Chemistry of Quinone Derivatives. Quinone Monoketals via Hydrolysis of Electrochemically Derived Quinone Bisketals[1,2]

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The monohydrolysis of nine naphthoquinone bisketals and nine benzoquinone bisketals has been studied. In the acetamido, bromo, methyl, methoxy, and thiomethyl monosubstituted compounds, hydrolysis occurs at the ketal more distant from the substituent. The regiochemistry is nearly exclusive in the naphthoquinone series and is highly selective in the benzoquinone series. For disubstituted benzoquinone and naphthoquinone bisketals, the monohydrolysis is often regiospecific but substituent dependent. The origin of the regioselectivity in the reactions is briefly discussed.

Introduction

Quinone and quinone-derived compounds encompass a wide range of naturally occurring systems. In the synthesis of these systems, the high reactivity of the quinone unit often requires that it be present in protected form. Commonly, the hydroquinone bisether is used as a latent quinone, the quinone moiety being generated by oxidation, while more recently the quinone bisketal has found utility in synthesis.[4-8] There has also been a developing interest in quinone derivatives wherein only one carbonyl group has been blocked. These compounds potentially greatly expand the chemistry of quinone functionalization and have already proven useful in the syntheses of bishomoquinone,[9] cymopol monomethyl ether,[10] the neolignans,[11] ryanodol,[12] asatone,[13] demethoxyisoasatone,[14] cheryllene,[15] β-dolabrin,[16] desacetamidocolchicine,[16] and gymnomitrol.[17]

Monoprotected quinones have been prepared by a variety of methods. Naphthoquinone bromo- and chlorophenoxyhydrins were reported in the early part of this century,[18] and species wherein a quinone carbonyl is masked as a geminal dihalogen[19-22] or diacetate[23] are also well characterized. Solvolysis of an ortho geminal dichloroquinone has also been reported to yield a quinone monoketal.[20] Although these species might permit selective reaction at the remaining quinone carbonyl under appropriate conditions, their preparations are not general and often proceed in low yield. The oxidation of *p*-alkoxyphenols was first reported in 1959,[24] and continued work has shown that a variety of oxidizing agents [ferric chloride,[24] potassium hexacyanoferrate(III),[24] ceric ammonium nitrate,[25,26] tetrachloroquinone,[25,26] *N*-bromosuccinimide,[25,26] manganese dioxide,[27] dichlorodicyanobenzoquinone (DDQ),[27] silver oxide,[27] copper(II)–pyridine complex and oxygen,[28] periodic acid,[29] and thallium(III) nitrate][30] can effect this conversion. The choice of oxidant is substrate dependent; however, fortunately, ferric chloride, thallium(III) nitrate, and DDQ often complement each other as successful oxidants.[31] Even anodic oxidation of *p*-methoxyphenols has been reported as a viable route to some quinone monoketals.[13,14,32] Finally, blocked cyanohydrins have been investigated as a method of protecting one carbonyl of quinones. When the reaction of trimethylsilyl cyanide with aldehydes[33] was extended to quinones,[34] a variety of the monoprotected compounds was obtained in high yield and often with good regioselectivity.

We have recently reported that the Belleau–Weinberg

(1) Part of this paper has been taken from the Ph.D. dissertations of M. J. Manning (1977) and D. R. Henton (1979), The Ohio State University.

(2) Some of the work presented here has been published in preliminary form: (a) Manning, M. J.; Henton, D. R.; Swenton, J. S. *Tetrahedron Lett.* **1977**, 333–337; (b) Henton, D. R.; Chenard, B. L.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1979**, 326–327.

(3) (a) Eastman Kodak graduate fellow, 1978–1979; (b) The Ohio State University Graduate Fellow, 1978–1979.

(4) Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Am. Chem. Soc.* **1976**, *98*, 5008–5010.

(5) Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *Tetrahedron Lett.* **1977**, 2383–2386.

(6) Swenton, J. S.; Jackson, D. K.; Manning, M. J.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6182–6188.

(7) Swenton, J. S.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6188–6195.

(8) Jackson, D. K.; Narasimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989–3990.

(9) (a) Heller, J. E.; Dreiding, A. S.; O'Connor, B. R.; Simmons, H. E.; Buchanan, G. L.; Raphael, R. A.; Taylor, R. *Helv. Chim. Acta* **1973**, *56*, 272–280. (b) Buchanan, G. L.; Raphael, R. A.; Taylor, R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 373–375.

(10) (a) Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1977**, 499–500. (b) Chenard, B. L.; Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 378–384.

(11) (a) Büchi, G.; Mak, C. P. *J. Am. Chem. Soc.* **1977**, *99*, 8073–8075. (b) Büchi, G.; Chu, P. *J. Org. Chem.* **1978**, *43*, 3717–3719.

(12) Deslongchamps, P. *Pure Appl. Chem.* **1977**, *49*, 1329–1359.

(13) Iguchi, M.; Nishijama, A.; Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1977**, 4511–4514.

(14) Iguchi, M.; Nishijama, A.; Terada, Y.; Yamamura, S. *Chem. Lett.* **1978**, 451–454.

(15) Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 1548–1557.

(16) (a) Evans, D. A.; Hart, D. J.; Koelsch, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 4593–4594. (b) Further work on the colchicine synthesis and the utilization of monoprotected quinones was recently published: Evans, D. A.; Hart, D. J.; Koelsch, P. M.; Cain, P. A. *Pure Appl. Chem.* **1979**, *51*, 1285–1300.

(17) Büchi, G.; Chu, P.-S. *J. Am. Chem. Soc.* **1979**, *101*, 6767–6768.

(18) Pummerer, R. *Chem. Ber.* **1919**, *52*, 1403–1413.

(19) Thomson, R. H. *J. Org. Chem.* **1948**, *13*, 371–376.

(20) Kumamoto, S.; Kato, T. *Kôgyô Kagaku Zasshi* **1957**, *60*, 1325–1328; *Chem. Abstr.* **1959**, *53*, 16997*f*.

(21) Taub, D. *Chem. Ind. (London)* **1962**, 558–559.

(22) Burdon, J.; Parsons, I. W. *Tetrahedron* **1975**, *31*, 2401–2422.

(23) Wessely, F.; Sonivel, F. *Monatsch. Chem.* **1950**, *81*, 1055–1070.

(24) Martius, C.; Eilingsfeld, H. *Ann. Chem.* **1959**, *607*, 159–168.

(25) Dürckheimer, W.; Cohen, L. A. *Biochemistry* **1964**, *3*, 1948–1952.

(26) Dürckheimer, W.; Cohen, L. A. *J. Am. Chem. Soc.* **1964**, *86*, 4388–4393.

(27) Coutts, I. G. C.; Humphreys, D. J.; Schofield, K. *J. Chem. Soc. C* **1969**, 1982–1986.

(28) Hewitt, D. G. *J. Chem. Soc. C* **1971**, 2967–2973.

(29) (a) Andersson, G.; Berntsson, P. *Acta Chem. Scand., Ser. B* **1975**, *29*, 948–952. (b) Andersson, G. *Ibid.* **1976**, *30*, 6470. (c) Andersson, G. *Ibid.* **1976**, *30*, 403–416.

(30) McKillip, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nogradi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282–287.

(31) Büchi, G.; Chu, P.; Hoppmann, A.; Mak, C.; Pearce, A. *J. Org. Chem.* **1978**, *43*, 3983–3985.

(32) (a) Nilsson, A.; Ronlan, A.; Parker, V. D. *Tetrahedron Lett.* **1975**, 1107–1110. (b) Nilsson, A.; Palmquist, U.; Pettersson, T.; Ronlan, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 696–707. (c) Nilsson, A.; Palmquist, U.; Pettersson, T.; Ronlan, A. *Ibid.* **1978**, 708–715. (d) Foster, C. H.; Payne, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 2834–2837.

(33) (a) Lidy, W.; Sundermeyer, W. *Chem. Ber.* **1973**, *106*, 587–593. (b) Neef, H.; Muller, R. *J. Prakt. Chem.* **1973**, *315*, 367–374. (c) For additional references, see: Hünig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2062–2067.

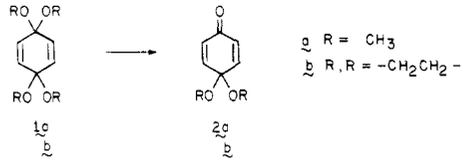
(34) (a) Evans, D. A.; Truesdale, L. K.; Carrol, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55–56. (b) Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822–5823. (c) Evans, D.; Wong, R. *J. Org. Chem.* **1977**, *42*, 350–352.

0022-3263/80/1945-3422$01.00/0

anodic oxidation of 1,4-dimethoxybenzene to benzoquinone bisketal is applicable to a wide variety of functionalized benzene and naphthalene derivatives.[2,35] In view of the ready availability of these systems and because of our synthetic efforts utilizing monoprotected quinones, the monohydrolyses of a variety of benzoquinone and naphthoquinone bisketals have been studied. We report here details which establish this procedure as often the method of choice for preparation of the synthetically versatile quinone monoketals.

Results

Monohydrolysis of Naphthoquinone Bisketals. At the inception of this work, two principal concerns related to the synthetic utility of the reactions. First, were the rates of hydrolysis of the first and second ketals sufficiently different that high yields of the monohydrolysis products would result at complete conversion of the bisketals? Second, would the regiospecificity of the hydrolysis be sufficient to avoid the laborious task involved in physical separation of isomeric monoketals? Previous to our studies only the monohydrolysis of the parent benzoquinone bisketals, **1a** and **1b**, had been studied. While given little

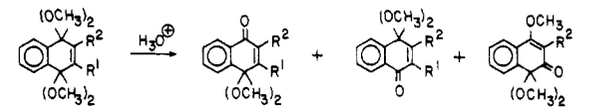


1a **1b** **2a** **2b**

attention until now, this was one of the first routes employed to prepare quinone monoketals.[36] The bis(ethylene glycol ketal) **1b** underwent clean acid-catalyzed hydrolysis to **2b**.[9a] Even though a kinetic study[37] had reported that acid-catalyzed hydrolysis of the second ketal of the methoxy system **1a** was 300 times slower than that of the first, apparently some difficulty had been encountered in taking advantage of this difference.[9b] Hydrolysis of **1a** under literature conditions[36] reportedly gave only benzoquinone. Thus, the conversion of **1a** to **2a** was effected with warm water.[9b] In this work, i.e., Tables I and II, it was observed that selective monohydrolysis of the quinone bisketals to the monoketals could be conveniently performed under appropriate experimental conditions. Only for the hydrolysis of the unsubstituted naphthoquinone bisketal **3** was a significant amount of the quinone (>5–10 mg/g of bisketal) obtained on a regular basis, and this may be due to further hydrolysis during silica gel chromatography. It was found near completion of this work that the use of silica gel that had been washed with 5% aqueous ammonium hydroxide and then distilled water and finally dried at 110 °C overnight prior to chromatography significantly reduced the amount of hydrolysis on silica gel chromatography. This procedure is recommended when hydrolysis of sensitive monoketals to quinones is occurring on chromatography.

The results of all the naphthoquinone bisketal hydrolyses performed are collected in Table I. Before discussion of particular points, several general comments are appropriate. First, consistent results were obtained for some systems only by addition of the acid to the bisketal at low temperature and then allowing the solution to warm to the required temperature for hydrolysis. Second, the time

Table I. Monohydrolysis of Naphthoquinone Bisketals



Bisketal (R^1,R^2)		Monoketal, Yield(%)		Monoketal, Yield(%)		Monoketal, Yield(%)	
3	H,H	12	93		—		
4	CH_3,H	13	90		a		
5	Br,H	14	85		a		
6	SCH_3,H	15	56[d]		a		
7	Br,CH_3	16	94		a		
8	CH_3,$Si(CH_3)_3$	17	57	18	7[b]		
9	SCH_3,CH_3	19	58	20	c		
10	OCH_3,H	21	27		a	22	64
11	OCH_3,CH_3	23	36	24	19	25	24

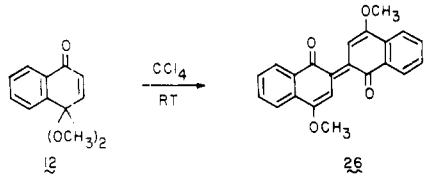
[a] Alternate hydrolysis product not seen. [b] Yield is based on aromatic precursor to **8**. GLC ratio of **17**/**18** was 88:12 in crude mixture. [c] Other isomer not isolated; NMR of Raney Ni reduction products indicated a **19**/**20** ratio of ca. 9:1. [d] Yield is overall from the bromo bisketal **5**.

required for the hydrolyses as described in the experimental section is sometimes critically dependent on the temperature and concentration of the reactants. In performing hydrolyses, it is best to monitor each hydrolysis by GLC (neutralizing aliquots before injection) or TLC. Since the starting bisketals are not easily visualized by fluorescence quenching or iodine staining, spraying the TLC plate with a 7% solution of phosphomolybdic acid in 95% ethanol followed by heating is often advantageous in following the disappearance of starting bisketal. Finally, since most of the anodic oxidations to produce the bisketals are very clean reactions, it is sometimes synthetically expedient to hydrolyze the crude electrolysis product to the monoketal.

