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Convergent Synthesis of Kibdelone C

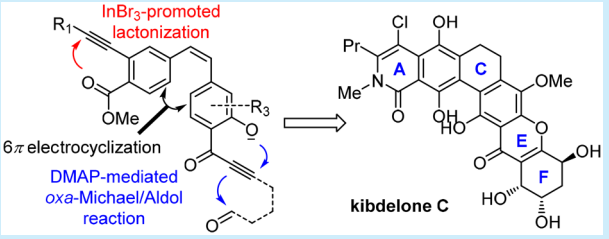
Yihua Dai,[†] Feixia Ma,[†] Yanfang Shen,[†] Tao Xie,[†] and Shuanhu Gao*[,†,‡]

[†]Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, China

[‡]Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, Shanghai 200062, China

Supporting Information

ABSTRACT: The synthesis of kibdelone C, a polycyclic natural xanthone isolated from a soil actinomycete, was achieved through a convergent approach. A 6π-electrocyclization was applied to construct the highly substituted dihydrophenanthrenol fragment (B−C−D ring). $InBr_3$-promoted lactonization was employed to build the isocoumarin ring, which served as a common precursor for the formation of isoquinolinone ring (A−B ring). A key DMAP-mediated *oxa*-Michael/aldol cascade reaction was developed to install the tetrahydroxanthone fragment (E−F ring). This approach provides a new solution to prepare its derivatives and structurally related natural products.



Polycyclic xanthone natural products (**1**−**8**) are a family of polyketides that share a common angular hexacyclic skeleton (Figure 1).[1] The kibdelones and isokibdelones (**1**−**5**), a subgroup of hexacyclic tetrahydroxanthone, were isolated from a rare soil actinomycete *Kibdelosporangium* sp. by Capon and co-workers,[2] and exhibit potent antibacterial activity, nematocidal activity, and cytotoxicity against several human cancer cell lines.[2a]

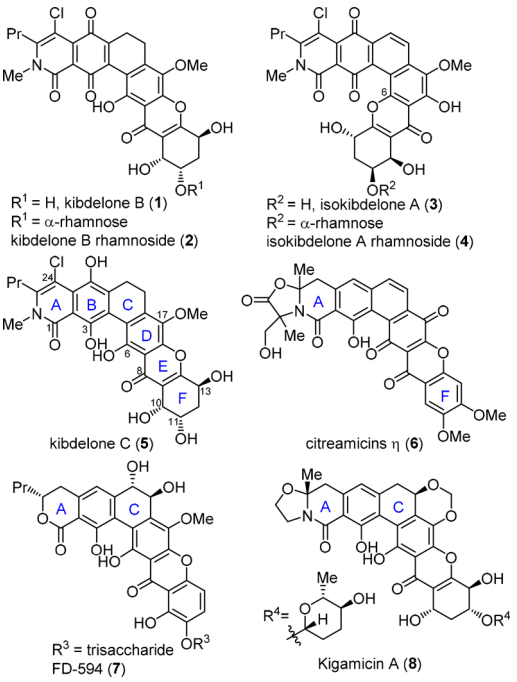


Figure 1. Polycyclic xanthone natural products.

Notably, kibdelone C (**5**) displays significant activities against a range of human tumors by the NCI 60-cell panel assays, such as the SR tumor cell line and SN12C cell carcinoma (GI_{50} < 1 nm).[2a] Structurally, the kibdelones possess the highly oxygenated hexacyclic rings containing isoquinolinone (A−B ring), dihydrophenanthrenol (B−C−D ring), and tetrahydroxanthone (D−E−F ring with three stereogenic hydroxyl groups on C-10, -11, and -13). The intriguing structures of polycyclic xanthones and their promising biological activities have attracted considerable attention from the synthetic community.[3] Synthetic landmarks of the polycyclic xanthones include Kelly's first total synthesis of cervinomycin A_1 and A_2[4] and Suzuki's first stereoselective total synthesis of FD-594 aglycon.[5] The synthetic breakthrough of the most challenging hexacyclic tetrahydroxanthones came when both the Porco[6] and Ready[7] groups reported the total synthesis of kibdelone C. More recently, the enantioselective total synthesis of simaomicin α was also completed by Ready and co-workers.[8] Moreover, these studies have also stimulated the related medical exploration of this family of natural products.[6b,7b] As part of our interest in the synthesis of natural xanthones, we have developed a photoinduced C−O bond formation to construct tetrahydroxanthones[9] and achieved the total synthesis of xanthone dimer ascherxanthone A.[10] Herein, we report a new approach for the synthesis of kibdelone C.

