A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201711084
Angew. Chem. 10.1002/ange.201711084

Link to VoR: http://dx.doi.org/10.1002/anie.201711084
http://dx.doi.org/10.1002/ange.201711084

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Total Synthesis of Maoecrystal P: The Application of a Strained Bicyclic Synthon

Fan Su[†], Yandong Lu[†], Lingran Kong, Jingjing Liu and Tuoping Luo*

Abstract: A new strategy was devised for the total syntheses of highly oxidized *ent*-kauranoids. A highly regio- and diastereoselective intermolecular Diels-Alder cycloaddition involving a diene embedded in a substituted bicyclo[4.1.0] skeleton was used to assemble all but the C17 carbon of the target molecule at the early stage of the synthesis. The subsequent synthetic steps including redox manipulations, SmI_2-mediated cyclization and isomerizations afforded the anti-tumor natural product, maoecrystal P.

Ent-kaurene diterpenoids comprise over 600 naturally occurring small molecules biosynthetically related to *ent*-kaurene (**1**).[1] A wide range of biological activities together with intriguing structures resulting from dense functionalization and varied oxidation patterns have piqued tremendous interest in this family of natural products.[2,3] Among them, maoecrystal P (**2**) has attracted our particular attention, because it has shown promising cytotoxicity against human tumor cells.[4] Owing to the Michael acceptor reactivity of the α-methylene-cyclopentanone unit that is present in most bioactive *ent*-kauranoids, valuable insights into their mechanism-of-action have been gathered using corresponding small-molecule probes.[5] As part of our continuing interest in compounds that can form covalent bonds with their protein targets,[6] we describe herein the first total synthesis of maoecrystal P (**2**).

The development of numerous synthetic strategies and methodologies during the past half century have significantly improved our capability to access the fascinating *ent*-kaurene diterpenoids, culminating in numerous successful total syntheses.[2,3] There has also been a recent resurgence of *de novo* synthesis of this important family of natural products, especially in an efficient and practical manner, as exemplified by the work on steviol and (−)-longikaurin E by the groups of Baran and Reisman respectively.[3r,3s] Meanwhile, several oxidatively cleaved or rearranged *ent*-kauranoids such as maoecrystal V and sculponeatin N, have been accomplished elegantly by a number of groups.[7] However, target molecules with both highly oxidized ring A and ring B still present tremendous challenges for chemical synthesis. In this regard, the convergent strategy developed by Ma and co-workers as well as the oxidative dearomatization-induced cycloaddition/1,2-migration cascade developed by the Ding group are both admirable achievements.[3v,3w] Nonetheless, in addition to the A/B ring oxidation state, the difficulty in forging the oxygenated C20 has prevented the total synthesis of **2**.

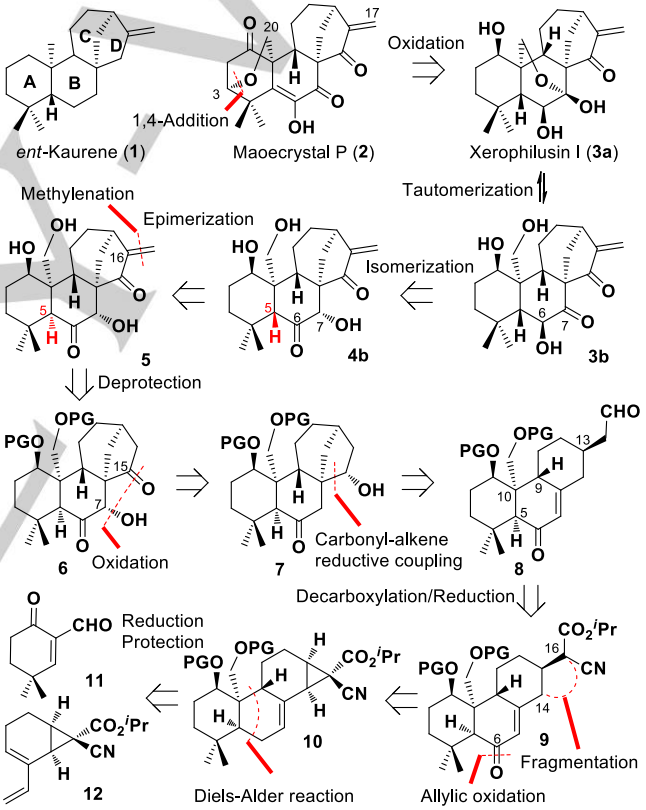

Figure 1. Maoecrystal P (**2**) and its retrosynthetic analysis.

