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Anodic cyclization reactions and the synthesis of (−)-crobarbatic acid

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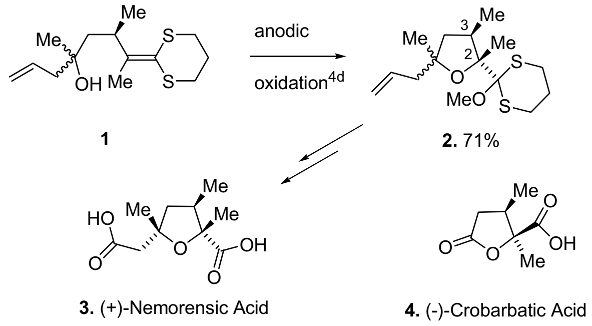
Abstract

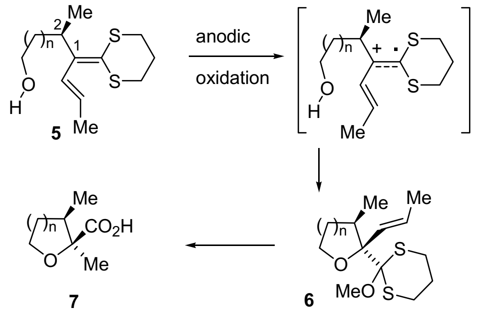
A synthesis of (−)-crobarbatic acid is reported along with the first use of a vinyl-substituted ketene dithioacetal as a coupling partner for an anodic cyclization reaction. The use of the vinyl-substituted ketene dithioacetal enables the construction of a cyclic product having a tetrasubstituted carbon with a relative stereochemistry opposite to that originally obtained from the cyclization.

Anodic olefin coupling reactions convert electron-rich double bonds that normally serve as nucleophiles into highly reactive radical cation intermediates that are in turn trapped by other nucleophiles.[1–3] The reactivity of the radical cation enables the reactions to generate a variety of quaternary and tetrasubstituted carbons.[4] For example, an anodic olefin coupling reaction between a ketene dithioacetal and an oxygen nucleophile was used in the synthesis of (+)-nemorensic acid (**3**) in order to generate the tetrasubstituted carbon at C_2 of the natural product (Scheme 1).[4d] In this reaction, the stereochemistry of the tetrasubstituted carbon was controlled by sterics with the large dithioorthoester group winding up trans to the methyl substituent at C_3. While the electrolysis reaction illustrated was ideal for synthesizing nemorensic acid, the natural propensity for the reaction to place the dithioorthoester trans to the methyl group at C_3 meant that an alternative synthetic route was needed to synthesize molecules like crobarbatic acid **4** that have the opposite relative stereochemistry at C_2.[5,6]

One method for solving this problem would be to incorporate functional groups into the electrolysis substrate that would allow for manipulation of product stereochemistry following the cyclization. For example, consider the chemistry outlined in Scheme 2. In this case, a vinyl-substituted ketene dithioacetal would be employed in the electrolysis reaction in order to afford product **6**. A net oxidation of



Scheme 1.



Scheme 2.

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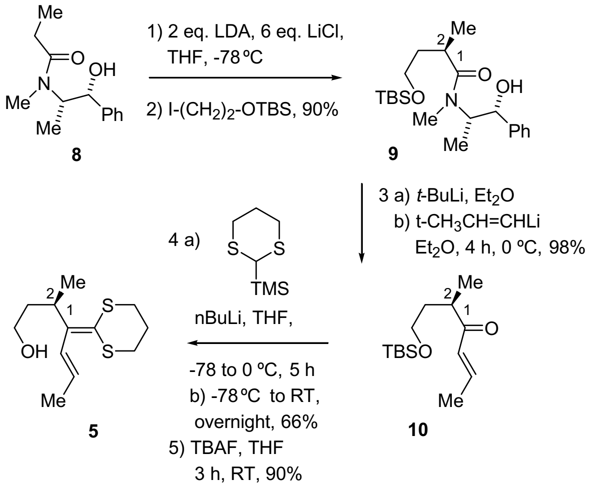
the olefin in **6** to a carboxylic acid and reduction of the orthoester to a methyl group would afford a product (**7**) with a tetrasubstituted carbon stereochemically opposite to that obtained in the nemorensic acid synthesis and ideal for synthesizing crobarbatic acid.

