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Part I: Synthesis, substitution chemistry and biological activity of D-ring fluorinated anthracyclinones. Part II: Spiroannulated cyclohexa-2,5-dienones via electrooxidation of para-aryl phenols. Part III: Spirodienones via a thermal [1,3]-oxygen to carbon migration

Morrow, Gary Wade, Ph.D.
The Ohio State University, 1988
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UMI
PART I: SYNTHESIS, SUBSTITUTION CHEMISTRY AND BIOLOGICAL ACTIVITY OF D-RING FLUORINATED ANTHRACYCLINONES

PART II: SPIROANNULATED CYCLOHEXA-2,5-DIENONES VIA ELECTROOXIDATION OF para-ARYL PHENOLS

PART III: SPIRODIENONES VIA A THERMAL [1,3]-OXYGEN TO CARBON MIGRATION

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of the Ohio State University

By

Gary W. Morrow, B.A.

* * * * *

The Ohio State University

1988

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Approved By

Advisor
Department of Chemistry
to

The Memory of Glenn Robert Morrow, Sr.
ACKNOWLEDGEMENTS

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Gary V. Morrow and John S. Swenton

"Synthesis of 1-Fluoro-, 4-Fluoro-, and 1,4-Difluoro-4-demethoxydaunomycinone. Interesting D-Ring Analogues of Adriamycin"
John S. Swenton, Gary W. Morrow, Joyce A. Filippi and Richard L. Wolgemuth

"Synthesis of Functionalized Hydroxyphthalides and Their Conversion to 3-Cyano-1(3H)-isobenzofuranones"
John S. Swenton, John N. Freskos and Gary W. Morrow

"A Convergent Synthesis of (+)-4-demethoxydaunomycinone and (+)-daunomycinone"
John S. Swenton, John N. Freskos, Gary W. Morrow, Anthony D. Sercel
"Synthesis of (Z,Z)-11,13-hexadecadienal, a Principle Component of Navel Orangeworm Pheromone"  
Clyde E. Bishop and Gary W. Morrow  

"1-Fluoro, 4-Fluoro, and 1,4-Difluoro Anthracycline Anticancer Antibiotics"  
U.S. Patent Nos. 4,663,445 and 4,697,005  

"Synthesis of the Navel Orangeworm Pheromone, (Z,Z)-11,13-Hexadecadienal"  
U.S. Patent No. 4,400,550  

"Anodic Cyclization Reactions of p-Aryl Phenols. Intramolecular Trapping of the Reactive Intermediate from Phenol Oxidation to form 4-Aryl-4-Alkyl-2,5-cyclohexadienones"  
John S. Swenton and Gary W. Morrow  
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"Studies in Anthracyclinone Chemistry. Mitoxantrone Analouges: Synthesis and Biological Activity"  
John S. Swenton and Gary W. Morrow  
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PART I

SYNTHESIS, SUBSTITUTION CHEMISTRY AND BIOLOGICAL ACTIVITY
OF D-RING FLUORINATED ANTHRACYCLINONES
Synthesis of 1-Fluoro-, 4-Fluoro-, and 1,4-Difluoro-4-demethoxydaunomycinone. Interesting D-Ring Analogues of Adriamycin

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The syntheses of racemic 1-fluoro- (4), 4-fluoro- (5), and 1,4-difluoro-4-demethoxydaunomycinone (6) and the (+) antipodes of the latter two compounds are reported. The synthetic route involved the anellation of a highly functionalized quinone monoketal with the appropriate cyanophthalide anion followed by deprotection. The cyanophthalides were obtained from the corresponding hydroxyphthalides, prepared by metalation routes. Interestingly, the oxazoline directing group afforded much better yields of metalation products than the similarly unsubstituted N,N-diethylamide compound in these fluorinated systems. The high reactivity of these D-ring-fluorinated anthracycinones in nucleophilic aromatic substitution reactions was demonstrated by reaction of 4 and 6 with 2-(2-aminoethyl)aminoethanol to produce mitoantrone analogues. The biological activity of the daunomycin coupling products of 4-6 in the P388 antitumor screen was comparable to 4-demethoxydaunomycinone, but the potency was dependent upon the fluorine substitution pattern.

Synthetic routes to anthracycinones have been of major interest in organic chemistry for the last decade. A major objective of this work has been the development of viable syntheses of anthracycinone aglycones that upon coupling with daunomycin or other glycon analogues, would yield new anthracycline systems. A more specific goal of such studies is to develop an efficacious and less toxic alternative to the widely used antineoplastic drug adriamycin (doxorubicin, 3). A popular synthetic strategy to rhodomydnone analogues of anthracycinone has been the anellation of a 1,4-dipole equivalent to quinone monoketals (Scheme I). This convergent route allows the formation of the fully functionalized anthracycinone in one key step and is an ideal strategy for synthesis of D-ring anthracycinone analogues.

Analogues 4-6, in which the hydrogens in the D-ring of anthracycinones are replaced by fluorine, were especially interesting candidates for synthesis. Substitution of hydrogen with fluorine in a drug often leads to significant biological effects, especially if metabolism at the site of substitution is an important in vivo process.

Scheme I. Anellation Strategy to Anthracycinones

(1) For leading references and a recent review of anthracycinones chemistry, see: Kelly, T. B., Ed. Tetrahedron 1984, 40, 4589-4729; Tetrahedron Symposium in Print N. 17.


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more, it is known that aromatic fluorine substituents are often subject to nucleofugic aromatic substitution if other electron-withdrawing groups are present on the ring. In fact, the room-temperature displacement of aromatic fluorine substituents by amino groups has recently been reported in simple anthraquinone systems.

We report herein the preparation of 1-fluoro (4), 4-fluoro (5), and 1,4-difluoro (6) derivatives of 4-dehydroxyanisomycinone, the nucleophilic aromatic substitution chemistry of the latter two molecules with 3-[[2-(2-aminoethyl)amino]ethanol, and the biological activity of the resultant anthrapyrylones and (alkylamino)anthrapyrylones.

Preparation of 3-fluoro, 4-fluoro, and 4,7-difluoro-3-cyanooxazolones. Previous studies have established the superiority of 3-cyanooxazolones (1) with respect to other functionalized quinone monoketals. A variety of methods are available for the preparation of hydroxyphthalides, which in turn may be conveniently converted to the corresponding cyano- and/or carboxylic acids. The hydroxyphthalide 7a was readily available from metathesis/carboxylation of the dimethyl acetal of commercially available m-fluorobenzaldehyde. At the time, the hydroxyphthalides 7c and 7d were unknown.

\[
\text{7b} \quad R = \text{OCH}_3 \\
\text{7c} \quad R = \text{F} \\
\text{7d} \quad R = \text{F}, R' = \text{H}
\]

Metathesis/functionality of appropriate commercially available fluoro-substituted aromatic compounds would be the most direct route to the required hydroxyphthalides. Because we had prepared 7b, the 7-methoxy analogue of 7e, in good yield by metathesis of the N,N-diethylamidine of m-methoxybenzonic acid followed by reaction of the resulting oxazolinium reagent with dimethylformamide and hydrolysis, gave 7d in 93% yield. It is interesting that the choice of directing group (diethylamino vs. oxazoline) is so important in the metathesis reaction of these particular systems.

Initially, some difficulty was experienced in conversion of the fluoro-substituted hydroxyphthalides 7e,d to the corresponding cyanophthalides 1e,d. It appears that these cyanohydrin intermediates are more subject to hydrolysis and/or decomposition than are the compounds studied previously. In reactions wherein cyanohydrin formation was allowed to occur at room temperature for several hours, products showing an amide carbonyl in the IR spectrum could be isolated. While these crude amides were dehydrated under the Vilsmeier conditions to the corresponding cyanophthalides, the overall yields were not high since the further hydrolysis of the amide to the carboxylic acid was difficult to control during the cyanohydrin formation. This complication was avoided by allowing cyanohydrin formation to proceed at 0 °C for 5 min and extracting the crude product directly from the reaction mixture with cold ethyl acetate. This material was then immediately reacted with the Vilsmeier reagent, yielding the cyanophthalides 1e,d in overall yields of 68 and 71%, respectively.

Synthesis of 1-fluoro, 4-fluoro, and 1,4-difluoro 4-dehydroxyanisomycinone. With the required cyanophthalides 1a,c,d readily available, the annelation reaction previously utilized for the synthesis of daunomycinone intermediates is so important in the metathesis reaction of these particular systems.

For preparation of the 4,7-difluoro system 7d, a route analogous to that used for preparation of 7a mentioned above was examined first. When the metathesis/carboxylation sequence was applied to 2,5-difluorobenzaldehyde dimethyl acetal, a poor yield of the desired hydroxyphthalide resulted. This parallel results obtained in the preparation of the dimethyl acetal of 2,5-difluorobenzaldehyde, wherein a poor yield of a hydroxyphthalide was reported. Thus, the oxazoline route was examined for this system in spite of the concern that displacement of the o-fluoro group by the alkylithium reagent could compete with the metathesis step. The required 4,7-difluorobenzoic acid was prepared in good yield by metathesis of 1,4-difluorobenzene followed by carboxylation of the resulting organolithium compound. Conversion of the above acid to the oxazoline 12, followed by metathesis and subsequent reaction with dimethylformamide and hydrolysis, gave 7d in 93% yield. It is interesting that the choice of directing group (diethylamine vs. oxazoline) is so important in the metathesis reactions of these particular systems.

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Initially, some difficulty was experienced in conversion of the fluoro-substituted hydroxyphthalides 7e,d to the corresponding cyanophthalides 1e,d. It appears that these cyanohydrin intermediates are more subject to hydrolysis and/or decomposition than are the compounds studied previously. In reactions wherein cyanohydrin formation was allowed to occur at 0 °C for several hours, products showing an amide carbonyl in the IR spectrum could be isolated. While these crude amides were dehydrated under the Vilsmeier conditions to the corresponding cyanophthalides, the overall yields were not high since the further hydrolysis of the amide to the carboxylic acid was difficult to control during the cyanohydrin formation. This complication was avoided by allowing cyanohydrin formation to proceed at 0 °C for 5 min and extracting the crude product directly from the reaction mixture with cold ethyl acetate. This material was then immediately reacted with the Vilsmeier reagent, yielding the cyanophthalides 1e,d in overall yields of 68 and 71%, respectively.

Synthesis of 1-fluoro, 4-fluoro, and 1,4-difluoro 4-dehydroxyanisomycinone. With the required cyanophthalides 1a,c,d readily available, the annelation reaction previously utilized for the synthesis of daunomycinone intermediates is so important in the metathesis reaction of these particular systems.
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mycostatin and its 6-demethoxy analogue was used to prepare the anthracyclines 4-6. The hydrolysis of bisketal 13 afforded a ca. 85:15 mixture of 14 and its regioisomer 18. The NMR spectrum of 14 showed a quartet centered at δ -113.3 and -113.5. A similar result was obtained for the products from the coupling reaction of 1a and the cyanophthalide 1a,c,d. The **F NMR spectrum showed a quartet centered at δ -113.3. The mother liquors from the crystallization showed in the **F NMR spectrum two quartets (central signal overlapping) centered at δ -113.3 and -113.5. A similar result was obtained for the products from the coupling reaction of 1a and 14 (see the Experimental Section).

15, a lto x a n tro n a

matography on silica gel afforded 18 as a dark purple semisolid (44%) and 19 as a deep blue solid (57%). While these hydroscopic compounds were obtained as amorphous solids that did not show sharp melting points, they were homogeneous by thin-layer chromatography. Additionally, the 500-MHz NMR, UV, IR, and FAB mass spectra indicated incorporation of the side chains and retention of A-ring integrity. In the case of 19, the high optical rotation suggests retention of chirality in the product, which would be expected in view of the mild reaction conditions. As with other anthracycline aglycons, compounds 18 and 19 were of very marginal activity in P388 screens, and no attempt to prepare the corresponding anthracycline derivatives has been undertaken.

This approach serves as an exceedingly mild and efficient method for the regiospecific introduction of an alkylamino side chain on the D-ring of fully functionalised daunomycinone derivatives. Furthermore, although no other nucleophilic agents were explored, this method suggests nucleophilic aromatic substitution on D-ring-fluorinated anthracyclines as a viable strategy for the synthesis of other daunomycinone D-ring analogues. In view of the mild reaction conditions, nucleophilic substitution on the fluoro-substituted anthracycline derivatives themselves may be possible, thus allowing attachment of...
The solvent in vacuo afforded a yellow solid that was filtered and dried to give the tetraacetyl ketal [3.8 g (95%); mp 215–218 °C], which was used directly in the next step. Recrystallization of a portion of this material from CHCl₃/CH₂Cl₂ gave analytically pure material: mp 227–229 °C; IR (KBr) 3500–3300 (br, m), 1705 (s), 1530 (s), 1430 (s), 1385 (s), 1330 (br), 1100 (s), 1030 (br), 3960 (br, m); "H NMR 13.53 (s, 1 H), 8.72 (s, 1 H), 7.40 (d, 2 H), 1.30 (s, 9 H), 0.89 (s, 6 H), 0.24 (s, 6 H). The twisted field component further coupled, 2 H), 2.2 (AB q, J = 14 Hz with lower field component split into pseudotriplets and higher field component split into doublets, 2 H), 1.45 (s, 3 H), "F NMR δ = -115.8 (ABX, dd, J = 15 Hz, J = 4.5 Hz, F). Anal. Calc'd for CH₂H₂O; C: 62.18%, H: 3.91%.

The solutions in vacuo were then concentrated in portions at room temperature, and the resulting slurry was extracted with CH₂Cl₂ (1200 mL), washed with brine, and dried. Concentration and drying in vacuo gave 4-fluoro-4-demethoxy-11-methoxy-11-deoxydaunomycin; 3.0 g (83%). This material was used directly in the next step. A small portion recrystallized from CH₂Cl₂/CH₃OH gave the analytically pure material: mp 215–218 °C; IR (KBr) 3500–3300 (br, m), 1705 (s), 1530 (s), 1430 (s), 1385 (s), 1330 (br), 1100 (s), 1030 (br), 3960 (br, m); "H NMR 13.53 (s, 1 H), 8.72 (s, 1 H), 7.40 (d, 2 H), 1.30 (s, 9 H), 0.89 (s, 6 H), 0.24 (s, 6 H). The twisted field component further coupled, 2 H), 2.2 (AB q, J = 14 Hz with lower field component split into pseudotriplets and higher field component split into doublets, 2 H), 1.45 (s, 3 H), "F NMR δ = -115.8 (ABX, dd, J = 15 Hz, J = 4.5 Hz, F). Anal. Calc'd for CH₂H₂O; C: 62.18%, H: 3.91%.

The optically pure compound obtained in 76% yield showed the following: mp 150–150.5 °C; [α] D = 1.1 CH₂OH/CH₃OH) +15.2%.

To a -78 °C solution of the above material (3.0 g) in CH₂Cl₂ (650 mL) was added BC (80 mL of a 1 M solution in CH₂Cl₂). The resulting dark purple solution was stirred for 2 h at -78 °C. The reaction was quenched with CH₂Cl₂, the solvent was removed in vacuo, and the resulting solid was dried overnight in vacuo. This material was dissolved in a boiling mixture of CH₂OH/CH₂Cl₂ (ca. 1:1), and the solution was refluxed for 1 h. Cooling and concentration in vacuo produced a voluminous red/orange solid that was filtered and dried in vacuo to give in three crops 4-fluoro-4-demethoxy-11-methoxy-11-deoxydaunomycin; 3.0 g (83%). This material was used directly in the next step. A small portion recrystallized from CH₂Cl₂/CH₃OH gave the analytically pure material: mp 215–218 °C; IR (KBr) 3500–3300 (br, m), 1705 (s), 1530 (s), 1430 (s), 1385 (s), 1330 (br), 1100 (s), 1030 (br), 3960 (br, m); "H NMR 13.53 (s, 1 H), 8.72 (s, 1 H), 7.40 (d, 2 H), 1.30 (s, 9 H), 0.89 (s, 6 H), 0.24 (s, 6 H). The twisted field component further coupled, 2 H), 2.2 (AB q, J = 14 Hz with lower field component split into pseudotriplets and higher field component split into doublets, 2 H), 1.45 (s, 3 H), "F NMR δ = -115.8 (ABX, dd, J = 15 Hz, J = 4.5 Hz, F). Anal. Calc'd for CH₂H₂O; C: 62.18%, H: 3.91%.

The optically pure material obtained in 83% yield showed the following: mp 213–215 °C; [α] D = 1.1 CH₂OH/CH₂Cl₂) +147%.

3-Fluorobenzoyl chloride was prepared in the usual fashion by reacting 3-fluorocinnamic acid (10 g, 0.017 mol) with excess SO₂Cl₂ at reflux for several hours. Distillation at reduced pressure afforded the acid chloride (9.9 g (87%); bp 95–100 °C (30 mm)) as a yellow oil that was then dissolved in CH₂Cl₂ (20 mL) and added...
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CHCl₃/CH₂OH gave the analytically pure material: mp 226-228 °C; IR (KBr) 3000-3200 (br, 1675 cm⁻¹, 1630 cm⁻¹, 1290 cm⁻¹, 1200 cm⁻¹ cm⁻¹); 1H NMR 7.82-7.30 (highly str, 10 H), 7.10 (s, 3 H), 5.22 (s, 1 H), 4.02 (s, 4 H). Anal. Calcd for C₃₈H₃₆N₂O₇: C, 62.90; H, 4.52.

To a -78 °C solution of 3-fluoro-4-cyano-1-(3H)-isobenzofuranone (1c; 0.76 g, 0.42 mmol) in CDCl₃ (13 mL) and dried through CaSO₄. Concentration in vacuo, followed by drying, gave a thick yellow oil that was used directly in the next step. Recrystallization of a portion from CH₂Cl₂ (2 x 30 mL) and dried through CaSO₄. Concentration in vacuo, followed by drying, gave an orange/yellow solid that was used directly in the next step. Crystallization of a portion from CH₂Cl₂ (2 x 100 mL) and dried through CaSO₄. Concentration in vacuo, followed by drying, gave an orange/yellow solid that was used directly in the next step. Recrystallization of a portion from CH₂Cl₂ (160 mL) was added BCl₃ (19.3 mL of a 1 M solution in CH₂Cl₂). After stirring for 15 min at -78 °C, the reaction mixture was warmed to room temperature. The resulting white solid was collected by filtration, dried, and then recrystallized from CH₂Cl₂ (2 x 100 mL) and dried through CaSO₄. Concentration in vacuo, followed by drying, gave an orange/yellow solid that was used directly in the next step.

The reaction was quenched by addition of CH₂Cl₂ (90 mL) and dried through CaSO₄. Concentration in vacuo, followed by drying, gave an orange/yellow solid that was used directly in the next step. Recrystallization of a portion from CH₂Cl₂ (160 mL) was added BCl₃ (19.3 mL of a 1 M solution in CH₂Cl₂). After stirring for 15 min at -78 °C, the reaction mixture was warmed to room temperature. The resulting white solid was collected by filtration, dried, and then recrystallized from CH₂Cl₂ (2 x 100 mL) and dried through CaSO₄. Concentration in vacuo, followed by drying, gave an orange/yellow solid that was used directly in the next step.

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afforded the crude acid chloride [bp 90-92 °C (30 mm)] as a yellow oil (17.5 g, 75%) that was then dissolved in CH₂Cl₂ (30 mL) and added dropwise to a 0 °C solution of 3-aminoo-butyric acid (17.5 g, 0.186 mol) in CH₂Cl₂ (118 mL). The resulting milky suspension was stirred at room temperature for 6 h, then poured into an equal volume of H₂O. Standard workup afforded the crude hydroxy amide as a yellow oil that was treated directly with SO₂ (50.2 mL). After 15 h, the thick oil was treated with Et₂O (180 mL) and the oily hydrochloride salt vigorously stirred. After decantation of the Et₂O, the salt was dissolved in a 20% KOH solution (50 mL), the aqueous layer was extracted with CH₂Cl₂ (X 3 = 25 mL), and the combined organic phases were washed with brine and dried over CaSO₄. Concentration in vacuo afforded a brown oil (7.86 g (23% from 1,4-difluorobenzene)). A light yellow oil: bp 22-26 °C (0.4 mm); IR (KBr) 1300 (m), 1460 (a), 1630 (a), 1700 (s, shoulder), 1160 (m), 1200 (m), 1070 (m). The crude hydroxy amide was essentially pure (82.6% by GLC). Analytically pure compound: mp 90-92 °C; [α]₂⁰ D +11.3 ° (1.0 CH₂Cl₂/CH₂OH); IR (KBr) 3450-3350 (br, s), 2920 (s), 1675 (s), 1585 (m), 1600 (s), 1665 (m), 1430 (s), 1380 (m), 1350 (m), 1260 (s), 1200 (s, cm⁻¹); ¹H NMR (600 MHz) 6 8.05 (d, 3 H), 8.15-7.81 (br, 4 H), 3.96 (s, 3 H). 3.65 (s, 3 H). 3.03 (d, 1 H). 2.36 (s, 3 H). 1.71 (s, 3 H). 1.22 (s, 6 H). Analytical Calcd for C₃₂H₃₈F₂O₃: C, 82.61; H, 4.41. Found: C, 82.61; H, 4.42.

4.8-Stereoselective hydroxylation of 4-substituted 2-cyclohexenones (4). To a 4 °C solution of the material prepared above (60.29 mg, 0.162 mmol) in CH₂Cl₂ (36 mL) was added CH₂Cl₂ (53 mL of a 1.0 M solution in CH₂Cl₂) dropwise via syringe. After 15 min, the reaction mixture was poured into an ice-cold H₂O (100 mL). The product was extracted into CH₂Cl₂, dried through CaSO₄, and concentrated in vacuo. The resulting crude hydroxy chloride bp 150-152 °C (30 mm), [α]₂⁰ D +11.3 ° (1:1 CH₂Cl₂/CH₂OH); IR (KBr) 3600-3200 (br, m), 1800 (m), 1600 (m). 1550 (m), 1420 (s), 1380 (m), 1360 (m), 1270 (m); ¹H NMR (600 MHz) 6 8.07 (d, 3 H), 8.13-7.86 (br, 4 H), 3.92 (s, 3 H), 3.78 (d, 1 H), 2.22 (s, 1 H), 2.13 (d, 1 H). Analytical Calcd for C₁₇H₂₇Cl₂F₂O₃: C, 82.61; H, 4.41. Found: C, 82.58; H, 4.52.
(30 mL) was added 2-[3-aminoethylamino]ethanol (118 mg, 1.13 mmol) whereupon the solution immediately turned dark purple. After 12 h at room temperature, no starting material remained by TLC analysis. The pyridine was removed in vacuo, and the dark purple residue was chromatographed on flash silica gel column (75:25 CHCl₃/CH₃OH as eluant). The highly polar product was finally eluted from the silica gel by adding a small amount of concentrated NH₄OH solution to the eluant. In this way, after concentration and drying in vacuo, a deep purple amorphous solid (54 mg) was obtained, melting over a broad range and decomposing above 150 °C: IR (KBr) 3600-3200 (br, s), 2920 (w), 1720 (w), 1600 (s), 1520 (w), 1440 (br, m), 1300 (w) cm⁻¹; ¹H NMR (500 MHz, pyridine-d₅) δ 10.74 (s, 1 H), 7.23 (d, 1 H), 5.69 (s, 2 H), 3.89 (s, 4 H), 3.23 (s, 2 H), 2.27 (s, 3 H); FAB, m/e 471 (0.21% of base peak).

(-)-1,4-Diamino[2-[N-(hydroxyethyl)amino]ethyl]amino]-4-dimethylaminomycyclohexane (19). To a solution of (+)-4-demethoxy-1,4-difluoroamycin C (10 mg, 0.025 mmol) in pyridine (0.25 mL) was added 2-[3-aminoethylamino]ethanol (0.124 mL of a 1.0 M pyridine solution), and the resulting mixture was stirred for 2 h at 75 °C. The pyridine was then removed in vacuo, and the residue was deposited on silica gel and chromatographed (CHCl₃/CH₃OH as eluant) until the product band remained behind. This was then eluted with an 80:20 mixture of CHCl₃/CH₃OH containing 2.5% concentrated NH₄OH. Concentration of the main fractions and drying in vacuo afforded the title compound (8.1 mg (57%)) as a deep blue hygroscopic amorphous solid with a broad melting range (100-150 °C): [α]D ⁰ ₉ ₅ = -185° (1:1 CHCl₃/CH₃OH); IR (KBr) 3600-3200 (br, s), 2920 (w), 1700 (m), 1600 (s), 1520 (w), 1420 (br, s) cm⁻¹; ¹H NMR (500 MHz, pyridine-d₅) δ 10.74 (s, 1 H), 7.23 (d, 1 H), 5.69 (s, 2 H), 3.89 (s, 4 H), 3.23 (s, 2 H), 2.27 (s, 3 H); FAB, m/e 471 (0.21% of base peak); UV (1:1 CHCl₃/CH₃OH) 600 nm (ε 18466), 628 (ε 12627).

Testing in Mice against the P388 Lymphocytic Leukemia Model. Test compounds were dissolved in 0.9% saline. Female CDF₁ and DBA/2 (Harlan Laboratory, Indianapolis, IN) housed in gang cages were fed Purina Laboratory Chow and water ad libitum and adapted to this regime for at least 1 week before use. The P388 tumor was maintained by continuous passage in DBA/2 mice. On day 0, ascitic fluid was removed and diluted with Hank's balanced salt solution, cells were counted, and 10⁶ tumor cells were implanted ip in a total volume of 0.1 mL. Twenty-four hours later, mice were randomly segregated into treatment groups, and drug was given ip to groups of seven mice for each dilution. The mice were observed for 30 days and T/C (percent) values were determined from the survival rate as compared to the controls.²³

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APPENDIX A:

NMR AND UV SPECTRA
80 MHz $^1$H NMR Spectrum of 10.
80 MHz $^1$H NMR Spectrum of 7c.
80 MHz $^1$H NMR Spectrum of 1c.
80 MHz $^1$H NMR Spectrum of 1.
80 MHz $^1$H NMR Spectrum of 7a.
80 MHz $^1H$ NMR Spectrum of 1a.
80 MHz $^1$H NMR Spectrum of 12.
80 MHz $^1$H NMR Spectrum of 7d.
80 MHz $^1$H NMR Spectrum of 1d.
500 MHz $^1$H NMR Spectrum of 15c.
500 MHz 1H NMR Spectrum of 16c.
500 MHz ¹H NMR Spectrum of 5.
300 MHz $^1$H NMR Spectrum of 15a.
$^1H$ NMR Spectrum of 16a.
500 MHz $^1$H NMR Spectrum of 4.
500 MHz $^1$H NMR Spectrum of 15d.
500 MHz $^1$H NMR Spectrum of 16c.
500 MHz 1H NMR Spectrum of 6.
500 MHz $^1$H NMR Spectrum of 18.
500 MHz $^1$H NMR Spectrum of 19.
$^{19}$F NMR Spectrum of 15c.
$^{19}F$ NMR Spectrum of 16b.
$^{19}$F NMR Spectrum of 5.
$^{19}$F NMR Spectrum of 15a.
$^{19}$F NMR Spectrum of 16a.
$^{19}$F NMR Spectrum of 4.
UV SPECTRA
UV Spectrum of 17.
UV Spectrum of 19.
PART II

SPIRO-ANNULATED CYCLOHEXA-2,5-DIENONES

VIA ELECTROOXIDATION OF para-ARYL PHENOLS
INTRODUCTION

The past two decades have seen a substantial growth in the understanding and utilization of electrochemical processes among organic chemists. A wide variety of chemical transformations of organic substrates may now be achieved through electrolysis, either by anodic or cathodic processes, and such methodology often provides an attractive alternative to conventional techniques relying on chemical oxidation or reduction reagents.

