Review of Synthetic Approaches Toward Maoecrystal V

Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-REV-04-2018-000909.R1
Article Type:	Review Article
Date Submitted by the Author:	11-May-2018
Complete List of Authors:	Njardarson, Jon; University of Arizona, Department of Chemistry and Biochemistry Smith, Brandon; University of Arizona, Chemistry and Biochemistry

Organic and Biomolecular Chemistry

ARTICLE

Review of Synthetic Approaches Toward Maoecrystal V

Brandon R. Smith and Jon T. Njardarson*

Synthetic approaches toward the complex natural product diterpenoid maoecrystal V are reviewed, including successful total syntheses, published synthetic efforts, and efforts compiled from dissertations. The review focuses on general synthetic strategies and chronicles efforts toward the molecule since its isolation in 2004, summarizing key contributions of these efforts to the broader synthetic community.

Introduction

Maoecrystal V (**1**) was first isolated in 1994 by Sun and coworkers, but its identity was not revealed to the scientific community until 2004 due to difficulties in definitive structural assignment**.** Eventually X-ray crystallography provided confirmation of maoecrystal V's unprecedented structure.[1] Isolated in southwestern China from the Isodon eriocalyx species of shrub, maoecrystal V constitutes a member of the ent-kauranoid (**2**) family of natural products. In general, this family of natural products has shown rich biological properties, and isodon eriocalyx species have been used in folk medicine for the treatment of sore throat, inflammation, influenza, hypertension, and dermatophytosis. Maoecrystal V also demonstrated exciting biological properties. It was reported to possess nanomolar level cytotoxicity towards a strain of cervical cancer cell lines, demonstrating an IC_{50} value of 20 ng/mL toward HeLa cell lines. In 2016, however, Baran and coworkers were the first to re-assess the biological activity of maoecrystal V and found that it had no anticancer properties.[2]

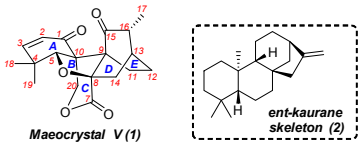
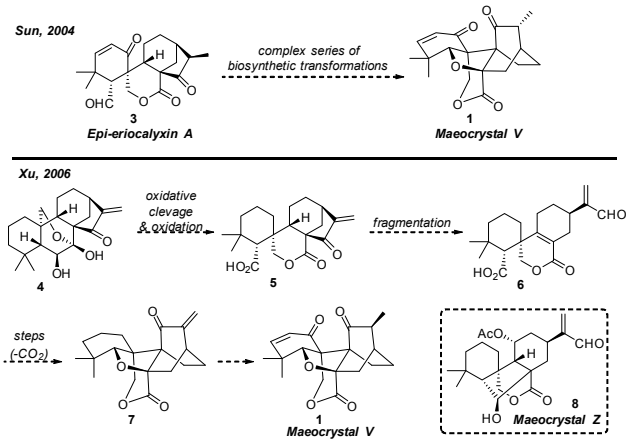


Figure 1: Maoecrystal V structure and numbering system

Structurally, maoecrystal V possesses an intriguing pentacyclic skeleton with four contiguous quaternary stereogenic centers at the core of the molecule. The D/E ring exists as a [2.2.2]-bicyclooctane with a fused lactone C ring. Lastly, the cyclohexenone A ring contains a gamma gem-dimethyl group that further congests the densely-packed skeleton. The combination of these factors has made maoecrystal V a particularly challenging target structure.



Scheme 1: Maoecrystal V biosynthesis proposals

At the time of publication of maoecrystal V's isolation in 2004, Sun and co-workers proposed a partial biosynthesis for maoecrystal V, suggesting that it arises from a [3.2.1] to [2.2.2]-bicyclooctane rearrangement from epi-eriocalyxin A (**3**) via a series of complex biological transformations (Scheme 1).[1] In 2006, upon the isolation of maoecrystal Z (**8**), an adduct lacking maoecrystal V's bicyclic system, Xu and co-workers presented an alternate biosynthesis proposal for maoecrystal V.[3] They proposed that [3.2.1]-bicyclooctane **4** could represent a common intermediate to both maoecrystal V and Z, oxidative cleavage and oxidation would generate [3.2.1]-bicyclooctane **5**. Fragmentation of the bicycle to aldehyde **6** would allow for differentiation into maoecrystal Z. Alternatively, decarboxylation and tetrahydrofuran ring formation would allow for formation of the [2.2.2]-

Department of Chemistry and Biochemistry
University of Arizona
1306 E. University Blvd.
Tucson, AZ 85721
USA

bicyclooctane as **7** which could then be further modified into maoecrystal V.

Maoecrystal V Completed Total Syntheses

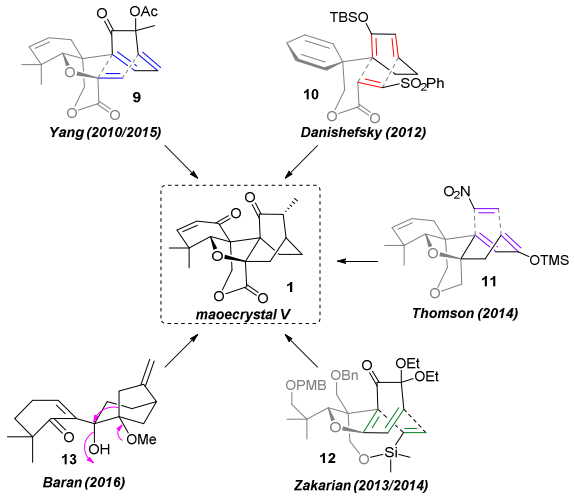
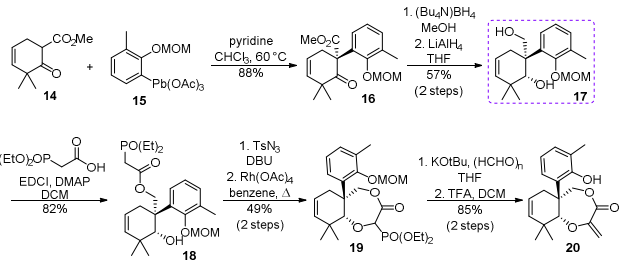


Figure 2: Summary of successful maoecrystal V total syntheses

Following maoecrystal V isolation, it immediately became a high-value target for synthetic organic chemists due to the combination of its complex structure and exciting originally-reported biological activity. To date there have been seven successful total syntheses[2,4] by five different research groups along with numerous synthetic attempts (Figure 2)[5,6]. All these syntheses, except Baran's most recent one, have utilized a Diels-Alder reaction to construct the [2.2.2]-bicyclooctane core. Baran employed a rearrangement approach, mimicking the originally proposed biosynthesis.

Yang's maoecrystal V total synthesis[4a, 4f]

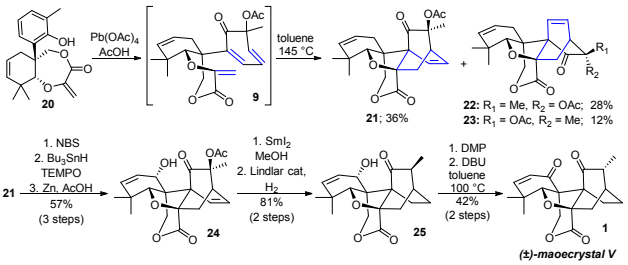
The first research group to complete a total synthesis of maoecrystal V was Yang and co-workers in 2010.[4a] They would later complete an asymmetric synthesis in 2015 utilizing similar chemistry.[5f] Their key step for the early synthetic strategy was a Pinhey arylation with trisubstituted aryl lead species **15** and cyclohexenone **14** which was executed in very good yield (Scheme 2). From there, much work was required to overcome the inherent shape selectivity in the double reduction to generate diol **17**. All conventional methods delivered the undesired trans diol upon reduction of the ketone, however it was eventually discovered that reduction with tetrabutylammonium borohydride could overcome this inherent reactivity to deliver their desired cis diol **17**. Acylation followed by a diazo transfer step and rhodium mediated O-H insertion afforded phosphonate **19**, which was then converted in two steps to Diels-Alder precursor **20**.



