slurry. As the sample warmed to room temperature, the reaction was complete. The samples were then manipulated in either a N_2 or Ar atmosphere or by syringe techniques.

Conductance Measurements (CH_2Cl_2). Approximately 0.1 g of the desired silane was syringed into a 200-mL, three-necked flask that had been dried, flushed with N_2 or Ar, and fitted with three rubber septa. The flask also contained a magnetic stirring bar. The silane was dissolved in 125 mL of freshly distilled CH_2Cl_2, and the system was placed under heavy N_2 (Ar) back-pressure. The tip of a buret containing CH_2Cl_2 solution of the desired trityl salt was pushed through one of the septa, and a pipet-type conductance cell was pushed through a second septum and into the silane solution. Addition of the trityl salt was performed in small aliquots, allowing 10 min after each addition for the reaction to take place. After this waiting period, some of the reaction mixture was drawn into the conductance cell, the measurement was taken, and the solution was forced back into the reaction vessel with a stream of N_2 or Ar. Measurements were continued until more than 1 equiv of the trityl salt had been added to the silane. Measured conductances were converted to absolute conductances by employing the cell constant, which had been determined by measuring the conductance of a standard KCl solution.

Conductance of $HClO_4$. Perchloric acid (70%) was added via microsyringe to a 100-mL flask that was equipped with a magnetic stirring bar and the pipet-type conductance cell and that contained approximately 50 mL of solvent. The solution was stirred for 10 min and then drawn into the conductance cell. A measurement was taken, and the solution was drained back into the flask.

Reduction of tris(2-propylthio)silyl perchlorate with diisobutylaluminum hydride (DIBAL-H) was performed under N_2 by cooling a CH_2Cl_2 solution of the silyl perchlorate to −78 °C in a dry ice/2-propanol bath, and adding 1 equiv of DIBAL-H (in diethyl ether) dropwise over a 15-min period. After being stirred at −78 °C for an additional 1 h, the colorless solution was allowed to warm slowly to room temperature. The solvent was removed under vacuum, and the residue was *carefully* distilled under high vacuum (*CAUTION*: explosion may occur). The boiling point, proton NMR spectrum, and IR spectrum of the material recovered were identical with those of a known sample of tris(2-propylthio)silane.

Spectroscopic Measurements (Sulfolane). Samples of the silyl perchlorates were produced in the same fashion as in CH_2Cl_2, except that the reactions were necessarily performed at ca. 30 °C rather than at −78 °C. The reaction temperatures were maintained by employing warm water baths.

Molecular Weight Determinations. A sample of freshly purified[34] sulfolane (vide infra) was syringed into a dry flask and weighed. This flask was placed under N_2 or Ar and immersed in a water bath at ca. 35 °C. Ice was added to the bath, and the temperature of the sulfolane was monitored and recorded every 30 s. Temperature readings were taken from a thermometer calibrated in 0.2 °C increments and certified by the National Bureau of Standards. From these data a cooling curve was made and the freezing point of the sulfolane was determined. Next, a weighed sample of the desired solute was added, and the experiment was repeated. In trials that required production of a silyl perchlorate, the freezing point depression was measured first on a weighed sample of trityl perchlorate, and then the silane was added and allowed to react. The freezing point of the sulfolane was then measured again to determine the depression caused by the silyl perchlorate and the triphenylmethane formed in the reaction. To determine the depression caused by the silyl perchlorate, the theoretical amount of Ph_3CH that should be formed in the reaction was calculated, and the freezing point depression that would be caused by this amount of material was determined and subtracted from the overall freezing point depression.

Sulfolane-*2,2,5,5-d*$_4$. Sulfolane (15.0 g, 0.125 mol) was added to 15 mL of D_2O (99.5% D) and 0.15 g of K_2CO_3. The system was heated to reflux under N_2 for 24 h, and the solution was frozen and lyophilized to remove the water. This procedure was repeated seven more times, and the four α positions in the sulfolane were shown to be 98% deuteriated at this point by ^1H NMR spectroscopy. The sulfolane-d_4 was then distilled from K_2CO_3 under vacuum: 12.8 g (85%); NMR ($CDCl_3$) δ 2.22 (br s).

Conductance Measurements (Sulfolane). Since the viscosity of sulfolane is very high, and the freezing point is ca. 28 °C, a conductance cell other than the pipet-type previously described was used. This cell was a cylindrical glass container with Pt electrodes, into which could be poured sulfolane solutions of the silyl perchlorates. The solutions were maintained in the liquid phase by employing a water bath at ca. 30 °C, and the cell constant was determined as previously described.

Dichloromethane and 1,2-Dichloroethane. The solvent was shaken with portions of concentrated H_2SO_4 until the acid was colorless. The solvent was then washed with H_2O, 5% $NaHCO_3$, and H_2O again. After having been predried over $CaCl_2$, the solvent was stirred over CaH_2 at ca. 30 °C for 2 h. The solvent was then distilled through a Vigreux column and collected in a flask containing 4A molecular sieves. The solvent was stored over 4A molecular sieves in a brown bottle out of direct sunlight.

Sulfolane was stirred over CaH_2 for 48 h and then distilled through a Vigreux column. The middle, constant-boiling fraction was collected in a flask containing 4A molecular sieves and stored in a brown bottle over 4A molecular sieves.

Acetonitrile was shaken with 4A molecular sieves and then stirred over CaH_2 until the evolution of H_2 ceased. The solvent was then fractionally distilled at very high reflux through a Vigreux column and collected in a flask containing 4A molecular sieves. This material was then slowly passed through a column (2 × 35 cm) containing 4A molecular sieves, collected, and stored in a brown bottle over 4A molecular sieves.[35]

(34) Perrin, P. D.; Armarigo, W. L.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: New York, 1980.

(35) After submission of this paper, another paper appeared on the subject of triphenylsilyl perchlorate.[36] Their observation of covalency in the solid has no direct bearing on our studies in solution but is consistent with our observation of association with increased concentration. Our ^{35}Cl studies at the dilute concentrations of the conductance and cryoscopic experiments support the ionic formulation. The ^{35}Cl and ^{29}Si spectra of Prakash et al.[36] were at high concentrations (>0.1 M) and correspond to the associated form; we had made these same observations and described them herein.

(36) Prakash, G. K. S.; Keyaniyan, S.; Aniszfeld, R.; Heibiger, L.; Olah, G. A.; Stevens, R. C.; Choi, H.-K.; Ban, R. *J. Am. Chem. Soc.* **1987**, *109*, 5123-5126.

Intramolecular Radical Cyclization of Phenolic Enolates

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Abstract: Phenol rings bearing three- or four-carbon chains terminated by enolic or enolizable groups have been subjected to oxidation at alkaline pH using aqueous potassium ferricyanide or potassium hexachloroiridate. Substrates in which the enolizable system is an indandione, a 1,3-cyclohexanedione, a malononitrile, a barbituric acid, a pyrazolinedione, an oxindole, or a benzopyrandione undergo such oxidative cyclization in moderate to good yields when a new five-membered ring can be formed. Cyclization was not observed for several acyclic enolizable end groups. Dienone–phenol rearrangements of several spirocyclic dienones derived from these oxidations were carried out in CH_2Cl_2–CF_3SO_3H. A hypothesis regarding the possible course of the oxidation sequence is presented.

Formation of carbon rings by free-radical cyclizations is exhibiting a renaissance in modern organic synthetic methodology.[1] We have recently described a novel intramolecular radical cyclization whereby the phenolic indandione **1** reacts with K_3Fe-

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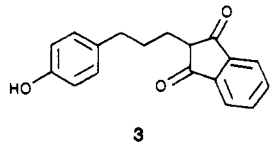
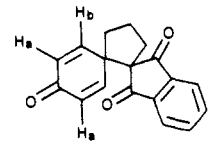
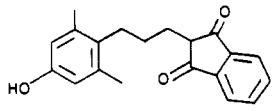
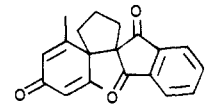
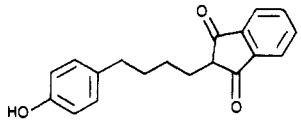
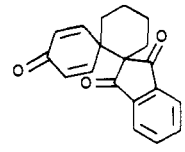
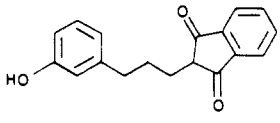
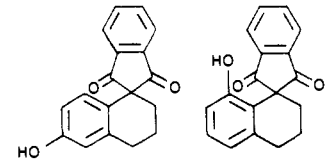
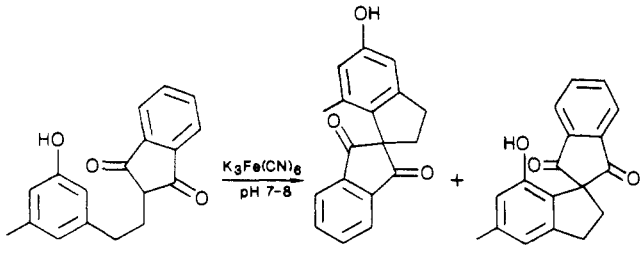
Table I

indandione	oxidn procedure	product	cyclizn yield, %
 3	dilute KOH, $K_3Fe(CN)_6$	 7	88
 4	0.5 M Na_2CO_3, $K_3Fe(CN)_6$	 8	57
 5	dilute KOH, $K_3Fe(CN)_6$	 9	~2
 6	0.5 M Na_2CO_3, $K_3Fe(CN)_6$	 10 (major) 11 (minor)	79

$(CN)_6$ in alkaline medium to yield the para- and ortho-coupling products **2a** and **2b**, respectively.[2]



1 **2a** (67%) **2b** (8%)

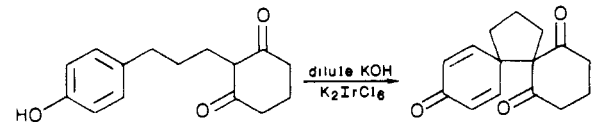
Although intramolecular oxidative "coupling" of phenoxy radicals is a well-described synthetic and biogenetic pathway,[3] and sporadic examples of intramolecular enolate to enolate oxidative couplings are known,[4] the oxidative cyclization of a phenolate with a stabilized enolate is essentially unprecedented.[5] We report here a survey of this novel chemistry in which the enolizable center is in a carbocyclic, acyclic, or heterocyclic environment.

