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Synthetic Study toward the Total Synthesis of Maoecrystal V

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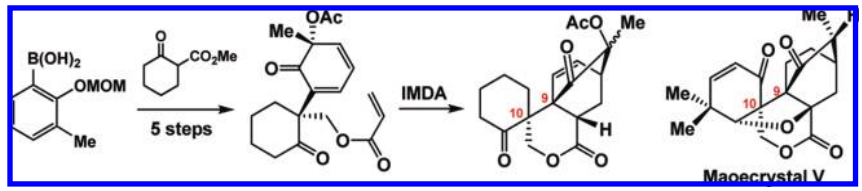
ABSTRACT



A novel and concise approach for the construction of the core structure of maoecrystal V (1) has been developed. Utilizing the lead-mediated arylation of β-ketoesters and oxidative dearomatization/IMDA reaction as key steps, the two consecutive all-carbon quaternary centers (C-9 and C-10) were constructed in a stereoselective manner. The developed chemistry paves the way for the total synthesis of this fascinating natural product.

In 2004, Sun and colleagues reported isolation of a cytotoxic diterpenoid maoecrystal V[1] (**1**) (Figure 1) with a novel C_{19} skeleton from the leaves of a Chinese medicinal herb, *Isodon eriocalyx*. Its structure was determined by comprehensive NMR and MS spectroscopic analysis and confirmed by single-crystal X-ray diffraction study.

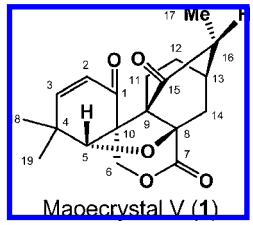


Figure 1. Naturally occurring maoecrystal V (**1**).

The highly compact arrangement of the angularly fused polycyclic structure of **1** and two chiral quaternary carbons and a tertiary alcohol in a contiguous setting served to pose interesting challenges to the science of chemical synthesis. Perhaps an equally compelling factor in attracting our attention to the synthesis of target **1** is that maoecrystal V was found to be remarkably active against HeLa cells (IC_{50} = 0.02 ug/mL).

Considering the biological activity and the intriguing structure of maoecrystal V, as well as the increasing number of analogues from its family,[2] we undertook a program directed to its total synthesis. Herein, we report our development of a concise approach for construction of the core of maoecrystal V (**1**) via lead-mediated arylation of β-ketoesters

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and oxidative dearomatization/IMDA reaction as key steps. The developed chemistry paves the way for the total synthesis of target **1**.

From the perspective of chemical synthesis, the most challenging work in the synthesis of maoecrystal V (**1**) appears to be that of stereoselective construction of the cagelike core. We, therefore, postulated several synthetic strategies for its construction and eventually chose the Wessely oxidative dearomatization/Diels−Alder reaction to synthesize **2** from **4** via intermediate **3** (Figure 2).[3] We also

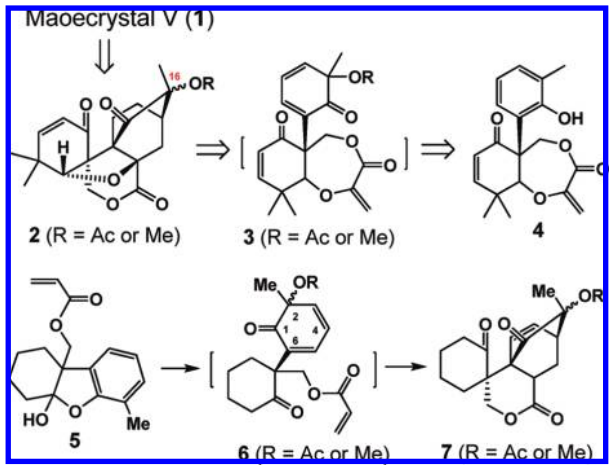
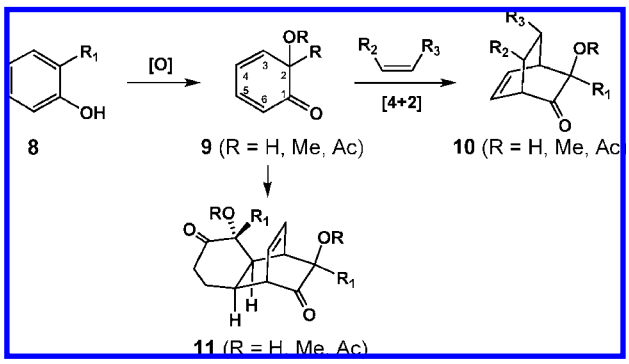


