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Total Synthesis of (±)-Maoecrystal V

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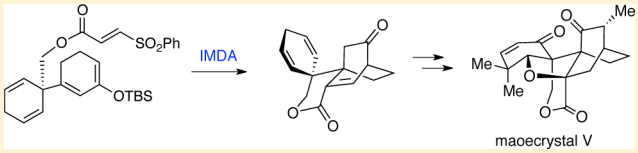
Supporting Information

ABSTRACT: The total synthesis of racemic maoecrystal V has been accomplished. Key steps include an intramolecular Diels–Alder cyclization to rapidly construct the core system from simple starting materials and the creation of the A–C ring *trans*-fusion through intramolecular delivery of a hydrogen to the hindered β-face of the ring system.



INTRODUCTION

Upon learning of the existence of maoecrystal V and, particularly, following contemplation of its compelling structure, we were already drawn to the prospect of undertaking a program directed to its total synthesis. While one could hardly be very confident, a priori, as to the outcome of such a venture, we were increasingly attracted to the challenge. Problems of this level of complexity often carry with them significant learning opportunities. In retrospect, maoecrystal V more than fulfilled our expectations in this regard.

Our interest in maoecrystal V as a fascinating chemical entity was further augmented by perceptions, however preliminary, that a successful synthesis program might enable the discovery of new antimitotic agents of value. Of late, the team of Han-Dong, from the Kunming Institute of Botany, has been particularly active in searching for biologically potent diterpenoids from the Isodon plants of the Laiatae family.[1] Indeed, maoecrystal V was first isolated in 1994 from Isodon eriocalyx Hara, which is distributed in Yunnan province. The source of vegetation from which maoecrystal V was obtained had been used in herbal medicine for some time. Eventually, in 2004, a single crystal of maoecrystal V was obtained.[2] Crystallographic analysis revealed its structure to be that shown in Figure 1. Moreover, maoecrystal V was evaluated for cytotoxicity against a variety of human tumor cell lines, and it was found to be selectively active, for instance, against the He La cell line, with an impressive IC_{50} value of approximately 20 ng/mL. While this lead has not, to our knowledge, been developed further, even these preliminary results raise the possibility that research directed to maoecrystal V could bring with it new compounds with therapeutically exploitable anticancer activity.

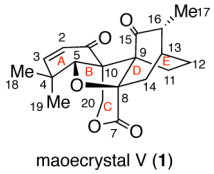


Figure 1. Structure of maoecrystal V (**1**).

Returning to the chemistry-based incentives, we could hardly help but notice a collection of familiar substructural motifs in maoecrystal V. The complexity of the total synthesis challenge posed by **1** arises from the highly compact architecture that interlocks these otherwise unexceptional patterns. Particularly conspicuous is the grouping of the fully substituted positions (8, 9, and 10). These carbon centers provide the basis for fusions between the C-ring d-lactone and the bicyclic AB system. Moreover, carbons 5 and 10 define an AB junction that is *trans*-fused. The β-displayed hydrogen atom at C_5 necessarily bears a 1,3-diaxial relationship with the C_9–C_{15} bond. It appeared that delivery of a hydrogen from an external source to this highly hindered β-face would be difficult. Also of interest in the A-ring is the arrangement of the γ-disposed gem-dimethyl cyclohexenone functionality incorporating carbons 1–4. It would be necessary to accommodate an α-disposed methyl group at the epimerizable C_{16}. Indeed, the only carbon centers on the maoecrystal V backbone lacking functional groups and stereogenicity are those at positions 11, 12, and 14.

We were not the first to be enticed into the maoecrystal V total synthesis challenge. Well before we took up the problem, a variety of fascinating approaches had been disclosed from other laboratories.[3] The extensive undertakings directed to **1** have culminated in its total synthesis by Yang and associates.[4] Below, we present our recently completed total synthesis of maoecrystal V as well an account of the planning and experimentation that enabled the reaching of that goal. To provide a proper setting, we need to briefly recapitulate our initially proposed, albeit ultimately unsuccessful, route. Important lessons, gleaned from the breakdown of our first approach, served to inform the eventually successful foray.

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RESULTS AND DISCUSSION

As mentioned before, there are several motifs that could serve to facilitate a retrosynthetic analysis in the context of what we have termed pattern recognition analysis (PRA).[5] Among the recognizable patterns that attracted our attention is the bridged bicyclo [2.2.2] octane domain (i.e., DE rings). The possibility of building this motif by a Diels–Alder (DA) reaction[6] between a usefully substituted cyclohexadiene and an appropriately activated ethylene presented itself [see (i) + (ii) → (iii), Figure 2]. At this early stage of analysis, we leave unspecified the nature of functional groups A and Y. Needless to say, delineation of these functions must be sensitive to the need for ensuring regio- and stereoselectivities in productive directions. Pursuing this line of analysis, it seemed that the bridgehead center marked with an asterisk corresponding to C_9 of the future maoecrystal V must already carry the means for connectivity to the eventually required rings, A, B, and C. The prospects for creating a carbon–carbon bond at C_9, subsequent to cycloaddition, did not seem promising.

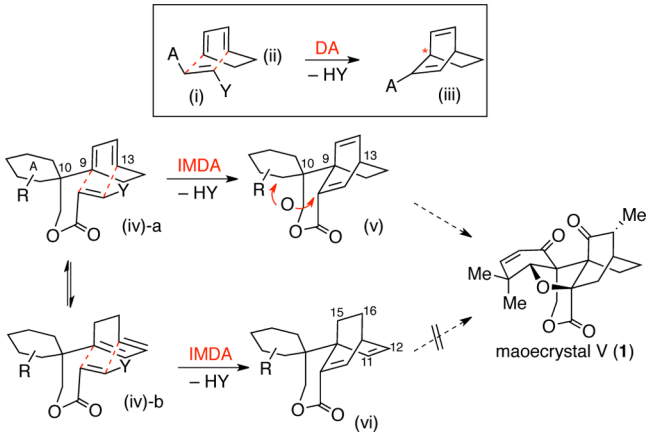

Figure 2. IMDA-based strategy toward maoecrystal.

