



Toward the total synthesis of maoecrystal V: an intramolecular Diels–Alder route to the maoecrystal V pentacyclic core with the appropriate relative stereochemistry

Feng Peng^a, Samuel J. Danishefsky^{a,b,*}

^a Department of Chemistry, Columbia University, Havemeyer Hall, 3000 Broadway, New York, NY 10027, United States

^b Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, NY 10065, United States

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ABSTRACT

A diastereoselective route to the maoecrystal V core compound (**6**) has been achieved. Key transformations include an intramolecular Diels–Alder cyclization and an *exo*-glycal epoxide rearrangement sequence.

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The unique and complex structure of maoecrystal V (**1**, Fig. 1), first isolated by Sun and co-workers in 2004, serves to render it a challenging target for total synthesis. Adding to the level of interest in maoecrystal, is its potent *in vitro* activity against HeLa cells (IC₅₀ = 20 ng/ml).¹ Particularly noteworthy in this regard is the apparent specificity of its cytotoxicity against gynecological cells.

Among the defenses which maoecrystal V mounts against those who would undertake its total synthesis, are two contiguous quaternary carbon stereocenters and a tertiary alcohol, embedded within a rigid pentacyclic scaffold. Notwithstanding the complexity of the problem, a number of groups, including our own,^{2c} have initiated investigations directed toward the total synthesis of maoecrystal V.²

In designing our program, we envisioned recourse to an intramolecular Diels–Alder (IMDA) cyclization, hoping thereby to gain access to the bicyclo [2.2.2]-octane core substructure of maoecrystal. In preliminary investigations, the highly functionalized precursor, **2**, was indeed found to undergo IMDA cyclization, albeit with the undesired sense of facial selectivity (Fig. 1).^{2c} We sought to circumvent this setback through the design of a modified sequence, featuring IMDA of a less densely functionalized and symmetrical precursor (cf. **4**→**5**). In devising this new route, we were not insensitive to the potential difficulties inherent in fashioning the requisite *trans*-fused furanoid ring junction³ (**6**, see ring B and its junction to ring A). Fortunately, these challenges have now been met, and a concise synthesis of the maoecrystal V core compound (**6**) in the required stereochemical sense has now been accomplished for the first time. The manner in which we reached this important milestone may well have broader implications in the design of total syntheses.

Our route to the IMDA precursor **4** commenced with a Birch-type vinylogous acylation between substrates **7** and **8**, thus providing intermediate **9**, possessing one of the requisite quaternary carbon centers (Scheme 1). The latter was subjected to global DIBAL-H reduction, followed by selective MnO₂-mediated reoxidation of the resulting allylic alcohol, to afford **10**. A two-step sequence, involving esterification with acyl chloride **11**,⁴ followed by formation of the TBS enol ether, provided the target IMDA substrate, **4**. In the event, compound **4** readily underwent thermally-induced IMDA cyclization in reasonable yield to generate the desired cycloadduct. Upon exposure to TBAF, the TBS group was hydrolyzed and the phenyl sulfone moiety suffered spontaneous elimination to afford key intermediate **5** in 62% isolated yield.

We next turned to the stereoselective emplacement of the requisite C₁₀ tertiary alcohol. Initial attempts to accomplish direct installation of the C₁₀ alcohol through a cascade 1,4-reduction/oxidation sequence resulted in a 1.5:1 diastereomeric mixture of compounds **12a** and **12b** (Scheme 2).⁵ Alternatively, we were able to gain access to **12a** as a single diastereomer through a three-step sequence. As shown, compound **5** was first treated with basic H₂O₂ to provide, with apparent stereospecificity, the desired epoxide **13**. The observed outcome is believed to arise from the presence of the C₁₆ ketone, which creates a stereoelectronic environment that promotes epoxidation from the β -face, as shown.⁶ Upon exposure to sequential epoxide opening and reduction of the resultant iodohydrin, epoxide **13** was converted to **12a** in good overall yield. With compound **12a** in hand, attentions were directed to installation of the tetrahydrofuran ring. Efforts to directly achieve etherification of **12a** through activation of the A-ring 5-*exo* alkene moiety were unsuccessful. However, a two-step solution was possible. Thus, upon exposure to *m*-CPBA, **12a** was found to undergo regio- and stereoselective epoxidation to afford intermediate **14**. Following treatment with *p*-TsOH · H₂O, a cyclized product was obtained in good yield, as a single diastereomer. However, X-ray analysis

* Corresponding author.

E-mail address: s-danishefsky@ski.mskcc.org (S.J. Danishefsky).

