Regiospecific Nucleophilic Aromatic Substitution: Conjugate Addition of Active Methylene Compounds to Quinone Monoacetals and Aromatization of the Adducts

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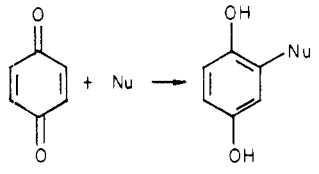
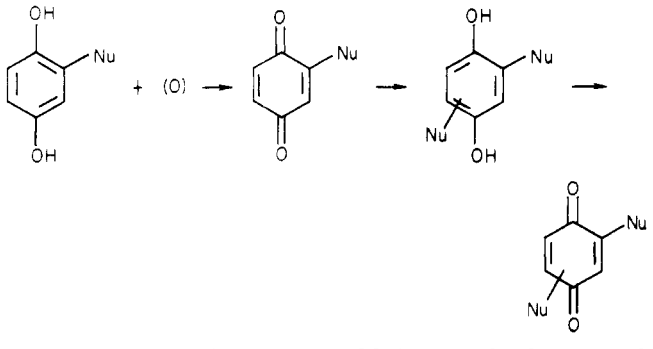
Diethyl malonate adds to a variety of quinone monoacetals in a Michael reaction; acid-catalyzed loss of methanol and enolization converts the adducts to hydroquinone monoethers substituted ortho to the alkoxy substituent. The same sequence applied to ethyl acetoacetate results in substituted benzo- or naphthofurans.

Introduction

Much of the known chemistry of quinones results from Michael-type addition of nucleophiles to the enone moiety contained in the quinone ring.[1]



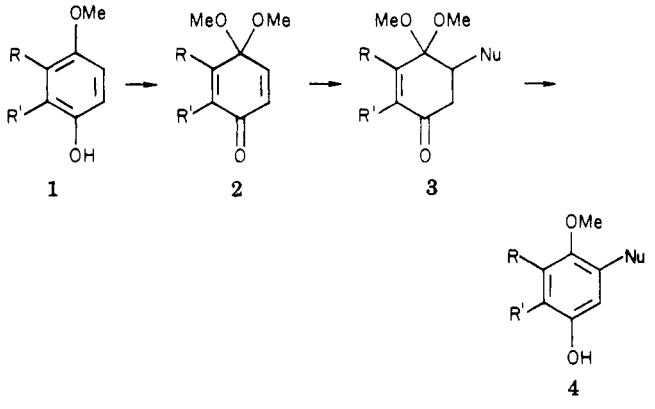
The synthetic utility of these 1,4-addition reactions may be limited by a lack of control of regiochemistry and also by further transformations of the adduct. For example, oxidation of the product by the starting quinone often leads to a new quinone which can add a second nucleophile leading to bis adducts.



While the regiochemistry of addition may be determined by an electron-withdrawing or electron-donating substituent so that hydroquinones with particular substitution patterns may be obtained in good yield, a more general method of controlling regiochemistry in these additions was sought.

Michael addition to quinone monoacetals (2) might suffer neither of the difficulties cited above. Addition would necessarily be regiospecific, and the adduct would be expected to be unreactive toward oxidation. In a separate step, aromatization of the adduct might afford the monoether of the substituted hydroquinone 4, a product not susceptible to side reactions. Varying the substituents R and R′ within broad limits was expected to have no effect on the sequence.[2]

Recently, synthetic methods for the one-step synthesis of quinone monoacetals (2) by the oxidation of hydroquinone monoethers (1) with thallium trinitrate, DDQ, or ferric chloride in anhydrous alcohol[3] and by the regioselective hydrolysis of bis acetals[4] have made these compounds readily available and therefore attractive as synthetic intermediates.



The net result of the sequence from starting material 1 to aromatized product 4 would be the regiospecific nucleophilic substitution of a hydroquinone monoether.

Background

Quinone monoacetals undergo 1,2-addition with a variety of reagents. This reaction has been used as the key step in the synthesis of azo-, nitroso-, and aminobenzenes[5] as well as quinols and *p*-quinone methide ketals.[6]

Only a few 1,4-additions to quinone acetals have been reported; benzoquinone methyl acetal undergoes conjugate addition with alcohols,[7a] thiols, and amines,[7] and benzo-

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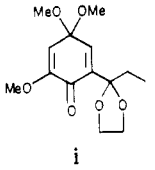
(1) A comprehensive review, K. T. Finley, "The Addition and Substitution Chemistry of Quinones" is contained in "The Chemistry of the Quinonoid Compounds", S. Patai, Ed., Wiley, New York, 1974, pp 887-1144.

(2) (a) In related work we were unable to add the sodium enolate of ethyl acetoacetate to quinone acetal i in which each enone system bears an α substituent (K. A. Parker and Joseph J. Petraitis, unpublished results).



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(b) A related method involves regioselective addition to quinone monoimides; see R. Adams and L. Whitaker, *J. Am. Chem. Soc.*, **78**, 658 (1956).

(3) (a) A. McKillop and E. C. Taylor et al., *J. Org. Chem.*, **41**, 282 (1976); (b) G. Buchi, P.-S. Chu, A. Hoppmann, C.-P. Mak, and A. Pearce, *J. Org. Chem.*, **43**, 3983 (1978).

(4) (a) M. J. Manning, D. R. Henton, and J. S. Swenton, *Tetrahedron Lett.*, 1679 (1977); (b) D. R. Henton, B. L. Chenard, and J. S. Swenton, *J. Chem. Soc., Chem. Commun.*, 326 (1979).

(5) E. C. Taylor, G. E. Jagdmann, Jr., and A. McKillop, *J. Org. Chem.*, **43**, 4385 (1978).

(6) D. J. Hart, P. A. Cain, and D. A. Evans, *J. Am. Chem. Soc.*, **100**, 1548 (1978).

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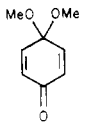
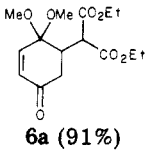
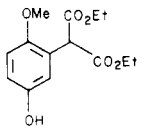
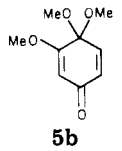
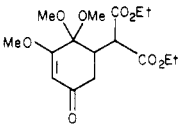
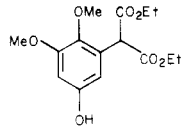
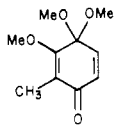
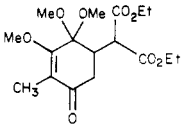
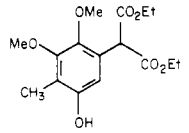
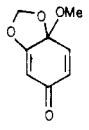
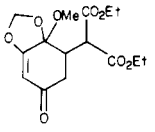
Table I. Addition of Diethyl Malonate to Quinone Monoacetals and Aromatization of Adducts

substrate	conditions	adduct	aromatized product (% yield)
 5a	NaOEt, EtOH	 6a (91%)	 7a (88%)
 5b	NaOEt, EtOH	 6b (83%)	 7b (63%)
 5c	NaH, THF	 6c (70%)	 7c (86%)
 5d	NaH, THF	 6d (44%)	

quinone ethylene ketal has been shown to form a bicyclic adduct with dimethyl acetonedicarboxylate.[8] The conjugate addition of dimethyloxosulfonium methylide to quinone ketals to give bicyclo[4.1.0] systems has been reported[9] and was recently utilized as a key step in the synthesis of tropolones.[9c]

Conjugate additions to 2,5-cyclohexadienones other than quinone monoacetals have been known for some time. Wessely demonstrated the 1,4-addition of cyanide[10a] and unsubstituted β-dicarbonyl compounds[10b] to 4-acetoxy-4-methyl-2,5-cyclohexadienone. Subsequent aromatization gave phenols in each case.[10,11]

Wenkert et al. investigated the analogous addition of malonate and acetoacetate to Reimer–Tiemann products;[12,13] these workers observed the formation of aldol products in the acetoacetate reactions.

