Published in final edited form as:

Eur J Med Chem. 2009 September ; 44(9): 3412–3424. doi:10.1016/j.ejmech.2009.02.006.

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

Michael Waibel^a, Meri De Angelis^a, Fabio Stossi^b, Karen J. Kieser^a, Kathryn E. Carlson^a, Benita S. Katzenellenbogen^b, and John A. Katzenellenbogen^a

^aDepartment of Chemistry, University of Illinois, 600 South Matthews Avenue, Urbana, Illinois 61801

^bDepartment of Molecular and Integrative Physiology, University of Illinois, 600 South Matthews Avenue, Urbana, Illinois 61801

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 ER α and ER β binding showed that certain substitution patterns engendered binding affinities that were >100-fold selective for ER β . When further investigated in cell-based gene transcription assays, some molecules showed similarly high relative transcriptional potency selectivity in favor of ER β . Interestingly, the most ER β -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 ER β , and they might lead to the development of more selective and thus safer pharmaceuticals.

Keywords

Estrogen receptor; estrogen receptor beta; stilbestrol; hexestrol; selective ligand

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

© 2009 Elsevier Masson SAS. All rights reserved.

For correspondence, contact: John A. Katzenellenbogen, Department of Chemistry, University of Illinois, 600 South Mathews Avenue, Urbana, IL 61801, 217 333 6310, jkatzene@uiuc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

[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, ER β was discovered in 1996 and is encoded by a gene different from the one encoding the classical receptor (now referred to as ER α) [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 ER α and ER β , however, are very similar and differ in only two amino acids, with Met421 and Leu384 in ER α being substituted in ER β by Ile373 and Met336, respectively. Perhaps more significantly, the internal volume of the ligand-binding pocket of ER β is somewhat smaller than in ER α [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 ER α vs. ER β selective binding affinity and transcriptional potency [16]. Such ER subtype-selective ligands could be effective probes of the respective biological roles of ER α and ER β . 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 ER β relative binding affinity selectivity, was the first compound known to be selective for ER β (Fig. 1) [16]. Among synthetic estrogens, the 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 ER β , respectively. The latter represents the most ER β -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 ER β relative binding selectivity (Fig. 2) [22]. Other compounds showing ER β 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 ER β -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 ER α .

Recently, we reexamined isobutestrol **6**, a compound that has long been known for its low affinity for ER α [29,30], and we were pleased to find that this simple compound had good affinity and an 18-fold relative binding selectivity for ER β . 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 ER β binding selectivity than its more familiar congeners, hexestrol **7** and diethylstilbestrol (DES) **8** [29] (cf., Table 1), although its absolute affinity is lower. Because of the encouraging ER β 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 ER β 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 BBr₃, 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 BBr₃ 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** 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 one equivalent 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 BBr₃ 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 α,ω -dibromoalkanes (Scheme 3). In the literature protocol we followed [37], the reaction is performed at room temperature and takes about two 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 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 (RBA) of the compounds we prepared were measured in a competitive radiometric binding assay using purified full-length human ER α and ER β [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 ER β 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 ER β 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 ER α increased faster than for ER β , resulting overall in lower ER β 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 di-substituted with small alkyl chains, the ER β selectivity was higher compared to the corresponding mono-substituted 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 7 α and 11 β 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 linking carbons, has lower affinity, but increased ER β selectivity. In this study, we found the same behavior in case of the stilbene analogs: Monoethylstilbestrol **27** had lower affinity than DES, but increased ER β 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 LBD pockets of the ERs. The decrease in ER β selectivity is consistent with the larger ligand-binding pocket of ER α , which is being better able to accommodate the large and constrained ligands than ER β . 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 ER α and ER β 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 ER α or ER β and an estrogen-responsive reporter gene [41]. The dose-response curves for these compounds are given in Fig. 4, and the EC₅₀ values are listed in Table 1. This table also includes the EC₅₀ values for our ER β -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 EC₅₀ 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 ER α in terms of binding (K_d [ER α] = 0.2 nM vs. [ER β] = 0.5 nM) and a 5-fold preference in terms of transcriptional potency (EC₅₀ [ER α] = 0.1 nM vs. [ER β] = 0.5 nM).

