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Communication

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Thiocarbonyl Ylide Chemistry Enables a Concise Synthesis of (±)-Hippolachnin A

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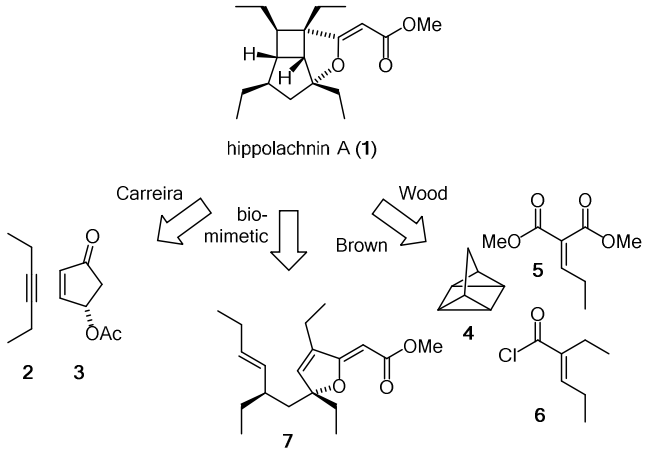
Supporting Information Placeholder

ABSTRACT: Hippolachnin A (**1**) is an antifungal polyketide that bristles with ethyl groups mounted onto a caged heterotricyclic core. It has shown potent activity against *Cryptococcus neoformans*, a yeast that can affect immunocompromised patients as an opportunistic pathogen. Herein we describe a concise, diversifiable, and scalable synthesis of (±)-hippolachnin A (**1**). It features a powerful photochemical opening step, a diastereoselective addition of an ethyl cuprate and an unusual strategy to install two additional ethyl groups that makes use of a thiocarbonyl ylide generated *in situ*.

Opportunistic infections with ubiquitous fungi represent a major challenge to the immunocompromised. The yeast *Cryptococcus neoformans*, for instance, can cause life-threatening meningitis and affect the lungs and skin of patients with advanced acquired immunodeficiency syndrome (AIDS).[1] Indeed, cryptococcosis is the second most common AIDS-related complication in sub-Saharan Africa. Although a combination of intravenously applied amphotericin and oral flucytosin provides an effective treatment, these drugs are associated with significant side effects, difficult administration regimes, high costs, and the emergence of resistance.[2] Therefore, the development of new drugs that target *C. neoformans* and related opportunistic fungal pathogens remains an important goal.

Hippolachnin A (**1**) could provide an important lead in this search. It was recently isolated from the South China Sea marine sponge *Hippospongia lachne*[3] and proved to be highly potent against several pathogenic fungi, including *C. neoformans* (MIC = 0.41 μM). Biosynthetically, it was identified as a polyketide of the gracilioether family. While it bears structural similarities to other members of this series, the 4-5-5 tricyclic core of hippolachnin A is unique.[4] Presumed to be of photochemical origin, it features six contiguous stereocenters and bears an unusual array of four ethyl groups on its convex face.

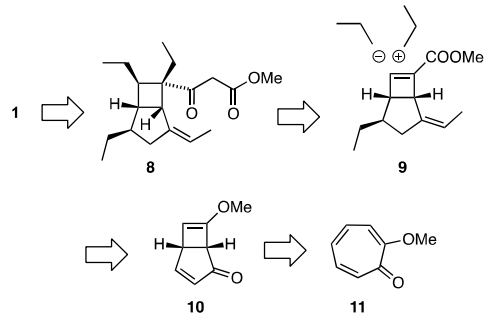
Given its attractive molecular structure and potent bioactivity, it is no surprise that hippolachnin A has attracted the attention of several synthetic groups (Scheme 1). The first total synthesis was achieved by Carreira in 2015.[5] In this case, the cyclobutane core was formed *via* photochemical [2+2] cycloaddition of 3-hexyne (**2**) to cyclopentenone **3** and the heterocycle was installed using an ene-type cyclization. In 2016 Brown and Wood reported a collaborative synthesis in which the cyclobutane was formed through a [2+2+2] cycloaddition of quadricyclane (**4**) to either **5** or **6** and the heterocycle through a late-stage allylic C-H oxidation.[6]