Our retrosynthetic analysis started from the recognition that the oxidation of xerophilusin I (**3a**)[8] followed by intramolecular 1,4-addition could lead to our target molecule **2** (Figure 1).[9] We hypothesized that the chain tautomer of **3a**, ketol **3b**, could be obtained by isomerization of ketol **4b**.[10] The epimerization of the C5 stereogenic center was then envisioned to provide **4b** from **5**, which could be traced back to ketol **6** *via* C16 methylenation and deprotection of the alcohols. The C7 hydroxyl group and C15 carbonyl group of **6** could be furnished by oxidation, and we assumed that the *ent*-kauranoid skeleton, tetracycle **7**, could be constructed from enone **8** *via* a SmI_2-mediated carbonyl-alkene

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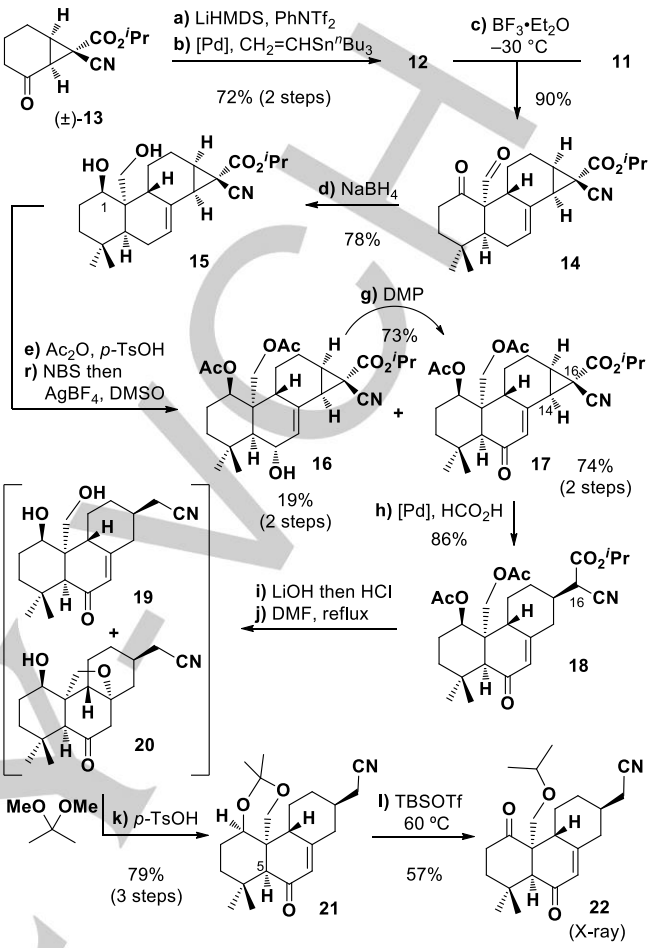
10.1002/anie.201711084

reductive coupling.[11] Even though the stereochemistry of C5, C9 and C10 were reminiscent of a disconnection *via* Diels-Alder cycloaddition, the absence of traditional neighboring controlling functionalities around C13 prompted us to undertake a unconventional approach for the stereoselective synthesis of **8**. Given **8** could be furnished by enone **9**, we strategically connected C16 and C14 *via* a carbon-carbon bond and proposed intermediate **10** as the key precursor. The incorporation of a substituted cyclopropane ring would dictate not only the regioselectivity of the allylic oxidation to forge the C6 carbonyl group, but also the facial selectivity during the formation of the Diels-Alder cycloadduct **10**. The employment of such an "overbred intermediate"[12] was inspired by Baran's synthesis of steviol[3r] as well as our recent application of strained bicycles to synthesize (−)-hibiscone C and lysergine.[13] Consequently, **10** could arise from the intermolecular Diels-Alder reaction of enone-aldehyde **11**[14] and diene **12**, followed by reduction and protection.