Cyclization of Carbocyclic Enols. To determine the scope of the indandione cyclizations exemplified by the closure of **1**, several phenols bearing indandione substituents attached by a three- or four-carbon chain meta or para to the phenolic OH were prepared. In each case the synthesis involved the intramolecular Claisen condensation of the appropriate ω-arylbutanoic ester or ω-arylpentanoic ester with dimethyl phthalate,[6] followed by O-demethylation as required. The indandione substrates listed in Table I were cyclized in a two-phase system of chloroform and aqueous sodium carbonate or dilute KOH with 6 molar equiv of $K_3Fe(CN)_6$ at room temperature to yield the cyclization products shown.

It is seen that the phenolic enolate systems tethered by a three-carbon chain cyclize in good yield when a new cyclopentane ring is formed and that such cyclization occurs whether the chain is meta or para to the phenolic OH. For the generation of a cyclohexane ring, the spirocyclization of the para-substituted case **5** proceeds in only a trace yield. On the other hand, the meta-substituted phenol **6** cyclizes in good yield to a ca. 2:1 ratio of para to ortho cyclization products, with the ratio **10** to **11** being temperature dependent.

The structures of the spirocyclic cyclohexadienones **7–9** were firmly established by analytical, infrared, and NMR characterization. In particular, the cyclohexadienone moiety of compound **7**, mp 143–144 °C, is confirmed by the symmetrical olefinic region showing two protons (H_α) as a doublet at δ 6.18 and two protons (H_β) as a doublet at δ 7.00 coupled to each other with J = 10.5 Hz.[7] The regiochemistries of **10** and **11** in turn were unambiguously assigned from the coupling patterns of the aromatic protons on the phenolic ring.

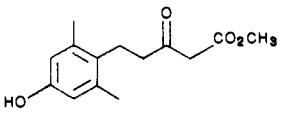
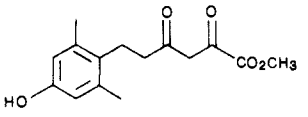
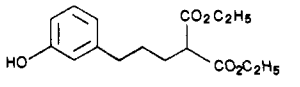
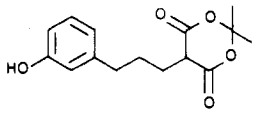
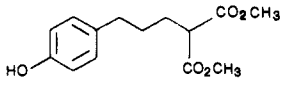
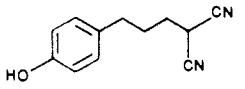
To establish whether the indandione system can be replaced by a simpler 1,3-dione, the synthesis of the phenolic cyclohexanedione **12** was undertaken. The latter was synthesized by alkylation of the lithium derivative of 1,5-dimethoxy-1,4-cyclohexadiene with 1-iodo-3-(4-methoxyphenyl)propane according to the precedent of Piers and Grierson.[8] The intermediate 2-[3-(4-methoxyphenyl)propyl]-1,3-cyclohexanedione, mp 114–116 °C, was a somewhat unstable white solid, which was gently demethylated with BBr_3 in CH_2Cl_2 at −78 °C to yield phenol **12** as



12 13

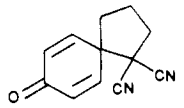
(1) For a recent survey of this area, see Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986.
(2) Kende, A. S.; Ebetino, F. H.; Ohta, T. *Tetrahedron Lett.* **1985**, *26*, 3063–3066.
(3) (a) *Oxidative Coupling of Phenols*; Battersby, A. R., Taylor, W. I., Eds.; Dekker: New York, 1967. (b) Dhingra, O. P. In *Oxidations in Organic Chemistry*; Trahanovsky, W. S., Ed.; Academic: New York, 1982, Part D, Chapter IV, and references therein.
(4) E.g., Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 649. Frasier, R. H., Jr.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408 and references therein.
(5) For a recent example involving nitronate species, see: Kende, A. S.; Koch, K. *Tetrahedron Lett.* **1986**, *27*, 6051–6054.
(6) Koelsch, C. F.; Byers, D. J. *J. Am. Chem. Soc.* **1940**, *62*, 560.
(7) Regel, W.; von Philipsborn, W. *Helv. Chim. Acta* **1969**, *52*, 1354.
(8) Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977**, *42*, 3755.

Table II

substrate	oxidn procedure	product	cyclizn yield, %
 14	dilute KOH, $K_3Fe(CN)_6$		0
 15	dilute KOH, $K_3Fe(CN)_6$		0
 16	dilute KOH, $K_3Fe(CN)_6$		0
 17	dilute KOH, or Na_2CO_3, $K_3Fe(CN)_6$		0
 18	dilute KOH, $K_3Fe(CN)_6$, or K_2IrCl_6		0
 19	dilute KOH, $K_3Fe(CN)_6$		0
19	dilute KOH, K_2IrCl_6	20	31

a chromatographically homogeneous oil with the correct high-resolution mass spectrum. Whereas oxidative coupling of **12** with alkaline $K_3Fe(CN)_6$ proceeded poorly, use of the more powerful K_2IrCl_6 as oxidant[9] in dilute KOH gave 43% of a crystalline cyclization product, mp 124–126 °C, shown by its ^1H NMR, IR, and high-resolution mass spectra to be the spirocyclic triketone **13**.

Cyclizations of Acyclic Enols. To further simplify the enolic unit, a variety of acyclic active methylene compounds attached by a chain to the meta or para position of a phenol ring were synthesized, and their oxidative cyclizations were explored. These structures are illustrated in Table II. The estimated pK_a values for the "enolic" moieties range from approximately 4.8 for the Meldrum's acid derivative **17** to 13 for the malonates **16** and **18**. For all but one of these substrates we were unable to discern any evidence for ring closure. The sole exception was malononitrile derivative **19**, where the "enolic" proton is estimated to have a pK_a of about 11. Although **19** was unaffected by alkaline ferricyanide, closure was successful by employing alkaline K_2IrCl_6 to yield the spirocyclic dinitrile **20**, mp 99–100 °C, in 31% yield.



20

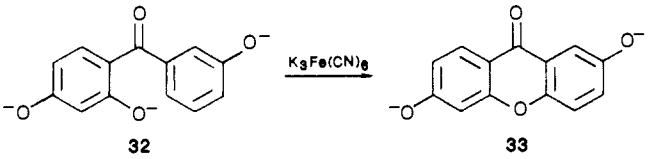
Cyclization of Heterocyclic Enols. Considerably greater success was observed by employing substrates having heterocyclic carbon acids attached by a chain to the para position of a phenol (Table III). We find that where such cyclic enolate species are stabilized by one or more CONH units, they undergo facile cyclization with alkaline $K_3Fe(CN)_6$ to yield spirocyclic dienones. Closure to a cyclopentane again is superior to formation of a cyclohexane. The pK_a values for the enolic segments range from approximately 4–5 for the barbituric acids **21**, **22**, and pyrazolinedione **23** to an estimated 12–14 for the oxindole **24**.

The benzopyrandione **25** gave mainly recovered starting material with alkaline ferricyanide. On the other hand, alkaline K_2IrCl_6 resulted in cyclization to give after chromatography a 33% yield of pale yellow crystals characterized as the spirocyclic diketo lactone **29**, mp 166–167 °C.

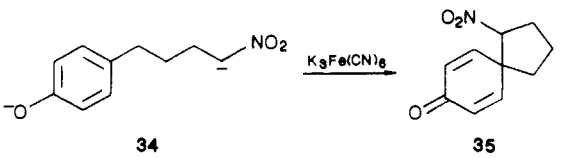
Dienone–Phenol Rearrangements. The novel availability of several polyfunctional 4,4-disubstituted 2,5-cyclohexadienones by the above ring closures has allowed us to examine the acid-catalyzed dienone–phenol rearrangements of some of these oxidation products. The compounds studied are **7** (derived from a phenolic indandione), **26** (derived from a phenolic barbituric acid), **27** (derived from a phenolic pyrazolinedione), and **28** (derived from a phenolic oxindole). The standard reaction conditions chosen were reaction in a dilute solution of CF_3SO_3H in CH_2Cl_2 at 0 °C for 2 h. Under these conditions substrate **26** was unchanged, but the other three substrates underwent rearrangement as pictured in Table IV. For the indandione **7**, rearrangement gave an 88% yield of a single phenol, mp 166–167 °C, identical with the major product **10** arising from oxidative cyclization of the meta-linked phenolic indanedione **6**. The pyrazolinedione **27** rearranged to give 38% of crystalline phenol **30**, mp 257–258 °C. The oxindole **28** rearranged to yield 91% of the crystalline phenol **31**, mp 244–245 °C. The regiochemistry of oxindole **31** may be provisionally assigned by comparison of the proton chemical shifts of the phenolic ring with those established for the known structure **10**. As shown in Table V, the chemical shift of H_x in oxindole **31** is abnormally upfield and must arise from shielding of that proton by the anisotropy of the peri aromatic moiety. For pyrazolinedione **30**, the dione ring has a modest shielding effect on H_x, whereas the "normal" δ 6.70 of H_b corresponds to that of H_b (δ 6.92) in 6-hydroxytetralin[10] and suggests the absence of a neighboring anisotropic unit; however, our regiochemical assignment of structure **30** must be regarded as tentative.

Discussion

Early hypotheses for the course of intramolecular phenol–phenol couplings envisioned the overall two-electron oxidation to proceed by coupling of two phenoxy radicals generated in the same time period from phenolate precursors.[11] Hamilton has examined kinetics of the ferricyanide oxidation of 2,3′,4-trihydroxybenzophenone trianion (**32**) and has concluded that the intramolecular coupling to 2,6-dihydroxyxanthone dianion (**33**) involves the addition of a phenoxy radical to a phenoxide ring, followed by a second (rapid) electron transfer from the radical anion intermediate to give the product.[12] We have suggested an analogous mechanism for the cyclization step of the phenolic nitronate **34** to the spirocycle **35**.[5]



32 **33**



34 **35**

Such stepwise, radical anion mechanisms are more likely than true radical–radical coupling since in general the rates and lifetimes of radical formation from each partner will differ. We suggest that the phenolate–enolate cyclizations of this paper

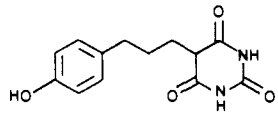
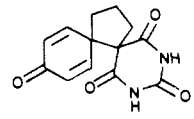
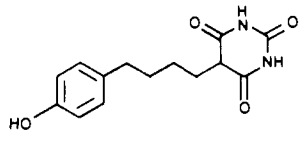
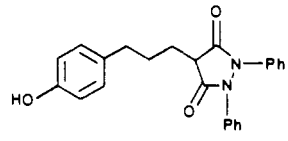
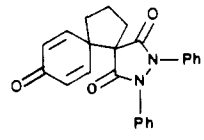
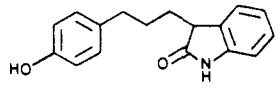
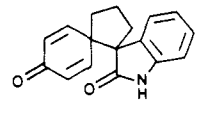
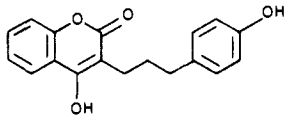
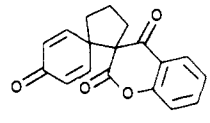
(9) Cecil, R.; Littler, J. S. *J. Chem. Soc. B* **1968**, 1420. Cecil, R.; Fear, A. J.; Littler, J. S. *Ibid.* **1970**, 632.

