

Published in final edited form as:

Tetrahedron Lett. 2009 November 25; 50(47): 6586. doi:10.1016/j.tetlet.2009.09.050.

Synthetic Studies towards Maoecrystal V

 Feng Peng^a, Maolin Yu^a, and Samuel J Danishefsky^{a,b}
^a Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, USA

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

Abstract

The investigation of an intramolecular Diels-Alder reaction, en route to a projected total synthesis of maoecrystal V, is described.

Our laboratory is devoted to the total synthesis and biological evaluation of structurally challenging natural products possessing promising biological activity. In this context, we took note of a recent report by Sun and coworkers of a novel natural product, termed maoecrystal V (**1**), which, due to its potent inhibitory activity against HeLa cells ($IC_{50} = 20$ ng/mL), is believed to hold promise as a lead anticancer agent.¹ As shown in Figure 1, maoecrystal V is a densely functionalized diterpene, possessing an unprecedented *ent*-kaurane skeleton, two contiguous quaternary carbon stereocenters, and a tertiary alcohol, embedded within a complex ring system. The structural complexity of **1**, coupled with its biological activity, prompted us to undertake a program directed toward its total synthesis. We report herein the development of some interesting chemistry en route to a projected total synthesis of maoecrystal V (**1**).

Using the logic of “pattern recognition”² to guide our synthetic design, we discerned a bicyclo [2.2.2]-octane core in maoecrystal V (red, **1**) and hypothesized that this motif could be synthesized from an intramolecular Diels-Alder (IMDA) cyclization (cf. **3**→**4**).³ It was further supposed that following construction of **4**, the tetrahydrofuran moiety would be installed (**4**→**5**). A series of functional group transformations providing access to maoecrystal V (Scheme 1) from **5** seemed to be feasible.

As outlined in Scheme 2, the synthesis commenced with a palladium-catalyzed ketone α -arylation of **6**,⁴ followed by etherification with TMSCHN₂, to provide **8** (90% overall yield). This intermediate was subjected to the Stork-Danheiser protocol,⁵ with Bu₃SnCH₂OMOM,⁶ to afford compound **9** in 75% yield. Following replacement of the MOM ether with a pivaloate ester, intermediate **10** was in hand. Luche reduction of **10** provided an allylic alcohol, which was protected as its MOM ether (**11**). Hydrolysis of **11** served to liberate the hydroxymethyl intermediate, which was then alkylated with α -iodomethyl tributylstannane to furnish the Wittig-Still precursor (**12**).⁷ Through careful control of the reaction temperature, we were able to achieve the desired [2,3] rearrangement, to provide alcohol **2** in 88% yield. It is appreciated that this bond reorganization establishes the requisite quaternary carbon center in a highly stereoregulated fashion.

Correspondence to: Samuel J Danishefsky.

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With advanced intermediate **2** in hand, we were now approaching the possibility of examining the feasibility of the key IMDA cyclization. To our surprise, when **13** subjected to Birch reduction conditions, the exomethylene group was also reduced, giving rise to **13** as a 1:3 α/β mixture of methyl epimers. It seems not unlikely that electron transfer from Birch reduction intermediates serves to facilitate reduction of the exomethylene group.

Although the reduction of the undesired exomethylene group rendered this particular synthetic route toward maoecrystal **V** problematic, we nevertheless felt that intermediate **13** could serve as a valuable model substrate, with which to probe the viability of the key proposed IMDA reaction. Accordingly, acidic hydrolysis of **13** furnished **14**, which was then subjected to esterification with a range of acid chlorides, to provide a series of IMDA precursors, **15a–c**. When compounds **15a** and **15b** were subjected to thermal reaction conditions, we observed no cycloadduct, but only isomerized diene (**17**). However, it was found that **15c** readily underwent cyclization, under thermal conditions, to furnish the Diels-Alder cycloadduct **16**. Subsequent fluoro-assisted deprotection afforded **18** in 48% overall yield from **15c**. The assignment of the stereochemistry of the Diels-Alder adduct **18** rests on NMR analysis. Thus, a key NOESY experiment revealed that the IMDA cycloaddition had, in fact, proceeded with the opposite sense of facial selectivity than that required for the plan. To account for the observed facial selectivity, we postulate the predominance of transition structure **A** (Figure 2), wherein the dienophile approaches the diene from the back face of the rotamer shown in **15c**. The preference for this rotamer in a Curtin-Hammet sense⁸ is not clear. This IMDA outcome surely complicates its application to a total synthesis of **1**. Nonetheless, programs to reach **1** from the general logic adumbrated above can still be imagined and are being evaluated⁹.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support was provided by the NIH (HL25848 and CA103823 to SJD). F.P. thanks Eli Lilly for a graduate fellowship. We thank Prof. Shengping Zheng (Hunter College) and Dr. Fay Ng and for helpful discussions. Special thanks to Ms. Rebecca Wilson for scientific advice, as well as editorial consultation. We acknowledge Ms. Dana Ryan for assistance with the preparation of the manuscript.