Scheme 2: Yang's synthesis of intramolecule Diels-Alder precursor

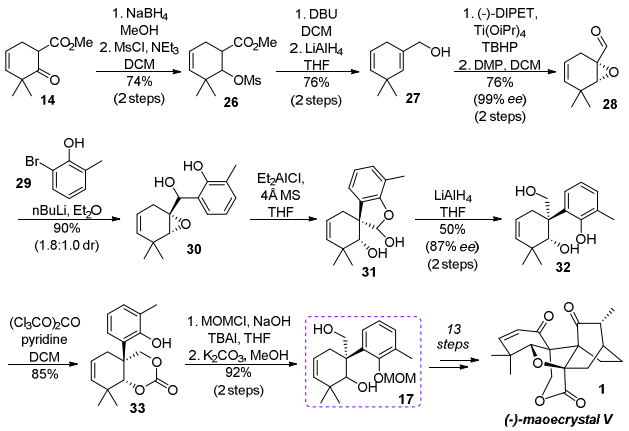
With phenol **20** in hand, attention shifted to the key intramolecular Diels-Alder (IMDA) reaction. Wessely oxidative acetoxylation delivered intermediate **9** as a mixture of isomers. Upon heating in toluene the desired Diels-Alder was achieved, but the desired bicycle, **21**, was generated in only 36% yield along with two other isomeric products **22** and **23**.

Yang's endgame consisted of a three-step installation of the oxygen at C1 of maoecrystal V (Scheme 3). Allylic bromination with NBS followed by treatment with tributyltin hydride generated a radical which was then trapped with TEMPO. Finally, cleavage of the tetramethylpiperidine unit delivered allylic alcohol **24**. Reductive cleavage of the acetoxy group followed by selective reduction of the strained bicyclic olefin delivered adduct **25**, albeit with improper methyl group stereochemistry. Lastly, oxidation of the alcohol with Dess-Martin periodinane followed by methyl isomerization delivered maoecrystal V.



Scheme 3: Yang's key IMDA and end game

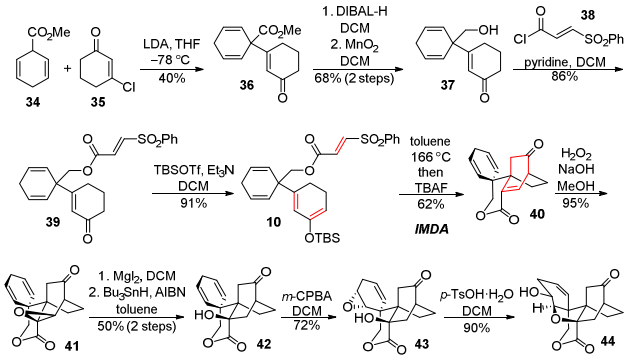
Yang would go on to complete an enantioselective synthesis of maoecrystal V in 2015 (Scheme 4)[4f]. The key IMDA reaction and endgame would be identical to that utilized in his 2010 racemic synthesis, converging upon the generation of diol **17** (boxed in dashed purple in Scheme 2). The key difference is that rather than accessing **17** via a Pinhey arylation, the enantioselective approach achieves asymmetry by a Sharpless asymmetric epoxidation to generate epoxide **28**. A semipinacol reaction was then utilized to rearrange the carbon skeleton. After reduction and protecting group manipulation, desired diol **17** was generated in enantiopure form.



Scheme 4: Yang's 2015 enantioselective maoecrystal V synthesis

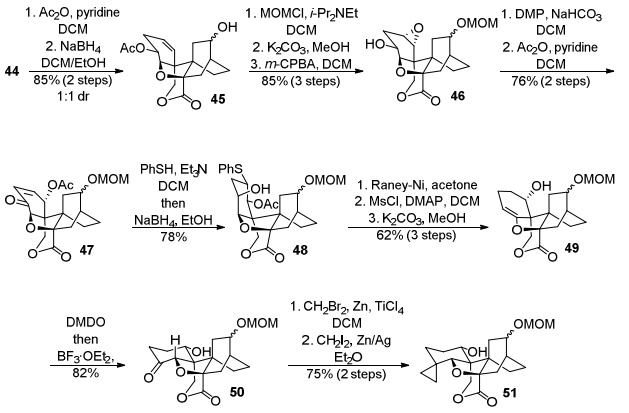
Danishefsky's maoecrystal V total synthesis[4b]

Following Yang's successful synthesis of maoecrystal V in 2010, Danishefsky and coworkers were the next to accomplish the feat, in 2012.[4b]



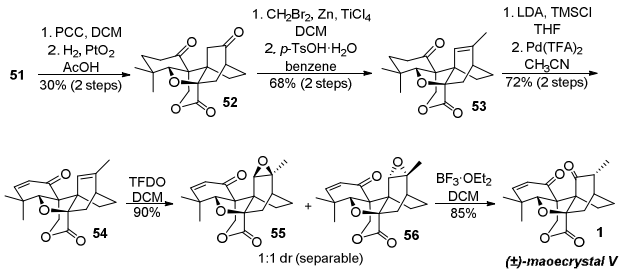
Scheme 5: Danishefsky's early stage IMDA reaction

Danishefsky's synthesis also utilized an IMDA reaction to construct the [2.2.2]-bicyclooctane of maoecrystal V. After initial struggles in achieving desired facial selectivity in their Diels-Alder reaction they ultimately found that substitution of a phenylsulfone group on the dienophile allowed them to achieve their goal (Scheme 5). Conveniently the phenylsulfone could also be eliminated in one pot using TBAF to generate [2.2.2.]-bicyclooctane **40**. Next the focus shifted to installation of the tetrahydrofuran ring, which required desymmetrization of the cyclohexadiene ring. This was achieved by first installing oxygen on the bicycle of **40** by epoxidation. The epoxide was selectively opened from the less hindered side using magnesium iodide and the resulting iodine was reductively removed by tributyltin hydride to generate alcohol **42**. The alcohol of **42** was used as a synthetic handle to allow for desymmetrization of the cyclohexene ring via directed epoxidation with *m*-CPBA. Epoxide **43** was opened, and the tetrahydrofuran ring generated under acidic conditions, but undesired A-ring stereochemistry could not be avoided, generating adduct **44**.



Scheme 6: Danishefsky's functionalization of pentacycle

The next phase of Danishefsky's synthesis focused on functionalizing the A ring of maoecrystal V and inverting the stereochemistry at the furan ring (Scheme 6). This was accomplished through a lengthy process. After a number of transformations, enol **49** was ultimately generated. Treatment of this enol with dimethyldioxirane (DMDO) followed by BF_3 etherate formed ketone **50** and allowed for C5-inversion objective to be achieved. The gem-dimethyl group was next installed by Lombardo olefination followed by a Simmons-Smith inspired cyclopropanation to **51**.



Scheme 7: Danishefsky's maoecrystal V end game

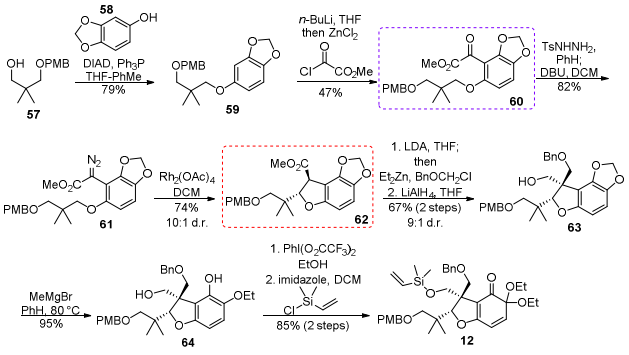
Following oxidation, cyclopropane **51** was reductively cleaved with platinum to deliver dimethyl-containing tricarbonyl compound **52** (Scheme 7). With **52** in hand Lombardo reagent was used to install the final carbon of maoecrystal V, and using acidic conditions the resulting olefin was isomerized to generate substrate **53**. A two-step procedure was used to install the unsaturation within the B-ring generating enone **54**. Epoxidation with TFDO delivered a separable mixture of epoxides **55** and **56**, the latter of which was then ring-opened with BF_3 etherate to generate maoecrystal V and complete the total synthesis.

