

Enantioselective Synthesis of (–)-Maoecrystal V by Enantiodetermining C–H Functionalization

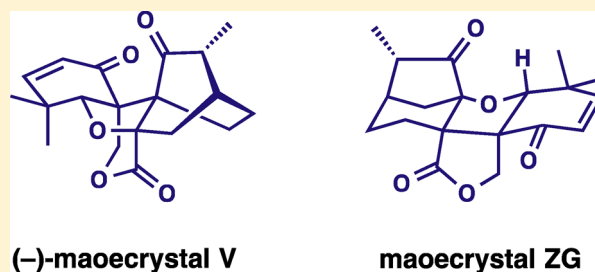
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S Supporting Information

ABSTRACT: The evolution of a program directed at the enantioselective total synthesis of maoecrystal V, a highly modified *ent*-kauranoid, is described. An early stage chiral auxiliary-directed asymmetric C–H functionalization for the construction of a key benzofuran intermediate enabled the first asymmetric synthesis of the natural enantiomer of maoecrystal V, confirming the assigned stereochemistry. A divergent course of the central intramolecular Diels–Alder reaction, which is dependent on the nature of the dienophile, initially led to the development of an unanticipated and previously unknown isomer of maoecrystal V, which we named maoecrystal ZG. In light of the reported selective and potent cytotoxic activity of maoecrystal V, the cytotoxic properties of maoecrystal ZG were also investigated.



INTRODUCTION

The first investigations of diterpenoids from plants in the *Isodon* genus date back over 100 years ago to 1910, when Yagi isolated a crystalline principle plectranthin from “enmei-so”, a medication from the leaves of *I. japonica* and *I. trichocarpa* that have been used for the treatment of gastrointestinal disorders in Japan for centuries.¹ In the Henan province in China, the leaves of *I. rubescens* are still used by residents for the treatment of respiratory and gastrointestinal bacterial infections, inflammation, and cancer. Enmein was the first compound isolated from *I. japonica* in 1958, and its structure was established in 1968 by X-ray crystallography.² Since then, over 600 individual diterpenoids from *Isodon* plants, displaying a broad spectrum of biological activity, have been characterized.³ Whereas the largest group is defined by the classic *ent*-kaurane carbon skeleton (Figure 1), another sizable structural type is 6,7-*seco*-*ent*-kauranes, examples of which include compounds like scuponeatin N, trichorabdals, longirabdolactone, and longikaurin. Related maoecrystals L⁴ and O⁵ were both isolated from *I. eriocalyx*.

More recently discovered constituents of *I. eriocalyx*, maoecrystals V⁶ and Z,⁷ are special members of the *ent*-kaurane diterpenoid family because of unprecedented, highly rearranged polycyclic ring systems found in their molecular structures. The structure of maoecrystal Z combines a *trans*-fused 6,5,6-carbotricyclic framework with a bridging six-membered lactone and has been classified as a 6,7:8,15-*diseco*-7,20-olide-6,8-cyclo-*ent*-kaurane. Maoecrystal V is characterized by an intricate blend of bicyclo[2.2.2]octan-2-one, δ -valerolactone, and cyclohexene subunits with a strained central oxolane ring. Both compounds have been found to display

notable cytotoxic activity. The potencies of maoecrystal Z were comparable across the three human cell lines examined: K562 leukemia (IC₅₀ 2.9 μ g/mL), MCF7 breast (IC₅₀ 1.6 μ g/mL), and A2780 ovarian (IC₅₀ 1.5 μ g/mL). Remarkably, maoecrystal V showed high selectivity against the HeLa cell line (IC₅₀ 2.9 μ g/mL), with the activities for K562, A549 lung carcinoma, and BGC-823 adenocarcinoma lower by at least 6 orders of magnitude.

The total syntheses of only a few *ent*-kauranoids have been accomplished. Some of the pioneering achievements have been disclosed by the Mander group who reported a total synthesis of 15-deoxyeffusin almost three decades ago.⁸ The same group accessed longirabdolactone from giberellic acid by semisynthesis.⁹ Steviol and isosteviol are other *ent*-kauranes with a classic polycyclic skeleton that stimulated early interest as synthesis targets. The first synthesis by Mori in 1970¹⁰ was followed by concise total syntheses by Ziegler,¹¹ Snider,¹² and Baran¹³ probing distinct strategies. Isolation of structurally unique maoecrystal V, and subsequently maoecrystal Z, is one of the recent events that reinvigorated interest in the synthesis of *ent*-kauranoid natural products. Reisman and co-workers developed and successfully executed a concise unified strategy for the synthesis of (–)-maoecrystal Z, (–)-trichorabdals, and (–)-longikaurin E.¹⁴ Earlier this year, total syntheses of scuponeatin N were reported by Zhai¹⁵ and Thomson.¹⁶ Maoecrystal V, with its intricate structure distinct from other *ent*-kauranes, proved to be an especially compelling synthesis target, and many research groups reported different strategies

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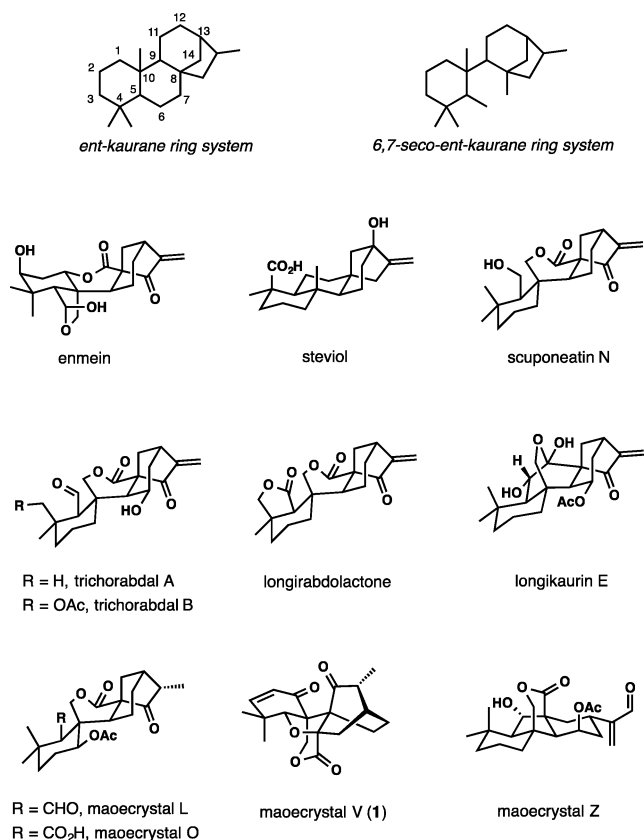
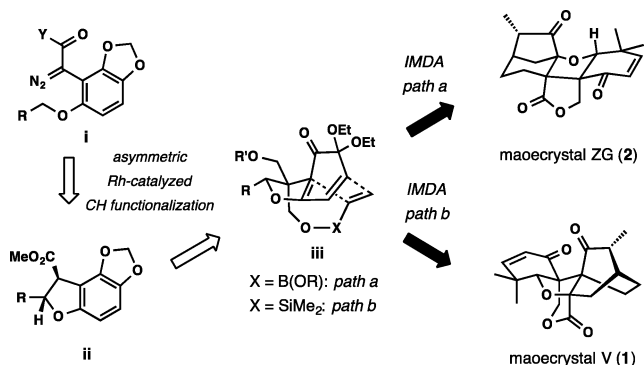


Figure 1. General structures and selected members of *ent*-kaurane diterpenoids from *Isodon* plants.

for its synthesis.^{17,18} Presently, the total synthesis of maoecrystal V in racemic form has been completed by the groups of Yang,¹⁹ Danishefsky,²⁰ and ours.²¹

Herein, we provide a full account of the enantioselective total synthesis of (–)-maoecrystal V²² and of its non-natural isomer maoecrystal ZG. The enantiodetermining step of the synthesis is a Rh-catalyzed C–H functionalization forming a dihydrobenzofuran intermediate **ii** (Scheme 1). We discovered that the course of the synthesis is critically dependent on the choice of dienophile partner in the central intramolecular Diels–Alder (IMDA) cycloaddition of intermediate **iii** forging the bicyclo[2.2.2]octan-2-one subunit. Our first effort unexpectedly delivered maoecrystal ZG, a structural isomer of the original target, which provided an opportunity to explore its

Scheme 1. Abbreviated Presentation of the Total Synthesis of (–)-Maoecrystal V (1) and Maoecrystal ZG (2)