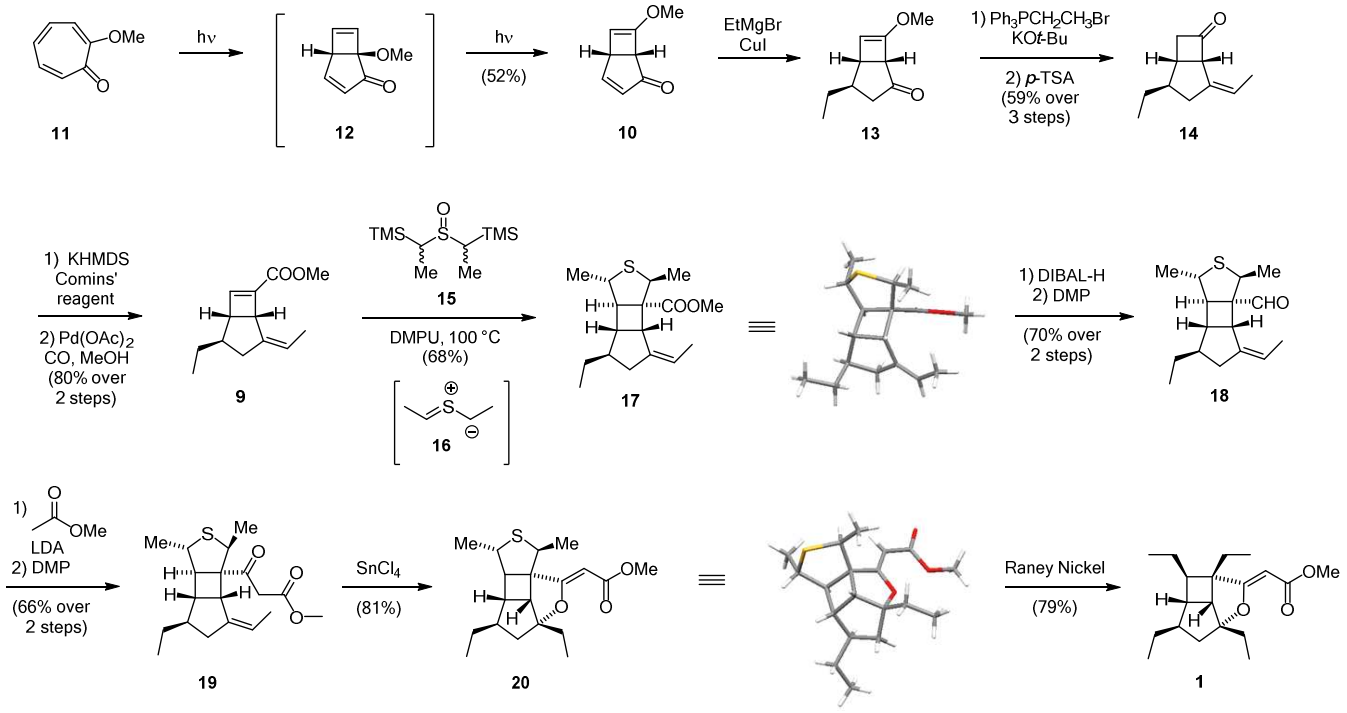
Scheme 1: Synthetic approaches to hippolachnin A

The synthesis of a presumed biomimetic precursor, compound **7**, which was isolated together with **1**, was described by Ohira *et al.* in 2005[7] and by Wu *et al*. in 2017.[8] However, irradiation of **7** with UV light did not yield **1** but only resulted in isomerization of the vinylogous ester moiety.[8] Possibly, the desired cyclization could be achieved using more biomimetic irradiation conditions, as has been recently demonstrated with other marine natural products.[9]

We now report a concise synthesis of hippolachnin A that is also based on a photochemical key step, albeit a decidedly non-biomimetic one. Our retrosynthetic analysis is shown in Scheme 2. In a deviation from previous syntheses, we planned to close the heterocyclic ring in **1** by *O*-alkylation of an enolized β-keto ester **8**.[10] The two vicinal ethyl groups would be installed by three-component coupling involving an ethyl nucleophile, an ethyl electrophile and the Michael acceptor **9**. This key intermediate, in



Scheme 2: Retrosynthetic analysis of hippolachnin A



Scheme 3: Total synthesis of hippolachnin A. KO*t*-Bu=potassium *tert*-butoxide, *p*-TSA= *para*-toluensulfonic acid, KHMDS=potassium hexamethyldisilazide, DMF=dimethylformamide, DMPU=1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, DIBAL-H=diisobutylaluminium hydride, DMP=Dess-Martin periodinane, LDA=lithium diisopropylamide, TBAB=tetrabutylammonium bromide, DCE=1,2-dichloroethane.

turn, could be traced back to the known bicyclo[3.2.0]heptadiene derivative **10**, a photoisomer of the readily available tropolone ether **11**.

