JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Total Synthesis of Swinholide A: An Exposition in Hydrogen-Mediated C−C Bond Formation

Inji Shin,[†] Suckchang Hong,[†] and Michael J. Krische*

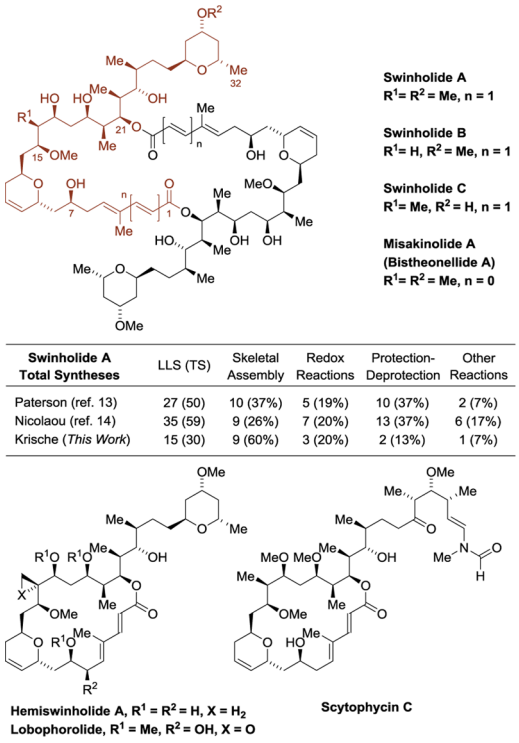
Department of Chemistry, University of Texas at Austin, Austin, Texas 78712, United States

Supporting Information

ABSTRACT: Diverse hydrogen-mediated C−C couplings enable construction of the actin-binding marine polyketide swinholide A in only 15 steps (longest linear sequence), roughly half the steps required in two prior total syntheses. The redox-economy, chemo- and stereoselectivity embodied by this new class of C−C couplings are shown to evoke a step-change in efficiency.

Natural products that modulate microtubule dynamics in the course of cell division have emerged as an important class of anti-cancer compounds.[1] Paclitaxel (taxol), docetaxel (taxotere), ixabepilone (ixempra), and eribulin mesylate (halaven) represent FDA-approved members of this compound class. Consequently, the prospect of utilizing actin-binding marine polyketides in cancer therapy has garnered increasing interest.[2] Swinholide A, first isolated from the Okinawan marine sponge *Theonella swinhoei* in 1985,[3,4] dimerizes actin ($K_d \approx 50$ nM).[5a] A highly resolved X-ray crystal structure of swinholide A affixed to two actin molecules has been acquired.[5c] The ability of swinholide A to disrupt the carefully regulated assembly of actin cytoskeletal constructs[5] confers cytotoxicity in the ng/mL range against diverse tumor cell lines,[6] making it the most potent member of its class (Figure 1).[7−9] Due to its well-understood mode of binding and potency, simplified functional analogues of swinholide A might serve as molecular probes or as starting points for the design of clinical candidates.[2] However, while analogues of other actin-binding natural products have been prepared,[10] synthetic congeners of swinholide A have not—a fact that may be attributed to the daunting structural complexity of swinholide A and that high levels of potency require preservation of the symmetric 44-membered macrodiolide ring.[11] Indeed, despite numerous synthetic studies,[12] to date, only two total syntheses of swinholide A have been accomplished in the laboratories of Paterson (1994)[13] and Nicolaou (1996).[14,15] Additionally, a total synthesis of preswinholide A was reported by Nakata (1996).[16]

The original paradigm for polyketide construction, which encompasses prior syntheses of swinholide A, relies largely on C−C bond formations mediated by pre-formed organometallic C-nucleophiles. We have developed a broad, new family of catalytic carbonyl reductive couplings induced via hydrogenation or hydrogen auto-transfer.[17a,b] These processes bypass pre-metalated reagents and streamline the synthesis of polyketide natural products by merging redox and C−C bond construction events (redox-economy).[17c,18] Additionally, by virtue of their highly chemo- and stereoselective nature, enantioselective C−C coupling can be achieved in the absence of protecting groups.[19] Collectively, these attributes contribute to a step-change in efficiency.[17b,c] Here, using diverse hydrogen-mediated C−C couplings, we report a 15-step (longest linear sequence, or LLS) total synthesis of swinholide A—a route roughly half the length of the two previous total syntheses.