Of the eight compounds tested, seven showed very good potency selectivity for ER β (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 ER β transcriptional potency preference yet had good ER β 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 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 structure, irrespective of their binding affinity. Compared to our previously prepared ER β -selective ligand, DPN **5**, some of the compounds we present here have higher ER β binding affinity (compounds **6**, **21**, **22**, **24**, **27**, **28**, and **37b**) and comparable or higher ER β binding selectivity (compounds **25**, **26**, **36b**, and **37b**) and somewhat less to nearly equivalent ER β 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 ER β binding affinity and selectivity, and good ER β transcriptional potency and selectivity. In terms of ER β binding affinity, the best bibenzyl is compound **22** and the best stilbene is **27**; in terms of ER β binding selectivity, the best in each series is **36b** and **26**. In terms of ER β 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 ER β binding selectivity of DPN (**5**), none matched or exceeded the ER β transcriptional potency selectivity of this compound. Nevertheless, these compounds represent new structures of remarkable simplicity that have high ER β activities, and they should thus serve as good probes to further investigate the biological functions of ER β in vivo, as well as to study ligand-induced conformations of ER β agonist complexes.

It is also remarkable that many of the ER β -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 ER β -selective bibenzyl systems we have studied share with other ER β -selective ligands an interior that is generally more “slender” and/or less “symmetrical” than typical for ER α -selective ligands, such as hexestrol (**7**) and DES (**8**). These ER β -selective slender ligands appear to have a better fit with the somewhat smaller ligand binding pocket of ER β compared to ER α [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 ER α and ER β —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 ER β .

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 F₂₅₄ 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 μ m silica gel packing. ¹H and ¹³C NMR 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

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 $\times$ 15 mL). The organic extracts were dried over Na₂SO₄ and the solvent was removed under vacuum.

1,2-Bis-(4-methoxy-phenyl)-propan-2-ol (10)—Use of methyl magnesium chloride (1.56 mL of a 3M solution in THF) gave **10** as a white solid (389 mg, 92% yield, mp 68 °C) after purification by flash chromatography (33% EtOAc/hexanes). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

1,2-Bis-(4-methoxy-phenyl)-butan-2-ol (11)—Use of ethyl magnesium bromide (4.68 mL of a 1M solution in THF) gave **11** as a white solid (344 mg, 77% yield, mp 63 °C) after purification by flash chromatography (33% EtOAc/hexanes). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

General procedure for the dehydroxylation of 1,2-Bis-(4-methoxy-phenyl)-alkan-2-ols—The starting material was dissolved in CH₂Cl₂ and the mixture was brought to 0 °C. Et₃SiH was added and after 2 min BF₃·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 Na₂SO₄ and the solvent was removed under vacuum.

1,2-Bis-(4-methoxy-phenyl)-propane (15)—Use of compound **10** (337 mg, 1.24 mmol), Et₃SiH (394 μL, 2.48 mmol) and BF₃·OEt (314 μL, 2.48 mmol) in 5 mL CH₂Cl₂

gave **15** as a white solid (313 mg, quant. yield, mp 68 °C) after purification by flash chromatography (25% EtOAc/hexanes). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

1,2-Bis-(4-methoxy-phenyl)-butane (16)—Use of compound **11** (330 mg, 1.05 mmol), Et₃SiH (320 μL, 2.01 mmol) and BF₃·OEt (253 μL, 2.01 mmol) in 5 mL CH₂Cl₂ gave **16** as a colorless oil (249 mg, 88%) after purification by flash chromatography (25% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (400 MHz, CDCl₃) 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).

1,2-Bis-(4-methoxy-phenyl)-pentane (17)—Use of compound **12** (306 mg, 1.02 mmol), Et₃SiH (325 μL, 2.04 mmol) and BF₃·OEt (259 μL, 2.04 mmol) in 5 mL CH₂Cl₂ gave **17** as a white solid (233 mg, 88%, mp 34 °C) after purification by flash chromatography (25% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (400 MHz, CDCl₃) 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).

