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# Synthesis Studies on the Lomaiviticin A Aglycone Core: Development of a Divergent, Two-Directional Strategy

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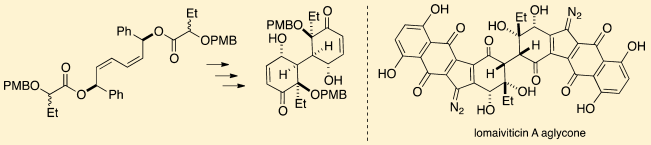
Supporting Information

**ABSTRACT:** The enantiomer of the bicyclic lomaiviticin aglycone A core was prepared via a two-directional, divergent approach featuring (1) a double Ireland Claisen rearrangement to establish key core bonds with correct relative stereochemistry and (2) a double olefin metathesis reaction to deliver both cyclohexene rings of the target.




## INTRODUCTION

Lomaiviticins A and B[1] (Figure 1) along with more recently reported lomaiviticins C, D and E[2] constitute a small but growing class of dimeric (or almost dimeric) isolates from a marine actinomycetes species that are characterized by incorporation of an unusual diazoparaquinone moiety. Although the similarity in structures have led to the suggestive speculation that **1** and **2** might be interconvertible by deglycosylation/glycosylation chemistry,[2] no experimental evidence addresses this point to date. Lomaiviticin C (mono diazo, monoacylfulvene) has been converted into lomaiviticin A (**1**) by treatment with a diazo transfer reagent by Herzon et al.[2]

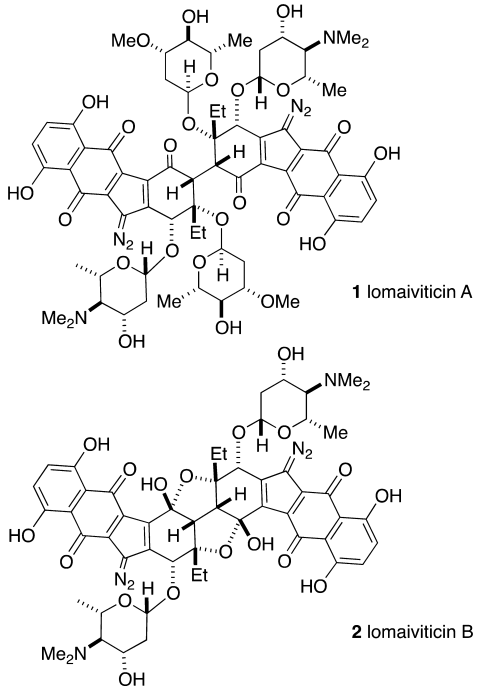



**Figure 1.** Lomaiviticins A and B.

Lomaiviticins D and E differ from lomaiviticin C only by the *O*-methylation level in the oleandrose fragments. Lomaiviticins A, C, D, and E all demonstrate potent cytotoxicity ($IC_{50}$'s of low nM to $\mu$M) against several cancer cell lines,[1,2] and the chemical/structural basis of this activity (and the cytotoxicity of the structurally related monodiazoparaquinone-containing kinamycins) has been the subject of much speculation.[3] It is noteworthy that the more active lomaiviticin structures have two diazoparaquinone units. He et al. in the original isolation report described the lomaiviticins as cleaving dsDNA under reducing conditions, but no further details were forthcoming.[1]

The intriguing structures of the lomaiviticins coupled with the aforementioned profound cytotoxicity and mechanism-of-action mystery has fueled a number of synthesis studies in the area, culminating in the remarkably concise preparation of the lomaiviticin aglycone by Herzon in 2011.[4] The dimeric (or almost dimeric) structure of the lomaiviticins naturally evokes retrosynthesis strategies that can be classified as either divergent or convergent, as illustrated in Scheme 1. Herzon's chemistry followed the convergent approach and featured a heroic dimerization sequence that coupled the two halves together. Approaches to the lomaiviticin structure that also suggested a planned monomer dimerization convergent strategy were authored by Shair[5a,c] and by Nicolaou.[5b] An alternative divergent strategy focuses on the early construction of a dimeric core structure with late-stage two-directional additions of the remainder of the polycyclic framework to that core. This approach can be seen in the work of Nicolaou[6a] and of Sulikowski.[6b,c] A priori, the convergent (dimerization) strategy would appear to enjoy the large benefit of synthesis efficiency, but at a high price; the late-stage dimerization is fraught with potential problems in the area of yield and diastereoselectivity. In fact, the successful Herzon chemistry illustrates this dichotomy; the entire route to the lomaiviticin aglycone proceeds in only 11 steps via tetracycle **4**, but the penultimate monomer dimerization step proceeds in <43% yield and

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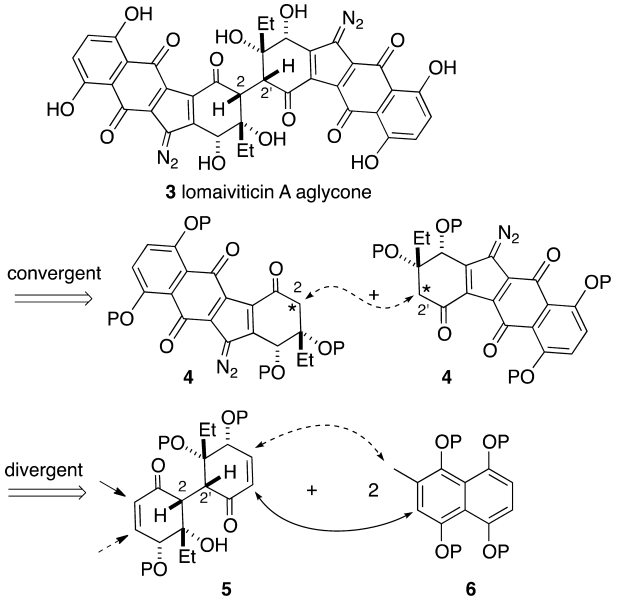
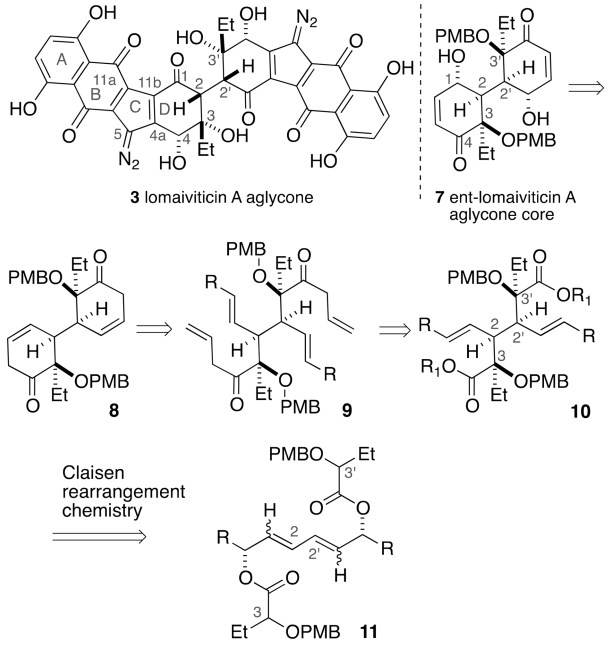
**Scheme 1. Convergent and Divergent Conceptualizations of a Lomaiviticin Synthesis**




**Scheme 2. Lomaiviticin A Aglycone, the (Enantiomeric) Bicyclic Core, and a Retrosynthetic Approach to This Bicyclic Core**

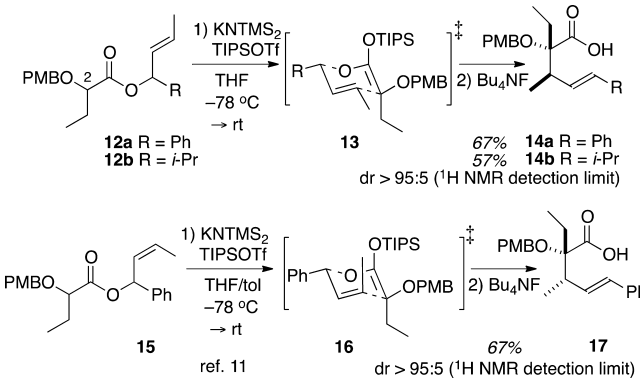



delivers a mixture of three diastereomers in an approximately 5:2:<1 ratio favoring the desired species.[4] Thus, there may be room for improvement by pursuit of a perhaps more conservative divergent strategy wherein the key stereochemical information (cf. **5**) is set with complete and predictable control early on in the route. Of course, such as divergent, two-direction growth strategy must necessarily place a high premium on optimizing (double) reaction yields.

We initiated a synthesis project directed toward the lomaiviticins, based upon a divergent strategic approach, which was designed to pass through a symmetrical, chiral, bis cyclohexenone core **7** en route to the final octacyclic material, Scheme 2. At the outset of this project, the absolute configurations of the lomaiviticins were not yet established,[2] and so we arbitrarily picked the enantiomer resulting from the cheaper chiral starting point. Both enantiomers should be accessible via this strategy. The crux of this approach can be seen in the precursor structures **8**–**11**, wherein a double Ireland Claisen rearrangement will be utilized to set the central C(2)–C(2′) relative and absolute stereochemistry, and then double ring-closing metathesis (RCM) will be employed to deliver the desired bicyclic core. Whereas the Claisen/RCM strategy has been used in many synthesis endeavors to set key stereochemistry in ring systems,[7] this work describes the first example of a *double* Claisen/*double* RCM sequence as a cornerstone for the construction of symmetrical (dimeric) bicycles. An important consideration in executing this strategy is the ability to conveniently access large amounts of a C2-symmetric chiral diester such as **11**, and it is here where Wang's chiral ligand-mediated asymmetric addition of alkyne anions to aldehydes[8] was used to great advantage. A preliminary account of this work has been published.[9]

Preliminary glycolate Claisen rearrangement studies were examined in order to test the feasibility of the basic premise that this transformation can deliver the desired C–C bonds with appropriate stereochemical control. Claisen rearrangements of simple (i.e., C(2) H and not alkyl) glycolates have been well-documented to proceed via chelation-controlled enolization to give a *Z*-enolate that then participates in [3,3] rearrangement through the standard chairlike transition state model.[10] However, the literature on glycolate Claisen rearrangements with C(2) alkylated substrates is less clear, with product formation rationalized through the intermediacy of either *Z*- or *E*-enolates.[7c] Since our system will utilize C(2) ethylated glycolates, some scouting experiments to test this stereochemical issue were pursued, Scheme 3.[11] After much optimization involving variation in silyl reagent, base, solvent, and Lewis acid additive, we arrived at the conclusion that the glycolate Claisen rearrangement protocol introduced by McIntosh (KN(TMS)$_2$, TIPSOTf)[12] offered the best outcome with respect to yield and diastereoselectivity in the simple monocyclic systems examined. Thus, the *E*-alkene substrates **12a** and **12b** both proceeded to acid products **14a** and **14b**, respectively, in moderate yield but with nearly complete diastereoselectivity for the isomers shown. This stereochemical outcome can be explained via reaction through the orthodox chairlike Claisen rearrangement model **13** with a *Z*-silyl ketene acetal, although a boat-like alternative and an *E*-silyl ketene

**Scheme 3. Ireland–Claisen Diastereoselectivity of Simple (*E*)- and (*Z*) Allylic 2-Ethyl Glycolates**





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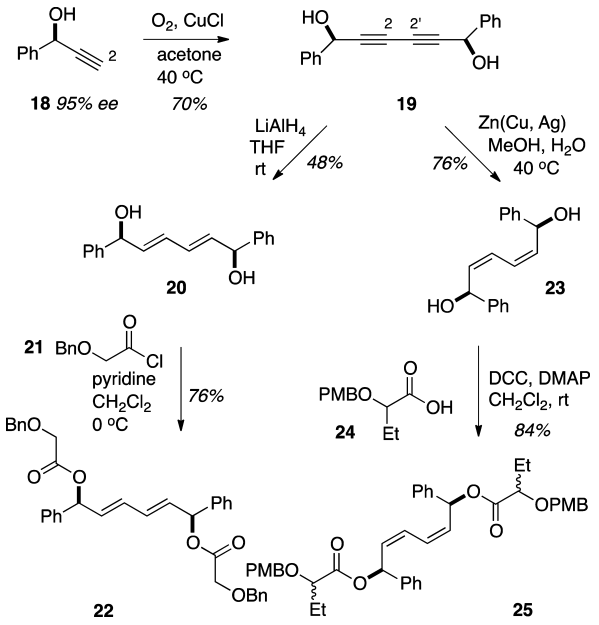
acetal cannot be rigorously excluded. This mechanistic conclusion was reinforced by use of the *Z*-alkene analogue **15**; once again, the stereochemical outcome supports reaction through the *Z*-silyl ketene acetal and a chairlike transition state. Since the lomaiviticin core synthesis objective requires access to the stereochemical arrangement shown in **17**, a double *Z*-alkene substrate is indicated (i.e., **11** in Scheme 2 with *Z*-alkenes).