Zakarian's maoecrystal V total synthesis[4c, 4d]

The next total synthesis of maoecrystal V came from the Zakarian group, which completed a racemic synthesis in 2013[4c] followed by an enantioselective synthesis in 2014[4d]. Once again, intramolecular Diels-Alder served as the key step to generate the [2.2.2]-bicyclooctane. In this case the

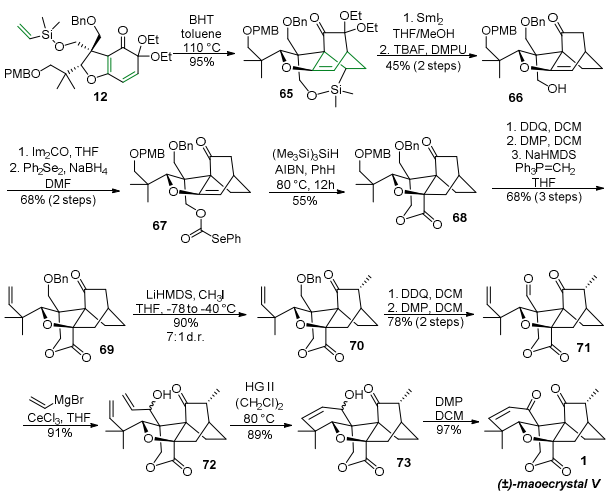
tetrahydrofuran ring was assembled with proper stereochemistry prior to the IMDA, avoiding the problems that plagued Danishefsky's synthesis and many of the synthetic attempts toward maoecrystal V. This approach required late stage assembly of the cyclohexenone A ring via allyl group installation and Grubbs cross-metathesis.

Starting with monoprotected diol **57**, a Mitsunobu reaction was used to attach sesamol (**58**) and generate adduct **59** (Scheme 8). Next an ortho-directed lithiation, followed by transmetallation with zinc and electrophile trapping delivered **60**. Ester **60** (boxed in purple) would later serve as the achiral precursor for Zakarian's enantioselective synthesis in 2014. The reactive ketoester was converted to a diazoester, allowing for C-H insertion chemistry using rhodium acetate to assemble the tetrahydrofuran ring. Next, alpha alkylation allowed for installation of the benzyl protected methylene alcohol. The ester group was reduced with lithium aluminum hydride and the formyl acetal was opened with methylmagnesium bromide to generate phenol **64**. The phenol was oxidized with trifluoromethyl iodobenzene diacetate to the ortho-quinone ketal, and the primary alcohol was then alkylated with dimethyl vinyl-silane to generate IMDA precursor **12**. Silicon proved to be the optimal removable tether group for ultimate differentiation into maoecrystal V.



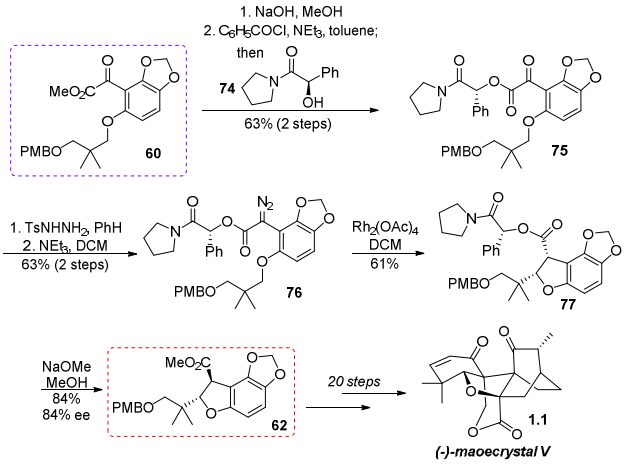
Scheme 8: Zakarian's IMDA precursor synthesis

Ortho-quinone ketal **12** was subjected to thermal conditions to evoke the desired IMDA reaction in excellent yield (Scheme 9). With Diels-Alder adduct **65** in hand the focus shifted to desilyation, which would pave the way for installation of the lactone ring via a radical cyclization. The ketal moiety of **65** was removed by reduction with samarium diiodide. After extensive optimization tetrabutylammonium fluoride (TBAF) proved to be the best reagent for desilylation, generating alcohol **66**, which was then converted to the selenocarbonate **67** over two steps. Initial attempts to utilize tributyltin hydride with multiple radical initiators resulted only in reduction of the intermediary acyl radical. This led to the selection of a less efficient hydrogen atom donor, allowing time for the desired radical cyclization to occur. Tris(trimethylsilyl)silane emerged as the ideal hydrogen source, achieving the desired cyclization to generate lactone **68**. With the lactone ring in place, the final hurdle was installation of the cyclohexenone ring by ring closing metathesis. First the PMB alcohol of **68** was converted to the vinyl group vi a deprotection, oxidation, and Wittig olefination sequence.



Scheme 9: Zakarian's key IMDA and end game

With adduct **69** in hand the methyl group on the bicyclooctane was installed. Next the benzyl alcohol was deprotected and oxidized to aldehyde **71**, which allowed for installation of the second vinyl group by addition of vinyl magnesium bromide, generating **72** as a mixture of alcohols. Finally, ring closing metathesis with Hoyveyda-Grubbs 2nd generation catalyst followed by oxidation completed the total synthesis of maoecrystal V.



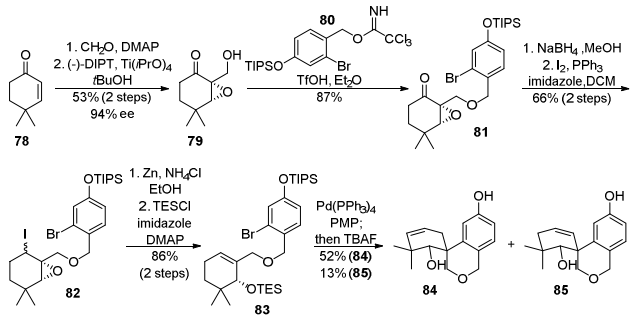
Scheme 10: Zakarian's enantioselective maoecrystal V synthesis

One year after the racemic synthesis, Zakarian published an enantioselective synthesis of maoecrystal V (Scheme 10)[4d]. Despite extensive efforts to improve upon the initial synthesis by altering the tether from silicon to boron and by including the vinyl group necessary for ring closing metathesis through the entire sequence they ultimately settled on a synthesis that was very similar to their original design.

Starting with ester **60** from their previous synthesis, enantioselectivity was achieved by installation of a chiral auxiliary (**74**) followed by C-H functionalization to generate **77**. Cleavage of the chiral auxiliary and concomitant isomerization of the ester generated **62** in 84% *ee*. Attempts to utilize chiral ligands on rhodium rather than the chiral auxiliary resulted in inferior enantioselectivity. From ester **63** an identical 20 step synthesis mirroring Zakarian's racemic synthesis was employed.

Thomson's maoecrystal V total synthesis[4e]

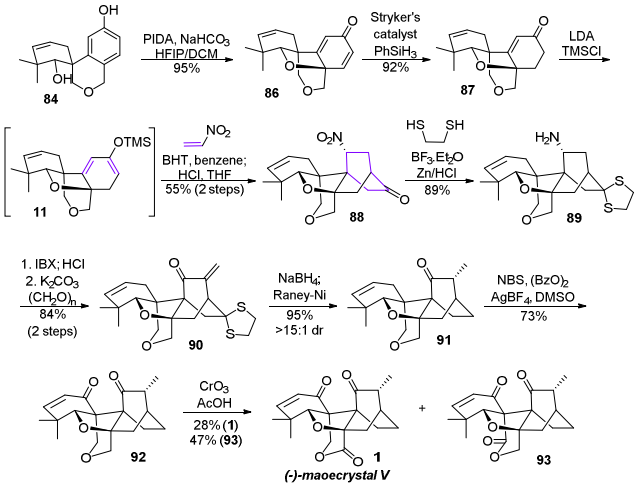
In 2014 the research group of Regan Thomson published an asymmetric synthesis of maoecrystal V.[4e] They executed an efficient synthesis hinging on a key intermolecular Diels-Alder reaction. The approach utilized what was termed a "west-to-east" strategy for assembly of the tetrahydrofuran ring, whereby the bond to the cyclohexene ring was set early to ensure proper stereochemistry and the bond to the bicycle was formed prior to Diels-Alder cycloaddition by an oxidative cyclodearomatization step.



Scheme 11: Thomson's early stage synthesis

Beginning with 4,4-dimethylcyclohexenone, **78**, Baylis-Hillman reaction was used to install the methylene alcohol and provide a synthetic handle for a Sharpless asymmetric epoxidation (Scheme 11). This early introduction of asymmetry ultimately sets the proper stereochemistry for the tetrahydrofuran ring. The next several steps set the stage for an intramolecular Heck reaction. Alcohol **79** was benzylated with **80** and reductive fragmentation was used to open the epoxide ring. The resulting alcohol was protected with triethylsilyl group to deliver **83**, which was then subjected to a diastereoselective Heck reaction and cleavage of the silyl protecting groups to afford desired spirocycle **84** as the major product, which resulted from olefin isomerization to more stable position.