Such concerns regarding the feasibility of progression, even beyond a successful bimolecular DA step, prompted consideration of an intramolecular Diels–Alder (IMDA) reaction[7] to assemble the DE motif. Upon further reflection, it seemed that an IMDA-based strategy would provide a means for dealing with the vicinal bis neopentyl motif represented by carbons 9 and 10. Indeed, we were struck by the thought that the C_{10} center of (i) might carry, as one of its substituents, the cyclohexadiene moiety previously described as (ii). In this way, a means of dealing with the worrisome issue of bis-quaternary C_9–C_{10} bond formation would already be in place. The activated olefin, destined to serve as the dienophile, would be connected to the quaternary center at C_{10} through some version of a hydroxymethyl linker. Theoretically, C_{10} could already be housed within a six-membered ring corresponding to the A-ring of maoecrystal V. This line of conjecture is captured in the generalized hypothetical IMDA substrate (iv). It is interesting to note that (iv) arises, conceptually, from amalgamation of the previously hypothesized (i) and (ii) through a C_α–C_β–O spacer, wherein C_α is actually part of a six-membered moiety destined to emerge as the A-ring of maoecrystal V.

Still at the planning stage, it is well to recognize an interesting stereochemical question in the projected IMDA reaction. There is a subtle issue of facial selectivity in the envisioned cycloaddition step. Thus, to reach maoecrystal V by the route discussed above, the IMDA reaction must occur in the rotameric sense [(iv)-a], which connects the emerging configurations at C_9 and C_{13} (in a relative sense) to the resident stereogenicity [see (iv)-a → (v)]. For instance, if the IMDA cycloaddition occurred through the alternative cyclohexadiene rotamer, (iv)-b, the product after elimination of HY would be (vi). The conversion of the hypothetical (vi) to maoecrystal V (**1**) would be quite problematic, if even doable. Such a

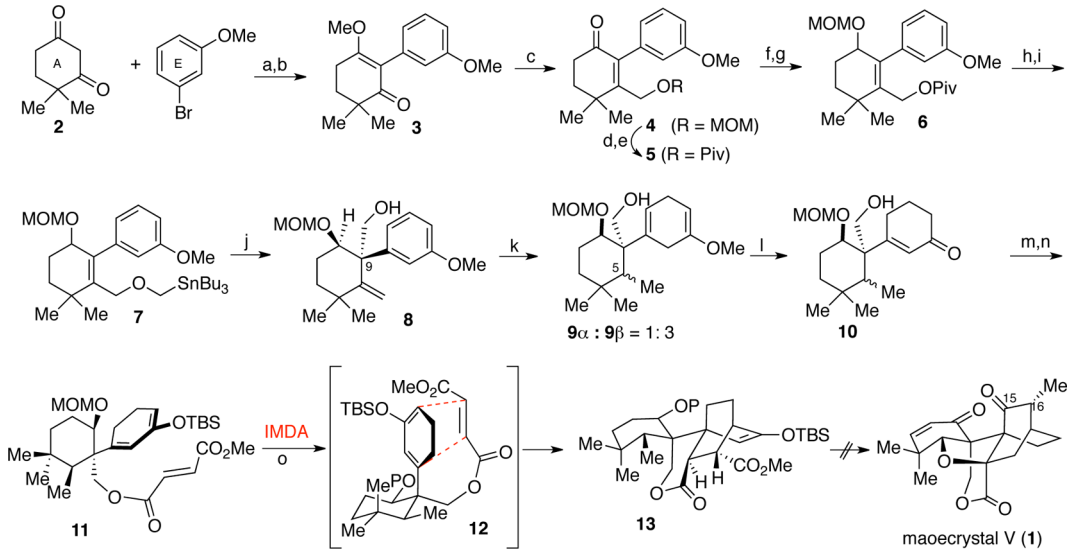

Figure 3. First attempted IMDA route toward maoecrystal V. Key: (a) $Pd(OAc)_2$, 2-di-*t*-butylphosphino-2′-methylbiphenyl, K_3PO_4, THF, 80 °C, 12 h, 91%; (b) $TMSCHN_2$, Hünig's base, CH_3CN/MeOH = 9:1, 6 h, 100%; (c) Bu_3SnCH_2OMOM, BuLi, THF, −78 to −40 °C, 30 min, 0.5% HCl workup, 75%; (d) HCl/MeOH, 50 °C, 75%; (e) PivCl, Py, DCM, 12 h, 96%; (f) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 2 h, 93%; (g) MOMCl, Hünig's base, DCM, 12 h, 95%; (h) DIBAL-H, −78 °C, DCM, 30 min, 95%; (i) KH, 18-crown-6, ICH_2SnBu_3, 0 °C, THF, 6 h, 90%; (j) *n*-BuLi, −78 to −20 °C, THF, 6 h, 88%; (k) Li, NH_3(l), *t*-BuOH/THF, −78 °C, 20 min, −33 °C, 40 min; (l) 1 N HCl, 0 °C, THF/MeOH (10/1), 8 h, two steps, 78%; (m) acid chloride, Py, DCM, 0 °C, 72%; (n) TBSOTf, TEA, DCM, 0 °C, 15 h, 81%; (o) 180 °C, sealed tube, toluene, 12 h.

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retrofitting would involve interchanging the etheno and ethano bridges. The former would have to emerge as the unfunctionalized carbons 11 and 12, while the latter would require transformation to the extensively functionalized C_{15} and C_{16} span.

