Articles

2-Arylindenes and 2-Arylindenones: Synthesis of Probes To Study the Binding Orientation of Unsymmetrical Nonsteroidal Ligands to the Estrogen Receptor

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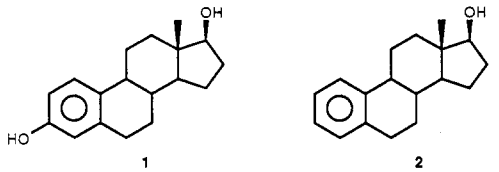
A set of 2-arylindene and -indenone systems, bearing a 3-ethyl or 3-aryl substituent and a single hydroxyl group either on the 6-position of the indene or 4′-position of the C-2 aryl group, have been synthesized in connection with a larger investigation of the orientation with which 2-arylindene nonsteroidal estrogens bind to the estrogen receptor. The 6-hydroxyl-substituted systems are prepared by α-benzylation or benzoylation of a benzyl ketone, followed by Friedel–Crafts cyclization to the indene or indenone. The 2-(4-hydroxyphenyl)-substituted systems were approached via a 2-arylindan-1,3-dione: Grignard addition–dehydration gave the corresponding indenones from which the indenes could be prepared by Wolff–Kishner reduction. 1,3-Diethyl-2-(4-hydroxyphenyl)indene was prepared by hydride reduction of a benzofulvene precursor. The molecular structures and estrogen receptor binding affinities of these 2-arylindene and -indenone systems will be presented elsewhere.

Of the two hydroxyl groups in estradiol (1), the phenolic hydroxyl at C-3 appears to be more important for estrogen receptor (ER) binding affinity: 3-deoxyestradiol (2) has a binding affinity that is only 1.7% that of estradiol, whereas 17-deoxyestradiol (3) has a receptor binding affinity of 14%.[1] This differential becomes a critical issue



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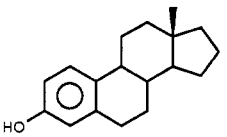

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in the design of inherently fluorescent ligands for the estrogen receptor such as the 2-arylindenes.[2] The desired emission properties (long emission wavelength, high environmental sensitivity) require the presence of a distinct electron acceptor (nitro, cyano, or acetyl group) and an electron donor (hydroxyl, amino) at the termini of a conjugated system.[3] The binding affinity of nonsteroidal systems depends critically upon their orientation within the receptor binding site, with higher affinity expected if the single allowable hydroxyl group mimics the C-3 hydroxyl of estradiol rather than the C-17 hydroxyl.[4] Thus, it is essential to know in prototypical donor/acceptor-substituted 2-arylindene systems (see Figure 1) whether the fused aryl group of the indene system or the pendant phenyl group at C-2 behaves as the A ring of estradiol.

We endeavored to determine the long-axis orientation of 3-aryl- and 3-alkyl-2-arylindenes by systematically varying the location of a single hydroxyl group, placing it either at the 6-position of the fused aryl ring or the 4′-position of the 2-aryl ring and investigating the consequent effect on receptor binding affinity. Further structural variation was introduced at the C-1 position of the indene system (CH_2 vs CO vs CH(Et)) to probe additional steric and electronic effects on the orientation of the 2-arylindenes in the ER binding site. The target molecules are shown in Figure 2, and their synthesis is described herein. In a forthcoming paper,[5] X-ray crystallographic structures of a representative member of each new structural class are presented, and the binding affinities of these compounds for the ER are reported; the molecular structures and binding data are used to derive hypothetical orientations of these compounds within the ER binding site. We have previously described the synthesis and estrogen receptor binding affinity of the 6-hydroxy-2,3-diphenylindenes and -indenones.[2a]

Results and Discussion

A general pattern of retrosynthetic disconnection is evident in the 2-arylindenes (Figure 3). If the system contains an activating substituent on the fused aryl ring, then Friedel–Crafts chemistry[6] can be used to form the

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(1) Hahnel, R.; Twaddle, E.; Ratajczak, T. *J. Steroid Biochem.* **1973**, *4*, 21.

(2) (a) Anstead, G. M.; Altenbach, R. J.; Wilson, S. R.; Katzenellenbogen, J. A. *J. Med. Chem.* **1988**, *31*, 1316. (b) Anstead, G. M.; Katzenellenbogen, J. A. *J. Med. Chem.* **1988**, *31*, 1754. (c) Anstead, G. M.; Katzenellenbogen, J. A. *J. Phys. Chem.* **1988**, *92*, 6249. (d) Anstead, G. M.; Katzenellenbogen, J. A. *Photochem. Photobiol.*, submitted for publication.

(3) Weber, G.; Farris, F. J. *Biochemistry* **1979**, *18*, 3075.

(4) A similar rationale was embraced by Pons and co-workers in their study of the binding orientation of triphenylacrylonitriles in the ER binding site; see: Pons, M.; Michel, F.; Crastes de Paulet, A.; Gilbert, J.; Miguel, J.-F.; Précigoux, G.; Hospital, M.; Ojasoo, T.; Raynaud, J.-P. *J. Steroid Biochem.* **1984**, *20*, 137.

(5) (a) Anstead, G. M.; Wilson, S. R.; Katzenellenbogen, J. A. *J. Med. Chem.*, submitted for publication. (b) For a preliminary report, see: Anstead, G. M.; Ensign, J. L.; Katzenellenbogen, J. A. *Abstracts of Papers*, 194th National Meeting of the American Chemical Society, New Orleans, LA, Aug–Sept 1987; American Chemical Society, Washington, DC, 1987, MEDI 012.

(6) Olah, G. *Friedel–Crafts and Related Reactions*; Interscience: New York, 1963–1964.

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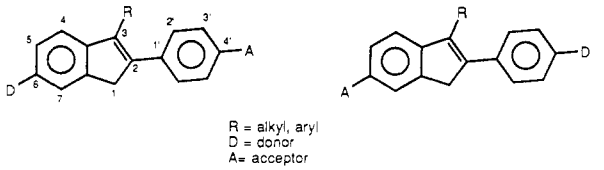


Figure 1. Numbering system and possible structures of donor-/acceptor-substituted 2-arylindenes.

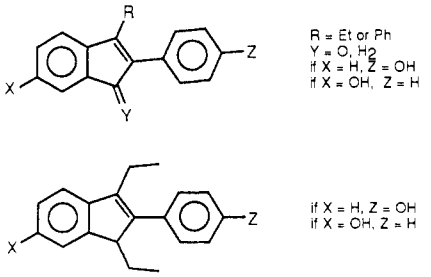


Figure 2. Summary of compounds to probe the orientational preference of the 2-arylindene system.

indene nucleus (Figure 3, bottom). In our case, the highly activating methoxy group directs ring closure predominately to the para position. However, Friedel–Crafts methodology is not efficacious for constructing indene systems lacking an activating group.[7] In these cases, an indandione nucleus is conveniently formed from phthalic anhydride,[8] with the C-3 substituents being affixed by subsequent organometallic additions (Figure 3, top). However, this approach cannot be used effectively for the synthesis of indene systems in which the fused aryl ring is substituted, because the asymmetry of these systems would give multiple products upon organometal addition. Thus, the two general synthetic routes were complementary.

