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Anodic Coupling Reactions: A Sequential Cyclization Route to the Arteannuin Ring Skeleton

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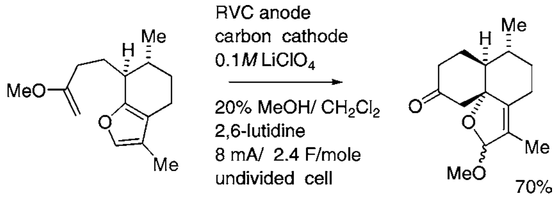
ABSTRACT



A pair of intramolecular anodic olefin coupling reactions has been used to construct the arteannuin ring skeleton. Both coupling reactions took advantage of a furan ring as one of the coupling partners. In the first, it was found that an enol ether derived from an aldehyde was not an effective initiating group for the reaction. Instead, the cyclization benefited strongly from the use of a N,O-ketene acetal initiating group. In the second cyclization, an endocyclic enol ether was coupled to the furan ring. This second electrolysis reaction generated the key tetrasubstituted carbon at the center of the arteannuin ring skeleton.

The anodic coupling of electron-rich olefins to furan rings provides an excellent method for synthesizing new ring skeletons.[1−5] It has been used for the synthesis of alliacol A,[3] the cyathin core ring skeleton,[4] and the synthesis of guanacastepene (Scheme 1).[5] In each case, the key transformation took advantage of the opportunity oxidation reactions offer for triggering interesting new umpolong reactions by coupling the normally nucleophilic carbon α to a carbonyl to a nucleophilic furan ring. The synthesis of guanacastepene accomplished by Trauner and co-workers was particularly noteworthy because of the alternative it offered to more traditional chemical methods that were not successful.[5]

For our part, we have been interested in both demonstrating the generality of the route used for the alliacol A synthesis and probing the reactivity of the radical cation intermediates involved in the cyclizations.[6] With this in mind, the arteannuin family of natural products posed an intriguing synthetic target.[7,8] We envisioned their construction using a pair of electrolysis reactions as outlined in Scheme 2. The first cyclization would illustrate the generality of the electrolysis used in the synthesis of alliacol A. The second would probe both the compatibility of the cyclization with

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(1) For a recent review of the use of electrochemistry in synthesis, see: Sperry, J. B.; Wright, D. L. *Chem. Soc. Rev.* **2006**, *35*, 605.

(2) For general references specifically dealing with oxidative enol ether−furan coupling reactions, see: (a) Moeller, K. D.; New, D. G. *Tetrahedron Lett.* **1994**, *35*, 2857. (b) Moeller, K. D.; Tesfai, Z. *J. Electrochem. Soc. Jpn. (Denki Kagaku)* **1994**, *62*, 1115. (c) New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578−1598. (d) Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Wright D. L. *Org. Lett.* **2002**, *4*, 3763. (e) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 3726. (f) Sperry, J. B.; Wright, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 8034. (g) Sperry, J. B.; Cnstanzo, J. R.; Jasinski, J.; Butcher, R. J.; Wright, D. L. *Tetrahedron Lett.* **2005**, *46*, 2789. (h) Sperry, J. B.; Wright, D. L. *Tetrahedron* **2006**, *62*, 6551.

(3) (a) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 36. (b) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106.

(4) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535.

(5) (a) Hughes, C. C.; Miller, A. K.; Trauner, D. *Org. Lett.* **2005**, *7*, 3425. (b) Miller, A. K.; Hughes, C. C.; Kennedy-Smith, J. J.; Gradl, S. N.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 17057.

(6) For recent work examining the reactivity of the radical cation intermediates involved in anodic olefin coupling reactions, see: Huang, Y.; Moeller, K. D. *Tetrahedron* **2006**, *62*, 6536 and references therein.

(7) For initial characterization studies, see: Sy, L.-K.; Borwn, G. D.; Haynes, R. *Tetrahedron* **1998**, *54*, 4345. For more recent structural and synthetic studies, see: (b) Sy, L.-K.; Cheung, K.-K.; Zhu, N.-Y.; Brown, G. D. *Tetrahedron* **2001**, *57*, 8481. (c) Sy, L.-K.; Zhu, N.-Y.; Brown, G. D. *Tetrahedron* **2001**, *57*, 8495.

