European Journal of Medicinal Chemistry 44 (2009) 3412–3424

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Bibenzyl- and stilbene-core compounds with non-polar linker atom substituents as selective ligands for estrogen receptor beta

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ARTICLE INFO

Article history:
Received 24 September 2008
Received in revised form
10 December 2008
Accepted 10 February 2009
Available online 20 February 2009

Keywords:
Estrogen receptor
Estrogen receptor beta
Stilbestrol
Hexestrol
Selective ligand

ABSTRACT

A series of structurally simple bibenzyl-diol and stilbene-diol core molecules, structural analogs of the well-known hexestrol and diethylstilbestrol non-steroidal estrogens, were prepared and evaluated as estrogen receptor (ER) subtype-selective ligands. Analysis of their ERα and ERβ binding showed that certain substitution patterns engendered binding affinities that were >100-fold selective for ERβ. When further investigated in cell-based gene transcription assays, some molecules showed similarly high relative transcriptional potency selectivity in favor of ERβ. Interestingly, the most ERβ-selective molecules were those bearing non-polar substituents on one of the internal carbon atoms. These compounds should be useful probes for determining the physiological roles of ERβ, and they might lead to the development of more selective and thus safer pharmaceuticals.

1. Introduction

The estrogen receptor (ER) is a member of a superfamily of nuclear receptors (NRs) that are ligand-modulated transcription factors mediating the action of steroid hormones and various other bioactive ligands [1]. ER ligands regulate not only the female reproductive system, but also play an important role in other tissues, maintaining bone mineral density, regulating blood–lipid profiles [2,3], and supporting brain function [4]. The positive effects of estrogens are generally the basis for their use in the treatment of postmenopausal osteoporosis [5], atherosclerosis [6], and Alzheimer's disease [7]. While the stimulation of ER has important benefits in some tissues, it can, however, increase the risk of cancer in the breast and uterus [8,9]. Much interest has therefore been focused on the development of more tissue-selective estrogens, notably the selective estrogen receptor modulators (SERMs) that might be safer and more effective pharmaceuticals [10]. The tissue selective effect of SERMs is thought to result from differential cell and promoter-specific interactions [11].

The newer ER subtype, ERβ was discovered in 1996 and is encoded by a gene different from the one encoding the classical receptor (now referred to as ERα) [12–16]. The overall amino acid identity of the two ER subtypes is 44%, with the DNA-binding domains being nearly identical but the ligand-binding domains (LBDs) being less conserved (58% amino acid sequence identity). The ligand-binding pockets (LBPs) of ERα and ERβ, however, are very similar and differ in only two amino acids, with Met421 and Leu384 in ERα being substituted in ERβ by Ile373 and Met336, respectively. Perhaps more significantly, the internal volume of the ligand-binding pocket of ERβ is somewhat smaller than in ERα [17].

The fact that the two ER subtypes have different patterns of tissue distribution and transcriptional regulation has opened new opportunities for creating SERMs with improved tissue selectivity that would derive from ERα vs. ERβ-selective binding affinity and transcriptional potency [16]. Such ER subtype-selective ligands could be effective probes of the respective biological roles of ERα and ERβ. They could also be used to study the conformation of receptor subtype agonist and antagonist complexes. Moreover, new ER subtype-selective SERMs might function as improved tissue-selective estrogens for the treatment of a variety of estrogen-linked diseases [15,18,19].

The isoflavone phytoestrogen, genistein **2**, with a ca. 20-fold ERβ relative binding affinity selectivity, was the first compound known to be selective for ERβ (Fig. 1) [16]. Among synthetic estrogens, the

Abbreviations: DPN, diarylpropionitrile; ER, estrogen receptor; LBD, ligand binding; NR, nuclear receptor; RBA, relative binding affinity; RTP, relative transcriptional potency; SERM, selective estrogen receptor modulator.

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doi:10.1016/j.ejmech.2009.02.006

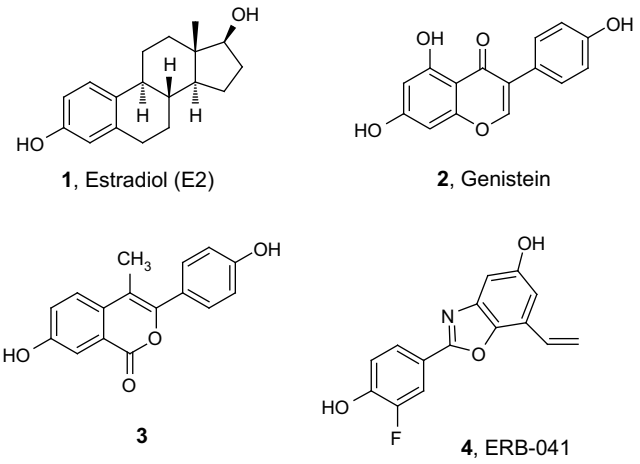


Fig. 1. Estradiol and some ER ligands being selective for ERβ.

isocoumarin **3** and the benzoxazole **4** (also known as ERB-041) are reported to have 40-fold [20] and 200-fold [21] relative binding affinity selectivities for ERβ, respectively. The latter represents the most ERβ-selective ligand known so far and has been in clinical trials. We previously described a series of compounds having a bibenzyl core and bearing polar substituents on the central ethylene unit. The most selective ligand of this series was diarylpropionitrile (DPN) **5**, which had a 70-fold ERβ relative binding selectivity (Fig. 2) [22]. Other compounds showing ERβ selectivity and possessing different core structures have been developed by us and others [20,23–28], and a pharmacophore model has evolved from these studies. According to this model, an ERβ-selective ligand has a structurally slender core with hydroxyl groups at both ends and polar or polarizable groups in the interior of the ligand; this pharmacophore (Fig. 3) is illustrated by DPN **5** and compounds **2**–**4** in Fig. 1. Notably, estradiol (**1**), the main endogenous estrogen and the typical standard for comparison with other ligands, has modest binding and transcriptional potency preference in favor of ERα.

Recently, we reexamined isobutestrol **6**, a compound that has long been known for its low affinity for ERα [29,30], and we were pleased to find that this simple compound had good affinity and an 18-fold relative binding selectivity for ERβ. Interestingly, isobutestrol **6** is rather non-polar at its center, which stands in contrast to the pharmacophore model (Fig. 3). Isobutestrol (**6**) also has much higher ERβ binding selectivity than its more familiar

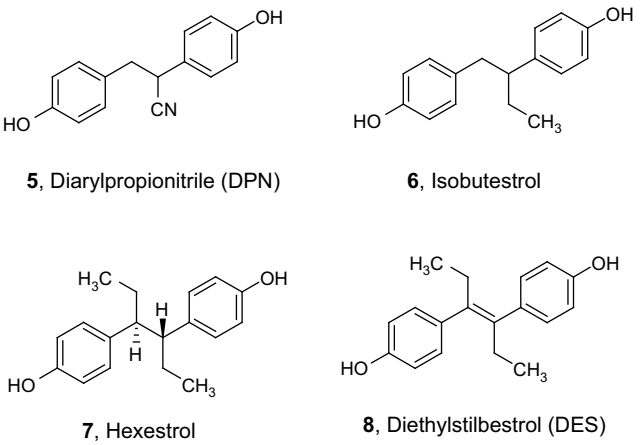


Fig. 2. ER ligands having either a bibenzyl- or a stilbene-core.

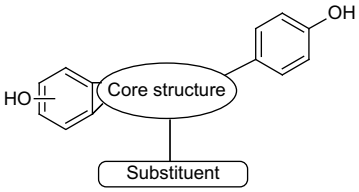


Fig. 3. ERβ pharmacophore model.

congeners, hexestrol **7** and diethylstilbestrol (DES) **8** [29] (cf., Table 1), although its absolute affinity is lower. Because of the encouraging ERβ selectivity of isobutestrol **6**, we decided to investigate analogs having various, mostly non-polar substitution patterns on the central ethylene group of the bibenzyl core, to see whether we might obtain ligands with even greater ERβ selectivities. In this study, we describe the synthesis and biological evaluation of such bibenzyl-core compounds, and, in some cases, evaluation of their unsaturated stilbene analogs.

2. Chemical synthesis

2.1. Synthesis of monoalkyl bibenzyl and stilbene diols

Scheme 1 illustrates the syntheses of bibenzyl-core compounds and stilbenes with one of the two carbons of the central ethylene unit bearing one alkyl chain. All syntheses started with the introduction of alkyl substituents into desoxyanisoin **9** by Grignard addition. Steric effects had a strong influence on the reaction yields, which were excellent for small and moderate for large Grignard reagents. To complete the preparation of the bibenzyl-core compounds, the intermediate alcohols **10**–**14** were dehydroxylated [31] to give molecules **15**–**19**. These conversions took only about 30 min and gave excellent yields. In the final deprotection step, the phenolic hydroxy groups were revealed in convenient overnight reactions at room temperature using BBr_3, furnishing the target compounds **6** and **21**–**25** in very good yields [32].

The stilbene derivatives **26**–**28** were obtained by treating racemic alcohols **10**–**12** with BBr_3 at low temperature, which effected dehydration as well as deprotection of the methoxy groups in a single step [32]. The elimination took place at −78 °C, and while no ether cleavage appeared at that temperature, when the reactions were allowed to warm to 0 °C, deprotection occurred rapidly, and the stilbenes were obtained in moderate yield. The stilbene derivatives proved to be much more sensitive to the acidic reaction conditions than their saturated analogs **6**, **21** and **22**. Extended reaction time especially at room temperature gave low yields, most possibly due to acid-catalyzed polymerization. However, it is noteworthy that the olefin formation occurred with remarkable regio- and stereoselectivity. In case of **27** and **28**, the trans-stilbenes were the major products, with only small amounts of the corresponding cis-isomers and both possible styrene derivatives being evident. In the case of compound **26**, the trans-isomer was the only product isolated. In addition, a certain amount of decomposition products were obtained, possibly a result of polymerization of possible styrene intermediates, which have a terminal and thus more reactive double bond than those of the stilbene species.

The geometry of the alkenes was assigned initially by the chemical shift of the olefinic proton. In accordance to literature data on similar molecules [33], we found that the signal of the vinylic proton of the trans-isomers was significantly shifted down field in comparison to the cis-isomers ($\Delta\delta \geq 0.25$). This assignment was verified further with NOE studies, exemplified with compounds **26**

Table 1
ERα and ERβ relative binding affinities (RBAs), relative transcriptional potency (RTP), transcriptional activity (EC_{50} values), and affinity and potency selectivities for bibenzyl core and related ligands.