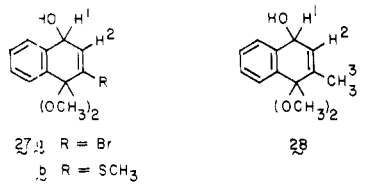
As shown in Table I, the hydrolysis of the bisketals to monoketals often proceeds in high yield with good regioselectivity, affording in some cases exclusively one isomer. Except for monoketals **12** and **17**, all were crystalline solids, and **12**, mp 26–27 °C, could be purified by low-temperature crystallization. In fact, for preparation of **12** on a larger scale, such a procedure would be preferable to the chromatography described in the experimental section. Whereas most monoketals are stable at room temperature for weeks or months at a time, **12** is unstable under these conditions. Whether it is most sensitive to acid, base, or heat is not known, but storage at ambient temperature slowly gives rise to an intensely blue crystalline compound, similar to that described by Willstätter.[38] This same material is formed as blue needles within 1 or 2 days from carbon tetrachloride solutions (NMR samples) of **12** or on distillation of **12**. It is also formed from 4-methoxy-1-naphthol on treatment with base (oxygen not excluded). The structure always assigned to the blue compound in the literature[38] is **26** although no attempt was made on our part to confirm this.

The structures of the monoketals in Table I have been rigorously established by (1) conversion to known compounds and/or (2) reduction with sodium borohydride to the respective alcohols, followed by NMR confirmation of the structure. Thus, **13**, **16**, and **19** were converted to

(35) Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369–377.
(36) Weinberg, N.; Brown, E. A. *J. Org. Chem.* **1966**, *31*, 4054–4058.
(37) Chaturvedi, R.; Adams, J.; Cordes, E. H. *J. Org. Chem.* **1968**, *33*, 1652–1653.
(38) Willstätter, R.; Schuler, L. *Chem. Ber.* **1928**, *61*, 362–372.

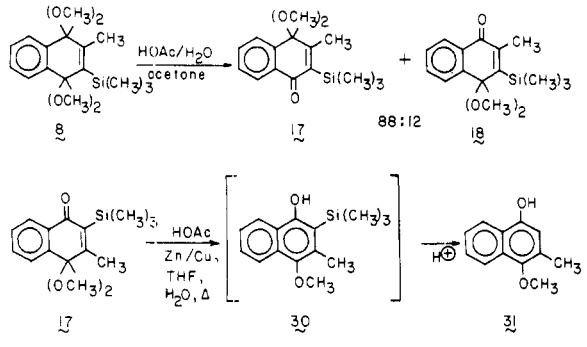


known compounds as outlined previously[2a] (for details, see paragraph at the end of paper about supplementary material). For the monosubstituted monoketals, examination of the NMR spectra of labile alcohols formed with sodium borohydride readily established the orientation shown. Compounds **27a** and **27b** showed the vinyl and tertiary



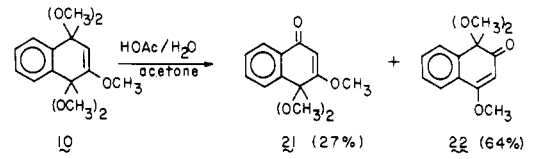
protons as clean doublets (J = 4 Hz) after the hydroxyl proton was exchanged for deuterium with deuterium oxide. Since a close model for the magnitude of the coupling constant could not be found, **13**, whose structure was established chemically,[2a] was reduced to **28**. With the aid of decoupling experiments, the coupling constants for **28** were J_{H^1,H^2} = 3 Hz, J_{H^1,H^3} = 1.2 Hz, and J_{H^2,H^3} = 1.2 Hz. The close agreement between J_{H^1,H^2} in **27a** and **27b** and J_{H^1,H^2} in **28** assures the monoketal assignments as shown.

Only for some disubstituted naphthoquinone bisketals were mixtures of regioisomers obtained, and these were generally separable by silica gel chromatography. For example, the bisketal **8** gave both **17** and **18** on hydrolysis.

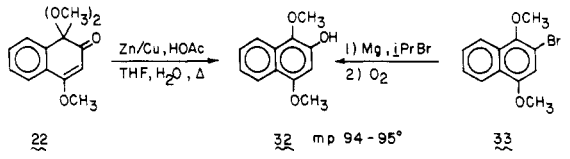


Monoketal **17** was shown to have the structure illustrated by reducing it, presumably to **30** which underwent a facile protiodesilylation under the conditions of the reduction to give the known **31**. At no time did an appreciable amount of **30** build up in the reaction. Once the structure of **17** was confirmed, the structure of **18** was inferred from spectroscopic data as being the other regioisomer. For **9** only the major isomer **19** was isolated. The presence of the alternate regioisomer was established by Raney-nickel reduction of the mixture to the known 2- and 3-methyl-4-methoxy-1-naphthols and NMR analysis of this mixture.

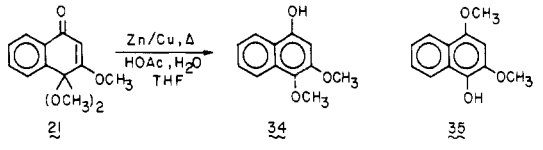
When the 1,4-naphthoquinone bisketal had a methoxy group in the 2-position, a new complication arose in the monohydrolysis. The methoxy group participated in the hydrolysis and part of the product came from attack by water to give β-keto products in addition to the usual α-keto products. For instance, the bisketal **10** gives a 30:70 mixture of **21**/**22**. This ratio of products apparently reflects a kinetic preference for attack by water at the β position, since the two monoketals were not interconvertible under the hydrolysis conditions. The structure of **22** was established by its reduction to the known naphthol



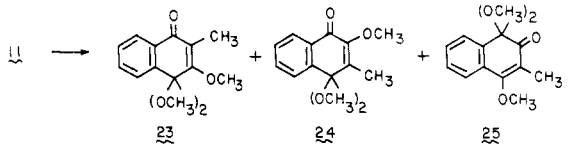
32, an authentic sample of which was synthesized from **33**.



The other monoketal **21** was reduced to the corresponding naphthol **34**, mp 168–173 °C. The only other possible naphthol is **35**, a known compound with a melting point of 77–83 °C.[39,40]

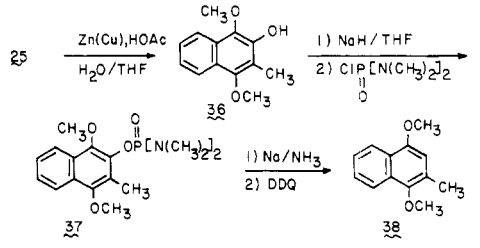


The most complex product mixture was encountered with the hydrolysis of bisketal **11**, all three possible products being obtained in comparable amounts (roughly 5:3:4 **23**/**24**/**25** by NMR). It was eventually found that



monoketal **24** could be easily separated from the mixture by silica gel chromatography, eluting with ether/petroleum ether. Monoketals **23** and **25** had identical R_f values with this solvent system but were readily separated when the eluant was changed to methylene chloride. Although all three components could be separated by using methylene chloride, the separation was much more difficult since **24** was eluted between **23** and **25**, creating overlap problems. This was one system in which using ammonia-washed silica gel instead of silica gel directly as obtained from the manufacturer markedly reduced further hydrolysis of the monoketals.

Since none of the requisite naphthols were known and all positions of the α,β-unsaturated system were substituted, the reactions utilized in previous structure proofs could not be directly applied to **23**–**25**. Thus, the structure of **25** was established by conversion to the known **38** as outlined below. Conceivably, a similar approach could

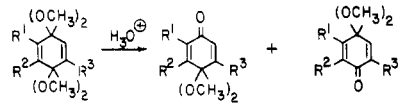


have been used to prove the structures of the two other monoketals; however, the corresponding dimethoxy-

(39) (a) Baldwin, J. E.; Basson, H. H. *J. Org. Chem.* **1969**, *34*, 2788–2790. (b) Brunner, O.; Hanke, P. *Monatsch. Chem.* **1954**, *85*, 88–91.

(40) The workers in ref 39b assign this compound to 1,2,4-trimethoxynaphthalene, but their analytical data and melting point are more in agreement with **35**.

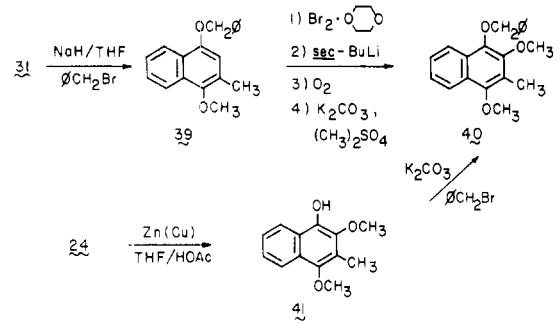
Table II. Monohydrolysis of Benzoquinone Bisketals



Bisketal (R^1,R^2,R^3)		Monoketal, Yield (%)		Monoketal, Yield (%)		Ratio[a]
42	H, H, Br	51	88	52	–	95/5
43	H, H, CH_3	53	64[b]	54	11[b]	85/15
44	H, H, $Si(CH_3)_3$	55	29[b]	56	38[b]	44/56
45	H, H, $CH(CH_3)(OCH_3)$	57	58[b]	58	19[b]	73/27
46	H, H, $NHC(O)CH_3$	59	79		e	
47	CH_3, CH_3, CH_3	60	90		e	
48	H, H, OCH_3	61	66[b]		e,f	
49	H, H, SCH_3	62	60[c]		e	
50	H, H, C(O)Ph[d]	63	42		e	

[a] Ratio determined by GLC, expressed as percent of crude hydrolysis product. [b] Overall yields of purified monoketals, based on the aromatic precursor to the bisketal, are given. [c] Yield is overall from the bisketal **42**. [d] Monohydrolysis performed by B. Chenard. [e] Alternate hydrolysis product not seen. [f] Other products observed; see text and experimental section.

naphthalenes were unknown. So the authentic synthesis of the benzyl ether of one of the naphthols derived from the monoketal was undertaken. While the benzyl ether **40** was prepared in a miserable 6% overall yield from **31**,



all of its spectroscopic properties were identical with those of the reduction–benzylation of monoketal **24** and different from those of the reduction–benzylation product of **23**. With the structures of **24** and **25** now rigorously established, the structure of **23** was assigned on the basis of its spectroscopic properties.

Monohydrolysis of Benzoquinone Bisketals. The results of Table II show that, as in the case of naphthoquinone bisketal hydrolysis, good selectivity was noted in the monohydrolysis of benzoquinone bisketals. However, there is somewhat less selectivity in the monosubstituted benzenoid system relative to the naphthalene system (compare **4** and **5** vs. **42** and **43**). For the monosubstituted 1,4-benzoquinone bisketal systems the structures of the monohydrolysis products were conclusively established by their NMR spectra (see Figure 1). The monoketals wherein the R group was adjacent to the carbonyl showed NMR spectra containing an AB quartet, with the more deshielded proton of the pair being meta coupled. The NMR spectra of the alternate monoketals displayed an AB quartet wherein the more shielded proton of the AB quartet showed meta coupling. For those monoketals wherein the AB quartet and coupling constants were indistinct, the integral for the vinyl region was just as informative. Those monoketals having two protons β to the carbonyl showed two protons which were deshielded relative to the third, whereas those with two protons α to the

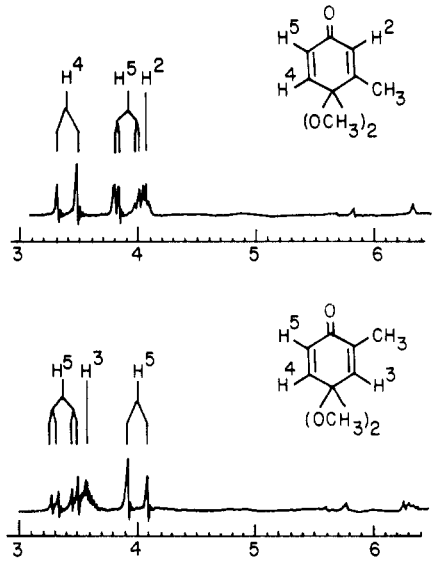
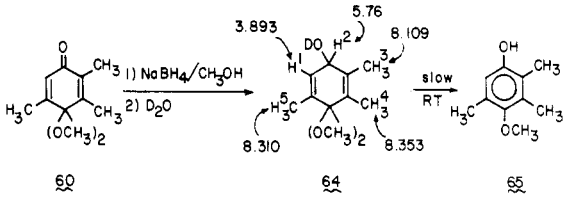


Figure 1. NMR spectra of regioisomers from hydrolysis of **43**.

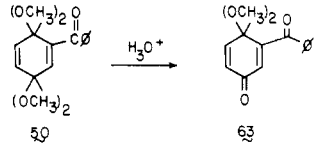
carbonyl had only one proton deshielded relative to the other two.

For monoketals **60** and **63**, the NMR spectra were not considered definitive; therefore, **60** was reduced to the labile alcohol **64** and its NMR spectrum (90 MHz, $CDCl_3$,

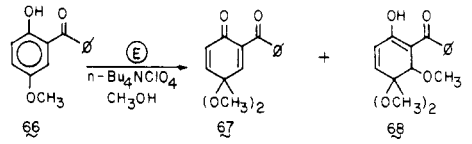


D_2O) analyzed with the aid of decoupling experiments. Some of the coupling constants were not precisely obtainable even with decoupling, since there was coupling over five bonds in some cases. The coupling constants obtained are $J_{H^1,H^2} = 3.5$ Hz, $J_{H^1,H^5} = 1.5$ Hz, J_{H^2,H^3} small, $J_{H^1,H^3} \simeq 0.9$ Hz, $J_{H^3,H^4} \simeq 0.9$ Hz, $J_{H^2,H^4} \simeq 1.3$ Hz. The coupling constant $J_{H^1,H^2} = 3.5$ Hz is only consistent with **64**; thus, monoketal **60** is produced in the monohydrolysis.