While considerable progress has been made in many areas of organic electrochemistry, developments related to carbon-carbon bond formation, the foundation of organic synthesis, have been limited. Nevertheless, a variety of organic substrates have been investigated in this regard and both anodic and cathodic carbon-carbon bond-forming reactions have been described in the literature. In particular, anodic reactions of aromatic systems have been studied extensively.

Methods such as anodic cyanation and the electrooxidative coupling of alkylbenzenes, phenols and phenol ethers are proven methods of effecting carbon-carbon bond formation electrochemically. Though limited in scope, the anodic coupling reaction has provided a useful approach to a variety of biaryls as well as the so-called spirodienones, an important class of compounds which will be examined
in detail later in this section. The discussion that immediately follows will deal primarily with the anodic carbon-carbon bond-forming reactions of aromatic substrates.

Anodic Cyanation

One of the simplest approaches to anodic carbon-carbon bond formation in aromatic systems involves oxidation in the presence of cyanide ion. Tsutsumi and co-workers reported the first anodic cyanation reaction from electrolysis of a solution of anisole in methanolic sodium cyanide, affording a mixture of ortho and para cyanoanisoles in 10\% yield (Scheme I). The mechanism initially postulated involved oxidation of cyanide ion to the corresponding radical, followed by attack on the aromatic nucleus.

\[
\begin{align*}
\text{OCH}_3 \text{OCH}_3 & \quad \text{NC} \quad \text{OCH}_3 \\
\text{I-1} & \quad \text{I-2} & \quad \text{I-3} (10\%)
\end{align*}
\]

Scheme I. Anodic Cyanation of Anisole

This interpretation was subsequently challenged by Parker and Burgert, who found that at a constant potential of 1.2 V, a mixture of anisole and cyanide ion yielded cyano radicals, but no
cyanoanisoles. Nevertheless, at a constant potential of 2.0 V, high enough to oxidize anisole, the expected products were formed. This led to a revised mechanistic interpretation wherein the initial step was a one-electron oxidation of anisole to its corresponding cation-radical, followed by nucleophilic attack by cyanide ion. Subsequent oxidation of the resulting aryl radical and loss of a proton would afford the cyanoanisoles (Scheme II).

\[
\begin{align*}
\text{OCH}_3 & \quad \text{CN}^- \quad \rightarrow \quad \text{NC}^+ \quad \text{OCH}_3 \\
\text{I-1} & \quad -e \\
\end{align*}
\]

\[
\begin{align*}
\left[ \text{OCH}_3 \quad \text{NC} \quad \text{OCH}_3 \right]^+ & \quad \rightarrow \quad \text{NC} \quad \text{OCH}_3 \\
\left[ \text{OCH}_3 \quad \text{OCH}_3 \right]^+ & \quad -\text{H}^+ \\
\text{I-2} & \quad \text{I-3}
\end{align*}
\]

Scheme II. Parker and Burgert’s Anodic Cyanation Mechanism

Nilsson\textsuperscript{5} offered further evidence for lack of participation by cyanide radical by comparing the isomer distribution of the above reaction with that obtained by photolysis of anisole in the presence of cyanide ion wherein a considerable amount of the meta isomer was obtained via attack by cyanide radical on the aromatic nucleus.
As might be expected, a variety of aromatic substrates may be anodically cyanated. Andreades and Zahnow reported replacement of either an aromatic hydrogen or a methoxyl group in the anodic cyanation of aromatic ethers as well as a direct cyanation of biphenyl (Scheme III).

Yoshida studied the anodic cyanation of 5-membered heterocycles, including 2,5-dimethyl furan and 2,5-dimethylthiophene, but reported unattractive mixtures of products in poor yield. More promising results were obtained in the anodic cyanation of N-methyl or N-phenylpyrroles. The same author also reported cyanation of diarylamines and diarylacetylenes, often in good yield (Scheme IV).

**Anodic Coupling of Alkylbenzenes**

The formation of biaryls and diphenylmethanes via anodic coupling of alkyl benzenes has been studied by Nyberg. As illustrated in Table 1, the reaction follows one or both of two paths, depending on the substitution pattern on the aryl ring. These reactions are believed to proceed via a radical-cation intermediate and the yields are somewhat disappointing.

Crossed-couplings leading to unsymmetrical biphenyls have also been reported by the above author via the co-electrolysis of naphthalene with mesitylene or tetra- and pentamethyl benzenes in 13%, 42% and 56% yields respectively, the remainder being binaphthyl.
Scheme III. Anodic Cyanations by Andreades and Zahnow
Scheme IV. Yoshida's Anodic Cyanations
Table 1. Nyberg's Anodic Coupling of Alkyl Benzenes

<table>
<thead>
<tr>
<th>Alkylbenzene (1a)</th>
<th>Ratio of 1b : 1c</th>
<th>Yield of 1b + 1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,4-Dimethylbenzene</td>
<td>1 : 99</td>
<td>10</td>
</tr>
<tr>
<td>1,2,4-Trimethylbenzene</td>
<td>46 : 54</td>
<td>38</td>
</tr>
<tr>
<td>1,3,5-Trimethylbenzene</td>
<td>100 : 0</td>
<td>63</td>
</tr>
<tr>
<td>1,2,4,5-Tetramethylbenzene</td>
<td>0 : 100</td>
<td>32</td>
</tr>
</tbody>
</table>
A related study of the anodic oxidation of biphenyls by Ronlân and Parker\textsuperscript{14} led to carbon-carbon bond formation via direct side-chain coupling, affording the phenanthrene V-2 (Scheme V).

![Scheme V. Ronlân and Parker's Anodic Phenanthrene Synthesis](image)

**Scheme V. Ronlân and Parker's Anodic Phenanthrene Synthesis**

**Anodic Reaction of Phenols with Alkenes**

Shizuri and Yamamura\textsuperscript{16} have reported the reactions of several alkenes with 3,4-dimethoxy-6-methylphenol (VI-1) and p-methoxyphenol (VI-2) via anodic oxidation in acetic anhydride with tetrabutylammonium fluoroborate as the electrolyte, leading to carbon-carbon bond formation (Scheme VI). The authors noted that when vinyl ethers were employed as carbon nucleophiles, addition occurred regiospecifically at the 2-position (ortho to the phenolic carbon), whereas oxygen nucleophiles such as methanol typically add at the corresponding 4-position. When 3,4-methylenedioxy styrene VI-8 was employed as the alkenyl carbon nucleophile, the bicyclic adducts
Scheme VI. Anodic Reactions of Phenols and Alkenes
VI-9 and VI-10 were obtained, a result related to earlier studies by the same authors in the synthesis of Aniba neolignans, a process believed to proceed via the intermediate VII-2 (Scheme VII).

![Scheme VII. Anodic Synthesis of Aniba Neolignans](image)

**Anodic Coupling of Phenols and Phenol Ethers**

Oxidative electrochemical coupling of phenols and phenol ethers represents one of the more synthetically interesting of the anodic carbon-carbon bond forming reactions, since a number of naturally occurring molecules have been shown to arise via biological phenolic coupling processes.

Fitcher was the first to report the electrooxidative coupling of phenol (Scheme VIII), giving rise to a number of products. The same investigator later demonstrated that anisole could be anodically coupled as well.
Vermillion and Pearl\textsuperscript{21} studied the anodic dimerization of sodium vanillate (Scheme IX), obtaining dehydrodivanillin IX-3 in 65\% yield. This was shown to occur via oxidation of the phenolate anion to the corresponding phenoxy radical.

Johnston\textsuperscript{22} anodically oxidized appropriately substituted phenolic ketones such as 2,6-dihydroxyacetophenone (IX-1) (Scheme X) at a platinum anode in aqueous methanolic sodium hydroxide, obtaining the dimeric product IX-2 in 52\% yield.
Scheme X. Anodic Coupling of Phenolic Ketones

A more synthetically useful variant of this process involves intramolecular anodic couplings. Ronlán and Parker\textsuperscript{23} anodically oxidized the 1,3-diarylpropane \textit{XI-1} (Scheme XI) to obtain the cyclized spirodienone \textit{XI-2} in good yield. This represents a simple example of anodic spirodienone formation, a method which has been exploited in the synthesis of naturally occurring alkaloids.\textsuperscript{24a,b}

Scheme XI. Ronlán and Parker's Intramolecular Phenolic Coupling
Such intramolecular couplings have been carried out from both phenol and phenolic ether precursors. The mechanistic rationale of Miller, Stermitz and Falck\textsuperscript{25} (Scheme XII) for the formation of O-methylflavaminantine (XI\texttext{-}4) from laudonosine (XI\texttext{-}1) is illustrative of such non-phenolic coupling processes. These authors noted that chemical-based oxidations of alkaloids typically afford yields of 10\% or less; thus, electrooxidative coupling represents what may be the method of choice in many instances, particularly for the synthesis of morphinandienone alkaloids.

\begin{center}
\[ \text{Scheme XII. Anodic Oxidation of Laudonosine} \]
\end{center}

\begin{center}
\textbf{Spirodienones in Natural Products}
\end{center}

There is in fact a considerable number of natural products containing the spirodienone unit in its native and reduced forms,
most of which may be thought of as arising from biological phenolic coupling processes. Further, spirodienones have been implicated as biosynthetic intermediates which undergo subsequent reactions, such as the dienol-benzene rearrangement (Scheme XIII).26a-e

For the purpose of clarity in the discussion that follows, the term spirodienone will refer specifically to cyclohexa-2,5-dienones which are spiro-substituted at the 4,4-position, although the same term has also been applied to the closely related cyclohexa-2,4-dienones, when spiro-substituted at the corresponding 6-position.

Selected Syntheses of Spirodienones

Because of its ubiquitous nature and the variety of transformations possible in cyclohexadienone systems,27 the synthesis of the spirodienone moiety has been the subject of considerable attention by a number of investigators.28

As has already been mentioned, intramolecular electrooxidative coupling of aromatics is a demonstrated method for the preparation of certain spirodienones. Nevertheless, a variety of chemical reagents are available for effecting such oxidative couplings, including potassium ferricyanide, ferric chloride, manganese dioxide and lead oxide.29a,b,c While the yield of coupled products using the aforementioned reagents is often disappointing, vanadium oxychloride30 and vanadium oxyfluoride31 appear to be reagents superior to those mentioned above for intramolecular phenolic couplings, with yields approaching those obtained via anodic
Scheme XIII. Spirodienone and Spirodienone-derived Natural Products
oxidation. Similarly, thallium trifluoroacetate has been shown to efficiently couple phenol ethers both inter- and intramolecularly.32

The mechanisms of these metal-mediated couplings are often not clearly understood, but in many cases are believed to involve radical or cation-radical intermediates33a,b as in the anodic oxidative couplings previously discussed. It should be noted that the toxic by-products produced from some metal-based oxidants constitute a serious drawback in preparative-scale synthesis, a problem conveniently circumvented by use of the electrochemical method.

Pschorr-Type Cyclizations

Though originally employed as a means of preparing phenanthrene derivatives, the classic Pschorr reaction34a,b may be extended to the preparation of certain spirodienones (Scheme XIV). Hey and co-workers35 found that the diazonium salt XIV-1 derived from the corresponding 4'-methoxy-2-amino-N-methylbenzanilide afforded upon heating, the spirodienone XIV-2. Mechanistically, such processes are thought to involve either homolytic or heterolytic cleavage of the

\[
\begin{align*}
\text{XIV-1} & \xrightarrow{\Delta} \text{XIV-2 (50%)}
\end{align*}
\]

Scheme XIV. Pschorr Cyclization Route to Spirodienones
carbon-nitrogen bond, depending on the reaction conditions employed, leading to intramolecular attack on the aromatic nucleus by the resulting radical or cation intermediate.

Photochemical variants of this methodology (Scheme XV) have been employed by Kametani and co-workers\(^{36}\) in the synthesis of morphinandienone alkaloids and related natural products. Thus, irradiation of \(\text{XV-1a (} X = N_2^{+} \, \text{)} \) or \(\text{XV-1b (} X = \text{Br} \, \text{)} \) leads to homolysis of the C-X bond and subsequent intramolecular radical attack on the isoquinoline benzenoid ring. For some systems, this approach may be complicated by further photochemical reaction of the resulting spirodienone, although this difficulty has been circumvented by carrying out the irradiation in the presence of sodium borohydride, wherein the dienone is reduced to the dienol in situ before further photoreaction can take place.\(^{37}\)

\[\text{hv}\]

Scheme XV. Photochemical Route to Morphinandienone Alkaloids
Additional Spirodienone Syntheses

As outlined in Scheme XVI, spirodienones are available via several additional methods, including the intramolecular para-alkylation of phenols. Thus, treatment of the brosylate XVI-1 with potassium t-butoxide in t-butyl alcohol afforded the corresponding spirodienone XVI-2 in 50% yield without any attempt at optimization of reaction conditions.

Cyclization of diazoketone-substituted phenols and phenol ethers under acidic conditions affords spirodienones in good to excellent yield, especially when the side-chain bearing the diazoketone moiety has restricted freedom of movement, as in the conversion of XVI-5 to XVI-6.

Photolysis of p-benzoquinone in the presence of symmetrical olefins such as cyclooctene has been employed by Gilbert and Bryce-Smith in the preparation of spirodienone oxetanes such as XVII-9, in surprisingly good yield.

Mention should be made of approaches to the spirodienone unit via aliphatic precursors. One example is the introduction of the spirodienone ring of the proaporphine alkaloid pronuciferine (XVII-2), which was achieved by Bernauer (Scheme XVII) via Michael addition of the anion of aldehyde XVII-1 to methyl ethynyl ketone, followed by subsequent intramolecular aldol condensation, albeit in exceedingly poor yield. The same author found that by substituting methyl vinyl ketone in the sequence, the yield of the corresponding spiro-fused cyclohexenone was a respectable 39%.
Scheme XVI. Additional Methods of Spirodienone Synthesis
Scheme XVII. Bernauer's Synthesis of Pronuciferine

Similar methodology (Scheme XVIII) was employed more recently by Natale and co-workers\textsuperscript{44} in an asymmetric synthesis of cannabispirenone-A (XVIII-3), which is believed to arise biosynthetically from the corresponding cannabspiradienone (XIII-1). Both natural products have been isolated from cannabis sativa extracts.\textsuperscript{44}

Scheme XVIII. Natale's Synthesis of Cannabispirenone-A
From the foregoing discussions, some points should be emphasized. First, electrochemically induced carbon-carbon bond formation has been explored to a reasonable extent in the anodic reactions of aromatic substrates. Nevertheless, the relatively mild conditions under which electrochemical oxidations are carried out, together with the absence of toxic by-products from such oxidations make further studies of anodic carbon-carbon bond formation in other aromatic systems an attractive area for continued research efforts.

In addition, it should be noted that the importance of the spirodienone moiety in the biosynthesis of natural products has led to substantial efforts by synthetic organic chemists in the development of methodologies for its preparation. Thus, additional contributions in this area would be meaningful.
RESEARCH OBJECTIVES

The goal of this research was to develop new methodology for the electrochemical formation of carbon-carbon bonds in aromatic systems. As originally envisioned, this work would explore the anodic oxidation of 2'-olefinic substituted p-arylphenols in the hope that an electrogenerated intermediate might interact with the 2'-olefinic side chain, leading to intramolecular carbon-carbon bond formation. The resulting products would be spiroannulated cyclohexa-2,5-dienones (spirodienones), an important class of compounds which was discussed in the introductory section. Further work would then focus on the effect of structural modification of the oxidation substrates on the course of the reaction. The findings of this study are presented in the RESULTS AND DISCUSSION section.
RESULTS AND DISCUSSION

The strategy for utilization of substituted p-aryl phenols as substrates for potential anodic carbon-carbon bond formation was originally motivated by two factors: first, the work of Ronlân, et al. on the anodic oxidation of p-phenyl phenol in methanolic lithium perchlorate (Figure 1) suggested that this efficient and high yield process could be explored as a means of effecting intramolecular carbon-carbon bond formation electrochemically by the introduction of simple 2'-olefinic substituents on the p-aryl ring; second, studies by Swenton and DeSchepper had demonstrated that 2'-substituted p-aryl phenols were readily accessible by the addition of aryllithium reagents to p-benzoquinone dimethylmonoketal, followed by ketal hydrolysis and subsequent zinc-copper couple reduction to the corresponding phenol (Figure 2).
Figure 2. General Approach to 2'-Substituted p-Aryl Phenols

The 2'-Alkenyl Substituted p-Aryl Phenol Strategy

A working hypothesis for the p-aryl phenol oxidation of Figure 1 involves initial one-electron oxidation of the phenol ring to a cation-radical intermediate which may then lose a proton and undergo a second oxidation to a phenoxonium ion which captures methanol at the 4-position of the dienone ring with subsequent loss of a second proton. Such an analysis has ample literature precedent\(^1\) and more will be said about this mechanistic interpretation later.

Our strategy (Figure 3) for anodic carbon-carbon (C-C) bond formation was centered around the possibility that an electrogenerated cationic center such as that described above could be captured intramolecularly by a 2'-olefinic substituent located on the p-aryl ring to effect carbon-carbon bond formation. In addition,
the presence of a 2'-substituent would further serve to sterically inhibit capture of solvent methanol (as in the reaction of Figure 1) prior to the desired C-C bond formation. Finally, the cationic center resulting from the intramolecular cyclization would be relatively stable, being either secondary or tertiary as well as benzylic, and could thus be captured by solvent to afford a product which would be stable towards further oxidation.

Figure 3. The 2'-Alkenyl-substituted p-Aryl Phenol Strategy
Preparation of the Model 2'-Alkenyl-substituted p-Aryl Phenol

It was hoped that by employing metal-halogen exchange chemistry on 2-(1-alkenyl)-bromobenzene derivatives as a source of the required aryllithium reagents, the approach outlined in Figure 2 could be employed for the preparation of target 2'-olefinic substituted p-aryl phenols (Figure 4). Unfortunately, when 2-isopropenyl bromobenzene 3 was employed in this sequence, an unexpected reaction pathway during hydrolysis of the quinol ketal led to cyclization and aromatization to the corresponding phenanthrene 5.

![Chemical Structures](image)

Figure 4. Phenanthrene Cyclization from p-Quinol Ketal Hydrolysis

The postulated mechanism for the phenanthrene cyclization outlined above suggested that alkenyl-substituted aryl bromides similar to 3 could not be employed to prepare other p-aryl phenols via this methodology since hydrolysis of the intermediate quinol ketals would
lead to the same fate. Although this cyclization was an undesirable process for the purpose at hand, it could well prove to be a useful approach to certain substituted phenanthrenes from relatively cheap starting materials.

A simple means of circumventing the difficulties mentioned above without modifying the approach significantly was achieved by methylation of the intermediate tertiary carbinol 7, using sodium hydride and methyl iodide (Figure 5). Subsequent metal halogen-exchange, followed by monoketal addition, hydrolysis and reduction afforded the corresponding p-aryl phenol 9 which was cleanly converted to the desired alkenyl derivative 10 via treatment with p-toluenesulfonic acid in chloroform. The overall yield for this sequence was quite good and thus, a model system for study of the anodic oxidation could be obtained in reasonable quantity from readily available starting materials.

**Anodic Oxidations of the Model System**

The standard conditions for anodic oxidation of p-phenyl phenol (Figure 1) involved single cell electrolysis at uncontrolled potential using methanol containing 1% by weight of lithium perchlorate as the solvent/electrolyte system. A cylindrical, perforated platinum sheet anode and a copper wire cathode generally gave consistent results in such oxidations and the above conditions were used as a starting point for a systematic study of the anodic oxidation of the model p-aryl phenol 10.
Figure 5. Preparation of the Model 2'-Substituted p-Aryl Phenol 10
Thus, a series of oxidations was carried out on fifty milligram scale, the reactions being monitored by thin-layer chromatography until complete. This was followed by standard work-up and analysis by high pressure liquid chromatography, using an internal standard and cutting and weighing of the respective recorder traces to determine the yield for each reaction (see Experimental Section). The most pertinent results are summarized in Table 2.

As may be seen from Entry 1, anodic oxidation of 10 under the usual conditions employed for oxidation of p-phenyl phenol 1 did in fact lead to the desired carbon-carbon bond formation, affording the corresponding spirodienone 11 in a modest 38% yield (Entry 1).

The structure assignment for 11 was established in part by analysis of the proton NMR (Figure 6) which showed replacement of the terminal vinyl hydrogens in the starting material by a saturated methylene group, exhibiting a simple AB quartet centered at 2.4 ppm, a pattern consistent with structure 11. Note that the absence of the side-chain terminal vinyl hydrogens of 10 effectively rules out the product arising from simple anodic addition of methanol at the 4-position of the dienone ring, the most likely product other than 12 to be expected from this reaction (as in the conversion of 1 to 2 in Figure 1). The dienone ring vinyl hydrogens appeared as an exceedingly complex multiplet, due apparently to the presence of the methoxyl-bearing chiral center. The IR spectrum showed the strong, characteristic dienone carbonyl stretch at 1665 cm\(^{-1}\). In addition,
Table 2. Experimental Variables in the Anodic Cyclization of 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Current Dens. (mA/cm²)</th>
<th>Anode</th>
<th>Additive</th>
<th>Yield (HPLC) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃OH</td>
<td>0.42</td>
<td>Pt</td>
<td>none</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>CH₃OH</td>
<td>0.42</td>
<td>Pt</td>
<td>2,6-lutidine</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>CH₃OH</td>
<td>0.42</td>
<td>C</td>
<td>AcOH (5 equiv)</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN/CH₃OH*</td>
<td>3.36</td>
<td>Pt</td>
<td>AcOH (5 equiv)</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>CH₃CN/CH₃OH*</td>
<td>1.68</td>
<td>Pt</td>
<td>AcOH (5 equiv)</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>CH₃CN/CH₃OH*</td>
<td>0.84</td>
<td>Pt</td>
<td>AcOH (5 equiv)</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>CH₃CN/CH₃OH*</td>
<td>0.42</td>
<td>Pt</td>
<td>CF₃CO₂H (5 equiv)</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>CH₃CN/CH₃OH*</td>
<td>0.42</td>
<td>Pt</td>
<td>AcOH (5 equiv)</td>
<td>83</td>
</tr>
</tbody>
</table>

* in a ratio of 4:1.
Figure 6. 80 MHz $^1$H NMR Spectrum of 11.
$^{13}$C NMR, exact mass measurement and combustion analysis were in good agreement with the assigned structure.

Following this initial success, a number of reaction variables were examined and it was found that the yield for this reaction was in part a function of the current density and anode material. Solvent effects were less significant, although a mixture of acetonitrile and methanol gave reaction mixtures which appeared cleaner by TLC and were more easily handled during work-up. More importantly, a mildly acidic medium (compare Entry 1 vs. Entry 8) was found to be most beneficial and this result deserves particular attention.

Before proceeding any further, the possible mechanistic aspects of this new anodic C-C bond-forming reaction should be discussed in light of information which is believed to be significant in carbon-carbon bond formation in other phenolic oxidation processes.

**Oxidative Phenolic Coupling**

Since the study of the phenol oxidations summarized in Table 2 was conducted in the hope of finding conditions to maximize oxidative carbon-carbon bond formation, one obvious question to consider was what conditions favor carbon-carbon bond formation in other phenol oxidations. It should be noted here that the reaction under consideration—anodic cyclization of 10 to 11—is unprecedented, making direct analogies difficult.
The oxidation of phenols has been studied to a remarkable extent and the intermediates thought to be involved in various phenolic coupling processes have included radicals, cation-radicals and phenoxonium ions. The plethora of literature in this area makes a short but comprehensive discussion on this subject nearly impossible, and only a brief attempt at correlating pertinent information with the results of Table 2 will be undertaken.

In a short but important paper, Waters draws upon the work of numerous authors in this area, concluding that oxidative phenolic coupling processes proceed by two distinct pathways. The first involves a one-electron oxidation of phenol as represented in Equation 1.

\[
\text{ArOH} \rightarrow \text{ArO}^+ + e^- + H^+ \quad (1)
\]

This reaction has been shown to be pH dependent, and the oxidation is accelerated in alkaline solutions. Waters points out that under appropriate experimental conditions, such aryloxy radicals preferentially undergo carbon-oxygen-carbon (C-O-C) coupling rather than carbon-carbon (C-C) coupling, often giving long chain polymers in intermolecular reactions. That C-O-C coupling should predominate is reasonable, since one would predict that in the canonical forms of such radicals (Figure 7), electron density would be higher on oxygen than on carbon, based on electronegativity considerations.
A second pathway involves subsequent one-electron oxidation of an aryloxy radical to the corresponding phenoxonium ion, as in Equation 2.

\[
\text{ArO}^- + e \rightarrow \text{ArO}^+ \quad (2)
\]

Such oxidations are now well-known. Waters points out that since the cation-radicals that result from a one-electron oxidation of un-ionized phenol are quite acidic (\(pK_a = -2\)),\(^{47}\) aryloxy radicals are thus formed during phenol oxidations conducted even under conditions of fairly low pH. But their further oxidation, as in Equation 2, is clearly pH independent, since no proton is involved. As was mentioned above, the reaction of Equation 1 is pH dependent and the relationship between pH and oxidation potential for this reaction is given by Equation 3.
Waters then concluded that if a plot of oxidation potential for a given phenol vs. pH for these two reactions is constructed, the lines must cross. His plot of equation (3) and the pH independent straight line corresponding to the reaction of equation (2) is reproduced in Figure 8.

![Figure 8. Plot of Phenol Oxidation Potential vs. pH for the Reactions of Equations 1 and 2.](image)

The point at which these lines cross corresponds to an equipotential pH, above which the reaction of Equation 1 is more favorable than the subsequent oxidation of Equation 2, leading to a relatively high concentration of phenoxy radicals. Under these
conditions, radical-radical type coupling products would be expected. However, when such an oxidation is conducted at a pH below the equipotential pH, the one-electron oxidation of un-ionized phenol predominates. The resulting highly acidic cation-radical would rapidly lose a proton to again afford a phenoxy radical, but the concentration of phenoxy radicals should remain low under these conditions, since the further oxidation reaction of Equation 2 is now more energetically favorable and should rapidly ensue. This would lead to phenoxonium ion formation and products resulting from electrophillic reactions of the phenoxonium ion with unoxidized phenol, i.e. C-C type coupling products.

Waters further suggested that of the canonical forms of the phenoxonium ion (Figure 9), those which bear positive charge on carbon rather than oxygen should be more significant contributors to the overall electronic structure of the species based on electronegativity considerations. Thus, electrophillic reactions should take place preferentially via carbon-carbon bond formation in phenolic coupling processes.