Swinholide A Total Syntheses	LLS (TS)	Skeletal Assembly	Redox Reactions	Protection-Deprotection	Other Reactions
Paterson (ref. 13)	27 (50)	10 (37%)	5 (19%)	10 (37%)	2 (7%)
Nicolaou (ref. 14)	35 (59)	9 (26%)	7 (20%)	13 (37%)	6 (17%)
Krische (*This Work*)	15 (30)	9 (60%)	3 (20%)	2 (13%)	1 (7%)

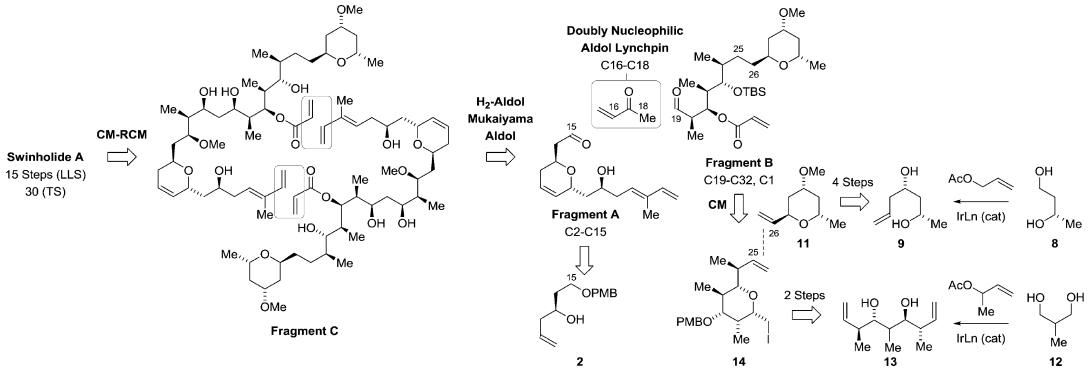
Figure 1. Structure of swinholide A, related secondary metabolites, and analysis of prior total syntheses of swinholide A. For graphical summaries of prior total syntheses, see Supporting Information (SI). LLS, longest linear sequence; TS, total steps. Only transformations in the LLS are considered in the analysis of reaction type.

Retrosynthetically, we envisioned access to swinholide A through a direct macrodiolide formation via successive cross-metathesis (CM)−ring-closing metathesis (RCM) of fragment **C** or a protected congener thereof (Scheme 1).[20] The two prior syntheses of swinholide A installed the macrodiolide ring through stepwise formation of ester/lactone linkages. The possibility that fragment **C** would engage in RCM (without initial CM) leading to formation of hemiswinholide rendered the

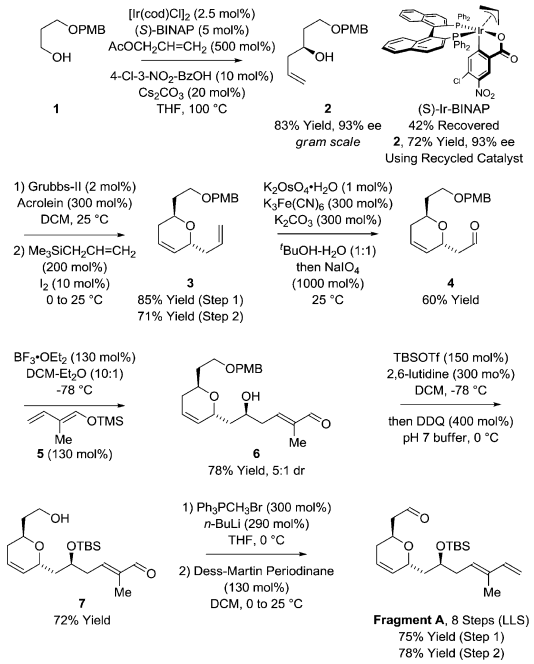
Received: October 11, 2016
Published: October 25, 2016

DOI: 10.1021/jacs.6b10645
J. Am. Chem. Soc. 2016, 138, 14246−14249

Scheme 1. Retrosynthetic Analysis of Swinholide A via C−C Bond-Forming Hydrogenation and Transfer Hydrogenation

