Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

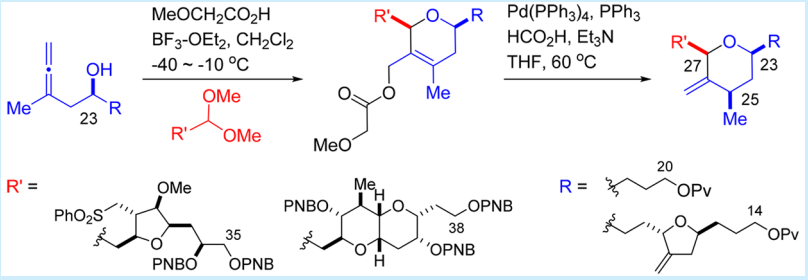
pubs.acs.org/OrgLett

Prins Reaction of Homoallenyl Alcohols: Access to Substituted Pyrans in the Halichondrin Series

Hyeong-wook Choi,* Francis G. Fang, Hui Fang, Dae-Shik Kim, Steven R. Mathieu, and Robert T. Yu

Integrated Chemistry Engine, Eisai AiM Institute, 4 Corporate Drive, Andover, Massachusetts 01810, United States

Supporting Information



ABSTRACT: Prins reaction of homoallenyl alcohols with aldehyde dimethylacetals in the presence of methoxyacetic acid directly affords tetrasubstituted pyrans relevant to halichondrins with complete control of the C27 stereogenic center. Regioselective Tsuji reduction of the resultant allylic acetates stereoselectively establishes the C25 stereogenic center and C26 exocyclic olefin. Building upon these findings, we achieved concise access to the halichondrin C14−C38 and eribulin C14−C35 fragments.

Halichondrins are polyether macrolides with potent in vitro and in vivo antitumor activity isolated from the marine sponge *Halichondria okadia* by Uemura, Hirata, and co-workers.[1] The first total synthesis of halichondrins was reported by the Kishi group in 1992.[2,3] Biological evaluation of synthetic intermediates revealed that the antitumor activity resides in the macrocyclic portion of halichondrin B, which has led to the discovery and development of eribulin (Figure 1).[4]

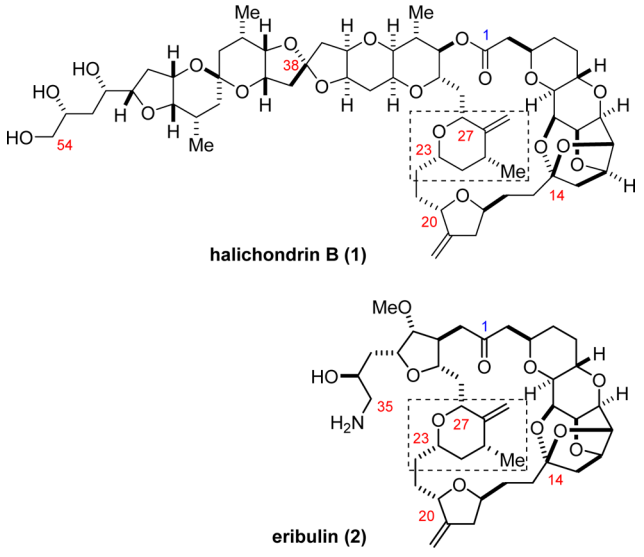


Figure 1. Halichondrin B and Eribulin.

Eribulin (**2**) is a highly potent tubulin binding agent approved for the treatment of breast cancer and soft tissue sarcoma in more than 50 countries. Among the common structural features of eribulin and halichondrins, the C23−C27 pyran moiety containing three stereogenic centers and one exocyclic olefin is notable as the central ring in the carbon-linked trisaccharide building units (i.e., C14−C35 and C14−C38 for eribulin and halichondrins, respectively). The manufacturing route for eribulin features iterative Nozaki−Hiyama−Kishi/Williamson ether syntheses to assemble C14−C35. While the conciseness and convergence of the synthetic route was notable, the need to establish each ring in two separate steps and employ metals in the C−C bond forming step suggested opportunities for improvement (Scheme 1).[5]

