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Title: Enantioselective Total Syntheses of (+)-Hippolachnin A, (+)-Gracilioether A, (-)-Gracilioether E and (-)-Gracilioether F

Year: 2018

Version:

Please cite the original version:

Li, Q., Zhao, K., Peuronen, A., Rissanen, K., Enders, D., & Tang, Y. (2018). Enantioselective Total Syntheses of (+)-Hippolachnin A, (+)-Gracilioether A, (-)-Gracilioether E and (-)-Gracilioether F. *Journal of the American Chemical Society*, 140(5), 1937-1944. <https://doi.org/10.1021/jacs.7b12903>

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Article

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b12903 • Publication Date (Web): 09 Jan 2018

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Enantioselective Total Syntheses of (+)-Hippolachnin A, (+)-Gracilioether A, (-)-Gracilioether E and (-)-Gracilioether F

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ABSTRACT: The *Plakortin* polyketides represent a structurally and biologically fascinating class of marine natural products. Herein, we report a unified strategy that enables the divergent syntheses of various *Plakortin* polyketides with high step-economy and overall efficiency. As proof-of-concept cases, the enantioselective total syntheses of (+)-hippolachnin A, (+)-gracilioether A, (-)-gracilioether E and (-)-gracilioether F have been accomplished based on a series of bio-inspired, rationally designed or serendipitously discovered transformations, which include 1) an organocatalytic asymmetric 1,4-conjugate addition to assemble the common chiral γ -butenolide intermediate *en route* to all of the aforementioned targets, 2) a challenging biomimetic [2+2]-photocycloaddition to forge the oxacyclobutapentalene core of (+)-hippolachnin A, 3) a [2+2]-photocycloaddition followed by one-pot oxidative cleavage of methyl ether/Baeyer-Villiger rearrangement to access (-)-gracilioether F, and 4) an unprecedented hydrogen-atom-transfer (HAT)-triggered oxygenation of vinylcyclobutane to afford (+)-gracilioether A and (-)-gracilioether E in one pot.

INTRODUCTION

The *Plakortin* polyketides constitute a growing family of marine natural products that display remarkable structural and biological diversity.¹ As one of the most prominent family members, hippolachnin A (**1**, Figure 1) was identified by Lin and co-workers from the South China Sea sponge *Hippospongia lachne* in 2013.² Preliminary biological evaluation revealed that hippolachnin A exhibited potent antifungal activity against three pathogenic fungi including *Cryptococcus neoformans*, *Trichophyton rubrum*, and *Microsporum gypsum*, with a MIC value of 0.41 μ M for each species.² Therefore, it represents a new chemotype of anti-fungal agents or leads. Further studies suggested that hippolachnin A could also potentially function as a therapeutic agent to treat various diseases such as renal fibrosis, chronic heart failure and rhinitis.³ Structurally, hippolachnin A bears an unprecedented molecular architecture that features a highly strained, bowl-shaped 5/5/4 tricyclic core. Moreover, it contains six consecutive stereogenic centers, four of which bear an ethyl substituent projected toward the convex orientation. Besides hippolachnin A, a series of closely relevant congeners, namely gracilioethers, have also been discovered in nature, as exemplified by the structures **2-8**.⁴ In analogy to hippolachnin A (**1**), most of gracilioethers possess a typical tricyclic system, in which the A and B rings are relatively conserved, but the C rings vary greatly in regard to the ring sizes (4-, 5- and 6-membered rings) and oxidation patterns (lactone, furan and 1,2-dioxane). Of note, the gracilioether family is also endowed with diverse biological profiles. For example, gracilioether A

Figure 1. Structures of hippolachnin A and gracilioethers.

(**2**) shows promising antimalarial activities against *Plasmodium falciparum* (IC_{50} = 10 μ g/mL) and gracilioether H (**6**) displays significant antiplasmodial activity against chloroquine resistant CR FC29 strain (IC_{50} = 3.26 μ M).^{4a,4b} In addition, several members of gracilioethers such as **3**, **5**, **7** and **8** exhibit notable pregnane-X-receptor (PXR) agonistic activity, which renders them the promising leads for the development of anti-inflammatory drugs.^{4c}

