JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Synthesis of Neurotrophic *Seco*-prezizaane Sesquiterpenes (1*R*,10*S*)-2-Oxo-3,4-dehydroneomajucin, (2*S*)-Hydroxy-3,4-dehydroneomajucin, and (−)-Jiadifenin

Xiayun Cheng and Glenn C. Micalizio*

Department of Chemistry, Burke Laboratory, Dartmouth College, Hanover, New Hampshire 03755, United States

Supporting Information

ABSTRACT: An asymmetric approach to the synthesis of neurotrophic *seco*-prezizaane sesquiterpenes is described that is based on the strategic application of a hydroxyl-directed metallacycle-mediated [2 + 2 + 2] annulation and an intramolecular radical cyclization cascade. Targets prepared are among the most potent members of the natural product class and include (1*R*,10*S*)-2-oxo-3,4-dehydroneomajucin, (2*S*)-hydroxy-3,4-dehydroneomajucin, and (−)-jiadifenin. In addition to representing the first application of the alkoxide-directed metallacycle-mediated hydrindane-forming annulation reaction in natural product synthesis and the first total synthesis of (2*S*)-hydroxy-3,4-dehydroneomajucin, these pursuits have resulted in the elucidation of a complex radical cascade process for installation of the C5 quaternary center common to the natural product class.

The search for agents that promote regeneration and growth of neurons is of great current interest, as axon degeneration and neuronal atrophy accompany chronic neurodegenerative disease and acute spinal cord injury.[1] While proteins that serve in this regard (neurotrophins) have been investigated as potential therapeutic agents, they suffer from a variety of suboptimal characteristics that negatively impact their potential utility in the clinic (i.e., low serum stability, poor oral bioavailability, and inefficient penetration into the central nervous system).[1a,2] As such, there has been growing interest in identifying small molecule neurotrophic agents that have a more favorable pharmacokinetic profile.[3] While early investigations of the seeds of the Japanese star anise (*Illicium anisatum, L.*) delivered anisatin,[4] a neurotoxic noncompetitive GABA antagonist,[5] more recent studies of *Illicium* terrestrial plants (evergreen shrubs/trees) have delivered a collection of complex carbocyclic natural products that have been shown to possess potent neurotrophic properties (Figure 1).[3] Perhaps not surprisingly, molecules in this class have emerged as attractive targets for chemical synthesis due to the combination of their potential therapeutically relevant biological activity and their interesting carbocyclic structures.[3,6] In 1990 Kouno and co-workers described the isolation of (1*R*,10*S*)-2-oxo-3,4-dehydroneomajucin (**1**) and (2*S*)-hydroxy-3,4-dehydroneomajucin (**2**) in 0.0006% and 0.007% yield, respectively, from the dried fruit of the Chinese *Illicium majus*.[7,8] These natural products, while structurally related to anisatin, did not exhibit convulsive toxicity in mice. Fourteen years later, in

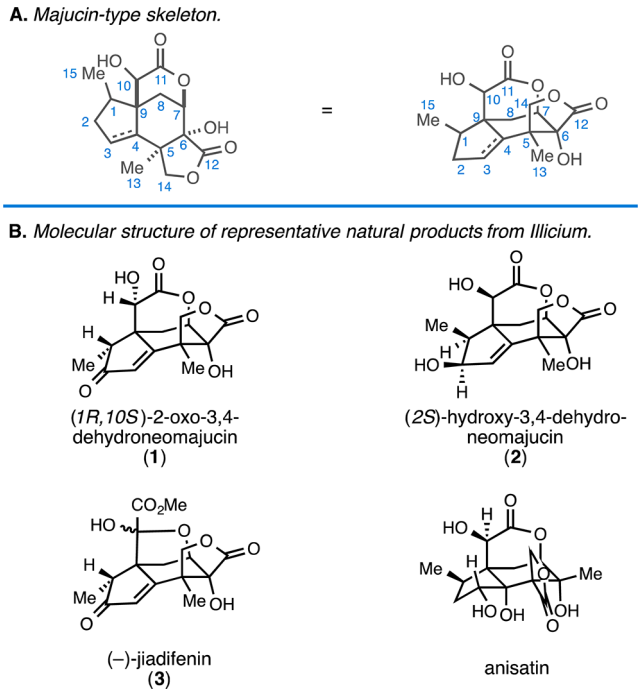

Figure 1. Introduction to majucin-type sesquiterpenes from *Illicium*.

