Studies toward the Synthesis of Maoecrystal V
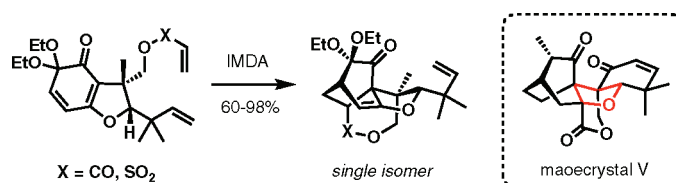
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ABSTRACT

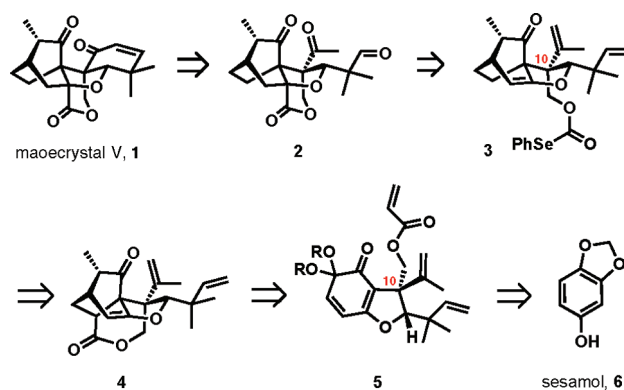X = CO, SO$_2$ single isomer   maoecrystal V

An approach toward the synthesis of maoecrystal V is described. The synthetic strategy for this approach was designed to address unique challenges posed by the strained tetrahydrofuran ring at the center of the target structure.

Maoecrystal V is a densely functionalized C$_{19}$ diterpenoid containing five highly congested rings and seven stereogenic centers, including two adjacent quaternary centers (**1**, Scheme 1). By far the most modified naturally occurring *ent*-kauranoid from *Isodon* species, it was isolated and characterized by Sun and co-workers in 2004.[1] Maoecrystal V exhibits selective cytotoxicity against HeLa cells (IC$_{50}$ = 0.02 μg/mL) and virtually no inhibitory activity against K562, A549, BGC-823, and CNE cells.

While the quaternary sterocenters clearly constitute a significant challenge associated with the synthesis of maoecrystal V, it is the central tetrahydrofuran ring that became the focus of attention in formulating our strategy. The five-membered heterocyle is flanked on both sides by *trans*-fused six-membered rings, which creates notable ring strain that contributes to difficulties in its construction. As a

Scheme 1. Synthesis Plan for Maoecrystal V

maoecrystal V, **1**   **2**   **3**

4   **5**   sesamol, **6**

testament to this analysis, many research groups provided successful solutions to the installation of the adjacent quaternary centers, yet the formation of the tetrahydrofuran ring remained unresolved.[2] Recently, Yang and co-workers completed the synthesis of racemic maoecrystal V by an intramolecular Diels−Alder (IMDA) reaction that in one event forms the central tetrahydrofuran and the bicyclo[2.2.2]octane ring systems.[3] The IMDA reaction is preceded by a Wessely oxidative dearomatization, and
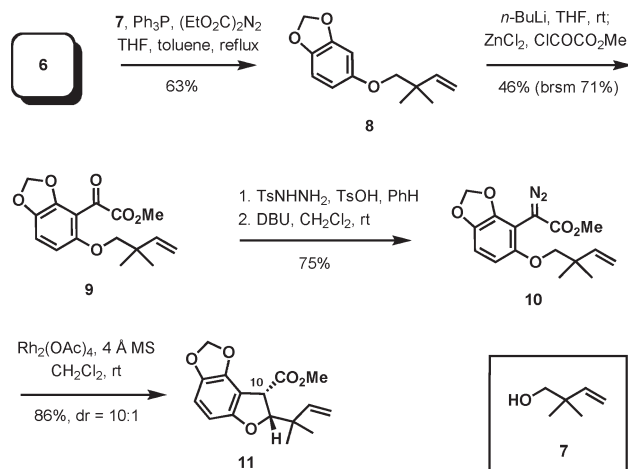
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Scheme 2

Scheme 3

although it suffers from poor facial selectivity, it does provide a successful synthetic path to (±)-**1**.