Finally, for **63**, even though the AB quartet and the meta



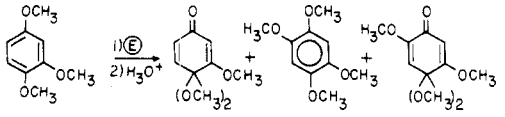
coupling were consistent with the assigned structure, confirmatory evidence was desired. Since the yield of **63** was only 42%, we were concerned with the stability of the alternate regioisomer **67** under the hydrolysis conditions. Electrolysis of **66** afforded **67** and **68**. Since the IR and



NMR spectra of **63** and **67** were clearly different, there can be no doubt about the structure of **63**. As expected, **67** is very susceptible to Michael addition of nucleophiles. A significant amount of the methanol adduct **68** was formed under the neutral conditions of the electrolysis. In fact **67** is converted to **68** to the extent of ~50% upon standing for 24 h at room temperature in methanol. However,

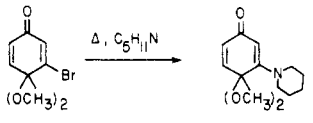
careful examination of the trifluoroacetic acid hydrolysis of **50** in methanol showed no evidence for **67** or **68**. Thus, we tentatively conclude that **67** is not formed appreciably in the monohydrolysis of **50**.

Finally, electrolysis–hydrolysis of **48** does not give the complication recorded for the naphthalene compounds **10** and **11**. However, hydrolysis of the crude electrolysis mixture from 1,2,4-trimethoxybenzene affords **61** in addition to small amounts of **69** and **70**. The latter materials would appear to come from the electrolysis step, but this was not rigorously established.



48 **61** (66%) **69** (~2%) **70** (~2%)

Selected Transformations of Monoketals and Bisketals. While the electrolysis–hydrolysis method serves as a route from hydroquinone dimethyl ethers to quinone monoketals, one limitation is the incompatibility of certain substituents with the anodic oxidation conditions. Aromatic systems having amino and acetamido substituents underwent electrolysis to bisketals only poorly or not at all.[35] However, simply heating **51** with 2 equiv of piperidine gave an 87% recrystallized yield of **71**. Since bromo

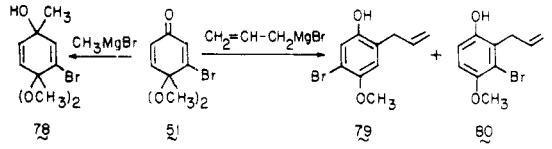


51 **71**

substituents strongly direct hydrolysis of the more distant ketal of the bisketal (i.e., **5**, **7**, **42**), the resulting monoketals are candidates for introduction of a variety of nucleophilic groups by displacement of bromine in a Michael–reverse-Michael reaction sequence.

In the course of structural investigations of the monoketals, it was noted that zinc/copper couple in wet tetrahydrofuran afforded good yields of the methoxynaphthols (Table III). One simple extension was that the naphthols (4-methoxy-1-naphthol and **31**) could be prepared directly from the respective bisketals in yields of 80 and 90% by an in situ hydrolysis–reduction method. The benzoquinone bisketal **42** likewise afforded 3-bromo-4-methoxyphenol in 73% yield.

Finally, the reactions of monoketal **51** with methyl, allyl, and *tert*-butyl Grignard reagents were examined. While addition of methyl Grignard gave the expected tertiary alcohol (84%), allyl Grignard afforded the phenols **79** and **80**, and *tert*-butyl Grignard gave primarily the reduction



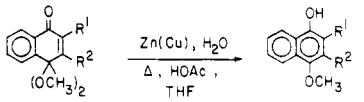
78 **51** **79** **80**

product 3-bromo-4-methoxyphenol. The structures of **79** and **80** were inferred by the production of the same two compounds by Claisen rearrangement of the allyl ether of 3-bromo-4-methoxyphenol. Thus, it appears that addition of organometallics to quinone monoketals may be dramatically dependent upon the nature of the organometallics and probably the structure of the monoketal.

Discussion

The data presented here indicate that a bromo, methoxy, acetamido, thiomethyl, and even a methyl substituent in

Table III. Zinc-Copper Couple Reduction of Monoketals

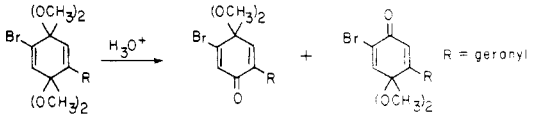


Monoketal (R^1, R^2)		Naphthol	Yield (%)
13	H, CH_3	31	90
14	H, Br	72	77
16	CH_3, Br	73	62
15	H, SCH_3	74	92
21	H, OCH_3	35	88
23	OCH_3, CH_3	41[a]	>90%
24	CH_3, OCH_3	75[a]	>90%

R^1		Yield (%)	
22	H	76	86
25	CH_3	77	69

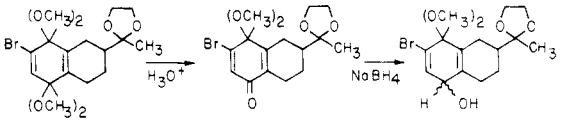
[a] Product not purified.

the monosubstituted bisketals give monoketals in which the ketal hydrolyzed is more distant from the substituent. Interestingly, a trimethylsilyl group has only a small effect on the regioselectivity of the hydrolysis. Two questions derive from these results: (1) will the directing effect of substituents noted here transfer to more complex systems of synthetic interest, and (2) what is the origin of the regioselectivity in these reactions? Two compounds suggest that the regioselectivity in the monohydrolyses noted here is applicable to more complex molecules. In the cymopol monoether synthesis,[10] hydrolysis of **81** was quite selective, yielding **82** and **83** in the ratio 4:1. Furthermore,



81 **82** **83**

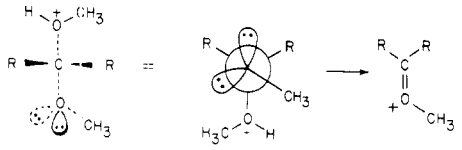
in projected anthracyclinone studies, the triketal **84** was hydrolyzed to **85** in 90% yield. The regiochemistry again involves hydrolysis of the ketal more distant from the bromine, with the ethylene glycol ketal of the methyl ketone remaining essentially untouched. The structure of the monohydrolysis product **85** was rigorously established by sodium borohydride reduction followed by NMR analysis of the resulting epimeric alcohol mixture.



84 **85** **86**

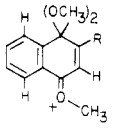
The second point—the origin of the regioselectivity of the molecule—cannot be discussed quantitatively in the absence of kinetic studies. However, a brief discussion of possible origins of the regioselectivity is appropriate. The results noted here could be due to loss of methanol from the protonated bisketal so as to yield the more stable cation. However, with this argument alone, it is not apparent why (1) comparatively substituted naphthoquinone bisketals show higher regioselectivity in their monohydrolysis than their benzoquinone analogues; (2) the hydrolysis of the disubstituted naphthoquinone systems,

Scheme I. Stereochemical Outcome of Ketal Hydrolysis



9 and 11, give mixtures; and (3) hydrolysis of the benzoyl system 50 appears to give exclusively 63.

Stereoelectronic control in ketal and orthoester hydrolysis and in the breakdown in tetrahedral intermediates has been thoroughly discussed,[41,42] and recent evidence strongly supports conformational dependence in ketal hydrolysis.[42b] In the transition state for the loss of the protonated methoxy group from a ketal, the remaining methoxy group should strongly delocalize the resultant positive charge. Thus, as the carbonium ion is formed, all the pictured atoms or groups must be in one plane to achieve the best overlap of one pair of the oxygen's nonbonding electrons with the cation center (Scheme I). Any steric effects generated on approaching this planar intermediate should raise the activation energy for hydrolysis of the ketal. In the monosubstituted naphthalenes only one, 87, of the four possible intermediates is relatively free



87

of steric interaction as the transition state is approached. Two possibilities have methoxy–peri hydrogen interactions, while the third transition state has a methoxy–R interaction. This model adequately explains the hydrolyses of all the monosubstituted naphthoquinone bisketals, 84, and 47. Furthermore, the rather long carbon–silicon bond, and thus the effectively smaller steric effect of the trimethylsilyl group, could explain the small effect of this moiety on the regioselectivity of hydrolysis.

However, extending this explanation to the disubstituted naphthoquinone[43] bisketals and monosubstituted benzoquinone bisketals is difficult because the hydrolyses here also show good selectivity. In the benzenoid series, selectivity is generally better than would be expected from a purely statistical viewpoint. Taking into account stereoelectronic considerations alone for a monosubstituted benzoquinone bisketal leads to the prediction that the hydrolysis ratio should be 2:1 in favor of hydrolysis of the less hindered ketal. Only for the hydrolysis of 45 is this ideal approached; therefore, the steric argument must be modified somewhat. It is reasonable to suppose that variations of the hydrolysis ratio from the predicted 2:1 ratio can be attributed to the additional stabilization or destabilization of the carbonium ion attempting to form at the less substituted end of the molecule. In the case of the disubstituted naphthoquinone bisketals, the substituents may prevent the ketal methoxy group from stabilizing the carbonium ion to its fullest extent. Even the relative size of the substituents could be of importance. Thus, for these disubstituted systems, the relative stabilizing effect of substituents on the carbonium ion intermediate may be the primary factor in determining the ratio of the hydrolysis products. In summary, as long as steric and electronic effects coincide, the hydrolysis will be highly regioselective, perhaps exclusive. Where the effects are competing with each other, the regioselectivity is less predictable.

Finally, it is instructive to compare the electrolysis–hydrolysis route to monoketals with the more standard oxidation of *p*-methoxyphenols. While the latter route requires the availability of the respective *p*-methoxyphenol and can require either expensive and/or toxic oxidizing agents, the former method utilizes the more readily available hydroquinone bisethers and employs aqueous acid for hydrolysis. Even when the *p*-methoxyphenol is available, the anodic oxidation–hydrolysis sequence is an excellent alternative procedure for preparing quinone monoketals. Furthermore, since the anodic oxidations are often very clean reactions, the crude electrolysis product can sometimes be hydrolyzed directly to the monoketal. In view of the recent uses of quinone monoketals, the accessibility of a wider range of these substances via the chemistry reported here opens new uses for these compounds in synthesis.[44]

Experimental Section[45]

Monohydrolysis of Naphthoquinone Bisketals. 3. To the bisketal **3** (1.00 g, 4.0 mmol) in 25 mL of tetrahydrofuran at 0 °C was added 8 mL of 2% aqueous acetic acid. After being stirred for 15 min at ca. 0 °C, it was stirred for an additional 3.25 h at room temperature. At this time, GLC (column A, 130 °C) indicated that the amount of naphthoquinone was increasing; thus, the reaction was quenched with 3–4 mL of saturated sodium bicarbonate solution. The reaction mixture was extracted with ether (4 × 5 mL). The ether was washed with saturated salt solution, 5 mL of benzene was added, and the solvent was removed in vacuo to give 0.817 g of a yellow-orange oil. Chromatography of this material on silica gel (35 g, 1.7 × 30 cm column, slurry

(41) Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463–2490.

(42) (a) For a general discussion of ketal and orthoester hydrolysis, see: Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581–603; Fife, T. *Acc. Chem. Res.* **1972**, *5*, 264–272. (b) Kirby, A. J.; Martin, R. J. *J. Chem. Soc., Chem. Commun.* **1978**, 803–804.

(43) That bisketal 11 gives products resulting from hydrolysis of both ketals may be because the β-methoxyl is held perpendicular to the π system, the nonbonding pairs on oxygen thus being unable to stabilize the carbonium ion, and in fact, destabilizing it inductively.

(44) Quinone monoketals can serve as Michael acceptors for carbanions. While we have examined this for only selected systems, Parker and Kang have examined this reaction more thoroughly (Parker, K. A.; Kang, S. *J. Org. Chem.* **1980**, *45*, 1218–1224).

(45) All melting points were taken with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Measurements of standard samples indicated that the observed melting points were probably 1–2 °C lower than the corrected value. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrometer and calibrated with the polystyrene band at 1601.4 cm^{-1}. ^1H NMR spectra were taken at 60 MHz with a Varian EM-360, EM-360L, or A-60A instrument of solutions in carbon tetrachloride, unless indicated otherwise. ^{13}C NMR spectra (tetramethylsilane reference) were recorded on a Bruker WP-80 instrument at 20.1 MHz by Dr. C. Cottrell. Mass spectra and exact-mass measurements were obtained by Mr. C. R. Weisenberger on a Consolidated Electronics MS-9 double-focusing mass spectrometer (ionization potential 70 eV). Analytical samples were determined by Scandinavian Microanalytical Laboratory, Herlev, Denmark, and were within 0.3% of calculated values. Aluminum oxide and silica gel were from E. Merck Co. In certain systems the silica gel was washed with 5% aqueous ammonia and distilled water and dried overnight at 110 °C prior to use in order to minimize acid-catalyzed hydrolysis of sensitive monoketals. Tetrahydrofuran was distilled from benzophenone ketyl directly into the reaction flask. *n*-Butyllithium in hexane, *sec*-butyllithium in cyclohexane, and methyllithium/lithium bromide complex in ether were obtained from Ventron Corp. and were titrated in tetrahydrofuran with triphenylmethane as the indicator. Ether (E), petroleum ether (PE, bp 35–50 °C), and all other solvents used in chromatography were dried and distilled before use. Three GLC columns were used for various purposes: column A, $^1/_8$ in. × 1 ft, 5% SE-30 on 60/80 mesh Chromasorb G; column B, $^1/_8$ in. × 6 ft, 3% SE-30 on 60/80 mesh Chromasorb G; and column C, $^1/_8$ in. × 25 ft, 5% SE-30 on 60/80 mesh Chromasorb G. The term workup implies extraction with ether, drying over Drierite, and concentration in vacuo. Where an extraction was already performed, only the last two operations would be valid. Unless noted otherwise, all reactions were performed under nitrogen.

packed in 3% E/PE) proceeded as follows: 100 mL of 3% E/PE, nil; 350 mL of 5% E/PE, nil; 125 mL of 5% E/PE, 100 mL of 7% E/PE, and 20 mL of 10% E/PE, naphthoquinone, 0.046 g; 80 mL of 10% E/PE, trace of monoketal and naphthoquinone; 175 mL of 12% E/PE and 120 mL of 15% E/PE, monoketal, 0.766 g (93%). This material was a clear oil at room temperature but crystallized in the refrigerator, remelting over the range of 26–27 °C. A small amount was molecularly distilled [bath 60 °C (0.05 mm)] for the analytical sample: IR (neat, NaCl) cm^{-1} 2937 (m), 2828 (m), 1670 (s), 1629 (m), 1600 (m), 1458 (m), 1387 (m), 1303 (s), 1248 (m), 1209 (w), 1140 (m), 1072 (s), 982 (m), 895 (w), 847 (w), 773 (s), and 684 (w); NMR τ 1.87–2.10 (m, 1 H), 2.25–2.80 (m, 3 H), 3.32 (AB q, J = 10 Hz, $\Delta\nu$ = 25.3 Hz, 2 H), 6.84 (s, 6 H).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.86; H, 6.15.

