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Synthetic studies towards Chlorahololides A: practical synthesis of a lindenane-type sesquiterpenoid core framework with a 5,6-double bond

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ABSTRACT

Towards Chlorahololides A: a lindenane-type sesquiterpenoid framework that contains a 5,6-double bond was synthesized from simple starting materials. The reductive cyclization of a 1,6-enyne and an unusual endo-type intramolecular Heck reaction was used as key steps for ring closure.

Chlorahololides A (Fig. 1) is a sesquiterpenoid dimer isolated from South China *Chloranthus holostegius* by Yue and co-workers in 2007.[1] It exhibits potent and selective inhibition of the delayed rectifier (I_K) K^+ current with an IC_{50} of 10.9 μM, and is 96 times as potent as the positive control, tetraethylammonium chloride, a classical blocker of the delayed rectifier (I_K) K^+ current. Potassium (K^+) channels play vital roles in the regulation of a variety of physiological processes, in association with many severe human diseases.

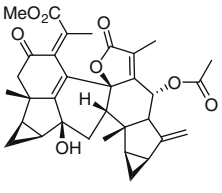
According to the biogenetic hypothesis proposed by Yue et al. (Scheme 1) for this complex natural product, Chlorahololides A might be formed through an enzymatic Diels–Alder cycloaddition of two molecular lindenane-type sesquiterpenoids (components A and B).[1] So far, more than 20 oligomers of lindenane-type sesquiterpenoids have been isolated.[2–13] Most of them are dimers that were formed through a 'Diels–Alder-type connection' of lindenane-type sesquiterpenoids. Some of them have demonstrated interesting bioactivities.[14]

Lindenane-type sesquiterpenoids have been isolated for more than 40 years[15–19] (Fig. 2 shows the carbon skeleton of lindenane-type sesquiterpenoids), and some of them have displayed meaningful bioactivity.[18,20] However, until now, synthetic studies on this type of sesquiterpenoid have been rare.[21] No reports are available on the synthesis of lindenane-type sesquiterpenoid frameworks that contain a 5,6-double bond (Scheme 1 component A), which actually serves as an important intermediate of Diels–Alder-type dimerization, and is especially useful for the synthesis of the natural product Chlorahololides A as proposed here.

Intrigued by the interesting biological activity and intricate structure of Chlorahololides A, we decided to study and develop a practical synthesis route for lindenane-type sesquiterpenoids with a 5,6-double bond, which can be used not only as a key step for total synthesis of Chlorahololides A, but is also applicable to the synthesis of other lindenane-type sesquiterpenoid dimers.

Herein, we report a practical route starting from simple materials to synthesize lindenane-type sesquiterpenoid frameworks with a 5,6-double bond by the use of a reductive cyclization of a 1,6-enyne and unusual endo-type intramolecular Heck reaction as the key steps for ring closure.

We envisaged that the precursors of the Diels–Alder cycloaddition, components A and B could all be reached from compound **1** under base and acid conditions, respectively. Compound **1** would be accessed from compound **2** in view of the chemical reactivity of the butenolide[22,23] (Scheme 2).



Chlorahololides A

Figure 1. Chlorahololides A.

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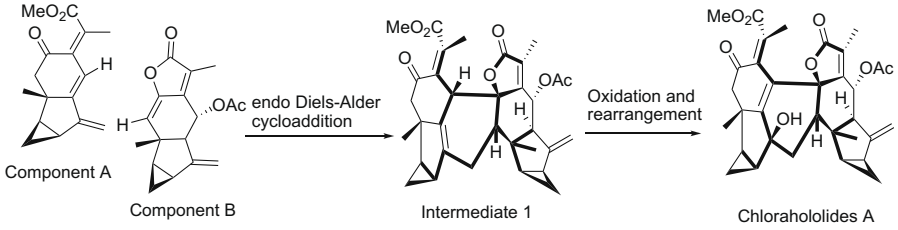


Scheme 1. Biogenetic pathway proposed for Chlorahololides A.

