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# Cyclization of Cross-Conjugated Trienes: The Vinylogous Nazarov Reaction

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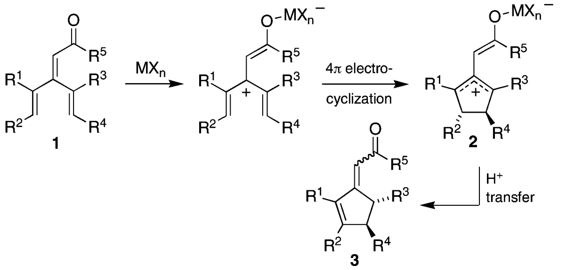
The Nazarov reaction, a well-established method for cyclopentenone construction, has enjoyed a resurgence of interest in recent years.[1] New approaches to stereocontrol have been reported,[2] and this transformation has also provided a versatile platform for domino and cascade processes, termed the "interrupted Nazarov" reaction.[3] In its most common form, the Nazarov reaction involves activation of a cross-conjugated dienone with Lewis or Brønsted acid, followed by electrocyclization of the resulting pentadienyl cation. Development of fresh advances utilizing this process may be hampered by the inherent limitations of dienone substitution pattern. With this in mind we have investigated alternative precursors to the pentadienyl intermediate.[4]

Variation of substitution at the pentadienyl 3-position was of particular interest, and would entail replacement of the dienone carbonyl moiety with an alternative substituent. Since complexation to a C-3 carbonyl is the usual means of substrate activation, its removal raises challenges with regard to initiation of the reaction.[5] We envisioned the placement of an electron-deficient alkene at C-3 in the form of cross-conjugated triene **1**, leaving the capability for activation at a remote site (Scheme 1). If the cationic character of a Lewis acid complexed enone carbonyl could be transmitted to the pentadienyl unit, a "vinylogous Nazarov" cyclization might occur to provide zwitterion **2**, and elimination would furnish conjugated alkylidenecyclopentene **3**. Here we describe the convenient preparation of a series of cross-conjugated trienes terminated with carbonyl functionality, and their cyclization via the first examples of the vinylogous Nazarov reaction.

***Scheme 1.*** The Vinylogous Nazarov Reaction



Assembly of the necessary triene substrates was initially challenging.[6] Metal-catalyzed cross coupling approaches were complicated by product sensitivity to the reaction conditions. Instead we focused on homologation of cross-conjugated dienones. While the dienone carbonyl is unreactive to standard olefination reagents, a two-step process utilizing the Meyer–Schuster rearrangement[7] of a bis(allylic) propargyl carbinol seemed feasible, given the high reactivity and minimal steric demand of the ethoxyacetylide anion. Moreover, the report of a successful homologation of a conjugated enone to a dienoate using catalytic $AuCl_3$ suggested that this method might be applicable to the intended cross-conjugated substrates.[8]

In preliminary experiments, dienones **4a** and **4b** underwent near quantitative addition of LiCCOEt to furnish carbinols **5a**,**b** (Scheme 2). Fortuitously, **5a** was cleanly converted to the desired trienoate **1a** during attempted chromatographic purification on silica gel, but these mild and convenient conditions were not general with other carbinols such as **5b**. The previously reported Au(III) conditions were capricious and gave inconsistent results with **5b**, likely due to intervention of other gold-mediated processes. However, catalytic $VO(acac)_2$ in toluene at 80 °C[9] efficiently and reproducibly converted **5b** to **1b**, and these conditions also effected the rearrangement of **5a** (albeit in lower yield). The two-step homologation protocol proved to be general, converting dienones **4a**–**g** to trienes **1a**–**g** in good overall yields (Table 1). For dienone **4g** (a 1:1 mixture of *E*/*E* and *E*/*Z* isomers), the *E*/*E* isomer more readily underwent acetylide addition; in this case the reaction was stopped at less than 50% conversion to avoid isomeric mixtures of **1g**.

