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Ready Access to Alkylidenecyclopentenones by Nazarov Cyclization/β-Elimination of 2-Hydroxyalkyl-1,4-dien-3-ones

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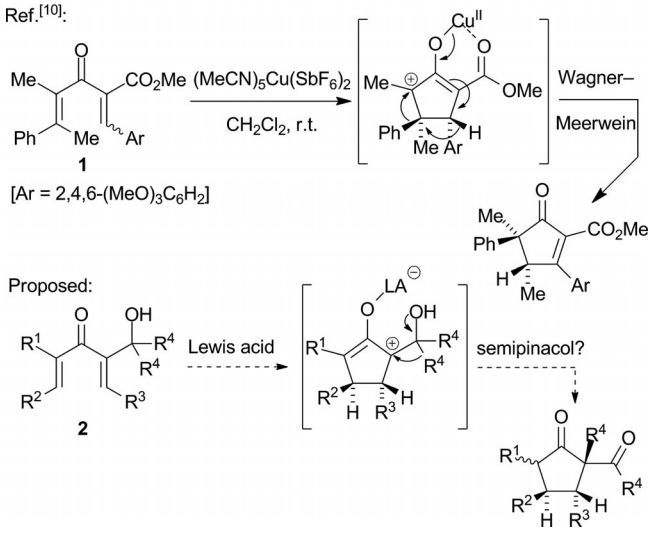
Cross-conjugated dienones bearing α-hydroxyalkyl substituents readily undergo Nazarov cyclization followed by deprotonation of the resulting cyclopentenyl cation, and β-elimination of the exocyclic hydroxy group to form alkylidenecyclopentenones in moderate yield. The deprotonation step occurs with complete regioselectivity opposite to the hydroxyalkyl substituent, with preferential introduction of an endocyclic olefin. The transformation is tolerant of a variety of substituents and occurs under relatively mild conditions.

Introduction

The Nazarov cyclization enjoys a well-deserved reputation as an efficient way to produce cyclopentanoid products.[1] Recent advances in Nazarov cyclization chemistry have focused on the development of catalytic activation methods,[2] the development of processes to induce asymmetry,[3] the use of unconventional substrates,[4] and the enhanced build-up of molecular complexity by interception of the cyclopentenyl cation intermediate.[5] Trapping of the oxyallyl cation intermediate can proceed by cycloaddition processes,[6] but nucleophilic capture at only one end of the allyl system can also be accomplished, leading to a variety of highly substituted cyclopentanone products. For example, we have recently demonstrated that siloxyalkenes,[7] electron-rich aromatics,[8] and organoaluminum reagents[9] react readily with the cyclopentenyl cation intermediate in an umpolung fashion to form α-functionalized cyclopentanones.

The Frontier group has described an innovative strategy for the intramolecular delivery of substituents to the remote terminus of a polarized Nazarov-derived oxyallyl cation.[10] This approach relies on sequential 1,2-Wagner–Meerwein rearrangements of adjacent groups on the former C-1 and C-5 termini of carboxy-substituted dienones **1**, with concomitant formation of a conjugated enone (Scheme 1). We set out to explore a related process, involving substrates **2**, in which the migrating group is initially bonded to an oxygenated carbon atom exocyclic to the newly formed cyclopentanoid. We envisioned that a sequential Nazarov electrocyclization and semipinacol rearrangement[11] would lead to 1,3-diketone products in which the initially formed stereocenters are preserved, and a new quaternary center is formed between the two carbonyl groups. In this paper, we describe the results of these studies, including an unexpected preference for a dehydrative double elimination pathway leading to alkylidenecyclopentenones.



Scheme 1. Cationic 1,2-shifts of the Nazarov intermediate.

Results and Discussion

A series of 2-hydroxyalkyl-1,4-dien-3-ones **2a**–**2i** was prepared, using the method of Lee and co-workers[12] (Table 1). Cross-conjugated enynones **3a**–**3d**[13] were treated with Ph_2CuLi at low temperature in the presence of acetone, cyclopentanone, cyclohexanone, or cyclobutanone to give the desired substrates in modest to good yields in a single step.

