Oxygenophilic Organoaluminum-Mediated Conjugate Addition of Alkyllithium and Grignard Reagents to Quinone Monoketals and Quinol Ethers. The Directing Effect of a Methoxy Group on the 1,4-Addition Process

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Complexation of quinone monoketals and quinol ethers with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), the MAD reagent, followed by addition of organolithium or Grignard reagents gives products from 1,4-addition of the organometallic reagent to the α,β-unsaturated ketone moiety. The success of these 1,4-additions stands in marked contrast to reported MAD-mediated additions of alkyllithium reagents to cyclohexenone, which afford 1,2-addition products. Interestingly, only one of the possible stereoisomers has been isolated from the reaction of quinol ethers, 4-substituted 4-methoxy-2,5-cyclohexadienones, with alkyllithium and Grignard reagents. X-ray analysis of the 1,4-addition product from MAD-mediated addition of 2-propenyllithium and 4-phenyl-4-methoxy-2,5-cyclohexadienone shows the methoxy and 2-propenyl group to be cis. These results suggest that the 4-methoxy moiety present in the quinone monoketals and quinol ethers performs a key function in facilitating these 1,4-addition reactions.

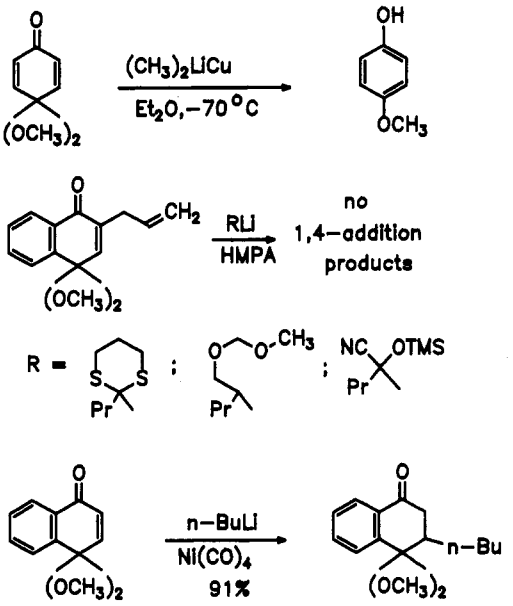
Introduction

Quinone monoketals serve as useful quinone equivalents[1] since they undergo 1,2-additions with a variety of organolithium species, 1,4-additions with soft nucleophiles,[2] and annelation reactions with 1,4-dipole equivalents.[1b] However, there are a limited number of methods for 1,4-addition of simple alkyl and aryl groups to quinone monoketals. The facile reduction of the quinone monoketal to the corresponding *p*-methoxyphenol by dimethylcuprate[3a] (Scheme I) and some Grignard reagents[3b] precludes standard conjugate addition conditions to effect 1,4-addition of alkyl groups to quinone monoketals. Mixed results were recorded on the use of acyl anion synthons for effecting 1,4-addition to quinone monoketals useful in synthesizing isochromanone antibiotics.[4] Only for the reaction of 2-propyl-2-lithio-1,3-dithiane with naphthoquinone monoketal in THF/HMPA was the 1,4-addition product obtained in good yield.[4]

Due to these failures, the reactions of acyl–nickel complexes[5] derived from alkyllithium reagents and nickel carbonyl with quinone monoketals were studied.[4] Although the acyl–nickel complexes of propyllithium and butyllithium worked adequately with the unsubstituted naphthoquinone monoketals (Scheme I), they failed with a substituted naphthoquinone monoketal. Furthermore, the nickel–acyl complexes failed to give the conjugate adducts when reacted with benzoquinone monoketals, giving instead nearly quantitative yields of the reductive cleavage products.

Most approaches to favoring 1,4-addition reactions of α,β-unsaturated carbonyl compounds involve modifying the nature of an organometallic reagent (e.g., cuprate chemistry) or the reaction media (e.g., addition of HMPA). A different method[6a-c] for effecting 1,4-addition to conjugate enones involves complexation of the carbonyl group with a very hindered reagent, methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)[6d-g] (MAD) so as to sterically disfavor 1,2-addition and render 1,4-addition more likely. Unfortunately, the method was limited when applied to cyclohexenones since compounds having relatively unhindered carbonyl groups (e.g., cyclohexenone and noncyclic enones) gave primarily 1,2-addition products.[6a] Furthermore, introduction of alkynes could not be achieved, and Grignard reagents were less reactive than

Scheme I. Selected Conjugate Additions of Organometallics to Quinone Monoketals



(1) For reviews and leading references, see: (a) Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74. (b) Swenton, J. S. *The Chemistry of the Quinoid Compound*; Rappoport, Z., Patai, S., Eds.; John Wiley: New York, 1988; Vol. 2, Part 2, p 899.

(2) Parker, K. A.; Kang, S.-K. *J. Org. Chem.* **1980**, *45*, 1218.

(3) (a) Nilsson, A.; Ronlân, A. *Tetrahedron Lett.* **1975**, 1107. (b) Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422.

(4) (a) Semmelhack, M. F.; Keller, L.; Sato, T.; Speiss, E. *J. Org. Chem.* **1982**, *47*, 4382. (b) Semmelhack, M. F.; Keller, L.; Sato, T.; Speiss, E.; Wulff, W. *Ibid.* **1985**, *50*, 5566.

(5) Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 1233.

(6) (a) Maruoka, K.; Nonoshita, K.; Yamamoto, H. *Tetrahedron Lett.* **1987**, *28*, 5723. (b) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588. (c) For another use of the MAD reagent, see: Maruoka, K.; Araki, Y.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3101. (d) Starowieyski, K. B.; Pasynkiewicz, S.; Skowronska-Ptasinska, M. *J. Organomet. Chem.* **1975**, *90*, C43. (e) Skowronska-Ptasinska, M.; Starowieyski, K. B.; Pasynkiewicz, S.; Carewska, M. *J. Organomet. Chem.* **1978**, *160*, 403. (f) Shreve, A. P.; Mulhaupt, R.; Fultz, W.; Calabrese, J.; Robbins, W.; Ittel, S. D. *Organometallics* **1988**, *7*, 409. (g) Healy, M. D.; Wierda, D. A.; Barron, A. R. *Organometallics* **1988**, *7*, 2543.

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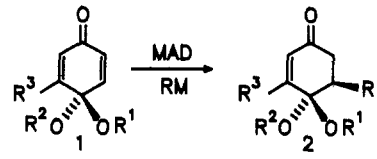
Table I. 1,4-Organometallic Additions to Quinone Monoketals



entry	compd	R^1	R^2	R^3	RM (equiv)	product (%)
1	**1a**	CH_3	CH_3	H	PhLi (1)	**2a** (78)
2	**1a**	CH_3	CH_3	H	PhMgBr (1.2)	**2a** (91)
3	**1a**	CH_3	CH_3	H	CH_2=CHMgBr (2.2)	**2b** (89)
4	**1a**	CH_3	CH_3	H	2-lithio-1,3-dithiane (1.5)	**2c** (70)
5	**1a**	CH_3	CH_3	H	TMSC≡CLi (2.4)	**2d** (86)
6	**1a**	CH_3	CH_3	H	*n*-BuLi (1.8)	**2e** (42)
7	**1a**	CH_3	CH_3	H	CH_3Li (2.2)	**2f** (24)
8	**1b**	CH_3	TBDMSi[a]	H	PhLi (1.2)	**2g** (80)
9	**1c**	CH_3	CH_3	Cl	PhLi (1.5)	**2h** (50)
10	**1d**	CH_3	CH_3	CH_3	PhLi (1.7)	**2i** (80)[b]
11	**1e**	CH_2CH_2		H	*n*-BuLi (1.1)	**2j** (18)
12	**1e**	CH_2CH_2		H	*t*-BuLi (1.1)	**2k** (35)

[a] TBDMSi = *t*-Bu$(CH_3)_2$Si. [b] An inseparable mixture of 1,4-adducts was obtained.

alkyllithium reagents, giving mixtures of products and recovered starting material.