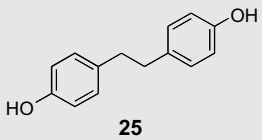
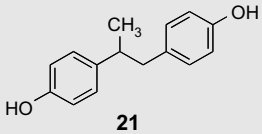
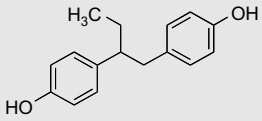
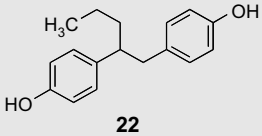
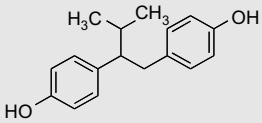
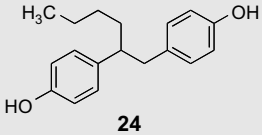
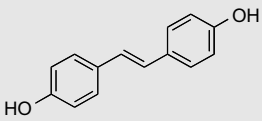
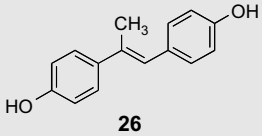
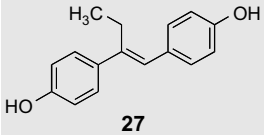
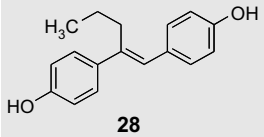
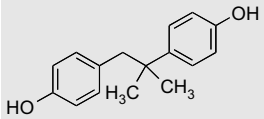
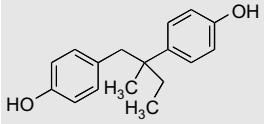
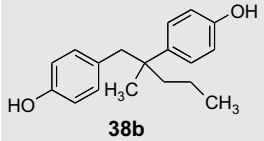
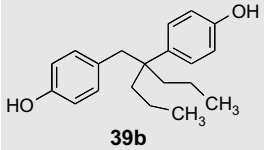
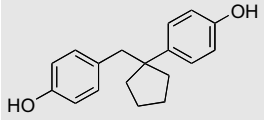
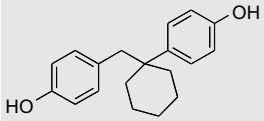
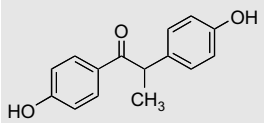
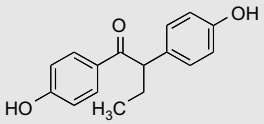
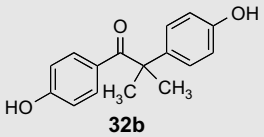
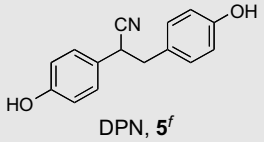
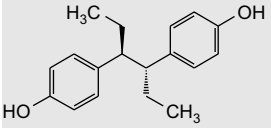
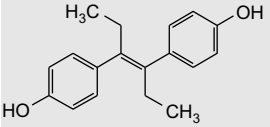
Ligand	Ligand binding			Transcription potency					
	RBA[a](%)		β/α affinity ratio[b]	RTP[c] (%)		β/α potency ratio[b]	EC_{50}[d] (nM)		β/α potency ratio[b]
	ERα	ERβ		ERα	ERβ		ERα	ERβ	
 **25**	0.057 ± 0.017	2.73 ± 0.23	48	0.13	5.38	41	75.1	9.3	8.1
 **21**	0.71 ± 0.08	20.5 ± 5.0	29	1.54	41.7	27	6.5	1.2	5.4
 Isobutestrol, **6**	2.2 ± 0.4	39.5 ± 8.4	18	ND[e]	ND	ND	NT[e]	NT	NT
 **22**	3.2 ± 1.0	68 ± 16	21	5.0	22	4.4	2.0	2.3	0.89
 **23**	1.62 ± 0.45	7.1 ± 1.8	4	ND	ND	ND	NT	NT	NT
 **24**	2.10 ± 0.55	22.2 ± 3.4	11	ND	ND	ND	NT	NT	NT
 **44**	0.45	3.55	8	ND	ND	ND	NT	NT	NT
 **26**	0.218 ± 0.025	12.2 ± 1.2	56	0.89	13.9	16	11.2	3.6	3.1

Table 1 (*continued*)

Ligand	Ligand binding			Transcription potency					
	RBA[a](%)		β/α affinity ratio[b]	RTP[c] (%)		β/α potency ratio[b]	EC_{50}[d] (nM)		β/α potency ratio[b]
	ERα	ERβ		ERα	ERβ		ERα	ERβ	
 **27**	4.09 ± 0.81	76 ± 14	19	19	23	1.2	0.52	2.21	0.24
 **28**	30.9 ± 6.0	21.8 ± 4.0	0.7	ND	ND	ND	NT	NT	NT
 **36b**	0.132 ± 0.002	16.5 ± 1.6	125	0.62	45.5	73	16.2	1.1	15
 **37b**	0.32 ± 0.04	21.5 ± 4.0	66	0.93	15.6	17	10.7	3.2	3.3
 **38b**	0.77 ± 0.06	13.6 ± 3.7	18	0.50	6.0	12	20.2	8.4	2.4
 **39b**	0.85 ± 0.26	6.8 ± 1.4	8	ND	ND	ND	NT	NT	NT
 **42b**	0.414 ± 0.021	2.81 ± 0.06	7	ND	ND	ND	NT	NT	NT
 **43b**	1.84 ± 0.20	2.74 ± 0.70	1.5	ND	ND	ND	NT	NT	NT
 **29b**	<0.004	0.018 ± 0.004	4.5	ND	ND	ND	NT	NT	NT

(*continued on next page*)

Table 1 (*continued*)

Ligand	Ligand binding			Transcription potency					
	RBA[a](%)		β/α affinity ratio[b]	RTP[c] (%)		β/α potency ratio[b]	EC_{50}[d] (nM)		β/α potency ratio[b]
	ERα	ERβ		ERα	ERβ		ERα	ERβ	
 **30b**	0.008 ± 0.001	0.018 ± 0.001	2.3	ND	ND	ND	NT	NT	NT
 **32b**	0.042 ± 0.006	0.018 ± 0.001	0.4	ND	ND	ND	NT	NT	NT
 DPN, **5**[f]	0.25 ± 0.15	18 ± 2	72	0.15	59	390	66.00	0.85	78
 Hexestrol, **7**	277 ± 57	697 ± 194	2.5	ND	ND	ND	NT	NT	NT
 DES, **8**	372 ± 106	278 ± 54	0.7	ND	ND	ND	NT	NT	NT

[a] Relative binding affinity (RBA) values are determined by competitive radiometric binding assays and are expressed as $EC_{50}^{[estradiol]}/EC_{50}^{[compound]} \times 100$ (RBA, estradiol = 100). All chiral compounds were tested as racemates. In these assays, the K_d for estradiol is 0.2 nM for ERα and 0.5 nM for ERβ. For details, see Experimental section.

[b] For each value, the β/α ratio is calculated such that the ratio is >1 for compounds having higher affinity or potency on ERβ than on ERα.

[c] Relative transcriptional potency (RTP) values are expressed as $EC_{50}^{(estradiol)}/EC_{50}^{(ligand)} \times 100$ (RTP, estradiol = 100). In these assays, the EC_{50} for estradiol is 0.1 nM for ERα and 0.5 nM for ERβ.

[d] Transcriptional activity was measured using a cotransfection assay in human endometrial cancer (HEC-1) cells (see Experimental and Fig. 4). All chiral compounds were tested as racemates. Transcriptional potency = EC_{50}.

[e] ND = not determined; NT = not tested.

[f] Data are from the literature [22].

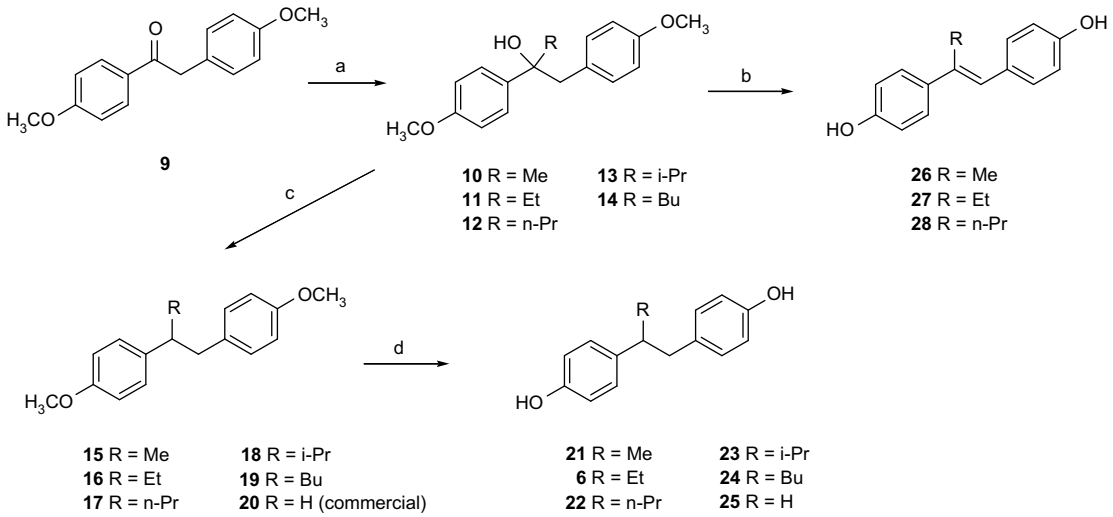
and **27**. Irradiation of the vinylic proton (δ 6.70, 6.54 for **26**, **27**, respectively) yielded enhancements of the neighboring aromatic protons meta to the phenolic hydroxyl (**26**: δ 7.39, 13.7%; δ 7.22, 8.3%; **27**: δ 7.33, 12.6%, δ 7.19, 8.3%), without exhibiting detectable enhancement of the methylene protons trans to it. These results are in agreement with those obtained with similar molecules that were also investigated by NOE studies [34].

2.2. Synthesis of geminally disubstituted bibenzyl diols

Scheme 2 shows the synthesis of bibenzyl-core compounds bearing either one or two alkyl chains on one of the carbons of the central ethylene, and in some cases having an additional carbonyl function on the other carbon. Starting with ketone **9**, the alkyl chains were introduced by enolate alkylation to obtain the substituted ketones **29a**, **30a** and **31** within only 30 min at room temperature. In accordance with literature precedent [35], an excess of base and alkylating agent gave the monoalkylated products in good yields, together with much smaller amounts of the corresponding bis-alkylated compounds. Since the enolate is not preformed in that procedure, it is noteworthy that when 1 equiv of base and iodoalkane were used, only a single alkyl chain was introduced selectively. In the next step, the second alkyl chain was introduced in the same manner to give the disubstituted ketones **32a** and **33**–**35**. Subsequent removal of the carbonyl oxygen [36] in convenient overnight reactions at room temperature furnished the protected products **36a**, **37a**, **38a** and **39a**. Employing the BBr_3 deprotection method described above gave the final bisphenol products **29b**, **30b**, **32b**, **36b**, **37b**, **38b** and **39b**.

2.3. Synthesis of spirocyclic bibenzyl diols

The introduction of spirocycles onto the central ethylene of the bibenzyl core started with the double alkylation of ketone **9** using



Scheme 1. (a) RMgCl, THF; (b) and (d) BBr_3, CH_2Cl_2; (c) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2.

