



Total Synthesis of (±)-Hippolachnin A**

Stefan A. Ruider, Tobias Sandmeier, and Erick M. Carreira*

Abstract: The first total synthesis of the marine polyketide (±)-hippolachnin A has been achieved in nine linear steps and an overall yield of 9 %. Rapid access to the oxacyclobutapentalene core structure was secured by strategic application of an ene cyclization.

Hippolachnin A (**1**, Figure 1 a) is a recently isolated marine polyketide characterized by an intriguing molecular framework and promising pharmacological activity.^[1,2] Its structure bears resemblance to other oxygenated pentalenes isolated from sponges, such as the gracilioethers (Figure 1 b).^[3,4] Initial studies attributed potent antifungal activity to **1**,^[1] as well as potential curative effects for the treatment of various diseases, including renal fibrosis,^[2a] acute renal failure,^[2b] chronic heart failure,^[2c] oral ulcer,^[2d] and rhinitis.^[2e] The structure of **1** features a highly substituted cyclobutane ring and six contiguous stereocenters, one of which is quaternary (C4). Along with its promising biological profile, the congested oxacyclobutapentalene core motif renders hippolachnin A (**1**) a veritable synthetic target. Herein, we describe the first total synthesis of (±)-hippolachnin A (**1**), which is remarkable for its conciseness and efficiency.^[5]

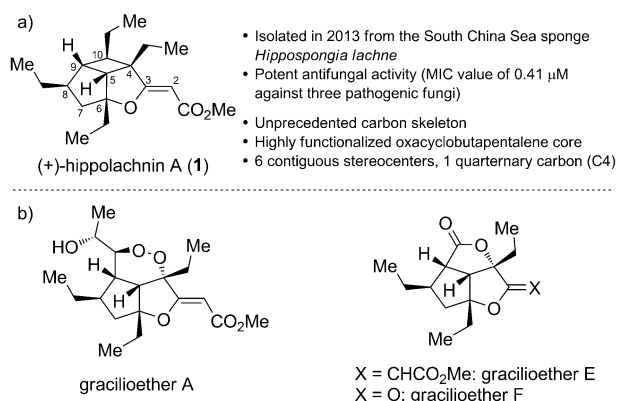


Figure 1. Marine polyketide (+)-hippolachnin A (**1**) and its related polyketides gracilioethers A, E, and F. MIC = minimum inhibitory concentration.

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On the basis of topological strategy analysis,^[6] we became intrigued by the possibility of forging the core skeleton by functionalization of a highly substituted cyclobutene. As outlined in Figure 2 a, a strategy involving formal regio- and stereoselective hydroalkylation of the cyclobutene by the

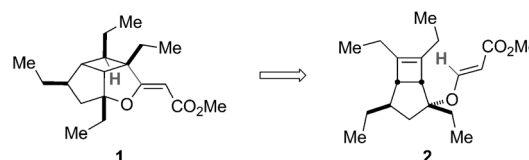
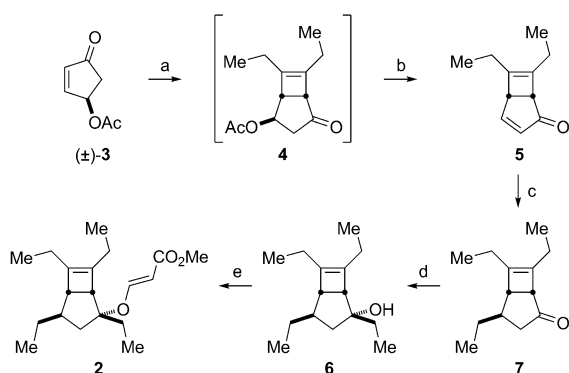


Figure 2. Topological-strategy-guided key disconnection.

