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A Concise Total Synthesis of (−)-Maoecrystal Z

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Supporting Information

ABSTRACT: The first total synthesis of (−)-maoecrystal Z is described. The key steps of the synthesis include a diastereoselective Ti^{III}-mediated reductive epoxide coupling reaction and a diastereoselective Sm^{II}-mediated reductive cascade cyclization reaction. These transformations enabled the preparation of (−)-maoecrystal Z in only 12 steps from (−)-γ-cyclogeraniol.

Maoecrystal Z (**6**) is an unusual rearranged 6,7-*seco*-*ent*-kauranoid natural product that was isolated in 2006 as a minor constituent from the Chinese medicinal herb *Isodon eriocalyx*.[1] Its compact tetracyclic ring system comprises six vicinal stereogenic centers, two of which are all-carbon quaternary centers. Maoecrystal Z is closely related to several additional 6,7-*seco*-*ent*-kauranoid natural products, including trichorabdals A (**1**)[2] and B (**2**),[3] shikodonin (**3**),[4] longirabdolactone (**4**),[5] and effusin (**5**),[6] as well as the rearranged *ent*-kauranoid maoecrystal V (**7**)[7] (Figure 1). Collectively, these compounds share a common central spiro-fused lactone. Compounds **1**−**3** exhibit in vivo antitumor activity against Ehrlich ascites carcinoma in mice,[4,8] while **6** and **7** display in vitro cytotoxicity toward A2780 ovarian and HeLa cancer cell lines, respectively.[1,7]

Although the structures and biological activities of **1**−**5** have been known for decades, there are few reports of synthetic studies leading toward the 6,7-*seco*-*ent*-kauranoid natural products. In 1986, Mander and co-workers reported a 33-step total synthesis of 15-desoxyeffusin from 3,5-dimethoxybenzoic acid;[9] 12 years later, the same group completed a 29-step semisynthesis of **4** from giberellic acid.[10] In contrast, since its isolation in 2004, several groups have published approaches to **7**,[11] with Yang and co-workers reporting the first total synthesis in 2010.[12] Our interest was drawn to maoecrystal Z, with the objective of developing a synthetic route to the central spirolactone core that may also provide access to the trichorabdals. In this communication, we report the first total synthesis of (−)-maoecrystal Z (**6**).

Retrosynthetically, it was envisioned that maoecrystal Z should be accessible from diol **9** and that the central C ring could be formed through an intramolecular aldol reaction (Scheme 1a). This synthetic plan was guided in part by a 1981 communication by Fujita and co-workers in which treatment of trichorabdal B (**2**) with dilute sodium hydroxide in methanol furnished methyl ester **8**, an oxidized congener of maoecrystal Z (Scheme 1b).[3] Tetracycle **8** presumably results from a methoxide-promoted retro-Dieckmann reaction followed by aldol ring closure of the transiently generated enolate. This finding suggests that the intramolecular aldol reaction to form the C ring of **6** should occur under mild conditions. In the context of our synthetic plan, we hypothesized

