Highly Diastereoselective Cycloisomerization of Acyclic Trienones. The Interrupted Nazarov Reaction

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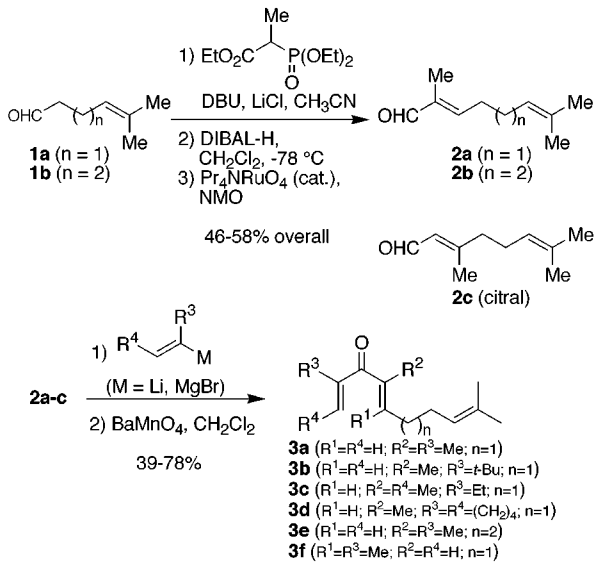
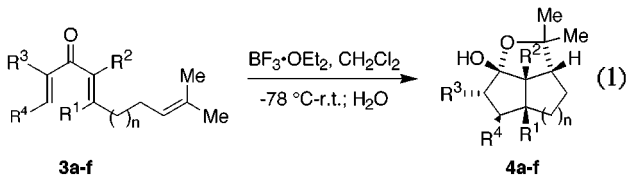
In the pursuit of synthetic efficiency,[1] high value is placed on transformations that create several new stereocenters and bonds in a single operation, in high yield and with good stereocontrol. The reorganization of polyolefinic reactants into fused polycyclic products under cationic conditions exemplifies these ideals and has proven especially useful in the construction of multiple six-membered rings,[2] but application of cation−olefin cyclizations to cyclopentanoid synthesis has been less common.[3] We previously described photocyclizations of pyran-4-ones bearing pendant olefin or arene nucleophiles to furnish functionalized diquinanes and hydrindans.[4] While yielding large increases in molecular complexity, certain aspects of this chemistry reduced its appeal: irradiation in trifluoroethanol raised concerns about scale-up, and necessary installation of an angular hydroxyl in the products was usually not desirable.[5] The Nazarov cyclization proceeds via oxyallyl intermediates analogous to those produced photochemically from pyran-4-ones;[6] however, reports of nucleophilic trapping of this intermediate are limited to a few cases of unexpected solvent capture.[7] We report here the first examples of deliberate trapping of the Nazarov oxyallyl intermediate via cationic cyclization onto pendant olefins, a process that efficiently converts acyclic, achiral trienones into diquinanes with the net formation of two new carbon−carbon bonds and four or five new stereocenters.

Trienone substrates were easily prepared using standard transformations (Scheme 1). Starting from readily available aldehydes **1a**[8] and **1b**,[9] Horner−Emmons olefination followed by DIBAL reduction and TPAP/NMO oxidation led to enals **2a** and **2b**. These materials, along with commercially available citral **2c**, were alkylated with the corresponding organolithium or Grignard reagents, and the resultant dienols were oxidized to the required dienone substrates **3a**−**f** with $BaMnO_4$.

Scheme 1



With these substrates in hand, common Lewis acids were surveyed,[10] and $BF_3{\cdot}OEt_2$ was found to cleanly effect the desired transformation. When dienone **3a** was treated with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C and then slowly warmed to room temperature, a single new product was formed (eq 1).



(1)

Upon workup, isolation, and analysis, the material was found to lack all alkene and carbonyl moieties and to have a molecular weight consistent with hydrated starting material. The product was identified as hemiketal **4a**, as confirmed by X-ray diffraction analysis.[11] All of the prepared substrates were subjected to these reaction conditions, and the results are summarized in Table 1. This process, termed the "interrupted Nazarov reaction", provides good isolated yields of the polycyclic hemiketal products **4** with complete diastereoselectivity when the dienone and alkene trap are linked by a two-carbon tether, and the dienone is substituted at both α positions (entries 1−4).