In the opening stages of the program, we hoped to address several issues. The first dealt with the matter of synthesizing a usefully functionalized version of the genus (iv). We would then probe the stereochemistry of the cycloaddition step, (i.e., which Curtin–Hammett rotamer of (iv) would define the cycloaddition event). We well recognized that, in principle, the direction and scope of that type of stereoselectivity could be a function of the particular A-ring groups selected. These groups must also be selected with the goal of complementarity as to regiodirectionality in the cycloaddition step. High-quality diene–dienophile regio-complementarity tends to lower the activation barrier for DA or IMDA reactions.

Original Synthetic Strategy toward Maoecrystal V. In our opening foray, we decided, initially, to introduce the cyclohexadiene ultimately for the IMDA reaction in the form of a stable anisole derivative. As was previously described,[8] the future cyclohexadiene (E ring) was joined to the future A ring by a palladium-mediated arylation[9] of **2**, using 3-bromoanisole (Figure 3). Following regiospecific O-methylation, **3** was in hand. Through standard and pleasing chemistry,[10] **3** was converted to **4** and, thence, after several high yielding steps, to **7**. This compound was transformed with high stereoselection to **8** via a Still–Wittig [2,3-sigmatropic] rearrangement.[11] Thus, a system bearing the ultimately required quaternary substituted C_9 was in hand.

We had already made the decision that the DA diene (ii) would, in the event, be presented as a cross-conjugated silyl enol ether. In this fashion, the eventual introduction of the required functionalities at C_{15} and C_{16} would have been enabled. For the moment, we were content to delay inclusion of the methyl group at the eventual C_{16}, confident that the required alkylation could be arranged at a later stage. There seemed to be required only the Birch reduction of **8** to generate a precursor to a viable cyclohexenone, which would be a candidate precursor to provide the required cross-conjugated siloxydiene. In practice, Birch reduction[12] of the anisole function **8** was nicely accomplished. However, these conditions, in our hands, also caused reduction of the exomethylene group (see formation of **9**) as a 3:1 mixture of epimers. In retrospect, the tendency of Birch-type conditions to effect reduction of proximal isolated unhindered olefins is not without precedent.[13]

For the case at hand, having come this far, we continued with the original plan. It was well appreciated that the presence of the methyl group at C_5 would pose a major obstacle to completion of the total synthesis goal. However, such a study could still serve as a model to evaluate the IMDA program. We thus took the diastereometric mixture **9** forward. We selected a fumarate function as the activated dienophile in the projected IMDA step, confident that at some stage, the extraneous carbomethoxyl group could be eliminated with the formation of a double bond between the future C_8 and C_{14}. Fortunately, after the acylation step, the C_5 isomers were separable. We moved forward with the major isomer, wherein the secondary methyl group is syn to the resident MOM function at C_1. Happily, enol silylation of the acylated substrate provided, as the major product, the desired cross-conjugated siloxydiene (see **11**). This compound was to serve as our IMDA substrate.

Thermolysis of compound **11** at 180 °C in a sealed tube gave rise to **13**. We were, of course, pleased to find that the IMDA reaction had indeed occurred. However, detailed NMR analysis showed convincingly that the stereochemistry of the [2.2.2] bicyclo-octane domain in **13** was of the undesired sort. Thus, **13** is not eligible for conversion to maoecrystal V for reasons discussed above, now further complicated by an extraneous methyl group.

While ultimately unsuccessful, potentially important messages were drawn from this effort. The progression described was seen to validate the general IMDA route adumbrated in Figure 1. In so doing, it underscored the difficulties associated with predicting the facial selectivity of the cycloaddition step. Thus, the overall rotameric state of the cyclohexadiene, which determines the outcome of the IMDA reaction, arises from several possible component factors. First, there might be an inherent preference, rooted in the effective "A-value" of the two relevant edges (i.e., whether the sp^2 or sp^3 carbons prefer to turn toward one or the other sectors of the incident cyclohexane). In the case at hand, it seems that the product obtained is arising from the rotamer in which the presumably more sterically demanding (sp^3) carbons of the cyclohexadiene are facing the more hindered side of the cyclohexane ring (bearing the C-methyl and geminal dimethyl substituents). However, the operative rotameric form of the cyclohexadiene also defines which of the *trans*-related activating groups of the dienophile (in the case of **11** as a fumarate) is presented in an *endo* fashion, and which emerges *exo*. In the case of **13**, the future lactonic ester group had emerged *endo*, whereas the carbomethoxyl group presented *exo*. In the end, it is the weighting of steric factors in the inherent rotameric distribution, with *endo*:*exo* presentational preferences in the transition state, which defines the total Curtin–Hammett[14] outcome. The difficulty of predicting the facial outcome was of particular concern because there is required a substantial number of steps in setting up the IMDA substrate in which this question is posed. Hence, the prospect of trying to solve the face selectivity uncertainty by noninformed screening of various possibilities was not attractive.

Modified IMDA Route to Maoecrystal V. It was in struggling with this problematic scenario that a rather interesting solution presented itself. Perhaps the six-membered A-ring could be presented in an achiral setting. In such a context, the only consequence of face selectivity in the IMDA step would relate to the *endo*:*exo* directivity of the two activating groups of the trans-diactivated dienophile. On closer reflection, even this question is, at most, of only temporary relevance, because it was our goal to install a double bond between carbons 8 and 14, thus rendering the original *endo*:*exo* question moot. Put differently, in real terms the operative dienophile would be a propiolate equivalent, wherein the *endo*:*exo* issue does not even arise.[15] A plan evolved wherein a 3,3-disubstituted cyclohexadiene would serve as an achiral version of the future A-ring of **1**. As above, we would hope to take recourse to a cross-conjugated siloxydiene as the diene component in the projected IMDA reaction. In this way, the enoxysilane functionality of the resultant IMDA product could be exploited to guide the emergence of the required functionality at the C_{15}–C_{16} bridge. As will be seen, a critical part of the new plan was the installation of the double bond between carbons 8 and 14. To increase the likelihood of success, we would attempt to employ an α,β-sulfonylacrylate system as our putative dienophile. We anticipated that if the

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IMDA reaction did indeed occur, the resultant adduct would be prone to simple β-elimination of phenylsulfinic acid to generate the required 8,14-double bond.