unsaturated ester in **2** was envisioned. Despite recent advances,^[7] the chemistry of cyclobutenes has not been extensively investigated. The proposed route to hippolachnin A provided an opportunity to examine whether the cyclobutene would be sufficiently reactive to be coupled to the electrophilic β-alkoxyacrylate. Such an approach, if successful, would constitute a rare example in which an unactivated cyclobutene is exploited for the generation of a quaternary stereocenter. Moreover, we hypothesized that the readily available 4-acetoxy-2-cyclopenten-1-one would provide entry into a scaffold that is common to a number of related marine natural products.^[3,8]

The synthesis commenced with cyclopentenone **3**, a common building block available in multigram quantities from furfuryl alcohol (Scheme 1).^[9] Irradiation of **3** and hex-3-yne in acetone at λ > 270 nm afforded bicyclo-[4.2.0]heptanone **4** in a diastereomeric ratio of 4:1.^[10,11] As the photoadduct was susceptible to elimination to form enone **5** during chromatography, ketone **4** was not isolated but directly converted into **5**. Treatment of the unpurified photo-reaction mixture with deactivated alumina and potassium carbonate furnished enone **5** in 54 % overall yield over two steps.^[12]

With enone **5** in hand, we turned our attention to the synthesis of α,β-unsaturated ester **2**. Copper-mediated 1,4-addition of ethylmagnesium bromide and subsequent Grignard 1,2-addition afforded alcohol **6** with complete *exo* diastereoselectivity in 66 % combined yield (2 steps). It should be noted that the 1,2-addition of ethylmagnesium bromide to **7** required the presence of Knochel's soluble lanthanide salts (LaCl₃·2LiCl)^[13] for complete conversion. Extensive experimentation was required to identify conditions for the formation of α,β-unsaturated ester **2** from **6**, because the *endo*-oriented tertiary alcohol in **6** proved to be highly hindered and difficult to functionalize. Exposure of **6** to a variety of conditions (e.g., PMe₃/methyl propionate,^[14a]



Scheme 1. Reagents and conditions: a) *hν* (Wisag TQ 150 W, Pyrex filter, 270–600 nm), hex-3-yne (10 equiv), acetone, RT; b) K_2CO_3 (5 equiv), basic Al_2O_3 (10 wt% H_2O), CH_2Cl_2 , RT, 54% over two steps (65% brsm); c) CuI (2.1 equiv), $EtMgBr$ (3 M in Et_2O , 4 equiv), $-78^\circ C$ to $-20^\circ C$, 73%; d) $EtMgBr$ (3 M in Et_2O , 3 equiv), $LaCl_3 \cdot 2 LiCl$ (0.5 M in THF, 1.02 equiv), $0^\circ C$, 90%; e) (*E*)-methyl-3-methoxyacrylate (40 equiv), PPTS (0.1 equiv), $80^\circ C$, 95%. brsm = based on recovered starting material, PPTS = pyridinium *para*-toluenesulfonate.