4. A solution of 1.50 g (5.7 mmol) of the bisketal **4** in 24 mL of acetone was cooled to 0 °C, and 10 mL of 2% aqueous acetic acid was added over 5 min, the progress of the reaction being monitored by GLC (column A, 130 °C). After 1.75 h, the hydrolysis was complete, and 12 mL of saturated sodium bicarbonate was added dropwise to neutralize the reaction mixture. The reaction mixture was extracted with ether (3 × 20 mL) and worked up to yield 1.24 g of a yellow solid which was recrystallized from E/PE to give 1.12 g (90%) of **13** as a light-yellow crystalline solid, mp 63.5–65 °C. An additional recrystallization raised the melting point to 64–65 °C: IR (KBr) cm^{-1} 2942 (m), 2832 (m), 1666 (s), 1637 (s), 1604 (s), 1585 (m), 1458 (m), 1445 (m), 1385 (m), 1319 (s), 1309 (s), 1270 (s), 1251 (m), 1220 (m), 1165 (m), 1086 (s), 1046 (s), 1024 (m), 946 (s), 916 (s), 772 (s), 701 (m), 690 (m), 657 (m), and 359 (m); NMR τ 1.87–2.17 (m, 1 H), 2.25–2.75 (m, 3 H), 3.58 (q, J = 1 Hz, 1 H), 7.12 (s, 6 H), 8.03 (d, J = 1 Hz, 3 H); exact mass for $C_{13}H_{14}O_3$ calcd m/e 218.0943, obsd m/e 218.0946, difference 0.0003.

5. To 0.720 g (2.2 mmol) of the bisketal **5** dissolved in 15 mL of tetrahydrofuran was added 15 mL of 1 N HCl and the mixture stirred at room temperature for 1.5 h. The mixture was neutralized with saturated sodium bicarbonate solution, extracted with ether (2 × 15 mL), and worked up as usual to afford a light-yellow solid, which was crystallized from E/PE to yield 0.496 g (85%) of pure monoquinone ketal **14** as a white, crystalline solid: mp 52–53 °C; IR (KBr) cm^{-1} 3050 (m), 1662 (s), 1309 (s), 1296 (s), 1253 (s), 1097 (s), 918 (m), 818 (m), 776 (s); NMR (CCl_4) τ 1.85–2.1 (m, 1 H), 2.2–2.5 (m, 3 H), 2.91 (s, 1 H), 7.00 (s, 6 H); exact mass for $C_{12}H_{11}O_3Br$ calcd m/e 281.9892, obsd m/e 281.9897, difference 0.0005.

6. To a stirred, cooled (−75 °C) solution of 0.980 g (2.98 mmol) of the bromo ketal **5** in 12 mL of dry tetrahydrofuran was added 1.4 mL of a 2.1 M solution of *n*-butyllithium dropwise via syringe, the system maintained under nitrogen. After the solution was stirred for 1 min at −75 °C, 0.256 g (2.98 mmol) of dimethyl disulfide dissolved in 1 mL of dry tetrahydrofuran was added via syringe while keeping the reaction temperature at −75 °C. The mixture was stirred at −75 °C for 30 min and then quenched with water (5 mL). The mixture was extracted with ether (2 × 15 mL) and worked up as usual to afford a yellow solid. The crude product was chromatographed on basic alumina (activity III, 24 × 1.5 cm column). Elution proceeded as follows: 70 mL of 10% E/PE, nil; 50 mL of 10% E/PE, 0.130 g of 1,1,4,4-tetramethoxy-1,4-dihydronaphthalene; 150 mL of 10% E/PE, 0.500 g of a white solid. The white solid was dissolved in 5 mL of acetone and cooled to 0 °C with stirring. Cold 2% acetic acid (5 mL) was added and the mixture stirred for 10 min at 0 °C. The solution was neutralized with saturated sodium bicarbonate solution and extracted with methylene chloride (2 × 20 mL); the organic layer was washed with saturated brine solution (5 mL) and dried over calcium sulfate; the solvent was removed in vacuo to afford a yellow solid, which was crystallized from E/PE to yield 0.415 g (56% yield based on the bromo bisketal) of pure **15** as a yellow solid: mp 85–86 °C; IR (KBr) cm^{-1} 2940 (w), 2840 (w), 1640 (s), 1568 (s), 1325 (s), 1260 (s), 1085 (s), 870 (m), 775 (m); NMR (CCl_4) τ 1.8–2.05 (m, 1 H), 2.25–2.7 (m, 3 H), 3.63 (s, 1 H), 7.03 (s, 6 H), 7.57 (s, 3 H); exact mass for $C_{13}H_{13}O_3S$ calcd m/e 250.0664, obsd m/e 250.0667, difference 0.0003.

7. To the bisketal **7** (0.200 g, 0.58 mmol) dissolved in 10 mL of tetrahydrofuran was added 10 mL of 1 N HCl, and the mixture was stirred at room temperature for 1 h. The mixture was neutralized with saturated sodium bicarbonate solution, extracted with ether (2 × 15 mL), and worked up as usual to afford a yellow solid, which was crystallized from E/PE to yield 0.164 g (94%) of pure quinone monoketal **16** as a light-yellow solid: mp 102–103 °C; IR (KBr) cm^{-1} 3000 (w), 1660 (s), 1320 (s), 1275 (s), 1095 (s), 960 (m), 785 (s), 715 (m), 655 (m); NMR (CCl_4) τ 1.8–2.1 (m, 1 H), 2.2–2.6 (m, 3 H), 7.08 (s, 6 H), 7.76 (s, 3 H); exact mass for $C_{13}H_{13}O_3Br$ calcd m/e 296.0049, obsd m/e 296.0053, difference 0.0004.

8. The crude bisketal **8** (1.10 g, 3.27 mmol) was dissolved in 25 mL of tetrahydrofuran and cooled in ice, and 25 mL of chilled 2% acetic acid in water was added slowly with stirring. The bisketal precipitated out, but the mixture was kept emulsified by vigorous stirring. The temperature was allowed to climb to 35 °C and the mixture was stirred for 8.5 h. The reaction was monitored by checking neutralized aliquots by GLC (column A, 165 °C). The reaction was worked up by pouring into 25 mL of saturated sodium bicarbonate solution and then extracting with ether (3 × 10 mL). Workup as usual gave 0.979 g of a yellow oil which was a 12:88 mixture of monoketals **18** and **17** by GLC (column B, 195 °C). This was chromatographed on 130 g of ammonia-washed silica gel slurry packed in 3% E/PE, with elution proceeding as follows: 100 mL of 3% E/PE, 100 mL of 5% E/PE, and 250 mL of 7% E/PE, 21 mg of unknown material; 40 mL of 7% E/PE and 80 mL of 10% E/PE, 8 mg of quinone; 80 mL of 10% E/PE, nil; 140 mL of 10% E/PE, 91.5 mg of monoketal **18** (mp 69–82 °C). This was recrystallized from 1 mL of PE at low temperature to give 70 mg (7.4%) of **18**, mp 82–84.5 °C. The analytical sample melted at 83.5–85 °C: IR (KBr) cm^{-1} 2994 (w), 2836 (w), 1652 (s), 1597 (m), 1324 (w), 1277 (s), 1258 (s), 1221 (w), 1083 (s), 1021 (w), 951 (w), 870 (m), 858 (m), 783 (m), 775 (shld), 725 (w); NMR τ 1.88–2.16 (m, 1 H), 2.36–2.81 (m, 3 H), 7.10 (s, 6 H), 7.86 (s, 3 H), 9.66 (s, 9 H); exact mass for $C_{16}H_{22}SiO_3$ calcd m/e 290.1338, obsd m/e 290.1345, difference 0.0007.

Continued elution proceeded as follows: 40 mL of 12% E/PE, 62 mg of a 1:2.2 mixture of **18** and **17** (by GLC); 60 mL of 12% E/PE and 200 mL of 15% E/PE, 0.614 g of monoketal **17** (65%) as a clear oil. This was molecularly distilled [125–130 °C (0.1 mm)] to give 0.54 g (57%) of **17** as a thick, faintly yellow oil: IR (neat, NaCl) cm^{-1} 2944 (m), 2830 (m), 1647 (s), 1600 (m), 1580 (m), 1457 (m), 1316 (s), 1281 (s), 1255 (s), 1229 (m), 1188 (m), 1082 (s), 1049 (m), 1038 (m), 1029 (m), 958 (m), 871 (s), 851 (s), 822 (m), 776 (s); NMR τ 1.80–2.17 (m, 1 H), 2.28–2.75 (m, 3 H), 7.13 (s, 6 H), 7.93 (s, 3 H), 9.68 (s, 9 H); exact mass for $C_{16}H_{22}SiO_3$ calcd m/e 290.1338, obsd m/e 290.1345, difference 0.0007.

Continued elution with 300 mL of 15% E/PE gave 68 mg of a 3.5:1 (by GLC) mixture of **17** and the bisketal.

9. To a stirred, cooled (−60 °C) solution of 0.626 g (1.8 mmol) of **7** in 20 mL of dry tetrahydrofuran was added 0.85 mL of a 2.1 M solution of *n*-butyllithium dropwise via syringe, the system being maintained under nitrogen. After the solution was stirred for 1 min at −60 °C, 0.172 g (1.8 mmol) of dimethyl disulfide dissolved in 1 mL of dry tetrahydrofuran was added via syringe, keeping the reaction temperature at −60 °C. The mixture was stirred for 30 min at −60 °C and then quenched with water (5 mL). The mixture was extracted with ether (2 × 10 mL) and worked up as usual to afford a yellow solid, which was crystallized from E/PE to yield 0.536 g (96%) of pure, light-yellow product: mp 100–101 °C; IR (KBr) cm^{-1} 2930 (w), 1265 (m), 1225 (m), 1080 (s), 1025 (m), 780 (m); NMR (CCl_4) τ 1.94 (s, 3 H), 2.55 (s, 3 H), 2.88 (s, 6 H), 2.98 (s, 6 H), 7.2–7.6 (m, 4 H); exact mass for $C_{16}H_{22}O_4S$ calcd m/e 310.1239, obsd m/e 310.1244, difference 0.0005.

To a stirred solution of 0.350 g (1.13 mmol) of the bisketal **9** in 12 mL of acetone was added 12 mL of 0.1 N HCl, the mixture being stirred at room temperature for 30 min. The mixture was neutralized with 10% sodium bicarbonate solution, extracted with ether (2 × 15 mL), and worked up to afford 0.274 g (92%) of a yellow oil which was about 94% pure monoquinone ketal **19** (by NMR). The oil solidified upon cooling and was crystallized at low temperature from E/PE to yield 0.172 g (58%) of pure quinone monoketal **19**: mp 38–40 °C; IR (KBr) cm^{-1} 2940 (m), 1650 (s), 1340 (s), 1320 (s), 1275 (s), 1085 (s), 850 (m), 780 (m), 712 (m); NMR (CCl_4) τ 2.07 (s, 3 H), 2.79 (s, 3 H), 2.98 (s, 6 H), 7.2–7.7 (m, 3 H), 7.8–8.2 (m, 1 H); exact mass for $C_{14}H_{16}O_3S$ calcd m/e 264.0820, obsd m/e 264.0827, difference 0.0007.