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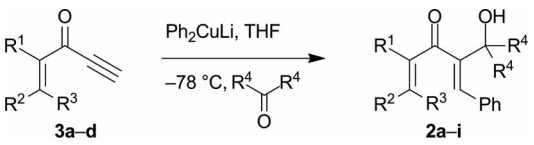
Exclusive addition to the β-alkynyl carbon atom was seen in all cases, and the resulting trisubstituted alkene was formed with complete selectivity for the (*E*) geometry.

Table 1. Preparation of dienone substrates **2a**–**2i**.[a]



Entry	Enynone	R^1	R^2	R^3	R^4	Product	Yield [%][b]
1	**3a**	Me	Ph	H	$(CH_2)_4$	**2a**	68
2	**3a**	Me	Ph	H	Me	**2b**	50
3	**3a**	Me	Ph	H	$(CH_2)_5$	**2c**	91
4	**3b**	Me	Me	H	$(CH_2)_4$	**2d**	35
5	**3b**	Me	Me	H	Me	**2e**	47
6	**3b**	Me	Me	H	$(CH_2)_5$	**2f**	35
7	**3c**	$(CH_2)_4$		H	$(CH_2)_4$	**2g**	55
8	**3c**	$(CH_2)_4$		H	Me	**2h**	63
9	**3d**	H	Ph	Me	$(CH_2)_4$	**2i**	61
10	**3d**	H	Ph	Me	$(CH_2)_3$	**2j**	76

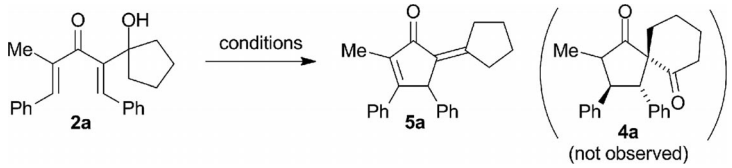
[a] Standard procedure: A solution of Ph_2CuLi (0.24 M in THF; 1.05 equiv.) was cooled to –78 °C. The ketone (1.1 equiv.) was added, followed immediately by the dropwise addition of enynone **3** (1 equiv.) in THF (0.75 M). After 0.5 h, the reaction was quenched with aq. HCl, followed by aqueous workup, and the crude product was purified by flash chromatography. See Supporting Information for additional details. [b] All yields given are for isolated products after purification.

Dienone **2a** was used for initial investigations. This substrate, if it underwent the desired semipinacol process, would give spirocyclic product **4a** (Table 2). Treatment with $BF_3{\cdot}OEt_2$ at low temperature followed by gradual warming resulted in the consumption of **2a**, but gave a complex and intractable mixture of products (Table 2, Entry 1). Similar results were seen with Me_3SiOTf (Table 2, Entry 2). Possible competition for complexation of the Lewis acid by the hydroxy group was considered, and so excess Me_3SiOTf in the presence of 1 equiv. amine base was also used, with the expectation that this would effect in situ silylation of the alcohol and so prevent any interference in the activation of the carbonyl group (Table 2, Entry 3). Unfortunately, in this case, the majority of the starting material was recovered, along with a small amount of an uncharacterizable mixture of products resulting from indiscriminate destruction under these conditions. Titanium(IV) Lewis acids potentially capable of bidentate complexation were also tested. $Ti(O{i}Pr)_4$ failed to consume **2a**, even after extended stirring. The more reactive $TiCl_4$ did give a new product in modest yield. However, this proved to be alkylidenecyclopentenone[14] **5a**, resulting from elimination of the tertiary hydroxy group. The use of Me_2AlCl improved the yield of **5a** to 51%; under none of the conditions tested was the desired semipinacol product (i.e., **4a**) observed.

The "double electrophile" structure of **5a** is found in a number of promising anticancer compounds[15] with cytotoxic and antiangiogenic[15b] properties. With this in mind, we examined the other substrates (i.e., **2b**–**2i**) under the conditions of Table 2, Entry 6 to evaluate the generality of this method for the production of alkylidenecyclopentenones (Table 3). Acetone adduct **2b** gave **5b** in only modest yield, but **2c** gave **5c** in 62% yield (Table 3, Entries 2 and 3). Substrates **2d**–**2f**, in which the phenyl group at R^2 was replaced with a methyl group, gave similar results (Table 3, Entries 4–6). Similar results were also obtained with **2g** and **2h**, which gave products **5g** and **5h**, with olefins at the shared edges of the fused hydrindenone ring systems (Table 3, Entries 7 and 8).