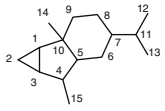
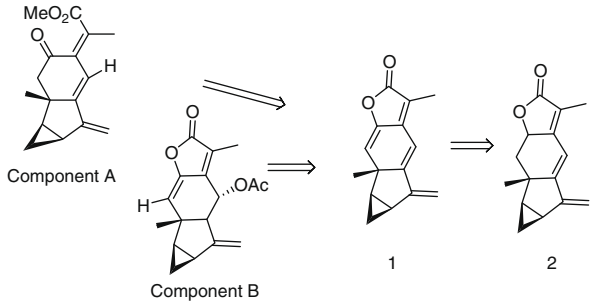


Figure 2. Carbon skeleton of lindenane-type sesquiterpenoids.

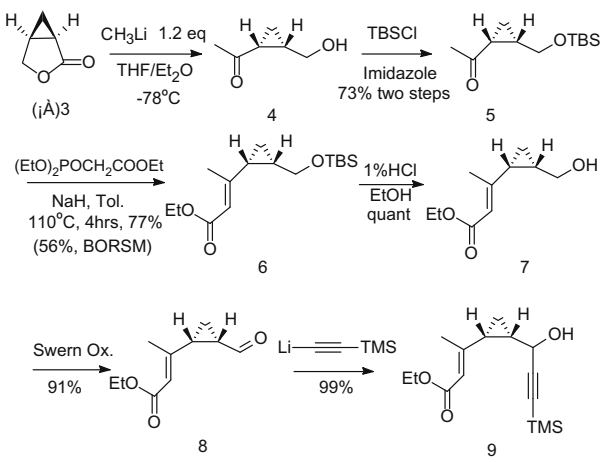


Scheme 2. Retrosynthetic analysis of the key intermediate.

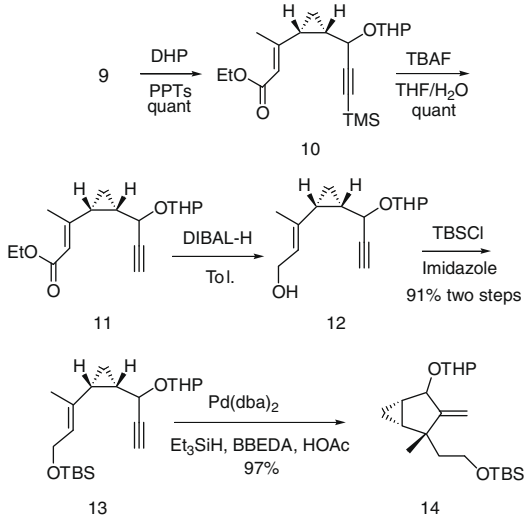
We started from the racemic bicyclic lactone **3**, which was prepared from copper-catalyzed intramolecular cyclopropanation of the allylic diazoacetate, as reported previously.[24] By controlling the addition speed of methyllithium solution in ether and the reaction temperature, alcohol **4** was obtained without any overmethylation product, and then the resulting primary hydroxyl group was protected by *tert*-butyldimethylsilyl (TBS) to afford ketone **5** in good yield from two steps. The HWE reaction of ketone **5** and triethyl phosphonoacetate was problematic because of the steric effect and tendency to be racemized under harsh base conditions. We accomplished the reaction after many trials using sodium hydride as base in toluene at reflux temperature for 4 h. The *E*-configuration α,β-unsaturated ester **6** was produced in 77% yield based on 56% conversion without *Z*-product. The unsaturated ester **6** obtained was then converted to alkynol **9** by deprotection, followed by Swern oxidation and further ethynylation in excellent yield (Scheme 3). Diastereomers were produced in the ethynylation reaction, which could be easily separated by silica-gel column chromatography. The ratio of diastereomers was 8:5. However, they could both be converted to the same compound **20** after oxidation of the hydroxyl group through our next reaction route; therefore, the mixture was used in the next step without further separation.

With alkynol **9** in hand, we next sought to investigate cyclization of the 1,6-enyne.[25] After hydroxyl group protection, desilylation, reduction of the α,β-unsaturated ester and protection of primary alcohol **13**, reductive cyclization was accomplished to provide the exomethylene product **14** (Scheme 4), using the method of Trost,[26] in 97% yield, and no other diastereomer, although it was confirmed that the configuration of the chiral methyl group of **14** is unexpected by NOE analysis of tetracyclic ketone **21** at a later stage (Fig. 3).