Acid-catalyzed additions to quinone monoacetals[14] and quinol acetals[15] have been shown to afford aromatic products, substituted ortho to the hydroxyls.

Results and Discussion

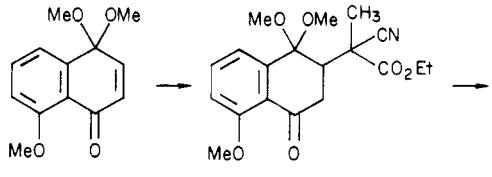
We chose to investigate the addition of malonate, cyanoacetate, and acetoacetate to quinone acetals and aromatization of the adducts. The two-step sequence afforded substituted hydroquinone monoethers as postulated when the nucleophile was malonate or cyanopropionate; fused furans were obtained when the nucleophile was acetoacetate.

The particular quinone acetals which we studied were chosen because they represent several substitution patterns and because the addition–aromatization products might be useful intermediates in natural product synthesis. The reaction of malonate with each of the quinone acetals **5a** to **5d** was studied (Table I).

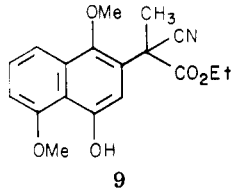
Addition of quinone acetal **5a**[3] or **5b**[9c,15] to the sodium enolate of diethyl malonate (from sodium hydride) in tetrahydrofuran gave a mixture of products as indicated by thin-layer chromatography. However, monoadduct **6a** was obtained in high yield when quinone acetal **5a** was added to diethyl malonate and 0.1 equiv of sodium ethoxide in ethanol at room temperature; likewise adduct **6b** was obtained from quinone acetal **5b**. Aromatization of each of these adducts was effected in good-to-excellent yield by *p*-toluenesulfonic acid in refluxing benzene; thus **7a** and **7b** were obtained.

Addition of the sodium enolate of diethyl malonate (from sodium hydride) to quinone acetals **5c** and **5d**[3] was effected in tetrahydrofuran. Aromatization of **6c** to **7c** with *p*-toluenesulfonic acid was accomplished in 86% yield; no attempt to aromatize **6d** was made.

The addition–aromatization sequence was also carried out in the naphthoquinone series. Ethyl cyanopropionate added to quinone acetal **5e** in the presence of 0.1 equiv of sodium ethoxide in ethanol to give adduct 8; aromatization with *p*-toluenesulfonic acid in benzene gave hydroquinone monoether **9** (84% yield overall).



5e **8**



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While the addition of malonate and cyanoacetate to quinone acetals and subsequent aromatization by acid is straightforward, the corresponding sequence applied to keto esters follows various alternative pathways (Table II).

For example, treatment of quinone monoacetal **5a** with ethyl acetoacetate in ethanol containing 0.1 equiv of sodium ethoxide afforded the novel bridged system **10a**, presumably resulting from an intermolecular Michael addition followed by an intramolecular Michael reaction of the adduct. Assignment of "O-alkylated" structure **10a** rests, to a considerable extent, on the NMR spectrum of the adduct which shows no signals in the vinyl region and a four-line multiplet at δ 4.61, suggestive of a proton on carbon bearing oxygen. Treatment of this adduct with *p*-toluenesulfonic acid in refluxing benzene afforded the substituted benzofuran **11**.

Adduct **10b**, obtained from monoacetal **5a** and the sodium enolate (from sodium hydride) of ethyl acetoacetate in anhydrous tetrahydrofuran, was also the product of consecutive intermolecular and intramolecular Michael

(7) (a) A. Nilsson, A. Ronlan, and V. D. Parker, *Tetrahedron Lett.*, 1107 (1975); (b) C. H. Foster and D. A. Payne, *J. Am. Chem. Soc.*, **100**, 2834 (1978).

(8) I. A. McDonald and A. S. Dreiding, *Helv. Chim. Acta*, **56**, 2523 (1973).

(9) (a) G. L. Buchanan, R. A. Raphael, and R. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 373 (1973); (b) J. E. Heller, A. S. Dreiding, B. R. O'Connor, H. E. Simmons, G. L. Buchanan, R. A. Raphael, and R. Taylor, *Helv. Chim. Acta*, **56**, 272 (1973); (c) D. A. Evans, D. H. Hart, and R. M. Koelsch, *J. Am. Chem. Soc.*, **100**, 4593 (1978).

(10) (a) F. Wessely, *Monatsh. Chem.*, **88**, 228 (1957); (b) W. Specht and F. Wessely, *ibid.*, **90**, 713 (1959).

(11) *o*-Quinol acetates also may be used to generate phenols by a conjugate addition–aromatization sequence; see T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.*, **100**, 2933 (1978).

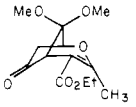
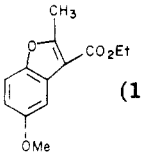
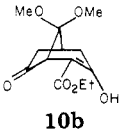
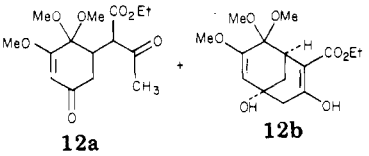
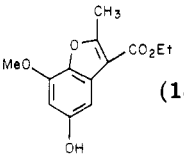
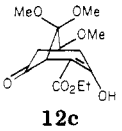
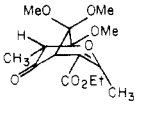
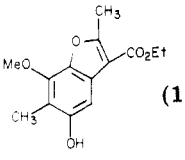
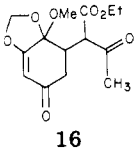
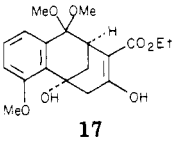
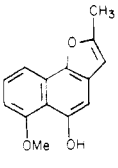
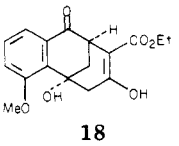
(12) E. Wenkert and T. E. Stevens, *J. Am. Chem. Soc.*, **78**, 5627 (1956).

(13) E. Wenkert, F. Haviv, and A. Zeitlin, *J. Am. Chem. Soc.*, **91**, 2299 (1969).

