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Catalytic Enantioselective Total Synthesis of Hypocrolide A

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Supporting Information

ABSTRACT: The first and catalytic enantioselective total synthesis of hypocrolide A (>99% ee) in 12 steps, as well as other botryanes, is described. The absolute configurations of these compounds have been unambiguously confirmed or reassigned accordingly. The key reactions in this study include an unusual rhodium-catalyzed intramolecular [4 + 2] cycloaddition and a biomimetic oxidative [3 + 2] cycloaddition based on our revised biogenetic pathway.

The botryanes **1**−**5** (Figure 1) are a series of sesquiterpene antibiotics[1] that were originally derived from the metabolites of the fungus *Botrytis cinerea*.[2] This fungus is the causal agent of gray mold disease, which is known to attack a wide range of plants (over 200 species), resulting in leaf-spot disease and mildew on lettuces, tomatoes, and grapes as well as leading to the rotting of berries. Most of the compounds belonging to this novel structural class are based on a unique hydrindane skeleton taht does not obey the simple isoprene rule.[3] Botrydial (**1**),[4] which was the first of these metabolites to be isolated in 1974, consists of a *cis*-fused and highly functionalized hydrindane system bearing six continuous chiral centers, including two quaternary centers. Hypocrolide A (**6**) is an unusual botryane metabolite, which was isolated by Che et al.[5] in 2013. Structurally, hypocrolide A, which is the most complex member of the botryane family, consists of a sterically compact 5/6/6/5/6/6-fused hexacyclic skeleton including a highly substituted 3,6-dihydro-2*H*-pyran and a dihydrofuran unit. This compound also contains six stereocenters, including two quaternary centers, and therefore represents a significant synthetic challenge. The botryanes have been reported to show a variety of interesting biological activities.[6] For example, botrydial is the primary phytotoxic metabolite produced by *B. cinerea* as a hypersensitive response (HR) inducer[7] and has been reported to show significant antibiotic activity against *Bacillus subtilis*[8] and *Pythium debaryanum*[4] as well as high levels of cytotoxicity against a series of human cancer cell lines.[9] Hypocrolide A has also been reported to exhibit moderate cytotoxicity against human tumor cell lines compared with cisplatin.[5] However, the relative scarcity of **6** from natural sources has impeded a more systematic evaluation of its biological activity, and the development of an efficient synthetic process for the construction of this complex molecule is therefore highly desired.

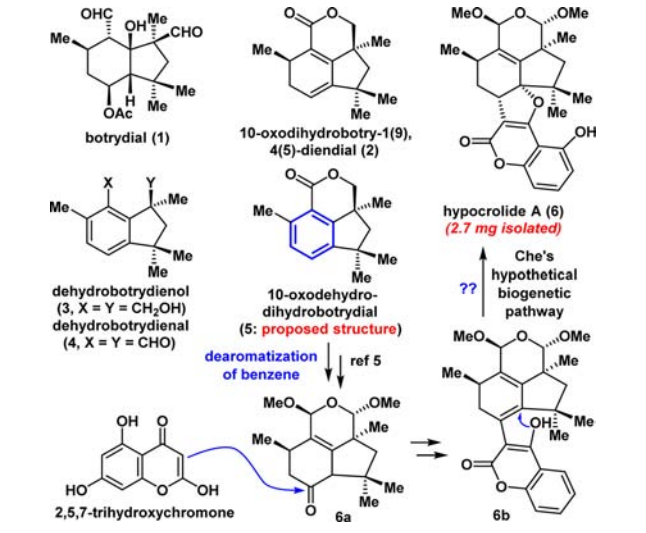

Figure 1. Hypocrolide A and other botryanes.

