Anodic Coupling Reactions: Probing the Stereochemistry of Tetrahydrofuran Formation. A Short, Convenient Synthesis of Linalool Oxide

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Received June 12, 2001

ABSTRACT



Intramolecular coupling reactions between enol ether radical cations and oxygen nucleophiles are primarily governed by stereoelectronics. By taking advantage of this observation, a tetrahydrofuran building block for use in constructing (+)-linalool oxide and rotundisine has been synthesized in four steps from a commercially available starting material. The synthesis of (+)-linalool oxide has been completed.

By reversing the polarity of enol ethers in the presence of alcohol nucleophiles, anodic oxidation reactions can provide a unique method for forming substituted tetrahydropyran and tetrahydrofuran ring systems (Scheme 1).^{1–3} Since these



reactions form a bond between an oxygen nucleophile and a carbon α to a carbonyl equivalent, they look ideal for constructing tetrahydrofuran containing natural products such as linalool oxide **5**⁴ and rotundisine **6**⁵ (Scheme 2). In both cases, one can envision using the anodic cyclization reaction to construct a common tetrahydrofuran building block 7. Yet while this reaction is easy to propose, it is not clear what factors determine the stereochemical outcome of such cyclizations. Can the anodic cyclization reaction of 8 really be used to synthesize 7 in a stereoselective fashion? We report herein that reactions of this type are controlled by stereoelectronic factors and that they can provide a convenient, stereoselective method for rapidly synthesizing both aldehyde 7 and linalool oxide 5.

ORGANIC LETTERS

2001 Vol. 3, No. 17

2685 - 2688

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The possibility that the oxidative cyclization of **8** might proceed in a stereoselective fashion was suggested by the earlier oxidation of **9a** (Scheme 3).² In this experiment, the



tetrahydrofuran product (10a) was obtained as a 3:1 mixture of isomers favoring the trans product. It was found that this selectivity was not dependent on the stereochemistry of the starting enol ether.⁶ Surprisingly, the analogous oxidation 9b to form a six-membered ring product was not stereoselective and afforded a 1:1 mixture of isomers. This result suggested that the reactions were under kinetic control since thermodynamics would have favored the formation of a sixmembered ring having the larger dimethoxyacetal group in an equatorial position.

Two possible explanations for the observed stereoselectivity appeared reasonable. First, it was possible that the selectivity obtained in the case of the five-membered ring resulted from a steric interaction between the developing acetal group and the neighboring methyl substituent on C_3 . If the transition state were "product-like", then this steric interaction would favor the formation of a product where the two groups were trans to each other. No such preference would be observed for the oxidation originating from **9b**. If the transition state leading to the six-membered ring were "product-like", then either an equatorial enol ether radical cation or an axial enol ether radical cation would have the same relationship to the equatorial methyl group controlling the coiling of the chain. Second, it was possible that formation of the trans isomer **10a** was favored by a stereoelectronic effect.⁷ If the alcohol attacked the π^* orbital of the radical cation, then the required overlap (attack along the Dunitz angle)⁸ would be maximized for a transition state like **11** relative to transition state **12** (Figure 1). No such



Figure 1. Stereoelectronic approaches.

difference would arise for the transition states leading to the six-membered ring products (13 and 14). Understanding which one of these two possibilities controlled the stereo-selectivity of the reaction was critical for predicting the utility of future cyclization reactions. If the stereoselectivity were dependent on the neighboring methyl group, then the oxidation of 8 would most likely be nonselective. If the reaction were controlled by stereoelectronics, then a stereoselective cyclization of 8 was reasonable to suggest.

With this in mind, a series of substrates was synthesized that removed the methyl group from C_3 and replaced it with a sterically bulky group at C_5 of the substrate (Scheme 4).



Six-membered ring substrates were made using the same chemistry starting from δ -valerolactone. In these examples, the alkyl group at C₅ (C₆ for a six-membered ring substrate) was expected to occupy a pseudoequatorial position in the

⁽⁶⁾ When combined with evidence that the reactions are under kinetic control, this observation is best explained by equilibration of the radical cations prior to cyclization.

transition state and thus control coiling of the chain. The substituent would exert little steric influence over the course of the reaction and hence the stereoselectivity observed for the reactions would be principally attributed to stereoelectronic factors.

Substrates 17a-c were electrolyzed using constant current conditions (8 mA/2.0 F/mols), a reticulated vitreous carbon (RVC) anode,⁹ an undivided cell, a Pt cathode, and a 0.03 M tetraethylammonium tosylate in 30% MeOH/THF electrolyte solution (Scheme 5).