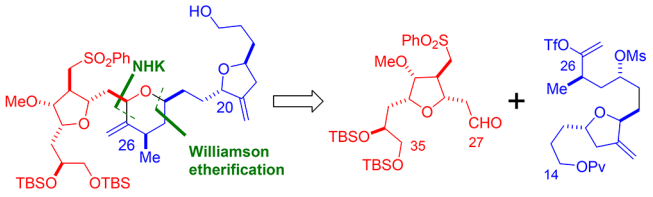
We were intrigued with the possibility that the central C23−C27 tetrasubstituted pyran could be assembled in a single sequence utilizing an overall "reductive" Prins reaction[6] of a homoallenyl alcohol (Scheme 2). Attractive features of such an approach included the potential to derive all of the stereochemical information from a single stereogenic center. Among the issues to be addressed were (1) viability of a homoallenyl alcohol as a Prins reaction substrate[7] and (2) regio- and stereoselective capture of the putative allylic carbocation intermediate with a hydride source. In this paper, we report the successful realization of these goals and a concise assembly of halichondrin C14−C38 and eribulin C14−C35 fragments.

Received: September 19, 2017

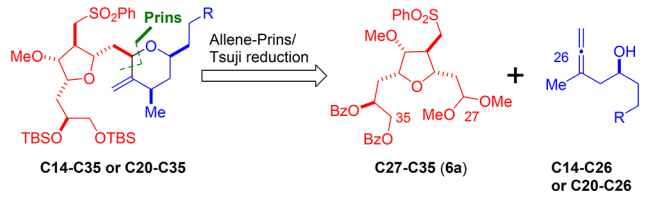
DOI: 10.1021/acs.orglett.7b02934
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Eribulin C14−C35 Fragment (Previous Works and This Work)

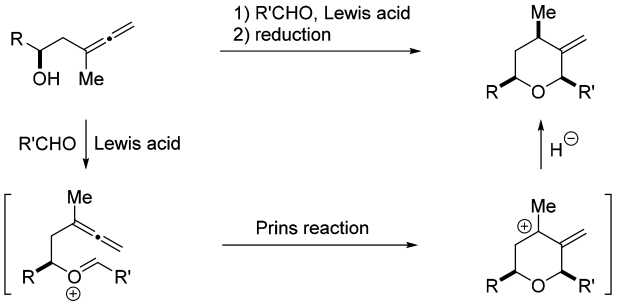
a) Reported synthesis of eribulin[5]



b) This work

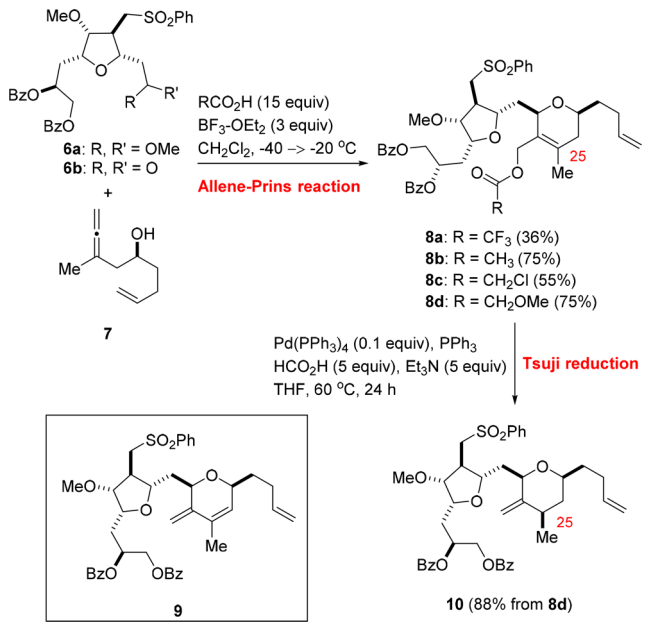


Scheme 2. Ovearall "Reductive" Prins Reaction to Tetrahydropyrans



Homoallenyl alcohol **7** served as a model system to test the viability of the Prins reaction (Scheme 3).[8] At the outset, it was decided to decouple the cyclization sequence from the allylic reduction of the presumed allylic carbocation intermediate. Mindful of Tsuji's work,[9] we decided that an allylic acetate could serve as a viable substrate for the allylic reduction and was thus the initial target for the Prins reaction. When allene **7** and aldehyde **6b** were subjected to the Prins reaction in the presence of trifluoroacetic acid,[10a] the desired product **8a** was obtained in 37% yield along with the diene **9** as a side product.[11] Encouraged by the initial success, efforts to improve the overall reaction profile focused on (1) evaluation of more nucleophilic carboxylic acids to more efficiently capture the tertiary allylic cation and (2) inclusion of a strong Lewis acid to allow the reaction to be conducted at lower temperature. Thus, the Prins reaction was attempted in the presence of acetic acid and various Lewis acids.[10] After screening the reaction conditions, we identified $BF_3{-}OEt_2$ as the preferred Lewis acid; 15 equiv of acetic acid provided the optimum yield of the allylic ester, and the temperature range of −40 to −20 °C gave the best reaction profile. Finally, even though both dimethyl acetal and the corresponding aldehyde could serve as the substrate for the allene-Prins reactions, dimethyl acetal gave slightly higher chemical yield with additional convenience in handling due to its stability. Under the optimized conditions, a mixture of homoallenyl alcohol **7** and dimethyl acetal **6a** in methylene chloride was treated with 15 equiv of acetic acid and 3 equiv of $BF_3{-}OEt_2$ at −40 to −20 °C. Typically, the reaction was completed in 1 h, and the desired product **8b** was obtained in 75% yield after column chromatographic purification.

