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Enantioselective Synthesis of (+)-Hippolide J and Reevaluation of Antifungal Activity

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Abstract

A synthesis of the reported antifungal agent (+)-hippolide J is presented. The rapid assembly of the natural product was enabled through implementation of an enantioselective isomerization/[2 + 2]-cycloaddition sequence. Due to the simplicity of the route, >100 mg of the natural product were prepared in a single pass. Antifungal assays of hippolide J, however, confirmed that it showed no activity against several fungal strains, contrary to the isolation report.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c02979>.

Experimental procedures and analytical data for all compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **1**, **12**, **13**, **15**, **17**, **18**, **19**, **21**, **23**, **25**, **SI-6**, **SI-8**, **SI-9**, **SI-10**, **SI-11** (ZIP)

(+)-Hippolide J (**1**) (Figure 1) is a complex natural product that was isolated from the marine sponge *Hippospongia lachne*.¹ Its structure and preliminary biological activity were reported in 2016, describing its antifungal activity against invasive fungal pathogens. Given the limited number of drugs available to treat invasive fungal infections, the emerging problem of antifungal drug resistance, and the increasing number of patients at risk for these infections,² (+)-hippolide J (**1**) has emerged as an encouraging avenue to explore. Interestingly, while the molecule was isolated as a racemate, the enantiomers were separated and both were found to have a similar biological profile. Finally, preliminary toxicity evaluation of (–)- and (+)-hippolide J (**1**) showed little activity against human cancer cell lines, thus confirming it as a promising lead compound. From a chemical standpoint, stereocontrolled assembly of the pentasubstituted cyclobutane ring of (+)-hippolide J (**1**) represents a challenge that would require improvement upon state-of-the-art in cyclobutane synthesis. Due to the limited availability of (+)-hippolide J (**1**), the desire to pursue biological investigation, and the intriguing structure, we elected to develop a scalable synthesis.

Our lab has taken an interest in [2 + 2] cycloadditions of alkenes with electron deficient allenes.^{3–6} Along these lines, we have reported catalytic and enantioselective cycloadditions of allenates with unactivated alkenes.³ In connection with these efforts, we investigated related cycloadditions of allenic ketones (**6**) (Scheme 1), which led to the development of an enantioselective isomerization⁷/stereoselective [2 + 2]-cycloaddition⁸ process (**4** to **6** to **8**) for the synthesis of bicyclo[4.2.0]octanes **8**.⁹ The scope of this method was evaluated and was found to be broad due to, in part, the straightforward synthesis of the alkyne precursors to the allene (**4**) from lithium acetylides (**2**) and epoxy alkenes (**3**).⁹ The utility of the method was demonstrated in the synthesis of *ent*-[3]-ladderanol⁹ and, in a more recent study, in the synthesis of (–)-cajanusine.¹⁰

Based on the aforementioned reaction methodology, a retrosynthesis of **1** was devised that would allow rapid synthesis of the cyclobutane containing core structure (**10**) from **11** by establishing three of the four stereogenic centers in a single operation (Scheme 2). Due to the pathway of [2 + 2]-cycloaddition, which would lead to positioning of the butenolide moiety on the concave face of the bicyclo[4.2.0]-octane, epimerization would be necessary (**10** to **9**). Finally, elaboration of the enone subunit of **9** to the allylic alcohol motif of **1** could be affected by stereocontrolled conjugate reduction and cross-coupling reactions.

Our studies commenced with synthesis of the allenic ketone necessary for stereoselective [2 + 2]-cycloaddition (Scheme 3). The requisite homopropargylic alcohols were prepared through addition of a lithium (trimethylsilyl)acetylide to epoxide **12** (derived from commercially available farnesylacetone in three steps; see Supporting Information (SI)). Cross-coupling with lactone **14** led to formation of **15**. Attempted oxidation under various conditions led to inseparable mixtures of the alkynyl ketone **11** and racemic allenic ketone **16**. The facile isomerization is likely due to the increased acidity of the hydrogens alpha to the ketone as a result of the electron-withdrawing butenolide unit.

