



Intramolecular Anodic Olefin Coupling Reactions: The Construction of Bridged Bicyclic Ring Skeletons

S. Hari Krishna Reddy and Kevin D. Moeller*

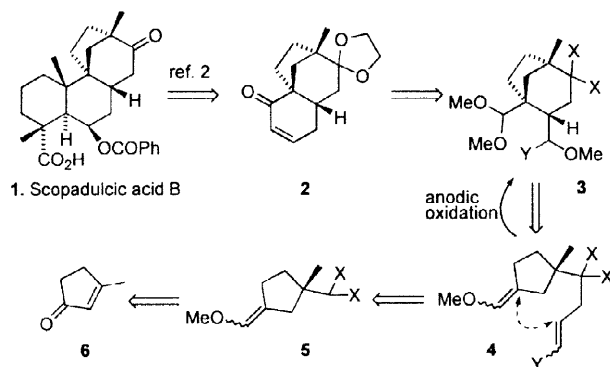
Department of Chemistry, Washington University, St. Louis MO 63130

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Abstract: Intramolecular anodic olefin coupling reactions have been used to construct both bicyclo[3.2.1]octane and bicyclo[2.2.1]heptane ring systems. The effect of substituents on the stereochemistry about the newly generated carbon-carbon bond was examined. © 1998 Elsevier Science Ltd. All rights reserved.

Scopadulcic acid B is a natural product with a broad range of biological activity.^{1,2} Its tetracyclic ring skeleton features a bicyclo[3.2.1]octane ring skeleton with a central quaternary carbon. Bicyclo[3.2.1]octane ring skeletons are commonly found in biologically relevant natural products and have been the focus of numerous synthetic studies,³ but few of these studies have utilized oxidative cyclization reactions to construct the bridged bicyclic core of the molecules.⁴ Oxidative cyclizations are potentially important reactions because they generate products that retain the functionality used to initiate the cyclization.⁵ For example, consider the retrosynthetic analysis of scopadulcic acid B outlined in Scheme 1. In this scheme, an intramolecular anodic olefin coupling

Scheme 1



reaction⁶ is used to couple the enol ether in compound 4 to a second electron-rich olefin in order to form both the key quaternary center and the bridged bicyclo[3.2.1]octane ring skeleton found in the final product. In the oxidation the enol ether of the starting material is converted to an acetal group that could then be used in the completion of the synthesis.

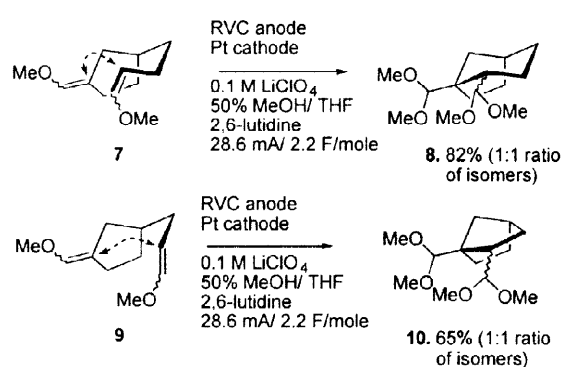
We had previously shown that, similar intramolecular anodic olefin coupling reactions were capable of constructing quaternary carbons with control of relative stereochemistry, and the resulting acetals were used in the synthesis of angularly fused tricyclic ring skeletons.⁷ But can an intramolecular anodic olefin coupling reaction be used to synthesize even more strained bridged bicyclic ring skeletons, or will the additional strain slow the cyclization to a point where decomposition of the radical cation intermediate competes? While radical anions generated from electron-poor olefins have led to the formation of bridged bicyclic ring skeletons,⁸ no such cyclization utilizing a radical cation derived from an electron-rich olefin has been reported. With this in mind, a program to investigate the utility of intramolecular anodic olefin coupling reactions in the synthesis of bridged bicyclic molecules was

undertaken. We report herein that the intramolecular coupling of two enol ethers can be used to synthesize both bicyclo[3.2.1]octane and bicyclo[2.2.1]heptane ring skeletons.

