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Oxidation-Initiated Nazarov Cyclization of Vinyl Alkoxyallenes

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Abstract

A mild method for the diastereoselective formation of C₄, C₅-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 $\pi 4_a$ 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 ($\pm$)-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

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

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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>.

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 C₁ and C₅ in high diastereoselectivity.⁴

Optimization of the cyclization was carried out with carbocyclic propargylic ether **1a** (Table 1). Conversion to allene **2a** was achieved via deprotonation. *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 using DMDO, which furnished bicycle **3a** in 63% yield.⁷

Using these optimized conditions, a variety of vinyl allenol ethers with variable substitution patterns was surveyed (Table 2). Because of the allenes' instability 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* stereochemistry⁸ (entry 1). Prolonged exposure to silica caused partial equilibration to the *trans*-diastereomer **3b**, presumably via ketoenol 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 10–11), 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). To our delight, 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.

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 Davis oxaziridine¹² instead of DMDO, an 8:1 mixture of diastereomers was obtained (Scheme 4).

Based on 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). Ultimately, these intermediates lead to pentadienyl cation **D**, which undergoes conrotatory electrocyclozation to give cyclopentenone **E** as a single diastereomer (products **3a**, **3c**, **3d**, **3f**, **3g**, **3h**, **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 **E'** is obtained (products **3j**, **3k**, **3m**). Thus, the selectivity of the oxidation is reflected in the product ratio, since we expect the electrocyclozation 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Oxidation-initiated Nazarov cyclization in the Synthesis of (±)-Rocaglamide.

Scheme 2.
Cyclization of Siloxy- and Hydroxyethyl-Substituted Vinyl Alkoxyallenes.
^a*dr* based on analogy to **3m**.

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

Scheme 4.
Cyclization of **2i** Using a Bulky Oxaziridine.

Scheme 5.
Proposed Mechanistic Rationale for Observed Diastereochemistry.

Table 1

Oxidant Screening.

entry	conditions	yield of 3a (% over 2 steps) ^b
1	<i>m</i> -CPBA (1 equiv), DMF, -20 °C to 0 °C	43
2	<i>i.</i> PhCN, K ₂ CO ₃ , MeOH <i>ii.</i> H ₃ O ₂ in H ₂ O	. ^c
3	VO(acac) ₂ , <i>t</i> -BuOOH/decane, CH ₂ Cl ₂	. ^c
4	MTO, H ₂ O ₂ -urea complex, CH ₂ Cl ₂	. ^d
5	Davis oxaziridine, acetone, 0 °C	50
6	DMDO, acetone, 0 °C	63 ^e

^a Conditions for allene formation: *t*-BuLi, TMEDA, Et₂O, -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 Based on ¹H NMR using DMF as an internal standard.

Table 2

yield % over 2 steps (1→3)/ Nazarov only(2→3) ^c	entry	alkoxyallene 2	diosphenol 3	yield % over 2 steps (1→3)/ Nazarov only(2→3) ^c
1	2	3	3a	57/67 ^e	7	2f	3g	64

<p>yield % over 2 steps (1→3)/ Nazarov only(2→3)^c</p>		<p>alkoxyallene 2</p>		<p>diosphenol 3</p>		<p>yield % over 2 steps (1→3)/ Nazarov only(2→3)^c</p>	
1	2	3	entry	8	28	3h ⁱ	44/58 ^h
<p>57/67^e</p>		<p>3bⁱ</p>		<p>3hⁱ</p>		<p>44/58^h</p>
<p>57/67^e</p>		<p>3bⁱ</p>		<p>3hⁱ</p>		<p>44/58^h</p>

yield % over 2 steps (1→3)/ Nazarov only(2→3) ^c
1	2	entry	alkoxyallene 2	diosphenol 3	yield % over 2 steps (1→3)/ Nazarov only(2→3) ^c
9			26
10			60/70 ^e

1	2	3	diosphenol 3	alkoxyallene 2	diosphenol 3	alkoxyallene 2	diosphenol 3	alkoxyallene 2
yield % over 2 steps (1→3)/ Nazarov only(2→3) ^c	yield % over 2 steps (1→3)/ Nazarov only(2→3) ^c	entry	56/65 ^e	11	57

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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).