

**Total Synthesis of (+)-Dactylolide. Studies on the Cascade Cyclization Reactions of
Epoxides/Polyepoxides Initiated by Single Electron Transfer**

by

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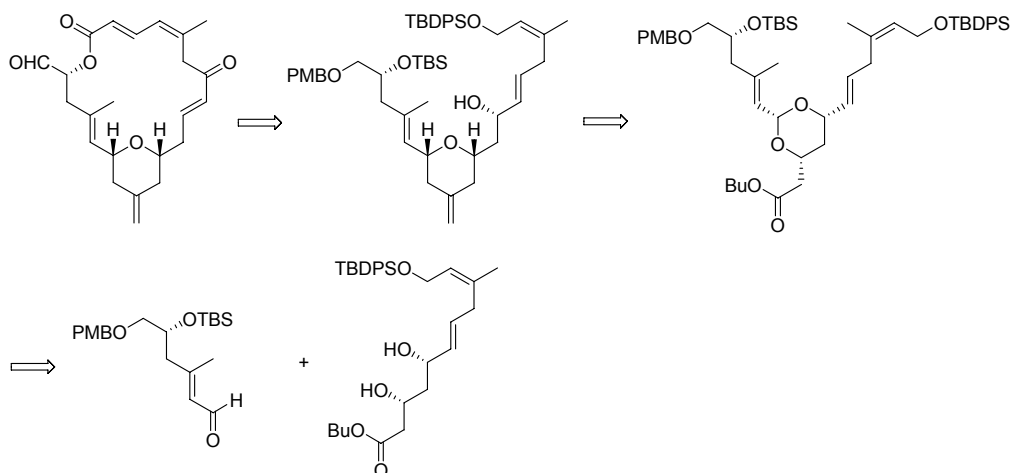
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Shuangyi Wan, M.S.

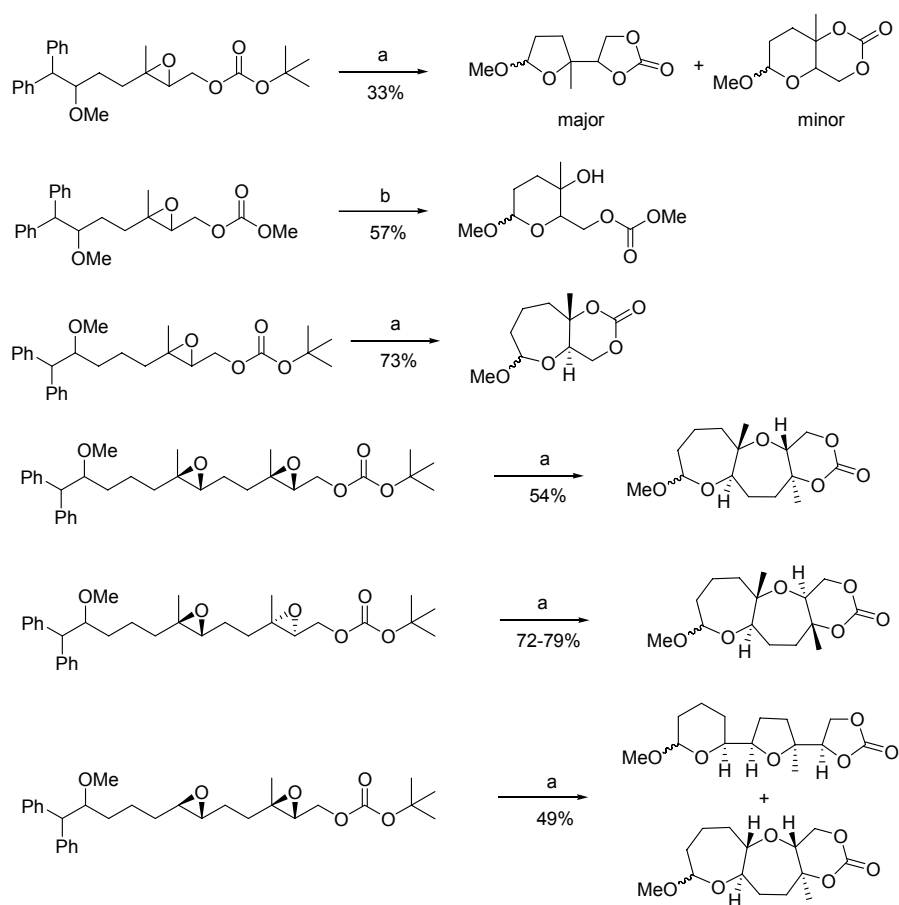
University of Pittsburgh, 2006

The total synthesis of the marine macrolactone (+)-dactylolide was achieved in a highly convergent and efficient way (Scheme I). The route involves the coupling of two functionalized fragments of the molecule, an α,β -unsaturated aldehyde and a 1,3-*syn*-diol, to form a cyclic α,β -unsaturated cyclic acetal. Both enantiopure fragments arise from asymmetric vinylogous Mukaiyama aldol reactions. The key transformations in this synthesis include a sequential Peterson olefination/Prins cyclization reaction to construct the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core efficiently and stereoselectively, a Mislow-Evans selenoxide-selenate [2,3] sigmatropic rearrangement to transpose allylic alcohol transposition and an intramolecular Horner-Emmons macrocyclization.



Scheme I. Retrosynthetic analysis of (+)-dactylolide

A systematic study on the cascade cyclizations of epoxides/polyepoxides initiated by single electron transfer has been carried out (Scheme II). Four monoepoxides and six diepoxides were tested. The results showed that the bicyclo[3.1.0] epoxonium ion intermediates formed in the cyclization favor 5-*exo*-cyclization in the nonpolar solvent (1,2-dichloroethane) while in the polar solvent (CH₃CN), they prefer 6-*endo*-selectivity. However, the bicyclo[4.1.0] epoxonium ion intermediates usually give 7-*endo* regiochemical selectivity in the presence of substitution-induced bias. However, without the substituent effect, 6-*exo* and 7-*endo*-cyclizations are two competitive pathways.



Reagents and conditions: (a) *hν*, O₂, Na₂S₂O₃, NaOAc, MS, NMQPF₆ (10 mol%), DCE/PhMe (5:1). (b) *hν*, O₂, Na₂S₂O₃, NaOAc, MS, NMQPF₆ (10 mol%), CH₃CN/PhMe (5:1).

Scheme II. Cyclization reaction of epoxides

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1.0 TOTAL SYNTHESIS OF (+)-DACTYLOLIDE

1.1 INTRODUCTION

(+)-Dactylolide (**1**, Figure 1.1), a cytotoxic marine macrolide, was isolated from the Vanauta sponge *Dactylospongia* sp. by Riccio and co-workers in 2001.¹ Spectroscopic analysis showed that (+)-dactylolide has a highly unsaturated 20-membered macrolactone structure with three stereogenic centers and an unusual α -acyloxyaldehyde, and the core of this molecule is a 2,6-*cis*-disubstituted-4-methylenetetrahydropyran. The relative stereochemistry at C11 and C15 was established in the original paper. However, the absolute configuration of the (+)-dactylolide stereocenters was not determined until the first total synthesis of (+)-dactylolide was completed by the Smith group in 2001.^{2,3}

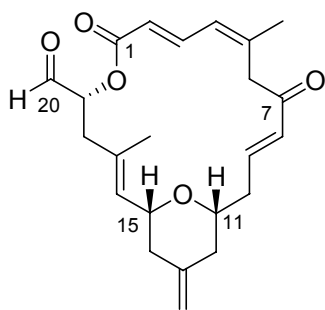


Figure 1.1 (+)-Dactylolide (**1**)

The cytotoxicity assay revealed that (+)-dactylolide has moderate activity against L1210 (lymphatic leukaemia of mice) and SK-OV-3 (carcinoma of the ovaries) tumor cells, causing 63% and 40% inhibition at 8.3 μ M, respectively.

1.2 TOTAL SYNTHESIS OF DACTYLOLIDE IN OTHER GROUPS

In 2001, Smith completed the first total synthesis of **1** soon after the discovery of this molecule, featuring the Petasis-Ferrier rearrangement⁴ to form the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core and Horner-Emmons macrocyclization⁵ as the two key steps in the longest linear sequence.²

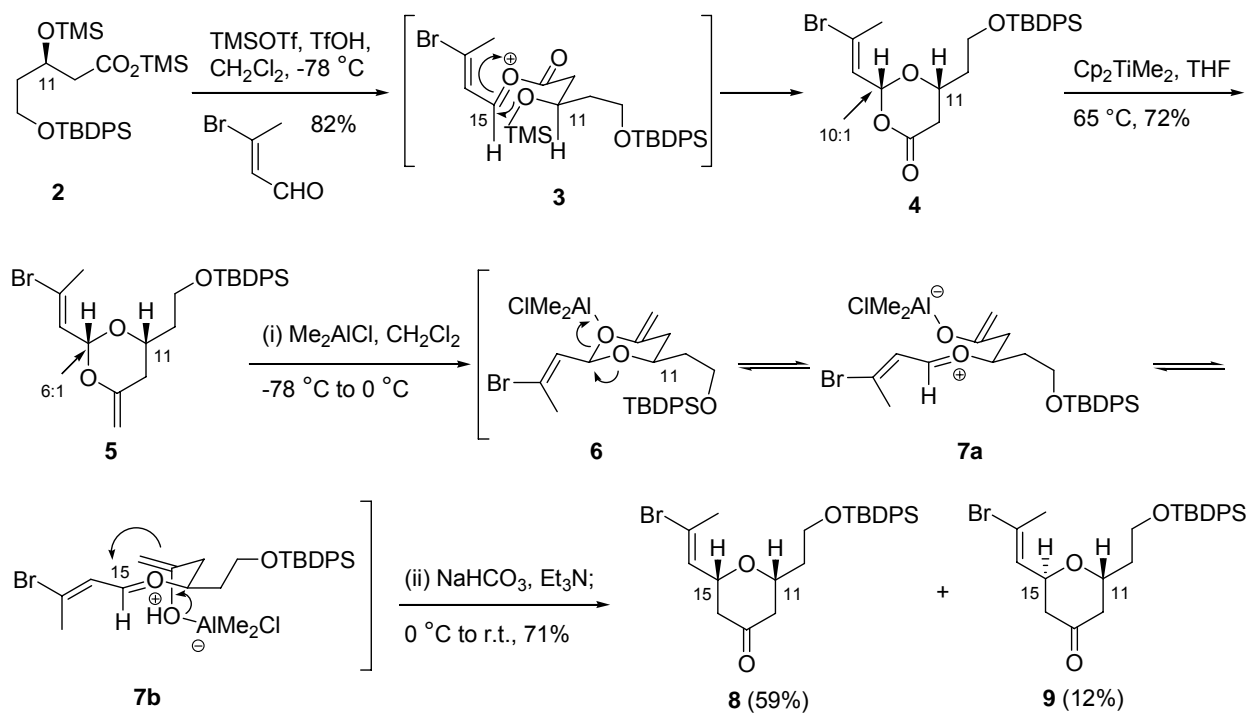


Figure 1.2 Petasis-Ferrier rearrangement

In order to get the 2,6-disubstituted tetrahydropyran core, the Petasis-Ferrier rearrangement⁴ was effectively utilized (Figure 1.2). Condensation of TMS ether **2**, which could be prepared from a known aldehyde in 5 steps using a Brown asymmetric allylation⁶ to set the C11 stereocenter in the final product, with 2-(*E*)-3-bromobut-2-enal afforded a 10:1 inseparable diastereomer of the dioxanone **4**. Reaction of **4** with Petasis-Tebbe reagent⁷ gave the enol ethers **5** as a 6:1 inseparable mixture. Treatment of **5** with dimethylaluminum chloride at -78 °C resulted in the Petasis-Ferrier rearrangement and provided the desired *cis*-pyranone **8** in 59% yield, together with a separable *trans*-pyranone **9** in 12% yield.

The Wittig reaction of pyranone **8** completed the tetrahydropyran core of the molecule (Figure 1.3). Silyl group removal, introduction of the sulfide by Mitsunobu reaction⁸ and oxidation of the sulfide to the sulfone afforded the Julia-Kocienski olefination⁹ substrate **13**.

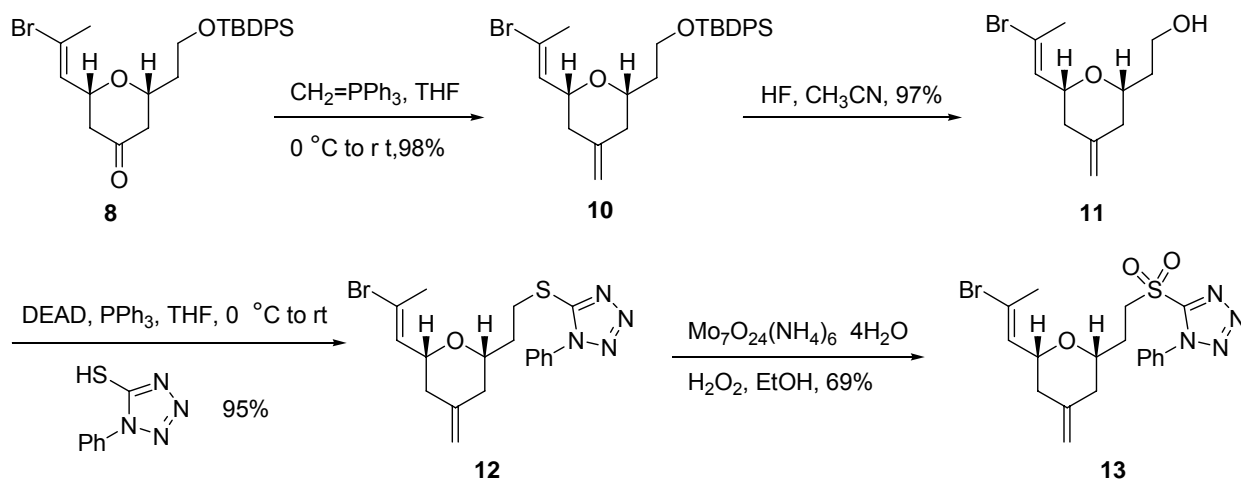


Figure 1.3 Completion of advanced intermediate **13**

Condensation of sulfone **13** with aldehyde **14** gave advanced intermediate **15** in excellent yield (Figure 1.4). Coupling of higher order cuprate derived from bromide **15** with (*R*)-2-((3,4-

dimethoxybenzyloxy)methyl)oxirane provided the secondary alcohol in an unoptimized yield of 40%. Acylation of the secondary alcohol with diethylphosphonoacetic acid provided phosphonoester **16** in excellent yield. Selective TBS removal of the primary silyl ether, Dess-Martin oxidation of the resulting primary alcohol and Horner-Emmons macrocyclization provided macrocycle **17** in good yield. Subsequently, the two successive deprotection and oxidation steps afforded the (+)-dactylolide (**1**). Through the total synthesis of **1**, Smith assigned the full stereochemistries of this molecule.^{2, 3} However, the discrepancy in optical rotation between natural ($[\alpha]_{\text{D}} = +30^{\circ}$, c 1.0, MeOH) and synthetic ($[\alpha]_{\text{D}} = +235^{\circ}$, c 0.52, MeOH) dactylolide precludes a firm conclusion with regard to its absolute stereochemistry.

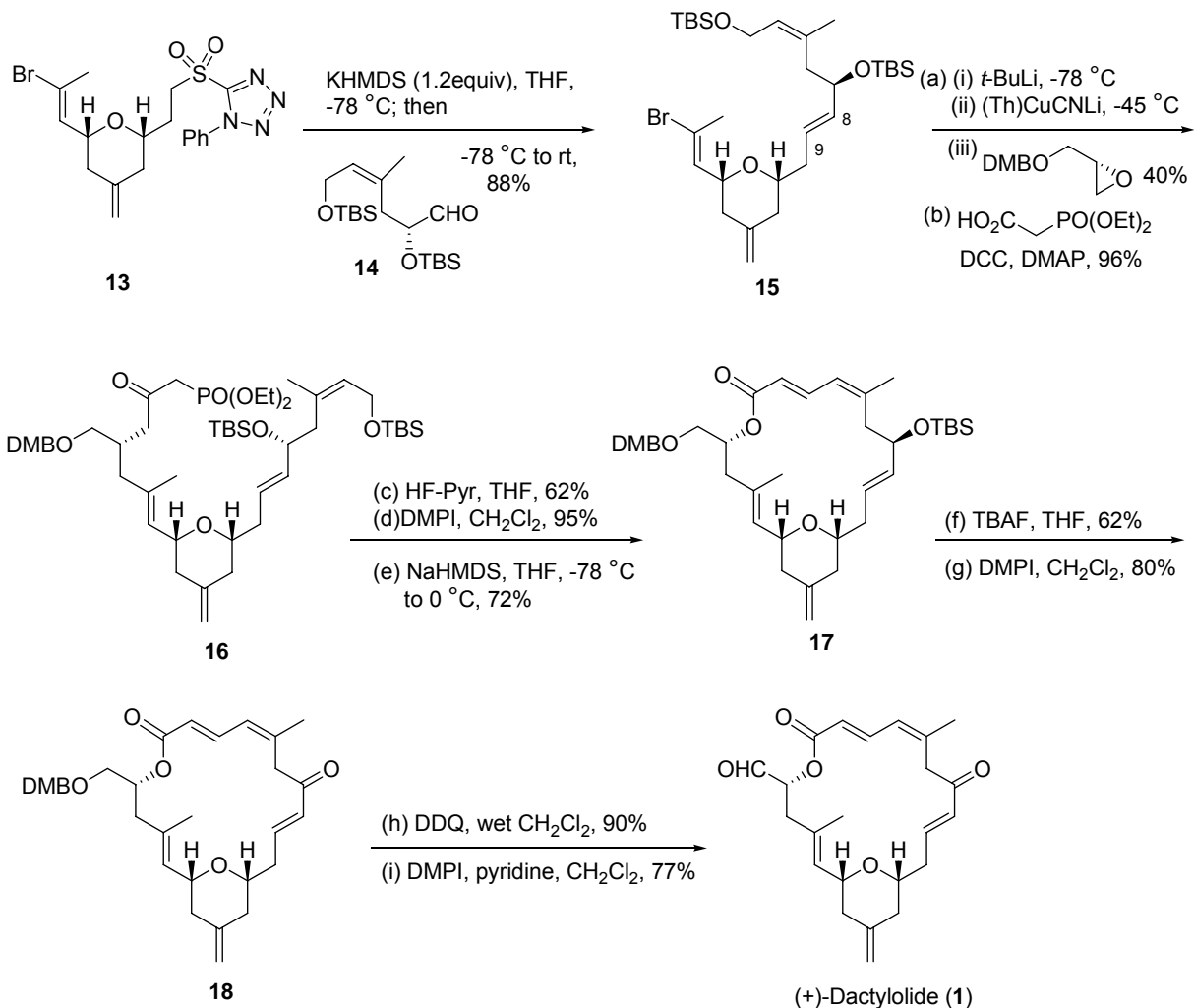


Figure 1.4 Completion of (+)-dactylolide

Recently, Hoyer reported the total synthesis of (-)-dactylolide **29**. The key transformations involved a Sakurai cyclization to construct the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core and an unprecedented macrolactonization through a Lewis acid-catalyzed epoxide opening by a carboxylic acid.¹⁰

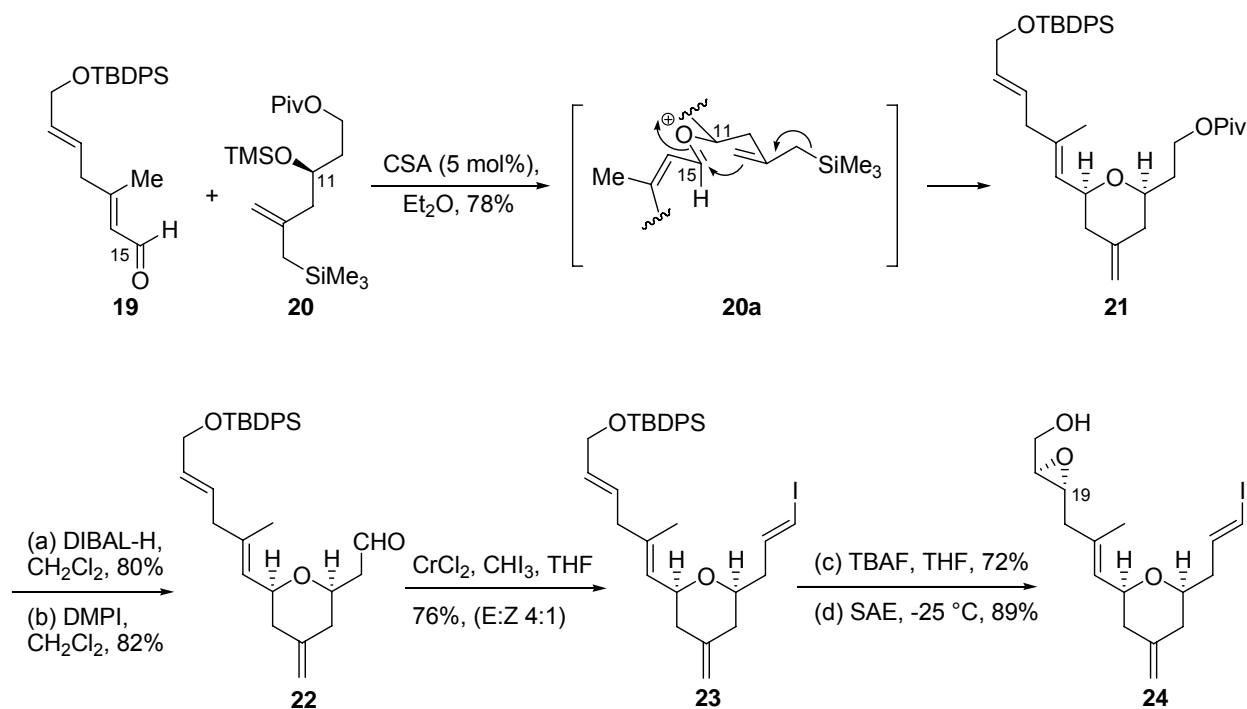


Figure 1.5 Hoyer's Sakurai cyclization to construct the (-)-dactylolide core

The synthesis of the 2,6-*cis*-disubstituted-4-methylene-tetrahydropyran core is shown in Figure 1.5. Condensation of enal **19** with allylic silane **20** (prepared through copper-catalyzed addition of the Grignard reagent generated from 2-bromo-3-trimethylsilylpropene to the nonracemic terminal epoxide generated from (*S*)-malic acid followed by protection of the resulting secondary alcohol as its TMS ether¹¹) catalyzed by camphorsulfonic acid furnished *cis*-**21** as a single diastereomer in 78% yield. Removal of the pivalate and Dess-Martin oxidation gave aldehyde **22**, which was converted into vinyl iodide **23** in 4:1 (*E/Z*) ratio. Removal of the TBDPS group with TBAF provided the allylic alcohol and it also benefited the removal of the minor *Z*-isomer which underwent E2-elimination to form the separable alkyne. Sharpless asymmetric epoxidation¹² of the allylic alcohol set the C19 stereocenter.

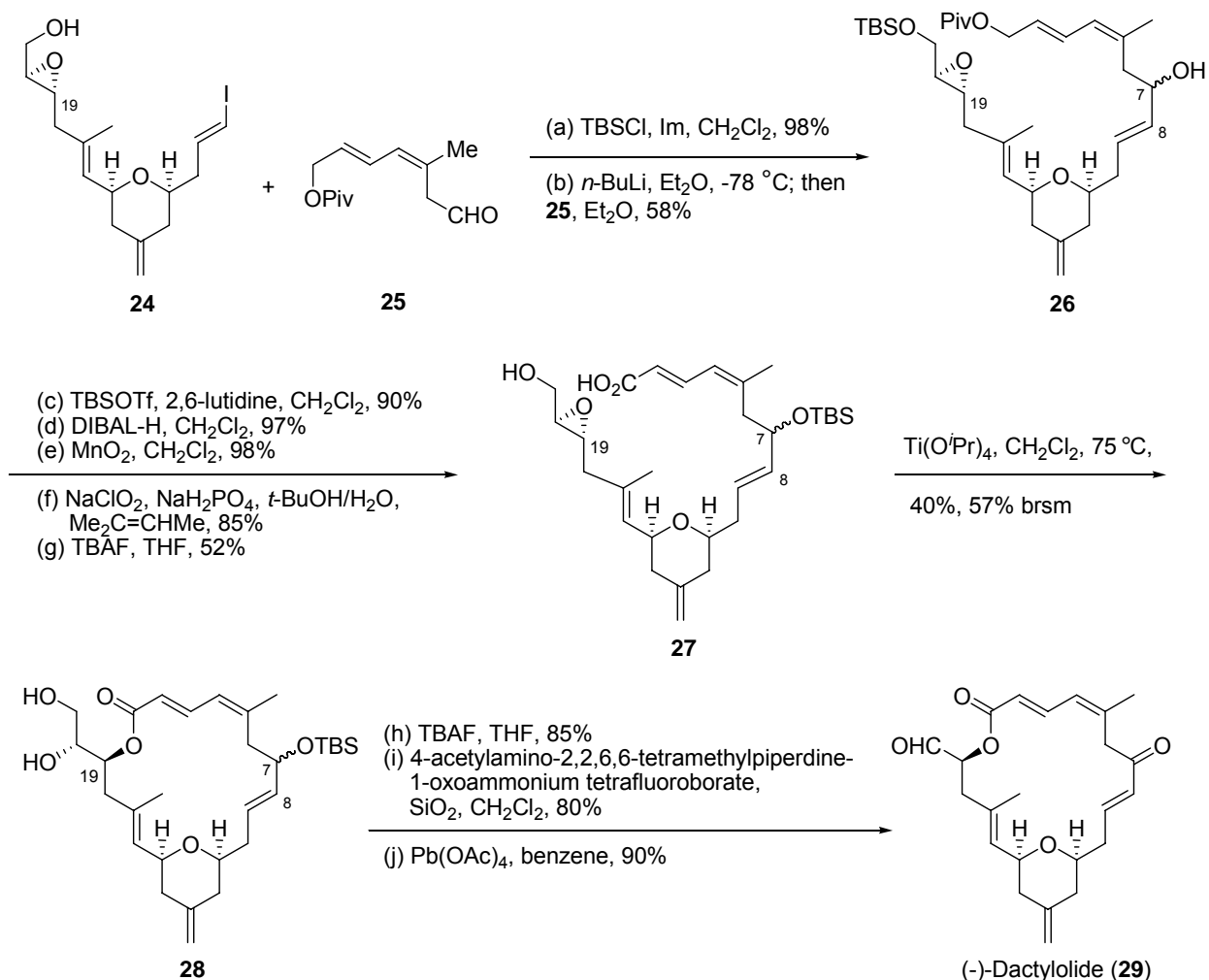
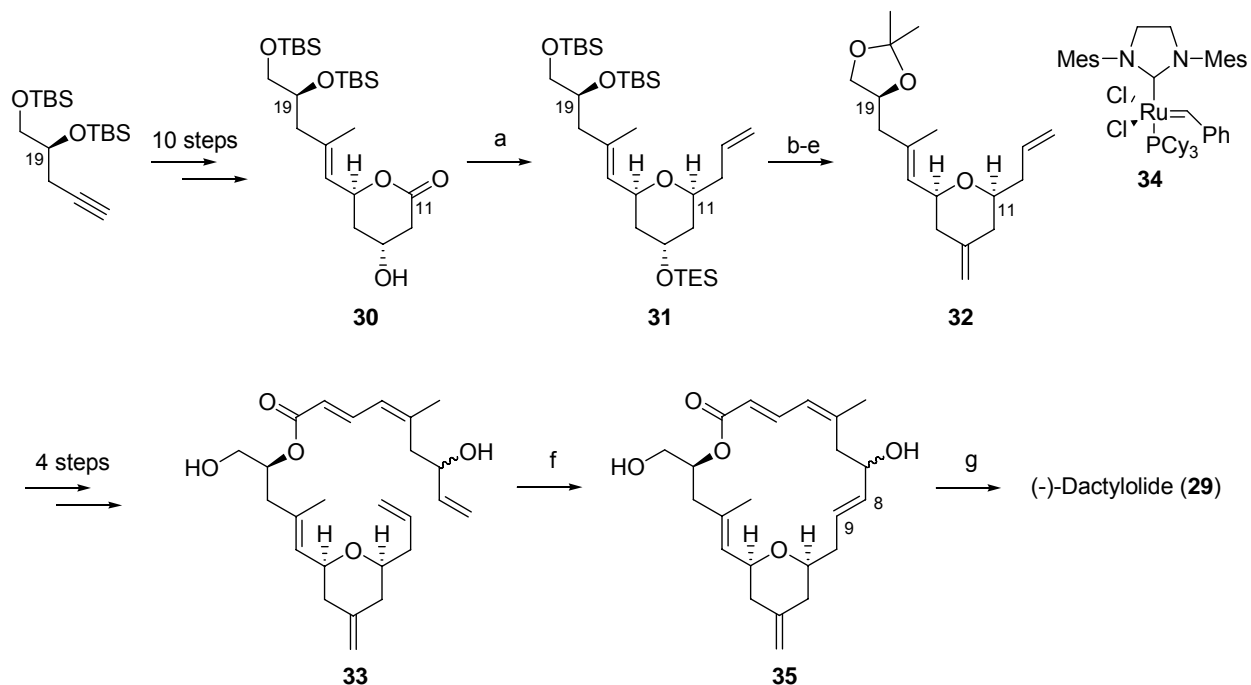


Figure 1.6 Completion of (-)-dactylolide (**29**)

Protection of epoxy alcohol **24** as a TBS ether followed by the addition of the vinylolithium species derived from the corresponding vinyl iodide to the C1-C7 **25** aldehyde provided carbinol **26** as a 1:1 mixture of epimers (Figure 1.6). Protection of the nascent secondary alcohol with TBS group, the pivalate removal, oxidation of the C1 primary alcohol to the carboxylic acid and desilylation of the C21 primary TBS ether provided epoxy-acid **27**, the substrate for the macrolactonization. Subjection of epoxy-acid **27** in CH₂Cl₂ (~2 mM) to Ti(O-*i*-Pr)₄ furnished macrolactone **28** in 40% yield as a 1:1 mixture of C7 epimers with recovered

starting material in 30% yield. TBS removal followed by selective oxidation of the allylic alcohol in the presence of the diol with 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate gave the enone diol in good yield. Finally, the cleavage of the diol with $\text{Pb}(\text{OAc})_4$ furnished (-)-dactylolide **29** ($[\alpha]_D = -128^\circ$, c 0.39, MeOH) in excellent yield.¹⁰

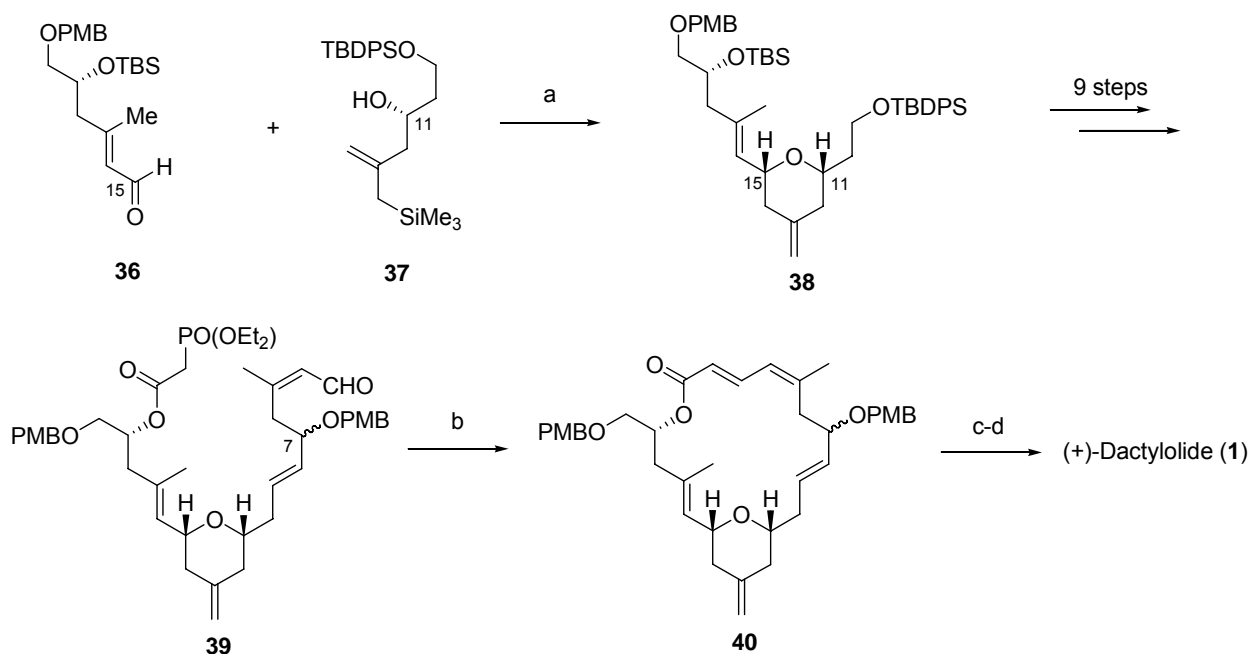


Reagents: (a) allylMgBr, Et_2O , -78°C ; then Et_3SiH , TFA, CH_2Cl_2 , -78°C to -40°C , 76%. (b) TBAF, THF. (c) 2,2-dimethoxypropane, TsOH, CH_2Cl_2 , 81%, two steps. (d) PCC, NaOAc, CH_2Cl_2 , 74%. (e) Ph_3PMeBr , $n\text{-BuLi}$, THF, -78°C , 15 min, then 0°C , 15 min, rt, 78%. (f) Grubbs' II catalyst **34** (10 mol%), CH_2Cl_2 (1mM), 93%. (g) DMPI, CH_2Cl_2 , 0°C to rt, 90%.

Figure 1.7 Key features in Jennings' synthesis of (-)-dactylolide (**29**)

Most recently, Jennings¹³ and Keck¹⁴ reported the total synthesis of (-)-dactylolide and (+)-dactylolide, respectively, with key transformations outlined below. In Jennings' synthesis, nucleophilic addition of allylmagnesium bromide to β -hydroxy lactone **30** gave the lactol, which was converted into the oxocarbenium ion promoted by trifluoroacetic anhydride and consequently diastereoselectively reduced by Et_3SiH to *cis*-**31** in 76% yield. (Figure 1.7)

Removal of the three silyl groups with TBAF, reprotection of the 1,2-diol as the acetonide, oxidation of the free hydroxy group to the ketone with PCC and the ensuing standard Wittig reaction furnished 2,6-*cis*-disubstituted-4-methylenetetrahydropyran **32**, the core of (-)-dactylolide. Finally, ring-closing olefin metathesis of **33**, a parallel of Hoyer's approach¹⁰ to zampanolide, was utilized to afford macrocycle **35** as a single olefinic isomer in excellent yield. Double oxidation of diol **35** with Dess-Martin periodinane removed the C7 stereogenic center and provided (-)-dactylolide ($[\alpha]_D = -136^\circ$, c 1.2, MeOH).



Reagents: (a) TMSOTf, Et₂O, -78 °C; then DIPEA, 85%. (b) NaHMDS, THF, -78 to 0 °C, 60%. (c) DDQ, wet CH₂Cl₂. (d) DMPI, pyr, CH₂Cl₂, 76%, two steps.

Figure 1.8 Key transformations in Keck's synthesis of (+)-dactylolide (**1**)

Keck employed a strategy similar to Hoyer's access¹⁰ to 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core. Unification of aldehyde **36** and hydroxyl allylsilane **37** with promotion of Lewis acid TMSOTf provided the diastereomerically pure *cis*-**38** in 85% yield.

(Figure 1.8) At the final stage, an intramolecular Horner-Emmons macrocyclization of **39** generated the 20-membered macrocycle **40** in modest yield. Removal of the two PMB groups followed by Dess-Martin oxidation of the resulting diol afforded (+)-dactylolide ($[\alpha]_D = +134^\circ$, c 0.065, MeOH) in 76% yield over two steps.

All the four groups above used convergent strategies to access the dactylolide. In the construction of the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core, Smith, Hoye and Keck used asymmetric induction based on what would ultimately become the C11 stereocenter to set the C15 stereocenter. Hoye and Keck's pyran annulation was ideally stereoselective to form the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran exclusively, while Smith's Petasis-Ferrier rearrangement was slightly less selective, providing approximately a 5:1 mixture of two diastereomers. However, Jennings used a different strategy, featuring a tandem nucleophilic addition-diastereoselective axial reduction of an in situ generated oxocarbenium ion to give rise to the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran ring formation. Macrocyclization is another key feature in their syntheses. Hoye developed a novel Lewis-acid-catalyzed epoxide opening macrolactonization to set the remote C19 stereocenter. Smith and Keck utilized Horner-Emmons macrocyclization to set *trans* C2-C3 olefin and Jennings employed a chemo- and diastereoselective ring-closing olefin metathesis to effect the macrocycle formation.

1.3 OUR SYNTHESIS

Our interest in the synthesis of **1** lies in the recent discovery in our laboratory that the 2,6-*cis*-disubstituted-4-methylenetetrahydropyrans could be efficiently accomplished via Prins cyclization reaction under very mild conditions.¹⁵ As shown in Figure 1.9, cyclic acetals **41a-c** attached with the allylsilane side chain, promoted by Lewis acid surfactant catalysts in water, could be transformed into 2,6-*cis*-disubstituted-4-methylenetetrahydropyrans **42a-c** in good yields.

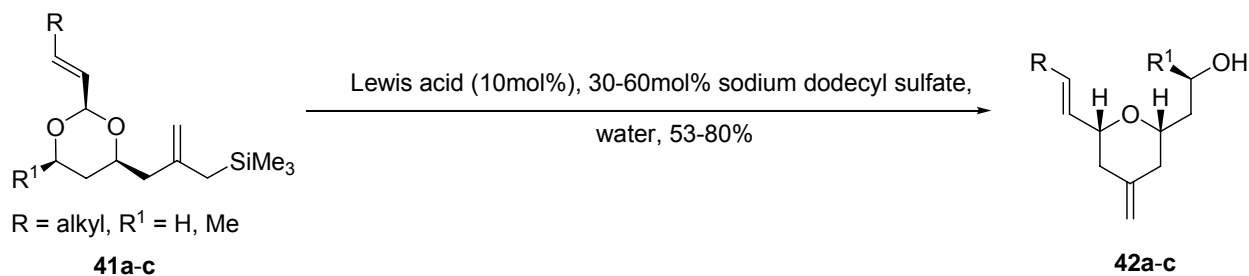


Figure 1.9 The aqueous Prins cyclization

The retrosynthetic analysis (Figure 1.10) based on the above strategy shows that **1** can be obtained from diol **43**, which can be accessed through transposition of allylic alcohol **44**. Acetal **45**, which would afford the methylenetetrahydropyran ring through Prins cyclization reaction, can be prepared from unification of aldehyde **46** and diol **47**.