1,2-Bis-(4-methoxy-phenyl)-3-methyl-butane (18)—Use of compound **13** (215 mg, 0.72 mmol), Et₃SiH (228 μL, 1.43 mmol) and BF₃·OEt (181 μL, 1.43 mmol) in 4.5 mL CH₂Cl₂ gave **18** as a colorless oil (168 mg, 82%) after purification by flash chromatography (25% EtOAc/hexanes). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

1,2-Bis-(4-methoxy-phenyl)-hexane (19)—Use of compound **14** (235 mg, 0.75 mmol), Et₃SiH (239 μL, 1.50 mmol) and BF₃·OEt (190 μL, 1.50 mmol) in 4.5 mL CH₂Cl₂ gave **19** as a colorless oil (207 mg, 93%) after purification by flash chromatography (25% EtOAc/hexanes). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

General procedure for the deprotection of methoxy groups with BBr₃—The starting material was dissolved in CH₂Cl₂ and brought to 0 °C. BBr₃ 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 Na₂SO₄ and the solvent was removed under vacuum.

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 1M 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). ^1H 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 $\text{C}_{15}\text{H}_{16}\text{O}_2$: 228.1150, found 228.1145. Anal. $\text{C}_{15}\text{H}_{16}\text{O}_2$ (C, H).

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 1M 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** was consistent with the data published previously [30].

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 1M 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). ^1H 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 ($\text{M}^+ - 1$, 81). HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{19}\text{O}_2$: 255.1385, found 255.1389 Anal. $\text{C}_{17}\text{H}_{20}\text{O}_2$ (C, H).

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 1M 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. ^1H 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 $\text{C}_{17}\text{H}_{20}\text{O}_2$: 256.1463, found 256.1457. Anal. $\text{C}_{17}\text{H}_{20}\text{O}_2$ (C, H).

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 1M 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). ^1H 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 $\text{C}_{18}\text{H}_{22}\text{O}_2$: 270.1620, found 270.1623. Anal. $\text{C}_{18}\text{H}_{22}\text{O}_2$ (C, H).

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 1M 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). ^1H 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 C₁₄H₁₄O₂: 214.0994, found 214.0993. Anal. C₁₄H₁₄O₂ (C, H).

1,2-Bis-(4-hydroxy-phenyl)-prop-1-ene (26)—The starting material (500 mg, 1.84 mmol) **10** was dissolved in 20 mL CH₂Cl₂ and brought to −78 °C. BBr₃ (7.4 mL of a 1M solution in CH₂Cl₂) 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 Na₂SO₄ 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). ¹H 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); ¹³C 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 C₁₅H₁₅O₂: 227.1072, found 227.1070. Anal. C₁₅H₁₄O₂: Calcd. C, 79.62; H, 6.24. Found C, 79.19; H, 6.17.

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 BBr₃ (5.59 mL of a 1M solution in CH₂Cl₂) in 16 mL CH₂Cl₂ 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. ¹H 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); ¹³C 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 C₁₆H₁₇O₂: 241.1229, found 241.1230. Anal. C₁₆H₁₆O₂: Calcd. C, 79.97; H, 6.72. Found C, 79.42; H, 6.70.

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 BBr₃ (6.65 mL of a 1M solution in CH₂Cl₂) in 19 mL CH₂Cl₂ 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. ¹H 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); ¹³C 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 C₁₇H₁₉O₂: 255.1385, found 255.1379. Anal. C₁₇H₁₈O₂: Calcd. C, 80.28; H, 7.13. Found C, 79.76; H, 7.15.

General procedure for the alkylation of desoxyanisoin (9) and 1,2-Bis-(4-methoxy-phenyl)-alkan-1-ones—KO^tBu 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 were 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.

1,2-Bis-(4-methoxy-phenyl)-propan-1-one (29a)—Use of KO^tBu (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 μ L, 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. ¹H NMR (500 MHz, CDCl₃)

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).

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 1M 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). ^1H 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 $\text{C}_{15}\text{H}_{14}\text{O}_3$: 242.0943, found 242.0946. Anal. $\text{C}_{15}\text{H}_{14}\text{O}_3 \cdot \text{H}_2\text{O}$: Calcd. C, 69.22; H, 6.20. Found C, 69.68; H, 5.70.

1,2-Bis-(4-methoxy-phenyl)-butan-1-one (30a)—Use of KO^tBu (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). ^1H 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 ($\text{M}^+ + 1$, 100).

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 1M 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). ^1H 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 $\text{C}_{16}\text{H}_{16}\text{O}_3$: 256.1099, found 256.1102. Anal. $\text{C}_{16}\text{H}_{16}\text{O}_3$ (C, H).

