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A Chelation Effect on the Pathway between Intramolecular Hydrodimerization and Pinacol Coupling

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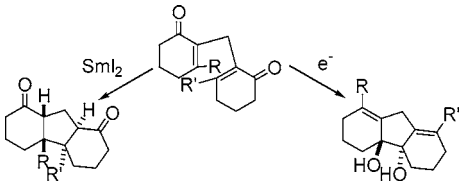
ABSTRACT

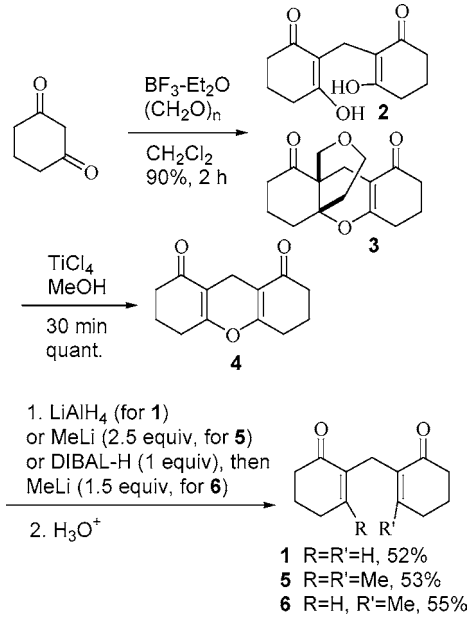


Depending upon the reaction conditions, the reductive cyclization affords either the pinacol or normal hydrodimerization-type products. This selectivity is highly dependent upon the substitution at the *β*-position of the enones.

The hydrodimerization reaction is a very powerful reaction that has been extensively studied over the years.[1] One particular variant of this reaction, the intramolecular hydrodimerization reaction, has received much less attention, despite its considerable synthetic potential.[2] Recently, we have begun a more thorough investigation of this reaction with the intent of understanding the effect of variables such as *β*-substitution, tether length, mixed enone/enoate systems, and the reaction conditions. Rather surprisingly, the studies of compounds with a one-carbon tether (such as substrate **1**), originally viewed as a potential route to linear triquinanes and other five-member-ring-containing materials, displayed very different behaviors depending upon the reaction conditions. This effect and its potential implications are the focus of this communication.

The preparation of **1** began with the synthesis of known ketone **2** by the condensation of 1,3-cyclohexanedione with paraformaldehyde in the presence of boron trifluoride-etherate.[3] Reaction time proved to be an important variable in this reaction, since longer reaction times (4 h) afforded mainly **3**. However, when the reaction was quenched after only 2 h, ketone **2** could be reliably obtained in 90% yield.

Scheme 1. Synthesis of Cyclization Substrates



(1) Nielsen, M. F.; Utley, J. H. P. Reductive Coupling. In *Organic Electrochemistry*, 4th ed.; Lund, H., Hammerich, O., Eds.; Marcel Dekker: New York, 2001; pp 795−882.
(2) Little, R. D.; Schwaebe, M. K. *Topics Curr. Chem.* **1997**, *185*, 1−48.
(3) Smith, A. B.; Dorsey, B. D.; Ohba, M.; Lupo, A. T.; Malamas, M. S. *J. Org. Chem.* **1988**, *53*, 4314−4325.

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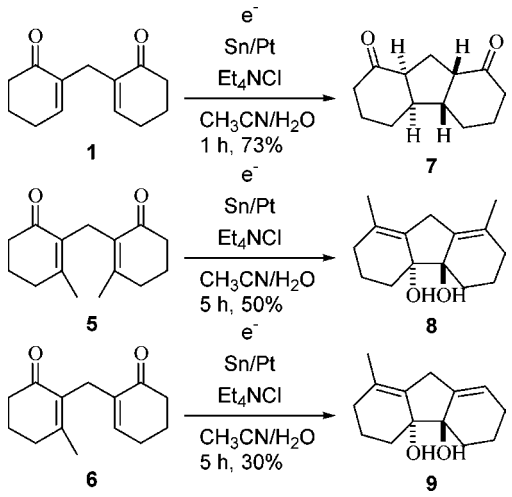
At this point, treatment with titanium tetrachloride served to form compound **4** in essentially quantitative yield.

