

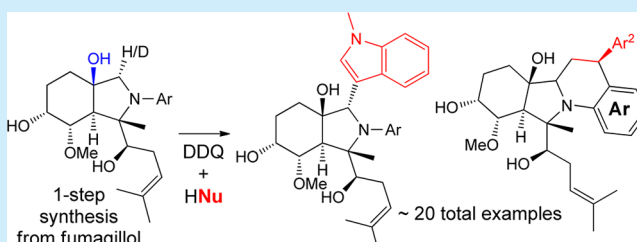
Remodeling of Fumagillol: Discovery of an Oxygen-Directed Oxidative Mannich Reaction

Alexander J. Grenning, John K. Snyder,* and John A. Porco, Jr.*

Center for Chemical Methodology and Library Development, Boston University, 590 Commonwealth Avenue, Boston, Massachusetts 02215, United States

S Supporting Information

ABSTRACT: An efficient, two-step construction of highly complex alkaloid-like compounds from the natural product fumagillol is described. This approach, which mimics a biosynthetic cyclase/oxidase sequence, allows for rapid and efficient structure elaboration of the basic fumagillol scaffold with a variety of readily available coupling partners. Mechanistic experiments leading to the discovery of an oxygen-directed oxidative Mannich reaction are also described.



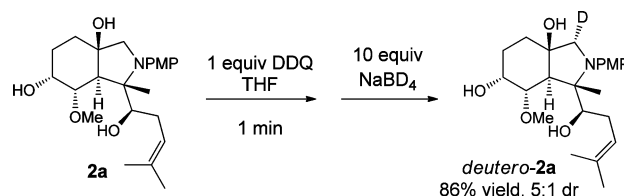
The use of abundant natural products as synthetic launching points for diversity-oriented synthesis (DOS) has garnered significant attention recently, as highly complex compounds can be rapidly prepared for biological evaluation.¹ Importantly, this approach utilizes the inherent complexity of the natural product which may be “structurally remodeled”^{2a} into a new architecture with unique biological activity in comparison to the parent natural product. Exemplary natural products include semisynthetic steroids,^{2b} bryonolic acid,^{2c} adrenosterone,^{2d} cinchonine,^{2d} gibberelic acid,^{2d} and steviol.^{2e}

We recently reported that the natural product fumagillol **1** can undergo controlled 5-*exo*- or 6-*endo*-bis-epoxide opening/cyclization, depending on the metal-catalyst additive, leading to highly complex alkaloidal perhydroisoindoles **2** and perhydroisoquinolines **3** (Scheme 1).^{2a} Due to the efficiency of these reactions, we considered further processing of this scaffold to increase diversity and complexity for biological evaluation. Herein we report a two-step diversity-oriented synthesis³ strategy using cascade cyclizations and oxidative Mannich

reactions,⁴ reminiscent of natural product biosynthesis⁵ (“cyclase” followed by “oxidase” as coined by Baran⁶), yielding alkaloid-like structures **4** with high levels of complexity (Scheme 1). Mechanistic experiments leading to the discovery of an oxygen-directed Mannich reaction are also outlined.

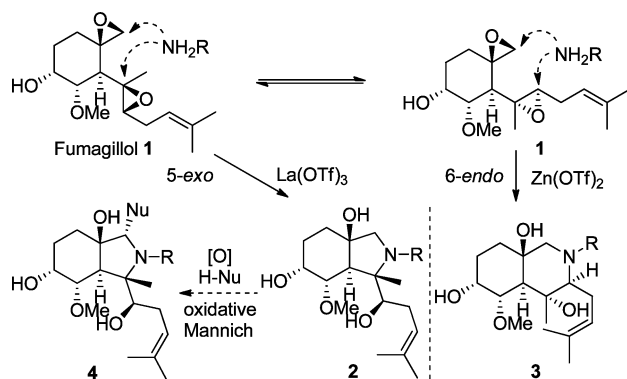
Following our previously reported preparation of fumagillol–anisidine adducts **2a**,^{2a,7} we began oxidative coupling studies on this scaffold. An oxidation screen led to the discovery of a rapid (<1 min, 100% conversion as monitored by UPLC analysis⁷) amine-to-iminium oxidation of scaffold **2a** when 1 equiv of DDQ was added in THF (Scheme 2).^{8,9} The site of oxidation was confirmed by a quench with sodium borodeuteride, stereoselectively yielding α -deutero-**2a** as the sole product in 83% isolated yield.