α,ω-dibromoalkanes (Scheme 3). In the literature protocol we followed [37], the reaction is performed at room temperature and takes about 2 days, but we were able to obtain compounds **40** and **41** within a few hours in good yields by refluxing the reaction mixtures. Despite our use of different bases and reaction conditions, we were unable to prepare smaller spirocycles by this method. The subsequent decarbonylation and deprotection reactions were performed as in the case of the acyclic analogs described above, to furnish molecules **42a**, **43a**, and the final compounds **42b**, **43b**.

3. Pharmacology

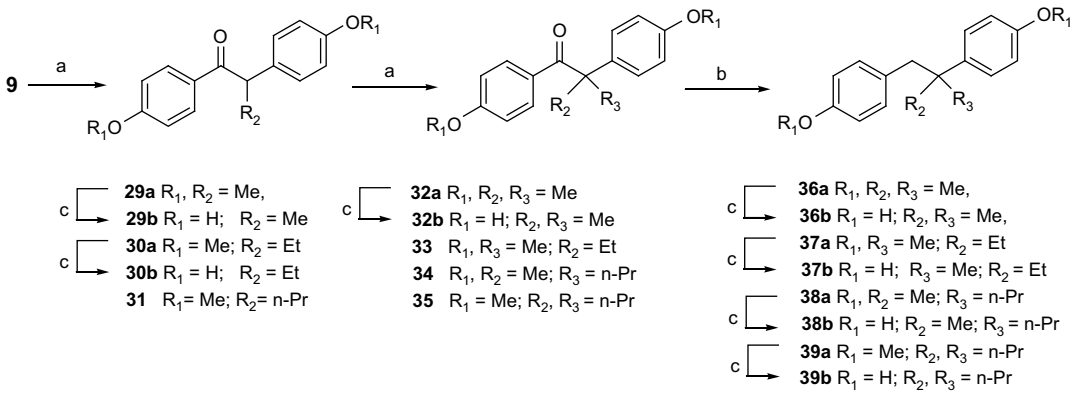
3.1. Estrogen receptor binding assays

The relative binding affinities (RBAs) of the compounds we prepared were measured in a competitive radiometric binding assay using purified full-length human ERα and ERβ [38,39]. The binding affinities are listed in Table 1 and are expressed as relative binding affinity (RBA) values, that is, relative to the affinity of estradiol, which is set at 100%. The table includes also the RBA values of isobutestrol **6**, DPN **5**, hexestrol **7**, and DES **8**. All chiral compounds were tested as racemates.

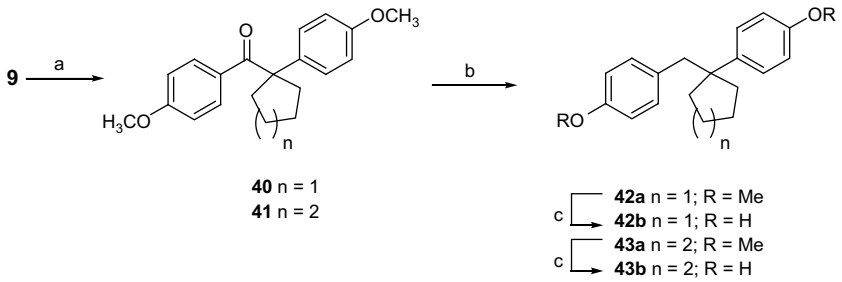
Among the 18 target compounds we have prepared, eight (**21**, **22**, **25**, **26**, **27**, **36b**, **37b**, **38b**) were found to have an ERβ selectivity equal to or higher than the reference compound isobutestrol **6**, with compounds **25**, **26**, **37b** and in particular **36b** being the most selective ones (48-, 56-, 66- and 125-fold, respectively). With the exception of compound **25**, all of these compounds had also quite good ERβ binding affinity. The highest affinity was observed with compounds **22** and **27**, having RBA values of 68 and 76, respectively, which is almost twice as high as isobutestrol **6** and even four times higher than DPN **5**.

The series of monosubstituted bibenzyl compounds having a propyl or shorter substituent R on the central ethylene showed an interesting trend: Compound **25** (R = H) was the most selective one, but it also had the lowest affinity. Increasing the chain length led to higher affinities; however, the affinity for ERα increased faster than for ERβ, resulting overall in lower ERβ selectivity. Thus, compound **22** (R = Pr) had the highest affinity, while still having good selectivity. On the other hand, branching or further increasing the size of the substituent lowered the selectivity as well as the affinity (**23**, **24**). Interestingly, when one of the two carbons of the ethylene unit was disubstituted with small alkyl chains, the ERβ selectivity was higher compared to the corresponding monosubstituted analogs (**36b**, **37b** vs. **21**, **6**).

It is known that the two ethyl chains of hexestrol **7** and diethylstilbestrol (DES) **8** fit nicely into the 7α and 11β subpockets of the ERs [40], resulting in high affinity but very low selectivity. In comparison, isobutestrol **6** with just one ethyl chain on the two



Scheme 2. (a) KO^{t}Bu, RI, 18-crown-6, THF; (b) Et_3SiH, CF_3COOH; (c) BBr_3, CH_2Cl_2.



Scheme 3. (a) NaH, $Br(CH_2)_{n+3}Br$, THF; (b) Et_3SiH, CF_3COOH; (c) BBr_3, CH_2Cl_2.

linking carbons, has lower affinity, but increased ERβ selectivity. In this study, we found the same behavior in the case of the stilbene analogs: Monoethylstilbestrol **27** had lower affinity than DES, but increased ERβ selectivity. The monomethylstilbestrol **26** had even higher selectivity than monoethylstilbestrol **27**, or compound **21**, the saturated analog of **26**.

In general, increasing the size of substituents (**36b**, **37b** vs. **38b**, **39b**) or constraining them into a spirocycle (**38b**, **39b** vs. **42b**, **43b**) gave lower selectivities and affinities for both ERs. These lower affinities suggest that these compounds are too large or too rigid to fit well into the ligand-binding pockets of the ERs. The decrease in ERβ selectivity is consistent with the larger ligand-binding pocket of ERα, which is being better able to accommodate the large and constrained ligands than ERβ. Another trend noted is that the compounds with a carbonyl function on the central ethylene had much lower affinities and selectivities than their reduced analogs (**29b** vs. **21**; **30b** vs. **6**; **32b** vs. **36b**).

3.2. Activity in gene transcription

Eight compounds (**21**, **22**, **25**, **26**, **27**, **36b**, **37b**, and **38b**) that showed good selectivity between ERα and ERβ in the binding assay were tested for their agonistic character as regulators of gene transcription. They were assayed in a cotransfection assay in human endometrial cancer (HEC-1) cells, using expression plasmids for either ERα or ERβ, and an estrogen-responsive reporter gene [41]. The dose–response curves for these compounds are given in Fig. 4, and the EC_{50} values are listed in Table 1. This table also includes the EC_{50} values for our ERβ-selective ligand, DPN **5**, for comparison. All chiral compounds were tested as racemates.

To facilitate comparisons of the ER subtype *transcriptional potencies* of our compounds with their ER subtype *binding affinities*, the EC_{50} values from the transcription assays were converted to relative transcriptional potency (RTP) values (see Table 1, footnote c). The RTPs provide a measure of transcriptional potency relative to that of estradiol and thus can be better compared to their binding affinities, which are also measured relative to estradiol by the competitive radiometric binding assays. Estradiol has a 2.5-fold preference in favor of ERα in terms of binding (K_d [ERα] = 0.2 nM vs. [ERβ] = 0.5 nM) and a 5-fold preference in terms of transcriptional potency (EC_{50} [ERα] = 0.1 nM vs. [ERβ] = 0.5 nM).

Of the eight compounds tested, seven showed very good potency selectivity for ERβ (note RTP ratio) that was either very similar to their RBA ratios (compounds **21**, **25**, **36b**, and **38b**) or at least of the same magnitude (compounds **22**, **26**, and **37b**); only compound **27** showed no ERβ transcriptional potency preference yet had good ERβ binding preference. Thus, our findings show overall a very good concordance of relative binding affinities and relative transcriptional potencies. This was not always the case, however, because affinity represents binding to the ER, whereas

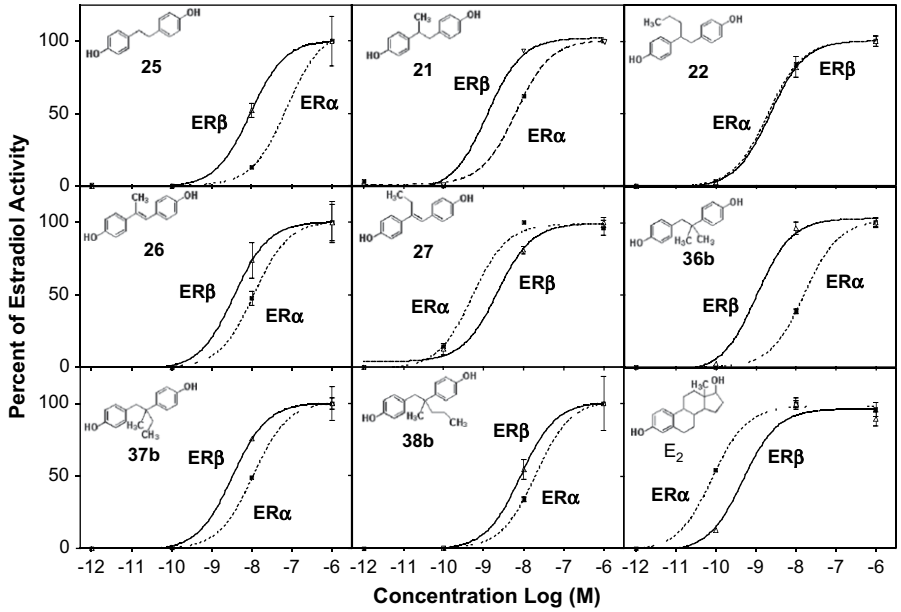


Fig. 4. Transcriptional activation by ERα and ERβ in response to ligands **21**, **22**, **25**–**27**, **36b**, **37b** and **38b** and estradiol (E_2, lowest panel right). Human endometrial cancer (HEC-1) cells were transfected with expression vectors for ERα and ERβ and the estrogen-responsive gene 2ERE-pS2-Luc, and were incubated with the indicated concentrations of ligand for 24 h. Luciferase and β-galactosidase activities were assayed as described [41]. Estradiol activity at 10 nM is set at 100%. All chiral compounds were tested as racemates.

potency can also depend on other factors that can depend on the cell and promoter context: The interactions that ER-agonist ligand complexes have with coregulators and promoter elements can vary, depending on the precise conformations of the ER that are induced by binding to ligands of different structures, irrespective of their binding affinity. Compared to our previously prepared ERβ-selective ligand, DPN **5**, some of the compounds we present here have higher ERβ binding affinity (compounds **6**, **21**, **22**, **24**, **27**, **28**, and **37b**) and comparable or higher ERβ binding selectivity (compounds **25**, **26**, **36b**, and **37b**) and somewhat less to nearly equivalent ERβ transcriptional potency (compounds **21** and **36b**).

