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Total Synthesis of (−)-Chromodorolide B

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Supporting Information

ABSTRACT: The first total synthesis of a chromodorolide diterpenoid is described. The synthesis features a bimolecular radical addition/cyclization/fragmentation cascade that unites butenolide and *trans*-hydrindane fragments while fashioning two C−C bonds and stereoselectively forming three of the ten contiguous stereocenters of chromodorolide B.

Chromodorolides A−E (**1**−**5**), which contain 10 contiguous stereocenters, are among the most structurally complex members of the rearranged spongian diterpenoids (Figure 1).[1,2] They have been isolated from nudibranches in the genus *Chromodoris* and the encrusting sponges on which these nudibranches potentially feed. The 6-acetoxy-2,7-dioxabicyclo[3.2.1]octan-3-one and 7-acetoxy-2,8-dioxabicyclo[3.3.0]octan-3-one rings embedded in the chromodorolides are distinctive features of many rearranged spongian diterpenes such as norrisolide (**6**),[3] norrlandin (**7**),[4] and aplyviolene (**8**).[5] In the chromodorolides, these dioxabicyclic rings are appended to an additional oxygenated cyclopentane ring. Although modest *in vitro* antitumor, nematocidal, and antimicrobial activities have been reported,[1b,c,e] the chromodorolides and analogues are of most interest for their potential effects on the Golgi apparatus.[5c] We report herein the first total synthesis of a chromodorolide, (−)-chromodorolide B (**1**), by a concise sequence that features a bimolecular radical addition/cyclization/fragmentation (ACF) cascade.

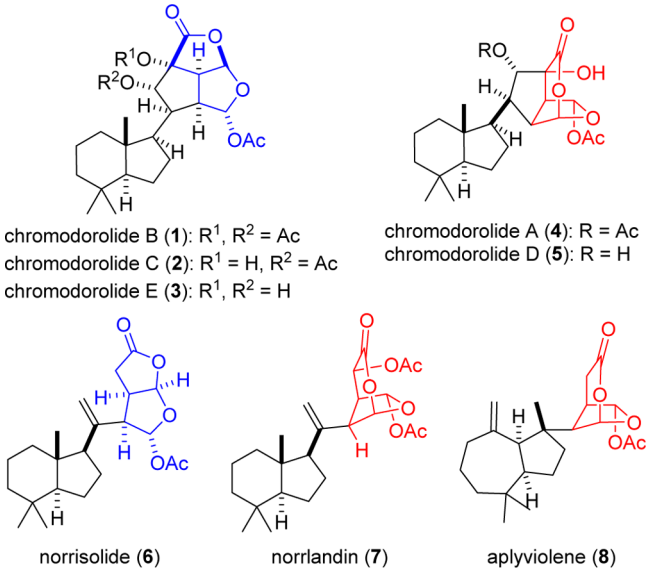
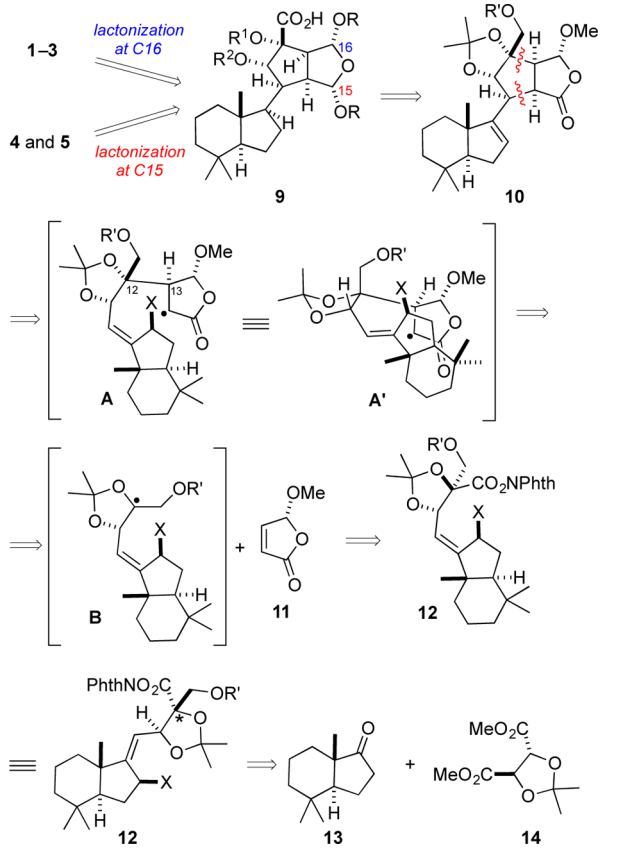


Figure 1. Chromodorolides and three structurally related rearranged spongian diterpenoids that also contain 6-acetoxy-2,7-dioxabicyclo-[3.2.1]octan-3-one (red) and 7-acetoxy-2,8-dioxabicyclo[3.3.0]octan-3-one (blue) fragments.

