

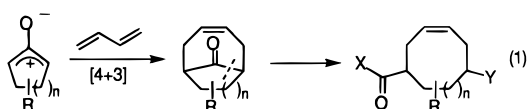
A Novel Cycloisomerization of Tetraenones: 4+3 Trapping of the Nazarov Oxyallyl Intermediate

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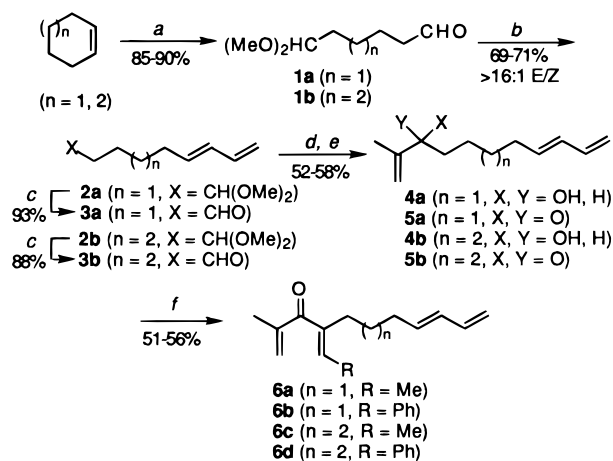
Among the approaches to medium sized rings, cycloadditions stand out for their ability to generate these structures in a single step from simple fragments.^{1,2} For example, [4+3]-cycloadditions employing oxyallyl units and 1,3-dienes offer an attractive route to cycloheptane adducts containing several useful handles for further functionalization.¹ We³ and others⁴ have noted that [4+3]-cycloadditions of cyclic oxyallyls provide access to eight-membered or larger rings via keto-bridged intermediates (eq 1).



The required precursors (pyran-4-ones or 2-halocyclopentanones bearing pendant dienes) and the conditions for their conversion to the short-lived oxyallyl intermediates (UV irradiation or treatment with LiClO₄ in ether) place some constraints on these approaches. Our recent observations that the oxyallyl cation formed during Nazarov cyclization of cross-conjugated dienones can be intercepted with a variety of intra- and intermolecular olefinic nucleophiles⁵ prompted us to investigate the viability of the corresponding 4+3 trapping with dienes. Here we report the preliminary results of these studies, a high-yield entry into polycyclic products via Lewis acid-catalyzed cycloisomerization of simple, acyclic tetraenone precursors.

Preparation of the initially examined tetraenone substrates was straightforward (Scheme 1). Ozonolysis of cyclohexene or cycloheptene with the Schreiber protocol⁶ provided differentiated dialdehyde synthons **1a** and **1b**. Homologation to the dienes **2a,b** was accomplished with high *E/Z* selectivity by using a variation of the Yamamoto method.⁷ Acetal hydrolysis,⁸ Grignard addition, oxidation, and an eliminative aldol addition completed the

Scheme 1^a



^a Reagents and conditions: (a) O₃, MeOH, –78 °C; then TsOH, room temperature; then NaHCO₃, Me₂S; (b) (EtO)₂P(=O)CH₂CH=CH₂, BuLi, THF, –78 °C; then **1a** or **1b** and HMPA; (c) HCl, THF, room temperature; (d) CH₂=C(CH₃)MgBr, THF, 0 °C; (e) DMSO, (ClCO)₂, CH₂Cl₂, –78 °C; Et₃N, 0 °C; (f) LDA, THF, –60 °C; then RCHO; then MsCl, Et₃N; then DBU, THF.

synthesis of **6a–d**. The *E*-geometry of the trisubstituted alkenes in **6** was confirmed by the observation of nOe interactions between protons of R and the nearest methylene group of the tether in the 2D NOESY NMR spectra.

Substrate **6b** was exposed to a variety of Lewis acids (BF₃·OEt₂, TiCl₄, SnCl₄, AlCl₃, Me₃SiOTf) to effect the Nazarov electrocyclization, and FeCl₃ in CH₂Cl₂ at –30 °C was found to be optimal (Scheme 2).⁹ Under these conditions, [4+3]-cycloadducts **7b** and **8b** were obtained in a combined 72% yield (1.3:1 ratio). An identical result could be achieved by using as little as 0.2 equiv of Lewis acid.¹⁰ An nOe interaction between the indicated protons in the 2D NOESY spectrum of **7b** provided strong support for that relative stereochemistry. A similar interaction was not seen with diastereomer **8b**. On this basis, we tentatively assigned the stereochemistry shown, epimeric at the bridgehead methine. The structure of **8b** was confirmed by X-ray diffraction analysis. Notably, two of the four possible diastereomeric cycloadducts, **9** and **10**, were not isolated. The observed product ratio appears to derive from a high diastereofacial selectivity in the cycloaddition, with preferred approach from the less hindered face of the cyclic oxyallyl cation, but only modest selectivity for endo vs exo orientation of the diene and oxyallyl.

