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Oxidation-Initiated Nazarov Cyclization of Vinyl Alkoxyallenes

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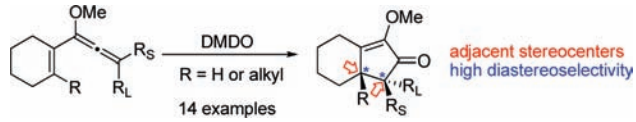
ABSTRACT



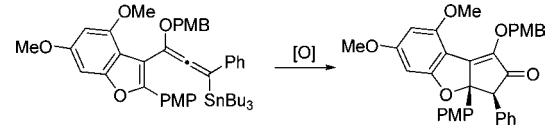
A mild method for the diastereoselective formation of C_4, C_5-disubstituted cyclopentenones has been developed, involving formation of a pentadienyl cation via diastereoselective oxidation of a vinyl alkoxyallene. Conrotatory electrocyclization provides the cyclopentenone product. The broad scope, mild conditions, and uncommon substitution pattern accessible through this transformation make it a useful addition to the existing repertoire of cyclopentenone synthetic methods.

Cyclopentenones are an architectural underpinning of a wide range of natural products and medicinal agents. Moreover, their practical use as intermediates en route to these compounds of interest makes the development of methods for their synthesis of perennial importance.

The Nazarov cyclization has, in recent times, played an increasingly prominent role in this capacity.[1] The prototypical version employs the Lewis acid activation of a divinyl ketone to generate a pentadienyl cation, which undergoes π^4_a conrotatory electrocyclization to form an oxyallyl cation. Subsequent elimination forms the cyclopentenone. Less commonly, access to the requisite pentadienyl cation is gained via routes that do not conform to this conventional rubric.[2]

Such an approach is exemplified in our laboratory's recent synthesis of (±)-Rocaglamide,[3] wherein the key step employs a novel Nazarov cyclization triggered by the oxidation of a vinyl alkoxyallene (Scheme 1). In this case, a pentadienyl cation is generated upon oxidation, instead of via exposure to an acidic promoter. Cyclization gives the cyclopentenone, and both stereocenters created during the electrocyclization are retained in the product.[4]

Scheme 1. Oxidation-Initiated Nazarov Cyclization in the Synthesis of (±)-Rocaglamide



This transformation is suspected to follow the same basic mechanism as the metabolic conversion of polyunsaturated

(1) (a) Nazarov, I. N.; Zaretskaya, I. I. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1941**, 211. (b) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. (c) Habermas, K. L.; Denmark, S. E.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.: New York, 1994; Vol. 45, pp 1−158. (d) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577. (e) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (f) Tius, M. A. *Eur. J. Org. Chem.* **2005**, *11*, 2193. (g) Grant, T. N.; Rieder, C. J.; West, F. G. *Chem. Commun.* **2009**, 5676. (h) Nakanishi, W.; West, F. G. *Curr. Opin. Drug Discov.* **2009**, *12*, 732.

(2) (a) Iso-Nazarov example: Miller, A. K.; Banghart, M. R.; Beaudry, C. M.; Suh, J. M.; Trauner, D. *Tetrahedron* **2003**, *59*, 8919. (b) Aza-Nazarov example: Dieker, J.; Fröhlich, R.; Würthwein, E.-U. *Eur. J. Org. Chem.* **2006**, *23*, 5339. (c) Metallo-Nazarov example: Lemiere, G.; Gandon, V.; Cariou, K.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2007**, *9*, 2207. (d) Dichlorocyclopropane Nazarov example: Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348. (e) Vinylogous Nazarov example: Rieder, C. J.; Winberg, K. J.; West, F. G. *J. Am. Chem. Soc.* **2009**, *131*, 7504. (f) Allenyl aryl carbinol Nazarov example: Cordier, P.; Aubert, C.; Malacria, M.; Lacote, E.; Gandon, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8757.

(3) Malona, J. A.; Cariou, K.; Frontier, A. J. *J. Am. Chem. Soc.* **2009**, *131*, 7560.