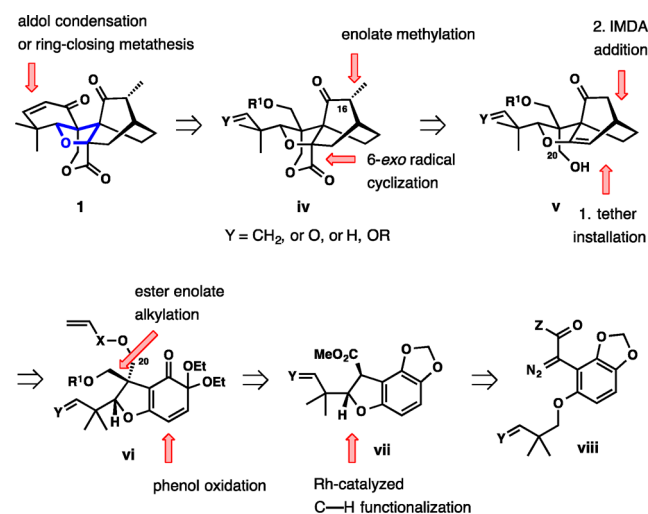


antiproliferative properties. Compound **2** appears to have an unprecedented ring system. Modification of the dienophile in **iii** allowed for the ultimate completion of the first enantioselective total synthesis of maoecrystal V.

RESULTS AND DISCUSSION

Synthesis Plan. A central factor that influenced the design of the synthesis was the realization that the assembly of the central tetrahydrofuran ring, highlighted in Scheme 2, at first a

Scheme 2. Synthesis Plan



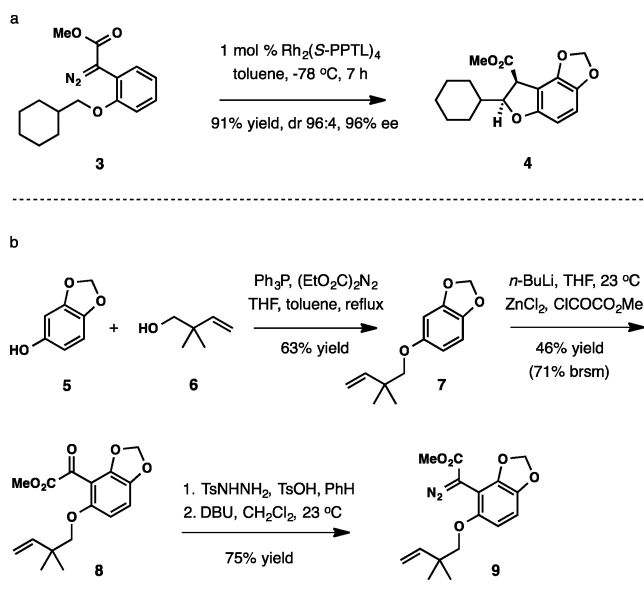
seemingly simple operation, was going to present a substantial challenge. This notion was validated by the growing number of reports on the progress toward the total synthesis of **1** from several groups that halted at this stage, after successfully addressing other challenges such as the installation of the quaternary centers.¹⁷ The challenge was ascribed to the well-recognized strain associated with the five-membered heterocycle in **1**. Guided in part by these observations, our goal was to preserve the oxolane ring for as long as reasonable during the progressive bond disconnection process. The cyclohexenone subunit was envisioned to arise from either an aldol cyclocondensation of a methyl ketone–aldehyde precursor or ring closing metathesis. Subsequent simplification was aimed at the C16 methyl group and the lactone ring. The six-membered lactone was to be constructed by a 6-*exo* radical cyclization of an acyl radical onto the enol ether. This risky blueprint was faced with potential complications due to (1) possible instability of the enol ether, (2) lack of precedent and therefore limited confidence in the reliability of radical cyclizations onto enol ethers within complex substrates, and (3) the need for the 6-*exo* cyclization to occur contrary to the electronic preferences of the enol ether. After installation of the tether at the C20 hydroxy group, the bicyclo[2.2.2]octan-2-one retron was disassembled via an IMDA process with a synthetic equivalent of ethylene. In addition to enabling the IMDA reaction, the function of the tether was to deliver the dienophile from the correct face of the cyclohexadione ring system. After further analysis, which involved ester enolate hydroxymethylation and phenol oxidation, dihydrobenzofuran **vii** was identified as an early synthesis target, thus fulfilling our goal to preserve the central oxolane ring during the course of the synthesis. Essential to the plan was the prospect of using the recent C–H functionalization technologies advanced by the groups of

Davies and Yu to effectively access dihydrobenzofuran **vii** from precursors like **viii**.^{23,26,28,30}

The main variables intentionally left open to experimental feedback were the identity of groups X, Y, and Z (Scheme 2). For group Y, the preferred options were either CH₂ or a protected hydroxyl group (aldehyde was deemed too reactive). We initially selected the methylene group because it promised a more direct elaboration to the cyclohexenone via RCM, recognizing its potential reactivity during the radical cyclization onto the enol ether. The nature of the tether (group X) was to be guided by two parameters: the ease of installation and then removal. The main purpose of group Z in diazo precursor **viii** was to support effective C–H functionalization, in terms of both chemical efficiency and enantioselectivity.

Development of the Enantioselective Synthesis of Benzofuran Intermediates by Rh-Catalyzed C–H Functionalization. Catalytic Asymmetric Approaches. Catalytic enantioselective synthesis of dihydrobenzofurans via intramolecular C–H insertions in the presence of chiral rhodium catalysts has been developed by Davies^{24,26} and Hashimoto.²⁵ These findings provided the basis for the development of the synthesis of (–)-maoecrystal V by the aforementioned strategy, in which the early construction of a dihydrobenzofuran intermediate would be the enantiodetermining stage of the synthesis. Although the majority of examples involve insertions into benzylic ether C–H bonds, a few examples with aliphatic ethers were also reported. Perhaps the most relevant precedent is illustrated in Scheme 3a.²⁴

Scheme 3



The synthesis of the first substrate for the enantioselective C–H functionalization studies began by O-alkylation of sesamol with readily accessible neopentyl alcohol **6** under Mitsunobu conditions (Scheme 3b). The resulting ether was advanced through directed *ortho*-metalation followed by acylation with methyl chloroacetate via an arylzinc intermediate. The diazo ester (**9**) was accessed in two steps from **8** by tosylhydrazone formation and subsequent fragmentation under basic conditions in the presence of DBU.

The initial screening focused on identifying the preferred catalyst/solvent system at ambient temperature (Table 1). The

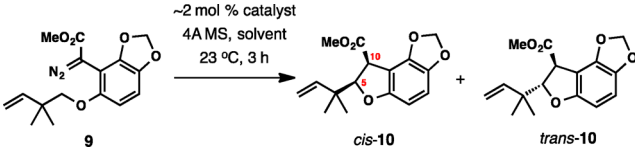
library of catalysts used in this study is depicted in Figure 2. With Rh₂(S-PTTL)₄ catalyst, the best diastereoselectivity and enantioselectivity were observed in dichloromethane (DCM), although moderately higher yields were obtained in hexane and toluene (entries 3, 4). Extensive catalyst screening in DCM was disappointingly unproductive, and generally did not lead to improvement in stereoselectivity, although a somewhat higher yield of 42% was observed with Rh₂(S-TCPTTL)₄ (entry 6).

Further incremental progress was reached when the temperature of the reaction was increased to reflux in DCM. The Rh₂(S-PTTL)₄ catalyst again had the best yield, delivering a 53% combined yield of the two diastereomers with a 10:1 ratio, in which the major isomer was formed in 60% ee (entry 8). Additional screening under these conditions (reflux in DCM) led to no further improvement and Rh₂(S-PTTL)₄ was found to be the optimal catalyst system for a potential application in total synthesis. Importantly, the high diastereoselectivity of 10:1 was critical to maintaining the original enantiomer ratio, because the catalyst controls the absolute stereochemistry at C10 rather than C5 (maoecrystal V numbering).²⁴ Position C10 is epimerizable and is in fact inverted later during synthesis with a net result of erosion of the ee.

Overall, although the results in entry 8 were found to fall short of those desired, they provided a reasonable starting point for a potential application in a total synthesis setting. In particular, a 53% yield and the observed 10:1 diastereoselectivity would minimize the impact of enantioselectivity erosion in subsequent transformations. Although the enantioselectivity at 60% was not very high, there was a reasonable expectation that it could be further upgraded during the course of the synthesis.

