Estrogen Receptor-β Potency-Selective Ligands: Structure−Activity Relationship Studies of Diarylpropionitriles and Their Acetylene and Polar Analogues

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Through an effort to develop novel ligands that have subtype selectivity for the estrogen receptors alpha (ERα) and beta (ERβ), we have found that 2,3-bis(4-hydroxyphenyl)propionitrile (DPN) acts as an agonist on both ER subtypes, but has a 70-fold higher relative binding affinity and 170-fold higher relative potency in transcription assays with ERβ than with ERα. To investigate the ERβ affinity- and potency-selective character of this DPN further, we prepared a series of DPN analogues in which both the ligand core and the aromatic rings were modified by the repositioning of phenolic hydroxy groups and by the addition of alkyl substituents and nitrile groups. We also prepared other series of DPN analogues in which the nitrile functionality was replaced with acetylene groups or polar functions, to mimic the linear geometry or polarity of the nitrile, respectively. To varying degrees, all of the analogues show preferential binding affinity for ERβ (i.e., they are ERβ affinity-selective), and many, but not all of them, are also more potent in activating transcription through ERβ than through ERα (i.e., they are ERβ potency-selective). *meso*-2,3-Bis(4-hydroxyphenyl)succinonitrile and *dl*-2,3-bis(4-hydroxyphenyl)-succinonitrile are among the highest ERβ affinity-selective ligands, and they have an ERβ potency selectivity that is equivalent to that of DPN. The acetylene analogues have higher binding affinities but somewhat lower selectivities than their nitrile counterparts. The polar analogues have lower affinities, and only the fluorinated polar analogues have substantial affinity selectivities. This study suggests that, in this series of ligands, the nitrile functionality is critical to ERβ selectivity because it provides the optimal combination of linear geometry and polarity. Furthermore, the addition of a second nitrile group β to the nitrile in DPN or the addition of a methyl substitutent at an ortho position on the β-aromatic ring increases the affinity and selectivity of these compounds for ERβ. These ERβ-selective compounds may prove to be valuable tools in understanding the differences in structure and biological function of ERα and ERβ.

Introduction

The estrogen receptor (ER), a member of the nuclear hormone receptor superfamily, mediates the activity of estrogens in the regulation of a number of important physiological processes, including the development and function of the female reproductive system and the maintenance of bone mineral density and cardiovascular health. While the stimulation of processes in these tissues has important health benefits, the stimulation of other tissues, such as the breast and uterus, can increase the risk of cancer at these sites. The development of selective ER modulators (SERMs) such as raloxifene and tamoxifen has been driven by the interest in discovering compounds with an improved endocrine profile that might be safer and more effective pharmaceuticals. Desirable tissue selectivity may result from the structural characteristics of a ligand that exploit differences in a variety of cell- and gene-specific factors.[1]

The recent discovery of a second estrogen receptor subtype (ERβ)[2,3] has prompted the search for ER ligands which are selective for either the classical estrogen receptor (ERα) or for ERβ. Such ligands would be useful for determining the respective biological roles of ERα and ERβ, and for examining the structural conformation of ERα/ERβ agonist/antagonist complexes. They might also prove to be of therapeutic value in treating a variety of estrogen-linked pathologies.[4]

The possibility of achieving selectivity at the receptor level has been supported by the difference in tissue distribution between ERα and ERβ.[2,5−7] Although the two ER subtypes are both activated by binding 17β-estradiol (**1**), the ligand binding domains (LBD) have only 56% amino acid identity.[2,3] This suggests that ligands may be developed which have different affinities, potencies, and agonist vs antagonist behavior for the two ER subtypes. Indeed, some known ligands have subtype-selective affinities and a degree of subtype selective agonist/antagonist character, although in most

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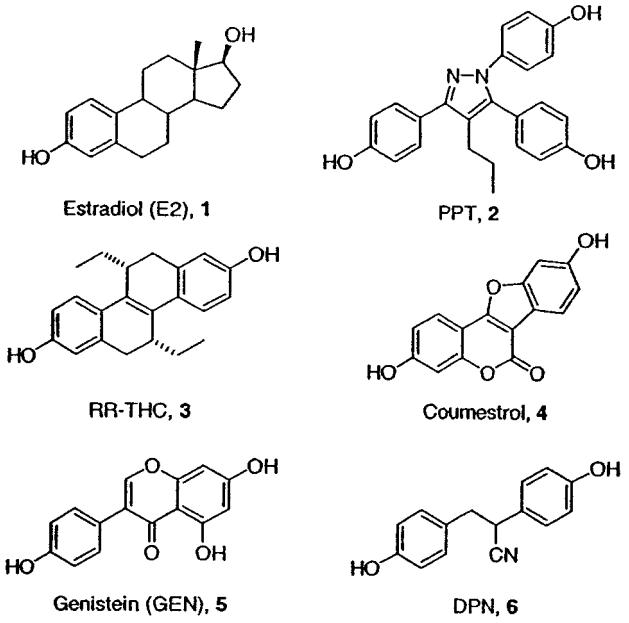
cases where this selectivity is high, it favors ERα.[5,8−10] For example, we have recently reported that tetrasubstituted propylpyrazole (PPT, **2**) has a 410-fold binding selectivity for ERα and is an ERα-specific agonist, as it activates gene transcription only through ERα.[11]

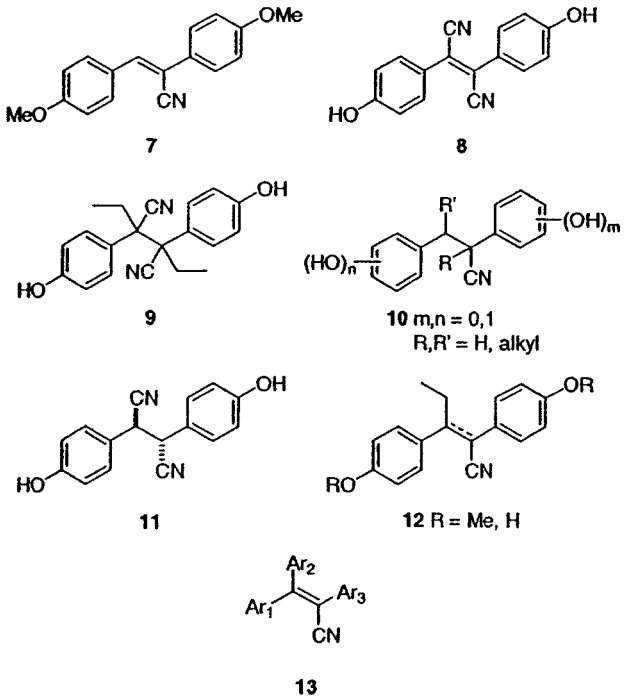
Currently, the most notable ER*β* subtype selective ligands are *cis*-tetrahydrochrysene (3, THC) and the phytoestrogens coumestrol (**4**) and genistein (**5**), which have ER*β* binding selectivities of 6-, 3-, and 19-fold, respectively.[10,12] We have shown that THC is also an ERα efficacy-selective ligand; i.e., it is a nearly full agonist on ERα but a complete antagonist on ER*β*.[9,10] Genistein and coumestrol are agonists on both ERα and ER*β*. Genistein is 3-fold more potent on ER*β* than ERα (ERα EC_{50} = 20 nM; ER*β* EC_{50} = 6 nM). However, although it is a full agonist on ERα, it is only a partial agonist on ER*β*.[8,12] Thus, the ER*β* selectivity of genistein is not ideal, although in some assays it appears to function preferentially through ER*β*.[5,13] Nevertheless, compounds with greater ER*β* potency selectivity that are also full ER*β* agonists would be expected to effect even more selective responses through ER*β*.



We have recently discovered an ER*β* potency-selective ligand, diarylpropionitrile (6, DPN), by screening a select group of compounds for transcriptional activity by ERα and ER*β* in human endometrial cancer (HEC-1) cells. DPN has a 70-fold ER*β* relative binding affinity (RBA) selectivity, and it is a full ER*β* agonist with a 78-fold ER*β* potency selectivity (ER*β* EC_{50} = 0.85 nM; ERα ER_{50} = 66 nM). This is a substantially higher level of ER*β* affinity and potency selectivity than genistein, and genistein is only a partial ER*β* agonist, whereas DPN is fully agonistic on ER*β*.

While nitriles are not a common functionality in nonsteroidal estrogens, cyanoestrogens are known. Niederl and Ziering described the synthesis and estrogenic character of a number of alkoxy cyanostilbenes (**7**−**9**),[14,15] but all had relatively low activity. Rorig investigated a number of bisphenolic alkanonitriles (**10**) for the treatment of cardiovascular disease and adrenocortical dysfunction;[16] the phenols were found to be nonestrogenic, but the methyl ether analogues had weak estrogenic activity. Nomura described *meso*-succinonitrile (**11**) as having low levels of estrogenic activity,[17] and the saturated and unsaturated valeronitriles (**12**) have been described as antifertility agents with very weak estrogenic character.[18,19] Higher affinity triarylacrylonitriles (**13**) are known to be full agonists or partial agonist/antagonists, depending on aryl substitution.[20]

While these compounds include and are quite similar to DPN, they were not investigated for their activity on ER*β*, because prior to 1996, this protein was not known. Furthermore, the common classical assays used in these earlier studies measured binding affinity to uterine cytosolic ER preparations or estrogenic activity through uterotropic growth; uterine tissue contains primarily ERα.[5,13]



The objective of this work was to optimize the ER***β*** selectivity of DPN and to understand its mode of selectivity. Toward these ends, we have synthesized numerous analogues of DPN, both with and without the nitrile functionality, and we have conducted structure−activity relationship (SAR) studies of these novel ER*β*-selective ligands. We have found a number of compounds that have ER*β* relative binding affinity selectivities of up to 70-fold and ER*β* relative potency selectivities of up to 170-fold in cell-based transcription assays. In this report, we describe the synthesis and structure−activity relationships of these compounds, as well as other compounds having nitriles or functional groups that mimic the polar or sp geometric nature of the nitrile group.

Results and Discussion

Chemical Synthesis. (a) Scope of Structure−Activity Relationship Study. To optimize the ER*β* selectivity of DPN, we prepared a number of nitrile analogues in which (1) the position of the hydroxy

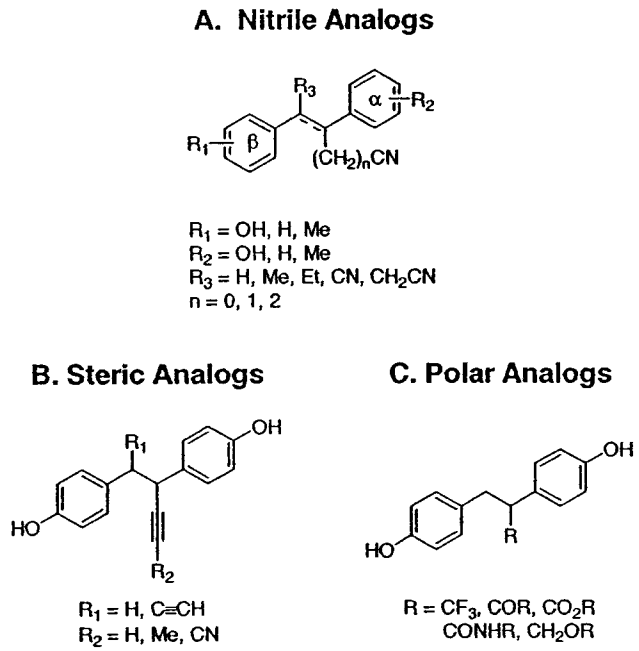


Figure 1. Scope of structure−activity relationship study.

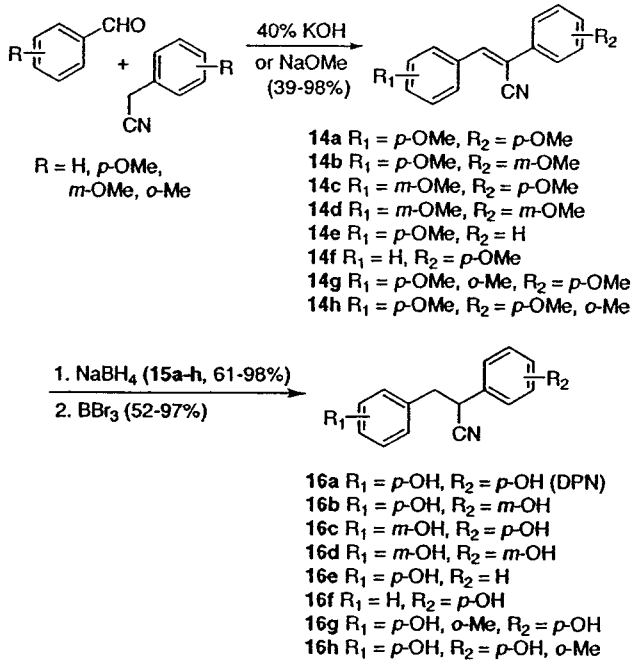
groups was varied, (2) the ligand steric bulk was increased by the introduction of alkyl groups to the ligand core, (3) the rotational flexibility of the aryl rings was limited by placement of methyl groups in the ortho position on the aryl rings, (4) the number and stereochemistry of the nitrile groups was varied, and (5) the degree of saturation of the ligand core was varied (Figure 1A). Also, to evaluate the importance of the nitrile sp geometry in effecting ERβ selectivity, we prepared steric analogues in which the nitrile group was replaced with an acetylenic group (Figure 1B), and to probe the role of the dipolar nature of the nitrile group, we prepared analogues having polar trifluoromethyl, ester, ketone, and amide groups (Figure 1C).

(b) Nitriles. To synthesize the diarylpropionitriles (**16a**−**h**), we prepared a-cyanostilbenes **14a**−**h** by the condensation of arylaldehydes and arylacetonitriles[21] (Scheme 1). 2-Methylanisaldehyde (**17**), prepared as previously described,[22] was transformed to give nitrile **19** by reduction with $NaBH_4$, conversion of the alcohol to the chloride, and cyanide displacement (Scheme 2). The yield of the cyanide displacement was poor because of competing attack by EtOH on the benzyl chloride.[23] Not unexpectedly, the condensation of these compounds bearing a methyl group in the ortho position (**14g**,**h**) resulted in lower yields. Conjugate reduction of unsaturated nitriles with $NaBH_4$ in EtOH[21] or DMF,[24] followed by deprotection of the aryl methyl ethers with boron tribromide, gave phenolic nitriles **16a**−**h** in good yields.

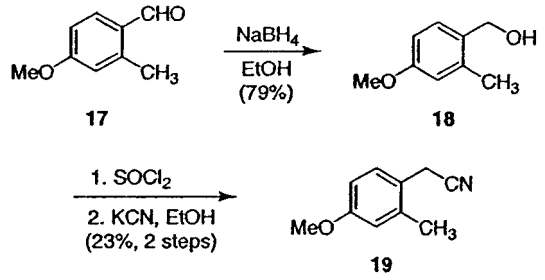
The one-carbon homologue (**25**) of DPN was prepared as outlined in Scheme 3. The Perkin condensation of *p*-anisaldehyde and (4-methoxyphenyl)acetic acid,[25] followed by hydrogenation of the cinnamic acid **20**, furnished propionic acid **21**. Reduction of acid **21**, methanesulfonylation of alcohol **22**, and cyanide displacement with *n*-tetrabutylammonium cyanide gave butyronitrile **24** in excellent yield. Methyl ether cleavage with BBr_3 afforded the desired bisphenolic derivative **25**.

The α-methyl analogue (**27**) of DPN was prepared by alkylation of propionitrile **15a** with iodomethane (Scheme

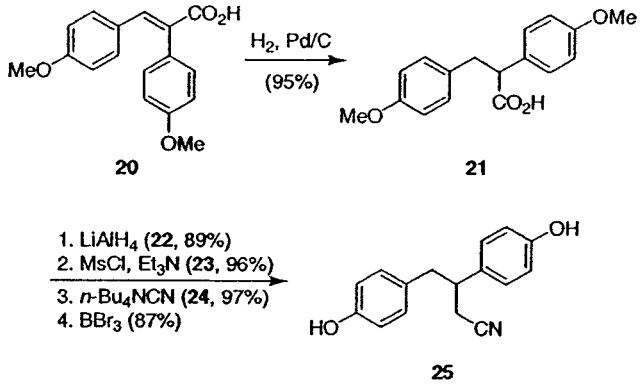
Scheme 1



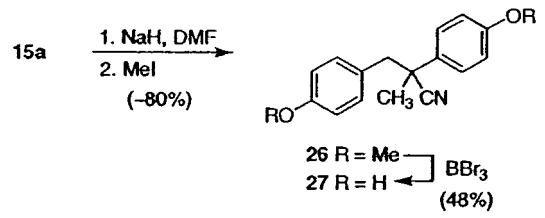
Scheme 2



Scheme 3

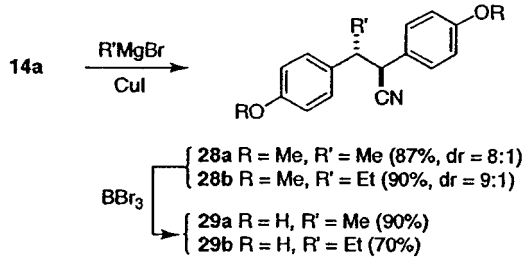


Scheme 4

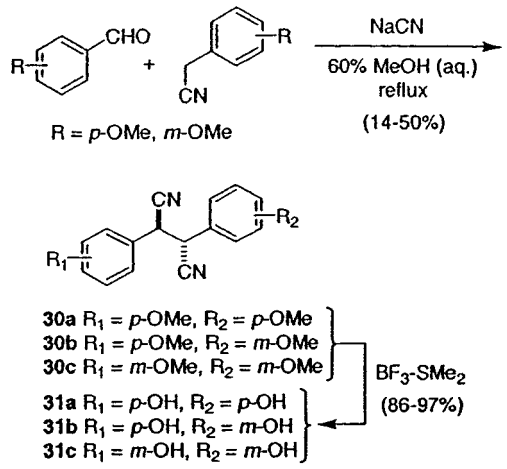


4). The desired product was accompanied by a small amount of starting material and an unidentified byproduct (~10%), which proved difficult to separate. However, after demethylation of the mixture with BBr_3, recrys-

Scheme 5



Scheme 6



tallization of the resulting bisphenols furnished pure nitrile **27** in moderate yield.

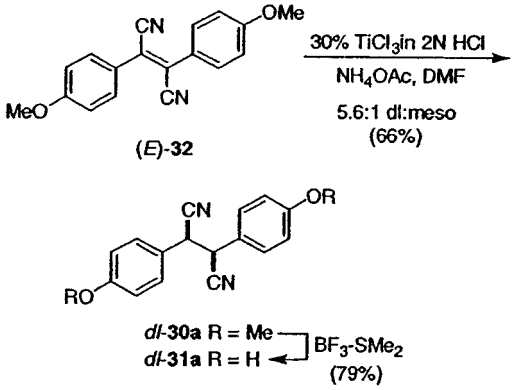
β-Methyl and ethyl[26] analogues (**28a**,**b**) were prepared with high diastereoselectivity by the conjugate addition of the corresponding Grignard reagent in the presence of CuI (Scheme 5).[26] Isolation of the erythro diastereomer by recrystallization, followed by deprotection with BBr_3 gave the desired alkylated nitriles **29a,b** in good yields.

meso-Succinonitriles and *erythro*-succinonitriles **31a**−**c** were prepared by the method of Davis and Ward,[27] as shown in Scheme 6. Condensation of *p*- and *m*-anisaldehydes with *p*- and *m*-methoxyphenylacetonitriles in the presence of NaCN gave only the meso/erythro diastereomers of the succinonitriles **30a**−**c**. Stereochemical assignments were based on analogy to *meso*-**30a**, a known compound.[28] Demethylation with $BF_3{\cdot}SMe_2$ gave the desired bisphenolic succinonitriles (**31a**−**c**).