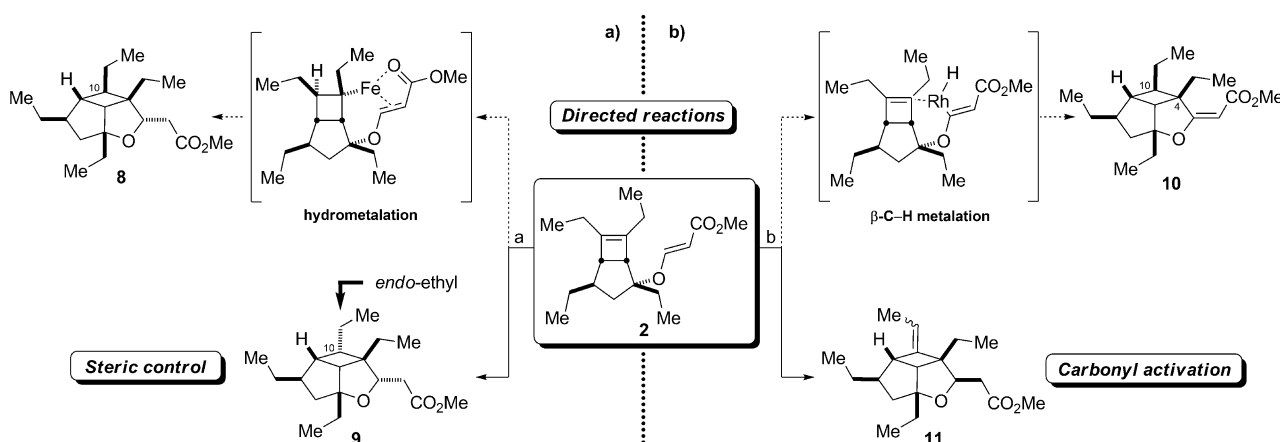
NEt_3 /methyl propiolate,^[14b] methoxy acrylate/PPTS,^[14c,d] and methoxy acrylate/*N*-methylmorpholine^[14c,d] only gave ester **2** in < 10% yield accompanied by considerable decomposition of the starting material. The inherently poor nucleophilicity of the shielded tertiary alcohol was successfully overcome by employing (*E*)-methyl-3-methoxyacrylate as the solvent. Accordingly, heating a 0.2 M solution of alcohol **6** in (*E*)-methyl-3-methoxyacrylate in the presence of PPTS at $80^\circ C$ furnished ester **2** in 95% yield.^[15]

With a scalable and reliable route to ester **2** established, the preparation of the highly congested core could be addressed. At the outset, we were drawn to investigating two distinct approaches: In the first of these, hydrometalation of the cyclobutene would be followed by C–C bond formation upon reaction with the unsaturated ester (Scheme 2a), whereas in the second approach, functionalization of the ester would precede the reaction with the cyclobutene

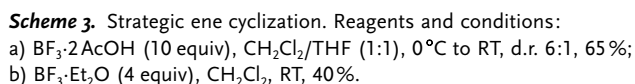
(Scheme 2b). To establish the correct stereochemical relationship in the products, both approaches would require the unsaturated ester to function as a suitable directing group in two distinct modes.

We were particularly interested in examining Baran's recent elegant work on the reductive coupling of olefins with Michael acceptors and probing whether it would be susceptible to directing effects,^[16,17] as low-valent iron species are known to coordinate to olefins (Scheme 2a).^[18] Submission of ester **2** to $[Fe(acac)_3]$ and $PhSiH_3$ indeed provided a cyclized ester, albeit in 24% yield. Unfortunately, NOE data revealed that the product (**9**) possessed one of the ethyl substituents in the *endo* configuration. Furthermore, the iron-mediated coupling suffered from low regiocontrol in the initial hydrometalation event, leading to an unwanted cyclization product.^[19] Interestingly, as the hydrometalation occurs in an *exo* fashion, the fact that cyclization of **2** into **9** takes place would suggest that the configuration of the initially formed Fe–C bond is labile.

In light of the regio- and stereochemical issues that conspired against the first approach, we then examined the second option, in which the core scaffold would be formed by first effecting the reaction of the pendant ester followed by intramolecular hydrovinylation of the cyclobutene (Scheme 2b).^[20,21] In this respect, we sought to examine whether it would be possible to effect β -C–H metalation with concomitant formation of the C4 and C10 stereocenters. Inspired by Murai's and Trost's pioneering work on β -alkylations of unsaturated esters and ketones with olefins,^[20a,b] we examined conditions using Ru^0 complexes, such as $[RuH_2(CO)(PPh_3)_3]$ ^[20a,b] and $[RuCl_2(C_6H_6)_2]/Zn$.^[20c] However, despite numerous efforts we never observed the formation of hydrovinylation product **10**. More recently, Bergman and Ellman reported the use of Rh^I catalysts in the β -functionalization of unsaturated imines, which provided an alternative.^[20d] Interestingly, whereas exposure of **2** to neutral Rh^I catalysts, for example, $[RhCl(coe)_2]/PCy_3$ (*coe* = cyclooctene),^[20d] only led to the decomposition of **2**, cationic Rh^I complexes, such as $[RhCl(cod)]_2/2 AgSbF_6$,^[22] provided small quantities of **11** at