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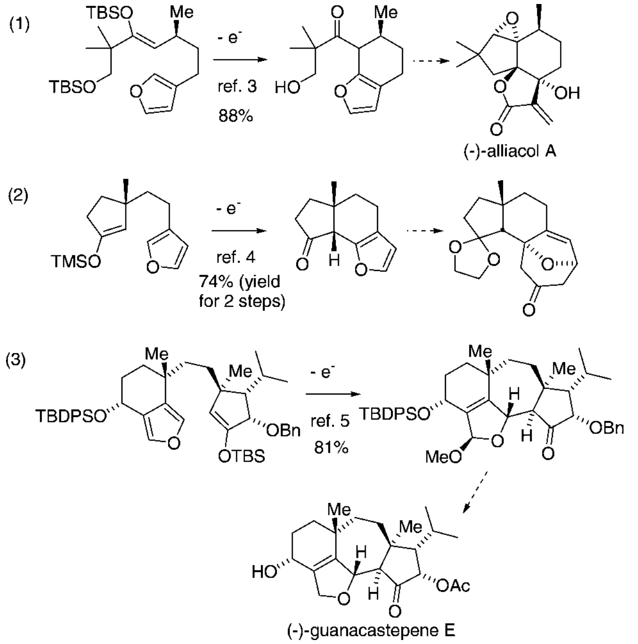
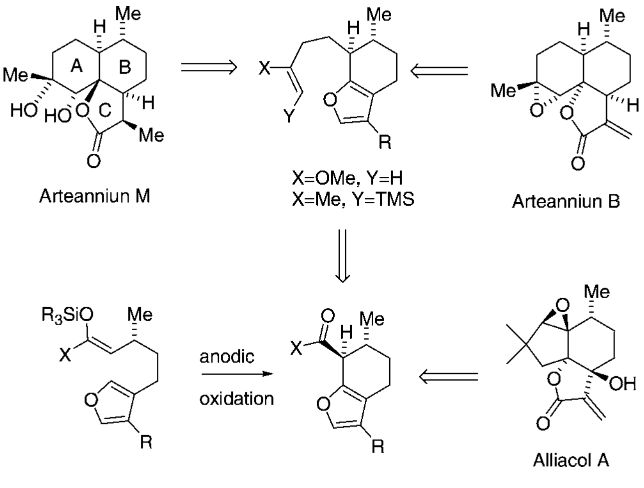
Scheme 1



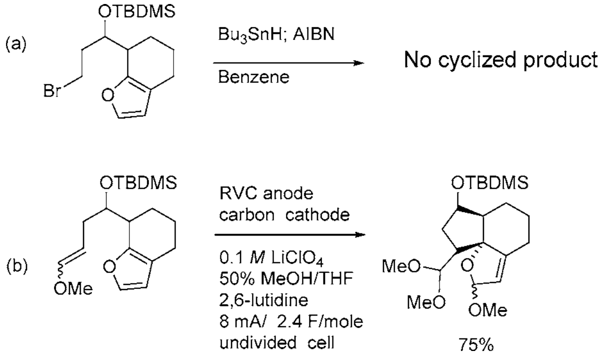
endocyclic enol ethers,[9] as well as determine whether the radical cation intermediate involved in the reaction was reactive enough to overcome the steric barriers associated with constructing the tetrasubstituted carbon at the core of the ring skeleton while making a six-membered ring.

This latter question of radical cation reactivity was of special interest since related radical cyclization reactions proved to be incapable of this transformation. As illustrated in Scheme 3, the radical cyclization to form a five-membered ring product while making the tetrasubstituted carbon and destroying the furan ring failed. The related radical cation initiated cyclization was successful.[3,10,11] Would the radical cation cyclization still be successful when challenged with an endocyclic enol ether and a more difficult to form six-membered ring? We report here the successful completion of both cyclizations and the synthesis of the arteannuin ring skeleton.