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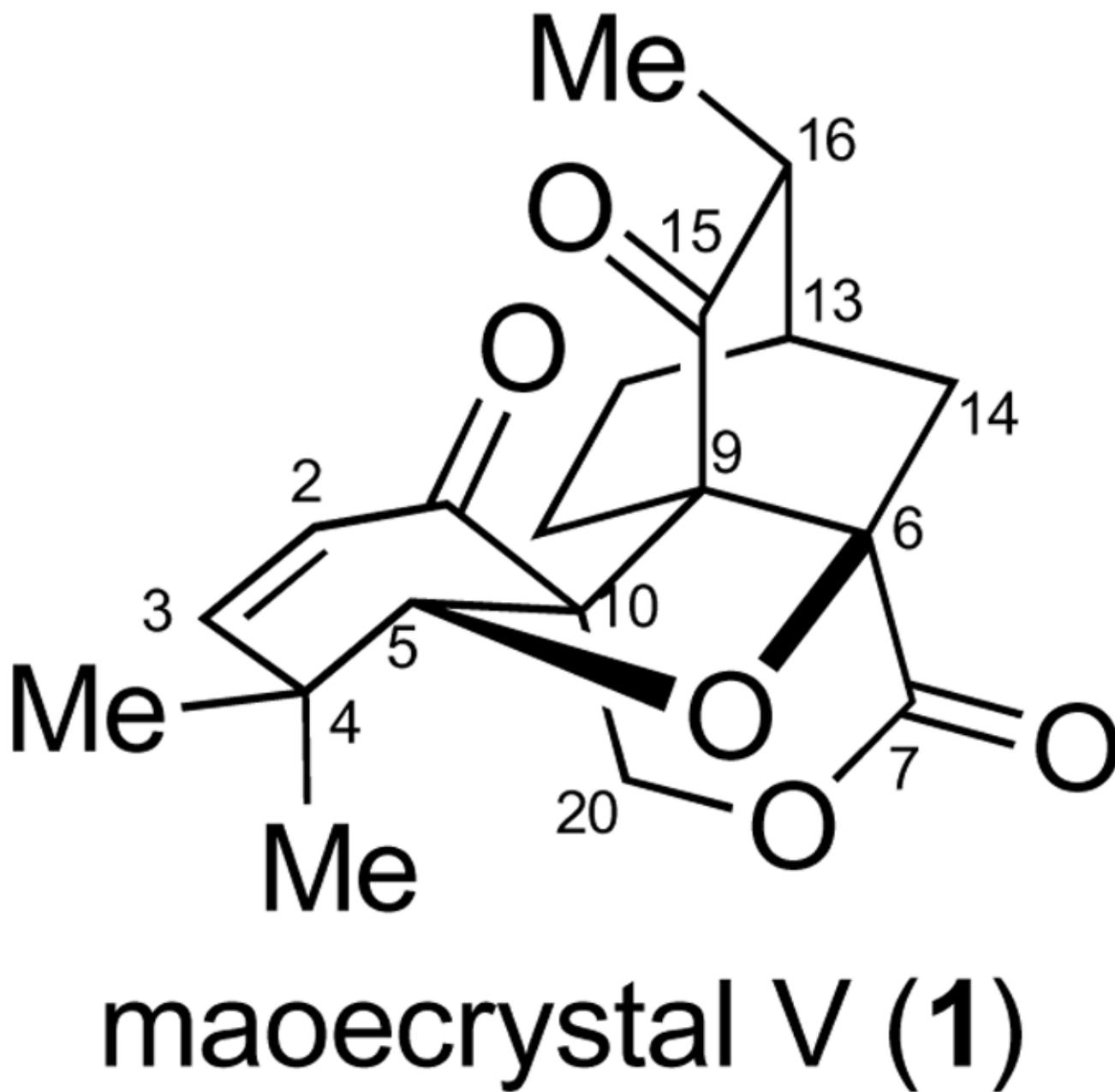


Figure 1.
Maoecrystal V (1).

