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Total Synthesis of (±) Maoecrystal V

Jianxian Gong,[†] Guang Lin,[†] Wenbo Sun,[†] Chuang-Chuang Li,*[,†] and Zhen Yang*[,†,‡]

Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen 518055, China, and Key Laboratory of Bioorganic Chemistry and Molecular Engineering, Ministry of Education and Beijing National Laboratory for Molecular Science, College of Chemistry, Peking University, Beijing 100871, China

Received October 2, 2010; E-mail: zyang@pku.edu.cn

Abstract: A concise first total synthesis of (±) maoecrystal V (**1**) is reported. The synthesis features a Wessely oxidative dearomatization of a phenol, an intramolecular Diels−Alder reaction, and a Rh-catalyzed O−H bond insertion as key steps.

Maoecrystal V (**1**, Scheme 1), which was isolated in 2004 by Sun and co-workers from the leaves of a Chinese medicinal herb called *Isodon eriocalyx*, is a novel C_{19} diterpenoid[1] and displays potent and selective inhibitory activity against HeLa cells (IC_{50} = 60 nM). Maoecrystal V possesses an unprecedented and highly congested pentacyclic framework with six stereocenters, among which three are vicinal quaternary stereocenters. This structure has been confirmed by X-ray crystallography.

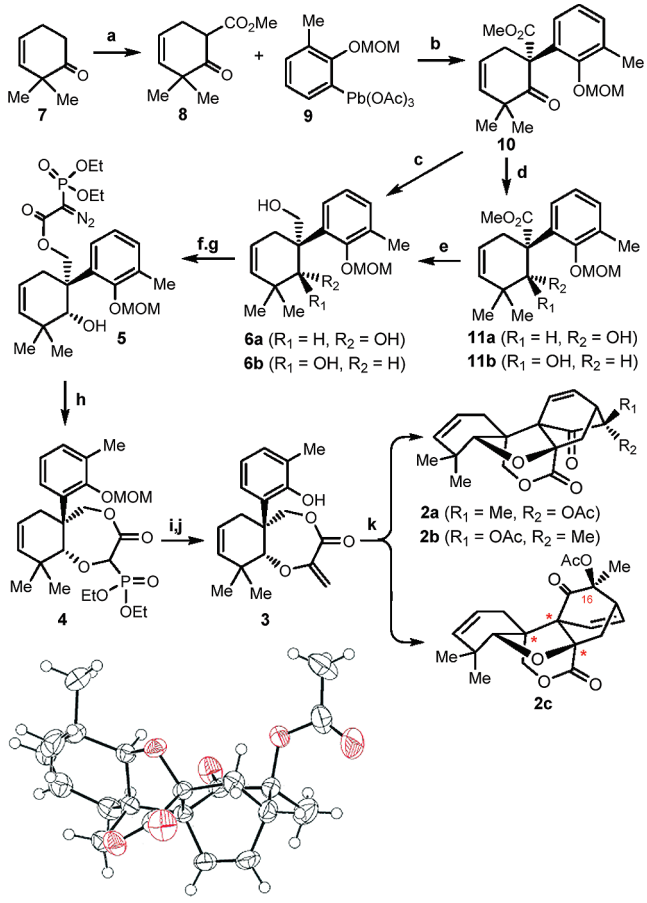
Given its fascinating structure and distinguished biological activity, maoecrystal V (**1**) attracted the attention of synthetic chemists worldwide.[2] Herein we report the successful development of a strategy that has enabled completion of the first total synthesis of maoecrystal V.

Previous investigations from our laboratories[2a] have revealed that Wessely oxidative dearomatization of a phenol[3] and a subsequent intramolecular Diels−Alder reaction (IMDA)[4] is an efficient method for the construction of the highly strained core of maoecrystal V. In our effort to pursue the total synthesis of maoecrystal V, we endeavored to adopt the above-mentioned strategy to construct **2** from **3** (Figure 1), a process in which two vicinal quaternary stereocenters and a three-rigid-ring system would directly arise in an IMDA reaction. We also envisaged that **3** could be prepared by a Horner−Wadsworth−Emmons[5] reaction from **4**, and **4** could be assembled from **5** through metal-catalyzed O−H bond insertion.[6] We further expected that the intermediate **5** could be derived from diol **6** by reaction with 2-(diethoxy-phosphoryl) acetic acid in the presence of condensation agents.

