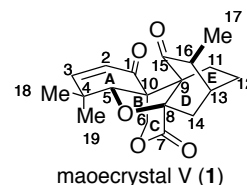


**Total Synthesis of (±)-Maoecrystal V**  
 Peng, F.; Danishefsky, S. J.\*  
*J. Am. Chem. Soc.* **2012**, *134*, 18860–18867.

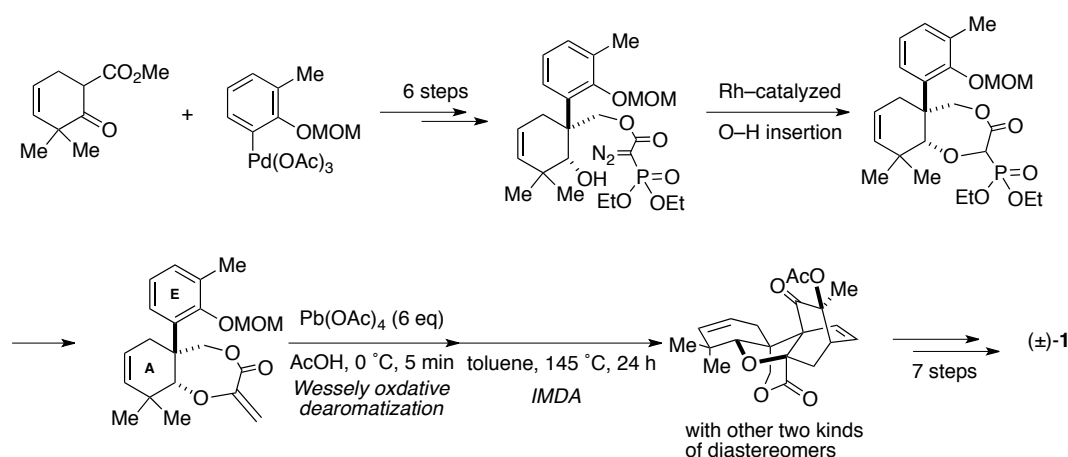
## 1. Introduction

### 1.1. Maoecrystal V

- Maoecrystal V was first isolated in 1994 from *Isodon eriocalyx* Hara, which is a vegetation distributed in Yunnan province.<sup>1</sup>
- While every substructure is quite basic, the whole structure of maoecrystal V is very complex. For example...
  - Fully substituted positions (C8, C9, C10)
  - Determinative of the AB ring junction (C5, C10)
- First total synthesis of (±)-maoecrystal V was achieved in 2010 using Wessely oxidative dearomatization of phenol, subsequent intramolecular Diels–Alder (IMDA) reaction and Rh-catalyzed O–H bond insertion (Figure 2).<sup>2</sup>



**Figure 1.**  
Structure of maoecrystal V (1)

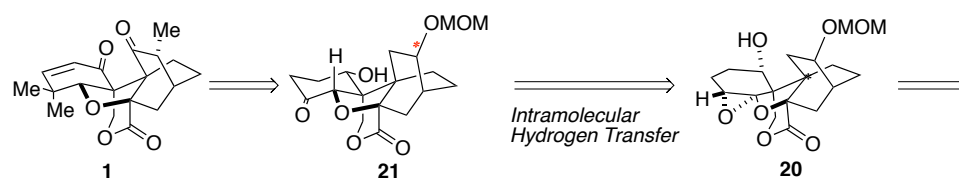


**Figure 2.** Strategy for first total synthesis of (±)-maoecrystal V

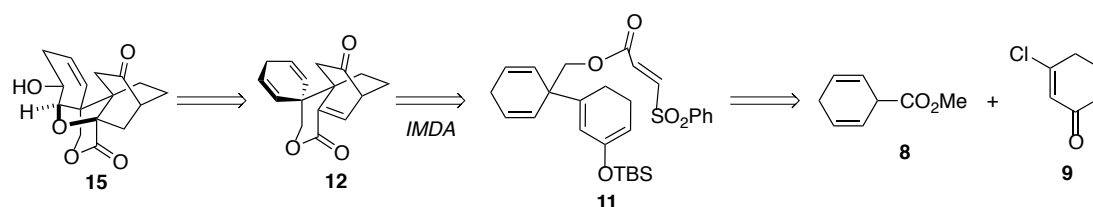
### 1.2. This Work

- Retrosynthetic analysis is shown in Scheme 1.
- Construction of the core system at the early stage of total synthesis by IMDA reaction
- A–C ring *trans*-fusion through intramolecular hydrogen transfer to the stereochemically hindered face