We report herein that these limitations are not attendant in MAD-mediated additions to cyclohexenone systems having a 4-methoxy group.[7]

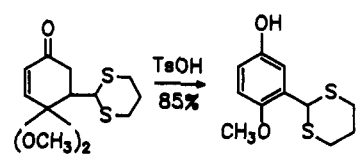
1,4-Addition of Organolithium and Grignard Reagents to Quinone Monoketals. In spite of the reported limitations associated with the MAD-mediated 1,4-additions, this methodology was examined for the simple quinone monoketal, 4,4-dimethoxycyclohexa-2,5-dienone, **1a**. Quinone monoketals are very reactive in Michael addition reactions, and it was hoped this would favor 1,4-addition for these compounds. Formation of the MAD reagent[6] in toluene from reaction of trimethylaluminum with 2,6-di-*tert*-butyl-4-methylphenol, BHT, cooling the mixture to −78 °C, and addition of a toluene solution of **1a** gave a brilliant purple solution. Dropwise addition of phenyllithium in diethyl ether proceeded essentially as a titration with the final color of the solution being light yellow. Workup consisted of adding water to the reaction mixture at −78 °C and allowing the mixture to warm to room temperature. Filtration of the aluminum salts followed by chromatography on silica gel gave the cyclohexenone **2a** in 78% yield (Table I). If the reaction mixture was warmed to room temperature prior to addition of water, mixtures of **2** and the phenol derived from aromatization of **2** were often obtained.

As illustrated by the results recorded in Table I, this reaction is successful for a variety of organolithium and Grignard reagents. The structures of the products of Table I were assigned on the basis of spectroscopic and analytical data. Especially informative for the 1,4-adducts of **1** were the carbonyl stretching vibration in the IR spectrum (1690–1700 cm^{-1}), the vinyl hydrogens of the cyclohexenone in the ^1H NMR spectrum [δ 6.9–6.7 (d of d, J = 10.4, ≃ 1 Hz) and δ 6.1–6.0 (d, J = 10.4 Hz)], and the carbonyl carbon resonance (δ 196–199) in the ^{13}C NMR spectrum. The amount of organometallic reagent listed in Table I for the reactions was that required to quench the intense purple color of the **1**–MAD complex. In some cases, fewer equivalents of organometallic reagent may be required if a longer reaction time is used.

The results (Table I) show that excellent yields were obtained with aryl and vinyl organometallics (entries 1–3), 2-lithio-1,3-dithiane (entry 4), and even an acetylenic lithium reagent (entry 5). A hindered carbonyl group is not required for production of the 1,4-addition product, a restriction noted for additions to simple enones.[6] However, the size of the organometallic reagent does appear to affect the yield of the reaction. Thus, the lowest yields of 1,4-addition products were recorded with *n*-butyl- and methyllithium (entries 6 and 7). For these cases, 1,2-addition products were isolated but not rigorously characterized. In fact minor amounts of 1,2-addition products may be formed in all of these reactions, but these alcohols are easily separated from the 1,4-addition products.

The effect of the ketal oxygen substituents on the yield of the 1,4-additions was not extensively studied. The *tert*-butyldimethylsilyl methyl ketal system[8] (entry 8) gave an excellent yield of adduct, and no special advantages accrue using the ethylene glycol monoketal (entries 11 and 12). Unfortunately, there is only modest regiochemical control in the 1,4-addition reaction when the quinone monoketal has substituents in the 3-position. The chloro system afforded the regioisomer shown in 50% yield (entry 9), but the methyl system (entry 10) afforded a difficult-to-separate mixture of 1,4-adducts.

Although the products from these 1,4-additions, **2**, are at the phenol oxidation state, these compounds can be chromatographed on silica gel without rearrangement and are stable to storage for months. Methods for aromatization of **2** have not been extensively studied; however, heating **2c** in benzene or tetrahydrofuran with a catalytic amount of *p*-toluenesulfonic acid afforded the phenol in good yield.



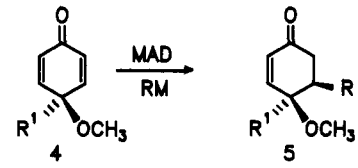
2c **3**

1,4-Addition of Organolithium and Grignard Reagents to Quinol Ethers. The MAD-mediated 1,4-addition chemistry affords a general method for functionalization of quinone monoketals; however, the marked contrast between this chemistry as applied to enones and monoketals presented an interesting question. Several

(7) For a preliminary account of part of the present study, see: Stern, A. J.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1988**, 1255.

(8) Stern, A.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 2763.

Table II. 1,4-Organometallic Additions to Quinol Ethers



entry	compd	R^1	RM (equiv)	product (%)
1	**4a**	Ph	PhLi (1.2)	**5a** (80)
2	**4a**	Ph	CH_2=C(CH_3)Li (1.5)	**5b** (75)
3	**4a**	Ph	2-lithio-1,3-dithiane (2.0)	**5c** (65)
4	**4a**	Ph	TMSC≡CLi (4.0)	**5d** (78)
5	**4b**	*p*-TBDMSiO-C_6H_4	CH_2=CHMgBr (2.5)	**5e** (66)
6	**4b**	*p*-TBDMSiO-C_6H_4	CH_2=CH(CH_3)MgBr (2.0)	**5f** (65)
7	**4c**	CH_2=CH	*p*-TBDMSiO-C_6H_4MgBr (2.1)	**5g** (57)

possibilities for the enhanced reactivity of the quinone monoketals seemed reasonable. First, the inductive effect of two alkoxy functions at the γ-carbon of the monoketals could increase the electron deficiency at the β-carbon, making these compounds more reactive in Michael-type additions. In fact, quinone monoketals are excellent substrates for Michael addition of soft nucleophiles. Second, the ether oxygen of the monoketals could be complexing with the organometallic reagent, thus faciliting the 1,4-addition process. If the methoxy group were acting as a directing group in the MAD-mediated additions, the entering group would be cis to the methoxy group in the product. Except for the mixed ketal (Table I, entry 8), no stereochemical information was available on these 1,4-additions. However, the formation of only one stereoisomer in good yield from the reaction of this mixed ketal encouraged us to examine quinol ethers as substrates in the MAD-mediated chemistry. Here the stereochemistry of the 1,4-addition could be established for a more general case.

Table II summarizes the 1,4-addition chemistry of quinol ethers with Grignard and organolithium reagents. In general the reactions were somewhat slower, judging from the disappearance of the color of the quinol ether–MAD complex. In some cases (see the Experimental Section) the color of the complex did not dissipate even when the solution had reached room temperature. The isolated yields of 1,4-adducts are also somewhat lower than those recorded in Table I; however, the substrates are somewhat more functionalized, and perhaps complications with other functionalities in the molecule contribute to the somewhat lower yields observed here.

