Quinone Bis- and Monoketals via Electrochemical Oxidation. Versatile Intermediates for Organic Synthesis

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Several years ago we became interested in highly substituted metalated quinone equivalents as intermediates in anthracyclinone synthesis (Scheme I). For mechanistic reasons, we required the molecule to have the quinone oxidation state, ruling out the use of an aromatic ether as a latent quinone that could then be oxidized to the quinone itself at a later stage of the synthesis. The chemistry employing quinone bis- and monoketals in anthracyclinone syntheses has been summarized and will not be presented here.[1] Instead, the research that was a prelude to the synthetic work—anodic oxidation studies of aromatic ethers—has resulted in efficient routes to two types of generally useful protected quinone systems. Thus, methoxylated aromatic systems furnish quinone bisketals via anodic oxidation and quinone monoketals via a sequence of anodic oxidation/hydrolysis. In this Account we point out the ease with which substituted quinone bis- and monoketals are readily made available, and we highlight some of their chemical transformations.

Preparation of Quinone Bisketals

In view of the widespread occurrence of the quinone entity in naturally occurring systems, we were somewhat surprised that few bisketals of quinones had been reported prior to 1975. The synthesis of the bis(ethylene glycol) ketal of benzoquinone from the bisketal of 1,4-cyclohexanedione rested on the availability of the requisite 1,4-dione.[2] However, this route appeared to be inapplicable to naphthoquinone bisketals and inconvenient for highly functionalized quinone systems. There remained the report by Belleau and Weinberg[3] that anodic oxidation of 1,4-dimethoxybenzene and 1,2,4-trimethoxybenzene at a platinum anode afforded the respective quinone bisketals in good yields. This route appeared especially convenient since the reaction was performed in 1% methanolic potassium hydroxide in a single-cell apparatus without requiring accurate control of the electrode potential. However, the anodic oxidation of many functionalities (benzylic methylene groups, benzylic secondary and tertiary alcohols, dimethyl ketals, aldehydes, amides, and conjugated esters)[4] had already been reported under conditions similar to those of the 1 → 2 oxidation (Table I). Thus, the use of the anodic oxidation to form quinone bisketals in functionalized systems depended upon the relative ease of the 1 → 2 oxidation vs. oxidation of the substituent. Fortunately, many substituted 1,4-dimethoxybenzenes and 1,4-dimethoxynaphthalenes (Table I) undergo high-yield oxidations to their respective quinone bisketals in a single-cell apparatus without requiring accurate potential control (current efficiencies range from 34 to 74%). Even the methyl-

Scheme I
Metalated Quinone Bisketal Approach to Anthracyclinones

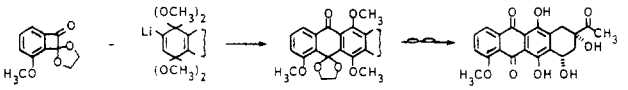
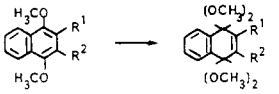


Table I
Anodic Oxidation in a Single Cell[4,5]

1 2

compd	R^1	R^2	R^3	yield, %
a	Br	H	H	78
b	Br	H	Br	58
c	CH_3	H	H	80
d	$Si(CH_3)_3$	H	H	93
e	CH_3	CH_3	CH_3	63
f	$CH(OCH_3)CH_3$	H	H	92
g	1,3-dioxolan-2-yl	H	H	88
h	$CH(OH)CH_3$	H	H	50[a]
i	$(CH_2)_3OH$	H	H	48[a]
j	$CH_2CH=CH_2$	H	H	81
k	SCH_3	H	H	54[b]



3 4

compd	R^1	R^2	yield, %
a	H	H	74
b	CH_3	H	75
c	OCH_3	H	83
d	CH_3	OCH_3	82
e	CH_3	$Si(CH_3)_3$	80

[a] Other products characterized from the reaction mixture. [b] Yield of quinone monoketal from direct hydrolysis of the reaction mixture.

John S. Swenton was born in Kansas City, KS. He graduated from the University of Kansas with a B.A. in chemistry in 1962. After receiving his Ph.D. with Howard Zimmerman at the University of Wiconsin, he spent a year as a postdoctoral student with Paul Bartlett at Harvard University. He joined the faculty at The Ohio State University in 1967 and is now professor of chemistry. His research interests comprise synthetic and mechanistic organic photochemistry and electrochemistry and synthesis of anthracycline antibiotics.

(1) (a) El Khadem, E., Ed. "Anthracycline Antibiotics"; Academic Press: New York, 1982. (b) Swenton, J. S.; Anderson, D. K.; Jackson, D. K.; Narasimhan, L. *J. Org. Chem.* **1981**, *46*, 4825. (c) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263.

(2) Heller, J. E.; Dreiding, A. S.; O'Connor, B. R.; Simmons, H. E.; Buchanan, G. L.; Rapheal, R. A.; Taylor, R. *Helv. Chem. Acta* **1973**, *56*, 272.

(3) (a) Belleau, B.; Weinberg, N. L. *J. Am. Chem. Soc.* **1963**, *85*, 2525. (b) Weinberg, N. L.; Belleau, B. *Tetrahedron* **1973**, *29*, 279.

(4) For leading references, see: Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369.

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

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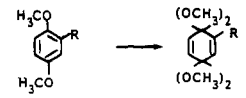
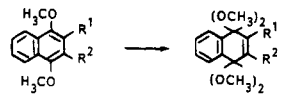
Table II
Anodic Oxidations in a Divided Cell[4,5]



1 2

compd	R	yield, %
o	$NHC(O)CH_3$	17
p	$(CH_2)_2CO_2CH_3$	61
q	$(CH_2)_2C(O)N(CH_3)_2$	68
r	$(CH_2)_2C(O)NH_2$	50
s	$CH{=}CHCO_2CH_3$	46
t	C(O)H	26, 59[a]



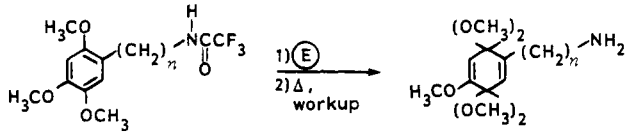
3 4

compd	R^1	R^2	yield, %
f	Br	H	84
g	Br	CH_3	85
h	Br	Br	50

[a] Reaction at a reticulated vitreous carbon electrode. The product is the bis(ketal) ester (R = CO_2CH_3).

thio group in the **1k** → **2k** transformation survives the anodic oxidation of the aromatic ring.