The choice of the vinyl-substituted ketene dithioacetal in this route appeared ideal because the vinyl group would be compatible with the synthesis of the ketene dithioacetal in **5**, would aid the subsequent anodic oxidation reaction by stabilizing the radical cation generated, and would nicely mask the carbonyl needed in the final product. Additionally, there was the attractive possibility that the vinyl group could be cleaved to form an acid in the same step used to convert a tetrahydrofuran product like **6** or **7** into the lactone needed for crobarbatic acid. However, it was also possible that the vinyl substituent on the radical cation intermediate might significantly alter the reactivity of the radical cation and prevent the cyclization. Certainly, earlier cyclization reactions were dramatically altered by the nature of a substituent bound to the radical cation.[4a]

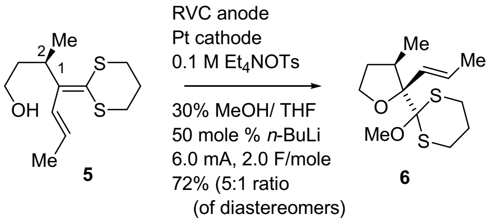
In order to address this question, the electrolysis substrate **5** was synthesized as outlined in Scheme 3.

The synthesis began with an alkylation of the known psuedoephedrine amide **8**.[7] Following the alkylation reaction, amide **9** was treated with one equivalent of *t*-BuLi to deprotonate the alcohol followed by 1-lithio-1-propene in order to form ketone **10**. The ketone was then converted into the ketene dithioacetal moiety needed for the electrolysis reaction using a Peterson olefination. In addition to the 66% yield of product obtained for the reaction, the Peterson olefination also led to a 31% yield of a 1,4-addition product. Finally, the silyl ether was deprotected using tetrabutylammonium fluoride.

With electrolysis substrate **5** in hand, we set out to determine if the vinyl substituent would interfere with the anodic cyclization reaction. Initially, reaction conditions identical to those used for oxidizing substrate **1** were employed.[4d] To this end, a constant current of 8 mA was passed through the cell using a reticulated vitreous carbon (RVC) anode and Pt cathode until 1.6–1.8 F/mol of charge had been passed. The reaction used a 0.1 M tetraethylamonium tosylate in 30% methanol/THF electrolyte solution and 2,6-lutidine as an acid scavenger. Using these conditions, a 57% isolated yield of product **6** was obtained as a 5:1 ratio of diastereomers (the major product is shown in Scheme 4). The yield of the reaction could not be raised by passing more current through the cell even though a stoichiometric amount of current (2 F/mol) was not consumed and some starting material was recovered. Additional current led to the consumption of the remaining starting material, but not increase in the amount of product isolated.



Scheme 3.

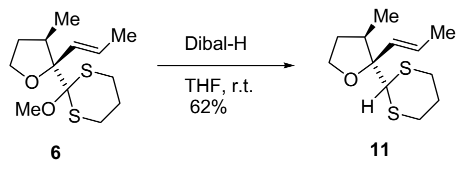


Scheme 4.

Fortunately, both the yield and cleanliness of the reaction could be improved by changing the base used as the acid scavenger in the reaction. While the electrolysis reaction as a whole is neutral, acid is generated at the anode and base at the cathode (the cathodic reaction involves the reduction of methanol). Conducting the reaction in a basic medium accelerates the rate at which the acid generated at the anode is neutralized. This serves to protect acid-sensitive oxidation substrates as they approach the anode. In the present reaction, replacing the 2,6-lutidine previously used with LiOMe (generated by adding 50 mol % of *n*-BuLi to the solution prior to the electrolysis) increased the effectiveness of this process and led to the generation of a 72% isolated yield of **6** (Scheme 4).

In analogy to earlier cyclization reactions (Scheme 1), the major stereoisomer obtained from the anodic oxidation had the large orthoester group in a position trans to the methyl at C_2. This stereochemical assignment was made using a NOESY experiment following the reduction of the electrolysis product to a dithioacetal with Dibal-H (Scheme 5).[8] The conversion of **6** to **11** was done in order to simplify the separation of the two stereoisomers.

