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# Oxidative Cyclization Based on Reversing the Polarity of Enol Ethers and Ketene Dithioacetals. Construction of a Tetrahydrofuran Ring and Application to the Synthesis of (+)-Nemorensic Acid

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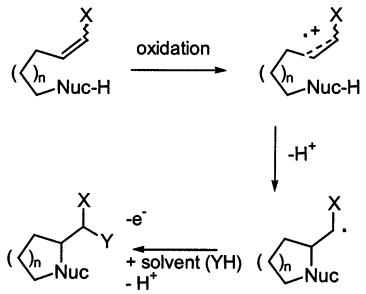
***Abstract:*** The utility of oxidative cyclization reactions for the construction of tetrahydrofuran rings has been examined. In these experiments, alcohol nucleophiles were found to be effective traps for radical cation intermediates generated from both enol ether and ketene dithioacetal groups. The reactivity of the alcohol trapping group appeared to lie between that of an enol ether and an allylsilane trapping group. The stereochemical outcome of cyclization reactions originating from the oxidation of an enol ether was found to be controlled by stereoelectronic factors. The utility of these cyclization reactions was illustrated with the synthesis of a key tetrahydrofuran building block for the synthesis of linalool oxide and rotundisine. Cyclization reactions triggered by the oxidation of a ketene dithioacetal led to far greater levels of stereoselectivity. The stereochemical outcome of these reactions was shown to arise from steric factors involving the larger ketene acetal group. The synthetic utility of cyclizations utilizing ketene dithioacetal derived radical cations was demonstrated by completing an asymmetric synthesis of (+)-nemorensic acid. Finally, the reactions were shown to be compatible with the use of an amide nucleophile and the direct formation of a lactone product.

## Introduction

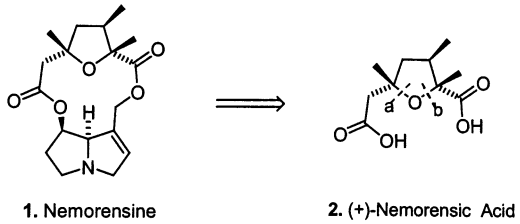
The anodic oxidation of an enol ether leads to the formation of a radical cation intermediate and a reversal in the polarity of the functional group (Scheme 1).[1,2] In this way, nucleophiles can be added to the normally nucleophilic carbon beta to the oxygen of the enol ether (and alpha to a carbonyl equivalent in the resulting product). The result is the potential for a series of umpolong reactions that can open up entirely new routes to the synthesis of natural products.

For example, consider (+)-nemorensic acid (Scheme 2). (+)-Nemorensic acid is the necic acid portion of the macropyrrolizidine alkaloid nemorensine (**1**).[3] If one considers the synthesis of the tetrahydrofuran ring found in this molecule from an acyclic precursor, then there are two potentially quite useful strategies.[4] The first would disconnect bond **a**, an approach that would require that the ring be generated by forming a bond between an oxygen nucleophile and the carbon beta to the carboxylic acid on C5 of the tetrahydrofuran ring. The second

***Scheme 1***




***Scheme 2***




**1.** Nemorensine **2.** (+)-Nemorensic Acid

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(1) For selected examples of prior work concerning the use of enol ether radical cations for the synthesis of carbon−carbon bonds see: (a) Hudson, C. M.; Marzabadi, M. R.; Moeller, K. D.; New, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 7372. (b) Moeller, K. D.; Tinao, L. V. *J. Am. Chem. Soc.* **1992**, *114*, 1032. (c) Tinao-Wooldridge, L. V.; Moeller, K. D.; Hudson, C. M. *J. Org. Chem.* **1994**, *59*, 2381. (d) Hudson, C. M.; Moeller, K. D. *J. Am. Chem. Soc.* **1994**, *116*, 3347. (e) New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578. (f) Frey D. A.; Reddy, S. H. K.; Wu, N.; Moeller, K. D. *J. Org. Chem.* **1999**, *64*, 2805. (g) Reddy, S. H. K.; Chiba, K.; Sun, Y.; Moeller, K. D. *Tetrahedron* **2001**, *57*, 5183. (h) Sun, Y.; Liu, B.; Kao, J.; d'Avignon, D. A.; Moeller, K. D. *Org. Lett.* **2001,** *3*, 1729.

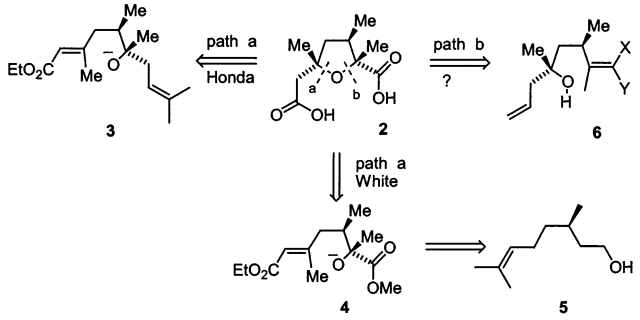
(2) For preliminary accounts of radical cation reactions using alcohol trapping groups see: (a) Sutterer, A.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 5636. (b) Duan, S.; Moeller, K. D. *Org. Lett.* **2001**, *3*, 2685. (c) Liu, B.; Moeller, K. D. *Tetrahedron Lett.* **2001**, *42*, 7163.

(3) Klasek, A.; Sedmera, P.; Boeva, A.; Santavy, F. *Collect. Czech. Chem. Commun.* **1973**, *38* (8), 2504.

(4) (a) For an alternate approach to the asymmetric synthesis of (+)-nemorensic acid see: Donohoe, T. J.; Guillermin, J-. B.; Frampton, C.; Walter, D. S. *J. Chem. Soc., Chem. Commun.* **2000**, 465. (b) For a previous racemic synthesis see: Klein, L. L. *J. Am. Chem. Soc.* **1985**, *107*, 2573.

10.1021/ja026739l CCC: $22.00 

**Scheme 3**

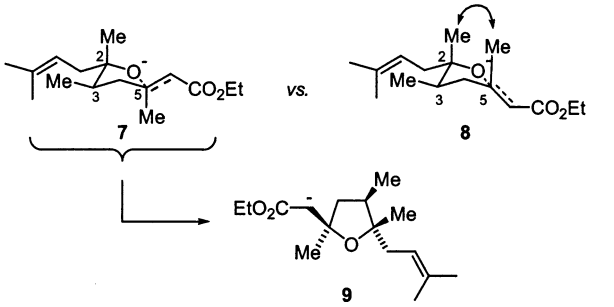



would disconnect bond **b**, an approach that would require that the ring be generated by forming a bond between an oxygen nucleophile and the carbon alpha to the carboxylic acid on C2 of the tetrahydrofuran ring. The first approach was used in order to complete the first two asymmetric syntheses of (+)-nemorensic acid (Scheme 3).[5a,b] Both of these syntheses utilized an intramolecular Michael reaction of an oxygen nucleophile onto a trisubstituted enoate to synthesize the tetrahydrofuran ring. Because the two routes were similar in their overall approach, they suffered from some of the same drawbacks. First, the intramolecular Michael reaction did not afford the correct stereochemistry at C5 of the tetrahydrofuran ring. For the synthesis described by Honda and co-workers,[5a] the tetrahydrofuran ring was formed as a 3.8:1 ratio of isomers favoring the opposite stereochemistry at C5. For the synthesis described by White and co-workers,[5b] a 4.5:1 ratio of isomers at C5 was obtained. Again, the isomer needed for the synthesis of (+)-nemorensic acid was the minor isomer. Second, both syntheses lost efficiency due to a need to remove carbons from the starting materials. For the synthesis proceeding through **4**, the initial starting material was first shortened and then rebuilt to form the enone. For the synthesis proceeding through **3**, the Michael reaction led to a tetrahydrofuran product having an allyl group masking the C2-carboxylic acid substituent of the final product. Unmasking of the acid involved an ozonolysis, reduction to form an alcohol, elimination using selenium, and then a second ozonolysis.

