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Model Studies for Anthracyclinone Synthesis. The Chemistry of 1-Lithio-3,3,6,6-tetramethoxycyclohexa-1,4-diene, an Umpolung† for Quinone‡[1]

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Abstract: Anodic oxidation of 2-bromo-1,4-dimethoxybenzene (**6b**) in 1–2% methanolic potassium hydroxide affords 1-bromo-3,3,6,6-tetramethoxycyclohexa-1,4-diene (**8**) in 70–80% yield. This bromo bisketal undergoes metal–halogen exchange with alkyllithiums at −70 °C to afford solutions of the corresponding lithio derivative, **9**. The resulting organolithium reagent reacts with cyclohexanone (81%), cycloheptanone (40%), benzaldehyde (68%), benzophenone (72%), benzil (60%), methyl benzoate (78%), benzoylpiperidine (68%), benzoyl chloride (67%), and dimethyl phthalate (70%) to form adducts in the indicated yields. This comprises a method for preparation of functionalized protected quinones. However, **9** yields adducts in poor yields with alkyl, allyl, and benzyl halides and easily enolized substrates. The regioselectivity of the reaction of **9** and dimethyl 3-methoxyphthalate involves attack at the more reactive and the less hindered 1-carbonyl group. A brief comparison is made of the reactions of **9** and 2-lithio-1,4-dimethoxybenzene.

Introduction

While the quinone moiety is widely represented in naturally occurring compounds, few methods are available for direct carbon–carbon bond formation on the quinone nucleus.[4] C-Alkylation has been accomplished via a radical addition–oxidation sequence[5] while C-arylation is generally performed in high yield by reaction of benzoquinones with diazonium salts.[6] Hegedus has extensively explored the utility of the coupling of quinones to allylic fragments via π-allyl nickel halide complexes.[7] Recent routes to the isoprenylation of naphthoquinones have involved the use of trimethylsilyl cyanide protected quinones[8] and quinone bisketal copper–lithium reagents.[9] Aside from the novel approach of Moore[10a] to 2,5-disubstituted 1,4-benzoquinones, conventional methodology for preparing substituted quinones has involved either additions to quinones to afford reduced derivatives followed by oxidation in a sub-

† A reagent which reverses the normal type of reactivity, in this case causing the quinone to be a nucleophile rather than an electrophile.
‡ Dedicated to Professor Melvin S. Newman on his 70th birthday.

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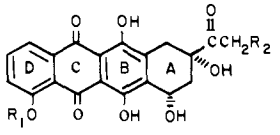
sequent step or functionalization of substituted hydroquinone ethers followed by oxidation.[10b]

Our interest in developing a new method for quinone functionalization derived from projected synthetic routes to anthracycline antibiotics. For this problem the known methods of quinone functionalization did not appear readily applicable for our intended synthetic strategy. We report here that anodic oxidation of brominated 1,4-dimethoxybenzenes affords bromoquinone bisketals. Metalation of the brominated bisketals at low temperature with alkyllithiums followed by reaction of the lithiated derivatives with electrophiles affords functionalized quinone bisketals. Finally, model studies for the utilization of these reagents in a regiospecific approach to anthracyclinones are presented.

Lithiated Quinone Bisketals

A central problem in the construction of the anthracyclinones (i.e., **1**) is the control of regioselectivity between the A



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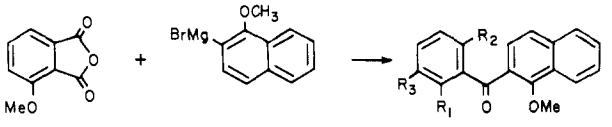
and D rings of the tetracyclic system.[11] Since the functionalities in the A and D ring are quite removed from each other, an approach involving selective attack of an organometallic reagent at the more reactive and less hindered carbonyl group at C_1 of a 3-methoxyphthalate derivative was considered. Some precedent for this proposal was available from a study of the reactions of 3-methylphthalic anhydride with Grignard reagents.[12] With increasing bulkiness in the Grignard reagent, attack at the less hindered carbonyl became more favored (Scheme I). At the time our work was initiated, the only investigation of a reaction of an organometallic reagent and a 3-methoxyphthalate derivative was that with the naphthyl Grignard **3**.[13a,b] Disappointingly, this reaction showed poor regioselectivity even with this somewhat bulky reagent, yielding **4** and **5** in the ratio 64:23.[13] The predominant attack

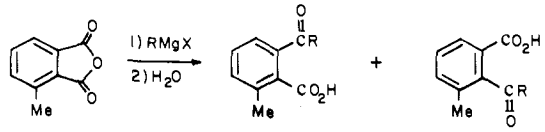


2 **3** **4** $R_1 = OCH_3, R_2 = CO_2H, R_3 = H$; **5** $R_1 = CO_2H, R_2 = H, R_3 = OCH_3$

at the more hindered carbonyl could be rationalized by assuming complexing of the reagent with the methoxy group, thus favoring attack at C_2.

In view of the above results we reasoned that a bulky organometallic species with a cation less susceptible to complexation by a methoxy group would afford the best opportunity for regiospecific addition to dimethyl 3-methoxyphthalate. A candidate for the desired reagent would be the organolithium derivative of a quinone bisketal. Since the anodic oxidation of

Scheme I. Effect of Bulkiness on Regioselectivity of Grignard Additions to 3-Methylphthalic Anhydride



R	% YIELD	% YIELD
ϕ	43	14
$2,4-(CH_3)_2C_6H_3$	39	4
$2,4,6-(CH_3)_3C_6H_2$	66	1

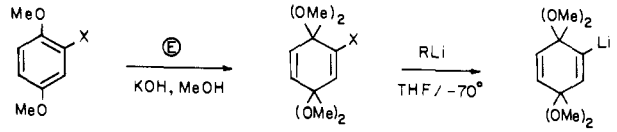
Table I. Reactions of 1-Lithio-3,3,6,6-tetramethoxy-1,4-cyclohexadiene

substrate	yield bisketal,[a] %	yield quinone,[a] %
cyclohexanone	81	80
cycloheptanone	40	83
benzaldehyde	68	88
benzophenone	72	74
benzil	60	88
methyl benzoate	78	*b*
benzoylpiperdine	68	*b*
benzoyl chloride	67	*b*
dimethyl phthalate	70[d]	*c*
dimethyl 3-methoxyphthalate	70	*c*
cyclopentanone		
CH_3I, CH_3CH_2I, CH_3COH, CH_3COCH_3, $PhCH_2Br$, $PhCH_2Cl$, CH_3COCl, $(CH_3)_2SO_4$	compounds affording low/no yields of adducts using 1 equiv of electrophile	

[a] Isolated yields of crystalline products. [b] Hydrolysis of these systems did not afford quinones. [c] Hydrolysis not studied. [d] A mixture of normal and pseudoester was obtained.

hydroquinone dimethyl ether to benzoquinone bisketal had been reported by Weinberg and Belleau[14,15] several years ago, an extension of this reaction to the problem at hand was explored. Anodic oxidation of 2-chloro- and 2-bromo-1,4-dimethoxybenzene afforded cleanly the respective bisketals in yields of 83 and 75%. The bromo derivative **8** proved more convenient for conversion to the anion; thus, all further studies were conducted with **8**.