Notably, in all instances, the initial deprotonative elimination occurred on the side distal to the hydroxyalkyl moiety, permitting the subsequent β-elimination of the exocyclic oxygen substituent (see below). Based on these results, we propose that the first equivalent of Lewis acid complexes to the hydroxy group, and that the second equivalent is required to activate the dienone carbonyl group (Scheme 2).[16] Electrocyclization then gives a cyclopentenyl cation **A**, which may be polarized, with a more positive character at the terminus opposite to the oxygenated sidechain. Elimination on this side gives an aluminum dienolate **B** that is poised to eject the Lewis-acid-complexed oxygen atom at the exocyclic β-position to provide the alkylidenecyclopentenone. Alternatively, a cationic chelate **C** involving an Me_2Al species and an $Me_2AlCl_2^-$ counterion, previously

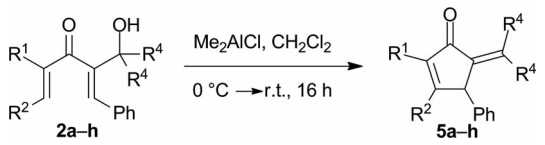
Table 2. Attempted Nazarov/semipinacol reaction of **2a**.



Entry	Conditions	Product	Yield [%][a]
1	$BF_3{\cdot}OEt_2$ (1.1 equiv.), CH_2Cl_2, –78 °C → room temp., 4 h	intractable mixture	–
2	Me_3SiOTf (1.1 equiv.), CH_2Cl_2, –78 °C → room temp., 4 h	intractable mixture	–
3	Me_3SiOTf (2.1 equiv.), $(i{Pr})_2NEt$ (1.0 equiv.), CH_2Cl_2, –78 °C → room temp., 48 h	minimal conversion	–
4	$Ti(O{i}Pr)_4$ (1.1 equiv.), CH_2Cl_2, 0 °C → room temp., 48 h	no conversion	–
5	$TiCl_4$ (1.1 equiv.), CH_2Cl_2, –78 → 0 °C, 2 h	**5a**	23
6[b]	Me_2AlCl (2.2 equiv.), CH_2Cl_2, 0 °C → room temp., 16 h	**5a**	51

[a] All yields given are for isolated products after purification. [b] Dienone **2a** was only partially consumed when 1.1 equiv. Me_2AlCl was used. An excess of this reagent was required for complete conversion.

Table 3. Conversion of **2a**–**2h** to alkylidenecyclopentenones.[a]



Entry	Dienone	R^1	R^2	R^4	Product	Yield [%][b]
1	**2a**	Me	Ph	$(CH_2)_4$	**5a**	51
2	**2b**	Me	Ph	Me	**5b**	36
3	**2c**	Me	Ph	$(CH_2)_5$	**5c**	62
4	**2d**	Me	Me	$(CH_2)_4$	**5d**	46
5	**2e**	Me	Me	Me	**5e**	43
6	**2f**	Me	Me	$(CH_2)_5$	**5f**	61
7	**2g**	$(CH_2)_4$		$(CH_2)_4$	**5g**	34
8	**2h**	$(CH_2)_4$		Me	**5h**	58

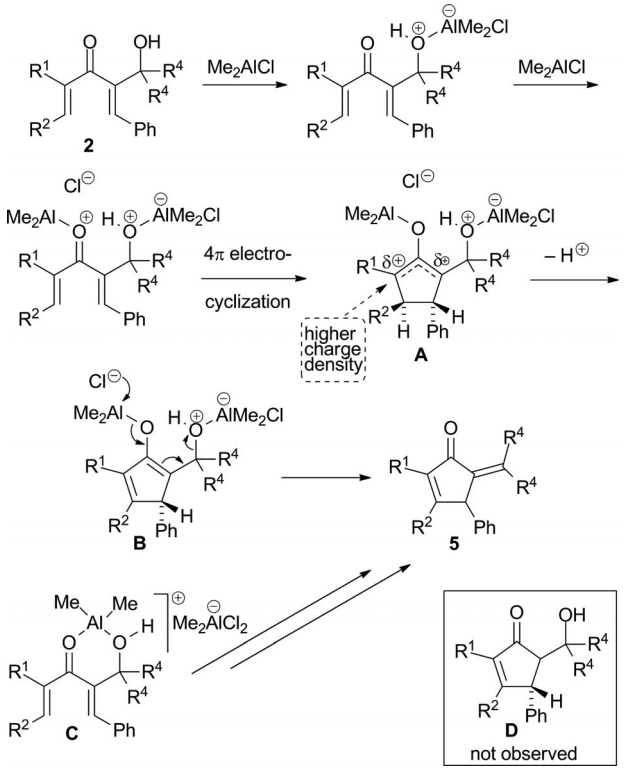
[a] Standard procedure: Dienone **2** was dissolved in CH_2Cl_2 (0.05 M), and the solution was cooled to 0 °C. A solution of Me_2AlCl in (1.0 M in hexanes; 2.2 equiv.) was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h, then it was warmed to room temp. and stirred for an additional 15.5 h, followed by HCl (1 N) quench, aqueous workup, and chromatographic purification. See Supporting Information for additional details. [b] All yields given are for isolated product after purification.