Limitations of the anodic oxidation of 1,4-dimethoxy aromatics to quinone bisketals arise primarily from the oxidation or reduction of substituent groups. In the former cases, oxidizable substituents can often be carried in protected form. For example, primary and secondary hydroxyl groups, primary and secondary amino groups, and aldehyde functions can complicate the conversions to quinone bisketals because of oxidation of the substituent. However, hydroxyl groups are stable as their respective ethers (i.e., methyl, methoxymethyl), amine systems can be anodically oxidized in good yield (>90%) to the respective bisketal if the amine is present as its trifluoroacetyl derivative (**1m,n**),[6]



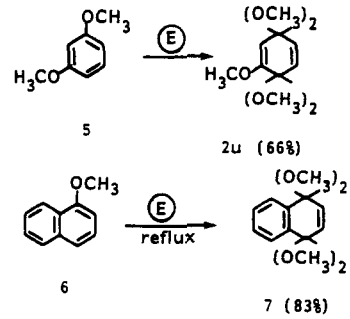
1 2

m, n = 2; n, n = 3

and carbonyl systems can be protected as their corresponding acetals.

For compounds having reducible functions, anodic oxidations conducted in divided cells (anode and cathode compartments separated) often allow the preparation of quinone bisketals (Table II). These divided-cell anodic oxidations are somewhat less convenient in the laboratory, but this technique does considerably expand the scope of quinone bisketal preparation.

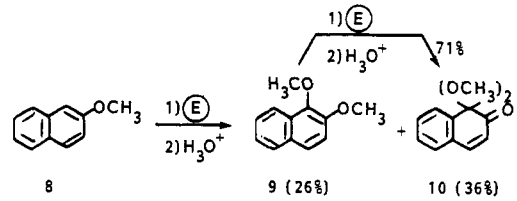
While anodic oxidation of 1,4-dimethoxy aromatic compounds is the most common route to quinone bisketals, in some systems the bisketal can be formed by four-electron[7-9] oxidation from a monooxygenated aromatic compound as illustrated below. In the cases of **5**[3] and **6**, the quinone bisketals are formed in good



5 2u (66%)

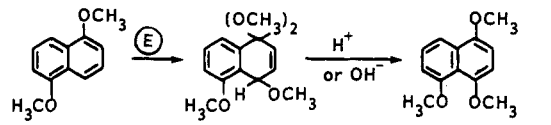
6 7 (83%)

overall yield via this four-electron oxidation.[8,9] Anodic oxidation of 2-methoxynaphthalenes gives **9** and **10**, the



8 9 (26%) 10 (36%)

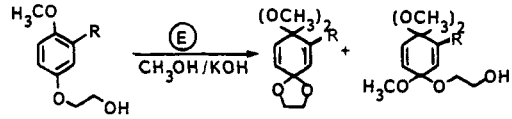
monoketal **10** arising from hydrolysis of the bisketal of 1,2-naphthoquinone.[9] In some methoxynaphthalene systems, the initial anodic addition products (i.e., **12**)



11 12 13 (85% overall)

are sufficiently stable to be isolated and subsequently aromatized to give good yields of oxygenated naphthalenes.[7,9] Depending on the system and the reaction temperature, anodic oxidation can serve as a route to quinone bisketals or oxygenated aromatic compounds.

The use of anodic oxidation to form bisketals with alcohols other than methanol has not been extensively studied. Anodic oxidation of 1,4-diethoxybenzene in ethanolic potassium hydroxide proceeds in lower yield (63 vs. 88%) than the analogous process in methanolic potassium hydroxide.[4,10] However, an intramolecular variant of this reaction can be performed conveniently as illustrated in the oxidation of **14a–d**.[11] These mixed

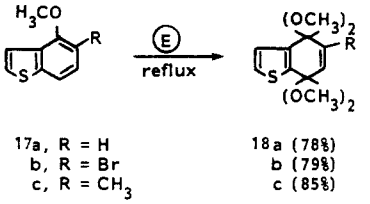


14a, R = H	15a (66%)	16a (15%)
b, R = CH_3	b (83%)	b (7%)
c, R = Br	c (81%)	c (13%)
d, R = OCH_3	d (86%)	d --

bisketals have utility in altering the regiochemistry of the hydrolysis to quinone monoketals (vide infra).

Thus far, the anodic oxidation of methoxylated heterocyclic compounds in methanolic potassium hydroxide has yielded synthetically useful results only with benzothiophenes.[12] The four-electron oxidation (**17** → **18**) is especially valuable in the benzothiophene series since the corresponding 4,7-dimethoxy compounds are

(6) Shih, C., unpublished results.
(7) Jackson, D. K.; Swenton, J. S. *Synth. Commun.* **1977**, *7*, 333.
(8) Dolson, M. G.; Jackson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1979**, 327.
(9) Dolson, M. G.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 2361 and references cited therein.
(10) See also: Carreño, M. C.; Fariña, F.; Galań, A.; Garcia Ruano, J. L. *J. Chem. Res., Synop.* **1979**, 296; *J. Chem. Res., Miniprint* **1979**, 3443.
(11) Dolson, M. G.; Swenton, J. S. *J. Org. Chem.* **1981**, *46*, 177; Margaretha, P.; Tissot, P. *Helv. Chim. Acta* **1975**, *58*, 933.
(12) Chenard, B. L.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1979**, 1172.