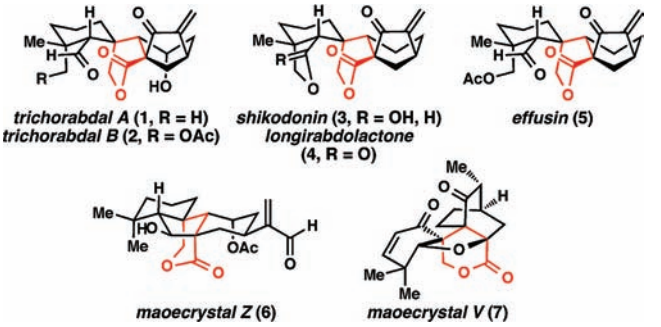
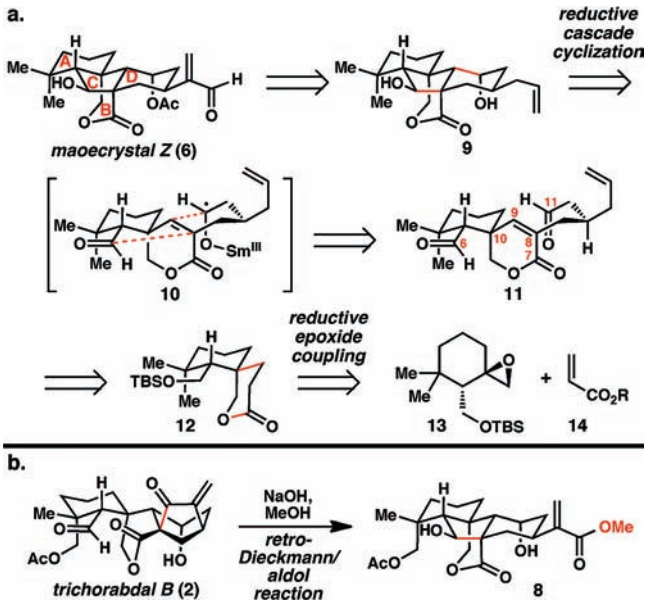


Figure 1

Scheme 1. (a) Retrosynthetic Analysis for Maoecrystal Z (**6**); (b) Methoxide-Mediated Retro-Dieckmann/Aldol Reaction of Trichorabdal B (**2**)



that it might be possible to construct *both* the six-membered D ring and five-membered C ring simultaneously from dialdehyde **11** through a Sm^{II}-mediated cascade cyclization reaction. Elegant studies by Procter and colleagues have recently demonstrated that SmI_2 can promote reductive cascade cyclizations of

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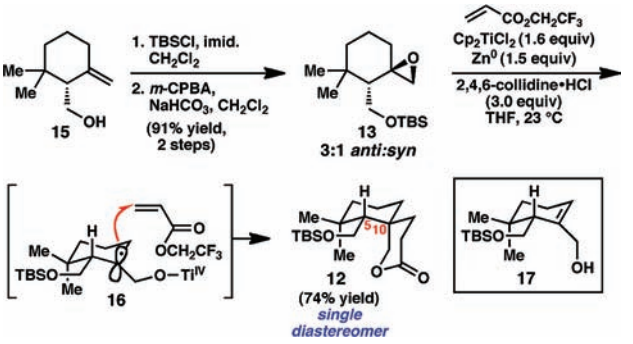
Scheme 2. Preparation of Spirolactone 12