Our synthesis began with the preparation of diol **6** (Scheme 1). Ester **8**, which was made from 2,2-dimethylcyclohex-3-enone **7** and dimethyl carbonate,[7] was subjected to an oxidative arylation to install the C-10 quaternary carbon by reaction with 2-(methoxymethoxy)-3-methylphenyl)triacetoxyplumbane **9**, affording β-ketoester **10** in 88% yield.

The synthesis of *cis*-diol **6a** was initially investigated by direct treatment of β-ketoester **10** with $LiAlH_4$ and DIBAL-H, respectively. However, the opposite diastereoselectivities were obtained in both cases, yielding almost a 1:6 ratio of *cis*-diol **6a** and *anti*-diol **6b**. We then elected to apply a stepwise strategy to generate **6a**. To this end, β-ketoester **10** was first treated with reducing agents, such as organoboranes,[9a] $NaBH_4$/Lewis acid,[8,9b,c] and hydrosilanes.[9d] Unfortunately, the undesired isomer **11b** came out as the major product in all cases. We eventually found out that treatment of **10** with $(n\text{-}Bu_4)NBH_4$[10] in methanol effected the desired reduction to produce **11a** in 65% yield as a sole isomer. We attributed this diastereoselectivity to the directing and accelerating effect of the cationic−π interaction[11] between ammonium salt [$(n\text{-}Bu_4)NBH_4$] and the phenyl ring in substrate **10**, which delivers the hydride to the ketone from its top face. Thus, after treatment

Scheme 1. Syntheses of **2a**, **2b**, and **2c**[a]



X-ray structure of **2c**

[a] Reagent and conditions: (a) dimethyl carbonate, NaH, THF, Δ, 92%; (b) 2-(methoxymethoxy)-3-methylphenyl)triacetoxy-plumbane **9**, pyridine, $CHCl_3$, 60 °C, 88%; (c) $LiAlH_4$, THF, rt, **6a** (12%) and **6b** (72%); (d) $(Bu_4N)BH_4$, MeOH, 40 °C, 65% (89% brsm); (e) $LiAlH_4$, THF, rt, 88%; (f) 2-(diethoxyphosphoryl)acetic acid, EDCI, DMAP, CH_2Cl_2, rt, 82%; (g) TsN_3, DBU, 0 °C, 81%; (h) $Rh_2(OAc)_4$, PhH, Δ, 60%; (i) ^{t}BuOK, $(HCHO)_n$, THF, 0 °C, 95%; (j) TFA, CH_2Cl_2, rt, 90%; (k) $Pb(OAc)_4$, AcOH, 0 °C, then PhMe, 145 °C, 24 h, **2a** (28%), **2b** (12%), and **2c** (36%).

[†] Shenzhen Graduate School of Peking University.
[‡] Peking University.

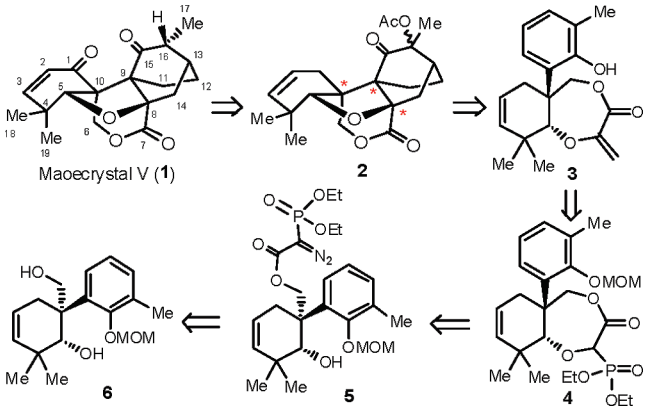
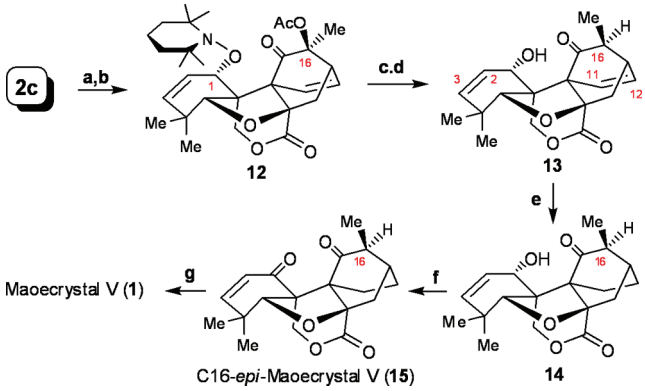


