Optimizing of 2,3-Diarylindenes as Fluorescent Estrogens: Variation of the Acceptor Group, Ortho Substitution of the 2-Ring, and C-1 Methylation

Gregory M. Anstead and John A. Katzenellenbogen*

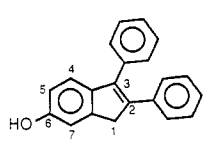
Department of Chemistry, University of Illinois, 1209 W. California St., Urbana, Illinois 61801. *Received February 3, 1988*

In an attempt to elucidate steric and electronic factors that affect the fluorescence and estrogen receptor binding properties of 2,3-diarylindenes, we have prepared and examined the behavior of 11 analogues bearing substituents on the 1-position or on the 2-aryl ring. These compounds were synthesized by alkylation of a 1,2-diarylethanone with 3-methoxybenzyl chloride, followed by cyclodehydration to the indene. The electronic spectra of those compounds without π-electron accepting groups on the 2-aryl ring display the absorbance and fluorescence of a hindered stilbene system; those with nitro and cyano substituents on the 2-aryl ring show charge-transfer character, having a more bathochromic absorption and fluorescence. One bisphenolic nitroindene, in particular, shows a strong, long-wavelength absorption and an intense emission, with a large Stokes' shift that is highly sensitive to solvent polarity. Estrogen receptor binding affinity measurements on these compounds indicate that substituents that twist the pendant aryl rings (such as a 1-methyl group, or an *o*-methyl or trifluoromethyl group on the 2-phenyl ring) increase binding affinity. Bulky (4-bromo) or electron-withdrawing groups (3- and 4-nitro, 4-cyano) on the 2-phenyl group, or its replacement with a 3-pyridyl group, greatly reduce binding affinity, suggesting that the complementary region of the receptor is relatively intolerant of bulk and may have specific hydrogen-bonding requirements. This investigation of the concurrent effects of substituents on the fluorescence properties and receptor binding affinity of 2,3-diarylindenes should assist in the development of effective, inherently fluorescent ligands for the estrogen receptor.

The estrogen receptor (ER) content of breast tumors is routinely assayed radiometrically as a prognostic indicator of patient response to endocrine therapy.[1] The absence of ER (ER^-) provides an excellent correlation for lack of hormone responsiveness; however, the presence of ER (ER^+) only provides a correlation of about 60%.[2] One explanation for the poor correlation obtained in the ER^+ cases is the cellular heterogeneity of the tumor. The radiometric assay, based on tissue homogenates, can provide only an average ER concentration. An ER^+ tumor may be composed of a large proportion of ER^+ cells with low ER content, or a low percentage of ER^+ cells with high ER titers. These differences may have a bearing on the clinical response to endocrine treatment.[3] This situation mandates the development of a technique for cell-by-cell determination of the ER content.[4]

ER-targeted fluorophores have been advocated for the quantitation of ER in individual cells by flow cytometry or fluorescence microscopy.[5] However, the existing fluorescent estrogens have not fulfilled the necessary biological (high ER binding affinity) and spectroscopic (long emission wavelength, high fluorescence quantum yield) criteria.[6]

The 2,3-diphenylindene 1 has been described as an inherently fluorescent ER ligand.[7] However, the ER binding affinity (RBA) of 1 was modest (9% of estradiol) and the emission maximum (at 420 nm) was in the range of cellular autofluorescence.[8] Thus, structural modifications were sought to enhance the RBA and bathochromically shift the emission maximum.



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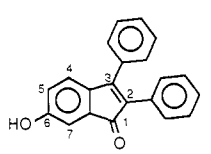

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The higher RBA of 2,3-diphenylindenone 2 (59% that of estradiol) and the crystallographic results obtained for 1 and 2 led to the hypothesis that as the torsional angles of the two pendant aryl rings increase, the RBA increases as well.[7] However, the introduction of the carbonyl at C-1 resulted in decreased fluorescence by facilitating intersystem crossing.[7] Therefore, modifications were considered that would increase the ring twist, but not totally disrupt the electronic integrity of the *trans*-stilbene fluorophore. To achieve the torsional increase, substitution at the 1-position of the indene and the ortho position of the 2-ring was examined. To achieve a red-shifted and environmentally sensitive fluorescence, a donor/acceptor system is necessary.[9] In this case, the 2-aryl ring was altered in an attempt to obtain these desirable fluorescence properties, but without severely compromising the RBA.

Table I. Steric and Electronic Constants of Acceptor and Other Groups[a]

group	E_s[b]	σ_p[c]	σ_p^-[d]
CN	−0.51	0.66	0.90
NO_2	−1.28	0.78	1.24
CF_3	−2.40	0.54	0.65
CH_3	−1.24	−0.14	−0.15
H	0.00	0.00	0.00
Br	−1.16	0.26	0.28
OH	−0.55	−0.22	−0.16

[a] Values are taken from ref 13. [b] Taft steric parameter. [c] Hammett σ_p electronic constant. [d] Hammett σ_p^- through resonance electronic constant.

* Address correspondence to John A. Katzenellenbogen, 461 Roger Adams Laboratory, Box 37, 1209 W. California St., University of Illinois, Urbana, IL 61801.

(1) Griffiths, K.; Nicholson, R. I.; Blaney, R. W.; Elston, C. W. In *Estrogen/Antiestrogen Action and Breast Cancer Therapy*; Jordan, V. C., Ed.; University of Wisconsin Press: Madison, 1986; pp 325–340.
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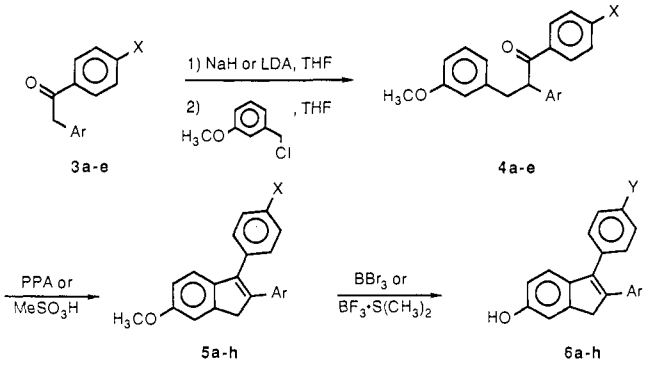
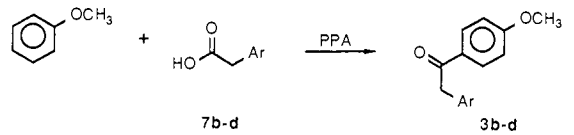
Scheme I



a,	Ar = 4-CN phenyl	f	Ar = 3-NO_2 phenyl
b	Ar = 4-Br phenyl	g	Ar = 4-NO_2 phenyl
c	Ar = 2-CF_3 phenyl	h	Ar = 4-NO_2 phenyl
d	Ar = 2-CH_3 phenyl		
e	Ar = 3-pyridyl	a-g	X = OCH_3, Y = OH
		h	X = Y = H

Scheme II



b, Ar = 4-Br phenyl
c, Ar = 2-CF_3 phenyl
d, Ar = 2-CH_3 phenyl

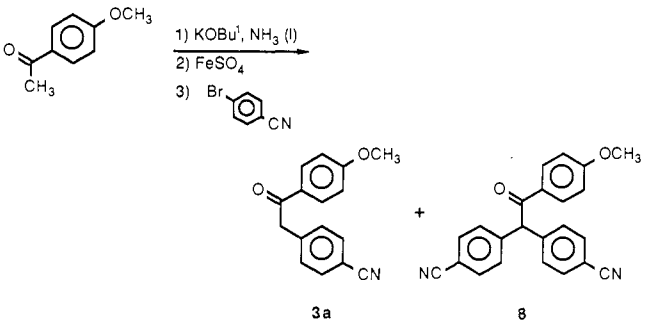
Classically, the acceptor group receives π-electron density in the excited state (i.e., intramolecular charge transfer (ICT) occurs).[10] Recently, the twisted intramolecular charge transfer (TICT) fluorescence mechanism has been formulated, in which the excited-state molecule exists as an intramolecular radical cation–radical anion pair.[11] Thus, if fluorescence emission proceeds by a TICT mechanism, it might be expected that any group capable of negative charge stabilization may be a useful acceptor group. Considering the possible exploitation of either an ICT or TICT emission pathway, we designed a series of donor/acceptor-substituted 2,3-diarylindenes (**6a–h**).

