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A Concise Construction of the Chloraholide Heptacyclic Core

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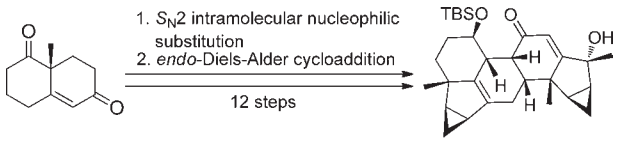
ABSTRACT



A concise and efficient strategy for the construction of the heptacyclic core of the chloranthaceae family has been developed. The key strategy comprises an S_N2-type intramolecular nucleophilic substitution and a biomimetic *endo*-Diels–Alder cycloaddition.

After the first isolation of a lindenane sesquiterpenoid dimer shizukaol A (**1**) from *Chloranthus japonicas*,[1] 42 similar structural dimers have been characterized from the chloranthaceae family to date (Figure 1).[2] Interesting biological activities were shown by these novel dimers, such as cell adhesion inhibition,[3] inhibition of the delayed rectifier K^+ current,[4,5] and antifungal,[6] cytotoxicity,[7] and tyrosinase inhibitory activity.[8]

In 2007 and 2008, Yue and co-workers isolated two novel lindenane sesquiterpenoid dimers, chloraholide A (**2**)[4,9] and chloraholide C (**3**),[5] from South China

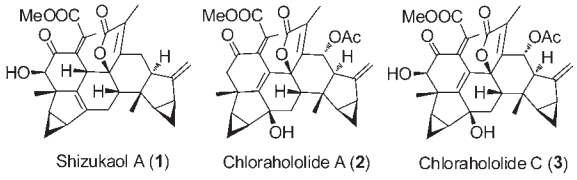


Figure 1. Chloranthaceae family.

Chloranthus holostegius and reported their potent and selective inhibition on the delayed rectifier (I_K) K^+ current, with IC_{50} values of 10.9 and 3.6 μM, respectively.[4,5] It is noteworthy that chloraholides A (**2**) and C (**3**) are 96- and 292-fold more potent than the positive control, tetraethylammonium chloride (IC_{50} = 1.05 mM), a classical blocker of the delayed rectifier (I_K) K^+ current.[4,5] However, the unique heptacyclic core that is characteristic of all 42 lindenane sesquiterpenoid dimers among the chloranthaceae family is unprecedented among known natural products. The obvious synthetic challenge posed by the chloranthaceae family, coupled with their impressive biological activity, has generated a significant interest from the synthetic community. However, as yet the total

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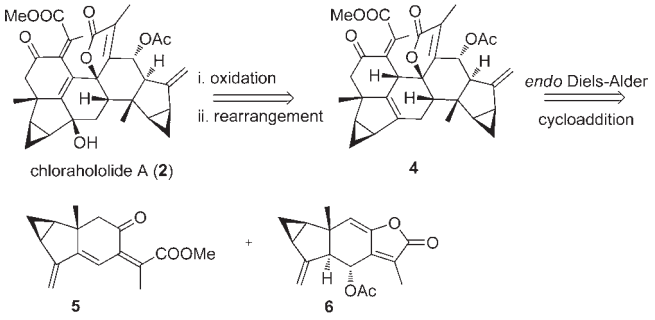
synthesis of any member from the chloranthaceae family has not been reported with the exception of some synthetic studies.[10] The low natural abundance of these chloranthaceae family compounds combined with their unprecedented molecular architectures and interesting biological properties prompted us to undertake their chemical synthesis. Herein, we present a concise approach which has led to the assembly of the heptacyclic core of chloraholide A (**2**) through a flexible synthetic strategy which we believe may be applied to the construction of other members of the intriguing chloranthaceae family.