4. Conclusion

By making various analogs of the bibenzyl non-steroidal estrogen isobutestrol and the related stilbenes, we have obtained a number of structurally simple compounds that have high ERβ binding affinity and selectivity, and good ERβ transcriptional potency and selectivity. In terms of ERβ binding affinity, the best bibenzyl is compound **22** and the best stilbene is **27**; in terms of ERβ binding selectivity, the best in each series is **36b** and **26**. In terms of ERβ transcriptional potency and selectivity, **36b** is the best bibenzyl, while among the stilbenes, **27** has the highest potency and **26** is the most selective. Although some of these compounds match the ERβ binding selectivity of DPN (**5**), none matched or exceeded the ERβ transcriptional potency selectivity of this compound. Nevertheless, these compounds represent new structures of remarkable simplicity that have high ERβ activities, and they should thus serve as good probes to further investigate the biological functions of ERβ in vivo, as well as to study ligand-induced conformations of ERβ agonist complexes.

It is also remarkable that many of the ERβ-selective ligands in this study are ones having non-polar substituents on the central ethylene unit, while previous studies by us and others have validated a pharmacophore model for non-steroidal estrogens having rather more polar substituents on the interior of the ligand. Despite differences in the polarity of the ligand interior, the ERβ-selective bibenzyl systems we have studied share with other ERβ-selective ligands an interior that is generally more "slender" and/or less "symmetrical" than typical for ERα-selective ligands, such as hexestrol (**7**) and DES (**8**). These ERβ-selective slender ligands appear to have a better fit with the somewhat smaller ligand-binding pocket of ERβ compared to ERα [17].

Further structural studies will be needed to elucidate this size/shape preference further, but the results we have obtained here indicate again that the estrogen receptors—both ERα and ERβ—have a rather eclectic taste for the refined features of ligand structure, so that even ligands of simple structure can discriminate between the two ER subtypes. Nevertheless, despite our lack of understanding of the detailed features of this discrimination, our findings open new strategies for designing ligands having high selectivity for ERβ.

5. Experimental section

5.1. Materials and methods

Reagents and solvents were purchased from Aldrich and Fisher Scientific; compound **44** was obtained from Aldrich. THF and dichloromethane were dried using a solvent-dispensing system (SDS) (neutral alumina columns) built by J.C. Meyer on the basis of a design developed by Pangborn et al. [42]. Glassware was oven- or flame-dried, assembled while hot, and cooled under nitrogen atmosphere. All reactions were performed in anhydrous solvents and under nitrogen atmosphere, unless stated otherwise. Reaction progress was monitored by thin-layer chromatography (TLC) using 0.25 mm Merck silica gel 60 glass plates containing F_{254} UV-Indicator. The plates were visualized by either UV light (254 nm), or by dipping in a solution of potassium permanganate followed by heating. Column chromatography was performed using Woelm 32–63 μm silica gel packing. ^{1}H and ^{13}C NMR spectra were recorded on Varian UNITY 400 or 500 MHz spectrometers. NOE experiments were performed with a Varian UNITY INOVIA 500NB instrument. Chemical shifts are reported in ppm and referenced from solvent references. NMR coupling constants are reported in Hertz. Mass spectra were obtained either on a Micromass 70-VSE spectrometer (EI, 70 eV; CI, methane), or a Fisons VG Quattro instrument (ESI, cone voltage 25 V). Melting point (mp) determinations were carried out on Thomas Hoover Unimelt capillary apparatus and are uncorrected. Elemental analyses were performed by the Microanalysis Service Laboratory of the University of Illinois. Analyses indicated by the symbols of the elements or functions were within ±0.4% of the theoretical values.

5.2. Chemical synthesis

5.2.1. General procedure for the Grignard addition to desoxyanisoin (*9*)

Desoxyanisoin **9** (400 mg, 1.56 mmol) was dissolved in 10 mL THF and the Grignard reagent (4.68 mmol) was added. The mixture was refluxed for 6 h (unless stated otherwise), then cooled to 0 °C, quenched with water (10 mL) and extracted with EtOAc (3 × 15 mL), The organic extracts were dried over Na_2SO_4 and the solvent was removed under vacuum.

*5.2.1.1. 1,2-Bis-(4-methoxy-phenyl)-propan-2-ol (**10**).* Use of methyl magnesium chloride (1.56 mL of a 3 M solution in THF) gave **10** as a white solid (389 mg, 92% yield, mp 68 °C) after purification by flash chromatography (33% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.8, 2H), 6.89 (d, J = 8.6, 2H), 6.86 (d, J = 8.8, 2H), 6.76 (d, J = 8.6, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.05 (d, J = 13.5, 1H), 2.94 (d, J = 13.5, 1H), 1.53 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.38, 158.23, 139.80, 131.55, 128.81, 126.22, 113.45, 113.28, 74.19, 55.23, 55.14, 49.65, 29.38; MS (ESI) m/z 255 (M^+ − 17, 100).

*5.2.1.2. 1,2-Bis-(4-methoxy-phenyl)-butan-2-ol (**11**).* Use of ethyl magnesium bromide (4.68 mL of a 1 M solution in THF) gave **11** as a white solid (344 mg, 77% yield, mp 63 °C) after purification by flash chromatography (33% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.8, 2H), 6.87–6.84 (m, 4H), 6.73 (d, J = 8.6, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.07 (d, J = 13.5, 1H), 2.96 (d, J = 13.5, 1H), 1.92 (dq, J = 14.7, 7.4, 1H), 1.79 (dq, J = 14.7, 7.4, 1H), 0.76 (t, J = 7.4, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.32, 158.01, 137.65, 131.61, 128.45, 126.76, 113.42, 113.18, 76.66, 55.15, 55.11, 48.47, 34.42, 7.83; MS (ESI) m/z 269 (M^+ − 17, 100).

*5.2.1.3. 1,2-Bis-(4-methoxy-phenyl)-pentan-2-ol (**12**).* Use of propyl magnesium chloride (2.34 mL of a 2 M solution in diethyl ether) gave **12** as yellow oil (349 mg, 75% yield) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.8, 2H), 6.87–6.83 (m, 4H), 6.74 (d, J = 8.8, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.07 (d, J = 13.5, 1H), 2.96 (d, J = 13.5, 1H), 1.88 (d, J = 13.7, 4.5, 1H), 1.85 (d, J = 13.7, 4.5, 1H), 1.37–1.26 (m, 1H) 1.13–1.00 (m, 1H), 0.84 (t, J = 7.4, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.45, 158.11, 138.19, 131.75, 128.52, 126.77, 113.58, 113.31, 76.64, 55.31, 55.27, 48.92, 44.50, 17.00, 14.54; MS (ESI) m/z 283 (M^+ − 17, 100).

*5.2.1.4. 1,2-Bis-(4-methoxy-phenyl)-3-methyl-butan-2-ol (**13**).* Use of isopropyl magnesium chloride (2.34 mL of a 2 M solution in THF)

gave **13** as pale yellow oil (215 mg, 46% yield) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.8, 2H), 6.83 (d, J = 8.8, 2H), 6.80 (d, J = 8.8, 2H), 6.68 (d, J = 8.8, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 3.16 (d, J = 13.5, 1H), 3.08 (d, J = 13.5, 1H), 2.11–2.06 (m, 1H), 1.00 (d, J = 6.8, 3H), 0.81 (d, J = 6.8, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.40, 158.12, 136.93, 131.81, 128.69, 127.61, 113.59, 112.99, 78.68, 55.29, 55.24, 44.87, 37.71, 18.01, 17.07; MS (CI) m/z 283 (M^+ − 17, 19).

*5.2.1.5. 1,2-Bis-(4-methoxy-phenyl)-hexan-2-ol (**14**).* Use of butyl magnesium chloride (2.34 mL of a 2 M solution in diethyl ether) and a reflux time of 4.5 h gave **14** as colorless oil (286 mg, 58% yield) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 9.0, 2H), 6.87–6.83 (m, 4H), 6.74 (d, J = 8.6, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.07 (d, J = 13.5, 1H), 2.96 (d, J = 13.5, 1H), 1.93–1.86 (m, 1H), 1.78–1.72 (m, 1H), 1.33–1.19 (m, 3H), 1.07–0.98 (m, 1H), 0.83 (t, J = 7.2, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 158.32, 157.98, 138.06, 131.62, 128.40, 126.64, 113.42, 113.17, 76.44, 55.13, 55.09, 48.80, 41.80, 25.68, 23.02, 14.02; MS (ESI) m/z 297 (M^+ − 17, 100).

5.2.2. General procedure for the dehydroxylation of 1,2-bis-(4-methoxy-phenyl)-alkan-2-ols

The starting material was dissolved in CH_2Cl_2 and the mixture was brought to 0 °C. Et_3SiH was added and after 2 min $BF_3\cdot OEt$ was added dropwise. The reaction was stirred for 30 min at 0 °C, quenched with water and extracted three times with EtOAc. The organic extracts were dried over Na_2SO_4 and the solvent was removed under vacuum.

*5.2.2.1. 1,2-Bis-(4-methoxy-phenyl)-propane (**15**).* Use of compound **10** (337 mg, 1.24 mmol), Et_3SiH (394 μL, 2.48 mmol) and $BF_3\cdot OEt$ (314 μL, 2.48 mmol) in 5 mL CH_2Cl_2 gave **15** as a white solid (313 mg, quant. yield, mp 68 °C) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, J = 8.6, 2H), 6.98 (d, J = 8.8, 2H), 6.83 (d, J = 8.8, 2H), 6.78 (d, J = 8.6, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 2.95–2.88 (m, 1H), 2.84 (dd, J = 13.5, 6.6, 1H), 2.69 (dd, J = 13.5, 6.6, 1H), 1.21 (d, J = 6.9, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.74, 157.71, 139.15, 133.00, 130.04, 127.92, 113.59, 113.42, 55.18, 44.30, 41.11, 21.26; MS (EI) m/z 256 (M^+, 9).

*5.2.2.2. 1,2-Bis-(4-methoxy-phenyl)-butane (**16**).* Use of compound **11** (330 mg, 1.05 mmol), Et_3SiH (320 μL, 2.01 mmol) and $BF_3\cdot OEt$ (253 μL, 2.01 mmol) in 5 mL CH_2Cl_2 gave **16** as a colorless oil (249 mg, 88%) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.8, 2H), 6.94 (d, J = 8.6, 2H), 6.82 (d, J = 8.8, 2H), 6.77 (d, J = 8.6, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 2.82–2.74 (m, 2H), 2.67–2.58 (m, 1H), 1.76–1.65 (m, 1H), 1.61–1.50 (m, 1H), 0.76 (t, J = 7.1, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.68, 157.56, 137.11, 133.04, 130.02, 128.64, 113.45, 113.33, 55.14, 49.08, 42.72, 28.36, 12.11; (EI) m/z 270 (M^+, 11).