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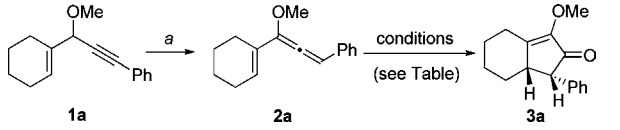
fatty acids to jasmonates in plants, wherein the enzymatic conversion of a vinyl allene to a vinyl allene oxide is followed by formation of a pentadienyl cation that cyclizes to the cyclopentenone.[5] Synthetic studies on the rearrangements of simple vinyl allene oxides to cyclopentenones have also been conducted.[6] Observations included formation of side products resulting from poor epoxidation selectivity[6a] and undesired trapping of the pentadienyl cation intermediate by nucleophiles present in the reaction mixture.[6d]

To expand the utility of the oxidation-initiated cyclization utilized in the rocaglamide synthesis, we sought to explore the oxidation/cyclization of type **2** allenes, which have an alkoxy group on the internal allene terminus (Table 1). Oxidation of these allenes should occur preferentially at the electron-rich internal double bond. Our choice of substrates exploits the cyclization's full potential by enabling the creation of adjacent stereocenters at C_1 and C_5 in high diastereoselectivity.[4b]

Table 1. Oxidant Screening



1a **2a** **3a**

entry	conditions	yield of **3a** (% over 2 steps)[b]
1	*m*-CPBA (1 equiv), DMF, −20 to 0 °C	43
2	(i) PhCN, K_2CO_3, MeOH (ii) H_2O_2 in H_2O	–[c]
3	$VO(acac)_2$, *t*-BuOOH/decane, CH_2Cl_2	–[c]
4	MTO, H_2O_2−urea complex, CH_2Cl_2	–[d]
5	Davis oxaziridine, acetone, 0 °C	50
6	DMDO, acetone, 0 °C	63[e]

[a] Conditions for allene formation: *t*-BuLi, TMEDA, Et_2O, −78 °C then MeOH, −78 °C to rt. [b] Yields reported are for isolated material after purification unless otherwise indicated. [c] Gave an unknown product. [d] Gave a complex product mixture. [e] On the basis of ^1H NMR, using DMF as an internal standard.

Optimization of the cyclization was carried out with carbocyclic propargylic ether **1a** (Table 1). Conversion to allene **2a** was achieved via base-induced isomerization. *m*-CPBA oxidation in different solvents resulted in poor to moderate conversions to bicycle **3a** with *cis*-diastereochemistry shown (entry 1). Payne conditions (entry 2) and vanadium peroxo-complex conditions (entry 3) each yielded different unidentifiable products. Methyltrioxorhenium conditions (entry 4) gave complex mixtures. Oxidation using the Davis oxaziridine gave a reasonable yield of 50%. However, the best results were obtained by using DMDO, which furnished bicycle **3a** in 63% yield.[7]

With use of these optimized conditions, a variety of vinyl allenol ethers with variable substitution patterns were surveyed (Table 2). Because of the instability of the allenes to workup and chromatography conditions, we carried them to the next step without purification. The crude allenes were of estimated 75−95% purity. Nazarov cyclization yields based on these estimations are reported alongside the yields calculated over two steps from the propargylic ether.

Cyclohexenyl allene **2a** cyclized to give bicycle **3a** with exclusively *cis* stereochemistry[8] (entry 1). Prolonged exposure to silica caused partial equilibration to the *trans*-diastereomer **3b**, presumably via keto−enol tautomerism. Interestingly, chromatography on triethylamine-deactivated silica allowed isolation of pure diastereomer **3b** in the same yield (entry 2). These results indicate that Nazarov cyclization leads to the thermodynamically less stable diastereomer. Cyclization of allene **2c**, bearing a methyl group on one of the cyclization termini, gave bicycle **3d** also as the *cis*-diastereomer (entry 4). Allene **2d** yielded **3e** as a single diastereomer, indicating that the methyl stereocenter in **2d** effects a completely torquoselective cyclization (entry 5).[9]

Cyclization of **2f**, bearing a methyl group on the allene terminus, allowed formation of a quaternary center on carbon 5 (entry 7), and placement of methyl groups on both termini (entry 8) cyclized to give bicycle **3h** as a single diastereomer containing adjacent quaternary centers. Cyclization of dihydropyran **2h** resulted in a lower yield, presumably due to competing epoxidation of the two enol ether double bonds (entry 9). With alkyl substitution on the allene terminus (entries 10 and 11), a mixture of diastereomers was observed.

