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Total Synthesis

Total Synthesis of Maoecrystal V

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Abstract: Maoecrystal V (**1**) is a novel diterpenoid, which was originally isolated from the leaves of the Chinese medicinal herb *Isodon eriocalyx* in 2004 by Sun et al.[1] It has been found to be selectively cytotoxic towards HeLa cells, with an IC_{50} value of 20 ng mL^{-1}. Significant research efforts have been devoted to the synthesis of maoecrystal V because of its intriguing biological properties, rarity in nature, and complex structural features. Herein, we describe our recent investigations, which have culminated in the total synthesis of (±)-maoecrystal V. The current strategy involved three key steps for the successful construction of the key tetrahydrofuran oxa-bridge skeleton, including a Wessely oxidative dearomatization, a novel intramolecular Diels–Alder reaction, and a Rh^{II}-catalyzed O–H insertion reaction.

Introduction

In 2004, Sun et al.[1] reported the isolation of maoecrystal V (**1**, Figure 1) from the leaves of the Chinese medicinal herb *Isodon eriocalyx*, which has been used for centuries in folk medicine for the treatment of sore throats, inflammation, influenza, hypertension, and dermatophytosis.[2] More than 600 diterpenoids have been isolated from *Isodon* species to date,[3] and a large number of these compounds have been reported to exhibit potent antitumor activities.[4]

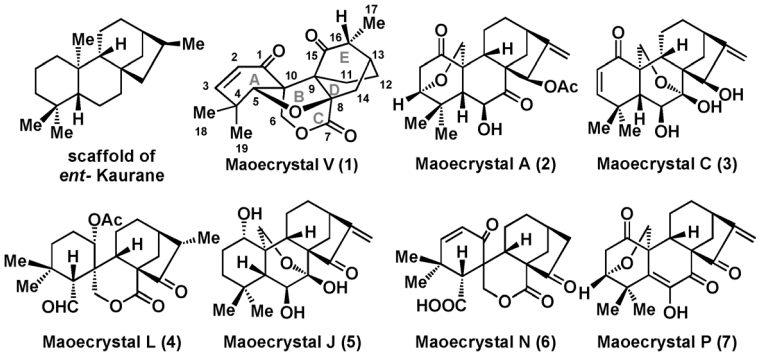

Figure 1. Naturally occurring *ent*-kaurane type maoecrystal compounds.

The cytotoxicity of maoecrystal V was evaluated against five human tumor cell lines, including K562, A549, BGC-823, CNE, and HeLa cells, and found to be selectively cytotoxic towards HeLa cells with an impressive IC_{50} value of approximately 20 ng mL^{-1}.[1] In light of the potent and selective cytotoxicity of this compound against gynecological cancer cells there is an urgent need for further investigation. However, the development of this lead compound has been severely limited by the fact that it can only be isolated in small amounts from natural sources (e.g., 5 mg/12 kg of dried leaves of the plant[1]).

Structurally, maoecrystal V (**1**) differs from other members of the *ent*-kauranoid maoecrystal family[3] such as **2**–**7** (Figure 1) because it contains a [2.2.2]-bicyclic ring system rather than a [3.2.1]-bicyclic ring system. Based on this difference in its molecular architecture, maoecrystal V (**1**) stands out as an atypical member of this class of natural products.

From a synthetic perspective, maoecrystal V (**1**) is a compact and highly functionalized cage-like molecule, which is regarded by many researchers to be one of the most challenging natural products in organic synthesis.[5] The biggest challenge posed by the total synthesis of maoecrystal V (**1**) arises from its pentacyclic framework, which contains six interlocking vicinal stereogenic centers; three of which are contiguous quaternary stereocenters[6] with two all-carbon centers at C9 and C10. Maoecrystal V (**1**) also contains a bicyclo[2.2.2]octan-2-one subunit (D/E-ring) and a strained and highly substituted central tetrahydrofuran ring (B-ring), which is flanked by a *trans*-fused six-membered ring (A-ring), and these structural features could also present a formidable challenge to its total synthesis.

In view of the intriguing structural features of maoecrystal V (**1**) and its potential applications as a biological probe and

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drug-discovery lead, numerous research efforts have been directed towards the synthesis of compounds belonging to this novel class of natural products,[7] culminating in the total synthesis of maoecrystal V (**1**) by the laboratories of Yang in 2010,[8] Danishefsky in 2012,[9] and Zakarian in 2013.[10a] The enantiosynthesis of (−)-maoecrystal V has been completed by Zakarian and co-workers.[10b]

In 2009, we reported our model study for the total synthesis of maoecrystal V (**1**).[7a] One of the key steps in this study was a lead-mediated Pinhey arylation reaction[11] involving the coupling of the aryl-lead tricarboxylate **8** to β-ketoester **9**. The product of this reaction was subjected to an oxidative Wessely dearomatization to give intermediate **10**, which underwent an intramolecular Diels–Alder (IMDA) reaction[12] to afford the tetracyclic compound **11**. The acetate group in **11** was subsequently removed by a SmI_2-mediated reductive deacetoxylation reaction[13] to yield **12**, which mimicked the carbon core of maoecrystal V (**1**) (Figure 2).