The reaction of **8** with commercial alkyllithium reagents at −70 °C in dry tetrahydrofuran resulted in rapid metal–halogen exchange to produce colorless solutions of the organolithium reagent. While phenyl-, methyl-, *n*-butyl-, *sec*-butyl-, and *tert*-butyllithium all effected metal–halogen exchange, the first two organolithiums were inferior to the latter three in the yield of the lithiated bisketal. For the reactions investigated here *n*-butyllithium was used exclusively. The lithiated bisketal is sufficiently reactive so that the electrophile usually reacts completely at −78 °C within 15–20 min. One run in which **9**

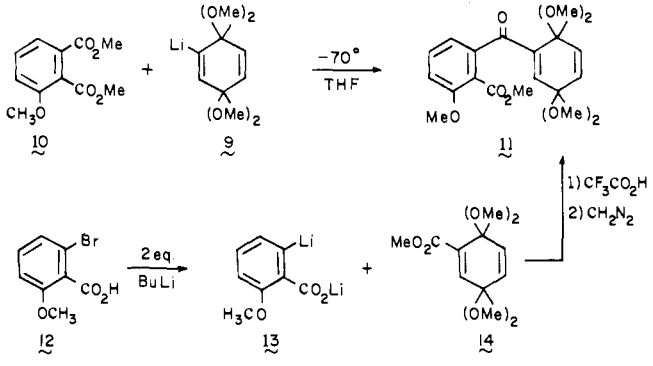


6 a X = Cl, b X = Br **7** X = Cl **8** X = Br **9**

was warmed to room temperature and then reacted with methyl benzoate at −70 °C gave a yield of adduct comparable with that from the reaction at low temperature. While the lithiated bisketal has some stability at room temperature, we consider it advisable to conduct both generation and reaction of the species at low temperature. Table I surveys the reactivity of **9** with representative carbonyl compounds. Several comments are in order: (1) the reagent reacts with difficultly enolizable ketones to give adducts in good yield while protonation is a problem with more readily enolizable substrates; (2) this hindered reagent reacts cleanly with aryl esters to give ketones; (3) hydrolysis of the adducts with aldehydes and ketones affords the parent quinones in high yield; and (4) the organolithium affords low yields of adducts with alkyl and allylic bromides.

Regioselectivity of the Reaction of the Lithiated Bisketal and Dimethyl 3-Methoxyphthalate

Of critical importance in the use of intermediates such as **9** in an anthracyclinone synthesis was the regioselectivity of its reaction with a 3-methoxyphthalate derivative. Gratifyingly, the reaction of **9** with **10** was quite clean. In addition to the nearly complete absence of pseudoesters, there was formed one adduct in 65–70% yield which could be isolated by direct recrystallization. There was no indication that a second regioisomer was formed since the majority of the remaining material was the unsubstituted bisketal and unreacted **10**. The position of attack was firmly established by an unequivocal alternate synthesis. Thus the laboriously prepared bromoacid **12**[16] was treated with 2 equiv of *n*-butyllithium at −95 °C by Parham's[17] procedure to afford a solution of **13**. Reaction of **13** with **14** followed by careful acidification at low temperature

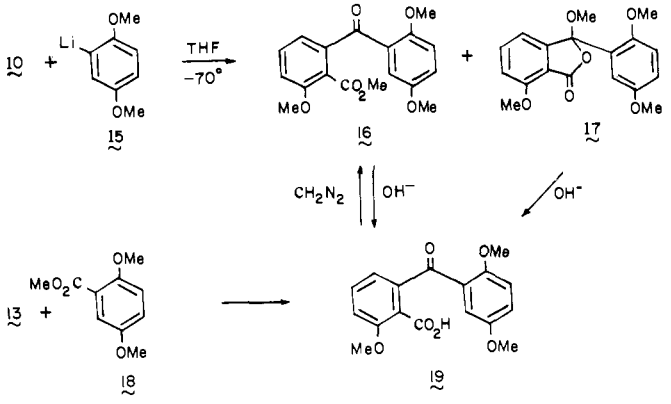


and esterification with diazomethane gave a product identical in all respects with **11**. Thus, the regiospecific addition of **9** to **10** provided strong precedent for this basic approach to the anthracyclinone ring systems.

Comparison of the Reactions of 2-Lithiobisketal and 2-Lithio-1,4-dimethoxybenzene

Our initial motivation in investigating the bisketal system was the desire to have a highly hindered organometallic center which we hoped would minimize neighboring group participation in the attack on a 3-methoxyphthalate derivative. Furthermore, the character of the bisketal offered possibilities for a second intramolecular ring closure not amenable to a fully aromatic compound. However, with the results from the bisketal system complete we have compared this chemistry with that of its aromatic counterpart.

The reaction of **10** with **15** afforded a crude product mixture which was much more complex in the methoxy region of the NMR spectrum than the analogous reaction of **9** and **10**. While the minor product **17** (9%) crystallized from an ethereal solution of the mixture, the major product **16** (ca. 40%) could not be obtained pure after chromatography. The structures assigned to **16** and **17** were established by synthesis and chemical interconversion. Reaction of **13** with **18** gave the crystalline

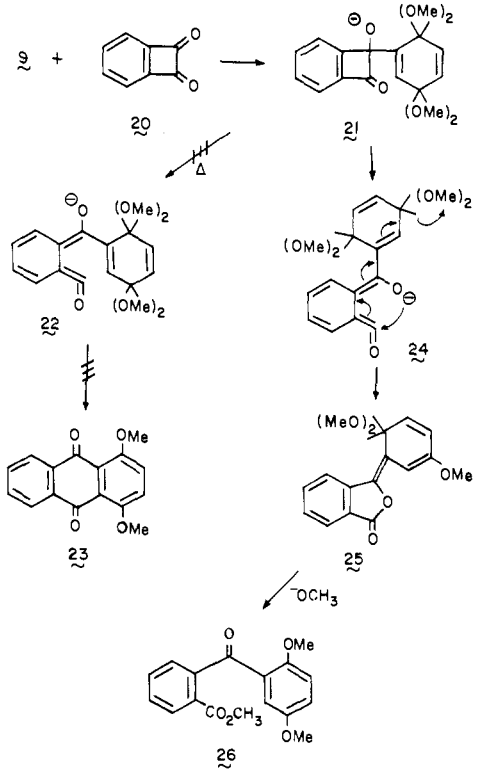


acid **19** in good yield. Hydrolysis of the impure ester **16** obtained in the reaction described above also gave **19**. That the minor product **17** was a pseudoester was apparent from the IR (C=O, 5.62 μ), the low-field methoxy resonance (τ 6.76), and the molecular formula. The orientation of **17** was assigned on the basis of its chemical conversion to **19** on saponification. Thus, the aromatic lithium reagent also shows regioselectivity in its reaction with dimethyl 3-methoxyphthalate. While the yields of adduct are similar, purification of the product is more complicated in the case of the aromatic system owing to the presence of the pseudoester and other unidentified minor impurities.