Scheme 3. Allene-Prins Reaction and Regio- and Stereoselective Tsuji Reduction

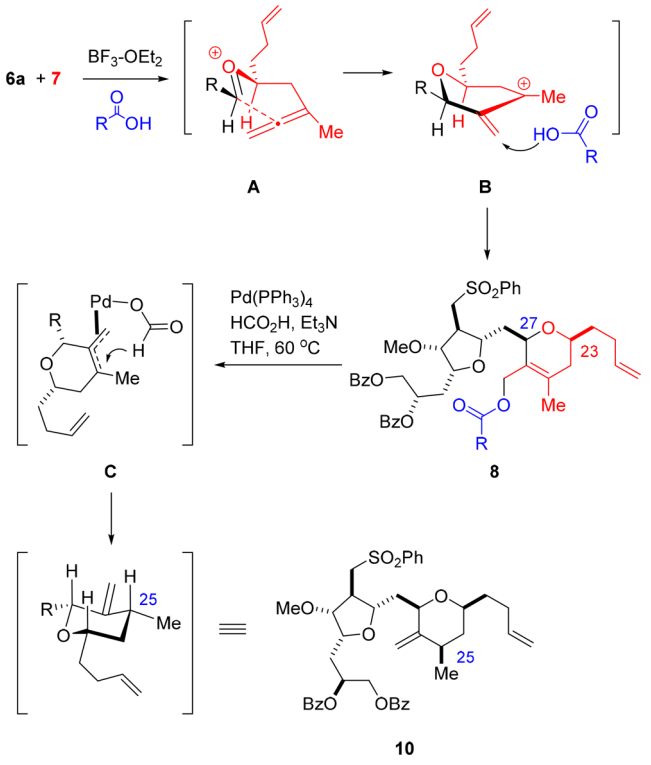


With the desired allylic acetates in hand, Tsuji reduction was attempted to convert the allylic esters to the corresponding exo-olefins (Scheme 3).[9] Even though the allylic acetate **8b** did not show any reaction progress under the reported conditions,[12] the corresponding trifluoroacetate **8a** showed a smooth conversion to the desired product **10** under the same reaction conditions. Apparently, trifluoroacetate has better leaving group ability to act as a more reactive substrate for the allylic reduction. However, because trifluoroacetic acid was a poor nucleophile for the Prins reaction, it seemed that a balance between the nucleophilicity of the carboxylic acid for the Prins reaction and the leaving group ability of the carboxylic acid for the Tsuji reduction would need to be struck to achieve an optimal overall reductive Prins sequence. After various carboxylic acids with different pK_a were screened, methoxyacetic acid was found to be optimal for the two-step procedure: 75% for the allene-Prins and 88% for the Tsuji reduction to give **10** as a single isomer by NMR. Several chiral and achiral palladium ligands for the allylic reduction were also investigated before concluding that triphenylphosphine is the optimal ligand. Regarding solvents, a faster reaction rate was observed in DMF even at lower reaction temperature (40 vs 60 °C). However, migration of the terminal olefin in **10** was observed as a side reaction in DMF, although the regio- and stereoselectivity was similar to that obtained in refluxing THF. Considering the presence of extra exo-olefin functionality at C19 in the halichondrins C14−C26 fragment, THF was chosen as the reaction solvent to avoid potential complications.