On the basis of their fascinating structural motifs and promising pharmacological properties, botryanes have attracted considerable interest from chemists working in a variety of different fields, resulting in many interesting investigations, including chemical transformations,[9] structure−activity relationships,[7] biosynthesis,[3,10] and synthetic studies.[11] Although more than 50 members of the botryane family of sesquiterpene metabolites have been isolated[12] since 1974, there have been no reports in the past 40 years pertaining to the total synthesis of any of the compounds belonging to this family. Furthermore, the absolute configurations of several botryanes (such as **2**−**5**) have not yet been determined, although Che[5] reported a hypothetical biogenetic pathway for the synthesis of hypocrolide A (**6**) from **5** by the diastereoselective dearomatization of benzene (blue in Figure 1), followed by a complex transformation. The transformation of dearomatization of benzene appears to be very difficult. In our continuing efforts toward the synthesis of biologically active natural products,[13] herein we describe the first

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catalytic enantioselective total synthesis of hypocrolide A based on our revised biogenetic pathway.

It was envisioned (Figure 2) that hypocrolide A (**6**) could be generated from coumarin **7** and 10-oxodihydrobotry-1(9),4(5)-

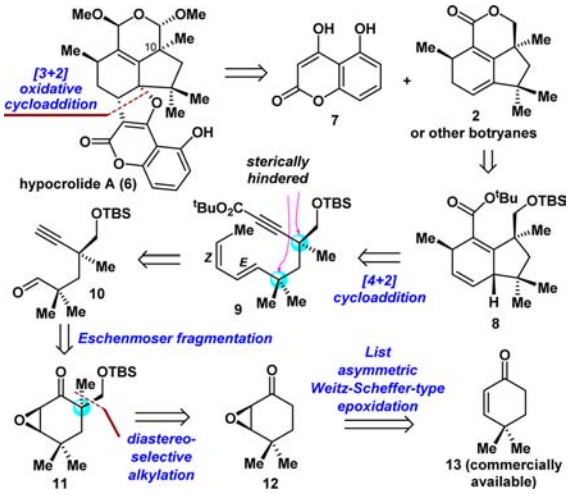


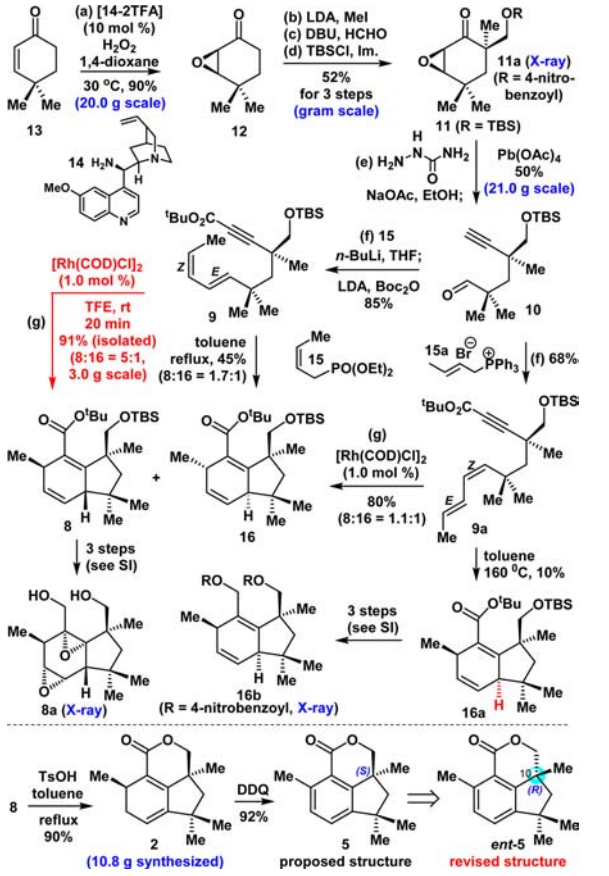
Figure 2. Retrosynthetic analysis of hypocrolide A.

diendial (**2**) via a [3 + 2] oxidative cycloaddition[14] according to our revised biogenetic pathway, followed by the formation of a 2*H*-pyran unit. Compound **2** could be synthesized from **8** via sequential lactonization and double bond migration processes. In turn, compound **8** could be formed from *Z*,*E*-dienyne **9** via an intramolecular [4 + 2] cycloaddition reaction. Compound **9** could be derived from **10**, which could be synthesized from epoxide **11** by the Eschenmoser fragmentation.[15] Lastly, compound **11** could be prepared from commercially available 4,4-dimethylcyclohex-2-enone (**13**) according to the asymmetric Weitz−Scheffer-type epoxidation developed by List,[16] followed by the sequential diastereoselective alkylation of **12** to install the all-carbon quaternary stereocenter.

