Organic LETTERS

Letter

pubs.acs.org/OrgLett

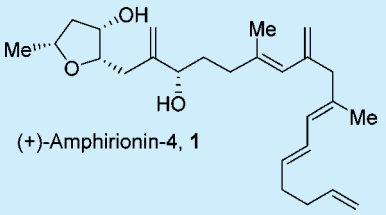
Enantioselective Total Synthesis of (+)-Amphirionin-4

Arun K. Ghosh* and Prasanth R. Nyalapatla

Department of Chemistry and Department of Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907, United States

Supporting Information

ABSTRACT: An enantioselective total synthesis of (+)-amphirionin-4 has been accomplished in a convergent manner. The synthesis features an efficient enzymatic lipase resolution to access the tetrahydrofuranol core in optically active form. The functionalized tetrahydrofuran derivative was synthesized via an oxocarbenium ion-mediated highly diastereoselective *syn*-allylation reaction. The polyene side chain was synthesized using Stille coupling reactions. Nozaki–Hiyama–Kishi coupling was utilized to construct the C-8 stereocenter and complete the synthesis of (+)-amphirionin-4.



Marine dinoflagellates of the genus *Amphidiuium species* are rich sources of bioactive polyketide-like natural products with intriguing biological properties.[1,2] Recently, Tsuda and co-workers isolated a number of polyketides, amphirionins-2, -4, and -5 from the dinoflagellate *Amphidiuium species*.[3−5] Among these, the linear polyketide (+)-amphirionin-4 (**1**, Figure 1) was isolated from the *Amphidiuium* KCA09051 strain in the benthic sea sand collected off the Iriomote Island. This compound exhibited exceptionally potent proliferation-promoting activity (95% promotion) on murine bone marrow stomal ST-2 cells at 0.1 ng/mL concentration. Interestingly, it did not show proliferation promotion when administered to MC3T3-E1 and NIH3TC cells.[4]

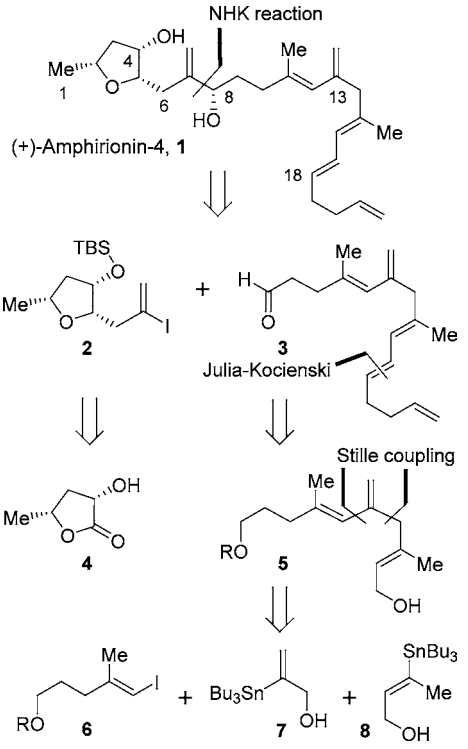


Figure 1. Retrosynthetic analysis of (+)-amphirionin-4.

The structure of (+)-amphirionin-4 was elucidated by Tsuda and co-workers using extensive NMR analysis and the absolute configuration of the C4 and C8 hydroxyl groups was determined by Mosher ester analysis.[4] Recently, Britton and co-workers have reported the first synthesis of amphirionin-4.[6] However, the specific rotation of the synthetic compound was opposite to that reported for natural amphirionin-4.[4,6] Considering the extreme proliferation-promoting activity of (+)-amphirionin-4 in ST-2 cells, its structural features, and its potential medicinal application, we sought to develop a convergent and concise enantioselective synthesis of (+)-amphirionin-4. Herein, we now report a route that proceeds in nine linear steps, starting from a readily available racemic butyrolactone.

