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COMMUNICATIONS

Published on Web 12/05/2002

Anodic Cyclization Reactions: The Total Synthesis of Alliacol A

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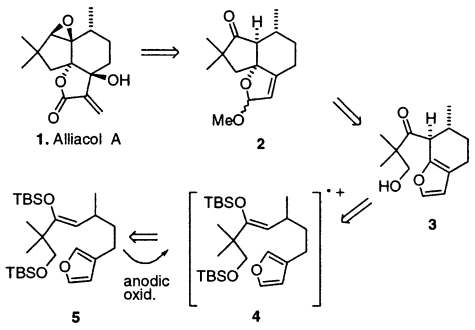
Anodic electrochemistry would appear to hold great promise as a tool for constructing organic molecules[1] because it can be used to reverse the polarity of known functional groups, thereby triggering interesting new umpolung reactions. Yet, despite numerous successes,[2] the use of anodic electrochemistry remains a vastly underutilized tool. Why? At least part of the reason appears to be a lack of examples where electrochemical methods have been employed in total synthesis efforts. Take, for example, the intramolecular anodic olefin coupling reaction. While a series of studies have demonstrated that the method can effectively make carbon−carbon bonds in model systems,[3] the reactions have not been utilized in a completed total synthesis.[4−6] Such efforts are important because they play a key role in demonstrating the overall utility of any new synthetic method, as well as in illustrating how and when the method can best be employed. For this reason, we have undertaken an effort to demonstrate the utility of anodic electrochemistry by exploiting intramolecular anodic olefin coupling reactions, and the insipient radical cations generated, as tools for synthesis. In this paper, we demonstrate how an anodic cyclization reaction can be used to provide a novel route to the tricyclic natural product alliacol A.[7,8]

Our retrosynthetic plan for the synthesis of alliacol A (**1**) is outlined in Scheme 1. This plan called for construction of the core tricyclic ring skeleton of the natural product using a sequential anodic cyclization/Friedel−Crafts alkylation strategy. In this approach, the anodic cyclization would be used to trigger an umpolung reaction where the normally nucleophilic β-carbon of an enol ether would be coupled to a nucleophilic furan ring.[4,9] This reaction would proceed by the generation and subsequent trapping of a radical cation intermediate (**4**), although it is not clear in this substrate whether the radical cation would initially be formed from the enol ether or the furan ring. In either case, bicyclic product **3** would be generated, and the stage would be set for an intramolecular Friedel−Crafts alkylation reaction that would in turn complete the synthesis of the required tricyclic skeleton (**2**).

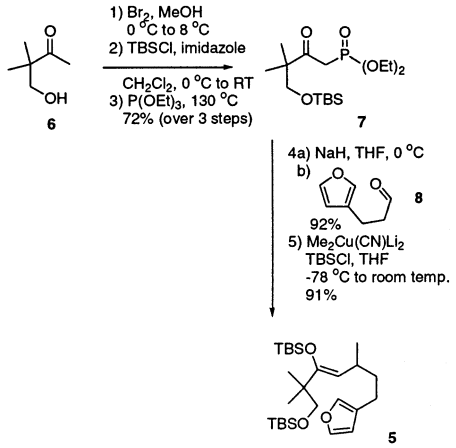
The synthesis began with the construction of the necessary electrolysis substrate (Scheme 2). To this end, bromination of the methyl carbon α to the ketone, protection of the alcohol, and then treatment of the resulting product with triethyl phosphite converted the known hydroxy ketone **6**[10] into phosphonate ester **7**. A Horner−Emmons−Wadsworth reaction using the known aldehyde **8**[9b] led to the formation of an enone that was then converted into the desired substrate using a Michael reaction.

Once synthesized, substrate **5** was oxidized in an undivided cell using a reticulated vitreous carbon anode (RVC), a carbon cathode, a 0.4 M $LiClO_4$ in methanol/dichloromethane (1:4) electrolyte solution, 2,6-lutidine as a proton scavanger, and a constant current of 15−20 mA (Scheme 3).[11] The reaction was run until 2.2 F/mol of charge had been passed. Following the oxidation, toluenesulfonic acid was added to the mixture, and the reaction was allowed to stir for 2 h. This subsequent acid step was necessary to eliminate methanol from the initially formed bicyclic product. An 88% isolated yield of the desired product **3** was obtained from the sequence. As expected, the product had trans stereochemistry with respect to the two substituents on the six-membered ring. It was not clear whether this stereochemical arrangement was obtained during the electrolysis reaction or during the subsequent acidic formation of the furan. Once **3** was obtained, the alcohol was treated with iodine in the presence of triphenylphosphine, and the resulting alkyl iodide was treated with silver nitrate to effect the