efforts targeting the synthesis of (±)-jiadifenin, Danishefsky reported that **1** is a highly active neurotrophic agent *in vitro*: 184% vs control at 300 nM,[6c,e] an activity that was later supported by structure−activity relationships reported by Theodorakis.[6n] Here, we report the first of our studies aimed at establishing an asymmetric synthesis of neurotrophic *seco*-prezizaane natural products and demonstrate the first application of an alkoxide-directed metallacycle-mediated annulative coupling reaction in natural product synthesis.[9] In addition, a powerful intramolecular radical cascade reaction has been found to be useful for installing the sterically congested C5 quaternary center common to the natural product class.

Our pursuits began by targeting the synthesis of **1** by Bu_3SnH-mediated intramolecular 5-*exo* trig cyclization of the phenylseleno-substituted radical precursor **4** (Figure 2). Synthesis of this substrate was planned from hydrindane **5** and would require differential functionalization of the TMS-

Received: December 4, 2015
Published: January 19, 2016

DOI: 10.1021/jacs.5b12694
J. Am. Chem. Soc. 2016, 138, 1150−1153

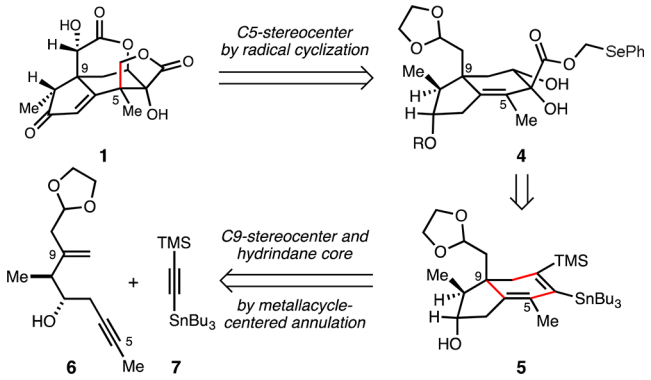

Figure 2. Retrosynthetic strategy for **1**.

and Bu_3Sn-substituted alkene. Finally, hydrindane **5** was expected to be accessible from union of enyne **6** with alkyne **7** by application of a recently developed regio- and stereoselective hydroxyl-directed titanium-mediated annulation reaction.

Synthesis was initiated by regioselective addition of the organometallic reagent derived from **9** to chiral epoxide **8**[10] (Figure 3A).[11] Conversion of the resulting homoallylic alcohol to enyne **6** was then accomplished by a sequence of desilylation (TBAF, THF), epoxide formation (TsCl, Et_3N, DMAP, then NaH, THF), and nucleophilic addition of propynyl lithium. In accord with our earlier observations regarding the regio- and stereoselective coupling of 4-hydroxy-1,6-enynes with TMS-alkynes,[9,12] exposure of stannyl-substituted TMS-acetylene **7** to the combination of Ti(O*i*-Pr)$_4$ and *n*-BuLi (−78 to 50 °C), followed by addition of the Li-alkoxide of enyne **6** (−78 °C to rt), generated hydrindane **5** in 73% yield (rs ≥20:1), where the C9 quaternary center was established with high levels of stereoselectivity (ds ≥20:1).

Treatment of hydrindane **5** with TBAF resulted in removal of the TMS-group and was followed by silylation of the secondary alcohol (TBDPSCl, imid., CH_2Cl_2). Subsequently, tin−lithium exchange was followed by carboxylation,[13] and esterification with $PhSeCH_2Cl$, a sequence that ultimately delivered the selenophenyl methyl ester **4**.[14] Site- and stereoselective dihydroxylation[15] then generated **11** in 85% yield as a single observable stereoisomer.