proposed by Evans and co-workers for nucleophilic additions to β-hydroxycarbonyl compounds,[17] may be involved. An alternative sequence involving direct elimination from **B** or from the corresponding chelate derived from **C** cannot be ruled out. Thus, a conventional Nazarov reaction to give hydroxyalkylcyclopentenone **D** (or its aluminum complex) could occur, followed by elimination in situ to give **5**. However, it should be noted that under no circumstances were intermediates such as **D** obtained in the product mixtures from these reactions.

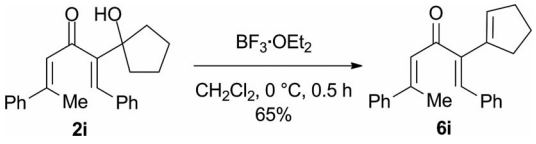
We next turned our attention to substrates **2i** and **2j**, which lack a proton at the preferred site of the deprotonative elimination (i.e., R^3 = Me instead of H). With the usual elimination unavailable, we envisioned that the desired semipinacol process might be able to compete with elimination. Moreover, the absence of a substituent at the α′-position was expected to alter the polarization of the allyl cation, increasing the positive-charge density adjacent to the hydroxyalkyl group at the α-position, and so again favoring the semipinacol pathway.

In the event, **2i** was not fully consumed under the conditions successfully used with **2a**–**2h**, even after 48 h in the presence of 4 equiv. Me_2AlCl. On the other hand, treatment with $BF_3{\cdot}OEt_2$ resulted in the rapid consumption of **2i** to give one main product after 30 min [Equation (1)]. Unfortunately, this product proved to be **6i**, resulting from elimination of the tertiary alcohol, with no Nazarov cyclization of either **2i** or **6i** having occurred.

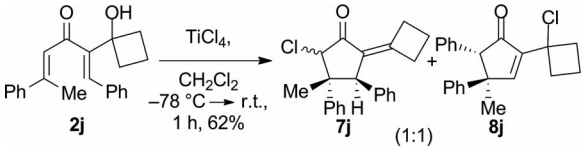
Similarly, **2j** was not consumed by treatment with Me_2AlCl under the described reaction conditions. After a short screening of Lewis acids, we discovered that $TiCl_4$ cleanly produced two new products upon warming to room temperature, and in contrast to the pilot studies with **2a**, we found that 2.1 equiv. of $TiCl_4$ was required for complete consumption of **2j**. Both products appeared to have undergone a Nazarov cyclization, but neither contained the sought-after 1,3-diketone structure, and were instead identified as **7j** and **8j** [Equation (2)].



Scheme 2. Proposed double elimination mechanism.