Though the structures are different in dozens of ways, polycyclic xanthones possess the same core structure of dihydrophenanthrenol fragment (B−C−D ring). Therefore, we envisioned building the tricyclic **12** first through 6π-electrocyclization, which could be used as a platform to install A ring and E−F ring through a convergent approach (Scheme 1). To access the tetrahydroxanthone fragment (E−F ring), a late-stage

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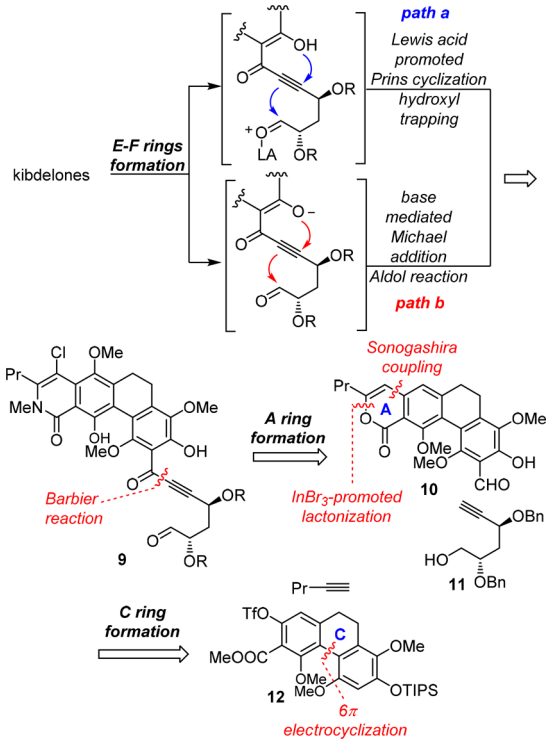
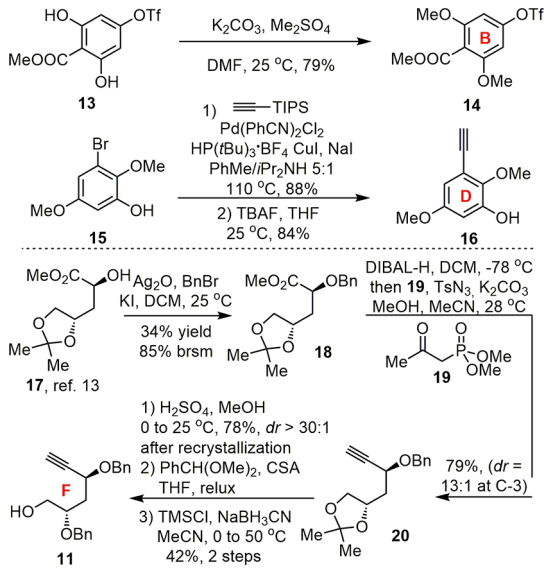
Scheme 1. Retrosynthetic Analysis of Kibdelones



cascade cyclization of precursor **9** was designed involving either a Lewis acid promoted alkyne−Prins/hydroxyl trapping cyclization (path a) or a base-mediated *oxa*-Michael/aldol cyclization (path b). Subsequently, the chiral alkyne **11** and tetracyclic moiety **10** could be connected via a Barbier reaction. We anticipated forming the isoquinolinone (A−B ring) from isocoumarin which can be introduced by a Sonogashira coupling of triflate **12** with pentyne followed by a Lewis acid promoted lactonization.