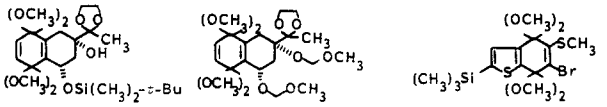


17a, R = H
b, R = Br
c, R = CH_3

18a (78%)
b (79%)
c (85%)

not readily available. In fact, the anodic oxidation of **17** followed by an acid hydrolysis serves as an excellent route to benzothiophene-4,7-quinones.

In summary, anodic oxidation of appropriate aromatic ethers serves as a reasonably general method for preparation of benzoquinone and naphthoquinone bisketals. When the reaction is being performed in a single cell without control of potential, virtually no electrochemical expertise is required to obtain good yields of the quinone bisketals. We have performed such reactions on a 0.5-mol scale and foresee no difficulty in scaling up the oxidation even further. In fact, our first oxidations were performed on 20 g of 1,4-dimethoxybenzene with equipment borrowed from a freshman chemistry electrolysis experiment. For more complex systems, a good quality potentiostat and a divided cell may be necessary to obtain good yields of product. Some examples of functionalized bisketals which were prepared via anodic oxidation of their



19 (quantitative) 20 (92%) 21 (85%)

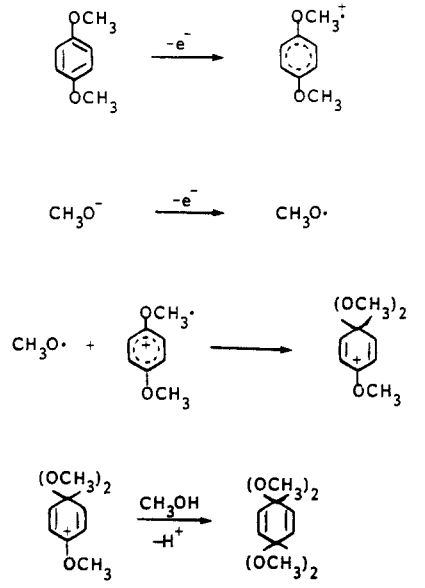
corresponding dimethoxy aromatic derivatives are **19**, **20**, and **21**; only **21** required a divided-cell apparatus with control of the electrode potential.[13]

Several practical comments on performing the reactions should be noted. First, for compounds difficultly soluble in methanol, the anodic oxidation can be run as a slurry, provided the bisketal is soluble in methanol, or tetrahydrofuran can be employed as a cosolvent. Second, the current efficiency for the reaction decreases as the amount of potassium hydroxide in methanol is increased;[9] 1% methanolic potassium hydroxide is a good medium for performing the oxidation. Third, the quinone bisketals are usually quite stable if surfaces are kept free of acid. In our laboratory, all glassware and pipets are rinsed with dilute ammonium hydroxide and oven-dried before coming into contact with the bisketals.

Finally, for full utilization of the anodic oxidations in synthesis, a knowledge of the mechanism of these reactions would be useful. Several mechanisms have been discussed for the anodic oxidation of 1,4-dimethoxybenzene to its quinone bisketal.[9] While the intimate details of the reaction mechanism are unknown, we favor the mechanism shown in Scheme II.[9] The key elements are the formation of an aromatic radical cation and a methoxy radical at the electrode surface followed by their rapid reaction to give the pentadienyl-type cation. Reaction of this species with methanol gives the bisketal. This reaction pathway, which involves two electrochemical steps (EE) and a radical coupling step (C_r) followed by a polar reaction (C_p), is termed the EEC_rC_p mechanism. While this reaction mechanism is

(13) Sercel, T.; Chenard, B., unpublished results.

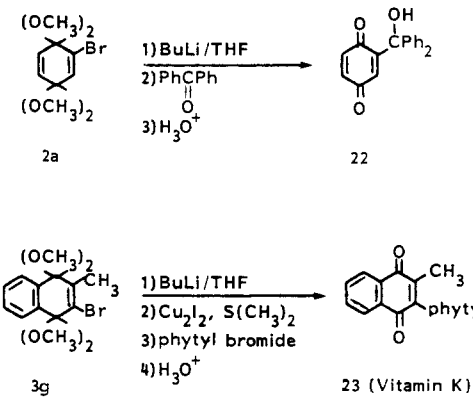
Scheme II
EEC_rC_p Mechanism for Anodic Oxidation of 1,4-Dimethoxybenzene



being used as a guide to examine extensions of the electrochemical oxidations noted here, more detailed electrochemical studies would be helpful to more fully define the mechanism of the oxidation.

Reactions of Bisketals

Our original intent was to utilize quinone bisketals as metalated quinone equivalents. Indeed, from bromo aromatic systems, a sequence of anodic oxidation, metalation, reaction of the resulting organolithium or cuprate derivative with an electrophile, and hydrolysis affords the functionalized quinone. The reactions of **2a** and **3g** illustrate this method, and two papers have explored the generality of this quinone functionalization.[14,15]



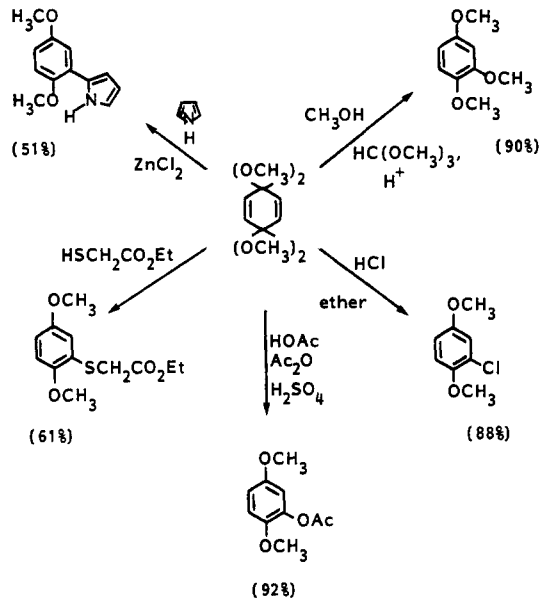
2a 22

3g 23 (Vitamin K)

Quinone bisketals can also be employed in the synthesis of substituted aromatic systems as illustrated by the reactions in Scheme III.[16] In this regard, quinone bisketals serve as synthons for nucleophilic aromatic substitution of 1,4-dimethoxy aromatics. While substituted benzoquinone bisketals have not been studied extensively in this type of substitution reaction, the

(14) Swenton, J. S.; Jackson, D. K.; Manning, M. J.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6182.
(15) Chenard, B. L.; Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 378.
(16) Konz, E.; Pistorius, R. *Synthesis* **1979**, 603. Groebel, B. T.; Konz, E.; Millauer, H.; Pistorius, R. *Ibid.* **1979**, 605. See also: Kikuchi, Y.; Hasegawa, Y.; Matsumoto, M. *Tetrahedron Lett.* **1982**, *23*, 2199.

