CH_2Cl_2 as eluent) gave tricycle **83** (0.012 g, 24%) as a light yellow oil. IR (thin film) 1290, 1126 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.09 (app. t, *J* = 8.1 Hz, 1H), 6.99 (s, 1H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 3.94 (dd, *J* = 10.1, 1.5 Hz, 2H), 3.86 (s, 1H), 3.81 (s, 3H) 2.53 (m, 1H), 2.37 (m, 1H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.86-1.74 (m, 2H), 1.63-1.56 (m, 2H), 0.91 (s, 9H), 0.82 (s, 9H), 0.05 (s, 6H), -0.01 (s, 3H), -0.36 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.5, 146.5, 138.0, 132.0, 128.5, 125.9, 120.3, 120.0, 119.7, 107.8, 107.4, 82.7, 55.6, 53.3, 34.6, 28.7, 27.4, 26.9, 26.1, 23.7, 19.5, 19.4, 18.4, -4.5, -6.2; LRMS (ESI) *m/z* (relative intensity) 574.4 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{31}H_{52}NO_3Si_2S]^+$, 574.3206, found 574.3193.



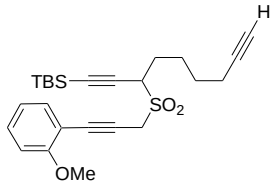
86

1-(*tert*-Butyldimethylsilanyl)nona-1,8-diyne-3-thiol (86). To a stirring solution of TBS acetylene (6.32 g, 44.9 mmol) in 80 mL of THF at 0 °C was added *n*-BuLi (2.5 M in hexanes, 18 mL, 45 mmol) dropwise. The reaction mixture was stirred for 10 min at 0 °C and then a solution of hept-6-ynal (**71**)[79] (4.95 g, 44.9 mmol) in 20 mL of THF was

added. The reaction mixture was stirred at room temperature for 2 d, and then saturated NH_4Cl (100 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic fractions were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% Et_2O/hexanes → 10% Et_2O/hexanes as eluent) afforded alcohol **84** (4.78 g, 43%) as a colorless oil. A yield of 60% was obtained on a 1.41 g scale. IR (thin film) 3400, 3307, 2175 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.36 (t, *J* = 5.1 Hz, 1H), 2.21-2.16 (m, 2H), 1.97 (brs, 1H), 1.93 (t, *J* = 2.1 Hz, 1H), 1.71-1.70 (m, 2H), 1.60-1.54 (m, 4H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 107.3, 87.7, 84.2, 68.4, 62.6, 37.3, 28.1, 26.0, 24.3, 18.3, 16.4, -4.7; LRMS (ESI) *m/z* (relative intensity) 251.3 (70%, $M + H^+$).

To a stirring solution of PPh_3 (4.28 g, 19.5 mmol) and alcohol **84** (4.44 g, 17.7 mmol) in 60 mL of THF at 0 °C was added DIAD (3.04 mL, 19.5 mmol) dropwise. The reaction mixture was stirred for 10 min at 0 °C and then treated with thiolacetic acid (1.06 mL, 19.5 mmol). After 2 h at 0 °C, the reaction mixture was concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (10% Et_2O/hexanes as eluent) afforded thiolacetate **85** (3.84 g, 70%) as a yellow oil. IR (thin film) 3295, 2150, 1690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.29 (t, *J* = 6.8 Hz, 1H), 2.32 (s, 3H), 2.19 (td, *J* = 6.7, 2.6 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.77-1.74 (m, 2H), 1.62-1.56 (m, 4H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.1, 104.2, 86.7, 84.1, 68.4, 35.5, 34.4, 30.2, 27.8, 26.0 (2), 18.2, 16.5, -4.7; LRMS (ESI) *m/z* (relative intensity) 309.2 (100%, $M + H^+$).

To a stirring suspension of K_2CO_3 (1.89 g, 12.4 mmol) in 130 mL of MeOH was added thiolacetate **85** (3.84 g, 12.4 mmol) in 20 mL of MeOH. The reaction mixture was stirred for 3 h at room temperature at which time 1 M H_3PO_4 (200 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic fractions were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give thiol **86** (2.84 g, 86%) as a yellow oil. A yield of 98% was obtained on a 4.91 g scale. IR (thin film) 3295, 2150 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.60 (app q, J = 6.5 Hz, 1H), 2.20 (td, J = 6.8, 2.5 Hz, 2H), 2.13 (d, J = 6.5 Hz, 1H), 1.94 (t, J = 2.5 Hz, 1H), 1.79-1.77 (m, 2H), 1.64-1.56 (m, 4H), 0.93 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 107.4, 86.0, 84.1, 68.5, 38.9, 29.4, 27.9, 26.1, 26.05, 18.3, 16.6, -4.7; LRMS (ESI) *m/z* (relative intensity) 267.2 (30%, M + H^+).



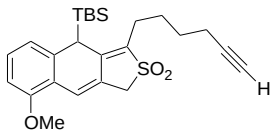
88

***tert*-Butyl-{3-[3-(2-(methoxy)phenyl)-prop-2-yne-1-sulfonyl]-nona-1,8-diynyl}-dimethylsilane (88).** To a stirring solution of solid LHMDS (3.39 g, 20.3 mmol) in 120 mL of THF at 0 °C was added a solution of thiol **86** (5.14 g, 19.3 mmol) in 120 mL of THF. The reaction mixture was stirred for 5 min at 0 °C and treated with bromide **68** (2.9 mL, 19 mmol). After 14 h, the reaction mixture was warmed to room temperature and H_2O (120 mL) was added. The resulting mixture was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 200 mL). The combined organic

fractions were washed with brine (500 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give sulfide **87** (7.15 g, 17.3 mmol) as a yellow oil that was used without further purification. IR (thin film) 3295, 2150 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.26 (td, *J* = 7.9, 1.8 Hz, 1H), 6.90-6.83 (m, 2H), 3.91 (t, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 3.80 (d, *J* = 16.9 Hz, 1H), 3.65 (d, *J* = 16.6 Hz, 1H), 2.19 (td, *J* = 6.5, 2.5 Hz, 2H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.83 (q, *J* = 7.0 Hz, 2H), 1.75-1.66 (m, 2H), 1.58 (q, *J* = 7.2 Hz, 2H), 0.95 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.0, 133.5, 129.4, 120.2, 112.1, 110.4, 105.1, 89.1, 86.9, 84.0, 79.4, 68.3, 56.0, 35.1, 34.0, 27.8, 26.1, 26.0, 20.2, 18.2, 16.4, -4.6; LRMS (ESI) *m/z* (relative intensity) 433.0 (100%, M + Na^+); HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{25}H_{38}NOSSi]^+$, 428.2443, found 428.2427.

To a stirring solution of sulfide **87** (7.15 g, 17.3 mmol) in 500 mL of CH_2Cl_2 was added 70-75% *m*-CPBA (8.57 g, 34.6 mmol). The reaction mixture was stirred for 1.5 h and then treated with Et_3N (5.2 mL, 37 mmol) followed by H_2O (500 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 400 mL). The organic fractions were washed with brine (800 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (8:1:1 hexanes/Et_2O/CH_2Cl_2 as eluent) afforded linear sulfone **88** (3.74 g, 44% over 2 steps) as a yellow oil. IR (thin film) 3284, 2355, 1326, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.33 (td, *J* = 3.9, 1.7 Hz, 1H), 6.93-6.85 (m, 2H), 4.55 (d, *J* = 16.9 Hz, 1H), 4.42 (dd, *J* = 10.5, 4.3 Hz, 1H), 4.13 (d, *J* = 16.9 Hz, 1H), 3.85 (s, 3H), 2.22 (td, *J* = 6.7, 2.6 Hz, 2H), 2.17-2.00 (m, 1H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.88-1.75 (m, 1H), 1.74-1.58 (m, 4H),

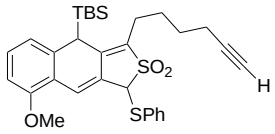
0.94 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 133.5, 130.5, 120.3, 110.8, 110.6, 97.4, 93.0, 84.3, 83.7, 79.9, 68.6, 55.7, 54.7, 44.1, 27.7, 26.0, 25.9, 25.8, 18.1, 16.6, -5.0; LRMS (ESI) *m/z* (relative intensity) 460.3 (90%, M + NH_4^+); HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{25}H_{38}NO_3SSi]^+$, 460.2342, found 460.2342.



90

***tert*-Butyl-(3-hex-5-ynyl-8-methoxy-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-c]thiophen-4-yl)-dimethylsilane (90).** To a refluxing solution of linear sulfone **88** (0.125 g, 0.282 mmol) in 10 mL of toluene was added Et_3N (59 μL, 0.42 mmol). The reaction mixture was held at reflux for 14 h and then cooled to room temperature and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient 10% Et_2O/hexanes → 20% Et_2O/hexanes as eluent) afforded tricycle **90** (80 mg, 64%) as a yellow oil. IR (thin film) 3300, 1290, 1120 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.10 (app t, *J* = 7.9 Hz, 1H), 7.00 (s, 1H), 6.71 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 4.01-3.82 (m, 3H), 3.82 (s, 3H), 2.58-2.50 (m, 1H), 2.45-2.36 (m, 1H), 2.21 (td, *J* = 7.0, 2.7 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.86-1.79 (m, 2H), 1.62-1.58 (m, 2H), 0.91 (s, 9H), 0.00 (s, 3H), -0.35 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.4, 146.6, 137.9, 131.8, 128.5, 125.8, 120.2, 120.1, 119.6, 107.8, 84.0, 68.6, 55.5, 53.3, 34.6, 28.1, 27.3, 26.8, 23.5, 18.4, 18.0, -4.5, -6.2; LRMS (ESI) *m/z* (relative intensity) 443.3 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{25}H_{38}NO_3SSi]^+$, 460.2342, found 460.2350.

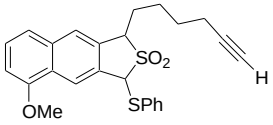
Conversion of Dimethoxy Sulfone 105 to Tricycle 90. To a refluxing solution of linear sulfone **105** (66 mg, 0.14 mmol) in 5 mL of toluene was added Et_3N (29 μL, 0.21 mmol). The reaction mixture was heated at reflux for 14 h, cooled to room temperature and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% Et_2O/hexanes → 30% Et_2O/hexanes as eluent) afforded tricycle **90** (17 mg, 28%) as a yellow oil.



91

***tert*-Butyl-(3-hex-5-ynyl-8-methoxy-2,2-dioxo-1-phenylsulfanyl-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-c]thiophen-4-yl)dimethylsilane (91).** To a stirring solution of tricycle **90** (0.24 g, 0.55 mmol) in 7 mL of THF at -78 °C was added *n*-BuLi (2.5M in hexanes, 220 μL, 0.55 mmol) dropwise. The reaction mixture was held at this temperature for 15 min and then diphenyl disulfide (1.2 g, 5.5 mmol) was added and the solution was warmed to 0 °C over 30 min. The mixture was held at this temperature for 4 h and then H_2O (10 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (95:5:2 hexanes/Et_2O/CH_2Cl_2 as eluent) afforded thiophenyl adduct **91** (0.197 g, 65%) as a yellow oil. IR (thin film) 3284, 1297, 1108 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 9.4, 1.8 Hz, 2H), 7.37-7.29 (m, 3H), 7.22 (s, 1H), 7.12 (dd,

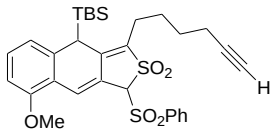
J = 7.9, 7.9 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 5.06 (d, *J* = 1.1 Hz, 1H), 3.92 (s, 1H), 3.83 (s, 3H), 2.58-2.50 (m, 1H), 2.43-2.37 (m, 1H), 2.21 (td, *J* = 7.0, 2.7 Hz, 2H), 1.92 (t, *J* = 2.7 Hz, 1H), 1.87-1.81 (m, 2H), 1.64-1.54 (m, 2H), 0.94 (s, 9H), 0.08 (s, 3H), -0.34 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.8, 145.3, 138.3, 133.0, 131.9, 130.4, 129.3, 129.2, 128.2, 127.5, 123.9, 120.3, 119.8, 107.9, 84.0, 68.7, 67.7, 56.3, 34.8, 28.2, 27.7, 26.8, 24.1, 18.5, 18.0, -4.0, -6.2; LRMS (ESI) *m/z* (relative intensity) 568.3 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{31}H_{42}NO_3S_2Si]^+$, 568.2375, found 568.2397.



92

1-Hex-5-ynyl-5-methoxy-3-phenylsulfanyl-1,3-dihydro-naphtho[2,3-c]thiophene 2,2-Dioxide (92). To a stirring solution of **91** (17 mg, 0.031 mmol) in 1 mL of THF at 0 °C was added Bu_4NF (1.0 M in THF, 33 μL, 0.032 mmol). The reaction mixture was stirred for 20 min at 0 °C and then H_2O (5 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give a 1:1 mixture of diastereomers of thiophenyl adduct **92** (12 mg, 86%) as a yellow oil. IR (thin film) 3284, 1314, 1102 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diastereomers) δ 8.52 (s, 1H), 8.46 (s, 1H), 7.76-7.59 (m, 6H), 7.44-7.30 (m, 10H), 6.85 (d, *J* = 7.3 Hz, 2H), 5.56 (s, 1H), 5.50 (s, 1H), 4.29 (t, *J* = 7.2 Hz, 1H), 4.17 (t, *J* = 7.1 Hz, 1H), 4.02 (s, 6H), 2.29-

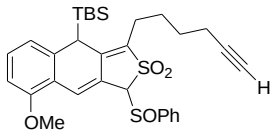
2.20 (m, 6H), 2.20-2.01 (m, 2H), 1.97-1.94 (m, 2H), 1.91-1.81 (m, 4H), 1.73-1.62 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$, mixture of diastereomers) δ 155.4 (2), 134.52, 134.48, 133.9, 133.1, 132.9 (2), 132.5, 131.2, 129.3 (2), 129.2 (2), 128.95, 128.93, 128.65, 128.62, 127.7 (2), 125.30, 125.26, 124.01, 123.8, 121.7, 121.5, 119.86, 119.84, 83.96, 83.93, 71.7, 70.6, 68.7 (2), 63.9, 62.2, 55.6 (2), 29.7, 28.16, 28.13, 26.1, 25.8, 25.6, 18.1 (2); LRMS (ESI) *m/z* (relative intensity) 454.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{25}H_{28}NO_3S_2]^+$, 454.155, found 454.1510.



93

(1-Benzenesulfonyl-3-hex-5-ynyl-8-methoxy-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-c]thiophen-4-yl)-*tert*-butyl(dimethyl)silane (93) To a stirring solution of thiophene **91** (72 mg, 0.13 mmol) in 5 mL of CH_2Cl_2 at room temperature was added 70% *m*-CPBA (86 mg, 0.34 mmol). The reaction mixture was stirred for 30 min at room temperature and saturated $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% Et_2O/hexanes → 20% Et_2O/hexanes as eluent) afforded sulfone **93** (45 mg, 59%) as a yellow oil. IR (thin film) 3284, 1303, 1108 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.2 Hz, 2H), 7.70-7.66 (m, 1H), 7.60-7.55 (m, 2H), 7.45 (s, 1H), 7.14 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H),

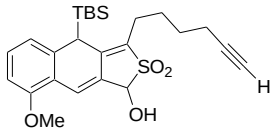
6.67 (d, J = 7.9 Hz, 1H), 5.07 (s, 1H), 3.96 (s, 1H), 3.83 (s, 3H), 2.47-2.43 (m, 1H), 2.36-2.34 (m, 1H), 2.17 (td, J = 7.0, 2.5 Hz, 2H), 1.92 (t, J = 2.5 Hz, 1H), 1.82-1.64 (m, 2H), 1.63-1.53 (m, 2H), 0.93 (s, 9H), 0.07 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 156.2, 147.0, 138.3, 138.2, 134.6, 130.4, 130.0, 129.7, 129.0, 127.4, 120.1, 120.0, 119.9, 108.1, 83.8, 78.3, 68.7, 55.5, 35.5, 28.0, 27.8, 27.4, 26.6, 23.8, 18.6, 17.9, -5.5, -7.0; LRMS (ESI) *m/z* (relative intensity) 600.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{31}H_{42}NO_5S_2Si]^+$, 600.2274, found 600.2277.



94

(1-Benzenesulfinyl-3-hex-5-ynyl-8-methoxy-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-c]thiophen-4-yl)-*tert*-butyl(dimethyl)silane (94). To a stirring solution of thiophene **91** (0.173 g, 0.314 mmol) in 25 mL of CH_2Cl_2 was added 70-75% *m*-CPBA (75 mg, 0.31 mmol). The reaction mixture was stirred for 2 h at room temperature and then saturated $NaHCO_3$ (25 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic fractions were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (17:3:1 hexanes/EtOAc/CH_2Cl_2 as eluent) afforded sulfoxide **94** (79 mg, 44%) as a yellow oil. A yield of 48% was obtained on a 427 mg scale. IR (thin film) 3295, 1291, 1149 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.94 (d, J = 4.0 Hz, 2H), 7.64-7.56 (m, 3H), 7.16 (app t, J = 7.9, 1H), 6.95 (s, 1H), 6.79 (d, J = 7.6

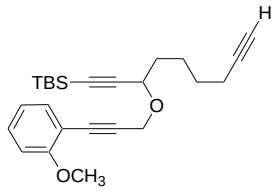
Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 4.60 (s, 1H), 3.97 (s, 1H), 3.81 (s, 3H), 2.56-2.52 (m, 1H), 2.48-2.39 (m, 1H), 2.27-2.19 (m, 2H), 2.00-1.95 (m, 1H), 1.91-1.73 (m, 2H), 1.67-1.55 (m, 2H), 1.01 (s, 9H), 0.22 (s, 3H), -0.14 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 156.1, 146.9, 142.9, 138.3, 131.9, 130.3, 129.39, 129.38, 126.4, 125.4, 121.3, 120.1, 119.7, 107.5, 83.8, 80.7, 68.7, 56.2, 34.8, 28.0, 27.7, 26.6, 23.6, 18.4, 17.9, -6.7; LRMS (ESI) *m/z* (relative intensity) 567.3 (100%, M + H^+).



96

4-(*tert*-Butyldimethylsilanyl)-3-hex-5-ynyl-8-methoxy-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-c]thiophen-1-ol (96). To a stirring solution of sulfoxide **94** (0.213 g, 0.376 mmol) in 5 mL of toluene was added Et_2NH (389 μL, 3.76 mmol). The reaction mixture was then heated at 65 °C for 36 h and then warmed at 110 °C for an additional 12 h. The reaction solution was cooled to room temperature and H_2O (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5-15% Et_2O/hexanes, then 30% EtOAc/hexanes as eluent) afforded a 3:1 mixture of diastereomers of alcohol **96** (49 mg, 28%) as a yellow oil. IR (thin film) 3389, 3295, 1269, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, major isomer) δ 7.24-7.07 (m, 2H), 6.65-6.60 (m, 2H), 5.35 (s, 1H), 3.93-3.78 (m, 1H), 3.78 (s, 3H), 2.60-2.44 (m, 1H), 2.44-2.30 (m, 1H), 2.26-2.10 (m, 2H), 1.89 (s, 1H),

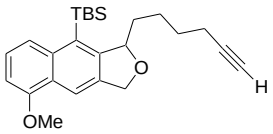
1.86-1.69 (m, 2H), 1.69-1.48 (m, 2H), 0.86 (s, 9H), -0.05 (s, 3H), -0.37 (s, 3H), OH not observed; ^{13}C NMR (90 MHz, $CDCl_3$, major isomer) δ 155.9, 146.1, 138.5, 129.8, 129.1, 127.8, 121.0, 119.9, 119.6, 107.9, 84.4, 83.9, 68.6, 55.9, 34.8, 28.0, 27.2, 26.7, 23.7, 18.3, 17.9, -4.6, -6.2; LRMS (ESI) *m/z* (relative intensity) 476.3 (90%, M + NH_4^+).



97

***tert*-Butyl-{3-[3-(2-(methoxy)phenyl)-prop-2-ynyloxy]-nona-1,8-diynyl}dimethylsilane (97).** To a stirring suspension of 60% NaH (0.080 g, 2.0 mmol) in 11 mL of THF at 0 °C was added a solution of alcohol **84** (0.453 g, 1.81 mmol) in 2 mL of THF. After 30 min, bromide **68** (0.407 g, 1.81 mmol) in 2 mL of THF was added and the mixture was warmed to room temperature and stirred for an additional 14 h. To the reaction mixture was added H_2O (10 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (93:5:2 hexanes/Et_2O/CH_2Cl_2 as eluent) afforded ether **97** (0.411 g, 58%) as a colorless oil. IR (thin film) 3295 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.6, 1.8, 1H), 7.24 (td, *J* = 7.9, 1.8 Hz, 1H), 6.88-6.81 (m, 2H), 4.58 (d, *J* = 15.8, 1H), 4.49 (d, *J* = 15.5, 1H), 4.39 (t, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 2.16 (td, *J* = 6.7, 2.9 Hz, 2H), 1.89 (t, *J* = 2.7 Hz, 1H), 1.77-1.72 (m, 2H), 1.60-1.52 (m, 4H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 160.0, 133.6, 129.7, 120.2, 111.7, 110.4,

104.6, 89.0, 88.9, 84.1, 82.4, 68.3, 68.2, 56.6, 55.6, 34.9, 28.0, 26.0, 24.3, 18.2, 16.4, -4.8; LRMS (ESI) *m/z* (relative intensity) 412.1 (100%, M + NH_4^+).

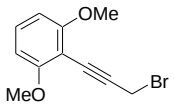


99

***tert*-Butyl-(3-hex-5-ynyl-8-methoxy-1,3-dihydronaphtho[2,3-c]furan-4-yl)dimethylsilane (99).** To a stirring suspension of KO^{t}Bu (0.023 g, 0.206 mmol) in 1.8 mL of benzene was added a solution of ether **97** (0.054 g, 0.137 mmol) in 0.2 mL of benzene. The mixture was warmed to reflux and stirred for an additional 14 h. The resulting solution was concentrated *in vacuo* to give a colorless oil. Purification of this oil by spherical SiO_2 flash column chromatography (1% Et_2O/hexanes as eluent) afforded naphthalene derivative **99** (0.0081 g, 15%) as a colorless oil. IR (thin film) 3295 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.78 (d, *J* = 10.6 Hz, 1H), 7.31 (t, *J* = 9.9 Hz, 1H), 6.75 (d, *J* = 11.0 Hz, 1H), 5.48 (br d, *J* = 10.0 Hz, 1H), 5.14 (d, *J* = 15.4 Hz, 1H), 5.05 (d, *J* = 15.3 Hz, 1H), 3.97 (s, 3H), 2.18 (td, *J* = 6.7, 2.6 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.74-1.55 (m, 6H), 0.94 (s, 9H), 0.58 (s, 3H), 0.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 151.2, 139.0, 136.6, 127.5, 125.1, 124.2, 122.7, 115.5, 103.2, 84.4, 84.2, 69.8, 68.3, 55.6, 36.3, 28.7, 28.5, 25.9, 18.9, 18.4, 1.2, 1.1; LRMS (ESI) *m/z* (relative intensity) 395.3 (80%, M + H^+).

Preparation of Tricycle 99 from Ether 130. A solution of dimethoxy ether **130** (10 mg, 0.02 mmol) and KO^{t}Bu (4 mg, 0.03 mmol) in 1 mL of toluene was brought to reflux. After refluxing for 14 h, the solution was cooled to room temperature and 1 M

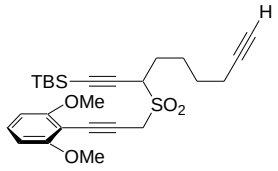
phosphoric acid (3 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (10% Et_2O/ hexanes as eluent) afforded tricycle **99** (2 mg, 22%) as a yellow oil.



103

2-(3-Bromoprop-1-ynyl)-1,3-(dimethoxy)benzene (103). To a stirring solution of 1-iodo-2,6-dimethoxybenzene (**101**) (15.0 g, 56.8 mmol) in 120 mL of pyrrolidine was added propargyl alcohol (**66**) (3.31 mL, 114 mmol) and $Pd(PPh_3)_4$ (3.33 g, 2.84 mmol). The reaction mixture was heated at 45 °C for 3 d and then saturated NH_4Cl (120 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 12:7:1 Et_2O/hexanes/CH_2Cl_2 → 8:1:1 Et_2O/hexanes/CH_2Cl_2) afforded propargylic alcohol **102** (9.39 g, 86%) as a white solid. mp 92-94 °C; IR (thin film) 3378, 2214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 4.56 (d, *J* = 5.1 Hz, 2H), 3.84 (s, 6H), 2.26 (t, *J* = 5.4 Hz, 1H) ; ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.4, 129.8, 103.3, 100.6, 96.0, 77.6, 55.9, 51.8; LRMS (ESI) *m/z* (relative intensity) 193.2 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{11}H_{13}O_3]^+$, 193.0865, found 193.0867.

To a stirring solution of PPh_3 (12.8 g, 48.9 mmol) in 125 mL of CH_2Cl_2 at 0 °C was added Br_2 (2.51 mL, 48.9 mmol). The reaction mixture was held at this temperature for 30 min and then a solution of propargylic alcohol **102** (9.39 g, 48.9 mmol) in 75 mL CH_2Cl_2 was added to the reaction solution. After an additional 2 h at 0 °C the reaction mixture was concentrated *in vacuo* to give an off-white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 17:2:1 hexanes/ Et_2O/CH_2Cl_2 → 3:6:1 hexanes/ Et_2O/CH_2Cl_2) afforded bromide **103** (2.77 g, 23%) as an off-white solid. A yield of 31% was obtained on a 75 mg scale. mp 90-92 °C; IR (thin film) 2205 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 8.4, 8.4 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 4.26 (s, 2H), 3.78 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 161.5, 130.2, 103.1, 99.9, 92.1, 79.4, 55.7, 16.2; LRMS (ESI) *m/z* (relative intensity) 255.1 (100%, $M + H^+$).



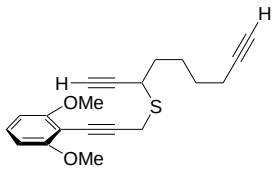
105

***tert*-Butyl-{3-[3-(2,6-(dimethoxy)phenyl)-prop-2-yne-1-sulfonyl]-nona-1,8-diynyl}dimethylsilane (105).** To a stirring solution of NaH (75 mg, 1.9 mmol) in 14 mL of THF at 0 °C was added a solution of thiol **86** (0.50 g, 1.9 mmol) in 3 mL of THF. The reaction mixture was held at this temperature for 15 min and then bromide **103** (0.479 g, 1.88 mmol) in 3 mL of CH_2Cl_2 was added to the reaction solution. After an additional 30 min at 0 °C, H_2O (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*

to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (5% Et_2O/hexanes) afforded sulfide **104** (0.657 g, 80%) as a yellow oil. IR (thin film) 3295, 2155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (app t, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 2H), 4.01 (t, *J* = 6.9 Hz, 1H), 3.85-3.79 (m, 1H), 3.83 (s, 6H), 3.66 (d, *J* = 16.8 Hz, 1H), 2.16 (td, *J* = 6.9, 2.6 Hz, 2H), 1.89 (t, *J* = 2.6 Hz, 1H), 1.82-1.77 (m, 2H), 1.73-1.52 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5, 129.4, 105.4, 103.3, 101.3, 93.5, 86.6, 84.1, 75.7, 68.3, 55.9, 34.9, 33.9, 27.9, 26.4, 26.0, 20.6, 18.2, 16.5, -4.6; LRMS (ESI) *m/z* (relative intensity) 441.1 (100%, $M + H^+$).

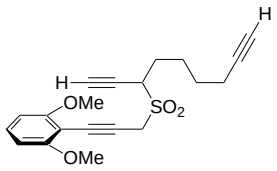
To a stirring solution of sulfide **104** (0.108 g, 0.243 mmol) in 10 mL of CH_2Cl_2 at room temperature was added 70-75% *m*-CPBA (0.123 g, 0.498 mmol). The reaction mixture was stirred for 3 h and then saturated $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 18:1:1 hexanes/Et_2O/CH_2Cl_2 → 4:5:1 hexanes/Et_2O/CH_2Cl_2) afforded sulfone **105** (98 mg, 85%) as a yellow oil. IR (thin film) 3284, 1326, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (app t, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 2H), 4.61 (dd, *J* = 10.5, 4.1 Hz, 1H), 4.57 (d, *J* = 17.0 Hz, 1H), 4.15 (d, *J* = 16.9 Hz, 1H), 3.86 (s, 6H), 2.24 (td, *J* = 6.7, 2.6 Hz, 2H), 2.08-2.05 (m, 1H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.95-1.82 (m, 1H), 1.75-1.60 (m, 4H), 0.97 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 131.3, 104.0, 98.3, 97.6, 93.2, 84.9, 84.4, 81.4, 69.0, 56.6, 54.8, 45.1, 28.4. 26.6, 26.5, 26.3, 18.6, 17.1, -4.6; LRMS (ESI) *m/z* (relative

intensity) 490.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{26}H_{40}NO_4SiS]^+$, 490.2447, found 490.2453.



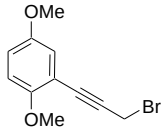
106

2-[3-(1-Ethynylhept-6-ynylsulfanyl)-prop-1-ynyl]-1,3-(dimethoxy)benzene (106). To a stirring solution of TBS alkyne **104** (0.101 g, 0.228 mmol) in 5 mL THF at 0 °C was added Bu_4NF (1.0 M in THF, 251 μL, 0.251 mmol) dropwise. The reaction mixture was stirred for 45 min at 0 °C then H_2O (5 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give terminal alkyne **106** (0.080 g, 100%) as a yellow oil. IR (thin film) 3284 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (t, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 4.04 (td, *J* = 6.5, 2.5 Hz, 1H), 3.88 (d, *J* = 16.5 Hz, 1H), 3.85 (s, 6H), 3.66 (d, *J* = 16.9 Hz, 1H), 2.37 (d, *J* = 2.4 Hz, 1H), 2.19 (td, *J* = 6.9, 2.7, 2H), 1.91 (t, *J* = 2.6 Hz, 1H) 1.88-1.78 (m, 2H), 1.74 (t, *J* = 2.6 Hz, 1H), 1.70-1.51 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 130.0, 103.8, 101.6, 93.7, 84.6, 83.6, 76.5, 72.4, 68.9, 56.5, 34.3, 34.2, 28.4, 26.9, 21.2, 18.7; LRMS (ESI) *m/z* (relative intensity) 344.1 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{20}H_{23}O_2S]^+$, 327.1419, found 327.1407.



107

1,3-Dimethoxy-2-[3-(nona-1,8-diyne-3-sulfonyl)-prop-1-ynyl]benzene (107). To a stirring solution of sulfide **106** (0.079 g, 0.243 mmol) in 5 mL of CH_2Cl_2 at room temperature was added 70-75% *m*-CPBA (0.123 g, 0.498 mmol). The reaction mixture was stirred for 2 h and then saturated $NaHCO_3$ (5 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (70:20:10 hexanes/Et_2O/CH_2Cl_2 as eluent) afforded sulfone **107** (41 mg, 47%) as a yellow oil. A yield of 63% from sulfide **104** was obtained on an 850 mg scale. was IR (thin film) 3272, 1320, 1102 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.22 (t, *J* = 8.5 Hz, 1H), 6.48 (d, *J* = 8.3 Hz, 2H), 4.64 (m, 1H), 4.59 (d, *J* = 16.9 Hz, 1H), 4.13 (d, *J* = 16.9 Hz, 1H), 3.82 (s, 6H), 2.55 (d, *J* = 2.2 Hz, 1H), 2.20-2.18 (m, 2H), 2.10 (m, 1H), 2.00 (m, 1H), 1.91 (t, *J* = 2.5 Hz, 1H), 1.82 (m, 1H), 1.70-1.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 130.6, 103.4, 99.9, 84.2, 83.7, 81.1, 76.7, 75.9, 68.7, 56.0, 52.7, 44.7, 27.7, 25.8, 25.6, 18.1; LRMS (ESI) *m/z* (relative intensity) 376.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for M + NH_4^+ $[C_{20}H_{26}NO_4S]^+$ 376.1583, found 376.1591.

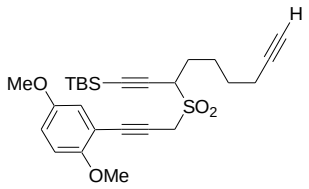


111

2-(3-Bromoprop-1-ynyl)-1,4-(dimethoxy)benzene (111). To a stirring solution of 1-bromo-2,5-dimethoxybenzene (**109**)[80] (17.0 g, 78.1 mmol) in 250 mL of pyrrolidine was added propargyl alcohol (**66**) (9.17 mL, 156 mmol) and $Pd(PPh_3)_4$ (4.76 g, 3.91 mmol). The reaction mixture was heated at reflux for 14 h, cooled to room temperature, and then saturated NH_4Cl (120 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 20% EtOAc/hexanes → 30% EtOAc/hexanes) afforded propargylic alcohol **110** (6.70 g, 45%) as an orange solid. A yield of 49% was obtained on a 100 mg scale of **109**. Spectral data matched those reported by Franks.[77]

To a stirring solution of PPh_3 (8.29 g, 31.6 mmol) in 80 mL of CH_2Cl_2 at 0 °C was added Br_2 (1.63 mL, 31.7 mmol). After 30 min, a solution of alcohol **110** (6.06 g, 31.5 mmol) in 40 mL CH_2Cl_2 was added to the reaction mixture. After an additional 5 h, the reaction solution was concentrated *in vacuo* to give an off-white solid. Purification of this solid by SiO_2 flash column chromatography (10% EtOAc/hexanes as eluent) afforded bromide **111** (7.47 g, 93%) as an off-white solid. mp 47-48 °C; IR (thin film) 2205 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.91 (d, J = 2.9 Hz, 1H), 6.84-6.73 (m, 2H), 4.18 (s, 2H), 3.78 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 154.6, 152.9, 118.2, 116.2,

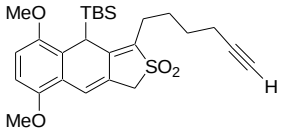
111.8, 111.5, 88.0, 83.0, 56.2, 55.6, 15.6; LRMS (ESI) *m/z* (relative intensity) 255.1 (80%, M + H^+).