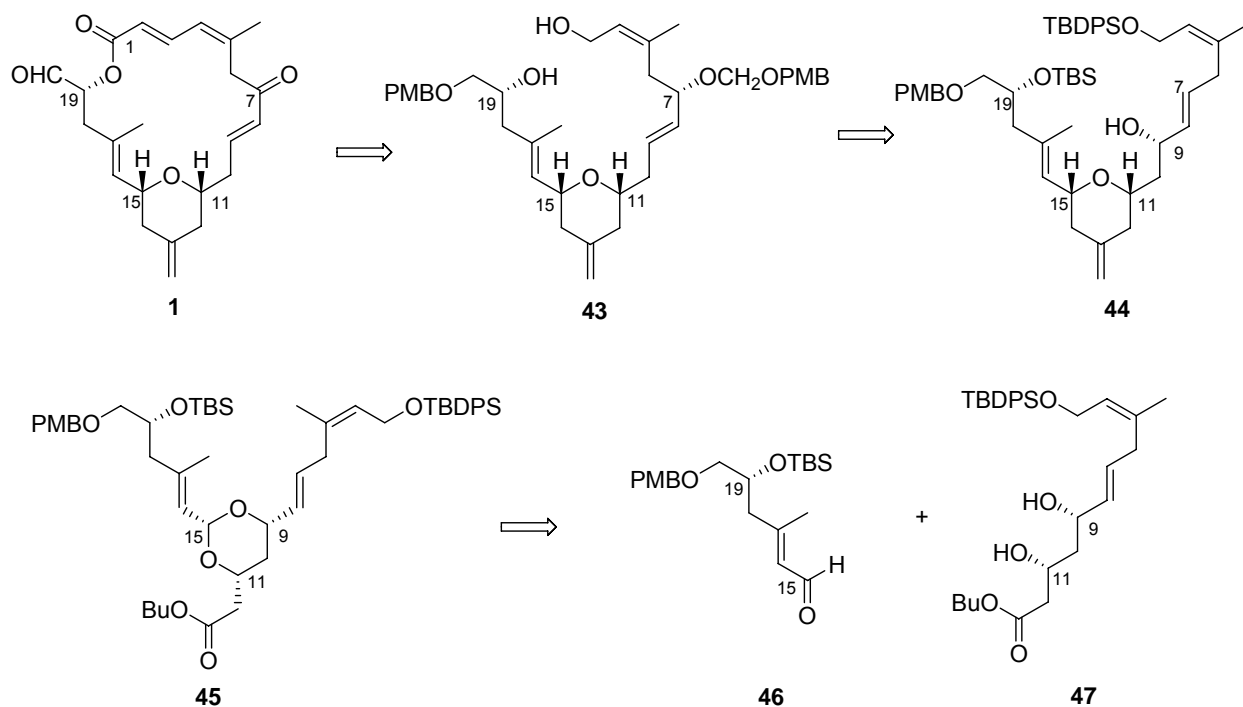
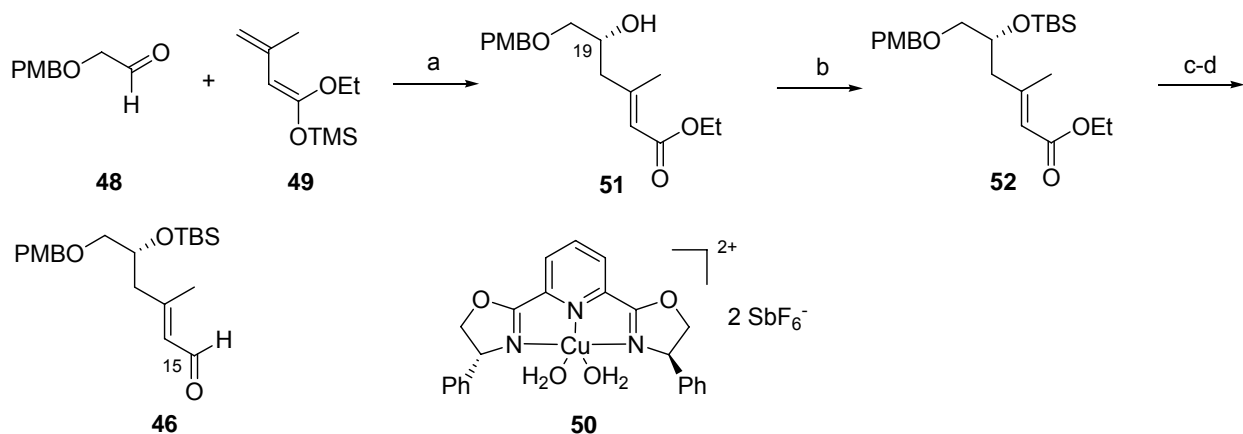


Figure 1.10 Retrosynthetic analysis

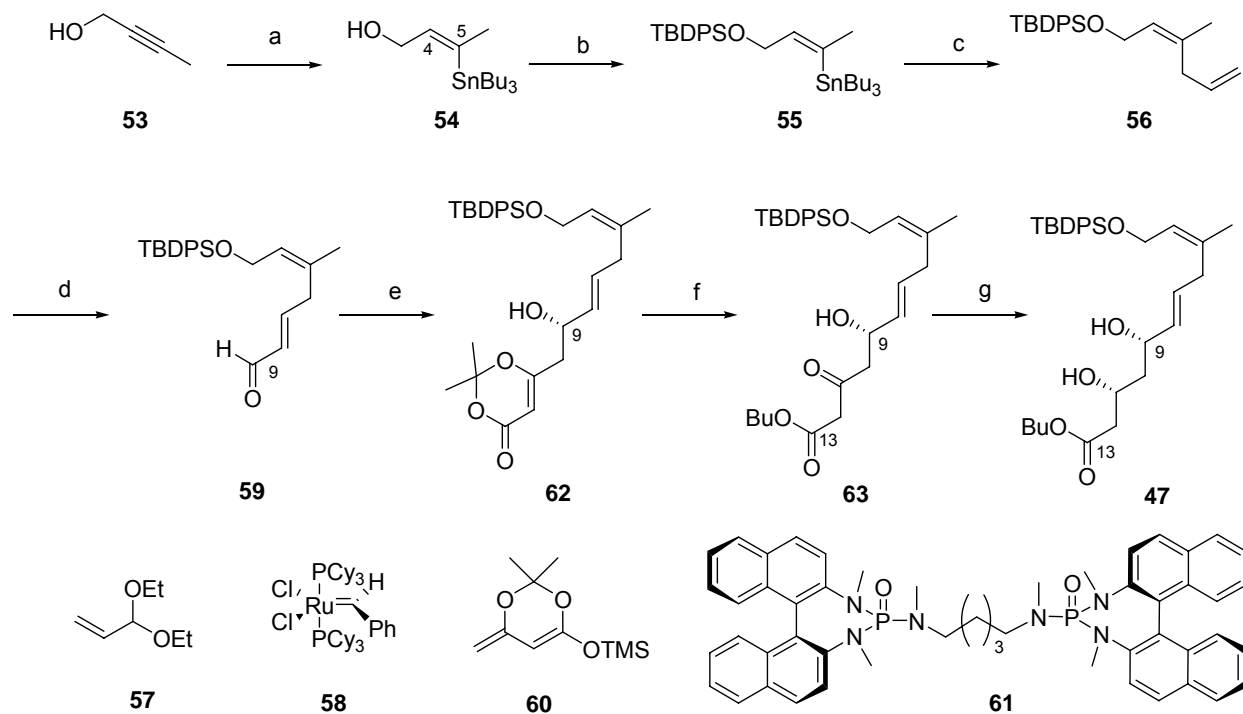


Reagents: (a) **50** (2.5 mol %), CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 82%, 95% ee. (b) TBSCl, Im, DMF, 89%. (c) LiAlH_4 , Et_2O . (d) MnO_2 , CH_2Cl_2 , 80%, 2 steps.

Figure 1.11 Synthesis of enal **46**

The synthesis of **46** follows the sequence devised by Evans in the total synthesis of callipeltoside (Figure 1.11).¹⁶ The vinyllogous aldol reaction between *p*-

methoxybenzoloxyacetaldehyde and silyl ketene acetal **49** catalyzed by Cu-pybox complex **50**¹⁷ provided α,β -unsaturated ester **51** in 82% yield and excellent enantioselectivity (95% *ee*) with the C19 stereocenter installed. Protection of **51** as a TBS ether, reduction of the ethyl ester and oxidation of the resulting allylic alcohol gave the desired enal **46** in good yields.

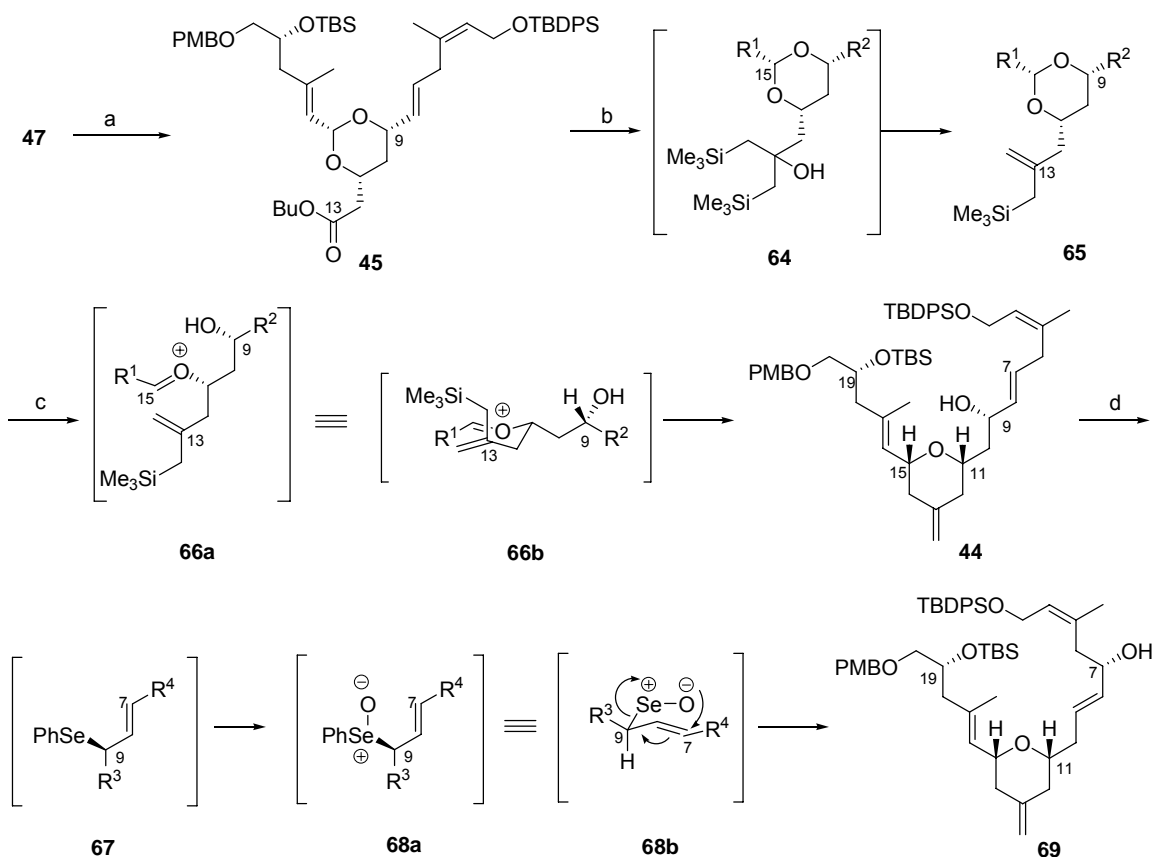


Reagents: (a) Red-Al, THF, 0 °C to rt; then Bu₃SnCl, 83% (93%). (b) TBDPSCI, Im, DMF, 81% (87%). (c) allylbromide, Pd(PPh₃)₄, PhMe, reflux, 80%; (d) **57**, **58**, CH₂Cl₂; then HCOOH/CH₂Cl₂, 88%; (e) **61**, SiCl₄, **60**, CH₂Cl₂, -78 °C, 66% (67%, 83% brsm), 93% *ee*. (f) *n*-BuOH, reflux, 74%. (g) Et₂BOMe, NaBH₄, THF, -78 °C, 83%.
^a The numbers in the parentheses are optimized yields.

Figure 1.12 Synthesis of diol **47**^a

A vinylogous aldol reaction¹⁸ was also utilized in the preparation of the other coupling component **47**. The synthesis of aldehyde **59**, one of the two components in the aldol reaction, is shown in Figure 1.12. Reduction of 2-butynol with Red-Al^{®19} followed by quenching with Bu₃SnCl gave vinyl stannane **54**. Protection of the primary alcohol as its TBDPS ether followed

by the Stille coupling²⁰ of the vinyl stannane with allyl bromide provided the skipped diene **56**. Cross metathesis²¹ of **56** with diethylacrolein acetal **57** in the presence of the Grubbs' 1st catalyst **58** followed by in situ hydrolysis of the acetal furnished aldehyde **59**. The absence of the chelating group in **59** precluded the use of the Evans' Cu-pybox complex **50** as the aldol catalyst. However, the Denmark's bisphosphoramidate **61**²² proved to be a suitable alternative. Condensation of **59** with silyl ketene acetal **60** using the catalyst **61** and SiCl₄ provided alcohol **62** in 66% yield and 93% *ee*. Thermolysis of **62** in refluxing BuOH followed by *syn*-reduction of the resulting β -keto ester with Et₂OMe and NaBH₄²³ afforded the desired diol **47**.



Reagents: (a) (i) TMSCl, Im, DMAP, DMF; (ii) **46**, TMSOTf (10 mol%), CH₂Cl₂, -78 °C, 71% (83%). (b) (i) Me₃SiCH₂MgCl, CeCl₃, THF, -78 °C to rt; then EtOAc, NaHCO₃; (ii) SiO₂, CH₂Cl₂, 66%. (c) PPTS, MgSO₄, CH₂Cl₂, 66%. (d) (i) PhSeCN, Bu₃P, THF, 0 °C; (ii) H₂O₂, Pyr, CH₂Cl₂, -30 °C, 58% (62%).

^a The numbers in the paratheses are optimized yields.

Figure 1.13 Intramolecular Prins cyclization and ensuing [2,3] sigmatropic rearrangement^a

Conversion of **47** into its bis-TMS ether followed by coupling with aldehyde **46** using Noyori's protocol²⁴ gave the cyclic acetal **45** in 71% yield without isomerization of the trisubstituted alkene. (Figure 1.13) Treatment of **45** with excess TMSCH₂MgCl and anhydrous CeCl₃^{25, 26} followed by quenching with EtOAc and saturated NaHCO₃ solution gave the crude tertiary alcohol **64**, which was further converted into allylsilane **65** in 66% yield by stirring with silica gel. Conversion of **65** into the Prins cyclization product, after attempts with a variety of Lewis and Brønsted acids, was effected by PPTS and anhydrous MgSO₄ in CH₂Cl₂ in 66% yield together with a 29% yield of unproductive byproduct arising from the competitive protodesilylation of the starting material. Following this key transformation, transposition of allylic alcohol **44** was required to finish the synthesis of (+)-dactylolide and **44** was first converted into a selenide with PhSeCN and PBU₃.²⁷ Oxidation of the crude selenide with H₂O₂/pyridine gave the selenoxide which concomitantly underwent Mislow-Evans [2,3] sigmatropic rearrangement²⁸ to provide the desired allylic alcohol **69** in 58% yield over two steps.

When I entered the laboratory, Danielle Aubele in our group demonstrated the transformations shown in Figure 1.11, 1.12 and 1.13. My project involved optimizing the reaction conditions (the optimized yields are listed in the parentheses in Figure 1.12 and 1.13) and completing the synthesis of (+)-dactylolide.

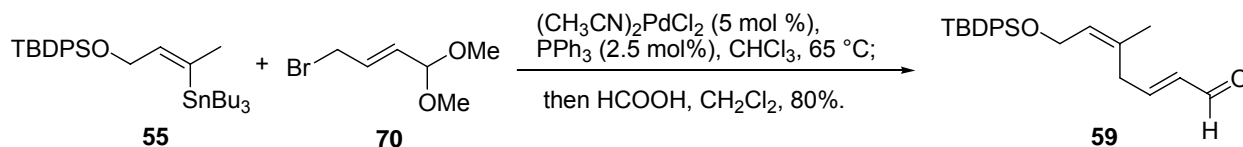


Figure 1.14 An alternate route for synthesis of aldehyde **59**

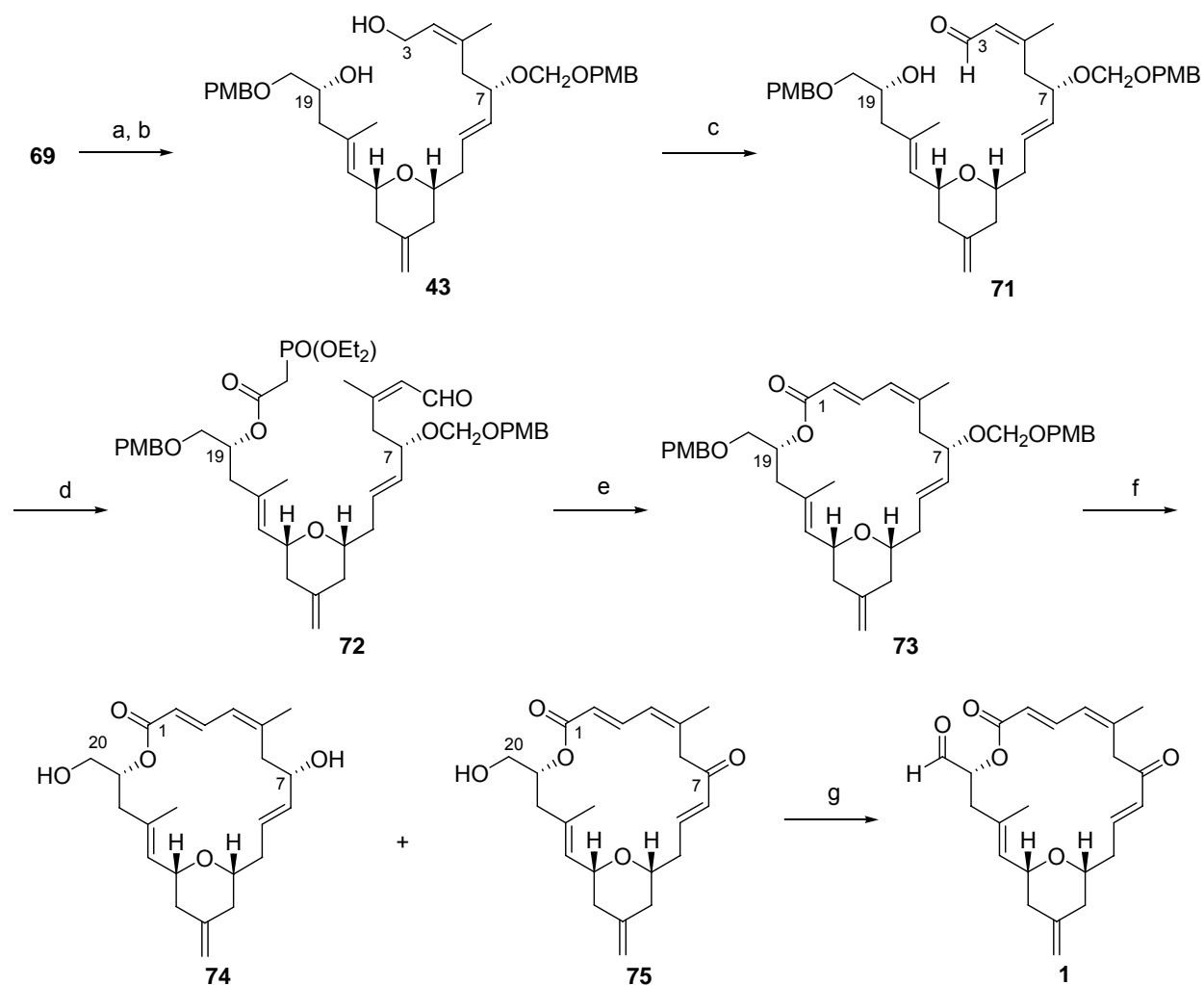
First, I attempted to obtain the aldehyde **59** directly from vinylstannane **55** in order to minimize the number of carbon-carbon bond-forming reactions and reduce one step in the longest linear sequence. Coupling of **55** with bromide **70**²⁹ using Pd(PPh₃)₄ in refluxing toluene followed by in situ hydrolysis of the dimethyl acetal gave **59** in 39% yield. Changing the ratio of **55** and **70** (1:1.5 and 1:2) resulted in complicated reactions. However, another palladium source, (CH₃CN)₂PdCl₂,²⁰ was effective and the reaction conducted in CHCl₃ followed by in situ hydrolysis of the acetal provided **59** in 80% yield (Figure 1.14). This is, to the best of our knowledge, the first example that bromide **70** acts as the electrophilic surrogate for crotonaldehyde in a cross coupling reaction.

Table 1.1 Screening of variable Prins cyclization conditions

Entry	Reaction conditions	Yield of 44 from 45
1	PPTS (40 eq), MgSO ₄ (40 eq), CH ₂ Cl ₂ , 18 h	56%
2	Pyridinium triflate (10 eq), MgSO ₄ (10 eq), CH ₂ Cl ₂ , 1 h	57%
3	Pyridinium triflate (1.3 eq), MgSO ₄ (1.3 eq), CH ₂ Cl ₂ , 1.5 h	59%
4	Pyridinium triflate (1.3 eq), MgSO ₄ (4 eq), CH ₂ Cl ₂ , 1.5 h	75%

Since the transformation from **45** to **44** is a key in our synthesis and the yield (44%, two steps, Figure 1.13) was not satisfactory, much attention was focused on its optimization. A few different Prins cyclization conditions were tried with the crude tertiary alcohol **64** obtained by quenching the TMSCH₂MgCl/CeCl₃ addition with saturated NaHCO₃ solution (Figure 1.13), as

shown in Table 1.1. Although PPTS and MgSO₄ effected the sequential Peterson olefination/Prins cyclization, the reaction was slow and resulted in the significant protodesilylation of allylsilane **65**. (Entry 1) On the other hand, the reaction was much faster in the presence of 10 equivalents of pyridinium triflate and MgSO₄ but it also caused a problem that the TBS and/or PMB groups were lost because of the acidic pyridinium triflate (Entry 2). Similar result was obtained with 1.3 equivalents of pyridinium triflate and MgSO₄. Fortunately, in the presence of 1.3 equivalents of pyridinium triflate and 4 equivalents of MgSO₄, the reaction proceeded smoothly and the Prins cyclization product **44** was obtained in 75% yield repeatedly without observing protodesilylation of allylsilane **65** or TBS/PMB loss. This result suggests that the non-nucleophilic triflate ion, the acidity of the reaction mixture and the desiccant conditions are necessary for the efficiency of this transformation.



Reagents: (a) PMBOCH₂Cl, DIPEA, DMAP, CH₂Cl₂. (b) HF-Pyr, Pyr, THF, 80%, two steps. (c) PhI(OAc)₂, TEMPO, CH₂Cl₂, 87%. (d) (EtO)₂P(O)CH₂CO₂H, DCC, DMAP, CH₂Cl₂, 95%. (e) NaHMDS, THF, -78 to 0 °C, 73%. (f) DDQ, CH₂Cl₂, pH 7 buffer, 63% (+ 14% enone). (g) DMPI, NaHCO₃, CH₂Cl₂, 77%.

Figure 1.15 Completion of (+)-dactylolide (**1**)

Despite the smooth transposition of the resulting allylic alcohol **44**, attempts to protect the C7 alcohol **69** as a PMB ether (PMBCl with NaH, or PMBOC(NH)CCl₃ with BF₃, or TsOH or TfOH, or PMBOC(O)S-2-pyridyl with AgOTf, AgBF₄, or AgPF₆) were not successful, resulting in low yields or decomposition of the starting material presumably due to the instability of **69** toward strong acid or base. Alternatively, protection of the C7 alcohol as the *p*-methoxybenzyloxymethyl ether³⁰ followed by double desilylation gave the C3, C19 diol **43** in

80% yield over the two steps. (Figure 1.15) Selective oxidation of the C3 alcohol **43** with TEMPO and $\text{PhI}(\text{OAc})_2$ ³¹ provided aldehyde **71** in 87% yield. Acylation of the C19 hydroxyl with commercially available diethylphosphonoacetic acid and DCC gave phosphonoacetate **72** in 95% yield. The next step in our synthetic sequence required closure of the macrocycle, employing Horner-Emmons macrocyclization by following Smith's method to provide **73** in 73% yield. Double deprotection of the C7 and C20 hydroxy groups with DDQ in buffered CH_2Cl_2 gave the C7, C20 diol **74** in 63% yield along with variable amounts of the C7 ketone **75**. Oxidation of the mixture of diol **74** and enone **75** by Dess-Martin periodiane^{32, 33} furnished the dactylolide **1** in 77% yield. The spectral data (¹H NMR, 500 MHz; ¹³C NMR, 125 MHz) and HRMS data of synthetic (+)-dactylolide are in full agreement with those previously reported.^{1-3, 10} The optical rotation ($[\alpha]_{\text{D}} = +163^\circ$, *c* 0.29, MeOH), although incongruous with the natural¹ and synthetic^{2, 3, 10, 13, 14} samples, is still within expected range.

In conclusion, our total synthesis was achieved in a highly convergent and efficient manner. Key features in this synthesis include two enantioselective vinylogous Mukaiyama aldol reactions, a sequential Peterson olefination/Prins cyclization reaction to construct the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core, a Mislow-Evans [2,3] sigmatropic rearrangement in the allylic alcohol transposition and an intramolecular Horner-Emmons macrocyclization.

1.4 CURRENT PROGRESS ON THE SECOND GENERATION OF THE TOTAL SYNTHESIS OF (+)-DACTYLOLIDE

During the synthesis of (+)-dactylolide, we realized that the stereochemistry of C9 in **47** (Figure 1.10) will not have any influence on the final product since the hydroxyl group will be transposed from C9 to C7 and be further oxidized to give the ketone at the final stage. However, the stereochemistry at C11 in **47** must be set since it was used to introduce the C15 stereocenter. Based on this concept, we developed a new synthetic plan (Figure 1.16), in which acetal **78** and the corresponding diol **79** were required to be prepared.

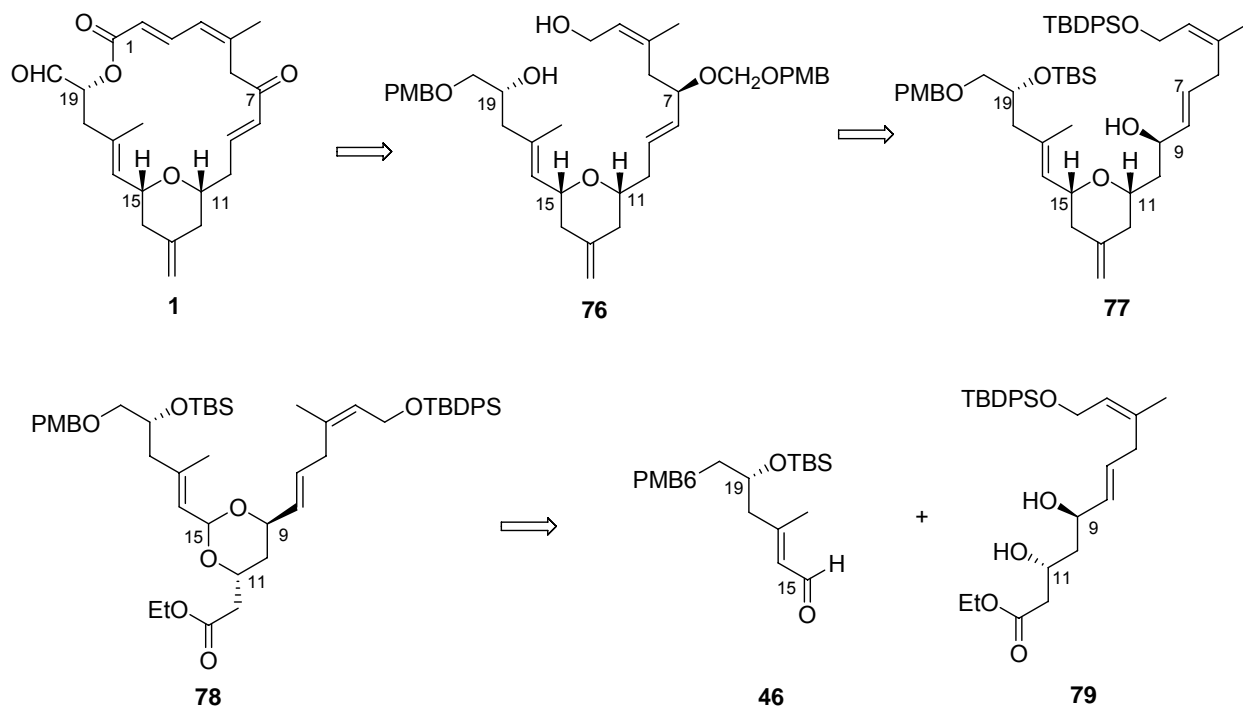
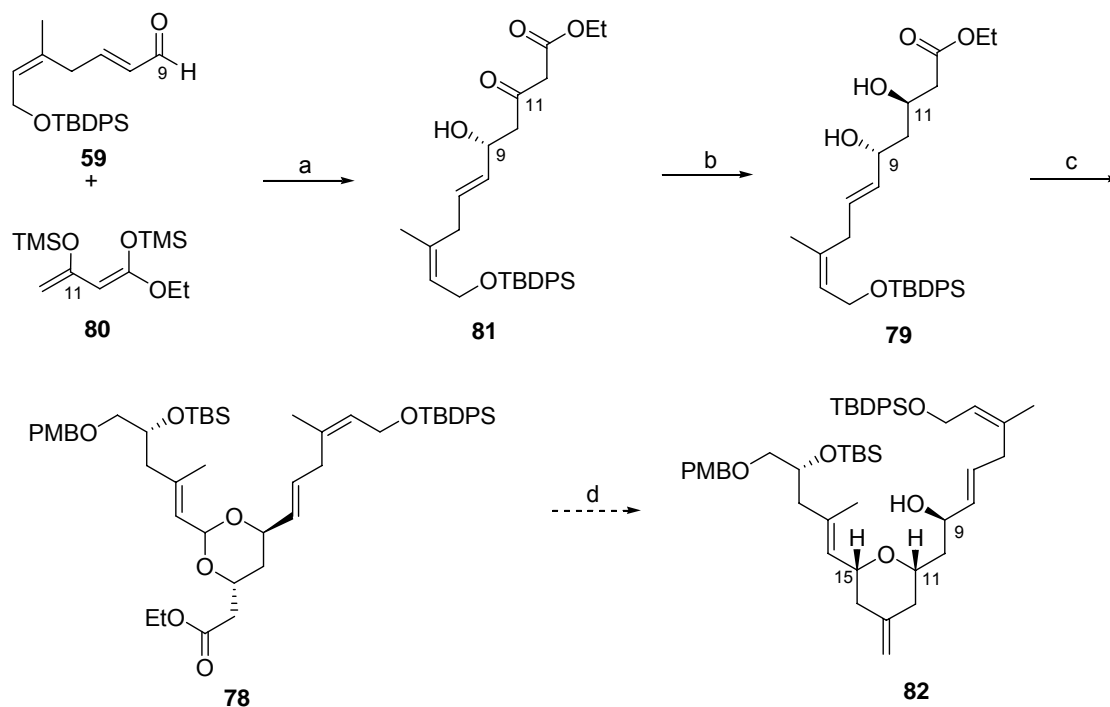


Figure 1.16 Retrosynthetic analysis of (+)-dactylolide (second generation)

As an entry into acetal **78**, the stereochemistry at C9 was set through a vinylogous Mukaiyama aldol reaction of aldehyde **59** with Chan-like diene **80**^{34, 35} using Denmark's bisphosphoroamide *ent*-**61**²² to give the corresponding β -keto ester **81** in 71% yield (83% brsm) (Figure 1.17). This modified aldol reaction using Chan-like diene compared with the previous example (Figure 1.7) allowed us to obtain the corresponding β -keto ester in a one-step manner without using the inefficient opening of the dioxinone ring in refluxing BuOH. 1,3-*Anti* reduction of the β -keto ester using Me₄NBH(OAc)₃ in CH₃CN/AcOH developed by Evans³⁶ provided *anti* diol **79** in excellent yield (90%) and high diastereoselectivity (*dr* = 16:1), which possessed all the functionality required for the synthesis of **78**. Conversion of **79** into its bis-TMS ether followed by coupling with aldehyde **46** mediated by TMSOTf gave the cyclic acetal **78** in 86% yield as two diastereomers (9% and 77%, respectively) at the C15 position. This substrate has not been used for the Prins cyclization reaction. In our previous studies, the corresponding butyl ester (BuO at C13 instead of EtO) afforded the Prins cyclization product **82** in 35-40% yield. The major problem associated with this reaction is that after TMSCH₂MgCl/CeCl₃ addition and acidic workup, the acetal/allylsilane became unstable and decomposed significantly.



Reagents: (a) *ent*-**61**, SiCl₄, CH₂Cl₂, -78 °C, 71%, 83% brsm; (b) Me₄NBH(OAc)₃, CH₃CN, AcOH, -35 °C, 90%, *dr* = 16:1; (c) (i) TMSCl, Im, DMAP, DMF; (ii) **46**, TMSOTf, CH₂Cl₂, -78 °C, 86%; (d) (i) TMSCH₂MgCl, CeCl₃, THF, -78 °C to rt; then AcOH or tartaric acid; (ii) Pyr·HOTf, MgSO₄, CH₂Cl₂.

Figure 1.17 Synthesis of advanced intermediate **82**

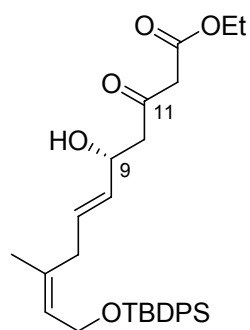
In the future, we will examine the conformation of the two diastereomers of acetal **78**. Most importantly, we will lay emphasis on the Prins cyclization. Some weaker acids, such as AcOH, tartaric acid, etc. will be attempted to slow down the decomposition of the acetal after TMSCH₂CeCl₂ addition. Once this problem is solved, the rest is not problematic based on our past experiences.

APPENDIX A

Total synthesis of (+)-dactylolide (Supporting Information)

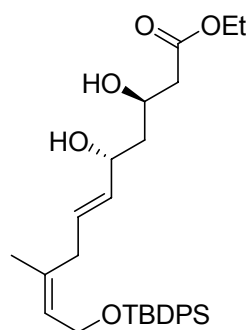
General Experimental Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 at 300 MHz and 75 MHz, respectively, or at Bruker Avance 500 spectrometers at 500 MHz and 125 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^1H NMR: $\text{CDCl}_3 = 7.27$ ppm, for ^{13}C NMR: $\text{CDCl}_3 = 77.23$ ppm. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; br = broad). High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2 . Optical rotations were measured on a Perkin-Elmer 241 polarimeter. HPLC analysis was performed with an HP series 1100 instrument using either a Chiracel OD-H or CHIRAPAK AD column. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Methylene chloride was distilled under N_2 from CaH_2 . Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

For syntheses and characterizations of **1, 43, 44, 45, 46, 47, 48, 49, 51, 52, 54, 55, 59, 60, 62, 63, 69, 71, 72, 73, 74, 75**, refer to Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2005**, *44*, 3485-3488.



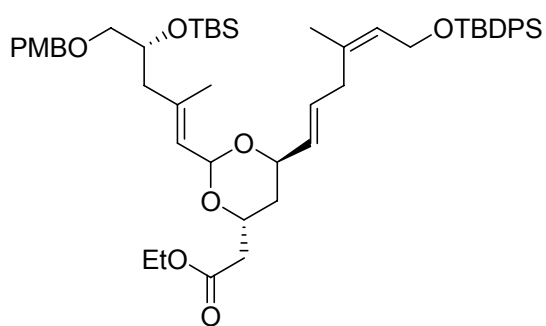
(*R,6E,9Z*)-Ethyl 11-(*tert*-butyldiphenylsilyloxy)-5-hydroxy-9-methyl-3-oxoundeca-6,9-dienoate (81)

To a stirring solution of (*R,R*)-*N,N'*-bis[4,5-dihydro-3,5-dimethyl-4-(3*H*-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]-2-oxodiazaphosphino)]-*N,N'*-dimethyl-1,5-pentanediamine (33.8 mg, 40 μ mol) and aldehyde **59** (1.514 g, 4.00 mmol) in CH_2Cl_2 (16 mL) at -78°C was added silicon tetrachloride (0.55 mL, 4.8 mmol). The trimethylsilyl ketene acetal **80** (1.647 g, 6.00 mmol, in 4 mL CH_2Cl_2) was added dropwise via syringe pump over 3.5 h. The reaction mixture was stirred at -78°C for 18 h, then was transferred via cannula to a stirring room temperature solution of 1M KH_2PO_4 (60 mL). The resulting biphasic mixture was allowed to warm to room temperature before filtration through a pad of celite. The filtrate was washed with 10% KF (50 mL) and the organic layer was dried (MgSO_4), filtered and concentrated. The resulting residue was purified by flash chromatography (22% - 30% EtOAc in hexanes) to afford the desired product (1.440 g, 70.8%, 82.6% based on recovered aldehyde **59**) as a pale yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 7.71-7.68 (m, 4H), 7.44-7.36 (m, 6H), 5.57-5.43 (m, 2H), 5.38 (dd, $J = 15.4, 6.1$ Hz, 1H), 4.52-4.47 (m, 1H), 4.20 (q, $J = 7.2$ Hz, 2H), 4.19 (d, $J = 6.2$ Hz, 2H), 2.69-2.66 (m, 2H), 2.59-2.54 (m, 3H), 1.67 (br s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 203.0, 167.0, 135.8, 135.2, 134.0, 131.7, 129.8, 129.4, 127.8, 125.9, 68.3, 61.7, 60.8, 50.1, 49.8, 27.0, 23.5, 19.3, 14.3; IR (neat) 3467, 2931, 2857, 1743, 1715, 1428, 1316, 1236, 1111, 1046, 823, 704; HRMS (ESI): m/z calcd for $\text{C}_{30}\text{H}_{40}\text{O}_5\text{SiNa}$ ($M + \text{Na}$) 531.2543, found 531.2498; $[\alpha]_{\text{D}}^{23} = +9.29^\circ$ (CHCl_3 , c 1.53).



(*3R,5R,6E,9Z*)-Ethyl 11-(*tert*-butyldiphenylsilyloxy)-3,5-dihydroxy-9-methylundeca-6,9-dienoate (79)

To a stirred solution of the β -hydroxy keto ester **81** (1.265 g, 2.49 mmol) in CH₃CN/CH₃COOH (30 mL, 2:1, v/v) at -30 °C was added dropwise the tetramethylammonium tri(acetoxy)boron hydride (3.145 g, 11.95 mmol, dissolved in 8.0 mL CH₃CN/CH₃COOH (30 mL, 2:1, v/v)) via syringe pump over 2 h. After addition, the mixture was stirred at -30 °C for 18 h, and then quenched with saturated sodium tartrate (10 mL). The mixture was allowed to warm to room temperature and extracted with CH₂Cl₂ (2 x 100 mL). The extracts were washed with saturated NaHCO₃ (100 mL), dried over MgSO₄ and evaporated. The residue was purified by column chromatography (40% EtOAc in hexanes) to give the anti diol (1.138 g, 89.6%) as a pale yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 7.72-7.68 (m, 4H), 7.46-7.36 (m, 6H), 5.55-5.39 (m, 3H), 4.38-4.24 (m, 2H), 4.21-4.14 (m, 4H), 2.59 (d, $J = 5.3$ Hz, 2H), 2.49-2.42 (m, 2H), 1.73-1.64 (m, 1H), 1.68 (s, 3H), 1.61-1.53 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.05 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.0, 135.8, 135.5, 134.1, 133.5, 129.8, 128.5, 127.8, 125.8, 69.8, 65.7, 61.0, 60.9, 42.2, 41.14, 35.2, 27.0, 23.6, 19.4, 14.4; IR (neat) 3434, 2932, 2857, 1732, 1428, 1376, 1161, 1111, 1049, 823, 740, 703; $[\alpha]_D^{23} = -0.10^\circ$ (CHCl₃, c 1.83).