10. The bisketal **10** (2.393 g, 8.54 mmol) was dissolved in 7.5 mL of acetone, and, with stirring, 40 mL of water was added, followed by 1.2 mL of acetic acid. The mixture was stirred for 20 min, after which the acid was neutralized with saturated sodium bicarbonate solution. A precipitate formed which consisted of the two monoketals. The yellow solution was extracted with ether (4 × 15 mL) and worked up as usual to give 1.944 g of a yellowish solid which was a 1.9:1 mixture of **22** and **21** by NMR. This material was chromatographed on 60 g of silica gel (33 × 2.3 cm, slurry packed in 45% E/PE) as follows: 150 mL of 45% E/PE and 100 mL of 50% E/PE, nil; 180 mL of 55% E/PE, 1.312 g of **22**. This was recrystallized from methanol/PE, giving 1.272 g (64%) of **22**, mp 100–102.5 °C. The analytical sample (sublimed, 85 °C (0.04 mm)) had a melting point of 101.9–102.8 °C: IR (KBr) cm^{-1} 2939 (m), 2833 (w), 1649 (vs), 1615 (vs), 1568 (s), 1460 (shld), 1448 (m), 1441 (shld), 1379 (vs), 1277 (m), 1253 and 1241 (s), 1209 (m), 1150 (m), 1080 (vs), 1018 (m), 1005 (m), 978 (m), 969 (m), 836 (s), 813 (m), 790 (s), 765 (m), 698 (w); NMR (CCl_4/$CDCl_3$) τ 2.12–2.82 (m, 4 H), 4.48 (s, 1 H), 6.07 (s, 3 H), 6.77 (s, 6 H); UV (CH_3OH) 229 nm (log ϵ 4.29), 316 (3.95).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.67; H, 5.99.

Continued elution showed the following: 20 mL of 55% E/PE and 10 mL of 60% E/PE, nil; 210 mL of 60% E/PE, 0.561 g of **21**. Recrystallization from methanol/PE gave 0.540 g (27%) as white needles, mp 100.5–101.5 °C. The analytical sample (sublimed, 85 °C (0.04 mm)) melted at 100.5–101.7 °C: IR (KBr) cm^{-1} 2944 (w), 2832 (w), 1645 (vs), 1621 (vs), 1598 (m), 1578 (s), 1459 (m), 1442 (shld, w), 1356 (s), 1336 (m), 1269 (m), 1239 (vs), 1212 (m), 1191 (s), 1166 (m), 1096 (vs), 1067 (s), 1022 (s), 869 (w), 810 (w), 798 (m), 783 (w); NMR τ 1.88–2.14 (m, 1 H), 2.29–2.74 (m, 3 H), 4.22 (s, 1 H), 6.11 (s, 3 H), 6.89 (s, 6 H); UV (CH_3OH) 248 nm (log ϵ 4.03), 284 (3.90).

Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.73; H, 6.15.

11. The bisketal **11** (1.25 g, 4.25 mmol) was dissolved in 20 mL of acetone at room temperature and stirred vigorously (magnetic stirrer). A 4 vol % solution of acetic acid in water (20 mL) was added over a period of about 1 min. The hydrolysis was monitored by GLC (column B, 180 °C). The peak for the product(s) had a lower retention time shoulder. The bright-yellow reaction mixture was quenched after 45 min by the addition of 20 mL of saturated sodium bicarbonate. The mixture was extracted with 20 mL of ether, followed by additional ether (3 × 10 mL), and worked up as usual to afford 1.065 g of a yellow oil showing two spots by TLC (40% E/PE, silica gel): R_f 0.44, mixture of **23** and **25**; R_f 0.33, **24**. An NMR spectrum indicated the three components (**25**/**23**/**24**) to be present in the ratio 4:4.9:3. This mixture was chromatographed on 100 g of silica gel slurry packed in 15% E/PE as follows: 105 mL of 15% E/PE and 190 mL of 20% E/PE, nil; 85 mL of 30% E/PE, trace of 2-methoxy-3-methylnaphthoquinone; 65 mL of 30% E/PE, nil; 170 mL of 30% E/PE, 0.73 g of a mixture of **23** and **25**; 85 mL of 30% E/PE, 0.153 g of a mixture of **23**–**25**; 105 mL of 30% E/PE and 85 mL of 40% E/PE, 0.151 g of monoketal **24**. The 153-mg mixture was rechromatographed on 50 g of silica gel slurry packed in 15% E/PE to give 88 mg of **24** for a total yield of 0.237 g, mp 57–63.5 °C. One recrystallization from 1.5 mL of 1:2 E/PE at low temperature gave 199 mg (19%) of **24**: mp 64–66 °C; IR (KBr) cm^{-1} 2992 (w), 2948 (w), 2924 (w), 2828 (w), 1669 (vs), 1648 (m), 1602 (m), 1455 (m), 1373 (w), 1325 (w), 1287 (s), 1265 (s), 1231 (m), 1212 (s), 1176 (m), 1081 (vs), 1042 (m), 1029 (s), 917 (s), 779 (s); NMR τ 1.88–2.18 (m, 1 H), 2.30–2.78 (m, 3 H), 6.18 (s, 3 H), 7.16 (s, 6 H), 8.12 (s, 3 H); UV (CH_3OH) 224 nm (ϵ 10300), 249 (9540), 287 (5480); exact mass for $C_{14}H_{16}O_4$ calcd m/e 248.1049, obsd m/e 248.1055, difference 0.0006.

The mixture of **23** and **25** was cleanly separated by TLC on silica gel using methylene chloride as the eluant: **25**, R_f 0.14; **23**, R_f 0.28. Thus, by use of a column of ammonia-washed silica gel (160 g), the 0.773 g mixture of **23** and **25** was separated as follows: 630 mL of CH_2Cl_2, 11 mg of unknown material; 1050 mL of CH_2Cl_2, 0.401 g of monoketal **23** (mp 45–47.5 °C). Monoketal **23** was recrystallized from 2 mL of PE at low temperature to give 379 mg (36%): mp 47–48 °C; IR (KBr) cm^{-1} 2952 (m), 2926 (m, shld), 2852 (w), 2830 (w), 1650 (s), 1627 (m), 1601 (m), 1584 (m), 1458 (m, br), 1373 (m), 1346 (m), 1294 (s), 1266 (m), 1242 (s), 1208 (m), 1172 (m), 1160 (m), 1075 (vs), 1009 (m), 954 (m), 923 (m), 775 (m), 702 (m); NMR τ 1.85–2.22 (m, 1 H), 2.35–2.78 (m, 3 H), 5.78 (s, 3 H), 7.02 (s, 6 H), 8.12 (s, 3 H); UV (CH_3OH) 230 nm (ϵ 12900), 248 (9740), 294 (5900), 310 (shld, 4720); exact mass for $C_{14}H_{16}O_4$ calcd m/e 248.1049, obsd m/e 248.1055, difference 0.0006.

Continued elution gave the following: 315 mL of CH_2Cl_2, 6 mg of unknown material; 40 mL of CH_2Cl_2 and 790 mL of 1% CH_3OH/CH_2Cl_2, 0.286 g of **25** as a yellow oil. The monoketal was recrystallized from 1.8 mL of 1:5 E/PE at low temperature to give 257 mg (24.4%) of **25**: mp 29–30.5 °C as a light-yellow solid; IR (neat, NaCl) cm^{-1} 2942 (m), 2840 (m), 1668 (s, br), 1623 (s), 1600 (m, shld), 1576 (m), 1486 (m), 1442 (m, br), 1377 (m), 1330 (s), 1305 (s), 1276 (s), 1259 (s), 1249 (s, shld), 1196 (m), 1156 (m), 1132 (m), 1076 (vs, br), 1046 (s, shld), 1018 (m), 1004 (m), 982 (s, shld), 969 (s), 936 (s), 818 (m), 792 (m), 773 (s); NMR τ 2.26–2.89 (m, 4 H), 6.16 (s, 3 H), 6.83 (s, 6 H), 8.10 (s, 3 H); UV (CH_3OH) 232 nm (ϵ 18500), 325 (7160); exact mass for $C_{14}H_{16}O_4$ calcd m/e 248.1049, obsd m/e 248.1055, difference 0.0006.

Monohydrolysis of Benzoquinone Bisketals. 42. A solution of 7.863 g (28.2 mmol) of **42** was dissolved in 80 mL of acetone and cooled to 0–5 °C in an ice bath after which, with rapid stirring, 40 mL of chilled 2% acetic acid in water was added. The mixture was allowed to warm to ~27 °C and was stirred for 7.25 h (until GLC indicated disappearance of starting material). The ratio of hydrolysis products was found to be 95:5 (**51**/**52**) by GLC (column C, 190 °C). The reaction was stopped by adding 40 mL of saturated sodium bicarbonate solution, and the product was extracted with ether (5 × 15 mL). Workup as usual afforded an orange oil which was filtered through 10 g of silica gel to remove color, using 20% E/PE as the eluant. Removal of solvent gave 6.313 g of a yellow oil (96% crude). One recrystallization at low temperature from 10 mL of 1:1 E/PE gave 5.828 g (89%) of **51** as a pale-yellow oil at room temperature showing <2% **52** and <1% **42** by NMR: IR (neat, NaCl) cm^{-1} 2949 (m), 2847 (w), 1673 (vs), 1635 (m), 1604 (s), 1463 (m), 1385 (m), 1318 (m), 1288 (s), 1222 (m), 1195 (m), 1090 (s, v br), 1021 (w), 984 (m), 964 (s), 896 (m), 829 (w), 729 (w); NMR τ 3.33 (m) and 3.48 (AB q, J = 10.1 Hz, $\Delta\nu$ = 28.9 Hz, "B" meta coupled, J = 1.8 Hz, 3 H), 6.74 (s, 6 H); exact mass for $C_8H_9O_3{}^{79}Br$ calcd m/e 231.9736, obsd m/e 231.9739, difference 0.0003.

43. A solution of 5.00 g (0.0329 mol) of 2-methyl-1,4-dimethoxybenzene was electrolyzed in 100 mL of 2% sodium methoxide in methanol for 1.75 h at 1.4–1.6 A at 15–25 °C. The reaction was worked up as before to give 6.308 g (90%, crude) of the bisketal **43** as a pale-yellow oil containing <10% of the monoketals by GLC (column B, 160 °C). This oil was dissolved in 100 mL of acetone and cooled to 0 °C, and 25 mL of chilled 2% acetic acid was slowly added with vigorous stirring. The reaction was maintained at 0 °C for 20 min, then allowed to warm to room temperature, and stirred an additional 0.5 h. The reaction was quenched by adding 25 mL of 10% sodium bicarbonate solution, and the mixture was extracted with 50 mL of ether, followed by ether (3 × 15 mL). Workup gave 5.325 g of a yellow oil which was an 85:15 mixture of the two monoketals (**53**/**54**) by GLC (column C, 165 °C). This was chromatographed on 195 g of silica gel (3.7 × 60 cm) slurry packed in 5% E/PE as follows: (25-mL fractions) 200 mL of 5% E/PE, 200 mL of 10% E/PE, 225 mL of 15% E/PE, and 675 mL of 20% E/PE, nil; 250 mL of 20% E/PE, trace of quinone; 175 mL of 20% E/PE, mixture, primarily **54**; 50 mL of 20% E/PE and 400 mL of 25% E/PE, monoketal **54**, 0.677 g. The crude monoketal was molecularly distilled at 105–110 °C (bath temperature, 10 mm) to give 0.590 g (10.7%) as a pale-yellow oil: IR (neat, NaCl) cm^{-1} 2934 (m), 2826 (m), 1678 (s), 1649 (s), 1453 (m), 1398 (w), 1382 (m), 1370 (m), 1315 (m), 1299 (m), 1250 (m), 1204 (m), 1156 (m), 1129 (s), 1088 (vs), 1072 (s), 1048 (s), 1026 (m), 969 (vs), 883 (w), 824 (m); NMR τ 3.51 (m) and 3.64 (AB q, J = 10.0 Hz, $\Delta\nu$ = 36 Hz, "A" meta coupled, J = 3.2 Hz, 3 H), 6.73 (s, 6 H), 8.15 (d, J = 1.4 Hz, 3 H); exact mass for $C_9H_{12}O_3$ calcd m/e 168.0786, obsd m/e 168.0790, difference 0.0004.

Continued elution gave the following: 25 mL of 25% E/PE and 25 mL 30% E/PE, 43-mg mixture of **53** and **54**; 100 mL of 30% E/PE, 300 mL of 20% E/PE, 300 mL of 35% E/PE, and 525 mL of 40% E/PE, 3.772 g of monoketal **53**. The monoketal was distilled at 105–110 °C (bath temperature, 10 mm) in a

molecular still to give 3.606 g (64.3%) of **53** as a pale-yellow oil at room temperature, which was crystalline in the refrigerator: IR (neat, NaCl) cm^{-1} 2939 (m), 2828 (m), 1754 (w), 1674 (s), 1641 (s), 1617 (m), 1443 (m), 1391 (m), 1374 (m), 1345 (w), 1299 (s), 1229 (m), 1212 (m), 1115 (s), 1070 (s, br), 1021 (m), 1001 (m), 974 (s), 886 (m), 813 (w), 722 (w), 676 (w); NMR τ 3.53 (AB q, J = 10.2 Hz, $\Delta\nu$ = 28.7 Hz, "B" meta coupled, J = 1.7 Hz) and 3.94 (m, 3 H), 6.77 (s, 6 H), 8.12 (d, J = 1.4 Hz, 3 H); exact mass for $C_9H_{12}O_3$ calcd m/e 168.0786, obsd m/e 168.0790, difference 0.0004.