*5.2.2.3. 1,2-Bis-(4-methoxy-phenyl)-pentane (**17**).* Use of compound **12** (306 mg, 1.02 mmol), Et_3SiH (325 μL, 2.04 mmol) and $BF_3\cdot OEt$ (259 μL, 2.04 mmol) in 5 mL CH_2Cl_2 gave **17** as a white solid (233 mg, 88%, mp 34 °C) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, J = 8.8, 2H), 6.94 (d, J = 8.6, 2H), 6.81 (d, J = 8.8, 2H), 6.76 (d, J = 8.6, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 2.84–2.69 (m, 3H), 1.67–1.50 (m, 2H), 1.22–1.10 (m, 2H), 0.83 (t, J = 7.3, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.64, 157.55, 137.37, 133.00, 130.00, 128.56, 113.44, 113.31, 55.11, 47.04, 43.07, 37.84, 20.62, 14.06; MS (EI) m/z 284 (M^+, 12).

*5.2.2.4. 1,2-Bis-(4-methoxy-phenyl)-3-methyl-butane (**18**).* Use of compound **13** (215 mg, 0.72 mmol), Et_3SiH (228 μL, 1.43 mmol) and $BF_3\cdot OEt$ (181 μL, 1.43 mmol) in 4.5 mL CH_2Cl_2 gave **18** as a colorless oil (168 mg, 82%) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, J = 8.8, 2H), 6.88 (d, J = 8.8, 2H), 6.77 (d, J = 8.8, 2H), 6.70 (d, J = 8.8, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.04 (dd, J = 13.6, 5.4, 1H), 2.74 (dd, J = 13.6, 9.5, 1H), 2.55–2.51 (m, 1H), 1.87 (qq, J = 6.7, 6.7, 1H), 0.98 (d, J = 6.7, 3H), 0.77 (d, J = 6.7, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.79, 157.59, 135.59, 133.61, 130.04, 129.79, 113.46, 113.24, 55.39, 54.31, 38.90, 32.40, 21.53, 19.91; MS (EI) m/z 284 (M^+, 7).

*5.2.2.5. 1,2-Bis-(4-methoxy-phenyl)-hexane (**19**).* Use of compound **14** (235 mg, 0.75 mmol), Et_3SiH (239 μL, 1.50 mmol) and $BF_3\cdot OEt$ (190 μL, 1.50 mmol) in 4.5 mL CH_2Cl_2 gave **19** as a colorless oil (207 mg, 93%) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, J = 8.6, 2H), 6.92 (d, J = 8.8, 2H), 6.81 (d, J = 8.6, 2H), 6.75 (d, J = 8.8, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 2.80 (dd, J = 13.4, 7.2, 1H), 2.78–2.67 (m, 2H), 1.68–1.61 (m, 1H), 1.59–1.51 (m, 1H), 1.31–1.08 (m, 4H), 0.81 (t, J = 7.3, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.68, 157.59, 137.45, 133.04, 130.02, 128.59, 113.47, 113.33, 55.13, 55.11, 47.28, 43.09, 35.33, 29.73, 22.69, 13.99; MS (EI) m/z 298 (M^+, 9).

5.2.3. General procedure for the deprotection of methoxy groups with BBr_3

The starting material was dissolved in CH_2Cl_2 and brought to 0 °C unless stated otherwise. BBr_3 was added dropwise and the mixture was brought to rt and stirred for 17 h. The reaction was brought to 0 °C, quenched with water and extracted three times with EtOAc. The organic extracts were dried over Na_2SO_4 and the solvent was removed under vacuum.

*5.2.3.1. 1,2-Bis-(4-hydroxy-phenyl)-propane (**21**).* Use of compound **15** (286 mg, 1.12 mmol) and BBr_3 (3.35 mL of a 1 M solution in CH_2Cl_2) in 11 mL CH_2Cl_2 gave **21** as a white solid (209 mg, 82%, mp 173–174 °C) after purification by flash chromatography (50% EtOAc/hexanes). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.02 (s, OH), 7.01 (d, J = 8.5, 2H), 6.91 (d, J = 8.5, 2H), 6.72 (d, J = 8.5, 2H), 6.68 (d, J = 8.5, 2H), 2.91–2.82 (m, 1H), 2.76 (dd, J = 13.3, 6.7, 1H), 2.65 (dd, J = 13.3, 8.0, 1H), 1.14 (d, J = 6.8, 3H); ^{13}C NMR (400 MHz, acetone-d_6) δ 156.24, 138.74, 132.60, 130.80, 128.68, 115.74, 115.59, 44.95, 41.97, 21.79; MS (EI) m/z 228 (M^+, 7). HRMS (EI) calcd for $C_{15}H_{16}O_2$: 228.1150, found 228.1145. Anal. $C_{15}H_{16}O_2$ (C, H).

*5.2.3.2. 1,2-Bis-(4-hydroxy-phenyl)-butane (**6**).* Use of compound **16** (250 mg, 0.93 mmol) and BBr_3 (2.79 mL of a 1 M solution in CH_2Cl_2) in 10 mL CH_2Cl_2 gave **6** as a white solid (209 mg, quant. yield,) after purification by flash chromatography (50% EtOAc/hexanes). The analytical data of compound **6** were consistent with the data published previously [30].

*5.2.3.3. 1,2-Bis-(4-hydroxy-phenyl)-pentane (**22**).* Use of compound **17** (203 mg, 0.71 mmol) and BBr_3 (2.14 mL of a 1 M solution in CH_2Cl_2) in 7 mL CH_2Cl_2 gave **22** as a white solid (157 mg, 86%, mp 99–100 °C) after purification by flash chromatography (50% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.00 (s, OH), 6.95 (d, J = 8.6, 2H), 6.86 (d, J = 8.4, 2H), 6.71 (d, J = 8.4, 2H), 6.65 (d, J = 8.6, 2H), 2.81–2.66 (m, 3H), 1.64–1.49 (m, 2H), 1.21–1.09 (m, 2H), 0.78 (d, J = 7.3, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 156.31, 156.19, 136.96, 132.63, 130.83, 129.42, 115.74, 115.57, 47.86, 43.77, 38.76, 21.26, 14.29; MS (ESI) m/z 255 (M^+ − 1, 81). HRMS (ESI) calcd for $C_{17}H_{19}O_2$: 255.1385, found 255.1389 Anal. $C_{17}H_{20}O_2$ (C, H).

*5.2.3.4. 1,2-Bis-(4-hydroxy-phenyl)-3-methyl-butane (**23**).* Use of compound **18** (139 mg, 0.49 mmol) and BBr_3 (1.48 mL of a 1 M solution in CH_2Cl_2) in 5 mL CH_2Cl_2 gave **23** as a white solid

(106 mg, 85%, mp 101 °C) after purification by flash chromatography (50% EtOAc/hexanes) and re-crystallization from toluene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, $J = 8.6$, 2H), 6.81 (d, $J = 8.6$, 2H), 6.68 (d, $J = 8.6$, 2H), 6.61 (d, $J = 8.6$, 2H), 5.00 (bs, OH), 3.03 (dd, $J = 13.6$, 5.1, 1H), 2.69 (dd, $J = 13.6$, 9.9, 1H), 2.48 (ddd, $J = 12.3$, 7.1, 5.3, 1H), 1.86 (qq, $J = 6.8$, 6.8, 1H), 0.98 (d, $J = 6.8$, 3H), 0.76 (d, $J = 6.8$, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 153.30, 153.10, 135.67, 135.61, 130.08, 129.79, 114.79, 114.65, 54.34, 38.83, 32.32, 21.33, 19.95; MS (EI) m/z 256 (M^+, 7). HRMS (EI) calcd for $C_{17}H_{20}O_2$: 256.1463, found 256.1457. Anal. $C_{17}H_{20}O_2$ (C, H).

*5.2.3.5. 1,2-Bis-(4-hydroxy-phenyl)-hexane (**24**).* Use of compound **19** (184 mg, 0.62 mmol) and BBr_3 (1.85 mL of a 1 M solution in CH_2Cl_2) in 6 mL CH_2Cl_2 gave **24** as a white solid (148 mg, 88%, mp 81 °C) after purification by flash chromatography (50% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.01 (s, OH), 7.98 (s, OH), 6.95 (d, $J = 8.6$, 2H), 6.86 (d, $J = 8.6$, 2H), 6.71 (d, $J = 8.6$, 2H), 6.65 (d, $J = 8.6$, 2H), 2.78–2.65 (m, 3H), 1.66–1.60 (m, 1H), 1.56–1.49 (m, 1H), 1.29–1.06 (m, 4H), 0.77 (t, $J = 7.3$, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 156.30, 156.18, 137.00, 132.64, 130.82, 129.42, 115.74, 115.56, 48.08, 43.80, 36.17, 30.49, 23.29, 14.24; MS (EI) m/z 270 (M^+, 8). HRMS (EI) calcd for $C_{18}H_{22}O_2$: 270.1620, found 270.1623. Anal. $C_{18}H_{22}O_2$ (C, H).

*5.2.3.6. 1,2-Bis-(4-hydroxy-phenyl)-ethane (**25**).* Use of commercially available 1,2-Bis-(4-methoxy-phenyl)-ethane **20** (32 mg, 0.13 mmol) and BBr_3 (0.5 mL of a 1 M solution in CH_2Cl_2) in 1 mL CH_2Cl_2 gave **25** as a white solid (27 mg, quant. yield, mp 196 °C) after purification by flash chromatography (50% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.06 (s, OH), 7.01 (d, $J = 8.6$, 4H), 6.72 (d, $J = 8.6$, 4H), 2.74 (s, 4H); ^{13}C NMR (500 MHz, acetone-d_6) δ 156.31, 133.57, 130.18, 115.80, 38.17; MS (EI) m/z 214 (M^+, 11). HRMS (EI) calcd for $C_{14}H_{14}O_2$: 214.0994, found 214.0993. Anal. $C_{14}H_{14}O_2$ (C, H).

*5.2.3.7. 1,2-Bis-(4-hydroxy-phenyl)-prop-1-ene (**26**).* The starting material (500 mg, 1.84 mmol) **10** was dissolved in 20 mL CH_2Cl_2 and brought to −78 °C. BBr_3 (7.4 mL of a 1 M solution in CH_2Cl_2) was added dropwise and the reaction was stirred for 90 min. The mixture was brought to 0 °C and stirred for another 2 h. The reaction was quenched with water and extracted three times with EtOAc. The organic extracts were dried over Na_2SO_4 and the solvent was removed under vacuum. After purification by flash chromatography (25% EtOAc/hexanes) and re-crystallization from EtOAc/hexanes, **26** was obtained as a white solid (212 mg, 51%, mp 176 °C). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.37 (s, OH), 8.35 (s, OH), 7.39 (d, $J = 8.6$, 2H), 7.22 (d, $J = 8.6$, 2H), 6.86–6.81 (m, 4H), 6.70 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 157.53, 156.80, 136.29, 135.44, 131.22, 130.90, 127.74, 126.13, 115.89, 115.85, 17.53; MS (CI) m/z 227 ($M^+ + 1$, 100). HRMS (CI) calcd for $C_{15}H_{15}O_2$: 227.1072, found 227.1070. Anal. $C_{15}H_{14}O_2$: Calcd. C, 79.62; H, 6.24. Found C, 79.19; H, 6.17.