Scheme 2. Discovery of a Chemoselective Oxidation



The scope of the oxidative coupling of fumagillol–aniline adducts **2** with various nucleophiles was next examined (Figure 1). Substrates **2a–2c** underwent clean oxidation and subsequent nucleophilic addition with *N*-methylindole to afford adducts **4a–4c**, respectively, in good yields.⁹ Similarly, substrates substituted with a *meta*-electron withdrawing group on the aniline subunit underwent chemoselective oxidation adjacent to nitrogen and were found to be suitable for the methodology (**2d** → **4d**, 81% yield). In general, substrates

Scheme 1. Fumagillol Bis-Epoxide Opening and Oxidative Mannich Strategy



Received: December 5, 2013

Published: January 10, 2014

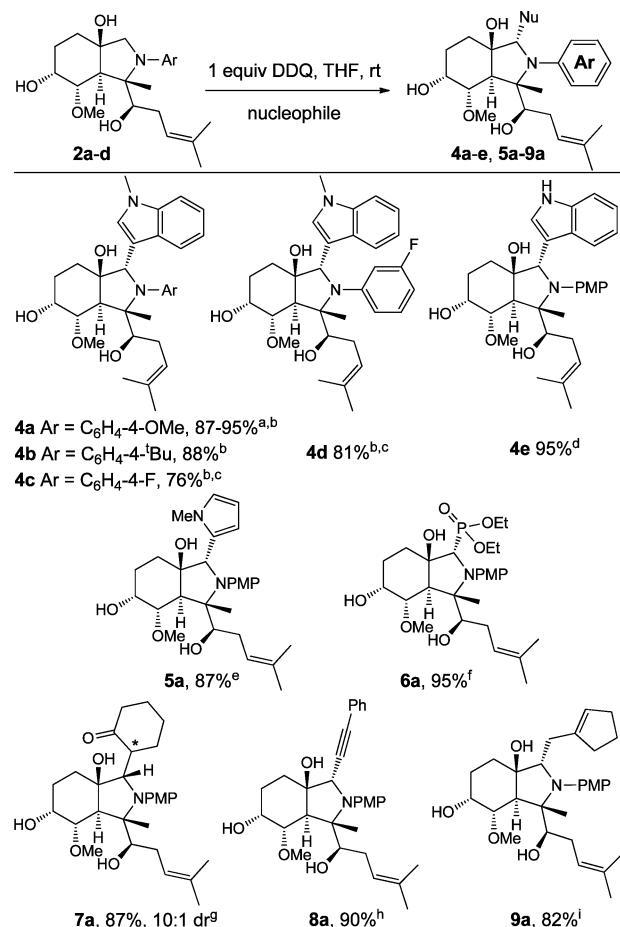


Figure 1. Scope of the oxidative coupling. ^aMultiple runs, 50–750 mg scale. ^bNucleophile = *N*-methylindole (1.1 equiv). ^cInitial oxidation required heating at 60 °C for 1–3 h to complete. Once complete, indole (1.1 equiv) was added and the reaction was stirred until coupling was complete as monitored by UPLC. ^dNucleophile = indole (1.1 equiv). ^eNucleophile = *N*-methylpyrrole (1.1 equiv). ^fNucleophile = diethylphosphite (10 equiv). ^gNucleophile = cyclohexane silylenol ether (1.5 equiv); the α -stereocenter could not be unambiguously assigned. ^hNucleophile = phenylacetylene (1.5 equiv) + CuI (10 mol %) and Et₃N (1.1 equiv). ⁱNucleophile = exomethylenecyclopentene (10 equiv). [DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, Ar = aryl, PMP = *p*-methoxyphenyl].

containing electron-withdrawing groups required heating (60 °C) to enable oxidation in a timely fashion (3 h). In addition to *N*-methylindole as the nucleophilic partner, simple indole was also compatible with the methodology and could be oxidatively coupled to scaffold **2a** to afford adduct **4e**. To illustrate the practicality of the couplings, product **4a** could be prepared on reaction scales from 50 to 750 mg. Thus, both the *bis*-epoxide opening and the oxidative coupling steps are applicable to near gram scale synthesis.