The conclusion that phenoxonium ion formation should enhance carbon-carbon coupling has been partly verified by the work of Abramovitch and co-workers\textsuperscript{18d} who generated phenoxonium ions thermally, in the presence of anisole. Products arising from intermolecular carbon-carbon crossed-coupling were formed almost exclusively, in the absence of electron-withdrawing groups on the ArO\textsuperscript{+} nucleus.
Figure 9. Canonical Forms of the Phenoxonium Ion.

The above considerations strongly suggest that the mechanistic course of phenolic couplings should be sensitive to changes in the solution pH. This conclusion may have important implications for other oxidation reactions of phenols which lead to carbon-carbon bond formation via a phenoxonium ion intermediate. Such reactions might be conducted most advantageously at a pH below the equipotential pH, the region in the graph of Figure 8 where oxidation of un-ionized phenol would occur.

In terms of practicality in the laboratory, it would not be especially convenient to have to determine the equipotential pH for every phenol/oxidant/solvent system that might be under consideration. But as a first approximation, one would clearly want to conduct such oxidations either in acidic solvents or in the presence of added acids.
Implications for the Model System Study

Clearly, the anodic cyclization of 10 to 11 is not strictly analogous to a phenolic coupling reaction. Nevertheless, one might reasonably expect that Waters' prediction of enhanced C-C bond formation via phenoxyonium ion intermediates would hold for the system under consideration and that the overall reaction might well exhibit a pH dependence. In the context of the results outlined in Table 2, it should be noted that at equivalent current densities, addition of acid to the reaction medium increased the yield of product arising from carbon-carbon bond formation from 36% (Entry 1) to 83% (Entry 8). Thus, at a lower pH the desired process is clearly favored, in line with Waters' prediction.

The addition of five equivalents of acetic acid could serve to adjust the solution pH to a value below the equipotential pH so as to insure that the first species to be oxidized is un-ionized phenol rather than phenoxide ion. At such a pH, the second oxidation to form a phenoxyonium ion would rapidly ensue after proton loss from the cation-radical, thereby suppressing undesirable side reactions resulting from radical-radical couplings.

However, the possibility also exists that the intramolecular ring-closure proceeds via the cation-radical intermediate and that the addition of acetic acid (pKa = 5) may simply inhibit proton loss from the cation-radical (pKa approximately = -2). The excess of acid used may compensate for the unfavorable pKa difference.
Indirect experimental evidence for the intermediacy of the phenoxonium ion in this oxidation was suggested by the reaction illustrated in Figure 10. When 9 was subjected to the optimal conditions for the anodic oxidation of 11, a 47% yield of 12 was obtained. A reasonable mechanism for the formation of this product would involve trapping of the cationic center by the methoxyl oxygen, followed by dealkylation, presumably by methanol attack, although there is no direct evidence for this. Nevertheless, it would be hard to envision this process proceeding via a radical intermediate.

As shown in Entry 7 of Table 2, substitution of trifluoroacetic acid for acetic acid gave a slightly lower yield of cyclized product. Since the desired overall reaction leads to formation of a spirodienone, the reaction medium should probably not be made too acidic or side-reactions, such as dienone-phenol rearrangements may ensue.

![Chemical structure](image)

Figure 10. Anodic Oxidation of 9

Dienone-phenol rearrangement may or may not account for the lower yield in Entry 7, although this reaction has been shown to
predominate in diene-forming phenolic couplings conducted in acidic solvents.* In any case, there is undoubtedly a limiting solution pH for this reaction, below which undesired side-reactions will emerge.

The lower yield noted in Entry 2 of Table 2 may also be rationalized in light of Waters' foregoing analysis. Anodic C-O-C polymerization may result from a higher solution pH brought about by addition of the base (2,6-lutidine) in this instance. In addition, the result in Entry 2 would seem to further mitigate against the 10 to 11 cyclization proceeding via a radical-type intermediate, since one might expect phenoxy radicals to predominate under these conditions and yet a poor yield of 11 was obtained.

It should be noted that unlike chemical oxidations occurring in solution, the critical interactions in the electrochemical cell occur on the surface of the electrode and it is not clear what significance relatively minor changes in the overall solution pH may have in relation to the environment near the anode surface—the region where reactive intermediates are generated. Nevertheless, certain electrochemical phenol oxidations have been shown to exhibit a pH dependence which may be understood at least in qualitative terms.1b

In any case, the series of reactions summarized in Table 2 demonstrated that not only was the overall strategy for electrochemical carbon-carbon bond formation viable, but that under well defined reaction conditions, a high yield of cyclized spirodienone product could be obtained. In view of these results, the next goal of the investigation was to explore the generality of this
new reaction by preparing additional 2'-alkenyl-substituted p-aryl phenols to determine what effect, if any, substituents on either the alkenyl side-chain or the p-aryl ring might have on the course of the reaction.

Preparation of Other Substituted p-Aryl Phenols

The preparation of a p-aryl phenol with a simple 2'-ethylenic side chain was undertaken, since anodic oxidation of this product would yield some insight into the relative importance of alkyl substitution (or lack thereof) on the alkene for the efficiency of the reaction. While a number of approaches to this compound were attempted, it was found subsequently that, unlike 2-isopropenyl bromobenzene 3, which led to phenanthrene cyclization during attempted preparation of 10 (Figure 4), utilization of 2'-bromostyrene 13 in the metalation sequence followed by hydrolysis of the quinol ketal gave the corresponding p-quinol with no evidence of phenanthrene formation. Reduction to the p-aryl phenol 14 was straightforward (Figure 11).

The simplest access to a 2'-alkenyl p-aryl phenol in which the alkenyl moiety contained alkyl substitution of defined stereochemistry at both ends of the double bond was to prepare a substrate wherein the double bond was contained within a ring.

Anodic cyclization of such a system would demonstrate the ability to form more complex ring systems as well as give additional insight into the importance of alkyl substitution on the olefinic side-chain (Figure 12). Thus, reaction of methyl ester 6 with the di-Grignard
Figure 11. Preparation of p-Aryl Phenol 14

Reagent derived from 1,4-dibromobutane afforded the cyclopentyl tertiary carbinol which was methoxylated as before to give 15. Using the same sequence of reactions as for the preparation of 10, the desired 2'-cyclopentenyl p-aryl phenol 17 was obtained as shown.

Figure 12. Preparation of p-Aryl Phenol 17
Since 2'-bromoacetophenone was commercially available, the preparation of \( \text{p-aryl phenol 21} \) (Figure 13) containing a phenyl-substituted alkenyl side chain was relatively straightforward, employing the methodology used for the previous systems 10 and 17. It was hoped that anodic oxidation of this substrate would indicate the relative importance of the stability of the postulated cationic center developed prior to solvent capture (see Figure 3), since the positive center in this case would be highly stabilized, being both tertiary and di-benzylic.

![Chemical structure diagram](image)

**Figure 13. Preparation of \( \text{p-Aryl Phenol 21} \)**

The preparation of substrates possessing methoxyl groups on the \( \text{p-aryl ring} \) was of interest for several reasons. As was shown in the previous chapter, a number of natural products possessing the spirodienone moiety contain oxygenated aryl rings. In addition,
appropriately positioned methoxyl groups could serve not only to stabilize the developing cationic centers suggested in the mechanistic analysis of Figure 3, but to enhance the nucleophilicity of the 2'-olefinic substituent. Finally, it would be important to establish whether or not competing oxidation of such an oxygenated ring would complicate the chemistry and diminish the synthetic potential of the overall process.

As was shown in Figure 11, synthesis of p-aryl phenol 14 via metal-halogen exchange on 2'-bromostyrene proceeded smoothly without competing phenanthrene formation. Nevertheless, when the corresponding methoxylated derivative 23 was employed in the same sequence of reactions, a complex mixture of products was produced during the hydrolysis of the p-quinol ketal, presumably due to acid-catalyzed ionization or rearrangement processes facilitated by the presence of the methoxyl groups (Figure 14).

The method of Stern and Swenton\textsuperscript{50} for removal of the ketal moiety of quinol ketals under non-acidic conditions proved to be extremely useful in this scheme. Thus, employment of the mixed silyl-methyl quinone monoketal 24 in the reaction sequence, followed by treatment with tetrabutyl ammonium fluoride afforded the desired quinol 25 which was smoothly reduced to the desired p-aryl phenol 26. The low overall yield (25%) obtained in the preparation of quinol 25 was due mainly to the lability of the methoxylated bromostyrene derivative 23, which polymerized rapidly and had to be prepared and used directly in crude form without purification.
Figure 14. Preparation of p-Aryl Phenol 26
It should be noted that the silyl-methyl quinone monoketal approach perhaps could have been employed in previous systems which would be subject to phenanthrene cyclization during the quinol ketal hydrolysis step. Nevertheless, the introduction of the alkenyl group at a later stage in the synthesis as was done for systems 10, 17 and 21 was a satisfactory solution and complements the silyl-methyl mixed ketal method.

As shown in Figure 15, preparation of methoxylated p-aryl phenol 33 possessing the 2'-isopropenyl group was initially attempted using essentially the same approach as for the non-methoxylated analogue 10. The attempted elimination of methanol from 29 under the conditions previously employed for alkene formation led to an unexpected, high melting (223-225 °C) aromatic product, assigned structure 30. This was based in part on the presence of a singlet in the proton NMR at 1.34 ppm, integrating for six hydrogens, suggesting the presence of two equivalent methyl groups (Figure 16). Further, irradiation of the gem dimethyl resonance of this fluorene product (Figure 17) revealed a Nuclear Overhauser Effect (NOE) for a single, meta-coupled hydrogen on the phenol ring, further confirming the assigned structure.

It was hoped that formation of fluorene 30 could be suppressed by rendering the phenol ring of 29 less electron-rich. Thus, acetylation of 29, followed by heating of the acetate 31 with p-toluenesulfonic acid in chloroform as before gave 32 as the only product. The desired p-aryl phenol 33 was readily obtained by cleavage of the
Figure 15. Formation of 30 and Preparation of p-Aryl Phenol 33.
Figure 16. 80 MHz 1H NMR Spectrum of 30.
Figure 17. 500 MHz $^1$H NMR Spectrum of 30 and NOE Experiment.
phenolic acetate with dilute methanolic potassium hydroxide followed by acidic work-up.

Another system of interest to prepare was \( p \)-aryl phenol 38, possessing a simple vinyl ether side-chain (Figure 18). Thus, metal-halogen exchange on the dimethyl acetal of 2'-bromoacetophenone 34 followed by monoketal addition and hydrolysis afforded the mixed quinol ketal 35. Zinc-copper couple reduction to \( p \)-aryl phenol 36, followed by ketalization, and conversion to the vinyl ether by the method of Newman affords the required \( p \)-aryl phenol 38.

Figure 18. Preparation of \( p \)-Aryl Phenol 38.
Anodic Oxidations of the Substituted Systems

The various p-aryl phenols prepared above were subjected on a preparative scale (0.2-0.3 g) to the optimum anodic oxidation conditions established in the previous study on the anodic cyclization of 10 to 11. The results of this study are presented in Table 3 as well as Figure 19. The spirodienones isolated from these oxidations all showed IR, NMR and exact mass or combustion analysis data consistent with the structures assigned.

Interestingly, it was found that under the optimal conditions previously established, the isolated yield of spirodienones resulting from the anodic cyclizations varied greatly, ranging from a poor 17% in the case of 43 (Entry 5) to an excellent 92% for 41 (Entry 4), depending on the substitution present on either the alkenyl side-chain or the p-aryl ring.

Before these results are analyzed in detail several points should be made. First, it should be mentioned that in those systems which gave modest or poor yields of spirodienone, the mass recovery after work-up of the crude reaction mixtures was good. Nevertheless, silica gel chromatography yielded no additional identifiable products (Entry 4 is an exception which will be discussed later) other than the spirodienone, the remainder of the weight being intractable tars or oils which could be eluted from the column only with very polar solvent mixtures.

Second, the question of stability of the spirodienone products under the reactions conditions, as well as the conditions of work-up...
Table 3. Spiro-Annulated Cyclohexa-2,5-dienones from p-Aryl Phenols

<table>
<thead>
<tr>
<th>Entry</th>
<th>p-Aryl Phenol</th>
<th>Prod.</th>
<th>Yield (%)</th>
<th>CE* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R₁, R₃, R₄ = H; R₂ = CH₃</td>
<td>11</td>
<td>65</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>R₃, R₄ = H; R₁ = R₂ = -(CH₂)₃-</td>
<td>38</td>
<td>69</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>R₁, R₂ = H; R₃, R₄ = OCH₃</td>
<td>40</td>
<td>70</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>R₁ = H; R₂ = CH₃; R₃, R₄ = OCH₃</td>
<td>41</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>R₁, R₂, R₃, R₄ = H</td>
<td>43</td>
<td>17</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>R₁, R₃, R₄ = H; R₂ = C₆H₅</td>
<td>44</td>
<td>22</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>R₁, R₃, R₄ = H; R₂ = OCH₃</td>
<td>45</td>
<td>21</td>
<td>71</td>
</tr>
</tbody>
</table>

* Current Efficiency for Product Formation.
Figure 19. Anodic Cyclizations of 2'-Alkenyl-p-Aryl Phenols.
and chromatographic isolation was addressed by subjecting a sample of pure spirodienone 45, which was assumed to be one of the most labile in the series, to the conditions of the anodic oxidation for an extended time, followed by work-up and chromatography as for the other systems. The spirodienone was recovered in near quantitative yield in this case, suggesting that the poor yield in this and other systems was probably a function of the anodic reaction itself and not extraneous factors.

Implications of the Anodic Cyclization of the Substituted Systems

To begin, an examination of the results from anodic oxidation of p-aryl phenol 14 (Entry 5, Table 3) is a useful starting point. This substrate gave the poorest yield of cyclized product in the series—only 16%—and yet the substitution differs from the model system 10 only by replacement of a methyl group with a hydrogen on the alkenyl side-chain. Further, this system represents the only one studied where the product of simple addition of methanol at the 4-position was observed (see Figure 19). More significantly, consider Entry 3 in Table 3, wherein the p-aryl phenol 26 gave a 70% yield of cyclized spirodienone 40. Again, substrate 14 differs only by the methoxyl groups present on the p-aryl ring of 26 and yet there is a considerable divergence in yield.

These examples point out what the author considers to be the factor of paramount importance for the efficiency of the process under consideration, namely relative nucleophilicity of the side-
chain double bond. In the model system 10, the presence of a methyl group must serve to enhance the relative nucleophilicity of the alkenyl moiety via hyperconjugation. For the methoxylated derivative 26, the unsubstituted double-bond is apparently rendered more nucleophilic via a resonance interaction with the para-oriented methoxy group on the aryl ring.

As was mentioned above, anodic oxidation of 14 also gave a modest yield of the product resulting from addition of methanol at the 4-position of the dienone ring. That this was observed only in this system is not entirely surprising, since the simple unsubstituted alkenyl side-chain would offer the least amount of steric hindrance to methanol attack at the 4-position of all the systems studied. It seems reasonable that if the rate of ring closure was slower for the oxidation intermediate arising from 14, due to a decrease in side-chain nucleophilicity, competing capture of methanol would be observed in this less sterically hindered system. Nevertheless, when double-bond nucleophilicity is enhanced as in 26, steric factors are overridden and a good yield of cyclized product is obtained (Figure 20).

The oxidation of p-aryl phenol 33, wherein both alkyl substitution of the double bond and methoxylation of the p-aryl ring were brought into play, led to an excellent 92% yield of spirodienone 41, further supporting the analysis that side-chain nucleophilicity is an essential ingredient for the obtaining of good yields in this anodic process.
In retrospect, it would have been interesting to try to separate
the effects resulting from the presence of each of the two methoxyl
groups on the \( p \)-aryl ring in systems 26 and 33. Although the methoxyl
group para to the side chain may serve the purpose described above,
the influence of the methoxyl group para to the phenolic ring may
also contribute substantially to the efficiency of the oxidation via
a resonance stabilization of the postulated phenoxonium ion
intermediate (Figure 21).

The systems 26 and 33 were chosen in part on the basis of their
ease of preparation. However, they served the further purpose of
demonstrating that spirodienones possessing methoxylated \( p \)-aryl
rings could be prepared by this methodology without complications arising from competing oxidation of the p-aryl ring. As was mentioned in the introductory section, a number of spirodienone-containing natural products possess a similar pattern of aryl ring methoxylation and thus, this anodic spiroannulation may well be of considerable use in natural products synthesis.

The yield from cyclization of 17 to 39 is relatively unremarkable, being approximately the same as that obtained for the model system 10. However, it not only demonstrates the ability to form a 5-5 ring system under mild, anodic conditions, but lends further support to the notion that the presence of electron-donating alkyl groups on the alkenyl side-chain is beneficial for the efficiency of the carbon-carbon bond-forming reaction.
The oxidation of \( p \)-aryl phenol 21, wherein the side-chain double bond is substituted with a phenyl group, appears to be anomalous at first glance. Since a low yield (22\%) of spirodienone was obtained in this instance, it would appear that during the cyclization process, the developing cationic center is not being stabilized in the manner expected for such a system, even though the cationic center prior to solvent capture would be both tertiary and di-benzylic. It was indeed surprising that this system compared unfavorably with the methyl-substituted system 10.

One possible explanation for this result may be that the developing positive charge during the cyclization is not stabilized because the side-chain phenyl ring is unable to achieve the required co-planarity with the double bond, due to steric interactions with the \( p \)-aryl ring (Figure 22). Indeed, when forced out of co-planarity, the phenyl group would act inductively as an electron-withdrawing group, thereby de-activating the olefin toward electrophillic addition. Such an analysis has been invoked by others\(^{52}\) to explain the anomalous rate retardations observed in certain reactions involving rate-determining protonation of olefins substituted with phenyl groups vs. methyl groups.

Unfortunately, the double-bond nucleophilicity argument would seem to break down in the face of the evidence resulting from anodic oxidation of \( p \)-aryl phenol 38. This system was prepared precisely because it was felt that the vinyl ether moiety would represent a highly nucleophilic alkenyl side-chain which should afford an
excellent yield of spirodienone if the above argument holds. Indeed, systems 26 and 33 might be thought of as vinylogous vinyl ethers, via aryl pi-system conjugation. In those instances, the methoxyl groups proved to be of significant benefit.

Nevertheless, oxidation of 38 gave consistently poor yields of cyclized product, in spite of numerous attempts at both controlled and uncontrolled potential oxidations. Indeed, it was concern over the stability of the resulting spirodienone product in this case that prompted the examination of its stability to the reaction and isolation conditions, as was mentioned earlier. It was also found that the phenol 38 was stable for at least 24 hours in the solvent/electrolyte system used for these oxidations, in the absence of current.

It is worth noting that the dimethyl ketal moiety of 45 could be hydrolyzed in reasonable yield to afford the corresponding diketone
46, as shown in Figure 19. This spirodienone showed a high melting point (188-190 °C, dec) and the expected IR carbonyl bands at 1710 cm⁻¹ and 1670 cm⁻¹. An alternate method of preparing this unusual system will be presented in Part III of this dissertation.

One possible explanation for the poor yield observed in the anodic cyclization leading to 45 would involve oxidation of the vinyl ether moiety itself. Although it was noted above that no improvement in yield was obtained even at controlled potential--conditions under which the phenol should be selectively oxidized in the presence of a simple vinyl ether--the possibility exists that resonance interaction between the phenolic hydroxyl group and the vinyl ether may serve to render side-chain oxidation a significant and deleterious competing process (Figure 23). Unfortunately, there is no direct evidence for this, since no identifiable side-products could be isolated from the tars that constituted the balance of the mass after isolation of 45.

It might be possible to test this hypothesis via preparation of a related substrate wherein placement of bulky alkyl substituents on the phenol ring would force the two rings of the biphenyl system into a perpendicular orientation, eliminating the resonance interaction outlined in Figure 23. Such an examination was not undertaken, however.

Another possible explanation considered for the poor yield in this case is illustrated by the dealkylative cyclization of 9 to 12 previously outlined in Figure 10. If a similar process were to occur for the vinyl ether derivative 38, the resulting product would be the
cyclic vinyl ether 47 as shown in Figure 24. Interestingly, when 47 was independently prepared (see Part III of this dissertation) and subjected to the standard anodic oxidation conditions, it was found to be unstable.

Figure 24. Possible Anodic Dealkylative Cyclization of 38.
The potential complications postulated in the anodic oxidation of 38 fail to explain two important experimental observations from the study of the other systems which gave low yields of spirodienones. First, as was mentioned earlier, mass balance for these reactions was good, but in the low yield systems the remainder of the material was a complex mixture of tars or polar oils; no appreciable amount of p-quinol ethers, with the exception of product 42, was observed. Second, a consistent feature of the poor yield electrolyses was a lower than expected current efficiency for the two-electron oxidation (compare entries 1 and 5, Table 3). These two observations taken together suggested that a competing four-electron anodic 1,2-addition of methanol might be occurring in these systems (Figure 25).

![Figure 25. Anodic 1,2-Addition of Methanol in Phenol Oxidation.](image-url)
That this might account for the lower yields observed for those systems possessing relatively non-nucleophilic side-chains seemed reasonable. A competing four-electron oxidation would make the current efficiency appear low, since the calculation for the reaction was based on the expected two-electron oxidation. In addition, competing 1,2-addition of methanol would be the expected reaction pathway in systems where the usual 1,4-addition mode was impeded by steric hindrance, as is the case in the 2'-substituted p-aryl phenol series. Further, the products resulting from competing anodic 1,2-addition of methanol are o-quinone monoketals. Such systems, unless appropriately substituted, are known to undergo rapid Diels-Alder reactions, affording mixtures of dimeric products, and might reasonably be expected to undergo similar condensations with the spirodienone products after their initial formation, further lowering the yield of the reaction.

To explore the possibility of such a side reaction, the sterically bulky (2'-phenyl)-p-phenyl phenol 49 was prepared from commercially available 2-bromobiphenyl 48 (Figure 26). Anodic oxidation of 49 under the usual conditions afforded in essentially quantitative yield a one-to-one mixture of the 1,2- and 1,4-oxidation products 51 and 50, the ratio being determined by integration of the methoxyl region of the proton NMR of the crude reaction mixture.

This offered clear evidence that competing anodic 1,2-addition of methanol in sterically hindered p-phenyl phenols can occur. Note that although the stability of the o-quinone monoketal 51 is probably
due to steric inhibition of Diels-Alder-type dimerization, no corresponding 1,2-adducts from the previously discussed systems were isolable. Nevertheless, in most cases these systems possessed groups in the 2'-position which were less sterically demanding than the phenyl group of 49, and the adducts may have dimerized and/or reacted with desired product rapidly after formation, accounting for the tars

![Chemical Reaction Diagram]

**Figure 26. Preparation and Anodic Oxidation of 49**

and oils that made up the balance of the mass from the reaction after product isolation.

In the absence of hard data on isolated reaction by-products, which this author was unable to obtain, such indirect experimental evidence for competing ortho-oxidation is the best explanation currently available for the low yields and current efficiencies for certain systems in this study.
A Chemical Equivalent of the Anodic Cyclization Process

As was pointed out in the introductory section, there are a variety of chemical means for effecting the oxidation of phenols. Indeed, most anodic oxidations of aromatic substrates can probably be effected by employing an appropriate chemical oxidant. One notable exception to this is the anodic oxidation of 1,4-dimethoxy benzene to its corresponding quinone bisketal. In any case, it seemed useful to briefly explore the oxidation of some of the substrates prepared in this study with a suitable chemical oxidant to determine whether or not the anodic cyclization of 2'-substituted p-aryl phenols was a process unique to the electrochemical cell.

It was assumed from the outset that a prerequisite for this study would be to find a reagent which would mimic the electrochemical oxidation of p-phenyl phenol to the corresponding p-quinol ether (see Figure 1). An initial attempt at oxidation of this substrate using DDQ (dichlorodicyanobenzoquinone) in methanol gave no appreciable amount of 2.

Recent interest in hypervalent iodine compounds as chemical oxidants has led to the development of methodologies for the two-electron oxidation of phenols with both iodobenzene diacetate and the corresponding trifluoroacetate derivative. Since the former reagent is the less expensive of the two, the oxidation of p-phenyl phenol was examined using this reagent.
In contrast to the previous DDQ reaction which failed, oxidation of \( p \)-phenyl phenol 1 with 1.1 equivalents of iodobenzene diacetate in methanol at room temperature afforded the corresponding \( p \)-quinol ether 2 in 71% yield (Figure 27). This may be contrasted with the electrochemical method, which affords 2 in essentially quantitative yield. Nevertheless, the iodobenzene diacetate oxidation was simple to carry out and was complete within 15 minutes.

![Chemical structure](attachment:chemical_structure.png)

**Figure 27.** Iodobenzene Diacetate Oxidation of Phenols 1 and 14.

The above result prompted a brief investigation of iodobenzene diacetate oxidations as a potential chemical equivalent for the anodic cyclization process. Thus, several of the 2'-alkenyl-substituted \( p \)-aryl phenols prepared for the electrochemical studies were treated with iodobenzene diacetate in methanol.

Interestingly, iodobenzene diacetate oxidation of the unsubstituted styrene derivative 14 gave only 42 (Figure 27), with no evidence for the cyclization product 43 which was obtained—albeit
Table 4. Spirodienones via Iodobenzene Diacetate Oxidation

<table>
<thead>
<tr>
<th>p-Aryl Phenol</th>
<th>Spirodienone</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10: R₁, R₃, R₄ = H; R₂ = CH₃</td>
<td>11</td>
<td>52 (65)</td>
</tr>
<tr>
<td>17: R₃, R₄ = H; R₁ = R₂ = -(CH₂)₃⁻</td>
<td>38</td>
<td>50 (69)</td>
</tr>
<tr>
<td>33: R₁ = H; R₂ = CH₃; R₃, R₄ = OCH₃</td>
<td>41</td>
<td>76 (92)</td>
</tr>
<tr>
<td>38: R₁, R₃, R₄ = H; R₂ = OCH₃</td>
<td>45</td>
<td>17 (21)</td>
</tr>
</tbody>
</table>

* Yield in parentheses is for the corresponding anodic oxidation.
in poor yield—from the anodic oxidation of 14 (see Table 3 and Figure 20). Nevertheless, spirodienone products were obtained via iodobenzene diacetate oxidation for a few selected systems in fair to good yield. The results of this brief study are summarized in Table 4. For clarity, the reader may wish to refer back to Figure 19 for the structures of the indicated starting materials and products.

As may be seen in Table 4, for systems which gave good to excellent yields of spirodienones via the anodic cyclization method, the corresponding iodobenzene diacetate oxidation afforded the same product in a somewhat lower, but nevertheless useful yield. That the chemical oxidation offered no advantage over the anodic oxidation is emphasized not only by the absence of cyclized product from oxidation of 14 (Figure 27) but by the last entry in Table 4, wherein oxidation of the vinyl ether substrate 38 afforded the spirodienone 45 in poor yield (17%). Although the anodic oxidation gave a poor yield in this system as well (21%), it is apparent that whatever factors are responsible for low yield oxidative cyclization of certain of these \( \text{p-aryl phenols, the problems are almost certainly not indigenous to} \)

Iodobenzene diacetate oxidation thus serves as a chemical equivalent to the anodic cyclization method developed in this study. The mechanism of the reaction has not been established, but may involve the same two-electron oxidation intermediates which are thought to arise in the anodic oxidation. Although the yields of spirodienone products obtained by this alternate oxidative method
were somewhat lower in the systems studied, these reactions proceeded rapidly under mild conditions and were simple to carry out. This method may be useful to others who might wish to employ such oxidative cyclization chemistry, but who lack the necessary electrochemical apparatus.