A stereochemical rationale for the observed selectivity in the allene-Prins reaction and Tsuji reduction sequence is depicted in Scheme 4. The allene-Prins reaction would generate the allylic tertiary carbocation **B** via the oxonium **A**, in which both C23 and C27 substituents reside in pseudoequatorial positions to selectively establish the C27 stereogenic center. It turned out the methyl substitution at the allene is critical for the success of the allene-Prins reactions.[13] It is conceivable that the methyl group stabilizes the resulting carbocations **B** to facilitate the

DOI: 10.1021/acs.orglett.7b02934
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Explanation of Regio- and Stereoselectivity



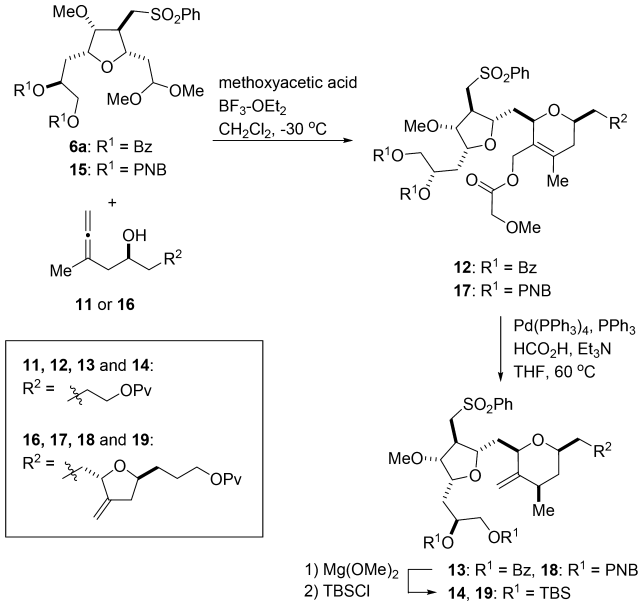
allene-Prins reaction. The resulting tertiary carbocation could be captured as a primary or tertiary ester due to its allylic nature. However, carboxylic acids would prefer to attack at the primary carbon rather than the sterically congested tertiary carbon to give **8** as the exclusive product.

Upon treatment with a palladium catalyst, allylic ester **8** would form a π-allyl palladium species (Scheme 4). As proposed by Tsuji,[9] the palladium species would prefer to reside on the primary carbon to deliver the hydride to the tertiary carbon to give the desired exo-olefin. The bulky palladium species would approach from the opposite face of two substituents at C23 and C27 and deliver the hydride to the same face via a cyclic intermediate **C** to set the C25 chiral center as the desired fashion. Consequently, the desired compound **10** was obtained as the only observable product by ^{1}H NMR.

The optimized allene-Prins reaction and Tsuji reduction sequence were applied to the synthesis of eribulin C20−C35 and C14−C35 fragments (Scheme 5). The allene-Prins reaction of dimethyl acetal **6a** with allene **11** gave allylic ester **12**, which was subjected to Tsuji reduction to furnish **13** in 74% yield in two steps as a single isomer by ^{1}H NMR. Chemoselective debenzoylation was accomplished with magnesium methoxide.[14] The resulting diol was protected as a bis-TBS ether to give the eribulin C20−C35 fragment **14**.

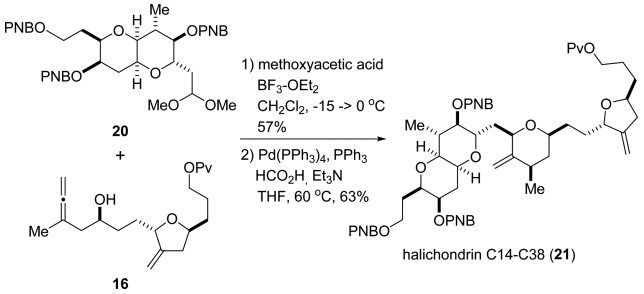
The allene **16** required for the preparation of the eribulin C14−C35 fragment was prepared from the corresponding vinyl triflate.[5b,15] The allene-Prins reaction of **16** with dimethyl acetal **15** proceeded smoothly to give **17** along with 7% of the corresponding diene. Tsuji reduction of **17** provided **18** in 70% yield in two steps. Protecting group manipulation of **18** as in the C20−C35 fragment gave the C14−C35 fragment **19** in 58% in two steps. The stereoselectivity at C25 was determined to be 48:1 by HPLC analysis.[16]

Scheme 5. Synthesis of Eribulin C20−C35 and C14−C35 Fragments via Allene-Prins Reaction



The allene-Prins approach was also applied to the synthesis of the halichondrin C14−C38 fragment (Scheme 6). The allene-

Scheme 6. Synthesis of the Halichondrin C14−C38 Fragment



Prins reaction of the halichondrin C27−C38 dimethyl acetal **20** with allene **16** gave the desired product in 57% yield under the standard conditions. Subsequent Tsuji reduction also proceeded smoothly to give the halichondrin C14−C38 fragment **21** in 63% yield.

