

Total Synthesis of Dixiamycin B by Electrochemical Oxidation

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S Supporting Information

ABSTRACT: N–N-linked dimeric indole alkaloids represent an unexplored class of natural products for which chemical synthesis has no practical solution. To meet this challenge, an electrochemical oxidative dimerization method was developed, which was applied as the pivotal step of the first total synthesis of dixiamycin B. This method is also general for N–N dimerization of substituted carbazoles and β -carboline, providing entry into seldom explored chemical space.

Synthetic chemists have long been enamored by the structures of oligomeric indole alkaloids. The myriad different C–C (e.g., 1, Figure 1A) and C–N (e.g., 2) linkages have inspired the development of numerous elegant methods to enable their chemical production.¹ Recently, the atropisomeric indoloterpenoid natural products dixiamycins A and B were isolated independently by Zhang and Hertweck (3a/b).² These molecules express a new and unexplored dimerization mode: an N–N linkage. Intriguingly, the N-linked dimeric forms of these antibacterial natural products are nearly an order of magnitude more potent than their monomeric siblings.^{2a} The current toolbox of methods for constructing N–N bonds of this type is poorly equipped (*vide infra*) to address the challenge of their practical preparation. In general, molecules containing an N–N bond are prepared using hydrazine,³ a non-viable option in a synthesis of 3a/b due to the overall inefficiency of a linear bis-functionalization route outward from a hydrazine core. Previous efforts from this laboratory (Figure 1B) demonstrated the practicality of an indole alkaloid synthesis plan in which two fragments were directly cross-coupled by oxidative C–C bond formation (formal loss of H₂).⁴ In a similar vein, the goal of this work was to invent a direct oxidative N–N dimerization of carbazoles to bring two monomers together and liberate H₂ as the sole byproduct. This Communication reports the realization of this goal through a remarkable electrochemical process that permits chemoselective access to this unexplored area of chemical space as exemplified by the first total synthesis of dixiamycin B (3b).

A successful synthesis of 3a/b clearly hinges on the ability to effect an N–N bond-forming event between two molecules of xiamycin A (4). While KMnO₄- or (PhCO₂)₂-mediated conversion of 4 to 3a/b is possible, as indicated by HPLC analysis, these reactions fail to deliver meaningful yields of product.^{2a,c} Additionally, the synthesis of N9–C4-linked bis-carbazole dimeric natural product murrastifoline F has been accomplished by treatment of a simple carbazole derivative with Pb(OAc)₄.⁵ Initial attention thus turned to the identification of a reliable oxidant to access N-linked carbazole dimers.

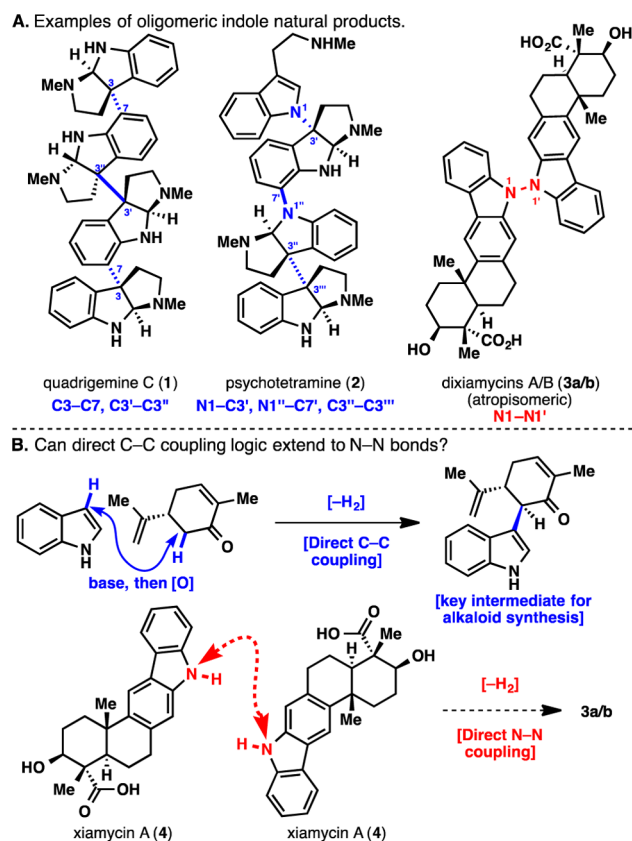


Figure 1. Inspiration and strategy for the total synthesis of dixiamycins A and B (3a/b).