Another reaction that was extensively studied with a view for a potential application in the enantioselective total synthesis of maoecrystal V is depicted in Table 2. The substrate (**11**) was prepared analogously to **9**.^{21,27} Here, the nature of the ester substituent was also varied (Me or *t*-Bu). In general, higher chemical yields of products *cis*-**12** and *trans*-**12** were observed with these substrates. One important conclusion from this study is that replacing the terminal alkene in **9** with *p*-methoxybenzyloxy resulted in a loss of diastereoselectivity across the range of catalysts in several solvents. Although rather high enantioselectivity of up to 80% could be achieved with catalysts Rh₂(S-PTTL)₄ and Rh₂(S-BPTV)₄, the low diastereoselectivity of ~1:1 observed for **11** (R = Me) negated the ability to control stereochemistry at C5 (entries 1 and 11). In fact, with any of the catalysts examined, the critically important diastereoselectivity never reached the levels observed for diazo ester **9**. Although the *tert*-butyl ester (**11**, R = *t*-Bu) generally displayed higher diastereoselectivity, the highest level among the studied reactions (3.8:1) was recorded for the methyl ester with catalyst Rh₂(S-BTPCP)₄ (**13**). However, enantioselectivity was low for both *cis*-**12** (ee 36%) and *trans*-**12** (ee 11%).

Davies and Yu recently reported an elegant enantioselective approach to 2,3-dihydrobenzofurans based on consecutive C–C and C–O bond-forming C–H functionalization reactions,²⁸ which we also explored for our purposes (Scheme 4). The desired transformation was complicated by the need to use challenging neopentyl ether **13** as the substrate whereas the precedent existed only for benzylic ethers. A preliminary evaluation of the first step of the process was carried out with ether **13** or **14** and Rh₂(OAc)₄ in dichloromethane.²⁹ No conversion was observed in this reaction, confirming that **13** is

Table 1. Enantioselective C–H Insertion with Diazo Ester 9^a


entry	catalyst	solvent	yield (%) ^a	cis:trans	ee, cis (%)	ee, trans (%)
1	Rh ₂ (S-PTTL) ₄	CH ₂ Cl ₂	25	9.1:1	70	50
2	Rh ₂ (S-PTTL) ₄	EtOAc	trace			
3	Rh ₂ (S-PTTL) ₄	hexane	34	6.7:1	51	
4	Rh ₂ (R-PTTL) ₄	PhMe	47	5.9:1	–60	–33
5	Rh ₂ (S-NTTL) ₄	CH ₂ Cl ₂	27	9.1:1	54	
6	Rh ₂ (S-TCPTTL) ₄	CH ₂ Cl ₂	42		30	18
7	Rh ₂ (R-BPTV) ₄	CH ₂ Cl ₂	trace			
8	Rh ₂ (S-PTTL) ₄	CH ₂ Cl ₂ ^c	53	10.0:1	60	
9	Rh ₂ (S-PTAD) ₄	CH ₂ Cl ₂ ^c	22	3.7:1	48	
10	Rh ₂ (R-BTPCP) ₄	CH ₂ Cl ₂ ^c	NR			
11	Rh ₂ (R-BPTV) ₄	CH ₂ Cl ₂ ^c	trace			
12	Rh ₂ (S-bitISP) ₂	CH ₂ Cl ₂ ^c	trace	1:1		
13	Rh ₂ (S-TCPTAD) ₄	CH ₂ Cl ₂ ^c	24	3:1	8	

^aDiastereomer ratios and enantiomeric excess were determined by HPLC analysis. ^bCombined isolated yield of *cis*-10 and *trans*-10. ^cAt reflux.

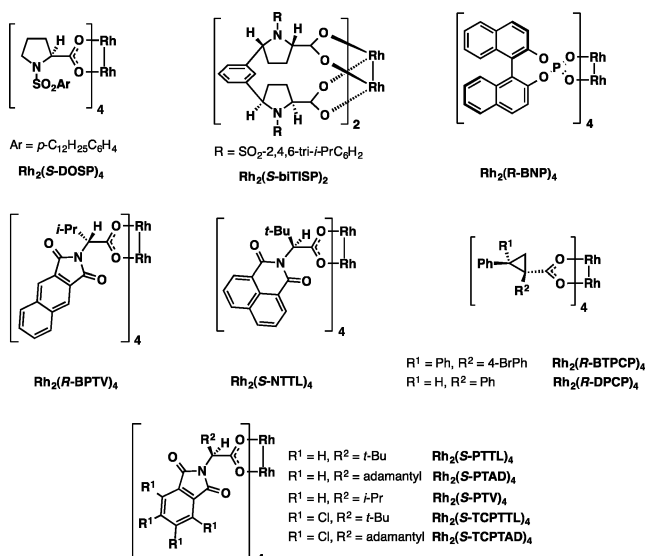


Figure 2. Chiral rhodium catalysts used in asymmetric C–H functionalization of 9, 11, and 22.

indeed a challenging substrate. To explore the C–O bond formation, substrate **15b** was prepared by aldol reaction between aldehyde **16** and ester methyl 2-(benzo[*d*][1,3]-dioxol-4-yl)acetate (99% yield, dr 12:1). After a partial separation of the *syn* and *anti* aldol products, the Pd-catalyzed oxidative cyclization to 2,3-dihydrobenzofuran was studied. Under the reported conditions,^{28,30} the pure *syn*-**15b** showed low reactivity, and only oxidation to keto ester **17** was observed. However, a mixture of *syn*-**15b** and *anti*-**15b** (~2:1) afforded *trans*-2,3-dihydrobenzofuran **24**, ketone **17**, and isomerically pure *syn*-**15b**.

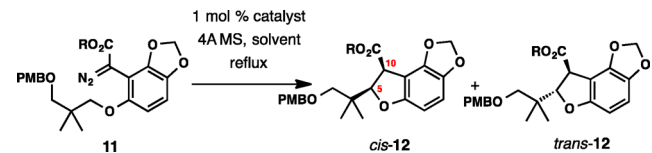
These outcomes suggest that, unlike *syn*-**15b**, *anti*-**15b** can potentially serve as a useful substrate for the synthesis of 2,3-dihydrobenzofuran **24** via oxidative C–H functionalization, provided it is accessible in an enantio- and diastereoselective fashion.

An approach based on a *trans*-annular cyclization was also assessed (Scheme 5). Nine-membered diazo lactone **19** was prepared from keto ester **18** in four steps. No CH insertion product **20** was observed upon treatment with Rh₂(OAc)₄, and only the corresponding keto lactone was isolated along with the recovered starting material.

In summary, among the catalytic asymmetric methods, the current results suggest that only the conversion of **9** to *cis*-**10** in the presence of Rh₂(S-PTTL)₄ at reflux in DCM (53% yield, 10:1 dr, 60% ee, Table 1, entry 8) could be considered for a potential application in the enantioselective total synthesis of **1**.

Auxiliary-Based Approaches. Chiral auxiliaries attached at the ester carbonyl group have been shown to be effective instruments for controlling stereochemistry in C–H functionalization reactions of diazo esters, with several applications in total synthesis.³¹ Our initial foray into the auxiliary-based methods began with menthol as the stereodirecting group, which was found to be ineffective. Significantly improved stereocontrol was achieved when pyrrolidine amides from lactic and mandelic acids were investigated. The preparation of the substrates from keto ester **18** was accomplished in four steps as illustrated in Scheme 6.