Not surprisingly, the fascinating molecular architectures and promising biological profiles of hippolachnin A and gracilioethers stimulated extensive interests from the synthesis community,⁵⁻⁶ which has culminated in a number of elegant total syntheses of these targets. In 2015, Carreira and co-workers completed the first total synthesis of (±)-hippolachnin A (**1**), with an intermolecular [2+2]-photocycloaddition and an intramolecular ene-cyclization employed as key steps.^{5a} Meanwhile, an asymmetric synthesis of the key intermediate *en route* to (+)-**1** was also described in this work. Subsequently, the Wood and Brown groups collaboratively accomplished a landmark seven-step total synthesis of (±)-**1**, which hinges on an intriguing [2π + 2σ + 2σ] cycloaddition of quadricyclane and a late-stage intramolecular allylic C-H oxidation.^{5b} More recently, another impressive total synthesis of (±)-**1** was achieved by the Trauner group, the key elements of which include the photoisomerization of tropolone and an unusual thiocarbonyl ylide-mediated [3+2] cycloaddition.^{5c} Besides above-mentioned total syntheses, a formal synthesis of (±)-**1** and an asymmetric synthesis of the tricyclic core of (+)-**1** were reported by the Wu^{5d} and Ghosh^{5e,5f} groups respectively, both of which employed the bio-inspired [2+2]-photocycloadditions as the key steps. As to the gracilioethers, the Brown group completed the first total synthesis of (±)-gracilioether F (**4**) in 2014, featuring a ketene-alkene [2+2] cycloaddition and a late-stage carboxylic acid directed C-H oxidation.^{6a} In 2016, another two total syntheses of (±)-gracilioether E (**3**) and (or) F (**4**) were successively reported by the Carreira^{6b} and Wong groups.^{6c} In the early of 2017, Wu and co-workers disclosed a total synthesis of **4** as well as a formal synthesis of **3**.^{5d} More recently, an asymmetric synthesis of (-)-gracilioether E (**3**) was achieved by the Ghosh group based on a chiral pool strategy.^{6d}

In spite of great advances, there exist some unmet challenges for the total syntheses of hippolachnin A and gracilioethers. First of all, most of the previous syntheses were achieved in a racemic manner. So far, only one asymmetric total synthesis of **3**^{6d} and one asymmetric formal synthesis of **1**^{5a} have been documented. In this context, the asymmetric syntheses of these targets remain relatively underdeveloped. Secondly, only limited members (**1**, **3** and **4**) of this family of natural products have been conquered by synthetic chemists, and some more challenging targets such as **2** and **5-8** have not yet succumbed to total synthesis. Thus, it has remained an unfulfilled task to develop a flexible synthetic approach enabling the access of diverse polycyclic *Plakortin* polyketides, particularly those ones bearing different frameworks. Last but not least, while the biosynthetic origins of hippolachnin A and gracilioethers seem to be inspiring, their real biomimetic syntheses have not been realized yet. Taking hippolachnin A as an example, although the bio-inspired [2+2]-photocycloadditions have been successfully realized with some truncated substrates,^{5d-f} the attempts to effect the [2+2]-photocycloaddition with the biosynthetic precursor to **1** turned out to be problematic,^{5d,6e} which casted a shadow on such a biomimetic approach. Herein, we report our own contribution on this topic, which led to the development of a unified synthetic route that can address all of the above-mentioned challenges encountered for the chemical syntheses of hippolachnin A and gracilioethers. Hinging on a series of bio-inspired, rationally designed or serendipitously discovered transformations, the presented chemistry enables the divergent syntheses of (+)-hippolachnin A, (+)-gracilioether A, (-)-gracilioether E and (-)-gracilioether F from a common intermediate with high step-economy and overall efficiency.

RESULTS AND DISCUSSION

A) Proposed biosynthetic origin of hippolachnin A and gracilioethers

B) Retrosynthetic analysis of hippolachnin A and gracilioethers

Figure 2. Synthetic strategy for hippolachnin A and gracilioethers.

