Short Enantioselective Total Syntheses of Cheloviolenes A and B and Dendrillolide C via Convergent Fragment Coupling Using a Tertiary Carbon Radical

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ABSTRACT: The development of a convergent fragment coupling strategy for the enantioselective total syntheses of a group of rearranged spongian diterpenoids that harbor the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one unit is described. The key bond disconnection relies on a late-stage fragment coupling between a tertiary carbon radical and an electron-deficient alkene to unite two ring systems and form two new stereocenters, one of which is quaternary, in a stereoselective and efficient manner. This strategy is applied towards scalable 14–15 step syntheses of three rearranged spongian diterpenoids, cheloviolenes A and B and dendrillolide C.

INTRODUCTION

Synthetic strategies that rely on independent syntheses of fragments, followed by their late-stage union are key to efficient preparation of complex molecules. The major drawback of this convergent approach is the small pool of privileged reactions that are reliable, chemoselective, and high-yielding. Some of the most widely used methods having these properties are Diels-Alder reactions, transition metal-catalyzed cross couplings, Nozaki–Hiayama–Kishi couplings, and olefin metathesis.[1] Bimolecular late-stage fragment couplings that form two new stereocenters are especially challenging, particularly in cases when one of the newly formed centers is quaternary.[2] Formation of such sterically congested sp^3–sp^3 σ bonds by intermolecular addition of nucleophilic tertiary radicals to electron deficient olefins is attractive for several reasons: the early transition state with a long forming bond (~2.5 Å) reduces the enthalpic penalty of bringing two bulky fragments together;[3] the high rates of addition[4] and stereoselection[4a,5] realized in additions of tertiary radicals to Michael acceptors often leads to efficient fragment-couplings with reliable stereochemical outcomes. Despite the aforementioned appealing features of the Giese reaction of tertiary carbon radicals, which were known since the 1980s,[4a,6] bimolecular radical reactions have not been used to unite complex fragments because of the large excesses (commonly 3–10-fold) of one of the coupling components often required. The recent advent of visible-light photoredox catalysis to generate carbon radicals under mild conditions,[7] a method that is compatible with most polar functional groups, led to a resurgence of radical-based approaches for convergent construction of complex molecules.[8] An overarching goal of our research has been to capitalize on the appealing features of the Giese reaction of tertiary carbon radicals to perform a late-stage union of two ring systems in 1:1 stoichiometry. One example of this approach leading to short enantioselective total syntheses of a family of rearranged spongian diterpenoids is the subject of this report.

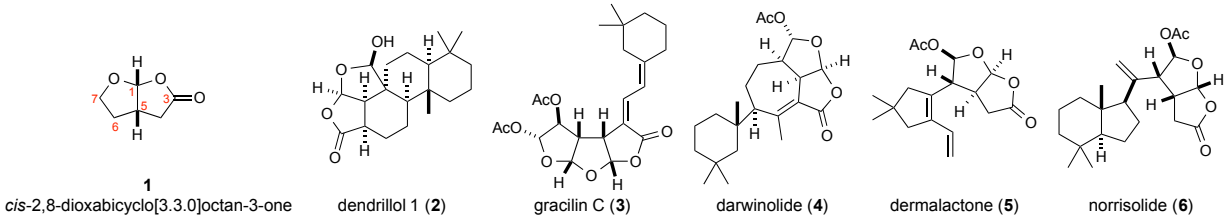
BACKGROUND

More than 100 natural products harbor a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one (**1**) fragment (Figure 1).[9] The marine diterpenoids dendrillol 1 (**2**),[10] gracilin C (**3**),[11] and darwinolide (**4**)[12] exemplify members of this group in which the dioxabicyclooctanone unit is fused to a larger polycyclic ring system. In others, such as the fungal sesquiterpenoid **5**,[13] the dioxabicyclic unit is isolated and joined by a single bond to a second cyclic or polycyclic fragment. Among these is a subset of rearranged spongian diterpenoids of marine origin, illustrated by **6**–**11**, having the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragment joined at C-6 to a fourteen-carbon bicyclic hydrocarbon fragment.[14] The first member of this diterpenoid group to be reported was norrisolide (**6**), whose structure and relative configuration were established by single-crystal X-ray diffraction analysis.[15] In the more common members of this group depicted in Figure 1B, the dioxabicyclo[3.3.0]octan-3-one fragment is joined by a single bond to a quaternary carbon of the hydrocarbon unit. The hydrocarbon fragment of these diterpenoids can reside on either the convex or concave face of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragment, as exemplified respectively by cheloviolene A (**7**)[16,17] and macfarlandin C (**9**).[18] A freely rotating single bond having three staggered conformers of roughly similar energies characterizes this group of rearranged spongian diterpenoids. As a result of this structural feature, relating the configurations of the two chiral bicyclic fragments is notably challenging in the absence of X-ray structures. Only the relative configurations of macfarlandin C (**9**) and cheloviolene A (**7**) are known with certainty by virtue of single-crystal X-ray analyses.[16,18] The relative configurations of the other diterpenoids in this family are proposed to be as depicted in Figure 1B as a result of their presumed biosynthe-

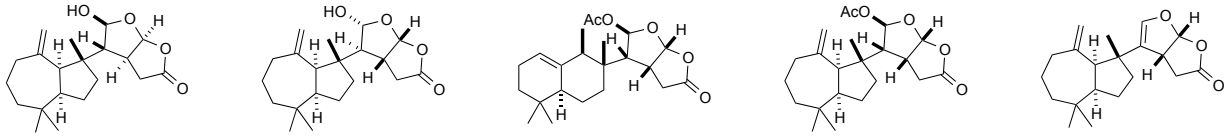
sis from precursors having a spongian skeleton (see Figure 1C).[11,19] Absolute configurations for these natural products have not been established experimentally and are also proposed on the basis of this biosynthetic hypothesis.[20]

Figure 1

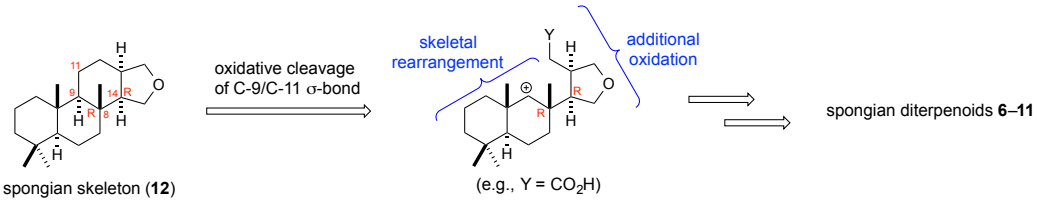
A. The *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one ring system and representative structurally diverse natural products harboring this structural fragment.



B. Rearranged spongian diterpenoids having a *cis*-dioxabicyclo[3.3.0]octan-3-one fragment attached to a quaternary carbon of a hydrocarbon fragment.

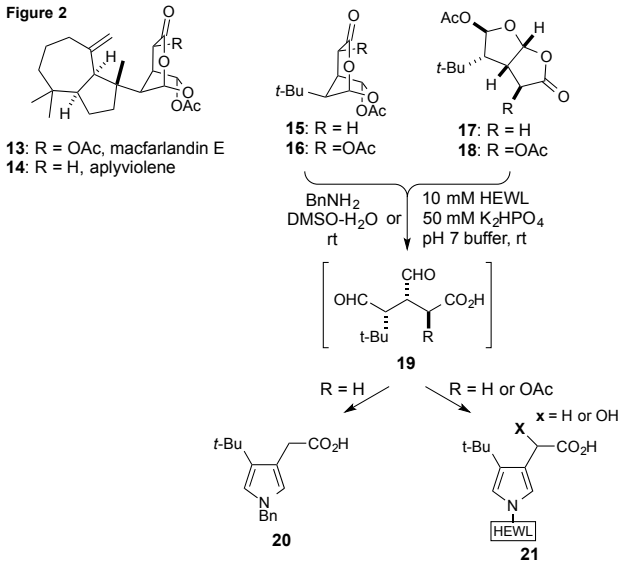


C. Proposed biogenesis of rearranged spongian diterpenoids such as **6**–**11** from a precursor having the spongian diterpenoid skeleton.



The biological activity of rearranged spongian diterpenoids of marine origin has been little explored.[17,18,21] Our recent interest in the group of natural products exemplified in Figure 1B was stimulated by Sütterlin's observations from a screen of small molecule marine natural products that macfarlandin E (**13**, Figure 2), a rearranged spongian diterpenoid harboring a 2,7-dioxabicyclo[3.2.1]octan-3-one fragment, exhibits unique Golgi-altering activity.[22] Macfarlandin E (**13**) induces irreversible fragmentation of the Golgi apparatus with the fragments remaining in the pericentriolar region of the cell. This phenotype contrasts with the effects of other natural products such as brefeldin A,[23] ilimaquinone,[24] and norissolide (**6**),[25] which cause Golgi fragmentation with the resulting fragments being delocalized throughout the cytosol. In our initial studies, we prepared racemic *tert*-butyl analogues **15**–**18** of the rearranged spongian diterpenoids macfarlandin E (**13**), aplyviolene (**14**) and dendrillolide A (**10**) and explored their chemical reactivity and effects on the Golgi apparatus (Figure 2).[22,26] Both the bridged and fused dioxabicyclooctanone ring systems were found to react with primary amines to form pyrrole products (e.g., **20**), presumably via the intermediacy of 1,4-dialdehyde **19** generated upon cleavage of the anomeric acetoxy group. Under physiologically relevant conditions, *tert*-butyl analogues **15**–**18** reacted with lysine chains of hen egg white lysozyme (HEWL) to form pyrrole conjugates **21**, a reaction that potentially could be the origin of the effects of these agents on the Golgi. The presence of an acetoxy substituent adjacent to the lactone carbonyl group in analogues **16** and **18** increased the extent of the lysine to pyrrole conversion and was important for induction of the macfarlandin E Golgi phenotype.[26] To further elucidate the mechanism by which dioxabiclyclooctanones **15**–**18** trigger Golgi fragmentation, a more efficient preparation of these molecules was necessary as our initial route required many steps.[26]

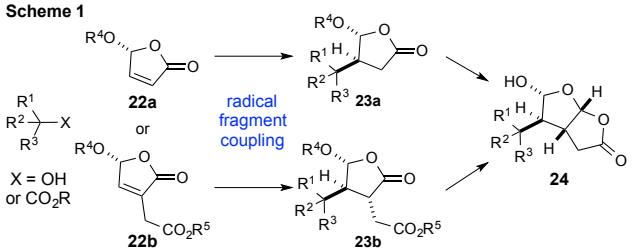
Figure 2



As analogues having the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one ring system were expected to be easier to access by chemical synthesis than their 2,7-dioxabicyclo[3.2.1]octan-3-one counterparts, our recent studies in this area focused on developing a short and versatile synthesis of 6-substituted *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones. Our plan was to employ fragment coupling reactions of tertiary carbon radicals generated from alcohol or carboxylic acid precursors by visible-light

photoredox catalysis[27] to unite tertiary carbon fragments with an unsubstituted 5-alkoxybutenolide **22a** or a butenolide such as **22b** containing the additional two carbons of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one product **24** (Scheme 1). In the former instance, alkylation of the coupled product **23a** with a haloacetate electrophile would be employed to append the additional two carbons. In either case, coupling of a tertiary radical with butenolides **22a** and **22b** was expected to proceed with high stereoselectivity from the face opposite to the 5-alkoxy substituent.[28] The task of relating the configurations of the hydrocarbon and dioxabicyclooctanone fragments in total syntheses of the rearranged spongian diterpenoids depicted in Figure 1B would be addressed by uniting enantiopure butenolide and tertiary hydrocarbon fragments to form the demanding bond joining the two attached ring systems.[29,30] The sequence delineated in Scheme 1 could potentially access a wide variety of dioxabicyclooctanones **24** in 3–4 steps, representing a significant improvement on our earlier synthesis of **17** which required 14 steps.[26] The successful development of the synthetic strategy outlined in Scheme 1 and its use to complete short enantioselective total syntheses of cheloviolenes A (**7**) and B (**8**), and dendrillolide C (**11**) are the subject of this report.[31,32]

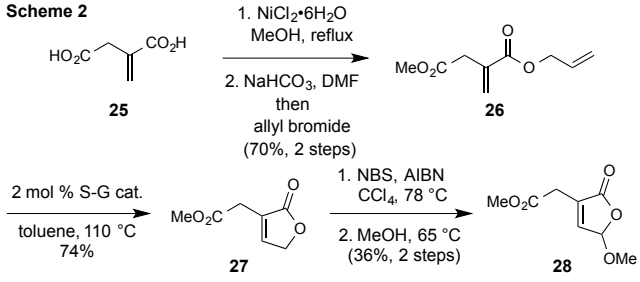
Scheme 1



RESULTS AND DISCUSSION

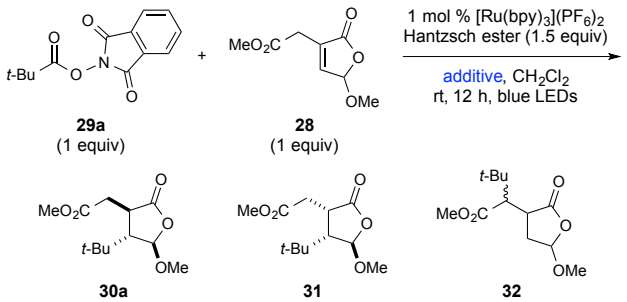
Initial Exploratory Investigations. We examined the proposed sequence initially with 5-methoxybutenolide **28** containing all the carbon atoms of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one ring system (Scheme 2). A ring closing metathesis route was developed for preparing racemic **28**.[33] The sequence starts with itaconic acid (**25**), which after converting selectively to the monomethyl ester by a known procedure,[34] was allylated to yield diester **26**. After examining several metathesis catalysts, the Stewart–Grubbs catalyst was found to be uniquely proficient at promoting the desired transformation to form butenolide **27**.[35] Optimization studies showed that reaction concentrations as high as 0.03 M could be employed before side products resulting from bimolecular metathesis were observed. The 5-methoxy substituent was introduced by initial bromination of **27** with NBS, followed by methanolysis[36] to deliver butenolide **28** in five steps from commercially available itaconic acid (**25**).

Scheme 2



The fragment coupling was explored initially with the *N*-hydroxyphthalimide (NHP) ester of pivalic acid **29a** as the precursor of *tert*-butyl radical (Scheme 3). Using the modification of Okada's conditions[37] developed during our first studies in this area,[30] the $Ru(bpy)_3$-catalyzed reaction of equimolar amounts of activated ester **29a** and butenolide **28** in the presence of low-intensity blue LEDs, 1.5 equiv of a Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate), and 1 equiv of *i*-Pr_2NEt proceeded to give the expected stereoisomeric products **30a** and **31** in a 10:1 ratio favoring the formation of the desired all-*trans* adduct **30a** (isolated in 72% yield).[4a,38] The relative configuration of these stereoisomers was assigned initially on the basis of vicinal coupling constants and ^1H NOE data.[39,40] In addition to products **30a** and **31**, lactone **32**, which would arise from base-promoted isomerization of the double bond prior to radical coupling, was formed in ~5% yield. As would be expected, increasing the amount of *i*-Pr_2NEt enhanced the formation of byproduct **32**, whereas replacing *i*-Pr_2NEt with *i*-$Pr_2NEt•HBF_4$ led to **32** being produced in trace amounts only. To our initial surprise, stereoselection was reduced significantly (to 2:1) in coupling reactions conducted in the presence of *i*-$Pr_2NEt•HBF_4$. Although not understood at the time these experiments were carried out, our recent investigations suggest that in the presence of the basic amine the α-acyloxy radical produced upon conjugate addition is terminated by single-electron transfer (SET) followed by protonation of the lactone enolate, whereas hydrogen-atom transfer (HAT) predominates in presence of *i*-$Pr_2NEt•HBF_4$.[41] It would not be surprising that the former termination process is more stereoselective.[42] Control experiments established that product ratios did not change with time and that adducts **30a** and **31** did not equilibrate at room temperature in the presence of excess *i*-Pr_2NEt.[43] Many reaction variables are reported to affect stereoselection in HAT.[44] We examined a number of these in the hope of enhancing the formation of the minor adduct **31**; however, no conditions were identified that led to this product in useful yield.

Scheme 3



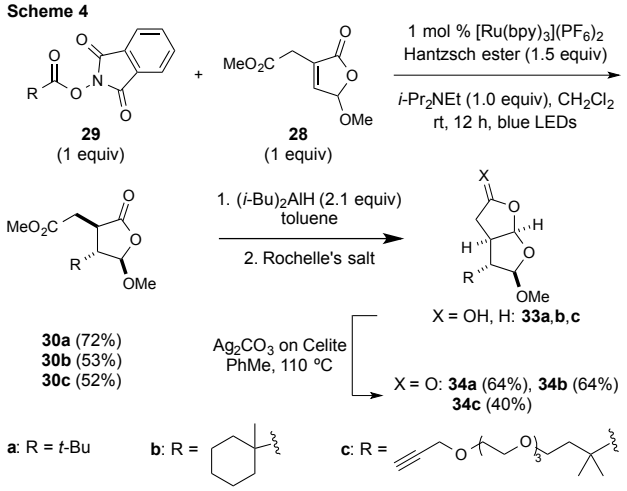
additive (equiv)	ratio **30a**:**31**:**32**[a]	yield of **30a**[b]
i-Pr_2NEt (1.0)	10:1:1	72%
i-Pr_2NEt (2.2)	10:1:2	ND
i-$Pr_2NEt•HBF_4$ (1.0)	2:1:ND	40%

[a]Determined by ^1H NMR integration of the crude reaction mixture. [b]Isolated yield.