Initially, bis enol ether substrates **7** and **9** were selected for study.⁹ Substrate **7** was considered an ideal model substrate because bis enol ether substrates have consistently led to high yields of cyclized products when oxidized at an anode,^{6d} and because a successful cyclization originating from substrate **7** would lead to the bicyclo[3.2.1]octane ring system needed for the proposed scopadulcic acid B synthesis. Substrate **9** was selected in order to examine what effect the additional strain of forming the bicyclo[2.2.1]heptane ring skeleton would have on the cyclization reaction.

The preparative electrolyses of **7** and **9** were achieved at a reticulated vitreous carbon (RVC) anode using a platinum wire cathode, an undivided cell, a 0.1 M lithium perchlorate in 50% MeOH/THF electrolyte solution, 2,6-lutidine as a proton scavenger, and a constant current of 28.6 mA.¹⁰ A total of 2.2 F/mole was passed. The reactions were run with a substrate concentration of 0.03 M and a scale ranging from 100 to 400 mg. In both cases, the electrolysis conditions were identical (Scheme 2). In the case of **7**, an 82% isolated yield of the desired bicyclo[3.2.1]octane ring product was obtained, whereas oxidation of **9** led to a 65% isolated yield of the desired bicyclo[2.2.1]heptane product. In both cases, the cyclization reaction led to a 1:1 mixture of isomers about the newly formed carbon-carbon bond.

Scheme 2

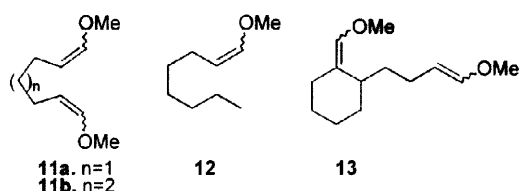


platinum wire cathode, an undivided cell, a 0.1 M lithium perchlorate in 50% MeOH/THF electrolyte solution, 2,6-lutidine as a proton scavenger, and a constant current of 28.6 mA.¹⁰ A total of 2.2 F/mole was passed. The reactions were run with a substrate concentration of 0.03 M and a scale ranging from 100 to 400 mg. In both cases, the electrolysis conditions were identical (Scheme 2). In the case of **7**, an 82% isolated yield of the desired bicyclo[3.2.1]octane ring product was obtained, whereas oxidation of **9** led to a 65% isolated yield of the desired bicyclo[2.2.1]heptane product. In both cases, the cyclization reaction led to a 1:1 mixture of isomers about the newly formed carbon-carbon bond.

As with earlier intramolecular anodic olefin coupling reactions, the cyclizations illustrated in Scheme 2 could be initiated with the use of a 6-volt lantern battery.¹¹ While these cyclizations demonstrated that electrochemical equipment was not needed to explore the potential utility of the reactions, the difference in yield between the two coupling reactions was much more pronounced when the less sophisticated reaction setup was utilized. When the anodic oxidation of **7** was repeated using the 6V-lantern battery (all of the other conditions were identical), a 70% isolated yield of the bicyclic product was obtained. This cyclization was clearly compatible with the use of the battery. However, the oxidation of **9** using the battery power supply did not fare as well and led to only a 33% isolated yield of the bicyclo[2.2.1]heptane ring product.

It was tempting to suggest that the lower yield of product obtained from **9** was due to the strain of the bicyclo[2.2.1]heptane ring skeleton causing the cyclization reaction to be slower. This would allow more time for the radical cation intermediate to decompose. However, this suggestion was not consistent with cyclic voltammetry data obtained for the two substrates. For a reaction that involves an electrochemical oxidation (or reduction) followed by a very fast chemical reaction, the potential measured for a substrate depends on the rate of the chemical reaction. For an oxidation reaction, a fast chemical step following the electron transfer lowers the potential