Cyclization of a siloxyethyl-substituted allene resulted in bicycle **3m** in 41% yield over 2 steps (from the vinyl propargyl ether; Scheme 2). Deprotection of the allene and subsequent cyclization of the free hydroxyl-containing allene yielded bicyclic product **3n** in 29% yield over 3 steps, without workup or purification of the intermediates.

(4) For an example of Nazarov cyclization triggered by protonation (rather than oxidation) of an allene, see: (a) Wu, Y. K.; West, F. G. *J. Org. Chem.* **2010**, *75*, 5410. For an example of a Nazarov cyclization that affords products similar to those described here, see: (b) Basak, A. K.; Shimada, N.; Bow, W. F.; Vicic, D. A.; Tius, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 8266.

(5) Recent reviews on the lipoxygenase pathway for jasmonate formation: (a) Schaller, A.; Stintzi, A. *Phytochemistry* **2009**, *70*, 1532. (b) Gfeller, A.; Dubugnon, L.; Liechti, R.; Farmer, E. E. *Sci. Signal.* **2010**, *3*, cm3.

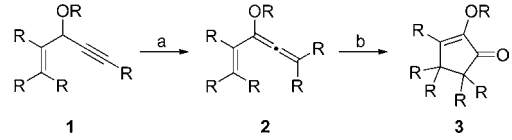
(6) (a) Grimaldi, J.; Bertrand, M. *Tetrahedron Lett.* **1969**, *38*, 3269. (b) Bertrand, M.; Dulcere, J.-P.; Grimaldi, J. *C. R. Seances Acad. Sci., Ser. C* **1974**, *279*, 805. (c) Bertrand, M.; Dulcere, J.-P.; Gil, G.; Roumestant, M. L. *Tetrahedron Lett.* **1979**, *21*, 1845. (d) Doutheau, A.; Gore, J.; Malacria, M. *Tetrahedron* **1977**, *33*, 2393. (e) Dulcere, J.-P.; Grimaldi, J.; Santelli, M. *Tetrahedron Lett.* **1981**, *22*, 3179. (f) Kim, S. J.; Cha, J. K. *Tetrahedron Lett.* **1988**, *29*, 5613.

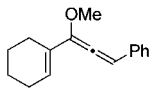
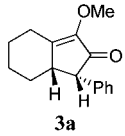
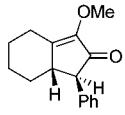
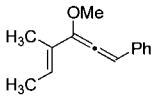
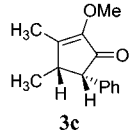
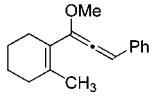
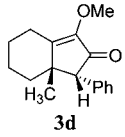
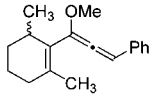
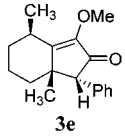
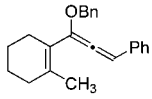
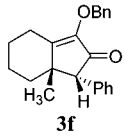
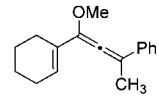
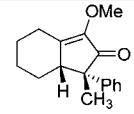
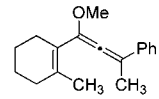
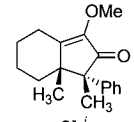
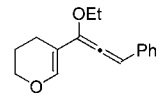
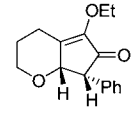
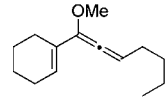
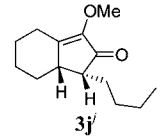
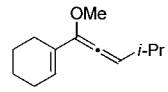
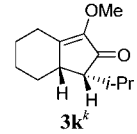
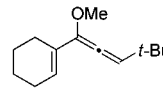
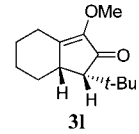
(7) For examples of formation of allene diepoxides with DMDO, see: (a) Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7108. (b) Zhang, Y.; Cusick, J. R.; Ghosh, P.; Shangguan, N.; Katukojvala, S.; Inghrim, J.; Emge, T. J.; Williams, L. J. *J. Org. Chem.* **2009**, *74*, 7707. (c) Ghosh, P.; Cusick, J. R.; Inghrim, J.; Williams, L. J. *Org. Lett.* **2009**, *11*, 4672.