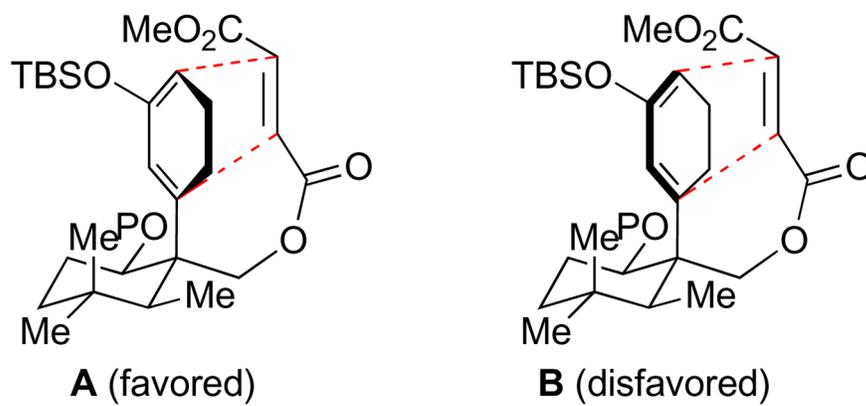
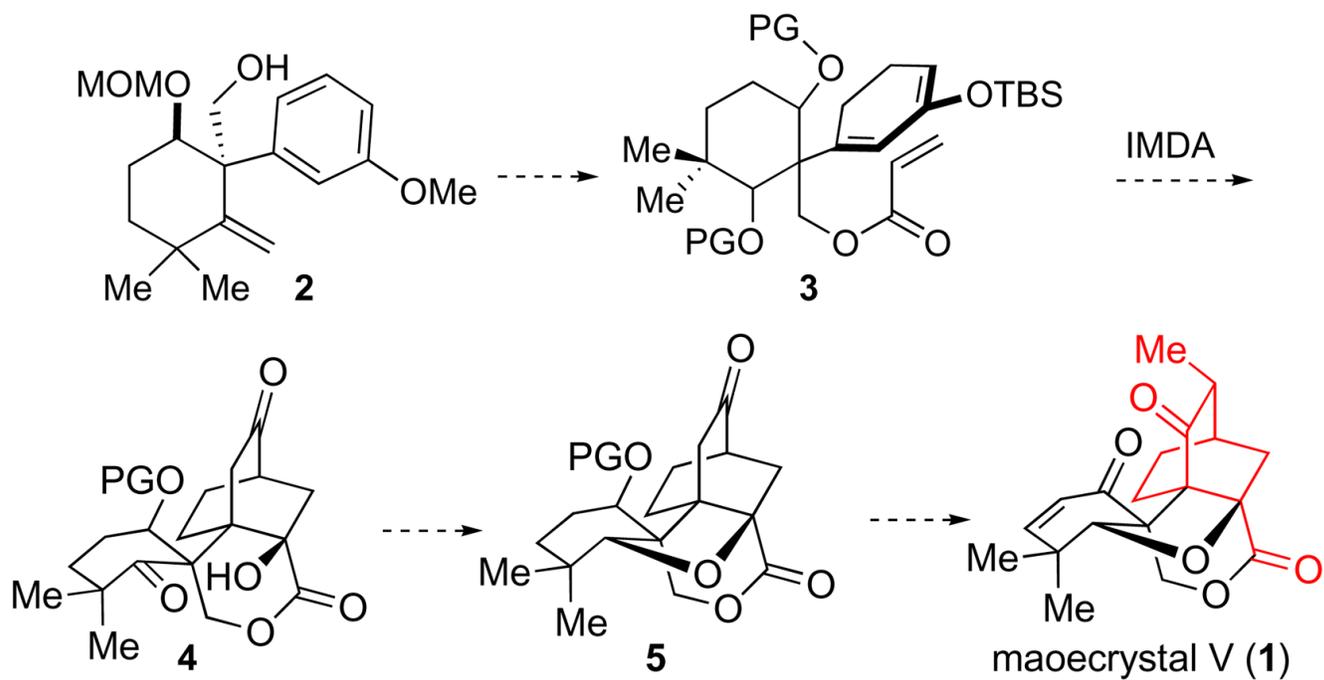