In principle, some of the challenges associated with the Michael reaction routes can be eliminated by using the synthetic route represented by path **b** in Scheme 3. In such a scenario, an anodic oxidation reaction would be used to generate either an enol ether or ketene acetal based radical cation that would in turn be trapped with an alcohol nucleophile in order to form a bond between the tetrahydrofuran oxygen and C2 of the ring. In this way, the direction of the synthesis developed by Honda would be reversed, thereby allowing the allyl group to mask the carboxylic acid side chain at C5 of the ring. The desired acid would then be derived using a simple ozonolysis reaction following the cyclization.

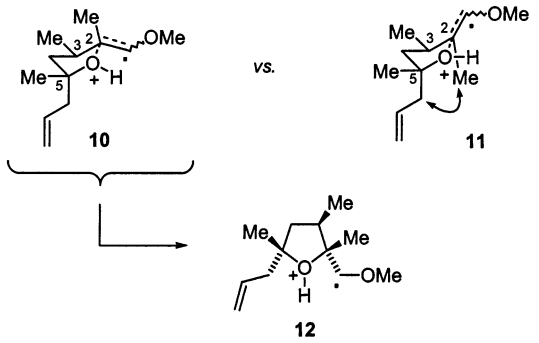
A synthesis of the ring along path **b** would also be expected to reverse the stereoselectivity of the cyclization. Honda and co-workers argue that the stereochemistry of the product arising from the Michael reaction of substrate **3** originates because of an interaction between the allylic methyl group on the $\beta$-carbon of the enone and the axial methyl group on the carbon bearing

**Scheme 4**




the oxygen (Scheme 4; **8**). This interaction raises the energy of transition state **8** relative to that of transition state **7** and leads to the formation of **9** as the major product. It is important to note that it is the 1,2-relationship between the quaternary center and the methyl group at C3 that places the axial methyl group at C2 cis to the methyl at C3 and forces the methyl group at C5 to the opposite face of the product. By reversing the direction of the cyclization (Scheme 5), the relationship between the

**Scheme 5**




quaternary carbon and the methyl substituent at C3 would be altered. In this scenario, a 1,3-relationship would exist between the quaternary carbon and the methyl group at C3. Hence, the pseudoaxial group in the transition state would be on the face of the molecule opposite to the C3 methyl group. If the same interaction observed earlier were to control this cyclization, then the methyl group at C2 would be forced to the top face of the molecule cis to the methyl group at C3. The cyclization would lead to the correct relative stereochemistry for completing the synthesis of (+)-nemorensic acid.

With this in mind, we set out to determine whether enol ether and ketene acetal radical cations could be efficiently trapped with alcohol nucleophiles and, if so, whether the ensuing reactions would prove useful for building quaternary carbons and synthesizing natural products such as nemorensic acid.

## Initial Studies

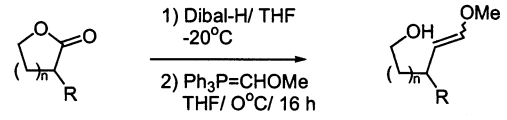
The compatibility of oxygen nucleophiles with the anodic cyclization reactions was examined using substrates **14a**−**e**.[6] The substrates were synthesized from the corresponding lactones by reducing the lactone to a lactol using Dibal-H and then introducing the enol ether with a Wittig reaction (Scheme 6). While the yields of these experiments were only moderate, they allowed us to rapidly assess the synthetic potential for the subsequent electrolysis reactions.

Once the substrates were available they were oxidized at a constant current of 8 mA in an undivided cell equipped with a

(5) (a) Honda, T.; Ishikawa, F. *J. Org. Chem.* **1999**, *64*, 5542. (b) Dillon, M. P.; Lee, N. C.; Stappenbeck, F.; White, J. D. *J. Chem. Soc., Chem. Commun.* **1995**, 1645.

(6) Substrate **14e** was made from 1,6-hexanediol using a monoprotection, Swern oxidation, Wittig, and then deprotection sequence.

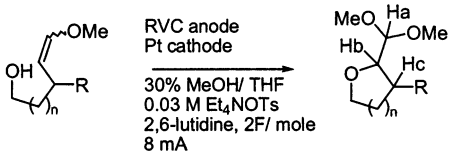
***Scheme 6***




**13a.** R=Me; n=1
**13b.** R=$CH_2$Ph; n=1
**13c.** R=H; n=2
**13d.** R=$CH_2$Ph; n=2

**14a.** 35%
**14b.** 61%
**14c.** 57%
**14d.** 33%

***Scheme 7***




**14a.** R=Me; n=1
**14b.** R=$CH_2$Ph; n=1
**14c.** R=H; n=2
**14d.** R=$CH_2$Ph; n=2
**14e.** R=H; n=3

**15a.** 96% (5:1 trans/cis)
**15b.** 95% (10:1 trans/cis)
**15c.** 80% (NMR yield)
**15d.** 51% (6:1 trans/cis)
**15e.** --

reticulated vitreous carbon (RVC) anode and a platinum cathode (Scheme 7).[7] A 0.03 M tetraethylammonium tosylate in 30% MeOH/THF electrolyte solution was used along with 2,6-lutidine as a proton scavenger.[8] The oxidation was continued until 2 F/mol of charge had been passed. These reaction conditions were selected because of their similarity to the conditions used for many of the reactions summarized in Scheme 1. The cyclization reactions leading to five- and six-membered ring products led to good to excellent yields. As in the earlier carbon−carbon bond forming reactions, the reactions leading to the formation of six-membered rings did prove to be less efficient than reactions leading to five-membered rings. Attempts to generate a seven-membered ring product (**15e**) were not successful. In this example, the product obtained resulted from methanol trapping of the radical cation.

For the cyclization reactions originating from **14a**, **14b**, and **14d** the major product had trans-stereochemistry. For the five-membered ring products, the stereochemistry of the substituents was established with the use of a NOESY experiment. This was accomplished by noting the larger interaction between methine protons $H_b$ and $H_c$ in the cis-isomer and the larger interaction between methines $H_a$ and $H_c$ in the trans-isomer. For the six-membered ring product, the stereochemistry of the major product was established using the 9.3 Hz coupling constant observed for the interaction between $H_b$ and $H_c$.

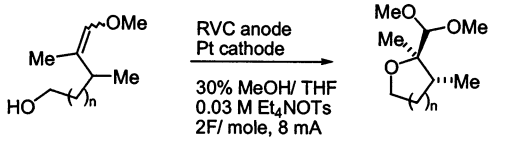
The success of the alcohol nucleophiles as trapping groups for the radical cations was intriguing because earlier anodic carbon−carbon bond forming reactions had been accomplished in methanol based solvent mixtures without the methanol solvent trapping the initial radical cation. This observation is currently thought to be a result of the electrochemical "double layer" that forms at the anode surface.[9] The double layer forms due to adsorption of the electrolyte onto the electrode surface, a process that excludes solvent from the area surrounding the electrode.[10] The net effect is to lower the concentration of the solvent in the region where the reactive intermediate is generated and thereby provide more time for the cyclization reaction. In fact, cyclizations that employ a very good radical cation trapping group like an enol ether[1b] or a furan[1e] can tolerate the use of pure methanol as the solvent for the reaction without evidence for methanol trapping. For less effective terminating groups such as an allylsilane, cosolvents such as THF and $CH_2Cl_2$ are required for optimizing the cyclizations. In these cases, the use of pure methanol solvent for the reaction leads to a competition between the intramolecular cyclization and solvent trapping of the radical cation. On the basis of these observations, the need for a cosolvent can be used to gain insight into the relative reactivity of trapping groups for the radical cation. In the case of the alcohol trapping groups, optimizing the yield of the cyclization did require the use of a cosolvent, a result that initially placed the reactivity of the intramolecular alcohol trapping group below that of an enol ether or furan and on par with that of an allylsilane. This conclusion was supported by the results obtained using substrate **14e**. While cyclization reactions utilizing allylsilane terminating groups also fail to afford seven-membered ring products, reactions terminated with the use of either a second enol ether or a furan ring are compatible with seven-membered ring formation.[1b,e]

The initial cyclizations were also compatible with the use of a 6 V lantern battery as the power supply.[11] Using the battery, the cyclization of **14a** led to a 74% isolated yield of the cyclized product. The cyclization of **14b** led to a 55% yield of product along with 25% of the recovered starting material. While the yields using the battery were not as high as previous trials, it was clear that the effectiveness of the cyclization could be evaluated without the need for specialized equipment.

