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Total Synthesis of (±)-Chloranthalactone A

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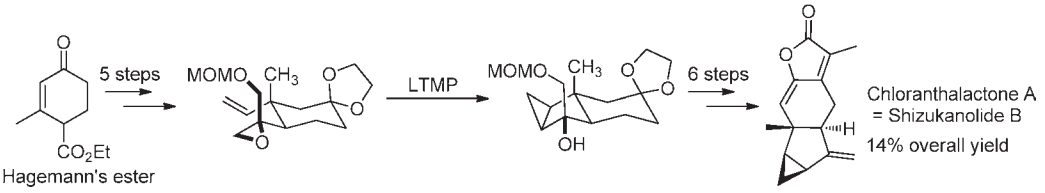
ABSTRACT



A total synthesis of (±)-chloranthalactone A was completed. It features substrate-controlled epoxidation of ketone and highly diastereoselective intramolecular cyclopropanation to construct the *cis*, *trans*-3/5/6 tricyclic skeleton.

Chloranthalactone A, also named shizukanolide B, was first isolated from the *Chloranthus* genus in 1978 (Figure 1).[1] Since then, a number of structurally related sesquiterpenoids in this family have been isolated continuously, including chloranthalactones B–G,[2] shizukanolides A–H,[2a,3] and so on. These siblings possess a novel polycyclic framework embedded with a sterically congested cyclopentane (ring B) and the unusual *trans*-5/6 ring junction. In addition, a series of dimeric sesquiterpenoids embracing the same skeleton have also been isolated, for instance shizukaols A–P,[4,3c] chloramultilides A–D,[5] chlorahololides A–F,[6] etc.[7] Moreover, many of them show impressive bioactivities, such as moderate antifungal activity for chloranthalactone A,[8] strong cytotoxic activity against VERO cells for oxyonoseriolide (IC_{50}: 0.2 μM),[9] and selective inhibition on the delayed rectifier (I_k) K^+ current for chlorahololide D (IC_{50}: 2.7 μM)[6b] as well as inhibition of PMA-induced homotypic aggregaton of HL-60 cells for shizukaol B (MIC: 34.1 nM).[10]

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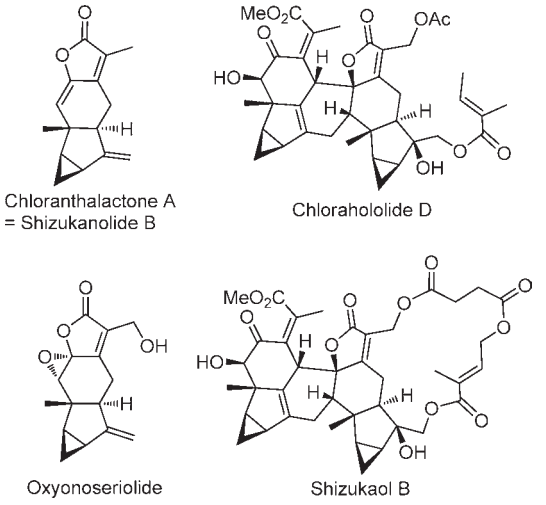
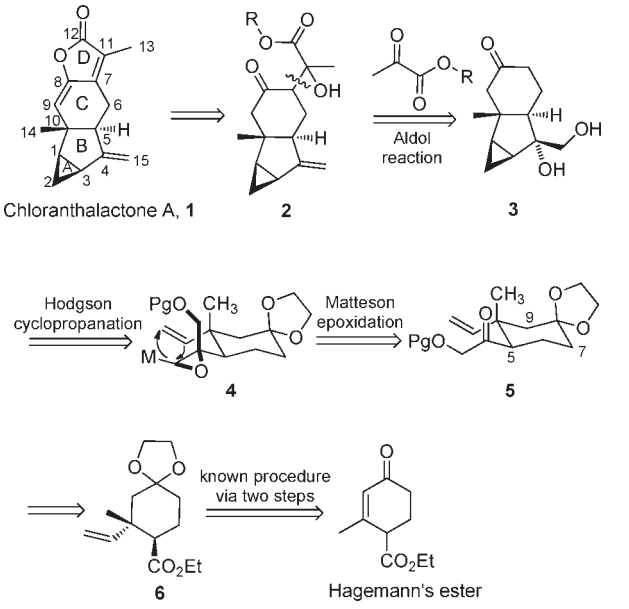


Figure 1. Structures of chloranthalactone A, oxyonoseriolide, chlorahololide D, and shizukaol B.

