Total Synthesis Hot Paper

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Asymmetric Total Synthesis of Hispidanin A

*Heping Deng, Wei Cao, Rong Liu, Yanhui Zhang, and Bo Liu**

Abstract: *Asymmetric total synthesis of the dimeric diterpenoid hispidanin A was accomplished by non-catalytic Diels–Alder cycloaddition at room temperature. The synthesis relies on iron-catalyzed coupling to construct a Z-configured trisubstituted alkene, an iron-catalyzed radical cascade to generate a labdane-type diene, and both Yamamoto cationic polyene cyclization and palladium-catalyzed Stille coupling to generate a totarane-type dienophile.*

In 2014, the Jiang group isolated four dimeric diterpernoids named hispidanins A–D (**1**–**4**) from the rhizomes of *Isodon hispida*, a medicinal plant in southwest China.[1] Hispidanins are toxic to several tumor cell lines, including SGC7901, SMMC7721, and K562, with IC_{50} values ranging from 9.8 to 13.7 μM. The corresponding labdane diterpenoids **5** and **6** were recently isolated from *Isodon yuennanensis*,[2] and their structures inspired the biogenetic hypothesis that hispidanins arise from Diels–Alder cycloaddition between a labdane-type diene (**5**/**6**) and a totarane-type dienophile (**7**).[1] The complex structure and intriguing bioactivity of hispidanins led us to attempt their synthesis. Herein we report our progress on asymmetric total synthesis of hispidanin A (**1**) as well as its natural precursor **5**.

Taking inspiration from the biosynthetic hypothesis proposed in Figure 1, we reasoned that hispidanin A could be retrosynthetically generated from **8** by reduction of ketone and acetylation; **8** can be synthesized by Diels–Alder cycloaddition of **5** and **9** (Scheme 1). The totarane-type **9** is an analogue of **7** but with greater dienophilicity because of its more electron-deficient alkene. Although we recently accomplished the semi-synthesis of **5** from (3*aR*)-(+)-sclareolide,[3] a total synthesis was highly anticipated since it could be extended to numerous bicyclic, tricyclic, and tetracyclic diterpenoids functionalized at C_{20} involving *ent*-kaurane[4] and abietane[5] compounds with intriguing bioactivities such as carnosol and carnosic acid.[6] Therefore we sought to synthesize **5** via nucleophilic attack of a methyl anion on the ketone **10,** accessible from the diene surrogate **11** and **12**. Compound **12** could be elaborated from chiral **13**, which in turn could be generated with a *trans*-fused decalin skeleton by

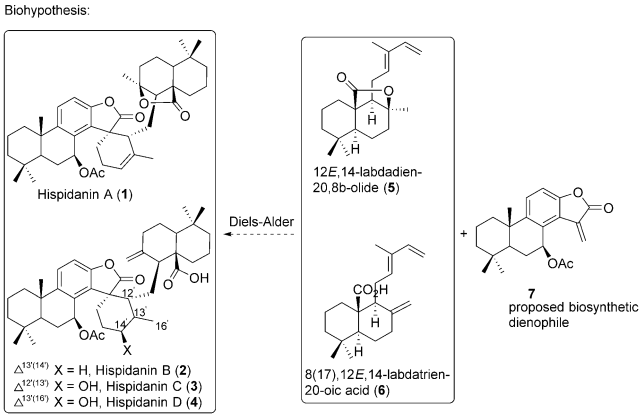
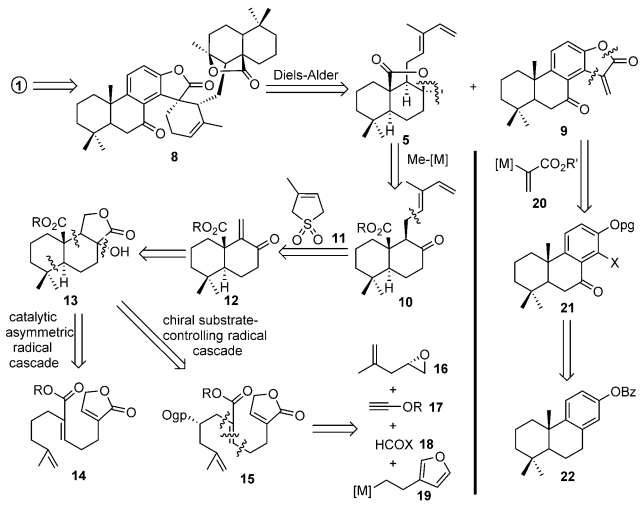


Figure 1. Structures of compounds **1**–**7** and their biogenetic relationships.