Interestingly, we were not able to characterize isomeric 1,4-products from any of these additions in spite of carefully examining the product mixtures in several of the cases. These compounds still could be formed in small amounts, but it is apparent that the reaction is very selective toward the formation of one set of diastereomers. Various ^{1}H NMR experiments (NOE effects and ^{1}H NMR and ^{13}C NMR correlations) were performed on selected adducts (entries 1 and 4) to establish the relative stereochemistry of the methoxy and the entering group. These experiments did not allow an unequivocal assignment of structure; therefore, an X-ray analysis was conducted on the product from **4a** and 2-propenyllithium. As illustrated from the ORTEP diagram (Figure 1), the X-ray determination establishes a cis relationship between the methoxy group and the 2-propenyl substituent. This stereochemistry has been assumed for the other MAD-mediated 1,4-additions.

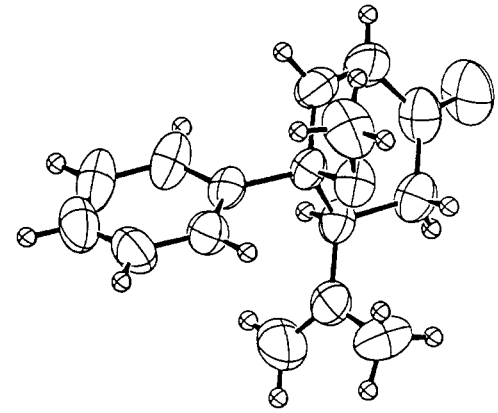


Figure 1. ORTEP drawing of **5b** (Table II).

Discussion

The importance of an ether[9,10] or hydroxyl function in directing metalation[11] and addition reactions of organolithium reagents[12,13] and to a lesser extent Grignard reagents to olefin linkages is well-known. Undoubtedly, the presence of a methyl ether function at the 4-position is important to the success of the conjugate additions reported herein. Presumably, the ether function complexes the organometallic reagent, thus providing an additional benefit to the 1,4- vs 1,2-addition process. This result is consistent with the cis relationship of the entering group and the methoxy moiety in the reactions involving quinol

(9) See discussion in ref 6b (ref 2).

(10) For more recent examples wherein a methoxy group may be exerting a directing effect, see: Swenton, J. S.; Jurcak, J. G. *J. Org. Chem.* **1988**, *53*, 1530. Padwa, A.; Woods Wannamaker, M. *Tetrahedron Lett.* **1986**, *27*, 2555. Klumpp, G. W.; Kool, M.; Schakel, M.; Schmitz, R. F.; Boutkan, C. *J. Am. Chem. Soc.* **1979**, *101*, 7065. Klumpp, G. W.; Kool, M.; Veefkind, A. H.; Schakel, M.; Schmitz, R. F. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 542.

(11) For alkoxide-directed metallations, see: Katsuura, K.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 9 and references cited therein. Katsuura, K.; Snieckus, V. *Can. J. Chem.* **1987**, *65*, 124.

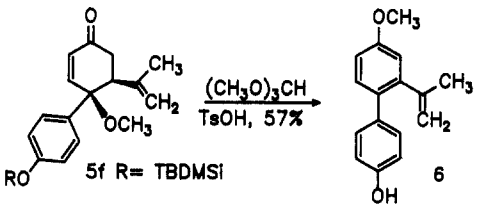
(12) Apparently, the first examples of alkoxide-directed organometallic additions to simple carbon–carbon bonds occurred in the reactions of Grignard reagents and organolithium reagents with allylic alcohols. See, for example: Eisch, J. J.; Husk, G. R. *J. Am. Chem. Soc.* **1965**, *87*, 4195. Chérest, M.; Felkin, H.; Frajerman, C.; Lion, C.; Roussi, G.; Swierczewski, G. *Tetrahedron Lett.* **1966**, 875. Crandall, J. K.; Clark, A. C. *Tetrahedron Lett.* **1969**, 325; *J. Org. Chem.* **1972**, *37*, 4236. Felkin, H.; Swierczewski, G.; Tambuté, A. *Tetrahedron Lett.* **1969**, 707. Newman-Evans, R. H.; Carpenter, B. K. *Tetrahedron Lett.* **1985**, *26*, 1141.

(13) Recently, complexation of a quinol alkoxide with Grignard reagents has been proposed to explain the high facial selectivity observed in the conjugate additions of Grignards to *p*-quinols: Solomon, M.; Jamison, W. C. L.; McCormick, M.; Liotta, D.; Cherry, D. A.; Mills, J. E.; Shah, R. D.; Rodgers, J. D.; Maryanoff, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 3702.

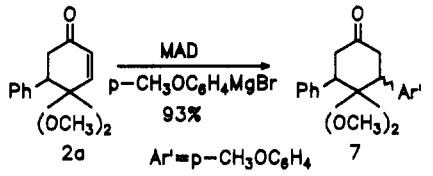
ethers. The absence of such a directing effect seems to be the most logical explanation for the failure of similar conjugate additions with cyclohexenone. The high-yield addition of an acetylenic lithium reagent was unexpected but could benefit synthetic strategies to antibiotics containing an acetylenic unit.[14]

An extensive survey of conditions to maximize the yields of conjugate additions has not been conducted; however, the choice of solvent is important. Tetrahydrofuran is not the preferred solvent for conducting these reactions. For example, conjugate additions involving vinyl Grignard, supplied commercially in tetrahydrofuran, proceeded in lower yield than if the tetrahydrofuran was removed in vacuo and replaced with dry methylene chloride. Either toluene or methylene chloride is an acceptable solvent for preparation of the MAD reagent. However, methylene chloride was preferred when the conjugate addition involved a Grignard reagent.

Although further chemistry of the initial 1,4-addition products has not been thoroughly examined, the adduct **2c** has been converted to the phenol **3** in good yield (vide supra). Furthermore, **5f** has been converted to **6** in good yield essentially under ketalization conditions. This has promise as a route to functionalized unsymmetrical biphenyls. Finally, the conjugate addition product from



reaction of a quinone monoketal can be reacted in a second step to produce a 3,5-disubstituted 4,4-dimethoxycyclohexanone as illustrated below for **2a**. The stereochemistry of **7** cannot be rigorously assigned although it seems reasonable that the two aryl groups are trans.



In summary, the MAD-mediated conjugate addition of organometallic reagents to quinone monoketals and quinol ethers, although not fully explored, offers a convenient route to 5-substituted and 4,5-disubstituted cyclohexenone derivatives. Many of the limitations associated with this chemistry when applied to cyclohexenones, e.g., the failure of acetylenic lithium compounds as reactants and the low yield experienced with Grignard reagents, are not general limitations for the reactions noted herein. Two limitations of the chemistry are that these additions appear to work best with sp^2 hybridized organometallic reagents or sp^3 organometallics having a bulky organic group and that chromatographic separation is necessary to separate the product from BHT formed in the hydrolysis step. However, this chromatographic separation is not difficult and could be solved by use of a polymeric BHT reagent. With the development of this chemistry, general methods are now available for performing either 1,2- or 1,4-addition of carbon nucleophiles to quinone monoketals.