## RESULTS AND DISCUSSION

The synthesis of the diene diester Claisen rearrangement precursor **25** commenced with chiral propargyl alcohol **18**, Scheme 4. This alcohol is commercially available, but it was

**Scheme 4. Synthesis of Dienyl Bis Glycolates as Ireland–Claisen Substrates**

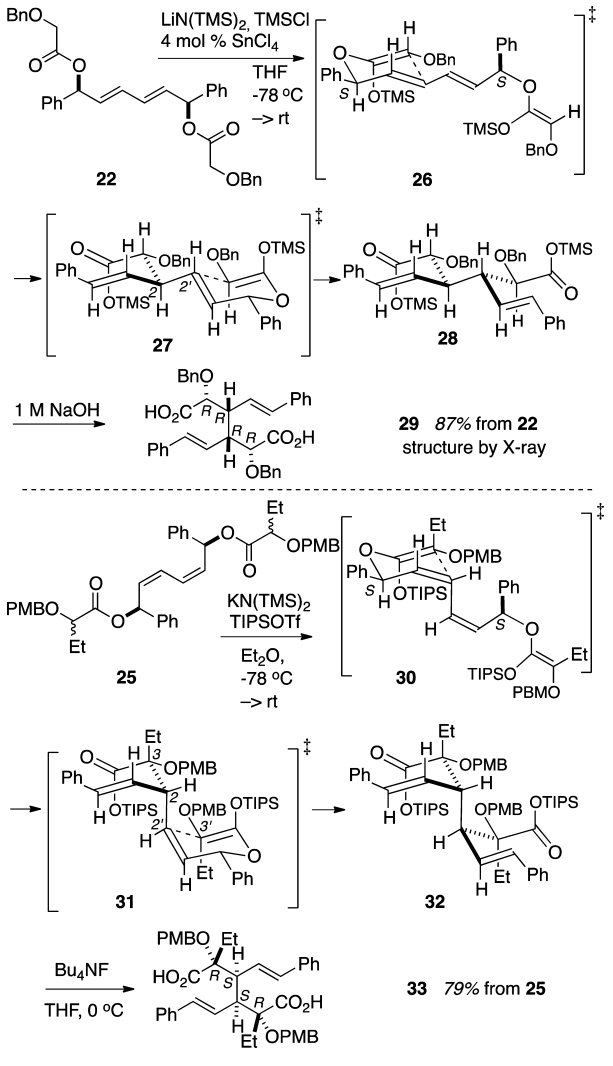



more conveniently prepared by the addition of (trimethylsilyl)-acetylene to benzaldehyde under the influence of both $Et_2Zn$ and the chiral ligand $PhCH_2CH(NHTs)C(Et)_2OH$ as reported by Wang.[8] Whereas several related approaches to chiral propargyl alcohol **25** have been described,[13] the Wang procedure in our hands proved to be quite convenient to execute, especially upon scale-up to 10–20 g batches. The enantiomeric excess of alcohol **25** was assayed by conversion to its Mosher ester and subsequent NMR analysis, which indicated an ee of >95% (NMR detection limit), in accord with the original Wang procedure. Simple Glaser coupling of alcohol **18** furnished the 6-carbon segment **19**, which contains atoms C(3)–C(2)–C(2′)–C(3′) of the lomaiviticin structure. Thus, in this early C–C bond forming step, the key connection between the two identical halves of the target structure (C(2)–C(2′)) has been formed. Reduction of the diyne within **19** to the requisite *Z*,*Z*-diene of **23** appeared problematic initially, as several attempts at semireduction via various Lindlar recipes invariably gave a monoene, monoyne product.[14] Fortunately, the Boland procedure[14] for diyne reduction (Zn/Cu/Ag couple) performed satisfactorily with **19**, and the *Z*,*Z*-diene diol **23** was procured in good yield and free of isomeric congeners. This "real" substrate **23** was acylated with the more complex ethylated glycolic acid **24** to give the double Claisen substrate **25**. The remainder of the lomaiviticin core synthesis route then focuses on *Z*,*Z*-diene diol **25** with the goals of (1) introducing C(4a)/C(4a′), (2) building in the correct stereochemistry for the C(3)–C(2)–C(2′)–C(3) array, and (3) attaching C(1)/C(1′) to C(11b)/C(11b′) (lomaiviticin numbering).

Since the planned downstream double Claisen rearrangement chemistry has scarcely been described,[15] we decided to prepare the analogous *E*,*E*-diene diol **20** as well with the expectation that we would use it as a simpler exploratory model system to probe both the feasibility and the stereochemical consequences of double Claisen rearrangement in this system. Simple $LiAlH_4$-mediated reduction of diyne diol **19** provided the *E*,*E*-series substrate **20** in modest yield. The diene diol **20** was acylated with the glycolic acid chloride **21** to provide the simple, unalkylated bis glycolate ester **22**.

The simple bis glycolate **22** was examined first in the Ireland Claisen rearrangement sequence, Scheme 5. The initial forays into double Claisen rearrangement of **22** utilized $NaN(TMS)_2$ or LDA as base (−78 °C) and either TIPSCl or TIPSOTf as the silylating agent (≥ room temperature or higher). These scouting experiments produced uniformly unfavorable results, with compound destruction and no evidence for rearrangement

**Scheme 5. Double Ireland-Claisen Rearrangements of Dienyl Glycolates 22 and 25**





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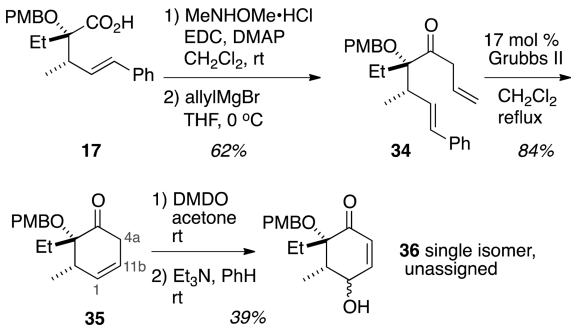
product(s) forthcoming (we had not yet completed our model system study of Claisen rearrangement conditions to guide us (Scheme 3) at this point). A subsequent control experiment whereby bis glycolate **22** was treated with $NaN(TMS)_2$ at −78 °C followed by AcOD provided a glimpse of the problem; the recovered **22** was deuterium-labeled at the allylic/benzylic position! Thus, it appeared that the dual acidifying effects of both the diene and the phenyl ring, as well as the deacidifying effects of the OBn moiety on the glycolate proton, conspired to direct deprotonation away from the $COCH_2OBn$ unit. To overcome this problem, perhaps a more Lewis acidic metal counterion (and inclusion of a bone fide Lewis acid as well?) to activate the glycolate carbonyl and hence selectively acidify the glycolate proton might suffice. In the event, switching the base to $LiN(TMS)_2$ and including 4 mol % $SnCl_4$ in the reaction solution completely changed the reaction outcome and the desired double Ireland Claisen rearrangement proceeded in excellent yield to deliver, after basic hydrolysis of an intermediate bis trimethylsilyl ester, the bis acid **29** as a single stereoisomer. The structure and stereochemistry of **29** was secured by single crystal X-ray analysis.[16] The stereochemical outcome can be rationalized by citing reaction of *Z*-silyl ketene acetals through two consecutive [3,3] sigmatropic reorganizations that proceed through the typically invoked canonical chairlike transition states[17] with equatorial phenyl anchors, **22** → **26** → **27** → **28**. Therefore, there was nothing surprising about this result; the only real issue to be tested was whether the formation of a sterically congested carbon center (C(2) in **27**) adjacent to the locus of C−C bond formation in the second [3,3] rearrangement (C(3′)-to-C(2′) bond formation) might negatively impact on the stereochemical fidelity of this second Claisen reaction. That only one diastereomer of **29** was formed would support the notion that this potential complication was not realized.

This favorable result prompted examination of the "real" system **25** bearing both *Z*-alkenes and the $\alpha$-ethyl unit in the glycolate portion of the substrate. This substrate raises the degree-of-difficulty in that now a more sterically hindered C−C bond (quaternary carbon-to-tertiary carbon) must be formed proximate to the nascent sterically hindered C(2) carbon (cf. **31**, C(3′)-to-C(2′) bond formation adjacent to C(2)). Much optimization was necessary to find conditions where this more challenging Ireland Claisen rearrangement proceeded in good yield. In this vein, variations in the base ($KN(TMS)_2$, $LiN(TMS)_2$, $NaN(TMS)_2$, LDA), silylating agent (TIPSCl, TIPSOTf, TBSCl, TMSCl, TMSOTf), Lewis acid additive (none, $SnCl_4$, $TiCl_4$, $ZnCl_2$) and solvent (THF, toluene, $CH_3CN$, $Et_2O$) were examined. From this collection of reaction conditions, a few trends emerged; (1) only the potassium salt of hexamethylsilazide gave any product—all other bases failed to provide even trace amounts of product, (2) the presence (or absence) of catalytic amounts of Lewis acids either had no material effect or decreased product yield, and (3) the yield increased in going from THF to 50:50 THF/toluene to $Et_2O$. In the final analysis, the optimized conditions ($KN(TMS)_2$, TIPSOTf, $Et_2O$) afforded the diacid product **33** in excellent yield following fluoride-mediated desilylation of the first-formed bis silyl ester. Once again, the stereoselectivity was absolute (within $^1H$ NMR detection limits), and the structure and relative stereochemistry of the product diacid **33** was ascertained by single crystal X-ray analysis of the downstream intermediate **40** (Scheme 8). As with the simpler system **22**, the stereochemical outcome of the double Ireland Claisen rearrangement of **25** can be understood through application of the classic transition state model, as applied to the two sequential transition states **30** and **31** (Scheme 5). Thus, at this juncture in the synthesis route, we have gained access to a complex intermediate featuring both correct relative stereochemistry and correct functionality in the C(3)−C(2)−C(2′)−C(3′) sector of the lomaiviticin core in just four steps.

Continuing the lomaiviticin core synthesis from diacid **33** requires several "double" reactions as we extend outward in two directions. Thus, yield maximization becomes paramount and so yield optimization chemistry with a monomeric model system was explored first, Scheme 6. Initial extension of the

**Scheme 6. Monomeric Model System Explorations: Part 1**




acid residue in **17** (available as per Scheme 3) with a three carbon unit introduces C(4a) and C(11a) (lomaiviticin numbering); this task was accomplished by conversion of the acid into its corresponding Weinreb amide, and then treatment of this acyl derivative with an allyl Grignard reagent. The two alkene units of **34** set the stage for a ring closing metathesis reaction, which proceeded smoothly to join C(11b) to C(1) (lomaiviticin numbering) and deliver **35**. Introduction of C(1) oxygenation was the next goal, a sequence that has been reported to occur smoothly in related cyclohex-3-ene-1-one systems by straightforward mCPBA-mediated alkene epoxidation followed by $SiO_2$-promoted epoxide isomerization.[18] Surprisingly, that chemistry did not work with **35**; the alkene was not epoxidized by mCPBA under a variety of conditions. Perhaps the electronegative OPMB substituent was just too inductively electron depleting, even two atoms removed from the alkene. Resorting to the more powerful oxidant DMDO did work as desired to form an intermediate epoxide as a single isomer (stereochemistry not determined). Treatment of this $\beta,\gamma$-ketoepoxide with mild base served to isomerize it to the desired allylic alcohol **36**, again as a single (unassigned) stereoisomer. That we could form **36** from **17** was encouraging, but the resistance of the alkene in **35** to oxidation was a warning flag, as we were soon to learn.

The mixed success with the simple monomeric model system of Scheme 6 prompted an examination of similar chemistry in a dimeric system, the des ethyl diacid **29**, Scheme 7. We already know that introduction of oxygen at C(1) will not be straightforward based upon the results with **35**; at issue here was the planned double Grubbs metathesis reaction. Would the two cyclohexenes be formed as desired, or would other pathways intervene?[19] To probe this question, the diacid **29** was converted directly into the corresponding bis Weinreb amide via the protocol of Hu,[20] and then into the bis allyl ketone **37** by allyl Grignard reagent addition to this bis Weinreb amide. The Grubbs II catalyst-mediated double ring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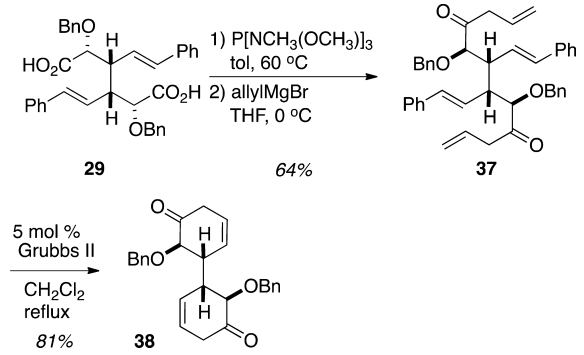
**Scheme 7. More Complex Model System; Divergent Synthesis of a Chiral Bis Cyclohexenone Core**

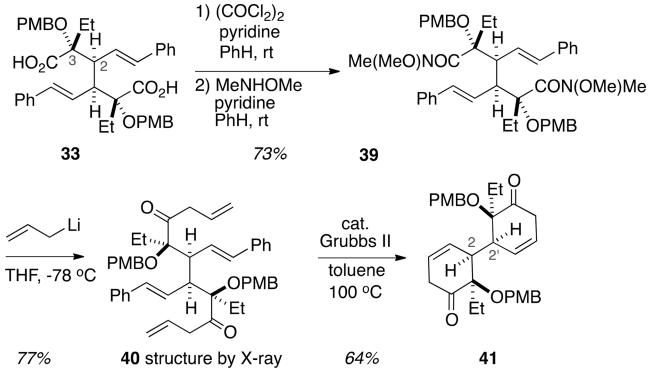



29 37 38

closing metathesis sequence proceeded uneventfully to deliver the desired bis cyclohexene product **38** in good yield and free of any isomers at the $^1$H NMR detection limit. Thus, a potential complication with cycloheptene formation remained unrealized. We decided to focus our C(1) oxygenation approaches on the real ethyl-containing system (vide infra) rather than **38**, given its greater steric hindrance compared to the simpler **38**.