### Building a Quaternary Carbon

The reactivity of a terminating group for an enol ether radical cation can also be probed by examining the compatibility of the cyclization reaction with the formation of a quaternary carbon. This was of special interest in the current case because of the need to generate a quaternary carbon during the synthesis of (+)-nemorensic acid. For this reason, substrates **16a** and **16b** were synthesized in a fashion directly analogous to the syntheses of substrates **14a**−**d** (vide supra). In this case, methyllithium was added to the lactone in order to generate a substrate for the Wittig reaction.

***Scheme 8***




**16a.** n=1
**16b.** n=2

**17a.** 74% (3:1 ratio)
**17b.** 56% (1:1 ratio)

Once synthesized the substrates were oxidized using the same conditions described above (Scheme 8). The cyclization orig-

(7) The electrolyses were conducted utilizing a Model 630 coulometer, a Model 410 potentiostatic controller, and a Model 420A power supply purchased from the Electrosynthesis Co., Inc.

(8) A proton scavenger is typically added to enol ether oxidation reactions in order to assist the removal of acid from the anode surface. This reduces the chance for methanolysis of the enol ether as it approaches the anode. It is important to note that the overall reaction remains neutral because the half-reaction that takes place at the cathode generates an equivalent of methoxide for every equivalent of acid generated at the anode.

(9) For discussions of the "double layer" see: (a) *Anodic Oxidation*; Ross, S. D., Finkelstein, M., Rudd, E. J., Eds.; Academic Press: New York, 1975; p 13. (b) *Synthetic Organic Electrochemistry*, 2nd ed.; Fry, A. J., Ed.; John Wiley and Sons: New York, 1989; p 37.

(10) For a discussion of how the adsorption of an electrolyte onto an electrode surface can exclude solvent and protect a reactive intermediate see: *Organic Electrochemistry*, 4th ed., Revised and Expanded; Lund, H., Hemmerich, O., Eds.; Marcel Dekker: New York−Basel, 2001; p 802.

(11) Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317.

inating from **16a** afforded the desired five-membered ring product **17a** in a 74% isolated yield. To our surprise, a 3:1 ratio of stereoisomers was formed, favoring the stereochemistry needed for the synthesis of (+)-nemorensic acid. The proper selectivity was obtained even without the quaternary center and hence the axial directing group at C5.

The cyclization to form the six-membered ring product (**17b**) led to a 56% isolated yield of two stereoisomers in a 1:1 ratio. The formation of this product helped to refine our initial view of the reactivity of the alcohol nucleophile toward the radical cation intermediate. While the earlier solvent studies put the reactivity of an alcohol trapping group for the enol ether radical cation on par with that of an allylsilane, the ability for the current cyclizations to overcome the barriers associated with the simultaneous formation of a six-membered ring and a quaternary center suggested that the alcohol was in fact more reactive toward the enol ether radical cation than an allylsilane trapping group. Cyclizations involving allylsilane trapping groups have proven to be incompatible with the simultaneous formation of a six-membered ring and a quaternary center.[1c,g]

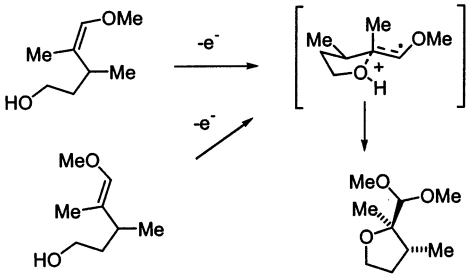
The observation that the cyclization arising from **17a** led to the product in a stereoselective fashion raised two questions. First, what was the origin of this selectivity, and second, how could the degree of selectivity obtained be optimized?

### Probing the Stereoselectivity of the Cyclization

The lack of selectivity for the cyclization arising from **17b** suggested that the reactions were under kinetic control. For the formation of a six-membered ring, a reaction that was controlled by thermodynamics would have been expected to show a preference for a trans-product having both the dimethoxy acetal group at C2 and the methyl group at C3 in equatorial positions. With that in mind, we began to consider why a kinetic controlled reaction might lead to a moderate level of stereoselectivity in the case of a five-membered ring product and no stereoselectivity for the corresponding reaction leading to a six-membered ring product.

The first question addressed was whether the stereoselectivity of the reaction originating from **16a** was dependent on the stereochemistry of the initial enol ether. To this end, the stereoisomers of **16a** were separated by chromatography, and each enol ether stereoisomer cyclized separately (Scheme 9).

***Scheme 9***

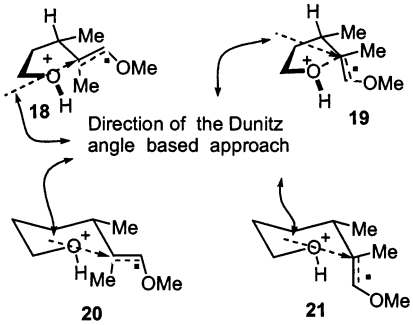



**17a.** (3:1 ratio of isomers)

As in earlier carbon−carbon bond forming reactions,[1a] the stereoselectivity of the cyclization reaction did not depend on the stereochemistry of the enol ether. Both starting material isomers led to the formation of a 3:1 ratio of product stereoisomers with the trans-product being favored. Since the reactions appeared to be under kinetic control, this result suggested that the configuration of the enol ether radical cations was not stable and that both starting enol ether isomers led to the same reactive intermediate.

Having established that the stereochemistry of the reaction did not depend on the stereochemistry of the initial enol ether, we turned our attention toward probing why the cyclization leading to the five-membered ring product would be more selective than the cyclization leading to the six-membered ring product. Two explanations appeared reasonable. First, it was possible that the selectivity observed in the cyclization leading to the five-membered ring was the result of a steric interaction between the forming dimethoxyacetal group and the neighboring methyl group at C3. If the transition state had product-like character, then a steric interaction of this nature would favor the formation of a five-membered ring product having the two groups trans to each other. However, no such preference would be observed for the cyclization leading to the six-membered ring product. For a "product-like" transition state leading to a six-membered ring the methyl group at C3 would be the same distance from either an equatorial enol ether radical cation or an axial enol ether radical cation intermediate. Second, it was possible that the formation of the trans-product **17a** was favored by a stereoelectronic effect.[12] If the alcohol attacked the $\pi^*$ orbital of the radical cation, then the required overlap (attack along the Dunitz angle)[13] would be maximized for a transition state like **18** relative to transition state **19** (Scheme 10). No such difference would arise for the transition states leading to the six-membered ring products (**20** and **21**).