Scheme 1. Retrosynthetic analysis of hispidanin A.

catalytic asymmetric radical cascade cyclization of polyene **14**.[7] Alternatively, chiral **13** could be generated in a substrate-controlling fashion via radical polycyclization of **15** and subsequent dehydroxylation. We opted for this latter approach to **13** because of the challenge of achieving a catalytic asymmetric radical cascade with **14**.[8] Achieving **13** from **14** or **15** through other mechanisms might be inefficient owing to difficulty in initiation of an anionic polycyclization and instability of a carbocation adjacent to an ester in cationic polycyclization process. Therefore we explored the synthetic efficacy of a radical cascade with **15,** which could be assembled from the easily available starting materials **16**–**19**. The lactone of dienophile **9** could be installed through transition metal-catalyzed cross-coupling

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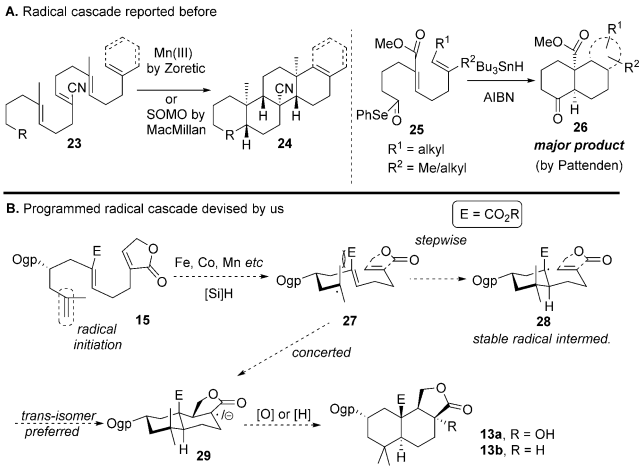
of **20** and **21**. Compound **21** could be generated by routine functionalization of **22**, which could be prepared by enantioselective cationic polyene cyclization.[9]

Biomimetic polyene cyclization to *trans*-decalin by a cationic cascade has been known for decades,[10] and asymmetric versions have been developed.[9] Although radical cascade cyclization of normal polyene toward *trans*-decalin has been achieved through single-electron transfer[10c] and conventional direct radical generation,[11] it has rarely been achieved for polyene substrates bearing electron-withdrawing groups, which would be useful for generating diterpenoid- or triterpenoid-like molecules with angular esters or formyl groups.

Along these lines, the Zoretic and the MacMillan groups reported elegant radical polycyclizations of unsaturated nitriles leading to 6/6/6/6 *trans*-fused polycycles (Scheme 2 A).[12] This approach of radical polycyclization may not

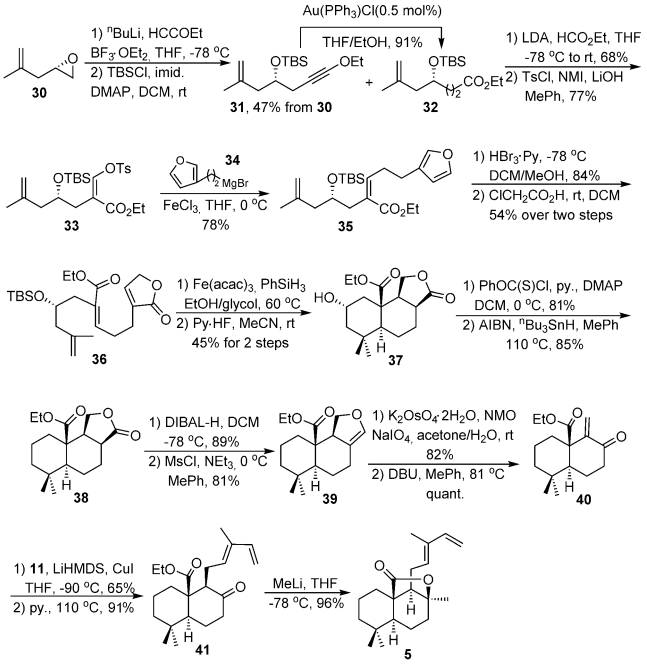


Scheme 2. Radical cascade transformation of polyene into a 6/6 bicycle.

provide adequate diastereoselectivity to deliver *trans*-fused polycycles if the starting material is an unsaturated ester. Indeed, the only example of such polycyclization, reported by the Pattenden group,[13] showed that the reaction with **25** delivered only *cis*-isomer **26** as the isolable product. This may reflect that esters show more severe steric repulsion during cyclization than unsaturated nitrile. Unfortunately, the cyclized intermediate with an angular ester is more attractive than the corresponding intermediate with angular nitrile, because it can be transformed to other functionalities in a more straightforward way. This indicated the challenge to engineer appropriate stereoselectivity into our devised radical cascade involving an unsaturated ester.