***Scheme 2.*** Homologation of Dienones to Trienes

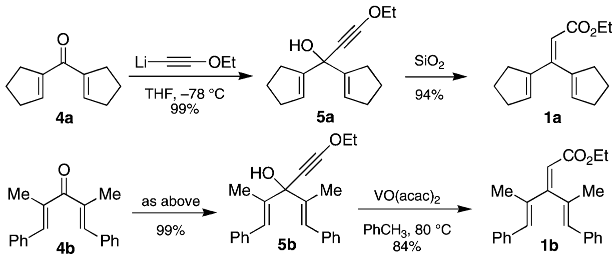
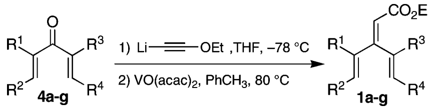


***Table 1.*** Meyer–Schuster Homologation of Dienones **4**



| dienone[a] | $R^1$ | $R^2$ | $R^3$ | $R^4$ | % yield[b] **5** | % yield[b] **1** |
|---|---|---|---|---|---|---|
| **4a** | $(CH_2)_3$ | | $(CH_2)_3$ | | 99 | 61 (94)[c] |
| **4b** | Me | Ph | Me | Ph | 99 | 84 |
| **4c** | Me | *i*-Pr | Me | *i*-Pr | 98 | 76 (97)[d] |
| **4d** | Me | Ph | Me | H | 92 | 81[e] |
| **4e** | $(CH_2)_4$ | | Me | H | 93 | 80[e] |
| **4f** | $(CH_2)_4$ | | $(CH_2)_4$ | | 96 | 78 |
| **4g** | Me | Me | Me | Me | 36[f] | 75 |

[a] Dienones **4** are all previously described (see Supporting Information). [b] All yields indicate isolated product after purification. [c] A two-step yield of 94% could be obtained by direct treatment of crude **5a** with $SiO_2$. [d] A higher yield of **1c** could be obtained using 10 mol % $TiCl_4$ at −78 °C. [e] Unsymmetrical dienones **4d** and **4e** furnished mixtures of geometrical isomers: **1d** (inseparable 1:1 mixture); **1e** (separable 7:3 *E*/*Z* mixture). [f] Unreacted **4g** enriched in *E*/*Z* isomer (61%) was recovered.

Trienes **1a**–**g** all were terminated with an ethyl ester. With a goal of probing the reactivity of other types of carbonyl groups,

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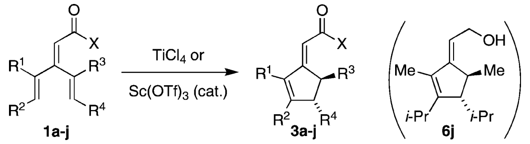
we subjected trienoate **1c** to (MeO)NHMe·HCl and *i*-PrMgCl[10] to obtain the Weinreb amide **1h** in 82% yield (see Table 2 for structures of **1h**−**j**). Treatment of **1h** with MeMgCl furnished trienone **1i**. Alternatively, DIBAL reduction of **1c** to the primary alcohol and oxidation with $MnO_2$ gave trienal **1j** in 97% yield (two steps).

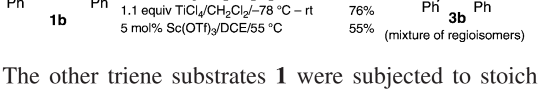
***Table 2.*** Vinylogous Nazarov Reaction of Trienes **1**[a]



| triene | $R^1$ | $R^2$ | $R^3$ | $R^4$ | X | % yield[b] **3** |
|---|---|---|---|---|---|---|
| **1a** | $(CH_2)_3$ | | $(CH_2)_3$ | | OEt | 83 (79)[c] |
| **1b** | Me | Ph | Me | Ph | OEt | 75 (93)[d] |
| **1c** | Me | *i*-Pr | Me | *i*-Pr | OEt | 88 (89) |
| **1d** | Me | Ph | Me | H | OEt | 75 |
| **1e** | $(CH_2)_4$ | | Me | H | OEt | *e* |
| **1f** | $(CH_2)_4$ | | $(CH_2)_4$ | | OEt | *e* |
| **1g** | Me | Me | Me | Me | OEt | 75 |
| **1h** | Me | *i*-Pr | Me | *i*-Pr | N(OMe)Me | 76[f] |
| **1i** | Me | *i*-Pr | Me | *i*-Pr | Me | 74[g] |
| **1j** | Me | *i*-Pr | Me | *i*-Pr | H | 86[h] |

