

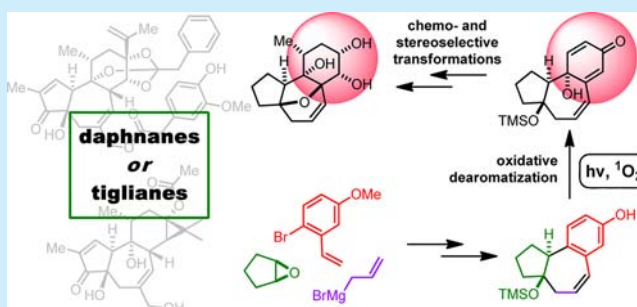
Stereocontrolled Construction of the Tricyclic Framework of Tiglanes and Daphnanes by an Oxidative Dearomatization Approach

Guanghu Tong, Zhi Liu, and Pengfei Li*

Frontier Institute of Science and Technology (FIST) and Frontier Institute of Chemistry, Xi'an Jiaotong University, Xi'an 710054, P. R. China

S Supporting Information

ABSTRACT: An appropriately functionalized [5–7–6] tricyclic framework of tiglane and daphane diterpenes containing seven contiguous stereocenters has been prepared in 10 steps from very simple building blocks in a modular and stereocontrolled fashion. The key features of this approach involve an efficient visible light-induced singlet oxygen oxidative dearomatization and an array of substrate-controlled highly diastereoselective transformations. This work provides a model strategy for rapid and diverted synthesis of natural and unnatural molecules sharing the common skeleton.



Tiglanes and daphnanes (Figure 1) are two families of diterpene natural products that share a characteristic [5–

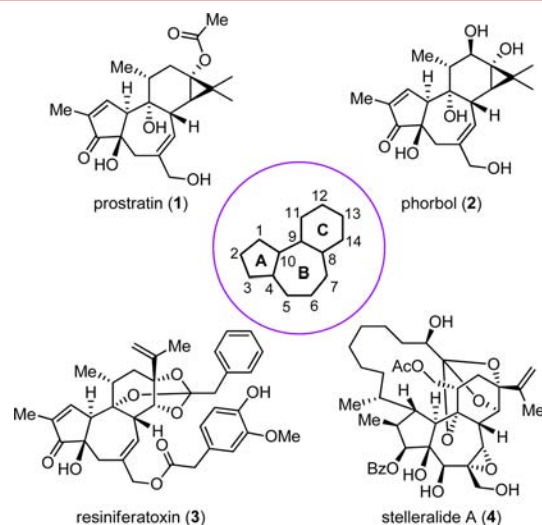


Figure 1. Representative tiglane and daphane diterpene natural products and their common tricyclic core structure.

7–6] tricyclic carbon framework with a congested substitution pattern and extensive oxygenation.¹ Members of these families exhibit a remarkable range of biological activities and have attracted significant research interest in drug discovery. Prostratin (1, Figure 1), for example, is under preclinical development for its potential to eliminate latent HIV viruses.² Phorbol (2) and its esters are potent tumor promoters that activate protein kinase C (PKC).³ Resiniferatoxin (3) holds

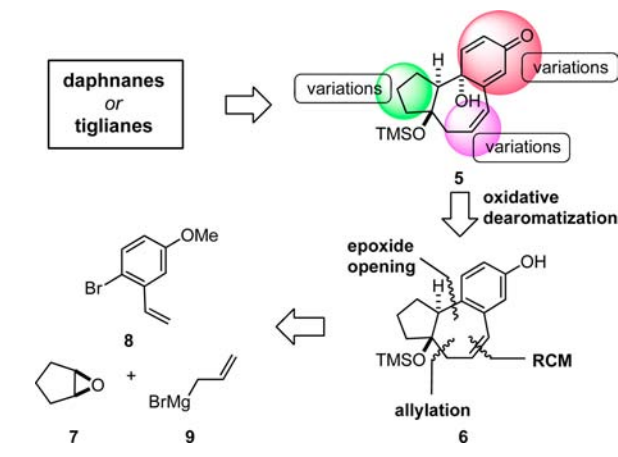
promise as an analgesic agent through the desensitization of nociceptive neurons.⁴ Stelleralide A⁵ (4) is an extremely potent and selective anti-HIV agent. Importantly, more and more natural products exhibiting antitumor,⁶ anti-HIV,⁷ and antiviral activities⁸ have been recently added to these two families. The structural complexity and the biological activities of these molecules, therefore, continuously render them highly attractive targets for organic synthesis.