Our synthetic strategy for hippolachnin A and gracilioethers was largely built on their plausible biosynthetic origins that are rationalized in Figure 2A. We assumed that both hippolachnin A and gracilioethers could be traced back to three monocyclic precursors **9a-c**.^{4a,7} In particular, hippolachnin A (**1**) could arise from **9a** through an intramolecular [2+2]-photocycloaddition,⁸ whereas gracilioether A (**2**) might be derived from **9b** through an aerobic [2+2+2]-photocycloaddition.⁹ In analogy, **9a** and **9c** could also undergo [2+2+2]-photocycloaddition to give the corresponding products **2a** and **2c**, which can further advance to the other gracilioether congeners through late-stage structural diversification. For example, **2a** could be converted to gracilioether H (**6**) through oxidative cleavage of the C2=C3 double bond, and **2c** might undergo sequential Kornblum-DeLaMare rearrangement (KDR),¹⁰ hemiketalization and oxa-Michael addition to afford gracilioether K (**8**). In addition, the hemiketal intermediate **11** could also divert to gracilioethers E (**3**) and F (**4**) through oxidative cleavage of the C10-C11 single bond or (and) C2=C3 double bond.

According to above rationalization, our retrosynthetic analysis is then traced back to the proposed biosynthetic precursors **9a-c**. Further bond-disconnection of **9a-c** reveals the chiral γ -butenolide **12** as a common precursor. Notably, although various methods have been developed for the synthesis of chiral butenolides,¹¹ a practical enantioselective

Scheme 1. Enantioselective Biomimetic Total Synthesis of (+)-Hippolachnin A

approach to access the highly functionalized chiral butenolides like **12** remained a considerable challenge at the outset of this work. Inspired by the pioneer work of MacMillan^{11b} and Pihko,^{11c,11d} we envisioned that an organocatalytic asymmetric Mukaiyama-Michael addition might meet this challenge, which necessitates the enal **13** and silyloxyfuran **14** as precursors. Coincidentally, a synthesis of racemic **12** was reported previously by Wu and co-worker.^{5d} However, their attempt to achieve the enantioselective synthesis of **12** through the asymmetric Mukaiyama-Michael reaction turned out to be unsuccessful.

Table 1. Optimization of the Organocatalytic Asymmetric Michael Reaction^a

entry	cat.	T (°C)	yield ^b	dr ^c (12:16)	ee ^d (12)	ee ^d (16)
1	A	0	61%	60:40	-26	-37
2	A	0	67%	62:38	-46	-54
3	B	0	49%	63:37	-8	-82
4	C	0	trace	—	—	—
5	D	0	trace	—	—	—
6	E	0	trace	—	—	—
7	F	0	67%	71:29	80	66
8 ^e	F	0	76%	71:29	88	84
9 ^e	F	-10	75%	78:22	91	78
10 ^e	F	-40	trace	—	—	—
11 ^{e,f}	F	-10	90%	75:25	91	80

^aReaction conditions: 1) **15** (1.0 equiv), TBSOTf (for entry 1) or TIPSOTf (for entries 2–11) (1.2 equiv), TEA (1.5 equiv); 2) **13** (2.0 equiv), catalyst (0.15 equiv), 4-NBA (0.15 equiv), H₂O (2.0 equiv), with reaction performed on a 0.45 mmol scale. ^bCombined yields of the isolated products. ^cDetermined by ¹H NMR. ^dDetermined by HPLC analysis on a chiral stationary phase after reduction. ^eReaction concentration = 0.4 M. ^fReaction was performed using 6.0 equiv of **13**. TEA = triethylamine, 4-NBA = 4-nitrobenzoic acid.

We commenced our study by exploring the organocatalytic asymmetric Mukaiyama-Michael addition. For this end, the known compound 3,5-diethylfuran-2(5H)-one **15**¹² was first converted to the silyloxyfuran **14a** in a quantitative yield under the standard conditions (TBSOTf/Et₃N). In view of the fragile nature of **14a**, it was directly used in the next step without purification. Initially, the readily accessible Jørgensen–Hayashi catalyst **A** was employed to effect the Mukaiyama-Michael addition. To our delight, the reaction did work, affording the desired product **12** and its diastereoisomer **16** in 61% combined yield albeit with low enantiomeric excess (entry 1, Table 1). Simply replacing the silyloxyfuran **14a** with **14b** increased the ee value slightly (entry 2). Striving for higher efficiency and asymmetric induction, a range of other organocatalysts were evaluated, among which the diphenylpyrrolidine catalyst **F** was proved to be the optimal choice by affording the notably improved ee and dr values (entry 7). Furthermore, the effect of reaction concentration and temperature were also examined. It was found that both the yield and ee value were improved when the reaction was conducted at the higher concentration and lower temperature (-10 °C) (entries 8 and 9). However, decreasing the temperature to -40 °C only resulted in a trace amount of the expected product (entry 10). Eventually, a satisfactory result was obtained when an excess amount of enal **13** was used, which delivered **12** in 68% yield and 91% ee (entry 11). The absolute configuration of **12** was assigned as (6*R*, 8*R*) by X-ray crystallographic analysis of its derivative **18**. Of note, the practical utility of this asymmetric Mukaiyama-Michael reaction was demonstrated by a gram-scale synthesis of **12** with no loss of enantiopurity (Scheme 1).