(14) (a) G. Buchi and P.-S. Chu, *J. Org. Chem.*, **43**, 3717 (1978); (b) G. Buchi and C.-P. Mak, *J. Am. Chem. Soc.*, **99**, 8073 (1977).

(15) D. A. Evans, P. A. Cain, and R. Y. Wong, *J. Am. Chem. Soc.*, **99**, 7083 (1977).

Table II. Addition of Ethyl Acetoacetate to Quinone Monoacetals and Conversion of the Adducts to Fused Furan Systems

substrate	conditions	adduct	conditions	furan product
5a	NaOEt, EtOH	 **10a**	*p*-TsOH, C_6H_6	 **(11)**
5a	NaH, THF	 **10b**		
5b	NaOEt, EtOH	 **12a** **12b**	*p*-TsOH, C_6H_6	 **(13)**
5b	NaH, THF	 **12c**		
5c	NaH, THF	 **14**	aqueous HCl, acetone	 **(15)**
5d	NaH, THF	 **16**		
5e	NaOEt, EtOH	 **17**	aqueous HCl, EtOH	 **(19)**
		 **18**		

reactions; however, unlike the sequence in ethanol, both of these Michael steps involve C-alkylation to afford the bicyclic system.

A conspicuous feature of the NMR spectrum of **10b** was the absorption represnting the enolic hydrogen at δ 12.1; an absorption at δ 4.6 representing a hydrogen on a bridgehead carbon bearing oxygen was absent (compare with the NMR spectrum of **10a**). The structural resemblance of this product to the adduct obtained by McDonald and Dreiding[8] should be noted.

Studies of adducts of quinone monoacetal **5b** and ethyl acetoacetate also showed a dependence on reaction conditions. Reaction in ethanol containing 0.1 equiv of sodium ethoxide gave material which appeared to be a mixture of the simple Michael adduct **12a** and its internal aldol condensation product **12b**. This mixture was converted by *p*-toluenesulfonic acid to benzofuran **13**.

Addition of the sodium enolate of ethyl acetoacetate to quinone monoacetal **5b** in tetrahydrofuran afforded adduct **12c**; the NMR spectrum of this material differs from that of **10b** only in that it lacks one aliphatic proton in the δ 2.0–3.48 region and it has an additional methoxyl at δ 3.53.

Addition of ethyl acetoacetate to quinone monoacetal **5c** in ethanol containing sodium ethoxide did not afford a clean product; unexpectedly addition of ethyl sodioacetoacetate to **5c** in tetrahydrofuran gave the "O-alkylated" product **14**. Assignment of this structure is based on NMR data. A doublet (δ 1.05 in $CDCl_3$, δ 1.32 in benzene-d_6) coupled with a proton in the 2.5-ppm region (as shown by a double resonance experiment) was assigned to the equatorial methyl α to the carbonyl.[16] A three-proton singlet at δ 2.22 in $CDCl_3$ (δ 2.20 in benzene-d_6) was assigned to the methyl on the vinylogous carbonate system; no enolic proton appeared in the spectrum. *p*-Toluenesulfonic acid in refluxing benzene converted this material to benzofuran **15**.

Quinone monoacetal **5d** formed an adduct when added to the sodium enolate of ethyl acetoacetate in tetrahydrofuran; the NMR spectrum of the adduct indicated that one vinyl proton remained and that no enolic proton was present; two sets of signals for the ethyl group indi-

(16) See B. J. L. Huff, F. Normal Tuller, and D. Caine, *J. Org. Chem.*, 34, 3070 (1969), and references therein.

cated that the adduct, assigned structure **16**, is a mixture of diastereomers. Treatment of adduct **16** with concentrated hydrochloric acid, *p*-toluenesulfonic acid in benzene, or trifluoroacetic acid led to tar.

Addition of ethyl acetoacetate to naphthoquinone monoacetal **5e** in the presence of 0.1 equiv of sodium ethoxide in ethanol afforded the adduct **17**, identified by its NMR spectrum which showed two exchangeable protons at δ 5.21 and 12.5 and no methyl at δ 2. An attempt to purify this adduct by preparative TLC on silica gel resulted in hydrolysis of the dimethyl ketal moiety. More drastic hydrolysis conditions, hydrochloric acid in ethanol, resulted in decarbethoxylation, retro-aldolization, and dehydrative cyclization to give the naphthofuran **19**.

Experimental Section

All reactions were carried out under a positive pressure of dry nitrogen. Solvents and reagents were routinely distilled before use. Infrared spectra were recorded on a Perkin-Elmer 257 grating infrared spectrometer. Nuclear magnetic resonance measurements were run on a Varian A-60A instrument with tetramethylsilane as an internal standard. Mass spectra were recorded at 50 eV on a Hitachi Perkin-Elmer Model RMU-60 spectrometer. Preparative thin-layer chromatography (TLC) was performed by using commercial plates spread with silica gel G (E. M. Laboratories). Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

2-Methyl-3,4,4-trimethoxycyclohexa-2,5-dienone (5c). To a stirred solution of $Tl(NO_3)_3 \cdot 3H_2O$ (0.65 g, 1.6 mmol) in 10 mL of dry MeOH cooled to −25 °C was added 2-methyl-3,4-dimethoxyphenol[17] (28 mg, 1.6 mmol) in 10 mL of dry MeOH. The reaction mixture was stirred at −25 °C for 5 min, allowed to warm to room temperature, and poured slowly into 30 mL of saturated $NaHCO_3$ solution. The resulting solution was extracted with five 30-mL portions of ether/ethyl acetate (4:1). The combined organic extract was dried over Na_2SO_4, concentrated, and subjected to chromatography on silica gel. Elution with benzene/ether (8:1) gave 0.26 g (79%) of an oil: IR ($CHCl_3$) 1660, 1634, and 1601 cm^{-1}; NMR ($CDCl_3$) δ 1.80 (s, 3 H), 3.31 (s, 6 H), 4.13 (s, 3 H), 6.25 (d, J = 10 Hz, 1 H), and 6.46 (d, J = 10 Hz, 1 H). An analytical sample was prepared by distillation. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.89; H, 7.41.

1,1,5-Trimethoxy-4-oxo-1,4-dihydronaphthalene (5e). To a stirred solution of 204 mg (1.0 mmol) of 4,8-dimethoxy-1-naphthol[18] in 10 mL of dry MeOH was added dichlorodicyano-*p*-benzoquinone (226 mg, 1.0 mmol) followed by finely powdered anhydrous $KHCO_3$ (100 mg, 1.0 mmol). The reaction mixture was stirred at room temperature for 45 min, concentrated, and washed through a column of alumina with CH_2Cl_2. Concentration and chromatography on silica gel with hexane/ethyl acetate (3:2) gave 181 mg (77%) of an oil: IR ($CHCl_3$) 1632 cm^{-1}; NMR ($CDCl_3$) δ 3.17 (s, 6 H), 3.95 (s, 3 H), 6.45 (d, J = 10 Hz, 1 H), 6.62 (d, J = 10 Hz, 1 H), and 6.8–7.8 (m, 3 H). An analytical sample was prepared by Kugelrohr distillation at 120 °C (25 μm). Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.45; H, 6.32.

