

A Bifunctional Lewis Acid Induced Cascade Cyclization to the Tricyclic Core of *ent*-Kaurenoids and Its Application to the Formal Synthesis of ($\pm$)-Platensimycin

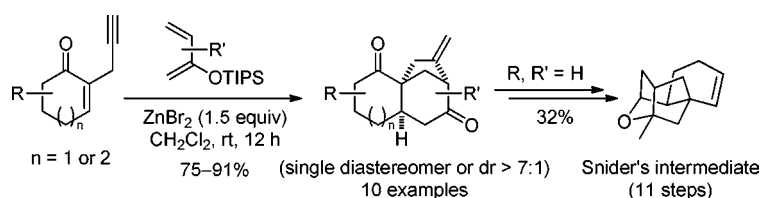
Lizhi Zhu, Yejian Han, Guangyan Du, and Chi-Sing Lee*

Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology,
Peking University Shenzhen Graduate School, Shenzhen University Town, Xili,
Shenzhen 518055, China

lizc@pkusz.edu.cn

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ABSTRACT



A mild and efficient bifunctional Lewis acid induced cascade cyclization reaction has been developed for construction of the tricyclic core of *ent*-kaurenoids. With ZnBr_2 as the bifunctional Lewis acid, a series of substituted enones and dienes underwent cascade cyclization smoothly at room temperature and provided the tricyclic products in one pot with good yields (75–91%) and high diastereoselectivity. The cyclized product has been successfully employed for the formal synthesis of ($\pm$)-platensimycin.

ent-Kaurene, including the 6,7-*seco-ent*-kaurene (Figure 1), is one of the major skeletons in diterpenes that was derived from *ent*-copalyl pyrophosphate (CPP).¹ This class of natural products exhibited a variety of important biological activities such as antibacterial, cytotoxic, anti-inflammatory, and immuno-suppressive properties.² The tricyclic fused ring system **I** is an important structural motif of the *ent*-kaurenoids (Figure 1).³ It could also be rapidly transformed into the cage structures of platensimycin⁴ **1** and

platencin⁵ **2**, which are potent antibiotics against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE) via inhibition of fatty acid biosynthesis in FASII^{4–6} and have attracted a tremendous amount of synthetic efforts.^{7–9} A recent study suggested that the biosynthesis of **1** involved an *ent*-kaurene type intermediate that was also derived from CPP.¹⁰ Due to the structural diversity and the intriguing biological activities of these *ent*-kaurene related natural products, we have decided to develop a bifunctional Lewis acid induced cascade cyclization reaction for rapid construction of the *ent*-kaurene framework, which could

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provide a general and efficient synthetic entry to this class of natural products.

Bifunctional Lewis acids¹¹ are very useful for developing cascade cyclization reactions since they could induce cyclization reactions via forming σ - and/or π -complexes with the substrates as well as the intermediate(s) that were generated *in situ*. We are particularly interested in developing bifunctional Lewis acid induced cascade cyclization reactions for natural product synthesis since it can usually construct the core structure of the synthetic target in a single operation under mild conditions.¹² Recently, we have developed the ZnBr₂ catalyzed Diels–Alder/carbo-cyclization cascade cyclization reaction for rapid construction of *cis*-hydrindanes and demonstrated its utilities in natural product synthesis.^{12c} As such, we have decided to employ this strategy for developing new cascade cyclization reactions that could quickly access the tricyclic core of *ent*-kaurene related natural products **I**. As shown in Figure 2,

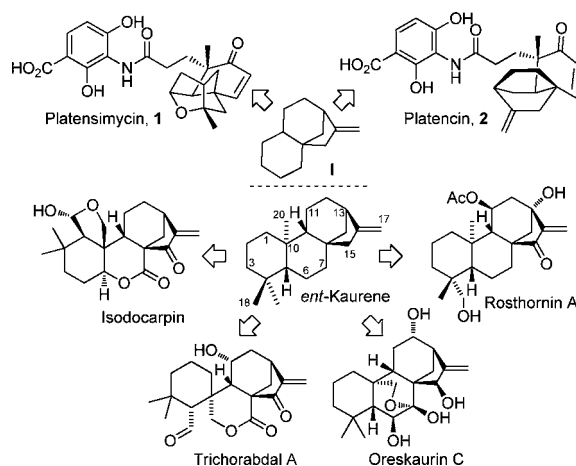


Figure 1. Examples of *ent*-kaurene related natural products.

