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Estrogenic activity of bis(4-hydroxyphenyl)methanes with cyclic hydrophobic structure

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ABSTRACT

Monoalkylated bis(4-hydroxyphenyl)methanes (e.g., **1**) are reported to show weak binding affinity for estrogen receptor (ER). We hypothesized that introduction of appropriately located hydrophobic substituents in these compounds would increase the binding affinity. Indeed, we found that bis(4-hydroxyphenyl)methane bearing a 3,3-dimethylcyclohexyl group (**7**) shows potent ERα binding affinity, comparable to that of estradiol. Bulkier substituents could be introduced at the 3,3-position without decreasing the affinity. However, the position of the substituents was critical: the 4,4-dimethylcyclohexyl derivative (**2**) showed very weak binding affinity. The compounds with high ER-binding affinity showed predominantly agonistic activity, together with weak antagonistic activity at high concentration, in cell proliferation assay with human breast cancer cell line MCF-7. Further structure–function studies of these compounds and their derivatives might lead to the development of more selective and potent estrogen receptor modulators.

1. Introduction

Estrogens, such as 17β-estradiol, play an important role in the female and male reproductive systems,[1] as well as in bone maintenance, in the central nervous system[2] and in the cardiovascular system.[3] The first step in the appearance of these activities is binding of the ligands to estrogen receptors α and β (ERα[4] and β[5]). This binding results in a conformational change of the receptor, inducing dimerization. The dimer functions as a transcription factor, which causes biological responses by binding to specific promoter elements of DNA to initiate gene transcription. It has been reported that ERα and ERβ have different tissue distributions[6] and biological roles, and they sometimes act in opposition to each other. Numerous subtype-selective ligands have been reported and ERβ-selective ligands are of potential clinical interest.[7] However, the nature of the differences between the two ER subtypes has not been fully established, possibly because ERα is predominant as a transcription factor, compared with ERβ.[8]

From a clinical point of view, there is great interest in selective estrogen receptor modulators (SERMs), which are tissue-selective ER agonists and antagonists. The major factor determining tissue selectivity is considered to be quantitative and qualitative differences of co-regulatory proteins in the ER-mediated transcriptional systems of each target tissue.[9] These co-regulatory proteins alter the conformational state of the ER–ligand complex to influence the transcriptional action. Similarly, the agonist/antagonist balance of SERMs is determined by the conformational state of the ER–ligand complex. These complex macromolecular systems can be controlled by low-molecular-weight ligands. Typical SERMs such as tamoxifen[10] and raloxifene[11] were found to be agonistic in bone and antagonistic in breast, but showed varying activity in uterus. The agonist/antagonist balances of the two SERMs are different: tamoxifen is more antagonistic and raloxifene is more agonistic. Therefore, elucidation of the structure–activity relationships of partial agonist/antagonists is important for elucidating ER activation mechanisms and for developing useful clinical medicines.

Based on the structure of the complex formed by estradiol and the human ER-α LBD (hERαLBD),[12] the phenolic hydroxyl group is hydrogen-bonded to Glu-353 and Arg394 of hERαLBD and the 17β-hydroxyl group is hydrogen-bonded to the δ-nitrogen of His-524. The importance of these two hydrogen-bondings is very different: the phenolic hydrogen-bonding is indispensable, whereas the 17-hydroxyl hydrogen-bonding can be replaced by hydrophobic interaction. Hydrophobic interaction of the steroidal skeleton of the ligand with the LBD also plays an important role for stabilization

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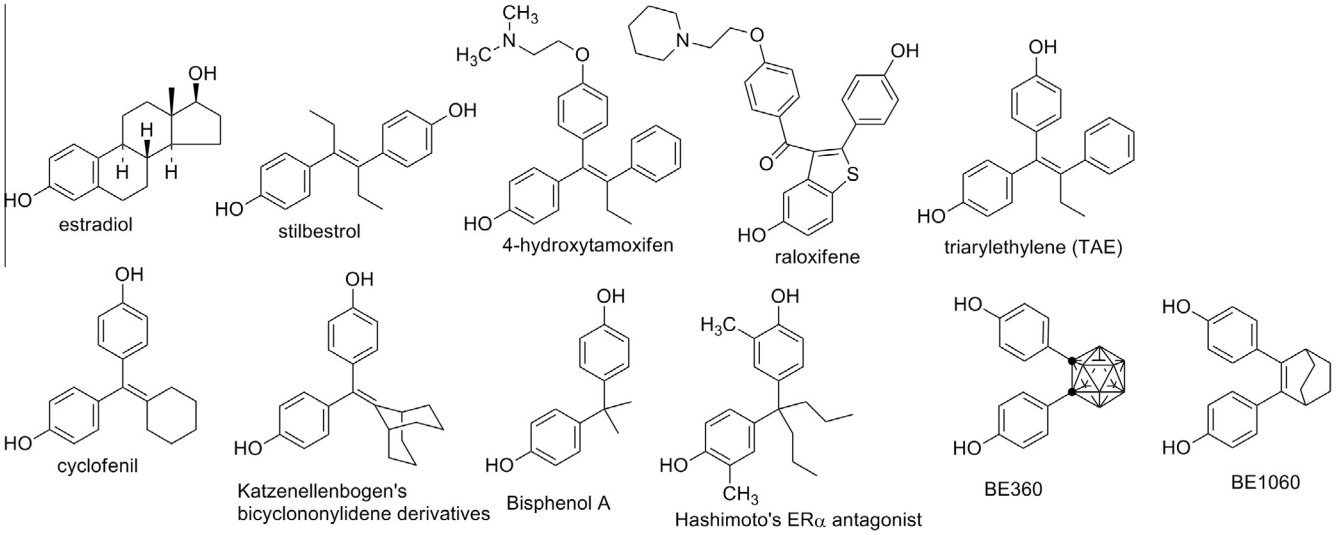
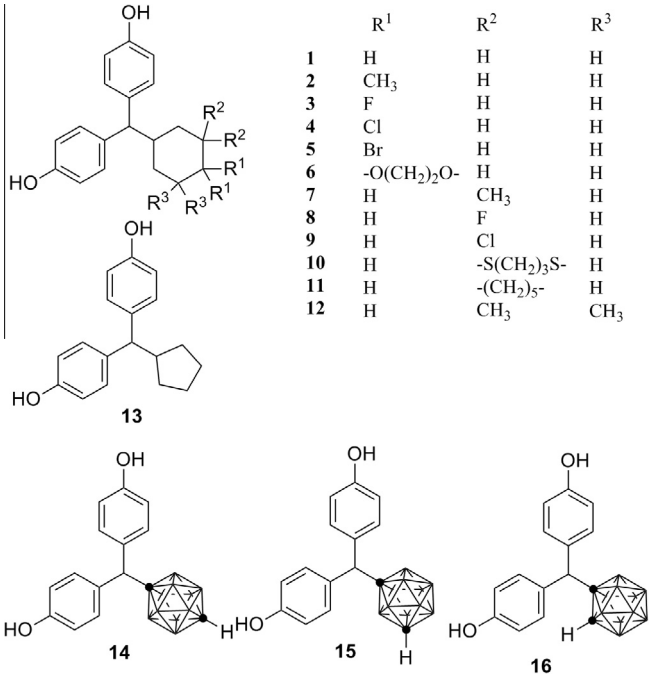