Diethyl (2,2-Dimethoxy-5-oxo-3-cyclohexenyl)malonate (6a) and Diethyl (5-Hydroxy-2-methoxyphenyl)malonate (7a). To a stirred solution of quinone monoacetal **5a**[3a] (86 mg, 0.56 mmol) in 1 mL of absolute EtOH was added 0.1 equiv of NaOEt (0.56 mL of a solution prepared from 103 mg of Na and 45.0 mL of EtOH), followed by diethyl malonate (89 mg, 0.51 mmol) in 1 mL of absolute EtOH. The reaction mixture was stirred at room temperature for 41 h, quenched with H_2O, and concentrated. The residue was partitioned between ether and H_2O. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and preparative TLC on silica gel with benzene/ether (1:1) gave 159 mg (91%) of an oil: IR ($CHCl_3$) 1751, 1721, and 1682 cm^{-1}; NMR ($CDCl_3$) δ 1.24 and 1.26 (2 overlapping t, J = 7 Hz, 6 H), 2.70 (d, J = 5 Hz, 2 H), 3.30 (s, 6 H), 3.40 (m, 1 H), 3.67 (d, J = 7 Hz, 1 H), 4.12 (q, J = 7 Hz, 2 H), 4.19 (q, J = 7 Hz, 2 H), 6.09 (d, J = 10 Hz, 1 H), and 6.87 (d, J = 10 Hz, 1 H). An analytical sample was prepared by distillation. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.31; H, 7.06. Found: C, 57.12; H, 7.27.

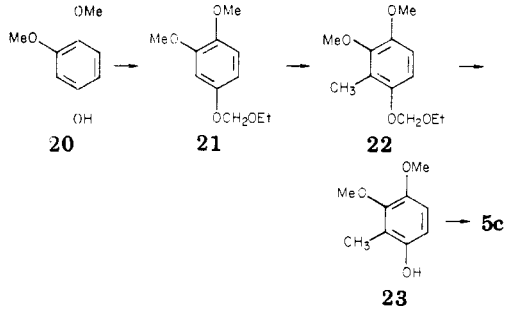
A solution of acetal **6a** (84 mg, 0.27 mmol) in 1 mL of dry benzene was added to a solution of *p*-toluenesulfonic acid (50 mg, 0.29 mmol) in 2 mL of refluxing benzene and stirred for 20 min under a Dean–Stark trap. The reaction mixture was cooled and concentrated to give a residue which was partitioned between ether and saturated $NaHCO_3$ solution. The ether solution was dried over $MgSO_4$ and concentrated. Preparative TLC on silica gel with benzene/ether (1:1) as eluant gave 67 mg (88%) of an oil: IR ($CHCl_3$) 3400 and 1717 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 6 H), 3.74 (s, 3 H), 4.21 (q, J = 7 Hz, 4 H), 5.08 (s, 1 H), 5.77 (br s, 1 H), and 6.7–6.8 (m, 3 H). Distillation at 140 °C (20 μm) afforded an analytical sample; mass spectrum, m/e (M^+) 282. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.76; H, 6.65.

Diethyl (2,2,3-Trimethoxy-5-oxo-3-cyclohexenyl)malonate (6b) and Diethyl (2,3-Dimethoxy-5-hydroxyphenyl)malonate (7b). To a stirred solution of quinone monoacetal **5b**[15] (98 mg, 0.54 mmol) in 1 mL of absolute EtOH was added NaOEt (0.1 equiv, 0.50 mL, prepared from 103 mg of Na and 45.0 mL of EtOH), followed by diethyl malonate (85 mg, 0.53 mmol) in 1 mL of absolute EtOH. The reaction mixture was stirred at room temperature for 24 h and quenched with H_2O. Solvent was evaporated and the residue was partitioned between ether and H_2O and dried over $MgSO_4$. Concentration and preparative TLC on silica gel with benzene/ether (1:1) as eluant gave 143 mg (83%) of an oil: IR ($CHCl_3$) 1744, 1718, 1651, and 1603 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 6 H), 2.67 (d, J = 6 Hz, 2 H), 3.15 (m, 1 H), 3.25 (s, 3 H), 3.33 (s, 3 H), 3.68 (d, J = 6 Hz, 1 H), 3.78 (s, 3 H), 4.13 (q, J = 7 Hz, 2 H), 4.17 (q, J = 7 Hz, 2 H), and 5.42 (s, 1 H). Distillation gave an analytical sample. Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.03. Found: C, 55.90; H, 7.22.

A solution of acetal **6b** (59 mg, 0.17 mmol) in 1 mL of dry benzene was added to *p*-toluenesulfonic acid (35 mg, 0.20 mmol) in 2 mL of benzene and the solution was stirred under a Dean–Stark trap for 10 min. The reaction mixture was cooled and concentrated to give a residue which was partitioned between ether and saturated $NaHCO_3$ solution. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and preparative TLC on silica gel gave 34 mg (63%) of a yellow oil: IR ($CHCl_3$) 3390 and 1721 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 6 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 4.22 (q, J = 7 Hz, 4 H), 5.10 (s, 1 H), 5.95 (br s, 1 H), 6.42 (d, J = 3 Hz, 1 H), and 6.52 (d, J = 3 Hz, 1 H). An analytical sample was prepared by distillation at 140 °C (15 μm); mass spectrum, m/e (M^+) 312. Anal. Calcd for $C_{15}H_{20}O_7$: C, 57.69; H, 6.45. Found: C, 57.63; H, 6.60.

Diethyl (2,2,3-Trimethoxy-4-methyl-5-oxo-3-cyclohexenyl)malonate (6c) and Diethyl (2,3-Dimethoxy-4-methyl-5-hydroxyphenyl)malonate (7c). To a stirred suspension of NaH (20 mg of a 50% oil dispersion, washed with *n*-hexane three times, 0.42 mmol) in 1 mL of dry THF was added cyclohexadienone **5c** (77 mg, 0.38 mmol) in 1 mL of dry THF, followed by diethyl malonate (60 mg, 0.38 mmol) in 1 mL of dry THF. The reaction mixture was stirred at 35 °C for 24 h and quenched with wet ether. Solvent was evaporated and the residue was partitioned between ether and H_2O. The organic phase was

(17) Prepared from 3,4-dimethoxyphenol[19] as shown below. Procedures for this scheme are included in the experimental section.



