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Ionic Hydrogenation of Oxyallyl Intermediates: The Reductive Nazarov Cyclization

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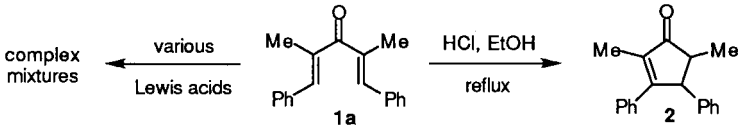
Abstract—Cyclization of tri- and tetrasubstituted dienones **1** under Lewis acidic conditions in the presence of triethylsilane led to formation of either silyl enol ethers **6** or cyclopentanones **7** in good to excellent yields, depending on work-up conditions. The proposed mechanism involves initial Nazarov cyclization to give oxyallyl intermediates **5**, which are intercepted via intermolecular transfer of hydride. The reactions proceeded cleanly with as little as 2 equiv. of silane and in most cases catalytic amounts of Lewis acid could be used. Trapping with Et_3SiD occurs at the less substituted terminus in unsymmetrical cases.

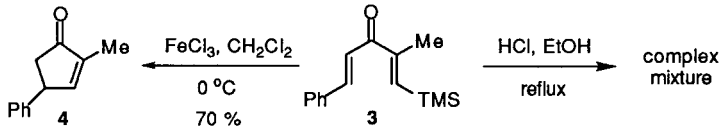
Introduction

The widespread occurrence of cyclopentanoid natural products has led to the development of a variety of diverse methods for the formation of five-membered carbocyclic rings.[1] Among cationic cyclopentannulation processes the Nazarov cyclization has emerged as a powerful transformation for rapid assembly of 2-cyclopentenones from acyclic cross-conjugated dienones.[2] Several factors, including the drastic reaction conditions (concentrated protic acid and high temperature) and typical formation of regioisomeric product mixtures, delayed the synthetic development of this reaction and the Nazarov cyclization was long regarded to be interesting mainly from a mechanistic viewpoint.[3] However, the introduction of Lewis acids as cyclization initiators in aprotic media[4] as well as the innovation of 'directed Nazarov cyclizations' employing β-silyl- or β-stannyl-substituted dienones[5] dramatically increased the synthetic significance of this reaction. Interestingly, these improvements are interconnected as vinylsilanes or stannanes are unstable toward strong protic acids at elevated temperatures[6] and Lewis acid-initiated Nazarov cyclizations require the availability of a facile termination event. While the remarkable abilities of silicon or tin to serve as electrofugal leaving groups allow for efficient removal of R_3Si^+ or R_3Sn^+, loss of H^+ is often unselective under the same conditions and results in formation of complex product mixtures. For example, when dienone **1a** was heated at reflux in ethanolic HCl a diastereomeric mixture of cyclopentenones **2** was obtained in 96% yield (Eq. (1)).[7] However, attempted Lewis acid-initiated cyclization of **1a** under a variety of conditions afforded only complex product mixtures. Cyclization of dienone **3** using $FeCl_3$ proceeded cleanly at 0°C to give cyclopentenone **4** in 70% yield (Eq. (2)). Treatment of an ethanolic solution of **3** with HCl at reflux for several hours afforded a complex product mixture which contained only minor amounts of **4**.

Our recent findings of efficient intramolecular nucleophilic trapping of Nazarov-derived oxyallyl intermediates[8] suggested that development of an effective *intermolecular* trapping sequence could render simple dienones (e.g. **1a**)



(1)



(2)

Keywords: annulation; cyclization; dienones; electrocyclic reactions; Nazarov reactions.

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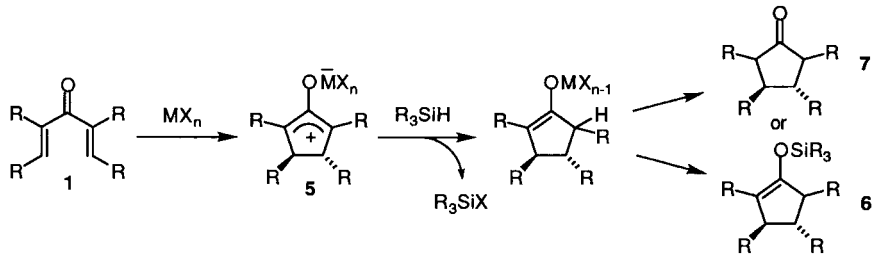


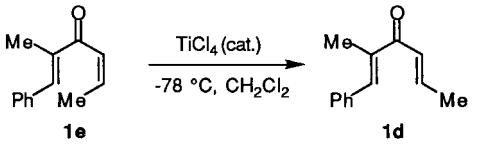
Scheme 1.