We next turned our attention to the radical cyclization process that was anticipated to establish the sterically congested C5 quaternary center. Heating selenophenyl methyl ester **11** in the presence of Bu_3SnH and AIBN resulted in the formation of two cyclized products **12** and **13** in 80% combined yield (notably, each of these products possessed the desired C5-quaternary center). While the formation of **12** was expected, observation of the ethyl ester-containing product **13** was unanticipated and, on further consideration, warmly welcomed. We speculate that this latter compound is produced from the sequence summarized in Figure 4, where formation of radical **I**

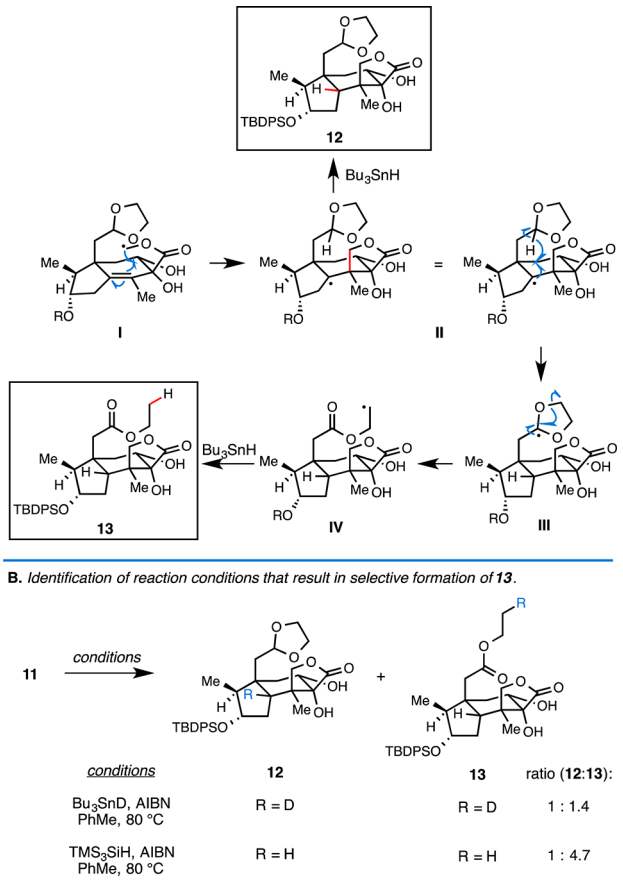

Figure 4. Proposed mechanism for the radical cascade reaction.

is followed by stereoselective 5-*exo* trig cyclization[16] en route to **II**. While intermolecular quenching of this tertiary radical with Bu_3SnH results in the expected product **12**, intramolecular hydrogen atom transfer from the acetal carbon (**II** → **III**), fragmentation (**III** → **IV**), and reduction deliver the ethyl ester-containing carbocycle **13**.

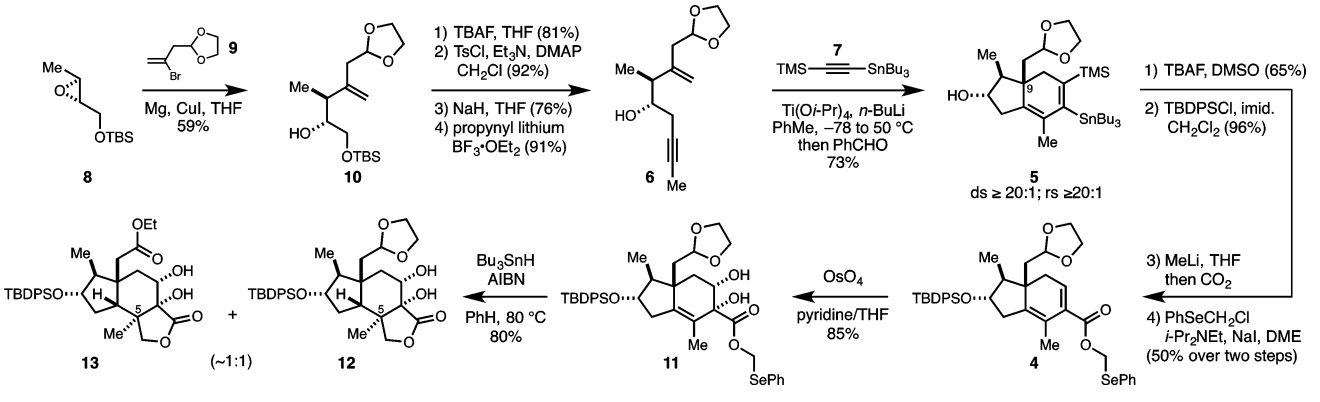

Figure 3. Establishment of the carbocyclic skeleton of the *seco*-prezizaane sesquiterpenes.