(10) Measured in $CDCl_3$ at 300 MHz.

(11) See for example the discussion by Scott, A. I. *Q. Rev., Chem. Soc.* **1965**, *19*, 1.

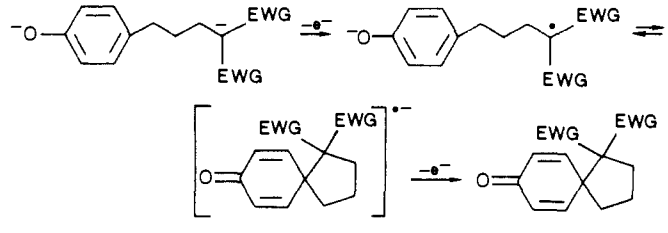
(12) McDonald, P. D.; Hamilton, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7752.

Table III

substrate	oxidn procedure	product	cyclizn yield, %
 **21**	dilute KOH, $K_3Fe(CN)_6$	 **26**	84
 **22**	dilute KOH, $K_3Fe(CN)_6$		0
 **23**	dilute KOH, $K_3Fe(CN)_6$	 **27**	42
 **24**	dilute KOH, $K_3Fe(CN)_6$	 **28**	57
 **25**	dilute KOH, $K_3Fe(CN)_6$		0
25	K_2IrCl_6	 **29**	33

probably fall into a similar category. Thus it is first necessary to convert the reactant predominantly to a dianion and then to oxidize the dianion by a one-electron oxidant to an open-radical anion, which can be in equilibrium with a cyclized radical anion. A rapid second one-electron oxidation of the cyclized intermediate will yield product. But if this were the whole story, then the unique value of K_2IrCl_6 in such cases as the cyclohexanedione **12**, malononitrile **19**, or benzopyrandione **25** would be unexplained, since in each case phenoxide to phenoxy radical oxidation would be feasible even with the weaker $K_3Fe(CN)_6$. Yet the substrates **16**, **18**, **19**, and **25** are recovered in good yield after treatment with $K_3Fe(CN)_6$. A rationalization of the K_2IrCl_6 effect is provided by the postulate that a prerequisite for coupling must be the one-electron oxidation of the *enolate unit of the reactant molecule to an enol radical*, an oxidation that may require in the cited systems the higher oxidation potential of K_2IrCl_6 (0.89 V) rather than that of the ferricyanide reagent (0.48 V). It is this enol radical that subsequently reacts with the phenolate ring (or possibly the phenoxy radical) to initiate the cyclization process, as illustrated in Scheme I.

Scheme I



Experimental Section

2-[3-(4-Hydroxyphenyl)propyl]-1,3-indandione (3). A 100-mL three-necked round-bottom flask equipped with a stopper, reflux condenser, magnetic stirrer, and a pressure-equalizing dropping funnel was flame-dried under a dry nitrogen atmosphere. Into the flask were placed 3.32 g of 50% sodium hydride dispersion in oil (0.0691 mol of NaH), dimethyl phthalate (4.46 g, 0.023 mol), and 20 mL of freshly distilled, anhydrous dimethylformamide. The mixture was stirred under nitrogen at 0 °C while methyl 5-(4-hydroxyphenyl)pentanoate (3.99 g, 0.0192 mol) in 10 mL of dry dimethylformamide was added dropwise. After the mixture was further stirred at room temperature for 10 min, the flask was immersed in an oil bath heated to 110 °C. The stirred reaction was heated at this temperature until gas evolution ceased (approximately 20 min). After cooling, the orange-red reaction mixture was poured into ice water, acidified with citric acid, and extracted once with methylene chloride. The organic layer was washed with water and saturated aqueous sodium bicarbonate, and then the organic layer was extracted with 5% aqueous sodium hydroxide. The hydroxide extract was reacidified to pH 5 and then extracted with methylene chloride. The methylene chloride layer was dried over anhydrous sodium sulfate and then evaporated to give the crude indanedione. Flash chromatography over silica gel (hexane–ether elution) gave essentially pure indandione **3** (1.67 g, 31% yield). The analytical sample was obtained from ether as off-white needles, mp 125–127 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.04–7.97 (2 H, m), 7.90–7.83 (2 H, m), 7.04 (2 H, d, J = 8 Hz), 6.76 (2 H, d, J = 8 Hz), 4.75 (1 H, s), 3.06 (1 H, t, J = 6 Hz), 2.58 (2 H, J = 7 Hz), 2.09–1.99 (2 H, m), 1.76–1.58 (2 H, m). IR ($CHCl_3$): 1739, 1705, 1592, 1508 cm^{-1}. Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.13; H, 5.75. Found: C, 77.00; H, 5.58.

2-[3-(2,6-Dimethyl-4-hydroxyphenyl)propyl]-1,3-indandione (4) was prepared in an analogous manner from dimethyl phthalate and methyl 5-(2,6-dimethyl-4-hydroxyphenyl)pentanoate and obtained in 30% yield,

Table IV

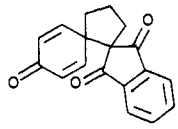
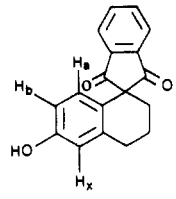
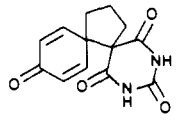
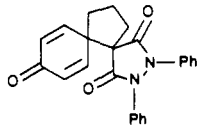
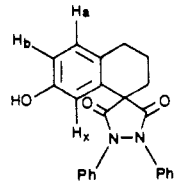
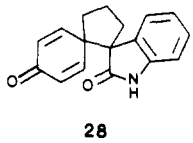
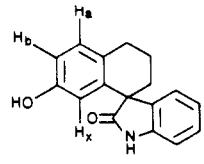
reactant	rearrangement product	yield, %
 7	 10	88
 26		0
 27	 30	38
 28	 31	91

Table V

	H_x (δ, J)	H_a (δ, J)	H_b (δ, J)
10	d, 6.58, J = 2.4	dd, 6.45, J = 8.4, 2.4	d, 6.36, J = 8.4
30	d, 6.30, J = 2.4	dd, 6.46, J = 8.4, 2.4	d, 6.70, J = 8.4
31	d, 6.03, J = 2.5	dd, 6.61, J = 8.0, 2.5	d, 6.87, J = 8.0
H_4-2-naphthol	d, 6.54, J = 2.0	dd, 6.58, J = 8.0, 2.0	d, 6.92, J = 8.0

mp 162–163 °C. Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.68; H, 6.29.

2-[4-(4-Hydroxyphenyl)butyl]-1,3-indandione (5). In a flame-dried, 50-mL two-necked flask equipped with a reflux condenser and a stopper were placed sodium hydride (60% in oil, 1.10 g, 27.6 mmol), dimethyl phthalate (1.8 mL, 9.2 mmol), and 7.7 mL of dry dimethylformamide. The condensation with methyl 6-(4-hydroxyphenyl)hexanoate[13] (1.70 g, 7.7 mmol) was carried out at 110 °C as described for indandione **3** and worked up by sodium hydroxide extraction as reported. There was obtained 1.40 g of a crude yellow oil containing by 300-MHz ^{1}H NMR analysis approximately 25–30% of the desired dione **5**. Attempted chromatography of the oil over silica gel (hexane–ether elution) led to extensive decomposition. However, approximately 60 mg of a homogeneous sample of dione **5** as an oil could be isolated and characterized. 300-MHz ^{1}H NMR ($CDCl_3$): δ 7.99–7.90 (2 H, m), 7.85–7.76 (2 H, m), 6.95 (2 H, d, J = 8 Hz), 6.72 (2 H, d, J = 8 Hz), 3.00 (1 H, t, J = 6 Hz), 2.43 (2 H, t, J = 7 Hz), 2.00–1.89 (2 H, m), 1.58–1.36 (4 H, m). HRMS: calcd for $C_{19}H_{18}O_3$ 294.1209, found 294.1256.

2-[3-(3-Hydroxyphenyl)propyl]-1,3-indandione (6) was obtained by the above procedure for **3** from dimethyl phthalate and methyl 5-(3-hydroxyphenyl)pentanoate and isolated after chromatography as a colorless oil in 40% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99–7.91 (2 H, m), 7.86–7.78 (2 H, m), 7.10 (1 H, t), 6.71 (1 H, d, J = 8 Hz), 6.63 (1 H, d, J = 8 Hz), 6.63 (1 H, d, J = 8 Hz), 6.59 (1 H, s), 4.79 (1 H, s), 3.02 (1 H, t, J = 6.5 Hz), 2.56 (2 H, t, J = 7 Hz), 2.05–1.94 (2 H, m), 1.77–1.64 (2 H, m). HRMS: calcd for $C_{18}H_{16}O_3$ 280.1099, found 280.1097.