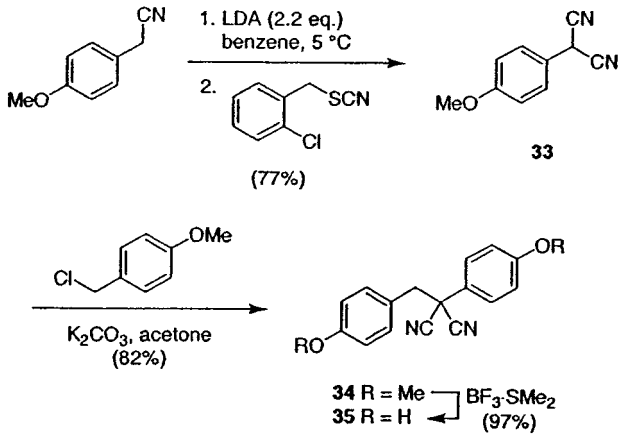
Succinonitrile *dl*-**31a** was prepared as shown in Scheme 7. The reduction of unsaturated succinonitrile (*E*)-**32** (see below) with $TiCl_3$ under acidic conditions similar to those described by Sera[29] gave a 5.6:1 ratio of dl:meso diastereomers, which were not separable by flash chromatography, but recrystallization improved the diastereomeric ratio (dr) to greater than 20:1. Demethylation with $BF_3{\cdot}SMe_2$ and recrystallization afforded the desired *dl*-**31a** (dr > 99:1).

The α-cyano analogue of DPN was prepared as shown in Scheme 8. Malononitrile **33** was prepared as previously described[30] by the cyanation of the lithium anion of (4-methoxyphenyl)acetonitrile with 2-chlorobenzylthiocyanate. Alkylation of **33** with 4-methoxybenzyl chloride and K_2CO_3, followed by demethylation with $BF_3{\cdot}Me_2$, gave the desired malonitrile **35** in excellent yield.

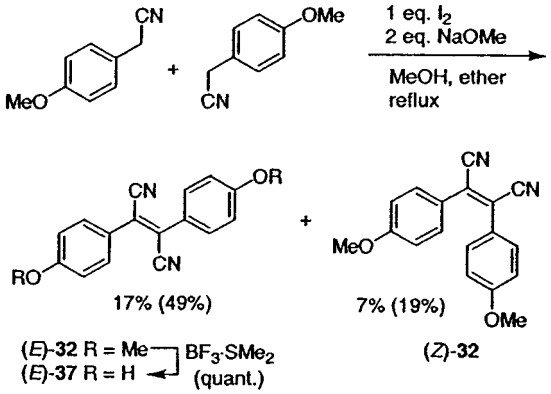
Scheme 7



Scheme 8



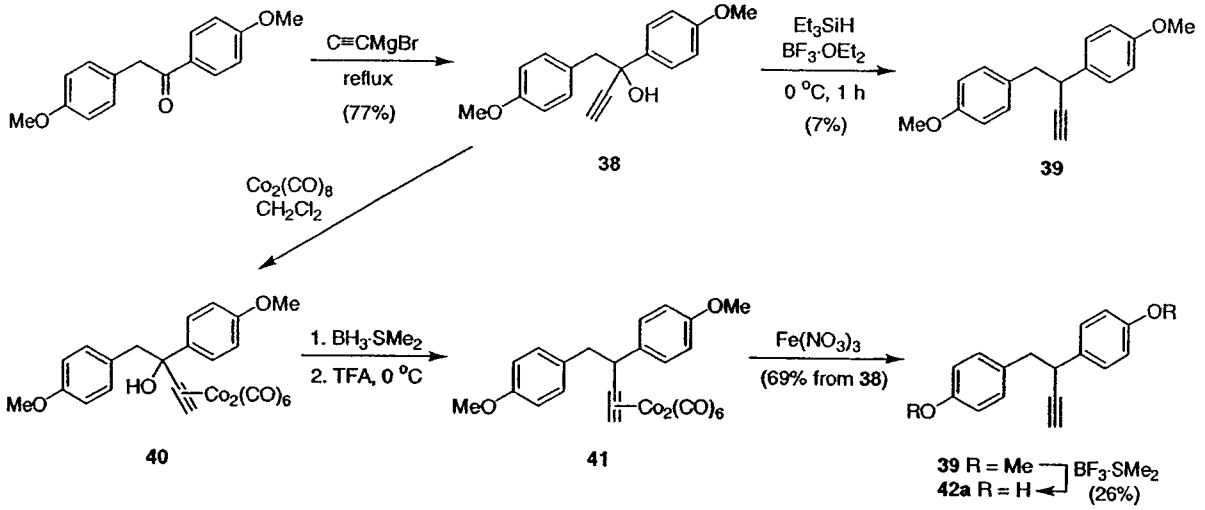
Scheme 9



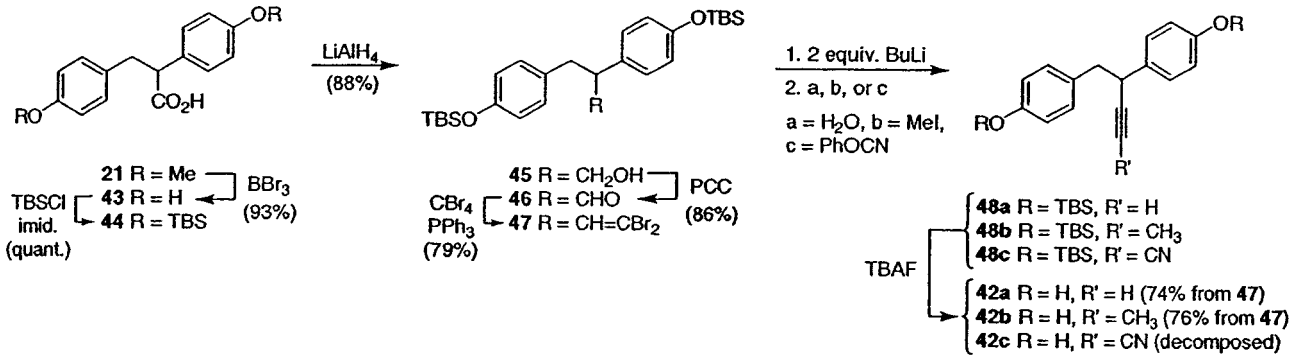
Unsaturated nitrile analogues were prepared as shown in Scheme 9. Acrylonitrile **14a** was demethylated with boron tribromide to give the desired unsaturated nitrile (*Z*)-**36** (not shown). (4-Methoxyphenyl)acetonitrile was dimerized with iodine and base according to the method of Niederl.[15] Unsaturated succinonitrile (*E*)-**32** precipitated directly from the reaction mixture, and additional E isomer as well as (*Z*)-**32** could be obtained by flash chromatography of the mother liquor. The E isomer was demethylated with $BF_3{\cdot}SMe_2$ to give (*E*)-**37**, but attempts to demethylate (*Z*)-**32** resulted in extensive double bond isomerization.

(c) Acetylenic Analogues. Two approaches to the synthesis of acetylene analogues of DPN were considered: (1) Grignard addition of ethynylmagnesium bromide to commercially available desoxyanisoin and (2) Corey−Fuchs transformation[31] of a diarylpropionalde-

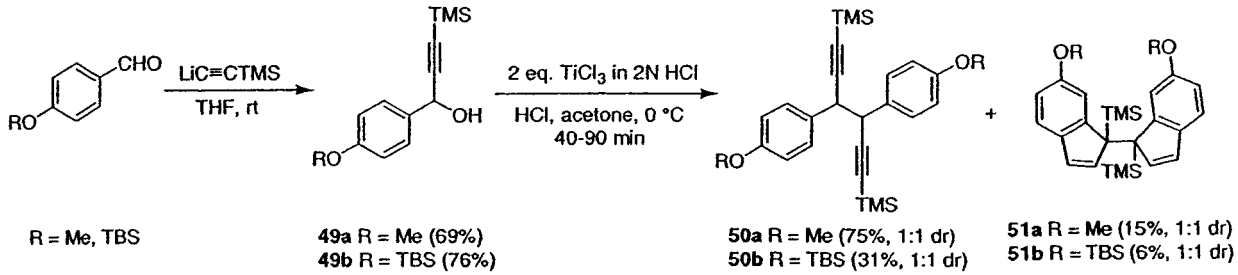
Scheme 10



Scheme 11



Scheme 12

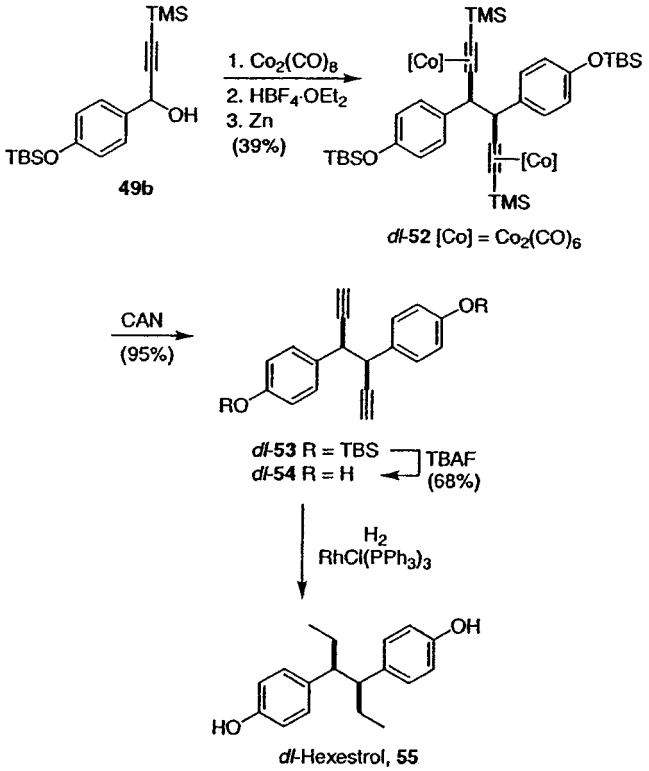


hyde. In the Grignard addition approach (Scheme 10), the addition of ethynylmagnesium bromide to desoxyanisoin proceeded in good yield to furnish propargyl alcohol **38**. Reduction of alcohol **38** with triethylsilane and TFA or $BF_3{\cdot}OEt_2$ was accompanied by extensive decomposition of the terminal acetylene, so the desired product (**39**) was isolated in only 7% yield. To circumvent this problem, the acetylene triple bond was protected by complexation with cobalt carbonyl.[32] Cobalt-complexed alcohol **40** was reduced with $BH_3{\cdot}SMe_2$ and TFA, and the acetylene demetalated with iron(III) nitrate to give the desired butyne **39** in 69% overall yield from propargyl alcohol **38**.[32,33] Demethylation with $BF_3{\cdot}SMe_2$ furnished the desired bisphenolic acetylene **42a**, although in low yield because of acetylene decomposition under the Lewis acid conditions.[34]

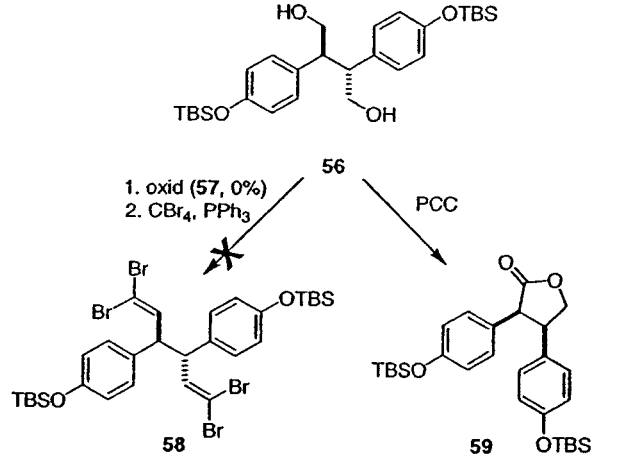
Alternatively, the terminal acetylenes **42a,b** could be prepared by the Corey−Fuchs route (Scheme 11). Given the difficulties in demethylating terminal acetylene **39**, propionic acid **21** was demethylated with BBr_3 and reprotected with TBSCl. Reduction of acid **44** with $LiAlH_4$, followed by PCC oxidation, gave aldehyde **46**, which was converted to the 1,1-dibromoolefin **47** with carbon tetrabromide and triphenylphosphine.[31,35] Decomposition of dibromoolefin **47** with 2 equiv of butyllithium, followed by protonation, gave **48a**.[31] Quenching the acetylide intermediate with MeI or PhOCN[36] gave methyl acetylene **48b** and cyanoacetylene **48c**, respectively. Cleavage of the silyl groups with TBAF gave the desired acetylenes **42a,b** in good yields from dibromoolefin **47**. Unfortunately, desilylation of cyanoacetylene **48c** resulted in rapid decomposition.

We envisioned that bisacetylene analogues of succinonitriles **31** could be prepared by two different routes: (1) a radical dimerization of an aryl propargyl alcohol and (2) the Corey−Fuchs transformation of a diaryl bisaldehyde. For the radical dimerization (Scheme 12), propargyl alcohols **49a,b**, readily obtained by the addition of lithium trimethylsilylacetylide to 4-methoxy- or 4-*tert*-butyldimethylsilanyloxybenzaldehyde, were re-

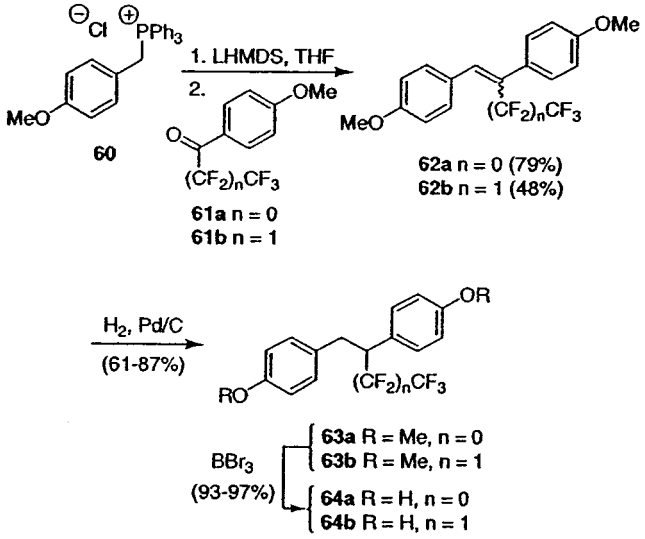
Scheme 13



Scheme 14



Scheme 15



duced with $TiCl_3$ under conditions similar to those described by Slaugh.[37] The reaction product consisted of a 1:1 mixture of diastereomers of 1,5-hexadiynes **50a,b** together with approximately 17% of an inseparable bisindene byproduct (**51a,b**) having the same molecular weight and diastereomeric ratio. These bisindenes represent the product of a formal dimerization of an allenic radical intermediate, followed by a double Friedel−Crafts cyclization.[38]

Formation of the inseparable bisindene byproduct was avoided by converting propargyl alcohol **49b** to the cobalt carbonyl complex prior to dimerization (Scheme 13).[39] The stabilized propargylium salt, generated from the cobalt complex with HBF_4, was reduced with powdered zinc to give the dimerization product **52a** in modest yield, as a single diastereomer after purification by flash chromatography. Demetalation with cerric ammonium nitrate, followed by desilylation with TBAF, gave bisalkyne **54** in good yield. This material was shown to be the *dl*-diastereomer by its hydrogenation to *dl*-hexestrol.

We attempted to prepare the meso isomer of **54** stereoselectively by the Corey−Fuchs method, but oxidation of 1,4-butanediol **56** with PCC gave only lactone **59** (Scheme 14). Swern oxidation of the 1,4-diol[40] gave neither succinaldehyde **57** nor lactone **59**. Because the succinaldehyde was not expected to be very stable, the Swern oxidation and the subsequent Wittig reaction were also attempted using a consecutive one-pot oxidation−Wittig method described by Ireland.[41] However, none of the products isolated were the desired tetrabromo olefin **58**. Further efforts toward *meso*-**54** were not made.

(d) Perfluoro Analogues. We prepared trifluoromethyl and pentafluoroethyl analogues **64a**,**b** (Scheme 15) in which perfluoroalkane groups mimic the effect of the dipole moment of the nitrile functionality of DPN. Triphenylphosphonium salt **60** was prepared by the reaction of 4-methoxybenzyl chloride and Ph_3P,[42] and perfluoroalkyl aryl ketones **61a**,**b** were prepared by the treatment of 4-methoxyphenylmagnesium bromide with ethyl trifluoroacetate[43] or pentafluoropropionic anhydride. Wittig condensation of **60** and **61a**,**b** with LHMDS gave a single isomer of olefins **62a**,**b**, of undetermined geometry; yields were lower with NaOMe, due to a haloform-like cleavage reaction. Olefins **62a**,**b** were hydrogenated and then demethylated with BBr_3 to furnish desired products **64a**,**b**.

(e) Polar Analogues. We prepared analogues **66**, **67**, **69**, and **71** having various polar functionalities as mimics of the dipole moment of the nitrile functionality of DPN (Scheme 16). Carboxylic acid **21** was esterified to afford methyl ester **65**, a common intermediate in the synthesis of ester **66**, amides **67a**,**b**, and trifluoroketone **68**. Demethylation of the aryl methyl ethers of **65** with BBr_3 and $BF_3{\cdot}SMe_2$ led to ester hydrolysis, but deprotection with $AlCl_3$ in refluxing benzene or $AlBr_3$ in EtSH at 0 °C was selective, affording the desired diol **66**, without significant ester hydrolysis. Complete demethylation of ester **65** with BBr_3, followed by quenching with *n*-propylamine or diethylamine,[44] gave the desired amides **67a**,**b** in satisfactory yields. Trifluoromethyl ketone **68** was accessed in moderate yield by treatment

Scheme 16

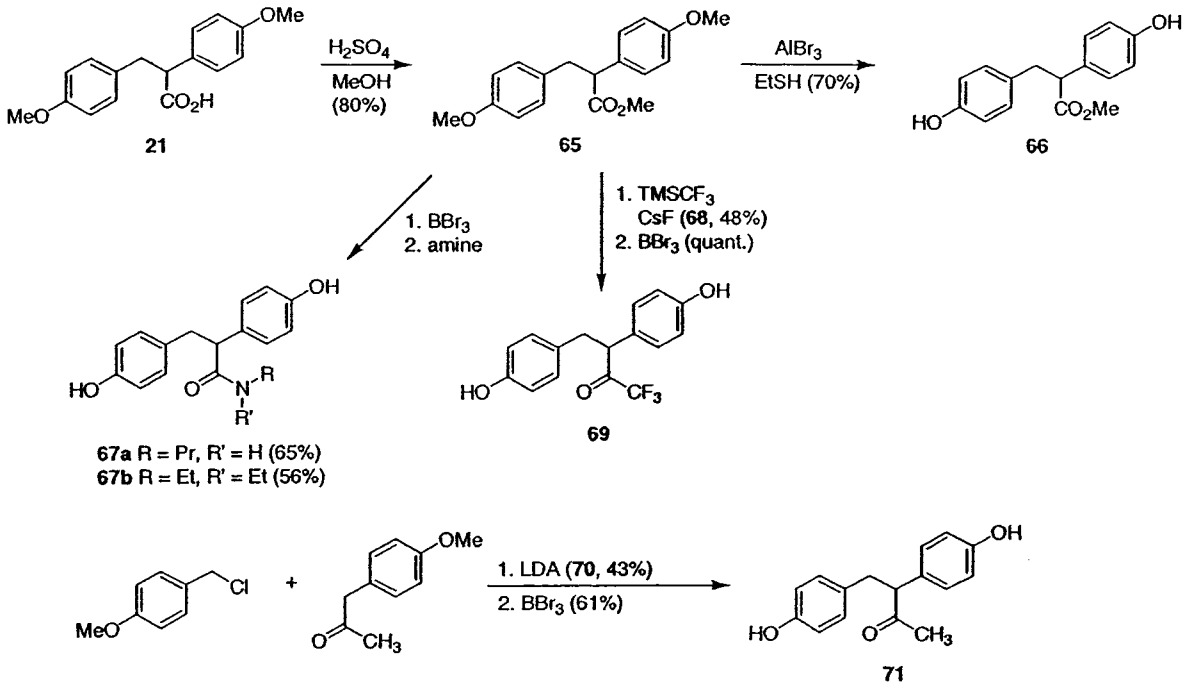
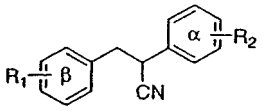


Table 1. Relative Binding Affinities (RBA)[a] of Nitriles **16a**−**h** for ERα and ERβ



				RBA (%)		
entry	ligand	R_1	R_2	hERα	hERβ	β:α
1	estradiol			100	100	
2	**16a**/DPN	*p*-OH	*p*-OH	0.25 ± 0.15	18 ± 2	72
3	**16b**	*p*-OH	*m*-OH	0.17 ± 0.04	2.9 ± 0.6	17
4	**16c**	*m*-OH	*p*-OH	0.03 ± 0.01	2.2 ± 0.6	73
5	**16d**	*m*-OH	*m*-OH	0.02 ± 0.00	0.14 ± 0.04	7
6	**16e**	*p*-OH	H	0.005	0.048	10
7	**16f**	H	*p*-OH	0.010	0.071	7
8	**16g**	*p*-OH, *o*-Me	*p*-OH	0.87 ± 0.18	60 ± 11	69
9	**16h**	*p*-OH	*p*-OH, *o*-Me	0.41 ± 0.21	18 ± 3	44

[a] Determined by a competitive radiometric binding assay with [^{3}H]estradiol using full-length human ERα and ERβ (PanVera); see Experimental Section.[46,47] Values are reported as the mean ± SD (n ≥ 2). Under these conditions, the K_d for estradiol is 0.3 nM.

of ester **65** with $TMSCF_3$ and a catalytic amount of CsF.[45] Ketone **68** was demethylated with BBr_3 to afford **69**. Methyl ketone **71** was prepared by the alkylation of 4-methoxyphenylacetone with 4-methoxybenzyl bromide in modest yield and then demethylated with BBr_3.