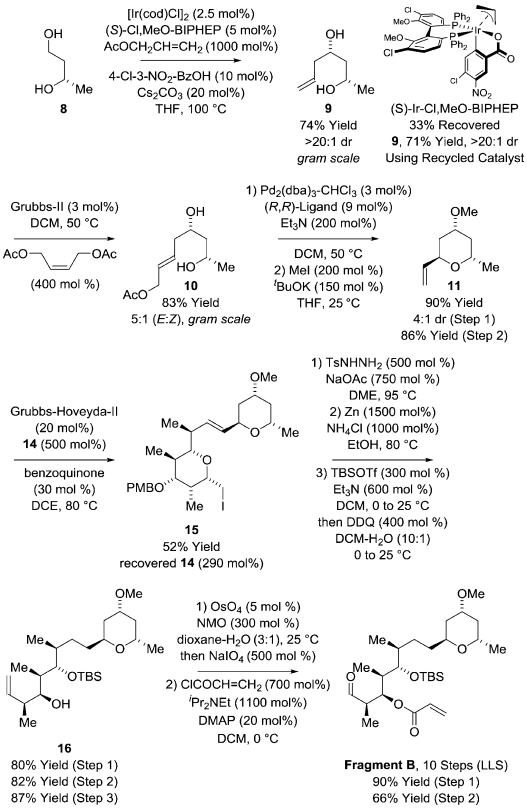


Scheme 2. Synthesis of Fragment A[a]



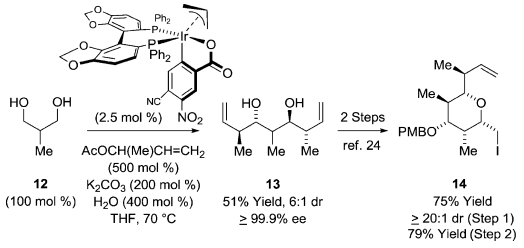
[a]Enantioselectivity was determined by chiral stationary phase HPLC analysis. See SI for further experimental details.

Scheme 3. Synthesis of Fragment B via Catalyst-Directed Diastereoselective and Site-Selective Allylation of Diol 8[a]



[a](*R*,*R*)-ligand = (1*R*,2*R*)-(+)-1,2-diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphinobenzoyl). See SI for further experimental details.

Scheme 4. Synthesis of Iodo Ether 14 via Diastereo- and Enantioselective Double *anti*-Crotylation of Diol 12[a]

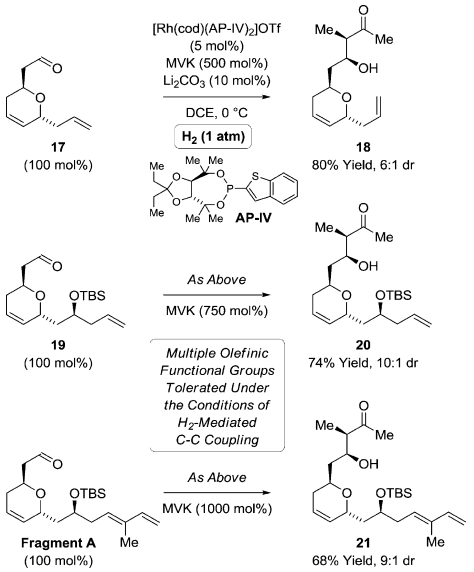


[a]Enantioselectivity was determined by chiral stationary phase HPLC analysis. See SI for further experimental details.

outcome of this approach uncertain. The planned synthesis of fragment **C** is highly convergent and involves the use of methyl vinyl ketone (MVK) as a doubly nucleophilic aldol lynchpin for the union of fragments **A** and **B**. Specifically, hydrogen-mediated reductive aldol reaction[21] of MVK with fragment **A** is followed by Mukaiyama aldol reaction[22] of the resulting methyl ketone with fragment **B**. This strategy requires exceptional chemoselectivity, as rhodium-catalyzed hydrogenation of MVK in the presence of fragment **A** must induce reductive coupling rather than conventional hydrogenation of the C2−C5 diene and C10−C11 olefin. Fragment **A** is prepared using one transfer hydrogenative alcohol C−H allylation[23] to form the C12−C13 carbon−carbon bond. As established in preliminary studies on the synthesis of the C19−C32 substructure of swinholide A,[24] fragment **B** is accessible through CM of the vinyl pyran **11** with iodo ether **14**. Vinyl pyran **11** is prepared through stereo- and site-selective allylation of commercially available (*S*)-1,3-butane diol **8**.[25] The iodo ether **14** is prepared from the pseudo-C_2-symmetric diol **13**, which, in turn, is obtained directly from 2-