We have also attempted to compare the relative reactivity of the lithiated bisketal vs. the lithiated aromatic compound. Both **9** and **15** were reacted independently with methyl benzoate at low temperature to afford the respective adducts in VPC yields of 84 and 90%. When a solution of **9** and **15** was reacted with 1 equiv of methyl benzoate the adduct of the bisketal was produced almost exclusively; however, the adduct was formed in only 40% yield. This result, which suggests high reactivity for **9**, is unfortunately clouded by the lower yield of the bisketal adduct in the competition experiment.

Reaction of the Lithiated Bisketal with Benzocyclobutene-1,2-dione

Aside from the high regioselectivity expected and found in the reaction of **9** and dimethyl 3-methoxyphthalate, the bisketal offered the possibility of effecting the formation of a subsequent ring closure under mild conditions. Thus, reaction of **9** with the dione **20** followed by electrocyclic ring opening and intramolecular Diels–Alder reaction would comprise a mild procedure for ring formation in the anthracyclinone. Precedent is available for both the ring opening with proper stereochemistry[18] and the intramolecular Diels–Alder reaction.[19] Reaction of anion **9** with **20** under a variety of experimental conditions afforded no evidence for the desired reaction. Instead a complex reaction mixture resulted from which **26**



(25%) was isolated. We are currently exploring modifications of this route to effect one-step C-ring formation.

Summary

The 2-lithio derivative of the bisketal of benzoquinone is a versatile reagent for the preparation of functionalized benzoquinone derivatives. This compound undergoes regiospecific coupling with dimethyl 3-methoxyphthalate, demonstrating the potential utility of this reaction in a regiospecific approach to anthracyclinones. Work described in the following paper has applied this chemistry to a regiospecific synthesis of adriamycinone while preliminary reports have established the utility of the protected quinones in the preparation of quinone monoketals[9b] and the synthesis of naturally occurring isoprenoid quinones.[9a]

Experimental Section[20]

2-Bromo-1,4-dimethoxybenzene (6b). This material is best prepared by bromination of hydroquinone in ether with dioxane dibromide followed by conventional workup and sublimation (96%, >95% pure). This 2-bromohydroquinone was then methylated with dimethyl sulfate and base in the standard fashion.

1-Chloro-3,3,6,6-tetramethoxy-1,4-cyclohexadiene (7). A solution of 3.44 g (0.02 mol) of 2-chloro-1,4-dimethoxybenzene and 0.4 g of potassium hydroxide in 80 mL of absolute methanol was electrolyzed for 3.5 h. The reaction was followed by VPC (6 ft × 1/8 in., 3% SE-30 on 60/80 Chromosorb G at 130 °C) until **6a** had disappeared; the trace showed one new compound at longer retention time. The methanol was removed in vacuo, affording a yellow semisolid; petroleum ether (200 mL) was added, the solution vacuum filtered, and the solvent removed in vacuo to afford a solid which was crystallized from petroleum ether to yield 3.9 g (83%) of pure, white, crystalline product: mp 60–61 °C; IR (KBr) cm^{-1} 2940 (m), 1395 (m), 1090 (s), 1080 (s), 1040 (s), 1020 (m), 965 (s), 945 (m), and 798 (m); NMR (CCl_4) δ 3.17 (s, 6 H), 3.24 (s, 6 H), and 5.90–6.30 (ABC m, 3 H).

Anal. Calcd for $C_{10}H_{15}O_4Cl$: C, 51.18; H, 6.44; Cl, 15.11. Found: C, 51.16; H, 6.41; Cl, 15.10.

1-Bromo-3,3,6,6-tetramethoxy-1,4-cyclohexadiene (8). A solution of 29.5 g (0.14 mol) of 2-bromo-1,4-dimethoxybenzene in 550 mL of 2% methanolic potassium hydroxide was electrolyzed for 10 h at 4–5 °C using the electrolysis cell shown in Figure 1. (For a description of the power supply see ref 20.) A constant potential of 2.2 V vs. a Pt reference electrode resulted in an initial current of 2.2 A which gradually dropped to 0.8 A after 10 h. At this point UV analysis indicated greater than 96% consumption of the aromatic compound. The methanol was removed in vacuo and the yellow, oily solid dissolved in 200 mL of ether and 100 mL of water. The ethereal layer was washed with saturated brine solution and dried over Drierite. After concentration the crude solid was recrystallized from low-boiling petroleum ether to afford 29.4 g (74%) of the bisketal in two crops: mp 63.5–64.0 °C; IR (KBr) cm^{-1} 1395 (m), 1125 (m), 1090 (s), 1120 (m), 1040 (s), and 960 (s); NMR (CCl_4) δ 3.15 (s, 6 H), 3.23 (s, 6 H), 5.93 (s, 1 H), 3.52 (A of AB, J = 10 Hz, 1 H) 6.13 (d of d, J = 10, 2.5 Hz, 1 H), and 6.48 (d, J = 2.5 Hz, 1 H).

Anal. Calcd for $C_{10}H_{15}O_4Br$: C, 43.03; H, 5.36; Br, 28.62. Found: C, 43.09; H, 5.43; Br, 28.64.

Reactions of 1-Lithio-3,3,6,6-tetramethoxy-1,4-cyclohexadiene. The reactions of the bromo bisketal were performed in dry tetrahydrofuran (~0.6 g of bisketal/10 mL of THF) under nitrogen by addition of an equimolar (in some instances a 5% excess of alkyllithium was employed) amount of butyllithium at −78 °C, stirring for 1 min, introduction of the other reactant via syringe, and stirring for 1 h. Workup consisted of addition of water at −70 °C, allowing the mixture to warm to room temperature, and then extraction with ether. The ether layers were combined and washed with saturated brine, dried over calcium sulfate, and concentrated in vacuo.

D_2O. The anion formed from 0.42 g (1.5 mmol) of bromo ketal and 690 μL of 2.2 M butyllithium was quenched with D_2O. Workup afforded a solid which was recrystallized from ether/petroleum ether to yield 0.26 g (86%) of the 1-deuterio compound, mp 40.5–41.5 °C. NMR analysis indicated >95% deuterium incorporation.