With diol **84** in hand, attention was turned to construction of the tetrahydrofuran ring which was accomplished by a clever oxidative cyclodearomatization using PIDA as the oxidant to deliver dienone **86** in excellent yield. Dienone **86** was selectively reduced using Stryker's catalyst ($[(PPh_3)CuH]_6$) to deliver enone **87** and set the stage for the key intermolecular Diels-Alder reaction. Enone **87** was converted to the unstable silyl-enol ether **11**, which was immediately exposed to nitroethylene to evoke the desired intermolecular Diels-Alder reaction, delivering bicyclooctane **88**. The greatest obstacle to overcome in this transformation was avoidance of fragmentation of the ether ring to regenerate phenol **84**.



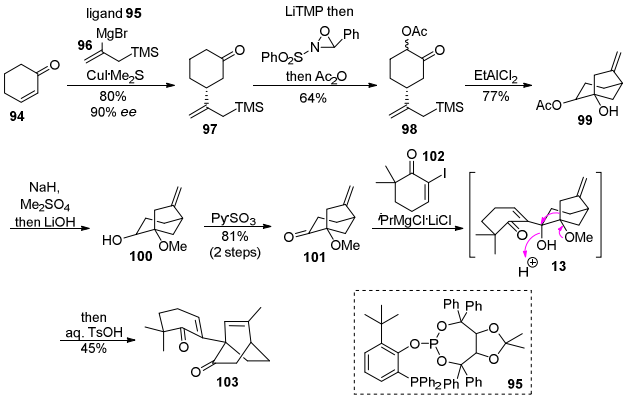
Scheme 12: Thomson's cyclodearomatization, Diels-Alder and end game

With the major carbocyclic framework of maoecrystal V constructed, the synthesis shifted to late stage modification of the core (Scheme 12). After considering various options it was determined that ketone **88** could be removed by conversion to the dithioketal followed by desulfuration with Raney nickel. The presence of the dithioketal proved important for gaining selectivity in the installation of the final methyl group of maoecrystal V. In practice bicyclooctane **88** was converted to the dithioketal then subjected to one-pot reduction of the nitro group to amine **89**. This was oxidized to an imine with IBX, and hydrolyzed with hydrochloric acid to deliver ketone **92**. The methylene group was installed via an aldol reaction with paraformaldehyde to deliver enone **90**. The presence of the dithioketal allowed for stereoselective reduction of enone **90** with sodium borohydride, which was followed by desulfuration with Raney nickel to afforf ketone **91**. At this point all that was needed to furnish maoecrystal V was installation of the ketone and lactone carbonyl moieties. Improving upon the precedent established by Yang whereby the ketone was installed over a four-step process, the Thomson group accomplished this transformation in a single step by a one pot allylic bromination /Kornblum oxidation to deliver enone **92**. The final oxidation of enone **92** to maoecrystal V was achieved with chromium trioxide in acetic acid, but the electronic factors favoring generation of lactone **93** could not be overcome, as this unwanted lactone was ultimately produced as the major product. In all, the Thomson group was still able to execute a very clever synthesis of maoecrystal V.

Baran's 2016 maoecrystal V total synthesis[2]

The final successful total synthesis of maoecrystal V was accomplished in 2016 by the Baran group.[2] Breaking from the

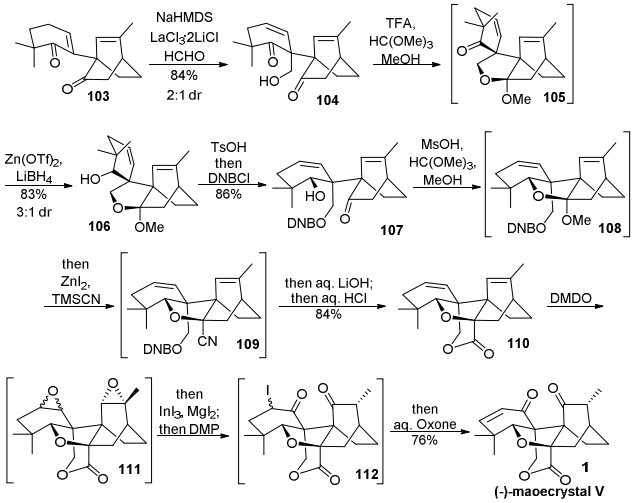
previous trend of assembling the [2.2.2]-bicyclooctane via a Diels-Alder reaction, the Baran group instead chose to access the bicycle via a rearrangement from a [3.2.1]-bicyclooctane scaffold, which mimics the originally proposed biosynthesis.



Scheme 13: Baran's key skeletal rearrangement

The Baran synthesis began with an enantioselective 1,4-addition of allyl silane **96** to cyclohexenone (Scheme 13). The selection and loading of the TADDOL-derived ligand **95** and copper catalyst were both critical to achieving desired enantioselectivity and suppressing dimerization of allyl silane **96**. The installation of electrophilic oxygen alpha to the carbonyl was achieved by Davis oxaziridine, followed by acylation with acetic anhydride. The desired [3.2.1]-bicyclooctane, **99**, was constructed via a Sakurai reaction, with the choice of Lewis acid proving critical to success. With **99** in hand the tertiary alcohol was methylated and the acetate protecting group cleaved to generate secondary alcohol **100**. Oxidation to ketone **101** by Parikh-Doering oxidation set the stage for exploration of the key skeletal rearrangement. The pinacol rearrangement was initiated by 1,2-addition of a Grignard reagent formed from **102** to the ketone, generating intermediate **13**. Treatment of this intermediate with aqueous *p*-toluenesulfonic acid and application of heat induced the desired pinacol rearrangement and concomitant olefin migration to deliver [2.2.2]-bicyclooctene **103**.

The most challenging step in the Baran synthesis proved to be the enolate-based hydroxymethylation of **103** (Scheme 14). The first challenge was achieving selectivity in formation of the more hindered conjugated enolate within the A ring rather than enolization of the ketone on the [2.2.2]-bicyclooctene. Once this challenge was overcome, they also needed to achieve regioselective hydroxymethylation at the desired position. After extensive screening the optimal solvent and reagent mixture finally emerged, allowing for the generation of primary alcohol **104**. To achieve reduction of the hindered ketone within the A ring, the bicyclic ketone was first converted to a ketal followed by in-situ reduction with lithium borohydride in the presence of zinc triflate. Ketal **106** was then reopened, and the primary alcohol protected. Subsequent treatment with acid allowed for ketalization from the secondary alcohol, generating **108** and forming the tetrahydrofuran ring of maoecrystal V. The intermediate mixed ketal **108** was treated with zinc iodide and TMS cyanide to install the nitrile group, which was subjected to hydrolysis. Upon deprotection of the primary alcohol, lactone **110** was generated. With lactone **110** in hand, maoecrystal V was generated in an impressive one-pot transformation. The cascade was initiated by epoxidation with DMDO to generate diepoxide **111**, which was directly treated with indium iodide and magnesium iodide, rupturing the epoxide within the A ring to form a iodohydrin and inducing a stereoselective 1,2-hydride shift that set the methyl group stereochemistry within the bicycle. Subsequent treatment with Dess-Martin periodinane delivered intermediate **112**. Finally, elimination of the iodide with Oxone delivered maoecrystal V in good yield directly from lactone **110**. Having greater than 80 mg of synthetic maoecrystal V in hand the Baran group set out to confirm the biological activity of maoecrystal V. Unfortunately, after screening the molecule against 32 different cancer cell lines in four different laboratories, no anticancer activity was detected, indicating that the originally reported biological activities were incorrect.

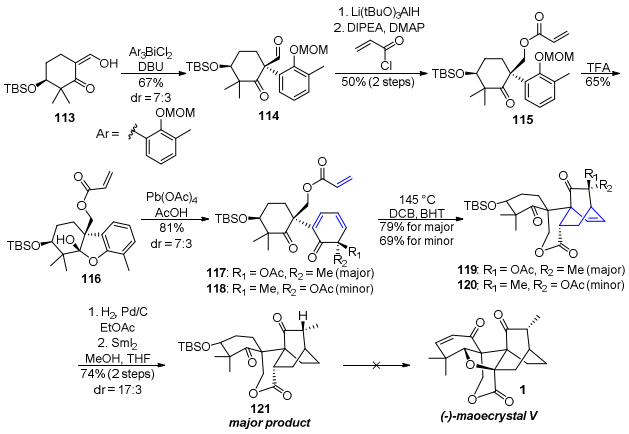


Scheme 14: Baran skeletal modification and end game

Maoecrystal V Synthetic Approaches

In addition to the total syntheses of maoecrystal V there have also been many synthetic attempts toward the molecule that have been reported since its discovery.[5] The following sections summarize these creative synthetic endeavours.