Figure 1. Various estrogen receptor modulators.

and binding activity of the ER–ligand complex. Since the discovery of the potent ER agonist diethylstilbestrol and SERM tamoxifen, triphenylethylene and diphenylethylene skeletons have attracted considerable attention as basic structures for ER ligands.[13] Katzenellenbogen et al. have reported that 1,1-diarylethylene derivatives with bridged bicyclic structures have high ER-binding activity, and these compounds mainly show ER antagonistic activity.[14] Jordan et al. reported that 1,1,2-triphenylethylenes with two or three hydroxyl groups in various phenyl rings showed ER agonistic activity.[15] Another important compound is bisphenol A, which has weak estrogenic activity but has been manufactured on a considerable scale as an industrial material for use in plastic products. Recently, Hashimoto et al. reported that bisphenol A derivatives with extended alkyl chains show selective ERα antagonistic activity[16] (see Fig. 1).



	R^1	R^2	R^3
1	H	H	H
2	CH_3	H	H
3	F	H	H
4	Cl	H	H
5	Br	H	H
6	$-O(CH_2)_2O-$	H	H
7	H	CH_3	H
8	H	F	H
9	H	Cl	H
10	H	$-S(CH_2)_3S-$	H
11	H	$-(CH_2)_5-$	H
12	H	CH_3	CH_3

Figure 2. ER Ligands with cyclic hydrophobic structures. In the icosahedral cage structure, ● represent carbon atoms and other vertices represent BH units.

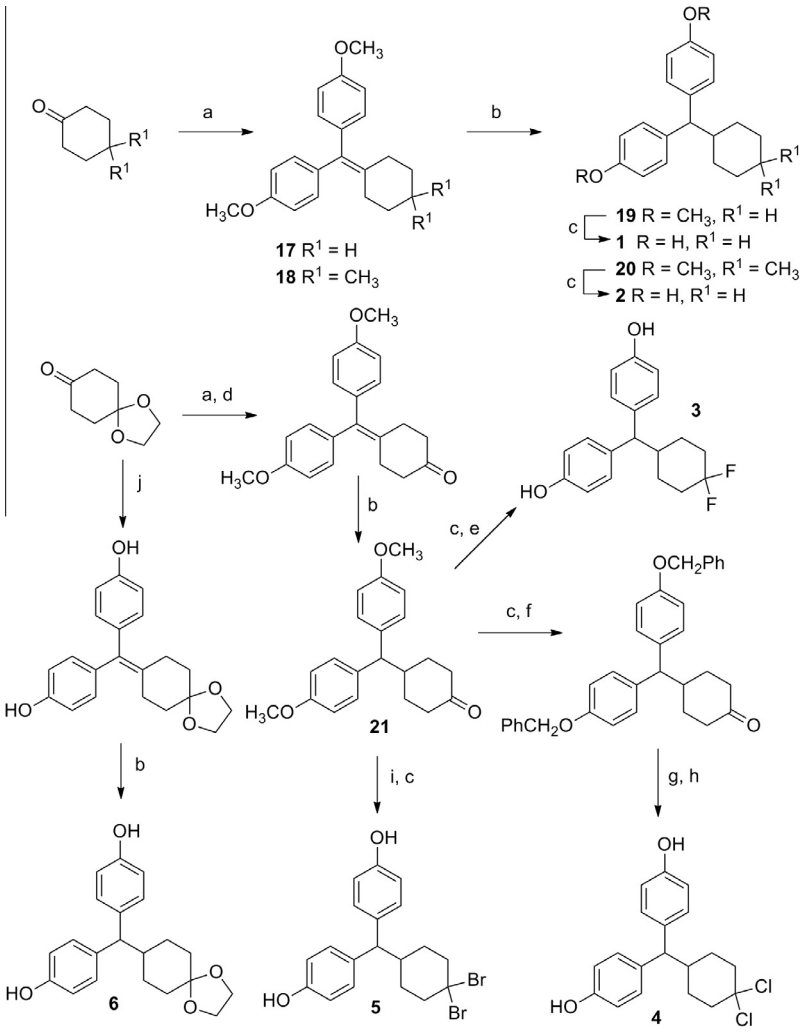
We have focused on the application of three-dimensional hydrophobic structural units, such as icosahedral boron clusters (carboranes[17]), that fit in the hydrophobic cavity of the ER LBDs.[18] In our design and biological activity studies of bisphenols with a hydrophobic core structure, we have found that the hydrophobic core structure has the ability to regulate agonist/antagonist balance. For example, BE360, bis(4-hydroxylphenyl)-*o*-carborane, showed partial antagonist activity towards ER.[19] However, BE1060, in which the carborane cage of BE360 is replaced with a hydrocarbon core, bicyclo[2,2,2]octene, exhibited potent ER agonistic activity, even though the two phenolic groups appear to be similarly directed.[20] Thus, differences in receptor–ligand complex structures arising from the presence of different hydrophobic structures in the ligand can influence biological activity. 1,1-Diarylethylene derivatives such as cyclofenil have potent binding affinity for ER, and show mixed agonist/antagonist activities.[21] On the other hand, hydrogenated 1,1-diarylmethane derivatives[22] have not received much attention because of their lower binding affinity.[14] However, we hypothesized that addition of appropriate hydrophobic substituents would improve the binding affinity and provide a means to regulate the agonist/antagonist activity balance. In this article, we describe the synthesis and biological evaluation of simple bisphenols, bis(4-hydroxyphenyl)methanes, bearing cyclic hydrophobic structures.

2. Results

2.1. Chemistry

We presumed that the first phenolic hydroxyl group would act as an anchor at the hydrogen-bonding site of ER, while the three-dimensional hydrophobic core would fill the hydrophobic cavity of ER. The steric and electronic effects of substituents on the hydrophobic core were expected to determine the nature of the estrogenic action. Therefore, we designed bis(4-hydroxyphenyl) methanes with a cyclohexyl group bearing various substituents (**1**–**12**), as shown in Figure 2. We also designed bis(4-hydroxyphenyl)methanes with a cyclopentyl group (**13**) and a carboranyl group (**14**–**16**).