Figure 1. Synthetic analysis.

of **11a** with $LiAlH_4$ in THF, the diastereselective synthesis of *cis*-diol **6** was eventually achieved in 88% yield.

We next shifted our attention to make precursor **3** of the proposed IMDA reaction. In that event, *cis*-diol **6** was coupled with 2-(diethoxyphosphoryl)-acetic acid in the presence of EDCI and DMAP to afford an ester in 85% yield, which was then treated with TsN_3 in the presence of DBU to give the diazo ester **5** in 69% yield in two steps. Diazo ester **5** was subjected to the $Rh_2(OAc)_4$-catalyzed O−H bond insertion[12] to give **4** (60%), which underwent consecutive Horner−Wadsworth−Emmons reaction with paraformylaldehyde[13] and deprotection of the MOM ether under acidic conditions, leading to phenol **3** in high yield. In the process of preparing the key intermediate **2**, phenol **3** was subjected to the Wessely oxidative acetoxylation,[2a,3] affording stable *o*-quinol acetates as a pair of diastereoisomers of C16, which without purification underwent IMDA reaction in toluene at 145 °C to give a separable mixture of products **2a**, **2b**, and **2c** in 28%, 12%, and 36% yield, respectively. The structure of **2c** was unambiguously confirmed by X-ray crystallography.

Scheme 2. Total Syntheses of Maoecrystal V (**1**)[a]



[a] Reagent and conditions: (a) NBS, $(PhCO_2)_2$, CCl_4, reflux, 2 h, 90%; (b) Bu_3SnH, TEMPO, PhH, reflux, 2 h, 75%; (c) Zn, AcOH, THF, H_2O, 70 °C, 2 h, 85%; (d) SmI_2, THF, MeOH, rt, 10 min, 88%; (e) Lindlar cat. MeOH, THF, rt, 2 h, 92%; (f) DMP, CH_2Cl_2, rt, 1 h, 88%; (g) DBU, toluene, 100 °C, 1 h, 48% (90% brsm).

To complete the total synthesis, **2c** was allowed to react with NBS in the presence of benzoyl peroxide[14] to introduce a Br at C1 (Scheme 2). This bromide was treated with Bu_3SnH to generate an allylic radical, which was then trapped with TEMPO[15] to give **12** in a 68% overall yield. Regioselective reductive cleavage of tetramethylpiperidine and acetoxy groups was achieved by the sequential treatment of **12** with Zn/AcOH[15a] and SmI_2,[2a,16] affording product **13** in 75% overall yield as a single stereoisomer. Regioselective hydrogenation of **13** in the presence of Lindlar catalyst gave **14**, which was then converted to **15** in high yield by oxidation with DMP. Thus the final target maoecrystal V (**1**) was eventually obtained in 48% (90% brsm) yield by the treatment of **15** with DBU in toluene at 100 °C for 1 h, affording a 1:1 mixture of **15** and **1**. Extension of the reaction time did not improve the conversion of **15** to **1**. The identity of the synthesized maoecrystal V (**1**) was confirmed by comparison of the NMR spectral data with that of natural product maoecrystal V (**1**).[1]

In summary, a concise total synthesis of maoecrystal V (**1**) has been achieved by employing a Wessely oxidative dearomatization, an IMDA reaction, and a Rh-catalyzed O−H bond insertion as key steps. The developed chemistry may find use in the synthesis of the analogue of maoecrystal V.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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