6-Hydroxyindenes and 6-Hydroxyindenones. Our route to the 3-ethyl- and 1,3-diethyl-6-hydroxy-2-arylindenes (**6** and **8**) exploited well-proven methodology for the construction of 2,3-diarylindenes[2,7] and the acidity of the indenyl methylene protons[9] (Scheme I). In brief, the thermodynamic enolate of ethyl benzyl ketone was alkylated with 3-methoxybenzyl chloride and cyclodehydrated to give the indene. The indene was then deprotected directly or converted to the indenyl anion, ethylated, and then deprotected. The synthesis of ethylindenone **11** employed chemistry similar to that used for the preparation of 2,3-diarylindenones[2a] (Scheme II). In this case, the acid chloride proved to be a much better aroylating agent for benzyl ketones than the *p*-nitrophenyl esters used previously.[2a] However, the yield in the methanesulfonic acid induced cyclization of ethyl diketone **9** was poorer than those of the triaryl diketones **13** and **14**.[2a] One lower R_f product predominates in the cyclization of **9**, but it is unstable and has been isolated only in small quantities. This compound has been identified as β,γ-enone **10**.[10] Although the "deconjugated" structure of compound **10** might seem surprising at first, the conjugative stabilization of the double bond in indenones is probably low, since it involves antiaromatic resonance forms.[11]

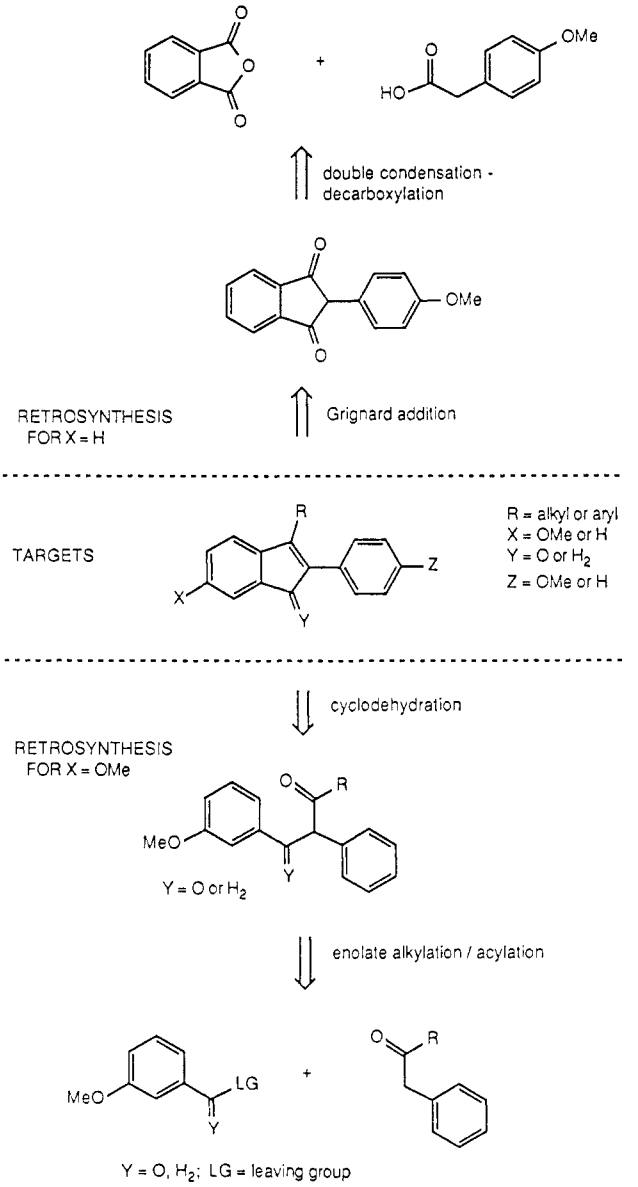
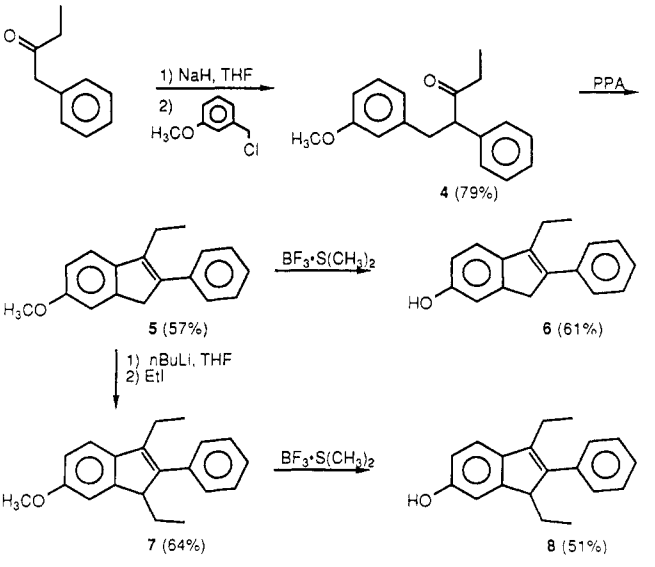


Figure 3. Retrosynthesis of 2-arylindene systems.

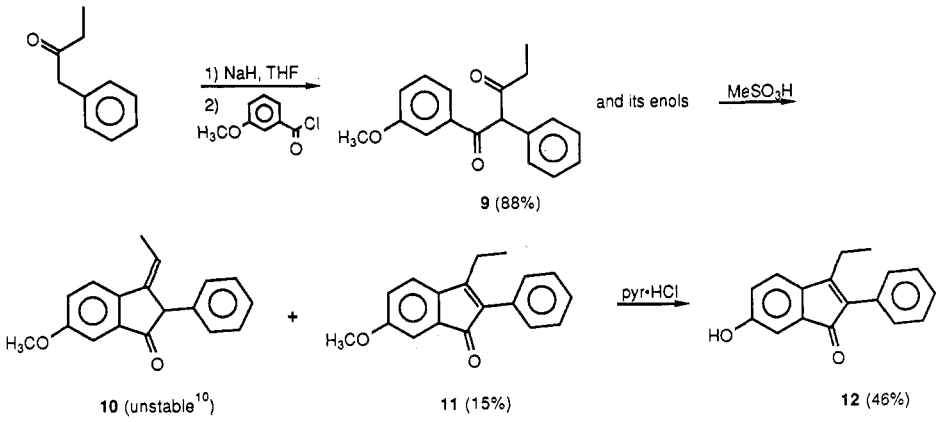
Scheme I



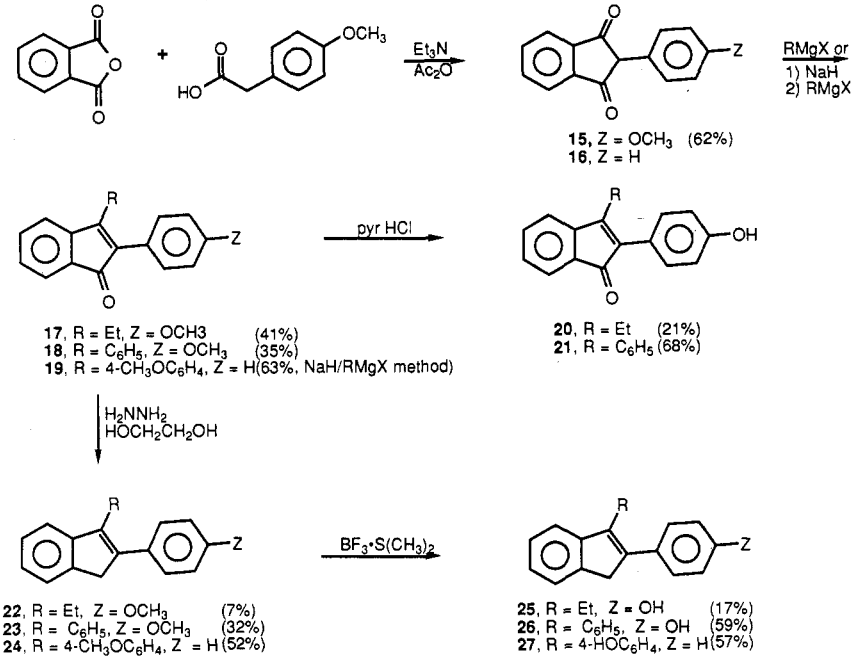
Ethyl diketone **9** has a much higher enol content than the triaryldiketones **13** and **14**. The proton nuclear mag-

