Organic LETTERS

Letter

pubs.acs.org/OrgLett

Total Synthesis of Aquatolide: Wolff Ring Contraction and Late-Stage Nozaki–Hiyama–Kishi Medium-Ring Formation

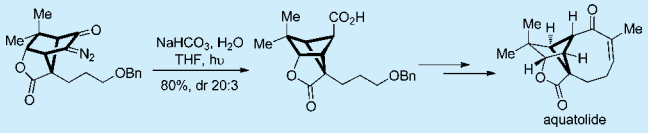
Bin Wang,[†] Yuanzhen Xie,[†] Qin Yang,[‡] Guozhu Zhang,*[,‡] and Zhenhua Gu*[,†]

[†]Department of Chemistry, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 230026, P. R. China

[‡]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China

Supporting Information

ABSTRACT: A total synthesis of the highly strained natural product aquatolide has been achieved. The synthesis featured a photoinduced Wolff ring contraction reaction for the construction of bicyclo[2.1.1]hexane from diazo compound with a bicyclo[2.2.1]heptane skeleton. The eight-membered enone was built by a late-stage intramolecular Nozaki–Hiyama–Kishi vinylation reaction of steric bulky vinyl iodide and aldehyde.



The humulanolide family of natural products, including asteriscunolides, asteriscanolide, naupliolide, and aquatolide, represent an important class of sesquiterpenes with a unique γ-lactone moiety (Figure 1).[1−4] Asteriscunolides A–D,

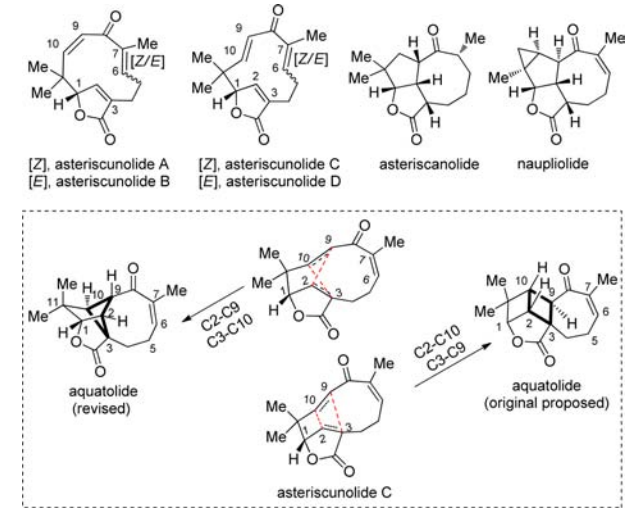
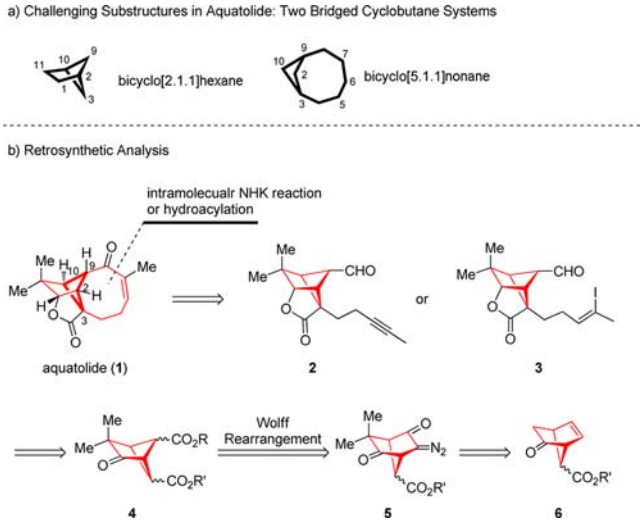


Figure 1. Representatives of humulanolide family natural products.

which are distinguished from each other by the different geometries of C–C double bonds (C6–C7 and C9–C10), has captured significant attention due to the synthetically challenging 11-membered carbon ring along with a bridged γ-lactone. Asteriscunolides A, C, and D showed higher activities against neoplasic cell lines than the antitumor agent cisplatin.[2b]