Baran's 2009 maoecrystal V approach[5b]

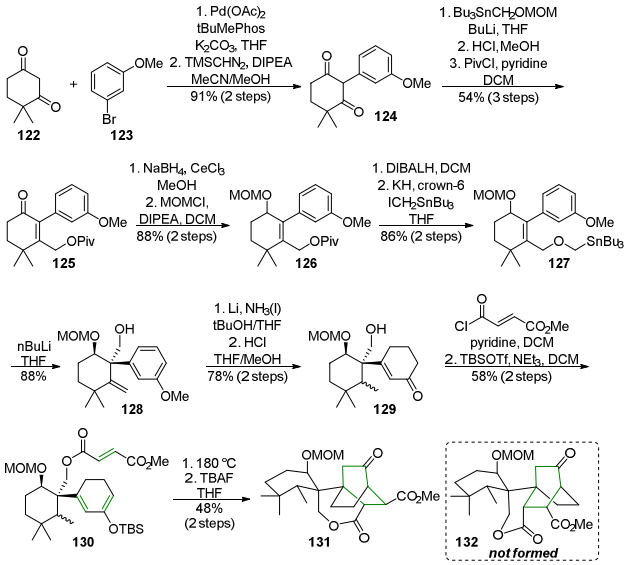


Scheme 15: Baran's IMDA approach to maoecrystal V

It is noteworthy that although the Baran group broke from the Diels-Alder mold in their 2016 successful synthesis of maoecrystal V, they had published an approach that hinged on an IMDA reaction seven years earlier in 2009 (Scheme 15)[5b]. Barton arylation of β-keto aldehyde **113** with an aryl substituted bismuth compound delivered keto-aldehyde **114**. Aldehyde reduction and acylation delivered ester **115**. Deprotection of the MOM group followed by Wessely oxidation with $Pb(OAc)_4$ delivered a separable mixture of hemi-acetals. Upon heating both the major and minor diene products underwent the desired intramolecular Diels-Alder reaction to forge the [2.2.2]-bicyclooctane (**119** and **120**). Following olefin reduction and removal of the acetate group with samarium diiodide both products converged to a single tricarbonyl compound **121** which contained four of the five rings of maoecrystal V and the correct stereochemistry at the methyl group. Despite this promising start, the Baran group was unable to form the pesky tetrahydrofuran ring and ultimately pursued a redesigned strategy for their successful maoecrystal V synthesis.

Danishefsky's 2009 maoecrystal V approach[5d]

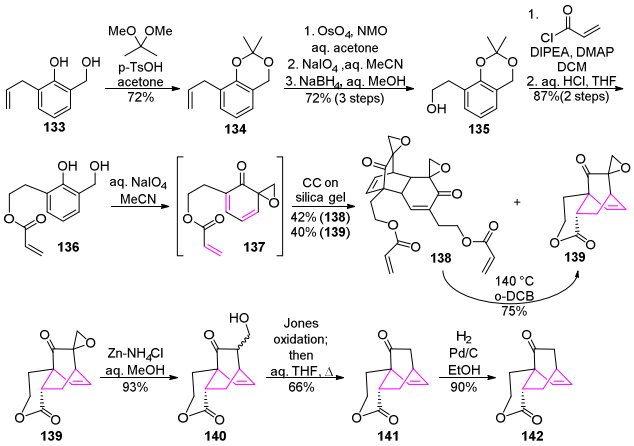
Danishefsky's research group also went through multiple iterations before their victorious effort toward maoecrystal V, having first published an approach in 2009 (Scheme 16). While the overall concept was similar to their successful effort they attempted to utilize a more functionalized A ring that included maoecrystal V's gem dimethyl group and a protected alcohol moiety. The quaternary stereocenter in the IMDA precursor was assembled by a Stille-Wittig [2,3]-rearrangement of stannane **127** to alcohol **128**. This approach was derailed when the Birch reduction of **128** unexpectedly resulted in concomitant reduction of exomethylene, which, following hydrolysis delivered ketone **129**. Despite the undesired exomethylene reduction, substrate **129** was advanced as a model system. The dienophile was installed from the corresponding acid chloride, followed by diene formation as silyl enol ether **130**. The IMDA was achieved under thermal conditions, however, upon silyl cleavage to ketone **131**, NMR analysis revealed that the IMDA had occurred from the undesired facial orientation. These observations ultimately led Danishefsky to advance an unsubstituted A ring and utilize a sulfone substitutent on the dienophile for their successful synthesis of maoecrystal V.



Scheme 16: Danishefsky's 2009 approach to maoecrystal V

Singh's 2010 maoecrystal V approach[5e]

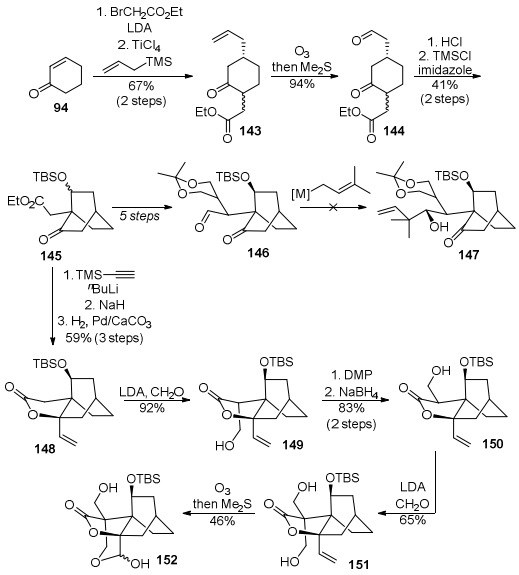
An additional intramolecular Diels-Alder approach toward maoecrystal V was published by the Singh research group in 2010 (Scheme 17).[5e] Their approach hinged on an Adler-Becker dearomatization step to generate an epoxide substituted quinone for IMDA. This was accomplished by the generation of phenol **136** over six steps from phenol **133**. Phenol **136** was subjected to and Adler-Becker oxidation with sodium periodate to generate quinone **137**. Upon purification on silica gel two adducts were formed, desired Diels-Alder adduct **139** along with dimerized quinone adduct **138** in nearly equal proportions. Fortunately, heating of dimer **138** induced a retro-Diels-Alder reaction to regenerate quinone **137** and allow the desired Diels-Alder reaction to proceed. With bicyclooctane **139** in hand, the epoxide was reduced with zinc. Oxidation to acid followed by decarboxylation delivered ketone **141**, which was then reduced to tricycle **142**, containing maoecrystal V's [2.2.2]-bicyclooctane and lactone rings. However, the Singh group was not able to advance this compound to maoecrystal V, nor were they able to apply this strategy to a more complex system.



Scheme 17: Singh's IMDA approach to maoecrystal V

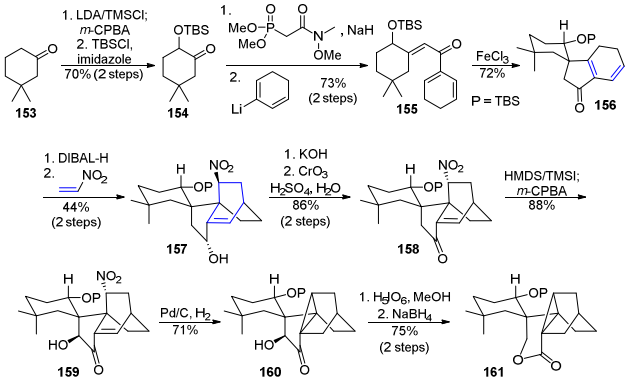
Trauner's 2010 maoecrystal V approach[5g]

In 2010 the Trauner's group published an approach toward maoecrystal V that did not assemble the [2.2.2]-bicyclooctane by IMDA, but rather by aldol cyclization (Scheme 18).[5g] The aldol precursor, **144**, was synthesized over three steps from cyclohexanone, **94**, by alkylation, Sakurai allylation, and ozonolysis. The aldol cyclization was accomplished in hydrochloric acid, and upon silyl protection delivered [2.2.2]-bicyclooctane **145**. Trauner then converted keto-ester **145** into keto-aldehyde **146** over five steps. The aim was to access the cyclohexanone ring of maoecrystal V by reverse prenylation to form homoallylic alcohol **147**, but this transformation could not be realized.



