J|A|C|S
COMMUNICATIONS

The *gem*-Dialkyl Effect in Electron Transfer Reactions: Rapid Synthesis of Seven-Membered Rings through an Electrochemical Annulation

Jeffrey B. Sperry and Dennis L. Wright*

Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Received March 22, 2005; E-mail: dwright@Dartmouth.edu

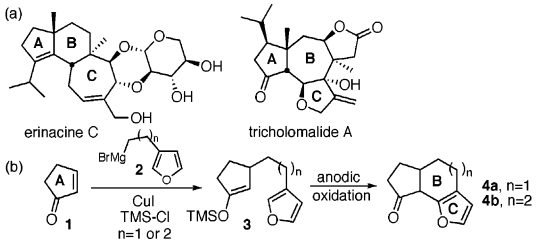
As part of a program to synthesize small molecule inducers of nerve growth factor (NGF) expression,[1] such as erinacine C[2] and tricholomalide A,[3] we have developed an electrochemical furan annulation strategy[4] to assemble key tricyclic intermediates for these complex natural products (Scheme 1).

Our overall synthetic plan involves the addition of a furyl-appended cuprate **2** to an appropriate A-ring enone **1** with in situ trapping of the intermediate as the silyl enol ether **3**. Anodic oxidation[5] of one of the two tethered electrophores to a radical cation intermediate effects a reversal of polarity that triggers the closure of a six- or seven-membered B-ring to give **4a/b**. The annulated furans in **4a/b** serve as versatile precursors to both the cycloheptyl C-ring of erinacine via [4 + 3] cycloaddition or the oxacyclic C-ring of tricholomalide through hydration/isomerization. We have previously reported[6] the conversion of an intermediate related to **4a** to the erinacine skeleton. We now wish to report on the successful extension of this methodology that not only offers a rapid and efficient method for the construction of seven-membered rings but also has provided valuable mechanistic insight about these electrochemical annulations (Scheme 2).

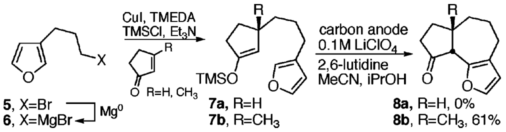
The Grignard reagent **6** was prepared directly from the bromide **5**, which is available in two steps from 3-bromofuran through reaction of the derived organolithium reagent with trimethylene oxide[7] and bromination of the resulting alcohol. Copper-catalyzed addition of **6** to cyclopentenone or 3-methylcyclopentenone in the presence of trimethylsilyl chloride gave the corresponding silyl enol ethers **7a** and **7b** that were directly taken on to the electrochemical oxidation without the benefit of further purification. Surprisingly, anodic oxidation of **7a** on a carbon electrode under conditions previously described for the closure of six-membered rings failed to produce any of the annulated furan **8a**. Changes in additives, anode material, or electrolyte were ineffectual in promoting the cyclization with only complex mixtures and polymeric materials being produced. Whereas the related six-membered closure behaved well and consumed close to the theoretical 2 F/mol required for the oxidative cyclization, the oxidation of **7a** required greater the 4 F/mol of current before starting material was completely consumed. In sharp contrast, however, silyl enol ether **7b** cyclized smoothly under identical conditions, producing the annulated furan **8b** in an overall 62% yield from 3-methylcyclopentenone. The closure occurred, as in previous cases, to give exclusively the cis-ring fusion in accord with a kinetically controlled cyclization.

This dramatic effect of a somewhat remote substituent had not been previously observed in other electrochemical cyclizations and prompted us to investigate the difference between these two substrates further. Unlike chemical oxidations, electrochemical processes can be studied directly by voltammetry. To gain a better understanding into the role of the remote substitution, we examined the cyclic voltammograms of representative substrates (see Supporting Information).

Scheme 1. Naturally Occurring Diterpenoids (a) that Upregulate the Expression of NGF (b) Strategy for Annulated Furan Intermediates



Scheme 2. Seven-Membered Electrochemical Annulation

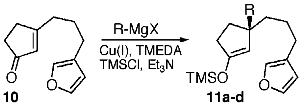


These substrates show a typical irreversible voltammogram with initial oxidation occurring at the silyl enol ether, consistent with earlier mechanistic proposals.[4b] The half-wave potential was determined both from the cyclic voltammogram and from differential pulse voltammetry. Enol ether **7b**, bearing the methyl substituent, has a significantly lower oxidation potential (0.70 V) than that of **7a** (0.81 V), which has a half-wave potential identical to that of an unsubstituted silyl enol ether (0.81 V). These measured potentials suggested that the pendent furan lowers the oxidation potential of the enol ether in **7b** but not **7a**. This difference of ~110 mV is absent in the analogous six-membered ring precursors. In the case of six-membered ring cyclizations, both substrates oxidize at the same half-wave potential as substrate **7b**. The fact that this difference is observed only in the seven-membered closures argues against preferential adsorption or transport to the electrode surface due to lipophilicity.