Since the late 1980s, a number of elegant approaches have been reported to construct the tricyclic core structure,⁹ and total syntheses of phorbol (2) and resiniferatoxin (3) by Wender and co-workers¹⁰ and a formal synthesis of phorbol (2) by Cha¹¹ have been accomplished. Recently, we have commenced a research program aiming at development of efficient and flexible synthetic approaches to natural and unnatural tiglanes and daphnanes. Because the highly substituted C ring poses significant challenges for all synthetic efforts and the substitution pattern on the C ring often shows dramatic impacts on the biological activities,^{2b,c,12} we were particularly interested in addressing these issues by a late-stage C-ring functionalization approach on an appropriate intermediate. We proposed molecule 5 (Scheme 1) as a key model to test our synthetic strategy because it includes not only the tricyclic core but also a cross-conjugated cyclohexadienone moiety for further multiple functionalizations. Moreover, variations of the building blocks and/or later stage transformations might produce a series of analogues. Retrosynthetically, 5 would be an oxidative dearomatization product of phenol 6 which in turn might be assembled from three simple

Received: March 19, 2014

Published: April 9, 2014

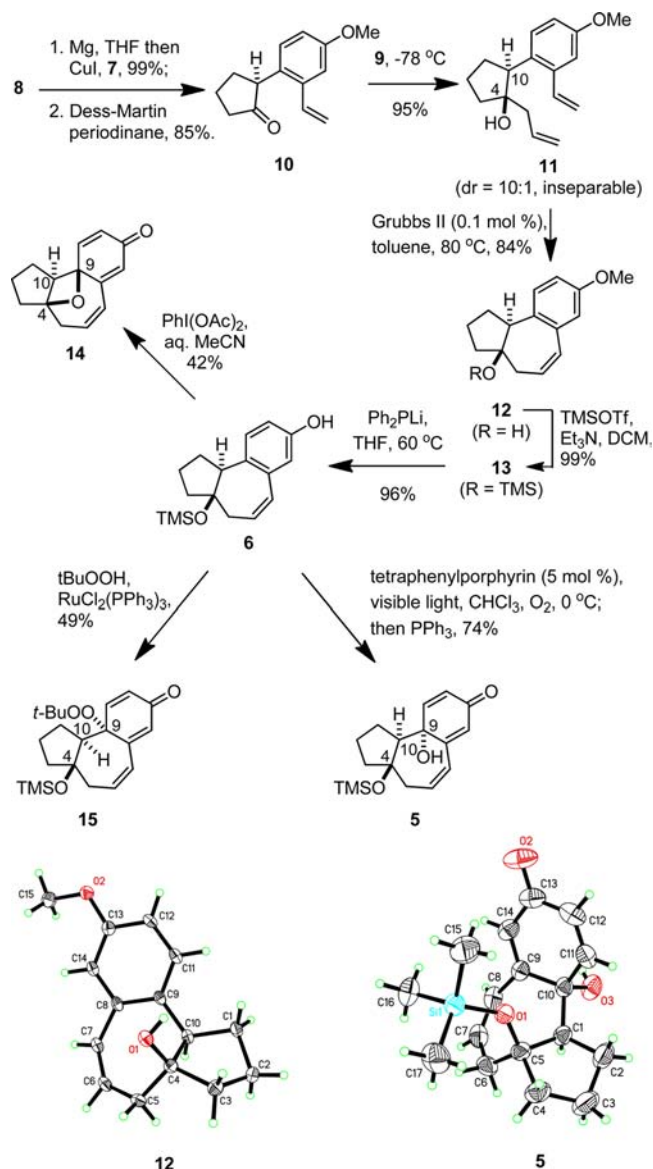
Scheme 1. Synthetic Plan of the Tricyclic Framework



building blocks, aryl bromide **8**, cyclopentene oxide **7**, and allylmagnesium bromide **9**, by epoxide opening, allylation reaction, and ring-closing metathesis (RCM). In this paper, we describe our synthetic studies that lead to a rapid access to **5** and preliminary explorations of chemo- and stereoselective functionalizations on the C ring.