Scheme III
Benzoquinone Bisketals in the Synthesis of Substituted 1,4-Dimethoxybenzenes



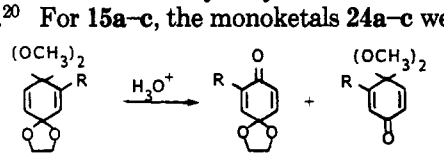
regiochemical outcome of such reactions could show good selectivity based on the known regiochemistry of the monohydrolyses of bisketals to quinone monoketals. Much useful chemistry may result from further studies in this area.

Preparation of Quinone Monoketals via Hydrolysis of Quinone Bisketals

We feel that the most important reaction of quinone bisketals is one of the simplest: hydrolysis to the synthetically versatile quinone monoketal. Earlier studies had shown that a variety of oxidizing agents converted *p*-methoxyphenols to quinone monoketals,[17-19] and uses of these synthetic intermediates began to appear shortly thereafter. Having established the general nature of the anodic oxidation route to quinone bisketals, we felt the direct hydrolysis of quinone bisketals to their monoketals offered an advantage over the more classical oxidations of *p*-methoxyphenols. The latter route requires the availability of the appropriate *p*-methoxyphenol and often employs expensive and/or toxic oxidizing agents. By contrast, the anodic oxidation–hydrolysis route uses the more available hydroquinone dimethyl ether and employs a simple acid hydrolysis.

Two points of initial concern were the selectivity in the monohydrolysis of the quinone bisketal to the quinone monoketal relative to bishydrolysis to the quinone and the regiochemistry of the hydrolysis of unsymmetrical quinone bisketals. For both benzoquinone and naphthoquinone bisketals, acid-catalyzed monohydrolysis afforded the respective quinone monoketals in synthetically useful yields. In the naphthalene systems (Table III) with R^1 = CH_3, Br, and SCH_3, the monohydrolysis is nearly regiospecific. In the benzenoid series (Table IV), the regioselectivity for the hydrolysis was highly selective with R = Br, NHC(=O)CH_3, OCH_3, or SCH_3, with an 85:15 mixture being observed with R = CH_3. The directing effect of these substituents also extends to more highly functionalized bisketals and to bisketals of benzothiophenes.[12] For most systems the pure monoketals could be obtained by simple recrystallization. Synthetically, it is often expedient not to purify the quinone bisketals but simply to hydrolyze the crude anodic oxidation product directly to the quinone monoketals.

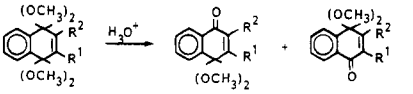
The bisketal hydrolyses noted above are synthetically useful in furnishing one of the quinone monoketal regioisomers. To make the other regioisomer available, we examined the monohydrolysis of the mixed bisketals **15a–d**.[20] For **15a–c**, the monoketals **24a–c** were formed



15 24 25

a, R = H; b, R = CH_3; c, R = Br; d, R = OCH_3

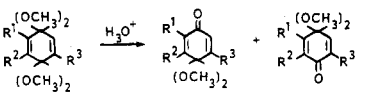
Table III
Monohydrolysis of Naphthoquinone Bisketals



bisketal (R^1, R^2)	mono-ketal yield, %	mono-ketal yield, %
H, H	93	
CH_3, H	90	*a*
Br, H	85	*a*
SCH_3, H	56	*a*
Br, CH_3	94	*a*
CH_3, $Si(CH_3)_3$	57[b]	7[b]
SCH_3, CH_3	58	*c*

[a] Alternate hydrolysis product not seen. [b] Yield is based on aromatic precursor. [c] Other isomer not isolated; NMR of Raney Ni reduction products indicated a 9:1 ratio of the respective monoketals.

Table IV
Monohydrolysis of Benzoquinone Bis(ketals)[18]



bisketal (R^1, R^2, R^3)	mono-ketal yield, %	mono-ketal yield, %
H, H, Br	88	
H, H, CH_3	64[a]	11[a]
H, H, $Si(CH_3)_3$	29[a]	38[a]
H, H, $CH(CH_3)(OCH_3)$	58[a]	19[a]
H, H, $NHC(O)CH_3$	79	*b*
CH_3, CH_3, CH_3	90	*b*
H, H, OCH_3	66[a]	*b*
H, H, SCH_3	60	*b*
H, H, C(O)Ph	42	*b*

[a] Overall yield based on the aromatic precursor. [b] Alternate monoketal not observed.

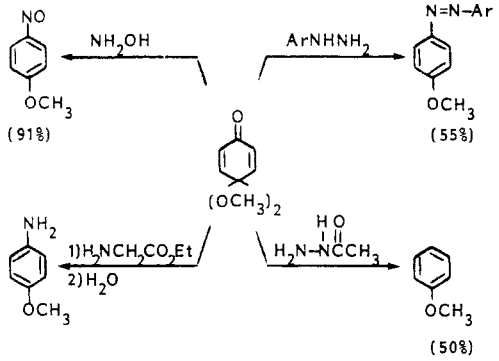
(17) Earlier references have been given in ref 18 except for the omission of the following: Goosen, A.; McCleland, C. *J. Chem. Soc., Chem. Commun.* **1975**, 655.

(18) Henton, D. R.; Anderson, D. K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422.