Synthesis of unsubstituted and 4,4-disubstituted cyclohexyl derivatives is summarized in Scheme 1. Cyclohexyl (**1**) and 4,4-dimethylcyclohexyl (**2**) derivatives were prepared by McMurry coupling reaction of 4,4-dimethoxybenzophenone with

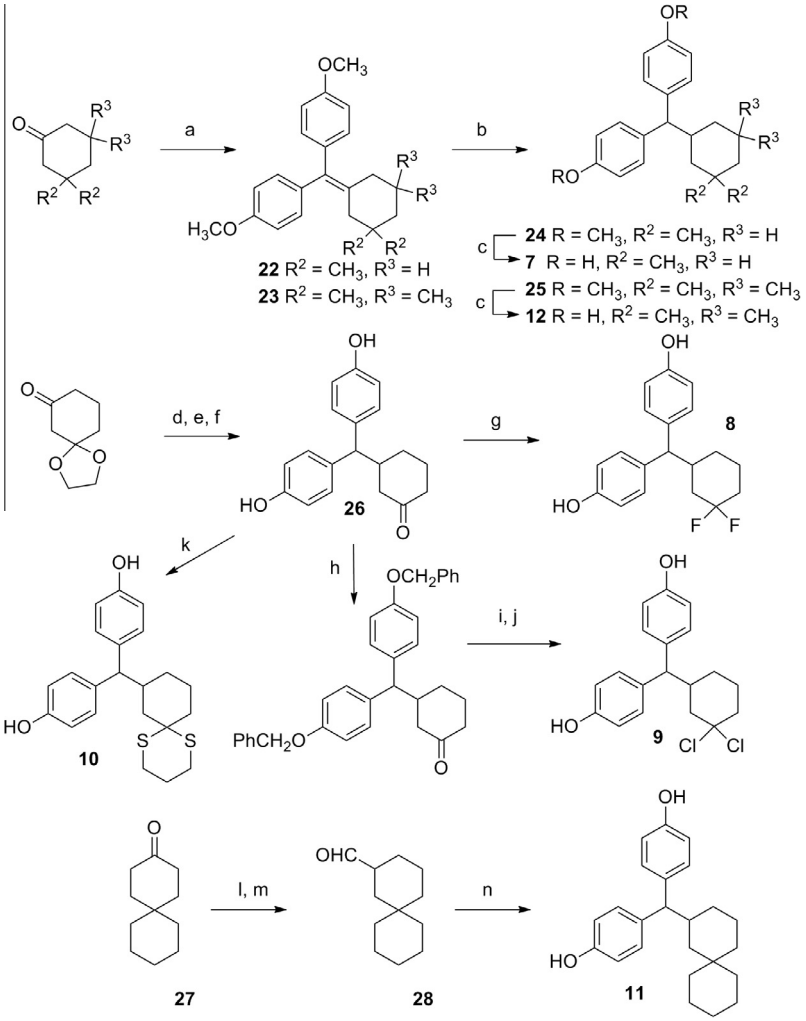


Scheme 1. Synthesis of unsubstituted and 4,4-disubstituted derivatives. Reagents and conditions: (a) 4,4′-dimethyoxybenzophenone, $TiCl_4$, Zn/THF, reflux, 74–85%; (b) H_2, Pd–C/$CH_3COOC_2H_5$, rt, 93–98%; (c) BBr_3/CH_2C1_2, −40 °C, 61–90%; (d) SiO_2, H_2SO_4/CH_2C1_2, rt, 80%; (e) (1) DAST/CH_2C1_2, rt, (2) OsO_4, NMO/acetone–H_2O, rt, 50%; (f) benzyl bromide, K_2CO_3/acetone, reflux, 86%; (g) (1) N_2H_4, MS4A/CH_3OH–CH_2C1_2, rt, (2) $CuCl_2$, Et_3N/CH_3OH–CH_2C1_2, rt, 32%; (h) $BC1_3/CH_2C1_2$, rt, 78%; (i) 2,3-dihydroxynaphthalene, BF_3OEt_2, TMSC1/CH_2C1_2, rt, 75%; (j) 4,4′-dihydroxybenzophenone, $TiCl_4$, Zn/THF, reflux, 69%.

cyclohexanone or 4,4-dimethylcyclohexanone to give **17** or **18**. Catalytic hydrogenation followed by deprotection afforded the desired compounds **1** and **2**, respectively. 4,4-Dihalogenated derivatives were prepared though the ketone **21** as an intermediate. McMurry coupling reaction of 4,4′-dimethoxybenzophenone with 1,4-cyclohexanedione mono-ethylene ketal, followed by acidic treatment and hydrogenation, gave ketone **21** in 53% yield. Deprotection followed by fluorination with (diethylamino)sulfur trifluoride (DAST) and treatment with OsO_4 for separation of olefin by-product afforded 4,4-difluorocyclohexyl derivative **3** in 50% yield. After conversion of the protected group of the ketone **21** into a benzyl group, reaction with hydrazine, followed by chlorination with copper(II) chloride and deprotection afforded 4,4-dichlorocyclohexyl derivative **4**. The carbonyl group of **21** was protected with 2,3-dihydroxynaphthalene ketal and treated with boron tribromide to afford 4,4-dibromocyclohexyl derivative **5**. The 4,4-ethylene ketal derivative (**6**) was prepared from 1,4-cyclohexanedione mono-ethylene ketal and 4,4′-dihydroxybenzophenone by means of the McMurry coupling reaction and catalytic hydrogenation.

Synthesis of 3,3-disubstituted and 3,3,5,5-tetrasubstituted cyclohexyl derivatives is summarized in Scheme 2. 3,3-Dimethylcyclohexyl (**7**) and 3,3,5,5-tetramethylcyclohexyl (**12**) derivatives were prepared by McMurry coupling reaction of 4,4-dimethoxybenzophenone with 3,3-dimethylcyclohexanone or 3,3,5,5-tetramethylcyclohexanone to give **22** or **23**. Palladium-catalyzed hydrogenation of **22** or **23** did not proceed smoothly, probably for a steric hindrance, in contrast to the case of the 4,4-dimethyl derivatives. Reduction of **22** or **23** with hydrogen iodide afforded **24** or **25** in low yield. Deprotection of the methyl group using BBr_3 gave the desired products **7** and **12**. 3,3-Dihalogenated cyclohexyl derivatives were prepared through the ketone **26**. McMurry coupling reaction of unprotected 4,4′-dihydroxybenzophenone with 1,3-cyclohexanedione mono-ethylene ketal followed by acidic treatment afforded the conjugated ketone in 33% yield. The conjugated ketone was readily hydrogenated to give ketone **26**. Fluorination of **26** with DAST afforded 3,3-difluorocylclohexyl derivative **8** in 46% yield. Chlorination of ketone **26** by a multi-step procedure in a similar manner to the preparation of **4** afforded 3,3-dichlorocylclohexyl derivative **9**. The ketone **26** was also converted to 3,3-dithoketal **10** by reaction with 1,3-propanedithiol in 78% yield. 3,3-Pentamethylene derivative (**11**) was prepared from spiro[5,5] undecan-3-one (**27**). Compound **27** was converted to carboxyaldehyde **28** and then Friedel–Crafts reaction with phenol gave the desired compound **11**.