(18) 4,8-Dimethoxy-1-naphthol was prepared from 4,8-dimethoxy-1-naphthalenecarboxaldehyde (N. P. Buu-Hoi and D. Lavit, *J. Org. Chem.*, **20**, 1191 (1955)) by a procedure essentially identical with that recently reported by R. L. Hannan, R. B. Barber, and H. Rapoport, *J. Org. Chem.*, **44**, 2153 (1979).

washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated. Chromatography of the residue on silica gel with benzene/ether (8:1) as eluant gave 96 mg (70%) of a yellow oil: IR ($CHCl_3$) 1742, 1728, and 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3 H), 1.32 (t, J = 7 Hz, 3 H), 1.80 (s, 3 H), 2.70 (d, J = 2 Hz, 1 H), 2.78 (d, J = 2 Hz, 1 H), 3.28 (s, 3 H), 3.32 (s, 3 H), 3.40 (m, 1 H), 3.66 (d, J = 6 Hz, 1 H), 3.90 (s, 3 H), 4.06 (q, J = 7 Hz, 2 H), and 4.18 (q, J = 7 Hz, 2 H).

A solution of acetal **6c** (29 mg, 0.10 mmol) in 1 mL of dry benzene was added to *p*-toluenesulfonic acid (17 mg, 0.10 mmol) in 2 mL of benzene and the solution was stirred at reflux for 15 min under a Dean–Stark trap. The reaction mixture was cooled and concentrated and the residue was partitioned between ether and saturated $NaHCO_3$ solution. The organic phase was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated. Chromatography on silica gel with benzene/ether (1:1) as eluant gave 23 mg (86%) of a yellow oil: IR ($CHCl_3$) 3360 and 1711 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 6 H), 2.10 (s, 3 H), 3.81 (s, 6 H), 4.25 (q, J = 7 Hz, 4 H), 5.05 (s, 1 H), 6.67 (s, 1 H), and 9.12 (s, 1 H, exchanges in D_2O). Distillation at 150–160 °C (20 μm) afforded an analytical sample; mass spectrum, m/e (M^+) 326. Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.80. Found: C, 58.85; H, 6.90.

Diethyl (2-Methoxy-2,3-methylenedioxy-5-oxo-3-cyclohexenyl)malonate (6d). To a stirred suspension of NaH (34 mg, 50% oil dispersion, 0.71 mmol, washed with *n*-hexane three times) in 1 mL of dry THF was added cyclohexadienone **5d**[3a] (112 mg, 0.67 mmol) in 1 mL of dry THF and diethyl malonate (110 mg, 0.68 mmol) in 1 mL of dry THF. The reaction mixture was stirred at 35 °C for 17 h and quenched with wet ether. Solvent was evaporated and the residue was partitioned between ether and H_2O. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and preparative TLC on silica gel with benzene/ether (8:1) as eluant gave 96 mg (44%) of an oil: IR ($CHCl_3$) 1748, 1725, and 1657 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3 H), 1.26 (t, J = 7 Hz, 3 H), 2.52 (d, J = 2 Hz, 1 H), 2.68, 3.00 (2 d, J = 4 Hz, 1 H), 3.44 (s, 3 H), 3.60 (m, 2 H), 4.14 (q, J = 7 Hz, 2 H), 4.18 (q, J = 7 Hz, 2 H), 5.48, 5.51, and 5.52 (2 d, J = 0.5 Hz, overlapping 1 s, 3 H). Distillation afforded an analytical sample. Anal. Calcd for $C_{15}H_{20}O_8$: C, 54.88; H, 6.14. Found: C, 54.98; H, 6.33.

Ethyl 2-(1,1,5-Trimethoxy-4-oxo-1,2,3,4-tetrahydro-2-naphthyl)-2-cyanopropionate (8) and Ethyl 2-(4-Hydroxy-1,5-dimethoxy-2-naphthyl)-2-cyanopropionate (9). To a stirred solution of naphthoquinone monoacetal **5e** (64.5 mg, 0.27 mmol) in 1 mL of absolute EtOH was added NaOEt (0.1 equiv, 0.30 mL of a solution prepared from 152 mg of Na and 50.0 mL of EtOH) and 35 mg (0.27 mmol) of ethyl 2-cyanopropionate in 1 mL of absolute ethanol. The reaction mixture was stirred at room temperature for 3–4 days and quenched with H_2O. Solvent was evaporated and the residue was partitioned between ether and H_2O. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and preparative TLC on silica gel with benzene/ether (1:2) gave 92 mg (92%) of an oil. An analytical sample was prepared by short-path distillation (Kugelrohr) at 230 °C (20 μm): IR ($CHCl_3$) 2262, 1738, 1677 cm^{-1}; NMR ($CDCl_3$) δ 1.24, 1.32 (2 t, J = 7 Hz, 3 H), 1.52, 1.60 (2 s, 3 H), 2.85 (s, 3 H), 2.7–3.5 (m, 6 H), 3.90 (s, 3 H), 4.21 (q, J = 7 Hz, 2 H), 6.9–7.7 (m, 3 H). Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.42; N, 3.88. Found: C, 62.93; H, 6.49; N, 3.91.

A solution of crude adduct 8 (44.6 mg, 0.11 mmol) was stirred for 10 min with *p*-TsOH (35 mg, 0.21 mmol) in 3 mL of refluxing benzene under a Dean–Stark trap. The reaction mixture was cooled and concentrated. The residue was partitioned between ether and saturated $NaHCO_3$ solution and dried over $MgSO_4$. Concentration and preparative TLC on silica gel with benzene/ether (1:2) gave 37.0 mg of an oil (91% yield, 84% from **5e**). An analytical sample was prepared by distillation at 200 °C (20 μm): IR ($CHCl_3$) 3500, 2270, 1731 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3 H), 2.06 (s, 3 H), 4.00 (s, 3 H), 4.09 (s, 3 H), 4.38 (q, J = 7 Hz, 2 H), 6.8–7.8 (m, 4 H), 9.0 (s, 1 H); mass spectrum, m/e (M^+) 329. Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.92. Found: C, 65.83; H, 5.95.

Michael Additions of Acetoacetic Ester and Quinone Monoacetal 5a. 1. With Sodium Ethoxide in Ethanol: Adduct 10a. To a stirred solution of 77 mg (0.5 mmol) of quinone acetal **5a** in 2.5 mL of absolute ethanol was added 0.5 mL of a solution of NaOEt in EtOH (prepared from 103 mg of Na and 45.0 mL of EtOH) and 65 mg (0.5 mmol) of ethyl acetoacetate. The reaction mixture stirred for 3 days at room temperature. Then water was added and the reaction mixture was concentrated and extracted twice with ether. The combined ether solution was washed with water and saturated sodium chloride solution, dried over magnesium sulfate, and concentrated to give 113 mg of an oil. Preparative TLC with benzene/ether (8:1) afforded 97 mg (69%) of an adduct: IR 1725, 1675 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3 H), 2.22 (s, 3 H), 2.63 (m, 4 H), 3.26 (m, 1 H), 3.32 (s, 3 H), 3.40 (s, 3 H), 4.17 (q, J = 7 Hz, 2 H), and 4.61 (m, 1 H); ^{13}C NMR δ 15.7, 21.0, 35.1, 43.6, 49.17, 49.24, 60.4, 72.1, 95.3, 102.4, 164.5, 193.6, and 204.9; mass spectrum, m/e (M^+) 284. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.09. Found: C, 59.39; H, 7.25.