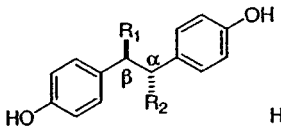
Biological Results. (a) Receptor Binding Studies and Structure−Binding Affinity Relationships. The phenolic nitriles and nitrile analogues were evaluated in competitive radiometric binding assays to determine their affinities for purified, recombinant full-length human ERα and ERβ. Binding affinities are expressed as relative binding affinity (RBA) values (estradiol = 100%), and were determined by the previously described methods.[46,47]

The lead compound, DPN (**16a**), is strongly ERβ selective (70-fold), and all of the derivatives presented here retain this ERβ selectivity to varying degrees. Compounds with various substitutions have been made, and they are divided into several groups: those with different aryl ring substitution patterns, different alkyl chain variations, dinitriles, unsaturated nitriles, steric analogues, and polar analogues. Most substituent changes that increase affinity for ERβ also increase affinity for ERα, resulting in a lowered subtype selectivity (see below).

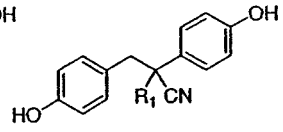
(1) Aryl Ring Substitution Patterns. Propionitriles **16a**−**h** have lower affinities than estradiol for both ER subtypes (Table 1). Their affinities for ERα are all less than 1% of estradiol, while their affinities for ERβ are higher, from 2 to 60% that of estradiol, giving ERβ affinity selectivities of 7−70. The affinity of these nitriles is quite dependent on the presence and position of both phenolic hydroxy groups. If either the α or the β hydroxy group is removed, the affinity for both receptors drops substantially (30−60-fold for ERα and 250−370-fold for ERβ; entries 2, 6, 7). The affinity drop is considerably greater for ERβ than for ERα, resulting in a 6-fold reduction in β/α selectivity.

If either hydroxy group is moved from the para to the meta position, moderate drops in affinity are shown (entries 2−4). Affinity for ERα is lowered only 2-fold if the α-OH is meta, but drops 10-fold if the β-OH is meta.

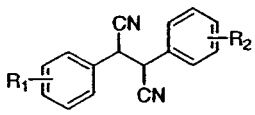
Table 2. Relative Binding Affinities (RBA) of Nitrile Analogues for the ERα and ER*β*



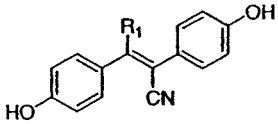
DPN, 25, 29a-b



27, 35



31a-c



36-37

				Relative Binding Affinity (RBA, (%)		
entry	ligand	R_1	R_2	hERα	hER*β*	*β*:α
1	DPN	H	CN	0.25 ± 0.15	18 ± 2	72
2	**25**	H	CH_2CN	0.16 ± 0.01	2.2 ± 0.0	14
3	**27**	Me		0.22 ± 0.06	6.6 ± 1.9	30
4	**29a**	Me	CN	1.7 ± 0.3	48 ± 3	27
5	**29b**	Et	CN	17 ± 5	75 ± 6	4
6	*meso*-**31a**	*p*-OH	*p*-OH	0.55 ± 0.07	29 ± 7	53
7	*dl*-**31a**	*p*-OH	*p*-OH	0.04 ± 0.01	2.8 ± 0.8	70
8	*erythro*-**31b**	*p*-OH	*m*-OH	0.063	3.4	54
9	*meso*-**31c**	*m*-OH	*m*-OH	0.011	0.18	16
10	**35**	CN		0.29 ± 0.04	2.5 ± 0.7	9
11	(*Z*)-**36**[a]	H		0.30 ± 0.06	17 ± 3	57
12	(*E*)-**37**	CN		9.8 ± 0.4	82 ± 4	8

[a] Prepared by deprotection of **14a** with BBr_3 (see Experimental Section).

For ER*β*, changing either the α or *β* ring hydroxy group to the meta position causes a comparable 6−8-fold drop. Thus, the *β*/α ratio is less favorable for a meta α-OH versus a meta *β*-OH. Nitrile **16d**, with both α- and *β*-OH groups in the meta position, has even lower affinities and lower *β*/α selectivity (entry 5). Placement of the hydroxy groups in the meta position alters the interatomic distance between the oxygen atoms, which presumably disposes these hydrogen bonding functions less optimally for binding to both receptors.

The addition of a methyl group in the ortho position of either ring has an interesting effect (entries **8** and 9). Nitrile **16g**, with an ortho methyl in the *β*-ring, has an increased affinity for ER*β*, so that its RBA rises to more than half that of estradiol (RBA = 60%). Its affinity for both ERα and ER*β* is increased 3-fold relative to DPN; so, it maintains its high *β*/α ratio. This methyl group must restrict rotation of the aryl ring and/or increase steric bulk of the ligand in ways that improve affinity and maintain selectivity. Based on what is found in other systems (see next sections), it is surprising that this increased bulk does not reduce the *β*/α ratio. By contrast, placement of the methyl group on the α-ring (**16h**) has surprisingly little effect on the binding affinity for either receptor subtype, although there is a slight erosion in ER*β* selectivity relative to DPN. Perhaps in this isomer the restricted rotation of the methylated α-ring forces the nitrile into a less favorable region of the ligand-binding pocket, such that the steric obstruction of the methyl group cancels its lipophilic benefit. These direct analogues of DPN demonstrate that modifications to the aryl ring substituents can affect binding affinity and ER*β* selectivities, and, in one case (**16g**), that the addition of a methyl group increases binding affinity without loss of ER*β* selectivity.

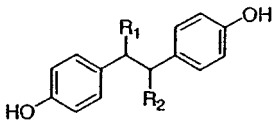
(2) Alkyl Chain Variations. The effect of variations in the alkyl chain portion of the lead nitrile DPN on binding affinity is demonstrated in Table 2. The extension of the nitrile position by the addition of a single methylene to DPN results in moderate losses in affinity for both ERα and ER*β*, resulting in a significant decrease in the *β*/α ratio (entries 1 and 2). Placement of a methyl group α to the nitrile (**27**) gives a more moderate loss in affinity and selectivity (entry 3), suggesting that the location of the nitrile group is very important for both binding affinity and selectivity. By contrast, increases in steric bulk at the *β* position tend to raise ligand affinity for both receptors substantially (entries 4 and 5), but at the expense of sequentially lower ER*β*/ERα selectivity ratios. Especially interesting is the change in affinity and selectivity moving from DPN to the *β*-methylated analogue **29a** and then the b-ethylated analogue **29b**. The addition of each carbon results in a 7−10-fold increase in affinity for ERα but only a 1.5−3-fold increase in affinity for ER*β*, resulting in diminished ER*β* selectivity.

(3) Dinitriles. Binding affinities for succinonitriles **31a**−**c** and malononitrile **35** are reported in Table 2. The affinity of *meso*-**31a** for both ERα and ER*β* are doubled relative to mononitrile DPN (entries 6 and 1, respectively). Intriguingly, in this succinonitrile series, the relative stereochemistry is important for affinity, but not for selectivity. Thus, the affinity of the dl isomer is 10-fold less than the meso isomer, whereas the ER*β* selectivity of both isomers remains high and comparable (entries 6 and 7).

The 10-fold lower affinity of the dl isomer can be partially accounted for by differences in the relative energies of the anti-periplanar and synclinal (with respect to the aryl rings) conformers of the diastereomers ***dl*-31a** and *meso*-**31a**. Koh and co-workers have reported that in the diphenylsuccinonitrile system the *meso*-diastereomer has a greater preference for the anti-periplanar conformer than does the *dl*-diastereomer.[48] Based on related studies by Kilbourn in the hexestrol series, it is known that the estrogen receptor strongly prefers to bind such molecules in the antiperiplanar conformation.[49] Thus, the lower affinity of *dl*-**31a** derives in part from its preference for the disfavored synclinal conformation.

As expected, the placement of one or both hydroxy groups in the meta position of the dinitriles results in successively greater losses in binding affinity for both receptor subtypes (entries 8 and 9). However, the 50-fold selectivity of *meso*-**31a** is retained in the meta/para analogue (*erythro*-**31b**), whereas much selectivity is lost

Table 3. Relative Binding Affinities (RBA) of Acetylene and Polar Analogues for ERα and ERβ



				Relative Binding Affinity (RBA, %)		
entry	compd	R_1	R_2	hERα	hERβ	β:α
1	**42a**	H	C≡CH	3.3 ± 0.9	78 ± 10	24
2	**42b**	H	C≡CCH$_3$	3.8 ± 0.6	43 ± 7	11
3	*dl*-**54**	C≡CH	C≡CH	0.48 ± 0.07	14 ± 4	29
4	**64a**	H	CF_3	0.71 ± 0.12	22 ± 4	31
5	**64b**	H	CF_2CF_3	10 ± 2	35 ± 10	4
6	**69**	H	$COCF_3$	0.11 ± 0.00	1.3 ± 0.0	12
7	**71**	H	$COCH_3$	0.24	2.3	10
8	**67a**	H	CONHPr	<0.01	0.043	
9	**67b**	H	$CONEt_2$	0.012	0.040	3
10	**66**	H	CO_2Me	0.76 ± 0.18	8.3 ± 1.2	11
11	**43**	H	CO_2H	0.013	0.016	1
12	**72**[a]	H	CH_2OH	0.045	0.071	2

[a] Prepared by deprotection of bis silyl ether **45** with TBAF (see Experimental Section).

in the meta/meta analogue (*meso*-**31c**), a trend that was seen in the mononitrile series (Table 1). While the addition of a second nitrile in the β-position in DPN actually slightly increases affinity for both receptors, the addition of a second nitrile group in the a-position, as in malononitrile **35**, has no effect on ERα binding but reduces ERβ affinity nearly 10-fold, resulting in a much lower β/α ratio (entry 10).

(4) Unsaturated Nitriles. The relative binding affinities of unsaturated analogues of DPN are reported in Table 2. The binding affinity of (*Z*)-**36** for purified ERα and ERβ is nearly identical to that of DPN (entries 11 and 1, respectively). The addition of a second nitrile group results in 32- and 5-fold increases in affinity for ERα and ERβ (entries 11 and 12), respectively, similar to the smaller increases of saturated bisnitrile *meso*-**31a** over DPN, but much of the β/α selectivity is lost.

(5) Steric Analogues. The relative binding affinities of acetylene analogues of DPN are shown in Table 3. Replacement of the nitrile group with an acetylene (**42a**) results in a 10-fold increase in affinity for ERα and a 4-fold increase in affinity for ERβ relative to nitrile DPN (entry 1 and Table 1, entry 2). Similarly, the affinity of propyne substituted **42b** increased 12-fold for ERα and 2−3-fold for ERβ, relative to DPN (entry 2). Both of these substituent changes result in 3−5-fold lower β/α affinity ratios. Bisacetylenic analogues of succinonitriles **31** also result in increased affinities for ERα and ERβ. *dl*-**54**, similarly, has a 12-fold greater affinity for ERα and a 5-fold affinity increase for ERβ relative to succinonitrile *dl*-**31a** (entry 3 and Table 2, entry 7). Thus, acetylenes, which mimic the linear sp geometry of the nitriles, have higher binding affinities than the nitriles, but somewhat lower ERβ selectivities, characteristics that might be attributed to the more lipophilic nature of acetylenes.

(6) Polar Analogues. The binding affinities of polar analogues of nitrile DPN and succinonitrile **31a** are presented in Table 3. Trifluoromethyl analogue **64a** (entry 4) has greater affinity for both ERα and ERβ relative to DPN, but only about half its β/α selectivity (Table 1, entry 2). An additional increase in perfluoroalkyl chain length increases ERα affinity significantly more than ERβ, thereby reducing β/α selectivity considerably (entry 5). Hartmann and co-workers have reported that a bistrifluoromethyl analogue, *meso*-1,1,1,4,4,4-hexafluoro-2,3-bis(4-hydroxyphenyl)butane, has a 50% RBA for the ER.[50] With such a high RBA, it is unlikely that this compound would have significant ERβ binding selectivity. The increase in binding affinity of **64a** and **64b** is presumably due both to an increase in steric bulk and in lipophilicity,[50] which in turn progressively lower the affinity selectivity for ERβ. Given this, the 30-fold selectivity of **64a** is surprising and may be due to stereoelectronic effects of the trifluoromethyl group.

Methyl ketones **69** and **71** exhibit significant ERβ binding selectivities (10−12-fold), although both the selectivity and affinities are lower than DPN (entries 6 and 7). Interestingly, methyl ester **66** has similar selectivity to methyl ketone **71**, but higher affinity for both ER subtypes (entry 10). Amides **67a**,**b**, carboxylic acid **43**, and carbinol **72** have very low affinities and poor selectivities, demonstrating the intolerance of both ERs for polar functionality at the core of the ligand (entries 8, 9, 11, and 12).

In general, simple polar substituents lower binding affinity and ERβ selectivity relative to DPN. Fluorinated compounds, perhaps due to the greater lipophilicity of their "polar" substituents, do not suffer as great a loss in affinity and ERβ selectivity. Both the dipolar nature and the sp linear geometry of the nitrile functionality appear to be important in eliciting the ERβ binding selectivity of the compounds in this series, because all of the polar analogues and the alkyne steric analogues show a significant loss in ERβ binding affinity selectivity with respect to their nitrile congeners. The behavior of the acetylene analogues, which mimic the linear sp geometry of the nitriles, is particularly instructive. They have higher binding affinities than the nitriles, but somewhat lower ERβ selectivities, a relationship that is true to a greater extent in compounds when two of these linear groups are present. These results suggest that both the sp geometry and the polarity of the nitrile functionality play an important role in the affinity of these ligands for the ER, but more so for ERα than for ERβ. Apparently, ERα has a lesser ability to tolerate the polar nature of the nitrile functionality, whereas

ERβ is less affected by the polar nature of the nitrile function than by the geometric requirement of the sp hybridization. As a result, ligands with linear groups (i.e., nitriles, acetylenes) have significant affinity selectivity for ERβ, but the increased polarity of the nitrile group reduces the affinity of the ligand for ERα, resulting in higher ERβ binding selectivities. Perhaps ERβ has a more flexible and more polar-tolerant binding pocket that can favorably accept a linear group and can tolerate the dipolar nature of the nitrile, whereas ERα may have a more restrictive pocket that has a lesser ability to accept linear and polar groups. Thus, the ERβ binding affinity selectivity of DPN has been conserved only in the presence of the nitrile functionality and with relatively few changes in ligand structure, namely, the placement of the β-ring hydroxyl in the meta position (**16c**), the addition of a methyl group in the ortho ring positions (**16g**,**h**), and the addition of a second nitrile group in the β-position (**31a**,**b**).

(b) Transcription Assays and Structure−Activity Relationships. The transcriptional activities of many of the nitrile, polar, and steric analogues of DPN were assayed in human endometrial cancer (HEC-1) cells transfected with expression plamids for ERα and ERβ and an estrogen-responsive reporter gene, either chloramphenicol acetyltransferase (CAT) or luciferase (Luc). Activities were normalized to that effected by 10^{-8} M estradiol, which is set at 100, as previously described.[9] As examples, full dose−response curves for estradiol and five selected compounds are presented in Figure 2.

As shown in this figure, the two bis-nitriles (*meso*- and *dl*-**31a**, Figure 2C,D) have potencies and selectivities that are quite similar to that of the original mononitrile (DPN/**16a**, Figure 2B). The β-methyl mononitrile (**29a**, Figure 2E) is somewhat more potent and similarly ERβ-selective, and the bis-acetylene (*dl*-**54**, Figure 2F) is less potent but still very ERβ−selective. The transcriptional potency of these and the other most interesting affinity- and potency-selective compounds are listed in Table 4 (nitriles) and Table 5 (acetylenes and polar analogues), where comparisons can be made in terms of ERβ potency selectivity and affinity selectivity. Compounds that failed to show full activation of either ERα or ERβ at 10^{-6} M (namely, **16b**−**f**, **31c**, and **72**) have been omitted from these tables.[51]

The transcriptional potencies of the various compounds acting through ERα and ERβ are listed in Tables 4 and 5 as EC_{50} values, and their selectivity is expressed as the ratio of the EC_{50} values, β/α (first three columns of numbers). However, because estradiol has a somewhat higher potency through ERα than through ERβ (2.2-fold in the Luc assay (see Figure 2A) and 5-fold in the CAT assay), the EC_{50} ratio of absolute potencies cannot be compared directly with the affinity selectivity expressed as the ratio of RBA values, because each RBA value is expressed relative to the affinity of estradiol.

A more useful comparative measure of potency is the relative estrogenic potency (REP, calculated as REP = 100 × [EC_{50}(estradiol)]/[EC_{50}(ligand)]),[12] an index that normalizes the potency of a compound on either ER subtype relative to that of estradiol on that subtype and is expressed as a percentage, just like the RBA value in binding affinity assays. (Because of the different EC_{50} values for estradiol on the two ER subtypes, the ratio of REP values (β/α) is greater than the ratio of EC_{50} values by a factor of 2.2 in Luc assays and a factor of 5.0 in CAT assays.) The REP values and the β/α ratio of each compound are also given in Tables 4 and 5 (middle three columns of numbers) where they can be directly compared with the RBA values (last three columns of figures). This comparison shows that there is quite a good correlation between the ERβ affinity selectivity and the potency selectivity of most of the compounds we have studied.

All of the nitriles examined were agonists on ERα and ERβ, although some low-affinity compounds did not reach full activity even at 1 mM concentrations and consequently are not shown in Table 4. In general, nitriles with the highest affinities also had the highest potencies. For example, nitriles **16g** and *meso*-**31a** have ERβ REP values of ca. 10, which indicates a potency that is twice as high as that of DPN (4.6), far greater than that of the ERβ-selective phytoestrogen genestein, and approaching within an order of magnitude that of the native ligand estradiol. These three ligands are also among those with the highest ERβ RBA values. Reasonably good correlations between β/α affinity selectivity and potency selectivity are also seen with most of the other nitriles, although in these other cases the individual ERβ affinities and potencies are lower. There are, however, some interesting exceptions.

The unsaturated nitriles **36** and **37**, both of which have ERβ affinities that are comparable to that of DPN and in one case have high affinity selectivity (56 for compound **36**), were found to have very weak transcriptional potencies and only modest ERβ potency selectivities (less than 10). The reduced potency of these compounds in the cell-based assay might result from the addition of cellular nucleophiles to the electrophilic alkene of these acrylonitrile or fumaronitrile systems.

Comparisons among isomers and homologues are also interesting. The epimeric bisnitriles *dl*- and *meso*-**31a** have nearly identical transcriptional potencies and selectivities, yet the dl isomer has a 10-fold lower affinity on both ER subtypes. This apparent discrepancy might be due to epimerization of the *dl*-**31a** to the more potent, lower energy meso diastereomer under the conditions of the assay. In the homologous series of β-substituted mononitriles, **16a** and **29a**,**b**, ERβ and ERα affinity and potency increase with the size of the β substituent, but β/α binding and potency selectivities steadily decrease, so that the lowest affinity compound (**16a**) is, in fact, the most selective. Repositioning of the nitrile functionality by a methylene spacer (**25**) or addition of a second nitrile in the a-position (**35**) resulted in lower transcriptional potencies and selectivities, with corresponding changes in their affinities.

Overall, a number of nitriles were found to be more potent and more selective on ERβ than the phytoestrogen genistein: **16a**, **16g**, *meso*- and *dl*-**31a**, and **29a**. From a practical standpoint, concentrations of 1 nM of both *meso*-**31a** and *dl*-**31a** could stimulate ERβ to about 70% of maximal activity without stimulating ERα, whereas DPN (**16a**) could only stimulate ERβ to about 45% the activity of estradiol without stimulating ERα (Figure 2).