Synthesis of the cyclopentyl derivative (**13**) was carried out according to the literature.[23] Friedel–Crafts reaction of cyclohexene oxide with anisole catalyzed by $AlCl_3$ afforded **29** via rearrangement of the carbon skeleton. Deprotection of the methyl group



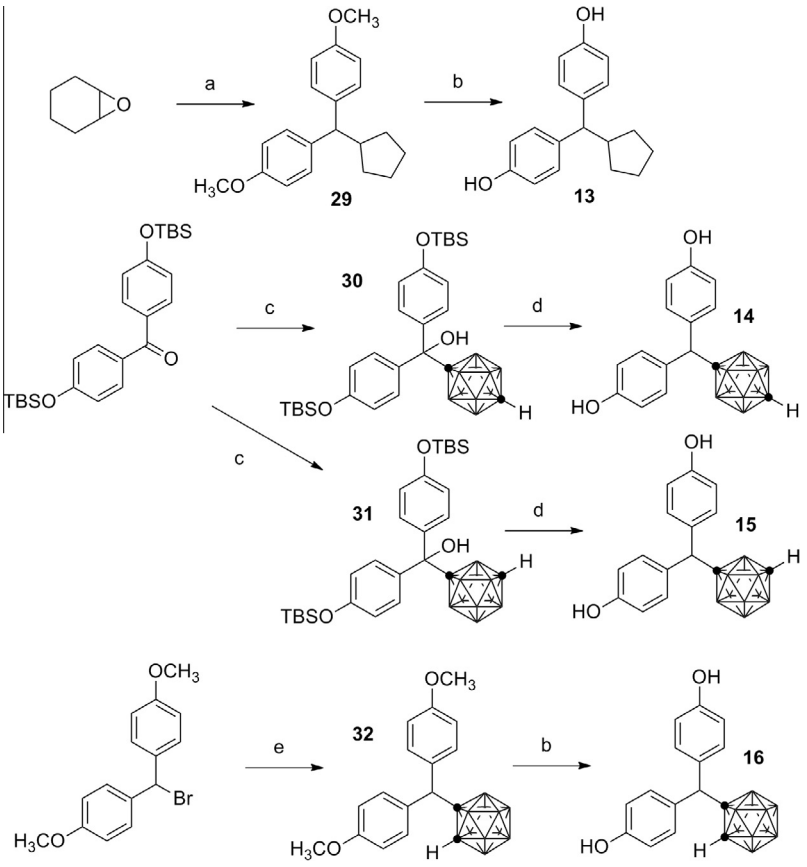
Scheme 2. Synthesis of 3,3-disubstituted and 3,3,5,5-tetrasubstituted derivatives. Reagents and conditions: (a) 4,4′-dimethoxybenzophenone, $TiCl_4$, Zn/THF, reflux, 83–90%; (b) HI/CH_2C1_2 reflux, 11%; (c) BBr_3/CH_2C1_2, rt, 96–98%; (d) 4,4′-dihydroxybenzophenone, $TiCl_4$, Zn/THF, reflux, 45%; (e) HCl/acetone rt, 74%; (f) H_2, Pd–C/C_2H_5OH, 88%; (g) DAST/CH_2C1_2, rt, 46%; (h) benzyl bromide, K_2CO_3/acetone, reflux, 70%; (i) (1) N_2H_4, MS4A/CH_3OH–CH_2C1_2, rt, (2) $CuCl_2$, Et_3N/CH_3OH–CH_2C1_2, rt, 11%; (j) $BC1_3/CH_2C1_2$, rt, 59%; (k) 1,3-propanedithiol, BF_3OEt_3, TMSC1/CH_2C1_2, rt, 78%; (l) DMF, $POC1_3/CH_2C1_2$, rt, 67%; (m) H_2, Pd–C, Et_3N/C_2H_5OH, rt, 84%; (n) Phenol, HC1, 70 °C, 32%.

gave **13** (Scheme 3). Carborane-containing compounds were prepared from TBDMS-protected 4,4′-dihydroxybenzophenone by reaction with lithiated *p*- or *m*-carborane, followed by reduction with triethylsilane, and then deprotection to afford the desired compounds **14** and **15** (Scheme 3). In the case of the *o*-carboranyl derivative, adduct of the 4,4′-dihydroxybenzophenone with *o*-carborane was not isolated because of its instability. Therefore, substitution of 4,4′-dimethoxydiphenylmethyl bromide with lithiated *o*-carborane was employed to give **33**. Deprotection using BBr_3 afforded **16**.

2.2. Biological evaluation

The binding activities of the synthesized compounds were examined by measurement of the inhibition of [6,7-^{3}H]17β-estradiol binding (K_d = 0.4 nM) to human recombinant ERα and β, using the nitrocellulose filter binding assay method. Table 1 summarizes the binding affinity data of the test compounds as relative binding affinity (RBA) with respect to that of estradiol (estradiol = 100). Simple unsubstituted cyclohexyl (**1**), cyclopentyl (**13**) and 4,4-dimethylcyclohexyl (**2**) derivatives showed weak binding affinity. Introduction of a 4,4-difluoro group (**3**) did not affect the binding affinity, and introduction of larger halogens (**4**, **5**, and **6**) and polar groups including oxygen on the 4,4-position decreased the binding affinity. In contrast, introduction of substituents at the 3,3-position had a quite different effect; the binding affinity of the 3,3-dimethylcyclohexyl compound (**7**) was significantly increased. Its potency for binding to ERα (RBA = 99) was almost the same as that of estradiol. The bulky trimethylenethioketal group (**10**) or pentamethylene group (**11**) slightly decreased the affinity. Introduction of halogen at the 3,3-position led to a decrease of the binding affinity. On the other hand, the 3,3,5,5-tetramethyl compound (**12**) showed somewhat lower binding affinity than **7**. Introduction of a bulkier carborane group (**14**, **15**, **16**) did not significantly affect the binding affinity. 3,3-Disubstituted and 4,4-disubstituted cyclohexyl derivatives (**2**–**12**) were not particularly selective for ERα or ERβ (βα in the range of 0.2–1.3). The compounds bearing carboranes showed similar selectivity (β/α values of 1.2–1.6).