Having **12** in hands, we then installed the C10–C12 side chain through a Julia-Kocienski olefination. Thus, deprotonation of **19** with KHMDS at -78 °C followed by addition of **12** led to **20** as a single (*E*)-isomer. Upon irradiation, **20** underwent [2+2]-photocycloaddition to give the tricycle **21** as a single diastereoisomer in 94% yield. It should be noted that an identical transformation was reported by Wu and co-workers.^{5d} Since **21** has been employed as an advanced intermediate in Wood and Brown's synthesis of hippolachnin A,^{5b} the above work represents a formal synthesis of **1**. Nevertheless, given that the biomimetic synthesis of **1** from its precursor **9a** had not been achieved yet, we decided to undertake this challenge. For this end, reduction of the lactone **20** was effected with DIBAL-H, which led to the corresponding hemiketal as a mixture of

diastereoisomers. Upon treatment with the ylide **22** in refluxing toluene, the hemiketal intermediate underwent a tandem Wittig reaction/oxa-Michael addition to give **23** in 91% yield over two steps.¹³ Finally, **23** was converted to **9a** through sequential selenylation and oxidative elimination.

Table 2. Optimization of the [2+2]-Photocycloaddition^a

entry	conditions	yield of products ^b		
		1	24	25
1	UV-lamp (254 nm), DCM, rt, N ₂ , 4 h	-	-	-
2	UV-lamp (365 nm), DCM, rt, N ₂ , 4 h	-	-	-
3	Tungsten lamp, DCM, rt, N ₂ , 24 h	-	-	-
4	Hg lamp, DCM, rt, N ₂ , 16 h	26%	7%	10%
5	Hg lamp, acetone, rt, N ₂ , 12 h	39%	16%	15%
6	Hg-lamp, acetone, 45 °C, N ₂ , 12 h	50%	17%	14%
7	Hg-lamp, acetone, -40 °C, N ₂ , 12 h	16%	24%	10%

^aAll reactions were carried out with 0.06 mmol of **9a** in 20 mL solvent. ^bIsolated yield.

With **9a** in hands, we focused our attention on exploring the key biomimetic [2+2]-photocycloaddition. At first, we attempted to effect the reaction under the conditions employed for the synthesis of **21**. Unfortunately, no desired product could be obtained (entry 1, Table 2), which was consistent with the results reported by the Wu⁷ and Perkins⁹ groups.^{5d,6e} To identify the suitable conditions to effect the transformation, we conducted a comprehensive condition screening. Initially, different light sources were evaluated. It turned out that the reactions irradiated with an UV-lamp (254 or 365nm) or tungsten-lamp failed to give satisfactory outcomes (entries 1-3). Comparably, a promising result was obtained using the high-pressure Hg-lamp (500 W), which delivered the desired cycloadduct **1** in a moderate yield (26%). Interestingly, two other products, namely 10-*epi*-hippolachnin A (**24**) (7%) and (2*E*)-hippolachnin A (**25**) (10%), were also identified in the reaction. Besides the light sources, we also examined various solvents (toluene, MeOH, CH₃CN and acetone), among which acetone was proved to be the optimal choice by providing the best yields (**1**: 39%; **24**: 16%; **25**: 15%). Furthermore, it was found that the reaction temperature also exerted a notable impact on the distribution of products. As shown, increasing the temperature to 45 °C resulted in an improved overall efficiency, favoring the formation of **1** as predominant product (50%) (entry 6). Comparably, the lower reaction temperature gave an inferior outcome (entry 7), wherein **24** was obtained as major isomer. Finally, we found that **1** and **25** could interchange from each other upon irradiation, generally favoring **1** as major product (dr = 2:1).