Figure 2. Retro-synthetic analysis.

envisaged that **2** could be easily converted to target **1** by reductive cleavage of its C-16 oxygenated substituent.[4]

To validate our strategy, we selected substrate **5** (Figure 2) as a testing model. Since the hemiactal in compound **5** is in equilibrium with its ketone and phenol, as a result, the free phenol can undergo oxidative dearomatization to give *o*-quinol acetate **6**, which in turn could undergo the IMDA reaction to afford the cage molecule **7**.

Scheme 1. Oxidative Dearomatization/Diels−Alder Reaction



o-Quinols (i.e., **9** in Scheme 1) are useful synthons that can serve as a diene to proceed with the Diels−Alder reaction with dienophiles for the formation of **10**. Based on this strategy, numerous polycyclic molecules have been achieved utilizing this synthetic method.[5] *o*-Quinols **9** can be made from their corresponding phenols **8** via oxidative dearomatization,[6] and the oxidative agents used are lead tetraacetate (LTA),[7] $Ti(NO_3)_3$,[8] and hypervalent iodide.[9] However, *o*-quinols **9** also have a tendency to form dimers **11**, which limits its application in the complex molecule synthesis.[10] To expand the synthetic scope of *o*-quinols in organic synthesis, several synthetic strategies have been tested to prevent such dimerization;[11] among them, introduction of substituent(s) to the newly formed diene was found to be effective.[12]

With this chemistry in mind, we believed that the tetracyclic core in compound **7** could be generated from *o*-quinol acetate **6** via the proposed IMDA reaction, since the existence of a bulky group at C-6 of intermediate **6** could force it to proceed with the IMDA reaction.

Our synthesis commenced with the preparation of key intermediate **16**. To do this, substrate **12** was first made from commercially available 2-hydroxy-3-methylphenyl boronic acid and then treated with $Pb(OAc)_4/Hg(OAc)_2$[13] to afford aryllead tricarboxylate **13**, which without isolation could

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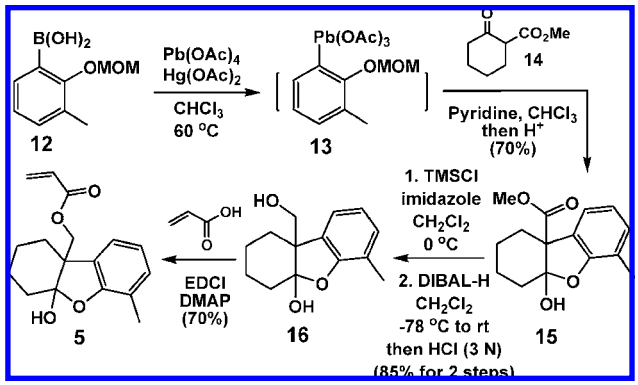
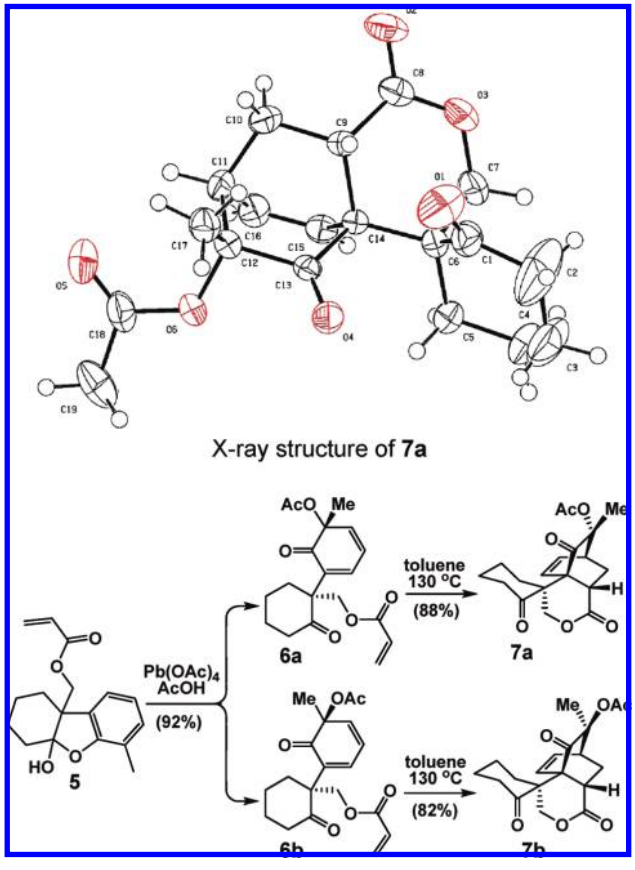
undergo oxidative arylation[14] with ketoester **14** to give product **15** in 70% overall yield (Scheme 2). Protection of