2. With Sodium Hydride in Tetrahydrofuran: Adduct 10b. To a stirred solution of NaH (50% oil dispersion, washed with *n*-hexane three times, 17 mg, 0.71 mmol) in 1 mL of dry THF was added cyclohexadienone **5a** (104 mg, 0.67 mmol) in 1 mL of dry THF followed by ethyl acetoacetate (87 mg, 0.67 mmol) in 1 mL of dry THF. The reaction mixture was stirred at 35 °C for 24 h and quenched with wet ether. Solvent was evaporated and the residue was partitioned between ether and H_2O. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and chromatography on silica gel with benzene/ether (8:1) as eluent gave 126 mg (66%) of a yellow oil: IR ($CHCl_3$) 1700 and 1650 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 2.3–3.4 (m, 8 H), 3.21 (s, 3 H), 3.37 (s, 3 H), 4.15 (q, J = 7 Hz, 2 H), and 12.1 (s, 1 H). Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.15; H, 7.09. Found: C, 59.37; H, 7.28.

3. Aromatization of Adduct 10a: Benzofuran 11. A solution of 42 mg (0.15 mmol) of adduct **10a** and 25 mg of *p*-toluenesulfonic acid in 2 mL of benzene was stirred at reflux for 20 min. The reaction mixture was allowed to cool to room temperature and solid sodium bicarbonate was added. The reaction mixture was partitioned between ether and water; the organic phase was washed with water and sodium chloride solution and dried over magnesium sulfate. Concentration and preparative TLC on silica gel with benzene/ether (2:1) gave 15 mg (42%) of an oil: IR ($CHCl_3$) 1682, 1576 cm^{-1}; NMR ($CDCl_3$) δ 1.43 (t, J = 7 Hz, 3 H), 2.73 (s, 3 H), 3.86 (s, 3 H), 4.42 (q, J = 7 Hz, 2 H), 6.81 (dd, J = 2.5 Hz, J = 8 Hz, 1 H), 7.28 (d, J = 8 Hz, 1 H), and 7.80 (d, J = 2.5 Hz, 1 H); mass spectrum, m/e (M^+) 234. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 67.01; H, 6.11.

Michael Additions of Acetoacetic Ester and Quinone Monoacetal 5b. 1. With Sodium Ethoxide in Ethanol: Adducts 12a and 12b. To a stirred solution of cyclohexadienone **5b** (97.5 mg, 0.53 mmol) in 1 mL of absolute EtOH was added NaOEt (0.1 equiv, 0.50 mL, prepared from 103 mg of Na and 45.0 mL of EtOH) followed by ethyl acetoacetate (69 mg, 0.53 mmol) in 1 mL of absolute EtOH. The reaction mixture was stirred at room temperature for 48 h and quenched with H_2O. Solvent was evaporated and the residue was partitioned between ether and H_2O. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and preparative TLC on silica gel with benzene/ether (2:3) gave 91 mg (55%) of an oil: IR ($CHCl_3$) 3440, 1721, 1699, and 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.27, 1.35 (2 t, J = 7 Hz, 3 H), 2.24, 2.26 (2 s, 3 H), 2.5–2.8 (m, 2 H), 3.17, 3.23, 3.32, 3.53, 3.78 (5 s, 11 H), 4.15 (m, 2 H), 4.72, 5.45 (2 s, 1 H), and 12.4 (s, <0.5 H). Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.06. Found: C, 57.42; H, 7.27.

2. With Sodium Hydride in Tetrahydrofuran: Adduct 12c. To a stirred solution of NaH (50% oil dispersion, washed three times with *n*-hexane, 66 mg, 2.8 mmol) in 5 mL of dry THF was added cyclohexadienone **5b** (518 mg, 2.8 mmol) in 5 mL of dry THF and ethyl acetoacetate (370 mg, 2.8 mmol) in 5 mL of dry THF. The reaction mixture was stirred at 35 °C for 40 h and quenched with wet ether. Solvent was evaporated and the residue was partitioned between ether and H_2O. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and chromatography on silica gel with benzene/ether (8:1) as eluant gave 623 mg (70%) of an oil: IR ($CHCl_3$) 1711, 1652 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3 H), 2.0–3.3 (m, 7 H), 3.32 (s, 3 H), 3.41 (s, 3 H), 3.53 (s, 3 H), 4.16 (q, J = 7 Hz, 2 H), and 12.0 (s, 1 H). Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.06. Found: C, 57.39; H, 7.44.

3. Aromatization of Adducts 12a/12b: Benzofuran 13. A solution of the adducts **12a/12b** (50 mg, 0.16 mmol) in 1 mL of dry benzene was stirred for 10 min with *p*-toluenesulfonic acid (35 mg, 0.20 mmol) in 2 mL of refluxing benzene under a Dean–Stark trap. The reaction mixture was cooled and concentrated to give a residue, which was partitioned between ether and saturated NaCl solution. The ether solution was dried over $MgSO_4$ and concentrated. Preparative TLC on silica gel with benzene/ether (1:1) gave 21 mg (52%) of a white solid: mp 175–176 °C; IR (KBr) 3425, 1682, and 1636 cm^{-1}; NMR (acetone-d_6) δ 1.30 (t, J = 7 Hz, 3 H), 2.63 (s, 3 H), 2.77 (br s, 1 H, exchanges in D_2O), 3.84 (s, 3 H), 4.26 (q, J = 7 Hz, 2 H), 6.37 (d, J = 2 Hz, 1 H), and 6.92 (d, J = 2 Hz, 1 H). Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.18; H, 5.76.

Addition of Acetoacetic Ester to Quinone Monoacetal 5c. 1. With Sodium Hydride in Tetrahydrofuran: Adduct 14. To a stirred solution of NaH (50% oil dispersion, washed with *n*-hexane three times, 12 mg, 0.50 mmol) in 1 mL of dry THF was added cyclohexadienone **5c** (91 mg, 0.46 mmol) in 1 mL of dry THF followed by ethyl acetoacetate (65 mg, 0.50 mmol) in 1 mL of dry THF. The reaction mixture was stirred at 35 °C for 24 h and quenched with wet ether. Solvent was evaporated and the residue was partitioned between ether and H_2O. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. After concentration, the residue was subjected to chromatography on silica gel. Elution with benzene/ether (8:1) gave 77 mg (51%) of a yellow oil: IR ($CHCl_3$) 1702 and 1673 cm^{-1}; NMR ($CDCl_3$) δ 1.05 and 1.25 (d, J = 7 Hz, and overlapping t, J = 7 Hz, 6 H), 2.22 (s, 3 H), 2.5–3.4 (m, 4 H), 3.26 (s, 3 H), 3.57 (s, 3 H), 3.62 (s, 3 H), and 4.12 (q, J = 7 Hz, 2 H); NMR (benzene-d_6) δ 0.92 (t, J = 7 Hz, 3 H), 1.32 (d, J = 7 Hz, 3 H), 2.20 (s, 3 H), 2.5–3.4 (m, 4 H), 2.99 (s, 3 H), 3.32 (s, 3 H), 3.52 (s, 3 H), and 4.03 (q, J = 7 Hz, 2 H); irradiation of the region at ~2.5 ppm resulted in collapse of the doublet at 1.32 ppm; ^{13}C NMR ($CDCl_3$) δ 208.9, 167.0, 164.3, 130.0, 103.4, 103.3, 98.3, 60.5, 53.9, 56.6, 51.1, 48.7, 44.0, 35.7, 19.4, and 6.9. Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.53; H, 7.36. Found: C, 58.75; H, 7.07.

