Organic LETTERS

Letter

pubs.acs.org/OrgLett

Total Synthesis of (±)-Gracilioether F

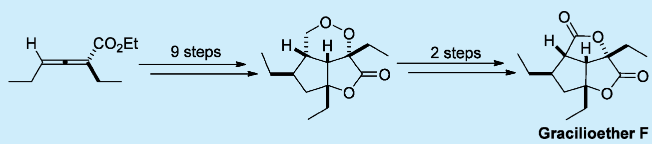
Xin-Yue Shen,[†] Xiao-Shui Peng,[†,‡] and Henry N. C. Wong*[,†,‡]

[†]Department of Chemistry, and State Key Laboratory of Synthetic Chemistry, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China

[‡]Shenzhen Municipal Key Laboratory of Chemical Synthesis of Medicinal Organic Molecules, Shenzhen Research Institute, The Chinese University of Hong Kong, No. 10, Second Yuexing Road, Shenzhen 518507, China

Supporting Information

ABSTRACT: Total synthesis of (±)-gracilioether F was achieved via a pivotal reductive cleavage of 1,2-dioxane from allenic ester in 11 steps. The key 1,2-dioxane species, derived from singlet oxygen and a diene, could be used as a common precursor for a stereocontrolled formation of the crucial 1,4-diol through a reductive cleavage.



Ever since the first isolation of the initial secondary metabolite, plakortin, by Faulkner in 1978 from sponges of the genus *Plakortis*,[1] many new family members of the *Plakortin* polyketides have been continuously characterized and reported. These compounds are characterized with rich chemical diversity and potential biological activities. To date, an impressive number of these marine sponge-derived natural products are known[2] as shown in Figure 1. Among these compounds, gracilioether A was isolated from the deep-sea sponge *Agelas gracilis* collected in southern Japan in 2009, showing antimalarial activity against *Plasmodium falciparum* with an IC_{50} value of 0.5−10 μg/mL.[2a] Subsequently, gracilioether F (**1**) was isolated from marine sponge *Plakinastrella mamillaris* in 2012,[2b] together with gracilioethers E, G, H, I, and K, recently isolated from marine sponges of the genera *Plakortis*, *Plakinastrella*, and *Agelas*.[2,3] A number of these family members demonstrate significant antimalarial and antifungal properties, as well as pregnane-X-receptor (PXR) agonistic efficacies, moderate inhibition of *Leishmaniasis major*.[3]

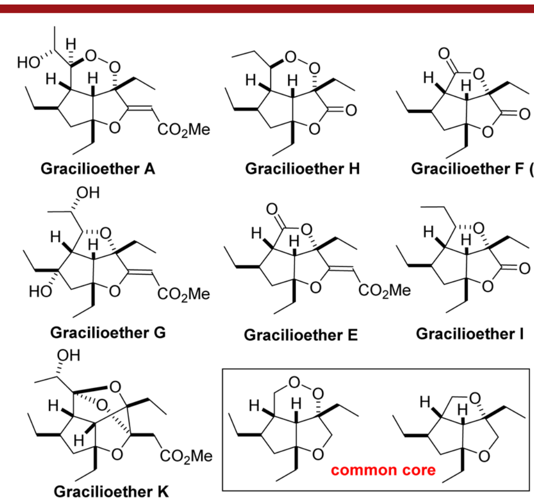


Figure 1. Selected members of gracilioether family.

Sponges of the genus *Plakortis* series are well-known for their ability to produce cyclic peroxides and related metabolites, such as gracilioethers A and H.[2,3] Therefore, in consideration that gracilioether A and gracilioether F (**1**) were isolated from marine sponges of the genera *Plakortis*, *Plakinastrella*, and *Agelas*, together with other gracilioethers, as shown in Figure 2, we reasoned that 1,2-dioxane species **2** could serve as a common precursor toward total syntheses of gracilioether members in a plausible biomimetic manner. As such, 1,2-dioxane species **2** could be readily transformed into an 1,4-diol, an actual synthetic precursor, for the realization of