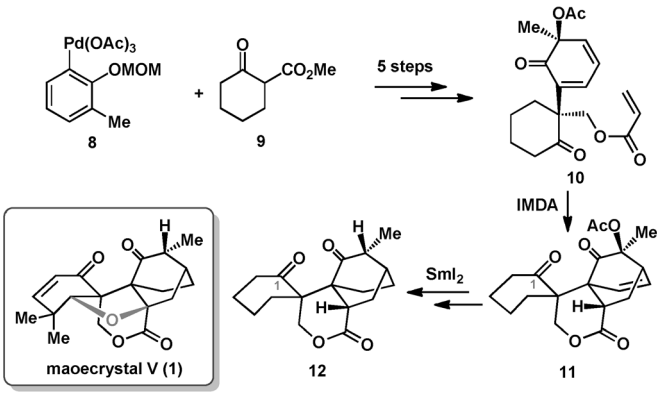


Figure 2. Model study of maoecrystal V (**1**).

The biggest difference between the model compound **12** and the natural product can be found in the tetrahydrofuran ring (B-ring), and the biggest challenge associated with the development of an efficient strategy for the total synthesis of maoecrystal V (**1**) must therefore focus on the construction of this key tetrahydrofuran oxa-bridge skeleton. With this in mind, we developed three strategies for the construction of this core scaffold, including an IMDA/oxidative C–O bond-forming approach; an intramolecular oxa-Michael reaction approach and a Rh^{II}-catalyzed O–H insertion approach and embarked on a study towards the total synthesis of maoecrystal V (**1**). Herein, we report the details of our total synthesis.

Results and Discussion

First Generation Approach: Oxidative C–O Bond Formation

The retrosynthetic strategy for our first generation total synthesis of maoecrystal V was based on the results of our previously reported model study (Figure 3). It was envisioned that maoecrystal V could be assembled from **13** through a late stage allylic oxidation and the SmI_2-mediated reductive cleavage of the oxygenated substituent at C16. It was anticipated that the tetrahydrofuran moiety of **13** could be constructed by a remote oxidative C–O bond forming reaction from the Diels–Alder product **14**, which could itself be formed through the IMDA reaction of **15**. Compound **15** could be synthesized in turn from the *cis*-diol **16**, which could be accessed by the stereoselective reduction of β-keto ester **17**.

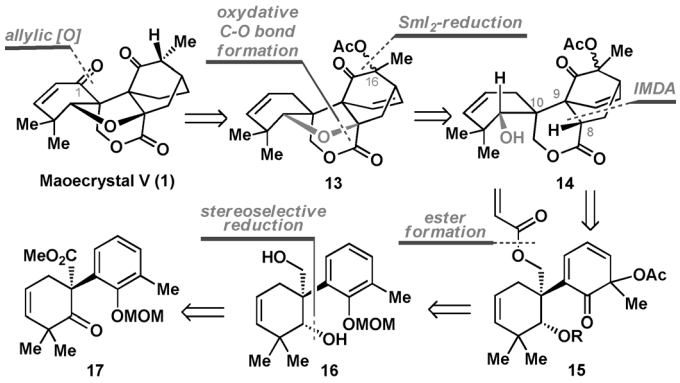
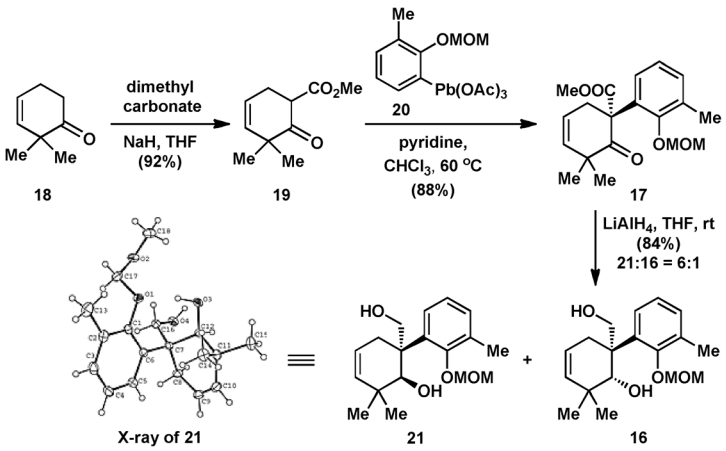


Figure 3. First generation retrosynthetic analysis.

