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Stereospecific Synthesis of Dienones via a Torquoselective Retro-Nazarov Reaction

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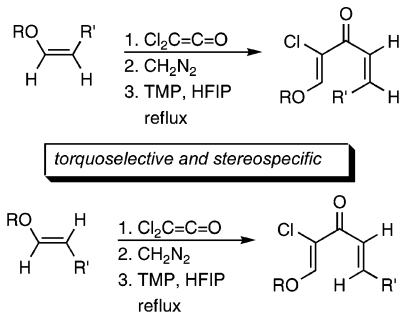
ABSTRACT

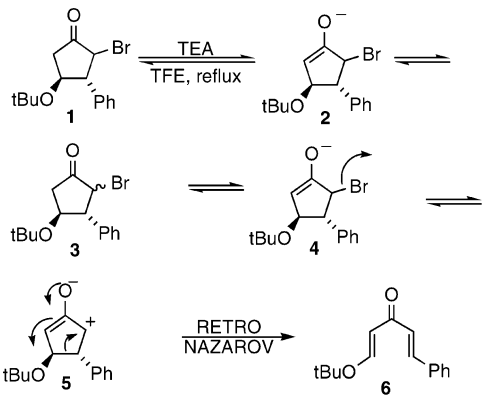


Enol ethers are cleaved via a three-step sequence involving cycloaddition with dichloroketene, ring expansion with diazomethane, and a base-mediated retro-Nazarov reaction. The latter conrotatory process proceeds torquoselectively and stereospecifically in accord with theoretical predictions.

We recently reported the first examples of the retro-Nazarov reaction. In our original work, treatment of a 2-bromocyclopentanone such as **1** with triethylamine (TEA) in refluxing trifluoroethanol (TFE) resulted in the formation of a dienone, presumably via a retro-electrocyclization of the cyclopentenyl oxyallylic cation **5**, in other words, a retro-Nazarov reaction (Scheme 1).[1]

We have examined this process computationally and are using the results to guide us in formulating guidelines involving the kind of substituents flanking the cleaving bond that will inhibit or promote the reaction.[2] We pursued an experimental study that showed that an alkoxy group was sufficient to promote the reaction, as shown in eq 1. Thus, treatment of **7** with TEA in refluxing TFE afforded **8** in 51% yield, a result of a retro-Nazarov reaction followed by a conjugate addition. However, a single aryl or even several alkyl groups flanking the cleaving bond did not promote the reaction.[2] An aryl group and an alkyl group flanking the cleaving bond resulted in retro-Nazarov reaction (eq 2).

Scheme 1



One of the predictions based on our calculations was that the retro-Nazarov reaction would be torquoselective. This

(1) Harmata, M.; Lee, D. R. *J. Am. Chem. Soc.* **2002**, *124*, 14328.
(2) Harmata, M.; Schreiner, P. R.; Lee, D. R.; Kirchhoefer, P. L. *J Am. Chem. Soc.* **2004**, 126, 10954.

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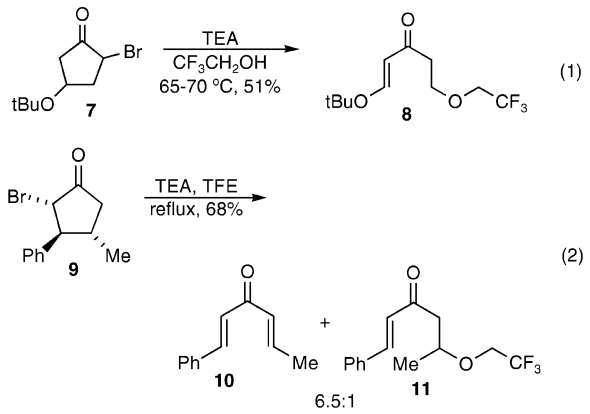
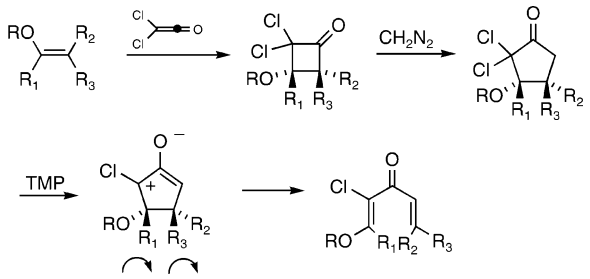