more tractable to Lewis acid-initiated Nazarov cyclization. In particular, in situ reduction of oxyallyl intermediates by intermolecular delivery of hydride would allow for the one-step conversion of acyclic dienones into cyclopentanones **7** or their corresponding enol silanes **6** with net preservation of the newly formed stereocenters at C-3 and C-4 (Scheme 1). Termination of the Nazarov cyclization by elimination generally destroys some of this stereochemical information (Eqs. (1) and (2)).[9] Moreover, the possibility exists for control of up to two additional stereocenters through selective delivery of hydride to **5** and protonation of the resulting enolate or **6**. We have examined the Nazarov cyclization of dienones **1a**–**e**[10] in the presence of the Lewis acid-tolerant hydride source Et_3SiH, and we wish to report here the full account of this investigation.[11]

Results

Dienones **1a**–**e** were cyclized under various Lewis acidic conditions in the presence of 2–10 equiv. of triethylsilane (Table 1). Initial cyclization of dienone **1a** employing either Et_2AlCl or $BF_3{\cdot}OEt_2$ afforded mixtures of silyl enol ether **6a** and cyclopentanones **7a** in excellent overall yield (entries 1 and 2).[12] As noted earlier, under identical cyclization conditions but in the absence of silane, complex product mixtures were formed in these reactions. Replacement of the aqueous quench by treatment with mild acid (1N HCl) furnished cyclopentanones **7a** as a 8.8:1 mixture of diastereomers in near quantitative yield (entry 3).[13] Notably, the amount of silane could be reduced to 2 equiv. in this case with no decrease in yield. Furthermore we found that the desired transformation could also be accomplished employing catalytic amounts of Lewis acid, albeit with somewhat diminished overall yield (entry 4).[14] Reductive Nazarov cyclization of dicyclopentenyl ketone **1b** afforded triquinane **7b** in 71% yield together with a small amount of the conjugate reduction product **8b** (entry 5). Formation of **8b** can be rationalized by considering the reduced reactivity of **1b** toward Nazarov cyclization, and not surprisingly catalytic amounts of $BF_3{\cdot}OEt_2$ or $TiCl_4$ in this case gave incomplete consumption of the starting material after 48 h at 25°C, while $SnCl_4$ afforded **8b** exclusively (entry 6).

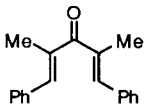
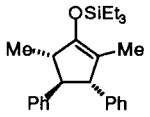
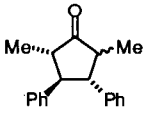
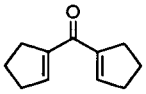
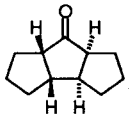
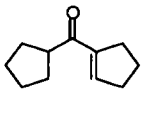
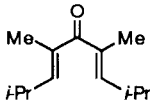
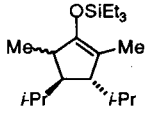
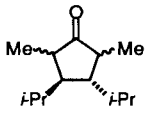
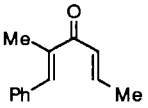
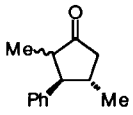
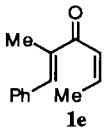
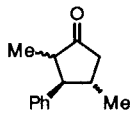
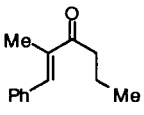
Cyclization of **1c** with $BF_3{\cdot}OEt_2$ followed by aqueous work-up afforded mixtures of silyl enol ether **6c** and cyclopentanones **7c**, while acidic quench gave **7c** only (entries 7 and 8). The formation of three diastereomers (1.2:2.8:1 ratio) in this reaction is somewhat surprising considering the formation of only two diastereomeric products (8.8:1 ratio) from cyclization of dienone **1a** (entry 8 vs. entry 4). Unsymmetrically substituted dienone **1d** cleanly furnished a 3.3:1 diastereomeric mixture of cyclopentanones **7d** in 77% combined yield (entry 9). Interestingly, cyclization of its (*Z*)-isomer, **1e**, under the same reaction conditions led to formation of an identical product mixture in comparable yield (81%) (entry 10). The *anti*-stereochemical relationship of the β and β′ substituents in **7d**, however, is only consistent with a conrotatory ring closure of the all-(*E*) isomer **7d**. These results suggest that Lewis acid-assisted *E*-*Z*-isomerization of dienone **1e** is facile at low temperatures and precedes the electrocyclization, furnishing cyclopentanone **7d** exclusively.[15] Experimental evidence for this hypothesis could be obtained by treatment of **1e** with catalytic amounts of $TiCl_4$ at low temperatures, which allowed for the isolation of dienone **1d** in high yield (Eq. (3)). Reductive cyclization of **1e** employing catalytic amounts of Lewis acid could be achieved using $SnCl_4$ which led to formation of **7d** along with small amounts of the conjugate reduction product **8d** (entry 11). Surprisingly, no silyl enol ether products could be isolated from reductive cyclizations of dienones **1d**–**e** even with bicarbonate work-up.