The salient results of our efforts to explore the scope of the fragment coupling step and to elaborate the conjugate-addition products to *cis*-2,8-dioxabicyclo[3.3.0]octan-3-ones are summarized in Scheme 4. The NHP esters **29b** and **29c**, the latter harboring a side chain chosen for use in future studies to pursue Golgi molecular targets, underwent stereoselec-

tive (dr = 5–10:1) reductive photoredox coupling with butenolide **28** in the presence of 1 equiv of *i*-Pr_2NEt to yield the all-*trans* trisubstituted products **30b** and **30c** in respectively 53% and 52% yield after purification on silica gel. In initial scouting studies, butyrolactone **30a** was allowed to react with 1 equiv of $(i\text{-Bu})_2AlH$ (DIBALH) at –78 ºC in the hope that the lactone carbonyl could be selectively reduced to give, after intramolecular lactonization, *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one **34a**. However, this reaction did not afford **34a**, but gave rise to a 1:1 mixture of the starting lactone ester **30a** and dioxabicyclic lactol **33a**, suggesting that intramolecular lactonization of the diisobutylaluminum lactol intermediate was faster than reduction of the starting butyrolactone. After screening several reductants and reaction conditions with only modest success, we turned to accomplishing the desired conversion in two steps. A quick survey showed that several oxidants, including Br_2, PCC, acetone (via Oppenhauer oxidation), and Ag_2CO_3 supported on Celite could transform **33a** to dioxabicyclooctanone **34a**, the latter leading to the highest yield of the desired product. The final sequence involved reduction of the coupled products **30** with 2.1 equiv of $(i\text{-Bu})_2AlH$ at –78 ºC and isolation of the crude mixture of lactol epimers **33a**–**c** after workup with an aqueous solution of Rochelle's salt. This crude mixture of lactol intermediates was then directly oxidized with Ag_2CO_3/Celite in refluxing toluene to give *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one **34a**–**c** in 40–64% yield.

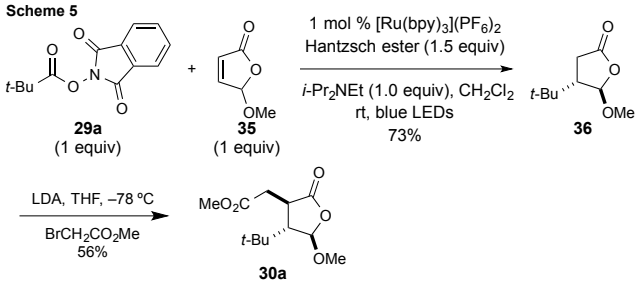
Scheme 4



Although the convergent construction of *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one was appealing, the yield of the all-*trans* product from the addition of tertiary radicals to butenolide **28** was compromised by the formation of the two additional isomeric products **31** and **32** depicted in Scheme 3. As a result, we examined the alternate sequence in which an unsubstituted 5-alkoxybutenolide would be the radical acceptor, an approach that could be advantageous because of the commercial availability of several butenolides of this type in high enantiomeric purity.[45] As summarized in Scheme 5, reductive photoredox-catalyzed coupling of the *tert*-NHP ester **29a** with racemic 5-methoxybutenolide (**35**) gave exclusively the *trans* product **36** in 73% yield. The reaction proceeded in identical yield, also with complete stereoselectivity, when *i*-$Pr_2NEt{\bullet}HBF_4$ was substituted for *i*-Pr_2NEt. Alkylation of the lithium enolate of **36** with methyl bromoacetate occurred stereoselectively to give a single product **30a** in 56% yield.

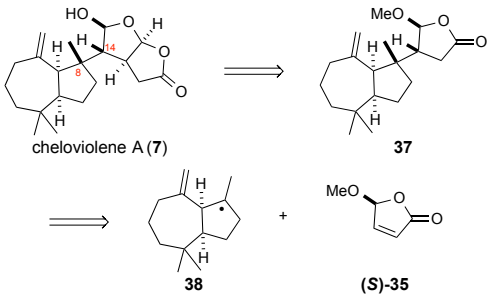
Although the transformations summarized in Schemes 3–5 likely could be further optimized, we chose to move forward to explore the application of this chemistry for the synthesis of rearranged-spongian diterpenoids that harbor a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragment.

Scheme 5



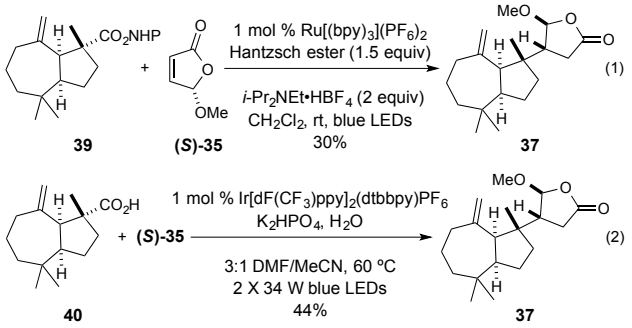
First-Generation Total Synthesis of (+)-Cheloviolene A. The plan for synthesis of (+)-cheloviolene A (**7**) using the approach developed in our exploratory studies is outlined in retrosynthetic format in Scheme 6. The decisive step would be the Giese coupling of *cis*-perhydroazulene radical **38** with butenolide **(*S*)-35** to form tricyclic adduct **37**. The configuration of the C-8 and C-14 stereocenters of the attached chiral bicyclic rings of (+)-cheloviolene A would derive from the expected high preference for this union to take place from the convex face of the *cis*-perhydroazulene radical[30] and the face opposite the methoxy substituent of butenolide **(*S*)-35** to form coupled product **37**.

Scheme 6



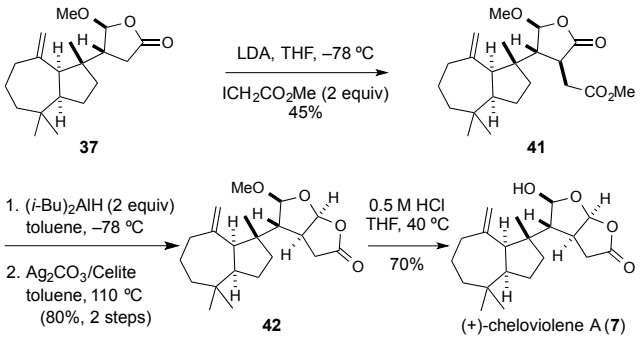
The pivotal radical coupling was examined initially using the enantiopure *cis*-perhydroazulene NHP ester **39**, which we had prepared earlier in 14 steps from (+)-fenchone.[30] Exposure of the activated ester **39** and butenolide **35** to Ni-catalyzed Giese reaction conditions did not lead to the formation of the desired product **37**.[46,47] In contrast, when equimolar amounts of coupling partners **39** and **35** were subjected to photoredox reaction conditions the desired lactone **37** was obtained as a single stereoisomer (eq 1). However, the efficiency of the reaction was poor, resulting in a modest 30% yield of coupled product **37**. The major byproducts were derived from premature reduction of the tertiary radical generated upon reductive cleavage of *N*-acyloxyphthalimide **39**. We hypothesized that the presence of Hantzsch ester, a known hydrogen atom donor,[48] was largely responsible for the undesired reduction of the intermediate tertiary radical. To circumvent premature reduction of the tertiary radical, we examined the coupling of *cis*-perhydroazulene carboxylic acid **40** with 1 equiv of **(*S*)-35** using the Ir(III)-catalyzed photoredox conditions developed by MacMillan[49] in which no external reductants or hydrogen atom sources are required. In this case, the desired product **37** was isolated in 44% yield. Once again premature reduction of the tertiary radical was observed,[50] suggesting that a more

activated acceptor would be required to efficiently trap sterically encumbered *cis*-perhydroazulene radical **38**.



Despite modest yields of the key coupling step, we turned our attention to elaboration of the lactone fragment of addition product **37** to a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one to conclude a first-generation total synthesis of (+)-cheloviolene A (**7**) (Scheme 7). Deprotonation of lactone **37** with LDA at –78 ºC, followed by addition of methyl iodoacetate furnished methyl ester **41**, as a single stereoisomer, in 45% yield. Next, reduction of **41** with excess DIBALH at –78 ºC, followed by direct oxidation of the resulting epimeric mixture of dioxabicyclic lactols under Fétizon oxidation conditions provided tetracyclic intermediate **42** in 80% yield. Finally, hydrolysis of **42** with dilute aqueous HCl at 40 ºC furnished (+)-cheloviolene A (**7**), mp: 157–158 ºC, in 70% yield. Synthetic **7** exhibits a higher optical rotation from the one reported in literature, synthetic: $[\alpha]_D^{22}$ +49 (*c* 0.11, $CHCl_3$), literature: $[\alpha]_D$ +4.5 (*c* 0.11, $CHCl_3$).[16] However, the spectroscopic data for synthetic **7** compared well with those reported for the natural product isolated from the New Zealand sponge *Chelonaplysilla violacea*, leaving little doubt as to their identity.[17] In addition, the structure of synthetic (+)-cheloviolene A was confirmed by single-crystal X-ray analysis.[40]

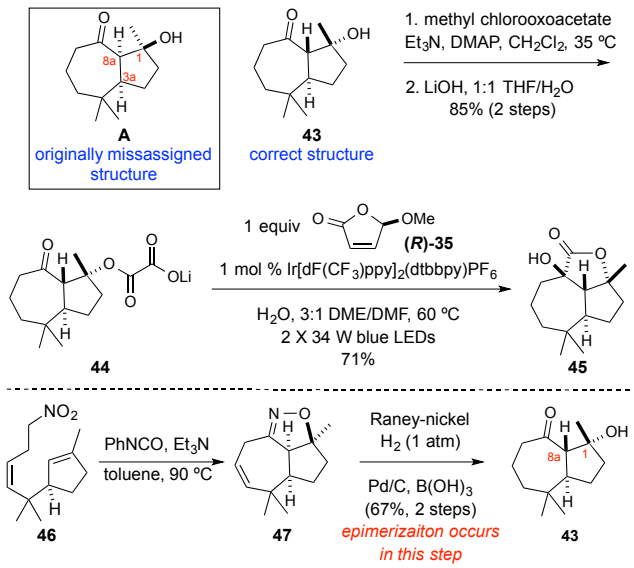
Scheme 7



Development of a More Concise Second-Generation Total Synthesis Strategy. Completion of the synthesis of (+)-cheloviolene A (**7**) validated our strategy and identified several problems that needed to be addressed to secure a concise approach to the family of spongian diterpenoids containing a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one fragment. First, the efficiency of the radical fragment-coupling step had to be improved, which would likely necessitate use of a more activated butenolide radical acceptor. Second, a shorter synthesis of a precursor of the *cis*-perhydroazulene tertiary radical **38** would be needed, as our earlier preparation of carboxylic acid **40** required 13 steps.[30] The recent development of convenient methods to generate tertiary radicals from tertiary alcohols[51,52] directed our attention to the use of a tertiary *cis*-perhydroazulene alcohol as the radical precursor.

Efficient Synthesis of *cis*-Perhydroazulenol 54. A *cis*-perhydroazulene tertiary alcohol, which at the time was assigned structure **A** (Scheme 8), was an intermediate in our earlier synthesis of *cis*-perhydroazulene carboxylic acid **40**.[30] As this alcohol was accessed on gram-scale in only eight steps from (+)-fenchone, we initially examined whether it, or potentially an exomethylene analogue, could be utilized in the crucial radical coupling event. To test the feasibility of this approach, alcohol **43** was condensed with methyl chlorooxoacetate and the resulting diester selectively saponified with 0.95 equiv of LiOH to provide *cis*-perhydroazulene lithium oxalate salt **44** in 85% yield. Upon attempted coupling of oxalate salt **44** with (*R*)-butenolide **(*R*)-35** using the Ir(III)-catalyzed photoredox conditions developed earlier,[51,52] no coupling product was observed, rather a tricyclic lactone **45**, whose structure was unambiguously established via single-crystal X-ray analysis of the 4-nitrobenzoate derivative, was isolated in 71% yield.[40] To our surprise, the perhydroazulene fragment of **45** is *trans*-fused and the configuration at C-1 is opposite to that expected from a precursor of structure **A**. Single-crystal X-ray analysis of the phenylhydrazone derivative of **43** confirmed that tertiary alcohol **43** has the stereostructure depicted in Scheme 8, with the C-1 and C-8a stereocenters opposite to those found in the originally misassigned structure **A**.[40] To the best of our knowledge, the addition of an alkoxyacyl radical to a ketone carbonyl group is without precedent.

Scheme 8

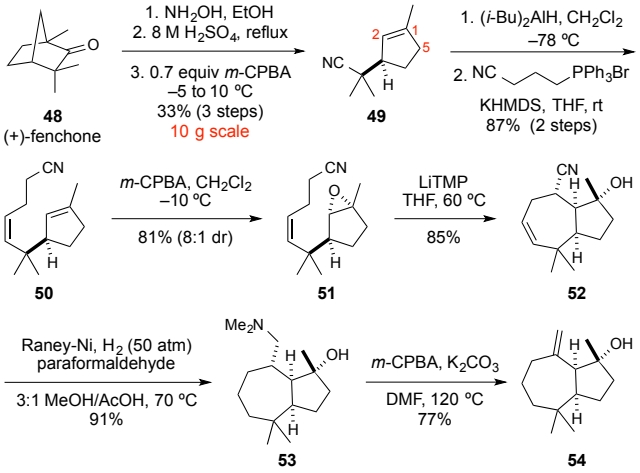


Brief comment on our original assignment of structure **A** to the perhydroazulenol intermediate used to prepare *cis*-perhydroazulene carboxylic acid **40** is warranted. First, this structural misassignment was not detected in our earlier studies because the next step in the synthesis of **40**, dehydration of tertiary alcohol **43** to form the corresponding conjugated enone, removed the C-1 and C-8a stereocenters of **43**.[30] In this earlier synthesis, the perhydroazulene ring was constructed by intramolecular nitrile oxide cycloaddition of nitro precursor **46** to yield an isoxazoline intermediate, whose

structure was assigned as **47** on the basis of excellent precedent.[53] Extensive 2D NMR experiments confirm the relative configuration of cycloadduct **47**. Thus, epimerization of the ring fusion and alcohol stereocenter in route to **43** must occur during reduction of isoxazoline **47** under acidic conditions.[54] This epimerization, which undoubtedly arises by a retro aldol/aldol sequence, has precedent in the unmasking of related tricyclic isoxazolines in the presence of boric acid.[55,56,57]

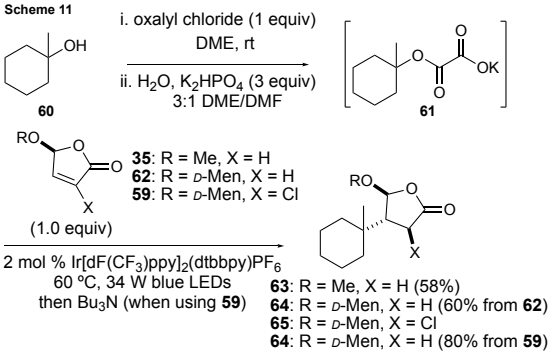
It was clear at this point that a new route to a *cis*-perhydroazulenol intermediate would be required. We conjectured in addition that the tertiary alcohol should reside on the convex face of the *cis*-perhydroazulene ring to avoid the possibility of unwanted cyclization of a transiently generated alkoxyacyl radical onto a proximal carbonyl or exomethylene functional group. Our development of a short enantioselective route to access such an intermediate, *cis*-perhydroazulenol **54**, is summarized in Scheme 9. The synthesis began with inexpensive (+)-fenchone, whose oxime derivative underwent a known Beckmann fragmentation when heated at reflux with aqueous sulfuric acid to give cyclopentene nitrile **49** and its $\Delta^{1,5}$ isomer in near-equal amounts.[58] Although these double-bond regioisomers can be separated by careful chromatography on silver nitrate-impregnated silica gel,[30] we found it more convenient on scale to selectively epoxidize the less-hindered $\Delta^{1,5}$ isomer of this mixture thereby allowing pure **49** to be obtained reliably on 10 g scales by simple flash chromatography. Conventional reduction of nitrile **49** and Wittig olefination of the aldehyde product gave dienyl nitrile **50** in 87% yield over two steps. As the prelude to forming the seven-membered ring, the trisubstituted double bond of **50** was selectively epoxidized by reaction with 1 equiv of *m*-CPBA at –10 ºC in CH_2Cl_2 to give an 8:1 mixture of stereoisomers from which the major isomer **51** was isolated after chromatographic purification in 81% yield. Deprotonation of **51** with 1 equiv of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) induced stereospecific cyclization to form *cis*-perhydroazulenol **52** in 85% yield.[59,60] To our knowledge, this is the first example of forming a seven-membered ring by Stork epoxy-nitrile cyclization,[61] an outcome undoubtedly assisted by the *cis*-double bond in the tether and the presence of *gem*-dimethyl substitution. After examining several non-conventional methods for transforming the nitrile substituent to an exomethylene group in one step, this transformation was ultimately realized in high yield by a two-step sequence. First, reaction of **52** with Raney-Ni and hydrogen (50 atm) in the presence of paraformaldehyde delivered amino alcohol **53** in 91% yield. Formation of the corresponding *N*-oxide and heating this crude intermediate to 120 ºC in DMF occasioned clean Cope elimination to provide alcohol **54** in 77% yield.[62]