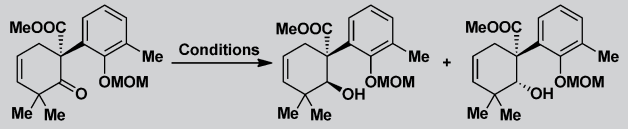
Our total synthesis began with the preparation of bicyclic compound **14**. Commercially available compound **18**[14] was treated with dimethyl carbonate in the presence of NaH to give the β-keto ester **19** in 92% yield, which was subjected to an oxidative arylation reaction with the aryl-lead reagent **20** to afford the key intermediate **17** in 88% yield (Scheme 1).

The β-keto ester **17** was initially reduced with $LiAlH_4$. However, this reaction did not proceed in a diastereoselective manner with both the *trans*-diol **21** and *cis*-diol **16** products being isolated in a combined yield of 84% in favor of the undesired product **21**. The failure of this reaction was attributed to the direction of the resulting primary alcohol, which would have allowed the reducing agent to access the ketone from the same side as the already reduced ester group (see the X-ray



Scheme 1. Synthesis of key intermediate **16**. Thermal ellipsoids are scaled to the 50% probability level.

Table 1. Screening of reducing agents for the selective reduction of **17**.



Entry	Solvent	Reagent	Temperature	Yield	Ratio of **22**/**23**
1	THF	L-selectride	−78 °C to rt	–[a]	–
2	THF	CBS/BH_3	rt	–[a]	–
3	CH_2Cl_2	DIBAL-H	−78 °C to rt	85%	5:1
4	MeOH	$NaBH_4$	rt	90%	3:2
5	MeOH	$CaCl_2$, $NaBH_4$	rt	95%	>30 :1
6	MeOH/THF	nBu_4NBH_4	40 °C	65%[b]	**23 only**
7	MeOH/THF	Me_4NBH_4	rt	81%[c]	**23 only**

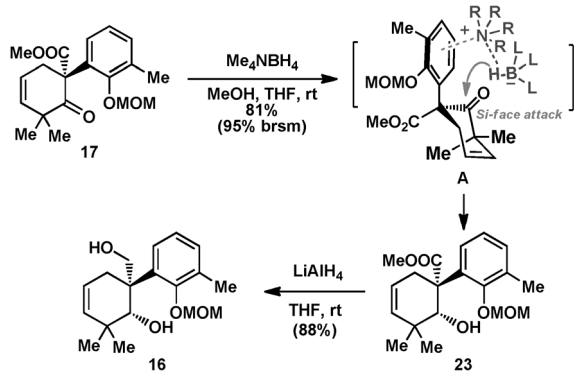
[a] No reaction, recovered starting material. [b] 89% BRSM (based on recovered starting material). [c] 95% BRSM.

structure of **21**). To achieve the desired product **16**, it was therefore necessary to use a stepwise reduction process and a variety of reducing agents were screened against the reaction, as illustrated in Table 1. Sterically hindered reducing agents such as L-selectride or the Corey–Bakshi–Shibata (CBS) catalyst were unsuccessful and resulted in the recovery of starting material (Table 1, entries 1 and 2). This result indicated that the ketone moiety of **17**, which is adjacent to two quaternary carbon centers, is difficult to access because of the steric hindrance imposed by the surrounding environment. When diisobutylaluminum hydride (DIBAL-H) was used as a reducing agent, compound **17** was selectively reduced to give compounds **22** and **23** in a combined yield of 85% and a ratio of 5:1 in favor of product **22** (Table 1, entry 3). $NaBH_4$ was also evaluated as a reducing agent, and gave compounds **22** and **23** in a combined yield of 90% and a ratio of 3:2 in favor of **22** (Table 1, entry 4). However, $NaBH_4/CaCl_2$[15] as the reducing agent led to a significant increase in the selectivity with compounds **22** and **23** being formed in a ratio of >30:1 in favor of **22** (Table 1, entry 5). Pleasingly, the treatment of **17** with $(nBu_4)NBH_4$ or Me_4NBH_4 in a mixed solvent of MeOH/THF at 40 °C or room temperature afforded the desired product **23** as the sole isomer in 65 and 81% yields, respectively.[16]