Replacement of the phenyl substituent of **6b** with methyl (**6a**) had very little effect on the outcome of the reaction: a 1.3:1 ratio of **7a** and **8a** was obtained in slightly lower (65%) yield.^{11a} However, homologous substrates **6c–d** each furnished a single diastereomeric cycloadduct, **8c** and **8d**, in 67 and 75% yields, respectively. Complete diastereofacial selectivity was obtained as before, but complete exo selectivity was also seen in these cases.^{11b} The large impact of an additional methylene group in the tether is surprising. The origins of this effect are not clear at

(9) (a) For a discussion of the use of anhydrous FeCl₃ in silicon-directed Nazarov reactions, see: Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. Other Lewis acids: (b) Tsuge, O.; Kanemasa, S.; Fujiwara, I.; Wada, E. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 325. (c) Santelli, M.; Dulcere, J.-P.; Morel-Fourrier, C. *J. Am. Chem. Soc.* **1991**, *113*, 8062. (d) Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696.

(10) We are aware of only one other example of the use of catalytic amounts of Lewis acid in the Nazarov reaction.^{5b}

(11) (a) The stereochemistry of **7a** and **8a** was assigned based on close spectral analogy to **7b** and **8b**. (b) The stereochemistry of **8d** was rigorously determined by X-ray diffraction analysis, and that of **8c** was assigned based on close spectral analogy to **8d**.

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(2) (a) Rigby, J. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 617–643. (b) Sieburth, S. McN.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251.

(3) West, F. G.; Hartke-Karger, C.; Koch, D. J.; Kuehn, C. E.; Arif, A. M. *J. Org. Chem.* **1993**, *58*, 6795.

(4) For recent examples, see: (a) Harmata, M.; Elomari, S. E.; Barnes, C. L. *J. Am. Chem. Soc.* **1996**, *118*, 2860. (b) Harmata, M.; Elahmad, S.; Barnes, C. L. *J. Org. Chem.* **1994**, *59*, 1241. (c) Cha, J. K.; Jin, S.-J.; Choi, J.-R.; Oh, J.; Lee, D. J. *J. Am. Chem. Soc.* **1995**, *117*, 10914. (d) Kim, H.; Ziani-Cherif, C.; Oh, J.; Cha, J. K. *J. Org. Chem.* **1995**, *60*, 792.

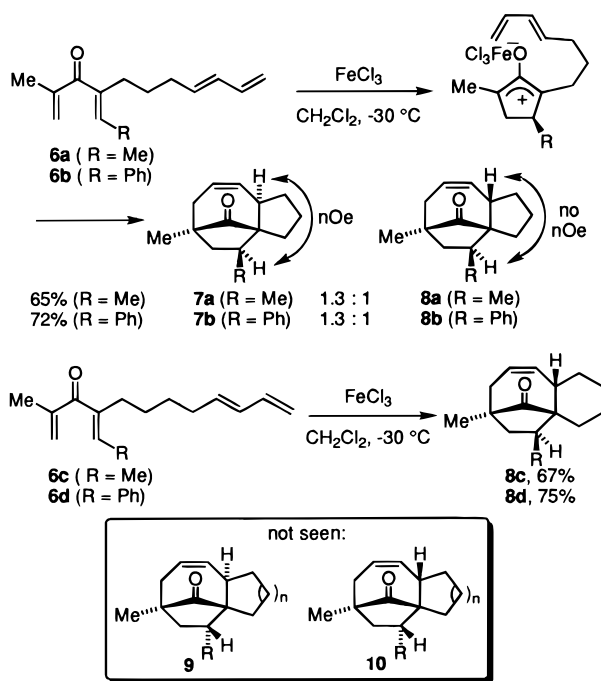
(5) (a) Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem.* **1998**, *63*, 2430. (b) Giese, S.; West, F. G. *Tetrahedron Lett.* **1998**, 8393. (c) Browder, C. C.; West, F. G. submitted for publication.

(6) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150.

(7) (a) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 723. (b) Wang, Y.; West, F. G. Manuscript in preparation.

(8) Aldehyde **3a** had been prepared previously by other routes: (a) Craig, D.; Geach, N. J.; Pearson, C. J.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 6071. (b) Wulff, W. D.; Powers, T. S. *J. Org. Chem.* **1993**, *58*, 2381. (c) Smith, D. A.; Houk, K. N. *Tetrahedron Lett.* **1991**, *32*, 1549. (d) Segi, M.; Takahashi, M.; Nakajima, T.; Suga, S.; Sonoda, N. *Synth. Commun.* **1989**, *19*, 2431. (e) Oppolzer, W.; Dupuis, D. *Tetrahedron Lett.* **1985**, *26*, 5437. (f) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200.