***Scheme 10***



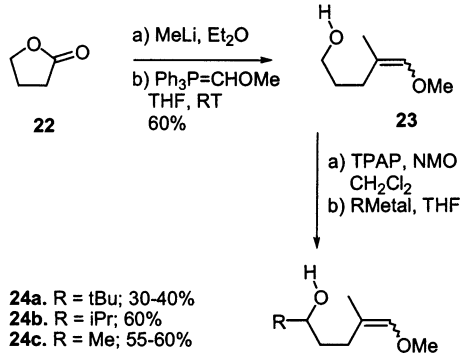

To differentiate between these two possibilities, substrates (**24a**−**c**) were synthesized from $\gamma$-butyrolactone as outlined in Scheme 11. In each of these substrates, the methyl group at C3 was removed in order to eliminate the potential steric preference for the formation of trans-product. A sterically bulky group was added to the carbon bearing the alcohol nucleophile (C5) in order to fix the conformation of the coiling chain. Since the bulky group would occupy a pseudoequatorial position in the transition state for the cyclization, it was expected to have little influence over the stereochemical course of the reaction. In this way, the stereoselectivity that was observed could be attributed to stereoelectronics.

Substrates **24a**−**c** were oxidized at a reticulated vitreous carbon anode using the conditions described above (Scheme 12). All three cyclizations showed the same selectivity observed

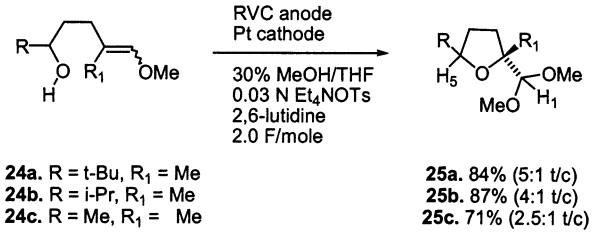
(12) Deslongchamps, P. *Stereoelectronic Effects in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1983. In particular, note pp 32 and 33. (b) For an example involving the cyclization of an oxygen nucleophile onto an oxonium ion see: Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta* **1992**, *75* (2), 604−20.

(13) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065. (c) Bürgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.

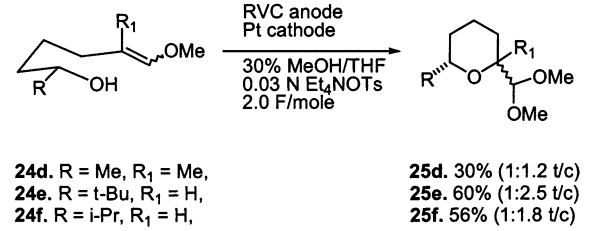
***Scheme 11***




***Scheme 12***




***Scheme 13***



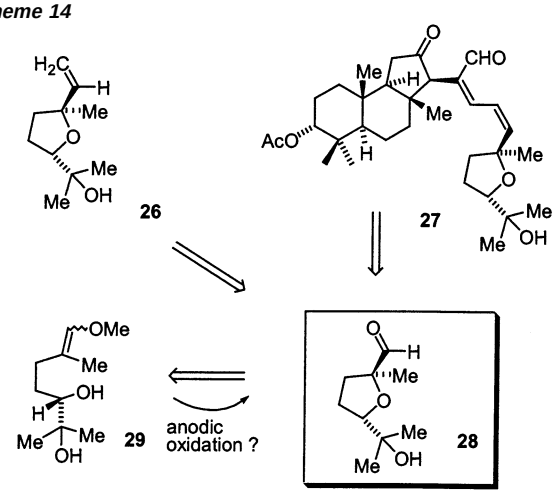

for the cyclization resulting from **16a**. The major products were assigned as having trans-stereochemistry because of the presence of an NOE interaction between H1 and H5. The degree of selectivity obtained for the case where R was equal to a methyl group (**24c**) was essentially the same as that obtained with from the oxidation of substrate **16a**. Clearly, sterics had little to do with the 3:1 ratio of isomers obtained for **17a,** and the origins of the selectivity observed was principally attributed to stereoelectronic factors. The selectivity obtained for products **25a** and **25b** did increase as the size of the substituent at C5 was increased. Presumably, this increase in selectivity reflected the ability of a larger substituent to better fix the conformation of the coiling chain into a single pseudochair orientation.

In a similar fashion, the analogous six-membered ring cyclization reactions were studied (substrates **24d**−**f**). These substrates were synthesized in a fashion that was identical to the five-membered ring substrates using $\delta$-valerolactone as the starting material. Once again, the reactions leading to six-membered ring products were less stereoselective than the corresponding reactions leading to five-membered ring products (Scheme 13). In these cases, the formation of a cis-product having both substituents in an equatorial position was favored. These assignments were made be examining the splitting pattern for the methine protons at C2 and C6 of the rings (for **25d** the dimethoxyacetal group was assumed to occupy a pseudoequatorial position). As with the earlier cyclizations, the reactions leading to six-membered ring products were not as efficient and led to lower yields relative to their five-membered ring counterparts. For example, the reaction originating from **24d** struggled to make both a quaternary carbon and a six-membered ring at the same time. Only a 30% isolated yield of the product was obtained. Similar reactions utilizing *tert*-butyl and isopropyl groups at C6 did not lead to any cyclized product. The reactions were more successful when the allylic methyl group, and therefore the need to generate a quaternary carbon, was removed. However, while improving the yield of the process the removal of this methyl group (which occupies a pseudoaxial position in the transition state leading to the major cis-product) did not significantly increase the stereoselectivity of the reaction. The cyclizations resulting from both **24e** and **24f** were still less selective than their five-membered ring forming counterparts (Scheme 12).

## Construction of a Building Block for the Synthesis of Tetrahydrofuran-Containing Compounds

The realization that the stereochemistry of cyclization reactions leading to five-membered rings could be controlled by stereoelectronics suggested that the reaction might be applicable to the synthesis of a wide variety of tetrahydrofuran products. For example, the tetrahydrofuran-containing natural products linalool oxide **26**[14] and rotundisine **27**[15] (Scheme 14) both

***Scheme 14***

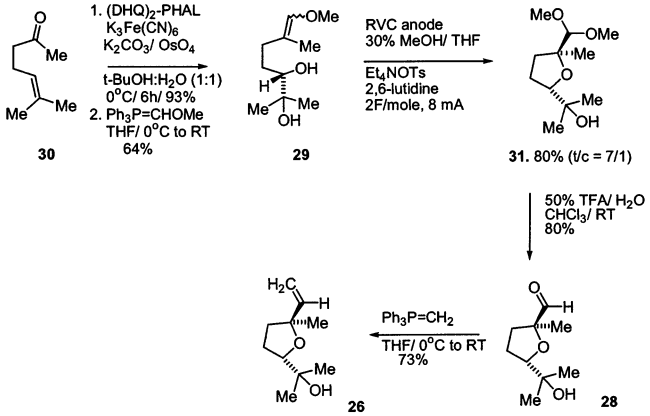



contain a tetrahydrofuran ring that can be envisioned as arising from building block **28**. Building block **28** can in turn be envisioned as arising from the anodic oxidation of substrate **29**. In this case, the sterically large (2′-hydroxy-2′-propyl) substituent on the carbon bearing the hydroxyl group would be expected to fix the conformation of the chain. The desired product would then arise from a transition-state conformation that allowed for the proper overlap of the hydroxyl nucleophile with the enol ether radical cation in direct analogy to the transition states illustrated in Scheme 10.