Scheme 9



Optimization in a Model Series of the Fragment Coupling Step and Elaboration of the Coupled Product to a 6-

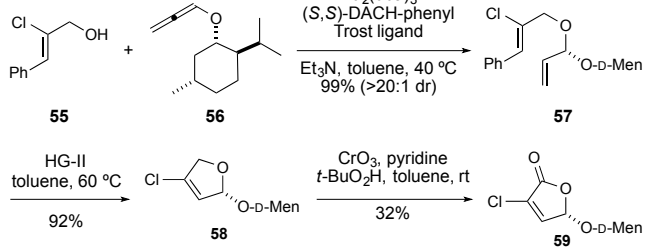
Scheme 11



Substituted *cis*-2,8-Dioxabicyclo[3.3.0]octan-3-one. In addition to developing an expedited route to a precursor of *cis*-perhydroazulene radical **38**, both the conjugate addition step and the elaboration of the butenolide fragment of the coupled product to a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one would need to be optimized significantly in order to define an efficient route to (+)-cheloviolene A (**7**) and congeners. Initially we wished to evaluate whether incorporation of a radical-stabilizing group at the α-position of a 5-alkoxybutenolide would increase the efficiency of the fragment-coupling step. An obvious choice would be a chlorine substituent.[30, 63] Undoubtedly reflecting the sensitivity of the allylic acetal functionality, our attempts to directly introduce chlorine at C-3 of a 5-alkoxybutenolide led to either decomposition or, when attempted with enantiopure 5-alkoxybutenolides, partial racemization.[64] As a result, our efforts shifted to the development of a new route to 3-chloro-5-alkoxybutenolides that would exploit Rhee's recent method for enantioselective synthesis of acetals (Scheme 10).[65] The sequence began with palladium-catalyzed enantioselective alkoxylation of (*D*)-menthol-derived allene **56** with allylic alcohol **55** to deliver mixed acetal **57** in 99% yield as a single detectable diastereomer by ^{1}H NMR analysis.[66] Subjection of diene **57** to the Hoveyda-Grubbs second-generation catalyst in toluene at 60 ºC gave rise to dihydrofuran **58** in excellent yield on gram-scale. Incorporation of the phenyl group in the alkenyl chloride fragment was crucial to the success of this ring-closing metathesis as reported by Dorta.[67,68] After much experimentation, we found that the demanding allylic oxidation of 58

could be accomplished with CrO_3 and *tert*-butylhydroperoxide[69] to reliably give butenolide **59** in 32% yield.[70–72] The opposite enantiomer of butenolide **59** was readily accessible by the same sequence, starting from (*L*)-menthol and employing the opposite enantiomer of the Trost ligand.

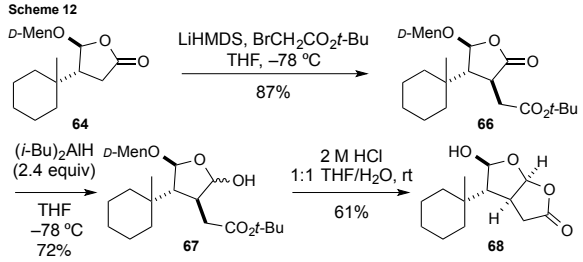
Scheme 10



Our exploratory studies, summarized in Scheme 11, aimed at developing a one-pot sequence for directly transforming a tertiary alcohol to a coupled product and optimizing the coupling with a 5-alkoxybutenolide. We eventually found that reaction of 1-methylcyclohexanol (**60**) with 1 equiv of oxalyl chloride at room temperature in DME, followed by addition of water and 3 equiv of K_2HPO_4 cleanly generated the potassium hemioxalate intermediate **61** *in situ*. Direct addition of 1 equiv of 5-methoxybutenolide (**35**), followed by photoredox-catalyzed coupling as described previously[51] provided *trans* adduct **63** as a single stereoisomer in 58% yield.[73] Using menthyloxybutenolide **62**,[74] coupled product **64** was generated, again as a single stereoisomer, in this case in 60% yield. The analogous coupling with butenolide **59** harboring a 3-chloro substituent was much more efficient delivering a 3:1 mixture of **65** and dechlorinated analogue **64** in 78% combined yield. Addition of 10 equiv of tri-*n*-butylamine to the reaction mixture following the initial fragment coupling with butenolide **59** and allowing the subsequent photocatalytic dechlorination[75] to proceed for 4 h gave conjugate addition product **64** in 80% yield in one-step from alcohol **60**.

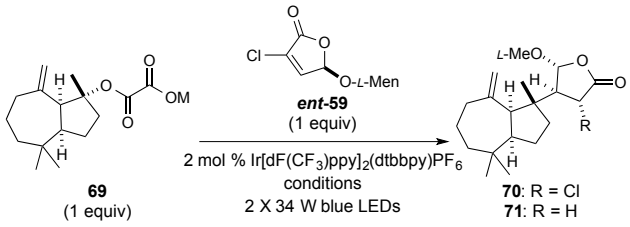
In our first-generation synthesis of (+)-cheloviolene A, a four-step sequence proceeding in 25% yield was used to fashion the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one moiety from the butyrolactone fragment of the coupled product (Scheme 7). We anticipated that this elaboration could be shortened by one step by introducing the acetic ester side chain as a *tert*-butyl ester. This sequence in the 1-methylcyclohexyl model series is summarized in Scheme 12. Enolization of coupled product **64** with LiHMDS, followed by trapping with *tert*-butyl bromoacetate took place stereoselectively to give *tert*-butyl ester **66** in high yield. As expected, the steric bulk of the *tert*-butyl ester simplified chemoselective reduction of the lactone carbonyl group of **66** such that reaction with 2.4 equiv of $(i\text{-Bu})_2AlH$ in toluene at –78 ºC delivered lactol **67** in 72% yield. Finally, exposure of this intermediate to 2 M HCl formed the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one moiety and cleaved the menthyl acetal to provide tricyclic product **68** in 61% yield. This expedited sequence furnished **68** in 38% yield over three steps from coupled product **64**.

Scheme 12



Total Syntheses of (+)-Cheloviolene B, (+)-Dendrillolide C and Second-Generation Total Synthesis of (+)-Cheloviolene A. Our studies began by optimizing the efficiency of the fragment-coupling reaction between butenolide ***ent*-59** and *cis*-perhydroazulene oxalate salts **69**. In this study, the oxalate salt intermediates were generated by selective hydrolysis of the mixed oxalate diester formed from *cis*-perhydroazulenol **54** and methyl chlorooxalate (Table 1).[51] An initial solvent screen revealed DME and THF to be superior to other solvents, with the Ir(III)-catalyzed visible-light photocatalytic reaction yielding mixtures of coupled product **70** and its dechlorinated analogue **71** in ~40% combined yield (entries 1–4).[76] We utilized THF in our further optimization experiments because of the overall cleaner reaction profile and lower amounts of dechlorinated product **71** in this solvent. Increasing the amount of water in the reaction was deleterious to reaction efficiency (entry 5). The yield of the transformation could be increased somewhat by using 1.5 equiv of the butenolide radical acceptor (entry 6). However, since our objective was to optimize the coupling step using equimolar amounts of the addends, 1 equiv of the butenolide was used in subsequent experiments.

Table 1. Optimization of the Fragment Coupling Between **69** and ***ent*-59**.



entry	M	conditions	**70**, yield (%)[a]	**71**, yield (%)[a]
1	Li	MeCN (0.05 M), H_2O (10 equiv)	0	0
2	Li	DMF (0.05 M), H_2O (10 equiv)	24	0
3	Li	DME (0.05 M), H_2O (10 equiv)	29	13
4	Li	THF (0.05 M), H_2O (10 equiv)	34	5
5	Li	THF (0.05 M), H_2O (100 equiv)	17	12
6[b]	Li	THF (0.05 M), H_2O (10 equiv)	48	0
7	Li	THF (0.6 M), H_2O (5 equiv)	73[c]	<5%
8[d]	Li	THF (0.6 M), H_2O (5 equiv)	0	75[c]
9	K	THF (0.6 M), H_2O (5 equiv)	72[c]	<5%

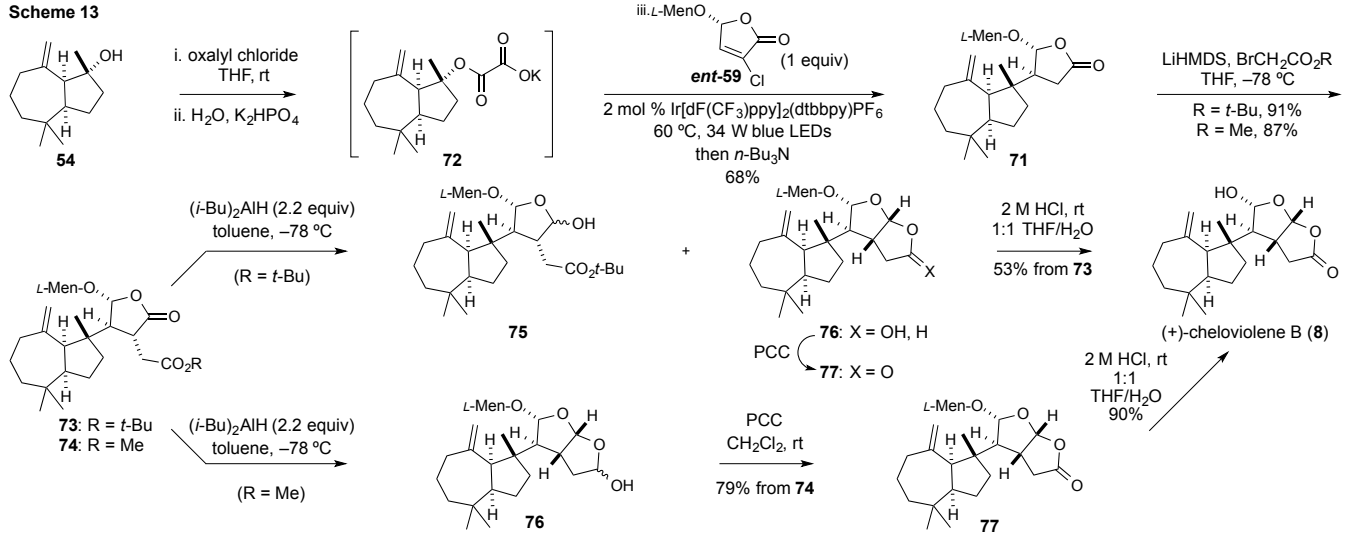
[a]Determined by ^1H NMR integration relative to an internal standard (1,2-dibromo-4,5-methylenedioxybenzene). [b]1.5 equiv of butenolide ***ent*-59** was utilized. [c]Isolated yield. [d]*n*-Bu_3N (10 equiv) was added after coupling.

The yield of the conjugate addition was dramatically enhanced when the concentration of the reaction was increased from 0.05 M to 0.6 M, providing coupled product **70** in 73% isolated yield (entry 7).[77] Notably, only minor amounts of the

dechlorinated product **71** were formed under these reaction conditions. Resubjection of **70** to the reaction conditions in the presence of *n*-Bu_3N led to a quantitative conversion of **70** to **71**.[75] Finally, we were able to perform the desired radical fragment coupling and dechlorination in one step to deliver **71** in 75% isolated yield by adding of *n*-Bu_3N after 18 h and allowing the subsequent dechlorination to proceed for 4 h (entry 8). As expected from our earlier studies,[51] the yield of the Ir(III) photoredox-mediated fragment coupling under optimized conditions was essentially identical when the oxalate counter ion was switched from Li to K. (entry 9).

With reaction conditions for the pivotal fragment coupling step optimized, we turned to investigate accomplishing this union in one step from *cis*-perhydroazulenol **54** and butenolide ***ent*-59** (Scheme 13). To this end, a THF solution of tertiary alcohol **54** was allowed to react with 1 equiv of oxalyl chloride at room temperature for 6 h and then water and 3 equiv of K_2HPO_4 were added to generate potassium oxalate intermediate **72**. Addition of butenolide ***ent*-59** (1 equiv), the photocatalyst and irradiation with high-intensity blue LEDs for 18 h at 60 ºC, followed by addition of excess *n*-Bu_3N and irradiation for an additional 4 h gave the desired product **71** in 68% yield after purification. This radical fragment coupling is noteworthy for several reasons: (1) it is the first example of a one-step coupling of an alcohol-derived tertiary radical with a Michael acceptor; (2) equimolar amounts of the two coupling partners are utilized; (3) the desired product **71** is obtained as a single diastereomer at both newly formed stereocenters; and (4) the reaction conditions allowed for selective isolation of either the direct coupling product, or its dehalogenated congener **71**.[40]

Scheme 13

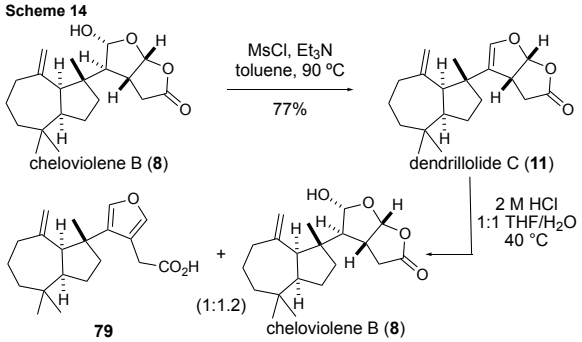


Elaboration of coupled product **71** to cheloviolene B (**8**) began with alkylation of the lactone fragment of **71** with *tert*-butyl bromoacetate to deliver ester **73** in 91% yield. In contrast to our earlier results in the model series, reduction of **73** with 2.2 equiv of DIBALH at – 78 ºC in toluene did not lead exclusively to the desired tricyclic lactol product **75**, but rather to a 2:1 mixture of **75** and **76**, both as mixtures of lactol epimers. Attempts to modify the reduction conditions to furnish **75** selectively were met with no success. To converge these products, **76** was oxidized with PCC to give tetracyclic product **77** harboring the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one moiety. At this point, **75** and **77** were combined and exposed to 2 M HCl in THF/H_2O at room temperature to give what turned out to be (+)-cheloviolene B (**8**), mp: 189–190 ºC, $[\alpha]^{21}_D$ +26.6, in 53% overall yield from intermediate **73.**

As the oxidation step in route to (+)-cheloviolene B (**8**) could not be avoided by introducing the two-carbon side chain as a *tert*-butyl ester, and processing both intermediates **75** and **76** was cumbersome, a more efficient route was developed to access (+)-cheloviolene B. In this sequence, the fragment-coupling product **71** was alkylated in high yield with methyl bromoacetate to give lactone ester **74**. In this methyl ester series, lactonization of the initially formed tricyclic lactol alkoxide intermediate generated upon exposure of **74** to excess DIBALH was sufficiently rapid at –78 ºC that tetracyclic lactol product **76** was formed in high yield. Without purification, this mixture of lactol epimers was directly oxidized with PCC to give **77** in 79% yield over the two steps. Exposure of **77** to 2 M HCl in THF/H_2O then afforded (+)-cheloviolene B. Using this four-step sequence, fragment-coupling product **71** was transformed to (+)-cheloviolene B (**8**) in 62% overall yield.

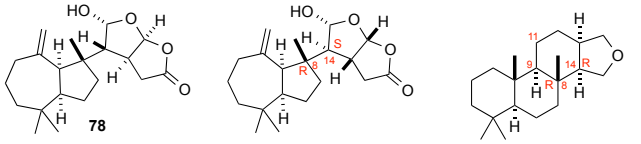
The relative configuration of synthetic (+)-cheloviolene B (**8**) was confirmed by single-crystal X-ray analysis,[40] whereas its absolute configuration follows rigorously from the absolute configuration of precursors **54** and ***ent*-59**. Structure **8** was originally proposed by Bobzin and Faulkner for a diterpenoid isolated from the marine sponge *Chelonaplysilla sp.* collected in Pohnpei, Federated States of Micronesia, and called chelonaplysin B.[17] Two years later, Taylor and coworkers reported that the ^{1}H NMR spectra of so-called chelonaplysin B was identical to that of (+)-cheloviolene A (**7**), one of a series of diterpenoids isolated from the sponge *Chelonaplysilla violacea* collected from coastal waters of New Zealand.[16] In addition to (+)-cheloviolene A (**7**), whose structure was confirmed by X-ray analysis, these workers isolated a related diterpenoid, (+)-cheloviolene B, which they assigned as the lactol epimer of cheloviolene A **78** (Figure 3).[16b] It is this sponge

Scheme 14



isolate whose reported ^{1}H and ^{13}C NMR spectra are indistinguishable from synthetic **8**. The structure of (+)-cheloviolene B must therefore be revised to be **8**.

