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# Toward the Total Synthesis of Maoecrystal V: Establishment of Contiguous Quaternary Stereocenters

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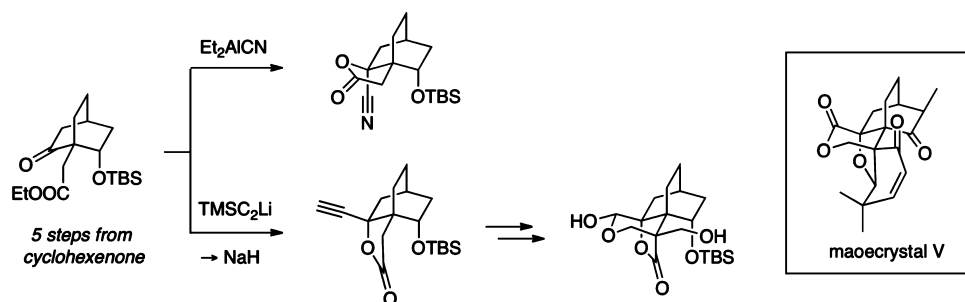
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## ABSTRACT



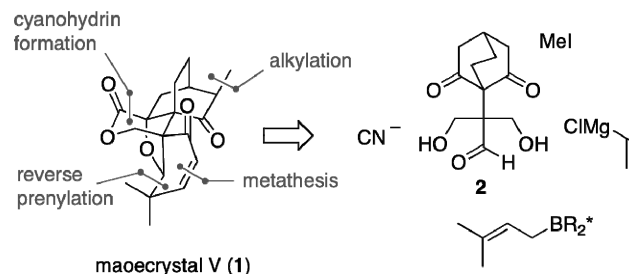
A synthetic strategy toward maoecrystal V has been identified. It has been shaped by the necessity to maneuver in sterically hindered molecular environments.

Maoecrystal V is a recently reported natural product with several unusual and attractive features (Scheme 1). Following its isolation from the Chinese medicinal herb *Isodon eriocalyx* by Sun and co-workers, it was shown to have significant cytotoxic properties, in particular against HeLa cancer cells.<sup>1</sup> The molecule appears to be a rearranged and oxidatively modified *ent*-kaurane diterpene that features a dense network of interwoven rings including a six-membered lactone, a tetrahydrofuran, a cyclohexenone, and a bicyclo[2.2.2]octane moiety. This ring system contains four highly substituted carbon atoms, three of which are contiguous, making maoecrystal V one of the most sterically compressed natural products known.

As a consequence, maoecrystal V has received considerable attention in the synthetic community. To date, five synthetic approaches have been published, all of which rely on a Diels–Alder reaction for the establishment of the bicyclo[2.2.2]octane ring system.<sup>2</sup>

(1) Li, S. H.; Wang, J.; Niu, X. M.; Shen, Y. H.; Zhang, H. J.; Sun, H. D.; Li, M. L.; Tian, Q. E.; Lu, Y.; Peng, C.; Zheng, Q. T. *Org. Lett.* **2004**, *6*, 4327–4330.

## Scheme 1. Structure and Retrosynthetic Analysis of Maoecrystal V



Herein, we report an alternative synthetic strategy, which employs a range of small nucleophiles and electrophiles to

(2) (a) Gong, J.; Lin, G.; Li, C.-C.; Yang, Z. *Org. Lett.* **2009**, *11*, 4770–4773. (b) Krawczuk, P. J.; Schöne, N.; Baran, P. S. *Org. Lett.* **2009**, *11*, 4774–4776. (c) Peng, F.; Yu, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 6586–6587. (d) Nicolaou, K. C.; Dong, L.; Deng, L.; Talbot, A. C.; Chen, D. Y.-K. *Chem. Commun.* **2010**, *46*, 70–72. (e) Lazarski, K. E.; Hu, D. X.; Stern, C. L.; Thomson, R. J. *Org. Lett.* **2010**, *12*, 3010–3013.

