Domino Pericyclic Processes

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Unexpected Participation of an Unconjugated Olefin during Nazarov Cyclization of Bridged Bicyclic Dienones**

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The Nazarov reaction is a well-established method for the generation of new cyclopentenone rings from simple dienone precursors.[1] This reaction has enjoyed considerable recent attention with regard to its use in tandem or domino processes,[2] as well as in approaches for controlling the absolute configuration of the stereocenters generated during or after the electrocyclization process.[3] We have recently

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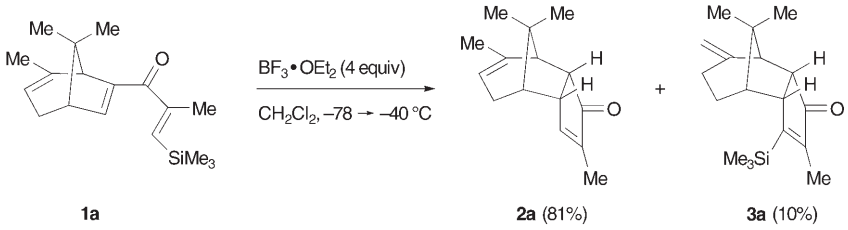
found that a variety of bridged bicyclic dienones undergo silyl-directed Nazarov cyclization with high or complete diastereoselectivity.[4] Whereas most dienones furnished the *exo*-disposed cyclopentenone, substrate **1a** provided the *endo* isomer **2a** in high yield, along with minor amounts of by-product **3a** (Scheme 1). The formation of this rearranged



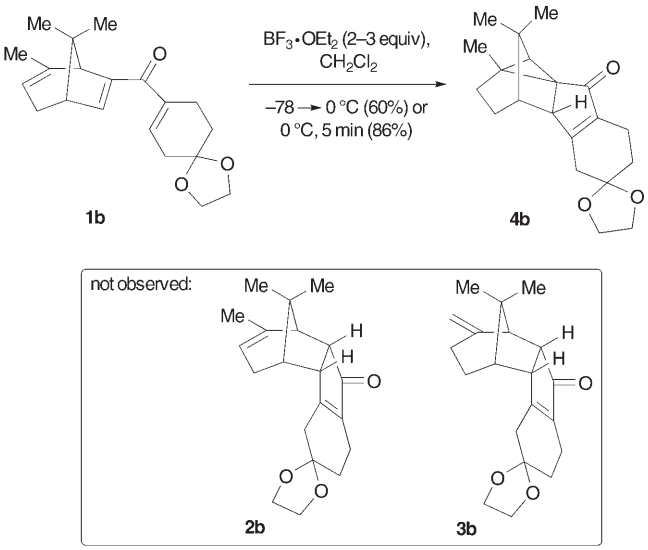
1a **2a** (81%) **3a** (10%)

Scheme 1. Unexpected formation of by-product **3a** in the Nazarov cyclization of dienone **1a**.

silyl-containing product was intriguing, and we set out to explore its formation in greater detail. Herein, we report two additional examples in which analogous products are formed exclusively, with the apparent involvement of the remote unconjugated alkene in the rearrangement process.

Substrates **1b–d** were prepared by the carbonylative Stille coupling using cocatalytic amounts of copper(I) iodide, followed by near-quantitative protection of the alcohols in the case of **1c** and **1d** to form **1e** and **1f**, respectively (Scheme 2).[5] These examples were chosen for their relevance to an approach to the taxane skeleton, but were also of interest because of the absence of β-silyl substituents in the case of **1b** and **1e**. Without a facile termination through desilylative elimination,[6] the Nazarov cyclopentenyl cation intermediate might be expected to undergo the alternative pathway to a significantly greater extent.

Initial experiments with **1b** entailed low-temperature treatment with $BF_3{\cdot}OEt_2$, in analogy to the conditions applied to **1a**. Careful monitoring showed no consumption of **1b** until the reaction was warmed to 0 °C, at which point a new product was rapidly produced in 60% yield (Scheme 3). Improved yields could be obtained by carrying out the reaction at 0 °C for 5 min rather than gradually warming from a lower temperature. The newly formed product displayed several surprising spectral features. The ^{1}H NMR spectrum contained no signals for olefinic protons, and all three methyl groups appeared as singlets at high field (approximately $\delta = 1$ ppm). The ^{13}C NMR spectrum revealed the presence of a conjugated ketone carbonyl functionality and a highly polarized tetrasubstituted alkene. Clearly, neither the "normal" Nazarov product **2b** nor the anticipated anomalous product **3b** had been formed. Moreover,