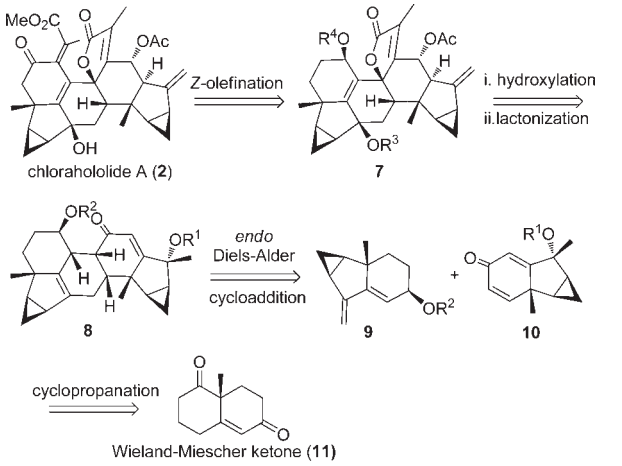
Scheme 1. Biogenetic Pathway Proposed for Chloraholide A (**2**)



Inspection of the structure of chloraholide A (**2**) reveals a linking six-membered ring, a common structural feature of all chloraholides. As shown in Scheme 1, a biogenetic hypothesis was proposed for chloraholide A (**2**) via the enzymatic *endo*-Diels–Alder cycloaddition of two molecular lindenane-type sesquiterpenoids (components **5** and **6**) followed by the oxidation and rearrangement of the corresponding cyclized product.[4,9,11,12] This is supported by a literature report that pyrolysis of shizukaol A (**1**) in a sealed tube results in retro *endo*-Diels–Alder fragmentation of the linking six-membered ring to furnish two products: the relatively unstable diene and the previously known chloranthalactone A, which are similar to **5** and **6**, respectively.[1]

In consideration that one of the Diels–Alder components is likely unstable,[1,4,10a] we reason that the synthesis of a simpler heptacyclic core and its full conversions to naturally occurring chloraholide A (**2**) and shizukaol A (**1**) should be an alternative approach. Therefore, according to the aforementioned proposed biogenetic pathway, the critical step for constructing skeletons relevant to those of chloraholides by mimicking the *endo*-Diels–Alder cycloaddition would then be the expedient and practical conversion of precursors **9** and **10** to the core intermediate **8**. The enantiopure cyclopropanyl precursors **9** and **10** could be generated from commercially available chiral Wieland–Miescher ketone **11** via an S_N2-type intramolecular nucleophilic substitution (Scheme 2). The pivotal core **8** could then undergo the formation of butenolide, and hydroxylation followed by *Z*-selective olefination of the resulting lactone **7** will be expected to eventually afford the synthetic chloraholide A (**2**) and shizukaol A (**1**).

Scheme 2. Retrosynthetic Analysis of Chloraholide A (**2**)



Our synthesis of the heptacyclic core commenced with commercially available (±)-Wieland–Miescher ketone **11** (Scheme 3), which was transformed into mesylate **12** through a stereoselective reduction followed by protection of the resulting secondary alcohol with methanesulfonyl chloride in 84% yield for two steps.[13] Regioselective formation of dienol acetate **13** from mesylate **12** followed by oxidation with *m*-CPBA afforded alcohols **14** or **15** with the γ-hydroxyl groups in 65% overall yield and a 1:3 ratio of α/β selectivity.[14] Upon treatment of **14** with Ac_2O/Py and treatment of **15** with AcOH under Mitsunobu reaction conditions, acetate **16** was smoothly obtained.[15] Having failed to directly protect the carbonyl group of enone **16** to the corresponding ketal or dithiane,[13,16] we then realized