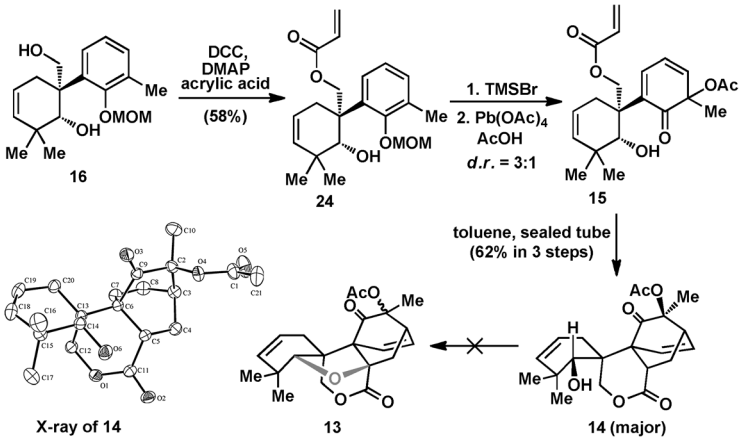
The diastereoselectivity of this process was attributed to the directing and accelerating effects of the cationic-π interaction[17] between the ammonium salt [$(n$-R)$_4NBH_4$] and the phenyl ring in substrate **17**, which would have ensured that the hydride was delivered to the *Si* face of the ketone in **17** to yield compound **23**. Pleasingly, the treatment of ester **23** with $LiAlH_4$ afforded the corresponding *cis*-configured diol **16** in 88% yield (Scheme 2).

With the desired *cis*-diol **16** in hand, we proceeded to investigate the formation of the tetracyclic core of maoecrystal V (**1**) using an IMDA reaction (Scheme 3). Thus, *cis*-diol **16** was condensed with acrylic acid at room temperature in the presence of 1,3-dicyclohexylcarbodiimide/4-dimethylaminopyridine (DCC/DMAP) to give the corresponding α,β-unsaturated ester **24** in 58% yield. Compound **24** was then treated with trimethylsilyl bromide (TMSBr) to remove its methoxymethyl (MOM) group, and the resulting phenol was subjected to a Wessely oxidative dearomatization reaction to give **15** as a mixture of diastereoisomers at C16 in a ratio of 3:1. To accelerate the IMDA reaction, compound **15** was dissolved in toluene and the resulting mixture was heated in a sealed tube at 120 °C to give the cyclized product **14** in a total yield of 62% for the last three steps. The relative stereochemistry of **14** was confirmed by X-ray crystallography. Thus, we achieved the diastereoselective formation of the tetracyclic core of maoecrystal V.

We then moved on to investigate the installation of the highly strained tetrahydrofuran ring system. Synthetically, it was envisaged that the tetrahydrofuran ring could be constructed through a direct C–H functionalization reaction, because several similar strategies have been reported in the literature.[18] With this in mind, compound **14** was subjected to a variety of different oxidative coupling conditions, including $PhI(OAc)_2/I_2/h\nu$[18c] and $Pd(OAC)_4/I_2/h\nu$,[18e] as well as the nitrite ester photolysis conditions developed by Barton et al.[19] However, none of these conditions provided access to the expected product **13** (Scheme 3), and it was therefore necessary to



Scheme 2. Diastereoselective synthesis of diol **16**.



Scheme 3. Construction of the core structure of Maoecrystal V through an IMDA. Thermal ellipsoids are scaled to the 50% probability level.

devise an alternative pathway for the construction of this challenging fragment of maoecrystal V.

Second Generation Approach: Oxa-Michael Addition

A second approach was developed to solve the issues associated with the late stage formation of the tetrahydrofuran ring. In this approach, it was envisaged that an IMDA reaction could be used to build up the [2.2.2]-bicyclic ring system together with the in-situ generation of the tetrahydrofuran ring in compound **25** (Figure 4), which could then be converted into maoecrystal V (**1**) through a series of standard synthetic transformations. The key step in our second generation approach for the synthesis of maoecrystal V (**1**) would therefore involve the intramolecular oxa-Michael reaction[20] of **27** for the formation of the key intermediate **26**, as shown in Figure 4.

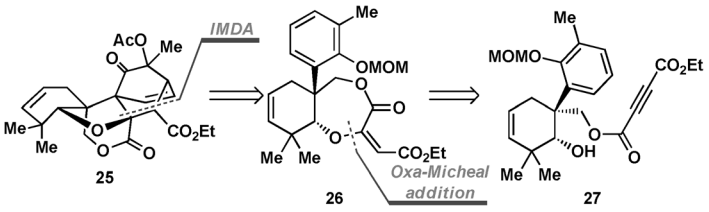


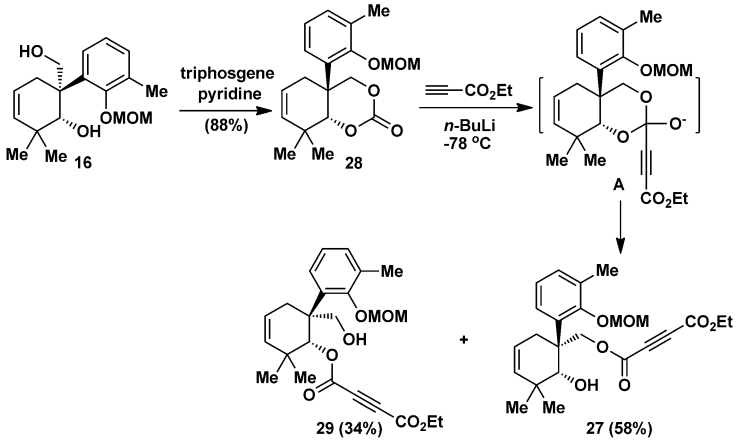
Figure 4. Retrosynthetic analysis of **25**.