We envisaged that the chromodorolides containing distinctive dioxatricyclic fragments of both fused (**1**, **2**, **3**) and bridged (**4**, **5**) motifs could be accessible from a common tetracyclic acid **9** (Scheme 1). In this analysis, the substituents at C-15 and C-16 of acid **9** would be differentiated to allow selective lactonization to construct either dioxatricyclic fragment. Further simplification of acid **9** leads to intermediate **10** having the C_{12} hydrocarbon and the highly oxidized fragment joined at a vinylic carbon of the hydrophobic fragment.[6] On the basis of our recent experience showing that fragment couplings of

Scheme 1



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nucleophilic tertiary radicals with alkenes can be high yielding,[5b] we envisioned a cascade sequence in which trisubstituted carbon radical **B**, generated by visible-light photoredox fragmentation of the *N*-acyloxyphthalimide substituent of intermediate **12**,[7] would couple with (*R*)-4-methoxybutenolide (**11**)[8] to generate *α*-acyloxy-radical intermediate **A**, which was hoped would undergo intramolecular 5-*exo* cyclization from a conformation such as **A′** depicted in Scheme 1 that minimizes destabilizing allylic $A^{1,3}$ interactions. The cascade would then be terminated by *β*-fragmentation of the adjacent C−X (X = halide) bond to deliver the desired coupled product **10**.[9] Essential for success of this proposed sequence would be correctly setting the C-12 and C-13 stereocenters in the union of the two fragments to form intermediate **A**. The desired configuration at C-13 was anticipated from the radical addition to the butenolide occurring preferentially from the face opposite the methoxy substituent.[10] Unclear at the outset was from which face radical intermediate **B** would couple, as few C−C bond-forming reactions of 2,2-dimethyl-1,3-dioxolane trisubstituted radicals have been described and preferences for both *syn* and *anti* addition have been reported.[11] In an exploratory model study, we confirmed that radical coupling at such a carbon would preferentially occur from the desired face *syn* to the vicinal substituent.[12] Further simplification of intermediate **12** leads to two readily available precursors: (*S*,*S*)-trimethylhydrindanone **13**[3] and (*R*,*R*)-tartaric acid derived acetonide **14**.

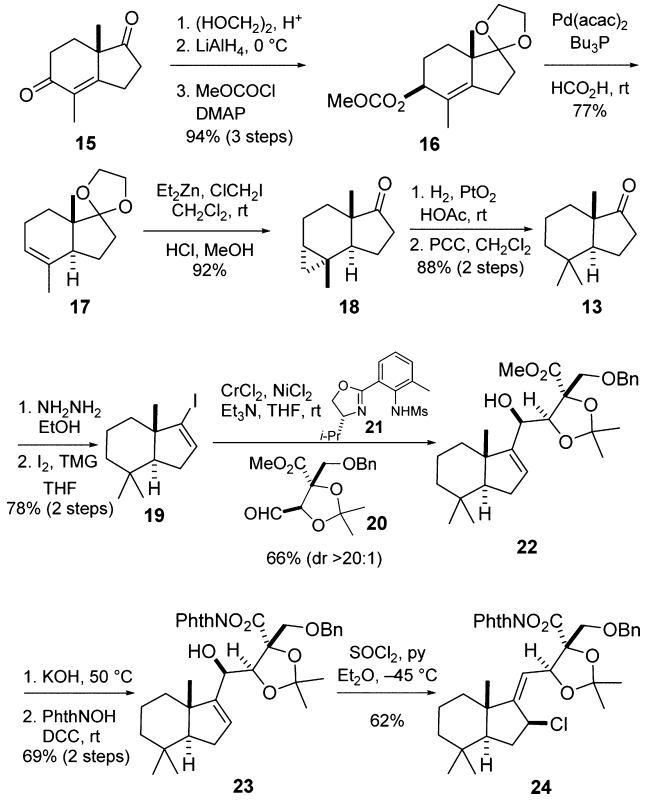
Although several enantioselective routes to *trans*-hydrindanone **13** have been reported,[3,13] a readily scalable, efficient synthesis had not been described. During our investigations, such a route was developed (Scheme 2). This sequence began with commercially available (*S*)-enedione **15**,[14] which alternatively can be prepared in 98% *ee* on a large scale in two steps from 2-methylcyclopentane-1,3-dione.[15] Selective ketalization of **15**, stereoselective 1,2-reduction of the enone, and methoxycarbonylation provided *β*-allylic carbonate **16** in 94% overall yield. Palladium-catalyzed reductive transposition of the allylic carbonate then gave *trans*-hydrindene ketal **17** in 77% yield.[16] Cyclopropanation of trisubstituted alkene **17** with diethylzinc and chloroiodomethane,[17] followed by acidic workup, produced ketone **18**. Subjection of cyclopropane **18** to hydrogenolysis conditions, followed by oxidation of the resulting secondary alcohol, delivered *trans*-hydrindanone **13** in 88% yield over two steps. The seven-step sequence summarized in Scheme 2 provides (*S*,*S*)-**13** of high enantiomeric purity (98% *ee*) on multigram scales in 59% overall yield from enedione **15**.