In addition to assigning the relative stereochemistry of the product, a check was made to determine if the molecule

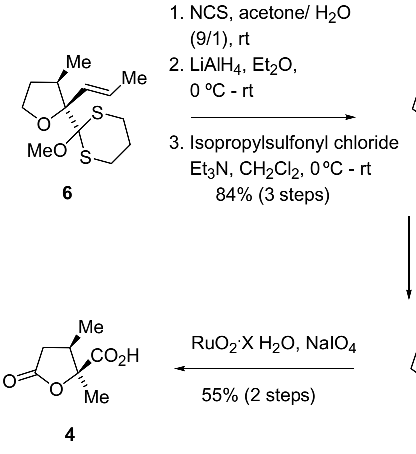


Scheme 5.

had racemized the stereogenic atom at C_2 during either the reaction to form the ketene dithioacetal or the electrolysis reaction. This was accomplished by comparing the major isomer of **11** with racemic material that was independently synthesized. HPLC analysis using a chiral stationary phase (CHIRALPAK®ADH) showed product **11** to have a enantiomeric excess greater that 97%, a value consistent with the alkylation reaction to form **9**.[7] No racemization had occurred.

While it was clear that the vinyl substituent had not interfered with the cyclization, the question remained as to whether its use would enable the synthesis of a product having the relative stereochemistry found in crobarbatic acid. Initial attempts to address this issue focused on the earlier reports that dithianes can be selectively reduced in the presence of an olefin.[9] Such a reduction would allow for conversion of the ortho ester into a methyl group followed by oxidative cleavage of the olefin and formation of a product with the correct C_2 stereochemistry for crobarbatic acid. However, with **11** this approach failed. Attempts to reduce the dithioacetal led to either incomplete reduction and the formation of thioethers or competitive reduction of the double bond.

For this reason, a different tact was taken (Scheme 6). An *N*-chlorosuccinimide-assisted hydrolysis of the dithiane moiety in **6** led to the formation of a methyl ester that was subsequently reduced with $LiAlH_4$ to afford an alcohol. Conversion of the alcohol to the isopropylsulfonyl ether (**12**, 84% over three steps) followed by superhydride reduction led to the desired methyl substituent on C_1. The isopropylsulfonyl group was used in this sequence instead of a mesylate because reduction of the mesylate led to only a small amount of the desired product **13** along with recovered alcohol.[10] No such problem occurred with the isopropyl sulfonyl ether. Due to its volatility, compound **13** was difficult to isolate. Therefore, it was carried forward with the use of cat. RuO_4 and $NaIO_4$ in order to generate (−)-crobarbatic acid (**4**) in a 55% yield (from **12**).[5e] During the course of the synthesis, the minor diastereomer from the electrochemical cyclization was 'lost' and only one diastereomer of the product was obtained. The absolute stereochemistry of **4** was established by comparing its optical rotation to the known literature values.[5e]



Scheme 6.

From a synthetic standpoint, the final oxidation step was very satisfying in that it did allow for both the cleavage of the olefin to the acid and the oxidation of the tetrahydrofuran ring in a single step. Interesting, this transformation did not proceed well unless both oxidations were conducted at the same time. The use of either a substrate having the lactone already in place or a substrate having the olefin already oxidized to the acid led to a reaction that failed to oxidize the group remaining in the reduced form.

In conclusion, we have developed a flexible synthetic approach to substituted anodic cyclization substrates. The route was used to study an anodic cyclization involving a vinyl-substituted radical cation intermediate. The electrolysis reaction proceeded nicely, and the product was converted into (−)-crobarbatic acid thereby illustrating the utility of the overall strategy for synthesizing products having relative stereochemistries opposite to that originally afforded by the cyclization. The route to the electrolysis substrate should allow us to probe the generality of anodic cyclization reactions for assembling a variety of functionalized molecules containing highly hindered tetrasubstituted carbons. While the approach was illustrated here using an oxygen trapping group for the radical cation, it should be compatible with a variety of carbon-based nucleophiles and the construction of new quaternary carbons.[4] Work along these lines is underway.

Acknowledgments

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