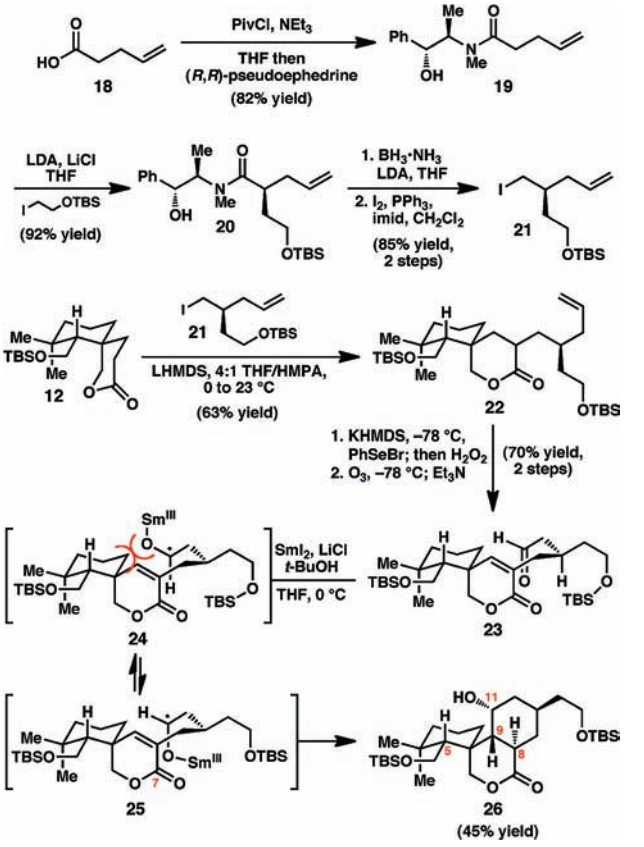


dialdehydes for rapid construction of polycyclic motifs.[13] It was envisioned that selective ketyl generation could be effected at the more accessible side-chain C11 aldehyde of **11**. Intramolecular addition to the unsaturated lactone followed by a second one-electron reduction would generate the C7−C8 enolate, which could undergo aldol ring closure with the proximal aldehyde in accord with the precedent of the Fujita system.[3] Because of the increased steric encumbrance imposed by the adjacent quaternary centers, samarium ketyl formation at the C6 aldehyde was expected to be kinetically disfavored. Approach of the C11 ketyl to the enoate face opposite the C6 aldehyde was anticipated to provide the correct configuration at C9; on the other hand, the stereochemical outcome at the two newly formed carbinol stereogenic centers was difficult to predict a priori. Notably, if diastereoselective, this transformation would serve to build two rings and set four stereogenic centers in a single step.

Dialdehyde **11** was expected to be derived from spirolactone **12** through sequential alkylation and desaturation (Scheme 1a). In a second key step, spirolactone **12** was anticipated to be accessible by the Ti^{III}-mediated reductive coupling of enantioenriched epoxide **13** and acrylic acid derivative **14**.[14] Epoxide **13** can be prepared in a short sequence from the known compound (−)-γ-cyclogeraniol[15] (**15**) (see Scheme 2).

The first stage of our synthesis focused on the preparation spirolactone **12**, which required the diastereoselective formation of the C10 all-carbon quaternary center. Starting with (−)-γ-cyclogeraniol (**15**), protection of the primary alcohol as the *tert*-butyldimethylsilyl (TBS) ether and epoxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) provided epoxide **13** as a 3:1 mixture of diastereomers (Scheme 2). We were pleased to find that use of methyl acrylate and Gansäuer's modified conditions[16] for reductive epoxide couplings [Cp_2TiCl_2 (0.5 equiv), Zn^0 (2.0 equiv), 2,4,6-collidine·HCl (2.5 equiv); not shown in Scheme 2] furnished spirolactone **12** as a *single* diastereomer,[17] albeit in a modest 28% yield. The major byproduct of the reaction was allylic alcohol **17**, potentially resulting from Lewis acid-mediated rearrangement of epoxide **13**. A screen of reaction parameters determined that use of 2,2,2-trifluoroethylacrylate, a more electrophilic coupling partner, and the portionwise addition of Cp_2TiCl_2 (1.6 equiv) to a suspension of Zn^0 (1.5 equiv) in the presence 2,4,6-collidine·HCl (3.0 equiv) in tetrahydrofuran (THF) provided lactone **12** in 74% yield. Under these conditions, the formation of **17** was minimal. As expected, separation of the anti and syn diastereomers of **13** and independent subjection of each to the Ti^{III}-mediated coupling conditions provided lactone **12** as a single diastereomer in 75 and 68% yield,

Scheme 3. Synthesis and Sm^{II}-Mediated Reductive Cyclization of Aldehyde 23



respectively, supporting the intermediacy of radical **16**.[18] The diastereoselectivity in this reaction is proposed to derive from approach of the acrylate syn to the C5 proton of **16**, minimizing nonbonding interactions with the adjacent siloxy and axial methyl substituents.

As described in the retrosynthetic analysis, we ultimately planned to utilize a Sm^{II}-mediated cascade cyclization reaction to simultaneously generate the C and D rings of **6**; however, a stepwise route was initially pursued in order to study the diastereoselectivity and efficiency of the first cyclization step. To this end, pent-4-enoic acid (**18**) was converted to pseudoephedrine amide **19**, which was alkylated with *tert*-butyl(2-iodoethoxy)-dimethylsilane following Myers's protocol[19] to furnish amide **20** in 92% isolated yield and >20:1 dr (Scheme 3). Reductive cleavage of amide **20** followed by treatment of the resulting alcohol with iodine and triphenylphospine provided enantioenriched alkyl iodide **21**. After considerable optimization, we were pleased to find that subjection of a mixture of lactone **12** and iodide **21** to lithium hexamethyldisilazide (LHMDS) at 0 °C followed by warming to room temperature furnished the alkylation product **22** in 63% yield as an inconsequential 1:1 mixture of diastereomers. Selenation/oxidation of **22** provided the unsaturated lactone, and chemoselective ozonolytic cleavage of the terminal alkene delivered aldehyde **23**.