In summary, an allene-Prins reaction/Tsuji reduction sequence of homoallenyl alcohols was demonstrated in the context of the halichondrin C23−C27 pyran. Notable features are the highly stereoselective establishment of C25 and C27 chiral centers from a single stereogenic center (C23). The described methods were successfully applied for concise syntheses of halichondrin C14−C38 and eribulin C14−C35 fragments. Additional applications of the Prins reaction in the halichondrin series are under investigation 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.7b02934.

Experimental procedures and characterization data for all new compounds (PDF)

DOI: 10.1021/acs.orglett.7b02934
Org. Lett. XXXX, XXX, XXX−XXX

AUTHOR INFORMATION

Corresponding Author

*E-mail: hyeongwook_choi@eisai.com.

ORCID

Hyeong-wook Choi: 0000-0002-5923-4878

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank our colleagues Dr. A. Endo, C.-A. Lemelin, and J. Cutter for the supply of compound **16**, and Dr. C.E. Chase for valuable feedback and proofreading.

DEDICATION

Dedicated to Prof. Yoshito Kishi at Harvard University on the occasion of his 80th birthday.

REFERENCES

(1) (a) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796. (b) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701.

(2) For the synthesis of halichondrins, see: (a) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162. (b) Jackson, K. L.; Henderson, J. A.; Motoyoshi, H.; Phillips, A. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2436. (c) Dong, C.-G.; Henderson, J. A.; Kaburagi, Y.; Sasaki, T.; Kim, D.-S.; Kim, J. T.; Urabe, D.; Guo, H.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15642. (d) Yamamoto, A.; Ueda, A.; Brémond, P.; Tiseni, P. S.; Kishi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 893. (e) Ueda, A.; Yamamoto, A.; Kato, D.; Kishi, Y. *J. Am. Chem. Soc.* **2014**, *136*, 5171. (f) Kishi, Y.; Fang, F. G.; Forsyth, C. J.; Scola, P. M.; Yoon, S. K. U.S. Patent 5338866; Int. Patent WO93/17690.

(3) Review of synthetic work on halichondrins: Jackson, K. L.; Henderson, J. A.; Phillips, A. J. *Chem. Rev.* **2009**, *109*, 3044 and refs cited therein.

(4) For eribulin reference, see: (a) Zheng, W.; Seletsky, B. M.; Palme, M. H.; Lydon, P. J.; Singer, L. A.; Chase, C. E.; Lemelin, C. A.; Shen, Y.; Davis, H.; Tremblay, L.; Towle, M. J.; Salvato, K. A.; Wels, B. F.; Aalfs, K. K.; Kishi, Y.; Littlefield, B. A.; Yu, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5551. (b) Littlefield, B. A.; Palme, M. H.; Seletsky, B. M.; Towle, M. J.; Yu, M. J.; Zheng, W. U.S. Patents 6214865 and 6365759; Int. Patent WO99/65894. (c) Vahdat, L. T.; Pruitt, B.; Fabian, C. J.; Rivera, R. R.; Smith, D. A.; Tan-Chiu, E.; Wright, J.; Tan, A. R.; DaCosta, N. A.; Chuang, E.; Smith, J.; O'Shaughnessy, J.; Shuster, D. E.; Meneses, N. L.; Chandrawansa, K.; Fang, F.; Cole, P. E.; Ashworth, S.; Blum, J. L. *J. Clin. Oncol.* **2009**, *27*, 2954.