Experimental Section[16]

Preparation of MAD. To a solution of BHT (2,6-di-*tert*-butyl-4-methylphenol) (1.76 g, 8 mmol) in toluene (20 mL) at 25 °C under N_2 was added trimethylaluminum (TMA) (2.0 mL, 2.0 M in toluene) via syringe. The mixture became warm and evolved methane rapidly. When gas evolution was complete (ca. 20 min), the reagent was ready to use. Alternatively, a stock solution of MAD may be made by adding trimethylaluminum (16 mL, 2.0 M in toluene) to a solution of CH_2Cl_2 (184 mL) [or toluene (184 mL)] and BHT (14.08 g). **Caution**: due to the large volume of methane produced, the addition of trimethylaluminum must be done carefully to avoid too violent a reaction. Stock solutions may be stored under N_2 for at least 2 weeks. Decomposition is indicated when the solution begins to turn orange or green.

General Comments on Conjugate Additions to Quinone Monoketals and Quinol Ethers. The experimental discriptions that follow typify the conditions used for these reactions. For the remaining reactions, the experimental details are given in the supplementary material, and only the spectral data are reported herein.

4,4-Dimethoxy-5-phenyl-2-cyclohexenone (2a). To freshly prepared MAD [BHT (11.4 g), TMA (13 mL), toluene (100 mL)] cooled to −78 °C was added 4,4-dimethoxy-2,5-cyclohexadienone[17] (2.00 g, 13 mmol) dissolved in toluene (2 mL). To the resulting deep purple solution was added dropwise phenyllithium (8.0 mL, 1.7 M, 13.6 mmol) via syringe over 4 min, turning the solution light yellow. Water (3 mL) was added, the cooling bath was removed, and the mixture was stirred for 1 h. As the mixture warmed, the light yellow color was replaced by dark red, which faded back to yellow. Filtration through Celite, and chromatography on silica gel [13 × 3.5 cm column, 5–30% Et_2O/petroleum ether (PE) (150 mL) as eluant] afforded the 1,4-adduct (2.36 g, 78%) as a slightly yellow oil. Recrystallization from CH_3OH/water gave white crystals, 57.5–58.5 °C: IR (melt) 1690, 1112, 1095, 1050 cm^{-1}; ^1H NMR δ 7.25 (s, 5 H), 6.92 (dd, J_{AB} = 10.4, 1 Hz, 1 H), 6.16 (d, J_{AB} = 10.4 Hz, 1 H), 3.66 (distorted t, J = 4.6 Hz, 1 H), 3.21 (s, 3 H), 3.19 (s, 3 H), 2.89–2.79 (four-line multiplet, 2 H); ^{13}C NMR δ 197.9, 148.4, 139.2, 131.3, 128.9, 128.2, 126.9, 98.0, 49.9, 48.9, 48.5, 43.0; mass spectrum, exact mass calcd for $C_{14}H_{16}O_3$ m/e 232.1100, obsd m/e 232.1113.

In a separate experiment, a solution of MAD [BHT (1.76 g), TMA (2.0 mL)] in CH_2Cl_2 (40 mL) was cooled to −78 °C under N_2. 4,4-Dimethoxy-2,5-cyclohexadienone (0.308 g, 2.00 mmol) in

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(16) Melting points were determined in capillaries in a Thomas-Hoover Unimelt apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 283B spectrometer on KBr disks, and strong peaks are reported unless otherwise noted. Routine ^1H NMR spectra were determined at 80 MHz on an IBM NR 80 spectrometer using deuteriochloroform as solvent and residual chloroform or tetramethylsilane as internal standard. Mass spectral and exact mass measurements were obtained by Richard Weisenberger on a Kratos MS-30 spectrometer. Alumina and silica gel (Kieselgel 60 230–400 mesh) were obtained from E. Merck Co. Tetrahydrofuran was purified by distillation from benzophenone ketyl. Thin-layer chromatography (TLC) was done using Merck silica gel 60 F_{254} precoated aluminum-backed plates, 0.2-mm thickness. All organometallic reactions were done under nitrogen or argon. Visualization was by UV or by spraying with 5% ethanolic phosphomolybdic acid and then heating. Throughout the Experimental Section, the following abbreviations are used: petroleum ether, bp 35–60 °C (PE), diethyl ether, (Et_2O), tetrahydrofuran (THF), *tert*-butyldimethylsilyl (TBDS). Amine-washed silica gel was prepared by packing an appropriate column with silica gel and passing five column volumes of a solution of triethylamine, ether, and hexane (1:1:8) through the column, equilibrating the column with the desired eluant, and running the column as usual.

(17) 4,4-Dimethoxy-2,5-cyclohexadienone is commercially available but can be easily prepared on a 50-g scale via the chemistry described in Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422, and Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369.

CH_2Cl_2 (0.5 mL) was added, turning the solution deep purple. Phenylmagnesium bromide (2.4 mL, ca. 1 M in Et_2O) was added until the purple color faded to light tan. After adding water (1 mL), warming to room temperature, and stirring for 1 h, the mixture was filtered, concentrated, and chromatographed on silica gel as before, affording the enone (0.422 g, 91%), which solidified upon standing. The ^1H NMR spectrum of this solid was identical with that described above.

4,4-Dimethoxy-5-vinyl-2-cyclohexenone (2b). Vinylmagnesium bromide (5 mL, 1 M in THF) was concentrated under vacuum until a constant weight was obtained, and then Et_2O (7 mL) was added, creating a slurry. To a stock solution of MAD in CH_2Cl_2 (25 mL, 0.16 M), cooled to −78 °C, was added a solution of 4,4-dimethoxy-2,5-cyclohexadienone (0.350 g, 2.27 mmol) in CH_2Cl_2 (1 mL), turning the solution deep purple. Pressure gradient transfer of the vinylmagnesium bromide slurry into the complex rapidly turned the mixture light yellow. After adding water (1 mL), warming to room temperature, and stirring for 2 h, the mixture was filtered, concentrated, and chromatographed on silica gel [11 × 2 cm column, 5–10% Et_2O/PE (200 mL) as eluant], affording the desired enone (0.370 g, 89%) as a pale yellow liquid: IR (NaCl plate) 1700, 1115, 1090, 1075, 1050, 960 cm^{-1} (m); ^1H NMR δ 6.70 (dd, J_{AB} = 10.4, 1.1 Hz, 1 H), 5.9–5.67 (m, 1 H), 5.27–5.02 (highly coupled m, 2 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 3.2–2.4 (structured m, 3 H); ^{13}C NMR δ 197.8, 146.6, 135.5, 130.7, 117.3, 98.0, 49.7, 47.8, 45.3, 40.5; mass spectrum, exact mass calcd for $C_9H_{14}O_2$ (M^+ − CO) m/e 154.0993, obsd m/e 154.1010.