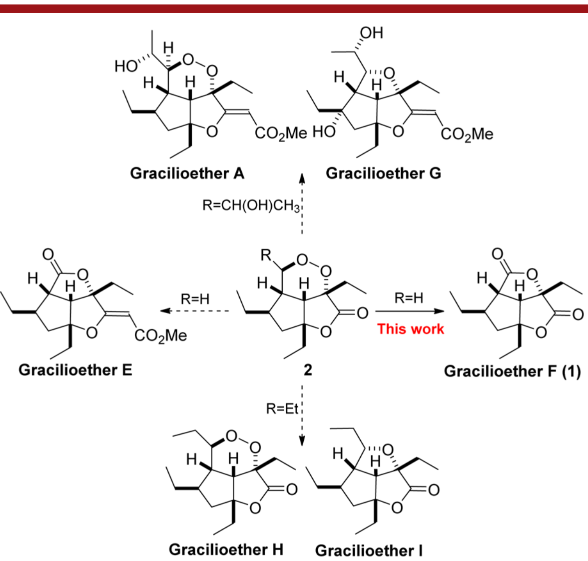


Figure 2. Plausible biogenetic pathway for gracilioethers.

Received: January 18, 2016

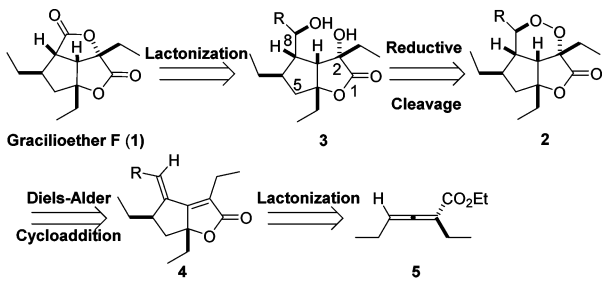
DOI: 10.1021/acs.orglett.6b00161
Org. Lett. XXXX, XXX, XXX−XXX

gracilioethers (E, F, G, H, I, and K) via a reductive cleavage. Thus, their stereochemical homology observed for the gracilioethers family could suggest a plausible common biogenetic pathway as depicted in Figure 2.

To our best knowledge, this intriguing molecular architecture with 1,2-dioxane has rarely been reported for synthetic approaches toward gracilioether A and its family members total synthesis.[4−6] The low natural abundance of these gracilioethers combined with their unprecedented molecular architectures and impressive biological properties prompted us to undertake their scalable total synthesis. As a continuation of our program involving the synthesis of polyketides family,[7] herein, we present a concise approach toward the total synthesis of gracilioether F (**1**) through a flexible synthetic strategy which we believe may be applied to the completion of other members of these structurally intriguing gracilioether family.

Inspired by our proposed biogenetic pathway, we lay out the retrosynthetic route for gracilioether F as demonstrated in Scheme 1. As can be seen, all gracilioethers share either a

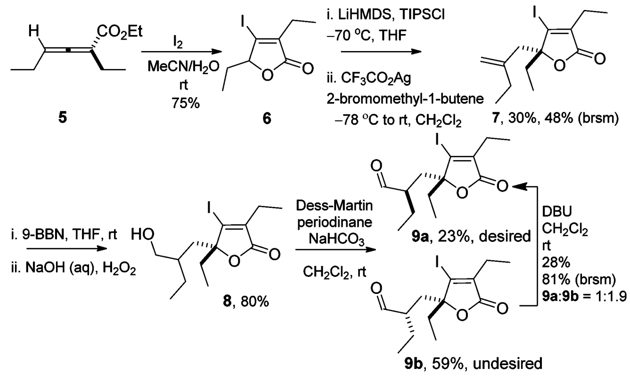
Scheme 1. Retrosynthetic Analysis towards Gracilioether F



unique 1,2-dioxane moiety fused with cyclopenta[*b*]furan-2-one or a fused unusual tricyclic core. Therefore, according to the aforementioned biogenetic pathway, we envisioned that 1,2-dioxane **2** (Scheme 1) could serve as a crucial intermediate to access total synthesis of gracilioether F.[1−6] Thus, 1,2-dioxane could then undergo a reductive cleavage to install stereospecifically a desired diol **3** with hydroxyl groups at C-2 and C-8 for completing the synthesis of gracilioether F. The critical step for constructing the 1,2-dioxane skeleton relevant to that of gracilioether A could come from an *endo*-Diels−Alder cycloaddition between the diene precursor **4** and singlet oxygen.[8] The diene precursor **4** could be generated through an intramolecular Heck reaction[9] and iodine-mediated lactonization[10] from available allenic ester **5**.