Our synthesis commenced with the preparation of the fragments **14** and **15** and the chiral alkyne **11** (Scheme 2). The

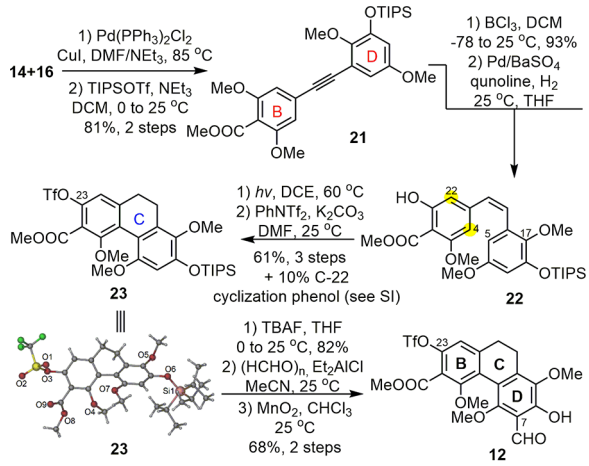
Scheme 2. Preparation of Fragments 14, 16, and 11



known aldehyde **13**[11] was efficiently transformed into triflate **14** (79%) through methylation on a large scale. Pd-catalyzed Sonogashira coupling of 3-bromo-2,5-dimethoxyphenol (**15**)[7a,12] with ethynyltriisopropylsilane followed by desilylation obtained terminal alkyne **16** (74%, two steps). The chiral hydroxyl groups of F ring was introduced from lactone **17**, which was prepared from commercially available D-(+)-xylose using the literature procedure.[13] Treatment of **17** with Ag_2O (using NaH as base led to racemization) and BnBr in the presence of catalytic KI[14] gave the benzylic ether **18** (85% brsm). The ester was reduced with diisobutylaluminum hydride (DIBAL-H) followed by treatment with freshly prepared Seyferth−Gilbert reagent to afford alkyne **20** (79%, *dr* = 13:1) in one pot.[15] After transformation of the acetonide to benzylidene acetal, the primary alcohol **11** was provided by reduction with TMSCl/$NaBH_3CN$[6a,16] in 42% yield.

With these fragments in hand, we started to build the dihydrophenanthrenol moiety (B−C−D ring). A second Sonogashira coupling reaction was applied to connect **14** with **16**, which furnished internal alkyne **21** (81%, two steps) after protection with triisopropylsilyl group (Scheme 3). One of the

Scheme 3. Construction of Fragment 12 Bearing B−C−D ring



methyl groups on the B ring was removed selectively with BCl_3 to give phenol, and then stereoselective hydrogenation using Lindlar catalyst yielded the desired *cis*-alkene **22**. To close the C ring, the photoinduced 6π-electrocyclization was investigated, and we found that the introduction of the bulky −OTIPS group helped to control the regioselectivity of the cyclization on C-5 over C-17. Finally, after irradiation of **22** under high-pressure mercury lamp, tricyclic triflate **23** was obtained in 61% yield over three steps by the following base-mediated triflation, and the structure of **23** was confirmed by X-ray crystal analysis. Moreover, the C-22 cyclization phenol (10%, three steps) was also obtained along with **23** after triflation (see details in the SI). Removal of the TIPS group using TBAF afforded the corresponding phenol, and Et_2AlCl was proved to be the best Lewis acid to introduce the hydroxymethyl on the *ortho*-position of the phenol group through Friedel−Crafts reaction. The resulting primary alcohol was oxidized with MnO_2 to give aldehyde **12** in 68% yield over two steps. We considered that **12**, containing the basic B−C−D tricyclic skeleton, could be used as a platform to install A ring and E−F ring through the modification of functional groups on C-7 and -23.