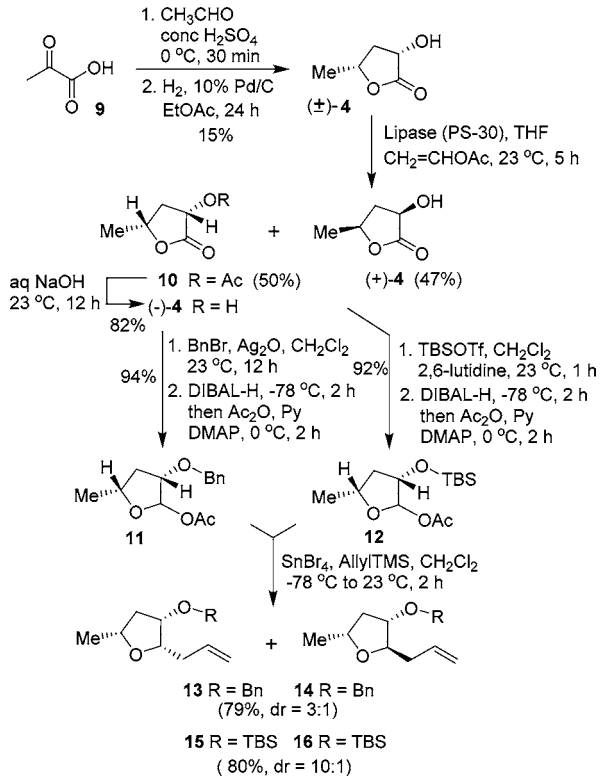
Our retrosynthesis of (+)-amphirionin-4 is shown in Figure 1. We planned to utilize a Nozaki–Hiyama–Kishi (NHK)[7,8] reaction similar to that reported by Britton and co-workers[6] to assemble amphirionin-4 from vinyl iodide **2** and polyene aldehyde **3** at a late stage in the synthesis. The functionalized tetrahydrofuran ring **2** would be constructed from optically active γ-lactone **4** via a *cis*-selective allylation of the corresponding oxocarbenium ion derived from lactone **4**. Optically active lactone **4** would be readily synthesized via acid-catalyzed condensation of pyruvic acid and acetaldehyde, followed by hydrogenation and lipase-catalyzed optical resolution of racemic lactone. This will provide rapid access to both enantiomers for structure–activity relationship studies of amphirionin-4. The polyene side chain **3** would be constructed by Julia–Kocienski olefination of the aldehyde derived from allylic alcohol **5**.[9] The requisite aldehyde precursor would be synthesized by iterative Stille cross-coupling reactions with appropriately protected vinyl iodide **6** and tributylstannanes **7** and **8**.

Our synthesis of functionalized tetrahydrofuran derivatives is shown in Scheme 1. Racemic lactone **4** was synthesized on gram scale by acid-catalyzed condensation of pyruvic acid **9** and

Received: April 1, 2016
Published: April 26, 2016

DOI: 10.1021/acs.orglett.6b00942
Org. Lett. 2016, 18, 2296–2299

Scheme 1. Synthesis of Substituted Tetrahydrofurans



acetaldehyde, followed by hydrogenation of the resulting unsaturated lactone over 10% Pd−C in EtOAc.[10,11] Racemic lactone **4** was then subjected to enzymatic resolution utilizing PS-30 in vinyl acetate at 23 °C for 5 h.[12,13] While the racemic lactone was obtained in low yield, it can be readily prepared in gram quantity and the current resolution protocol provided optically active alcohol (+)-**4** and acetate derivative **10** in 47% and 50% yields, respectively, with high optical purity. Acetate **10** was saponified with aqueous sodium hydroxide in methanol to provide optically active alcohol (−)-**4** in 82% yield.[14] The depicted absolute stereochemistry of lactones (+)-**4** and (−)-**4** was assigned based upon Kazlauskas' model[15] and comparison with the reported specific rotations.[16] Optically active lactone (−)-4 was protected as the benzyl ether (>90% ee by chiral HPLC analysis of this benzyl derivative). Dibal-H reduction of the protected lactone provided the corresponding lactol, which was treated with acetic anhydride and pyridine in the presence of DMAP to provide acetate **11** in excellent yield. The hydroxyl group of lactone (−)-**4** was also protected as the TBS ether. Dibal-H reduction of that lactone provided a mixture of lactols, which were converted to the acetate **12**. The reaction of acetate **11**, bearing a C2 benzyl ether, with allyltrimethylsilane in the presence of $SnBr_4$ in CH_2Cl_2 at −78 to 23 °C provided the allyl derivatives **13** and **14** as a 3:1 mixture of diastereomers by ^{1}H NMR analysis. The corresponding reaction of acetate **12** containing a C2 silyl ether with allyltrimethylsilane under similar conditions furnished allylation products **15** and **16** in 80% yield. However, the diastereomeric ratio of **15** and **16** improved to 10:1 (by ^{1}H NMR analysis). The relative stereochemistry of alkenes **13**, **14**, and **15** was assigned by ^{1}H NMR NOESY analysis.