In the forward direction (Scheme 1), we started from the known ketone **13**.[15] The installation of a triflate followed by Stille coupling afforded diene **12** in 72% yield over two steps on 10 g scale. Even though the intermolecular Diels-Alder reaction of enone-aldehyde **11** has been predicted to proceed via an *endo* transition state with regard to the aldehyde[16] and **11** would preferentially approach diene **12** from the side opposite to that occupied by the cyclopropane ring, the level of regioselectivity was uncertain in this scenario. Therefore, we were delighted to find the desired transformation proceeded smoothly in the presence of 2.0 equiv BF_3•OEt_2 at −30 °C to afford **14** in 90% yield; 1.3 equiv of **12** was employed to ensure the complete conversion of **11**. The observation that other regio- and stereoisomers were not isolated under these conditions needs to be further explored. The reduction of both the ketone and aldehyde in **14** by $NaBH_4$ afforded diol **15** in 78% yield. During the evaluation of different protecting groups, we obtained a derivative of **15** and confirmed its structure by X-ray diffraction (see Figure S1 in Supporting Information for details).[17] Eventually, we adopted diacetylation of compound **15** followed by a one-pot allylic oxidation procedure to furnish enone **17** in 74% overall yield;[7g,18] the major side product **16** could also be oxidized to **17**. Pd-catalyzed hydrogenolysis of the cyclopropane ring selectively cleaved the C14−C16 bond and afforded enone **18** in high yield.[19] Enone **18** existed as a pair of diastereoisomers at C16, although the C16 stereochemistry was inconsequential for subsequent steps. The hydrolysis of the ester group followed by decarboxylation provided both **19** and intramolecular *oxo*-Michael addition product **20** as revealed by the crude NMR of the reaction product. Therefore, the crude product was directly subjected to acetonide protection, leading to enone **21** in 79% yield over 3 steps. At this stage, we evaluated methods to effect the epimerization of C5 stereogenic center. While treatment of **21** with bases (e.g. DBU) in refluxing toluene only resulted in starting material recovery, we accidentally obtained enone **22** in 57% yield in the presence of TBSOTf at an elevated temperature, the structure of which was unambiguously determined by X-ray diffraction.[17] The mechanism of this transformation might involve an intramolecular hydride transfer (Figure S2), so we delayed the epimerization of C5 to a later stage in the synthesis.

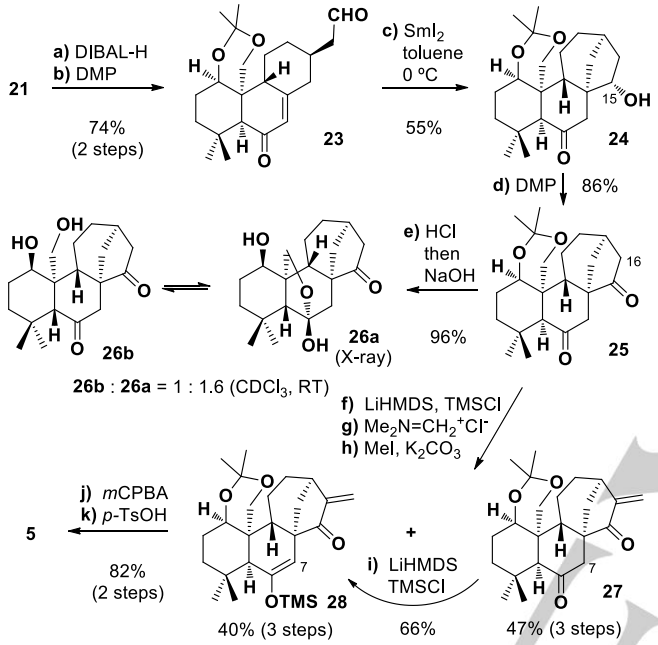


Scheme 1. Synthesis of diene **12** and the intermolecular Diels-Alder reaction. Reagents and conditions: a) LiHMDS (1.1 equiv), $PhNTf_2$ (1.1 equiv), THF, −78 to 0 °C, 78%; b) $Pd(PPh_3)_4$ (0.02 equiv), tributyl(vinyl)tin (1.05 equiv), LiCl (5.0 equiv), THF, reflux, 92%; c) **11** (1.0 equiv), **12** (1.3 equiv), BF_3•Et_2O (2.0 equiv), toluene, −30 °C, 90%; d) $NaBH_4$ (2.2 equiv), MeOH, 0 °C, 78%; e) Ac_2O (4.3 equiv), *p*-TsOH•H_2O (0.2 equiv), toluene, 100 °C; f) NBS (1.1 equiv), AIBN (0.05 equiv), CCl_4, reflux; then $AgBF_4$ (1.2 equiv), Et_3N (3.9 equiv), DMSO, RT, **16**, 19% (2 steps); **17**, 74% (2 steps); g) DMP (1.2 equiv), $NaHCO_3$ (10 equiv), DCM, RT, 73%; h) $Pd_2(dba)_3$•$CHCl_3$ (0.005 equiv), P^nBu_3 (0.04 equiv), HCOOH (2.0 equiv), TEA (3.0 equiv), dioxane, reflux, 86%; i) LiOH•H_2O (10 equiv), THF/H_2O (1:1), RT, then HCl; j) DMF, reflux; k) *p*-TsOH•H_2O (0.1 equiv), 2,2-dimethoxypropane, 80 °C, 79% (3 steps); l) TBSOTf (4.9 equiv), DCE, 60 °C, 57%.