Highly efficient oxidative couplings of remodeled scaffold **2a** with other nucleophiles were also found to be successful (Figure 1, products **5–9**). Under the optimized conditions, oxidative couplings with *N*-methylpyrrole, diethyl phosphite,¹⁰ cyclohexanone silyl enol ether,¹¹ phenylacetylene,¹² and methylenecyclopentane¹¹ produced products **5a–9a**, respectively.

The use of styrenes as nucleophilic partners in the oxidative couplings yielded Povarov products **10** (Figure 2).¹³ Importantly, this oxidative Povarov reaction allowed for

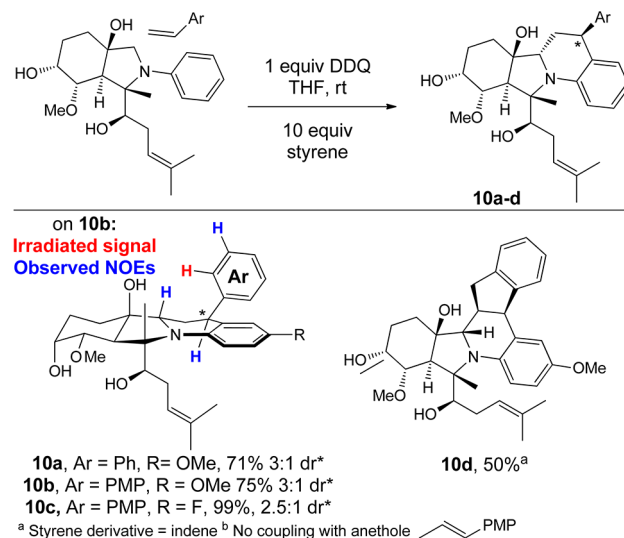


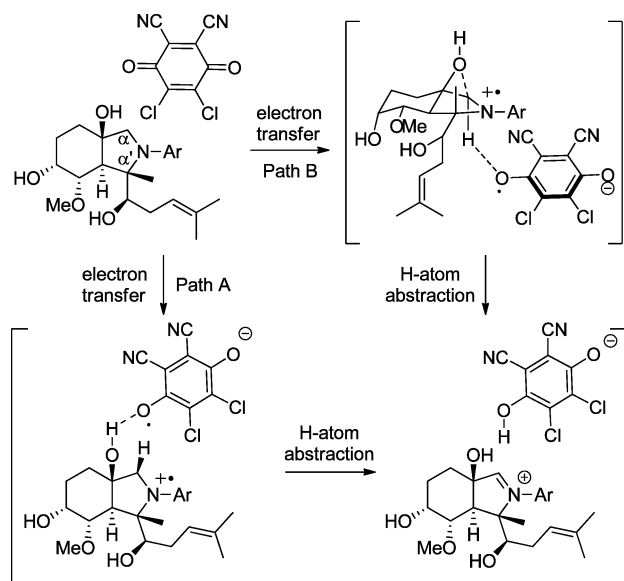
Figure 2. Oxidative Povarov cyclization.

additional structural complexity to be achieved by constructing multiple bonds in a single transformation. Simple styrenic nucleophiles including styrene and *p*-methoxystyrene underwent Povarov cycloaddition with the *in situ* generated iminium ion. Adducts **10a–c** were isolated in good to excellent yields with the electronically differentiated fumagillol scaffolds **2b** and **2c** containing *p*-methoxy and *p*-fluoro groups, respectively. In all cases, the diastereoselectivity of the newly formed benzylic stereocenter was modest (dr = 2.5–3:1). However, in the case of **10b–c**, the products could be diastereomerically enriched (to >20:1 dr) by recrystallization, allowing for stereochemistry determination by NOE analysis.⁷ By utilizing indene, the highly complex adduct **10d** was prepared as a single diastereomer. Unfortunately, the *trans*-styrene derivative anethole did not react with the *in situ* generated iminium (Figure 2, note b).