(5) For the synthesis of eribulin, see: (a) Chase, C. E.; Fang, F. G.; Lewis, B. M.; Schnaderbeck, M. J.; Wilkie, G. D.; Zhu, X. *Synlett* **2013**, *24*, 323−326. (b) Austad, B. C.; Benayoud, F.; Calkins, T. L.; Campagna, S.; Chase, C. E.; Choi, H.-w.; Christ, W.; Costanzo, R.; Cutter, J.; Endo, A.; Fang, F. G.; Hu, Y.; Lewis, B. M.; Lewis, M. D.; McKenna, S.; Noland, T. A.; Orr, J. D.; Pesant, M.; Schnaderbeck, M. J.; Wilkie, G. D.; Abe, T.; Asai, N.; Asai, Y.; Kayano, A.; Kimoto, Y.; Komatsu, Y.; Kubota, M.; Kuroda, H.; Mizuno, M.; Nakamura, T.; Omae, T.; Ozeki, N.; Suzuki, T.; Takigawa, T.; Watanabe, T.; Yoshizawa, K. *Synlett* **2013**, *24*, 327. (c) Austad, B. C.; Calkins, T. L.; Chase, C. E.; Fang, F. G.; Horstmann, T. E.; Hu, Y.; Lewis, B. M.; Niu, X.; Noland, T. A.; Orr, J. D.; Schnaderbeck, M. J.; Zhang, H.; Asakawa, N.; Asai, N.; Chiba, H.; Hasebe, T.; Hoshino, Y.; Ishizuka, H.; Kajima, T.; Kayano, A.; Komatsu, Y.; Kubota, M.; Kuroda, H.; Miyazawa, M.; Tagami, K.; Watanabe, T. *Synlett* **2013**, *24*, 333. (d) Belanger, F.; Chase, C. E.; Endo, A.; Fang, F. G.; Li, J.; Mathieu, S. R.; Wilcoxen, A. Z.; Zhang, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 5108. (e) Lee, J. H.; Li, Z.; Osawa, A.; Kishi, Y. *J. Am. Chem. Soc.* **2016**, *138*, 16248.

(6) Reviews on Prins reaction: (a) Crane, E. A.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 8316. (b) Pastor, I. M.; Yus, M. *Curr. Org. Chem.* **2007**, *11*, 925. (c) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, *1977*, 661.

(7) For the Prins-type reaction with homoallenyl alcohols, see: (a) Cho, Y. S.; Karupaiyan, K.; Kang, H. J.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Chang, M. H. *Chem. Commun.* **2003**, 2346. (b) Kang, H. J.; Kim, S. H.; Pae, A. N.; Koh, H. Y.; Chang, M. H.; Choi, K. I.; Han, S.-Y.; Cho, Y. S. *Synlett* **2004**, *2004*, 2545.

(8) For the preparation of **6** and **7**, see Supporting Information.

(9) (a) Tsuji, J.; Minami, I.; Shimizu, I. *Synthesis* **1986**, *1986*, 623. (b) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron* **1994**, *50*, 475. (c) Mandai, T.; Kaihara, Y.; Tsuji, J. *J. Org. Chem.* **1994**, *59*, 5847. (d) Ma, D.; Wu, W.; Deng, P. *Tetrahedron Lett.* **2001**, *42*, 6929. (e) Chau, A.; Paquin, J.-F.; Lautens, M. *J. Org. Chem.* **2006**, *71*, 1924. (f) Cheng, H.-Y.; Sun, C.-S.; Hou, D.-R. *J. Org. Chem.* **2007**, *72*, 2674.

(10) (a) Bahnck, K. B.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2008**, *130*, 13177. (b) Woo, S. K.; Kwon, M. S.; Lee, E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3242.

(11) Primary allylic esters **8** were obtained as the allene-Prins products (rather than the corresponding tertiary esters) presumably due to the preferred nucleophilic attack on the primary carbon rather than the sterically congested tertiary carbon. Structure of **8d** was unambiguously determined by 2D NMR experiments.

(12) Allylic reduction of **8b** showed no reaction or very low conversion under the tested reaction conditions with a combination of palladium source ($Pd(OAc)_2$, $Pd_2(dba)_3$, or $Pd(PPh_3)_4$), ligands (PPh_3, PBu_3, or (t-Bu)$_2$P(biphenyl)), and solvents (THF, DMF, or CH_3CN).

(13) Allene substrates missing the 3-methyl substituent (i.e., nona-1,2,8-trien-5-ol or 4-methylnona-1,2,8-trien-5-ol) did not give any desired products under the same reaction conditions.

(14) (a) Xu, Y.-C.; Lebeau, E.; Walker, C. *Tetrahedron Lett.* **1994**, *35*, 6207. (b) Xu, Y.-C.; Bizuneh, A.; Walker, C. *Tetrahedron Lett.* **1996**, *37*, 455.

(15) For the preparation of **16**, see Supporting Information.

(16) HPLC analysis was conducted using C18 column, and the ratio was determined based on comparison of retention times with those of the authentic samples. The minor isomer was not detectible by ^{1}H NMR analysis (400 MHz).

DOI: 10.1021/acs.orglett.7b02934
Org. Lett. XXXX, XXX, XXX−XXX