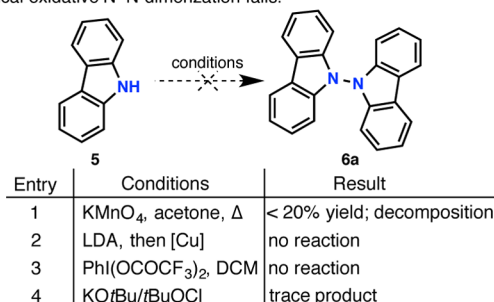
Early optimization attempts focused on the dimerization reaction of the readily available parent carbazole 5 (Figure 2A). An exhaustive survey of chemical oxidants generally resulted in little to no substrate conversion (for other failed experiments, see the Supporting Information). For example, deprotonation of 5 with LDA and treatment of the resulting anion with copper 2-ethylhexanoate, conditions known to facilitate oxidative C–C bond formation, resulted only in recovered starting material.^{4a} Exposure of 5 to KMnO₄ in refluxing acetone, an approach envisioned to be incompatible with xiamycin's vulnerable functionality, afforded the corresponding dimer 6a irreproducibly and in low yield, confirming that the most promising oxidation method was inadequate.

With the failure of chemical transformations, we became intrigued with the possibility of an *electrochemical* oxidation

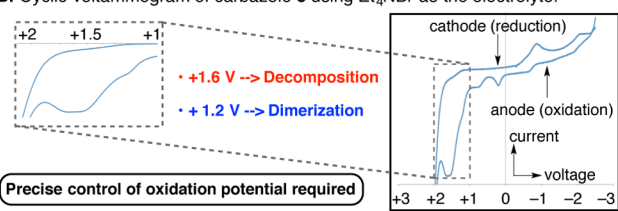
Received: February 7, 2014

Published: April 3, 2014

A. Chemical oxidative N–N dimerization fails.



B. Cyclic voltammogram of carbazole **5** using Et₄NBr as the electrolyte.



C. Optimization of electrochemical dimerization of carbazole.

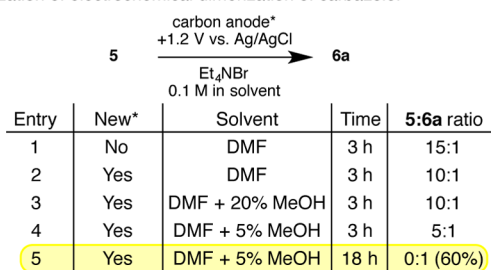
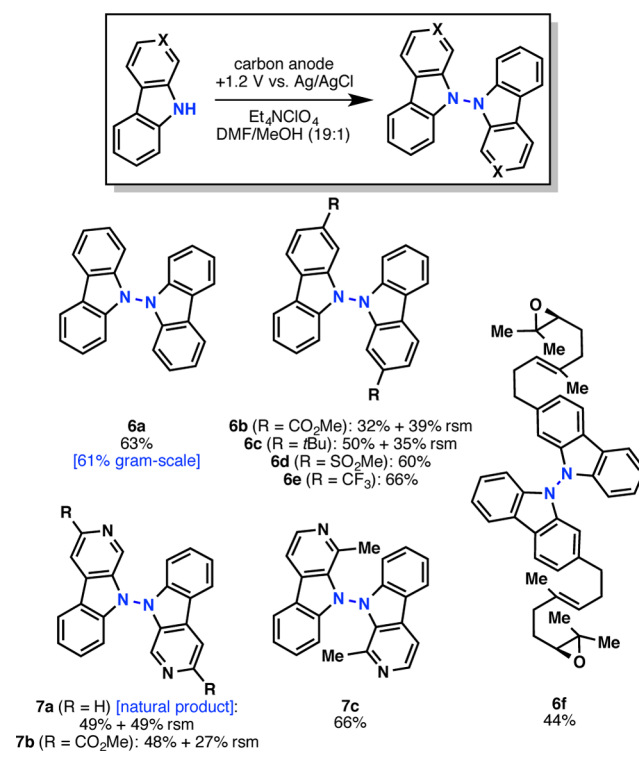