Oxidative Cyclization of 2-[3-(4-Hydroxyphenyl)propyl]-1,3-indandione (3). To indandione **3** (85 mg, 0.30 mmol) in an Erlenmeyer flask was added 0.67 mL of 1 M potassium hydroxide solution in 10 mL of water. The mixture was stirred under nitrogen until complete solution occurred (ca. 20 min). This solution was added dropwise over 10 min to a two-phase, stirred mixture of potassium ferricyanide (401 mg, 1.22 mmol) in 20 mL of water and 20 mL of chloroform at 0–5 °C. The mixture was stirred for an additional 15 min and then quenched to pH 5 with citric acid. The mixture was extracted twice with 30 mL of chloroform, and the combined organic layers were washed twice with brine and then dried over anhydrous magnesium sulfate. The crude product remaining after evaporation of solvent was dissolved in 1:1 hexane–ethyl acetate, filtered through Florisil, and then evaporated to give 73 mg (88%) of chromatographically homogeneous spirocycle **7**. The analytical sample was recrystallized once from ether–hexane, mp 142–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03–7.92 (2 H, m), 7.92–7.80 (2 H, m), 7.00 (2 H, d, J = 10.5 Hz), 6.18 (2 H, d, J = 10.5 Hz), 2.50–2.25 (6 M, m). IR ($CHCl_3$): 1733, 1696, 1660, 1618, 1590, 1264 cm^{-1}. HRMS: calcd 278.0939, found 278.0917. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.52; H, 5.05.

Oxidative Cyclization of 2-[3-(2,6-Dimethyl-4-hydroxyphenyl)propyl]-1,3-indandione (4). To the indandione (0.25 g, 0.81 mmol) in a round-bottom flask was added 1 N KOH (1.79 mL). The mixture was stirred until the solid dissolved and then diluted with 30 mL of water. This solution was added dropwise over a period of 15 min to a two-phase mixture of 30 mL of water, 30 mL of chloroform and 3.2 mmol of potassium ferricyanide at 0 °C. The mixture was stirred for 25 min, and solid citric acid was added to pH 5. The layers were separated, and the aqueous phase was extracted with 2 × 70 mL of chloroform. The combined organic phases were washed with 2 × 100 mL of brine and dried over magnesium sulfate, and solvent was removed to yield a yellow solid. This solid was chromatographed on a silica gel column with 40% EtOAc–60% hexane to yield 0.142 g of **8** (57% yield), mp 123–124 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82–7.71 (4 H, m), 5.57 (1 H, s), 5.32 (1 H, s), 2.61–1.99 (6 H, m), 1.90 (3 H, s), 1.45 (3 H, s). ^{13}C NMR ($CDCl_3$): δ 201.52, 199.94, 199.48, 151.97, 149.51, 142.55, 142.21, 135.51, 135.16, 126.43, 123.90, 123.23, 122.61, 69.93, 69.88, 31.28, 30.97, 26.26, 22.78, 21.75. IR (Nujol mull): 3020, 2940, 1730, 1690, 1660, 1600, 1260, 1020, 850, 780 cm^{-1}. Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.34; H, 5.90.

Oxidative Cyclization of 2-[4-(4-Hydroxyphenyl)butyl]-1,3-indandione (5). A sample of crude indandione **5** (257 mg, 0.87 mmol) was dissolved in 1.92 mL of 1 M potassium hydroxide under nitrogen. Degassed water (29 mL) was added, and the red dianion was stirred for 15 min. The solution was then added over 10 min at 0 °C to a stirred two-phase mixture of potassium ferricyanide (1.15 g, 3.49 mmol) in 58 mL of water and 30 mL of chloroform. After an additional period of stirring for 15 min at 0 °C, the reaction mixture was quenched with excess 10% aqueous citric acid and filtered through a plug of Celite, and the aqueous layer was extracted with 3 × 20 mL of chloroform. The combined organic layers were washed with brine and then dried over anhydrous magnesium sulfate. Removal of solvent gave 87 mg of a yellow oil. Column chromatography (4:1 to 1:1 hexane–ether) and then recrystallization from ether gave 4 mg of colorless crystals of spirocycle **9**, mp 172–173 °C. ^{1}H NMR (300 MHz in $CDCl_3$): δ 7.89–7.85 (2 H, m), 7.80–7.70 (2 H, m), 7.09 (2 H, d, J = 10.2 Hz), 6.16 (2 H, d, J = 10.2 Hz), 2.00–1.90 (6 H, m), 1.84–1.78 (2 H, m). IR ($CHCl_3$): 1741, 1706, 1667, 1625 cm^{-1}. HRMS: calcd for $C_{19}H_{16}O_3$ 292.1099, found 292.1073.

Oxidative Cyclization of 2-[3-(3-Hydroxyphenyl)propyl]-1,3-indandione (6). The indandione **6** (40 mg, 0.143 mmol) was dissolved at room temperature in 5.7 mL of 0.5 M sodium carbonate solution to give a red solution. Methanol (2 mL) was added, and the mixture was stirred at 0 °C for 20 min. A solution of 1.70 mL of 0.5 M potassium ferricyanide solution was then added to the stirred solution over several minutes, and the mixture was stirred at 0 °C for 30 min. The reaction was quenched to pH 5 with citric acid and extracted with 3 × 20-mL portions of ether. Drying of the ether layers over anhydrous magnesium sulfate, followed by removal of solvent gave 41 mg of a 1.4 to 1 mixture of para to ortho coupling products (by ^{1}H NMR analysis). Column chromatography over silica gel, using 4:1 to 1:1 hexane–ethyl acetate gradient, gave first 12 mg of pure ortho product **11** and then 19 mg of the para product **10** (combined yield 79%).

The major product **10** was recrystallized (hexane–ether) to give a colorless solid, mp 166–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–8.02 (2 H, m), 7.90–7.87 (2 H, m), 6.49 (1 H, d, J = 2.4 Hz), 6.41 (1 H, dd, J = 8.4, 2.4 Hz), 6.33 (1 H, d, J = 8.4 Hz), 5.47 (1 H, s), 2.81 (2 H, t, J = 6.1 Hz), 2.09–2.02 (4 H, m). Anal. Calcd for $C_{18}H_{14}O$: C, 77.68; H, 5.05. Found: C, 77.52; H, 5.17.

The minor product **11** was recrystallized from ether–hexane, mp 229–230 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00–7.94 (2 H, m), 7.88–7.82 (2 H, m), 7.06 (1 H, t, J = 8, 2 Hz), 6.82 (1 H, d, J = 8 Hz), 6.43 (1 H, d, J = 8 Hz), 5.30 (1 H, s), 2.91 (2 H, br s), 2.01 (4 H, br

(13) Papa, D.; Schwenk, E.; Hawkin, H. *J. Am. Chem. Soc.* **1947**, *69*, 7018.

s). IR ($CHCl_3$): 3583, 1740, 1708, 1595, 1582, 1463 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O$: C, 77.68; H, 5.05. Found: C, 77.61; H, 5.08.

When the cyclization was carried out at 65 °C instead of 0 °C by the above procedure, workup and purification gave 86% of only the para coupling product **10**.

2-[3-(4-Hydroxyphenyl)propyl]-1,3-cyclohexanedione (12). Alkylation of the lithium derivative of 1,5-dimethoxy-1,4-cyclohexadiene following the exact procedure of Piers and Grierson[8] but with the use of 1-iodo-3-(4-methoxyphenyl)propane as alkylating agent, followed by in situ hydrolysis of the alkylation mixture with excess 10% hydrochloric acid and stirring for 30 min at room temperature, gave on workup and trituration with ether 39% yield of the unstable 2-[3-(4-methoxyphenyl)-propyl]-1,3-cyclohexanedione, mp 112–114 °C.

To a stirred solution of the above dione (1.04 g, 4.0 mmol) in 16 mL of dry methylene chloride at −78 °C under nitrogen was added 12 mL of 1 M boron tribromide in methylene chloride over 3 min. The red solution was stirred at −78 °C for 15 min and then at 0–5 °C for 2 h. The mixture was quenched by pouring into cold saturated ammonium chloride solution, the pH was adjusted to 6.0 with 0.1 M sodium hydroxide, and the organic layer was separated. The aqueous layer was extracted three times with 30 mL each of chloroform, and the combined organic layers were washed once with brine and then dried over anhydrous magnesium sulfate. Evaporation gave crude phenolic product, which was subjected to flash chromatography over silica gel using a gradient of 4:1 to 1:1 hexane–ethyl acetate. Solvent removal gave 679 mg of homogeneous phenolic diketone **12** as a yellow oil (69% yield). ^1H NMR (300 MHz, Me_2CO-d_6): δ 6.93 (2 H, d, J = 8 Hz), 6.62 (2 H, d, J = 8 Hz), 4.95 (2 H, br s), 2.51–2.17 (8 H, m), 1.95–1.80 (2 H, m), 1.62–1.47 (2 H, m). IR ($CHCl_3$): 1700, 1585, 1510, 1380 cm^{-1}. HRMS: calcd for $C_{15}H_{18}O_3$ 246.1255, found 246.1261.

Oxidative Cyclization of Diketone 12 with K_2IrCl_6. To 74 (0.30 mmol) mg of diketone **12** was added 0.75 mL 1 M KOH, and the resulting slurry was diluted with 10 mL of water. This mixture was stirred for 10 min and then added under nitrogen over 5 min to a stirred 4 °C solution of 434 mg (0.90 mmol) of potassium hexachloroiridate(IV) in 50 mL of water. The oxidation mixture was stirred for 15 min and then quenched with citric acid solution to pH 5. Solid sodium chloride was added to saturate the solution, and the aqueous mixture was extracted with 4 × 40 mL of ethyl acetate. The combined organic extracts were washed once with water and brine and then dried over anhydrous magnesium sulfate. Removal of solvent and flash chromatography on silica gel (3:1 ether–hexane) gave the spirocyclic triketone **13**, mp 124–126 °C (31 mg, 43% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 6.74 (2 H, d, J = 11 Hz), 6.30 (2 H, d, J = 11 Hz), 2.61–2.33 (7 H, m), 2.08 (2 H, m), 2.00–191 (3 H, m). IR: 1712, 1683, 1656, 1615 cm^{-1}. HRMS: calcd for $C_{15}H_{16}O_3$ 244.1099, found 244.1086. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.03; H, 6.68.