With access to aldehyde **23**, we were poised to study the Sm^{II}-mediated reductive cyclization reaction (Scheme 3).[20] Initial reactions conducted with SmI_2 in THF at 0 °C resulted in rapid decomposition of the starting material, although trace

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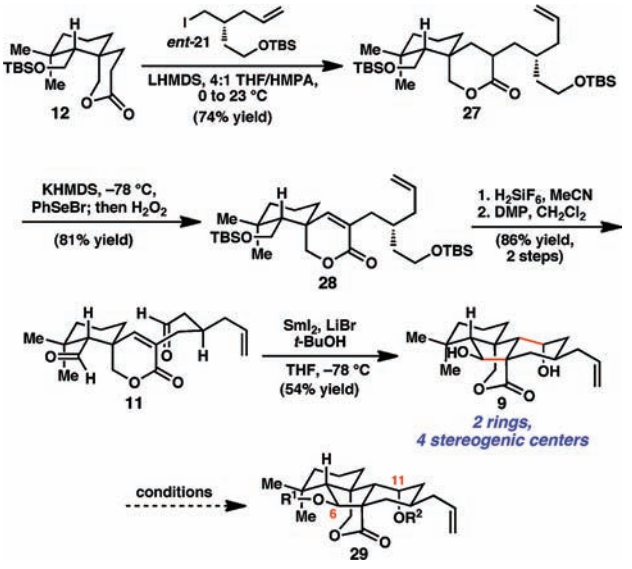
Scheme 4. Reductive Cascade Cyclization of Dialdehyde 11



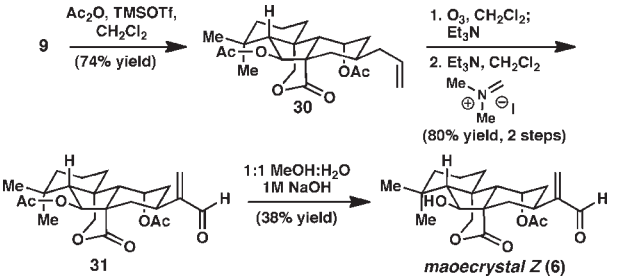
quantities of the desired product were observed. In order to modulate the reactivity of SmI_2, several additives were evaluated. This screen revealed that treatment of **23** with SmI_2 in the presence of LiCl[21] and *t*-BuOH at 0 °C provided the desired tricycle **26** in 45% yield *as a single diastereomer*.[22]

The stereochemical outcome of this transformation can be rationalized as the result of reaction through the ketyl conformation shown as **25**. It is hypothesized that in the disfavored conformation **24**, the samarium ketyl experiences a destabilizing nonbonding interaction with the methylene of the spiro-fused cyclohexane. In conformation **25**, the potentially destabilizing 1,3-diaxial interaction is alleviated by the fact that C7 is sp^2-hybridized.

Encouraged by the high diastereoselectivity observed in this transformation, we turned our attention to the preparation of the key dialdehyde double-cyclization substrate (Scheme 4). To this end, spirolactone **12** was alkylated with iodide *ent*-**21**[23] and elaborated to enoate **28** by a selenation/selenoxide elimination sequence analogous to that described above. Double deprotection of the silyl ethers was accomplished smoothly with fluorosilicic acid, and the corresponding diol was oxidized to dialdehyde **11** with Dess–Martin periodinane.[24] In the event, exposure of dialdehyde **11** to SmI_2 and LiCl in the presence of *t*-BuOH at −78 °C provided tetracyclic diol **9**, albeit in low yield. In this case, use of LiBr as an additive provided improved results, delivering diol **9** in 54% yield. The stereochemistry of the product was assigned by 1D and 2D NMR methods. Notably, both the C6 and C11 carbinols possessed the correct relative stereochemistry for advancement to **6**. The major byproduct of the reaction appeared to be that resulting from monocyclization to form the D ring followed by protonation of the enolate.