*5.2.3.8. 1,2-Bis-(4-hydroxy-phenyl)-but-1-ene (**27**).* The reaction was performed as described above for **26**. Use of **11** (400 mg, 1.40 mmol) and BBr_3 (5.59 mL of a 1 M solution in CH_2Cl_2) in 16 mL CH_2Cl_2 gave **27** as a white solid (156 mg, 46%, mp 109 °C) after purification by flash chromatography (25% EtOAc/hexanes) and re-crystallization from diethyl ether/hexanes. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.35 (s, OH), 7.33 (d, $J = 8.8$, 2H), 7.19 (d, $J = 8.8$, 2H), 6.86–6.81 (m, 4H), 6.54 (s, 1H), 2.70 (quart., $J = 7.5$, 2H), 1.03 (t, $J = 7.5$, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 157.52, 156.89, 142.66, 134.80, 130.79, 130.73, 128.33, 126.22, 115.96, 115.92, 23.46, 13.86; MS (CI) m/z 241 ($M^+ + 1$, 100). HRMS (CI) calcd for $C_{16}H_{17}O_2$: 241.1229, found 241.1230. Anal. $C_{16}H_{16}O_2$: Calcd. C, 79.97; H, 6.72. Found C, 79.42; H, 6.70.

*5.2.3.9. 1,2-Bis-(4-hydroxy-phenyl)-pent-1-ene (**28**).* The reaction was performed as described above for **26**. Use of **12** (500 mg, 1.67 mmol) and BBr_3 (6.65 mL of a 1 M solution in CH_2Cl_2) in 19 mL CH_2Cl_2 gave **28** as a white solid (224 mg, 53%, mp 117 °C) after purification by flash chromatography (25% EtOAc/hexanes) and re-crystallization from EtOAc/hexanes. ^{1}H NMR (500 MHz, acetone-d_6) δ 8.36 (s, OH), 8.33 (s, OH), 7.33 (d, $J = 8.8$, 2H), 7.18 (d, $J = 8.8$, 2H), 6.86–6.81 (m, 4H), 6.56 (s, 1H), 2.65 (t, $J = 7.9$, 2H), 1.48–1.40 (m, 2H), 0.89 (t, $J = 7.4$, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 157.49, 156.87, 141.45, 135.29, 130.82, 130.81, 128.33, 126.92, 115.94, 115.92, 32.57, 22.71, 14.27; MS (CI) m/z 255 ($M^+ + 1$, 100). HRMS (CI) calcd for $C_{17}H_{19}O_2$: 255.1385, found 255.1379. Anal. $C_{17}H_{18}O_2$: Calcd. C, 80.28; H, 7.13. Found C, 79.76; H, 7.15.

*5.2.3.10. General procedure for the alkylation of desoxyanisoin (**9**) and 1,2-bis-(4-methoxy-phenyl)-alkan-1-ones.* KO^{t}Bu and 18-crown-6 were added to THF at rt and the suspension was stirred for 15 min. A solution of the alkyl iodide and starting material was added at rt and stirring was continued for 30 min. The mixture was filtered and the filter cake was washed with EtOAc. The filtrate was absorbed on silica gel and the solvent was removed under vacuum. The silica gel was charged on a column and flash chromatography was performed as usual.

*5.2.3.11. 1,2-Bis-(4-methoxy-phenyl)-propan-1-one (**29a**).* Use of KO^{t}Bu (524 mg, 4.68 mmol) and 18-crown-6 (41 mg, 0.156 mmol) in 13 mL THF, as well as **9** (400 mg, 1.56 mmol) and methyl iodide (390 μL, 6.24 mmol) in 3 mL THF gave **29a** as a colorless oil (233 mg, 55%) after purification by flash chromatography (20% EtOAc/hexanes). In addition, 129 mg (29%) of the dimethylated product **32a** were isolated. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, $J = 8.8$, 2H), 7.20 (d, $J = 8.8$, 2H), 6.85 (d, $J = 8.8$, 2H), 6.82 (d, $J = 8.8$, 2H), 4.60 (quart., $J = 6.9$, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 1.49 (d, $J = 6.9$, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 199.03, 163.08, 158.32, 133.90, 130.97, 129.36, 128.63, 114.25, 113.57, 55.33, 55.13, 46.52, 19.52; MS (EI) m/z 270 (M^+, 6).

*5.2.3.12. 1,2-Bis-(4-hydroxy-phenyl)-propan-1-one (**29b**).* The reaction was performed according to the general procedure for the deprotection of methoxy groups. Use of **29a** (73 mg, 0.27 mmol) and BBr_3 (1.62 mL of a 1 M solution in CH_2Cl_2) in 2 mL CH_2Cl_2 gave **29b** as a white solid (38 mg, 58%, mp 151 °C) after purification by flash chromatography (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 7.92 (d, $J = 8.8$, 2H), 7.14 (d, $J = 8.6$, 2H), 6.83 (d, $J = 8.8$, 2H), 6.74 (d, $J = 8.6$, 2H), 4.70 (quart., $J = 6.9$, 1H), 1.37 (d, $J = 6.9$, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 199.06, 162.37, 157.00, 134.03, 132.01, 129.58, 116.38, 115.86, 46.54, 19.89; MS (EI) m/z 242 (M^+, 4). HRMS (EI) calcd for $C_{15}H_{14}O_3$: 242.0943, found 242.0946. Anal. $C_{15}H_{14}O_3 \cdot H_2O$: Calcd. C, 69.22; H, 6.20. Found C, 69.68; H, 5.70.

*5.2.3.13. 1,2-Bis-(4-methoxy-phenyl)-butan-1-one (**30a**).* Use of KO^{t}Bu (2.63 mg, 23.45 mmol) and 18-crown-6 (410 mg, 1.55 mmol) in 130 mL THF, as well as **9** (4.00 g, 15.63 mmol) and ethyl iodide (1.52 mL, 18.76 mmol) in 30 mL THF gave **30a** as a colorless oil (27 mg, 92%) after purification by flash chromatography (20% EtOAc/hexanes.) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, $J = 8.8$, 2H), 7.21 (d, $J = 8.6$, 2H), 6.86 (d, $J = 8.8$, 2H), 6.81 (d, $J = 8.6$, 2H), 4.34 (t, $J = 7.3$, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 2.19–2.11 (m, 1H), 1.85–1.77 (m, 1H), 0.88 (t, $J = 7.3$, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 198.82, 163.12, 158.40, 132.06, 130.87, 129.93, 129.14, 114.13, 113.58, 55.37, 55.14, 54.08, 27.05, 12.27; MS (CI) m/z 285 ($M^+ + 1$, 100).

*5.2.3.14. 1,2-Bis-(4-hydroxy-phenyl)-butan-1-one (**30b**).* The reaction was performed according to the general procedure for the

deprotection of methoxy groups. Use of **30a** (225 mg, 0.79 mmol) and BBr_3 (3.17 mL of a 1 M solution in CH_2Cl_2) in 8 mL CH_2Cl_2 gave **30b** as a white solid (100 mg, 49%, mp 117 °C) after purification by flash chromatography (40% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 7.95 (d, J = 8.6, 2H), 7.17 (d, J = 8.6, 2H), 6.85 (d, J = 8.6, 2H), 6.75 (d, J = 8.6, 2H), 4.48 (t, J = 7.2, 1H), 2.12–2.03 (m, 1H), 1.77–1.68 (m, 1H), 0.84 (t, J = 7.4, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 198.89, 162.41, 157.07, 132.15, 131.92, 130.10, 130.05, 116.27, 115.89, 54.07, 27.78, 12.44; MS (EI) m/z 256 (M^+, 6). HRMS (EI) calcd for $C_{16}H_{16}O_3$: 256.1099, found 256.1102. Anal. $C_{16}H_{16}O_3$ (C, H).

*5.2.3.15. 1,2-Bis-(4-methoxy-phenyl)-pentan-1-one (**31**).* Use of KO^{t}Bu (1.96 g, 17.54 mmol) and 18-crown-6 (154 mg, 0.58 mmol) in 50 mL THF, as well as **9** (1.50 g, 5.86 mmol) and propyl iodide (2.28 mL, 23.4 mmol) in 10 mL THF gave **31** as a colorless oil (1.13 g, 65%) after purification by flash chromatography (10% EtOAc/hexanes). In addition, 259 mg (13%) of dipropylated product **35** were isolated. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.8, 2H), 7.22 (d, J = 8.8, 2H), 6.87 (d, J = 8.8, 2H), 6.82 (d, J = 8.8, 2H), 4.34 (t, J = 7.3, 1H), 3.81 (s, 3H), 3.74 (s, 3H) 2.15–2.07 (m, 1H), 1.81–1.74 (m, 1H), 1.36–1.20 (m, 2H), 0.91 (t, J = 7.4, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 198.87, 163.14, 158.40, 132.24, 130.88, 129.91, 129.11, 114.13, 113.60, 55.34, 55.11, 52.00, 36.10, 20.78, 14.03; MS (CI) m/z 299 (M^+ + 1, 100).

*5.2.3.16. 1,2-Bis-(4-methoxy-phenyl)-2-methyl-propan-1-one (**32a**).* Use of KO^{t}Bu (417 mg, 3.72 mmol) and 18-crown-6 (2.3 mg, 0.009 mmol) in 8 mL THF, as well as **29a** (250 mg, 0.93 mmol) and methyl iodide (232 μL, 3.72 mmol) in 2 mL THF gave **32a** as a white solid (186 mg, 70%, mp 60 °C) after purification by flash chromatography (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 9.0, 2H), 7.21 (d, J = 8.8, 2H), 6.88 (d, J = 8.8, 2H), 6.71 (d, J = 9.0, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 1.57 (s, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.27, 162.15, 158.20, 137.95, 132.22, 128.65, 126.68, 114.25, 113.06, 55.22, 55.16, 50.46, 28.14; MS (EI) m/z 285 (M^+ + 1, 34).

*5.2.3.17. 1,2-Bis-(4-hydroxy-phenyl)-2-methyl-propan-1-one (**32b**).* The reaction was performed according to the general procedure for the deprotection of methoxy groups. Use of **32a** (100 mg, 0.35 mmol) and BBr_3 (1.06 mL of a 1 M solution in CH_2Cl_2) in 3.5 mL CH_2Cl_2 gave **32b** as a white solid (24 mg, 27%, mp 140 °C) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 7.50 (d, J = 9.0, 2H), 7.13 (d, J = 8.8, 2H), 6.83 (d, J = 8.8, 2H), 6.70 (d, J = 9.0, 2H), 1.51 (s, 6H); ^{13}C NMR (500 MHz, acetone-d_6) δ 201.99, 163.18, 156.95, 137.53, 132.87, 129.53, 127.53, 116.54, 113.86, 55.66, 50.94; MS (EI) m/z 256 (M^+, 4). HRMS (EI) calcd for $C_{16}H_{16}O_3$: 256.1099, found 256.1106. Anal. $C_{16}H_{16}O_3$ (C, H).