Accordingly, our synthesis opens with the photochemical conversion of **11** into methoxy bicyclo[3.2.0]heptadienone **10** (Scheme 3). This unusual photochemical reaction has been studied in detail by Dauben *et al.* and proceeds *via* disrotatory 4π-electrocyclization of **11** to yield **12**, which then undergoes an excited state rearrangement to afford **10**.[11] Stereoselective conjugate addition of ethyl cuprate[12] from the convex side to **10**, followed by Wittig olefination[13] and hydrolysis of the enol ether,[14] gave rise to ketone **14** as a 10:1 mixture of *Z*- and *E*-isomers (major isomer shown). Homologation of ketone **14** was then achieved by formation of the vinyl triflate **[15]** and subsequent carbomethoxylation.[16]

The stage was now set for the introduction of the two remaining ethyl groups. As outlined in our retrosynthesis (Scheme 1), we planned to achieve this by addition of an ethyl nucleophile, followed by alkylation with an ethyl electrophile. Ethyl cuprate addition to unsaturated ester **9** indeed occurred with complete regio- and stereoselectivity at C_{10}. However, the subsequent deprotonation and alkylation with iodoethane only afforded a 1:2 mixture of diastereoisomers in favor of the desired isomer (see Supporting Information).[17] Although the major isomer could be easily converted into an advanced intermediate of the Wood-Brown synthesis,[6] we felt that such a low level of selectivity was not acceptable for an efficient synthesis of **1**.

To overcome this issue, we turned to a cycloaddition chemistry. We reasoned that the 1,3-dipolar addition of thiocarbonyl ylide **16** to the more reactive double bond of **9**, followed by reductive desulfurization of the resulting tetrahydrothiophene, would deliver both ethyl groups to the convex side.[18] To this end, we synthesized the sulfoxide **15** as a precursor of the highly reactive **16**. Compound **15** is a homologue of the parent reagent introduced by Achiwa and was prepared in two steps from sodium sulfide and 1-chloroethyl trimethylsilane (see Supporting Information).[19] Indeed, heating of **15** in the presence of **9** afforded tetrahydrothiophene **17** as a single diastereomer. Single crystal X-ray structure analysis showed that the methyl groups adopt a *trans*-configuration with respect to the tetrahydrothiophene ring, which can be explained by the stepwise nature of thiocarbonyl ylide cycloadditions.[20]

The final phase of our synthesis required the elongation of the methyl ester into a β-keto ester and its closure to a tetrahydrofuran to obtain the full carbon skeleton of hippolachnin A. Unfortunately, all attempts at a crossed Claisen condensation or even hydrolysis of **17** failed, presumably due to steric hindrance.[21]. However, a reduction-oxidation sequence gave rise to aldehyde **18** in good yield. Aldol addition[22] of methyl acetate then afforded the corresponding β-hydroxy ester, which could easily be oxidized to yield β-keto ester **19**. Formation of the tin enolate followed by chelation-controlled trapping of the simultaneously generated tertiary carbocation[10] gave rise to (*Z*)-configured vinylogous carbonate **20**.[23] Desulfurization with Raney nickel in THF[24] then provided hippolachnin A. Overall, the synthesis proceeds in 12 steps from the known bicyclo[3.2.0]heptane **10** and provides **1** on a 100 mg scale.

Our synthesis will serve as a platform for the development of more potent and more soluble antifungal agents as well as molecular probes with which to identify the biological target(s) of hippolachnin A. It relies on a photoisomerization of a tropolone to construct the bicyclic carbon core of the natural product. Asymmetric variants of this rearrangement have been described.[25] The distinctive four ethyl substituents of **1** are introduced by a cuprate conjugate addition, a Wittig olefination, followed by etherification, and a thiocarbonyl ylide cycloaddition, followed by eventual reductive desulfurization. The latter amounts to the addition of an alkane over an (electron poor) alkene. Despite its high strategic value, this sequence has been rarely used in synthesis.[26] This may be because, apart from the parent system, precursors of the requisite thiocarbonyl ylides have not been widely available. Future studies will expand on this chemistry and explore its usefulness in the synthesis of hippolachnin A derivatives as well as other complex natural products. Biological investigations of analogs of hippolachnin A, in particular compound **20** and its oxidation products, are currently ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

CIF file for compound **17** (CCDC 1563493).
CIF file for compound **20** (CCDC 1563492).
Experimental procedures, spectroscopic data and copies of NMR-spectra.
The CIF files are also available free from charge on https://www.ccdc.cam.ac.uk/structures/.

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Notes

The authors declare no competing financial interest.

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