Aquatolide was first isolated from *Asteriscus aquaticus* by San Feliciano and co-workers in 1989, which was proposed as a ladderane structure.[5] In 2012, Shaw, Tantillo, and co-workers revisited the compound and revised the structure by quantum-chemical NMR calculations and experimental NMR studies and finally by single-crystal X-ray analysis (Figure 1).[6] Structurally, both the misassigned aquatolide and the revised structure could be regarded as formal [2 + 2] cycloaddition products of asteriscunolides C, where the formation of C2–C10 and C3–C9 bonds was revised to the formation of C2–C9 and C3–C10 bonds. Aquatolide has a very unique cyclobutane moiety bearing two bridged rings: C3 and C9 tether an eight-membered enone to form bicyclo[5.1.1]nonane, and C2 and C10 tether a two-carbon chain containing a *gem*-dimethyl quaternary carbon center to form bicyclo[2.1.1]hexane (Scheme 1a). These highly stained and bridged subunits proved particularly challenging for the synthesis of aquatolide.

Scheme 1. Retrosynthetic Analysis



Received: September 13, 2016
Published: October 5, 2016

DOI: 10.1021/acs.orglett.6b02767
Org. Lett. 2016, 18, 5388–5391

Because of their promising biological activities and intriguing structures, the humulanolide family of natural products became popular molecules for synthetic organic chemists. Asteriscanolide has been particularly popular: first the group of Wender (1988),[7] then the groups of Paquette (2000),[8] Snapper (2000),[9] Krafft (2000),[10] and Yu (2001),[11] respectively, accomplished its synthesis. The Trost group first finished the total synthesis of asteriscunolides D via thionium ion initiated macroring formation.[12] Fernandes reported the first synthesis of (−)-asteriscunolide C.[13] Li et al. realized a collective synthesis of seven members of the humulanolides by utilizing cascade olefin metathesis. In their studies, the first total syntheses of 6,7,9,10-tetrahydroasteriscunolide and 6,7,9,10-tetradehydroasteriscanolide were achieved.[14] Hiemstra and coworkers realized an elegant total synthesis of aquatolide by the use of photoinduced [2 + 2] cycloaddition.[15] In 2016, the Ito group finished the first total synthesis of naupliolide, whose cyclooctene ring was constructed via Ru-catalyzed olefin metathesis.[16] Herein, we report our results on the total synthesis of aquatolide, which features the cyclobutane building via Wolff ring contraction and medium-ring synthesis by an intramolecular Nozaki−Hiyama−Kishi reaction.[17,18]

Our retrosynthetic plan for the synthesis of aquatolide (**1**) is shown in Scheme 1b. Undoubtedly, the main challenges here are the construction of the strained bicylco[2.1.1]hexane and bicyclo[5.1.1]nonane systems. Thus, in this synthetic plan, special attention was paid to these bicyclic moieties. We assumed that the target compound could be gained via hydroacylation[19] of alkynyl aldehyde **2** or intramolecular Nozaki−Hiyama−Kishi cyclization of vinyl iodide **3**.[20,21] Both **2** and **3** can be accessed from a fairly symmetric dicarboxylic ester **4**, whose highly strained cyclobutane structure was intended to be constructed via photoinduced Wolff ring contraction reaction of α-keto diazo compound **5**. Finally, **5** was supposed to be prepared from the bicyclo[2.2.1]hept-5-en-2-one compound **6**.