113

***tert*-Butyl-{3-[3-(2,5-(dimethoxy)phenyl)-prop-2-yne-1-sulfonyl]nona-1,8-diynyl}dimethylsilane (113).** To a stirring solution of NaH (0.118 g, 2.96 mmol) in 30 mL of THF at 0 °C was added a solution of thiol **86** (0.789 g, 2.96 mmol) in 10 mL of THF. After 15 min, a solution of bromide **111** (0.755 g, 2.96 mmol) in 5 mL of CH_2Cl_2 was added to the reaction solution. After an additional 30 min at 0 °C, H_2O (50 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give sulfide **112** as a yellow oil. This material was used without further purification. IR (thin film) 3284 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.8 Hz, 1H), 6.79 (d, *J* = 2.8 Hz, 1H), 6.77 (s, 1H), 3.87 (t, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 3.78 (d, *J* = 19.3 Hz, 1H), 3.72 (s, 3H), 3.62 (d, *J* = 16.7 Hz, 1H), 2.17 (td, *J* = 6.9, 2.6 Hz, 2H), 1.90 (t, *J* = 2.6 Hz, 1H), 1.81-1.77 (m, 2H), 1.70-1.66 (m, 2H), 1.64-1.53 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 153.1, 118.3, 115.4, 112.7, 111.9, 105.0, 89.3, 87.1, 84.1, 79.4, 68.4, 56.3, 55.7, 35.3, 34.1, 27.9, 26.4, 26.1, 20.2, 18.2, 16.5, -4.6; LRMS (ESI) *m/z* (relative intensity) 441.3 (100%, M + H^+).

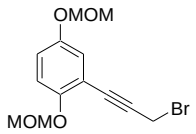
To a stirring solution of the crude sulfide **112** in 45 mL of CH_2Cl_2 at room temperature was added 70-75% *m*-CPBA (1.61 g, 5.92 mmol). The reaction mixture was stirred for 1 h and then Et_3N (883 μL, 6.34 mmol) was added followed by saturated $NaHCO_3$ (50 mL). The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give an orange oil. Purification of this oil by SiO_2 flash column chromatography (10% EtOAc/hexanes as eluent) afforded sulfone **113** (0.657 g, 47% over 2 steps) as an orange oil. IR (thin film) 3284, 1326, 1126 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.9 Hz, 1H), 6.85 (d, *J* = 3.2 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 1H), 4.51 (d, *J* = 16.6 Hz, 1H), 4.39 (dd, *J* = 10.4, 4.3 Hz, 1H), 4.10 (d, *J* = 16.9 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 2.19 (td, *J* = 6.7, 2.7 Hz, 2H), 2.13-2.03 (m, 1H), 1.90 (t, *J* = 2.5 Hz, 1H), 1.86-1.72 (m, 1H), 1.64-1.50 (m, 4H), 0.92 s, 9H), 0.11 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.1, 153.0, 118.1, 116.4, 111.9, 111.2, 97.4, 92.9, 84.1, 83.6, 79.9, 68.6, 56.2, 55.7, 54.8, 44.0, 27.6, 25.9 (2), 25.8, 18.0, 16.5, -5.1; LRMS (ESI) *m/z* (relative intensity) 490.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for M + NH_4^+, $[C_{26}H_{40}NO_4SiS]^+$, 490.2447, found 490.2438.



114

***tert*-Butyl-(3-hex-5-ynyl-5,8-dimethoxy-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-c]thiophen-4-yl)dimethylsilane (114).** To a solution of sulfone **113** (0.206

g, 0.434 mmol) in 10 mL of toluene at 110 °C was added Et_3N (90 μL, 0.65 mmol). The reaction mixture was held at reflux for 14 h, cooled to room temperature and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (10% Et_2O/hexanes as eluent) afforded tricycle **114** (95 mg, 46%) as a tacky yellow solid. IR (thin film) 3284, 1284, 1114 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.64 (d, *J* = 9.0 Hz, 1H), 6.57 (d, *J* = 9.0 Hz, 1H), 4.25 (s, 1H), 3.95 (d, *J* = 15.1 Hz, 1H), 3.86 (d, *J* = 15.5 Hz, 1H), 3.74 (s, 6H), 2.53-2.44 (m, 2H), 2.16 (td, *J* = 5.6, 2.2 Hz, 2H), 1.91-1.87 (m, 1H), 1.86-1.73 (m, 2H), 1.59-1.53 (m, 2H), 0.84 (s, 9H), -0.04 (s, 3H), -0.38 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 149.7, 148.5, 147.1, 132.1, 126.6, 125.7, 120.9, 120.0, 109.9, 107.5, 83.9, 68.5, 55.8, 54.8, 53.3, 28.0, 27.8, 27.0, 26.7, 23.7, 18.3, 17.9, -4.3, -5.7; LRMS (ESI) *m/z* (relative intensity) 473.2 (100%, M + H^+).



120

2-(3-Bromoprop-1-ynyl)-1,4-bis-(methoxymethoxy)benzene (120). To a stirring suspension of 60% NaH (2.8 g, 53 mmol) in 100 mL of DMF at 0 °C was added a solution of bromohydroquinone (**115**) (5.00 g, 26.5 mmol) in 50 mL of DMF. After 10 min, chloromethyl methyl ether (4.4 mL, 53 mmol) was added and the mixture was warmed to room temperature and stirred for an additional 14 h. To the reaction mixture was added H_2O (300 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined

organic fractions were washed with H_2O (3 x 300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give bis-MOM ether **116** (7.34 g, 100%) as a colorless oil. IR (thin film) 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 2.9 Hz, 1H), 7.09 (dd, *J* = 9.0, 0.8 Hz, 1H), 6.95 (ddd, *J* = 9.0, 2.9, 0.8 Hz, 1H), 5.18 (d, *J* = 1.0 Hz, 2H), 5.11 (d, *J* = 1.0 Hz, 2H), 3.53 (d, *J* = 1.0 Hz, 3H), 3.48 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 148.8, 121.3, 117.4, 116.3, 113.2, 95.7, 94.9, 56.2, 55.8.

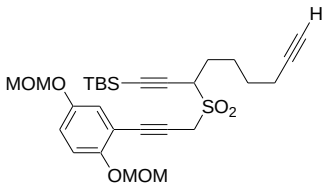
To a stirring suspension of NaH (0.174 g, 7.25 mmol) in 150 mL of THF was added a solution of bromide **116** (7.07 g, 25.5 mmol) in 20 mL of THF. After 30 min, the reaction mixture was cooled to -84 °C and *n*-BuLi (2.5 M in hexanes, 12.3 mL, 30.6 mmol) was added dropwise via syringe. The reaction solution was held at this temperature for 10 min after which a solution of I_2 (13.0 g, 51.0 mmol) in 45 mL of THF was added. The reaction mixture was allowed to warm to room temperature and aqueous $Na_2S_2O_3$ was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give aryl iodide **119** (8.01 g, 97%) as a light brown oil. IR (thin film) 1478 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.08-6.92 (m, 2H), 5.14 (s, 2H), 5.07 (s, 2H), 3.49 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 152.6, 151.3, 127.2, 117.3, 115.8, 95.6, 95.0, 87.3, 56.3, 55.9. LRMS (ESI) *m/z* (relative intensity) 294.1 (10%, $M + NH_4^+$).

To a stirring solution of aryl iodide **119** (3.27 g, 10.1 mmol) in 100 mL of pyrrolidine was added propargyl alcohol (**66**) (1.20 mL, 19.7 mmol) and $Pd(PPh_3)_4$ (0.563 g, 0.505 mmol). The reaction mixture was heated at reflux for 16 h, and then allowed to cool to room temperature. Saturated NH_4Cl (100 mL) was added. The

resulting solution was partitioned between EtOAc and H_2O, and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (60% Et_2O/hexanes as eluent) afforded alcohol **117** (1.22 g, 48%) as a light brown oil. A yield of 66% was obtained on a 23 mg scale. IR (thin film) 3425 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.05-7.04 (m, 1H), 6.98 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.91-6.88 (m, 1H), 5.12 (s, 2H), 5.04 (s, 2H), 4.45 (d, *J* = 1.8 Hz, 2H), 3.45 (s, 3H), 3.40 (s, 3H), 1.16 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 152.8, 151.6, 121.0, 118.2, 116.8, 114.0, 95.6, 94.9, 91.7, 81.3, 56.1, 55.8, 51.4; LRMS (ESI) *m/z* (relative intensity) 253.2 (100%, $M + H^+$).

To a stirring solution of propargyl alcohol **117** (1.22 g, 4.83 mmol) and Et_3N (2.0 mL, 14 mmol) in 20 mL of Et_2O at 0 °C was added MsCl (416 μL, 5.40 mmol). After 1 h, saturated $NaHCO_3$ (30 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (25 mL) followed by EtOAc (25 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the mesylate. To the crude mesylate was added 20 mL of $CHCl_3$ and NBu_4Br (2.46 g, 7.63 mmol). The resulting solution was refluxed for 30 min and concentrated *in vacuo*. EtOAc (20 mL) was added to the crude mixture, washed with H_2O (20 mL) followed by brine (20 mL). The organic fraction was dried with Na_2SO_4 and concentrated *in vacuo* to give bromide **120** (1.48 g, 97%) as a tacky orange solid. This material was used without further purification. IR (thin film) 2226 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.06 (d, *J* = 2.9 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 1H), 6.92 (dd, *J* = 9.0, 2.9 Hz, 1H), 5.13 (s, 2H), 5.05 (s, 2H), 4.15 (s, 2H), 3.47 (s, 3H), 3.41 (s, 3H); ^{13}C

NMR (90 MHz, $CDCl_3$) δ 153.0, 151.6, 120.9, 118.7, 116.9, 113.5, 95.6, 94.8, 87.9, 82.8, 56.1, 55.7, 15.3; LRMS (ESI) *m/z* (relative intensity) 315.0 (90%, $M + H^+$).

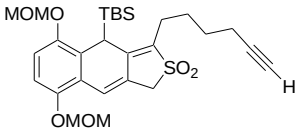


122

{3-[3-(2,5-Bis(methoxymethoxy)phenyl)-prop-2-yne-1-sulfonyl]nona-1,8-diynyl}-*tert*-butyl(dimethyl)silane (122). To a stirring solution of LHMDS (0.742 g, 4.19 mmol) in 30 mL of THF at 0 °C was added a solution of thiol **86** (1.12 g, 4.19 mmol) in 15 mL of THF. After 15 min, a solution of bromide **120** (1.32 g, 4.19 mmol) in 10 mL of THF was added to the reaction solution and after an additional 14 h at 0 °C, H_2O (60 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (95:4:1 hexanes/Et_2O/CH_2Cl_2 as eluent) afforded sulfide **121** (1.33 g, 63%) as a yellow oil. A yield of 68% was obtained on a 389 mg scale. IR (thin film) 3295, 2155 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.05 (d, J = 2.9 Hz, 1H), 6.99 (d, J = 9.0, 1H), 6.91 (dd, J = 9.0, 2.9 Hz, 1H), 5.14 (s, 2H), 5.07 (s, 2H), 3.87 (t, J = 7.0 Hz, 1H), 3.76 (d, J = 16.9 Hz, 1H), 3.60 (d, J = 16.6 Hz, 1H), 3.49 (s, 3H), 3.44 (s, 3H), 2.18 (td, J = 6.8, 2.5 Hz, 2H), 1.91 (t, J = 2.7 Hz, 1H), 1.82-1.76 (m, 2H), 1.70-1.60 (m, 2H), 1.60-1.53 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 153.0, 151.8, 121.0, 117.9, 117.1, 114.7, 105.0, 95.7, 95.0, 89.2, 87.1, 84.1, 79.2, 68.4, 56.2, 55.9, 35.2, 34.0, 27.9, 26.4,

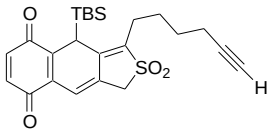
26.1, 20.2, 18.2, 16.5, -4.6; LRMS (ESI) *m/z* (relative intensity) 518.3 (100%, M + NH_4^+).

To a stirring solution of sulfide **121** (0.830 g, 1.66 mmol) in 50 mL of CH_2Cl_2 at room temperature was added *m*-CPBA (0.857 g, 3.49 mmol). After 90 min, additional *m*-CPBA (82 mg, 0.33 mmol) was added to the reaction mixture. After 30 min, saturated $NaHCO_3$ (50 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic fractions were washed with 1 M phosphoric acid (50 mL). The aqueous fraction was back-extracted with CH_2Cl_2 (50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% Et_2O/hexanes → 15% Et_2O/hexanes as eluent) afforded linear sulfone **122** (0.528 g, 60%). IR (thin film) 3284, 1331, 1149 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.03 (d, *J* = 2.5 Hz, 1H), 6.98-6.90 (m, 2H), 5.10 (s, 2H), 5.02 (s, 2H), 4.48 (d, *J* = 16.9 Hz, 1H), 4.35 (dd, *J* = 10.4, 4.1 Hz, 1H), 4.10 (d, *J* = 16.9 Hz, 1H), 3.42 (s, 3H), 3.37 (s, 3H), 2.16-2.13 (m, 2H), 2.09-1.92 (m, 2H), 1.90 (t, *J* = 2.5 Hz, 1H), 1.82-1.69 (m, 1H), 1.62-1.47 (m, 3H), 0.86 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 153.2, 151.4, 120.6, 118.7, 116.5, 112.8, 97.3, 95.2, 94.6, 92.8, 83.7, 83.5, 79.9, 68.7, 55.9, 55.6, 54.7, 43.7, 27.5, 25.7 x 2, 25.6, 17.8, 16.3, -5.2; LRMS (ESI) *m/z* (relative intensity) 550.0 (100%, M + NH_4^+).



123

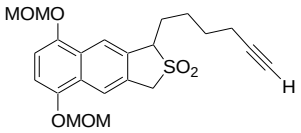
***tert*-Butyl-(3-hex-5-ynyl-5,8-bis(methoxymethoxy)-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-c]thiophen-4-yl)dimethylsilane (123).** A solution of sulfone **122** (0.528 g, 0.991 mmol) in 10 mL of benzene was heated to reflux and then treated with Et_3N (242 μL, 1.49 mmol). The reaction mixture was held at this temperature for 3 d, cooled to room temperature, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 10% Et_2O/hexanes → 40% Et_2O/hexanes as eluent) afforded tricycle **123** (0.237 g, 45%) as yellow oil. IR (thin film) 3284, 1284, 1114 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.89 (d, *J* = 9.4 Hz, 1H), 6.76 (d, *J* = 9.0 Hz, 1H), 5.16-5.02 (m, 4H), 4.23 (s, 1H), 3.95 (d, *J* = 15.1 Hz, 1H), 3.86 (d, *J* = 15.1 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 2.53-2.40 (m, 2H), 2.12 (td, *J* = 5.6, 2.2 Hz, 2H), 1.87 (s, 1H), 1.80-1.74 (m, 2H), 1.56-1.50 (m, 2H), 0.83 (s, 9H), -0.05 (s, 3H), -0.34 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 148.0, 147.3, 146.6, 132.3, 126.3, 121.7, 119.9, 119.8, 114.6, 111.9, 95.1, 95.0, 83.7, 68.4, 56.1, 55.8, 53.2, 27.8, 26.89, 26.87, 26.6, 23.5, 18.1, 17.7, -4.5, -5.7; LRMS (ESI) *m/z* (relative intensity) 533.3 (100%, M + H$^+$).



125

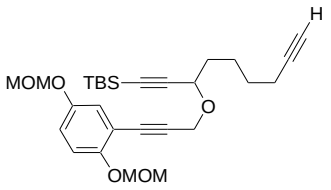
4-(*tert*-Butyl(dimethyl)silanyl)-3-hex-5-ynyl-2,2-dioxo-2,4-dihydro-1*H*-2λ^6-naphtho[2,3-c]thiophene-5,8-dione (125). A stirring solution of MOM-protected diol **123** (47 mg, 0.088 mmol) in 1 mL of MeOH was treated with acetyl chloride (25.2 μL, 0.352 mmol). After 3 h, H_2O (10 mL) was added to the reaction solution. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give dihydroquinone **124** as a colorless oil. This material was used without further purification.

To a stirring solution of this crude dihydroquinone **124** in 1.5 mL of CH_2Cl_2 was added iodobenzene diacetate (31 mg, 0.097 mmol). After 15 min, the reaction mixture was concentrated *in vacuo* to give a pink oil. Purification of this oil by flash column chromatography (Florisil, 20% EtOAc/hexanes as eluent) afforded quinone **125** (33 mg, 39% over 2 steps) as a pink oil. IR (thin film) 3284, 1643 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, *J* = 10.1 Hz, 1H), 6.89 (d, *J* = 10.0 Hz, 1H), 6.71 (s, 1H), 4.22 (s, 1H), 3.97-3.96 (m, 2H), 2.55-2.44 (m, 2H), 2.22 (td, *J* = 6.9, 2.6 Hz, 2H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.90-1.79 (m, 2H), 1.63-1.56 (m, 2H), 0.92 (s, 9H), 0.05 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 183.4, 143.9, 140.7, 136.7, 136.4, 135.6, 134.8, 132.1, 117.1, 83.7, 69.0, 52.9, 29.3, 28.0, 27.1, 26.5, 24.2, 18.0, 1.0, -4.0, -5.0; LRMS (ESI) *m/z* (relative intensity) 443.2 (100%, M + H$^+$).



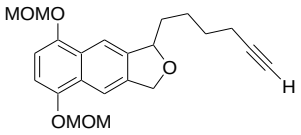
127

1-Hex-5-ynyl-5,8-bis(methoxymethoxy)1,3-dihydronaphtho[2,3-c]thiophene 2,2-Dioxide (127). To a stirring solution of sulfone **123** (0.101 g, 0.189 mmol) in 5 mL of THF at 0 °C was added Bu_4NF (1.0 M in THF, 208 μL, 0.208 mmol) dropwise. The reaction mixture was stirred for 45 min at 0 °C and then H_2O (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient 15% EtOAc/hexanes → 20% EtOAc/hexanes as eluent) afforded ticycle **127** (0.055 g, 69%) as a yellow oil. IR (thin film) 3272, 1308, 1143 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.10 (s, 1H), 7.02 (app s, 2H), 5.31 (s, 2H), 5.29 (s, 2H), 4.43 (s, 2H), 4.31 (t, *J* = 2.6 Hz, 1H), 3.52 (s, 3H), 3.50 (s, 3H), 2.31-2.20 (m, 3H), 2.13 (m, 1H), 1.95 (br s, 1H), 1.83-1.77 (m, 2H), 1.68-1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 147.2, 133.8, 127.9, 126.3, 126.2, 119.5, 118.8, 108.81, 108.79, 95.2, 95.1, 83.9, 68.7, 65.1, 56.18, 56.15, 55.2, 29.1, 28.2, 25.6, 18.1; LRMS (ESI) *m/z* (relative intensity) 436.3 (100%, $M + NH_4^+$).



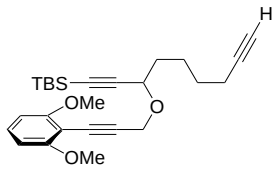
128

{3-[3-(2,5-Bis(methoxymethoxy)phenyl)-prop-2-ynyloxy]nona-1,8-diynyl}-*tert*-butyl(dimethyl)silane (128). To a stirring suspension of 60% NaH (0.018 g, 0.44 mmol) in 3 mL of THF at 0 °C was added a solution of alcohol **84** (0.100 g, 0.399 mmol) in 1 mL of THF. After 10 min, a solution of bromide **120** (0.126 g, 0.399 mmol) in 1 mL of THF was added and the mixture was warmed to room temperature and stirred for an additional 14 h. The reaction mixture was added to ice. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (7% Et_2O/ hexanes as eluent) afforded ether **128** (0.078 g, 40%) as a yellow oil. IR (thin film) 3295 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.08 (d, *J* = 2.8, 1H), 6.99 (d, *J* = 9.0 Hz, 1H), 6.91 (dd, *J* = 9.0, 2.9 Hz, 1H), 5.13 (s, 2H), 5.06 (s, 2H), 4.56 (d, *J* = 15.7 Hz, 1H), 4.47 (d, *J* = 15.9 Hz, 1H), 4.38 (t, *J* = 6.3, 1H), 3.47 (s, 3H), 3.42 (s, 3H), 2.18-2.12 (m, 2H), 1.90 (t, *J* = 2.5 Hz, 1H), 1.79-1.59 (m, 2H), 1.63-1.50 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 151.7, 121.0, 118.2, 117.0, 114.2, 104.4, 95.6, 94.9, 89.3, 88.9, 84.2, 82.2, 68.3, 68.2, 62.5, 56.5, 56.1, 55.8, 37.1, 34.9, 28.1, 26.0, 24.4, 18.2, 16.4, -4.7; LRMS (ESI) *m/z* (relative intensity) 501.9 (90%, $M + NH_4^+$).



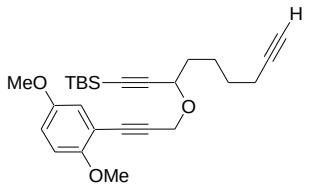
129

1-Hex-5-ynyl-5,8-bis(methoxymethoxy)1,3-dihydronaphtho[2,3-c]furan (129). To a stirring suspension of KO^{t}Bu (0.078 g, 0.66 mmol) in 4 mL of toluene was added a solution of ether **128** (0.215 g, 0.443 mmol) in 1 mL of toluene. The mixture was warmed to reflux and stirred for an additional 14 h. The reaction mixture was cooled to room temperature and 1 M phosphoric acid (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient 1% EtOAc/hexanes → 4% EtOAc/hexanes as eluent) afforded tricycle **129** (0.006 g, 3%) as a colorless oil. IR (thin film) 3284 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.97 (s, 1H), 6.97 (app s, 2H), 5.32 (s, 2H), 5.31 (s, 2H), 5.24 (d, *J* = 13.0 Hz, 1H), 5.16 (d, *J* = 12.6 Hz, 1H), 3.53 (s, 3H), 3.52 (s, 3H), 3.45 (m, 1H), 2.20 (d, *J* = 2.5 Hz, 2H), 2.00 (m, 1H), 1.92 (t, *J* = 2.2 Hz, 1H), 1.88-1.72 (m, 2H), 1.69-1.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9, 147.8, 141.3, 138.6, 126.7, 126.6, 113.7, 113.5, 107.9, 107.8, 95.32, 95.27, 84.5, 83.3, 72.0, 68.3, 56.2 x 2, 35.7, 28.6, 24.5, 18.4; LRMS (ESI) *m/z* (relative intensity) 388.3 (60%, M + NH_4^+).



130

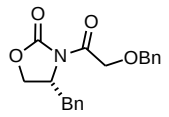
***tert*-Butyl-{3-[3-(2,6-(dimethoxy)phenyl)-prop-2-ynyloxy]nona-1,8-diynyl}dimethylsilane (130).** To a stirring suspension of 60% NaH (0.053 g, 1.3 mmol) in 8 mL of THF at 0 °C was added a solution of alcohol **84** (0.30 g, 1.2 mmol) in 1 mL of THF. After 30 min, a solution of bromide **103** (0.306 g, 1.2 mmol) in 1 mL of THF was added and the mixture was warmed to room temperature and stirred for an additional 14 h. To the reaction mixture was added H_2O (10 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with H_2O (3 x 10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (10% Et_2O/ hexanes as eluent) afforded ether **130** (0.356 g, 70%) as a yellow oil. IR (thin film) 3284 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.16 (t, *J* = 8.3 Hz, 1H), 6.46 (d, *J* = 8.6 Hz, 2H), 4.46 (t, *J* = 6.3 Hz, 1H), 3.80 (s, 6H), 2.14 (br s, 2H), 1.87 (t, *J* = 2.5 Hz, 1H), 1.76-1.70 (m, 2H), 1.62-1.50 (m, 4H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.4, 129.6, 104.8, 103.2, 100.8, 93.3, 88.7, 84.2, 78.5, 77.2, 68.2, 67.9, 56.7, 55.8, 34.9, 28.0, 25.9, 24.3, 18.2, 16.3, -4.8; LRMS (ESI) *m/z* (relative intensity) 425.3 (10%, $M + H^+$).



132

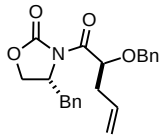
***tert*-Butyl-{3-[3-(2,5-(dimethoxy)phenyl)prop-2-ynyloxy]nona-1,8-diynyl}dimethylsilane (132).** To a stirring suspension of 60% NaH (0.053 g, 1.3 mmol) in 8 mL of THF at 0 °C was added a solution of ether **84** (0.202 g, 0.808 mmol) in 1 mL of THF. After 30 min, bromide **111** (0.206 g, 0.808 mmol) in 1 mL of THF was added and the mixture was warmed to room temperature and stirred for an additional 14 h. Ice was added to the reaction mixture. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient 2% Et_2O/ hexanes → 5% Et_2O/ hexanes as eluent) afforded ether **132** (0.215 g, 63%) as a yellow oil. IR (thin film) 3295 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.90 (d, *J* = 2.2 Hz, 1H), 6.77 (dd, *J* = 9.4, 2.9 Hz, 1H), 6.71 (d, *J* = 9.0 Hz, 1H), 4.55 (d, *J* = 15.8 Hz, 1H), 4.46 (d, *J* = 15.8 Hz, 1H), 4.36 (t, *J* = 6.3, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 2.16-2.12 (m, 2H), 1.87 (t, *J* = 1.5 Hz, 1H), 1.77-1.68 (m, 2H), 1.62-1.49 (m, 4H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 152.9, 118.9, 115.5, 112.2, 111.7, 104.5, 89.0, 88.8, 84.0, 82.3, 68.3, 68.2, 56.4, 56.1, 55.4, 34.8, 29.5, 28.0, 25.9, 24.3, 18.1, 16.3, -4.8; LRMS (ESI) *m/z* (relative intensity) 441.8 (100%, M + NH_4^+).

2.3.3 Efforts Towards Lomaiviticinone A Experimentals



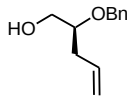
233

4-Benzyl-3-(2-benzyloxyacetyl)oxazolidin-2-one (233). To a stirring solution of (*R*)-(+)-4-benzyl-2-oxazolidinone (1.0 g, 5.6 mmol) in 25 mL of THF at -78 °C was added *n*-BuLi (2.5 M in hexanes, 2.7 mL, 6.8 mmol) dropwise. After 15 min, benzyloxyacetyl chloride (1.1 mL, 7.3 mmol) was added, the solution was allowed to warm to 0 °C, stirred for 2 h, and then saturated NH_4Cl (25 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 10% Et_2O/hexanes → 40% Et_2O/hexanes as eluent) gave **233** as a colorless oil (1.84 g, 100%). IR (thin film) 1778, 1713 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.27 (m, 8H), 7.19 (d, *J* = 7.4 Hz, 2H), 4.70-4.65 (m, 5H), 5.21-4.17 (m, 2H), 3.28 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.88 (dd, *J* = 13.3, 9.4 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.9, 153.2, 137.0, 134.8, 129.2, 128.8, 128.3, 127.84, 127.79, 127.2, 73.3, 69.5, 67.0, 54.5, 37.4; LRMS (ESI) *m/z* (relative intensity) 326.4 (90%, $M + H^+$).



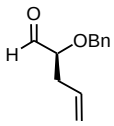
235

(*S*)-4-Benzyl-3-(2(benzyloxy)pent-4-enoyl)oxazolidin-2-one (235). To a stirring solution of NaHMDS (1.0 M in THF, 102.6 mL, 102.6 mmol) in 300 mL of THF at -78 °C was added a solution of oxazolidinone **233** (22.3 g, 68.4 mmol) in 175 mL of THF dropwise over 15 min. After 30 min at -78 °C, a solution of allyl iodide (31.2 mL, 342 mmol) in 155 mL THF was added dropwise and the mixture was stirred for 30 min at -78 °C. The solution was warmed to -45 °C, stirred for 2 h, and then saturated NH_4Cl (500 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give an orange oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 60% EtOAc/hexanes as eluent) gave **235** as an orange oil (21.9 g, 88%, single diast.). IR (thin film) 1778, 1708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40-7.24 (m, 8H), 7.19 (d, *J* = 7.2 Hz, 2H), 5.97 (m, 1H), 5.27-5.11 (m, 3H), 4.60 (m, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.16-4.09 (m, 2H), 3.22 (dd, *J* = 11.2, 3.6 Hz, 1H), 2.73-2.56 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.8, 152.7, 137.2, 134.7, 132.8, 129.1, 128.6, 128.0, 127.8, 127.5, 127.0, 117.9, 76.5, 72.1, 66.4, 54.6, 37.5, 36.9; LRMS (ESI) *m/z* (relative intensity) 388.1 (10%, $M + Na^+$).



236

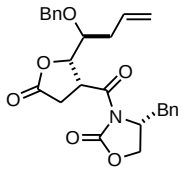
(*S*)-2(Benzyloxy)pent-4-en-1-ol (236). To a stirring solution of oxazolidinone **235** (16.8 g, 46.1 mmol) in 200 mL of THF and 25 mL of MeOH at 0 °C was added $LiBH_4$ (3.36 g, 138 mmol) portionwise over 30 min. After 15 min at 0 °C, the solution was warmed to room temperature and stirred for 14 h. The solution was cooled to 0 °C and 200 mL of 15% NaOH(aq) was added dropwise. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 60% EtOAc/hexanes → EtOAc as eluent) gave alcohol **236** as a colorless oil (8.59 g, 97%). IR (thin film) 3413cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 4.2 Hz, 2H), 7.34-7.28 (m, 3H), 5.83 (m, 1H), 5.14 (d, *J* = 15.9 Hz, 1H), 5.10 (d, *J* = 9.3, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.7 Hz, 1H), 3.63 (t, *J* = 7.7 Hz, 1H), 3.56-3.53 (m, 2H), 2.78 (br s, 1H), 2.42-2.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 134.0, 128.2, 127.52, 127.45, 117.2, 79.0, 71.3, 63.6, 35.1; LRMS (ESI) *m/z* (relative intensity) 225.4 (5%, M + MeOH + H^+).



237

(*S*)-2(Benzyloxy)pent-4-enal (237). To a stirring solution of oxalyl chloride (8.00 mL, 93.2 mmol) in 300 mL of CH_2Cl_2 at -60 °C was added a solution of DMSO

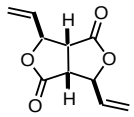
(13.7 mL) in 30 mL of CH_2Cl_2. After 10 min at -60 °C, a solution of alcohol **236** (15.4 g, 80.0 mmol) in 50 mL of CH_2Cl_2 was added and stirring was continued for 45 min at -60 °C. Et_3N (54 mL, 390 mmol) was added, and the solution was warmed to 0 °C. Saturated $NaHCO_3$ (500 mL) was added to the solution. The resulting mixture was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (25% EtOAc/hexanes as eluent) gave aldehyde **237** as a yellow oil (15.2 g, 100%). IR (thin film) 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.36 (d, *J* = 4.3 Hz, 2H), 7.34-7.29 (m, 3H), 5.82 (m, 1H), 5.18-5.11 (m, 2H), 4.67 (d, *J* = 11.8, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 3.83 (t, *J* = 6.0 Hz, 1H), 2.53-2.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 137.1, 132.2, 128.3, 127.9, 127.8, 118.2, 82.6, 72.2, 34.4; LRMS (ESI) *m/z* (relative intensity) 245.4 (100%, M + Na^+ + MeOH).



241

4-Benzyl-3-[2-(1(benzyloxy)but-3-enyl)-5-oxotetrahydrofuran-3-carbonyl]-oxazolidin-2-one (241). To a stirring solution of succinic acid derivative **220**[52] (0.070 g, 0.16 mmol) in 771 μL of CH_2Cl_2 at 0 °C was added *N,N*-diisopropylethylamine (73 μL, 0.42 mmol) followed by Bu_2BOTf (1.0 M in CH_2Cl_2, 352 μL, 0.352 mmol) dropwise. The resulting solution was stirred 30 min at 0 °C, cooled to -78 °C, and freshly distilled aldehyde **237** (68 μL, 0.42 mmol) was added dropwise. After 30 min, the solution was

warmed to 0 °C, stirred for 2.5 h at 0 °C, 630 μL of Hydrion pH 7.00 buffer followed by 950 μL of MeOH and 630 μL of 30% H_2O_2 in H_2O was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and EtOAc (5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 15% EtOAc/hexanes as eluent) gave bis oxazolidinone **241** (0.038 g, 52%) as a colorless oil. IR (thin film) 1778, 1696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-6.91 (m, 10H), 5.97 (m, 1H), 5.24-5.18 (m, 2H), 4.93 (t, *J* = 6.3 Hz, 1H), 4.75 (d, *J* = 11.1 Hz, 1H), 4.63 (m, 1H), 4.48-4.41 (m, 2H), 4.04 (d, *J* = 8.9 Hz, 1H), 3.75 (dd, *J* = 10.7, 5.3 Hz, 1H), 3.63 (t, *J* = 8.5 Hz, 1H), 3.19 (dd, *J* = 12.2, 4.0 Hz, 1H), 3.06 (dd, *J* = 17.6, 9.8 Hz, 1H), 2.80 (dd, *J* = 13.3, 9.5 Hz, 1H), 2.68-2.42 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.1, 171.4, 152.9, 137.7, 134.7, 132.5, 129.3, 128.9, 128.3, 127.8, 127.51, 127.49, 118.7, 81.2, 79.6, 72.1, 66.2, 55.1, 41.3, 37.7, 34.6, 33.7; LRMS (ESI) *m/z* (relative intensity) 472.1 (15%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{26}H_{28}NO_6]^+$, 450.1917, found 450.1906.