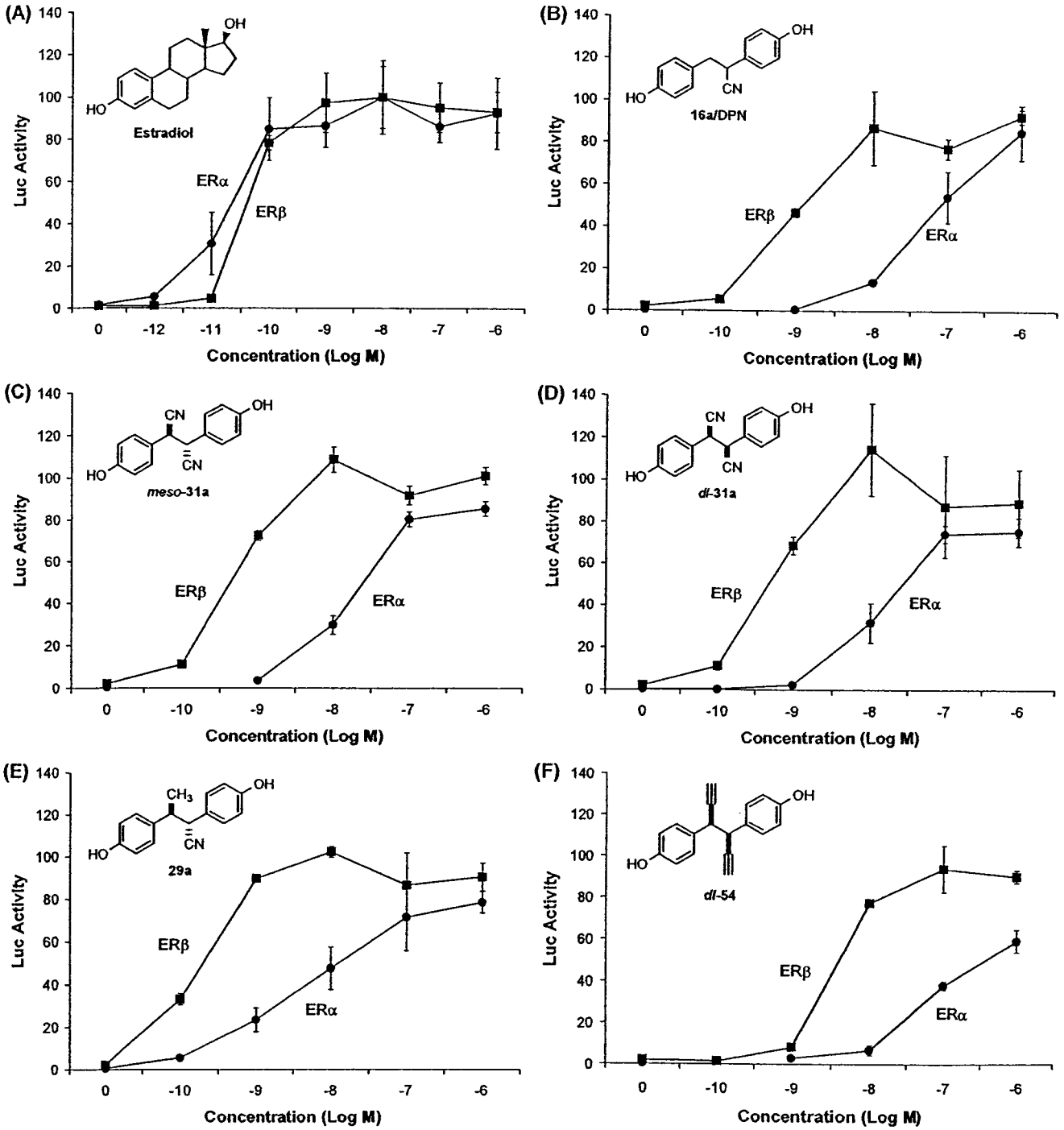
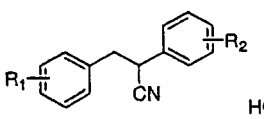


Figure 2. Transcription activation by ERα (circle symbols) and ERβ (square symbols) in response to estradiol, **16a**/DPN, *meso*-**31a**, *dl*-**31a**, **29a**, and *dl*-**54**. Human endometrial cancer (HEC-1) cells were transfected with expression vectors for ERα or ERβ and the estrogen responsive $(ERE)_4$-TATA-LUC reporter gene and were treated with the indicated concentrations of ligand for 24 h. The dual-luciferase reporter assay system was used for the luciferase activity assay. Values are expressed as a percent of the ERα or ERβ response with 10^{-8} M estradiol. All experiments were performed in triplicate, and the values are given as the mean SD. In some cases, the error bars may be too small to be visible.

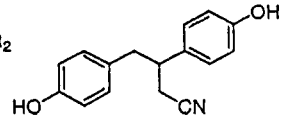
Despite having some significant ERβ binding selectivity, nearly all of the polar and steric analogues have only modest transcriptional potency selectivity (Table 5). The one exception is bisacetylene analogue *dl*-**54** (Figure 2F), which has a 29-fold ERβ affinity selectivity and a 44-fold ERβ potency selectivity; the latter is about 2-fold lower than the corresponding succinonitrile *dl*-**31a** (Figure 2D). The bisacetylene *dl*-**54** is also less potent than its succinonitrile analogue by nearly an order of magnitude. In contrast, the monoalkyne **42a** and the trifluoromethyl analogue **64a** are more potent than the nitrile analogue DPN, but they are less ERβ potency-selective.

On the basis of the transcriptional activity of these nitriles and their steric and polar analogues through the ER subtypes, we can make the following conclusions: (1) The nitriles with the highest binding selectivities have the greatest transcriptional potency selectivities, particularly those with higher affinities and hydroxy groups in the para position. (2) As expected, nitriles with higher affinities and low binding selectivities have high potencies but little or no transcriptional

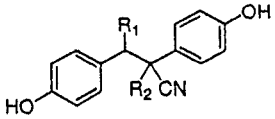
Table 4. Transcriptional Potencies[a] of Nitriles and for ERα and ERβ



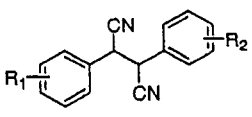
16a,g-h



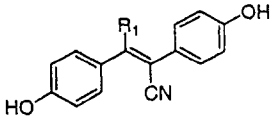
25



27,29a-b,35



31a-c

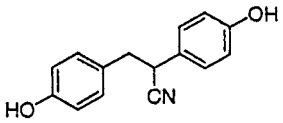


36-37

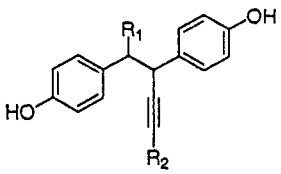
			EC$_{50}$ (nM)			REP[b] (%)			RBA[c] (%)		
ligand	R_1	R_2	hERα	hERβ	β:α	hERα	hERβ	β:α	hERα	hERβ	β:α
estradiol			0.018	0.039	0.46	(100)	(100)	(1)	(100)	(100)	(1)
genistein[d]			20	6.0	3	0.025	0.8	32	0.7	13	19
16a/DPN	*p*-OH	*p*-OH	66	0.85	78	0.027	4.6	170	0.25	18	72
16g	*p*−H, *o*-Me	*p*-OH	6.7	0.37	18	0.27	11	41	0.87	60	69
16h	*p*-OH	*p*-OH, *o*-Me	16	1.7	9	0.11	2.3	21	0.41	18	44
25[e]			130	30	4	0.017	0.37	22	0.16	2.2	14
27	H	Me	23	8.0	3	0.078	0.49	6	0.22	6.6	30
29a	Me	H	5.2	0.14	37	0.35	28	80	1.8	48	27
29b[e]	Et	H	0.064	0.15	0.43	34	73	2	17	75	4
meso-**31a**	*p*-OH	*p*-OH	18	0.42	43	0.10	9.3	93	0.55	29	53
dl-**31a**	*p*-OH	*p*-OH	14	0.41	34	0.13	9.5	73	0.04	2.8	70
erythro-**31b**	*p*-OH	*m*-OH	150	110	1	0.012	0.035	3	0.63	3.4	54
35[e]	H	CN	40	21	2	0.055	0.52	9	0.29	2.5	9
(*Z*)-**36**[e]	H		95	140	0.7	0.023	0.079	3	0.30	17	57
(*E*)-**37**[e]	CN		400	220	2	0.0055	0.050	9	9.8	82	8

[a] Transcriptional activity (transcriptional potency = EC$_{50}$) was measured using the luciferase (Luc) assay, unless indicated otherwise. [b] Relative estrogenic potency (REP) = (EC$_{50}$(estradiol)/(EC$_{50}$(ligand)). [c] RBA = relative binding affinity. [d] Transcriptional activities were measured with a Luc reporter gene in transfected 293 human embryonal kidney cells and are taken from ref 8. RBA values are taken from ref 12. [e] Transcriptional activity was measured using CAT assay. The EC$_{50}$ values of estradiol for ERα and ERβ in the CAT assay are 0.022 nM and 0.11 nM, respectively, resulting in a ratio of β:α of 0.20.

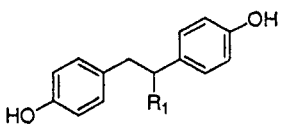
Table 5. Transcriptional Potencies[a] of Acetylenes and Polar Analogues and for ERα and ERβ



16a



42a-b,54



64a-b,66,69,71

			Transcriptional Potency (EC$_{50}$, (nM)			Relative Estrogenic Potency (REP, %)			Relative Binding Affinity (RBA,[c] %)		
ligand	R_1	R_2	hERα	hERβ	β: α	hERα	hERβ	β: α	hERα	hERβ	β: α
estradiol			0.018	0.039	0.46	(100)	(100)	(1)	(100)	(100)	(1)
genistein[d]			20	6.0	3	0.025	0.8	32	0.7	13	19
16a/DPN			66	0.85	78	0.027	4.6	170	0.25	18	72
42a[e]	H	H	3.1	1.4	2	0.71	7.9	11	3.3	78	24
42b[e]	H	Me	0.38	2.1	0.2	5.8	5.2	0.9	3.8	43	11
dl-**54**	CCH	H	73	3.7	20	0.025	1.1	44	0.48	14	29
64a[e]	CF_3		2.9	2.0	2	0.76	5.5	7	0.71	22	31
64b	CF_2CF_3		42	15	3	0.043	0.26	6	10	35	4
66[e]	CO_2Me		2.7	4.9	0.6	0.81	2.2	3	0.76	8.3	11
69	$COCF_3$		464	160	3	0.003 9	0.024	6	0.11	1.3	12
71	COMe		18	35	0.5	0.10	0.11	1	0.24	2.3	10

[a] Transcriptional activity (EC$_{50}$ = transcriptional potency) was measured using the luciferase (Luc) assay, unless indicated otherwise. [b] Relative estrogenic potency (REP) = (EC$_{50}$(estradiol)/(EC$_{50}$(ligand)). [c] RBA = relative binding affinity. [d] Transcriptional activities were measured with a Luc reporter gene in transfected 293 human embryonal kidney cells and are taken from ref 8. RBA values are taken from ref 12. [e] Transcriptional activity was measured using CAT assay. The EC$_{50}$ values of estradiol for ERα and ERβ in the CAT assay are 0.022 nM and 0.11 nM, respectively, resulting in a ratio of β:α of 0.20.

selectivities. (3) Despite their high binding affinity and moderate binding selectivity, unsaturated nitriles are much less potent in transcriptional assays and have lost all transcriptional potency selectivity. (4) Despite some significant ERβ binding selectivity, nearly all of the polar and steric analogues have little or no transcriptional potency selectivity, with the exception of bisacetylene analogue *dl*-**54**, which has an 44-fold ERβ REP selectivity.

While many of the nitrile analogues have high affinity selectivities for ERβ, selectivity in terms of transcriptional potency is more difficult to achieve. Thus, within this series, binding affinity selectivity appears to be a prerequisite for ERβ potency selectivity, but affinity selectivity does not necessarily ensure potency selectivity. Furthermore, the potency of these compounds does not always correlate directly with binding affinity, and it appears that ERβ affinity selectivities of greater than 25-fold are generally required for ERβ potency selectivities to reach comparable values. It is also of note that nearly all of the ligands we have investigated are chiral, and we have studied them only as racemates. Thus, it

is possible that single enantiomers of these chiral ligands might display different ER subtype selectivity (most likely enhanced over that of the racemates). This is an aspect that we intend to investigate in the future.

Conclusion

We have synthesized a number of diarylpropionitriles, diarylsuccinonitriles as well as acetylene and polar analogues of these nitriles. These ligands all have considerable ERβ binding affinity selectivity, with some of the diarylproprionitriles and diarylsuccinonitriles having the highest known selectivities of 50−70-fold, based on EC_{50} ratios or 80−170-fold based on REP ratios. Some of these compounds have affinities for ERβ that are almost the same as that of the native ligand estradiol. Furthermore, acetylene analogues, and some fluorinated polar analogues (CF_3 and $COCF_3$), have higher binding affinities, but have only about half the binding selectivity of their nitrile counterparts. These results suggest that the nitrile functionality represents the optimal combination of linear sp geometry and local polarity, and it is the best functional group for ligands of this type with respect to ERβ binding affinity selectivity. The compounds described in this paper should be especially useful in probing the biological role of ERβ.

Experimental Section

General. Reagents and solvents were purchased from Aldrich, Acros, Fisher, Mallinckrodt, and Strem. THF was distilled immediately prior to use from sodium/benzophenone. CH_2Cl_2 and benzene were distilled from CaH_2. *n*-Butyllithium was titrated against *N*-pivaloyl-*o*-toluidine.[52] Et_3N was distilled over CaH_2. All reactions were carried out under nitrogen or argon, using oven- or flame-dried glassware, unless stated otherwise. Reaction progress was monitored by analytical thin-layer chromatography using 0.25 mm HLF silica plates with UV254 indicator, and visualization was achieved by UV light (254 nm) or phosphomolybdic acid indicator. Hexane was distilled prior to use in chromatography. Flash chromatography was performed using Woelm 32−63 mm silica gel packing.

Melting points were determined on a Thomas-Hoover Unimelt capillary apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with Varian UNITY 400 and 500 MHz spectrometers. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane and referenced from solvent references. NMR coupling constants are reported in hertz. Carbon spectra were determined using the attached proton test (APT) experiment. Low- and high-resolution electron impact (EI, 70 eV) and chemical ionization (CI) mass spectra were obtained on a Micromass 70-VSE spectrometer. Low- and high-resolution fast atom bombardment (FAB) mass spectra were obtained on Micromass ZAB-SE and 70-SE-4F spectrometers, respectively. Elemental analyses were performed by the Microanalytic Service Laboratory at the University of Illinois. Minimum purity for target compounds which did not give satisfactory elemental analyses were established by both normal phase (EtOAc/Hexanes) and reverse phase (acetonitrile/water) HPLC analysis.

General Methods for Arylacetonitrile/Aldehyde Condensation. (a) Method A. A solution of the appropriate arylacetonitrile (1 equiv) and arylaldehyde (1 equiv) in absolute EtOH (0.7 mL/mmol) was treated with NaOMe (0.1 equiv) portionwise, stirred at room temperature for 2 h, cooled to 0 °C, and filtered. The precipitate was washed with cold EtOH.

(b) Method B. A solution of 40% aqueous KOH (0.23 mL/mmol nitrile) was diluted with EtOH (0.46 mL/mmol nitrile) and added at room temperature to a solution of the arylaldehyde (1.1 equiv) and arylacetonitrile (1.0 equiv) in EtOH (0.35 mL/mmol nitrile), often resulting in the immediate formation of an off-white precipitate. The reaction was stirred for 1.5 h to overnight. The precipitate was collected by vacuum filtration and washed with water and cold EtOH. In some cases, an alternative workup was required (aqueous workup): The reaction mixture was concentrated, and the resulting residue was partitioned between water and EtOAc. The aqueous layer was neutralized with 6 M HCl and extracted with EtOAc two more times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo.

(Z)-2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile (14b). α-Cyanostilbene **14b** was prepared by method B from (3-methoxyphenyl)acetonitrile (616 mL, 4.41 mmol) and *p*-anisaldehyde (590 mL, 4.85 mmol) as an off-white solid which was dried in vacuo (1.11 g, 4.18 mmol, 95%): mp 64−66.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.3, 2H), 7.46 (s, 1H), 7.34 (t, J = 8.1, 1H), 7.23−7.26 (m, 1H), 7.17 (t, J = 2.1, 1H), 6.98 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.5, 2H), 6.91 (dd, J = 8.1, 2.1, 1H), 3.87 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 160.0, 142.1, 136.2, 131.2, 130.0, 126.4, 118.5, 118.2, 114.3, 114.3, 111.4, 108.5, 55.4, 55.4; MS (EI) *m*/*z* 265 (M^+, 100). HRMS (EI) calcd for $C_{17}H_{15}NO_2$: 265.1103, found 265.1099.

(Z)-2-(4-Methoxyphenyl)-3-(3-methoxyphenyl)acrylonitrile (14c). α-Cyanostilbene **14c** was prepared according to method A from (4-methoxyphenyl)acetonitrile (13.6 g, 100 mmol) and *m*-anisaldehyde (14.7 g, 100 mmol) as a white solid which was dried in vacuo (16.1 g, 60.7 mmol, 61%): mp 48−50 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.7, 2H), 7.48 (t, J = 1.8, 1H), 7.38−7.41 (m, 1H), 7.39 (s, 1H), 7.35 (t, J = 7.8, 1H), 6.96−6.99 (m, 1H), 6.96 (XX′ of AA′XX′, J_{AX} = 9.0, $J_{XX'}$ = 2.6, 2H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.4, 159.7, 140.0, 135.1, 129.8, 127.3, 126.8, 121.9, 118.1, 116.5, 114.4, 113.3, 111.3, 55.3, 55.3; MS (EI) *m*/*z* 265 (M^+, 100). HRMS (EI) calcd for $C_{17}H_{15}NO_2$: 265.1103, found 265.1102.

2-(3-Methoxyphenyl)-3-(4-methoxyphenyl)propionitrile (15b). $NaBH_4$ (120 mg, 3.16 mmol, 1 equiv) was added slowly to a 60−70 °C solution of acrylonitrile **14b** (838 mg, 3.16 mmol) in 10 mL of EtOH under a N_2 atmosphere. After stirring for 2.5 h at 60−70 °C, the reaction was cooled to room temperature and quenched with water. The reaction mixture was diluted with 100 mL of water and acidified with 6 M HCl. After extraction with ether (3 × 50 mL), the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated to furnish a yellow oil (825 mg). Flash chromatography (25% EtOAc/hexanes) gave **15b** as a yellow tinted oil (825 mg, 3.09 mmol, 98%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 8.0, 1H), 7.07 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.84−6.88 (m, 2H), 6.83 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.6, 2H), 6.78 (t, J = 2.1, 1H), 3.93 (X of ABX, dd, J = 8.2, 6.4, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.10 (AB of ABX, n_A = 1560, n_B = 1543, J_{AB} = 14.0, J_{AX} = 8.8, J_{BX} = 6.8, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 158.9, 136.7, 130.3, 130.0, 128.3, 120.4, 119.7, 114.0, 113.6, 113.1, 55.3, 55.2, 41.2, 40.0; MS (EI) *m*/*z* 267 (M^+, 4). HRMS (EI) calcd for $C_{17}H_{17}NO_2$: 267.1259, found 267.1261.

2-(4-Methoxyphenyl)-3-(3-methoxyphenyl)propionitrile (15c). $NaBH_4$ (1.08 g, 28.6 mmol, 1.5 equiv) was added portionwise to a solution of acrylonitrile **14c** (5.00 g, 18.9 mmol) in 70 mL EtOH under a N_2 atm. After refluxing for 4 h, the solution was cooled to room temperature. A white precipitate formed. The mixture was placed in a freezer for 1 h. The white precipitate was filtered and dried under vacuum to give **15c** (4.751 g, 17.8 mmol, 94%): mp 92−93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, J = 7.9, 1H), 7.18 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.6, 2H), 6.88 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.6, 2H), 6.81 (ddd, J = 8.3, 2.6, 0.8, 1H), 6.73 (d, J = 7.6, 1H), 6.67 (t, J = 2.0, 1H), 3.95 (X of ABX, dd, J = 8.4, 6.6, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.11 (AB of ABX, n_A = 1572, n_B = 1536, J_{AB} = 13.5, J_{AX} = 8.4, J_{BX} = 6.3, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 159.4, 137.9, 129.6, 128.6, 127.2, 121.5, 120.6, 114.7, 114.3, 112.8, 55.3, 55.1, 42.2, 38.8; MS (EI) *m*/*z* 267 (M^+, 25), 146 (M − $ArCH_2$, 52), 121 ($ArCH_2$, 100). HRMS (EI) calcd for $C_{17}H_{17}NO_2$: 267.1259, found 267.1260.