5-(1,3-Dithian-2-yl)-4,4-dimethoxycyclohex-2-en-1-one (2c). To a mixture of 1,3-dithiane (0.5 g, 4.17 mmol) in Et_2O (5 mL) at −25 °C was added *n*-BuLi (2.80 mL, 1.45 M, 4.06 mmol),[18] forming a white precipitate, and the mixture was stirred for 1 h. To freshly prepared MAD [BHT (1.76 g), TMA (2.0 mL)] in toluene (20 mL) at −78 °C was added a solution of 4,4-dimethoxy-2,5-cyclohexadienone (0.308 g, 2.0 mmol) in toluene (1 mL), turning the solution deep purple. While being vigorously stirred, the heterogeneous 2-lithio-1,3-dithiane was transferred via pressure gradient into the purple complex, turning the mixture orange. Water (1.5 mL) was added, the cooling bath was removed, and the mixture was stirred for 2 h. Filtration through Celite and concentration in vacuo afforded an oil. Chromatography on silica gel (3:7 CH_2Cl_2/PE as eluant) afforded a pale yellow solid (0.384 g, 70%), mp 131–133 °C. Trituration (Et_2O) afforded a white solid, mp 133–134.5 °C: IR (KBr) 1680, 1112, 1073 (m), 1048, 958 cm^{-1} (m); ^1H NMR δ 6.69 (dd, J_{AB} = 10.5, 1 Hz, 1 H), 6.03 (d, J_{AB} = 10.5 Hz, 1 H), 4.33 (d, J = 2.6 Hz, 1 H), 3.27 (s, 3 H), 3.17 (s, 3 H), 2.95–2.64 (br m, 7 H), 1.95–1.6 (m, 2 H); ^{13}C NMR δ 196.1, 146.5, 132.3, 97.3, 49.5, 48.9, 47.2, 46.0, 36.5, 31.2, 30.8, 25.0; mass spectrum, exact mass calcd for $C_{12}H_{18}O_3S_2$ m/e 274.074, obsd. m/e 274.0692.

5-(2-(Trimethylsilyl)ethynyl)-4,4-dimethoxycyclohexenone (2d). To a solution of Et_2O (2 mL), hexane (2 mL), and (trimethylsilyl)acetylene (1.0 mL, 0.695 g, 7.1 mmol) at 0 °C under N_2 was added *n*-BuLi (5.0 mL, 1.4 M, 7.1 mmol). The solution was stirred for 1 h, cooled to −78 °C, and transferred via pressure gradient into a previously prepared solution of MAD (25 mL in toluene stock solution) and 4,4-dimethoxy-2,5-cyclohexadienone (0.31 g, 2 mmol) at −78 °C. The deep purple complex faded to tan after a few minutes. The reaction was quenched by adding 5.5% acetic acid (2.0 mL), and the solution was warmed to room temperature and stirred for 45 min. Filtration through Celite, concentration, and chromatography on silica gel [10 × 2 cm column, 5–15% Et_2O/PE as eluant] afforded the enone (0.435 g, 86%) as a clear oil: IR (NaCl plate) 2970, 2180 (m), 1700, 1255, 1230, 1120, 1105, 1060, 970, 850, 765 cm^{-1}; ^1H NMR δ 6.64 (dd, J_{AB} = 10.5, 1.8 Hz, 1 H), 5.99 (dd, J_{AB} = 10.5, 0.9 Hz, 1 H), 3.4–3.2 (hidden, 1 H), 3.32 (s, 3 H), 3.25 (s, 3 H), 2.75–2.59 (m, 2 H), 0.04 (s, 9 H); ^{13}C NMR δ 196.5, 146.0, 130.2, 103.3, 97.4, 88.3, 49.9, 48.1, 40.5, 36.3 −0.2; FAB mass spectrum 253.11 (M + 1).

5-*n*-Butyl-4,4-dimethoxy-2-cyclohexenone (2e): IR (NaCl plate) 2960 (m), 2940 (m), 1695, 1115, 1090 (m), 1050 cm^{-1} (m); ^1H NMR δ 6.62 (dd, J_{AB} = 10.4, 2 Hz, 1 H), 5.95 (dd, J_{AB} = 10.4, 1 Hz, 1 H), 3.21 (s, 3 H), 3.18 (s, 3 H), 2.65–2.45 (m, 2 H), 2.3–2.2 (br, 1 H), 1.4–0.6 (br, 9 H); ^{13}C NMR δ 205.8, 146.9, 130.8, 99.0, 49.6, 47.6, 40.9, 38.8, 29.5, 27.8, 22.7, 13.8; mass spectrum, exact mass calcd for $C_{12}H_{20}O_3$ m/e 212.1426, obsd m/e 212.1419.

4,4-Dimethoxy-5-methyl-2-cyclohexenone (2f): IR (NaCl plate) 2960 (m), 2940 (m), 1690, 1382 (m), 1205 (m), 1130, 1110, 1065, 1040, 965 (m), 925 cm^{-1} (m); ^1H NMR δ 6.67 (dd, J_{AB} = 10.4, 2 Hz, 1 H), 6.03 (dd, J_{AB} = 10.4, 1.2 Hz, 1 H), 3.29 (s, 3 H), 3.27 (s, 3 H), 3–2.1 (complex m, 3 H), 1.0 (d, J = 6 Hz, 3 H); ^{13}C NMR δ 198.5, 146.3, 130.1, 99.0 49.6, 47.4, 42.0, 35.3, 14.7; mass spectrum, exact mass calcd for $C_9H_{14}O_3$ m/e 170.0943, obsd m/e 170.0983.

5-Phenyl-4-((*tert*-butyldimethylsilyl)oxy)-4-methoxycyclohex-2-en-1-one (2g): IR (neat) 2950 (m), 2930 (m), 1695, 1255 (m), 1130 (broad), 1090 (m), 1055 (m), 1040 (m), 835 (m), 775 (m), 695 cm^{-1} (m); ^1H NMR δ 7.25 (br s, 5 H), 6.93 (br d, J_{AB} = 10 Hz, 1 H), 6.08 (d, J_{AB} = 10 Hz, 1 H), 3.56 (t, J = 7 Hz, 1 H), 3.24 (s, 3 H), 2.84 (d, 2 H), 0.84 (s, 9 H), 0.05 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR δ 198.4, 150.0, 138.8, 129.6, 129.4, 127.9, 126.9, 97.0, 65.7, 51.7, 49.8, 43.1, 25.6, 18.2, 15.1, −2.9, −3.08, −3.12. Anal. Calcd for $C_{19}H_{28}O_3Si$: C, 68.67; H, 8.43. Found: C, 68.76; H, 8.50.

3-Chloro-4,4-dimethoxy-5-phenylcyclohexenone (2h): IR (NaCl plate) 1689, 1115 (m), 1160 (m), 855 (m), 698 cm^{-1} (m); ^1H NMR δ 7.27 (s, 5 H), 6.43 (s, 1 H), 3.75 (distorted t, 1 H), 3.30 (s, 3 H), 3.29 (s, 3 H), 2.98–2.87 (m, 2 H); ^{13}C NMR δ 197.6, 156.7, 138.3, 131.3, 128.8, 128.4, 127.3, 98.3, 51.2, 49.9, 48.3, 43.2; mass spectrum, exact mass calcd for $C_{14}H_{15}O_3Cl$ m/e 266.0709, obsd m/e 266.0706.

4,4-(Ethylenedioxy)-5-*n*-butyl-2-cyclohexenone (2j): IR (NaCl plate) 2960 (m), 2930 (m), 1690, 1160 (m), 1110 (m), 1015 (m), 915 cm^{-1} (m); ^1H NMR δ 6.75 (d, J_{AB} = 10.2 Hz, 1 H), 5.92 (d, J_{AB} = 10.2 Hz, 1 H), 4.10–3.93 (m, 4 H), 2.74–2.10 (m, 3 H), 1.8–0.6 (br m, 9 H); ^{13}C NMR δ 198.7, 146.5, 129.2, 105.8, 65.3, 64.9, 42.6, 40.2, 28.8, 27.4, 22.5, 13.7; mass spectrum, exact mass calcd for $C_{12}H_{18}O_3$ m/e 210.1256, obsd m/e 210.1287.