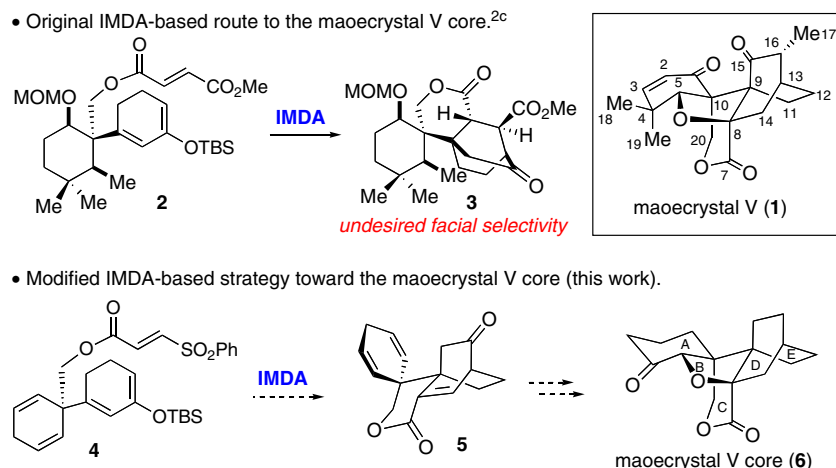
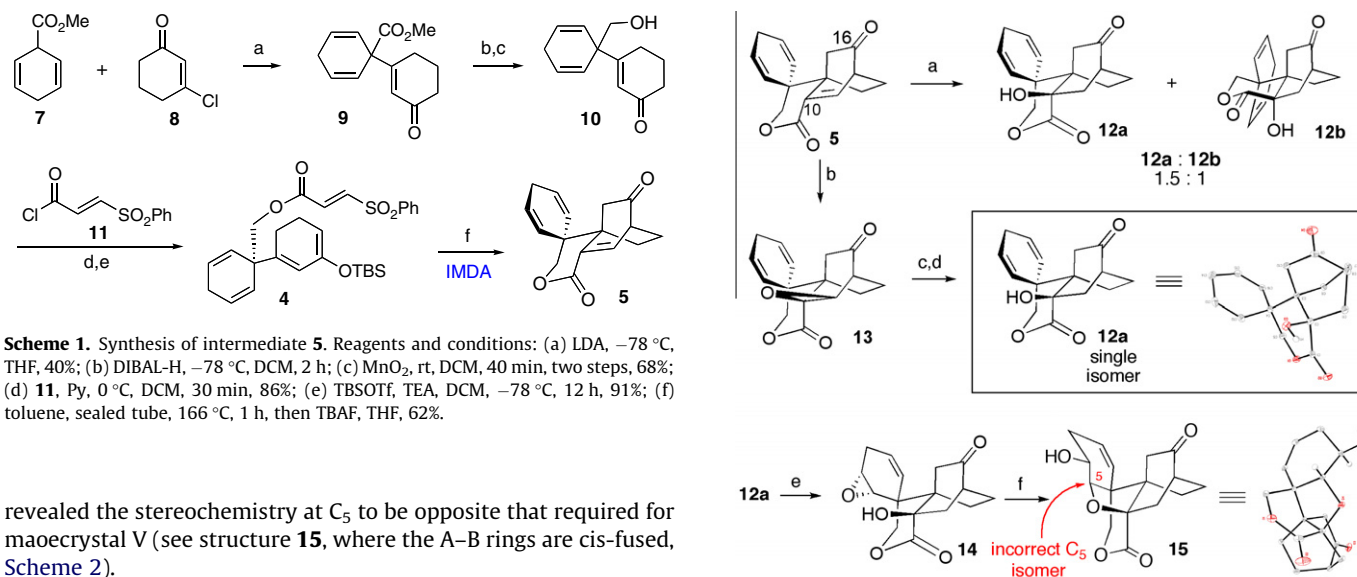


Figure 1.

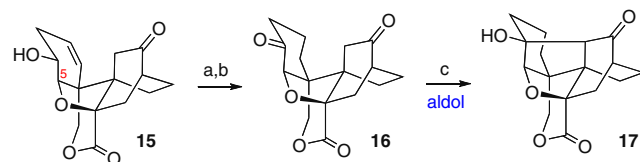
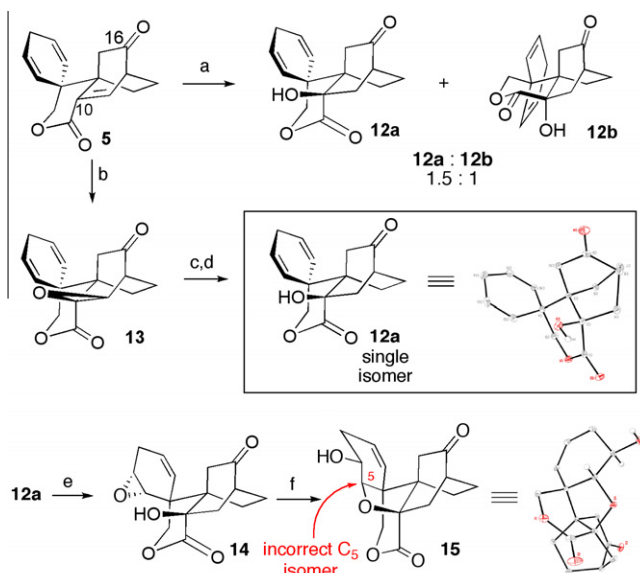


revealed the stereochemistry at C_5 to be opposite that required for maoecrystal V (see structure **15**, where the A–B rings are cis-fused, Scheme 2).

