Tetrahedron Letters 58 (2017) 4459–4464

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Concise synthesis and revision of the proposed biogenesis of helicascolides

Kuan Zheng [a,b], Changmin Xie [a,b], Ran Hong [a,*]

[a] CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry (CAS), Shanghai 200032, China
[b] University of Chinese Academy of Sciences, 19A Yuquan Road, Beijing 100049, China

ARTICLE INFO

Article history:
Received 19 September 2017
Accepted 9 October 2017
Available online 13 October 2017

Keywords:
Helicascolides A–C
δ-Lactones
Biogenesis
Biomimetic synthesis
Boronate

ABSTRACT

A concise synthesis of helicascolides A, B and C was achieved in three to five steps from commercially available materials. The key transformations of the synthesis include an Evans-Metternich *anti*-aldol reaction of the known β-keto imide **10** and strategic base-mediated one-pot cyclization/alkylation. Based on the new chemical evidence of ring-opening reaction of β-keto ester under biocompatible basic conditions, Krohn's proposal for the biosynthetic relationship between helicascolide A (**1**) and a naturally co-existing acyclic dienone **4** was suggested in a reverse manner.

Marine microorganisms have been intensely exploited for their novel bioactive secondary metabolites from diverse biosynthetic origins.[1] Helicascolides A (**1**) and B (**2**) (Fig. 1) were first isolated by Gloer and co-workers from the marine fungus *Helicascus kanaloanus* (ATCC 18591) in 1989.[2] Recently, Tarman and co-workers reported the characterization of structurally related helicascolide C (**3**) from an Indonesian marine algicolous strain *Gracilaria* sp. SGR-1.[3] Interestingly, only helicascolide C (**3**) shows a notable ability to inhibit the growth of *Cladosporium cucumerinum*, a pathogenic plant fungus that affects cucumbers. In 2006, Krohn and co-workers[4] isolated the biologically active linear metabolite (4*E*,6*E*)-2,4,6-trimethylocta-4,6-dien-3-one (**4**) along with helicascolide A (**1**) from the endophytic fungus *Nodulisporium* sp. From a structural perspective, helicascolides (**1**–**3**) belong to a small family of partially dehydrated tetraketides that are characterized by a highly congested δ-lactone ring system with *gem*-dimethyl substitution at the C2 position.

With the ongoing interest in the development of bioinspired synthetic strategies for the efficient syntheses of bioactive polyketides,[5] the molecular architecture of helicascolides captured our interest, since the specific scaffold is found in various natural products or natural product-like synthetic intermediates (**5**–**7** in Fig. 1).[6,7] The first total synthesis of **1** and **3**, disclosed by Krishna and co-workers,[8] featured a one-pot acid-catalyzed acetonide removal and subsequent lactonization. The Yadav group[9] achieved a concise total synthesis of **1**–**3** by employing a similar ring-forming strategy and utilizing iterative aldolization to access the precursor in a more efficient manner.[10] In 2016, Breit and co-workers[11] also accomplished the total syntheses of **1**–**3** by intramolecular Rh-catalyzed diastereoselective additions of chiral ω-allenyl carboxylic acids. Herein, we present a short synthesis of all the representatives of the helicascolide family, which were assembled with the longest linear sequences ranging from three to five steps.

Retrosynthetically, we envisioned that structurally simpler helicascolide C (**3**), for which the most oxidized carbon is C3, could serve as the primary target and a branching intermediate to access the other congeners of the family via late-stage stereoselective reduction of the C3-ketone (Scheme 1). By taking advantage of this distinctly different tactic, methylation at C2 of cyclic β-keto ester enolate **8** should be feasible. This synthetic strategy is largely simulating a possible biosynthetic pathway that involves chain elongation and methylation initiated by SAM (*S*-adenosyl methionine). Anionic intermediate **8** should be accessible from the cyclization of aldolate anion **9**, in which the entire tetraketide backbone could be derived from the reaction of known Evans' dipropionate synthon **10**[12] with tiglic aldehyde. Integral to this approach was the dramatic increase in the kinetic acidity of the C2 position of **8**, which was a result of the enolization favoring a cyclized product conformation in which better orbital overlap between σ-C2-H and π*-C3-O could be realized[13].

Chiral β-keto imide **10** was readily prepared in a two-step protocol (Scheme 2) that included an Evans *syn*-aldol reaction

* Corresponding author.
E-mail address: rhong@sioc.ac.cn (R. Hong).