Work on the real system **33** commenced with the two-directional chain extension of the carboxylic acid units into the allyl ketones required for the double ring closing metathesis sequence, Scheme 8. The increased steric hindrance at C(3) in

**Scheme 8. Preparation of a Chiral Bis Cyclohexenone En Route to the Ent-lomaiviticin A Core**



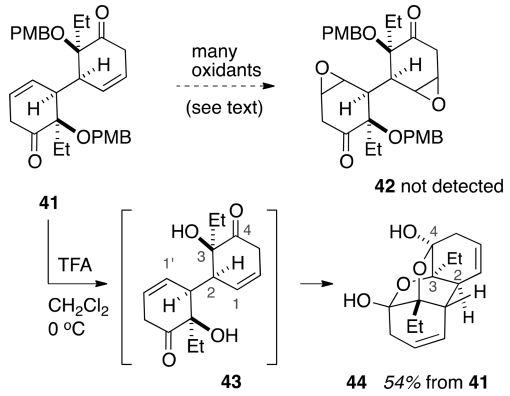

33 39 41

the butyric acid chain of **33** had immediate impact on the chemistry, as the convenient one-step Weinreb amidation procedure of Hu that was successful with **29** failed completely with **33**. Consequently, a standard two-step workaround was executed, leading to the bis Weinreb amide **39** in good yield. Fortunately, using an oxalyl chloride-based procedure activated both acid units faster than monoactivation/cyclization to form a 7-membered anhydride, a problem that derailed the use of milder (i.e., MeNH(OMe), EDC) acid activators. Allylation of the bis amide **39** did not proceed smoothly with a Grignard reagent as per **29** → **30**, as only mixtures of products that appeared to incorporate just one allyl unit resulted. Apparently, once again the enhanced steric hindrance abutting the carbonyl became manifest, and so an alternative was required. The more nucleophilic allyl lithium sufficed, and by this procedure the desired bis allyl ketone metathesis substrate **40** was formed in satisfactory yield. The structure and stereochemistry of this species was determined by single crystal X-ray analysis.[17]

Happily, the double ring closing metathesis reaction of **40** was not victimized by this added C(3) steric burden, and the desired bis cyclohexene product **41** was formed in overall good yield, in analogy with the **37** → **38** conversion in the simpler model system. Much reagent exploration undergirded the identification of the optimized conditions for this pivotal ring closing metathesis. The critical observation was that even trace oxygen exposure depressed the yield dramatically, and so only after thoroughly degassing the sample via three sequential freeze−thaw cycles were reproducible and satisfactory yields of **41** obtained.

The failure to oxidize the simple monomeric model system **35** (Scheme 6) with mCPBA was a concern, but since DMDO did achieve this oxidation, that reagent served as a starting point for the double oxidation of the bis cyclohexene **41**, Scheme 9.

**Scheme 9. Failed Epoxidation of Bis Cyclohexene 41; Formation of a Cage Compound**




41 42 not detected 43 44

Unfortunately, DMDO as well as an assortment of other alkene oxidation protocols (e.g., peracetic acid, trifluoroperacetic acid, Mn(ppei)(OAc)$_6$) all failed to yield bis epoxide product **42** or even a monoepoxide analogue. An attempt to access a bis homoallylic alcohol system **43** that might presage hydroxyl-directed epoxidation led instead via double hemiketalization to the caged compound **44**. Thus, a major reconfiguration of the synthesis route was in order.

Further model system work to address the C(1) oxygenation problem seemed appropriate at this juncture, Scheme 10. Toward this end, the cyclohexenone **48** was prepared from *E*-allylic alcohol **45** through the chemistry we established for the synthesis of **48**'s diastereomer **35** (Scheme 6). The choice of **48** as a model was predicated on its ease of synthesis; *E*-isomer **45** was available in quantity from acrolein whereas the perhaps more stereochemically relevant model **35** required a precursor *Z*-allylic alcohol that was difficult to access at scale in our hands. The new plan involved formation of a dienyl silyl ether derived from **48**, a species that now potentially offered enhanced reactivity at C(1) compared to **48** itself. Both the trimethylsilyl- and the (*t*-butyl)dimethylsilyl dienol ethers **49a** and **49b**, respectively, could be prepared from **48** under standard conditions; these species were formed in essentially quantitative yields ($^1$H NMR assay) but were not stable enough to be purified by chromatography without substantial loss and thus were used "as is" in subsequent transformations. One such thrust utilized a [4$\pi$ + 2$\pi$] cycloaddition of **49a** with nitrosobenzene, which, after product desilylation, furnished the hydroxylamine product **50** as a single stereoisomer in modest yield. The structure and stereochemistry of **50** was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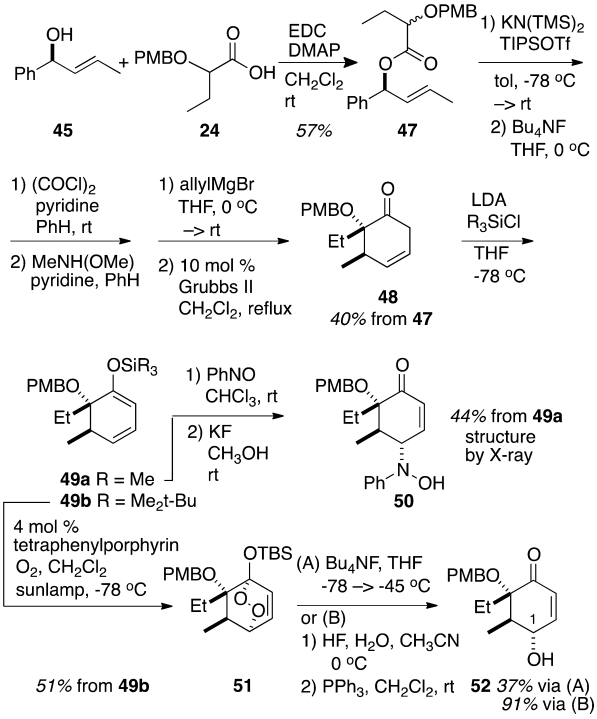
**Scheme 10. Further Monomeric Model System Work in Support of Cyclohexenone γ-Oxidation; Part 2**

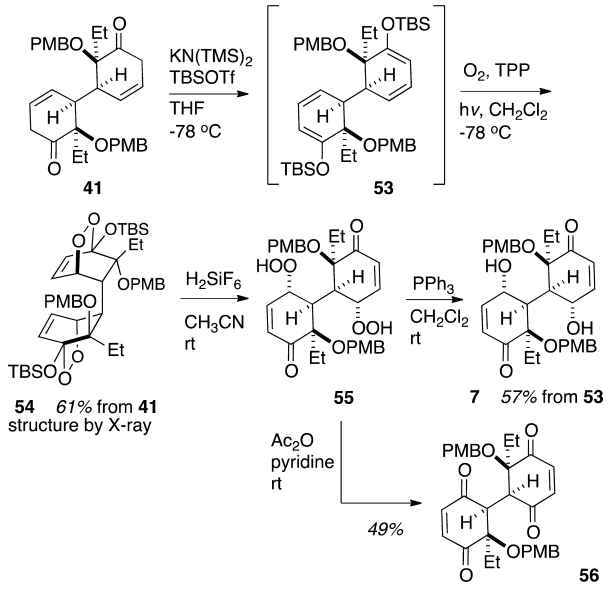



secured by single crystal X-ray analysis.[17] The plan for **50** involved activation of the alcohol as a leaving group and then E2 elimination to give a transient imine en route to the corresponding C(1) ketone via imine hydrolysis. However, this indirect approach to C(1) oxygenation failed at the E2 elimination stage; the tosylate derived from **50** (TsCl, pyridine) was destroyed upon treatment with either DBU or KOH/EtOH without any evidence for formation of an imine or carbonyl product.

A more productive direction was found, however, upon singlet-oxygen-promoted [4π + 2π] cycloaddition to **49b**. In this instance, a single diastereomer of the endoperoxide **51** resulted. The stereochemical assignment of **51** rests on an argument-by-analogy with the stereochemistry of the PhNO cycloadduct and therefore should be considered as provisional. This endoperoxide could in principle be processed on to the desired C(1) oxygenated cyclohexenone **52** by two operations; (1) desilylative rupture of the endoperoxide bridge, and (2) reduction of the O−O bond. That both of these operations occurred when **51** was treated with a fluoride source was surprising, as it was not clear what species served as the O−O bond reductant. [Note: we cannot exclude the possibility that O−O bond reduction occurred either during workup or chromatographic purification.] The modest yield of this transformation may relate to that concern. A far better yield attended a two-step procedure wherein first a C(1) hydroperoxide was liberated by HF-mediated desilylation, and then the peroxide was reduced to the desired alcohol by added $PPh_3$. An alternative C(1) oxygenation procedure with **49b** was explored briefly; Rubottom oxidation (mCPBA) of the dienyl silyl ether led to α-oxygenation only. Thus, by the $^1O_2$ cycloaddition chemistry, we have identified a potential solution to the C(1) oxygenation problem; whether it exports successfully to the double reaction system **41** remains to be seen.

Implementation of the C(1) oxygenation fix developed with the monocyclic model **49b** with the real system **41** constitutes the final task en route to completion of the lomaiviticin bicyclic core synthesis, Scheme 11. This approach to C(1) oxygenation

**Scheme 11. Completion of the Ent-lomaiviticin A Core Bicycle**




is not without its perils in the double reaction series, as attempts to form a bis enolate juxtaposed on a compact framework conjures up concerns about internal aldol and/or Michael additions that might divert the chemistry of obligatory monoenolate/monoenone intermediates. These concerns turned out to be unfounded, however, as bis deprotonation of the two carbonyls in **41** was not hampered by competitive destructive processes, and bis silylation of the stable bis dienolates afforded the bis silyl dienol ether **53** in almost quantitative yield. As with the monocyclic series, chromatographic instability precluded purification of **53** without significant yield loss, and so typically it was used in the subsequent oxygenation reaction as a crude isolate. Exposure of this tetraene to the singlet oxygenation conditions established in the monocyclic model series led to isolation of a single bis endoperoxide **54**, whose structure and stereochemistry were determined unambiguously via single crystal X-ray analysis,[17] in good yield. Apparently $^1O_2$ cycloaddition proceeded on the diene faces opposite of the bulky attached rings in each case. The two-step desilylation/O−O bond reduction sequence developed earlier worked satisfactorily in the double reaction system as well, with one caveat; the desilylation accomplished with HF(aq.)/$CH_3CN$ on the monomeric model system **51** gave irreproducible results with the dimeric bis endoperoxide substrate **54**, and so a screening of alternative fluoride sources was undertaken. Hexafluorosilicic acid almost uniquely cleaved the silyl ether without competitive compound destruction. Thus, the desired bis C(1)/C(1′) diol product **7** was formed in overall moderate yield from the bis endoperoxide **54**. In addition, the bis hydroperoxide **55** served as an effective precursor to the bis enedione **56** via an acylation/elimination sequence. This compound was stable to storage and showed no tendency to eliminate the elements of *p*-methoxybenzyl alcohol.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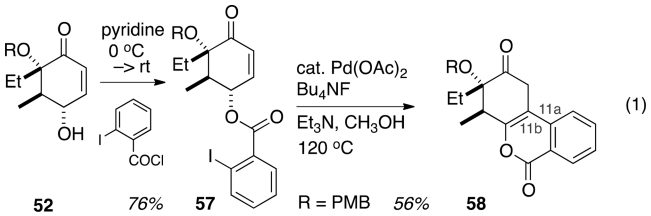
Advancing this bicyclic core unit to lomaiviticinone requires two-directional growth of the oxygenated naphthyl cyclopenteneone units from the enone moieties. The functionality present in the bis γ-hydroxyenone **53** (or bis enedione **54**) is, in principle, set up to enable this extension in a regioselective manner. One example of how the hydroxyl group might be employed to direct addition of an aryl ring into the enone unit is illustrated with the monomeric model system **52** (prepared in Scheme 10), eq 1. Acylation of the sterically hindered alcohol




with 2-iodobenzoyl chloride furnished the ester **57**, a substrate for Heck-type cyclization. Toward that end, treatment of this aryl iodide under modified Jeffrey conditions[21] led to formation of a tricyclic product **58** that effectively established the required C(11a)/C(11b) connection for lomaiviticinone. This model system points out the possible, but there are other approaches that also may be fruitful; work toward that goal is ongoing.

## CONCLUSIONS

An enantiomeric version of the bicyclic lomaiviticinone core **7** was prepared with complete diastereoselectivity over the course of 11 steps from the chiral and commercially available alkynol **18**. This chemistry hews to a two-directional inside-out strategy for lomaiviticinone synthesis in which the critical core C–C bond and adjacent stereochemistry is set early in the route. The fulcrum of the synthesis plan is a double Ireland-Claisen-rearrangement/double-ring-closing-metathesis sequence that transforms a linear precursor into the bis cyclohexenone core. This core will serve as the platform for exploration of the double ring annelation chemistry required to complete the synthesis of lomaiviticinone.