(8) Stereochemistry of Nazarov products was determined by NOE analysis (see the Supporting Information).

(9) This stereochemical assignment is based upon past observations, which indicate that bond formation occurs on the least hindered face of the pentadienyl cation: (a) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821. (b) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168. (c) Denmark, S. E.; Wallace, M. A.; Walker, C. B., Jr. *J. Org. Chem.* **1990**, *55*, 5543. (d) Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610. (e) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P. *J. Org. Chem.* **2003**, *68*, 9728. (f) Prandi, C.; Ferrali, A.; Guarna, A.; Venturello, P.; Occhiato, E. G. *J. Org. Chem.* **2004**, *69*, 7705.

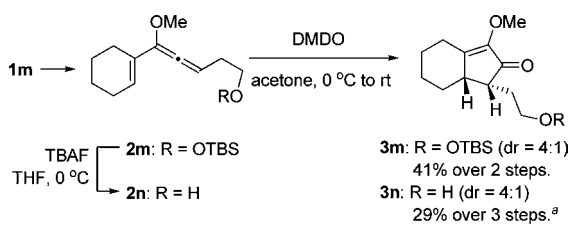
Table 2. Oxidation-Initiated Nazarov Cyclizations



entry	alkoxyallene **2**	diosphenol **3**	yield % over 2 steps (**1**→**3**)/ Nazarov only(**2**→**3**)[c]
1[d]	 **2a**	 **3a**	57/67[e]
2[f]	**2a**	 **3b**	57/67[e]
3	 **2b**	 **3c**	41/48[e]
4	 **2c**	 **3d**	47/55[e]
5	 **2d**[g]	 **3e**	56/65[e]
6	 **2e**	 **3f**	39/52[h]
7	 **2f**	 **3g**	64
8	 **2g**	 **3h**[i]	44/58[h]
9	 **2h**	 **3i**	26
10	 **2i**	 **3j**[j]	60/70[e]
11	 **2j**	 **3k**[k]	57
12	 **2k**	 **3l**	40

[a] *t*-BuLi, TMEDA, Et_2O, −78 °C then MeOH, −78 °C to rt. [b] DMDO, acetone, 0 °C to rt. [c] Yields of Nazarov cyclizations are estimated in cases when allene formation was not quantitative. [d] Extremely fast silica gel chromatography yielded the *cis* diastereomer. [e] Allene estimated to be 85% pure. [f] Et_3N-deactivated silica gel chromatography yielded the *trans* diastereomer. [g] 2:1 mixture of diastereomers. [h] Allene estimated to be 75% pure. [i] Diastereochemical assignment based on NOE analysis of carbonyl reduction product. [j] Isolated as a 4:1 mixture of diastereomers (major shown). [k] Isolated as a 3:1 mixture of diastereomers (major shown).

Scheme 2. Cyclization of Siloxy- and Hydroxyethyl-Substituted Vinyl Alkoxyallenes[a]

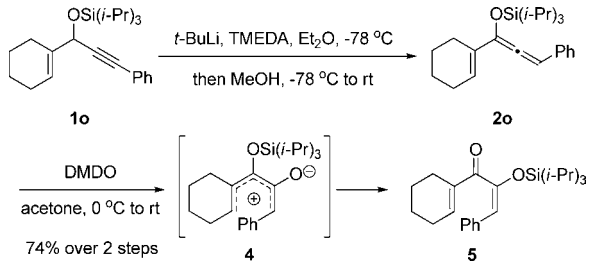


[a] dr based on analogy to **3m**.