On the basis of above observations and some related precedents,^{5e,8e} we assume that the [2+2]-photocycloaddition of **9a** proceeds through a stepwise mechanism (Scheme 2). Following the so-called rule of five, the 1,4-diradical intermediate **I-1** would be generated first, which may adopt two conformers, as represented by **I-1a** (path a) and **I-1b** (path b). Apparently, **I-1a** is thermodynamically more stable than **I-1b**, since its bulky ethyl substituent on the C-10 radical center is projected toward

Scheme 2. Mechanistic Rationalization of the [2+2]-Photocycloaddition of 9a

the less hindered convex orientation. As a result, **I-1a** would be preferentially adopted in the following cyclization step, thus leading to **1** as major product. As to another product **25**, it may be generated from **1** directly through the photo-induced C2=C3 double bond isomerization. Alternatively, it could also arise from **9a** through sequential C2=C3 double bond isomerization and [2+2]-photocycloaddition (path c). In both cases, the formation of **25** is unfavorable because of the visible steric effect between the carboxylate and ethyl substituent at C-4. Of note, although another isomer **26** could also be generated theoretically (path d), we did not identify any trace amount of this product in practice, presumably attributed to its kinetically and thermodynamically unfavorable nature.

Scheme 3. Total Synthesis of (-)-Gracilioether F

With the total synthesis of **1** secured, we went on to synthesize gracilioether F (**4**), another popular target in the gracilioether family (Scheme 3).⁶ Thus, treatment of aldehyde **12** with the *in situ* generated ylide MeOCH=PPH₃ provided methyl vinyl ether **27** as a mixture of Z/E isomers (1:5) in 70% yield. Without separation, **27** was directly irradiated with high-pressure Hg-lamp (500 W) in DCM in the presence of Et₃N, which led to the [2+2] adduct **28** as a single diastereoisomer in 83% yield. Of note, the usage of Et₃N as additive was crucial

for securing the high reaction yield. Otherwise, the severe hydrolysis of the methyl vinyl ether **27** was observed in the reaction. Subsequently, oxidative cleavage of the methyl ether of **28** was effected with $\text{RuCl}_3/\text{NaIO}_4$ under ultrasonic irradiation,¹⁴ which led to the cyclobutanone **29** in 80% yield. Upon treatment with *m*-CPBA in the presence of NaHCO_3 , **29** was smoothly converted to gracilioether F (**4**) and its regioisomer **30** via Baeyer–Villiger oxidation in an excellent combined yield (90%) but with no chemoselectivity (**4**:**30** = 1:1).¹⁵ It should be noted that the Baeyer–Villiger oxidation has also been employed as the key step in Brown's and Carreira's studies, both of which displayed excellent chemoselectivity.^{6a,6b} We assumed that the different stereoelectronic effect associated with these substrates may account for the observed results. For the case of **29**, the more substituted C4–C10 bond is adjacent to an electron-withdrawing carbonyl group, which exerts a detrimental effect on the desired reaction leading to **4**. In order to improve the regioselectivity, we examined various conditions by using different oxidants and additives, but failed to get satisfactory results. Serendipitously, we found that if the transformation from **28** to **29** was conducted with extending reaction time (16 h), a small amount of gracilioether F (**4**) could also be detected. Importantly, the regioisomer **30** was not identified in the scenario. Inspired by this interesting discovery, an operationally one-pot protocol was developed to effect the oxidative cleavage of the methyl ether and Baeyer–Villiger rearrangement, which delivered the desired regioisomer **4** in 60% overall yield.

Scheme 4. Failed Attempts to Synthesize (+)-Gracilioethers A and H

To further prove the flexibility of our synthetic strategy, the total syntheses of gracilioether A (**2**) and H (**6**), two more challenging targets that have not yet achieved in the previous studies,⁶ were undertaken by us. Initially, we sought to assemble gracilioether H (**6**) through the proposed biomimetic [2+2+2]-photocycloaddition (Scheme 4A). Both **20** and **9a** were evaluated as potential substrates in the reaction. However, we failed to get promising result after extensive tries. In most cases, the severe decomposition of substrates occurred. Thus, we had to search for a new strategy to achieve this goal. Among the many known approaches to access cyclic peroxides,¹⁶ the radical-mediated formal [3+2] cycloaddition of 1-vinylcyclopropane with molecular oxygen caught our attention.¹⁷ We envisioned that the 1,2-dioxane ring of **2** and **6** could be assembled from the vinylcyclobutane precursor **31** through an analogous formal [4+2]-cycloaddition. To test this idea, we first obtained the requisite precursor **31** from the aldehyde **12** through seven steps (for the details, see Scheme 5). However, to our disappointment, when we submitted **31** to the standard conditions (Ph_2Se_2 , AIBN, CH_3CN , 0 °C) reported by Feldman,^{17b,d} we failed to obtain the

desired product **32**, with most of the starting material recovered (Scheme 4B).