In six subsequent steps, hydrindanone **13** was elaborated to radical coupling precursor **24**. This sequence began by conversion of ketone **13** to known vinyl iodide **19**.[3] The other fragment, sensitive aldehyde **20**, is accessible in three steps from acetonide **14**.[12] A variety of standard conditions were examined for the Nozaki−Hiyama−Kishi coupling of iodide **19** with aldehyde **20**;[18] however, only low yields (<20%) and modest diastereoselectivities (3:1) were observed. In contrast, in the presence of (*R*)-sulfonamide ligand **21** introduced by Kishi,[19] allylic alcohol **22** was obtained in 66% yield as a single alcohol epimer. Saponification of the ester and subsequent esterification with *N*-hydroxyphthalimide provided crystalline ester **23** in 69% yield, whose structure was confirmed by single-crystal X-ray analysis.[20a] Exposure of this intermediate to thionyl chloride and pyridine at −45 °C in diethyl ether mediated suprafacial allylic transposition[21] to give crystalline allylic chloride **24**[20b] in 62% yield.

We then examined the key ACF cascade that ideally would set two new C−C bonds and four stereocenters of **1** in a single step. Initial experiments employed conditions previously used in the coupling of tertiary radicals with (*R*)-methoxybutenolide **11** (Scheme 3, entry 1).[7b,10] Two products arising from the ACF cascade sequence, **25** and **26**, were isolated.[22,23] Detailed analysis of their NMR spectra showed that these products were epimeric at C-8. Particularly diagnostic were ^{1}H NOE correlations between the C-8, C-17, and C-14 methine hydrogens.[12] Confirmation of the structures of these epimers was obtained by eventual conversion of cascade product **25** to (−)-chromodorolide B (*vide infra*). The third predominant product retained the alkylidene chlorohydrindane fragment of precursor **24** and showed ^{1}H NOE data consistent with a *cis* relationship of the allylic hydrogen at C-17 and the benzyloxymethyl substituent. Products **25**−**27** all arose from coupling of the dioxolane radical with the chiral butenolide *syn* to the vicinal hydrophobic fragment, with **27** resulting from premature trapping of the *α*-acyl radical intermediate. ACF product **25** derives from the 5-*exo* cyclization occurring in the desired orientation as depicted in intermediate **A′** (Scheme 1), whereas epimer **26** arises from the cyclization taking place from the alternate face of the alkylidene double bond. The fourth product **28** is tentatively assigned as the C12 epimer of **27**,[24] which would arise from radical addition to the butenolide occurring from the face of the 1,3-dioxolane *anti* to the vicinal hydrophobic fragment.[12]

A number of experiments were conducted to minimize the formation of byproduct **27** arising from premature quenching of the coupled radical.[12] Removal of *i*-Pr_2EtN, which was expected to minimize amine-mediated reduction of intermedi-

Scheme 2



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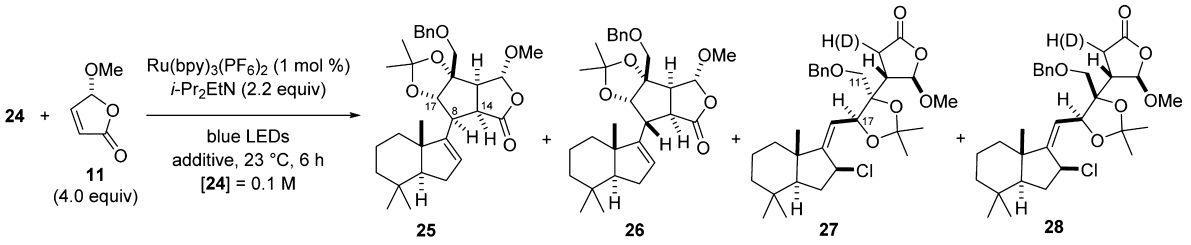
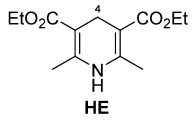
Scheme 3