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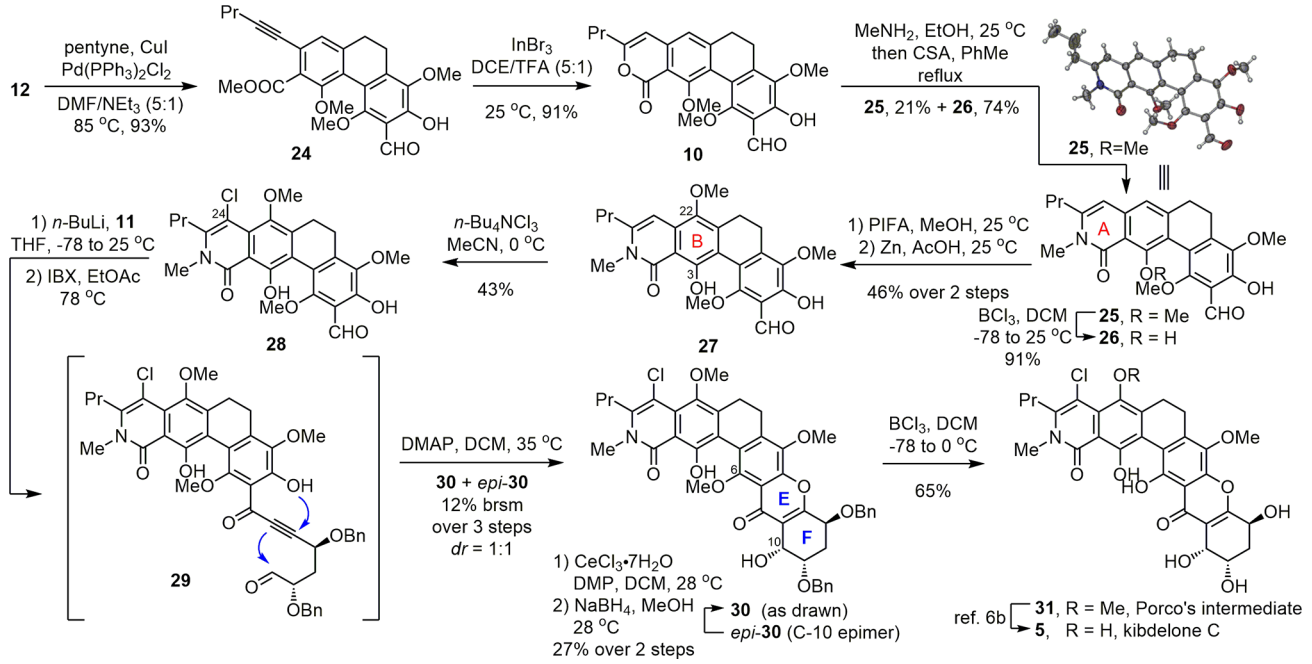
Scheme 4. Convergent Synthesis of Kibdelone C