The estrogenic activity of the synthesized compounds was evaluated by cell proliferation assay with human breast cancer cell line MCF-7. The EC_{50} values and IC_{50} values of these compounds are summarized in Table 2. Measurement of antagonistic activity was performed in the presence of 1×10^{-11} M estradiol. Unsubstituted cyclohexyl (**1**) and 4,4-disubstituted cyclohexyl (**2**–**6**) derivatives showed weak agonistic activity ($EC_{50} < 10^{-7}$ M). The potency



Scheme 3. Synthesis of cyclopentyl derivative and carborane derivatives. Reagents and conditions: (a) anisole, BE_3 OEt_2, 50 °C, 22%; (b) BBr_3/CH_2C1_2, rt, 78–92%; (c) *m*- or *p*-carborane, *n*-BuLi/$(C_2H_5)_2O$, rt to −30 °C; (d) Et_3SiH, BF_3 OEt_2, −30 °C, 51–57% (two steps); (e) *o*-carborane, *n*-BuLi/$(C_2H_5)_2O$, rt, 28%.

Table 1
Relative binding affinity (RBA) of the compound estrogen receptors α and β

Compound	RBA (*E*2 = 100)[a]		*β*/α
	ERα	ERβ	
1	6.71	15.5	2.3
2	3.64	3.02	1.2
3	2.71	3.93	1.3
4	0.662	0.158	0.2
5	0.957	0.180	0.2
6	0.465	0.219	0.5
7	98.8	30.7	0.3
8	5.78	4.29	0.7
9	15.3	15.7	1.0
10	50.6	8.43	0.2
11	21.9	29.3	1.3
12	28.4	35.2	1.2
13	4.61	13.7	3.0
14	4.08	5.86	1.4
15	8.06	6.80	1.2
16	11.1	18.4	1.6

[a] Relative binding affinity (RBA) values were determined by radiometric binding assay with [^{3}H]estradiol and ERα and ERβ. Binding assay were performed in duplicate (n = 2). The RBA of estradiol (*E*2) is defined as 100.

Table 2
Estrogenic activities of the compounds in cell proliferation assay using MCF-7 cells

Compound	Agonistic activity		Antagonistic activity
	EC_{50}[a] (nM)	E_{max}[b] (%)	IC_{50}[a] (nM)
1	54.1	79	>1000
2	68.4	72	>1000
3	22.5	80	>1000
4	304	78	>1000
5	211	64	>1000
6	—	22	>1000
7	2.40	74	64.9
8	16.6	58	19.6
9	4.60	70	>1000
10	0.39	80	>1000
11	0.80	74	>1000
12	—	32	63.1
13	48.8	69	>1000
14	22.1	73	>1000
15	2.13	86	>1000
16	3.42	78	>1000

[a] MCF-7 cells were treated with the test compounds (1×10^{-13}–1×10^{-6} M) alone or in the presence of 0.1 nM E2. Cell proliferation assay was performed in triplicate (n = 3). EC_{50} and IC_{50} values were estimated from the sigmoidal dose–response curves using GraphPad Prism 4 software.

[b] E_{max} values indicate the efficacy for cell proliferation, based on the value for *E*2 taken as 100.

was strongly correlated to the binding affinity for ERα. Among these compounds, unsubstituted cyclohexyl compound **1** showed very weak antagonistic activity at high concentration. 3,3-Disubstituted cyclohexyl derivatives (**7**–**11**) showed moderate to potent agonistic activity (EC_{50} 10^{-7}–10^{-10} M). 3,3-Dimethyl (**7**) and 3,3-trimethylenethioketal (**10**) derivatives showed potent ER agonistic activity, with weak antagonistic activity at high concentration. The potency of agonistic activity was also correlated to the binding affinity for ERα. 3,3-Difluorocyclohexyl compound **8** also showed very weak antagonistic activity at high concentration. The compounds containing a carborane group (**14**, **15**, **16**) were moderate agonists, reflecting their moderate ERα binding affinity. In contrast, the 3,3,5,5-tetramethyl derivative (**12**) was a very weak partial

agonist with a maximum activity of 32% of that of estradiol. These compounds showed antagonistic activity at concentrations of 10^{-8} M order.

2.3. Discussion

The crystal structure of the ERα LBD has been elucidated in the complex with estradiol.[12] The phenolic hydroxyl group of estradiol is hydrogen-bonded to Glu353 and Arg394 of ERα LBD and the 17-β-hydroxyl group is hydrogen-bonded to the δ-nitrogen of His524. Hydrophobic interaction with hydrophobic amino acid residues along the body of the steroid skeleton also contributes to the stability of the complex. Interestingly, the lack of the second hydrogen-bonding with His524 can be compensated by hydrophobic interaction or by alternative hydrogen-bonding, especially with Thr347. For example, bisphenol bearing bicyclo[2,2,2]octane (BE1060),[20] and many 1,1-diarylethylene derivatives[14] have potent binding affinity for ER. It was reported that reduction of 1,1-diarylethylene derivatives greatly decreased the binding affinity.[14] Indeed, the binding affinity of compound **1**, which corresponds to hydrogenated cyclofenil, was much lower than that of cyclofenil. Introduction of methyl at the 4,4-position (**2**) did not increase the hydrophobic interaction. Introduction of a larger halogen (**4**, and **5**), or polar group including oxygen (**6**) at the 4,4-position decreased the binding affinity. In contrast, the 3,3-dimethyl derivative (**7**) showed greatly increased binding affinity for ER. This is an example where increased hydrophobic interaction due to the introduction of a hydrophobic substituent at an appropriate location has a dramatic effect on the binding affinity. We performed docking simulation of compounds **7**, **11**, **12** and **2** into ERα (1ERE). Compounds **7** and **11** are racemic, so both enantiomers were examined. Among the compounds, the most stable complex was obtained in the case of *S*-**7**. Figure 3 shows docking simulation of *S*-**7** with ERα using 1ERE. The first hydroxyl group is hydrogen-bonded to Glu353 and Arg394, and the second hydroxyl group is hydrogen-bonded to Thr347. The hydrophobic 3, 3-dimethylcyclohexyl group is located in a hydrophobic pocket surrounded by hydrophobic amino acid residues Leu346, Ile424, Leu428 and Leu391. In docking simulations of **7** using the coordinates of bisphenol A with mutated ER (3UU7)[24] and bisphenol C with ER (3UUC),[24] similar stable structures were obtained. Thus, high binding affinity is associated with the presence of bulky 3,3 substituents. On the other hand, introduction of a carboranyl structure did not increase the hydrophobic interaction. The compounds in this series were not particularly selective for ERα or ERβ. The difference of ERα and ERβ within the ligand-binding pockets is limited to two amino acids, that is, Leu384 and Met421 in ERα correspond to Met336 and Ile 373 in ERβ. It seem not to be effective for distinction between the differences.