General Methods for Deprotection of Aryl Methyl Ethers. (a) Method C. BBr_3 (1.0 M in CH_2Cl_2) was added slowly to a stirred solution of the aryl methyl ether in CH_2Cl_2 (~0.2 M) at −78 °C. The solution was allowed to warm to room temperature and stirred overnight. The solution was cooled in an ice bath, quenched with water, and partitioned between EtOAc and 1 M HCl. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. In some cases, a basic workup was used: The quenched reaction was diluted with CH_2Cl_2 and extracted with 1 N NaOH twice. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated.

(b) Method D. BF_3·SMe_2 (50 equiv) was added to a solution of the aryl methyl ether in CH_2Cl_2 (~0.3 M) under an atmosphere of nitrogen. The solution was stirred at ambient temperature overnight. The solution was concentrated under a stream of nitrogen, partitioned between 1 M HCl and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated.

2,3-Bis(4-hydroxyphenyl)propionitrile (16a/DPN). Nitrile **15a** (500 mg, 1.87 mmol) was deprotected with BBr_3 (4 equiv) according to method C. Recrystallization from EtOAc/hexanes gave **16a** as a white solid (234 mg, 0.979 mmol, 52%): mp 199−201 °C (lit.[16] mp 197.5−199.5 °C); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.43 (s, 1H), 8.21 (s, 1H), 7.18 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.6, 2H), 7.05 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.4, 2H), 6.83 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.6, 2H), 6.75 (XX′ of AA′XX′, J_{AX} = 8.5, J_{XX}' = 2.5, 2H), 4.15 (X of ABX, dd, J = 8.1, 7.1, 1H), 3.05 (AB of ABX, n_A = 1222, n_B = 1214, J_{AB} = 13.5, J_{AX} = 8.2, J_{BX} = 7.0, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 157.9, 157.3, 131.2, 129.6, 128.9, 127.9, 121.7, 116.4, 115.9, 41.8, 39.3; MS (EI) m/z 239 (M^+, 4). Anal. ($C_{15}H_{13}NO_2$·0.1H_2O) C, H, N.

2-(3-Hydroxyphenyl)-3-(4-hydroxyphenyl)propionitrile (16b). Nitrile **15b** (430 mg, 1.61 mmol) was deprotected with BBr_3 (4 equiv) according to method C. Flash chromatography (10% MeOH/CH_2Cl_2) gave **16b** as an off-white solid (353 mg, 1.48 mmol, 92%): mp 151−153 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.48 (br s, 1H), 8.25 (br s, 1H), 7.20 (t, J = 8.1, 1H), 7.08 (AA′ of AA′XX′, J_{AX} = 8.3, $J_{AA'}$ = 2.5, 2H), 6.84−6.86 (m, 2H), 6.79 (ddd, J = 8.1, 2.3, 1.1, 1H), 6.75 (XX′ of AA′XX′, J_{AX} = 8.4, $J_{XX'}$ = 2.5, 2H), 4.18 (X of ABX, dd, J = 8.3, 7.0, 1H), 3.07 (AB of ABX, n_A = 1539, n_B = 1533, J_{AB} = 13.8, J_{AX} = 6.8, J_{BX} = 8.3, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.6, 157.4, 138.7, 131.2, 130.8, 128.8, 121.4, 119.5, 116.0, 115.7, 115.4, 41.6, 40.0; MS (EI) m/z 239 (M^+, 5). Anal. ($C_{15}H_{13}NO_2$) C, H, N.

2-(4-Hydroxyphenyl)-3-(3-hydroxyphenyl)propionitrile (16c). Nitrile **15c** (203 mg, 0.759 mmol) was deprotected with BBr_3 (4 equiv) according to method C. Flash chromatography (5% MeOH/CH_2Cl_2) gave **16c** as a viscous clear oil which solidified on standing (171 mg, 0.715 mmol, 94%): mp 114−116.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.50 (br s, 1H), 8.31 (br s, 1H), 7.22 (AA′ of AA′XX′, J_{AX} = 8.4, $J_{AA'}$ = 2.6, 2H), 7.10 (t, J = 7.7, 1H), 6.83 (XX′ of AA′XX′, J_{AX} = 8.8, J_{XX}' = 2.6, 2H), 6.70−6.75 (m, 3H), 4.21 (X of ABX, dd, J = 8.4, 7.0, 1H), 3.07 (AB of ABX, n_A = 1540, n_B = 1531, J_{AB} = 13.6, J_{AX} = 8.4, J_{BX} = 6.9, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.3, 158.0, 139.7, 130.2, 129.6, 127.9, 121.7, 121.2, 117.1, 116.5, 114.8, 42.4, 38.8; MS (EI) m/z 239 (M^+, 31). HRMS (EI) calcd for $C_{15}H_{13}NO_2$: 239.0946, found 239.0945. Anal. ($C_{15}H_{13}NO_2$) C, H, N.

2,3-Bis(3-hydroxyphenyl)propionitrile (16d). Nitrile **15d** (179 mg, 0.668 mmol) was deprotected with BBr_3 (4 equiv) according to method C. Flash chromatography (10% MeOH/CH_2Cl_2) gave **16d** as a viscous clear oil (156 mg, 0.650 mmol, 97%): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.39 (br s, 2H), 7.21 (td, J = 7.7, 0.6, 1H), 7.11 (t, J = 7.8, 1H), 6.86−6.90 (m, 2H), 6.80 (ddd, J = 8.1, 2.0, 1.0, 1H), 6.73−6.77 (m, 2H), 6.72 (ddd, J = 8.0, 2.5, 1.0, 1H), 4.24 (X of ABX, dd, J = 8.3, 6.9, J_{AX} = 6.9, J_{BX} = 8.4, 1H), 3.10 (AB of ABX, n_A = 1552, n_B = 1545, J_{AB} = 14.0, J_{AX} = 6.9, J_{BX} = 8.5, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.7, 158.3, 139.6, 138.6, 130.9, 130.2, 121.3, 121.2, 119.4, 117.1, 115.8, 115.4, 114.9, 42.2, 39.5; MS (EI) m/z 239 (M^+, 19). Anal. ($C_{15}H_{13}NO_2$·0.4H_2O) C, H, N.

3-(4-Hydroxyphenyl)-2-phenylpropionitrile (16e). Nitrile **15e** (200 mg, 0.843 mmol) was deprotected with BBr_3 (3 equiv) according to method C. Flash chromatography (35% EtOAc/hexanes) gave a clear oil which solidified in vacuo to give **16e** as a white solid (181 mg, 0.811 mmol, 96%) Recrystallization from EtOAc/hexanes gave an analytical sample (73 mg): mp 100−101.5 °C (lit.[53] mp 100 °C); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.26 (s, 1H), 7.30−7.40 (m, 5H), 7.07 (AA′ of AA′XX′, J_{AX} = 8.4, $J_{AA'}$ = 2.4, 2H), 6.75 (XX′ of AA′XX′, J_{AX} = 8.6, J_{XX}' = 2.5, 2H), 4.28 (t, J = 7.6, 1H), 3.10 (d, J = 7.5, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.4, 137.3, 131.3, 129.7, 128.7, 128.7, 128.5, 121.4, 116.0, 41.6, 40.1; MS (CI) m/z 223 (M^+, 5). HRMS (EI) calcd for $C_{15}H_{13}NO$: 223.0997, found 223.1002. Anal. ($C_{15}H_{13}NO$) C, H, N.

2-(4-Hydroxyphenyl)-3-phenylpropionitrile (16f). Nitrile **15f** (202 mg, 0.851 mmol) was deprotected with BBr_3 (3 equiv) according to method C. Flash chromatography (35% EtOAc/hexanes) gave a clear oil which solidified in vacuo to give **16f** as a white solid (168 mg, 0.752 mmol, 88%). Recrystallization from EtOAc/hexanes gave an analytical sample (158 mg): mp 111−112.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.48 (s, 1H), 7.22−7.31 (m, 5H), 7.21 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.84 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.5, 2H), 4.25 (t, J = 7.6, 1H), 3.15 (d, J = 7.6, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.0, 138.2, 130.2, 129.7, 129.2, 127.8, 127.8, 121.6, 116.4, 42.4, 38.9; MS (EI) m/z 223 (M^+, 100). HRMS (EI) calcd for $C_{15}H_{13}NO$: 223.0997, found 223.0992. Anal. ($C_{15}H_{13}NO$) C, H, N.

3-(4-Hydroxy-2-methylphenyl)-2-(4-hydroxyphenyl)-propionitrile (16g). Nitrile **15g** (292 mg, 1.04 mmol) was deprotected with BBr_3 (4 equiv) according to method C. Recrystallization from EtOAc/hexanes afforded **16g** as an off-white solid (242 mg, 0.955 mmol, 92%): mp 170.5−172 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.46 (s, 1H), 8.12 (s, 1H), 7.19 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 7.02 (d, J = 8.1, 1H), 6.83 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.6, 2H), 6.64 (d, J = 2.6, 1H), 6.60 (dd, J = 8.1, 2.7, 1H), 4.10 (X of ABX, dd, J = 8.8, 6.5, 1H), 3.05 (AB of ABX, n_A = 1548, n_B = 1504, J_{AB} = 13.9, J_{AX} = 9.0, J_{BX} = 6.5, 2H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.0, 157.2, 138.7, 132.1, 129.6, 128.1, 127.2, 121.9, 117.9, 116.5, 113.6, 39.2, 38.5, 19.5; MS (EI) m/z 253 (M^+, 3). Anal. ($C_{16}H_{15}NO_2$) C, H, N.

2-(4-Hydroxy-2-methylphenyl)-3-(4-hydroxyphenyl)-propionitrile (16h). Nitrile **15h** (57.1 mg, 0.203 mmol) was deprotected with BBr_3 (4 equiv) according to method C. Recrystallization from EtOAc/hexanes afforded **16h** as a white solid (38.7 mg, 0.153 mmol, 75%): mp 177−178.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.34 (s, 1H), 8.24 (s, 1H), 7.22 (d, J = 8.4, 1H), 7.05 (AA′ of AA′XX′, J_{AX} = 8.8, J_{AA}' = 2.5, 2H), 6.75 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.5, 2H), 6.71 (dd, J = 8.4, 2.6, 1H), 6.67 (d, J = 2.8, 1H), 4.23 (X of ABX, dd, J = 8.6, 6.6, 1H), 3.02 (AB of ABX, n_A = 1523, n_B = 1493, J_{AB} = 13.7, J_{AX} = 8.7, J_{BX} = 6.4, 2H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.8, 157.4, 137.9, 131.2, 129.7, 129.0, 126.2, 122.0, 118.3, 116.0, 114.2, 40.7, 36.4, 19.2; MS (EI) m/z 253 (M^+, 5). Anal. ($C_{16}H_{15}NO_2$·0.1H_2O) C, H, N.

2,3-Bis(4-methoxyphenyl)propionic Acid (21). A 5% Pd/C (280 mg) sample was added to a solution of α,β-unsaturated acid **20** in EtOAc (60 mL) and EtOH (45 mL) and stirred under an atmosphere of hydrogen overnight. After evacuation of the hydrogen under vacuum and evaporation under a stream of nitrogen, the solid was dissolved in EtOAc and filtered through a pad of Celite. Recrystallization from $CHCl_3$/hexanes gave **21** as a white solid (2.40 g, 8.38 mmol, 95%): mp 125−127 °C (lit.[54] mp 123−124 °C); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.27 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.5, 2H), 7.11 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.5, 2H), 6.86 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.6, 2H), 6.77 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.5, 2H), 3.80 (dd, J = 8.7, 6.9, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.27 (dd, J = 13.9, 8.7, 1H), 2.89 (dd, J = 13.8,

7.0, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 174.9, 159.7, 159.1, 132.3, 132.3, 130.8, 129.8, 114.6, 114.3, 55.4, 55.3, 53.4, 39.6; MS (EI) *m/z* 286 (M^+, 2).

2,3-Bis(4-methoxyphenyl)propan-1-ol (22). A solution of $LiAlH_4$ (5.0 mL, 1.0 M in diethyl ether, 5.0 mmol, 2 equiv) was added dropwise to a solution of propionic acid **21** (706 mg, 2.47 mmol) in THF (35 mL) at 0 °C. The solution was allowed to warm to room temperature and was quenched by the successive addition of water (190 mL), 15% NaOH (190 mL), and water (570 mL). The resulting precipitate was filtered off and the filtrate was concentrated to give a clear oil which solidified under vacuum to give **22** as a white solid (565 mg, 2.08 mmol, 84%): mp 78.5−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.5, 2H), 6.99 (AA′ of AA′XX′, J_{AX} = 8.7, $J_{AA'}$ = 2.5, 2H), 6.85 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.5, 2H), 6.76 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.6, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.75 (AB of ABX, n_A = 1506, n_B = 1490, J_{AB} = 10.8, J_{AX} = 5.3, J_{BX} = 7.3, 2H), 3.00 (X of ABX, qd, *J* = 7.5, 5.5, 1H), 2.87 (AB of ABX, n_A = 1174, n_B = 1124, J_{AB} = 13.4, J_{AX} = 7.1, J_{BX} = 7.5, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 157.7, 133.8, 132.0, 129.9, 129.0, 114.0, 113.5, 66.4, 55.2, 55.1, 49.5, 37.9; MS (EI) *m/z* 272 (M^+, 7). Anal. ($C_{17}H_{20}O_3$) C, H.

Methanesulfonic Acid 2,3-Bis(4-methoxyphenyl)propyl Ester (23). Methanesulfonyl chloride (300 mL, 3.89 mmol, 2 equiv) was added to a solution of propanol **22** (530 mg, 1.95 mmol) and triethylamine (1.63 mL, 11.7 mmol, 6 equiv) in CH_2Cl_2 (30 mL) at 0 °C. After stirring 15 min at 0 °C, the solution was concentrated under reduced pressure. Filtration through a pad of silica gel with 40% EtOAc/hexanes gave a clear oil that was triturated with ether at −20 °C. Mesylate **23** was recovered as a white waxy solid (654 mg, 1.87 mmol, 96%): mp 62.5−63.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.97 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.4, 2H), 6.84 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.5, 2H), 6.76 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.6, 2H), 4.31 (d, *J* = 6.7, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.20 (X of ABX, quint, *J* = 7.0, 1H), 2.94 (AB of ABX, n_A = 1501, n_B = 1440, J_{AB} = 13.9, J_{AX} = 7.1, J_{BX} = 7.9, 2H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 158.1, 132.1, 130.7, 130.0, 129.0, 114.0, 113.8, 72.8, 55.2, 55.2, 46.3, 37.5, 37.1; MS (EI) *m/z* 350 (M^+, 16), 254 (M − $HOSO_2CH_3$, 10). HRMS (EI) calcd for $C_{18}H_{22}O_5S$: 350.1188, found 350.1183. Anal. ($C_{18}H_{22}O_5S$) C, H.

3,4-Bis(4-methoxyphenyl)butyronitrile (24). A solution of mesylate **23** (607 mg, 1.73 mmol) in THF (10 mL) was treated with tetra-*n*-butylammonium cyanide (1.16 g, 4.33 mmol, 2.5 equiv) and refluxed overnight (19 h). The reaction was quenched with water and extracted with EtOAc twice. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (25% EtOAc/hexanes) yielded **24** as a clear oil which was triturated with ether at −20 °C to give a white powder (472 mg, 1.68 mmol, 97%): mp 81.5−82.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 7.01 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.87 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.6, 2H), 6.80 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.6, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.14 (X of ABX, m, 1H), 2.98 (AB of ABX, n_A = 1491, n_B = 1483, J_{AB} = 13.9, J_{AX} = 6.7, J_{BX} = 8.3, 2H), 2.54 (AB of ABX, n_A = 1278, n_B = 1255, J_{AB} = 16.7, J_{AX} = 5.7, J_{BX} = 7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 158.3, 133.4, 130.5, 130.0, 128.2, 118.6, 114.1, 113.9, 55.2, 55.2, 43.2, 40.4, 23.7; MS (EI) *m/z* 281 (M^+, 3). Anal. ($C_{18}H_{19}NO_2$) C, H, N.

3,4-Bis(4-hydroxyphenyl)butyronitrile (25). Butyronitrile **24** (201 mg, 0.714 mmol) was demethylated with BBr_3 according to method C. Flash chromatography (50% EtOAc/hexanes) and recrystallization from $CHCl_3$/acetone/hexanes gave **25** as off-white crystals (157 mg, 0.618 mmol, 87%): mp 165−167 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.17 (br s, 2H), 7.12 (AA′ of AA′XX′, J_{AX} = 8.2, $J_{AA'}$ = 2.5, 2H), 6.96 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.77 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.6, 2H), 6.70 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.6, 2H), 3.16 (X of ABX, m, 1H), 2.90 (AB of ABX, n_A = 1459, n_B = 1443, J_{AB} = 12.8, J_{AX} = 6.0, J_{BX} = 6.7, 2H), 2.67 (AB of ABX, n_A = 1338, n_B = 1329, J_{AB} = 16.9, J_{AX} = 6.1, J_{BX} = 7.7, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.2, 156.7, 133.8, 130.9, 130.8, 129.4, 119.6, 116.0, 115.9, 44.2, 41.5, 24.0; MS (EI) *m/z* 253 (M^+, 9). Anal. ($C_{16}H_{15}NO_2$) C, H, N.

2,3-Bis(4-hydroxyphenyl)-2-methylpropionitrile (27). NaH as a 60% dispersion in mineral oil (58 mg, 1.46 mmol, 1.3 equiv) was rinsed with hexanes, taken up in DMF (2 mL), and cooled to 0 °C. A solution of nitrile **15a** (300 mg, 1.12 mmol) in DMF (3 mL) was added to the mixture which was allowed to warm to room temperature for 1 h. The mixture was cooled to 0 °C and treated with methyl iodide (700 mL, 11.2 mmol, 10 equiv). The reaction was stirred overnight at room temperature (20 h). The mixture was poured into saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with saturated LiCl twice, water, and brine, dried over Na_2SO_4, and concentrated. Recrystallization from EtOH gave 2,3-bis(4-methoxyphenyl)-2-methylpropionitrile (**26**) as an off-white solid (271 mg) which was contaminated with an inseparable byproduct (∼7%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (AA′ of AA′XX′, J_{AX} = 9.0, $J_{AA'}$ = 2.7, 2H), 6.92 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.6, 2H), 6.87 (XX′ of AA′XX′, J_{AX} = 9.0, $J_{XX'}$ = 2.7, 2H), 6.76 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.6, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.05 (s, 2H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 158.8, 131.7, 131.4, 127.3, 127.1, 123.5, 113.9, 113.5, 55.3, 55.2, 47.9, 42.9, 26.0; MS (EI) *m/z* 281 (M^+, 3), 160 (M − $ArCH_2$, 11), 121 ($ArCH_2$, 100). HRMS (EI) calcd for $C_{18}H_{19}NO_2$: 281.1416, found 281.1419.

Nitrile **26** (251 mg, ∼0.830 mmol, 93% pure) was deprotected with BBr_3 (4 equiv) according to method C. Recrystallization from EtOAc/hexanes followed by $CHCl_3$/acetone/hexanes gave **27** as a white solid (100 mg, 0.395 mmol, 48%): mp 176−178.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.44 (s, 1H), 8.22 (s, 1H), 7.26 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.7, 2H), 6.90 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.83 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.6, 2H), 6.69 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.5, 2H), 3.06 (s, 2H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.7, 157.4, 132.3, 132.0, 128.0, 127.6, 124.2, 116.1, 115.5, 48.0, 43.8, 26.5; MS (EI) *m/z* 253 (M^+, 5). Anal. ($C_{16}H_{15}NO_2 \cdot 0.1H_2O$) C, H, N.