The cyclization reactions leading to five-membered rings (17a-c) afforded selectivities that ranged from 5:1 and 4:1 when R was either a *tert*-butyl or an isopropyl group to 2.5:1 when R was a methyl group. The major products were assigned as having trans stereochemistry because of the presence of an NOE interaction between H₁ and H₅ (Scheme 5). The lower selectivity observed for the cyclization originating from **17c** was attributed to the inability of the smaller methyl group to effectively control the conformation of the coiling chain. The selectivities obtained for the oxidations of **17a** and **17b** suggested that the stereochemistry of the reactions was governed by stereoelectronic factors. This suggestion was supported by the oxidations leading to six-membered ring products.

As in earlier intramolecular anodic coupling reactions,^{1,2} reactions leading to six-membered rings were not as efficient as their five-membered ring counterparts. In the case of **17d** the cyclization led to only a 30% isolated yield of the cyclized product. Similar reactions using isopropyl and *tert*-butyl substituents in position R did not lead to any cyclized material. These cyclizations were hindered by *both* the formation of the quaternary center and the substituent at C₆.

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(9) A 100 PPI electrode was used (available from The Electrosynthesis Co., Inc.). 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. As an alternative the reactions can be accomplished with a simple setup using a 6-V lantern battery as the power supply. Frey, D. A.; Wu, N.; Moeller, K. D. *Tetrahedron Lett.* **1996**, *37*, 8317. The earlier substrate leading to the formation of a quaternary carbon with no substituent on C_6 (9b) and substrates having the substituent on C_6 that did not require the formation of a quaternary carbon (17e,f) all led to satisfactory yields of the cyclized products. While the cyclization originating from 17d did not lead to a high yield of the cyclized product, it was informative in that it generated the cyclized products that did form in an approximately 1:1 ratio. As in the earlier cyclization of 9b there was no preference for the enol ether radical cation to occupy a psuedoequatorial position. The stereoselectivity of the cyclizations did not improve greatly when the allylic methyl group (and hence the axial substituent in a transition state like 13, Figure 1) was removed from the substrate. Despite the absence of this methyl group, the oxidation of both 17e and 17f still led to levels of selectivity that were low relative to the selectivities obtained for the oxidations leading to five-membered ring products (17e vs 17a and 17f vs 17b). Clearly, the stereochemistry of the reactions was not controlled by placing the enol ether radical cation in the sterically less hindered psuedoequatorial position, a situation that would have been favored by both the more clearly defined equatorial and axial positions of a sixmembered ring transition state and the absence of the pseudoaxial methyl group. The data supported the view that the reactions were controlled by stereoelectronics.

With that backdrop, we turned our attention to the synthesis of tetrahydrofuran building block 7. For this cyclization it was hoped that the substituent at C_5 of the substrate would approximate the size of a *tert*-butyl group and lead to a synthetically useful degree of stereoselectivity (Scheme 6). This effort began with an asymmetric cis-



⁽⁷⁾ Deslongchamps, P. *Stereoelectronic Effects in Organic Synthesis*; Pergamon Press: Oxford, 1983. In particular note pages 32 and 33. 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, 604.

hydroxylation of the commercially available ketone **23** using the previously reported procedure.¹⁰ The resulting product was then transformed into the desired electrolysis substrate with the use of a Wittig reaction. The anodic oxidation reaction was conducted using the same conditions utilized for the model systems. In this case, the reaction led to an 80% yield of the cyclized product. A 7:1 ratio of trans to cis isomers was obtained. A hydrolysis reaction then completed the synthesis of **7** in just four steps. To confirm the absolute stereochemistry of the product, aldehyde **7** was converted into (+)-linalool oxide **5** with the use of a Wittig reaction.

In conclusion, the intramolecular trapping of an enol ether radical cation by an alcohol nucleophile appears to be controlled by stereoelectronics. Reactions generating fivemembered ring products that would be expected to have larger stereoelectronic differences between competing transition states consistently led to higher stereoselectivities than their six-membered ring forming counterparts that would

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have larger steric differences between competing transition states. When the conformation of the coiling chain was effectively controlled, the reactions led to five-membered rings with synthetically useful levels of stereoselectivity. This information was used to develop an efficient, four-step synthesis of a key tetrahydrofuran building block **7**.

Acknowledgment. We thank the National Science Foundation (CHE-9023698) for their generous support of this work. We also gratefully acknowledge the Washington University High Resolution NMR facility, partially supported by NIH grants RR02004, RR05018, and RR07155, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.

Supporting Information Available: A sample for the experimental electrochemical procedure is included along with characterization data for the electrochemical substrates and corresponding products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0162670