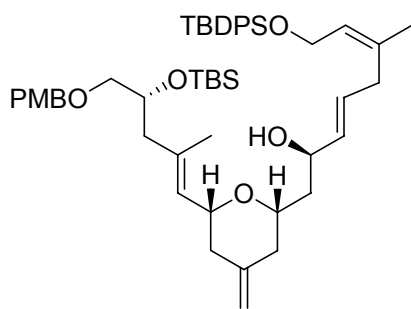
Ethyl 2-(4*R*,6*R*)-(2-(*R*,*E*)-[4-(tert-butyl dimethylsilyloxy)-5-(4-methoxybenzyloxy)-2-methylpent-1-enyl]-6-(1*E*,4*Z*)-[6-(tert-butyl diphenylsilyloxy)-4-methylhexa-1,4-dienyl]-[1,3]-dioxan-4-yl)acetate

(78)

To a stirring solution of diol **79** (766 mg, 1.50 mmol) in anhydrous DMF (7.5 mL) was added imidazole (510 mg, 7.5 mmol). The reaction mixture was stirred for 5 min and

chlorotrimethylsilane (358 mg, 3.30 mmol) was added, followed by 4-dimethylaminopyridine (9.2 mg). The reaction mixture was stirred for 18 h, and then quenched with ice chips. The reaction mixture was extracted into hexanes, and the water layer was washed with hexanes (3 x 20 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated. The resulting residue was dissolved in CH₂Cl₂ (12.0 mL) and the temperature was decreased to -78 °C before **46** (568 mg, 1.50 mmol) and TMSOTf (33 mg, 0.15 mmol) were added. The reaction mixture was stirred for 45 min, then quenched with pyridine (14 mg, 0.18 mmol), warmed to room temperature and washed with saturated NaHCO₃ (10 mL). The organic layer was dried (MgSO₄), filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography (10% - 14% EtOAc in hexanes) to afford the desired cyclic acetal. Fast eluting fraction (123 mg, 9.4%): ¹H NMR (300 MHz, CDCl₃) δ 7.70-7.67 (m, 4H), 7.43-7.36 (m, 6H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.58-5.37 (m, 3H), 5.32 (d, *J* = 5.2 Hz, 1H), 5.22 (d, *J* = 6.2 Hz, 1H), 4.43 (s, 2H), 4.20-4.05 (m, 6H), 3.98-3.89 (m, 1H), 3.81 (s, 3H), 3.38-3.28 (m, 2H), 2.65-2.52 (m, 3H), 2.40 (dd, *J* = 15.8, 6.0 Hz, 1H), 2.26 (dd, *J* = 13.3, 4.8 Hz, 1H), 2.13 (dd, *J* = 13.3, 7.1 Hz, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 1.61-1.55 (m, 1H), 1.42-1.34 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 170.9, 159.2, 139.2, 135.8, 135.4, 134.1, 130.9, 130.8, 129.8, 129.4, 127.8, 125.8, 125.4, 113.9, 98.4, 76.6, 74.6, 73.1, 72.7, 70.3, 60.9, 60.8, 55.4, 45.0, 41.1, 36.6, 35.3, 27.0, 26.1, 23.6, 19.4, 18.4, 18.0, 14.4, -4.3, -4.6; IR (neat) 2930, 2856, 1737, 1514, 1428, 1249, 1111, 1037, 1004, 836, 703; Slow eluting fraction (1.004 g, 76.8%): ¹H NMR (300 MHz, CDCl₃) δ 7.72-7.69 (m, 4H), 7.46-7.36 (m, 6H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.66-5.48 (m, 3H), 5.44 (d, *J* = 6.0 Hz, 1H), 5.26 (d, *J* = 5.6 Hz, 1H), 4.62-4.55 (m, 1H), 4.44 (s, 2H), 4.30-4.19 (m, 3H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.97-3.89 (m, 1H), 3.82 (s, 3H), 3.35 (d, *J* = 5.3 Hz, 2H), 2.68-2.55 (m,

3H), 2.39 (dd, $J = 15.8, 6.0$ Hz, 1H), 2.29-2.19 (m, 1H), 2.15-2.06 (m, 1H), 1.97-1.87 (m, 1H), 1.72 (s, 3H), 1.66 (s, 3H), 1.72-1.64 (m, 1H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.06 (s, 9H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.8, 159.2, 139.3, 135.8, 135.2, 134.1, 131.6, 130.8, 129.8, 129.4, 127.8, 126.0, 125.6, 113.9, 92.6, 74.5, 73.1, 71.8, 70.4, 69.0, 60.8, 60.7, 55.4, 44.9, 41.3, 35.5, 33.3, 27.0, 26.1, 23.6, 19.4, 18.3, 17.9, 14.4, -4.3, -4.6; IR (neat) 2930, 2856, 1737, 1514, 1472, 1428, 1249, 1174, 1111, 1036, 979, 835, 777, 704.



**(2*R*,3*E*,6*Z*)-1-(2*S*,6*R*)-{6-(*R*,*E*)-[4-(*tert*-
Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2-
methylpent-1-enyl]-4-methylenetetrahydropyran-2-yl}-8-
(*tert*-butyldiphenylsilyloxy)-6-methylocta-3,6-dien-2-ol**
(82)

Cerium(III) chloride (307 mg, 1.24 mmol) was dried with vigorous stirring under vacuum (0.2 mm Hg) at 150 °C for 2 h, then cooled to room temperature, flushed with N_2 and suspended in THF (3.0 mL). The suspension was sonicated for 2 h, and then transferred to a -78 °C cold bath. Trimethylsilylmethylmagnesium chloride (1.0 M in Et_2O , 3.16 mL, 3.16 mmol) was added dropwise to form a pale yellow suspension, which was stirred for 1 h. After that time, the corresponding butyl ester (the equivalent of **78**, 170.0 mg, 0.189 mmol, dissolved in 0.6 mL of THF) was added dropwise, and the flask formerly containing the butyl ester was rinsed with THF (2 x 0.5 mL). The reaction mixture was allowed to gradually warm to room temperature and stir for 18h. The temperature was then decreased to -78 °C and the reaction was quenched by the dropwise addition of HCl (5%, 3.0 mL). After stirred for 20 min, the reaction mixture was warmed to room temperature. The two layers were separated and the aqueous layer was washed

with Et₂O (2 x 10 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo with water bath at 40 °C. The residue was kept under vacuum for 20 min, and then loaded onto a column packed with silica gel. After standing there for 7 min, the mixture was eluted with 5% - 10% EtOAc in hexanes to give pure **82** (9.0 mg) as a colorless oil and a mixture of **82**, aldehyde **46** and its isomer (20.4 mg). For **82**: ¹H NMR (300 MHz, CDCl₃) δ 7.70-7.67 (m, 4H), 7.45-7.35 (m, 6H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.52-5.36 (m, 3H), 5.22 (d, *J* = 7.5 Hz, 1H), 4.72 (s, 2H), 4.45 (s, 2H), 4.30 (br s, 1H), 4.19 (d, *J* = 6.6 Hz, 1H), 3.98-3.89 (m, 2H), 3.81 (s, 3H), 3.65-3.55 (m, 1H), 3.33 (d, *J* = 5.3 Hz, 2H), 2.75-2.74 (m, 1H), 2.58 (d, *J* = 5.7 Hz, 2H), 2.27 (dd, *J* = 13.5, 6.0 Hz, 1H), 2.15-1.94 (m, 4H), 1.79-1.59 (m, 2H), 1.67 (br s, 6H), 1.05 (s, 9H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 159.3, 144.3, 136.5, 135.8, 134.1, 133.9, 130.8, 129.8, 129.4, 128.4, 127.8, 125.6, 113.9, 109.1, 75.8, 74.3, 73.1, 70.7, 69.6, 60.9, 55.5, 45.0, 42.5, 40.8, 40.6, 35.2, 27.1, 26.1, 23.6, 19.4, 18.4, 18.0, -4.3, -4.5; IR (neat) 3485, 2930, 2856, 1513, 1428, 1249, 1111, 1040, 835, 776, 702; HRMS (ESI): *m/z* calcd for C₅₁H₇₄O₆Si₂Na (M + Na) 861.4922, found 861.4984.

2.0 STUDIES ON THE CASCADE CYCLIZATION REACTIONS OF EPOXIDES/POLYEPOXIDES INITIATED BY SINGLE ELECTRON TRANSFER

2.1 INTRODUCTION

In the past decades, a variety of marine natural products were discovered, a majority of which contain polycyclic ether structures.^{37, 38} Biosynthetically, these complex compounds can be synthesized from the requisite polyepoxide precursors via cascade cyclization reactions. Based on their individual structural features, they could be divided into three classes: (1) those that could be prepared solely from *endo*-cyclizations, such as hemibrevetoxin B,³⁹ **1**; (2) those that could be prepared exclusively from *exo*-cyclizations, such as bullatacin,⁴⁰ **2**; and (3) those that could be prepared from a combination of *exo*- and *endo*-cyclizations, such as lactodehydrothysiferol,⁴¹ **3**. (Figure 2.1) Besides the diverse and complex structures, their interesting and significant biological activities have attracted considerable attention from synthetic community. Up to now, several methods towards their total syntheses have been documented.^{42, 43}

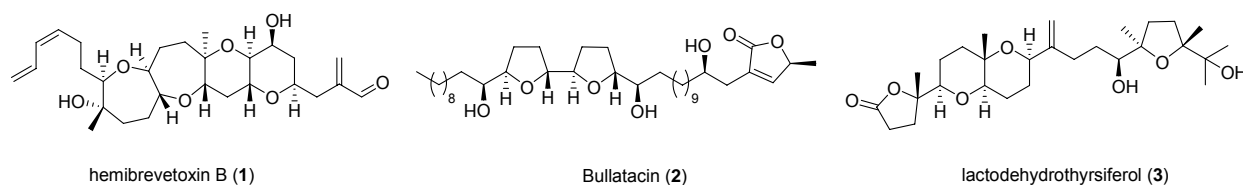


Figure 2.1 Polycyclic ether natural products

During the process of studying the ring opening of epoxy alcohols, *exo*-cyclizations were well understood. For example, under acid-catalyzed conditions, epoxy alcohol **4** gave predominantly tetrahydrofuran product **6** with *exo*-selectivity. (Figure 2.2) However Lerner⁴⁴ reported that, in the presence of the catalytic antibody IgG26D9 elicited from a tertiary amine oxide antigen (hapten) **7**, only tetrahydropyran product **9** was observed, which formally violated the Baldwin's rules⁴⁵ for ring closure reactions. Ab initio calculations by Houk^{46, 47} and Coxon^{48, 49} showed that the five-membered transition state is favored due to the nearly ideal trajectory of the S_N2 attack of the hydroxyl oxygen to C4 and consequently has a lower energy than the six-membered transition state. On the other hand, the antibody-catalyzed formation of tetrahydropyran **9**, although ascribed to the similarities between the transition state **8** and hapten **7**, still remains undelineated. Subsequently, the competitive selectivity between 6-*exo* and 7-*endo* was also investigated in the Lerner group.⁵⁰ (Figure 2.2) Under acid-catalyzed conditions, epoxy alcohol **10** gave a pyran (**11**)/oxepane (**12**) product ratio of 98:2. When the reaction was performed with antibody IgG26D9 catalyst, oxepane **12** was obtained in >98% yield. This result confirmed that 6-*exo*-cyclization is chemically favored whereas 7-*endo*-annulation is enzymatically preferred. During the past two decades, cascade *exo*-cyclizations were effectively utilized in the total syntheses of Class 2 natural products.

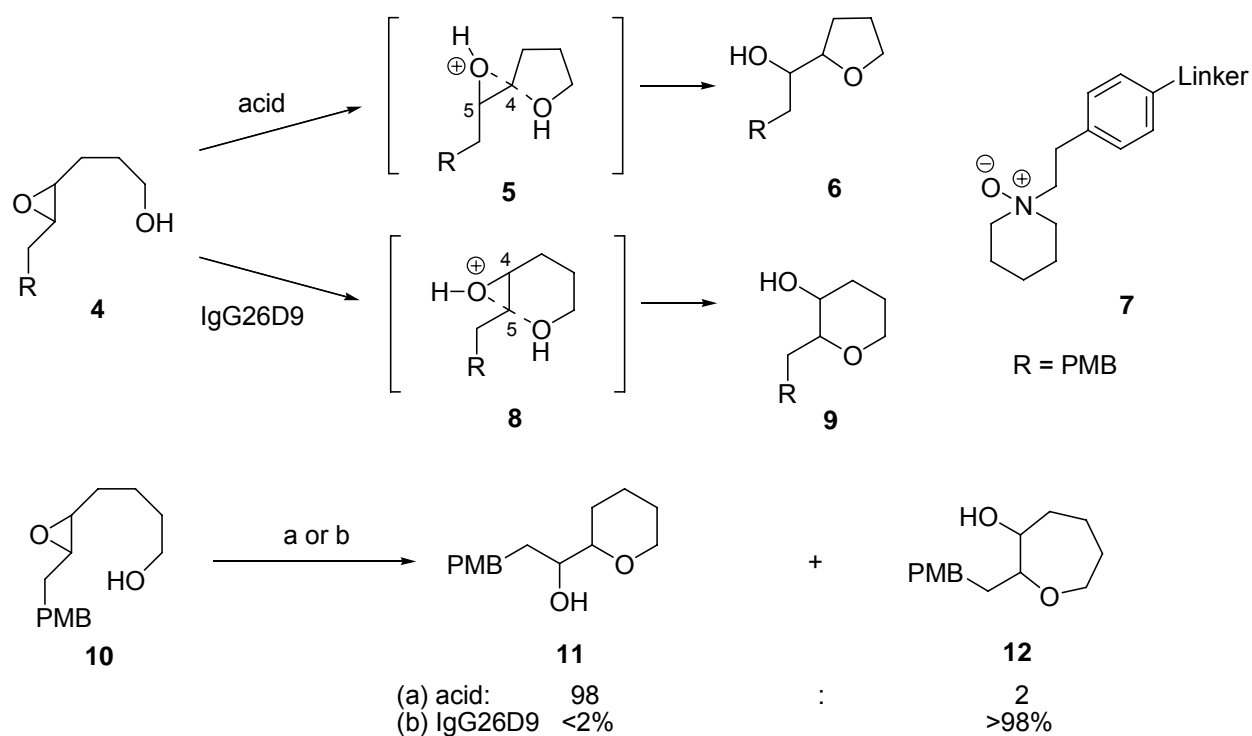


Figure 2.2 Acid-catalyzed and antibody-catalyzed cyclization of epoxy alcohols

Besides the use of catalytic antibodies, substituent effects⁵¹⁻⁵⁵ and Co-salen catalysis⁵⁶ were also used to successfully achieve *endo*-selectivity in cyclization of the monoepoxide systems. These strategies, especially substitution effects, were frequently used in the syntheses of Class 1 polycyclic ethers, albeit usually in a stepwise manner to form each ether ring. In contrast, cascade *endo*-cyclizations of polyepoxides, a more efficient fashion compared with the stepwise manner, to forge fused polycyclic ethers in one step, still serve as a great challenge to organic chemists.

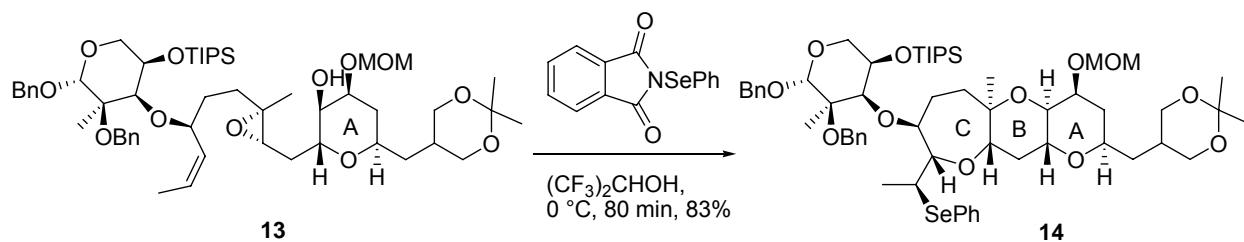


Figure 2.3 Key transformation in Holton's synthesis of hemibrevetoxin B

Recently, Holton⁵⁷ reported the first convergent total synthesis of hemibrevetoxin B in which a cascade cyclization of epoxy alcohol was employed. As shown in Figure 2.3, epoxy alcohol **13**, upon treatment with *N*-(phenylseleno)phthalimide in $(\text{CF}_3)_2\text{CHOH}$ at $0\text{ }^\circ\text{C}$, smoothly afforded the desired fused product **14** as a single diastereomer in 83% yield. Therefore, the B and C rings were efficiently assembled in one step.

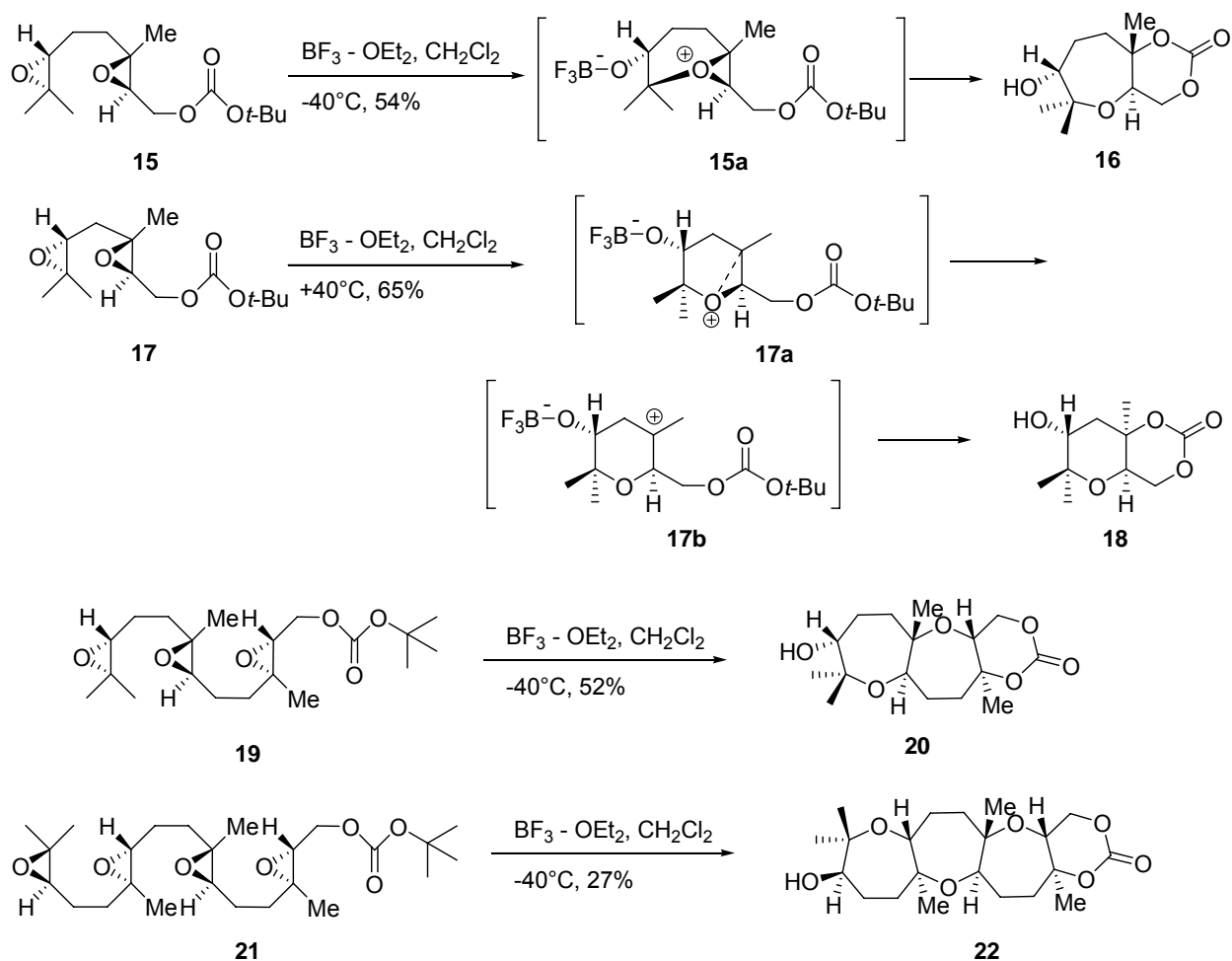


Figure 2.4 Cyclization of polyepoxides

Mimicking the biosynthesis of fused polycyclic ether natural products to achieve *endo*-selectivity has been becoming a prevailing subject. The first example of the cascade *endo*-selective oxacyclization was reported by Murai in 2000 yet with less than 10% yield.⁵⁸ Facing this challenge, McDonald extensively investigated cyclizations of polyepoxides and achieved *endo*-selectivity by a nonenzymatic strategy to form oxepanes and polyoxepanes effectively. Four typical examples are shown in Figure 2.4.⁵⁹⁻⁶¹ Both diepoxides **15** and **17**, promoted by Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$, provided fused bicyclic and tetracyclic compounds **16** and **18**, respectively, with all-*endo* selectivity in good yields. In the case of **15**, the *trans*-fused product **16** was

obtained, resulting from the S_N2-like attack of the carbonyl oxygen to the epoxonium ion intermediate. However, in the case of **17**, the *cis*-fused product **18** was proposed to arise from the carbonyl oxygen addition to the tertiary carbocation intermediate **17b**. In addition to the diepoxides, both tri- and tetraepoxides **19** and **21** regioselectively and stereoselectively gave the fused products **20** and **22**, respectively, in good yields.

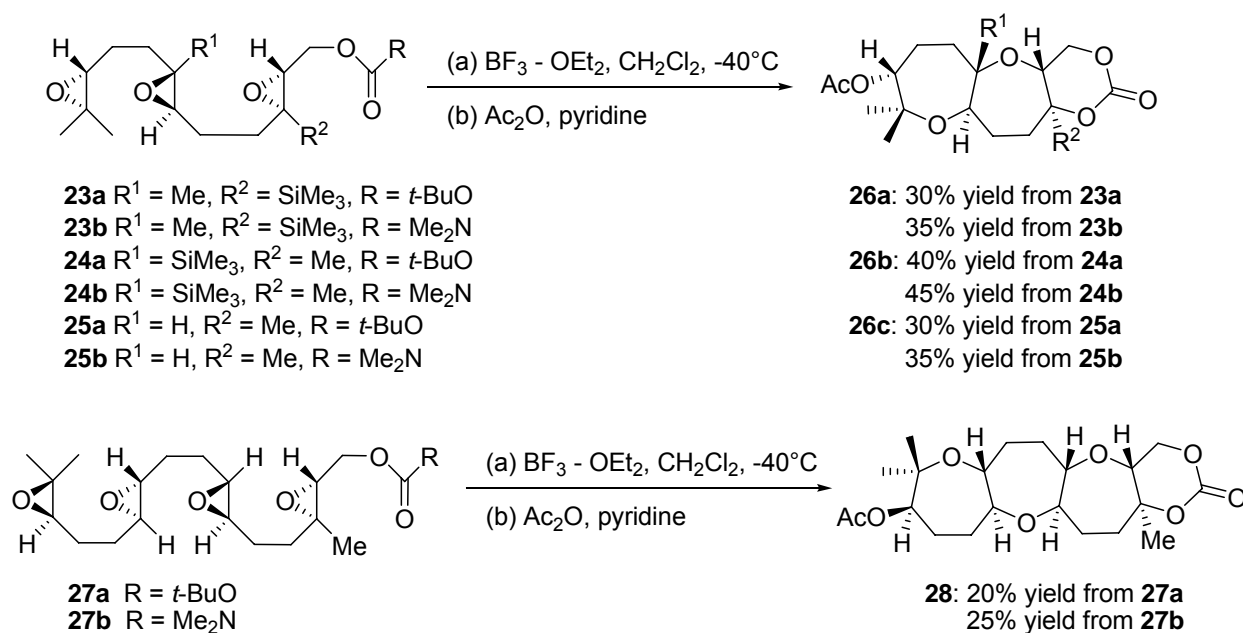
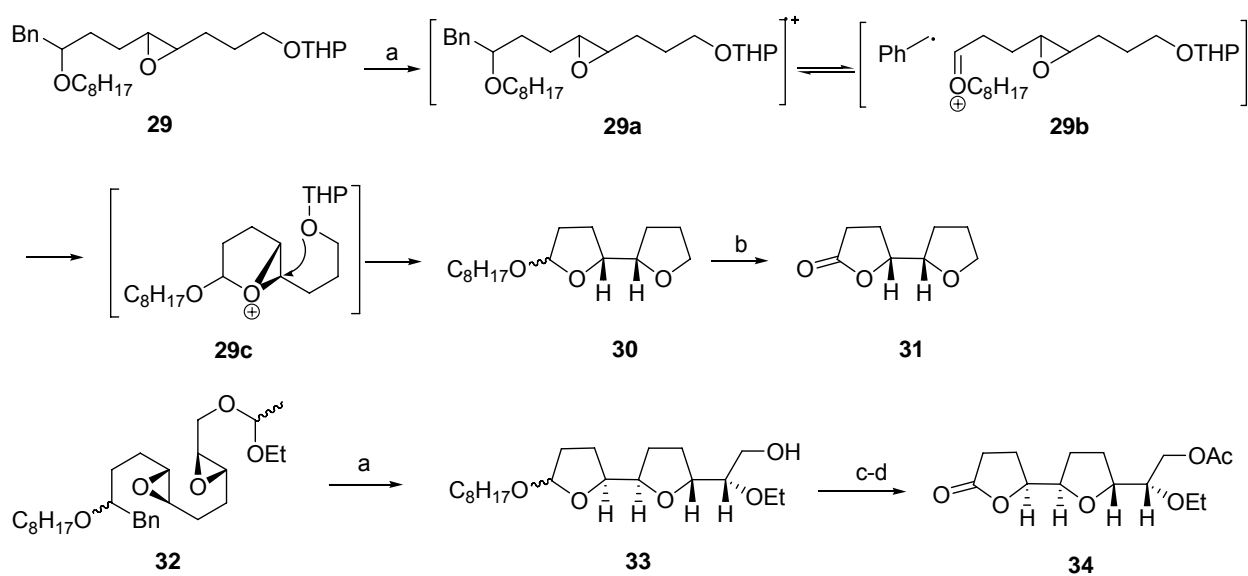


Figure 2.5 Cyclization of tri- and tetraepoxides

Most recently, the McDonald group⁶² reported a few more remarkable results. (Figure 2.5) Not only the triepoxides containing two internal trisubstituted epoxides (**23** and **24**), but also the polyepoxides containing one or two internal disubstituted epoxides (**25** and **27**), with the promotion of the Lewis acid, furnished the all-*endo* cyclization products (**26** and **28**, respectively) in good yields. The all-*endo* oxacyclization products **26c** and **28** were not expected and were attributed to the nucleophile-driven regiochemical control from the nucleophilic epoxides or

carbonyl group. These fascinating findings demonstrated that the naturally occurring fused polycyclic ethers or their core structures could be conveniently approached by this Lewis-acid mediated cyclizations of polyepoxides.



Reagents: (a) *hν*, NMQPF₆ (2.5 mol%), NaOAc, Na₂S₂O₃, DCE/PhMe (6:1, v/v) (from **29**, 73% yield; from **32**, 69% yield). (b) Jones reagent, acetone, 0 °C, 70%. (c) Acetylation. (d) Jones reagent, acetone, 0 °C.

Figure 2.6 Electron transfer initiated cyclization of mono- and diepoxides **29** and **32**

Cascade cyclization reactions of epoxides/polyepoxides were also carried out in our laboratory. Two typical examples are shown in Figure 2.6. Both monoepoxide **29** and diepoxide **32** gave *exo* and *exo,exo* products, respectively, as a 1:1 mixture of the two anomers when they were subjected to our electron transfer initiated cyclization (ETIC) conditions.⁶³ Oxidation of the anomers with Jones reagent⁶⁴ resulted in single lactones **31** and **34**, respectively. These observations were consistent with Houk and Coxon's calculations due to the kinetic and stereoelectronic factors that five-membered ring formation was more favored.

2.2 CYCLIZATION STUDIES ON MONOEPOXIDES

We extended the single electron transfer initiated cascade cyclization of epoxides/polyepoxides to a more systematic study and expected to obtain more detailed information about the selectivities in the cascade cyclizations. At the very beginning, we did some preliminary studies on the cascade cyclization reactions of four monoepoxides. First, *t*-butyl carbonate **35** and methyl carbonate **36** were exposed to under our standard ETIC conditions. The syntheses of these two compounds are shown in Figure 2.7. Protection of alcohol **37** as a TBS ether followed by epoxidation gave epoxide **38** in excellent yields. Epoxide opening using Yamamoto's protocol⁶⁵ provided allylic alcohol **39** in 90% yield. Johnson-Claisen rearrangement⁶⁶ of **39** in the presence of triethyl orthoacetate catalyzed by propionic acid afforded ethyl ester **40** in 96% yield. DIBAL-H reduction of **40** followed by diphenylmethyl lithium addition gave secondary alcohol **41**, which was converted into epoxy alcohol **43** after methylation, removal of silyl group and epoxidation. Protection of **43** with (Boc)₂O⁶⁷ provided *t*-butyl carbonate **35**. Alternatively, reaction of **39** with methyl chloroformate gave methyl carbonate **36**.

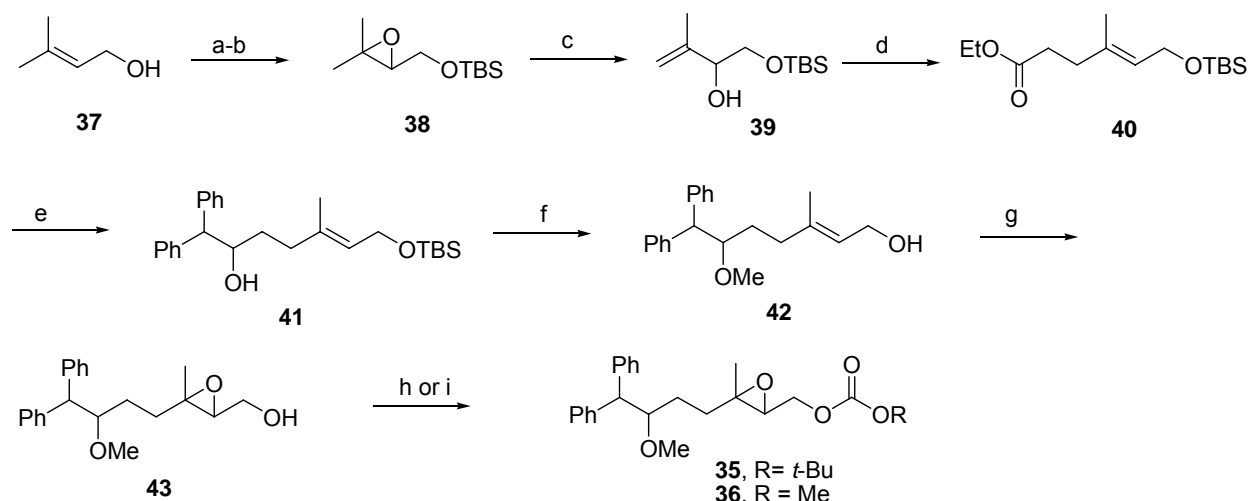


Figure 2.7 Syntheses of the substrates **35** and **36**

Subjecting **35** to our ETIC conditions (*hv*, 0.10 equiv of NMQPF₆, gentle aeration, Na₂S₂O₃, NaOAc, 4Å MS, 1,2-dichloroethane/toluene(5:1, v/v)) gave a mixture of 5-*exo* and 6-*endo* products in 33% yield with a molar ratio of 4.8:1. (Figure 2.8) However, conducting the reaction in CH₃CN/PhMe (5:1, v/v) gave a 34% yield of 6-*endo* product **47** and a 20% yield of a mixture of the 5-*exo* products **45** and **49**. Subsequently, reaction of methyl carbonate **36** in DCE/PhMe (5:1, v/v) gave a mixture of *exo* and *endo* product **45** and **47**, respectively, with about 1:1 ratio in poor yield. Interestingly, reaction of **36** in CH₃CN/PhMe (5:1, v/v) gave exclusively the *endo* product **47** in 57% yield and no *exo* selectivity was observed. The stereochemistry of **47** will be determined after formation of cyclic carbonate **49**.

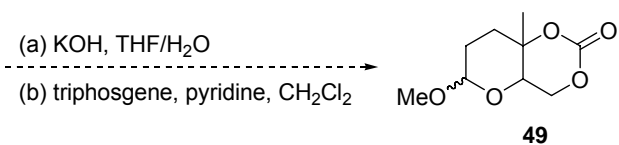
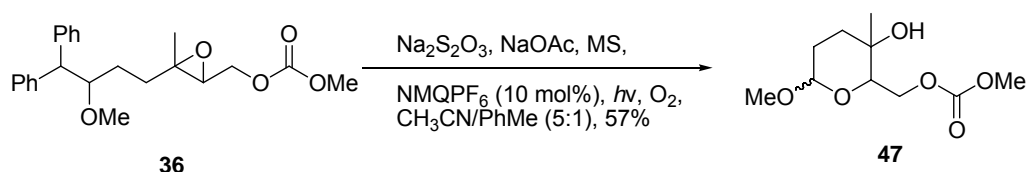
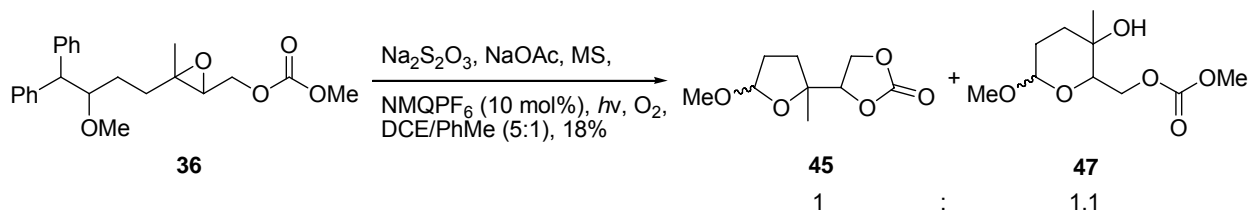
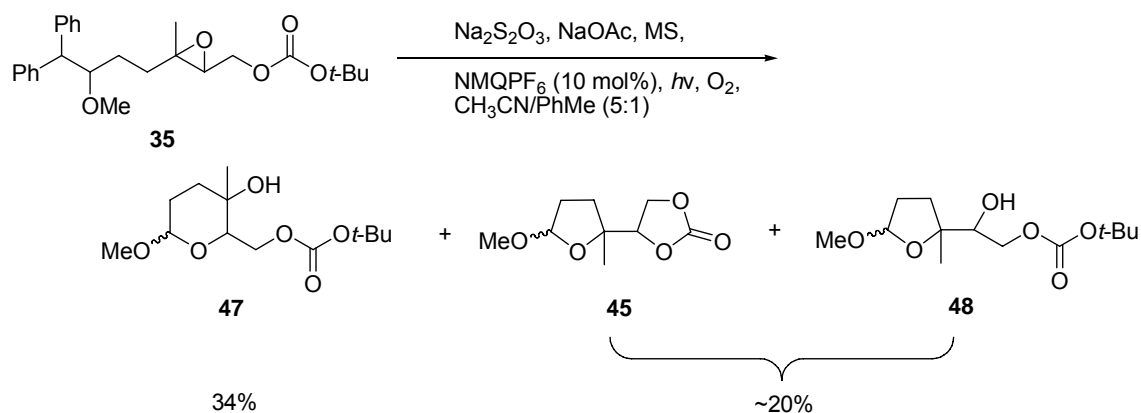
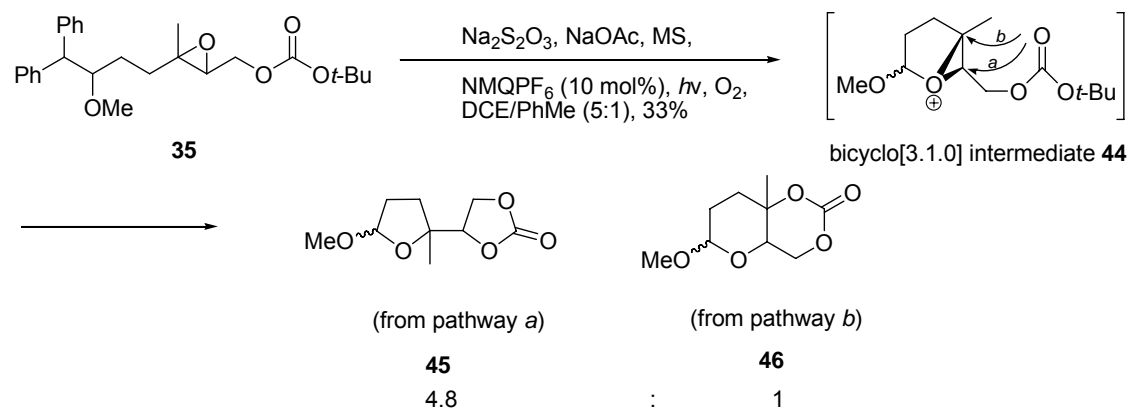
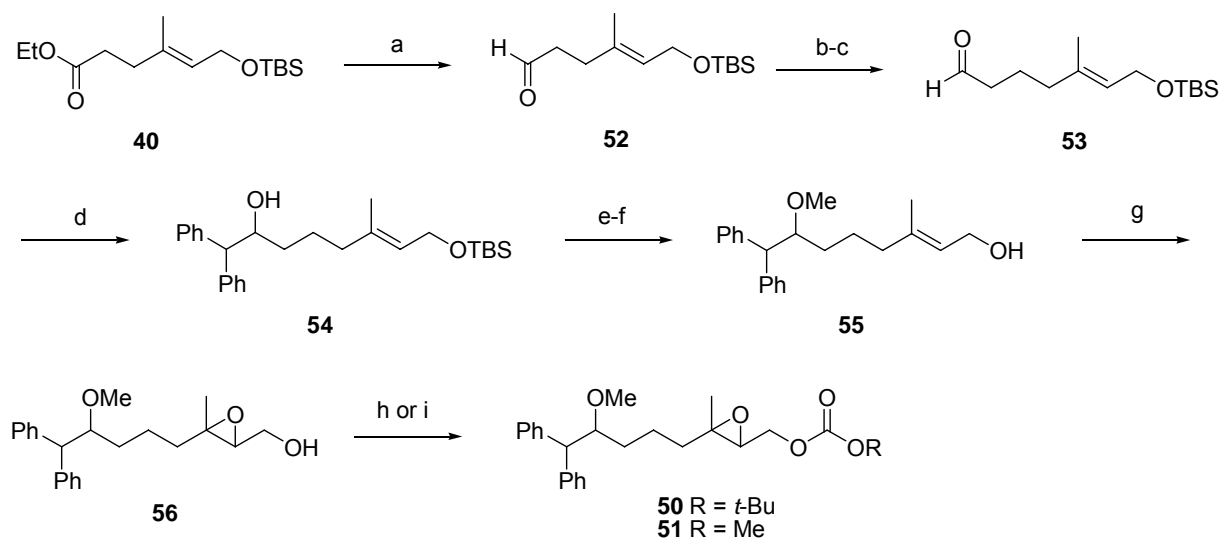


Figure 2.8 Cascade cyclization of two monoepoxides **35** and **36**

In our previous study, homobenzylic ethers (such as **29** and **32**, Figure 2.6) were used in ETIC reactions to form the bicyclic acetals in good yields. Mechanistic study showed that radical cation, for example, **29a**, which arose from oxidation of substrate **29** by photoexcited *N*-methylquinolinium ion, fell apart into the benzyl radical and the oxocarbenium ion. The benzyl radical and oxocarbenium ion could combine with each other to re-form radical cation **29a**. In the presence of a nucleophilic, such as epoxide oxygen, the oxocarbenium ion gave rise to epoxonium ion **29c**, which resulted in the product formation ultimately. Our initial study showed that the nearby oxygen-containing group decreased the nucleophilicity of the epoxide (*cf.* **35** and **36**) thus the pair of the corresponding benzyl radical and the oxocarbenium ion re-formed the radical cation, and no reactivity was obtained. Subsequently, diphenylmethyl (in **35** and **36**) was used instead of benzyl due to the benefit that diphenylmethyl radical was more stable than benzyl radical and the epoxide oxygen could have sufficient time to add to the oxocarbenium ion.