prediction was in line with work by Houk on related electrocyclic processes.[3] This report documents that the retro-Nazarov reaction is torquoselective and that the process is not just mechanistically interesting. It can be used to prepare compounds not easily accessible by other means.

We initially decided to prepare a set of appropriate substrates using the general approach shown in Scheme 2.

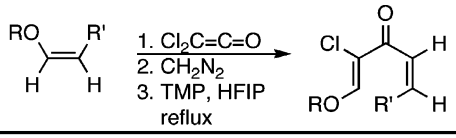
Scheme 2

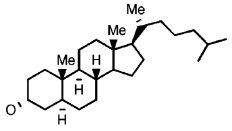
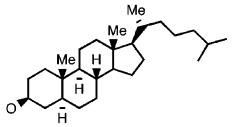
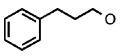


Cycloaddition of dichloroketene to an enol ether would lead to a dichlorocyclobutanone. Ring expansion with diazomethane would then afford a dichlorocyclopentanone, which would be subjected to treatment with base to effect the retro-Nazarov reactions. At the outset of the work, it was not clear how the presence of a chloro substituent in the oxyallylic cation would affect the retro-electrocyclization, but it turned out to be inconsequential.

Our results using *cis* enol ethers are shown in Table 1. Dichloroketene was generated via reductive elimination of trichloroacetyl chloride in the presence of an appropriate enol ether.[4] The latter were in general formed by the isomerization of the corresponding allylic ethers or by reduction of ynol ethers.[5,6] Details are given in Supporting Information. The ring expansion of cyclobutanones using diazomethane had already been described.[7] Purification of intermediates was generally not performed and quoted yields include all three steps. Reactions were conducted in refluxing hexafluoroisopropanol (HFIP) in the presence of 2,2,6,6-tetramethylpiperidine (TMP) as base.[8]

Table 1. Retro-Nazarov Reactions of *cis*-3,4-Disubstituted Cyclopentenones



entry	OR	R'	yield (%)[c]
1	*t*-BuO	Et	51(80)
2	*t*-BuO	*n*-Pr	54(81)
3	*t*-BuO	*n*-Bu	52(80)
4	*t*-BuO	*n*-heptyl	57(83)
5	*t*-BuO	1-phenethyl	51(80)
6	OAd[a]	*n*-Bu	56(82)
7	OAd	1-phenethyl	51(80)
8	OAd	Me	53(81)
9		Me	52(80)
10		Me	58(83)
11		Me	55(82)
12[b]		Et	51(80)[d]

[a] 1-Adamantyl. [b] *Z*:*E* ratio of enol ethers was 93:7 by NMR analysis. [c] Numbers in parentheses are average yields per step. [d] A 7% yield of the *E* isomer was also isolated. NMR analysis of the crude product indicated a 91:9 ratio of *Z*:*E* isomers.

According to our computational predictions,[2] *cis* enol ethers should undergo conrotatory ring opening to place the alkoxy group on the outside of the transition structure to give a dienone with two (*Z*)-alkenes. The basis for this preference has been discussed in the context of cyclobutene ring openings[3a] as as well as cyclopentenyl cation ring openings,[3b] and the concept should be general.

As illustrated in entries 1−11 of Table 1, we found that our procedure produced *single diastereomers of products*. The coupling constant for the protons on carbons 4 and 5 on the dienone were in the range of 11.5−11.6 Hz. This was at the high end of a *cis* coupling constant and the low end of a *trans* coupling constant. We were nevertheless confident in our assignment, since dienones that we had

(3) (a) Dolbier, W. R., Jr.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471. (b) Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 6006.