1,2-Bis-(4-methoxy-phenyl)-pentan-1-one (31)—Use of KO^tBu (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. ^1H 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 ($\text{M}^+ + 1$, 100).

1,2-Bis-(4-methoxy-phenyl)-2-methyl-propan-1-one (32a)—Use of KO^tBu (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). ^1H 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 ($\text{M}^+ + 1$, 34).

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 1M 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). ^1H 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 $\text{C}_{16}\text{H}_{16}\text{O}_3$: 256.1099, found 256.1106. Anal. $\text{C}_{16}\text{H}_{16}\text{O}_3$ (C, H).

1,2-Bis-(4-methoxy-phenyl)-2-methyl-butan-1-one (33)—Use of KO^tBu (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). ^1H 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 ($\text{M}^+ + 1$, 49).

1,2-Bis-(4-methoxy-phenyl)-2-methyl-pentan-1-one (34)—Use of KO^tBu (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). ^1H 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 ($\text{M}^+ + 1$, 25).

1,2-Bis-(4-methoxy-phenyl)-2-propyl-pentan-1-one (35)—Use of KO^tBu (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). ^1H 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 ($\text{M}^+ + 1$, 16).

General procedure for the deoxygenation with $\text{Et}_3\text{SiH/TFA}$ —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.

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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

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 BBr₃ (780 μL of a 1M solution in CH₂Cl₂) in 2.5 mL CH₂Cl₂ gave **36b** as a white solid (50 mg, 79%, mp 113 °C) after purification by flash chromatography (20% EtOAc/hexanes). ¹H 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); ¹³C 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 C₁₆H₁₈O₂: 242.1307, found 242.1307. Anal. C₁₆H₁₈O₂: Calcd. C, 79.31; H, 7.49. Found C, 78.90; H, 7.51.

1,2-Bis-(4-methoxy-phenyl)-2-methyl-butane (37a)—Use of **33** (1.00 g, 3.36 mmol) and Et₃SiH (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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

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 BBr₃ (8.87 mL of a 1M solution in CH₂Cl₂) in 20 mL CH₂Cl₂ gave **37b** as a white solid (486 mg, 86%, mp 106 °C) after purification by flash chromatography (25% EtOAc/hexanes). ¹H 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); ¹³C 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 C₁₇H₁₉O₂: 255.1385, found 255.1381. Anal. C₁₇H₂₀O₂ (C, H).

1,2-Bis-(4-methoxy-phenyl)-2-methyl-pentane (38a)—Use of **34** (285 mg, 1.07 mmol) and Et₃SiH (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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

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 BBr₃ (1.91 mL of a 1M solution in CH₂Cl₂) in 6.5 mL CH₂Cl₂ gave **38b** as a white solid (270 mg, quant. yield, mp 55 °C) after purification by flash chromatography (25% EtOAc/hexanes). ¹H 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 $\text{C}_{18}\text{H}_{22}\text{O}_2$: 270.1620, found 270.1616.

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). ^1H 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 ($\text{M}^+ -1$, 7).

1,2-Bis-(4-hydroxy-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 1M solution in CH_2Cl_2) in 1.2 mL CH_2Cl_2 gave **39b** as a white solid (35 mg, quant. yield, mp 137 $^\circ\text{C}$) after purification by flash chromatography (20% EtOAc/hexanes). ^1H 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 ($\text{M}^+ -1$, 2). HRMS (CI) calcd for $\text{C}_{20}\text{H}_{25}\text{O}_2$: 297.1855, found 297.1858. Anal. $\text{C}_{20}\text{H}_{26}\text{O}_2$: Calcd. C, 80.50; H, 8.78. Found C, 79.61; H, 8.89.

(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 $^\circ\text{C}$ and the reaction was continued for 4 h at rt. 1,4-dibromo-butane (344 μL , 2.93 mmol) was added at 0 $^\circ\text{C}$ 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%). ^1H 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 ($\text{M}^+ +1$, 11).

(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). ^1H 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 ($\text{M}^+ +1$, 21).

