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Synthesis of 5-Hydroxycyclopent-2-enones from Allenyl Vinyl Ketones via an Interrupted Nazarov Cyclization

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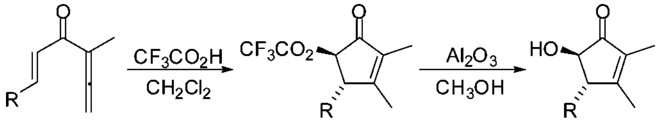
ABSTRACT

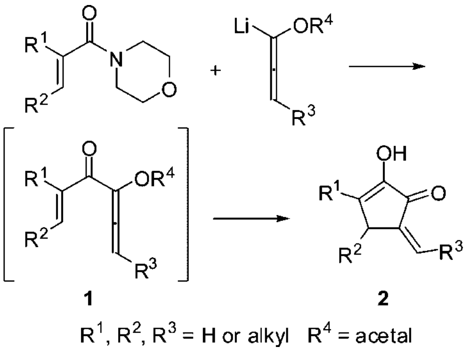


R = H, Me, *i*-Pr, Ph, 4-MeOPh, 4-CF_3Ph, 2-furyl
overall yields 56 - 99%

Treatment of an allenyl vinyl ketone with trifluoroacetic acid leads to Nazarov cyclization, and the intermediate carbocation is trapped efficiently by trifluoroacetate. Hydrolysis of the ester with methanol and basic alumina provides, in good to excellent overall yield, a 5-hydroxycyclopent-2-enone in which the alcohol is predominantly *trans* to a substituent at C-4.

The Nazarov cyclization has become a powerful tool for the construction of substituted cyclopentenones.[1] Strong acids are normally required to induce the cyclization with divinyl ketone substrates, but the reactivity of the substrate can be enhanced by electron-donating or electron-withdrawing substituents. Frontier and co-workers[2] have carefully studied experimentally the electronic effects of substituents. A number of more recent examples of Nazarov cyclizations employ substrates substituted in the α position by an oxygen.[3,4] The Tius group has greatly developed the use of allenyl vinyl ketones **1**, activated by an α oxygen substituent on the allene, as substrates for the preparation of a variety of 2-hydroxycyclopent-2-enone derivatives **2**, which are enolized 1,2-diketones (Scheme 1).[5−7] In addition to the α oxygen, the use of an allene accelerates cyclization as evidenced by the work of Hashmi and co-workers,[8] who showed that Nazarov cyclization of

Scheme 1. Outline of Tius Nazarov Cyclizations with Allenyl Vinyl Ketones



R^1, R^2, R^3 = H or alkyl R^4 = acetal

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[1] Reviews: (a) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479–6517. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577–7606. (c) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193–2206.

[2] (a) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14278–14279. (b) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003–1011.

[3] (a) Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett.* **2003**, *5*, 4927–4930. (b) Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931–4934. (c) Liang, G.; Trauner, D. *J. Am. Chem. Soc.* **2004**, *126*, 9544–9545. (d) Batson, W. A.; Sethumadhavan, D.; Tius, M. A. *Org. Lett.* **2005**, *7*, 2771–2774. (e) Prandi, C.; Deagostino, A.; Venturello, P.; Occhiato, E. G. *Org. Lett.* **2005**, *7*, 4345–4348. (f) Janka, M.; He, W.; Haedicke, I. E.; Fronczek, F. R.; Frontier, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **2006**, *128*, 5312–5313. (g) Williams, D. R.; Robinson, L. A.; Nevill, C. R.; Reddy, J. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 915–918. (h) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097–2100. (i) Amere, M.; Blanchet, J.; Lasne, M.-C.; Rouden, J. *Tetrahedron Lett.* **2008**, *49*, 2541–2545.

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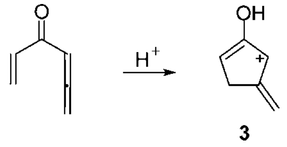
allenyl vinyl ketones that lack an oxygen substituent can take place during chromatography on silica gel.

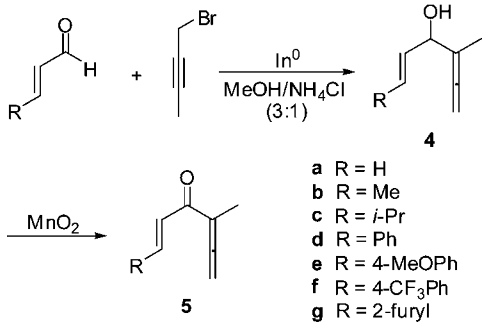
The initial, cationic intermediate of the Nazarov cyclization can be intercepted, or “interrupted,” by a nucleophile.[7,9,10] This process has been cleverly exploited synthetically by West.[11] We hypothesized that the cationic intermediate **3** (Scheme 2) derived by the Nazarov cyclization of allenyl vinyl ketones might be particularly well suited to intermolecular interception by a nucleophile because termination of the process by proton loss from **3** might be disfavored, as this would lead to a fulvene. However, in order to trap the intermediate carbocation derived from the allenyl vinyl ketone **1** with an amine, Tius and co-workers[7] were obliged to conduct the Nazarov cyclization in the absence of solvent and in the presence of silica gel and the amine. Thus, it was our intention to examine the Nazarov cyclizations of some allenyl vinyl ketones under more conventional conditions with the expectation that these would lead to interrupted reactions.

