Organic LETTERS

Letter

pubs.acs.org/OrgLett

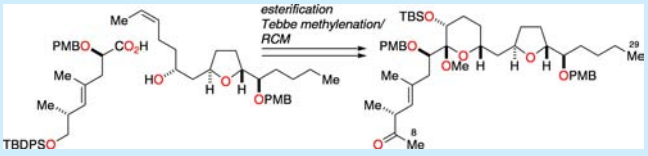
Toward the Total Synthesis of Amphidinolide N: Synthesis of the C8−C29 Fragment

Yuki Kawashima,[†] Atsushi Toyoshima,[†] Haruhiko Fuwa,* and Makoto Sasaki*

Graduate School of Life Sciences, Tohoku University, 2-1-1 Katahira, Aoba-ku, Sendai 980-8577, Japan

Supporting Information

ABSTRACT: A synthesis of the C8−C29 fragment of amphidinolide N, a potent cytotoxic macrolide isolated from the marine dinoflagellate *Amphidinium* sp., has been achieved. The key features of the synthesis involve a convergent union of the C9−C15 and C16−C29 fragments by Steglich esterification and the construction of a pyran unit through a Tebbe methylenation/ring-closing metathesis sequence.



Amphidinolides are a series of cytotoxic marine macrolides isolated from cultured *Amphidinium* sp. associated with the Okinawan flatworm, *Amphiscolops* sp., by Kobayashi and co-workers.[1] Amphidinolide N (**1**) (Figure 1), isolated from

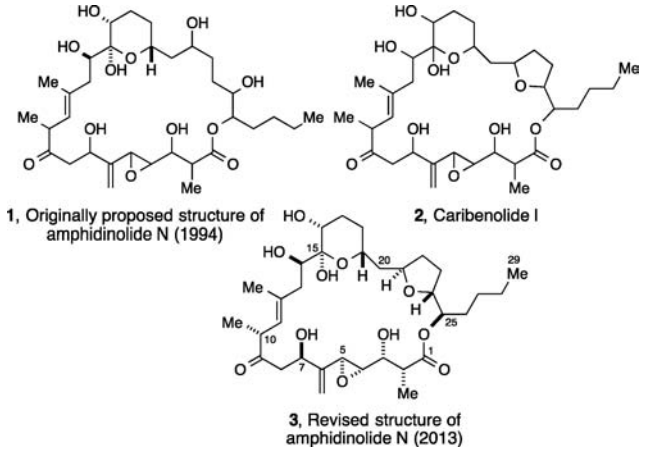


Figure 1. Structures of amphidinolide N and caribenolide I.

Amphidinium sp. (Y-5 strain) in 1994, is the most potent cytotoxic member of the amphidinolides, with IC_{50} values of 0.05 and 0.06 ng/mL against murine lymphoma L1210 and human epidermoid carcinoma KB cells, respectively.[2] The gross structure of **1**, including a partial configurational assignment, was proposed on the basis of extensive 2D NMR analysis and consists of a 26-membered macrolide backbone containing an α-methylene epoxide, a six-membered hemiacetal, and 13 stereogenic centers. Almost simultaneously, Shimizu and co-workers independently reported a closely related macrolide, caribenolide I (**2**), isolated from the cultured free-swimming Caribbean dinoflagellate, *Amphidinium* sp. S1-36-5.[3] Most importantly, caribenolide I showed in vivo antitumor activity against murine tumor P388 (T/C: 150 at a dose of 0.03 mg/kg). Recently, the structure of amphidinolide N with a full configurational assignment was revised to be represented as **3**, with the same gross structure as caribenolide I.[4]

The extremely potent cytotoxicity and complex molecular architecture of amphidinolide N and calibenolide I have attracted considerable attention in the synthetic community.[5−7]

Very recently, Hayashi and co-workers reported the total synthesis of 7,10-*epi*-amphidinolide N.[8] We previously reported a synthesis route to the C13−C29 segment of **3**.[9] However, we were unable to advance the synthesis because of the difficulties associated with protecting group manipulations. To address this problem, we decided to reconsider the overall synthesis plan, and herein we report a synthesis of the C8−C29 fragment of amphidinolide N.