**CONCLUSIONS**

The anodic cyclization of 2'-alkenyl-substituted p-aryl phenols as presented here represents not only a new method of electrochemical intramolecular carbon-carbon bond formation but a new approach to spiro-substituted 4-ary1-4-alkyl-cyclohexa-2,5-dienones. Significantly, the carbon-carbon bond formed in these reactions affords a quaternary center, among the more difficult centers to prepare in organic synthesis.

The required p-aryl phenols for this process are accessible by employing various modifications of a simple strategy—reaction of aryl lithium reagents with quinone monoketals, followed by hydrolysis and reduction.

The anodic cyclization reaction was found to proceed most efficiently in a mildly acidic medium, conditions under which a phenoxonium ion intermediate from phenol ring oxidation is most likely to be formed. The cyclization process is thought not to occur via radical processes.

The limitation of the anodic cyclization process may be related to the relative nucleophilicity of the 2'-alkenyl side-chain. In cases
where the alkenyl side-chain may be less nucleophilic, it has been proposed that 1,2-anodic addition of methanol may be the competing process which leads to poor yields of cyclized product.

When methoxyl groups are appropriately positioned on the ε-aryl ring of the oxidation substrates, spirodienone products are obtained in good to excellent yield and competing oxidation of the methoxylated ring does not occur. The importance of the spirodienone moiety and the aromatic systems arising via its biological intermediacy in natural products makes this new electrochemical approach to such oxygenated spirodienones a potentially useful synthetic tool.

Iodobenzene diacetate oxidation of several of the 2'-alkenyl-substituted ε-aryl phenols prepared in this study serves as a chemical equivalent to the anodic cyclization method, affording the same spirodienone products, although in somewhat lower yields. This brief study suggested that some of the limitations observed for the anodic cyclization method are probably not related to the electrochemical mode of oxidation.
EXPERIMENTAL

General Procedures. Melting points were determined in capillaries in a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Infrared spectra (IR, bands reported in cm⁻¹) were determined on a Perkin-Elmer Model 283B spectrometer. Routine ¹H nuclear magnetic resonance spectra (NMR, signals reported in ppm) were determined at 80 MHz on an IBM NR 60 spectrometer using deuterochloroform as solvent and residual chloroform as standard. All ¹³C NMR spectra were determined at 20 MHz on the above instrument. The 500 MHz ¹H NMR spectra were measured by Dr. Charles Cottrell in deuterochloroform on a Bruker model AM-500 spectrometer. Mass spectral and exact mass measurements were obtained by Mr. Richard Weisenberger on a Kratos MS-30 spectrometer connected to a DS-55 data system. Combustion analyses were performed by Scandanavian Microanalytical Laboratory, Herlev, Denmark. High pressure liquid chromatography analyses (HPLC) were conducted using an Altec Model 110-A pump, a 10 cm X 250 cm Lichrosorb SI-60 column and an Altec Model 153 Analytical UV detector at 254 nm. Constant current anodic oxidations employed a Kepco D.C. power supply and a cylindrical, perforated platinum sheet anode, measuring 4.8 cm in height X 2.5 cm in diameter with an estimated total surface area of 60.3 cm². All reagents or compounds not explicitly referenced were obtained from the Aldrich Chemical Co.
Alumina and silica gel were obtained from E. Merck Co. Tetrahydrofuran (THF) was purified by distillation from benzophenone ketyl. Throughout the experimental the following abbreviations are used: petroleum ether, bp 35-60 °C (PE), diethyl ether (Et₂O), acetonitrile (CH₃CN), methanol (CH₃OH), acetone ((CH₃)₂CO), acetic acid (HOAc), ethyl acetate (EtOAc), p-toluene sulfonic acid (p-TsOH), n-butyllithium (n-BuLi), Amperes (A) and thin layer chromatography (TLC).

**Chemical Oxidation of 1 and Preparation of 2**

To a solution of 1 (0.25 g, 1.47 mmol) in CH₃OH (25 mL) were added HOAc (0.4 mL) and iodobenzene diacetate (0.52 g, 1.6 mmol), and the resulting solution was stirred for 15 min and then concentrated in vacuo. The residue was dissolved in Et₂O (50 mL), and then was washed with sat NaHCO₃ (25 mL) and brine (25 mL). After drying through a CaSO₄ cone, the Et₂O/product solution was concentrated in vacuo, and the residue (0.294 g) was chromatographed on silica gel (6" X 1/4" column, 30% Et₂O/PE as eluant) to afford 2 (0.208 g, 71%) as light tan solid: mp 88-90 °C (lit mp 85-87 °C).
Preparation of 6

To a solution of 2-bromobenzoic acid (15 g, 74.7 mmol) in CH₃OH (100 mL) was added conc. HCl (10 mL), and the resulting solution was heated at reflux on a steam bath for 14 h. After cooling, the mixture was concentrated, and the product was extracted into CHCl₃ (2 x 50 mL), washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The residue was distilled at reduced pressure to afford 6 (13.5 g, 84%) as a water white oil: bp 93-95 °C/0.8 mm (lit 52 bp 131-132 °C/16 mm).

Preparation of 7

To a 1.0 M ethereal solution of methyl magnesium iodide (214 mmol) prepared in the usual fashion was added methyl-2-bromobenzoate 6 (20.0 g, 93.0 mmol) in Et₂O (50 mL) dropwise over 30 min, and the resulting mixture was stirred for 16 h at room temperature. After hydrolysis with saturated NH₄Cl solution (75 mL), the layers were separated and the aqueous was back extracted with Et₂O (2 x 50 mL). The combined organics were washed with brine (100 mL), dried through CaSO₄ and concentrated in vacuo. The residue
was distilled at reduced pressure to afford 7 (9.5 grams, 48%) as a water-white oil, bp 95-100 °C/0.4 mm Hg: IR (NaCl Plates) 3600-3300 (br, m), 2990 (m), 1470 (m), 1430 (m), 1370 (m), 1270 (m), 1170 (m), 1120 (m), 950 (m), 755 (m), 725 (m); 1H NMR (80 MHz) 7.7-7.0 (h str m, 4 H), 2.76 (s, 1 H), 1.75 (s, 6 H); mass spectrum, exact mass calcd for C₁₀H₁₁OBr m/e 213.9993, obsd 214.0002.

Preparation of 3

To a solution of 7 (8.2 g, 38 mmol) in CHCl₃ (50 mL) was added thionyl chloride (4.1 mL), and the resulting mixture was heated to reflux for 2 h, then poured into cold water (100 mL). The layers were shaken and separated and the organic layer was washed with brine (2 X 50 mL) and dried through CaSO₄. Concentration afforded a dark brown oil (7.6 g) which was chromatographed on silica gel (6" X 2" column, hexane as eluant) to yield 3 (4.1 g, 55%) as a water-white oil: IR (NaCl plates) 1475 (m), 1440 (m), 1030 (m), 903 (m), 760 (m), 730 (m); 1H NMR (80 MHz): 7.7-7.0 (str m, 4 H), 5.2 (m, 1 H), 4.9 (m, 1 H), 2.1 (m, 3 H); mass spectrum, exact mass calcd for C₉H₉Br m/e 197.9867, obsd 197.9864.

Preparation of 5

To a -78 °C solution of 3 (3.4 g, 17 mmol) in THF (30 mL) was added n-BuLi (11.7 mL of a 1.6 M solution) dropwise over 5 min, and
the resulting solution was stirred for 1 h. Next, a solution of 4,4-
dimethoxy-2,5-cyclohexadienone (2.6 g, 2.4 mL) in THF (5 mL) was added dropwise over 10 min, and the resulting brown solution was stirred for 1 h at -78 °C, then allowed to warm to room temperature. The reaction was then quenched with saturated NH₄Cl (10 mL) and diluted with Et₂O (150 mL). The layers were separated, and the organic phase was washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The crude 1-quinol was then dissolved in THF (30 mL), zinc-copper couple (3.0 g) was added, and the mixture was heated to reflux with stirring while 5% HOAc (30 mL) was added dropwise. After heating and stirring for 30 min, the reaction mixture was cooled and diluted with Et₂O (75 mL). The layers were separated and the organic phase was washed with brine (2 X 50 mL) and dried through CaSO₄. Concentration in vacuo afforded a thick, oily semi-solid (2.9 g) which was recrystallized from EtOAc/hexane to afford the phenanthrene 5 (1.61 g, 42% overall) as tan crystals, mp 115-117 °C: IR (KBr) 1620 (m), 1500 (m), 1241 (s), 1202 (m), 1180 (m), 1036 (m), 895 (m), 741 (m); 'H NMR (80 MHz): 8.7-8.5 (str m, 2 H), 8.1-8.0 (str m, 1 H), 7.7-7.5 (str m, 3 H), 7.3-7.2 (str m, 2 H), 3.9 (s, 3 H), 2.7 (br s, 3 H); mass spectrum, exact mass calcd for C₁₆H₁₄O m/e 222.1044, obsd 222.1044.
Preparation of 8

To a suspension of NaH (60% by wt in mineral oil, 2.7 g, 66 mmol) in THF (50 mL) was added 7 from above (9.5 g, 44 mmol) in THF (30 mL), and the resulting mixture was stirred and heated to reflux for 16 h. Next, methyl iodide (12.5 g, 5.5 mL) was added dropwise and the resulting mixture was heated to reflux for 2 h. After cooling, the reaction was quenched with water (25 mL), Et₂O (100 mL) was added and the layers were separated. The organic layer was washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The residue was distilled at reduced pressure to afford 8 (8.8 g, 87%) as a clear oil, bp 82-85 °C/0.45 mm Hg; IR (NaCl Plates) 3000 (m), 2942 (m), 2880 (m), 1472 (m), 1430 (m), 1387 (m), 1370 (m), 1280 (m), 1250 (m), 1180 (s), 1080 (s), 1025 (s), 760 (s), 730 (m), 650 (m); ¹H NMR (80 MHz) 7.58-7.18 (h str m, 4 H), 3.10 (s, 3 H), 1.67 (s, 6 H); mass spectrum, exact mass calcd for C₁₀H₁₃OBr m/e 228.0149, obsd 228.0134.

Preparation of 9

To a -78 °C solution of 8 from above (8.5 g, 37.0 mmol) in THF (125 mL) was added n-BuLi (25.5 mL of a 1.6 M solution) dropwise over 15 min. The
resulting mixture was stirred at this temperature for 3 h, then a solution of 4,4-dimethoxy-2,5-cyclohexadienone\textsuperscript{53} (5.7 g, 5.15 mL) in THF (15 mL) was added dropwise over 15 min. After stirring for 1 h at -78 °C, the reaction mixture was allowed to warm to room temperature over 16 h and was then quenched with saturated NH\textsubscript{4}Cl solution (50 mL). The layers were separated, the aqueous back-extracted with Et\textsubscript{2}O (2 x 25 mL), and the combined organics were washed with brine (50 mL). After concentration in vacuo, the residue was dissolved in (CH\textsubscript{3})\textsubscript{2}CO (350 mL), 5% HOAc was added (60 mL) and the mixture was stored at 0 °C overnight to effect the hydrolysis of the p-quinol ketal to the p-quinol. The bulk of the solvent was removed in vacuo and the residue was poured into saturated NaHCO\textsubscript{3} solution (50 mL). The crude p-quinol was extracted into CH\textsubscript{2}Cl\textsubscript{2} (3 x 75 mL), washed with brine (50 mL), dried through CaSO\textsubscript{4} and concentrated in vacuo to afford the crude p-quinol (9.5 g, 99%), suitable for use directly in the next step without further purification.

The p-quinol from above was dissolved in THF (50 mL) and added to a suspension of zinc-copper couple (4.5 g) in 5% HOAc (50 mL), and the resulting mixture was heated to reflux for 1 h. After cooling, the mixture was poured into 5% HCl (50 mL), Et\textsubscript{2}O (250 mL) was added and the layers were shaken and then separated. The organic phase was washed with brine (100 mL), dried through CaSO\textsubscript{4} and concentrated in vacuo to afford 9 (8.4 g, 94%) as a light tan solid, mp 134-137 °C, which was deemed suitable for use in the next step without further purification. Recrystallization of a portion from Et\textsubscript{2}O/PE gave the
analytical sample as white needles: mp 143.5-145 °C; IR (KBr) 3280-3190 (br, m), 1520 (m), 1480 (m), 1440 (m), 1265 (m), 1230 (m), 1160 (m), 840 (m), 765 (m); \(^1\)H NMR (80 MHz) 7.6-7.2 (str m, 4 H), 6.9 (AB \(q\), \(\delta v = 28 \text{ Hz, } J_{AB} = 9 \text{ Hz, } 4 \text{ H}\)), 5.19 (s, 1 H), 3.04 (s, 3 H), 1.36 (s, 6 H); mass spectrum, exact mass calcd for \(\text{C}_16\text{H}_14\text{O}\) \(m/e\) 242.1337, obsd 242.1322.

**Preparation of 10**

The \(p\)-arylphenol \(9\) from above (2.3 g, 9.5 mmol) was dissolved in \(\text{CHCl}_3\) (150 mL), \(p\)-TsOH (0.035 g) was added, and the mixture was heated to reflux for 20 min after which time no starting material remained by TLC (75:25 PE/Et\(_2\)O). The reaction mixture was poured into saturated \(\text{NaHCO}_3\) solution (50 mL), the layers were separated, and the organic phase was washed with brine (50 mL), dried through CaSO\(_4\) and concentrated in vacuo to afford a dark brown oil (1.9 g). Chromatography on silica gel (6" X 1/2" column, \(\text{CH}_2\text{Cl}_2\) as eluant) gave \(10\) (1.6 g, 80%) as a clear oil: IR (NaCl Plates) 3600-3150 (br, m), 1600 (m), 1520 (m), 1485 (m), 1250 (br, m), 1180 (m), 840 (m), 760 (m); \(^1\)H NMR (80 MHz) 7.19 (s, 4 H), 6.9 (AB \(q\), \(\delta v = 38 \text{ Hz, } J_{AB} = 9 \text{ Hz, } 4 \text{ H}\)), 4.96 (ABX d of d, further coupled, 2 H), 1.59 (broadened s, 3 H); mass spectrum, exact mass calcd for \(\text{C}_16\text{H}_{14}\text{O}\) \(m/e\) 210.1044, obsd 210.1044.
General Procedure for Anodic Oxidation Studies of Model System 10

A stock solution of 10 (2.0 ml of a 0.12 M solution in methanol) was placed in a calibrated cylindrical glass electrolysis cell equipped with a magnetic stirring bar and diluted with the solvent/electrolyte system of choice to the 50 mL mark. The desired electrodes were immersed in the solution, stirring was initiated, and an ice bath was placed around the cell to maintain the temperature at or near 0 °C throughout the course of the reaction. Additives (if any) were injected, then current was passed at 0.05 A for twice the calculated time required for the two-electron oxidation (28 min) or until no starting material remained by TLC analysis (2:1 Et2O/PE). The crude reaction mixture was then poured into cold water (100 mL), the organics were extracted into CH2Cl2, (3 X 50 mL) and the combined extracts were washed with brine (50 mL), dried through CaSO4 and concentrated in vacuo. The residue was weighed to insure correct mass balance, then dissolved in 20% EtOAc/PE, transferred to a 50 mL volumetric flask and diluted to the mark. To this solution (1.0 mL) was added a stock solution (0.5 mL) of 45 (0.5 mg/mL) as an internal standard. After mixing, the resulting solution was injected on a HPLC apparatus equipped with a UV detector and pen recorder. The yield for each reaction was then calculated via equation 4 after cutting and weighing the recorder tracings of the product and internal standard peaks in the usual fashion.

\[
\text{mg 11} = K \left( \frac{\text{wt of 11 peak}}{\text{wt of 45 peak}} \right) \left( 0.5 \text{ mg 45/mL} \right) \left( 50 \text{ mL} \right)
\]  (4)
In the above expression, \( K \) was previously calculated to be 2.92 from HPLC injections of mixtures of pure 11 and pure 45.

**Anodic Oxidation of 10 and Preparation of 11**

A solution of the \( \text{p-aryl phenol} \) 10 from above (0.535 g, 2.5 mmol) in 4:1 CH\(_3\)CN/CH\(_3\)OH (300 mL) containing HOAc (0.75 mL) and 1% by wt of LiClO\(_4\) as electrolyte was anodically oxidized at 0 °C in a single cell at a constant current of 0.05 A using a perforated cylindrical platinum sheet anode and copper wire cathode for 180 min (91% current efficiency) after which time no starting material remained by TLC (2:1 PE/Et\(_2\)O). The reaction mixture was concentrated in vacuo at room temperature, and the residue was diluted with Et\(_2\)O (75 mL) and poured into sat NaHCO\(_3\) solution (50 mL). The layers were separated, and the organic layer was washed with brine (50 mL), dried through CaSO\(_4\) and concentrated in vacuo to afford a dark orange oil (0.57 g) which was chromatographed on silica gel (6" X 3/4" column, 10% Et\(_2\)O/hexane as eluant) to yield 11 (0.397 g, 65%) as a white solid: mp 109-110 °C. Recrystallization of a portion from Et\(_2\)O/PE gave the analytically pure material: mp 110-111 °C; IR (KBr) 1665 (s), 1625 (m), 1105 (r o), 855 (m); \(^1\)H NMR (80 MHz) 7.65-6.64 (highly str m, 6 H), 6.37-6.0 (str m, 2 H), 3.12 (s, 3 H), 2.38 (AB q, \( J_{ab} = 26 \text{ Hz}, J_{ab} = 4 \text{ Hz}, 2 \text{ H} \)), 1.61 (s, 3 H); \(^1\)C NMR 186.0 (1 C), 153.9 (1 C), 153.2 (1 C), 144.8 (1 C), 143.0 (1 C), 129.4 (1 C), 128.7 (1 C),
128.2 (1 C), 126.2 (1 C), 124.9 (1 C), 124.8 (1 C), 85.0 (1 C), 52.1
(1 C), 50.6 (1 C), 49.1 (1 C), 23.3 (1 C); mass spectrum, exact mass
calcd for C$_{16}$H$_{16}$O$_2$ m/e 240.1150, obsd 240.1178.

Anal. Calcd for C$_{16}$H$_{16}$O$_2$: C, 79.97; H, 6.67. Found: C, 79.59; H,
6.77%.

Chemical Oxidation of 10 and Preparation of 11

To a solution of 10 (0.5 g, 2.4 mmol) in CH$_3$OH (25 mL) were
added HOAc (0.75 mL) and iodobenzene diacetate (0.85 g, 2.6
mmol), and the resulting solution was stirred for 15 min and then
concentrated in vacuo. The residue was dissolved in Et$_2$O (150 mL),
and was then washed with sat NaHCO$_3$ (50 mL) and brine (50 mL). After
drying through a CaSO$_4$ cone, the Et$_2$O/product solution was
concentrated in vacuo, and the residue was chromatographed on silica
gel (6" X 1/4" column, 20% Et$_2$O/PE as eluant) to afford 11 (0.3 g,
52%) as a white solid. The product showed mp 109-111 °C and was
identical in all respects to the material prepared by the anodic
oxidation reaction above.

Anodic Oxidation of 9 and Preparation of 12

A solution of 9 (0.5 g, 2.0 mmol) in a 4:1 mixture of
CH$_3$CN/CH$_3$OH (300 mL) containing HOAc (0.56 mL) and 1% by wt of LiClO$_4$
as electrolyte was anodically oxidized in a single cell at 0 °C,
using a perforated cylindrical platinum sheet anode and a copper wire cathode at a constant current of 0.05 A for 145 min (87% current efficiency) after which time no starting material remained by TLC (1:1 Et₂O/PE). The reaction mixture was then concentrated in vacuo at room temperature, and the residue was dissolved in Et₂O (100 mL) and poured into saturated NaHCO₃ (50 mL). The layers were shaken and separated, and the organic phase was washed with brine (50 mL), dried through a CaSO₄ cone and concentrated in vacuo. The residue was chromatographed on silica gel (6" X 1/2" column, 20% Et₂O/PE as eluant) to afford 12 (0.221 g, 47%) as white crystals: mp 140-142 °C; IR (KBr) 2990 (s), 1670 (vs), 1630 (s), 1605 (m), 1151 (s), 1061 (m), 1030 (s), 1020 (m), 970 (s), 945 (m), 871 (s), 850 (s), 770 (s); ¹H NMR (80 MHz) 7.4-6.8 (str m, 4 H), 6.45 (AB q, ν = 49 Hz, JAB = 10 Hz, 4 H), 1.6 (s, 6 H); ¹³C NMR (20 MHz) 185.2 (1 C), 150.3 (2 C), 147.4 (1 C), 136.7 (1 C), 129.1 (1 C), 128.2 (1 C), 126.6 (2 C), 122.1 (1 C), 121.5 (1 C), 87.5 (1 C), 82.1 (1 C), 30.7 (2 C); mass spectrum, exact mass calcd for C₁₅H₁₄O₂ m/e 226.0994, obsd 226.1002.
Preparation of 14

To a -78 °C solution of 2'-bromostyrene (4.0 g, 21.9 mmol) in THF (60 mL) was added n-BuLi (15 mL of 1.6 M solution) dropwise over 10 min, and the resulting mixture was stirred at this temperature for 3 h. Next, a solution of 4,4-dimethoxy-2,5-cyclohexadienone (3.4 g, 3.0 mL) in THF (15 mL) was added dropwise over 10 min, and the resulting solution was stirred for 1 h at -78 °C and then allowed to warm to room temperature over 16 h. The reaction was then quenched with 5% HOAc (25 mL) and allowed to stir for 30 min to insure complete hydrolysis of the quinol ketal to the quinol. After dilution with Et₂O (150 mL), the layers were separated, and the organic phase was washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The resulting crude p-quinol (4.5 g) was dissolved in THF (26 mL) and added to a suspension of zinc-copper couple (2.6 g) in 5% HOAc (26 mL), and the mixture was stirred and heated to reflux for 1 h. After cooling to room temperature, the reaction mixture was poured into 5% HCl (25 mL), Et₂O (100 mL) was added, the layers were shaken and separated, and the organic phase was washed with brine (2 X 50 mL), dried through CaSO₄ and concentrated in vacuo to afford a thick orange oil (3.9 g). Chromatography on silica gel (8" X 1" column, CH₂Cl₂ as eluant)
afforded 14 (2.27 g, 53% overall) as a clear oil: IR (NaCl plates) 3600-3150 (br, m), 1620 (m), 1520 (m), 1480 (m), 1260 (m), 1230 (br, m), 1180 (m), 910 (m), 838 (m), 760 (m); 1H NMR (80 MHz) 7.8-7.2 (h str m, 6 H), 7.0-6.5 (AB overlapping X component of AMX, 3 H), 5.7 (AMX d of d, JAM = 1.5 Hz, JAX = 17.5 Hz, 1 H), 5.18 (AMX d of d, JM = 1.5 Hz, JMX = 11 Hz, 1 H), 4.7 (br s, 1 H); mass spectrum, exact mass calcd for C14H12O m/e 196.0888, obsd 196.0892.

Anodic Oxidation of 14 and Preparation of 42 and 43

A solution of 14 (0.5 g, 2.55 mmol) in 4:1 CH3CN/CH3OH (300 mL) containing HOAc (0.75 mL) and 1% by weight LiClO4 as electrolyte was anodically oxidized at 0 °C in a single cell with perforated cylindrical platinum sheet anode and copper wire cathode at a constant current of 0.05 A for 290 min (57% current efficiency) until no starting material remained by TLC (1:1 Et2O/hexane). The analysis indicated the reaction was not clean, giving two major products plus numerous UV active spots and material remaining at the origin. The reaction mixture was concentrated in vacuo at room temperature, the residue was diluted with Et2O (100 mL) and poured into saturated NaHCO3 (50 mL). The layers were shaken and separated, and the organic phase was washed with brine (50 mL), dried through CaSO4 and concentrated in vacuo. The residue was chromatographed on silica gel (6" X 1/2" column, 10% Et2O/hexane as
eluant) to afford 42 (0.11 g, 19%) as a clear oil with spectral data identical to material previously prepared and characterized\(^4\). Concentration of subsequent fractions afforded the spiroadienone 43 (0.095 g, 16%) as a light yellow oil: IR (NaCl plates): 1675 (s), 1635 (m), 1095 (m), 860 (m), 760 (m); \(^1\)H NMR (80 MHz) 7.5-6.0 (h str, m, 8 H), 4.8 (ABX d of d, \(J_{AX} = 6\) Hz, \(J_{BX} = 2\) Hz, 1 H), 3.4 (s, 3 H), 2.39 (ABX m, 2 H); mass spectrum, exact mass calcd for C\(_{15}\)H\(_{14}\)O\(_2\) m/e 226.0993, obsd 226.1009.

**Chemical Oxidation of 14 and Preparation of 42**

To a solution of 14 (0.5 g, 2.6 mmol) in CH\(_3\)OH (50 mL) were added HOAc (0.8 mL) and iodosobenzene diacetate (0.92 g, 2.9 mmol), and the resulting solution was stirred for 15 min and then concentrated in vacuo. The residue was dissolved in Et\(_2\)O (150 mL), and then was washed with sat NaHCO\(_3\) (75 mL) and brine (75 mL). After drying through a CaSO\(_4\) cone, the Et\(_2\)O/product solution was concentrated in vacuo, and the residue was chromatographed on silical gel (6" X 1/4" column, 30% Et\(_2\)O/PE as eluant) to afford 42 (0.269 g, 46%) as a light yellow oil identical in all respects to material previously prepared and characterized.\(^4\)
Preparation of 15

To the Grignard reagent of 1,4-dibromobutane\textsuperscript{49} (11.4 g, 5.3 mmol) prepared in the usual fashion in THF (130 mL) was added a solution of methyl-2-bromobenzoate 6 (10.0 g, 46.0 mmol) in THF (40 mL) over 30 min at 0 °C, and the resulting mixture was stirred for an additional 2 h. The reaction was hydrolyzed with saturated NH\textsubscript{4}Cl (75 mL), Et\textsubscript{2}O (100 mL) was added, and the layers were separated. The organic phase was washed with brine (75 mL), dried through CaSO\textsubscript{4} and concentrated in vacuo to afford the crude carbinol (11.0 g) which was used without further purification in the next step. The carbinol was dissolved in THF (30 mL) and added to a suspension of NaH (60% by weight in mineral oil, 3.0 g, 75.0 mmol) in THF (50 mL), and the mixture was heated at reflux for 2 h. Methyl iodide (6.2 mL) was added, and heating was continued for an additional 2 h after which time the reaction mixture was poured into H\textsubscript{2}O (50 mL). Et\textsubscript{2}O was added (100 mL), and the layers were shaken and separated. The aqueous layer was back extracted with Et\textsubscript{2}O (2 x 25 mL), and the combined organics were washed with brine (50 mL), dried through CaSO\textsubscript{4} and concentrated in vacuo. The residue was distilled at reduced pressure to afford 15 (6.7 g, 57%) as a water-white oil: bp 105-110 °C/0.5 mm Hg; IR (NaCl plates) 2970 (br, s), 2882 (m), 2830 (m), 1470 (m), 1437 (m), 1120 (m), 1070 (br, s), 1025 (m), 785 (m); \textsuperscript{1}H NMR (80 MHz) 7.7-7.0
(str m, 4 H), 2.9 (broadened s, 3 H), 2.7-1.6 (highly str m, 8 H); mass spectrum, exact mass calcd for C₁₂H₁₅BrO m/e 254.0306, obsd 254.0289.