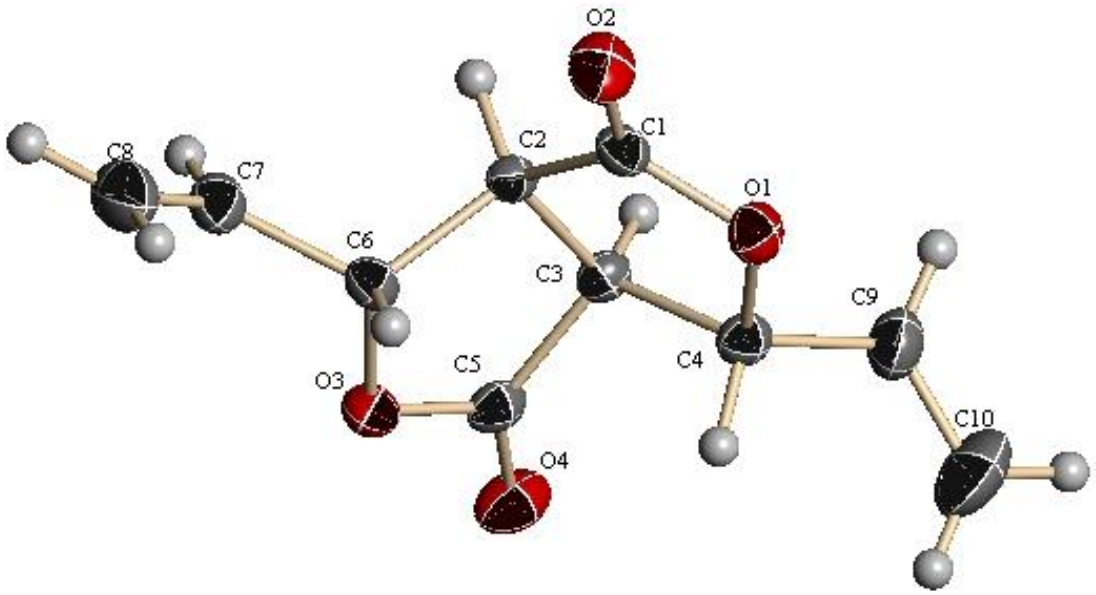


243

3,6-Divinyltetrahydrofuro[3,4-c]furan-1,4-dione (243). To a stirring solution of **220**[52] (4.2 g, 9.6 mmol) in CH_2Cl_2 at 0 °C was added *N*,*N*-diisopropylethylamine (4.37 mL, 21.1 mmol) followed by Bu_2BOTf (1.0 M in CH_2Cl_2, 21.2 mL, 21.2 mmol) dropwise. The resulting solution was stirred for 30 min at 0 °C, cooled to -78 °C, and freshly distilled acrolein (**242**) (1.8 mL, 25.0 mmol) was added dropwise. After 30 min,

the solution was warmed to 0 °C and stirred for 2.5 h at 0 °C. Hydrion pH 7.00 buffer (38 mL) followed by 63 mL of MeOH and 38 mL of 30% H_2O_2 in H_2O was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL) and EtOAc (100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a white solid. Purification of this solid by SiO_2 flash column chromatography (15% EtOAc/hexanes as eluent) gave bis lactone **243** (1.07 g, 57%) as a white solid. A sample of this solid was recrystallized using MeCN/CH_2Cl_2 to obtain X-ray quality crystals. mp 80-81 ºC; IR (thin film) 1780 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 16.2, 10.8, 3.6 Hz, 2H), 5.47 (dd, *J* = 16.2, 3.6 Hz, 2H), 5.36 (dd, *J* = 10.8, 3.6 Hz, 2H), 5.31 (d, *J* = 3.6 Hz, 2H), 3.30 (s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.3, 133.8, 117.9, 80.4, 44.8; LRMS (ESI) *m/z* (relative intensity) 195.4 (5%, $M + H^+$).

X-ray data for 243 (CCD# 897153)

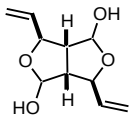


A colorless flat-needle shaped crystal of **243** (C10 H10 O4) with approximate dimensions 0.08 x 0.10 x 0.30 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 138(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1950 frames were collected with a scan width of 0.3º in ω and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 4555 reflections to a maximum θ angle of 28.36° (0.90 Å resolution), of which 2319 were independent, completeness = 98.2%, R_{int} = 0.0234, R_{sig} = 0.0334 and 2180 were greater than 2σ(I). The final cell constants: a = 9.665(2)Å, b = 5.4050(13)Å, c = 9.975(3)Å, α = 90°, β = 112.828(7)°, γ = 90°, volume = 480.3(2)Å^3, are based upon the refinement of the XYZ-centroids of 2332 reflections above 20σ(I) with 2.286° <θ <28.273°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.8190.

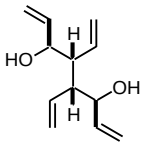
The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P2(1), with Z = 2 for the formula unit, C10 H10 O4 . The final anisotropic full-matrix least-squares refinement on F^2 with 127 variables

converged at R1 = 3.81%, for the observed data and wR2 = 10.26% for all data. The goodness-of-fit was 1.015. The largest peak on the final difference map was 0.298 $e^-/Å^3$ and the largest hole was -0.192 $e^-/Å^3$. Based on the final model, the calculated density of the crystal is 1.343 g/cm^3 and F(000) amounts to 204 electrons.



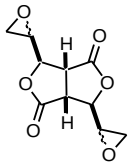
244

3,6-Divinyltetrahydrofuro[3,4-c]furan-1,4-diol (244). To a stirring solution of bis lactone **243** (0.500 g, 2.57 mmol) in 15 mL of THF at -78 ºC was added DIBAL-H (1.0 M in hexanes, 11.4 mL, 11.4 mmol) dropwise. After 2.5 h at -78 ºC, 3.6 mL of *t*-BuOH and 3.6 mL of H_2O were added and the solution was warmed to room temperature. The resulting mixture was concentrated *in vacuo* to give a white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 30% EtOAc/hexanes → 50% EtOAc/hexanes as eluent) gave bis lactol **244** (0.248 g, 49%) as a white solid. A 50% yield was obtained on a 131 mg scale. mp 157-159 ºC; IR (thin film) cm^{-1}; ^1H NMR (360 MHz, MeOD) δ 6.05-5.95 (m, 2H), 5.29 (s, 2H), 5.23 (d, *J* = 18.0 Hz, 2H), 5.10 (d, *J* = 10.8 Hz, 2H), 4.26 (t, *J* = 10.8 Hz, 2H), 2.78 (dd, *J* = 5.4, 3.6 Hz, 2H); ^{13}C NMR (90 MHz, MeOD) δ 141.5, 116.1, 102.7, 86.0, 58.7; LRMS (ESI) *m/z* (relative intensity) 221.4 (10%, $M + Na^+$).



245

4,5-Divinylocta-1,7-diene-3,6-diol (245). To a stirring solution of bis TBS ether **262** (0.319 g, 0.753 mmol) in 4 mL of THF at 0 °C was added Bu_4NF (1.0 M in THF, 4.5 mL, 4.5 mmol). The reaction mixture was warmed to room temperature, stirred for 12 h and then H_2O (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give a white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, hexanes → EtOAc as eluent) gave diol **245** (0.101 g, 69%) as a white solid. A 72% yield was obtained on a 285 mg scale. mp 110-111 ºC; IR (thin film) 3260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94-5.82 (m, 2H), 5.64-5.51 (m, 2H), 5.26-5.13 (m, 8H), 4.09 (t, *J* = 6.8 Hz, 2H), 2.65 (t, *J* = 7.8 Hz, 2H), 1.77 (s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 139.7, 135.6, 119.0, 115.6, 73.0, 50.2; LRMS (ESI) *m/z* (relative intensity) 217.0 (5%, M + Na^+).

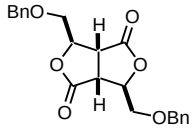


246

3,6-Bis-oxiranyl-tetrahydro-furo[3,4-c]furan-1,4-dione (246). Reaction Conditions A. To a stirring solution of bis lactone **243** (0.200 g, 1.03 mmol) in 1 mL of

acetone at 0 ºC was added freshly prepared precooled DMDO[81] (0.05 M, 80 mL, 4.0 mmol). The solution was stirred for 30 min at room temperature and concentrated *in vacuo* to give as a colorless crude oil. Purification of this oil by SiO_2 flash column chromatography (1:1 hexanes/EtOAc as eluent) gave bis epoxide **246** (0.166 g, 71%, 2.5:1 dr). IR (thin film) 1772 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$, major diast. reported) δ 5.04 (t, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 3.38-3.34 (m, 2H), 2.92-2.89 (m, 2H), 2.85 (t, *J* = 3.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, major diast. reported) δ 174.3, 80.5, 76.5, 52.6, 43.9; LRMS (ESI) *m/z* (relative intensity) 313.3 (30%, M + Na^+).

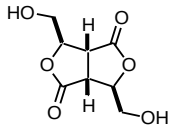
Reaction Conditions B. To a stirring solution of $Mn_3(ppei)_2(OAc)_6$[54] (0.003 g) in 1 mL of MeCN was added bis lactone **243** (0.023 g, 0.117 mmol) in 200 μL of MeCN followed by peracetic acid (32% in dilute acetic acid, 50 μL). The solution was stirred for 30 min at room temperature and concentrated *in vacuo* to give bis epoxide **246** as a colorless crude oil. Purification of this oil by SiO_2 flash column chromatography (1:1 hexanes/EtOAc as eluent) gave bis epoxide **246** (0.021 g, 80%, 1.6:1 dr)



249

3,6-Bis(benzyloxymethyl)tetrahydrofuro[3,4-c]furan-1,4-dione (**249**). To a stirring solution of bis oxazolidinone **220**[52] (1.0 g, 2.29 mmol) in 11 mL of CH_2Cl_2 at 0 °C was added *N*,*N*-diisopropylethylamine (1.04 mL, 5.95 mmol) followed by Bu_2BOTf (1.0 M in CH_2Cl_2, 5.04 mL, 5.04 mmol) dropwise. The resulting solution was stirred for 30 min at 0 °C, cooled to -78 °C, and benzyloxyacetaldehyde (**248**) (1.0 mL, 6.0 mmol)

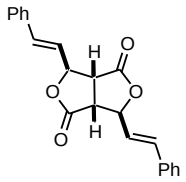
was added dropwise. After 30 min, the solution was warmed to 0 °C and stirred for 2.5 h at 0 °C. Hydrion pH 7.00 buffer (9 mL) followed by 14 mL of MeOH and 9 mL of 30% H_2O_2 in H_2O were added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and EtOAc (20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, hexanes → 15% EtOAc/hexanes as eluent) gave bis benzylether **249** (0.233 g, 27%) as a tacky white solid. IR (thin film) 1766 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35-7.26 (m, 10H), 4.92 (app s, 2H), 4.62 (d, *J* = 10.8 Hz, 2H), 4.53 (d, *J* = 10.8 Hz, 2H), 3.81 (d, *J* = 10.8 Hz, 2H), 3.69 (d, *J* = 10.8 Hz, 2H), 3.52 (s, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.9, 136.9, 128.2, 127.7, 127.2, 80.1, 73.2, 70.5, 44.7; LRMS (ESI) *m/z* (relative intensity) 400.2 (20%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{22}H_{26}NO_6]^+$, 400.1760, found 400.1774.



250

3,6-Bis(hydroxymethyl)tetrahydrofuro[3,4-c]furan-1,4-dione (250). To a stirring solution of bis benzylether **249** (0.093 g, 0.24 mmol) in 2.5 mL of CH_2Cl_2 at -78 °C was added a solution of BCl_3 (1.0 M in CH_2Cl_2, 535 μL, 0.53 mmol) dropwise. After 15 min, H_2O (5 mL) was added and the solution was warmed to room temperature. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and EtOAc (10 mL). The combined organic fractions

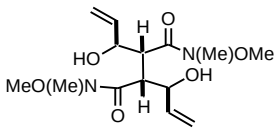
were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a white solid. Purification of this solid by a $CHCl_3$ rinse gave diol **250** (0.026 g, 53%) as a white solid. mp 89-91 ºC; IR (thin film) cm^{-1}; ^1H NMR (360 MHz, MeOD) δ 4.69 (t, *J* = 3.6 Hz, 2H), 3.77 (dd, *J* = 12.6, 3.6 Hz, 2H), 3.63 (dd, *J* = 10.8, 3.6 Hz, 2H), 3.49 (s, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 206.0, 82.5, 63.9, 45.1; LRMS (ESI) *m/z* (relative intensity) 220.4 (80%, M + NH_4^+).



252

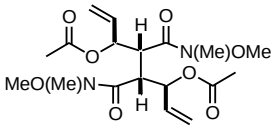
3,6(Distyryltetrahydro)furo[3,4-c]furan-1,4-dione (252). To a stirring solution of bis oxazolidione **220**[52] (1.0 g, 2.3 mmol) in 11 mL of CH_2Cl_2 at 0 °C was added *N*,*N*-diisopropylethylamine (1.04 mL, 5.95 mmol) followed by Bu_2BOTf (1.0 M in CH_2Cl_2, 5.04 mL, 5.04 mmol) dropwise. The resulting solution was stirred for 30 min at 0 °C, cooled to -78 °C, and cinnamaldehyde (**251**) (749 μL, 5.95 mmol) was added dropwise. After 30 min, the solution was warmed to 0 °C and stirred for 2.5 h at 0 °C. Hydrion pH 7.00 buffer (9 mL) followed by 14 mL of MeOH and 9 mL of 30% H_2O_2 in H_2O were added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and EtOAc (20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 2% EtOAc/hexanes → 10% EtOAc/hexanes as eluent) gave bis lactone **252** (0.279 g, 35%) as a white solid. mp 166-167 ºC; IR (thin film) 1760 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 7.40-7.22 (m, 10H), 6.75 (dd, *J* = 15.8, 1.0 Hz, 2H), 6.19 (dd, 15.8, 6.0 Hz, 2H), 5.51 (d, *J* = 6.0 Hz, 2H), 3.50 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 134.7, 133.5, 128.8, 128.7, 126.8, 124.4, 81.1, 45.9; LRMS (ESI) *m/z* (relative intensity) 364.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{22}H_{22}NO_4]^+$, 364.1549, found 364.1543.



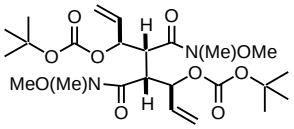
253

2,3-Bis-(1-hydroxyallyl)-*N,N'*-dimethoxy-*N,N'*-dimethylsuccinamide (253). A solution of bis lactone **243** (0.300 g, 1.54 mmol) in 2 mL of CH_2Cl_2 was added to a stirring solution of MeONHMe·HCl[55] (1.2 g, 12 mmol) in 18 mL of CH_2Cl_2. After 30 min, the solution was cooled to 0 °C, Me_2AlCl (1.0 M in hexanes, 12.3 mL, 12.3 mmol) was added dropwise, and the solution was warmed to room temperature. After 14 h, Hydrion pH 7.00 buffer (20 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and EtOAc (20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give bis Weinreb amide **253** (0.416 g, 85%) as a tacky orange solid. A 94% yield was obtained on a 20 mg scale. IR (thin film) 3390, 1643 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.91-5.81 (m, 2H), 5.31 (d, *J* = 14.4 Hz, 2H), 5.16 (d, *J* = 7.2 Hz, 2H), 4.49 (app t, *J* = 5.4 Hz, 2H), 3.76 (s, 6H), 3.57 (d, *J* = 7.2 Hz, 2H), 3.12 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.6, 137.9, 116.6, 73.6, 61.2, 47.1, 32.1; LRMS (ESI) *m/z* (relative intensity) 339.3 (100%, M + Na^+).



254

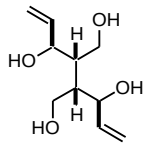
Acetic Acid 4-Acetoxy-2,3-bis(methoxymethylcarbamoyl)-1-vinylhex-5-enyl Ester (254). To a stirring solution of bis Weinreb amide **253** (0.111 g, 0.351 mmol) and DMAP (0.429 g, 3.51 mmol) in 4 mL of MeCN was added acetic anhydride (199 μL, 2.11 mmol). After 48 h, 1 M phosphoric acid (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 50% EtOAc/hexanes → EtOAc as eluent) gave bis acetic ester **254** (0.069 g, 49%) as a yellow solid. A 52% yield was obtained on a 20 mg scale. mp 126-128 ºC; IR (thin film) 1737, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.95 (pent., J = 9.8 Hz, 2H), 5.51-5.42 (m, 4H), 5.33 (d, J = 10.4 Hz, 2H), 3.72-3.70 (m, 2H), 3.71 (s, 6H), 3.20 (s, 6H), 1.99 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.0, 132.2, 120.2, 74.0, 60.9, 41.9, 31.9, 21.1; LRMS (ESI) *m/z* (relative intensity) 423.2 (60%, $M + Na^+$).



255

Carbonic Acid 4-*tert*(Butoxycarbonyloxy)-2,3-bis (methoxymethylcarbamoyl)-1-vinylhex-5-enyl Ester *tert*-Butyl Ester (255). To a

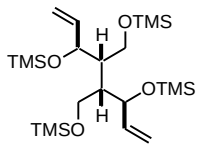
stirring solution of diol **253** (0.080 g, 0.25 mmol) and DMAP (0.062 g, 0.51 mmol) in 3 mL of MeCN was added di-*t*-butyl dicarbonate (0.221 g, 1.01 mmol). After 12 h, 1 M phosphoric acid (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a green oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 80% EtOAc/hexanes → EtOAc as eluent) gave bis Boc ester **255** (0.046 g, 35%) as a green oil. IR (thin film) 1737, 1654 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.96 (pent., J = 7.2 Hz, 2H), 5.52 (d, J = 18.0 Hz, 2H), 5.35 (d, J = 10.8 Hz, 2H), 5.34-5.30 (m, 2H), 3.83 (s, 2H), 3.73 (s, 6H), 3.12 (s, 6H), 1.45 (s, 18H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.0, 152.4, 132.4, 120.2, 81.9, 77.3, 60.8, 42.6, 32.0, 27.7; LRMS (ESI) *m/z* (relative intensity) 517.4 (90%, M + H^+).



256

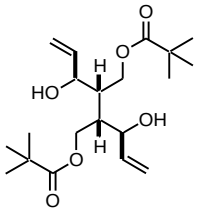
4,5-Bis(hydroxymethyl)octa-1,7-diene-3,6-diol (256). To a stirring solution of bis lactone **243** (6.00 g, 30.9 mmol) in 315 mL of THF/H_2O (20:1) at 0 °C was added $LiBH_4$ (2.9 g, 120 mmol) portionwise. The solution was warmed to room temperature, stirred for 2.5 h at that temperature, and MeOH (300 mL) was added. The resulting solution was concentrated *in vacuo* to give a white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, EtOAc → 50% EtOAc/MeOH as eluent) gave tetraol **256** (5.88 g, 94%) as a white solid. mp 103-104 ºC; IR (thin film) 3307 cm^{-1};

^{1}H NMR (360 MHz, MeOD) δ 5.91-5.82 (m, 2H), 5.32 (d, *J* = 15.8, 3.6 Hz, 2H), 5.20 (d, *J* = 10.8 Hz, 2H), 4.32 (t, *J* = 5.4 Hz, 2H), 3.77-3.68 (m, 4H), 2.12 (q, *J* = 6.0 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 141.6, 115.5, 73.0, 61.0, 44.8; LRMS (ESI) *m/z* (relative intensity) 225.2 (30%, M + Na^+).



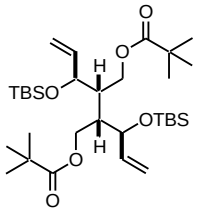
257

3,6-Bis(trimethylsilanyloxy)-4,5-bis(trimethylsilanyloxymethyl)octa-1,7-diene (257). To a stirring solution of tetraol **256** (0.007 g, 0.03 mmol) in 1 mL of THF at -5 ºC was added *N*-methylmorpholine (31 μL, 0.28 mmol) followed by TMSCl (26 μL, 0.20 mmol). After 1 h, the solution was warmed to 35 ºC, stirred for 5 h at that temperature, and cooled to room temperature. The solution was diluted with 5 mL of toluene, cooled to 0 ºC, and H_2O (5 mL) was added dropwise. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 10% Et_2O/hexanes as eluent) gave tetra TMS ether **257** (0.016 g, 98%) as a pale yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.67 (ddd, *J* = 18.0, 10.8, 3.6 Hz, 2H), 5.19 (dt, *J* = 18.0, 3.6 Hz, 2H), 5.08 (dt, *J* = 10.8, 3.6 Hz, 2H), 4.64-4.60 (m, 2H), 3.85 (dd, *J* = 10.8, 3.6 Hz, 2H), 3.42 (t, *J* = 10.8 Hz, 2H), 1.74 (dt, *J* = 10.8, 3.6 Hz, 2H), 0.09 (s, 18H), 0.08 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 113.7, 71.6, 59.9, 42.9, 0.1, -0.3; LRMS (ESI) *m/z* (relative intensity) 513.3 (5%, M + Na^+).



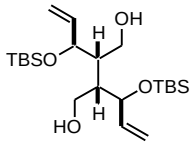
258

2,2-Dimethylpropionic Acid 3-(2,2-Dimethylpropionyloxymethyl)-4-hydroxy-2-(1-hydroxyallyl)-hex-5-enyl Ester (258). To a stirring solution of tetraol **256** (0.040 g, 0.20 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added pyridine (320 μL, 4.0 mmol) followed by trimethylacetyl chloride (195 μL, 1.6 mmol). The solution was warmed to room temperature, stirred for 2.5 h at that temperature, and saturated NH_4Cl (10 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and EtOAc (10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5 → 40% EtOAc/hexanes as eluent) gave bis pivalic ester **258** (0.036 g, 49%) as a yellow oil. IR (thin film) 3483, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.2, 10.6, 5.3 Hz, 2H), 5.31 (d, *J* = 17.2 Hz, 2H), 5.20 (d, *J* = 10.5 Hz, 2H), 4.33 (dd, *J* = 11.4, 3.9 Hz, 4H), 4.19 (dd, *J* = 11.3, 7.6 Hz, 2H), 2.82 (br s, 2H), 2.12-2.03 (m, 2H), 1.19 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 139.3, 115.9, 72.2, 63.2, 41.2, 38.7, 27.1; LRMS (ESI) *m/z* (relative intensity) 393.2 (100%, $M + Na^+$).



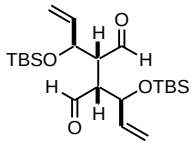
259

2,2-Dimethylpropionic Acid 4-((*tert*-Butyl(dimethyl)silanyloxy)-2-[1-(*tert*-butyl(dimethylsilanyloxy))allyl]-3-(2,2(dimethylpropionyloxymethyl))-hex-5-enyl Ester (259). To a stirring solution of diol **258** (1.6 g, 4.3 mmol) in 40 mL of CH_2Cl_2 at 0 °C was added 2,6-lutidine (2.0 mL, 17 mmol) followed by TBSOTf (5.9 mL, 26 mmol). The solution was warmed to room temperature, stirred for 2 h at that temperature, and H_2O (40 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 40 mL). The resulting solution was washed with saturated $NaHCO_3$ (40 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 5% Et_2O/hexanes as eluent) gave bis TBS ether **259** (2.1 g, 83%) as a colorless oil. IR (thin film) 1731 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 18.0, 10.8, 7.2 Hz, 2H), 5.18-5.11 (m, 4H), 4.35 (app t, *J* = 7.2 Hz, 2H), 4.25 (dd, *J* = 10.8, 3.6 Hz, 2H), 4.17 (dd, *J* = 10.8, 7.2 Hz, 2H), 2.24-2.22 (m, 2H), 1.21 (s, 18H), 0.86 (s, 18H), -0.01 (s, 12H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.0, 140.1, 115.7, 73.1, 62.8, 41.2, 38.7, 27.3, 25.8, 18.1, -4.1, -5.2; LRMS (ESI) *m/z* (relative intensity) 616.4 (70%, M + NH_4^+).



260

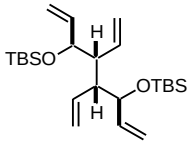
2,3-Bis-[1-(*tert*-butyl(dimethylsilanyloxy))-allyl]-butane-1,4-diol (260). To a stirring solution of bis pivalic ester **259** (2.13 g, 3.56 mmol) in 35 mL of CH_2Cl_2 at -78 °C was added DIBAL-H (1.5 M in toluene, 9.5 mL, 14 mmol). The solution was stirred for 20 min, saturated Na_2SO_4(aq) (20 mL) and saturated $NaHCO_3$ (20mL) were added and the mixture was stirred for 1 h at room temperature. The resulting solution was filtered through Celite, rinsed with CH_2Cl_2 (20 mL) and EtOAc (20 mL), and concentrated *in vacuo* to give diol **260** (1.51 g, 98%) as a colorless oil. IR (thin film) 3331 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.81-5.69 (m, 2H), 5.21 (d, *J* = 9.6 Hz, 2H), 5.17 (app s, 2H), 4.45-4.40 (m, 2H), 3.79 (t, *J* = 9.0 Hz, 2H), 3.62-3.59 (m, 4H), 2.13-2.04 (m, 2H), 0.91 (s, 18H), 0.09 (s, 6H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 115.8, 75.2, 61.2, 44.2, 25.8, 18.1, -4.3, -5.1; LRMS (ESI) *m/z* (relative intensity) 453.3 (30%, $M + Na^+$).



261

2,3-Bis-[1-(*tert*-butyl(dimethylsilanyloxy)) allyl] Succinaldehyde (261). To a stirring solution of oxalyl chloride (688 μL, 7.75 mmol) in 15 mL of CH_2Cl_2 at -60 °C was added a solution of DMSO (1.20 mL, 16.9 mmol) in 15 mL of CH_2Cl_2. After stirring

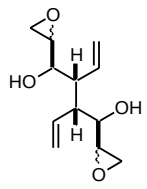
the solution for 15 min, a solution of diol **260** (1.51 g, 3.51 mmol) in 5 mL of CH_2Cl_2 was added. After stirring the mixture for 1.5 h at -60 °C, Et_3N (4.7 mL, 34 mmol) was added, the solution was warmed to 0 °C over 30 min, and saturated $NaHCO_3$ (50 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL) and EtOAc (50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give bis aldehyde **261** (1.48 g, 99%) as a yellow oil. IR (thin film) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 2H), 5.79-5.68 (m, 2H), 5.29-5.19 (m, 4H), 4.83-4.81 (m, 2H), 2.85 (s, 2H), 0.85 (18H), 0.07 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 138.7, 116.7, 71.3, 54.3, 25.8, 18.1, -4.4, -5.0; LRMS (ESI) *m/z* (relative intensity) 449.1 (10%, $M + Na^+$).



262

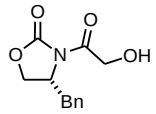
3,6-Bis-(*tert*-butyl(dimethylsilanyloxy))-4,5-divinylocta-1,7-diene (262). To a stirring solution of bis aldehyde **261** (0.500 g, 1.17 mmol) in 8 mL of THF at 0 °C was added Tebbe's reagent (0.5 M in toluene, 5.1 mL, 2.6 mmol) dropwise. The solution was warmed to room temperature and stirred for 30 min, and then Et_2O (10 mL) and MeOH (10 drops) were added. The resultant solution was filtered through Celite, rinsing with Et_2O, and the filtrate was concentrated *in vacuo* to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (3% EtOAc/hexanes as eluent) gave tetraene **262** (0.241 g, 49%) as a light yellow oil. A 64% yield was obtained on a 25 mg

scale. ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.74-5.64 (m, 2H), 5.51-5.41 (m, 2H), 5.10-4.98 (m, 8H), 4.00 (t, *J* = 9.0 Hz, 2H), 2.63 (t, *J* = 7.2 Hz, 2H), 0.90 (s, 18H), 0.07 (s, 6H), 0.04 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 141.1, 136.7, 117.4, 115.3, 75.2, 50.3, 25.9, 18.2, -3.5, -4.7; LRMS (ESI) *m/z* (relative intensity) 486.3 (20%, M + Na^+ + MeCN).



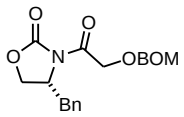
263

1,4-Bis(oxiranyl)-2,3(divinylbutane)-1,4-diol (263). To a stirring solution of tetraene **245** (0.050 g, 0.26 mmol) and $VO(acac)_2$ (3 mg, 0.013 mmol) in 2 mL of CH_2Cl_2 was added *t*-butyl hydroperoxide (5.2 M in isooctane, 198 μL, 1.03 mmol) dropwise. After 4 h, an additional 99 μL of a 5.2 M *t*-butyl hydroperoxide solution was added. After stirring for 12 h, the resulting solution was concentrated to give a white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, hexanes → 70% EtOAc/hexanes as eluent) gave bis epoxide **263** (0.043 g, 73%, 2.3:1 dr) as a white solid. IR (thin film) 3260 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 2.3:1 mix diastereomers) δ 5.72-5.51 (m, 2H), 5.34-5.21 (m, 4H), 3.83 (d, *J* = 9.8 Hz, 1H), 3.43 (m, 1H), 3.08-3.05 (m, 2H), 2.84-2.67 (m, 4H), 2.05 (s, 1H), 1.78 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.7, 133.6, 133.4, 133.3, 120.2, 120.1, 120.0, 70.5, 70.3, 66.9, 66.7, 54.4, 53.7, 48.6 ,48.3, 48.1, 46.0, 42.8; LRMS (ESI) *m/z* (relative intensity) 249.10 (80%, M + Na^+).



270

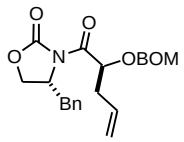
4-Benzyl-3-(2-hydroxyacetyl)oxazolidin-2-one (270). To a stirring solution of benzyl ether **233** (1.84 g, 5.64 mmol) in 60 mL of CH_2Cl_2 at -78 °C was added BCl_3 (1.0 M in CH_2Cl_2, 7.0 mL, 6.8 mmol) dropwise. After 15 min, H_2O (60 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 30% EtOAc/hexanes → 90% EtOAc/hexanes as eluent) gave alcohol **270** (1.08 g, 81%) as a white solid. A yield of 95% from **231** was obtained on a 23.6 g scale. mp. 89-90 ºC; IR (thin film) 1778, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.19 (m, 3H), 7.16 (d, *J* = 6.9 Hz, 2H), 4.69-4.62 (m, 3H), 4.25-4.15 (m, 2H), 3.63 (m, 1H), 3.23 (dd, *J* = 13.5, 2.9 Hz, 1H), 2.88 (dd, *J* = 13.5, 9.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 152.9, 134.5, 129.0, 128.5, 126.9, 67.0, 62.7, 54.3, 37.0; LRMS (ESI) *m/z* (relative intensity) 253.3 (40%, M + NH_4^+).



271

4-Benzyl-3-(2(benzyloxymethoxyacetyl))oxazolidin-2-one (271). To a stirring solution of alcohol **270** (13.94 g, 59.3 mmol) in 600 mL of CH_2Cl_2 at 0 °C was added

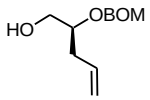
Hunig's base (21.7 mL, 125 mmol) dropwise, followed by BOMCl (18.1 mL, 131 mmol). After 30 min, the solution was allowed to warm to room temperature, stirred for 24 h at that temperature, and then saturated NH_4Cl (500 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 500 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 20% EtOAc/hexanes → 60% EtOAc/hexanes as eluent) gave BOM ether **271** as a tacky solid (18.8 g, 89%). A 92% yield was obtained on a 29.6 g scale. IR (thin film) 1778, 1708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36-7.24 (m, 8H), 7.17 (d, *J* = 6.8 Hz, 2H), 4.90 (d, *J* = 23.4 Hz, 2H), 4.84 (d, *J* = 23.2 Hz, 2H), 4.71-4.65 (m, 2H), 4.59 (br s, 1H), 4.13-4.08 (m, 2H), 3.21 (d, *J* = 13.3 Hz, 1H), 2.78 (t, *J* = 11.2 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.1, 152.6, 136.9, 134.4, 128.6, 128.1, 127.6, 127.1, 127.0, 126.5, 93.9, 69.1, 66.4, 66.1, 53.8, 36.7; LRMS (ESI) *m/z* (relative intensity) 378.2 (80%, M + NH_4^+).



272

(*S*)-4-Benzyl-3-(2(benzyloxymethoxypent)4-enoyl)oxazolidin-2-one (272). To a stirring solution of NaHMDS (1.0 M in THF, 61.2 mL, 61.2 mmol) in 250 mL of THF at -78 °C was added a solution of BOM-ether **271** (14.5 g, 40.8 mmol) in 125 mL of THF dropwise over 15 min. After 30 min at -78 °C, a solution of allyl iodide (18.6 mL, 204 mmol) in 125 mL of THF was added dropwise and stirred for 30 min at -78 °C. The

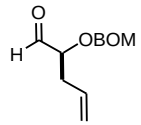
solution was warmed to -45 °C, stirred for 2 h, and then saturated NH_4Cl (500 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 20% EtOAc/hexanes as eluent) gave allylation product **272** as a colorless oil (11.7 g, 71%). IR (thin film) 1778, 1708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.24 (m, 8H), 7.15 (d, *J* = 7.6 Hz, 2H), 5.92 (m, 1H), 5.38 (dd, *J* = 6.8, 5.0 Hz, 1H), 5.20 (d, *J* = 17.3 Hz, 1H), 5.14 (d, *J* = 10.1 Hz, 1H), 4.86-4.79 (m, 2H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.37 (m, 1H), 4.05 (dd, *J* = 9.0, 2.9 Hz, 1H), 3.93 (t, *J* = 8.5 Hz, 1H), 3.21 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.69-2.54 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.2, 153.1, 137.6, 135.0, 132.7, 129.2, 128.8, 128.2, 127.7, 127.6, 127.2, 118.5, 94.8, 74.5, 69.7, 66.5, 54.9, 37.8, 37.2; LRMS (ESI) *m/z* (relative intensity) 413.2 (100%, M + NH_4^+).