Inspired by the recently published metal-catalyzed reductive radical addition of alkene,[14] we devised a radical cascade triggered by hydrogen atom transfer (HAT) (Scheme 2 B). The *gem*-disubstituted terminal alkene in **15**, which features the least steric hindrance and greatest electronic density, would generate a tertiary radical (**27**) in the presence of metal catalyst and silane. After intramolecular capture of the radical, **28** would form via a transition state in a chair conformation. Although the possibility of direct transformation from **27** to **29** through a concerted mechanism cannot be completely ruled out, we reasoned that neither SOMO–LUMO nor SOMO–HOMO interactions would support fast radical trapping because of the electron-deficient character of both the tertiary radical and the alkene as radical acceptor in **28**.[15] In this way, **28** should be a relatively stable intermediate, ensuring diastereoselectivity of the final radical cyclization to afford **29** with *trans*-decalin architecture either as a radical or as an anion. This anion could be generated by reducing the radical in the presence of [FeH] species in the system. Quenching **29** with oxygen or silane would deliver, respectively, **13a** or **13b** with a *cis*-fused 5/6 bicycle motif. Using a five-membered unsaturated lactone could minimize formation of a *trans*-fused 5/6 bicycle, which is less favorable than the *cis*-fused bicycle,[16] making this radical cascade more efficient.

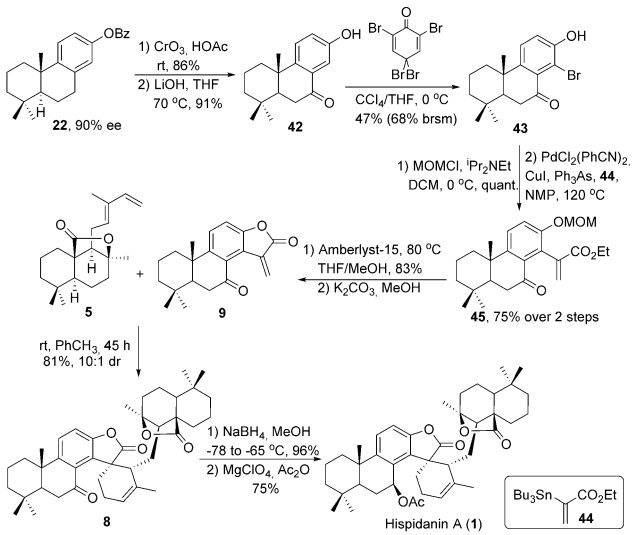
We initiated our total synthesis by conducting epoxide-opening of **30**, an enantiomeric antipode of a known compound,[17] with alkynyl lithium. Subsequent silyl protection of the resulting secondary alcohol afforded **31** in 47 % overall yield; furthermore, **32** was produced during workup and purification in 5 % overall yield (Scheme 3). To circumvent facile formation of a five-membered lactone under other conditions such as catalysis with $HgCl_2$, HCl, $AuCl_3$, and $Sc(OTf)_3$,[18] we developed a mild hydration method to transform **31** into **32** using 0.5 mol % of $Au(PPh_3)Cl$ without silver salt, which is a rare case of gold catalysis without promotion by silver.[19] A formyl group was introduced proximal to the ester in **32**, and the intermediate was converted into enol tosylate **33** in the *Z*-configuration using the procedure developed by Tanabe et al.[20] In the presence of iron(III) chloride catalyst, **33** was coupled with the Grignard reagent **34** to afford **35** with retention of the



Scheme 3. Synthesis of **5**.