Benzophenone. To the anion formed as above was added dropwise 0.273 g (1.5 mmol) of benzophenone in 1 mL of dry tetrahydrofuran. The reaction mixture was stirred for 15 min at −78 °C and an additional 1 h at room temperature. Workup afforded a solid which was recrystallized from ether/petroleum ether to yield 0.415 g (72%) of crystalline product: mp 94–95 °C; IR (KBr) cm^{-1} 3540 (s), 1450 (s), 1395 (s), 1130 (s), 1040–1060 (s, br), 975 (s), 785 (m), and 715 (m); NMR (CCl_4) δ 3.06 (s, 6 H), 3.09 (s, 6 H), 4.90 (s, 1 H), 5.55 (d, J = 2.5 Hz, 1 H) 5.80 (A of AB, J = 10 Hz, 1 H), 6.16 (d of d, J = 10, 2.5 Hz, 1 H), and 7.1–7.3 (m, 10 H); ^{13}C NMR ($CDCl_3$) ppm 49.69, 51.09, 83.03, 93.23, 98.57, 126.95, 127.60, 127.87, 128.63, 131.22, 133.75, 142.92, and 146.16.

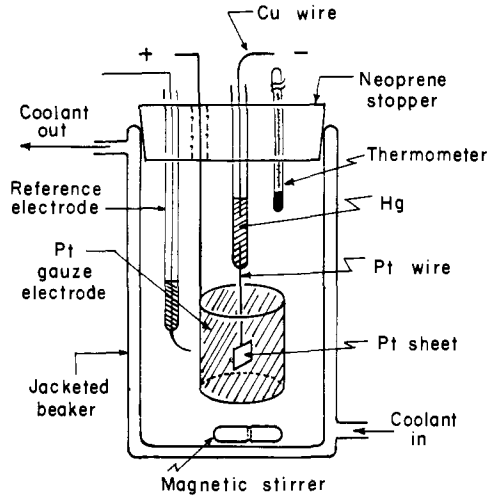


Figure 1. Apparatus for electrolysis.

Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.20; H, 6.74.

Benzaldehyde. To the anion formed from 0.84 g (3.0 mmol) of **8** and 1.4 mL of 2.2 M butyllithium in 15 mL of tetrahydrofuran was added dropwise 0.318 g (3.0 mmol) of benzaldehyde. The mixture was stirred at −78 °C for 1 h and worked up to afford a light-yellow oil. The crude product was chromatographed on neutral alumina (activity III, 28 × 1.5 cm column). Elution proceeded as follows: 20% ether/petroleum ether (150 mL), 0.216 g of benzaldehyde and 3,3,6,6-tetramethoxy-1,4-cyclohexadiene; 50% ether/petroleum ether (200 mL), 0.620 g (68%) of a pure, white, crystalline solid [mp 50–51 °C; IR (KBr) cm^{-1} 3430 (s), 1410 (s), 1115 (s), 1075 (s), 1045 (s), 980 (s), 955 (s), 905 (m), and 710 (m); NMR (CCl_4) δ 2.95 (s, 3 H), 3.08 (s, 3 H), 3.13 (s, 3 H), 3.24 (s, 3 H), 5.45 (s, 1 H), 5.7–6.2 (m, 3 H), and 7.1–7.4 (m, 5 H)].

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.75; H, 7.33.

Benzil. To the anion formed from 0.42 g (1.5 mmol) of **8** and 690 μL of 2.2 M butyllithium in 10 mL of tetrahydrofuran, 0.315 g (1.5 mmol) of benzil in 2 mL of tetrahydrofuran was added dropwise. Workup afforded a yellow oil which was chromatographed on neutral alumina (activity, III, 15 × 1.5 cm column). Elution proceeded as follows: 10% ether/petroleum ether (100 mL), 0.374 g (60%) of pure, white, crystalline product [mp 95–96 °C; IR (KBr) cm^{-1} 3425 (m), 1680 (s), 1245 (s), 1130 (s), 1095 (s), 1085 (s), 1070 (s), 1055 (s), 970 (s), and 745 (s); NMR (CCl_4) δ 3.05 (s, 3 H), 3.10 (s, 3 H), 3.23 (s, 6 H), 5.4–5.6 and 5.9–6.1 (m, 4 H), and 7.1–7.8 (m, 10 H)].

Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found: C, 70.31; H, 6.39.

Methyl Benzoate. To the anion formed from 1.26 g (4.5 mmol) of **8** and 2.1 mL of 2.2 M butyllithium was added 0.612 g of methyl benzoate. Workup afforded a yellow liquid which was chromatographed on neutral alumina (activity III, 28 × 1.5 cm column). Elution proceeded as follows: 20% ether/petroleum ether (50 mL), 0.210 g of methyl benzoate and 3,3,6,6-tetramethoxy-1,4-cyclohexadiene (200 mL), 1.078 g (78%) of pure, white, crystalline solid [mp 66–67 °C; IR (KBr) cm^{-1} 1670 (s), 1265 (s), 1130 (s), 1110 (s), 1085 (s), 1070 (s), 1055 (s), and 972 (s); NMR (CCl_4) δ 3.24 (s, 6 H), 3.27 (s, 6 H), 6.0–6.15 (m, 3 H), 7.3–7.5 (m, 3 H), and 7.75–8.0 (m, 2 H)].

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.62; H, 6.48.

Benzoylpiperidine. To the anion derived from 0.84 g (3.0 mmol) of **8** in the usual manner, 0.57 g (3.0 mmol) of benzoylpiperidine in 2 mL of tetrahydrofuran was added. Workup afforded a yellow liquid which was chromatographed on neutral alumina (activity III, 21 ×

1.8 cm column). Elution proceeded as follows: 15% ether/petroleum ether (150 mL), nil; 25% ether/petroleum ether (50 mL), 0.153 g of 3,3,6,6-tetramethoxy-1,4-cyclohexadiene; 25% ether/petroleum ether (200 mL), 0.621 g (68%) of pure, white, crystalline solid, mp 66–67 °C.

Benzoyl Chloride. The alkyllithium compound was generated by adding 1.4 mL of 2.2 M solution of butyllithium to a cooled (−60 °C) solution of 0.84 g (3.0 mmol) of the bromo bisketal **8** in 10 mL of dry tetrahydrofuran. This was added via a glass-jacketed dropping funnel containing dry ice-2-propanol to a stirred, cooled (−60 °C) solution of 0.633 g (4.5 mmol) of benzoyl chloride in 5 mL of dry tetrahydrofuran. After the addition, the mixture was stirred for 0.5 h at −60 °C. The reaction mixture was quenched with water (5 mL) and extracted with ether (2 × 10 mL). The ether layer was washed with saturated brine solution (5 mL) and dried over calcium sulfate, and the solvent was removed in vacuo to afford a yellow liquid. The crude product was chromatographed on neutral alumina (activity III, 28 × 1.5 cm column). Elution proceeded as follows: 20% ether/petroleum ether (100 mL), 0.120 g of 3,3,6,6-tetramethoxy-1,4-cyclohexadiene; (200 mL), 0.610 g (67%) of product as a pure, white, crystalline solid, mp 66–67 °C.