Figure 3



78

originally proposed incorrect structure of cheloviolene B

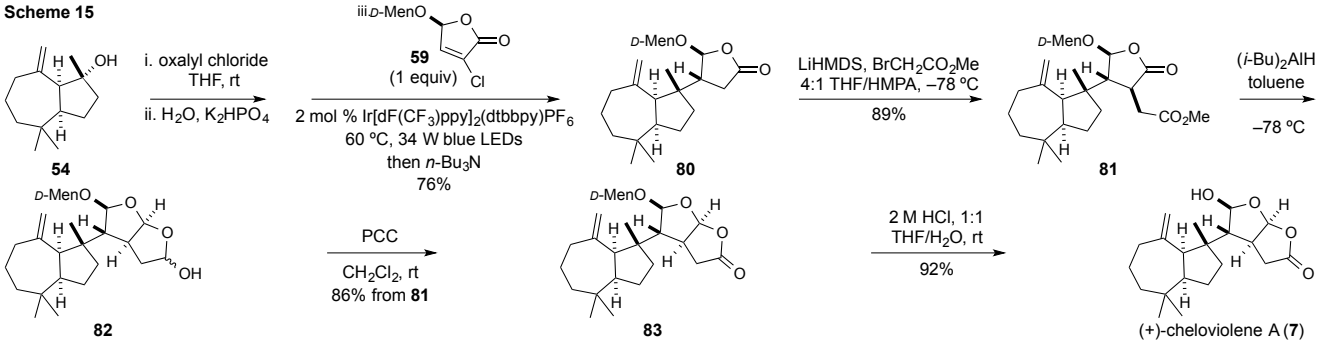
cheloviolene B (**8**) (corrected structure)

spongian skeleton (**12**)

As first pointed out by Faulkner, a diterpenoid of structure **8** would be an outlier in the group of rearranged spongian diterpenoids exemplified in Figure 1B, because the relative configuration of its attached carbons, C-8 and C-14, differs at C-14 from that expected from a precursor having the spongian skeleton **12** (see Figure 1).[17] They suggested that the unexpected *S* configuration at C-14 of a diterpenoid of structure **8** might arise by hydration of the corresponding enol ether double bond of another spongian diterpenoid, dendrillolide C, which this research group had isolated earlier from the sponge *Dendrilla sp.* obtained from a marine lake of Palau and assigned structure **11**.[78] To confirm the structure of dendrillolide C, establish its absolute configuration, and pursue Faulkner's suggestion for the origin of the unexpected stereostructure of cheviolene B (**8**), we carried out the experiments summarized in Scheme 14. Reaction of **8** with 2.5 equiv of MsCl and excess Et_3N in toluene at 90 ºC provided (+)-dendrillolide C (**11**), $[\alpha]^{21}_{D}$ +133, in 77% yield. ^{1}H NMR and optical rotation data of synthetic dendrillolide C (**11**) were indistinguishable from those reported for the diterpenoid isolated from the sponge *Dendrilla sp*.[77] Exposing synthetic dendrillolide C (**11**) to 2 M HCl in THF/H_2O at 40 ºC led to the formation of a 1.2:1 mixture of cheloviolene B (**8**) and tricyclic furan **79**. Careful analysis of the ^{1}H NMR spectra of this crude product mixture showed that stereoisomers of **8** were not present in significant amounts.[40] Other acidic conditions (both Lewis and protic) that we investigated resulted in exclusive formation of furan **79** or intractable mixtures of products. That dendrillolide C (**11**) undergoes protonation at C14 preferentially from the *Si* face is consistent with the Faulkner initial proposal and with torsional effects dictating the stereochemical outcome of the hydration reaction *in vitro*.[79]

Besides efficiency, the ability to access analogues by varying the structure of late-stage fragments is a distinct advantage of convergent synthesis strategies. The second-generation total synthesis of (+)-cheloviolene A (**7**) illustrates this point (Scheme 15). In this case, the fragment coupling step employed butenolide **59**, which trapped the tertiary radical generated from *cis*-pehydroazulenol **54** to give tricyclic lactone **80** as the only detectable stereoisomer in 76% yield. The 10% higher yield of this step than the analogous one employing ***ent*-59** (Scheme 13) reflects a match of the chirality of the enantiopure fragments combining to yield **80**. Processing of this product by the identical four-step sequence used to prepare (+)-cheloviolene B (**8**) gave (+)-cheloviolene A (**7**) in 70% overall yield from intermediate **80**.

Scheme 15



CONCLUSION

Enantioselective total syntheses of rearranged spongian diterpenoids **7**, **8**, **11** exemplify advantages of convergent synthesis strategies based upon late-stage fragment coupling between a tertiary carbon radical and an electron-deficient alkene to unite two ring systems and form two new stereocenters, one of which is quaternary, in a stereoselective and efficient manner. (+)-Cheloviolene A (**7**) and (+)-cheloviolene B (**8**) were prepared in 11 steps from the known cyclopentene nitrile **49**[58] in respectively 22% and 18% overall yield, and in 14 steps and 5–7% overall yield from (+)-fenchone. These short synthetic sequences are made possible in part by the one-step generation of tertiary radical **38** from tertiary alcohol **54** and its *in situ* trapping with chlorobutenolides ***59*** and ***ent*-59**. Of critical importance, these fragment unions were accomplished using equimolar amounts of the two coupling partners. It should be noted that while this strategy has allowed us to access diterpenoids such as (+)-cheloviolenes A (**7**) and B (**8**) that bear the fourteen-carbon hydrophobic fragment on the convex face of the *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one unit, we have so far been unsuccessful in developing a complimentary stereoselective approach to diterpenoids such as dendrillolide A (**11**) in which the *cis*-perhydroazulene resides on the concave face.[40] We anticipate that the convergent strategy described in this paper, namely late-stage union of a structurally complex tertiary carbon radical with an acceptor, will find applications in future syntheses of a variety of stereochemically elaborate natural products.

EXPERIMENTAL SECTION

Unless stated otherwise, reactions were conducted in oven-dried glassware under an atmosphere of nitrogen or argon. Tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), dimethylformamide (DMF), toluene, dichloromethane, methanol (MeOH), *N,N*-diisopropylethylamine (*i*-Pr_2NEt), and triethylamine (Et_3N) were dried by passage through activated alumina. Methyl bromoacetate and *tert*-butyl bromoacetate were distilled under reduced pressure and stored in a Schlenk flask. All other commercial reagents were used as received

unless otherwise noted. Reaction temperatures were controlled using a temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or by *p*-anisaldehyde, ceric ammonium molybdate, and potassium permanganate staining ($KMnO_4$). Silica gel 60 (particle size 0.040–0.063mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded at 500 or 600 MHz and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectra were recorded at 126 or 151 MHz. Data for ^{13}C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on a FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained with an LCT spectrometer. Optical rotation readings were obtained using JASCO P-1010 polarimeter. Kessil KSH150B LED Grow Light 150, Blue (34 W blue LED lamps) was purchased from http://www.amazon.com. Low-intensity blue LEDs (30 cm, 1 watt) were purchased from http://www.creativelightings.com (product code CL-FRS5050-12WP-12V) and were powered by 8 AA batteries. See JOC Standard Abbreviations and Acronyms for abbreviations (available at http://pubs.acs.org/paragonplus/submission/joceah/joceah_abbreviations.pdf).

Preparation of Ester 26: A round-bottom flask was charged with 4-methyl 2-methylenesuccinate (**S1**) (3.0 g, 21 mmol, 1.0 equiv),[34] DMF (15 mL, 2.0 M), and a magnetic stir bar under an atmosphere of argon. Next, sodium bicarbonate (3.53 g, 42.0 mmol, 2.0 equiv) was added portionwise to the solution and the resulting heterogeneous mixture was stirred at rt for 1 h. After 1 h, allyl bromide (2.7 mL, 31 mmol, 1.5 equiv) was added dropwise to the mixture that was then stirred vigorously at rt for 12 h. After 12 h, H_2O (50 mL) was added to the reaction mixture and the resulting solution was transferred to a separatory funnel and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with H_2O (3 x 50 mL), dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was purified by flash chromatography on silica gel using 10:90 ethyl acetate:hexanes to yield ester **26** as a clear oil (3.0 g, 16 mmol, 78% yield): R_f = 0.35 (10:90 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.38 (s, 1H), 5.94 (dddd, *J* = 22.4, 16.2, 10.7, 5.4 Hz, 1H), 5.75 (s, 1H), 5.34 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.5 Hz, 1H), 4.68 (d, *J* = 5.5 Hz, 2H), 3.71 (s, 3H), 3.37 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3, 165.9, 133.8, 132.0, 128.9, 118.3, 65.8, 52.2, 37.7; IR (thin film) 1744, 1642 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_9H_{12}O_4Na$ 207.0633; Found 207.0637.

Preparation of Butenolide 27: A round-bottom flask was charged with diene **26** (800 mg, 4.3 mmol, 1.0 equiv), toluene (440 mL, 0.01 M), and a magnetic stir bar under an atmosphere of argon. Next, Stewart-Grubbs catalyst (50 mg, 0.09 mmol, 0.02 equiv)[35] was added to the reaction mixture and the resulting solution was heated to 110 ºC for 18 h. After 18 h, the solution was allowed to cool to rt and concentrated by use of a rotary evaporator to yield a brown oil. The residue was purified by flash column chromatography on silica gel using 20:80 ethyl acetate:hexanes → 40:60 ethyl acetate:hexanes as eluent to yield butenolide **27** as a brown oil (500 mg, 3.2 mmol, 74% yield): R_f = 0.29 (50:50 ethyl acetate:hexanes, stained with $KMnO_4$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (s, 1H), 4.87 (s, 2H), 3.75 (s, 3H), 3.38 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.7, 170.1, 148.1, 127.1, 70.8, 52.5, 30.5; IR (thin film) 2955, 2871, 1737, 1657, 1438, 1349, 1223, 1078, 1049 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_7H_8O_4Na$ 179.0320; Found 179.0312.

Preparation of Butenolide 28: A round-bottom flask was charged with butenolide **27** (490 mg, 3.1 mmol, 1.0 equiv), CCl_4 (21 mL, 0.15 M), *N*-bromosuccinimide (1.7 g, 9.4 mmol, 3.0 equiv), AIBN (52 mg, 0.31 mmol, 0.1 equiv), and a magnetic stir bar under an atmosphere of argon. The mixture was irradiated with a 100 W compact fluorescent light bulb and heated to 75 ºC for 3 h. After 3 h, additional *N*-bromosuccinimide (560 mg, 3.1 mmol, 1.0 equiv) and AIBN (52 mg, 0.31 mmol, 0.1 mmol) were added. The mixture was stirred at 75 ºC for 1 h, at which point TLC analysis indicated complete consumption of starting material **27**. The reaction was then cooled to 0 ºC, vacuum filtered and concentrated by use of a rotary evaporator to yield the crude 5-bromo analogue as a yellow oil. Diagnostic ^{1}H NMR shifts (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.2 Hz, 1H), 6.90 (d, *J* = 1.2 Hz, 1H), 3.76 (s, 3H), 3.44 (br s, 2H). A round-bottom flask was charged with the crude intermediate, MeOH (7 mL, 0.45 M), and a magnetic stir bar under an atmosphere of argon. The solution was heated to 70 ºC for 12 h. After 12 h the solution was allowed to cool to rt and concentrated by use of a rotary evaporator. The residue was purified by flash chromatography on silica gel using 10:90 ethyl acetate:hexanes → 25:75 ethyl acetate:hexanes as eluent to yield butenolide **28** as a yellow oil (210 mg, 1.1 mmol, 36% yield over 2 steps): R_f = 0.28 (30:70 ethyl acetate:hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 (d, *J* = 1.2 Hz, 1H), 5.83 (d, *J* = 1.2 Hz, 1H), 3.74 (s, 3H), 3.57 (s, 3H), 3.38 (d, *J* = 1.2 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.7, 169.5, 145.6, 131.2, 103.0, 57.1, 52.6, 30.4; IR (thin film) 1780, 1750 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_8H_{10}O_5Na$ 209.0426; Found 209.0418.

Preparation of Carboxylic Acid S2: A round-bottom flask was charged with *i*-Pr_2NH (9.0 mL, 68 mmol, 2.6 equiv), THF (200 mL, 0.13 M), and a magnetic stir bar under an atmosphere of argon. After cooling the solution to –78 ºC, 2.4 M *n*-BuLi in hexanes (27 mL, 65 mmol, 2.5 equiv) was added dropwise. The resulting solution was then warmed to 0 ºC stirred for 30 min. Next, isobutyric acid (2.4 mL, 26 mmol, 1.0 equiv) was added dropwise at 0 ºC. The reaction was maintained at 0 ºC for 20 min, followed by a dropwise addition of a solution of 1-iodo-3,6,9,12-tetraoxapentadec-14-yne (10.2 g, 28.6 mmol, 1.1 equiv)[80] in THF (60 mL, 0.43 M). The resulting heterogeneous mixture was allowed to warm to rt and stirred vigorously for 12 h. After 12 h, the reaction was quenched via addition of H_2O (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (2 x 200 mL). The aqueous layer was acidified with sat. NH_4Cl (aq) and extracted with CH_2Cl_2 (2 x 300 mL). The combined organic layers, resulting from extracting the acidified aqueous layer, were dried over $MgSO_4$ and concentrated by use of a rotary evaporator to yield **S2** as a clear oil

(3.8 g, 13 mmol, 48% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (d, *J* = 2.3 Hz, 2H), 3.73–3.56 (m, 14H), 2.43 (br s, 1H), 1.87 (t, *J* = 5.9 Hz, 2H), 1.23 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.5, 79.7, 74.7, 70.9, 70.6, 70.4, 70.3, 70.2, 69.2, 67.8, 58.5, 40.4, 40.0, 25.5; IR (thin film) 3251, 1728, 1700, 1103 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{26}O_6Na$ 325.1627; Found 325.1636.

Preparation of NHP Ester 29c: A round-bottom flask was charged with acid **S2** (1.9 g, 7.4 mmol, 1.0 equiv), CH_2Cl_2 (50 mL, 0.2 M), DCC (2.0 g, 9.6 mmol, 1.3 equiv), DMAP (180 mg, 1.5 mmol, 0.2 equiv), and a magnetic stir bar under an atmosphere of argon. The resulting heterogeneous mixture was stirred at rt for 15 min. Next, *N*-hydroxyphthalimide (1.4 g, 8.8 mmol, 1.2 equiv) was added in one portion and the mixture was stirred at rt for 16 h. After 16 h, the reaction was quenched via addition of sat. NH_4Cl (aq). The resulting biphasic mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was purified by flash chromatography on silica gel using 50:50 ethyl acetate:hexanes as eluent to yield *N*-acyloxyphthalimide **29c** as a clear oil (1.6 g, 4.0 mmol, 54% yield): R_f = 0.35 (50:50 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.6, 4.7 Hz, 2H), 7.79 (dd, *J* = 5.4, 3.2 Hz, 2H), 4.20 (d, *J* = 2.4 Hz, 2H), 3.71–3.61 (m, 14H), 2.43–2.42 (m, 1H), 2.06 (t, *J* = 7.0 Hz, 2H), 1.44 (s, 6H); ^{13}CNMR (126 MHz, $CDCl_3$) δ 173.8, 162.2, 134.8, 129.2, 124.0, 79.8, 74.6, 70.8, 70.7, 70.5, 70.4, 69.2, 67.7, 58.5, 40.9, 39.7, 25.6; IR (thin film) 3273, 1782, 1743 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{23}H_{29}NO_8Na$ 470.1791; Found 470.1777.

General Procedure for the Photoredox-mediated Couplings of 29a–c with 28: A 1-dram scintillation vial was charged with *N*-acyloxyphthalimide **29a–c** (1.0 equiv), butenolide **28** (1.0 equiv), Hantzsch ester (1.5 equiv),[81] $[Ru(bpy)_3](PF_6)_2$ (0.01 equiv), followed by either *i*-Pr_2NEt (1.0 equiv) or *i*-$Pr_2NEt{\bullet}HBF_4$ (2.2 equiv),[82] and a magnetic stir bar. The vial was sealed with a screw cap bearing a Teflon septum and CH_2Cl_2 (0.15 M, sparged with argon for 10 min) was added. Next, the vial was placed in the center of a 30 cm-loop of low-intensity blue LEDs. Heterogeneous reaction mixture was irradiated by low intensity blue LEDs and stirred vigorously at rt for 18 h. The mixture was filtered over silica gel using Et_2O as eluent and concentrated by use of a rotary evaporator to yield a yellow residue that was further purified by flash chromatography on silica gel.

Preparation of Lactone 30a: Following the general procedure, *N*-acyloxyphthalimide **29a** (27 mg, 0.11 mmol, 1.0 equiv) and butenolide **28** (20 mg, 0.11 mmol, 1.0 equiv) were coupled in the presence of *i*-Pr_2NEt (19 µL, 0.11 mmol, 1.0 equiv), $[Ru(bpy)_3](PF_6)_2$ (1 mg, 0.001 mmol, 0.01 equiv), and Hantzsch ester (41 mg, 0.16 mmol, 1.5 equiv) in CH_2Cl_2 (0.75 mL). Purification of the crude residue by flash chromatography on silica gel using 10:90 ethyl acetate:hexanes as eluent yielded **30a** as a clear oil (19 mg, 0.076 mmol, 72% yield): R_f = 0.45 (10:90 ethyl acetate:hexanes, stained with $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.17 (d, *J* = 2.3 Hz, 1H), 3.71 (s, 3H), 3.51 (s, 3H), 2.85–2.73 (m, 3H), 1.95 (app s, *J* = 1.9 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 171.3, 106.5, 57.2, 56.6, 52.1, 38.7, 36.9, 31.8, 27.1; IR (thin film) 1644, 1633 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{20}O_5Na$ 267.1208; Found 267.1209.

The reaction performed in the presence of *i*-$Pr_2NEt{\bullet}HBF_4$ (53 mg, 0.24 mmol, 2.2 equiv) in place of *i*-Pr_2NEt led to product **30a** (17 mg, 0.69 mmol, 66% yield) that was isolated after purification by flash chromatography on silica gel. The product ratios shown in Scheme 3 arise from ^{1}H and ^{13}C NMR analysis of crude reaction mixtures.

