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Highly Stereoselective 6π Electrocyclization of Bridged Bicyclic 1,3,5-Trienes

Chantel L. Benson and F. G. West*

Department of Chemistry, University of Alberta, Edmonton, AB, Canada T6G 2G2

frederick.west@ualberta.ca

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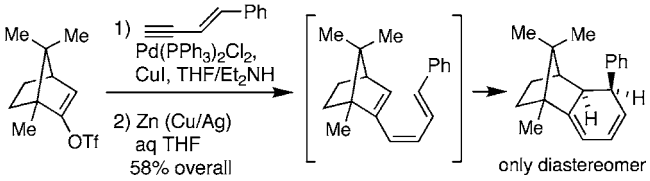
ABSTRACT

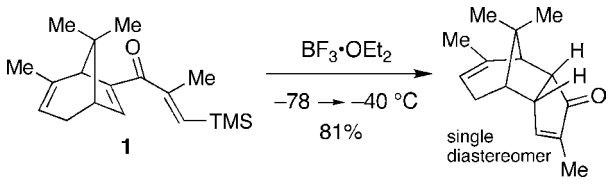


Conjugated 1,3,5-hexatrienes encased in bridged bicyclic skeletons are prepared by cross-coupling followed by half-reduction of the resulting dienynes. The trienes undergo 6π electrocyclization at an ambient or elevated temperature to furnish complex, polycyclic cyclohexadienes. In all cases, complete selectivity in favor of cyclization from the *exo* face of the bridged bicyclic system was seen, in contrast to the corresponding 4π Nazarov cyclizations.

Electrocyclization reactions offer a powerful ring-forming strategy, with the possibility for simultaneous creation of one or two new stereocenters.[1] We have recently investigated the 4π Nazarov electrocyclizations of cross-conjugated dienones in which one of the alkene units is encased within an enantiomerically pure bridged bicyclic skeleton.[2,3] In these studies, high diastereoselectivity for cyclization from the *exo* face of the bicyclic system was seen in most cases; however, bicyclo[3.2.1]octadiene systems such as **1** displayed complete *endo* selectivity in their cyclizations (Scheme 1). Although the origins of this stereochemical reversal are obscure, the presence of the remote olefin was found to be critical for *endo* cyclization to be observed. As a cationic process, the Nazarov cyclization is expected to be sensitive to electronic effects. We wondered whether the corresponding disrotatory 6π electrocyclization of neutral trienes would display the same stereodivergence as a function of different bicyclic skeletons.

Electrocyclizations of conjugated trienes containing the bornene system are known. Magomedov and co-workers examined the enolization of a camphor-based dienone in the presence of the bulky Lewis acid MAD, observing a single (*exo*) diastereomeric cyclohexenone product.[4] Fallis and co-workers also described the generation and cyclization of several bicyclic trienes via vinylmagnesiation of propargyl alcohols, including one possessing the bornene nucleus.[5] However, in those cases the stereochemical outcome was not considered, since the cyclized products were immediately

Scheme 1. *Endo*-Selective Nazarov Cyclization



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(2) (a) Mazzola, R. D., Jr.; White, T. D.; Vollmer-Snarr, H. R.; West, F. G. *Org. Lett.* **2005**, *7*, 2799−2801. (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.

(3) Recent reviews of the Nazarov reaction: (a) Pellisier, H. *Tetrahedron* **2005**, *61*, 6479−6517. (b) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577−7606. (c) Review: Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193−2206.

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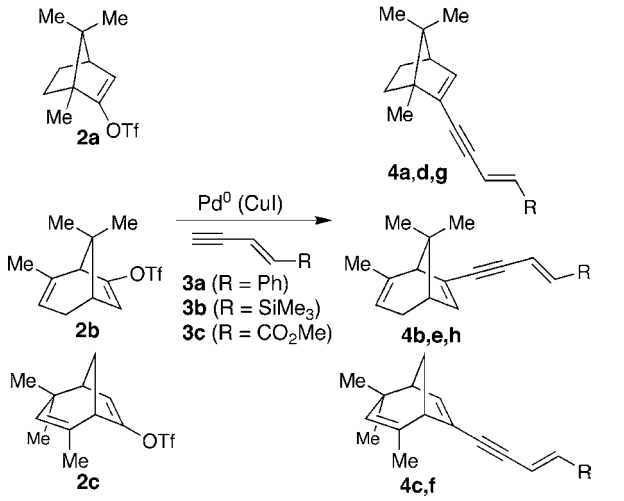
oxidized to the corresponding aromatic systems. Here we report the generation of conjugated trienes containing several different bridged bicyclic ring systems from readily formed dienyne precursors, and their subsequent stereoselective 6π electrocyclization to afford complex polycyclic cyclohexadiene products.