4-Methoxy-2,6-dimethylbenzaldehyde. To a stirred solution of 4-bromo-3,5-dimethylanisole (30.8 g, 0.143 mol) in 500 mL of tetrahydrofuran at −78 °C under argon was added 100 mL of 1.45 M *n*-butyllithium in hexanes dropwise over a period of 1 h. The mixture was stirred at −78 °C for 30 min, and then anhydrous dimethylformamide (7.45 mL, 0.145 mol) was added dropwise over a period of 10 min. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stir for 1 h. The mixture was poured over 500 mL of crushed ice, and then the quenched reaction was acidified to pH 1 with 6 N hydrochloric acid. The layers were separated, the aqueous layer was extracted with 3 × 100 mL of ether, and all organic layers were combined. The organic layer was washed with 2 × 150 mL of brine and then dried over anhydrous magnesium sulfate. Solvent removal gave a yellow solid, which was crystallized from hexane to yield 12.3 g (53%) of white, crystalline aldehyde, mp 40–41 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 10.40 (1 H, s), 6.51 (2 H, s), 3.77 (3 H, s), 2.53 (6 H, s). MS: m/e 164 (M^+), 163, 135, 91, 77. Anal. Calcd for $C_{10}H_{12}O$: C, 73.15; H, 7.37. Found: C, 73.19; H, 7.47.

4-(4-Methoxy-2,6-dimethylphenyl)-2-butanone. To a stirred solution of 4-methoxy-2,6-dimethylbenzaldehyde (4.0 g, 0.024 mol) in 150 mL of ethanol were added 17.7 mL (0.244 mol) of acetone and 0.1 g of powdered sodium hydroxide. The mixture was stirred at 25 °C for 24 h. Solvent was removed at reduced pressure, and 200 mL of methylene chloride was added to the residue. After 100 mL of water was added, the organic layer was separated, washed with 100 mL of brine, and then dried over anhydrous magnesium sulfate. Solvent removal gave 3.6 g of the crude arylideneacetone, which was dissolved in 200 mL of methanol. To the solution was added 150 mg of 5% Pd–C, and the mixture was hydrogenated on a Parr shaker at 50 psi of hydrogen for 3 h at room temperature. After removal of the catalyst by filtration through Celite, the solvent was removed to yield on trituration with methanol 3.4 g (69%) of the pure butanone, mp 50–51 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 6.55 (2 H, s), 3.73 (3 H, s), 2.52 (t, J = 9.6 Hz, 2 H), 2.81 (t, J = 9.6 Hz, 2 H), 2.26 (6 H, s), 2.15 (3 H, s). MS: m/e 206 (M^+), 150, 149, 91. IR: 3040, 2920, 2900, 1710, 1650, 1600, 1480, 1460, 1310, 1290 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 76.17; H, 8.93.

3-(4-Methoxy-2,6-dimethylphenyl)propionic Acid. To a stirred solution of (carbethoxymethyl)triphenylphosphonium bromide (14.9 g, 0.036 mol) in 300 mL of anhydrous dimethylformamide under argon at 25 °C was added 0.072 mol of freshly prepared lithium methoxide in methanol (50 mL). This solution was stirred for 30 min and then was added to a solution of 4-methoxy-2,6-dimethylbenzaldehyde (5.88 g, 0.036 mol) in 50 mL of anhydrous dimethylformamide. The reaction mixture was stirred at 25 °C under N_2 for 3 days and then poured onto 200 mL of crushed ice, and the resultant mixture was extracted with 3 × 200 mL of ether. The organic phase was washed with 2 × 150 mL of brine and then dried over anhydrous magnesium sulfate. Removal of solvent gave a yellow oil, which was flash chromatographed over silica gel with methylene chloride to yield 6.10 g (78%) of the yellow, crystalline cinnamic acid. The crystals were dissolved in 250 mL of methanol, 100 mg of 5% Pd–C was added, and the mixture was hydrogenated on a Parr apparatus at 50 psi of H_2 for 3 h at 25 °C. The catalyst was removed by filtration through Celite, and removal of solvent gave 6.0 g of the clear dihydro ester. This was directly saponified by stirring with 200 mL of 3 N sodium hydroxide in 50% aqueous methanol at 25 °C overnight. Removal of most of the solvent at reduced pressure, acidification to pH 1 with 1 N hydrochloric acid, and extraction with 3 × 250 mL of ethyl acetate gave an organic layer, which was washed with 2 × 100 mL of brine, dried over anhydrous magnesium sulfate, and evaporated to yield 3.7 g (50.2%) of crystalline white solid, mp 85–87 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 6.57 (2 H, s), 3.57 (3 H, s), 2.92 (2 H, t, J = 8.4 Hz), 2.46 (2 H, t, J = 8.4 Hz), 2.30 (6 H, s). MS: m/e 208 (M^+), 149, 91, 77. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.49; H, 8.01.

Methyl 5-(4-Hydroxy-2,6-dimethylphenyl)-3-oxopentanoate (14). To a solution of 3-(4-methoxy-2,6-dimethylphenyl)propionic acid (0.75 g, 3.6 mmol) in 50 mL of dry methylene chloride under argon was added 4.0 mL of thionyl chloride. The solution was refluxed for 90 min, the solvent was removed and replaced by 50 mL of benzene, and then this solvent was also removed at reduced pressure. This crude acid chloride in a few drops of benzene was added to a solution of 0.477 g (3.31 mmol) Meldrum's acid in 0.54 mL of pyridine held at 0 °C under argon. After being stirred for 1 h at 0 °C, the reaction mixture was poured onto 50 cc of ice and extracted with 3 × 100 mL methylene chloride. The organic phase was washed with 2 × 50 mL saturated ammonium chloride and then 2 × 50 mL of brine, dried over anhydrous sodium sulfate, and evaporated to yield 1.05 g of crude acylated Meldrum's acid as a yellow oil. The crude oil was refluxed for 3.5 h in 50 mL of methanol, and the solvent was evaporated to yield the methoxy β-keto ester (0.78 g, 80%).

The above methoxy compound was dissolved in 60 mL of methylene chloride and cooled to −78 °C under argon, and 13.3 mL of 1 M boron tribromide in methylene chloride was added dropwise. The reaction mixture was warmed to 0 °C over a period of 2 h, poured onto 50 mL of ice, and extracted with 2 × 100 mL of methylene chloride. The organic phase was washed with 2 × 100 mL of methylene chloride. The organic phase was washed with 2 × 75 mL of brine, dried over anhydrous magnesium sulfate, and evaporated to a yellow oil. Purification by flash chromatography (silica gel, CH_2Cl_2) gave 0.38 g (52%) of the pure phenolic β-keto ester as a nearly colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 6.47 (2 H, s), 4.7–4.6 (1 H, br s), 3.71 (3 H, s), 3.42 (2 H, s), 2.82 (2 H, t), 2.63 (2 H, t), 2.21 (6 H, s). HRMS: calcd for $C_{14}H_{18}O_4$ 250.1204, found 250.1223.

Methyl 6-(4-Hydroxy-2,6-dimethylphenyl)-2,4-dioxohexanoate (15). To a solution of 4-(4-methoxy-2,6-dimethylphenyl)-2-butanone (1.0 g, 4.85 mmol) and dimethyl oxalate (0.63 g, 5.34 mmol) in 75 mL of dry tetrahydrofuran at 0 °C was added sodium hydride (0.12 g, 5.34 mmol). The reaction mixture was warmed to room temperature and stirred for 16 h. The mixture was then poured over 100 mL of ice and extracted with 3 × 100 mL of ether. The organic phase was washed with 2 × 100 mL of brine, dried over anhydrous magnesium sulfate, and then evaporated to an orange oil. This was purified by flash chromatography over silica gel using methylene chloride to yield 0.55 g of a yellow oil. This crude methoxy diketo ester was dissolved in 100 mL of methylene chloride and cooled to −78 °C, and then 12.5 mL of 1 M boron tribromide in methylene chloride was added dropwise over a 30-min period. The mixture was stirred at −78 °C for 2 h, warmed to 0 °C, and poured onto 100 mL of ice. The organic phase was washed with 2 × 50 mL of brine, dried over anhydrous magnesium sulfate, and then evaporated to give 0.50 g of a brown oil. This was purified by preparative TLC (silica gel, CH_2Cl_2) to give 0.150 g of a pure yellow oil, 11% yield. ^1H NMR (300 MHz, $CDCl_3$): δ 6.51 (2 H, s), 6.30 (1 H, s), 5.30 (2 H, s), 3.88 (3 H, s), 2.88 (2 H, t), 2.55 (2 H, t), 2.22 (6 H, s). MS: m/e 218, 175, 135,

91. IR (film): 3400, 3010, 2970, 1730, 1630, 1450, 1130, 1020, 900, 730 cm^{-1}.

Diethyl [3-(3-Hydroxyphenyl)propyl]malonate (16). The precursor [3-(3-methoxyphenyl)propyl]malonic acid was prepared from 3-methoxybenzaldehyde according to the procedure of Gardner.[14] Esterification by gentle reflux in absolute ethanol containing concentrated sulfuric acid gave a 73% yield of the corresponding diethyl ester.

Demethylation of the diester with BBr_3 as described previously, followed by column chromatography over silica gel (1:3 acetone–pentane), gave a 76% yield of malonate **16** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.16 (1 H, t, J = 8 Hz), 6.76 (1 H, d, J = 8 Hz), 6.67 (2 H, br s), 4.74 (1 H, s), 4.21 (4 H, q, J = 7 Hz), 3.62 (2 H, t, J = 8 Hz), 3.36 (1 H, t, J = 7 Hz), 2.03–1.92 (2 H, m), 1.74–1.66 (2 H, m), 1.29 (6 H, t, J = 7 Hz). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.54. Found: C, 65.29; H, 7.47.

2,2-Dimethyl-5-[(3-hydroxyphenyl)propyl]-1,3-dioxane-4,6-dione (17). To 900 mg of malonic ester **16** in a 250-mL flask was added 90 mL of 3 M sodium hydroxide. The mixture was stirred for 3 days, acidified to pH 3, saturated with salt, and repeatedly extracted with ethyl acetate. The organic layers were combined, dried over anhydrous magnesium sulfate, and then evaporated to give 859 mg of the crude malonic acid.