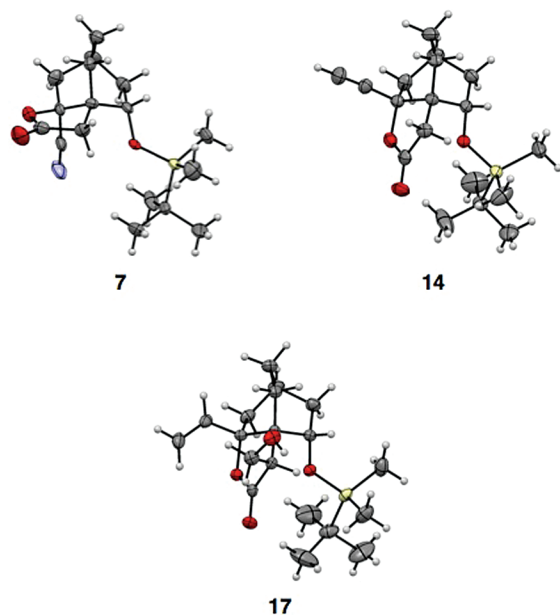
deal with the steric hindrance of the macrocyclic ring system. Thus far, our efforts have yielded a structure with four of the five rings of macrocyclic V in place and, most importantly, the two contiguous quaternary carbons and adjacent tertiary alcohol moiety that make this natural product such a challenging synthetic target.

Our initial retrosynthetic analysis centered around the highly symmetric bicyclo[2.2.2]octane derivative **2**, which already incorporates two of the three quaternary carbons of the target molecule (Scheme 1). We envisioned an asymmetric reverse prenylation,<sup>3</sup> cyanohydrin formation, and olefin metathesis<sup>4</sup> as key components of our synthetic plan.

The synthesis of the bicyclo[2.2.2]octane system started with a diastereomeric mixture of cyclohexenones **3**, easily obtained via alkylation of cyclohexenone with ethyl bromoacetate, followed by Sakurai allylation.<sup>5</sup> Ozonolysis of **3** yielded the corresponding aldehydes **4**, which, when subjected to acidic conditions, cleanly underwent intramolecular aldol addition to afford hydroxy bicyclo[2.2.2]octanone **5** as a 7:1 mixture of *endo* and *exo* isomers.<sup>6</sup> Following silylation, this mixture could be separated, and the major diastereomer **6** was further processed. It should be noted that an asymmetric version of this general synthetic approach to bicyclo[2.2.2]octanes has been developed by Kitahara et al.<sup>5</sup>

At this stage, we decided to explore a departure from the retrosynthetic analysis outlined above and attempt the installation of the requisite tertiary alcohol through cyanohydrin formation. Treatment of ketone **6** with Nagata's reagent ( $\text{Et}_2\text{AlCN}$ )<sup>7</sup> not only resulted in the formation of the cyanohydrin but also effected transesterification to yield lactone **7**.

Unfortunately, X-ray analysis of this product determined that the undesired diastereomer had formed (Figure 1). Since

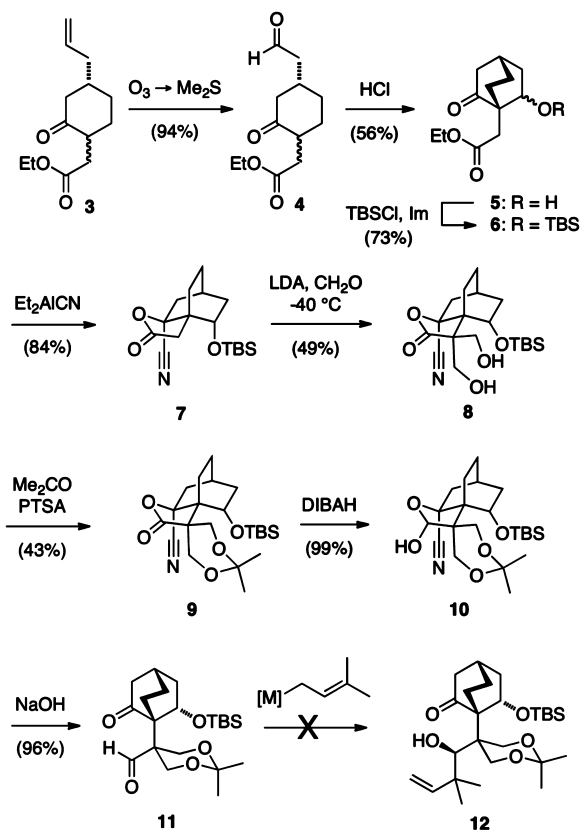


**Figure 1.** X-ray structures of key bicyclo[2.2.2]octanes **7**, **14**, and **17**.

the addition of cyanide under Nagata conditions is known to be reversible,<sup>7b</sup> this result could reflect the relative thermodynamic stability of the initially formed cyanohydrins.

