Total Synthesis of (-)-Chromodorolide B By a Computationally-Guided Radical Addition/Cyclization/Fragmentation Cascade

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ABSTRACT: The first total synthesis of a chromodorolide marine diterpenoid is described. The core of the diterpenoid is constructed by a bimolecular radical addition/cyclization/fragmentation cascade that unites two complex fragments and forms two C-C bonds and four contiguous stereogenic centers of (-)-chromodorolide B in a single step. This coupling step is initiated by visible-light photocatalytic fragmentation of a redox-active ester, which can be accomplished in the presence of an iridium or a less-precious electron-rich dicyanobenzene photocatalyst, and employs equimolar amounts of the two addends. Computational studies guided the development of this central step of the synthesis and provide insight into the origin of the observed stereoselectivity.

INTRODUCTION

Convergent strategies where advanced fragments of a target molecule are prepared in parallel and joined together at the latest possible stage in a synthesis are nearly always more efficient than linear strategies. A corollary of this fact is the importance of reactions that are capable of combining complex molecules efficiently with high regio- and stereoselectivity. Recent investigations have shown that bimolecular-coupling reactions of tertiary carbon radicals can unite advanced synthetic fragments of structurally complex natural products in an efficient fashion. Cascade reactions in which an intermediate produced in a bond-forming reaction propagates to construct additional bonds of a target molecule also typically increase efficiency in a chemical synthesis. Radical cascade reactions, in particular intramolecular radical cascades, have long played a significant role in the efficient construction of complex molecules. Much less developed are strategies in which a bimolecular radical coupling reaction initiates a further bond-forming cascade sequence. The discovery of such a stereoselective sequence, whose optimization was guided by computational analysis, led to the first total synthesis of the marine diterpenoid chromodorolide B and is the subject of this article.

BACKGROUND

The rearranged spongian diterpenoids are a large and structurally diverse family of natural products, which have been isolated largely from marine sources (Figure 1). Distinct members of this group are characterized by the presence of a hydrophobic unit connected by a single bond to a highly oxygenated cis-2,8-dioxabicyclo[3.3.0]octan-3-one fragment, as exemplified by dermalactone (1), norrisolide (2), cheloviolene A (3), macfarladin C (4), or a 2,7-dioxabicyclo[3.2.1]octan-3-one fragment as found in aplyviolene (5), macfarlandin E (6), shahamin F (7), verrielactone (8), and norrandin (9). In chromodorolides A-E (10-14), these bicyclic frameworks are appended to an additional oxygenated cyclopentane ring. The chromodorolides have been isolated from nudibranchs in the genus Chromodoris and from encrusting sponges on which these nudibranchs potentially feed. Chromodorolide A (10) was first reported in 1989 by Anderson and Clardy, with its novel structure being revealed by X-ray crystallography. Two years later these workers described a second diterpenoid found in skin extracts of the tropical dorid nudibranch Chromodoris cavae, which showed a high frequency carbonyl stretching band at 1812 cm⁻¹ in its IR spectrum. Detailed analyses of ¹H and ¹³C NMR spectra indicated that this diterpenoid, chromodorolide B (11), had the same chromodorane carbon skeleton as chromodorolide A, but the bridging lactone ring in this case was 5-membered. Analogues of 10 and 11, chromodorolides C-E (12-14) that display different degrees of acetylation of the vicinal hydroxyl substituents were isolated subsequently from two different marine sponges. The chromodorolides are the most structurally intricate of the spongian diterpenoids, with 10...
contiguous stereocenters arrayed upon their pentacyclic ring systems. Prior to the investigations reported in this account, the absolute configuration of the chromodorolides was proposed upon the basis of their presumed biosynthesis from diterpenoids having the spongian ring system.²⁰

Modest in vitro antitumor, nematocidal and antimicrobial activities have been reported for various chromodorolides.²⁰,²¹,²²,²³ Because of their structural relationship with molecules such as norrisolide (2), chelovirole A (3) and macfarlandin E (6),²¹,²²,²³ which have pronounced effects on the Golgi apparatus, the activity of the chromodorolides on the structure and function of the Golgi apparatus is potentially more significant. In our own investigations of analogues harboring 2,7-dioxabicyclo[3.2.1]octan-3-one or cis-2,8-dioxabicyclo[3.3.0]octan-3-one fragments, we have identified conjugation of these ring systems with lysine side chains of proteins to form pyrrole adducts as potentially involved in the biological activities of diterpenoids such as those depicted in Figure 1.²² As a result of the little-studied biological activity of the chromodorolides, and the challenge apparent in assembling these densely functionalized diterpenoids, we initiated studies to develop chemical syntheses of the chromodorolides. In this account, we detail the investigations that led to a concise, stereocontrolled total synthesis of (−)-chromodorolide B (11).