As demonstrated in Scheme 2, our synthetic step toward diene **4** commenced with an iodine-mediated cyclization of allenic ester **5** in MeCN/H_2O to form butenolide **6**.[10] Then, upon γ-alkylation of butenolide **6** using silver-mediated coupling between silyloxyfuran intermediate and 2-bromomethyl-1-butene in the presence of LiHMDS and TIPSCl,[11] compound **7** was obtained in 30% yield (48% based on recovered starting material) over two steps. During this process, some relevant α-alkylation product was also formed, probably due to the steric hindrance caused by the ethyl group on the C-4 position. Then, regioselective hydroboration of terminal olefin in **7** followed by oxidative workup gave the corresponding alcohol **8** with a pair of inseparable diastereoisomers.[12] However, upon conversion of alcohol **8** into aldehydes **9a** and **9b** using Dess-Martin periodinane,[13] aldehydes **9a** and **9b** were successfully purified using column

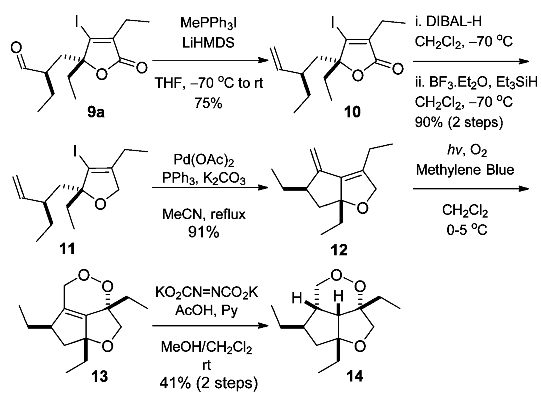
Scheme 2. Synthesis of Aldehyde 9a



chromatography on silica gel in 23% and 59% yield, respectively. The structure of **9a** was also indirectly confirmed by an X-ray crystallographic analysis of **16**. Aldehyde **9a** was therefore proven to be our desired precursor. Upon treatment of the undesired aldehyde **9b** with a catalytic amount of DBU in CH_2Cl_2, aldehyde **9a** was afforded through an epimerization of aldehyde **9b** in an overall 45% yield after several cycles (**9a**:**9b** = 1:1.9; 28% for each operation, 81% brsm).

With aldehyde **9a** secured, we then focused on the synthesis of the pivotal 1,2-dioxane moiety, which would also pave the way toward the peroxide part in the gracilioether family, as well as toward our desired diol species **3**. Aldehyde **9a** was subjected to a classic Wittig olefination[14] to give alkene **10** in 75% yield (Scheme 3). However, we failed to obtain the relevant peroxide

Scheme 3. Synthesis of 14



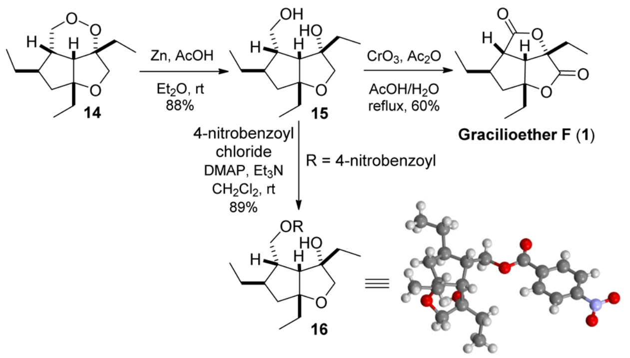
compound via the Diels−Alder cyclization between a similar diene lactone derived from lactone **10** and singlet oxygen, presumably due to the electron-deficient nature of the diene lactone. Therefore, in order to render the diene precursor more electron-rich, partial reduction of lactone **10** with DIBAL-H followed by $BF_3 \cdot Et_2O$ and Et_3SiH[15] gave dihydrofuran **11** in 90%. Then, **11** underwent an intramolecular Heck reaction in the presence of $Pd(OAc)_2$, forming diene **12** in 91% yield.[16] Subsequently, the [4 + 2] cyclization of diene **12** was achieved under an atmosphere of molecular oxygen at 0−5 °C under sun-lamp irradiation to exclusively afford peroxide **13** in a moderate yield.[17] The stereoselectivity is probably due to the special concave structure of diene **12**. Moreover, bubbling of pure oxygen to the reaction mixture effected the formation of 1,2-dioxane moiety **13** within 2−3 h. It is noteworthy that the reaction temperature is very sensitive for the formation of 1,2-dioxane moiety **13**. Thus, the reaction was sluggish if the

DOI: 10.1021/acs.orglett.6b00161
Org. Lett. XXXX, XXX, XXX−XXX

reaction was carried out at below 0 °C, and the peroxide **13** decomposed readily at a temperature over 10 °C in the presence of sun-lamp irradiation. Due to the decomposition of 1,2-dioxane **13**, we used **13** without further purification in the next step. A further mild diimide reduction[18] of the double bond in crude 1,2-dioxane **13** afforded **14** in 41% yield over two chemical operations.