Cyclohexanone. To a solution of the lithio compound formed in the usual way from 0.84 g (3.0 mmol) of **8** was added 0.294 g (3.0 mmol) of cyclohexanone dropwise. Workup afforded a light-yellow solid which was recrystallized from ether/petroleum ether to yield 0.692 g (82%) of crystals: mp 71–72 °C; IR (KBr) cm^{-1} 3532 (m), 2920 (s, br), 1055 (s, br), and 950 (s); NMR (CCl_4) δ 0.8–2.1 (m, br, 10 H), 3.26 (s, 6 H), 3.30 (s, 6 H), 3.83 (s, 1 H), and 5.8–6.4 (m, 3 H).

Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.44; H, 8.78. Found: C, 64.42; H, 8.82.

Cycloheptanone. To a solution of the lithio compound formed from 0.42 g (1.5 mmol) of **8** in the usual way was added 0.168 g (1.5 mmol) of cycloheptanone dropwise. Workup afforded a yellow liquid which was chromatographed on basic alumina (activity III, 25 × 1.3 cm column). Elution proceeded as follows: 10% ether/petroleum ether (100 mL), 0.025 g of cycloheptanone; (300 mL), 0.09 g of 3,3,6,6-tetramethoxy-1,4-cyclohexadiene; 50% ether/petroleum ether (200 mL), 0.186 g (40%) of a pure, white, crystalline solid [mp 72–73 °C; IR (KBr) cm^{-1} 3560 (m), 2950 (s, br), 1135 (s), 1065 (s), 1040 (s), and 960 (s); NMR (CCl_4) δ 1.20–2.1 (br, m, 12 H), 3.20 (s, 12 H), 3.50 (s, 1 H), and 5.9–6.1 (m, 3 H)].

Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.34; H, 8.89.

Dimethyl Phthalate. To a solution of the anion formed in the usual manner from 0.84 g (3.0 mmol) of **8** was added 0.58 g (3.0 mmol) of dimethyl phthalate dissolved in 1 mL of tetrahydrofuran. After reaction for 10 min, the mixture was quenched with water and worked up to afford 1.02 g of yellow oil. The crude product was chromatographed on neutral alumina (activity III, 25 × 1.5 cm column). Elution proceeded as follows: 20% ether/petroleum ether (50 mL), nil; (75 mL), 0.060 g of dimethyl phthalate and 3,3,6,6-tetramethoxy-1,4-cyclohexadiene (50 mL), nil; 50% ether/petroleum ether (40 mL), 0.180 g (17%) of pure, white, crystalline pseudoester [mp 106–108 °C; IR (KBr) cm^{-1} 1760 (s), six bands 1030–1130 (s), 970 (s), and 940 (s); NMR (CCl_4) δ 2.75 (s, 3 H), 3.08 (s, 3 H), 3.13 (s, 3 H), 3.32 (s, 3 H), 3.34 (s, 3 H), 5.76 (A of AB, J = 10 Hz, 1 H), 6.12 (d of d, J = 10, 2.5 Hz, 1 H), 6.93 (d, J = 2.5 Hz, 1 H), 7.4–7.6 (m, 3 H), and 7.7–7.9 (m, 1 H); ^{13}C NMR ($CDCl_3$) ppm 49.96, 50.10, 50.72, 51.07, 93.23, 96.23, 106.56, 123.59, 124.80, 128.33, 130.14, 130.24, 130.43, 133.29, 136.66, 147.05, and 168.44; exact mass $C_{19}H_{22}O_7$; calcd *m/e* 362.136 53, obsd *m/e* 362.136 97, difference 0.0004].

Elution with an additional 60 mL of solvent afforded 0.595 g (54%) of the normal ester as a colorless liquid homogeneous by TLC: IR (neat) cm^{-1} 2940 (s), 1720 (s), 1690 (s), 1670 (sh), 1285 (s, br), 1090–1030 (s, br), and 970 (s); NMR ($CDCl_4$) δ 3.03 (s, 6 H), 3.25 (s, 6 H), 3.74 (s, 3 H), 5.8 (A of AB, J = 10 Hz, 1 H), 6.05 (d of d, J = 10, 2 Hz, 1 H), 6.68 (d, J = 2 Hz, 1 H), 7.2–7.5 (m, 3 H), and 7.7–7.9 (m, 1 H); ^{13}C NMR ($CDCl_3$) ppm 50.03, 50.90, 52.22, 93.25, 95.62, 127.84, 129.13, 129.31, 129.52, 130.06, 130.42, 131.77, 139.68, 140.88, 142.65, 166.66, and 195.40; exact mass $C_{19}H_{22}O_7$; calcd *m/e* 362.136 539 9, obsd *m/e* 362.137 239 8, difference 0.0007.

Dimethyl 3-Methoxyphthalate. A 250-mL flask equipped with a mechanical stirrer with a Teflon paddle, rubber septum, low-temperature thermometer, and a nitrogen-vacuum inlet containing a solution of 5.0 g (17.9 mmol) of **8** in 120 mL of tetrahydrofuran was cooled to −80 °C. To the rapidly stirred solution was added 7.16 mL (17.9 mmol) of 2.5 M *n*-butyllithium as rapidly as possible. After 120 s a solution of 4.2 g of **10** in 5 mL of tetrahydrofuran was added rapidly. The solution was stirred below −65 °C for 5 min, then quenched with 5 mL of methanol. After removal of solvent in vacuo and workup the crude material was crystallized twice from ether/CH_2Cl_2 to afford 3.75 g (53%) of analytically pure **11.** This yield is lower than those obtained in smaller runs (1 g of **9,** 75%) owing to some mechanical loss in this larger run: mp 153–154 °C; IR (KBr) cm^{-1} 1740 (s), 1665 (m), 1280 (s), 1265 (s), 1115 (s), and 978 (s); NMR ($CDCl_3$) δ [3.28 (sh) and 3.29 (s), 12 H], [3.85 (sh) and 3.86 (s), 6 H], 6.15 (m, 2 H), 6.38 (br, s, 1 H), and 7.1–7.5 (m, 3 H); ^{13}C NMR ($CDCl_3$) ppm 49.91, 51.15, 52.55, 56.33, 92.80, 95.50, 115.19, 122.91, 123.61, 129.87, 130.30, 137.26, 138.23, 139.42, 156.95, 167.63, and 193.37; exact mass $C_{20}H_{24}O_8$; calcd *m/e* 392.147 103 2, obsd *m/e* 392.147 557 3, difference 0.0004.