(19) (a) Goosen, A.; McCleland, C. W. *J. Chem. Soc., Perkin Trans. 1* **1978**, 646. (b) Coutts, I. G. C.; Hamblin, M. R.; Welsby, S. E. *Ibid.* **1981**, 493. (c) Coutts, I. G. C.; Edwards, M.; Musto, D. R.; Richards, D. J. *Tetrahedron Lett.* **1980**, *21*, 5055. (d) Stewart, R. F.; Miller, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 4999. (e) Hart, T. W.; Scheinmann, F. *Tetrahedron Lett.* **1980**, *21*, 2295. (f) Crouse, D. J.; Wheeler, D. M. S. *Ibid.* **1979**, 4797; *J. Org. Chem.* **1981**, *46*, 1814. (g) Fujita, S. *J. Chem. Soc., Chem. Commun.* **1981**, 425. (h) Warrener, R. N.; Gee, P. S.; Russell, R. A. *Ibid.* **1981**, 1100.

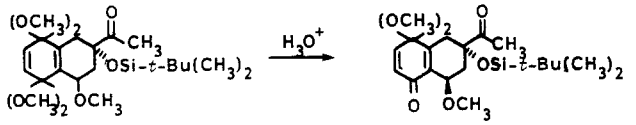
(20) Dolson, M. G.; Swenton, J. S. *J. Org. Chem.* **1981**, *46*, 177.

Scheme IV
Reaction of Monoketals with Ammonia Derivatives



in yields of 94, 93, and 78%, respectively, while for **15d**, the monoketal **25d** was formed in 68% yield. Thus, the slower rate of hydrolysis of an ethylene ketal allows selective hydrolysis to afford monoketals of the regiochemistry shown by **24** in good yield. However, if R is a good electron-donating group (i.e., OCH_3), the monoketal **25d** will result. This method is then valuable in forming monoketals of the regiochemistry shown by **24** only if R is not a group which strongly directs the monohydrolysis.

Thus far, substituents on the quinone bisketal have been shown to control the regiochemistry of the hydrolysis. However, in more complex systems, even subtle changes can lead to synthetically useful directing effects of bisketal hydrolysis. Thus, an allylic methoxy group directs hydrolysis of **26** to afford **27** in 85% yield.



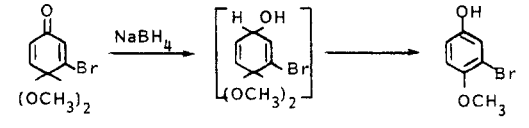
26 **27**

In systems akin to **26** in which this allylic oxygen function is absent, hydrolysis gives quinone monoketal regioisomers with little selectivity.[1c]

Reactions of Quinone Monoketals

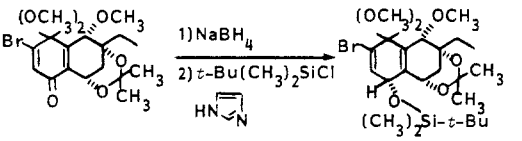
The chemistry of quinone monoketals can be discussed in three general sections:[21] transformations at the carbonyl group, 1,4-addition reactions, and acid-catalyzed reactions. One of the earlier systematic studies of quinone monoketal reactivity dealt with the reaction of the monoketal of benzoquinones with ammonia derivatives (Scheme IV).[22] While such transformations have not yet been used extensively in synthesis, they allow for the replacement of the quinone monoketal carbonyl group by the nitroso, azo, or amino groups, or a hydrogen atom with production of an aromatic system.

Not unexpectedly, sodium borohydride reduction of quinone monoketals affords labile alcohols.[18] With



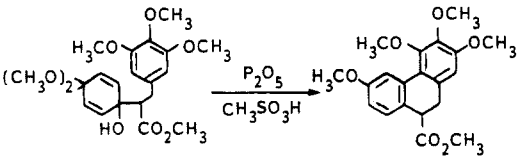
28

monosubstituted systems, sodium borohydride reduction yields alcohols that usually eliminate on standing to form the corresponding *p*-methoxyphenol. However, when the quinone monoketal is more substituted, the alcohols are reasonably stable and can even be functionalized in good yield as illustrated for **29**.



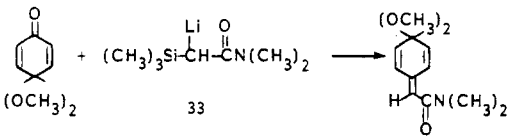
29 **30** (70%)

A major synthetic use of quinone monoketals is the addition reactions of organometallic reagents to the carbonyl group. A main advantage here is the unambiguous regiochemical outcome of the reaction relative to the quinone. Furthermore, the quinone monoketals seem less susceptible to electron-transfer-mediated reduction processes than do the corresponding quinones.[21b,23,24] A number of organolithium and Grignard reagents [e.g., $LiCH_2CO_2$-*t*-Bu, Ar'CH(Li)CON$(CH_3)_2$, $PhSO_2CH_2Li$] react to give the corresponding protected *p*-quinols (e.g., **31**) in good yield.[21b] These adducts can

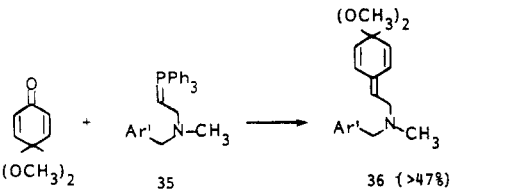


31 **32** (77%)

be employed in synthesis as illustrated by the **31** → **32** cyclization.[26] Peterson[22,26a] and Wittig[26a] reactions on



33 **34** (77%)



35 **36** (>47%)

quinone monoketals have also been reported to yield protected quinone methides (e.g., **34** and **36**).

While quinone monoketals are less susceptible to electron-transfer type reduction processes than the

(21) Discussions of quinone bis- and monoketal chemistry have appeared: see: (a) Fujita, S. *Yuki Gosei Kagaku Kyokaishi* **1981**, 307. (b) Koelsch, P. M.; Tanis, S. P. *Kodak Lab. Chem. Bull.* **1980**, *52*, 1.