In practice, this approach to **28** worked very well (Scheme 15). The commercially available **30** was treated using asymmetric dihydroxylation conditions in order to form a keto diol product[16] that was then converted into the desired electrolysis substrate **29** with the use of a Wittig reaction. The anodic

(14) For previous syntheses see: (a) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1997**, *53*, 4353. (b) Mischitz, M.; Faber, K. *Synlett* **1996**, 978. (c) Corma, A.; Iglesias, M.; Sánchez, F. *J. Chem. Soc., Chem. Commun.* **1995**, 1635. (d) Garcia, M. A.; Méou, A.; Brun, P. *Synlett.* **1994**, 911. (e) Méou, A.; Bouanah, N.; Archelas, A.; Zhang, X. M.; Guglielmetti, R.; Furstoss, R. *Synthesis* **1990**, *91*, 752. (f) Howell, A. R.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1990**, 103. (g) Howell, A. R.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2715.
(15) Gill, M. *Nat. Prod. Rep.* **1999**, *16*, 301.
(16) Brimble, M. A.; Rowan, D. D.; Spicer, J. A. *Synthesis* **1995**, 1263.

**Scheme 15**

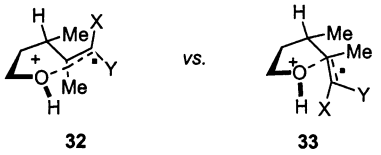



cyclization reaction then afforded the dimethoxy acetal of **31** in an 80% isolated yield as a 7:1 mixture of trans- and cis-isomers. A hydrolysis reaction then completed the synthesis of **28** in just four steps. The stereochemistry of the building block was established by conversion of the major isomer into (+)-linalool oxide.

### Improving the Stereoselectivity of the Reactions: Use of a Ketene Acetal Initiating Group

While the use of stereoelectronics to govern the stereoselectivity of the reaction has proven useful, the best way to increase the stereoselectivity of the reaction further would be to introduce a steric preference for the major isomer. For example, consider the two possible transition states illustrated in Chart 1. If a

**Chart 1**

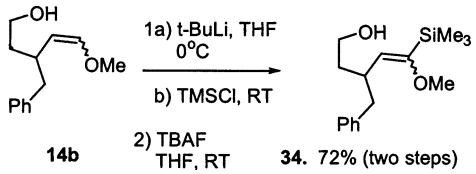



second substituent (X) were added to the original enol ether, then the radical cation group would be much larger. This would increase the size of the steric interaction between the radical cation and the methyl group at C3 of the chain. In **32**, the two groups would be trans to each other. Hence, the steric interactions would be larger in transition state **33** and both sterics and stereoelectronics would work in concert to favor the desired isomer.

If an electron donating group was added to the enol ether, then the proposed cyclization would require the oxidation of a ketene acetal equivalent.[17] Such a scenario was very attractive for the synthesis of (+)-nemorensic acid since the ensuing reaction would lead directly to the formation of a carboxylic acid derivative.

Efforts to determine the utility of this approach began with the synthesis of a substrate containing a trimethylsilyl substituted enol ether as the initiating olefin (**34,** Scheme 16).[18] This

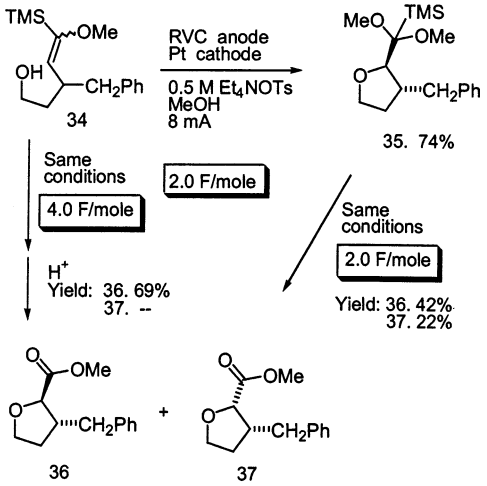
**Scheme 16**




substrate was synthesized from **14b** using a deprotonation strategy after efforts to effect its synthesis from lactone **13b** using a Peterson olefination reaction met with failure.

The anodic oxidation of substrate **34** was initially conducted using the same electrolysis conditions described earlier but without the 2,6-lutidine proton scavenger (vide infra). When the oxidation was continued until 2.0 F/mol of charge had been passed (Scheme 17), a 74% isolated yield of cyclized product

**Scheme 17**




**35** was obtained. A small amount of a second (cis?) isomer was evident in the $^1$H NMR of the crude reaction product; however, this product was not isolated following purification. The stereochemistry of **35** was determined with the use of a NOESY experiment that showed that the methine proton at C3 of the ring and the methoxy and TMS groups of the C2 substituent were on the same face of the five-membered ring.

The two-electron oxidation product **35** could be resubjected to the oxidation conditions (another 2 F/mol) in order to remove the TMS group and form a methyl ester (the initially formed ortho ester was not stable to the aqueous workup conditions used for the reaction).[19]

Interestingly, this reaction scrambled the stereochemistry at C2 of the furan ring leading to both *trans*- (**36**) and *cis*-methyl ester (**37**) products in a 64% isolated yield. Apparently, the reaction conditions led to equilibrium amounts of an elimination product (Figure 1). While the cis-product **37** could be converted back into the trans-isomer **36** with the use of an aqueous acid wash, the formation of the elimination product was worrisome since the resulting ketene acetal would be expected to have a very low oxidation potential. Oxidation of this product would detract from the overall yield of the desired process. With this in mind, the reactions were attempted without the 2,6-lutidine that is normally added to electrolysis reactions in order to protect

(17) Examples of cyclizations resulting from the oxidation of a ketene acetal with chemical oxidants are not common. (a) For a single example of a cyclic ketene acetal being coupled to an allylsilane terminating group with the use of a vanadium(V) ester see: Ryter K.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 2658. (b) A pair of oxidative cyclization reactions resulting from the intramolecular coupling of a ketene dithioacetal group with a trisubstituted olefin using ceric ammonium nitrate and a related coupling using a styrene terminating group have been reported: Snider, B. B.; Shi, B.; Quickley, C. A. *Tetrahedron* **2000**, *56*, 10127.

(18) For the use of silyl substituted enol ethers as participants in anodic carbon−carbon bond forming reactions, see ref 1g.

(19) (a) Yoshida, J.; Maekawa, T.; Murata, T.; Matsunaga, S.; Isoe, S. *J. Am. Chem. Soc.* **1990**, *112*, 1962. (b) Toshida, J.; Watanabe, M.; Toshioka, H.; Imagawa, M.; Suga, S. *Chem. Lett.* **1998**, 1011, and references therein.

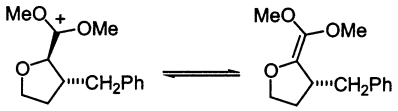


***Figure 1.***

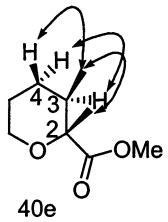



***Figure 2.***

the enol ether from protonation at the anode surface. While these experiments did not dramatically improve the yield of the reactions, they did demonstrate that the 2,6-lutidine was not necessary for the success of the cyclizations.

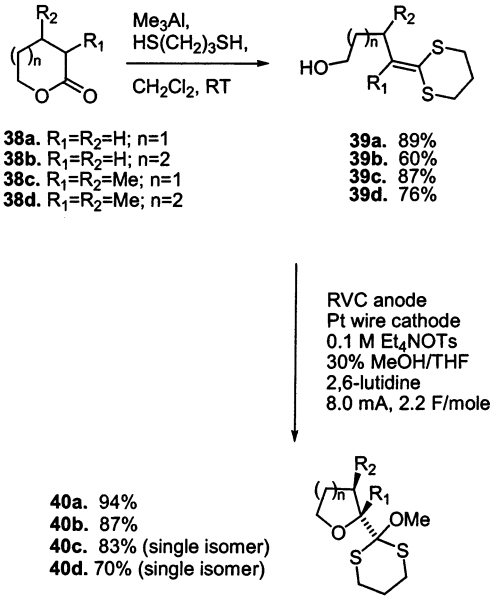
As an alternative to the two-step oxidation process, the desired methyl ester product **36** could be generated directly from substrate **34** with the use of a 4 F/mol oxidation reaction. The crude reaction mixture was treated with aqueous acid during the workup in order to convert the cis-product **37** into **36**. This one pot procedure afforded a 69% isolated yield of **36**.