DOI: 10.1021/jacs.5b12694
J. Am. Chem. Soc. 2016, 138, 1150−1153

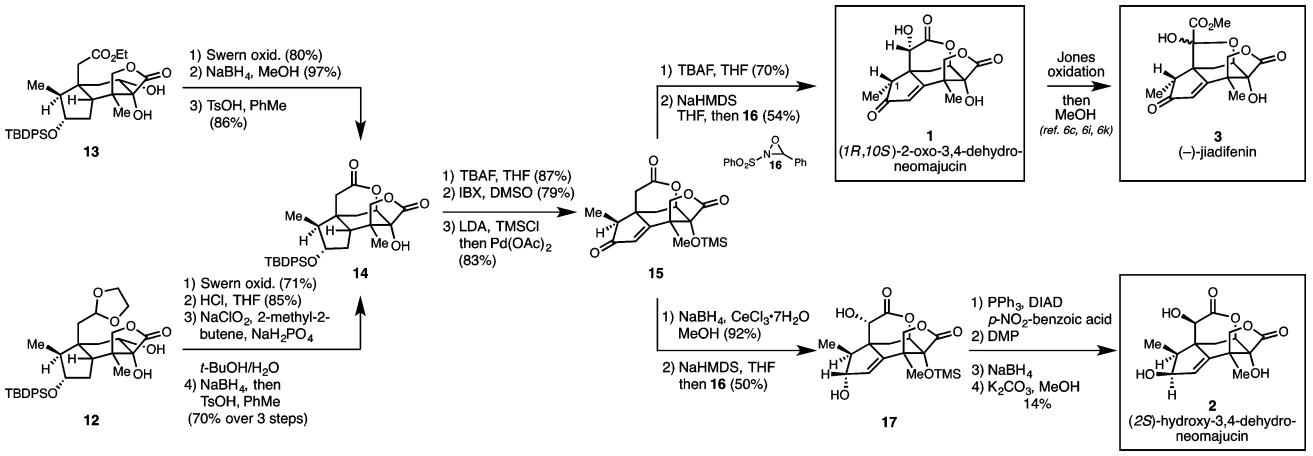

Figure 5. Total syntheses of (1*R*,10*S*)-2-oxo-3,4-dehydroneomajucin, (−)-jiadifenin, and (2*S*)-3,4-dehydroneomajucin.

With the goal of influencing the course of this radical cascade reaction, we anticipated that slowing the rate of intermolecular reduction of **II** would result in the production of a greater quantity of ester **13**. While simply decreasing the concentration of Bu_3SnH would be anticipated to have such an effect, slow addition by syringe pump (over 3 h) did little to affect selectivity. Use of Bu_3SnD was hypothesized as an alternative means to slow the rate of reduction of **II** through exploiting the primary deuterium isotope effect,[17] yet this modification resulted in only a minor shift in selectivity favoring the formation of **13**(D) (1.4:1; Figure 4B). Satisfyingly, use of TMS_3SiH instead of Bu_3SnH in this radical cascade reaction resulted in a more substantial change in ratio to favor the ethyl ester containing product **13** (4.7:1).

As illustrated in Figure 5, both products of the radical cyclization were converted to the tetracyclic bis-lactone **14** by a sequence of straightforward functional group manipulations. Desilylation of **14** with TBAF and sequential oxidation (IBX, then Saegusa) then delivered enone **15**. Finally, removal of the tertiary TMS-ether that was generated during the Saegusa oxidation, and α-hydroxylation[18] delivered (1*S*,10*R*)-2-oxo-3,4-dehydroneomajucin (**1**) through a process that was accompanied by epimerization at C1. As reported by Danishefsky, oxidation and methanolysis of **1** were successful for producing synthetic (−)-jiadifenin (**3**).[6c,i,k]

The complex tetracyclic intermediate **15** also served as a precursor to one of the most active neurotrophic agents in this natural product family, (2*S*)-hydroxy-3,4-dehydroneomajucin (**2**).[7] First, stereoselective reduction of the enone and α-hydroxylation of the lactone delivered **17**. A subsequent Mitsunobu reaction with *p*-nitrobenzoic acid, followed by a sequence of oxidation to the α-keto-lactone (Dess Martin periodinane), stereoselective reduction ($NaBH_4$), hydrolysis of the *p*-nitrobenzoate, and deprotection of the TMS ether (K_2CO_3, MeOH) furnished the first synthetic sample of (2*S*)-3,4-dehydroneomajucin **2**.