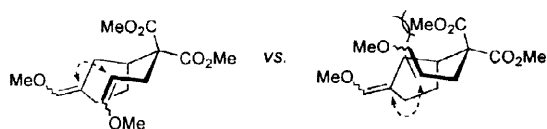
measured for the substrate. Intramolecular anodic olefin coupling reactions between enol ethers have typically shown this behavior.^{6d} For example, the oxidation potential measured for bis enol ether substrate **11a** was *ca.* 200 mV lower than the potential measured for methyl enol ether derived from heptanal (**12**).^{6d,12} The potential obtained for substrate **11b** leading to a six-membered ring product was *ca.* 100 mV lower than the potential measured for **12**,



suggesting that the six-membered ring cyclization was slower than the five-membered ring cyclization as expected. The oxidation potential for **13** was 150 mV lower than the potential measured for the methyl enol ether derived from cyclohexanone in spite of the generation of a new quaternary carbon. In the current study, the $E_{p/2}$ values (vs. Ag/AgCl) obtained for **7**, **9**, and 1-methoxymethylidene cyclopentane were +1.13 V, +1.10 V, and +1.14 V respectively. The closeness of the potentials measured for both **7** and **9** to the parent 1-methoxymethylidene cyclopentane indicated that neither cyclization reaction proceeded at a rate equivalent to the previous cyclization reaction that had generated a quaternary carbon (**13**). Presumably, this was due to the strain of the ring system being synthesized following the oxidation of **9** and the formation of a six-membered ring following the oxidation of **7**. The slightly lower potential measured for **9** indicated that the radical cation derived from **9** cyclized faster than the radical cation derived from **7**. Evidently, the formation of a six-membered ring slows the cyclization down to greater extent than does the added strain of the bicyclo[2.2.1]heptane ring skeleton.

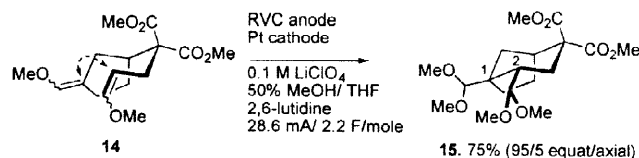
Finally, substrate **14** was studied in order to determine if substituents on the chain connecting the olefins

Figure 1

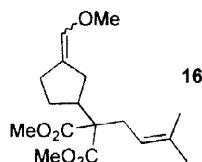


would allow for stereocontrol of the groups surrounding the newly generated carbon bond. In this example, it was hoped that the presence of an axial ester group in the transition state of the cyclization would force the disubstituted enol ether into a equatorial position (Figure 1). This proved to be the case. The oxidation of **14** led to a 75% isolated yield of a bicyclo[3.2.1]octane product having a 19:1 ratio of isomers about the newly formed carbon-carbon bond (Scheme 3). The major product was assigned as having the C2 dimethoxyacetal substituent in an equatorial position by examining proton NMR coupling constants.

Scheme 3



In this assignment, the methine proton at C₂ gave rise to a doublet of triplets in the NMR with $J_d = 12.7$ Hz and $J_t =$



4.0 Hz. Clearly, the 12.7 Hz coupling constant was the result of a trans diaxial coupling, placing the substituent in the equatorial position. Substrate **14** was also studied using cyclic voltammetry. In this case, the $E_{p/2}$ (vs. Ag/AgCl) obtained was +1.15 V. The higher value for the potential relative to earlier cases was a result of the ester substituents on the sidechain. As a

reference, the $E_{p/2}$ value obtained for compound **16** which did not cyclize was +1.17 V vs. Ag/AgCl.

In conclusion, we have found that the intramolecular anodic coupling of enol ethers can be used to generate bridged bicyclic ring skeletons. While the reactions are not inherently stereoselective, the stereochemistry of the cyclization products can be controlled with the use of substituents on the chain between the olefins. Work aimed at utilizing these reactions to synthesize scopadulcic acid B is underway and will be reported in due course.

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12. All CV data was measured using a BAS 100B Electrochemical Analyzer, Pt working and auxiliary electrodes, a Ag/AgCl reference electrode, a 0.1 M LiClO₄ in acetonitrile electrolyte solution, a substrate concentration of 0.025 M, and a sweep rate of 25 mV/sec. The MeOH/THF solvent used in the preparative studies and the presence of 2,6-lutidine were avoided because they complicated the voltammograms. The relevance of the data reported to the preparative experiments was checked by measuring the E_{p/2} value for substrate **7** under both sets of conditions. No difference was observed.