(3)

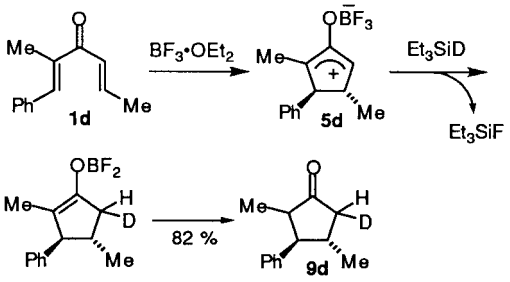
We also were interested in examining the regiochemistry of trapping in the case of the unsymmetrical substrate **1d**. Based on results obtained from nucleophilic trapping of photochemically generated oxyallyl intermediates, we anticipated delivery of hydride to the more substituted terminus due to greater charge localization at that carbon.[16] However, recent results obtained from intermolecular trapping experiments of Nazarov-derived oxyallyl intermediates suggested that other factors also contribute to the regiochemical outcome.[17] Since it was not possible to isolate the silyl enol ether products in this case, the reductive Nazarov cyclization of **1d** in the presence of Et_3SiD was carried out. In the event, cyclization of **1d** in the presence of Et_3SiD gave a diastereomeric mixture (ca. 4:1) of cyclopentanones-d_1 **9d** in 82% overall yield resulting from attack of deuteride at the less substituted terminus of oxyallyl intermediate **5d** (Eq. (4)). The regioselectivity was apparent from the presence of two methyl doublets in the ^1H NMR spectra of each diastereomer, indicating the presence of a proton rather than a deuteron at the more substituted α carbon. Additional evidence came from a simplification of the pattern due to the two methylene protons at the other α carbon and the formation of a molecular ion with *m*/*z* 189. We also briefly investigated the use of trimethylsilyl cyanide in the intermolecular trapping of Nazarov

Table 1. Reductive Nazarov cyclization of dienones **1a–e**

entry	substrate	conditions[a]	products (yield)[b]
1	 **1a**	1.1 equiv. Et_2AlCl, 10 equiv. Et_3SiH; H_2O	 **6a** (49%)  **7a** (44%; 4.5:1 β-Me/α-Me)
2	**1a**	1.1 equiv. BF_3•OEt_2, 10 equiv. Et_3SiH; H_2O	**6a** (44%), **7a** (54%; 3.5:1 β-Me/α-Me)
3	**1a**	1.1 equiv. BF_3•OEt_2, 2 equiv. Et_3SiH; 1N HCl	**7a** (98%; 8.8:1 β-Me/α-Me)
4	**1a**	0.1 equiv. BF_3•OEt_2, 2 equiv. Et_3SiH; 1N HCl	**7a** (80%; 7.0:1 β-Me/α-Me)
5	 **1b**	1.1 equiv. BF_3•OEt_2, 2 equiv. Et_3SiH; 1N HCl	 **7b** (71%)  **8b** (14%)
6	**1b**	0.1 equiv. $SnCl_4$, 2 equiv. Et_3SiH; 1N HCl	**8b** (61%)
7	 **1c**	1.1 equiv. BF_3•OEt_2, 10 equiv. Et_3SiH; H_2O	 **6c** (24%; 5.7:1 Me epimers)  **7c** (69%; 2.6:1 Me epimers)
8	**1c**	1.1 equiv. BF_3•OEt_2, 2 equiv. Et_3SiH; 1N HCl	**7c** (84%; 1.2:2.8:1 ratio of 3 diast.)
9	 **1d**	1.1 equiv. BF_3•OEt_2, 10 equiv. Et_3SiH; H_2O	 **7d** (77%; 3.3:1 α-Me/β-Me)
10	 **1e**	1.1 equiv. BF_3•OEt_2, 10 equiv. Et_3SiH; H_2O	**7d** (81%; 3.3:1 α-Me/β-Me)
11	**1e**	0.1 equiv. $SnCl_4$, 2 equiv. Et_3SiH; H_2O	 **7d** (63%; 5.6:1 α-Me/β-Me)  **8d** (12%)

[a] All reactions were carried out at −78°C in CH_2Cl_2.
[b] Isolated yields after chromatography. All new compounds were characterized by IR, ^1H NMR, ^{13}C NMR and combustion analysis or HRMS.

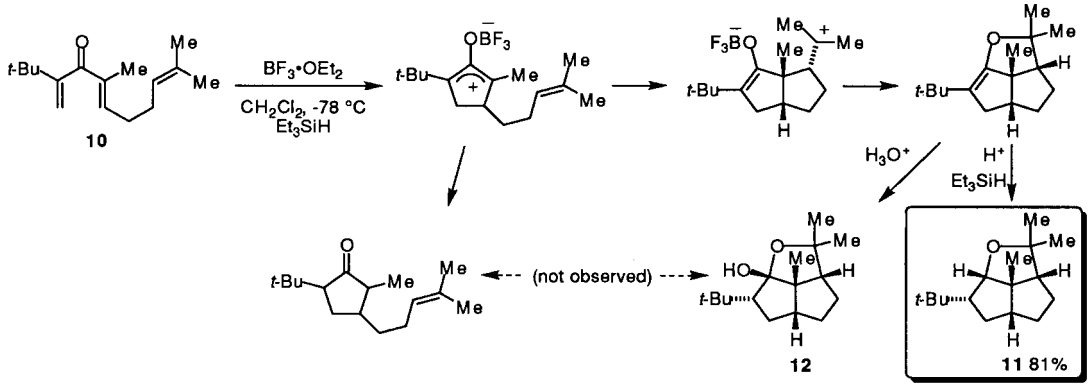
intermediates. However, BF_3·OEt_2-induced cyclization of dienones **1a** and **d** in the presence of 10 equiv. of TMSCN furnished complex product mixtures, while **1b** gave the desired product only in low yield together with large amounts of the conjugate addition product.



