

Intramolecular Hydrodimerization Reaction - Variations  
and Mechanistic Studies

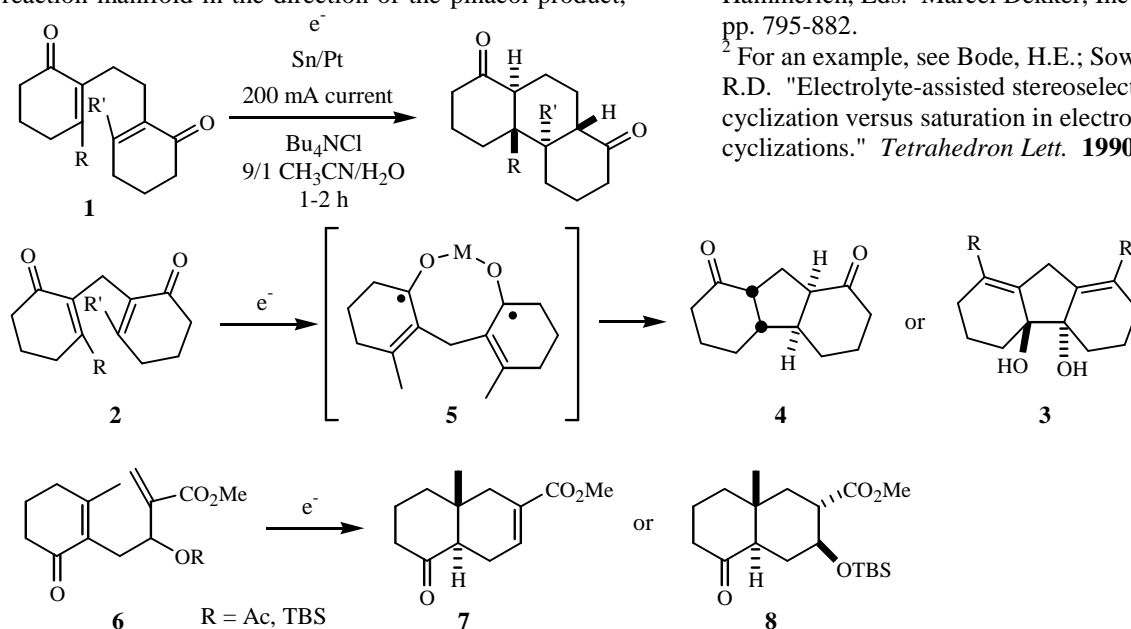
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In the course of our efforts studying the intramolecular hydrodimerization reaction of cyclic enones, we have made a number of interesting observations. An early discovery was that the cyclization of tethered bis-enone systems such as **1** under electrochemical conditions resulted in the formation of the tricyclic products as single isomers so long as at least one of the  $\beta$ -positions is disubstituted. A different situation was encountered with compounds such as **2** have a one-carbon tether between the two enones. Unlike the two-carbon tether series, the choice of cyclization conditions played an important role in determining what type of product was obtained. Thus, cyclization of substrates with disubstitution at either or both of the  $\beta$ -positions under the electrochemical conditions afforded the trans pinacol products such as **3**. Only in the unsubstituted case was the anticipated hydrodimerization type product **4** obtained.

In an effort to understand this difference in behavior, it was noted that all of the CV's of the two-carbon tether compounds show one reduction peak at around -2.4 V (versus Ag/AgCl). On the other hand, the one-carbon tether compound **2** (R=R'=Me) exhibits two reduction peaks, one at around -2.5 V and the other at an even more negative potential of -2.8 V. This may indicate a change in reaction mechanism upon going from the one-carbon tether series to the two-carbon tether series.

In addition to this CV data, we have hypothesized that this change between hydrodimerization and pinacol type products may be due to the formation of a metal chelate intermediate such as **5** under the electrochemical conditions.<sup>1</sup> The sacrificial anode conditions will form Lewis acidic tin(II) or even tin(IV) species that would be capable of forming cyclic structures such as **5**. In terms of the difference between the disubstituted and monosubstituted compounds, the increase in steric strain of bond formation in the disubstituted cases pushes the reaction manifold in the direction of the pinacol product,



whereas in the absence of such substitution, the strain present in the cyclic intermediate favors formation of the hydrodimerization product.

This hypothesis is further supported by the observation that the use of samarium diiodide as the electron source afforded the anticipated hydrodimerization products. Here the rationale is the fact that one molecule of samarium diiodide is required for the reduction of each enone to the radical anion, so presumably a bis-samarium enolate intermediate is formed. Although samarium is capable of forming Lewis acid complexes,<sup>2</sup> the steric bulk of each samarium and its coordination sphere precludes this pathway, meaning that hydrodimerization operates regardless of degree of  $\beta$ -substitution.

On the other hand, the use of magnesium in methanol affords the same results as the sacrificial anode conditions. Magnesium should again be capable of forming a cyclic chelated intermediate and also capable of donating more than one electron into the enone systems. Further validation of this hypothesis and its possible extension to the more general question of altering the selectivity of hydrodimerization versus pinacol coupling of enone systems is underway.

A second area of study is the extension of the intramolecular hydrodimerization reaction to substrates with functionalization in the tether. In this respect, compound **6** has been studied. As the acetate, subjecting to the standard electrochemical conditions afforded product **7**, in which the acetoxy group has undergone elimination to afford a new enoate product. A key mechanistic question is whether this elimination occurs after cyclization ( $\beta$ -elimination at the intermediate enolate stage) or prior to cyclization to afford an allylic radical or anion which then cyclizes on the other enone. What is clear is that changing the acetoxy group to less-readily eliminated silyl ether results in the formation of product **8** in which the ether group not only is retained, but serves to direct the cyclization since a single isomer of **8** is formed. Further studies of this reaction, including the use of enantioenriched starting materials is underway.

<sup>1</sup> Nielsen, M.F.; Utley, J.H.P. "Reductive Coupling." In *Organic Electrochemistry*, 4<sup>th</sup> Ed. H. Lund and O. Hammerich, Eds. Marcel Dekker, Inc: New York, 2001, pp. 795-882.

<sup>2</sup> For an example, see Bode, H.E.; Sowell, C.G.; Little, R.D. "Electrolyte-assisted stereoselection and control of cyclization versus saturation in electroreductive cyclizations." *Tetrahedron Lett.* **1990**, 31, 2525-2528.