Diastereoselective C–H insertions with lactamide **22a** and mandelamide **22b** have been investigated with a selected group of catalysts under different reaction conditions. Although only the *cis*-**23a** and *cis*-**23b** are shown in Table 3, up to four diastereomeric products are produced in the reaction. To simplify analysis, the mixture of diastereomers was subjected to a rather facile methanolysis (CH₃ONa, CH₃OH, 23 °C, 5 min). Doing so also accomplishes complete isomerization at C10, giving only the *trans*-substituted product (**24**) in pure form, the enantiomeric excess of which was then measured by HPLC. The initial screening with Rh₂(R-DOSP)₄ catalyst revealed that CH₂Cl₂ was the optimal solvent, although the reactivity was lower in toluene and, especially, in cyclohexane (entries 4 and 8–10), whereas the use of acetonitrile resulted in decomposition. The diastereoselectivity was low in dichloroethane (entry 7). The catalysts Rh₂(S-PTAD)₄, Rh₂(R-PTAD)₄, and Rh₂(pfb)₄ were also unreactive (entries 1, 2, and 6). The highest yields and diastereoselectivities in the formation of **23a**

Table 2. Enantioselective C–H Insertion with Diazo Esters 11^a


entry	R	catalyst	solvent	yield % ^b	cis:trans	ee, cis (%)	ee, trans (%)
1	Me	Rh ₂ (S-PTTL) ₄	DMB	71	1.4:1	45	80
2	Me	Rh ₂ (S-PTTL) ₄	CHCl ₃	63	1.6:1	49	67
3	Me	Rh ₂ (S-PTTL) ₄	<i>c</i> -C ₆ H ₁₂	69	1.6:1	41	77
4	<i>t</i> -Bu	Rh ₂ (S-PTTL) ₄	DMB	55	3.0:1	<5	66
5	<i>t</i> -Bu	Rh ₂ (S-PTTL) ₄	CHCl ₃	28	3.0:1	<5	57
6	<i>t</i> -Bu	Rh ₂ (S-PTTL) ₄	<i>c</i> -C ₆ H ₁₂	70	3.5:1	23	59
7	Me	Rh ₂ (S-PTA) ₄	<i>c</i> -C ₆ H ₁₂	79	1.0:1	18	57
8	Me	Rh ₂ (R-PTV) ₄	<i>c</i> -C ₆ H ₁₂	76	1:1.1	~42	~78
9	Me	Rh ₂ (S-NTTL) ₄	<i>c</i> -C ₆ H ₁₂	74	2.2:1	29	56
10	Me	Rh ₂ (S-PTAD) ₄	<i>c</i> -C ₆ H ₁₂	79	1.4:1	41	54
11	Me	Rh ₂ (R-BPTV) ₄	<i>c</i> -C ₆ H ₁₂	76	1:1.1	~43	~80
12	Me	Rh ₂ (S-biTISP) ₄	<i>c</i> -C ₆ H ₁₂	78	1:1.4	~10	38
13	Me	Rh ₂ (S-BTPCP) ₄	<i>c</i> -C ₆ H ₁₂	65	3.8:1	~36	~11
14	Me	Rh ₂ (R-DPCP) ₄	<i>c</i> -C ₆ H ₁₂	74	1:1.1	19	~18
15	Me	Rh ₂ (S-DOSP) ₄	<i>c</i> -C ₆ H ₁₂	71	1.0:1	<5	7
16	Me	Rh ₂ (S-BNP) ₄	<i>c</i> -C ₆ H ₁₂	73	1.9:1	~19	~45
17	<i>t</i> -Bu	Rh ₂ (S-BTPCP) ₄	<i>c</i> -C ₆ H ₁₂	77	2.8:1	42	63
18	<i>t</i> -Bu	Rh ₂ (S-biTISP) ₂	<i>c</i> -C ₆ H ₁₂	77	2.5:1	~46	46
19	<i>t</i> -Bu	Rh ₂ (S-BNP) ₄	<i>c</i> -C ₆ H ₁₂	83	3.3:1	13	24

^aDiastereomer ratios determined by ¹H NMR analysis of crude reaction mixture. Enantiomeric excesses were determined by HPLC analysis.^bCombined isolated yield of *cis*-12 and *trans*-12.

were first observed with both Rh₂(S-DOSP)₄ and Rh₂(R-DOSP)₄ (entries 3 and 4). After methanolysis, the same enantiomer of **24** was produced from both catalysts in 62 and 70% ee, respectively. The use of the simple achiral catalyst Rh₂(OAc)₄ led to comparable results, giving **24** in 65% ee in good yield (entry 5). Further improvements were achieved with mandelamide substrate **22b**. Although the enantiomeric purity of the final methanolysis product **24** was somewhat lower with Rh₂(S-DOSP)₄ and Rh₂(R-DOSP)₄ (entries 11 and 12), dirhodium tetraacetate provided **24** in 76% ee.

The optimal enantiomeric purity of 84% ee was obtained from **22b** with Rh₂(OAc)₄ after a careful chromatographic purification of the major diastereomer, which prevented erosion of enantiomeric purity upon methanolysis (entry 14). Overall, this result provided a practical entry point to enantioenriched 2,3-dihydrobenzofuran **24** for application in the total synthesis of maoecrystal V.³²

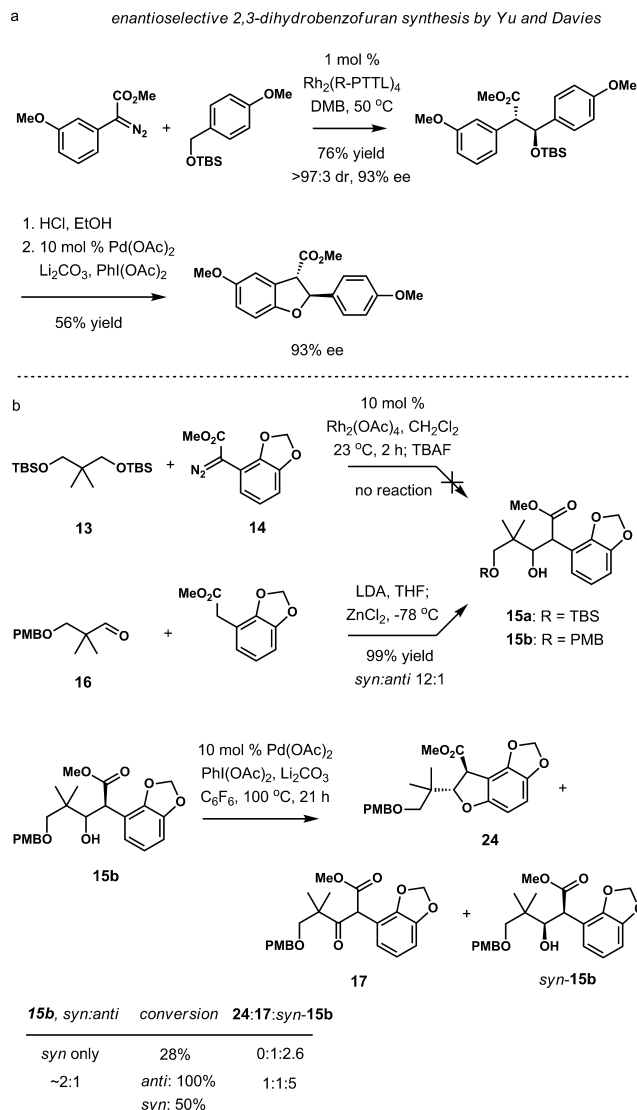
Investigation of the IMDA Reaction. As illustrated in Schemes 1 and 2, a key reaction en route to **1** is the formation of the bicyclo[2.2.2]octan-2-one subunit by an IMDA addition.³³ We intended to pursue a tether-based delivery of ethylene as a dienophile in the IMDA reaction. The range of tether groups that we considered for this purpose is indicated in Figure 3. Among constraints placed on the tether groups for the total synthesis applications are (1) efficient installation, (2) capacity to enable a high-yielding IMDA process, and (3) efficient removal, ideally solved in one step. We previously described preliminary studies that targeted compounds **25a–c**.³⁴ Although they have been very informative in validating the IMDA approach, the third constraint was not fulfilled as the tether removal from compounds **25a–c** required several steps at best and was deemed inefficient.

The butyl boronate (**25d**) and dimethylsilyl tethers (**25e**) appeared to be more promising. We were especially intrigued by the boronate tether because it has limited application in the context of total synthesis and promised the development of new chemistry during the course of its removal.³⁵ With the goal of exploring the boronate tether, the synthesis of the substrate (**29**) was initiated by the benzyloxymethylation of *trans*-**10** (Scheme 7). Within our previous experience, the enolate alkylation was consistently best performed through the intermediacy of the zincate enolate.³⁶ Alkylation product **26** was produced in 95% yield as a single isomer. Reduction of the methyl ester with LiAlH₄ was followed by elaboration of the dioxolane ring in **27** by the action of methylmagnesium bromide at 80 °C in benzene, which delivered 2-ethoxy phenol **28** in 91% yield over the 2 steps. A rapid oxidation of the phenol with PhI(O₂CCF₃)₂ in ethanol (15 min, 94% yield) provided the substrate for the IMDA reaction.