The agonist/antagonist balance of ER ligands depends on the helix 12 capping conformation of the ER–ligand complex and the consequent relationship with the steroid receptor coactivator-1 (SRC-1) peptide.[12] The characteristic activated conformations of ER are 'agonist conformation' and 'antagonist conformation', but the change of agonist/antagonist balance appears to be continuous, not stepwise, and small changes of the ligand structure causes changes of the biological activities. Consequently, there are many partial agonist/antagonists with various characteristics as regards potency and agonist/antagonist balance. On the whole, the compounds with 3,3-disubstituted cyclohexyl groups have agonistic activity together with weak antagonistic activity at high concentration, and their potency corresponds well to their ERα binding affinity. Some of them possessed different agonist/antagonist balances, such as **10** and **11**, which were more agonistic. 3,3,5,5-Tetramethyl derivative (**12**) was conversely more antagonistic. Antagonistic activity of unsubstituted and 4,4-disubstituted compounds did not appear, presumably because of their essentially weak activity.

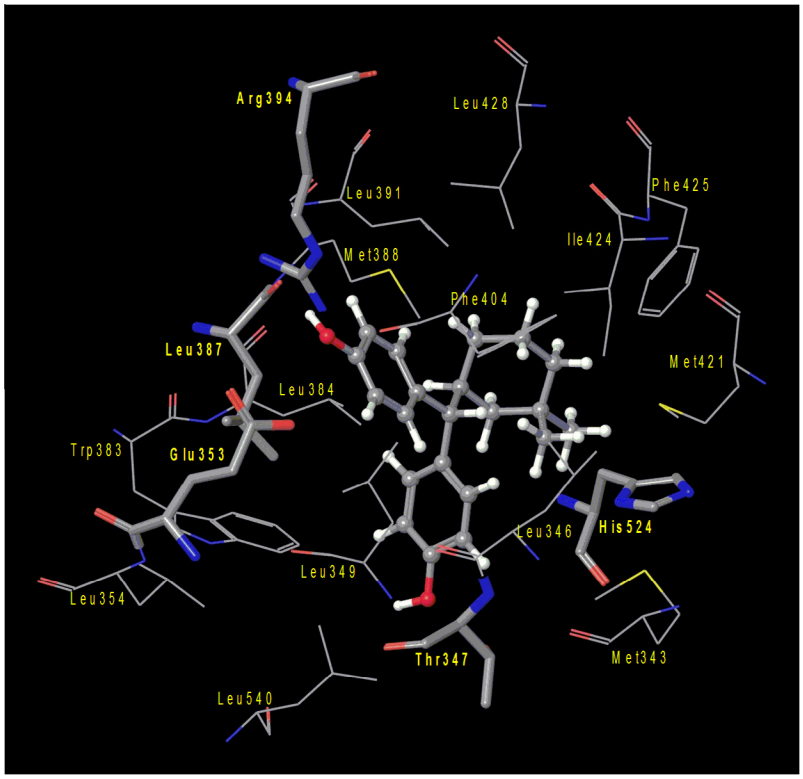


Figure 3. Docking simulation of 5–7 into ERa LBD (1ERE).

3. Conclusion

In this paper, we investigated the influence of structural modification of bis(4-hydroxyphenyl)methanes with cyclic hydrophobic structure on ER binding affinity and agonist/antagonist balance. Among the synthetic compounds, 3,3-disubstituted cyclohexyl derivatives (**7**–**11**) possessed potent ERα binding affinity and agonistic activity, together with weak antagonistic activity at high concentration. This result confirms the importance of hydrophobic structure for binding and modulation of ER activity. Partial agonists with various agonist/antagonist activity balances should be candidates for tissue-selective estrogen receptor modulators. Further structure–function studies of these compounds and their derivatives could lead to the development of more selective and potent estrogen receptor modulators.

4. Experimental section

4.1. General remarks

Melting points were determined with a Yanaco micro melting point apparatus and were not corrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with JEOL JNM-LA-400 spectrometers. Chemical shifts for ^{1}H NMR spectra were referenced to tetramethylsilane (0.0 ppm) as an internal standard. Chemical shifts for ^{13}C NMR spectra were referenced to residual ^{13}C present in deuterated solvents. The splitting patterns are designated as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectra were recorded on a JEOL JMS-DX-303 spectrometer. Elemental analyses were performed with a Perkin Elmer 2400 CHN spectrometer. Column chromatography was carried out using Merck silica gel 60 (0.063–0.200 μm) and TLC was performed on Merck silica gel F254. Carboranes were purchased from Katchem s.r.o. (Prague, Czech Republic). Other reagents were purchased from Wako Pure Chemical Industries, Ltd, Sigma–Aldrich Co., and Tokyo Chemical Industry, Ltd (TCI). All solvents were commercial products of reagent quality, and were used without further purification.

4.2. Synthesis

4.2.1. 1,1′-(Cyclohexylidenemethylene)bis(4-methoxy)benzene (17)

To a suspension of zinc powder (6.30 g, 97.0 mmol) in THF (65 mL) was added dropwise titanium (IV) chloride (5.20 mL, 47.3 mmol) at −10 °C under Ar. The mixture was refluxed with stirring for 18 h. To the reaction mixture was added dropwise a solution of 4,4′-dimethoxybenzophenone (3.10 g, 12.8 mmol) and cyclohexanone (1.30 g, 13.3 mmol) in THF (60 mL). The mixture was refluxed with stirring for 4.5 h, then cooled to room temperature, and poured slowly into saturated aqueous $NaHCO_3$. Et_2O was added to the aqueous solution, and the heterogeneous solution was filtered through Celite. The filtrate was extracted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 20:1) gave **17** (74%). ^{1}H NMR ($CDCl_3$) δ 1.55–1.65 (6H, m), 2.20–2.28 (4H, m), 3.78 (6H, s), 6.80 (4H, ddd, J = 8.8, 2.9, 2.4 Hz), 7.02 (4H, ddd, J = 8.8, 2.9, 2.4 Hz); HRMS Calcd for $C_{21}H_{24}O_2$ 308.1777. Found 308.1785.

4.2.2. 1,1′-(Cyclohexylmethylene)bis(4-methoxy)benzene (19)

A suspension of **17** (92.4 mg, 0.300 mmol) and 10% palladium on carbon (15.9 mg, 0.0150 mmol) in AcOEt (3 mL) was stirring at room temperature under hydrogen gas for 24 h. The mixture was filtered through Celite, and the filtrate was concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 100:1) gave **19** (93%). ^{1}H NMR ($CDCl_3$) δ 0.83 (2H, qua, J = 11.4 Hz), 1.11–1.25 (3H, m), 1.57–1.66 (5H, m), 2.00 (1H, quat, J = 10.6, 3.4 Hz), 3.38 (1H, s, J = 10.6 Hz), 3.75 (6H, s), 6.79 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.16 (4H, ddd, J = 8.7, 2.9, 1.9 Hz); HRMS Calcd for $C_{21}H_{26}O_2$ 310.1934. Found 310.1933.