(4-methoxy-phenyl)- [1-(4-methoxy-phenyl)-methyl]-cyclopentane (42a)—The reaction was performed according to the general procedure for the deoxygenation with Et₃SiH/TFA. Use of **40** (360 mg, 1.16 mmol) and Et₃SiH (921 μ L, 5.80 mmol) in 895 μ L TFA gave **42a** as a colorless oil (286 mg, 83%) after purification by flash chromatography (10% EtOAc/hexanes). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

(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 BBr₃ (2.64 mL of a 1M solution in CH₂Cl₂) in 9 mL CH₂Cl₂ gave **42b** as a white solid (205 mg, 87%, mp 121 °C) after purification by flash chromatography (25% EtOAc/hexanes). ¹H 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); ¹³C 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 C₁₈H₁₉O₂: 267.1385, found 267.1389. Anal. C₁₈H₂₀O₂ (C, H).

(4-methoxy-phenyl)- [1-(4-methoxy-phenyl)-methyl]-cyclohexane (43a)—The reaction was performed according to the general procedure for the deoxygenation with Et₃SiH/TFA. Use of **41** (250 mg, 0.77 mmol) and Et₃SiH (613 μ L, 3.86 mmol) in 600 μ L TFA gave **43a** as a colorless oil (178 mg, 78%) after purification by flash chromatography (10% EtOAc/hexanes). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (500 MHz, CDCl₃) 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).

(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 BBr₃ (1.74 mL of a 1M solution in CH₂Cl₂) in 6 mL CH₂Cl₂ gave **43b** as a white solid (130 mg, 79%, mp 122 °C) after purification by flash chromatography (33% EtOAc/hexanes). ¹H 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); ¹³C 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 C₁₉H₂₁O₂: 281.1542, found 281.1549. Anal. C₁₉H₂₂O₂ (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 [³H]estradiol as tracer (GE Healthcare, Piscataway, NJ), and purified full-length human ER α and ER β (PanVera/InVitrogen, Carlsbad, CA). Incubations were for 18–24 h at 0 °C, then the receptor-ligand complexes were absorbed 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 $\pm$ range or SD of two or more independent determinations. All chiral compounds were tested as racemates. Estradiol binds to ER α with a K_d of 0.2 nM and to ER β 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 and 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% CO₂-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 activity 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.).

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

References

1. Katzenellenbogen JA, Katzenellenbogen BS. *Chemistry and Biology*. 1996; 3:529–536. [PubMed: 8807884]
2. Gennari L, De Paola V, Merlotti D, Martini G, Nuti R. *Expert Opinion on Pharmacotherapy*. 2007; 8:537–553. [PubMed: 17376011]
3. Sammartino A, Cirillo D, Mandato VD, Di Carlo C, Nappi C. *Journal of Endocrinological Investigation*. 2005; 28:80–84. [PubMed: 16550729]
4. Markou A, Duka T, Prelevic GM. *Hormones (Athens)*. 2005; 4:9–17. [PubMed: 16574627]
5. Barret-Connor E, Cox DA, Anderson PW. *Trends Endocrinol Metab*. 1999; 10:320–325. [PubMed: 10481163]
6. Arnal JF, Gourdy P, Elhage R, Garmy-Susini B, Delmas E, Bouchet L, Castano C, Barreira Y, Couloumiers JC, Prats H, Prats AC, Bayard F. *European Journal of Endocrinology*. 2004; 150:113–117. [PubMed: 14763907]
7. Yaffe K, Sawaya G, Lieberburg I, Grady D. *JAMA, the Journal of the American Medical Association*. 1998; 279:688–695. [PubMed: 9496988]
8. Beresford SA, Weiss NS, Voigt LF, McKnight B. *Lancet*. 1997; 349:458–461. [PubMed: 9040575]
9. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. *J Natl Cancer Inst*. 1998; 90:1371–1388. [PubMed: 9747868]

10. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, Norton L, Nickelsen T, Bjarnason NH, Morrow M, Lippman ME, Black D, Glusman JE, Costa A, Jordan VC. JAMA. 1999; 281:2189–2197. [PubMed: 10376571]
11. McDonnell DP. Trends in Endocrinology and Metabolism. 1999; 10:301–311. [PubMed: 10481160]
12. Katzenellenbogen BS, Katzenellenbogen JA. Breast Cancer Research. 2000; 2:335–344. [PubMed: 11250726]
13. Katzenellenbogen JA, O'Malley BW, Katzenellenbogen BS. Molecular Endocrinology. 1996; 10:119–131. [PubMed: 8825552]
14. Mosselman S, Polman J, Dijkema R. FEBS Letters. 1996; 392:49–53. [PubMed: 8769313]
15. Kuiper GG, Carlsson B, Grandien K, Enmark E, Haggblad J, Nilsson S, Gustafsson JA. Endocrinology. 1997; 138:863–870. [PubMed: 9048584]
16. Kuiper GG, Enmark E, Peltö-Huikko M, Nilsson S, Gustafsson JA. Proceedings of the National Academy of Sciences of the United States of America. 1996; 93:5925–5930. [PubMed: 8650195]
17. Pike AC, Brzozowski AM, Hubbard RE, Bonn T, Thorsell AG, Engstrom O, Ljunggren J, Gustafsson JA, Carlquist M. EMBO Journal. 1999; 18:4608–4618. [PubMed: 10469641]
18. Harris HA. Ernst Schering Found Symp Proc. 2006; 1:149–161. [PubMed: 17824176]
19. Harris HA. Mol Endocrinol. 2007; 21:1–13. [PubMed: 16556737]
20. De Angelis M, Stossi F, Waibel M, Katzenellenbogen BS, Katzenellenbogen JA. Bioorganic & Medicinal Chemistry. 2005; 13:6529–6542. [PubMed: 16099659]
21. Harris HA, Albert LM, Leathurby Y, Malamas MS, Mewshaw RE, Miller CP, Kharode YP, Marzolf J, Komm BS, Winneker RC, Frail DE, Henderson RA, Zhu Y, Keith JC Jr. Endocrinology. 2003; 144:4241–4249. [PubMed: 14500559]
22. Meyers MJ, Sun J, Carlson KE, Marriner GA, Katzenellenbogen BS, Katzenellenbogen JA. Journal of Medicinal Chemistry. 2001; 44:4230–4251. [PubMed: 11708925]
23. De Angelis M, Stossi F, Carlson KA, Katzenellenbogen BS, Katzenellenbogen JA. Journal of the American Chemical Society. 2005; 127:1132–1144.
24. Malamas MS, Manas ES, McDevitt RE, Gunawan I, Xu ZB, Collini MD, Miller CP, Dinh T, Henderson RA, Keith JC Jr, Harris HA. Journal of Medicinal Chemistry. 2004; 47:5021–5040. [PubMed: 15456246]
25. Norman BH, Dodge JA, Richardson TI, Borromeo PS, Lugar CW, Jones SA, Chen K, Wang Y, Durst GL, Barr RJ, Montrose-Rafizadeh C, Osborne HE, Amos RM, Guo S, Boodhoo A, Krishnan V. Journal of Medicinal Chemistry. 2006; 49:6155–6157. [PubMed: 17034120]
26. Richardson TI, Norman BH, Lugar CW, Jones SA, Wang Y, Durbin JD, Krishnan V, Dodge JA. Bioorganic & Medicinal Chemistry. 2007; 17:3570–3574.
27. Schopfer U, Schoeffter P, Bischoff SF, Nozulak J, Feuerbach D, Floersheim P. Journal of Medicinal Chemistry. 2002; 45:1399–1401. [PubMed: 11906280]
28. Vu AT, Campbell AN, Harris HA, Unwalla RJ, Manas ES, Mewshaw RE. Bioorganic & Medicinal Chemistry Letters. 2007; 17:4053–4056. [PubMed: 17482813]
29. De Angelis M, Katzenellenbogen JA. Bioorganic & Medicinal Chemistry Letters. 2004; 14:5835–5839. [PubMed: 15501051]
30. Kilbourn MR, Arduengo AJ, Park JT, Katzenellenbogen JA. Molecular Pharmacology. 1981; 19:388–398. [PubMed: 6267445]
31. Adlington MG, Orfanopoulos M, Fry JL. Tetrahedron Letters. 1976:2955–2958.
32. Felix AM. Journal of Organic Chemistry. 1974; 39:1427–1429.
33. Krohn K, Kulikowski K, Leclercq G. Journal of Medicinal Chemistry. 1989; 32:1532–1538. [PubMed: 2738889]
34. Tingoli M, Tiecco M, Testaferri L, Temperini A, Pelizzi G, Bacchi A. Tetrahedron. 1995; 51:4691–4700.
35. Kamada A, Sasaki A, Kitazawa N, Okabe T, Nara K, Hamaoka S, Araki S, Hagiwara H. Chemical & Pharmaceutical Bulletin. 2004; 52:79–88.
36. West CT, Donnelly SJ, Kooistra DA, Doyle MP. Journal of Organic Chemistry. 1973; 38:2675–2681.