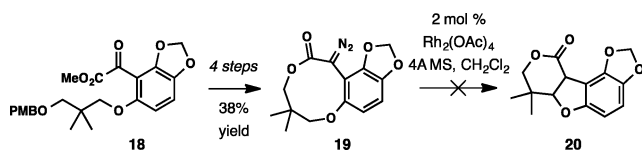
Vinylboronate **30a** was generated from **29** and commercially available vinylboronic acid dibutyl ester in situ through a facile exchange reaction. Upon heating at 130 °C in *o*-dichlorobenzene, a new product was formed in 72% yield in a rather clean reaction. Contrary to our expectations, the product was not the direct IMDA addition product **25d** but appeared to lack the boronic ester group. Based on NMR studies of the product, including NOE and homodecoupling experiments, our initial hypothesis was that we fortuitously obtained protodeboronation product **32** (Scheme 7), which is well suited for our synthesis plans. However, the true identity of the product has only been conclusively deduced after completion of the total synthesis, which revealed that the product (**31**) contained the rearranged bicyclo[3.2.1]octan-7-one ring system (*vide infra*).

Several reaction pathways can be considered for the formation of **31** from **30a**. Although details are not clear at

Scheme 4



Scheme 5



present, our current hypothesis favors the simplest path and involves the initial formation of [4+2] cycloadduct **25d**. Proton transfer to enol ether **25d** forms a stabilized oxycarbenium ion **30b**. The 1,2-shift of the acyl group, which should be further facilitated by the properly aligned carbon—boron bond, leads directly to deborylation product **30c**. After hydrolytic workup, the final product **31** with a free hydroxyl is isolated. An alternative, more complex pathway is depicted in Scheme 8. Here, the first step is an admittedly speculative and, as far as we know, unprecedented formation of cyclopropanol intermediate **33** from the initial [4+2] cycloadduct **25d**. This apparent intramolecular nucleophilic attack of an alkylboronate on the carbonyl group is possibly aided by a secondary overlap between the $\pi_{C=O}$ and σ^*_{C-B} bonds. The resulting enol ether in **33** should be particularly susceptible to protonation because

Scheme 6

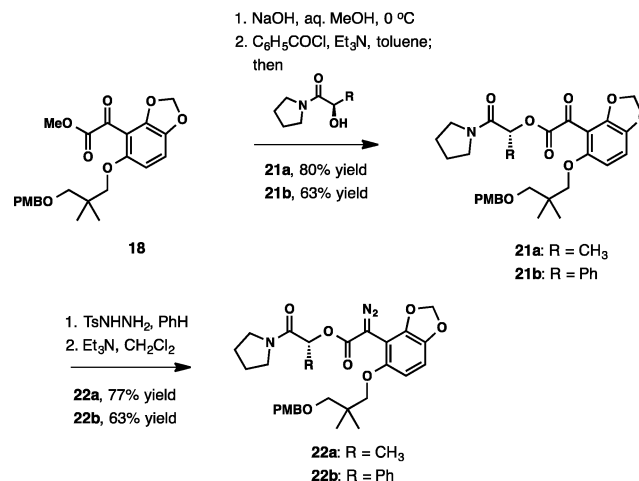
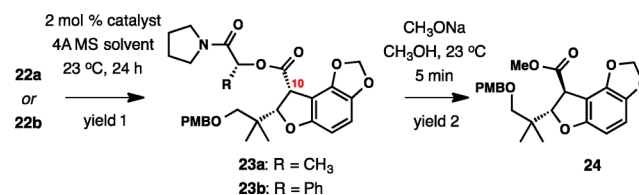


Table 3. Lactamide and Mandelamide as Chiral Auxiliaries



entry	starting material	catalyst	solvent	yield 1 (%) ^a	yield 2 (%) ^b	ee % ^c
1	22a	Rh ₂ (S-PTAD) ₄	CH ₂ Cl ₂	<10		
2	22a	Rh ₂ (R-PTAD) ₄	CH ₂ Cl ₂	<10		
3	22a	Rh ₂ (S-DOSP) ₄	CH ₂ Cl ₂	63	83	62
4	22a	Rh ₂ (R-DOSP) ₄	CH ₂ Cl ₂	74	86	70
5	22a	Rh ₂ (OAc) ₄	CH ₂ Cl ₂	84	84	65
6	22a	Rh ₂ (O ₂ CC ₄ F ₉) ₄	CH ₂ Cl ₂	0		
7	22a	Rh ₂ (R-DOSP) ₄	(CH ₂ Cl) ₂	72		
8	22a	Rh ₂ (R-DOSP) ₄	PhMe	61		
9	22a	Rh ₂ (R-DOSP) ₄	<i>c</i> -C ₆ H ₁₂	<10		
10	22a	Rh ₂ (R-DOSP) ₄	CH ₃ CN	0		
11	23b	Rh ₂ (S-DOSP) ₄	CH ₂ Cl ₂	84	89	59
12	23b	Rh ₂ (R-DOSP) ₄	CH ₂ Cl ₂	57	77	52
13	23b	Rh ₂ (OAc) ₄	CH ₂ Cl ₂	72	85 ^c	76
14	23b	Rh ₂ (OAc) ₄	CH ₂ Cl ₂	61 ^d	84	84

^aIsolated yield. ^bCombined isolated yield. ^cIsolated yield, complete isomerization to the *trans* isomer observed. ^dMajor diastereomer isolated in pure form by column chromatography. ^eDetermined by HPLC.

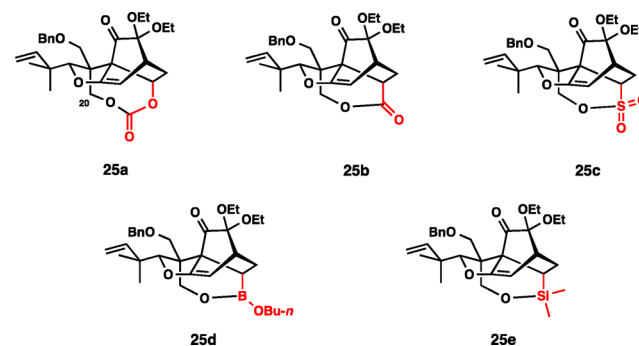
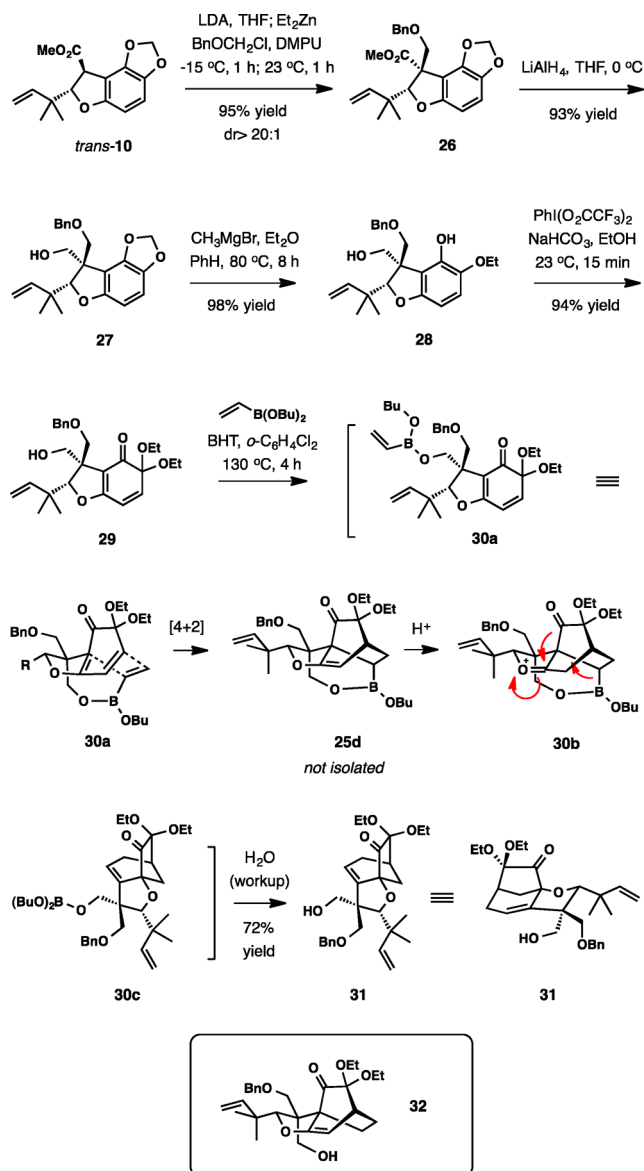
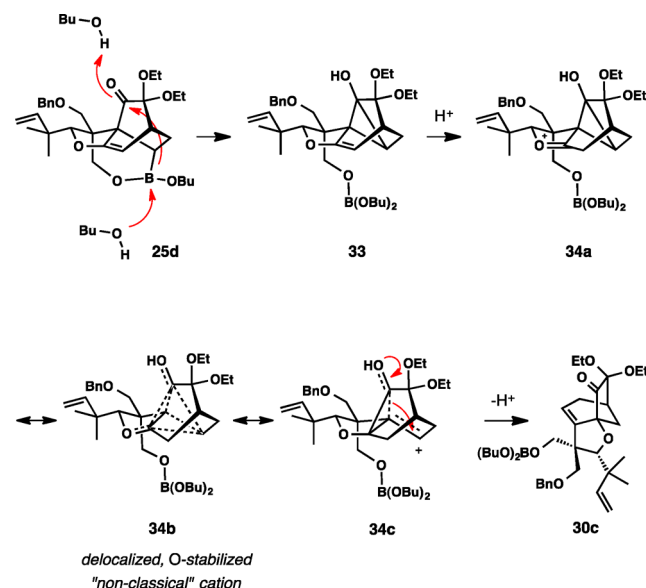