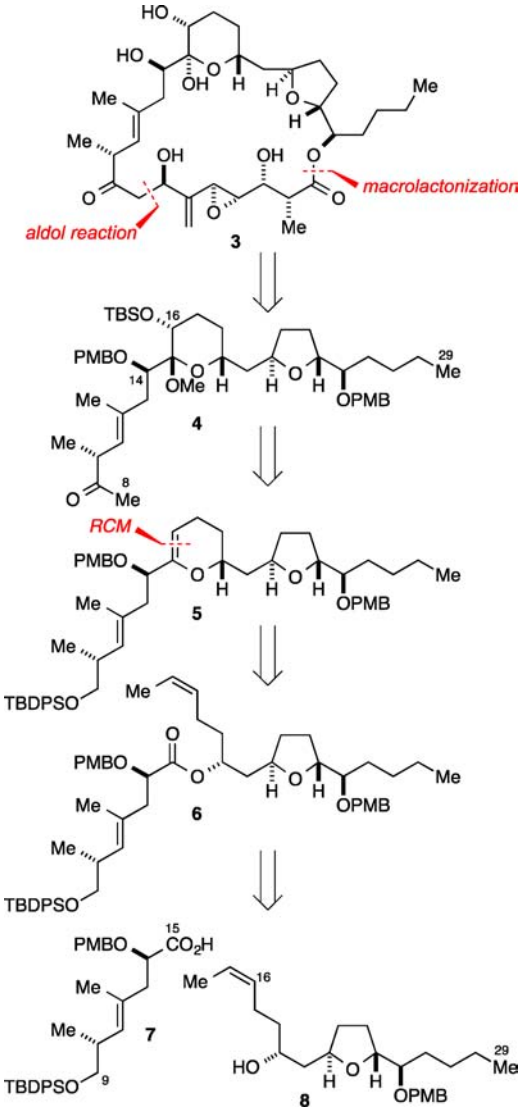
Our retrosynthetic analysis for the C8−C29 fragment **4** is depicted in Scheme 1. For the construction of the challenging six-membered acetal unit with α,α'-dihydroxy substituents at C14−C16, Nicolaou[5] and Hayashi[8] utilized the hydrazone alkylation chemistry developed by Enders and co-workers.[10] By contrast, we envisioned that an epoxidation and in situ methanolysis[11] of dihydropyran **5** would enable access to six-membered acetal **4**. In turn, on the basis of previous work[12,13] we considered that dihydropyran **5** could be traced back to ester **6** via a methylenation and a ring-closing metathesis (RCM). Ester **6** would in turn be accessed from two components of comparable complexity, carboxylic acid **7** and alcohol **8**.

The synthesis of carboxylic acid **7** started with the known internal alkyne **9**[14] (Scheme 2). Silylcupration of **9** using Fleming's reagent $(PhMe_2Si)_2Cu(CN)Li_2$[15] (THF, −78 to 0 °C) provided vinylsilane **10** as a single regio- and stereoisomer. Subsequent iododesilylation with NIS (MeCN, 0 °C to room temperature)[16] proceeded with complete retention of configuration to afford vinyl iodide **11** in 83% yield for the two steps (E/Z >20:1). Halogen−lithium exchange of **11** using *t*-BuLi (THF, −78 °C) followed by addition of PMB-protected

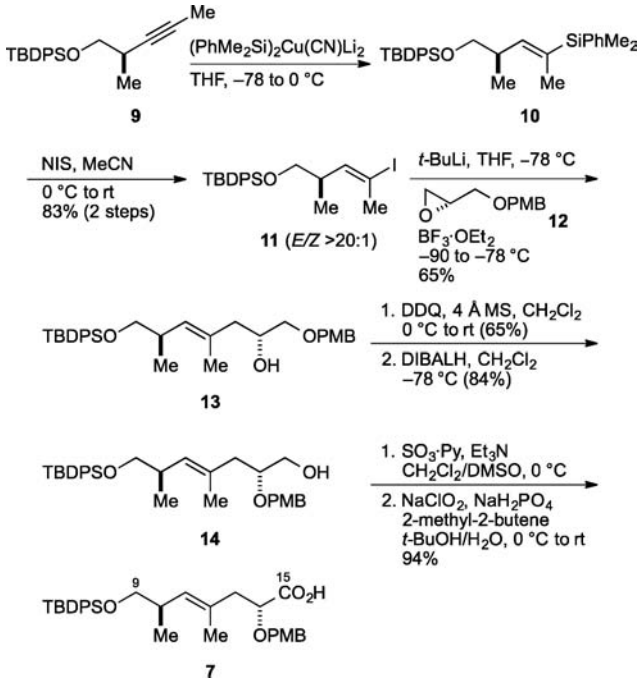
Received: March 25, 2016
Published: April 26, 2016