In the forward direction of our synthesis (Scheme 2), the Grignard reagent derived from aryl bromide **8**¹³ was mixed with cyclopentene oxide **7** in the presence of copper(I) iodide to effect the epoxide opening reaction, affording the desired product in quantitative yield. The resulting alcohol was subsequently treated with Dess–Martin periodinane¹⁴ to form the racemic α -aryl ketone **10** in high yield (85%). Addition of allyl magnesium bromide (**9**) to a solution of **10** produced the tertiary alcohol **11** in excellent yield (95%) and good diastereoselectivity (dr = 10:1 based on crude ¹H NMR). After formation of the seven-membered B ring by a ring-closing metathesis (RCM) using 0.1 mol % of the Grubbs second-generation catalyst,¹⁵ the two diastereomers were separated by column chromatography and the major isomer **12** was isolated in 84% yield. Its relative configuration was then confirmed as the desired 4,10-*trans* relationship by X-ray diffraction analysis. Attempted removal of the methyl group by heating **12** or its trimethylsilyl ether **13** together with sodium ethylthiolate led to variable yields (30–60%) of the corresponding demethylation products accompanied by side products derived from competitive dehydration at the tertiary alcohol and thiol addition to the alkene. Other methods using boron tribromide, lithium iodide, etc. led to decomposition of the starting materials. Finally, we found that the methyl group of **13** could be efficiently cleaved by treatment with lithium diphenylphosphide,¹⁶ and the resulting phenol **6** was isolated in excellent yield (96%).

At this stage, the crucial oxidative dearomatization reaction was investigated. Hypervalent iodine reagents are arguably the most widely used oxidants for dearomatization reactions of phenols.¹⁷ In the case of phenol **6**, however, we did not observe the desired product **5** using various hypervalent iodine oxidants. When it was treated with PhI(OAc)₂ in a mixture of acetonitrile and water, oxetane **14** was formed as the only isolable product. To the best of our knowledge, this represents the first example of oxetane ring formation by an oxidative dearomatization. The result clearly demonstrated the unique reactivity of this rigid substrate. Consequently, other oxidative dearomatization methods were tested. A ruthenium-catalyzed peroxidation¹⁸ of

Scheme 2. Synthesis of the Cyclohexadienone **5**

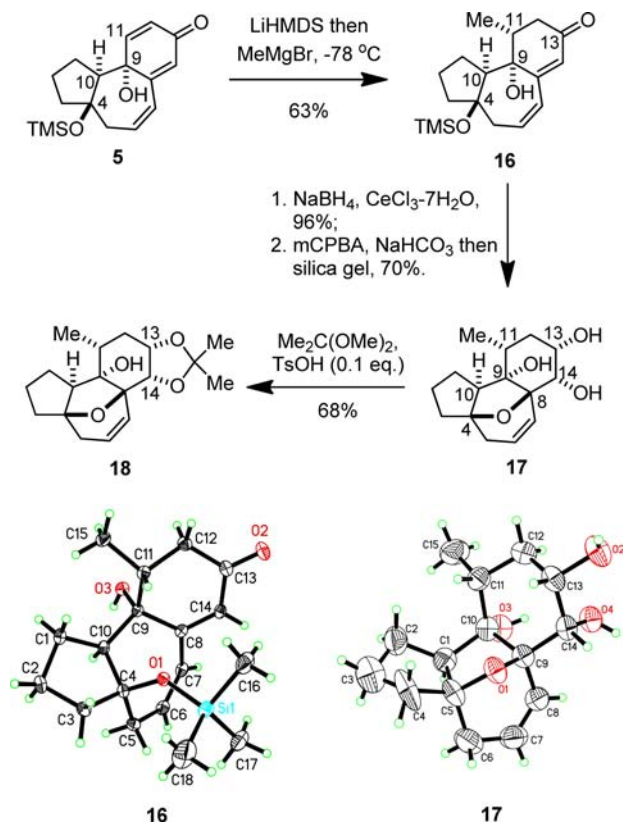
6 afforded the peroxide **15** in 49% yield. Unfortunately, neither reductive cleavage of the O–O bond to form the desired *tert*-alcohol¹⁹ nor direct use of this peroxide for next investigations was successful.

Singlet oxygen has been reported to react with phenols to produce peroxy quinols which, after reductive cleavage of the O–O bond, produce *tert*-alcohols.²⁰ Therefore, using **6** as the substrate, we tested several protocols to effect such a transformation. Finally, to our delight, when an oxygen-saturated solution of **6** in chloroform containing tetraphenylporphyrin (TPP) as a photosensitizer was irradiated by strong visible light (400 W sodium lamp), the unstable peroxy quinol was observed in high yield by crude ¹H NMR. Therefore, after full conversion, triphenylphosphine was added to reduce the peroxy quinol, and the hydroxylated cyclohexadienone **5** could be directly isolated in 74% yield as a single diastereoisomer. A single crystal of **5** suitable for X-ray diffraction was obtained, and thus, the relative configuration was unambiguously established as the desired one. Probably because the trimethylsilyl ether moiety occupies the concave space and strongly shields one of the two faces of the phenol plane, singlet

oxygen preferably reacts from the less hindered convex side to exclusively form **5**.