#### Scheme 1. Retrosynthetic analysis of maoecrystal V



## Scheme 1. (continued)

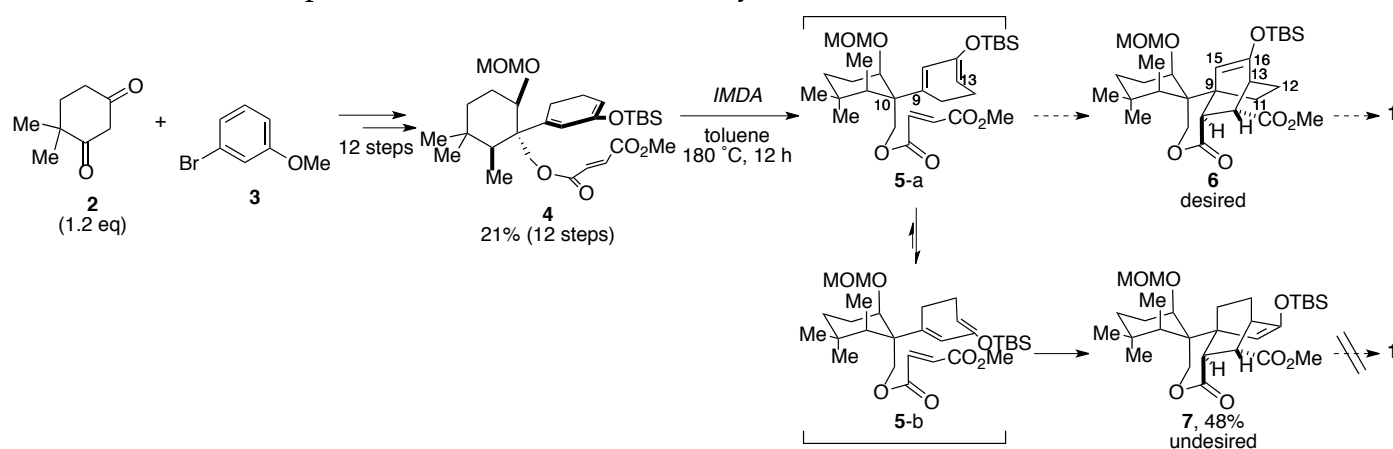


## 2. Results and Discussion

### 2.1. Original Synthetic Strategy (Unsuccessful)

- First, authors tried to make D ring by IMDA reaction of chiral precursor (Scheme 2).
- 12 steps from starting materials 2 and 3 afforded IMDA substrate 4.
- IMDA reaction on 4 proceeded with undesired stereochemistry due to rotation of C9–C10 bond.

### Scheme 2. First attempt IMDA route toward maoecrystal V



### 2.2. Modified Synthetic Route

- To make stereochemical problem simple, authors used achiral cyclohexa-1,4-diene ring as a future A ring in the IMDA substrate.
- This modified IMDA substrate determines only *endo:exo* position of the two activating groups, which converges by  $\beta$ -elimination on enantiomers (Figure 3), and both of the enantiomers can be derivatized to racemic ( $\pm$ )-maoecrystal V.

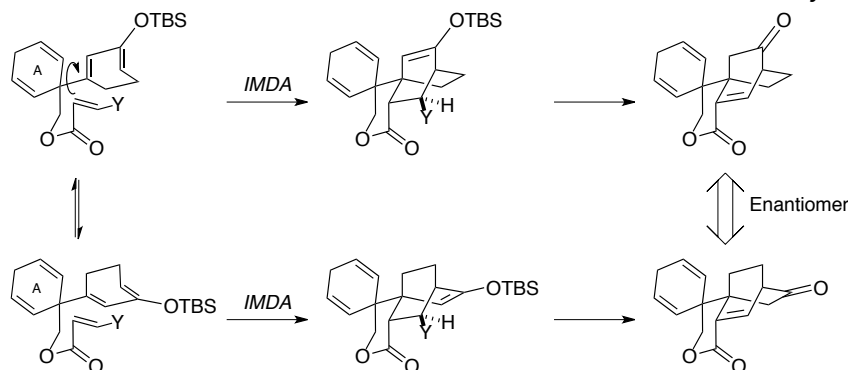
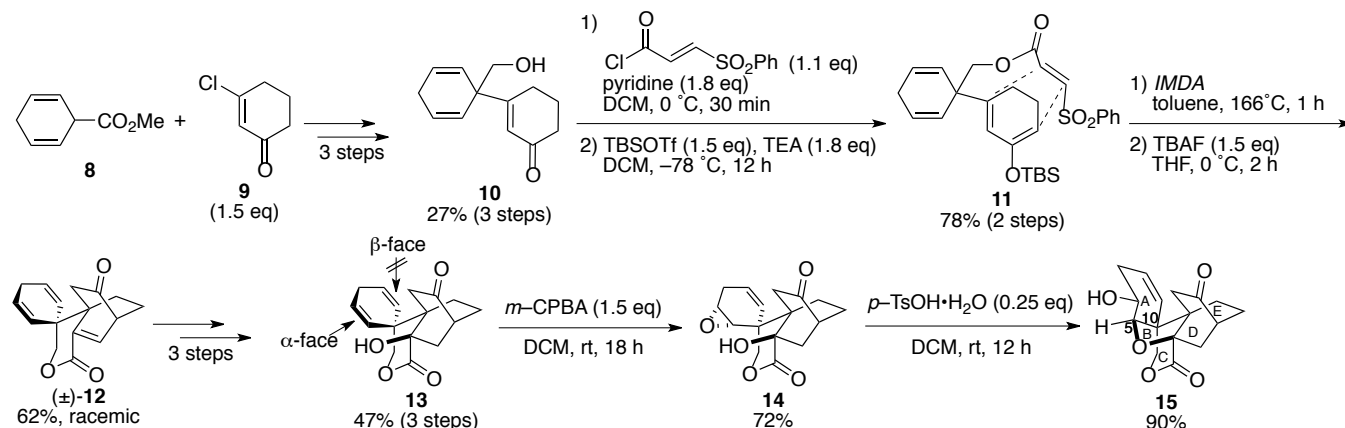