**RESULTS AND DISCUSSION**

**General Synthetic Strategy.** Retrosynthetically, we envisioned disconnecting the lactone bonds in 10 and 12 to arrive at a common tetracyclic acid intermediate 15 (Scheme 1). We hypothesized that both bridged and fused tricyclic frameworks could be prepared from acid 15 by site-selective oxocarbenium ion formation, followed by intramolecular lactonization. The cis-2,8-dioxabicyclo[3.3.0]octan-3-one fragment of chromodorolide C (12) is likely to be accessed most readily, as kinetic favored 5-membered ring closure of 17 could dominate even if oxocarbenium ion formation were unselective yet reversible.²² In contrast, to construct the 2,7-dioxabicyclo[3.2.1]octan-3-one fragment found in chromodorolide A (10) regioselective activation at C-15 would be required to permit less-kinetically favored lactonization of oxocarbenium ion 16. The successful development of a strategy to form tetracyclic intermediate 15 and its conversion to (−)-chromodorolide B (11) is detailed in this report.²⁰

**Early Studies.** Our initial thoughts on accessing the highly oxygenated bicyclic motif found in 15 envisaged late-stage dihydroxylation of an alkene precursor (Scheme 2). We expected that oxidation of an intermediate such as 18 would take place from the convex face opposite the bulky hydridane fragment to generate 19. As this step would occur late in the synthesis, we examined this conversion initially in a model.
system harboring an isopropyl group in place of the hydrindane fragment. \textsuperscript{23} cis-Oxabicyclo[3.3.0]octenone 20 was readily assembled from an allenoate precursor by a diastereoselective phosphine-promoted (3+2) annulation.\textsuperscript{24} To our surprise, dihydroxylation of 20 took place with high stereoselectivity from the concave face to give mainly diol 21. Other oxidants such as \textit{m}-chloroperoxybenzoic acid or dimethyldioxirane behaved similarly, giving crystalline epoxide 23 as the predominant product.\textsuperscript{25,26a} Computational studies by the Houk group suggested that the contrasteric selectivity for dihydroxylation of the enoate 20 arose from torsional effects.\textsuperscript{23,27} Torsional, electrostatic and steric effects can all influence stereoselection in dihydroxylations of \textit{cis}-bicyclo[3.3.0]octenes, and a more general discussion of this issue has been published.\textsuperscript{23}

\textbf{Revised Synthesis Plan: A Bimolecular Radical Addition/Cyclization/Fragmentation Cascade.} As installation of the \textit{cis}-diol functionality did not appear to be feasible from a \textit{cis}-oxabicyclo[3.3.0]octenone precursor, we turned to a plan wherein the \textit{cis}-diol would be incorporated early in the synthetic sequence (Figure 2A). Disconnection of the lactone ring of chromodorolides A or B series leads to intermediate 24. Further simplification leads...
undergo 5-alkoxyacyl radical precursor acetonide (2,2-dimethyl-1,3-dioxolane) radical enantiopure starting materials: chromodorolides from three well known derived acetonide vinyl iodide alcohol hydrindane acetonide alkoxybutenolide acetonide carboxylate cyclopentane ring of key intermediate functionalities at C-11, C-12 and C-17.

We were attracted to a carbon radical-based methyl substituent to install the C-9 stereocenter. The stage hydrogenation of its double bond would be compatible with pre-installed oxygen.

We envisioned the trans-hydrindane acetonide 26 evolving from allylic alcohol 28, which in turn would result from the addition of a vinylic nucleophile generated from vinyl iodide 29 and aldehyde 30. As (S,S)-trimethylhydrindanone 31 is the obvious precursor of iodide 29, and (R,R)-tartaric acid derived acetonide 32 of aldehyde 30, the plan outlined in Figure 2A projects assembling the chromodorolides from three well known enantiopure starting materials: 27, 31, and 32.

In the projected cascade sequence, chiral acetonide (2,2-dimethyl-1,3-dioxolane) radical A, formed from oxidative decarboxylation of precursor 26, would couple with butenolide 27 to generate alkoxyacyl radical B which would undergo 5-exo cyclization with the proximal alkene to generate intermediate C (Figure 2B). The radical cascade would then be terminated by β-fragmentation of the C-X bond (X = Cl or SR) of this intermediate to yield pentacyclic product 25. If successful, the proposed bimolecular radical addition/cyclization/fragmentation (ACF) cascade would form two C-C bonds and four contiguous stereocenters of the chromodorolides in a single step. The stereochemical outcome of two steps would be critical to the efficiency of the proposed cascade sequence (Figure 2B). First, the Giese reaction to unite acetonide radical A with butenolide 27 would have to correctly set the C-12 and C-13 stereocenters.33,34 Ample precedent existed that this union would take place from the butenolide face opposite to the alkoxy group to correctly set the C-12 stereocenter.33,34 Less certain would be the facial selectivity of the reaction of trisubstituted acetonide radical A. To correctly form the C-12 stereocenter, this coupling would have to take place from the acetonide radical face proximal to the vinylic β-substituent. As few C-C bond-forming reactions of 2,2-dimethyl-1,3-dioxolane trisubstituted radicals had been described, with both syn- and anti-addition being observed,36 it was uncertain at the outset from which face radical intermediate A would couple. We took some encouragement from the report by Renaud that a bulky β-substituent (tert-butyl)
favored bond formation cis to the substituent, although in these precedents the alkene was unsubstituted at its bond-forming terminus.\textsuperscript{36a} The second step whose stereochemical outcome would be critical is the 5-exo cyclization of tetracyclic radical intermediate B. We expected that this conversion would take place as depicted in Figure 2B by a conformation that minimizes destabilizing non-covalent interactions between both experimentally and computationally.