## EXPERIMENTAL SECTION

Note that copies of $^1$H NMR and $^{13}$C NMR spectra for **19**, **23**, **25**, **33**, **39**, **40**, **41**, **44**, **54**, **7**, and **56** can be found in the Supporting Information of ref 9; in addition, ref 9's Supporting Information includes CIF files for **40** and **54**.

**(*R,R*)-1,6-Diphenyl-hexa-2,4-diyne-1,6-diol (19).** To a stirring solution of CuCl (0.98 g, 9.3 mmol) in 450 mL of acetone was added TMEDA (1.50 mL, 10.0 mmol) dropwise followed by bubbling $O_2$ through the solution. A solution of propargyl alcohol **18**[8] (12.3 g, 92.7 mmol) in 50 mL of acetone was added and the solution was heated to 40 °C. After stirring for 14 h at this temperature while bubbling $O_2$ through the solution, the mixture was concentrated in vacuo. To the crude mixture was added 250 mL of 1 M HCl. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 250 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give an orange solid. Purification of this solid by $SiO_2$ flash column chromatography (gradient, 3 → 30% EtOAc/hexanes as eluent) gave (*R,R*)-diyne diol **19** (8.54 g, 70%) as an orange solid. mp 82–84 °C; $[\alpha]^{20}_D$ = −34 (*c* 10.0, MeOH); IR (thin film) 3272, 2355 cm$^{-1}$; $^1$H NMR (360 MHz, MeOD) δ 7.39 (d, *J* = 3.6 Hz, 4H), 7.26–7.18 (m, 6H), 5.40 (s, 2H); $^{13}$C NMR (90 MHz, MeOD) δ 141.4, 129.4, 129.2, 127.5, 81.1, 70.4, 65.0; LRMS (ESI) *m/z* (relative intensity) 371.2 (5%, M + Na$^+$). HRMS (ESI) *m/z* calcd for $[C_{18}H_{13}O]^+$, 245.0966, found 245.0972.

**(*R,R*)-Benzyloxyacetic Acid 6-(2-Benzyloxyacetoxy)-1,6-diphenylhexa-2,4-dienyl Ester (22).** To a stirring solution of bis alkyne **19** (1.23 g, 4.69 mmol) in 45 mL of THF at 0 °C was added $LiAlH_4$ (0.710 g, 26.9 mmol) and the solution was warmed to room temperature. After stirring for 2 h at room temperature, another portion of $LiAlH_4$ (0.710 g, 26.9 mmol) was added. After stirring for an additional 14 h at room temperature, $H_2O$ (1.42 mL) followed by 1.42 mL of 15% NaOH(aq.) and then 4.26 mL of $H_2O$ were added. The suspension was filtered and rinsed with EtOAc. The filtrate was dried with $Na_2SO_4$, filtered, and concentrated in vacuo to give a colorless oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 5 → 40% EtOAc/hexanes as eluent) gave diene **20** (0.597 g, 48%) as a yellow solid. IR (thin film) 3342 cm$^{-1}$; $^1$H NMR (300 MHz, THF-$d^8$) δ 7.45 (d, *J* = 7.7 Hz, 2H), 7.36 (app. t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 6.38 (m, 1H), 5.92 (m, 1H), 5.24 (m, 1H), 4.87 (d, *J* = 3.6 Hz, 1H); $^{13}$C NMR (75 MHz, THF-$d^8$) δ 145.3, 137.7, 129.7, 128.8, 127.6, 127.0, 74.7.

To a stirring solution of diol **20** (0.343 g, 1.29 mmol) in 13 mL of $CH_2Cl_2$ at 0 °C was added pyridine (437 μL, 2.84 mmol) and benzyloxyacetyl chloride (448 μL, 2.84 mmol). The solution was warmed to room temperature, stirred for 1 h at that temperature, and concentrated in vacuo. To the crude mixture was added $H_2O$ (15 mL). The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a colorless oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 1:1:98 → 50:2:48 EtOAc/benzene/hexanes as eluent) gave bis benzyloxyglycolate **22** (0.553 g, 76%) as a colorless oil. $[\alpha]^{20}_D$ = +7° (*c* 1.2, $CHCl_3$); IR (thin film) 1749 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) δ 7.38–7.26 (m, 20H), 6.39 (d, *J* = 6.5 Hz, 2H), 6.25 (dd, *J* = 11.7, 2.9 Hz, 2H), 5.90–5.84 (m, 2H), 4.62 (s, 4H), 4.16 (d, *J* = 18.0 Hz, 2H), 4.11 (d, *J* = 18.0 Hz, 2H); $^{13}$C NMR (90 MHz, $CDCl_3$) δ 169.2, 138.2, 136.9, 132.2, 131.5, 128.5, 128.31, 128.25, 127.9, 127.8, 126.9, 75.9, 73.2, 67.1; LRMS (ESI) *m/z* (relative intensity) 580.3 (10%, M + $NH_4^+$); HRMS (ESI) *m/z* calcd for $[C_{36}H_{38}NO_6]^+$, 580.2699, found 580.2671.

**(*S,S*)-1,6-Diphenyl-hexa-2,4(*Z,Z*)-diene-1,6-diol (23).** Argon was bubbled through a stirring suspension of Zn dust (70 g, 1.1 mol) in 420 mL of $H_2O$. After 15 min, $Cu(OAc)_2{\cdot}H_2O$ (7.0 g, 35 mmol) was added. After an additional 15 min, $AgNO_3$ (7.0 g, 41 mmol) was added. After stirring for 30 min, the mixture was filtered and the solid was washed successively with $H_2O$, MeOH, acetone, and $Et_2O$. The solid was added to 250 mL of a 1:1 mixture of MeOH/$H_2O$ followed by a solution of (*R,R*)-diyne diol **19** (3.50 g, 13.3 mmol) in 30 mL of MeOH. The reaction mixture was heated at 40 °C for 36 h, filtered through Celite with MeOH, and concentrated in vacuo. The remaining aqueous layer was extracted with EtOAc (3 × 400 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a crude orange solid. Purification of this solid by $SiO_2$ flash column chromatography (gradient, 15 → 60% EtOAc/hexanes as eluent) gave (*S,S*)-diene diol **23** (2.71 g, 76%) as an orange solid. mp 107–110 °C; $[\alpha]^{20}_D$ = +69 (*c* 6.20, MeOH); IR (thin film) 3284 cm$^{-1}$; $^1$H NMR (400 MHz, THF-$d^8$) δ 7.35 (d, *J* = 7.3 Hz, 4H), 7.24 (t, *J* = 7.5 Hz, 4H), 7.14 (t, *J* = 7.3 Hz, 2H), 6.60–6.58 (m, 2H), 5.63 (s, 4H), 4.53 (m, 2H); $^{13}$C NMR (75 MHz, THF-$d^8$) δ 145.8, 137.4, 128.8, 127.4, 126.6, 123.7, 69.4; LRMS (ESI) *m/z* (relative intensity) 249.1 (100%, M − OH$^-$); HRMS (ESI) *m/z* calcd for $[C_{18}H_{17}O]$, 249.1279, found 249.1261.

**(*S,S*)-2-(4-(Methoxy)benzyloxy)butyric Acid 6-[2-(4-(Methoxy)benzyloxy)-butyryloxy]-1,6-diphenylhexa-(*Z,Z*)-2,4-dienyl Ester (25).** To a stirring solution of 2-(4-(methoxy)-benzyloxy)butyric acid (**24**)[11] (5.90 g, 26.3 mmol) and (*S,S*)-diene diol **23** (3.19 g, 12.0 mmol) in 120 mL of $CH_2Cl_2$ was added DMAP (365 mg, 4.00 mmol) and DCC (5.92 g, 28.7 mmol). After 16 h at room temperature, the solution was concentrated in vacuo to give a crude yellow oil. Purification of this oil by deactivated silica (2% $Et_3N$ in hexanes) flash column chromatography (gradient, 5 → 15% EtOAc/hexanes as eluent) gave bis PBM glycolate **25** (5.41 g, 67%) as a colorless oil (1:1 mixture of diastereomers). An 84% yield was obtained on a 94 mg scale. IR (thin film) 1737 cm$^{-1}$; $^1$H NMR (400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MHz, $CDCl_3$) $\delta$ 7.43−7.33 (m, 10H), 7.29 (d, $J$ = 8.1 Hz, 4H), 6.90 (d, $J$ = 9.3 Hz, 4H), 6.86 (d, $J$ = 4.2 Hz, 2H), 6.82−6.79 (m, 2H), 5.93−5.85 (m, 2H), 4.68 (d, $J$ = 9.5 Hz, 1H), 4.65 (d, $J$ = 9.5 Hz, 1H), 4.37 (d, $J$ = 12.5 Hz, 2H), 3.95 (t, $J$ = 7.0 Hz, 2H), 3.84 (s, 6H), 1.87−1.80 (m, 4H), 1.00 (t, $J$ = 7.7 Hz, 3H), 0.96 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.84, 171.78, 159.3 (×2), 139.0, 138.9, 131.3, 131.2 (2 carbons), 131.1, 129.6 (2 carbons), 128.6 (2 carbons), 128.2, 128.1, 126.6, 126.5, 125.7, 125.5, 113.7 (2 carbons), 78.9, 78.8, 71.7 (2 carbons), 71.4, 71.2, 55.2 (2 carbons), 26.2, 26.1; LRMS (ESI) $m/z$ (relative intensity) 696.4 (20%, M + $NH_4^+$). HRMS (ESI) $m/z$ calcd for $[C_{42}H_{50}NO_8]^+$, 696.3536, found 696.3520.

**(*R*,*R*,*S*,*S*)-2,5-Bis(benzyloxy)3,4-distyrylhexanedioic Acid (29).** To a stirring solution of LHMDS (267 $\mu$L, 1.0 M in THF, 0.27 mmol) in 1 mL of THF at −78 °C was added dropwise TMSCl (34 $\mu$L, 0.27 mmol). A solution of bis benzyloxyglycolate **22** (0.050 g, 0.089 mmol) in 200 $\mu$L of THF was added dropwise followed by $SnCl_4$ (4 $\mu$L, 1.0 M in $CH_2Cl_2$, 0.004 mmol). The solution was stirred at −78 °C for 30 min, at 0 °C for 30 min, and then warmed to room temperature. After stirring the mixture for an additional 14 h at room temperature, 1 M NaOH (6 mL) was added and the reaction mixture was stirred vigorously for 1 h. $Et_2O$ (10 mL) then was added. The resulting solution was partitioned between $Et_2O$ and 1 M NaOH and the organic layer was extracted with 1 M NaOH (10 mL). The combined aqueous fractions were acidified with 3 M HCl, extracted with EtOAc (3 × 20 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give dicarboxylic acid **29** (0.043 g, 87%) as a light-yellow solid that decomposed >200 °C. A portion of this solid was crystallized from MeCN/hexanes to obtain X-ray quality crystals. $[\alpha]^{20}_D$ = −78° ($c$ 4.0, MeOH); IR (thin film) 3400−3000, 1719 cm$^{-1}$; $^1$H NMR (400 MHz, MeOD) $\delta$ 7.28−7.03 (m, 20H), 6.08 (d, $J$ = 15.7 Hz, 2H), 5.91 (dd, $J$ = 15.7, 10.0 Hz, 2H), 4.53 (d, $J$ = 11.5 Hz, 2H), 4.15 (d, $J$ = 11.5 Hz, 2H), 3.76 (d, $J$ = 9.7 Hz, 2H), 3.07 (td, $J$ = 10.0, 2.3 Hz, 2H); $^{13}$C NMR (75 MHz, THF-$d^8$) $\delta$ 172.9, 139.0, 138.3, 135.3, 129.1, 129.0, 128.4, 128.3, 128.0, 127.3, 125.7, 81.0, 72.6, 47.5; LRMS (ESI) $m/z$ (relative intensity) 580.2 (100%, M + $NH_4^+$); HRMS (ESI) $m/z$ calcd for $[C_{36}H_{38}NO_6]^+$, 580.2699, found 580.2704.

**(2*R*,3*S*,4*S*,5*R*)-2,5-Diethyl-2,5-bis-(4-(methoxy)benzyloxy)-3,4-(distyryl)hexanedioic Acid (33).** To a stirring solution of KHMDS (0.50 M in toluene, 31.6 mL, 15.8 mmol) in 20 mL of $Et_2O$ at −100 °C was added a solution of bis PMB glycolate **25** (1.58 g, 2.32 mmol) in 10 mL of $Et_2O$. After stirring for 40 min at that temperature, TIPSOTf (2.49 mL, 9.28 mmol) was added dropwise. After stirring for an additional 30 min at −100 °C, the solution was warmed to −60 °C. After stirring for 2 h at −60 °C, the solution was warmed to −20 °C. After stirring for 2 h at −20 °C, the solution was warmed to room temperature. After stirring for 2.5 h at room temperature, saturated $NaHCO_3$ (40 mL) was added. The resulting solution was partitioned between $Et_2O$ and $H_2O$ and the aqueous layer was extracted with $Et_2O$ (3 × 40 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give bis TIPS ester **32** (1.81 g, 79%) as a yellow oil that was used without further purification. IR (thin film) 1713 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.20 (m, 14H), 6.79 (d, $J$ = 8.5 Hz, 4H), 6.51 (d, $J$ = 15.8 Hz, 2H), 6.23 (dd, $J$ = 15.8, 10.9 Hz, 2H), 4.56 (d, $J$ = 10.0 Hz, 2H), 4.41 (d, $J$ = 10.1 Hz, 2H), 3.84−3.81 (m, 2H), 3.81 (s, 6H), 2.07−1.89 (m, 4H), 1.22−1.14 (m, 6H), 1.00−0.91 (m, 42H); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 171.8, 158.6, 137.5, 134.3, 131.4, 129.0, 128.1, 127.4, 126.9, 126.4, 113.2, 84.8, 65.5, 55.2, 45.7, 25.7, 17.8, 17.71, 17.67, 12.3, 11.9, 7.4; LRMS (ESI) $m/z$ (relative intensity) 948.8 (100%, M + $NH_4^+$).

