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ARTICLE

Efficient synthesis of bicyclo[6.3.0]undecadienones by Nazarov cyclization/regioselective elimination

Carson D. Matier, Yonghoon Kwon, and F.G. West

Abstract: Easily accessible cyclooctadienyl vinyl ketones can generate fused bicyclic 8-5 (bicyclo[6.3.0]undecadienone) ring systems via the Nazarov cyclization when treated with Lewis acid. The resultant products contain three new stereocenters as well as olefins suitably situated to allow further structural elaboration. This concise sequence allows for the rapid preparation of intermediates that should be applicable to a variety of natural product targets containing this bicyclic core.

Key words: divinyl ketone, medium rings, Nazarov cyclization, electrocyclization.

Résumé : Les cyclooctadiényl vinyl cétones, faciles à obtenir, peuvent générer des systèmes à noyau 8-5 (bicyclo[6.3.0]undecadiénone) bicyclique fusionné par cyclisation de Nazarov lorsqu'elles sont traitées par des acides de Lewis. Les produits résultants contiennent trois nouveaux stéréocentres, ainsi que des oléfines bien situées pour permettre une élaboration structurale plus poussée. Cette séquence concise permet de préparer rapidement des produits qui devraient s'appliquer à toute une gamme de substances naturelles cibles contenant ce noyau bicyclique. [Traduit par la Rédaction]

Mots-clés : divinyl cétone, électrocyclisation, cyclisation de Nazarov, noyaux de taille moyenne.

Introduction

The many diverse modalities in which the Nazarov cyclization can by employed to form complex cyclopentanoids products have rendered it a powerful synthetic tool, with many new variations appearing in recent years.[1] The cyclization is typically performed by treating a cross-conjugated dienone (divinyl ketone) with a Lewis or Brønsted acid, generating a pentadienyl cation, which after cyclization yields an oxyallyl cation that undergoes elimination to furnish a conjugated enone. Since its discovery in 1949, the Nazarov reaction has been extensively studied and modified. There is an array of methods to access the pentadienyl cation intermediates with various substrates and acid promotors.[2] Asymmetric versions of the Nazarov cyclization have also been investigated, allowing torquoselective conrotary ring closure.[3]

Development of the interrupted Nazarov cyclization, where the oxyallyl cation is trapped with a nucleophile, has provided methods to furnish new rings and stereocenters, resulting in substantial increases in molecular complexity. Both intermolecular and intramolecular trapping with hydrides, electron-rich arenes, olefins, heteronucleophiles, halides, and [3+2] and [3+4] cycloadditions have been shown.[4] In the late 1990s, the first examples of intramolecular trapping of the oxyallyl cation with pendent olefins were reported.[5,6] On the other hand, transannular trapping of an oxyallyl cation intermediate has not been described to date. For example, transannulation by the distal olefin of a 1,5-cyclooctadiene-derived Nazarov intermediate would rapidly assemble a triquinane skeleton, in analogy to the pioneering studies of Wender[7] and Mehta[8] (Scheme 1). Here, we describe our efforts to apply this approach, resulting in a short and effective route to 8-5 bicyclic ring systems via Nazarov cyclization followed by a highly regioselective elimination step.

Results and discussion

There are only a few examples of Nazarov cyclization to annulate a new cyclopentenyl cation onto a preexisting cyclooctene ring. These have typically involved unconventional precursors rather than the usual cross-conjugated dienones, including dichlorohomoallyl alcohols,[9] propargyl alcohols,[10] vinylcyclobutanones,[11] organomanganese intermediates,[12] or pyran-4-ones.[13] Thus, at the outset, we could not be sure that the dienone precursors envisioned would be suitable Nazarov substrates. Moreover, we required a straightforward route to such substrates.

A succinct synthesis of the target trienones was possible via a simple, two-step protocol (Table 1). Using well-established chemistry by Grunewald and Meier, 1,5-cyclooctadiene and 1-cyclooctene were dibromoinated[14] using pyridinium hydrobromide perbromide and eliminated[15] with potassium *tert*-butoxide to give bromides **1** and **5**, respectively. Bromides **1** and **5** then underwent a lithium–halogen exchange using *tert*-butyllithium. To these lithiated species was added an array of 2-propenal analogues, which coupled by a 1,2-addition to give trienols **2a–2e** and dienol **6**. These doubly allylic alcohols were then oxidized with manganese dioxide to give their corresponding ketones (**3a–3e** and **7**) in moderate to high yields.

Initial experiments using **3a** in the presence of $BF_3{\cdot}OEt_2$ at low temperature gave rapid consumption of the dienone substrate, but the product proved to be bicyclic dienone **4a** rather than the desired triquinane (Table 2, entry 1). Thus, it appeared that following electrocyclization, elimination of a cyclooctenyl proton was preferred over transannular olefin trapping. On the assumption that other activating reagents might modulate the electrophilicity of the intermediate cyclopentenyl cation or affect the rate of elimination, we then examined a number of other Lewis and Brønsted acids (Table 2, entries 2–7).