Preparation of 16

To a -78 °C solution of 15 (2.5 g, 10.0 mmol) in THF (25 mL) was added n-BuLi (6.4 mL of 1.4 M solution) dropwise, and the resulting milky yellow solution was stirred for 1 h. Next, a solution of 4,4-dimethoxy-2,5-cyclohexadienone (1.4 mL) in THF (5 mL) was added dropwise, and the mixture was stirred at -78 °C for 2 h and then allowed to warm to room temperature over 16 h. The reaction was quenched with saturated NH₄Cl (10 mL) and diluted with Et₂O (75 mL). The layers were separated, and the organic phase was washed with brine (25 mL), dried through CaSO₄, concentrated in vacuo, and then diluted with (CH₃)₂CO (75 mL). Next, 5% HOAc (15 mL) was added and the mixture was stored in a 0 °C refrigerator for 16 h to effect the hydrolysis to the p-quinol. The mixture was poured into saturated NaHCO₃ (50 mL) and concentrated in vacuo. The product was extracted into CH₂Cl₂ (2 X 75 mL), and the combined organics were washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The resulting crude p-quinol was then dissolved in THF (13 mL) and added to a suspension of zinc-copper couple (1.2 g) in 5%
HOAc (13 mL), and the mixture was stirred and heated at reflux for 1 h. After cooling, the reaction mixture was poured into 5% HCl (50 mL) and diluted with Et₂O (100 mL). The layers were separated, and the organic phase was washed with brine (50 mL) and dried through CaSO₄. Concentration in vacuo gave an oil which was chromatographed on silica gel (6" X 1/2" column, 4:1 PE/EtOAc as eluant). There was obtained in this way 16 (0.565 g, 21% overall) as a white solid, mp 139-143 °C, suitable for use in the next step: Repeated crystallization from Et₂O/PE gave the analytical sample: mp 157-158.5 °C; IR (KBr) 3500-3200 (br, m), 1521 (m), 1271 (m), 1228 (m), 1050 (m), 770 (m); ¹H NMR (80 MHz) 7.5-7.3 (str m, 4 H), 7.0 (AB q, J = 8 Hz, with lower field component partially obscured, 4 H), 4.88 (br s, 1 H), 3.0 (s, 3 H), 2.2-1.4 (str m, 8 H); mass spectrum, exact mass calcd for C₁₈H₂₀O₂ m/e 268.1474, obsd 268.1481.

Preparation of 17

The p-aryl phenol 16 (2.33 g, 8.7 mmol) was dissolved in CHCl₃ (150 mL) containing p-TsOH (0.035 g) and the solution was stirred and heated at reflux for 20 min until no starting material remained by TLC (3:1 PE/EtOAc). After cooling, the mixture was poured into saturated NaHCO₃ (50 mL), and the layers were separated.
The organic phase was washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The crude product (1.82 g) was rapidly chromatographed on silica gel (4" X 1/2" column, CH₂Cl₂ as eluant) to afford 1.56 g (76%) of 17 as a waxy white solid, mp 105-108 °C, suitable for use in the next step. Recrystallization of a portion from Et₂O/PE gave the analytically pure material: mp 107.5-109 °C; IR (KBr) 3400-3100 (br, m), 1520 (m), 1455 (m), 1250 (s), 835 (m), 758 (m); ¹H NMR (80 MHz) 7.2 (s, 4 H), 6.95 (AB q, ²ν = 44 Hz, J_ab = 9 Hz, with lower field component partially obscured, 4 H), 5.55 (m, 1 H), 4.66 (s, 1 H), 2.5-1.5 (str m, 6 H); mass spectrum, exact mass calcd for C₁₇H₁₆O m/e 236.1201, obsd 236.1217.

Anodic Oxidation of 17 and Preparation of 39

A solution of 17 (0.5 g, 2.11 mmol) in 4:1 CH₃CN/CH₃OH (300 mL) containing HOAc (0.75 mL) and 1% by weight of LiClO₄ as the electrolyte was anodically oxidized at 0 °C in a single cell with a perforated cylindrical platinum sheet anode and copper wire cathode at a constant current of 0.05 A for 145 min (95% current efficiency) after which time no starting material remained by TLC (2:1 PE/Et₂O). The reaction mixture was concentrated in vacuo at room temperature, diluted with Et₂O (100 mL) and poured into saturated NaHCO₃ (50 mL). The layers were shaken and separated, and the organic phase was washed with brine (50 mL), dried through CaSO₄ and
concentrated in vacuo. The resulting yellow-orange oil (0.552 g) was chromatographed on silica gel (6" X 3/4" column, 2% Et$_2$O/CH$_2$Cl$_2$ as eluant) to afford the spirodienone 39 (0.389 g, 69%) as an off-white solid, mp 111-115 °C. Recrystallization of a portion from Et$_2$O/PE gave the analytically pure material: mp 118-120 °C; IR (KBr) 1672 (s), 1630 (m), 1090 (m), 1080 (m), 775 (m); 'H NMR (500 MHz) 7.42 (d, J = 7 Hz, 1 H), 7.35 (t, J = 7 Hz, 1 H), 7.29 (t, J = 7 Hz, 1 H), 6.93 (d, J = 7 Hz, 1 H), 6.67 (AB q, J$_{ab}$ = 225 Hz, J$_{AB}$ = 10.2 Hz, 2 H), 6.62 (AB q, J$_{ab}$ = 450 Hz, J$_{AB}$ = 9.9 Hz, 2 H), 3.24 (s, 3 H), 2.91 (t, 1 H), 2.29 (h str m, 1 H), 2.11 (h str m, 1 H), 1.89 (h str m, 2 H), 1.67 (h str m, 2 H); mass spectrum, exact mass calcd for C$_{18}$H$_{18}$O$_2$ m/e 266.1307, obsd 266.1312.

Anal. Calcd for C$_{18}$H$_{18}$O$_2$: C, 81.17; H, 6.76. Found: C, 80.98; H, 6.82%.

Chemical Oxidation of 17 and Preparation of 39

To a solution of 17 (0.1 g, 0.42 mmol) in CH$_3$OH (10 mL) were added HOAc (0.13 mL) and iodobenzene diacetate (0.15 g, 0.46 mmol), and the resulting solution was stirred for 15 min and then concentrated in vacuo. The residue was dissolved in Et$_2$O (50 mL), and then was washed with sat NaHCO$_3$ (25 mL) and brine (25 mL). After drying through a CaSO$_4$ cone, the Et$_2$O/product solution was
concentrated in vacuo, and the residual oily solid was triturated with hexane and dried in vacuo to afford 39 (55 mg, 50%) as a white solid. The product showed mp 117-120 °C and was identical in all respects to the material prepared above by anodic oxidation.

**Preparation of 19**

To a solution of phenyl magnesium bromide (16.6 mmol) prepared in the usual fashion in THF (10 mL) was added 2'-bromoacetophenone (3.0 g, 15.1 mmol) in THF (5 mL) dropwise, the resulting mixture was heated at reflux for 2 h, and then cooled to room temperature and quenched with sat NH₄Cl solution (10 mL). After dilution with Et₂O (100 mL), the layers were separated, and the organic phase was washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo to afford the crude carbinol (3.4 g). After dilution with dry THF (10 mL), the carbinol was added to a suspension of NaH (0.91 g of 60% by wt in mineral oil, washed with 2 x 5 mL hexane) in THF (15 mL), and the resulting mixture was stirred at reflux for 2 h. Methyl iodide (1.9 mL) was added and heating was continued for an additional 2 h after which time the mixture was cooled, and the reaction was quenched with water (15 mL). Dilution with Et₂O (75 mL), followed by separation of the layers, washing of the organic phase with brine (50 mL), drying through CaSO₄ and concentration in vacuo afforded a dark oil (2.9 g). Chromatography
on silica gel (6" X 1/2" column, hexane as eluant) afforded 19 (1.08 g, 27% overall) as a water white oil: IR (NaCl Plates): 2980 (m), 2940 (m), 2825 (w), 1465 (m), 1450 (m), 1430 (m), 1130 (m), 1090 (br, m), 1060 (m), 1020 (m), 752 (s), 695 (s); 1H NMR (80 MHz) 7.8-7.0 (str m, 4 H), 7.25 (br s, 5 H), 3.07 (s, 3 H), 1.94 (s, 3 H); mass spectrum, exact mass calcd for C15H15OBr m/e 290.0306, obsd 290.0304.

Preparation of 20

To a -78 °C solution of 19 (1.04 g, 3.57 mmol) in THF (15 mL) was added n-BuLi (2.6 mL of a 1.45 M solution) dropwise over 10 min. After stirring for an additional 2 h, a solution of 4,4-dimethoxy-2,5-cyclohexadienone\(^{53}\) (0.55 g) in THF (5 mL) was added dropwise and the resulting mixture was stirred at -78 °C for 1 h, then allowed to warm to room temperature over 12 h. After quenching the reaction with sat NH\(_4\)Cl solution (10 mL), the mixture was poured into Et\(_2\)O (100 mL), the layers were separated, and the organic phase was washed with brine (2 X 50 mL), dried through CaSO\(_4\) and concentrated in vacuo. The residue was dissolved in a mixture of acetone (30 mL) and 5% HOAc (10 mL) to effect hydrolysis of the quinol ketal. After 10 min, sat NaHCO\(_3\) was added (25 mL), the mixture was poured into Et\(_2\)O (100 mL), the layers were separated and the organic phase was washed with brine (50 mL), dried through CaSO\(_4\) and concentrated in
vacuo. The resulting white foam was dissolved in THF (5 mL), 5% HOAc was added (5 mL) followed by zinc-copper couple (0.5 g), and the mixture was stirred and heated at reflux for 1 h. After cooling, the reaction mixture was poured into cold 5% HCl (25 mL), the product was extracted into Et₂O (75 mL) and the organic phase was washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (6" X 1/2" column, 1:1 Et₂O/hexane as eluant) to afford 20 (0.325 g, 30% overall) solid, mp 152-155 °C. Recrystallization of a portion from Et₂O/hexane gave the analytical sample: mp 155-157 °C; IR (KBr) 3320 (s), 1615 (m), 1518 (m), 1278 (m), 1212 (m), 1079 (m), 1060 (m), 829 (m), 765 (m), 700 (m); ¹H NMR (60 MHz) 7.9-6.8 (str m, 9 H), 6.46 (s, 4 H), 4.52 (s, 1 H), 3.04 (s, 3 H), 1.70 (s, 3 H); mass spectrum, exact mass calcd for C₂₁H₂₀O₂ m/e 304.1463, obsd 304.1463.

Preparation of 21

To a solution of 20 (0.285 g, 0.937 mmol) in CHCl₃ (75 mL) was added p-TsOH, (10 mg) and the resulting mixture was heated at reflux temperature for 1 h, after which time, TLC (1:1 Et₂O/PE) indicated completion of the reaction. The mixture was poured into cold water (50 mL), the layers were separated, and the organic phase was washed with brine (25 mL), dried through CaSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel
(6" X 1/2" column, CH₂Cl₂ as eluant) to afford 21 (0.242 g, 95%) as a clear oil; IR (NaCl Plates) 3500-3300 (br, m), 1612 (m), 1518 (m), 1448 (m), 1121 (m), 830 (m), 760 (m); ¹H NMR (80 MHz) 7.42 (s, 4 H), 7.16 (s, 5 H), 6.9 (AB q, 2v = 41 Hz, Jₐₜₜ = 9 Hz, 4 H), 5.65 (d, J = 1 Hz, 1 H), 5.28 (d, J = 1 Hz, 1 H), 5.09 (s, 1 H); mass spectrum, exact mass calcd for C₂₀H₁₆O m/e 272.1201. obsd 272.1205.

Anodic Oxidation of 21 and Preparation of 44

A solution of 21 (0.2 g, 0.73 mmol) in 4:1 CH₃CN/CH₃OH (100 mL) containing HOAc (0.2 mL) and 1% by weight LiClO₄ as electrolyte was anodically oxidized at 0 °C in a single cell with a perforated cylindrical platinum sheet anode and a copper wire cathode at a constant current of 0.05 A for 90 min (52% current efficiency) until no starting material remained by TLC (1:1 Et₂O/hexane). The crude reaction mixture was poured into sat NaHCO₃ solution (25 mL), the product was extracted into Et₂O (3 X 25 mL), and the combined organics were washed with brine (2 X 25 mL), dried through CaSO₄ and concentrated in vacuo. The dark orange residue (0.272 g) was chromatographed on silica gel (6" X 1/4" column, 5% EtOAc/hexane as eluant) to afford a yellow oil (0.078 g) which was dissolved in a minimum of Et₂O/hexane and allowed to crystallize at 0 °C. Vacuum
filtration and air drying afforded the spirodienone 44 (0.048 g, 22%) as white crystals: mp 147-149 °C; IR (KBr) 1672 (s), 1092 (m), 860 (m), 768 (m), 701 (m); ¹H NMR (80 MHz) 7.5-7.2 (m, 9 H), 7.2-6.1 (highly str m, 4 H), 3.13 (s, 3 H), 2.61 (AB q, J = 18 Hz, J_AB = 14 Hz, 2 H); mass spectrum, exact mass calcd for C₂₁H₁₆O₂ m/e 302.1307, obsd 302.1314.

Preparation of 22

To a solution of 3,4-dimethoxybenzaldehyde (20 g, 120 mmol) in HOAc (100 mL) was added bromine (7.0 mL) all at once and the resulting mixture was allowed to stir at room temperature for 1 h, after which time the mixture became very thick. After stirring for 16 h, a 10% NaHSO₃ solution (10 mL) was added followed by dilution of the reaction mixture with water (100 mL). The suspended solid was collected by vacuum filtration to afford a fluffy white solid which was dried in a vacuum desiccator for 12 h. There was obtained in this way 6-bromo veratraldehyde 22 (20 g, 68%), mp 143-145 °C (lit mp 147 °C) which was used without further purification in subsequent steps.

Preparation of 23

To a 0 °C solution of trimethylsilylmethyl magnesium chloride (44.0 mmol) in THF (50 mL), prepared in the usual fashion was added a solution of 6-bromo veratraldehyde 22 (9.7 g, 39.6 mmol) in THF
(50 mL), and the resulting mixture was stirred for 30 min, then heated to reflux for 2 h. After cooling, the reaction mixture was poured into sat NH₄Cl (100 mL) and diluted with Et₂O (150 mL). The layers were shaken and separated, and the organic phase was washed with brine (2 x 50 mL), dried through CaSO₄ and concentrated in vacuo. The crude carbinol was then dissolved in THF (100 mL), NaH was added (1.84 g of 60% by wt in mineral oil, washed 2 x 5 mL of hexane), and the mixture was heated to reflux for 1 h. After cooling, the mixture was poured into cold water (100 mL), Et₂O (100 mL) was added, and the layers were shaken and separated. The organic phase was washed with brine (50 mL) and dried through CaSO₄. After the addition of hydroquinone (0.3 g) as a polymerization inhibitor, the product was concentrated in vacuo to afford the crude styrene 23 (6.5 g, 66%) as a yellow oil which was used without purification in the next step since the product underwent rapid polymerization during most purification attempts. A small portion was rapidly chromatographed on silica gel (6" X 1/4" column, hexane as eluant) to afford the analytically pure material as a waxy, white solid: mp 39-41 °C; IR (KBr) 1601 (m), 1505 (s), 1468 (m), 1420 (m), 1385 (m), 1260 (s), 1211 (s), 1163 (m), 1030 (m); 'H NMR (80 MHz) 7.2-6.8 (m, X component of ABX, partially obscured, 1 H), 7.04 (s, 1 H), 7.0 (s, 1 H), 5.58 (d, A component of ABX, further coupled, JABX = 17 Hz, 1 H),
5.25 (d, B component of ABX, further coupled, $J_{Bx} = 11$ Hz, 1 H), 3.90 (s, 3 H), 3.87 (s, 3 H); mass spectrum, exact mass calcd for C$_{10}$H$_{11}$O$_2$Br m/z 241.9942, obsd 241.9940.

**Preparation of 25**

To a -78 °C solution of 23 (2.35 g, 9.7 mmol) in THF (30 mL) was added n-BuLi (7.0 mL of a 1.45 M solution) dropwise. After stirring for 2 h, a solution of 4-methoxy-4-trimethylsiloxy-2,5-cyclohexadienone$^{49}$ (2.5 g) in THF (10 mL) was added dropwise, and the resulting mixture was stirred for 1 h at -78 °C and then allowed to warm to room temperature over 1 h. After quenching the reaction with sat NH$_4$Cl (50 mL) and diluting the mixture with Et$_2$O (150 mL), the layers were separated, and the organic phase was washed with brine (2 X 50 mL), dried through CaSO$_4$ and concentrated in vacuo. The residue was dissolved in THF (150 mL) and treated with (n-Bu)$_4$NF (4.0 g) at 0 °C. After 30 min, the reaction mixture was poured into cold brine (150 mL), Et$_2$O (200 mL) was added, and the layers were shaken and separated. The organic phase was washed once more with brine (50 mL), dried through CaSO$_4$ and concentrated in vacuo at room temperature. The residue was chromatographed on silica gel (6" X 1/2" column, 1:1 EtOAc/hexane as eluant) to afford 25 (0.66 g, 25% overall) as a white solid, mp 154-158 °C. Recrystallization of a portion from Et$_2$O/hexane
gave the analytical sample: mp 157-159 °C; IR (KBr) 3422 (m), 1660 (s), 1620 (m), 1505 (m), 1261 (m), 1212 (m), 1105 (m), 1036 (m), 860 (m); $^1$H NMR (80 MHz) 7.23 (s, 1 H), 6.58 (AB q, $\Delta v = 58$ Hz, $J_{ab} = 10$ Hz, 4 H), 7.25-6.90 (m, X component of ABX, partially obscured, 1 H), 6.92 (s, 1 H), 5.4 (d of d, A component of ABX, $J_{ax} = 17$ Hz, 1 H), 5.15 (d of d, B component of ABX, $J_{bx} = 11$ Hz, 1 H), 3.88 (d, 6 H), 2.34 (s, 1 H); mass spectrum, exact mass calcd for C$_{16}$H$_{16}$O$_4$ m/e 272.1049, obsd 272.1058.

Preparation of 26

To a solution of 25 (0.5 g, 1.8 mmol) in THF (5 mL) was added zinc-copper couple (0.25 g), and the resulting slurry was heated to reflux with vigorous stirring. Next, 5% HOAc (5 ml) was added dropwise over 5 min, and the mixture was heated and stirred for an additional 10 min. After cooling, the mixture was poured into 5% HCl (25 mL), Et$_2$O was added (25 mL), and the layers were separated. The organic phase was washed with brine (25 mL), dried through CaSO$_4$ and concentrated in vacuo to afford 26 (0.39 g, 83%) as a white solid, mp 127-131 °C. Recrystallization of a portion from Et$_2$O/hexane gave the analytically pure material: mp 130-132 °C; IR (KBr) 3460 (m), 1610 (m), 1502 (s), 1270 (m), 1260 (m), 1235 (m), 1210 (m), 1198 (m), 1190 (m), 1135 (m); $^1$H NMR (80 MHz) 7.10 (s, 1 H), 7.0 (AB q, $\Delta v = 27$ Hz, $J_{ab} = 8$ Hz, 4 H), 6.8-6.48 (m, X component of ABX, partially
obscured, 1 H), 6.73 (s, 1 H), 5.53 (d of d, A component of ABX, \( \text{J}_{AX} = 17 \text{ Hz, 1 H} \)), 5.06 (d of d, B component of ABX, \( \text{J}_{BX} = 11 \text{ Hz, 1 H} \)), 3.93 (s, 3 H), 3.86 (s, 3 H); mass spectrum, exact mass calcd for \( \text{C}_{16}\text{H}_{16}\text{O}_{3} \text{ m/e 256.1100, obsd 256.1091}. \)

Anodic Oxidation 26 and Preparation of 40

A solution of 26 (0.25 g, 0.975 mmol) in 4:1 CH\(_3\)CN/CH\(_3\)OH (150 mL) containing HOAc (0.28 mL) and 1% by weight LiClO\(_4\) as the electrolyte was anodically oxidized at 0 °C in a single cell with a perforated cylindrical platinum sheet anode and copper wire cathode at a constant current of 0.05 A for 80 min (79% current efficiency) until no starting material remained by TLC (2:1 Et\(_2\)O/hexane). The crude reaction mixture was poured into sat NaHCO\(_3\) solution (50 mL), the product was extracted into Et\(_2\)O (3 X 50 mL), and the combined organics were washed with brine (2 X 25 mL), dried through CaSO\(_4\) and concentrated in vacuo. The dark orange residue was chromatographed on silica gel (6" X 1/4" column, 1:1 EtOAc/hexane as eluant) to afford 40 (0.195 g, 70%) as a light yellow oil which slowly crystallized to give waxy crystals: mp 85-87 °C; IR (KBr) 1660 (s), 1640 (m), 1501 (m), 1461 (m), 1295 (m), 1180 (m), 860 (m); 1H NMR (80 MHz) 7.1-6.1 (highly str m, 4 H), 6.95 (s, 1 H), 6.38 (s, 1 H), 4.8 (ABX d of d, \( \text{J}_{AX} = 9 \text{ Hz, J}_{BX} = 2 \text{ Hz, 1 H} \)), 3.87 (s, 3 H).
3.76 (s, 3 H), 3.44 (s, 3 H), 2.4 (ABX m, 2 H); mass spectrum, exact mass calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4$, m/e 286.1206, obsd 286.1221.

Preparation of 27

The 6-bromo veratraldehyde 22 (10 g, 41 mmol) from above was dissolved in (CH$_3$)$_2$CO (500 mL) and added to a 1:1 mixture of (CH$_3$)$_2$CO/H$_2$O (1000 mL) containing KMnO$_4$ (9.7 g, 61 mmol). The resulting mixture was stirred for 14 h at room temperature and then filtered to remove the MnO$_2$. The filtrate was concentrated in vacuo and acidified with a 5% HCl solution (75 mL). The resulting voluminous precipitate (crude carboxylic acid) was collected by vacuum filtration and was directly dissolved in CH$_3$OH (150 mL). After the addition of conc HCl (15 mL), the solution was heated at reflux for 12 h, then concentrated in vacuo. The residue was poured into H$_2$O (50 mL), and the product was extracted into into CH$_2$Cl$_2$ (3 x 50 mL), washed with brine (50 mL), dried through CaSO$_4$ and concentrated in vacuo. The resulting solid was recrystallized from Et$_2$O/hexane to afford in two crops, methyl-6-bromo-3,4-dimethoxybenzoate 27 (6.4 g, 57%) as a white solid: mp 80-82 °C; IR (KBr) 1742 (m), 1720 (m), 1510 (m), 1432 (m), 1348 (m), 1265 (s), 1210 (s), 1171 (m); 1H NMR (80 MHz) 7.42 (s, 1 H), 7.10 (s, 1 H), 3.92 (br s, 9 H); mass spectrum, exact mass calcd for $\text{C}_{10}\text{H}_{11}\text{O}_4\text{Br}$, m/e 275.9820, obsd 275.9837.
Preparation of 28

To a 1.0 M ethereal solution of methyl magnesium iodide (32.13 mmol) prepared in the usual fashion was added a solution of the above methyl ester 27 (4.2 g, 15.3 mmol) in THF (25 mL) dropwise at 0 °C, and the resulting thick mixture was stirred for 1 h, then warmed to reflux for an additional 2 h. After quenching the reaction with sat NH₄Cl solution (25 mL), the mixture was diluted with Et₂O (150 mL), the aqueous phase was discarded, and the organic phase was washed with brine (2 X 50 mL), dried through CaSO₄ and concentrated in vacuo. The resulting crude carbinol was then dissolved in THF (15 mL) and added to a suspension of NaH (0.92 g of 60% by wt in mineral oil, washed with 2 X 5 mL hexane) in THF (25 mL) and heated at reflux for 2 h. Next, methyl iodide (1.9 mL) was added, and the mixture was heated for an additional 2 h. After cooling to room temperature, the reaction was quenched with H₂O, and the mixture was diluted with Et₂O (100 mL). The aqueous phase was discarded, and the organic layer was washed with brine (2 X 50 mL), dried through CaSO₄ and concentrated in vacuo. The resulting brown solid was recrystallized from Et₂O/hexane to afford in 2 crops, 28 (2.61 g, 59% overall) as a white solid, mp 101-104 °C. The analytical sample was obtained by recrystallization from Et₂O/hexane and showed: mp 103-105 °C; IR
(KBr) 1520 (m), 1505 (m), 1445 (m), 1365 (m), 1260 (s), 1200 (s), 1170 (s), 1070 (m), 1030 (m), 850 (m), 788 (m); 1H NMR (80 MHz) 7.08 (s, 1 H), 7.0 (s, 1 H), 3.87 (s, 6 H), 3.13 (s, 3 H), 1.66 (s, 6 H); mass spectrum, exact mass calcd for C_{12}H_{17}O_{3}Br m/e 290.0341, calcd 290.0341.

Preparation of 29

To a -78 °C solution of 28 (1.5 g, 5.2 mmol) in THF (25 mL) was added n-BuLi (3.8 mL of 1.45 M solution) dropwise over 10 min, and the resulting mixture was stirred for 2 h at this temperature. Next, a solution of 4,4-dimethoxy-2,5-cyclohexadienone\textsuperscript{53} (0.721 mL) in THF (10 mL) was added dropwise, and the mixture was stirred at -78 °C for 1 h, then allowed to warm to room temperature over 12 h. After quenching the reaction with sat NH\textsubscript{4}Cl (5 mL), the mixture was diluted with Et\textsubscript{2}O (75 mL), the layers were separated, and the organic phase was washed with brine (2 x 50 mL), dried through CaSO\textsubscript{4} and concentrated in vacuo. The residue was dissolved in (CH\textsubscript{3})\textsubscript{2}CO (100 mL), 5% HOAc (30 mL) was added, and the mixture was allowed to stand at room temperature and was monitored by TLC (1:1 Et\textsubscript{2}O/PE) until hydrolysis of the quinol ketal was complete (5 min). Sat NaHCO\textsubscript{3} (50 mL) was added, the mixture was concentrated in vacuo, and the product was extracted into CHCl\textsubscript{3} (3 x 25 mL). The combined organics were washed with brine (25 mL), dried through CaSO\textsubscript{4} and
concentrated in vacuo. The residue was dissolved in THF (10 mL) and was added to a suspension of zinc-copper couple (0.75 g) in 5% HOAc (8 mL). The resulting mixture was then stirred and heated to reflux for 1 h. After cooling, the mixture was poured into 5% HCl (25 mL) and diluted with Et₂O (100 mL). The organic phase was washed once with brine (50 mL), dried through CaSO₄ and concentrated in vacuo to afford 29 (1.45 g, 92%) as an off-white solid, mp 145-150 °C, suitable for use in the next step. Recrystallization of a portion from Et₂O/hexane gave white crystals: mp 153.5-155 °C; IR (KBr) 3211 (m), 1502 (m), 1362 (m), 1222 (m), 1195 (m), 1168 (m), 1052 (m), 1030 (m); 1H NMR (80 MHz) 7.15 (s, 1 H), 6.96 (AB q, J_AB = 26 Hz, J_ab = 9 Hz, 4 H), 6.56 (s, 1 H), 5.0 (s, 1 H), 3.93 (s, 3 H), 3.82 (s, 3 H), 3.06 (s, 3 H), 1.3 (s, 6 H); mass spectrum, exact mass calcd for C₁₆H₂₀O₄ m/e 302.1518, obsd 302.1491.