With the oxidative dearomatization product **5** in hand, we explored the possibility of stereocontrolled transformations on the C ring (Scheme 3). Most tigliane and daphnane natural

Scheme 3. Chemo- and Stereoselective Functionalizations of the Tricyclic Core



products incorporate an 11-methyl group which is *cis* to the 9-hydroxyl group, and sometimes, such as with stellerlide A (**4**), the methyl group is further oxidized. Therefore, 1,4-addition of alkyl metallic reagents onto **5** was investigated. After extensive experimentation, we were able to stereoselectively introduce the methyl group using a substrate-controlled 1,4-addition of methylmagnesium bromide.²¹ Other methods based on copper,^{22a,b} zinc,^{22c,d} and aluminum^{22e} reagents did not give any desired product. Thus, after deprotonation with lithium hexamethyl disilazide, the resulting 9-alkoxide directs the reaction's regioselectivity as well as facial selectivity probably via complexation with the magnesium reagent. The product **16** was isolated in 67% yield as a single isomer, and the relative configuration was again confirmed by X-ray diffraction analysis. The 13-carbonyl group was then reduced under the Luche conditions,²³ producing the secondary alcohol in excellent yield and diastereoselectivity (*dr* = 24:1). Treatment of the secondary alcohol with *m*-chloroperoxybenzoic acid (*m*-CPBA) formed an unstable epoxide intermediate which, upon silica gel chromatography, transformed into a triol **17** as the sole isolable product. The *cis* relationship between the 13-OH and 14-OH was proposed because the 13-OH might direct the facial selection of the epoxidation reaction. Together with the facile epoxide opening process presumably via S_N2 type attack, we reasoned that the 13-OH should be *cis* to the 9-OH and 11-

Me groups too. This deduction was consistent with the observed H-13/H-14 coupling constant (3J = 4.8 Hz) of the acetal **18** and further confirmed by the crystal structure of **17**, which unambiguously established the relative configurations of the seven contiguous stereocenters.

In summary, we have described a rapid and modular synthetic approach for construction of the highly functionalized tricyclic framework of tigliane and daphnane diterpenoids containing multiple stereocenters. The synthetic route features several substrate-controlled highly stereoselective reactions including the key visible light-induced singlet oxygen oxidative dearomatization, directed 1,4-addition of methylmagnesium bromide, and the 13-carbonyl reduction using the Luche protocol. The applications of this approach in synthesis of relevant natural products and their analogues are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, copies of all spectral data, and X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lipengfei@mail.xjtu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support by the NSFC (No. 21202129), the MOST (No. 2014CB548200), and Xi'an Jiaotong University. We thank Mr. Guojun Zhou, Frontier Institute of Science and Technology, Xi'an Jiaotong University, for his help with X-ray diffraction analysis.