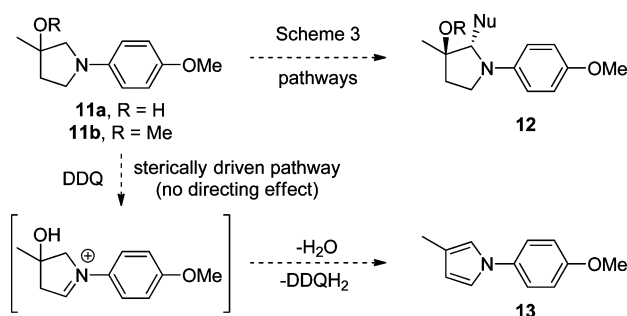
Having defined a wide scope for our oxidative coupling methodology, the possibility for an “oxygen”-directed oxidation mechanism for the initial DDQ conversion of the aniline to an iminium intermediate was next examined. Two possible mechanisms by which the hydroxy group could influence the oxidation were envisioned (Scheme 3): the hydroxyl group could function (1) as a general acid catalyst for DDQ activation and direction (pathway A) or (2) as a neighboring nucleophile (pathway B *via* anchimeric assistance) to facilitate formal hydride delivery to the DDQ oxidant. Since the α' -position of the fumagillol substrate is fully substituted and therefore cannot undergo oxidation, it was not clear whether there was also a hydroxy-directing, regioselectivity effect¹⁴ in addition to the diastereocontrol in nucleophilic addition to the iminium ion intermediate.

As shown in Scheme 4, if there is an intrinsic hydroxyl-directing effect, one would expect products of type **12** to arise from either the simplified hydroxy (**11a**) and/or ether (**11b**) substrates thus allowing for development of a general methodology toward vicinally chiral pyrrolidinols. However, if there is no directing effect, a sterically driven oxidation would be expected, likely resulting in the formation of pyrrole **13**.^{8c} Thus, the directed oxidation would produce compounds of increased complexity containing vicinal stereocenters whereas the steric oxidation would result in a loss of complexity, likely leading to *N*-arylpyrrole **13** *via* enamine formation and dehydration.¹⁵

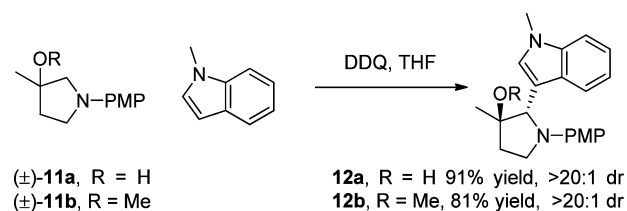
Scheme 3. Possible Pathways for Oxygen-Directed Oxidation



Scheme 4. Possible Outcomes for Oxidative Mannich Reaction of 11



We were pleased to find that the simplified substrate **11a** indeed underwent the oxidative Mannich reaction with *N*-methylindole in the direction of the hydroxy group affording adduct **12a** in 91% yield as a single diastereomer (Scheme 5).

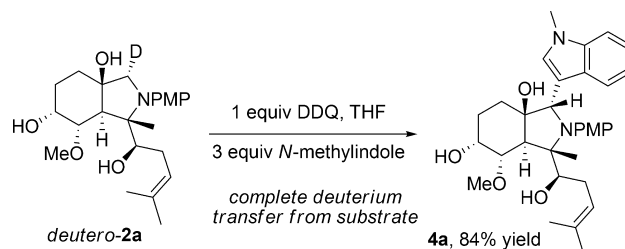
Scheme 5. A Simplified Variant^a

^aStandard conditions: 1 equiv DDQ, THF (0.5M), 5 equiv, indole derivative, 12 h, rt.