The proposed mechanism for formation of **4** is shown in Scheme 2. Complexation of the Lewis acid by the carbonyl of the dienone **3** results in the expected four-electron conrotatory electrocyclic closure, establishing a new C−C bond, one or two stereocenters, and a new oxyallyl cation **5**. The cation is then trapped by the pendant olefin in a 5-exo cyclization, establishing a second C−C bond, two more stereocenters, and a tertiary carbocation (**6**). To explain the eventual oxygenation present at the site of the tertiary carbocation, we envisage its subsequent capture by the boron

(1) (a) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3. (b) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 27−66.

(2) Reviews: (a) Taylor, S. K. *Org. Prep. Proc. Int.* **1992**, *24*, 245. (b) Sutherland, J. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 341−377. (c) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341−409.

(3) Examples: (a) Mehta, G.; Rao, K. S.; Reddy, M. S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 693. (b) Wender, P. A.; Correira, C. R. D. *J. Am. Chem. Soc.* **1987**, *109*, 2523. (c) Amupitan, J. A.; Scovell, E. G.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 755. (d) Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800. (e) Lansbury, P. T.; Demmin, T. R.; DuBois, G. E.; Haddon, V. R. *J. Am. Chem. Soc.* **1975**, *97*, 394.

(4) (a) West, F. G.; Fisher, P. V.; Arif, A. M. *J. Am. Chem. Soc.* **1993**, *115*, 1595. (b) West, F. G.; Willoughby, D. W. *J. Org. Chem.* **1993**, *58*, 3796.

(5) For an exception, see: Amann, C. M.; Fisher, P. V.; Arif, A. M.; West, F. G. *J. Org. Chem.*, in press.

(6) (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React. (N.Y.)* **1994**, *45*, 1. (b) Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 751−784. (c) Ramaiah, M. *Synthesis* **1984**, 529. (d) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429.

(7) (a) Hirano, S.; Takagi, S.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 169. (b) Shoppee, C. W.; Cooke, B. J. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2271.

(8) Marbet, R.; Saucy, G. *Helv. Chim. Acta* **1967**, *50*, 2095.

(9) Takano, S.; Chiba, H.; Kudo, J.; Takahashi, M.; Ogasawara, K. *Heterocycles* **1967**, *26*, 2461.

(10) Both $TiCl_4$ and $SnCl_4$ caused oligomerization of the starting materials at −78 °C. $FeCl_3$ provided the desired products, but in lower overall yield than with $BF_3{\cdot}OEt_2$.

(11) A similar hemiketal product was observed as a side product during diene trapping of an alkoxyallyl cation: Harmata, M.; Elomari, S.; Barnes, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 2860.

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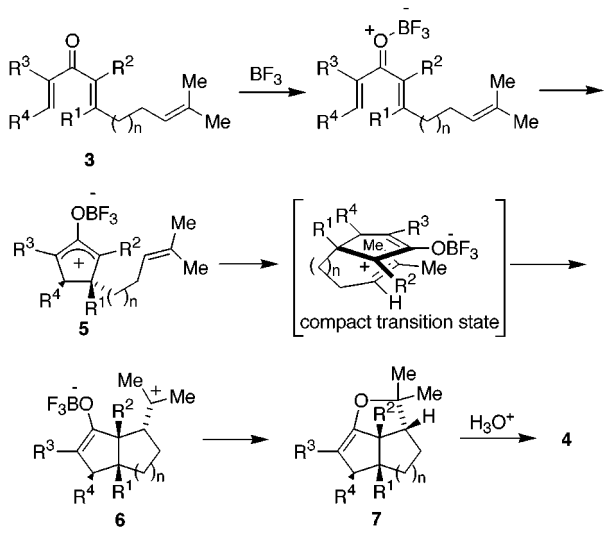
Table 1. Cycloisomerization of Dienones 3a−f to Polycyclic Hemiketals 4a−f[a]

entry	dienone	R^1	R^2	R^3	R^4	n	yield of **4**[b] (%)
1	**3a**	H	CH_3	CH_3	H	1	75
2	**3b**	H	CH_3	$C(CH_3)_3$	H	1	89[c]
3	**3c**	H	CH_3	CH_2CH_3	CH_3	1	73
4	**3d**	H	CH_3	$-(CH_2)_4-$		1	62
5	**3e**	H	CH_3	CH_3	H	2	42[d]
6	**3f**	CH_3	H	CH_3	H	1	*e*