double-bond configuration.[20] Our attempts to construct the trisubstituted alkene in **35** directly by the Wadsworth–Horner–Emmons reaction afforded an inseparable 1:1 *Z*/*E* mixture. Oxidative elaboration of furan[21] followed by acid-mediated rearrangement delivered **36**.[22] We then attempted to set up a radical cascade with **36** using different metal catalysts and phenylsilane as hydrogen source.[23] No cyclization product was detected with $Co(acac)_2$ or $Mn(dpm)_3$ as the catalyst in the presence of oxygen; this likely reflects the failure of radical initiation at the *gem*-disubstituted alkene.[24] To our delight, HAT-triggered radical cascade polycyclization in the Fe-catalyzed conditions[25] and subsequent silyl deprotection generated the tricyclic compound **37** with proper stereochemistry in 45% isolated yield over two steps. It also generated an inseparable mixture of another three diastereomers in 19% combined yield over two steps.[26] This cascade simultaneously afforded two carbocycles and four contiguous stereogenic centers. Then the secondary alcohol in **37** was removed by a radical process, affording **38**.[27] Partial reduction of the lactone and subsequent elimination generated **39**. Oxidative cleavage of the double bond and base-promoted elimination delivered the enone **40**. Michael addition of compound **11** and pyrolysis of the resulting intermediate released one molecule of SO_2 and generated **41**. Finally, nucleophilic addition of methyl lithium to the ketone, followed by lactone formation, afforded the diene **5**.

We then began synthesizing the dienophile **9** from compound **22** (Scheme 4),[28] which was prepared in 90% *ee* using Yamamoto's enantioselective polyprenoid cyclization.[29] Benzylic oxidation of **22**[30] and basic hydrolysis afforded **42**. Site-selective bromination with 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO) could be smoothly achieved to afford **43**,[31] once the reaction was timely quenched to prevent formation of dibrominated product and other byproducts. Other brominating reagents, such as NBS, bromine and TBAB, led to either complex mixture or an unfavorable product brominated at the *para*-position of ketone on phenyl ring.[26b] Subsequent protection of phenol with MOMCl and Stille cross-coupling with the tin reagent **44** afforded **45**. Final deprotection and base-promoted lactonization produced the dienophile **9**, which is labile and was thus used directly in the next step without purification.



Scheme 4. Synthesis of **9** and hispidanin A.

Diels–Alder cycloaddition between **5** and **9** produced **8** and its diastereomer as *endo*-cycloadducts in 81% combined yield in a 10:1 ratio. Although Diels–Alder cycloaddition has been well applied in organic synthesis and natural product synthesis,[32] this cycloaddition proceeded surprisingly well at room temperature. Such a spontaneous process is uncommon,[33] suggesting that this reaction may participate in the real biosynthesis of hispidanin A through a nonenzymatic pathway, even though the biosynthetic hypothesis from the Jiang group[1] does not involve cycloaddition between **5** and **9.** Diastereoselective reduction of ketone and then acid-promoted acetylation completed the total synthesis of hispidanin A (**1**), for which characterization data matched those of a natural sample.[1]

In conclusion, we have accomplished the asymmetric total synthesis of the dimeric diterpenoid hispidanin A. The synthesis involves 1) stereoselective construction of *Z*-alkene in **35** via Tanabe's iron catalysis; 2) HAT-triggered and iron-catalyzed radical polyene cyclization to generate the *trans*-decalin architecture of the natural diterpenoid **5**; 3) Yamamoto's cationic polyene cyclization to construct the basic skeleton of the dienophile fragment; 4) site-selective bromination with TBCO and Stille cross-coupling to afford the dienophile **9**; and 5) a final step of bioinspired Diels–Alder connection of the two diterpenoid monomers. The radical polycyclization involving electron-deficient alkenes described herein can likely be extended to total synthesis of other diterpenoids functionalized at position C20.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: diterpenoids · labdane · radical cascade · total synthesis · totarane

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Communications

Total Synthesis

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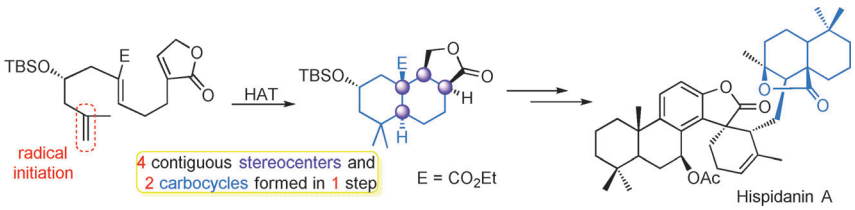
Asymmetric Total Synthesis of Hispidanin A



Radical is radical: Asymmetric total synthesis of a dimeric diterpenoid, hispidanin A, has been accomplished through spontaneous [4+2] cycloaddition without catalysis at room temperature. Construction of the diene fragment features a designed radical polyene cyclization triggered by metal-catalyzed hydrogen atom transfer, while subsequent asymmetric cationic polyene cyclization generates the dienophile fragment.