[a] Method A: $TiCl_4$ (1.1 equiv; 1.0 M in $CH_2Cl_2$) was added dropwise to a −78 °C $CH_2Cl_2$ solution (0.01 M) of **1**. After 2 h, the reaction was allowed to warm to room temp and quenched with sat. $NaHCO_3$. Method B: a solution of **1** in $ClCH_2CH_2Cl$ (0.07 M) was added to a flask containing $Sc(OTf)_3$ (3 mol %) and the resulting mixture was stirred at 55 °C for 24 h. After cooling to room temp, the reaction mixture was filtered through a short pad of silica gel. [b] All yields indicate isolated product after purification. Values in parentheses were obtained using method B. [c] In the case of cyclization product **3a**, $R^3$ and $R^4$ are cis rather than trans. [d] Diene regioisomeric mixtures of **3b** were obtained: 2.6:1 (*exo*/*endo*) by method A and 1.3:1 by method B. [e] No conversion to **3e** or **3f** was observed despite extended stirring at room temp. [f] Method A conditions were performed at 0 °C instead of −78 °C. [g] Yield over two steps from Weinreb amide. [h] Following aqueous workup, product was immediately dissolved in EtOH and treated at room temp with $NaBH_4$ and $CeCl_3$ (1.1 equiv each). Yield refers to primary alcohol **6j**.

With substrates **1a**−**j** in hand, we were ready to probe the feasibility of the vinylogous Nazarov process. Substrate **1b** was used for evaluation of activation conditions. In the event, a number of Brønsted (HCl, $H_3PO_4$, $CF_3CO_2H$) and Lewis acids ($FeCl_3$, $SnCl_4$) commonly used to effect Nazarov cyclization of dienones resulted in little or no consumption of **1b** even after extended stirring. On the other hand, either $BF_3 \cdot OEt_2$ or $TiCl_4$ (1.1 equiv) at low temperature cleanly converted **1b** to cyclized product **3b** in good yields as a mixture of diene regioisomers (eq 1). Catalytic amounts of $TiCl_4$ gave only partial conversion, indicating slow turnover of the Lewis acid. However, effective catalysis was achieved using 5 mol % $Sc(OTf)_3$ when the reaction was carried out at higher temperatures.[11] *To the best of our knowledge, these represent the first examples of the vinylogous Nazarov reaction.*



(1)

The other triene substrates **1** were subjected to stoichiometric $TiCl_4$, and in some cases catalytic $Sc(OTf)_3$ (Table 2). Most substrates underwent efficient conversion to cyclized products **3**. The two exceptions were **1e** and **1f**, which showed no evidence of cyclization under a variety of conditions. The reasons for the unusual lack of reactivity in these two cyclohexene-containing substrates are unclear.[12]

Notably, all successful examples except **1b** furnished a single diene regioisomer (with an exocyclic double bond in conjugation to the carbonyl group). Furthermore, the exocyclic alkene was formed as a single stereoisomer, with the carbonyl group *trans* to the cyclopentene double bond (presumably to minimize allylic strain). Amide **1h**, ketone **1i**, and aldehyde **1j** all underwent efficient cyclization, although the amide required higher temperatures, and the sensitivity of aldehyde cyclization product **3j** required its immediate reduction to the corresponding primary alcohol **6j**.

From these preliminary studies, it is apparent that replacement of the carbonyl of cross-conjugated dienones with enoate, enamide, enone, or enal functionality does not impede their ability to participate in Nazarov-like cyclization processes. Moreover, catalytic amounts of $Sc(OTf)_3$ are sufficient for effecting the reaction, albeit under more vigorous conditions. Efforts to intercept the cyclized intermediate and to understand the unusual reactivity of **1e**,**f** are currently underway, and will be described elsewhere.

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**Supporting Information Available:** Experimental procedures and spectral data for **5a**−**g**, **1a**−**j**, **3a**−**d**,**g**-**i** and **6j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) In contrast to **1e**,**f**, the corresponding dienones **4e**,**f** do undergo Nazarov cyclization under typical conditions.

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