The observed *cis*-diastereoselectivity is consistent with a C2-benzyloxy substituted tetrahydrofuranyl substrate examined by Woerpel and co-workers.[17] It appears that substituents at the C4-position, as in acetate **11**, did not influence overall *cis*-diastereoselectivity. The observed stereochemical outcome can be rationalized using similar steric and electronic arguments to those proposed by Woerpel and co-workers.[17] Presumably, the oxocarbenium ion intermediate **17** is preferred over **18** due to pseudoequatorial orientation of the C-2 alkoxy group (Figure 2).

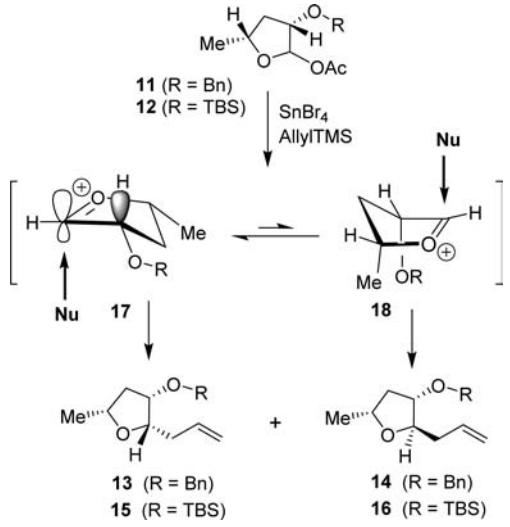
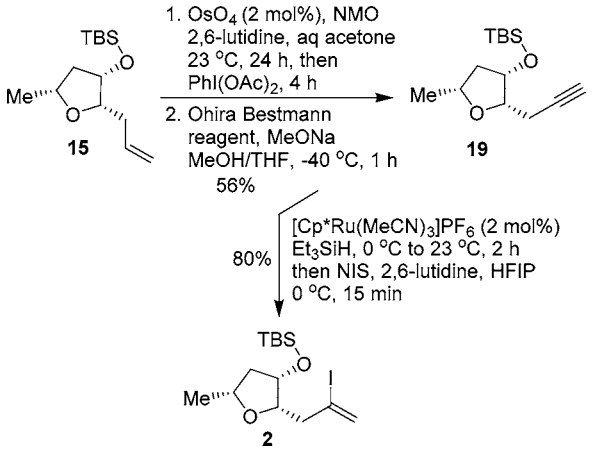


Figure 2. Stereochemical analysis for *cis*-allylation.

The σC−H orbital at C2 maximizes electron donation to the adjacent vacant orbital of the oxocarbenium ion. The bulky C2 siloxy group further enhances the pseudoequatorial orientation, and therefore the overall *cis*-selectivity.