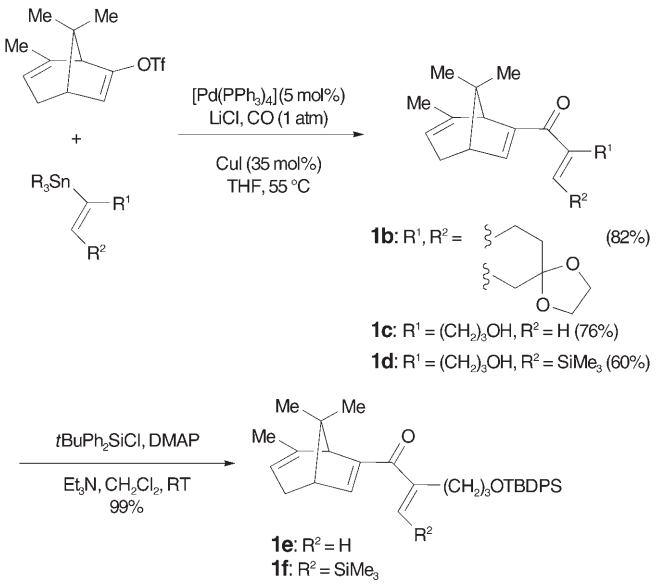


1b **4b** **2b** **3b**

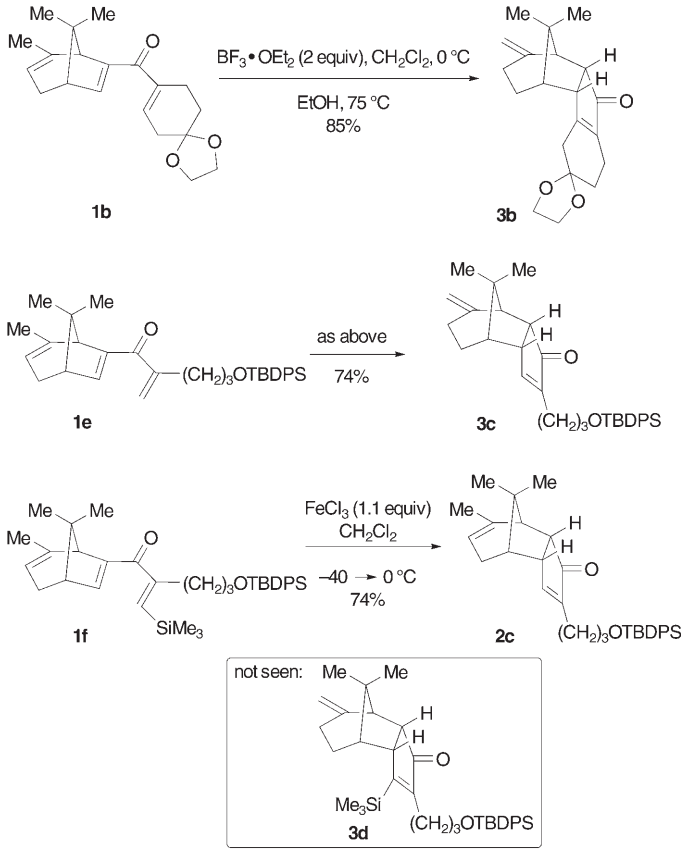
Scheme 3. Unexpected formation of cyclopropyl ketone **4b**.

the unconjugated alkene had been consumed while leaving the former allylic methyl group intact and apparently next to a quaternary center. These data suggested cyclopropyl ketone **4b** as a likely structure.