Scheme 2. Carbocation Intermediate from the Nazarov Cyclization of an Allenyl Vinyl Ketone



Our studies began with the preparation of a series of allenyl vinyl ketones (Scheme 3). An indium-mediated Barbier-type coupling reaction[12,13] was employed to react 1-bromo-2-butyne with a variety of α,*β*-unsaturated aldehydes to furnish allenyl alcohols **4a−g** efficiently. However, Dess−Martin periodinane oxidation gave very low yields of the corresponding ketones **5a−g**, which were accompanied by significant amounts of impurities that were difficult to remove. Oxidation of **4a−g** with MnO_2 was somewhat better, but the yields of the ketones ranged from only 21% for **5a** up to 71% for **5f** (over the two steps). These ketones have a methyl group in the α position, which should further stabilize the carbocation intermediate (similar to **3**) and make nucleophilic attack at one of the α positions more sterically encumbered.

Scheme 3. Preparation of Allenyl Vinyl Ketones



Conditions to effect Nazarov cyclizations were surveyed with the allenyl vinyl ketone **5d**, and the results are summarized in Table 1. In contrast with the examples of Hashmi and Tius,[7,8] treatment of **5d** with silica gel failed to provide any cyclized product. Indeed, **5a−g** were purified successfully by column chromatography on silica gel. Whereas concentrated HCl gave no Nazarov cyclization product (entry 1), other Brønsted acids (entries 2−4) provided an oxygen-trapped compound **6** as a single diastereomer in modest to excellent yields. No product with an exocyclic double bond was isolated. The relative stereochemistry of **6** was confirmed by X-ray crystallography. Of the triflates tested (entries 6−8), $Cu(OTf)_2$ slowly destroyed **5d**, but $Sc(OTf)_3$ and $Yb(OTf)_3$ both yielded **6** also. $Yb(OTf)_3$ uniquely gave the alcohol product as an epimeric mixture.

White and West[11b] had observed the trapping of a Nazarov intermediate by chloride when a cyclization had been promoted by $TiCl_4$. Treatment of **5d** with $TiCl_4$ led to the destruction of the substrate, and the result was the same with $AlCl_3$ and $FeCl_3$ (entries 9−11). Compound **5d** was rapidly transformed in the

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(4) Two computational studies of Nazarov cyclizations confirm the facilitation of Nazarov cyclization by an α oxygen substituent: (a) Cavalli, A.; Masetti, M.; Recanatini, M.; Prandi, C.; Guarna, A.; Occhiato, E. G. *Chem. Eur. J.* **2006**, *12*, 2836–2845. (b) Polo, V.; Andrés, J. *J. Chem. Theory Comput.* **2007**, *3*, 816–823.

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(8) Hashmi, A. S.; Bats, J. W.; Choi, J.-H.; Schwarz, L. *Tetrahedron Lett.* **1998**, *39*, 7491–7494. This use of an allene in a Nazarov cyclization was preceded by the following report, in which an oxygen-substituted allene underwent Nazarov cyclization during workup: Tius, M. A.; Kwok, C.-K.; Gu, X.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871–885.

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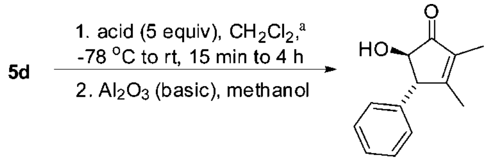
(10) Photochemical Nazarov cyclizations involve trapping of the intermediate by solvent: Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **1994**, *45*, 1–158, and references therein.

(11) Recent examples by West: (a) Browder, C. C.; Marmsäter, F. P.; West, F. G. *Can. J. Chem.* **2004**, *82*, 375–385. (b) White, T. D.; West, F. G. *Tetrahedron Lett.* **2005**, *46*, 5629–5632. (c) Giese, S.; Mazzola, R. D., Jr.; Amann, C. M.; Arif, A. M.; West, F. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 6546–6549. (d) Grant, T. N.; West, F. G. *J. Am. Chem. Soc.* **2006**, *128*, 9348–9349. (e) Rostami, A.; Wang, Y.; Arif, A. M.; McDonald, R.; West, F. G. *Org. Lett.* **2007**, *9*, 703–706. (f) Mahmoud, B.; West, F. G. *Tetrahedron Lett.* **2007**, *48*, 2091–5094. (g) Grant, T. G.; West, F. G. *Org. Lett.* **2007**, *9*, 3789–3792. (h) Rieder, C. J.; Fradette, R. J.; West, F. G. *Chem. Commun.* **2008**, 1572–1574.

(12) (a) Isaac, M. B.; Chan, T.-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003–1004. (b) Alcaide, B.; Almendros, P.; Rodrígues-Acebes, R. *J. Org. Chem.* **2005**, *70*, 3198–3204.