As shown in Scheme 4, according to the proposed biogenetic pathway, we turned our attention toward the total synthesis of

Scheme 4. Total Synthesis of Gracilioether F



gracilioether F. Peroxide **14** was then treated with zinc in acetic acid to generate 1,4-diol **15** in an excellent yield through a proposed reductive cleavage of the O−O bond in **14**. This transformation was proven to be an efficient and practical pathway to provide 1,4-diol **15** with the desired hydroxyl groups for the gracilioether family, matching with their desired stereochemical homology. Moreover, upon selective protection of the primary alcohol in **15**, compound **16** was obtained in 89% yield. After many trials, compound **16** gave eventually satisfactory single crystals from CH_2Cl_2. Gratifyingly, an X-ray diffraction study convincingly showed that the molecular structure of compound **16** contained a desired stereochemistry consistent with that of gracilioether F. Afterward, we set out to complete the total synthesis of gracilioether F (**1**). Although considerable attempts were devoted to form the lactone moiety using either *in situ* generated RuO_4 ($RuCl_3 \cdot 6H_2O/NaIO_4$)[19] or PCC[20] and other oxidative protocols (CrO_3/py),[21] synthetic gracilioether F was still not observed. Gratifyingly, when 1,4-diol **15** was subjected to an excess of CrO_3 in a hot aqueous mixture of Ac_2O and AcOH, gracilioether F (**1**) was provided in 60% yield. This protocol was also employed by Carreira in his total synthesis of (±)-gracilioether F (**1**).[2] The spectroscopic data, including MS, IR, and NMR, are in full agreement with those of the naturally occurring and synthetic gracilioether F (**1**) reported by Zampella,[2b] Carreira,[4] and Brown.[6]

In summary, we have first illustrated a synthetic pathway toward the total synthesis of (±)-gracilioether F (**1**) via a reductive cleavage of the 1,2-dioxane moiety, starting from readily available allenic ester **5** in 11 steps. The key 1,2-dioxane species (**13**, **14**), derived from the [4 + 2] cyclization of singlet oxygen with a diene, should be useful as common synthetic precursors for the total synthesis of other gracilioethers. The rapid stereocontrolled access to the crucial 1,4-diol moiety **15** was secured by strategic application of a reductive cleavage of 1,2-dioxane **14**. Notably, with efficient completion of the total synthesis of gracilioether F (**1**) by this concise pathway, we believe that other members of the *Plakortin* polyketides could also be likewise obtained.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00161.

Detailed synthetic procedures and spectroscopic data for all new compounds, including X-ray data (PDF)
Crystallographic data for **16** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hncwong@cuhk.edu.hk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a grant to the State Key Laboratory of Synthetic Chemistry from the Innovation and Technology Commission. Grants from the National Natural Science Foundation of China/Research Grants Council Joint Research Scheme (N_CUHK451/13), the Research Grants Council of the Hong Kong SAR, China (GRF Project 403012 and CRF Project PolyU C5023-14G with The Hong Kong Polytechnic University), The Chinese Academy of Sciences-Croucher Foundation Funding Scheme for Joint Laboratories, and the National Natural Science Foundation of China (No. 21272199), Shenzhen Science and Technology Innovation Committee for the Municipal Key Laboratory Scheme (ZDSY20130401150914965), and the Shenzhen Basic Research Program (JCYJ20140425184428455) are also gratefully acknowledged.