Hydrolyses of Bisketals to Quinones. The hydrolyses were conducted at room temperature for the indicated time using 1:1 0.1 N HCl/acetone or 1:1 1.0 N HCl/acetone. Workup as usual afforded yellow solids which were recrystallized from ether/petroleum ether to give the reported yields of product.

Hydrolysis of 0.21 g (0.55 mmol) of the benzophenone adduct in 6 mL of solution (0.1 N HCl/acetone) for 4 h afforded 0.117 g (74%) of yellow quinone: mp 151–153 °C; IR (KBr) cm^{-1} 3490 (m), 1660 (m, sh), 1650 (s), 1450 (m), 1285 (m), 1025 (m), 765 (m), and 710 (m); NMR (CCl_4) δ 4.55 (s, 1 H), 5.95 (s, 1 H), 6.70 (s, 2 H), and 7.25 (s, 10 H).

Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.69; H, 4.94.

Hydrolysis of 0.15 g (0.49 mmol) of the benzaldehyde adduct in 4 mL of solution (1.0 N HCl/acetone) for 18 h yielded 0.092 g (88%) of yellow quinone: mp 63–64 °C (lit.[21] mp 64.5–65.5 °C); IR (KBr) cm^{-1} 3310 (m, br), 1655 (s), 1601 (m), 1130 (m); 1005 (m), 865 (m), 780 (m), and 710 (m); NMR ($CDCl_3$) δ 2.92 (br, s, 1 H), 5.78 (s, 1 H), 6.68 (m, 2 H), 6.84 (m, 1 H), and 7.34 (s, 5 H).

Hydrolysis of 0.30 g (1 mmol) of cyclohexanone adduct in 4 mL of solution (1.0 N HCl/acetone) for 4 h yielded 0.166 g (80%) of quinone: mp 59–60 °C; IR (KBr) cm^{-} 3540 (m), 2960 (m), 1650 (s), 1605 (m), 1340 (m), 1295 (m), 990 (m), and 910 (m); NMR ($CDCl_3$) δ 1.5–1.9 (m, br, 10 H), 3.13 (s, 1 H), and 6.73 (s, 3 H).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.84; H, 6.86.

Hydrolysis of 0.11 g (0.35 mmol) of the cycloheptanone adduct in 6 mL of solution (1.0 N HCl/acetone) for 12 h yielded 0.064 g (83%) of quinone: mp 54–55 °C; IR (KBr) cm^{-1} 3525 (m), 2940 (m), 1650 (s), 1605 (m), 1340 (m), 1295 (m), 1215 (m), and 930 (m); NMR ($CDCl_3$) δ 1.5–2.0 (m, br, 12 H), 3.08 (s, 1 H), and 6.62 (s, 3 H).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.58; H, 7.32. Found: C, 70.54; H, 7.35.

Hydrolysis of 0.10 g (0.24 mmol) of benzil adduct in 5 mL of solution (0.1 N HCl/acetone) for 5 h yielded 0.069 g (88%) of quinone: mp 138–139 °C; IR (KBr) cm^{-1} 3480 (m, br), 1655 (s), 1600 (m), 1450 (m), 1285 (m), 1260 (m), 885 (m), 745 (m), and 710 (m); NMR (CCl_4) δ 4.77 (s, 1 H), 5.98 (s, 1 H), 6.76 (s, 2 H), 7.2–7.6 (m, 3 H), and 7.8–8.0 (m, 2 H).

Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43. Found: C, 75.27; H, 4.58.

1-Carbomethoxy-3,3,6,6-tetramethoxy-1,4-cyclohexadiene (14). A solution of 1.0 g of KOH and 2.0 g (1.02 mmol) of methyl 2,5-dimethoxybenzoate in 60 mL of methanol was anodically oxidized as for **8,** its progress being followed by the decrease in the UV maximum at 317 nm. Workup in the standard manner afforded 2.52 g of light-yellow oil, 90% pure by GLC (5 ft × 1/8 in., 3% SE-30 on 60/80 Chromosorb G at 170 °C), which was utilized for synthetic work after molecular distillation. The major impurity, which was not identified, was difficultly separated by chromatography on neutral alumina (1:3 ether/hexane eluent). A pure fraction was obtained, however, which showed after molecular distillation (80 °C/2 × 10^{-2} Torr): IR (neat) cm^{-1} 1740 (s), 1714 (s), 1682 (w), 1461 (m), 1439 (m), 1400 (m), 1277 (s), 1117 (s), 1058 (s), and 976 (s); NMR (CCl_4) δ 3.12 (s, 6 H), 3.23 (s, 6 H), 3.72 (s, 3 H), 5.83 (A of AB, J = 10.5 Hz, 1 H), 6.12 (d of d, J = 10.5, 2 Hz, 1 H), and 6.83 (d, J = 2 Hz, 1 H).

Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.80; H, 7.02. Found: C, 55.73; H, 7.07.

11. A solution of 0.250 g (1.05 mmol) of 2-bromo-6-methoxybenzoic acid in 40 mL of tetrahydrofuran in a flask equipped with rubber

septum, argon inlet, thermometer, and mechanical stirrer was cooled to an internal temperature of −90 to −95 °C with a liquid nitrogen–mixed solvents bath. *n*-Butyllithium (0.96 mL of 2.2 M solution, 2.01 equiv) was added to the vigorously stirred solution over 10 min; a yellow color developed as the second equivalent of base was added. The metalation was not noticeably exothermic. After the solution was warmed to −70 °C, 0.270 g (1.05 mmol) of **14** in 0.7 mL of tetrahydrofuran was added in one portion via syringe. The mixture was stirred for 2 h at −70 °C and quenched at this temperature by adding 0.115 g of trifluoroacetic acid. After the solution was warmed to ca. −10 °C an excess of ethereal diazomethane was added, and the solution was allowed to come to room temperature. All but ca. 10 mL of solvent was removed; the residue was taken up in 20 mL of methylene chloride, washed once with 30 mL of 5% sodium bicarbonate solution, and dried with calcium sulfate. Solvent removal and addition of 5 mL of ether to the residue gave 0.310 g (49%) of a crystalline solid, mp 145–149 °C. The solid was triturated with 3 mL of ether and recrystallized from methylene chloride/ether to give 0.184 g of an off-white solid, mp 150–152 °C, with NMR and IR spectra identical, peak for peak, with the sample of **11** prepared from **9** and **10.** The mixture melting point was undepressed.