### Ketene Dithioacetals as Initiating Groups

While the initial work concerning the use of a ketene acetal group was successful at selectively synthesizing products having the ester and C3 methyl groups trans, it was hampered by both the length of the substrate synthesis and the fact that substrates having an allylic methyl group on the $\beta$-carbon of the enol ether (C2) could not be synthesized. Because of this limitation, the cyclization reaction could not be used to generate a quaternary carbon and therefore had little applicability to the synthesis of (+)-nemorensic acid. With this in mind, we turned our attention toward examining the utility of ketene acetal equivalents that were easier to synthesize, were stable to isolation, and had oxidation potentials that were low enough to allow for the presence of a wide variety of substituents. To this end, a ketene diothioacetal appeared to be an ideal choice.[20] Ketene dithioacetals can be readily synthesized from both aldehyde[21] and ester functional groups,[22] and they had proven to be useful initiators for earlier carbon−carbon bond forming reactions.[1g,h]

Substrates **39a**−**d** were synthesized by treating the corresponding lactone[23] with trimethylaluminum and 1,3-propanedithiol in dichloromethane and then oxidized in order to ascertain the compatibility of the ketene dithioacetal group with the anodic formation of tetrahydrofuran and tetrahydropyran products (Scheme 18). The electrolyses were conducted using the same conditions described earlier. In each case, a high yield of the cyclized product was obtained. The cyclization reactions originating from **39a** and **39b** indicated that the electrolyses had the potential to synthesize both five- and six-membered ring ether products in high yield, while the cyclization reactions originating from **39c** and **39d** probed the effectiveness of the

***Scheme 18***




ketene dithioacetal group with respect to controlling the stereochemistry of the reactions.

The cyclization originating from **39a** was accomplished using either a commercially available setup for doing preparative electrolyses (94%),[7] a 6 V lantern battery (86%),[11] or a $15 multivoltage power adapter from RadioShack (80%).[24] The advantage of the power adapter over the battery is that its voltage can be adjusted to accommodate a variety of substrates. For example, the oxidation of an amide requires the use of a 12 V battery.[11] Using either setup, it was again clear that the reactions did not require the use of specialized equipment.

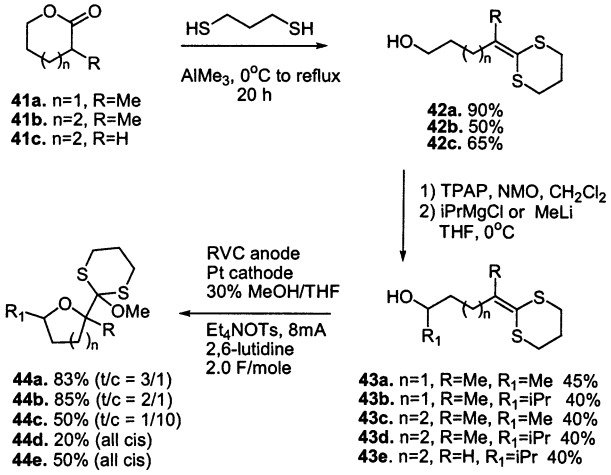
In the case of **39c**, the anodic oxidation led to an 83% isolated yield of *a single tetrahydrofuran product* having the correct stereochemistry for the synthesis of (+)-nemorensic acid. The stereochemistry of the product was determined with the use of a NOESY experiment that used the methine proton at C3 to establish the stereochemistry of the C4 methylene protons. An NOE interaction between the C4 methylene proton on the $\beta$-face of the molecule and both methyl groups then established the stereochemistry of C2 as having the methyl group on the $\beta$-face of the molecule cis to the methyl group at C3, the exact stereochemistry needed for the synthesis of (+)-nemorensic acid.

We also hoped that the use of the ketene dithioacetal initiating group would improve the stereoselectivity of cyclizations leading to six-membered ring products. Since the transition state leading to the formation of a six-membered ring has well-defined pseudoequatorial and pseudoaxial positions, it was thought that the use of a larger initiating group would increase the preference for the radical cation to occupy a pseudoequatorial position thereby favoring the formation of a trans-product. In practice, this proved to be the case and the oxidation of substrate **39d** led to a single tetrahydropyran product. The stereochemistry of this product was assigned by first converting it to the methyl ester product **40e** (Figure 2) and then taking advantage of a NOESY experiment. In this experiment, the methine proton at C3 was used to establish the stereochemistry of the C4 methylene protons. An NOE cross-peak was then observed for the interaction between the C4 methylene proton on the $\beta$-face

(20) For a review on the use of ketene dithioacetals in synthesis see: Kolb, M. *Synthesis* **1990**, 171.
(21) Iorga, B.; Mouriès, V.; Savignac, P. *Bull. Chem. Soc. Fr.* **1997**, *134*, 891.
(22) Corey, E. J.; Kozikowski, A. P. *Tetrahedron Lett.* **1975**, *16*, 925.
(23) For the formation of ketene dithioacetals from lactones see: (a) Chamberlin, A. R.; Nguyen, G. D.; Chung, J. Y. L. *J. Org. Chem.* **1984**, *49*, 1682. (b) Corey, E. J.; Beames, J. D. *J. Am. Chem. Soc.* **1973**, *95*, 5829.

(24) A "Multi-Voltage 800 mA" power adapter (Model 273-1667) was used.

*Scheme 19*

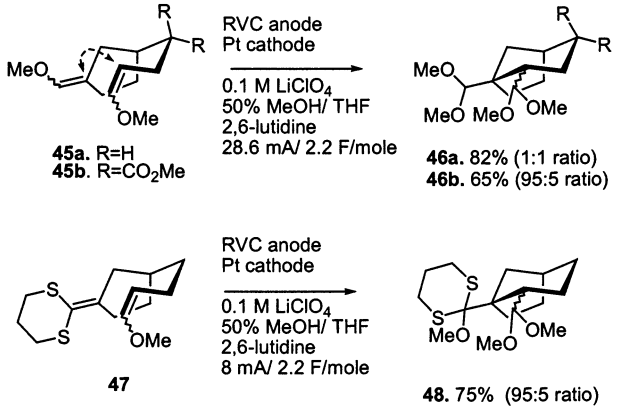



of the molecule and the methyl group at C3. An NOE interaction between the methyl groups at C3 and C2 and the lack of an interaction between the methyl at C2 and the methine at C3 then established the methyl groups as being cis.

To test the steric arguments made for the control of stereoselectivity in these reactions, substrates **43a**−**e** were synthesized (Scheme 19). In these substrates, the substituent at C3 was removed and a substituent added to the carbon bearing the oxygen nucleophile. In the case of the five-membered ring substrates (**43a,b**), such a change would be expected to detract from the degree of stereoselectivity obtained because the increase in selectivity for the cyclizations using the ketene dithioacetal group was presumably a result of a steric interaction between the methyl group at C3 and the radical cation derived from the ketene dithioacetal. However, in the case of a six-membered ring forming reaction the degree of stereoselectivity would be expected to remain the same since the selectivity observed for the cyclization of **39d** was presumably the result of the radical cation occupying a pseudoequatorial position in the transition state. As discussed in connection with Scheme 10, the equatorial methyl groups at C3 in a six-membered ring transition state would interact equally with either an equatorial or an axial radical cation.