DOI: 10.1021/jacs.6b10645
J. Am. Chem. Soc. 2016, 138, 14246−14249

Scheme 5. Hydrogen-Mediated Reductive Aldol Couplings of Methyl Vinyl Ketone[a]



[a]See SI for further experimental details.

methyl-1,3-propanediol **12** via double diastereo- and enantioselective diol C−H *anti*-crotylation.[26]

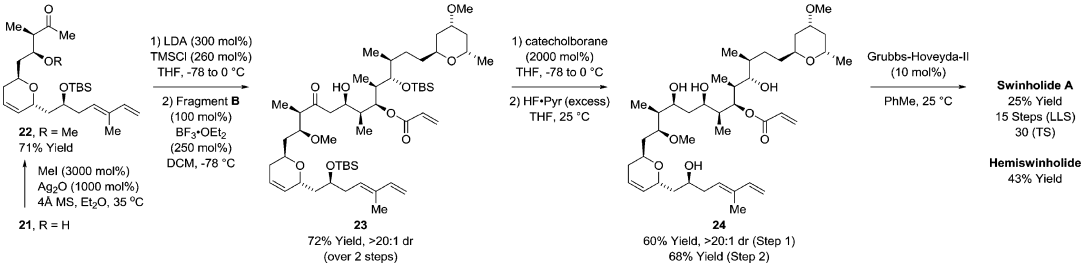
The synthesis of fragment **A** begins with enantioselective iridium-catalyzed alcohol *C*-allylation[23] of the commercially available alcohol **1** (Scheme 2). The homoallylic alcohol **2** is formed in 83% yield and 93% enantiomeric excess. The iridium catalyst is readily recovered and recycled in a second round of allylation to provide additional quantities of alcohol **2**. Cross-metathesis with acrolein followed by treatment of the resulting enal with allyltrimethylsilane results in allylation of a transient cyclic oxacarbenium ion to provide the *trans*-2,6-disubstituted pyran **3** with good levels of diastereocontrol.[27] Chemoselective oxidative cleavage[28] of the terminal olefin of pyran **3** delivers aldehyde **4**. In close analogy to the work of Paterson,[13c] exposure of aldehyde **4** to BF_3-etherate in the presence of silyl dienol ether **5**[29] triggers vinylogous Mukaiyama aldol addition to provide enal **6**. As predicted by the Cram−Reetz model,[30] good levels of 1,3-stereoinduction are observed. Protection of the alcohol as the TBS ether with subsequent addition of DDQ provides enal **7**. The resulting enal **7** was subjected to Wittig methylenation to form the C2−C5 diene. This sequence avoids problematic PMB deprotection in the presence of the diene. Finally, Dess−Martin oxidation of the C15 alcohol delivers fragment **A** in 8 steps (LLS).

The synthesis of fragment **B** begins with catalyst-directed diastereo- and site-selective allylation of commercially available (*S*)-1,3-butanediol **8** (Scheme 3).[24,25] The homoallylic alcohol **9**, which forms as a single diastereomer, is then subjected to CM with *cis*-1,4-diacetoxy-2-butene to provide the allylic acetate **10** as a 5:1 (*E*:*Z*)-mixture of olefin stereoisomers. Exposure of **10** to the indicated chiral palladium catalyst results in Tsuji−Trost cyclization to form the 2,6-*trans*-disubstituted pyran in 90% yield as a 4:1 mixture of diastereomers. Diastereoselectivity is independent of the olefin geometry of **10**. Subsequent *O*-methylation provides **11**. Cross-metathesis of **11** with iodoether **14**, previously prepared in our laboratory (Scheme 4),[26] was challenging due to competing alkene isomerization of **14**. Using the second-generation Grubbs−Hoveyda catalyst with 1,4-benzoquinone,[31] the desired metathesis product **15** was obtained in 52% yield. Diimide reduction[32] of the C25−C26 double bond, Bernet−Vasella cleavage[33] of the iodoether followed by TBS protection of the alcohol with subsequent oxidative removal of the PMB-ether provides **16**. Alkene oxidative cleavage and acryloylation of the β-hydroxy aldehyde converts **16** to fragment **B** in 10 steps (LLS).