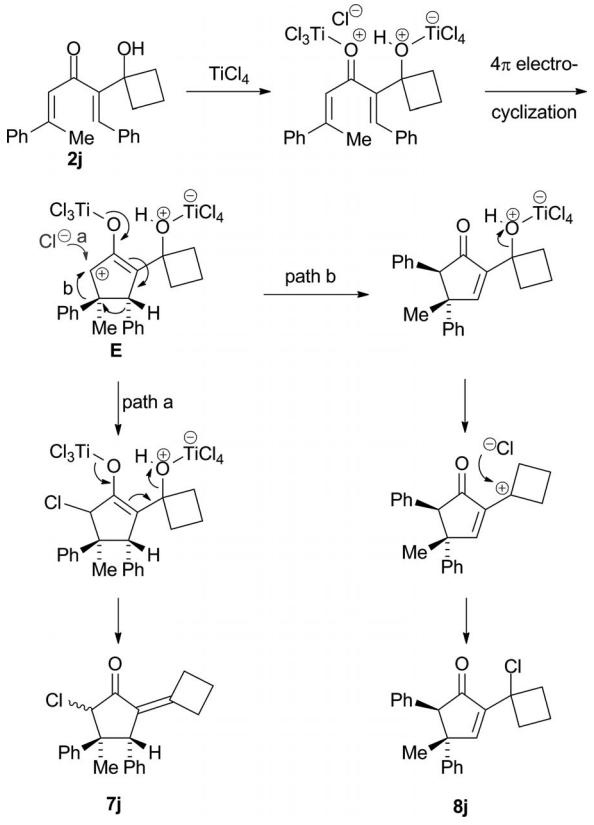


(1)



(2)

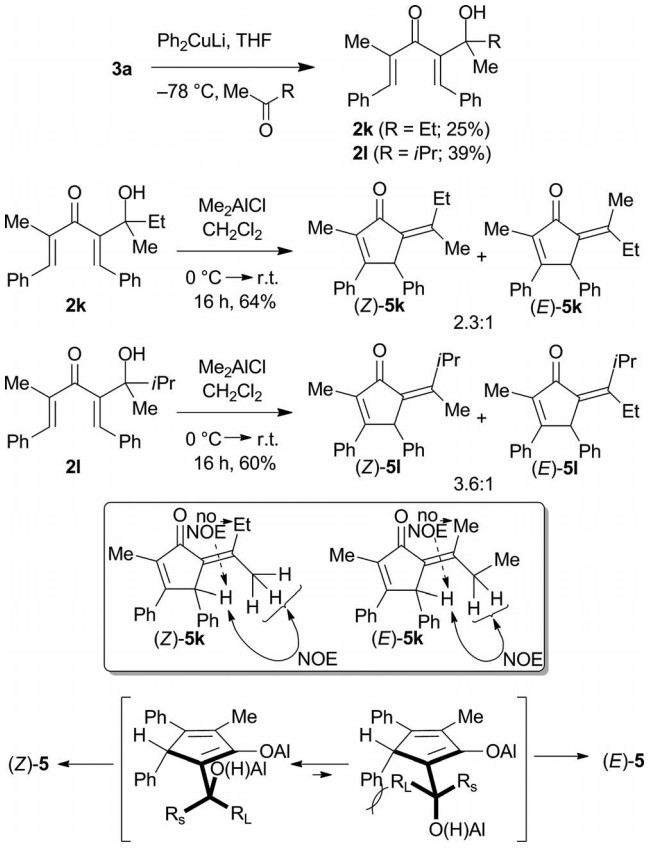
Alkylidenecyclopentanone **7j** is presumed to arise from trapping of oxyallyl cation **E** with chloride, followed by elimination of the hydroxy group (Scheme 3, path a). Notably, the chloride adduct was isolated as a single diastereomer (unassigned). Cyclopentenone **8j** appears to have been produced by a Nazarov cyclization followed by two consecutive 1,2-phenyl migrations, similar to the previously discussed work of the Frontier group (Scheme 3, path b).[10] Subsequent elimination of the hydroxy group would then give an allylic cation that can be trapped by chloride.



Scheme 3. Proposed mechanism for the formation of **7j** and **8j**.

The results seen with dienone **2j** further support the hypothesis that there is a higher charge density at the α-position distal to the hydroxy substituent in the Nazarov intermediate – so much so that even the potential relief of the ring strain present in the cyclobutyl substituent by semipinacol ring-expansion is not favored as a termination event. Instead, either chloride trapping at that site or consecutive 1,2-shifts of the phenyl groups occurs.