As we had most concern about the facial selectivity in the bimolecular radical coupling step, particularly with regard to facial selectivity of the reaction of a trisubstituted acetonide radical, we chose to examine this aspect of the ACF cascade in a model system having a terminal alkyne substituent at the $\beta$ carbon of the acetonide radical (Scheme 3). Starting with L-arabinose (33), enantiopure $N$-acyloxyphthalimide 35 was prepared in 10 steps by way of the known acetonide alcohol 34.\textsuperscript{37,38} Using a slight modification\textsuperscript{39} of visible-light photoredox conditions pioneered by Okada for generating radicals from $N$-acyloxyphthalimides,\textsuperscript{40} the coupling of 35 with 2.2 equiv of enantiopure (R)-5-L-methoxybutenolide (36)\textsuperscript{30b,c} gave the crystalline tricyclic lactone 37 in 38% yield. X-ray analysis of 37 confirmed that the coupling step had taken place as desired.\textsuperscript{26b} The other isolable product, formed in 7% yield, was 38.\textsuperscript{1}H NMR NOE analysis confirmed that this product formed from coupling of the trisubstituted acetonide radical from the face opposite to the alkyne substituent, resulting in the coupled radical being quenched rather than undergoing 5-exo cyclization with the trans-oriented alkyne substituent. In subsequent studies published elsewhere, the coupling of a broad selection of trisubstituted acetonide radicals harboring $\beta$-substituents was studied both experimentally and computationally.\textsuperscript{41} The origin of the observed syn stereoselection for the addition of the trisubstituted radical formed from 35 to butenolides such as 36 is ascribed to destabilizing non-covalent interactions between the alkynyl substituent and silyl-protected hydroxymethyl substituent in the transition state.\textsuperscript{36b,41} Since the $\beta$-substituent of the trisubstituted radical A (Figure 2B) in the proposed ACF cascade is certainly larger than an alkene, we were encouraged to proceed ahead to assemble the fragments to examine this pivotal step in our synthesis plan.

\textbf{Synthesis of (S,S)-Trimethylhydridanone 31 and Vinyl Iodide 29.} Several syntheses of enantioenriched trans-hydridanone 31 have been reported.\textsuperscript{31} We initially examined the short route reported by Granger and Snapper to prepare this ketone from 2-methylcyclopenten-2-one and prenylmagnesium bromide.\textsuperscript{31b} After slight modification, this approach provided initial quantities of (S,S)-trans-hydridanone 31 for our early studies. However, this route was deemed impractical for a large-scale preparation of 31 because of its modest overall yield (20%) and scalability issues in several steps.\textsuperscript{37}