This result confirmed that there is an oxygen-directing effect; however it does not distinguish between the H-bonding and anchimeric-assisted mechanisms (Paths A and B, Scheme 3). Interestingly, ether substrate **11b** also underwent directed oxidative Mannich reaction with *N*-methylindole in good yield producing **12b** as the sole product, suggesting that preorganization of the DDQ and the substrate through a hydrogen bond is not required, thus supporting the anchimeric-assisted mechanism (Pathway B).

The nature of the oxygen-directed oxidative Mannich reaction was further explored using a deuterium labeling experiment.¹⁶ Stereoselective oxidation was observed on the deuterated-fumagillol scaffold *deutero-2a* wherein complete deuterium transfer to the DDQ oxidant was observed and *deuterium-free* product **4a** was isolated in high yield following nucleophilic quench with *N*-methylindole (Scheme 6). This result is in line with the hypothesis that the oxygen atom activates its *anti*-hydrogen toward transfer *via* anchimeric, σ^* -orbital overlap (Pathway B, Scheme 3).^{14a}

Scheme 6. Deuterium Labeling Study



In conclusion, we have outlined a rapid approach for the construction of highly complex alkaloid-like “unnatural products” from the natural product scaffold fumagillol utilizing a cascade of *bis*-epoxide opening (“structure remodeling”) followed by a diversifying chemo- and stereoselective oxidative Mannich/coupling protocol. Mechanistic experiments including a deuterium labeling study as well as oxidations with simpler pyrrolidine substrates were used to define the nature of the oxygen-directed oxidative Mannich reaction and support an “anchimeric-assisted” mechanism. Further studies including additional applications and biological evaluation of alkaloid-like products are currently in progress and will be reported in due course.

■ ASSOCIATED CONTENT

§ Supporting Information

Experimental procedures, compound characterization, and ¹H/¹³C NMR reprints. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: porco@bu.edu.

*E-mail: snyder@bu.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the National Institutes of Health (P50 GM067041) is gratefully acknowledged. We thank Professors Scott Schaus (Boston University) and Corey Stephenson (University of Michigan) for helpful discussions. We thank Madeline Weber (CMLD-BU) for assistance with preparative HPLC purification and Gina Kim for full spectroscopic analysis of fumagillol.

■ REFERENCES

- (1) Morrison, K. C.; Hergenrother, P. J. *Nat. Prod. Rep.* **2014**, *31*, 6–14.