Lactone 31 was isolated in 22% yield from the above reaction when *i*-$Pr_2NEt{\bullet}HBF_4$ was used: R_f = 0.47 (10:90 ethyl acetate:hexanes, stained with $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (s, 1H), 3.74 (s, 3H), 3.63–3.59 (m, 1H), 3.48 (s, 3H), 2.97 (dd, *J* = 17.5, 6.1 Hz, 1H), 2.74 (dd, *J* = 17.5, 9.3 Hz, 1H), 2.36 (d, *J* = 8.2 Hz, 1H), 0.97 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 172.0, 105.9, 56.6, 54.2, 52.3, 38.3, 32.3, 32.0, 28.3; IR (thin film) 2956, 2922, 1783, 1742 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{20}O_5Na$ 267.1208; Found 267.1201.

Lactone 32 was isolated in 1% yield as a 1.5:1 mixture of diastereomers from the above reaction when *i*-Pr_2NEt was used: R_f = 0.42 (10:90 ethyl acetate:hexanes, stained with $KMnO_4$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.40 (app t, *J* = 5.8 Hz, 1H), 5.36 (dd, *J* = 6.9, 5.2 Hz, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.57 (s, 3H), 3.54 (s, 3H), 3.11 (ddd, *J* = 11.8, 10.5, 9.3 Hz, 1H), 3.01 (d, *J* = 3.1 Hz, 1H), 2.88 (dd, *J* = 9.5, 3.0 Hz, 1H), 2.69 (ddd, *J* = 13.9, 9.0, 5.2 Hz, 1H), 2.57 (ddd, *J* = 13.7, 10.4, 6.2 Hz, 1H), 2.45 (d, *J* = 10.3 Hz, 1H), 2.38 (ddd, *J* = 14.6, 9.3, 5.7 Hz, 1H), 2.00 (app dt, *J* = 12.0, 6.9 Hz, 1H), 1.06 (s, 9H), 1.03 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.0, 175.2, 173.8, 172.6, 104.5, 103.9, 58.1, 57.7, 55.8, 54.1, 51.6, 51.5, 41.3, 39.8, 35.9, 33.1, 32.3, 28.6, 28.5, 15.4. IR (thin film) 1770, 1644 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{20}O_5Na$ 267.1208; Found 267.1199.

Preparation of Lactone 30b: Synthesized according to the general procedure from the *N*-acyloxyphthalimide **29b** (77 mg, 0.27 mmol, 1.0 equiv),[41] butenolide **28** (50 mg, 0.27 mmol, 1.0 equiv), *i*-Pr_2NEt (47 µL, 0.27 mmol, 1.0 equiv), $[Ru(bpy)_3](PF_6)_2$ (2 mg, 0.003 mmol, 0.01 equiv) and Hantzsch ester (100 mg, 0.4 mmol, 1.5 equiv) in CH_2Cl_2 (1.8 mL). Purification of the crude residue by flash chromatography on silica gel using 10:90 ethyl acetate:hexanes as eluent yielded **30b** (41 mg, 0.14 mmol, 53% yield) as a colorless solid: R_f = 0.61 (30:70 diethyl ether:pentanes, stained with $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (d, *J* = 2.1 Hz, 1H), 3.71 (s, 3H), 3.50 (s, 3H), 2.89–2.72 (m, 3H), 2.06 (br s, 1H), 1.60–1.21 (m, 10H), 0.89 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 171.4, 106.0, 57.2, 52.2, 37.9, 37.0, 35.43, 35.38, 34.4, 26.1, 21.53, 21.47; IR (thin film) 2929, 2855, 1777, 1738 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{24}O_5Na$ 307.1521; Found 307.1523.

Preparation of Lactone 30c: Synthesized according to the general procedure from *N*-acyloxyphthalimide **29c** (30 mg, 0.07 mmol, 1.0 equiv), butenolide **28** (13 mg, 0.07 mmol, 1.0 equiv), *i*-Pr_2NEt (12 µL, 0.07 mmol, 1.0 equiv), $[Ru(bpy)_3](PF_6)_2$ (0.6 mg, 0.0007 mmol, 0.01 equiv) and Hantzsch ester (25 mg, 0.10 mmol, 1.5 equiv) in CH_2Cl_2 (0.45 mL). Purification of the crude residue by flash chromatography on silica gel using 10:90 acetone:hexanes as eluent

yielded **30c** (16 mg, 0.036 mmol, 52% yield) as a clear oil: R_f = 0.40 (70:30 ethyl acetate:hexanes, stained with $KMnO_4$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.20 (d, *J* = 2.3 Hz, 1H), 4.21 (d, *J* = 2.4 Hz, 2H), 3.76–3.45 (m, 20H), 2.89–2.74 (m, 3H), 2.43 (app t, *J* = 2.4 Hz, 1H), 2.06 (dd, *J* = 4.5, 2.3 Hz, 1H), 1.58 (app t, *J* = 7.0 Hz, 2H), 0.94 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 171.3, 106.2, 79.8, 74.7, 70.8, 70.7, 70.6, 70.4, 69.2, 67.6, 58.6, 57.2, 55.8, 52.2, 39.1, 38.4, 36.9, 33.7, 24.6, 24.2; IR (thin film) 3267, 2932, 2873, 1775, 1739, 1440, 1364, 1111, 939 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{36}O_9Na$ 467.2257; Found 467.2248.

General Procedure for the Reduction/Cyclization/Oxidation to Generate Dioxabicyclo[3.3.0]octanones 34a–c: A round-bottom flask was charged with the coupled product **30a–c** (1.0 equiv), toluene (0.1 M), and a magnetic stir bar under an atmosphere of argon. After cooling the solution to –78 ºC, *i*-Bu_2AlH (2.1 equiv, 1 M in toluene) was added dropwise. The solution was maintained at –78 ºC for 30 min. The reaction was quenched by the addition of saturated solution of Rochelle's salt (aq) (0.1 M) at –78 ºC. The mixture was allowed to warm to rt and stirred at rt for 1 h. The biphasic mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by use of a rotary evaporator to yield a crude mixture of bicyclic lactol epimers **33a–c**. A 1-dram scintillation vial was charged with this crude mixture of bicyclic lactol epimers **33a–c** (1.0 equiv), toluene (0.1 M), Ag_2CO_3 (50 wt. % on Celite, 3.0 equiv), and a magnetic stir bar under an atmosphere of argon. The reaction vessel was capped and heated to 110 ºC. After 1 h, the black suspension was allowed to cool to rt, filtered over Celite and concentrated by use of a rotary evaporator. The resulting residue was purified by flash column chromatography on silica gel to yield bicyclic lactones **34a–c**.

Preparation of Dioxabicyclo[3.3.0]octan-3-one 34a: Synthesized according to the general procedure described above from **30a** (50 mg, 0.21 mmol, 1.0 equiv) and 1 M solution of *i*-Bu_2AlH in toluene (430 µL, 0.43 mmol, 2.2 equiv) in toluene (2 mL, 0.1 M). Diagnostic data for lactol intermediate **33a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (d, *J* = 12.1 Hz, 1H, OH confirmed by D_2O exchange); MS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{20}O_4Na$ 239.1; Found 239.1. Conversion of lactol **33a** to lactone **34a** was achieved with Ag_2CO_3 (340 mg, 0.62 mmol, 3.0 equiv) in toluene (2 mL, 0.1 M). Purification of the crude residue by flash chromatography on silica gel using 20:80 ethyl acetate:hexanes as eluent yielded **34a** (28 mg, 0.13 mmol, 64% yield; 73% based on recovered starting material) as a colorless solid: R_f = 0.45 (30:70 ethyl acetate:hexanes, stained with ceric ammonium molybdate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (d, *J* = 6.1 Hz, 1H), 5.04 (s, 1H), 3.36 (s, 3H), 2.97–2.93 (m, 1H), 2.86 (dd, *J* = 18.1, 11.2 Hz, 1H), 2.62 (dd, *J* = 18.1, 3.6 Hz, 1H), 1.95 (d, *J* = 1.4 Hz, 1H) 0.93 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 109.1, 108.7, 64.4, 55.0, 39.2, 36.6, 31.5, 27.5; IR (thin film) 1784 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{18}O_4Na$ 237.1103; Found 237.1110.

Preparation of Dioxabicyclo[3.3.0]octan-3-one 34b: Synthesized according to the general procedure described above from **30b** (33 mg, 0.12 mmol, 1.0 equiv) and 1 M solution of *i*-Bu_2AlH in toluene (240 µL, 0.24 mmol, 2.2 equiv) in toluene (1.2 mL, 0.1 M). Diagnostic data for lactol intermediate **33b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (d, *J* = 12.0 Hz, 1H, OH confirmed by D_2O exchange). Conversion of lactol **33b** to lactone **34b** was achieved with Ag_2CO_3 (190 mg, 0.35 mmol, 3.0 equiv) in toluene (1.2 mL, 0.1 M). Purification of the crude residue by flash chromatography on silica gel using 15:85 ethyl acetate:hexanes as eluent yielded **34b** (18 mg, 0.071 mmol, 64% yield) as a colorless solid: R_f = 0.45 (30:70 ethyl acetate:hexanes, stained with ceric ammonium molybdate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (d, *J* = 6.1 Hz, 1H), 5.07 (s, 1H), 3.35 (s, 3H), 3.01–2.95 (m, 1H), 2.86 (dd, *J* = 18.1, 11.0 Hz 1H), 2.61 (dd, *J* = 18.1, 3.5 Hz, 1H), 2.04 (br s, 1H), 1.56–1.19 (m, 10H), 0.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 109.2, 108.3, 55.0, 38.4, 36.8, 35.8, 35.7, 33.9, 26.2, 21.6, 20.8; IR (thin film) 1785 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{22}O_4Na$ 277.1416; Found 277.1417.

Preparation of Dioxabicyclo[3.3.0]octan-3-one 34c: Synthesized according to the general procedure described above from **30c** (94 mg, 0.21 mmol, 1.0 equiv) and 1 M solution of *i*-Bu_2AlH in toluene (460 µL, 0.46 mmol, 2.2 equiv) in toluene (2.1 mL, 0.1 M). Conversion of lactol **33c** to lactone **34c** was achieved with Ag_2CO_3 (340 mg, 0.63 mmol, 3.0 equiv) in toluene (2.1 mL, 0.1 M). Purification of the crude residue by flash chromatography on silica gel using 30:70 ethyl acetate:hexanes as eluent yielded **34c** (35 mg, 0.08 mmol, 40% yield) as a colorless solid: R_f = 0.30 (30:70 ethyl acetate:hexanes, stained with ceric ammonium molybdate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (d, *J* = 6.1 Hz, 1H), 5.03 (s, 1H), 4.21 (d, *J* = 2.3 Hz, 2H), 3.72–3.50 (m, 14H), 3.00–2.95 (m, 1H), 2.86 (dd, *J* = 18.3, 11.2 Hz, 1H), 2.63 (dd, *J* = 18.3, 3.8 Hz, 1H), 2.43 (t, *J* = 2.3 Hz, 1H), 2.10 (s, 1H), 1.65–1.48 (m, 2H), 0.95 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 109.0, 108.5, 79.8, 74.7, 70.7, 70.6, 70.5, 69.2, 67.8, 63.1, 58.6, 54.9, 39.9, 39.1, 36.6, 33.4, 25.2, 24.9; IR (thin film) 1781 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{34}O_8Na$ 437.2151; Found 437.2149.

Preparation of Lactone 36: Synthesized according to the general fragment coupling procedure from *N*-acyloxyphthalimide **29a** (150 mg, 0.6 mmol, 1.0 equiv), butenolide **35** (69 mg, 0.60 mmol, 1.0 equiv), i-Pr_2NEt (100 µL, 0.6 mmol, 1.0 equiv), $[Ru(bpy)_3](PF_6)_2$ (5 mg, 0.006 mmol, 0.01 equiv) and Hantzsch ester (230 mg, 0.90 mmol, 1.5 equiv) in CH_2Cl_2 (4 mL). Purification of the crude residue by flash chromatography on silica gel using 5:95 ethyl acetate:hexanes → 10:90 ethyl acetate:hexanes as eluent yielded **36** (75 mg, 0.44 mmol, 73% yield) as a clear oil: R_f = 0.27 (10:90 ethyl acetate:hexanes; stained with $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (d, *J* = 2.5 Hz, 1H), 3.49 (s, 3H), 2.65 (dd, *J* = 18.5, 10.0 Hz, 1H), 2.35 (dd, J = 18.5, 5.5 Hz, 1H), 2.14 (ddd, J = 10.0, 5.5, 3.0 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 176.5, 107.4, 57.0, 51.7, 31.5, 30.0, 27.0; IR (thin film) 2965, 1779, 1175, 1115 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_9H_{16}O_3Na$ 195.0997; Found 195.0993.

Preparation of Ester 30a: A round-bottom flask was charged with *i*-Pr_2NH (110 µL, 0.75 mmol, 3.8 equiv), THF (4.6 mL, 0.1 M), and a magnetic stir bar under an atmosphere of argon. After cooling the solution to –78 ºC, 1.93 M *n*-BuLi in hexanes (260 µL, 0.50 mmol, 2.5 equiv) was added drop-

wise. The resulting solution was then warmed to 0 ºC and stirred for 30 min. Next, an aliquot of the LDA solution (3 mL, 0.3 mmol, 1.5 equiv) was added dropwise to a solution of **36** (34 mg, 0.20 mmol, 1.0 equiv) in THF (2 mL, 0.1 M) at –78 ºC. After 1 h at –78 ºC, a solution of methyl bromoacetate (45 mg, 0.30 mmol, 1.5 equiv) in THF (0.3 mL) was added dropwise. The reaction was allowed to warm to rt, H_2O (5 mL) was added, and the resulting biphasic mixture was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated by use of a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel using 5:95 ethyl acetate:hexanes as eluent to yield **30a** (27 mg, 0.11 mmol, 56% yield) as a clear oil: R_f = 0.45 (10:90 ethyl acetate:hexanes; stained with $KMnO_4$).

Preparation of Lactone 37 from 39: A 1-dram scintillation vial was charged with *N*-acyloxyphthalimide **39** (25 mg, 0.066 mmol, 1.0 equiv), butenolide **(*S*)-35** (8 mg, 0.07 mmol, 1.0 equiv), Hantzsch ester (25 mg, 0.11 mmol, 1.5 equiv), $[Ru(bpy)_3](PF_6)_2$ (0.6 mg, 0.0007 mmol, 0.01 equiv), *i*-$Pr_2NEt{\bullet}HBF_4$ (29 mg, 0.13 mmol, 2.2 equiv), and a magnetic stir bar. The vial was sealed with a screw cap bearing a Teflon septum and CH_2Cl_2 (0.1 M, sparged with argon for 10 min) was added. Next, the vial was placed in the center of a 30 cm-loop of low-intensity blue LEDs. Heterogeneous reaction mixture was irradiated by low intensity blue LEDs and stirred vigorously at rt for 18 h. The mixture was filtered over silica gel using Et_2O as eluent and concentrated by use of a rotary evaporator. The resulting yellow residue was purified by flash chromatography on silica gel using 5:95 ethyl acetate:hexanes as eluent to yield **37** (12 mg, 0.039 mmol, 30% yield) as a clear oil: R_f = 0.30 (10:90 ethyl acetate:hexanes; stained with $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (d, *J* = 1.7 Hz, 1H), 4.83 (d, *J* = 1.7 Hz, 1H), 4.60 (br s, 1H), 3.50 (s, 3H), 2.75 (dd, *J* = 19.6, 11.2 Hz, 1H), 2.51 (d, *J* = 8.7 Hz, 1H), 2.46–2.47 (m, 1H), 2.43–2.41 (m, 1H), 2.35 (dd, *J* = 12.5, 5.2 Hz, 1H), 1.97–1.91 (m, 1H), 1.82–1.73 (m, 4H), 1.64 (dd, *J* = 13.9, 4.1 Hz, 1H), 1.61–1.56 (m, 2H), 1.45–1.34 (m, 1H), 1.28–1.25 (m, 1H), 0.98 (s, 3H), 0.94 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 153.5, 114.9, 107.6, 66.1, 57.0, 56.2, 54.3 52.0, 47.1, 37.9, 37.7, 37.0, 36.4, 34.6, 28.9, 26.2, 25.9, 20.9, 15.5; IR (thin film) 1787 cm^{-1}; $[\alpha]^{23}_D$ +90.8, $[\alpha]^{23}_{577}$ +93.2, $[\alpha]^{23}_{546}$ +106, $[\alpha]^{23}_{435}$ +181 (*c* = 1.0, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{19}H_{30}O_3Na$ 329.2093; Found 329.2099.