Scheme 2



Scheme 3



One of the strengths of our previous synthesis of alliacol A was that the absolute stereochemistry of the molecule was set early with an asymmetric Michael reaction. It was our hope that the same strategy could be employed for a synthesis of the arteannuins (Scheme 4). Due to the sensitivity of electron-rich furans, it was not known whether the best synthetic approach would be to start with a methylated furan or, as in the synthesis of alliacol A, add a methyl group to the five-membered ring derived from the furan late in the synthesis. For this reason, synthetic routes using both the methylated and unmethylated furan were pursued. The syntheses started from bromides **1a** and **1b**. Metalation with *n*-BuLi followed by an alkylation with trimethylene oxide led to the alcohols **2a** and **2b**. The alcohols were then oxidized and submitted to a Horner−Emmons−Wadsworth reaction to afford substrates for the asymmetric Michael reaction. The asymmetry of the Michael reactions was controlled using an oxazolidinone-based chiral auxiliary. In both cases, the reaction afforded the methylated product in greater than 98% de. The resulting imide products were reduced to aldehydes and then converted into the silyl enol ethers needed for the first anodic cyclization.

Anodic oxidation of the nor-methyl substrate proceeded uneventfully using the same electrolysis conditions employed in the earlier alliacol A synthesis.[3] Namely, substrate **4a** was

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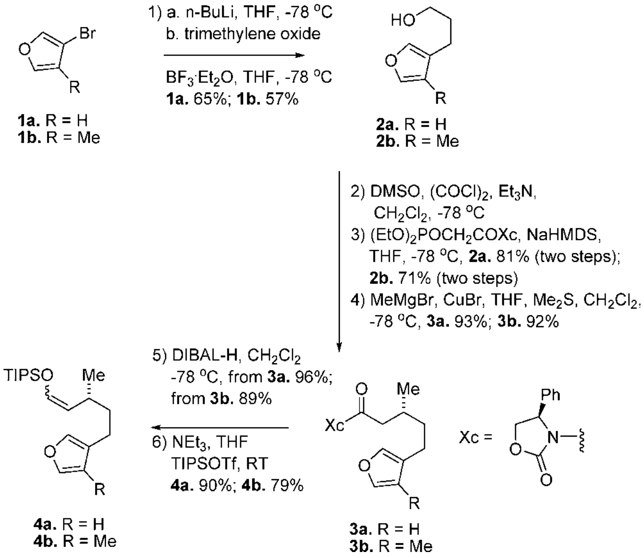
(8) For previous synthetic approaches to the arteanniuns and related molecules, see: (a) Bariault, L.; Deon, D. H. *Org. Lett.* **2001**, *3*, 1925. (b) Sy, L.-K.; Ngo, K.-S.; Brown, G. D. *Tetrahedron* **1999**, *55*, 15127. (c) Nowak, D. M.; Lansbury, P. T. *Tetrahedron* **1998**, *54*, 319. (d) Schwaebe, M.; Little, R. D. *J. Org. Chem.* **1996**, *61*, 3240. (e) Jefford, C. W.; Velarde, J.; Bernardinelli, G. *Tetrahedron Lett.* **1989**, *30*, 4485. (f) Zhou, W. S.; Zhang, L.; Fan, Z. C.; Xu, X. X. *Tetrahedron* **1986**, *42*, 4437. (g) Lansbury, P. T.; Mojica, C. A. *Tetrahedron Lett.* **1986**, *27*, 3967. (h) Xu, X.; Zhu, J.; Huang, D.; Xhou, W. *Tetrahedron* **1986**, *42*, 819.

(9) For a previous anodic olefin coupling reaction utilizing an endocyclic enol ether and a simple olefin trapping group, see: Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372.

(10) For related electrochemical cyclizations forming five-membered rings through the dearomatization of a furan, see: Sperry, J. B.; Ghiviriga, I.; Wright, D. L. *Chem. Commun.* **2006**, *2*, 194.

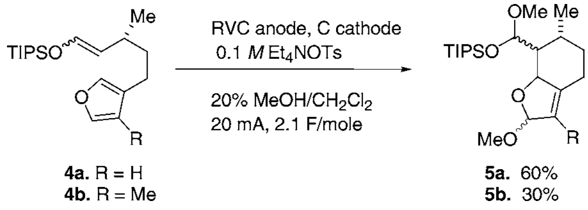
(11) For radical cyclization reactions involving furan rings, see: (a) Parsons, P. J.; Penverne, M.; Pinto, I. L. *Synlett* **1994**, 721. (b) Demircan, A.; Parsons, P. J. *Eur. J. Org. Chem.* **2003**, 1729.