■ REFERENCES

- (a) Liao, S.-G.; Chen, H.-D.; Yue, J. M. *Chem. Rev.* **2009**, *109*, 1092–1140. (b) He, W.; Cik, M.; Appendino, G.; Van Puyvelde, L.; Leysen, J. E.; De Kimpe, N. *Mini-Rev. Med. Chem.* **2002**, *2*, 185–200.
- (a) Johnson, H. E.; Banack, S. A.; Cox, P. A. *J. Nat. Prod.* **2008**, *71*, 2041–2044. (b) Wender, P. A.; Kee, J.-M.; Warrington, J. M. *Science* **2008**, *320*, 649–652. (c) Beansa, E. J.; Fournogerakis, D.; Gauntlett, C.; Heumann, L. V.; Kramer, R.; Marsden, M. D.; Murray, D.; Chun, T.-W.; Zack, J. A.; Wender, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 11698–11703. (d) AIDS Research Alliance website: <http://aidsresearch.org/cure-research/prostratin> (accessed Feb 2014).
- Newton, A. C. *Chem. Rev.* **2001**, *101*, 2353–2364.
- (a) Szallasi, A.; Blumberg, P. M. *Neuroscience* **1989**, *30*, 515–520. (b) Wong, G. Y.; Gavva, N. R. *Brain Res. Rev.* **2009**, *60*, 267–277. (c) Kissin, I.; Szallasi, A. *Curr. Top. Med. Chem.* **2011**, *11*, 2159–2170.
- (a) Asada, Y.; Sukemori, A.; Watanabe, T.; Malla, K. J.; Yoshikawa, T.; Li, W.; Koike, K.; Chen, C.-H.; Akiyama, T.; Qian, K.; Nakagawa-Goto, K.; Morris-Natschke, S. L.; Lee, K.-H. *Org. Lett.* **2011**, *13*, 2904–2907. (b) Miyamae, Y.; Villareal, M. O.; Abdrabbah, M. B.; Isoda, H.; Shigemori, H. *J. Nat. Prod.* **2009**, *72*, 938–941. (c) Zhan, Z.-J.; Fan, C.-Q.; Ding, J.; Yue, J.-M. *Bioorg. Med. Chem.* **2005**, *13*, 645–655. (d) Hong, J.-Y.; Chung, H.-J.; Lee, H.-J.; Park, H. J.; Lee, S. K. *J. Nat. Prod.* **2011**, *74*, 2102–2108.
- (a) Asada, Y.; Sukemori, A.; Watanabe, T.; Malla, K. J.; Yoshikawa, T.; Li, W.; Kuang, X.; Koike, K.; Chen, C.-H.; Akiyama, T.; Qian, K.; Nakagawa-Goto, K.; Morris-Natschke, S. L.; Lu, Y.; Lee, K.-H. *J. Nat. Prod.* **2013**, *76*, 852–857. (b) Zhang, L.; Luo, R.-H.; Wang,