273

(*S*)-2(Benzyloxymethoxy)pent-4-en-1-ol (273). To a stirring solution of oxazolidinone **272** (15.5 g, 39.2 mmol) in 175 mL of THF and 17 mL of MeOH at 0 °C was added $LiBH_4$ (3.78 g, 157 mmol) portionwise over 20 min. After 15 min at 0 °C, the solution was warmed to room temperature. After stirring for 14 h at room temperature, the solution was cooled to 0 °C, and 200 mL of 15% NaOH(aq) was added dropwise. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic fractions were dried over

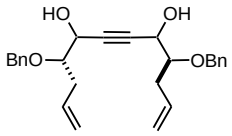
Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (30% EtOAc/hexanes as eluent) gave alcohol **273** as a colorless oil (7.48 g, 86%). IR (thin film) 3425cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34-7.24 (m, 5H), 5.80 (m, 1H), 5.11 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.07 (d, *J* = 9.4, 1H), 4.86 (d, *J* = 7.2 Hz, 1H), 4.78 (d, *J* = 7.2 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 3.70 (m, 1H), 3.63-3.59 (m, 1H), 3.52 (m, 1H), 3.18 (br s, 1H), 2.36-2.26 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.2, 134.0, 128.4, 127.80, 127.75, 117.4, 94.4, 80.0, 69.8, 64.7, 36.1; LRMS (ESI) *m/z* (relative intensity) 240.2 (10%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{13}H_{22}NO_3]^+$, 240.1600, found 240.1613.



274

(*S*)-2(Benzyloxymethoxy)pent-4-enal (274). To a stirring solution of oxalyl chloride (3.27 mL, 38.1 mmol) in 115 mL of CH_2Cl_2 at -60 °C was added a solution of DMSO (5.61 mL) in 12 mL of CH_2Cl_2. After 10 min at -60 °C, a solution of alcohol **273** (7.29 g, 32.8 mmol) in 25 mL of CH_2Cl_2 was added. After stirring the mixture for 45 min at -60 °C, 22 mL of Et_3N was added, and the solution was warmed to 0 °C. To the solution was added saturated $NaHCO_3$ (150 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 150 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (20% EtOAc/hexanes as eluent) gave aldehyde **274** as a yellow oil (9.36 g, 75%). IR

(thin film) 1719 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.36-7.27 (m, 5H), 5.81 (m, 1H), 5.19 (d, *J* = 5.7 Hz, 1H), 5.17 (dd, *J* = 13.9, 1.2 Hz, 1H), 4.86 (d, *J* = 7.1 Hz, 1H), 4.82 (d, *J* = 7.1 Hz, 1H), 4.65 (d, *J* = 3.8 Hz, 1H), 4.05 (td, *J* = 6.3, 1.3 Hz, 1H), 2.55-2.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 132.2, 128.2 (x 2), 127.62, 127.58, 118.4, 94.3, 81.2, 69.8, 34.3; LRMS (ESI) *m/z* (relative intensity) 238.2 (10%, M + NH_4^+).



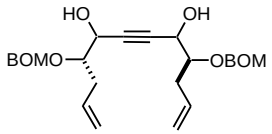
280

4,9-Bis(benzyloxydodeca)1,11-dien-6-yne-5,8-diol (280). To a stirring solution of TMS acetylene (**275**) (6.9 mL, 47 mmol) in 300 mL of THF at -78 °C was added *n*-BuLi (2.5 M in hexanes, 18.8 mL, 47.1 mmol) dropwise. After 30 min, a solution of aldehyde **237** (8.14 g, 42.8 mmol) in 60 mL of THF was added. The reaction solution was stirred 1 h -78 °C, and then H_2O (400 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 400 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give TMS protected alkyne **276** as a yellow oil. This material was used without any further purification.

To a stirring solution of this TMS-protected alkyne **276** in 300 mL of MeOH at room temperature was added K_2CO_3 (23.1 g, 167 mmol). The reaction mixture was stirred for 30 min at room temperature and then 1 M phosphoric acid (300 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous

layer was extracted with EtOAc (3 x 300 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give alkyne **278** as a yellow oil. This material was used without any further purification.

To a stirring solution of acetylene **278** in 300 mL of THF at -78 °C was added *n*-BuLi (2.5 M in hexanes, 26.4 mL, 65.9 mmol) dropwise. After 30 min, a solution of aldehyde **237** (8.14 g, 42.8 mmol) in 20 mL of THF was added dropwise. The reaction solution was warmed to room temperature, stirred for 20 h at that temperature, and then H_2O (400 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 400 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% EtOAc/hexanes → 50% EtOAc /hexanes as eluent) gave diol **280** (8.83 g, 51% over 3 steps) as a colorless oil (~1:1 mixture of diastereomers). IR (thin film) 3389 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.47-7.28 (m, 10H), 5.90-5.79 (m, 2H), 5.19-5.09 (m, 4H), 4.68-4.42 (m, 6H), 3.66-3.52 (m, 4H), 2.51-2.32 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.1, 137.9, 134.2, 134.0, 128.23, 128.18, 127.8, 127.7, 127.6, 127.5, 117.33, 117.37, 81.1, 81.0, 78.9, 72.8, 72.4, 71.3, 63.8, 63.7, 35.1, 34.9; LRMS (ESI) *m/z* (relative intensity) 429.3 (30%, $M + Na^+$).



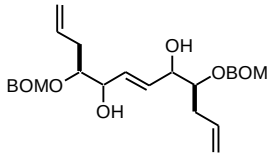
281

4,9-Bis(benzyloxymethoxydodeca)1,11-dien-6-yne-5,8-diol (281). To a stirring solution of TMS acetylene (**275**) (3.69 mL, 25.4 mmol) in 200 mL of THF at -78 °C was added *n*-BuLi (2.5 M in hexanes, 10.2 mL, 25.4 mmol) dropwise. After 30 min, a solution of aldehyde **274** (5.09 g, 23.1 mmol) in 20 mL of THF was added. Stirring was continued for 1 h at -78 °C and then H_2O (200 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give TMS acetylene **277** as a yellow oil. This material was used without any further purification.

To a stirring solution of this TMS-protected alkyne **277** in 200 mL of MeOH was added K_2CO_3 (16.0 g, 116 mmol). The reaction solution was stirred for 30 min and then 1 M phosphoric acid (200 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give alkyne **279** as a yellow oil. This material was used without any further purification.

To a stirring solution of alkyne **279** in 200 mL of THF at -78 °C was added *n*-BuLi (16.9 mL, 2.5 M in hexanes, 42 mmol) dropwise. After 30 min, a solution of aldehyde **274** (4.16 g, 16.9 mmol) in 20 mL of THF was added dropwise. The reaction

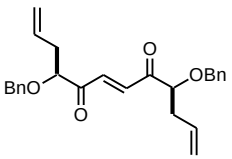
solution was warmed to room temperature, stirred for 20 h at that temperature, and then H_2O (200 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% EtOAc/hexanes → 50% EtOAc /hexanes as eluent) gave diol **281** (4.96 g, 63% over 3 steps) as a colorless oil (~1:1 mixture of diastereomers). IR (thin film) 3401 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34-7.24 (m, 10H), 5.84-5.72 (m, 2H), 5.16-5.06 (m, 4H), 4.94-4.58 (m, 8H), 4.48-4.35 (m, 2H), 3.73-3.70 (m, 2H), 2.58-2.41 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.3, 137.0, 133.92, 133.94, 128.3, 128.2, 127.82, 127.80, 127.7, 127.6, 117.54, 117.52, 95.0, 94.8, 84.8, 84.1, 82.5, 80.8, 69.9, 69.7, 64.5, 64.2, 35.9, 35.5; LRMS (ESI) *m/z* (relative intensity) 484.4 (100%, M + NH_4^+).



283

4,9-Bis(benzyloxymethoxydodeca)-1,6,11-triene-5,8-diol (283). To a stirring solution of alkyne **281** (4.84 g, 10.4 mmol) in 100 mL of THF at 0 °C was added $LiAlH_4$ (1.66 g, 41.5 mmol) portionwise. After 30 min, the solution was warmed to room temperature, stirred for 3 h, and then cold H_2O (100 mL) was added dropwise. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give diol **283** (4.04 g, 83%) as a colorless

oil (~1.1 mix diast.). IR (thin film) 3413 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38-7.24 (m, 10H), 5.99-5.76 (m, 4H), 5.22-5.06 (m, 4H), 4.92-4.56 (m, 6H), 4.22-4.16 (m, 2H), 3.76-3.57 (m, 2H), 3.13-2.73 (m, 2H), 2.37-2.24 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 142.6, 136.8, 134.5, 133.1, 130.8, 128.55, 128.49, 127.8, 126.3, 126.2, 118.7, 117.9, 117.5, 95.1, 95.0, 82.6, 81.7, 74.3, 73.2, 70.0, 64.9, 35.7, 35.5; LRMS (ESI) *m/z* (relative intensity) 486.4 (70%, M + NH_4^+).

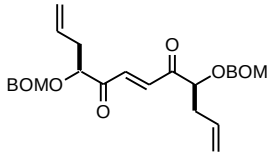


284

4,9-Bis(benzyloxydodeca)1,6,11-triene-5,8-dione (284). To a stirring solution of alkyne **280** (4.42 g, 10.9 mmol) in 100 mL of THF at 0 °C was added $LiAlH_4$ (1.74 g, 43.4 mmol) portionwise. After 30 min, the solution was warmed to room temperature, stirred for 3 h, and then H_2O (1.74 mL) was added dropwise followed by 15% NaOH (1.74 mL) and another 5.22 mL of H_2O. The resulting suspension was filtered, rinsing with Et_2O (100 mL). The filtrate was dried over Na_2SO_4, and concentrated *in vacuo* to give diol **282** (3.81 g) as a crude colorless oil (~1:1 mixture of diastereomers) that was used without further purification.

To a stirring solution of crude diol **282** (3.81 g, 9.33 mmol) in 80 mL of CH_2Cl_2 was added Dess-Martin periodinane (15.8 g, 63.3 mmol). The solution was stirred for 1 h at room temperature, saturated $Na_2S_2O_3$ (70 mL) was added, and stirring was continued for an additional 15 min. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 70 mL). The combined

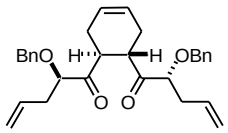
organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (5% EtOAc/hexanes as eluent) gave enedione **284** (2.88 g, 65% from **280**) as a yellow oil. IR (thin film) 1684 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38-7.26 (m, 12H), 5.83-5.72 (m, 2H), 5.11-5.07 (m, 4H), 4.56 (d, *J* = 11.9 Hz, 2H), 4.47 (d, *J* = 11.5 Hz, 2H), 4.05 (t, *J* = 6.3 Hz, 2H), 2.53-2.43 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 200.5, 136.8, 132.8, 132.1, 128.2, 127.8, 127.78, 118.2, 83.6, 72.2, 36.1; LRMS (ESI) *m/z* (relative intensity) 427.3 (100%, $M + Na^+$).



285

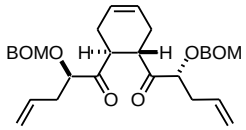
4,9-Bis(benzyloxymethoxy)dodeca-1,6,11-triene-5,8-dione (285). To a stirring solution of diol **283** (3.80 g, 8.17 mmol) in 70 mL of CH_2Cl_2 was added Dess-Martin periodinane (17.3 g, 40.9 mmol). The solution was stirred for 1 h at room temperature, saturated $Na_2S_2O_3$ (70 mL) was added, and stirring was continued for an additional 15 min. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 70 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (33% EtOAc/hexanes as eluent) gave enedione **285** (3.18 g, 84%) as a yellow oil. IR (thin film) 1684 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.24 (m, 12H), 5.79-5.69 (m, 2H), 5.12-5.06 (m, 4H), 4.78 (d, *J* = 7.2 Hz, 2H), 4.73 (d, *J* = 7.2 Hz, 2H), 4.58 (d, *J* = 12.2 Hz, 2H), 4.55 (d, *J* =

13.0 Hz, 2H), 4.27 (t, *J* = 6.3 Hz, 2H), 2.44 (t, *J* = 6.7 Hz, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.3, 137.2, 133.2, 132.2, 128.4, 127.7, 127.5, 118.7, 94.4, 81.7, 70.2, 36.2; LRMS (ESI) *m/z* (relative intensity) 487.3 (90%, M + Na^+).



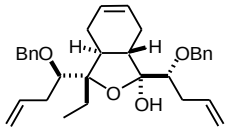
286

2-Benzyloxy-1-[6-(2-(benzyloxypent)4-enoyl)cyclohex-3-enyl]-pent-4-en-1-one (286). To a stirring solution of enedione **284** (0.053 g, 0.13 mmol) in 2 mL of CH_2Cl_2 at -78 °C was added $SnCl_4$ (31 μL, 0.26 mmol) dropwise. After 15 min, butadiene (**269**) (111 μL, 1.31 mmol) was added. The reaction solution was stirred for 15 min and then H_2O (5 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 5% EtOAc/hexanes as eluent) gave Diels-Alder adduct **286** (0.056 g, 94%) as a colorless oil. An 87% yield was obtained on a 1.0 g scale. IR (thin film) 1708 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37-7.28 (m, 10H), 5.83-5.74 (m, 2H), 5.71-5.65 (m, 2H), 5.12 (d, *J* = 16.9 Hz, 2H), 5.07 (d, *J* = 10.4 Hz, 2H), 4.79 (d, *J* = 11.9 Hz, 2H), 4.51 (d, *J* = 11.9 Hz, 2H), 4.03 (dd, *J* = 6.1, 4.3 Hz, 2H), 3.40-3.37 (m, 2H), 2.60-2.54 (m, 2H), 2.51-2.38 (m, 4H), 1.88-1.81 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 214.3, 137.6, 133.8, 128.2, 127.7, 127.6, 124.9, 117.5, 83.2, 72.5, 43.8, 36.3, 27.9; LRMS (ESI) *m/z* (relative intensity) 481.3 (40%, M + Na^+).



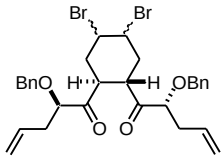
287

2-Benzyloxymethoxy-1-[6-(2(benzyloxymethoxy)pent-4-enoyl)cyclohex-3-enyl]pent-4-en-1-one (287). To a stirring solution of enedione **285** (0.824 g, 1.77 mmol) in 20 mL of CH_2Cl_2 at -78 °C was added $SnCl_4$ (414 μL, 3.54 mmol) dropwise. After 15 min, butadiene (**269**) (1.5 mL, 18 mmol) was added. The reaction mixture was stirred at -78 °C for an additional 15 min, and then H_2O (20 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5% EtOAc/hexanes → 10% EtOAc/hexanes as eluent) gave Diels-Alder adduct **287** (0.619 g, 75%) as a colorless oil. A 78% yield was obtained on a 205 mg scale. IR (thin film) 1713 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.28 (m, 10H), 5.89-5.78 (m, 2H), 5.68 (d, *J* = 2.9 Hz, 2H), 5.17 (dd, *J* = 16.9, 1.4 Hz, 2H), 5.11 (d, *J* = 11.9 Hz, 2H), 4.84 (d, *J* = 7.2 Hz, 2H), 4.79 (d, *J* = 6.8 Hz, 2H), 4.66 (d, *J* = 11.9 Hz, 2H), 4.59 (d, *J* = 11.9 Hz, 2H), 4.37 (dd, *J* = 7.9, 4.0 Hz, 2H), 3.36-3.24 (m, 2H), 2.70-2.63 (m, 2H), 2.57-2.37 (m, 4H), 1.88-1.81 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 213.0, 137.5, 133.8, 130.0, 128.4, 128.0, 125.0, 118.0, 94.2, 80.5, 69.9, 44.1, 36.2, 28.0; LRMS (ESI) *m/z* (relative intensity) 536.3 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{32}H_{42}NO_6]^+$, 536.3012, found 536.3016.



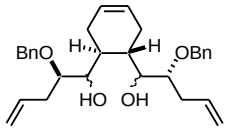
293

1,3-Bis-(1(benzyloxybut)-3-enyl)-3-ethyl-1,3,3a,4,7,7a-hexahydroisobenzofuran-1-ol (293). To a stirring solution of diketone **286** (0.128 g, 0.279 mmol) in 3 mL of CH_2Cl_2 at 0 ºC was added EtMgBr (558 μL, 3.0 M in Et_2O, 1.7 mmol) dropwise. After 30 min, saturated NH_4Cl (5 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and EtOAC (10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a light yellow oil. Purification of this oil by SiO_2 flash column chromatography (5% EtOAc/hexanes as eluent) gave hemiacetal **293** (0.020 g, 14%) as a colorless oil. IR (thin film) 3436 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.25 (m, 10H), 5.99-5.88 (m, 2H), 5.69-5.61 (m, 2H), 5.19-5.00 (m, 4H), 4.81-4.62 (m, 4H), 3.78 (s, 1H), 3.65 (t, *J* = 5.3 Hz, 1H), 3.55 (dd, *J* = 9.7, 2.9 Hz, 1H), 2.59-2.07 (m, 10H), 1.59-1.45 (m, 2H), 0.99 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 139.0, 137.4, 136.8, 135.5, 128.5, 128.4, 128.2, 127.9, 127.8, 127.4, 127.35, 125.6, 117.2, 116.1, 105.3, 87.4, 83.0, 81.0, 75.1, 74.2, 44.0, 39.1, 36.1, 35.7, 28.1, 27.6, 26.1, 7.7; LRMS (ESI) *m/z* (relative intensity) 511.5 (25%, M + Na^+).



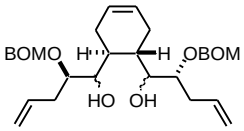
297

2-Benzyloxy-1-[2-(2(benzyloxypent)-4-enoyl)-4,5-dibromocyclohexyl]pent-4-en-1-one (297). To a stirring solution of cyclohexene **286** (0.050 g, 0.11 mmol) in 1 mL of CH_2Cl_2 was added Et_4NBr (0.229 g, 1.09 mmol). After 30 min, the solution was cooled to -78 ºC, a solution of Br_2 (1.19 M in CH_2Cl_2, 100 μL, 0.119 mmol) was added. After stirring for 1.5 h at -78 ºC, 0.2 eq of additional Br_2 solution was added and the solution was warmed to room temperature. After 1 h, saturated $Na_2S_2O_3 \cdot 5H_2O$ (2 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give dibromide **297** (0.086 g, 100%, 1:1 mix diast.) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.30 (m, 10H), 5.86-5.72 (m, 2H), 5.17-5.08 (m, 4H), 4.70-4.50 (m, 4H), 4.07-4.03 (m, 2H), 3.86-3.62 (m, 2H), 2.62-2.15 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 211.9, 137.1, 137.0, 133.2, 133.1, 128.7, 128.4, 128.2, 128.0, 127.7, 127.5, 117.8, 117.7, 83.2, 80.9, 72.7, 73.1, 50.5, 50.3, 42.2, 41.9, 37.9, 35.9, 29.9, 29.5; LRMS (ESI) *m/z* (relative intensity) 439.0 (30%, M + Na^+).



299

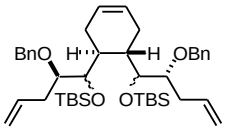
2-Benzyloxy-1-[6-(2(benzyloxy)-1-hydroxypent-4-enyl)-cyclohex-3-enyl]-pent-4-en-1-ol (299). To a stirring suspension of $LiAlH_4$ (0.074 g, 0.19 mmol) in 4 mL of THF at 0 °C was added a solution of diketone **286** (0.202 g, 0.441 mmol) in 1 mL of THF. After 1.5 h at 0 °C, 74 μL of H_2O followed by 74 μL of 15% NaOH solution and an additional 222 μL of H_2O were added. The resulting solution was filtered and rinsed with EtOAc (10 mL) to give diol **299** (0.204 g, 100%) as a colorless oil following evaporation of the filtrate (mix diast.). IR (thin film) 3448 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48-7.25 (m, 10H), 6.06-5.94 (m, 2H), 5.83-5.68 (m, 2H), 5.25-5.12 (m, 4H), 4.79-4.66 (m, 2H), 4.63-4.52 (m, 2H), 4.02-3.85 (m, 2H), 3.66-3.50 (m, 2H), 3.12-2.98 (m, 2H), 2.55-2.31 (m, 6H), 2.10 (br s, 2H), 1.95-1.72 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 138.3, 138.0, 137.9, 135.6, 134.5, 128.1, 127.7, 127.5, 127.4, 126.8, 125.5, 124.2, 117.2, 116.4, 80.1, 79.8, 78.9, 72.5, 72.4, 71.3, 71.2, 37.6, 36.7, 35.0, 34.8, 32.6, 32.5, 25.4, 24.9, 23.6; LRMS (ESI) *m/z* (relative intensity) 485.4 (90%, M + Na^+).



300

2(Benzyloxymethoxy)-1-[6-(2(benzyloxymethoxy)-1-hydroxypent-4-enyl)-cyclohex-3-enyl]pent-4-en-1-ol (300). To a stirring suspension of $LiAlH_4$ (0.104 g, 2.73 mmol) in 6 mL of THF at 0 °C was added a solution of diketone **287** (0.641 g, 1.24

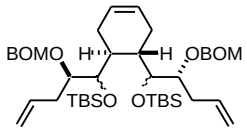
mmol) in 1 mL of THF. After 1 h, 0.641 g of additional $LiAlH_4$ was added. The solution was stirred for an additional 40 min at 0 °C, and 208 μL of H_2O followed sequentially by 208 μL of 15% NaOH solution and 624 μL of H_2O. The resulting suspension was filtered and rinsed with EtOAc (10 mL) to give diol **300** (0.500 g, 77%) as a colorless oil after evaporation of the filtrate (mix diast.). IR (thin film) 3460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (m, 10H), 5.97-5.82 (m, 2H), 5.71-5.58 (m, 2H), 5.16-5.06 (m, 4H), 4.92-4.77 (m, 4H), 4.69-4.60 (m, 4H), 3.91-3.62 (m, 4H), 3.22 (br s, 1H), 3.20 (br s, 1H), 2.44-2.28 (m, 6H), 2.04-1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 137.35, 137.29, 137.2, 135.4, 135.3, 134.8, 134.1, 128.04, 128.0, 127.5, 127.4, 127.2, 127.1, 126.5, 125.2, 124.2, 117.1, 116.8, 116.6, 94.3, 93.4, 93.2, 93.1, 78.7, 78.3, 77.6, 77.4, 77.0, 76.6, 73.2, 73.0, 72.1, 72.0, 69.5, 69.4, 38.0, 36.5, 35.4, 34.2, 32.53, 32.47, 26.0, 24.1, 23.6, 20.5, 13.8; LRMS (ESI) *m/z* (relative intensity) 545.2 (100%, M + Na^+).



301

4,5-bis-[2-Benzyloxy-1-(*tert*-butyl(dimethylsilanyloxy))pent-4-en]cyclohexene (301). To a stirring solution of diol **299** (0.204 g, 0.441 mmol) in 4 mL of CH_2Cl_2 at 0 °C was added 2,6-lutidine (370 μL, 3.13 mmol) followed by TBSOTf (560 μL, 2.43 mmol). After 1 h, H_2O (10 mL) was added and the reaction mixture was warmed to room temperature. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil.

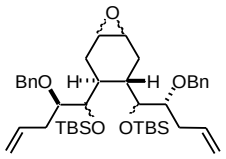
Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 5% EtOAc /hexanes as eluent) gave bis TBS ether **301** (0.286 g, 94%) as a colorless oil (mix diast.). IR (thin film) 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.24 (m, 10H), 5.94-5.70 (m, 2H), 5.65-5.50 (m, 2H), 5.10-4.81 (m, 4H), 4.59-4.42 (m, 4H), 3.92-3.84 (m, 2H), 3.45-3.33 (m, 2H), 2.47-2.00 (m, 10H), 0.88 (s, 18H), 0.11 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.7, 138.6, 137.00, 136.98, 136.96, 128.1, 128.09, 127.72, 127.70, 127.3, 127.2, 127.18, 126.9, 126.0 (x2), 125.2 (x2), 124.5, 124.4, 116.0, 115.9, 115.8, 84.2 (x2), 81.7, 81.3, 73.2 (x2), 72.7, 72.6, 71.6, 71.5, 70.4, 33.9, 33.8, 33.6, 33.5, 33.3 (x2), 26.2, 26.1, 26.0 (x2), 25.8, 25.7, 23.6, 23.3, 22.0, 18.8, 18.7, 17.9, -2.95, -3.00, -3.2, -3.3, -4.3, -4.8, -4.9, -5.4 (x2), -5.67, -5.71; LRMS (ESI) *m/z* (relative intensity) 713.2 (30%, $M + Na^+$).



302

4,5-bis-[2-Benzyloxymethoxy-1-(*tert*-butyl(dimethylsilanyloxy))pent-4-en]cyclohexene (302). To a stirring solution of diol **300** (0.500 g, 0.956 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added 2,6-lutidine (801 μL, 6.79 mmol) followed by TBSOTf (1.20 mL, 5.26 mmol). After 1.5 h, H_2O (10 mL) was added and the solution was warmed to room temperature. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient,

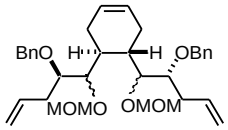
hexanes → 3% EtOAc /hexanes as eluent) gave bis TBS ether **302** (0.614 g, 85%) as a colorless oil (mix diast.). IR (thin film) 3389 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.27 (m, 10H), 6.00-5.84 (m, 2H), 5.65-5.51 (m, 2H), 5.11 (d, *J* = 16.9 Hz, 2H), 5.03 (d, *J* = 8.6 Hz, 2H), 4.78-4.54 (m, 8H), 3.89-3.62 (m, 4H), 2.50-2.02 (m, 8H), 1.80-1.74 (m, 2H), 0.96-0.88 (m, 18H), 0.17-0.02 (m, 12H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 137.90, 137.87, 136.9, 136.85, 136.8, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 125.9, 125.1, 124.4, 116.3 (x2), 94.1, 93.0, 92.8, 81.8, 78.8, 78.0, 74.5, 73.9, 71.6, 69.5, 69.4, 34.2, 33.81, 32.98, 33.4, 33.1, 26.2, 26.1, 25.7, 23.5, 23.0, 21.8, 18.7, 18.6, 17.9, -3.1, -3.2, -4.2, -5.0, -5.6; LRMS (ESI) *m/z* (relative intensity) 773.4 (60%, M + Na^+).



304

3,4-Bis-[2-benzyloxy-1-(*tert*-butyl(dimethylsilanyloxy))pent-4-enyl]-7-oxabicyclo[4.1.0]heptane (304). To a stirring solution of cyclohexene **301** (0.535 g, 0.774 mmol) in 8 mL of CH_2Cl_2 was added 70-75% *m*-CPBA (0.210 g, 0.851 mmol) in two portions 30 min apart. The solution was stirred for 3 h, 0.063 g more *m*-CPBA was added, and the solution was stirred for an additional 1 h. Saturated $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 4% Et_2O/hexanes as eluent) gave epoxide **304** (0.202 g, 37%, complex mix of isomers) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$, major diast. reported) δ 7.39-

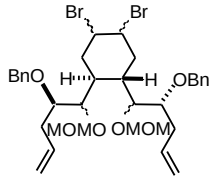
7.26 (m, 10H), 5.92-5.81 (m, 2H), 5.10-4.93 (m, 4H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.62-4.57 (m, 2H), 4.46 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.28 (d, *J* = 10.3 Hz, 1H), 3.76 (dd, *J* = 8.3, 3.3 Hz, 1H), 3.51 (d, *J* = 9.2 Hz, 1H), 3.46 (d, *J* = 9.2 Hz, 1H), 3.09 (s, 2H), 2.46-1.71 (m, 10H), 0.90 (s, 9H), 0.87 (s, 9H), 0.09 (s, 6H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.6, 136.9, 136.5, 128.2, 128.1, 128.0, 127.8, 127.3, 127.1, 116.3, 115.7, 83.7, 80.1, 72.9, 72.8, 71.9, 71.2, 51.7, 49.8, 35.4, 33.6, 33.5, 32.0, 26.1, 25.8, 22.1, 20.7, 18.5, 17.9, -3.4, -4.0, -4.7, -5.2; LRMS (ESI) *m/z* (relative intensity) 724.7 (35%, M + NH_4^+).



306

4,5-bis-[2(Benzyloxy)-1-(methoxymethoxy)pent-4-en]cyclohexene (306). To a stirring suspension of 60% NaH in mineral oil (0.035 g, 0.87 mmol) in 3 mL of DMF at 0 ºC was added a solution of diol **299** (0.182 g, 0.397 mmol) in 1 mL of DMF. After stirring for 30 min, chloromethyl methyl ether (67 μL, 0.87 mmol) was added dropwise and the solution was warmed to room temperature. After stirring the mixture for 30 min at room temperature, H_2O (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 8% EtOAc/hexanes as eluent) gave bis MOM ether **306** (0.075 g, 34% over 2 steps, 1:1 diast. mix) as a yellow oil. A yield of 49% from **286** was obtained

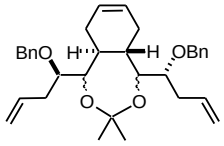
on a 103 mg scale. IR (thin film) 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.26 (m, 10H), 5.95-5.81 (m, 2H), 5.72-5.52 (m, 2H), 5.09 (d, *J* = 17.0 Hz, 2H), 5.04 (d, *J* = 9.3 Hz, 2H), 4.96-4.90 (m, 2H), 4.73-4.41 (m, 6H), 3.96-3.87 (m, 2H), 3.69-3.57 (m, 2H), 3.42-3.34 (m, 6H), 2.46-1.62 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 138.2, 135.9, 135.8, 128.2, 128.1, 128.0, 127.8, 127.6, 127.5, 126.4, 124.2, 98.3, 97.3, 80.7, 80.5, 79.1, 72.4, 71.4, 71.3, 56.2, 56.0, 34.8, 34.6, 34.1, 33.3, 23.6, 22.4; LRMS (ESI) *m/z* (relative intensity) 573.2 (50%, M + Na^+).



307

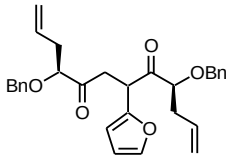
4,5-bis-[2(Benzyloxy)-1-(methoxymethoxy)pent-4-en]-1,2-bromocyclohexane (307). To a stirring solution of cyclohexene **306** (0.075 g, 0.14mmol) in 2 mL of CH_2Cl_2 was added Et_4NBr (0.284 g, 1.35 mmol). After 30 min, the solution was cooled to -78 ºC and Br_2 (8.0 μL, 0.15 mol) was added. After stirring for 1.5 h at -78 ºC, the solution was warmed to room temperature. After 1 h at room temperature, saturated $Na_2S_2O_3 \cdot 5H_2O$ (2 mL) was added. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 8% EtOAc/hexanes as eluent) gave dibromide **307** (0.064 g, 67%, complex isomer mixture) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 10H), 6.06-5.65 (m, 2H),

5.16-4.98 (m, 4H), 4.77-4.44 (m, 8H), 3.99-3.52 (m, 4H), 3.46-3.31 (m, 6H), 2.67-1.61 (m, 10H), 1.2 (m, 2H); LRMS (ESI) *m/z* (relative intensity) 731.0 (5%, M + Na^+).



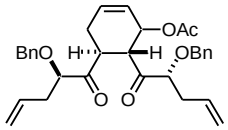
310

5,9-Bis-(1(benzyloxy)but-3-enyl)-7,7-dimethyl-1,4,4a,5,9,9a-hexahydro-6,8-dioxabenzocycloheptene (310). To a stirring solution of diol **299** (0.110 g, 0.237 mmol) and pyridinium *p*-toluenesulfonate (0.006 g, 0.02 mmol) in 4 mL of DMF was added 2-methoxypropene (46 μL, 0.47 mmol). After 12 h, H_2O (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 5% Et_2O/hexanes as eluent) gave cyclic acetal **310** (0.070 g, 59%, 1:1 mix diast.) as a colorless oil. ^1H NMR (360 MHz, $CDCl_3$) δ 7.37-7.30 (m, 10H), 6.01-5.88 (m, 2H), 5.71 (d, *J* = 11.9 Hz, 1H), 5.66 (d, *J* = 11.8 Hz, 1H), 5.17-5.03 (m, 4H), 4.81-4.44 (m, 4H), 4.16-3.92 (m, 2H), 3.57-3.44 (m, 2H), 2.62-2.47 (m, 2H), 2.37-1.94 (m, 8H), 1.50 (s, 3H), 1.46 (s, 6H), 1.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 138.3, 138.2, 136.5, 136.0, 134.9, 128.3, 128.22, 128.2, 128.1, 128.0, 127.7, 127.6, 127.55, 127.3, 127.0, 126.9, 125.9, 116.8, 116.4, 116.1, 100.9, 100.5, 79.9, 79.2, 78.8, 75.1, 74.3, 72.9, 72.7, 71.8, 71.5, 44.6, 42.3, 42.28, 36.4, 33.8, 33.2, 30.7, 30.0, 29.0, 27.8, 25.2, 21.6; LRMS (ESI) *m/z* (relative intensity) 541.3 (60%, M + K^+).