Scheme 2



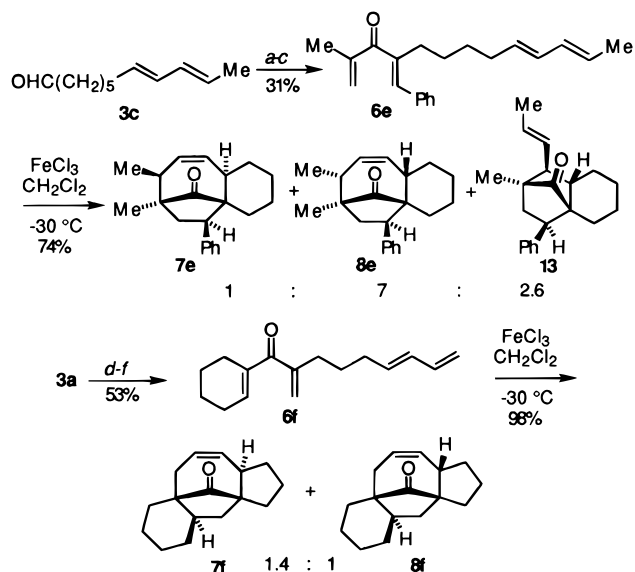
this time and merit further study, though preliminary analysis suggests unfavorable interactions between the diene unit and the tether may be significantly different in the endo and exo transition states.¹²

Two other examples possessing alternative substitution patterns were examined (Scheme 3). Substrate **6e**, containing an additional methyl substituent on the 1,3-diene, was prepared from aldehyde **3c** in analogous fashion to the previously described route (Scheme 1). Application of the standard conditions for tandem electrocycloaddition/[4+3]-cycloaddition led to three products in a combined yield of 74%. Exo cycloadduct **8e** was obtained as the major product along with trace quantities of **7e**. An additional product, **13**, was also isolated. This formal 3+2 adduct is presumed to arise from a stepwise nucleophilic trapping of the oxallyl, followed by enolate closure onto the resulting allylic carbocation.¹³ Its formation solely from **6e** may be a consequence of the greater nucleophilicity of the substituted diene, as well as the more sterically demanding [4+3] transition state.

Finally, aldehyde **3a** was converted to tetraenone **6f** by a variation on the standard sequence. In this case, an unsubstituted methylene group was introduced¹⁴ prior to the addition of cyclohexenyllithium, and the resulting tetraenol was oxidized by using the Dess–Martin conditions.¹⁵ Unlike **6a–e**, this substrate lacked a β substituent on the proximal alkene of the dienone system, but was substituted on both carbons of the distal alkene,

(12) Endo and exo refer to the orientation of the diene in relation to the central carbon of the oxallyl unit. There is some precedent for greater exo/endo selectivity in intramolecular [4+3]- and [4+4]-cycloadditions: (a) Harmata, M.; Herron, B. F. *J. Org. Chem.* **1993**, *58*, 7393. (b) Sieburth, S. McN.; Hiel, G.; Lin, C.-H.; Kuan, D. P. *J. Org. Chem.* **1994**, *59*, 80. (c) Sieburth, S. McN.; Chen, J.; Ravindran, K.; Chen, J. *J. Am. Chem. Soc.* **1996**, *118*, 10803.

(13) For related examples of stepwise 3+2 trapping of cyclic oxallyl cations by 1,3-dienes, see: (a) Harmata, M.; Carter, K. W. *Tetrahedron Lett.* **1997**, *38*, 7985. (b) Giguere, R. J.; Tassely, S. M.; Rose, M. I.; Krishnamurthy, V. V. *Tetrahedron Lett.* **1990**, *31*, 4577. We have also observed this type of reactivity with simple alkene traps.^{5c}

Scheme 3^a

^a Reagents and conditions: (a) $CH_2=C(CH_3)MgBr$, THF, 0 °C; (b) DMSO, $(ClCO)_2$, CH_2Cl_2 , -78 °C; Et_3N , 0 °C; (c) LDA, THF, -60 °C; then PhCHO; then $MsCl$, Et_3N ; then DBU, THF; (d) $CH_2=NMe_2Cl$, Et_3N , CH_2Cl_2 ; then SiO_2 ; (e) cyclohexenyllithium, THF, -78 °C; (f) Dess–Martin periodinane, CH_2Cl_2 , $NaHCO_3$.

and we were interested in what effect this would have on the diastereoselectivity. In the event, the usual conditions furnished endo and exo cycloadducts **7f** and **8f** in a ratio of 1.4:1 and in near quantitative yield. Thus, substituents at either β position of the cyclic oxallyl intermediate exert a powerful bias for approach of the diene from the opposite face, but three-carbon tether once again led to low exo/endo selectivity.

We have described a new class of tandem reactions, involving an initial Nazarov-type electrocyclic closure of a 1,4-dien-3-one, followed by intramolecular [4+3]-cycloaddition of the resulting oxallyl cation with a pendant 1,3-diene. The stereocenter set during the electrocycloaddition leads to complete facial selectivity in the subsequent cycloaddition, and high exo selectivity can be obtained in the cycloaddition of substrates containing a four-carbon tether. This process converts acyclic, achiral reactants into complex, tricyclic products in good to excellent yield, with the concomitant formation of three new carbon–carbon bonds and up to five new stereocenters. Additional studies of the scope of this reaction and its application to complex targets containing these skeletons will be reported elsewhere.

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Supporting Information Available: Experimental procedures and physical data for **2–8** and **13** and X-ray data for **8b** and **8d** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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