Although Magomedov's enolization method[4] and Fallis' carbometallation approach[5] proved effective in generating the required 3,4-*cis*-trienes, both strategies required the presence of very specific groups along the triene chain. To limit the conformational variables in our investigation of the stereochemical outcomes of these cyclizations, we sought to prepare a series of trienes with minimal substitution. Specifically, we wanted to vary the bicyclic system containing C-1 and C-2, as well as the substituent at the other terminus (C-6), while keeping the other three carbons unsubstituted. Cis reduction of the corresponding 1,5-dien-3-ynes seemed to be the most straightforward method to accomplish this. Thus, initial efforts focused on the construction of the necessary dienynes via Sonogashira or Negishi cross-coupling[6] of bicyclic vinyl triflates **2a**−**c**[7] with enynes **3a**−**c**[8] (Table 1). In the event, Sonogashira conditions afforded **4a**−**c** in excellent yields. However, with enynes **3b**,**c**, Sonogashira reactions were complicated by undesired homocoupling pathways. In these cases, use of the Zn-acetylide was effective, affording **4d**−**f** in good to excellent yields, and **4g**,**h** in acceptable yields.

With the dienynes **4a**−**h** in hand, methods for partial acetylene reduction were examined with use of **4a**. Inital attempts focused on semihydrogenation with the Lindlar catalyst, conditions that were employed effectively in Nicolaou's elegant biomimetic synthesis of the endiandric acids,[9] as well as in the construction of 1α,25-dihydroxyvitamin D3 analogues by Okamura[10] and Gotor.[11]

Although this method produced small amounts of the desired trienes, over-reduced products predominated. This problem has been noted in several other examples involving attempted partial reduction of alkynes in systems with extended conjugation.[12] Inclusion of additives[13] such as 1-octene or pyridine led only to recovery of starting dienyne.

Table 1. Preparation of Dienynes **4a**−**h**



entry	vinyl triflate	enyne	conditions[a]	product	yield,[b] %
1	**2a**	**3a**	A	**4a**	87
2	**2b**	**3a**	A	**4b**	100
3	**2c**	**3a**	A	**4c**	94
4	**2a**	**3b**	B	**4d**	80
5	**2b**	**3b**	B	**4e**	100
6	**2c**	**3b**	B	**4f**	100
7	**2a**	**3c**	B	**4g**	57
8	**2b**	**3c**	B	**4h**	63

[a] Condition A: Vinyl triflates **2** were dissolved in 1:1 THF/Et_2NH (0.02 M) with $Pd(PPh_3)_2Cl_2$ (5 mol %) and CuI (10 mol %). After flushing with Ar, a solution of enyne **3a** (1.2 equiv) in THF (2 mL) was added via cannula, and the reaction was stirred at reflux for 12 h. The reaction was cooled to rt and concentrated, and the crude product was immediately submitted to chromatographic purification (neutral alumina). Condition B: A solution of alkyne **3** (2.0 equiv) in THF (0.6 M) was cooled to −78 °C and treated with 1.0 equiv of BuLi (**3b**) or LDA (**3c**). After 0.5 h, a solution of anhydrous $ZnCl_2$ (2.0 equiv) in THF (0.6 M) was added via cannula, and the resulting solution was warmed to 0 °C. Vinyl triflate **2** (1.0 equiv) in THF (0.3 M) was then added via cannula, followed by $Pd(PPh_3)_4$ (3 mol %) in a single solid portion. The reaction mixture was then stirred at rt (entry 4) or reflux (entries 5−8) until consumption of **2** was observed (TLC). After aqueous workup and extraction (Et_2O), the crude product was subjected to chromatographic purification (silica gel treated with Et_3N or neutral alumina). [b] Yields given are for isolated product after purification.

