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Electro-oxidative Annulations with Furans in Natural Product Synthesis

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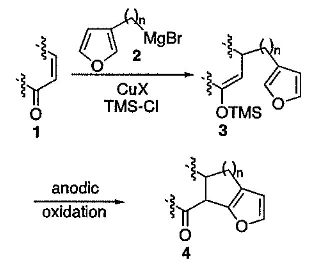
Simple furan derivatives are readily available, highly reactive and can serve as direct precursors to a wide range of different structural moieties. Because of this high degree of synthetic flexibility, furans have frequently been employed in the total synthesis of natural products. Furan can serve as a synthon for the difficult to prepare 1,4-dicarbonyl functionality though hydrolytic or oxidative ring opening. Cycloaddition chemistry can be used to convert a furan to six and seven-membered ring following opening of the ether bridge.

Application of these types of reactions to annulated furans would be expected to produce much more complex systems than those routinely prepared from simple furan derivatives. Although the synthesis of annulated furans has been the focus of several investigations and have found some use in total synthesis, general methods for their construction are lacking. We have been interested in developing simple methodologies for the rapid assembly of annulated furans for use in the synthesis of terpenoid natural products. Along these lines, we envisioned a two-step sequence involving the initial conjugate addition of a furyl appended organometallic **2** to an α,β-unsaturated carbonyl compound **1** with *in situ* silylation to deliver an intermediate silyl enolether **3** (Scheme 1). The second step of the ring-forming procedure would involve the coupling of the α-carbon of the enolether to the 2-position of the pendant heterocycle. Anodic oxidation directly produces **4** in very good yields. This overall process is an oxidation and involves the formal loss of an equivalent of hydrogen. The ring-closure involves the coupling of two nucleophilic carbons and requires an umpolong of one of these carbons to an electrophilic species through oxidation.

The reaction was shown to be quite general for the formation of six-membered rings in good yields and was tolerant of a variety of different functional groups. The ring closure was highly stereoselective, leading to the formation of *cis*-fused systems. Cyclic voltammetry and probe molecules were used to gain mechanistic insight into the reaction. These studies suggested that the key ring closure involved an initial oxidation of the silyl enolether to a radical cation followed by a furan terminated cyclization. These polycyclic furan derivatives can serve, through transformation of the furan, as important precursors to terpenoid natural products such as erinacine C, celafolin A-1 and sarcodictyin (Figure 1). Details about the electrochemical annulation and progress on the synthesis of these terpenoid targets will be discussed.



Scheme 1. Synthesis of annulated furans

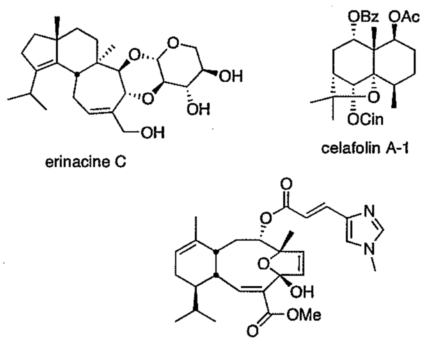


Figure 1. Natural product targtes for annulated furans