https://doi.org/10.1016/j.tetlet.2017.10.021
0040-4039/

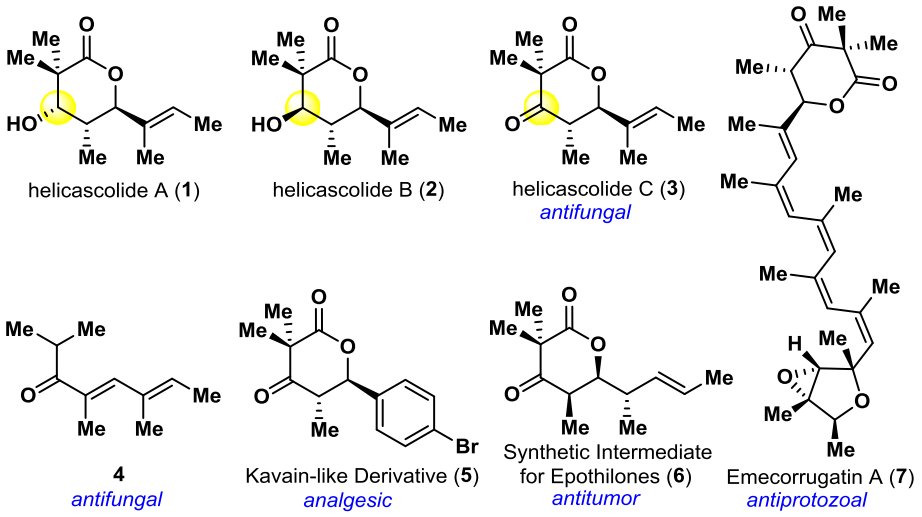
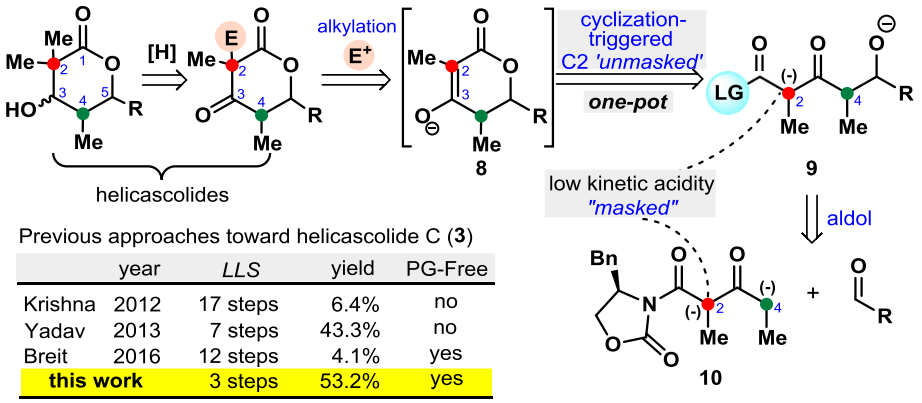


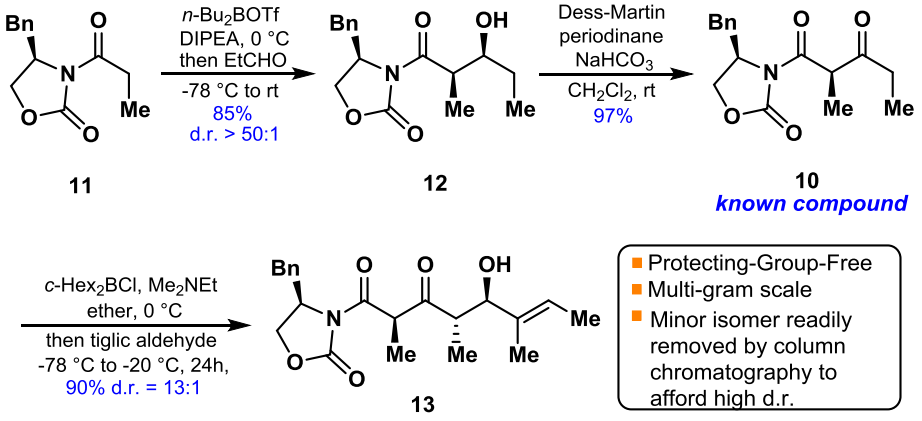
Fig. 1. Helicascolides and structurally related compounds.



Previous approaches toward helicascolide C (**3**)

	year	*LLS*	yield	PG-Free
Krishna	2012	17 steps	6.4%	no
Yadav	2013	7 steps	43.3%	no
Breit	2016	12 steps	4.1%	yes
this work		3 steps	53.2%	yes

Scheme 1. Retrosynthetic analysis of the helicascolides. [H] = reduction; R = substituent; LG = leaving group; LLS = the longest linear steps; PG = protecting group.



Scheme 2. Synthesis of compound **13**.

between commercially available *N*-acyloxazolidinone **11** and propanal followed by Dess-Martin oxidation of corresponding alcohol **12**. Addition of the (*E*)-boron enolate pre-formed from **10** to tiglic aldehyde provided two *anti*-aldol adducts in 90% combined yield with a diastereomeric ratio (d.r.) of 13:1.[14] A second purification using flash column chromatography further enriched the d.r. up to 30:1.

With several grams of the requisite acyclic tetraketide **13** in hand, we were in a position to test the feasibility of the crucial cyclization/alkylation cascade (conversion of **9** to **3** shown in Scheme 1). Initially, the cyclization reaction was carried out under conventional conditions[15] for analogous substrates bearing a C3-hydroxyl group; however, extensive decomposition was observed (entries 1 and 2 in Table 1). Next, we found that treatment of **13**