We next turned to a protocol using Zn activated by successive treatment with $Cu(OAc)_2$, and $AgNO_3$,[14] which has been used for reduction of conjugated alkynes with high *Z*-selectivity and with little accompanying isomerization or over-reduction.[15] When dienyne **4a** was stirred in the presence of the activated Zn for 11 days at room temperature, a 67% yield of the product **6a** was obtained as a single (*exo*) diastereomer (Scheme 2).[16] This compound is presumed to result from half-reduction to **5a**, followed by room temperature electrocyclization. The high *exo* selectivity is consonant with the

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(5) Tessier, P. E.; Nguyen, N.; Clay, M. D.; Fallis, A. G. *Org. Lett.* **2005**, *7*, 767−770.
(6) For a review of Pd-catalyzed alkynylation chemistry, see: Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979−2018.
(7) Mazzola, R. D., Jr.; Giese, S.; Benson, C. L.; West, F. G. *J. Org. Chem.* **2004**, *69*, 220−223.
(8) (a) **3a**: Michel, P.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* **1999**, *40*, 8575−8578. (b) **3b**: Fiandanese, V.; Marchese, G.; Punzi, A.; Ruggieri, G. *Tetrahedron Lett.* **1996**, *37*, 8455−8458. (c) **3c**: Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815−3818.
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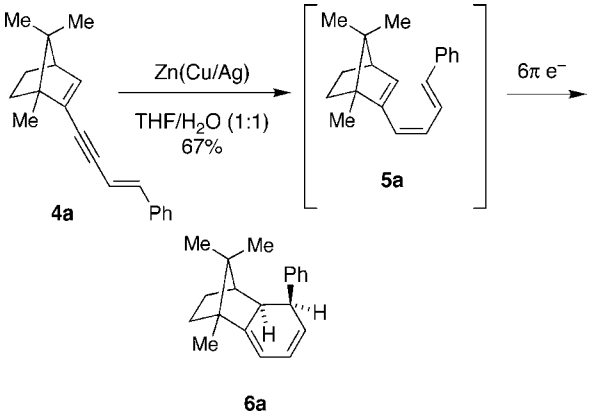
(13) (a) Nicolaou, K. C.; Ladduwahetty. T.; Taffer, I. M.; Zipkin, R. E. *Synthesis* **1986**, 344−347. (b) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1998**, *110*, 2248−2256.
(14) Boland, W.; Schroer, N.; Sieler, C.; Feigel, M. *Helv. Chim. Acta* **1987**, *70*, 1025−1040.
(15) (a) Alami, M.; Crousse, B.; Linstrumelle, G. *Tetrahedron Lett.* **1994**, *35*, 3543−3544. (b) Borhan, B.; Souto, M. L.; Um, J. M.; Zhou, B.; Nakanishi, K. *Chem. Eur. J.* **1999**, *5*, 1172−1175. (c) Nesnas, N.; Rando, R. R.; Nakanishi, K. *Tetrahedron* **2002**, *58*, 6577−6584.
(16) Relative stereochemistry was determined with 2D-TROESY NMR experiments, and ^1H NMR chemical shift trends. See the Supporting Information for a discussion.

Scheme 2. Reduction and *in* Situ Electrocyclization of **4a**



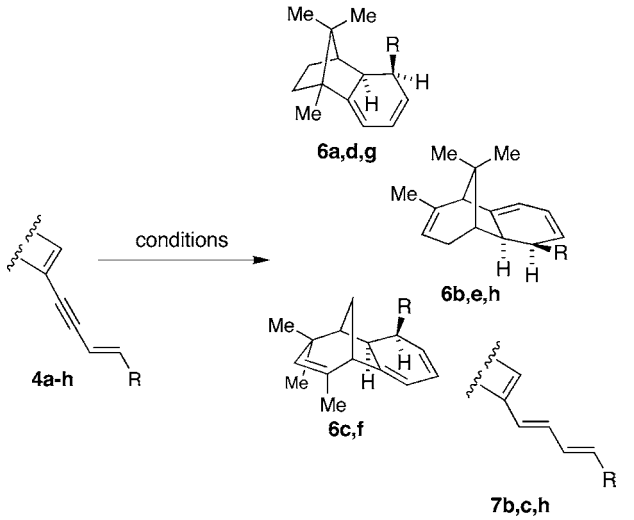
stereochemical course of Nazarov cyclizations of camphor-derived dienones,[2a] as well as the observations of Magomedov and co-workers.[4]