The desired allyl derivative **15** was converted to the corresponding vinyl iodide as shown in Scheme 2. Oxidative

Scheme 2. Synthesis of Vinyl Iodide 2

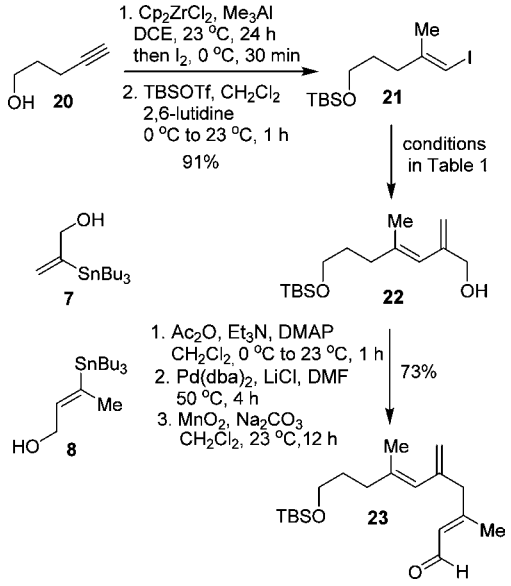


cleavage of alkene **15** using $PhI(OAc)_2$, NMO, and catalytic OsO_4 provided the corresponding aldehyde in 80% yield.[18] Alkynylation of the resulting aldehyde with the Ohira−Bestmann reagent[19,20] and MeONa in a mixture of MeOH and THF gave alkyne **19** in 70% yield. Hydrosilylation of the resulting alkyne **19** using Trost's procedure[21] with ($[Cp^*Ru(MeCN)_3]PF_6$) and triethylsilane followed by iododesilylation[22] with NIS and 2,6-lutidine in hexafluoroisopropanol (HFIP) furnished vinyl iodide **2** in 80% yield.

Synthesis of the amphirionin-**4** side chain is shown in Scheme 3. A zirconium-catalyzed carboalumination of 4-pentyne-1-ol **20** followed by reaction with iodine provided the corresponding

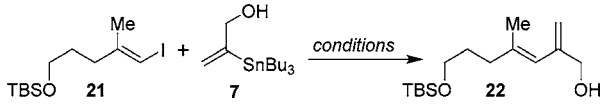
DOI: 10.1021/acs.orglett.6b00942
Org. Lett. 2016, 18, 2296−2299

Scheme 3. Synthesis of Aldehyde 23



vinyl iodide. TBS protection of the alcohol provided the vinyl iodide **21** in 91% yield.[23] We then investigated the Stille coupling of vinyl iodide **21** with the known[24] tributylstannane **7** under a variety of conditions. The results are summarized in Table 1.

Table 1. Stille-Coupling Conditions to Access Diene 22

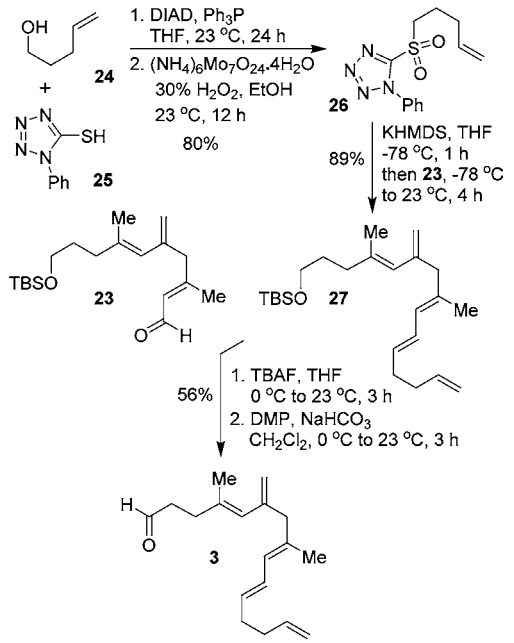


entry	catalyst and additive	mol (%)	solvent	time (h)	yield (%)
1	$Pd(MeCN)_2Cl_2$	10	DMF	24	30
2	$Pd(MeCN)_2Cl_2$	20	DMF	24	30
3	$Pd(MeCN)_2Cl_2$	30	DMF	96	28
4	$Pd_2(dba)_3$	30	DIPEA, NMP	24	25
5	$Pd(PPh_3)_4$ CuCl, LiCl	10	DMSO	2	90