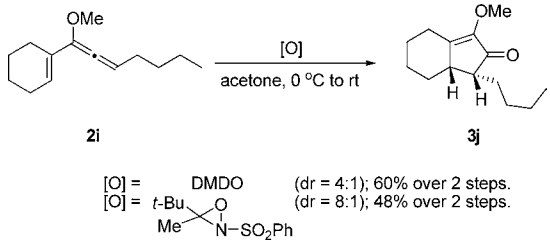
In an attempted cyclization of triisopropylsiloxy allene **1o**, formation of ketone **5** was observed, presumably via transfer of the TIPS group to the adjacent anionic oxygen (see **4**, Scheme 3).[10] Its stereochemistry suggests that oxidation occurs on the face of the internal allene double bond away from the phenyl group, which is consistent with literature precedent.[7,11] However, in substrates with an alkyl group on the allene terminus instead of a phenyl group, selectivity was not as high (Table 2, entry 10; 4:1 mixture of diastereomers). If **2i** was treated with a bulky version of the

(10) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319.

Scheme 3. Rubottom Oxidation of *O*-Silylated Allenol Ethers



Scheme 4. Cyclization of **2i** with Use of a Bulky Oxaziridine



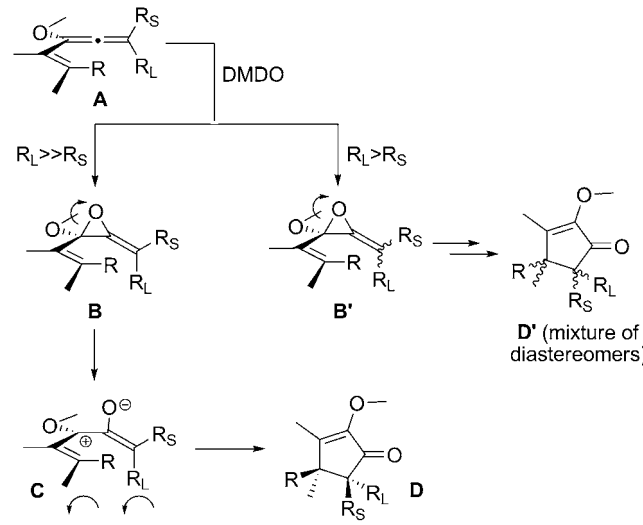
Davis oxaziridine[12] instead of DMDO, an 8:1 mixture of diastereomers was obtained (Scheme 4).

On the basis of these results and the stereochemistries of the remaining cyclization products, we hypothesize that in cases where there is a large difference between steric bulk of the two substituents on the allene terminus ($R_L \gg R_S$, Scheme 5), DMDO oxidation of the allene occurs on the face opposite R_L. This produces either allene oxide **B** (as a single diastereomer) or generates **C** directly (with control of enolate geometry). Pentadienyl cation **C** then undergoes conrotatory electrocyclization to give cyclopentenone **D** as a single diastereomer (products **3a**, **3c**, **3d**, **3f**, **3g**, **3h**, and **3i**).

For reactions in which the steric difference between R_L and R_S is smaller, our results suggest that the oxidation does not occur exclusively opposite R_L (see **A** to **B′**; Scheme 5), and a mixture of diastereomers **D′** is obtained (products **3j**, **3k**, and **3m**). Thus, the selectivity of the oxidation is reflected in the product ratio, since we expect the electrocyclization to occur stereospecifically.[13] As demonstrated in Scheme 4, selectivity was improved with the use of a bulkier oxidant.

In summary, we have developed a mild, oxidation-initiated Nazarov cyclization. The use of vinyl alkoxyallenes controls the regioselectivity of oxidation, which occurs on the more

Scheme 5. Proposed Mechanistic Rationale for Observed Diastereochemistry



electron-rich internal allene double bond. This rearrangement offers an attractive two-step conversion of vinyl propargylic ethers to cyclopentenones with high diastereoselectivity, and the ability to install adjacent quaternary carbons. Development of an enantioselective version of this cyclization is currently underway in our laboratory.

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Note Added after ASAP Publication. Reviewer comments, including text, references, and Scheme 5 changes, are included in the version reposted January 11, 2011.

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

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