We turned to examine a biomimetically inspired polyene cyclization route to trans-hydridanone 31.\textsuperscript{32} Based on the reports from the Yamamoto\textsuperscript{39} and Corey\textsuperscript{44} laboratories, we conjectured that dienyne 39, obtained in two steps from geranyl chloride,\textsuperscript{37} would undergo enantioselective proton-initiated polyene cyclization upon exposure to a chiral BINOL derivative in the presence of a strong Lewis acid, forming the alkylidene trans-hydridane 42b (Scheme 4).\textsuperscript{45} In our hands, subjection of dienyne 39 to the reaction conditions reported by Corey,\textsuperscript{44} using SbCl$_5$ in combination with (R)-o,o'-'dichloro-BINOL 41 (X = Cl) led to a 1:3 mixture of two regioisomeric bicyclic products 42a and 42b in 35% combined yield (entry 1). Ozone-mediated cleavage of the exocyclic double bond of 42b provided racemic trans-hydridanone 31. Examination of other Lewis acids (entries 2 and 3) revealed SnCl$_4$ to be superior in terms of reaction efficiency and enantiomutation. Unfortunately, further variation of reaction temperatures and the use of unsubstituted BINOL (41, X = H) led to no appreciable improvements in enantioselectivity or selectivity in forming 42b (entries 4–6). Unable to eliminate formation of the trans-decalin product 42a, we examined cyclization of propargylic silane 40.\textsuperscript{46} However, reactions of this precursor gave 43 in low yield only (e.g., entry 7).\textsuperscript{47}
The scalable route we finally developed to provide (S,S)-trans-hydrindanone 31 is summarized in Scheme 5. This sequence hinged on stereospecific reductive transposition of an allylic alcohol intermediate to set the thermodynamically disfavored trans ring fusion of 31.48,49 The preparation begins with commercially available (S)-enedione 44,50 which alternatively can be obtained reliably in 98% ee on >20 g scales in two steps from 2-methylcyclopentane-1,3-dione.51 Selective ketalization of 44, followed by stereoselective 1,2-reduction of the enone provided allylic alcohol 45 in 98% yield after a simple distillation. A number of approaches were investigated to convert allylic alcohol 45 to the desired trans-hydrindene ketal 48. Treatment of 45 with α-nitrobenzenesulfonfylhydrazine followed by warming of the reaction to room temperature, as described by Myers,52 led to the desired trans-fused ketal 48 as a minor component of a complex mixture of product. Unable to perform the desired transformation in a single step, we turned to examine Tsuji’s palladium-mediated stereospecific reductive transpositions of β-allylic carbonates and formates.49 Carbonate 46 readily underwent the desired reductive transposition upon treatment with Pd(acac)2, (n-Bu)3P, and finely crushed NH2HCO2H to provide trans-hydrindene ketal 48 in 77% yield. The choice of phosphine was critical to the success of the reaction, as the use of other phosphines (Cy3P, t-Bu3P, Ph3P) led largely to recovery of starting carbonate. The more commonly used allylic formate,47, was found to be inert under our reaction conditions. Stereoselective cyclopropanation of the trisubstituted double bond of 48 was achieved by reaction with diethylzinc and chloroiodomethane,53 which after acidic workup delivered cyclopropyl ketone 49 in 92% yield. It was important to use chloroiodomethane in this reaction, as use of diiodomethane led largely to recovery of the starting alkene. Hydrogenolysis of cyclopropane 49 using PtO2 in acetic acid,54 followed by PCC oxidation of the resulting secondary alcohol gave trans-hydrindanone 31 in 88% yield over two steps. This sequence delivered (S,S)-trans-hydrindanone 31 (98% ee) in 7 steps and 59% overall yield from enone 44. Using the method of Barton,55 hydrindanone 31 was converted to the known vinyl iodide 2956 in 78% yield. The sequence summarized in Scheme 5 readily provided 7 g of the light-sensitive iodide 29 in a single pass.

Synthesis of Aldehyde 30 and its Coupling with a trans-Hydrindene Nucleophile. With streamlined access to vinyl iodide 29 in hand, we turned our attention to the synthesis of the aldehyde coupling partner 30 (Scheme 6). The sequence began with tartrate-derived acetonide 32, which was desymmetrized by LDA-mediated alkylation with BOM-Cl, as reported by Crich, to give benzyl ether 33 in 93% yield and high purity.57 Selective reduction of the less hindered ester group of 50 with DIBALH provided primary alcohol 51 in 45% yield along with 36% of recovered starting material 50. All our attempts to improve the efficiency of this conversion were unsuccessful, as the use of alternate reductants (e.g., LiAlH4, Red-Al) or extra equivalents of DIBALH led to complex mixtures of various reduction products. Oxidation of primary alcohol 51 to aldehyde 30 could be achieved by a number of conventional methods; however, purification of 30 proved to be challenging. We ultimately elected to oxidize alcohol 51 with the Dess-Martin reagent (DMP) in CH2Cl2 and filter the resulting mixture with n-hexanes over Celite to remove the insoluble byproducts and give aldehyde 30 in 93% yield and high purity.58 As a result of its unexpected instability, aldehyde 30 was used immediately in the ensuing coupling step (vide infra).59 This proved to be a short and...
scalable approach to aldehyde coupling partner 30, with >8 g being readily prepared in a single pass, albeit in modest overall yield.

Next, we focused on uniting the trans-hydrindene and aldehyde fragments. Early attempts to directly couple the vinyllithium intermediate formed from vinyl iodide 29 with aldehyde 30 provided low yields (<20% yields) of adducts as an equimolar mixture of allylic alcohol epimers. We turned to the use of the Nozaki-Hiyama-Kishi (NHK reaction) to achieve the desired fragment-coupling (Scheme 7). Conditions that had been employed earlier to couple this iodide led to the formation of adduct 52 in low yields and 3:1 stereoselectivity. To accelerate the rate of NHK coupling and improve stereoselection, we elected to employ the oxazoline ligands developed by the Kishi group. To our delight, use of ligand (R)-53 resulted in the formation of adduct 52 as a single diastereomer in 28% yield. The identical reaction using the enantiomeric ligand, led to inversion of diastereoselectivity, giving the allylic alcohol epimer in 18% yield and 4:1 dr. Upon further optimization of the reaction with ligand (R)-53, we discovered that employing the sensitive aldehyde 30 in a slight excess (1.6 equiv) and performing the reaction on a larger scale (3 mmol) led to the formation of the desired product 52 in 66% isolated yield.