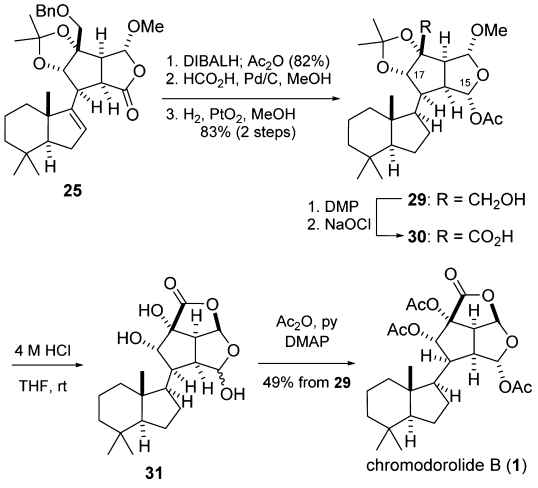


Entry	Conditions	Yields (1H NMR with internal standard) 25	26	27	28
1	**HE** (1.5 equiv), CH_2Cl_2	20%	35%	29%	11%
2	**HE** (1.5 equiv), no *i*-Pr_2EtN, CH_2Cl_2	18%	34%	14% (d1)	7% (d1)
3	d2-**HE** (1.5 equiv), no *i*-Pr_2EtN, CH_2Cl_2	25%	45%	6% (d1)	10% (d1)
4	d2-**HE** (1.5 equiv), no *i*-Pr_2EtN, MeCN	28%	37%	8% (d1)	13% (d1)

ate **A** to its corresponding enolate,[7b] reduced formation of byproduct **27** (entry 2). However, as intermediate **A** can also be quenched by hydrogen-atom transfer from the Hantzsch ester,[7b] this pathway also needed attenuation. Employing 4,4-dideuterio Hantzsch ester in the absence of *i*-Pr_2EtN (entry 3), which was expected to minimize hydrogen-atom transfer to the initially generated coupled radical, significantly decreased the formation of product **27**, increasing the combined yield of ACF products **25** and **26** to a 70% yield. Attempts thus far to improve the ratio of epimeric products **25**/**26** have been less successful.[12] This ratio was slightly improved in reactions conducted in acetonitrile (entry 4), allowing product **25** to be formed in 28% yield (by ^{1}H NMR with internal standard) and isolated in 27% yield.

As summarized in Scheme 4, cascade product **25** was readily transformed to (−)-chromodorolide B (**1**). Reduction of the

Scheme 4



lactone carbonyl of **25** with (*i*-Bu)$_2$AlH at −78 °C and *in situ* acetylation with Ac_2O and DMAP afforded the acetoxy acetal as a single epimer at C-15. ^{1}H NOE correlations between the C-17 and C-15 methine hydrogens revealed that the acetoxy group was oriented *α*.[25] Following removal of the benzyl protecting group, the trisubstituted double bond was hydrogenated selectively (dr >20:1) from the face opposite the angular methyl group to yield product **29** in 68% overall yield from **25**. Without purifying subsequent intermediates, **29** was oxidized to carboxylic acid **30**, which upon exposure to 4 M HCl in THF at room temperature underwent acetonide deprotection and lactonization to form lactol **31**. Exhaustive acetylation of this triol gave (−)-chromodorolide B (**1**), $[\alpha]_D$ = −66.8 (*c* = 0.12, CH_2Cl_2), in 49% overall yield from intermediate **29**. This product showed ^{1}H and ^{13}C NMR data and optical rotation in close accord to those reported for a natural sample.[1b,c] In addition, synthetic **1** provided single crystals, which allowed the structure of chromodorolide B to be unambiguously confirmed by X-ray analysis.[20c]

In summary, the enantioselective total synthesis of (−)-chromodorolide B (**1**) was completed in 21 steps and 1.2% overall yield from commercially available enedione **15**. An unprecedented photoredox radical cascade reaction allowed butenolide and *trans*-hydrindane fragments to be combined while forming two C−C bonds and stereoselectively creating three of the ten contiguous stereocenters of **1**. As with almost all first total syntheses of a unique and structurally complex natural product, several aspects of the synthetic route can be improved upon. Toward this end, our current efforts focus on discovering the origins of diastereoselectivity of both Csp^3–Csp^3 bond-forming steps in the radical cascade and improving the diastereoselectivity of the 5-*exo* cyclization step.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b00541.

Experimental details; NMR data (PDF)
Crystallographic data for **1** (CIF)
Crystallographic data for **23** (CIF)
Crystallographic data for **24** (CIF)
Crystallographic data for **S4** (CIF)

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Notes

The authors declare no competing financial interest.

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