On the other hand, carbonates **50** and **51**, gave entirely different result upon cyclization. The synthesis of these two compounds is outlined in Figure 2.9. Reduction of ethyl ester **40** to aldehyde **52** followed by homologation gave aldehyde **53**. Diphenylmethyl lithium addition, methylation, removal of silyl group and epoxidation provided epoxy alcohol **56**. The epoxy alcohol reacting with (Boc)₂O or MeOCOCl gave *t*-butyl carbonate **50** or methyl carbonate **51**.



(a) DIBAL-H, CH₂Cl₂, -78 °C, 87%. (b) Ph₃P⁺CHOCH₃Cl⁻, NaHMDS, -78 °C. (c) Hg(OAc)₂, THF-H₂O (10:1, v/v); then saturated KI solution, 82%, two steps. (d) Ph₂CH₂, *n*-BuLi, THF, 0 °C, 79%. (e) NaH, DMF, 0 °C; then MeI, 0 °C to rt. (f) TBAF, THF, 97%, two steps. (g) MCPBA, NaHCO₃, CH₂Cl₂, 0 °C, 99%; (h) (Boc)₂O, 1-methylimidazole, PhMe, 0 °C, 89%; (i) ClCO₂Me, pyr, DMAP, CH₂Cl₂, 0 °C, 87%.

Figure 2.9 Synthesis of epoxides **50** and **51**

Cyclization of **50** in DCE/PhMe (5:1) gave *endo* product **58** in 73% yield as a mixture of the two epimers in 1.2:1 ratio. (Figure 2.10) On the other hand, the methyl carbonate **51** gave the same product only in 34% yield with a 4:1 ratio of the two epimers upon cyclization.

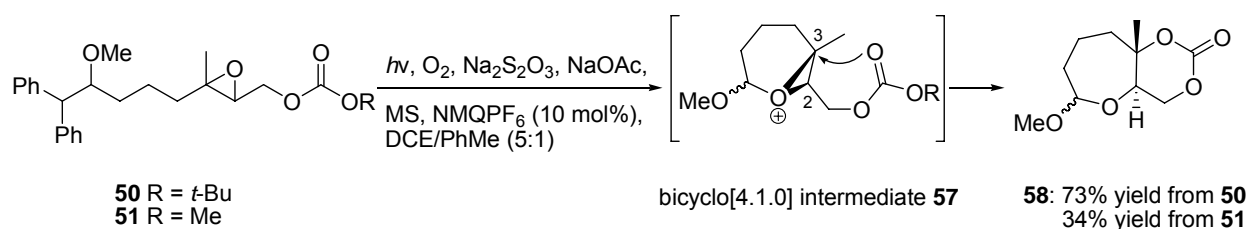


Figure 2.10 Cyclization of monoepoxides **50** and **51**

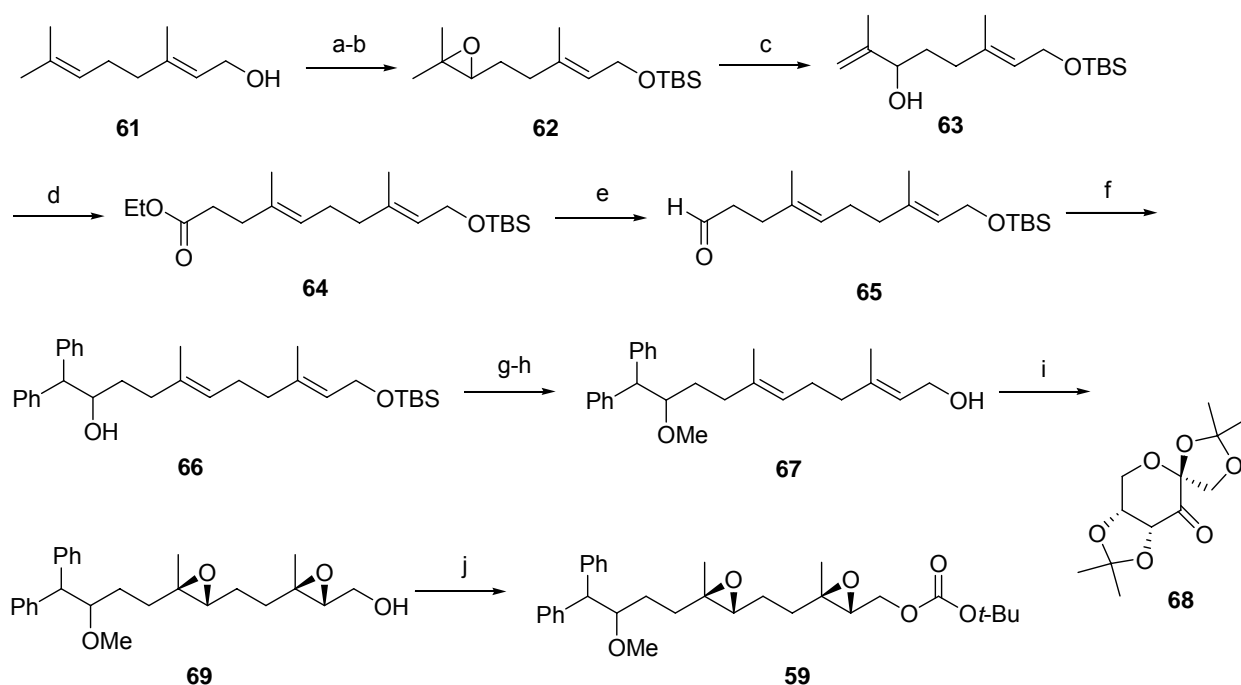
Our preliminary results showed that in nonpolar solvent (DCE), the bicyclo[3.1.0] intermediate (for example, **44**) usually favors *exo*-selectivity while in polar solvent (CH₃CN), *endo*-cyclization is more favored. However, the bicyclo[4.1.0] intermediate, **57**, gave

predominantly *endo* product in nonpolar solvent probably due to the fact that C3 is better disposed to tolerate cationic character or easier attacked by the carbonyl oxygen than C2.

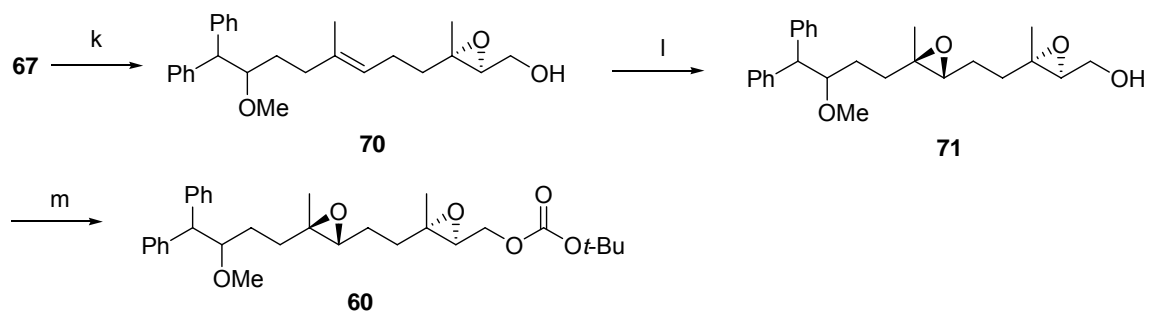
In McDonald's case, both diepoxides **15** and **17** gave exclusively *endo*-selectivity (Figure 2.4) whereas in our case, the selectivity of **35** and **36** depends on the reaction solvents although complete *endo* selectivity was observed from **50** and **51**. The difference between epoxonium ion **17a** and **44** is that **17a** arose from combining an epoxide with a non-stabilized carbocation (a stronger Lewis acid) while **44** was formed from coupling an epoxide with an oxocarbenium ion (a weaker Lewis acid). The different reactivity between these two kinds of epoxonium ions resulted in the observed selectivities. That is, more activated epoxonium ion **17a** further generated tertiary carbocation intermediate **17b**, which afforded *cis*-fused product **18** by carbonyl oxygen addition to the tertiary carbocation. However, less activated epoxonium ion **44** did not exhibit good regioselectivity, providing a mixture of *exo* and *endo* products. Nevertheless, carbonate **50** gave a similar result as **15**, suggesting that bicyclo[4.1.0] epoxonium ion intermediates **57** and **15a**, although activated from two different kinds of electrophiles, make C3 more accessible to addition from carbonyl oxygen relative to C2 to a similar extent.

2.3 CYCLIZATION STUDIES ON DIEPOXIDES

On the basis of our preliminary cyclization results, we extended our study to the diepoxides to construct tricyclic compounds. Diepoxides **59** and **60** were tested first. The synthesis of these two compounds is shown in Figure 2.11. Protection of geraniol **61** with TBSCl followed by regioselective epoxidation gave monoepoxide **58**. Epoxide opening followed by Johnson-Claisen rearrangement of allylic alcohol **63** in the presence of triethyl orthoacetate gave ethyl ester **64** in excellent yields. DIBAL-H reduction and subsequent diphenylmethyl lithium addition to aldehyde **65** yielded secondary alcohol **66**. Methylation followed by silyl group removal provided common intermediate **67**. Double Shi epoxidation⁶⁸ followed by protection with (Boc)₂O afforded **59**. On the other hand, Sharpless asymmetric epoxidation¹², Shi epoxidation⁶⁸ and protection with (Boc)₂O provided substrate **60**.



Reagents: (a) TBSCl, Im, DMF, 97%. (b) MCPBA, CHCl_3 , 0 °C, 77%. (c) 2,2,6,6-tetramethylpiperidine, *n*-BuLi, Et_2AlCl , benzene, 0 °C, 92%. (d) $(\text{EtO})_3\text{CCH}_3$, $\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$, 145 °C, 94%. (e) DIBAL-H, CH_2Cl_2 , -78 °C, 92%. (f) Ph_2CH_2 , *n*-BuLi, THF, 0 °C, 80%. (g) NaH, DMF, 0 °C; then MeI, 0 °C to rt. (h) TBAF, THF, 97%, two steps. (i) Shi ketone **68**, Oxone, $(\text{CH}_3\text{O})_2\text{CH}_2/\text{CH}_3\text{CN}/\text{H}_2\text{O}$, pH 11.4, 0 °C, 88%. (j) $(\text{Boc})_2\text{O}$, 1-methylimidazole, PhMe, 0 °C to rt, 93%.



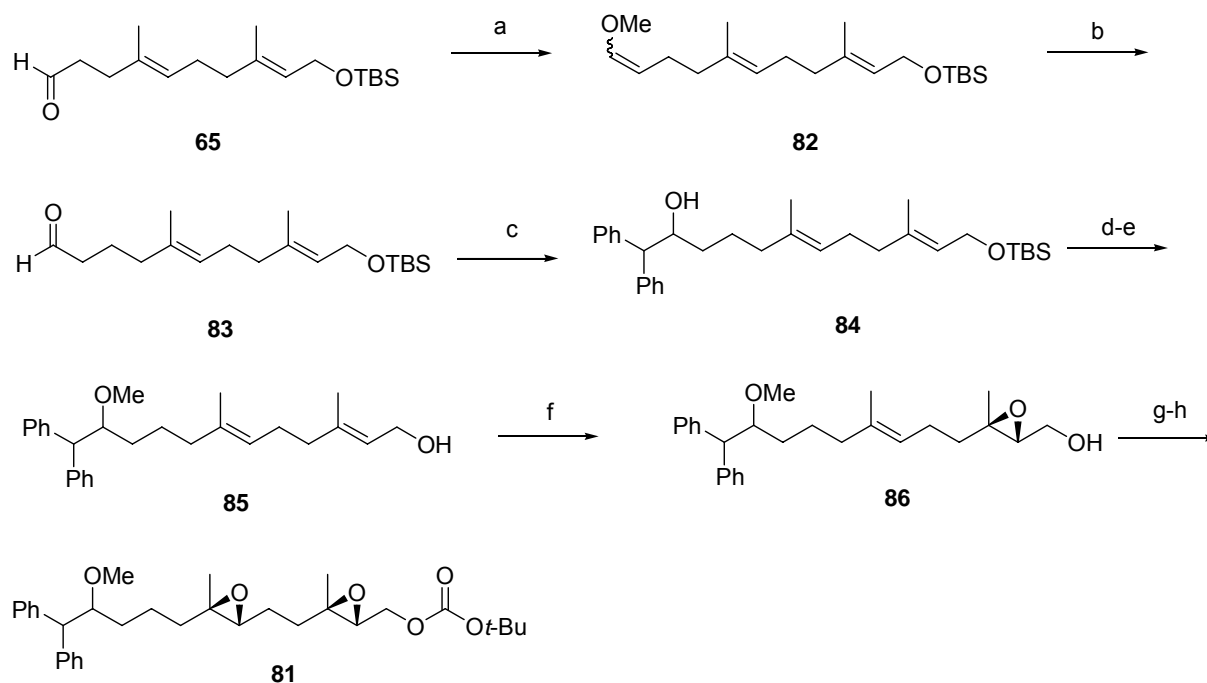
Reagents: (k) L-(+)-DIPT, $\text{Ti}(\text{O}-i\text{Pr})_4$, *t*-BuOOH, CH_2Cl_2 , -25 to -20 °C, 96%. (l) Shi ketone, **68**, Oxone, $(\text{CH}_3\text{O})_2\text{CH}_2/\text{CH}_3\text{CN}/\text{H}_2\text{O}$, pH 11.4, 0 °C, 91%. (m) $(\text{Boc})_2\text{O}$, 1-methylimidazole, PhMe, 0 °C to rt, 86%.

Figure 2.11 Synthesis of diepoxides **59** and **60**

Reaction of **59** under ETIC conditions afforded an inseparable mixture of *exo,exo* and *endo,endo* products **73** and **74**, respectively, in combined 40% yield with the former compound predominating. (Figure 2.12) Similarly, cyclization of **60** also gave an inseparable mixture of *exo,exo* and *endo,endo* products **77** (major) and **78** (minor), respectively, in combined 61% yield. These results are consistent with our expectations since the bicyclo[3.1.0] intermediate **72a** favored *exo* selectivity to give **72b** as the major intermediate which still acted as a bicyclo[3.1.0] intermediate to predominantly give **73** as the *exo,exo* product. The minor intermediate **72c** from *endo*-selectivity of **72a** was a bicyclo[4.1.0] epoxonium ion and resulted in the formation of **74**. (*vide supra*) Similar analysis could also be applied to formation of **77** and **78**.

Oxidation of the mixture of **73** and **74** with Jones reagent afforded lactone **75** and unreacted acetal **74** which will be converted into lactone **76** upon treatment with MCPBA and $\text{BF}_3 \cdot \text{OEt}_2$ followed by addition of Et_3N .^{69, 70} Likewise, oxidation of the acetal mixture **77** and **78** with Jones reagent gave lactone **79** and the recovered **78** will be fully characterized by conversion into the corresponding lactone **80**.

Based on McDonald's of triepoxides results (Figure 2.4 and 2.5) and our study on the cyclization result of monoepoxide **50**, we postulated that the diepoxide **81** would also give *endo,endo*-selectivity upon cyclization. The synthetic approach to **81** is schematically shown in Figure 2.13. Homologation of aldehyde **65** followed by diphenylmethyl lithium addition gave secondary alcohol **84** which was converted into dienol **85** after methylation and silyl group removal. Sharpless asymmetric epoxidation of **85**, Shi epoxidation of the internal olefin and protection of the primary alcohol as a *t*-butyl carbonate provided substrate **81** in good yield.



Reagents: (a) $\text{Ph}_3\text{P}^+\text{CH}_2\text{OCH}_3\text{Cl}^-$, NaHMDS, $-78\text{ }^\circ\text{C}$, 1 h; then **65**; (b) $\text{Hg}(\text{OAc})_2$, THF- H_2O (10:1, v/v), 91%, two steps; (c) Ph_2CH_2 , *n*-BuLi, $75\text{ }^\circ\text{C}$, 1 h; then **83**, $0\text{ }^\circ\text{C}$, 80%; (d) NaH, DMF, $0\text{ }^\circ\text{C}$; then MeI; (e) TBAF, THF, 98%, two steps; (f) D-(-)-DIPT, $\text{Ti}(\text{O-}i\text{-Pr})_4$, *t*-BuOOH, CH_2Cl_2 , -35 to $-30\text{ }^\circ\text{C}$, 95%; (g) Shi ketone **68**, Oxone, $(\text{CH}_3\text{O})_2\text{CH}_2/\text{CH}_3\text{CN}/\text{H}_2\text{O}$, pH 11.4, $0\text{ }^\circ\text{C}$; (h) $(\text{Boc})_2\text{O}$, 1-methylimidazole, PhMe, $0\text{ }^\circ\text{C}$ to rt, 86%, two steps.

Figure 2.13 Synthesis of diepoxide **81**

Subjecting **81** to our standard ETIC conditions gave expected *endo,endo* product **88** in 54% yield as a mixture of the two epimers. (Figure 2.14) During this process, both of the two bicyclo[4.1.0] intermediates **87a** and **87b** gave exclusively *endo*-regioselectivity, which resulted in formation of **88** eventually.

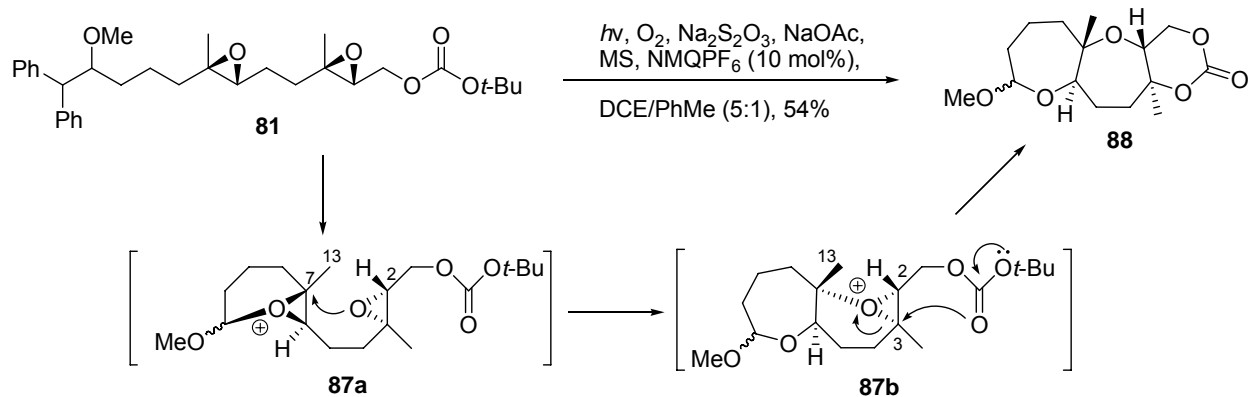


Figure 2.14 Cyclization of **81**

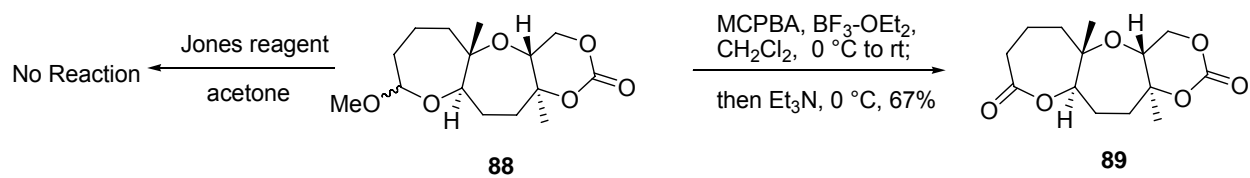


Figure 2.15 Oxidation of acetal **88** to lactone **89**

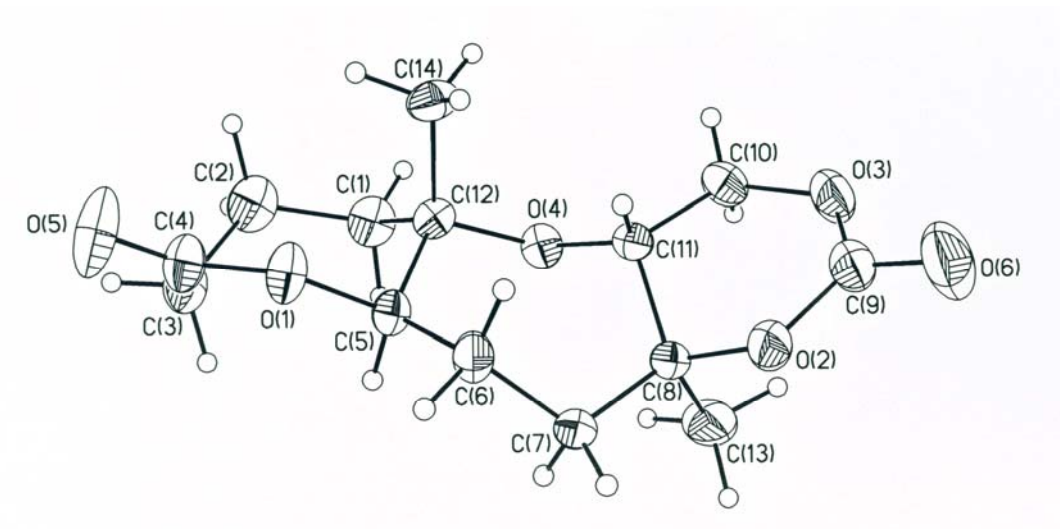
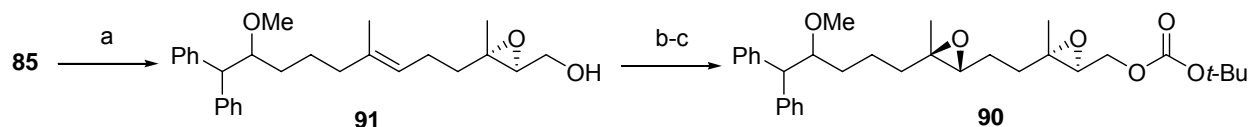


Figure 2.16 X-ray crystal structure of **89**

In order to simplify the characterization, acetal **88** was required to be oxidized to the corresponding lactone. Jones' reagent⁶⁴ was used but no reaction was observed. Alternatively, a combination of MCPBA with $\text{BF}_3 \cdot \text{OEt}_2$ followed by addition of Et_3N ^{69, 70} effected this transformation. (Figure 2.15) Spectroscopic analysis (^1H and ^{13}C NMR, IR, MS) indicated that the corresponding lactone **89** is a single compound, whose structure was further confirmed by X-ray single crystal diffraction (Figure 2.16) and all the stereochemical outcomes match exactly what we expected.

Likewise, cyclization of **90**, which was synthesized in a similar way to **81** as illustrated in Figure 2.17, also provided *endo,endo* product **92** in 72-79% yield. (Figure 2.18) Oxidation of the acetal with MCPBA/ $\text{BF}_3 \cdot \text{OEt}_2$ and the following addition of Et_3N ^{69, 70} gave lactone **93**. Spectroscopic analysis (^1H and ^{13}C NMR, IR and MS) showed that **93** is a single compound and the proposed structure based on cyclization of **81** is shown in 2.18. It is worth noting that a better yield was obtained from the cyclization of **90** compared with **81**. We presume that in the case of **81**, formation of **87b** from **87a** was partially encumbered by the steric repulsion between the methyl group at the C7 and the incoming C2 proton while in the case of **90**, the corresponding steric interaction was absent and a higher efficiency of ring formation was observed.



Reagents: (a) L-(+)-DIPT, $\text{Ti}(\text{O}-i\text{Pr})_4$, $t\text{-BuOOH}$, CH_2Cl_2 , -35 to -30 °C, 97%; (b) Shi ketone **68**, Oxone, $(\text{CH}_3\text{O})_2\text{CH}_2/\text{CH}_3\text{CN}/\text{H}_2\text{O}$, pH 11.4, 0 °C; (c) $(\text{Boc})_2\text{O}$, 1-methylimidazole, PhMe, 0 °C to rt, 82%, two steps.

Figure 2.17 Synthesis of diepoxide **90**

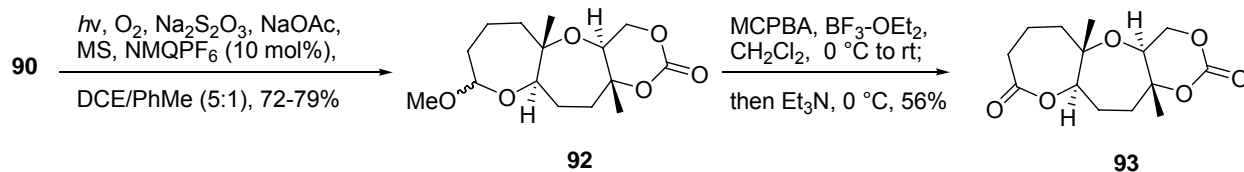
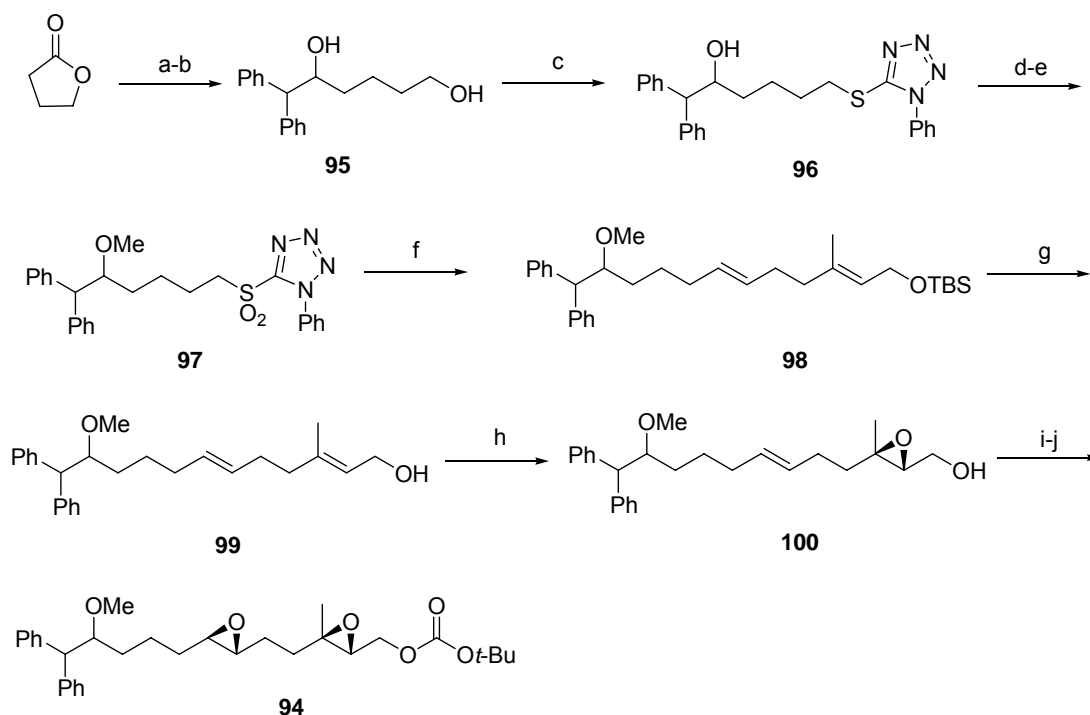


Figure 2.18 Cyclization of **90**

With these two successful examples in hand, we turned our attention to exploit a general method to effectively construct polycyclic ether rings present in hemibrevetoxin B and structurally related natural products. Towards this end, we synthesized substrate **94**, as outlined in Figure 2.19. Reduction of the δ -valerolactone to the lactol followed by diphenylmethyl lithium addition gave diol **95** in 82% yield over the two steps. Selective conversion of the primary hydroxyl group under Mitsunobu conditions provided thioether **96** in 97% yield. Methylation of **96** followed by oxidation of the sulfide gave sulfone **97** in 81% yield. The Julia-Kocienski olefination of sulfone **97** with aldehyde **52** provided *trans* olefin **98** in 63% yield. Removal of silyl group, Sharpless asymmetric epoxidation, Shi epoxidation and protection with (Boc)₂O produced substrate **94** in 66% yield over four steps.



Reagents: (a) DIBAL-H, CH_2Cl_2 , $-78\text{ }^\circ\text{C}$. (b) Ph_2CH_2 , *n*-BuLi, THF, reflux; then crude tetrahydrofuran-2-ol, $0\text{ }^\circ\text{C}$, 82%, two steps. (c) 1-phenyl-1H-tetrazole-5-thiol, PPh_3 , DIAD, THF, 0 to $20\text{ }^\circ\text{C}$, 97%. (d) NaH, DMF, $0\text{ }^\circ\text{C}$; then MeI, 0 to $20\text{ }^\circ\text{C}$, 85%. (e) MCPBA, NaHCO_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 95%. (f) KHMDS, DME, $-78\text{ }^\circ\text{C}$; then **52**, $-78\text{ }^\circ\text{C}$ to rt, 63%. (g) TBAF, THF, 95%. (h) D-(-)-DIPT, $\text{Ti}(\text{O}-i\text{-Pr})_4$, *t*-BuOOH, CH_2Cl_2 , $-30\text{ }^\circ\text{C}$, 95%. (i) Shi ketone **68**, Oxone, $(\text{CH}_3\text{O})_2\text{CH}_2/\text{CH}_3\text{CN}/\text{H}_2\text{O}$, pH 11.4, $0\text{ }^\circ\text{C}$. (j) $(\text{Boc})_2\text{O}$, 1-Methylimidazole, PhMe, 0 to $20\text{ }^\circ\text{C}$, 73%, two steps.

Figure 2.19 Synthesis of diepoxide **94**

Cyclization of **94** gave a mixture of *exo,exo* and *endo,endo* products **102** and **103** in combined 49% yield. (Figure 2.20) After further purification, a small amount of nearly pure **103** was oxidized to the corresponding lactone **104** and its skeleton and stereochemical outcomes were confirmed by X-ray single crystal diffraction. (Figure 2.21)

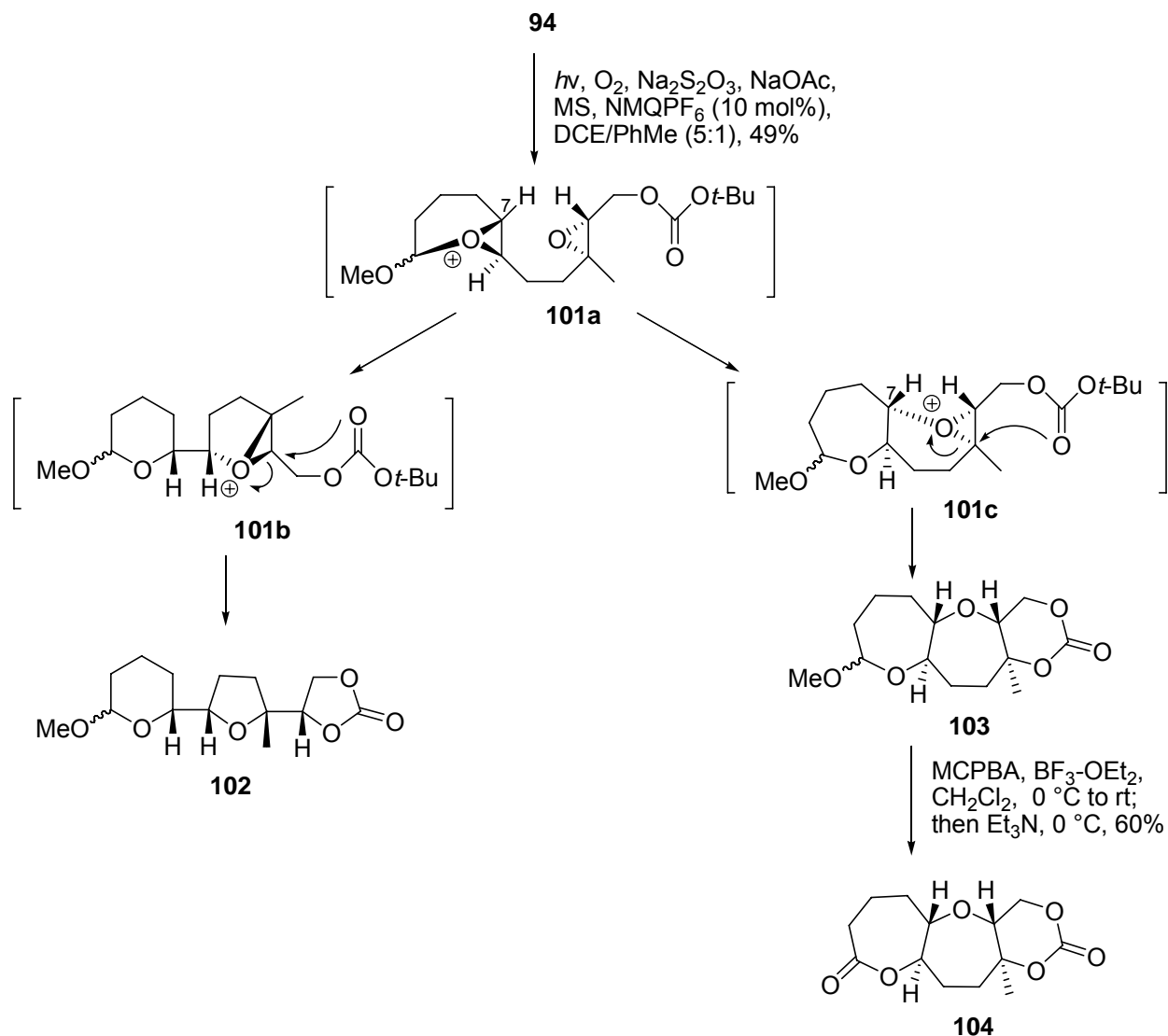


Figure 2.20 Cyclization of **94**

It is manifest that without methyl group at C7, no exclusive regiochemical control could be accomplished in contrast to **81**. To achieve *endo*-selectivity completely, the methyl group at C7 is mandatory. In McDonald's case, *endo*-selectivity was still observed from **25a** and **25b** (Figure 2.5) and they attributed this to the minimization of the ring strain in formation of the fused bicyclo[4.1.0] epoxonium ion relative to the bicyclo[3.1.0] intermediate. However, in our

case, the epoxonium ion activated by oxocarbenium ion has different Lewis acidity from that activated by a non-stabilized tertiary carbocation in McDonald's case (Figure 2.5, **25a** and **25b**) and without the substitution bias, the competition between 6-*exo* (**101b**) and 7-*endo* (**101c**) cyclizations from **101a** resulted in formation of the above two sets of products.