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Scheme 1. Angular triquinane approach via interrupted Nazarov reaction.

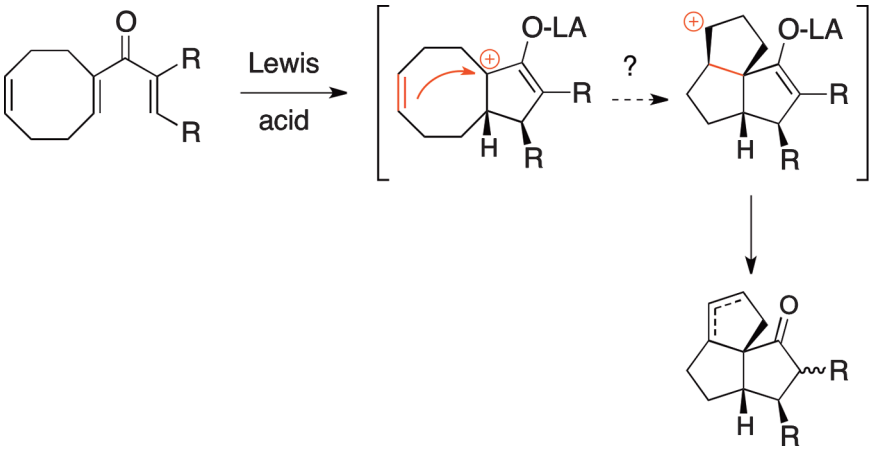
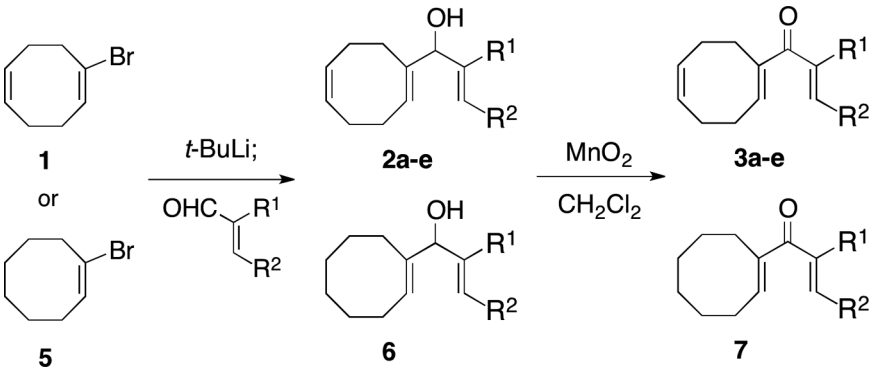


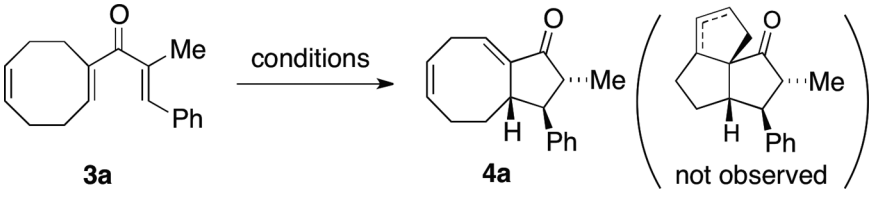
Table 1. Preparation of dienone substrates.



Entry	R^1	R^2	Product	Yield (%)[a]
1	Me	Ph	**3a**	39
2	Me	Me	**3b**	39
3	H	Ph	**3c**	81
4	Me	H	**3d**	50
5		$-(CH_2)_4-$	**3e**	51
6	Me	Ph	**7**	84

[a]Isolated yield over two steps.

Table 2. Effect of acid activator on Nazarov cyclization of **3a**.