The activated zinc conditions were then applied to the other dienyne substrates, with mixed success (Table 2). Dienynes **4b**,**c** (entries 2 and 3) furnished significant quantities of the undesired (*E*)-trienes, along with the desired cyclohexadienes **6b**,**c**. Low yields of **6c** may be attributed to the ready decomposition of this product under the reaction conditions. Silyl-substituted substrates **4d**−**f** were unreactive under the conditions used for **4a**−**c**, but were consumed when the reaction was conducted at 45 °C. Camphor-derived substrate **4d** was efficiently converted to **6d**, while **6e** was formed in moderate yield with some decomposition. As in the case of **4c**, **4f** and its reduction products were extremely sensitive and underwent rapid decomposition to a complex mixture of unidentifiable compounds. Finally ester-substituted substrates **4g**,**h** failed to furnish any of the desired cyclohexadienes with activated Zn, but Lindlar reduction did provide cyclohexadienes **6g**,**h** in poor to moderate yield (entries 7 and 8). In these cases, partial reduction occurred quickly, and electrocyclization was effected by continued stirring at room temperature. Use of higher temperatures caused triene isomerization and rearrangement of cyclohexadiene products by 1,5-hydride shift.

In all cases involving successful conversion to cyclohexadienes **6**, exclusive formation of the product of cyclization from the *exo* face of the bicyclic olefin was observed, regardless of terminal substituent (R) or bicyclic ring system. The propensity for norbornene systems and related compounds to undergo various addition processes with high or complete *exo* selectivity has been addressed extensively,[17] and these arguments were also applied to the *exo*-selective Nazarov cyclizations seen previously.[2a] Importantly, the disrotatory electrocyclization of these trienes results in a cis

(17) (a) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1967**, *89*, 701−703. (b) Brown, H. C.; Kawakami, J. H.; Liu, K.-T. *J. Am. Chem. Soc.* **1973**, *95*, 2209−2216. (c) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054−4061. (d) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2436−2438. (e) Rondan, N. G.; Paddon-Row, M. N.; Caramella, P.; Mareda, J.; Mueller, P. H.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4974−4976.

Table 2. Reduction/Cyclization of Dienynes **4a**−**h**

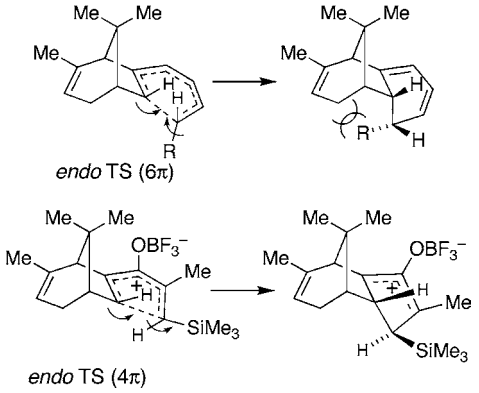


entry	dienyne	conditions[a]	cyclization product	yield,[b] %	other products (% yield)
1	**4a**	A	**6a**	67	
2	**4b**	A[c]	**6b**	50	**7b** (36)
3	**4c**	A[c]	**6c**	20	**7c** (4)
4	**4d**	B	**6d**	90	
5	**4e**	B	**6e**	55	
6	**4f**	B	**6f**		
7	**4g**	C	**6g**	45	
8	**4h**	C	**6h**	27[d]	**7h** (13)[d]

[a] Condition A: Activated Zn (excess; see the Supporting Information for preparation) was added to a flask containing H_2O and THF in a 4:3 ratio. A solution of compound **4** in THF (sufficient volume to furnish a final solvent ratio of 4:4) was added, and the resulting mixture was stirred at rt in the dark until **4** was consumed (6 h to 11 d). Zinc dust was removed by filtration, and washed with large amounts of Et_2O and H_2O. The organic layer was separated, dried ($MgSO_4$), and concentrated, and the crude material was purified by flash chromatography (silica gel). Condition B: Reactants were combined as in Condition A, then stirred at 45 °C in the dark until **4** was consumed (3−6 d). Reactions were worked up as in Condition A, and crude product was purified by chromatography on alumina. Condition C: Compound **4** was dissolved in CH_2Cl_2 (0.02 M), and quinoline (0.66 equiv) was added, followed by Lindlar catalyst (equal amount to **4** by weight). H_2 gas was slowly bubbled through the resulting solution, then the reaction was stirred under an atmosphere of H_2 (balloon) until **4** was consumed (0.5−2 h). The reaction mixture was flushed with argon gas, then filtered through Celite and concentrated, and purified by flash chromatography (silica gel pretreated with Et_3N). [b] Yields given are for isolated product after purification. [c] After consumption of **4**, the crude reduction product **5** was redissolved in THF (**4b**) or $PhCH_3$ (**4c**) and stirred at reflux to effect electrocyclization. [d] **6h** and **7h** were isolated as an inseparable mixture.