Preparation of Lactone 37 from 40: A 1-dram scintillation vial was charged with **40** (47 mg, 0.2 mmol, 1.0 equiv), K_2HPO_4 (38 mg, 0.22 mmol, 1.1 equiv), $(Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5 mg, 0.004 mmol, 0.02 equiv), 3:1 DMF:CH_3CN (0.5 mL, 0.4 M), H_2O (36 µL, 2.0 mmol, 10 equiv), **(*S*)-35** (23 mg, 0.2 mmol, 1.0 equiv), and a magnetic stir bar. The vial was then sealed with a screw cap bearing Teflon septum. The septum of the vial was pierced with a 21 gauge x 1.5'' needle that was inserted just barely through the septum with the tip of the needle kept above the fluid level inside the vial. A separate 22 gauge x 3'' needle attached to a flow of argon was also pierced through the septum, and the tip of the needle was pushed to the bottom of the vial and submersed in the fluid. The reaction mixture was degassed by sparging with argon for 15 min. Both needles were removed, and the sealed vial was then placed on a stir plate equipped with 2 x 34 W blue LED lamps and a rack to hold the vial inside of a cardboard box to block light pollution from entering the lab. The vial was placed approximately 4 cm from the lamps and stirred vigorously. The sample was irradiated by the lamps for 18 h inside the closed box, allowing the temperature of the reaction mixture to rise to 60 ºC and the air inside the box to 40–45 ºC because of heat given off from the LEDs. The reaction was allowed to cool to rt and transferred to a separatory funnel and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was purified by flash column chromatography on silica gel using 5:95 ethyl acetate:hexanes as eluent to yield **37** (27 mg, 0.088 mmol, 44% yield) as a clear oil.

Preparation of Ester 41: A round-bottom flask was charged with *i*-Pr_2NH (280 µL, 2.0 mmol, 13 equiv), THF (3 mL, 0.05 M), and a magnetic stir bar under an atmosphere of argon. After cooling the solution to –78 ºC, 2.3 M *n*-BuLi in hexanes (800 µL, 1.8 mmol, 12 equiv) was added dropwise. The resulting solution was then warmed to 0 ºC and stirred for 30 min. Next, an aliquot of the LDA solution (550 µL, 0.22 mmol, 1.5 equiv) was added dropwise to a solution of **37** (46 mg, 0.149 mmol, 1.0 equiv) in THF (1.5 mL, 0.1 M) at –78 ºC. After 1 h at –78 ºC, a solution of methyl iodoacetate (60 mg, 0.3 mmol, 2.0 equiv) in THF (0.3 mL) was added dropwise. The reaction was allowed to warm to rt, H_2O (5 mL) was added, and the resulting biphasic mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated by use of a rotary evaporator. The resulting residue was purified by flash chromatography on silica gel using 5:95 ethyl acetate:hexanes as eluent to yield **41** (26 mg, 0.069 mmol, 45% yield) as a clear oil: R_f = 0.30 (10:90 ethyl acetate:hexanes; stained with $KMnO_4$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 (s, 1H), 4.84 (d, *J* = 1.8 Hz, 1H), 4.70 (br s, 1H), 3.74 (s, 3H), 3.50 (s, 3H), 2.94–2.90 (m, 1H), 2.81–2.78 (m, 2H), 2.63 (d, *J* = 8.5 Hz, 1H), 2.34 (dd, *J* = 12.8, 5.7 Hz, 1H), 2.19 (br d, *J* = 2.1 Hz, 1H), 1.95–1.89 (m, 1H), 1.83–1.70 (m, 3H), 1.65 (dd, *J* = 13.9, 4.0 Hz, 1H), 1.61–1.58 (m, 2H), 1.43–1.35 (m, 1H), 1.27–1.25 (m, 2H), 1.00 (s, 3H), 0.94 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 171.3, 153.4, 115.0, 107.2, 57.1, 57.0, 54.9, 54.1, 52.3, 47.4, 39.6, 37.82, 37.79, 37.0, 36.4, 34.5, 29.0, 26.1, 25.8, 21.2; IR (thin film) 1781, 1742 cm^{-1}; $[\alpha]^{23}_D$ +73.0, $[\alpha]^{23}_{577}$ +76.4, $[\alpha]^{23}_{546}$ +86.1, $[\alpha]^{23}_{435}$ +146 (*c* = 1.0, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{34}O_5Na$ 401.2304; Found 401.2295.

Preparation of Dioxabicyclo[3.3.0]octan-3-one 42: A round-bottom flask was charged with **41** (4 mg, 0.01 mmol, 1.0 equiv), toluene (0.1 mL, 0.1 M), and a magnetic stir bar under an atmosphere of argon. After cooling the solution to –78 ºC, 1 M solution of *i*-Bu_2AlH in toluene (22 µL, 0.022 mmol, 2.2 equiv) was added dropwise. The solution was maintained at –78 ºC for 30 min. The reaction was quenched by the addition of saturated solution of Rochelle's salt (aq) (0.1 mL) at –78 ºC. The mixture was allowed to warm to rt and stirred at rt for 1 h. Biphasic mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by use of a rotary evaporator to yield a crude

mixture of biyclic lactol epimers **S3**. Diagnostic chemical shifts of the lactol intermediate **S3**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86 (d, *J* = 6.0 Hz, 1H), 5.75 (d, *J* = 12.0 Hz, 1H), 5.47 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.96 (s, 1H), 4.85 (d, *J* = 2.4 Hz, 1H), 4.64 (d, *J* = 1.8 Hz, 1H), 3.50 (s, 3H).

A 1-dram scintillation vial was charged with crude mixture of bicyclic lactol epimers **S3,** toluene (0.1 mL, 0.1 M), Ag_2CO_3 (50 wt. % on Celite, 17 mg, 0,03 mmol, 3.0 equiv), and a magnetic stir bar under an atmosphere of argon. The reaction vessel was capped and heated to 110 ºC. After 1 h, the black suspension was allowed to cool to rt, filtered over Celite and concentrated by use of a rotary evaporator. The resulting residue was purified by flash column chromatography on silica gel using 10:90 ethyl acetate:hexanes as eluent to yield lactone **42** (3.5 mg, 0.01 mmol, 80%) as a clear oil: R_f = 0.30 (10:90 ethyl acetate:hexanes; stained with $KMnO_4$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.06 (d, *J* = 6.6 Hz, 1H), 4.98 (s, 1H), 4.84 (d, *J* =1.8 Hz, 1H), 4.62 (br s, 1H), 3.36 (s, 3H), 3.07–3.05 (m, 1H), 2.90 (dd, *J* = 18.6, 11.4 Hz, 1H), 2.66 (dd, *J* = 18.6, 3.6 Hz, 1H), 2.53 (d, *J* = 9.0 Hz, 1H), 2.37–2.34 (m, 1H), 2.22 (s, 1H), 1.96–1.91 (m, 1H), 1.85–1.80 (m, 1H), 1.80–1.71 (m, 3H), 1.63 (dt, *J* = 13.8, 4.2 Hz, 1H), 1.59–1.56 (m, 2H), 1.44–1.38 (m, 1H), 1.31–1.23 (m, 1H), 1.00 (s, 3H), 0.95 (s, 3H), 0.80 (s, 3H); ^{13}CNMR (126 MHz, $CDCl_3$) δ 175.5, 154.1, 114.6, 109.4, 109.3, 66.0, 56.6, 55.0, 54.5, 47.0, 39.9, 38.7, 37.8, 37.0, 36.8, 36.3, 34.6, 28.9, 26.4, 25.8, 21.2; IR (thin film) 2929, 2865, 1787, 1175, 1074, 1003, 932 cm^{-1}; $[\alpha]^{23}_D$ +73.9, $[\alpha]^{23}_{577}$ +77.2, $[\alpha]^{23}_{546}$ +89.4, $[\alpha]^{23}_{435}$ +153 (*c* = 1.0, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{32}O_4Na$ 371.2198; Found 371.2193.

Preparation of (+)-Cheloviolene A (7): A 1-dram scintillation vial was charged with lactone **42** (13 mg, 0.036 mmol, 1.0 equiv), 1:1 1N HCl (aq):THF (1.4 mL, 0.025 M), and a magnetic stir bar under ambient atmosphere. The resulting biphasic mixture was stirred vigorously at 40 ºC for 12 h. The reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was purified by flash column chromatography on silica gel using 20:80 ethyl acetate:hexanes as eluent to yield (+)-cheloviolene A (**7**) as a colorless solid (9 mg, 0.026 mmol, 70% yield): R_f = 0.30 (20:80 ethyl acetate:hexanes, stained with $KMnO_4$). Recrystallization of the solid from hexanes:ethyl acetate afforded (+)-cheloviolene A (**6**) as a colorless crystalline solid. The ^{1}H and ^{13}C NMR data in $CDCl_3$ and IR data were identical to that reported earlier for synthetic (+)-cheloviolene A.[31] $[\alpha]^{21}_D$ +49.1, $[\alpha]^{21}_{577}$ +52.7, $[\alpha]^{21}_{546}$ +56.2, $[\alpha]^{21}_{435}$ +77.6 (*c* = 0.11, $CHCl_3$); mp: 155 – 156 ºC (recrystallized from hexanes:ethyl acetate).

Preparation of Methyl Oxalate S4: A round-bottom flask was charged with **43** (146 mg, 0.694 mmol, 1.0 equiv), CH_2Cl_2 (7 mL, 0.1 M), DMAP (170 mg, 1.4 mmol, 2.0 equiv), Et_3N (210 mg, 2.1 mmol, 3.0 equiv), methyl chlorooxoacetate (190 µL, 2.1 mmol, 3.0 equiv), and a magnetic stir bar under ambient atmosphere. The resulting solution was heated to 35 ºC and maintained at that temperature for 30 min. After 30 min, the reaction was allowed to cool to rt, quenched with H_2O, transferred to a separatory funnel, and extracted with CH_2Cl_2 (3 x 10 mL). Combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The resulting residue was purified by flash column chromatography on silica gel using 10:90 ethyl acetate:hexanes as eluent to yield **S4** (181 mg, 0.61 mmol, 88% yield) as a clear oil: R_f = 0.12 (10:90 ethyl acetate:hexanes; stained with *p*-anisaldehyde); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.84 (s, 3H), 2.79 (td, *J* = 12.2, 3.2 Hz, 1H), 2.48–2.32 (m, 3H), 2.18 (d, *J* = 12.5 Hz, 1H), 1.98 (ddd, *J* = 15.2, 10.0, 2.9 Hz, 1H), 1.88–1.72 (m, 2H), 1.75 (s, 3H), 1.61–1.43 (m, 3H), 1.44–1.30 (m, 1H), 0.97 (s, 3H), 0.77 (s, 3H); ^{13}CNMR (126 MHz, $CDCl_3$) δ 212.5, 158.5, 156.3, 95.8, 63.2, 53.6, 49.1, 45.1, 44.1, 36.3, 34.3, 30.8, 25.2, 24.0, 20.8, 19.4; IR (thin film) 3021, 2964, 2873, 1742, 1646, 1216, 1161 cm^{-1}; $[\alpha]^{23}_D$ –104, $[\alpha]^{23}_{577}$ –113, $[\alpha]^{23}_{546}$ –131, $[\alpha]^{23}_{435}$ –247 (*c* = 0.4, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{24}O_5Na$ 319.1521; Found 319.1522.

Preparation of Lithium Oxalate 44: A round-bottom flask was charged with **S4** (177 mg, 0.597 mmol, 1.0 equiv), 1:1 THF:H_2O (6 mL, 0.1 M), and a magnetic stir bar under ambient atmosphere. After cooling the biphasic mixture to 0 ºC, 0.5 N LiOH (aq) (1.1 mL, 0.57 mmol, 0.95 equiv) was added dropwise. The mixture was then vigorously stirred at 0 ºC for 5 min. Next, the homogenous solution was concentrated by use of a rotary evaporator (50 ºC, 12 torr). The resulting colorless solid was washed with pentanes (3 x 5 mL) and dried further under high vacuum (rt, 0.5 torr) to yield **44** as a colorless solid (158 mg, 0.547 mmol, 97% yield): ^{1}H NMR (600 MHz, CD_3OD) δ 2.92 (td, *J* = 12.1, 3.3 Hz, 1H), 2.60 (td, *J* = 12.0, 6.8 Hz, 1H), 2.42 (dt, *J* = 15.0, 8.7 Hz, 1H), 2.32 (ddd, *J* = 12.3, 6.9, 2.5 Hz, 1H), 2.14 (dd, *J* = 12.5, 1.9 Hz, 1H), 1.92 (ddd, *J* = 15.0, 10.2, 3.0 Hz, 1H), 1.88–1.78 (m, 2H), 1.70 (s, 3H), 1.63–1.41 (m, 3H), 1.40–1.30 (m, 1H), 0.99 (s, 3H), 0.77 (s, 3H); ^{13}CNMR (151 MHz, CD_3OD) δ 215.7, 166.7, 166.1, 94.0, 65.2, 46.1, 45.1, 37.6, 35.1, 31.2, 26.2, 24.5, 22.1, 19.6; IR (thin film) 3513, 2900, 2819, 1694, 1448, 1420, 1050 cm^{-1}; $[\alpha]^{21}_D$ –95.8, $[\alpha]^{21}_{577}$ –101, $[\alpha]^{21}_{546}$ –116, $[\alpha]^{21}_{435}$ –199 (*c* = 0.6, CH_3OH); HRMS (ESI-TOF) m/z: $[M]^-$ Calcd for $C_{15}H_{21}O_5$ 281.1389; Found 281.1388.

Preparation of Lactone 45: A 1-dram scintillation vial was charged with **44** (29 mg, 0.1 mmol, 1.0 equiv), $(Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2 mg, 0.002 mmol, 0.02 equiv), 3:1 DME:DMF (2 mL, 0.05 M), H_2O (18 µL, 1.0 mmol, 10 equiv), **(*R*)-35** (11 mg, 0.1 mmol, 1.0 equiv), and a magnetic stir bar. The vial was then sealed with a screw cap bearing Teflon septum. The septum of the vial was pierced with a 21 gauge x 1.5'' needle that was inserted just barely through the septum with the tip of the needle kept above the fluid level inside the vial. A separate 22 gauge x 3'' needle attached to a flow of argon was also pierced through the septum, and the tip of the needle was pushed to the bottom of the vial and submersed in the fluid. The reaction mixture was degassed by sparging with argon for 15 min. Both needles were removed, and the sealed vial was then placed on a stir plate equipped with 2 x 34 W blue LED lamps and a rack to hold the vial inside of a cardboard box to block light pollution from entering the lab. The vial was placed approximately 4 cm from the lamps and stirred vigorously. The sample was irradiated by the lamps for 18 h inside the closed box, allowing the temperature of the reaction mixture to rise to 60 ºC and the air inside the box to 40–45 ºC because of heat given off from the LEDs. The reaction was allowed to cool to rt and transferred to a separatory funnel and extracted with Et_2O (3

x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was purified by flash column chromatography on silica gel using 10:90 ethyl acetate:hexanes → 15:85 ethyl acetate:hexanes as eluent to yield **45** (17 mg, 0.071 mmol, 71% yield) as a colorless solid: R_f = 0.30 (20:80 ethyl acetate:hexanes; stained with *p*-anisaldehyde); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.13 (d, *J* = 11.9 Hz, 2H), 1.99–1.85 (m, 3H), 1.72 (dddd, *J* = 24.7, 12.7, 8.8, 5.6 Hz, 4H), 1.64–1.50 (m, 2H), 1.56 (s, 3H), 1.34 (qd, *J* = 12.2, 8.3 Hz, 1H), 1.25 (td, *J* = 13.4, 13.0, 2.6 Hz, 1H), 0.91 (s, 3H), 0.87 (s, 3H); ^{13}CNMR (151 MHz, $CDCl_3$) δ 178.6, 93.1, 79.6, 56.5, 51.0, 46.5, 38.6, 37.5, 35.0, 31.6, 28.0, 27.7, 19.6, 19.0; IR (thin film) 3419, 1754, 1651, 1644, 1289, 1130 cm^{-1}; $[\alpha]^{21}_D$ +55.6, $[\alpha]^{23}_{577}$ +52.2, $[\alpha]^{23}_{546}$ +57.5, $[\alpha]^{23}_{435}$ +85.6 (*c* = 0.2, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{22}O_3Na$ 261.1467; Found 261.1466.

Preparation of Benzoate Ester S5: A 1-dram scintillation flask was charged with **45** (17 mg, 0.71 mmol, 1.0 equiv), CH_2Cl_2 (1.4 mL, 0.05 M), DMAP (9 mg, 0.07 mmol, 1.0 equiv), Et_3N (25 µL, 0.18 mmol, 2.5 equiv), 4-nitrobenzoyl chloride (16 mg, 0.085 mmol, 1.2 equiv), and a magnetic stir bar under an atmosphere of argon at rt. The flask was capped and heated to 35 ºC for 18 h. The reaction was quenched with addition of sat. $NaHCO_3$ (aq). The resulting biphasic mixture was transferred to a separatory funnel and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The resulting residue was purified by flash column chromatography on silica gel using 10:90 ethyl acetate:hexanes as eluent to yield **S5** (22 mg, 0.057 mmol, 80% yield) as a colorless solid: R_f = 0.27 (10:90 ethyl acetate:hexanes; stained with *p*-anisaldehyde). Recrystallization of the solid from hot hexanes afforded a crystal suitable for single-crystal x-ray diffraction analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 2.58 (d, *J* = 11.9 Hz, 1H), 2.47 (ddd, *J* = 15.8, 6.0, 3.1 Hz, 1H), 2.11–1.85 (m, 5H), 1.79 (dq, *J* = 11.2, 5.7, 5.3 Hz, 2H), 1.64–1.57 (m, 1H), 1.56 (s, 3H), 1.41–1.30 (m, 2H), 0.99 (s, 3H), 0.94 (s, 3H); ^{13}CNMR (126 MHz, $CDCl_3$) δ 173.8, 162.7, 151.0, 135.4, 131.1, 123.9, 92.0, 87.2, 55.4, 52.4, 44.2, 40.0, 34.9, 34.3, 30.3, 27.1, 27.0, 21.1, 20.0; IR (thin film) 2958, 2934, 2869, 1771, 1731, 1530, 1348, 1281 cm^{-1}; $[\alpha]^{22}_D$ +38.7, $[\alpha]^{22}_{577}$ +40.5, $[\alpha]^{22}_{546}$ +45.4, $[\alpha]^{22}_{435}$ +80.8 (*c* = 0.8, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{21}H_{25}NO_6Na$ 410.1580; Found 410.1599; mp: 135–137 ºC (recrystallized from hexanes).