(7) Crenshaw, R. R.; Jenks, T. A.; Baily, G. *J. Med. Chem.* **1974**, *17*, 1127.
(8) Godfrey, J. C.; Barnes, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 3903.
(9) (a) Bordwell, F. G.; Drucker, G. E. *J. Org. Chem.* **1980**, *45*, 3325. (b) Manning, C.; McClory, M. R.; McCollough, J. J. *J. Org. Chem.* **1981**, *46*, 919.
(10) 2-Aryl-1,3-indandiones, in a similar state of unsaturation as β,γ-enone **10**, are known to undergo facile oxidation; see: DeVries, J.; Engel, D. J. C.; Koekkoek, P. H. *J. Chromatogr.* **1975**, *108*, 117.

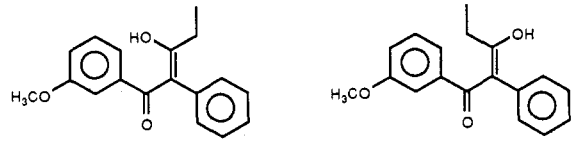
Scheme II

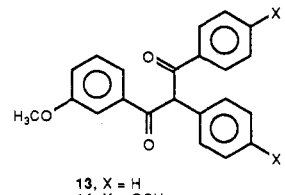


Scheme III



netic resonance (^{1}H NMR) spectrum of analytically pure **9** in $CDCl_3$ showed at least three species present, as indicated by the three singlets in the methoxy region (δ 3.4–4). The ^{1}H NMR spectrum of triaryl diketone **13** shows only one methoxy signal and one downfield singlet (δ 6.55), consistent with the diketo form.[2a] From the integrated intensities of the methoxy groups, the enol forms **9a** and **9b** comprise 75% of **9**.[12] In general, ketones conjugated with aromatic rings do not exist as enols to an appreciable degree, whereas ketones such as **9**, in which the double bond of the enol form can conjugate with a phenyl ring, enolize readily.[13]

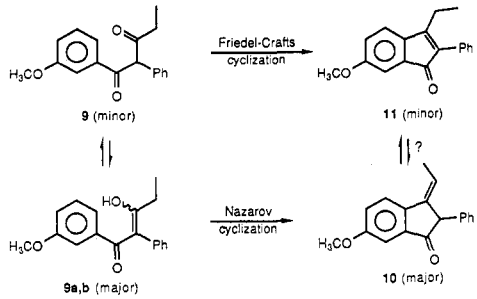




The indenones were demethylated with molten pyridine hydrochloride, since our previous results have shown that indenones are unstable to Lewis acids.[2a]

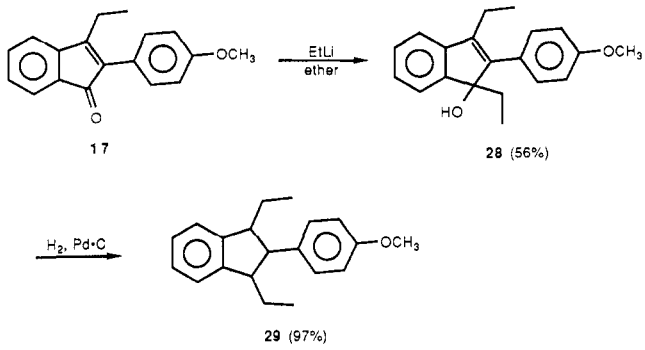
(11) The antiaromatic character of the indenones is manifest in the chemical instability of less substituted indenones. See: Martens, H.; Hoornaert, G. *Synth. Commun.* **1972**, *2*, 147.

(12) The presence of enols **9a** and **9b**, which have a divinyl ketone moiety, may allow the alternate Nazarov cyclization mechanism (see: Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 430) to occur, and this may also account for the formation of β,γ-enone **10**.



(13) Capon, B.; Guo, B.-Z.; Kwok, F. C.; Siddharta, A. K.; Zucco, C. *Acc. Chem. Res.* **1988**, *21*, 136.

Scheme IV



2-(4′-Hydroxyphenyl)indenes and -indenones. In the synthesis of indenes and indenones with an unsubstituted fused aryl ring, the first step was the double condensation–decarboxylation of 4-methoxyphenylacetic acid with phthalic anhydride (Scheme III).[8] The resulting indandione **15** (or its commercially available analogue **16**) was then allowed to react with 2 equiv of the appropriate Grignard reagent to provide the indenones **17–19**. The first equivalent of Grignard reagent serves to deprotonate the symmetric indandione, giving a monoenolized diketone. The second equivalent of the Grignard reagent then adds to the remaining unenolized carbonyl group. In this way, the high acidity of the indandiones[14] is utilized to provide in situ protection from organometal addition for the second ketone. Higher yields were obtained in the case of indenone **19** when sodium hydride was used for the initial deprotonation.

The reduction of α,β-unsaturated ketones to unrearranged olefins is a difficult transformation.[15] Wolff–Kishner reduction of the indenones (**17–19**)[9] provided the corresponding indenes **22–24** in poor to moderate yields. Treatment of the ethylindenone **17** with other reagents that are known to effect carbonyl to methylene conversion (acidic Et_3SiH,[16] $LiAlH_4/AlCl_3$,[17] $NaBH_4/ZnI_2$[18]) gave only the allylic alcohol derived from **17**. This resistance to further reduction can be rationalized by the nature of the π-electron system in the indenes; any reaction that proceeds through a cationic intermediate or transition state would be disfavored due to its antiaromatic character ($4n$ π-electrons).[19]

The inefficient synthesis of the indenes without activating substituents on the fused ring prompted other approaches to 1,3-diethyl-2-(4-methoxyphenyl)indene (see Schemes IV and V). Ethyllithium addition to the carbonyl group of ethylindenone **17** afforded the diethylindenyl alcohol **28** (Scheme IV); an attempted hydrogenolysis[20] of the indenyl alcohol group in **28**, however, proceeded with concomitant reduction of the double bond, despite its tetrasubstitution and extensive conjugation.