Of some possible acceptor groups (Table I), chemically stable groups of minimal steric demand, capable of either accommodation of π-electron transfer (p-NO_2, p-CN) or radical anion stabilization (m-NO_2, o-CF_3, 3-pyridyl), were selected. Although the strength of donor groups is provided by a theoretically meaningful and experimentally accessible property, the ionization energy, the strength of an acceptor group, the electron affinity, is not so easily obtained.[12] Thus, σ constants were examined as a guide to acceptor strength (Table I).

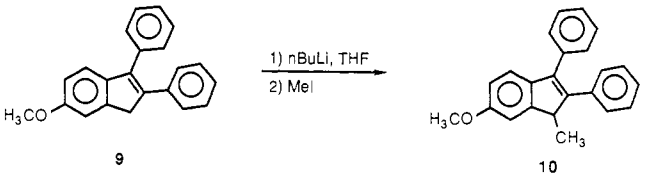
Results and Discussion

Synthesis. The 2-ring-modified 2,3-diarylindenes **6a–e** were elaborated from the deoxybenzoins **3a–e** in three steps (Scheme I). The syntheses of nitroindenes **5f–h** have been described elsewhere.[14] The p-methoxydeoxybenzoin systems **3b–d** were prepared by Friedel–Crafts acylation of anisole with the appropriately substituted phenylacetic acid (Scheme II). Pyridylethanone **3e** was prepared as previously described.[15]

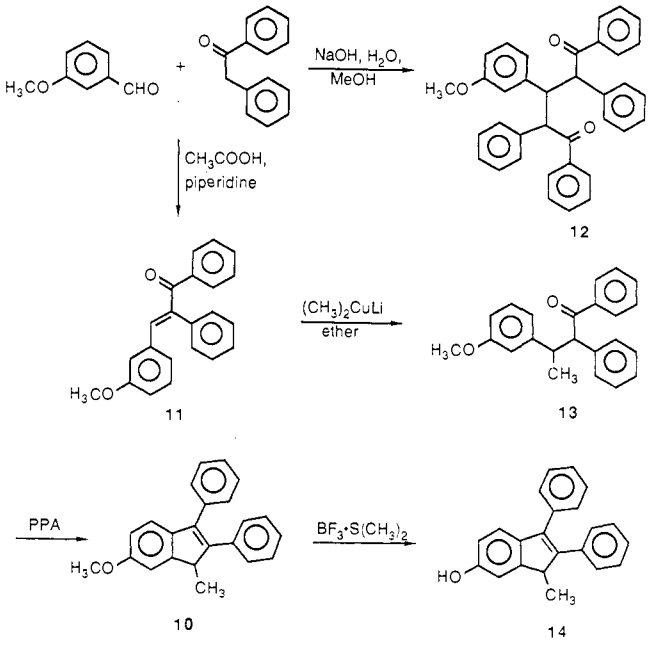
Scheme III



Scheme IV



Scheme V



Due to the hydrolytic instability of the nitrile to the conditions of Scheme II, the ferrous ion catalyzed $S_{RN}1$ reaction[16] was used to prepare cyanodeoxybenzoin **3a** (Scheme III). The hydrolytic instability of the nitrile also necessitated a milder method for the cyclodehydration step of Scheme I. Treatment of the cyanotriaryl ketone **4a** with polyphosphoric acid gave the desired indene **5a**, but also the corresponding acid and amide hydrolysis products. The extent of nitrile hydrolysis in the cyclodehydration was reduced by the use of $MeSO_3H/P_2O_5$ as the condensing agent.[17] Attempts to prepare cyanoindene **5a**

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Table II. Absorption and Emission Maxima of Indene Methyl Ethers and Related Compounds[a]

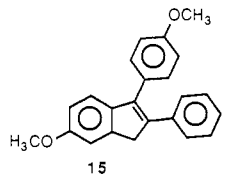
compd	λ_{abs}, nm	ϵ	λ_{em}, nm	Stokes' shift, cm^{-1}
15[b]	318	19600	412	7180
5a	358	24000	438	5100
5c	280	12400	409	11260
5d	290	11800	420	10670
5e	324	18100	424	7280
5f[b]	330	18000	620	14170
5g[b]	400	16200	569	7430
5h[b]	394	20600	565	7680
10	312	17200	416	8010
4-methoxy-*trans*-stilbene[b]	304	27800	354	4650
4-methoxy-*cis*-stilbene[c,d]	280	10600	*e*	*f*

[a] Spectra were obtained in EtOAc, unless otherwise indicated. [b] Reference 14. [c] Spectrum obtained in 95% ethanol. [d] Reference 25. [e] No fluorescence observed for fluid solutions at room temperature (ref 26). [f] Not applicable.

from the bromoindene **5b** by aromatic cyanation (CuCN[18] or NaCN and $Pd(PPh_3)_4$[19]) were not successful.

The first attempt to prepare 1-methyl-2,3-diphenylindene **10** involved methylation of the indenyl anion of **9** (Scheme IV). Although this procedure did provide the desired product, it was difficult to separate it from unreacted starting material. Alternatively, the methyl group was introduced by conjugate addition to enone **11** (Scheme V). If typical aldol conditions[20] (NaOH, MeOH) are employed in the condensation of *p*-anisaldehyde and deoxybenzoin, only the product (**12**) of sequential aldol condensation/conjugate addition of deoxybenzoin anion is obtained. However, the conditions of Mittal et al.[21] (acetic acid, piperidine) proved to be more efficacious for the preparation of enone **11**. The assumed *E* stereochemistry of enone **11** is based on literature precedent;[21] TLC and ^1H NMR showed no evidence for the presence of both geometric isomers. The diastereomeric ketones **13** were not rigorously separated, but carried on to the next step.

Absorption and Emission Properties. The absorption and emission maxima of the indene methyl ethers **5a,c–h** and **10** are listed in Table II. Data for dimethoxyindene **15** and 4-methoxy-*trans*- and -*cis*-stilbene are included as well. The absorbance and fluorescence properties of **15**, **5f–h**, and 4-methoxy-*trans*-stilbene have been treated in more detail elsewhere.[14]



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With respect to their absorption and fluorescence behavior, the indenes can be divided into two classes: the sterically hindered *trans*-stilbenoids **15**, **5c**, **5d**, **5e**, and **10** and the charge-transfer compounds **5a** and **5f-h**. The former are characterized by their reduced extinction coefficient compared to 4-methoxy-*trans*-stilbene, the absence of extreme bathochromic shifts in the absorbance or fluorescence spectra, or, in the cases of severe steric hindrance (**5c** and **5d**), a substantial hypsochromic shift of the absorbance maxima.

Table III. Solvent Sensitivities of the Absorption and Emission Maxima for **6g**

solvent	E_T[a]	λ_{abs}, nm	ϵ_{em}, nm	ϕ_F
heptane		402	490	0.041
cyclohexane	31.2	404	496	*b*
CCl_4	32.5	406	529	*b*
benzene	34.5	408	541	0.870
ether	34.6	406	554	*b*
dioxane	36.0	404	572	*b*
tetrahydrofuran	37.4	412	589	0.520
ethyl acetate	38.1	406	581	0.480
chloroform	39.1	410	634	*b*
CH_2Cl_2	41.4	408	624	*b*
dimethylacetamide	43.7	424	668	*b*
acetonitrile	46.0	406	672	*b*
1-butanol	50.8	416	602	*b*
ethanol	51.9	412	601	*b*
water	63.1	414	*c*	*b*

[a] Empirical solvent polarity parameter (ref 29). [b] Not determined. [c] Not observed.