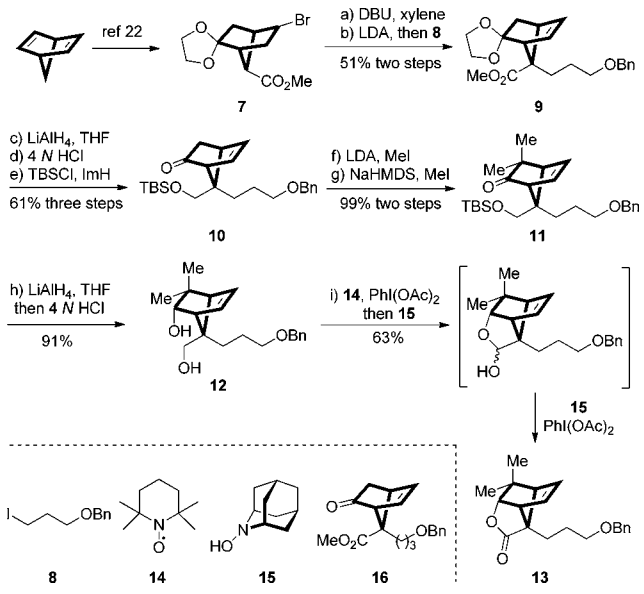
Our synthesis began from the known bromo ester **7**, which was readily prepared from 2,5-norbornadiene on a multigram scale (Scheme 2).[22] Compound **9** was stereoselectively accessed via 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted elimination, followed by alkylation with iodide **8**. Reduction of the ester moiety of **9** with $LiAlH_4$, followed by ketal deprotection and silylation of the hydroxyl group, gave **10** in good overall yield. α-Dimethylation of **10** was successfully achieved via a two-step operation. The direct α-dimethylation of keto ester **16**, which was prepared via acidic hydrolysis of **9**, failed during introduction of the second methyl group under various conditions. Reduction of the carbonyl group of **11** followed by acid-mediated desilylation stereoselectively gave diol **12** in excellent yield, which underwent oxidative lactonization to deliver tricyclic compound **13**. To obtain a reasonable yield, it was necessary to treat **12** with TEMPO and $PhI(OAc)_2$ first (formation of hemiketal as the sole intermediate and small amount of **13**), and then less bulky *N*-hydroxylamine **15** was added to the reaction mixture as the second catalyst after complete consumption of diol **12** via TLC analysis.[23]

The diazo compound **18** could be accessed uneventfully from **13** via dihydroxylation and oxidation followed by the condensation with tosyl hydrazine and detosylation with basic Al_2O_3 (Scheme 3). The initial plan for preparation of **20** via the Wolff rearrangement in MeOH followed by hydrolysis collapsed due to the unacceptably low yield. The reaction gave only 38% of **19** along with a considerable amount of unidentified side products. On the other hand, irradiation of the diazo compound with 125 W high-pressure mercury lamp in THF/H_2O mixed solvent in the presence of $NaHCO_3$ gave **20** in good yield.[24,25] Chemoselective reduction of the carboxylic acid group with $NaBH_4$ via mixed anhydride intermediate, and subsequent protection with TBSOTf gave **21** in decent yield.

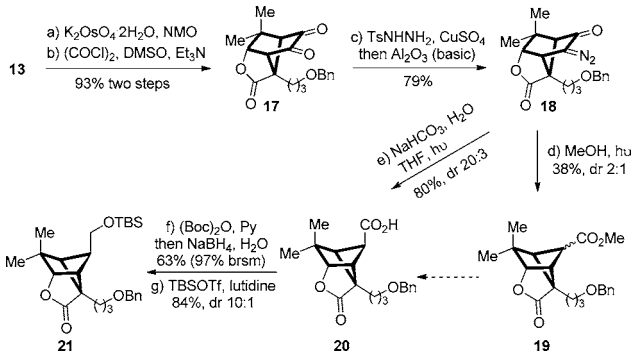
After removal of the benzyl group in **21** through hydrogenation, the free hydroxyl group was oxidized to aldehyde. Subsequently aldehyde was converted to alkyne **23** via Seyferth−Gilbert homologation (with Bestmann−Ohira reagent **25**) and methylation (Scheme 4).[26] Two-step operation of **23**, desilylation and oxidation, delivered the alkynyl aldehyde **24** with a 1.46:1 isomer ratio. To our disappointment, under various hydroacylation conditions,[19] no desired cyclization product could be detected and the starting material **24** remained.

