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Total synthesis of (+)-chloranthalactone F†

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Sequential biomimetic elaborations, featured by CrO_3-mediated oxidative lactonization, and DDQ-involved oxidative enol-lactonization, ensured the concise total synthesis of (+)-chloranthalactone F.

Since the first isolation of shizukaol A, a large number of lindenane sesquiterpenoid dimers, with various biological activities, have been isolated from the plants of chloranthaceae.[1] Biogenetically, these unique dimers are supposed to be formed through a [2+2] or [4+2] cycloaddition process,[2] like chloranthalactone F (**1**)[1k,l] and chlorahololide A (**2**),[1m] respectively (Fig. 1). Efforts on this class and related monomer had been reported.[3]

Chloranthalactone F was isolated from the leaves of chloranthus glaber. The structure of chloranthalactone F (**1**, Fig. 1), which was originally misassigned by Takeda and co-workers,[1k] was revealed as a result of the pioneering studies of the group of Nakatani.[1l] Structurally, chloranthalactone F features two cyclopropane rings bearing two adjacent angular methyl groups, a highly congested cyclobutane ring, two exocyclic double bonds, and twelve contiguous stereogenic centers. Although the structure of this compound was determined as shown,[1l] its absolute configuration and biological activities have not been reported thus far. Herein, we describe a concise and enantioselective synthesis of chloranthalactone F (**1**).

Given the axial symmetry of chloranthalactone F (**1**) and the biogenetical hypothesis on its formation, a biomimetic

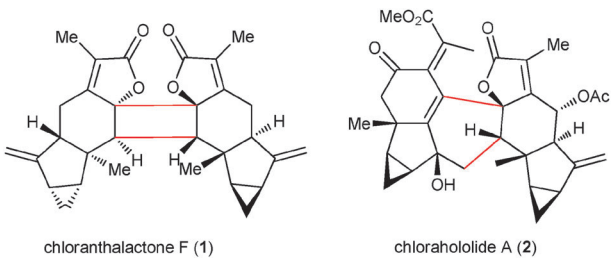

Fig. 1 Representative molecular structures of lindenane sesquiterpenoid dimers.

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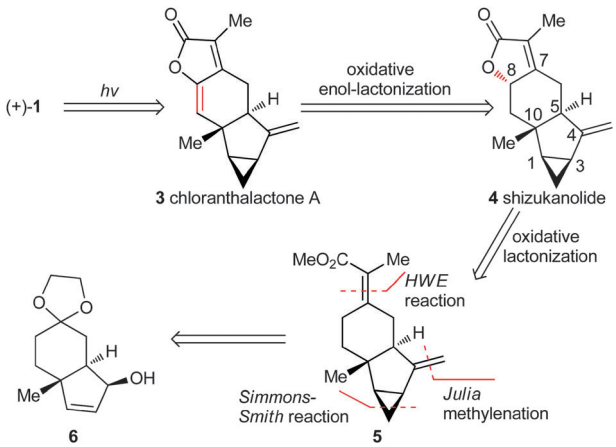
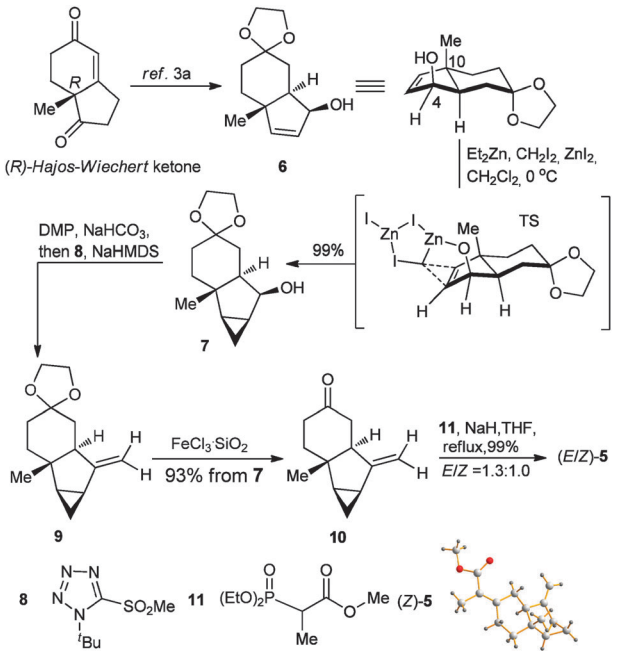