An increased Stokes' shift ($energy_{absorbance} - energy_{fluorescence}$) is also indicative of steric hindrance to planarity in stilbenes.[22] On the basis of Stokes' shifts of the sterically hindered stilbenes, the order of increasing planarity is *o*-trifluoromethylindene **5c** < *o*-methylindene **5d** < 1-methylindene **10** < pyridylindene **5e** ≈ dimethoxyindene **15**. The calculation of a torsional angle for the *trans*-stilbene unit of the indenes, based on the relationship $\cos^2 \theta = \epsilon/\epsilon_0$,[23] where θ is the torsional angle, ϵ_0 and ϵ are the extinction coefficients of the model planar compound (in this case, 4-methoxy-*trans*-stilbene) and the test compound, respectively, is only valid for cases of ideal sp^2 hybridization.[24] In the indenes, substantial distortions of the olefinic bond angles occur in the indenyl nucleus, invalidating this approach.[7]

X-ray crystallography of an analogous compound suggests a twist angle of 27° for the 2-ring in **15**;[7] on the basis of UV and fluorescence data, a qualitative picture of the molecular geometry in the sterically hindered indenes is possible. Presumably, **5e** is topographically similar to **15**, 1-methylindene **10** has greater torsion, and in **5c** and **5d** the torsion is quite severe.

The charge-transfer compounds are recognized by their sizeable bathochromic shifts in absorption and emission maxima relative to **15**. These shifts are quite modest for cyanoindene **5a**, indicating only a small degree of charge transfer. Both *p*-nitroindenes **5g** and **5h** show low-energy absorbance and highly red-shifted emission, suggestive of an ICT fluorescence mechanism. The *m*-nitroindene shows only a slightly red-shifted absorbance band, but a tremendously bathochromic emission, indicative of the very polar TICT state.[11]

The short-wavelength emission of cyanoindene **5a** is not useful for whole cell studies because of interference from intracellular fluors that emit below 500 nm.[8] Although *m*-nitroindene **5f** satisfies the requirement for long-wavelength emission, the emission intensity is low, typical of fluorescence arising from a TICT state.[11] Due to the limited number of ER targets in a cell, this low-intensity fluorescence presents a severe limitation.[27] The *p*-nitro-

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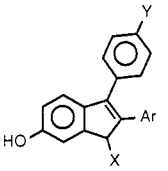
Table IV. Estrogen Receptor Binding Affinities[a]



no.	X	Y	Ar	RBA,[b] %
1[c]	H	H	C_6H_5	8.9
6a	H	OH	4-CN-C_6H_4	1.0
6b	H	OH	4-Br-C_6H_4	0.76
6c	H	OH	2-CF_3-C_6H_4	38
6d	H	OH	2-CH_3-C_6H_4	30
6e	H	OH	3-pyridyl	0.05
6f	H	OH	3-NO_2-C_6H_4	0.60
6g	H	OH	4-NO_2-C_6H_4	0.69
6h	H	H	4-NO_2-C_6H_4	0.46
14	CH_3	H	C_6H_5	12
16[d]	H	OH	C_6H_5	4.7
17[c]	H	OH	4-HO-C_6H_4	15
18[d]	H	H	4-HO-C_6H_4	28

[a] Determined by competitive radiometric binding assay using rat uterine cystosol as a source of receptor, [^{3}H]estradiol as tracer, and dextran-coated charcoal as absorbant for free ligand. For details, see ref 30. [b] Binding affinities are expressed relative to that of estradiol =100% (RBA = relative binding affinity) and are the average of duplicate determinations. [c] Reference 7. [d] Reference 31.

indenes **5g**,h show intense emission beyond the wavelength range of cellular autofluorescence. Furthermore, the long absorption wavelength permits low-energy excitation, minimizing photodamage in a biological system.

To confirm the utility of the nitroindene fluorochrome in a phenolic system that had potential for ER binding, the absorbance and fluorescence properties of diphenolic nitroindene **6g** were evaluated in a number of solvents (Table III). In the UV–vis spectra, the lowest energy $\pi \rightarrow \pi^*$ band shows a moderate red shift as solvent polarity increases. Under neutral conditions, the absorption band varies from 402 to 426 nm. The emission maximum is extremely solvent-dependent, ranging from 490 nm in heptane to 672 nm in acetonitrile. The fluorescence intensity of **6g** is greatest in ethereal solvents and low in alkanes and alcohols. Quantum yields range from 0.041 in heptane to 0.87 in benzene. The compound is essentially nonfluorescent in water, but does emit (at 570 nm) in buffer solutions of bovine serum albumin.

To assess the predictability of solvent response, a plot[28] of the emission frequency vs E_T,[29] an empirical solvent polarity parameter, gave a straight line with a correlation coefficient of –0.96 for the aprotic solvents. Upon inclusion of ethanol and 1-butanol, the correlation coefficient dropped to –0.66. From the results in pure solvents, it is apparent that emission from **6g** demonstrates tremendous environmental sensitivity and satisfies the spectroscopic requirements of a fluorophore intended for use in biological systems.[14]

The pyridylindene **5e** and the trifluoromethyl indene **5c** show no evidence for charge transfer in the absorption or emission spectra. Although pretwisting in the ground state predisposes a system toward TICT emission, the weak methoxy donor and weak acceptor unit of the trifluoromethyl indene and pyridylindene must not meet the energetic requirements for the formation of a TICT state.[11a]

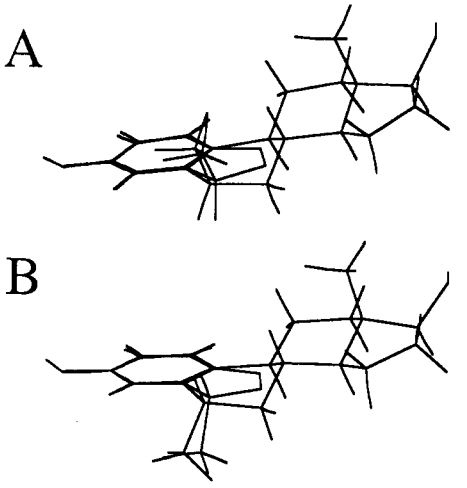


Figure 1. (A) Superposition of (*S*)-14 with 6β-methylestradiol. (B) Superposition of (*R*)-14 with 6α-methylestradiol. The structures in each case were determined by molecular mechanics. The pendant aryl rings of 14 are omitted due to the uncertainty of the torsional angles by the current force field method. For superpositions, a rigid fit of the indene phenol with the steroid phenol was adopted.

Structure–Receptor Binding Affinity Relationships. The ER binding affinities (RBA) were determined in a competitive protein binding assay (see Table IV). Analogous compounds are included for the purpose of comparison.

The *o*-trifluoromethyl indene **6c** and *o*-methyl indene **6d** show 8.1- and 6.4-fold enhancements, respectively, in RBA relative to the protio analogue **16**.[31] In agreement with earlier observations in other triarylethylenes,[7,32] the RBA increase in these compounds parallels the increase in the torsional angles of the pendant aryl groups: **16** < **6d** < **6c**. This order is consistent with the increasing size (and thus, torsional influence) of the ortho substituents: H < CH_3 < CF_3 (cf. Table I). A priori, the RBA enhancement cannot be ascribed in toto to the regional alteration in the overall molecular shape produced by the torsional change in the pendant aryl groups. The lipophilic methyl and trifluoromethyl groups may also enhance binding affinity by local hydrophobic and dispersive interactions with the ER. There appears to be no detrimental electronic perturbation produced by the highly electron-withdrawing trifluoromethyl group.[33]

The RBA enhancement of 1-methylindene **14** compared to its protio analogue monohydroxindene **1** is quite modest. Bear in mind that **14** is a racemate; so if only one enantiomer were active, its RBA value could be as high as 24% (i.e., 2 × 12%). Still, this is only a 2.7-fold increase relative to hydroxyindene **1**, less than half of the effect of *o*-methyl substitution on the RBA of dihydroxyindene **15**. The results from the UV and fluorescence spectra indicate a more planar structure for 1-methylindene **14** than *o*-

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methylindene **6d**, again consistent with a model in which RBA increases with increasing torsion. However, there may be different local steric and electronic constraints of the indene 1-position and the ortho position of the 2-ring. If an orientation of the receptor-bound 2,3-diarylindenes is assumed in which the indene nucleus imitates the steroid AB rings,[34] the indenyl 1-position approximates the steroid 6-position. The 6α-[35] and 6β-methyl[36] analogues of estradiol both have a lower RBA than the parent compound (31% and 3.6%, respectively). From Figure 1, it is suggested that both 1-methylindene enantiomers may partially mimic the steric effect produced by the introduction of a 6-methyl group on estradiol. Perhaps there are competing influences on the RBA of **14**: an increase in binding free energy due to the torsional enhancement and a decrease in binding free energy due to the steric interference with the receptor-essential volume[37] at a quasi-steroidal 6-position.