Scheme 5. Total Syntheses of (+)-Gracilioether A and (-)-Gracilioether E

The above failure led us to reconsider our synthetic strategy towards **2** and **6**. Recently, a landmark total synthesis of (+)-cardamom peroxide, a 1,2-dioxane-containing natural product, was reported by Maimone and co-workers,¹⁸ which employed an interesting hydrogen-atom-transfer (HAT)-triggered double peroxidation reaction to install the two requisite oxygenated functionalities (one peroxide and one hydroxyl) in a single step.¹⁹ Inspired by this seminal work, a seemingly daring design came into our minds: the characteristic 1,2-dioxane ring and the hydroxyl group at C-11 of gracilioether A (**2**) could also be assembled from the vinylcyclobutane derivative **31** through a HAT-triggered double peroxidation reaction. To validate this idea, we had to obtain the requisite precursor **31** first. For this end, the aldehyde **12** was converted to the 1,3-diene **34** through Horner–Wadsworth–Emmons olefination. Upon irradiation, **34** underwent [2+2]-photocycloaddition smoothly, giving rise to the vinylcyclobutane **35** as a single isomer. Subsequently, a three-step sequence (reduction, acetylation and addition of silyl ketene acetal **36**) was used to introduce the carboxylate side chain,^{5b} which afforded **37** in 87% overall yield. After selenylation and oxidative elimination, **37** was converted to the corresponding α,β -unsaturated ester as a mixture of *Z/E* isomers (**31**/**38** = 1:1) in 79% combined yield. Of note, the (*2E*)-isomer (**38**) could convert to the desired (*2Z*)-isomer (**31**) upon treatment with HCl/MeOH , thus improving the overall yield of **31** to 68%.

Having **31** in hands, we then attempted the designed HAT-triggered double peroxidation reaction using the identical conditions reported by the Maimone's group (entry 1, Table 3). Encouragingly, although the reaction products appeared complicated, we did identify a small amount of the expected product gracilioether A (**2**) (5%)! Unexpectedly, another natural product, gracilioether E (**3**), was also detected in the reaction (7%). Although the efficiency of the transformation was far from ideal, the preliminary result indicated that our new strategy was feasible. To improve the reaction, we further evaluated several

Table 3. Optimization of the HAT-Trigged Oxygenation of Vinylcyclobutane^a

entry	conditions	yield (%) ^b		
		2	2c	3
1	Mn(dpm) ₃ (0.2 equiv.), PhSiH ₃ (2.5 equiv.), TBHP (1.5 equiv.), O ₂ , <i>i</i> PrOH/DCM, rt, 12 h	5	0	7
2	Co(acac) ₂ (0.2 equiv.), PhSiH ₃ (2.5 equiv.), TBHP (1.5 equiv.), O ₂ , <i>i</i> PrOH/DCE, rt, 12 h	25	18	24
3	Co(acac) ₂ (0.2 equiv.), PhSiH ₃ (2.5 equiv.), TBHP (1.5 equiv.), O ₂ , <i>i</i> PrOH/DCE, rt, 6 h	39	16	15
4	Co(acac) ₂ (0.2 equiv.), PhSiH ₃ (2.5 equiv.), TBHP (1.5 equiv.), O ₂ , <i>i</i> PrOH/DCE, rt, 24 h	15	9	30

^aReaction performed on a 0.06 mmol scale in 4.0 mL solvent. ^bIsolated yield. TBHP = *tert*-butyl hydroperoxide, dpm = 2,2,6,6-tetramethyl-3,5-heptanedionate, acac = acetylacetonate, DCM = dichloromethane, DCE = 1,2-dichloroethane.

reaction parameters including the metal species, solvent, temperature. Gratifyingly, we found that the Mukaiyama/Isayama hydrosilylperoxidation reaction system [Co(acac)₂, PhSiH₃, *t*-BuOOH, *i*PrOH, DCE]^{19b-d} displayed superior reactivity, affording **2** and **3** in 25% and 24% yields, respectively (entry 2). In addition, substantial amounts of another product was also isolated in this case, which was determined to be **2c** on the basis of extensive spectroscopic study (for details, see Supporting Information). Furthermore, it was found that decreasing the reaction time (6 h) enabled the access of **2** as a major product (39%) (entry 3). Comparably, the longer reaction time (24 h) mainly resulted in **3** in 30% yield (entry 4).