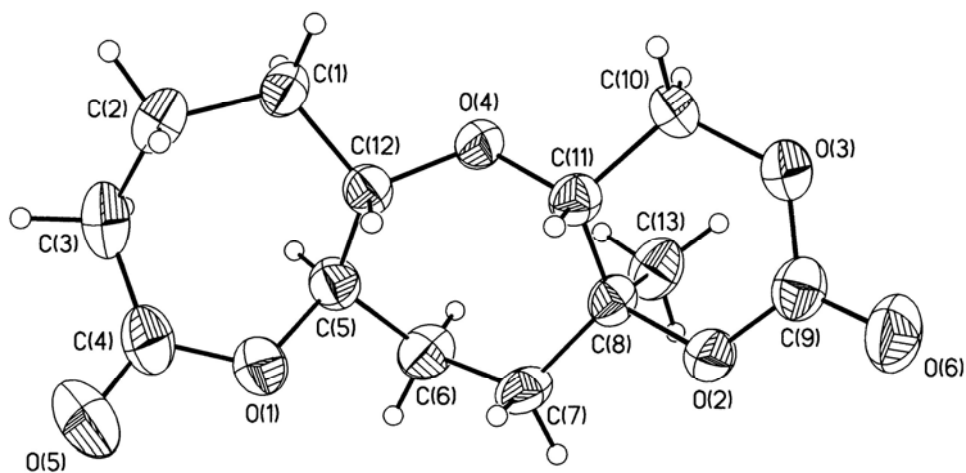
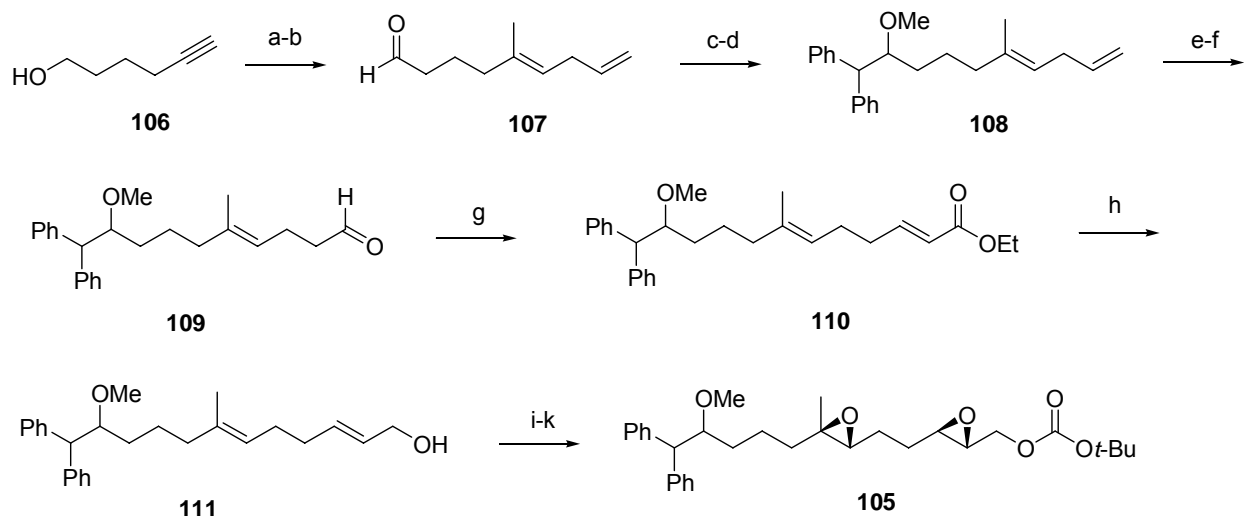


Figure 2.21 X-ray crystal structure of **104**

In order to further investigate the substitution effect on the cyclization selectivity, we synthesized diepoxide **105** containing one internal disubstituted epoxide with synthetic approach depicted in Figure 2.22. Carboalumination of 5-heptyn-1-ol mediated by Cp_2ZrCl_2 followed by in situ coupling of the resulting vinyl aluminum species with allyl bromide⁷¹⁻⁷³ gave the crude dienol, which was oxidized to dienal **107**. The diphenylmethyl lithium addition to aldehyde **107** and the following methylation of the nascent secondary alcohol provided skipped diene **108** in 72% yield. Hydroboration⁷⁴ of the terminal olefin followed by oxidation of the primary alcohol afforded aldehyde **109**, which was converted into α,β -unsaturated ester **110** under the standard

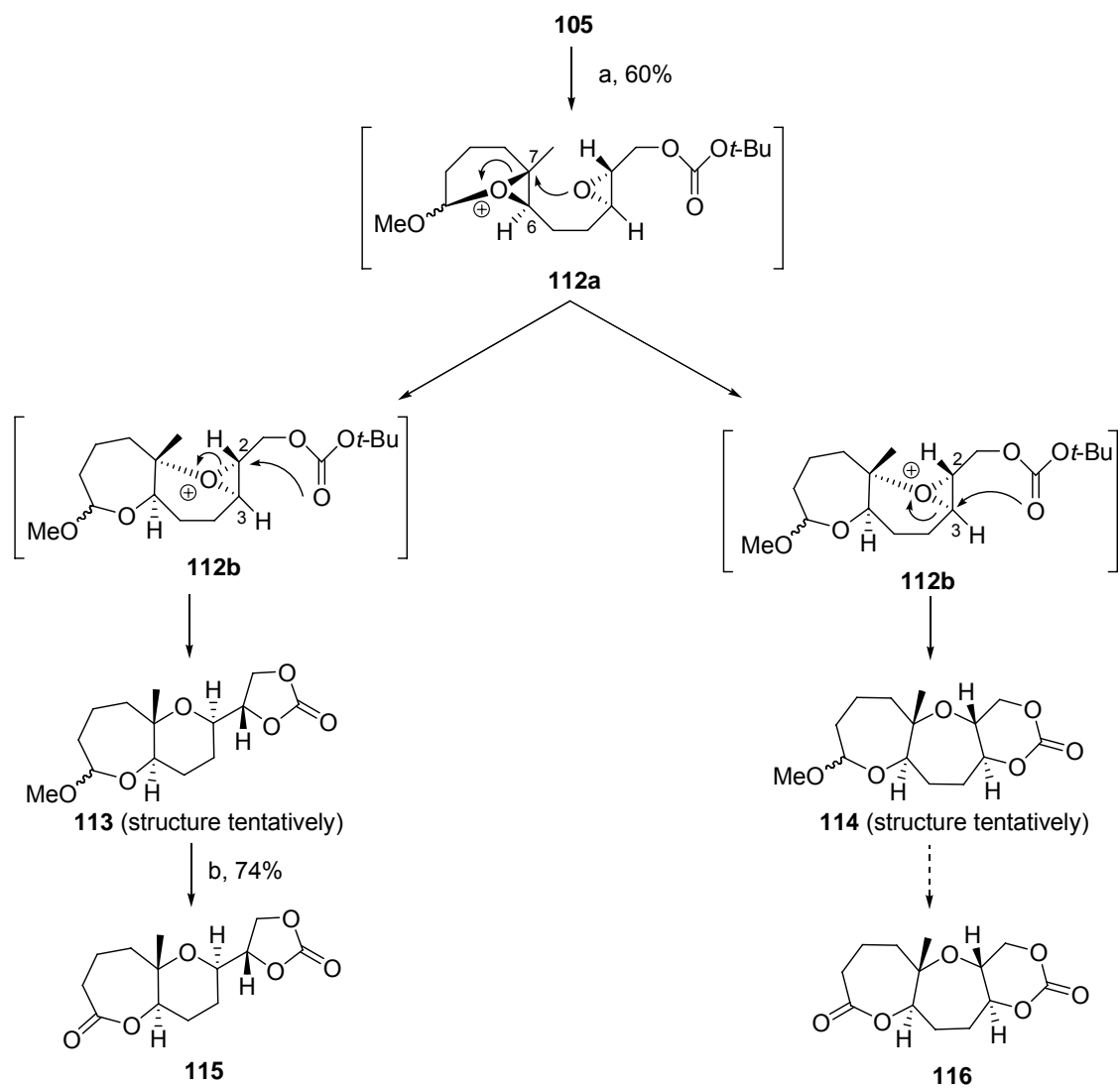
Horner-Emmons conditions. Reduction of the ethyl ester, Sharpless asymmetric epoxidation, Shi epoxidation and protection with (Boc)₂O provided **105** in good yield.



Reagents: (a) AlMe₃, Cp₂ZrCl₂, CH₂Cl₂; then allyl bromide, Pd(PPh₃)₄, THF. (b) DMPI, NaHCO₃, CH₂Cl₂, 30.3%, two steps. (c) Ph₂CH₂, *n*-BuLi, THF, 73.3%. (d) NaH, DMF, 0 °C; then MeI, 0 °C to rt, 98.3%. (e) (Sia)₂BH, THF; then H₂O₂, NaOH, 70%. (f) TEMPO, NaHCO₃, iodobenzene diacetate, CH₂Cl₂, 74%. (g) triethylphosphonoacetate, NaH, THF, 0 °C, 96%. (h) DIBAL-H, THF, -78 °C, 88%. (i) D-(-)-DIPT, Ti(O-*i*-Pr)₄, *t*-BuOOH, CH₂Cl₂, -25 °C, 95.2% (j) Shi ketone **68**, Oxone, (CH₃O)₂CH₂/CH₃CN/H₂O, pH 11.4, 0 °C, 90.1%. (m) (Boc)₂O, 1-methylimidazole, PhMe, 0 °C to rt, 96.5%

Figure 2.22 Synthesis of diepoxide **105**

Diepoxide **105**, upon ETIC conditions, gave a mixture of *endo,exo* and *endo,endo* product with the former predominating. (Figure 2.23) In terms of the mechanism, bicyclo[4.1.0] intermediate **112a**, which arose from addition of the proximal epoxide oxygen to the oxocarbenium ion, gave rise to bicyclo[4.1.0] epoxonium ion from addition of the second epoxide oxygen to the *endo* position C7. However, intermediate **112b** (*cf.* **87b**), without the methyl group at C3, provided a mixture of two separable tricyclic products **113** and **114**. Oxidation of **113** gave the lactone **115**, which will be extensively analyzed, as well as **116**.



(a) $h\nu$, O_2 , $Na_2S_2O_3$, $NaOAc$, MS, $NMQPF_6$ (10 mol%), $DCE/PhMe$ (5:1). (b) MCPBA, $BF_3 \cdot OEt_2$, CH_2Cl_2 , $0^\circ C$ to rt; then Et_3N , $0^\circ C$

Figure 2.23 Cyclization of **105**

2.4 CONCLUSION

In summary, four monoepoxides and six diepoxides were investigated in single electron transfer initiated cascade cyclization and conclusions were drawn as follows:

1. The bicyclo[3.1.0] epoxonium ion intermediates formed in the cyclization favor 5-*exo*-cyclization in the nonpolar solvent (1,2-dichloroethane) while in the polar solvent (CH₃CN), they prefer 6-*endo*-selectivity.
2. The bicyclo[4.1.0] epoxonium ion intermediates usually give 7-*endo* regiochemical selectivity in the presence of substitution-induced bias (the angular methyl group here). However, without the substitution effect, 6-*exo* and 7-*endo*-cyclizations are two competitive pathways.

2.5 FUTURE WORK

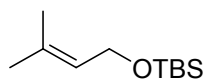
After finishing full characterizations of the cyclization products, we will utilize CAChe[®] program to calculate the energy of the HOMOs of the nucleophilic epoxides and LUMOs of the electrophilic epoxides to have a better insight into the selectivities we observed.

APPENDIX B

Studies on the cascade cyclization reactions of epoxides/polyepoxides initiated by single electron transfer (Supporting Information)

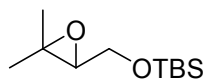
Some of the cyclization products are partially assigned and the full characterizations will be ensued soon.

General Experimental: Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded at 300 MHz and 75 MHz, respectively, at 500 MHz and 125 MHz or at 600 MHz and 150 MHz if specified. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as reference values. For ^1H NMR: $\text{CDCl}_3 = 7.27$ ppm. For ^{13}C NMR: $\text{CDCl}_3 = 77.23$ ppm. For proton data: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublets; ddt = doublet of doublet of triplets; ddq = doublet of doublet of quartets; br = broad; m = multiplet; app t = apparent triplet; app q = apparent quartet; app p = apparent pentet. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2 . Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Reagent grade ethyl acetate and hexanes (commercial mixture) were used without further purification for chromatography. Reagent grade methylene chloride (CH_2Cl_2) was distilled from CaH_2 . Diethyl ether (Et_2O) and tetrahydrofuran (THF) were dried by passing through aluminum drying column. Anhydrous methanol (MeOH), benzene (C_6H_6) and acetonitrile (CH_3CN) were distilled according to the standard procedure. All reactions were conducted under a nitrogen atmosphere unless otherwise specified.



(3-Methylbut-2-enyloxy)(*tert*-butyl)dimethylsilane

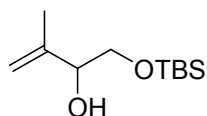
The alcohol (6.029 g, 70.0 mmol) in DMF (70.0 mL) was treated with imidazole (5.718 g, 84.0 mmol) and TBSCl (11.606 g, 77.0 mmol). The reaction mixture was stirred at room temperature for 18 h, then quenched with water (50 mL) and extracted with Et₂O (3 x 50 mL). The extracts were dried over MgSO₄, evaporated and purified by column chromatography (10% Et₂O in hexanes) to give the desired product (13.324 g, 95.0%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 5.31 (app t, *J* = 6.4 Hz, 1H), 4.18 (d, *J* = 6.4 Hz, 2H), 1.72 (s, 3H), 1.64 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 133.9, 124.7, 60.5, 26.2, 26.0, 18.7, 18.1, -4.9; IR (neat) 2957, 2929, 2857, 1472, 1380, 1255, 1119, 1070, 834, 774.



((3,3-Dimethyloxiran-2-yl)methoxy)(*tert*-butyl)dimethylsilane (38)

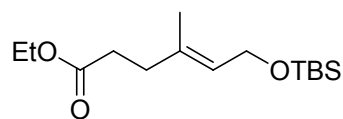
A solution of the TBS ether (6.0117 g, 30.0 mmol) in CH₂Cl₂ (300 mL) at 0 °C was treated with NaHCO₃ powder (5.040 g, 60.0 mmol) followed by *m*-chloroperbenzoic acid (70-75%, 7.2479 g, 31.5 mmol). The reaction mixture was stirred at 0 °C for 1.5 h and then quenched with saturated Na₂S₂O₃ solution (100 mL). After warmed to room temperature, the biphasic mixture was poured into water (100 mL) and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 x 150 mL) and the combined organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (15% Et₂O in hexanes) to give the epoxide (6.3115 g, 97.2%) as a colorless liquid: ¹H NMR (300 MHz, CDCl₃) δ 3.75 (d, *J* = 5.3 Hz, 1H), 3.74 (d, *J* = 5.4 Hz, 1H), 2.91 (t, *J* = 5.4 Hz, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 64.2,

62.5, 58.3, 26.1, 24.9, 19.0, 18.5, -5.0, -5.2; IR (neat) 2958, 2930, 2886, 2858, 1472, 1379, 1256, 1140, 1086, 838, 778.



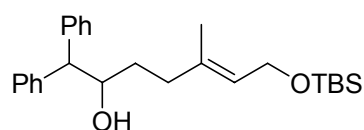
1-(*tert*-Butyldimethyl-silyloxy)-3-methylbut-3-en-2-ol (39)

A solution of 2,2,6,6-tetramethylpiperidine (2.8252 g, 20.0 mmol) in anhydrous benzene (12.0 mL) at 0 °C was treated dropwise with *n*-BuLi (1.6 M in hexanes, 12.5 mL, 20.0 mmol). After 10 min, diethylaluminum chloride (1.0 M in heptanes, 20.0 mL, 20.0 mmol) and the resulting white suspension was stirred at 0 °C for 30 min. The epoxide **38** (1.7311 g, 8.00 mmol, dissolved in 8.0 mL of anhydrous benzene) was added dropwise and the flask formerly containing the epoxide was rinsed twice with benzene (2 x 4.0 mL). The reaction mixture was stirred further for 1.5 h at 0 °C and then quenched with saturated sodium tartrate solution (50 mL). The biphasic mixture was poured onto water (100 mL) and extracted with Et₂O (3 x 50 mL). The organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was purified by column chromatography (15% Et₂O in hexanes) to give allylic alcohol **39** (1.5581 g, 90.0%) as a colorless liquid: ¹H NMR (300 MHz, CDCl₃) δ 5.04 (m, 1H), 4.92 (m, 1H), 4.12 (m, 1H), 3.71 (dd, *J* = 9.9, 3.6 Hz, 1H), 3.48 (dd, *J* = 9.9, 8.0 Hz, 1H), 2.66 (d, *J* = 3.0 Hz, 1H), 1.75 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 144.0, 112.0, 75.4, 66.4, 26.0, 19.0, 18.4, -5.2; IR (neat) 3446, 2955, 2929, 2858, 1472, 1256, 1113, 899, 836, 777; HRMS (EI): *m/z* calcd for C₇H₁₅O₂Si (M – C₄H₉) 159.0841, found 159.0811.



**Ethyl (*E*)-6-(*tert*-butyldimethylsilyloxy)-4-methylhex-4-enoate
(40)**

A mixture of **39** (2.7093 g, 12.52 mmol), triethyl orthoacetate (freshly distilled, 9.2 mL, 50.08 mmol) and propionic acid (46.4 mg, 0.626 mmol) in a two-neck round bottomed flask equipped with a short path was heated to 145 °C and kept at this temperature for 4 h. (During this period of time, a lot of volatiles were distilled out.) The unreacted triethyl orthoacetate was removed by simple distillation and the residue was purified by column chromatography (5% EtOAc in hexanes) to give ethyl ester **40** (3.4331 g, 95.7%) as a colorless liquid: ¹H NMR (300 MHz, CDCl₃) δ 5.32 (qt, *J* = 6.3, 1.2 Hz, 1H), 4.20 (d, *J* = 6.3 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.46-2.40 (m, 2H), 2.37-2.30 (m, 2H), 1.64 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 173.5, 135.3, 125.3, 60.5, 60.4, 34.6, 33.0, 26.2, 18.6, 16.6, 14.5, -4.9; IR (neat) 2956, 2930, 2857, 1739, 1472, 1255, 1158, 1110, 1068, 836, 776; HRMS (EI): *m/z* calcd for C₁₅H₂₉O₃Si (M - H) 285.1886, found 285.1840.

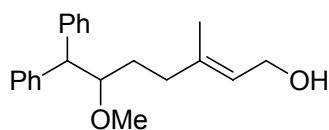


(*E*)-7-(*tert*-Butyldimethylsilyloxy)-5-methyl-1,1-diphenylhept-5-en-2-ol (41)

Ethyl ester **40** (1.000 g, 3.491 mmol) in CH₂Cl₂ (10.0 mL) at -78 °C was treated dropwise with DIBAL-H (1.0 M in hexanes, 3.67 mL, 3.67 mmol). The reaction mixture was stirred at -78 °C for 1 h and then quenched with saturated sodium tartrate solution (15 mL). After warmed up to room temperature, the mixture was stirred vigorously for 30 min and extracted with CH₂Cl₂ (3 x 30 mL). The organic extracts were dried over MgSO₄, filtered and concentrated.

In a separate two-necked round-bottomed flask, a solution of diphenylmethane (1.76 g, 10.5 mmol) in THF (10.0 mL) was treated dropwise with *n*-BuLi (1.6 M in hexanes, 6.54 mL,

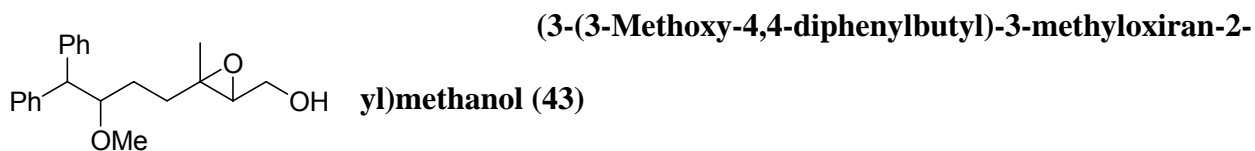
10.5 mmol) and the resulting deep orange solution was refluxed for 1 h, and then cooled to 0 °C. The as-prepared crude aldehyde (dissolved in 2.0 mL of THF) was added dropwise and the flask formerly containing the aldehyde was rinsed with THF (2 x 0.5 mL). The reaction mixture was stirred at 0 °C for 1 h, then warmed to room temperature and quenched by slow addition of saturated NaHCO₃ solution (10 mL). The mixture was poured onto water (20 mL) and extracted with Et₂O (3 x 40 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (3% - 12% EtOAc in hexanes) to give the secondary alcohol (0.997 g, 69.6%, two steps) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.17 (m, 10H), 5.32 (qt, *J* = 6.4, 1.2 Hz, 1H), 4.40-4.29 (m, 1H), 4.18 (d, *J* = 6.2 Hz, 2H), 3.92 (d, *J* = 8.4 Hz, 1H), 2.30-2.20 (m, 1H), 2.17-2.07 (m, 1H), 1.66 (d, *J* = 3.4 Hz, 1H), 1.70-1.60 (m, 1H), 1.56 (s, 3H), 1.58-1.44 (m, 1H), 0.92 (s, 9H), 0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 142.6, 141.7, 136.9, 129.0, 128.8, 128.4, 127.0, 126.7, 125.0, 73.5, 60.4, 59.0, 35.9, 33.1, 26.2, 18.6, 16.4, -4.8; IR (neat) 3458, 2954, 2928, 2856, 1599, 1494, 1451, 1386, 1254, 1112, 1067, 835, 776.



(*E*)-6-Methoxy-3-methyl-7,7-diphenylhept-2-en-1-ol (42)

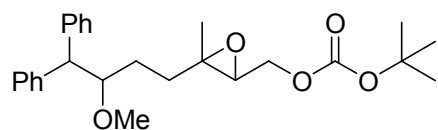
Alcohol **41** (0.908 g, 2.21 mmol) in anhydrous DMF (10.0 mL) at 0 °C was treated with NaH (60% dispersion in mineral oil, 0.221 g, 5.52 mmol) and the suspension was stirred at 0 °C for 30 min. MeI (0.55 mL, 8.84 mmol) was added dropwise and the reaction mixture was allowed to warm up to room temperature. After stirred for 3 h, the reaction was quenched with water (30 mL) cautiously and extracted with Et₂O (3 x 50 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The resulting residue was dissolved in THF (11.0 mL) and TBAF monohydrate (0.693 g, 5.730 mmol) was added in one

portion. The yellow solution was stirred for 1.5 h and then concentrated. The residue was purified by column chromatography (30% - 40% EtOAc in hexanes) to give alcohol **42** (0.684 g, 99.7%, two steps) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.08 (m, 10H), 5.37 (qt, $J = 6.9, 1.2$ Hz, 1H), 4.12 (d, $J = 6.8$ Hz, 2H), 4.02 (d, $J = 8.4$ Hz, 1H), 3.92 (ddd, $J = 8.2, 6.4, 4.1$ Hz, 1H), 3.17 (s, 3H), 2.22-2.03 (m, 2H), 1.73-1.48 (m, 2H), 1.58 (s, 3H), 1.30 (br s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.9, 142.5, 139.7, 129.0, 128.7, 128.4, 126.6, 126.5, 123.8, 83.4, 59.5, 58.1, 56.4, 35.1, 30.5, 16.4; IR (neat) 3396, 3026, 2929, 1599, 1494, 1451, 1374, 1241, 1102, 1002, 756, 703; HRMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{26}\text{O}_2\text{Na}$ ($\text{M} + \text{Na}$) 333.1831, found 333.1817.



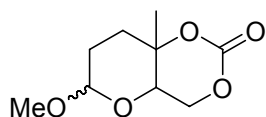
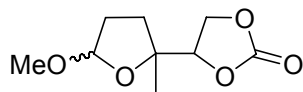
A solution of **42** (252.0 mg, 0.8118 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C was treated with NaHCO_3 powder (136.4 mg, 1.624 mmol) followed by *m*-chloroperbenzoic acid (pure, 147.1 mg, 0.8524 mmol). The reaction mixture was stirred at 0 °C for 1 h and then quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (2.0 mL). After warmed to room temperature, the biphasic mixture was poured onto water (5 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (40% - 50% EtOAc in hexanes) to give the epoxy alcohol (251.4 mg, 94.9%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.17 (m, 10H), 4.00-3.91 (m, 2H), 3.81-3.73 (m, 1H), 3.68-3.59 (m, 1H), 3.16/3.14 (s, 3H), 2.91-2.85 (m, 1H), 1.80-1.38 (m, 4H), 1.19/1.17 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.7, 142.4, 142.3, 128.9, 128.8, 128.6, 128.5, 126.7, 126.5,

83.4, 83.3, 63.0, 62.7, 61.5, 61.5, 61.4, 58.1, 57.9, 56.4, 56.2, 33.9, 33.7, 27.5, 27.0, 17.0, 16.7; IR (neat) 3418, 2931, 1599, 1495, 1452, 1385, 1099, 1032, 747, 704; HRMS (ESI): m/z calcd for $C_{21}H_{26}O_3Na$ (M + Na) 349.1780, found 349.1766.



tert-Butyl (3-(3-methoxy-4,4-diphenylbutyl)-3-methyloxiran-2-yl)methyl carbonate (35)

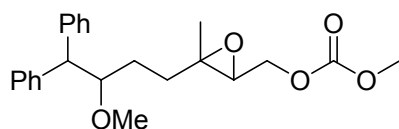
Epoxy alcohol **43** (192.0 mg, 0.5882 mmol) in anhydrous toluene (5.8 mL) at 0 °C was treated with 1-methylimidazole (46.9 μ L, 0.588 mmol) followed by (Boc)₂O (320.8 mg, 1.470 mmol). The reaction mixture was stirred at 0 °C for 4 h, then diluted with CH₂Cl₂ (20 mL) and poured onto water (10 mL). The biphasic mixture was separated and the aqueous layer was washed with CH₂Cl₂ (3 x 15 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (10% - 12.5% EtOAc in hexanes containing 0.5% Et₃N) to give the *t*-butyl carbonate (215.8 mg, 86.3%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.17 (m, 10H), 4.20-4.14 (m, 1H), 4.09 (dd, J = 11.8, 6.1 Hz, 1H), 3.99-3.91 (m, 2H), 3.15/3.14 (s, 3H), 2.97-2.91 (m, 1H), 1.83-1.42 (m, 4H), 1.50 (s, 9H), 1.20/1.18 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 153.5, 142.6, 142.4, 142.3, 128.9, 128.9, 128.7, 128.6, 128.4, 126.7, 126.5, 83.2, 83.0, 82.7, 65.7, 65.6, 60.8, 60.6, 59.6, 59.2, 58.1, 57.8, 56.4, 56.2, 33.5, 33.3, 27.9, 27.4, 27.1, 17.1, 16.7; IR (neat) 2980, 2933, 1743, 1495, 1453, 1370, 1327, 1279, 1163, 1098, 859, 738, 704; HRMS (ESI): m/z calcd for $C_{26}H_{34}O_5Na$ (M + Na) 449.2304, found 449.2278.



4-(Tetrahydro-5-methoxy-2-methylfuran-2-yl)-1,3-dioxolan-2-one (45)

and **Hexahydro-6-methoxy-8a-methylpyrano[3,2-d][1,3]dioxin-2-one (46)**

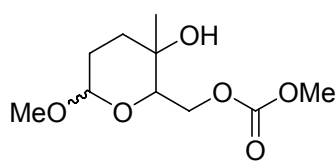
To *tert*-butyl carbonate **35** (125.2 mg, 0.2935 mmol) in dichloroethane/toluene (11.3 mL, 5:1, v/v) in borosilicate flask at room temperature were added the activated 4Å molecular sieves (250.4 mg), anhydrous Na₂S₂O₃ (250.4 mg, 1.584 mmol), NaOAc (250.4 mg, 3.052 mmol) and *N*-methylquinolinium hexafluorophosphate (8.5 mg, 29.4 μmol). The mixture was photoirradiated with gentle air bubbling for 2.5 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the residue was washed with EtOAc (30 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (30% - 45% EtOAc in hexanes) to provide a mixture of compounds **45** and **46** (19.7 mg, 33.2%) with a molar ratio of 4.8:1: IR (neat) 2929, 2835, 1794, 1754, 1463, 1375, 1170, 1084, 1034, 951.



(3-(3-Methoxy-4,4-diphenylbutyl)-3-methyloxiran-2-yl)methyl methyl carbonate (36)

A solution of **43** (0.2480 g, 0.760 mmol) in CH₂Cl₂ (5.0 mL) at 0 °C was treated with anhydrous pyridine (0.18 mL, 2.28 mmol), methyl chloroformate (0.18 mL, 2.28 mmol) and 4-dimethylaminopyridine (4.6 mg, 38.0 μmol) sequentially. The resulting white suspension was stirred at 0 °C for 10 min, then at room temperature for 50 min and quenched with water (10 mL). The mixture was extracted with CH₂Cl₂ (3 x 30 mL) and the combined extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (15% - 20% EtOAc in hexanes containing 0.5% Et₃N) to give the methyl carbonate (0.2639 g, 90.3%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.17 (m, 10H), 4.28-4.13 (m, 2H), 3.99-3.93 (m, 2H), 3.81/3.80 (s, 3H), 3.15/3.14 (s, 3H), 2.97-2.92

(m, 1H), 1.83-1.42 (m, 4H), 1.21/1.19 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 155.8, 142.6, 142.3, 142.2, 128.9, 128.8, 128.8, 128.6, 128.4, 126.7, 126.5, 83.1, 82.9, 66.7, 60.9, 60.7, 59.5, 59.0, 58.1, 57.8, 56.4, 56.2, 55.2, 33.4, 33.2, 27.3, 27.0, 17.1, 16.7; IR (neat) 3026, 2956, 1751, 1599, 1495, 1450, 1371, 1272, 1100, 965, 792, 747, 705; HRMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{28}\text{O}_5\text{Na}$ (M + Na) 407.1839, found 407.1834.



(Tetrahydro-3-hydroxy-6-methoxy-3-methyl-2H-pyran-2-yl)methyl methyl carbonate (47)

To methyl carbonate **36** (261.9 mg, 0.6812 mmol) in acetonitrile/toluene (25.8 mL, 5:1, v/v) in borosilicate flask at room temperature were added the activated 4Å molecular sieves (523.8 mg), anhydrous $\text{Na}_2\text{S}_2\text{O}_3$ (523.8 mg, 3.313 mmol), NaOAc (523.8 mg, 6.385 mmol) and *N*-methylquinolinium hexafluorophosphate (19.7 mg, 68.1 μmol). The mixture was photoirradiated with gentle air bubbling for 7.5 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the residue was washed with EtOAc (50 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (40% - 50% EtOAc in hexanes) to provide a mixture of the titled compounds. Fast eluting product (59.3 mg, 37.2%): ^1H NMR (300 MHz, CDCl_3) δ 4.70 (app t, $J = 2.2$ Hz, 1H), 4.47 (dd, $J = 11.2, 2.7$ Hz, 1H), 4.20 (dd, $J = 11.2, 8.4$ Hz, 1H), 3.85 (dd, $J = 8.4, 2.7$ Hz, 1H), 3.80 (s, 3H), 3.36 (s, 3H), 1.96-1.75 (m, 2H), 1.66-1.58 (m, 2H), 1.24 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.1, 97.3, 73.0, 68.7, 67.1, 55.1, 54.6, 35.2, 28.7, 20.0; IR (neat) 3468, 2956, 2919, 1749, 1442, 1274, 1125, 1053, 1017, 964; HRMS (ESI): m/z calcd for $\text{C}_{10}\text{H}_{18}\text{O}_6\text{Na}$ (M + Na) 257.1001, found 257.0995. Slow eluting product (31.7 mg, 19.9%): ^1H NMR (300 MHz, CDCl_3) δ 4.45-4.42 (m, 1H), 4.43 (dd, $J = 11.3, 3.5$ Hz, 1H), 4.25 (dd, $J = 11.3,$

7.7 Hz, 1H), 3.81 (s, 3H), 3.58 (dd, $J = 7.9, 3.5$ Hz, 1H), 3.50 (s, 3H), 1.87-1.60 (m, 4H), 1.29 (s, 3H); IR (neat) 3467, 2957, 2921, 1749, 1444, 1272, 1067, 966; HRMS (ESI): m/z calcd for $C_{10}H_{18}O_6Na$ ($M + Na$) 257.1001, found 257.0992.



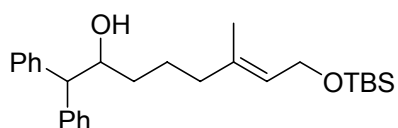
The ethyl ester **40** (5.84 g, 20.4 mmol) in CH_2Cl_2 (58.0 mL) at -78 °C was treated dropwise with DIBAL-H (1.0 M in hexanes, 21.4 mL, 21.4 mmol). The reaction mixture was stirred at -78 °C for 2 h and then quenched with saturated disodium tartrate solution (120 mL). After warmed up to room temperature, the mixture was extracted with CH_2Cl_2 (3 x 70 mL) and the organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (6% - 8% EtOAc in hexanes) to give the aldehyde (4.31 g, 87.4%) as a colorless liquid: 1H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, $J = 1.7$ Hz, 1H), 5.33 (qt, $J = 6.2, 1.3$ Hz, 1H), 4.19 (d, $J = 6.2$ Hz, 2H), 2.59-2.54 (m, 2H), 2.35 (app t, $J = 7.7$ Hz, 2H), 1.65 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 135.0, 125.6, 60.3, 42.1, 31.7, 26.2, 18.6, 16.7, -4.9; IR (neat) 2955, 2929, 2857, 2714, 1728, 1472, 1255, 1114, 1074, 836, 776; HRMS (EI): m/z calcd for $C_{13}H_{25}O_2Si$ ($M - H$) 241.1624, found 241.1606.



The (methoxymethyl)triphenylphosphonium chloride (2.587 g, 7.55 mmol) in a dry flask under high vacuum was heated with heat gun for 3 min to remove the moisture. The flask was cooled to 0 °C and THF (8.0 mL) was added in. NaHMDS (7.55 mL, 7.55 mmol) was added

dropwise and the resulting deep orange suspension was stirred at 0 °C for 1 h. Aldehyde **52** (0.6100 g, 2.516 mmol, dissolved in 1.0 mL of THF) was added dropwise and the flask formerly containing the aldehyde was rinsed twice with THF (2 x 0.5 mL). The reaction mixture was stirred at 0 °C for 1 h, then quenched with saturated NaHCO₃ (10 mL) and extracted with Et₂O (3 x 30 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (3.5% EtOAc in hexanes) to give the methyl vinyl ether.

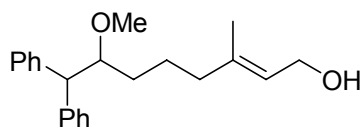
The methyl vinyl ether in THF–H₂O (10:1, 40 mL) was treated with Hg(OAc)₂ (1.2769 g, 4.007 mmol). The reaction mixture was stirred for 20 min and saturated KI (20 mL) were added. The resulting yellowish green mixture was stirred for 1 h, then diluted with Et₂O (50 mL). The two layers were separated and the organic layer was washed with saturated KI (40 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (4% - 6% EtOAc in hexanes) to give aldehyde **53** (0.5263 g, 81.6%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 9.78 (t, *J* = 1.5 Hz, 1H), 5.32 (qt, *J* = 6.2, 1.0 Hz, 1H), 4.19 (d, *J* = 6.3 Hz, 2H), 2.42 (dt, *J* = 7.3, 1.5 Hz, 2H), 2.04 (t, *J* = 7.3 Hz, 2H), 1.76 (pent, *J* = 7.6 Hz, 2H), 1.62 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 202.6, 136.0, 125.9, 60.5, 43.5, 39.0, 26.3, 20.3, 18.7, 16.4, -4.8; IR (neat) 2930, 2856, 2713, 1728, 1472, 1387, 1255, 1115, 1080, 836, 776; HRMS (ESI): *m/z* calcd for C₁₄H₂₈O₂SiNa (M + Na) 279.1756, found 279.1745.



(E)-8-(tert-Butyldimethylsilyloxy)-6-methyl-1,1-diphenyl-oct-6-en-2-ol (54)

A solution of diphenylmethane (0.80 mL, 4.768 mmol) in THF (4.5 mL) was treated with *n*-BuLi (1.6 M in hexanes, 2.74 mL, 4.386 mmol) and the resulting deep-orange solution was refluxed for 2 h. After cooling to room temperature, the solution was cooled further to 0 °C and

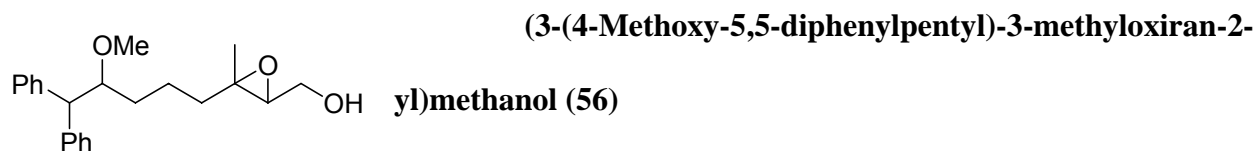
aldehyde **53** (0.4890 g, 1.907 mmol, dissolved in 1.0 mL of THF) was added dropwise. The flask formerly containing the aldehyde was rinsed with THF (2 x 0.5 mL). The deep-orange solution was stirred at 0 °C for 1 h, then quenched by slow addition of saturated NaHCO₃ (10 mL). The biphasic mixture was diluted with Et₂O (10 mL) and poured onto water (10 mL). The two layers were separated and the aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (7% - 13% EtOAc in hexanes) to give the alcohol (0.6376 g, 78.7%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.16 (m, 10H), 5.26 (qt, *J* = 6.4, 1.2 Hz, 1H), 4.36 (dt, *J* = 8.3, 3.0 Hz, 1H), 4.16 (d, *J* = 6.3 Hz, 2H), 3.88 (d, *J* = 8.3 Hz, 1H), 1.99-1.92 (m, 2H), 1.70-1.35 (m, 4H), 1.57 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 142.6, 141.6, 137.1, 129.0, 128.8, 128.4, 127.1, 126.7, 124.7, 73.8, 60.5, 59.0, 39.6, 34.8, 26.2, 24.0, 18.6, 16.4, -4.8; IR (neat) 3458, 2928, 2856, 1599, 1494, 1386, 1254, 1082, 835, 702; HRMS (ESI): *m/z* calcd for C₂₇H₄₀O₂SiNa (M + Na) 447.2695, found 447.2741.



(E)-7-Methoxy-3-methyl-8,8-diphenyloct-2-en-1-ol (55)

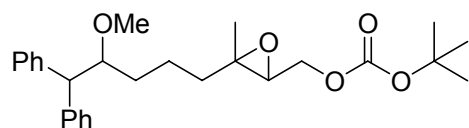
Alcohol **54** (0.6376g, 1.501 mmol) in anhydrous DMF (10 mL) at 0 °C was treated with NaH (60% dispersion in mineral oil, 0.1501 g, 3.752 mmol) and the yellow suspension was stirred at 0 °C for 0.5 h. MeI (0.37 mL, 6.004 mmol) was added dropwise and the reaction mixture was stirred overnight at room temperature. The flask was cooled to 0 °C and the reaction was quenched with ice chips. The mixture was poured into water (20 mL) and extracted with Et₂O (3 x 30 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was dissolved in THF (7.5 mL) and TBAF monohydrate (0.4709 g, 1.801 mmol) was added in. The yellow solution

was stirred for 1.5 h and then concentrated in vacuo. The residue was purified by flash chromatography (25% - 35% EtOAc in hexanes) to give the allylic alcohol (0.4746 g, 97.4%) as a colorless oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.42-7.19 (m, 10H), 5.36 (qt, $J = 6.9, 1.0$ Hz, 1H), 4.11 (d, $J = 6.9$ Hz, 2H), 4.04 (d, $J = 8.4$ Hz, 1H), 3.97-3.92 (m, 1H), 3.19 (s, 3H), 1.98-1.96 (m, 2H), 1.62 (s, 3H), 1.58-1.41 (m, 4H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 142.9, 142.5, 139.4, 128.9, 128.6, 128.4, 126.5, 126.4, 123.7, 83.6, 59.3, 58.0, 56.2, 39.5, 31.6, 22.9, 16.2; IR (neat) 3386, 2934, 1667, 1599, 1495, 1451, 1380, 1186, 1100, 1002, 746, 703; HRMS (ESI): m/z calcd for $\text{C}_{22}\text{H}_{28}\text{O}_2\text{Na}$ ($M + \text{Na}$) 347.1987, found 347.1966.



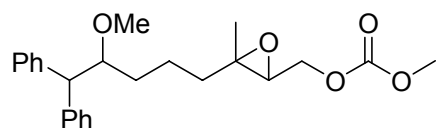
A solution of **55** (85.0 mg, 0.262 mmol) in CH_2Cl_2 (2.6 mL) at 0 °C was treated with NaHCO_3 powder (55.0 mg, 0.655 mmol) followed by *m*-chloroperbenzoic acid (pure, 47.5 mg, 0.275 mmol). The reaction mixture was stirred at 0 °C for 50 min and then quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (2.0 mL). After warmed to room temperature, the biphasic mixture was poured into water (5 mL) and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 x 10 mL) and the combined organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (40% - 45% EtOAc in hexanes containing 0.5% Et_3N) to give the epoxy alcohol (88.7 mg, 99.4%) as a colorless oil: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.38-7.17 (m, 10H), 4.00 (d, $J = 8.4$ Hz, 1H), 3.91-3.89 (m, 1H), 3.80-3.74 (m, 1H), 3.65 (dd, $J = 12.1, 6.6$ Hz, 1H), 3.17/3.16 (s, 3H), 2.92-2.87 (m, 1H), 1.64-1.34 (m, 6H), 1.23 (br s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 142.8, 142.4, 128.9, 128.9, 128.7, 128.6, 128.4, 126.6, 126.4, 83.6, 83.5, 63.1, 63.0, 61.5, 61.4,

58.1, 58.0, 56.3, 38.6, 32.1, 32.0, 20.7, 20.6, 16.8, 16.7; IR (neat) 3420, 2935, 1599, 1495, 1452, 1385, 1249, 1100, 1031, 862, 747, 704; HRMS (ESI): m/z calcd for $C_{22}H_{28}O_3Na$ ($M + Na$) 363.1936, found 363.1947.