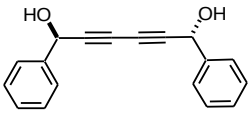
315

4,9-Bis(benzyloxy)-6-furan-2-yl-dodeca-1,11-diene-5,8-dione (315). To a solution of $AlBr_3$ (0.024 g, 0.093 mmol) in 1 mL of CH_2Cl_2 at -40 ºC was added (*S*)-(-)-*o*-tolyl-CBS oxazolidinone (206 μL, 0.5 M in toluene, 0.1 mmol) dropwise. After 30 min, the solution was cooled to -78 ºC, and a solution of enedione **284** (0.104 g, 0.258 mmol) in 1 mL of CH_2Cl_2 followed by furan (**313**) (188 μL, 2.58 mmol) was added dropwise. The solution was then warmed to -40 ºC. After 3 d at -40 ºC, MeOH (2 mL) was added, the solution was warmed to room temperature, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (20% EtOAc/hexanes as eluent) gave **315** (0.073 g, 59%) as a yellow oil (3:1 mix diastereomers). IR (thin film) 1708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.26 (m, 11H), 6.34 (dd, *J* = 2.5, 2.2 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 5.83-5.70 (m, 2H), 5.15-5.01 (m, 4H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.68 (d, *J* = 11.9 Hz, 1H), 4.56-4.42 (m, 2H), 4.27 (d, *J* = 11.9 Hz, 1H), 3.92 (t, *J* = 5.9 Hz, 1H), 3.74 (dd, *J* = 19.1, 10.4 Hz, 1H), 2.76 (d, *J* = 19.1, 4.0 Hz, 1H), 2.51-2.38 (m, 1H), 2.47 (t, *J* = 6.5 Hz, 3H), 2.34-2.25 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 210.2, 206.7, 149.8, 142.4, 137.6, 137.4, 133.5, 132.8, 128.4, 128.2, 127.94, 127.89, 127.85, 127.6, 118.1, 117.6, 110.8, 108.4, 83.8, 82.5, 72.5, 72.0, 42.4, 38.8, 36.8, 35.9; LRMS (ESI) *m/z* (relative intensity) 473.2 (25%, $M + H^+$).



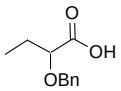
318

Acetic Acid 5,6-Bis(2(benzyloxypent)-4-enoyl)-cyclohex-2-enyl Ester (318). A solution of enedione **284** (0.022 g, 0.054 mmol) in 300 μL (2.53 mmol) of 1-acetoxy-1,3-butadiene (**317**) was heated to 90 ºC in a sealed tube. After 14 h at 90 ºC, the solution was cooled to room temperature and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (25% Et_2O/hexanes as eluent) gave Diels-Alder adduct **318** (0.016 g, 56%) as a colorless oil (single unassigned isomer). IR (thin film) 1725, 1707 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48-7.32 (m, 10H), 6.02-5.78 (m, 4H), 5.23-5.11 (m, 4H), 4.93 (d, *J* = 11.3 Hz, 1H), 4.77 (d, *J* = 11.4 H, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.19-4.17 (m, 1H), 4.11-4.08 (m, 1H), 3.83 (td, *J* = 11.7, 4.2 Hz, 1H), 3.64 (d, *J* = 11.7 Hz, 1H), 2.65-2.45 (m, 5H), 1.99 (s, 3H), 1.91-1.81 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 213.9, 209.5, 169.5, 137.5, 137.3, 133.7, 133.3, 130.7, 128.1, 127.9, 127.7, 127.5, 127.48, 127.4, 123.3, 117.6, 117.5, 83.6, 83.5, 72.6, 72.4, 65.6, 48.3, 38.3, 36.1, 36.07, 28.1, 20.6; LRMS (ESI) *m/z* (relative intensity) 555.1 (100%, M + K^+); HRMS (ESI) *m/z* calcd for $[C_{32}H_{40}NO_6]^+$, 534.2856, found 534.2846.



324

(*R*,*R*)-1,6(Diphenylhexa)-2,4-diyne-1,6-diol (324). To a stirring solution of CuCl (0.98 g, 9.3 mmol) in 450 mL of acetone was added TMEDA (1.50 mL, 10.0 mmol) dropwise, followed by bubbling O_2 through the solution. A solution of propargyl alcohol (**325**)[68,69] (12.3 g, 92.7 mmol) in 50 mL of acetone was added and the solution was heated at 40 ºC. After stirring for 14 h at this temperature while bubbling O_2 through the solution, the mixture was concentrated *in vacuo*. To the crude mixture was added 250 mL of 1 M HCl. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give an orange solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 3 → 30% EtOAc/hexanes as eluent) gave diyne **324** (8.54 g, 70%) as an orange solid. mp 82-84 ºC; $[\alpha]^{20}_D$ = -34° (10.0, MeOH); IR (thin film) 3272, 2355 cm^{-1}; ^1H NMR (360 MHz, MeOD) δ 7.39 (d, *J* = 3.6 Hz, 4H), 7.26-7.18 (m, 6H), 5.40 (s, 2H); ^{13}C NMR (90 MHz, MeOD) δ 141.4, 129.4, 129.2, 127.5, 81.1, 70.4, 65.0; LRMS (ESI) *m/z* (relative intensity) 371.2 (5%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{18}H_{13}O]^+$, 245.0966, found 245.0972.

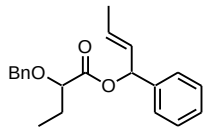


328 (known compound, unique synthesis)

2-Benzyloxybutyric Acid (328)[82]. To a suspension of NaH (1.42 g, 59.2 mmol) in 300 mL of THF at 0 ºC was added benzyl alcohol (5.80 mL, 56.4 mmol). After stirring the mixture for 30 min at 0 ºC, ethyl 2-bromobutyrate (7.60 mL, 51.3 mmol) was added dropwise. The solution was warmed to room temperature and stirred for 1 h. To the crude mixture was added H_2O (300 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (5% EtOAc/hexanes as eluent) gave 2-benzyloxybutyric acid ethyl ester (10.3 g, 90%) as a colorless oil.

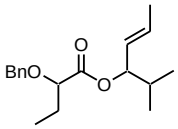
To a solution of 2-benzyloxybutyric acid ethyl ester (10.3 g, 46.3 mmol) in 600 mL of THF at 0 ºC was added aqueous LiOH (0.2 M, 600 mL). After 30 min, the solution was warmed to room temperature, stirred for 16 h, and concentrated *in vacuo* to half the volume. The aqueous phase was washed with Et_2O, and the Et_2O washes were extracted with saturated $NaHCO_3$. The aqueous layers were combined, acidified to pH 4 with 1 M HCl and extracted with EtOAc. The combined EtOAc layers were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give carboxylic acid **328** (7.67 g, 85%) as a colorless oil. IR (thin film) 3450-3000, 1713 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 3.99 (t, *J* = 5.1 Hz, 1H), 1.95-1.85 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4,

137.0, 128.3, 128.1, 126.4, 78.4, 72.2, 25.8, 9.4; LRMS (ESI) *m/z* (elative intensity) 217.4 (90%, M + Na^+).



329

2-Benzyloxybutyric Acid 1-Phenyl-but-2-enyl Ester (329). To a stirring solution of alcohol **326**[65] (0.150 g, 1.01 mmol) and carboxylic acid **328** (0.216 g, 1.11 mmol) in 25 mL of CH_2Cl_2 was added DMAP (15 mg, 0.12 mmol) and EDC (216 mg, 1.39 mmol). After stirring for 14 h, the reaction mixture was washed with H_2O (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (5% EtOAc/ hexanes as eluent) gave benzyloxyglycolate **329** (0.197 g, 60%) as a colorless oil. IR (thin film) 1731 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.28 (m, 10H), 6.35 (d, *J* = 7.2 Hz, 1H), 5.86-5.67 (m, 2H), 4.72 (d, *J* = 14.4 Hz, 1H), 4.41 (d, *J* = 14.4 Hz, 1H), 3.95-3.92 (m, 1H), 1.88-1.80 (m, 2H), 1.75 (t, *J* = 7.2 Hz, 3H), 1.02-0.94 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.7, 139.5, 137.6, 130.1, 129.2, 128.4, 128.3, 127.9, 127.7, 126.9, 126.7, 79.3, 76.5, 72.1, 26.1, 17.7, 9.6; LRMS (ESI) *m/z* (relative intensity) 347.1 (5%, M + Na^+).

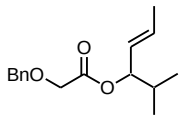


330

2-Benzyloxybutyric Acid 1-Isopropylbut-2-enyl Ester (330). To a stirring solution of crotonaldehyde (450 μL, 5.50 mmol) in 40 mL of Et_2O at 0 ºC, was added *i*-PrMgCl (2.0 M in Et_2O, 3.85 mL, 7.70 mmol) dropwise. After stirring the mixture for 1 h at 0 ºC, saturated NH_4Cl (40 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and distilled at 50 ºC under atmospheric pressure to give alcohol **327** as a crude yellow oil.

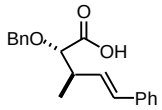
To the stirring solution of crude alcohol **327** and carboxylic acid **328** (1.18 g, 6.08 mmol) in 100 mL of CH_2Cl_2 was added DMAP (84 mg, 0.69 mmol) and EDC (1.16 g, 6.05 mmol). After stirring for 14 h, the reaction mixture was washed with saturated $NaHCO_3$ (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a pale yellow oil. Purification of this oil by neutral alumina flash column chromatography (gradient, hex → 4% EtO/hexanes as eluent) gave benzyloxyglycolate **330** (0.953 g, 60% from **327**) as a pale yellow oil. IR (thin film) 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 5.80-5.69 (m, 1H), 5.46-5.36 (m, 1H), 5.18-5.06 (m, 1H), 4.72 (t, *J* = 10.6 Hz, 1H), 4.40 (dd, *J* = 11.6, 2.0 Hz, 1H), 3.88 (td, *J* = 6.2, 1.5 Hz, 1H), 1.93-1.76 (m, 3H), 1.71 (td, *J* = 5.6, 1.3 Hz, 3H), 1.01-0.95 (m, 3H), 0.91 (app t, *J* = 5.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 171.8, 137.63, 137.60, 130.4, 130.0, 128.1 (x2), 127.8, 127.7 (x2), 127.5, 127.47, 127.4, 79.9, 79.8, 79.2, 79.17, 71.9, 71.8, 31.8 (x2),

26.1, 26.0, 18.0, 17.97, 17.6 (x2), 9.5 (x2); LRMS (ESI) *m/z* (relative intensity) 313.3 (20%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{18}H_{30}NO_3]^+$, 308.2226, found 308.2224.



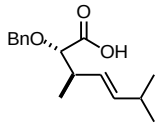
335

Benzyloxyacetic Acid 1-*iso*Propyl-but-2-enyl Ester (335). To a stirring solution of crude alcohol **327** in 40 mL of CH_2Cl_2 at 0 ºC was added pyridine (979 μL, 12.1 mmol) and benzyloxyacetyl chloride (**334**) (955 μL, 6.05 mmol). The solution was warmed to room temperature, stirred for 1 h, and concentrated *in vacuo*. To the crude mixture was added 40 mL of H_2O. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by neutral alumina flash column chromatography (gradient, hexanes → 3% Et_2O as eluent) gave benzyloxyglycolate **335** (0.835 g, 59% from crotonaldehyde) as a colorless oil. IR (thin film) 1749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.80-5.71 (m, 1H), 5.40 (dd, *J* = 4.0, 1.4 Hz, 1H), 5.11 (app t, *J* = 7.2 Hz, 1H), 4.64 (s, 2H), 4.094 (s, 1H), 4.091 (s, 1H), 1.86 (app octet, *J* = 6.8 Hz, 1H), 1.71 (dd, *J* = 6.8, 1.3 Hz, 3H), 0.91 (d, *J* = 4.9 Hz, 3H), 0.90 (d, *J* = 4.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 137.1, 130.5, 128.3, 127.9, 127.7, 127.2, 80.1, 73.1, 67.1, 31.8, 18.0, 17.9, 17.6; LRMS (ESI) *m/z* (relative intensity) 285.1 (15%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{16}H_{26}NO_3]^+$, 280.1913, found 280.1905.



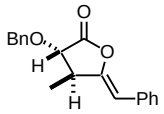
349

2-Benzyloxy-3-methyl-5(phenylpent)-4-enoic Acid (349). To a stirring solution of LHMDS (1.0 M in THF, 405 μL, 0.404 mmol) in 2.8 mL of THF at -78 ºC, was added TMSCl (53 μL, 0.40 mmol) dropwise. A solution of benzyloxyglycolate **345** (0.080 g, 0.27 mmol) in 200 μL of THF was added dropwise followed by $SnCl_4$ (11 μL, 1.0 M in CH_2Cl_2, 0.011 mmol). The solution was stirred at -78 ºC for 30 min, 0 ºC for 30 min, and then warmed to room temperature. After 14 h at room temperature, 1 M NaOH (5 mL) was added, the mixture was stirred vigorously for 1 h, and Et_2O (10 mL) then was added. The resulting solution was partitioned between Et_2O and 1 M NaOH and the organic layer was extracted with 1 M NaOH (5 mL). The combined aqueous fractions were acidified with 3 M HCl, extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give carboxylic acid **349** (0.080 g, 100%, 94% dr) as a colorless oil. IR (thin film) 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, major isomer reported) δ 7.37-7.15 (m, 10H), 6.49 (d, *J* = 15.7 Hz, 1H), 6.21 (dd, *J* = 15.6, 7.7 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.02 (br s, 1H), 2.93 (br s, 1H), 1.23 (d, *J* = 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 137.7, 137.5, 131.35, 131.26, 129.0, 128.9, 128.6, 128.5, 127.8, 126.7, 82.0, 73.5, 40.9, 15.7; LRMS (ESI) *m/z* (relative intensity) 314.2 (30%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{19}H_{24}NO_3]^+$, 314.1756, found 314.1745.



353

2-Benzyloxy-3,6-dimethylhept-4-enoic Acid (353). To a stirring solution of LHMDS (171 μL, 1.0 M in THF, 0.171 mmol) in 800 μL of THF at -78 ºC, was added TMSCl (22 μL, 0.17 mmol) dropwise. A solution of benzyloxyglycolate **346** (0.030 g, 0.114 mmol) in 200 μL of THF was added dropwise followed by $SnCl_4$ (3 μL, 1.0 M in CH_2Cl_2, 0.003 mmol). The solution was stirred at -78 ºC for 30 min, 0 ºC for 30 min, and then warmed to room temperature. After 14 h at room temperature, 1 M NaOH (3 mL) was added, the mixture was stirred vigorously for 1 h, and Et_2O (10 mL) then was added. The resulting solution was partitioned between Et_2O and 1 M NaOH and the organic layer was extracted with 1 M NaOH (5 mL). The combined aqueous fractions were acidified with 3 M HCl, extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give carboxylic acid **353** (0.028 g, 93%) as a colorless oil. IR (thin film) 3400-3000, 1713 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 10.5 (br s, 1H), 5.53 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.38 (dd, *J* = 15.5, 7.6 Hz, 1H), 4.78 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 3.88 (d, *J* = 5.4 Hz, 1H), 2.70-2.65 (m, 1H), 2.31-2.25 (m, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 2.2 Hz, 3H), 0.98 (d, *J* = 1.8 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.2, 139.0, 137.1, 128.4, 128.0, 127.99, 127.5, 82.2, 72.9, 40.0, 31.0, 22.4, 22.37, 15.6; LRMS (ESI) *m/z* (elative intensity) 285.3 (100%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{16}H_{21}O_3]^-$, 261.1491, found. 261.1488.

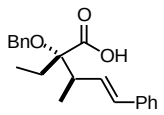


360

5(Benzylidene)-3-benzyloxy-4(methyldihydrofuran)-2-one (360). To a stirring solution of carboxylic acid **349** (0.0502 g, 0.169 mmol) in 1.5 mL of CH_2Cl_2 was added pyridine (42 μL, 0.51 mmol). After 30 min, the reaction solution was cooled to -78 ºC and a solution of PhSeCl (52 mg, 0.27 mmol) in 200 μL of CH_2Cl_2 was added dropwise. After 1 h, the mixture was allowed to warm to room temperature. After stirring the mixture for 14 h at room temperature, $CHCl_3$ (10 mL) was added and the organics were washed with 1 M HCl (10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow crude oil. Purification of this oil by silica flash column chromatography (gradient, 3 → 20% Et_2O/hexanes as eluent) gave selenide **359** (0.060 g, 78%) as a colorless oil.

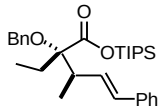
To a stirring solution of crude selenide **359** (0.060 g, 0.13 mmol) in 2 mL of CH_2Cl_2 was added 70-75% *m*-CPBA (98 mg, 0.40 mmol). After stirring the mixture for 20 min, saturated $NaHCO_3$ (6 mL) followed by 1 M $Na_2S_2O_3$ (1 mL) were added and the resulting mixture was stirred vigorously for 5 min. The resulting solution was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted with CH_2Cl_2 (10 mL) followed by EtOAc (10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by silica flash column chromatography (gradient, 0 → 5% Et_2O/hexanes as eluent) gave lactone **360** (0.015 g, 39%) as a colorless oil. IR (thin film) 1813 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.8 Hz, 2H), 7.48-7.37 (m, 7H), 7.30-7.26 (m, 1H), 5.58 (d, *J*

= 1.6 Hz, 1H), 5.17 (d, *J* = 11.7 Hz, 1H), 4.86 (d, *J* = 11.7 Hz, 1H), 3.99 (d, *J* = 9.5 Hz, 1H), 3.33- 3.24 (m, 1H), 1.39 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.4, 150.0, 136.8, 133.4, 128.7, 128.6, 128.4, 127.1, 104.6, 78.1, 72.8, 41.1, 14.9; LRMS (ESI) *m/z* (relative intensity) 312.2 (50%, M + NH_4^+).



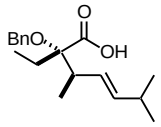
362

2-Benzyloxy-2-ethyl-3-methyl-5(phenylpent)-4-enoic Acid (362). To a stirring solution of TIPS ester **366** (0.085 g, 0.18 mmol) in 2 mL of THF at 0 ºC was added Bu_4NF (194 μL, 1.0 M, 0.19 mmol) dropwise. After 20 min at 0 ºC, 1 M HCl (2 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (50 % EtOAc/hexanes as eluent) gave carboxylic acid **362** (0.057 g, 100%) as a colorless oil. IR (thin film) 3330-2900, 1708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (br s, 1H), 7.50-7.24 (m, 10H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.21 (dd, *J* = 15.8, 8.6 Hz, 1H), 4.71 (d, *J* = 10.3 Hz, 1H), 4.52 (d, *J* = 10.3 Hz, 1H), 3.04-3.00 (m, 1H), 2.17-2.03 (m, 2H), 1.28 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.9, 137.5, 137.0, 131.7, 129.8, 128.42, 128.40, 127.8, 127.4, 127.3, 126.1, 86.1, 65.7, 42.9, 25.4, 15.6, 8.1; LRMS (ESI) *m/z* (relative intensity) 347.3 (40%, M + Na^+).



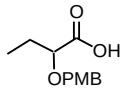
366

2-Benzyloxy-2-ethyl-3-methyl-5(phenylpent)-4-enoic Triisopropylsilyl Ester (366). To a stirring solution of benzyloxyglycolate **329** (0.250 g, 0.770 mmol) in 6 mL of toluene at -78 ºC was added NaHMDS (809 μL, 1.0 M in THF, 0.81 mmol) dropwise. The solution was stirred for 45 min at -78 ºC and TIPSCl (198 μL, 0.924 mmol) was added dropwise. The reaction mixture was stirred for 10 min at -78 ºC and then allowed to warm to room temperature. After stirring the mixture for 2 h at room temperature, saturated NH_4Cl (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 3% EtOAc/hexanes as eluent) gave TIPS ester **366** (0.151 g, 41%, >95% dr) as a colorless oil. IR (thin film) 1708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.2 Hz, 2H), 7.46-7.28 (m, 2H), 6.56-6.54 (m, 2H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.72 (d, *J* = 10.8 Hz, 1H), 3.03 (app quint, *J* = 7.2 Hz, 1H), 2.22-2.05 (m, 2H), 1.45-1.38 (m, 3H), 1.35 (d, *J* = 7.2 Hz, 21 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.9, 139.4, 137.7, 131.5, 130.3, 128.3, 128.1, 127.0 (x 2), 126.9, 126.1, 85.5, 65.9, 26.1, 17.8, 17.6, 15.8, 12.0, 8.2, 1.0; LRMS (ESI) *m/z* (relative intensity) 503.2 (25%, M + Na^+).



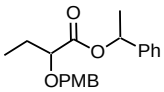
368

2-Benzyloxy-2-ethyl-3,6-dimethylhept-4-enoic Acid (368). To a stirring solution of LHMDS (155 μL, 1.0 M in THF, 0.155 mmol) in 800 μL of THF at -78 ºC was added TMSCl (20 μL, 0.16 mmol) dropwise. A solution of benzyloxyglycolate **330** (0.030 g, 0.10 mmol) in 200 μL of THF was added dropwise followed by $SnCl_4$ (1.0 M in CH_2Cl_2, 2 μL, 0.002 mmol). The solution was stirred at -78 ºC for 30 min, 0 ºC for 30 min, and then warmed to room temperature. After 14 h at room temperature, 1 M NaOH (3 mL) was added, the reaction mixture was stirred vigorously for 1 h, and then Et_2O (10 mL) was added. The resulting solution was partitioned between Et_2O and 1 M NaOH and the organic layer was extracted with 1 M NaOH (5 mL). The combined aqueous fractions were acidified with 3 M HCL, extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give carboxylic acid **368** (0.0129 g, 43%, ≥ 95:5 dr) as a pale yellow oil. IR (thin film) 3400-3000, 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.33 (m, 5H), 5.54 (dd, *J* = 15.4, 6.6 Hz, 1H), 5.39 (dd, *J* = 15.4, 8.2 Hz, 1H), 4.65 (d, *J* = 10.3 Hz, 1H), 4.45 (d, *J* = 10.3 Hz, 1H), 2.79-2.74 (m, 1H), 2.31-2.25 (m, 1H), 2.10-1.93 (m, 2H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.20-1.00 (m, 3H), 0.99 (d, *J* = 2.4 Hz, 3H), 0.97 (d, *J* = 2.6 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 173.3, 140.4, 137.0, 128.6, 128.1, 127.7, 126.5, 86.7, 65.3, 42.1, 31.2, 25.0, 22.5, 15.8, 8.1, 1.0; LRMS (ESI) *m/z* (relative intensity) 313.3 (15%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{18}H_{25}O_3]^-$, 289.1804, found 289.1791.



373

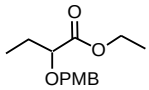
2-(4-Methoxybenzyloxy)butyric Acid (373). To a solution of ethyl ester **376** (6.93 g, 27.5 mmol) in 450 mL of THF at 0 ºC was added LiOH(aq) (0.2 M, 465 mL). After 30 min at 0 ºC, the solution was warmed to room temperature, stirred for 16 h at room temperature, and concentrated *in vacuo* to half of the volume. The aqueous phase was extracted with Et_2O (500 mL), and the Et_2O phase was extracted with saturated $NaHCO_3$ (2 x 300 mL). The aqueous layers were combined, acidified to pH 4 with 3 M HCl and extracted with EtOAc. The combined organic phases were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give carboxylic acid **373** (6.30 g, 100%) as a yellow oil. IR (thin film) 3107, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.4 (br s, 1H), 7.34 (d, *J* = 9.4 Hz, 2H), 6.93 (d, *J* = 9.5 Hz, 2H), 4.71 (d, *J* = 12.5 Hz, 1H), 4.45 (d, *J* = 12.4 Hz, 1H), 3.97 (t, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 1.91-1.83 (m, 2H), 1.04 (t, *J* = 8.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 159.3, 129.8, 129.5, 129.2, 113.7(x2), 78.4, 71.9, 55.2, 25.8, 9.5; LRMS (ESI) *m/z* (relative intensity) 242.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{12}H_{20}NO_4]^+$, 424.1392, found 242.1381.



374

1-Phenylethyl 2-(4-Methoxybenzyloxy)-butyrate (374). To a stirring solution of carboxylic acid **373** (0.551 g, 2.46 mmol) in 35 mL of toluene at 0 ºC was added DMAP (0.321 g, 2.63 mmol) and a solution of 1-phenylethanol (0.300 g, 2.46 mmol) in 5

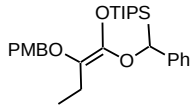
mL of Et_2O. To this solution was added Et_3N (1.78 mL, 11.4 mmol) and 2,4,6-trichlorobenzoyl chloride (434 μL, 2.78 mmol). After 1 h, saturated $NaHCO_3$ (50 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow crude oil. Purification of this oil by deactivated silica (2% Et_3N in hexanes) flash column chromatography (gradient, 1 → 10% Et_2O/hexanes as eluent) gave PMB glycolate **374** (0.593 g, 73%) as a colorless oil (3:1 mix diast., major reported). IR (thin film) 1743 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41 (d, *J* = 4.3 Hz, 3H), 7.39-7.34 (m, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.90 (dd, *J* = 6.7, 1.9 Hz, 2H), 6.03 (q, *J* = 6.6 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 3.90 (dd, *J* = 6.9, 5.7 Hz, 1H), 3.84 (s, 3H), 1.89-1.78 (m, 2H), 1.61 (d, *J* = 6.6 Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.8, 159.1, 141.2, 129.5, 129.4, 128.3, 127.7, 125.8, 113.5, 78.7, 72.4, 71.5, 55.0, 26.0, 22.0, 9.5, ; LRMS (ESI) *m/z* (relative intensity) 351.3 (100%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{20}H_{28}NO_4]^+$, 346.2018, found 346.2018.



376

Ethyl 2-(4-Methoxybenzyloxy)butyrate (376). To a suspension of NaH (1.29 g, 53.8 mmol) in 300 mL of THF at 0 ºC was added freshly distilled *p*-methoxybenzyl alcohol (6.71 mL, 53.8 mmol). After stirring the mixture for 30 min at 0 ºC, ethyl 2-bromobutyrate (7.57 mL, 51.3 mmol) was added dropwise followed by tetrabutylammonium iodide (18.9 g, 51.3 mmol). The solution was warmed to room

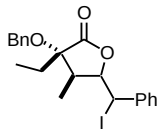
temperature and stirred for 16 h. To the crude mixture was added H_2O (300 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give ethyl ester **376** (6.93 g, 54%) as a colorless oil. IR (thin film) 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.24 (qd, *J* = 7.1, 2.3 Hz, 2H), 3.87 (t, *J* = 6.3 Hz, 1H), 3.82 (s, 3H), 1.85-1.73 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 127.8, 159.3, 129.7, 129.6, 113.7, 78.9, 71.8, 60.6, 55.2, 26.2, 14.2, 9.7; LRMS (ESI) *m/z* (relative intensity) 275.3 (40%, $M + Na^+$).



377

Triisopropyl-[2-(4-methoxybenzyloxy)-1-(1-phenylethoxy)-but-1-enyloxy]-silane (377). To a stirring solution of KHMDS (456 μL, 0.5 M in toluene, 0.2 mmol) in 1.0 mL of 2:1 THF/toluene at -78 ºC was added dropwise a solution of PMB glycolate **374** (0.050 g, 0.152 mmol) in 200 μL of THF. The solution was stirred for 30 min at -78 ºC and TIPSOTf (49 μL, 0.182 mmol) was added dropwise. The reaction mixture was stirred for 30 min at -78 ºC and then warmed to 0 ºC. After stirring for 30 min at 0 ºC, cold saturated NH_4Cl (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give TIPS enol ether **377** (0.082 g) as colorless oil. ^1H NMR (360 MHz, $CDCl_3$) δ

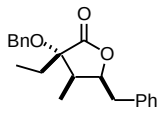
7.40-7.34 (m, 5H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.15 (q, *J* = 6.5 Hz, 3H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 3.85 (s, 3H), 2.13-2.03 (m, 1H), 1.97-1.83 (m, 1H), 1.55 (d, *J* = 6.6 Hz, 3H), 1.34-1.20 (m, 3H), 1.17-1.12 (m, 18H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.9, 143.9, 142.0, 131.0, 129.3, 128.1, 127.7, 127.0, 75.6, 71.3, 55.2, 21.5, 20.4, 17.9, 13.0, 2.1.



378

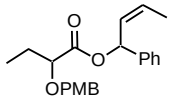
3-Benzyloxy-3-ethyl-5-(iodophenylmethyl)-4-(methyldihydrofuran)-2-one (378). To a stirring solution of carboxylic acid **362** (0.030 g, 0.093 mmol) in 1 mL of THF at 0 ºC, was added recrystallized *N*-iodosuccinimide (0.025 g, 0.11 mmol). After stirring for 1.25 h at 0 ºC, the solution was concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 10% Et_2O/hexanes as eluent) gave iodolactone **378** (0.029 g, 70%, ~1:1 mix diastereomers) as a colorless oil. IR (thin film) 1778 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.21 (m, 20H), 5.54 (dd, *J* = 11.9, 3.9 Hz, 1H), 5.39 (d, *J* = 8.0 Hz, 1H), 4.87 (d, *J* = 11.9 Hz, 1H), 4.62 (dd, *J* = 8.0, 4.4 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.39 (app t, *J* = 10.6 Hz, 2H), 4.19 (d, *J* = 11.0 Hz, 1H), 2.85 (m, 1H), 2.67 (m, 1H), 2.29 (m, 1H), 2.02 (m, 1H), 1.63-1.49 (m, 2H), 1.13 (d, *J* = 7.3 Hz, 3H), 1.05 (t, *J* = 8.4 Hz, 6H), 1.05-1.03 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.2, 174.1, 140.1, 139.0, 137.5, 137.4, 128.8, 128.7, 128.55, 128.53, 128.48, 128.45, 128.41, 128.36, 128.9, 127.8 (two signals), 127.76, 87.2,

85.3, 83.6, 82.4, 66.5, 66.4, 43.2, 41.5, 31.9, 28.5, 21.7, 19.0, 13.5, 7.7, 7.0, 6.3; LRMS (ESI) *m/z* (relative intensity) 468.0 (30%, M + NH_4^+).



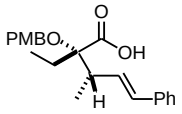
379

5-Benzyl-3-benzyloxy-3-ethyl-4-(methyldihydrofuran)-2-one (379). To a stirring solution of iodolactone **378** (0.408 g, 0.906 mmol) in 30 mL of toluene was added *n*-Bu_3SnH (2.43 mL, 9.06 mmol). The solution was heated to 105 ºC and a solution of AIBN (0.740 g, 9.06 mmol) in 10 mL of toluene was added dropwise. After stirring for 16 h at 105 ºC, the reaction mixture was cooled to room temperature and concentrated *in vacuo* to give a crude colorless oil. Purification of this oil by silica flash column chromatography (gradient, hexanes → 10% Et_2O as eluent) gave lactone **379** (0.113 g, 38%) as a colorless oil. IR (thin film) 1766 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.31 (m, 10H), 5.17 (app. pent., *J* = 4.6 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 3.11 (dd, *J* = 14.4, 9.0 Hz, 1H), 2.85 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.55 (m, 1H), 2.33 (sextet, *J* = 7.7 Hz, 1H), 1.61 (m, 1H), 1.04-0.99 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.3, 137.5, 137.0, 129.0, 128.5, 128.3, 127.7 (two signals), 126.7, 84.8, 81.7, 66.3, 42.3, 36.2, 17.6, 12.2, 6.4; LRMS (ESI) *m/z* (relative intensity) 347.2 (40%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{21}H_{28}NO_3]^+$, 342.2069, found 342.2068.



381

2-(4-Methoxybenzyloxy)butyric Acid 1-Phenylbut-2-enyl Ester (381). To a stirring solution of carboxylic acid **373** (1.15 g, 5.13 mmol) and alcohol **380**[64] (0.691 g, 4.66 mmol) in 50 mL of CH_2Cl_2 was added DMAP (59 mg, 0.65 mmol) and EDC (0.983 g, 5.6 mmol). After stirring for 16 h at room temperature, the solution was concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by deactivated silica (2% Et_3N in hex) flash column chromatography (gradient, 5 → 15 % EtOAc/hexanes as eluent) gave PMB glycolate **381** (1.16 g, 70%) as a light yellow oil (1:1 mix diast.). IR (thin film) 1743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.34 (m, 5H), 7.32-7.25 (m, 2H), 6.91-6.86 (m, 2H), 6.75 (d, *J* = 8.6 Hz, 1H), 5.91-5.65 (m, 2H), 4.68 (d, *J* = 11.3 Hz, 1H), 4.37 (dd, *J* = 11.3, 2.2 Hz, 1H), 3.93 (t, *J* = 6.2 Hz, 1H), 3.83 (s, 3H), 1.90-1.88 (m, 3H), 1.88-1.78 (m, 2H), 1.02-0.94 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (two signals), 159.2 (two signals), 139.7 (two signals), 129.7 (two signals), 129.6 (two signals), 128.6 (two signals), 128.5 (two signals), 128.4, 128.3, 127.8 (two signals), 126.5, 126.4, 113.7 (two signals), 78.9, 78.8, 71.7, 71.6, 71.5 (two signals), 55.1 (two signals), 26.2, 26.1, 13.7, 13.4, 9.6 (two signals); LRMS (ESI) *m/z* (relative intensity) 377.3 (5%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{22}H_{27}O_4]^+$, 355.1909, found 355.1909.