37. Scribner AW, Haroutounian SA, Carlson KE, Katzenellenbogen JA. *Journal of Organic Chemistry*. 1997; 62:1043–1057.
38. Carlson KE, Choi I, Gee A, Katzenellenbogen BS, Katzenellenbogen JA. *Biochemistry*. 1997; 36:14897–14905. [PubMed: 9398213]
39. Katzenellenbogen JA, Johnson HJ Jr, Myers HN. *Biochemistry*. 1973; 12:4085–4092. [PubMed: 4745660]
40. Shiau AK, Barstad D, Loria PM, Cheng L, Kushner PJ, Agard DA, Greene GL. *Cell*. 1998; 95:927–937. [PubMed: 9875847]
41. McInerney EM, Tsai MJ, O'Malley BW, Katzenellenbogen BS. *Proceedings of the National Academy of Sciences of the United States of America*. 1996; 93:10069–10073. [PubMed: 8816752]
42. Pangborn AB, Giardello MA, Grubbs RH, Rosen RK, Timmers FJ. *Organometallics*. 1996; 15:1518–1520.

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

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

Fig. 3.
ERβ pharmacophore model

Fig. 4. Transcriptional activation by ERα and ERβ in response to ligands **21**, **22**, **25**, **26**, **27**, **36b**, **37b** and **38b** and estradiol (E₂, 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 24h. Luciferase and β-galactosidase activity were assayed as described [41]. Estradiol activity at 10 nM is set at 100%. All chiral compounds were tested as racemates.

Scheme 1.

(a) RMgCl, THF; (b) and (d) BBr₃, CH₂Cl₂; (c) Et₃SiH, BF₃·OEt₂, CH₂Cl₂

Scheme 2.

(a) KOt-Bu, RI, 18-crown-6, THF; (b) Et₃SiH, CF₃COOH; (c) BBr₃, CH₂Cl₂

Scheme 3.

(a) NaH, Br(CH₂)_{n+3}Br, THF; (b) Et₃SiH, CF₃COOH; (c) BBr₃, CH₂Cl₂

Table 1

ER α and ER β relative binding affinity (RBA), relative transcriptional potency (RTP), transcriptional activity (EC₅₀ 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
	ER α	ER β		ER α	ER β		ER α	ER β
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

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
26	0.218 ± 0.025	12.2 ± 1.2	56	0.89	13.9	16	11.2	3.6	3.1
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

Ligand	Ligand Binding		Transcription Potency				
	RBA ^a (%)		β/α affinity ratio ^b	RTP ^c (%)		β/α potency ratio ^b	EC ₅₀ ^d (nM)
	ERα	ERβ		ERα	ERβ
43b	1.84 ± 0.20	2.74 ± 0.70	1.5	ND	ND	ND	NT
29b	< 0.004	0.018 ± 0.004	4.5	ND	ND	ND	NT
30b	0.008 ± 0.001	0.018 ± 0.001	2.3	ND	ND	ND	NT
32b	0.042 ± 0.006	0.018 ± 0.001	0.4	ND	ND	ND	NT
DPN, 5f	0.25 ± 0.15	18 ± 2	72	0.15	59	390	66.00
Hexestrol, 7	277 ± 57	697 ± 194	2.5	ND	ND	ND	NT
DES, 8	372 ± 106	278 ± 54	0.7	ND	ND	ND	NT

^aRelative binding affinity (RBA) values are determined by competitive radiometric binding assays and are expressed as EC₅₀[estradiol]/EC₅₀[compound] × 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.

^bFor 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.

^cRelative transcriptional potency (RTP) values are expressed as EC₅₀(estradiol)/EC₅₀(ligand) × 100 (RTP, estradiol = 100). In these assays, the EC₅₀ 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 = EC₅₀.

^e ND = not determined; NT = not tested.

^f Data are from the literature [22].