Scheme 4



oxidized in a three-neck round-bottom flask using a reticulated vitreous carbon (RVC) anode, a carbon rod cathode, a 0.1 M tetraethylammonium tosylate in 20% MeOH/CH_2Cl_2 electrolyte solution, and a constant current of 20 mA until 2.1 F/mol of charge had been passed. With no further optimization, the reaction afforded a 60% yield of product as a mixture of stereoisomers (Scheme 5).

Scheme 5

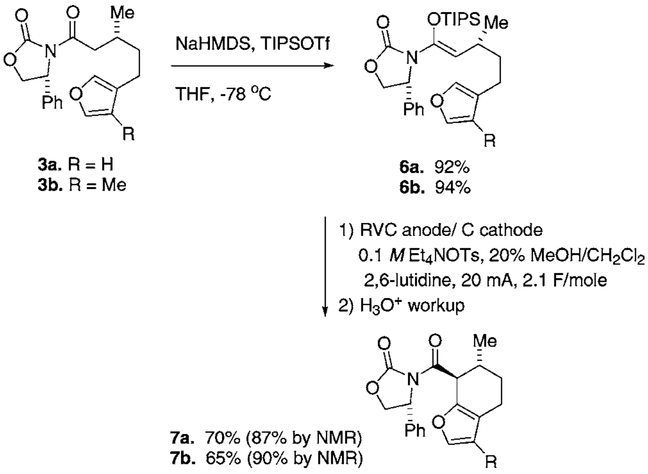


To our surprise, the anodic cyclization originating from the methylated substrate (**4b**) did not proceed well and led to only a 30% isolated yield of the bicyclic product. Apparently, the reaction was not compatible with the more electron-rich furan ring. For comparison, the oxidation potential ($E_{p/2}$) measured for a 3-alkylsubstituted furan such as the one employed in **4a** was +1.64 V vs Ag/AgCl.[12] The oxidation potential ($E_{p/2}$) measured for a 3-alkyl-4-methyl-substituted furan such as the one used in **4b** was +1.46 V vs Ag/AgCl, a value that is competitive with the oxidation potential of the enol ether initiating group ($E_{p/2}$ = +1.44 V vs Ag/AgCl).[6]

The conclusion that the more electron-rich furan ring was problematic for the cyclization was surprising since the reaction conducted by Trauner and co-workers gave a high yield of cyclized product while employing a very similar furan ring. However, the cyclization reaction accomplished by the Trauner group was significantly different in that it used a ketone enol ether as the coupling partner for the furan instead of the aldehyde enol ether employed in **4a** and **4b**. Recently, we found that the nature of the substituents on a radical cation intermediate can have a large influence on its propensity to generate new carbon−carbon bonds.[6] In the cyclization studied by the Trauner group, was the extra substituent on the enol ether relative to **4b**, and hence the higher electron density of the subsequent radical cation responsible for the success of the cyclization? If so, then could the problems arising during the cyclization of **4b** be circumvented with the use of a more electron-rich olefin coupling partner? While the proposed synthesis of the arteannuins was not amenable to the use of a ketone enol ether, it was ideally suited for the use of a more electron-rich N,O-ketene acetal initiating group. N,O-Ketene acetals have proven to be outstanding initiating groups for the formation of carbon−carbon bonds in anodic olefin coupling reactions and have a significantly lower oxidation potential ($E_{p/2}$ = +1.15 V vs Ag/AgCl) than either of the furan rings used in **4a** or **4b**.[6]

In order to take advantage of a ketene acetal initiating group, the overall synthetic scheme was modified so that reduction of the imide product from the Michael reaction was conducted following the initial electrochemical cyclization. To this end, the Michael products **3a** and **3b** were converted into ketene acetals **6a** and **6b** as illustrated in Scheme 6.

Scheme 6



Anodic oxidation of both **6a** and **6b** using the same reaction conditions employed above led to excellent yields of the desired bicyclic product. Little difference was observed between the reactions. An NMR spectrum of each crude reaction mixture showed that both cyclizations proceeded in a very clean fashion with yields in the neighborhood of 90% as measured by integration versus an internal standard.