To a stirring solution of crude bis TIPS ester **32** (1.28 g, 1.29 mmol) in 15 mL of THF at 0 °C was added $Bu_4NF$ (1.0 M in hexanes, 3.89 mL, 3.9 mmol) dropwise. After stirring for 30 min, $H_2O$ (20 mL) was added. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a crude yellow solid. $CH_3CN$ (20 mL) was added and this solution was washed with hexanes (5 × 20 mL) and the $CH_3CN$ phase was separated and concentrated in vacuo to give diacid **33** (0.876 g, 100%) as a white solid which was used without further purification. mp 116−118 °C; $[\alpha]^{20}_D$ = −42 ($c$ 5.00, MeOH); IR (thin film) 3354, 1702 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 7.37 (d, $J$ = 7.3 Hz, 4H), 7.28 (t, $J$ = 7.2 Hz, 4H), 7.22 (d, $J$ = 7.2 Hz, 2H), 7.17 (d, $J$ =8.2 Hz, 4H), 6.81 (d, $J$ = 8.5 Hz, 4H), 6.50 (d, $J$ = 15.8 Hz, 2H), 6.37 (dd, $J$ = 15.6, 10.6 Hz, 2H), 4.29 (d, $J$ = 9.2 Hz, 2H), 4.20 (d, $J$ = 9.4 Hz, 2H), 3.80 (s, 6H), 3.32 (d, $J$ = 10.4 Hz, 2H), 1.73−1.58 (m, 4H), 0.82 (t, $J$ = 7.1 Hz, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 175.2, 159.9, 137.6, 135.4, 130.2, 128.9, 127.3, 127.1, 125.8, 114.1, 83.8, 65.0, 55.7, 45.4, 26.5, 7.1; LRMS (ESI) $m/z$ (relative intensity) 696.3 (100%, M + $NH_4^+$). HRMS (ESI) $m/z$ calcd for $[C_{42}H_{50}NO_8]^+$, 696.3536, found 696.3550.

**5-Ethyl-5-(4-methoxybenzyloxy)-6-methyl-8-phenylocta-1,7-dien-4-one (34).** To a stirring solution of DMAP (0.276 g, 2.26 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (0.147 g, 1.50 mmol) in 7 mL of $CH_2Cl_2$ was added a solution of carboxylic acid **17**[12] (0.267 g, 0.752 mmol) in 1 mL of $CH_2Cl_2$, followed by EDC (0.288 g, 1.50 mmol). After stirring the mixture for 14 h at room temperature, saturated $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a colorless oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 2 → 10% EtOAc/hexanes as eluent) gave an intermediate Weinreb amide as a colorless oil (0.221 g, 74%). IR (thin film) 1649 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.44 (d, $J$ = 7.4 Hz, 2H), 7.38−7.30 (m, 4H), 7.23 (m, 1H), 6.94 (d, $J$ = 8.6 Hz, 2H), 6.54 (dd, $J$ = 15.9, 7.5 Hz, 1H), 6.46 (d, $J$ = 16.0 Hz, 1H), 4.56 (d, $J$ = 10.3 Hz, 1H), 4.43 (d, $J$ = 10.2 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H), 3.43 (s, 3H), 3.09−3.04 (m, 1H), 2.23 (m, 1H), 2.05 (m, 1H), 1.27 (d, $J$ = 6.9 Hz, 3H), 1.02 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.2, 158.8, 137.4, 132.2, 130.1, 129.5, 128.8, 128.2, 126.7, 125.9, 113.5, 87.0, 64.4, 60.1, 54.9, 43.0, 36.7, 26.1, 15.6, 8.4; LRMS (ESI) $m/z$ (relative intensity) 398.3 (30%, M + $H^+$).

To a stirring solution of the Weinreb amide from above (0.221 g, 0.557 mmol) in 6 mL of THF at 0 °C, was added dropwise allylmagnesium bromide (1.0 M in $Et_2O$, 1.7 mL, 1.7 mmol). The solution was stirred for 30 min at 0 °C and then for 1 h at room temperature. The reaction mixture was added to a cold solution of saturated $NH_4Cl$ (10 mL). The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a colorless crude oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 2 → 4% $Et_2O$/hexanes as eluent) gave allylation product **34** (0.176 g, 84%) as a colorless oil. IR (thin film) 1713 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.50−7.45 (m, 4H), 7.39 (t, $J$ = 7.6 Hz, 2H), 7.29 (m, 1H), 7.04 (d, $J$ = 8.6 Hz, 2H), 6.48 (d, $J$ = 15.8 Hz, 1H), 6.38 (dd, $J$ = 15.8, 8.5 Hz, 1H), 6.05 (m, 1H), 5.26 (d, $J$ = 10.3 Hz, 1H), 5.17 (dd, $J$ = 17.2, 1.4 Hz, 1H), 4.61 (d, $J$ = 10.6 Hz, 1H), 4.49 (d, $J$ = 10.6 Hz, 1H), 3.89 (s, 3H), 3.58 (d, $J$ = 6.4 Hz, 2H), 2.91 (m, 1H), 2.10 (m, 1H), 1.89 (m, 1H), 1.22 (d, $J$ = 7.0 Hz, 3H), 0.91 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 213.1, 158.9, 137.3, 131.2, 130.9, 130.4, 130.3, 128.4, 128.36, 127.0, 126.1, 118.1, 113.7, 89.5, 63.0, 55.1, 45.9, 42.8, 26.3, 15.7, 7.9; LRMS (ESI) $m/z$ (relative intensity) 401.4 (100%, M + $Na^+$); HRMS (ESI) $m/z$ calcd for $[C_{25}H_{31}O_3]^+$, 379.2273, found 379.2257.

**6-Ethyl-6-(4-methoxybenzyloxy)-5-methylcyclohex-3-enone (35).** To a refluxing solution of diene **34** (0.151 g, 0.399 mmol) in 4 mL of $CH_2Cl_2$ was added dropwise a solution of Grubbs II catalyst[22] (60 mg, 0.71 mmol) in 1 mL of $CH_2Cl_2$. After refluxing for 2 h, the solution was cooled to room temperature and concentrated in vacuo to give a crude brown oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 4 → 10% $Et_2O$/hexanes as eluent) gave $\beta,\gamma$-unsaturated enone **35** (0.092 g, 84%) as a light brown oil. IR (thin film) 1719 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.33 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 5.77 (m, 1H), 5.62 (dt, $J$ = 9.8, 3.4 Hz, 1H), 4.48 (d, $J$ = 10.8 Hz, 1H), 4.35 (d, $J$ = 10.8 Hz, 1H), 3.80 (s, 3H), 2.97−2.95 (m, 2H), 2.85 (m, 1H), 2.11 (m, 1H), 1.94 (m, 1H), 1.04 (d, $J$ = 7.1 Hz, 3H), 0.92 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 208.5, 158.8, 132.0, 130.8, 128.3, 122.1, 113.5, 84.9, 63.9, 55.1, 40.2, 39.7, 23.5, 15.6, 7.9; LRMS (ESI) $m/z$ (relative intensity)


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297.5 (100%, M + $Na^+$); HRMS (ESI) $m/z$ calcd for $[C_{17}H_{26}NO_3]^+$, 292.1913, found 292.1901.

**6-Ethyl-4-hydroxy-6-(4-methoxybenzyloxy)-5-methylcyclohex-2-enone (36).** To a stirring solution of $\beta,\gamma$-unsaturated enone **35** (0.044 g, 0.16 mmol) in 1 mL of acetone was added freshly prepared DMDO (0.10 M in acetone, 3.2 mL, 0.32 mmol). The solution was stirred for 30 min at room temperature and concentrated in vacuo to give an epoxide product as a colorless crude oil (single diastereomer, unassigned) that was used without further purification. IR (thin film) 1725 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.21 (d, $J$ = 8.6 Hz, 2H), 6.88 (dd, $J$ = 6.8, 1.9 Hz, 2H), 4.41 (d, $J$ = 11.2 Hz, 1H), 4.02 (d, $J$ = 11.2 Hz, 1H), 3.81 (s, 3H), 3.47 (t, $J$ = 3.0 Hz, 1H), 3.02 (d, $J$ = 3.9 Hz, 1H), 2.88 (dd, $J$ = 17.0, 3.3 Hz, 1H), 2.76 (d, $J$ = 17.0 Hz, 1H), 2.40 (q, $J$ = 7.4 Hz, 1H), 2.16 (m, 1H), 1.53 (m, 1H), 1.28 (t, $J$ = 7.4 Hz, 3H), 0.89 (t, $J$ = 7.4 Hz, 3H); LRMS (ESI) $m/z$ (relative intensity) 313.3 (30%, M + $Na^+$).

To a stirring solution of this crude epoxide in 1 mL of benzene was added $Et_3N$ (45 $\mu$L, 0.32 mmol). The solution was stirred for 12 h at room temperature and then concentrated in vacuo to give a colorless crude oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 10 → 30% EtOAc/hexanes as eluent) gave $\gamma$-hydroxyenone **36** (0.018 g, 39% from **35**, single diastereomer, unassigned) as a colorless oil. IR (thin film) 3425, 1672 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.10 (d, $J$ = 8.6 Hz, 2H), 6.88 (dd, $J$ = 10.3, 1.8 Hz, 1H), 6.82 (d, $J$ = 8.7 Hz, 2H), 5.93 (dd, $J$ = 10.3, 2.1 Hz, 1H), 4.49 (m, 1H), 4.35 (d, $J$ = 11.0 Hz, 1H), 4.02 (d, $J$ = 11.0 Hz, 1H), 3.78 (s, 3H), 2.47 (m, 1H), 2.11 (m, 1H), 1.77 (d, $J$ = 7.2 Hz, 1H), 1.46 (m, 1H), 1.25 (d, $J$ = 6.6 Hz, 3H), 0.80 (t, $J$ = 7.4 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 196.5, 158.9, 152.5, 130.9, 128.6, 126.6, 113.6, 81.9, 64.9, 64.6, 55.2, 44.8, 21.1, 10.0, 8.4; LRMS (ESI) $m/z$ (relative intensity) 313.2 (100%, M + $Na^+$); HRMS (ESI) $m/z$ calcd for $[C_{17}H_{26}NO_4]^+$, 308.1862, found 308.1867.

**(*R*,*R*,*S*,*S*)-5,8-Bis-benzyloxy-6,7-distyryldodeca-1,11-diene-4,9-dione (37).** To a stirring solution of dicarboxylic acid **29** (1.48 g, 2.62 mmol) in 25 mL of toluene was added $P[NCH_3(OCH_3)]_3$[20] (517 $\mu$L, 2.62 mmol). The solution was heated to 60 °C, stirred for 2 h at that temperature, cooled to room temperature, and saturated $NaHCO_3$ (25 mL) was added. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a yellow crude oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 25 → 60% EtOAc/hexanes as eluent) gave an intermediate bis Weinreb amide (1.23 g, 73%) as a pale yellow oil. A yield of 100% was obtained on a 20 mg scale. IR (thin film) 1666 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.41–7.28 (m, 20H), 6.33 (d, $J$ = 15.7 Hz, 2H), 6.20–6.13 (m, 2H), 4.72 (d, $J$ = 13.4 Hz, 2H), 4.43–4.31 (m, 4H), 3.40 (s, 6H), 3.4 (m, 2H), 2.99 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 173.7, 138.2, 137.7, 135.5, 128.9, 128.8, 128.7, 128.3, 127.9, 126.8, 125.0, 73.7, 72.1, 61.7, 48.0, 33.2; LRMS (ESI) $m/z$ (relative intensity) 649.4 (100%, M + $H^+$).