(22) Taylor, E. C.; Jagdmann, G. E.; McKillop, A. *J. Org. Chem.* **1978**, *43*, 4385.

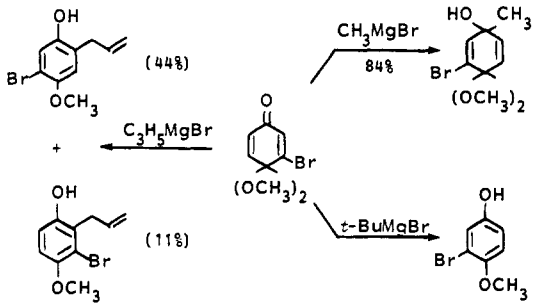
(23) Recent work has been reported on direct reaction of quinones with alkyllithium reagents: Fischer, A.; Henderson, G. N. *Tetrahedron Lett.* **1980**, *21*, 701. See also: Moore, H. W.; Sing, Y. L.; Sidhu, R. S. *J. Org. Chem.* **1977**, *42*, 3320.

(24) Quinones monoprotected as their (trimethylsilyl)oxy cyanide derivatives have also been utilized in the synthesis of *p*-quinols[25] and quinone methides.[26] A direct comparison of the reaction of organometallic reagents with these protected quinone derivatives vs. the analogous reaction with quinone monoketals is unavailable.

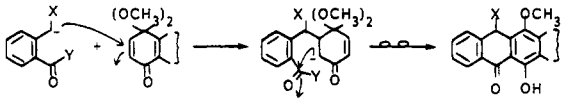
(25) Evans, D. A.; Hoffman, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 1983. Evans, D. A.; Wong, R. Y. *J. Org. Chem.* **1977**, *42*, 350. Parker, K. A.; Andrade, J. R. *Ibid.* **1979**, *44*, 3964. Guildford, A. J.; Turner, R. W. *Tetrahedron Lett.* **1981**, *22*, 4835.

(26) For leading references J.; the Evans' contributions in this area, see: (a) Evans, D. A.; Cain, P. A.; Wong, R. Y. *J. Am. Chem. Soc.* **1977**, *99*, 7083. (b) Hart, D. J.; Cain, P. A.; Evans, D. A. *Ibid.* **1978**, *100*, 1548. (c) Evans, D. A.; Hart, D. J.; Koelsch, P. M.; Cain, P. A. *Pure Appl. Chem.* **1979**, *51*, 1285. (d) Evans, D. A.; Tanis, S. P.; Hart, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 5813.

Scheme V
Reaction of Allyl, Methyl, and *tert*-Butyl Grignard Reagents with a Quinone Monoketal

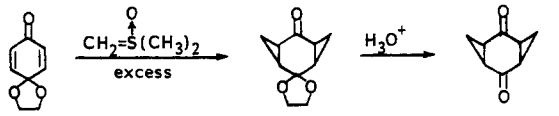


Scheme VI
General Strategy for Annelation Using Quinone Monoketals



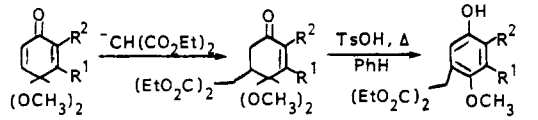
corresponding quinones, such reactions can still be significant in certain instances. Thus, reaction of lithium dimethylcuprate with benzoquinone monoketal was reported to yield *p*-methoxyphenol.[27] Some of the reaction pathways utilized by Grignard reagents are illustrated in Scheme V.[18] While methylmagnesium bromide reacts to form the normal addition product, the *tert*-butyl Grignard gives reduction of the monoketal, and allyl Grignard gives ring-alkylated products.

While cuprate 1,4 additions are preempted by reduction, Michael additions to quinone monoketals are quite general.[17,28] The simple monoketal **24a** was re-



24a **38** (74%) **39** (81%)

acted with excess dimethylsulfoxonium methylide to furnish **38**, which was hydrolyzed to bis(homobenzoquinone).[2] Likewise, addition of diethyl malonate to a series of benzoquinone monoacetals gave adducts of structure **41**, which were subsequently aromatized to **42**.[28] Addition of β-keto esters[28] to quinone monoketals



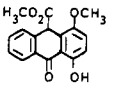
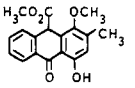
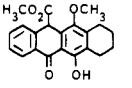
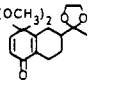
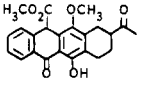
40	R^1	R^2	**41**	**42**
	H	H	(91%)	(88%)
	H_3CO	H	(83%)	(63%)
	H_3CO	CH_3	(70%)	(86%)

followed several alternative pathways that will not be discussed here.

Quinone monoketals are particularly useful for the regiospecific synthesis of polycyclic ring systems. Scheme VI illustrates the general strategy for the utilization of quinone monoketals in regiospecific annelation reactions. Since highly functionalized monoketals

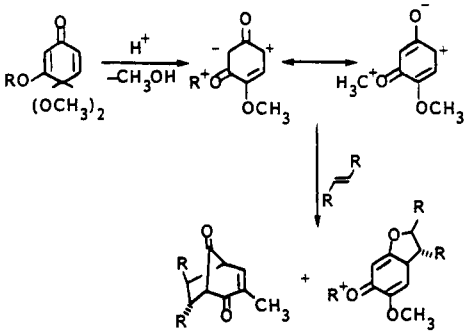
(27) Nilsson, A.; Ronlan, A. *Tetrahedron Lett.* **1975**, 1107.
(28) Parker, K. A.; Kang, S. *J. Org. Chem.* **1980**, *45*, 1218.

Table V
Reaction of Dimethyl Homophthalate with Quinone Monoketals

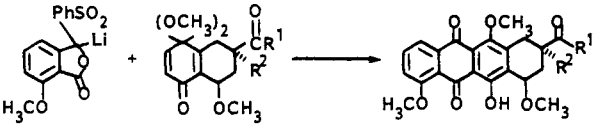
entry	monoketal	product	yield,[a] %
1			60
2			40
3			60
4			41

[a] Yield of recrystallized product, not optimized.