Figure 3. Potential products of the key IMDA reaction considered for the total synthesis of maoecrystal V.

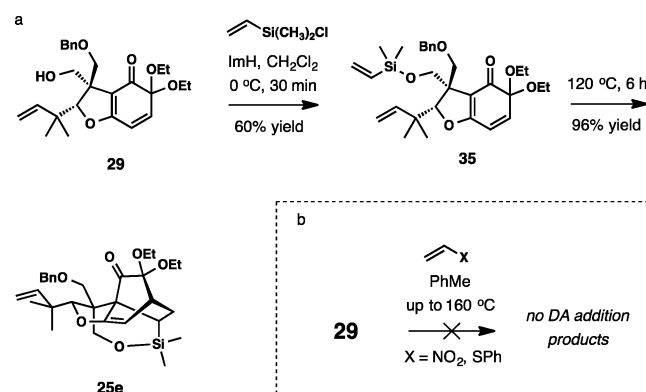
Scheme 7



Scheme 8



Scheme 9



of the strong stabilizing effect of the adjacent cyclopropanol substituent, which should give a highly stabilized nonclassical carbocation represented by resonance forms **34a**, **34b**, and **34c**. Its deprotonation affords **30c** directly.³⁷

Evaluation of the silicon tether began with silylation of intermediate **29** with dimethylvinylchlorosilane (Scheme 9a). The IMDA reaction of silyl ether **35** took place smoothly upon heating at 120 °C for 6 h, giving the intended product in an excellent 96% yield.

An intermolecular variant of Diels–Alder reaction with two dienophiles, nitroethylene and vinyl phenyl sulfide,³⁸ was also examined for the construction of the bicyclo[2.2.2]octan-2-one ring system of maoecrystal V (Scheme 9b). If successful, the nitro or phenylthio group could be removed by reduction under radical conditions.³⁹

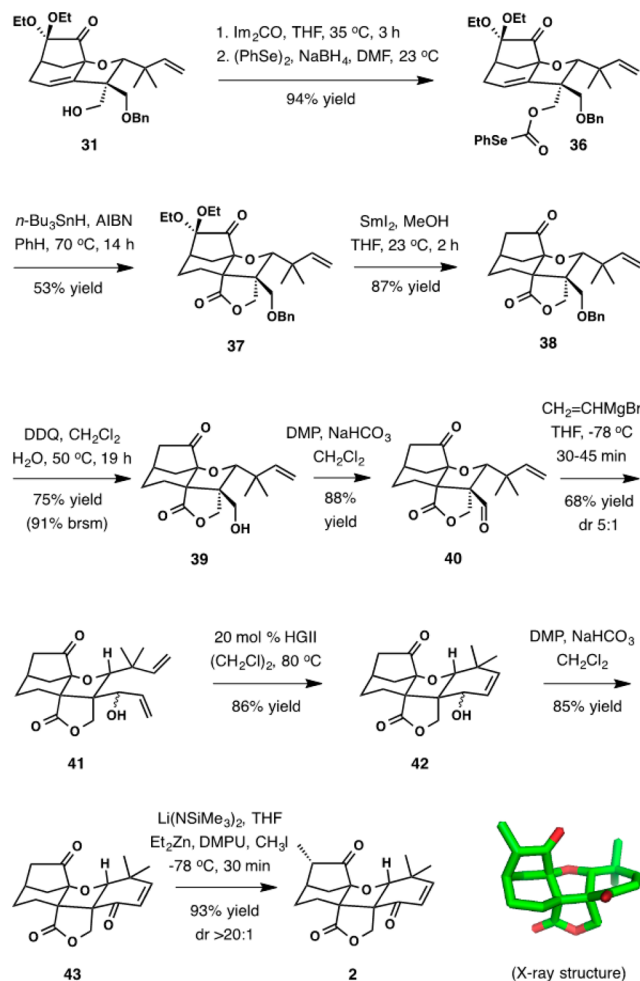
The principal lessons that we drew from these studies are (1) the IMDA reactions with the boron and silicon tethers were the most valuable in meeting our synthetic needs, albeit giving drastically different outcomes, and (2) intermolecular Diels–

Alder reactions with nitroethylene and vinyl phenyl sulfide as ethylene equivalents did not appear to be promising.

Total Synthesis of Maoecrystal ZG (2). Even with some uncertainty whether compound **32** was the product of the reaction between cyclohexadienone **29** and dibutyl vinylboronate, the synthesis was advanced as delineated in scheme 10. In retrospect, it became clear that the actual product was in fact **31**. Formation of the lactone by radical cyclization was set up by the efficient conversion of **31** to phenyl selenocarbonate **36** in 94% yield. Lactone **37** formed readily upon treatment of **36** with tri-*n*-butyltin hydride in the presence of AIBN at reflux in benzene, requiring little optimization (53% yield). Minor reduction to the corresponding formate was also observed (~5%), in addition to other unidentified byproducts. At this stage the *gem*-ethoxy substituents were removed by reduction with samarium(II) iodide in the presence of methanol (87% yield). Cleavage of the benzyl ether was achieved under forcing conditions upon heating at 50 °C with DDQ, which afforded primary alcohol **39** in 75% yield along with recovered starting material.

The final phase of the synthesis began with oxidation of **39** to aldehyde **40** with Dess–Martin periodinane (DMP) (88% yield) followed by chemoselective addition of vinylmagnesium bromide to aldehyde in the presence of the lactone and ketone groups (68% yield, dr 5:1). Ring-closing metathesis in the

Scheme 10



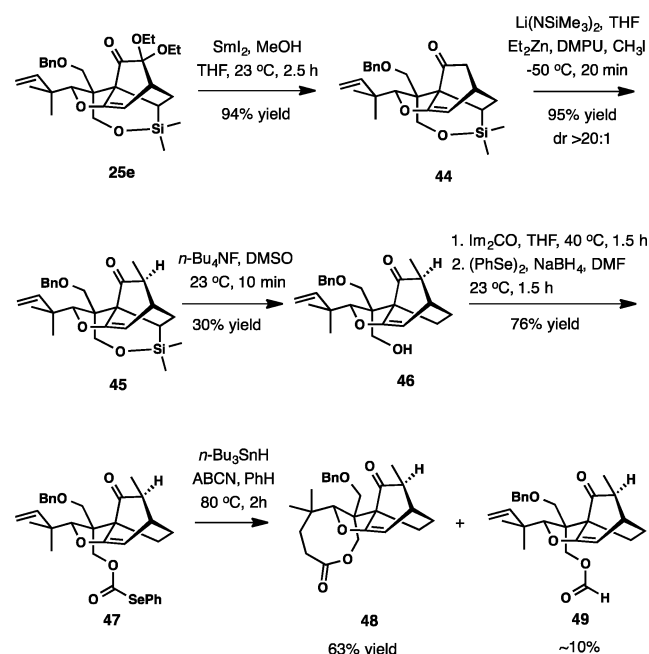
presence of 20 mol % Hoveyda-Grubbs II catalyst (HGII) accomplished the formation of the last ring of the target compound in 86% yield. The resulting product was oxidized to enone **43** with DMP in 85% yield. In the final step, methylation of zincate enolate generated from **43** with $\text{LiN}(\text{SiMe}_3)_2$ and Et_2Zn occurred in excellent yield and essentially complete diastereocontrol. NMR data of the final product did not match those published for maoecrystal V, which prompted X-ray crystallographic analysis of the product. A single crystal suitable for analysis was produced by crystallization of the compound from ethyl acetate and hexane. The XRD analysis revealed the fascinating, unexpected structure **2**, which we refer to as maoecrystal ZG. Its origin was traced to **31**, the product of the unusual reaction between cyclohexadienone **29** and dibutyl vinylboronate, and allowed for unambiguous assignment of its structure.