The aggregate of these considerations prompted us to formulate specific compound **14** as our proposed IMDA substrate (Figure 4). As seen, the operative rotameric state of

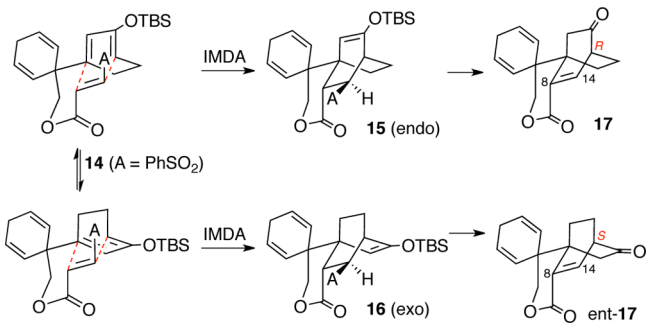

Figure 4. Revised IMDA route toward maoecrystal V.

the siloxyhexadiene determines only the *endo*:*exo* disposition of the two activating groups (see structures **15** and **16**). Following β-elimination, the two permutations converge (see enantiomeric structures **17** and *ent*-**17**, which anticipate cleavage of the silyl enol ether). We note that at the stage of **17**, the two nonconjugated double bonds in the putative A-ring are diastereotopic.

If all would have proceeded well to this point, the central challenge of the synthesis would then lie in translating this diastereotopic distinction to allow for chemoselectivity between the two double bonds of the A-ring. At first glance, the prospects for realizing differentiation over these olefinic linkages based on inherent levels of steric hindrance were not promising. Fortunately, an interesting solution to this problem also presented itself. As was alluded to above, a C_8-C_{14} double bond, at the stage of **17**, was central to our proposed solution. This α,β-unsaturated ester double bond would hopefully be chemically distinct from the isolated olefins of the putative A ring joining C_1 and C_2 as well as C_4 and C_5. The thought was to exploit the α,β-unsaturated carbonyl character at C_8-C_{14} double bond to introduce, in some manner, a hydroxyl group at C_8 (Figure 5). This alcohol would, in turn, confer selective activation to the proximal C_4-C_5 double bond, thereby allowing for the installation of the missing A-ring functionality. Eventually, the tetrahydrofuranoid C-ring would arise from joining the newly introduced C_8 hydroxyl to C_4 ultimately in the required stereochemical sense (i.e., with a trans AC

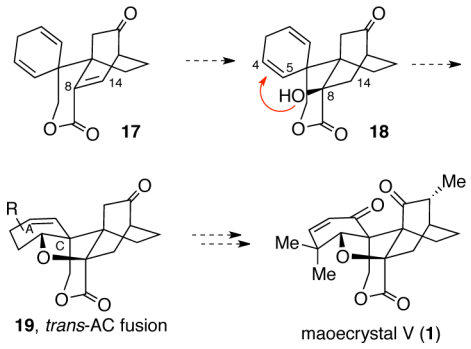

Figure 5. Proposed completion of maoecrystal V synthesis.

junction). Below, we relate the experiments by which this general plan was reduced to practice.

The campaign to implement these conceptions began on a rather positive note.[16] Thus, two readily available compounds **20** and **21** could be joined, as shown, to provide **22** (Figure 6).[17] Clearly, the reaction involved generating the enolate of **19**,

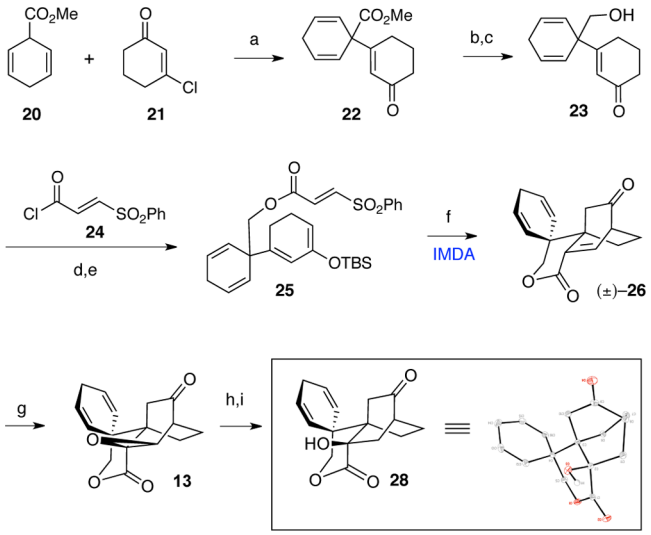

Figure 6. Synthesis of intermediate **28** en route to maoecrystal V. Key: (a) LDA, −78 °C, THF, 40%; (b) DIBAL-H, −78 °C, DCM, 2 h; (c) MnO_2, room temperature, DCM, 40 min, two steps, 68%; (d) **24**, Py, 0 °C, DCM, 30 min, 86%; (e) TBSOTf, TEA, DCM, −78 °C, 12 h, 91%; (f) toluene, sealed tube, 166 °C, 1 h, then TBAF, THF, 62%; (g) H_2O_2, NaOH, MeOH, 0 °C, 95%; (h) MgI_2, DCM, 45 °C; (i) Bu_3SnH, AIBN, toluene, reflux, two steps, 50%.