Due to the aforementioned challenges encountered with early stage incorporation of the butenolide unit, a revised approach was investigated that would incorporate the motif at a

later stage. It was envisioned that a protected hydroxyl methylene unit could serve as a versatile precursor for butenolide synthesis and the required alkynyl ketone would be less prone to premature isomerization.

The second-generation approach commenced with preparation of alkynyl ketone **17** (undesired isomerization was not observed), from farnesylacetone in five steps on multigram scale (see SI). Enantioselective isomerization and stereoselective [2 + 2]-cycloaddition proceeded smoothly to generate cyclobutane **18** in excellent diastereoselectivity and enantioselectivity (Scheme 4). This reaction is noteworthy because it was easily performed on gram scale and it established three contiguous stereogenic centers with control of enantioselectivity and diastereoselectivity.

1,4-Reduction of **18** and in situ generation of vinyl triflate **19** allowed for cross-coupling with trifluoroborate **20** to be investigated (Scheme 4). Initial attempts to carry out this reaction under Pd-catalysis were unsuccessful, as low yield and significant proto-detriflation were observed.¹¹ To address this challenge, we elected to explore an emerging set of transformations that employ photocatalysis in conjunction with Ni-catalyzed cross-coupling. Under these conditions, **21** was formed in good yield with minimal formation of byproducts.¹²

Deprotection and oxidation generated the corresponding aldehyde **22** (Scheme 4).¹³ Epimerization of the stereogenic center was accomplished with DBU to deliver **23**. This reaction is driven by release of steric pressure of the aldehyde from the concave face of the bicycle. Benzoin condensation with formaldehyde promoted by precatalyst **24** led to formation of α -hydroxy ketone **25**.¹⁴ Finally, sequential treatment with the Bestmann ketene (**26**)¹⁵ and DDQ led to the formation of (+)-hippolide J (**1**).¹⁶ Due to the simplicity of the route, synthesis of 135 mg of (+)-hippolide J (**1**) was easily achieved in a single pass.

With a scalable synthesis developed, attention was turned to biological evaluation of (+)-hippolide J (**1**) against human fungal pathogens (Table 1). However, under the same conditions (CLSI methodology)¹⁷ the authors of the isolation report described, (+)-hippolide J showed no activity at 8–256-fold above the reported MIC for *Candida albicans*, *Candida glabrata*, *Aspergillus fumigatus*, and *Cryptococcus neoformans* using both reference strains and clinical isolates. Importantly, we tested the same isolate of *Candida albicans* (SC5314) as tested in the initial report.¹⁸ The source of the discrepancy is not known at this time.¹⁹

Through the implementation of an enantioselective isomerization/chirality transfer process, the synthesis of (+)-hippolide J was achieved. The synthesis also serves to highlight an emerging set of transformation in metallo-photoredox catalysis. Finally, the biological evaluation of synthetic (+)-hippolide J revealed that the molecule was inactive against all tested fungal strains.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structures of (+)-hippolide J (**1**).

Scheme 1.

Enantioselective Isomerization/[2 + 2]-Cycloaddition Sequence for Bicyclo[4.2.0]octane

Scheme 2.
Initial Retrosynthesis of (+)-Hippolide J (1)

Scheme 3.
Challenges with Initial Route

Scheme 4.
Synthesis of (+)-Hippolide J (1)

Table 1.

Biological Testing of (+)-Hippolide J (1)

Species	Strain	MIC ₅₀ (μg/mL)		
		natural (+)-1	natural (–)-1	synthetic (+)-1
<i>C. albicans</i>	SC5314	0.125 ^a	0.125 ^a	>32
	Y0109	4 ^a	2 ^a	–
<i>C. glabrata</i>	ATCC2001	–	–	>32
	4720	–	–	>32
	537	0.125 ^a	0.25 ^a	–
<i>C. neoformans</i>	H99	–	–	>32
	DUMC	–	–	>32
	101.24			
	32609	0.5 ^a	0.25 ^a	–
<i>A. fumigatus</i>	CEA10	–	–	>32
	AF293	–	–	>32
	07544	4 ^a	2 ^a	–

^aFrom ref 1.