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our strategy involved a Lewis acid induced Diels–Alder (DA) cycloaddition of enone **III** and **IV** with diene **V**. The resulting silyl enol ether of the DA adducts **VI** and **VII** could undergo intramolecular carbocyclization with the alkyne to form the bicyclo[3.2.1]octane moiety of **I** and **II** in a one-pot manner. This strategy required a mild bifunctional Lewis acid that can form σ -complexes with enone **III/IV** for inducing DA cycloaddition and π -complexes with intermediate **VI/VII** for inducing carbocyclization without causing hydrolysis of silyl enol

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ether **V** and **VI/VII**. We herein reported the development of a new two-component cascade cyclization reaction for establishing the 6,6,5-tricyclic fused ring system **I** in one pot and its application to the formal synthesis of ($\pm$)-platensimycin **1**.

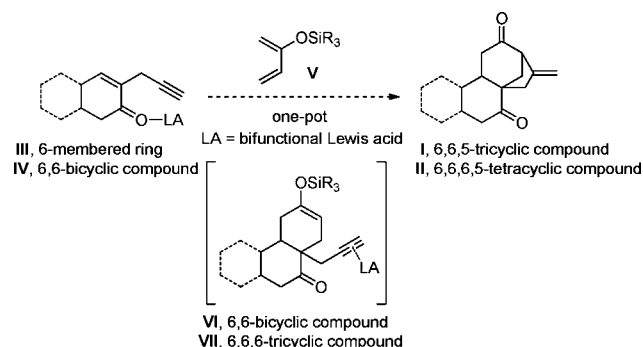
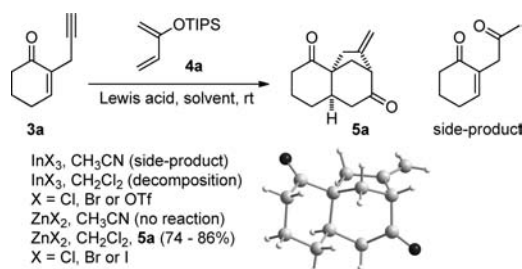


Figure 2. A bifunctional Lewis acid induced cascade cyclization approach to the skeleton of *ent*-kaurenoids.

Since we have previously demonstrated that both In(III) and Zn(II) are useful bifunctional Lewis acids for inducing cascade cyclization reactions,¹² the reaction between enone **3a** and diene **4a** was studied using a variety of In(III) and Zn(II) based Lewis acids. As shown in Scheme 1, In(III) halides or triflates in acetonitrile led to the side product via hydration of the alkyne moiety of **3a** even under anhydrous conditions. These results indicated that the ketone moiety could be cyclized with the activated alkyne and form an unstable cyclic enol ether, which could be hydrolyzed to form the methyl ketone side product upon workup. Switching the solvent to dichloromethane resulted in rapid decomposition of the substrates. No reaction was observed by using Zn(II) halides in acetonitrile. Finally, we found that the cascade cyclization went smoothly by using Zn(II) halides in dichloromethane and afforded the tricyclic product **5a** bearing the *cis*-decalin efficiently and diastereoselectively. The optimal conditions were found to be 1.5 equiv of ZnBr₂ in CH₂Cl₂ at room temperature for 12 h. These mild conditions afforded the expected cyclized product **5a** in 86% yield as a single diastereomer. The stereochemistry of the cyclized product **5a** was characterized unambiguously by NMR experiments¹³ and X-ray crystallography.¹⁴

With the optimal conditions in hand, the scope of the substrates was studied with a series of substituted enones (**3a–h**) and dienes (**4a–c**). As shown in Table 1, the methyl substituents at C1 to C4 of the enone are well tolerated and gave comparable yields and diastereoselectivities of the cyclized products (**5b–e**) (entries 2–5). More importantly, the geminal dimethyl substituent at C3 also afforded

Scheme 1. Screening of Bifunctional Lewis Acids



cyclized product **5f** in good yield (entry 6). This result suggested that the sterically demanding substrate **IV** (Figure 2) could also be cyclized to provide tetracyclic fused ring system **II** (Figure 2) under this cyclization condition. Introducing an OTBS moiety at C5 afforded **5g** also in good yield and diastereoselectivity (entry 7). These results indicated that these substituted enones and dienes not only afford comparable results but also provide a handle for developing asymmetric reactions via substrate control. Moreover, the seven-membered enone **3h** also gave cyclized product **5h** in good yield and diastereoselectivity (entry 8), which could be a useful building block for the synthesis of grayanane-type diterpenes.¹⁵ Diene **4b**, which bears two methyl substituents at the reaction site (C6), also smoothly underwent DA cycloaddition and gave the cyclized product (**5i**) as a single diastereomer¹⁴ (entry 9). The potential side product that arose from the Michael addition between **3a** and **4b** was not observed under this reaction condition. Diene **4c** bears a methyl group at C7 (the reaction site for the carbocyclization) affording the cyclized product **5j** also in very good yield (91%) and diastereoselectively (entry 10).