The formation of alkylidenecyclopentenones **5a**–**5h** did not involve any issues concerning alkene geometry, since in all cases, the R^4 substituents on the tertiary alcohol were identical. We wondered whether substrates derived from unsymmetrical ketones would show any selectivity in the elimination step. With this in mind, substrates **2k** and **2l** were prepared by the standard method (Scheme 4). Treatment under the conditions used in Table 3 gave alkylidenecyclopentenones **5k** and **5l** in fair yields, which were formed in each case as a mixture of alkene geometrical isomers. In the case of **5k**, the two isomers were obtained in a ratio of 2.3:1 and could be separated by preparative TLC for full analysis. NOE experiments showed clear correlations in each isomer between the C-4 benzylic methine group and the alkyl group in a *cis* relationship to it. Significant chemical shift differences between the (*E*) and (*Z*) isomers of **5k** for the allylic protons *cis* or *trans* to the ketone carbonyl group were seen, and similar differences were also apparent for the isomers of **5l** (formed in a 3.6:1 ratio), which allowed their assignment by analogy to **5k**. The origin of the selectivity in favor of the (*Z*) isomer in both cases is uncertain at this time, but it may result from a transition state for the elimination that minimizes the steric clash between the larger substituent (R_L) of the tertiary alcohol and the methine carbon atom at C-4.



Scheme 4. Stereoselective elimination in unsymmetrically substituted cases.

Conclusions

Cross-conjugated dienones with hydroxyalkyl substituents at one of the α-positions undergo a domino Nazarov cyclization/dehydration process to give highly unsaturated alkylidenecyclopentenones in modest to good yields, in preference to an alternative semipinacol pathway that is potentially available. Unsymmetrically substituted hydroxyalkyl groups show modest stereoselectivity in the elimination step. Further studies with these substrates and biological evaluation of the dienone products **5** will be described in due course.

Experimental Section

Representative Procedure for Enynone Synthesis. 2-Methyl-1-phenylpent-1-en-4-yn-3-one (3a): 2-Methyl-*N*-methoxy-*N*-methylcinnamamide (5.12 g, 25 mmol) was dissolved in THF (60 mL), then the flask was flushed with argon, and the mixture cooled to 0 °C. A solution of ethynylmagnesium bromide (0.5 M in THF; 60 mL, 30 mmol, 1.2 equiv.) was added slowly over 2 min. The solution was then stirred at this temperature until the starting mate-

rial was consumed (as determined by TLC analysis). The reaction was then quenched with HCl (1 N aq.; 50 mL), and the mixture was extracted with Et_2O (2× 50 mL). The organic layers were combined, washed with H_2O (50 mL) and brine (50 mL), and dried with $MgSO_4$. After filtration, the solution was concentrated by rotary evaporation, and the product was purified by flash chromatography (silica gel; hexanes/EtOAc, 20:1) to give enynone **3a** (2.68 g, 63%) as a yellow solid. R_f = 0.43 (hexanes/EtOAc, 8:1). M.p. 58–60 °C. IR (film): $\tilde{\nu}$ = 3259, 3049, 2965, 2092, 1629 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (br. s, 1 H), 7.52–7.49 (m, 2 H), 7.47–7.42 (m, 2 H), 7.41–7.37 (m, 1 H), 3.32 (s, 1 H), 2.13 (d, J = 1.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.1, 146.7, 137.8, 135.3, 130.2, 129.5, 128.6, 79.9, 79.8, 12.1 ppm. HRMS (EI): calcd. for $C_{12}H_{10}O$ $[M]^+$ 170.0732; found 170.0729.

Representative Procedure for Dienone Synthesis. 2-(1-Hydroxycyclopentyl)-4-methyl-1,5-diphenylpenta-1,4-dien-3-one (2a): A suspension of CuBr·SMe_2 (322 mg, 1.57 mmol, 1.05 equiv.) in THF (5 mL) was flushed with argon and cooled to 0 °C. A solution of phenyllithium (1.9 M in dibutyl ether; 1.65 mL, 3.15 mmol, 2.1 equiv.) was added dropwise. The mixture was stirred for 45 min, during which time the solid slowly dissolved, and the solution turned dark brown. The solution was then cooled to –78 °C. Cyclopentanone (259 μL, 1.65 mmol, 1.1 equiv.) was added, immediately followed by the dropwise addition of a solution of enynone **3a** (255 mg, 1.5 mmol) in THF (2 mL). The resulting solution was stirred at this temperature for 30 min, and the reaction was then quenched with HCl (1 N aq.; 5 mL). The mixture was extracted with Et_2O (2× 10 mL). The organic layers were combined, washed with H_2O (15 mL) and brine (10 mL), and dried with $MgSO_4$. After filtration, the solution was concentrated by rotary evaporation, and the resulting oil was purified by flash chromatography (silica gel; hexanes/EtOAc, 5:1) to give dienone **2a** (339 mg, 68%) as a white solid. R_f = 0.51 (hexanes/EtOAc, 2:1). M.p. 107–108 °C. IR (film): $\tilde{\nu}$ = 3445, 3025, 2961, 1637 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 (br. s, 1 H), 7.30–7.27 (m, 2 H), 7.25–7.21 (m, 3 H), 7.18–7.16 (m, 1 H), 7.15–7.12 (m, 2 H), 7.08 (br. s, 1 H), 7.07–7.04 (m, 2 H), 2.85 (s, 1 H), 2.02–1.96 (m, 2 H), 1.95 (d, J = 1.3 Hz, 3 H), 1.94–1.86 (m, 4 H), 1.78–1.74 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 204.1, 144.8, 143.3, 137.4, 136.4, 135.8, 129.4 (2×), 128.6 (2×), 128.4, 128.3, 127.8, 83.5, 39.1, 23.1, 12.5 ppm. HRMS (ESI): calcd. for $C_{23}H_{25}O_2$ $[M + H]^+$ 333.1849; found 333.1852.