Overall, we report an enantioselective pathway for the synthesis of several neurotrophic seco-prezizaanes by way of an alkoxide-directed metallacycle-mediated [2 + 2 + 2] annulation and intramolecular radical cyclization. This marks the first demonstration of such a metallacycle-centered annulation reaction in natural product synthesis and demonstrates the utility of a selenophenylmethyl ester-based radical cyclization cascade to generate the congested quaternary center at C5 of this natural product family. We look forward to further developing chemistry capable of producing neurotrophic agents inspired by the seco-prezizaanes and to exploring the broad utility of alkoxide-directed metallacycle-centered annulative cross-coupling reactions in natural product synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12694.

Experimental procedures and tabulated spectroscopic data for new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*glenn.c.micalizio@dartmouth.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support of this work by the National Institutes of Health − NIGMS (GM080266). The authors also thank Dr. Haruki Mizoguchi and Dr. Christopher am Ende for helpful discussions and Professor Yoshiyasu Fukuyama for NMR spectra of **2**.

■ REFERENCES

(1) (a) Price, R. D.; Milne, S. A.; Sharkey, J.; Matsuoka, N. *Pharmacol. Ther.* **2007**, *115*, 292−306. (b) Dakas, P.-Y.; Parga, J. A.; Höing, S.; Schöler, H. R.; Sterneckert, J.; Kumar, K.; Waldmann, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 9576−9581. (c) Burch, P.; Binaghi, M.; Scherer, M.; Wentzel, C.; Bossert, D.; Eberhardt, L.; Neuburger, M.; Scheiffele, P.; Gademann, K. *Chem. - Eur. J.* **2013**, *19*, 2589−2591.
(2) Skaper, D. S.; Walsh, F. S. *Mol. Cell. Neurosci.* **1998**, *12*, 179−193.
(3) Xu, J.; Lacoske, M. H.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 956−987.
(4) (a) Lane, J. F.; Koch, W. T.; Leeds, N. S.; Gorin, G. *J. Am. Chem. Soc.* **1952**, *74*, 3211−3215. (b) Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 199−229.
(5) Kudo, Y.; Oka, J.-I.; Yamada, K. *Neurosci. Lett.* **1981**, *25*, 83−88.
(6) (a) Birman, V. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2080−2081. (b) Inoue, M.; Sato, T.; Hirama, M. *J. Am. Chem. Soc.* **2003**, *125*, 10772−10773. (c) Cho, Y. S.; Carcache, D. A.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 14358−14359. (d) Meng, Z.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1511−1513. (e) Carcache, D. A.; Cho, Y. S.; Hua, Z.; Tian, Y.; Li, Y.-

DOI: 10.1021/jacs.5b12694
J. Am. Chem. Soc. 2016, 138, 1150−1153

M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1016−1022. (f) Inoue, M.; Sato, T.; Hirama, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4843−4848. (g) Mehta, G.; Singh, S. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 953−955. (h) Mehta, G.; Shinde, H. M. *Tetrahedron Lett.* **2007**, *48*, 8297−8300. (i) Trzoss, L.; Xu, J.; Lacoske, M. H.; Mobley, W. C.; Theodorakis, E. A. *Org. Lett.* **2011**, *13*, 4554−4557. (j) Xu, J.; Trzoss, L.; Chang, W. K.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3672−3676. (k) Yang, Y.; Fu, X.; Chen, J.; Zhai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 9825−9828. (l) Mehta, G.; Shinde, H. M. *J. Org. Chem.* **2012**, *77*, 8056−8070. (m) Chen, J.; Gao, P.; Yu, F.; Yang, Y.; Zhu, S.; Zhai, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 5897−5899. (n) Trzoss, L.; Xu, J.; Lacoske, M. H.; Mobley, W. C.; Theodorakis, E. A. *Chem. - Eur. J.* **2013**, *19*, 6398−6408. (o) Paterson, I.; Xuan, M.; Dalby, S. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 7286−7289. (p) Siler, D. A.; Mighion, J. D.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5332−5335. (q) Lu, H.-H.; Martinez, M. D.; Shenvi, R. A. *Nat. Chem.* **2015**, *7*, 604−607. For recent reviews, see: (r) Wilson, R. M.; Danishefsky, S. J. *Acc. Chem. Res.* **2006**, *39*, 539−549. (s) Urabe, D.; Inoue, M. *Tetrahedron* **2009**, *65*, 6271−6289 and ref 3..