DOI: 10.1021/acs.orglett.6b00871
Org. Lett. 2016, 18, 2232−2235

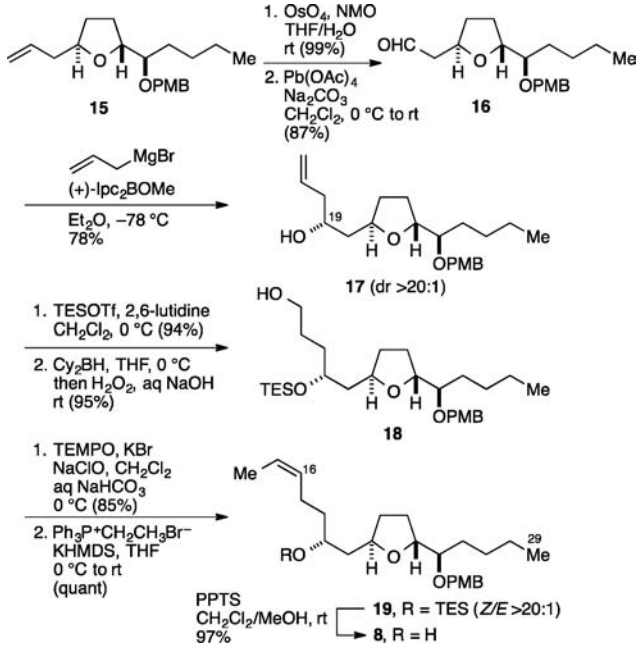
Scheme 1. Retrosynthesis of the C8−C29 Fragment 4



Scheme 2. Synthesis of Carboxylic Acid 7



Scheme 3. Synthesis of Alcohol 8



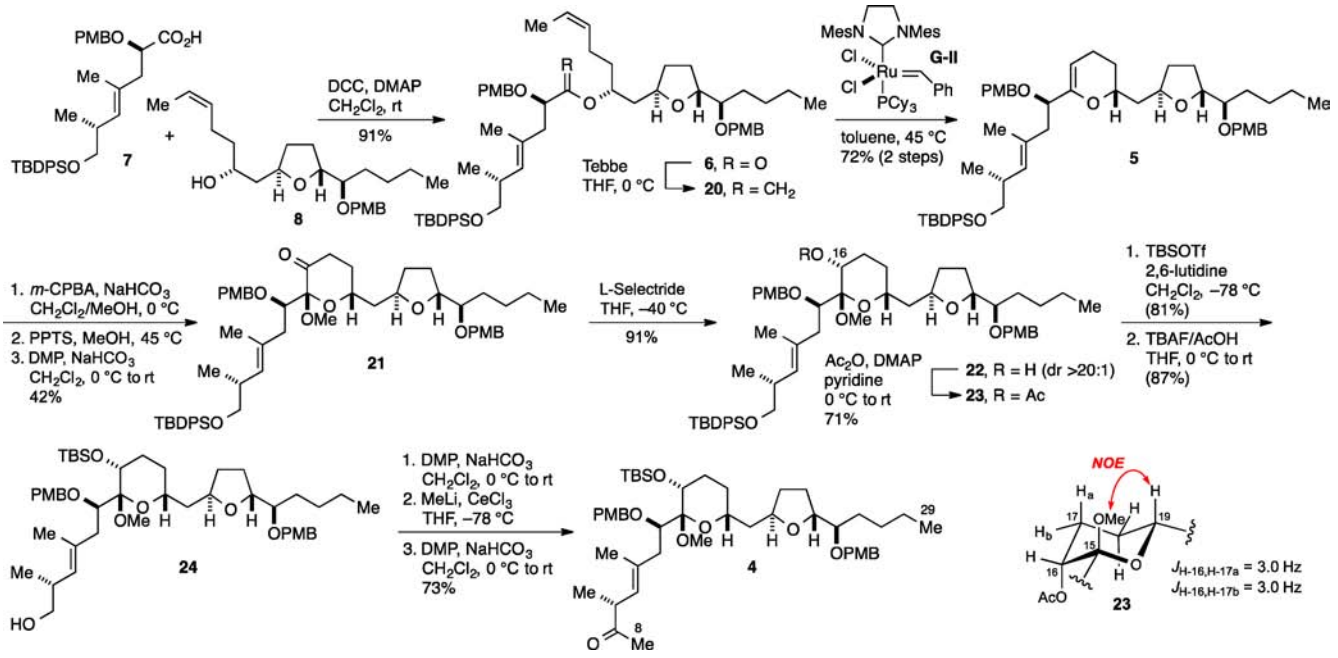
glycidol **12**[17] and $BF_3{\cdot}OEt_2$ (−90 to −78 °C) provided alcohol **13** in 65% yield.[18] Oxidative acetalization of PMB ether **13** using DDQ under anhydrous conditions[19] gave a *p*-methoxybenzylidene acetal (65%), which was regioselectively cleaved with DIBALH to provide primary alcohol **14** in 84% yield.[20] A two-stage oxidation[21,22] of alcohol **14** delivered carboxylic acid **7** in 94% yield for the two steps.