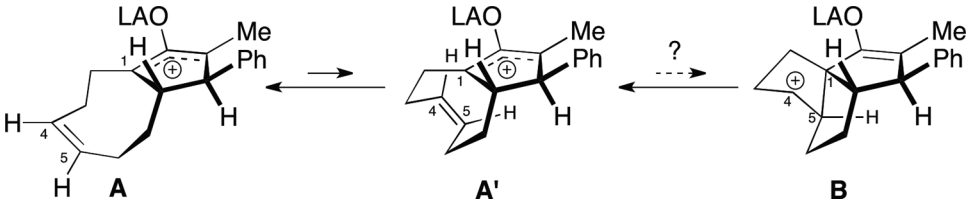


Entry	Acid	Equivalents	Solvent	Temperature (°C)	Time	Product (% yield)[a]
1	$BF_3{\cdot}OEt_2$	1.1	CH_2Cl_2	−78	20 min	**4a** (72)
2	$BF_3{\cdot}OEt_2$	1.1	85% HCO_2H	0	3 h	**4a** (trace) + intractable mixture
3	$Sc(OTf)_3$	0.2	CH_2Cl_2	rt	20 min	**4a** (53)
4	$TiCl_4$	1.1	CH_2Cl_2	−78	20 min	**4a** (33)
5	Et_2AlCl	1.1	CH_2Cl_2	−78	20 min	**4a** (28) + mixture
6	HCO_2H	400	neat	Reflux	2 h	Intractable mixture
7	CF_3CO_2H	1.1	THF	Reflux	2 h	**3a** only

[a]Yields are for isolated product after chromatographic purification.

Use of $BF_3{\cdot}OEt_2$ at higher temperatures in 85% formic acid to nucleophilically assist the cation–olefin cyclization was examined (Table 2, entry 2); however, these conditions furnished an intractable mixture from which only traces of the simple elimination product **4a** could be isolated. Other Lewis acids such as scandium(III) triflate and titanium tetrachloride also effected conversion to **4a** in CH_2Cl_2 at −78 °C (Table 2, entries 3 and 4), albeit in lower yields than was obtained with the original

Scheme 2. Intermediates en route to transannular cyclization.



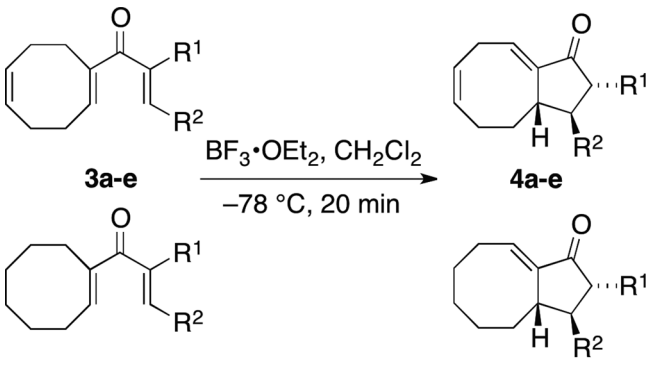
BF_3·OEt_2 conditions. However, it is notable that effective conversion of **3a** to **4a** could be accomplished with only catalytic quantities of $Sc(OTf)_3$.[16] Diethylaluminum chloride also furnished **4a** (Table 2, entry 5), but with diminished yields and the formation of multiple side-products. Finally, two Brønsted acids, formic acid and trifluoroacetic acid, were examined (Table 2, entries 6 and 7) but gave either intractable mixtures or unconsumed starting material.

Failure to observe any triquinane formation from **3a** under all conditions surveyed indicates that the transannulation step is difficult. We envision two possible explanations (Scheme 2). First, the cyclooctene ring fused to the initially formed cyclopentenyl cation **A** must assume a tub-like conformation (**A′**) to bring C-1 and C-5 within bonding distance, which may be disfavored in the conformational equilibrium. Furthermore, cyclization of **A′** to triquinane **B** would afford a relatively high-energy secondary carbocation at C-4, which is likely to raise the barrier for transannulation. Notably, previous successful intramolecular trapping reactions of the Nazarov intermediate by olefins proceeded through tertiary carbocations.[5,6] Moreover, Mehta and Rao found that it was necessary to use a trisubstituted alkene to see efficient transannulation in their triquinane strategy.[8] With this in mind, it is unlikely that the desired process can be effected without substantial redesign of the substrates. However, clean formation of **4a** under several conditions with no regio- or stereoisomers offers a valuable synthetic tool. The bicyclo[6.3.0]undecane skeleton is found in a variety of diverse terpenoid natural products, including precapnelladiene,[17] dactylol,[18] pleuromutilin,[19] and variecolin.[20] With this in mind, we examined all of the substrates (**3a–3e** and **7**) under the optimal conditions to evaluate the generality of this useful transformation (Table 3).

Like **3a**, substrates **3b** and **3c** also underwent conversion to the corresponding bicyclo[6.3.0]undecadienones **4b** and **4c** (Table 3, entries 2 and 3). However, dimethyl product **4b** was not formed with complete diastereoselectivity, furnishing a 4:1 mixture of *anti* and *syn* isomers at C-9/C-10. Substrate **3c**, lacking an α-substituent on the dienone moiety, reacted cleanly but required higher temperature (0 °C) compared with the other cases. Removal of the β-substituent, as in the case of **3d**, was far more damaging to the success of the transformation (Table 3, entry 4). In this case, a complex mixture from which no characterizable product could be isolated was obtained. Cyclohexenyl ketone **3e** cyclized to the tricyclic product **4e** in very good yield (Table 3, entry 5), although in contrast with the other examples, it provided exclusively the 9,10-*syn* diastereomer.[21] In this case, we presume that the conformational restrictions of a somewhat strained hydrindanone skeleton exerted a strong preference for a *syn* relationship at the two bridgehead carbons. In all cases, we observed the expected 8,9-*anti* relative configuration, established in the initial 4π conrotatory electrocyclization.