To a stirring solution of this bis Weinreb amide (1.23 g, 1.90 mmol) in 20 mL of THF at 0 °C was added dropwise allylmagnesium bromide (1.0 M in $Et_2O$, 11.4 mL, 11 mmol). The solution was stirred for 30 min at 0 °C and then added to a cold solution of saturated $NH_4Cl$ (20 mL) and HOAc (1 ML). The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a colorless crude oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 4 → 5% EtOAc/hexanes as eluent) gave bis allylation product **37** (0.517 g, 45%) as a colorless oil. A yield of 64% was obtained on a 176 mg scale. $[\alpha]^{20}_D$ = −73° ($c$ 11.1, MeOH); IR (thin film) 1708 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.39–7.38 (m, 10H), 7.30–7.21 (m, 6H), 7.18–7.16 (m, 4H), 6.01 (dd, $J$ = 15.9 Hz, 4.8 Hz, 2H), 5.84–5.72 (m, 4H), 5.12–5.03 (m, 4H), 4.58 (d, $J$ = 11.7 Hz, 2H), 4.29 (d, $J$ = 11.6 Hz, 2H), 3.78 (d, $J$ = 10.0 Hz, 2H), 3.38–3.32 (m, 2H), 3.20–3.13 (m, 4H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 209.5, 136.9, 136.2, 135.3, 130.2, 128.6, 128.5, 128.4, 128.2, 127.8, 126.4, 122.9, 118.7, 85.1, 72.5, 45.7, 42.4; LRMS (ESI) $m/z$ (relative intensity) 628.3 (100%, M + $NH_4^+$); HRMS (ESI) $m/z$ calcd for $[C_{42}H_{46}NO_4]^+$, 628.3427, found 628.3425.

**(*R*,*R*,*S*,*S*)-2,2′-Bis-benzyloxy-bicyclohexyl-5,5′-diene-3,3′-dione (38).** To a refluxing solution of tetraene **37** (0.100 g, 0.164 mmol) in 35 mL of freeze–pump–thawed $CH_2Cl_2$ was added dropwise a solution of Grubbs II catalyst[22] (7 mg, 0.008 mmol) in 250 $\mu$L of $CH_2Cl_2$. After holding at reflux for 2 h, the solution was cooled to room temperature and concentrated in vacuo to give a crude white solid. Purification of this solid by $SiO_2$ flash column chromatography (gradient, 20 → 40% $Et_2O$/hexanes as eluent) gave bicycle **38** (0.041 g, 62%) as a tacky white solid. A yield of 81% was obtained on a 15 mg scale. $[\alpha]^{20}_D$ = +123° ($c$ 0.86, $CHCl_3$); IR (thin film) 1719 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.32–7.24 (m, 10H), 5.65 (dd, $J$ = 9.9, 2.4 Hz, 2H), 5.32 (d, $J$ = 10.0 Hz, 2H), 4.87 (d, $J$ = 11.7 Hz, 2H), 4.39 (d, $J$ = 11.7 Hz, 2H), 3.98 (d, $J$ = 10.2 Hz, 2H), 3.16 (d, $J$ = 9.1 Hz, 2H), 3.04 (d, $J$ = 23.0 Hz, 2H), 2.94 (d, $J$ = 20.9 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 207.2, 137.2, 128.4, 128.3, 127.9, 125.7, 124.2, 79.9, 72.2, 43.3, 40.2; LRMS (ESI) $m/z$ (relative intensity) 420.2 (80%, M + $NH_4^+$); HRMS (ESI) $m/z$ calcd for $[C_{26}H_{30}NO_4]^+$, 420.2175, found 420.2161.

**(2*R*,3*S*,4*S*,5*R*)-2,5-Diethyl-2,5-bis-(4-(methoxy)benzyloxy)-3,4-(distyryl)hexanedioic Acid Bis-(methoxymethylamide) (39).** To a stirring solution of diacid **33** (0.045 g, 0.066 mmol) in 1 mL of benzene was added pyridine (32 $\mu$L, 0.40 mmol). After stirring for 15 min, oxalyl chloride (23 $\mu$L, 0.26 mmol) was added dropwise. After stirring for an additional 30 min, the reaction mixture was concentrated in vacuo, $Et_2O$ (10 mL) was added, and the suspension was filtered through a thin pad of Celite with $Et_2O$ rinsing (10 mL). The combined organics were concentrated in vacuo to afford the bis acid chloride, which was used without further purification. IR (thin film) 1778 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.43–7.25 (m, 14H), 6.84 (d, $J$ = 10.0 Hz, 4H), 6.66 (d, $J$ = 15.5 Hz, 2H), 6.34 (dd, $J$ = 15.8, 10.7 Hz, 2H), 4.53 (d, $J$ = 10.1 Hz, 2H), 4.47 (d, $J$ = 10.2 Hz, 2H), 3.85 (s, 6H), 3.65 (d, $J$ = 10.6 Hz, 2H), 2.14–2.00 (m, 4H), 0.98 (t, $J$ = 7.3 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 177.2, 159.0, 136.9, 136.7, 129.7, 128.9, 128.5, 127.7, 126.6, 124.2, 113.5, 90.3, 65.5, 55.2, 47.3, 27.0, 7.2; LRMS ($ESI^-$) $m/z$ (relative intensity) 677.5 (100%, M − H − $Cl^-$).

To a stirring solution of this crude bis acid chloride in 45 mL of benzene was added pyridine (32 $\mu$L, 0.40 mmol) dropwise followed by *N*,*O*-dimethylhydroxylamine (23 $\mu$L, 0.26 mmol). After stirring for 15 h, the reaction mixture was concentrated in vacuo to afford a crude pale yellow oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 20 → 50% EtOAc/hexanes as eluent) gave bis Weinreb amide **39** (0.037 g, 73% from **33**) as a yellow solid. A 42% yield was obtained from **25** on a 2.69 g scale. mp 51–54 °C; $[\alpha]^{20}_D$ = +13 ($c$ 2.67, MeOH); IR (thin film) 1637 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 (d, $J$ = 7.5 Hz, 4H), 7.32–7.19 (m, 10H), 6.74 (d, $J$ = 8.2 Hz, 4H), 6.55–6.50 (m, 4H), 4.50 (d, $J$ = 9.5 Hz, 2H), 4.42–4.37 (m, 2H), 3.79 (s, 6H), 3.63–3.57 (m, 2H), 3.46 (s, 6H), 3.08 (br s, 6H), 2.13–2.07 (m, 4H), 0.99 (t, $J$ = 6.7 Hz, 6H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 172.5, 158.7, 138.0, 132.5, 130.9, 129.5, 128.8, 128.4, 126.8, 126.4, 113.2, 87.3, 64.9, 60.7, 55.2, 47.8, 35.5, 26.4, 8.5; LRMS (ESI) $m/z$ (relative intensity) 765.4 (100%, M + $H^+$). HRMS (ESI) $m/z$ calcd for $[C_{46}H_{56}N_2O_8]^+$, 765.4115, found 765.4119.

**(2*R*,3*S*,4*S*,5*R*)-5,8-Diethyl-5,8-bis-(4-(methoxy)benzyloxy)-6,7-(distyryl)dodeca-1,11-diene-4,9-dione (40).** To a stirring solution of freshly prepared allyllithium[23] (0.48 M in 2:1 THF/$Et_2O$, 14.5 mL, 6.7 mmol) at −78 °C was added dropwise a solution of bis Weinreb amide **39** (1.28 g, 1.67 mmol) in 4 mL of THF. After stirring for 1 h at −78 °C, saturated $NH_4Cl$ (25 mL) was added. The resulting solution was partitioned between $Et_2O$ and $H_2O$ and the aqueous layer was extracted with $Et_2O$ (3 × 25 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by $SiO_2$ flash column chromatography (2 → 8% $Et_2O$/hexanes then 15% EtOAc/hexanes as eluent) gave tetraene **40** (0.83 g, 72%) as a yellow solid. A 77% yield was obtained on a 109 mg scale. A sample of this solid was crystallized from EtOH to give an X-ray quality crystal. mp 116–118 °C; $[\alpha]^{20}_D$ =


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−58 (*c* 2.10, MeCN); IR (thin film) 1713 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (d, *J* = 7.4 Hz, 4H), 7.34 (t, *J* = 7.5 Hz, 4H), 7.28−7.25 (m, 6H), 6.95 (d, *J* = 8.5 Hz, 4H), 6.52 (dd, *J* = 15.8, 9.4 Hz, 2H), 6.43 (d, *J* = 15.8 Hz, 2H), 5.51−5.37 (m, 2H), 4.86 (d, *J* = 10.3 Hz, 2H), 4.67 (d, *J* = 17.2 Hz, 2H), 4.45 (d, *J* = 11.2 Hz, 2H), 4.41 (d, *J* = 11.2 Hz, 2H), 3.88 (s, 6H), 3.47 (dd, *J* = 19.0, 6.0 Hz, 2H), 3.39 (d, *J* = 9.3 Hz, 2H), 3.32 (dd, *J* = 19.0, 7.6 Hz, 2H), 2.00−1.91 (m, 2H), 1.80−1.71 (m, 2H), 0.76 (t, *J* = 7.3 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 212.9, 158.8, 136.9, 133.4, 130.9, 130.2, 128.4, 127.6, 127.4, 127.3, 126.5, 117.8, 113.7, 88.5, 62.5, 55.2, 48.6, 47.1, 28.4, 7.6; LRMS (ESI) *m*/*z* (relative intensity) 744.5 (100%, M + $NH_4^+$). HRMS (ESI) *m*/*z* calcd for $[C_{48}H_{58}NO_6]^+$, 744.4264, found 744.4262.

**(*1S*,1′*S*,2*R*,2′*R*)-2,2′-Diethyl-2,2′-bis-(4-(methoxy)-benzyloxy)-bicyclohexyl-5,5′-diene-3,3′-dione (41).** To a freeze−pump−thawed solution of tetraene **40** (0.147 g, 0.202 mmol) in 10 mL of toluene in a sealable tube was added Grubbs II catalyst (0.069 g, 0.081 mmol) and the tube was sealed. After freeze−pump−thawing the solution again, the reaction mixture was heated at 100 °C. After heating at this temperature for 4 h, the crude solution was cooled to room temperature and concentrated in vacuo to give a green oil. Purification of this oil by $SiO_2$ flash column chromatography (10 → 30% EtOAc/hexanes as eluent) gave bis cyclohexenone **41** (0.067 g, 64%) as a green solid. mp 135−137 °C; $[\alpha]^{20}_D$ = −100 (*c* 1.00, MeCN); IR (thin film) 1719 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.39 (d, *J* = 8.6 Hz, 4H), 6.93 (d, *J* = 8.6 Hz, 4H), 5.76−5.70 (m, 4H), 4.81 (d, *J* = 10.8 Hz, 2H), 4.41 (d, *J* = 10.9 Hz, 2H), 3.85 (s, 6H), 3.41 (d, *J* = 3.6 Hz, 2H), 2.87 (s, 4H), 1.99−1.85 (m, 4H), 0.82 (t, *J* = 7.3 Hz, 6H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 209.8, 158.9,130.9, 128.3, 126.8, 126.3, 113.7, 83.7, 64.3, 55.2, 45.3, 40.7, 24.8, 7.1; (ESI) *m*/*z* (relative intensity) 536.4 (100%, M + $NH_4^+$); HRMS (ESI) *m*/*z* calcd for $[C_{32}H_{42}NO_6]^+$, 536.3012, found 536.3008.

**Pentacyclic Bis Hemiacetal Diene (44).** To a solution of bis cyclohexenone **41** (0.022 g, 0.042 mmol) in 1 mL of $CH_2Cl_2$ at 0 °C was added TFA (32 μL, 0.42 mmol). After stirring for 15 min at 0 °C, the reaction mixture was concentrated in vacuo to give a crude yellow oil. Purification of this oil by $SiO_2$ flash column chromatography (10 → 15% EtOAc/hexanes as eluent) gave pentacyclic bis hemiketal diene **44** (8 mg, 70%) as a yellow solid. mp 167−170 °C; $[\alpha]^{20}_D$ = −64 (*c* 0.44, MeCN);IR (thin film) 3413 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.77 (m, 2H), 5.47 (m, 2H), 3.84 (s, 2H), 2.48−2.31 (m, 6H), 1.83 (m, 2H), 1.46 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 130.5, 123.0, 97.9, 73.4, 41.2, 38.2, 23.8, 6.9; LRMS (ESI) *m*/*z* (relative intensity) 261.1 (100%, M − $OH^-$); HRMS (ESI) *m*/*z* calcd for $[C_{16}H_{21}O_3]^-$, 261.1491, found 261.1474.

**1-Phenylbut-2-enyl 2-(4-Methoxybenzyloxy)butyrate (47).** To a stirring solution of alcohol **45**[24] (2.32 g, 15.6 mmol) and carboxylic acid **24**[11] (3.74 g, 16.6 mmol) in 150 mL of $CH_2Cl_2$ was added DMAP (198 mg, 1.62 mmol) and EDC (3.29 mg, 17.2 mmol). After stirring the mixture for 14 h at room temperature, the organics were washed with $H_2O$ (25 mL), dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a colorless oil. Purification of this oil by deactivated $SiO_2$ (2% $Et_3N$/hex) flash column chromatography (2 → 15% $Et_2O$/hexanes as eluent) gave PMB glycolate **47** (3.36 g, 57%) as a colorless oil (1:1 mix of diastereomers). IR (thin film) 1749 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.46−7.26 (m, 12H), 6.92−6.87 (m, 4H), 6.35 (d, *J* = 6.8 Hz, 2H), 5.88−5.72 (m, 4H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 3.94−3.89 (m, 4H), 3.84 (s, 3H), 3.83 (s, 3H), 1.89−1.80 (m, 4H), 1.77 (d, *J* = 4.7 Hz, 3H), 1.76 (d, *J* = 3.4 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 171.7, 171.68, 159.2 (two signals), 139.4, 139.37, 129.9, 129.63, 129.6, 129.57, 129.52, 129.5, 129.22, 129.2, 128.3, 127.9, 127.8, 126.8, 126.6, 113.9, 113.6, 78.9, 78.8, 76.4, 76.39, 71.65, 71.58, 55.0 (two signals), 26.06, 26.0, 17.6 (×2), 9.6, 9.5; LRMS (ESI) *m*/*z* (relative intensity) 372.3 (100%, M + $NH_4^+$); HRMS (ESI) *m*/*z* calcd for $C_{22}H_{26}NaO_4$, 377.1729, found 377.1718.