Despite the promising bioactivity and the structural complexity and diversity, there have been only limited reports on the synthesis of lindenane sesquiterpenoids over the decades.[11]Involved in natural product synthesis,[12] we were interested in developing a general synthetic strategy toward these lindenane sesquiterpenoids and the dimers. Herein we disclose our total synthesis of racemic chloranthalactone A.

From a retrosynthetic viewpoint, ring D of chloranthalactone A could be constructed via an intramolecular ring closure from intermediate **2** (Scheme 1), which could be achieved through an aldol reaction and the olefination from intermediate **3**. Due to the relative thermodynamical instability of the *trans*-5/6 fused ring system over the *cis* one,[13] we preferred not to introduce any C_4 functionality, a C_4 ketone for example,[11a] that might induce the interconversion between the *trans*- and *cis*-5/6 fused ring system. While intramolecular cyclopropanation of unsaturated terminal epoxide to bicyclo[3.1.0]-2-ol has been explored by Hodgson et al.,[14] the reaction with a geminally disubstituted epoxide has not been reported. We were interested in extending such a strategy to set up the skeleton of the 3/5/6 polycyclic framework of the lindenane sesquiterpenoids and control the proper stereochemistry through the optimal chair conformation of cyclohexane ring B (intermediate **4**). The geminally disubstituted epoxide in intermediate **4** might be obtained in a substrate-controlled manner from ketone **5**. Therefore a commercially available compound, Hagemann's ester, could be deduced as the starting point.

Scheme 1. Retrosynthetic Analysis of Chloranthalactone A



A synthetic route toward chloranthalactone A is outlined in Scheme 2. The known compound **6** was achieved according to the two-step literature procedure including vinyl Michael addition to Hagemann's ester and ketone protection with glycol.[15] Subsequently, **6** was treated with LiN(OMe)Me to give the corresponding Weinreb amide, which was attacked by in situ generated $LiCH_2OMOM$ to obtain ketone **7** in 90% yield over two steps.[16] The combination of *n*-butyllithium and dibromomethane promoted Matteson epoxidation[17] of **7**, affording epoxide **8** with excellent stereoselectivity (dr $>$ 20:1). However, the epoxidation of **7** with sulfur ylide or sulfonium ylide proved inefficient; the reaction was sluggish and accompanied with a complex mixture of products, and the C_5 epimerization was observed during the reaction process. Treatment of **8** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) smoothly generated the 3/5/6 tricyclic compound **9** in 90% yield. It is worth noting that replacing the methoxymethyl (MOM) protective group by a *tert*-butyldimethylsilyl (TBS) group in **8** failed to realize the intramolecular cyclopropanation, with a complex mixture formed. With the key tricyclic compound in hand, we next introduced the terminal olefin at C_4. Global deprotection of compound **9**, followed by treament with 1,1′-thiocarbonyldiimidazole in the presence of DMAP, provided