There are at least three regiochemical options for the elimination event: (*i*) endocyclic (relative to the newly formed cyclopentenyl cation) towards C-8 to afford the ring-fusing alkene isomer **C**, (*ii*) endocyclic towards C-9 to give cyclopentenone **D**, or (*iii*) exocyclic into the cyclooctene ring, the observed pathway that provides **4a–4c** and **4e** (Scheme 3). Exocyclic elimination from C-10 is also an option for all but **3c**, giving alkylidene cyclopentenone **E**. The high regioselectivity seen in these cases was surprising, prompting us to consider

Table 3. Nazarov cyclization and *exo*-elimination of trienones **3** and dienone **7**.



Entry	Substrate	R^1	R^2	Product (% yield)[a]
1	**3a**	Me	Ph	**4a** (72)
2	**3b**	Me	Me	**4b** (61)[b]
3	**3c**	H	Ph	**4c** (64)[c]
4	**3d**	Me	H	—[d]
5	**3e**	$-(CH_2)_4-$		**4e** (80)[e]
6	**7**	Me	Ph	**8** (80)

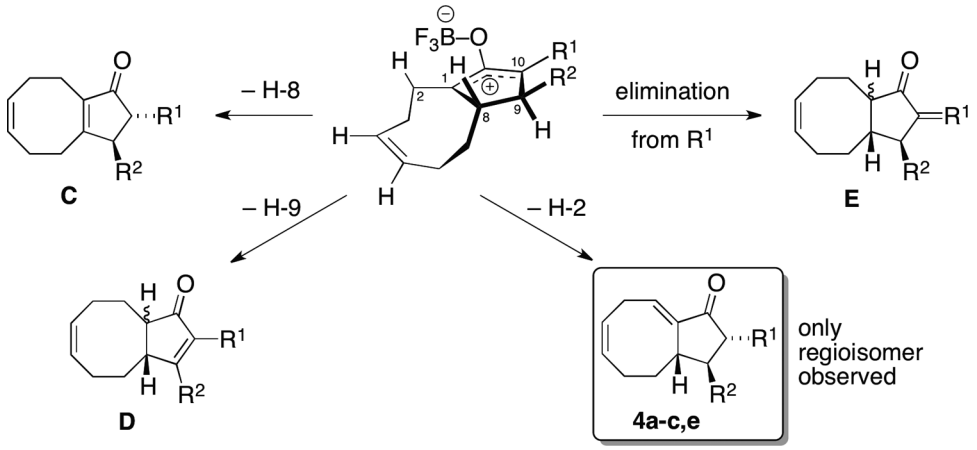
[a]Yields are for isolated product after chromatographic purification.
[b]A 4:1 mixture of *anti*:*syn* diastereomers at R^1 was obtained.
[c]Reaction done at 0 °C.
[d]Reaction formed a complex mixture of products.
[e]R^1 and R^2 (cyclohexano ring methylene carbons) are *syn* in the case of **4e**.

whether a cyclooctene conformation favoring rapid elimination towards C-2 might predominate.[22] We imagined that the remote alkene might be exerting an effect on the conformational preferences, and to evaluate this possibility, we subjected dienone **7** lacking that unsaturation to the standard conditions (Table 3, entry 6). In the event, this substrate was found to undergo efficient electrocyclization and exclusive exocyclic elimination to give **8** in high yield. Further computational studies to evaluate transition state energies for the various elimination pathways may help elucidate this high selectivity. Regardless of its origin, this general regioselectivity is welcome, especially as it preserves the two adjacent stereocenters at C-8 and C-9, set in the electrocyclization, in contrast with the outcome had **C** or **D** predominated.

Conclusion

We have described above an efficient and succinct route to generate fused bicyclic 8-5 ring systems, a common substructure in a variety of natural products. This method generates three new stereocenters, two of which form stereospecifically and the other stereoselectively. The cyclization is effected by several common Lewis acids. Finally, products **4a–4e** and **8** portend synthetic utility, as the elimination occurs with high regioselectivity and the remaining olefins are situated for further elaboration to more complex natural products. The origins of this regioselectivity are under current investigation. Domino transannulation to afford triquinane systems was not observed for **3a–3e**, suggesting the need for structural augmentation of the proposed trapping alkene.

Scheme 3. Possible regiochemical outcomes of elimination step.



Supplementary material

Supplementary information including experimental procedure, characterization data, and NMR spectra and spectral data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2013-0456.

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