We resorted to the second approach: intramolecular NHK reaction. Aldehyde **22** was converted to **27** in moderate yield via Bestmann (*Z*)-vinyl iodide synthesis by following the Stork−Zhao procedure (Scheme 5).[27] Subsequently, desilylation under acidic conditions followed by oxidation afforded aldehyde **3b** in 41% yield along with the undesired isomer **3a** in 53% yield. The stereochemistry of compounds **3a** and **3b** was

Scheme 2. Synthesis of 13

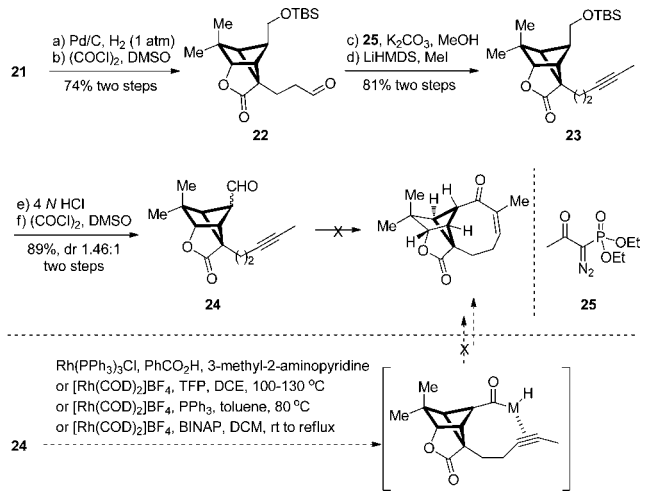


Scheme 3. Synthesis of 21

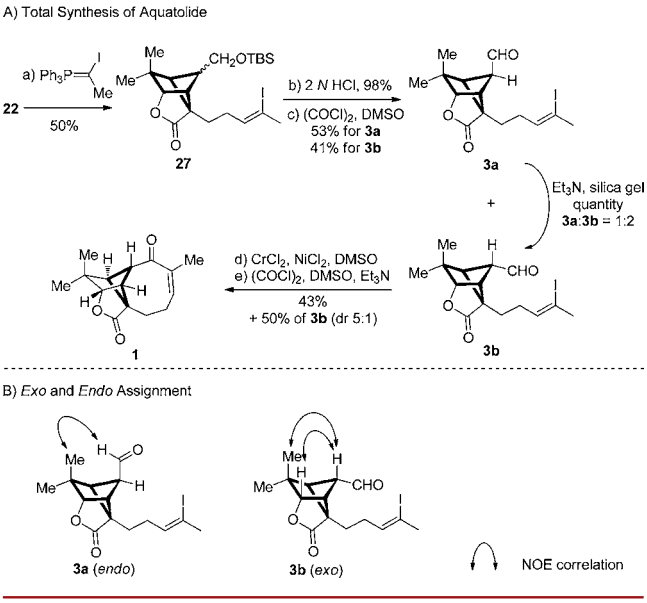


DOI: 10.1021/acs.orglett.6b02767
Org. Lett. 2016, 18, 5388−5391

Scheme 4. Attempt for Synthesis of Aquatolide via Hydroacylation



Scheme 5. Total Synthesis of Aquatolide 1



assigned by NOE correlation studies. Basic desilylation with TBAF caused the elimination of vinyl iodide to form a C−C triple bond. Pleasingly, stereoisomer **3a** could be partially converted to the required aldehyde **3b**: simply stirring **3a** with Et_3N and silica gel in dichloromethane at room temperature gave a 1:2 mixture of isomers favoring the desired *exo* compound **3b**. Eventually, treatment of **3b** with $CrCl_2$ and a catalytic amount of $NiCl_2$ in diluted DMSO,[20] after oxidation (Swern), gave aquatolide **1** in 43% overall yield along with 50% of starting material **3b**. The trisubstituted (*Z*)-vinyl halides possibly underwent geometrical isomerization in classic NHK conditions.[28] Pleasingly, it was not an issue for our case, and the (*Z*)-stereochemistry was retained in both the recovered material and cyclization product. The obtained molecule **1** was identical with the reported data of authentic natural compound.