Having forged all of the C-C bonds of the radical cascade precursor, efforts were focused on allylic transposition of the alcohol functionality to a heteroatom capable of undergoing radical β-cleavage, while setting the required E-configuration of the exocyclic double bond of the product (Scheme 8). We first investigated the possibility of performing a [3,3]-sigmatropic rearrangement to an allylic thiocarbonate. To this end, deprotonation of alcohol 52 with KHMDS at -78 ºC, followed by addition of phenyl chlorothionoformate (54) resulted in thioacylation and spontaneous [3,3]-sigmatropic rearrangement upon warming to room temperature to give allylic thiocarbonate 55 as a single stereoisomer in 68% yield. However, we were unable to selectively cleave the methyl ester group of 55 in the presence of the sensitive thiocarbonate functionality under a variety of classical saponification, S_n2 demethylation, or other non-basic methods. To circumvent this selectivity issue, the order of transformations was reversed. Saponification of methyl ester 52 and subsequent esterification with N-hydroxyphthalimide (NHP) provided the crystalline NHP ester 56 in 69% yield, whose structure was confirmed by single-crystal X-ray analysis. Unfortunately, subjection of allylic alcohol 56 to the reaction conditions that were successful for thioacylation of 52 led to immediate decomposition of the N-acloyphthalimide functionality. Deprotonation of 56 with LiHMDS or NaHMDS followed by reaction with 54 led to recovery of the starting material, whereas reaction of 56 with other potassium bases uniformly resulted in instantaneous decomposition. Unable to selectively activate hindered allylic alcohol 56 for thioacylation with phenyl chlorothionoformate (54), we turned to investigating allylic OH → Cl transformations. Reaction of alcohol 56 with 2 equiv of SOCl_2 in a 10:1 mixture of Et_2O/pyridine at -40 ºC induced the desired suprafacial rearrangement to deliver crystalline N-acloyphthalimide radical precursor 57, whose structure was confirmed by single-crystal X-ray analysis, in 62% yield on gram-scale. This stereoselective conversion could also be accomplished on the product of the NHK coupling 52, followed by saponification to the corresponding carboxylic acid. However, in contrast to NHP ester 57, the non-crystalline acid produced was difficult to purify.
Although the initial coupling of dioxolane radical to butenolide 58 occurred with 7.6:1 diastereoselectivity favoring the desired adduct, minimizing premature reduction of the α-acyl radical intermediate leading to the significant byproduct, lactone 61, would be important for optimizing the efficiency of the ACF cascade. Formation of product 61 indicated that quenching of the α-acyl radical produced in the Giese coupling step by either single-electron transfer (SET) to form an enolate followed by protonation or by hydrogen atom abstraction from Hantzsch ester 59 was competitive with 5-exo cyclization.\(^{39}\) In an attempt to minimize the SET pathway,\(^{39}\) i-Pr$_3$NEt was omitted from the reaction mixture, significantly decreasing the yield of product 61 to 14% (entry 2). To further reduce premature quenching of the radical intermediate, we performed the reaction at higher dilution, resulting in a further decrease in the yield of product 61 to 3% (entry 3). However, these more dilute conditions also resulted in less efficient coupling of the dioxolane radical and butenolide 58 leading to lower yields of pentacyclic products 62 and 63. To attenuate hydrogen atom abstraction by the α-acyl radical in reactions carried out at higher concentration, we employed 4,4-dideutero analogue of Hantzsch ester 59 (entry 4). Under these conditions, the combined yield of cyclization products 62 and 63 increased to 70%, with tetracyclic lactone 61 being formed in only 6% yield.

Having attenuated premature quenching of the α-acyl radical intermediate, we sought to explore the effects of temperature, solvent, and structural modifications of butenolide 58 on diastereoselection of the 5-exo cyclization. As illustrated in Scheme 9, the major pentacyclic product 62 arose from cyclization taking place by a transition state related to radical conformer D, not by way of a transition structure related to conformer E. Varying the temperature of the reaction (0 ºC to 40 ºC) did not have a significant impact on the ratio of the epimeric products 62 and 63. Likewise, using butenolides harboring acetoxy or menthoxy substituents at the acetal stereocenter, led to no improvement in the yield of the desired tetracyclic product 63. The ratio was slightly enhanced in reactions conducted in acetonitrile, allowing the desired epimer 63 to be isolated in 27% yield (entry 5). Unable to further increase the yield of the desired ACF product 63, we decided to advance pentacyle forward to validate our post fragment-coupling strategy.
Completion of a First-Generation Total Synthesis of (-)-chromodorolide B. Product 63 of the ACF cascade was converted to (-)-chromodorolide B (11) by way of two isolated and purified intermediates, 64 and 65 (Scheme 10). Reduction of 63 with DIBALH at −78 °C and in situ acetylation with Ac₂O and DMAP afforded diacetal 64 as a single epimer at C-15, which was assigned the α-orientation on the basis of 1H NOE correlations between the C-15 and C-17 methines. We speculate that stereoselection in this reduction resulted from prior coordination of DIBALH with the benzyl ether substituent. Following unsuccessful attempts to accomplish reduction of the alkene and deprotection of the benzyl ether in one step, we first unveiled the primary alcohol under transfer-hydrogenation conditions, followed by conventional PtO₂-mediated alkene hydrogenation. The latter step proceeded exclusively from the alkene face opposite the angular methyl group to afford a single product 65 in 86% yield. Without purifying subsequent intermediates, the primary alcohol of 65 was oxidized to carboxylic acid 66, which upon exposure of the crude reaction mixture to 1:1 solution of 4 M HCl and THF for 72 h at room temperature delivered pentacyclic intermediate 67 as a mixture of lactol epimers. Reaction of a pyridine solution of this intermediate with a large excess of acetic anhydride in the presence of DMAP gave (-)-chromodorolide B (11) as a colorless solid in 49% overall yield from tetracyclic alcohol precursor 65. Spectroscopic data for synthetic 11 compared well with that reported for the natural product. The magnitude of the levorotatory rotation, [α]D = −67 (c = 0.12, CH₂Cl₂), was somewhat less than that reported, [α]D = −95 (c = 0.12, CH₂Cl₂), for a non-crystalline sample of the natural product. Recrystallization of synthetic (-)-chromodorolide B (11) provided single crystals, mp = 236–238 °C, allowing its structure to be unambiguously confirmed by X-ray analysis.