The key step in our current strategy was the intramolecular [4 + 2] cycloaddition reaction to install the 5−6 bicyclic skeleton. Although the thermal intramolecular Diels−Alder (IMDA) reaction of 1,3,8-dienynes (where the diene moiety is linked to an alkyne via three atoms) has been reported for the synthesis of 5−6 bicyclic systems,[17] there have been very few reports pertaining to the application of this method to the total synthesis of natural products. The lack of reports in this area has been primarily attributed to the tendency of the cycloadducts resulting from these reactions to undergo unexpected aromatization processes.[17g] It can also be difficult to control the diastereoselectivity of these reactions, especially for acetylene dienophiles positioned in close proximity to a stereocenter.[17d] Furthermore, the steric effect of two quaternary centers adjacent to both the diene and the dienophile in **9**, as well as the potential for the thermally induced [1,5] H shift,[18a] and/or the isomerization of the acyclic *Z*,*E*-diene to the more stable *E*,*E*-diene prior to the cycloaddition under heating conditions,[18b−d] make this IMDA reaction particularly challenging. The transition-metal-catalyzed intramolecular [4 + 2] cycloaddition reactions of unactivated alkyne-tethered 1,3-dienes have recently emerged as synthetically useful processes,[19] although particularly aggressive reaction conditions are usually required to achieve these thermal cycloaddition reactions. However, to the best of our knowledge, there have been no reports pertaining to the use of electron-deficient alkynes as the dienophile in transition-metal-catalyzed [4 + 2] cycloadditions, and the application of this process to the total synthesis of natural products remains rare.

Our synthesis began with the asymmetric preparation of dienyne **9** (Scheme 1). According to List's method, using the

Scheme 1. Catalytic Asymmetric Synthesis of 8, 2, and 5



Cinchona alkaloid-derived primary amine **14** as a catalyst with aqueous hydrogen peroxide as an oxidant, we achieved the enantioselective Weitz−Scheffer-type epoxidation of **13** to give **12** in 90% yield (20.0 g scale). The sequential diastereoselective alkylation of **12** with MeI and formaldehyde under different bases (LDA and DBU), followed by the TBS protection of the resulting alcohol, provided **11** (R = TBS) with an all-carbon quaternary stereocenter in 52% overall yield (gram scale). The structure of **11** was later confirmed by the X-ray crystallographic analysis of its derivative **11a** (R = 4-nitrobenzoyl). The epoxy ketone **11** underwent a modified Eschenmoser fragmentation to give the acetylene aldehyde **10** in acceptable yield (21.0 g scale). Aldehyde **10** reacted cleanly with Wittig reagent **15** or **15a**, followed by the treatment of the resulting dienyne with LDA and Boc_2O in the same pot, to give the terminal *Z*,*E*-diene **9** in 85% yield and the internal *Z*,*E*-diene **9a** in 68% yield (6.6 g scale), respectively.

With **9** and **9a** in hand, we proceeded to investigate our proposed intramolecular [4 + 2] cycloaddition reaction to synthesize the 5−6 bicyclic system of the botryanes (Scheme 1). Interestingly, when the reaction was carried out in refluxing toluene for 12 h, compound **9** readily underwent the expected IMDA reaction to afford **8** and **16** (1.7:1 mixture), together with several unidentified byproducts. Compounds **8** and **16** were readily separated by flash column chromatography (45%

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combined yield). The structure of **8** was determined by 2D-NMR and later confirmed by X-ray crystallographic analysis of its derivative **8a**. Unfortunately, the IMDA reaction of **9a** did not occur in refluxing toluene. However, when the reaction of **9a** was carried out in toluene in a sealed tube at 160 °C for 12 h, compound **16a**, instead of **8** and **16**, was observed in very low yield, together with several unidentified byproducts. The structure of **16a** was later confirmed by X-ray crystallographic analysis of its derivative **16b**. This result showed that the internal *Z,E*-diene **9a** is more difficult to undergo the thermal IMDA reaction than the terminal *Z,E*-diene **9** and had undergone an isomerization reaction to give the more stable *E,E*-diene prior to the cycloaddition reaction under high temperature.