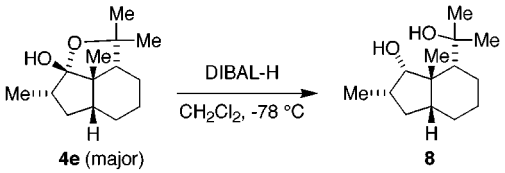
[a] See eq 1. Standard procedure: $BF_3{\cdot}OEt_2$ (4.0 equiv) was added dropwise to a stirring solution of **3** (10 mM) in CH_2Cl_2 at −78 °C. The reaction mixture was allowed to warm to room temperature and stirred for 5 min and then quenched with H_2O and subjected to a standard aqueous workup. [b] Isolated yields after chromatography. [c] Only 2.0 equiv of $BF_3{\cdot}OEt_2$ was used. [d] A 5:1 ratio of epimerizable diastereomers was obtained. [e] Multiple unidentified products were obtained.

Scheme 2



enolate oxygen. This final ring closure can only occur if the carbocation is endo-disposed, which results from cationic cyclization of **5** to **6** exclusively via a compact transition state. Upon aqueous workup, the strained enol ether **7** is hydrated with selective protonation from the convex face to form the last stereocenter, resulting in hemiketal **4**.

When the tether length was increased by one carbon, the hemiketal was produced in diminished yield and as a 5:1 ratio of diastereomers (entry 5). We experienced initial difficulty in assigning the relative stereochemistry of these diastereomers; however, during a 2D NMR experiment on the major diastereomer, we noted the gradual appearance of the minor diastereomer. We then showed that a pure sample of the major diastereomer and an enriched sample of the minor diastereomer in $CDCl_3$ each equilibrated to a 5:1 ratio of diastereomers over a 4 d period. The isomers are presumed to be epimeric at the position adjacent to the hemiketal via a bicyclic enol intermediate, but with the same relative stereochemistry at the other stereogenic centers. In support of this, the major diastereomer was reduced with DIBAL to the crystalline diol **8** and the relative stereochemistry rigorously determined by X-ray diffraction analysis (eq 2). From this, it can be inferred that the 6-exo cyclization largely follows the same stereochemical course as the 5-exo cyclizations of substrates **3a**−**d**.



(2)

The resistance of **3f** to cycloisomerization is also notable (entry 6). Systematic variation of reaction conditions resulted only in multiple products that could not be characterized. It is possible that β-disubstitution sterically impedes the initial electrocyclic closure; however, there are many reports of highly substituted dienones undergoing successful Nazarov cyclizations.[12] A more likely explanation involves the lack of α and α' disubstitution. This should substantially increase the populations of undesired "sickle" (s-cis/s-trans) and "w" (s-cis/s-cis) conformations at the expense of the "u" (s-trans/s-trans) conformation required for the cyclization, permitting alternative reaction pathways to compete with electrocyclization. Also, to the extent that Nazarov cyclization occurs, greater positive charge density should reside at the more distant, substituted carbon of the oxyallyl system, thus reducing the efficiency of the subsequent cation−olefin cyclization. Efforts to develop a more complete understanding of these substituent effects are ongoing.

We have described the first examples using the Nazarov oxyallyl intermediate to initiate cationic cyclizations. This process converts simple trienones to functionalized polycyclic products under straightforward conditions. Four or five stereocenters are set with high control during a cascade of events: (1) electrocyclic conrotatory closure, (2) cation−olefin cyclization via a compact transition state, and (3) face-selective enol ether protonation. Efforts are underway to probe the scope of this new cycloisomerization, including the use of other trapping groups and the development of methods for controlling absolute stereochemistry, and their results will be disclosed at a future date.

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Supporting Information Available: Experimental procedures and physical data for **2a**,**b**, **3a**−**f**, **4a**−**e** and **8**, NMR spectra for **2a**,**b**, **3b**−**d**, and **4a**,**e**, and ORTEP structures and positional parameters for **4a** and **8** (20 pages).

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(12) See, for example: (a) Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168. (b) Mehta, G.; Krishnamurthy, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1319. (c) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500.