Scheme VII
Oxygenated Quinones as Positively Charged 1,3-Dipoles in Their Reactions with Olefins



are readily available via the anodic oxidation–hydrolysis route, this route is especially attractive to linearly fused natural products. Two particular reagents have been successfully employed with quinone monoketals in synthesizing these linear fused-ring systems. Reaction of dimethyl homophthalate (X = CO_2CH_3, Y = OCH_3, Scheme VI) afforded the adducts shown in modest yields (Table V).[29] The reaction of the lithiated lactone sulfone, **43**,[30] with monoketals is reasonably general and



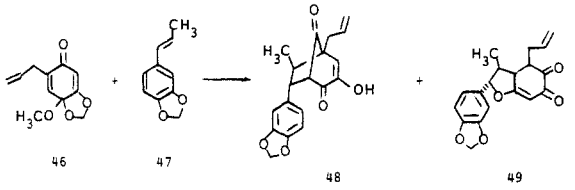
43	R^1	R^2	
	44a, OCH_3	H	**45a**
	b, OCH_3	OH	**b**
	c, OCH_3	$OSi(CH_3)_3$	**c**
	27, CH_3	$OSi\text{-}t\text{-}Bu(CH_3)_2$	

proceeds in about 50% yield.[1c,31] This annelation, together with the selective monohydrolysis of **26** mentioned earlier, has led to a convergent regiospecific route to the daunomycinone–adriamycinone type aglycons.[1c] One factor contributing to the moderate yields of an-

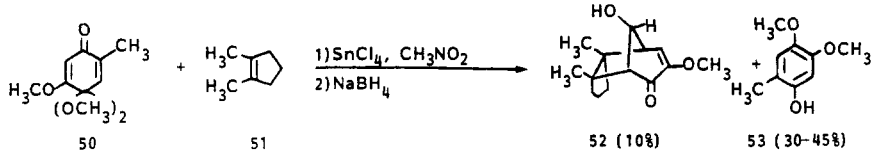
(29) Chenard, B. L.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, 932.
(30) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378 and references cited therein.
(31) See also: Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1981**, 108.

nelated products with **43** is the competing Michael addition of $PhSO_2^-$, released in the cyclization reaction, to the starting quinone monoketals. Use of a system in which this side reaction is minimized could substantially improve the overall yields of annelation products.

A second class of annelation reactions consists of acid-catalyzed reactions of oxygen-substituted monoketals with olefins. Such reactions can be visualized as proceeding via a positively charged 1,3-dipole reactant (Scheme VII). This type of reaction (illustrated by **46** + **47**) has been used to obtain key intermediates for

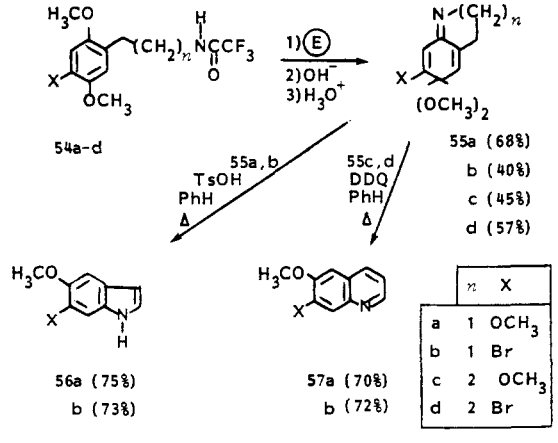


elaboration of neolignan-type natural products.[32] An especially short synthesis of gymnomitrol employed as a key step the acid-catalyzed addition of monoketal **50** and 1,2-dimethylcyclopentene to give **52**. However, the



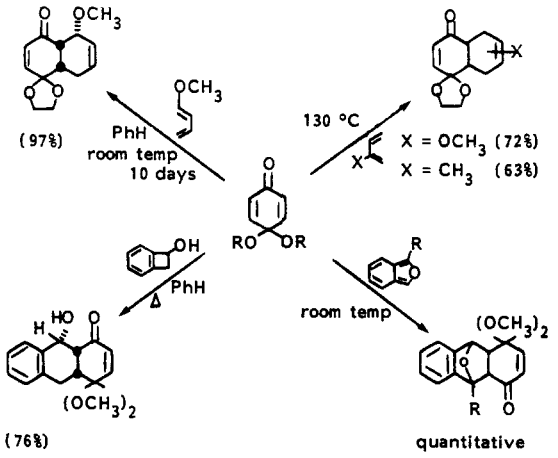
reduced product **53** is the major product from the reaction. We have also observed formation of reduced products from treatment of quinone monoketals with acid in the absence of good nucleophiles. Presumably, ionization of the quinone monoketal is followed by hydride transfer from the alcohol moiety.

Finally, the ability to successfully form quinone bisketals anodically in the presence of other reducible and oxidizable functions allows intramolecular reactions of monoketals generated in situ to be studied.[6] Thus, the amines **54a–d**, through a reaction sequence of anodic



oxidation, base hydrolysis of the trifluoroacetyl group, and treatment with aqueous acid, afford the iminoquinone monoketals **55a–d** in good overall yield. These systems are then readily transformed to their respective indole and quinoline derivatives. Much more chemistry

Scheme VIII
Representative Diels–Alder Reactions of Quinone Monoketals



of these nitrogen analogues of quinone monoketals remains to be explored.

Thus far, the thermal addition reactions of quinone monoketals have been limited to Diels–Alder chemistry.[10,33,34] The benzoquinone monoketals undergo Diels–Alder reaction with 1-methoxybutandiene, isoprene, and 2-methoxybutadiene (Scheme VIII). The former reaction is highly regiospecific, while the latter two reactions show virtually no regioselectivity. Interestingly, Diels–Alder reactions with benzocyclobutenol[10,33a] and isobenzofurans[33b] (12 examples) have also been reported in connection with projected routes to anthracyclinone natural products. While quinones themselves show high Diels–Alder reactivity, the Diels–Alder adducts of quinone monoketals may offer a special advantage when selective functionalization of one of the quinone carbonyl groups is required in a subsequent step.