- (2) (a) Balthaser, B. R.; Maloney, M. C.; Beeler, A. B.; Porco, J. A., Jr.; Snyder, J. K. *Nat. Chem.* **2011**, *3*, 969–973. (b) Kumar, N.; Kiuchi, M.; Tallarico, J. A.; Schreiber, S. L. *Org. Lett.* **2005**, *7*, 2535–2538. (c) Ignatenko, V. A.; Han, Y.; Tochtrop, G. P. *J. Org. Chem.* **2012**, *78*, 410–418. (d) Huigens, R. W.; Morrison, K. C.; Hicklin, R. W.; Flood, T. A.; Richter, M. F.; Hergenrother, P. J. *Nat. Chem.* **2013**, *5*, 195–202. (e) Hutt, O. E.; Doan, T. L.; Georg, G. I. *Org. Lett.* **2013**, *15*, 1602–1605. (f) Schwarz, O.; Jakupovic, S.; Ambrosi, H.-D.; Haustedt, L. O.; Mang, C.; Müller-Kuhrt, L. *J. Comb. Chem.* **2007**, *9*, 1104–1113. (g) Sumskaya, Y. G.; Whitney, P. S., III; Bergmeier, S. C.; McMills, M. C.; Priestley, N. D.; Wright, D. L. *ARKIVOC* **2011**, 144–166. (h) Kesavan, S.; Marcaurelle, L. A. *Nat. Chem. Biol.* **2013**, *9*, 210–213. (i) Li, J.; Cisar, J. S.; Zhou, C.-Y.; Vera, B.; Williams, H.; Rodríguez, A. D.; Cravatt, B. F.; Romo, D. *Nat. Chem.* **2013**, *5*, 510–517.
- (3) (a) O'Connor, C. J.; Beckmann, H. S. G.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 4444–4456. (b) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463–472. (c) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74–84. (d) Spring, D. R. *Org. Bio. Mol. Chem.* **2003**, *1*, 3867–3870. (e) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969.
- (4) (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780–1824. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2010**, *111*, 1293–1314. (d) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335–344. (e) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490–1501.
- (5) (a) Ames, B. D.; Haynes, S. W.; Gao, X.; Evans, B. S.; Kelleher, N. L.; Tang, Y.; Walsh, C. T. *Biochemistry* **2011**, *50*, 8756–8769. (b) Ames, B. D.; Liu, X.; Walsh, C. T. *Biochemistry* **2010**, *49*, 8564–8576.
- (6) (a) Ishihara, Y.; Baran, P. S. *Synlett* **2010**, 1733–1745. (b) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824–828. (c) Foo, K.; Usui, I.; Götz, D. C. G.; Werner, E. W.; Holte, D.; Baran, P. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 11491–11495.
- (7) See the Supporting Information for complete details.
- (8) DDQ is a common oxidant in various cross-dehydrogenative coupling (CDC) reactions; see: (a) Zhang, Y.; Li, C.-J. *Angew. Chem., Int. Ed.* **2006**, *45*, 1949–1952. (b) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243. (c) Tu, W.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184–4187. (d) Zhai, L.; Shukla, R.; Rathore, R. *Org. Lett.* **2009**, *11*, 3474–3477. (e) Liu, L.; Floreancig, P. E. *Org. Lett.* **2010**, *12*, 4686–4689. (f) Brizgys, G. J.; Jung, H. H.; Floreancig, P. E. *Chem. Sci.* **2012**, *3*, 438–442. (g) Clausen, D. J.; Floreancig, P. E. *J. Org. Chem.* **2012**, *77*, 6574–6582.
- (9) For select examples of oxidative Mannich reactions, see: (a) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648–5649. (b) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. *Org. Lett.* **2010**, *12*, 5214–5217. (c) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464–1465. (d) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2011**, *14*, 94–97. (e) Allen, J. M.; Lambert, T. H. *J. Am. Chem. Soc.* **2011**, *133*, 1260–1262.
- (10) Alagiri, K.; Devadig, P.; Prabhu, K. R. *Chem.—Eur. J.* **2012**, *18*, 5160–5164.
- (11) Huang, L.; Zhang, X.; Zhang, Y. *Org. Lett.* **2009**, *11*, 3730–3733.
- (12) (a) Su, W.-K.; Yu, J.-B.; Li, Z.-H.; Jiang, Z.-J. *J. Org. Chem.* **2011**, *76*, 9144–9150. (b) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075–7078.
- (13) (a) Richter, H.; García Mancheño, O. *Org. Lett.* **2011**, *13*, 6066–6069. (b) Rohlmann, R.; Stopka, T.; Richter, H.; García Mancheño, O. *J. Org. Chem.* **2013**, *78*, 6050–6064. (c) Jia, X.; Wang, Y.; Peng, F.; Huo, C.; Yu, L.; Liu, J.; Wang, X. *J. Org. Chem.* **2013**, *78*, 9450–9456.
- (14) (a) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743–4748. (b) Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. *J. Org. Chem.* **1997**, *62*, 3119–3125. (c) Archibald, G.; Lin, C.-P.; Boyd, P.; Barker, D.; Caprio, V. *J. Org. Chem.* **2012**, *77*, 7968–7980.
- (15) Takasu, N.; Oisaki, K.; Kanai, M. *Org. Lett.* **2013**, *15*, 1918–1921.
- (16) For deuterium-labeling studies of DDQ-mediated oxidative Prins cyclizations, see: Jung, H. H.; Floreancig, P. E. *Tetrahedron* **2009**, *65*, 10830–10836.