From compound **4**, three different cyclization substrates were prepared. For the simple, β-unsubstituted compound **1**, treatment with excess lithium aluminum hydride, followed by acidic hydrolysis of the intermediate diol, afforded the desired compound **1** in 52% yield. The dimethyl substrate **5** was prepared in similar fashion by adding an excess of methyllithium, followed by acidic hydrolysis. Finally, the monomethyl substrate **6** was prepared by addition first of 1 equiv of DIBAL-H, then 1 equiv of methyllithium, and finally acidic hydrolysis. This sequence afforded compound **6** in a reasonable 55% yield overall.

With these three compounds in hand, the reductive cyclization was first explored under electrochemical conditions (Scheme 2). Subjection of compound **1** to a constant current of 200 mA for 1 h using a sacrificial tin anode and a platinum cathode in aqueous acetonitrile with tetraethylammonium chloride as the supporting electrolyte afforded the anticipated cyclization product **7** in 73% yield as a single isomer.[4] The stereochemistry of this product was confirmed to be cis/anti/cis by double Wolff−Kishner reduction to afford the known perhydrofluorene compound.[5]

Scheme 2. Electrochemical Cyclizations



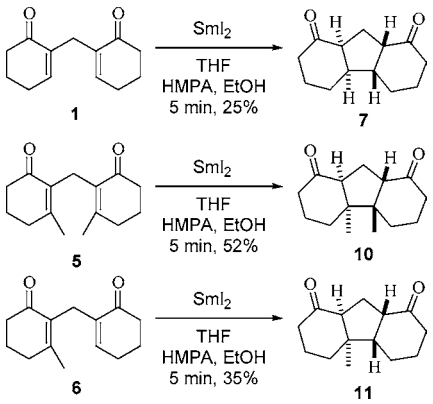
Interestingly, the reductive cyclizations of substrates **5** and **6** did not follow the same pattern. Both of these compounds afforded only the pinacol-type products **8** and **9** under electrochemical conditions. Although somewhat surprising, this is not unprecedented, since steric hindrance at the β-position is known to favor the pinacol product in the intermolecular hydrodimerization of cyclic enones.[6] The stereochemistry of the pinacol products is assigned as being trans, since it is not readily cleaved to afford the starting materials **5** and **6** by treatment with sodium periodate.

Since nonelectrochemical conditions are also known to promote the reductive cyclization reaction, we chose to investigate one of these alternatives and determine what effect it had on the cyclization and product outcome of these reactions.[7] Our choice was the use of samarium diiodide. Treatment of substrate **1** with 3 equiv of samarium diiodide at room temperature in THF under argon afforded the anticipated cyclization product **7** in 25% yield. Again, the product was isolated as a single isomer, the same as under the electrochemical conditions. Interestingly, treatment of **5** and **6** under these samarium diiodide conditions also afforded the reductive cyclization products **10** and **11** as single isomers, with none of the pinacol product being detected. The stereochemistry of product **11** is assigned as cis/anti/cis on the basis of the stereochemistry of product **7** and the fact that product **11** is symmetrical (only eight signals observed in the ^{13}C NMR spectrum and only one methyl signal observed in the ^{1}H NMR spectrum). Further evidence for the cis ring fusion comes from the observation of an NOE between the ring fusion methyl and the ring fusion proton. The cis/anti/cis arrangement of product **10** is assigned by analogy with the outcome of the other two cyclizations.

While these results clearly indicated that reductive cyclizations can be achieved on these shorter tether compounds, they also raised the question as to why the electrochemical conditions were leading to pinacol and the samarium diiodide conditions to reductive cyclization. This question is even more perplexing, since no similar difference was observed in the cyclization of a compound related to **5** but with two carbons in the tether between the two enones.[8] In examining these systems, one possible hypothesis is that chelation and steric effects play the determining factor. Assuming that the reductive cyclization of these compounds is proceeding via a one-electron reduction of each enone to a radical anion, followed by radical/radical coupling (the most commonly postulated mechanism for such reactions), then the situation outlined in Scheme 4 could help to explain the observed results.[1]

When there is no hindrance at the β-position, then the reaction proceeds via the normal reductive cyclization

Scheme 3. Samarium Diiodide Cyclizations

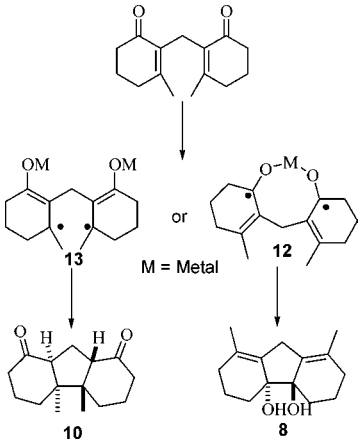


(4) Conditions were adapted from those reported by Kise and co-workers. Kise, N.; Iitaka, S.; Iwasaki, K.; Ueda, N. *J. Org. Chem.* **2002**, *67*, 8305−8315.