The union of fragments **A** and **B** using MVK as a doubly nucleophilic aldol lynchpin begins with the hydrogen-mediated reductive aldol coupling[21] of fragment **A**. Tolerance of multiple olefinic functional groups, including a terminal diene, to the conditions of rhodium-catalyzed hydrogenation could not be assumed. Hence, the reaction of model aldehydes **17** and **19** was initially explored (Scheme 5). To our delight, the respective adducts **18** and **20** were formed in good yields without competing hydrogenation of the alkene functional groups. Good selectivity with respect to discrimination of the diastereotopic aldehyde π-faces was accompanied by complete aldol *syn*-diastereoselectivity. Encouraged by these results, fragment **A** was exposed to conditions for hydrogen-mediated reductive aldol coupling. The requisite aldol **21** was formed in 68% yield.

To complete the synthesis of swinholide A, aldol **21** was methylated to form **22**, which was converted to the enol silane and treated with fragment **B** in the presence of BF_3-etherate (Scheme 6). The product of Mukaiyama aldol addition **23** is formed in 72% yield as a single diastereomer, as predicted by the Felkin−Anh and Cram−Reetz models.[30] Hydroxy-directed reduction of the ketone[34] followed by removal of silyl protecting groups provides the acrylic ester **24**. Exposure of **24** to the second-generation Grubbs−Hoveyda catalyst provides the product of successive CM-RCM, swinholide A, in 25% yield along with the product of RCM, hemiswinholide, in 43% yield. The CM-RCM pathway appears critically dependent on preorganization derived from the internal network of hydroxyl

Scheme 6. Total Synthesis of Swinholide A via Successive Cross-Metathesis−Ring-Closing Metathesis[a]



[a]See SI for further experimental details.

DOI: 10.1021/jacs.6b10645
J. Am. Chem. Soc. 2016, 138, 14246−14249

hydrogen bonds, as the silyl-protected precursors to **24** exclusively form RCM products under metathesis conditions.

In summary, by merging the characteristics of hydrogenation and carbonyl addition, we have unlocked a broad, new family of catalytic C−C couplings that streamline chemical synthesis by virtue of their redox-economy, chemo- and stereoselectivity. As illustrated in the present synthesis of swinholide A, wherein 10 C−C bonds are formed by hydrogenative coupling, the target compound is made in 15 steps (LLS), roughly half the steps required in two prior total syntheses. A comparable step-change in efficiency is evident in other polyketide total syntheses utilizing our methods.[17c] Future work will focus on expanding the lexicon of hydrogen-mediated C−C bond formations, including the use of α-olefins as pronucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10645.

Experimental procedures and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*mkrische@mail.utexas.edu

Author Contributions

†I.S. and S.H. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Welch Foundation (F-0038), the NIH-NIGMS (RO1-GM093905), and the National Research Foundation of Korea, funded by the Ministry of Education (2014058834, S.H. postdoctoral fellowship), are acknowledged for partial support of this research.

■ REFERENCES

(1) Reviews: (a) Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253. (b) Dumontet, C.; Jordan, M. A. *Nat. Rev. Drug Discovery* **2010**, *9*, 790. (c) Rohena, C. C.; Mooberry, S. L. *Nat. Prod. Rep.* **2014**, *31*, 335.

(2) Reviews: (a) Yeung, K.-S.; Paterson, I. *Angew. Chem., Int. Ed.* **2002**, *41*, 4632. (b) Giganti, A.; Friederich, E. *Prog. Cell Cycle Res.* **2003**, *5*, 511. (c) Kita, M.; Kigoshi, H. *Nat. Prod. Rep.* **2015**, *32*, 534.

(3) Isolation and structure determination of swinholide A: (a) Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511. (b) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Kitagawa, I. *Tetrahedron Lett.* **1989**, *30*, 2963. (c) Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Tanaka, J.; Doi, M.; Ishida, T. *J. Am. Chem. Soc.* **1990**, *112*, 3710. (d) Kobayashi, M.; Tanaka, J.; Katori, T.; Matsuura, M.; Yamashita, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1990**, *38*, 2409. (e) Doi, M.; Ishida, T.; Kobayashi, M.; Kitagawa, I. *J. Org. Chem.* **1991**, *56*, 3629.

(4) Swinholide A was assumed to derive from symbiotic cyanobacteria,[3c] but was later shown to be linked to the presence heterotrophic unicellular bacteria: Bewley, C. A.; Holland, N. D.; Faulkner, D. J. *Experientia* **1996**, *52*, 716.