(7) Kouno, I.; Baba, N.; Hashimoto, M.; Kawano, N.; Takahashi, M.; Kaneto, H.; Yang, C.-S. *Chem. Pharm. Bull.* **1990**, *38*, 422−425.

(8) (2*S*)-Hydroxy-3,4-dehydroneomajucin has also recently been isolated from *Illicium jiadifengpi*, along with a collection of related *seco*-prezizaane-type sesquiterpenes; see: (a) Yokoyama, R.; Huang, J.-M.; Yang, C.-S.; Fukuyama, Y. *J. Nat. Prod.* **2002**, *65*, 527−531. (b) Liu, J.-F.; Li, Y.-C.; Wang, L.; Wang, Y.-F.; Jia, L.; Bi, Y.-F.; Zhang, Y.-B. *Tetrahedron Lett.* **2014**, *55*, 2942−2944.

(9) (a) Greszler, S. N.; Reichard, H. A.; Micalizio, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 2766−2774. (b) Jeso, V.; Aquino, C.; Cheng, X.; Mizoguchi, H.; Nakashige, M.; Micalizio, G. C. *J. Am. Chem. Soc.* **2014**, *136*, 8209−8212. (c) Cheng, X.; Micalizio, G. C. *Org. Lett.* **2014**, *16*, 5144−5147.

(10) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(11) For a similar regioselective addition reaction, see: Baker, R.; Castro, J. L. *J. Chem. Soc., Chem. Commun.* **1989**, 378−381.

(12) Mizoguchi, H.; Micalizio, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 6624−6628.

(13) (a) Boeckman, R. K.; Wrobleski, S. T. *J. Org. Chem.* **1996**, *61*, 7238−7239. (b) Lander, P. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 8126−8132. (c) Fleming, I.; Taddei, M. *Synthesis* **1985**, *1985*, 898.

(14) (a) Beckwith, A. L. J.; Pigou, P. E. *Aust. J. Chem.* **1986**, *39*, 77−87. (b) Singh, R.; Singh, G. C.; Ghosh, S. K. *Eur. J. Org. Chem.* **2007**, *2007*, 5376−5385. (c) Kumamoto, H.; Takahashi, N.; Shimamura, T.; Tanaka, H.; Nakamura, K. T.; Hamasaki, T.; Baba, M.; Abe, H.; Yano, M.; Kato, N. *Tetrahedron* **2008**, *64*, 1494−1505.

(15) (a) Yaji, K.; Shindo, M. *Tetrahedron* **2010**, *66*, 9808−9813. (b) Ohyoshi, T.; Funakubo, S.; Miyazawa, Y.; Niida, K.; Hayakawa, I.; Kigoshi, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 4972−4975. (c) Caldwell, J. J.; Colman, R.; Kerr, W. J.; Magennis, E. J. *Synlett* **2001**, *2001*, 1428−1430.

(16) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−736.

(17) For examples of the use of isotope effects in synthesis, see: (a) Clive, D. L. J.; Cantin, C.; Khodabocus, A.; Kong, X.; Tao, Y. *Tetrahedron* **1993**, *49*, 7917−1930. (b) Vedejs, E.; Little, J. *J. Am. Chem. Soc.* **2002**, *124*, 748−749. (c) Dudley, G. B.; Danishefsky, S. J.; Sukenick, G. *Tetrahedron Lett.* **2002**, *43*, 5605−5606. (d) Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495−499.

(18) (a) Davis, F. A.; Nadir; Upender, K.; Kluger, E. W. *J. Chem. Soc., Chem. Commun.* **1977**, 25−26. (b) Davis, F. A.; Lamendola, J.; Nadir, U.; Kluger, E. W.; Sedergran, T. C.; Panunto, T. W.; Billmers, R.; Jenkins, R.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000−2005.

DOI: 10.1021/jacs.5b12694
J. Am. Chem. Soc. 2016, 138, 1150−1153