Scheme 4 shows the synthesis of intermediate **27**, which is an important precursor for the proposed oxa-Michael reaction. For the synthesis of compound **27**, diol **16** was initially treated with triphosgene in the presence of pyridine to give the corresponding carbonate **28** in 88% yield.[21] The subsequent treatment of carbonate **28** with lithium acetylide afford esters **29** and **27** in 34 and 58% yields, respectively. Notably, ester **29** could be converted back into the starting diol **16** by treatment with KOH in MeOH.

With precursor **27** in hand, we then began to explore the feasibility of the proposed tandem oxa-Michael addition and IMDA reactions for the synthesis of compound **25**. Thus, the MOM ether group in ester **27** was removed with H_2SO_4 (3 N) to give the corresponding phenol **30** in 93% yield, which was subjected to a Wessely oxidation to afford **31** in 86% yield as a mixture of diastereoisomers at C16 in a ratio of 3:1. The proposed tandem oxa-Michael addition/IMDA reaction of compound **31** was investigated under a wide variety of reaction conditions but failed to provide any of the desired product **25**. The direct IMDA reaction of **33** also failed to provide the desired product (Scheme 5).

Third Generation Approach: Rh^{II}-catalyzed O–H Insertion

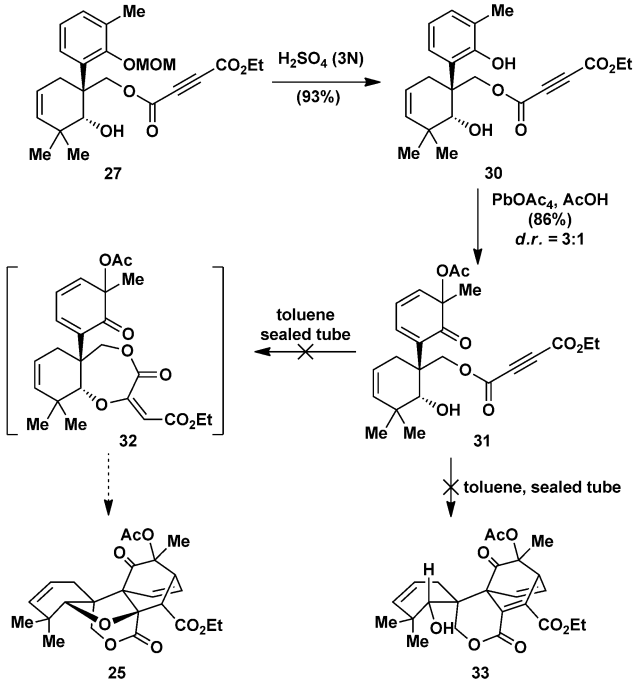
Given that strategies based on conventional synthetic methods failed to allow for the formation of the sterically hindered C–O bond, it was clear that a novel synthetic strategy would have



Scheme 4. Synthesis of compound **27**.

to be developed for the construction of this challenging bond. The Rh-catalyzed intramolecular OH insertion reaction[22] has emerged as an effective method for the formation of C–O bonds. In this context, α-diazo carbonyl compounds can be converted into carbene species in the presence of a Rh^{II} catalyst. The resulting carbene species can then undergo an intramolecular O–H bond insertion reaction to form C–O bonds, and strategies of this type have been successfully applied to the construction of medium-sized ring systems.[23]

With this chemistry in mind, we began to explore a third generation strategy for the construction of the pentacyclic core of maoecrystal V using the Rh^{II}-catalyzed C–O insertion and IMDA reactions as key steps in the process, as shown in Figure 5. It was envisioned that diol **16** could be converted into its corresponding phosphate de-



Scheme 5. The attempt of intramolecular oxa-Michael addition.