The synthesis of alcohol **8** commenced with the known tetrahydrofuran **15**.[9] The terminal olefin of **15** was oxidatively cleaved by a two-step sequence (OsO_4/NMO then $Pb(OAc)_4$) to give aldehyde **16** (Scheme 3). Brown asymmetric allylation[23] of **16** delivered homoallylic alcohol **17** in 78% yield as a single diastereomer (dr > 20:1). The absolute configuration of the C19[24] stereogenic center was established by a modified Mosher analysis.[25,26] After protection of the secondary alcohol of **17** as its TES ether (TESOTf, 2,6-lutidine, 94%), the terminal olefin was hydroborated using dicyclohexylborane to provide alcohol **18** in 95% yield. Oxidation of **18** with TEMPO/NaClO[27] followed by Wittig reaction of the resultant aldehyde using $Ph_3P^+CH_2CH_3Br^-$/KHMDS delivered (*Z*)-olefin **19** in 85% yield for the two steps (*Z*/*E* > 20:1). Removal of the TES group of **19** under acidic conditions gave rise to alcohol **8** in 97% yield.

With the requisite two fragments in hand, we next focused on their coupling and crucial formation of a pyran unit, as depicted in Scheme 4. Condensation of carboxylic acid **7** and alcohol **8** was performed using DCC/DMAP[28] to yield ester **6** in 91% yield. We initially attempted direct olefinic ester cyclization of a model compound closely related to ester **6** using the Takai−Uchimoto reduced titanium reagent[29] according to the Rainier protocol,[30] but this process resulted only in recovery of the starting material (90−98%), and no desired dihydropyran was obtained. Therefore, we decided to construct the dihydropyran

DOI: 10.1021/acs.orglett.6b00871
Org. Lett. 2016, 18, 2232−2235

Scheme 4. Synthesis of the C8−C29 Fragment 4



ring of **5** by employing a stepwise Tebbe methylenation and RCM.[12] Thus, treatment of ester **6** with Tebbe reagent[31] ($Cp_2Ti(Cl)CH_2AlMe_2$, THF, 0 °C) afforded enol ether **20**, which was subjected to RCM using the second-generation Grubbs catalyst (G-II)[32] to furnish dihydropyran **5** in 72% yield for the two steps.[12,33]