The synthesis plan depicting our approach is outlined in Scheme 1. This plan features an early installation of the tetrahydrofuran ring followed by an intramolecular Diels−Alder reaction with an *o*-quinone subunit to construct the bicyclo[2.2.2]octane ring system incorporating a potentially sensitive enol ether.[4] The enol ether is intended to serve as a radical acceptor for the eventual assembly of the six-membered lactone.[5] The synthesis will be concluded by the formation of the cyclohexenone via intramolecular aldol cyclization of ketoaldehyde **2**.[6] Sesamol (**6**) was identified as the starting material for synthesis of IMDA reaction substrate **5**. Lability of the enol ether in intermediates such as **3** and **4** was of concern during the design stages of this investigation.

Alkylation of sesamol with hindered neopentylic alcohol **7**[7] was carried out under the Mitsunobu conditions in 63% yield (Scheme 2).[8] *ortho*-Metalation of **8** with *n*-butyllithium in THF at room temperature followed by transmetalation with zinc chloride to the corresposnding arylzinc chloride reagent and coupling with methyl chloroxoacetate delivered ketoester **9** in 46% yield along with
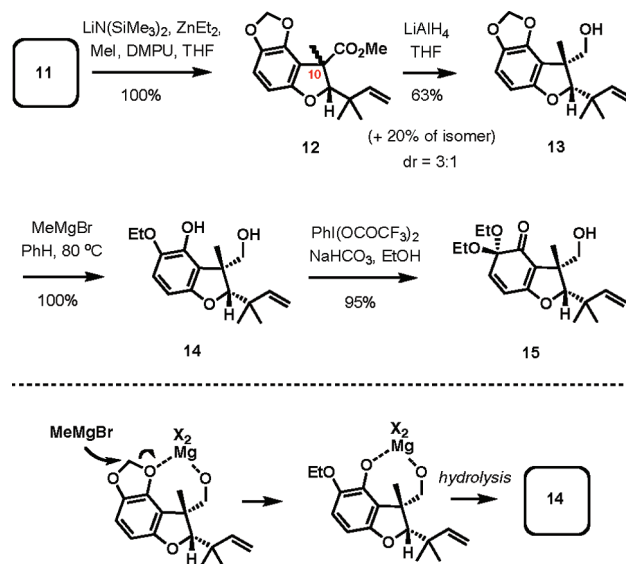
the recovery of 25% of the starting material.[9] The α-ketoester was advanced to α-diazoester **10** by a two-step process involving the intermediacy of the tosylhydrazone generated from **9** and its fragmentation under basic conditions (DBU) in CH$_2$Cl$_2$ at room temperature.[10]

Diazoester **10** served as a substrate for the formation of requisite benzofuran **11** by an intramolecular C−H functionalization process. Exposure of **10** to a catalytic amount of rhodium acetate (1 mol %) in carefully degassed dry CH$_2$Cl$_2$ in the presence of 4 Å molecular sieves resulted in a clean transformation affording **11** in 86% yield with 10:1 diastereoselectivity.[11,12]

In order to explore the feasibility of the IMDA process that forms the basis of our synthesis plan, we chose to introduce a methyl substituent at the C10 position as a mimic of the related quaternary center in the natural product. Thus, for the purposes of this study, the zincate enolate generated from ester **11** by enolization with LiN-(SiMe$_3$)$_2$ and addition of diethylzinc was treated with iodomethane in the presence of DMPU, affording the alkylation product in quantitative yield as an inseparable mixture of diastereomers (3:1, Scheme 3).[13] Methylation using a more standard procedure without the addition of diethylzinc (LiN(SiMe$_3$)$_2$, THF) afforded less than 10% yield of the desired product and was complicated by the formation of intractable mixture of products. Upon

