Nazarov-Initiated Diastereoselective Cascade Polycyclization of Aryltrienones[1]

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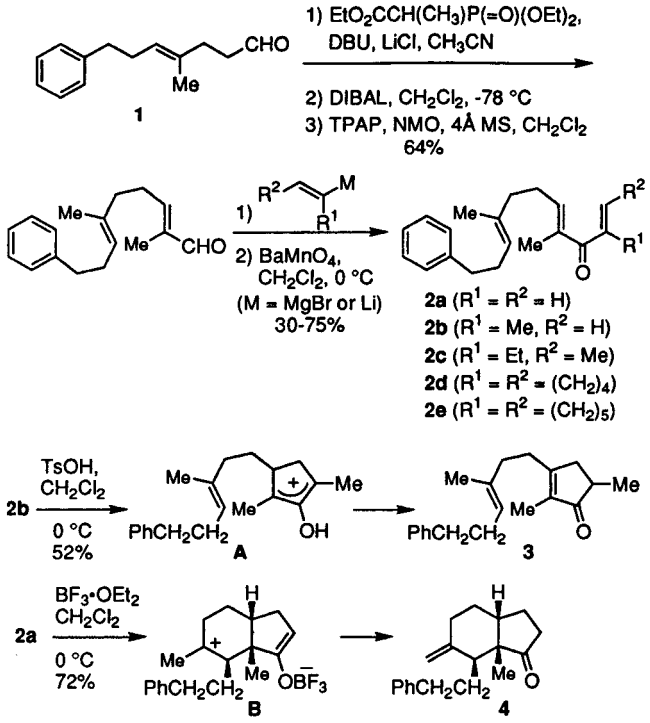
Cationic olefin polycyclizations[2−4] occupy a special position among synthetic methods employing tandem or domino-type reactions.[5] The elegant work of Johnson and others has demonstrated the effectiveness of this approach in the construction of sterol skeletons and related structures.[6] We have recently noted that alkenes and conjugated dienes may function as effective traps of the oxyallyl cation formed upon electrocyclization during the Nazarov reaction.[7,8] These observations prompted an examination of the corresponding cascade polycyclization processes, in which a pendant alkene would function as a reactivity relay between the oxyallyl unit and a terminating aryl moiety. Here we describe our initial result, a high-yield and diastereoselective method for the construction of tetra- or pentacyclic skeletons from simple aryl trienone precursors.

The necessary substrates **2a**−**e** were easily prepared from the known aldehyde **1**[9] through a five-step sequence (Scheme 1). Conditions for effecting the desired cyclization were then examined. Treatment of **2b** with protic acid led to the "traditional" Nazarov cyclization product **3**, while **2a** furnished hydrindenone **4** in the presence of $BF_3{\cdot}OEt_2$. In each case, the desired polycyclization process had been truncated, diverting to elimination products either at the point of the oxyallyl intermediate **A** or the tertiary cation **B** resulting from 6-endo cyclization. Exclusive formation of the exocyclic olefin isomer **4** from **B** is surprising,[10] suggesting a possible intramolecular proton-transfer mechanism.

We have observed that cation elimination pathways predominate only at higher temperatures.[7c] This suggested the use of a stronger Lewis acid in conjunction with a low temperature for the initial electrocyclization. After a survey of several Lewis acids and conditions, we found that the use of $TiCl_4$ at −78 °C cleanly produced cascade polycyclization products **5**, with no apparent

Scheme 1



admixture of elimination products **3** and **4** (eq 1). As noted in

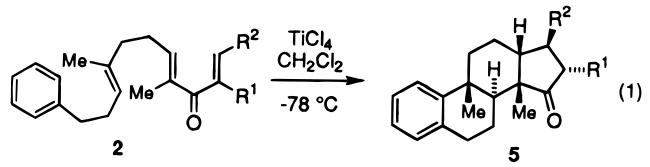


Table 1, substrates **2b**−**e** provided the tetra- or pentacyclic products **5b**−**e** in good to excellent yields. *Importantly, this efficient conversion was accomplished with complete diastereoselectivity in all cases, establishing up to six contiguous stereocenters in a single step.* One apparent limitation is the requirement for α-substitution on the acyclic portion of the dienone, as evidenced by the exclusive oligomerization of unsubstituted substrate **2a**.

The high concentration of overlapping aliphatic protons made structural elucidation by NMR methods difficult. Fortunately, pentacycle **5d** was isolated as a crystalline solid and its structure unambiguously assigned by single-crystal X-ray diffraction analysis. The structures of the closely related **5b**,**c**,**e** were assigned by analogy. The trans B/C ring fusion is expected based upon precedented cationic polycyclization processes,[4] and the cis C/D ring fusion is consistent with simpler 6-endo cyclization examples.[7c] The relationship between the C/D bridgehead proton and R^2 on the neighboring carbon is established by the conrotatory cyclization mandated by orbital symmetry considerations (Scheme 2). Finally, the trans disposition of R^1 relative to R^2 results from

(1) Presented in preliminary form: Bender, J. A.; West, F. G. *Abstracts of Papers*, 213th National Meeting of the American Chemical Society, San Francisco, CA, April 1997; American Chemical Society: Washington, DC, 1997; ORGN 585.