Figure 3. Revised route toward maoecrystal V

- IMDA substrate 11 was prepared from two commercially available compounds in 5 steps (Scheme 3).

- **11** underwent IMDA reaction, and after treatment with TBAF, racemate (not diastereomer) **12** was obtained.
- Conjugated double bond of enone **12** was selectively epoxidized with hydrogen peroxide and resultant epoxide was converted to  $\alpha$ -hydroxylactone **13**.
- Selective epoxidation only from  $\alpha$ -face by bulky peroxide of *m*-CPBA gave a single epoxide **14** because of high steric hindrance of  $\beta$ -face.
- Reaction on **14** with *p*-toluenesulfonic acid indeed introduced tetrahydrofuranoid B-ring. Five backbone rings were constructed, but inversion of stereochemistry at C5 was necessary.

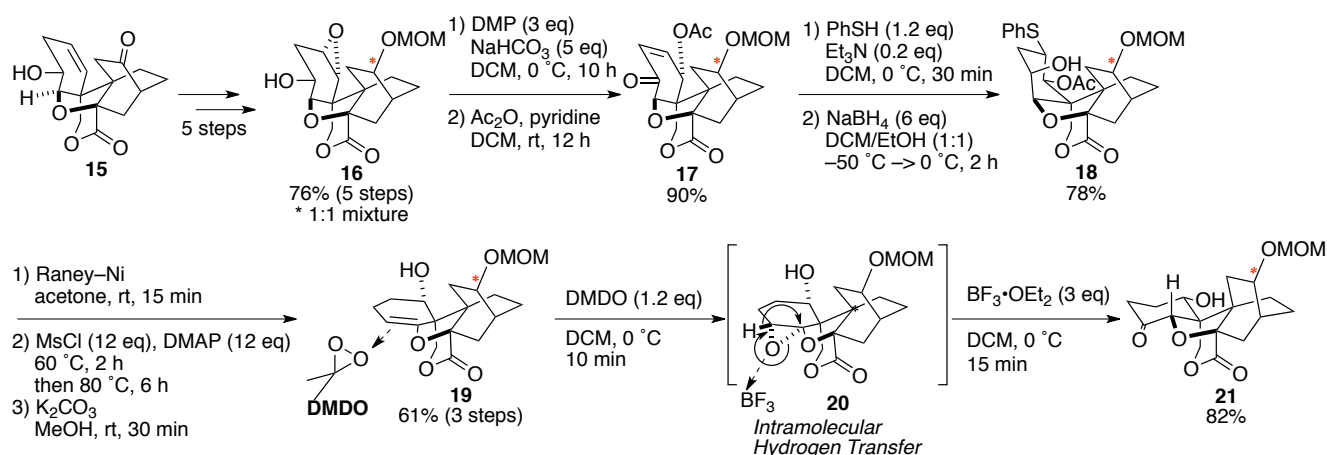
**Scheme 3.** Synthesis of intermediate ( $\pm$ )-**12** and construction of B-ring



### 2.3. Epimerization of C5

- To make the junction of A- and C-rings *trans*, it was necessary to introduce a hydrogen to stereochemically hindered  $\beta$ -face of C5.
- Ketone group on **17** was stereoselectively reduced to *exo*-glycol at C4–C5 position because it was easier for hydride to attack from opposite side of epoxide (Scheme 4).
- Since it was difficult for an external hydrogen to reach  $\beta$ -face of C5, compound **21** was achieved through intramolecular hydrogen transfer.