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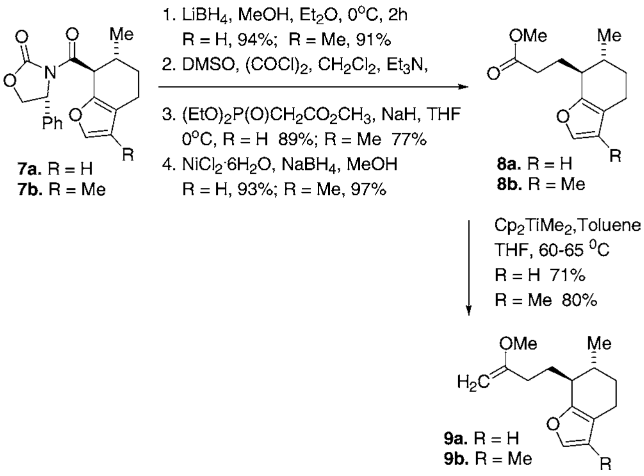
[12] CVs were run using a Pt anode and a Ag/AgCl reference electrode from BAS. All CVs were run with a scan rate of 25 mV/s, a 0.1 M $LiClO_4$ in acetonitrile electrolyte solution, and a 0.025 M concentration of substrate.

Clearly, use of the more electron-rich N,O-ketene acetal solved the problems associated with the additional methyl group on the furan ring.

The cyclized products were sensitive to the acid used in the workup to both wash away the 2,6-lutidine used as a proton scavenger in the reactions and regenerate the furan ring from the initially formed methanol trapping product.[3,4] Current efforts to optimize the reactions further are focusing on working-up the reactions while minimizing acid.

Once the bicyclic products were available, they were converted into substrates for the second anodic cyclization (Scheme 7). To this end, the imide was reduced to an alcohol, and then the alcohol oxidized to an aldehyde. A Horner–Emmons–Wadsworth reaction was used to construct an enoate. Selective hydrogenation of the enoate double bond and conversion of the ester to an enol ether using the Petasis reagent[13] afforded the electrolysis substrates **9a** and **9b**.

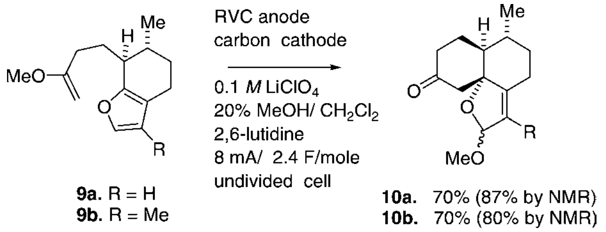
Scheme 7



Anodic oxidation of both substrates **9a** and **9b** led to excellent yields of the tricyclic product (Scheme 8). In both cases, an NMR of the crude reaction product showed that the cyclization afforded the desired product in greater than 80% yield. The methyl group did not appear to make any difference in the cyclization. Of course, the substrate did employ the use of a ketone enol ether. Neither the endocyclic enol ether, formation of the tetrasubstituted carbon, nor the need to form a six-membered ring presented a problem for the cyclizations.

Once again, the isolated yields for the product appeared to be sensitive to the amount of acid used in the workup. In this case, the cyclizations also benefited from a shift in the electrolyte used to lithium perchlorate. This change helped with the isolation of the product because of the greater water solubility of the perchlorate salt.

Scheme 8



The compatibility of the reactions with the simultaneous formation of the tetrasubstituted carbon and a six-membered ring in light of the failure of related radical cyclizations leading to five-membered rings once again highlighted the greater reactivity associated with the enol ether radical cation.[14]

A comparison of the two routes to the arteannuin skeleton, one with the methyl substituent on the furan and one without, suggests that both are feasible and worthy of further attention. The route including the methyl on the furan removes the need to add this carbon late in the synthesis. However, the presence of the methyl group does make the furan more sensitive and harder to handle. Therefore, it may be best to add the methyl group after the furan ring has been used to assemble the tricyclic core of the natural product. Of course, such a conclusion can be dramatically altered by the success of the reactions needed to add the carbon to the furanone late in the synthesis. For the time being, both routes are being pursued.

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Supporting Information Available: A sample experimental procedure is included for the oxidation reaction along with characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Petasis, N. A. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley: New York, 2004; Vol. 1, p 427.

(14) Horner, J.; Taxil, E.; Newcomb, M. *J. Am. Chem. Soc.* **2002**, *124*, 5402.