The low yield and poor diastereoselectivity of this process prompted us to investigate the transition-metal-catalyzed intramolecular [4 + 2] cycloaddition of **9** or **9a** under mild conditions because it was envisaged that the diastereoselectivity of this process could be controlled via the coordination of the alkyne/diene moieties to a metal center.[19j]

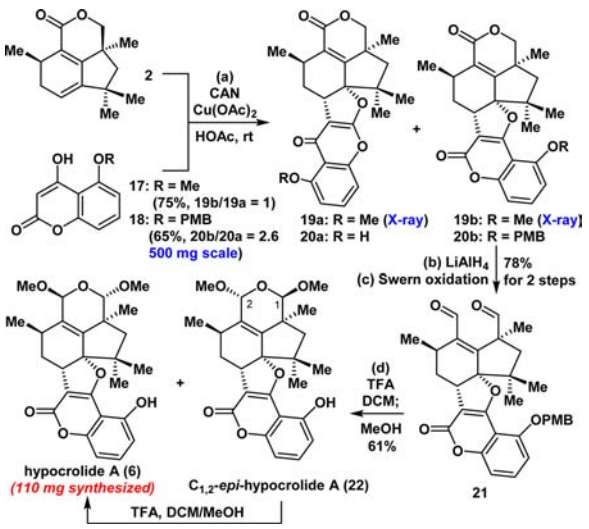
The transition-metal-catalyzed intramolecular [4 + 2] cycloaddition reaction of **9** was therefore evaluated using several different catalysts (Ni, Rh, Au, and Pd) in a variety of different solvents (DCM, CH_3CN, toluene, and TFE). The results of these screening reactions revealed that the use of $[Rh(COD)Cl]_2$ in TFE gave the best results. Pleasingly, compound **9** readily underwent the required intramolecular [4 + 2] cycloaddition reaction in the presence of $[Rh(COD)Cl]_2$ (1.0 mol %) in TFE at room temperature to afford **8** and **16** (5:1) in 91% isolated yield (3.0 g scale). Interestingly, the internal *Z,E*-diene **9a** also readily underwent the desired rhodium-catalyzed [4 + 2] cycloaddition under mild conditions to afford **8** and **16** in good yield. However, **8** and **16** was in a ratio of 1.1:1. These results indicated that the geometric features of the dienes would be important for the diastereoselectivity of the transition metal-catalyzed intramolecular [4 + 2] cycloaddition reactions.

The subsequent treatment of **8** with TsOH in refluxing toluene afforded **2**[12b] in high yield. The TsOH played a variety of different roles in this reaction, including (i) removing the TBS group; (ii) mediating the lactonization of the resulting alcohol with the ester moiety; and (iii) promoting the chemoselective migration of the double bond. Notably, this route allowed for the facile synthesis of 10.8 g of **2** (see the Supporting Information for details), thereby highlighting the robust nature of this chemistry. Compound **2** was readily dehydrogenated in the presence of DDQ (Scheme 1) to generate 10-oxodehydrodihydrobotrydial (**5**)[12a] in 92% yield. The ^1H and ^{13}C NMR spectra of **5** were identical to those of the natural product, except for the sign of its optical rotation. Based on this result, the absolute configuration of naturally occurring **5** was reassigned to that shown in the figure for *ent*-**5**.