(2*R*,3S)-2,3-Bis(4-methoxyphenyl)butyronitrile (*erythro*-28a).** Methylmagnesium bromide (3.0 M in diethyl ether, 1.2 mL, 3.6 mmol, 3 equiv) was added to a solution of α,β-unsaturated nitrile **14a** (300 mg, 1.13 mmol, 1 equiv) and CuI (20 mg, 0.105 mmol, 0.1 equiv) in THF (16 mL) at −20 °C. The reaction was allowed to come to room temperature and was acidified with saturated NH_4Cl and stirred for 5 h. The solution was partitioned between saturated NH_4Cl and EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. Recrystallization from EtOAc/hexane furnished **28a** as a white solid (262 mg, 87% yield, dr = 8:1, erythro:threo). Repeated recrystallization from EtOAc/hexanes gave pure *erythro*-**28a**: mp 131−133 °C (lit.[55] mp 131−133 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 3.1, 2H), 7.00 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.5, 2H), 6.82 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.5, 2H), 6.80 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.5, 2H), 3.87 (d, *J* = 7.6, 1H), 3.79 (s, 3H), 3.79 (s, 3H), 3.31 (quintet, *J* = 7.0, 1H), 1.34 (d, *J* = 7.1, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 158.8, 133.1, 129.4, 128.8, 126.3, 120.2, 114.0, 113.7, 55.3, 55.2, 45.0, 18.8. Anal. ($C_{18}H_{19}NO_2 \cdot 0.1H_2O$) C, H, N.

(2*R*,3S)-2,3-Bis(4-hydroxyphenyl)butyronitrile (*erythro*-29a).** Butyronitrile *erythro*-**28a** (174 mg, 0.618 mmol, 1 equiv) was demethylated with BBr_3 according to method C. Flash chromatography (50% EtOAc/hexanes) and recrystallization from acetone/hexanes gave *erythro*-**29a** as a white crystalline solid (142 mg, 0.561 mmol, 90%): mp 252−254 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.45 (s, 1H), 8.22 (s, 1H), 7.09 (AA′ of AA′XX′, J_{AX} = 8.7, $J_{AA'}$ = 2.1, 2H), 7.09 (AA′ of AA′XX′, J_{AX} = 8.7, $J_{AA'}$ = 2.0, 2H), 6.82 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.1, 2H), 6.76 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.1, 2H), 4.12 (d, *J* = 8.1, 1H), 3.16 (quintet, *J* = 7.1, 1H), 1.23 (d, *J* = 7, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.0, 156.4, 133.1, 129.3, 128.7, 126.3, 122.3, 120.4, 115.4, 115.1, 44.1, 44.0, 18.9. Anal. ($C_{16}H_{15}NO_2 \cdot 0.2H_2O$) C, H, N.

(2*R*,3S)-2,3-Bis(4-hydroxyphenyl)pentanenitrile (*erythro*-29b).** Nitrile *erythro*-**28b**[26] (443 mg, 1.50 mmol) was demethylated with BBr_3 according to method C. Filtration through neutral alumina (EtOAc) gave *erythro*-**29b** as a white solid (281 mg, 70%). An analytical sample was obtained by recrystallization from 95% EtOH: mp 215.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) 8.43 (s, 1H), 8.22 (s, 1H), 7.06 (AA′ of AA′XX′, $J_{AX} = 8.6$, $J_{AA'} = 2.1$, 2H), 7.03 (AA′ of AA′XX′, $J_{AX} = 8.6$, $J_{AA'} = 2.7$, 2H), 6.80 (XX′ of AA′XX′, $J_{AX} = 8.5$, $J_{XX'} = 3.1$, 2H), 6.77 (XX′ of AA′XX′, $J_{AX} = 8.6$, $J_{XX'} = 3.0$, 2H), 4.19 (d, $J = 8.1$, 1H), 2.87 (ddd, $J = 9.9$, 8.0, 5.2, 1H), 1.68, (m, 2H), 0.72 (t, $J = 7.2$, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.0, 156.5, 130.9, 129.4, 129.3, 126.5, 120.4, 115.4, 115.2, 115.0, 114.9, 51.5, 42.9, 26.0, 11.2; MS (EI) *m/z* 267 (M^+, 4). Anal. ($C_{17}H_{17}NO_2$) C, H, N.

(2*R*,3S)-2,3-Bis(4-methoxyphenyl)succinonitrile (*meso*-30a).** A solution of NaCN (556 mg, 11.3 mmol, 3 equiv) in water (2.0 mL) was added slowly to a solution of *p*-anisaldehyde (509 mg, 3.74 mmol, 1 equiv) and (4-methoxyphenyl)-acetonitrile (557 mg, 3.78 mmol, 1 equiv) in MeOH (3.0 mL), and the mixture was refluxed for 16 h. After cooling to room temperature, the precipitate was filtered and washed with water and 75% MeOH (aqueous) to give a pale beige solid. Recrystallization from hot acetic acid gave *meso*-**30a** as white needles (448 mg, 1.53 mmol, 42%): mp 234−235.5 °C (lit.[28] mp 239−241 °C); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.13 (AA′ of AA′XX′, $J_{AX} = 8.8$, $J_{AA'} = 2.6$, 4H), 6.90 (XX′ of AA′XX′, $J_{AX} = 8.8$, $J_{XX'} = 2.6$, 4H), 4.22 (s, 2H), 3.81 (s, 6H); MS (EI) *m/z* 292 (M^+, 100), 265 (M − HCN, 88). Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

(2*R*,3S)-2,3-Bis(4-hydroxyphenyl)succinonitrile (*meso*-31a).** Succinonitrile *meso*-**30a** (113 mg, 0.387 mmol) was demethylated with $BF_3{\cdot}SMe_2$ according to method D. Recrystallization from EtOAc/acetone/hexanes gave *meso*-**31a** as an off-white powder (87.5 mg, 0.331 mmol, 86%): mp 276 °C dec (lit.[17] mp 276 °C); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.64 (s, 2H), 7.16 (AA′ of AA′XX′, $J_{AX} = 8.6$, $J_{AA'} = 2.5$, 4H), 6.84 (XX′ of AA′XX′, $J_{AX} = 8.6$, $J_{XX'} = 2.5$, 4H), 4.69 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.9, 130.8, 123.8, 119.2, 116.5, 42.2; MS (EI) *m/z* 264 (M^+, 7), 132 (M − ArCHCN, 100). HRMS (EI) calcd for $C_{16}H_{12}N_2O_2$: 264.0899, found 264.0894. Anal. ($C_{16}H_{12}N_2O_2$) C, H, N.

(2*R*,3S)-2-(3-Hydroxyphenyl)-3-(4-hydroxyphenyl)-succinonitrile (*erythro*-31b).** Succinonitrile *erythro*-**30b** (101 mg, 0.347 mmol) was demethylated with $BF_3{\cdot}SMe_2$ according to method D. Flash chromatography (20% acetone/CH_2Cl_2) gave *erythro*-**31b** as an off-white solid (85.7 mg, 0.336 mmol, 97%). An analytical sample was obtained by recrystallization from EtOAc/hexanes to give a white solid: mp 238−239 °C dec; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.63 (br s, 2H), 7.22 (t, $J = 7.6$, 1H), 7.18 (AA′ of AA′XX′, $J_{AX} = 8.6$, $J_{AA'} = 2.6$, 2H), 6.86 (ddd, $J = 8.0$, 2.4, 0.9, 1H), 6.84 (XX′ of AA′XX′, $J_{AX} = 8.8$, $J_{XX'} = 2.6$, 2H), 6.84 (m, 1H), 6.82 (ddd, $J = 7.6$, 1.7, 0.9, 1H), 4.73 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.0, 158.6, 134.5, 130.8, 130.8, 123.7, 120.5, 119.1, 118.9, 116.8, 116.5, 116.4, 42.8, 41.9; MS (EI) *m/z* 264 (M^+, 11), 132 (M − ArCHCN, 100). HRMS (EI) calcd for $C_{16}H_{12}N_2O_2$: 264.0899, found 264.0900. Anal. ($C_{16}H_{12}N_2O_2$) C, H, N.

(2*R*,3S)-2,3-Bis(3-hydroxyphenyl)succinonitrile (*meso*-31c).** Succinonitrile *meso*-**30c** (157 mg, 0.538 mmol) was demethylated with $BF_3{\cdot}SMe_2$ according to method D. Flash chromatography (10% MeOH/CH_2Cl_2) gave *meso*-**31c** as an off-white solid (127 mg, 0.481 mmol, 89%). An analytical sample was obtained by recrystallization from EtOAc/hexanes to give a white solid: mp 209−210.5 °C dec; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.62 (br s, 2H), 7.21 (td, $J = 7.6$, 1.2, 2H), 6.82 (m, 6H), 4.78 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.6, 134.4, 130.9, 120.5, 118.8, 116.9, 116.3, 42.4; MS (EI) *m/z* 264 (M^+, 6), 132 (M − ArCHCN, 100). HRMS (EI) calcd for $C_{16}H_{12}N_2O_2$: 264.0899, found 264.0902. Anal. ($C_{16}H_{12}N_2O_2$) C, H, N.

(2*S*,3S)-2,3-Bis(4-methoxyphenyl)succinonitrile (*dl*-30a).** The following procedure was modified from that of Sera et al.[29] A solution of NH_4OAc (1.66 g in 8 mL H_2O, 23 equiv) was added to a $TiCl_3$ solution [3.0 mL, 30% (w/w) in 2 N HCl (∼1.9 M, purchased from Acros), 6 equiv] at 0 °C. The solution was allowed to warm to room temperature and a solution of dicyanostilbene (*E*)-**30** (272 mg, 0.937 mmol) in DMF (10 mL) was added, followed by a 10 mL rinse with THF. The reaction was allowed to stir at room temperature for 48 h. The mixture was poured into water, acidified with 3 N HCl, and extracted with benzene. The combined organic layers were washed with half-saturated sodium bicarbonate, water, and brine, dried over Na_2SO_4, and concentrated to give a yellow-white solid (180 mg, 5.6:1 *dl:meso*, 66% yield). Recrystallization from benzene gave *dl*-**30a** as white crystals (dr > 20:1): mp 191.5−193 °C (lit.[28] mp 189−190 °C); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.20 (AA′ of AA′XX′, $J_{AX} = 8.7$, $J_{AA'} = 2.6$, 4H), 6.92 (XX′ of AA′XX′, $J_{AX} = 8.9$, $J_{XX'} = 2.6$, 4H), 4.22 (s, 2H), 3.81 (s, 6H); MS (EI) *m/z* 292 (M^+, 1), 146 (M − ArCHCN, 100). Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

(2*S*,3S)-2,3-Bis(4-hydroxyphenyl)succinonitrile (*dl*-31a).** Succinonitrile *dl*-**30a** (80.8 mg, 0.276 mmol, dr > 20:1) was demethylated with $BF_3{\cdot}SMe_2$ according to method D. Filtration through a plug of silica gel with EtOAc furnished *dl*-**31a** as a yellow solid (58 mg, 0.219 mmol, dr = 20:1, 79% yield) Recrystallization from EtOAc gave a white powder (dr > 99:1): mp 254−255.5 °C dec; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.62 (s, 2H), 7.28 (AA′ of AA′XX′, $J_{AX} = 8.4$, $J_{AA'} = 2.4$, 4H), 6.87 (XX′ of AA′XX′, $J_{AX} = 8.4$, $J_{XX'} = 2.4$, 4H), 4.65 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.9, 130.5, 124.1, 119.0, 116.6, 43.0; MS (EI) *m/z* 264 (M^+, 6), 132 (M − ArCHCN, 100). HRMS (EI) calcd for $C_{16}H_{12}N_2O_2$: 264.0898, found 264.0907. Anal. ($C_{16}H_{12}N_2O_2$) C, H, N.

2-(4-Methoxybenzyl)-2-(4-methoxyphenyl)malononitrile (34). K_2CO_3 (178 mg, 1.29 mmol, 2 equiv) was added to a solution of malononitrile **33** in dry acetone (2.5 mL) at room temperature. After stirring the suspension for 5 min, 4-methoxybenzyl chloride was added (100 mL, 0.738 mmol, 1.25 equiv) and was stirred overnight (23 h). Filtration and concentration of the filtrate gave a light yellow solid. Recrystallization from EtOH furnished **34** as an off-white solid (142 mg, 0.484 mmol, 82%): mp 142.5−143.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (AA′ of AA′XX′, $J_{AX} = 8.8$, $J_{AA'} = 2.8$, 2H), 7.04 (AA′ of AA′XX′, $J_{AX} = 8.8$, $J_{AA'} = 2.5$, 2H), 6.94 (XX′ of AA′XX′, $J_{AX} = 8.8$, $J_{XX'} = 2.8$, 2H), 6.83 (XX′ of AA′XX′, $J_{AX} = 8.8$, $J_{XX'} = 2.6$, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.38 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 159.9, 131.6, 127.5, 123.5, 123.2, 115.0, 114.7, 114.0, 55.5, 55.2, 47.9, 43.6; MS (CI) *m/z* 293 (MH^+, 4), 266 (M − HCN, 13). Anal. ($C_{18}H_{16}N_2O_2$) C, H, N.

2-(4-Hydroxybenzyl)-2-(4-hydroxyphenyl)malononitrile (35). Malononitrile **34** (103 mg, 0.353 mmol) was demethylated with $BF_3{\cdot}SMe_2$ according to method D. Filtration through a silica plug (50% EtOAc/hexanes), followed by recrystallization from EtOAc/hexanes gave **35** as white crystals (90.2 mg, 0.341 mmol, 97%): mp 213.5−214.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.91 (br s, 1H), 8.48 (br s, 1H), 7.39 (AA′ of AA′XX′, $J_{AX} = 8.8$, $J_{AA'} = 2.7$, 2H), 7.09 (AA′ of AA′XX′, $J_{AX} = 8.6$, $J_{AA'} = 2.4$, 2H), 6.97 (XX′ of AA′XX′, $J_{AX} = 8.8$, $J_{XX'} = 2.7$, 2H), 6.79 (XX′ of AA′XX′, $J_{AX} = 8.6$, $J_{XX'} = 2.5$, 2H), 3.53 (s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.5, 158.6, 132.7, 128.5, 124.4, 123.6, 117.0, 116.4, 116.0, 47.2, 44.6; MS (CI) *m/z* 265 (MH^+, 11), 238 (M − HCN, 100). Anal. ($C_{16}H_{12}N_2O_2$) C, H, N.

(*Z*)-2,3-*Bis*(4-hydroxyphenyl)acrylonitrile ((*Z*)-36). Nitrile (*Z*)-**14a** (200 mg, 0.754 mmol) was deprotected with BBr_3 (4 equiv) according to Method C. Flash chromatography (40% EtOAc/hexanes) gave (*Z*)-**36** as a pale yellow solid (138 mg, 0.582 mmol, 77%) Recrystallization from MeOH gave an analytical sample: mp 248.5−249.5 °C (lit.[56] mp 243 °C); ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (AA′ of AA′XX′, $J_{AX} = 8.5$, $J_{AA'} = 2.5$, 2H), 7.50 (AA′ of AA′XX′, $J_{AX} = 8.8$, $J_{AA'} = 2.6$, 2H), 7.49 (s, 1H), 6.85 (XX′ of AA′XX′, $J_{AX} = 8.8$, $J_{XX'} = 2.6$, 2H), 6.84 (XX′ of AA′XX′, $J_{AX} = 8.8$, $J_{XX'} = 2.6$, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 160.9, 159.5, 141.3, 132.2, 128.1, 127.6, 127.3, 120.1, 116.9, 116.8, 108.4; MS (EI) *m/z* 237 (M^+, 100). Anal. ($C_{15}H_{11}NO_2{\cdot}0.2H_2O$) C, H, N.

(*E*)-2,3-Bis(4-hydroxyphenyl)but-2-enedinitrile ((*E*)-37). Dicyanostilbene (*E*)-**32** (25 mg, 0.0861 mmol) was de-

methylated with BF_3·SMe_2 according to method D. Flash chromatography (10% MeOH/CH_2Cl_2) and recrystallization from MeOH/H_2O gave (*E*)-**37** as a yellow solid (24 mg, quantitative yield): mp 274−276 °C dec (lit.[57] mp 287−288 °C dec); ^{1}H NMR (500 MHz, acetone-d_6) δ 9.22 (br s, 2H), 7.74 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.5, 4H), 7.03 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.5, 4H); ^{13}C NMR (125 MHz, acetone-d_6) δ 161.1, 131.5, 124.9, 123.6, 118.1, 116.8; MS (EI) *m*/*z* 262 (M^+, 100). HRMS (EI) calcd for $C_{16}H_{10}N_2O_2$: 262.0742, found 262.0740. Purity >96% (HPLC).

1,2-Bis(4-methoxyphenyl)but-3-yne (39). According to a procedure previously described,[33] octacarbonyldiobalt (125 mg, 0.366 mmol, 1 equiv) was added to a stirred solution of propargyl alcohol **38** (99.5 mg, 0.352 mmol, 1 equiv) in methylene chloride (2 mL) at room temperature. After the evolution of carbon monoxide (approximately 15 min), the brown reaction solution was stirred an additional 6 h. The reaction was cooled to 0 °C and treated with borane−dimethyl sulfide complex (370 mL of a 2.0 M solution in toluene, 0.739 mmol, 2.1 equiv). After 3 min, TFA (350 mL) was added, and the dark reaction mixture was stirred for 30 min at 0 °C. The reaction mixture was poured into ice water and extracted with methylene chloride. The combined organic layers (20 mL) were washed with water. The vigorously stirred solution was treated with ground $Fe(NO_3)_3$·$9H_2O$ (600 mg, 1.49 mmol, 4.2 equiv) at room temperature. After 2.75 h, the organic layer was decanted, dried over $MgSO_4$, and concentrated. Flash chromatography (20−25% EtOAc/hexanes) gave **39** as an off-white solid (65 mg, 0.243 mmol, 69%): mp 94−95.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.6, 2H), 7.04 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.85 (XX′ of AA′XX′, J_{AX} = 8.7, $J_{XX'}$ = 2.6, 2H), 6.81 (XX′ of AA′XX′, J_{AX} = 8.7, $J_{XX'}$ = 2.5, 2H), 3.80 (X of ABX, m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.98 (AB of ABX, n_A = 1501, n_B = 1476, J_{AB} = 13.5, J_{AX} = 8.0, J_{BX} = 6.5, 2H), 2.28 (d, *J* = 2.4, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 158.2, 132.8, 130.8, 130.3, 128.6, 113.7, 113.4, 85.8, 71.6, 55.2, 55.1, 43.8, 39.2; MS (EI) *m*/*z* 266 (M^+, 22), 145 (M − $ArCH_2$, 37). Anal. ($C_{18}H_{18}O_2$) C, H.

1,2-Bis(4-hydroxyphenyl)but-3-yne (42a). Method E. Methyl ether **39** (50 mg, 0.187 mmol) was demethylated with BF_3·SMe_2 according to aryl methyl ether deprotection method D. Flash chromatography (50% EtOAc/hexanes) gave **42a** as an off-white solid (12 mg, 0.050 mmol, 27%): mp 131−133 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.20 (s, 1H), 8.09 (s, 1H), 7.14 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.97 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.4, 2H), 6.75 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.3, 2H), 6.69 (XX′ of AA′XX′, J_{AX} = 8.4, $J_{XX'}$ = 2.5, 2H), 3.78 (td, *J* = 7.3, 2.6, 1H), 2.88 (d, *J* = 7.7, 2H), 2.63 (d, *J* = 2.6, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.1, 156.8, 132.9, 131.2, 130.7, 129.5, 115.9, 115.6, 86.9, 72.8, 44.8, 39.9; MS (EI) *m*/*z* 238 (M^+, 9), 131 (M − $ArCH_2$, 53). HRMS (EI) calcd for $C_{16}H_{14}O_2$: 238.0994, found 238.0996. Anal. ($C_{16}H_{14}O_2$·$0.1H_2O$) C, H.

2,3-Bis(4-hydroxyphenyl)propionic Acid (43). Carboxylic acid **21** (1.00 g, 3.51 mmol) was demethylated with BBr_3 (17.5 mmol, 5 equiv) according to method C (basic workup). Recrystallization from EtOAc/hexanes furnished **43** as a light beige solid (844 mg, 3.27 mmol, 93%): mp 200−202 °C (lit.[58] mp 198 °C); ^{1}H NMR (400 MHz, acetone-d_6) δ 10.58 (br s, 1H), 8.22 (br s, 1H), 8.08 (br s, 1H), 7.17 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 7.00 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.5, 2H), 6.76 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.5, 2H), 6.68 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.5, 2H), 3.74 (dd, *J* = 8.7, 6.7, 1H), 3.23 (dd, *J* = 13.7, 8.8, 1H), 2.84 (dd, *J* = 13.7, 6.8, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 175.0, 157.3, 156.6, 131.3, 131.2, 130.8, 129.9, 116.0, 115.7, 53.5, 39.8; MS (EI) *m*/*z* 258 (M^+, 4), 212 (M − HCO_2H, 6). HRMS (EI) calcd for $C_{15}H_{14}O_4$: 258.0892, found 258.0886. Anal. ($C_{15}H_{14}O_4$) C, H.