As a successful alternative (Scheme V), ethylindenone **17** was converted into the corresponding methylbenzofulvene **30**, following the procedure of Padwa et al.[21] From the ^1H NMR spectrum, the less hindered E isomer predominates over the Z isomer in a 3:1 ratio. The geometry assignment is made on the basis of the upfield shift experienced by the $=CHCH_3$ protons of the Z isomer. Hydride addition to the exocyclic double bond[22] afforded the stabilized indenyl anion, which upon protonation gave the desired diethylindene **31**.

Conclusion

The set of monohydroxy 2-arylindenes and -indenones whose preparation is described here, together with a few others whose synthesis has been described previously,[2a] provide a complete set of monohydroxy 2-arylindene and -indenone systems needed to map the orientation with which these nonsteroidal estrogens bind to the estrogen receptor. The binding-orientation studies will be presented elsewhere.[5]

Experimental Section

General. Melting points (uncorrected) were determined on a Thomas-Hoover apparatus. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel F-254 glass-backed plates. Flash chromatography was done as previously described,[23] using Woelm 32–63-μm silica gel.

Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a Varian XL-200 (200 MHz) or a General Electric QE-300 (300 MHz) spectrometer; chemical shifts are reported downfield from a tetramethylsilane internal standard (δ scale). Carbon-13 nuclear magnetic resonance spectra were recorded on a General Electric QE-300 spectrometer at 75 MHz; chemical shifts are reported on the δ scale using the center peak of deuteriochloroform (77 ppm) as the internal standard. Infrared (IR) spectra were obtained on a Perkin-Elmer 1320 or a Nicolet 700 spectrometer in the indicated phase: prominent and diagnostic peaks are reported. Ultraviolet (UV) spectra were determined with a Hewlett-Packard 8451A spectrophotometer. Low-resolution mass spectra (MS) were done in the electron-impact mode on the Varian CH-5 spectrometer. The reported data are for an electron energy of 70 eV and follows the form: m/z (intensity relative to base peak = 100). High-resolution mass spectra (HRMS) were obtained in the electron-impact mode on a Varian MAT-371 spectrometer. The corrected fluorescence emission spectra were acquired on a Spex Fluorolog 2, Model IIIC instrument. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois. Indandione **15** was prepared as described.[8]

Unless otherwise noted, a standard procedure for product isolation was used; this involved quenching by addition of water or an aqueous solution, exhaustive extraction with an organic solvent, washing the extracts, drying with $MgSO_4$, and solvent evaporation under reduced pressure. The quenching media, extraction solvents, and aqueous washes used are noted parenthetically after the phrase "product isolation".

1-(3-Methoxyphenyl)-2-phenyl-3-pentanone (4). Sodium hydride (320 mg, 6.8 mmol) was rinsed with hexane and suspended in THF (5 mL). 1-Phenyl-2-butanone (1.00 g, 6.8 mmol) was dissolved in THF (10 mL) and was added over 5 h. After 2 h, 3-methoxybenzyl chloride (2.12 g, 14 mmol) in THF (5 mL) was added. The reaction solution was stirred at 50 °C for 48 h. Product isolation (5% HCl, ether) and flash chromatography (19:1 hexane–EtOAc) gave 1.42 g (79%) of **4** as a clear oil: IR (neat) 3010, 2920, 1705, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.05 (m, 6 H, Ar*H*), 6.72–6.53 (m, 3 H, Ar*H* ortho and para to OCH_3), 3.92 (t, 1 H, J = 8 Hz, $COCHPh$), 3.71 (s, 3 H, CH_3O), 3.40 (dd, 1 H, J = 14, 8 Hz, $ArCH_2$), 2.88 (dd, 1 H, J = 14, 7 Hz, $ArCH_2$), 2.32 (m, 2 H, $COCH_2CH_3$), 0.91 (t, 3 H, J = 7 Hz, CH_2CH_3); MS 268 (21, M^+), 211 (100), 178 (13), 165 (10), 121 (26), 117 (15), 103 (14). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.60; H, 7.46. Found: C, 80.46; H, 7.65.

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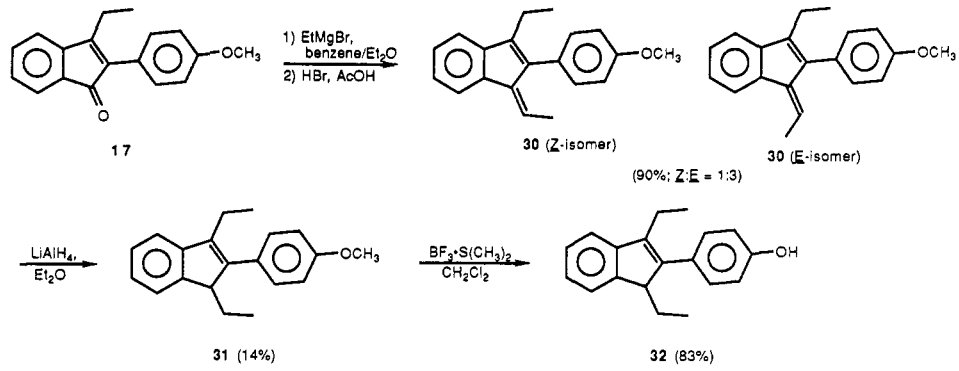
(22) Rio, G.; Cherki, M. *C. R. Acad. Sci. Paris* **1964**, *259*, 3786.
(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme V



2-Phenyl-3-ethyl-6-methoxyindene (5). Ketone **4** (1.12 g, 4.18 mmol) was mixed with polyphosphoric acid (PPA, 11.0 g) and stirred mechanically at 60 °C for 3.5 h. Product isolation (ice water, EtOAc, 10% $NaHCO_3$), followed by recrystallization, provided 0.6 g (57%) of white flakes: mp 118.5–119.5 °C; ^1H NMR (acetone-d_6) δ 7.53–7.22 (m, 6 H, Ar*H*), 7.11 (d, 1 H, J = 2 Hz, Ar*H* on C-7), 6.89 (dd, 1 H, J = 8 Hz, CH_2CH_3), 1.28 (t, 3 H, J = 8 Hz, CH_2CH_3); MS 250 (100, M^+), 235 (45), 221 (60), 178 (20). Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.17; H, 7.27.

1,3-Diethyl-2-phenyl-6-methoxyindene (7). Indene **5** (350 mg, 1.40 mmol) was dissolved in 10 mL of THF, and the solution was cooled to −78 °C. A solution of *n*-butyllithium in hexanes (1.6 M, 0.96 mL, 1.54 mmol) was added, generating an orange anion. After 1 h, ethyl iodide (437 mg, 2.80 mmol) was added. The solution was warmed to room temperature and stirred for 28 h. Product isolation (0.1 M $Na_2S_2O_3$, EtOAc) and flash chromatography (97:3 hexane–EtOAc) provided 0.280 g (64%) of a clear, viscous oil: ^1H NMR ($CDCl_3$) δ 7.49–7.22 (m, 6 H, Ar*H*), 7.05 (d, 1 H, J = 2 Hz, Ar*H* on C-7), 6.89 (dd, 1 H, J = 9, 2 Hz, Ar*H* on C-5), 3.90 (t, 1 H, J = 5 Hz, $CHCH_2CH_3$), 3.86 (s, 3 H, OCH_3), 2.66 (q, 2 H, J = 8 Hz, $=CCH_2CH_3$), 2.11–1.60 (m, 2 H, $CHCH_2CH_3$), 1.21 (t, 3 H, J = 7 Hz, $=CCH_2CH_3$), 0.45 (t, 3 H, J = 7 Hz, $CHCH_2CH_3$); MS 278 (100, M^+), 263 (14), 249 (64), 234 (13), 135 (7); HRMS ($C_{20}H_{22}O$) calcd/found 278.1671/278.1674.