We then switched our attention to install the isoquinolinone ring (A−B ring). A third Pd-catalyzed Sonogashira coupling of **12** with pentyne forged **24** (Scheme 4). Inspired by Sakai and Arcadi's work,[17] we explored the $InBr_3$-mediated ring closure of **24**, which underwent the 6-*endo*-*dig* cyclization process to form isocoumarin **10** (91%) stereospecifically. Treatment of the resulting isocoumarin with methylamine in EtOH and dehydration afforded isoquinolinone **25**,[6a,18] whose structure was confirmed by X-ray crystal analysis. The C-3 demethylation product **26** (74%) was achieved when the amount of CSA was increased to 8 equiv. Compound **25** was also effectively transformed into **26** using BCl_3 in 91% yield. The methoxyl group on C-22 was introduced by oxidation of **26** with PIFA and a subsequent Zn reduction (46%, 2 steps). Chlorination of **28** proved to be challenging due to its unstable structure. After an extensive survey of the chlorine sources (NCS, NaClO, Cl_2, TBAC/Oxone, NaCl/Oxone, etc.), we found that the freshly prepared Mioskowski's reagent (n-Bu_4NCl_3)[19] in MeCN was the best reagent for the chlorination and gave the chloride **28** in 43% yield. Next, we evaluated the construction of the key tetrahydroxanthone (E−F ring) through the aforementioned cascade cyclization. Deprotonation of terminal alkyne **11** with n-BuLi generated an alkynyllithium reagent that could participate in a nucleophilic addition to aldehyde **28**. After separation of the unreacted **11** and **28**, the resulting product was oxidized with IBX[20] to produce the highly reactive intermediate **29**, which could be cyclized via a 5-*exo* pathway during the purification on silica gel. Therefore, it was directly used in the next cyclization. We first investigated the acid-promoted cascade process[21] (pathway a, Scheme 1; see details in the Supporting Information) in a model study (using **25** instead of **28**). $TiCl_4$/TBAI, reported by the Frontier group,[22] yielded an iodine-addition product that was unstable under subsequent base conditions (NaOH, Cs_2CO_3, K_2CO_3). We envisioned the $TiCl_4$ may react with the phenol group and generate the intermediate **33** first (Figure 2), and then the α, β-unsaturated ketone **34** is afforded by halo-Michael addition followed by protonation.[23] Other Lewis acids (I_2, $In(OTf)_3$, $AuNTf_2(PPh_3)$, $AuCl(PPh_3)$) or Brønsted acids

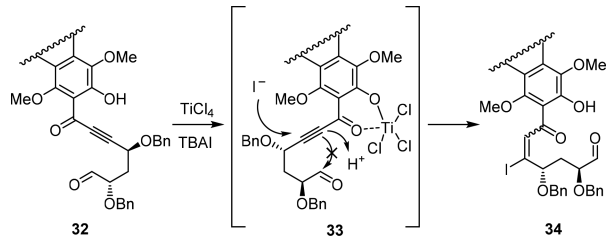


Figure 2. Proposed mechanism for the $TiCl_4$/TBAI system.

(PTSA, TfOH, HCl, TFA) led to a complicated system. On the other hand, the base-mediated *oxa*-Michael/aldol cascade reaction was also explored. The reactions were either complicated or decomposed when hydroquinine, MeONa, TBAF, Cs_2CO_3, or NaOH was used (for more details, see the SI). Inspired by the Dake group's work,[24] DMAP was used and yielded the expected 6-*endo* product. We also inferred that the existence of the highly reactive free phenol made the corresponding compounds unstable under most of the aforementioned conditions. Finally, treatment of the freshly prepared intermediate **29** with DMAP in dichloromethane provided the desired cyclized product **30** and its C-10 epimer in 12% brsm yield over three steps (dr = 1:1). The C-10 epimer *epi*-**30** could be transform to **30** over two steps. Removal of benzyl groups and the methyl group on C-6 using BCl_3 yielded the intermediate **31** in 65% yield, which gave ^1H NMR, ^{13}C NMR, high-resolution mass spectrometric, and optical rotation ($[\alpha]_D^{22}$ = +66 (c = 0.14, $CHCl_3$), $[\alpha]_D^{23}$ = +90 (c = 0.20, $CHCl_3$) reported data) results identical to those previously reported by the Porco[6a] and Ready[7b] groups. Then the total synthesis of kibdelone C (**5**) could be achieved using the known procedure developed by the Porco group[6a] through a two-step sequence.

In summary, we developed a convergent approach for the synthesis of kibdelone C. The highly substituted dihydrophenanthrenol fragment (B−C−D ring) served as a platform for the formation of the angular hexacyclic skeleton, which was efficiently built through a 6π-electrocyclization. It also laid the

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foundation for the preparation of structurally related natural products, such as citreamicins. The isocoumarin ring, constructed via a $InBr_3$-promoted lactonization, was employed as the precursor of the isoquinolinone ring (A−B ring). This rational design will facilitate the preparation of the derivatives through the aminolysis and ring-regeneration process using different amines or amino acids. A key DMAP-mediated *oxa*-Michael/aldol cascade reaction was utilized to install the tetrahydroxanthone fragment (E−F ring). This approach provided a new strategy to prepare the derivatives and structurally related polycyclic xanthones. We are currently studying the divergent synthesis of citreamicins and kigamicins, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00901.