4,4-(Ethylenedioxy)-5-*tert*-butyl-2-cyclohexenone (2k): IR (NaCl plate) 2960 (m), 2900 (m), 1690, 1130 (m), 1090 (m), 1070 (m), 1020 (m), 950 (m), 905 cm^{-1} (m); ^1H NMR δ 6.54 (d, J_{AB} = 10.1 Hz, 1 H), 5.90 (broad d, J_{AB} = 10.1 Hz, 1 H), 4.04 (s, 4 H), 2.65 (two-line signal, downfield resonance broadened, 2 H), 2.16 (distorted t, J = 7 Hz, 1 H), 0.99 (s, 9 H); ^{13}C NMR δ 200.0, 147.3, 128.0, 107.7, 64.4, 63.2, 49.9, 38.8, 33.2, 29.4; mass spectrum, exact mass calcd for $C_{12}H_{18}O_3$ m/e 210.1256, obsd m/e 210.1261.

4,5-Diphenyl-4-methoxy-2-cyclohexenone (5a). To a solution of MAD [BHT (0.88 g, 4 mmol), TMA (1.0 mL)] in toluene cooled to −78 °C was added a solution of 4-methoxy-4-phenyl-2,5-cyclohexadienone[19] (0.200 g, 1 mmol) in CH_2Cl_2 (1 mL), forming a deep purple complex. Phenyllithium (1.0 mL, 1.7 M) in 7:3 cyclohexene/Et_2O was added via syringe, until the purple color was replaced by a light tan color. The reaction was quenched by adding water (0.5 mL), the solution was warmed to room temperature and stirred for 1 h, and the mixture was filtered, concentrated, and chromatographed on silica gel [8 × 2 cm column, 10–15% Et_2O/PE as eluant], affording the desired enone (0.235 g, 85%) as a crystalline white solid, mp 128–130 °C. Recrystallization of a small portion from Et_2O/PE afforded the analytical sample: mp 131–132 °C; IR (KBr) 1683, 1105 (m), 1080 (m), 1060 (m), 770 (m), 705 cm^{-1} (m); ^1H NMR δ 7.25–6.75 (highly structured m, 11 H), 6.87 (dd, J_{AB} = 10, 1.5 Hz, 1 H), 3.5–3.27 (m, 2 H), 3.25 (s, 3 H), 2.55 (broadened d, 1 H); ^{13}C NMR (80 MHz) δ 199.7, 151.1, 141.1, 138.3, 131.9, 129.6, 127.7, 127.2 (2 C), 126.8, 126.4, 77.6, 54.3, 52.0, 40.2; mass spectrum, exact mass calcd for $C_{18}H_{15}O$ (M^+ − CH_3O) m/e 247.1123, obsd m/e 247.1098. Anal. Calcd for $C_{19}H_{18}O_2$: C, 82.01; H, 6.47. Found: C, 81.78; H, 6.55.

4-Methoxy-4-phenyl-5-(2-propenyl)-2-cyclohexenone (5b). To a solution of *t*-BuLi (3.5 mL, 1.7 M in pentane, 6 mmol) in Et_2O (3.0 mL) at −78 °C under N_2 was added a solution of 2-bromopropene (0.363 g, 0.266 mL, 3 mmol) in Et_2O (0.25 mL), and the mixture was stirred for 35 min. To freshly prepared MAD [BHT (0.88 g), TMA (1.0 mL)] in toluene (15 mL) cooled to −78 °C was added a solution of the quinol ether (0.200 g, 1 mmol) in CH_2Cl_2 (1 mL), turning the solution deep purple. The 2-lithiopropene was transferred to the complex until the color disappeared (ca. half the 2-lithiopropene). After adding water (0.75 mL), warming to room temperature, and stirring for 1 h, the mixture

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was filtered, concentrated, and chromatographed on silica gel [8 × 2 cm column, 10–15% Et_2O/PE as eluant], affording the desired enone (0.135 g, 75%) as a clear oil. The oil solidified upon standing and was recrystallized from Et_2O/PE, giving white crystals, mp 68–69 °C; IR (KBr) 1690, 1100 (m), 1060 (m), 700 cm^{-1} (m); ^1H NMR δ 7.36–7.27 (m, 5 H), 7.11 (d, J_{AB} = 10.3 Hz, 1 H), 6.32 (dd, J_{AB} = 10.3, 1 Hz, 1 H), 4.72–4.68 (structured m, 1 H), 4.36 (br s, 1 H), 3.28 (s, 3 H), 3.17–2.68 (structured m, 2 H), 2.42 (dd, J = 3, 1 Hz, 0.5 H), 2.25 (dd, J = 3, 1 Hz, 0.5 H), 1.53 (finely coupled m, 3 H); ^{13}C NMR δ 199.9, 150.8, 143.0, 141.6, 131.6, 128.1, 127.4, 126.5, 115.4, 78.6, 55.3, 52.3, 39.6, 22.2; mass spectrum, exact mass calcd for $C_{16}H_{18}O_2$ m/e 242.1307, obsd m/e 242.1295.

5-(1,3-Dithian-2-yl)-4-methoxy-4-phenylcyclohex-2-en-1-one (5c). To a solution of 1,3-dithiane (0.24 g, 2.01 mmol) in Et_2O (2 mL) at −25 °C was added a 1.0 M solution of *n*-BuLi (1.9 mL, 1.9 mmol).[18] The temperature was raised to 0 °C, and the mixture was stirred for 1 h. To a stirred solution of BHT (0.88 g, 4.0 mmol) in distilled toluene (10 mL) under N_2 was added a 2.0 M solution of trimethylaluminum (1.0 mL, 2.0 mmol), and the solution was stirred for 15 min. The solution was cooled to −78 °C, after which time was added 4-phenyl-4-methoxy-2,5-cyclohexadienone (0.21 g, 1.03 mmol) dissolved in distilled toluene (1 mL). To the resulting purple reaction mixture was added via pressure gradient the 2-lithiodithiane prepared above. The cooling bath was removed, and the solution was warmed until the color changed to light purple, after which time water (1 mL) was added. The solution was warmed to room temperature, during which time the color changed to yellow and salts formed. Silica gel (ca. 2 g) was added, and the mixture was stirred until gas evolution ceased. The solution was filtered, and the product was separated by column chromatography (5–10% Et_2O/PE as eluant) and recrystallized (Et_2O/PE) to afford white crystals (0.21 g, 65%): mp 154–156 °C; IR (KBr) 2900, 1675, 1448, 1425, 1387, 1185, 1092, 1075, 943, 741, 702 cm^{-1}; ^1H NMR (500 MHz) δ 7.5–7.4 (m, 5 H), 7.05 (d, J = 10 Hz, 1 H), 6.32 (d, J = 10 Hz, 1 H), 4.31 (d, J = 10 Hz, 1 H), 3.28 (s, 3 H), 3.10 (dd, J = 11, 5.5 Hz, 1 H), 2.8–2.5 (m, 6 H), 2.0–1.95 (m, 1 H), 1.8–1.7 (m, 1 H); mass spectrum, exact mass calcd for $C_{17}H_{20}O_2S_2$ m/e 320.0904, obsd m/e 320.0919.