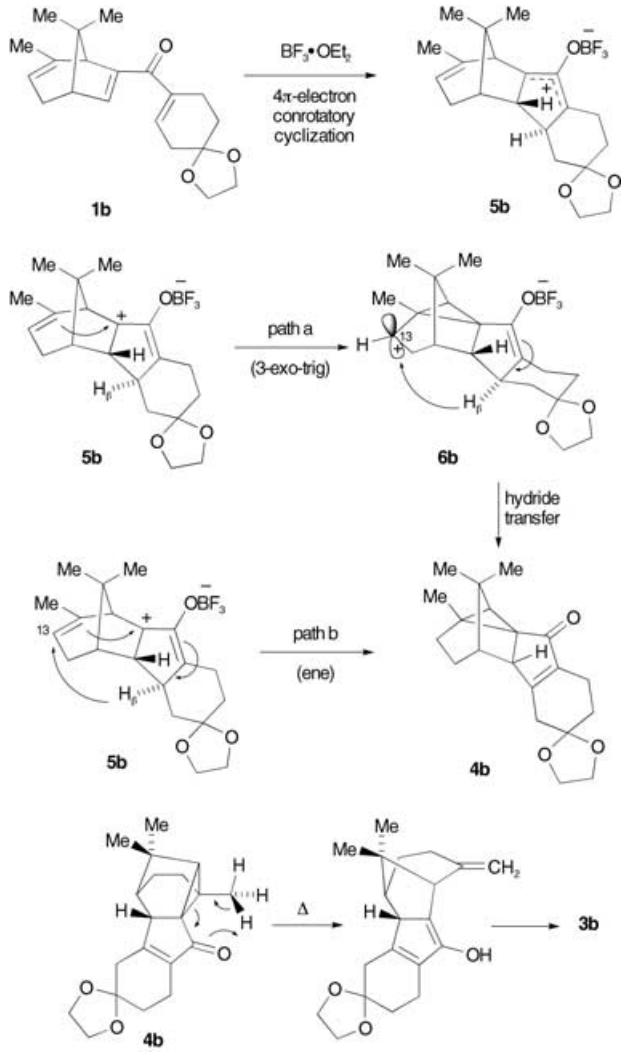
As this material was a solid, it was recrystallized from Et_2O/pentane and subjected to single-crystal X-ray diffraction studies.[7] Much to our surprise, the structure generated from X-ray analysis was that of **3b**. Spectroscopic analysis of the recrystallized material showed that it had undergone a rearrangement and now possessed only two methyl groups and an exocyclic methylene functionality, as in the case of **3a**. Subsequent studies indicated that the initially formed **4b** undergoes facile conversion into **3b** at slightly elevated temperatures. Given the thermal lability of this compound, direct conversion of **1b** into **3b** was examined (Scheme 4). In the event, a convenient procedure was developed in which the crude product obtained from the Nazarov cyclization of **1b** was heated at 75 °C in EtOH to provide **3b** in 85% yield. A similar procedure with **1e** furnished **3c** in 74% yield. For



Scheme 2. Preparation of substrates **1b–f** by carbonylative Stille cross-coupling. DMAP = dimethylaminopyridine, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 4. Direct conversion of **1b** and **1e** into **3b** and **3c**, and formation of **2c** by the silyl-directed Nazarov cyclization of **1f**.



Scheme 5. Proposed mechanisms for the formation **4b** and **3b**.

comparison, reaction of **1f** under standard silyl-directed Nazarov cyclization conditions was performed. In this case, authentic **2c** was produced in good yield and, interestingly, none of the silyl-containing product **3d**, analogous to **3a**, was isolated.

Formation of **4b** presumably involves an initial Nazarov electrocyclization to give the 2-oxidocyclopentenyl cation **5b** (Scheme 5). Conversion into the cyclopropyl ketone could involve a homoallyl/cyclopropylcarbinyl rearrangement to give **6b** (path a), with subsequent intramolecular hydride transfer of H_β to the secondary cyclopropylcarbinyl center.[8] Alternatively, direct conversion of **5b** into **4b** is possible through a concerted ene-like rearrangement (path b).[9] In either mechanism, delivery of H_β should be facile because of its proximity to C13, which results from the complete selectivity of the Nazarov electrocyclization in which the new cyclopentenyl ring is appended in an *endo* disposition. This stereoselectivity is in accord with that seen in the silyl-directed Nazarov reactions of **1a**[4] and **1f**. The thermal conversion of **4b** into **3b** most likely occurs by the precedented homo-1,5-hydrogen shift or "enolene" rearrangement of alkyl-substituted cyclopropyl ketones,[10] followed by enol→keto tautomerization; notably, this thermal conversion typically occurs at much higher temperatures. The ease with which **4b** undergoes rearrangement is likely to be a result of the additional ring strain that resides in its polycyclic skeleton, as compared with simpler cyclopropyl ketones. Given the exclusive formation of **3c**, dienone **1e** is presumed to follow an analogous mechanistic pathway.

In summary, a new class of novel and mechanistically fascinating "interrupted" Nazarov reactions has been observed. In these systems, a nonconjugated alkene held near the dienone nucleus undergoes intramolecular trapping of the Nazarov 2-oxidocyclopentenyl intermediate to yield a strained polycyclic cyclopropyl ketone intermediate. This process may occur by stepwise cation–olefin cyclization/hydride transfer or by a direct ene-like mechanism. Involvement of the alkene is possible because of the high diastereoselectivity of the initial conrotatory electrocyclization. The resulting cyclopropyl ketones undergo thermal opening to provide the anomalous products **3**. In systems that lack a low-energy desilylative termination option, this transformation occurs in high yield, thus providing convenient access to elaborate polycyclic products of potential use in the construction of naturally occurring taxane natural products and their structural analogues. Further studies along these lines will be reported in due course.