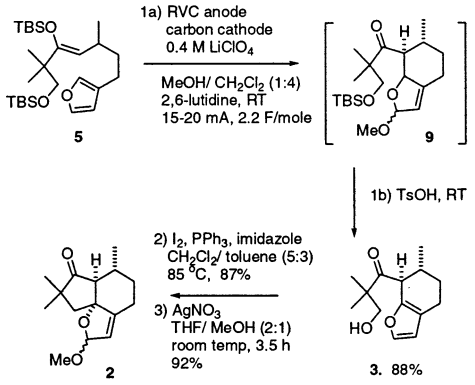
Scheme 1



Scheme 2

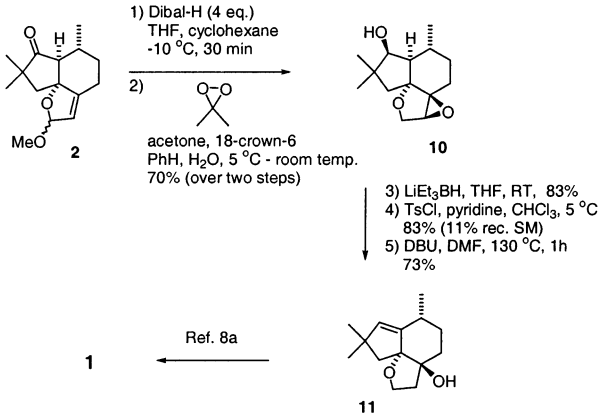


Scheme 3



10.1021/ja029064v CCC: $25.00

Scheme 4



Friedel−Crafts alkylation reaction and form the tricyclic core of the natural product.

In connection with this sequence, it is important to note that the electrochemical cyclization reaction did not require the use of specialized equipment. When the electrolysis reaction was repeated using a 6 V lantern battery as the power supply,[12] an 82% isolated yield of product **3** was obtained. In this case, the electrolysis reaction was monitored by TLC and run until no further starting material remained. All other conditions were identical to those of the previous oxidation. In this manner, 296 mg of the substrate was oxidized in approximately 90 min.

Initial plans for converting **2** into alliacol A were to utilize the ketone to generate the epoxide in the product while capitalizing on the lactol functionality obtained in the cyclization to assemble the lactone ring of the product. However, efforts along these lines were impeded by difficulties associated with both the reactivity of the lactol or lactone ring and the inability to introduce a double bond into the A-ring of the natural product before establishing the bridgehead hydroxyl group of the final product. For this reason, the synthesis of alliacol A was completed by converting the tricyclic product **2** to compound **11** (Scheme 4). Compound **11** had previously been transformed to alliacol A by Lansbury, Le Clair, and co-workers in just three steps.[8a] To accomplish the conversion of **2** into **11**, the ketone in **2** was reduced with diisobutylaluminum hydride. The reaction proceeded in a highly stereoselective fashion (only one isomer was observed) while also reducing the acetal group in the molecule. A stereoselective epoxidation of the olefin afforded intermediate **10**. Reductive opening of the epoxide, selective tosylation of the secondary alcohol, and an E_2-elimination then afforded the desired **11**.

Two aspects of this sequence deserve further comment. First, the selective tosylation reaction (Scheme 4, reaction 4) was complicated by elimination of the bridgehead alcohol. However, the side reaction could be avoided if the reaction was not pushed to completion. For this reason, the tosylation was allowed to proceed at 5 °C until it was about 38% complete. At that point, the starting material was separated and then reexposed to the reaction conditions. After four such cycles, an 83% isolated yield of the desired product could be obtained along with 11% of the recovered diol starting material. Second, while it was initially bothersome to reduce the acetal functionality in **2** knowing that a lactone was needed at the same position in the final product, the sequence of steps utilized in Scheme 4 is actually shorter than an alternative route that would preserve the acetal functionality. Because the acetal was reduced at the same time as the required reduction of the ketone, and the carbonyl of the lactone can be introduced into **11** in a single step,[8a] the approach taken adds only one step to the overall synthesis. An alternative that would preserve the acetal would later require a two-step deprotection−oxidation sequence to generate the lactone.

In conclusion, a sequential anodic cyclization−Friedel−Crafts alkylation strategy has been used to rapidly assemble the core ring skeleton of alliacol A. The electrochemical reaction allows for the coupling of two nucleophiles: a silylenol ether and a furan ring. The cyclization proceeded in high yield, did not require the use of specialized equipment, and led to a product that contained all of the carbons and functional groups necessary for rapidly completing the synthesis of the natural product. Efforts are now underway to utilize the route developed to complete the first asymmetric synthesis of alliacol A.

Acknowledgment. We thank the National Science Foundation (CHE-9023698) for their generous support of this work. We also gratefully acknowledge the Washington University High Resolution NMR facility, partially supported by NIH grants RR02004, RR05018, and RR07155, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.

Supporting Information Available: Experimental procedures along with characterization data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA029064V