1-(3-Methoxyphenyl)-2-phenyl-1,3-pentanedione (9) and Its Enol Tautomers (9a and 9b). Sodium hydride (1.07 g, 22 mmol) was washed with hexane and suspended in THF (10 mL). 1-Phenyl-2-butanone (3 g, 20 mmol) in 25 mL of THF was added dropwise over 2 h. After an additional hour, 3-methoxybenzoyl chloride (1.15 g, 6.8 mmol) was added in 10 mL of THF. After 18 h, product isolation (5% HCl, EtOAc) commenced. A clear, yellow oil (1.67 g, 88%) was obtained after flash chromatography (9:1 hexane–EtOAc): IR ($CHCl_3$) 3010, 1710, 1670, 1600, 1220, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50–7.05 (m, Ar*H*), 6.91–6.73 (three sets of peaks, Ar*H* ortho to OCH_3), 5.70 (s, C(O)C*H*(Ph)C(O)), 3.81, 3.69, 3.52 (3 s, 6:13:5 integrated intensity ratio, OCH_3; the peak at δ 3.81 is assigned to the diketo form **9**, in analogy to the chemical shift of the methoxy group in diketone **13**[2a]), 2.71–2.52 (m, CH_2CH_3 of keto form), 2.47 (q, J = 7 Hz, CH_2CH_3 of enol form), 2.33 (q, J = 7 Hz, CH_2CH_3 of enol form), 1.10–1.00 (overlapping t, CH_2CH_3); MS 282 (10, M^+), 253 (8), 226 (17), 165 (6), 148 (12), 135 (28), 118 (6), 91 (50), 57 (100). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.20; H, 6.53.

Cyclization of Diketone 9. Diketone **9** (1.04 g, 3.94 mmol) was dissolved in CH_2Cl_2 (30 mL), and the solution was cooled to 0 °C. Methanesulfonic acid (1 mL) in CH_2Cl_2 (10 mL) was added dropwise over 1 h. The solution was stirred for 18 h at 25 °C. Product isolation (10% $NaHCO_3$, CH_2Cl_2, brine, $MgSO_4$) and flash chromatography (two runs: 9:1 hexane–EtOAc; 19:1 hexane–EtOAc) provided two compounds in order of increasing retention of the column.

2-Phenyl-3-ethyl-6-methoxyindenone (11). The fractions homogeneous in a higher R_f red compound were pooled, evaporated, and recrystallized from pentane–diisopropyl ether at −30 °C, providing glistening red flakes (93 mg, 15%): mp 93–94 °C; ^1H NMR ($CDCl_3$) δ 7.46–7.33 (m, 6 H, Ar*H*), 7.12 (d, 1 H, J = 2 Hz, Ar*H* on C-7), 7.09 (d, 1 H, J = 8 Hz, Ar*H* on C-4), 6.84 (dd, 1 H, J = 8, 2 Hz, Ar*H* on C-5), 3.85 (s, 3 H, OCH_3), 2.70 (q, 2 H, J = 8 Hz, CH_2CH_3), 1.32 (t, 3 H, J = 8 Hz, CH_2CH_3); MS 264 (M^+, 100), 249 (11), 221 (7). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.82; H, 6.10.

(*Z*)-2-Phenyl-3-ethylidene-6-methoxy-1-indanone (10). At an R_f below that of indenone **11** was a compound that displayed blue fluorescence on TLC under UV light. This compound was unstable[10] and decomposed to a red, low R_f material. However, a small amount of the pure compound was secured by pooling of the fractions enriched in the compound, followed by recrystallization from hexane–EtOAc at −30 °C. Off-white prisms were obtained: mp 95–97 °C; ^1H NMR ($CDCl_3$) δ 7.68 (d, 1 H, J = 9 Hz, Ar*H* meta to CO), 7.35–7.21 (m, 6 H, Ar*H*), 7.14 (d, 1 H, J = 2 Hz, Ar*H* ortho to CO), 6.32 (q, 1 H, J = 7 Hz, $=CHCH_3$), 4.30 (s, 1 H, C*H*Ph), 3.83 (s, 3 H, OCH_3), 1.60 (d, 3 H, J = 7 Hz, $=CHCH_3$); ^{13}C NMR ($CDCl_3$) 16 signals (16 nonidentical carbons) δ 202.4 (*C*=O), 160.3 ($COCH_3$), 144.9 (*C*-3a), 137.4 (*C*-7a), 136.7 ($C=CHCH_3$), 136.1 (*C* of Ph), 128.8 (two *C*H of Ph), 127.9 (two *C*H of Ph), 126.9 (*C*H of Ph), 125.1 (*C*-5), 121.6, 119.0 (*C*-4 and *C*-7), 104.8 (C=*C*HCH$_3$), 56.1 (*C*HC=O), 55.7 (OCH_3), 15.2 (=CH*C*H$_3$); MS 264 (100, M^+), 249 (13), 221 (16), 186 (9), 135 (20). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.74; H, 6.04.

2-(4-Methoxyphenyl)-3-ethylindenone (17). Magnesium (3.5 g, 0.14 mol) was suspended in benzene–ether (2.3:1, 65 mL). Ethyl iodide (16 g, 0.10 mol) was added, and the suspension was heated at reflux for 1 h. After cooling to 25 °C, the indandione **15**[8] (8.7 g, 0.035 mol) was added. The mixture was stirred for 24 h. Product isolation (6 M HCl, ether) and flash chromatography (9:1 hexane–EtOAc) provided 3.7 g (41%) of an orange solid: mp 115–116 °C; IR 1705, 1610, 1590, 1510, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) 7.47 (d, 1 H, J = 7 Hz, Ar*H* on C-7), 7.38–7.32 (m, 1 H, Ar*H* on C-5), 7.34 (d, 2 H, J = 9 Hz, Ar*H* meta to OCH_3), 7.24–7.14 (m, 2 H, Ar*H* on C-4, C-6), 6.97 (d, 2 H, Ar*H* ortho to OCH_3), 2.71 (q, 2 H, J = 8 Hz, CH_2CH_3), 1.32 (t, 3 H, J = 8 Hz, CH_2CH_3); MS 264 (100, M^+), 249 (50), 234 (11), 221 (16), 217 (13), 178 (14). Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 82.11; H, 6.34.

2-(4-Methoxyphenyl)-3-phenylindenone (18). This compound was prepared from bromobenzene and indandione **15** in the manner described for the synthesis of **17**. The product was purified by flash chromatography (1:1 hexane–CH_2Cl_2); a red powder was obtained (854 mg, 35%): mp 127–128 °C (lit.[9b] mp 118–119 °C); ^1H NMR ($CDCl_3$) δ 7.54 (dd, 1 H, J = 9, 1 Hz, Ar*H* on C-7), 7.41 (s, 5 H, Ar*H* of Ph), 7.40–7.29 (m, 2 H, Ar*H* on C-5, C-6), 7.23 (d, 2 H, J = 9 Hz, Ar*H* meta to OCH_3), 7.12 (d, 1 H, J = 9 Hz, Ar*H* on C-4), 6.80 (d, 2 H, J = 9 Hz, Ar*H* ortho to OCH_3), 3.78 (s, 3 H, OCH_3); MS 312 (100, M^+), 297 (14), 239 (27), 165 (14), 149 (23), 135 (21). Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.18; H, 5.32.