Representative Procedure for Alkylidenecyclopentenone Synthesis. 5-Cyclopentylidene-2-methyl-3,4-diphenylcyclopent-2-enone (5a): A solution of **2a** (50 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) was flushed with argon and cooled to 0 °C. A solution of $AlMe_2Cl$ (1.0 M in hexanes; 0.33 mL, 2.2 equiv.) was added dropwise, and the color of the solution turned dark orange. After 30 min, the cooling bath was removed, and the reaction mixture was stirred for 16 h. After the starting material had been consumed (as shown by TLC analysis), HCl (1 N aq.; 1 mL) was added slowly to quench the reaction. The mixture was then extracted with CH_2Cl_2 (5 mL). The organic phase was washed sequentially with water (5 mL) and brine (5 mL), and then dried with $MgSO_4$. The mixture was then filtered and concentrated by rotary evaporation, and the residue was purified by flash chromatography (silica gel; hexanes/EtOAc, 10:1) to give **5a** (24 mg, 51%) as a yellow semisolid. R_f = 0.38 (hexanes/EtOAc, 8:1). IR: $\tilde{\nu}$ = 3060, 2929, 1682, 1648 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2 H), 7.25–7.21 (m, 3 H), 7.17–7.13 (m, 2 H), 7.10–7.0.5 (m, 3 H), 4.69 (br. s, 1 H), 3.02–2.92 (m, 2 H), 2.32–2.26 (m, 2 H), 2.00 (d, J = 1.9 Hz, 3 H), 1.83–1.72 (m, 2 H), 1.62–1.57 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.1, 162.3, 158.7, 140.2, 139.4, 135.3, 131.4, 128.5, 128.4 (2×), 128.2 (2×), 126.5, 52.5, 33.3, 32.8, 26.5, 25.3, 10.0 ppm. HRMS (EI): calcd. for $C_{23}H_{22}O$ $[M]^+$ 314.1671; found 314.1670.

Nazarov Reaction of Dienone 2j. Formation of Alkylidenecyclobutane (7j) and Chlorocyclobutane (8j): Dienone **2j** (30 mg, 0.094 mmol) was dissolved in CH_2Cl_2 (3 mL), and the solution was cooled to –78 °C. $TiCl_4$ (1.0 M in toluene; 200 μL, 2.1 equiv.) was added dropwise, resulting in a reddish brown color. The mixture was stirred at this temperature for 30 min, then it was warmed to room temperature where it remained for 45 min. The reaction was then quenched with water (5 mL), and the mixture was extracted with CH_2Cl_2 (2× 5 mL). The combined organic extracts were washed with water (2× 5 mL) and brine (5 mL), dried with $MgSO_4$, and concentrated by rotary evaporation. The products were then purified by flash chromatography (hexanes/EtOAc, 15:1) to give **7j** (10 mg, 31%) and **8j** (10 mg, 31%), both as yellow oils.