44. A stirred solution of 1.001 g (4.76 mmol) of 2-(trimethylsilyl)-1,4-dimethoxybenzene in 100 mL of 2 wt % potassium hydroxide in methanol (11 g/600 mL) was electrolyzed for 35 min at a constant current of 1.2 A, using power supply D[35] and maintaining the temperature at ≤15 °C. Roughly 2500 coulombs were passed (36% efficiency). The reaction was worked up as before to give 1.254 g (97%) of **44** as a pale-yellow oil. This was dissolved in 20 mL of acetone and cooled in an ice bath; then with vigorous stirring, 5 mL of chilled 2% acetic acid was added in one portion. After being stirred for 0.5 h at 0 °C, the reaction was allowed to warm to room temperature and was stirred for an additional 1.5 h. The hydrolysis was monitored by GLC (column B, 170 °C). Aliquots injected on column must first be neutralized ($NaHCO_3$) in order to obtain an accurate gauge of the extent of hydrolysis. The reaction was stopped by adding 6 mL of saturated sodium bicarbonate solution, and the products were extracted with ether (4 × 10 mL). Workup as usual gave 1.036 g of a yellow oil which was determined to be a 44:56 mixture of **55**/**56** by GLC (column C, 195 °C). This material was chromatographed on 110 g of silica gel slurry packed in 5% E/PE as follows: 150 mL of 5% E/PE, 400 mL of 7% E/PE, and 250 mL of 10% E/PE, 29 mg of a mixture of the quinone and other impurities; 335 mL of 10% E/PE, 0.45 g of monoketal **56**. **56** was molecularly distilled (70–80 °C (0.1 mm)) to give 0.408 g (38%) of a yellow oil (at room temperature) which was crystalline in the refrigerator: IR (neat, NaCl) cm^{-1} 2952 (m), 2906 (m), 2816 (m), 1661 (s), 1630 (s), 1465 (m), 1396 (m), 1383 (m), 1352 (s), 1306 (m), 1282 (m), 1253 (s), 1235 (s), 1204 (m), 1186 (m), 1115 (s, br), 1070 (s), 1045 (s), 972 (s), 849 (s, br), 766 (m), 733 (m), 701 (m); NMR τ 3.19 (m) and 3.57 (AB q, J = 10.7 Hz, $\Delta\nu$ = 32.8 Hz, "A" meta coupled, J = 3.3 Hz, 3 H), 6.70 (s, 6 H), 9.83 (s, 9 H); exact mass for $C_{11}H_{18}O_3Si$ calcd m/e 226.1025, obsd m/e 226.1031, difference 0.0006.

Continued elution gave the following: 85 mL of 10% E/PE, 51 mg of a mixture of **55** and **56**; 20 mL of 10% E/PE and 315 mL of 15% E/PE, 0.339 g of monoketal **55**. The monoketal was a yellow crystalline solid, mp 31.5–33.5 °C. One recrystallization at low temperature from PE (2 mL) gave 311 mg (29%) of **55** as small pale-yellow needles: mp 35–36 °C; IR (neat, NaCl) cm^{-1} 2944 (m), 2896 (w), 2828 (w), 1673 (vs), 1627 (s), 1588 (w), 1463 (w), 1384 (m), 1326 (w), 1284 (s), 1253 (s), 1225 (m), 1208 (m), 1122 (s), 1104 (s), 1066 (vs), 1016 (m), 972 (s), 846 (vs), 763 (w), 716 (m), 641 (w); NMR τ 3.48 (AB q, J = 10.1 Hz, $\Delta\nu$ = 3.3 Hz, "B" meta coupled, J = 1.7 Hz) and 3.62 (d, J = 1.7 Hz, 3 H), 6.75 (s, 6 H), 9.80 (s, 9 H); exact mass for $C_{11}H_{18}O_3Si$ calcd m/e 226.1025, obsd m/e 226.1031, difference 0.0006.

45. A solution of 1.012 g (5.16 mmol) of 2-(1-methoxyethyl)-1,4-dimethoxybenzene was electrolyzed for 55 min at a constant current of 1 A in a stirred, cooled solution (130 mL) of 2% sodium methoxide in methanol, using power supply D[35] (30% efficiency). The reaction was worked up as before to give 1.321 g of **45** as a pale-yellow oil. This was dissolved in 20 mL of acetone and cooled in an ice bath, after which 10 mL of chilled 2% acetic acid in water was added slowly with vigorous stirring, the solution becoming slightly cloudy due to the reduced solubility of the bisketal. The reaction was monitored by GLC (column B, 175 °C). The mixture was stirred and allowed to warm to room temperature. After 25 min, the reaction was quenched by adding 10 mL of 10% sodium bicarbonate solution and the products were extracted with ether (4 × 10 mL). Workup as usual gave 1.062 g of the two monoketals [a 73:27 mixture of **57**/**58** by GLC (column C, 185 °C)]. The oil was chromatographed on 100 g of silica gel slurry packed in 12% E/PE as follows: 300 mL of 12% E/PE, 500 mL of 16% E/PE, and 225 mL of 20% E/PE, nil; 400 mL of 20% E/PE, 0.246 g of monoketal **58**. This monoketal was molecularly distilled (80 °C (0.1 mm)) to give 0.209 g (19%) of **58** as a clear oil: IR (neat, NaCl) cm^{-1} 2970 (m), 2930 (m), 2895 (m), 2826 (m), 1681 (s), 1650 (s), 1461 (m), 1396 (m), 1376 (m), 1328 (m), 1301 (m), 1236 (m), 1210 (m), 1197 (m), 1123 (s, br), 1072 (s), 1046 (s), 1013 (m), 979 (s), 841 (m); NMR τ 3.16–3.46 (m, 2 H), 3.77–4.05 (m, 1 H), 5.76 (q with allylic coupling, $J_a \leq$ 1 Hz, J = 6.6 Hz, 1 H), 6.68 and 6.76 (overlapping s, 9 H), 8.78 (d, J = 6.6 Hz, 3 H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.19; H, 7.60.

Continued elution proceeded as follows: 40 mL of 20% E/PE, 15 mg of a mixture of **57** and **58**; 35 mL of 20% E/PE, 300 mL of 25% E/PE, and 265 mL of 30% E/PE, 0.665 g of monoketal **57** as a yellow solid (mp 30–34 °C). This monoketal was recrystallized from 2 mL of 20% E/PE at low temperature to give 0.630 g (58%) of **57**: mp 34.5–35.5 °C; IR (neat, NaCl) cm^{-1} 2970 (m), 2935 (m), 2828 (m), 1672 (vs), 1639 (s), 1618 (m), 1459 (m, br), 1374 (m), 1291 (s), 1209 (s), 1144 (m, shld), 1111 (s, br), 1063 (s), 1014 (m), 999 (m), 973 (s), 900 (m), 725 (m); NMR τ 3.51 (AB q, J = 10.2 Hz, $\Delta\nu$ = 32.4 Hz, "B" meta coupled, J = 1.6 Hz) and 3.72 (m, 3 H), 5.92 (q, J = 6.4 Hz, 1 H), 6.75, 6.77, and 6.82 (overlapping s, 9 H), 8.72 (d, J = 6.4 Hz, 3 H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.25; H, 7.57.

46. The bisketal **46** (0.229 g, 0.89 mmol) was dissolved in 7.5 mL of acetone at room temperature, to the stirred solution was added a 2% solution of acetic acid in water (3.8 mL) in one portion, and the mixture was stirred 20 min. The reaction was quenched with 4 mL of saturated sodium bicarbonate solution, and then the product was extracted with methylene chloride (4 × 8 mL). Workup gave 160 mg of a tan solid which was one spot by TLC (silica gel, ether). One recrystallization from chloroform/PE gave (in two crops) 0.149 g (79%) of **59**: mp 153–155 °C; IR (KBr) cm^{-1} 3292 (s), 2942 (w), 2844 (w), 1705 (vs), 1674 (s), 1632 (s), 1615 (m), 1523 (vs), 1468 (m), 1392 (m), 1371 (m), 1335 (m), 1316 (m), 1244 (s), 1214 (s), 1124 (m), 1090 (vs), 1061 (m), 893 (m); NMR ($CDCl_3$) τ 2.35 (br s, 1 H), 2.67 (d, J = 1.7 Hz, 1 H), 3.54 (AB q, J = 10.3 Hz, $\Delta\nu$ = 7.6 Hz, "B" meta coupled, J = 1.7 Hz, 2 H), 6.73 (s, 6 H), 7.79 (s, 3 H); exact mass for $C_{10}H_{13}NO_4$ calcd m/e 211.0844, obsd m/e 211.0849, difference 0.0005.

47. The bisketal **47** (0.201 g, 0.829 mmol), mp 66–69 °C, was dissolved in 5 mL of acetone and cooled in ice, and with vigorous stirring, 1 mL of chilled 2% acetic acid was added. The mixture was stirred for 25 min in the ice bath and allowed to warm to room temperature, stirring for an additional 75 min until GLC indicated the complete disappearance of starting material (column A, 140 °C). The reaction was quenched by pouring into 5 mL of 5% bicarbonate solution, and then the product was extracted with ether (4 × 5 mL). Workup gave 0.159 g of a white solid, mp 70–73.5 °C. One recrystallization from 3 mL of PE (crystallization induced by cooling in ice and then cooling further with dry ice) gave 0.147 g (90%) of **60** as white needles:[46] mp 74–75.5 °C; IR (KBr) cm^{-1} 2940 (m), 2844 (m), 1680 (s), 1632 (s), 1454 (m), 1443 (m), 1383 (m), 1376 (m), 1325 (m), 1259 (m), 1232 (m), 1191 (m), 1084 (vs), 1051 (m), 1031 (m), 912 (m), 685 (m); NMR τ 3.82 (q, J = 1.5 Hz, 1 H), 7.07 (s, 6 H), 8.17 (br s, 9 H); exact mass for $C_{11}H_{16}O_3$ calcd m/e 196.1099, obsd m/e 196.1103, difference 0.0004.

48. A solution of 3.504 g (20.8 mmol) of 1,2,4-trimethoxybenzene in 175 mL of 2% sodium methoxide in methanol was electrolyzed below 15 °C for approximately 2 h with power supply C.[35] The reaction was monitored by the disappearance of a UV absorption at 286 nm. The starting current was 2.2 A at 0.975 V and the final current 75 mA at 1.105 V (with respect to Ag/AgCl), the current efficiency being 73%. The methanol was removed on the rotary evaporator and the residue partitioned between 20 mL of ether and 20 mL of 1:1 saturated salt/water. The organic layers were dried over Drierite and concentrated to give 4.429 g of a yellow oil which appeared to be a mixture of bis- and monoketals (~2.6:1) by NMR. This was dissolved in 80 mL of acetone at room temperature, and 40 mL of 2% acetic acid in water was added with vigorous stirring which was continued for 45 min. The mixture was poured into 40 mL of 10% sodium bicarbonate and

(46) After this work was completed, a reference[29b] was found in which monoketal **66** has been prepared in 4% yield via periodic acid oxidation of 2,3,5-trimethylphenol in methanol (lit.[29b] mp 74–75 °C).

extracted with ether (3 × 20 mL) and methylene chloride (2 × 15 mL). Workup gave 3.377 g of a yellow oil which was mostly **61** by NMR, but which showed four spots by TLC (silica gel, ether): R_f 0.48, 1,2,4,5-tetramethoxybenzene (**69**); R_f 0.48, yellow compound(s), not identified; R_f 0.40, **61**; R_f 0.16, **70**. This material was chromatographed on 50 g of silica gel (24.5 × 2.2 cm) slurry packed in 20% E/PE, with the elution proceeding as follows: 100 mL of 20% E/PE, nil; 175 mL of 30% E/PE, nil; 100 mL of 30% E/PE, 85.8 mg of **69**. This was recrystallized from E/PE to give 70 mg (1.7%): mp 100–101.5 °C (lit.[47] mp 102–103 °C); IR (KBr) cm^{-1} 2840 (w), 1528 (s), 1472 (m), 1443 (m), 1398 (m), 1232 (s), 1209 (vs), 1191 (m), 1046 (m), 1035 (s), 861 (m), 838 (m); NMR ($CDCl_3$) τ 3.46 (s, 2 H), 6.19 (s, 12 H).

Continued elution proceeded as follows: 35 mL of 30% E/PE and 50 mL of 35% E/PE, mixture of **69**, unknown material, and **61**, ~0.25 g; 25 mL of 35% E/PE, mostly **61**, 0.2 g; 125 mL of 35% E/PE, 200 mL of 40% E/PE, and 150 mL of 50% E/PE, 2.486 g of **61**. The 0.2-g fraction was recrystallized from E/PE to give 0.192 g of **61**. This was combined with the 2.486-g fraction and the entire quantity recrystallized from E/PE to give 2.535 g (66%) of **61**: mp 62–64.5 °C (lit.[15] 63.5–64.5 °C) as a white solid; IR (KBr) cm^{-1} 2841 (w), 1659 (s), 1625 (s), 1600 (vs), 1465 (m), 1363 (s), 1318 (w), 1237 (vs), 1126 (m), 1090 (s), 988 (m), 875 (m), 745 (w); NMR τ 3.77 (AB q, J = 10.1 Hz, $\Delta\nu$ = 20.1 Hz, "B" meta coupled, J = 1.5 Hz, 2 H), 4.57 (d, J = 1.5 Hz, 1 H), 6.23 (s, 3 H), 6.73 (s, 6 H); exact mass for $C_9H_{12}O_4$ calcd m/e 184.0734, obsd m/e 184.0741, difference 0.0007.

Further elution with pure ether gave a small amount of **70** (≤2%). This material is unstable on the silica gel used; better results would most likely be obtained with ammonia-washed silica gel. It is difficult to remove **70** from **61** by recrystallization: NMR ($CDCl_3$) τ 4.40 (s, 1 H), 4.63 (s, 1 H), 6.20 (s, 3 H), 6.30 (s, 3 H), 6.71 (s, 6 H).