To construct the D ring, DIBAL-H reduction of **21** followed by DMP oxidation provided the cyclization precursor **23** (Scheme 2). By screening a series of reaction conditions (Tables S1 and S2), we eventually found that the treatment of **23** with excess SmI_2 in toluene at 0 °C robustly afforded ketol **24** in 50-60% yield as a single diastereomer. The modest yield of **24** was acceptable given this remarkable transformation forged a hindered quaternary center and a strained ring system, completing the skeleton of *ent*-kauranoids. Oxidation of **24** by DMP afforded diketone **25** in 86% yield, which could then be used to explore the conditions for C5 epimerization. Gratifyingly, the removal of the acetonide protecting group followed by treatment with aqueous NaOH

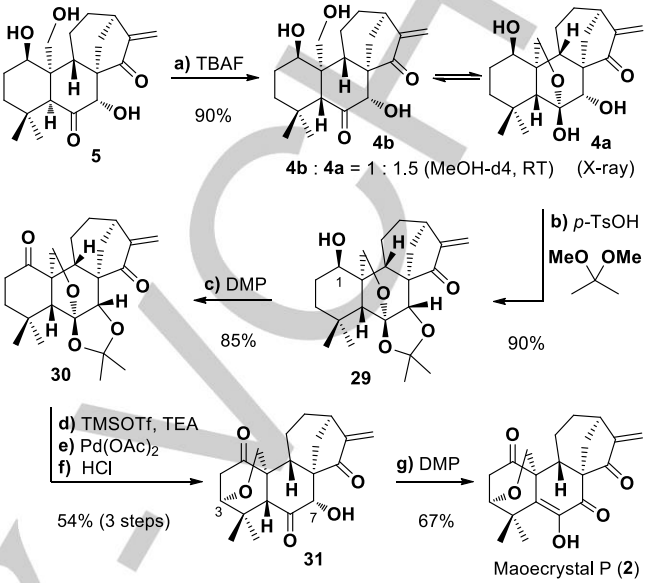
10.1002/anie.201711084

solution resulted in clean conversion to the ring-chain tautomers **26a/b**.[20] The X-ray crystallographic analysis of **26a** confirmed the C5 stereochemistry and the facile formation of the hemi-ketal.[17] We subsequently realized selective methylenation of the C16 position by a three-step sequence,[7b] affording ketone **27** and its trimethylsilyl enol ether **28** in 47% and 40% overall yields, respectively. The introduction of the hydroxyl group on the sterically demanding C7 position was achieved by the Rubottom method,[21] which was followed by deprotection to provide **5** as a single diastereomer.



Scheme 2. SmI_2-mediated cyclization and construction of the *ent*-kauranoid skeleton. Reagents and conditions: a) DIBAL-H (3.0 equiv), DCM, 0 °C; b) DMP (1.5 equiv), DCM, 0 °C, 74% (2 steps); c) SmI_2 (7.0 equiv), toluene, 0 °C, 55%; d) DMP (1.5 equiv), $NaHCO_3$ (10 equiv), DCM, 0 °C to RT, 86%; e) HCl, THF/H_2O (1:1), RT, then NaOH, RT, 96%; f) LiHDMS (2.0 equiv), TMSCl (1.1 equiv), THF, 0 °C; g) Eschenmoser's salt (5.0 equiv), DMF, 50 °C; h) MeI/ether (1:5), then DCM, K_2CO_3 (sat., aq.), **27**, 47% (3 steps); **28**, 40% (3 steps); i) LiHDMS (2.0 equiv), TMSCl (2.5 equiv), 66%; j) *m*-CPBA (3.0 equiv), DCM, 0 °C; k) *p*-TsOH•H_2O (3.0 equiv), MeOH, 0 °C, 82% (2 steps).