Completion of the synthesis required acetylation of the C11 carbinol and installation of the enal. Unfortunately, treatment of diol **9** with acetic anhydride and 4-dimethylaminopyridine (DMAP) resulted in rapid monoacetylation of the C6 carbinol (**29**, R^1 = Ac, R^2 = H). Use of excess reagent and longer reaction times provided the corresponding diacetate along with an isomeric compound that appeared to result from skeletal rearrangement.[25] Attempts at sequential monoprotection of the C6 carbinol

Scheme 5. Completion of the Synthesis of (−)-Maoecrystal Z (6)



and acetylation of the C11 carbinol were problematic, often providing complex mixtures.[26] In no case were we able to protect the C6 carbinol selectively, acetylate the C11 carbinol, and then reveal the C6 carbinol selectively in serviceable yields.

After considerable efforts to optimize conditions for selective C11 monoacetylation, we elected to pursue instead the monodeacetylation of acetyl-maoecrystal Z (**31**). To this end, treatment of **9** with acetic anhydride and catalytic TMSOTf provided diacetate **30** in 74% yield (Scheme 5). Ozonolytic cleavage of the alkene and treatment of the aldehyde with Eschenmoser's salt[27] and triethylamine gave enal **31**. Exposure of **31** to sodium hydroxide in aqueous methanol delivered maoecrystal Z (**6**) in 38% yield. Characterization data obtained for synthetic **6** were fully consistent with the data for the natural compound reported by Han and co-workers.[1] The modest yield of the final step was due to competitive bis-deacetylation to the corresponding diol as well as monodeactylation of the C11 acetate.[28] Notably, this synthesis proceeded in just 12 synthetic steps from (−)-γ-cyclogeraniol (**15**).

In summary, the first total synthesis of (−)-maoecrystal Z has been described. The key steps include a highly diastereoselective Ti^{III}-mediated reductive epoxide coupling and a Sm^{II}-mediated reductive cascade cyclization. Collectively, these transformations illustrate the utility of single-electron chemistry for the preparation of congested polycyclic systems bearing vicinal stereogenic centers. Efforts to employ readily accessible spirolactone **12** in the syntheses of additional *seco-ent*-kauranoid natural products, such as trichorabdals A and B, are the subject of ongoing research in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization and spectral data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The stereochemistry was confirmed by single-crystal X-ray diffraction of the corresponding desilylated compound [see the Supporting Information (SI)].

(18) When a reaction employing a 2.3:1 anti/syn mixture of diastereomers was run to 56% conversion, the unreacted starting material was recovered as a 1.3:1 mixture, indicating that the major anti diastereomer is reduced faster.

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(22) The stereochemistry of the corresponding acetate ester was assigned by extensive characterization using 1D and 2D NMR techniques (^1H-^1H COSY, HMQC, HMBC, and NOESY) and three-bond $^1H-^1H$ coupling constant analysis (see the SI).

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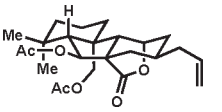
(25) On the basis of a strong stretch at 1775 cm^{-1} in the FTIR spectrum, the rearranged product was tentatively assigned as the lactone shown below (see the SI for details).



(26) Several protecting groups (PGs) for R^1 were evaluated, including TMS, $-COCF_3$, $-COCH_2Cl$, $-CO_2t$-Bu, and $-CO$(4-ClPh). These groups resulted in either increased levels of rearrangement, low yields of **29** (R^1 = PG, R^2 = Ac), or poor selectivity during the PG-removal step.

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(28) For a selection of results utilizing different conditions in the final deprotection step, see the SI.