relationship for the large groups on the two newly formed adjacent stereocenters of the cyclohexadiene product (Scheme 3). The transition state for 6π cyclization from the *endo* face may entail significant energetic penalties resulting from movement of the terminal R group into a sterically demanding location within the concave portion of the tricyclic skeleton. As a result, even substrates possessing the bicyclo[3.2.1]octadiene nucleus of **2b** undergo *exo* cyclization. In contrast, the conrotatory Nazarov cyclization of substrates such as **1** permits cyclization from the *endo* face, since the bulky terminal group will rotate outward. In addition, the greater polar character of the Nazarov cyclization may render it more sensitive to perturbation by the remote alkene.

Scheme 3. Steric Factors in Electrocyclization Reactions



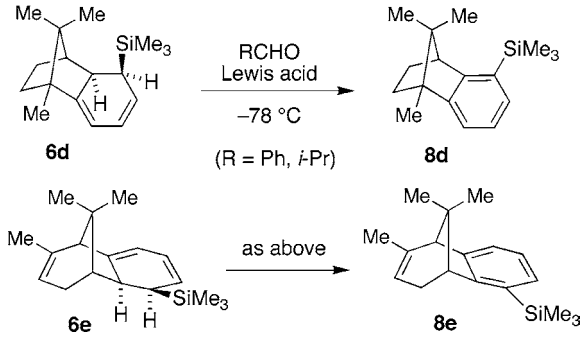
Cyclization in the *endo* mode could be favored since it permits continued homoconjugative overlap between the developing cyclopentenyl cation and the neighboring alkene; the formation of products resulting from apparent interrupted Nazarov reaction in some of these systems[2c] offers support for such an interaction. In contrast, no significant benefit from overlap is expected in the charge-neutral 6π cyclization.

Stereoselective functionalization of the tricyclic products **6** should be possible via a number of processes. We were especially interested in the potential reactivity of dienyl silanes **6d**,**e**, which were expected to undergo reaction with a variety of electrophiles. In preliminary experiments, both compounds were treated with benzaldehyde or isobutyraldehyde in the presence of Lewis acids[18] (Scheme 4). To our surprise, the major products in all cases were aromatic compounds **8d**,**e**, resulting from an apparent dehydrogenation process. Related oxidative aromatizations of cyclohexadienes have been observed previously.[19] The identity of the oxidant is not clear, since the reactions were carried out under an

(18) Lewis acids surveyed: $SnCl_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$, and $InCl_3$.

(19) (a) Suffert, J.; Salem, B.; Klotz, P. *J. Am. Chem. Soc.* **2001**, *123*, 12107−12108. (b) von Essen, R.; Frank, D.; Sünnemann, H. W.; Vidovic, D.; Magull, J.; de Meijere, A. *Chem. Eur. J.* **2005**, *11*, 6583−6592.

Scheme 4. Aromatization of **6d** and **6e**



inert atmosphere. Although the Lewis acid-complexed aldehyde may serve as a possible hydride acceptor, it should be noted that minor amounts of **8d**,**e** were occasionally observed during the reductive cyclization of **4d**,**e**.

As with the Nazarov cyclization, the 6π electrocyclization of bridged bicyclic trienes has been shown to be highly stereoselective. Selectivity for cyclization from the *exo* face was seen in all cases, even those involving the bicyclic skeleton found to undergo *endo*-selective cyclization in the Nazarov process. Substrates are readily prepared by a two-step alkynylation/half-reduction sequence. The resulting products possess unique and complex skeletons, which may be subject to a variety of stereoselective functionalization. Preliminary attempts to carry out allylation reactions with aldehydes resulted in a surprising aromatization pathway. Further studies of these interesting systems will be discussed in future publications.

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Supporting Information Available: Experimental procedures and spectral data for cyclization substrates, precursors, and cyclization products. This material is available free of charge via the Internet at http://pubs.acs.org.

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