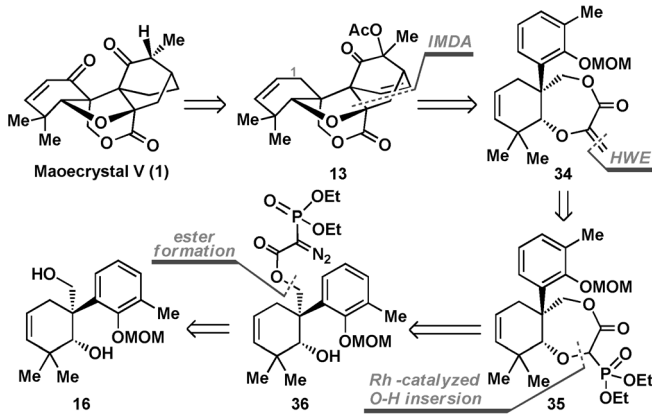


Figure 5. Retrosynthetic analysis of the third generation approach.

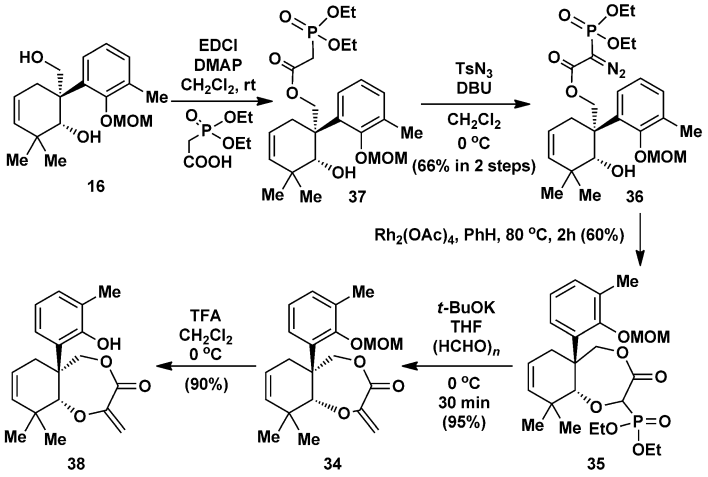
rived α-diazo carbonyl compound **36**, which would undergo the proposed Rh^{II}-catalyzed intramolecular O–H bond insertion reaction to allow for the formation of the C–O bond. The Horner–Wadsworth–Emmons reaction of resulting phosphate **35** would give **34**, which would undergo the expected Wessely oxidative dearomatization followed by an IMDA reaction to afford the product **13** with the desired pentacyclic core of maoecrystal V (**1**). Thus, the total synthesis of **1** could be accomplished by sequential SmI_2-mediated deacetylation and allylic oxidation[25] reactions, with the installation of the carbonyl group at C1 being a key step.

In practice, *cis*-diol **16** was coupled with diethylphosphono-acetic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride(EDCI) and DMAP in CH_2Cl_2 to give ester **37**, which was subsequently treated with toluenesulfonyl azide[25] in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 at 0 °C to give the α-diazo carbonyl compound **36** in 66% yield over the two steps. Treatment of **36** with the $Rh_2(OAc)_4$ catalyst at 80 °C in anhydrous benzene gave lactone **35** in 60% yield, which was then subjected to a Horner–Wadsworth–Emmons reaction[26] with paraformaldehyde to afford **34** in 95% yield. The MOM group in **34** was subsequently removed by the treatment of this compound with trifluoroacetic acid (TFA) in CH_2Cl_2 at 0 °C over 30 min to afford phenol **38** in 90% yield (Scheme 6).

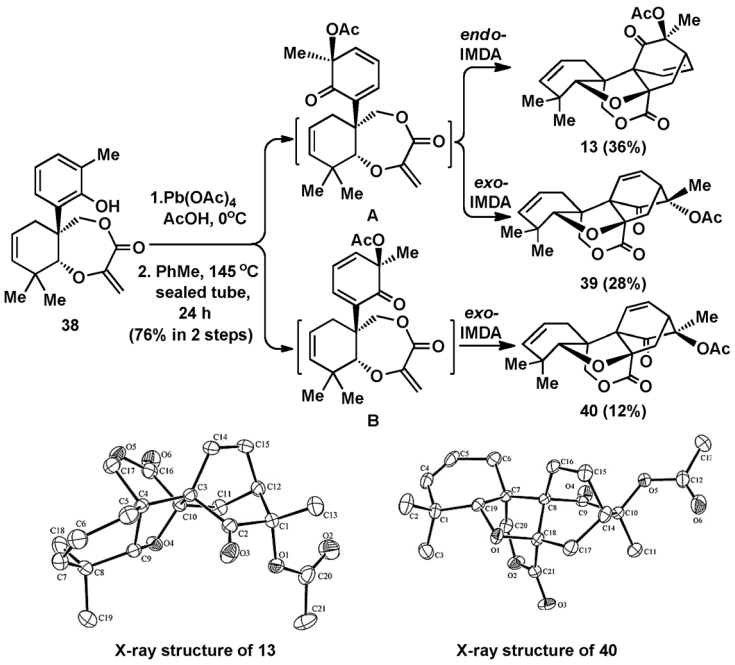
With phenol **38** in hand, we proceeded to evaluate its performance in the annulation reaction for the formation of product **13** with the pentacyclic core of maoecrystal V. In practice, the treatment of phenol **38** with $Pb(OAc)_4$ in acetic acid allowed for the Wessely oxidation reaction to proceed smoothly to give the corresponding dienes as a pair of regioisomers. This regioisomeric mixture was then progressed into the next stage without separation and was heated in a sealed tube for 24 h in toluene at 145 °C to give the *endo*-selective product **13** in 36% yield, together with its regioisomers **39** (*exo*-selective product) and **40** (*exo*-selective product) in 28 and 12% yields, respectively (Scheme 7). The structures of **13** and **40** were confirmed by X-ray crystallography.