which underwent a 1,4 addition to the β-chloroenone function of **21**. Ejection of chloride from this intermediate afforded **22**. Although the yield of **22** was modest (40%), this easily obtained compound contains all of the carbon−carbon bonds necessary to elaborate the dienic component of the envisioned IMDA cycloaddition reaction required for maoecrystal. To pave the way for setting up the fully equipped IMDA substrate, the ester and ketone functions were reduced, as shown, and the allylic alcohol arising from the ketone reduction underwent selective oxidation with manganese dioxide to afford the ketone **23** in reasonable yield. Fortunately, the primary (neopentyl!) alcohol function of **23** underwent smooth acylation with acyl chloride **24**[18] under the conditions shown, to provide, following enol silylation, the required IMDA substrate **25**.

Moreover, as was previously found (cf., **11**→**13**, Figure 3), **25** underwent thermally induced IMDA reaction to provide a cycloadduct, which was not, per se, characterized. Happily, on treatment of this product with TBAF, there was obtained (presumably by β-elimination of phenylsulfinate) the α,β-unsaturated lactone bearing a ketone at a carbon bridge of the [2.2.2] bicyclooctane matrix. It will be appreciated that, for a given direction (α or β) of attack on the diene, the "molecular decision" between the two cyclohexadiene rotamers determines only the enantiomeric state of the product after elimination of the phenylsulfinate.

We have thus far not dealt with the problem of synthesizing the natural enantiomer of maoecrystal V, because in the first instance we anticipated being fully occupied, even with the challenge of reaching its racemate. However, it is apparent on reflection that if racemate **26** could indeed be established as a

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competent precursor for maoecrystal V, the task of reaching the enantiomerically pure version of the natural product could be accomplished through catalytically induced enantiospecificity in the IMDA cycloaddition of achiral **25**. Precedents for successfully achieving control of enantiomeric outcomes in the Diels–Alder reaction provide some basis for hope in this regard.[19]

Happily, chemoselective nucleophilic epoxidation of the conjugated double bond in structure **26** was readily accomplished, as shown, to provide epoxide **27**. Moreover, as hoped, the epoxide could be opened at its secondary carbon with magnesium iodide to provide a vicinal iodohydrin.[20] Reduction of the iodo function was achieved via its reaction with tri *n*-butyltin hydride. At this stage, we had in hand the α-hydroxylactone **28**, wherein the required trans fusion of the B:D rings had been accomplished. The position "claimed" to this point was fully secured by a crystallographic verification of structure **28**.

We next turned our attention to building the required tetrahydrofuranoid substructure (i.e., ring B). It was our expectation that the hydroxyl group, in place at C_8 in structure **28**, could be exploited to differentiate the two diastereotopically related double bonds present in the A-ring of **28**. Happily, this turned out to be the case. As shown in Figure 7, treatment of

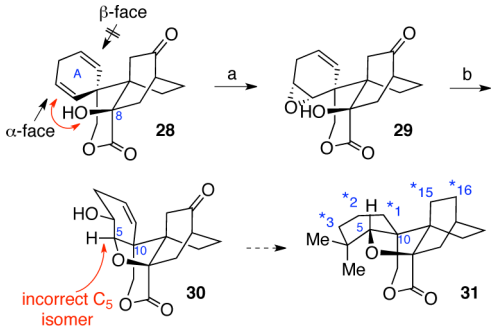

Figure 7. Installation of the tetrahydrofuranoid B-ring. Key: (a) *m*-CPBA, DCM, room temperature, 18 h, 72%; (b) *p*-TsOH·H_2O, DCM, room temperature, 12 h, 90%.

28 with *m*-CPBA indeed gave rise to, apparently, a single epoxide (**29**). While, in principle, the peracid oxidant could have attacked **28** from its β-face under direction from the hydroxyl function, the trajectory for such an epoxidation would have been quite hindered. However, the C_8 hydroxyl group provides sufficient activation, even for the α-face of the C_4–C_5 double bond to distinguish it from the noncompetitive C_1–C_2 olefin.[21] When this compound was subjected to the action of *p*-toluenesulfonic acid, as shown, the anticipated cyclization reaction occurred, undoubtedly with inversion at C_5, to generate the requisite tetrahydrofuranoid B-ring. However, as fully expected, the junction of the A- and B-rings in structure **30** was *cis*.

It was hoped that the hydroxyl group at C_4 would eventually become a ketone that would serve as a precursor for introduction of the gem dimethyl group at this center.[22] However, it would, of course, be necessary to correct the non-natural relative stereochemistry at C_5 before the two methyl groups were introduced at C_4. In other words, a means must be found for the α-disposed hydrogen at C_5 in compound **30** to eventually occupy a β-configuration corresponding to the natural configuration of maoecrystal V. A hypothetical candidate for advancement would be a system such as **31**, wherein the configuration at C_5 has somehow been corrected such that the A:B junction is trans. The problem we faced was that, as discussed above, external delivery of a hydrogen to the required β-face of C_5 would be highly disfavored from a purely steric hindrance perspective. This β-face corresponds to the inside of a molecular cavity arising from the interlocking of the ABCD matrix.