Preparation of Hydrazone S6: A 1-dram vial was charged with **43** (10 mg, 0.05 mmol, 1.0 equiv), 1:1 THF:H_2O (0.5 mL, 0.1 M), *p*-toluenesulfonyl hydrazide (28 mg, 0.15 mmol, 3.0 equiv), CSA (3 mg, 0.02 mmol, 0.3 equiv), and a magnetic stir bar under ambient atmosphere at rt. The resulting biphasic mixture was stirred vigorously for 18 h at rt. The mixture was transferred to a separatory funnel, diluted with H_2O (5 mL), and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated by use of a rotary evaporator. The resulting residue was purified by flash column chromatography on silica gel using 20:80 ethyl acetate:hexanes as eluent to yield **S6** (18 mg, 0.048 mmol, 95% yield) as a colorless solid: R_f = 0.2 (20:80 ethyl acetate:hexanes; stained with $KMnO_4$). Recrystallization of the solid from benzene and pentanes via a vapor diffusion method afforded a crystal suitable for single-crystal x-ray diffraction analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 2.42 (s, 3H), 2.39–2.34 (m, 1H), 2.32 (d, *J* = 9.9 Hz, 1H), 2.19 (ddd, *J* = 18.4, 10.1, 6.1 Hz, 1H), 2.02–1.88 (m, 2H), 1.67–1.52 (m, 4H), 1.51–1.43 (m, 1H), 1.26 (ddd, *J* = 12.9, 11.4, 9.1 Hz, 1H), 1.13 (s, 3H), 1.07 (ddd, *J* = 13.7, 9.1, 4.7 Hz, 1H), 0.87 (s, 3H), 0.84 (s, 3H). ^{13}CNMR (151 MHz, $CDCl_3$) δ 165.5, 144.7, 135.1, 130.1, 128.4, 81.2, 52.5, 51.9, 44.6, 40.7, 35.0, 31.9, 31.6, 26.1, 25.3, 21.8, 18.9, 18.8; IR (thin film) 3426, 3224, 2964, 1633, 1598, 1455, 1336, 1166 cm^{-1}; $[\alpha]^{23}_D$ –79.2, $[\alpha]^{23}_{577}$ –81.1, $[\alpha]^{23}_{546}$ –105, $[\alpha]^{23}_{435}$ –183 (*c* = 1.3, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{30}N_2O_3Na$ 401.1875; Found 401.1868; mp: 153–156 ºC (recrystallized benzene and pentanes via a vapor diffusion method).

Preparation of Ester 66: A round-bottom flask was charged with lactone **64** (58 mg, 0.17 mmol, 1.0 equiv),[31] tetrahydrofuran (1.7 mL, 0.1 M), and a magnetic stir bar under an argon atmosphere. The solution was cooled to –78 ºC and a 1 M solution of LiHMDS in tetrahydrofuran (210 µL, 0.21 mmol, 1.2 equiv) was added dropwise. After stirring the reaction mixture for 1 h at –78 ºC, *tert*-butyl bromoacetate (38 µL, 0.26 mmol, 1.5 equiv) was added dropwise. After 1 h at –78 ºC, the reaction was quenched by addition of sat. NH_4Cl (aq) (5 mL). The resulting mixture was allowed to warm to rt and transferred to a separatory funnel and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The residue was purified by flash column chromatography on silica gel using 5:95 ethyl acetate:hexanes as eluent to yield product **66** as a clear oil (67 mg, 0.15 mmol, 87% yield): R_f = 0.19 (5:95 ethyl acetate:hexanes, stained with *p*-anisaldehyde); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.53 (d, *J* = 1.9 Hz, 1H), 3.51 (td, *J* = 10.7, 4.1 Hz, 1H), 2.88 (dt, *J* = 9.0, 4.8 Hz, 1H), 2.67 (dd, *J* = 15.4, 5.4 Hz, 1H), 2.59 (dd, *J* = 15.4, 8.1 Hz, 1H), 2.12 (dtd, *J* = 22.4, 13.1, 11.4, 5.5 Hz, 2H), 1.99 (t, *J* = 2.9 Hz, 1H), 1.68–1.60 (m, 2H), 1.60–1.15 (m, 22H), 0.98 (dt, *J* = 10.4, 6.7 Hz, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.91–0.79 (m, 8H), 0.76 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 178.6, 170.2, 101.0, 81.4, 77.2, 56.4, 47.9, 39.7, 38.9, 38.3, 35.5, 35.3, 34.6, 31.6, 28.2, 26.2, 25.4, 23.0, 22.5, 21.6, 21.5, 21.2, 20.3, 15.5; IR (thin film) 2953, 2929, 1770, 1727, 1369, 1151 cm^{-1}; $[\alpha]^{21}_D$ +78.5, $[\alpha]^{21}_{577}$ +82.1, $[\alpha]^{21}_{546}$ +88.5, $[\alpha]^{21}_{435}$ +138 (*c* = 0.27, $CHCl_3$); **HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{46}O_5Na$ 473.3243; Found 473.3250.**

Preparation of Lactol 67: A round-bottom flask was charged with **66** (64 mg, 0.14 mmol, 1.0 equiv), THF (1.2 mL, 0.1 M), and a magnetic stir bar under an argon atmosphere. After 30 min at –78 ºC, TLC analysis of the reaction (10:90 ethyl acetate:hexanes, stained with ceric ammonium molybdate) indicated presence of the starting material and additional 1M solution of DIBALH in toluene (85 µL, 0.085 mmol, 0.6 equiv) was added, followed by another portion of 1M solution of DIBALH in toluene (85 µL, 0.085 mmol, 0.6 equiv) after 30 min (total 1M solution of DIBALH in toluene added: 340 µL, 0.34 mmol, 2.4 equiv). After 30 min at –78 ºC, TLC analysis of the reaction (10:90 ethyl acetate:hexanes, stained with ceric ammonium molybdate) indicated complete consumption the starting material and the reaction was quenched by addition of 100 µL of MeOH, followed by the

addition of saturated solution of Rochelle's salt (aq) (5 mL) at –78 ºC. The reaction was allowed to warm to rt and stirred at rt for 30 min. Biphasic mixture was transferred to a separatory funnel and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by use of a rotary evaporator. The residue was purified by flash column chromatography on silica gel using 10:90 ethyl acetate:hexanes as eluent to yield a 2.1:1 mixture of lactol epimers **67** as a colorless solid (46 mg, 0.10 mmol, 72% yield): R_f = 0.21 (10:90 ethyl acetate:hexanes, stained with ceric ammonium molybdate); ^{1}H NMR (600 MHz, C_6D_6) δ 5.84 (t, *J* = 6.3 Hz, 1H), 5.53 (s, 2H), 5.37 (d, *J* = 2.3 Hz, 2H), 5.34 (d, *J* = 2.6 Hz, 1H), 3.65 (qd, *J* = 10.9, 3.9 Hz, 3H), 3.23 (d, *J* = 5.5 Hz, 2H), 2.97–2.80 (m, 2H), 2.69–2.62 (m, 1H), 2.62–2.46 (m, 8H), 2.41 (dt, *J* = 9.9, 4.9 Hz, 2H), 2.21 (d, *J* = 12.3 Hz, 1H), 2.16 (d, *J* = 11.9 Hz, 2H), 2.05–1.98 (m, 1H), 1.85–1.74 (m, 2H), 1.60–1.07 (m, 71H), 1.03 (d, *J* = 6.9 Hz, 6H), 1.01 (d, *J* = 7.1 Hz, 6H), 0.98–0.87 (m, 16H), 0.85 (d, *J* = 6.5 Hz, 6H), 0.83 (d, *J* = 6.5 Hz, 4H), 0.80–0.71 (m, 6H); ^{13}C NMR (151 MHz, C_6D_6) δ 172.8, 172.3, 104.7, 103.2, 102.0, 101.0, 80.9, 80.4, 75.6, 75.4, 61.1, 58.9, 49.2, 49.1, 44.8, 41.5, 40.9, 40.8, 40.5, 37.7, 37.6, 37.2, 36.8, 36.7, 35.4, 35.3, 32.2, 32.1, 28.7, 28.6, 27.1, 27.0, 25.8, 23.9, 23.6, 23.1, 22.52, 22.47, 22.45, 22.4, 22.03, 21.95, 21.4, 21.1, 16.54, 16.46; IR (thin film) 3463, 3438, 2924, 2867, 1704, 1636, 1367, 1152 cm^{-1}; $[\alpha]^{21}_D$ +101, $[\alpha]^{21}_{577}$ +101, $[\alpha]^{21}_{546}$ +112, $[\alpha]^{21}_{435}$ +159 (*c* = 0.15, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{27}H_{48}O_5Na$ 475.3399; Found 475.3395.

Preparation of Dioxabicyclo[3.3.0]octan-3-one 68: A 2-dram scintillation vial was charged with lactol **67** (34 mg, 0.075 mmol, 1.0 equiv), 1:1 4 M HCl (aq):THF (3 mL, 0.025 M), and a magnetic stir bar under ambient atmosphere. The resulting biphasic mixture was stirred vigorously at rt for 30 min. The reaction mixture was transferred to a separatory funnel and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated by use of a rotary evaporator. The residue was purified by flash column chromatography on silica gel using 10:90 ethyl acetate:hexanes → 25:75 ethyl acetate:hexanes as eluent to yield product **68** as a colorless solid (11 mg, 0.046 mmol, 61% yield): R_f = 0.30 (30:70 ethyl acetate:hexanes, stained with ceric ammonium molybdate). Spectral data were consistent with reported values.[31]

Preparation of Methyl Oxalate S7: A round-bottom flask was charged with **54** (560 mg, 2.7 mmol, 1.0 equiv), DMAP (33 mg, 0.27 mmol, 0.1 equiv), dichloromethane (13 mL, 0.20 M), and a stir bar under ambient atmophere. Next, Et_3N (0.45 mL, 3.2 mmol, 1.2 equiv) and methyl chlorooxoacetate (0.30 mL, 3.2 mmol, 1.2 equiv) were added sequentially. The resulting yellow solution was maintained at rt for 10 min, at which point TLC analysis (10:90 ethyl acetate:hexanes, stained with *p*-anisaldehyde) indicated complete consumption of the starting material. The reaction was quenched via addition of sat. NH_4Cl (aq) (15 mL). The resulting biphasic mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The crude product was purified by flash column chromatography on silica gel using 5:95 ethyl acetate:hexanes as eluent to yield the desired product **S7** as a clear oil (720 mg, 2.45 mmol, 91% yield): R_f = 0.43 (10:90 ethyl acetate:hexanes, stained with *p*-anisaldehyde); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.92 (d, *J* = 2.3 Hz, 1H), 4.86 (d, *J* = 2.3 Hz, 1H), 3.88 (s, 3H), 3.20 (dd, *J* = 8.1, 1.7 Hz, 1H), 2.44 (dddd, *J* = 12.0, 10.1, 3.4, 1.6 Hz, 1H), 2.38–2.26 (m, 2H), 1.92–1.72 (m, 4H), 1.69–1.59 (m, 2H), 1.49 (s, 3H), 1.45–1.31 (m, 1H), 1.25 (dt, *J* = 14.3, 3.5 Hz, 1H), 0.98 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.3, 157.1, 150.2, 117.2, 99.7, 57.7, 53.5, 50.9, 37.6, 37.3, 36.2, 35.9, 33.9, 28.7, 26.1, 24.3, 21.7; IR (thin film) 2953, 2937, 2867, 1766, 1739, 1154 cm^{-1}; $[\alpha]^{23}_D$ +11.5, $[\alpha]^{23}_{577}$ +13.6, $[\alpha]^{23}_{546}$ +14.4, $[\alpha]^{23}_{435}$ +29.1 (*c* = 1.0, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{26}O_4Na$ 317.1729; Found 317.1732.

Preparation Lithium Oxalate 69: A round-bottom flask was charged with **S7** (700 mg, 2.38 mmol, 1.0 equiv), 1:1 THF:H_2O (4.8 mL, 0.5 M), and a stir bar under ambient atmosphere. The resulting biphasic mixture was cooled to 0 ºC. Next, 0.5N LiOH (aq) (4.8 mL, 1.0 equiv) was added dropwise. The mixture was then stirred vigorously at 0 ºC for 5 min. The stir bar was removed and homogenous solution was concentrated by use of a rotary evaporator with water bath warmed gradually from rt to 45 ºC. The resulting colorless solid was washed with pentanes (3 x 5 mL) and dried further under high vacuum to yield product **69** as a colorless solid (680 mg, 2.38 mmol, 100% yield); ^{1}H NMR (500 MHz, CD_3OD) δ 4.91 (d, *J* = 2.6 Hz, 1H), 4.86 (d, *J* = 2.6 Hz, 1H), 2.51–2.37 (m, 2H), 2.35–2.27 (m, 1H), 1.95–1.84 (m, 1H), 1.84–1.67 (m, 5H), 1.46 (s, 3H), 1.43–1.34 (m, 1H), 1.31–1.15 (m, 1H), 1.00 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (126 MHz, CD_3OD) δ 167.0, 166.3, 152.7, 116.8, 97.0, 58.5, 51.9, 38.6, 38.5, 37.0, 36.9, 34.2, 29.8, 26.4, 25.1, 22.2; IR (thin film) 2954, 2935, 2865, 1710, 1693, 1667, 1251, 1161 cm^{-1}; $[\alpha]^{23}_D$ +20.9, $[\alpha]^{23}_{577}$ +22.7, $[\alpha]^{23}_{546}$ +21.4, $[\alpha]^{23}_{435}$ +40.4 (*c* = 0.6, MeOH); HRMS (ESI-TOF) m/z: $[M]^-$ Calcd for $C_{16}H_{23}O_4$ 279.1596; Found 279.1595.

Preparation of Potassium Oxalate 72: A round-bottom flask was charged with **S7** (81 mg, 0.28 mmol, 1.0 equiv), 1:1 THF:H_2O (1.4 mL, 0.2 M), and a stir bar under ambient atmosphere. The resulting biphasic mixture was cooled to 0 ºC. Next, 0.85N KOH (aq) (320 µL, 1.0 equiv) was added dropwise. The mixture was then stirred vigorously at 0 ºC for 5 min. The stir bar was removed and homogenous solution was concentrated by use of a rotary evaporator with water bath warmed gradually from rt to 45 ºC. The resulting colorless solid was washed with pentanes (3 x 5 mL) and dried further under high vacuum to yield product **72** as a colorless solid (86 mg, 0.28 mmol, 99% yield); ^{1}H NMR (600 MHz, CD_3OD) 4.93–4.89 (m, 2H), 2.49–2.38 (m, 2H), 2.31 (d, *J* = 12.9 Hz, 1H), 1.93–1.84 (m, 1H), 1.84–1.69 (m, 5H), 1.48–1.44 (m, 3H), 1.41 (q, *J* = 12.3, 11.4 Hz, 1H), 1.25 (d, *J* = 13.8 Hz, 1H), 1.00 (t, *J* = 2.5 Hz, 3H), 0.95–0.91 (m, 3H); ^{13}C NMR (151 MHz, CD_3OD) δ 166.9, 166.5, 152.8, 117.0, 97.2, 58.7, 52.0, 38.7, 38.6, 37.2, 37.1, 34.3, 30.0, 26.5, 25.3, 22.4; IR (thin film) 3608, 1713, 1663, 1641, 1233, 893 cm^{-1}; $[\alpha]^{23}_D$ +14.6, $[\alpha]^{23}_{577}$ +14.9, $[\alpha]^{23}_{546}$ +16.7, $[\alpha]^{23}_{435}$ +31.2 (*c* = 1.7, MeOH); HRMS (ESI/TOF) *m/z* calculated for $C_{16}H_{23}O_4$ $[M]^-$ 279.1596, observed 269.1598. HRMS (ESI-TOF) m/z: $[M]^-$ Calcd for $C_{16}H_{23}O_4$ 279.1596; Found 279.1598.