*5.2.3.18. 1,2-Bis-(4-methoxy-phenyl)-2-methyl-butan-1-one (**33**).* Use of KO^{t}Bu (3.56 g, 31.8 mmol) and 18-crown-6 (280 mg, 1.06 mmol) in 90 mL THF, as well as **30a** (3.00 g, 10.6 mmol) and methyl iodide (2.63 mL, 42.3 mmol) in 20 mL THF gave **33** as a colorless oil (1.55 g, 50%) after purification by flash chromatography (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 9.0, 2H), 7.18 (d, J = 8.8, 2H), 6.87 (d, J = 8.8, 2H), 6.70 (d, J = 9.0, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.17–2.10 (m, 1H), 2.06–1.98 (m, 1H), 1.51 (s, 3H), 0.73 (t, J = 7.5, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.33, 162.08, 158.20, 137.04, 131.95, 129.37, 127.26, 114.16, 113.05, 55.24, 55.18, 54.02, 32.25, 24.21, 8.61; MS (CI) m/z 299 (M^+ + 1, 49).

*5.2.3.19. 1,2-Bis-(4-methoxy-phenyl)-2-methyl-pentan-1-one (**34**).* Use of KO^{t}Bu (676 mg, 6.04 mmol) and 18-crown-6 (53 mg, 0.2 mmol) in 17 mL THF, as well as **31** (600 mg, 2.01 mmol) and methyl iodide (501 μL, 8.05 mmol) in 4 mL THF gave **34** as a colorless oil (334 mg, 53%) after purification by flash chromatography (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 9.0, 2H), 7.18 (d, J = 9.0, 2H), 6.87 (d, J = 9.0, 2H), 6.70 (d, J = 9.0, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.09–1.90 (m, 2H), 1.53 (s, 3H), 1.19–1.01 (m, 2H), 0.84 (t, J = 7.2, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 202.23, 162.02, 158.12, 137.28, 131.93, 129.28, 127.15, 114.12, 113.02, 55.24, 55.18, 53.80, 42.07, 25.00, 17.50, 14.75; MS (CI) m/z 340 (M^+ + 1, 25).

*5.2.3.20. 1,2-Bis-(4-methoxy-phenyl)-2-propyl-pentan-1-one (**35**).* Use of KO^{t}Bu (752 mg, 6.71 mmol) and 18-crown-6 (177 mg, 0.67 mmol) in 14 mL THF, as well as **31** (500 mg, 1.68 mmol) and propyl iodide (654 μL, 6.71 mmol) in 3 mL THF gave **35** as a colorless oil (257 mg, 45%) after purification by flash chromatography (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 9.0, 2H), 7.16 (d, J = 8.8, 2H), 6.86 (d, J = 9.0, 2H), 6.68 (d, J = 8.8, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 2.06–1.93 (m, 4H), 1.09–0.90 (m, 4H), 0.80 (t, J = 7.2, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.46, 161.92, 158.13, 136.06, 131.68, 129.75, 127.76, 113.96, 112.97, 57.11, 55.17, 55.11, 37.31, 16.75, 14.69; MS (EI) m/z 341 (M^+ + 1, 16).

5.2.4. General procedure for the deoxygenation with Et_3SiH/TFA

The starting material was dissolved in TFA, and Et_3SiH was added dropwise at rt. The reaction was stirred for 24 h, quenched with water and extracted three times with diethyl ether. The organic extracts were dried over Na_2SO_4 and the solvent was removed under vacuum.

*5.2.4.1. 1,2-Bis-(4-methoxy-phenyl)-2-methyl-propane (**36a**).* Use of **32a** (100 mg, 0.35 mmol) and Et_3SiH (140 μL, 0.88 mmol) in 2.70 mL TFA gave **36a** as a white solid (90 mg, quant. yield, mp 50 °C) after purification by flash chromatography (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 9.0, 2H), 6.86 (d, J = 9.0, 2H), 6.75–6.70 (m, 4H), 3.83 (s, 3H), 3.77 (s, 3H), 2.81 (s, 2H), 1.31 (s, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.78, 157.38, 141.12, 131.26, 131.07, 127.19, 113.11, 112.79, 55.13, 55.04, 50.30, 38.15, 28.29; MS (EI) m/z 270 (M^+, 3).

*5.2.4.2. 1,2-Bis-(4-hydroxy-phenyl)-2-methyl-propane (**36b**).* The reaction was performed according to the general procedure for the deprotection of methoxy groups. Use of **36a** (70 mg, 0.26 mmol) and BBr_3 (780 μL of a 1 M solution in CH_2Cl_2) in 2.5 mL CH_2Cl_2 gave **36b** as a white solid (50 mg, 79%, mp 113 °C) after purification by flash chromatography (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.07 (s, OH), 8.02 (s, OH), 7.12 (d, J = 8.8, 2H), 6.74 (d, J = 8.8, 2H), 6.66 (d, J = 8.6, 2H), 6.59 (d, J = 8.6, 2H), 2.73 (s, 2H), 1.23 (s, 6H); ^{13}C NMR (500 MHz, acetone-d_6) δ 156.39, 155.94, 140.71, 132.08, 130.66, 127.95, 115.35, 115.00, 50.81, 38.65, 28.72; MS (EI) m/z 242 (M^+, 3). HRMS (EI) calcd for $C_{16}H_{18}O_2$: 242.1307, found 242.1307. Anal. $C_{16}H_{18}O_2$: Calcd. C, 79.31; H, 7.49. Found C, 78.90; H, 7.51.

*5.2.4.3. 1,2-Bis-(4-methoxy-phenyl)-2-methyl-butane (**37a**).* Use of **33** (1.00 g, 3.36 mmol) and Et_3SiH (1.33 mL, 8.4 mmol) in 2.57 mL TFA gave **37a** as a colorless oil (679 mg, 70%) after purification by flash chromatography (5% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 8.9, 2H), 6.83 (d, J = 8.9, 2H), 6.70–6.65 (m, 4H), 3.81 (s, 3H), 3.75 (s, 3H), 2.85 (d, J = 13.3, 1H), 2.72 (d, J = 13.3, 1H), 1.94–1.86 (m, 1H), 1.59–1.52 (m, 1H), 1.19 (s, 3H), 0.70 (t, J = 7.4, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.71, 157.25, 138.88, 131.37, 130.85, 127.91, 113.09, 112.73, 55.11, 55.06, 49.82, 41.71, 34.37, 22.80, 8.71; MS (CI) m/z 283 (M^+ − 1, 3).

*5.2.4.4. 1,2-Bis-(4-hydroxy-phenyl)-2-methyl-butane (**37b**).* The reaction was performed according to the general procedure for the deprotection of methoxy groups. Use of **37a** (630 mg, 2.22 mmol) and BBr_3 (8.87 mL of a 1 M solution in CH_2Cl_2) in 20 mL CH_2Cl_2 gave

37b as a white solid (486 mg, 86%, mp 106 °C) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.08 (s, OH), 8.02 (s, OH), 7.05 (d, J = 8.9, 2H), 6.74 (d, J = 8.9, 2H), 6.63–6.56 (m, 4H), 2.81 (d, J = 13.2, 1H), 2.66 (d, J = 13.2, 1H), 1.92–1.85 (m, 1H), 1.55–1.47 (m, 1H), 1.14 (s, 3H), 0.64 (t, J = 7.4, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 156.35, 155.90, 138.30, 132.19, 130.38, 128.71, 115.39, 114.94, 50.41, 42.29, 35.19, 23.03, 9.00; MS (CI) m/z 255 ($M^+ - 1$, 3). HRMS (EI) calcd for $C_{17}H_{19}O_2$: 255.1385, found 255.1381. Anal. $C_{17}H_{20}O_2$ (C, H).

*5.2.4.5. 1,2-Bis-(4-methoxy-phenyl)-2-methyl-pentane (**38a**).* Use of **34** (285 mg, 1.07 mmol) and Et_3SiH (425 μL, 2.68 mmol) in 820 μL TFA gave **38a** as a colorless oil (212 mg, 66%) after purification by flash chromatography (5% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 8.8, 2H), 6.85 (d, J = 8.8, 2H), 6.72–6.68 (m, 4H), 3.83 (s, 3H), 3.77 (s, 3H), 2.88 (d, J = 13.2, 1H), 2.74 (d, J = 13.2, 1H), 1.83 (dd, J = 13.0, 4.0, 1H), 1.52 (dd, J = 13.0, 4.5, 1H), 1.28–1.18 (m, 4H), 1.08–0.96 (m, 1H), 0.87 (t, J = 7.4, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.67, 157.22, 139.29, 131.37, 130.75, 127.76, 127.70, 113.07, 113.03, 112.70, 55.08, 55.03, 50.00, 44.59, 41.47, 23.42, 17.48, 14.70; MS (EI) m/z 298 (M^+, 3).

*5.2.4.6. 1,2-Bis-(4-hydroxy-phenyl)-2-methyl-pentane (**38b**).* The reaction was performed according to the general procedure for the deprotection of methoxy groups. Use of **38a** (190 mg, 0.64 mmol) and BBr_3 (1.91 mL of a 1 M solution in CH_2Cl_2) in 6.5 mL CH_2Cl_2 gave **38b** as a white solid (270 mg, quant. yield, mp 55 °C) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.07 (s, OH), 8.01 (s, OH), 7.06 (d, J = 8.7, 2H), 6.74 (d, J = 8.7, 2H), 6.63–6.56 (m, 4H), 2.81 (d, J = 13.2, 1H), 2.67 (d, J = 13.2, 1H), 1.80 (dd, J = 13.0, 4.0, 1H), 1.46 (dd, J = 13.0, 4.7, 1H), 1.22–1.11 (m, 4H), 1.02–0.90 (m, 1H), 0.80 (t, J = 7.3, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 156.36, 155.87, 138.79, 132.20, 130.33, 128.54, 115.38, 114.97, 50.59, 45.52, 42.04, 23.77, 18.16, 15.04; MS (EI) m/z 270 (M^+, 2). HRMS (EI) calcd for $C_{18}H_{22}O_2$: 270.1620, found 270.1616.