Figure 2. Development of the N–N dimerization reaction of carbazole **5**.

leading to dimerization.⁷ Specifically, we were drawn to investigations into the reactivity of carbazolium radical ions by Ambrose and co-workers.^{7a} These studies explored the dimerization of 3-substituted and 3,6-disubstituted carbazoles at N, C3, and C6 but lacked information regarding other substitution patterns or functional group tolerance. This tactic would have inherent advantages such as the absence of reagents and a chemoselectivity that can be “dialed in” by running the reaction at the exact potential required for dimerization.⁸ Examination of the cyclic voltammogram of **5** provided insight into the inability of chemical oxidants to selectively deliver the desired dimerization mode. As shown in Figure 2B, when a sample of **5** is subjected to potentials above +1.6 V, extensive decomposition is observed, while experiments employing a constant potential below +1.1 V result in low conversion. Gratifyingly, subjecting carbazole **5** to electrochemical oxidation in DMF–Bu₄NBr at a potential of +1.2 V led to ca. 5% conversion to **6a**, along with unreacted **5** (Figure 2C, entry 1). Employing a new carbon electrode⁹ and introducing a small amount of methanol¹⁰ further improved conversion to ca. 17% (entry 4), while extending the reaction time to 18 h led to complete consumption of starting material and 60% isolated yield of **6a** (entry 5; structure verified by X-ray crystallographic analysis, matching the known structure present in the Cambridge Crystallographic Data Centre).

In order to test the generality of these reaction conditions, N–N dimerization reactions of several simple carbazole derivatives were evaluated (Table 1). These results indicate that a variety of substituents at C2 are tolerated, including an ester (**6b**), an alkyl group (**6c**), and a sulfone bearing acidic

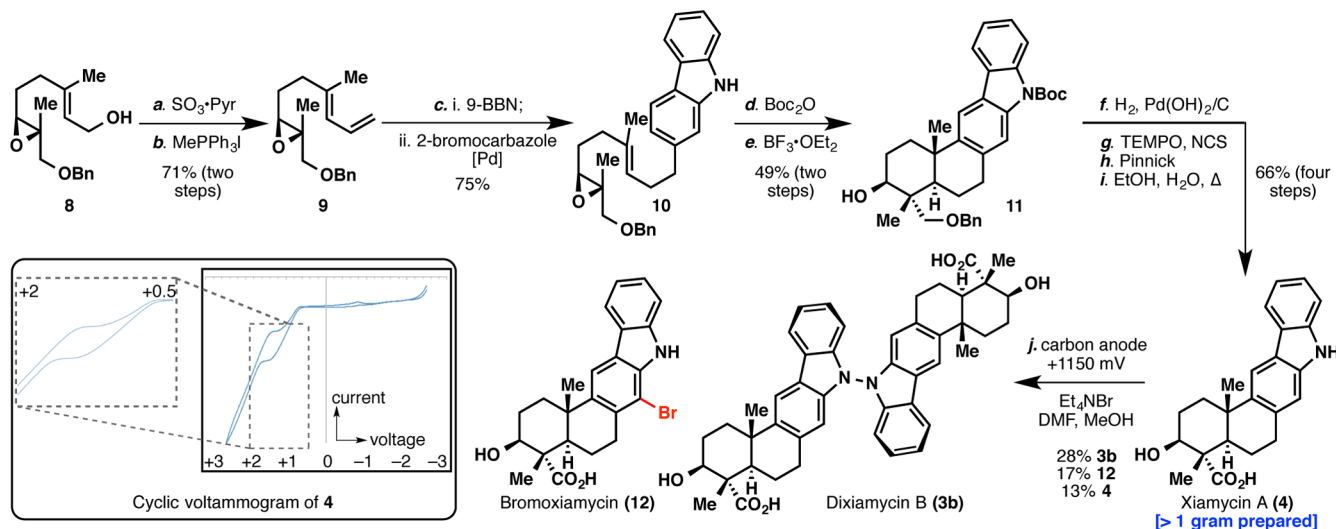
Table 1. Scope of the N–N Dimerization Reaction of Carbazoles and Carbolines