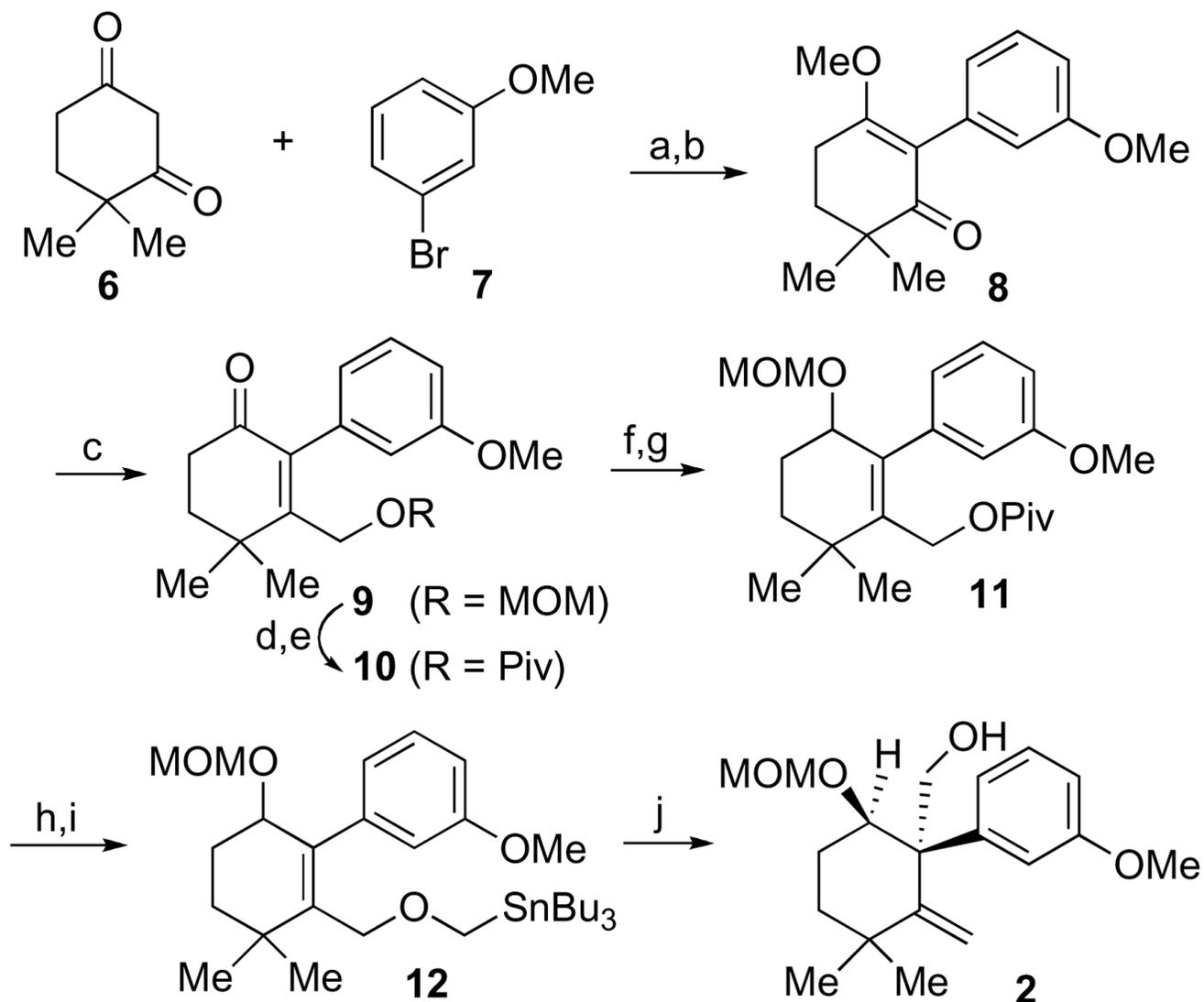