Although falling short of completing the total synthesis of **1**, this effort resulted in several important contributions. First, the efficient conversion of cyclohexadienone **29** to **31** in the presence of vinylboronic esters is of fundamental interest and provides an effective entry to functionalized bicyclo[3.2.1]-octan-6-one ring systems. Second, maoecrystal ZG, an isomer of **1**, appears to be a new natural-product-like chemical entity. Its pentacyclic 6,7-dinor-5,8;9a,20-diepoxy-*ent*-kaurane skeleton appears to have no precedent among natural products or other known organic compounds. Given its fairly efficient synthesis in 18 straightforward steps and ~4% overall yield from sesamol,

over 10 mg was produced after the first effort, an amount sufficient for a preliminary biological evaluation of **2**.

Enantioselective Total Synthesis of (–)-Maoecrystal V (1). Given the unforeseen creation of **2**, the approach to maoecrystal V had to be reevaluated. The success was eventually achieved through the use of the silyl tether in the key IMDA reaction (cf. **25e**, Scheme 9). The initial incursion entailed desilylation of **25e**, which turned out to be challenging. During the course of our work we found it to be advantageous to carry out the removal of the *gem*-ethoxy substituents and enolate methylation first. In the event, treatment of **25e** with SmI_2 and subsequent exposure of the zincate enolate from **44** to CH_3I provided intermediate **45** (Scheme 11). Its elaboration

Scheme 11

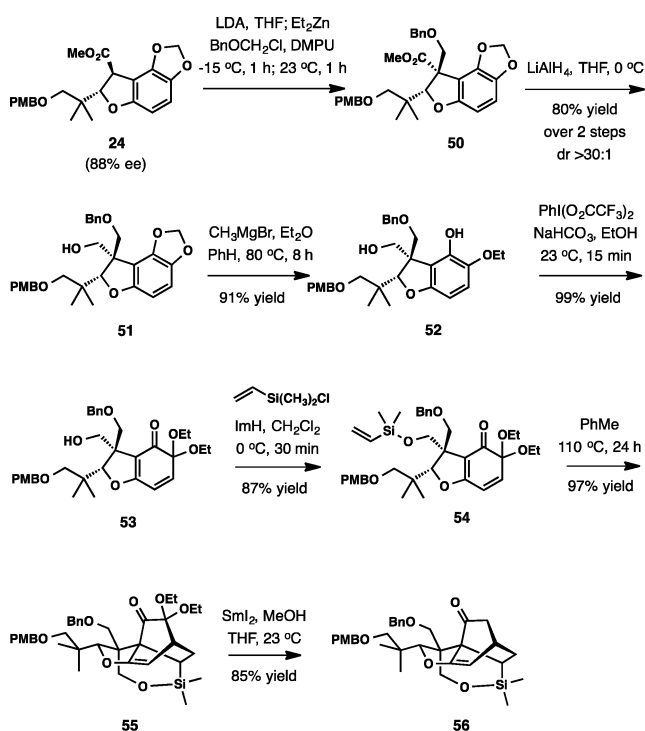


to selenocarbonate **47** was followed by radical cyclization upon treatment with $n\text{-Bu}_3\text{SnH}$ and azobis(cyclohexanecarbonitrile) (ABCN) at 80 °C in benzene. Surprisingly, eight-membered lactone **48** was the major product, which was produced in addition to ~10% of formate **49**. None of the expected six-membered lactone formed by cyclization of the acyl radical onto the enol ether was observed.

After exploring alternatives, a decision was made to set the synthesis back to *p*-methoxybenzyl ether **24** that lacks the terminal olefin competing in the radical cyclization (Scheme 12). Starting with enantioenriched **24** (84% ee), the synthesis followed the same blueprint through the IMDA reaction. The lithium enolate generated from **24** was successively treated with Et_2Zn and $\text{BnOCH}_2\text{Cl}/\text{DMPU}$, affording **50** in 20:1 dr. Reduction of the methyl ester, dioxolane cleavage, phenol oxidation, and silylation with vinyltrimethylchlorosilane provided the precursor of the IMDA reaction **54**. In accord with the previous experience, its clean conversion to [4+2] adduct **55** was achieved after heating in toluene at 110 °C for 24 h, which was followed by reductive removal of the two geminal ethoxy groups with samarium(II) iodide.

Desilylation of **56** and related [4+2] cycloadducts was complicated by competing formation of rearranged products **b** and **c** (Table 4). The reaction was studied in greater detail to

Scheme 12



optimize the yield of the requisite product **a**. The initial attempts focused on screening solvents using *n*-Bu₄NF as the reagent (entries 1–11). These studies revealed that the ratio of the three products was significantly influenced by the choice of solvent. Low reactivity was observed in protic solvents. Among the polar aprotic solvents, DMPU emerged as the optimal medium to maximize the fraction of the requisite product **a** (entry 8). Tetrabutylammonium triphenyldifluorosilicate, a milder desilylation reagent, strongly favored rearranged product **b** (entry 13), or showed no reactivity in *tert*-butanol (entry 14), as did cesium fluoride (entry 12). These data indicate that a balance between the pH and reactivity is needed to achieve the desired outcome in the desilylation reaction.

We also found that carrying out desilylation immediately after the IMDA reaction before removal of the *gem*-ethoxy substituents (*X* = OEt) was less efficient than postremoval desilylation (entries 15–18, *cf.* entries 15 and 18). The presence of the ethoxy groups favored the formation of rearranged byproduct to a greater extent.

Finally, desilylation of the selected total synthesis intermediate **56** (*X* = H, *Y* = H, OPMB, entry 20, Table 4) was best accomplished upon treatment with tetrabutylammonium fluoride at 0 °C for 1 h, which afforded the desired product in 50% yield. It is noteworthy that the desilylation was greatly activated by the C15 carbonyl group. The reactivity of the corresponding C15 alcohol was substantially lower, requiring heating at 80 °C for 12 h for the reaction to reach completion.

Table 4

entry	X	Y	reagent solvent	temp (°C), time (h)	a:b:c ^a (yield, a)
1	H	H, OBn	Bu ₄ NF, DMSO	0, 0.2	1.0:1.8:1 (20%)
2	H	H, OBn	Bu ₄ NF, DMSO	23, 0.2	0.9:1.5:1
3	H	H, OBn	Bu ₄ NF, DMF	–20, 2	1.5:1.3:1
4	H	H, OBn	Bu ₄ NF, DMF	0, 0.5	2.3:1.8:1
5	H	H, OBn	Bu ₄ NF, DMF	23, 0.3	1.9:1.6:1
6	H	H, OBn	Bu ₄ NF, DMF, (slow addition)	23, 3.2	1.6:1.3:1
7	H	H, OBn	Bu ₄ NF, NMP	0, 1.0	1.4:1.7:1
8	H	H, OBn	Bu ₄ NF, DMPU	0, 1.0	3.2:1.8:1
9	H	H, OBn	Bu ₄ NF, DMA	0, 0.5	2.4:1.7:1
10	H	H, OBn	Bu ₄ NF, DMSO– <i>t</i> -BuOH (4:1)	75, 1	0.3:1.2:1
11	H	H, OBn	Bu ₄ NF, AcOH, THF	0, 1.0	no reaction
12	H	H, OBn	CsF, <i>t</i> -BuOH	70, 15	no reaction
13	H	H, OBn	Bu ₄ NPh ₃ SiF ₆ , DMSO	50, 36	0:20:1
14	H	H, OBn	Bu ₄ NPh ₃ SiF ₆ , <i>t</i> -BuOH	50, 15	no reaction
15	OEt	CH ₂	Bu ₄ NF, DMF	23, 0.2	0.8:5.1:1 (7%)
16	OEt	CH ₂	Bu ₄ NF, THF	23, 0.5	no reaction
17	OEt	CH ₂	Bu ₄ NF, MeCN	23, 0.2	0:3.4:1
18	H	CH ₂	Bu ₄ NF, DMF	23, 0.5	1.1:3.6:1
19	H	H, OPMB	Bu ₄ NF, DMA	0, 1.0	2.9:2.2:1
20	H	H, OPMB	Bu ₄ NF, DMPU	0, 1.0	3.2:1.9:1 40–50%