Reactions with $Pd(MeCN)_2Cl_2$ (10 or 20 mol %) in DMF at 23 °C resulted in 30% yield (entries 1 and 2). Catalyst loading was then increased to 30 mol % and reaction temperature was increased to 50 °C for 96 h. This also resulted in low yield of coupling product **22** (entry 3). Coupling with $Pd_2(dba)_3$ (30 mol %) at 23 °C in a mixture of DIPEA/NMP again resulted in low yield of product (25%, entry 4). We believe that these low yields can be attributed to the disubstituted vinylstannane due to a slow transmetalation step and a competing *cine* substitution.[25] In an attempt to enhance the transmetalation step, we decided to use cuprous chloride as a promoter in the Stille-coupling reactions as described by Corey and co-workers.[25] Modified Stille-coupling of vinyl iodide **21** and tributylstannane **7** in the presence of CuCl and LiCl at 23 °C for 2 h furnished the desired diene **22** in excellent (90%) yield. Acetylation of diene **22** furnished the corresponding allyl acetate in 95% yield. Stille-coupling[26] of the resulting allyl acetate with the known[27] hydroxystannane **8** using $Pd(dba)_2$ and LiCl in DMF at 50 °C afforded the coupling product in 96% yield. MnO_2 oxidation of the resulting allylic alcohol furnished the aldehyde **23** in 80% yield.

Our synthesis of the polyene derivative **3** is shown in Scheme 4. Sulfone **26** was prepared in good yield by the reaction of 4-

Scheme 4. Synthesis of Aldehyde 3



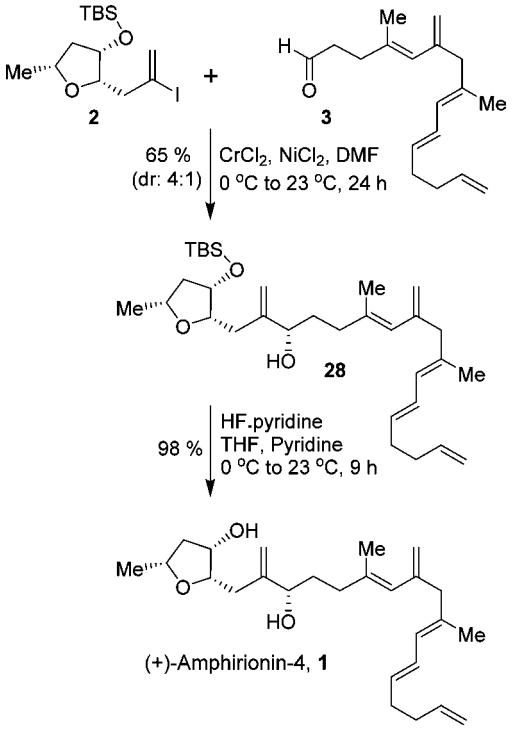
penten-1-ol **24** with 1-phenyl-1*H*-tetrazole-5-thiol **25**, followed by oxidation using catalytic ammonium molybdate and hydrogen peroxide. Julia–Kocienski olefination[9] between aldehyde **23** and sulfone **26** gave the polyene **27** in 89% yield and only the *E*-isomer was formed (by ^{1}H NMR analysis). Removal of the TBS group followed by DMP oxidation of the resulting alcohol provided aldehyde **3** in good yield.

The final synthesis of (+)-amphirionin-4 is outlined in Scheme 5. NHK coupling[6] between aldehyde **3** and vinyl iodide **2** was carried out in DMF at 0° to 23 °C for 24 h. This provided TBS-protected amphirionin-4 **28** as the major diastereomer (4:1) in 65% yield. The diastereomers were separated by silica gel chromatography. Deprotection of the TBS group using 70% HF, 30% pyridine in the presence of excess pyridine furnished synthetic (+)-amphirionin-4 (**1**) in 98% yield. The ^{1}H and ^{13}C NMR of our synthetic amphirionin-4 {$[\alpha]_D^{23}$ + 6.4 (*c* 0.08, $CHCl_3$)} are identical to the reported spectra for the natural (+)-amphirionin-4 {lit[4] $[\alpha]_D^{20}$ + 6 (*c* 0.29, $CHCl_3$)}, thus confirming the absolute configuration of our synthetic material.