The remaining challenge was to install the C15 and C16 oxygen functionalities in a stereoselective fashion, but this proved to be more problematic than expected. Epoxidation of **5** with *m*-CPBA ($NaHCO_3$, CH_2Cl_2/MeOH, 0 °C) followed by in situ epoxide ring opening with MeOH afforded the desired hydroxy methyl acetal as a mixture of the C16-epimeric alcohols, along with the unexpected C15-OH and its *m*-chlorobenzoate derivatives. Treatment of this mixture with PPTS (MeOH, 45 °C) effected the conversion of these unwanted products to the corresponding methyl acetal. Subsequent oxidation with Dess−Martin periodinane[34] delivered ketone **21** in 42% yield for the three steps. Reduction of **21** using L-Selectride (THF, −40 °C) proceeded in a highly stereoselective manner to furnish alcohol **22** (91% yield, dr >20:1). The relative configuration of the C15 and C16 stereogenic centers was unambiguously established by conversion to the acetate derivative **23** and its $^3J_{H,H}$ values and NOE data as shown. Protection of the secondary alcohol of **22** with TBSOTf/2,6-lutidine followed by selective removal of the primary TBDPS group with TBAF/AcOH[35] delivered primary alcohol **24**. Finally, alcohol **24** was converted to the desired C8−C29 fragment **4** using a three-step sequence involving Dess−Martin oxidation,[34] methylation using MeLi/$CeCl_3$,[36] and a second oxidation (73% yield for the three steps).

In conclusion, we have achieved a convergent synthesis of the C8−C29 fragment of amphidinolide N. The key feature of the synthesis route includes coupling of two fragments **7** and **8** by a Steglich esterification and a Tebbe methylenation/RCM sequence to construct a dihydropyran ring. Further studies aimed at the total synthesis of amphidinolide N are underway and 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.6b00871.

Experimental procedures, characterization data for all new compounds, modified Mosher analysis of compound **17**, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: masasaki@m.tohoku.ac.jp.
*E-mail: hfuwa@m.tohoku.ac.jp.

Author Contributions

†Y.K. and A.T. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Kaneka Corporation for donating (*S*)-Roche ester. This work was financially supported in part by a Grants-in-Aid for Scientific Research (B) (25282228) and Scientific Research on Innovative Areas "Chemical Biology of Natural Products" (23102016)[37] from the Japan Society for the Promotion of Science (JSPS).

■ REFERENCES

(1) For a review, see: Kobayashi, J. *J. Antibiot.* **2008**, *61*, 271−284 and references cited therein.
(2) Ishibashi, M.; Yamaguchi, N.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc., Chem. Commun.* **1994**, 1455−1456.
(3) Bauer, I.; Maranda, L.; Young, K. A.; Shimizu, Y.; Fairchild, C.; Cornell, L.; MacBeth, J.; Huang, S. *J. Org. Chem.* **1995**, *60*, 1084−1086.