(4) (a) Nebois, P.; Greene, A. E. *J. Org. Chem.* **1996**, *61*, 5210. (b) Mehta, G.; Rao, H. S. P. *Synth. Commun.* **1985**, *15*, 991. (c) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949.

(5) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560.

(6) Kann, N.; Bernards, V.; Greene, A. E. *Org. Synth.* **1997**, *74*, 13.

(7) Greene, A. E.; Deprés, J.-P. *J. Am. Chem. Soc.* **1979**, *101*, 4003.

(8) These reaction conditions have largely superseded those involving triethylamine in refluxing trifluoroethanol.

prepared earlier[2] and that were expected to possess the *E* configuration had vicinal coupling constants between the corresponding protons of 15.1−16.2 Hz, strongly supporting a *trans* relationship.

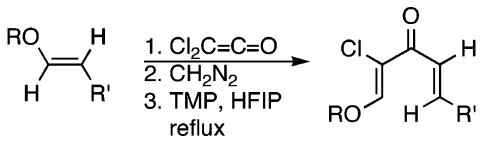
After considerable effort with several systems, we were able to produce very nice crystals of the product from entry 8 of Table 1. The crystal structure of this compound proved our stereochemical assignment and it is this structure, along with our NMR data, which we used to make stereochemical assignments of all the other compounds.

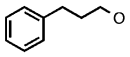
We were interested in examining the stereospecificity of this reaction. Entry 12 of Table 1 suggests that the reaction may be stereospecific, but the ratio of isomers in the products and starting materials do not correlate perfectly. We think this may be due to inherent errors in such measurements. We decided to examine several configurationally pure *E* enol ethers and examine the outcome of the retro-Nazarov reaction derived from such species. The results are shown in Table 2.

In all cases, *only single diastereomers* of dienone products were detected by NMR in crude reaction mixtures. Thus, starting with enol ethers that were pure *E* by NMR resulted in products that were pure *E* by NMR. Stereochemical assignments of the 4,5-double bond were made on the basis of coupling constants (15.1−16.2 Hz). An X-ray structure was obtained for the product of entry 3 in Table 2. The enol ether *E*/*Z* mixture shown in entry 5 of Table 2 gave a good correlation withthe products derived from the retro-Nazarov reaction sequence (79:29 vs 81:19, *E*:*Z*). We thus conclude that this reaction is both torquoselective and stereospecific.

In summary, we have demonstrated a stereospecific and torquoselective cleavage of enol ethers via a process that includes a retro-Nazarov reaction. The synthesis of the product dienones would not be trivial by other methods and the process represents the stereoselective synthesis of both di- and trisubstituted alkenes in a single molecule. Further studies of this process and application of the products produced are in progress, and new results will be reported in due course.

Table 2. Retro-Nazarov Reaction of *trans*-3,4-Disubstituted Cyclopentenones



entry	OR	R'	yield (%)[d]
1		Et	52(80)
2	OCy[a]	Et	59(84)
3	OAd[b]	Et	53(81)
4		Et	52(80)
5[c]	OMe	cyclohexyl	45(77)[e]

[a] Cyclohexyl. [b] 1-Adamantyl. [c] *E*:*Z* ratio of enol ethers was 79:21 by NMR. NMR analysis of the crude product indicated a 81:19 ratio of *E*:*Z* isomers. [d] Numbers in parentheses are average yields per step. [e] An 8.6% yield of the *Z* isomer was also isolated.

Acknowledgment. We thank the National Science Foundation for support of this work. Fluorinated solvents used in this study were a gift from Halocarbon Products Corporation, to whom we are grateful. We also thank referees for valuable suggestions.

Supporting Information Available: Experimental procedures, spectral data, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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