Conclusion

Anodic oxidation of oxygenated benzene and naphthalene derivatives in methanolic potassium hydroxide at a platinum or carbon anode serves as a versatile route to quinone bisketals. Even systems with a high degree of functionality can be obtained in good yield if the functional groups are present in protected form. Hydrolysis of these quinone bisketals usually affords good yields of quinone monoketals with a high degree of regioselectivity. This anodic oxidation/hydrolysis sequence complements the previously developed chemical oxidation methods for forming quinone monoketals. In most cases, we feel the former procedure is the method of choice for large-scale preparation of these compounds.

Both quinone bis- and monoketals are versatile reagents for preparation of functionalized aromatic

(32) Büchi, G.; Chu, P. *J. Am. Chem. Soc.* **1979**, *101*, 6767 and references cited therein.

(33) (a) Carreño, M.; Fariña, F.; Galan, A.; Ruano, J. *J. Chem. Res., Synop.* **1981**, 370; *J. Chem. Res., Miniprint* **1981**, 4310. (b) Warrener, R. N.; Hammer, B.; Russell, R. *J. Chem. Soc., Chem. Commun.* **1981**, 942.

(34) See also: Brownbridge, P.; Chan, T. *Tetrahedron Lett.* **1980**, *21*, 3431.

systems. The quinone monoketals are especially valuable as regiospecific quinone equivalents. They undergo reactions with a variety of organometallic reagents, the products of which serve as key intermediates in the formation of *p*-quinols and quinone methides. The annelation chemistry of the quinone monoketals allows regiospecific routes to linear polycyclic natural products. Since most of the chemistry reported here has been published since 1976,[35] new reactions and synthetic applications of quinone bisketals and monoketals remain to be reported.

(35) It has not been possible to discuss all of the applications of quinone monoketals in synthesis. References 18 and 21 cite most of the other published work.

We gratefully acknowledge support from the National Science Foundation that initially allowed this venture into organic electrochemistry and its application to organic synthesis. Much of the chemistry discussed herein was directed at the synthesis of quinone natural products and was supported by the National Institutes of Health. The author is grateful to his students who not only carried out the majority of the laboratory work but also contributed immeasurably in certain cases to the synthetic strategy. Thanks also go to B. Chenard, D. Henton, J. Richardson, and especially L. Spangler for numerous helpful comments and criticisms concerning this manuscript.

Pericyclic Reactions of Vinylallenes: From Calciferols to Retinoids and Drimanes

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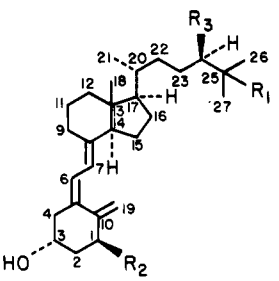
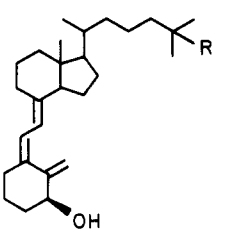
Vitamin D (Calciferol)

It is now established that, before vitamin D_3 (**1a**, D_3) can elicit its classic physiological responses, intestinal calcium absorption and bone calcium mobilization, it must undergo successive hepatic and renal hydroxylation to afford 25-hydroxyvitamin D_3 (**1b**) and 1α,25-dihydroxyvitamin D_3 (**1c**, 1α,25-$(OH)_2$-D_3), respectively.[1] Of the numerous metabolites of D_3 that have now been isolated and chemically characterized, **1b** and **1c** are considered the principal metabolites, although another renal metabolite, (24*R*)-24,25-dihydroxyvitamin D_3 (**1d**), appears to be required for at least some of the vitamin D mediated biological responses.[2] Particularly intriguing is the emergence of the notion that the vitamin D endocrine system resembles that of the classical steroid hormones such as estradiol, progesterone, testosterone, cortisone, and aldosterone. Thus, 1α,25-$(OH)_2D_3$ should no longer be considered a vitamin, but rather it should be considered a steroid hormone both structurally and functionally.[1a]

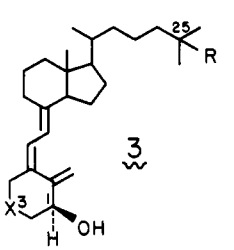
In order to develop a more detailed understanding of the vitamin D endocrine system, we and others have focussed attention on the chemical synthesis of metabolites and analogues of vitamin D. The studies at Riverside have progressed through collaborative efforts between the author's research group and that of Professor Anthony W. Norman of the Department of Biochemistry. Analogues of biologically active molecules, which can be classed as *agonists*, *antagonists*, or *synergists*, are useful biochemical research tools and are of potential value for clinical applications. Biologically



1a, $R_1=R_2=R_3=H$
b, $R_1=OH; R_2=R_3=H$
c $R_1=R_2=OH; R_3=H$
d $R_1=R_3=OH; R_2=H$



2a, R=OH
b R=H



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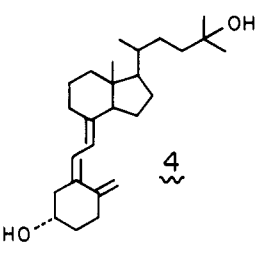

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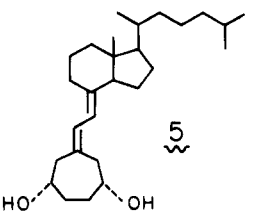

5

William Okamura was born in 1941 in Los Angeles, CA. He received his B.S. from UCLA in 1962 and his Ph.D. from Columbia University with Thomas J. Katz in 1966. After postdoctural studies at Cambridge University with the late Franz Sondheimer, he joined the faculty of the University of California, Riverside, in 1967; he is currently Professor of Chemistry at the same institution. His major research interests are in the synthetic organic chemistry area, especially synthetic and structure–activity studies of vitamins A and D, pericyclic reactions of allenes, and the synthesis of natural products and molecules of theoretical interest.

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