In considering this problem, it seemed that a possible solution might involve delivery of a proton to the β-face of C_5 by suprafacial rearrangement of an already β-disposed hydrogen from within the molecule. This line of conjecture led us to consider an epoxide of the type **33** (Figure 8). We could

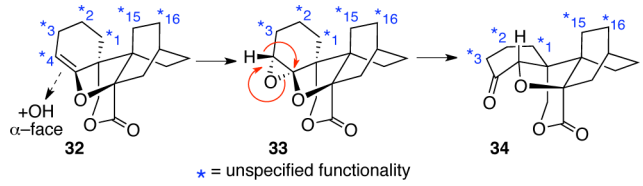

Figure 8.

confidently predict that, if access could be gained to an *exo*-glycal of the type **32**, attack by an external source of $^{+}$OH would occur from the outside α-face. For the moment, we leave unspecified (see asterisks) the functionality elsewhere that might be compatible with reaching **32** and converting it to epoxide **33**. The key argument was that it ought to be possible to prompt the rearrangement of **33** to **34** by Lewis acid catalysis wherein suprafacial "hydride" migration of the β-hydrogen from C_4 would deliver it to the desired (albeit highly hindered) β-face at C_5, thereby producing **34**.

In a previous disclosure,[16] operating in a model series, a compound corresponding in broad concept to **33**, wherein carbon centers 1, 2, 3, 15, and 16 were all methylene groups, was synthesized. Indeed, the postulated α-face epoxidation occurred, as did the rearrangement to the C_4 ketone, C_5-β-H product, corresponding to **34**. Below, we describe how this strategic design was reduced to practice in a series of compounds bearing the chemical implements necessary to reach maoecrystal V. For this purpose, we must return to compound **30**.

Completion of Synthesis of Maoecrystal V. Having demonstrated the feasibility of the *exo*-glycal epoxide rearrangement sequence in the context of a model system,[16] we now turned our attention to achieving this transformation in the suitably functionalized maoecrystal V series. Because the C_{16} ketone would be incompatible with the proposed conditions, we elected to temporarily protect this functionality as a MOM ether. In the event, intermediate **30** was converted to compound **35**, bearing a C_{16} secondary alcohol. Unfortunately, as shown in Figure 9, the $NaBH_4$ reduction of ketone **30** was not stereoselective, and **35** was isolated as a 1:1 mixture of C_{16} isomers. Although highly troubling from an aesthetic perspective, the lack of selectivity in the reduction step did not materially impact on the overall efficiency or yield of the synthesis. It proved possible to carry the mixture of isomers through the synthesis, until the point at which reoxidation of the alcohol epimers served to eliminate the issue of C_{16} stereointegrity (see ketone **44**). Thus, the epimeric C_{16} secondary alcohols were masked with MOM protecting groups to furnish intermediate **36**, which, upon stereospecific

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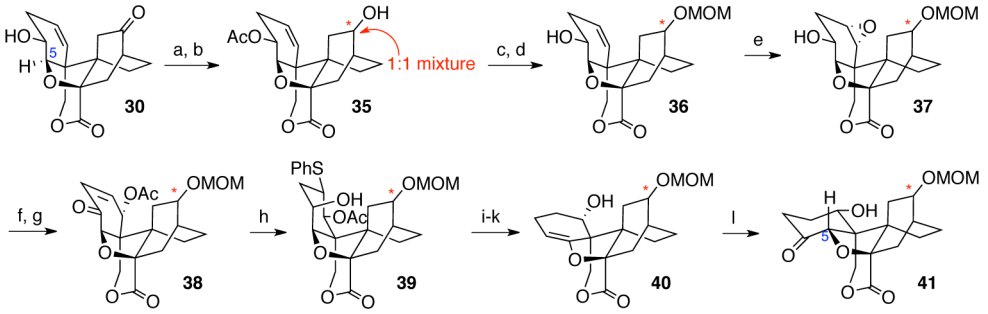

Figure 9. A-Ring functionalization and epimerization of C_5. Key: (a) Ac_2O, Py, DCM; (b) $NaBH_4$, DCM/EtOH, 85% yield over two steps; (c) MOMCl, *i*-Pr_2NEt; (d) K_2CO_3, MeOH, 90% yield over two steps; (e) *m*-CPBA, room temperature, 95%; (f) DMP, $NaHCO_3$, DCM, 0 °C, 85%; (g) Ac_2O, Py, DCM, 90%; (h) PhSH, Et_3N; then $NaBH_4$, EtOH/DCM, 78%; (i) Raney-Ni; (j) MsCl, DMAP, 65% over two steps; (k) K_2CO_3/MeOH, room temperature, 95%; (l) DMDO; then $BF_3{\cdot}OEt_2$, 82%.

epoxidation (*m*-CPBA) of the 1,2-double bond afforded **37**, bearing exclusively the α-oriented C_1-C_2 epoxide. At this stage, Dess–Martin oxidation of the secondary alcohol, followed by attempted silica gel purification, afforded a γ-hydroxyenone, which was readily converted to its acetate, **38**. The next goal was the installation of an olefin corresponding to an *exo*-glycal at the C_4-C_5 position. Happily, this goal could be accomplished in a surprisingly straightforward fashion. Thus, conjugate addition of thiophenol to the double bond of **38**, followed by reduction of the resultant β-thiophenoxy ketone with $NaBH_4$, yielded **39**. The latter was subjected to Raney-Ni desulfurization, followed by dehydration and C_1 acetate deprotection, to afford the key substrate **40**. We were pleased to observe that, upon exposure of this *exo*-glycal to the previously described conditions, compound **40** rapidly underwent the hoped-for sequence of *exo*-glycal epoxidation/rearrangement to deliver **41** as a single epimer at carbons 1 and 5, although with epimeric –OMOM groups at C_{16}.