Preparation of 30

A solution of 29 (0.400 g, 1.3 mmol) in CHCl₃ (25 mL) was heated to reflux for 10 min and then poured into brine (25 mL). The layers were shaken and separated, and the aqueous layer was extracted with additional CHCl₃ (25 mL). The combined organic layers were dried through CaSO₄ and concentrated in vacuo to afford 30 (0.343 g, 96%) as a light tan solid, mp 226-228 °C. Recrystallization
from Et₂O/PE gave the analytical sample: mp 229.5-231 °C; IR (KBr) 3420 (s), 1479 (s), 1440 (m), 1330 (m), 1310 (m), 1261 (m), 1251 (m), 1200 (m), 1168 (m), 1025 (m); 1H NMR (80 MHz) 7.5-6.7 (str m, 5 H), 4.0 (s, disappears with D₂O wash, 1 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 1.41 (s, 6 H); mass spectrum, exact mass calcd for C₁₇H₁₈O₃ m/e 270.1256, obsd 270.1254.

Preparation of 31

A solution of 29 (1.25 g, 4.1 mmol) in acetic anhydride (50 mL) was heated at reflux for 1 h. The excess acetic anhydride was then removed in vacuo, and the residue was crystallized from Et₂O/hexane to afford in two crops, 31 (0.944 g, 64%) as a white solid, mp 130-134 °C. Repeated recrystallization from Et₂O/hexane gave the analytical sample: mp 137-139 °C; IR (KBr) 1755 (s), 1502 (s), 1336 (m), 1258 (m), 1242 (s), 1219 (s), 1200 (s), 1171 (s), 1080 (m), 1030 (m); 1H NMR (80 MHz) 7.14 (AB q, δv = 18 Hz, Jₐ₉ = 9 Hz, 4 H), 7.13 (s, 1 H), 6.56 (s, 1 H), 3.91 (s, 3 H), 3.80 (s, 3 H), 3.02 (s, 3 H), 2.31 (s, 3 H), 1.27 (s, 6 H); mass spectrum, exact mass calcd for C₂₀H₂₄O₅ 344.1624, obsd 344.1595.

Preparation of 32

To a solution of 31 (0.675 g, 1.96 mmol) in CHCl₃ (335 mL) was added p-TsOH (35 mg), and the resulting mixture was heated at reflux for 15 min after which time TLC (2:1 Et₂O/PE) indicated completion.
After cooling, the mixture was poured into H$_2$O (100 mL), the layers were shaken and separated, and the organic phase was washed once with brine (50 mL), dried through CaSO$_4$ and concentrated in vacuo to afford 32 (0.567 g, 93%) as a white solid, mp 95-99 °C, suitable for use in the next step. Recrystallization of a portion from Et$_2$O/hexane gave white crystals: mp 101-103 °C; IR (KBr) 1770 (m), 1601 (m), 1520 (s), 1462 (m), 1370 (s), 1340 (m), 1200 (br, s), 1130 (m), 750 (m); 1H NMR (60 MHz) 7.22 (AB q, $\nu_v$ = 27 Hz, $\nu_{AB}$ = 9 Hz, 4 H), 6.79 (s, 2 H), 5.0 (str m, 2 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 2.30 (s, 3 H), 1.66 (br s, 3 H); mass spectrum, exact mass calcd for C$_{19}$H$_{20}$O$_4$ m/e 312.1361, obsd 312.1361.

Preparation of 33

A solution of 32 (0.56 g, 1.8 mmol) in CH$_3$OH (50 mL) containing 1% by weight KOH was stirred at room temperature for 15 min after which time TLC (2:1 Et$_2$O/PE) indicated completion of the reaction. The bulk of the CH$_3$OH was removed in vacuo, and the residue was diluted with 5% HOAc (50 mL). The product was extracted into Et$_2$O (3 X 25 mL), and the combined organics were washed with sat
NaHCO₃ (25 mL), brine (25 mL), then dried through CaSO₄ and concentrated in vacuo. The resulting brown oil was dissolved in a minimum of Et₂O/hexane and allowed to crystallize. The product was collected by vacuum filtration and air dried to afford 33 (0.396 g, 81%) as a white, crystalline solid, mp 109-111 °C. Recrystallization of a portion from Et₂O/hexane gave the analytically pure material as white needles: mp 110-111 °C; IR (KBr) 3428 (m), 1505 (s), 1445 (m), 1350 (m), 1265 (m), 1250 (br, m), 1211 (m), 1201 (m), 1175 (m); ¹H NMR (60 MHz): 7.05 (AB q, Jᵥ = 37 Hz, Jᵥab = 9 Hz, with both components partially obscured, 4 H), 6.78 (d, J = 1 Hz, 2 H), 5.0 (str m, 2 H), 4.65 (s, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 1.66 (br s, 3 H); mass spectrum, exact mass calcd for C₁₇H₁₈O₃ m/z 270.1256, obsd 270.1234.

**Anodic Oxidation of 33 and Preparation of 41**

A solution of 33 (0.25 g, 0.92 mmol) in 4:1 CH₃CN/CH₃OH (150 mL) containing HOAc (0.28 mL) and 1% by weight LiClO₄ as the electrolyte was anodically oxidized at 0 °C in a single cell with perforated cylindrical platinum sheet anode and copper wire cathode at a constant current of 0.05 A for 60 min (92% current efficiency) until no starting material remained by TLC (2:1 Et₂O/hexane). The crude reaction mixture was poured into sat NaHCO₃ solution (50 mL), the product was extracted into Et₂O (3 X 50 mL),
and the combined organics were washed with brine (2 X 25 mL), dried through CaSO₄, concentrated in vacuo and dried at 0.5 mm Hg for 12 h. There was obtained in this way 41 (0.255 g, 92%) as a light yellow powder, mp 143-146 °C. Recrystallization of a portion from Et₂O/PE gave the analytical sample: mp 145.5-147 °C; IR (KBr) 1660 (s), 1501 (s), 1460 (m), 1445 (m), 1290 (m), 1280 (m), 1219 (m), 1065 (m), 850 (m); ¹H NMR (80 MHz) 7.15-6.13 (highly str m, 4 H), 6.83 (s, 1 H), 6.37 (s, 1 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.18 (s, 3 H), 2.42 (AB q, J_AB = 26 Hz, 2 H), 1.64 (s, 3 H); mass spectrum, exact mass calcd for C₁₈H₂₀O₄ m/e 300.1361, obsd 300.1344.

Anal. Calcd for C₁₈H₂₀O₄: C, 71.98; H, 6.66. Found: C, 71.89; H, 6.76%.

Chemical Oxidation of 33 and Preparation of 41 and 41a

To a solution of 33 (0.10 g, 0.37 mmol) in CH₃OH (10 mL) were added HOAc (0.10 mL) and iodo-benzene diacetate (0.131 g, 1.6 mmol), and the resulting solution was stirred for 15 min and then concentrated in vacuo. The residue was dissolved in Et₂O (75 mL), and then was washed with sat NaHCO₃ (25 mL) and brine (25 mL). After drying through a CaSO₄ cone, the Et₂O/product solution was concentrated in vacuo, and the residue (0.115 g) was chromatographed on silical gel (6" X 1/4" column, 30% Et₂O/PE as eluant) to afford 41
(0.73 g, 67%) as a white solid, together with a small amount of the olefinic product 41a (10 mg) which resulted from elimination of methanol from 41 during the column chromatography purification.

Product 41 showed mp 143-145 °C and was identical in all respects to the material prepared above by the anodic oxidation. The corrected yield for the reaction was 76%, taking into account the amount of 41a which was isolated. Product 41a showed the following properties: mp 139-142 °C; IR (KBr) 1661 (s), 1491 (m), 1334 (m), 1210 (m), 850 (m); 1H NMR (80 MHz) 6.9 (s, 1 H), 6.7 (s, 1 H), 5.9 (s, 4 H), 5.6 (d, 1 H), 3.9 (s, 3 H), 3.8 (s, 3 H), 2.2 (d, 3 H); mass spectrum, exact mass calcd for C_{17}H_{16}O_{3} 268.1100, obsd 268.1094.

Preparation of 34

To a solution of 2'-bromoacetophenone (5.0 g, 25.1 mmol) in CH_{3}OH (25 mL) was added trimethylorthoformate (5 mL) and p-TsOH (50 mg), and the resulting solution was stirred for 6 h. After neutralizing with 1% KOH/CH_{3}OH (10 mL), the solvent was removed in vacuo, and the product was dissolved in CHCl_{3} (100 mL) and washed with brine (50 mL), dried through CaSO_{4} and concentrated in vacuo. Distillation of the residue at reduced pressure afforded 34 (6.0 g, 97%) as a water white oil:
bp 93-95 °C/0.4 mm; IR (NaCl plates) 2990 (m), 2940 (br, m), 2830 (m), 1460 (m), 1428 (m), 1371 (m), 1280 (m), 1245 (m), 1189 (m), 1140 (m), 1095 (m), 1050 (m), 1035 (m), 1020 (m), 875 (m), 755 (m); 1H NMR (80 MHz) 7.9-7.0 (str m, 4 H), 3.2 (s, 6 H), 1.6 (s, 3 H); mass spectrum, exact mass calcd for C_{10}H_{13}O_2Br m/e 246.0078, obsd 246.0080.

**Preparation of 35**

To a -78 °C solution of 34 (2.5 g, 10.2 mmol) in THF (25 mL) was added n-BuLi (7.0 mL of a 1.6 M solution) dropwise over 10 min, and the resulting solution was stirred for 2 h at this temperature. To the milky suspension was added a solution of 4,4-dimethoxy-2,5-cyclohexadienone\(^5\) (1.6 g) in THF (5.0 mL) dropwise over 10 min, and the resulting solution was stirred at -78 °C for 1 h, then allowed to warm to room temperature. After quenching the reaction with sat NH\(_4\)Cl (5.0 mL), Et\(_2\)O (100 mL) was added, the layers were separated and the organic layer was washed with brine (2 X 50 mL) and dried through a CaSO\(_4\) cone. After concentration in vacuo, the crude \(\alpha\)-quinol ketal was dissolved in (CH\(_3\))\(_2\)CO (75 mL), 8% H\(_2\)OAc (15 mL) was added, and the solution was stored in a 0 °C refrigerator for 16 h. After concentration in vacuo, the product was extracted into CH\(_2\)Cl\(_2\) (2 X 75 mL), the combined organics were washed with brine (100 mL) and dried through a CaSO\(_4\) cone. Concentration in vacuo afforded 35...
(1.9 g, 78%) as a white solid, mp 145-151 °C, which was deemed suitable for use in the next step without further purification. Recrystallization of a portion from Et₂O gave the analytically pure material: mp 161-162 °C; IR (KBr) 3000 (w), 2935 (w), 1672 (vs), 1630 (m), 1170 (m), 1065 (m), 1025 (m), 870 (m), 841 (m), 770 (m); 1H NMR (80 MHz) 7.5-6.2 (h str m, 8 H), 3.25 (s, 3 H), 1.83 (s, 3 H); mass spectrum, exact mass calcd for C₁₆H₁₄O₃ m/z 242.0942, obsd 242.0942.

**Preparation of 36**

To a solution of 35 (0.5 g, 2.0 mmol) in THF (2.5 mL) were added zinc-copper couple (0.24 g) and 8% HOAc (2.5 mL), and the resulting mixture was heated at reflux for 30 min, then cooled to room temperature. Cold 5% HCl (25 mL) was added, the product was extracted into Et₂O (2 x 25 mL), and the combined organic layers were washed once with brine (15 mL) and dried through CaSO₄. Concentration in vacuo afforded a light yellow oil which crystallized upon standing. There was obtained in this way 36 (0.41 g, 96%), mp 115-118 °C. Recrystallization of a portion from Et₂O/PE gave the analytically pure material: mp 118-119.5 °C; IR (KBr) 3380 (m), 3260 (m), 1685 (s), 1621 (m), 1250 (m), 830 (m); 1H NMR (80 MHz) 7.6-7.3 (str m, 4 H), 7.0 (AB q, J = 25 Hz, Jₐₜ₉ = 9 Hz, 4 H), 5.15 (s, 1 H), 2.0 (s, 3 H); mass spectrum, exact mass calcd for C₁₄H₁₂O₂ m/z
212.0837, obsd 212.0819.

**Preparation of 37**

To a solution of 36 (6.66 g, 31.4 mmol) in CH₃OH (100 mL) were added trimethylorthoformate (20 mL) and p-TsOH (5 mg), and the resulting mixture was stirred for 16 h, during which time the solution became dark red. Saturated NaHCO₃ (10 mL) was added, whereupon the solution lightened in color. After concentration in vacuo, the product was dissolved in Et₂O (100 mL), the layers were separated, and the organic phase was washed with brine (50 mL) and dried through CaSO₄ to afford, after concentration and drying in vacuo, 37 (6.9 g, 85%) as a greenish-brown solid, mp 138-141 °C, which was deemed suitable for use in the next step. Recrystallization of a portion from Et₂O/PE gave a white powder: mp 149-150.5 °C; IR (KBr) 3300 (br, s), 2940 (m), 2830 (w), 1615 (m), 1515 (m), 1365 (m), 1150 (m), 1080 (m), 1025 (m), 830 (m), 755 (m); ¹H NMR (80 MHz) 7.8-7.2 (str m, 4 H), 6.9 (AB q, with lower field component partially obsc, δv = 26 Hz, JAB = 9 Hz, 4 H), 4.72 (s, 1 H), 3.1 (s, 6 H), 1.39 (s, 3 H); mass spectrum, exact mass calcd for C₁₆H₁₈O₃ m/e 258.1256, obsd 258.1266.
Preparation of 38

A solution of succinic anhydride (0.525 g) and benzoic acid (0.024 g) in pyridine (3.9 mL) was stirred and heated to 120 °C for 15 min, after which time a solution of 37 (0.8 g, 3.1 mmol) in pyridine (1.0 mL) was added dropwise over 5 min, and the resulting solution was stirred at 120 °C for 1 h. The mixture was then cooled and poured into sat NaHCO₃ (50 mL), the product was extracted into Et₂O (2 x 75 mL), and the combined organic layers were washed with brine (50 mL). After drying through CaSO₄ and concentration in vacuo, there was obtained a brown oil which was chromatographed on neutral alumina (4" X 1/2" column, 1:1 Et₂O/PE as eluant) to afford 38 (0.448 g, 64%) as a water-white oil: IR (NaCl Plates) 3600-3200 (br, m), 1620 (s), 1525 (s), 1320 (m), 1270 (s), 840 (m), 765 (m), 740 (s); ¹H NMR (80 MHz) 7.5-7.3 (str, 4 H), 7.0 (AB q, partially obs, J₆₇ = 7 Hz, 4 H), 4.2 (t, 2 H), 3.4 (s, 3 H); mass spectrum, exact mass calcd for C₁₅H₁₄O₂ m/e 226.0994, obsd 226.0985.

Anodic Oxidation of 38 and Preparation of 45

A solution of 38 (0.5 g, 2.2 mmol) in a 4:1 mixture of CH₃CN/CH₃OH (300 mL) containing HOAc (0.75 mL) and 1% by wt of LiClO₄ as the electrolyte was anodically oxidized in a single cell at 0 °C, using a perforated cylindrical platinum sheet anode and a copper wire
cathode at a constant current of 0.05 A for 203 min (71% current efficiency), after which time no starting material remained by TLC (1:1 Et$_2$O/PE). The reaction mixture was then concentrated in vacuo at room temperature, and the residue was dissolved in Et$_2$O (100 mL) and poured into saturated NaHCO$_3$ (50 mL). The layers were shaken and separated, and the organic phase was washed with brine (50 mL), dried through a CaSO$_4$ cone and concentrated in vacuo. The crude residue (0.526 g) was chromatographed on silica gel (6" X 1/2" column, 10% Et$_2$O/PE as eluant) to afford spiroadienone 45 (0.130 g, 23%) as white crystals, mp 133-135 °C. The stability of 45 under the conditions of the purification was established by repeating the column chromatography on the pure material from above (0.130 g) and isolating as usual to afford the spiroadienone (0.128 g) which showed spectral data identical to the material isolated previously. Similarly, 45 (0.05 g) was subjected to the conditions of the electrolysis for 30 min, after which time work up as above afforded the unchanged spiroadienone (0.048 g): IR (KBr) 1670 (s), 1630 (m), 1140 (m), 1092 (m), 870 (m), 778 (m); $^1$H NMR (80 MHz) 7.3-6.9 (str m, 3 H), 6.5 (AB q, $\delta v = 53$ Hz, $\delta$AB = 10 Hz with lower field component overlapped, 5 H), 3.2 (s, 6 H), 2.4 (s, 2 H); mass spectrum, exact mass calcd for C$_{16}$H$_{16}$O$_3$ m/z 256.1100, obsd 256.1040.
Chemical Oxidation of 38 and Preparation of 45

To a solution of 38 (0.50 g, 2.2 mmol) in CH$_3$OH (50 mL) were added HOAc (0.8 mL) and iodo-benzene diacetate (0.78 g, 1.76 mmol), and the resulting solution was stirred for 15 min and then concentrated in vacuo. The residue was dissolved in Et$_2$O (50 mL), and then was washed with sat NaHCO$_3$ (25 mL) and brine (25 mL). After drying through a CaSO$_4$ cone, the Et$_2$O/product solution was concentrated in vacuo, and the residue (0.512 g) was chromatographed on silica gel (6" X 1/4" column, 25% Et$_2$O/PE as eluant) to afford material which was slightly impure as judged by a low mp (120-124 °C.) Trituration with hexane, followed by drying in vacuo afforded 25 (0.097 g, 17%) as white solid. The product showed mp 129-132 °C and was identical in all respects to the material prepared by the anodic oxidation described above.

Preparation of 46

The spirodienone 45 (0.12 g, 0.57 mmol) was dissolved in Et$_2$O (15 mL), 5% HCl was added (10 mL), and the mixture was vigorously stirred for 15 min, after which time no starting material remained by TLC (2:1 Et$_2$O/PE). The layers were separated, and the organic
phase was washed with brine (2 x 5 mL), dried through CaSO₄ and concentrated in vacuo. The residue was triturated with cold 1:1 Et₂O/PE and then dried in vacuo to afford 46 (0.074 g, 75%) as an off-white solid, mp 181-185 °C (dec). Attempts to purify this material by chromatography on silica gel or neutral alumina resulted in rapid decomposition of 46 to a blue oil of unknown composition. Recrystallization from Et₂O gave a white solid which darkened at 187 °C and melted at 188-190 °C, leaving a dark purple liquid: IR (KBr) 1710 (vs), 1667 (vs), 1628 (m), 1598 (m), 1405 (m), 1232 (m), 858 (m), 765 (m); ¹H NMR (80 MHz) 8.0-7.2 (h str m, 4 H), 6.6 (AB q, δν = 34 Hz, ΔνAB = 10 Hz, 4 H), 2.9 (s, 2 H); ¹³C NMR (20 MHz) 201.9 (1 C), 185.0 (1 C), 153.5 (1 C), 151.0 (2 C), 135.7 (1 C), 129.5 (1 C), 128.4 (2 C), 47.5 (1 C), 46.7 (1 C); mass spectrum, exact mass calcd for C₁₄H₁₀O₂ m/e 210.0681, obsd 210.0681.

Preparation of 47

A solution of succinic anhydride (0.715 g) and benzoic acid (0.013 g) in a mixture of pyridine (2.0 mL) and diglyme (2.0 mL) was stirred and heated to 110 °C for 15 min, after which time 35 (1.0 g, 4.1 mmol) was added all at once. The resulting clear solution was heated and stirred for 2 h but TLC analysis (2:1 PE/Et₂O) indicated some 35 remaining. Additional succinic anhydride (0.05 g) was added, and the mixture was
heated and stirred for an additional 30 min, and was then allowed to cool to room temperature. The crude reaction mixture was then poured into sat NaHCO₃ (50 mL), and the product was extracted into Et₂O (75 mL). The organic layer was washed with brine (3 x 50 mL), dried through CaSO₄ and concentrated in vacuo to give a brown oil which was chromatographed on silica gel (6" X 1" column, 10% Et₂O/PE as eluant) to afford the vinyl ether 47 (0.431 g, 50%) as a fluffy white solid: mp 89-91 °C; IR (KBr) 1671 (vs), 1630 (s), 1466 (m), 962 (m), 761 (m); ¹H NMR (60 MHz) 7.6-7.0 (str m, 4 H), 6.5 (AB q, ß = 40 Hz, JAB = 10 Hz, 4 H), 4.65 (pseudo triplet, ß = 3 Hz, 2 H); mass spectrum, exact mass calcd for C₁₄H₁₀O₂, m/e 210.0681. obsd 210.0693.

Preparation of 49

To a -78 °C solution of 2-bromobiphenyl (2.0 g, 8.6 mmol) in THF (30 mL) was added n-BuLi (5.9 mL of a 1.6 M solution) dropwise over 10 min, and the resulting mixture was stirred for 2 h. Next, a solution of 4,4-dimethoxy-2,5-cyclohexadienone (1.32 g, 1.2 mL) in THF (5 mL) was added dropwise, and the resulting mixture was stirred at -78 °C for 1 h and then allowed to warm to room temperature over 16 h. After quenching with sat NH₄Cl (5 mL) and dilution with Et₂O (100 mL), the layers were shaken and separated, and the organic phase was washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The light brown residue was
dissolved in a mixture of \((\text{CH}_3)_2\text{CO} \ (75 \text{ mL})\) and 5% HOAc (20 mL), and the resulting solution was stored in a 0 °C refrigerator for 48 h. The mixture was then poured into sat NaHCO₃ (50 mL) and the bulk of the \((\text{CH}_3)_2\text{CO}\) was removed via rotary evaporator. The product was extracted from the aqueous phase with Et₂O (2 X 50 mL), and the combined organics were washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo to afford the crude \(p\)-quinol as a yellow solid (2.03 g), mp 185-189 °C. The quinol was then dissolved in THF (9 mL), zinc-copper couple was added (0.885 g), followed by 5% HOAc (9 mL), and the resulting mixture was heated to reflux with vigorous stirring for 1 h. After cooling, the reaction mixture was diluted with Et₂O (75 mL) and poured into 5% HCl (50 mL). The layers were shaken and separated, and the organic phase was washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo to afford 49 (1.78 g, 86% overall) as a solid, mp 105-110 °C, which was homogeneous by TLC and clean by NMR but yellow in color. Slow recrystallization from Et₂O/PE gave white crystals: mp 127-128.5 °C; IR (KBr) 3400-3100 (br, m), 1521 (m), 1445 (m), 1350 (s), 835 (m), 765 (m), 750 (m), 700 (m); \(^1\text{H} \text{NMR (80 MHz)} \ 7.38 \ (s, \ 5 \ H), \ 7.18 \ (br \ s, \ 4 \ H), \ 6.8 \ (AB \ q, \ \delta v = 21 \ Hz, \ J_{AB} = 2 \ Hz, \ 4 \ H), \ 4.6 \ (s, \ 1 \ H); \ mass \ spectrum, \ exact \ mass \ calcd \ for \ C_{18}H_{14}O \ m/e \ 246.1045, \ obsd \ 246.1039.

Anodic Oxidation of 49 and Preparation of 50 and 51

A solution of the above \(p\)-aryl phenol 49 (0.25 g, 1 mmol) in 4:1 CH₃CN/CH₃OH (75 mL) containing 1% by wt of LiClO₄ as electrolyte
was anodically oxidized at 0 °C in a single cell using a perforated cylindrical platinum sheet anode and copper wire cathode at a constant current of 0.1 A for 65 minutes (50% current efficiency) until no starting material remained by TLC (CHCl₃ as eluant, 3 elutions). The yellow solution was concentrated via rotary evaporator, and the residue was diluted with Et₂O (100 mL), then washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The resulting yellow residue (0.283 g) was analyzed by both TLC (as above) and ¹H NMR, both of which indicated a clean mixture of two products in a ratio of approximately 1:1 as determined by integration of the methoxyl region of the NMR. A small amount of each component was isolated from the difficultly separable mixture as follows; slow recrystallization from 4:1 PE/Et₂O afforded 50 (13 mg) as a white crystalline solid, mp 128-130 °C, with the following spectral properties: IR (KBr) 1670 (s), 1630 (m), 1060 (m), 760 (m), 700 (m); ¹H NMR (80 MHz): 8.0-7.9 (m, 1 H), 7.5-7.1 (str m, 8 H), 6.2 (AB q, v AB = 47 Hz, JAB = 10 Hz, 4 H), 3.15 (s, 3 H); mass spectrum, exact mass calcd for C₁₉H₁₄O₂ m/z 276.1150, obsd 276.1170.

Chromatography of the mother liquors from the above crystallization on silica gel (6" X 1/2" column, CHCl₃ as eluant) afforded a single fraction containing pure 51 (5 mg) as a yellow oil with the following spectral properties: IR (NaCl plates) 1680 (m),
1100 (m), 1675 (m), 1035 (m), 750 (m), 745 (m), 700 (m); \textsuperscript{1}H NMR (80 MHz) 7.42 (s, 4 H), 7.35 (s, 5 H), 6.35 (s, 1 H), 6.25 (AB q, $\omega v = 54$ Hz, $J_{AB} = 10$ Hz, with lower field component partially obscured, 2 H), 3.33 (s, 6 H); mass spectrum, exact mass calcd for C$_{20}$H$_{18}$O$_3$ m/e 306.1256, obsd 306.1250.
APPENDIX B:

NMR SPECTRA
80 MHz $^1$H NMR Spectrum of 7.
80 MHz $^1$H NMR Spectrum of 3.
80 MHz 1H NMR Spectrum of 5.
80 MHz $^1$H NMR Spectrum of 8.
80 MHz 1H NMR Spectrum of 9.
80 MHz 1H NMR Spectrum of 10.
80 MHz $^1$H NMR Spectrum of 11.
80 MHz 1H NMR Spectrum of 12.
80 MHz $^1$H NMR Spectrum of 14.
80 MHz 1H NMR Spectrum of 42.
80 MHz $^1$H NMR Spectrum of 43.
80 MHz $^1$H NMR Spectrum of 15.
80 MHz $^1$H NMR Spectrum of 16.
80 MHz $^1$H NMR Spectrum of 17.
80 MHz $^1$H NMR Spectrum of 39.
80 MHz $^1$H NMR Spectrum of 19.
80 MHz $^1$H NMR Spectrum of 20.
80 MHz $^1$H NMR Spectrum of 21.
80 MHz 1H NMR Spectrum of 44.
80 MHz 1H NMR Spectrum of 23.
$80 \text{ MHz } ^1\text{H NMR Spectrum of 25.}$
80 MHz $^1$H NMR Spectrum of 26.
80 MHz $^1$H NMR Spectrum of 40.
80 MHz $^1H$ NMR Spectrum of 27.
80 MHz $^1$H NMR Spectrum of 28.
80 MHz 1H NMR Spectrum of 29.
80 MHz $^1$H NMR Spectrum of 30.
80 MHz $^1H$ NMR Spectrum of 31.
80 MHz $^1$H NMR Spectrum of 32.
80 MHz 1H NMR Spectrum of 33.
80 MHz $^1$H NMR Spectrum of 41.
$\text{Br(OC\textsubscript{3})}_2$

$\text{CH}_3$

$\text{34}$

80 MHz $^1\text{H}$ NMR Spectrum of 34.
80 MHz $^1$H NMR Spectrum of 35.
80 MHz $^1$H NMR Spectrum of 36.
80 MHz $^1$H NMR Spectrum of 37.
80 MHz $^1$H NMR Spectrum of 38.
80 MHz 1H NMR Spectrum of 45.
80 MHz 1H NMR Spectrum of 46.
80 MHz $^1$H NMR Spectrum of 47.
80 MHz 1H NMR Spectrum of 49.
80 MHz 1H NMR Spectrum of 50.
80 MHz $^1$H NMR Spectrum of 51.
REFERENCES


(44) see ref 26a.