4.2.3. 4,4′-(Cyclohexylmethylene)bisphenol (1)

To a solution of **19** (9/96.4 mg, 3.21 mmol) in CH_2Cl_2 (10 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (3.90 mL, 3.90 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 48 h, then BBr_3 in CH_2Cl_2 (2.20 mL, 2.20 mmol) was added at 0 °C, and stirring was continued at room temperature for 24 h. The reaction mixture was poured into ice water, and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica column chromatography (eluent: *n*-hexane/AcOEt, 3:1) gave **1** (62%). **1**: white fibrous solid (CH_2Cl_2); mp 228–229 °C; ^{1}H NMR (DMSO-d_6) δ 0.74 (2H, br qua, J = 10.6 Hz), 1.00–1.21 (3H, br m), 1.46 (2H, br d, J = 12.6 Hz), 1.51–1.64 (3H, br m), 1.97 (1H, br qua, J = 10.6 Hz), 3.25 (1H, d, J = 10.6 Hz), 6.61 (4H, d, J = 7.7 Hz), 7.04 (4H, d, J = 7.7 Hz), 9.07 (2H, s); ^{13}C NMR (DMSO-d_6) δ 25.7, 26.1, 29.8, 31.6, 56.8, 115.0, 128.5, 135.5, 155.1; HRMS Calcd for $C_{19}H_{22}O_2$ 282.1621. Found 282.1625; Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found C, 80.76; H, 7.45.

4.2.4. 1,1′-(4,4-Dimethylcyclohexylidenemethylene)bis (4-methoxy)benzene (18)

McMurry coupling of 4,4′-dimethoxybenzophenone and 4,4-dimethylcyclohexanone was performed by the same method as that used for preparation of **17**. Purification by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 40:1) gave **18** (85%). ^{1}H NMR ($CDCl_3$) δ 0.98 (6H, s), 1.37 (4H, t, J = 6.4 Hz), 2.27 (4H, t, J = 6.4 Hz), 3.79 (6H, s), 6.81 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.03 (4H, ddd, J = 8.7, 2.9, 1.9 Hz); HRMS Calcd for $C_{23}H_{28}O_2$ 336.2090. Found 336.2095.

4.2.5. 1,1′-(4,4-Dimethylcyclohexylmethylene)bis(4-methoxy) benzene (20)

Compound **20** was prepared from **18** by the same method as that used for preparation of **19**. Purification by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 100:1) gave **20** (quant). ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, s), 0.87 (3H, s), 1.03 (2H, quad, J = 13.1, 2.8 Hz), 1.14 (2H, td, J = 13.1, 2.8 Hz), 1.32 (2H, d, J = 13.2 Hz), 1.41 (2H, d, J = 13.2 Hz), 1.92 (1H, quat, J = 10.7, 3.4 Hz), 3.40 (1H, d, J = 10.7 Hz), 3.74 (6H, s), 6.79 (4H, ddd, J = 8.8, 2.9, 2.0 Hz), 7.16 (4H, ddd, J = 8.8, 2.9, 2.0 Hz); HRMS Calcd for $C_{23}H_{30}O_2$ 338.2247. Found 338.2247.

4.2.6. 4,4′-[(4,4-Dimethylcyclohexyl)methylene]bisphenol (2)

Deprotection of **18** was performed by the same method as that used for preparation of **1**. Purification by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 2:1) gave **2** (90%). **2**: white needles (Et_2O–*n*-hexane); mp 221 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, s), 0.87 (3H, s), 1.02 (2H, quad, J = 13.0, 2.9 Hz), 1.14 (2H, td, J = 13.0, 2.9 Hz), 1.32 (2H, br d, J = 13.0 Hz), 1.40 (2H, br d, J = 13.0 Hz), 1.89 (1H, quat, J = 11.1, 3.4 Hz), 3.38 (1H, d, J = 11.1 Hz), 4.53 (2H, s), 6.72 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.10 (4H, ddd, J = 8.7, 2.9, 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ 24.4, 27.8, 39.9, 32.7, 39.2, 41.6, 57.5, 115.2, 129.0, 137.3, 153.5; HRMS Calcd for $C_{21}H_{26}O_2$ 310.1934. Found 310.1939; Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found C, 81.28; H, 8.59.

4.2.7. 4-[Bis(4-dimethoxyphenyl)methylene]cyclohexanone (21)

McMurry coupling of 4,4′-dimethoxybenzophenone and 1,4-cyclohexanedione mono-ethylene ketal was performed by the

same method as that used for preparation of **17**. Purification by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 5:1) gave a mixture of ethylene ketal product and deprotected product (98:2, 8.50 g). To a suspension of the mixture (8.50 g) and silica gel (104 g) in CH_2Cl_2 (229 mL) was added 15% aqueous H_2SO_4 (14.8 mL) at room temperature. The mixture was stirred at room temperature for 44 h, then filtered, and the filtrate was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was used for the next reaction. A suspension of the residue (7.00 g) and 10% palladium on carbon (4.60 g, 4.34 mmol) in AcOEt (70 mL) was stirred at room temperature under hydrogen gas for 48 h. The mixture was filtered through Celite, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 3:1) gave **21** (53%, 3 steps). ^{1}H NMR ($CDCl_3$) δ 1.33–1.43 (2H, m), 1.89–1.99 (2H, m), 2.29–2.37 (4H, m), 2.50 (1H, quat, J = 10.7, 3.4 Hz), 3.49 (1H, d, J = 10.7 Hz), 3.76 (6H, s), 6.82 (4H, ddd, J = 8.8, 2.9, 2.0 Hz), 7.20 (4H, ddd, J = 8.8, 2.9, 2.0 Hz). HRMS Calcd for $C_{21}H_{24}O_3$ 324.1726. Found 324.1734.