2. Aromatization of Adduct 14: Benzofuran 15. To a stirred solution of adduct **14** (35 mg, 0.11 mmol) in 2 mL of acetone was added 0.1 mL of concentrated HCl. The reaction mixture was stirred at reflux for 20 min, cooled, and concentrated. The residue was partitioned between ether and saturated $NaHCO_3$ solution. The organic phase was washed with H_2O three times, dried over $MgSO_4$, and concentrated. Recrystallization from ether gave 21 mg (75%) of a white solid: mp 198–199 °C; IR (KBr) 3320 and 1662 cm^{-1}; NMR (Me_2SO-d_6) δ 1.32 (t, J = 7 Hz, 3 H), 2.08 (s, 3 H), 2.67 (s, 3 H), 3.96 (s, 3 H), 4.27 (q, J = 7 Hz, 2 H), 7.02 (s, 1 H), and 9.23 (s, 1 H, exchanges in D_2O); mass spectrum, m/e (M^+) 264. Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.49; H, 6.25.

Addition of Acetoacetic Ester to Quinone Monoacetal 5d: Adduct 16. With Sodium Hydride in Tetrahydrofuran. To a stirred solution of NaH (50% oil dispersion, washed with *n*-hexane three times, 17 mg; 0.71 mmol) in 1 mL of dry THF was added cyclohexadienone **5d** (112 mg, 0.68 mmol) in 1 mL of dry THF and ethyl acetoacetate (87 mg, 0.67 mmol) in 1 mL of dry THF. The reaction mixture was stirred at 35 °C for 14 h and quenched with wet ether. Solvent was evaporated and the residue was partitioned between ether and H_2O. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and preparative TLC on silica gel with benzene/ether (1:1) as eluant gave 128 mg (65%) of an oil: IR ($CHCl_3$) 1708 and 1657 cm^{-1}; NMR ($CDCl_3$) δ 1.24, 1.26 (two overlapping t, J = 7 Hz, 3 H), 2.22 (s, 3 H), 2.52 (m, 2 H), 3.46 (s, 3 H), 3.63 (m, 2 H), 4.14, 4.16 (two overlapping q, J = 7 Hz, 2 H), and 5.48 (s overlapping m, 3 H); mass spectrum, m/e (M^+) 298. Anal. Calcd for $C_{14}H_{18}O_7$: C, 56.37; H, 6.08. Found: C, 56.51; H, 6.25.

Additon of Acetoacetic Ester to Quinone Monoacetal 5e. 1. With Sodium Ethoxide in Ethanol: Adduct 17 and Ketone 18. To a stirred solution of acetal **5e** (114 mg, 0.49 mmol) in 1 mL of absolute EtOH was added NaOEt (0.1 equiv, 0.50 mL, prepared from 103 mg of Na and 45.0 mL of EtOH), followed by ethyl acetoacetate (64 mg, 0.49 mmol) in 1 mL of absolute EtOH. The reaction mixture was stirred at room temperature for 20 h and quenched with H_2O. Solvent was evaporated, and the residue was partitioned between ether and H_2O. The organic layer was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration gave 120 mg of a crude adduct: IR ($CHCl_3$) 3520, 1730, 1700, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 3.00 (s, 3 H), 3.40 (s, 3 H), 3.89 (s, 3 H), 4.28 (q, J = 7 Hz, 2 H), 5.21 (br s, 1 H), 6.7–7.4 (m, 3 H), and 12.5 (s, 1 H).

Preparative TLC on silica gel with benzene/ether (1:2) gave 78 mg (51%) of a new material: IR ($CHCl_3$) 3520, 1700, 1639 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (t, J = 7 Hz, 3 H), 3.98 (s, 3 H), 4.23, 4.27 (2 q, J = 7 Hz, 2 H), 5.27 (br s, 1 H), 7.0–7.7 (m, 3 H), and 12.5 (s, 1 H).

2. Aromatization of Ketone 18: Naphthofuran 19. To a stirred solution of ketone **18** (52 mg, 0.14 mmol) in 1.5 mL of absolute EtOH was added 1.5 mL of concentrated HCl. The reaction mixture was stirred at reflux for 5 h. Solvent was evaporated and the residue was partitioned between ether and saturated $NaHCO_3$ solution. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and preparative TLC on silica gel with benzene/ether (1:1) gave 26 mg (69%) of a white solid: mp 154–155 °C; IR ($CHCl_3$) 3405 cm^{-1}; NMR ($CDCl_3$) δ 2.50 (s, 3 H), 4.00 (s, 3 H), 6.37 (s, 1 H), 6.6–7.9 (m, 4 H), and 9.02 (s, 1 H); mass spectrum, m/e (M^+) 228.

(3,4-Dimethoxyphenoxy)methyl Ethyl Ether (21). To a stirred solution of NaH (50% oil dispersion, washed three times with *n*-hexane, 0.48 g, 20.0 mmol) in 8 mL of dry DMF at 0 °C was slowly added 3.10 g (20.0 mmol) of phenol **20**[19] in 8 mL of dry DMF; 1.92 g (20.0 mmol) of chloromethyl ethyl ether was added over 30 min. The reaction mixture was stirred at 0 °C for 10 min and quenched with wet ether. The resulting solution was partitioned between ether and H_2O. The organic phase was washed with H_2O five times and dried over $MgSO_4$. Concentration and distillation at 122 °C (1.3 mm) gave 3.74 g (86%) of a colorless liquid: IR ($CHCl_3$) 1598 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3 H), 3.72 (q, J = 7 Hz, 2 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 5.12 (s, 2 H), and 6.61 (m, 3 H).

(3,4-Dimethoxy-2-methylphenoxy)methyl Ethyl Ether (22). To a stirred solution of ether **21** (3.26 g, 15.3 mmol) in 10 mL of dry THF was added 11.0 mL of *n*-butyllithium (1.90 M, 1.25 equiv). The reaction mixture was stirred at room temperature for 1 h. To this was added 7.5 g (excess) of methyl iodide in 5 mL of dry THF. The reaction mixture was stirred at room temperature for 2 h and quenched with H_2O. Solvent was evaporated and the residue was partitioned between ether and H_2O. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Concentration and distillation at 145 °C (3.5 mm) gave 2.55 g (73%) of a colorless liquid: IR ($CHCl_3$) 2880, 1424 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3 H), 2.17 (s, 3 H), 3.72 (q, J = 7 Hz, 2 H), 3.78 (s, 6 H), 5.14 (s, 2 H), 6.62 (d, J = 9 Hz, 1 H), and 6.79 (d, J = 9 Hz, 1 H).