Having successfully prepared the $\alpha,\beta,\gamma,\delta$-unsaturated lactone **2** and the hydroxycoumarins **7**, **17**, and **18** (see the Supporting Information for details), we were eager to investigate the application of our proposed biomimetic [3 + 2] oxidative cycloaddition to the rapid construction of the hexacyclic core in hypocrolide A. Heiba and Dessau developed an efficient procedure for the formation of dihydrofurans via the oxidative cycloaddition of 1,3-dicarbonyl compounds to alkenes in 1974.[20a] In the context of the current study, it was envisaged that the desired dihydrofurocoumarin moiety in hypocrolide A (**6**) could be generated in a single step using an oxidative [3 + 2] cycloaddition. Although this reaction would allow for the formation of two stereocenters, including one quaternary center, in a single step, we expected that it would be challenging to control the diastereo- and regioselectivity of this transformation.

We initially investigated the intermolecular oxidative [3 + 2] cycloaddition of **2** with **7** in acetonitrile in the presence of cerium(IV) ammonium nitrate (CAN),[20b−d] which was added as a one-electron metal oxidant. However, these conditions failed to afford any of the desired product. Several other conditions that had been used for related examples were also evaluated, but also failed to provide any of the desired product. Notably, all of these conditions led to the decomposition of **7**, showing that they were incompatible with the unprotected phenol moiety.[20b] When 4-hydroxy-5-methoxycoumarin (**17**) was used as the substrate (Scheme 2), the reaction provided only trace quantities of the

Scheme 2. Enantioselective Synthesis of Hypocrolide A



desired product **19b** together with the separable regioisomer **19a**, as a 1:1 mixture. We subsequently evaluated a variety of different reaction conditions in an attempt to modulate the reactivity and found that the use of 3.0 equiv of CAN with 1.5 equiv of $Cu(OAc)_2$ in acetic acid gave the best results. Under these conditions, the oxidative [3 + 2] cycloaddition of **2** and **17** provided the cycloaddition products **19a** and **19b** as a 1:1 mixture in 75% yield. The structures of these compounds were unambiguously confirmed by X-ray crystallography. Pleasingly, this reaction also proceeded smoothly with **2** (500 mg scale) and **18** (R = PMB, 4-methoxybenzyl), where the ratio of the desired product **20b** to the undesired compound **20a** improved to 2.6:1.

With **20b** in hand, we continued toward the final stage of our synthesis via the installation of the dimethoxydihydro-2*H*-pyran unit. The sequential reduction and oxidation of **20b** gave dialdehyde **21** in 78% overall yield. Pleasingly, the subsequent treatment of **21** with TFA in DCM/MeOH allowed for the removal of the PMB group with the concomitant formation of the dimethoxydihydro-2*H*-pyran moiety, giving a 1:1 mixture of hypocrolide A (**6**) and C1,2-*epi*-hypocrolide A (**22**) in an overall yield of 61%. Interestingly, the treatment of **22** with TFA in DCM/MeOH led to the regeneration of **6** in 84% yield (brsm). Using this route, we successfully synthesized more than 110 mg of **6** (>99% ee), which represents more than 40 times the amount previously isolated from the natural sources.

In summary, we have achieved the first and catalytic enantioselective total synthesis of hypocrolide A (>99% ee) as well as the synthesis of other botryanes. The absolute

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configurations of these compounds have been unambiguously confirmed or reassigned. The highly functionalized hydrindane system of botryanes was constructed efficiently via an unusual rhodium-catalyzed intramolecular [4 + 2] cycloaddition, which not only proceeded under mild conditions but represents the first reported example of the use of an electron-deficient alkyne as a dienophile in a transition metal-catalyzed [4 + 2] cycloaddition. Furthermore, the challenging hexacyclic skeleton of hypocrolide A was successfully installed using a biomimetic oxidative [3 + 2] cycloaddition based on our revised biogenetic pathway. The concise and scalable total synthesis of hypocrolide A proceeded in 12 steps from a commercially available starting material.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02414.

Detailed experimental procedure, ^{1}H NMR and ^{13}C NMR spectra, as well as X-ray data information (PDF)
X-ray data for compound **8a** (CIF)
X-ray data for compound **11a** (CIF)
X-ray data for compound **16b** (CIF)
X-ray data for compound **19a** (CIF)
X-ray data for compound **19b** (CIF)

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Notes

The authors declare no competing financial interest.

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