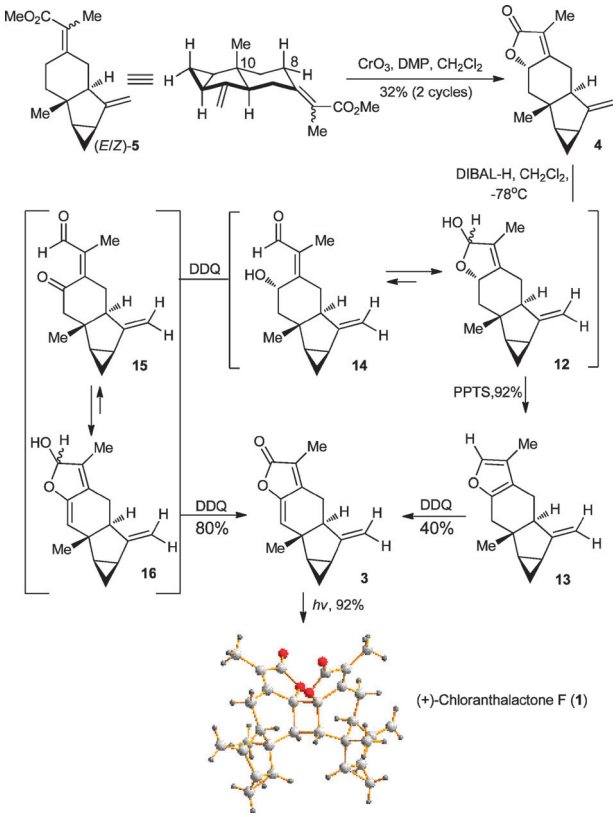
Scheme 1 Retrosynthetic analysis of chloranthalactone F.

strategy was taken for its total synthesis (Scheme 1). [2+2] photocycloaddition of enol lactone **3**, known as chloranthalactone A,[1l,4] would provide chloranthalactone F. Furthermore, it was anticipated that enol lactone **3** could be obtained through oxidative enol-lactonization from **4**, named shizukanolide.[4a,b] And lactone **4** would then be accessible by stereocontrolled oxidative lactonization[5] at C8 of precursor **5**. Overall, the proposed retrosynthetic strategy was designed, with minimal protecting-group used and tandem reactions included,[6] to allow investigation into the potentially biosynthetic interconnectivity between chloranthalactone F, **3** and **4**.

Our synthesis began with the cyclopropanation of the allylic alcohol **6** (Scheme 2), which was available with a scalable and highly efficient synthetic route.[3a] Previous approaches for the construction of the chiral cyclopropane unit include $Cu(acac)_2$-catalyzed intramolecular cyclopropanation reaction taken by Baldwin and co-workers,[3b] and a chiral pool strategy followed by Pd-catalyzed enyne cyclization adopted by Liu and Nan,[3e] However, both methods gave products with the newly formed cyclopropane *anti* to the C10-methyl group as favored by sterics, which is opposite to the configuration present in the natural product. Herein, it was presumed that the well-documented directing effect[7] of the hydroxyl group at C4 of **6** in Simmons–Smith's cyclopropanation would override the stereocontrol of the C10 methyl group to deliver the product with the correct configuration. Indeed, initial investigation from our lab has disclosed that Simmons–Smith's reaction is an effective method for the construction of the highly strained 3–5 bicyclic framework,[3a] whereas long reaction



Scheme 2 Preparation of ester **5**.



Scheme 3 Total synthesis of (+)-chloranthalactone F.

time and tedious operation were included. To our delight, further screening conditions revealed that treatment of **6** with excess of $ZnEt_2$ and CH_2I_2 in the presence of ZnI_2[8] as additive afforded the desired cyclopropane **7** in a nearly quantitative yield as a single diastereoisomer in 12 h. As the excellent diastereoselectivity was ascribed to the hydroxyl group acting as the directing group to create an orderly transition state, we hypothesized that the ZnI_2 could be responsible for shortening the reaction time due to the enhanced reaction rate *via* the proximity effect (TS, Scheme 2). Subsequent oxidation of **7** with Dess–Martin periodinane[9] together with $NaHCO_3$ as neutralizer was followed by methylenation using an improved Julia reagent **8**[10] to deliver the desired exocyclic methylene adduct **9**. Removal of the ketal in **9** with $FeCl_3{\cdot}SiO_2$[11] furnished the tricyclic ketone **10** in an excellent yield (overall yield 93% from **7**) and its relative stereochemical structure was confirmed by a nOe experiment. Also mentionable here is that the four synthetic steps from **6** to **10** could be done with only one chromatographic purification on silica gel. Treating ketone **10** with phosphite ester derivative **11** resulted in an inseparable 1.3 : 1.0 mixture of **5** in a quantitative yield favoring the desired (*E*)-isomer, the stereochemistry of which was determined by extensive spectroscopic studies and a single crystal X-ray diffraction analysis of the (*Z*)-isomer. Stereoselectivity improvement was tried by the application of the Peterson olefination and treatment with $(RO)_2POCH(Me)CO_2Me$ (R = Me or ^{i}Pr), which resulted in no reaction or gave no improvement on the ratio of *E*/*Z* (*ca.* 1.3 : 1.0), respectively.