■ REFERENCES

(1) (a) Higgs, M. D.; Faulkner, D. J. *J. Org. Chem.* **1978**, *43*, 3454−3457. (b) Ravi, B. N.; Armstrong, R. W.; Faulkner, D. J. *J. Org. Chem.* **1979**, *44*, 3109−3113.
(2) (a) Ueoka, R.; Nakao, Y.; Kawatsu, S.; Yaegashi, J.; Matsumoto, Y.; Matsunaga, S.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2009**, *74*, 4203−4207. (b) Festa, C.; De Marino, S.; D'Auria, M. V.; Deharo, E.; Gonzalez, G.; Deyssard, C.; Petek, S.; Bifulco, G.; Zampella, A. *Tetrahedron* **2012**, *68*, 10157−10163.
(3) Festa, C.; D'Amore, C.; Renga, B.; Lauro, G.; De Marino, S.; D'Auria, M. V.; Bifulco, G.; Zampella, A.; Fiorucci, S. *Mar. Drugs* **2013**, *11*, 2314−2327.
(4) Ruider, S. A.; Carreira, E. M. *Org. Lett.* **2016**, *18*, 220−223.
(5) For studies towards the synthesis of a different structural subclass of the gracilioethers and first total synthesis of gracilioethers B and C, see: (a) Norris, M. D.; Perkins, M. V. *Tetrahedron* **2013**, *69*, 9813−9818. (b) Norris, M. D.; Perkins, M. V.; Sorensen, E. J. *Org. Lett.* **2015**, *17*, 668−671.
(6) For the first total synthesis of (±)-gracilioether F, see: Rasik, C. M.; Brown, M. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 14522−14526.
(7) (a) Zhao, Q.; Wong, H. N. C. *Tetrahedron* **2007**, *63*, 6296−6305. (b) Xie, X.-G.; Wu, X.-W.; Lee, H.-K.; Peng, X.-S.; Wong, H. N. C. *Chem. - Eur. J.* **2010**, *16*, 6933−6941. (c) Sun, X.-Y.; Tian, X.-Y.; Li, Z.-W.; Peng, X.-S.; Wong, H. N. C. *Chem. - Eur. J.* **2011**, *17*, 5874−5880. (d) Tian, X.-Y.; Han, J.-W.; Zhao, Q.; Wong, H. N. C. *Org. Biomol. Chem.* **2014**, *12*, 3686−3700. (e) Peng, X.-S.; Wong, H. N. C. *Chem. - Asian J.* **2006**, *1*, 111−120. (f) Xu, X.-S.; Li, Z.-W.; Zhang, Y.-Z.; Peng, X.-S.; Wong, H. N. C. *Chem. Commun.* **2012**, *48*, 8517−8519. (g) Peng, X.-S.; Ylagan, R. M. P.; Siu, Y. M.; Wong, H. N. C. *Chem. - Asian J.* **2015**, *10*, 2070−2083.

(8) For reviews about cyclic peroxides, see: (a) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601–636. (b) McCullough, K. J. *Contemp. Org. Synth.* **1995**, *2*, 225–249.
(9) For reviews on intramolecular Heck reactions, see: (a) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7395. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963.
(10) Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2005**, *2005*, 3942–3945.
(11) Huang, Q.; Rawal, V. H. *Org. Lett.* **2006**, *8*, 543–545.
(12) Makabe, H.; Kong, L.-K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27–29.
(13) (a) Dess, D.-B.; Martin, J.-C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Yamashita, S.; Iso, K.; Kitajima, K.; Himuro, M.; Hirama, M. *J. Org. Chem.* **2011**, *76*, 2408–2425.
(14) Seizert, C. A.; Bumbu, V. D.; Birman, V. B. *Org. Lett.* **2010**, *12*, 3472–3475.
(15) Kraus, G. A.; Frazier, K. A.; Roth, B. D.; Taschner, M. J.; Neuenschwander, K. *J. Org. Chem.* **1981**, *46*, 2417–2419.
(16) (a) Nagasawa, K.; Ishihara, H.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 2523–2529. (b) Chen, C.; Crich, D. *Tetrahedron* **1993**, *49*, 7943–7954.
(17) (a) Blay, G.; Garcia, B.; Molina, E.; Pedro, J. R. *Org. Lett.* **2005**, *7*, 3291–3294. (b) Paquette, L. A.; Green, K. E.; Gleiter, R.; Schäfer, W.; Gallucci, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 8232–8240.
(18) Sun, L.; Shah, F.; Helal, M. A.; Wu, Y.; Pedduri, Y.; Chittiboyina, A. G.; Gut, J.; Rosenthal, P. J.; Avery, M. A. *J. Med. Chem.* **2010**, *53*, 7864–7868.
(19) (a) Sarkar, T. K.; Basak, S. *Org. Lett.* **2004**, *6*, 2925–2927. (b) Li, C.; Li, X.; Hong, R. *Org. Lett.* **2009**, *11*, 4036–4049.
(20) (a) Salim, H.; Piva, O. *J. Org. Chem.* **2009**, *74*, 2257–2260. (b) Bonini, C.; Iavarone, C.; Trogolo, C.; Di Fabio, R. D. *J. Org. Chem.* **1985**, *50*, 958–961.
(21) Schlosser, M.; Kotthaus, M. *Eur. J. Org. Chem.* **1999**, *1999*, 459–462.

DOI: 10.1021/acs.orglett.6b00161
Org. Lett. XXXX, XXX, XXX–XXX