Scheme 2. Initial attempts of constructing the core skeleton. Reagents and Conditions: a) $[Fe(acac)_3]$ (2 equiv), $PhSiH_3$ (4 equiv), DCE/ethylene glycol (5:1), $80^\circ C$, 24% **9**; b) $[RhCl(cod)]_2$ (5 mol%), $AgSbF_6$ (10 mol%), DCE, RT, 6% **11**. *acac* = acetylacetonate, *cod* = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane.



Access to hippolachnin A (**1**) from alkene **11** required the stereoselective hydrogenation of the exocyclic double bond and installation of the vinyl-
ous carbonate. Inspection of the natural product suggested that the cyclobutane with *exo*-oriented ethyl groups would be thermodynamically preferred. However, density functional theory (DFT) calculations^[26] at the B3LYP/6-311 + G(d,p)^[27] level of theory indicated that ester **13** (*endo* at C10) would be more stable by $\Delta\Delta G^0 = 1.0$ kcal mol⁻¹ than the corresponding epimeric, desired structure **14** (*exo* at C10; Table 1). This substrate provided a test case for Shenvi's recently described method for the reduction of alkenes to give the thermodynamically preferred products.^[28, 29] Indeed, as shown in Table 1, ester **13** (*endo* at C10) was found to be selectively accessible under Shenvi's conditions (entries 1–3). Thus, exposure of alkene **11** to phenylsilane, *tert*-butyl hydroperoxide, and catalytic amounts of [Mn(dpm)₃], [Co(acac)₂], or [Fe(acac)₃] gave exclusively ester **13** in 46–75 % yield. Alternatively, we found that hydrogenation conditions afforded mixtures of both epimers, favoring in all cases all-*exo* product **14** (entries 4, 6–10). Heterogeneous conditions employing palladium catalysts provided the best results, whereas Wilkinson's or Crabtree's catalyst only led to low or no conversion (entries 4 and 5). Ultimately,

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Having developed a concise route to ($\pm$)-hippolachnin A (**1**), we decided to explore strategies to access enone **5** in enantioenriched form. Ultimately, this would set the stage for a formal enantioselective synthesis of (+)-**1**. Our efforts towards the asymmetric preparation of enone **5** relied on the photocycloaddition between hex-3-yne and (+)-**3**, which is available in one step from commercial material.^[30] Thus, irradiation of enone (+)-**3** and hex-3-yne, followed by elimination afforded enone (+)-**5** in 94% *ee* (28% over 2 steps; see the Supporting Information for further information).

In conclusion, we have achieved the first total synthesis of ($\pm$)-hippolachnin A (**1**) in a sequence of nine linear steps from known cyclopentenone **3** in an overall yield of 9%. The synthesis relies on the strategic application of an ene cyclization, which efficiently provides access to the oxacyclobutapentalene core skeleton. We have demonstrated that enone **5** can be obtained in a high enantiomeric ratio, thus providing a formal enantioselective route to the total synthesis of (+)-hippolachnin A (**1**). In a broader sense, we anticipate that the various intermediates of the synthesis route, in particular enone **5**, may serve as useful building blocks amenable to the synthesis of other members of this intriguing class of natural products. Studies are on-going and will be reported as they become available.

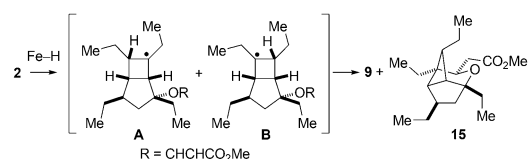
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