2-Phenyl-3-(4-methoxyphenyl)indenone (19). Sodium hydride (0.43 g, 18 mmol) was suspended in ether (25 mL). 2-Phenylindandione (**16**, 4.0 g, 18 mmol) and 30 mL of ether were added. After 3 h, a solution of (4-methoxyphenyl)magnesium bromide (prepared from 4-bromoanisole (6.73 g, 36 mmol) and magnesium (0.42 g, 17 mmol) in refluxing THF overnight) was added. The reaction mixture was heated at reflux for 8 h. The solvent was evaporated, and the residue was suspended in 5% HCl in methanol (50 mL). The mixture was heated at reflux for 4 h. Product isolation (water, EtOAc, brine) and flash chroma-

tography (4:1 hexane–EtOAc) afforded a red solid (3.56 g, 63%): mp 119–121 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (d, 1 H, ArH on C-7), 7.45–7.22 (m, 10 H, Ar*H*), 6.92 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3), 3.84 (s, 3 H, OCH_3); MS 312 (100, M^+), 281 (9). Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.74; H, 5.26.

2-(4-Methoxyphenyl)-3-ethylindene (22). Ethylindenone **17** (1.13 g, 4.27 mmol) was dissolved in ethylene glycol (50 mL) and hydrazine hydrate (30 mL), and the solution was heated at 150 °C for 5 h. Product isolation (water, EtOAc, water (multiple washes)), followed by flash chromatography (9:1 hexane–EtOAc), afforded 75.9 mg (7%) of a white powder: mp 59–60 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, 1 H, *J* = 9 Hz, Ar*H* on C-4), 7.41–7.04 (m, 5 H, Ar*H*), 6.89 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3), 3.78 (s, 3 H, OCH_3), 3.63 (s, 2 H, CH_2), 2.67 (q, 2 H, *J* = 7 Hz, CH_2CH_3), 1.24 (t, 3 H, *J* = 7 Hz, CH_2CH_3); MS 250 (100, M^+), 235 (18), 221 (46); HRMS ($C_{18}H_{18}O$) calcd/found 250.1358/250.1353.

2-(4-Methoxyphenyl)-3-phenylindene (23). This compound was prepared from indenone **18** in the manner described for **22**. Purification was achieved by flash chromatography (4:1 hexane–ether), followed by recrystallization from hexane–EtOAc, providing a light pink solid (77 mg, 32%): mp 115–117 °C (lit.[9b] mp 124–126 °C); ^{1}H NMR ($CDCl_3$) δ 7.55–7.19 (m, 9 H, Ar*H*), 7.22 (d, 2 H, *J* = 9 Hz, Ar*H* meta to OCH_3), 6.75 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3), 3.89 (s, 2 H, CH_2), 3.78 (s, 3 H, OCH_3); MS 298 (100, M^+), 283 (16), 252 (19), 239 (12); HRMS ($C_{22}H_{18}O$) calcd/found 298.1358/298.1366.

2-Phenyl-3-(4-methoxyphenyl)indene (24). This compound was prepared from indenone **19** in the manner described for the preparation of **22**. Flash chromatography (4:1 hexane–EtOAc) provided 1.49 g (52%) of a white powder: mp 112–113 °C (lit.[9b] mp 105–110 °C); ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1 H, *J* = 6 Hz, Ar*H* on C-4), 7.32–7.18 (m, 10 H, Ar*H*), 6.95 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3), 3.89 (s, 2 H, CH_2), 3.85 (s, 3 H, OCH_3); MS 298 (100, M^+), 283 (5). Anal. Calcd for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.30; H, 6.24.

1-Hydroxy-1,3-diethyl-2-(4-methoxyphenyl)indene (28). Indenone **17** (1.0 g, 3.8 mmol) was dissolved in ether (30 mL). A solution of ethyllithium in benzene (organometallics; 1.4 M, 3.0 mL, 1.4 mmol) was added. The solution was stirred at 25 °C for 16 h, but starting ketone remained. The solution was cooled to 0 °C, and an additional 5 mL of the ethyllithium solution was added. After 2.5 h, product isolation commenced (water, EtOAc). The material was subjected to flash chromatography (9:1 hexane–EtOAc). Fractions containing the main component were pooled and evaporated. Recrystallization from pentane at −30 °C afforded a white, microcrystalline solid (0.62 g, 56%): mp 87–88 °C; ^{1}H NMR ($CDCl_3$) δ 7.49 (d, 2 H, *J* = 9 Hz, Ar*H* meta to OCH_3), 7.39 (d, 1 H, *J* = 7 Hz, Ar*H* on C-4), 7.31–7.21 (m, 3 H, Ar*H*), 6.96 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3), 3.85 (s, 3 H, OCH_3), 2.51 (q, 2 H, *J* = 7 Hz, $=CCH_2CH_3$), 2.71 (s, 1 H, O*H*), 2.10–1.95 (m, 1 H, $C(OH)CH_2CH_3$), 1.90–1.73 (m, 1 H, $C(OH)CH_2CH_3$), 1.23 (t, 3 H, *J* = 7 Hz, $=CCH_2CH_3$), 0.49 (t, 3 H, *J* = 7 Hz, $C(OH)CH_2CH_3$); MS 294 (72, M^+), 276 (8), 265 (100), 186 (13), 157 (36), 129 (22). Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.66; H, 7.58.

1,3-Diethyl-2-(4-methoxyphenyl)indan (29). Indenyl alcohol **28** (200 mg, 0.68 mmol) was dissolved in EtOH, and 400 mg of Pd/C catalyst (5% Pd by weight) was added. The mixture was agitated under a hydrogen atmosphere (25 atm) for 4 h at 25 °C in a Parr apparatus. The suspension was then filtered through a short silica column and evaporated; a clear, viscous oil was obtained (200 mg, 97%): MS 280 (100, M^+), 251 (87), 172 (37), 143 (27), 121 (34); HRMS ($C_{20}H_{24}O$) calcd/found 280.1827/280.1823.