With all carbons properly installed, we continued to complete the total synthesis of maoecrystal P (Scheme 3). Treatment of **5** with aqueous NaOH solution led to significant decomposition; however, we eventually obtained **4a**, which was in equilibrium with its tautomer **4b**, in high yield by stirring **5** in a TBAF solution at room temperature.[17] Unfortunately, after screening a variety of reaction conditions (Table S3), we did not manage to effect the isomerization to xerophilusin I (**3a**). Therefore, an alternative approach was taken. Treatment of **4** with 2,2-dimethoxypropane in the presence of catalytic tosylic acid afforded **29**, leaving only the C1 hydroxyl group unprotected. Sequential DMP and Saegusa oxidation installed the correct oxidation level on the A ring, whereas the intramolecular conjugated addition took place simultaneously during the removal of the acetonide protection to give **31** as the final product. Maoecrystal P (**2**) was ultimately obtained by oxidation of the C7 alcohol. The spectroscopic data of the synthesized samples of **2** were in good agreement with those reported in the literature (Table S4).[4a]



Scheme 3. Total synthesis of maoecrystal P (**2**). Reagents and conditions: a) TBAF (5.0 equiv), RT, 90%; b) *p*-TsOH•H_2O (0.1 equiv), 2,2-dimethoxypropane, RT, 90%; c) DMP (4.4 equiv), $NaHCO_3$ (15 equiv), DCM, RT, 85%; d) TMSOTf (20 equiv), TEA, 60 °C; e) $Pd(OAc)_2$ (4.0 equiv), CH_3CN, RT; (f) HCl, THF/H_2O (1:1), RT, 54% (3 steps); (g) DMP (2.0 equiv), $NaHCO_3$ (9 equiv), DCM, RT, 67%.

In summary, we developed a synthesis of maoecrystal P (**2**) with 27 steps in the longest linear sequence from commercially available 2-bromocyclohex-2-one (Scheme S1). Notably, the unique cyclopropyl ring in **13** facilitated 1) the regioselective preparation of the vinyl triflate intermediate; 2) the highly stereoselective intermolecular Diels-Alder reaction; 3) the regioselective allylic oxidation; and 4) the facile reductive scission of the C14−C16 bond. This novel strategy has the potential to be applied for the preparation of other highly oxidized *ent*-kauranoids and their analogues for biological evaluations. For instance, synthesized **2** and our intermediates with the *ent*-kaurene skeleton (**4**, **29**, **30** and **31**) all significantly inhibit the growth of HCT116 tumor cells with IC50s ranging from 1 to 5 μM (Figure S3). Related investigations are ongoing in our laboratory and will be reported in due course.

Acknowledgements

This work was supported by generous start-up funds from the National "Young 1000 Talents Plan" Program, College of Chemistry and Molecular Engineering, Peking University and Peking-Tsinghua Center for Life Sciences, and the National Science Foundation of China (Grant Nos. 21472003, 31521004 and 21672011). We thank Dr. Nengdong Wang and Prof. Wenxiong Zhang (Peking University) for their help in analyzing

the X-ray crystallography data, and Prof. Jianxin Pu and Prof. Handong Sun (Kunming Institute of Botany) for providing us the sample of eriocalyxin B.

Keywords: total synthesis • *ent*-kaurane • cyclopropane • Diels-Alder reaction • radical cyclization

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10.1002/anie.201711084

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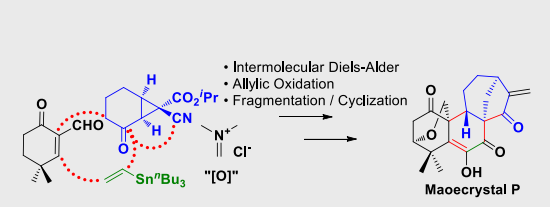

A new strategy was devised to achieve the total synthesis of the highly oxidized and bioactive *ent*-kauranoid maoecrystal P. Starting from a strained bicyclo[4.1.0] ketone, intermolecular Diels-Alder cycloaddition, allylic oxidation, SmI_2-mediated cyclization and late-stage oxidations were performed in sequence to accomplish the target molecule.

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