In summary, we have achieved an enantioselective synthesis of (+)-amphirionin-4 (**1**). The synthetic route is convergent and readily scalable. The longest linear path is nine steps from readily available racemic butyrolactone. The synthesis featured lipase resolution of a racemic lactone to give highly optically pure isomers. Other key reactions include a highly diastereoselective *syn*-allylation reaction, an efficient Stille coupling to construct the polyene side chain and a NHK coupling to establish the C8 allylic alcohol diastereoselectively. Our synthesis has provided rapid access to (+)-amphirionin-4 (**1**) and structural variants for biological studies. Further investigations of structural and biological studies are in progress.

DOI: 10.1021/acs.orglett.6b00942
Org. Lett. 2016, 18, 2296–2299

Scheme 5. Synthesis of (+)-Amphirionin-4 (1)



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00942.

Experimental procedures and ^{1}H- and ^{13}C- NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: akghosh@purdue.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support of this work was provided in part by the National Institutes of Health and Purdue University.

■ REFERENCES

(1) (a) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77−93. (b) Kobayashi, J.; Kubota, T. J. *J. Nat. Prod.* **2007**, *70*, 451−460.
(2) Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2008**, *25*, 35−94.
(3) Kumagai, K.; Minamida, M.; Akakabe, M.; Tsuda, M.; Konishi, Y.; Tominaga, A.; Tsuda, M.; Fukushi, E.; Kawabata, J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 635−638.
(4) Minamida, M.; Kumagai, K.; Ulanova, D.; Akakabe, M.; Konishi, Y.; Tominaga, A.; Tanaka, H.; Fukushi, E.; Kawabata, J.; Masuda, A.; Tsuda, M. *Org. Lett.* **2014**, *16*, 4858−4861.
(5) Akakabe, M.; Kumagai, K.; Tsuda, M.; Konishi, Y.; Tominaga, A.; Tsuda, M.; Fukushi, E.; Kawabata, J. *Tetrahedron Lett.* **2014**, *55*, 3491−3494.
(6) Holmes, M.; Kwon, D.; Taron, M.; Britton, R. *Org. Lett.* **2015**, *17*, 3868−3871.
(7) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281−5284.
(8) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646.
(9) Blakemore, P. R.; Cole, W. J.; Kocienski, P.; Morley, A. *Synlett* **1998**, *1998*, 26−28.
(10) MaGee, D.; Mallais, T. C.; Mayo, P. D. M.; Strunz, G. M. *Tetrahedron* **2006**, *62*, 4153−4161.
(11) Kang, H. Y.; Ji, Y.; Yu, Y. K.; Yu, J. Y.; Lee, Y.; Lee, S. J. *Bull. Korean Chem. Soc.* **2003**, *24*, 1819−1826.
(12) Bianchi, D.; Cesti, P.; Battistel, E. *J. Org. Chem.* **1988**, *53*, 5531−34.
(13) Ghosh, A. K.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 505−508.
(14) Enders, D.; Sun, H.; Leusink, F. R. *Tetrahedron* **1999**, *55*, 6129−6138.
(15) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999.
(16) Ahrens, H.; Paetow, M.; Hoppe, D. *Tetrahedron Lett.* **1992**, *33*, 5327−5330.
(17) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879−10884.
(18) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552−1555.
(19) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564.
(20) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, *1996*, 521−522.
(21) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644−17655.
(22) Llardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727−1730.
(23) Zheng, Y. F.; Oehlschlager, A. C.; Hartman, P. G. *J. Org. Chem.* **1994**, *59*, 5803−5809.
(24) Bellina, F.; Carpita, A.; Santis, M. D.; Rossi, R. *Tetrahedron* **1994**, *50*, 4853−4872.
(25) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605.
(26) Del Valle, L.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019−3023.
(27) Chellat, M. F.; Proust, N.; Lauer, M. G.; Stambuli, J. P. *Org. Lett.* **2011**, *13*, 3246−3249.

DOI: 10.1021/acs.orglett.6b00942
Org. Lett. 2016, 18, 2296−2299