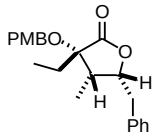


383

2-Ethyl-2-(4-methoxybenzyloxy)-3-methyl-5-phenylpent-4-enoic Acid (383). To a stirring solution of PMB glycolate **381** (0.600 g, 1.69 mmol) in 10 mL of toluene at -78 ºC was added KHMDS (10.1 mL, 0.5 M in toluene, 5 mmol) dropwise. The solution was stirred for 45 min at -78 ºC and TIPSOTf (1.36 mL, 5.07 mmol) was added dropwise. The mixture was stirred for 10 min at -78 ºC and allowed to warm to room temperature. After stirring for 1 h at room temperature, the solution was warmed to 40 ºC and stirred for 1.5 h. After cooling to room temperature, saturated $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give TIPS ester **387** as a light yellow oil that was used without further purification. IR (thin film) 1719 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.32 (m, 6H), 7.26-7.22 (m, 1H), 6.92 (dd, *J* = 2.7, 2.1 Hz, 2H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.37 (dd, *J* = 15.8, 8.6 Hz, 1H), 4.61 (d, *J* = 10.2 Hz, 1H), 4.43 (d, *J* = 10.3 Hz, 1H), 3.85 (s, 3H), 2.92-2.88 (m, 1H), 2.13-1.99 (m, 2H), 1.41-1.35 (m, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.14 (dd, *J* = 7.4, 1.7 Hz, 18H), 1.04-1.00 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 158.9, 137.4, 131.3, 131.1, 130.6, 128.8, 128.3, 127.0, 126.1, 113.5, 85.1, 65.3, 55.1, 42.7, 25.1, 17.91, 17.90, 17.6, 15.7, 12.0, 7.2.

To a stirring solution of this crude TIPS ester **387** in 10 mL of THF at 0 ºC was added dropwise Bu_4NF (1.0 M in hexanes, 5.24 mL, 5.24 mmol). After 20 min at 0 ºC, saturated NH_4Cl (10mL) was added. The resulting solution was partitioned between

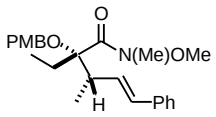
EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (hex → 60 % EtOAc/hexanes as eluent) gave carboxylic acid **383** (0.427 g, 71% over 2 steps, 6:1 dr) as a colorless oil (major diast. reported). IR (thin film) 3354-2900, 1708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.1 Hz, 2H), 7.36-7.33 (m, 4H), 7.31-7.24 (m, 1H), 6.98 (dd, *J* = 6.7, 2.0 Hz, 2H), 6.46 (d, *J* = 6.8 Hz, 2H), 4.55 (d, *J* = 9.9 Hz, 1H), 4.45 (d, *J* = 9.8 Hz, 1H), 3.88 (s, 3H), 2.91 (pd, *J* = 6.8, 1.8 Hz, 1H), 2.21-2.07 (m, 1H), 1.97-1.86 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 159.3, 137.0, 131.0, 130.5, 129.3, 129.2, 128.3, 127.1, 126.1, 85.8, 64.4, 55.0, 42.4, 25.6, 15.5, 7.6; LRMS (ESI) *m/z* (relative intensity) 377.4 (40%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{22}H_{30}NO_4]^+$, 372.2175, found 372.2166.



392

5-Benzyl-3-ethyl-3-(4-methoxybenzyloxy)-4-methyldihydrofuran-2-one (392). To a stirring solution of carboxylic acid **383** (0.427 g, 1.21 mmol) in 12 mL of THF at 0 ºC, was added recrystallized *N*-iodosuccinimide (0.327 g, 1.45 mmol). After stirring for 1.25 h at 0 ºC, the solution was concentrated *in vacuo* to give a crude orange tacky solid. Purification of this tacky solid by SiO_2 flash column chromatography (gradient, hexanes → 20% Et_2O/hexanes as eluent) gave iodolactone **391** as an orange tacky solid that was carried on without further purification.

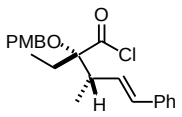
To a stirring solution of this crude iodolactone **391** in 25 mL of toluene was added *n*-Bu_3SnH (2.11 mL, 7.87 mmol). The solution was heated to 105 ºC, and a solution of AIBN (0.644 g, 7.88 mmol) in 8 mL of toluene was added dropwise. After stirring for 16 h at 105 ºC, the reaction mixture was cooled to room temperature and concentrated *in vacuo* to give a crude colorless oil. Purification of this oil by silica flash column chromatography (gradient, hexanes → 6% Et_2O as eluent) gave lactone **392** (0.089 g, 22% over 2 steps) as a colorless oil. IR (thin film) 1760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.32 (m, 4H), 7.28 (d, *J* = 6.2 Hz, 1H), 7.22 (d, *J* = 7.1 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 4.75 (d, *J* = 11.0 Hz, 1H), 4.73-4.66 (m, 1H), 4.61 (d, *J* = 10.9 Hz, 1H), 3.84 (s, 3H), 3.07 (dd, *J* = 14.5, 10.4 Hz, 1H), 2.89 (dd, *J* = 14.6, 3.4 Hz, 1H), 2.70 (app pent., 7.1 Hz, 1H), 2.02 (q, *J* = 7.4 Hz, 2H), 1.20 (d, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 159.0, 137.7, 130.2, 129.05, 129.0, 128.3, 126.4, 113.7, 82.1, 80.3, 65.1, 55.1, 40.5, 37.5, 23.2, 8.2, 8.1; LRMS (ESI) *m/z* (relative intensity) 372.3 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{22}H_{30}NO_4]^+$, 372.2175, found 372.2173.



394

2-Ethyl-2-(4-methoxybenzyloxy)-3-methyl-5-phenylpent-4-enoic Acid *N,N*-Methoxymethylamide (394). To a stirring solution of DMAP (0.276 g, 2.26 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (**393**) (0.147 g, 1.50 mmol) in 7 mL of CH_2Cl_2 was added a solution of carboxylic acid **383** (0.267 g, 0.752 mmol) in 1 mL of CH_2Cl_2, followed by EDC (0.288 g, 1.50 mmol). After stirring the mixture for 14 h at

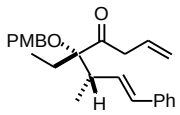
room temperature, saturated $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 2 → 10% EtOAc/hexanes as eluent) gave Weinreb amide **394** as a colorless oil (0.221 g, 74%). IR (thin film) 1649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.4 Hz, 2H), 7.38-7.30 (m, 4H), 7.23 (m, 1H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.54 (dd, *J* = 15.9, 7.5 Hz, 1H), 6.46 (d, *J* = 16.0 Hz, 1H), 4.56 (d, *J* = 10.3 Hz, 1H), 4.43 (d, *J* = 10.2 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.43 (s, 3H), 3.09-3.04 (m, 1H), 2.23 (m, 1H), 2.05 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.8, 137.4, 132.2, 130.1, 129.5, 128.8, 128.2, 126.7, 125.9, 113.5, 87.0, 64.4, 60.1, 54.9, 43.0, 36.7, 26.1, 15.6, 8.4; LRMS (ESI) *m/z* (relative intensity) 398.3 (30%, $M + H^+$).



395

2-Ethyl-2-(4-methoxybenzyloxy)-3-methyl-5-phenylpent-4-enoyl Chloride (395). To a stirring solution of carboxylic acid **383** (0.063 g, 0.18 mmol) in 2 mL of benzene at room temperature was added pyridine (43 μL, 0.53 mmol). After stirring for 15 min, oxalyl chloride (31 μL, 0.36 mmol) was added dropwise. After stirring for 1 h at room temperature, the reaction mixture was concentrated *in vacuo*, Et_2O (5 mL) added, and this solution was filtered through Celite washing with Et_2O (10 mL). The resultant solution was concentrated *in vacuo* to afford acid chloride **395** (0.061 g, 92%) as a

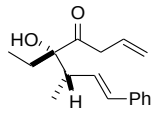
colorless oil. IR (thin film) 1790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.24 (m, 7H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.29 (dd, *J* = 15.8, 8.6 Hz, 1H), 4.61 (d, *J* = 10.3 Hz, 1H), 4.55 (d, *J* = 10.1 Hz, 1H), 3.86 (s, 3H), 3.03 (m, 1H), 2.24-2.04 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 159.1, 137.0, 131.5, 129.8, 129.5, 128.9, 128.5, 127.4, 126.2, 113.1, 91.2, 66.4, 55.2, 43.0, 25.8, 15.1, 7.8.



397

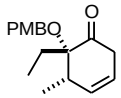
5-Ethyl-5-(4-methoxybenzyloxy)-6-methyl-8-phenylocta-1,7-dien-4-one (397). To a stirring solution of Weinreb amide **394** (0.221 g, 0.557 mmol) in 6 mL of THF at 0 ºC, was added dropwise allylmagnesium bromide (1.0 M in Et_2O, 1.7 mL, 1.7 mmol). The solution was stirred for 30 min at 0 ºC and then for 1 h at room temperature. The reaction mixture was added to a cold solution of saturated NH_4Cl (10 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless crude oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 2 → 4% Et_2O/hexanes as eluent) gave allylation product **397** (0.176 g, 84%) as a colorless oil. IR (thin film) 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.45 (m, 4H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (m, 1H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.38 (dd, *J* = 15.8, 8.5 Hz, 1H), 6.05 (m, 1H), 5.26 (d, *J* = 10.3 Hz, 1H), 5.17 (dd, *J* = 17.2, 1.4 Hz, 1H), 4.61 (d, *J* = 10.6 Hz, 1H), 4.49 (d, *J* = 10.6 Hz, 1H), 3.89 (s, 3H), 3.58 (d, *J* = 6.4 Hz, 2H), 2.91 (m, 1H), 2.10

(m, 1H), 1.89 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 158.9, 137.3, 131.2, 130.9, 130.4, 130.3, 128.4, 128.36, 127.0, 126.1, 118.1, 113.7, 89.5, 63.0, 55.1, 45.9, 42.8, 26.3, 15.7, 7.9; LRMS (ESI) *m/z* (relative intensity) 401.4 (100%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{25}H_{31}O_3]^+$, 379.2273, found 379.2257.



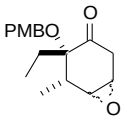
398

5-Ethyl-5-hydroxy-6-methyl-8-phenylocta-1,7-dien-4-one (398). To a stirring solution of PMB ether **397** (0.060 g, 0.16 mmol) in 1.5 mL of CH_2Cl_2 was added dropwise trifluoroacetic acid (122 μL, 1.60 mmol). The solution was stirred for 1 h at room temperature and concentrated *in vacuo* to give a colorless crude oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 2 → 4% Et_2O/hexanes as eluent) gave alcohol **398** (0.034 g, 83%) as a colorless oil. IR (thin film) 3472, 1702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 6.41 (d, J = 16.0 Hz, 1H), 6.08 (dd, J = 16.0, 9.0 Hz, 1H), 5.86 (m, 1H), 5.19 (d, J = 11.1 Hz, 1H), 5.13 (dd, J = 16.6, 1.3 Hz, 1H), 3.88 (br s, 1H), 3.39-3.23 (m, 2H), 2.71 (m, 1H), 2.00 (m, 1H), 1.77 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H), 0.80 (t, J = 7.4 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 211.8, 137.0, 131.0, 130.5, 130.0, 128.5, 127.4, 126.3, 118.9, 84.1, 44.7, 41.7, 28.8, 14.8, 7.7. LRMS (ESI) *m/z* (relative intensity) 259.2 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{23}O_2]^+$, 259.1698, found 259.1685.



400

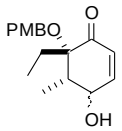
6-Ethyl-6-(4-methoxybenzyloxy)-5-methylcyclohex-3-enone (400). To a refluxing solution of diene **397** (0.151 g, 0.399 mmol) in 4 mL of CH_2Cl_2 was added dropwise a solution of Grubbs II catalyst[83] (60 mg, 0.71 mmol) in 1 mL of CH_2Cl_2. After refluxing for 2 h, the solution was cooled to room temperature and concentrated *in vacuo* to give a crude brown oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 4 → 10% Et_2O/hexanes as eluent) gave β,γ-unsaturated enone **400** (0.092 g, 84%) as a light brown oil. IR (thin film) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.77 (m, 1H), 5.62 (dt, *J* = 9.8, 3.4 Hz, 1H), 4.48 (d, *J* = 10.8 Hz, 1H), 4.35 (d, *J* = 10.8 Hz, 1H), 3.80 (s, 3H), 2.97-2.95 (m, 2H), 2.85 (m, 1H), 2.11 (m, 1H), 1.94 (m, 1H), 1.04 (d, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 158.8, 132.0, 130.8, 128.3, 122.1, 113.5, 84.9, 63.9, 55.1, 40.2, 39.7, 23.5, 15.6, 7.9; LRMS (ESI) *m/z* (relative intensity) 297.5 (100%, $M + Na^+$); HRMS (ESI) *m/z* calcd for $[C_{17}H_{26}NO_3]^+$, 292.1913, found 292.1901.



401

4-Ethyl-4-(4-methoxybenzyloxy)-5-methyl-7-oxabicyclo[4.1.0]heptan-3-one (401). To a stirring solution of β,γ-unsaturated enone **400** (0.044 g, 0.16 mmol) in 1 mL of acetone was added freshly prepared DMDO (0.10 M in acetone, 3.2 mL, 0.32 mmol). The solution was stirred for 30 min at room temperature and concentrated *in vacuo* to

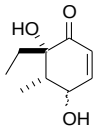
give epoxide **401** as a colorless crude oil (single diastereomer, unassigned) that was used without further purification. IR (thin film) 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 2H), 6.88 (dd, *J* = 6.8, 1.9 Hz, 2H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.02 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.47 (t, *J* = 3.0 Hz, 1H), 3.02 (d, *J* = 3.9 Hz, 1H), 2.88 (dd, *J* = 17.0, 3.3 Hz, 1H), 2.76 (d, *J* = 17.0 Hz, 1H), 2.40 (q, *J* = 7.4 Hz, 1H), 2.16 (m, 1H), 1.53 (m, 1H), 1.28 (t, *J* = 7.4 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); LRMS (ESI) *m/z* (relative intensity) 313.3 (30%, M + Na^+).



402

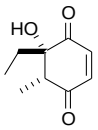
6-Ethyl-4-hydroxy-6-(4-methoxybenzyloxy)-5-methylcyclohex-2-enone (402). To a stirring solution of this crude epoxide **401** in 1 mL of benzene was added Et_3N (45 μL, 0.32 mmol). The solution was stirred for 12 h at room temperature and then concentrated *in vacuo* to give a colorless crude oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 10 → 30% EtOAc/hexanes as eluent) gave γ-hydroxyenone **402** (0.018 g, 39% from **400**, single diast., unassigned) as a colorless oil. IR (thin film) 3425, 1672 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.88 (dd, *J* = 10.3, 1.8 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.93 (dd, *J* = 10.3, 2.1 Hz, 1H), 4.49 (m, 1H), 4.35 (d, *J* = 11.0 Hz, 1H), 4.02 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H), 2.47 (m, 1H), 2.11 (m, 1H), 1.77 (d, *J* = 7.2 Hz, 1H), 1.46 (m, 1H), 1.25 (d, *J* = 6.6 Hz, 3H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5, 158.9, 152.5, 130.9, 128.6, 126.6, 113.6, 81.9, 64.9, 64.6, 55.2, 44.8, 21.1, 10.0, 8.4; LRMS (ESI) *m/z* (relative

intensity) 313.2 (100%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{26}NO_4]^+$, 308.1862, found 308.1867.



403

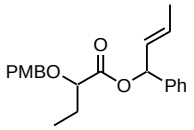
6-Ethyl-4,6-dihydroxy-5-methylcyclohex-2-enone (403). To a stirring solution of PMB ether **402** (0.018 g, 0.063 mmol) in 1 mL of CH_2Cl_2 was added dropwise trifluoroacetic acid (48 μL, 6.3 mmol). The solution was stirred for 1 h at room temperature and then concentrated *in vacuo* to give a colorless crude oil. Purification of this crude reaction product by SiO_2 flash column chromatography (gradient, 15 → 50% EtOAc/hexanes as eluent) gave alcohol **403** (0.0087 g, 82%, single diast., unassigned) as a colorless oil. IR (thin film) 3413, 1672 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 10.0, 3.5 Hz, 1H), 6.05 (d, *J* = 10.1 Hz, 1H), 4.40 (br s, 1H), 2.99 (s, 1H), 2.89 (m, 1H), 2.10 (br s, 1H), 2.02-1.83 (m, 2H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 147.4, 126.5, 78.0, 70.5, 43.5, 31.4, 12.9, 7.6; LRMS (ESI) *m/z* (relative intensity) 241.4 (10%, M + MeOH + K^+).



404

5-Ethyl-5-hydroxy-6-methylcyclohex-2-ene-1,4-dione (404). To a stirring solution of γ-hydroxyenone **403** (0.005 g, 0.03 mmol) in 1 mL of CH_2Cl_2 was added activated MnO_2 (0.023 g, 0.3 mmol). The suspension was stirred for 1 h at room

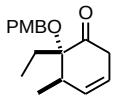
temperature and concentrated *in vacuo* to give a yellow crude oil. Purification of this oil by Celite filtration using EtOAc as eluent, followed by SiO_2 flash column chromatography of the crude residue (gradient, 15 → 20% EtOAc/hexanes as eluent) gave enedione **404** (0.002 g, 47%) as a yellow oil. IR (thin film) 3472, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (d, *J* = 10.3 Hz, 1H), 6.68 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.70 (s, 1H), 3.08 (qd, *J* = 7.3 Hz, 1.5 Hz, 1H), 1.88-1.67 (m, 2H), 1.16 (d, *J* = 7.3 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 201.1, 140.1, 136.8, 80.9, 55.2, 34.1, 14.0, 7.8.



405

1-Phenylbut-2-enyl 2-(4-Methoxybenzyloxy)butyrate (405). To a stirring solution of alcohol **326**[65] (2.32 g, 15.6 mmol) and carboxylic acid **373** (3.74 g, 16.6 mmol) in 150 mL of CH_2Cl_2 was added DMAP (198 mg, 1.62 mmol) and EDC (3.29 mg, 17.2 mmol). After stirring the mixture for 14 h at room temperature, the organics were washed with H_2O (25 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by deactivated SiO_2 (2 % Et_3N/hex) flash column chromatography (2 → 15 % Et_2O/ hexanes as eluent) gave PMB glycolate **405** (3.36 g, 57%) as a colorless oil (1:1 mix of diastereomers). IR (thin film) 1749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.26 (m, 12H), 6.92-6.87 (m, 4H), 6.35 (d, *J* = 6.8 Hz, 2H), 5.88-5.72 (m, 4H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 3.94-3.89 (m, 4H), 3.84 (s, 3H), 3.83 (s, 3H),

1.89-1.80 (m, 4H), 1.77 (d, *J* = 4.7 Hz, 3H), 1.76 (d, *J* = 3.4 Hz, 3H) , 0.99 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.68, 159.2 (two signals), 139.4, 139.37, 129.9, 129.63, 129.6, 129.57, 129.52, 129.5, 129.22, 129.2, 128.3, 127.9, 127.8, 126.8, 126.6, 113.9, 113.6, 78.9, 78.8, 76.4, 76.39, 71.65, 71.58, 55.0 (two signals), 26.06, 26.0, 17.6 (x 2), 9.6, 9.5; LRMS (ESI) *m/z* (relative intensity) 372.3 (100%, M + NH_4^+).



409

6-Ethyl-6-(4-methoxybenzyloxy)-5-methylcyclohex-3-enone (409). To a stirring solution of KHMDS (0.5 M in toluene, 56.8 mL, 30 mmol) in 40 mL of toluene at -78 ºC was added dropwise a solution of PMB glycolate **405** (3.36 g, 9.47 mmol) in 10 mL of toluene. The solution was stirred for 15 min at -78 ºC and TIPSOTf (7.6 mL, 28.3 mmol) was added dropwise. The reaction mixture was stirred for 30 min at -78 ºC, stirred for 20 min at 0 ºC, and then allowed to warm to room temperature. After stirring for 30 min at room temperature, saturated NH_4Cl (50 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give TIPS ester **388** as colorless oil that was carried on without any further purification.

To a stirring solution of crude TIPS ester **388** in 60 mL of THF at 0 ºC was added dropwise Bu_4NF (1.0 M in hexanes, 30.3 mL, 30.3 mmol). After 20 min at 0 ºC, H_2O (50 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the

aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give carboxylic acid **384** as a white solid that was carried on without further purification.

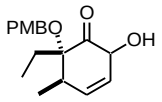
To a stirring solution of the crude carboxylic acid **384** in 50 mL of benzene was added pyridine (2.3 mL, 28 mmol). After stirring the mixture for 15 min, oxalyl chloride (1.6 mL, 19 mmol) was added dropwise. After stirring for 1 h, the reaction solution was concentrated *in vacuo*, Et_2O (50 mL) was added, and the suspension was filtered through Celite with Et_2O rinsing (50 mL). The resulting solution was concentrated *in vacuo* to afford the crude acid chloride **406** as a yellow solid that was carried on without further purification.

To this crude acid chloride **406** in 50 mL of benzene was added pyridine (2.3 mL, 28.4 mmol) followed by *N,O*-dimethylhydroxylamine **396**[86] (1.2 mL, 13 mmol). After stirring for 14 h at room temperature, the solution was concentrated *in vacuo* and filtered through Celite with Et_2O to give a crude yellow solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 2 → 20 % EtOAc/hexanes as eluent) gave Weinreb amide **407** (2.42 g, 64% over 4 steps) as a yellow solid.

To a stirring solution of Weinreb amide **407** (2.42 g, 6.08 mmol) in 40 mL of THF at 0 ºC was added dropwise allylmagnesium bromide (1.0 M in Et_2O, 18.2 mL, 18 mmol). The solution was stirred for 30 min at 0 ºC and then for 1 h at room temperature. This reaction mixture then was added to a cold solution of saturated NH_4Cl (50 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless crude oil. Purification of

this oil by SiO_2 flash column chromatography (gradient, 2 → 10% Et_2O/hexanes as eluent) gave allylation product **408** (1.88 g, 84%) as a colorless oil.

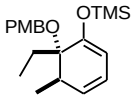
To a refluxing solution of crude allylation product **408** (1.14 g, 3.02 mmol) in 48 mL of CH_2Cl_2 was added dropwise a solution of Grubbs II catalyst[83] (256 mg, 0.302 mmol) in 1 mL of CH_2Cl_2. After holding at reflux for 2 h, the solution was cooled to room temperature and concentrated *in vacuo* to give a crude brown oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hexanes → 10% Et_2O/hexanes as eluent) gave β,γ-unsaturated enone **409** (0.640 g, 77%) as a light brown oil. IR (thin film) 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.75-5.64 (m, 2H), 4.54 (d, *J* = 10.7 Hz, 1H), 4.17 (d, *J* = 10.7 Hz, 1H), 3.83 (s, 3H), 3.14 (m, 1H), 3.02 (m, 1H), 2.85 (m, 1H), 1.95 (m, 1H), 1.77 (m, 1H), 0.97 (d, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 158.9, 131.3, 130.6, 128.6, 121.9, 113.7, 85.4, 65.7, 55.2, 40.2, 39.2, 20.5, 15.2, 6.3; LRMS (ESI) *m/z* (relative intensity) 297.5 (60%, M + Na^+).



410

6-Ethyl-2-hydroxy-6-(4-methoxybenzyloxy)-5-methylcyclohex-3-enone (410). To a stirring solution of freshly prepared LDA (12 μL *i*-Pr_2NH + 32 μL of 2.5 M *n*-BuLi in hexanes; 0.080 mmol) in 800 μL of THF at -78 ºC was added dropwise a solution of β,γ-unsaturated enone **409** (0.020 g, 0.073 mmol) in 100 μL of THF. After 10 min, the solution was warmed to -25 ºC. After stirring the mixture for 15 min at -25 ºC, MoOPh[84] (48 mg, 0.11 mmol) was added. The reaction mixture was stirred for an additional 30

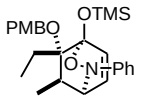
min at -25 ºC and then saturated sodium sulfite (5 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 20 → 40% Et_2O/hexanes as eluent) gave alcohol **410** (0.014 g, 65%) as a yellow oil. IR (thin film) 3472, 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.81-5.63 (m, 2H), 5.07 (br s, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.19 (d, *J* = 11.5 Hz, 1H), 3.82 (s, 3H), 3.23 (d, *J* = 4.3 Hz, 1H), 2.99 (m, 1H), 2.07 (m, 1H), 1.83 (m, 1H), 0.94 (t, *J* = 7.6 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 212.2, 159.3, 132.1, 129.7, 128.6, 127.3, 114.0, 86.2, 72.1, 66.2, 55.3, 43.4, 19.4, 16.4, 5.6.



412

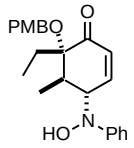
[6-Ethyl-6-(4-methoxybenzyloxy)-5-methylcyclohexa-1,3-dienyloxy]-trimethylsilane (412). To a stirring solution of freshly prepared LDA (230 μL *i*-Pr_2NH + 612 μL of 2.5 M *n*-BuLi in hexanes; 1.53 mmol) in 10 mL of THF at -78 ºC was added dropwise a solution of β,γ-unsaturated enone **409** (0.400 g, 1.46 mmol) in 3 mL of THF. After 15 min, freshly distilled TMSCl (389 μL, 3.08 mmol) was added. After stirring the mixture for 2 h at -78 ºC, saturated NH_4Cl (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give TMS dienol ether **412** as a yellow oil which required

no further purification. IR (thin film) 1696 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.76 (ddd, *J* = 9.4, 5.9, 1.3 Hz, 1H), 5.53 (dd, *J* = 9.3, 4.2 Hz, 1H), 5.28 (d, *J* = 5.8 Hz, 1H), 4.44 (br s, 2H), 3.82 (s, 3H), 2.86 (m, 1H), 2.09 (m, 1H), 1.45 (m, 1H), 1.00 (d, *J* = 7.4 Hz, 3H), 0.99 (t, *J* = 7.6 Hz, 3H), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 153.3, 132.2, 12.8, 127.3, 120.7, 113.4, 103.2, 81.6, 65.1, 55.2, 47.3, 36.8, 22.5, 19.2, 13.3, 7.4, 0.2; LRMS (ESI) *m/z* (relative intensity) 405.3 (60%, M + MeCN + NH_4^+).



414

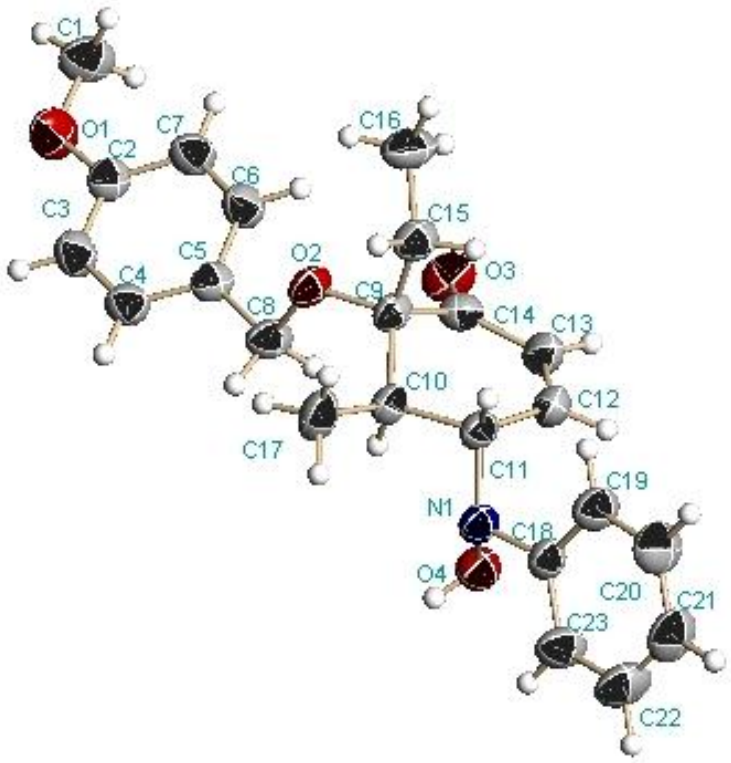
7-Ethyl-7-(4-methoxybenzyloxy)-8-methyl-3-phenyl-1-trimethylsilanyloxy-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (414). To a stirring solution of the crude TMS dienol ether **412** (0.506 g, 1.46 mmol) in 13 mL of chloroform was added nitrosobenzene (**413**) (158 mg, 1.47 mmol, recrystallized from EtOH). After 24 h, the reaction mixture was concentrated *in vacuo* to give the alkylhydroxylamine bridged product **414** as a crude green oil that was used without further purification. IR (thin film) 1696 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.95 (t, *J* = 7.2 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.30 (d, *J* = 8.4 Hz, 1H), 6.14 (dd, *J* = 8.4, 5.3 Hz, 1H), 4.75 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.19 (m, 1H), 3.83 (s, 3H), 2.71 (m, 1H), 1.70 (m, 1H), 1.59 (m, 1H), 1.07 (d, *J* = 7.5 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 151.3, 135.4, 132.1, 129.1, 128.3, 128.1, 121.4, 116.7, 113.2, 103.4, 81.5, 64.7, 62.6, 54.9, 39.1, 24.2, 16.3, 9.0, 2.0.



415

6-Ethyl-4-(hydroxyphenyl-amino)-6-(4-methoxybenzyloxy)-5-methyl-cyclohex-2-enone (415). To a stirring solution of this crude alkylhydroxylamine bridged species **414** (662 mg, 1.46 mmol) in 15 mL of MeOH was added anhydrous KF (102 mg, 1.75 mmol). After stirring the mixture for 1 h at room temperature, Et_2O (15 mL) and H_2O (15 mL) were added and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude green solid. Purification of this green solid by SiO_2 flash column chromatography (gradient, 20 → 40% Et_2O/hexanes as eluent) gave hydroxylamine **415** (0.246 g, 44% from **409**) as a white solid. A portion of this solid was crystallized from EtOH to obtain X-ray quality crystals. mp. 127-129 ºC; IR (thin film) 1678 cm^{-1}; ^1H NMR (360 MHz, THF-D_8) δ 7.45 (d, *J* = 8.4 Hz, 2H), 7.34-7.23 (m, 4H), 6.96 (t, *J* = 6.8 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 10.4 Hz, 1H), 6.02 (dd, *J* = 10.3, 1.9 Hz, 1H), 4.50 (d, *J* = 10.0 Hz, 1H), 4.33 (d, *J* = 10.1 Hz, 1H), 4.26 (br d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.26 (m, 1H), 1.98 (m, 1H), 1.68 (m, 1H), 1.35 (d, *J* = 6.6 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (90 MHz, THF-D_8) δ 197.8, 159.2, 152.8, 147.8, 131.5, 130.0, 128.9, 128.5, 121.1, 116.2, 113.1, 84.1, 69.4, 67.3, 64.6, 54.4, 38.7, 25.5, 24.1, 10.4, 6.8; LRMS (ESI) *m/z* (relative intensity) 382.3 (10%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{23}H_{28}NO_4]^+$, 382.2018, found 382.2015.

X-ray data for 415 (CCD# 870267)

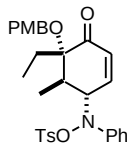


A colorless plate shaped crystal of **415** (C23 H27 N O4) with approximate dimensions 0.07 x 0.12 x 0.20 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 298(2) K, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3º in ω and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame

integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 16187 reflections to a maximum θ angle of 28.39° (0.90 Å resolution), of which 4966 were independent, completeness = 99.0%, R_{int} = 0.0300, R_{sig}= 0.0340 and 3599 were greater than 2σ(I). The final cell constants: a = 13.130(5)Å, b = 8.462(2)Å, c = 18.001(4)Å, α = 90°, β = 94.050(16)°, γ = 90°, volume = 1995.0(10)$Å^3$, are based upon the refinement of the XYZ-centroids of 2438 reflections above 20σ(I) with 2.266° <θ <25.635°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.6381.

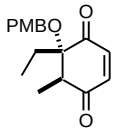
The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P2(1)/n, with Z = 4 for the formula unit, C23 H27 N O4. The final anisotropic full-matrix least-squares refinement on F^2 with 257 variables converged at R1 = 5.88%, for the observed data and wR2 = 16.56% for all data. The goodness-of-fit was 1.012. The largest peak on the final difference map was 0.290 $e^-/Å^3$ and the largest hole was -0.225 $e^-/Å^3$. Based on the final model, the calculated density of the crystal is 1.270 g/cm^3 and F(000) amounts to 816 electrons.



416

6-Ethyl-4-(toluenesulfonylhydroxyphenylamino)-6-(4-methoxybenzyloxy)-5-methylcyclohex-2-enone (416). To a stirring solution of hydroxylamine **415** (0.015 g, 0.039 mmol) and *p*-toluenesulfonyl chloride (0.016 g, 0.083 mmol) in 1.5 mL of

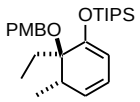
$ClCH_2CH_2Cl$ was added DMAP (0.010 g, 0.083 mmol). The solution was heated to reflux. After stirring for 2 h at reflux, the solution was cooled to room temperature and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 30 → 50% Et_2O/hexanes as eluent) gave tosylate **416** (0.009 g, 44%) as a yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.7 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.30-7.27 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.96-6.93 (m, 4H), 6.68-6.54 (m, 3H), 5.97 (d, *J* = 10.1 Hz, 1H), 4.41 (d, *J* = 10.3 Hz, 1H), 4.21 (d, *J* = 10.0 Hz, 1H), 3.98 (br s, 1H), 3.83 (s, 3H), 2.47-2.45 (m, 1H), 2.46 (s, 3H), 1.87-1.81 (m, 2H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H).