In conclusion, we reported a 22-step total synthesis of aquatolide from bromide **7**. In comparison with Hiemstra's photopromoted [2 + 2]-strategy,[15] the highly strained bicyclo[2.1.1]hexane was constructed via a photoinduced Wolff ring contraction reaction. The eight-membered medium ring was constructed via a late-stage intramolecular Nozaki−Hiyama−Kishi reaction. The synthesis displayed the power of the NHK reaction for the construction of medium rings in complex natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02767.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: guozhuzhang@sioc.ac.cn,
*E-mail: zhgu@ustc.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the "973" project (2015CB856600), NSFC (21272221, 21472179, 21622206, and 21421091), Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000), and Fundamental Research Funds for the Central Universities (WK 2060190028, 2060190026).

■ REFERENCES

(1) Isolation of asteriscunolides A−D: (a) San Feliciano, A.; Barrero, A. F.; del Corral, J. M. M.; Ledesma, E.; Sánchez-Ferrando, F. *Tetrahedron Lett.* **1982**, *23*, 3097. (b) San Feliciano, A.; Barrero, A. F.; Medarde, M.; del Corral, J. M.; Aramburu Aizpiri, A.; Sanchez-Ferrando, F. *Tetrahedron* **1984**, *40*, 873. (c) San Feliciano, A.; Barrero, A. F.; Medarde, M.; del Corral, J. M. M.; Aramburu, A.; Perales, A.; Fayos, J.; Sanchez-Ferrando, F. *Tetrahedron* **1985**, *41*, 5711.

(2) Isolation of 6,7,9,10-tetrahydroasteriscunolide: (a) Rauter, A. P.; Branco, I.; Bermejo, J.; Gonzalez, A. G.; García-Gravalos, M. D.; San Feliciano, A. *Phytochemistry* **2001**, *56*, 167. (b) Chaari, A.; Jannet, H. B.; Mighri, Z.; Robinot, C.; Kunesch, N. *Nat. Prod. Lett.* **2001**, *15*, 419.

(3) Isolation of asteriscanolide: San Feliciano, A.; Barrero, A. F.; Medarde, M.; Miguel del Corral, J. M.; Aramburu, A.; Perales, A.; Fayos, J. *Tetrahedron Lett.* **1985**, *26*, 2369.

(4) Isolation of naupliolide: Akssira, M.; Mellouki, F.; Salhi, A.; Alilou, H.; Saouf, A.; El Hanbali, F.; Arteaga, J. F.; Barrero, A. F. *Tetrahedron Lett.* **2006**, *47*, 6719.

(5) San Feliciano, A.; Medarde, M.; Miguel del Corral, J. M.; Aramburu, A.; Gordaliza, M.; Barrero, A. F. *Tetrahedron Lett.* **1989**, *30*, 2851.

(6) Lodewyk, M. W.; Soldi, C.; Jones, P. B.; Olmstead, M. M.; Rita, J.; Shaw, J. T.; Tantillo, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 18550.

(7) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904.

(8) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742.

(9) Limanto, J.; Snapper, M. L. *J. Am. Chem. Soc.* **2000**, *122*, 8071.

(10) (a) Krafft, M. E.; Cheung, Y.-Y.; Juliano-Capucao, C. A. *Synthesis* **2000**, *2000*, 1020. (b) Krafft, M. E.; Cheung, Y.-Y.; Abboud, K. A. *J. Org. Chem.* **2001**, *66*, 7443.

(11) (a) Liang, Y.; Jiang, X.; Yu, Z.-X. *Chem. Commun.* **2011**, *47*, 6659. (b) Liang, Y.; Jiang, X.; Fu, X.-F.; Ye, S.; Wang, T.; Yuan, J.; Wang, Y.; Yu, Z.-X. *Chem. - Asian J.* **2012**, *7*, 593.