General experimental procedures, characterization data, ^1H and ^{13}C NMR spectra of new compounds, and X-ray data for **23** and **25** (PDF)

Accession Codes

CCDC 1821857−1821858 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shgao@chem.ecnu.edu.cn.

ORCID

Shuanhu Gao: 0000-0001-6919-4577

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Bräse, S.; Encinas, A.; Keck, J.; Nising, C. F. *Chem. Rev.* **2009**, *109*, 3903. (b) Masters, K. S.; Brase, S. *Chem. Rev.* **2012**, *112*, 3717. (c) Winter, D. K.; Sloman, D. L.; Porco, J. A., Jr. *Nat. Prod. Rep.* **2013**, *30*, 382. (d) Wezeman, T.; Brase, S.; Masters, K. S. *Nat. Prod. Rep.* **2015**, *32*, 6.

(2) (a) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Chem. - Eur. J.* **2007**, *13*, 1610. (b) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Org. Lett.* **2006**, *8*, 5267.

(3) (a) Duthaler, R. I.; Mathies, P.; Petter, W.; Heuberger, C.; Scherrer, V. *Helv. Chim. Acta* **1984**, *67*, 1217. (b) Zhang, W.; Wang, L.; Kong, K.; Wang, T.; Chu, Y.; Deng, Z.; You, D. *Chem. Biol.* **2012**, *19*, 422. (c) Mehta, G.; Shah, S. R. *Tetrahedron Lett.* **1991**, *32*, 5195. (d) Rao, A. V.; Yadav, J. S.; Reddy, K.; Upender, V. *Tetrahedron Lett.* **1991**, *32*, 5199. (e) Blumberg, S.; Martin, S. F. *Org. Lett.* **2017**, *19*, 790. (f) Yang, J.; Knueppel, D.; Cheng, B.; Mans, D.; Martin, S. F. *Org. Lett.* **2015**, *17*, 114. (g) Knueppel, D.; Yang, J.; Cheng, B.; Mans, D.; Martin, S. F. *Tetrahedron* **2015**, *71*, 5741.

(4) Kelly, T. R.; Jagoe, C. T.; Li, Q. *J. Am. Chem. Soc.* **1989**, *111*, 4522.

(5) Masuo, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3462−3465.

(6) (a) Sloman, D. L.; Bacon, J. W.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2011**, *133*, 9952. (b) Sloman, D. L.; Mitasev, B.; Scully, S. S.; Beutler, J. A.; Porco, J. A., Jr *Angew. Chem., Int. Ed.* **2011**, *50*, 2511. (c) Winter, D. K.; Endoma-Arias, M. A.; Hudlicky, T.; Beutler, J. A.; Porco, J. A., Jr *J. Org. Chem.* **2013**, *78*, 7617 For the synthetic studies of dimeric xanthones by the Porco groups, see:. (d) Qin, T.; Iwata, T.; Ransom, T. T.; Beutler, J. A.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2015**, *137*, 15225. (e) Qin, T.; Johnson, R. P.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2011**, *133*, 1714. (f) Qin, T.; Porco, J. A., Jr *Angew. Chem., Int. Ed.* **2014**, *53*, 3107. (g) Qin, T.; Skraba-Joiner, S. L.; Khalil, Z. G.; Johnson, R. P.; Capon, R. J.; Porco, J. A., Jr *Nat. Chem.* **2015**, *7*, 234. (h) Reichl, K. D.; Smith, M. J.; Song, M. K.; Johnson, R. P.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2017**, *139*, 14053.