418

Synthesis of 5-Ethyl-5-(4-methoxybenzyloxy)-6-methylcyclohex-2-ene-1,4-dione (418) from Peroxide 425. To a stirring solution of peroxide **425** (0.0080 g, 0.027 mmol) in 600 μL of pyridine was added $CuCl_2$ (1 mg, 0.01 mmol). After stirring for 14 h at room temperature, the crude mixture was filtered through a small pad of SiO_2 with EtOAc rinsing to afford enedione **418** (0.0077 g, 100%) as a yellow oil. IR (thin film) 1684 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 10.4 Hz, 1H), 6.71 (d, *J* = 10.3 Hz, 1H), 4.48 (d, *J* = 10.4 Hz, 1H), 4.17 (d, *J* = 10.3 Hz, 1H), 3.83 (s, 3H), 3.34 (q, *J* = 7.1 Hz, 1H), 1.86-1.78 (m, 2H), 1.22 (d, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 199.3, 159.2, 139.7, 138.4, 129.7, 129.2, 113.7, 85.8, 66.1, 55.2, 50.3, 23.5, 10.2, 6.5.

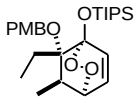
Synthesis of Enedione 418 from Alcohol 427. To a stirring solution of γ-hydroxyenone **427** (0.0107 g, 0.0369 mmol) in 1 mL of CH_2Cl_2 was added SiO_2 (12 mg) followed by pyridinium chlorochromate (12 mg, 0.055 mmol). After stirring for 14 h at room temperature, the crude mixture was filtered through a small pad of SiO_2 with EtOAc to afford enedione **418** (0.0105 g, 99%) as a yellow oil.



420

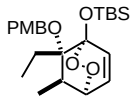
[6-Ethyl-6-(4-methoxybenzyloxy)-5-methylcyclohexa-1,3-dienyloxy]-trimethylsilane (420). To a stirring solution of freshly prepared LDA (12 μL *i*-Pr_2NH + 32 μL of 2.5 M *n*-BuLi in hexanes; 0.080 mmol) in 800 μL of THF at -78 ºC was added dropwise a solution of β,γ-unsaturated enone **409** (0.021 g, 0.077 mmol) in 200 μL of THF. After stirring the mixture at -78 ºC for 15 min, TIPSOTf (25 μL, 0.092 mmol) was added. The reaction mixture was then warmed to room temperature. After stirring for 1 h at room temperature, a few drops of MeOH were added and the reaction mixture was concentrated *in vacuo*. The crude mixture was filtered through Celite with Et_2O rinsing to give TIPS dienol ether **420** as a yellow oil following concentration *in vacuo* that required no further purification. IR (thin film) 1249 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.74 (dd, *J* = 9.2, 5.9 Hz, 1H), 5.55 (dd, *J* = 9.3, 5.1 Hz, 1H), 5.26 (d, *J* = 5.8 Hz, 1H), 4.46 (d, *J* = 10.8 Hz, 1H), 4.41 (d, *J* = 10.8 Hz, 1H), 3.78 (s, 3H), 2.66 (m, 1H), 2.26 (m, 1H), 1.45 (m, 1H), 1.31-1.23 (m, 3H), 0.97 (t, *J* = 10.3 Hz, 3H), 0.93 (d, *J* = 7.3 Hz, 3H), 1.13-1.10 (m, 18H); ^{13}C NMR (90 MHz,

$CDCl_3$) δ 158.6, 152.6, 132.2, 128.9, 127.1, 120.2, 113.5, 102.5, 81.4, 65.0, 55.2, 37.2, 21.7, 18.2, 18.1, 17.6, 13.7, 12.8, 7.2, 1.0.



422

[7-Ethyl-7-(4-methoxybenzyloxy)-8-methyl-2,3-dioxabicyclo[2.2.2]oct-5-en-1-yloxy]triisopropylsilane (422). To a stirring solution of crude TIPS dienol ether **420** (32 mg, ~0.071 mmol) in CH_2Cl_2 at -78 ºC was added tetraphenylporphyrin (2 mg, 0.003 mmol). The sample was irradiated with a 275W sun lamp while bubbling O_2 through the solution at -78 ºC. After 45 min, the reaction mixture was warmed to room temperature and concentrated *in vacuo* to give a pink oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 2 → 20% Et_2O/hexanes as eluent) gave endoperoxide **422** as a yellow oil (0.016 g, 49% from **409**). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.62 (dd, *J* = 8.5, 5.5 Hz, 1H), 6.44 (d, *J* = 8.6 Hz, 1H), 4.69 (d, *J* = 11.3 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.31 (m, 1H), 3.84 (s, 3H), 2.73 (m, 1H), 1.75 (m, 1H), 1.63 (m, 1H), 1.15-1.05 (m, 6H), 1.09 (d, *J* = 5.4 Hz, 18H), 0.98 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.6, 136.5, 132.0, 131.5, 128.6, 113.4, 103.7, 81.2, 65.1, 55.2, 40.9, 24.2, 18.05, 17.99, 15.3, 13.3, 9.3; LRMS (ESI) *m/z* (relative intensity) 463.5 (10%, $M + H^+$).

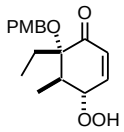


424

***tert*-Butyl-[7-ethyl-7-(4-methoxybenzyloxy)-8-methyl-2,3-dioxa-bicyclo[2.2.2]oct-5-en-1-yloxy]dimethylsilane (424).** To a stirring solution of KHMDS (292 μL, 0.50 M in toluene, 0.156 mmol) in 1 mL of THF at -78 ºC was added dropwise a solution of β,γ-unsaturated enone **409** (0.020 g, 0.073 mmol) in 200 μL of THF. After 40 min at -78 ºC, TBSOTf (34 μL, 0.15 mmol) was added. After stirring the mixture for 2 h at -78 ºC, saturated $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, hex → 5% Et_2O/hexanes as eluent) gave TBS dienol ether **423** as a yellow oil (0.027 g, 96%).

To a solution of TBS dienol ether **423** (0.027 g, 0.070 mmol) in CH_2Cl_2 at -78 ºC was added tetraphenylporphorphyrin (2 mg, 0.003 mmol). The sample was irradiated with a 275W sun lamp while bubbling O_2 through the solution at -78 ºC. After 45 min, the reaction mixture was warmed to room temperature and concentrated *in vacuo* to give a pink oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 2 → 20% Et_2O/hexanes as eluent) gave endoperoxide **424** as a pink oil (0.016 g, 54%). IR (thin film) 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.60 (dd, *J* = 8.6, 5.5 Hz, 1H), 6.37 (d, *J* = 8.6 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.32 (m, 1H), 3.82 (s, 3H), 2.69 (m, 1H), 1.76-1.59

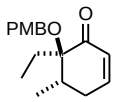
(m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H), 1.00-0.95 (m, 3H), 0.96 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 136.3, 132.3, 131.5, 128.2, 113.4, 104.3, 80.9, 77.5, 65.0, 55.2, 41.0, 25.7, 24.2, 18.0, 14.9, 9.4, -2.3, -3.0; LRMS (ESI) *m/z* (relative intensity) 421.3 (30%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{23}H_{36}O_5SiNa]^+$, 443.2230, found 443.2233.



425

6-Ethyl-4-hydroperoxy-6-(4-methoxybenzyloxy)-5-methylcyclohex-2-enone (425). To a stirring solution of endoperoxide **424** (0.111 g, 0.271 mmol) in 3 mL of MeCN at 0 ºC was added 46% HF(aq.) (18 μL, 0.410 mmol). After stirring the mixture for 1 min, H_2O(5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 10 → 50% EtOAc/hexanes as eluent) gave peroxide **425** (0.085 g, 100%) as a yellow oil. IR (thin film) 3353, 1682 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.42 (br s, 1H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.08 (dd, *J* = 10.4, 2.0 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 6.14 (dd, *J* = 10.4, 2.0 Hz, 1H), 4.54 (m, 1H), 4.43 (d, *J* = 10.0 Hz, 1H), 4.24 (d, *J* = 10.0 Hz, 1H), 3.83 (s, 3H), 2.90 (m, 1H), 1.90 (m, 1H), 1.55 (m, 1H), 1.26 (d, *J* = 6.7 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 158.9, 147.4, 130.5, 129.5, 129.2, 113.6,

84.9, 83.9, 65.0, 55.2, 38.7, 24.3, 10.5, 7.1; LRMS (ESI) *m/z* (relative intensity) 324.4 (5%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{26}NO_5]^+$, 324.1811, found 324.1801.

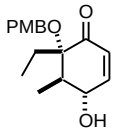


426

Synthesis of 6-Ethyl-6-(4-methoxybenzyloxy)-5-methylcyclohex-2-enone (426) from β,γ-Unsaturated Enone 409. To a stirring solution of β,γ-unsaturated enone **409** (0.100 g, 0.364 mmol) in 4 mL of CH_2Cl_2 was added DBU (163 μL, 1.09 mmol). The solution was heated to reflux. After holding at reflux for 1 h, the solution was cooled to room temperature, washed with 2 M sodium phosphate solution (10 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (10% Et_2O/hexanes as eluent) gave α,β-unsaturated enone **426** (0.077 g, 78%) as a yellow oil. IR (thin film) 1678 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.86 (m, 1H), 6.01 (d, *J* = 10.0 Hz, 1H), 4.40 (d, *J* = 10.3 Hz, 1H), 4.18 (d, *J* = 10.3 Hz, 1H), 3.83 (s, 3H), 2.79 (m, 1H), 2,69 (m, 1H), 2.19 (m, 1H), 1.95 (m, 1H), 1.69 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 199.8, 159.0, 148.1, 131.0, 129.1, 128.4, 113.6, 83.2, 65.1, 55.3, 34.7, 32.8, 20.7, 14.3, 6.4; LRMS (ESI) *m/z* (relative intensity) 292.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{26}NO_3I]^+$, 292.1913, found 292.1899.

Preparation of 6-Ethyl-6-(4-methoxybenzyloxy)-5-methylcyclohex-2-enone (426) from Aryl Iodide 474. To a freeze pump thawed solution of aryl iodide **474** (0.020 g, 0.038 mmol), Bu_4NBr (0.025 g, 0.077 mmol), sodium formate (0.003 g, 0.05

mmol), and Et_3N (12 μL, 0.084 mmol) in 1 mL of DMF at 80 ºC was added a freeze pump thawed solution of Hermann's catalyst[85] (0.002 g, 0.002 mmol) in 1 mL of DMF. After stirring for 2 h at room temperature, the reaction mixture was warmed to 100 ºC. After stirring for 14 h at 100 ºC, the crude mixture was cooled to room temperature, filtered through Celite, and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (5 → 20% EtOAc/hexanes as eluent) gave α,β-unsaturated enone **426** as a yellow oil (0.009 g, 100%).

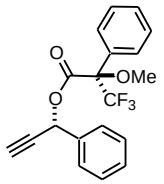


427

Preparation of 6-Ethyl-4-hydroxy-6-(4-methoxybenzyloxy)-5-methylcyclohex-2-enone (427) from Endoperoxide 424. To a stirring solution of endoperoxide **424** (0.148 g, 0.351 mmol) in 3 mL of THF at - 78 ºC was added dropwise Bu_4NF (1.0 M in hexanes, 386 μL, 0.39 mmol), and the solution was warmed to -45 ºC. After stirring the mixture for 30 min at -45 ºC, H_2O (5 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 10 → 60% EtOAc/hexanes as eluent) gave γ-hydroxyenone **427** (0.037 g, 37%) as a colorless oil. A yield of 91% was obtained on a 24 mg scale. IR (thin film) 3448, 1678 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.21 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 6.87 (m, 1H), 6.03 (d, J = 10.1 Hz, 1H), 4.33 (d, J =

10.1 Hz, 1H), 4.05 (d, *J* = 10.1 Hz, 1H), 4.05 (m, 1H), 3.81 (s, 3H), 3.48 (br s, 1H), 2.60 (m, 1H), 2.13 (m, 1H), 1.52 (m, 1H), 0.98-0.93 (m, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.6, 159.3, 147.2, 129.5, 129.4, 126.7, 113.8, 83.9, 70.6, 65.4, 55.2, 41.0, 19.8, 13.0, 5.6; LRMS (ESI) *m/z* (relative intensity) 313.3 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{17}H_{26}NO_4]^+$, 308.1862, found 308.1867.

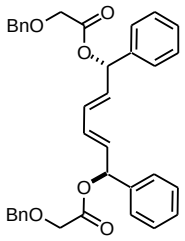
Conversion of Peroxide 425 to Alcohol 427. To a stirring solution of peroxide **425** (0.024 g, 0.077 mmol) in 1 mL of $CHCl_3$ was added PPh_3 (30 mg, 0.12 mmol). After stirring for 5 min at room temperature, the reaction mixture was concentrated *in vacuo* to give a crude green oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 20 → 40% EtOAc/hexanes as eluent) gave γ-hydroxyenone **427** (0.020 g, 91%).



433

(*R*,*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic Acid 1-Phenylprop-2-ynyl Ester (433). To a stirring solution of alcohol **325**[69] (0.010 g, 0.076 mmol) and DMAP (0.023 g, 0.19 mmol) in 1 mL of THF at room temperature was added dropwise (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (**432**) (36 μL, 0.19 mmol). After stirring the mixture for 1 h, H_2O (3 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and

concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (15% EtOAc/hexanes as eluent) gave Mosher's ester **433** (0.021 g, 79%, 98% *ee*) as a colorless oil. IR (thin film) 1749 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.56-7.26 (m, 10H), 6.65 (d, *J* = 3.6 Hz, 1H), 3.48 (s, 3H), 2.71 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.5, 136.1, 131.9, 129.6, 129.5, 128.8, 128.3, 127.9, 127.4, 124.7, 121.5, 78.6, 76.7, 67.4, 55.5; LRMS (ESI) *m/z* (relative intensity) 371.2 (5%, M + Na^+).

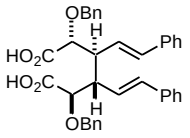


435

(*R*,*R*)-Benzyloxyacetic Acid 6-(2-Benzyloxyacetoxy)-1,6-diphenylhexa-2,4-dienyl Ester (435). To a stirring solution of bis alkyne **324** (1.23 g, 4.69 mmol) in 45 mL of THF at 0 ºC was added $LiAlH_4$ (0.710 g, 26.9 mmol) and the solution was warmed to room temperature. After stirring for 2 h at room temperature, another portion of $LiAlH_4$ (0.710 g, 26.9 mmol) was added. After stirring for an additional 14 h at room temperature, H_2O (1.42 mL) followed by 1.42 mL of 15% NaOH(aq) and then 4.26 mL of H_2O were added. The suspension was filtered and rinsed with EtOAc. The filtrate was dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 5 → 40% EtOAc/hexanes as eluent) gave diene **434** (0.597 g, 48%) as a yellow solid. IR (thin film) 3342 cm^{-1}; ^1H NMR (300 MHz, THF-d^8) δ 7.45 (d, *J* = 7.7 Hz, 2H), 7.36 (app. t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 6.38 (m, 1H), 5.92 (m, 1H), 5.24 (m, 1H), 4.87

(d, J = 3.6 Hz, 1H); ^{13}C NMR (75 MHz, THF-d8) δ 145.3, 137.7, 129.7, 128.8, 127.6, 127.0, 74.7.

To a stirring solution of diol **434** (0.343 g, 1.29 mmol) in 13 mL of CH_2Cl_2 at 0 ºC was added pyridine (437 μL, 2.84 mmol) and benzyloxyacetyl chloride (448 μL, 2.84 mmol). The solution was warmed to room temperature, stirred for 1 h at that temperature, and concentrated *in vacuo*. To the crude mixture was added H_2O (15 mL). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 1:1:98 → 50:2:48 EtOAc/benzene/hexanes as eluent) gave bis benzyloxyglycolate **435** (0.553 g, 76%) as a colorless oil. $[\alpha]^{20}_D$ = + 7° (1.2, $CHCl_3$); IR (thin film) 1749 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38-7.26 (m, 20H), 6.39 (d, J = 6.5 Hz, 2H), 6.25 (dd, J = 11.7, 2.9 Hz, 2H), 5.90-5.84 (m, 2H), 4.62 (s, 4H), 4.16 (d, J = 18.0 Hz, 2H), 4.11 (d, J = 18.0 Hz, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.2, 138.2, 136.9, 132.2, 131.5, 128.5, 128.31, 128.25, 127.9, 127.8, 126.9, 75.9, 73.2, 67.1; LRMS (ESI) *m/z* (relative intensity) 580.3 (10%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{36}H_{38}NO_6]^+$, 580.2699, found 580.2671.

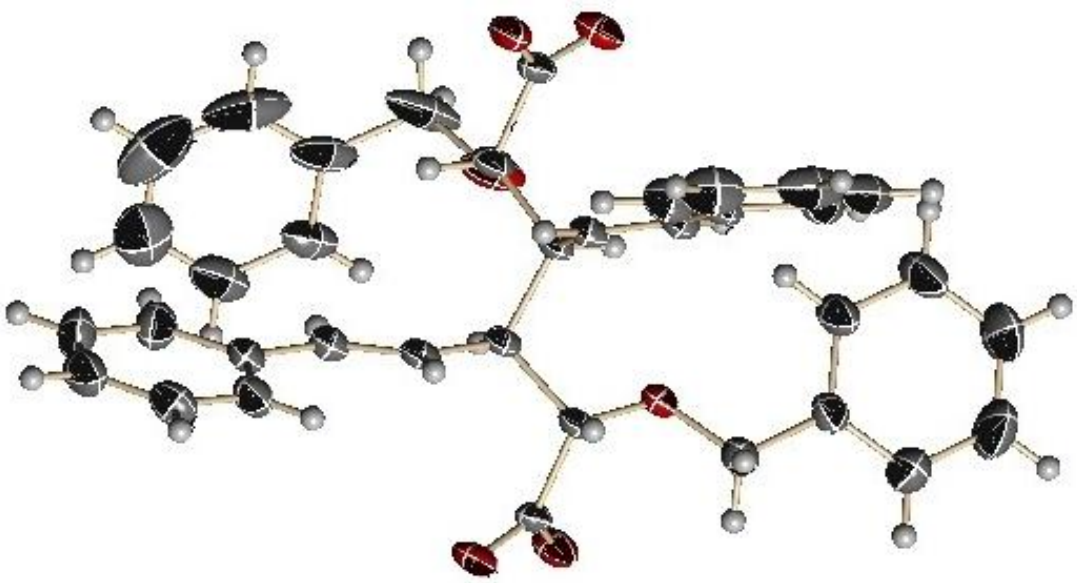


439

(*R,R,S,S*)-2,5-Bis(benzyloxy)3,4-distyrylhexanedioic Acid (439). To a stirring solution of LHMDS (267 μL, 1.0 M in THF, 0.27 mmol) in 1 mL of THF at -78 ºC was

added dropwise TMSCl (34 μL, 0.27 mmol). A solution of bis benzyloxyglycolate **435** (0.050 g, 0.089 mmol) in 200 μL of THF was added dropwise followed by $SnCl_4$ (4 μL, 1.0 M in CH_2Cl_2, 0.004 mmol). The solution was stirred at -78 ºC for 30 min, at 0 ºC for 30 min, and then warmed to room temperature. After stirring the mixture for an additional 14 h at room temperature, 1 M NaOH (6 mL) was added and the reaction mixture was stirred vigorously for 1 h. Et_2O (10 mL) then was added. The resulting solution was partitioned between Et_2O and 1 M NaOH and the organic layer was extracted with 1 M NaOH (10 mL). The combined aqueous fractions were acidified with 3 M HCl, extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give dicarboxylic acid **439** (0.043 g, 87%) as a light yellow solid that decomposed > 200 ºC. A portion of this solid was crystallized from MeCN/hexanes to obtain X-ray quality crystals. $[\alpha]^{20}_D$ = -78° (4.0, MeOH); IR (thin film) 3400-3000, 1719 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.28-7.03 (m, 20H), 6.08 (d, *J* = 15.7 Hz, 2H), 5.91 (dd, *J* = 15.7, 10.0 Hz, 2H), 4.53 (d, *J* = 11.5 Hz, 2H), 4.15 (d, *J* = 11.5 Hz, 2H), 3.76 (d, *J* = 9.7 Hz, 2H), 3.07 (td, *J* = 10.0, 2.3 Hz, 2H); ^{13}C NMR (75 MHz, THF-D_6) δ 172.9, 139.0, 138.3, 135.3, 129.1, 129.0, 128.4, 128.3, 128.0, 127.3, 125.7, 81.0, 72.6, 47.5; LRMS (ESI) *m/z* (relative intensity) 580.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{36}H_{38}NO_6]^+$, 580.2699, found 580.2704.

X-ray Data for Dicarboxylic Acid 439 (CCD# 867255)

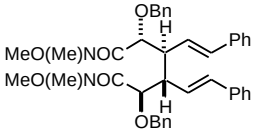


A colorless block shaped crystal of dicarboxylic acid **439** (C36 H32 O6, 2(C H3 C N)) with approximate dimensions 0.08 x 0.10 x 0.20 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 173(2) K, cooled by Rigaku-MSC X-Stream 2000, on a Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3º in ω and an exposure time of 20 seconds/frame. The total data collection time was about 15 hours. The frames were integrated with the Bruker SAINT software package using a narrow-

frame integration algorithm. The integration of the data using a Triclinic unit cell yielded a total of 8745 reflections to a maximum θ angle of 28.33° (0.90 Å resolution), of which 7132 were independent, completeness = 97.4%, R_{int} = 0.0131, R_{sig} = 0.0304 and 6670 were greater than 2σ(I). The final cell constants: a = 9.822(2)Å, b = 9.849(2)Å, c = 10.995(3)Å, α = 95.962(4)°, β = 112.616(4)°, γ = 106.985(4)°, volume = 910.4(4)Å^3, are based upon the refinement of the XYZ-centroids of 4388 reflections above 20σ(I) with 2.395° <θ <28.143°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.8510.

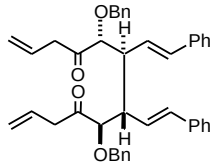
The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P1, with Z = 1 for the formula unit, C40 H38 N2 O6. The final anisotropic full-matrix least-squares refinement on F^2 with 435 variables converged at R1 = 4.07%, for the observed data and wR2 = 10.99% for all data. The goodness-of-fit was 1.027. The largest peak on the final difference map was 0.289 e^-/Å^3 and the largest hole was -0.161 e^-/Å^3. Based on the final model, the calculated density of the crystal is 1.172 g/cm^3 and F(000) amounts to 340 electrons.



440

(*R*,*R*,*S*,*S*)-2,5-Bis(benzyloxy)3,4-distyrylhexanedioic Acid Bis(*N*-methoxy-*N*-methylamide) (440). To a stirring solution of dicarboxylic acid **439** (1.48 g, 2.62 mmol) in 25 mL of toluene was added $P[NCH_3(OCH_3)]_3$[71] (517 μL, 2.62 mmol). The solution

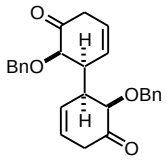
was heated to 60 ºC, stirred for 2 h at that temperature, cooled to room temperature, and saturated $NaHCO_3$ (25 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow crude oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 25 → 60% EtOAc/hexanes as eluent) gave bis Weinreb amide **440** (1.23 g, 73%) as a pale yellow oil. A yield of 100% was obtained on a 20 mg scale. IR (thin film) 1666 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.28 (m, 20H), 6.33 (d, *J* = 15.7 Hz, 2H), 6.20-6.13 (m, 2H), 4.72 (d, *J* = 13.4 Hz, 2H), 4.43-4.31 (m, 4H), 3.40 (s, 6H), 3.4 (m, 2H), 2.99 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 138.2, 137.7, 135.5, 128.9, 128.8, 128.7, 128.3, 127.9, 126.8, 125.0, 73.7, 72.1, 61.7, 48.0, 33.2; LRMS (ESI) *m/z* (relative intensity) 649.4 (100%, M + H^+).



441

(*R,R,S,S*)-5,8-Bis-benzyloxy-6,7-distyryldodeca-1,11-diene-4,9-dione (441). To a stirring solution of bis Weinreb amide **440** (1.23 g, 1.90 mmol) in 20 mL of THF at 0 ºC was added dropwise allylmagnesium bromide (1.0 M in Et_2O, 11.4 mL, 11 mmol). The solution was stirred for 30 min at 0 ºC and then added to a cold solution of saturated NH_4Cl (20 mL) and HOAc (1 ML). The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo*

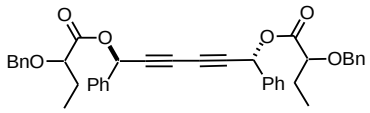
to give a colorless crude oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 4 → 5% EtOAc/hexanes as eluent) gave bis allylation product **441** (0.517 g, 45%) as a colorless oil. A yield of 64% was obtained on a 176 mg scale. $[\alpha]^{20}_D$ = -73° (11.1, MeOH); IR (thin film) 1708 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.38 (m, 10H), 7.30-7.21 (m, 6H), 7.18-7.16 (m, 4H), 6.01 (dd, *J* = 15.9 Hz, 4.8 Hz, 2H), 5.84-5.72 (m, 4H), 5.12-5.03 (m, 4H), 4.58 (d, *J* = 11.7 Hz, 2H), 4.29 (d, *J* = 11.6 Hz, 2H), 3.78 (d, *J* = 10.0 Hz, 2H), 3.38-3.32 (m, 2H), 3.20-3.13 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 136.9, 136.2, 135.3, 130.2, 128.6, 128.5, 128.4, 128.2, 127.8, 126.4, 122.9, 118.7, 85.1, 72.5, 45.7, 42.4; LRMS (ESI) *m/z* (relative intensity) 628.3 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{42}H_{46}NO_4]^+$, 628.3427, found 628.3425.



442

(*R,R,S,S*)-2,2'-Bis-benzyloxy-bicyclohexyl-5,5'-diene-3,3'-dione (442). To a refluxing solution of tetranene **441** (0.100 g, 0.164 mmol) in 35 mL of freeze-pump-thawed CH_2Cl_2 was added dropwise a solution of Grubbs II catalyst[83] (7 mg, 0.008 mmol) in 250 μL of CH_2Cl_2. After holding at reflux for 2 h, the solution was cooled to room temperature and concentrated *in vacuo* to give a crude white solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 20 → 40% Et_2O/hexanes as eluent) gave bicycle **442** (0.041 g, 62%) as a tacky white solid. A yield of 81% was obtained on a 15 mg scale. $[\alpha]^{20}_D$ = +123° (0.86, $CHCl_3$); IR (thin film) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.24 (m, 10H), 5.65 (dd, *J* = 9.9, 2.4 Hz, 2H), 5.32 (d, *J*

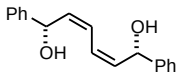
= 10.0 Hz, 2H), 4.87 (d, *J* = 11.7 Hz, 2H), 4.39 (d, *J* = 11.7 Hz, 2H), 3.98 (d, *J* = 10.2 Hz, 2H), 3.16 (d, *J* = 9.1 Hz, 2H), 3.04 (d, *J* = 23.0 Hz, 2H), 2.94 (d, *J* = 20.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.2, 137.2, 128.4, 128.3, 127.9, 125.7, 124.2, 79.9, 72.2, 43.3, 40.2; LRMS (ESI) *m/z* (relative intensity) 420.2 (80%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{26}H_{30}NO_4]^+$, 420.2175, found 420.2161.



443

(*R,R*)-2-Benzyloxybutyric Acid 6-(2-Benzyloxybutyryloxy)-1,6-diphenylhexa-2,4-diynyl Ester (324). To a stirring solution of carboxylic acid **328** (0.148 g, 0.761 mmol) in 9 mL of toluene at 0 ºC was added DMAP (99 mg, 0.81 mmol) and a solution of diol **324** (100 mg, 0.381 mmol) in 1 mL of Et_2O. To the solution was added Et_3N (550 μL, 3.94 mmol) and 2,4,6-trichlorobenzoyl chloride (134 μL, 0.858 mmol). After stirring the mixture for 1 h at 0 ºC, saturated $NaHCO_3$ (15 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow crude oil. Purification of this oil by deactivated silica (2% Et_3N in hexanes) flash column chromatography (gradient, 5 → 10% EtOAc/hexanes as eluent) gave diester **443** (0.185 g, 79%, 1:1 mix diast.) as a colorless oil. IR (thin film) 1749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.23 (m, 20H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 4.75-4.71 (m, 2H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.00-3.96 (m, 2H), 1.89-1.77 (m, 4H), 1.04 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.34, 171.27, 137.3(two

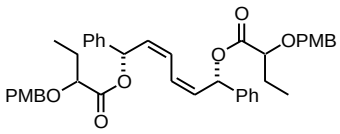
signals), 135.6, 135.5, 129.3(two signals), 128.8(two signals), 128.3(two signals), 128.0(two signals), 127.8(two signals), 127.6(two signals), 78.9(two signals), 76.35, 76.28, 72.2(two signals), 71.0(two signals), 65.8(two signals), 26.06, 25.99, 9.5, 9.4; LRMS (ESI) *m/z* (relative intensity) 632.3 (40%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{40}H_{42}NO_6]^+$, 632.3012, found 632.3012.



445

(*S*,*S*)-1,6-Diphenylhexa-(*Z*,*Z*)-2,4-diene-1,6-diol (445). Ar was bubbled through a stirring suspension of Zn dust (70 g, 1.1 mol) in 420 mL of H_2O. After stirring and bubbling for 15 min, $Cu(OAc)_2 \cdot H_2O$ (7.0 g, 35 mmol) was added. After an additional 15 min, $AgNO_3$ (7.0 g, 41 mmol) was added. After stirring for 30 min, the mixture was filtered and the solid was washed successively with H_2O, MeOH, acetone, and Et_2O. The activated Zn dust was added to 250 mL of a 1:1 mixture of MeOH/H_2O followed by a solution of diyne **324** (3.50 g, 13.3 mmol) in 30 mL of MeOH. The reaction mixture was heated at 40 ºC for 36 h, cooled to room temperature, filtered through Celite with MeOH rinsing, and concentrated *in vacuo*. The remaining aqueous layer was extracted with EtOAc (3 x 400 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude orange solid. Purification of this solid by SiO_2 flash column chromatography (gradient, 15 → 60 % EtOAc/hexanes as eluent) gave diene **445** (2.71 g, 76%) as an orange solid. mp 107-110 ºC; $[\alpha]^{20}_D$ = +69° (6.20, MeOH); IR (thin film) 3284 cm^{-1}; ^1H NMR (400 MHz, THF-d^8) δ 7.35 (d, *J* = 7.3 Hz, 4H), 7.24 (t, *J* = 7.5 Hz, 4H), 7.14 (t, *J* = 7.3 Hz, 2H), 6.60-6.58

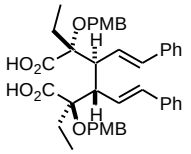
(m, 2H), 5.63 (s, 4H), 4.53 (m, 2H); ^{13}C NMR (75 MHz, THF-d8) δ 145.8, 137.4, 128.8, 127.4, 126.6, 123.7, 69.4; LRMS (ESI) *m/z* (relative intensity) 249.1 (100%, M – OH^-); HRMS (ESI) *m/z* calcd for $[C_{18}H_{17}O]^-$, 249.1279, found 249.1261.



446

(*S,S*)-2-(4-Methoxybenzyloxy)butyric Acid 6-[2-(4-Methoxybenzyloxy)-butyryloxy]-1,6-diphenylhexa-(*Z,Z*)-2,4-dienyl Ester (446). To a stirring solution carboxylic acid **373** (5.90 g, 26.3 mmol) and diol **445** (3.19 g, 12.0 mmol) in 120 mL of CH_2Cl_2 at room temperature was added DMAP (365 mg, 4.00 mmol) and DCC (5.92 g, 28.7 mmol). After stirring for 16 h at room temperature, the solution was concentrated *in vacuo* to give a crude yellow oil. Purification of this oil on deactivated silica (2% Et_3N in hexanes) by flash column chromatography (gradient, 5 → 15 % EtOAc/hexanes as eluent) gave bis PMB glycolate **446** (5.41 g, 67%) as a colorless oil (1:1 mix diast.). An 84% yield was obtained on a 94 mg scale. IR (thin film) 1737 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.33 (m, 10H), 7.29 (d, *J* = 8.1 Hz, 4H), 6.90 (d, *J* = 9.3 Hz, 4H), 6.86 (d, *J* = 4.2 Hz, 2H), 6.82-6.79 (m, 2H), 5.93-5.85 (m, 2H), 4.68 (d, *J* = 9.5 Hz, 1H), 4.65 (d, *J* = 9.5 Hz, 1H), 4.37 (d, *J* = 12.5 Hz, 2H), 3.95 (t, *J* = 7.0 Hz, 2H), 3.84 (s, 6H), 1.87-1.80 (m, 4H), 1.00 (t, *J* = 7.7 Hz, 3H), 0.96 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.84, 171.78, 159.3 (two signals), 139.0, 138.9, 131.3, 131.2 (two signals), 131.1, 129.6 (two signals), 128.6 (two signals), 128.2, 128.1, 126.6, 126.5, 125.7, 125.5, 113.7 (two signals), 78.9, 78.8, 71.7 (two signals), 71.4, 71.2, 55.2 (two signals), 26.2,

26.1; LRMS (ESI) *m/z* (relative intensity) 696.4 (20%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{42}H_{50}NO_8]^+$, 696.3536, found 696.3520.