Computational Analysis of Stereoselection in the 5-exo Radical Cyclization Step of ACF Cascade. As discussed earlier, we had predicted erroneously that the 5-exo cyclization in the ACF cascade would occur preferentially from a conformation wherein A₁₃ interactions would dictate which face of the alkene would be attacked. In an attempt to gain insight into the observed stereoselection of this step, we analyzed the origin of the stereoselectivity computationally. Two mechanistic scenarios for the 5-exo cyclization were considered: (1) direct cyclization of an α-acyl radical onto the pendant alkene (the scenario outlined in Figure 2 and Scheme 9), and (2) initial SET to the radical intermediate formed in the bimolecular coupling step to form a lactone enolate that subsequently undergoes S₅'₂ cyclization. To identify the most likely pathway, energies and structures of diastereomeric transition states for the stereochemistry-determining step of both modes of cyclization were computed using the TPSS and TPSSh functionalities and the def2-TZVP basis sets in combination with the B3-LZ-damped D3-dispersion correction. In the case of the radical pathway, the lowest-energy transition state, TS-
**A-trans**, leading to the undesired C-8 epimer 62, was found to be 1.0 kcal/mol (in CH$_2$Cl$_2$) or 0.5 kcal/mol (in MeCN) lower in energy than **TS-A-cis** leading to epimer 63 having the C-8 configuration of (–)-chromodorolide B. The computed ratio of cyclized products 62:63 of 2.5:1 in MeCN agreed reasonably well with the experimentally observed ratio of 1.4:1. In contrast, computed diastereomeric transition states for the polar reaction pathway (enolate formation followed by concerted S$_{N}$2' cyclization, Supporting Information Figure S2) found the transition state leading to product 63 to be lower in energy by 0.7 kcal/mol (in MeCN) or 0.5 kcal/mol (in CH$_2$Cl$_2$). Although the energy differences of the computed diastereoisomeric transitions states in the two mechanisms are small, the radical pathway, which we consider the most plausible, was more consistent with the observed reaction outcome. As a result, further computational studies focused on this pathway.

Examination of the transition structures of the two diastereomeric transition states of the radical pathway (Figure 3A) was instructive. The lower-energy diastereomeric transition structure, **TS-A-trans**, has a longer forming bond (2.38 vs 2.25 Å) and a somewhat helical shape. Further analysis suggested a potential destabilizing steric interaction between the chloride of the hydrindane fragment and a substituent larger than hydrogen at the α-carbon of the butenolide fragment in a transition structure analogous to **TS-A-trans**. If the α-carbon of the butenolide carried a chloride or bromide substituent, the halogen substituents would clash a helical trans-transition structure, yet would point in opposite directions in a cis-transition structure. In addition, introduction of a halogen should shift the transition states later by decreasing the nucleophilicity of the butenolide radical, which could further increase a destabilizing halogen-halogen interaction.

The computationally predicted lowest energy transition structures for the 3-chloride analogue are shown in Figure 3B. As envisioned, the **TS-B-trans** is affected significantly, with the forming C-C bond distance decreased from 2.38 Å to 2.18 Å. As a consequence, the kinetic barrier for forming the trans product is increased from 7.9 kcal/mol to 11.3 kcal/mol (Supporting Information Figure S5). The forming bond in **TS-B-cis** is also shortened slightly (from 2.25 Å to 2.15 Å) and the kinetic barrier slightly is increased from 8.9 kcal/mol to 9.4 kcal/mol. The transition state that would lead to the ACF product having the C-8 configuration of (–)-chromodorolide B, **TS-B-cis**, is now predicted to be more stable by 1.9 kcal/mol. For the bromide analogue, the selectivity is predicted to be even slightly higher (Table 1).