The above transformation was noteworthy, since it enables the simultaneous generation of the natural products **2** and **3** in one pot with high step-economy. Mechanistically, we assumed that the reaction should proceed through a hydrogen-atom-transfer (HAT)-triggered cascade process illustrated in Scheme 6. Thus, the transfer of a hydrogen atom from HCo(III) complex to the terminal alkene of **31** affords the radical species **I-3**, which readily undergoes cyclobutane ring-opening to form the radical intermediate **I-4**. Subsequently, **I-4** can be trapped by dioxygen to give the peroxy radical **I-5**, which then undergoes 6-exo-trig cyclization to yield the radical species **I-6**. Next, the second dioxygen insertion takes place to afford the peroxy radical **I-7**, which can further advance to **2** and **2c** through hydrogen abstraction followed by peroxide reduction.

As to gracilioether E (**3**), we assumed that it could be generated from **2** and **2c** through a series of intriguing transformations. As shown, both **2** and **2c** could undergo Co(II)-catalyzed ring-opening reaction to afford the oxygen-centered radical **I-8**. Subsequently, 1,5-hydrogen atom abstraction takes place to form the carbon radical **I-9**, which then advances to the ketone **10** with the regeneration of Co(II) species. Once formed, **10** readily undergo a hemiketalization to give the lactol **11**, which can further advance to the final product **3** through the oxidative cleavage of the 1,2-diol with the action of Co(II)-catalyst and molecular oxygen. Interestingly, both the Co(II)-catalyzed Kornblum-DeLaMare-type endoperoxide rearrangement²⁰ and the Co(II)-catalyzed aerobic oxidative cleavage of the 1,2-diol have been well documented,²¹ which supports our mechanistic rationalization. More convincingly, we proved that

Scheme 6. Mechanistic Rationalization of the HAT-Induced Oxygenation of Vinylcyclobutane

both **2** and **2c** could convert to **3** smoothly upon treatment with Co(acac)₂ in the presence of molecular oxygen (Scheme 6).

In conclusion, we have developed a unified synthetic route that enables the divergent syntheses of various polycyclic *Plakortin* polyketides including (+)-hippolachnin A, (+)-gracilioether A, (-)-gracilioether E and (-)-gracilioether F. A rationally designed organocatalytic asymmetric 1,4-conjugate addition was employed to access the pivotal chiral γ -butenolide intermediate *en route* to all of the targets achieved in this study. The first biomimetic total synthesis of (+)-hippolachnin A (**1**) was completed through a challenging [2+2]-photocycloaddition. More strikingly, (+)-gracilioether A, one of the most complicated congeners of *Plakortin* polyketides, was synthesized for the first time through an unprecedented HAT-triggered oxygenation of vinylcyclobutane. Additionally, two serendipitously discovered one-pot transformations, the RuCl₃/NaIO₄-mediated oxidative cleavage of methyl ether/Baeyer-Villiger rearrangement and the Co(II)-catalyzed Kornblum-DeLaMare-type rearrangement/oxidative cleavage of the 1,2-diol, allowed us to obtain (-)-gracilioether F (**4**) and E (**3**) with high step-economy. Owing to its biomimetic feature, the present work provides valuable information to decipher the underlying biogenetic pathways of the *Plakortin* polyketides. Rewardingly, some natural product-like compounds such as **24**, **25** and **2c** were also obtained along with our synthetic tour, which could be naturally occurring substances that have yet to be discovered. Further application of the developed chemistry to synthesize other structurally related natural products is undertaken by us and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures, spectroscopic data and copies of NMR-spectra (PDF)
CIF file for compound **18** (CCDC 1574958) (CIF files are also available free from charge on <https://www.ccdc.cam.ac.uk/structures/>) (CIF)

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We gratefully acknowledge the financial supports from National Natural Science Foundation of China (21572112, 21772109) and Beijing Natural Science Foundation (2172026).

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