Our initial attempt to convert **15** to the requisite [6,5] trans-fused system through epimerization⁷ of the C_5 stereocenter is outlined in Scheme 3. Compound **15** was converted to **16** in a straightforward manner. However, exposure of **16** to the action of sodium methoxide in methanol afforded a new product, which was determined to be compound **17**. Thus, under these conditions, compound **16** had undergone an intramolecular aldol reaction, while the non-natural cis-fusion of the A–B junction persisted.

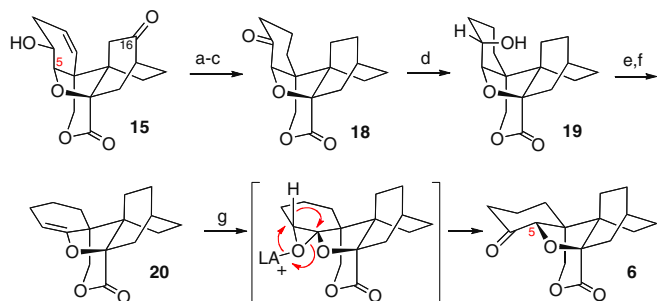
In order to circumvent the undesired aldol pathway, we sought to remove the C_{16} ketone functionality. As shown in Scheme 4, dithioketal formation, followed by reduction with Raney-Ni and subsequent oxidation with Dess–Martin reagent furnished the target monoketone **18** in 70% overall yield. This intermediate served as a useful model compound in the context of the actual maoecrystal V synthesis. With **18** in hand, we examined its susceptibility to thermal, base-induced epimerization, hoping to generate at least some traces of trans-fused epimer. Unfortunately, under standard conditions (NaOMe , MeOH, 50°C), no epimerization was observed. Apparently, the β -face of the A-ring is too congested to allow for the intermolecular delivery of a proton to the ring junction position.

There occurred to us the possibility of intramolecular transfer of a strategically placed hydrogen atom to allow for generation of the required A–B trans-fusion.⁸ We proceeded as follows (Scheme 4). Reduction of compound **18** with NaBH_4 afforded intermediate **19**

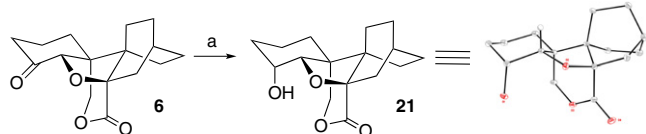


as a single diastereomer. A two-step dehydration sequence provided *exo*-glycal **20** in good yield.⁹ In the key transformation, *exo*-glycal epoxide formation was accomplished through exposure to DMDO.¹⁰ Happily, in situ treatment with $\text{BF}_3 \cdot \text{OEt}_2$ generated the rearrangement product, target compound **6**. The structure of the reduced product **21** was verified by X-ray analysis (Scheme 5).¹¹

In summary, we have accomplished the stereoselective synthesis of the maoecrystal V pentacyclic core structure (**6**). Key trans-



Scheme 4. Epimerization of **15** and synthesis of the maoecrystal V core (**6**). Reagents and conditions: (a) ethanedithiol, $\text{BF}_3 \cdot \text{OEt}_2$, DCM; (b) Raney-Ni, ethanol, 75°C , 8 h; (c) DMP, DCM, rt, 12 h, three steps, 70%; (d) NaBH_4 , DCM/MeOH, -78°C to -50°C , 96%; (e) MsCl , DMAP, DCM, 50°C , 12 h, 58%, 95% brsm; (f) DBU, toluene, 128°C , 4 h, 90%; (g) DMDO, DCM, 0°C , then ether, BF_3 , 75%.



Scheme 5. Synthesis and X-ray structure of compound **21**. Reagents and conditions: (a) NaBH_4 , -78°C to -50°C , 95%.

formations include an IMDA reaction (**4**→**5**) and apparently for the first time, an *exo*-glycal epoxide rearrangement sequence to install the rigid tetrahydrofuran moiety. Efforts are underway to apply these teachings to the total synthesis of maoecrystal V.¹²

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.029.

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- Following acceptance of this paper, two elegant manuscripts have been published in this area. (a) The first total synthesis of maoecrystal has been accomplished by Yang and co-workers. See: Gong, J.; Lin, G.; Sun, W.; Li, C. C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, doi:10.1021/ja108907x; (b) A progress toward maoecrystal has been reported by Trauner and co-workers. See: Bailing, I.; Mayer, P.; Trauner, D. *Org. Lett.* **2010**, doi:10.1021/ol102446u.