To 574 mg (2.41 mmol) of this malonic acid in a dry test tube under nitrogen were added 0.50 mL (5.3 mmol) of acetic anhydride, 3 drops of concentrated sulfuric acid, and 0.21 mL (2.9 mmol) of acetone. The yellow solution was briefly stirred at 25 °C and then placed in the refrigerator at 0 °C for 2 days, during which a small amount of solid precipitated. This solid was filtered, the filtrate was diluted with 5 mL of methylene chloride, and the pH of the stirred mixture was adjusted to 5 with dilute sodium bicarbonate. Extraction with methylene chloride and drying of the organic layer over anhydrous magnesium sulfate were followed by removal of the solvent to give the crude *O*-acetyl derivative of the Meldrum's acid. Chromatography over silica gel (2:1 ether–hexane elution) and then recrystallization from ether–hexane gave 366 mg of the *O*-acetyl derivative, mp 91–92 °C. The *O*-acetyl compound was dissolved in 20 mL of ether, 50 mL of 10% sodium carbonate was added, and the mixture was stirred vigorously for 4 h at 25 °C. Acidification to pH 3, extraction with ethyl acetate, drying over magnesium sulfate, solvent removal, and crystallization from ether gave 310 mg (67% yield) of pure **17**, mp 123–124 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (1 H, t, J = 8 Hz), 6.79 (1 H, d, J = 8 Hz), 6.71 (1 H, s), 6.49 (1 H, d, J = 8 Hz), 5.17 (1 H, br s), 3.53 (1 H, t, J = 5 Hz), 2.68 (2 H, t, J = 7 Hz), 2.23–2.12 (2 H, m), 1.89–1.75 (2 H, m), 1.79 (6 H, s). IR ($CHCl_3$): 3582, 1729, 1582, 1250, 1076 cm^{-1}. MS: m/e 278 (M^+), 262, 220, 194, 174, 148, 120. Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.53; H, 6.46.

Dimethyl [3-(4-Hydroxyphenyl)propyl]malonate (18). To a stirred solution of dimethyl [3-(4-methoxyphenyl)propyl]malonate (1.20 g, 4.28 mmol) in 17 mL of dry methylene chloride at −78 °C was slowly added 21.4 mL of 1 M boron tribromide in methylene chloride (21.4 mmol). The red solution was stirred at −78 °C for 15 min and then for 2 h at 0 °C. The mixture was poured into 80 mL of cold, saturated ammonium chloride solution, and the pH was adjusted to 6 with 0.1 M sodium hydroxide. The layers were separated, and the aqueous layer was extracted with 3 × 20 mL of chloroform. The combined organic layers were dried over magnesium sulfate, the solvent was evaporated, and the product was chromatographed over silica gel (1:1 hexane–ether) to give 863 mg (76% yield) of the colorless diester **18** as a clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.00 (2 H, d, J = 9 Hz), 6.71 (2 H, d, J = 9 Hz), 4.84 (1 H, s), 3.70 (6 H, s), 3.35 (1 H, t, J = 7 Hz), 2.54 (2 H, t, J = 7 Hz), 1.94–1.86 (2 H, m), 1.62–1.54 (2 H, m). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 62.48; H, 6.84.

[3-(4-Hydroxyphenyl)propyl]malononitrile (19). To a slurry of 60% NaH–oil dispersion (3.2 g) in 60 mL of dry dimethyl sulfoxide at 0 °C under nitrogen was added dropwise a solution of malononitrile (2.64 g, 29.4 mmol) in 12 mL of dimethyl sulfoxide. Hydrogen gas evolved during the addition. The slurry was stirred at 0 °C for 30 min and then allowed to warm to 25 °C. To the slurry was now added 3-(4-methoxyphenyl)propyl iodide (5.8 g, 21.1 mmol) in 12 mL of dimethyl sulfoxide over 10 min. The reaction was stirred 6 h, quenched with saturated ammonium chloride solution (80 mL), and then extracted with 3 × 50 mL of ethyl acetate. The organic extracts were washed with water, dried over anhydrous magnesium sulfate, and then evaporated to give 4.28 g of crude malononitrile product. This was directly demethylated with boron tribromide as previously described to yield a brown oil, which on silica gel column chromatography (hexane–EtOAc, 3:1) gave 0.76 g pure malononitrile **19** (19% yield overall). ^1H NMR (300 MHz, $CDCl_3$): δ 8.14 (1 H, s), 7.01 (2 H, d, J = 8 Hz), 6.73 2 H, d, J = 8 Hz), 4.46 (1 H, t, J = 7 Hz), 2.61 (2 H, t, J = 7 Hz), 2.12–1.96 (2 H, m), 1.89–1.76 (2 H, m). IR ($CHCl_3$): 2259, 1613, 1595, 1510, 1443 cm^{-1}. HRMS: calcd for $C_{12}H_{12}N_2O$ 200.0945, found 200.0972.

Cyclization of Malononitrile 19. To 67 mg (0.33 mmol) of malononitrile **19** in 30 mL of 0.5 M sodium carbonate being stirred at room temperature was added 435 mg (0.90 mmol) of potassium hexachloroiridate powder in portions over a period of 1 min. The reaction mixture was quenched by neutralization with excess citric acid and extracted with ethyl acetate. The organic extract was washed with brine and dried over magnesium sulfate. Evaporation of solvent followed by column chromatography (silica gel, 1:1 hexane–ether) gave 31% of the dienone **20** as a white solid. Recrystallization gave off-white needles, mp 99–100 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (2 H, d, J = 10.2 Hz), 6.50 (2 H, d, J = 10.2 Hz), 2.77 (2 H, t, J = 7.2 Hz), 2.33–2.16 (4 H, m). IR ($CDCl_3$): 2242, 1669, 1627, 1400, 1252, 850 cm^{-1}. HMRS: calcd for $C_{12}H_{10}N_2O$ 198.0793, found 198.0829.

5-[3-(4-Hydroxyphenyl)propyl]-2,4,6-pyrimidinetrione (21). To a slurry of 4.1 g (32 mmol) of barbituric acid in 32 mL of dry pyridine at room temperature was added dropwise 7.00 g (35 mmol) of 3-(4-methoxyphenyl)propionyl chloride. The mixture was stirred for 18 h and then poured onto ice. The pH was adjusted to 1 with 6 N hydrochloric acid, the mixture was allowed to stand 18 h at 0 °C, and the precipitated acylbarbituric acid was filtered, washed with cold water, and dried in a vacuum desiccator to yield 7.6 g (74% yield) of an off-white solid, mp 244–246 °C.

The crude acid (4.4 g, 15 mmol) was slurried in 50 mL of acetic acid. To the stirred slurry was added portionwise over 2 min 2.00 g (32 mmol) of sodium cyanoborohydride. Upon the mixture being warmed to 60 °C, the solid went into solution. The solution was held at 60 °C for 1 h and then allowed to cool to room temperature. The mixture was poured onto ice, acidified to pH 3, cooled to 0 °C overnight, and then filtered to yield 3.89 g (93% yield) of nearly pure [(methoxyphenyl)propyl]barbituric acid, mp 190–191 °C.

Demethylation with boron tribromide in methylene chloride as previously described, extraction with 5% sodium hydroxide, and acidification of the aqueous layer to pH 1 gave on standing at 0 °C a 93% yield of the pure alkylbarbituric acid **21**, mp 210–211 °C (recrystallized from ethanol). ^1H NMR (300 MHz, DMSO-d_6): δ 9.05 (1 H, s), 6.89 (2 H, d, J = 8 Hz), 6.59 (2 H, d, J = 8 Hz), 3.46 (1 H, t, J = 4 Hz), 2.37 (2 H, t, J = 7 Hz), 1.88–1.77 (2 H, m), 1.50–1.36 (2 H, m). Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.28; N, 10.68. Found: C, 58.99; H, 5.43; N, 10.46.

Oxidation of Pyrimidinetrione 21 with $K_3Fe(CN)_6$. The pyrimidinetrione **21** (79 mg, 0.3 mmol) was dissolved in 10 mL of 0.1 M aqueous potassium hydroxide. This solution was added over 10 min to a 4 °C stirred solution of 400 mg of potassium ferricyanide in 20 mL of water. After being stirred for 15 min at 0 °C, the reaction mixture was quenched with citric acid to pH 5 and extracted with 2 × 20 mL of ethyl acetate. The solvent was dried, and the solution was filtered through Florisil and evaporated to give 65 mg (84%) of essentially pure spirocyclization product **26**. Recrystallization from 2-propanol gave a white powdery product, mp 240–242 °C dec. ^1H NMR (300 MHz, Me_2CO-d_6): δ 10.07 (1 H, s), 6.87 (2 H, d, J = 10.2 Hz), 6.12 (2 H, d, J = 10.2 Hz), 2.58 (2 H, t, J = 8.4 Hz), 2.20–2.13 (2 H, m), 2.06–2.00 (2 H, m). IR (Nujol): 3308, 1759, 1700, 1666, 1622 cm^{-1}. Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65, N, 10.76. Found: C, 59.73; H, 4.56; N, 10.65.

5-[4-(4-Hydroxyphenyl)butyl]-2,4,6-pyrimidinetrione (22). To a stirred mixture of barbituric acid (11.5 g, 0.09 mol) in 100 mL of dry pyridine at room temperature was added dropwise 4-(4-methoxyphenyl)butyryl chloride (0.09 mol, freshly distilled). A moderate exotherm occurred. The mixture was stirred 16 h at 25 °C, poured into 400 mL of ice water, acidified to pH 2, and allowed to stand at 0 °C overnight. The filtered crude solid was dried and recrystallized from methanol to yield 10.6 g (35%) of the acylbarbituric acid, mp 199–200 °C.

To a stirred slurry of 6.0 g (20 mmol) of this acylbarbituric acid in 100 mL of acetic acid was added in portions over several minutes 2.48 g (39.5 mmol) of sodium cyanoborohydride.[15] The slurry was warmed to 60 °C to give a clear solution. After 90 min, the solution was cooled and poured into ice water. The precipitate was allowed to stand at 0 °C for 18 h, filtered, dried, and recrystallized from ethanol to give 4.96 g (87%) of 5-[4-(4-methoxyphenyl)butyl]-2,4,6-pyrimidinetrione, mp 184–186 °C. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 61.97; H, 6.29; N, 9.38.

Demethylation of this methoxy compound (1.0 g, 3.5 mmol) in 14 mL of methylene chloride with boron tribromide (14 mL of 1 M, in CH_2Cl_2, 14 mmol) at −78 °C for 20 min and then at 0 °C for 2 h, followed by

(14) Gardner, P. D.; Horton, W. J.; Thompson, G.; Twelves, R. R. *J. Am. Chem. Soc.* **1952**, *74*, 5527.