Scheme 18: Trauner's aldol approach to maoecrystal V

To circumvent the reverse prenylation problem, keto ester **145** was instead converted to allyl-substituted lactone **148** over three steps. Attempts to achieve one-pot double alkylation of lactone **148** to diol **151** were unsuccessful due to steric hindrance in the second alkylation, but the transformation could be achieved by a four-step process through stereochemical inversion of the mono-alkylated alcohol **149** to the less sterically hindered alcohol **150**, which could then be alkylated to deliver diol **151**. Subsequent ozonolysis delivered lactol **152**, but Trauner was unable to access maoecrystal V from this late stage intermediate.



Scheme 19: Thomson's 2010 approach to maoecrystal V

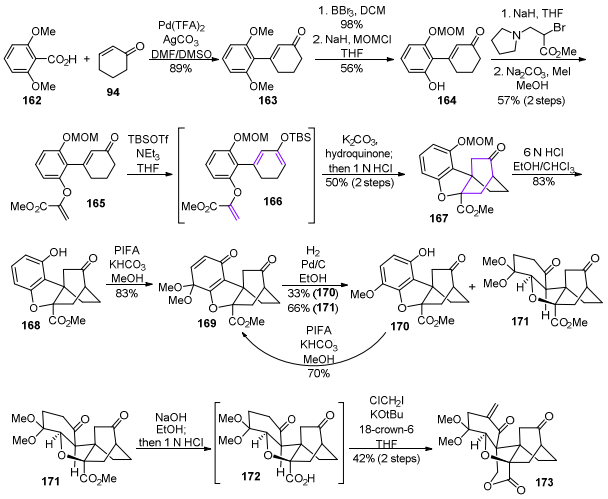
Thomson's 2010 maoecrystal V approach[5f]

The Thomson research group also went through multiple iterations before their successful "west-to-east" synthesis of maoecrystal V. In 2010 they published an "east-to-west" approach (Scheme 19) that hinged on late stage assembly of the tetrahydrofuran ring. In this approach cyclopentanone fused cyclohexadiene **156** was synthesized over five steps. Following ketone reduction, Diels-Alder cycloaddition with nitroethylene delivered adduct **157**. The nitro group was isomerized and the alcohol oxidized to deliver cyclopentanone **158**. Efforts to convert the nitro group to a ketone by Nef reaction were unsuccessful, and attempts to install the tetrahydrofuran ring were met with an unexpected Grob fragmentation. Attention instead shifted to installation of the lactone ring which began with alpha hydroxylation to form **159**. An additional problem emerged when the reduction of **159** resulted in the formation of cyclopropane **160**. The lactone was ultimately installed by oxidative cleavage of **160** and ketone reduction to deliver **161**. While this substrate could not be advanced to maoecrystal V, the lessons learned in this endeavour motivated Thomson to pursue the west-to-east approach that successfully delivered the natural product.

Nicolaou and Chen's 2010 maoecrystal V approach[5c]

Another IMDA approach to maoecrystal V was published by Nicolaou and Chen in 2010 (Scheme 20).[5c] A decarboxylative Heck reaction was utilized to assemble cyclohexene-substituted arene **163**. Substituted arene **165** was then constructed over four steps, which paved the way for the key IMDA reaction. Conversion of the cyclohexenone to the silyl-enol-ether generated the requisite diene, **166**; and upon heating in toluene in the presence of potassium carbonate and

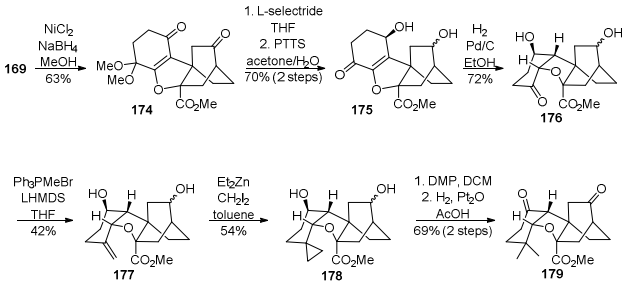
hydroquinone the desired Diels-Alder reaction occurred. One-pot treatment with HCl delivered [2.2.2]-bicyclooctane **167**. Phenol deprotection and dearomatization delivered para-quinone ketal **169**. All attempts to reduce **169** from the top face of the molecule failed, instead delivering ketone **171** as the major product, with incorrect stereochemistry at the tetrahydrofuran ring. Despite this, **171** was advanced, and the lactone ring was installed by saponification followed by a triple alkylation to deliver pentacycle **173**. The Nicolaou group reported that biological tests on pentacycle **173** revealed moderate activity against various tumor cell lines in the range of 3.6-6.7 μM [breast (MCF-7), CNS (SF268), lung (NCI-H460, and cervical (HeLa)].



Scheme 20: Nicolaou's and Chen's IMDA approach to maoecrystal V

Chen's 2011 maoecrystal V approach[5j]

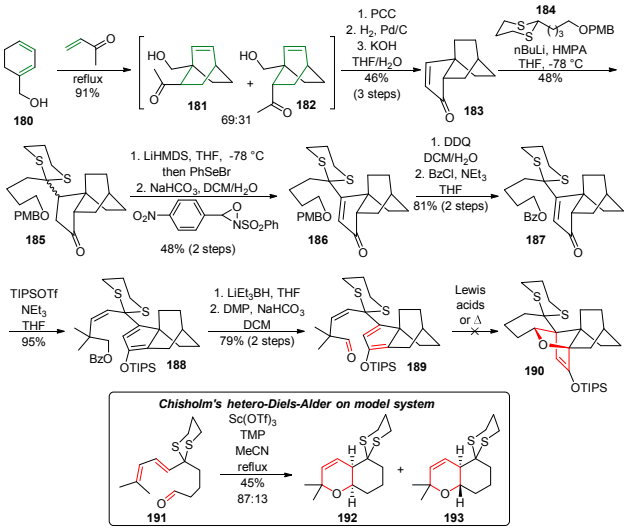
Upon establishing his own independent research laboratory, Chen carried on the project (Scheme 21).[5j] Starting from para-quinone-ketal **169** he sought to establish the correct stereochemistry at the tetrahydrofuran ring. He was ultimately successful in this effort by first performing a selective reduction of the disubstituted olefin to form ketone **174**. Reduction of ketone **174** by L-selectride provided a synthetic handle to direct the hydrogenation from the desired face of the molecule, delivering diol **176** with proper tetrahydrofuran stereochemistry. Wittig olefination followed by Simmons-Smith cyclopropanation installed the cyclopropane ring. Following oxidation, the cyclopropane was opened with platinum oxide to deliver **179** which possessed the gem-dimethyl group found in maoecrystal V. Unfortunately, the Chen group was unable to construct the lactone ring and advance this substrate to maoecrystal V.



Scheme 21: Chen's maoecrystal V approach

Chisholm's 2013 maoecrystal V approach[5l]

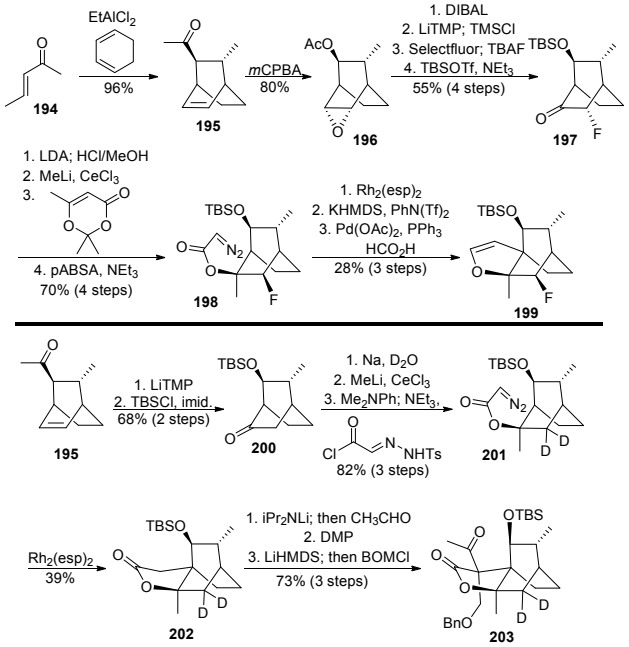
In 2013 Chisholm published a hetero-Diels-Alder approach to maoecrystal V (Scheme 22).[5l] This approach sought to use an early-stage intermolecular Diels-Alder to construct the [2.2.2]-bicyclooctane then a late stage intramolecular hetero-Diels-Alder to assemble the tetrahydrofuran ring. The construction of cyclopentenone-fused-[2.2.2]bicyclooctane **183** occurred via classic chemistry including intermolecular Diels-Alder, oxidation, reduction, and aldol condensation. A 1,4-addition of thioketal **184** delivered a mixture of diasteromers which was inconsequential as the conjugated ketone was reinstalled in two steps to form adduct **186**. After struggles with the PMB protecting group, it was ultimately exchanged for a benzoyl protecting group, forming **187**. The cyclopentenone was converted to the TIPS protected cyclopentadiene. Upon deprotection of the benzoyl group and oxidation, aldehyde **189** was generated and tests on the hetero-Diels-Alder commenced. Despite extensive efforts, the Chisholm group could not realize the hetero-Diels-Alder under Lewis acid or thermal conditions. This was in contrast to a model system in which adduct **191** did undergo Lewis acid catalyzed hetero-Diels-Alder in modest yield and selectivity. The combination of the bulky TIPS protecting group and floppy alkyl chain within adduct **189** likely hindered their efforts.