Aside from para hydroxylation of the 2-ring (as in **17** and **18**) and ortho substitution (as in **6c** and **6d**), the 2-ring did not show tolerance for substitution. The higher RBA of phenols **17** and **18** may be attributed to a hydrogen-bonding interaction with the ER.[31] Nitro and cyano groups may accept a hydrogen bond (although more poorly than a phenol),[38] suggesting perhaps that the hydroxyl in this position is a hydrogen-bond donor. The intolerance of the 2-ring to modification is not specific to the para position; *m*-nitroindene **6f** has an affinity similar to its *p*-nitro isomer **6a**.

Of all the 2-ring modified compounds, pyridylindene **6e** has the lowest RBA. Although the ER accommodates basic groups outside the central steroidal or nonsteroidal framework (i.e., as in the basic ether sidechains of the antiestrogens[39]), it is less tolerant of nitrogen substitution in the molecular core area.[40,41] The polarity of the nitrogen function may disrupt the requisite hydrophobic interactions within the ER binding pocket.[41,42] The lower RBA of monophenolic nitroindene **6h** compared to diphenolic nitroindene **6g** is anomalous, considering that the 3-ring *p*-hydroxyl group decreases the RBA in a comparison of **1** with **16** or **17** with **18**.

Conclusions

The goal of preparing a practical fluorescent estrogen remains elusive. Although the *p*-nitroindenes **6g** and **6h** display excellent fluorescence properties, the RBA of these compounds are less than 1% of estradiol, too low to be useful in heterogeneous preparations of the ER or in whole cells. On the basis of results reported herein, however, several strategies for the future development of an improved fluorescent estrogen based on the 2-arylindene system are evident. We are currently exploring additional structure–RBA–fluorescence interrelations in the 2-arylindenes.

Experimental Section

General Procedures. 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,[43] with Woelm 32–63-μm silica gel.

Proton nuclear magnetic resonance (^{1}H 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). Infrared (IR) spectra were obtained on 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 (unless otherwise noted) and follow the following 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. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois.

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".

Fluorescence. The corrected emission spectra were acquired on a Spex Fluorolog 111 spectrofluorimeter. Quantum yields were calculated as previously described,[44] with acridine yellow G as the standard.[45] To minimize any special solvent effects,[46] the compound was dissolved in an inert solvent (THF) and diluted 100–400 times.

Molecular Mechanics and Graphics. Molecular mechanics calculations were performed with the MAXIMIN option of the SYBYL Molecular Modeling System (Version 3.4, Tripos Associates, St. Louis, MO). The initial geometries of 6α- and 6β-methylestradiol were based on the crystal structure of estradiol hemihydrate.[47] The initial structure of 1-methyl-2,3-diphenyl-6-hydroxyindene was based on the crystal structure of 2,3-bis-(4-methoxyphenyl)-6-methoxyindene.[7] Molecular superpositions were performed with the SYBYL system using the FIT command.

General Conditions for the $S_{RN}1$ Reaction. Potassium *tert*-butoxide (1.30 g, 11.6 mmol) and 4-methoxyacetophenone (1.50 g, 10.0 mmol) were added to dry liquid ammonia (100 mL). After 50 min, $FeSO_4$ (45 mg, 0.3 mmol) and 4-bromobenzonitrile (346 mg, 2.00 mmol) were added. The reaction was quenched after 4 h by addition of NH_4NO_3. Product isolation (water, ether), Kugelrohr distillation (200 °C, 4 Torr), and flash chromatography (4:1 hexane–EtOAc) of the pot residue afforded **3a** and **8**, in order of elution.

1-(4-Methoxyphenyl)-2-(4-cyanophenyl)ethanone (3a). This compound was obtained as a white solid (244 mg, 48%): mp 102–105 °C; IR ($CHCl_3$) 2220, 1670, 1600, 1260, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to CO), 7.63 (d, 2 H, *J* = 8 Hz, Ar*H* ortho to CN), 7.37 (d, 2 H, *J* = 8 Hz, Ar*H* ortho to CH_2), 6.96 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3), 4.31 (s, 2 H, CH_2), 3.88 (s, 3 H, OCH_3); MS (10 eV), *m/z* 251 (0.4, M^+), 135 (100). Anal. ($C_{16}H_{13}NO_2$) C, H, N.

2,2-Bis(4-cyanophenyl)-4-(methoxyphenyl)ethanone (8). This compound was obtained as a foamy white solid: mp 70–72

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°C; NMR ($CDCl_3$) δ 7.94 (d, 2 H, J = 9 Hz, Ar*H* ortho to CO), 7.64 (d, 4 H, J = 8 Hz, Ar*H* ortho to CN), 7.37 (d, 4 H, J = 8 Hz, Ar*H* meta to CN), 6.92 (d, 2 H, J = 9 Hz, Ar*H* ortho to OCH_3), 6.08 (s, 1 H, C*H*), 3.86 (s, 3 H, OCH_3); MS (10 eV), m/z 352 (1, M^+), 217 (7), 136 (100), 107 (79), 92 (21). Anal. ($C_{23}H_{18}N_2O_2$) C, H, N; C: calcd, 78.39; found, 77.52.

General Method for Preparation of 4-Anisyl Benzyl Ketones. The substituted phenylacetic acid (16.5 mmol) and anisole (21.5 mmol) were added to polyphosphoric acid (PPA; 10 times the weight of the acid). The mixture was stirred at 40–70 °C and monitored by TLC. The reaction was complete in 0.5–5 h. Product isolation (ice water, EtOAc, saturated $NaHCO_3$) was followed by purification as described.

1-(4-Methoxyphenyl)-2-(4-bromophenyl)ethanone (3b). This compound was purified by recrystallization from methanol at −20 °C. A white solid was obtained (2.26 g, 81%): mp 135–137 °C (lit.[48] mp 140–141 °C); ^1H NMR ($CDCl_3$) δ 7.99 (d, 2 H, J = 9 Hz, Ar*H* ortho to CO), 7.44 (d, 2 H, J = 8 Hz, Ar*H* ortho to Br), 7.13 (d, 2 H, J = 8 Hz, Ar*H* meta to Br), 6.93 (d, 2 H, J = 9 Hz, Ar*H* ortho to OCH_3), 4.18 (s, 2 H, CH_2), 3.86 (s, 3 H, OCH_3); MS (10 eV), m/z 306 (2, M^+), 304 (2, M^+), 135 (100), 107 (4). Anal. ($C_{15}H_{13}BrO_2$) C, H, Br.

1-(4-Methoxyphenyl)-2-(2-methylphenyl)ethanone (3d). This compound was purified by recrystallization from methanol (two crops; at −30 and −78 °C). A White solid was obtained (1.24 g, 78%): mp 80–81 °C; IR ($CHCl_3$) 3010, 1675, 1600, 1260, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (d, 2 H, J = 9 Hz, Ar*H* ortho to CO), 7.25–7.10 (m, 4 H, Ar*H*), 6.94 (d, 2 H, Ar*H* ortho to OCH_3), 4.25 (s, 2 H, CH_2), 3.86 (s, 3 H, OCH_3); MS (10 eV), m/z 240 (1, M^+), 135 (100), 107 (6). Anal. ($C_{16}H_{16}O_2$) C, H.

1-(4-Methoxyphenyl)-2-[2-(trifluoromethyl)phenyl]ethanone (3c). Purification was achieved by flash chromatography (hexane–EtOAc 5:1). A clear oil was obtained (1.24 g, 91%): IR ($CHCl_3$) 1690, 1600, 1325, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (d, 2 H, J = 9 Hz, Ar*H* ortho to CO), 7.69 (d, 1 H, J = 9 Hz, Ar*H* ortho to CF_3), 7.58–7.30 (m, 3 H, Ar*H*), 6.96 (d, 2 H, J = 9 Hz, Ar*H* ortho to OCH_3), 4.45 (br s, 2 H, CH_2), 3.88 (s, 3 H, OCH_3); MS, m/z 135 (100), 77 (18). Anal. ($C_{16}H_{13}F_3O_2$) C, H, F.