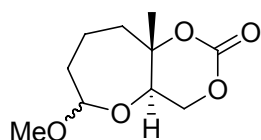
***tert*-Butyl (3-(4-methoxy-5,5-diphenylpentyl)-3-methyloxiran-2-yl)methyl carbonate (50)**

Epoxy alcohol **56** (72.9 mg, 0.214 mmol) in anhydrous toluene (2.0 mL) at 0 °C was treated with 1-methylimidazole (22 μ L, 0.278 mmol) followed by (Boc)₂O (186.8 mg, 0.856 mmol, dissolved in 0.5 mL of toluene). The reaction mixture was stirred at 0 °C for 4 h, then diluted with CH₂Cl₂ (5.0 mL) and poured into water (6 mL). The biphasic mixture was separated and the aqueous layer was washed with CH₂Cl₂ (3 x 5 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (10% - 15% EtOAc in hexanes containing 0.5% Et₃N) to give the *t*-butyl carbonate (83.9 mg, 89.0%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.17 (m, 10H), 4.18 (dd, $J = 11.9, 4.8$ Hz, 1H), 4.09 (dd, $J = 11.9, 6.3$ Hz, 1H), 4.00 (d, $J = 6.3$ Hz, 1H), 3.93-3.87 (m, 1H), 3.17 (br s, 3H), 2.98-2.94 (m, 1H), 1.64-1.41 (m, 6H), 1.52 (s, 9H), 1.24 (br s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 153.4, 142.8, 142.4, 128.9, 128.6, 128.5, 128.4, 126.5, 126.4, 83.5, 82.6, 65.7, 60.6, 59.5, 59.4, 58.1, 58.0, 56.2, 38.3, 32.0, 27.9, 20.5, 20.5, 16.8, 16.8; IR (neat) 2934, 1742, 1495, 1452, 1369, 1279, 1255, 1163, 1098, 859, 704; HRMS (ESI): m/z calcd for $C_{27}H_{36}O_5Na$ ($M + Na$) 463.2460, found 463.2462.



(3-(4-Methoxy-5,5-diphenylpentyl)-3-methyloxiran-2-yl)methyl methyl carbonate (51)

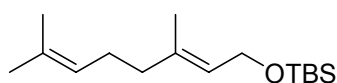
At 0 °C, epoxy alcohol **56** (88.7 mg, 0.260 mmol) in CH₂Cl₂ (2.6 mL) was treated with anhydrous pyridine (63 μL, 0.780 mmol), methyl chloroformate (60 μL, 0.780 mmol) and catalytic amount of DMAP (1.6 mg, 13 μmol). The reaction mixture was stirred at 0 °C for 10 min, then at room temperature for 20 min, and quenched with water (5 mL). The biphasic mixture was extracted with CH₂Cl₂ (3 x 10 mL) and the extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (15% - 20% EtOAc in hexanes containing 0.5% Et₃N) to give the methyl carbonate (89.9 mg, 86.6%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.08 (m, 10H), 4.27 (ddd, *J* = 11.9, 4.7, 1.5 Hz, 1H), 4.16 (ddd, *J* = 11.9, 6.4, 1.4 Hz, 1H), 4.01 (d, *J* = 8.4 Hz, 1H), 3.93-3.89 (m, 1H), 3.82/3.82 (s, 3H), 3.17/3.17 (s, 3H), 2.99-2.93 (m, 1H), 1.62-1.32 (m, 6H), 1.25/1.25 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.8, 142.8, 142.4, 128.9, 128.7, 128.6, 128.4, 126.6, 126.4, 83.5, 83.5, 66.7, 60.7, 59.3, 59.2, 58.1, 58.0, 56.2, 55.1, 38.2, 38.2, 32.0, 20.5, 20.5, 16.8; IR (neat) 2952, 1750, 1495, 1450, 1372, 1270, 1102, 964, 792, 747, 704.



**(4aR,9aS)-Hexahydro-6-methoxy-9a-methyl-4H-
[1,3]dioxino[5,4-b]oxepin-2-one (58)**

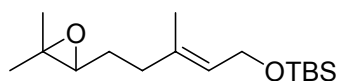
To *tert*-butyl carbonate **50** (65.8 mg, 149.4 μmol) in dichloroethane/toluene (5.7 mL, 5:1, v/v) in borosilicate flask at room temperature were added the activated 4Å molecular sieves (131.6 mg), anhydrous Na₂S₂O₃ (131.6 mg, 0.832 mmol), NaOAc (131.6 mg, 1.604 mmol) and *N*-methylquinolinium hexafluorophosphate (4.3 mg, 14.9 μmol). The mixture was photoirradiated with gentle air bubbling for 2 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the residue was washed with EtOAc (20 mL). The filtrate was concentrated and the resulting residue was

purified by flash chromatography (5% - 15% EtOAc in hexanes) to provide the desired compound (23.7 mg, 73.4%) as a mixture of two diastereomers with a 1.0:1.2 ratio: ^1H NMR (300 MHz, CDCl_3) δ 4.76 (t, $J = 3.8$ Hz, 0.5H), 4.66 (dd, $J = 8.8, 5.8$ Hz, 0.5H), 4.34 (dd, $J = 10.8, 6.4$ Hz, 0.5H), 4.29-4.27 (m, 0.5H), 4.24-4.18 (m, 1H), 4.19 (t, $J = 10.8$ Hz, 0.5H), 3.88 (dd, $J = 10.6, 6.4$ Hz, 0.5H), 3.42/3.35 (s, 3H), 2.23-2.01 (m, 1.5H), 1.96-1.92 (m, 0.5H), 1.75-1.58 (m, 3.5H), 1.51/1.48 (s, 3H), 1.45-1.35 (m, 0.5H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.2, 148.0, 104.3, 102.8, 84.2, 83.0, 68.1, 66.7, 66.3, 62.7, 56.3, 55.7, 43.2, 41.7, 34.5, 34.4, 19.6, 19.3, 18.3, 16.7; IR (neat) 2941, 1755, 1464, 1384, 1252, 1199, 1128, 1091, 1050, 969; HRMS (EI): m/z calcd for $\text{C}_9\text{H}_{13}\text{O}_4\text{Na}$ (M – CH_3O) 185.0814, found 185.0811.



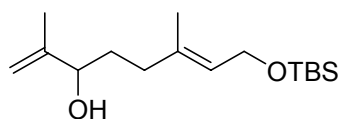
((E)-3,7-Dimethylocta-2,6-dienyloxy)(tert-butyl)dimethylsilane

The geraniol (8.68 mL, 50.0 mmol) in DMF (50.0 mL) was treated with imidazole (8.290 g, 55.0 mmol) and TBSCl (3.744 g, 55.0 mmol). The reaction mixture was stirred at room temperature for 18 h, then quenched with water (100 mL) and extracted with Et_2O (3 x 75 mL). The extracts were dried over MgSO_4 , evaporated and purified by column chromatography (5% Et_2O in hexanes) to give the desired product (12.984 g, 96.7%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 5.31 (qt, $J = 6.3, 1.2$ Hz, 1H), 5.11 (tt, $J = 6.7, 1.4$ Hz, 1H), 4.21 (d, $J = 6.3$ Hz, 2H), 2.14-1.99 (m, 4H), 1.69 (s, 3H), 1.63 (s, 3H), 1.61 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H).



((E)-3-Methyl-5-(3,3-dimethyloxiran-2-yl)pent-2-enyloxy)(tert-butyl)dimethylsilane (62)

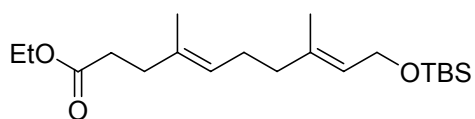
The TBS ether (5.370 g, 20.0 mmol) in CHCl₃ (180.0 mL) at 0 °C was treated with *m*-chloroperoxybenzoic acid (70-75%, 5.621 g, 22.8 mmol) in small portions. The white suspension was stirred at 0 °C for 30 min, and then quenched with saturated Na₂S₂O₃ solution (20 mL) and saturated NaHCO₃ solution (100 mL). The mixture was warmed up to room temperature and the two layers were separated. The aqueous was washed with CH₂Cl₂ (2 x 100 mL) and the combination of the organic extracts were dried over MgSO₄ and evaporated. The residue was purified by column chromatography (8%-12% Et₂O in hexanes) to give the desired monoepoxide (4.375 g, 76.9%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 5.36 (qt, *J* = 6.3, 1.2 Hz, 1H), 4.20 (dd, *J* = 6.3, 0.7 Hz, 2H), 2.72 (t, *J* = 6.2 Hz, 1H), 2.25-2.06 (m, 2H), 1.65 (s, 3H), 1.71-1.61 (m, 2H), 1.31 (s, 3H), 1.27 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H).



(*E*)-8-(*tert*-Butyldimethylsilyloxy)-2,6-dimethylocta-1,6-dien-3-ol (63)

A solution of 2,2,6,6-tetramethylpiperidine (5.297 g, 37.5 mmol) in anhydrous benzene (25.0 mL) at 0 °C was treated dropwise with *n*-BuLi (1.6 M in hexanes, 23.4 mL, 37.5 mmol). After 10 min, diethylaluminum chloride (1.0 M in heptanes, 37.5 mL, 37.5 mmol) and the resulting white suspension was stirred at 0 °C for 30 min. Monoepoxide **62** (4.2676 g, 15.0 mmol, dissolved in 5.0 mL of anhydrous benzene) was added dropwise and the flask formerly containing the epoxide was rinsed twice with benzene (2 x 2.5 mL). The reaction mixture was stirred further at 0 °C for 1.5 h and then quenched with saturated sodium tartrate solution (100 mL). The biphasic mixture was poured into water (100 mL) and extracted with Et₂O (3 x 150 mL). The organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was purified by column chromatography (12%-21% Et₂O in hexanes) to give

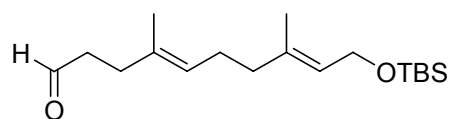
the allylic alcohol (3.9238 g, 91.9%) as a colorless liquid: ^1H NMR (300 MHz, CDCl_3) δ 5.34 (qt, $J = 6.3, 1.2$ Hz, 1H), 4.94 (t, $J = 0.8$ Hz, 1H), 4.84 (t, $J = 1.5$ Hz, 1H), 4.19 (d, $J = 6.3$ Hz, 2H), 4.05 (t, $J = 6.2$ Hz, 1H), 2.17-1.95 (m, 2H), 1.73 (s, 3H), 1.64 (s, 3H), 1.70-1.60 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.6, 136.8, 124.9, 111.3, 75.8, 60.4, 35.7, 33.0, 26.2, 18.6, 17.8, 16.6, -4.9; IR (neat) 3382, 2929, 2857, 1472, 1382, 1255, 1112, 1070, 836, 776; HRMS (EI): m/z calcd for $\text{C}_{12}\text{H}_{23}\text{O}_2\text{Si}$ ($M - \text{C}_4\text{H}_9$) 227.1467, found 227.1450.



(4E,8E)-Ethyl 10-(tert-butyltrimethylsilyloxy)-4,8-dimethyl-deca-4,8-

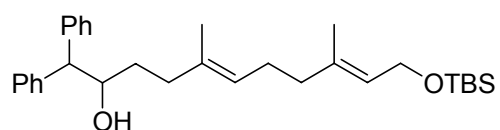
dienoate (64)

A mixture of **63** (3.6710 g, 12.90 mmol), triethyl orthoacetate (freshly distilled, 10.46 g, 64.5 mmol) and propionic acid (47.8 mg, 0.645 mmol) in a two-neck round bottomed flask equipped with a short path was heated to 145 °C and kept at this temperature for 1.5 h. (During this period of time, a lot of volatiles were distilled out.) The unreacted triethyl orthoacetate was removed by simple distillation and the residue was purified by column chromatography (3% EtOAc in hexanes) to give the ethyl ester (4.2813 g, 93.6%) as a colorless liquid: ^1H NMR (300 MHz, CDCl_3) δ 5.30 (qt, $J = 6.3, 1.2$ Hz, 1H), 5.14 (qt, $J = 6.9, 1.2$ Hz, 1H), 4.19 (dd, $J = 6.3, 0.6$ Hz, 2H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.42-2.35 (m, 2H), 2.31-2.26 (m, 2H), 2.14-2.06 (m, 2H), 2.02-1.97 (m, 2H), 1.62 (s, 3H), 1.61 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.7, 136.9, 133.7, 125.0, 124.7, 60.5, 60.4, 39.6, 34.9, 33.5, 26.4, 26.2, 18.6, 16.5, 16.1, 14.5, -4.8; IR (neat) 2929, 2856, 1739, 1463, 1254, 1158, 1063, 836, 776; HRMS (ESI): m/z calcd for $\text{C}_{20}\text{H}_{38}\text{O}_3\text{SiNa}$ ($M + \text{Na}$) 377.2488, found 377.2513.



(4E,8E)-10-(tert-Butyldimethylsilyloxy)-4,8-dimethyldeca-4,8-dienal (65)

Ethyl ester **64** (2.3345g, 6.583 mmol) in CH_2Cl_2 (20.0 mL) at $-78\text{ }^\circ\text{C}$ was treated dropwise with DIBAL-H (1.0 M in hexanes, 6.91 mL). The reaction mixture was stirred at $-78\text{ }^\circ\text{C}$ for 40 min and DIBAL-H (1.0 M in hexanes, 0.66 mL, 0.66 mmol) were added. The mixture was stirred for 30 min more and then quenched with saturated sodium tartrate solution (30 mL). After warmed up to room temperature, the mixture was extracted with CH_2Cl_2 (3 x 40 mL) and the organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (4% - 20% EtOAc in hexanes) to give the aldehyde (1.8837g, 92.1%) as a colorless liquid: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.75 (t, $J = 1.9$ Hz, 1H), 5.30 (qt, $J = 6.3$, 1.1 Hz, 1H), 5.15 (qt, $J = 6.8$, 1.0 Hz, 1H), 4.19 (d, $J = 6.3$ Hz, 2H), 2.52 (dt, $J = 7.9$, 1.7 Hz, 2H), 2.32 (t, $J = 7.5$ Hz, 2H), 2.15-2.08 (m, 2H), 2.03-1.98 (m, 2H), 1.62 (br s, 6H), 0.91 (s, 9H), 0.08 (s, 6H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 202.8, 136.8, 133.4, 125.3, 124.8, 60.5, 42.4, 39.5, 32.0, 26.4, 26.2, 18.6, 16.5, 16.3, -4.8; IR (neat) 2928, 2856, 1728, 1472, 1386, 1254, 1110, 1066, 836, 776; HRMS (ESI): m/z calcd for $\text{C}_{18}\text{H}_{35}\text{O}_2\text{Si}$ (M + H) 311.2406, found 311.2386.



(5E,9E)-11-(tert-Butyldimethylsilyloxy)-5,9-dimethyl-1,1-diphenylundeca-5,9-dien-2-ol (66)

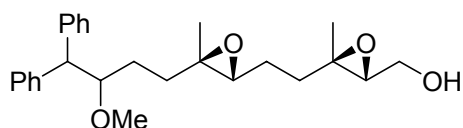
A solution of diphenylmethane (1.625 g, 9.660 mmol) in THF (9.0 ml) was treated dropwise with *n*-BuLi (1.6 M in hexanes, 6.04 mL, 9.660 mmol). The resulting deep orange solution was stirred at $75\text{ }^\circ\text{C}$ for 1 h and cooled to $0\text{ }^\circ\text{C}$. Aldehyde **65** (1.000 g, 3.220 mmol, dissolved in 2.0 mL of THF) was added dropwise and the flask formerly containing the aldehyde was rinsed with THF (2 x 0.5 mL). The reaction mixture was stirred at $0\text{ }^\circ\text{C}$ for 1 h and quenched

by slow addition of saturated NaHCO₃ solution (10 mL). The mixture was poured onto water (15 mL) and extracted with Et₂O (3 x 30 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (4% - 10% EtOAc in hexanes) to give the secondary alcohol (1.243 g, 80.6%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.16 (m, 10H), 5.30 (qt, *J* = 6.3, 1.1 Hz, 1H), 5.14 (app t, *J* = 6.2 Hz, 1H), 4.38-4.30 (m, 1H), 4.18 (d, *J* = 6.3 Hz, 2H), 3.91 (d, *J* = 8.4 Hz, 1H), 2.20-2.00 (m, 6H), 1.62 (s, 3H), 1.52 (s, 3H), 1.67-1.42 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 142.7, 141.8, 137.1, 135.2, 129.0, 129.0, 128.8, 128.5, 127.0, 126.7, 124.8, 124.6, 73.6, 60.5, 58.9, 39.7, 36.1, 33.3, 26.5, 26.2, 18.6, 16.6, 16.1, -4.8; IR (neat) 3466, 2928, 2855, 1598, 1494, 1450, 1384, 1254, 1067, 835, 776, 702; HRMS (ESI): *m/z* calcd for C₃₁H₄₆O₂SiNa (M + Na) 501.3165, found 501.3150.



Alcohol **66** (1.200 g, 2.507 mmol) in anhydrous DMF (14.0 mL) at 0 °C was treated with NaH (60% dispersion in mineral oil, 0.2507 g, 6.268 mmol) and the suspension was stirred at 0 °C for 30 min. MeI (0.62 mL, 10.03 mmol) was added dropwise and the reaction mixture was allowed to warm up to room temperature. After stirred for 3 h, the reaction was quenched with water (25 mL) cautiously and extracted with Et₂O (3 x 35 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The resulting residue was dissolved in THF (12.5 mL) and TBAF monohydrate (0.7866 g, 3.008 mmol) was added in one portion. The yellow solution was stirred for 1.3 h and then concentrated. The residue was purified by flash chromatography (20% - 30% EtOAc in hexanes) to give the allylic

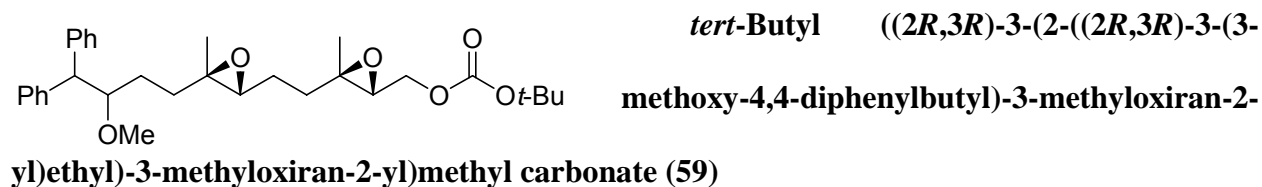
alcohol (0.9230 g, 97.2%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.16 (m, 10H), 5.40 (qt, $J = 6.9, 1.1$ Hz, 1H), 5.10 (t, $J = 5.5$ Hz, 1H), 4.14 (d, $J = 6.7$ Hz, 2H), 4.02 (d, $J = 8.3$ Hz, 1H), 3.92-3.87 (m, 1H), 3.16 (s, 3H), 2.11-2.01 (m, 6H), 1.68 (s, 3H), 1.51 (s, 3H), 1.62-1.46 (m, 2H), 0.92 (br s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.0, 142.5, 139.8, 135.3, 129.1, 128.7, 128.6, 128.4, 126.5, 126.4, 124.3, 123.6, 83.3, 59.6, 58.0, 56.2, 39.7, 35.3, 30.8, 26.4, 16.5, 16.1; IR (neat) 3388, 3026, 2925, 1599, 1494, 1451, 1382, 1189, 1102, 1002, 755, 703; HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{34}\text{O}_2\text{Na}$ ($\text{M} + \text{Na}$) 401.2457, found 401.2477.



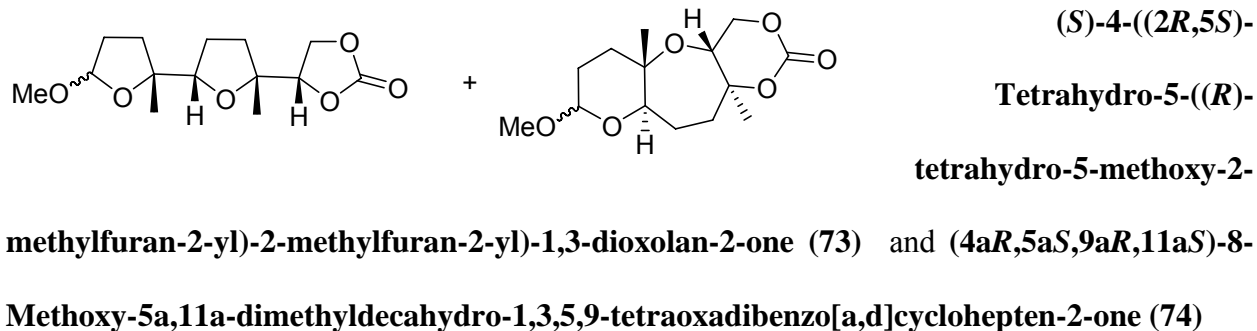
((2R,3R)-3-(2-(((2R,3R)-3-(3-Methoxy-4,4-diphenylbutyl)-3-methyloxiran-2-yl)ethyl)-3-methyloxiran-2-yl)methanol (69)

To a solution of dienol **67** (100.0 mg, 0.264 mmol) in $\text{CH}_3\text{CN}/\text{DMM}$ (8.0 mL, 1:2, v/v) were added a 0.05 M solution of $\text{Na}_2\text{B}_4\text{O}_7$ in 4×10^{-4} M $\text{Na}_2(\text{EDTA})$ (5.2 mL), Bu_4NHSO_4 (7.2 mg, 21.1 μmol) and Shi ketone **68** (68.2 mg, 0.264 mmol) sequentially. The mixture was cooled to 0 $^\circ\text{C}$, and the Oxone (448 mg, 0.729 mmol), dissolved in 4×10^{-4} M $\text{Na}_2(\text{EDTA})$ (3.4 mL), and K_2CO_3 (424 mg, 3.065 mmol), dissolved in water (3.4 mL), were added simultaneously via a syringe pump over 2.0 h. After the addition was completed, the slightly blue reaction mixture was stirred further for 15 min at 0 $^\circ\text{C}$, then diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (40% - 80% EtOAc in hexanes) to give the diepoxy alcohol (95.8 mg, 88.4%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.42-7.17 (m, 10H), 4.00-3.85 (m, 2H), 3.81-3.61 (m, 2H), 3.16/3.14 (s, 3H), 2.96 (t, $J = 6.0$ Hz, 1H), 2.64-2.60 (m, 1H), 2.01 (br s, 1H), 1.86-1.73 (m, 2H), 1.66-1.42 (m, 6H), 1.31/1.30 (s, 3H), 1.15/1.13

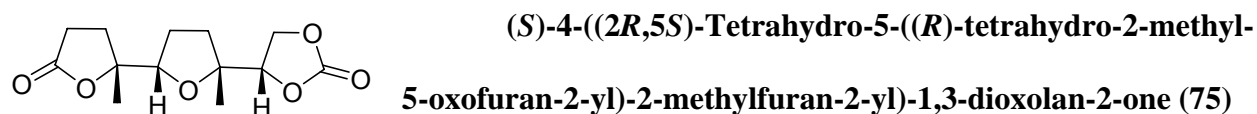
(s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.7, 142.4, 142.2, 129.0, 128.9, 128.7, 128.7, 128.6, 128.4, 126.7, 126.5, 83.3, 63.1, 62.6, 62.5, 61.4, 61.2, 61.1, 61.0, 60.7, 58.2, 57.9, 56.4, 56.1, 35.2, 33.9, 33.8, 27.6, 27.3, 24.4, 17.1, 16.8, 16.4; IR (neat) 3435, 3026, 2929, 1495, 1452, 1386, 1100, 1032, 747, 704; $[\alpha]_{\text{D}} = +13.3^\circ$ (CHCl_3 , c 1.34).



To a solution of diepoxy alcohol **69** (112.0 mg, 0.273 mmol) in anhydrous toluene (2.7 mL) at 0 °C were added 1-methylimidazole (22 μL , 0.273 mmol) and $(\text{Boc})_2\text{O}$ (119.2 mg, 0.546 mmol) and the reaction mixture was stirred overnight, allowing the temperature to warm to room temperature slowly. After that time, the reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was azeotroped with hexanes (3 x 10 mL) and then purified by flash chromatography (20% - 25% EtOAc in hexanes containing 0.5% Et_3N) to give the *tert*-butyl carbonate (129.1 mg, 92.7%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.17 (m, 10H), 4.27-4.10 (m, 2H), 4.00-3.88 (m, 2H), 3.17/3.16 (s, 3H), 3.02 (t, $J = 5.8$ Hz, 1H), 2.63-2.59 (m, 1H), 1.84-1.38 (m, 8H), 1.52 (s, 9H), 1.32 (s, 3H), 1.14/1.13 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.5, 142.7, 142.4, 142.3, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 126.7, 126.5, 83.3, 82.8, 65.6, 61.1, 61.0, 60.3, 59.2, 58.2, 57.9, 56.4, 34.8, 33.9, 33.8, 27.9, 27.4, 24.3, 17.2, 16.9, 16.8, 16.4; IR (neat) 2978, 2932, 1743, 1495, 1453, 1370, 1279, 1256, 1163, 1098, 858, 756, 704; $[\alpha]_{\text{D}} = +17.3^\circ$ (CHCl_3 , c 1.49).



To diepoxide **59** (129.1 mg, 0.253 mmol) in dichloroethane/toluene (9.7 mL, 5:1, v/v) in borosilicate flask at room temperature were added the activated 4Å molecular sieves (258 mg), anhydrous Na₂S₂O₃ (258 mg, 1.633 mmol), NaOAc (258 mg, 3.148 mmol) and *N*-methylquinolinium hexafluorophosphate (7.3 mg, 25.3 μmol). The mixture was photoirradiated with gentle air bubbling for 4.5 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the residue was washed with EtOAc (40 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (35% - 50% EtOAc in hexanes) to provide a mixture of **73** and **74** (28.7 mg, 39.6%) as a colorless oil: IR (neat) 2926, 1796, 1754, 1460, 1374, 1166, 1085, 1036, 1006, 952.



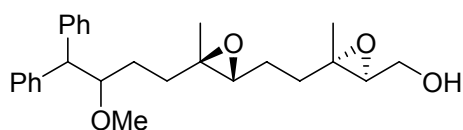
A mixture of acetals **73** and **74** (20.8 mg, 72.6 μmol) in acetone (2.1 mL) at 0 °C was treated dropwise with Jones reagent (0.2 mL). The mixture was stirred at 0 °C for 10 min, then at room temperature for 1.5 h and purified without workup by column chromatography (50% - 90% EtOAc in hexanes) to give the unreacted acetal **74** (3.2 mg, nearly pure) and lactone **75** (13.8 mg, ~80%). For **75**: ¹H NMR (300 MHz, CDCl₃) δ 4.60 (dd, *J* = 8.4, 6.2 Hz, 1H), 4.50 (t, *J* = 8.6 Hz, 1H), 4.38 (dd, *J* = 8.7, 6.2 Hz, 1H), 4.08 (dd, *J* = 8.6, 6.3 Hz, 1H), 2.64-2.58 (m, 2H), 2.31-2.19

(m, 1H), 2.10-2.04 (m, 2H), 1.94-1.73 (m, 3H), 1.39 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.7, 155.1, 86.9, 83.5, 83.2, 79.5, 66.0, 34.1, 29.3, 29.2, 26.7, 23.8, 21.0; IR (neat) 2958, 2924, 2853, 1790, 1770, 1456, 1382, 1248, 1166, 1085, 1020, 944, 770, 728; $[\alpha]_{\text{D}} = +4.5^\circ$ (CHCl_3 , c 0.24).



A suspension of the activated 4Å molecular sieves powder (95 mg) in CH_2Cl_2 (2.4 mL) was treated with L-(+)-DIPT (8.0 μL , 38.0 μmo) and the mixture was cooled to -35 to -30 $^\circ\text{C}$. The mixture was stirred for 10 min and $\text{Ti}(\text{O}-i\text{-Pr})_4$ (9.5 μL , 31.7 μmol) was added and the mixture was stirred for 15 min more. After that time, *t*-butyl hydroperoxide (5.0-6.0 M in decane, 0.19 mL, 0.951 mmol) was added dropwise and the mixture was stirred for 30 min. Dienol **67** (120.0 mg, dissolved in 0.5 mL of CH_2Cl_2) was added dropwise and the flask formerly containing the dienol was rinsed with CH_2Cl_2 (2 x 0.1 mL). The reaction mixture was stirred at -35 to -30 $^\circ\text{C}$ for 40 min and then water (0.5 mL) was added. The mixture was allowed to warm up to 0 $^\circ\text{C}$ and stirred for 1 h. A solution of 30% of NaOH saturated with NaCl (0.3 mL) was added and the mixture was warmed up to room temperature and stirred for 1.5 h. The suspension was filtered through a pad of celite and the filtrate was dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (30% - 40% EtOAc in hexanes) to give the monoepoxy alcohol (120.0 mg, 95.9%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.17 (m, 10H), 5.07 (app t, $J = 6.7$ Hz, 1H), 4.01 (d, $J = 8.3$ Hz, 1H), 3.92-3.86 (m, 1H), 3.81-3.75 (m, 1H), 3.71-3.63 (m, 1H), 3.15 (s, 3H), 2.94 (dd, $J = 6.5$, 4.5 Hz, 1H), 2.11-2.04 (m, 4H), 1.74-1.43 (m, 4H), 1.51 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75

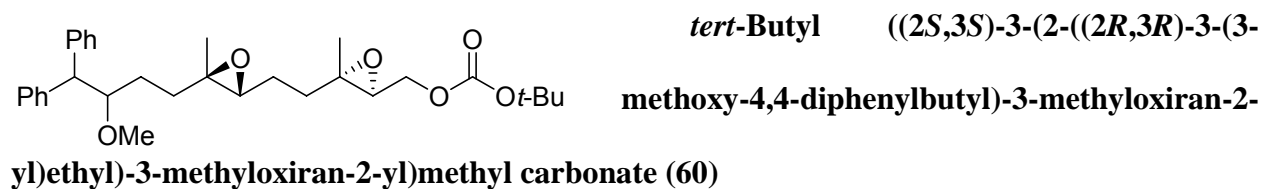
MHz, CDCl₃) δ 142.9, 142.5, 135.8, 135.7, 129.0, 128.6, 128.4, 126.5, 126.4, 123.7, 123.6, 83.3, 83.2, 63.1, 61.6, 61.2, 58.0, 57.8, 56.2, 38.6, 35.2, 30.7, 30.6, 23.8, 16.9, 16.0; IR (neat) 3423, 3026, 2930, 1598, 1494, 1451, 1384, 1103, 1032, 862, 746, 704; [α]_D = -3.8° (CHCl₃, c 1.08).



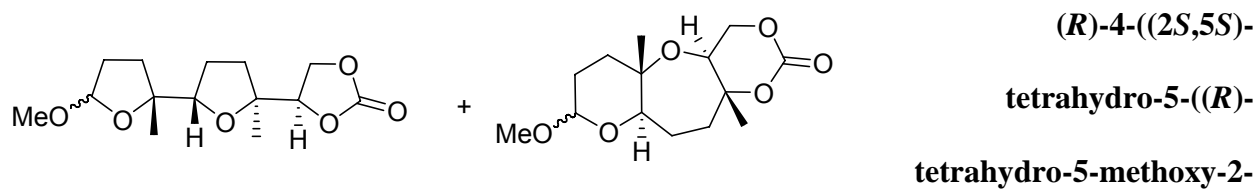
((2*S*,3*S*)-3-(2-(((2*R*,3*R*)-3-(3-Methoxy-4,4-diphenylbutyl)-3-methyloxiran-2-yl)ethyl)-3-methyloxiran-2-yl)methanol (71)

To a solution of monoepoxy alcohol **70** (170.0 mg, 0.431 mmol) in CH₃CN/DMM (6.5 mL, 1:2, v/v) were added a 0.05 M solution of Na₂B₄O₇ in 4x10⁻⁴ M Na₂(EDTA) (4.3 mL), Bu₄NHSO₄ (5.8 mg, 17.2 μmol) and Shi ketone (55.6 mg, 0.216 mmol) sequentially. The mixture was cooled to 0 °C, and the Oxone (366 mg, 0.595 mmol), dissolved in 4x10⁻⁴ M Na₂(EDTA) (2.8 mL), and K₂CO₃ (346 mg, 2.50 mmol), dissolved in water (2.8 mL), were added simultaneously via a syringe pump over 2.0 h. After the addition was completed, the blue reaction mixture was stirred further for 15 min at 0 °C, then diluted with water (15 mL) and extracted with CH₂Cl₂ (3 x 30 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (50% - 80% EtOAc in hexanes) to give the diepoxy alcohol (160.6 mg, 90.8%): ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.17 (m, 10H), 3.99-3.95 (m, 1H), 3.93-3.87 (m, 1H), 3.83-3.73 (m, 1H), 3.71-3.60 (m, 1H), 3.15/3.14 (s, 3H), 2.98-2.90 (m, 1H), 2.67-2.60 (m, 1H), 2.35-2.28 (m, 1H), 1.91-1.86 (m, 1H), 1.78-1.71 (m, 2H), 1.69-1.55 (m, 3H), 1.52-1.44 (m, 3H), 1.30 (s, 3H), 1.16/1.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 142.6, 142.6, 142.3, 142.2, 128.9, 128.8, 128.7, 128.6, 128.4, 126.6, 126.5, 83.3, 83.1, 63.6, 63.0, 63.0, 61.4, 61.2, 61.0, 60.8, 58.2, 57.8, 56.2, 56.0, 36.1, 34.0, 33.7, 27.6, 27.1, 24.7,

16.9, 16.5, 16.4; IR (neat) 3438, 3026, 2929, 1495, 1452, 1385, 1100, 1032, 746, 704; $[\alpha]_D = +19.3^\circ$ (CHCl_3 , c 1.55).

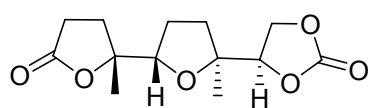


To a solution of diepoxy alcohol **71** (145.1 mg, 0.353 mmol) in anhydrous toluene (3.5 mL) at 0 °C were added 1-methylimidazole (28 μL , 0.353 mmol) and $(\text{Boc})_2\text{O}$ (154 mg, 0.706 mmol). The reaction mixture was stirred overnight, allowing the temperature to warm to room temperature slowly. The reaction was quenched with water (15 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (20% - 25% EtOAc in hexanes containing 0.5% Et_3N) to give the *tert*-butyl carbonate (154.8 mg, 85.8%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.41-7.18 (m, 10H), 4.29-4.21 (m, 1H), 4.19-4.11 (m, 1H), 4.02-3.92 (m, 2H), 3.18/3.17 (s, 3H), 3.04 (dd, $J = 6.2, 4.8$ Hz, 1H), 2.63-2.59 (m, 1H), 1.82-1.40 (m, 8H), 1.53 (s, 9H), 1.32 (s, 3H), 1.17/1.15 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.5, 142.7, 142.4, 142.2, 129.0, 128.7, 128.6, 128.4, 126.6, 126.4, 83.3, 82.7, 65.6, 63.1, 62.7, 60.9, 60.3, 59.8, 58.1, 57.8, 56.3, 56.1, 35.2, 33.9, 33.8, 27.9, 27.6, 27.3, 24.5, 16.9, 16.8, 16.4; IR (neat) 2977, 2932, 1742, 1495, 1453, 1370, 1279, 1256, 1163, 1097, 858, 704; $[\alpha]_D = +1.3^\circ$ (CHCl_3 , c 2.15).



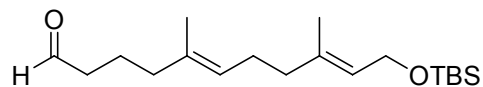
methylfuran-2-yl)-2-methylfuran-2-yl)-1,3-dioxolan-2-one (77) and (4a*S*,5a*S*,9a*R*,11a*R*)-8-Methoxy-5a,11a-dimethyldecahydro-1,3,5,9-tetraoxadibenzo[*a,d*]cyclohepten-2-one (78)

To diepoxide **60** (150.0 mg, 0.294 mmol) in dichloroethane/toluene (11.3 mL, 5:1, v/v) in borosilicate flask at room temperature were added the activated 4Å molecular sieves (300.0 mg), anhydrous Na₂S₂O₃ (300.0 mg, 1.897 mmol), NaOAc (300.0 mg, 3.657 mmol) and *N*-methylquinolinium hexafluorophosphate (8.5 mg, 29.4 μmol). The mixture was photoirradiated with gentle air bubbling for 4.5 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the residue was washed with EtOAc (40 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (35% - 50% EtOAc in hexanes) to provide a mixture of **77** and **78** (51.2 mg, 60.9%): IR (neat) 2925, 1797, 1750, 1462, 1384, 1259, 1167, 1120.



(*R*)-4-((2*S*,5*S*)-tetrahydro-5-((*R*)-tetrahydro-2-methyl-5-oxofuran-2-yl)-2-methylfuran-2-yl)-1,3-dioxolan-2-one (79)

A mixture of acetals **77** and **78** (34.9 mg, 122 μmol) in acetone (1.8 mL) at 0 °C was treated dropwise with Jones reagent (0.3 mL). The mixture was stirred at 0 °C for 10 min, then at room temperature for 1.5 h and purified without workup by column chromatography (50% - 90% EtOAc in hexanes) to give the unreacted acetal **78** (4.9 mg, nearly pure) and lactone **79** (22.1 mg, ~81%). For **79**: ¹H NMR (300 MHz, CDCl₃) δ 4.58 (dd, *J* = 8.3, 6.1 Hz, 1H), 4.48 (t, *J* = 8.4 Hz, 1H), 4.32 (dd, *J* = 8.8, 6.1 Hz, 1H), 4.08 (dd, *J* = 8.8, 5.6 Hz, 1H), 2.65-2.59 (m, 2H), 2.24 (ddd, *J* = 12.9, 9.6, 6.9 Hz, 1H), 2.07-1.81 (m, 5H), 1.38 (s, 3H), 1.27 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 176.7, 155.0, 86.9, 85.1, 83.1, 80.3, 66.2, 34.5, 29.4, 29.1, 27.0, 23.4, 21.3; IR (neat) 2979, 2880, 1790, 1767, 1454, 1382, 1170, 1111, 1085, 944; [α]_D = -11.3° (CHCl₃, *c* 1.03).