(2) For recent examples of cationic cascade reactions in total syntheses, see: (a) Corey, E. J.; Luo, G.; Lin, L. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126. (b) Corey, E. J.; Luo, G. L.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927. (c) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765. (d) Corey, E. J.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 11982. (e) Romero, A. G.; Leiby, J. A.; Mizak, S. A. *J. Org. Chem.* **1996**, *61*, 6974. (f) Burke, S. D.; Kort, M. E.; Strickland, S. M. S.; Organ, H. M.; Silks, L. A., III. *Tetrahedron Lett.* **1994**, *35*, 1503. (g) Harring, S. R.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 9229.

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(7) (a) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430. (b) Wang, Y.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 876. (c) Browder, C. C.; West, F. G. *Synlett.* **1999**, In press.

(8) Recent reviews of the Nazarov reaction: (a) Habermas, K. L.; Denmark, S. E.; Jones, T. K. *Org. React.* **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.

(9) Brinkmeyer, R. S. *Tetrahedron Lett.* **1979**, 207.

(10) In the BF_3-mediated 6-endo cyclization of Nazarov-derived oxyallyl cations bearing a simple 1,1-disubstituted alkene, elimination of the tertiary cation typically leads to a mixture of exo- and endocyclic olefin products.[7c]

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Table 1. Cycloisomerization of Aryltrienones **2**[a]

substrate	R^1	R^2	product	yield (%)[b]
2a	H	H	**5a**	—[c]
2b	Me	H	**5b**	99
2c	Me	Et	**5c**	73[d]
2d	$-(CH_2)_4-$		**5d**	98
2e	$-(CH_2)_5-$		**5e**	74[d]

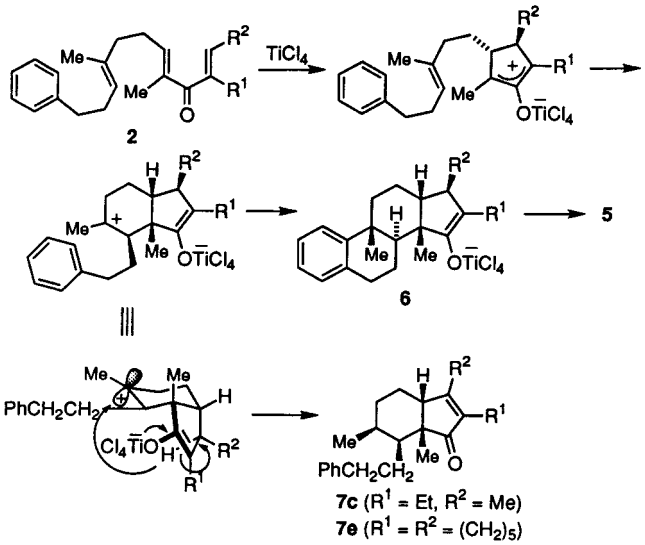
[a] See eq 1. Standard procedure: A CH_2Cl_2 solution of **2** was cooled to −78 °C and treated with 1.1 equiv of $TiCl_4$. After 5 min, the reaction was quenched with brine. Standard aqueous workup and chromatography yielded **5**. [b] Isolated yields after chromatography. In all cases, **5** was isolated as a single diastereomer. [c] The expected product **5a** was not observed; instead, an apparent oligomeric material was isolated. [d] Products **5c** and **5e** were accompanied by small amounts of **7c** (23%) and **7e** (15%), respectively.

exclusive protonation of the titanium enolate **6** from the more accessible convex face of the hydrindan ring system, as we have noted previously.[7a,c]

The yields of polycyclization products **5c** and **5e** were eroded slightly in comparison to the others, and in each of these cases we also isolated a second minor product. The spectral data for these products (**7c**,**e**) were puzzling, as they clearly retained a monosubstituted phenyl group and possessed a cyclopentenone ring, consistent with the simple Nazarov product **3** described above. However, the intervening trisubstituted alkene was no longer present, and the formerly allylic methyl group now appeared as a doublet in the upfield aliphatic region of the proton NMR spectrum. We believe these compounds to be the products of a minor hydride-shift pathway, which would furnish **7c** and **7e** as indicated. Products of this type have also been observed in simple 6-endo cyclizations analogous to these.[7c] The origin of the apparent dependence on substituents is not clear and will be investigated in detail in future studies.

The work described here presents a novel application of the Nazarov cyclization as an initiating step for a cascade polycyclization. Readily prepared aryl trienones **2** can be converted to

Scheme 2



polycycles **5** in high yield and with complete diastereoselectivity. Minor products are also isolated in two cases, apparently resulting from a surprising transannular hydride transfer following 6-endo cyclization. Studies focusing on the construction of other polycyclic frameworks are underway and will be reported elsewhere.

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Supporting Information Available: Experimental procedures, physical data and NMR spectra for **2a**−**e**, **3**, **4**, **5b**−**e**, **6c**,**e** and synthetic intermediates, and X-ray data for **5d** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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