Figure 2.
Transition structures for the Diels-Alder reaction.

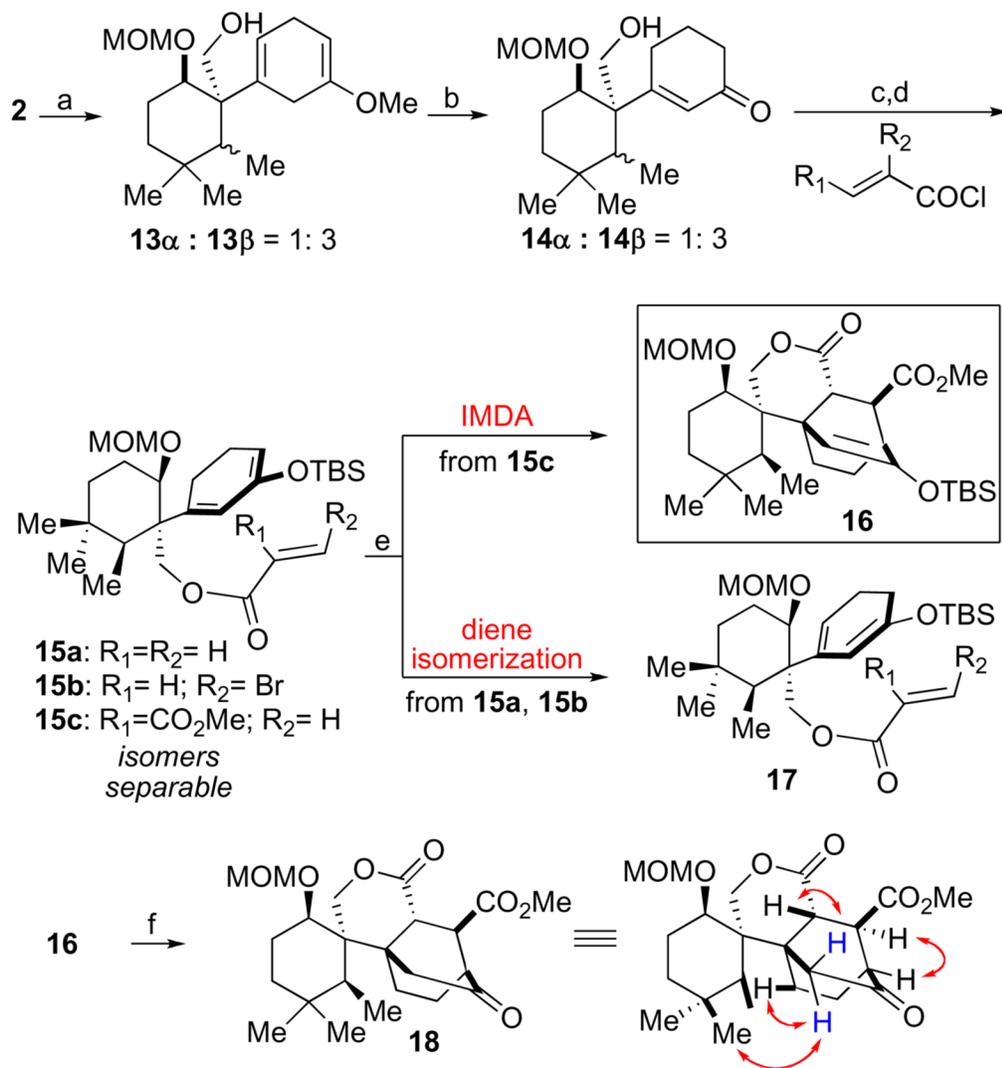


Scheme 1.
A proposed route to maoecrystal V.

**Scheme 2.**

Synthesis of intermediate 2.

Reagents and conditions: (a) Pd(OAc)₂, 2-di-*t*-butylphosphino-2'-methylbiphenyl, K₃PO₄, THF, 80 °C, 12 h, 91%; (b) TMSCHN₂, Hunig's base, CH₃CN/MeOH = 9:1, 6 h, 100%; (c) Bu₃SnCH₂OMOM, BuLi, THF, -78 °C to -40 °C, 30 min, 0.5% HCl work-up, 75%; (d) HCl/MeOH, 50 °C, 75%; (e) PivCl, Py, DCM, 12 h, 96%; (f) NaBH₄, CeCl₃, MeOH, 0 °C, 2 h, 93%; (g) MOMCl, Hunig's base, DCM, 12 h, 95%; (h) DIBAL-H, -78 °C, DCM, 30 min, 95%; (i) KH, 18-crown-6, ICH₂SnBu₃, 0 °C, THF, 6 h, 90%; (j) *n*-BuLi, -78 °C to -20 °C, THF, 6 h, 88%.

**Scheme 3.**

Intramolecular Diels-Alder reaction of **15c**.

Reagents and conditions: (a) Li, NH₃(l), *t*-BuOH/THF, -78 °C, 20 min, -33 °C, 40 min; (b) 1 N HCl, 0 °C, THF/MeOH (10/1), 8 h, 2 steps, 78%; (c) acid chloride, Py, DCM, 0 °C. **15a** : 70%, **15b** : 75%, **15c** : 72%; (d) TBSOTf, TEA, DCM, 0 °C, 15 h, 81%; (e) 180 °C, sealed tube, toluene, 12 h; (f) TBAF, 0 °C, THF, 2 steps, 48%.