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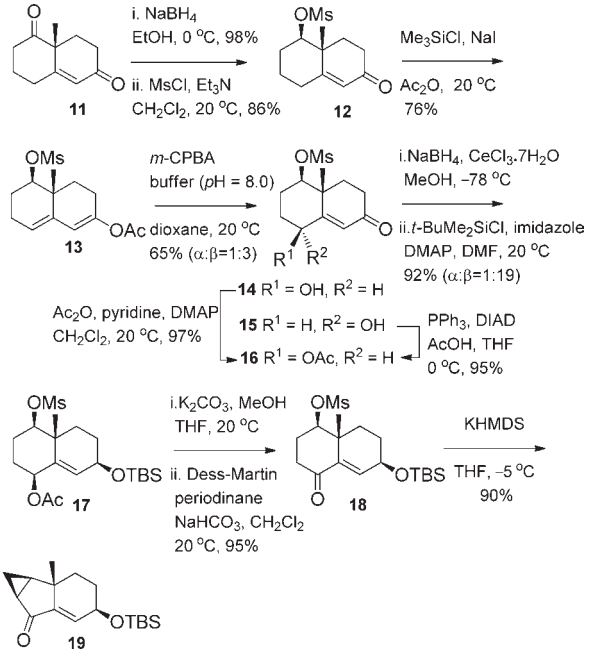
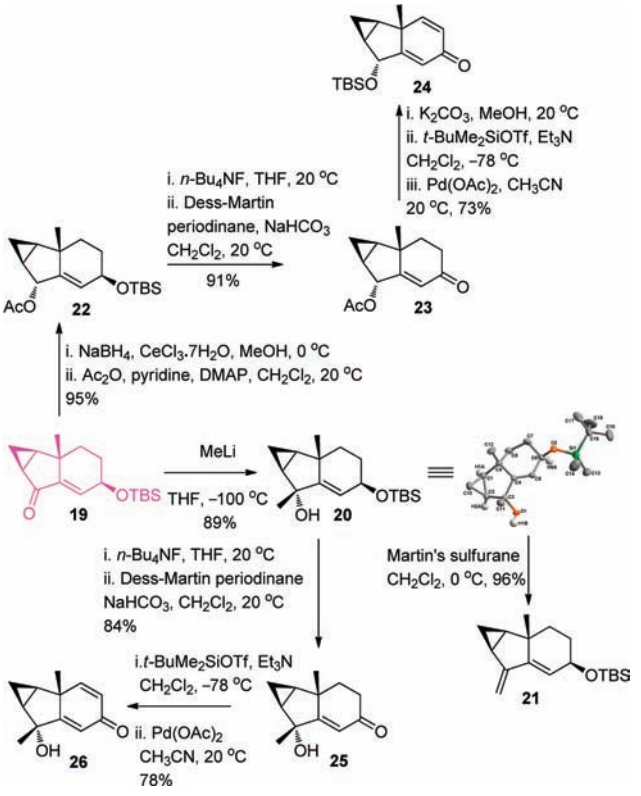
Scheme 3. Synthesis of Cyclopropane **19**



Scheme 4. Synthesis of Diene **21** and Dienophiles **24** and **26**



the related β-allylic alcohol from enone **16** under Luche conditions at −78 °C in 92% yield and with an excellent diastereoselectivity (dr = 19:1, detected by ^{1}H NMR spectrometry).[17] The resulting alcohol was converted to enone **18** after the protection of the free hydroxyl group with *tert*-butyldimethylsilyl chloride followed by removal of the acetyl group and subsequent oxidation with Dess–Martin periodinane.[18] Gratifyingly, upon treatment of enone **18** with KHMDS, the desired cyclopropyl enone **19** was exclusively achieved from enone **18** via an S_N2-type intramolecular nucleophilic substitution in 90% yield.[19] The desired stereochemistry of enone **19** was confirmed by further evidence from an X-ray crystallographic analysis of the late allylic alcohol **20** (Scheme 4).

With cyclopropyl enone **19** in hand, we then turned our attention to its transformation into diene **21** and dienophile **24** (Scheme 4). The modified Julia–Kocienski conditions[10,20] were then investigated to install the terminal olefin in diene **21**; however, the major product from 1,4-Michael addition between enone **19** and the deprotonated Julia reagent was obtained instead. To this end, treatment of enone **19** with MeLi followed by Martin's sulfurane-mediated elimination of the resulting tertiary hydroxyl group from **20** provided the desired diene **21** in 85% overall yield for two steps.[21] To furnish dienophile **24**, Luche reduction[17] of enone **19** followed by protection of the resulting alcohol with Ac_2O gave rise to acetate **22** in excellent yield, which was subsequently treated with TBAF and Dess–Martin periodinane[18] to afford enone **23** in 91% yield. Enone **23** was converted into dienophile **24** through the TBS-enol ether formation followed by a Saegusa procedure in 73% yield.[22] As shown in Scheme 4, conversion of **20** via a similar aforementioned transformation of enone **23** into **24** provided the corresponding dienophile **26** for the following studies toward total synthesis of chloraholide A (**2**) via *endo*-Diels–Alder cycloaddition.