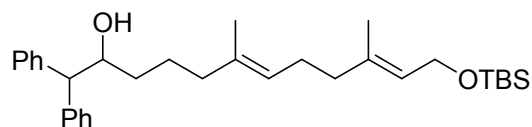


(5E,9E)-11-(*tert*-Butyldimethylsilyloxy)-5,9-dimethylundeca-5,9-dienal (83)

The (methoxymethyl)triphenylphosphonium chloride (1.6558 g, 4.830 mmol) in a dry flask under high vacuum was heated with heat gun for 3 min to remove the moisture. After the flask was cooled to room temperature, THF (8.0 mL) was added in and the suspension was cooled to 0 °C. NaHMDS (1 M in THF, 4.83 mL, 4.83 mmol) was added dropwise and the resulting deep orange suspension was stirred at 0 °C for 1 h. Aldehyde **65** (0.5000 g, 1.610 mmol, dissolved in 2.0 mL of THF) was added dropwise and the flask formerly containing the aldehyde was rinsed with THF (2 x 1.0 mL). The reaction mixture was stirred at 0 °C for 1 h, then quenched with saturated NaHCO₃ (10 mL) and poured into water (20 mL). The mixture was extracted with Et₂O (3 x 30 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (3.5% EtOAc in hexanes) to give the methyl vinyl ether.

The methyl vinyl ether in THF–H₂O (10:1, 16.5 mL) was treated with Hg(OAc)₂ (0.5580 g, 1.648 mmol). The reaction mixture was stirred for 30 min and saturated KI (30 mL) was added. The resulting yellow – green mixture was stirred for 1 h, then diluted with Et₂O (30 mL). The two layers were separated and the aqueous layer was extracted with Et₂O (2 x 40 mL). The combination of the organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (3% - 5% EtOAc in hexanes) to give the titled aldehyde (0.4742 g, 90.7%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 9.77 (t, *J* = 1.7 Hz, 1H), 5.30 (qt, *J* = 6.3, 1.1 Hz, 1H), 5.12 (qt, *J* = 6.9, 1.1 Hz, 1H), 4.20 (d, *J* = 6.3 Hz, 2H), 2.39 (dt, *J* = 7.3, 1.7 Hz, 2H), 2.17-2.08 (m, 2H), 2.01 (app t, *J* = 7.9 Hz, 4H), 1.74 (pent, *J* = 7.3 Hz,

2H), 1.62 (s, 3H), 1.59 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.8, 136.9, 134.2, 125.5, 124.8, 60.5, 43.4, 39.6, 39.0, 26.4, 26.2, 20.4, 18.6, 16.5, 15.9, -4.8; IR (neat) 2929, 2856, 2712, 1728, 1472, 1386, 1254, 1110, 1068, 836, 776; HRMS (ESI): m/z calcd for $\text{C}_{19}\text{H}_{36}\text{O}_2\text{SiNa}$ ($M + \text{Na}$) 347.2382, found 347.2402.



**(6E,10E)-12-(*tert*-Butyldimethylsilyloxy)-
6,10-dimethyl-1,1-diphenyldodeca-6,10-dien-2-ol**

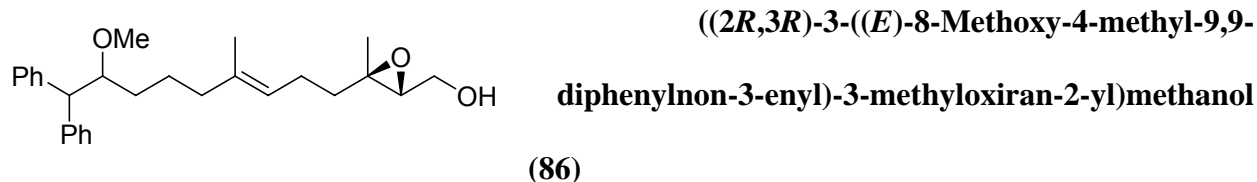
(84)

A solution of diphenylmethane (0.66 mL, 3.933 mmol) in THF (3.9 mL) was treated with *n*-BuLi (1.6 M in hexanes, 2.46 mL, 3.933 mmol) and the resulting deep-orange solution was refluxed for 1 h. After cooling to room temperature, the solution was cooled further to 0 °C and aldehyde **83** (0.4255 g, 1.311 mmol, dissolved in 1.0 mL of THF) was added dropwise. The flask formerly containing the aldehyde was rinsed with THF (2 x 0.5 mL). The deep-orange solution was stirred at 0 °C for 2 h, then quenched with saturated NaHCO_3 (5 mL). The biphasic mixture was poured into water (25 mL) and extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (3% - 9% EtOAc in hexanes) to give the secondary alcohol (0.5186 g, 80.3%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.38-7.13 (m, 10H), 5.28 (qt, $J = 6.3, 1.1$ Hz, 1H), 5.03 (qt, $J = 6.9, 1.0$ Hz, 1H), 4.37-4.29 (m, 1H), 4.18 (d, $J = 6.3$ Hz, 2H), 3.86 (d, $J = 8.3$ Hz, 1H), 2.08-2.00 (m, 2H), 1.96-1.85 (m, 4H), 1.60 (s, 3H), 1.52 (s, 3H), 1.69-1.30 (m, 4H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.8, 141.7, 137.1, 135.2, 129.0, 129.0, 128.8, 128.5, 127.0, 126.7, 124.6, 124.3, 73.9, 60.6, 59.0, 39.7, 39.6, 34.8, 26.5, 26.2, 24.2, 18.6,

16.6, 16.0, -4.8; IR (neat) 3467, 2928, 2856, 1599, 1494, 1451, 1384, 1253, 1107, 1065, 1005, 835, 775, 702; HRMS (ESI): m/z calcd for $C_{32}H_{48}O_2SiNa$ ($M + Na$) 515.3321, found 515.3317.

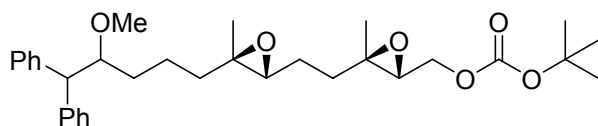


Alcohol **84** (0.4732g, 0.9602 mmol) in anhydrous DMF (5.0 mL) at 0 °C was treated with NaH (60% dispersion in mineral oil, 96.0 mg, 2.40 mmol) and the yellow suspension was stirred at 0 °C for 30 min. MeI (0.24 mL, 3.84 mmol) was added dropwise and the reaction mixture was stirred for 2.5 h at room temperature. The reaction was quenched with water (10 mL) and extracted with Et₂O (3 x 30 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was dissolved in THF (5.0 mL) and TBAF monohydrate (0.3013 g, 1.152 mmol) was added in. The yellow solution was stirred for 2 h and then concentrated in vacuo. The residue was purified by flash chromatography (20% - 30% EtOAc in hexanes) to give the dienol (0.3675 g, 97.5%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.16 (m, 10H), 5.40 (qt, $J = 6.9, 1.2$ Hz, 1H), 5.05 (qt, $J = 6.8, 1.0$ Hz, 1H), 4.16 (d, $J = 6.8$ Hz, 2H), 4.02 (d, $J = 8.3$ Hz, 1H), 3.94-3.88 (m, 1H), 3.18 (s, 3H), 2.13-1.98 (m, 4H), 1.93-1.90 (m, 2H), 1.68 (s, 3H), 1.54 (s, 3H), 1.58-1.30 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 143.1, 142.6, 139.7, 135.4, 129.1, 128.7, 128.6, 128.4, 126.5, 126.4, 124.2, 123.7, 83.8, 59.6, 58.0, 56.3, 39.8, 39.7, 31.7, 26.4, 23.4, 16.4, 16.0; IR (neat) 3388, 3026, 2931, 1667, 1599, 1495, 1451, 1382, 1186, 1102, 1003, 745, 703; HRMS (ESI): m/z calcd for $C_{27}H_{36}O_2Na$ ($M + Na$) 415.2613, found 415.2607.



A suspension of the activated 4Å molecular sieves powder (500 mg) in CH₂Cl₂ (3.3 mL) was treated with D-(-)-DIPT (12.9 μL, 60.8 μmol) and the mixture was cooled to -35 to -30 °C. The mixture was stirred for 10 min and Ti(O-*i*-Pr)₄ (15.2 μL, 50.7 μmol) was added and the mixture was stirred for 15 min more. After that time, *t*-butyl hydroperoxide (5.0-6.0 M in decane, 0.30 mL, 1.521 mmol) was added dropwise and the mixture was stirred for 30 min. Alcohol **85** (199.0 mg, dissolved in 1.0 mL of CH₂Cl₂) was added dropwise and the flask formerly containing the allylic alcohol was rinsed with CH₂Cl₂ (2 x 0.5 mL). The reaction mixture was stirred at -35 to -30 °C for 1.5 h and then water (1.0 mL) was added. The mixture was allowed to warm up to 0 °C and stirred for 1 h. A solution of 30% of NaOH saturated with NaCl (0.2 mL) was added and the mixture was warmed up to room temperature and stirred for 1.5 h. The suspension was filtered through a pad of celite and the filtrate was poured into a separating funnel containing 15 mL of water, the two layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (30% - 40% EtOAc in hexanes) to give the monoepoxy alcohol (207.1 mg, 95.0%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.17 (m, 10H), 5.04 (t, *J* = 6.4 Hz, 1H), 4.00 (d, *J* = 8.3 Hz, 1H), 3.94-3.88 (m, 1H), 3.86-3.78 (m, 1H), 3.72-3.64 (m, 1H), 3.17 (s, 3H), 2.98-2.93 (m, 1H), 2.10-2.02 (m, 2H), 1.95-1.86 (m, 2H), 1.84-1.80 (m, 1H), 1.71-1.61 (m, 1H), 1.64 (s, 1H), 1.54 (s, 3H), 1.51-1.34 (m, 4H), 1.30 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.1, 142.6, 135.9, 129.1, 128.7, 128.7, 128.4, 126.5, 126.4, 123.6, 83.8, 63.1, 61.7, 61.2, 58.0, 56.4, 39.8, 38.7, 31.8, 23.8, 23.4,

17.0, 16.0; IR (neat) 3436, 3026, 2932, 1599, 1494, 1451, 1384, 1103, 1032, 746, 703; HRMS (ESI): m/z calcd for $C_{27}H_{36}O_3Na$ ($M + Na$) 431.2562, found 431.2563; $[\alpha]_D = +3.9^\circ$ ($CHCl_3$, c 1.48).

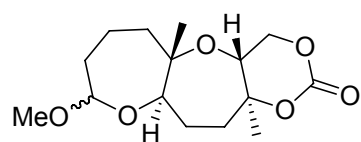


***tert*-Butyl ((2*R*,3*R*)-3-(2-((2*R*,3*R*)-3-(4-methoxy-5,5-diphenylpentyl)-3-methyloxiran-2-yl)ethyl)-3-methyloxiran-2-**

yl)methyl carbonate (81)

To a solution of monoepoxy alcohol **86** (180.2 mg, 0.4410 mmol) in CH_3CN/DMM (6.6 mL, 1:2, v/v) were added a 0.05 M solution of $Na_2B_4O_7$ in 4×10^{-4} M $Na_2(EDTA)$ (4.4 mL), Bu_4NHSO_4 (6.0 mg, 17.6 μ mol) and Shi ketone **68** (56.9 mg, 0.2205 mmol) sequentially. The mixture was cooled to 0 $^\circ C$, and the Oxone (374.1 mg, 0.6086 mmol), dissolved in 4×10^{-4} M $Na_2(EDTA)$ (2.9 mL), and K_2CO_3 (353.5 mg, 2.558 mmol), dissolved in water (2.9 mL), were added simultaneously via a syringe pump over 1.3 h. After the addition was completed, the blue reaction mixture was stirred further for 15 min at 0 $^\circ C$, then diluted with water (5 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was dissolved in toluene (4.4 mL) and cooled to 0 $^\circ C$. 1-Methylimidazole (45.7 μ L, 0.573 mmol) and $(Boc)_2O$ (385.0 mg, 1.764 mmol) were added sequentially. The reaction mixture was stirred overnight, allowing the temperature to warm to room temperature slowly. The reaction was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The extracts were dried over $MgSO_4$, filtered and concentrated. The residue was azeotroped with hexanes (3 x 20 mL) to removed *t*-BuOH and the residue was purified by column chromatography (15% - 25% EtOAc in hexanes containing 0.5% Et_3N) to give the

desired product (198.5 mg, 85.8%, contaminated with about 2% Shi ketone): ^1H NMR (300 MHz, CDCl_3) δ 7.41-7.18 (m, 10H), 4.30-4.14 (m, 2H), 4.02 (d, $J = 8.4$ Hz, 1H), 3.98-3.85 (m, 1H), 3.19/3.18 (s, 3H), 3.05 (t, $J = 5.7$ Hz, 1H), 2.66-2.63 (m, 1H), 1.81-1.39 (m, 8H), 1.52 (s, 9H), 1.35 (s, 3H), 1.20/1.19 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.5, 142.9, 142.5, 142.4, 129.0, 128.9, 128.7, 128.6, 128.4, 126.6, 126.4, 83.7, 83.6, 82.7, 65.6, 62.9, 62.8, 61.0, 60.3, 59.3, 58.1, 58.0, 56.3, 38.8, 38.8, 34.8, 32.2, 27.9, 24.4, 20.9, 20.8, 17.1, 16.5, 16.5; IR (neat) 3026, 2934, 1743, 1495, 1453, 1370, 1279, 1256, 1163, 1098, 859, 747, 705; HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{44}\text{O}_6\text{Na}$ ($M + \text{Na}$) 547.3036, found 547.3002.

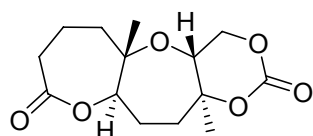


(4aR,5aS,10aR,12aS)-9-Methoxy-5a,12a-dimethyldecahydro-1,3,5,10-tetraoxabenzob[heptalen]-2-one

(88)

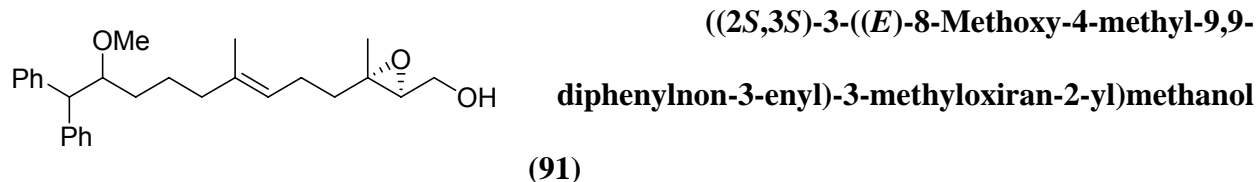
To diepoxide **81** (145.0 mg, 276.3 μmol) in dichloroethane/toluene (10.6 mL, 5:1, v/v) in borosilicate flask at room temperature were added the activated 4Å molecular sieves (290.0 mg), anhydrous $\text{Na}_2\text{S}_2\text{O}_3$ (290.0 mg, 1.834 mmol), NaOAc (290.0 mg, 3.535 mmol) and *N*-methylquinolinium hexafluorophosphate (8.0 mg, 27.6 μmol). The mixture was photoirradiated with gentle air bubbling for 2 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the residue was washed with EtOAc (40 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (25% - 35% EtOAc in hexanes) to provide the cyclization product (44.8 mg, 54.0%) as two diastereomers: ^1H NMR (300 MHz, CDCl_3) δ 4.54-4.48 (m, 1H), 4.25-3.98 (m, 3H), 3.92-3.85 (m, 0.5H), 3.56 (dd, $J = 11.2, 2.4$ Hz, 0.5H), 3.40/3.37 (s, 3H), 3.24 (dd, $J = 10.8, 3.8$ Hz, 0.5H), 2.26-1.94 (m, 2.5H), 1.91-1.72 (m, 3.5H), 1.65-1.52 (m, 3.5H), 1.47/1.44 (s, 3H), 1.33/1.29 (s,

3H), 1.21-1.18 (m, 0.5H); ^{13}C NMR (75 MHz, CDCl_3) δ 149.0, 148.6, 105.2, 102.6, 83.3, 83.2, 81.4, 80.3, 79.7, 75.6, 67.0, 67.0, 65.2, 63.8, 56.1, 55.9, 44.6, 43.3, 37.5, 37.0, 35.3, 33.6, 27.6, 26.2, 22.3, 21.6, 19.2, 17.7, 17.0, 16.7; IR (neat) 2940, 1759, 1454, 1384, 1209, 1111, 1053, 1008, 921; HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{24}\text{O}_6\text{Na}$ ($\text{M} + \text{Na}$) 323.1471, found 323.1500; $[\alpha]_{\text{D}} = +31.5^\circ$ (CHCl_3 , c 1.45).

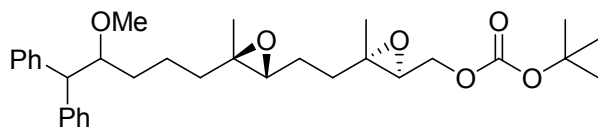


(4aR,5aS,10aR,12aS)-5a,12a-Dimethyldecahydro-1,3,5,10-tetraoxabenzob[b]heptalene-2,9-dione (89)

A solution of acetal **88** (15.6 mg, 51.9 μmol) in CH_2Cl_2 (0.5 mL) at 0°C was treated with *m*-chloroperbenzoic acid (pure, 11.6 mg, 67.5 μmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (7.2 μL , 57.1 μmol) sequentially. After stirred at 0°C for 10 min, then at room temperature for 1 h, the mixture was cooled to 0°C and Et_3N (36.2 μL , 256 μmol) was added dropwise. The mixture was stirred at 0°C for 1.5 h, then quenched with a mixture of saturated NaHCO_3 /saturated $\text{Na}_2\text{S}_2\text{O}_3$ (4 mL, 1:1, v/v). The mixture was poured onto water (5 mL) and extracted with Et_2O (3 x 25 mL). The extracts were dried over MgSO_4 , filtered and concentrated, and the resulting residue was purified by column chromatography (10% - 20% EtOAc in CH_2Cl_2) to give the desired lactone (9.9 mg, 66.9%) as a white crystalline solid: ^1H NMR (300 MHz, CDCl_3) δ 4.26-4.20 (m, 2H), 4.14-4.06 (m, 2H), 2.70-2.55 (m, 2H), 2.35-2.23 (m, 2H), 1.99-1.81 (m, 4H), 1.77-1.68 (m, 2H), 1.46 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 173.3, 148.6, 84.3, 82.2, 78.9, 66.8, 64.3, 43.2, 36.2, 33.6, 26.6, 22.0, 20.0, 15.8; IR (neat) 2989, 2941, 2871, 1748, 1727, 1501, 1454, 1365, 1328, 1272, 1212, 1098, 1040; HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{20}\text{O}_6\text{Na}$ ($\text{M} + \text{Na}$) 307.1158, found 307.1158. $[\alpha]_{\text{D}} = +50.4^\circ$ (CHCl_3 , c 0.42).



A suspension of the activated 4Å molecular sieves powder (115.0 mg) in CH₂Cl₂ (3.3 mL) was treated with L-(+)-DIPT (9.6 μL, 45.8 μmol) and the mixture was cooled to -35 to -30 °C. The mixture was stirred for 10 min and Ti(O-*i*-Pr)₄ (11.4 μL, 38.2 μmol) was added and the mixture was stirred for 15 min more. After that time, *t*-butyl hydroperoxide (5.0-6.0 M in decane, 0.23 mL, 1.15 mmol) was added dropwise and the mixture was stirred for 30 min. Dienol **85** (150.0 mg, 0.382 mmol, dissolved in 1.0 mL of CH₂Cl₂) was added dropwise and the flask formerly containing the allylic alcohol was rinsed with CH₂Cl₂ (2 x 0.5 mL). The reaction mixture was stirred at -35 to -30 °C for 1.5 h and then water (0.6 mL) was added. The mixture was allowed to warm up to 0 °C and stirred for 1 h. A solution of 30% of NaOH saturated with NaCl (0.2 mL) was added and the mixture was warmed up to room temperature and stirred for 1.5 h. The suspension was filtered through a pad of Celite and the filtrate was dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (30% - 40% EtOAc in hexanes) to give the monoepoxy alcohol (156.0 mg, 97.3%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.23 (m, 10H), 5.09 (t, *J* = 6.6 Hz, 1H), 4.06 (d, *J* = 8.3 Hz, 1H), 3.99-3.93 (m, 1H), 3.86-3.83 (m, 1H), 3.70 (dd, *J* = 12.0, 6.6 Hz, 1H), 3.22 (s, 3H), 3.02-2.99 (m, 1H), 2.46 (br s, 1H), 2.10 (q, *J* = 7.7 Hz, 2H), 1.96-1.91 (m, 2H), 1.72-1.43 (m, 6H), 1.59 (s, 3H), 1.33 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.0, 142.5, 135.7, 128.9, 128.6, 128.3, 126.4, 126.3, 123.5, 83.6, 63.2, 61.5, 61.2, 57.9, 56.2, 39.6, 38.6, 31.6, 23.6, 23.2, 16.9, 15.9; IR (neat) 3425, 3027, 2934, 1599, 1495, 1452, 1385, 1103, 1032, 910, 733, 703; HRMS (ESI): *m/z* calcd for C₂₇H₃₆O₃Na (M + Na) 431.2562, found 431.2556; [α]_D = -3.8° (CHCl₃, *c* 1.17).

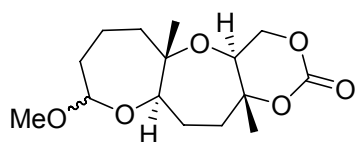


***tert*-Butyl ((2*S*,3*S*)-3-(2-((2*R*,3*R*)-3-(4-methoxy-5,5-diphenylpentyl)-3-methyloxiran-2-yl)ethyl)-3-methyloxiran-2-**

yl)methyl carbonate (90)

To a solution of monoepoxy alcohol **91** (145.0 mg, 0.3549 mmol) in CH₃CN/DMM (5.3 mL, 1:2, v/v) were added a 0.05 M solution of Na₂B₄O₇ in 4x10⁻⁴ M Na₂(EDTA) (3.5 mL), Bu₄NHSO₄ (4.8 mg, 14.2 μmol) and Shi ketone **68** (45.8 mg, 0.1774 mmol) sequentially. The mixture was cooled to 0 °C, and the Oxone (301.1 mg, 0.4898 mmol), dissolved in 4x10⁻⁴ M Na₂(EDTA) (2.3 mL), and K₂CO₃ (284.4 mg, 2.058 mmol), dissolved in water (2.3 mL), were added simultaneously via a syringe pump over 2.0 h. After the addition was completed, the blue reaction mixture was stirred further for 15 min at 0 °C, then diluted with water (5 mL) and extracted with CH₂Cl₂ (3 x 25 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was dissolved in toluene (3.5 mL) and cooled to 0 °C. 1-Methylimidazole (36.8 μL, 0.4614 mmol) and (Boc)₂O (232.4 mg, 1.065 mmol) were added sequentially. The reaction mixture was stirred overnight, allowing the temperature to warm to room temperature slowly. The reaction was quenched with water (5 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The extracts were dried over MgSO₄, filtered and concentrated. The residue was azeotroped with hexanes (3 x 20 mL) to removed *t*-BuOH and the residue was purified by column chromatography (12% - 24% EtOAc in hexanes containing 0.5% Et₃N) to give the desired product (153.5 mg, 82.4%, contaminated with about 2% Shi ketone): ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.07 (m, 10H), 4.29 (dd, *J* = 11.9, 4.8 Hz, 1H), 4.17 (dd, *J* = 11.9, 6.3 Hz, 1H), 4.04 (d, *J* = 8.4 Hz, 1H), 3.99-3.90 (m, 1H), 3.20/3.19 (s, 3H), 3.07 (t, *J* = 5.3 Hz, 1H), 2.67-2.62

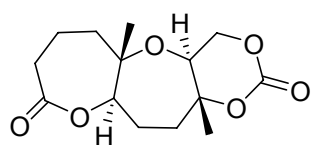
(m, 1H), 1.77-1.42 (m, 10H), 1.54 (s, 9H), 1.35 (s, 3H), 1.22 (br s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 153.4, 142.8, 142.4, 142.4, 128.9, 128.8, 128.6, 128.5, 128.3, 126.5, 126.4, 83.5, 83.5, 82.6, 65.6, 63.0, 62.9, 60.8, 60.8, 60.3, 59.7, 58.0, 57.9, 56.2, 38.7, 38.7, 35.1, 32.1, 27.8, 24.4, 20.8, 20.6, 16.8, 16.5, 16.4; IR (neat) 2979, 2935, 1743, 1495, 1453, 1370, 1279, 1163, 1098, 912, 859, 733, 704; HRMS (ESI): m/z calcd for $\text{C}_{32}\text{H}_{44}\text{O}_6\text{Na}$ ($\text{M} + \text{Na}$) 547.3036, found 547.3031.



(4a*S*,5a*S*,10a*R*,12a*R*)-9-Methoxy-5a,12a-dimethyldecahydro-1,3,5,10-tetraoxabenzob[7]heptalen-2-one
(92)

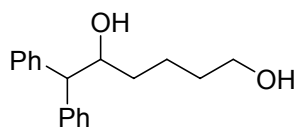
To diepoxide **90** (48.2 mg, 91.9 μmol) in dichloroethane/toluene (3.5 mL, 5:1, v/v) in borosilicate flask at room temperature were added the activated 4Å molecular sieves (96.4 mg), anhydrous $\text{Na}_2\text{S}_2\text{O}_3$ (96.4 mg, 0.610 mmol), NaOAc (96.4 mg, 1.175 mmol) and *N*-methylquinolinium hexafluorophosphate (2.6 mg, 9.2 μmol). The mixture was photoirradiated with gentle air bubbling for 3 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the residue was washed with EtOAc (30 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (25% - 35% EtOAc in hexanes) to provide the cyclization product (21.7 mg, 78.6%) as two diastereomers: ^1H NMR (300 MHz, CDCl_3) δ 4.69 (dd, $J = 3.8, 2.2$ Hz, 0.5H), 4.54 (dd, $J = 8.9, 5.7$ Hz, 0.5H), 4.17 (dd, $J = 10.7, 6.6$ Hz, 1H), 4.02 (t, $J = 10.7$ Hz, 1H), 3.90 (dd, $J = 10.7, 6.6$ Hz, 1H), 3.90-3.85 (m, 0.5H), 3.52 (dd, $J = 10.1, 0.8$ Hz, 0.5H), 3.40/3.37 (s, 3H), 2.08-2.00 (m, 2H), 1.89-1.53 (m, 8H), 1.44 (s, 3H), 1.21/1.17 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 151.6, 148.0, 102.7, 102.4, 83.6, 83.6, 81.3, 80.6, 78.8, 74.1, 67.0 (2C), 64.0, 63.9, 56.0, 55.8, 40.5,

40.2, 39.8, 39.5, 33.7, 33.4, 27.3 (2C), 20.8, 20.3, 19.4, 19.3, 19.3, 17.5; IR (neat) 2940, 1755, 1461, 1382, 1246, 1223, 1116, 1051, 913; HRMS (ESI): m/z calcd for $C_{15}H_{24}O_6Na$ ($M + Na$) 323.1471, found 323.1462; $[\alpha]_D = +26.6^\circ$ ($CHCl_3$, c 0.55).



(4a*S*,5a*S*,10a*R*,12a*R*)-5a,12a-Dimethyldecahydro-1,3,5,10-tetraoxabenzob[b]heptalene-2,9-dione (93)

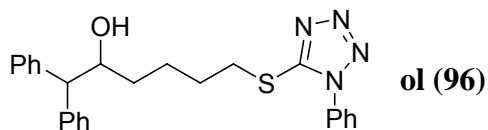
A solution of acetal **92** (16.2 mg, 53.9 μ mol) in CH_2Cl_2 (0.5 mL) at 0 $^\circ C$ was treated with *m*-chloroperbenzoic acid (pure, 12.1 mg, 70.1 μ mol) and $BF_3 \cdot OEt_2$ (3.4 μ L, 27.0 μ mol) sequentially. After stirred at 0 $^\circ C$ for 10 min, then at room temperature for 2.5 h, the mixture was cooled to 0 $^\circ C$ and Et_3N (37.6 μ L, 270 μ mol) was added dropwise. The mixture was stirred at 0 $^\circ C$ for 1.5 h, the quenched with a mixture of saturated $Na_2S_2O_3$ (2 mL). The mixture was poured onto water (5 mL) and extracted with Et_2O (3 x 25 mL). The extracts were dried over $MgSO_4$, filtered and concentrated, and the resulting residue was purified by column chromatography (60% - 70% $EtOAc$ in hexanes) to give the desired lactone (8.6 mg, 56.2%) as a white crystalline solid: 1H NMR (300 MHz, $CDCl_3$) δ 4.44 (dd, $J = 10.1, 1.1$ Hz, 1H), 4.21 (dd, $J = 10.6, 6.4$ Hz, 1H), 4.06 (t, $J = 10.4$ Hz, 1H), 3.96 (dd, $J = 10.4, 6.4$ Hz, 1H), 2.69-2.65 (m, 2H), 2.17-1.67 (m, 8H), 1.48 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 147.7, 83.7, 82.6, 79.0, 66.8, 64.7, 39.4, 38.4, 33.4, 26.4, 20.4, 19.2, 19.1; IR (neat) 2984, 2941, 1747, 1732, 1444, 1388, 1274, 1252, 1200, 1116, 1100, 1070, 1049; HRMS (EI): m/z calcd for $C_{14}H_{20}O_6$ (M) 284.1260, found 284.1254; $[\alpha]_D = +17.2^\circ$ ($CHCl_3$, c 0.52).



6,6-Diphenylhexane-1,5-diol (95)

In a round-bottomed flask, the δ -valerolactone (1.82 mL, 20.0

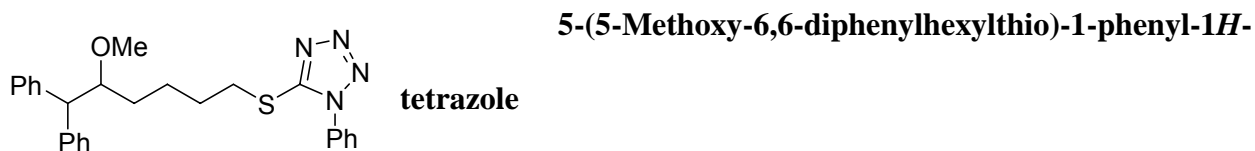
mmol) in CH₂Cl₂ (20.0 mL) at -78 °C was treated dropwise with DIBAL-H (1 M in hexanes, 22.0 mL, 22.0 mmol). The mixture was stirred at -78 °C for 1h, then quenched with saturated sodium tartrate (80 mL) and extracted with Et₂O (3 x 100 mL). The extracts were dried over MgSO₄, filtered and concentrated. In another two-necked round-bottomed flask, diphenylmethane (13.4 mL, 80.0 mmol) in THF (50.0 mL) was treated dropwise with *n*-butyllithium (1.6 M in hexanes, 50.0 mL, 80.0 mmol). The resulting deep orange solution was refluxed for 1 h and then cooled to 0 °C. The as-prepared crude lactol (dissolved in 5 mL THF) was added dropwise and the flask formerly containing the lactol was rinsed with THF (2 x 1.5 mL). The deep-orange mixture was stirred at 0 °C for 0.5 h, then quenched with saturated NH₄Cl (80 mL) and extracted with Et₂O (3 x 100 mL). The combined extracts were dried over MgSO₄ and evaporated. The resulting residue was purified by column chromatography (40% - 80% EtOAc in hexanes) to give the diol (4.42 g, 81.8%) as a white crystalline solid: ¹H NMR (300 MHz, CDCl₃) δ 7.57-7.18 (m, 10H), 4.38 (app t, *J* = 8.0 Hz, 1H), 3.90 (d, *J* = 8.5 Hz, 1H), 3.59 (t, *J* = 5.7 Hz, 2H), 1.88 (br s, 1H), 1.81 (br s, 1H), 1.67-1.42 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 142.6, 141.7, 129.0, 129.0, 128.8, 128.4, 127.0, 126.7, 73.9, 62.7, 59.0, 34.6, 32.6, 22.0; IR (neat) 3358, 3023, 2948, 1596, 1493, 1450, 1345, 1039, 696; HRMS (ESI): *m/z* calcd for C₁₈H₂₂O₂Na (M + Na) 293.1517, found 293.1537.



6-(1-Phenyl-1H-tetrazol-5-ylthio)-1,1-diphenylhexan-2-

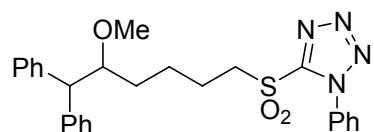
At 0 °C, to a mixture of diol **95** (1.000 g, 3.699 mmol), 1-phenyl-1H-tetrazole-5-thiol (0.791 g, 4.439 mmol) and Ph₃P (1.164 g, 4.439 mmol) in THF (30.0 mL) was added dropwise DIAD (0.82 mL, 4.069 mmol). The mixture was warmed to room

temperature and stirred for 20 min. The reaction was quenched with water (60 mL) and extracted with Et₂O (3 x 70 mL). The organic extracts were dried over MgSO₄ and evaporated. The resulting residue was purified by column chromatography (25% - 40% EtOAc in hexanes) to give the crude product which was further purified by column chromatography (3.5% Et₂O in CH₂Cl₂) to give the pure product (1.542 g, 96.8%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.60-7.50 (m, 5H), 7.40-7.15 (m, 10H), 4.39-4.33 (m, 1H), 3.86 (d, *J* = 8.5 Hz, 1H), 3.35 (t, *J* = 7.1 Hz, 2H), 1.86-1.38 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 154.6, 142.4, 141.5, 133.8, 130.2, 129.9, 129.0, 128.9, 128.8, 128.3, 127.0, 126.8, 124.0, 73.6, 59.1, 34.4, 33.4, 29.1, 25.0; IR (neat) 3439, 3026, 2942, 1597, 1499, 1451, 1387, 1243, 1088, 1015, 910, 760, 733, 704; HRMS (ESI): *m/z* calcd for C₂₅H₂₆N₄OSNa (M + Na) 453.1725, found 453.1705.



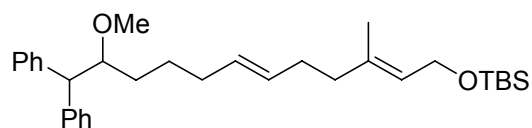
Secondary alcohol **96** (1.444 g, 3.354 mmol) in anhydrous DMF (17.0 mL) at 0 °C was treated with NaH (60% dispersion in mineral oil, 0.335 g, 8.38 mmol) and the yellow suspension was stirred at 0 °C for 30 min. MeI (0.84 mL, 13.42 mmol) was added dropwise and the reaction mixture was stirred for 4 h at room temperature. The reaction was quenched with water (60 mL) and extracted with Et₂O (3 x 50 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (13% - 20% EtOAc in hexanes) to give the desired product (1.268 g, 85.0%) as a pale yellow oil: ¹H NMR (300 MHz, CDCl₃) δ 7.59-7.56 (m, 5H), 7.381-7.17 (m, 10H), 3.98 (d, *J* = 8.4 Hz, 1H), 3.93-3.88 (m, 1H), 3.34 (t, *J* = 7.2 Hz, 2H), 3.15 (s, 3H), 1.86-1.70 (m, 2H), 1.65-1.40 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 154.6, 142.8, 142.4, 133.9, 130.2, 129.9, 128.9,

128.7, 128.6, 128.4, 126.6, 126.4, 124.0, 83.5, 58.1, 56.3, 33.4, 31.7, 29.3, 24.2; IR (neat) 3026, 2938, 1597, 1498, 1451, 1386, 1242, 1102, 759, 697; HRMS (ESI): m/z calcd for $C_{26}H_{28}N_4OSNa$ ($M + Na$) 467.1882, found 453.1876.



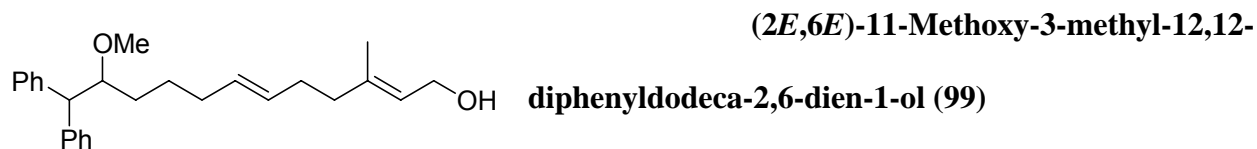
5-(5-Methoxy-6,6-diphenylhexylsulfonyl)-1-phenyl-1H-tetrazole (97)

At 0 °C, $NaHCO_3$ (311.7 mg, 3.711 mmol) was added to a solution of the thioether (330.0 mg, 0.7422 mmol) in CH_2Cl_2 (10.0 mL) and then *m*-chloroperoxybenzoic acid (pure, 435.4 mg, 2.523 mmol) was added in small portions. The mixture was stirred at 0 °C for 15 min, then at room temperature overnight. The reaction was quenched with saturated $Na_2S_2O_3$ solution (20 mL), stirred for 30 min and extracted with CH_2Cl_2 (3 x 25 mL). The extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (16% - 24% EtOAc in hexanes) to give the desired sulfone (336.0 mg, 95.0%) as a colorless oil: 1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.60 (m, 5H), 7.38-7.17 (m, 10H), 3.99 (d, $J = 8.5$ Hz, 1H), 3.94-3.88 (m, 1H), 3.72-3.64 (m, 2H), 3.15 (s, 3H), 1.96-1.84 (m, 2H), 1.68-1.53 (m, 3H), 1.49-1.43 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.7, 142.6, 142.3, 133.2, 131.6, 129.9, 128.9, 128.8, 128.6, 128.5, 126.7, 126.6, 125.3, 83.4, 58.2, 56.4, 56.1, 31.7, 23.9, 22.3; IR (neat) 3027, 2934, 2828, 1597, 1496, 1452, 1342, 1153, 1103, 762, 705; HRMS (ESI): m/z calcd for $C_{26}H_{28}N_4O_3SNa$ ($M + Na$) 499.1780, found 499.1787.



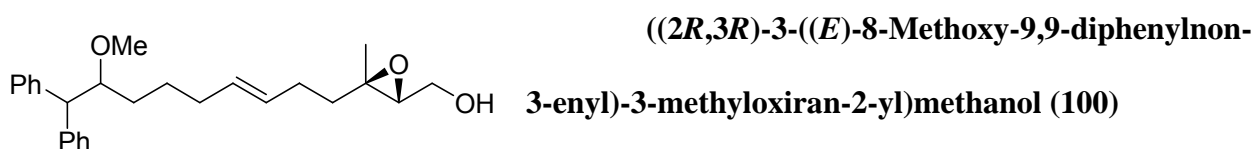
((2E,6E)-11-Methoxy-3-methyl-12,12-diphenyldodeca-2,6-dienyloxy)(tert-butyl)dimethylsilane (98)

A solution of sulfone **97** (300.0 mg, 0.6295 mmol, azeotropically dried with benzene) in anhydrous 1,2-dimethoxyethane (3.8 mL) at -78 °C was treated dropwise with KHMDS (0.5 M in 1,2-dimethoxyethane, 1.51 mL, 0.755 mmol) and the resulting yellow mixture was stirred at this temperature for 1 h. After that time, (*E*)-6-(*tert*-butyldimethylsilanyloxy)-4-methylhex-4-enal (183.1 mg, 0.7554 mmol, dissolved in 0.5 mL of 1,2-dimethoxyethane) was added dropwise. The reaction mixture was stirred at -78 °C for 1.5 h, then at room temperature overnight. The reaction was quenched with saturated NH₄Cl solution (5 mL), poured onto water (10 mL) and extracted with Et₂O (3 x 30 mL). The extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (2% - 3% EtOAc in hexanes) to give the desired diene (196.4 mg, 63.3%) as a pale yellow oil: ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.17 (m, 10H), 5.35-5.33 (m, 2H), 5.30 (qt, *J* = 6.3, 1.0 Hz, 1H), 4.20 (d, *J* = 6.3 Hz, 1H), 4.00 (d, *J* = 8.2 Hz, 1H), 3.91-3.88 (m, 1H), 3.17 (s, 3H), 2.09-2.05 (m, 2H), 2.20-1.99 (m, 2H), 1.92-1.91 (m, 2H), 1.61 (s, 3H), 1.52-1.48 (m, 2H), 1.45-1.40 (m, 2H), 0.92 (s, 9H), 0.08 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 143.2, 142.6, 136.9, 130.4, 130.3, 129.1, 128.7, 128.6, 128.4, 126.5, 126.4, 124.7, 83.8, 60.5, 58.0, 56.3, 39.8, 32.7, 31.7, 31.1, 26.2, 25.2, 18.6, 16.6, -4.8; IR (neat) 3027, 2928, 2855, 1599, 1495, 1451, 1381, 1254, 1105, 1062, 836, 775, 701.