Reaction of 10 with 15. A solution of 0.372 g (1.71 mmol) of 2-bromo-1,4-dimethoxybenzene in 20 mL of tetrahydrofuran in a flask equipped with magnetic stirrer, gas inlet, and thermometer was treated at −70 °C with 0.80 mL (1.76 mmol) of 2.2 M *n*-butyllithium. After 5 min a solution of 0.40 g (1.71 mmol) of **10** in 1 mL of tetrahydrofuran was added all at once. After stirring at −70 °C for 5 min the reaction was quenched with 2 mL of methanol, and tetrahydrofuran was removed at reduced pressure. The residue was taken up in 20 mL of methylene chloride, washed once with water, and dried by passing it through calcium sulfate. Removal of solvent yielded 0.634 g of a light-yellow oil which, when diluted with 2 mL of ether, deposited 50 mg (9%) of **17** as a white solid melting at 173–175 °C with sweating from 160 °C. Recrystallization from 0.5 mL of methylene chloride and 4 mL of ether at −20 °C gave 37 mg (7%) of **17:** mp 176.5–178.5 °C; IR (KBr) cm^{-1} 1778 (s), 1613 (w), 1601 (w), 1599 (s), 1588 (m), 1295 (s), 1236 (m), 1218 (m), 1095 (s), 1073 (m), 1056 (m), and 1021 (m); NMR ($CDCl_3$) δ 3.23 (s, 3 H), 3.55 (s, 3 H), 3.80 (s, 3 H), 4.02 (s, 3 H), 6.7–7.1 (m, 4 H), and 7.35–7.75 (m, 2 H); exact mass $C_{18}H_{18}O_6$, calcd *m/e* 330.110 327 4, obsd *m/e* 330.111 116 8, difference 0.0008. The support for the assigned structure was strengthened when ca. 20 mg of **17** was hydrolyzed to give **19** in good yield, mp 187–188.5 °C, with an IR spectrum identical with that of the authentic sample. The noncrystalline portion was chromatographed (10 g of silica gel, 1 × 30 cm column, ether). After a small forerun of dimethoxybenzene, 0.134 g of unreacted **10** eluted, followed by 0.234 g (41%) of a thick gum which was principally **16** but not pure. The major (>90%) product in the gum was identified as **16** by comparison of the NMR spectrum and TLC with material obtained from the esterification of **19.** Saponification of this crude **16** gave **19.**

19. A solution of 0.300 g (1.27 mmol) of 2-bromo-6-methoxybenzoic acid dissolved in 25 mL of tetrahydrofuran was cooled to −80 to −90 °C, and 1.1 mL (2.75 mmol) of 2.5 M *n*-butyllithium was added via syringe over 15 min with vigorous stirring. A mixture of 0.300 g (1.53 mmol) of methyl 2,5-dimethoxybenzoate in 0.2 mL of tetrahydrofuran was added as rapidly as possible at −85 °C, and the mixture was allowed to reach room temperature over the period of 1 h. Solvent was removed at reduced pressure and the residue, diluted with 25 mL of 5% sodium bicarbonate, was washed twice with methylene chloride and once with hexane. The alkaline layer was added to excess 5% hydrochloric acid, and 0.302 g (75%) of a white solid was obtained which melted at 181–183 °C with shrinking from 175 °C. One crystallization from methylene chloride and ether gave a fine, white powder: mp 186–188 °C; IR (KBr) cm^{-1} 1765 (m), 1737 (s), 1616 (w), 1604 (s), 1491 (s), 1300 (m), 1232 (m), and 1053 (s); NMR ($CDCl_3$) δ 3.65 (s, 3 H), 3.87 (s, 3 H), 4.00 (s, 3 H), 6.3–7.4 (m, 5 H), and 7.5–7.8 (m, 1 H); exact mass $C_{17}H_{16}O_6$, calcd *m/e* 316.094 678 2, obsd 316.095 249 7, difference 0.0006.

16 from 19. Compound **19** was quantitatively esterified with diazomethane. Removal of solvent gave a gum which was pure by GLC (SE-30, 240 °C) but which could not be induced to crystallize. After many weeks at room temperature the gum crystallized spontaneously and the analytical sample was prepared by recrystallization from ether–methylene chloride. Large, very pale-yellow plates were obtained which melted very slowly: mp 85–87 °C; IR (KBr) cm^{-1} 1730 (s), 1666 (s), 1585 (m), 1499 (s), 1475 (s), 1434 (s), 1424 (s), 1299 (s), 1272 (s), 1234 (s), and 999 (s); NMR ($CDCl_3$) δ 3.62 (s, 3 H), 3.75 (s, 6 H), 3.87 (s, 3 H), and 6.7–7.5 (m, 6 H); exact mass $C_{18}H_{18}O_6$, calcd *m/e* 330.110 327 4, obsd *m/e* 330.110 852 8, difference 0.0005.

Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.57; H, 5.56.

Comparison of the Efficiency of Organolithium Production with *n*-, *sec*-, and *tert*-Butyllithium. To a flame-dried, nitrogen-filled, 50-mL three-necked flask equipped for magnetic stirring was added 20 mL of tetrahydrofuran and 0.279 g (1.0 mmol) of 1-bromo-3,3,6,6-tetramethoxycyclohexa-1,4-diene. The solution was cooled to −68 °C and treated with 1.05 mL (1.05 mmol) of 1 M *sec*-butyllithium in cyclohexane [or 0.58 mL (1.05 mmol) of 1.80 M *tert*-butyllithium in pentane or 0.44 mL of 2.4 M *n*-butyllithium in hexane]. The temperature rose to −63 °C and then fell to −65 °C as the solution was stirred for 100 s before 131 μL (143 mg, 1.05 mmol) of methyl benzoate was added all at once. Stirring was continued for 10 min and the mixture was quenched at −65 °C with 1 mL of methanol. Solvent was removed and the residue was partitioned between water and methylene chloride. Drying with sodium sulfate and removal of solvent gave 0.315 ± 0.01 g of crude product (theoretical weight 0.304 g). The result of the reaction was evaluated by comparing the size of the singlet at δ 5.92 arising from the four vinylic protons of 3,3,6,6-tetramethoxycyclohexa-1,4-diene with the rest of the spectrum which was identical with pure 1-benzoyl-3,3,6,6-tetramethoxycyclohexa-1,4-diene. The only other peak in the NMR spectrum was a singlet, δ 3.87, due to methyl benzoate. The results with *tert*, *sec*-, and *n*-butyllithium were identical and indicated a ca. 95% conversion of starting material to product. Stirring the solution of 1-lithio-3,3,6,6-tetramethoxycyclohexa-1,4-diene at −65 °C for 1 h or at 2 °C for 2 min prior to addition of methyl benzoate at −65 °C gave the same result.