3-Methoxybenzylation of Deoxybenzoins. Method A. This method (with minor variations) was used for the synthesis of triaryl ketones **4b**, **4d**, and **4e**. Sodium hydride (8.6 mmol, 50% dispersion in oil) was rinsed with hexane and suspended in THF (5 mL). The substituted deoxybenzoin (6.88 mmol), dissolved in THF (30 mL), was added dropwise over 1 h. After enolate formation was complete (ca. 2 h), the enolate solution was transferred via cannula into a solution of 3-methoxybenzyl chloride (13.8 mmol) in THF (5 mL). The solution was heated at 40–50 °C until the reaction was complete, as determined by TLC. Product isolation (5% HCl, ethyl acetate, brine) was followed by purification as described.

1-(4-Methoxyphenyl)-2-(4-bromophenyl)-3-(3-methoxyphenyl)-1-propanone (4b). Purification was achieved by trituration with ether (−30 °C) and recrystallization from methanol at −30 °C. The mother liquors were flash chromatographed (9:1 hexane–THF) and recrystallized as above. A white solid (2.47 g, 85%) was obtained: mp 88–89 °C; ^1H NMR ($CDCl_3$) δ 7.88 (d, 2 H, J = 9 Hz, Ar*H* ortho to CO), 7.38 (d, 2 H, J = 8 Hz, Ar*H* ortho to Br), 7.15–7.05 (m, 3 H, Ar*H*), 6.85 (d, 2 H, J = 9 Hz, Ar*H*, meta to CO), 6.72–6.55 (m, 3 H, Ar*H*), 4.72 (t, 1 H, J = 7 Hz, C*H*(Ar)CO), 3.81 (s, 3 H, $COArOCH_3$), 3.70 (s, 3 H, OCH_3), 3.48 (dd, 1 H, J = 14, 7 Hz, CH_2), 3.00 (dd, 1 H, J = 14, 7 Hz, CH_2); MS, m/z 424 (1, M^+), 201 (6), 149 (3), 135 (100), 107 (5). Anal. ($C_{23}H_{21}BrO_3$) C, H, Br.

1-(4-Methoxyphenyl)-2-(2-methylphenyl)-3-(3-methoxyphenyl)-1-propanone (4d). The preparation was similar to that above, except the enolate generation required 8 h and LiI (0.15 molar equiv) was added with the 3-methoxybenzyl chloride. Purification was achieved by flash chromatography (4:1 hexane–acetone) and rechromatography of the mixed fractions (9:1 hexane–EtOAc); a clear oil was obtained (1.43 g, 96%): IR ($CHCl_3$) 3020, 1730, 1670, 1260, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, 2 H, J = 9 Hz, Ar*H* ortho to CO), 7.30–7.08 (m, 6 H, Ar*H*), 6.79 (d, 2 H, J = 9 Hz, Ar*H* meta to CO), 6.70 (d, 1 H, J = 8 Hz, Ar*H* para to CH_2), 6.59 (s, 1 H, Ar*H* ortho to OCH_3, ortho to CH_2), 4.87 (t, 1 H, J = 8 Hz, C*H*(Ar)CO), 3.77 (s, 3 H, $COArOCH_3$), 3.67 (s, 3 H, OCH_3), 3.49 (dd, 1 H, J = 11, 7 Hz, CH_2), 2.91 (dd, 1 H, J = 13, 6 Hz, CH_2); MS, m/z 360 (2, M^+), 178 (1), 135 (100), 107 (6). Anal. ($C_{24}H_{24}O_3$) C, H.

1-(4-Methoxyphenyl)-2-(3-pyridyl)-3-(3-methoxyphenyl)-1-propanone (4e). The preparation was similar to that above, except DMF was used as the solvent. After product isolation (water, EtOAc, water), the product was purified by flash chromatography (ether) and rechromatography (ether) of the mixed fractions. A yellowish oil was obtained (916 mg, 60%): ^1H NMR ($CDCl_3$) δ 8.44 (d, 2 H, J = 2 Hz, pyridyl C*H* adjacent to N), 7.90 (d, 2 H, J = 9 Hz, Ar*H* ortho to CO), 7.64 (m, 1 H, pyridyl C*H* adjacent to CH), 7.22 (dd, 1 H, J = 8, 5 Hz, pyridyl C*H* meta to CH), 7.12 (t, 1 H, J = 8 Hz, Ar*H* meta to CH_2), 6.85 (d, 2 H, J = 9 Hz, Ar*H* meta to CO), 6.69 (dd, 1 H, J = 8, 2 Hz, Ar*H* ortho to CH_2, para to OCH_3), 6.65 (d, 1 H, J = 8 Hz, Ar*H* para to CH_2), 6.58 (d, 1 H, J = 2 Hz, Ar*H* ortho to OCH_3, ortho to CH_2), 4.80 (t, 1 H, J = 7 Hz, C*H*(Ar)CO), 3.81 (s, 3 H, $COArOCH_3$), 3.70 (s, 3 H, OCH_3), 3.51 (dd, 1 H, J = 14, 7 Hz, CH_2), 3.03 (dd, 1 H, J = 14, 7 Hz, CH_2); MS, 347 (15, M^+), 227 (3), 135 (100), 106 (7). Anal. ($C_{22}H_{21}NO_3$) C, H, N.

3-Methoxybenzylation of Deoxybenzoins. Method B. The following procedure, exemplified by the synthesis of cyano ketone **4a**, was also used for the synthesis of trifluoromethyl ketone **4c**.

1-(4-Methoxyphenyl)-2-(4-cyanophenyl)-3-(3-methoxyphenyl)-1-propanone (4a). Diisopropylamine (201 mg, 1.99 mmol) was dissolved in THF (5 mL) and the solution was cooled to 0 °C. *n*-Butyllithium (1.2 mL of a 1.6 M solution in hexane, 1.95 mmol) was added. After 0.5 h, cyanodeoxybenzoin **3a** (500 mg, 1.99 mmol), dissolved in THF (30 mL), was added dropwise over 1 h. After 2 h, 3-methoxybenzyl chloride (467 mg, 2.99 mmol) and LiI (0.0995 mmol) were added, and the reaction was heated at reflux overnight. Product isolation (5% HCl, EtOAc), flash chromatography (4:1 hexane–EtOAc), and rechromatography of the edge fractions provided 665 mg (90%) of a clear, slightly yellow oil: ^1H NMR ($CDCl_3$) δ 7.88 (d, 2 H, J = 9 Hz, Ar*H* ortho to CO), 7.55 (d, 2 H, J = 8 Hz, Ar*H* ortho to CN), 7.35 (d, 2 H, Ar*H* meta to CN), 6.86 (d, 2 H, Ar*H* meta to CO), 6.75–6.55 (m, 4 H, Ar*H*), 4.83 (t, 1 H, J = 7 Hz, C*H*(Ar)CO), 3.83 (s, 3 H, $COArOCH_3$), 3.71 (s, 3 H, OCH_3), 3.55 (dd, 1 H, J = 14, 8 Hz, CH_2), 3.03 (dd, 1 H, J = 14, 8 Hz, CH_2); MS, m/z 371 (0.4, M^+), 236 (1), 203 (1), 190 (1), 172 (1), 165 (1), 135 (100); HRMS calcd/found ($C_{24}H_{21}NO_3$) 371.1521/371.1514.

1-(4-Methoxyphenyl)-2-[2-(trifluoromethyl)phenyl]-3-(3-methoxyphenyl)-1-propanone (4c). This compound was purified by flash chromatography (9:1 hexane–EtOAc). A yellowish oil was obtained (1.26 g, 93%): IR ($CHCl_3$) 1670, 1600, 1310, 1260, 1240, 1170, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) 7.84 (d, 2 H, J = 9 Hz, Ar*H* ortho to CO), 7.70 (d, 1 H, J = 8 Hz, Ar*H* ortho to CF_3), 7.64–6.85 (m, 3 H, Ar*H*), 6.80 (d, 2 H, J = 9 Hz, Ar*H* ortho to OCH_3), 6.69 (dd, 1 H, J = 8, 2 Hz, Ar*H* para to CH_2), 5.29 (dd, 1 H, J = 10, 4 Hz, CH_2), 3.89 (t, 1 H, J = 10 Hz, C*H*(Ar)CO), 3.77 (s, 3 H, OCH_3 para to CO), 3.74 (s, 3 H, OCH_3), 2.97 (dd, 1 H, J = 10, 4 Hz, CH_2); MS, m/z 414 (1, M^+), 165 (1), 135 (100), 77 (11). Anal. ($C_{24}H_{21}F_3O_3$) C, H, F.