**6-Ethyl-6-(4-methoxybenzyloxy)-5-methylcyclohex-3-enone (48).** To a stirring solution of KHMDS (0.5 M in toluene, 56.8 mL, 28.4 mmol) in 40 mL of toluene at −78 °C was added dropwise a solution of PMB glycolate **47** (3.36 g, 9.47 mmol) in 10 mL of toluene. The solution was stirred for 15 min at −78 °C and TIPSOTf (7.6 mL, 28.3 mmol) was added dropwise. The reaction mixture was stirred for 30 min at −78 °C, stirred for 20 min at 0 °C, and then allowed to warm to room temperature. After stirring for 30 min at room temperature, saturated $NH_4Cl$ (50 mL) was added. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give an intermediate TIPS ester as colorless oil that was carried on without any further purification.

To a stirring solution of this crude TIPS ester in 60 mL of THF at 0 °C was added dropwise $Bu_4NF$ (1.0 M in hexanes, 30.3 mL, 30.3 mmol). After 20 min at 0 °C, $H_2O$ (50 mL) was added. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a carboxylic acid product as a white solid that was carried on without further purification.

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

To this crude acid chloride in 50 mL of benzene was added pyridine (2.3 mL, 28 mmol) followed by *N*,*O*-dimethylhydroxylamine (1.2 mL, 13 mmol). After stirring for 14 h at room temperature, the solution was concentrated in vacuo and filtered through Celite with $Et_2O$ to give a crude yellow solid. Purification of this solid by $SiO_2$ flash column chromatography (gradient, 2 → 20% EtOAc/hexanes as eluent) gave the corresponding Weinreb amide (2.42 g, 64% over 4 steps) as a yellow solid.

To a stirring solution of this Weinreb amide (2.42 g, 6.08 mmol) in 40 mL of THF at 0 °C was added dropwise allylmagnesium bromide (1.0 M in $Et_2O$, 18.2 mL, 18.2 mmol). The solution was stirred for 30 min at 0 °C and then for 1 h at room temperature. This reaction mixture then was added to a cold solution of saturated $NH_4Cl$ (50 mL). The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a colorless crude oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 2 → 10% $Et_2O$/hexanes as eluent) gave the allylation product (1.88 g, 84%) as a colorless oil.

To a refluxing solution of this crude allylation product (1.14 g, 3.02 mmol) in 48 mL of $CH_2Cl_2$ was added dropwise a solution of Grubbs II catalyst[22] (256 mg, 0.302 mmol) in 1 mL of $CH_2Cl_2$. After holding at reflux for 2 h, the solution was cooled to room temperature and concentrated in vacuo to give a crude brown oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, hexanes →10% $Et_2O$/hexanes as eluent) gave *β*,*γ*-unsaturated enone **48** (0.640 g, 77%) as a light brown oil. IR (thin film) 1713 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.33 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.75−5.64 (m, 2H), 4.54 (d, *J* = 10.7 Hz, 1H), 4.17 (d, *J* = 10.7 Hz, 1H), 3.83 (s, 3H), 3.14 (m, 1H), 3.02 (m, 1H), 2.85 (m, 1H), 1.95 (m, 1H), 1.77 (m, 1H), 0.97 (d, *J* = 7.3 Hz, 3H), 0.91 (t, *J* = 7.5 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 210.4, 158.9, 131.3, 130.6, 128.6, 121.9, 113.7, 85.4, 65.7, 55.2, 40.2, 39.2, 20.5, 15.2, 6.3; LRMS (ESI) *m*/*z* (relative intensity) 297.5 (60%, M + $Na^+$); HRMS (ESI) *m*/*z* calcd for $[C_{17}H_{26}NO_3]^+$ 292.1913, found 292.1897.

**6-Ethyl-4-(hydroxyphenyl-amino)-6-(4-methoxybenzyloxy)-5-methyl-cyclohex-2-enone (50).** To a stirring solution of freshly prepared LDA (230 μL *i*-$Pr_2NH$ + 612 μL of 2.5 M *n*-BuLi in hexanes; 1.53 mmol) in 10 mL of THF at −78 °C was added dropwise a solution of *β*,*γ*-unsaturated enone **48** (0.400 g, 1.46 mmol) in 3 mL of THF. After 15 min, freshly distilled TMSCl (389 μL, 3.08 mmol) was added. After stirring the mixture for 2 h at −78 °C, saturated $NH_4Cl$ (10 mL) was added. The resulting solution was partitioned between


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EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give TMS dienol ether **49a** as a yellow oil which required no further purification. IR (thin film) 1696 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.31 (d, $J$ = 8.6 Hz, 2H), 6.88 (d, $J$ = 8.5 Hz, 2H), 5.76 (ddd, $J$ = 9.4, 5.9, 1.3 Hz, 1H), 5.53 (dd, $J$ = 9.3, 4.2 Hz, 1H), 5.28 (d, $J$ = 5.8 Hz, 1H), 4.44 (br s, 2H), 3.82 (s, 3H), 2.86 (m, 1H), 2.09 (m, 1H), 1.45 (m, 1H), 1.00 (d, $J$ = 7.4 Hz, 3H), 0.99 (t, $J$ = 7.6 Hz, 3H), 0.29 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.6, 153.3, 132.2, 12.8, 127.3, 120.7, 113.4, 103.2, 81.6, 65.1, 55.2, 47.3, 36.8, 22.5, 19.2, 13.3, 7.4, 0.2; LRMS (ESI) $m/z$ (relative intensity) 405.3 (60%, M + MeCN + $NH_4^+$).

To a stirring solution of the crude TMS dienol ether **49a** (0.506 g, 1.46 mmol) in 13 mL of chloroform was added nitrosobenzene (158 mg, 1.47 mmol, recrystallized from EtOH). After 24 h, the reaction mixture was concentrated in vacuo to give the alkylhydroxylamine bridged product as a crude green oil that was used without further purification. IR (thin film) 1696 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.39 (d, $J$ = 8.5 Hz, 2H), 7.25 (t, $J$ = 7.6 Hz, 2H), 7.09 (d, $J$ = 7.8 Hz, 2H), 6.95 (t, $J$ = 7.2 Hz, 1H), 6.90 (d, $J$ = 8.5 Hz, 2H), 6.30 (d, $J$ = 8.4 Hz, 1H), 6.14 (dd, $J$ = 8.4, 5.3 Hz, 1H), 4.75 (d, $J$ = 11.5 Hz, 1H), 4.67 (d, $J$ = 11.5 Hz, 1H), 4.19 (m, 1H), 3.83 (s, 3H), 2.71 (m, 1H), 1.70 (m, 1H), 1.59 (m, 1H), 1.07 (d, $J$ = 7.5 Hz, 3H), 1.04 (t, $J$ = 7.4 Hz, 3H), 0.29 (s, 9H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.3, 151.3, 135.4, 132.1, 129.1, 128.3, 128.1, 121.4, 116.7, 113.2, 103.4, 81.5, 64.7, 62.6, 54.9, 39.1, 24.2, 16.3, 9.0, 2.0.

To a stirring solution of this crude hydroxylamine bridged species from above (662 mg, 1.46 mmol) in 15 mL of MeOH was added anhydrous KF (102 mg, 1.75 mmol). After stirring the mixture for 1 h at room temperature, $Et_2O$ (15 mL) and $H_2O$ (15 mL) were added and the aqueous layer was extracted with $Et_2O$ (3 × 20 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a crude green solid. Purification of this green solid by $SiO_2$ flash column chromatography (gradient, 20 → 40% $Et_2O$/hexanes as eluent) gave hydroxylamine **50** (0.246 g, 44% from **49a**) as a white solid. A portion of this solid was crystallized from EtOH to obtain X-ray quality crystals. mp 127−129 °C; IR (thin film) 1678 $cm^{-1}$; $^1H$ NMR (360 MHz, THF-$d^8$) $\delta$ 7.45 (d, $J$ = 8.4 Hz, 2H), 7.34−7.23 (m, 4H), 6.96 (t, $J$ = 6.8 Hz, 1H), 6.90 (d, $J$ = 8.5 Hz, 2H), 6.78 (d, $J$ = 10.4 Hz, 1H), 6.02 (dd, $J$ = 10.3, 1.9 Hz, 1H), 4.50 (d, $J$ = 10.0 Hz, 1H), 4.33 (d, $J$ = 10.1 Hz, 1H), 4.26 (br d, $J$ = 10.0 Hz, 1H), 3.80 (s, 3H), 3.26 (m, 1H), 1.98 (m, 1H), 1.68 (m, 1H), 1.35 (d, $J$ = 6.6 Hz, 3H), 0.87 (t, $J$ = 7.3 Hz, 3H); $^{13}C$ NMR (90 MHz, THF-$d^8$) $\delta$ 197.8, 159.2, 152.8, 147.8, 131.5, 130.0, 128.9, 128.5, 121.1, 116.2, 113.1, 84.1, 69.4, 67.3, 64.6, 54.4, 38.7, 25.5, 24.1, 10.4, 6.8; LRMS (ESI) $m/z$ (relative intensity) 382.3 (10%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{23}H_{28}NO_4]^+$, 382.2018, found 382.2015.

***tert*-Butyl-[7-ethyl-7-(4-methoxybenzyloxy)-8-methyl-2,3-dioxa-bicyclo[2.2.2]oct-5-en-1-yloxy]dimethylsilane (51).** To a stirring solution of KHMDS (292 $\mu$L, 0.50 M in toluene, 0.156 mmol) in 1 mL of THF at −78 °C was added dropwise a solution of $\beta,\gamma$-unsaturated enone **48** (0.020 g, 0.073 mmol) in 200 $\mu$L of THF. After 40 min at −78 °C, TBSOTf (34 $\mu$L, 0.15 mmol) was added. After stirring the mixture for 2 h at −78 °C, saturated $NaHCO_3$ (10 mL) was added. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, hexanes → 5% $Et_2O$/hexanes as eluent) gave TBS dienol ether **49b** as a yellow oil (0.027 g, 96%) that was used as crude material in the next transformation.

To a solution of TBS dienol ether **49b** (0.027 g, 0.070 mmol) in $CH_2Cl_2$ at −78 °C was added tetraphenylporphyrin (2 mg, 0.003 mmol). The sample was irradiated with a 275W sun lamp while bubbling $O_2$ through the solution at −78 °C. After 45 min, the reaction mixture was warmed to room temperature and concentrated in vacuo to give a pink oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 2 → 20% $Et_2O$/hexanes as eluent) gave endoperoxide **51** as a pink oil (0.016 g, 54%). IR (thin film) 1249 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.36 (d, $J$ = 8.6 Hz, 2H), 6.89 (d, $J$ = 8.6 Hz, 2H), 6.60 (dd, $J$ = 8.6, 5.5 Hz, 1H), 6.37 (d, $J$ = 8.6 Hz, 1H), 4.76 (d, $J$ = 11.6 Hz, 1H), 4.63 (d, $J$ = 11.5 Hz, 1H), 4.32 (m, 1H), 3.82 (s, 3H), 2.69 (m, 1H), 1.76−1.59 (m, 2H), 1.03 (t, $J$ = 7.4 Hz, 3H), 1.00−0.95 (m, 3H), 0.96 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 158.6, 136.3, 132.3, 131.5, 128.2, 113.4, 104.3, 80.9, 77.5, 65.0, 55.2, 41.0, 25.7, 24.2, 18.0, 14.9, 9.4, −2.3, −3.0; LRMS (ESI) $m/z$ (relative intensity) 421.3 (30%, M + $H^+$); HRMS (ESI) $m/z$ calcd for $[C_{23}H_{36}O_5SiNa]^+$, 443.2230, found 443.2233.

**6-Ethyl-4-hydroxy-6-(4-methoxybenzyloxy)-5-methylcyclohex-2-enone (52).** To a stirring solution of endoperoxide **51** (0.111 g, 0.271 mmol) in 3 mL of MeCN at 0 °C was added 46% HF(aq.) (18 $\mu$L, 0.410 mmol). After stirring the mixture for 1 min, $H_2O$ (5 mL) was added. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a yellow oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 10 → 50% EtOAc/hexanes as eluent) gave a peroxide-containing product (0.085 g, 100%) as a yellow oil. IR (thin film) 3353, 1682 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.42 (br s, 1H), 7.42 (d, $J$ = 8.5 Hz, 2H), 7.08 (dd, $J$ = 10.4, 2.0 Hz, 1H), 6.91 (d, $J$ = 8.6 Hz, 2H), 6.14 (dd, $J$ = 10.4, 2.0 Hz, 1H), 4.54 (m, 1H), 4.43 (d, $J$ = 10.0 Hz, 1H), 4.24 (d, $J$ = 10.0 Hz, 1H), 3.83 (s, 3H), 2.90 (m, 1H), 1.90 (m, 1H), 1.55 (m, 1H), 1.26 (d, $J$ = 6.7 Hz, 3H), 0.88 (t, $J$ = 7.4 Hz, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 199.3, 158.9, 147.4, 130.5, 129.5, 129.2, 113.6, 84.9, 83.9, 65.0, 55.2, 38.7, 24.3, 10.5, 7.1; LRMS (ESI) $m/z$ (relative intensity) 324.4 (5%, M + $NH_4^+$); HRMS (ESI) $m/z$ calcd for $[C_{17}H_{26}NO_5]^+$, 324.1811, found 324.1801.