(4)

Discussion

The efficiency with which bimolecular hydride trapping of the oxyallyl intermediate can compete with eliminative termination (the traditional Nazarov pathway) suggests that it is a relatively long-lived intermediate under these reaction conditions. Additional support for this notion can be found in the successful intermolecular trapping by allylic silanes[17] or 1,3-dienes[18] of the Nazarov intermediates derived from simple dienones. However, when trienone **10**[8a] was subjected to Lewis acid in the presence of triethylsilane, tricyclic ether **11** was formed in high yield (Scheme 2). Notably, no products derived from hydride trapping of the oxyallyl intermediate or the tertiary cation resulting from 5-*exo* cyclization could be isolated and tricyclic



Scheme 2.

hemiketal **12**, the product expected under nonreductive conditions, was also not observed. This result suggests that cation–olefin cyclization occurs at a significantly faster rate than hydride trapping, and that the resulting intermediate undergoes rapid closure to the enol ether. Formation of **11** occurs via ionic hydrogenation[19] of the enol ether.

The regioselectivity observed in the case of **1d** for attack at the less substituted terminus contradicts that obtained from the solvent trapping reactions of photochemically-generated 4-pyrone derived oxyallyl zwitterions. However, it is consistent with earlier findings of Noyori and can be rationalized in terms of enolate stability with preferred formation of the more substituted enolate isomer.[20] In addition, significant diastereoselectivity was seen in several cases. Exclusive formation of the *cis-anti-cis* triquinane diastereomer **7b** (entry 5) is not surprising: conrotatory electrocyclization necessarily establishes an *anti* relationship for the adjacent bridgehead carbons, and hydride attack and protonation should display a strong preference for formation of *cis* ring fusions. Formation of all-*trans* enol silane **6a** (entry 1) is perhaps more surprising, as it involves delivery of hydride from the same face as the larger phenyl group on the neighboring carbon. This may be due to avoidance of developing non-bonded interactions between the phenyl and methyl groups in the transition state (B) for attack from the same face as hydrogen (Scheme 3). Diastereoselectivity seen in cases employing acidic work-up (entries 3,4,7 and 8) was variable, and most likely derives from epimerization under those conditions.

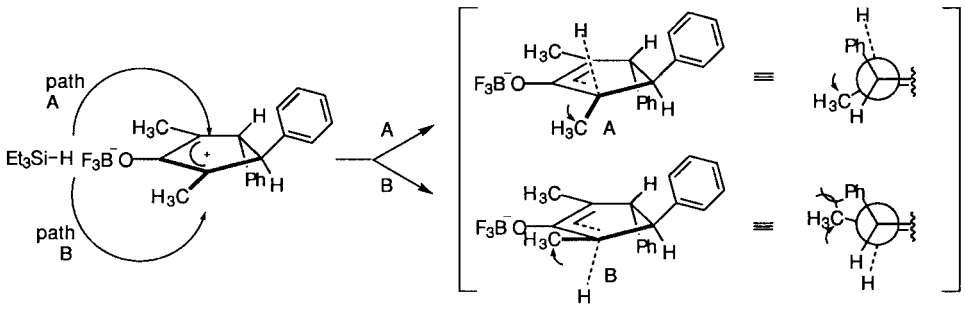
Conclusion

This methodology offers a novel, one-step synthesis of cyclopentanones via in situ reduction of Nazarov-derived oxyallyl intermediates by intermolecular delivery of hydride. Lewis acid-initiated Nazarov cyclization can be effected using simple dienones that furnish complex product mixtures under the normal eliminative conditions. While conjugate reduction of the starting material was an occasional side reaction with less reactive dienones, in no case did we observe any of the cyclopentenones expected from the normal eliminative pathway. In unsymmetrically substituted dienone substrates, hydride attack appears to occur preferentially at the less substituted terminus, and good diastereoselectivity was obtained in several cases. Overall, this chemistry gives access to cyclopentanones in high yield from acyclic dienone precursors, with concomitant introduction of up to four new stereocenters. Further applications involving intermolecular trapping of the Nazarov intermediate will be reported elsewhere.