protons (**6d**). Anodic oxidation of the parent carbazole **6a** was accomplished in 63% yield, with virtually no change in isolated yield when conducted on gram scale (61%).¹¹ As a testament to the chemoselectivity of this transformation, the more sensitive epoxy–olefin dimer **6f** was also prepared, a result that would be impossible using an oxidant like KMnO₄ (*vide supra*). Bis-β-carboline products, including the unnamed natural product **7a**,¹¹ could also be prepared in reasonable yields (49% + 49% recovered starting material). Substitution at C1 of the carboline was tolerated (**7c**), indicating that steric crowding about the dimerization site does not inhibit reactivity. In all cases where comparison is possible, electrochemical oxidation is superior to any reported means of effecting this transformation, highlighting the precise control of oxidation potential allowed by electrochemistry.

Having established the feasibility of an electrochemical carbazole N–N dimerization reaction, we pursued the synthesis of xiamycin A (**4**). Following the procedure of Tanis and co-workers,¹³ enantioenriched alcohol **8** was prepared on greater than 10 g scale (Scheme 1). Parikh–Doering oxidation and Wittig olefination afforded diene **9**. Hydroboration/Suzuki coupling with 2-bromocarbazole gave cyclization precursor carbazole **10** in 75% yield on gram scale. Treatment of this substrate with BF₃·OEt₂ resulted in formation of the desired pentacycle **11** in low yield along with several isomers; regioselectivity was improved by N-protection with Boc₂O before the cation–olefin cyclization, resulting in an isolated yield of **11** of 49% (two steps), along with 15% unreacted starting material. Simple hydrogenolysis of the benzyl group, two-step oxidation of the primary alcohol, and Boc deprotection gave xiamycin A (**4**). Using this sequence, more than 1 g of **4** has been synthesized to date.

With substantial quantities of **4** in hand, we next evaluated the key electrochemical reaction of **4**. Analysis of the cyclic

Scheme 1. Total Synthesis of Dixiamycin B (3b) by Electrochemical Oxidation of Xiamycin A (4)^a

^aReagents and conditions: (a) $\text{SO}_3\cdot\text{pyr}$ (3 equiv), Et_3N (4 equiv), DMSO, DCM; (b) MePPh_3I (1.2 equiv), $n\text{-BuLi}$ (1.2 equiv), THF; (c) i. **9** (1.75 equiv), 9-BBN (1.75 equiv), THF, then ii. 2-bromocarbazole (1 equiv), $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.1 equiv), 10% NaOH, 60 °C; (d) Boc_2O (1.2 equiv), Et_3N (1.5 equiv), DMAP (0.1 equiv), THF; (e) $\text{BF}_3\cdot\text{OEt}_2$ (2 equiv), DCM, -78 °C; (f) H_2 (1 atm), $\text{Pd}(\text{OH})_2/\text{C}$ (0.2 wt equiv), MeOH; (g) TEMPO (0.15 equiv), NCS (3 equiv), Bu_4NI (0.15 equiv), DCM, aq $\text{NaHCO}_3/\text{K}_2\text{CO}_3$; (h) NaClO_2 (6 equiv), $\text{NaH}_2\text{PO}_4\cdot\text{H}_2\text{O}$ (10 equiv), 2-methyl-2-butene (10 equiv), $t\text{-BuOH}$, H_2O ; (i) H_2O , EtOH, 100 °C; (j) carbon electrode, +1150 mV, Et_4NBr , DMF, MeOH.