(5) Meusinger, R.; Rohloff, J.; Schumann, F.; Herzschuh, R. *J. Prakt. Chem./Chem.-Ztg.* **1997**, *339*, 128−134.

(6) In addition to ref 1, for a specific example, see: Tissot, P.; Surbeck, J.-P.; Guelacar, F. O.; Margaretha, P. *Helv. Chim. Acta* **1977**, *60*, 1472−1477.

Scheme 4. Mechanistic Rationale



manifold. As this hindrance becomes an issue, however, then chelation to form intermediate **12** can occur.[9] This will be particularly facile under the sacrificial anode conditions, since Lewis acidic tin(II) and/or tin(IV) salts will be generated. These salts can then coordinate to the two carbonyls and form an eight-member chelate that favors reaction at the carbonyls to form the pinacol products.

For the samarium diiodide conditions, chelation plays less of a role since each one of the enones must be reduced by one molecule of samarium diiodide to form a samarium(III) enolate and the β-radical. Assuming that radical/radical coupling proceeds faster than any reorganization of the coordination sphere of the samarium ions, then no cyclic chelate would result and the hydrodimerization product would be formed. Indeed, in this case the steric hindrance at the carbonyl is now increased due to the samarium ion and its ligands (such as HMPA and THF), thereby further favoring reaction at the β-position.

(7) Photochemical: Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 8777−8787. Pandey, G.; Ghorai, M. K.; Hajra, S. *Tetrahedron Lett.* **1998**, *39*, 1831−1834. Pandey, G.; Chorai, M. K.; Hajra, S. *Tetrahedron Lett.* **1998**, *39*, 8341−8344. Tin Hydride: Enholm, E. J.; Kinter, K. S. *J. Org. Chem.* **1995**, *60*, 4850−4855. Samarium Diiodide: Cabrera, A.; Lagadec R. L.; Sharma, P.; Arias. J. L.; Toscano, R. A.; Velasco, L.; Gavino, R.; Alvarez, C.; Salmon, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3609−3617.

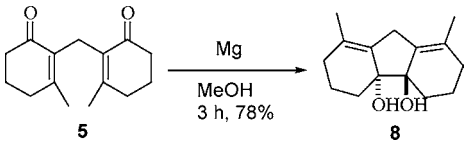
(8) Mandell, L.; Daley, R. F.; Day, Jr., R. A. *J. Org. Chem.* **1976**, *26*, 4087−4089. Handy, S. T.; Omune, D. Unpublished results.

(9) Chelation has been implicated in the selectivity of prior hydrodimerization reactions, particularly those done in protic solvents. For an example, see: Tissot, P.; Surbeck, J.-P.; Guelacar, F. O.; Margaretha, P. *Helv. Chim. Acta* **1981**, *64*, 1570−1574.

The absence of any pinacol products in the two-carbon tether compound related to **5** can also be explained using this rationale, since attempts to form a tin-chelated intermediate would require the formation of an even larger nine-member chelate. Entropic considerations now favor the more typical reductive cyclization product.

On the basis of this mechanistic rationale, it was expected that reductive cyclizations with metals capable of chelation should favor the pinacol pathway for compounds **5** and **6**, while metals incapable of chelation should favor the reductive cyclization pathway. To test this hypothesis, a reductive cyclization of **5** was performed using magnesium metal in MeOH (Scheme 5). On the basis of the previous rationale,

Scheme 5. Cyclization Using Magnesium in Methanol



it was anticipated that this reaction should afford the pinacol product **8**. Indeed, this was the sole reaction product, isolated in 78% yield, and was identical to that obtained using the electrochemical conditions.

In conclusion, we have noted that tethered bis-enones with one-carbon tethers can successfully undergo the reductive cyclization. Choice of reaction conditions is important in these cases to avoid a competing pinacol process, which is rationalized on the basis of a metal-chelated intermediate coupled with steric hindrance to cyclization at the β-position. Further studies of this reaction, the mechanism, and synthetic applications are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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