Experimental

General

Reactions were conducted in oven-dried (120°C) or flame-dried glassware under a positive atmosphere of nitrogen unless otherwise stated. Transfer of anhydrous solvents or air-sensitive reagents was accomplished with oven-dried syringes or cannula. Solvents were distilled before use:



Scheme 3.

dichloromethane (CH_2Cl_2) from calcium hydride, diethyl ether (Et_2O) and tetrahydrofuran (THF) from sodium-benzophenone ketyl. Commercial reagents and solutions were used as received unless otherwise stated. Thin layer chromatography (TLC) was performed on plates of silica precoated with 0.25 mm Kieselgel 60 F_{254} (Merck). Flash columns were packed with 230–400 mesh silica gel (Merck or Baxter). Radial chromatography was performed on a Harrison Research Chromatotron Model 7924T with plates of silica precoated with 2 and 4mm Silica Gel 60 F_{254} Containing Gypsum (EM Science). Ramping of solvent polarity is indicated by the '→' symbol in the respective sections. Melting points were obtained on a Thomas–Hoover apparatus in open capillary tubes and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a 300 MHz Varian Unity or 500 MHz Varian VXR instrument. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 75 MHz (Unity) or at 125 MHz (VXR). Infrared (IR) spectra were measured with a Matteson FT-IR 3000 spectrophotometer. Mass spectra were determined on a VG Micromass 7050E mass spectrometer equipped with a VG 2000 data system.

1,5-Diisopropyl-2,4-dimethyl-1,4-pentadien-3-one 1c. A 500 mL round-bottom flask fitted with a reflux condenser and magnetic stir bar was charged with NaOH (8.8 g, 0.22 mol), H_2O (200 mL) and MeOH (160 mL) and the clear solution was cooled to 0°C. At this temperature a mixture of 3-pentanone (8.6 g, 0.1 mol) and isobutyraldehyde (14.4 g, 0.2 mol) was added via cannula. The resulting solution was stirred at 0°C for 5 h and was then heated at reflux overnight. The reaction mixture was cooled to 10°C, neutralized using 2N HCl and concentrated under reduced pressure to a total volume of approximately 200 mL. EtOAc (100 mL) was added, the layers were separated and the aqueous layer was extracted with EtOAc (2×100 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude mixture was partly purified by flash chromatography (hexanes/EtOAc 9:1) to give an oil which contained mainly two products by TLC, one of which could be removed by Kugelrohr distillation (4 Torr, 45–50°C). The remaining residue was further purified by flash chromatography (hexanes/EtOAc 40:1) to give 1,5-diisopropyl-2,4-dimethyl-1,4-pentadien-3-one (1.5 g, 7.7 mmol, 8 %) as a colorless oil: R_f 0.63 (hexanes/EtOAc 4:1); IR (thin film) 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (d, J=9.7 Hz, 1H), 2.76–2.59 (m, 1H), 1.83 (s, 3H), 1.01 (d, J=6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 149.5, 133.7, 28.2, 22.3, 13.0; HRMS for $C_{13}H_{22}O$ calcd 194.1671, found 194.1664.

1-Phenyl-2,5-dimethyl-1,4-pentadien-3-one. In a flame-dried 50 mL round-bottom flask, a solution of α-methyl cinnamaldehyde (1.0 g, 6.8 mmol) was prepared in dry THF (10 mL). To this solution was added dropwise a solution of 1-propenylmagnesium bromide (0.5 M mixture of isomers in THF, 16.4 mL, 8 mmol) at −5°C. The resulting mixture was stirred at 0°C for 1 h before the reaction was worked up by the addition of sat. NH_4Cl solution (20 mL). The mixture was stirred vigorously until two clear layers were obtained, the layers were separated and the aqueous layer was extracted with Et_2O (2×35 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was partly purified by running it through a short plug of silica gel (hexanes/EtOAc 7:3) to give after removal of solvent a yellow oil which was dissolved in dry CH_2Cl_2 (150 mL). The solution was cooled to 0°C and $BaMnO_4$ (13.2 g, 51.3 mmol) was added in one portion. The mixture was stirred at 0°C for 30 min and was then allowed to warm to rt and stirred overnight. Filtration through a short plug of Celite and concentration in vacuo gave a yellow oil which was purified by flash chromatography (silica gel, hexanes/EtOAc 30:1→25:1→20:1) to yield the two isomeric dienones.

(*E*,*E*)-1-Phenyl-2,5-dimethyl-1,4-pentadien-3-one 1d. R_f 0.34 (hexanes/EtOAc 7:1); IR (thin film) 1661, 1615 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (q, J= 1.2 Hz, 1H), 7.43–7.39 (m, 4H), 7.34–7.31 (m, 1H), 6.95 (dq, J=15.2, 6.8 Hz, 1H), 6.80 (dqd, J=15.2, 1.6, 0.4 Hz, 1H), 2.11 (d, J=1.3 Hz, 3H), 1.96 (dd, J=6.8, 1.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.1, 143.4, 138.7, 138.2, 136.2, 129.9, 128.9, 128.6, 127.2, 18.7, 13.9; HRMS for $C_{13}H_{14}O$ calcd 186.1045, found 186.1035.