Comparison of the Reactivity of 9 and 15. The following is typical of several independent determinations. To a solution of **9** at −65 °C prepared from 0.28 g (1 mmol) of **8** and 413 μL of 2.42 M *n*-butyllithium was added via syringe a solution of **15** prepared from 0.21 g (1 mmol) of the bromo aromatic and 413 μL of 2.42 M butyllithium. To this mixture of anions at −65 °C was added 0.136 g (1 mmol) of methyl benzoate. After stirring for 0.5 h workup afforded 0.489 g of yellow oil which was analyzed by VPC (1 ft × 1/8 in. column, 5% SE-30 on 60/80 Chromosorb G at 130 °C) using docosane as internal standard. The respective products were formed in yields of 35.2 and 3.6%. When the reactions were conducted independently and analyzed by VPC the yields of adducts were 84 and 90%, respectively.

Preparation of 26. To a stirred, cooled (−60 °C) solution of 0.65 g (3 mmol) of 2-bromo-1,4-dimethoxybenzene in 10 mL of dry tetrahydrofuran under nitrogen was added dropwise 1.2 mL of a 2.5 M solution of butyllithium. After stirring for 1 min at −60 °C, 0.582 g (3 mmol) of dimethyl phthalate in 1 mL of dry tetrahydrofuran was added via syringe. The mixture was stirred for 1 h at −60 °C and then quenched with water (5 mL). Workup in the standard manner afforded a yellow oil which was chromatographed on neutral alumina (activity III, 30 × 1.5 cm column). Elution proceeded as follows: 20% ether/petroleum ether (40 mL), nil; (150 mL), 0.25 g of dimethyl phthalate and 1,4-dimethoxybenzene; 50% ether/petroleum ether (100 mL), 0.45 g (50%) of a white solid which was a mixture of the normal and pseudoester in the ratio 4:1.

The mixture, 0.10 g (0.33 mmol), was refluxed for 0.5 h with 10 mL of 4% potassium hydroxide solution. The aqueous phase was extracted with chloroform (3 × 5 mL), acidified with concentrated hydrochloric acid, and then extracted with chloroform (3 × 5 mL). After drying and concentration, the crude acid was esterified with diazomethane to afford 0.096 g (96%) of crude **26.** Trituration of this material with hexane afforded 0.085 g (85%) of **26**, mp 84–86 °C.

Reaction of 20. To a solution of the anion formed in the usual way from 0.279 g (1 mmol) of **8** in 5 mL of tetrahydrofuran and 0.413 mL of 2.42 M butyllithium was added 0.132 g (1 mmol) of **20** in 1.5 mL of tetrahydrofuran and the reaction mixture stirred at −65 °C for 0.5 h and then at room temperature for 0.5 h. Workup in the usual manner afforded 0.257 g of yellow oil in the neutral layer which was chromatographed on neutral alumina (activity III, 21 × 1.8 cm column). Elution proceeded as follows: 10% ether/petroleum ether (150 mL), nil; 10% ether/petroleum ether (90 mL), 0.026 g of bisketal; 10% ether/petroleum ether (120 mL), nil; 25% ether/petroleum ether (240 mL), 0.067 g (25%) of **26** [mp 84–86 °C; IR (KBr) cm^{-1} 1710 (s), 1650 (s), 1495 (s), 1420 (s), 1290 (s), 1280 (s), 1270 (s), 1050 (m), 980 (s), 725 (m), and 640 (m); NMR ($CDCl_3$) δ 3.45 (s, 3 H), 3.63

(s, 3 H), 3.80 (s, 3 H), and 6.77–8.03 (m, 7 H); exact mass $C_{17}H_{16}O_5$, calcd *m/e* 300.0998, obsd *m/e* 300.1005, difference 0.0007].

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(20) 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 values. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrometer. ^1H NMR spectra were taken at 60 MHz with Varian EM-360 or A-60A instruments, with the latter observed for all critical work. ^{13}C NMR spectra were recorded on a Bruker HX-90 instrument by Dr. Charles Cottrell. Mass spectra and exact mass measurements were obtained by Mr. C. R. Weisenberger on a Consolidated Electronic MS-9 double-focusing mass spectrometer. Analytical samples were determined by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Aluminum oxide and silica gel were from E. Merck Co. Tetrahydrofuran was distilled from benzophenone ketyl directly into the reaction flask. Reactions run in an inert atmosphere made use of a three-way stopcock with $^{14}/_{20}$ ground joint which allowed the flask to be flame dried under vacuum and filled with purified nitrogen. Butyllithium in hexane (Ventron) was titrated in tetrahydrofuran with 1,10-phenanthroline as the indicator. The earlier anodic oxidations were performed on a cooled, magnetically stirred solution using the power supply previously described[1] and the cell in Figure 1 but without the reference electrode. More recent work was performed at constant potential relative to a platinum reference electrode using a Kepco power supply with currents between 0.5 and 2.0 A using the platinum gauze anode previously described. This potentiostat was designed by R. McCreery and built by D. Henton. Other than reducing the time of electrolysis by a factor of 2–3, the results are identical for the two systems.
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A Regiospecific Synthesis of the Anthracycline Aglycones, Daunomycinone and Adriamycinone‡

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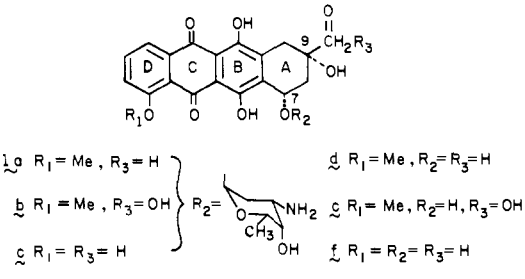
Abstract: A synthesis of (±)-7,9-deoxydaunomycinone has been accomplished in 14% overall yield from the known 3-bromo-2,5-dimethoxybenzaldehyde. This compound can be converted by known steps into daunomycin and adriamycin. The key step involves the regiospecific coupling of the eventual AB-ring system in the form of a lithiated quinone bisketal to dimethyl 3-methoxyphthalate. The utility of the analogous 2-lithio-1,4-dimethoxytetralin derivative coupling to dimethyl 3-methoxyphthalate was also studied and the reaction product converted to (±)-7,9-deoxydaunomycinone.

Introduction

The anthracyclines daunomycin (**1a**), adriamycin (**1b**), and carminomycin (**1c**) are important antibiotics of much current interest clinically, biologically, and chemically.[3] Inasmuch as the glycone, daunosamine, has been synthesized[4] and the coupling of glycone and the aglycone achieved,[5] a synthesis of the anthracycline aglycone constitutes a formal synthesis of these important compounds. Furthermore, since daunomycinone (**1d**) has been converted chemically to both adriamycinone[6] (**1e**) and carminomycinone[7] (**1f**), a synthesis of **1d** serves as a route to **1e** and **1f**. Much methodology[7-11] has



been explored for the synthesis of these aglycones, and several formal syntheses of daunomycinone[8] have been report-

‡ Dedicated to Professor Melvin S. Newman on his 70th birthday.

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