**Table 1. The relative Gibbs free energies of TS-cis and TS-trans for α-H, α-Cl and α-Br butenolide substrates in CH$_2$Cl$_2$.**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>TS-cis (kcal/mol)</th>
<th>TS-trans (kcal/mol)</th>
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<tr>
<td>α-H</td>
<td>0.0</td>
<td>1.0</td>
</tr>
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<td>α-Br</td>
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</table>

**Figure 3.** Structures and energies of diastereoisomeric transition states of the 5-exo radical cyclization step of the ACF cascade. **A.** For the intermediate generated by addition of the acetonide radical to (R)-5-methoxybutenolide. **B.** For the intermediate generated by addition of the acetonide radical to (R)-3-chloro-5-methoxybutenolide. Values enclosed in parentheses are relative energies computed using the TPSS functional and def2-TZVP basis set (CH$_2$Cl$_2$ solvent); the values by the dotted line are the lengths of the forming C-C bond in Å. The transition structures labeled “cis” lead to the formation of the configuration at C-8 found in (–)-chromodorolide B. To reduce computation time, the benzyloxy substituent at C-11 was replaced with methoxy.
Second-Generation Total Synthesis of (-)-Chromodorolide B by Way of a Stereoselective ACF Cascade. We opted to explore this computational prediction by utilizing a 3-chlorobutenolide in the radical coupling step. This possibility was particularly attractive, as we have shown previously that the addition of a 3-Cl substituent to a butenolide increases the yields of radical coupling reactions, and in addition the α-chloride substituent in a coupled product can be removed directly in the photoredox-catalyzed coupling step. Salient results of our investigation of the enantiopture 3-chlorobutenolide 68 in the ACF cascade are summarized in Table 2. Using the reaction conditions optimized earlier (entry 5, Scheme 9) and carrying out the reaction with 1 equiv of both N-acyloxyphthalimide 57 and chlorobutenolide 68, followed by addition of n-Bu₃N and additional irradiation to promote dechlorination, provided an ACF cascade product that still contained the chloride substituent. Hypothesizing that under these conditions the dechlorination step was slow, the crude product after aqueous extraction was isolated and re-subjected to dechlorination using n-Bu₃N and the iridium photocatalyst, Ir[6F(CF₃)ppy]₂(dbbpy)PF₆. This sequence provided a single ACF cascade product 69 in 41% yield (Table 2, entry 1). The pentacyclic C-8 epimer of 69 was not detectable by NMR analysis. Increasing the concentration of the reaction to 0.6 M led to ACF product 69 being formed in 58% yield (entry 2). We eventually found that the desired cascade sequence and dechlorination of the product could be accomplished in a single step by utilizing 2 mol % of Ir[6F(CF₃)ppy]₂(dbbpy)PF₆ as the sole photocatalyst (entry 3). The yield of 69 was similar using Hantzsch ester 59 (entry 4), which was expected as by-products resulting from premature quenching of the α-acyloxy radical intermediate had not been observed. In addition, we were able to use an organic photocatalyst, 4CzIPN, in place of the Ir catalyst, giving the desired ACF cascade product in 54% isolated yield (entry 5). Thus, the computationally-guided structural modification of the butenolide coupling partner resulted in doubling the yield of the pivotal pentacyclic intermediate 69 and decreasing the amount of butenolide acceptor required in this step by four-fold.

Table 2. Optimization of the fragment coupling between NHP ester 57 and chlorobutenolide 68.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 mol % [Ru2(bpy)3]PF6, d2-Hantzsch ester 59, MeCN (0.1 M)</td>
<td>41%</td>
</tr>
<tr>
<td>2</td>
<td>2 mol % [Ir6F(CF3)ppy]2(dbbpy)PF6, n-Bu3N, THF (0.1 M)</td>
<td>58%</td>
</tr>
<tr>
<td>3</td>
<td>2 mol % [Ir6F(CF3)ppy]2(dbbpy)PF6, d2-Hantzsch ester 59, MeCN (0.6 M)</td>
<td>56%</td>
</tr>
<tr>
<td>4</td>
<td>2 mol % [Ir6F(CF3)ppy]2(dbbpy)PF6, Hantzsch ester 59, THF (0.6 M), then Bu3N</td>
<td>57%</td>
</tr>
<tr>
<td>5</td>
<td>2 mol % 4CzIPN, Hantzsch ester 59, THF (0.6 M), then Bu3N</td>
<td>54%</td>
</tr>
</tbody>
</table>

To confirm that the chloride, and not the menthox, substituent was responsible for the high stereoselection observed in the fragment coupling summarized in Table 2, we examined the reaction of NHP ester 57 with 3-chloro-5-methoxybutenolide. Although this butenolide is not available in enantioenriched form, this investigation could be carried out using racemic 3-chloro-5-methoxybutenolide (70), as authentic samples of the diastereomeric ACF products 62 and 63 were available. As summarized in eq 1, the reaction of NHP ester 57 with racemic butenolide 70 provided 63 as the major product, with no trace of its C-8 epimer, 62, being seen by careful 1H NMR analysis of the crude reaction mixture.