49. To a stirred, cooled (−60 °C) solution of 0.840 g (3 mmol) of the bromo ketal **42** in 10 mL of dry tetrahydrofuran was added 1.4 mL of a 2.1 M solution of *n*-butyllithium dropwise via syringe, the system being maintained under nitrogen. After the mixture was stirred for 1 min at −60 °C, 0.282 g (3 mmol) of dimethyl disulfide in 1 mL of dry tetrahydrofuran was added via syringe, keeping the temperature at −60 °C. The mixture was stirred for 15 min at −60 °C and then 15 min at room temperature and quenched with water (5 mL). Workup afforded a light-yellow liquid which was dissolved in 5 mL of acetone and cooled to 0 °C with stirring. Cold 2% acetic acid (5 mL) was added and the mixture stirred at 0 °C for 10 min. The mixture was neutralized with saturated sodium bicarbonate solution, extracted with ether (2 × 10 mL), and worked up to afford a yellow solid. The crude product was crystallized from E/PE to yield 0.340 g (57% based on **42**) of yellow crystals: mp 74–75 °C; IR (KBr) cm^{-1} 1650 (s), 1615 (s), 1570 (s), 1305 (s), 1185 (s), 1008 (m), 885 (m); NMR ($CDCl_3$) τ 7.65 (s, 3 H), 6.78 (s, 6 H), 3.99 (d, J = 2 Hz, 1 H), 3.70 (d of d, J = 2, 10 Hz, 1 H), 3.31 (d, J = 10 Hz, 1 H) (the chemical shift of the doublet of the AB system is reported as the center of the doublet); exact mass for $C_9H_{12}O_3S$ calcd m/e 200.0507, obsd m/e 200.0509, difference 0.0002.

50. A solution of 200 mg (0.65 mmol) of **50**, 15 mL of wet tetrahydrofuran, and trifluoroacetic acid (0.5 mL) was stirred for 7 h at room temperature and then concentrated at reduced pressure. Workup as usual gave 149 mg of an orange-yellow oil which was chromatographed on neutral alumina (activity III, 2.5 × 6 cm column). Elution proceeded as follows: 90 mL of 10% E/PE, nil; 120 mL of 25% E/PE, 65 mg (42%) of **63** as a light-yellow solid (mp 74.5–75 °C). **63**: IR (KBr) cm^{-1} 3005 (w), 2960 (w), 2945 (w), 2842 (w), 1676 (s), 1667 (s), 1635 (m), 1595 (m), 1459 (m), 1355 (m), 1295 (m), 1253 (s), 1212 (m), 1192 (m), 1130 (m), 1110 (s), 1066 (s), 1019 (m), 979 (m), 908 (m), 836 (m), 802 (w), 741 (m), 725 (m), 711 (m); NMR (CCl_4) τ 1.8–2.2 (m, 2 H), 2.4–2.8 (m, 3 H), 3.2 (d, J = 10 Hz, 1 H), 3.84 (d of d, J = 2, 10 Hz, 1 H), 4.02 (d, J = 2 Hz, 1 H), 6.67 (s, 6 H).

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.79; H, 5.64.

When the trifluoroacetic acid hydrolysis was conducted in water/methanol (1:10) for 24 h at room temperature and worked up as usual, a product mixture was obtained in which **63** was the major component with no trace of **67** or **68** by NMR analysis.

3-Piperidyl-4,4-dimethoxycyclohexadienone (71). To a solution of **51** (0.500 g, 2.15 mmol) in 6 mL of methanol in a 10-mL flask equipped with a reflux condenser and stirred magnetically was added 0.43 mL of piperidine (0.37 g, 4.35 mmol). The solution was stirred for 3.5 h at room temperature and then refluxed for an additional 1.25 h. Workup gave 0.518 g of dark-green solid after pumping in vacuo. This was filtered through 15 g of silica gel packed in ether, using ether as the eluant, in order to remove some of the color. The first 80 mL contained a small amount of brown material; the next 340 mL contained 0.472 g of **71** as yellow crystals, mp 78.5–81 °C (93%). One recrystallization from E/PE gave 0.442 g (87%) as yellow platelets: mp 80–81.5 °C; IR (KBr) cm^{-1} 2942 (m), 2874 (w), 2841 (w), 1658 (m), 1599 (s), 1562 (s, br), 1445 (m), 1438 (m), 1394 (m), 1311 (m), 1268 (m), 1254 (m), 1083 (vs), 1070 (m, shld), 1061 (m, shld), 1027 (m), 1009 (m), 859 (m); NMR τ 3.85 (s, 2 H), 4.76 (s, 1 H), 6.47 (m, 4 H), 6.78 (s, 6 H), 8.37 (m, 6 H); exact mass for $C_{13}H_{19}NO_3$ calcd m/e 237.1365, obsd m/e 237.1371, difference 0.0006.

Conversion of Selected Bisketals and Monoketals to *p*-Methoxyphenols. General Procedure for Reduction. The bisketal or monoketal was dissolved in tetrahydrofuran, zinc/copper[48] was added, and the solution was heated to reflux. To this vigorously stirred solution was added the acid, and refluxing was continued until reaction was complete. Workup afforded the naphthol. Below are listed the amount of bisketal, acid, reaction time, and yields for these reactions and the spectroscopic properties of the products. The specific procedure for 3-bromo-4-methoxyphenol is given below.

3-Bromo-4-methoxyphenol. The bisketal **42** (12.6 g, 45.1 mmol) was dissolved in 140 mL of tetrahydrofuran, zinc/copper couple (4.40 g, 60 mmol) was added, and the solution was heated to reflux. With vigorous stirring, as soon as the solution was refluxing, 16 mL of 25 vol % acetic acid in water was quickly added through the condenser. The solution foamed vigorously and became nearly colorless. After the solution was refluxed for 1 h, the tetrahydrofuran was distilled off, 10 mL of 10% hydrochloric acid was added, and the mixture was extracted with ether (4 × 25 mL). The ether was washed successively with 5 mL of saturated salt solution, 10% sodium bicarbonate solution (4 × 5 mL), and 5 mL of saturated salt solution. Drying and concentration gave 8.62 g of a light-yellow solid, mp 55–70 °C. Recrystallization from carbon tetrachloride/PE gave 5.51 g of the product in the first crop. Two recrystallizations of the material in the mother liquors gave 1.16 g additional, for a total yield of 6.67 g (73%) of the phenol: mp 74–76 °C (lit.[49] mp 77–78 °C); IR (KBr) cm^{-1} 3257 (m, br), 2846 (w), 1592 (w), 1498 (vs), 1460 (s), 1440 (vs), 1288 (m), 1275 (m), 1246 (s), 1216 (vs), 1193 (m), 1056 (s), 1025 (m), 880 (w), 868 (m), 809 (m), 752 (s), 579 (w); NMR (CCl_4/$CDCl_3$) τ 3.07 (m, 1 H), 3.38 (m, 2 H), 4.96 (s, 1 H), 6.24 (s, 3 H); exact mass for $C_7H_7O_2$ ^{79}Br calcd m/e 201.9630, obsd m/e 201.9634, difference 0.0004.

4-Methoxy-1-naphthol. Conditions: 0.50 g of **3**, 0.26 g of zinc/copper couple, 5 mL of 25% acetic acid, 50 min. Physical data: 80%, mp 128.5–129.5 °C (lit.[50] 130 °C).

3-Bromo-4-methoxy-1-naphthol (72). Conditions: 0.104 g of **14**, 0.05 g of zinc/copper couple, acetic acid/water (6:1), 1 h. Physical data: 77%; mp 145.5–146 °C dec; IR (KBr) cm^{-1} 3305 (s), 2944 (w), 1624 (w), 1590 and 1583 (s), 1517 (w), 1470 (w), 1396 (w), 1349 (vs), 1260 (m), 1237 (m), 1081 (s), 1069 (m), 974 (s), 967 (m), 838 (s), 796 (w), 772 (vs), 721 (m); NMR (CCl_4/acetone-d_6) τ 1.03 (s, 1 H), 1.68–2.23 (m, 2 H), 2.37–2.80 (m, 2 H), 3.05 (s, 1 H), 6.15 (s, 3 H); exact mass for $C_{11}H_9O_2$ ^{79}Br calcd m/e 251.9786, obsd m/e 251.9791, difference 0.0005.

3-Bromo-4-methoxy-2-methylnaphthol (73). Conditions: 0.80 g of **16**, 1.4 g of zinc/copper couple, 2 mL of 75% acetic acid, 6 h. Physical data: 62%; mp 121–122.5 °C dec (bubbling and turning dark red); IR (KBr) cm^{-1} 3416 (s, br), 1586 (m), 1574 (m), 1453 (m), 1373 (s), 1287 (s), 1281 (s), 1262 (w), 1200 (m), 1185 (m), 1155 (w), 1091 (s), 1035 (w), 987 (m), 967 (w), 942 (s), 792

(47) Benington, F.; Morin, R. D.; Clark, L. C. *J. Org. Chem.* **1955**, *20*, 102–108.

(48) Blankenship, R. M.; Burdett, K. A.; Swenton, J. S. *J. Org. Chem.* **1974**, *39*, 2300–2301.

(49) Irvine, F. M.; Smith, J. C. *J. Chem. Soc.* **1927**, 74–77.

(50) Hantzsch, A.; Czapp, E. *Chem. Ber.* **1930**, *63*, 566–567.

(w), 778 (s); NMR ($CDCl_3$/acetone-d_6) τ 1.74–2.17 (m, 2 H), 2.39–2.82 (m, 2 H), 3.67–3.99 (br s, 1 H), 6.08 (s, 3 H), 7.51 (s, 3 H); exact mass for $C_{12}H_{11}O_2$ ^{79}Br calcd m/e 265.9943, obsd m/e 265.9950, difference 0.0007.

4-Methoxy-3-(thiomethyl)-1-naphthol (74). Conditions: 0.14 g of **15**, 0.11 g of zinc/copper couple, acetic acid/water (6:1), 3.5 h. Physical data: 92%; mp 131.5–132.5 °C; IR (KBr) cm^{-1} 3316 (s), 2979 (w), 2940 (w), 1622 (m), 1587 (s), 1517 (m), 1438 (m), 1374 (s), 1356 (vs), 1258 (s), 1241 (s), 1162 and 1158 (m), 1081 and 1073 (s), 983 (m), 973 (s), 869 (m), 839 (s), 804 (m), 771 (vs), 715 (m); NMR (CCl_4/acetone-d_6) τ 1.21 (s, 1 H), 1.67–2.23 (m, 2 H), 2.38–2.85 (m, 2 H), 3.21 (s, 1 H), 6.13 (s, 3 H), 7.55 (s, 3 H); exact mass for $C_{12}H_{12}O_2S$ calcd m/e 220.0558, obsd m/e 220.0562, difference 0.0004.

Reaction of Allyl Grignard and 51. To the monoketal **51** (0.500 g, 2.15 mmol, 0.323 mL) in 10 mL of tetrahydrofuran at 0 °C was added 8.6 mL of allyl Grignard solution (0.53 M in ether, 4.56 mmol). A blue-green color formed initially; this gradually faded to give a colorless solution and then a white solid suddenly precipitated. After the mixture was stirred for 15 min in the ice bath, 5 mL of 10% HCl was added, the aqueous phase was extracted with ether (2 × 10 mL), and the ether extracts were concentrated in vacuo. The residue was worked up as usual to give 0.547 g of a yellow-orange oil. The oil was taken up in 15 mL of 1:1 E/PE and extracted with Claisen's alkali (3 × 5 mL), the alkaline washes being drained directly into 30 mL of 10% hydrochloric acid. The acidified base washes were extracted in turn with ether (3 × 8 mL) and the ether layer was washed with saturated salt solution (3 mL) and dried over Drierite. Removal of the ether gave 0.394 g of a yellow oil which was primarily **79** by NMR. The oil was chromatographed on 50 g of silica gel slurry packed in 15% E/PE as follows: 120 mL of 15% E/PE, nil; 20 mL of 15% E/PE, a few milligrams of a mixture including **79**; 120 mL of 15% E/PE, 0.253 g of **79**. This material was recrystallized twice from 1 mL of 10% E/PE at low temperature to give 0.227 g (44%) of **79**: mp 61–62 °C; IR (KBr) cm^{-1} 3248 (m, br), 3018 (w), 2932 (w), 1637 (w), 1502 (s), 1464 (m, shld), 1452 (m), 1431 (s), 1416 (m, shld), 1288 (w), 1244 (m), 1218 (s), 1204 (vs), 1057 (m), 1004 (w), 980 (w), 931 (w), 917 (w), 877 (m), 818 (w), 772 (w), 759 (w); NMR τ 3.17 (s, 1 H), 3.44 (s, 1 H), 3.66–4.48 (m) and 4.25 (s, OH, 2 H), 4.79–5.01 (m, 1 H), 5.01–5.24 (m, 1 H), 6.29 (s, 3 H), 6.61–6.93 (rough d, 2 H); exact mass for $C_{10}H_{11}O_2$ ^{79}Br calcd m/e 241.9943, obsd m/e 241.9949, difference 0.0006.

Continued elution proceeded as follows: 20 mL of 15% E/PE, mixture of **79** and **51**; 100 mL of 15% E/PE, small amount of **51**; 140 mL of 25% E/PE, 58 mg (~11%) of **80**. This material was not further purified, but comparison of IR and NMR spectra with those of a purified authentic sample (see below) established the identity of this component.