After desilylation of **14**, Swern oxidation of primary alcohol **15** led to aldehyde **16** in excellent yield. Then aldehyde **16** was treated with Grignard reagent **17**[27] to afford butenolide diastereomers **18a** and **18b** (diastereomer ratio >10:1) that could be separated by silica-gel column chromatography. The butenolide **18a** was converted to the precursor of the intramolecular Heck reaction through deprotection and Swern oxidation. Although an exo-type intramolecular Heck reaction is impossible for this substrate,[28] the endo-type ring closure was still problematic. No desired product was detected under Overman's conditions.[29] After many reaction condition screenings, tetracyclic ketone **21** was produced in a 40% yield based on 50% conversion under ligand-free conditions.



Scheme 3. Synthesis of intermediate **9**.



Scheme 4. Synthesis of first ring-closing intermediate **14**.

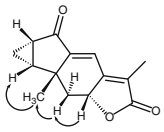
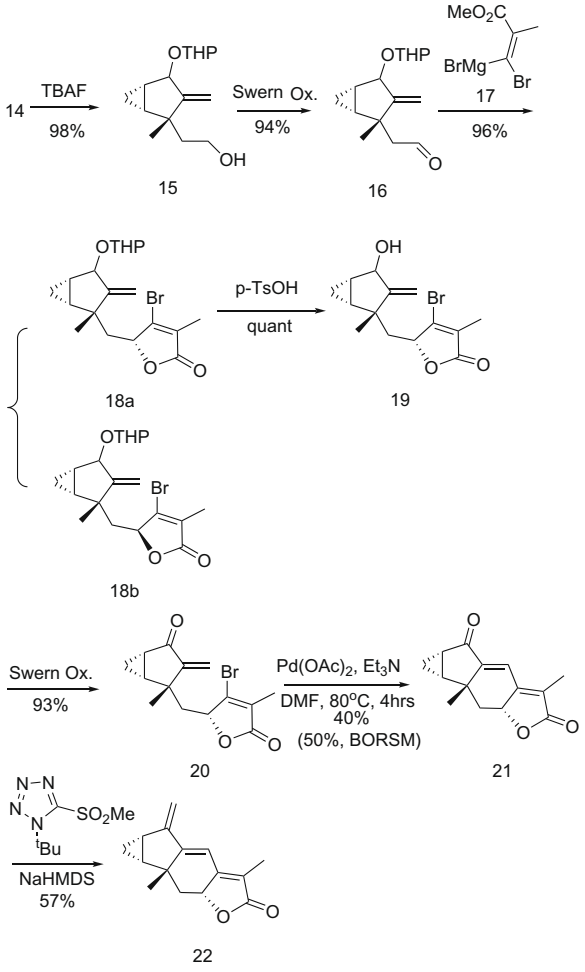


Figure 3. NOE analysis of tetracyclic ketone **21**.



Scheme 5. Synthesis of lindenane-type sesquiterpenoid framework **22**.

NOE analysis of **21** (Fig. 3) provided all relative stereochemistry characteristics. Finally, the methylenation reaction was achieved under modified Julia–Kocienski conditions[21] in moderate yield to give compound **22**,[30] which possesses a typical lindenane-type sesquiterpenoid framework with a 5,6-double bond (Scheme 5). Compared with the desired key intermediate for the synthesis of natural product Chloraholides A, only the 14-methyl group is epimeric.

In summary, we have developed a practical synthesis of the lindenane-type sesquiterpenoid framework containing a 5,6-double bond. Although it gives an unexpected 14-epi methyl configuration in cyclization of the 1,6-enyne, it is still valuable for the synthesis of the lindenane-type sesquiterpenoid framework. The chiral 14-methyl configuration could be redressed in the early stage of synthesis to construct the correct final product. Currently we are working on this and the results will be described elsewhere.

Acknowledgement

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30. *Characterization data of compound* **22**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.54 (s, 1H), 5.34 (s, 1H), 5.13 (s, 1H), 4.97–5.03 (m, 1H), 2.43 (dd, J = 5.1, 11.7 Hz, 1H), 1.94–2.00 (m, 1H), 1.89 (s, 3H), 1.48–1.57 (m, 2H), 1.27 (s, 3H), 0.74–0.81 (m, 1H), 0.12–0.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.9, 156.4, 154.9, 149.6, 119.5, 113.7, 107.2, 77.0, 45.6, 40.1, 28.6, 26.2, 20.5, 12.2, 8.7; HRMS (EI) m/z [M+] calcd for $C_{15}H_{16}N_4O_2$: 228.1150, found: 228.1154.