Experimental Section

4b: Trienone **1b** (912 mg, 2.90 mmol) was dissolved in CH_2Cl_2 (290 mL) in a 500-mL round-bottom flask under N_2 and cooled to 0 °C. $BF_3{\cdot}OEt_2$ (0.71 mL, 5.8 mmol) was added by syringe, and the resulting yellow reaction mixture was stirred at 0 °C for 10 min. Water (100 mL) was added, the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to furnish a solid residue, which was purified by flash chromatography (silica gel, gradient increasing from 15→20→25→30→35% EtOAc in hexanes) to provide **4b** as a tan solid (775 mg, 85%). M.p.: 98–101 °C; $R_f = 0.31$ (20% acetone/hexanes); IR (thin film): $\tilde{\nu} = 1690\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.02$–3.99 (m, 4H), 3.34 (br s, 1H), 2.66 (dd, $J = 18.6$, 1.9 Hz, 1H), 2.54 (dd, $J = 18.8$, 1.8 Hz, 1H), 2.42–2.29 (m, 2H), 1.98 (s, 1H), 1.81 (dd, $J = 6.5$, 6.5 Hz, 1H), 1.78 (ddd, $J = 14.8$, 11.9, 4.6 Hz, 1H), 1.66–1.59 (m, 2H), 1.53 (ddd, $J = 14.9$, 12.0, 4.4 Hz, 1H), 1.45 (ddd, $J = 8.3$, 2.9, 2.9 Hz, 1H), 1.40–1.33 (m, 1H), 1.13 (s, 3H), 1.05 ppm (s, 3H), 0.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 197.7, 163.7, 142.6, 108.4, 64.9, 64.8, 50.3, 49.8, 45.4, 45.1, 38.4, 37.8, 33.2, 30.9, 26.9, 23.6, 21.4 (2 overlapping C nuclei), 19.7, 18.6 ppm; elemental analysis (%) calcd for $C_{20}H_{26}O_3$: C 76.40, H 8.33; found: C 76.47, H 8.37.

3b: Trienone **1b** was treated with $BF_3{\cdot}OEt_2$ as described above (on the same scale). The solid residue obtained after aqueous work up was dissolved under N_2 in absolute EtOH (70 mL), and the resulting solution was heated to 75 °C for 3 h. The reaction mixture was cooled and carefully concentrated under reduced pressure to leave a solid residue, which was purified by flash chromatography (silica gel, gradient increasing from 10→15→20→25→30→35% EtOAc in hexanes) to furnish **3b** as a white solid (775 mg, 85%). M.p.: 119–120 °C; $R_f = 0.24$ (20% acetone/hexanes); IR (thin film): $\tilde{\nu} = 1695$, 1646 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.66$ (dd, $J = 2.3$, 2.3 Hz, 1H), 4.64 (dd, $J = 2.1$, 2.1 Hz, 1H), 4.01–4.00 (m, 4H), 3.40–3.37 (m, 1H), 3.21 (dd, $J = 7.6$, 7.6 Hz, 1H), 2.64 (d, $J = 18.1$ Hz, 1H), 2.53 (d, $J = 7.9$ Hz, 1H), 2.51 (s, 1H), 2.37–2.30 (m, 1H), 2.28–2.21 (m, 1H), 2.03–1.96 (m, 1H), 1.85–1.68 (m, 5H), 1.46–1.39 (m, 1H), 1.09 (s, 3H), 0.93 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 207.8$, 168.5, 147.1, 140.0, 110.2, 108.5, 64.9, 64.8, 54.4, 54.0, 50.0, 48.1, 43.3, 38.9, 30.8, 26.9, 26.7, 23.6, 23.2, 19.2 ppm; elemental analysis (%) calcd for $C_{20}H_{26}O_3$: C 76.40, H 8.33; found: C 76.11, H 8.35.

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[7] Crystal data for **3b**: $C_{20}H_{26}O_3$, $M_r = 314.41$, prismatic crystal ($0.44 \times 0.42 \times 0.39\ mm^3$), triclinic, space group $P\bar{1}$, $a = 7.333(1)$, $b = 10.578(1)$, $c = 11.255(2)$ Å, $\alpha = 98.038(10)$, $\beta = 93.278(10)$, $\gamma = 96.230(10)°$, $V = 857.0(2)$ $Å^3$, $Z = 2$, $\rho_{calcd} = 1.218\ g\,cm^3$, $F(000) = 340.0$, $T = 293(2)$ K, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å, $\mu = 0.08\ mm^{-1}$), data collected with a Nonius CAD4 diffractometer; of 2945 measured reflections (2θ: 3.22–52.72°, θ: 2θ scan), a psi-scan absorption correction was applied with min./max. transmission factors of 0.965/0.969; structure solved by SIR97, refined by using SHELXL97; final agreement factors were $R1 = 0.0458$ (2330 observed reflections, $F^2 > 4\sigma(F^2)$) and $wR2 = 0.1134$; data/restraints/parameters 2945/0/295; GOF = 1.045. CCDC-272581 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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