(46) DeSchepper, R.E., Ph.D. Dissertation, The Ohio State University, Columbus, Ohio, 1986.


(48) See ref 1a, p 142 and references cited therein.


(54) Kahovec, L.; Wagner, J., Monatsh. 74, 1943, 279.


PART III

SPIRODIENONES VIA A THERMAL [1,3]-OXYGEN TO CARBON MIGRATION
INTRODUCTION

Thermally induced alkyl shifts from oxygen to carbon are best represented by the classical Claisen rearrangement of allyl ethers, a reaction which has been studied mechanistically and exploited synthetically to a remarkable extent (Scheme I).

\[ \text{I-1} \xrightarrow{\Delta} \text{I-2} \]

\[ \text{I-3} \xrightarrow{\Delta} \text{I-4} + \text{I-5} \]

Scheme I. Claisen Rearrangements in Alkyl and Aryl Systems.

A related, but less well known process is the thermal [1,3]-oxygen to carbon migration observed in the thermolysis of vinyl ethers. Again, it was Claisen in 1896 who first reported the formation of 2-substituted acetophenones via thermal rearrangement of 1-alkoxystyrene derivatives (Scheme II). The ease of rearrangement qualitatively followed the order \( n\text{-propyl} > \text{ethyl} > \text{methyl} \).
Although representing a novel method for the formation of carbon-carbon bonds, this thermal [1,3]-alkyl shift has received relatively little attention from organic chemists over the years. In 1921, Wislecenus and Schrotter\textsuperscript{3} reported the rearrangement of the methoxymethylene phenyl acetic acid ester III-1 to the 1-methyl-1-formyl derivative III-2. (Scheme III). Similarly, Staudinger and Rudzicka\textsuperscript{4} described the thermal rearrangement of cyclopentenone III-3 to the cyclopentandione III-4, although no yield was given.
Mechanistic Studies of Thermal [1,3]-Oxygen to Carbon Migrations

The mechanistic aspects of this rather obscure rearrangement were initially examined by Lauer and Spielman. To begin, they confirmed the earlier work of Claisen, obtaining alkylated acetophenones in reasonable yield via thermolysis of the corresponding 1-alkoxystyrenes (Scheme IV).

\[
\text{OR} \quad \text{CH}_2 \quad \frac{300^\circ C}{1 \text{ h}} \quad \text{KO} \\
\text{IV-1} \quad R=\text{CH}_3, 65\% \\
\text{IV-2} \quad R=n-\text{Bu}, 74\%
\]

Scheme IV. Lauer and Spielman's Thermolysis of Alkoxy styrenes.

To address the question of whether the reaction proceeded via intra- or intermolecular pathways, these investigators conducted a simple crossover experiment (Scheme V) and found that all four of the possible alkylated acetophenones were obtained. Thus, the reaction was apparently intermolecular in nature.

Lauer and Spielman questioned the existence of discrete free radical intermediates in this process, since obvious radical combination products were usually not observed, and disproportionation of the migrating alkyl group was a relatively
minor side reaction. Based on their observations, these authors proposed two possible mechanisms for the rearrangement (Scheme VI), both of which reflected the intermolecularity of the process.

Scheme VI. Lauer and Spielman's Mechanistic Analyses.
In spite of the above rationales, the authors were unable to account mechanistically for an interesting side-reaction that was observed for certain systems in their study. Thus, as illustrated in Scheme VII, a small quantity of the diaryl diketone XVI-3 and methane were formed during the thermolysis of 1-methoxy styrene. The isolation of gaseous methane accounted for the pressure observed during opening of the sealed tube from the experiment.

Scheme VII. Side Reaction in the Thermolysis of 1-Methoxystyrene

Further studies on the mechanistic aspects of the rearrangement of 1-alkoxy- and 1-benzyloxy styrenes were reported in a series of papers by Wiberg and co-workers. The intermolecularity of the process was confirmed both by kinetic methods and by a crossover experiment using a mixture of unlabeled and 13C-labeled vinyl ethers. Concerted pathways were ruled out by the thermolysis of the chiral vinyl ether VIII-1 (Scheme VIII), affording VIII-2 which was found to be > 95% racemic (substrates such as VIII-1 were found not to racemize easily under the reaction conditions). Since inversion of configuration
would be expected for a thermal, concerted four electron process, the reaction is apparently a [1,3]-shift only in the formal sense.

Scheme VIII. Wiberg's Thermal Rearrangement of 1-(2-Butoxy)-Styrene.

In an attempt to rule out intermediates resulting from heterolytic cleavage of the C-O bond during this thermal reaction (Scheme IX), Wiberg heated 1-neopentoxy styrene IX-1 for four hours to obtain IX-2, with no evidence for the skeletal rearrangement of the migrating neopentyl group which might be expected for a carbonium ion intermediate.

Scheme IX. Rearrangement of 1-Neopentoxy styrene.
Since the foregoing evidence suggested that radical intermediates were likely in this process, Wiberg examined the possibility that the reaction could be catalyzed by free radical initiators. Thus, heating of 1-benzyloxystyrene X-1 at 70-80 °C in the presence of azobisisobutyronitrile (AIBN) afforded 2-benzylacetophenone X-2 (Scheme X). In the absence of initiator, a temperature of 180 °C was required for the reaction to take place.

![Scheme X. AIBN-catalyzed Rearrangement of 1-Benzylxystyrene.](image)

Wiberg then proposed that the mechanism of such rearrangements proceeded via a free radical initiated chain process (Scheme XI). He further pointed out that such an analysis conveniently accounted for the side-reaction observed previously by Lauer and Spielman (Scheme VII).

Nevertheless, Wiberg noted that the reaction was not inhibited by the addition of hydroquinone, chloranil, diphenylamine or trinitrobenzene—typical free radical inhibitors. Although he suggested that this observation might have been due to the alkoxy styrenes effectively competing with inhibitors in the capture
Scheme XI. Wiberg's Free Radical Mechanism.
of free radical intermediates, he conceded that there might well have been a purely thermal process of undetermined mechanism operating under such conditions.

Synthetic Applications

As was mentioned earlier, such thermal [1,3]-oxygen to carbon migrations have received relatively scant attention from organic chemists in general and from synthetic chemists in particular. This is probably due in part to the modest-to-poor yields reported for many of these reactions and the rather harsh conditions required to effect the transformation.

In addition, the reaction appears to lack generality, since certain substrates which would be expected to react, such as ethyl-3-ethoxy-2-butenoate, 3-methoxy-4-methyl-3-penten-2-one and phenyl vinyl ether fail to undergo the rearrangement. Nevertheless, it should be noted that these very early studies were not conducted under conditions of free radical initiation and might bear re-examination in light of Wiberg’s later mechanistic work.

More recently, Trost and co-workers employed a palladium-catalyzed intramolecular variant of these [1,3]-shifts in the preparation of intermediates for prostaglandin and steroid synthesis (Scheme XII). Even with Pd(0) catalysis, relatively high temperatures (120-150 °C) were often required. It is worth noting that these authors were apparently unaware of the early literature in this area, further emphasizing the relative obscurity of these processes.
Scheme XII. Trost's Pd(0)-Catalyzed [1,3]-Oxygen to Carbon Shifts.
Other Thermal [1,3]-Migrations

A brief reference should be made to some related processes involving aromatic and heterocyclic substrates. As with the systems described previously, these examples involve alkyl migration from a heteroatom (oxygen or nitrogen)9a-c (Scheme XIII). The many examples of [1,3]-shifts from carbon to carbon lie beyond the scope of the present discussion, and interested readers are referred to any one of the more recent advanced texts on mechanism in organic chemistry.

Scheme XIII. Selected Thermal [1,3]-Shifts in Aryls and Heterocycles.
RESEARCH OBJECTIVES

The goal of this research was to explore the preparation and thermal rearrangement of exocyclic vinyl ethers derived from \( \text{p-aryl quinols} \). Should the required vinyl ethers prove to be accessible, their thermal rearrangement via a [1,3]-oxygen to carbon migration would result in formation of a quaternary carbon-carbon bond, leading to spiroannulated cyclohexa-2,5-dienones (spirodienones), an important class of compounds discussed in detail in the introductory section of PART II of this dissertation. If successful, further efforts would be directed toward a study of the effect of substituents on the vinyl ether moiety with respect to the relative ease of the thermal rearrangement. The findings of this investigation are presented in the RESULTS AND DISCUSSION section that follows.
RESULTS AND DISCUSSION

Much of the synthetic utility of quinone monoketals 1 is derived from classical organic transformations of the conjugated carbonyl group.\textsuperscript{10} In particular, the addition of organometallics in a 1,2-fashion followed by ketal hydrolysis serves as a useful method for the preparation of \(\text{p-quinol derivatives 2 (Figure 1).}

\[
\begin{align*}
\text{R-Li} & \quad + \quad \begin{array}{c} \text{O} \\
\text{(OR)}_2 \end{array} \quad \text{1} & \quad \rightarrow & \quad \begin{array}{c} \text{O} \\
\text{(OR)}_2 \end{array} \quad \text{2} & \quad \text{H}_3\text{O}^+ \\
\text{HO} & \quad \text{R} & \quad \text{HO} & \quad \text{R}
\end{align*}
\]

Figure 1. Quinone Monoketal Route to \(\text{p-Quinols.}

Methodology for converting the tertiary carbon-oxygen bond in \(\text{p-quinols 2 to a carbon-carbon bond would greatly extend their value as synthetic intermediates, due in part to the considerable number of naturally occurring molecules which contain—or are derived from intermediates containing—a 4,4-substituted cyclohexadienone ring.}\textsuperscript{11} However, the susceptibility of \(\text{p-quinol derivatives to reduction or}

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rearrangement processes\textsuperscript{1,2} and the general difficulty of forming carbon-carbon bonds at such quaternary centers place severe constraints on the development of such a C-O to C-C bond transformation.

The Thermal $[1,3]$-Alkyl Shift Strategy

It was pointed out in the introduction that thermal rearrangement of vinyl ethers represents a novel, if rather obscure method for converting a carbon-oxygen bond to a carbon-carbon bond. The strategy for effecting quaternary carbon-carbon bond formation in $p$-quinols via such a thermal $[1,3]$-oxygen to carbon migration would involve preparation of $p$-quinol-derived exocyclic vinyl ethers $3$. Thermolysis of such substrates could then afford spirodienones $4$ via the envisioned intramolecular rearrangement (Figure 2).

![Figure 2. The Thermal $[1,3]$-Shift Strategy Toward Spirodienones.](image)

In most of the recorded examples of this kind of rearrangement, the reaction is forced to proceed via an intermolecular mechanism, since the migrating alkyl group dissociates from the parent molecule. The result is modest-to-poor yields, due in part to secondary
bimolecular radical processes. Such difficulties should be circumvented if the reaction is conducted on substrates such as 3, which would force the reaction to proceed in an intramolecular fashion. Further, cleavage of the C-O bond in 3 would lead to resonance stabilized intermediates (Figure 3) and thus, the formal [1,3]-shift might occur at moderate temperatures and in good yield.

![Figure 3. Resonance Stabilization in Thermolysis of 3.](image)

**Preparation and Thermolysis of the Parent System**

The preparation of the first vinyl ether substrate for this study is outlined in Figure 6. Thus, metal-halogen exchange on the dimethyl ketal of o-bromoacetophenone 5, followed by reaction of the resulting aryllithium reagent with quinone monoketal 6a and hydrolysis afforded the mixed quinol ketal 7 in good overall yield. Treatment of 7 with succinic anhydride and benzoic acid in pyridine/diglyme according to the method of Newman, followed by chromatography afforded 8 in reasonable yield.
When a degassed solution of 8 in benzene was heated to 170 °C for 18 hours in a sealed tube, the anticipated rearrangement occurred, affording the spirodienone 9 in quantitative yield. This unusual diketone product (Figure 7) was identical in all respects to material previously prepared by the anodic cyclization method described in PART II of this dissertation.

The thermal rearrangement of 8 proved to be a far more direct and efficient approach to 9, since the electrochemical cyclization of 10 (followed by ketal hydrolysis) afforded 9 in only 16% overall yield. Clearly, if this thermal rearrangement strategy could be extended to substituted systems, it would offer a complementary approach to other keto-substituted spirodienones—potentially useful intermediates which would probably be less accessible by the anodic method.
Preparation and Thermolysis of Some Substituted Systems

It was of considerable interest to prepare substrates related to 8 with alkyl or aryl substitution at the terminus of the vinyl ether moiety. Although the question of the true mechanism of this intramolecular [1,3]-shift remains open, it seemed reasonable that substitution at this position might perturb the transition state energy for the rearrangement sufficiently to lower the temperature requirement, via stabilization of the alpha-keto radical moiety.

Thus, o-bromopropiophenone dimethyl ketal 12 was employed in a manner analogous to that used for the preparation of 7. Interestingly, in contrast to the formation of the mixed quinol ketal 7 (Figure 4), hydrolysis of the intermediate ketal from this sequence afforded the uncyclized quinol 13 (Figure 8). After several attempts,
the mixed quinol ketal 14 was finally obtained by treatment of 13 with pyridinium p-toluenesulfonate in methylene chloride.

\[
\begin{align*}
\text{Br} & \quad (OCH_3)_2 \\
\text{12} & \quad \xrightarrow{1) \ n-BuLi} \quad \text{13 (43%)} \\
& \quad \xrightarrow{2) O=OCH_3} \quad \text{6a} \\
& \quad \xrightarrow{3) H_3O^+} \quad \text{14 (45%)} \\
\end{align*}
\]

Figure 8. Preparation of Mixed Quinol Ketal 14.

As before, the mixed ketal 14 was subjected to the Newman conditions for vinyl ether formation. Workup and chromatography afforded the desired vinyl ether 15 along with a small amount of a more polar component which was subsequently identified as the rearrangement product, spirodienone 16 (Figure 9). It was assumed, though not immediately verified, that heating a sample of 14 for an extended period of time under the same conditions would result in complete conversion to 16.

It should be noted that the structure assignment for vinyl ether 15 is tentative. Although a mixture of isomeric vinyl ethers is
possible, steric considerations should favor the indicated assignment. The NMR spectrum (Figure 10) showed a trace of what was presumably the minor isomer, as evidenced by a small doublet methyl resonance at slightly lower field from the doublet for the major isomer. Thus, it is not clear what effect, if any, the sterochemistry of the vinyl ether might have on the subsequent rearrangement.

\[
\begin{align*}
14 & \\
\text{Diglyme, PhCO}_2\text{H} & \\
\Delta & \\
15 \text{ (38%)} & + \\
16 \text{ (7%)} &
\end{align*}
\]

Figure 9. Conversion of 14 to Vinyl Ether 15 and Spirodienone 16.

The formation of the rearrangement product 16 under conditions for vinyl ether formation suggested that alkyl substitution of the vinyl ether moiety facilitated the rearrangement process, presumably through stabilization of the alpha-keto radical moiety. Since the overall yield for formation of 15 in the sequence employed was modest at best, it seemed prudent to attempt the in situ formation of 15 and thence, spirodienone 16 directly from the p-quinol 13.

Indeed, heating of 13 under the Newman conditions for 8.5 hours at 160 °C afforded the spirodienone 16 directly, in 52% isolated yield (Figure 11). The intermediacy of the mixed quinol ketal 14 and vinyl ether 15 in this process was presumed but not rigorously
Figure 10. 80 MHz 1H NMR Spectrum of 15.
established, although periodic monitoring of the reaction by TLC analysis indicated that this was almost certainly the case.

The product showed the expected IR carbonyl stretches at 1721 cm\(^{-1}\) and 1662 cm\(^{-1}\), and the proton NMR (Figure 12) showed a doublet methyl group signal and a quartet for the hydrogen alpha to the benzylic carbonyl group. The vinyl hydrogens of the spirodienone ring showed a complex splitting pattern, due to the lack of a plane of symmetry in the molecule. A simple AB pattern is observed for these hydrogens in the symmetrical precursor 15 (see Figure 10). In addition, \(^{13}\)C NMR, mass spectrum and combustion analysis data were in good agreement with the assigned structure. Thus, a spirodienone of relatively complex substitution could be obtained in reasonable yield in a single step from a readily available \(p\)-quinol precursor.

![Diagram](image)

**Figure 11. Direct Formation of Spirodienone 16 from \(p\)-Quinol 13.**

To further explore the effect of substitution of the vinyl ether unit on the ease of this rearrangement, the preparation of a phenyl-substituted vinyl ether derivative was explored. Although this and other derivatives would be accessible in principle by preparing the appropriate \(o\)-bromo aryl ketones, a more convergent approach was envisioned, starting with commercially available \(o\)-bromoacetophenone.
Figure 12. 80 MHz $^1$H NMR Spectrum of 16.
The preparation of the phenyl derivative 21 is outlined in Figure 13. Thus, the lithium reagent derived from 5 was reacted with quinone monoketal 6b to afford the quinol ketal derivative 17. As in the preparation of 16, the quinol was subjected to the conditions for vinyl ether formation to afford 18 directly in good yield. There was no evidence for rearrangement of 18 under these conditions. Selective bromination of the vinyl ether moiety was achieved by treatment of 18 with N-bromosuccinimide, affording the vinyl bromide 19. The phenyl group was then introduced by treatment of 19 with phenyl magnesium bromide in the presence of a catalytic amount of dichloro[1,3-bis-(diphenylphosphino) propanenickel(II)]. Regiospecific hydrolysis of the ethylene glycol ketal of 20 afforded the desired vinyl ether derivative 21 as a bright yellow solid.

Examination of the NMR spectrum of 19 (Figure 14) suggested that the vinyl bromide was probably a single geometrical isomer. The structure assignment is nevertheless tentative, being based on steric considerations. The nickel-catalyzed coupling reaction of Grignards with vinyl bromides employed to prepare 20 is known to be stereospecific, providing the basis for subsequent structure assignments.

The introduction of substituents by organometallic couplings with vinyl bromide 19 should provide a simple and convergent approach to such derivatives. However, it should be noted that reaction of 19 with lithium dimethyl cuprate failed. This may be due to the presence of the oxygen of the vinyl ether linkage in bromide 19.
Figure 13. Preparation of Vinyl Ether 21.
Figure 14. 80 MHz $^1$H NMR Spectrum of 19.
Such an electron-rich vinyl bromide may serve to suppress certain electron transfer-mediated processes.

As expected, thermal rearrangement of 21 could be effected at a relatively reduced temperature. Thus, heating of a degassed toluene solution of 21 at reflux for four hours afforded the diketone 22 in good yield (Figure 15).

![Figure 15. Thermal Rearrangement of 21 and Preparation of 22.](image)

As was shown in Figure 3, one of the critical factors in this thermal rearrangement was presumed to be stabilization of the radical intermediates resulting from cleavage of the vinyl ether C=O bond. Thus, it was of interest to determine whether the rearrangement would proceed even with the quinol carbonyl group blocked as the corresponding ethylene glycol ketal. Although elimination of the phenoxy radical as a potential reaction intermediate in this way could hinder the rearrangement energetically, the product from such a rearrangement would have the respective carbonyl groups differentiated chemically, thereby enhancing the overall synthetic potential of the process.
In a manner analogous to the preparation of vinyl ether 18, the ethylene glycol ketal-protected vinyl ether 24 was prepared as outlined in Figure 16. Again, the vinyl ether was obtained in good yield directly from the corresponding p-quinol 23. As before, the reaction gave what appeared to be a single geometrical isomer, and the tentative structure assignment for 24 was based mainly on steric considerations.

![Chemical Structure](image)

Figure 16. Preparation of Vinyl Ether 24.

Though modest in yield, the thermal rearrangement of 24 in refluxing o-dichlorobenzene afforded the protected spirodienone 25 (Figure 17). This result was gratifying in light of the fact that thermolysis of the unsubstituted analogue 18 in o-dichlorobenzene at 180-190 °C in a sealed tube yielded a black polymer on the walls of
the tube. Thus, the alkyl substitution of vinyl ether 24 proved to be crucial in terms of the relative ease of the rearrangement. All spectral and exact mass data for 25 were in good agreement with the assigned structure.

![Figure 17. Thermal Rearrangement of 24 and Preparation of 25.](image)

The differentiation of the carbonyl groups in 25 would be synthetically useful only if the ethylene glycol ketal moiety could be subsequently removed without incurring a dienone-phenol-type rearrangement. Treatment of 25 with 5% acetic acid in acetone afforded in essentially quantitative yield the corresponding spirodienone 16 (Figure 18) which had been previously prepared and characterized (see Figure 11). This also offered further evidence for the structural assignment of 25.

![Figure 18. Hydrolysis of the Ketal Moiety of 25.](image)
CONCLUSIONS

The thermal rearrangement of p-quinol-derived exocyclic vinyl ethers serves as a new and convenient method for the preparation of certain spirodienones—an important class of compounds—from readily available starting materials, often in excellent yield. This nicely complements the preparation of similar spirodienones via the method of anodic cyclization of 2'-alkenyl-substituted p-aryl phenols, the development of which was described in PART II of this dissertation.

This route to spirodienones represents one of the few examples of synthetic utilization of the thermal [1,3]-oxygen to carbon migration reaction of vinyl ethers, an obscure but potentially useful reaction for the formation of carbon-carbon bonds, especially at quaternary centers.

In this study, it was found that alkyl or aryl substitution of the vinyl ether terminus in these systems lowered the temperature requirement for the thermal rearrangement. In one case, a spirodienone could be obtained directly in a single step from a simple p-quinol precursor under the conditions employed for vinyl ether formation.

The methods employed for the preparation of a phenyl-substituted vinyl ether derivative via organometallic coupling to a vinyl bromide intermediate would appear to represent a potentially simple and convergent approach to systems of similar substitution.
Since the products from these rearrangements were diketones, one example involved thermal rearrangement of the ethylene glycol ketal of a p-quinol-derived vinyl ether, affording the corresponding spirodienone in protected form. Thus, differentiation of the carbonyl groups in this system was achieved. Such protected spirodienones are as yet unavailable via the previously described anodic cyclization method. Significantly, the ketal moiety could be removed later without evidence of dienone-phenol rearrangement.

Clearly, this is not a complete study. Additional examples of spirodienone synthesis would be useful, as would be the preparation of a simple natural product employing this methodology. A study of the kinetics of this process and the preparation of other structural analogues have already been undertaken by other members of this research group. Certainly, a palladium-catalyzed variant of this process would be worth investigating. Nevertheless, the work completed up to this point has served to delineate several of the salient features of this chemistry.

Indeed, the intramolecularity of the process, the often high yields, and the modest temperature requirements for substituted systems are important factors which might permit a more detailed mechanistic study of such thermal [1,3]-shifts in the future without certain of the various problems associated with earlier studies in intermolecular systems.
EXPERIMENTAL

General Procedures. Melting points were determined in capillaries in a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Infrared spectra (IR, bands reported in cm⁻¹) were determined on a Perkin-Elmer Model 283B spectrometer. Routine ¹H nuclear magnetic resonance spectra (NMR, signals reported in ppm) were determined at 80 MHz on an IBM NR 80 spectrometer using deuterochloroform as solvent and residual chloroform as standard. All ¹³C NMR spectra were determined at 20 MHz on the above instrument. Mass spectral and exact mass measurements were obtained by Mr. Richard Weisenberger on a Kratos MS-30 spectrometer connected to a DS-55 data system. Combustion analyses were performed by Scandanavian Microanalytical Laboratory, Herlev, Denmark. All reagents or compounds not explicitly referenced were obtained from the Aldrich Chemical Co. Alumina and silica gel were obtained from E. Merck Co. Tetrahydrofuran (THF) was purified by distillation from benzophenone ketyl. Throughout the experimental the following abbreviations are used: petroleum ether, bp 35-60 °C (PE), diethyl ether (Et₂O), methanol (CH₃OH), acetone (CH₃₂CO), acetic acid (HOAc), ethyl acetate (EtOAc), p-toluene sulfonic acid (p-TsOH), n-butyllithium (n-BuLi), and thin layer chromatography (TLC).
Preparation of 5

To a solution of 2'-bromoacetophenone (5.0 g, 25.1 mmol) in CH₃OH (25 mL) was added trimethylorthoformate (5 mL) and p-TsOH (50 mg), and the resulting solution was stirred for 6 h. After neutralizing with 1% KOH/CH₃OH (10 mL), the solvent was removed in vacuo, and the product was dissolved in CHCl₃ (100 mL) and washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. Distillation of the residue at reduced pressure afforded 5 (6.0 g, 97%) as a water white oil: bp 93-95 °C/0.4 mm; IR (NaCl plates) 2990 (m), 2940 (br, m), 2830 (m), 1460 (m), 1428 (m), 1371 (m), 1280 (m), 1245 (m), 1189 (m), 1140 (m), 1095 (m), 1050 (m), 1035 (m), 1020 (m), 875 (m), 755 (m); ¹H NMR (80 MHz) 7.9-7.0 (str m, 4 H), 3.2 (s, 6 H), 1.6 (s, 3 H); mass spectrum, exact mass calcd for C₁₀H₁₃O₂Br m/e 246.0078, obsd 246.0080.