With the tetrahydrofuranoid B-ring now in place, the next milestone for completion of the total synthesis would require installation of the γ-dimethyl-α,β-unsaturated ketone functionality on the A-ring. The sequence by which this functional motif was installed is shown in Figure 10. Thus, the C_4 ketone of intermediate **41** was converted to a cyclopropane (**43**) through a two-step sequence consisting of Lombardo olefination[23] (see compound **42**) followed by Zn/Ag-mediated Simmons–Smith inspired cyclopropanation.[24] Interestingly, under these conditions, the MOM protecting group underwent CH_2 insertion (see MOM→MOE, **43**). Upon exposure to PCC conditions, the MOE group was removed and the epimeric alcohols were oxidized to deliver the bis-ketone intermediate, **44**, as a single entity. The cyclopropane ring was then reductively cleaved to furnish intermediate **45**, possessing the key C_4 gem-dimethyl motif.

We next turned our attention to the selective functionalization of the C_{16} ketone. In the event, we were pleased to find that substrate **45** readily underwent regioselective olefination, again via the Lombardo reagent, to afford *exo*-olefin **46**. At this stage, we were able to realize acid-mediated isomerization of the *exo*-methylene group of **46** to afford **47**, bearing the trisubstituted olefin.[25] Subsequent dehydrogenation of ketone **47**, to install the requisite α,β-unsaturation, initially proved to be quite challenging, presumably due to the neopentyl character of the ketone. Ultimately, under our optimized conditions, **47** was treated with LDA and TMSCl to generate a stable TMS enol ether. Upon exposure to $Pd(TFA)_2$, the hoped-for Saegusa oxidation proceeded in good yield to afford

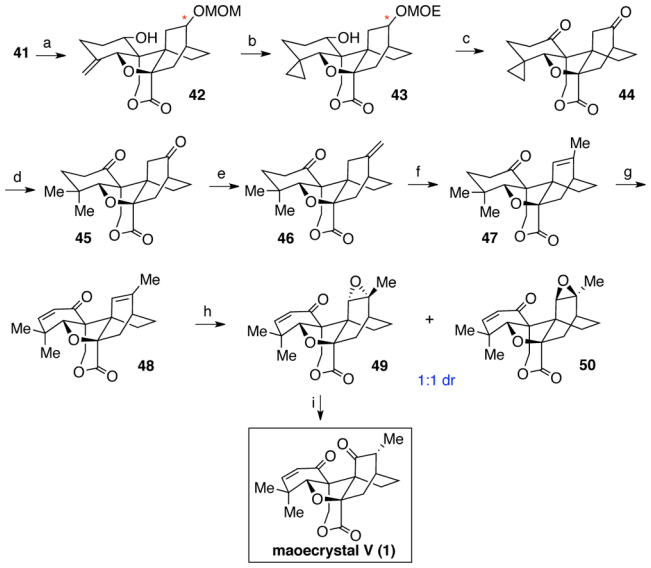

Figure 10. Completion of the synthesis of maoecrystal V (**1**). Key: (a) Lombardo reagent, DCM, room temperature, 85%; (b) CH_2I_2, Zn/Ag, Et_2O, 36 °C, 88%; (c) PCC, DCM, room temperature, 76%; (d) H_2, PtO_2, AcOH, 40%; (e) Lombardo reagent, DCM, 0 °C, 80%; (f) *p*-TsOH·H_2O, benzene, 76 °C, 85%; (g) LDA, TMSCl, THF, −78 °C, 90%; then $Pd(TFA)_2$, CH_3CN, 80%; (h) TFDO, CH_2Cl_2, −78 °C→0 °C, dr = 1:1, 90%; (i) $BF_3{\cdot}OEt_2$, DCM, room temperature, 85%.

the critical intermediate **48**. At this stage, all that remained was the installation of the C_{15}-oxo, C_{16} α-methyl functionality. We hoped to accomplish this goal. In the event, epoxidation of **48** with TFDO[26] afforded a chromatographically separable diastereomeric mixture of epoxides **49** and **50** (92% yield, 1:1 dr). Although we had anticipated that epoxide formation would predominantly occur from the less hindered side of the olefin,[27] to deliver **49** as the major isomer, we speculate that the observed lack of stereoselectivity may be attributed to subtle differences in the electronic environment surrounding the two faces of the olefin under attack.[28] In any case, the epoxide isomers were readily separated, and, in the final step of the synthesis, olefin **49** was treated with $BF_3{\cdot}OEt_2$ to deliver maoecrystal V (**1**) as a single isomer in 85% isolated yield.[29] The ^1H and ^{13}C NMR data were in full accord with those reported for the natural product itself. The mission of synthesizing the racemate of maoecrystal V had been accomplished.

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CONCLUSION

In summary, the total synthesis of maoecrystal V, albeit as a racemate, has been completed. Among the key steps was the IMDA reaction of **28**, which served to construct virtually the entire core system from a precursor obtained in one step from readily available starting materials. Key features of the synthesis included solution of the facial selectivity problem in the IMDA reaction by utilization of an achiral A-ring equivalent. Another feature involved creating the required *trans*-fusion of the A- and C-rings through intramolecular delivery of a hydrogen to the otherwise hindered β-face of C_5 (see epoxidation of intermediate **40** and rearrangement of the oxirane to **41**). The same logic was used to control the methyl group at C_{16}, although in this instance the elegance of the scheme was compromised by a surprising nonstereospecific epoxidation of the trisubstituted olefin between carbons 15 and 16.

The general directions that can be anticipated for an improved synthesis are clear. Ideally, one would be able to achieve enantiomeric control in the critical IMDA reaction. Moreover, it would be preferable if the trisubstituted olefin, eventually between carbons 15 and 16, could be introduced at a much earlier point. Finally, it could well be hoped to achieve stereoselectivity in the epoxidation of this 15−16 double bond by fine-tuning the electronic characteristics of the A-ring.[28] Future studies along these general lines are envisioned. However, even in advance of these very important upgrades, soon to be pursued, we feel that much has already been learned from "operation maoecrystal V".