- F.; Jiang, M.-Y.; Dong, Z.-J.; Yang, L.-M.; Zheng, Y.-T.; Liu, J.-K. *Org. Lett.* **2010**, *12*, 152–155.
- (8) Bourjot, M.; Delang, L.; Nguyen, V. H.; Neyts, J.; Gueritte, F.; Leyssen, P.; Litaudon, M. *J. Nat. Prod.* **2012**, *75*, 2183–2187.
- (9) (a) Catino, A. J.; Sherlock, A.; Shieh, P.; Wzorek, J. S.; Evans, D. A. *Org. Lett.* **2013**, *15*, 3330–3333. (b) Murai, K.; Katoh, S.; Urabe, D.; Inoue, M. *Chem. Sci.* **2013**, *4*, 2364–2368. (c) Stewart, C.; McDonald, R.; West, F. G. *Org. Lett.* **2011**, *13*, 720–723. (d) Ritter, T.; Zarotti, P.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 4371–4374. (e) Jackson, S. R.; Johnson, M. G.; Mikami, M.; Shiokawa, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2694–2697. (f) Chairgulprasert, V.; Drew, M. G. B.; Jahans, A.; Harwood, L. M. *ARKIVOC* **2002**, (ix), 37–45. (g) Drew, M. G. B.; Harwood, L. M.; Macias-Sanchez, A. J.; Scott, R.; Thomas, R. M.; Uguen, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2311–2313. (h) Ovaska, T. V.; Reisman, S. E.; Flynn, M. A. *Org. Lett.* **2001**, *3*, 115–117. (i) Carroll, G. L.; Little, R. D. *Org. Lett.* **2000**, *2*, 2873–2876. (j) Shigeno, K.; Ohne, K.; Yamaguchi, T.; Sasai, H.; Shibasaki, M. *Heterocycles* **1992**, *33*, 161–171. (k) Shigeno, K.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 4937–4940. (l) Sugita, K.; Neville, C. F.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1995**, *36*, 1067–1070. (m) Sato, H.; Kim, Y. S.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 2973–2976. (n) Sekine, A.; Kumagai, N.; Uotsu, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *41*, 509–513. (o) Rigby, J. H.; Kierkus, P. C. *J. Am. Chem. Soc.* **1989**, *111*, 4125–4126. (p) Rigby, J. H.; Kierkus, P. C.; Head, D. *Tetrahedron Lett.* **1989**, *30*, 5073–5076. (q) Harwood, L. M.; Ishikawa, T.; Phillips, H.; Watkin, D. *J. Chem. Soc., Chem. Commun.* **1991**, 527–530. (r) Paquette, L. A.; Sauer, D. R.; Edmondson, S. D.; Friedrich, D. *Tetrahedron* **1994**, *50*, 4071–4086. (s) McMills, M. C.; Zhuang, L.; Wright, D. L.; Watt, W. *Tetrahedron Lett.* **1994**, *35*, 8311–8314. (t) Magar, S. S.; Desai, R. C.; Fuchs, P. L. *J. Org. Chem.* **1992**, *57*, 5360–5369. (u) Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.* **1993**, *58*, 7635–7637. (v) Page, P. C. B.; Jennens, D. C.; Porter, R. A.; Baldock, A. N. *Synlett* **1991**, 472–474. (w) Page, P. C. B.; Jennens, D. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2587–2589. (x) Eckert, J. M. Efforts toward the total syntheses of phorbol and CP-225917. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1997. (y) Wender, P. A.; Keenan, R. M.; Lee, H. Y. *J. Am. Chem. Soc.* **1987**, *109*, 4390–4392.
- (10) (a) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976–12977. (b) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897–7898. (c) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D., Jr.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957–8958. (d) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954–8957. (e) Wender, P. A.; McDonald, F. E. *J. Am. Chem. Soc.* **1990**, *112*, 4956–4958.
- (11) Lee, K.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 5590–5591.
- (12) Stanoeva, E.; He, W.; De Kimpe, N. *Bioorg. Med. Chem.* **2004**, *13*, 17–28. (b) Wender, P. A.; Bi, F. C.; Buschmann, N.; Gosselin, F.; Kan, C.; Kee, J.-M.; Ohmura, H. *Org. Lett.* **2006**, *8*, 5373–5376.
- (13) Grigg, R. D.; Hovel, R. V.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 16131–16134.
- (14) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
- (15) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041.
- (16) (a) Ireland, R. E.; Walba, D. M. *Org. Synth.* **1977**, *56*, 44–48. (b) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319–6337.
- (17) (a) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068–4093. (b) Marson, C. M.; Pink, J. H.; Hall, D.; Hursthouse, M. B.; Malik, A.; Smith, C. J. *Org. Chem.* **2003**, *68*, 792–798.
- (18) (a) Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Noda, S. *J. Am. Chem. Soc.* **1996**, *118*, 2509–2510. (b) Murahashi, S.-I.; Miyaguchi, N.; Noda, S.; Naota, T.; Fujii, A.; Inubushi, Y.; Komiyama, N. *Eur. J. Org. Chem.* **2011**, 5355–5365.
- (19) (a) Dai, P.; Dussault, P. H.; Trullinger, T. K. *J. Org. Chem.* **2004**, *69*, 2851–2852. (b) Murahashi, S.-I.; Miyaguchi, N.; Noda, S.; Naota, T.; Fujii, A.; Inubushi, Y.; Komiyama, N. *Eur. J. Org. Chem.* **2011**, 5355–5365. (c) Ratnikov, M. O.; Farkas, L. E.; Doyle, M. P. *J. Org. Chem.* **2012**, *77*, 10294–10303.
- (20) (a) Matsuura, T.; Omura, K.; Nakashima, R. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1358–1362. (b) Wasserman, H. H.; Ives, J. L. *Tetrahedron* **1981**, *37*, 1825–1852. (c) Prein, M.; Maurer, M.; Peters, E. M.; Peters, K.; Schnering, H. G.; Adam, W. *Chem.—Eur. J.* **1995**, *1*, 89–94. (d) Jones, K. M.; Hillringhaus, T.; Klusmann, M. *Tetrahedron Lett.* **2013**, *54*, 3294–3297.
- (21) (a) Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D. *J. Am. Chem. Soc.* **1988**, *110*, 3702–3704. (b) Brocksom, T. J.; Coelho, F.; Depres, J.-P.; Greene, A. E.; Lima, M. E. F.; Hamelin, O.; Hartmann, B.; Kanazawa, A. M.; Wang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15313–15325.
- (22) (a) Zimmerman, H. E.; Zhu, Z. *J. Am. Chem. Soc.* **1995**, *117*, 5245–5262. (b) Taber, D. F.; Christos, T. E.; Rahimizadeh, M.; Chen, B. *J. Org. Chem.* **2001**, *66*, 5911–5914. (c) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2001**, *57*, 2485–2489. (d) Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Org. Lett.* **1999**, *1*, 623–625. (e) Flemming, S.; Kabbara, J.; Nickisch, K.; Neh, H.; Westermann, J. *Synthesis* **1995**, 317–320.
- (23) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.