(15) Nutaitis, C. F.; Schultz, R. A.; Obaza, J.; Smith, R. X. *J. Org. Chem.* **1980**, *45*, 4606.

alkali extraction of the reaction mixture and subsequent reacidification to pH 3, gave an off-white powder, which was recrystallized from aqueous methanol to give 0.83 g (86% yield) of phenolic barbituric acid **22**, mp 182 °C dec. ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.12 (1 H, s), 9.00 (1 H, s), 6.87 (2 H, d, J = 8.1 Hz), 6.59 (2 H, d, J = 8.1 Hz), 3.48 (1 H, t, J = 4.8 Hz), 2.35 (2 H, t, J = 7 Hz), 1.92–1.78 (2 H, m), 1.48–1.34 (2 H, m), 1.25–1.13 (2 H, m). IR (Nujol): 1721, 1672, 1566, 1515 cm^{-1}. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.66; H, 5.77; N, 10.09.

Attempts to cyclize **22** with $K_3Fe(CN)_6$ or K_2IrCl_6 led to severe mixtures, which by NMR analysis did not show the presence of the anticipated spirocyclization product.

1,2-Diphenyl-4-[3-(4-methoxyphenyl)propyl]-3,5-pyrazolinedione. To a stirred solution of commercial potassium *tert*-butoxide (1.12 g, 0.01 mol) in 25 mL of anhydrous methanol was added 1.57 g (0.0115 mol) of dimethyl malonate. The solution was stirred under nitrogen at 50 °C, and to it was added 2.55 g (0.01 mol) of 3-(4-methoxyphenyl)propyl iodide dropwise over several minutes. The solution was refluxed 16 h, the solvent was removed under vacuum, saturated ammonium chloride solution (40 mL) was added, and the mixture was extracted with 3 × 40 mL of ether. The combined ether extracts were washed once with water, dried over anhydrous magnesium sulfate, and evaporated. The crude oily product was chromatographed on silica gel (4:1 hexane–ether) to yield 1.26 g (45%) of a colorless oil. This arylpropyl malonic ester was directly used in the second step.

To the above ester (1.21 g, 4.33 mmol) in 20 mL of absolute ethanol was added 0.535 g (4.77 mmol) of commercial potassium *tert*-butoxide, followed by 0.878 g (4.77 mmol) of 1,2-diphenylhydrazine. All solvent was removed at reduced pressure, and the dry residue was heated under nitrogen at 200 °C for 30 min to give a red melt. After being cooled to room temperature, the red mass was triturated with 30 mL of 5% sodium hydroxide, and the aqueous layer was washed with ether. The aqueous layer was now acidified with dilute hydrochloric acid to pH 2 and then extracted with 3 × 50 mL of ether. The combined portions of ether from this second extraction were washed once with brine and then dried over anhydrous magnesium sulfate. Solvent removal gave 1.33 g of a yellow solid, which was recrystallized from ether to yield 1.11 g (66%) of off-white needles, mp 96–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (8 H, m), 7.24–7.18 (2 H, m), 7.15 (2 H, d, J = 8 Hz), 6.78 (2 H, d, J = 8 Hz), 3.75 (3 H, s), 3.38 (1 H, t, J = 6 Hz), 2.59 (2 H, t, J = 7 Hz), 2.13–2.05 (2 H, m), 1.91–1.78 (2 H, m). IR ($CHCl_3$): 1750, 1718, 1596, 1512, 1493, 1202 cm^{-1}. Anal. Calcd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04; N, 6.99. Found: C, 74.77; H, 6.20; N, 7.13.

Preparation and Cyclization of Pyrazolinedione 23. The demethylation of 976 mg (4 mmol) of the above methoxy compound was carried out with BBr_3 in methylene chloride as described earlier to give a 67% yield of the phenolic pyrazolinedione **23**, mp 171–176 °C dec. Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.20; H, 5.82; N, 7.48.

Oxidative cyclization of 116 mg (0.3 mmol) of phenol **23** with potassium ferricyanide, as described for **3**, gave in 42% yield the crystalline dienone **27**, mp 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.15 (10 H, m), 7.00 (2 H, d, J = 11 Hz), 6.29 (2 H, d, J = 11 Hz), 2.54–2.51 (2 H, m), 2.36–2.30 (4 H, m). IR ($CHCl_3$): 1742, 1708, 1662, 1621, 1304 cm^{-1}. Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.29. Found: C, 74.69; H, 5.16; N, 7.12.

3-[3-(4-Hydroxyphenyl)propyloxindole (24). Alkylation of the dianion of oxindole on a 5-mmol scale with 3-(4-methoxyphenyl)propyl iodide following the procedure of Kende and Hodges[16] gave 41% yield of the C-3 monoalkylation product after silica gel column chromatography (3:1 ether–hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (1 H, br s), 7.22–7.14 (2 H, m), 7.17–6.97 (3 H, m), 6.86–6.75 (3 H, m), 3.76 (3 H, s), 3.46 (1 H, t, J = 6 Hz), 2.60–2.52 (2 H, m), 2.05–1.93 (2 H, m), 1.75–1.57 (2 H, m). MS: m/e 281 (M^+).

Boron tribromide demethylation as previously described, followed by silica gel column chromatography (4:1 to 1:1 hexane–ethyl acetate) gave a 79% yield of the phenolic oxindole **24**, mp 133–134 °C (recrystallized from hexane–ethyl acetate). ^{1}H NMR (300 MHz, Me_2CO-d_6): δ 9.35 (1 H, s), 8.04 (1 H, s), 7.18 (1 H, d, J = 7 Hz), 7.11 (1 H, t, J = 7 Hz), 6.93–6.88 (3 H, m), 6.83 (1 H, d, J = 7 Hz), 6.66 (2 H, d, J = 8 Hz), 3.37 (1 H, t, J = 6 Hz), 2.46 (2 H, t, J = 8 Hz), 1.96–1.80 (2 H, m), 1.63–1.50 (2 H, m). HRMS: calcd for $C_{17}H_{17}NO_2$ 267.1259, found 267.1274. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.39; H, 6.41; N, 5.24. Found: C, 76.09; H, 6.55; N, 5.14.

Oxidation of Oxindole 24. A solution of 80 mg (0.3 mmol) of oxindole **24** in a mixture of 1.8 mL of 1 M potassium hydroxide in 10 mL of water was added over 10 min to a two-phase mixture of 400 mg of potassium ferricyanide in 20 mL of chloroform and 20 mL of water at 4 °C. After 15 min of stirring, the mixture was brought to pH 5 with citric acid, and the reaction mixture was extracted with 2 × 30 mL of chloroform. The organic layers were washed with brine and then dried over anhydrous magnesium sulfate. Solvent removal followed by silica gel column chromatography (4:1 $CHCl_3$–EtOAc) gave 45 mg (57% yield) of white crystalline dienone **28**, mp 214–216 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (1 H, s), 7.17–7.07 (2 H, m), 7.00–6.91 (3 H, m), 6.78 (1 H, d, J = 8 Hz), 6.23 (1 H, dd, J = 10, 2 Hz), 6.14 (1 H, dd, J = 10, 2 Hz), 2.73–2.66 (1 H, m), 2.48–2.28 (4 H, m), 2.10–2.00 (1 H, m). IR ($CHCl_3$): 3452, 1712, 1670, 1625, 1477 cm^{-1}. HRMS: calcd for $C_{17}H_{15}NO_2$ 265.1103, found 265.1138. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.57; H, 5.93; N, 5.31.

3-[3-(4-Hydroxyphenyl)propyl]-4-hydroxycoumarin (25). To a stirred solution of 4-hydroxycoumarin (5.6 g, 34.3 mmol) in 52 mL of dry pyridine containing 7 drops of piperidine was added neat 3-(4-methoxyphenyl)propionyl chloride (10.2 g, 51.5 mmol) over 5 min. The solution was brought to reflux for 16 h, cooled, and poured into 200 mL of ice. The mixture was acidified to pH 2 with 6 M hydrochloric acid and then allowed to stand at 0 °C overnight. The precipitated solid was filtered, and the filtrate was adjusted to pH 3 and extracted with 3 × 60 mL of ethyl acetate. The combined organic layers and the precipitate were mixed, and the solution was washed with water and then brine and then dried over anhydrous magnesium sulfate. Solvent removal gave 6.3 g (57% yield) of the pale yellow crude acylcoumarin, used directly in the subsequent reduction. An analytical sample was obtained by recrystallization from ethanol as yellow-brown needles, mp 148–149 °C. Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.03; H, 4.91.

To a slurry of the above acylcoumarin (0.98 g, 3.0 mmol) in 10 mL of acetic acid was added 0.399 g (6.35 mmol) of sodium cyanoborohydride[15] in portions over 2 min. The mixture was warmed to 60 °C for 1 h, allowed to cool, poured into ice, acidified to pH 3, and allowed to stand overnight at 0 °C. Filtration and water wash, followed by recrystallization from ethyl acetate–hexane gave 0.81 g (87%) of pure alkylcoumarin, mp 166–167 °C. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.38; H, 5.53.

Demethylation with boron tribromide as described previously, followed by recrystallization of the product from 1:1 chloroform–ethyl acetate, gave a nearly quantitative yield of the phenolic coumarin **25**, white crystals melting at 142–143 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.03 (1 H, br s), 7.86 (1 H, dd, J = 7, 1 Hz), 7.53 (1 H, dt, J = 7, 1 Hz), 7.30 (1 H, d, J = 7 Hz), 7.28 (1 H, t, J = 7 Hz), 6.92 (2 H, d, J = 8 Hz), 6.59 (2 H, d, J = 8 Hz), 2.47 (4 H, m), 1.62 (2 H). HRMS: calcd for $C_{18}H_{16}O_4$ 296.1048, found 296.1046.

Oxidation of Coumarin 25 with K_2IrCl_6. A solution of 74 mg (0.25 mmol) of coumarin **25** was dissolved in 0.6 mL of 1 M potassium hydroxide, 12 mL of water was added, and the solution was slowly added over 5 min to a solution of 434 mg (0.90 mmol) of potassium hexachloroiridate in 30 mL of water at 0 °C. The mixture was stirred for 15 min at 0 °C and then neutralized with citric acid, sodium chloride was added to saturate the water, and the product was extracted with 2 × 40 mL of ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate. Solvent removal followed by column chromatography (silica gel, 1:1 chloroform–ethyl acetate) gave 24 mg (33% yield) of pale yellow dienone **29**, recrystallized from acetone as yellow crystals, mp 166–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (1 H, dd, J = 8, 1 Hz), 7.58 (1 H, dt, J = 8, 1 Hz), 7.23–7.16 (1 H, m), 7.07 (1 H, d, J = 8 Hz), 6.79 (1 H, dd, J = 11, 3 Hz), 6.64 (1 H, dd, J = 11, 3 Hz), 6.02 (2 H, d, J = 11 Hz), 3.00–2.91 (1 H, m), 2.67–2.58 (1 H, m), 2.36–2.20 (3 H, m), 1.97–1.91 (1 H, m). IR ($CDCl_3$): 1758, 1682, 1660, 1604, 1453, 1302 cm^{-1}. HRMS: calcd for $C_{18}H_{14}O_4$ 294.0892, found 294.0887.