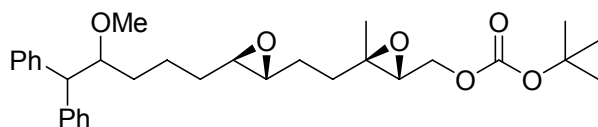
To a solution of **98** (196.4 mg, 0.3985 mmol) in THF (4.0 mL) was added TBAF monohydrate (125.0 mg, 0.4782 mmol). The yellow solution was stirred for 1.5 h and the concentrated. The resulting residue was purified by flash chromatography (20% - 30% EtOAc in hexanes) to give the allylic alcohol (143.1 mg, 94.8%) as

a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.49-7.18 (m, 10H), 5.44-5.36 (m, 3H), 4.15 (d, J = 6.8 Hz, 2H), 4.04 (d, J = 8.3 Hz, 1H), 3.96-3.91 (m, 1H), 3.19 (s, 3H), 2.14-2.02 (m, 4H), 2.00-1.90 (m, 2H), 1.75 (br s, 1H), 1.68 (s, 3H), 1.60-1.39 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.0, 142.5, 139.1, 130.4, 130.0, 129.0, 128.6, 128.3, 126.4, 126.3, 123.8, 83.7, 59.3, 57.9, 56.2, 39.6, 32.6, 31.6, 30.9, 25.0, 16.4; IR (neat) 3390, 3026, 2930, 1599, 1495, 1451, 1101, 1003, 969, 745, 703; HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{34}\text{O}_2\text{Na}$ ($\text{M} + \text{Na}$) 401.2457, found 401.2464.



A suspension of the activated 4Å molecular sieves powder (96.0 mg) in CH_2Cl_2 (2.5 mL) was treated with D-(-)-DIPT (8.2 μL , 38.4 μmol) and the mixture was cooled to -35 to -30 °C. The mixture was stirred for 10 min and $\text{Ti}(\text{O}-i\text{-Pr})_4$ (9.6 μL , 32.0 μmol) was added and the mixture was stirred for 15 min more. After that time, *t*-butyl hydroperoxide (5.0-6.0 M in decane, 0.19 mL, 0.96 mmol) was added dropwise and the mixture was stirred for 30 min. Allylic alcohol **99** (121.0 mg, 0.3196 mmol, dissolved in 0.5 mL of CH_2Cl_2) was added dropwise and the flask formerly containing the allylic alcohol was rinsed with CH_2Cl_2 (2 x 0.25 mL). The reaction mixture was stirred at -35 to -30 °C for 1.3 h and then water (0.6 mL) was added. The mixture was allowed to warm up to 0 °C and stirred for 1 h. A solution of 30% of NaOH saturated with NaCl (0.2 mL) was added and the mixture was warmed up to room temperature and stirred for 1.5 h. The suspension was filtered through a pad of celite and the filtrate was dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (30% - 40% EtOAc in hexanes containing 0.5% Et_3N) to give the monoepoxy alcohol (119.4 mg, 94.8%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.39-

7.16 (m, 10H), 5.42-5.29 (m, 2H), 4.01 (d, $J = 8.3$ Hz, 1H), 3.93-3.88 (m, 1H), 3.80-3.78 (m, 1H), 3.68-3.59 (m, 1H), 3.16 (s, 3H), 2.95 (sept, $J = 6.4, 4.2, 2.0$ Hz, 1H), 2.36-2.34 (m, 1H), 2.15-2.05 (m, 2H), 1.95-1.87 (m, 2H), 1.73-1.66 (m, 1H), 1.51-1.41 (m, 5H), 1.28 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 143.0, 142.5, 130.9, 129.4, 129.0, 128.6, 128.4, 126.5, 126.4, 83.7, 63.2, 61.5, 61.1, 58.0, 56.3, 38.5, 32.6, 31.7, 28.3, 25.0, 16.9; IR (neat) 3423, 3027, 2935, 2857, 1599, 1495, 1452, 1384, 1102, 1032, 970, 911, 733, 704.

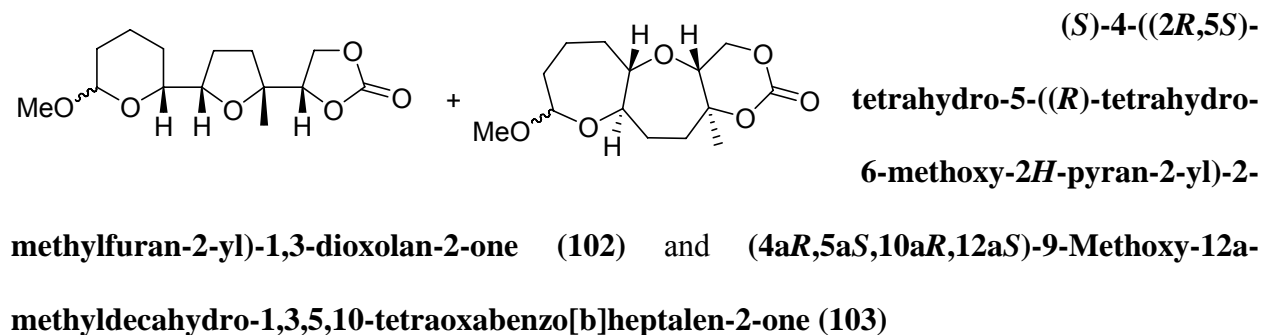


***tert*-Butyl ((2*R*,3*R*)-3-(2-((2*R*,3*R*)-3-(4-methoxy-5,5-diphenylpentyl)oxiran-2-yl)ethyl)-3-methyloxiran-2-yl)methyl**

carbonate (94)

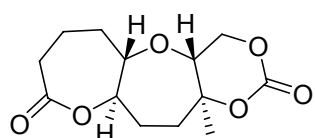
To a solution of monoepoxy alcohol **100** (109.5 mg, 0.2775 mmol) in $\text{CH}_3\text{CN}/\text{DMM}$ (4.2 mL, 1:2, v/v) were added a 0.05 M solution of $\text{Na}_2\text{B}_4\text{O}_7$ in 4×10^{-4} M $\text{Na}_2(\text{EDTA})$ (2.8 mL), Bu_4NHSO_4 (3.8 mg, 11.1 μmol) and Shi ketone **68** (35.8 mg, 0.139 mmol) sequentially. The mixture was cooled to 0 $^\circ\text{C}$, and the Oxone (235.4 mg, 0.3830 mmol), dissolved in 4×10^{-4} M $\text{Na}_2(\text{EDTA})$ (1.8 mL), and K_2CO_3 (222.4 mg, 1.610 mmol), dissolved in water (1.8 mL), were added simultaneously via a syringe pump over 2.0 h. After the addition was completed, the blue reaction mixture was stirred further for 15 min at 0 $^\circ\text{C}$, then diluted with water (15 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was dissolved in toluene (2.8 mL) and cooled to 0 $^\circ\text{C}$. 1-Methylimidazole (22.1 μL , 0.278 mmol) and $(\text{Boc})_2\text{O}$ (121.1 mg, 0.555 mmol) were added sequentially. The reaction mixture was stirred overnight, allowing the temperature to warm to room temperature slowly. The reaction was quenched with water (15 mL) and extracted with

CH₂Cl₂ (3 x 30 mL). The extracts were dried over MgSO₄, filtered and concentrated. The residue was azeotroped with hexanes (3 x 20 mL) to remove *t*-BuOH and the residue was purified by column chromatography (12% - 24% EtOAc in hexanes containing 0.5% Et₃N) to give the desired product (103.5 mg, 73.0%, contaminated with about 2.5% Shi ketone) as a colorless oil: ¹H NMR (600 MHz, CDCl₃) δ 7.38-7.17 (m, 10H), 4.21 (dd, *J* = 11.9, 4.9 Hz, 1H), 4.14 (dd, *J* = 12.0, 6.2 Hz, 1H), 4.00 (d, *J* = 8.3 Hz, 1H), 3.90 (app t, *J* = 7.9 Hz, 1H), 3.17/3.16 (s, 3H), 3.02 (t, *J* = 5.0 Hz, 1H), 2.62-2.59 (m, 2H), 1.71-1.44 (m, 10H), 1.50 (s, 9H), 1.31 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 153.5, 142.9, 142.4, 129.0, 128.7, 128.6, 128.4, 126.6, 126.4, 83.70, 82.8, 65.6, 60.2, 59.3, 58.8, 58.8, 58.2, 58.1, 56.3, 34.2, 32.2, 27.9, 27.6, 21.7, 17.1; IR (neat) 2978, 2934, 1743, 1495, 1453, 1370, 1279, 1256, 1163, 1097, 859, 746, 704.



To diepoxide **94** (42.0 mg, 82.2 μmol) in dichloroethane/toluene (3.2 mL, 5:1, v/v) in borosilicate flask at room temperature were added the activated 4Å molecular sieves (84.0 mg), anhydrous Na₂S₂O₃ (84.0 mg, 0.531 mmol), NaOAc (84.0 mg, 1.024 mmol) and *N*-methylquinolinium hexafluorophosphate (2.4 mg, 8.2 μmol). The mixture was photoirradiated with gentle air bubbling for 3 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the residue was washed with EtOAc (20 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (20% -

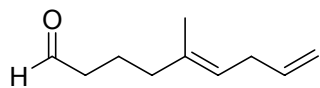
45% EtOAc in hexanes) to provide the cyclization products (11.5 mg, 49%) as a mixture of **102** and **103**: IR (neat) 2935, 2870, 1797, 1756, 1456, 1384, 1205, 1109, 1085, 1039, 999. Further purification by column chromatography (4% - 10% Et₂O in CH₂Cl₂) yielded nearly pure **103** (~2.1 mg) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 4.56 (dd, *J* = 8.6, 5.6 Hz, 0.5H), 4.48 (dd, *J* = 6.6, 3.9 Hz, 0.5H), 4.40-4.34 (m, 1H), 4.15-4.07 (m, 1H), 3.94 (dd, *J* = 11.1, 6.4 Hz, 0.5H), 3.85 (dd, *J* = 11.0, 6.4 Hz, 0.5H), 3.80-3.55 (m, 1.5H), 3.48 (d, *J* = 3.2 Hz, 0.5H), 3.42 (s, 1.5H), 3.39 (s, 1.5H), 2.18-1.80 (m, 6H), 1.66-1.55 (m, 2H), 1.48/1.46 (s, 3H); IR (neat) 2937, 1759, 1456, 1384, 1206, 1108, 1049, 998, 769.



(4a*R*,5a*S*,10a*R*,12a*S*)-12a-Methyldecahydro-1,3,5,10-

tetraoxa-benzo[*b*]heptalene-2,9-dione (**104**)

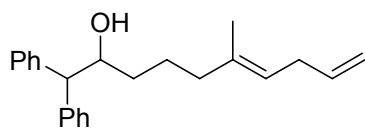
The solution of acetal **103** (2.1 mg, 7.3 μmol) in CH₂Cl₂ (0.3 mL) at 0 °C was treated with *m*-chloroperbenzoic acid (pure, 1.6 mg, 9.5 μmol) and BF₃·OEt₂ (1.0 μL, 8.1 μmol) sequentially. After stirred at 0 °C for 10 min, then at room temperature for 2.5 h, the mixture was cooled to 0 °C and Et₃N (5.1 μL, 36.6 μmol) was added dropwise. The mixture was stirred at 0 °C for 1.5 h, the quenched with a mixture of saturated Na₂S₂O₃ (2 mL). The mixture was poured onto water (5 mL) and extracted with Et₂O (3 x 10 mL). The extracts were dried over MgSO₄, filtered and concentrated, and the resulting residue was purified by column chromatography (65% - 80% EtOAc in hexanes) to give the desired lactone (1.2 mg, 60.0%) as a white crystalline solid: ¹H NMR (300 MHz, CDCl₃) δ 4.45-4.37 (m, 2H), 4.14 (t, *J* = 11.2 Hz, 1H), 3.86 (dd, *J* = 11.0, 6.4 Hz, 1H), 3.56-3.51 (m, 1H), 2.70-2.58 (m, 2H), 2.24-2.15 (m, 2H), 2.07-1.89 (m, 4H), 1.78-1.67 (m, 2H), 1.48 (s, 3H); IR (neat) 2922, 2850, 1747, 1732, 1453, 1387, 1273, 1204, 1106, 1058, 1015.



(E)-5-Methylnona-5,8-dienal (107)

To a stirring solution of Cp_2ZrCl_2 (0.595 g, 2.04 mmol) in CH_2Cl_2 (17.0 mL) at $-25\text{ }^\circ\text{C}$ was added AlMe_3 (2 M in hexanes, 7.64 mL, 15.3 mmol) dropwise, following by addition of water (92 mg, 5.1 mmol) slowly and the resulting mixture was stirred at this temperature for 10 min. After that time, a mixture of 5-hexyn-1-ol (0.500 g, 5.09 mmol) and AlMe_3 (2 M in hexanes, 0.86 mL, 1.72 mmol) in CH_2Cl_2 (4.3 mL) (made by adding AlMe_3 solution dropwise to the hexynol solution in CH_2Cl_2 at $0\text{ }^\circ\text{C}$ and the resulting mixture was stirred at room temperature for 20 min.) was added dropwise. The resulting mixture was warmed up to room temperature and stirred for 4 h. A mixture of allyl bromide (0.44 mL, 5.09 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.176 g, 0.153 mmol) in THF (8.6 mL) (made by adding allyl bromide dropwise to the $\text{Pd}(\text{PPh}_3)_4$ solution and resulting mixture was stirred for 5 min.) was added dropwise to the reaction mixture. The flask formerly containing the allyl bromide was rinsed with THF (2 x 1.0 mL). The mixture was warmed up to room temperature and stirred for 4 h. After that time, the reaction was quenched with dropwise addition of saturated K_2CO_3 (5 mL) at $0\text{ }^\circ\text{C}$ followed by saturated sodium tartrate (30 mL) and water (50 mL). The biphasic mixture was stirred vigorously for 20 min and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was purified by column chromatography (15% - 20% EtOAc in hexanes). The crude product (0.694 g, ~4.5 mmol) was dissolved in CH_2Cl_2 (20 mL) and NaHCO_3 powder (3.02 g, 36.0 mmol) was added followed by Dess-Martin periodinane (5.73 g, 13.5 mmol). The mixture was stirred for 2 h, then quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3$ (30 mL) with caution and poured onto water (50 mL). The biphasic mixture was extracted with CH_2Cl_2 (3 x 30 mL) and the extracts were dried over MgSO_4 , filtered

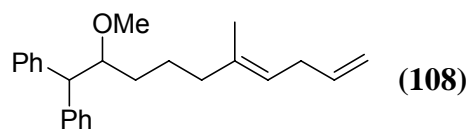
and concentrated. The residue was purified by column chromatography (3% EtOAc in hexanes) to give the aldehyde (0.235 g, 30%) as a colorless liquid: ^1H NMR (300 MHz, CDCl_3) δ 9.77 (t, $J = 1.7$ Hz, 1H), 5.79 (ddt, $J = 16.4, 12.5, 6.2$ Hz, 1H), 5.18 (qt, $J = 9.6, 1.2$ Hz, 1H), 5.40-4.93 (m, 2H), 2.75 (dt, $J = 6.4, 0.6$ Hz, 2H), 2.40 (dt, $J = 7.3, 1.7$ Hz, 2H), 2.05 (t, $J = 7.3$ Hz, 2H), 1.76 (p, $J = 7.2$ Hz, 2H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.8, 137.4, 135.5, 122.8, 114.5, 43.4, 39.0, 32.4, 20.4, 15.9; IR (neat) 3079, 2938, 2720, 1727, 1638, 1454, 1412, 1390, 1112, 995, 910.



(E)-6-Methyl-1,1-diphenyldeca-6,9-dien-2-ol

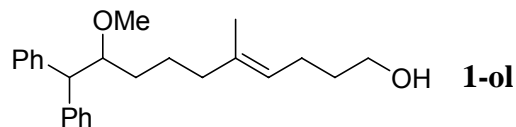
To a solution of diphenylmethane (0.76 mL, 4.53 mmol) in THF (4.0 mL) was added dropwise with *n*-BuLi (1.6 M in hexanes, 2.8 mL, 4.53 mmol). The resulting deep orange solution was stirred at 75 °C for 1 h and cooled to 0 °C. Aldehyde **107** (0.230 g, 1.51 mmol, dissolved in 1.0 mL of THF) was added dropwise and the flask formerly containing the aldehyde was rinsed twice with THF (2 x 0.5 mL). The reaction mixture was stirred at 0 °C for 1 h and quenched by slow addition of saturated NH_4Cl solution (15 mL). The mixture was poured onto water (20 mL) and extracted with Et_2O (3 x 25 mL). The organic extracts were dried over MgSO_4 , filtered and concentrated. The residue was purified by flash chromatography (3% - 7% EtOAc in hexanes) to give the secondary alcohol (0.355 g, 73.3%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.42-7.13 (m, 10H), 5.78 (ddt, $J = 16.3, 12.4, 6.2$ Hz, 1H), 5.12 (qt, $J = 7.2, 1.2$ Hz, 1H), 5.03-4.92 (m, 2H), 4.39-4.36 (m, 1H), 3.90 (d, $J = 8.3$ Hz, 1H), 2.73 (t, $J = 6.9$ Hz, 2H), 2.01-1.93 (m, 2H), 1.72-1.33 (m, 4H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.7, 141.7, 137.6, 136.6, 129.0, 128.8, 128.4, 127.0, 126.7,

121.7, 114.3, 73.9, 59.0, 39.6, 34.7, 32.4, 24.2, 16.0; IR (neat) 3454, 3027, 2914, 1637, 1599, 1494, 1451, 1082, 1032, 910, 756, 745, 703.



(E)-9-Methoxy-5-methyl-10,10-diphenyldeca-1,4-diene

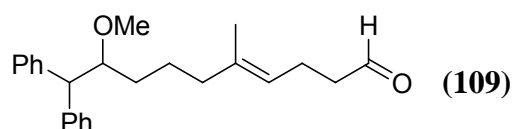
To the secondary alcohol (0.343 g, 1.07 mmol) in anhydrous DMF (6.5 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.107 g, 2.68 mmol). The suspension was stirred at 0 °C for 30 min and MeI (0.27 mL, 4.28 mmol) was added dropwise. The reaction mixture was warm up to room temperature, stirred for 3 h and then quenched with water (30 mL). The mixture was extracted with Et₂O (3 x 30 mL) and the organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography (3% EtOAc in hexanes) to give the diene (0.352 g, 98.3%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.41-7.16 (m, 10H), 5.78 (ddt, *J* = 16.3, 12.4, 6.2 Hz, 1H), 5.12 (qt, *J* = 7.2, 1.2 Hz, 1H), 5.04-4.93 (m, 2H), 4.02 (d, *J* = 8.3 Hz, 1H), 3.95-3.89 (m, 1H), 3.18 (s, 3H), 2.73 (t, *J* = 6.4 Hz, 2H), 1.93 (app t, *J* = 7.1 Hz, 2H), 1.68-1.33 (m, 4H), 1.56 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.1, 142.6, 137.6, 136.5, 129.0, 128.7, 128.4, 126.5, 126.4, 121.7, 114.3, 83.7, 58.0, 56.3, 39.8, 32.4, 31.6, 23.3, 16.0; IR (neat) 3027, 2931, 1637, 1599, 1495, 1451, 1104, 1032, 909, 745, 702.



(E)-9-Methoxy-5-methyl-10,10-diphenyldec-4-en-

At 0 - 5 °C, the solution of 2-methylbutene (0.44 mL, 4.12 mmol) in THF (4.0 mL) was treated dropwise with (1 M in THF, 2.06 mL, 2.06 mmol). The

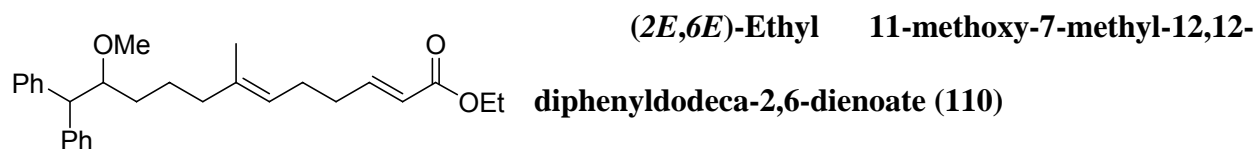
mixture was stirred at this temperature for 1 h and then added slowly to a solution of diene **108** (0.345 g, 1.03 mmol) in THF (4.0 mL) at 0 - 5 °C. The mixture was stirred for 1.3 h and the residual hydride was quenched with water (0.3 mL) cautiously. The organoborane was oxidized by adding NaOH (10%, 1.0 mL) and H₂O₂ (30%, 1.0 mL) and the mixture was warmed up to room temperature. After 1 h, the mixture was diluted with water (20 mL) and extracted with Et₂O (3 x 25 mL). the ether solution was washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo. The residue was purified by column chromatography (20% - 30% EtOAc in hexanes) to give alcohol (0.256 g, 70.3%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.16 (m, 10H), 5.08 (qt, *J* = 7.2, 1.2 Hz, 1H), 4.02 (d, *J* = 8.3 Hz, 1H), 3.95-3.89 (m, 1H), 3.61 (q, *J* = 6.3 Hz, 2H), 3.18 (s, 3H), 2.05 (q, *J* = 7.1 Hz, 2H), 1.95-1.91 (m, 2H), 1.67-1.34 (m, 6H), 1.56 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.1, 142.6, 135.8, 129.0, 128.7, 128.4, 126.5, 126.4, 124.1, 83.7, 62.8, 58.0, 56.3, 39.8, 32.9, 31.7, 24.4, 23.3, 16.0; IR (neat) 3390, 3061, 3026, 2934, 1599, 1495, 1451, 1101, 1063, 1032, 910, 733, 702.



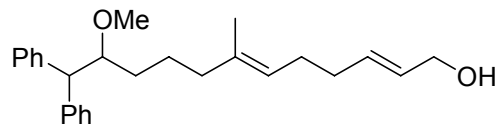
(E)-9-Methoxy-5-methyl-10,10-diphenyldec-4-enal

To a solution of the primary alcohol (230 mg, 0.652 mmol) in CH₂Cl₂ (6.5 ml) were added TEMPO (10.2 mg, 65 μmol), NaHCO₃ (320 mg, 3.91 mmol) and bis(acetoxy)iodobenzene (420 mg, 1.30 mmol). The mixture was stirred for 2 h and quenched cautiously with water (10 ml) and saturated Na₂S₂O₃ solution (5 ml). The mixture was extracted with CH₂Cl₂ (3 x 20 ml) and the combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. Flash chromatography (10% EtOAc in hexanes) gave the aldehyde (170 mg, 74.2%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 9.75 (t, *J* = 1.6 Hz,

1H), 7.40-7.19 (m, 10H), 5.04 (qt, $J = 7.0, 1.2$ Hz, 1H), 4.02 (d, $J = 8.4$ Hz, 1H), 3.95-3.89 (m, 1H), 3.18 (s, 3H), 2.45-2.40 (m, 2H), 2.30 (q, $J = 6.9$ Hz, 2H), 1.97-1.87 (m, 2H), 1.66-1.33 (m, 4H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.8, 143.1, 142.6, 136.9, 129.0, 128.6, 128.4, 126.5, 126.4, 122.3, 83.6, 58.0, 56.3, 44.1, 39.7, 31.5, 23.1, 20.9, 16.0; IR (neat) 3026, 2934, 2825, 2720, 1724, 1495, 1451, 1100, 746, 703.



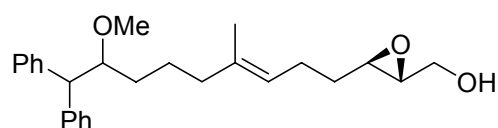
To a suspension of NaH (60% dispersion in mineral oil, 36 mg, 0.90 mmol) in THF (2.5 mL) at 0 °C was added triethyl phosphonoacetate (0.20 mL, 0.90 mmol) and the solution was stirred for 30 min. Aldehyde **109** (158 mg, 0.451 mmol, dissolved in 1.0 mL of THF) was added dropwise and the flask formerly containing the aldehyde was rinsed with THF (2 x 0.5 mL). The mixture was stirred at 0 °C for 1 h, then quenched with saturated NH_4Cl solution (5 mL) and water (10 mL), and extracted with Et_2O (3 x 15 mL). The organic extracts were dried over MgSO_4 , filtered and concentrated in vacuo. The residue was purified by column chromatography (6% - 8% EtOAc in hexanes) to give the ethyl ester (183 mg, 96.4%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 7.39-7.14 (m, 10H), 6.96 (td, $J = 15.6, 6.4$ Hz, 1H), 5.82 (td, $J = 15.6, 1.4$ Hz, 1H), 5.04 (qt, $J = 6.9, 1.0$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 4.00 (d, $J = 8.3$ Hz, 1H), 3.93-3.88 (m, 1H), 3.17 (s, 3H), 2.22-2.07 (m, 4H), 1.91-1.86 (m, 2H), 1.59-1.36 (m, 4H), 1.53 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.9, 149.1, 143.1, 142.6, 136.4, 129.0, 128.6, 128.4, 126.5, 126.4, 123.0, 121.6, 83.6, 60.3, 57.9, 56.3, 39.7, 32.6, 31.6, 26.6, 23.2, 16.0, 14.5; IR (neat) 3026, 2935, 1720, 1654, 1495, 1451, 1367, 1266, 1184, 1099, 1043, 976, 746, 703.



(2E,6E)-11-Methoxy-7-methyl-12,12-

diphenyldodeca-2,6-dien-1-ol (111)

At -78 °C, to the solution of ethyl ester **110** (178 mg, 0.423 mmol) in THF (3.0 mL) was added dropwise DIBAL-H (1 M in hexanes, 1.06 mL, 1.06 mmol). The mixture was stirred at this temperature for 1.2 h, and then quenched with saturated NH₄Cl (5 mL), saturated sodium tartrate (5 mL) and water (10 mL). The mixture was warmed to room temperature and extracted with Et₂O (3 x 20 mL). The organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography (20% - 30% EtOAc in hexanes) to give the alcohol (141 mg, 87.8%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.20 (m, 10 H), 5.75-5.61 (m, 2H), 5.75-5.05 (m, 1H), 4.11 (d, *J* = 4.1 Hz, 2H), 4.05 (d, *J* = 8.3 Hz, 1H), 3.98-3.95 (m, 1H), 3.21 (s, 3H), 2.09-2.07 (m, 4H), 2.01-1.94 (m, 2H), 1.63-1.38 (m, 4H), 1.57 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.0, 142.6, 135.5, 133.0, 129.3, 129.0, 128.6, 128.4, 126.4, 126.4, 124.0, 83.7, 63.9, 58.0, 56.2, 39.7, 32.6, 31.6, 27.7, 23.3, 16.0; IR (neat) 3384, 3026, 2932, 1599, 1495, 1451, 1372, 1101, 1003, 969, 746, 702.

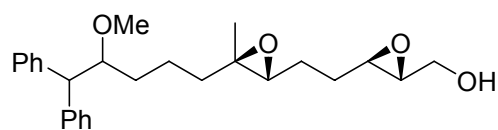


((2R,3R)-3-((E)-8-Methoxy-4-methyl-9,9-

diphenylnon-3-enyl)oxiran-2-yl)methanol

A suspension of the activated 4Å molecular sieves powder (108 mg) in CH₂Cl₂ (2.5 mL) was treated with D-(-)-DIPT (9.1 μL, 42.8 μmol) and the mixture was cooled to -35 to -30 °C. The mixture was stirred for 10 min and Ti(O-*i*-Pr)₄ (10.7 μL, 35.7 μmol) was added and the mixture was stirred for 15 min more. After that time, *t*-butyl hydroperoxide (5.0-6.0 M in decane, 0.21 mL, 1.07 mmol) was added dropwise and the mixture was stirred for 30 min. The allylic

alcohol **111** (135.0 mg, dissolved in 0.5 mL of CH₂Cl₂) was added dropwise and the flask formerly containing the allylic alcohol was rinsed with CH₂Cl₂ (2 x 0.25 mL). The reaction mixture was stirred at -25 to -20 °C for 2 h and then water (0.5 mL) was added. The mixture was allowed to warm up to 0 °C and stirred for 1 h. A solution of 30% of NaOH saturated with NaCl (0.3 mL) was added and the mixture was warmed up to room temperature and stirred for 1.5 h. The suspension was filtered through a pad of celite and the filtrate was dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (30% - 40% EtOAc in hexanes containing 0.5% Et₃N) to give the monoepoxy alcohol (133.9 mg, 95.2%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.16 (m, 10H), 5.08 (qt, *J* = 7.2, 1.1 Hz, 1H), 4.02 (d, *J* = 8.3 Hz, 1H), 3.93-3.87 (m, 2H), 3.66-3.58 (m, 1H), 3.18 (s, 3H), 2.97-2.90 (m, 2H), 2.12 (q, *J* = 7.3 Hz, 2H), 1.98-1.91 (m, 2H), 1.86-1.82 (m, 1H), 1.63-1.32 (m, 6H), 1.56 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 143.1, 142.6, 136.2, 129.0, 128.6, 128.4, 126.5, 126.4, 123.3, 83.7, 61.9, 58.7, 58.0, 56.3, 55.8, 39.7, 31.9, 31.7, 24.5, 23.3, 16.0; IR (neat) 3429, 3026, 2932, 1599, 1495, 1451, 1102, 1031, 910, 733, 703; [α]_D = +13.7° (CHCl₃, *c* 1.70).

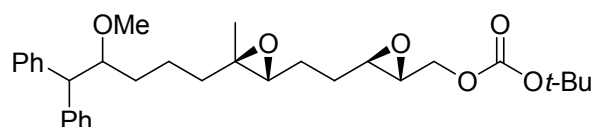


((2R,3R)-3-(2-(((2R,3R)-3-(4-Methoxy-5,5-diphenylpentyl)-3-methyloxiran-2-yl)ethyl)oxiran-2-

yl)methanol

To a solution of the monoepoxy alcohol (131.0 mg, 0.332 mmol) in CH₃CN/DMM (5.0 mL, 1:2, v/v) were added a 0.05 M solution of Na₂B₄O₇ in 4x10⁻⁴ M Na₂(EDTA) (3.3 mL), Bu₄NHSO₄ (4.5 mg, 13.3 μmol) and Shi ketone **68** (42.9 mg, 0.166 mmol) sequentially. The mixture was cooled to 0 °C, and the Oxone (281.6 mg, 0.458 mmol), dissolved in 4x10⁻⁴ M Na₂(EDTA) (2.2 mL), and K₂CO₃ (266.1 mg, 1.93 mmol), dissolved in water (2.2 mL), were

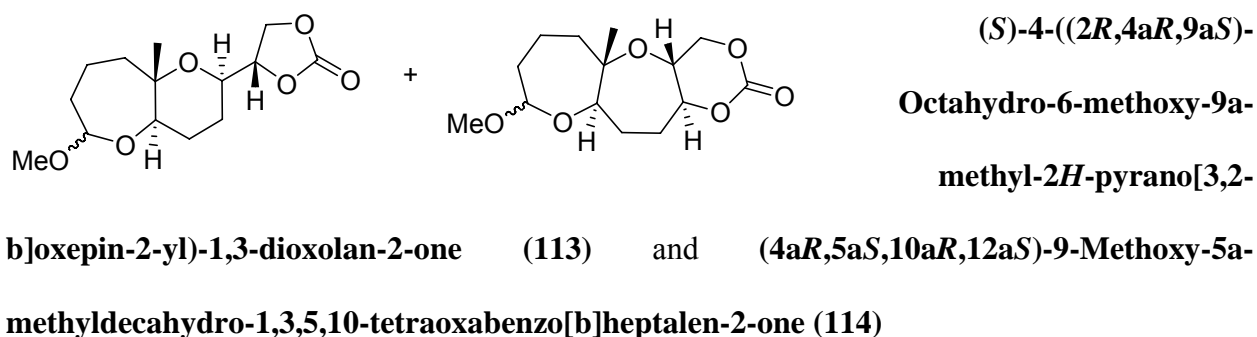
added simultaneously via a syringe pump over 2.0 h. After the addition was completed, the blue reaction mixture was stirred further for 15 min at 0 °C, then diluted with water (15 mL) and extracted with CH₂Cl₂ (3 x 25 mL). The organic extracts were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (40% - 80% EtOAc in hexanes containing 0.5% Et₃N) to give the diepoxy alcohol (122.8 mg, 95.2%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.18 (m, 10H), 4.02 (d, *J* = 8.4 Hz, 1H), 3.93-3.84 (m, 2H), 3.78-3.64 (m, 1H), 3.18/3.17 (s, 3H), 3.05-3.01 (m, 1H), 2.97-2.94 (m, 1H), 2.73-2.68 (m, 1H), 2.01-1.97 (m, 1H), 1.76-1.33 (m, 10H), 1.22/1.21 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 142.8, 142.5, 129.0, 128.9, 128.7, 128.6, 128.4, 126.6, 126.4, 83.6, 63.0, 62.8, 61.9, 61.2, 61.1, 58.4, 58.2, 58.0, 56.3, 55.5, 38.8, 38.8, 32.2, 28.7, 25.3, 20.9, 20.8, 16.6, 16.5; IR (neat) 3439, 3027, 2934, 1599, 1495, 1452, 1385, 1266, 1102, 1032, 887, 736, 705; [α]_D = +15.4° (CHCl₃, *c* 0.56).



***tert*-Butyl ((2*R*,3*R*)-3-(2-((2*R*,3*R*)-3-(4-methoxy-5,5-diphenylpentyl)-3-methyloxiran-2-yl)ethyl)oxiran-2-yl)methyl carbonate (105)**

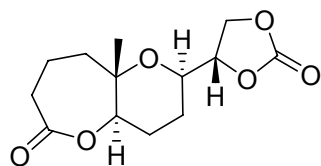
The diepoxy alcohol (117.0 mg, 0.285 mmol) was dissolved in toluene (2.8 mL) and cooled to 0 °C. 1-Methylimidazole (23 μL, 0.285 mmol) and (Boc)₂O (124.4 mg, 0.570 mmol) were added sequentially. The reaction mixture was stirred overnight, allowing the temperature to warm to room temperature slowly. The reaction was quenched with water (15 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The extracts were dried over MgSO₄, filtered and concentrated. The residue was azeotroped with hexanes (3 x 20 mL) to remove *t*-BuOH and the residue was purified by column chromatography (20% - 25% EtOAc in hexanes containing 0.5% Et₃N) to give the desired product (140.4 mg, 96.5%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ

7.42-7.18 (m, 10H), 4.32-4.26 (m, 1H), 4.08-4.01 (m, 2H), 3.98-3.85 (m, 1H), 3.19/3.18 (s, 3H), 3.06-3.04 (m, 1H), 2.96-2.93 (m, 1H), 2.72-2.69 (m, 1H), 1.81-1.28 (m, 10H), 1.52 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 153.3, 142.8, 142.4, 142.4, 128.9, 128.9, 128.6, 128.6, 128.4, 126.5, 126.4, 83.5, 83.5, 82.7, 67.0, 62.7, 62.5, 61.0, 61.0, 58.1, 58.0, 56.2, 56.0, 55.2, 38.8, 38.7, 32.1, 28.5, 27.8, 25.1, 20.8, 20.7, 16.5, 16.4; IR (neat) 2980, 2938, 1743, 1495, 1452, 1370, 1280, 1255, 1163, 1102, 859, 737, 704; [α]_D = +16.7° (CHCl₃, c 1.03).



To diepoxide **105** (51.2 mg, 100 μmol) in dichloroethane/toluene (3.8 mL, 5:1, v/v) in borosilicate flask at room temperature were added the activated 4Å molecular sieves (102 mg), anhydrous Na₂S₂O₃ (102 mg, 0.645 mmol), NaOAc (102 mg, 1.24 mmol) and *N*-methylquinolinium hexafluorophosphate (2.9 mg, 10 μmol). The mixture was photoirradiated with gentle air bubbling for 1.7 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the residue was washed with EtOAc (20 mL). The filtrate was concentrated and the resulting residue was purified by flash chromatography (35% - 50% EtOAc in hexanes) to provide the cyclization products (16.7 mg, 58.2%) as a mixture of **113** and **114**: IR (neat) 2941, 1809, 1759, 1454, 1376, 1171, 1110, 1082, 1050, 1008. Further purification by column chromatography (4% - 12% Et₂O in CH₂Cl₂) provided *endo,exo* product **113** (6.3 mg) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 4.71-4.55 (m, 2H), 4.52-4.42 (m,

2H), 3.86-3.75 (m, 1.5H), 3.50 (dd, $J = 11.3, 5.2$ Hz, 0.5H), 3.41/3.37 (s, 3H), 2.11-1.52 (m, 10H), 1.18/1.13 (s, 3H); IR (neat) 2941, 1814, 1447, 1376, 1170, 1081, 1051.



(2*R*,4*aR*,9*aS*)-Octahydro-9*a*-methyl-2-((*S*)-2-oxo-1,3-dioxolan-4-yl)pyrano[3,2-*b*]oxepin-6-one (115)

A solution of acetal **113** (6.3 mg, 22.0 μmol) in CH_2Cl_2 (0.5 mL) at 0 $^\circ\text{C}$ was treated with *m*-chloroperbenzoic acid (pure, 4.9 mg, 28.6 μmol) and $\text{BF}_3 \cdot \text{OEt}_2$ (3.0 μL , 24.2 μmol) sequentially. After stirred at 0 $^\circ\text{C}$ for 5 min, then at room temperature for 20 min, the mixture was cooled to 0 $^\circ\text{C}$ and Et_3N (15.3 μL , 110.0 μmol) was added dropwise. The mixture was stirred at 0 $^\circ\text{C}$ for 20 min, and then purified by column chromatography (65% - 80% EtOAc in hexanes) to give the desired lactone (4.3 mg, 72.9%) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 4.64-4.58 (m, 1H), 4.52-4.42 (m, 2H), 4.39-4.32 (m, 1H), 3.89-3.82 (m, 1H), 2.72-2.59 (m, 2H), 2.08-1.66 (m, 8H), 1.15 (s, 3H); IR (neat) 2945, 2872, 1798, 1732, 1447, 1275, 1173, 1069, 769, 730.

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