(13) Yields with indium seem to be better than via the tin compound. For instance, **4d** synthesized via the propargyltin was produced in 21% yield, as a 94:6 mixture with the corresponding acetylenic alcohol: Masuyama, Y.; Watabe, A.; Ito, A.; Kurusu, Y. *Chem. Commun.* **2000**, 2009–2010.

Table 1. Nazarov Cyclization of **5d** to **6**[a]



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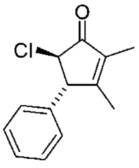
entry	acid	yield (%) of **6**[b]
1	HCl	0[c]
2	*p*-TsOH	71
3	Amberlyst-15	30
4	CF_3CO_2H	96
5	$BF_3{\cdot}Et_2O$	0[d]
6	$Cu(OTf)_2$	0[d]
7	$Sc(OTf)_3$	54
8	$Yb(OTf)_3$	70[e]
9	$TiCl_4$	0[d]
10	$AlCl_3$	0[d]
11	$FeCl_3$	0[d]
12	$AuCl_3$	32 (of**7**)

[a] 0.01 M solutions of **5d**. [b] Isolated yields. [c] Products of the addition of HCl across the π bonds of the allene were obtained. [d] Compound **5d** was completely consumed, but only intractable material was produced. [e] A 1:1 mixture of the *cis* and the *trans* isomers.

presence of $AuCl_3$ (entry 12), but in this case a modest amount of a cyclized product was recovered, and the identity of this product was shown by NMR and MS to be the chloride-trapped compound **7** as a single diastereomer.



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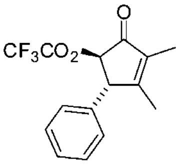

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Trifluoroaceticacid was clearly the best acid for the formation of **6**. The origin of the alcohol oxygen of **6** was trifluoroacetate. This was obvious from the NMR data of the cyclization product, the ester **8**, prior to chromatography on basic alumina. The remaining allenyl vinyl ketones **5a**−**c**,**e**−**g** were reacted using CF_3CO_2H. The trifluoroacetate esters were not purified, but chromatography on basic alumina afforded the 5-hydroxycyclopent-2-enones **9**−**14** with good to excellent yields (Figure 1).[14] The *trans* stereochemistry was assigned to the major product **10a** (from **5b**) and to **11**−**14** on the basis of the similarity of the coupling constants in their ^{1}H NMR data with the corresponding data for **6**. That only **5b** gave a significant amount of *cis* alcohol **10b** suggests that the stereochemistry develops as a result of steric interactions with the substituent at C-4. The reactions of **5f** and **5g** were slower than the reactions of the other allenyl vinyl ketones, and the yields of the corresponding cyclized products **13** and **14** were lower than the yields of **6** and **9**−**12** as a result of the production of less polar byproducts, which were not characterized.

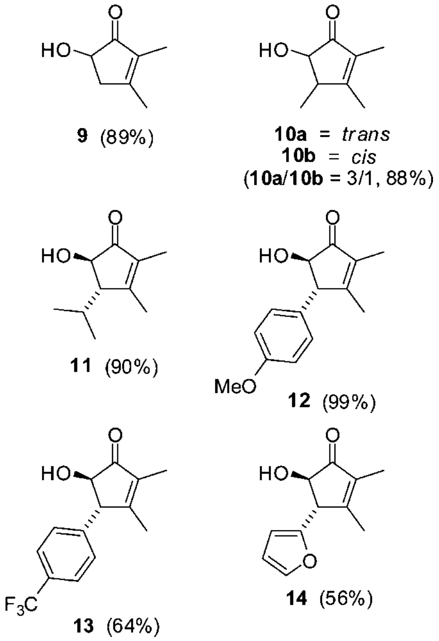

Figure 1. Products of the interrupted Nazarov cyclizations of **5a**−**c**,**e**−**g** (with yields).

In summary, a variant of the Nazarov cyclization has been presented in which the intermediate from an allenyl vinyl ketone has been trapped by trifluoroacetate. Al_2O_3-promoted hydrolysis then provided a 5-hydroxycyclopent-2-enone. When there was a substituent at C-4 in the product, the predominant stereochemistry of the product was *trans*. This intermolecular trapping of a Nazarov cyclization by an oxygen nucleophile offers an opportunity for the production of a variety of cyclopent-2-enones bearing oxygen functionality at the 5-position in good to excellent yield. In addition, the trapping of a similarly derived cation with chloride suggests that allenyl vinyl ketones may be generally amenable to interrupted Nazarov cyclizations. Research in this direction is currently underway.

Acknowledgment. We thank Prof. T. Stanley Cameron for the X-ray crystal structure. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the Killam Foundation for financial support.

Supporting Information Available: Experimental procedures and characterization data; ^{1}H and ^{13}C NMR spectra of compounds **4a**−**g**, **5a**−**g**, and **6**−**14**; ORTEP plot and CIF file for the X-ray analysis of **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Compound (−)-**9** has been isolated from the fermentation broth of ascomycete strain A23−98: Weidler, M.; Rether, J.; Anke, T.; Erkel, G.; Sterner, O. *J. Antibiot.* **2001**, *54*, 679–681.