3,4-Dimethoxy-2-methylphenol (23). Concentrated HCl (0.02 mL) was added dropwise to a stirred solution of ether **22** (2.48 g, 10.8 mmol) in 15 mL of 99% EtOH. The resulting solution was stirred at reflux for 2 h. Solvent was evaporated and the residue was partitioned between ether and saturated $NaHCO_3$ solution. The organic phase was washed with H_2O and saturated NaCl solution and dried over $MgSO_4$. Solvent was removed and the residue was chromatographed on silica gel. Elution with benzene/ether (8:1) gave 1.23 g (67%) of a white solid: mp 99–100 °C; IR ($CHCl_3$) 3598, 3400 cm^{-1}; NMR ($CDCl_3$) δ 2.18 (s, 3 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 5.58 (br s, 1 H), 6.43 (d, J = 9 Hz, 1 H), and 6.64 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.42.

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Sworin for assistance in recording spectra.

Registry No. 5a, 935-50-2; **5b**, 64701-03-7; **5c**, 72796-36-2; **5d**, 57197-23-6; **5e**, 72796-37-3; **6a**, 72796-38-4; **6b**, 72796-39-5; **6c**, 72796-40-8; **6d**, 72796-41-9; **7a**, 72796-42-0; **7b**, 72796-43-1; **7c**, 72796-44-2; **8**, 72796-45-3; **9**, 72796-46-4; **10a**, 72796-47-5; **10b**, 72796-48-6; **11**, 7287-51-6; **12a**, 72796-49-7; **12b**, 72796-50-0; **12c**, 72811-85-9; **13**, 72796-51-1; **14**, 72796-52-2; **15**, 72796-53-3; **16**, 72796-54-4; **17**, 72796-55-5; **18**, 72796-24-8; **19**, 72796-25-9; **20**, 2033-89-8; **21**, 72796-26-0; **22**, 72796-27-1; **23**, 50827-64-0; 2-methyl-3,4-dimethoxyphenol, 50827-64-0; 4,8-dimethoxy-1-naphthol, 3843-55-8; diethyl malonate, 105-53-3; ethyl 2-cyanopropionate, 1572-99-2; ethyl acetoacetate, 141-97-9; chloromethyl ethyl ether, 3188-13-4; methyl iodide, 74-88-4.

Conformation of 1-Thiacyclooctan-5-one

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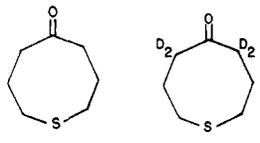
^1H and ^{13}C NMR spectra of 1-thiacyclooctan-5-one (1) have been measured from room temperature to −150 °C. One dynamic NMR effect is observed in the ^{13}C spectra; on the other hand, the ^1H NMR spectra show the presence of two such effects. these results show that there are two conformational processes in 1 and that the free-energy barriers associated with these processes are 6.7 and 8.15 kcal/mol. 1 is deduced to have an unsymmetrical boat–chair conformation, and the lower and higher energy barriers are assigned to pseudorotation and ring inversion processes, respectively.

Medium-ring compounds containing carbonyl groups and suitably placed heteroatoms can exhibit transannular interactions.[1] Such interactions are very weak in eight-membered rings when the heteroatom is an ether function,[1c] but are reported to be significantly stronger for the sulfur analogue.[1c] In their original work on 1, Leonard and co-workers[1c] interpreted the high dipole moment (μ = 3.80) in terms of "folded" conformations, but at that time little was known about the relative energies of the conformations of eight-membered rings. Transannular interactions should be reflected in the barriers to conformational processes in these rings.[2] Since the conformations and conformational barriers in cyclooctanone[3] and 1-oxacyclooctan-5-one[2] have been determined, it has become of interest to investigate the conformational properties of 1-thiacyclooctan-5-one (1) for comparison with these two compounds, and we now report a variable-temperature ^1H and ^{13}C NMR study of 1 and of a tetradeuterio derivative of 1.



(1) 1-d_4

Experimental Section

1-Thiacyclootan-5-one was synthesized by the Dieckmann cyclization of diethyl γ,γ'-thiabis(butyrate) using potassium *tert*-butoxide in xylene under high dilution conditions.[1] Sublimation of the compound (1 mm) gave white needles: mp 53–54 °C (lit.[1] 53–54 °C); ^1H NMR ($CDCl_3$, 348 MHz) δ 2.68 (2,8-CH_2), 2.44 (4,6-CH_2), and 2.23 (3,7-CH_2); ^{13}C NMR ($CDFCl_2$–CF_2Cl_2, 50 MHz, ^1H noise decoupled) δ 28.8 (3,7-$^{13}CH_2$), 32.0 (2,8-$^{13}CH_2$), 41.9 (4,6-$^{13}CH_2$), and 219 (^{13}C=O).

Table I. ^{13}C NMR Chemical Shifts in 1-Thiacyclooctan-5-one

temp, °C	sym-metry	chemical shifts, ppm[a] CH_2(3,7)	CH_2(2,8)	CH_2(4,6)	C=O
−70	C_2[b]	28.8	32.0	41.9	219
−140	C_1[b]	23.9, 33.3	30.0, 33.5	38.3, 45.2	219

[a] In parts per million downfield from internal Me_4Si. [b] Time-averaged symmetry.

Table II. NMR Kinetic Parameters for Thiacyclooctan-5-one

nucleus observed	chemical shift separation, Hz	coalescence temp (T_c), °C	k at T_c, s^{-1}	$\Delta G^{\ddagger}$ at T_c, kcal/mol
^1H	66[a]	−105 ± 2	148	8.15 ± 0.1
^1H	238[b]	−125 ± 2	530	6.7 ± 0.1
^{13}C	488[c]	−115 ± 2	1087	6.7 ± 0.1

[a] For protons on C-3 and C-7. [b] For protons on C-2 and C-8. [c] For C-3 and C-7 carbons.

^1H NMR spectra measured on a superconducting solenoid NMR spectrometer operating at 82 kG.[4] The proton spectra were obtained with standard 5-mm sample tubes in a frequency-sweep mode. The ^{13}C spectra were measured on a Bruker WP-200 operating at 47 kG and are Fourier transforms of accumulated free induction decays obtained with 10-mm tubes under the following conditions: 30° pulse angle, 16 K data points, 12500-Hz spectrum width, and an exponential broadening function corresponding to a 2-Hz broadening. A mixture of $CDFCl_2$/CHF_2Cl (1:2) was used as the solvent and a deuterium line of the solvent was employed for lock purposes. All temperatures were measured with a copper-constantan thermocouple situated in the probe a few centimeters below the sample.

Line-shape calculations were carried out with a Fortran program on a Data General Corp. Nova computer.

Results and Discussion

NMR Data. Carbon-13 NMR spectra of 1 have been obtained over the temperature range of −50 to −150 °C,

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