DOI: 10.1021/acs.orglett.6b02767
Org. Lett. 2016, 18, 5388−5391

(12) Trost, B. M.; Burns, A. C.; Bartlett, M. J.; Tautz, T.; Weiss, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1474.
(13) Fernandes, R. A.; Chavan, V. P. *Chem. Commun.* **2013**, *49*, 3354.
(14) Han, J.-C.; Li, F.; Li, C.-C. *J. Am. Chem. Soc.* **2014**, *136*, 13610.
(15) Saya, J. M.; Vos, K.; Kleinnijenhuis, R. A.; van Maarseveen, J. H.; Ingemann, S.; Hiemstra, H. *Org. Lett.* **2015**, *17*, 3892.
(16) Abe, H.; Morishita, T.; Yoshie, T.; Long, K.; Kobayashi, T.; Ito, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 3795.
(17) For the synthesis of natural product solanoeclepin A containing the cyclo[2.1.1]hexane moiety, see: (a) Tanino, K.; Takahashi, M.; Tomata, Y.; Tokura, H.; Uehara, T.; Narabu, T.; Miyashita, M. *Nat. Chem.* **2011**, *3*, 484. (b) Kleinnijenhuis, R. A.; Timmer, B. J. J.; Lutteke, G.; Smits, J. M. M.; De Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *Chem. - Eur. J.* **2016**, *22*, 1266. Also see: (c) Tsao, K.-W.; Cheng, C.-Y.; Isobe, M. *Org. Lett.* **2012**, *14*, 5274. (d) Chuang, H.-Y.; Isobe, M. *Org. Lett.* **2014**, *16*, 4166.
(18) Synthesis of the bicyclo[3.1.1]heptane unit from (+)-carvone: Masarwa, A.; Weber, M.; Sarpong, R. *J. Am. Chem. Soc.* **2015**, *137*, 6327.
(19) (a) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296. (b) Jun, C.-H.; Lee, H.; Hong, J.-B.; Kwon, B.-I. *Angew. Chem., Int. Ed.* **2002**, *41*, 2146. (c) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 8078. (d) Tanaka, K.; Sasaki, K.; Takeishi, K.; Hirano, M. *Eur. J. Org. Chem.* **2007**, *2007*, 5675.
(20) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (c) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (d) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (e) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Chem. Soc. Rev.* **1999**, *28*, 169. (f) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (g) Tian, Q.; Zhang, G. *Synthesis* **2016**, DOI: 10.1055/s-0036-1589457.
(21) The NHK reaction is known to be effective for medium-ring cyclization: (a) Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735. (b) Kress, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999. (c) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391. (d) Pilli, R. A.; Victor, M. M.; de Meijere, A. *J. Org. Chem.* **2000**, *65*, 5910. (e) Takao, K.; Hayakawa, N.; Yamada, R.; Yamaguchi, T.; Morita, U.; Kawasaki, S.; Tadano, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3426. (f) Baker, T. M.; Edmonds, D. J.; Hamilton, D.; O'Brien, C. J.; Procter, D. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5631. (g) Killen, J. C.; Axford, L. C.; Newberry, S. E.; Simpson, T. J.; Willis, C. L. *Org. Lett.* **2012**, *14*, 4194.
(22) (a) Peel, R.; Sutherland, J. K. *J. Chem. Soc., Chem. Commun.* **1974**, 151. (b) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Miyashita, M.; Masaki, Y.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 4111.
(23) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412.
(24) (a) Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *325*, 129. (b) For a review, see: Kirmse, W. *Eur. J. Org. Chem.* **2002**, *2002*, 2193.
(25) (a) Eaton, P. E.; Nyi, K. *J. Am. Chem. Soc.* **1971**, *93*, 2786. (b) Kirmse, W.; Wroblowsky, H.-J. *Chem. Ber.* **1983**, *116*, 1118. (c) Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 3118. (d) Chapman, L. M.; Beck, J. C.; Wu, L.; Reisman, S. E. *J. Am. Chem. Soc.* **2016**, *138*, 9803.
(26) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Müller, S.; Liepold, B.; Roth, G.; Bestmann, H. J. *Synlett* **1996**, *1996*, 521.
(27) (a) Bestmann, H. J.; Bomhard, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 545. (b) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.
(28) Liu, X.; Li, X.; Chen, Y.; Hu, Y.; Kishi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 6136.

DOI: 10.1021/acs.orglett.6b02767
Org. Lett. 2016, 18, 5388−5391