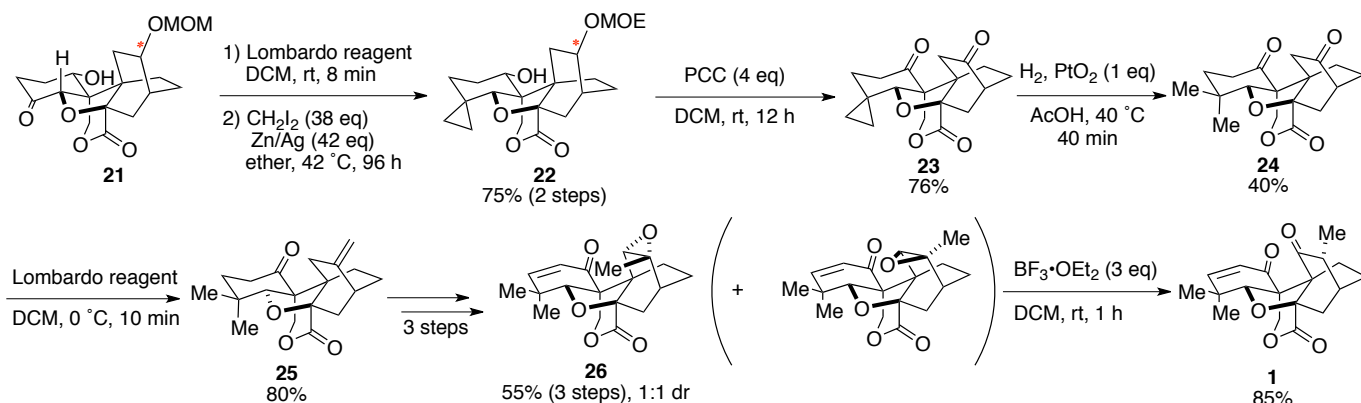
**Scheme 4.** Conversion of the *cis* junction of A- and B-rings to *trans*



## 2.4. Completion of Synthesis (Scheme 5)

- Ketone group of compound **21** was converted to cyclopropane with Lombardo olefination followed by Zn/Ag-mediated Simmons–Smith-inspired cyclopropanation. During cyclopropanation, methoxy methyl protection was converted to ethoxy methyl.
- Cyclopropane ring on **23** was reductively cleaved by hydrogen gas with platinum dioxide as a catalyst.
- Finally, (±)-maoecrystal V (**1**) was synthesized and characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR and HRMS.

Scheme 5. Completion of the synthesis of maoecrystal V

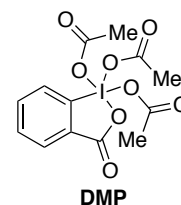


## 3. Conclusion

- Total synthesis of maoecrystal V was achieved in a racemic form. Overall yield was 0.090% through 32 steps.
- This work was actually inferior to the first total synthesis in point of overall yield or steps (overall yield of first total synthesis was 1.1% through 17 steps), but some reactions for achievement of this work offered new insight into organic chemistry.
  - Achiral IMDA substrate and followed by β-elimination solves *endo:exo* and diastereomeric problems though product is racemate.
  - Intramolecular hydride transfer enables introduction of a hydrogen stereoselectively and even it is possible to introduce a hydrogen to sterically hindered face.

### Abbreviation

TBSOTf: *tert*-butyldimethylsilyl trifluoromethanesulfonate; TBAF: tetra-*n*-butylammonium fluoride; *m*-CPBA: *m*-chloroperoxybenzoic acid; TsOH: *p*-toluenesulfonic acid; DMP: 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess–Martin periodinane); MsCl: methanesulfonyl chloride; DMAP: *N,N*-dimethyl-4-aminopyridine; Lombardo reagent: 1.5CH<sub>2</sub>Br<sub>2</sub> + 3Zn + 1.1TiCl<sub>4</sub>; PCC: pyridinium chlorochromate;



### References

- <sup>1</sup> Li, S. H.; Niu, X. M.; Shen, Y. H.; Zhang, H. J.; Sun, H. D.; Li, M. L.; Tian, Q. E.; Lu, Y.; Cao, P.; Zhang, Q. T. *Org. Lett.* **2004**, *6*, 4327–4330.
- <sup>2</sup> Gong, J.; Lin, G.; Sun, W.; Li, C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745–16746.