(*E*)-3-(3-Methoxyphenyl)-1,2-diphenyl-2-propen-1-one (11). Deoxybenzoin (3.0 g, 0.015 mol) and 3-anisaldehyde (2.1 g, 0.015 mol) were dissolved in 80 mL of benzene. Acetic acid (3 mL) and piperidine (1 mL) were added, and the solution was heated at reflux. Water and wet benzene were removed with a Dean–Stark trap, with fresh benzene also added. After 36 h, product isolation (water, EtOAc, brine) and flash chromatography (9:1 hexane–EtOAc) afforded a pinkish oil (3.8 g, 79%); an analytical sample was obtained by recrystallization from EtOAc–hexane at −30 °C. The resulting white powder had the following characteristics: mp 84–85.5 °C; IR ($CHCl_3$) 1660, 1590, 1570, 1270, 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00 (d, 2 H, J = 7 Hz, Ar*H* ortho to CO), 7.55–7.08 (m, 9 H, Ar*H* and =C*H*), 6.93–6.81 (m, 3 H, Ar*H*), 6.71 (dd, 1 H, J = 9, 2 Hz, Ar*H* para to =C, ortho to OCH_3), 3.63 (s, 3 H, Ar*H*); MS, m/z 314 (100, M^+), 283 (14), 209 (12), 105 (100). Anal. ($C_{22}H_{18}O_2$) C, H.

1,2,4,5-Tetraphenyl-3-(3-methoxyphenyl)-1,5-pentanedione (12). Deoxybenzoin (2.0 g, 0.015 mol) and 3-anisaldehyde (2.1 g, 0.015 mmol) were dissolved in methanol (25 mL), and this

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solution was added to 20 mL of 2.5 M NaOH. After 18 h at 25 °C, the reaction mixture was heated at reflux for 4 h. The mixture was cooled to 0 °C and the resulting white precipitate was recovered (2.6 g, 65%): mp 208–210 °C; ^{1}H NMR ($CDCl_3$) δ 7.78–7.55 (m, 4 H, Ar*H* ortho to CO), 7.45–7.10 (m, 11 H, Ar*H*), 7.05 (s, 5 H, Ph*H*), 6.89 (t, 1 H, *J* = 8 Hz, Ar*H* meta to OCH_3), 6.70 (dd, 1 H, *J* = 8, 1 Hz, Ar*H* para to OCH_3), 6.59 (br s, 1 H, Ar*H* ortho to OCH_3, CH), 6.45 (m, 1 H, Ar*H* ortho to OCH_3, para to CH), 5.22 (d, 1 H, *J* = 11 Hz, PhC*H*CO), 5.02 (d, 1 H, 8 Hz, PhC*H*CO), 4.84 (dd, 1 H, *J* = 11, 7 Hz, 3-MeOArC*H*), 3.62 (s, 3 H, OCH_3); MS, *m/z* 315 (11), 300 (27), 210 (47), 196 (17), 105 (100). Anal. ($C_{36}H_{30}O_3$) C, H.

1,2-Diphenyl-3-methyl-3-(3-methoxyphenyl)propan-1-one (13). Methyllithium (12.7 mmol, 10.6 mL of a 1.2 M solution in ether) was added to 10 mL of ether. The solution was cooled to 0 °C and Cu_2Br_2 (910 mg, 6.36 mmol CuBr) was added. Enone 11 (2.00 g, 6.36 mmol), dissolved in ether (60 mL), was added. The solution was stirred overnight. Product isolation (5% HCl, EtOAc, brine) and flash chromatography (9:1 hexane–EtOAc) afforded a mixture of two diastereomers. A sample greatly enriched in the less mobile diastereomer could be obtained as a white solid (mp 155–160 °C) by recrystallization from methanol at −30 °C and trituration with pentane–ether. The combined mother liquors were chromatographed as above. The two diastereomers were pooled to obtain a clear oil. The combined yield was 1.37 g (65%): MS (of solid), 330 (6, M^+), 225 (9), 196 (100), 135 (73), 105 (70); HRMS (of solid), calcd/found ($C_{23}H_{22}O_2$) 330.1620/330.1617.

2-(4-Cyanophenyl)-3-(4-methoxyphenyl)-6-methoxyindene (5a). Cyano ketone **4a** (365 mg, 0.98 mmol) was dissolved in CH_2Cl_2 (9 mL). A solution of P_2O_5 (100 mg) in $MeSO_3H$ (1 mL) was added. An additional quantity of P_2O_5 (100 mg) was added. After 24 h, product isolation (ice water, EtOAc, saturated $NaHCO_3$) commenced. Flash chromatography (1:1 hexane–EtOAc) and recrystallization from methanol–EtOAc at −30 °C provided fine yellow needles (142 mg, 41%): mp 155–157 °C; IR ($CHCl_3$) 2220, 1600, 1210 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 7.59 (d, 2 H, *J* = 8 Hz, Ar*H* ortho to CN), 7.47 (d, 2 H, *J* = 8 Hz, Ar*H* meta to CN), 7.27 (d, 2 H, *J* = 9 Hz, Ar*H* meta to OCH_3 on 3-ring), 7.19 (d, 1 H, *J* = 1 Hz, Ar*H* ortho to CH_2), 7.12 (d, 1 H, *J* = 8 Hz, Ar*H* meta to CH_2), 7.05 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3 on 3-ring), 6.88 (dd, 1 H, *J* = 7, 2 Hz, Ar*H* para to CH_2), 3.95 (s, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3); MS, *m/z* 353 (100, M^+), 338 (13), 310 (2). Anal. ($C_{24}H_{19}NO_2$) C, H.

General Procedure for Polyphosphoric Acid (PPA) Cyclizations. This method was used for the synthesis of indenes **5b–d** and **10**. The triaryl ketones **4b–d** and **13** were mixed with 20 times their weight of polyphosphoric acid (PPA). The mixture was mechanically stirred under nitrogen at 40–50 °C and monitored carefully by TLC. Product isolation (ice water, EtOAc, saturated $NaHCO_3$) was followed by purification of the residue as described.

2-(4-Bromophenyl)-3-(4-methoxyphenyl)-6-methoxyindene (5b). A white solid (0.674 g, 70%) was obtained by recrystallization from ethyl acetate at −30 °C: mp 173–174 °C; ^{1}H NMR ($CDCl_3$) δ 7.35–7.22 (m, 3 H, Ar*H*), 7.18–7.05 (m, 3 H, Ar*H*), 6.95 (d, 2 H, *J* = 89 Hz, Ar*H* ortho to OCH_3 on 3-ring), 6.83 (dd, 1 H, *J* = 8, 2 Hz, Ar*H* para to CH_2), 3.87 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.82 (s, 2 H, CH_2); MS, *m/z* 408 (100, M^+), 406 (100, M^+), 393 (28), 391 (29), 377 (14), 375 (15), 327 (13), 312 (17), 252 (23), 126 (20). Anal. ($C_{23}H_{19}BrO_2$) C, H, Br.

2-[2-(Trifluoromethyl)phenyl]-3-(4-methoxyphenyl)-6-methoxyindene (5c). This compound was purified by recrystallization from methanol at −30 °C; white crystals (527 mg, 56%) were obtained. An analytical sample was procured by a second recrystallization from methanol at 25 °C: mp 124–126 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 1 H, *J* = 7 Hz, Ar*H* ortho to CF_3), 7.58–7.26 (m, 5 H, Ar*H*), 7.18 (d, 2 H, *J* = 9 Hz, Ar*H* meta to OCH_3 of 3-ring), 6.89 (dd, 1 H, *J* = 8, 2 Hz, Ar*H* para to CH_2), 6.82 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3 of 3-ring), 3.85 (s, 3 H, OCH_3), 3.77 (s, 2 H, CH_2), 3.76 (s, 3 H, OCH_3); MS, *m/z* 396 (88, M^+), 381 (22), 365 (9), 135 (57), 43 (100). Anal. ($C_{24}H_{19}F_3O_2$) C, H.