(*E*,*Z*)-1-Phenyl-2,5-dimethyl-1,4-pentadien-3-one 1e. R_f 0.39 (hexanes/EtOAc 7:1); IR (thin film) 1654, 1617 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (q, J= 1.3 Hz, 1H), 7.44–7.39 (m, 4H), 7.35–7.32 (m, 1H), 6.61 (dq, J=11.6, 1.7 Hz, 1H), 6.27 (dq, J=11.6, 7.2 Hz, 1H), 2.11 (d, J=1.4 Hz, 3H), 2.04 (dd, J=7.2, 1.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 140.9, 139.7, 138.9, 136.2, 129.9, 128.7, 128.6, 126.2, 16.1, 13.2; HRMS for $C_{13}H_{14}O$ calcd 186.1045, found 186.1033.

1-Phenyl-4-methyl-5-(trimethylsilyl)-1,4-pentadien-3-one 3. In a sealed tube a solution of cinnamoyl chloride (1.67 g, 10 mmol) was prepared in $CHCl_3$ (2 mL) under air and benzyl chlorobis(triphenylphosphine) palladium[21] (15.0 mg, 0.02 mmol) was added. In a separate flask a solution of (*E*)-1-(trimethylsilyl)-2-(tributylstannyl)-propene[22] (4.23 g, 10.5 mmol) was prepared in $CHCl_3$ (8 mL) and this solution was added to the sealed tube via cannula. The sealed tube was closed and heated to 65°C for 6 h at which time palladium metal had precipitated. The mixture was cooled to 25°C, transferred to a separatory funnel and washed with aqueous KF solution (4 g KF/40 mL H_2O; 20 mL). Removal of the precipitate by filtration was followed by repeated washing with aqueous KF solution (20 mL). The layers were separated and the organic layer was washed with sat. NaCl. Separation of the layers, drying ($MgSO_4$) of the organic layer and removal of solvent was followed by flash chromatography (silica gel, hexanes/EtOAc 50:1→40:1→30:1→20:1) to give 1-phenyl-4-methyl-5-(trimethylsilyl)-1,4-pentadien-3-one **3** (1.37 g, 56%) as a slightly yellow oil: R_f 0.44 (hexanes/EtOAc 9:1); IR (thin film) 1657, 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J=15.7 Hz, 1H), 7.60–7.37 (m, 5H), 7.36 (d, J=15.7 Hz, 1H), 6.70 (br s, 1H), 2.05 (d, J=0.9 Hz, 3H), 0.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 152.8, 143.7, 139.9, 135.3, 130.4, 129.1, 128.5, 121.7, 17.3, −0.3.

1-Phenyl-4-methyl-cyclopent-3-enone 4. A solution of dienone **3** (100 mg, 0.41 mmol) in CH_2Cl_2 (41 mL) was cooled to −40 °C and $FeCl_3$ (70.0 mg, 0.43 mmol) was

added in one solid portion. The resulting dark reaction mixture was stirred vigorously and was allowed to warm to 0 °C. After 1 h at 0°C the reaction was quenched by the addition of H_2O (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Purification was achieved by radial chromatography (silica gel, 2 mm rotor, hexanes/EtOAc 15:1→12:1) to give 1-phenyl-4-methyl-cyclopent-3-one **4** (49 mg, 70%) as a clear oil: R_f 0.26 (hexanes/EtOAc 8:1); IR (thin film) 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.22 (m, 4H), 7.15–7.12 (m, 2H), 4.03 (dddq, J=6.8, 2.4, 2.4, 2.4 Hz, 1H), 2.93 (dd, J=19.0, 6.8 Hz, 1H), 2.35 (dd, J=19.0, 2.4 Hz, 1H), 1.87 (dd, J=2.2, 1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 160.5, 142.5, 142.0, 129.1, 127.3, 127.2, 44.4, 44.4, 10.3.

General procedure for the reductive Nazarov cyclization

In a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar and rubber septum was prepared a solution of dienone **1** (1 equiv.) and triethylsilane (2 equiv.) in CH_2Cl_2 (0.01 M in **1**). To this solution was added $BF_3{\cdot}OEt_2$ (1.1 equiv.) via syringe at −78°C. The resulting solution was slowly warmed and the disappearance of starting material was monitored by TLC. Upon complete consumption of starting material (0°C for **1a**,**c** and 10°C for **1b**,**d**,**e**) the reaction was quenched by the addition of 1N HCl (or H_2O) (10 mL). The resulting mixture was allowed to stir at 25°C overnight. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification was achieved using radial chromatography (silica gel, hexanes/EtOAc 25:1→20:1→15:1)

1-(Triethylsilyloxy)-2,5-dimethyl-3,4-diphenyl-cyclopent-1-ene 6a. R_f 0.61 (hexanes/EtOAc 7:1); IR (thin film) 1684, 1601 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29–7.04 (m, 10 H), 3.63 (d, J=7.0 Hz, 1H), 2.77–2.71 (m, 1H), 2.61 (dd, J=7.1, 7.1 Hz, 1H), 1.46–1.45 (m, 3H), 1.16 (d, J=6.8 Hz, 3H), 1.08 (t, J=7.9 Hz, 9H), 0.77 (q, J=7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 145.1, 145.1, 128.5, 128.5, 128.2, 127.9, 126.3, 126.3, 113.9, 61.4, 60.2, 48.5, 19.0, 11.3, 7.1, 5.8; Anal. Calcd for $C_{25}H_{34}OSi$: C, 79.29; H, 9.07. Found: C, 79.35; H, 9.01.