Scheme 2. Synthesis of Intermediate **5**



the newly generated alcohol in **15** with TMS was followed by treatment with DIBAl-H and then coupled with acrylic acid in the presence of EDCI and DMAP to give **5** in 60% yield.

Scheme 3. Wessely Oxidation



With compound **5** in hand, we then explored the Wessely oxidative dearomatization/Diels−Alder cascade reaction for the formation of cage molecules **7a** and **7b** (Scheme 3).

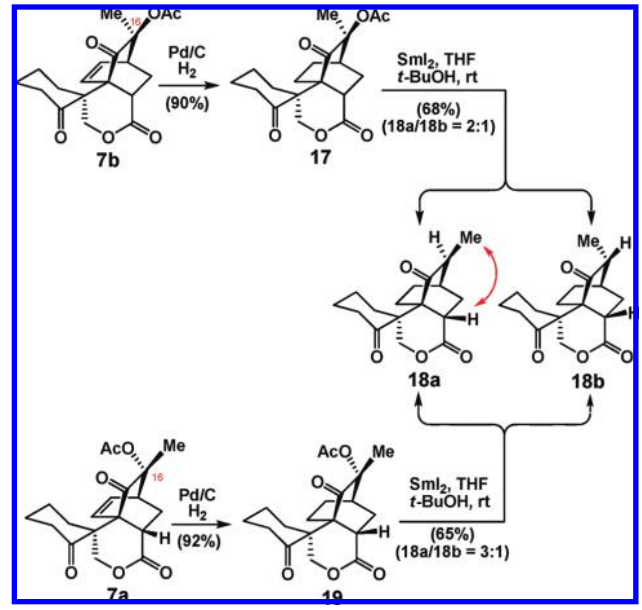
Initially, we chose to employ the commercially available hypervalent iodides [such as $PhI(O_2CCF_3)_2$ and $PhI(OAc)_2$] as oxidants. Unfortunately, we did not get any desired products when MeOH and CH_2Cl_2 were used as solvents. We then performed Wessely oxidative acetoxylation[6] in AcOH with $Pb(OAc)_4$ as the oxidative agent and found that the stable *o*-quinol acetates **6a** and **6b** were obtained in 92% yield in a 1:2 ratio (Scheme 3). It is worthwhile to mention that **6a** and **6b** are stable at room temperature and no dimerized products were observed even when the compounds were storied at room temperature for a couple of days.

On the basis of this result, we then started to carry out their annulation in refluxing toluene. As expected, the desired products **7a** and **7b** were obtained in 88% and 82% yield, respectively. The structures of compound **7a** was determined by ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic analysis and unambiguously confirmed through single-crystal X-ray diffraction study.