(5) (a) Bubb, M. R.; Spector, I.; Bershadsky, A. D.; Korn, E. D. *J. Biol. Chem.* **1995**, *270*, 3463. (b) Saito, S-y.; Karaki, H. *Clin. Exp. Pharmacol. Physiol.* **1996**, *23*, 743. (c) Klenchin, V. A.; King, R.; Tanaka, J.; Marriott, G.; Rayment, I. *Chem. Biol.* **2005**, *12*, 287.

(6) Kobayashi, M.; Kawazoe, K.; Okamoto, T.; Sasaki, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 19.

(7) For swinholides B−K and ankaraholides A and B, see literature cited in ref 24.

(8) Preswinholide A (swinholide A seco acid): Todd, J. S.; Alvi, K. A.; Crews, P. *Tetrahedron Lett.* **1992**, *33*, 441.

(9) The misakinolides (bistheonellides) and scytophycin C are structurally related to swinholide A. See literature cited in ref 24.

(10) Analogues of reidispongiolide, rhizopodin, and bistramide: (a) Perrins, R. D.; Cecere, G.; Paterson, I.; Marriott, G. *Chem. Biol.* **2008**, *15*, 287. (b) Herkommer, D.; Dreisigacker, S.; Sergeev, G.; Sasse, F.; Gohlke, H.; Menche, D. *ChemMedChem* **2015**, *10*, 470.

(11) Isoswinholide A, an isomeric 46-membered macrodiolide, is significantly less potent.

(12) For a summary of synthetic studies, see literature cited in ref 24.

(13) (a) Paterson, I.; Yeung, K.-S.; Ward, R. A.; Cumming, J. G.; Smith, J. D. *J. Am. Chem. Soc.* **1994**, *116*, 9391. (b) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393. (c) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413. (d) Paterson, I.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K.-S. *Tetrahedron* **1995**, *51*, 9437. (e) Paterson, I.; Yeung, K.-S.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9467.

(14) (a) Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khatuya, H.; Richter, P. K.; Bertinato, P. *J. Am. Chem. Soc.* **1996**, *118*, 3059. (b) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. - Eur. J.* **1996**, *2*, 847.

(15) Review on the synthesis of macrodiolide natural products: Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348.

(16) (a) Nakata, T.; Komatsu, T.; Nagasawa, K. *Chem. Pharm. Bull.* **1994**, *42*, 2403. (b) Nakata, T.; Komatsu, T.; Nagasawa, K.; Yamada, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 8225. (c) Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6881. (d) Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6885.

(17) Selected reviews on hydrogen-mediated C−C bond formation: (a) Hassan, A.; Krische, M. J. *Org. Process Res. Dev.* **2011**, *15*, 1236. (b) Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 9142. (c) Feng, J.; Kasun, Z. A.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138*, 5467.

(18) Review on redox-economy: Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

(19) Review on protecting group-free synthesis: (a) Saicic, R. N. *Tetrahedron* **2014**, *70*, 8183;(b) *Tetrahedron* **2015**, *71*, 2777.

(20) Selected reviews of alkene metathesis in the total synthesis: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (b) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086.

(21) Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746.

(22) Review of the Mukaiyama aldol reaction in total synthesis: Kan, S. B. J.; Ng, K. K.-H.; Paterson, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 9097.

(23) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891. (c) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett.* **2009**, *11*, 3112.

(24) Shin, I.; Krische, M. J. *Org. Lett.* **2015**, *17*, 4686.

(25) (a) Shin, I.; Wang, G.; Krische, M. J. *Chem. - Eur. J.* **2014**, *20*, 13382. (b) Shin, I.; Krische, M. J. *Top. Curr. Chem.* **2015**, *372*, 85.

(26) (a) Gao, X.; Han, H.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 12795. (b) Gao, X.; Woo, S. K.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 4223.

(27) Mohapatra, D. K.; Das, P. P.; Pattanayak, M. R.; Yadav, J. S. *Chem. - Eur. J.* **2010**, *16*, 2072.

(28) Wipf, P.; Kim, Y.; Goldstein, D. M. *J. Am. Chem. Soc.* **1995**, *117*, 11106.

(29) Gieseler, M. T.; Kalesse, M. *Org. Lett.* **2011**, *13*, 2430.

(30) (a) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4019. (b) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729.

(31) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

(32) Dewey, R. S.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1961**, *83*, 3729.

(33) (a) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990. (b) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 2400.

(34) Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190.

DOI: 10.1021/jacs.6b10645
J. Am. Chem. Soc. 2016, 138, 14246−14249