2,5-Dimethyl-3,4-diphenyl-cyclopentanone $7a_\beta$. Mp 120°C; R_f 0.26 (hexanes/EtOAc 7:1); IR (thin film) 1744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.09 (m, 10H), 2.94 (dd, J=12.0, 10.5 Hz, 1H), 2.94 (dd, J=12.0, 10.5 Hz, 1H), 2.47 (dq, J=12.0, 7.0 Hz, 1H), 2.47 (dq, J=12.0, 7.0 Hz, 1H), 1.14 (d, J=7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.8, 140.3, 128.7, 127.8, 127.1, 57.0, 51.8, 13.2; Anal. Calcd for $C_{19}H_{20}O$: C, 86.31; H, 7.64. Found: C, 86.32; H, 7.70.

2,5-Dimethyl-3,4-diphenyl-cyclopentanone $7a_\alpha$. Mp 82°C; R_f 0.21 (hexanes/EtOAc 7:1); IR (thin film) 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29–7.12 (m, 10 H), 3.89 (dd, J=11.9, 8.5 Hz, 1H), 3.28 (dd, J=11.9, 11.9 Hz, 1H), 2.85 (dqd, J=9.6, 8.1, 1.3 Hz, 1H), 2.45 (dqd, J=10.2, 6.9, 1.6 Hz, 1H), 1.12 (d, J=7.0 Hz, 3H), 0.78 (d, J=7.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.7, 141.0, 138.3, 129.0, 128.9, 128.4, 127.8, 127.1, 126.7, 53.4, 51.3, 50.4, 47.3, 13.1, 12.7; Anal. Calcd for $C_{19}H_{20}O$: C, 86.31; H, 7.64. Found: C, 86.19; H, 7.57.

Triquinane 7b. R_f 0.38 (hexanes/EtOAc 7:1); IR (thin film) 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.62 (ddd, J=9.1, 9.1, 3.6 Hz, 1H), 2.39–2.34 (m, 1H), 1.94–1.75 (m, 3H), 1.57–1.49 (m, 2H), 1.34 (dddd, J=13.0, 6.6, 6.6, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 227.2, 52.7, 46.7, 35.1, 30.4, 26.4; Anal. Calcd for $C_{11}H_{16}O$: C, 80.42; H, 9.84. Found: C, 80.53; H, 9.79.

Cyclopentenyl cyclopentyl ketone 8b. R_f 0.43 (hexanes/EtOAc 7:1); ^1H NMR (500 MHz, $CDCl_3$) δ 6.72–6.71 (m, 1H), 3.36 (dddd, J=8.0, 8.0, 8.0, 8.0 Hz, 1H), 2.57–2.52 (m, 4H), 1.94–1.88 (m, 2H), 1.81–1.76 (m, 4H), 1.70–1.64 (m, 2H) 1.61–1.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.0, 145.8, 143.1, 47.3, 34.1, 31.1, 30.4, 26.5, 23.0.

1-(Triethylsilyloxy)-2,5-dimethyl-3,4-diisopropyl-cyclopent-1-en 6c. Major diastereomer: R_f 0.77 (hexanes/EtOAc 7:1); IR (thin film) 1691, 1458 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.19–2.13 (m, 1H), 2.08–2.05 (m, 1H), 1.86–1.77 (m, 1H), 1.56–1.52 (m, 1H), 1.46 (dd, J=2.0, 1.1 Hz, 3H), 1.26 (dd, J=8.3, 3.8 Hz, 1H), 1.04 (d, J=7.0 Hz, 3H), 0.99 (t, J=7.9 Hz, 9H), 0.89 (d, J=6.8 Hz, 3H), 0.86 (d, J=7.0 Hz, 3H), 0.80 (d, J=6.7 Hz, 3H), 0.74 (d, J=7.0 Hz, 3H), 0.67 (q, J=7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 114.3, 54.1, 48.9, 40.8, 33.1, 29.3, 21.0, 20.5, 20.3, 18.3, 17.7, 11.3, 7.0, 5.7; HRMS for $C_{19}H_{38}OSi$ calcd 310.2692, found 310.2678.

Mixture of ketones 7c from Entry 7. (Inseparable mixture of two diastereomers; 2.6:1 ratio by ^1H NMR integration.) R_f 0.41 (hexanes/EtOAc 7:1); IR (thin film) 1739 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 225.4, 222.0, 46.9, 46.4, 46.1, 44.9, 43.2, 41.9, 33.4, 27.2, 27.1, 22.5, 21.3, 21.1, 19.3, 19.0, 17.4, 15.1, 10.8, 9.4.