*5.2.4.7. 1,2-Bis-(4-methoxy-phenyl)-2-propyl-pentane (**39a**).* Use of **35** (180 mg, 0.53 mmol) and Et_3SiH (210 μL, 1.32 mmol) in 407 μL TFA gave **39a** as a colorless oil (36 mg, 21%) after purification by flash chromatography (5% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 9.0, 2H), 6.82 (d, J = 9.0, 2H), 6.67–6.57 (m, 4H), 3.81 (s, 3H), 3.74 (s, 3H), 2.81 (s, 2H), 1.64–1.49 (m, 4H), 1.31–1.15 (m, 4H), 0.88 (t, J = 7.3, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 157.59, 157.09, 139.10, 131.06, 130.71, 127.86, 113.00, 112.75, 55.10, 55.04, 44.45, 44.14, 38.70 16.93, 14.71; MS (CI) m/z 325 ($M^+ - 1$, 7).

*5.2.4.8. 1,2-Bis-(4-hyroxy-phenyl)-2-propyl-pentane (**39b**).* The reaction was performed according to the general procedure for the deprotection of methoxy groups. Use of **39a** (40 mg, 0.12 mmol) and BBr_3 (370 μL of a 1 M solution in CH_2Cl_2) in 1.2 mL CH_2Cl_2 gave **39b** as a white solid (35 mg, quant. yield, mp 137 °C) after purification by flash chromatography (20% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.07 (s, OH), 8.01 (s, OH), 7.06 (d, J = 8.8, 2H), 6.75 (d, J = 8.8, 2H), 6.58–6.52 (m, 4H), 2.79 (s, 2H), 1.61–1.48 (m, 4H), 1.28–1.13 (m, 4H), 0.85 (t, J = 7.3, 6H); ^{13}C NMR (500 MHz, acetone-d_6) δ 156.31, 155.80, 138.57, 131.88, 130.22, 128.65, 115.40, 115.03, 44.75, 44.66, 39.60 17.54, 14.95; MS (CI) m/z 297 ($M^+ - 1$, 2). HRMS (CI) calcd for $C_{20}H_{25}O_2$: 297.1855, found 297.1858. Anal. $C_{20}H_{26}O_2$: Calcd. C, 80.50; H, 8.78. Found C, 79.61; H, 8.89.

*5.2.5. (4-Methoxy-phenyl)-[1-(4-methoxy-phenyl)-cyclopentyl]-methanone (**40**)*

NaH (312 mg of a 60% dispersion in oil, 7.80 mmol) was dissolved in 20 mL THF at rt and stirred for 20 min. **9** (500 mg, 1.95 mmol) was added as a solid at 0 °C and the reaction was continued for 4 h at rt. 1,4-dibromo-butane (344 μL, 2.93 mmol) was added at 0 °C and the mixture was refluxed for 3.5 h. After cooling to rt, the reaction was quenched with NH_4Cl (sat. aqueous solution) and extracted three times with EtOAc. The organic extracts were dried over Na_2SO_4 and the solvent was removed under vacuum. After purification by flash chromatography (10% EtOAc/hexanes), **40** was obtained as a colorless oil (390 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.8, 2H), 7.20 (d, J = 8.8, 2H), 6.84 (d, J = 8.8, 2H), 6.73 (d, J = 8.8, 2H), 3.77 (s, 6H), 2.47 (ddd, J = 11.9, 6.4, 6.4, 2H), 2.05 (ddd, J = 11.9, 5.9, 5.9, 2H), 1.78–1.64 (m, 4H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.72, 162.21, 158.01, 137.12, 132.30, 128.70, 126.96, 114.13, 113.06, 62.38, 55.25, 55.15, 37.60, 24.54; MS (CI) m/z 311 ($M^+ + 1$, 11).

*5.2.6. (4-Methoxy-phenyl)-[1-(4-methoxy-phenyl)-cyclohexyl]-methanone (**41**)*

The reaction was performed as described above for **40**. Use of NaH (312 mg of a 60% dispersion in oil, 7.80 mmol), **9** (500 mg, 1.95 mmol), and 1,4-dibromo-pentane (400 μL, 2.93 mmol) in 20 mL THF gave **41** as a colorless oil (371 mg, 59%) after purification by flash chromatography (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.6, 2H), 7.31 (d, J = 8.6, 2H), 6.90 (d, J = 8.6, 2H), 6.71 (d, J = 8.6, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 2.49 (d, J = 13.3, 2H), 1.74 (dt, J = 13.3, 3.4, 2H), 1.67–1.57 (m, 3H), 1.49–1.38 (m, 2H), 1.31–1.20 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 203.24, 161.75, 158.30, 136.82, 131.17, 130.65, 127.13, 114.27, 112.95, 55.19, 55.14, 54.45, 36.39, 25.84, 23.27; MS (CI) m/z 325 ($M^+ + 1$, 21).

*5.2.7. (4-Methoxy-phenyl)-[1-(4-methoxy-phenyl)-methyl]-cyclopentane (**42a**)*

The reaction was performed according to the general procedure for the deoxygenation with Et_3SiH/TFA. Use of **40** (360 mg, 1.16 mmol) and Et_3SiH (921 μL, 5.80 mmol) in 895 μL TFA gave **42a** as a colorless oil (286 mg, 83%) after purification by flash chromatography (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, J = 8.6, 2H), 6.78 (d, J = 8.6, 2H), 6.64 (d, J = 8.6, 2H), 6.52 (d, J = 8.6, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 2.74 (s, 2H), 1.96–1.66 (m, 8H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.67, 157.32, 140.47, 131.27, 131.10, 128.37, 112.89, 112.66, 55.14, 55.06, 51.69, 46.53, 36.83, 22.88; MS (CI) m/z 295 ($M^+ - 1$, 4).

*5.2.8. (4-Hydroxy-phenyl)-[1-(4-hydroxy-phenyl)-methyl]-cyclopentane (**42b**)*

The reaction was performed according to the general procedure for the deprotection of methoxy groups. Use of **42a** (260 mg, 0.88 mmol) and BBr_3 (2.64 mL of a 1 M solution in CH_2Cl_2) in 9 mL CH_2Cl_2 gave **42b** as a white solid (205 mg, 87%, mp 121 °C) after purification by flash chromatography (25% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.04 (s, OH), 7.98 (s, OH), 6.89 (d, J = 8.8, 2H), 6.68 (d, J = 8.8, 2H), 6.54 (d, J = 8.6, 2H), 6.45 (d, J = 8.6, 2H), 2.70 (s, 2H), 1.92–1.62 (m, 6H); ^{13}C NMR (500 MHz, acetone-d_6) δ 156.31, 155.94, 139.85, 131.86, 130.83, 129.05, 115.17, 114.91, 52.43, 47.22, 37.55, 23.42; MS (CI) m/z 267 ($M^+ - 1$, 6). HRMS (CI) calcd for $C_{18}H_{19}O_2$: 267.1385, found 267.1389. Anal. $C_{18}H_{20}O_2$ (C, H).

*5.2.9. (4-Methoxy-phenyl)-[1-(4-methoxy-phenyl)-methyl]-cyclohexane (**43a**)*

The reaction was performed according to the general procedure for the deoxygenation with Et_3SiH/TFA. Use of **41** (250 mg, 0.77 mmol) and Et_3SiH (613 μL, 3.86 mmol) in 600 μL TFA gave **43a** as a colorless oil (178 mg, 78%) after purification by flash chromatography (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (d, J = 8.6, 2H), 6.81 (d, J = 8.6, 2H), 6.63 (d, J = 8.6, 2H), 6.51 (d, J = 8.6, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 2.67 (s, 2H), 2.09 (d, J = 13.3, 2H),

1.59–1.45 (m, 5H), 1.38–1.24 (m, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.66, 157.15, 131.42, 130.19, 128.43, 113.15, 112.54, 55.11, 55.06, 42.08, 35.87, 26.58, 22.30; MS (CI) m/z 309 ($M^+ - 1$, 6).

5.2.10. (4-Hydroxy-phenyl)-[1-(4-hydroxy-phenyl)-methyl]-cyclohexane (**43b**)

The reaction was performed according to the general procedure for the deprotection of methoxy groups. Use of **43a** (180 mg, 0.58 mmol) and BBr_3 (1.74 mL of a 1 M solution in CH_2Cl_2) in 6 mL CH_2Cl_2 gave **43b** as a white solid (130 mg, 79%, mp 122 °C) after purification by flash chromatography (33% EtOAc/hexanes). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.06 (s, OH), 7.97 (s, OH), 6.96 (d, $J = 8.8$, 2H), 6.72 (d, $J = 8.8$, 2H), 6.53 (d, $J = 8.6$, 2H), 6.45 (d, $J = 8.6$, 2H), 2.62 (s, 2H), 2.07 (d, $J = 13.3$, 2H), 1.56–1.42 (m, 5H), 1.35–1.25 (m, 3H); ^{13}C NMR (500 MHz, acetone-d_6) δ 156.25, 155.74, 132.19, 129.65, 129.14, 115.48, 114.78, 42.65, 36.49, 27.29, 23.02; MS (CI) m/z 281 ($M^+ - 1$, 6). HRMS (CI) calcd for $C_{19}H_{21}O_2$: 281.1542, found 281.1549. Anal. $C_{19}H_{22}O_2$ (C, H).

5.3. Estrogen receptor binding affinity assays

Relative binding affinities were determined by a competitive radiometric binding assay as previously described [38,39], using 10 nM [^{3}H]estradiol as tracer (GE Healthcare, Piscataway, NJ), and purified full-length human ERα and ERβ (PanVera/InVitrogen, Carlsbad, CA). Incubations were for 18–24 h at 0 °C, then the receptor–ligand complexes were adsorbed onto hydroxyapatite (BioRad, Hercules, CA) and unbound ligand was washed away. The binding affinities are expressed as relative binding affinity (RBA) values, with the RBA of estradiol set to 100. The values given are the average ± range or SD of two or more independent determinations. All chiral compounds were tested as racemates. Estradiol binds to ERα with a K_d of 0.2 nM and to ERβ with a K_d of 0.5 nM.

5.4. Cell culture and transient transfections

Human endometrial cancer (HEC-1) cells were maintained in Minimum Essential Medium (MEM) plus phenol-red supplemented with 5% calf serum. Cells were changed to phenol-red-free Improved MEM and 5% charcoal dextran-treated calf serum (CDCS) for 3–4 days before use in experiments. Transfection assays were performed in 24-well plates using a mixture of 0.35 mL of serum-free improved MEM medium and 0.15 mL of Hank's balanced salt solution containing 5 μg of lipofectin (Life Technologies, Inc., Gaithersburg, MD), 20 μg of transferrin (Sigma, St. Louis, MO), 0.2 μg of pCMV β-galactosidase as internal control, 0.5 μg of 2ERE-pS2-Luc, and 50 ng of ER expression vector per well. The cells were incubated at 37 °C in a 5% CO_2-containing incubator for 6 h. The medium was then replaced with fresh Improved MEM supplemented with 5% CDCS plus the desired concentrations of ligands. Cells were harvested 24 h later. Luciferase and β-galactosidase activities were assayed as described [41]. All chiral compounds were tested as racemates.

Acknowledgments

This work was supported through grants from the National Institutes of Health (R37DK15556 and P01AG024387 to J.A.K., and R01CA18119 to B.S.K.).

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