2,3-Bis[4-(*tert*-butyldimethylsilanyloxy)phenyl]propan-1-ol (45). Dry DMF (10 mL) was added to diol **43** (647 mg, 2.51 mmol), TBSCl (1.24 g, 8.02 mmol, 3.2 equiv), and imidazole (1.13 g, 16.0 mmol, 6.4 equiv) and was stirred overnight at room temperature. The solution was partitioned between EtOAc and water, washed with saturated LiCl twice, water, and brine, dried over $MgSO_4$, and concentrated to give a mixture of 2,3-bis[4-(*tert*-butyldimethylsilanyloxy)phenyl]-propionic acid (**44**) and 2,3-bis[4-(*tert*-butyldimethylsilanyloxy)-phenyl]propionic acid *tert*-butyldimethylsilanyl ester as a brown oil which solidified on standing (1.51 g). A solution of $LiAlH_4$ (5.0 mL, 1.0 M in diethyl ether, 5.0 mmol, 2 equiv) was added dropwise to a solution of the crude product (1.51 g, 2.51 mmol) in ether (40 mL) at 0 °C. The solution was allowed to warm to room temperature (30 min) and was quenched by the successive addition of water (190 mL), 15% NaOH (190 mL), and water (570 mL). The resulting precipitate was filtered off and rinsed with ether, and the filtrate was concentrated. Flash chromatography (20% EtOAc/hexanes) gave **45** as a clear oil (1.04 g, 2.20 mmol, 88% from diol **43**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (AA′ of AA′XX′, J_{AX} = 8.4, $J_{AA'}$ = 2.5, 2H), 6.89 (AA′ of AA′XX′, J_{AX} = 8.4, $J_{AA'}$ = 2.4, 2H), 6.77 (XX′ of AA′XX′, J_{AX} = 8.4, $J_{XX'}$ = 2.5, 2H), 6.68 (XX′ of AA′XX′, J_{AX} = 8.4, $J_{XX'}$ = 2.5, 2H), 3.74 (AB of ABX, n_A = 1878, n_B = 1863, J_{AB} = 10.8, J_{AX} = 5.4, J_{BX} = 7.6, 2H), 2.97 (X of ABX, qd, *J* = 7.3, 5.7, 1H), 2.83 (AB of ABX, n_A = 1446, n_B = 1380, J_{AB} = 13.5, J_{AX} = 7.3, J_{BX} = 7.5, 2H), 1.33 (br s, 1H), 0.98 (s, 9H), 0.97 (s, 9H), 0.19 (s, 6H), 0.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 153.8, 134.4, 132.6, 129.9, 129.0, 120.1, 119.8, 66.3, 49.7, 38.3, 25.7, 18.2, −4.5, −4.5; MS (EI) *m*/*z* 472 (M^+, 2), 251 (M − $ArCH_2$, 100). HRMS (EI) calcd for $C_{27}H_{44}O_3Si_2$: 472.2829, found 472.2818.

2,3-Bis[4-(*tert*-butyldimethylsilanyloxy)phenyl]propionaldehyde (46). Pyridinium chlorochromate (34 mg, 0.159 mmol, 1.5 equiv) was added slowly to a solution of alcohol **45** in methylene chloride (4 mL) at room temperature. After 3 h, the dark mixture was diluted with ether and filtered through a plug of Florisil and eluted with ether. Flash chromatography (15% EtOAc/hexanes) afforded **46** as a clear oil (43 mg, 0.0913 mmol, 86%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.5, 1H), 6.93 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.5, 2H), 6.85 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.7, 2H), 6.78 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.4, 2H), 6.66 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.5, 2H), 3.67−3.71 (m, 1H), 3.33 (dd, *J* = 14.0, 6.7, 1H), 2.84 (dd, *J* = 14.0, 8.1, 1H), 0.97 (s, 9H), 0.96 (s, 9H), 0.18 (s, 6H), 0.15 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.4, 155.2, 154.0, 131.5, 130.1, 130.0, 128.3, 120.6, 119.8, 60.4, 35.5, 25.6, 25.6, 18.2, −4.5, −4.5; MS (EI) *m*/*z* 470 (M^+, 2), 441 (M − CHO, 2), 221 ($ArCH_2$, 100). HRMS (EI) calcd for $C_{27}H_{42}O_3Si_2$: 470.2673, found 470.2665.

1,1-Dibromo-3,4-bis[4-(*tert*-butyldimethylsilanyloxy)-phenyl]but-1-ene (47). Triphenylphosphine (569 mg, 2.17 mmol, 2.10 equiv) was added to a solution of aldehyde **46** (488 mg, 1.04 mmol) and carbon tetrabromide (361 mg, 1.09 mmol, 1.05 equiv) in methylene chloride (3 mL) at 0 °C. Stirred 1.5 h at room temperature. Concentration and flash chromatography (5% Et_2O/hexanes) afforded **47** as a clear oil (517 mg, 0.825 mmol, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.5, 2H), 6.87 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.4, 2H), 6.75 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.5, 2H), 6.70 (XX′ of AA′XX′, J_{AX} = 8.4, $J_{XX'}$ = 2.5, 2H), 6.57 (d, *J* = 9.6, 1H), 3.73 (dt, *J* = 9.6, 7.5, 1H), 2.91 (d, *J* = 7.5, 2H), 0.98 (s, 9H), 0.97 (s, 9H), 0.19 (s, 6H), 0.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 154.0, 141.1, 133.9, 131.5, 130.1, 128.5, 120.1, 119.8, 89.2, 50.8, 41.3, 25.7, 25.7, 18.2, 18.2, −4.5, −4.5; MS (FAB) *m*/*z* 625 (MH^+, 1), 547 (M − Br, 2), 441 (M − CH=CBr_2, 21), 221 ($ArCH_2$, 100).

1,2-Bis(4-hydroxyphenyl)but-3-yne (42a). Method F. *n*-BuLi (97 mL of 1.29M solution in hexanes, 0.125 mmol, 2.05 equiv) was added to a solution of dibromoolefin **47** (38.1 mg, 0.0608 mmol) in THF (1.0 mL) at −78 °C. After stirring for 30 min, the solution was allowed to warm to room temperature for 40 min. The reaction was quenched by the addition of water, diluted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated to give 1,2-bis[4-(*tert*-butyldimethylsilanyloxy)phenyl]but-3-yne (**48a**) as a light yellow residue (26.3 mg, 0.0563 mmol, 93%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.5, 2H), 6.89 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.4, 2H), 6.74 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.5, 2H), 6.69 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$

= 2.4, 2H), 3.75 (X of ABX, td, J = 7.2, 2.4, 1H), 2.94 (AB of ABX, n_A = 1495, n_B = 1445, J_{AB} = 13.4, J_{AX} = 7.5, J_{BX} = 6.8, 2H), 2.27 (d, J = 2.4, 1H), 0.98 (s, 9H), 0.98 (s, 9H), 0.19 (s, 6H), 0.18 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 154.2, 133.3, 131.4, 130.4, 128.6, 119.9, 119.6, 86.0, 71.4, 44.1, 39.2, 25.7, 18.2, 18.2, −4.5.

A solution of crude silyl ether 48a (26.3 mg, 0.0563 mmol) in THF (1.0 mL) was treated with TBAF (124 mL of a 1.0 M solution in THF, 0.124 mmol, 2.2 equiv) at room temperature and was stirred for 20 min. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with saturated NH_4-Cl, water, and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (30% EtOAc/hexanes) afforded **42a** as a white solid (10.8 mg, 0.0453 mmol, 81%).

1,2-Bis(4-hydroxyphenyl)pent-3-yne (42b). *n*-BuLi (323 mL of 1.29M solution in hexanes, 0.417 mmol, 2.05 equiv) was added to a solution of dibromoolefin **47** (128 mg, 0.203 mmol) in THF (3.0 mL) at −78 °C and warmed in an ice bath for 75 min. The reaction was quenched by the addition of MeI (126 mL, 2.03 mmol, 10 equiv) and stirred overnight (15 h) at room temperature. The solution was diluted with ether, washed with saturated NH_4Cl, water, and brine, dried over $MgSO_4$, and concentrated to give 1,2-bis[4-(*tert*-butyldimethylsilanyloxy)-phenyl]pent-3-yne (**48b**) as a light yellow oil (127 mg): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.86 (AA′ of AA′XX′, J_{AX} = 8.4, $J_{AA'}$ = 2.4, 2H), 6.71 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.4, 2H), 6.68 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.4, 2H), 3.67 (X of ABX, m, 1H), 2.88 (AB of ABX, n_A = 1466, n_B = 1410, J_{AB} = 13.3, J_{AX} = 7.2, J_{BX} = 6.9, 2H), 1.83 (d, J = 2.4, 3H), 0.97 (s, 9H), 0.97 (s, 9H), 0.17 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 154.0, 134.6, 132.0, 130.4, 128.6, 119.7, 119.5, 80.9, 78.9, 44.6, 39.6, 25.7, 18.2, 3.6, −4.5.

The crude product was dissolved in THF (2.0 mL), cooled in an ice bath, and treated with TBAF (609 mL of 1.0 M solution in THF, 0.609 mmol, 3 equiv) as described for **42a** (method F). Flash chromatography (40% EtOAc/hexanes) afforded **42b** as a clear oil (38.8 mg, 0.154 mmol, 76% from **47**): ^{1}H NMR (500 MHz, acetone-d_6) δ 8.14 (s, 1H), 8.06 (s, 1H), 7.10 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.4, 2H), 6.95 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.4, 2H), 6.73 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.5, 2H), 6.68 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.5, 2H), 3.68 (tq, J = 7.3, 2.4, 1H), 2.82 (d, J = 7.3, 2H), 1.76 (d, J = 2.6, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 156.8, 156.6, 134.0, 132.5, 131.2, 131.1, 115.7, 115.5, 81.9, 79.2, 45.3, 40.2, 3.3; MS (EI) *m*/*z* 252 (M^+, 10), 237 (M − CH_3, 10), 145 (M − $ArCH_2$, 100). HRMS (EI) calcd for $C_{17}H_{16}O_2$: 252.1150, found 252.1144. Anal. ($C_{17}H_{16}O_2$·0.3H2O) C, H.

(3R*,4R*)-3,4-Bis[4-(tert-butyldimethylsilanyloxy)-phenyl]-1,6-bis(trimethylsilanyl)hexa-1,5-diyne (dl-53). According to the method of Nicholas and co-workers,[39,59] octacarbonyldicobalt (550 mg, 1.61 mmol, 1.1 equiv) was added to a stirred solution of propargyl alcohol **49b** (490 mg, 1.46 mmol) in methylene chloride (6 mL) at room temperature. After the evolution of carbon monoxide (approximately 15 min), the brown reaction solution was stirred an additional 5 h. The solution was concentrated and purged with argon. The brown residue was dissolved in 1.5 mL of dry propionic anhydride, cooled to −8 °C in an ice/salt bath, and treated with HBF_4·OEt_2 (500 μL, 3.67 mmol, 2.5 equiv). After 30 min, the solution was concentrated and diluted with methylene chloride (20 mL). Powdered zinc (955 mg, 14.6 mmol, 10 equiv) was added, and the mixture was stirred for 4 h at room temperature. The mixture was filtered and concentrated. Flash chromatography (2% Et_2O/hexanes) furnished the dl-isomer of the dodecacarbonyltetracobalt complex of the title compound as a dark red residue (346 mg, 0.287 mmol, 39%), which was dissolved in dry acetone (3 mL) and treated with a solution of CAN (1.26 g, 2.30 mmol, 8 equiv) in acetone (8 mL) at −78 °C. The mixture was allowed to warm to room temperature over 20 min and was stirred an additional 60 min at room temperature. The mixture was poured into brine and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (10% Et_2O/hexanes) gave dl-**53** as a tinted oil (173 mg, 0.272 mmol, 95%, 37% from **49b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.02 (d, J = 8.6, 4H), 6.69 (d, J = 8.4, 4H), 3.90 (s, 2H), 0.97 (s, 18H), 0.18 (s, 12H), 0.18 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 130.7, 129.9, 119.3, 105.8, 89.5, 45.9, 25.7, 0.0, −4.5; MS (EI) m/z 632 (M − 2H, 2), 317 (M − ArCHC≡CTMS, 100). HRMS (EI) calcd for $C_{36}H_{56}O_2Si_4$ (M − 2): 632.3357, found 632.3352.

(3R*,4R*)-3,4-Bis(4-hydroxyphenyl)hexa-1,5-diyne (dl-54). A solution of bisalkyne dl-**53** (171 mg, 0.269 mmol) in THF (4.0 mL) was treated with TBAF (1.21 mL of a 1.0 M solution in THF, 1.21 mmol, 4.5 equiv) at 0 °C. The reaction was stirred for 50 min and then was quenched with 0.5 mL of water and stirred at room temperature for 30 min. The mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (40% EtOAc/5% AcOH/hexanes) and recrystallization from AcOH afforded dl-**54** as fine white needles (48 mg, 0.182 mmol, 68%): mp 178−179 °C dec; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.32 (br s, 2H), 7.20 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.5, 4H), 6.73 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.5, 4H), 3.93 (br s, 2H), 2.72 (br s, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 157.4, 130.6, 130.4, 115.5, 84.3, 74.3, 45.5; MS (EI) m/z 262 (M^+, 11), 131 (M − ArCHC≡CH, 100). HRMS (EI) calcd for $C_{18}H_{14}O_2$: 262.0994, found 262.0999. Anal. ($C_{18}H_{14}O_2$·0.2H_2O) C, H.

dl-Hexestrol (55). Reduction of Bisalkyne 54. Wilkinson's catalyst (8.1 mg) was added to a solution of bisalkyne **54** (9.7 mg, 0.037 mmol) in EtOAc (2 mL). The system was evacuated and purged three times with hydrogen, and the mixture was allowed to stir overnight under an atmosphere of hydrogen. The hydrogen was evacuated and the reaction mixture was concentrated. Filtration through a pad of silica gel with 5% MeOH/CH_2Cl_2 gave a light brown residue (16 mg) as a single isomer of hexestrol. Comparison of ^{1}H NMR spectra with authentic samples of meso- and dl-hexestrol confirmed the stereochemistry of bisalkyne dl-**54**. Compound **55**: ^{1}H NMR (500 MHz, acetone-d_6) δ 7.93 (br s, 2H), 6.73 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 4H), 6.60 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.5, 4H), 2.60−2.66 (m, 2H), 1.79−1.88 (m, 2H), 1.45−1.55 (m, 2H), 0.69 (t, J = 7.3, 6H).

3,3,3-Trifluoro-1,2-bis(4-methoxyphenyl)prop-1-ene (62a). (a) Method G. 4-Methoxybenzyltriphenylphosphonium chloride (**60**) was prepared from 4-methoxybenzyl chloride and triphenylphosphine as previously described.[42] 2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanone (**61a**) was prepared from 4-methoxyphenylmagnesium bromide and ethyl trifluoroacetate as previously described.[43] NaOMe (122 mg, 3.18 mmol, 1.1 equiv) was added to a solution of phosphonium salt **60** (1.21 g, 2.89 mmol, 1.0 equiv) and ketone **61a** (590 mg, 2.89 mmol, 1.0 equiv) in MeOH (8.0 mL) at room temperature. The solution was refluxed overnight (23 h). The solution was concentrated, and most of the triphenylphosphine oxide was removed by trituration with ether and filtration. Flash chromatrograph (5% EtOAc/hexanes) yielded olefin **62a** as a white solid and a single isomer (518 mg, 1.68 mmol, 58%). Recrystallization from EtOH/H_2O gave an analytically pure sample: mp 75−76.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 2.5, 2H), 7.12 (q, J = 1.8, 1H), 6.98 (AA′ of AA′XX′, J_{AX} = 8.9, $J_{AA'}$ = 2.6, 2H), 6.93 (XX′ of AA′XX′, J_{AX} = 8.9, $J_{XX'}$ = 2.5, 2H), 6.70 (XX′ of AA′XX′, J_{AX} = 9.0, $J_{XX'}$ = 2.6, 2H), 3.85 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 159.8, 132.4 (q, J = 6.1, *C*H=CCF$_3$), 131.6, 131.2, 127.4 (q, J = 29.0, CH=*C*CF$_3$), 126.2, 125.0, 124.1 (q, J = 273, CF_3), 114.4, 113.7, 55.1, 55.1; MS (EI) *m*/*z* 308 (M^+, 100). Anal. Calcd for $C_{17}H_{15}O_2F_3$: C, 66.23; H, 4.90. Found: C, 66.30; H, 4.81.

(b) Method H. LHMDS (600 mL of 1.0 M THF solution, 1.0 equiv) was added slowly to a suspension of phosphonium salt **60** (250 mg, 0.597 mmol, 1.0 equiv) in THF (3.0 mL) in an ice bath. After stirring for 15 min, the dark red mixture was treated with a solution of ketone **61a** (131.5 mg, 0.644 mmol, 1.08 equiv) in THF (3.0 mL). The pale yellow mixture was allowed to warm to room temperature and refluxed overnight (16 h). The clear solution was concentrated to give a yellow oil. Most of the triphenylphosphine oxide was removed by

trituration with ether and filtration. The filtrate was concentrated and purified by flash chromatography (benzene) to give olefin **62a** as a pale yellow tinted oil (145 mg, 0.471 mmol, 79%). A trace of the minor olefin isomer was observed in the ^{1}H NMR spectra.

3,3,4,4,4-Pentafluoro-1,2-bis(4-methoxyphenyl)but-1-ene (62b). Olefin **62b** was prepared according to method G from NaOMe (171 mg, 3.17 mmol, 1.2 equiv), phosphonium salt **60** (1.11 g, 2.64 mmol, 1.0 equiv), and ketone **61b** (671 mg, 2.64 mmol, 1.0 equiv). Flash chromatography (benzene) furnished methyl 4-methoxybenzoate (132 mg, 0.793 mmol, 30%) as a byproduct and the desired olefin **62b** as a white solid and a single isomer (228 mg, 0.636 mmol, 24%): mp 89.5−91.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, J = 8.6, 2H), 7.12 (s, 1H), 6.95 (d, J = 8.8, 2H), 6.94 (d, J = 8.8, 2H), 6.70 (d, J = 9.0, 2H), 3.85 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 159.8, 135.5 (t, J = 8.5, *C*H=CCF$_2$), 131.8, 131.6, 126.5, 126.4 (t, J = 21, CH=*C*CF$_2$), 125.2, 119.4 (qt, J = 285, 40, CF$_2$*C*F$_3$), 114.4, 113.7, 113.3 (tq, J = 255, 37, *C*F$_2$-CF$_3$), 55.1; MS (EI) m/z 358 (M$^+$, 100). HRMS (EI) calcd for $C_{18}H_{15}O_2F_5$: 358.0992, found 358.0986.

Olefin 62b was also prepared according method H from LHMDS (600 mL of 1.0 M THF solution, 1.0 equiv), phosphonium salt **60** (250 mg, 0.597 mmol, 1.0 equiv), and ketone **61b** (157 mg, 0.618 mmol, 1.03 equiv). Flash chromatography (benzene) afforded olefin **62b** as a white solid (104 mg, 0.289 mmol, 48%, dr = 94:6).

3,3,3-Trifluoro-1,2-bis(4-methoxyphenyl)propane (63a). Olefin **62a** (136 mg, 0.440 mmol) was hydrogenated over 10% Pd/C (10 mg) in EtOH (5 mL) under a hydrogen atmosphere overnight (15 h). The mixture was purged with nitrogen, filtered through Celite with EtOAc, and concentrated. Filtration through a plug of silica gel (10% EtOAc/hexanes) gave **63a** as a clear oil (119 mg, 0.383 mmol, 87%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (AA′ of AA′XX′, J_{AX} = 8.7, $J_{AA'}$ = 2.6, 2H), 6.88 (AA′ of AA′XX′, J_{AX} = 8.7, $J_{AA'}$ = 2.6, 2H), 6.82 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 2.6, 2H), 6.71 (XX′ of AA′XX′, J_{AX} = 8.7, $J_{XX'}$ = 2.6, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.41 (dqd, J = 11.0, 9.3, 3.9, 1H), 3.29 (dd, J = 14.0, 4.0, 1H), 3.01 (dd, J = 14.0, 11.1, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 158.1, 130.2, 129.9, 129.8, 126.9 (q, J = 281, CF_3), 126.3, 113.9, 113.7, 55.1, 55.1, 51.6 (q, J = 26, *C*HCF$_3$), 34.7; MS (EI) m/z 310 (M$^+$, 5), 189 (M − ArCH$_2$, 4), 121 (ArCH$_2$, 100). HRMS (EI) calcd for $C_{17}H_{17}O_2F_3$: 310.1181, found 310.1189.