To establish the stereochemistry of **7b**, we first carried out hydrogenation to remove the double bond in **7b** followed by reductive removal of its acetyl group by treatment with SmI_2 at room temperature for 20 min to give ketones **18a** and **18b** (2:1 in ratio) in 68% yield as a pair of diastereoisomers. Our reason for using SmI_2 as a reductant is because of its exceedingly high chemoselectivity[4d] which could tolerate sensitive functional groups (such as lactone and ketone) when we carried out the α-oxygenated ketone reduction.

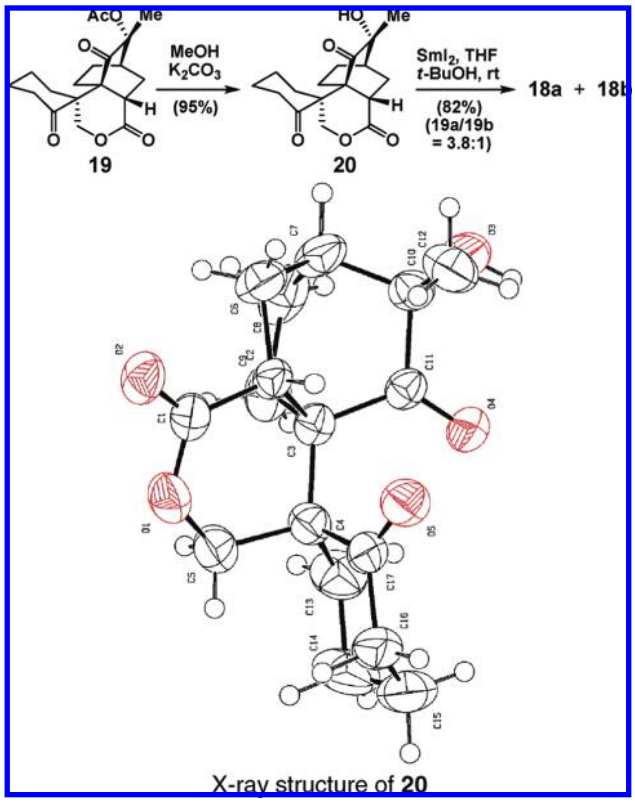
We then converted **7a** to its corresponding saturated product **19** via hydrogenation and then treated it with SmI_2 under the identical conditions listed in Scheme 4. To our

Scheme 4. Reduction of α-Oxygenated Ketones **17** and **19**



delight, both substrates **17** and **19** gave the identical products **18a** and **18b** after comparison of their spectroscopic data of

Scheme 5. Reduction of Compound **20** to **18a** and **18b** X-ray Structure of **20**



proton NMR, indicating both Diels−Alder products **7a** and **7b** could be utilized for the study toward the total synthesis of target molecule **1**. The unambiguous confirmation of structure **18a** through single-crystal X-ray diffraction is currently underway.

To optimize the reaction, we then tested this reduction with α-hydroxy ketone **20** as the substrate.

Thus, under the identical conditions listed in Scheme 5, substrate **20** was treated with SmI_2 and gave products **18a** and **18b** (in a ratio of 3.8:1) in 82% yield. It is worthwhile to mention that unlike the results reported by Molander,[4d] reduction of α-hydroxy ketone **20** gave a better result than its corresponding α-acetoxy ketone **19**, indicating this type of reaction is highly substrate dependent. Further studies are required to achieve better diastereoselectivity of the reduction of α-oxygenated ketones.

In summary, a novel and concise approach for the construction of the core structure of maoecrystal V (**1**) has been developed, and the two consecutive all-carbon quaternary centers were stereoselectively constructed by lead-mediated arylation of *β*-ketoesters and oxidative dearomatization/IMDA reaction as key steps. The described chemistry offers us an opportunity to synthesize maoecrystal V (**1**), and the synthetic study toward the total synthesis of target molecule maoecrystal V is currently underway in our laboratory.

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Supporting Information Available: Experimental procedure, ^{1}H NMR and ^{13}C NMR spectra, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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