Preparation of Lactone 70 from 69: On the bench under ambient atmosphere, 1-dram scintillation vial was charged with **69** (86 mg, 0.30 mmol, 1.0 equiv), ***ent*-59** (82 mg, 0.30 mmol, 1.0 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (7 mg, 0.006

mmol, 0.02 equiv), tetrahydrofuran (500 µL, 0.6 M), H_2O (27 µL, 1.5 mmol, 5 equiv), and a stir bar. The vial was then sealed with screw cap bearing Teflon septum. The septum of the vial was pierced with a 21 gauge x 1.5'' needle that was inserted just barely through the septum with the tip of the needle kept above the fluid level inside the vial. A separate 22 gauge x 3'' needle attached to a flow of argon was also pierced through the septum, and the tip of the needle was pushed to the bottom of the vial and submersed in the fluid. The reaction mixture was degassed by sparging with argon for 15 min. Both needles were removed, and the sealed vial was then placed on a stir plate equipped with 2 x 34 W blue LED lamps and a rack to hold the vial inside of a cardboard box to block light pollution from entering the lab. The vial was placed approximately 4 cm from the lamps and stirred vigorously. The sample was irradiated by the lamps for 18 h inside the closed box, allowing the temperature of the reaction mixture to rise to 60 ºC and the air inside the box to 40–45 ºC because of heat given off from the LEDs. The reaction was allowed to cool to rt, diluted with Et_2O (1 mL) and filtered over $MgSO_4$. The filtrate was concentrated by use of a rotary evaporator. The crude product was purified by flash column chromatography on silica gel using 2:98 ethyl acetate:hexanes as eluent to yield the desired product **70** as a thick colorless foam (102 mg, 0.22 mmol, 73% yield): R_f = 0.33 (5:95 ethyl acetate:hexanes, stained with *p*-anisaldehyde); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.59 (d, *J* = 3.3 Hz, 1H), 4.87 (s, 1H), 4.62 (s, 1H), 3.59 (td, *J* = 10.7, 4.7 Hz, 1H), 2.68–2.59 (m, 2H), 2.36 (dd, *J* = 12.3, 5.4 Hz, 1H), 2.26–2.17 (m, 1H), 2.14 (d, *J* = 11.1 Hz, 1H), 2.05 (q, *J* = 9.8 Hz, 1H), 1.83–1.73 (m, 5H), 1.73–1.57 (m, 5H), 1.45–1.34 (m, 2H), 1.28 (dd, *J* = 12.4, 6.7 Hz, 2H), 1.03–0.97 (m, 4H), 0.97–0.92 (m, 7H), 0.92–0.86 (m, 4H), 0.84 (s, 3H), 0.80 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.6, 153.4, 115.2, 101.9, 77.7, 60.9, 55.7, 53.7, 52.2, 48.1, 47.9, 40.0, 37.7, 37.4, 37.0, 36.5, 34.5, 31.6, 28.9, 25.8, 25.7, 25.4, 23.2, 22.5, 21.2, 21.1, 15.7; IR (thin film) 2953, 2922, 2868, 1789, 1364 cm^{-1}; $[\alpha]^{23}_{D}$ –52.0, $[\alpha]^{23}_{577}$ –54.3, $[\alpha]^{23}_{546}$ –65.8, $[\alpha]^{23}_{435}$ –104 (*c* = 0.6, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{45}ClO_3Na$ 487.2955; Found 487.2971.

Preparation of Lactone 70 from 72: On the bench under ambient atmosphere, 1-dram scintillation vial was charged with **72** (63 mg, 0.20 mmol, 1.0 equiv), ***ent*-59** (55 mg, 0.20 mmol, 1.0 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5 mg, 0.004 mmol, 0.02 equiv), tetrahydrofuran (330 µL, 0.6 M), H_2O (18 µL, 1.0 mmol, 5 equiv), and a stir bar. The vial was then sealed with screw cap bearing Teflon septum. The septum of the vial was pierced with a 21 gauge x 1.5'' needle that was inserted just barely through the septum with the tip of the needle kept above the fluid level inside the vial. A separate 22 gauge x 3'' needle attached to a flow of argon was also pierced through the septum, and the tip of the needle was pushed to the bottom of the vial and submersed in the fluid. The reaction mixture was degassed by sparging with argon for 15 min. Both needles were removed, and the sealed vial was then placed on a stir plate equipped with 2 x 34 W blue LED lamps and a rack to hold the vial inside of a cardboard box to block light pollution from entering the lab. The vial was placed approximately 4 cm from the lamps and stirred vigorously. The sample was irradiated by the lamps for 18 h inside the closed box, allowing the temperature of the reaction mixture to rise to 60 ºC and the air inside the box to 40–45 ºC because of heat given off from the LEDs. The reaction was allowed to cool to rt, diluted with Et_2O (1 mL) and filtered over $MgSO_4$. The filtrate was concentrated by use of a rotary evaporator. The crude product was purified by flash column chromatography on silica gel using 2:98 ethyl acetate:hexanes as eluent to yield the desired product **70** as a thick colorless foam (67 mg, 0.14 mmol, 72% yield): R_f = 0.33 (5:95 ethyl acetate:hexanes, stained with *p*-anisaldehyde).

Preparation of Lactone 71 from 70: On the bench under ambient atmosphere, 1-dram scintillation vial was charged with **70** (86 mg, 0.18 mmol, 1.0 equiv), Bu_3N (44 µL, 1.8 mmol, 10 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (4 mg, 0.004 mmol, 0.02 equiv), tetrahydrofuran (1.8 mL, 0.1 M), H_2O (33 µL, 1.8 mmol, 10 equiv), and a stir bar. The vial was then sealed with screw cap bearing Teflon septum. The septum of the vial was pierced with a 21 gauge x 1.5'' needle that was inserted just barely through the septum with the tip of the needle kept above the fluid level inside the vial. A separate 22 gauge x 3'' needle attached to a flow of argon was also pierced through the septum, and the tip of the needle was pushed to the bottom of the vial and submersed in the fluid. The reaction mixture was degassed by sparging with argon for 15 min. Both needles were removed, and the sealed vial was then placed on a stir plate equipped with 2 x 34 W blue LED lamps and a rack to hold the vial inside of a cardboard box to block light pollution from entering the lab. The vial was placed approximately 4 cm from the lamps and stirred vigorously. The sample was irradiated by the lamps for 4 h inside the closed box, allowing the temperature of the reaction mixture to rise to 60 ºC and the air inside the box to 40–45 ºC because of heat given off from the LEDs. The reaction was allowed to cool to rt and transferred to a separatory funnel with Et_2O (10 mL). The solution was then sequentially washed with 1N HCl (aq) (10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The crude product was purified by flash column chromatography on silica gel using 2:98 ethyl acetate:hexanes as eluent to yield the desired product **71** as a thick colorless foam (79 mg, 0.18 mmol, 100% yield): R_f = 0.28 (5:95 ethyl acetate:hexanes, stained with *p*-anisaldehyde). Spectral data were consistent with reported values.[31]

Preparation of Lactone 71 from 69: On the bench under ambient atmosphere, 1-dram scintillation vial was charged with 69 (86 mg, 0.30 mmol, 1.0 equiv), *ent*-59 (82 mg, 0.30 mmol, 1.0 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (7 mg, 0.006 mmol, 0.02 equiv), tetrahydrofuran (500 µL, 0.6 M), H_2O (27 µL, 1.5 mmol, 5 equiv), and a stir bar. The vial was then sealed with screw cap bearing Teflon septum. The septum of the vial was pierced with a 21 gauge x 1.5'' needle that was inserted just barely through the septum with the tip of the needle kept above the fluid level inside the vial. A separate 22 gauge x 3'' needle attached to a flow of argon was also pierced through the septum, and the tip of the needle was pushed to the bottom of the vial and submersed in the fluid. The reaction mixture was degassed by sparging with argon for 15 min. Both needles were removed, and the sealed vial was then placed on a stir plate equipped with 2 x 34 W blue LED lamps and a rack to hold the vial inside of a cardboard box to block light pollution from entering the lab. The vial was placed approximately 4 cm from the lamps and stirred vigor-

ously. The sample was irradiated by the lamps for 18 h inside the closed box, allowing the temperature of the reaction mixture to rise to 60 ºC and the air inside the box to 40–45 ºC because of heat given off from the LEDs. After 18 h, a degassed solution of Bu_3N (0.7 mL, 3 mmol, 10 equiv) in tetrahydrofuran (2.5 mL, 0.12 M) was added via syringe. The sample was irradiated by lamps for additional 4 h inside the closed box. The reaction was allowed to cool to rt and transferred to a separatory funnel with Et_2O (15 mL). The solution was then sequentially washed with 1N HCl (aq) (10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The crude product was purified by flash column chromatography on silica gel using 2:98 ethyl acetate:hexanes as eluent to yield the desired product 71 as a thick colorless foam (97 mg, 0.23 mmol, 75% yield): R_f = 0.28 (5:95 ethyl acetate:hexanes, stained with *p*-anisaldehyde). Spectral data were consistent with reported values.[31]

Preparation of Ester 73: A round-bottom flask was charged with **71** (420 mg, 0.98 mmol, 1.0 equiv), tetrahydrofuran (10 mL, 0.1 M), and a stir bar under an argon atmosphere. The solution was cooled to –78 ºC. Next, a 1M solution of LiHMDS in tetrahydrofuran (1.2 mL, 1.2 mmol, 1.2 equiv) was added dropwise. After stirring the reaction mixture for 15 min at –78 ºC, *tert*-butyl bromoacetate (220 µL, 1.5 mmol, 1.5 equiv) was added dropwise. After 1 h at –78 ºC, the reaction was quenched via addition of sat. NH_4Cl (aq) (10 mL). The resulting mixture was allowed to warm to rt and transferred to a separatory funnel and extracted with Et_2O (3 x 25 mL). Combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The crude product was purified by flash column chromatography on silica gel using 2:98 ethyl acetate:hexanes as eluent to yield the desired product **73** as a clear oil (480 mg, 2.45 mmol, 91% yield): R_f = 0.31 (5:95 ethyl acetate:hexanes, stained with *p*-anisaldehyde); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.58 (d, *J* = 1.3 Hz, 1H), 4.85 (d, *J* = 2.2 Hz, 1H), 4.62 (d, *J* = 2.1 Hz, 1H), 3.55 (td, *J* = 10.7, 4.2 Hz, 1H), 2.86 (ddd, *J* = 8.6, 5.3, 2.8 Hz, 1H), 2.72 (dd, *J* = 15.3, 5.3 Hz, 1H), 2.62 (d, *J* = 8.8 Hz, 1H), 2.60 (d, *J* = 9.0 Hz, 1H), 2.37–2.30 (m, 1H), 2.18–2.08 (m, 3H), 2.02 (dt, *J* = 11.2, 8.0 Hz, 1H), 1.82–1.71 (m, 3H), 1.71–1.60 (m, 5H), 1.47 (s, 9H), 1.46–1.42 (m, 2H), 1.38 (dt, *J* = 13.7, 3.3 Hz, 2H), 1.25 (dd, *J* = 10.4, 3.3 Hz, 2H), 1.03–0.95 (m, 4H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.89–0.82 (m, 2H), 0.79 (s, 3H), 0.77 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 179.1, 170.5, 154.2, 114.9, 102.4, 81.7, 57.0, 56.3, 53.8, 48.3, 48.1, 40.2, 40.0, 39.5, 38.0, 37.5, 37.2, 36.7, 34.74, 34.70, 31.8, 29.3, 28.49, 28.46, 26.00, 25.95, 25.8, 23.2, 22.7, 21.5, 21.3, 15.7; IR (thin film) 2953, 2924, 2869, 1780, 1732, 1456, 1367, 1152 cm^{-1}; $[\alpha]^{23}_{D}$ –41.9, $[\alpha]^{23}_{577}$ –45.2, $[\alpha]^{23}_{546}$ –52.6, $[\alpha]^{23}_{435}$ –83.9 (*c* = 0.9, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{34}H_{56}O_5Na$ 567.4025; Found 567.4030.

Preparation of (+)-Cheloviolene B (8): A round-bottom flask was charged with **73** (278 mg, 0.51 mmol, 1.0 equiv), toluene (5.1 mL, 0.1 M), and a stir bar under an argon atmosphere. The solution was cooled to to –78 ºC. Next, a 1M solution of DIBALH in toluene (610 µL, 0.61 mmol, 1.2 equiv) was added dropwise. After 1 h, TLC analysis of the reaction (10:90 ethyl acetate:hexanes, stained with ceric ammonium molybdate) indicated presence of the starting material and additional 1M solution of DIBALH in toluene (300 µL, 0.3 mmol, 0.5 equiv) was added, followed by another portion of 1M solution of DIBALH in toluene (300 µL, 0.3 mmol, 0.5 equiv) after 30 min (total 1M solution of DIBALH in toluene added: 1.2 mL, 1.2 mmol). After 30 min, TLC analysis indicated complete consumption of the starting material and the reaction was quenched via addition of 100 µL of MeOH, followed by the addition of saturated solution of Rochelle's salt (aq) (10 mL) at –78 ºC. The reaction was allowed to warm to rt and stirred at rt for 30 min. Biphasic mixture was transferred to a separatory funnel and extracted with Et_2O (3 x 25 mL). Combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The crude product was quickly passed though a pH 7 silica gel[83] column using 5:95 ethyl acetate:hexanes to elute crude lactol epimers **75** as a clear oil [crude mass: 155 mg; 1.1:1 dr; R_f minor = 0.45; R_f major = 0.3 (10:90 ethyl acetate:hexanes, stained with ceric ammonium molybdate); diagnostic ^{1}H NMR shifts (600 MHz, $CDCl_3$): major: δ 5.26 (t, *J* = 4.6 Hz, 1H), 5.23 (d, *J* = 1.5 Hz, 1H), 4.82 (d, *J* = 2.3 Hz, 1H), 4.65 (d, *J* = 2.3 Hz, 1H); minor: δ 5.52 (dd, *J* = 7.9, 5.7 Hz, 1H), 5.20 (d, *J* = 2.3 Hz, 1H), 4.81 (d, *J* = 2.2 Hz, 1H), 4.60 (d, *J* = 2.3 Hz, 1H)] and 10:90 ethyl acetate:hexanes to elute crude bicyclic lactol epimers **76** a a clear oil [crude mass: 72 mg; 1.7:1 dr; R_f = 0.15 (10:90 ethyl acetate:hexanes, stained with ceric ammonium molybdate); diagnostic ^{1}H NMR shifts (600 MHz, $CDCl_3$): major: δ 5.81 (d, *J* = 6.0 Hz, 1H), 5.46 (dd, *J* = 11.1, 5.5 Hz, 1H), 5.25 (s, 1H), 4.84 (s, 1H), 4.60 (s, 1H); minor: δ 5.89 (d, *J* = 5.8 Hz, 1H), 5.67–5.62 (m, 1H), 5.35 (s, 1H), 4.82 (s, 1H), 4.61 (s, 1H)].

A 2-dram scintillation vial was charged with crude bicyclic lactol epimers **76** (72 mg, 0.15 mmol, 1.0 equiv), dichloromethane (1.5 mL, 0.1 M), and a stir bar under ambient atmosphere. Next, PCC (65 mg, 0.30 mmol, 2.0 equiv) was added in one portion at rt. Heterogeneous reaction mixture was stirred vigorously at rt for 6 h, at which point TLC analysis (10:90 ethyl acetate:hexane, stained with ceric ammonium molybdate) indicated complete consumption of the starting material. The reaction mixture was filtered over pH 7 silica gel plug using 10:90 ethyl acetate:hexanes and concentrated by use of a rotary evaporator to yield crude bicyclic lactone **77** as a clear oil [crude mass: 70 mg; R_f = 0.24 (10:90 ethyl acetate:hexanes, stained with ceric ammonium molybdate); diagnostic ^{1}H NMR shifts (600 MHz, $CDCl_3$) δ 6.03 (d, *J* = 6.0 Hz, 1H), 5.42 (s, 1H), 4.84 (d, *J* = 2.1 Hz, 1H), 4.61 (d, *J* = 2.1 Hz, 1H)].

A 20 mL scintillation vial was charged with crude lactol epimers **75** (155 mg, 0.28 mmol, 1.0 equiv), crude bicyclic lactone **77** (70 mg, 0.15 mmol, 1.0 equiv), 1:1 4N HCl (aq):THF (17 mL, 0.025 M), and a stir bar under ambient atmosphere. The resulting biphasic mixture was stirred vigorously at rt for 24 h. The reaction mixture was transferred to a separatory funnel and extracted with Et_2O (3 x 25 mL). Combined organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. The crude product was purified by flash column chromatography on silica gel using 10:90 ethyl acetate:hexanes → 20:80 ethyl acetate:hexanes as eluent to yield (+)-cheloviolene B (**8**) as a colorless solid (90 mg, 0.27 mmol, 53% yield from **73**): R_f = 0.15 (20:80 ethyl acetate:hexanes, stained with ceric ammonium molybdate). Spectral data were consistent with reported values.[31]

Acid-Catalyzed Hydration of (+)-Dendrillolide C (11): A 1-dram scintillation vial was charged with **11** (9 mg, 0.028

mmol, 1 equiv), 1:1 4 M HCl (aq):THF (0.6 mL, 0.025 M), and a magnetic stir bar. The resulting heterogeneous mixture was stirred vigorously at 40 ºC for 18 h. The reaction mixture was diluted with H_2O (1 mL) and extracted with Et_2O (3 x 2 mL). Organic layers were dried over $MgSO_4$ and concentrated by use of a rotary evaporator. Integration of ^1H NMR spectrum [$CDCl_3$, 600 MHz: shifts corresponding to **8**: δ 6.09 (d, *J* = 6.0 Hz, 1H), 5.64 (s, 1H), 4.83 (d, *J* = 2.0 Hz, 1H), 4.61 (d, *J* = 2.0 Hz, 1H); shifts corresponding to **79**: δ 7.42 (d, *J* = 1.6 Hz, 1H), 7.21(d, *J* = 1.7 Hz, 1H), 4.89 (d, *J* = 2.2 Hz, 1H), 4.71 (d, *J* = 2.1 Hz, 1H), 3.63 (s, 2H)] of the crude reaction mixture was used to establish the ratio of the two products formed, 1.2 : 1 (+)-cheloviolene B (**8**) : furan **79**.[31]

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and CIF files for X-ray structures of compounds **7**, **S5**, **S6**, ***ent*-59**, and **8**. 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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