To demonstrate the utilities of this cascade cyclization reaction, diketone **5a** was employed as the building block for the synthesis of platensimycin **1**. As shown in Scheme 2, diketone **5a** was first converted to the di-TMS enol ether **6**. Epoxidation using magnesium monoperoxyphthalate (MMPP) provided α -hydroxy ketone **7** selectively in 65% yield along with 20% of **5a** being recovered. Hydroxyl-directed reduction of the ketone moiety of **7** followed by elimination of the resulting diol afforded **8** in good yields.¹⁶ Silyl enol formation followed by MMPP epoxidation of **8** provided α -hydroxyl ketone **9** as a single diastereomer, which can be equilibrated to the more stable α -hydroxyl ketone **10** qualitatively upon prolonged treatment with acid. The α -hydroxylation and equilibration can be done conveniently in a one-pot manner, and the diastereomer bearing the *trans*-decalin was not observed under these reaction conditions. The resulting alcohol of **10** was then acetylated and deacetoxylation using SmI₂. Finally, reduction of ketone **11** with K-selectride followed

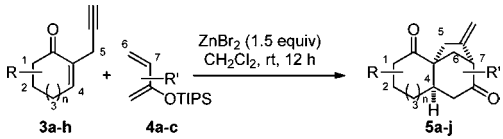
(13) The NMR data are available in the Supporting Information.

(14) CCDC-909564 (**5a**) and CCDC-909565 (**5i**) 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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Table 1. Study on the Scope of Substrates^a

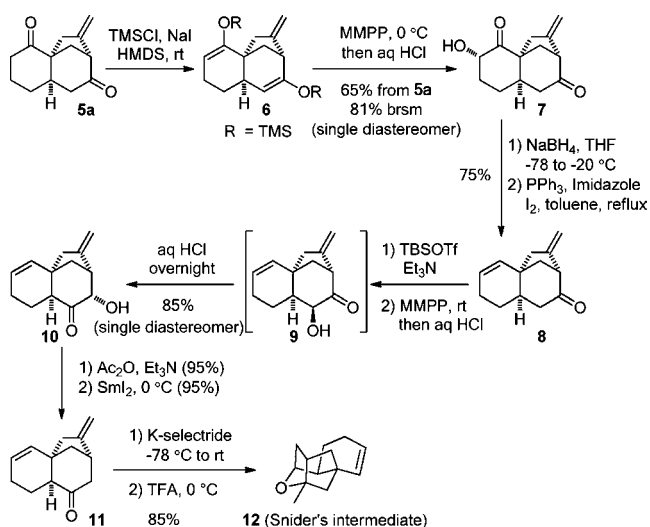


entry	enones	dienes	products	yields ^b (dr)
1				86% ^c
2				81% (8:1)
3				88% ^c
4				85% (16:1)
5				80% ^c
6				80% ^c
7				75% (7:1)
8				82% ^c
9				79% ^c
10				91% ^c

^aThe general procedures were followed. ^bIsolated yields. ^cSingle diastereomer.

by treatment of trifluoroacetic acid^{8m} afforded the Snider intermediate^{8c} **12**, which could be converted to **1** according to the literature procedures.^{8a,c}

Scheme 2. Formal Formal Synthesis of (±)-Platensimycin **1**



MMPP = magnesium monoperoxyphthalate

In summary, we have developed a mild bifunctional Lewis acid induced cascade cyclization reaction for rapid construction of the tricyclic core of *ent*-kaurene. With ZnBr_2 (1.5 equiv) in CH_2Cl_2 at room temperature, a variety of substituted enones **3a–h** and dienes **4a–c** underwent cascade cyclization smoothly and afforded the cyclized products **5a–j** in one pot with good yields and high diastereoselectivity. The utilities of this new reaction have been successfully demonstrated by employing cyclized product **5a** as the precursor for the formal synthesis of (±)-platensimycin **1** (32% overall yields for the Snider intermediate **12** in 11 steps from cyclized product **5a**). We are currently studying the cascade cyclization for construction of the tetracyclic system and exploring its utilities in the synthesis of other bioactive *ent*-kaurene related natural products.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.