Claisen Rearrangement. Authentic Synthesis of 79 and 80. Sodium hydride (0.14 g, 5.8 mmol) was added to a solution of 0.50 g (2.46 mmol) of 3-bromo-4-methoxyphenol in 5 mL of tetrahydrofuran under nitrogen, followed by 0.5 mL (0.7 g, 5.8 mmol) of allyl bromide. The mixture was refluxed overnight (16.75 h) and then poured into 5 mL of water. The aqueous phase was washed once with 5 mL of ether; the ether layers were combined and washed with 2 mL of Claisen's alkali, dried over Drierite, and concentrated to give 0.596 g (99%) of a yellow oil with the expected NMR spectrum: τ 3.01 (t, J = 1.8 Hz, 1 H), 3.36 (d, J = 1.8 Hz, 2 H), 3.71–4.39 (m, 1 H), 4.51–4.99 (m, 2 H), 5.54–5.79 (m, 2 H), 6.30 (s, 3 H). The crude allyl ether was dissolved in 3 mL of diethylene glycol monoethyl ether (carbitol) and heated under nitrogen in an oil bath maintained at 200–210 °C. After being heated for 6 h and cooled, the reaction mixture was diluted with 10 mL of ether. The ether solution was washed with water (3 × 3 mL) and the aqueous washes were back extracted with 4 mL of ether. The combined ether extracts were diluted with 5 mL of PE and extracted with Claisen's alkali (3 × 5 mL). The alkaline washes were drained directly into 15 mL of chilled 10% hydrochloric acid. The acidified extracts were in turn extracted with ether (3 × 8 mL), and the ether layer was dried over magnesium sulfate and evaporated in vacuo to give 594 mg of an orange oil. TLC on silica gel (25% E/PE) showed three major spots: **79**, R_f 0.32; starting phenol, R_f 0.22; **80**, R_f 0.14. The oil was chromatographed on 30 g of silica gel slurry packed in 15% E/PE as follows: 120 mL, small amount of a mixture of three high R_f components by TLC; 80 mL, 0.259 g (43%) of **79**. This was not further purified, but comparison of its IR and NMR spectra with those of the major product from the Grignard reaction confirmed that they were identical.

Continued elution proceeded as follows: 80 mL, 99 mg of a mixture of **79**, starting phenol, and **80**; 160 mL, 0.152 g of **80** as an oil. **80** eventually crystallized in the refrigerator, mp 34.5–37 °C. One recrystallization from PE at low temperature gave 0.129 g (22%) of **80**: mp 43.5–45.5 °C; IR (KBr) cm^{-1} 3435 (s, br), 3084 (w), 3010 (w), 2936 (m), 2846 (w), 1636 (m), 1584 (m), 1485 (vs), 1472 (vs), 1453 (w), 1427 (vs), 1318 (m, br), 1263 (vs), 1207 (m, br), 1185 (m), 1131 (m, br), 1069 (s), 1002 (w), 950 (m), 935 (m), 923 (m), 829 (m), 810 (s), 769 (m), 738 (m); NMR τ 3.48 (s, 2 H), 3.78–4.58 (m, 2 H (included OH)), 4.79–5.23 (m, 2 H), 6.30 (s, 3 H), 6.34–6.59 (m, 2 H); exact mass for $C_{10}H_{11}O_2$ ^{79}Br calcd m/e 241.9943, obsd m/e 241.9951, difference 0.0008. Comparison of the IR and NMR spectra of this material with those of the minor component from the Grignard reaction showed that they were identical.

Grignard Reaction of 51. A solution of 1.0 g (4.3 mmol) of **51** in 15 mL of dry ether was treated with 15 mL (4.5 mmol) of a 0.3 M ether solution of methylmagnesium bromide at room temperature. After being stirred for 2 h the reaction was quenched with water and worked up to yield 0.87 g (81%) of **78** as off-white crystals after two recrystallizations from E/PE: mp 88.5–91 °C; IR (KBr) cm^{-1} 3440 (s), 2960 (w), 2930 (w), 1620 (w), 1450 (w), 1370 (w), 1360 (w), 1310 (w), 1125 (m), 1075 (s), 925 (w), 790 (w), 770 (w), 708 (w); NMR ($CDCl_3$) τ 3.41 (d, J = 2 Hz, 1 H), 4.03 (AB q, J = 10 Hz, $\Delta\nu$ = 32 Hz, with lower field component meta coupled, J = 2 Hz, 2 H), 6.76 (s, 3 H), 6.84 (s, 3 H), 7.51 (s, 1 H), 8.62 (s, 3 H).

Anal. Calcd for $C_9H_{13}O_3Br$: C, 43.39; H, 5.26. Found: C, 43.36; H, 5.28.

Monohydrolysis of 84. A solution of **84** (1.48 g, 3.53 mmol) in 20 mL of acetone was treated with 10 mL of 8% aqueous acetic acid at 0 °C. The solution was warmed to room temperature and the reaction followed by the disappearance of the bisketal methoxy resonances at τ 6.78 and 6.84. After a total of 2 h of reaction time, 5% sodium bicarbonate was added dropwise until the solution was slightly basic. The solution was extracted with methylene chloride (5 × 6 mL) and worked up to yield 1.33 g of light-yellow oil which crystallized on standing. Recrystallization of this material from E/PE gave 1.16 g (88%) of the monoketal: mp 83–86 °C; IR (KBr) cm^{-1} 2955 (w), 2900 (w), 1665 (s), 1615 (w), 1387 (w), 1233 (m), 1195 (m), 1098 (s), 1048 (m), 890 (w); NMR ($CDCl_3$) τ 3.08 (s, 1 H), 6.04 (s, 4 H), 6.88 (s, 3 H), 6.93 (s, 3 H), 7.1–8.6 (m, 7 H), 8.66 (s, 3 H).

Anal. Calcd for $C_{16}H_{21}O_5Br$: C, 51.49; H, 5.67. Found: C, 51.50; H, 5.68.

Sodium Borohydride Reduction of 85. A solution of 568 mg (1.52 mmol) of **85** in 20 mL of methanol was treated with 142 mg (3.75 mmol) of sodium borohydride at room temperature over 10 min and the solution stirred for an additional 50 min. The methanol was removed in vacuo at room temperature and the residue partitioned between water (15 mL) and methylene chloride (3 × 10 mL). Workup of the organic layer gave 528 mg (93%) of a white foam which solidified on standing under vacuum to a white solid, mp 39–55 °C (diastereomeric mixture). The NMR showed a doublet (J = 3.5 Hz) centered at τ 3.24.

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72054-85-4; **69**, 2441-46-5; **70**, 67271-97-0; **71**, 74097-25-9; **72**, 64648-87-9; **73**, 74097-26-0; **74**, 64648-88-0; **75**, 74097-27-1; **76**, 74097-20-4; **77**, 74097-28-2; **79**, 74097-29-3; **80**, 74097-30-6; **84**, 64791-61-3; **85**, 74097-31-7; *cis*-**86**, 74097-32-8; *trans*-**86**, 74097-33-9; dimethyl disulfide, 624-92-0; 2-methyl-1,4-dimethoxybenzene, 24599-58-4; 2-(trimethylsilyl)-1,4-dimethoxybenzene, 72054-75-2; 2-(1-methoxyethyl)-1,4-dimethoxybenzene, 72054-77-4; 1,2,4-trimethoxybenzene, 135-77-3; piperidine, 110-89-4; 3-bromo-4-methoxyphenol, 17332-12-6; 4-methoxy-1-naphthol, 84-85-5; allyl bromide, 106-95-6; methyl bromide, 74-83-9.

Supplementary Material Available: Experimental details of reactions utilized in establishing the structures of the monoketals and spectroscopic data of compounds formed in these reactions (15 pages). Ordering information is given on any current masthead page.

Thallium in Organic Synthesis. 57. Reaction of Chalcones and Chalcone Ketals with Thallium(III) Trinitrate[1]

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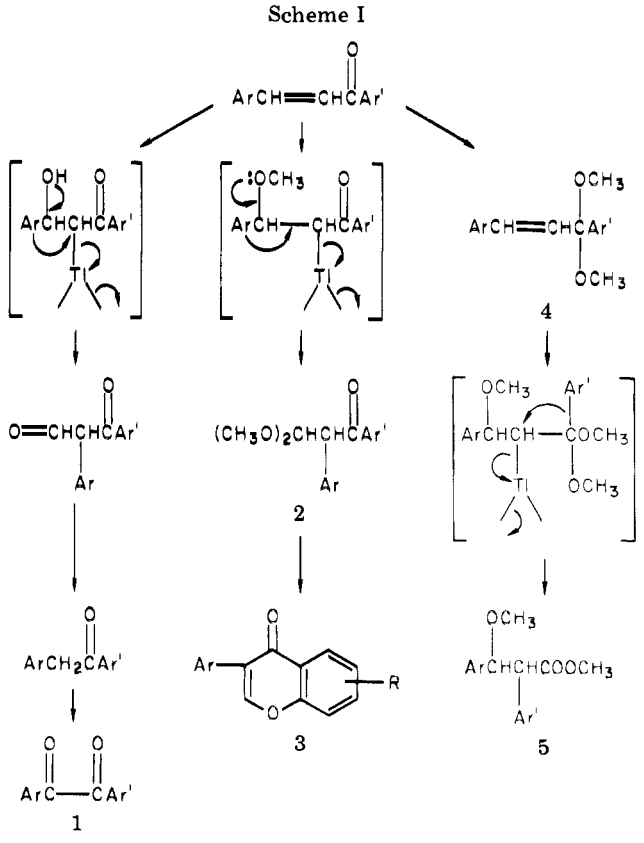
Treatment of chalcones (ArCH=CHCOAr') with thallium(III) trinitrate (TTN) in acidic methanol or in trimethyl orthoformate (TMOF) gives 3,3-dimethoxy-1,2-diarylpropan-1-ones (oxythallation, Ar rearrangement) and/or methyl 2,3-diaryl-3-methoxypropanoates (in situ ketal formation, oxythallation, Ar' rearrangement). The effect of substituents on Ar and Ar' on the ratio of the above rearrangement products has been examined.

Thallium(III) trinitrate (TTN) is now firmly established as a useful and extremely versatile reagent in organic synthesis.[2] Among the readily accessible substrates which have been shown to undergo novel oxidative rearrangement reactions with TTN are chalcones. Thus, oxidation of chalcones in aqueous acidic glyme constitutes a convenient synthesis of benzils (**1**).[3] In addition, the TTN-mediated oxidative rearrangement of chalcones in acidic methanol provides a route to 3,3-dimethoxy-1,2-diarylpropan-1-ones (**2**), key intermediates in the synthesis of isoflavones (**3**) when the Ar' ring possesses an *o*-hydroxyl group, and this reaction has now been extensively exploited.[4] Furthermore, transformation of chalcones into their ketals (**4**) followed by reaction with TTN in trimethyl orthoformate (TMOF) as solvent has recently been shown to give methyl 2,3-diaryl-3-methoxypropanoates (**5**; see Scheme I).[5]

This latter transformation of chalcone ketals to **5** was discovered during an intensive study of TTN oxidations in TMOF as solvent. Thus, although treatment of chalcone itself (Ar = Ar' = C_6H_5) with TTN in acidic methanol yields 3,3-dimethoxy-1,2-diphenylpropan-1-one (**2**, Ar = Ar' = C_6H_5), we found that reaction in TMOF as solvent gave a 50:50 mixture of the latter compound and methyl 2,3-diphenyl-3-methoxypropanoate (**5**, Ar = Ar' = C_6H_5). The keto acetal **2** was obviously formed by the usual Ar ring migration, but the ester **5** must have resulted from the migration of the Ar' group, an unprecedented oxidative rearrangement of chalcones. Formation of the ester **5** may

Scheme I



(1) For the previous paper in this series, see E. C. Taylor, G. E. Jagdmann, Jr., and A. McKillop, *J. Org. Chem.*, **45**, in press.

(2) See A. McKillop and E. C. Taylor, *Endeavour*, **35**, 88 (1976). See also the previous papers in this series.

(3) A. McKillop, B. P. Swann, M. E. Ford, and E. C. Taylor, *J. Am. Chem. Soc.*, **95**, 3641 (1973).

(4) (a) L. Farkas, A. Gottsegen, M. Nogradi, and S. Antus, *J. Chem. Soc., Perkin Trans 1*, 305 (1974); (b) S. Antus, L. Farkas, M. Nogradi, and P. Sohar, *J. Chem. Soc., Chem. Commun.*, 799 (1974); (c) L. Farkas, S. Antus, and M. Nogradi, *Acta Chim. Acad. Sci. Hung.*, **82**, 225 (1974); (d) A. Levai and L. Balogh, *Pharmazie*, **30**, 747 (1975); (e) S. Antus, L. Farkas, Z. Kardos-Balogh, and M. Nogradi, *Chem. Ber.*, **108**, 3883 (1975); (f) S. Antus, L. Farkas, A. Gottsegen, Z. Kardos-Balogh, and M. Nogradi, *ibid.*, **109**, 3811 (1976); (g) M. A. Leon and M. C. Cabaleiro, *An. Asoc. Quim. Argent.*, **64**, 331 (1976); (h) T. G. Fourie, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 125 (1977); (i) M. E. Oberholzer, G. J. H. Rall, and D. G. Roux, *ibid.*, 423 (1977); (j) Z. Kardos-Balogh, L. Farkas, and A. Wolfner, *Acta Chim. Acad. Sci. Hung.*, **94**, 75 (1977); (k) S. Antus, F. Boross, L. Farkas, and M. Nogradi in "Flavonoids and Bioflavonoids: Proceedings of the 5th Hungarian Bioflavonoid Symposium", 1977, pp 171–180; (l) F. R. van Heerden, E. V. Brandt, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 137 (1978); (m) S. Antus and M. Nogradi, *Chem. Ber.*, **112**, 480 (1979).

(5) E. C. Taylor, R. A. Conley, D. K. Johnson, and A. McKillop, *J. Org. Chem.*, **42**, 4167 (1977).

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