(*E*)- and (*Z*)-1-Methyl-3-(4-methoxyphenyl)-4-ethylbenzofulvene (30). Ethylmagnesium bromide was prepared by treating magnesium (0.420 g, 1.73 mmol) with ethyl bromide (1.41 g, 12.9 mmol) in benzene–ether (2:1, 60 mL). Indenone **11** (1.14 g, 4.30 mmol) was added, and the solution was refluxed for 90 min. Product isolation (satd NH_4Cl, ether, $MgSO_4$) and evaporation gave a yellow oil. The oil was treated with HBr (48%, 8 mL) and ether (8 mL) for 3 h. Product isolation (water, ether, $MgSO_4$) and flash chromatography (9:1 hexane–EtOAc) provided a yellow oil (1.00 g, 90%): ^{1}H NMR ($CDCl_3$) δ 7.81 (d, 1 H, *J* = 9 Hz, Ar*H* ortho to $=CHCH_3$, *E* isomer), 7.58 (d, 1 H, *J* = 9 Hz, Ar*H* ortho to $=CHCH_3$), *Z* isomer), 7.40–7.18 (m, Ar*H*), 6.98 (overlapping d, Ar*H* ortho to OCH_3, *E* and *Z* isomers), 6.71 (q, 1 H, *J* = 9 Hz, $=CHCH_3$ of *Z* isomer), 6.15 (q, 1 H, *J* = 9 Hz, $=CHCH_3$ of *E* isomer), 3.90 (s, OCH_3), 2.58–2.42 (overlapping q, CH_2CH_3), 2.35 (d, 3 H, *J* = 7 Hz, $=CHCH_3$, *E* isomer), 1.62 (d, 3 H, *J* = 7 Hz, $=CHCH_3$, *Z* isomer), 1.22–1.05 (overlapping t, CH_2CH_3); MS 276 (93, M^+), 261 (40), 247 (55), 231 (25), 215 (47), 202 (30); HRMS ($C_{20}H_{20}O$) calcd/found 276.1515/276.1520.

1,3-Diethyl-2-(4-methoxyphenyl)indene (31). Lithium aluminum hydride (500 mg, 13.2 mmol) was suspended in ether (10 mL) and cooled to 0 °C. Methylfulvenes **30** (1.00 g, 3.62 mmol), dissolved in ether (15 mL), were added over 5 min. After 30 min at 0 °C, the solution was stirred at 25 °C for 8 h. Product isolation (careful addition of 6 N HCl, ether, $MgSO_4$) and flash chromatography (96:4 hexane–EtOAc) yielded 139 mg (14%) of a slightly yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.50–7.19 (m, 4 H, Ar*H*), 7.28 (d, 2 H, *J* = 9 Hz, Ar*H* meta to OCH_3), 6.97 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3), 3.87 (t (obscured by adjacent signal), 1 H, *J* = 5 Hz, $CHCH_2CH_3$), 3.85 (s, 3 H, OCH_3), 2.65 (q, 2 H, *J* = 8 Hz, $C=CCH_2CH_3$), 1.93 (m, 1 H, $CHCH_2CH_3$), 1.63 (m, 1 H, $CHCH_2CH_3$), 1.28 (t, 3 H, $C=CCH_2CH_3$), 0.45 (t, 3 H, $CHCH_2CH_3$); MS 278 (50, M^+), 249 (100), 234 (31), 219 (23), 202 (22); HRMS ($C_{20}H_{22}O$) calcd/found 278.1671/278.1671.

Preparation of Hydroxyindenes 6, 8, 25–27, and 32. Demethylation of methoxyindenes **5**, **7**, **22–24**, and **31** was achieved with boron trifluoride–dimethyl sulfide complex,[24] as previously described,[25,26] to provide hydroxyindenes **6**, **8**, **25–27**, and **32**.

2-Phenyl-3-ethyl-6-hydroxyindene (6). This compound was purified by flash chromatography (4:1 hexane–EtOAc), followed by recrystallization (ether–hexane). Light green needles (86 mg, 61%) were obtained: mp 102–104 °C; UV (EtOH) λ_{max} (ε) 308 (22 500), 232 sh (10 700), 208 (30 000) nm; fluorescence (EtOH) λ_{em} 385 nm (excitation at 308 nm); ^{1}H NMR (acetone-d_6) δ 8.22 (s, 1 H, D_2O exch, ArO*H*), 7.53–7.22 (m, 6 H, Ar*H*), 7.01 (d, 1 H, *J* = 2 Hz, Ar*H* on C-7), 6.80 (dd, 1 H, *J* = 8, 2 Hz, Ar*H* on C-5), 3.67 (s, 2 H, CH_2), 2.72 (q, 2 H, *J* = 8 Hz, CH_2CH_3), 1.28 (t, 3 H, *J* = 8 Hz, CH_2CH_3); MS 236 (100, M^+), 221 (77), 207 (99), 202 (14), 189 (12), 178 (26). Anal. Calcd for $C_{17}H_{16}O$: C, 86.41; H, 6.82. Found: C, 86.36; H, 6.64.

1,3-Diethyl-2-phenyl-6-hydroxyindene (8). Purification was achieved by flash chromatography (19:1 hexane–EtOAc), followed by trituration with pentane. A light tan solid was obtained (96 mg, 51%): mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 7.50–7.15 (m, 7 H, Ar*H*), 6.98 (d, 1 H, *J* = 2 Hz, Ar*H* on C-7), 6.82 (dd, 1 H, *J* = 8, 2 Hz, Ar*H* on C-5), 4.79 (br s, 1 H, ArO*H*), 3.88 (t, 1 H, *J* = 4 Hz, $CHCH_2CH_3$), 2.65 (q, 2 H, *J* = 7 Hz, $=CCH_2CH_3$), 2.10–1.81 (m, 1 H, $CHCH_2CH_3$), 1.75–1.55 (m, 1 H, $CHCH_2CH_3$), 1.27 (t, 3 H, *J* = 7 Hz, $=CCH_2CH_3$), 0.45 (t, 3 H, *J* = 7 Hz, $CHCH_2CH_3$); MS 264 (100, M^+), 249 (12), 235 (63), 220 (6); HRMS ($C_{19}H_{20}O$) calcd/found 264.1514/264.1514.

2-(4-Hydroxyphenyl)-3-ethylindene (25). This material was purified by flash chromatography (4:1 hexane–EtOAc; multiple runs), followed by trituration with hexane–Et_2O. A white powder was obtained (13 mg, 17%): mp 94–95 °C; ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1 H, D_2O exch, ArO*H*), 7.39 (d, 1 H, *J* = 7 Hz, Ar*H* on C-4), 7.38–7.25 (m, 3 H, Ar*H* meta to OH and Ar*H* on C-7), 7.22 (t, 1 H, *J* = 7 Hz, Ar*H* on C-6), 7.09 (t, *J* = 7 Hz, Ar*H* on C-5), 6.86 (d, 2 H, *J* = 7 Hz, Ar*H* ortho to OH), 3.64 (s, 2 H, CH_2), 2.69 (q, 2 H, *J* = 7 Hz, CH_2CH_3), 1.25 (t, 3 H, *J* = 7 Hz, CH_2CH_3); MS 236 (100), 221 (32), 207 (73); HRMS ($C_{17}H_{16}O$) calcd/found 236.1201/236.1200.

2-(4-Hydroxyphenyl)-3-phenylindene (26). This compound was purified by flash chromatography (7:3 hexane–EtOAc). Rotary evaporation of a pentane–Et_2O solution afforded a white powder (36 mg, 69%): mp 175 °C dec; ^{1}H NMR (acetone-d_6) δ 8.45 (s, 1 H, ArO*H*), 7.58–7.08 (m, 11 H, Ar*H*), 6.70 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OH), 3.91 (s, 2 H, CH_2); MS 284 (100, M^+), 267 (3), 207 (7), 141 (6); HRMS ($C_{21}H_{16}O$) calcd/found 284.1201/284.1194.