Scheme 22: Chisholm's hetero-Diels-Alder maoecrystal V approach

May's 2016 maoecrystal V approach[5m]

In 2016 May published an exploration of bridgehead C-H insertion entry into the maoecrystal V skeleton (Scheme 23).[5m] While advancing a model system they were able to validate the feasibility of this approach. Studies began with construction of [2.2.2]-bicyclooctene **195** by a Diels-Alder reaction. Next, the resulting olefin was converted to a ketone over several steps, and various alpha substituents were examined. It was found that hydrogen substitution in the alpha position resulted in undesired C-H insertion pathways; however fluorine and deuterium substitution encouraged the desired insertion pathway. This is illustrated with fluoride substituted diazoester **198**, which was synthesized in nine steps from Diels Alder adduct **195**. With fluorine substitution in the equatorial position the desired C-H insertion could be realized in the presence of rhodium catalyst. The lactone product could then be converted into vinyl ether **199** over two steps. Alternatively, Diels Alder adduct **195** could be converted to the geminal-deuterium substituted diazoester **201** over five steps. This adduct also engages in a productive C-H insertion to produce lactone **202**. Lactone **202** could be alkylated to **203**, demonstrating the feasibility of installing maoecrystal V's cyclohexanone ring system. To date May and coworkers have not advanced past this tricyclic intermediate.

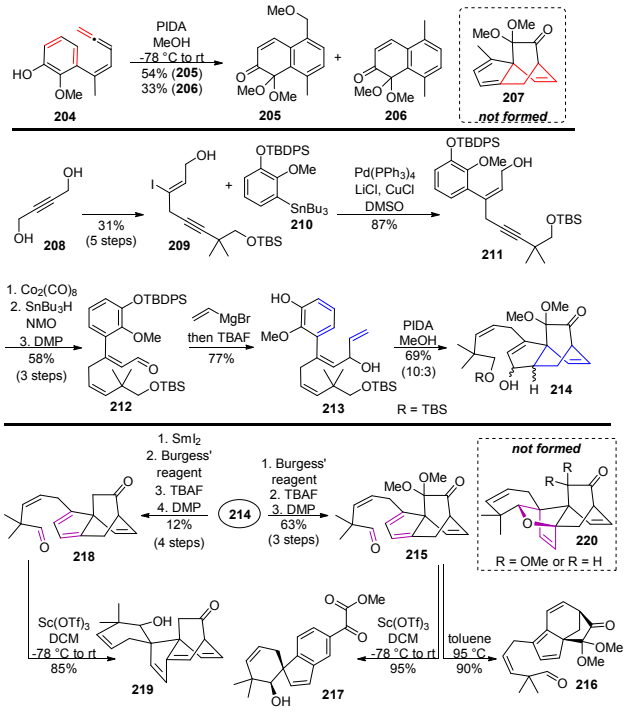


Scheme 23: May's C-H insertion approaches to maoecrystal V

Njardarson's 2017 maoecrystal V approach[5n]

In 2017 Njardarson published the most recent foray into the maoecrystal V system by a double-Diels-Alder approach (Scheme 24).[5n] Their strategy initially sought to access the core of maoecrystal V from an allene-substituted phenol via an IMDA/hetero-IMDA cascade. However, model studies revealed that, allene **204** engaged in a 6π electrocyclization upon dearomatization to yield fused ring adducts **205** and **206**, rather than desired IMDA adduct **207**. To circumvent this problem the IMDA was executed via an allylic alcohol.

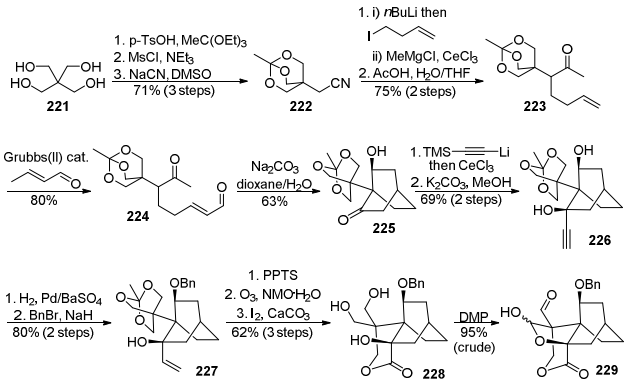
In their advanced system toward maoecrystal V the key aryl junction was forged via Stille coupling, delivering alcohol **211**. To overcome steric hindrance the cis olefin contained within the maoecrystal V's A ring was unconventionally installed by Isobe reaction and the resulting alcohol oxidized to aldehyde **212**. The IMDA precursor was then synthesized in one step, and paved the way for IMDA cyclization to form cyclopentene-fused [2.2.2]-bicyclooctene **214**. With **214** in hand two different cyclopentadienes (**215** and **218**) were synthesized to explore the hetero-Diels-Alder to form maoecrystal V's cyclohexene and tetrahydrofuran rings. With the dimethoxyketal moiety present, cyclopentadiene **215** underwent unexpected skeletal fragmentations. Under thermal conditions **215** cleanly rearranged to [3.2.1]-bicyclooctene **216**. Conversely, in Lewis-acid conditions the desired cyclohexene ring formed but was accompanied by skeletal fragmentation to deliver indene product **217**. It was discovered that removal of the dimethoxyketal supressed the fragmentation pathways, however the hetero-Diels-Alder reaction of cyclopentadiene **218** in Lewis acid conditions was interrupted by alpha deprotonation to deliver [2.2.2]-bicyclooctadiene **219**.



Scheme 24: Njardarson's Diels-Alder maoecrystal V approaches

In addition to the published synthesis approaches toward maoecrystal V, creative research contributions from the Christie and Sorensen labs have been chronicled in PhD dissertations over the years.[6] This section will detail these efforts.

Christie's 2012 maoecrystal V approach[6a]

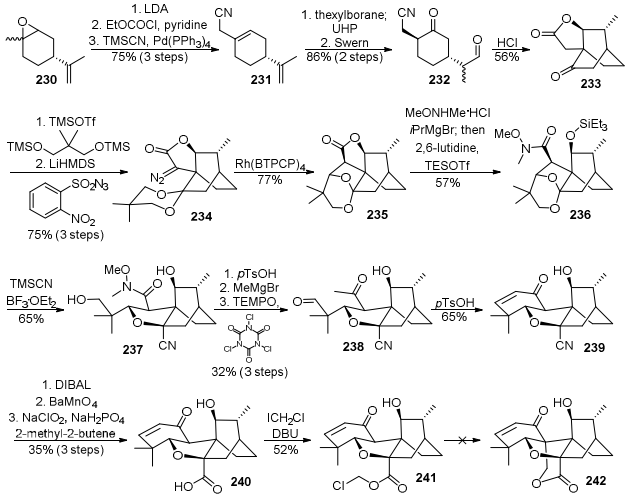


Scheme 25: Christie's aldol approach to maoecrystal V

In 2012 a dissertation from the research lab of Hamish Christie described an aldol-based approach toward maoecrystal V (Scheme 25). Desymmetrization of a pendent orthoester then sought to access maoecrystal V's tetrahydrofuran, lactone, and cyclohexanone rings. The approach began with the synthesis of nitrile substituted orthoester **222** over three steps from tetraol **221**. The nitrile was converted to ketone **223** which was subjected to Grubbs cross metathesis to form conjugated aldehyde **224**. The aldol cyclization was executed under base catalysed conditions to assemble [2.2.2]-bicyclooctane **225**. Addition of TMS-acetylene and silyl cleavage delivered alkyne **226**, which was reduced and benzyl protected to allylic alcohol **227**. Cleavage of the orthoester delivered a triol and upon ozonolysis resulted in lactol ring formation. The lactol was mildly oxidized to lactone **228** in the presence of iodine and base. Oxidation of the primary alcohols delivered hemiacetal **229**, however Christie was unable to further advance this intermediate toward maoecrystal V.