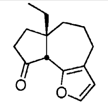
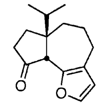
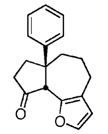
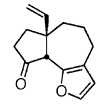
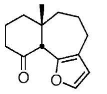
We propose that this dramatic difference in reaction profile results from the *gem*-dialkyl effect,[8] which has been shown to substantially increase the rate of intramolecular reactions. The effect observed here may be so dramatic because adiabatic electron-transfer reactions occur ~10^6 times faster than conformational changes. The pendant furan in **7b** is likely to be disposed to undergo ring closure, perhaps concomitantly with oxidation. This preorganization is evident from the oxidation potentials, whereby the tethered furan in **7b** donates electron density to the silyl enol ether. The corresponding radical cation arising from **7a** is more likely to be in a nonreactive conformer during the initial oxidation. The relatively slow conformational change required for **7a** to cyclize may not be competitive with additional fast electron transfers from the radical cation intermediate, giving rise to polymers and other products and being responsible for the consumption of excessive charge. The difference in oxidation potential of ~110 mV corre-

10.1021/ja051826+ CCC: $30.25

Table 1. Electrochemical Cyclizations



10 **11a-d**

entry	conditions[a]	enolether	R	product[c]	yield[d]
1	A	**11a**	Et	 **12a**	60%
2	A	**11b**	iPr	 **12b**	63%
3	B	**11c**	Ph	 **12c**	62%
4	A	**11d**	vinyl	 **12d**	63%
5	N/A	**11e**[b]	Me	 **12e**	61%

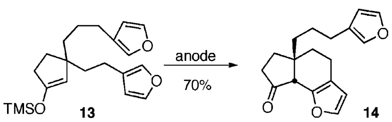
[a] Conditions: A, RMgX, CuI; B, RMgX, CuBr•Me$_2$S. [b] Prepared via addition of **6** to 3-methylcyclohexenone. [c] The cis-isomer formed exclusively. [d] Overall yield for two steps from the enone.

sponds to lowering the activation barrier for formation of the radical cation by ~2.2 kcal/mol.[9] Similar effects have been observed both in small molecules[10] and in DNA.[11]

If this type of effect is indeed responsible for the successful cyclization of **7b**, then groups other than methyl would be expected to show similar reactivity. To examine this, a series of additional substrates were prepared through a modified route and examined in the electrochemical cyclization (Table 1).

Copper-promoted addition of various organomagnesium reagents to enone **10**[12] produced the corresponding silyl enol ethers **11a**–**d**. Electrolysis under the standard conditions resulted in smooth cyclization in all cases to produce the annulated furans **12a**–**d** in very good overall yields, again exclusively as the cis-fused products. A related enol ether **11e** from 3-methylcyclohexenone also underwent an efficient cyclization to produce a single diastereomeric adduct **12e** at a difficult to control 6–7 ring junction. This efficient method of preparing these precursors also allowed the study of an interesting probe molecule **13** that sets up a direct competition between a six- and seven-membered ring closure (Scheme 3).

Scheme 3. Competition Study



Electrolysis of **13** produced a single product **14** resulting from exclusive cyclization of the six-membered ring.[13] This probe also supports prior mechanistic models that suggested the silyl enol ether as the initial site of electron transfer rather than the furyl group, which would be expected to produce a mixture of products.

This electrochemical annulation represents a powerful method for the formation of annulated furans containing seven-membered rings and forms the basis for an approach to the NGF stimulator tricholomalide A. The reactions proceed in good overall yield with excellent diastereocontrol, producing cis-fused 5–7 and 6–7 ring systems. The presence of substituents on the tether to control the fate of the electrochemically generated intermediates is crucial for the reaction and provides direct evidence as to the magnitude of the reactive rotamer effect on an electron-transfer reaction. Current studies involve the placement of other conformational control elements in the tether and efforts toward the synthesis of tricholomalide A.

Acknowledgment. We would like the National Science Foundation for support of this work. We would also like to thank Professor William Geiger and Derek Laws (University of Vermont) for assistance with analytical voltammetry.

Supporting Information Available: Full experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Carswell, S. *Exp. Neurol.* **1993**, *124*, 36–42.
(2) (a) Wright, D. L.; Whitehead, C. R. *Org. Prep. Proc. Int.* **2000**, 307. (b) Kawagishi, H.; Shimada, A.; Shirai, R.; Okamoto, K.; Ojima, F.; Sakamoto, H.; Ishiguro, Y.; Furukawa, S. *Tetrahedron Lett.* **1994**, *35*, 1569.
(3) Tsukamoto, S.; Macabalang, A. D.; Nakatani, K.; Obara, Y.; Nakahata, N.; Ohta, T. *J. Nat. Prod.* **2003**, *66*, 1578.
(4) (a) Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Wright, D. L. *Org. Lett.* **2002**, *4*, 3763. (b) Sperry, J. B.; Whitehead, C. R.; Ghiviriga, I.; Walczak, R. M.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 3726.
(5) For application in total synthesis, see: (a) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2003**, *125*, 36. (b) Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106. (c) Review: Moeller, K. D. *Tetrahedron* **2000**, *56*, 9527–9554.
(6) Wright, D. L.; Whitehead, C. R.; Sessions, E. H.; Ghiviriga, I.; Frey, D. A. *Org. Lett.* **1999**, *1*, 1535.
(7) Clayden, J.; Kenworthy, M. N. *Org. Lett.* **2002**, *4*, 787.
(8) (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224. (b) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 10789. (c) Parrill, A. L.; Dolata, D. P. *J. Mol. Struct. (THEOCHEM)* **1996**, *370*, 187. (d) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(9) Zuman, P. *Prog. Phys. Org. Chem.* **1967**, *5*, 81.
(10) Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1033.
(11) Yoshioka, Y.; Kitagawa, Y.; Takano, Y.; Yamaguchi, K.; Nakamura, T.; Saito, I. *J. Am. Chem. Soc.* **1999**, *121*, 8712.
(12) Prepared by the addition of **6** to 3-methoxycyclopentenone followed by acidic workup.
(13) A minor byproduct arising from oxidation of the pendant furan ring of **14** was also identified.

JA051826+