2-Phenyl-3-(4-hydroxyphenyl)indene (27). The product was purified by flash chromatography (4:1 hexane–EtOAc); a white solid was obtained (113 mg, 57%): mp 160–161 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 2 H, *J* = 6 Hz, Ar*H* on C-4), 7.40–7.10 (m, 10

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H, ArH), 6.89 (d, 2 H, J = 9 Hz, ArH ortho to OH), 5.16 (s, 1 H, ArOH), 3.89 (s, 2 H, CH_2); MS 284 (100, M^+), 265 (11), 252 (19), 239 (16), 207 (16); HRMS ($C_{21}H_{16}O$) calcd/found 284.1201/284.1199.

1,3-Diethyl-2-(4-hydroxyphenyl)indene (32). Purification was achieved by flash chromatography (7:3 hexane–EtOAc), affording a clear, viscous oil (110 mg, 83%): ^{1}H NMR ($CDCl_3$) δ 7.50–7.25 (m, 4 H, ArH), 7.22 (d, 2 H, J = 9 Hz, ArH meta to OH), 6.89 (d, 2 H, J = 9 Hz, ArH ortho to OH), 4.86 (s, 1 H, ArOH), 3.86 (t, 1 H, J = 5 Hz, $CHCH_2CH_3$), 2.66 (q, 2 H, J = 8 Hz, $=CCH_2CH_3$), 2.05–1.57 (m, 2 H, $CHCH_2CH_3$), 0.47 (q, 3 H, J = 7 Hz, $CHCH_2CH_3$); MS 264 (18, M^+), 235 (30), 41 (100); HRMS ($C_{19}H_{20}O$) calcd/found 264.1514/264.1519.

Preparation of Hydroxyindenones 12, 20, and 21. Demethylation of methoxyindenones **11**, **17**, and **18** was performed in molten pyridine hydrochloride, as previously described,[26,2a] providing hydroxyindenones **12**, **20**, and **21**, respectively.

2-Phenyl-3-ethyl-6-hydroxyindenone (12). The crude product was purified by flash chromatography (4:1 hexane–EtOAc), followed by recrystallization from CCl_4–pentane. Lustrous, dark purple-red flakes (30 mg, 46%) were obtained: mp 118–120 °C; ^{1}H NMR (acetone-d_6) δ 8.01 (s, 1 H, ArOH), 7.45–7.30 (m, 5 H, ArH), 7.21 (d, 1 H, J = 8 Hz, ArH on C-4), 6.95 (d, 1 H, J = 2 Hz, ArH on C-7), 6.90 (dd, 1 H, J = 8, 2 Hz, ArH on C-5), 2.76 (q, 2 H, J = 8 Hz, CH_2CH_3), 1.32 (t, 3 H, J = 8 Hz, CH_2CH_3); MS 250 (100, M^+), 235 (20), 207 (16); HRMS ($C_{17}H_{14}O_2$) calcd/found 250.0994/250.0988.

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2-(4-Hydroxyphenyl)-3-ethylindenone (20). The crude product was purified by flash chromatography (7:3 hexane–EtOAc), followed by recrystallization (hexane–EtOAc). Dark red prisms (44 mg, 21%) were obtained: mp 144–147 °C; ^{1}H NMR ($CDCl_3$) δ 7.48 (d, 1 H, J = 7 Hz, ArH on C-7), 7.40 (t, 1 H, J = 7 Hz, ArH on C-5), 7.28 (d, 2 H, J = 9 Hz, ArH meta to OH), 7.24 (t?, 1 H, J = 7 Hz, ArH on C-6), 7.17 (d, 1 H, J = 7 Hz, ArH on C-4), 6.90 (d, 2 H, J = 9 Hz, ArH ortho to OH), 4.90 (s, 1 H, ArOH), 2.72 (q, 2 H, J = 8 Hz, CH_2CH_3), 1.33 (t, 3 H, J = 8 Hz, CH_2CH_3); MS 250 (100, M^+), 235 (36), 217 (11), 207 (28), 189 (11); HRMS ($C_{17}H_{14}O_2$) calcd/found 250.0994/250.0995.

2-(4-Hydroxyphenyl)-3-phenylindenone (21). Purification was achieved by flash chromatography (7:3 hexane–EtOAc), followed by recrystallization from ether–hexane at −30 °C. A red powder was obtained (200 mg, 68%): mp 165–166 °C; IR (KBr) 3400, 1700, 1610, 1590, 1510 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (d, 1 H, J = 7 Hz, ArH on C-7), 7.45–7.21 (m, 7 H, ArH), 7.17 (d, 2 H, J = 9 Hz, ArH meta to OH), 7.11 (d, 1 H, J = 7 Hz, ArH on C-4), 6.73 (d, 2 H, J = 9 Hz, ArH ortho to OH), 4.95 (s, 1 H, ArOH); MS 298 (100, M^+), 281 (60), 269 (40), 252 (32), 239 (64); HRMS ($C_{21}H_{14}O_2$) calcd/found 298.0989/298.0994.

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Substituted Lithium (*E*)-3-Lithio-3-tosyl-2-propenolates: Useful Intermediates in Organic Synthesis†

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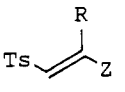
The lithiation of substituted tosylated epoxides **7** derived from allylic sulfones with methyllithium leads to lithium (*E*)-3-lithio-3-tosyl-2-propenolates **5** in a stereoselective manner. The further reaction of these intermediates with different electrophilic reagents (water, deuterium oxide, alkyl halides such as methyl iodide, allyl bromide, or methallyl chloride, and aldehydes such as crotonaldehyde, isobutyraldehyde, or benzaldehyde) in the presence or not of an additive [a copper(I) or magnesium salt and/or tetramethylethylenediamine] affords the functionalized tosylated allylic alcohols **10** in a regio- and stereoselective manner. The oxidation of primary alcohols **10** with manganese dioxide yields the corresponding α,β-unsaturated aldehydes **12**. When enediols **10** are treated with *p*-toluenesulfonic acid, the corresponding tosylated 2,5-dihydrofurans **13** are prepared. Tosylated furans **14** are isolated by oxidative cyclization of diols **10** using pyridinium chlorochromate (PCC) or manganese dioxide followed by dehydration with *p*-toluenesulfonic acid. Finally, for primary diols **10** (R^2 = H), the above-described PCC oxidation leads to the corresponding tosylated α,β-butenolides **16**.

Introduction

The chemistry of vinyl sulfones has been the subject of great attention in recent years due to their versatility in organic synthesis.[1-4] Recently,[5] we described a general method to prepare β-functionalized vinyl sulfones **2** by a tandem iodosulfonylation–dehydroiodination process starting from the appropriate electrophilic olefins **1**. Compounds of the type **2** are interesting in synthesis because they can act as β-acylvinyl cations[5,6] or anions[7,8] when in the last case they have been previously deprotonated. So, this dual behavior represents a typical case of normal or umpoled reactivity,[9] respectively. The lithiated derivatives of 4-tosylbutenone dimethyl ketal **3**[7] and of *N*-isopropyl-3-tosylacrylamide **4**[8] have been recently used as

1



2

R = H, Me
Z = CHO, COMe, CO_2H, CO_2Me, CONHPr, $CON(CH_2)_5$, CN

† Dedicated to Professor E. J. Corey on his 60th birthday.

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(1) For reviews, see: (a) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. (b) Schank, K. In *Methoden der Organischen Chemie* (*Houben-Weyl*); Georg Thieme Verlag: Stuttgart, 1985; Vol. E/11, pp 1132–1298.

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