Preparation of 7

To a -78 °C solution of 5 (2.5 g, 10.2 mmol) in THF (25 mL) was added n-BuLi (7.0 mL of a 1.6 M solution) dropwise over 10 min, and the resulting solution was stirred for 2 h at this temper-
ature. To the milky suspension was added a solution of p-benzoquinone dimethyl monoketal 6a (1.6 g) in THF (5.0 mL) dropwise over 10 min, and the resulting solution was stirred at -78 °C for 1 h, then allowed to warm to room temperature. After quenching the reaction with sat NH₄Cl (5.0 mL), Et₂O (100 mL) was added, the layers were separated and the organic layer was washed with brine (2 x 50 mL) and dried through a CaSO₄ cone. After concentration in vacuo, the crude p-quinol ketal was dissolved in (CH₃)₂CO (75 mL), 8% HOAc (15 mL) was added, and the solution was stored in a 0 °C refrigerator for 16 h. After concentration in vacuo, the product was extracted into CH₂Cl₂ (2 x 75 mL), the combined organics were washed with brine (100 mL) and dried through a CaSO₄ cone. Concentration in vacuo afforded 7 (1.9 g, 78%) as a white solid, mp 145-151 °C, which was deemed suitable for use in the next step without further purification. Recrystallization of a portion from Et₂O gave the analytically pure material: mp 161-162 °C; IR (KBr) 3000 (w), 2935 (w), 1672 (vs), 1630 (m), 1170 (m), 1065 (m), 1025 (m), 870 (m), 841 (m), 770 (m); ¹H NMR (80 MHz) 7.5-6.2 (h str m, 8 H), 3.25 (s, 3 H), 1.83 (s, 3 H); mass spectrum, exact mass calcd for C₁₀H₁₄O₃ m/e 242.0943, obsd 242.0942.

Preparation of 8

A solution of succinic anhydride (0.715 g) and benzoic acid (0.013 g) in a mixture of pyridine (2.0 mL) and diglyme (2.0 mL) was stirred and heated to 110
°C for 15 min, after which time 7 (1.0 g, 4.1 mmol) was added all at once. The resulting clear solution was heated and stirred for 2 h but TLC analysis (2:1 PE/Et₂O) indicated some 7 remaining. Additional succinic anhydride (0.05 g) was added, and the mixture was heated and stirred for an additional 30 min, then allowed to cool to room temperature. The crude reaction mixture was then poured into sat NaHCO₃ (50 mL), and the product was extracted into Et₂O (75 mL). The organic layer was washed with brine (3 X 50 mL), dried through CaSO₄ and concentrated in vacuo to give a brown oil which was chromatographed on silica gel (6" X 1" column, 10% Et₂O/PE as eluant) to afford the vinyl ether 8 (0.431 g, 50%) as a fluffy white solid: mp 89-91 °C; IR (KBr) 1671 (vs), 1630 (s), 1466 (m), 962 (m), 761 (m); ¹H NMR (80 MHz) 7.6-7.0 (str m, 4 H), 6.5 (AB q, Jᵥ = 40 Hz, 4 H), 4.65 (pseudo triplet, J = 3 Hz, 2 H); mass spectrum, exact mass calcd for C₁₄H₁₀O₂, m/e 210.0681. obsd 210.0693.

Thermal Rearrangement of 8 and Preparation of 9

A solution of 8 (0.250 g, 1.0 mmol) in freshly distilled benzene (25 mL) was placed in a heavy walled Pyrex tube and degassed by three freeze-thaw cycles. After sealing under N₂, the tube was placed in a silicon oil bath at 170 °C for 18 h. After cooling, the tube was opened, the contents were transferred to a 50-mL round
bottomed flask, and the solvent was removed in vacuo. The resulting light tan solid 9 (0.250 g, 99%) showed mp 184-188 °C (dec) and was found to be identical in all respects to compound 46 prepared by the method described previously in the Experimental section of Part II of this dissertation, under Preparation of 46.

**Preparation of 11**

Fresh o-bromobenzoyl chloride was prepared in the usual fashion by treatment of o-bromobenzoic acid (25 g, 0.124 mol) with thionyl chloride (30 mL) and a catalytic amount of dimethyl formamide (0.1 mL) at reflux for several hours. Distillation afforded the acid chloride (25.3 g, 93%) as a light yellow oil, bp 135-140 °C/20 mm (lit16 bp 181-182/125 mm) which was used directly in the next step.

A solution of the above acid chloride (3.0 g, 13.7 mmol) in THF (30 mL) was cooled to -78 °C, and an ethereal solution of ethyl magnesium bromide (7.34 mL, 14.7 mmol) was added over 0.5 h. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 4 h. Addition of sat NH₄Cl (20 mL) gave two layers, and the organic layer was separated and concentrated, and the residue was partitioned between Et₂O and water. Workup and drying (Na₂SO₄) gave a light yellow oil which was distilled to afford the colorless ketone 11 (2.6 g, 89%), bp 85-89 °C/1 mm (no lit17 bp given).
Preparation of 12

To a solution of 11 (6.5 g, 30.5 mmol) in CH$_3$OH (35 mL) were added trimethylorthoformate (7 mL) and p-TsOH (15 mg), and the resulting mixture was stirred at room temperature for 12 h. Solid KOH (0.1 g) was added and allowed to dissolve, then the mixture was concentrated in vacuo, and the product was extracted into Et$_2$O (2 X 50 mL). The combined extracts were washed with brine (50 mL), dried through CaSO$_4$ and concentrated in vacuo to give a light yellow oil which was distilled at reduced pressure to afford 12 (7.2 g, 91%) as a water-white oil; bp 115-118/0.4 mm; IR (NaCl Plates) 2985 (m), 2940 (m), 2825 (m), 1468 (m), 1430 (m), 1398 (m), 1185 (m), 1150 (m), 1130 (m), 1110 (m), 1090 (m), 1060 (m), 1025 (m), 950 (m), 759 (m); $^1$H NMR (80 MHz) 7.9-7.1 (str m, 4 H), 3.23 (s, 6 H), 2.24 (q, $J = 7$ Hz, 2 H), 0.6 (t, $J = 7$ Hz, 3 H).

Anal. Calcd for C$_{11}$H$_{14}$O$_2$Br: C, 50.98; H, 5.79. Obsd: C, 51.56; H, 5.76%.

Preparation of 13

To a -78 °C solution of the ketal 12 (4.0 g, 15.4 mmol) in THF (50 mL) was added n-BuLi (11.2 mL of 1.45 M solution) dropwise. After stirring at this temperature for 2 h, a solution of $p$-benzoquinone dimethyl monoketal 6a$^{10}$ (2.37 g) in THF (10 mL) was added dropwise.
The resulting mixture was stirred for 1 h, allowed to warm to room temperature over 12 h, and the reaction was then quenched with sat \( \text{NH}_4\text{Cl} \) solution (15 mL). \( \text{Et}_2\text{O} \) was added (100 mL), the layers were separated, and the organic phase was washed with brine (2 x 50 mL), dried through CaSO_4 and conc in vacuo. The residue was then dissolved in \( (\text{CH}_3)_2\text{CO} \) (150 mL) and cooled to -12 °C. Cold 5% H\( \text{OAc} \) (50 mL) was added, and the homogeneous mixture was stored in a freezer at -12 °C for 24 h. Addition of sat NaHCO_3 solution (50 mL) followed by concentration in vacuo afforded a dark oil which slowly solidified upon standing. Crystallization from \( \text{Et}_2\text{O}/\text{hexane} \) gave in two crops, 13 (1.85 g, 43%) as white crystals: mp 99-101 °C; IR (KBr) 3362 (m), 1670 (s), 1090 (m), 1058 (m), 1030 (s), 955 (m), 859 (m), 751 (m); \( ^1\text{H NMR} \) (60 MHz) 7.7-7.3 (str m, 4 H), 6.4 (AB q, \( \delta v = 65 \text{ Hz} \), \( J_{AB} = 10 \text{ Hz} \), 4 H), 3.29 (s, 6 H), 2.2 (q, \( J = 8 \text{ Hz}, 2 \text{ H} \), 0.75 (t, \( J = 8 \text{ Hz}, 3 \text{ H} \)); mass spectrum, exact mass calcd for \( \text{C}_{17}\text{H}_{20}\text{O}_4 \), \( m/e \) 288.1324; obsd 288.1324.

**Preparation of 14**

To a solution of 13 (0.5 g, 1.7 mmol) in \( \text{CH}_2\text{Cl}_2 \) (200 mL) was added pyridinium \( p \)-toluenesulfonate toluenesulfonate\(^{14} \) (10 mg), and the resulting mixture was stirred for
10 min, then poured into sat NaHCO₃ (100 mL). The organic layer was dried through CaSO₄ and concentrated in vacuo. The residue was dissolved in a minimum of Et₂O/PE and allowed to crystallize. There was obtained in 2 crops 14 (0.2 g, 45%) as a white solid, mp 108-111 °C. Repeated crystallization from Et₂O/PE gave the analytically pure material: mp 112-114 °C; IR (KBr) 1662 (s), 1632 (m), 1068 (m), 1030 (m), 910 (m); ¹H NMR (80 MHz) 7.5-6.2 (highly str m, 8 H), 3.24 (s, 3 H), 2.1 (pseudo octet, J = 7 Hz, 2 H), 1.0 (t, J = 7 Hz, 3 H).

Anal. Calcd for C₁₅H₁₆O₃: C, 74.98; H, 6.29. Obsd: C, 74.84; H, 6.37%.

Preparation of 15

To a solution of 14 (0.1 g, 0.39 mmol) in a mixture of pyridine (0.5 mL) and diglyme (0.5 mL) were added succinic anhydride (0.07 g) and benzoic acid (1.0 mg), and the resulting mixture was heated for 1 h at 120 °C with stirring. After cooling, the reaction mixture was poured into sat NaHCO₃ (10 mL), and the product was extracted into Et₂O (3 X 25 mL). The combined organics were washed with brine (2 X 50 mL), dried through CaSO₄ and concentrated in vacuo. The residue was chromatographed on silica gel (6" X 1/4" column, 10% Et₂O/PE as eluant) to afford 15 (0.033 g, 36%) as a white crystalline solid, mp 110-112 °C. Subsequent fractions were found to
contain a small amount of the spirodienone 16 (7 mg, 7%), the preparation and characterization of which is described under Preparation of 16 (see below). Compound 15 showed the following spectral properties: IR (KBr) 1690 (m), 1671 (s), 1635 (m), 1048 (m), 990 (m), 855 (m), 770 (m); 1H NMR (80 MHz) 7.5-6.8 (str m, 4 H), 6.44 (AB q, J = 42 Hz, J_AB = 10 Hz, 4 H), 5.0 (q, J = 7 Hz, 1 H), 1.75 (d, J = 7 Hz, 3 H); mass spectrum, exact mass calcd for C_{15}H_{12}O_2 m/e, 224.0838; obsd 224.0842.

In Situ Generation and Thermal Rearrangement of 15:
Preparation of 16

To a solution of 13 (0.25 g, 0.87 mmol) in a mixture of pyridine (2.5 mL) and diglyme (2.5 mL) were added succinic anhydride (0.5 g) and benzoic acid (5 mg), and the resulting mixture was heated to 160 °C for 8.5 h. After cooling, the reaction mixture was poured into sat NaHCO_3 (25 mL), the product was extracted into Et_2O (3 x 25 mL), and the combined organics were washed with brine (2 x 25 mL), dried through CaSO_4 and concentrated in vacuo. The residual pyridine and diglyme were removed in vacuo at 0.2 mm Hg over 12 h, and the residue was dissolved in a minimum of CH_3OH and allowed to slowly crystallize at 0 °C. Filtration and drying in vacuo afforded 0.075 g spirodienone 16 (0.075 g) as a light yellow solid, mp 143-145 °C. The mother liquors from the above crystallization were
chromatographed on silica gel (6" X 1/4" column, 10% EtOAc/PE as eluant) to afford an additional 0.025 g, mp 143-145 °C for a total of 0.100 g of 16 (52%). Repeated crystallization of a portion from Et₂O/PE gave the analytically pure material as white crystals: mp 149-150 °C; IR (KBr) 1721 (s), 1662 (s), 1621 (m), 1598 (m), 1460 (m), 1408 (m), 1222 (m), 855 (m); ¹H NMR (80 MHz) 7.7-7.1 (highly str m, 4 H), 7.0-6.2 (highly str m, 4 H), 2.95 (q, J = 7 Hz, 1 H), 1.14 (d, J = 7 Hz, 3 H); ¹³C NMR (20 MHz) 204 (1 C), 185.4 (1 C), 152 (1 C), 150.5 (1 C), 150.2 (1 C), 135.4 (1 C), 130.2 (1 C), 129.4 (1 C), 128.8 (1 C), 125.4 (1 C), 124.9 (1 C), 53 (1 C), 52.2 (1 C), 10 (1 C).

Anal. Calcd for C₁₅H₁₂O₂: C, 80.34; H, 5.35. Found: C, 80.09; H, 5.47%.

Preparation of 17

To a -78 °C solution of 5 (15.0 g, 61.2 mmol) in THF (150 mL) was added n-BuLi (43 mL of 1.45 M solution) dropwise over 15 min, and the resulting mixture was stirred for 2 h. Next, a solution of p-benzoquinone monoethylene glycol ketal 6b₁⁰ (9.3 g) in THF (30 mL) was added dropwise, stirring was continued at -78 °C for 1 h and the solution was then allowed to warm to room temperature over 2 h. The reaction was quenched with water (125 mL), and Et₂O was added (300 mL). The layers were separated, and the organic phase was
washed with brine (2 X 50 mL), dried through CaSO₄ and concentrated in vacuo. The resulting oily solid was triturated with Et₂O/PE and filtered to afford 17 (15.2 g, 79%) as a white solid, mp 95-98 °C, which was suitable for use in the next step. Recrystallization of a portion from Et₂O/PE gave the analytical sample: mp 103-106 °C; IR (KBr) 3370 (vs), 1450 (m), 1380 (m), 1190 (m), 1150 (m), 1112 (s), 1040 (s), 1010 (s), 968 (s), 942 (m), 875 (m), 762 (m); ¹H NMR (80 MHz) 7.5-7.1 (str m, 4 H), 6.7 (s, 1 H), 6.10 (AB q, JAB = 4.9 Hz, JAB = 10 Hz, 4 H), 4.08 (s, 4 H), 3.28 (s, 6 H), 1.78 (s, 3 H).

Anal. Calcd for C₁₇H₂₂O₅: C, 67.91; H, 6.91. Obsd: C, 67.94; H, 7.03%.

Preparation of 18

To a solution of 17 (6.0 g, 18.8 mmol) in a mixture of pyridine (27 mL) and diglyme (27 mL) were added succinic anhydride (6.6 g) and benzoic acid (0.07 g), and the resulting mixture was heated to 140-150 °C with stirring for 2.5 h. After cooling, the reaction mixture was poured into sat NaHCO₃ (125 mL), and the resulting precipitate was collected by vacuum filtration and washed with water (50 mL) to remove residual pyridine and diglyme. The moist solid was dissolved in EtOAc (100 mL), washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo to afford 18 (3.95 g,
83%) as a tan solid, mp 118-121 °C, which was deemed suitable for use directly in the next step. Recrystallization of a portion from Et₂O/PE gave the analytical sample as white needles: mp 123-125 °C; IR (KBr) 1662 (m), 1470 (m), 1405 (m), 1290 (m), 1250 (m), 1115 (s), 1005 (m), 975 (m), 960 (s), 940 (m), 760 (m); ¹H NMR (80 MHz) 7.4-7.0 (str m, 4 H), 5.87 (s, 4 H), 4.47 (q, 2 H), 4.0 (s, 4 H); mass spectrum, exact mass calcd for C₁₆H₁₄O₃ m/e 254.0943, obsd 254.0933.

Preparation of 19

To a 0 °C solution of 18 (1.0 g, 4.0 mmol) in THF (40 mL) were added pyridine (0.35 mL) and N-bromosuccinimide (0.8 g, 4.5 mmol). After 15 min, no starting material remained by TLC analysis (1:1 Et₂O/PE). The reaction mixture was then poured into sat NaHCO₃ solution (50 mL), and the product was extracted into Et₂O (2 X 75 mL). The combined organics were washed with brine (50 mL), dried through CaSO₄ and conc in vacuo. The gummy residue was chromatographed on silica gel (6" X 1/2" column, 20% Et₂O/PE as eluant) to afford 19 (0.862 g, 65%) as off-white crystals, mp 127-129 °C. Recrystallization of a portion from Et₂O/PE gave the analytically pure material: mp 128-129.5 °C; IR (KBr) 3010 (m), 1660 (m), 1404 (m), 1168 (s), 1104 (m), 1068 (s), 1001 (m), 960 (s), 945 (m), 770 (m), 762 (m); ¹H NMR (80 MHz) 7.34-7.0 (str m, 4 H), 5.89 (s, 4 H), 5.58 (s, 1 H), 4.05 (s, 4 H); mass spectrum, exact mass calcd for
Preparation of 20

To a 0 °C solution of 19 (1.5 g, 4.5 mmol) in Et₂O (100 mL) containing a catalytic amount of dichloro [1,3-bis-(diphenylphosphino) propan] nickel (II) (20 mg) was added phenyl magnesium bromide (5.4 mL of a 2.1 M solution in Et₂O) dropwise, and after 5 min, dark crystals of magnesium bromide began to appear on the sides of the flask. After stirring for 1 h at room temperature, TLC analysis (1:1 Et₂O/PE, 2 elutions) indicated no 19 remaining. The reaction was carefully quenched with sufficient water (2 mL) to coagulate the magnesium salts, the Et₂O/product solution was decanted off, and the magnesium salts were washed with Et₂O (2 x 25 mL). The combined organics were washed with sat NaHCO₃ (50 mL) and brine (50 mL), dried through CaSO₄ and concentrated in vacuo. The residue was crystallized from Et₂O/PE to afford 20 (0.735 g, 49%) in two crops as white crystals: mp 168-170 °C (dec); IR (KBr) 1650 (m), 1460 (m), 1398 (m), 1115 (s), 1105 (s), 1055 (s), 995 (m), 970 (m), 958 (s), 940 (s), 751 (m); ¹H NMR (80 MHz) 7.8-7.0 (str m, 9 H), 6.0 (s, 4 H), 5.98 (s, 1 H), 4.1 (s, 4 H); mass spectrum, exact mass calcd for C₂₂H₁₆O₃ m/e 330.1256, obsd 330.1261.
Preparation of 21

To a 0 °C solution of 20 (0.5 g, 1.51 mmol) in THF (20 mL) was added chilled 0.1N HCl, (10 mL) and the resulting homogeneous mixture was stored in a 0 °C refrigerator for 12 h. TLC analysis (2:1 PE/Et2O) indicated some starting material remaining, so the mixture was allowed to warm to room temperature for 4 h, after which time TLC showed the hydrolysis to be complete. The mixture was poured into sat NaHCO₃ (25 mL), and the resulting precipitate was collected by vacuum filtration and dried in vacuo to afford 21 (0.414 g, 96%) as a light yellow solid, mp 138-140 °C. Recrystallization of a portion from Et₂O/PE gave the analytical sample as bright yellow crystals: mp 141-142 °C; IR (KBr) 1679 (s), 1630 (m), 1460 (m), 1065 (m), 1055 (m), 960 (s), 868 (m), 758 (s), 690 (m); 1H NMR (80 MHz) 7.8-7.0 (str m, 9 H), 6.5 (AB q, J = 40 Hz, JAB = 10 Hz, 4 H), 6.0 (s, 1 H); mass spectrum, exact mass calcd for C₂₀H₁₄O₂ m/z 286.0994, obsd 286.0988.

Thermal Rearrangement of 21 and Preparation of 22

A solution of 21 (0.25 g, 0.87 mmol) in toluene (10 mL) containing 2,6-di-t-butylhydro-quinone (2.0 mg) was degassed by three freeze-thaw cycles and heated to reflux for 4 h, after which time TLC analysis (1:1 Et₂O/PE) indicated no starting material remaining and a
single, slower moving spot. The reaction mixture was concentrated in vacuo, and the solid residue was triturated with cold Et$_2$O and dried to afford 22 (0.207 g, 83%) as light tan crystals, mp 152-155 °C. Recrystallization of a portion from Et$_2$O/PE gave the analytically pure material: mp 155-157 °C; IR (KBr) 1715 (s), 1670 (s), 1630 (m), 1595 (m), 866 (m), 761 (m); $^1$H NMR (80 MHz) 7.9-6.9 (highly str m, 9 H), 6.4-5.8 (highly str m, 4 H), 4.2 (s, 1 H); $^{13}$C NMR: 201.7 (1 C), 185.1 (1 C), 151.5 (1 C), 150.3 (1 C), 150.0 (1 C), 135.8 (1 C), 135.6 (1 C), 134.0 (1 C), 129.7 (1 C), 129.5 (1 C), 129.0 (2 C), 128.6 (2 C), 128.3 (2 C), 125.6 (1 C), 125.0 (1 C), 63.4 (1 C), 53.4 (1 C); mass spectrum, exact mass calcld for C$_{20}$H$_{14}$O$_2$ m/e 286.0993, obsd 286.0979.

Preparation of 23

To a -78 °C solution of 12 (18.2 g, 70.3 mmol) in THF (250 mL) was added n-BuLi (49.2 mL of a 1.5 M solution) dropwise, and the resulting mixture was stirred for 2 h. Next, a solution of p-benzoquinone monoethylene glycol ketal 6b$^{10}$ (10.7 g) in THF (50 mL) was added dropwise, and the solution was allowed to stir at -78 °C
for 1 h and then at room temperature for 12 h. After quenching the reaction with water (50 mL), Et₂O (200 mL) was added, the layers were separated, and the organic phase was washed with brine (100 mL), dried through CaSO₄ and concentrated in vacuo. The residue was dissolved in a minimum of Et₂O/PE and allowed to crystallize, affording 23 (14.8 g, 63%) in three crops as a white solid, mp 102-104 °C, which was deemed suitable for use directly in the next step without further purification. Recrystallization of a portion from Et₂O/PE gave the analytical sample: mp 105-106 °C; IR (KBr) 3345 (m), 1140 (m), 1112 (s), 1098 (m), 1058 (m), 1042 (m), 1021 (m), 970 (s), 890 (m); ¹H NMR (80 MHz) 7.5-7.0 (str m, 4 H), 6.85 (s, 1 H), 5.9 (AB q, δv = 38 Hz, J̅AB = 10 Hz, 4 H), 3.95 (s, 4 H), 3.13 (s, 6 H), 2.1 (q, J = 8 Hz, 2 H), 0.6 (t, J = 8 Hz, 3 H).

Anal. Calcd for C₁₉H₂₄O₆: C, 68.66; H, 7.28. Obsd: C, 68.56; H, 7.25%.

Preparation of 24

To a solution of 23 (6.0 g, 18 mmol) in a mixture of pyridine (26 mL) and diglyme (26 mL) were added succinic anhydride (6.2 g) and benzoic acid (65 mg), and the resulting solution was heated to 140-150 °C for 2.5 h. After cooling to room temperature, the reaction mixture was poured into sat NaHCO₃ (125 mL), and the resulting precipitate was collected by vacuum filtration and washed with 5%
NaHCO₃ (2 X 50 mL). The moist solid was dissolved in EtOAc (100 mL), washed with brine (50 mL), dried through CaSO₄ and concentrated in vacuo. There was obtained in this way 24 (3.8 g, 79%) as chunky, brown crystals, mp 108-115 °C. Recrystallization of a portion from Et₂O/PE gave the analytical sample: mp 115-117 °C; IR (KBr) 1600 (m), 1461 (m), 1405 (m), 1311 (s), 1091 (m), 1006 (m), 995 (m), 970 (s), 955 (m), 942 (m), 750 (m); ¹H NMR (80 MHz) 7.3-7.0 (str m, 4 H), 5.87 (s, 4 H), 4.9 (q, J = 7 Hz, 1 H), 4.0 (s, 4 H), 1.73 (d, J = 7 Hz, 3 H); mass spectrum, exact mass calcd for C₁₇H₁₆O₃ m/e 268.1100, obsd 268.1111.

Thermal Rearrangement of 24 and Preparation of 25

A solution of 24 (0.25 g, 0.93 mmol) in o-dichlorobenzene (10 mL) containing 2,6-di-t-butylhydroquinone (2.0 mg) was degassed by three freeze-thaw cycles and heated to reflux under N₂ for 16 h, after which time TLC analysis (1:1 Et₂O/PE) indicated no starting material remaining. The solvent was removed in vacuo, and the residue was chromatographed on silica gel (6" X 1/2" column, 20% EtOAc/PE as eluant) to afford 25 (0.122 g, 49%) as a clear oil: IR (NaCl Plates) 2970 (m), 2880 (m), 1720 (br, s), 1600 (m), 1462 (m), 1412 (m), 1210 (m), 1210 (m), 1100 (br, s), 1030 (m), 1015 (m), 960 (br, s), 925 (m), 750 (m); ¹H NMR (80 MHz) 7.8-7.2 (str m, 4 H), 5.9-5.4 (highly
str m, 4 H), 4.0 (s, 4 H), 2.7 (q, J = 7 Hz, 1 H), 1.1 (d, J = 7 Hz, 3 H); \textsuperscript{13}C NMR: 205.7 (1 C), 155.7 (1 C), 135.3 (1 C), 135.0 (1 C), 134.5 (1 C), 128.4 (1 C), 127.3 (1 C), 125.8 (1 C), 125.7 (1 C), 123.8 (1 C), 65.3 (1 C), 65.1 (1 C), 53.1 (1 C), 49.1 (1 C), 9.8 (1 C); mass spectrum, exact mass calcd for C\textsubscript{17}H\textsubscript{16}O\textsubscript{3} m/e 268.1100, obsd 268.1084.

The structural assignment for 25 was further confirmed by hydrolysis of the ethylene glycol ketal moiety as follows: To a solution of 25 (0.018 g, 0.067 mmol) in (CH\textsubscript{3})\textsubscript{2}CO (10 mL) was added 5% HOAc (5 mL), and the mixture was allowed to stand at room temperature for 12 h. Next, the reaction mixture was poured into sat NaHCO\textsubscript{3} (10 mL), and the solvent was removed in vacuo. The product was extracted into Et\textsubscript{2}O (2 X 10 mL), and the combined organics were washed with brine (5 mL), dried through CaSO\textsubscript{4} and concentrated in vacuo to afford 16 (0.015 g, 99%), mp 144-147 °C, with spectral properties identical to material previously prepared by the method described in this section under Preparation of 16.
APPENDIX C:

NMR SPECTRA
80 MHz 1H NMR Spectrum of 5.
80 MHz $^1H$ NMR Spectrum of 7.
80 MHz ¹H NMR Spectrum of 8.
80 MHz 1H NMR Spectrum of 9.
$80 \text{ MHz } ^1\text{H NMR Spectrum of 12.}$
$80 \text{ MHz } ^1\text{H NMR Spectrum of 13.}$
80 MHz $^1$H NMR Spectrum of 14.
80 MHz 1H NMR Spectrum of 15.
80 MHz 1H NMR Spectrum of 16.
$80 \text{ MHz } ^1\text{H NMR Spectrum of 17.}$
80 MHz $^1$H NMR Spectrum of 18.
80 MHz $^1$H NMR Spectrum of 19.
80 MHz $^1$H NMR Spectrum of 20.
80 MHz $^1$H NMR Spectrum of 21.
80 MHz $^1$H NMR Spectrum of 22.
80 MHz $^1$H NMR Spectrum of 23.
$80 \text{ MHz } ^1\text{H NMR Spectrum of 24.}$
80 MHz $^1$H NMR Spectrum of 25.
REFERENCES AND NOTES


(11) For several examples and leading references, see the introductory section of PART II of this dissertation.

(12) DeSchepper, R.E., Ph.D. Dissertation, The Ohio State University, Columbus, Ohio, 1986, and references cited therein.