voltammogram of **4** indicated that a potential of +1.2 V would be appropriate (see inset voltammogram). Thus, anodic oxidation of **4** for 1 h afforded small amounts of **3b** alongside substantial recovered starting material and several byproducts. A slight decrease in applied potential (+1.15 V) and an increase in reaction time (4 h) improved the isolated yield to 28%, along with 13% recovered **4**; furthermore, bromoxiamycin **12** was isolated in 17% yield. Given that chloroxiamycin (the chlorinated analogue of **12**) has been isolated,^{2a} it is possible that **12** represents a yet unisolated natural product. Furthermore, attempts to reproduce the procedure of Ambrose^{7a} (a challenge due to the “home-built potentiostat” employed) resulted in no reaction, and attempts to adapt elements of that procedure to our system (addition of collidine) led to comparable results. Interestingly, although we had initially anticipated that any N–N dimerization of **4** would unselectively give a mixture of **3a/b**, analysis of the crude NMR spectrum of the reaction indicated only formation of **3b** along with what appear to be various N–C and C–C dimers. At this stage it is unclear whether **3a** forms under the reaction conditions and rapidly decomposes or **3b** is formed selectively. The observed atropselectivity is complementary to that reported by Zhang and co-workers,^{2a} whereby alongside several side products, trace amounts of **3a** were detected by HPLC analysis of the reaction between **4** and KMnO_4 without detection of **3b**.

Given the infrequent appearance of N–N-linked carbazoles in the literature, several properties of **6a** were investigated. **6a** was found to be stable to acid (excess TFA, 24 h), base (0.5 M KOH, MeOH, 24 h), light (220 nm, 24 h), and even elevated temperature (at 165 °C, $T_{1/2}$ = 8 h). The high stability of **6a** suggests that dimerized carbazoles could represent viable building blocks for potential use in the pharmaceutical, agrochemical, and materials industries.

In summary, a unique method of electrochemical dimerization of carbazoles and carbolines has been reported. This ability to selectively “dial in” oxidation potential has enabled the first

total synthesis of dixiamycin B (**3b**), a rare N–N-linked dimeric natural product. This approach to late-stage N–N bond formation is strategically unique in that it obviates the need for bis-functionalization otherwise required by the use of a hydrazine derivative. Moreover, it is difficult to envision an alternative chemical means of accomplishing this transformation that would compare with the practicality of anodic oxidation. Further studies on electrochemical functionalization of heterocycles for the synthesis of natural products are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental procedures and analytical data (^1H and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by the NIH/NIGMS (GM-073949) and the NSF for a predoctoral fellowship to B.R.R. We are grateful to Pfizer Inc. for a postdoctoral fellowship to A.G.O. We are grateful to Prof. A. Rheingold and Dr. C. E. Moore (UCSD) for X-ray crystallographic analysis, Dr. D.-H. Huang and Dr. L. Pasternack for assistance with NMR spectroscopy, and Dr. Y. Ishihara for helpful discussions.