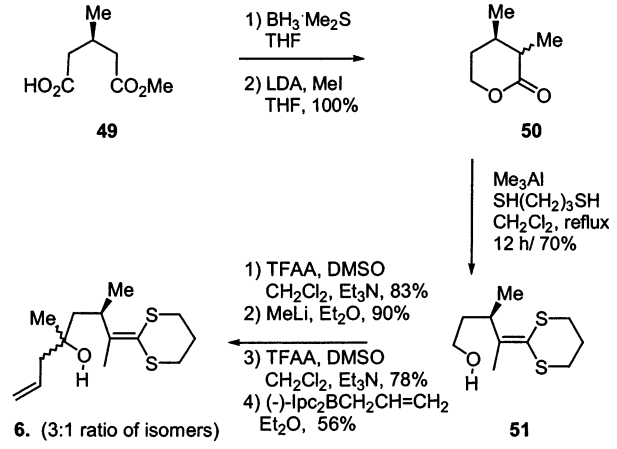
The oxidation of substrates **43a** and **43b** did lead to products with a decreased level of selectivity. For the oxidation of **43a**, an 83% yield of product was obtained as a 3:1 ratio of trans- to cis-isomers. Once the steric interaction was removed, the reaction returned to a level of selectivity that was consistent with the earlier stereoelectronically controlled cyclizations. For the oxidation of **43b**, an 85% isolated yield of product was obtained as a 2:1 ratio of trans- to cis-isomers. As with earlier cases, the cyclization reactions leading to six-membered rings were not as efficient as their five-membered ring counterparts. Nevertheless, the oxidation of **43c** did lead to a 50% isolated yield of the product as a 10:1 ratio of cis- to trans-isomers (in this case the cis-product was the result of both substituents occupying pseudoequatorial positions in the transition state). Clearly, the stereoselectivity of the cyclization was retained in this case. When a sterically larger isopropyl group was added to the carbon bearing the oxygen in the substrate (**43d**), the yield of the reaction dropped off to 20%. The yield of this reaction could only be raised by removing the allylic methyl group from the substrate (**43e**) and hence the need for generating a quaternary carbon in the product.

*Scheme 20*

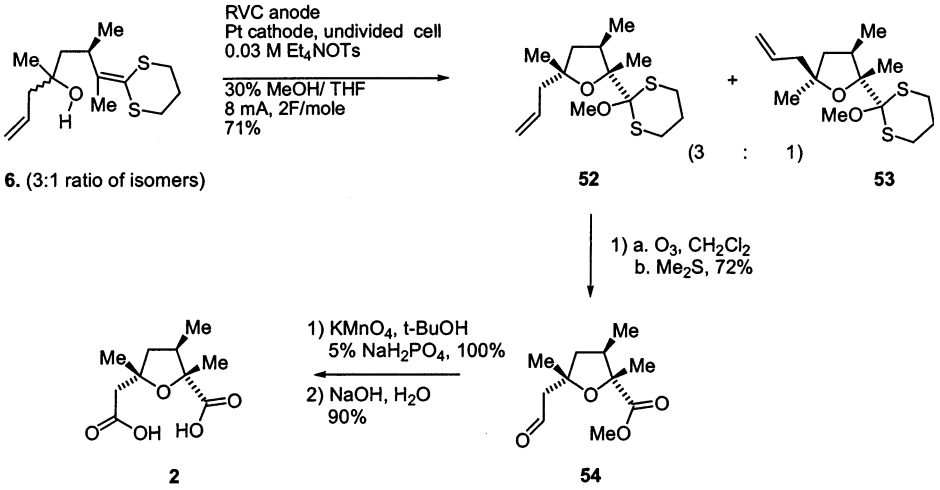



While the kinetic arguments made above are consistent with the experimental observations, it is important to note that the cyclization reactions originating from the ketene dithioacetal moieties can also be explained by thermodynamic considerations. While we have evidence for the enol ether derived cyclizations being under kinetic control, there is no guarantee that the change from the enol ether initiating group to the ketene dithioacetal group did not also alter the mechanism of the reaction. In fact, evidence obtained from a previous carbon−carbon bond forming reaction (Scheme 20) supports this possibility.[1g] In this experiment, the anodic oxidation of **45a** led to the formation of a pair of stereoisomeric products in a 1:1 ratio. The ratio of stereoisomers obtained could be altered by adding gem dimethyl ester substituents to the substrate. In this case, a 1,3-diaxial interaction interfered with the transition state leading to one of the isomers and a 95:5 ratio favoring the isomer having the dimethoxy acetal substituent in an equatorial position was obtained. The ratio of isomers obtained from the cyclizaton could also be altered by changing the nature of the initiating group. When the cyclization was initiated by the oxidation of a ketene dithioacetal (**47**), the reaction again led to the products in a stereoselective fashion even without the directing methyl ester groups. It is difficult to see how the use of the ketene dithioacetal group would alter the preference of the terminating enol ether for a pseudoequatorial position in the transition state relative to the reaction originating from **45a**. However, the stereochemistry obtained from the cyclization would be consistent with thermodynamic control of the reaction.

*Scheme 21*



***Scheme 22***




## Total Synthesis of (+)-Nemorensic Acid

Irrespective of the mechanism of the reaction, it was clear that the use of the ketene dithioacetal group would enable the electrochemical cyclization reaction to construct tetrahydrofuran rings with the correct stereochemistry for synthesizing (+)-nemorensic acid. With this in mind, a substrate for the electrolysis was synthesized as outlined in Scheme 21. The synthesis began with the reduction of methyl (*R*)-(+)-3-methylglutarate according to the known procedure.[25] The resulting lactone was alkylated and then treated with 1,3-propanedithiol and trimethylaluminum in order to generate **51**. Oxidation of the alcohol followed by treatment with methyllithium, a second oxidation, and then treatment of allyl-*β*-isopinocamphenyl-9-borabicyclo[3.3.1]nonane[26] afforded the desired substrate **6**. The substrate was generated as a 3:1 mixture of stereoisomers at the quaternary center. The isomers at this center could not be separated until after the electrochemical cyclization. Alternatively, the final step could be accomplished by treating the ketone with allymagnesium bromide to afford **6** in near quantitative yield as a 1:1 ratio of isomers. Again, the isomers were separated following the cyclization reaction.

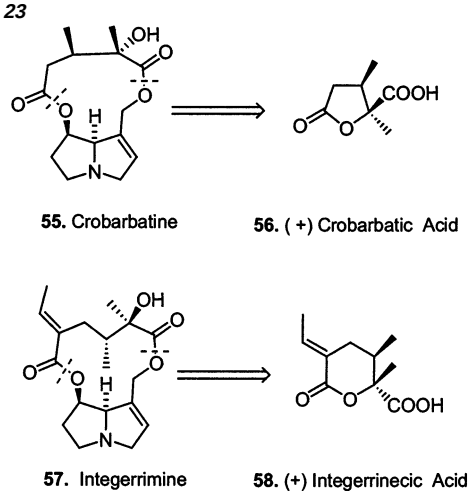
Substrate **6** was oxidized using the same reaction conditions described earlier (Scheme 22). The cyclization reaction led to a 71% isolated yield of the product. At this point the two isomers at C5 were separated. Both isomers had the methyl groups at C2 and C3 cis to each other. The major stereoisomer was then treated under ozonolysis conditions to both cleave the double bond to an aldehyde and convert the dithioortho ester to a methyl ester. In this way, the carbonyls at both ends of the molecule could be unmasked in a single step.

Following the formation of **54**, the aldehyde was oxidized to an acid and the methyl ester saponified in order to complete the 11-step synthesis of (+)-nemorensic acid.