With sufficient amounts of lactone 69 in hand, we elaborated it to (-)-chromodorolide B (11) by a seven-step sequence that paralleled the final steps of our first-generation synthesis (Scheme 11). Reduction of lactone functionality of 69 and in situ acetylation of the resulting aluminum hemiacetal intermediate with Ac₂O proceeded smoothly to deliver diacetal 71 in 98% yield.
Deprotection of the primary alcohol proved challenging once again. Debenzylation of 71 employing the acidic transfer hydrogenolysis conditions developed during our first-generation synthesis of 11, resulted in cyclization of the newly unveiled C-11 alcohol onto C-16 forming a bridging tetrahydrofuran ring. We were able to suppress this undesired cyclization by performing the reaction with basic Pd(OH)$_2$ and $\text{H}_2$. Without purification, the trisubstituted alkene was reduced stereoselectively with $\text{PtO}_2$ to deliver saturated-pentacyclic product 72 in 88% over two steps. Finally, we successfully converted 72 to (−)-chromodorolide B (11) in 45% yield over four steps by the sequence of transformations employed in our first-generation synthesis.

CONCLUSION
The structurally intricate marine diterpenoid chromodorolide B, which harbors 10 contiguous stereocenters and two chiral attached ring fragments, has been successfully synthesized. This total synthesis establishes the absolute configuration of chromodorolide B, which had previously been proposed on biogenetic grounds. The synthetic sequence features a novel late-stage radical addition/cyclization/fragmentation (ACF) cascade that unites two chiral fragments by forming two C-C bonds and four contiguous stereocenters in a single, highly stereoselective step. A notable feature of this late-stage fragment union is the use of the two coupling partners in equimolar amounts. The coupling step is initiated by visible-light photocatalytic fragmentation of a redox-active ester, which can be accomplished in the presence of 2 mol % of an iridium photocatalyst or 2 mol % of a less-precious electron-rich dicyanobenzene photocatalyst. The high degree of stereocntrol eventually realized in the cascade sequence was made possible by in-depth DFT computational modeling of the 5-exo cyclization step of the ACF cascade. Our second-generation total synthesis of (−)-chromodorolide B (11) proceeds in 21 steps from commercially available (S)-enedione 44 in 2% overall yield. We anticipate that the results delineated in this study will find applications in future syntheses of other structurally intricate natural products.

ASSOCIATED CONTENT
Supporting Information
Experimental procedures, characterization data, and CIF files for X-ray structures of compounds 11, 23, 37, 56, and 57. 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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REFERENCES


(7) For a preliminary report of a portion of these studies, see: Tao, D. J.; Slutsky, Y.; Overman, L. E. J. Am. Chem. Soc. 2016, 138, 2186–2189.


(20) All natural products having the spongian skeleton are reported to have the absolute configuration depicted in a.


(25) See the Supporting Information for a summary of the dihydroxylation conditions studied. These compounds were characterized by single-crystal X-ray analysis; X-ray coordinates were deposited with the Cambridge Crystallographic Data Centre: (a) 23. CCDC1810845; (b) 37. CCDC144714; (c) 56. CCDC1446028; (d) 57. CCDC1446026; (e) 11. CCDC1446027.


(34) See Supporting Information for details.


(37) See Supporting Information for details.


(45) Highly enantioenriched samples of both the (R)- and (S)-enantioenriched samples can be purchased from Accel Pharmtech or Proactive Molecular Research.


(47) 1H NMR analysis of the crude reaction mixture showed multiple polyene byproducts that are believed to be the result of undesired protonation of the propargylic silane in preference to the terminal alkene.


(63) The structural assignment of 52 was verified by single-crystal X-ray diffraction analysis of the (N-acyloxy)phthalimide analogue 56.  


(68) Addition of KHMDS to a colorless solution of 56 at –78 °C led to an immediate color change to red, indicating formation of phthalimide anion.


(70) We have failed to isolate 60 in pure form.


(75) For a detailed discussion of the computational methods utilized in the study, see the Supporting Information.

(76) As the chloride substituent could lower the reduction potential of the α-acyloxy radical intermediate and favor reactivity by the enolate pathway, we confirmed that formation of the ACF product having the C-8 configuration of (–)-chromodorolide B would also be favored by the enolate pathway, see Supporting Information, Figure S7.

(77) Use of an α-bromobutenolide is also predicted to favor formation of the desired ACF product (Table 1). However, this prediction could not be verified experimentally because of decomposition of the bromide-containing butenolide upon irradiation with blue LEDs.


(83) Use of other transfer hydrogenation reagents such as 1,4-cyclohexadiene or ammonium formate did not result in debenzylation of 71.
Bimolecular Radical Cascade

2 C-C Bonds
4 Stereocenters
54% yield (>20:1 dr)

(-)-chromadorolide B