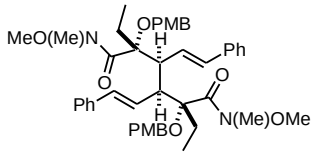


450

(*R*,*R*,*S*,*S*)-2,5-Diethyl-2,5-bis-(4(methoxy)benzyloxy)-3,4(distyryl)hexanedioic Acid (450). To a stirring solution of KHMDS (31.6 mL, 0.50 M in toluene, 16 mmol) in 20 mL of Et_2O at -100 ºC was added a solution of bis PMB glycolate **446** (1.58 g, 2.32 mmol) in 10 mL of Et_2O. After stirring the mixture for 40 min at -100 ºC, TIPSOTf (2.49 mL, 9.28 mmol) was added dropwise. The solution was stirred for an additional 30 min at -100 ºC and then warmed to -60 ºC. After stirring for 2 h at -60 ºC, the solution was warmed to -20 ºC and stirred for 2 h at -20 ºC. The solution was then warmed to room temperature. After stirring for 2.5 h at room temperature, saturated $NaHCO_3$ (40 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give bis TIPS ester **449** as a yellow oil (1.81 g, 79%) which was used without further purification. IR (thin film) 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37-7.20 (m, 14H), 6.79 (d, *J* = 8.5 Hz, 4H), 6.51 (d, *J* = 15.8 Hz, 2H), 6.23 (dd, *J* = 15.8, 10.9 Hz, 2H), 4.56 (d, *J* = 10.0 Hz, 2H), 4.41 (d, *J* = 10.1 Hz, 2H), 3.84-3.81 (m, 2H), 3.81 (s, 6H), 2.07-1.89 (m, 4H), 1.22-1.14 (m, 6H), 1.00-0.91 (m, 42H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 171.8, 158.6, 137.5, 134.3,

131.4, 129.0, 128.1, 127.4, 126.9, 126.4, 113.2, 84.8, 65.5, 55.2, 45.7, 25.7, 17.8, 17.71, 17.67, 12.3, 11.9, 7.4; LRMS (ESI) *m/z* (relative intensity) 948.8 (100%, M + NH_4^+).

To a stirring solution of crude bis TIPS ester **449** (1.28 g, 1.29 mmol) in 15 mL of THF at 0 ºC was added dropwise Bu_4NF (3.89 mL, 1.0 M in hexanes, 3.9 mmol). After stirring for 30 min at 0 ºC, H_2O (20 mL) was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a crude yellow solid. CH_3CN (20 mL) was added and this solution was washed with hexanes (5 x 20 mL) and the CH_3CN phase was separated and concentrated *in vacuo* to give dicarboxylic acid **450** (0.876 g, 100%) as a white solid which was used without further purification. mp. 116-118 ºC; $[\alpha]^{20}_D$ = -42° (5.00, MeOH); IR (thin film) 3354, 1702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.3 Hz, 4H), 7.28 (t, *J* = 7.2 Hz, 4H), 7.22 (d, *J* = 7.2 Hz, 2H), 7.17 (d, *J* =8.2 Hz, 4H), 6.81 (d, *J* = 8.5 Hz, 4H), 6.50 (d, *J* = 15.8 Hz, 2H), 6.37 (dd, *J* = 15.6, 10.6 Hz, 2H), 4.29 (d, *J* = 9.2 Hz, 2H), 4.20 (d, *J* = 9.4 Hz, 2H), 3.80 (s, 6H), 3.32 (d, *J* = 10.4 Hz, 2H), 1.73-1.58 (m, 4H), 0.82 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 159.9, 137.6, 135.4, 130.2 (two signals), 128.9, 127.3, 127.1, 125.8, 114.1, 83.8, 65.0, 55.7, 45.4, 26.5, 7.1; LRMS (ESI) *m/z* (relative intensity) 696.3 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{42}H_{50}NO_8]^+$, 696.3536, found 696.3550.

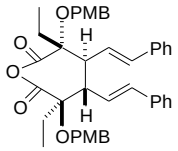


451

(*R*,*R*,*S*,*S*)-2,5-Diethyl-2,5-bis(4-(methoxy)benzyloxy)-3,4-distyryl)hexanedioic Acid Bis(*N*-methoxy-*N*-methylamide) (451). To a stirring solution of dicarboxylic acid **450** (0.045 g, 0.066 mmol) in 1 mL of benzene at room temperature was added pyridine (32 μL, 0.40 mmol). After stirring the mixture for 15 min, oxalyl chloride (23 μL, 0.26 mmol) was added dropwise. After stirring for 30 min at room temperature, the reaction mixture was concentrated *in vacuo*, Et_2O (10 mL) was added, and the suspension was filtered through a thin pad of Celite with Et_2O rinsing (10 mL). The combined organics were concentrated *in vacuo* to afford bis acid choride **453**, which was used without further purification. IR (thin film) 1778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.25 (m, 14H), 6.84 (d, *J* = 10.0 Hz, 4H), 6.66 (d, *J* = 15.5 Hz, 2H), 6.34 (dd, *J* = 15.8, 10.7 Hz, 2H), 4.53 (d, *J* = 10.1 Hz, 2H), 4.47 (d, *J* = 10.2 Hz, 2H), 3.85 (s, 6H), 3.65 (d, *J* = 10.6 Hz, 2H), 2.14-2.00 (m, 4H), 0.98 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 159.0, 136.9, 136.7, 129.7, 128.9, 128.5, 127.7, 126.6, 124.2, 113.5, 90.3, 65.5, 55.2, 47.3, 27.0, 7.2; LRMS (ESI^-) *m/z* (relative intensity) 677.5 (100%, M - H - Cl^-).

To a stirring solution of crude bis acid chloride **453** in 45 mL of benzene at room temperature was added dropwise pyridine (32 μL, 0.40 mmol) followed by *N*,*O*-dimethylhydroxylamine (**396**)[86] (23 μL, 0.26 mmol). After stirring for 15 h at room temperature, the reaction mixture was concentrated *in vacuo* to afford a crude pale yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 20 → 50 %

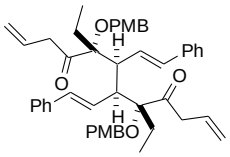
EtOAc/hexanes as eluent) gave bis Weinreb amide **451** as a yellow solid (0.037 g, 73% from **451**). A 42% yield was obtained from **446** on a 2.69 g scale. mp. 51-54 ºC; $[\alpha]^{20}_{D}$ = +13° (2.67, MeOH); IR (thin film) 1637 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.5 Hz, 4H), 7.32-7.19 (m, 10H), 6.74 (d, *J* = 8.2 Hz, 4H), 6.55-6.50 (m, 4H), 4.50 (d, *J* = 9.5 Hz, 2H), 4.42-4.37 (m, 2H), 3.79 (s, 6H), 3.63-3.57 (m, 2H), 3.46 (s, 6H), 3.08 (br s, 6H), 2.13-2.07 (m, 4H), 0.99 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.5, 158.7, 138.0, 132.5, 130.9, 129.5, 128.8, 128.4, 126.8, 126.4, 113.2, 87.3, 64.9, 60.7, 55.2, 47.8, 35.5, 26.4, 8.5; LRMS (ESI) *m/z* (relative intensity) 765.4 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{46}H_{57}NO_8]^+$, 765.4115, found 765.4119.



452

(*R,R,S,*S)-3,6-Diethyl-3,6-bis-(4(methoxybenzyloxy)-4,5-distyryloxepane-2,7-dione (452). To a stirring solution of dicarboxylic acid **450** (0.026 g, 0.038 mmol) in 1 mL of 1,2-dichloroethane at room temperature was added DMAP (19 mg, 0.15 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (0.011 g, 0.11 mmol), and EDC (0.022 g, 0.11 mmol). The solution was heated to 65 ºC and held at that temperature for 14 h, cooled to room temperature, and saturated $NaHCO_3$ (5 mL) was added. The resulting mixture was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a colorless oil. Purification of this oil by SiO_2 flash column chromatography (5 → 10% EtOAc/hexanes as eluent) gave cyclization

product **452** (0.015 g, 37%) as a colorless oil. IR (thin film) 1755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* =8.5 Hz, 4H), 7.22-7.13 (m, 6H), 7.01 (d, *J* = 8.6 Hz, 4H), 6.91-6.88 (m, 4H), 6.38 (d, *J* = 15.8 Hz, 2H), 6.30 (d, *J* = 15.3 Hz, 2H), 4.46 (d, *J* = 8.9 Hz, 2H), 4.35 (d, *J* = 9.0 Hz, 2H), 3.93 (s, 6H), 3.00 (d, *J* = 8.2 Hz, 2H), 2.10-1.93 (m, 4H), 0.88 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6, 159.6, 136.9, 131.0, 130.3, 129.4, 128.8, 128.3, 127.3, 126.3, 113.9, 84.4, 65.9, 55.3, 52.9, 23.9, 5.4; LRMS (ESI) *m/z* (relative intensity) 678.4 (50%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{42}H_{48}NO_7]^+$, 678.3431, found 678.3444.

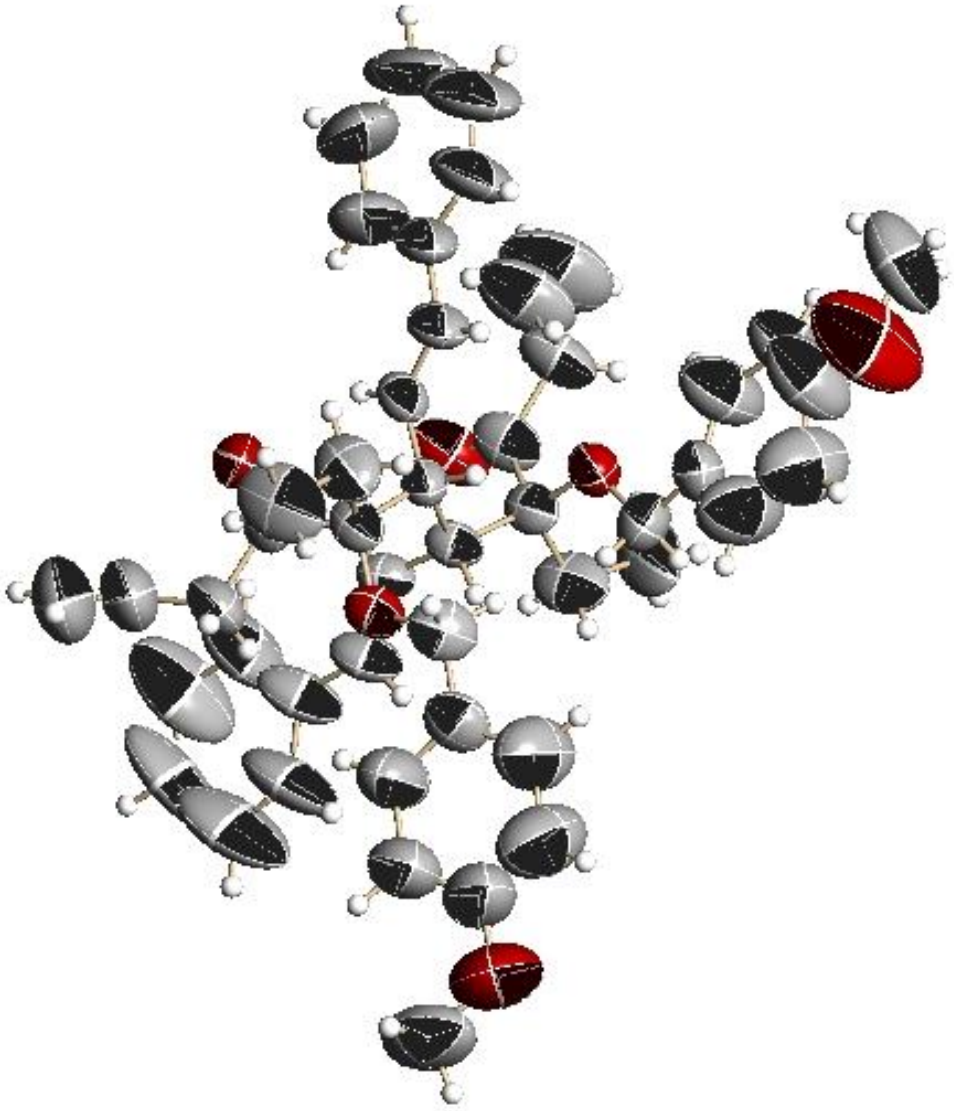


455

(*R*,*R*,*S*,*S*)-5,8-Diethyl-5,8-bis-(4-(methoxy)benzyloxy)-6,7-(distyryl)dodeca-1,11-diene-4,9-dione (455). To a stirring solution of freshly prepared allyllithium[87] (14.5 mL, 0.48 M in 2:1 THF/Et_2O, 6.7 mmol) at -78 ºC was added dropwise a solution of bis Weinreb amide **451** (1.28 g, 1.67 mmol) in 4 mL of THF. After stirring the mixture for 1 h at -78 ºC, saturated NH_4Cl (25 mL) was added. The resulting solution was partitioned between Et_2O and H_2O and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow oil. Purification of this oil by SiO_2 flash column chromatography (2 → 8% Et_2O/hexanes then 15% EtOAc/hexanes as eluent) gave bis allylation product **455** (0.83 g, 72%) as a yellow solid. A 77% yield was obtained on a 109 mg scale. A sample of this solid was recrystallized from EtOH to give an X-ray

quality crystal. mp 116-118 ºC; $[\alpha]^{20}_{D}$ = -58° (2.10, MeCN); IR (thin film) 1713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.4 Hz, 4H), 7.34 (t, *J* = 7.5 Hz, 4H), 7.28-7.25 (m, 6H), 6.95 (d, *J* = 8.5 Hz, 4H), 6.52 (dd, *J* = 15.8, 9.4 Hz, 2H), 6.43 (d, *J* = 15.8 Hz, 2H), 5.51-5.37 (m, 2H), 4.86 (d, *J* = 10.3 Hz, 2H), 4.67 (d, *J* = 17.2 Hz, 2H), 4.45 (d, *J* = 11.2 Hz, 2H), 4.41 (d, *J* = 11.2 Hz, 2H), 3.88 (s, 6H), 3.47 (dd, *J* = 19.0, 6.0 Hz, 2H), 3.39 (d, *J* = 9.3 Hz, 2H), 3.32 (dd, *J* = 19.0, 7.6 Hz, 2H), 2.00-1.91 (m, 2H), 1.80-1.71 (m, 2H), 0.76 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 158.8, 136.9, 133.4, 130.9, 130.2, 128.4, 127.6, 127.4, 127.3, 126.5, 117.8, 113.7, 88.5, 62.5, 55.2, 48.6, 47.1, 28.4, 7.6; LRMS (ESI) *m/z* (relative intensity) 744.5 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{42}H_{50}NO_8]^+$, 744.4264, found 744.4262.

X-ray Data for bis Allylation Product 455 (CCD# 867255)



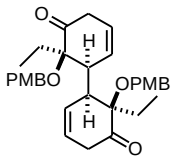
A colorless pyramid shaped crystal of bis allylation product **455** (C46 H54 O6) with approximate dimensions 0.11 x 0.16 x 0.17 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 298(2) K, on a

Bruker SMART APEX CCD area detector system equipped with a graphite monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3º in ω and an exposure time of 10 seconds/frame. The total data collection time was about 8 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Tetragonal unit cell yielded a total of 21947 reflections to a maximum θ angle of 28.42° (0.90 Å resolution), of which 5331 were independent, completeness = 99.5 %, R_{int} = 0.0795, R_{sig} = 0.1063 and 1917 were greater than 2σ(I). The final cell constants: a = 8.966(2)Å, b = 8.966(2)Å, c = 53.26(2)Å, α = 90°, β = 90°, γ = 90°, volume = 4282(2)$Å^3$, are based upon the refinement of the XYZ-centroids of 1195 reflections above 20σ(I) with 1.886° <θ <15.811°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.0506.

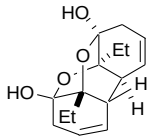
The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P4(3)2(1)2, with Z = 4 for the formula unit, C48 H54 O6. The final anisotropic full-matrix least-squares refinement on F^2 with 247 variables converged at R1 = 14.00 %, for the observed data and wR2 = 42.75 % for all data. The goodness-of-fit was 1.136. The largest peak on the final difference map was

0.512 $e^-/Å^3$ and the largest hole was -0.268 $e^-/Å^3$. Based on the final model, the calculated density of the crystal is 1.128 g/cm^3 and F(000) amounts to 1560 electrons.



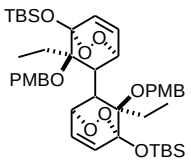
456

(*R*,*R*,*S*,*S*)-2,2'-Diethyl-2,2'-bis-(4-(methoxy)benzyloxy)-bicyclohexyl-5,5'-diene-3,3'-dione (456). To a freeze-pump-thawed solution of tetraene **455** (0.147 g, 0.202 mmol) in 10 mL of toluene in a sealable tube was added Grubbs II catalyst[83] (0.069 g, 0.081 mmol) and the tube was sealed. After freeze-pump-thawing the solution again, the reaction mixture was heated at 100 ºC. After heating at this temperature for 4 h, the crude solution was cooled to room temperature and concentrated *in vacuo* to give a green oil. Purification of this oil by SiO_2 flash column chromatography (10 → 30% EtOAc/hexanes as eluent) gave bicycle **456** (0.067 g, 64%) as a green solid. mp 135-137 ºC; $[\alpha]^{20}_D$ = -100° (1.00, MeCN); IR (thin film) 1719 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.6 Hz, 4H), 6.93 (d, *J* = 8.6 Hz, 4H), 5.76-5.70 (m, 4H), 4.81 (d, *J* = 10.8 Hz, 2H), 4.41 (d, *J* = 10.9 Hz, 2H), 3.85 (s, 6H), 3.41 (d, *J* = 3.6 Hz, 2H), 2.87 (s, 4H), 1.99-1.85 (m, 4H), 0.82 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.8, 158.9,130.9, 128.3, 126.8, 126.3, 113.7, 83.7, 64.3, 55.2, 45.3, 40.7, 24.8, 7.1; (ESI) *m/z* (relative intensity) 536.4 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{32}H_{42}NO_6]^+$, 536.3012, found 536.3008.



458

Pentacycic Bis Hemiacetal Diene (458). To a solution of bicycle **456** (0.022 g, 0.042 mmol) in 1 mL of CH_2Cl_2 at 0 ºC was added TFA (32 μL, 0.42 mmol). After stirring for 15 min at 0 ºC, the reaction mixture was concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (10 → 15 % EtOAc/hexanes as eluent) gave pentacycic bis hemiacetal diene **458** as light yellow solid (8 mg, 70%). $[\alpha]^{20}_D$ = -64° (0.44, MeCN); IR (thin film) 3413 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (m, 2H), 5.47 (m, 2H), 3.84 (s, 2H), 2.48-2.31 (m, 6H), 1.83 (m, 2H), 1.46 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.5, 123.0, 97.9, 73.4, 41.2, 38.2, 23.8, 6.9; LRMS (ESI) *m/z* (relative intensity) 261.1 (100%, M – OH^-); HRMS (ESI) *m/z* calcd for $[C_{16}H_{21}O_3]^-$, 261.1491, found 261.1474.



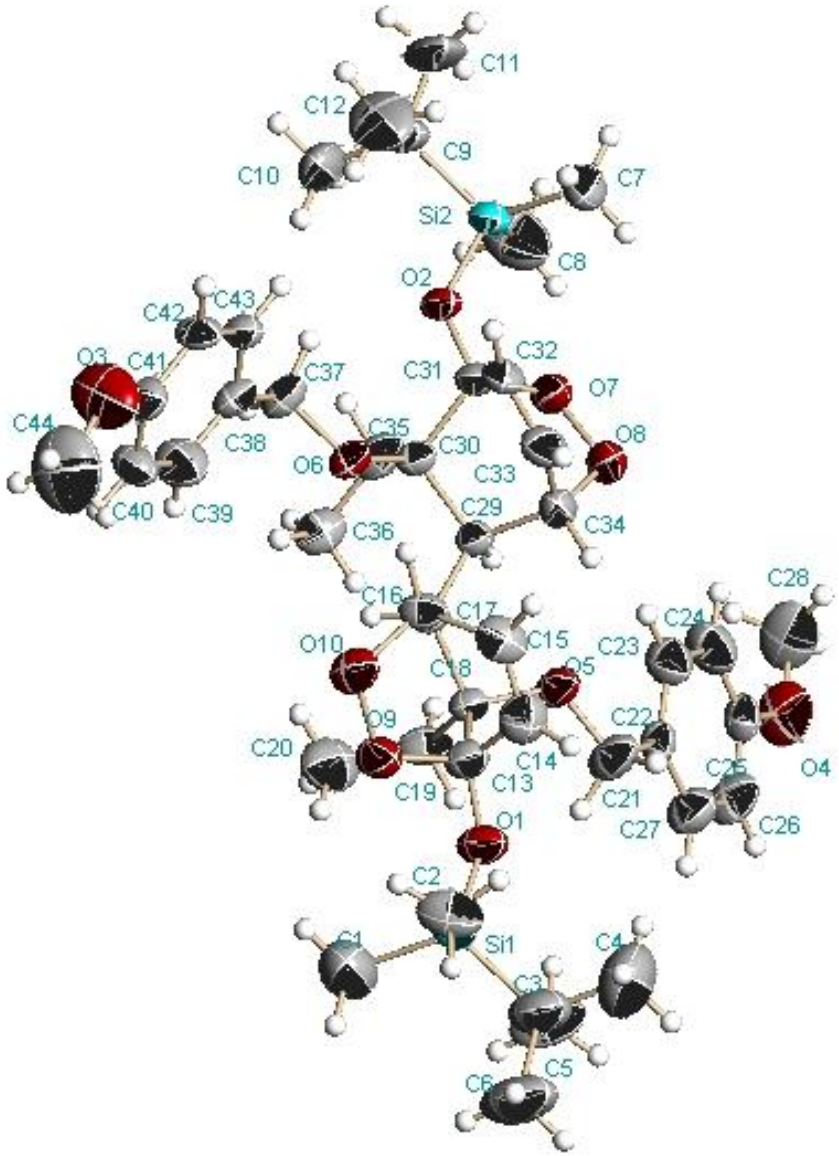
460

1,1'-Bis-(*tert*-butyl-(dimethyl)silanyloxy)-6,6'-diethyl-6,6'-bis-(4-methoxy)benzyloxy)-[5,5']bi[2,3-dioxabicyclo[2.2.2]octyl]-7,7'-diene (460). To a stirring solution of KHMDS (848 μL, 0.50 M in toluene, 0.42 mmol) in 800 μL of THF at -78 ºC was added dropwise a solution of bicycle **456** (0.055 g, 0.11 mmol) in 400 μL of THF. After 40 min at -78 ºC, TBSOTf (98 μL, 0.42 mmol) was added. After stirring the

mixture for 2 h at -78 ºC, saturated $NaHCO_3$ (10 mL) solution was added. The resulting solution was partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give TBS dienol ether **459** as a crude yellow oil which was used without further purification.

To a solution of the crude TBS dienol ether **459** in 10 mL of CH_2Cl_2 at -78 ºC was added tetraphenylporphyrin (2 mg, 0.003 mmol). The sample was irradiated with a 275W sun lamp while bubbling O_2 through the solution. After 45 min irradiating at -78 ºC, the reaction mixture was concentrated *in vacuo* to give a pink oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 2 → 20% Et_2O/hexanes as eluent) gave bis endoperoxide **460** as a fluffy pink solid (0.057 g, 67% over 2 steps). A sample of this solid was crystallized in 1:1 hexanes/THF to obtain colorless X-ray quality crystals. mp. 120-122 ºC; $[\alpha]^{20}_D$ = +94° (1.80, MeCN); IR (thin film) 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.4 Hz, 4H), 6.88 (d, *J* = 8.5 Hz, 4H), 6.58 (dd, *J* = 8.6, 5.6 Hz, 2H), 6.38 (d, *J* = 8.3 Hz, 2H), 4.81 (d, *J* = 6.1 Hz, 2H), 4.64 (d, *J* = 11.2 Hz, 2H), 4.53 (d, *J* = 11.3 Hz, 2H), 3.81 (s, 6H), 3.04 (br s, 2H), 2.19-2.16 (m, 4H), 1.18 (t, *J* = 7.3 Hz, 6H), 1.01 (s, 18H), 0.24 (s, 12H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.6, 135.1, 131.8, 131.2, 127.8, 113.8, 103.5, 82.4, 74.2, 65.8, 55.2, 43.3, 25.7, 21.7, 18.0, 8.5, -2.4, -3.3; LRMS (ESI) *m/z* (relative intensity) 811.6 (100%, M + H^+); HRMS (ESI) *m/z* calcd for $[C_{44}H_{67}O_{10}Si_2]^+$, 811.4273, found 811.4238.

X-ray Data for bis Endoperoxide 460 (CCD# 894557)

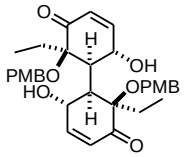


A colorless block shaped crystal of bis endoperoxide **460** (C44 H66 O10 Si2) with approximate dimensions 0.15 x 0.18 x 0.23 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured at 298(2) K, on a Bruker SMART APEX CCD area detector system equipped with a graphite

monochromator and a MoKα fine-focus sealed tube (λ = 0.71073Å) operated at 1600 watts power (50 kV, 32 mA). The detector was placed at a distance of 5.8 cm from the crystal.

A total of 1850 frames were collected with a scan width of 0.3º in ω and an exposure time of 30 seconds/frame. The total data collection time was about 17 hours. The frames were integrated with the Bruker SAINT software package using a narrow-frame integration algorithm. The integration of the data using a Monoclinic unit cell yielded a total of 22112 reflections to a maximum θ angle of 28.35° (0.90 Å resolution), of which 10354 were independent, completeness = 99.2%, R_{int} = 0.0361, R_{sig} = 0.0596 and 7105 were greater than 2σ(I). The final cell constants: a = 7.2313(12)Å, b = 21.911(4)Å, c = 14.668(2)Å, α = 90°, β = 94.760(3)°, γ = 90°, volume = 2316.0(7)$Å^3$, are based upon the refinement of the XYZ-centroids of 4621 reflections above 20σ(I) with 2.323° <θ <21.984°. Analysis of the data showed negligible decay during data collection. Data were corrected for absorption effects using the multiscan technique (SADABS). The ratio of minimum to maximum apparent transmission was 0.6951.

The structure was solved and refined using the Bruker SHELXTL (Version 6.1) Software Package, using the space group P2(1), with Z = 2 for the formula unit, C44 H66 O10 Si2. The final anisotropic full-matrix least-squares refinement on F^2 with 519 variables converged at R1 = 7.39%, for the observed data and wR2 = 20.81% for all data. The goodness-of-fit was 1.013. The largest peak on the final difference map was 1.346 $e^-/Å^3$ and the largest hole was -0.534 $e^-/Å^3$. Based on the final model, the calculated density of the crystal is 1.163 g/cm^3 and F(000) amounts to 876 electrons.

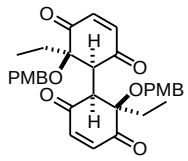


462

2,2'-Diethyl-6,6'-dihydroxy-2,2'-bis-(4(methoxy)benzyloxy)bicyclohexyl-4,4'-diene-3,3'-dione (462). To a stirring solution of bis endoperoxide **460** (0.036 g, 0.045 mmol) in 1 mL of MeCN at 0 ºC was added dropwise fluorosilicic acid (117 μL, 20-25 wt% in H_2O, 0.20 mmol). After stirring the mixture for 40 min at 0 ºC, H_2O (1 mL) was added. The resulting solution was partitioned between EtOAc (10 mL) and H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give crude bis peroxide **461** as a yellow oil which was used without further purification.

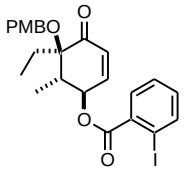
To a stirring solution of the crude bis peroxide **461** in 1 mL of CH_2Cl_2 at 0 ºC was added PPh_3 (0.035 g, 0.13 mmol). After stirring for 30 min at 0 ºC, the crude mixture was concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 15 → 30% EtOAc/hexanes as eluent) gave lomaiviticinone A core **462** as a yellow oil (0.014 g, 57% over 2 steps, 4:1 inseparable mix diast.). $[\alpha]^{20}_D$ = +131° (6.20, MeCN); IR (thin film) 3425, 1672 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$, major isomer) δ 7.08 (d, *J* = 8.5 Hz, 4H), 6.97 (d, *J* = 10.3 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 4H), 6.01 (d, *J* = 10.2 Hz, 2H), 5.53 (s, 2H), 4.76 (d, *J* = 8.0 Hz, 2H), 4.41 (d, *J* = 10.3 Hz, 2H), 4.12 (d, *J* = 10.2 Hz, 2H), 3.77 (s, 6H), 2.71 (d, *J* = 8.4 Hz, 2H), 2.31 (m, 2H), 1.89 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (90 MHz, $CDCl_3$, major isomer) δ 195.3, 159.6, 153.9, 129.8, 127.7, 124.6, 114.0, 83.8, 66.7, 64.8, 55.2,

49.6, 21.4, 8.7; LRMS (ESI) *m/z* (relative intensity) 573.2 (80%, M + Na^+); HRMS (ESI) *m/z* calcd for $[C_{32}H_{38}O_8Na]^+$, 573.2464, found 573.2449.



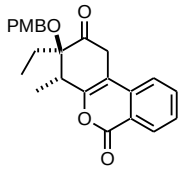
463

6,6'-Diethyl-6,6'-bis-(4-methoxybenzyloxy)-bicyclohexyl-3,3'-diene-2,5,2',5'-tetraone (463). To a solution of crude bis peroxide **460** (0.0050 g, 0.0085 mmol) in 500 μL of acetic anhydride at room temperature was added pyridine (2 uL, 0.03 mmol). After 14 h at room temperature, the reaction mixture was concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (gradient, 10 → 30% EtOAc/hexanes as eluent) gave enedione **463** as a light yellow oil (0.014 g, 49% from **460**). IR (thin film) 1691, 1690 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.6 Hz, 4H), 6.87 (d, *J* = 8.5 Hz, 4H), 6.27 (br s, 4H), 4.88 (m, 2H), 4.43 (d, *J* = 10.5 Hz, 2H), 3.84 (s, 6H), 3.79 (s, 2H), 2.08 (m, 2H), 1.94 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 197.5 (two signals), 159.1, 139.2 (two signals), 129.9, 129.6, 113.5, 93.8, 82.2, 68.0, 55.2, 25.6, 7.7; LRMS (ESI) *m/z* (relative intensity) 564.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{32}H_{38}NO_8]^+$, 564.2597, found 564.2595.



474

2-Iodobenzoic Acid 5-Ethyl-5-(4-methoxybenzyloxy)-6-methyl-4-oxocyclohex-2-enyl Ester (474). To a stirring solution of freshly prepared 2-iodobenzoyl chloride (**473**)[74] (0.090 g, 0.34 mmol) in 800 μL of pyridine at 0 ºC was added a solution of alcohol **427** (0.020 g, 0.068 mmol) in 200 μL of pyridine. After stirring for 1.5 h at 0 ºC, the reaction mixture was allowed to warm to room temperature. After stirring for an additional 14 h at room temperature, the crude mixture was concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (10% EtOAc/hexanes as eluent) gave ester **474** as a white solid (0.027 g, 76%). mp. 132-133 ºC; IR (thin film) 1731, 1684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.9 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.42 (m, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.22 (td, *J* = 7.6, 1.6 Hz, 1H), 6.90 (d, *J* = 8.7, 2H), 6.89 (m, 1H), 6.15 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.80 (dt, *J* = 9.3, 2.0 Hz, 1H), 4.45 (d, *J* = 10.0 Hz, 1H), 4.24 (d, *J* = 10.0 Hz, 1H), 3.82 (s, 3H), 2.96 (m, 1H), 1.98 (m, 1H), 1.71 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 165.9, 159.0, 145.0, 141.5, 134.2, 133.0, 130.9, 130.5, 129.9, 129.2, 128.0, 113.6, 94.2, 83.8, 75.0, 65.1, 55.2, 41.1, 24.0, 10.9, 7.0; LRMS (ESI) *m/z* (relative intensity) 538.1 (10%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{24}H_{39}NO_5I]^+$, 538.1091, found 538.1093.



475

3-Ethyl-3-(4-methoxybenzyloxy)-4-methyl-3,4-dihydro-1H-benzo[c]chromene-2,6-dione (475). To a solution of aryl iodide **474** (0.020 g, 0.038 mmol) in 1 mL of DMF in a sealable tube was added $Pd(OAc)_2$ (1 mg, 0.004 mmol), Bu_4NBr (5 mg, 0.02 mmol), Et_3N (54 μL, 0.38 mmol) and 8 μL of MeOH. The tube was sealed and the reaction mixture was warmed to 120 ºC. After stirring for 14 h at 120 ºC, the reaction mixture was cooled to room temperature, filtered through Celite and concentrated *in vacuo* to give a crude yellow oil. Purification of this oil by SiO_2 flash column chromatography (10% EtOAc/hexanes as eluent) gave cyclization product **475** as a yellow oil (8 mg, 56%). IR (thin film) 1721, 1719 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.37 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.19 (d, *J* = 11.2 Hz, 1H), 3.77 (s, 3H), 3.57 (d, *J* = 19.2 Hz, 1H), 3.35 (d, *J* = 19.4 Hz, 1H), 3.31 (q, *J* = 7.5 Hz, 1H), 2.17 (m, 1H), 1.80 (m, 1H), 1.18 (d, *J* = 7.3 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H) ; ^{13}C NMR (90 MHz, $CDCl_3$) δ 207.4, 162.5, 159.2, 153.4, 136.6, 135.0, 130.2, 129.6, 128.5, 127.0, 121.4, 120.3, 113.8, 105.1, 84.6, 66.1, 55.3, 42.3, 36.1, 18.8, 14.9, 5.9; LRMS (ESI) *m/z* (relative intensity) 410.2 (100%, M + NH_4^+); HRMS (ESI) *m/z* calcd for $[C_{24}H_{28}NO_5]^+$, 410.1967, found 410.1980.

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2) Feldman, K. S.; **Selfridge, B. R.** *Tetrahedron Lett.* **2012**, 825-828.

1) Feldman, K. S; **Selfridge, B. R.** *Heterocycles* **2010**, 117-143.