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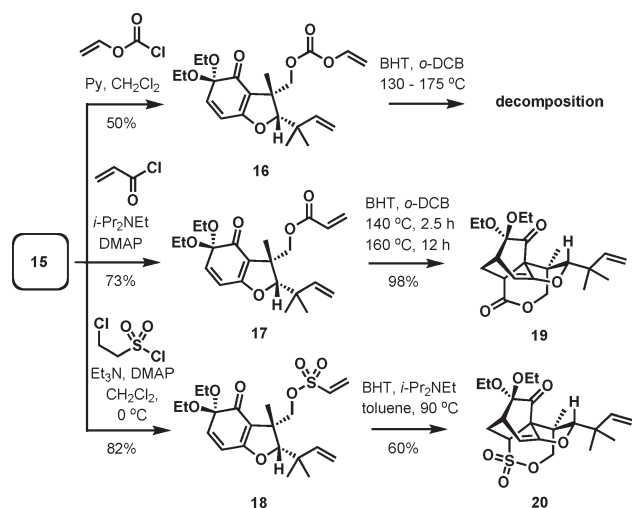
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Scheme 4

reduction of the ester with lithium aluminum hydride, the diastereomers could be separated by column chromatography and alcohol **13** was isolated in 63% yield. Initial attempts at removal of the methylidene group from the catechol using Pb(OAc)$_4$−AcOH[14] or BBr$_3$ were unproductive;[15] however, treatment of **13** with methylmagnesium bromide (6 equiv) in benzene at reflux afforded the desired monoprotected catechol derivative (**14**) as a single regioisomer in a quantitative yield.[16] The high regioselectivity can be attributed to the directing affect of the primary hydroxyl group in addition to steric effect considerations.

Oxidative dearomatization of **14** with PhI(O$_2$CCF$_3$)$_2$ in ethanol readily afforded protected *o*-quinone **15** that exhibited sufficient stability to be suitable for further studies.[17]

A set of substrates for the IMDA cyclization study was prepared as illustrated in Scheme 4. Vinyl carbonate **16**, acrylate **17**, and vinylsulfonate **18** were prepared in good yields by treatment of **15** with vinyl chloroformate, acryloyl chloride, and 2-chloroethanesulfonyl chloride, respectively. Heating of vinyl carbonate **16** in 1,2-dichlorobenzene (*o*-DCB) at temperatures in the range 130−175 °C

in the presence of 2,6-di-*tert*-butyl-2-methylphenol (BHT) only led to decomposition if any conversion was observed. In contrast, thermal activation of acrylate **17** (160 °C, *o*-DCB) resulted in an efficient cycloaddition affording lactone **19** in an essentially quantitative yield.[18] Notably, compound **19** containing the enol ether functionality was stable to silica gel chromatography and showed no decomposition upon storage at room temperature for several days, documenting its feasibility for an eventual elaboration to maoecrystal V. Treatment of vinyl sulfonate **18** as a solution in toluene or *o*-DCB at ∼90 °C in the presence of BHT resulted in decomposition, and no cycloaddition product could be detected. We hypothesized that a trace amount of acid resulting from exposure of **20** to elevated temperatures could lead to decomposition of the initially formed product. This could be prevented by buffering the reaction medium with a base, and indeed, when **18** was heated at 90 °C in toluene in the presence of BHT and *i*-Pr$_2$NEt, the cycloaddition product was isolated in 60% yield. As with **19**, enol ether **20** displayed excellent stability to silica gel chromatography and storage.

In conclusion, we reported our progress toward the synthesis of maoecrystal V. Preparation and stability of advanced tricyclic enol ether intermediates **19** and **20** was evaluated. The synthesis features a rhodium-catalyzed C−H functionalization in the synthesis of dihydrobenzofuran **11** and an intramolecular Diels−Alder reaction to form bicyclo[2.2.2]octane ring system from a masked *o*-quinone via an IMDA reaction. The efficient Grignard reagent-mediated regioselective modification of the catechol methylidene acetal enabled access to the masked *o*-quinone intermediate in a concise manner.

Supporting Information Available. Detailed experimental procedures, copies of ^{1}H and ^{13}C NMR spectra for compounds described in this letter. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Compound **16** is stable at −20 °C for a few days.

(18) The relative configuration of the product and the corresponding *endo*-selectivity of the IMDA reaction are confirmed by NOE studies.