With lactone **7** in hand, we investigated the installment of the second quaternary carbon through double aldol addition to formaldehyde, a very small electrophile.<sup>8</sup> Ultimately, this was effected by gradually warming **7** with a large excess of LDA and formaldehyde, the latter obtained through thermal depolymerization of dry paraformaldehyde. Under these conditions, 1,3-diol **8** was isolated in 49% yield (Scheme 2). This remarkable reaction presumably proceeds

**Scheme 2.** Opening Sequence and First-Generation Approach to Macrocyclic V



through an initial deprotonation and aldol addition, followed by what is, in essence, a Fráter–Seebach alkylation.<sup>9</sup> Pro-

(3) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432–439.

(4) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.

(5) Kitahara, T.; Miyake, M.; Kido, M.; Mori, K. *Tetrahedron: Asymmetry* **1990**, *1*, 775–782.

(6) Santis, B. D.; Iamiceli, A. L.; Bettolo, R. M.; Migneco, L. M.; Scarpelli, R.; Cerichelli, G.; Fabrizi, G.; Lamba, D. *Helv. Chim. Acta* **1998**, *81*, 2375–2387.

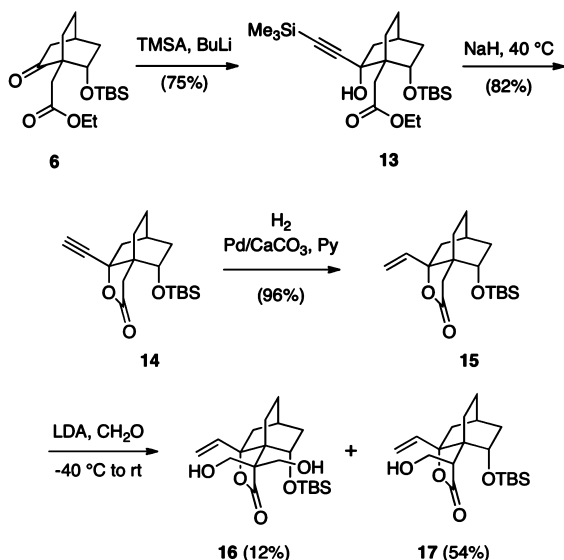
(7) (a) Yoshioka, M.; Hirai, S.; Nagata, W. *J. Am. Chem. Soc.* **1972**, *94*, 4635–4643. (b) Yoshioka, M.; Murakami, M.; Nagata, W. *J. Am. Chem. Soc.* **1972**, *94*, 4644–4653. (c) Orsini, F.; Pelizzoni, F.; Wimmer, Z. *Gazz. Chim. Ital.* **1984**, *114*, 363–367. (d) Watanabe, S.-i.; Cordova, A.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2002**, *4*, 4519–4522.

(8) Shing, T. K. M.; Uhu, X. Y.; Yeung, Y. Y. *Chem.—Eur. J.* **2003**, *9*, 5489–5500.

tection of the resulting diol **8** as an acetal yielded **9**, which could be selectively reduced with DIBAL<sup>10</sup> to furnish the lactol **10**. Upon treatment with 2 M aqueous NaOH, the lactol moiety underwent fragmentation with loss of cyanide to afford keto aldehyde **11**. The stereochemically undesired cyanohydrin in **7** therefore serves as a protecting group for a carbonyl group. Since **11** resembles the symmetrical aldehyde **2** (cf. Scheme 1), we decided to explore its participation in a reverse prenylation reaction. To date, however, we have not been able to effect this transformation.

While these studies were ongoing, we investigated the addition of other small nucleophiles to ketone **6** to overcome the undesired stereoselectivity of the Nagata cyanohydrin formation (Scheme 3).