Sorensen's maoecrystal V approaches[6b-d]

The research group of Eric Sorensen published three PhD dissertations on studies toward maoecrystal V in 2010, 2013, and 2014.[6b-d] Both an aldol-based approach and a Diels-Alder based approach were explored. The results of these studies are summarized in Schemes 26 and 27.

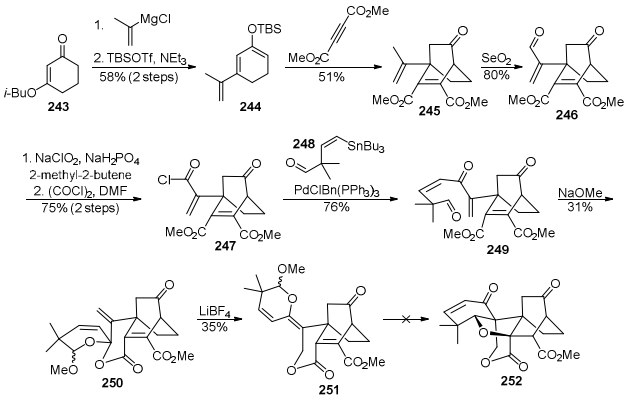


Scheme 26: Sorensen's aldol approach to maoecrystal V

Sorensen's aldol approach toward maoecrystal V (Scheme 26) commenced with the synthesis of ketoaldehyde **232** over five steps. The aldol reaction was conducted in the presence of hydrochloric acid to deliver lactone-fused [2.2.2]-bicyclooctane **233**. Ketone protection and conversion to the diazoester delivered **234**, and C-H insertion chemistry in the presence of rhodium catalyst forged the tetrahydrofuran ring, forming **235**. The cyclohexanone A ring of maoecrystal V was then accessed over six steps, delivering tetracycle **239**. The Sorensen group then set out to synthesize the lactone ring and complete the synthesis of maoecrystal V. The nitrile of **239** was converted to carboxylic acid **240** over three steps. The methylene group was then installed, delivering primary chloride **241**. Unfortunately, all efforts to achieve alpha alkylation to forge the lactone ring to form pentacycle **242** were unsuccessful.

The Sorensen group's Diels-Alder studies toward maoecrystal V (Scheme 27) began with the synthesis of diene **244** over two steps. Diels-Alder cyclization with diester alkyne delivered cycloadduct **245**. Allylic oxidation with selenium

dioxide afforded aldehyde **246**, which was converted to acid chloride **247** over two steps. The requisite carbons for the cyclohexanone ring of maoecrystal V were then installed via a Stille coupling with vinyl stannane **248**. The aim was to execute a carbonyl cascade to assemble the cyclohexanone, tetrahydrofuran, and lactone of maoecrystal V in a single transformation, but this could not be realized. In an effort to execute the transformation in a stepwise manner diester **247** was selectively hydrolysed with sodium methoxide and lactonized to methyl ketal containing lactone **250**. This lactone was then isomerized to the enol ether lactone **251**. Efforts to advance either intermediate **250** or **251** to maoecrystal V were unsuccessful.



Scheme 27: Sorensen's Diels-Alder approach to maoecrystal V

Conclusions

Since the disclosure in 2004 of its unique structure and exciting biological properties, maoecrystal V has been the target of extensive research efforts from the synthetic organic chemistry community. This has culminated in seven successful total syntheses, three racemic and four enantioselective, completed by five different research groups. Numerous other creative approaches have been reported, which serve as a testament to the challenge it poses to assemble compact hindered diterpenoid natural products like maoecrystal V. In the end, through the power of total synthesis the Baran group not only completed the most recent total synthesis but also challenged claims about maoecrystal V's much heralded biological potential.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We would like to thank the National Science Foundation (CHE 1565500) for support of our synthetic efforts in this area.

Notes and references

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.; Cao, P.; Zheng, Q.-T. *Org. Lett.* 2004, **6**, 4327.

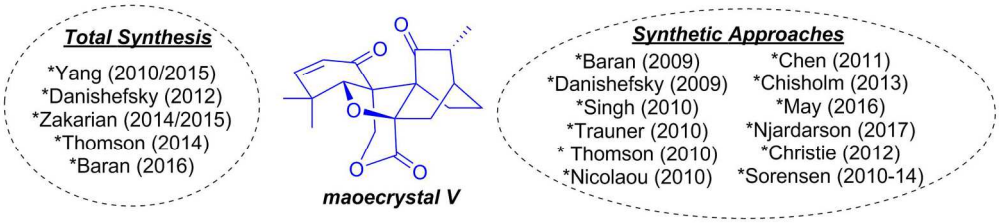
2. Cernijenko, A.; Risgaard, R.; Baran, P. S. *J. Am. Chem. Soc.* 2016, **138**, 9425.

3. Han, Q.-B.; Cheung, S.; Tai, J.; Qiao, C.-F.; Song, J.-Z.; Tso, T.-F.; H.-J.; Sun, Xu, H.-X. *Org. Lett*. 2006, **8**, 4727.

4. (a) Gong, J.; Lin, G.; Sun, W.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* 2010, **132**, 16745; (b) Peng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* 2012, **134**, 18860; (c) Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* 2013, **135**, 14552; (d) Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* 2014, **136**, 17738; (e) Zheng, C.; Dubovyk, I.; Lazarski, K. E.; Thomson, R. J. *J. Am. Chem. Soc*. 2014, **136**, 17750; (f) Zhang, W.-B.; Shao, W.-B.; Li, F.-Z.; Gong, J.-X.; Yang, Z. *Chem*. *Asian J.* 2015, **10**, 1874.

5. (a) Gong, J.; Lin, G.; Li, C.; Yang, Z. *Org. Lett.* 2009, **11**, 4770; (b) Krawczuk, P. J.; Schone, N.; Baran, P. S. *Org. Lett.* 2009, **11**, 4774; (c) Nicolaou, K. C.; Dong, L.; Deng, L.; Talbot, A. C.; Chen, D. Y.-K. *Chem. Commun*. 2010, **46**, 70; (d) Peng, F.; Yu, M.; Danishefsky, S. J. *Tetrahedron Lett*. 2009, **50**, 6586; (e) Singh, V.; Bhalerao, P.; Movin, S. M. *Tetrahedron Lett.* 2010, **51**, 3337; (f) Lazarski, K. E.; Hu, D. X.; Stern, C. L.; Thomson, R. J. *Org. Lett.* 2010, **12**, 3010; (g) Baitinger, I.; Mayer, P.; Trauner, D. *Org. Lett*. 2010, **12**, 5656; (h) Peng, F.; Danishefsky, S. J. *Tetrahedron Lett*. 2011, **52**, 2104; (i) Gu, Z.; Zakarian, A. *Org. Lett.* **2011**, 13, 1080; (j) Dong, L.; Deng, L.; Lim, Y.-H.; Leung, G. Y. C.; Chen, D. Y.-K. *Chem. Eur. J.* 2011, **17**, 5778; (k) Lazarski, K. E.; Akpinar, B.; Thomson, R. J. *Tetrahedron Lett*. 2013, **54**, 635; (l) Carberry, P.; Viernes, D. R.; Choi, L. B.; Fegley, M. W.; Chisholm, J. D. *Tetrahedron Lett.* 2013, **54**, 1734; (m) Jansone-Popova, S.; May, J. A. *Tetrahedron* 2016, **72**, 3734; (n) Smith, B. R.; Njardarson, J. T. *Org. Lett*. 2017, **19**, 5316.

6. (a) Chang, T. M. PhD Dissertation, University of Arizona, 2012; (b) M^{c}Leod, D. D. PhD Dissertation, Princeton University, 2010; (c) Smith, M. J. PhD Dissertation, Princeton University, 2013; (d) Naylor, M. R. PhD Dissertation, Princeton University, 2014.


Total Synthesis
*Yang (2010/2015)
*Danishefsky (2012)
*Zakarian (2014/2015)
*Thomson (2014)
*Baran (2016)
O
O
O
O
O
maoecrystal V
Synthetic Approaches
*Baran (2009)
*Danishefsky (2009)
*Singh (2010)
*Trauner (2010)
* Thomson (2010)
*Nicolaou (2010)
*Chen (2011)
*Chisholm (2013)
*May (2016)
*Njardarson (2017)
*Christie (2012)
*Sorensen (2010-14)