We then proceeded to the final stage in the completion of this total synthesis, where we attempted to achieve the direct conversion of **13** to enone **41** (Scheme 8). Unfortunately, however, we were unable to form enone **41**, despite testing various allylic oxidation conditions, and the failure of this approach was attributed to steric hindrance at the C1 position of **13** from the adjacent quaternary carbon atom.

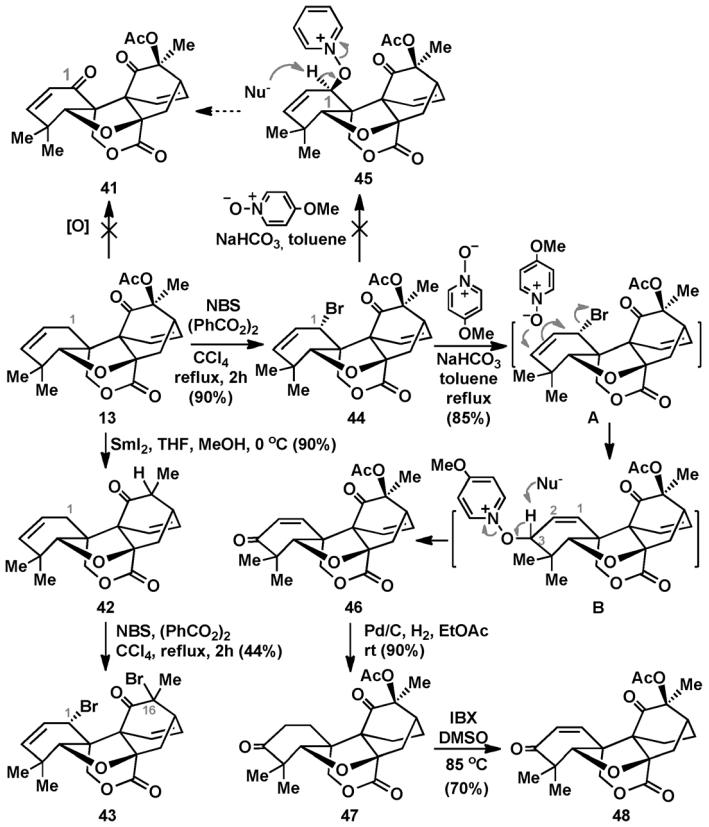
In our final attempt to achieve the total synthesis of maoecrystal V (**1**), we explored the possibility of using a stepwise strategy for the formation of product **41**. It was envisaged that



Scheme 6. Synthesis of key intermediate **35**.



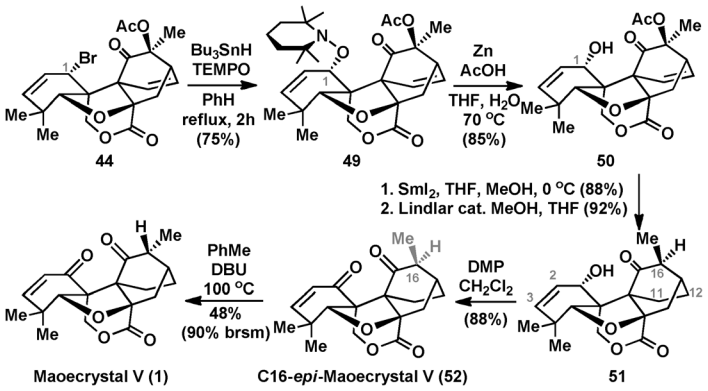
Scheme 7. The Wessely dearomatization/IMDA sequence. Thermal ellipsoids are scaled to the 50% probability level.