(7) (a) Butler, J. R.; Wang, C.; Bian, J.; Ready, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 9956. (b) Rujirawanich, J.; Kim, S.; Ma, A. J.; Butler, J. R.; Wang, Y.; Wang, C.; Rosen, M.; Posner, B.; Nijhawan, D.; Ready, J. M. *J. Am. Chem. Soc.* **2016**, *138*, 10561.

(8) Wang, Y.; Wang, C.; Butler, J. R.; Ready, J. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10796.

(9) Xiao, Z.; Cai, S.; Shi, Y.; Yang, B.; Gao, S. *Chem. Commun.* **2014**, *50*, 5254.

(10) Xiao, Z.; Li, Y.; Gao, S. *Org. Lett.* **2017**, *19*, 1834.

(11) Bender, C. F.; Yoshimoto, F. K.; Paradise, C. L.; De Brabander, J. K. *J. Am. Chem. Soc.* **2009**, *131*, 11350.

(12) Kawada, K.; Arimura, A.; Tsuri, T.; Fuji, M.; Komurasaki, T.; Yonezawa, S.; Kugimiya, A.; Haga, N.; Mitsumori, S.; Inagaki, M.; Nakatani, T.; Tamura, Y.; Takechi, S.; Taishi, T.; Kishino, J.; Ohtani, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 973.

(13) (a) Okabe, M.; Sun, R. C.; Zenchoff, G. B. *J. Org. Chem.* **1991**, *56*, 4392. (b) Jimmidi, R.; Guduru, S. K. R.; Arya, P. *Org. Lett.* **2015**, *17*, 468. (c) Sun, R. C.; Okabe, M. *Org. Synth.* **1995**, *72*, 48.

(14) Dahlgren, A.; Kvarnström, I.; Vrang, L.; Hamelink, E.; Hallberg, A.; Rosenquist, A.; Samuelsson, B. *Bioorg. Med. Chem.* **2003**, *11*, 827.

(15) (a) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *1996*, 521. (b) Dickson, H. D.; Smith, S. C.; Hinkle, K. W. *Tetrahedron Lett.* **2004**, *45*, 5597.

(16) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

(17) (a) Sakai, N.; Annaka, K.; Konakahara, T. *J. Org. Chem.* **2006**, *71*, 3653. (b) Bianchi, G.; Chiarini, M.; Marinelli, F.; Rossi, L.; Arcadi, A. *Adv. Synth. Catal.* **2010**, *352*, 136.

(18) Ahmed, H.; Rama, N.; Malana, M.; Qadeer, G. *Indian J. Chem. Sect. B* **2006**, *45*, 820.

(19) (a) Schlama, T.; Gabriel, K.; Gouverneur, V.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2342. (b) Schnermann, M. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 9576. (c) Huwyler, N.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 13066.

(20) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

(21) (a) Ma, D.; Zhong, Z.; Liu, Z.; Zhang, M.; Xu, S.; Xu, D.; Song, D.; Xie, X.; She, X. *Org. Lett.* **2016**, *18*, 4328. (b) Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073. (c) Lin, N.-H.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062. (d) Overman, L. E.; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, *114*, 368. (e) Li, H.; Chen, Q.; Lu, Z.; Li, A. *J. Am. Chem. Soc.* **2016**, *138*, 15555. (f) Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925. (g) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. (h) Chavre, S. N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. *J. Org. Chem.* **2008**, *73*, 7467.

(22) (a) Ciesielski, J.; Canterbury, D. P.; Frontier, A. J. *Org. Lett.* **2009**, *11*, 4374. (b) Ciesielski, J.; Gandon, V.; Frontier, A. J. *J. Org. Chem.* **2013**, *78*, 9541.

(23) Dai, Y.; Shen, Y.; Gao, S. *Chin. J. Org. Chem.* **2018**, 38.

(24) Castillo-Contreras, E. B.; Dake, G. R. *Org. Lett.* **2014**, *16*, 1642.

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