2-(2-Methylphenyl)-3-(4-methoxyphenyl)-6-methoxyindene (5d). Purification was performed by recrystallization from hexane–ether at −30 °C to furnish off-white crystals (0.758 g, 61%): mp 102–104 °C; IR ($CHCl_3$) 3020, 1600, 1510, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38 (d, 2 H, *J* = 8 Hz, Ar*H* meta to OCH_3 on 3-ring), 7.21–7.08 (m, 4 H, Ar*H*), 6.89 (dd, 1 H, *J* = 9, 1 Hz, Ar*H* para to CH_2), 6.81 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3 on 3-ring), 3.87 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.74 (s, 2 HO, CH_2), 1.96 (s, 3 H, CH_3); MS, *m/z* 342 (100, M^+), 327 (23), 311 (10). Anal. ($C_{24}H_{22}O_2$) C, H.

1-Methyl-2,3-diphenyl-6-methoxyindene (10). This compound was purified by flash chromatography (19:1 hexane–acetone), followed by recrystallization from MeOH at −30 °C, providing fine white needles (479 mg, 51%): mp 115–117 °C; IR ($CHCl_3$) 3000, 2360, 1470, 1290, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.38–7.10 (m, 7 H, Ar*H*), 7.34 (s, 5 H, Ph*H*), 6.83 (dd, 1 H, *J* = 9, 2 Hz, Ar*H* para to CH_2), 4.01 (q, 1 H, *J* = 7 Hz, C*H*), 3.87 (s, 3 H, OCH_3), 1.30 (d, 3 H, *J* = 8 Hz, $CHCH_3$); MS, *m/z* 312 (100, M^+), 297 (30). Anal. ($C_{23}H_{20}O$) C, H.

2-(3-Pyridyl)-3-(4-methoxyphenyl)-6-methoxyindene (5e). Pyridyl ketone **4e** (315 mg, 0.907 mmol) was dissolved in 10 mL of CH_2Cl_2. Methanesulfonic acid (1 mL) was added. After 30 h at 25 °C, product isolation (saturated $NaHCO_3$, EtOAc) commenced. Flash chromatography (ether) and recrystallization (ether, −30 °C) provided the title compound as fine white needles (142 mg, 48%): mp 133–135 °C; ^{1}H NMR (acetone-d_6) δ 8.45 (d, 1 H, *J* = 2 Hz, isolated pyridyl C*H* adjacent to N), 8.31 (dd, 1 H, *J* = 5, 1 Hz, nonisolated pyridyl C*H* adjacent to N), 7.59 (d, 1 H, *J* = 8 Hz, pyridyl C*H* at position 4 relative to N), 7.25 (d, 2 H, *J* = 9 Hz, Ar*H* meta to OCH_3 on 3-ring), 7.20 (m, 1 H, pyridyl C*H* at position 3 relative to N), 7.17 (s, Ar*H* ortho to CH_2), 7.08 (d, 1 H, *J* = 9 Hz, Ar*H* meta to CH_2), 7.01 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OCH_3 on 3-ring), 3.90 (s, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3); MS, *m/z* 329 (100, M^+), 314 (30), 298 (13), 286 (9), 242 (8). Anal. ($C_{22}H_{19}NO_2$) C, H, N.

2-(4-Cyanophenyl)-3-(4-hydroxyphenyl)-6-hydroxyindene (6a). Cyanoindene **5a** (80 mg, 0.226 mmol) was dissolved in CH_2Cl_2 (10 mL) and the solution was cooled to −78 °C. A solution of BBr_3 in CH_2Cl_2 (1 M, 0.724 mL, 0.724 mmol) was added.[49] After 32 h, product isolation (ice water, EtOAc, brine) commenced. Flash chromatography (3:2 hexane–EtOAc) and rechromatography (7:3 hexane–EtOAc) of the edge fractions gave 70 ng (95%) of a yellow powder: mp 225 °C dec; ^{1}H NMR (acetone-d_6) δ 8.43 (s, 1 H, ArO*H*), 8.25 (s, 1 H, ArO*H*), 7.50 (d, 2 H, *J* = 8 Hz, Ar*H* ortho to CN), 7.41 (d, 2 H, *J* = 8 Hz, Ar*H* meta to CN), 7.14 (d, 2 H, *J* = 9 Hz, Ar*H* meta to OH on 3-ring), 7.02 (d, 2 H, Ar*H* metal and ortho to CH_2), 6.91 (d, 2 H, *J* = 8 Hz, Ar*H* ortho to OH on 3-ring), 6.75 (dd, 1 H, *J* = 8, 2 Hz, Ar*H* para to CH_2), 3.84 (s, 2 H, CH_2); MS, *m/z* 325 (100, M^+), 308 (3), 232 (3); HRMS, calcd/found ($C_{22}H_{15}NO_2$) 325.1103/325.1098.

General Procedure for Methyl Ether Deprotection. This method was used for the preparation of **6b–h** and **14**. Boron trifluoride–dimethyl sulfide complex was prepared as previously described.[50] The substrate (compounds **5b–h**; typically 0.3 mmol) was dissolved in CH_2Cl_2 and the solution was cooled to 0 °C. A large excess of $BF_3{\cdot}S(CH_3)_2$[51] was added (4 mL of 1:1 w/w solution). The reaction was followed by TLC and was typically complete within 24 h. Product isolation (water, EtOAc) was followed by purification as described.

2-(4-Bromophenyl)-3-(4-hydroxyphenyl)-6-hydroxyindene (6b). This compound was purified by flash chromatography (7:3 hexane–EtOAc) and recrystallization from hexane–EtOAc at 25 °C; a yellowish powder was obtained (45 mg, 34%): mp 185 °C dec; ^{1}H NMR (acetone-d_6) δ 8.01 (s, 1 H, ArO*H*), 7.39 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to Br), 7.24 (d, 2 H, *J* = 9 Hz, Ar*H* meta to Br), 7.17 (d, 2 H, *J* = 9 Hz, Ar*H* meta to OH of 3-ring), 7.10–6.99 (m, 2 H, Ar*H*), 6.94 (d, 2 H, *J* = 9 Hz, Ar*H* ortho to OH on 3-ring), 6.77 (dd, 1 H, *J* = 8, 2 Hz, Ar*H* para to CH_2), 3.83 (s, 2 H, CH_2); MS, *m/z* 380 (100, M^+), 378 (100, M^+), 299 (24), 281 (12), 223 (15). Anal. ($C_{21}H_{15}BrO_2$) C, H, Br.

2-[2-(Trifluoromethyl)phenyl]-3-(4-hydroxyphenyl)-6-hydroxyindene (6c). Purification was achieved by flash chromatography (4:1 hexane–EtOAc); a yellowish solid was obtained (45 mg, 61%): mp 73 °C dec; ^{1}H NMR (acetone-d_6) δ 8.18 (s, 1

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H, ArO*H*), 8.13 (s, 1 H, ArO*H*), 7.68–7.23 (m, 4 H, Ar*H*), 7.19 (d, 2 H, Ar*H* metal to OH on 3-ring), 7.08 (d, 2 H, Ar*H* ortho and meta to CH_2), 6.78 (dd, 1 H, J = 8, 1 Hz, Ar*H* para to CH_2), 6.72 (d, 2 H, J = 9 Hz, Ar*H* ortho to OH on 3-ring), 3.70 (s, 2 H, CH_2); MS (10 eV), m/z 368 (50, M^+), 299 (6), 223 (7), 87 (18), 69 (8), 45 (100); HRMS, calcd/found ($C_{22}H_{15}F_3O_2$) 368.1024/368.1018.

2-(2-Methylphenyl)-3-(4-hydroxyphenyl)-6-hydroxyindene (6d). Flash chromatography (73:27 hexane–EtOAc), followed by recrystallization from 2-propanol–pentane at −30 °C gave off-white crystals (96 mg, 95%): mp 120 °C; ^{1}H NMR (acetone-d_6) δ 8.28 (s, 1 H, ArO*H*), 8.14 (s, 1 H, ArO*H*), 7.25 (d, 2 H, J = 8 Hz, Ar*H* meta to OH on 3-ring), 7.19–7.03 (m, 5 H, Ar*H*), 6.81 (dd, 1 H, J = 8, 1 Hz, Ar*H* para to CH_2), 6.76 (d, 2 H, J = 8 Hz, Ar*H* ortho to OH on 3-ring), 3.68 (s, 2 H, CH_2), 1.96 (s, 3 H, CH_3); MS, m/z 314 (100, M^+), 299 (10); HRMS, calcd/found ($C_{22}H_{18}O_2$) 314.1307/314.1305.