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral and other characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Sun, H. D.; Xu, Y. L.; Jiang, B. *Diterpenoids from Isodon Species*; Science Press: Beijing, China, October 2001.

(2) 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.

(3) (a) Gong, J.; Lin, G.; Li, C. C.; Yang, Z. *Org. Lett.* **2009**, *11*, 4770−4773. (b) Krawczuk, P. J.; Schone, N.; Baran, P. S. *Org. Lett.* **2009**, *11*, 4774−4776. (c) Nicolaou, K. C.; Dong, L.; Deng, L. J.; Talbot, A. C.; Chen, D. Y. K. *Chem. Commun.* **2010**, *46*, 70−72. (d) Lazarski, K. E.; Hu, D. X.; Sterm, C. L.; Thomson, R. J. *Org. Lett.* **2010**, *12*, 3010−3013. (e) Singh, V.; Bhalerao, P.; Mobin, S. M. *Tetrahedron Lett.* **2010**, *51*, 3337−3339. (f) Baitinger, I.; Mayer, P.; Trauner, D. *Org. Lett.* **2010**, *12*, 5656−5659. (g) Gu, Z.; Zakarian, A. *Org. Lett.* **2011**, *13*, 1080−1082. (h) Dong, L.; Deng, L.; Lim, Y. H.; Leugn, G. Y. C.; Chen, D. Y.-K. *Chem.-Eur. J.* **2011**, *17*, 5778−5781. For an elegant synthesis of maoecrystal Z, see: (i) Cha, J. Y.; Yeoman, J. T. S.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 14964−14967.

(4) Gong, J.; Lin, G.; Sun, W.; Li, C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 16745−16746.

(5) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2007**, *72*, 4293−4305.

(6) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. *5*, pp 513−550.

(7) (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (b) Liao, C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856−866. (c) Ihara, M. *Chem. Pharm. Bull.* **2006**, *54*, 765−774.

(8) Peng, F.; Yu, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 6586−6587.

(9) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. *J. Am. Chem. Soc.* **2000**, *122*, 1360−1370.

(10) Stork, G.; Danheiser, R. *J. Org. Chem.* **1973**, *38*, 1775.

(11) Still, C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927−1928.

(12) Rabideau, P. W. *Tetrahedron* **1989**, *45*, 1579−1603.

(13) (a) Whitesides, G. M.; Whmann, W. J. *J. Org. Chem.* **1970**, *35*, 3565−3567. (b) Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 915−918.

(14) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 84−134.

(15) In our hands, in related cases, attempted use of a propiolate ester for the IMDA reaction was unsatisfactory. Insofar as reaction occurred, it was followed by aromatization.

(16) Peng, F.; Danishefsky, S. J. *Tetrahedron Lett.* **2011**, *52*, 2104−2106.

(17) For the application of Birch-type alkylation in natural product synthesis: (a) Kondo, K.; Sodeaka, M.; Mori, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4219−4223. (b) Schultz, A. G.; Holoboski, M. A.; Smvth, M. S. *J. Am. Chem. Soc.* **1996**, *118*, 6210−6219. (c) Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* **1998**, *120*, 8259−8260.

(18) (a) Strekowski, L.; Kong, S.; Battiste, M. A. *J. Org. Chem.* **1988**, *53*, 901−904. (b) Guan, Z. H.; Zuo, W.; Zhao, L. B.; Ren, Z. H.; Liang, Y. M. *Synthesis* **2007**, 1465−1470. (c) Danishefsky, S. J.; Harayama, T.; Singh, R. K. *J. Am. Chem. Soc.* **1979**, *101*, 7008−7012. (d) Danishefsky, S. J.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591−7599.

(19) (a) Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502−5503. (b) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808−3809. (c) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388−6390. (d) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.

(20) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4435−4436.

(21) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(22) Oppolzer, W.; Godel, T. *J. Am. Chem. Soc.* **1978**, *100*, 2583−2584.

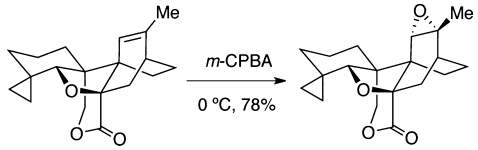
(23) (a) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293−4294. (b) Lombardo, L. *Organic Syntheses* **1987**, *65*, 81−83.

(24) (a) Rousseau, G.; Conia, J. M. *Tetrahedron Lett.* **1981**, *22*, 649−652. (b) Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549−551.

(25) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080−2081.

(26) (a) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749−6757. (b) D'Accolti, L.; Dinoi, A.; Fusco, C.; Russo, A.; Curci, R. *J. Org. Chem.* **2003**, *68*, 7806−7810.

(27) Indeed, in a model system, lacking the α,β-unsaturated ketone functionality, we did observe selective epoxidation from the less hindered face of the olefin.



(28) Woodward first postulated that if the unhindered face of an olefin is electron-depleted, then an electron-deficient reagent might be less likely to pass over that face. Thus, in such circumstances, electronic and steric factors play competing roles, leading to the formation of diastereomeric product mixtures. See: footnote, page 6, in Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *2*, 1−57.

(29) (a) Nii, K.; Tagami, K.; Kijima, M.; Munakata, T.; Ooi, T.; Kusumi, T. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 562−573. (b) Jung, M. E.; Allen, D. A. *Org. Lett.* **2008**, *10*, 2039−2041. (c) Falrweather, K. A.; Mander, L. N. *Org. Lett.* **2006**, *8*, 3395−3398. (d) Zhou, W.-S. *Huaxue Xuebao* **1985**, *43*, 237−242. (e) Sudha, R.; Narasimhan, K. M.; Waraswathy, V. G.; Sankararaman, S. *J. Org. Chem.* **1996**, *61*, 1877−1879. (f) Ireland, R. E.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 3652−3653.

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