Scheme 8. The attempt to install the carbonyl group at C1.

the C1 position could be brominated using an N-bromosuccinimide (NBS)-mediated radical reaction, and that the resulting bromide could be converted into the corresponding ketone using a 4-methoxypyridine-*N*-oxide-mediated S_N2 reaction.[27] In practice, compound **13** was initially treated with SmI_2 to remove its acetyl group, and subsequently brominated with NBS in the presence of benzoyl peroxide.[28] Unfortunately, however, these reaction conditions led to the formation of the dibrominated product **43**. To avoid bromination at C16, **13** was used as the substrate in the bromination reaction, where it was treated with NBS in the presence of benzoyl peroxide to give the mono-brominated **44** in 90% yield. With the brominated precursor in hand, we proceeded to explore the proposed S_N2 reaction for the installation of the C1 oxygen. Interestingly, treatment of **44** with 4-methoxypyridine-*N*-oxide under the standard conditions did not give the expected product **45** through the proposed S_N2-type reaction, but instead gave **46** in 85% yield by an S_N2'-type mechanism through intermediates **A** and **B** (Scheme 8). Furthermore, **46** was converted into **47** in good yields under standard hydrogenation conditions. Although compound **47** is an isomer of the desired product **41**, it could still be used as a model to reinstall the C1–C3 enone system. With this in mind, **47** was treated with o-iodoxybenzoic acid (IBX) in dimethyl sulfoxide (DMSO) at 85 °C to give **48** in 70% yield.

This result revealed that we were close to achieving our goal of the total synthesis of maoecrystal V (**1**). In an attempt to overcome the problems caused by this unexpected S_N2'-type reaction mechanism, we became interested in the possibility of using a radical fragmentation process to achieve the proposed S_N2-type cleavage of the bromine motif. It was envisaged that the carbon–bromine bond in **44** could be homolytically cleaved using a tin hydride reagent, and that the resulting carbon radical could be trapped by an oxygen atom source such as O_2 or 2,2,6,6-tetramethylpiperidin-1-oxyl radical (TEMPO) in a similar manner to those reported by the research groups of Boger and Leighton.[29a,b] To test this strategy, we initially treated **44** with Bu_3SnH in the presence of TEMPO in refluxing benzene. Pleasingly, product **49** was obtained in 75% yield. Encouraged by this result, we treated **49** with zinc in a mixture of acetic acid and THF, and this led to the formation of **50** bearing a hydroxy group at C1 in 85% yield. The acetoxy group in **51** was removed by a SmI_2-mediated reductive cleavage reaction,[13d] and a subsequent regioselective hydrogenation using Lindlar catalyst afforded **51** in 81% yield over the two steps. To complete the total synthesis, alcohol **51** was oxidized with Dess–Martin periodinane (DMP) in CH_2Cl_2 at room temperature to give **52** as C16-*epi*-maoecrystal V, which was isomerized with DBU at 100 °C to give maoecrystal V (**1**) in 48% yield (90% brsm) as a racemic mixture. The identity of the synthesized maoecrystal V (**1**) was confirmed through a comparison of its NMR spectral data with those of natural maoecrystal V (**1**) (Scheme 9).



Scheme 9. Total synthesis of maoecrystal V (**1**).

Conclusions

Following a series of systematic synthetic investigations, the concise total synthesis of maoecrystal V (**1**) has been achieved using a Wessely oxidative dearomatization, IMDA reaction, and an Rh-catalyzed O–H bond insertion as key steps in the strategy. Notably, this strategy allowed for the total synthesis of (±)-maoecrystal V (**1**) in 18 steps in a total yield of 1.3% from

the commercially available compound **18**, and this chemistry could be used to achieve the synthesis of several analogues of maoecrystal V.

Experimental Section

The synthetic procedures and characterization of the compounds studied herein can be found in the Supporting Information. CCDC 864996 (**13**), CCDC 1038436 (**14**), CCDC 1038437 (**21**), and CCDC 1038435 (**40**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Keywords: Diels–Alder reaction · natural products · rhodium · total synthesis · oxidative dearomatization

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FULL PAPER

Total Synthesis

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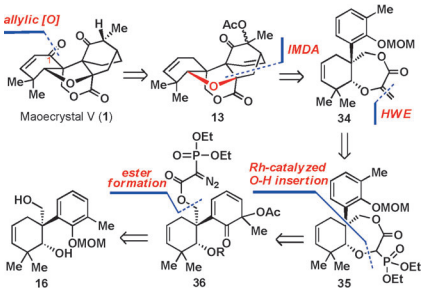
■■ – ■■

Total Synthesis of Maoecrystal V



The total synthesis of maoecrystal V (**1**) has been achieved by employing a Wessely oxidative dearomatization, an intramolecular Diels–Alder (IMDA) reaction, and a Rh-catalyzed O–H bond insertion as key steps; this total synthesis of (±)-maoecrystal V was completed in 18 steps in a total yield 1.3%.