To complete the total synthesis, we firstly turn our attention to realize the activation of γ-methylene at C8 of ester **5** (Scheme 3). Considering the innate structural character, competitive reactions due to the discrepancy of chemoselectivity[12] between the exocyclic methylene group and α,β-unsaturated ester would make this pivotal transformation very challenging. Incipient experimentations for oxidant screening, including SeO_2,[13a] $Mn(OAc)_3/^tBuOOH$,[13b] $Pd(OH)_2/^tBuOOH$,[13c] PCC,[13d] and PDC,[13e] resulted in no reaction or numerous unidentified impurities which probably originated from the release of the severe ring-strain of cyclopropane and **5–6** bicycle. Gratifyingly, it was found that employing ester **5**, CrO_3 and 3,5-dimethylpyrazole (DMP)[5] in a mole ratio of 1 : 2 : 4 in dried CH_2Cl_2 at reflux for 12 h provided **4** in reproducibly respectable yields (32%) for this complex system, with complete diastereoselectivity. As the moderate yield was imputed to the low conversion, which was caused by ligand reorganization or polymerization of the oxidant under reflux,[5a] the sole stereoselectivity was probably attributed to the unpreferred β-hydrogen abstraction at C8 which was blocked due to the 1,3-diaxial interaction with the C10 methyl group. With a reliable route to **4** secured, sequential biomimetic elaboration was tried to obtain **3** and **1**. Reduction of lactone **4** with DIBAL-H in CH_2Cl_2 at −78 °C afforded hemiacetal **12**, which was subjected to DDQ[14] in the presence of PPTS to deliver **3** by way of furan derivate **13** in three steps (36%). Further studies here show that enol lactone **3** could be formed directly from lactol **12** in 80% yield by means of DDQ. In view of the unfeasibility from lactone **4** to **3** in the presence of DDQ (see the ESI† for details), two possible pathways for DDQ-mediated oxidative enol-lactonization were proposed (Scheme 3), in which furan derivate **13** and keto-aldehyde **15** were involved, respectively. At this juncture, exposure of the enol lactone **3** in hexanes to a high pressure Hg lamp (125 W) in quartz at rt[1*l*] furnished (+)-chloranthalactone F (**1**) smoothly in 92% yield, the absolute configuration of which was confirmed unequivocally

by X-ray crystallography.‡ Besides, all spectral data ($[\alpha]_D$, NMR, HRMS) of the synthetic materials were identical to those reported.

In summary, we have accomplished the asymmetric total synthesis of chloranthalactone F (**1**) in 14 steps from Hajos–Wiechert ketone[15] using CrO_3-mediated oxidative lactonization, and DDQ-involved oxidative enol-lactonization as key steps. Additionally, the present work, which disclosed the potential biosynthetic interconnectivity between chloranthalactone F, **3** and **4**, paves a consulting synthetic strategy to the other dimers. Efforts in this direction are being actively pursued in our lab and the results will be reported in due course.

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‡ *Crystal data*: CCDC 839420: M = 246.34, orthorhombic, $P2(1)2(1)2(1)$, a = 7.0704(14), b = 9.5189(19), c = 20.411(4) Å, β = 90°, V = 1373.7(5) Å^3, Z = 4, D = 1.191 Mg m^{-3}, ρ = 0.077 mm^{-1}, $F(000)$ = 536; 7496 reflections measured, of which 2691 were unique (R_{int} = 0.0215). 166 refined parameters, final R_1 = 0.0390, wR_2 = 0.1004 for reflections with $I > 2\sigma(I)$, GOF = 1.051. Final largest diffraction peak and hole: 0.157 and −0.152 e Å^{-3}. CCDC 839421: M = 456.56, orthorhombic, $P2(1)2(1)2(1)$, a = 11.7192(9), b = 12.3720(9), c = 16.8928(12) Å, β = 90°, V = 2449.3(3) Å^3, Z = 4, D = 1.238 Mg m^{-3}, ρ = 0.081 mm^{-1}, $F(000)$ = 976; 13321 reflections measured, of which 4813 were unique (R_{int} = 0.0219). 311 refined parameters, final R_1 = 0.0376, wR_2 = 0.0959 for reflections with $I > 2\sigma$ (I), GOF = 1.027. Final largest diffraction peak and hole: 0.168 and −0.148 e Å^{-3}.

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