5-(2-(Trimethylsilyl)ethynyl)-4-phenyl-4-methoxycyclohex-2-en-1-one (5d). To a solution of (trimethylsilyl)acetylene (0.57 mL, 4.0 mmol) in Et_2O (2.5 mL) at 0 °C was added a 1.5 M solution of *n*-BuLi (2.67 mL, 4.01 mmol), and the solution was stirred for 1 h. To a stirred solution of BHT (0.88 g, 4.0 mmol) in toluene (10 mL) under nitrogen was added trimethylaluminum (1 mL, 2.0 mmol), and the solution was stirred for 15 min. The solution was then cooled to −78 °C, and 4-phenyl-4-methoxy-2,5-cyclohexadienone (0.20 g, 1.01 mmol) dissolved in toluene (2 mL) was added. To this purple solution was transferred via pressure gradient the lithium acetylide solution prepared above, producing no color change. The −78 °C bath was removed, and the solution was allowed to warm to room temperature. The solution turned light pink, and the reaction was quenched by adding H_2O (1 mL). The solution was stirred for ca. 45 min and filtered through Celite. Workup and column chromatography (12.7 cm × 2 cm column, 5–10% Et_2O/PE as eluant) gave a white solid, which was recrystallized from PE to afford white crystals (0.233 g, 78%): mp 109–110.5 °C; IR (KBr) 2280 (w), 1678, 1242, 1101, 1040, 1032, 858, 839, 831 cm^{-1}; ^1H NMR (300 MHz) δ 7.5–7.4 (m, 5 H), 7.12 (d, J = 10 Hz, 1 H), 6.31 (d, J = 10 Hz, 1 H), 3.27 (s, 3 H), 3.17 (dd, J = 10.5, 4.0 Hz, 1 H), 2.92 (dd, J = 18, 10 Hz, 1 H), 2.53 (dd, J = 18, 4 Hz, 1 H), 0.1 (s, 3 H); mass spectrum, exact mass calcd for $C_{18}H_{22}O_2Si$ m/e 298.1389, obsd m/e 298.1344.

4-Methoxy-4-(*p*-(*tert*-butyldimethylsiloxy)phenyl)-5-vinyl-2-cyclohexenone (5e): mp 85.5–86.5 °C; IR (KBr) 2960, 2930, 1690, 1610, 1511, 1287, 1270, 1092, 1062, 925, 835 (s, br), 780 cm^{-1}; ^1H NMR δ 7.3–7.0 (overlapping d, 3 H), 6.82 (d, J = 9 Hz, 2 H), 6.31 (d, J = 10 Hz, 1 H), 5.9–5.6 (m, 1 H), 5.2–4.6 (m, 2 H), 3.20 (s, 3 H), 2.8–2.2 (m, 3 H), 0.96 (s, 9 H), 0.16 (s, 6 H); ^{13}C NMR δ 199.0, 155.2, 149.8, 136.1, 133.6, 131.5, 127.9, 119.7, 116.8, 78.0, 52.0, 51.8, 39.9, 25.7, 18.2, −3.81; mass spectrum, exact mass calcd for $C_{21}H_{30}O_3Si$ m/e 358.1964, obsd m/e 358.1936.

4-Methoxy-4-(*p*-(*tert*-butyldimethylsiloxy)phenyl)-5-(2-propenyl)-2-cyclohexenone (5f): mp 94.5–95.5 °C; IR (KBr) 2955, 2935, 1685, 1505, 1261, 1252, 1242, 1085, 910, 845 cm^{-1}; ^1H NMR δ 7.5–7.2 (structured m, 3 H), 7.15 (d, J = 9 H, 2 H), 6.51 (d, J = 10 Hz, 1 H), 4.95 (br s, 1 H), 4.62 (br s, 1 H), 3.45 (s, 3 H), 3.4–2.4 (m, 3 H), 1.77 (br s, 3 H), 1.22 (s, 9 H), 0.43, (s, 6 H); mass spectrum, exact mass calcd for $C_{22}H_{32}O_3Si$ m/e 372.2120, obsd m/e 372.2156.

4-Methoxy-4-vinyl-5-(*p*-(*tert*-butyldimethylsiloxy)phenyl)-2-cyclohexenone (5g): IR (NaCl) 2959, 2935, 1690, 1510, 1260, 1090, 912, 835 cm^{-1}; ^1H NMR δ 7.2–7.0 (m, 3 H), 6.71 (d, J = 8.8 Hz, 2 H), 6.22 (d, J = 9.6 Hz, 1 H), 5.9–5.05 (m, 3 H), 3.19, (s, 3 H), 3.0–3.3 (m, 2 H), 2.3–2.4 (m, 1 H), 0.96 (s, 9 H), 0.1 (s, 6 H); mass spectrum, exact mass calcd for $C_{21}H_{30}O_3Si$ m/e 358.1964, obsd m/e 358.1961.

3-Phenyl-5-(*p*-methoxyphenyl)-4,4-dimethoxycyclohexanone (7). To MAD in CH_2Cl_2 (13 mL, 0.16 M) cooled to −78 °C was added a solution of 4,4-dimethoxy-5-phenyl-2-cyclohexenone (0.232 g, 1 mmol) in CH_2Cl_2 (1 mL), turning the solution orange. To this was added (*p*-methoxyphenyl)magnesium bromide (0.7 mL, 1.6 M in Et_2O, 1.1 mmol), turning the mixture light yellow. The reaction was quenched by adding water (2 mL), and the mixture was warmed to room temperature and stirred for 3 h. The CH_2Cl_2 was decanted from the pasty magnesium salts and concentrated. Chromatography on amine-washed silica gel [2 × 12 cm column, 10% Et_2O/PE (200 mL) as eluant] afforded the 1,4-adduct (0.371 g) as a white solid. Recrystallization from methanol afforded 0.272 g, mp 123–125 °C. Concentration of the mother liquor and chromatography on silica gel afforded an additional 45 mg, making the total yield 0.317 g (93%): IR (KBr) 1710, 1516, 1262, 1245 (m), 1122, 1045 cm^{-1}; ^1H NMR δ 7.26 (s, 5 H), 7.21 (d, J_{AB} = 9 Hz, 2 H), 6.81 (d, J_{AB} = 9 Hz, 2 H), 3.78 (s, 3 H), 3.47 (2 overlapping t, J = 7 Hz, 4 H), 3.05 (s, 3 H), 3.04 (s, 3 H), 2.81 (distorted t, J = 5 Hz, 4 H); ^{13}C NMR δ 208.3, 158.0, 140.5, 132.4, 130.6, 129.7, 128.0, 126.8, 113.4, 101.7, 56.1, 50.1, 46.0, 45.3, 45.1, 45.0; mass spectrum, exact mass calcd for $C_{21}H_{24}O_4$ m/e 340.1675, obsd m/e 340.1690.