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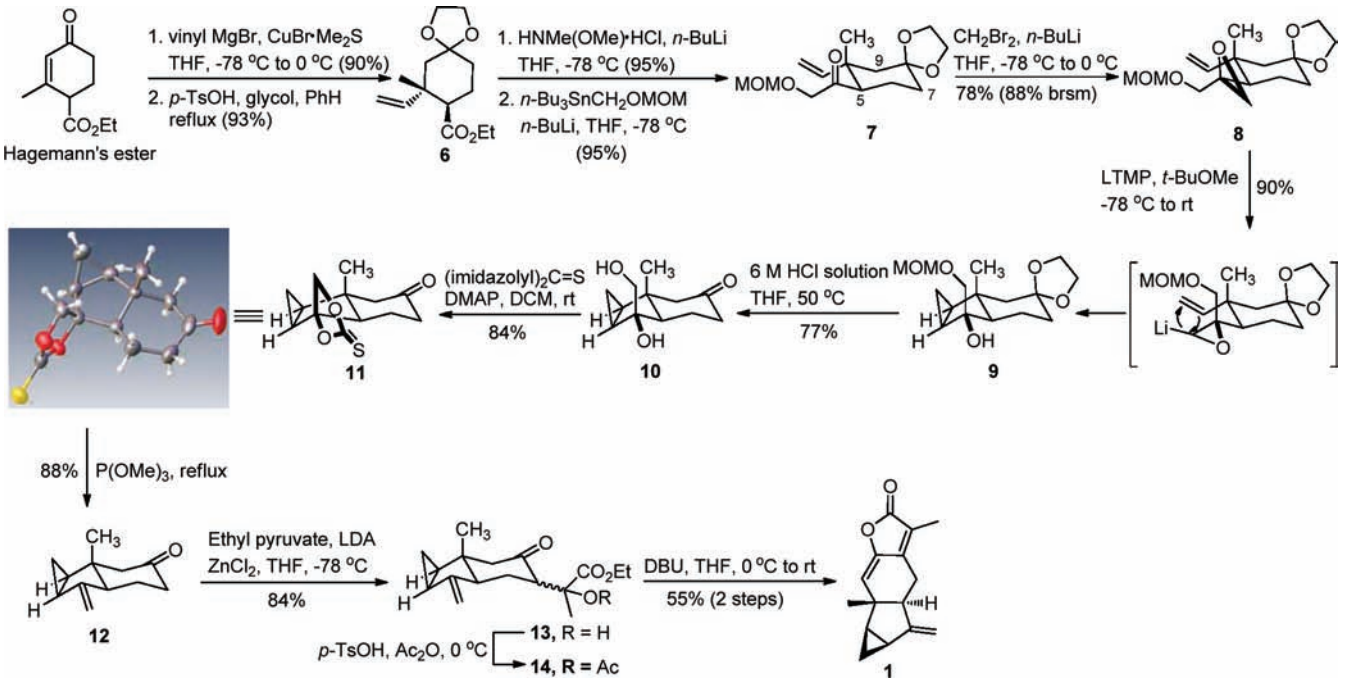
Scheme 2. Total Synthesis of Chloranthalactone A



dioxolanethione **11** in 65% yield over two steps.[18] The structure and stereochemistry of **11** were confirmed by X-ray crystallographic analysis (Scheme 2). Corey olefination of **11** with trimethyl phosphite led to the formation of desired compound **12** cleanly in 88% yield.[19] To fulfill the final transformation, we applied a three-step strategy to construct the γ-alkylidenebutenolide segment of chloranthalactone A. Aldol reaction of **12** with ethyl pyruvate produced compound **13** as a diastereomeric mixture in 84% yield.[20] Protecting the tertiary hydroxyl in **13** as an acetate is necessary for facilitating the last base-promoted ring formation, since retro-aldol reaction of **13** in the presence of base formed **12**. While routine acetylation of compound **13** proved inefficient, we succeeded in getting compound **14** with *para*-toluenesulfonic acid in acetic anhydride.[21] Finally, the DBU-promoted cyclization of **14** furnished chloranthalactone A in 55% yield over two steps. This base-promoted cyclization is crucial to leave the exocyclic alkene on the ring B unimpacted, because its isomerization to an internal alkene in the presence of acid has been reported.[8] The characterization data of our synthetic sample are in good accord with those of the natural product.[22]

In summary, we accomplished the total synthesis of chloranthalactone A in 12 steps and 14% overall yield from the commercially available Hagemann's ester. Our current synthesis features a highly diastereoselective epoxidation of ketone, an efficient intramolecular cyclopropanation to construct the *cis*, *trans*-3/5/6 skeleton, and a DBU-promoted cyclization for the γ-alkylidenebutenolide ring formation. Further studies to synthesize other interesting lindenane sesquiterpenoids and the dimers by this strategy are in progress.

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Supporting Information Available. Experimental procedures, characterization data for new compounds, and selected copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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