3,3,4,4,4-Pentafluoro-1,2-bis(4-methoxyphenyl)-butane (63b). Olefin **62b** (193 mg, 0.539 mmol) was hydrogenated over 10% Pd/C by the procedure described for **63a**. Flash chromatography (10% EtOAc/hexanes) gave **63b** as a clear oil (119 mg, 0.330 mmol, 61%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, J = 8.4, 2H), 6.81 (d, J = 8.8, 2H), 6.79 (d, J = 8.8, 2H), 6.68 (d, J = 8.8, 2H), 3.78 (s, 3H), 3.72 (s, 3H), 3.28−3.43 (m, 2H), 2.98 (dd, J = 13.8, 11.7, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.1, 130.5, 130.0, 129.7, 125.7 (d, J = 7), 119.3 (qt, J = 287, 37, CF$_2$*C*F$_3$), 115.9 (tq, J = 257, 36, *C*F$_2$CF$_3$), 113.8, 113.6, 55.1, 49.5 (t, J = 21, *C*HCF$_2$), 33.8; MS (EI) m/z 360 (M$^+$, 7), 239 (M − ArCH$_2$, 3), 121 (ArCH$_2$, 100). HRMS (EI) calcd for $C_{18}H_{17}O_2F_5$: 360.1149, found 360.1139. Anal. ($C_{18}H_{17}O_2F_5$) C, H.

3,3,3-Trifluoro-1,2-bis(4-hydroxyphenyl)propane (64a). Fluoroalkane **63a** (98 mg, 0.317 mmol) was demethylated with BBr_3 (0.951 mmol, 3 equiv) according to method C (basic workup). Flash chromatography (40% EtOAc/hexanes) afforded **64a** as a clear oil which solidified upon prolonged standing at room temperature to give a white solid (83.1 mg, 0.294 mmol, 93%): mp 115−117.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.34 (s, 1H), 8.07 (s, 1H), 7.14 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.6, 2H), 6.91 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.6, 2H), 6.76 (XX′ of AA′XX′, J_{AX} = 8.7, $J_{XX'}$ = 2.6, 2H), 6.63 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.6, 2H), 3.64 (dqd, J = 11.3, 9.7, 4.1, 1H), 3.23 (dd, J = 14.0, 4.1, 1H), 3.04 (dd, J = 14.0, 11.3, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.0, 156.7, 131.4, 130.9, 129.4, 128.3 (q, J = 282, CF_3), 125.9, 116.0, 115.8, 51.6 (q, J = 26, *C*HCF$_3$), 34.7 (d, J = 1.9, *C*H$_2$CF$_3$); MS (EI) m/z 282 (M$^+$, 3), 175 (M − ArCH$_2$, 3), 107 (ArCH$_2$, 100). HRMS (EI) calcd for $C_{15}H_{13}O_2F_3$: 282.0865, found 282.0868. Anal. ($C_{15}H_{13}O_2F_3$) C, H.

3,3,4,4,4-Pentafluoro-1,2-bis(4-hydroxyphenyl)-butane (64b). Fluoroalkane **63b** (84.7 mg, 0.235 mmol) was demethylated with BBr_3 (0.500 mmol, 2.1 equiv) according to method C (basic workup). Flash chromatography (50% EtOAc/hexanes) afforded **64b** as a clear oil which solidified upon storage at −20 °C to give a white solid (76 mg, 0.229 mmol, 97%): mp 82−84 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.35 (s, 1H), 8.06 (s, 1H), 7.09 (d, J = 8.4, 2H), 6.85 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.5, 2H), 6.74 (d, J = 8.8, 2H), 6.60 (XX′ of AA′XX′, J_{AX} = 8.6, $J_{XX'}$ = 2.5, 2H), 3.58 (dtd, J = 23.9, 11.5, 3.3, 1H), 3.30 (dd, J = 13.8, 3.3, 1H), 3.02 (dd, J = 13.7, 11.8, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 158.1, 156.7, 131.7, 131.0, 129.2, 125.2 (d, J = 6.5), 120.3 (qt, J = 286, 37, CF$_2$*C*F$_3$), 117.2 (tq, J = 256, 35, *C*F$_2$CF$_3$), 116.1, 115.8, 49.6 (t, J = 20, *C*HCF$_2$), 33.9; MS (EI) m/z 332 (M$^+$, 6), 225 (M − ArCH$_2$, 2), 107 (ArCH$_2$, 100). HRMS (EI) calcd for $C_{16}H_{13}O_2F_5$: 332.0836, found 332.0841. Anal. ($C_{16}H_{13}O_2F_5$) C, H.

Methyl 2,3-Bis(4-hydroxyphenyl)propionate (66). A solution of ester **65** (104 mg, 0.346 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was added to a solution of $AlBr_3$ (767 mg, 2.88 mmol, 8 equiv) and EtSH (1.24 mL, 16.7 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After 1 h at 0 °C, the reaction was quenched with MeOH and evaporated under a stream of nitrogen overnight. The resulting solid was partitioned between 1 M HCl and EtOAc, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated to yield a brown oil. The product was passed though a silica plug (50% EtOAc/hexanes) to afford **66** as a beige solid (66.0 mg, 0.242 mmol, 70%). An analytical sample was obtained by recrystallization from EtOAc/hexanes: mp 86−88 °C;^{1}H NMR (500 MHz, acetone-d_6) δ 8.27 (br s, 1H), 8.12 (br s, 1H), 7.15 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.0, 2H), 6.99 (AA′ of AA′XX′, J_{AX} = 9.0, $J_{AA'}$ = 2.5, 2H), 6.67 (XX′ of AA′XX′, J_{AX} = 9.0, $J_{XX'}$ = 2.0, 2H), 6.68 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.0, 2H), 3.75 (X of ABX, dd, J = 9.0, 7.0, 1H), 3.53 (s, 3H), 3.75, (X of ABX, dd, J = 9.0, 7.0, 1H), 3.22 (AB of ABX, n_A = 1606, n_B = 1427, J_{AB} = 13.7, J_{AX} = 8.9, J_{BX} = 6.6, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.7, 156.5, 155.7, 130.3, 130.2, 130.1, 129.2, 115.4, 115.1, 60.3, 52.8, 39.0; MS (EI) m/z 272.2 (M$^+$, 44); HRMS (EI) calcd for $C_{16}H_{16}O_4$: 272.1049, found 272.1042. Anal. ($C_{16}H_{16}O_4$·0.3 H_2O) C, H.

2,3-Bis(4-hydroxypheny)l-*N*-propyl propionamide (67a). A 1.0 M solution of BBr_3 in CH_2Cl_2 (4 mL, 4 mmol, 6 equiv) was added to a solution of ester **65** (206 mg, 0.686 mmol, 1 equiv) in CH_2Cl_2 (10 mL) at −78 °C. The solution was allowed to warm to room temperature overnight. The reaction was quenched with excess propylamine (12.5 mL, 120 mmol). The reaction mixture was concentrated, the partitioned between EtOAC and water. The organic layer was washed twice with water, once with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (5% MeOH/$CHCl_3$) yielded the desired product as a beige solid (133 mg, 0.443 mmol, 65%). mp 193−195 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 7.20 (AA′ of AA′XX′, J_{AX} = 8.0, $J_{AA'}$ = 3.5, 2H), 7.07 (br t, J = 5.5, 1H), 6.99 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 3.0, 2H), 6.74 (XX′ of AA′XX′, J_{AX} =8.5, $J_{XX'}$ = 3.5, 2H), 6.68 (XX′ of AA′XX′, J_{AX} = 9.0, $J_{XX'}$ = 3.0, 2H), 3.57 (X of ABX, dd, J = 9.0, 6.0, 1H), 3.03 m, 2H), 3.22 (AB of ABX, n_A = 1640, n_B = 1376, J_{AB} = 13.4, J_{AX} = 9.1, J_{BX} = 6.0, 2H), 1.33 (sextet, J = 7.4, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 174.3, 157.4, 156.8, 133.0, 132.0, 131.0, 129.0, 116.1, 115.0, 55.2, 41.8, 40.1, 23.6, 11.8; MS (EI) m/z 299 (M$^+$,-11), 193 (M − ArCH$_2$, 100); HRMS (EI) calcd for $C_{18}H_{21}NO_3$ 299.1521, found 299.1518. Purity > 96% (HPLC).

***N,N*-Diethyl-2,3-bis(4-hydroxyphenyl)propionamide (67b).** Amide **67b** was prepared as described for **67a** using diethylamine as the quenching agent. Flash chromatography (50% EtOAc/hexane) yielded the product as a white crystalline solid (188 mg, 0.377 mmol, 56%). mp 219−221 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.23 (s, 1H), 8.06 (s, 1H), 7.19 (AA′ of AA′XX′, J_{AX} = 8.6, $J_{AA'}$ = 2.0, 2H), 7.00 (AA′ of AA′XX′, J_{AX} = 8.4, 2H), 6.76 (XX′ of AA′XX′, J_{AX} =8.5, $J_{XX'}$ = 3.0, 2H), 6.68

(XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 3.0, 2H), 3.95 (X of ABX, J = 5.7, 8.9, 1H), 3.32 (m, 2H), 3.29 (AB of ABX, n_A = 1643, n_B = 1349, J_{AB} = 13.3, J_{AX} = 4.3, J_{BX} = 5.6, 2H), 3.17 (m, 2H), 0.96 (t, J = 7, 3H), 0.86 (t, 1H, J = 7.5, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 171.5, 159.6, 159.3, 131.8, 131.3, 130.1, 129.0, 115.1, 115.0, 114.7, 114.6, 50.0, 41.3, 41.0, 39.9, 13.9, 12.3; MS (EI) m/z 313 (M^+, 12); HRMS (EI) calcd for $C_{19}H_{23}NO_3$: 313.1678, found 313.1677. Anal. ($C_{19}H_{23}NO_3 \cdot 0.3H_2O$) C, H, N.

1,1,1-Trifluoro-3,4-bis(4-methoxyphenyl)butan-2-one (68). CsF was dried under vacuum overnight at 130 °C. A solution of ester **65** (238 mg, 0.793 mmol, 1 equiv), $TMSCF_3$ (0.5 M sol'n in THF, 1.9 mL, 0.950 mmol, 1.2 equiv), and CsF (28.2 mg, 0.186 mmol, 0.1 equiv) was stirred at room temperature for 3 days. The reaction was acidified with 3 N HCl and partitioned between ether and water. The combined ether layers were dried over $MgSO_4$ and concentrated. Flash chromatography (25% EtOAc/hexanes) and recrystallization from EtOH afforded **68** as white crystals (129 mg, 0.381 mmol, 48%): mp 101.5−102.5; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 3.0, 2H), 6.98 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 3.0, 2H), 6.86 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 3.0, 2H), 6.77 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 3.0, 2H), 4.23 (X of ABX, t, J = 7.5, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.34 (AB of ABX, n_A = 1669, n_B = 1483, J_{AB} = 13.7, J_{AX} = 7.6, J_{BX} = 7.5, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.4, 159.5, 159.3, 130.0, 129.7, 126.7, 116.8, 114.7, 114.5, 113.8, 55.2, 55.1, 54.4, 38.0; MS (EI) m/z 338 (M^+, 1), 121 (M − $ArCHCOCF_3$, 100); HRMS (EI) calcd for $C_{18}H_{17}O_3F_3$: 338.1130, found 338.1124.

1,1,1-Trifluoro-3,4-bis(4-hydroxyphenyl)butan-2-one (69). Ketone **68** (35.0 mg, 0.103 mmol) was demethylated with BBr_3 according to method C. Flash chromatography (50% EtOAc/hexanes) gave **69** as pale yellow solid (216 mg, 0.616 mmol, quant.). An analytical sample was obtained by recrystallization from chloroform: mp 141−143 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.13 (s, 1H), 7.08 (AA′ of AA′XX′, J_{AX} = 8.8, $J_{AA'}$ = 3.0, 2H), 6.95 (AA′ of AA′XX′, J_{AX} = 9.2, $J_{AA'}$ = 3.0, 2H), 6.82 (XX′ of AA′XX′, J_{AX} = 9.2, $J_{XX'}$ = 2.5, 2H), 6.68 (XX′ of AA′XX′, J_{AX} = 8.8, $J_{XX'}$ = 3.0, 2H), 4.47 (X of ABX, t, J = 7.5, 1H), 3.30 (AB of ABX, n_A = 1646, n_B = 1466, J_{AB} = 13.8, J_{AX} = 7.0, J_{BX} = 8.0, 2H). ^{13}C NMR (100 MHz, acetone-d_6) δ 205.2, 158.2, 156.8, 130.9, 130.8, 129.8, 126.3, 123.2, 116.7, 115.8, 55.1, 38.3; MS (EI) m/z 310 (M^+, 2), 107 (M − $ArCHCOCF_3$, 100); HRMS (EI) calcd for $C_{16}H_{13}O_3F_3$ 310.0817, found 310.0810. Anal. ($C_{16}H_{13}F_3O \cdot 0.6\ H_2O$) C,H.

3,4-Bis(4-methoxyphenyl)butan-2-one (70). *n*-Butyllithium (21.6 mL, 1.29 M solution in hexanes, 27.9 mmol, 1.1 equiv) was added dropwise to a solution of diisopropylamine (4.6 mL, 32.8 mmol, 1.1 equiv) and LiCl (3.810 g, 90.1 mmol, 3 equiv) in THF (50 mL) at −78 °C. The reaction was warmed to 0 °C, stirred for 15 min, and recooled to −78 °C. 4-Methoxyphenylacetone (4.20 mL, 27.3 mmol, 1.1 equiv) was added dropwise over 10 min. The solution was warmed to room temperature for 10 min, recooled to −78 °C, and then 4-methoxybenzyl chloride (4.0 mL, 29.7 mmol, 1.1 equiv) was added slowly. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was partitioned between water and EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to give a yellow oil. Flash chromatography (25% EtOAc/hexanes) followed by recrystallization from EtOH afforded **70** as a white solid (3.32 g, 11.7 mmol, 43%; 64% when corrected for recovered starting material): mp 72−73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.0, 2H), 6.95 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.5, 2H), 6.84 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.0, 2H), 6.74 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.0, 2H), 3.81 (X of ABX, t, J = 7.3, 1H) 3.79 (s, 3H), 3.75 (s, 3H), 3.31 (AB of ABX, n_A = 1655, n_B = 1404, J_{AB} = 13.9, J_{AX} = 7.4, J_{BX} = 7.2, 2H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.2, 159.0, 158.1, 131.8, 130.4, 129.9, 129.3, 114.2, 114.1, 113.7, 113.5, 55.2, 37.5, 29.4; MS (EI) m/z 284 (M^+, 4), 121 (M − $ArCH_2$-COMe, 100), HRMS (EI) calcd for $C_{18}H_{20}O_3$: 284.1412, found 284.1416. Anal. ($C_{18}H_{20}O_3$): C, H.

3,4-Bis(4-hydroxyphenyl)butan-2-one (71). Ketone **70** (403 mg, 1.41 mmol) was demethylated with BBr_3 according to method C. Flash chromatography (5% MeOH/$CHCl_3$) gave **71** as yellow oil (311 mg, 1.21 mmol, 61%). Recrystallization from acetone/hexane yielded a sample for analysis: mp 194−195 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.27 (s, 1H), 8.03 (s, 1H), 7.05 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.0, 2H), 6.91 (AA′ of AA′XX′, J_{AX} = 8.5, $J_{AA'}$ = 2.5, 2H), 6.77 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.0, 2H), 6.65 (XX′ of AA′XX′, J_{AX} = 8.5, $J_{XX'}$ = 2.5, 2H), 3.95 (X of ABX, t, J = 7.5, 1H), 3.27 (AB of ABX, n_A = 1307, n_B = 1094, J_{AB} = 13.4, J_{AX} = 9.1, J_{BX} = 6.1, 2H), 1.96 (s, 3H); ^{13}C NMR (125 MHz, acetone-d_6) δ 170.0, 156.5, 155.5, 130.7, 129.8, 129.8, 129.4, 115.4, 114.8, 60.1, 37.2, 19.9; MS (EI) m/z 256 (M^+, 10), 151 (M − $ArCH_2$, 100), HRMS (EI) calcd for $C_{16}H_{16}O_3$ 256.1099, found 256.1101. Purity > 97% (HPLC).

2,3-Bis(4-hydroxyphenyl)propan-1-ol (72). A solution of silyl ether **45** (86.4 mg, 0.183 mmol) in THF (1.5 mL) was treated with TBAF (402 mL of a 1.0 M solution in THF, 0.402 mmol, 2.2 equiv) at 0 °C. The solution was allowed to warm to room temperature for 30 min and was then quenched with saturated NH_4Cl and extracted with EtOAc. The combined organic layers were washed with saturated NH_4Cl, water, and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (10% MeOH/CH_2Cl_2) afforded **72** as a white solid (36.3 mg, 0.149 mmol, 81%): mp 167−168.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 8.03 (s, 1H), 7.98 (s, 1H), 6.99 (d, J = 8.4, 2H), 6.88 (d, J = 8.6, 2H), 6.69 (d, J = 8.6, 2H), 6.63 (d, J = 8.6, 2H), 3.61−3.66 (m, 2H), 3.51 (t, J = 5.6, 1H), 3.03 (dd, J = 13.5, 6.0, 1H), 2.85−2.91 (m, 1H), 3.03 (dd, J = 13.4, 8.7, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 156.6, 156.2, 134.7, 132.4, 130.8, 129.9, 115.7, 115.6, 66.8, 50.9, 38.6; MS (EI) m/z 244 (M^+, 24), 226 (M − H_2O, 17), 137 (M − $ArCH_2$, 100). HRMS (EI) calcd for $C_{15}H_{16}O_3$: 244.1099, found 244.1099. Anal. ($C_{15}H_{16}O_3$) C, H.

Biological Procedures. Relative Binding Affinity Assay. Relative binding affinities were determined by competitive radiometric binding assays using 10 nM [^{3}H]estradiol as tracer, as previously described,[46,47] using purified full-length human ERα and ERβ purchased from Pan Vera (Madison, WI). Incubations were done at 0 °C for 18−24 h, and hydroxyapatite was used to absorb the purified receptor−ligand complexes.[47] The binding affinities are expressed as relative binding affinity (RBA) values, where the RBA of estradiol is 100%. These values are reproducible in separate experiments with a CV of 0.3.

Transcriptional Activation Assay. CAT Assay. Human endometrial cancer (HEC-1) cells were maintained in culture and transfected as described previously.[60]-62 Transfection of HEC-1 cells in 60 mm dishes used 0.4 mL of a calcium phosphate precipitate containing 2.5 mg of pCMVβGal as internal control, 0.5 mg of the reporter gene plasmid, 100 ng of ER expression vector, and carrier DNA to a total of 5 mg DNA. CAT activity, normalized for the internal control β-galactosidase activity, was assayed after 24 h as previously described.[61,62]

Transcriptional Activation Assay. Luciferase Assay. HEC-1 cells, maintained in MEM containing 5% CS and 5% FCS, were seeded into 24-well plates in transfection media (IMEM containing 5% FCS, and were transfected at about 50% confluency using lipofectin−transferrin. For each well, 1 mg of 4ERE-TATA-LUC, 5 ng of pRL-CMV, and 50−100 ng of pCMV5-ERα or pCMV5-ERβ were mixed with 5 mL of lipofectin (GIBCO, BRL) and 1.6 mL of 1 mg/mL transferrin in 150 mL of HBSS. The mixture was applied to the cells with 350 mL of serum-free IMEM media for each well, and the cells were incubated at 37 °C in the 5% CO_2 containing incubator for 6 h. The media was replaced by transfection media containing different concentrations of ligands and incubation was continued for 24 h in the presence of ligand. The dual-luciferase reporter assay system (Promega) was used for the luciferase activity assay. The activity of estradiol ($10^{-}8$ M) on ERα or ERβ was set as 100%, and the relative activity was adjusted on the basis of the transfection efficiency, which was monitored by the renilla luciferase from the cotransfected pRL-CMV plasmid.

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Supporting Information Available: Text describing experimental details and characterization data for compounds **14a**,**d**−**h**, **15a**,**d**−**h**, **18**−**20**, **30b,c**, **32**, **33**, **38**, **48c**, **49b**, **61b**, and **65** and figures showing HPLC traces for (*E*)**-37**, **71**, and **67a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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