To a stirring solution of this peroxide (0.024 g, 0.077 mmol) in 1 mL of $CHCl_3$ was added $PPh_3$ (30 mg, 0.12 mmol). After stirring for 5 min at room temperature, the reaction mixture was concentrated in vacuo to give a crude green oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 20 → 40% EtOAc/hexanes as eluent) gave $\gamma$-hydroxyenone **52** (0.020 g, 91%). IR (thin film) 3448, 1678 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.21 (d, $J$ = 8.2 Hz, 2H), 6.87 (d, $J$ = 8.2 Hz, 2H), 6.87 (m, 1H), 6.03 (d, $J$ = 10.1 Hz, 1H), 4.33 (d, $J$ = 10.1 Hz, 1H), 4.05 (d, $J$ = 10.1 Hz, 1H), 4.05 (m, 1H), 3.81 (s, 3H), 3.48 (br s, 1H), 2.60 (m, 1H), 2.13 (m, 1H), 1.52 (m, 1H), 0.98−0.93 (m, 6H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 198.6, 159.3, 147.2, 129.5, 129.4, 126.7, 113.8, 83.9, 70.6, 65.4, 55.2, 41.0, 19.8, 13.0, 5.6; LRMS (ESI) $m/z$ (relative intensity) 313.3 (100%, M + $NH_4^+$); HRMS (ESI) $m/z$ calcd for $[C_{17}H_{26}NO_4]^+$, 308.1862, found 308.1867.

**Preparation of Alcohol 52 Directly from Endoperoxide 51.** To a stirring solution of endoperoxide **51** (0.148 g, 0.351 mmol) in 3 mL of THF at −78 °C was added dropwise $Bu_4NF$ (1.0 M in hexanes, 386 $\mu$L, 0.386 mmol), and the solution was warmed to −45 °C. After stirring the mixture for 30 min at −45 °C, $H_2O$ (5 mL) was added. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give a colorless oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 10 → 60% EtOAc/hexanes as eluent) gave $\gamma$-hydroxyenone **52** (0.037 g, 37%) as a colorless oil. A yield of 91% was obtained on a 24 mg scale.

**1,1′-Bis-(*tert*-butyl(dimethyl)silanyloxy)-6,6′-diethyl-6,6′-bis-(4-(methoxy)benzyloxy)-[5,5′]bi[2,3-dioxabicyclo[2.2.2]-octyl]-7,7′-diene (54).** To a stirring solution of KHMDS (0.50 M in toluene, 848 $\mu$L, 0.424 mmol) in 800 $\mu$L of THF at −78 °C was added dropwise a solution of bis cyclohexenone **41** (0.055 g, 0.11 mmol) in 400 $\mu$L of THF. After stirring for 40 min at −78 °C, TBSOTf (98 $\mu$L, 0.42 mmol) was added. After stirring for 2 h at −78 °C, saturated $NaHCO_3$ solution (10 mL) was added. The resulting solution was partitioned between EtOAc and $H_2O$ and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give bis TBS dienol ether **53** as a crude yellow oil that was used without further purification.

To a solution of this crude bis OTBS dienyl ether **53** in 10 mL of $CH_2Cl_2$ at −78 °C was added tetraphenylporphyrin (2 mg, 0.003


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mmol). The sample was irradiated with a 275W sun lamp while bubbling $O_2$ through the solution. After irradiation for 45 min at −78 °C, the reaction mixture was concentrated in vacuo to give a pink oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 2 → 20% $Et_2O$/hexanes as eluent) gave bis endoperoxide **54** (0.057 g, 67% over 2 steps) as a pink solid. A sample of this solid was crystallized from 1:1 hexanes/THF to obtain colorless X-ray quality crystals. mp 120−122 °C; $[\alpha]^{20}_D$ = +94 (*c* 1.80, MeCN); IR (thin film) 1243 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.18 (d, *J* = 8.4 Hz, 4H), 6.88 (d, *J* = 8.5 Hz, 4H), 6.58 (dd, *J* = 8.6, 5.6 Hz, 2H), 6.38 (d, *J* = 8.3 Hz, 2H), 4.81 (d, *J* = 6.1 Hz, 2H), 4.64 (d, *J* = 11.2 Hz, 2H), 4.53 (d, *J* = 11.3 Hz, 2H), 3.81 (s, 6H), 3.04 (br s, 2H), 2.19−2.16 (m, 4H), 1.18 (t, *J* = 7.3 Hz, 6H), 1.01 (s, 18H), 0.24 (s, 12H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 158.6, 135.1, 131.8, 131.2, 127.8, 113.8, 103.5, 82.4, 74.2, 65.8, 55.2, 43.3, 25.7, 21.7, 18.0, 8.5, −2.4, −3.3; LRMS (ESI) *m*/*z* (relative intensity) 811.6 (100%, M + $H^+$). HRMS (ESI) *m*/*z* calcd for $[C_{44}H_{67}O_{10}Si_2]^+$, 811.4273, found 811.4238.

**2,2′-Diethyl-6,6′-dihydroxy-2,2′-bis-(4-(methoxy)-benzyloxy)-bicyclohexyl-4,4′-diene-3,3′-dione (53).** To a stirring solution of bis endoperoxide **54** (0.036 g, 0.045 mmol) in 1 mL of MeCN at 0 °C was added dropwise fluorosilicic acid (117 μL, 20−25 wt % in $H_2O$, ∼ 0.2 mmol). After stirring for 40 min at 0 °C, $H_2O$ (1 mL) was added. The resulting solution was partitioned between EtOAc (10 mL) and $H_2O$ (10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered, and concentrated in vacuo to give crude bis peroxide **55** as a yellow oil that was used without further purification.

To a stirring solution of the crude bis peroxide **55** in 1 mL of $CH_2Cl_2$ at 0 °C was added $PPh_3$ (0.035 g, 0.13 mmol). After stirring for 30 min at 0 °C, the crude mixture was concentrated in vacuo to give a crude yellow oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 15 → 30% EtOAc/hexanes as eluent) gave lomaiviticinone core **7** (0.014 g, 57% over 2 steps) as a yellow oil contaminated by a small amount of an inseparable unidentified compound. $[\alpha]^{20}_D$ = +131 (*c* 6.2, MeCN); IR (thin film) 3425, 1672 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$, major isomer) $\delta$ 7.08 (d, *J* = 8.5 Hz, 4H), 6.97 (d, *J* = 10.3 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 4H), 6.01 (d, *J* = 10.2 Hz, 2H), 5.53 (s, 2H), 4.76 (d, *J* = 8.0 Hz, 2H), 4.41 (d, *J* = 10.3 Hz, 2H), 4.12 (d, *J* = 10.2 Hz, 2H), 3.77 (s, 6H), 2.71 (d, *J* = 8.4 Hz, 2H), 2.31 (m, 2H), 1.89 (m, 2H), 1.63 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 6H); $^{13}C$ NMR (90 MHz, $CDCl_3$, major isomer) $\delta$ 195.3, 159.6, 153.9, 129.8, 127.7, 124.6, 114.0, 83.8, 66.7, 64.8, 55.2, 49.6, 21.4, 8.7; LRMS (ESI) *m*/*z* (relative intensity) 573.2 (80%, M + $Na^+$). HRMS (ESI) *m*/*z* calcd for $[C_{32}H_{38}O_8Na]^+$, 573.2464, found 573.2449.

**6,6′-Diethyl-6,6′-bis-(4-(methoxy)benzyloxy)-bicyclohexyl-3,3′-diene-2,5,2′,5′-tetraone (56).** To a solution of crude bis peroxide **55** (0.0050 g, 0.0085 mmol) in 500 μL of acetic anhydride was added pyridine (2 μL, 0.03 mmol). After 14 h of stirring at room temperature, the reaction mixture was concentrated in vacuo to give a crude yellow oil. Purification of this oil by $SiO_2$ flash column chromatography (gradient, 10 → 30% EtOAc/hexanes as eluent) gave bis enedione **56** (0.014 g, 49% from **55**) as a light yellow oil. IR (thin film) 1691 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.19 (d, *J* = 8.6 Hz, 4H), 6.87 (d, *J* = 8.5 Hz, 4H), 6.27 (br s, 4H), 4.88 (m, 2H), 4.43 (d, *J* = 10.5 Hz, 2H), 3.84 (s, 6H), 3.79 (s, 2H), 2.08 (m, 2H), 1.94 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 6H); $^{13}C$ NMR (150 MHz, $CDCl_3$) $\delta$ 197.5(2 carbons), 159.1, 139.2 (2 carbons), 129.9, 129.6, 113.5, 93.8, 82.2, 68.0,, 55.2,, 25.6, 7.7; LRMS (ESI) *m*/*z* (relative intensity) 564.2 (100%, M + $NH_4^+$). HRMS (ESI) *m*/*z* calcd for $[C_{32}H_{38}NO_8]^+$, 564.2597, found 564.2595.

**2-Iodobenzoic Acid 5-Ethyl-5-(4-methoxybenzyloxy)-6-methyl-4-oxocyclohex-2-enyl Ester (57).** To a stirring solution of freshly prepared 2-iodobenzoyl chloride[25] (0.090 g, 0.34 mmol) in 800 μL of pyridine at 0 °C was added a solution of alcohol **52** (0.020 g, 0.068 mmol) in 200 μL of pyridine. After stirring for 1.5 h at 0 °C, the reaction mixture was allowed to warm to room temperature. After stirring for an additional 14 h at room temperature, the crude mixture was concentrated in vacuo to give a crude yellow oil. Purification of this oil by $SiO_2$ flash column chromatography (10% EtOAc/hexanes as eluent) gave ester **57** as a white solid (0.027 g, 76%). mp. 132−133 °C; IR (thin film) 1731, 1684 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.05 (d, *J* = 7.9 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.42 (m, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.22 (td, *J* = 7.6, 1.6 Hz, 1H), 6.90 (d, *J* = 8.7, 2H), 6.89 (m, 1H), 6.15 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.80 (dt, *J* = 9.3, 2.0 Hz, 1H), 4.45 (d, *J* = 10.0 Hz, 1H), 4.24 (d, *J* = 10.0 Hz, 1H), 3.82 (s, 3H), 2.96 (m, 1H), 1.98 (m, 1H), 1.71 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 198.3, 165.9, 159.0, 145.0, 141.5, 134.2, 133.0, 130.9, 130.5, 129.9, 129.2, 128.0, 113.6, 94.2, 83.8, 75.0, 65.1, 55.2, 41.1, 24.0, 10.9, 7.0; LRMS (ESI) *m*/*z* (relative intensity) 538.1 (10%, M + $NH_4^+$); HRMS (ESI) *m*/*z* calcd for $[C_{24}H_{29}NO_5I]^+$, 538.1091, found 538.1093.

**3-Ethyl-3-(4-methoxybenzyloxy)-4-methyl-3,4-dihydro-1H-benzo[c]chromene-2,6-dione (58).** To a solution of aryl iodide **57** (0.020 g, 0.038 mmol) in 1 mL of DMF in a sealable tube was added $Pd(OAc)_2$ (1 mg, 0.004 mmol), $Bu_4NBr$ (5 mg, 0.02 mmol), $Et_3N$ (54 μL, 0.38 mmol) and 8 μL of MeOH. The tube was sealed and the reaction mixture was warmed to 120 °C. After stirring for 14 h at 120 °C, the reaction mixture was cooled to room temperature, filtered through Celite and concentrated in vacuo to give a crude yellow oil. Purification of this oil by $SiO_2$ flash column chromatography (10% EtOAc/hexanes as eluent) gave cyclization product **58** as a yellow oil (8 mg, 56%). IR (thin film) 1721, 1719 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.37 (d, *J* = 7.6 Hz, 1H), 7.79 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.19 (d, *J* = 11.2 Hz, 1H), 3.77 (s, 3H), 3.57 (d, *J* = 19.2 Hz, 1H), 3.35 (d, *J* = 19.4 Hz, 1H), 3.31 (q, *J* = 7.5 Hz, 1H), 2.17 (m, 1H), 1.80 (m, 1H), 1.18 (d, *J* = 7.3 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H) ; $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 207.4, 162.5, 159.2, 153.4, 136.6, 135.0, 130.2, 129.6, 128.5, 127.0, 121.4, 120.3, 113.8, 105.1, 84.6, 66.1, 55.3, 42.3, 36.1, 18.8, 14.9, 5.9; LRMS (ESI) *m*/*z* (relative intensity) 410.2 (100%, M + $NH_4^+$); HRMS (ESI) *m*/*z* calcd for $[C_{24}H_{28}NO_5]^+$, 410.1967, found 410.1980.

## ■ ASSOCIATED CONTENT

### Supporting Information

General experimental, details from the X-ray crystallographic determination of **29** and **50** including CIF files, and copies of $^1H$ and $^{13}C$ NMR spectra for **20**, **22**, **29**, **34**, **35**, **36**, **37**, **38**, **47**, **48**, **49a**, **50**, **51**, **52**, **57**, and **58**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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