## Extending the Methodology to the Synthesis of Lactone Rings

It is tempting to suggest that the overall approach used to construct (+)-nemorensic acid might also be applicable to other related pyrrolizidine alkaloid natural products. For example, both crobarbatine and integerrimine were synthesized by constructing lactone rings (**56** and **58**) that were then opened to form the necic acid portion of the natural products (Scheme 23).[27] In analogy to (+)-nemorensic acid, both lactones have the oxygen in the ring bound to the carbon alpha to a carboxylic acid. However, in both cases the oxygen in the ring is also part of the ester functional group. Hence, a retrosynthetic analysis of **56** and **58** that was analogous to the route taken in the nemorensic acid synthesis would require the use of a new nucleophile for the anodic cyclization. While a straightforward disconnection of the lactone would suggest the use of a carboxylic acid as the nucleophile (**59** for the synthesis of (+)-crobarbatic acid; Scheme 24), such a cyclization would not be possible due to Kolbe electrolysis of the acid.[28] With this in mind, we began to wonder if either the carbonyl of an ester or the carbonyl of an amide might trap a radical cation derived from the dithioketene acetal in order to directly form the lactone ring.

***Scheme 23***



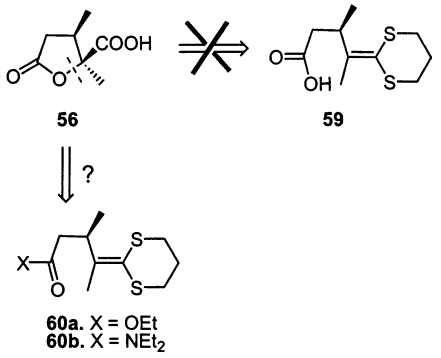

(25) Alvarez, E.; Cuvingny, T.; Hervé du Penuoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 119.

(26) Jadhav, P. K.; Bhat, K. K.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

(27) Honda, T.; Ishikawa, F.; Yamane, S. *J. Chem. Soc., Perkin Trans I* **1996**, 1125, and references therein.

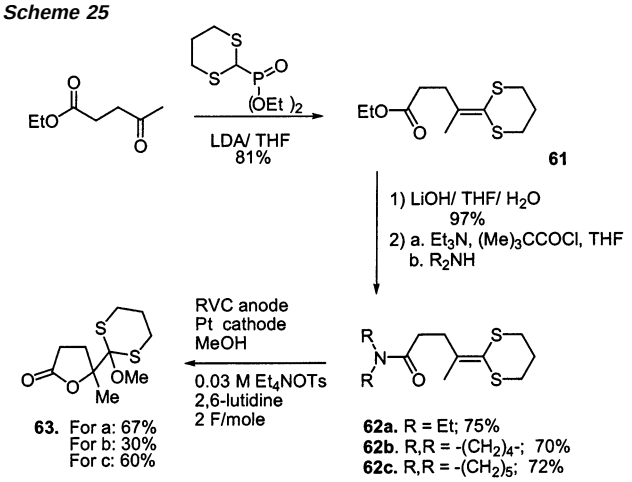
(28) For a review see: Schäfer, H. J. *Top. Curr. Chem.* **1990**, *152*, 91.

*Scheme 24*



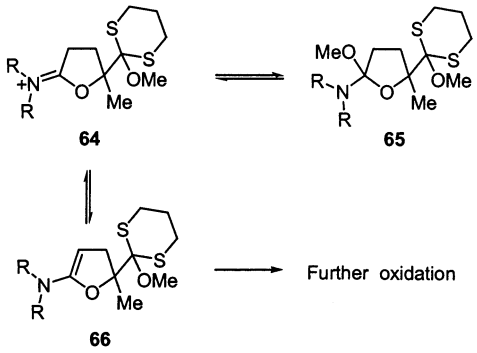

To test the feasibility of this idea, substrates **61** and **62a**−**c** were synthesized and then oxidized using an electrolysis procedure that was nearly identical to the procedure employed in the alcohol terminated cyclizations (Scheme 25). For these substrates, the dithioketene acetal was made using a Horner−Emmons−Wadsworth procedure.[29] The anodic oxidation of **61** did not afford any of the desired cyclized product. However, the oxidation of **62a** led to the formation of the cyclic product **63** in a 67% isolated yield. Presumably, the greater propensity for forming cyclic products from the oxidation of **62a** relative to the oxidation of **61** was related to the greater nucleophilicity associated with the amide carbonyl relative to that of the ester.

*Scheme 25*




The cyclization reaction benefited from the use of pure methanol as the solvent. When the cyclization was conducted using the 30% MeOH/THF conditions employed in the earlier experiments, the oxidation of **62a** led to only a 50% yield of the cyclized product **63**. This result was surprising since anodic cyclization reactions (including the examples using alcohol nucleophiles described above) normally benefit from the use of a cosolvent. One potential explanation for this observation is illustrated in Scheme 26. In this scenario, it is assumed that the initial trapping of the radical cation by the amide is followed by the loss of a second electron and then trapping of the resulting cation by methanol to afford iminium ion **64**. The iminium ion is then trapped by methanol to produce a product (**65**) that subsequently hydrolyzes upon workup to afford the observed lactone **63**. If the trapping of **64** with methanol were either slow or not favored thermodynamically, then the elimination of a proton from the iminium ion would interfere with this process by converting **64** into a second ketene acetal derivative **66**. Compound **66** would have a lower oxidation potential than the initial substrate, and its formation would lead to further oxidation reactions. If this were the case, then the use of a greater concentration of methanol would favor formation of the trapping product **65** relative to **66** and improve the yield of the desired lactone product.

*Scheme 26*




The yield of the lactone product formed was also found to be dependent on the nature of the amide. When a pyrrolidine based amide **62b** was used in place of the diethylamide in **62a**, the yield of the cyclization reaction fell to 30%. The use of a piperidine based amide **62c** returned the yield of cyclized product to 60%. At present, it is not known whether the presence of the five-membered ring in the pyrrolidine amide serves to reduce the overall nucleophilicity of the amide carbonyl or destabilize the iminium ion product initially formed by the cyclization.

The success of the cyclization reactions using either the diethyl amide or the piperidine amide suggests that it may be possible to directly form lactone products relating to **56** and **58** from an anodic cyclization directly analogous to the one employed for the synthesis of nemorensic acid. Efforts to understand the factors that control stereochemistry in the amide-based reactions, as well as the compatibility of these cyclizations with the six-membered ring lactone required for the synthesis of (+)-integerrinecic acid are currently underway.

## Conclusions

The anodic oxidation of enol ethers and ketene dithioacetal groups in the presence of an alcohol nucleophile provides a unique method for the construction of both tetrahydrofuran rings and quaternary carbons. For reactions originating from the anodic oxidation of an enol ether, the stereoselectivity of the reactions appears to be controlled by stereoelectronic factors. For reactions using a larger ketene dithioacetal group as the initiating olefin, the stereoselectivity of the reaction is determined by steric considerations. The cyclization reactions were utilized to synthesize the tetrahydrofuran rings of rotundisine, (+)-linalool oxide, and (+)-nemorensic acid. In the case of nemorensic acid, the synthesis demonstrated how the use of an anodic oxidation reaction reverses the direction in which a synthesis is pursued, an option that both shortened previous synthetic efforts and avoided the stereochemical problems encountered with previous Michael reaction strategies. Recent

(29) Lee, T.-J.; Holtz, W. J.; Smith, R. L. *J. Org. Chem.* **1982**, *47*, 4750.

studies have shown that the cyclization reactions can also be used to directly form a lactone ring.

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**Supporting Information Available:** Full experimental details in addition to proton and carbon NMR spectra for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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