Data for 7j: R_f = 0.73 (hexanes/EtOAc, 8:1). IR (film): $\tilde{\nu}$ = 3060, 2959, 1728, 1661 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 4 H), 7.22–7.18 (m, 5 H), 6.82 (br. s, 1 H), 5.07 (s, 1 H), 4.22 (app quintet, J = 3.0 Hz, 1 H), 3.41–3.32 (m, 1 H), 3.26–3.18 (m, 1 H), 2.42–2.34 (m, 1 H), 2.14–2.00 (m, 3 H), 1.14 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.9, 164.9, 141.9, 135.8, 130.0, 128.4, 127.6, 127.2, 127.0, 126.4, 125.4, 72.1, 56.3, 51.1, 35.0, 33.4, 18.5, 16.6 ppm. HRMS (EI): calcd. for $C_{22}H_{21}{}^{35}ClO$ $[M]^+$ 336.1281; found 336.1281.

Data for 8j: R_f = 0.82 (hexanes/EtOAc, 8:1). IR (film): $\tilde{\nu}$ = 3059, 2955, 1713, 1600 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.60 (s, 1 H), 7.41–7.36 (m, 2 H), 7.33–7.28 (m, 4 H), 7.24–7.21 (m, 2 H), 6.96–6.92 (m, 2 H), 3.86 (s, 1 H), 3.02–2.95 (m, 2 H), 2.75–2.68 (m, 2 H), 2.37 (app dtt, J =18.0, 9.2, 6.7 Hz, 1 H), 1.97 (app dtt, J = 17.3, 8.7, 6.1 Hz, 1 H), 1.17 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 205.4, 163.5, 145.8, 145.5, 136.2, 130.1, 128.9, 128.4, 127.3, 127.0, 125.9 67.8, 64.9, 49.4, 38.0, 23.5, 16.6 ppm. HRMS (EI): calcd. for $C_{22}H_{21}{}^{35}ClO$ $[M]^+$ 336.1281; found 336.1280.

Representative Synthesis of Unsymmetrical Alkylidene Cyclopentenones. (*Z*)-5k and (*E*)-5k: According to the standard procedure for alkylidenecyclopentenone synthesis (see above), **2k** (40 mg, 0.12 mmol) was transformed into a mixture of (*Z*)-**5k** and (*E*)-**5k** (24 mg, 64%) in a 2.3:1 ratio (determined by integration of upfield ethyl triplets in the ^1H NMR spectrum), as a yellow oil after flash chromatography (silica gel; pentane/EtOAc, 30:1). The isomers were then separated by preparatory TLC (silica gel; two successive elutions with hexanes/EtOAc, 30:1 and then hexanes/EtOAc, 15:1) for analytical purposes.

Data for (*Z*)-5k: R_f = 0.48 (hexanes/EtOAc, 20:1). IR (film): $\tilde{\nu}$ = 3026, 2962, 1677, 1621 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.24 (m, 3 H), 7.18–7.12 (m, 4 H), 7.09–7.02 (m, 3 H), 4.73 (q, J = 2.0 Hz, 1 H), 2.91 (dq, J = 12.0, 7.5 Hz, 1 H), 2.87 (dq, J = 12.0, 7.5 Hz, 1 H), 1.95 (d, J = 1.9 Hz, 3 H), 1.66 (s, 3 H), 1.07 (app t, J = 7.8 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.0, 162.5, 153.3, 140.9, 139.3, 135.3, 133.9, 128.5, 128.4, 128.2 (2×), 128.1, 126.4, 52.5, 26.7, 21.4, 12.6, 9.8 ppm. HRMS (EI): calcd. for $[M]^+$ $C_{22}H_{22}O$ 302.1671; found 302.1670.

Data for (*E*)-5k: R_f = 0.46 (hexanes/EtOAc, 20:1). IR (film): $\tilde{\nu}$ = 3026, 2972, 1677, 1621 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.24 (m, 3 H), 7.20–7.17 (m, 2 H), 7.16–7.12 (m, 2 H), 7.09–7.04 (m, 2 H), 4.79 (br. s, 1 H), 2.33 (d, J = 0.8 Hz, 3 H), 2.06 (m, 2 H), 1.97 (d, J = 1.9 Hz, 3 H), 0.63 (app t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.0, 162.2, 152.1, 141.3, 139.5, 135.2, 133.8, 128.5, 128.4, 128.2 (2×), 128.1, 126.4, 52.1, 30.5, 17.8, 10.7, 9.9 ppm. HRMS (EI): calcd. for $C_{22}H_{22}O$ $[M]^+$ 302.1671; found 302.1670.

Supporting Information (see footnote on the first page of this article): General methods, representative procedures, ^{1}H and ^{13}C NMR spectra, and IR and HRMS data.

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