**Scheme 3.** Overcoming the Undesired Stereoselectivity



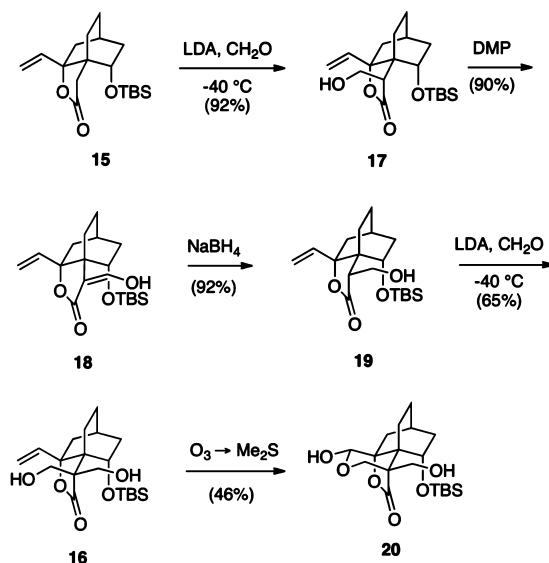
Potassium cyanide, TMSCN, and 2-furyllithium gave unsatisfactory results, and vinyl magnesium bromide or the corresponding organocerium reagent proved unreactive. The slender anion of TMS-acetylene (TMSA), however, added cleanly to the bicyclic ketone **6** and, this time, gave only the desired stereoisomer **13**.<sup>11</sup> Treatment of the tertiary alcohol with NaH resulted in lactone formation with concomitant desilylation to afford tricyclic lactone **14**, the structure of which was confirmed by X-ray crystallography (Figure 1). Lindlar reduction of **14** gave lactone **15**, whose vinyl group serves as a synthetic equivalent of a carbonyl group.

Unfortunately, the double aldol addition of **15** to formaldehyde proved more challenging than the corresponding

transformation of **7**, presumably due to its different steric environment. Under optimized conditions, we only obtained low yields of the 1,3-diol **16**, together with larger amounts of the monoaddition product **17**. The structure of **17** was again established by X-ray crystallography (Figure 1).

Given the low yield of the double addition product **16**, we decided to take a stepwise approach (Scheme 4). A single

**Scheme 4.** Stepwise Approach to the Two-Fold Aldol Addition



hydroxymethylation of lactone **15** under carefully controlled conditions ( $-40\text{ }^{\circ}\text{C}$ ) gave aldol addition product **17** in good yield and as a single diastereomer. The high diastereoselectivity of this reaction is probably due to the “open-book effect” of the 1-oxabicyclo[4.3.0]nonane subunit, which results in addition from the convex side.

All attempts to carry out a second addition using **17** as a starting material, however, gave unsatisfactory results. We reasoned that this was due to the considerable steric hindrance that would be encountered in the formation of the requisite dianion through double deprotonation of **17**. We therefore oxidized **17** to the corresponding 1,3-dicarbonyl compound, which primarily exists in its enolized form **18**. Once again, steric hindrance interfered with a subsequent attempt to C-alkylate. Selective reduction of **18** with sodium borohydride, however, was possible and gave hydroxymethyl lactone **19**, a diastereomer of **17**, as a single isomer. With the  $\alpha$ -proton now more accessible, Fráter–Seebach-type double deprotonation and hydroxymethylation proceeded with relative ease to yield **16** in satisfactory yield.

Ozonolysis of **16** yielded lactol/lactone **20** as a single diastereomer. This compound features the two contiguous quaternary carbons and the adjacent tertiary alcohol (in the form of a lactone) characteristic of maoecrystal V. It also provides three functional handles in three different oxidation states that could be used to carry on the synthesis.

In summary, we have outlined a synthetic strategy toward maoecrystal V that addresses issues that any synthesis of this

(9) (a) Fráter, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2828. (b) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269–1277. (c) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197–200.

(10) Corey, E. J.; Wu, Y.-J. *J. Am. Chem. Soc.* **1993**, *115*, 8871–8872.

(11) (a) Keegan, D. S.; Midland, M. M.; Werley, R. T.; McLoughlin, J. I. *J. Org. Chem.* **1991**, *56*, 1185–1191. (b) Smith, A. L.; Pitsinos, E. N.; Hwang, C.-K.; Mizuno, Y.; Saimoto, H.; Scarlato, G. R.; Suzuki, T.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1993**, *115*, 7612–7624.

fascinating target will face. So far, our approach has yielded an advanced intermediate, compound **20**, which has suitably differentiated functional groups and features four of the five rings of the target. Attempts to streamline our synthetic route and render it asymmetric are currently underway. The continuation of our synthetic endeavor will most likely require additional strategies to overcome steric hindrance, such as high-pressure reactions or intramolecularization.

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**Note Added in Proof.** Since this paper was accepted, the first total synthesis of maoecrystal V has been published,

also following a Diels–Alder approach: Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745–16746.

**Note Added after ASAP Publication.** Figure 1 contained an error in the version published ASAP November 18, 2010; the correct version reposted December 10, 2010.

**Supporting Information Available:** Spectroscopic and analytical data for compounds **3–20**. Crystallographic data for compounds **7**, **14**, and **17** have been deposited at the Cambridge Crystallographic Data Centre (CCDC 796309, 796310, and 796311, respectively). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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