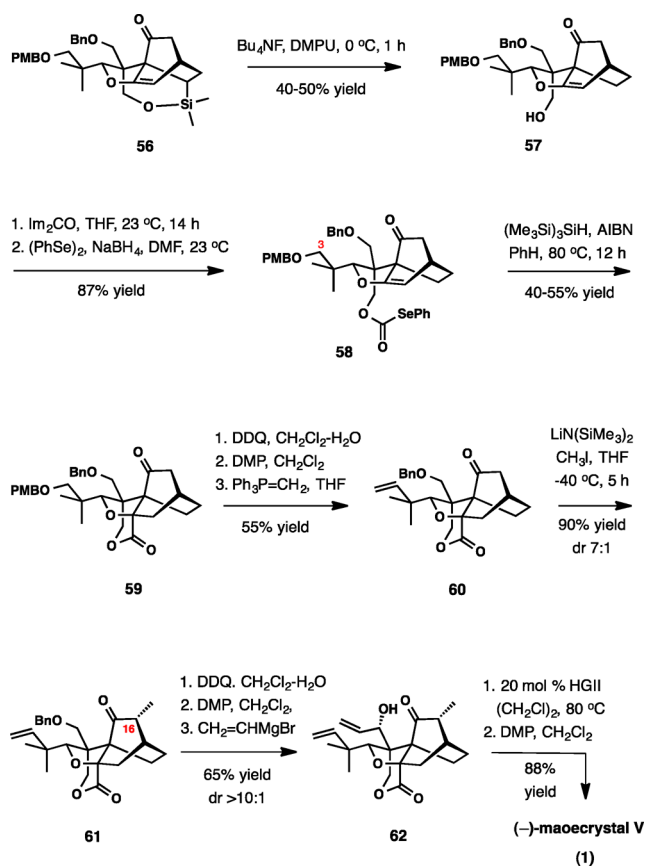
^aDetermined by NMR analysis of the crude mixture of products. Isolated yield of **a** is given in parentheses.

No improvement in the chemical yield was observed with the reduced substrate.

There are some noteworthy similarities in the results of the desilylation reaction in Table 4 and the proposed formation of **30c** depicted in Scheme 8. In particular, the structures of cyclopropanol byproduct **c** in Table 4 and intermediate **33** (Scheme 8) are very similar. Both appear to be unstable and readily converted to distinct bicyclo[3.2.1]octan-6-one derivatives **b** (Table 4) or **30c** (Scheme 8), respectively, although the reasons for the divergent reactivity of the cyclopropanol intermediates are not clear.

The next immediate goal after desilylation of **56** was introduction of the six-membered lactone by radical cyclization onto enol ether, with regioselectivity opposite to its electronic preferences (Scheme 13). This is a relatively uncommon

Scheme 13



transformation with only a few examples reported in the literature.⁴⁰ In our case, only one regiochemical outcome is possible due to structural constraints within the starting material. In the current substrate, selenocarbonate **58**, the 4-methoxybenzyloxy substituent at C3 replaces the terminal double bond to avoid competitive cyclization onto eight-membered lactone, the reactivity mode overwhelmingly favored for selenocarbonate **47** (Scheme 11).

In analogy to selenocarbonate **47**, the initial attempts at the radical cyclization of **58** utilized the *n*-Bu₃SnN/AIBN reagent system under various conditions. The results were disappointing. Although the acyl radical was clearly generated, the rate of the 6-*exo*-cyclization onto the enol ether was very low in comparison to its reduction to the corresponding formate ester, which occurred in up to 84% yield. To reduce the rate of

hydrogen abstraction by the acyl radical, and thus favor the cyclization, we investigated tris(trimethylsilyl)silane as a replacement for *n*-Bu₃SnH.⁴¹ An immediate improvement was observed, apparently due to the longer lifetime of the acyl radical. Under optimized reaction conditions, the isolated yields of the desired lactone **59** were in the range of 40 to 55%. Notably, the main side product in this reaction results from decarboxylative fragmentation of the acyl radical rather than its reduction to the formate.²¹

The final phase of the total synthesis began with a three-step conversion of **59** to alkene **60** by oxidative removal of the PMB ether with DDQ, oxidation of the primary alcohol with Dess–Martin periodinane (DMP), and Wittig methylenation (55% yield over three steps). Diastereoselective installation of the methyl group at C16 has been problematic in the previously reported total syntheses of **1**.^{19,20} With ketone **60** as the substrate, α -methylation at C16 was accomplished with 7:1 diastereoselectivity in excellent yield. If this alkylation reaction is postponed until the last step after installation of the cyclohexenone, a 1:1 mixture of diastereomers is produced. Also, when LDA is used in place of LiN(SiMe₃)₂ for enolate generation, substantially lower yields of **61** were observed due to unidentified side reactions.

Oxidative cleavage of the benzyl ether (**61**) was accomplished in the presence of DDQ in aqueous dichloromethane at 50 °C for 12 h. Oxidation with DMP followed by the addition of vinylmagnesium bromide in the presence of CeCl₃ afforded allylic alcohol **62** as a single diastereomer in 65% overall yield after the three steps. Ring-closing metathesis (20 mol % Hoveyda–Grubbs II catalyst, 1,2-dichloroethane, 80 °C, 3 h) afforded a mixture of the expected allylic alcohol along with the oxidation product, (–)-maoecrystal V. A full oxidation of the mixture with DMP completed the enantioselective synthesis of **1**, affording 10 mg of the natural products: [α]_D²⁵ –101.1° (*c* 0.3, CH₃OH); lit.⁶ [α]_D²⁵ –92.9° (*c* 0.7, CH₃OH).

Investigation of Antiproliferative Properties of Maoecrystal ZG (2). Maoecrystal V (**1**) has shown potent and selective cytotoxic activity against the HeLa cell line, with activity for K562, A549 lung carcinoma, and BGC-823 adenocarcinoma reduced by at least 6 orders of magnitude. Because maoecrystal ZG (**2**) and the artificial structural isomer of **1** retain the electrophilic cyclohexenone moiety of the natural product and apparently represent a novel chemical entity, we explored its cytotoxic properties with the assistance of the NCI-60 DPT human tumor cell line screen. Somewhat remarkably, **2** showed virtually no growth inhibition at 10 μ m concentration across the entire cell panel, underscoring the remarkable cytotoxicity profile of maoecrystal V.

CONCLUSION

The first enantioselective synthesis of (–)-maoecrystal V was enabled by a stereoselective Rh-catalyzed C–H functionalization as the enantiodetermining step. This reaction provided the key 2,3-dihydrobenzofuran precursor in 84% ee. Catalytic asymmetric and auxiliary-enabled approaches have been investigated. Although both proved promising, the auxiliary-based approach was ultimately used because it performed best in the presence of functional groups necessary for the total synthesis application. The synthesis required 26 linear steps from sesamol (three steps longer than our synthesis of racemic **1**), affording (–)-maoecrystal V in ~0.21% overall yield.

An unexpected course of the IMDA reaction with a tethered vinylboronate led to the initial synthesis of an isomeric product,

which we refer to as maoecrystal ZG (2). This compound has a rearranged pentacyclic 6,7-dinor-5,8,9a,20-diepoxy-*ent*-kaurane skeleton that apparently has no precedent in the realm of natural products, or in fact of any known organic compounds. Evaluation of its cytotoxic activity in the NCI 60 cell panel revealed no growth inhibition across the entire panel, underscoring the unique and selective activity of maoecrystal V itself, which displays selective nanomolar activity against the HeLa cell line.

The expected outcome of the central IMDA reaction using a silicon tether provided the bicyclo[2.2.2]octan-2-one ring system, thus enabling the successful completion of the enantioselective total synthesis of (–)-maoecrystal V, which confirmed the assignment of its absolute stereochemistry.

■ ASSOCIATED CONTENT

■ Supporting Information

Detailed experimental procedures, characterization data, copies of ¹H and ¹³C NMR spectra, HPLC traces, and a crystallographic CIF file. 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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