DOI: 10.1021/acs.orglett.6b00871
Org. Lett. 2016, 18, 2232−2235

(4) Takahashi, Y.; Kubota, T.; Imachi, M.; Wälchli, M. R.; Kobayashi, J. *J. Antibiot.* **2013**, *66*, 277−279.
(5) (a) Nicolaou, K. C.; Brenzovich, W. E.; Bulger, P. G.; Francis, T. M. *Org. Biomol. Chem.* **2006**, *4*, 2119−2157. (b) Nicolaou, K. C.; Bulger, P. G.; Brenzovich, W. E. *Org. Biomol. Chem.* **2006**, *4*, 2158−2183.
(6) (a) Seck, M.; Seon-Meniel, B.; Jullian, J.-C.; Franck, X.; Hocquemiller, R.; Figadére, B. *Lett. Org. Chem.* **2006**, *3*, 390−395. (b) Seck, M.; Franck, X.; Seon-Meniel, B.; Hocquemiller, R.; Figadére, B. *Tetrahedron Lett.* **2006**, *47*, 4175−4180. (c) Jalce, G.; Franck, X.; Seon-Meniel, B.; Hocquemiller, R.; Figadére, B. *Tetrahedron Lett.* **2006**, *47*, 5905−5908.
(7) Trost, B. M.; Rey, J. *Org. Lett.* **2012**, *14*, 5632−5635.
(8) (a) Ochiai, K.; Kuppusamy, S.; Yasui, Y.; Okano, T.; Matsumoto, Y.; Gupta, N. R.; Takahashi, Y.; Kubota, T.; Kobayashi, J.; Hayashi, Y. *Chem. - Eur. J.* **2016**, *22*, 3282−3286. (b) Ochiai, K.; Kuppusamy, S.; Yasui, Y.; Harada, K.; Gupta, N. R.; Takahashi, Y.; Kubota, T.; Kobayashi, J.; Hayashi, Y. *Chem. - Eur. J.* **2016**, *22*, 3287−3291.
(9) Sasaki, M.; Kawashima, Y.; Fuwa, H. *Heterocycles* **2015**, *90*, 579−599.
(10) For a review, see: Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1304−1325.
(11) For related examples, see: (a) Kasai, Y.; Ito, T.; Sasaki, M. *Org. Lett.* **2012**, *14*, 3186−3189. (b) Liao, X.; Wu, Y.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1648−1652. (c) Wender, P. A.; Koehler, M. F. T.; Sendzik, M. *Org. Lett.* **2003**, *5*, 4549−4552. (d) Hale, K. J.; Frigerio, M.; Manaviazar, S. *Org. Lett.* **2001**, *3*, 3791−3794. (e) Wender, P. A.; De Brabander, J.; Harran, P. G.; Jimenez, J.-M.; Koehler, M. F. T.; Lippa, B.; Park, C.-M.; Shiozaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4534−4535. (f) Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999**, *121*, 7540−7552.
(12) Holson, E. B.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3719−3722.
(13) (a) Fuwa, H.; Sasaki, M. *Org. Lett.* **2008**, *10*, 2549−2552. (b) Fuwa, H.; Ishigai, K.; Hashizume, K.; Sasaki, M. *J. Am. Chem. Soc.* **2012**, *134*, 11984−11987.
(14) Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103−106.
(15) (a) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527−2532. (b) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822−7824.
(16) Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8647−8650.
(17) Gaunt, M. J.; Hook, D. F.; Tanner, H. R.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4815−4818.
(18) (a) Frost, J. R.; Pearson, C. M.; Snaddon, T. N.; Booth, R. A.; Ley, S. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 9366−9371. (b) Zurwerra, D.; Gertsch, J.; Altmann, K.-H. *Org. Lett.* **2010**, *12*, 2302−2305.
(19) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889−892.
(20) (a) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1984**, 201−202. (b) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593−1596.
(21) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.
(22) (a) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175−1176.
(23) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065−5069.
(24) The carbon numbering of compounds in this paper corresponds to that of amphidinolide N.
(25) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.
(26) See the Supporting Information for details.
(27) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, F. *J. Org. Chem.* **1987**, *52*, 2559−2562.
(28) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522−524.
(29) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668−2670.
(30) (a) Majumder, U.; Rainier, J. D. *Tetrahedron Lett.* **2005**, *46*, 7209−7211. (b) Iyer, K.; Rainier, J. D. *J. Am. Chem. Soc.* **2007**, *129*, 12604−12605. For related one-pot methylenation/RCM sequences, see: (c) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565−1566. (d) Nicolaou, K. C.; Postema, M. H. D.; Yu, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335−10336.
(31) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613. (b) Pine, S. H.; Zahler, R.; Evans, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 3270−3272. (c) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212−1216.
(32) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.
(33) Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179−181.
(34) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(35) Higashibayashi, S.; Shinko, K.; Ishizu, T.; Hashimoto, K.; Shirahama, H.; Nakata, M. *Synlett* **2000**, 1306−1308.
(36) (a) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904−3912. (b) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398. (c) Imamoto, T. *Pure Appl. Chem.* **1990**, *62*, 747−752. For a review, see: (d) Bartoli, G.; Marcantoni, E.; Marcolini, M.; Sambri, L. *Chem. Rev.* **2010**, *110*, 6104−6143.
(37) Ueda, M. *Chem. Lett.* **2012**, *41*, 658−666.

DOI: 10.1021/acs.orglett.6b00871
Org. Lett. 2016, 18, 2232−2235