2-(5-Hydroxy-2-methoxyphenyl)-1,3-dithiane (3). To a solution of **2c** (200 mg, 0.73 mmol) in dry THF (10 mL) was added *p*-toluenesulfonic acid monohydrate (10 mg). The solution was heated to reflux and allowed to cool and then stand overnight. TLC analysis of the mixture showed two components: a major component with the same R_f as the enone and a polar, minor component. The THF was removed in vacuo, and the gummy residue was chromatographed on silica gel (5 × 2 cm column, 1:1:3 Et_2O/CH_2Cl_2/PE as eluant), affording the phenol as a white solid (153 mg, 85%). Recrystallization of a portion from Et_2O/PE gave white crystals: mp 121–122 °C; IR (KBr) 3340, 1500, 1460 (m), 1445 (m), 1435 (m), 1420 (m), 1300 (m), 1275 (m), 1250 (m), 1218, 1185 (m), 1175 (m), 1100 (m), 1035 (m), 810 (m), 741 cm^{-1} (m); ^1H NMR δ 7.11–7.06 (three-line m, 1 H), 6.76 (m, 2 H), 5.65 (s, 1 H), 4.57 (s, 1 H), 3.82 (s, 3 H), 3.3–2.7 (complex m, 4 H), 2.3–1.6 (complex m, 2 H); mass spectrum, exact mass calcd for $C_{11}H_{14}O_2S_2$ m/e 242.0435, obsd m/e 242.0435.

4-[4-Methoxy-2-(2-propenyl)phenyl]phenol (6). The enone **5f** (0.549 g, 1.5 mmol) was dissolved in CH_3OH (100 mL) and trimethyl orthoformate (10.0 mL), and a catalytic amount of *p*-TsOH (0.02 g) was added. The system was heated to reflux; after 48 h TLC (50:50 Et_2O/PE) indicated that the reaction was complete. The system was allowed to cool to room temperature, and then a saturated solution of $NaHCO_3$ (20 mL) was added. The CH_3OH was removed in vacuo, and the organic phase was extracted into Et_2O (3 × 30 mL). The combined ethereal layers were washed with brine (30 mL), dried through $CaSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (3 in. × 0.5 in. column, 175 mL of 20% Et_2O/PE) and crystallized from 1:20 Et_2O/PE to yield slightly off-white crystals (0.204 g, 57%, >98% pure). Two additional recrystallizations gave white crystals: mp 124–124.5 °C; IR (KBr) 3405, 1605, 1490, 1258, 1220 cm^{-1}; ^1H NMR δ 7.3–7.0 (m, 3 H), 6.8–6.6 (m, 4 H), 4.9 (br s, 2 H), 4.65 (br s, 1 H), 3.76 (s, 3 H), 1.59 (s, 3 H); mass spectrum, exact mass calcd for $C_{16}H_{16}O_2$ m/e 240.1150, obsd m/e 240.1140.

X-ray Determination for 5b. The crystal used for data collection was a colorless rectangular plate. The unit cell constants a = 15.228 (6) Å, b = 7.216 (2) Å, c = 25.559 (1) Å, and β = 96.50 (1)° and the space group, $C2/c$, were determined at room temperature. Data were collected by the ω scan method on a Rigaku AFC5 diffractometer. The structure was solved by direct methods, and the model was completed by standard Fourier methods. Hydrogen atoms were added to the model as fixed contributions

in calculated positions with the assumption C–H = 0.98 Å. The final full-matrix least-squares refinement yielded agreement indices of R 0.067 and R_w 0.058 for the 1079 intensities with $F_o^2 > 1\sigma(F_o^2)$ and the 163 variables (anisotropic non-hydrogen atoms and hydrogen atoms fixed). The final difference electron density map contained maximum and minimum peak heights of 0.19 and −0.19 e/Å^3.

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Supplementary Material Available: Preparation of **2e–g** and 1-chloro-3,3,6,6-tetramethoxy-1,4-cyclohexadiene; monohydrolysis of chloro tetramethyl quinone bis(ketal) and **2h**; addition of phenyllithium to 3-methyl-4,4-dimethoxy-2,5-cyclohexadienone, **2j**, **2k**, *p*-(*tert*-butyldimethylsiloxy)bromobenzene, 4-methyl-4-(*p*-(*tert*-butyldimethylsiloxy)phenyl)-2,5-cyclohexadienone, **5e**, **5f**, **5g**, 4-hydroxy-4-vinyl-2,5-cyclohexadienone ethylene glycol ketal, and 4-methoxy-4-vinyl-2,5-cyclohexadienone; crystallographic details for *rel*-(4*S*,5*S*)-*cis*-4-methoxy-5-propenyl-4-phenylcyclohex-2-en-1-one; and bond lengths, angles, positional and thermal parameters, and diagrams for $C_{16}H_{18}O_2$ (19 pages); tables of structure factors (8 pages). Ordering information is given on any current masthead page.

Highly Stereoselective Ring Contraction of Heterocyclic Enamines: Total Synthesis of Perhydrohistrionicotoxin and Its 2,6-Epimer

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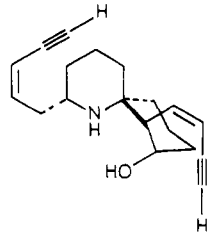
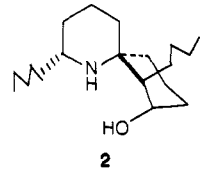
The total syntheses of perhydrohistrionicotoxin (PHTX) and its 2,6-epimer in which the pentyl group, introduced in the early stages, controls the relative configuration of C6 in a highly stereoselective manner are described. Seven-membered heterocyclic enamino ester **8**, enamino aldehyde **9**, and enamino acetal **12** underwent highly stereoselective ring contractions giving gem-bifunctionalized piperidines **10a**, **11a**, and **11b**, respectively. The resultant aldehydes **11a** and **10a** were respectively converted into two diastereoisomeric azaspiro enones **17a** and **17b**. The total synthesis of PHTX and its 2,6-epimer was completed from the azaspiro enone **17b**.

Introduction

Natural histrionicotoxin **1** [(−)-HTX] and its fully hydrogenated unnatural derivative, perhydrohistrionicotoxin (**2**) (PHTX), are now considered to be important biochemical tools for studying the mechanism of the action of cholinergic agonists in the neuromuscular system.[2] Owing to the unusual structure of the azaspiro[5.5]undecane ring system and their remarkable pharmacologic properties as neurotoxins in conjunction with their low natural occurrence, much work over the last 10 years has been devoted to the study of the synthesis of these molecules.[2-8]

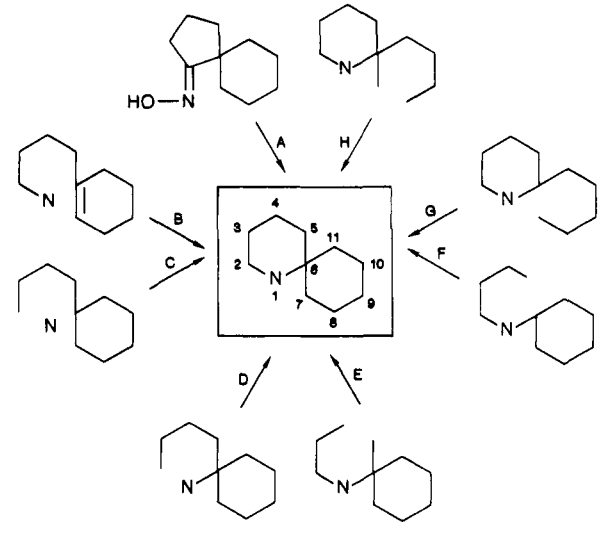


1



2

Scheme I



One of the main problems in these studies is how to approach the azaspiro[5.5]undecane ring system with the

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