Diastereomer A (major). ^1H NMR (500 MHz, $CDCl_3$) δ 2.54 (dqd, J=9.9, 7.1, 2.6 Hz, 1H), 2.08 (qqd, J=7.0, 7.0, 2.5 Hz, 1H), 1.99 (ddd, J=9.9, 2.8, 2.8 Hz, 1H), 1.85 (qqd, J=6.8, 6.8, 3.1 Hz, 1H), 1.75 (dqd, J=6.7, 6.7, 6.7, 1H), 1.46 (ddd, J=6.3, 6.3, 2.6 Hz, 1H), 1.10 (d, J=7.2 Hz, 3H), 1.02 (d, J=7.0 Hz, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.95 (d, J=6.7 Hz, 3H), 0.88 (d, J=7.0 Hz, 3H), 0.54 (d, J=6.8 Hz, 3H).

Diastereomer B (minor). ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (dq, J=9.7, 7.4 Hz, 1H), 2.11 (dd, J=9.8, 2.6 Hz, 1H), 1.95 (qqd, J=6.8, 6.8, 2.7 Hz, 1H), 1.09 (d, J=7.3 H, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.69 (d, J=6.8 Hz, 3H).

Mixture of ketones 7c from Entry 8. (Inseparable mixture of three diastereomers, including diastereomers A and B from above; 2.8:1.2:1 ratio by ^1H NMR integration.) R_f 0.41 (hexanes/EtOAc 7:1); IR (thin film) 1739 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 225.4, 223.7, 222.0, 51.0, 46.9, 46.4, 46.1, 44.9, 44.4, 43.2, 41.9, 33.4, 29.4, 27.2, 27.1, 22.5, 22.2, 21.3, 21.1, 19.3, 19.0, 17.8, 17.4, 17.1, 15.1, 10.8, 9.4.

Diastereomer C (major). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.05–2.02 (m, 1H), 1.92–1.88 (m, 1H), 1.48–1.44 (m, 1H), 1.12 (d, J=7.0 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H), 0.87 (d, J=7.0 Hz, 3H).

2,4-Dimethyl-3-phenyl-cyclopentanones 7d. (Inseparable mixture of two diastereomers; 3.3:1 ratio by ^{1}H NMR integration.) R_f 0.30 (hexanes/EtOAc 7:1); IR (thin film) 1740 cm^{-1}.

Major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.14 (m, 5H), 2.70 (dd, J=18.5, 6.8 Hz, 1H), 2.38–2.26 (m, 3H), 1.94 (dd, J=18.7, 11.0 Hz, 1H), 1.01 (d, J=6.1 Hz, 3H), 0.99 (d, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.0, 141.1, 128.8, 127.8, 127.1, 59.3, 53.2, 46.3, 37.1, 18.2, 12.5.

Minor diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.14 (m, 5H), 3.14 (dd, J=8.9, 8.9 Hz, 1H), 2.71–2.64 (m, 2H), 2.59 (dq, J=7.9, 7.9 Hz, 1H), 2.06 (ddd, J=20.8, 12.3, 1.4 Hz, 1H), 1.13 (d, J=6.1 Hz, 3H), 0.75 (d, J=7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 220.7, 139.2, 128.7, 128.6, 126.8, 54.3, 48.4, 32.4, 19.3, 12.0 (one resonance obscured by overlapping mixture of diastereomers).

Cyclopentanones-d_1 9d. According to the general procedure for the reductive Nazarov cyclization dienone **1d** was treated with $BF_3{\cdot}OEt_2$ in the presence of Et_3SiD[23] to give cyclopentanones **9d** in 82% yield: (Inseparable mixture of two main diastereomers; ca. 4:1 ratio by GC.) R_f 0.30 (hexanes/EtOAc 7:1); IR (thin film) 1740 cm^{-1}.

Major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.14 (m, 5H), 2.69–2.67 (m, 1H), 2.37–2.30 (m, 3H), 1.02 (d, J=6.1 Hz, 3H), 1.00 (d, J=6.4 Hz, 3H); MS (EI/70 eV): m/z (%) 189 (M^+, 41), 118 (100).[24]

Minor diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.14 (m, 5H), 3.15 (dd, J=8.9, 8.9 Hz, 1H), 2.70–2.64 (m, 2H), 2.60 (dq, J=7.9, 7.9 Hz, 1H), 1.14 (d, J=6.1 Hz, 3H), 0.76 (d, J=7.7 Hz, 3H); MS (EI/70 eV): m/z (%) 189 (M^+, 49), 118 (100).[24]

Tricyclic ether 11. R_f 0.72 (hexanes/EtOAc 7:1); IR (thin film) 1465, 1455, 1375, 1362 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 (d, J=3.1 Hz, 1H), 1.87–1.42 (m, 9H), 1.22 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H), 0.97 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 89.3, 82.3, 63.3, 60.6, 54.6, 52.2, 31.9, 31.2, 30.9, 29.6, 28.5, 27.0, 26.9, 24.4; Anal. Calcd for $C_{16}H_{28}O$: C, 81.27; H, 11.96. Found: C, 81.27; H, 11.89.

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24. Two additional methyl doublets from a third, very minor diastereomer could also be detected in the ^{1}H NMR spectrum of **9d**. Mass spectra for the two major diastereomers were obtained separately via GC–MS.