With the desired diene **21** and dienophile **24** secured, the construction of the linking six-membered ring was pursued (Scheme 5). After considerable experiments to carry out the Diels–Alder cycloaddition reaction between diene **21** and dienophile **24**,[23] it was found that treatment of diene **21** (2.25 equiv) and dienophile **24** (1.0 equiv) with butylated hydroxytoluene (BHT)[24] in reflux toluene (160 °C, sealed

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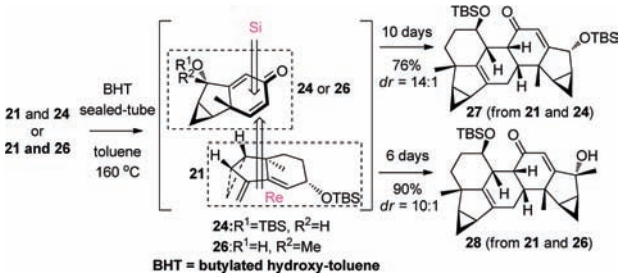
Scheme 5. Synthesis of the Heptacyclic Cores **27** and **28** via *endo*-Diels–Alder Cycloaddition



tube) furnished the desired *endo*-Diels–Alder cyclization product **27** in 76% yield (92% yield on BRSM) and good diastereoselectivity (dr = 14:1, detected by ^{1}H NMR spectrometry). Presumably, the angular methyl and cyclopropyl groups in **24** served to preferablely direct the Diels–Alder addition to the less hindered *Re* face, as indicated in Scheme 5. The stereochemistry of the desired heptacyclic core **27** was assigned by NMR spectroscopic analysis (HMBC, NOESY correlations, see the Supporting Information).

Encouraged by the success in the preparation of the heptacyclic core **27** via an expected *endo*-Diels–Alder cycloaddition, conversion of diene **21** (2.5 equiv) and dienophile **26** (1.0 equiv) under similar aforementioned conditions also smoothly afforded the desired *endo*-Diels–Alder cyclization product **28** with the direction of the angular methyl and cyclopropyl groups in 82% yield and good diastereoselectivity (dr = 10:1, detected by isolated yield). The stereochemistry of the desired heptacyclic core **28** was unambiguously confirmed by its X-ray crystallographic analysis (Figure 2).

In summary, we have illustrated a concise and efficient strategy for the construction of the heptacyclic core of the chloranthaceae family, together with the high stereoselective generation of the three contiguous stereocenters, via a biomimetic *endo*-Diels–Alder cycloaddition as the pivotal step. The crucial precursors **27** and **28** were prepared in only 12 linear steps from commercially available Wieland–Miescher ketone **11**, and the strategy developed here is directly amenable to an asymmetric

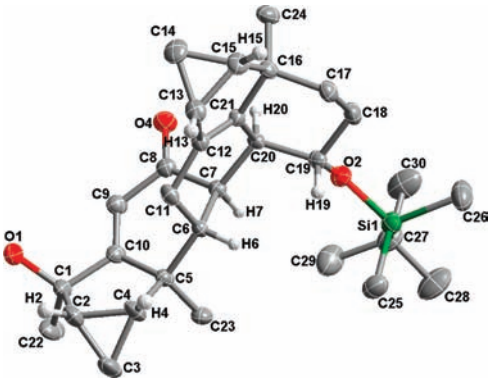


Figure 2. X-ray derived ORTEP drawing of alcohol **28**.

synthesis starting from the commercially available enantiopure Wieland–Miescher ketone **11**. Application of the disclosed strategy here to the total synthesizes of chlorahololide A (**2**) and shizukaol A (**1**) from the desried core **28** are underway and will be reported in due course.

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Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.