REFERENCES

- (1) For C3–C3 formation, see: (a) Lebsack, A. D.; Tink, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008–9009. (b) Movassaghi, M.; Schmidt, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725–3728. (c) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238–241. (d) Iwasa, E.; Hamashima, Y.; Fujishiro, S.; Higuchi, E.; Ito, A.; Yoshida, M.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4078–4079. (e) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2716–2719. (f) DeLorbe, J. E.; Jabri, S. Y.; Mennen, S. M.; Overman, L. E.; Zhang, F.-L. *J. Am. Chem. Soc.* **2011**, *133*, 6549–6552. (g) Mitsunuma, H.; Shibasaki, M.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 5217–5221. For N1–C3 formation, see: (h) Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125–128. (i) Newhouse, T.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 10886–10887. (j) Newhouse, T.; Lewis, C. A.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 6360–6361. For C3–C6 formation, see: (k) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 14940–14943. (l) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 5557–5560. (m) Tadano, S.; Mukaeda, Y.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2013**, *42*, 7990–7994. For C3–C7 formation, see: (n) Govek, S. P.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 9468–9469.
- (2) (a) Zhang, Q.; Mándi, A.; Li, S.; Chen, Y.; Zhang, W.; Tian, X.; Zhang, H.; Li, H.; Zhang, W.; Zhang, S.; Ju, J.; Kurtán, T.; Zhang, C. *Eur. J. Org. Chem.* **2012**, 5256–5262. (b) Xu, Z.; Baunach, M.; Ding, L.; Hertweck, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 10293–10297. (c) Baunach, M.; Ding, L.; Bruhn, T.; Bringmann, G.; Hertweck, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 9040–9043. For the isolation of xiamycin A, see: Ding, L.; Münch, J.; Goerls, H.; Maier, A.; Fiebig, H.-H.; Lin, W.-H.; Hertweck, C. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6685–6687.
- (3) For a review on natural products that contain an N–N bond, see: (a) Blair, L. M.; Sperry, J. *J. Nat. Prod.* **2013**, *76*, 794–812. For recent syntheses of molecules containing an N–N bond employing a hydrazine derivative, see: (b) Wang, C.; Sperry, J. *Chem. Commun.* **2013**, 49, 4349–4351. (c) Meyer, F.; Ueberschaar, N.; Hertweck, C. *Eur. J. Org. Chem.* **2013**, 4242–4244. (d) Beveridge, R. E.; Batey, R. A. *Org. Lett.* **2013**, *15*, 3086–3089. (e) Le Goff, G.; Roulland, E.; Ouazzani, J. *Tetrahedron Lett.* **2013**, *54*, 5299–5301.
- (4) (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450–7451. (b) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 609–612. (c) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857–12869. (d) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569. (e) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228. (f) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126–9129. (g) Teng, M.; Zi, W.; Ma, D. *Angew. Chem., Int. Ed.* **2014**, *126*, 1845–1848. (h) Casey, B. M.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2011**, *133*, 11492–11495.
- (5) Bringmann, G.; Tasler, S.; Endress, H.; Kraus, J.; Messer, K.; Wohlfarth, M.; Lobin, W. *J. Am. Chem. Soc.* **2001**, *123*, 2703–2711.
- (6) Perkin, W. H.; Tucker, S. H. *J. Chem. Soc.* **1921**, 216–225.
- (7) (a) Ambrose, J. F.; Carpenter, L. L.; Nelson, R. F. *J. Electrochem. Soc.* **1975**, *122*, 876–894. (b) Bobbitt, J. M.; Kuljarni, C. L.; Willis, J. P. *Heterocycles* **1981**, *15*, 495–516. (c) Berti, C.; Greci, L.; Andruzzi, R.; Trazza, A. *J. Org. Chem.* **1985**, *50*, 368–373. For a related photochemical transformation, see: (d) Balsells, R. E.; Frasca, A. R. *Tetrahedron Lett.* **1984**, *25*, 5363–5366.
- (8) For a review on synthetic applications of anodic electrochemistry, see: (a) Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527–9554. For recent total syntheses featuring electrochemical oxidation, see: (b) Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101–10111. (c) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 36–37. (d) Hughes, C. C.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 3425–3428. (e) Xu, H.-C.; Brandt, J. D.; Moeller, K. D. *Tetrahedron Lett.* **2008**, *49*, 3868–3971.
- (9) Ideal results were obtained with new carbon electrodes; however, electrodes could be reused without any decrease in yield as long as the outer layer was scraped with a razor before reuse. For more information, see the Supporting Information.
- (10) Methanol is likely reduced to methoxide anion at the cathode in this reaction; for more on this mechanistic phenomenon, see ref 8a.
- (11) On larger scales, carbon fiber cloth was used in place of carbon rods. For more information, see the Supporting Information.
- (12) Kearns, P. S.; Coll, J. C.; Rideout, J. A. *J. Nat. Prod.* **1995**, *58*, 1075–1076.
- (13) Tanis, S. P.; Chuang, Y.-H.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929–4938.