2-(3-Pyridyl)-3-(4-hydroxyphenyl)-6-hydroxyindene (6e). The residue from the extraction was dissolved in ethanol and filtered through silica. The filtrate was evaporated and triturated with cold ether (−30 °C); a light yellow powder was recovered (56 mg, 74%): mp 225 °C dec; ^{1}H NMR (acetone-d_6) δ 8.60 (s, 1 H, ArO*H*), 8.52 (d, 1 H, J = 2 Hz, isolated pyridyl C*H* adjacent to N), 8.37 (s, 1 H, ArO*H*), 8.32 (dd, 1 H, J = 5, 1 Hz, nonisolated pyridyl C*H* adjacent to N), 7.62 (d, 1 H, J = 8 Hz, pyridyl C*H* at position 4 relative to N), 7.22 (d ?, 1 H, pyridyl C*H* at position 3 relative to N), 7.19 (d, 2 H, J = 8 Hz, Ar*H* metal to OH or 3-ring), 7.08 (d, 1 H, J = 1 Hz, Ar*H* ortho to CH_2), 7.04 (d, J = 8 Hz, Ar*H* meta to CH_2), 6.94 (d, 2 H, J = 8 Hz, Ar*H* ortho to OH on 3-ring), 6.79 (dd, 1 H, J = 8, 2 Hz, Ar*H* para to OCH_3), 3.88 (s, 2 H, CH_2); MS, m/z 301 (100, M^+), 284 (5); HRMS, calcd/found ($C_{20}H_{15}NO_2$) 301.1103/301.1104.

2-(3-Nitrophenyl)-3-(4-hydroxyphenyl)-6-hydroxyindene (6f). Flash chromatography (3:2 hexane–EtOAc) and trituration with CH_2Cl_2–pentane (9:1, −30 °C) afforded a yellow powder (75 mg, 81%): mp 170–171 °C; ^{1}H NMR (acetone-d_6) δ 8.37 (br s, 2 H, ArO*H*), 8.09 (s, 1 H, Ar*H* ortho to NO_2, ortho to C=C), 7.91 (d, 1 H, J = 9 Hz, Ar*H* ortho to NO_2, para to C=C), 7.60 (d, 1 H, J = 8 Hz, Ar*H* para to NO_2), 7.39 (t, 1 H, J = 9 Hz, Ar*H* meta to NO_2), 7.14 (d, 2 H, J = 8 Hz, Ar*H* meta to OH on 3-ring), 7.02 (d, 2 H, Ar*H* meta and ortho to CH_2), 6.91 (d, 2 H, J = 9 Hz, Ar*H* ortho to OH on 3-ring), 6.75 (dd, 1 H, Ar*H* para to CH_2), 3.87 (s, 2 H, CH_2); MS, m/z 345 (100, M^+), 298 (18), 223 (10). Anal. ($C_{21}H_{15}NO_4$) C, H, N; C: calcd, 73.04; found, 72.52.

2-(4-Nitrophenyl)-3-(4-hydroxyphenyl)-6-hydroxyindene (6g). Purification was achieved by flash chromatography (4:1 CH_2Cl_2–EtOAc), followed by recrystallization from hexane–EtOAc at −30 °C; an orange-red solid was obtained (32 mg, 43%): mp 240–241 °C; ^{1}H NMR (acetone-d_6) δ 8.65 (br s, 2 H, ArO*H*), 8.07 (d, 2 H, J = 9 Hz, Ar*H* ortho to NO_2), 7.53 (d, 2 H, J = 9 Hz, Ar*H* meta to NO_2), 7.20 (d, 2 H, J = 9 Hz, Ar*H* meta to OH on 3-ring), 7.10–7.01 (m, 2 H, Ar*H*), 6.94 (d, 2 H, J = 9 Hz, Ar*H* ortho to OH on 3-ring), 6.81 (dd, 1 H, J = 8, 2 Hz, Ar*H* para to CH_2), 3.93 (s, 2 H, CH_2); MS, m/z 345 (100, M^+), 328 (3), 315 (3), 299 (9), 298 (8). Anal. ($C_{21}H_{15}NO_4$) C, H, N.

2-(4-Nitrophenyl)-3-phenyl-6-hydroxyindene (6h). This compound was purified by flash chromatography (7:3 hexane–EtOAc) and recrystallization from hexane–EtOAc at −33 °C. An orange-red solid was secured (80 mg, 84%): mp 270 °C dec; ^{1}H NMR (acetone-d_6) δ 8.42 (s, 1 H, ArO*H*), 8.07 (d, 2 H, J = 9 Hz, Ar*H* ortho to NO_2), 7.47–7.30 (m, 6 H, Ar*H*), 7.13 (d, 1 H, J = 1 Hz, Ar*H* para to CH_2), 7.02 (d, 1 H, J = 9 Hz, Ar*H* meta to CH_2), 6.79 (dd, 1 H, J = 9, 1 Hz, Ar*H* para to CH_2), 3.97 (s, 2 H, CH_2); MS, m/z 329 (100, M^+), 299 (3), 283 (9). Anal. ($C_{21}H_{15}NO_3$) C, H, N.

1-Methyl-2,3-diphenyl-6-hydroxyindene (14). Flash chromatography (4:1 hexane–EtOAc), followed by trituration (hexane–EtOAc), provided a light tan powder (35 mg, 37%): mp 152–154 °C; ^{1}H NMR (acetone-d_6) δ 8.45 (s, 1 H, ArO*H*), 7.55–7.05 (m, 12 H, Ar*H*), 6.84 (d, 1 H, J = 8 Hz, Ar*H* para to CH), 4.12 (q, 1 H, J = 7 Hz, C*H*CH$_3$), 1.23 (d, 3 H, J = 8 Hz, CHC*H*$_3$); MS, m/z 298 (100, M^+), 283 (32). Anal. ($C_{22}H_{18}O$) C, H.

Acknowledgment. We are grateful for support of this research through a grant from the National Institutes of Health (Grant PHS 2R37 DK 15556). High-field NMR spectra and high-resolution mass spectra were obtained on instruments supported by grants from the National Institutes of Health (Grants RR 02299 and GM 27029, respectively). We are thankful to Kathryn E. Carlson for performing the estrogen receptor binding assays and to Chad S. Peterson and Serkos A. Haroutounian for technical assistance.

Registry No. **3a**, 62066-32-4; **3b**, 67205-73-6; **3c**, 114583-91-4; **3d**, 33509-94-3; **3e**, 52700-25-1; **4a**, 114583-92-5; **4b**, 114583-93-6; **4c**, 114583-94-7; **4d**, 114583-95-8; **4e**, 114583-96-9; **5a**, 114583-97-0; **5b**, 114583-98-1; **5c**, 114583-99-2; **5d**, 114584-00-8; **5e**, 114584-01-9; **5f**, 114584-02-0; **5g**, 114584-03-1; **5h**, 114584-04-2; **6a**, 114584-05-3; **6b**, 114584-06-4; **6c**, 114584-07-5; **6d**, 114584-08-6; **6e**, 114584-09-7; **6f**, 114584-10-0; **6g**, 114584-11-1; **6h**, 114584-12-2; **7b**, 1878-68-8; **7c**, 3038-48-0; **7d**, 644-36-0; **8**, 114584-14-4; **9**, 53347-55-0; **10**, 114584-16-6; **11**, 98042-48-9; **12**, 38177-14-9; **13** (isomer 1), 114584-15-5; **13** (isomer 2), 114584-17-7; **14**, 114584-13-3; (CH_3)$_2$CuLi, 15681-48-8; 4-methoxyacetophenone, 100-06-1; anisole, 100-66-3; 3-methoxybenzyl chloride, 824-98-6; 3-anisaldehyde, 591-31-1; deoxybenzoin, 451-40-1; 4-bromobenzonitrile, 623-00-7.