Dienone–Phenol Rearrangement of Indandione Spirocycle 7. To a stirred slurry of spirocyclic dienone **7** (42 mg, 0.15 mmol) in 5 mL of anhydrous methylene chloride at −78 °C under dry nitrogen was added trifluoromethanesulfonic acid (1.1 mL, 12 mmol) dropwise. The stirred reaction mixture was then held at 0–5 °C for 2 h. The solution was slowly poured into 10 mL of ice-cold 1 M ammonium hydroxide. The resulting mixture was then extracted with 3 × 10 mL of chloroform. The combined chloroform extracts were dried over magnesium sulfate. Removal of solvent followed by chromatography of the crude product over silica gel using 2:1 ether–hexane gave 36 mg (88% yield) of the tetrahydronaphthol **10**, mp 166–167 °C. The TLC, mp, and 300-MHz NMR spectrum of this product were identical with those of the major product **10** from oxidative cyclization of indandione **6** described earlier.

Dienone–Phenol Rearrangement of Pyrazolinedione 27. The rearrangement of 115 mg (0.30 mmol) of the pyrazolinedione spirocycle **27** was carried out as in the preceding example. Column chromatography of the crude product over silica gel using 10:1 chloroform–ethyl acetate led to 4% recovery of **27** and 44 mg (38%) of pure crystalline tetrahydronaphthol derivative **30**, mp 257–258 °C. ^{1}H NMR (300 MHz,

(16) Kende, A. S.; Hodges, J. C. *Synth. Commun.* **1982**, *12*, 1.

$CDCl_3$): δ 7.40–7.30 (8 H, m), 7.21 (2 H, t, J = 8 Hz), 6.70 (1 H, d, J = 8.4 Hz), 6.46 (1 H, dd, J = 8.4, 2.4 Hz), 6.29 (1 H, d, J = 2.4 Hz), 6.02 (1 H, s), 2.74 (2 H, t, J = 6 Hz), 2.32–2.23 (2 H, m), 2.16–2.07 (2 H, m). IR ($CHCl_3$): 3585, 1751, 1710, 1598, 1500, 1297 cm^{-1}. HRMS: calcd 384.1473, found 384.1487. Anal. Calcd for $C_{24}H_{20}N_2O_3$: C, 74.98; H, 5.24; N, 7.25. Found: C, 74.80; H, 5.26; N, 7.31.

Dienone–Phenol Rearrangement of Oxindole 28. The rearrangement of 80 mg (0.30 mmol) of the oxindole dienone **28** was carried out as described above for **7**. Column chromatography of the crude reaction mixture over silica gel using 2:1 chloroform–ethyl acetate gave 73 mg (91% yield) of pure, crystalline tetrahydronaphthol derivative **31**, mp 244–245 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.72 (1 H, br s), 7.20 (1 H, dt, J = 9.6, 1.0 Hz), 7.03–6.93 (3 H, m), 6.87 (1 H, d, J = 8.0 Hz), 6.61 (1 H, dd, J = 8.0, 2.5 Hz), 6.03 (1 H, d, J = 2.5 Hz), 4.93 (1 H, br s), 2.90–2.85 (2 H, m), 2.29–2.14 (2 H, m), 2.02–1.90 (2 H, m). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.59; H, 5.98; N, 5.55.

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Organobis(cuprates): A New Class of Reagents and Method for Spiroannelation[1]

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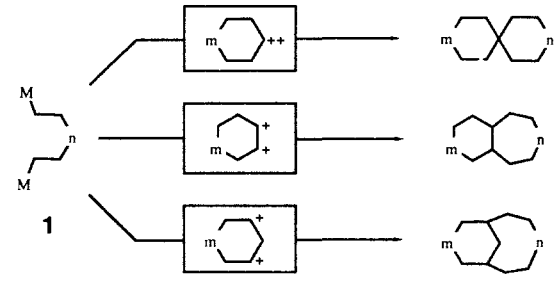
Abstract: A one-step spiroannelation method applicable to the synthesis of the commonly encountered spirocyclic systems is described. The method involves the reaction of 3-halocycloalk-2-enones with a new type of cuprate reagent prepared from organodilithium reagents and copper thiophenoxide and is shown to provide efficient access to spiro[4.4]nonanes, spiro[4.5]decanes, and spiro[5.5]undecanes. The effects of temperature, concentration, and halogen variations on the efficiency of this process are reported for the reactions of 3-halo-5,5-dimethylcyclohex-2-enones **2a–c** with 1,4-bis(CuSPhLi)butane (**3**). Under optimal conditions, chloroenone **2a** reacts with reagent **3** to provide 9,9-dimethylspiro[4.5]decan-7-one (**5**) in 96% yield. The optimized conditions are found to apply generally to variously substituted halocyclopentenones and halocyclohexenones, providing the corresponding spirocyclic products in 76–93% yield. The preparation of new dilithium reagents is also described along with their use in the spiroannelation procedure. The stability of the organobis(cuprates) is found to be influenced by the hybridization of the metal-bearing centers, with alkyl reagents more stable than alkenyl reagents.

Organodimetallic reagents **1** constitute a large and diverse class of important reactive intermediates.[2] From a theoretical and mechanistic viewpoint, these compounds provide the opportunity to study interactions between metal centers in a relatively controllable structural context and to explore how these interactions influence physical properties and reactivity.[2,3] In synthesis, such systems offer service as bis(nucleophiles),[4] by allowing in one operation for the formation of two bonds to a substrate bearing two electrophilic sites. Depending on the disposition of these electrophilic sites, access to spiro, fused, and bridged ring systems is possible (Scheme I). In a preliminary report on this subject,[1b]

Scheme I



we described the preparation of the first members of a new class of organodimetallic reagents, the organobis(heterocuprates) (e.g., **3**),[5] in connection with the development of a fundamentally new spiroannelation method (eq 1). A major advantage and unique

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(2) Studies on organodimetallic compounds are extensively documented in current texts. For examples and lead references, see: (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. In *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987. (b) Wakefield, B. S. In *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974. (c) For an early review, see: Millar, I. T.; Heaney, H. *Q. Rev., Chem. Soc.* **1957**, *11*, 109.

(3) For lead references and recent representative studies, see: (a) Schleyer, P. v. R.; Kos, A. J.; Kaufman, E. *J. Am. Chem. Soc.* **1983**, *105*, 7617. (b) Negishi, E.-i.; Takahashi, T. *Ibid.* **1986**, *108*, 3402. (c) Brown, K. J.; Murdoch, J. R. *Ibid.* **1984**, *106*, 7843. (d) Bates, R. B.; Hess, B. A.; Ogle, C. A.; Schaad, L. J. *Ibid.* **1981**, *103*, 5052. (e) Agranat, I.; Skancke, A. *Ibid.* **1985**, *107*, 867. (f) Meyers, G. F.; Hall, M. B.; Chin, J. W.; Lagow, R. J. *Ibid.* **1985**, *107*, 1413. (g) Cotton, F. A.; Lahuerta, P.; Sanau, M.; Schwotzer, W. *Ibid.* **1985**, *107*, 8284. (h) Bors, D. A.; Streitweiser, A. *Ibid.* **1986**, *108*, 1397.

(4) For lead references and representative examples, see: (a) Bates, R. B.; Gordon, B.; Highsmith, T. K.; White, J. J. *J. Org. Chem.* **1984**, *49*, 2981. (b) Scott, F.; Mafunda, B. G.; Normant, J. F.; Alexakis, A. *Tetrahedron Lett.* **1983**, *24*, 5767. (c) Takahashi, S.; Suzuki, Y.; Sonogashira, K.; Hagihara, N. *J. Chem. Soc., Chem. Commun.* **1976**, 839. (d) Cabiddu, S.; Floris, C.; Melis, S. *Tetrahedron Lett.* **1986**, *27*, 4625. (e) Hylton, T.; Bockelheide, V. *J. Am. Chem. Soc.* **1968**, *90*, 6887. (f) Canonne, P.; Bernatchez, M. *J. Org. Chem.* **1986**, *51*, 2147. (g) Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1987**, *109*, 576.

(5) (a) The reagent structures given in this paper follow the convention established for the mono(cuprate) analogues[10] and do not necessarily reflect their structures in solution. For important discussions on the structures of mono(cuprates) and organodimetallic compounds, see: House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59. Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371. Schleyer, P. v. R.; Spitznagel, G. W.; Chandrasekhar, J. *Tetrahedron Lett.* **1986**, *27*, 4411; references 3 and 10 and studies cited therein. Related studies on this class of reagents include the following: (*b*) Cyclocuprates: Scott, F.; Mafunda, B. G.; Normant, J. F.; Alexakis, A. *Tetrahedron Lett.* **1983**, *24*, 5767. (c) A coupling process "apparently" proceeding via a bis(cuprate): (House, H. O.; Koepsel, D. G.; Campbell, W. J. *J. Org. Chem.* **1972**, *37*, 1003. Wittig, G.; Klar, G. *Justus Liebigs Ann. Chem.* **1967**, *704*, 91. Kauffmann, T.; Beissner, G.; Sahn, W.; Wottermann, *Angew. Chem., Int. Ed. Engl.* **1976**, *9*, 808. McLoughlin, J. C. R.; Thower, J. *Tetrahedron* **1969**, *25*, 5921. (d) Oxidative coupling of dilithium and dimagnesium reagents through a copper(I) ate complex: Whitesides, G. M.; San Filippo, J.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302. (e) Copper-catalyzed Michael reactions of dimagnesium alkyls, e.g.: Schisla, R. M.; Hammann, W. C. *J. Org. Chem.* **1970**, *35*, 3224. Reaction of a copper phosphine complex of 1,4-dilithiobutane with CO: Schwartz, J. *Tetrahedron Lett.* **1972**, 2803.

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