4.2.8. 4,4′-[(4,4-Difluorocyclohexyl)methylene]bisphenol (3)

To a solution of **21** (0.970 g, 2.99 mmol) in CH_2Cl_2 (30 mL) was added dropwise a 1.0 M solution of BBr_3 in CH_2Cl_2 (12.0 mL, 12.0 mmol) at −60 °C under argon gas. The mixture was stirred at −40 °C for 21 h, then poured into ice water, and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt = 2:1) gave the phenol (61%). ^{1}H NMR (acetone-d_6) δ 1.29 (2H, br quad, J = 12.1, 4.3 Hz), 1.79–1.89 (2H, m), 2.16 (2H, br t, J = 14.5 Hz), 2.30 (2H, br td, J = 13.6, 5.5 Hz), 2.59 (1H, quat, J = 10.6, 3.4 Hz), 3.50 (1H, d, J = 11.1 Hz), 6.71 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.17 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 8.08 (2H, s). HRMS Calcd for $C_{19}H_{20}O_3$ 296.1413. Found 296.1412. To a solution of the crude compound (210 mg, 0.709 mmol) in CH_2Cl_2 (10 mL) was added DAST (0.560 mL, 4.17 mmol) at room temperature under Ar. The mixture was stirred at room temperature for 28 h. To the reaction mixture was added MeOH/H_2O (1:1), and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. The residue was used directly for the next reaction. To a solution of the residue and 97% NMO (337 mg, 2.80 mmol) in acetone/water (4:1, 35 mL) was added 0.1 M OsO_4 in THF (0.350 mL, 0.0350 mmol) at 0 °C. The mixture was stirred at room temperature for 63 h, then $NaHSO_3$ (35.0 mg) was added, and the whole was concentrated. The residue was diluted with Et_2O, and washed with H_2O. The organic layer was extracted with 10% aqueous NaOH. The water layer was acidified with 10% aqueous HCl to pH 1–2, and extracted with Et_2O. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 3:1) gave **3** (50%). **3**: White needles (Et_2O–*n*-hexane); mp 194–195 °C; ^{1}H NMR (DMSO-d_6) δ 1.00–1.09 (2H, m), 1.51 (2H, br d, J = 13.5 Hz), 1.72 (2H, br dt, J = 32.8, 13.4 Hz), 1.90–1.95 (2H, br m), 2.18 (1H, br qua, J = 9.7 Hz), 3.36 (1H, d, J = 11.1 Hz), 6.62 (4H, d, J = 8.7 Hz), 7.08 (4H, d, J = 8.7 Hz), 9.12 (2H, s); ^{13}C NMR ($CDCl_3$) δ 27.9, 33.5, 39.8, 56.3, 115.4, 123.7, 128.8, 136.4, 153.9; HRMS Calcd for $C_{19}H_{20}F_2O_2$ 318.1432. Found 318.1428; Anal. Calcd for $C_{19}H_{20}F_2O_2$: C, 71.68; H, 6.33. Found C, 71.49; H, 6.34.

4.2.9. 4,4′-[(4,4-Dichlorocyclohexyl)methylene]bisphenol (4)

Compound **21** was deprotected by the same method as that used for preparation of **3**. A suspension of the phenol (0.940 g, 3.17 mmol), benzyl bromide (0.830 mL, 6.80 mmol) and K_2CO_3 (1.30 g, 9.42 mmol) in acetone (64 mL) was refluxed with stirring for 31 h under Ar, then cooled to room temperature, and filtered. The filtrate was concentrated. The residue was dissolved in CH_2Cl_2, and this solution was washed with H_2O and brine, dried over Na_2SO_4, and concentrated. Purification by trituration (*n*-hexane) gave the benzyl-protected product (86%). ^{1}H NMR ($CDCl_3$) δ 1.33–1.43 (2H, m), 1.94 (2H, br d, J = 12.2 Hz), 2.27–2.35 (4H, m), 2.49 (1H, quat, J = 10.7, 2.5 Hz), 3.49 (1H, d, J = 10.7 Hz), 5.01 (4H, s), 6.90 (4H, ddd, J = 8.8, 2.9, 2.0 Hz), 7.20 (4H, ddd, J = 8.8, 2.9, 2.0 Hz), 7.29–7.42 (10H, m); HRMS Calcd for $C_{33}H_{32}O_3$ 476.2353. Found 476.2348. To a suspension of active MS4A (2.80 g) in MeOH (14 mL) was added hydrazine monohydrate (2.80 mL, 57.7 mmol) at room temperature under argon gas. After 1 h, a solution of the benzyl-protected compound (1.30 g, 2.75 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was stirred at room temperature for 2 h, then filtered, and concentrated. Excess hydrazine was further removed from the residue under vacuum (1–2 Torr) with heating at 30 °C for 4 h. The residue was used for the next reaction. To a solution of $CuCl_2$ (2.20 g, 16.5 mmol) in MeOH (17 mL) was added Et_3N (1.20 mL, 8.26 mmol) with stirring at room temperature. After 30 min, a solution of the residue in CH_2Cl_2 (10 mL) was added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 4 h, then 28% aqueous NH_3 was added. The whole was extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 300:1) gave the dichloro product (32%, 2 steps). ^{1}H NMR ($CDCl_3$) δ 1.40 (2H, br quad, J = 12.7, 3.4 Hz) 1.60 (2H, br d, J = 11.6 Hz), 2.02–2.18 (3H, br m), 2.47 (2H, br d, J = 13.5 Hz), 3.43 (1H, d, J = 11.1 Hz), 5.00 (4H, s), 6.88 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.16 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.32–7.39 (10H, m); HRMS Calcd for $C_{33}H_{32}{}^{35}Cl_2O_2$ 530.1781. Found 530.1770. To a solution of the compound (210 mg, 0.395 mmol) in CH_2Cl_2 (4 mL) was added dropwise a 1.0 M solution of BCl_3 in CH_2Cl_2 (0.800 mL, 0.800 mmol) at 0 °C. The mixture was stirred at room temperature for 19 h, then poured into ice water, and the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography (eluent: CH_2Cl_2/AcOEt, 25:1) gave **4** (78%). **4**: white plates (toluene); mp 77–78 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (2H, br qua, J = 12.2 Hz), 1.47 (2H, br d, J = 11.6 Hz), 2.19 (3H, br t, J = 11.3 Hz), 2.38 (2H, br d, J = 13.5 Hz), 3.34 (1H, d, J = 7.7 Hz), 6.62 (4H, d, J = 8.7 Hz), 7.07 (4H, d, J = 8.7 Hz), 9.11 (2H, s); ^{13}C NMR ($CDCl_3$) δ 29.1, 39.8, 45.9, 56.6, 91.6, 115.4, 128.8, 136.3, 153.9; HRMS Calcd for $C_{19}H_{20}{}^{35}Cl_2O_2$ 350.0842. Found 350.0838; Anal. Calcd for $C_{19}H_{20}Cl_2O_2 \cdot 1/2C_7H_8$: C, 68.01; H, 6.09. Found: C, 67.66; H, 6.23.

4.2.10. 4,4′-[(4,4-Dibromocyclohexyl)methylene]bisphenol (5)

To a solution of **21** (1.30 g, 4.01 mmol) and 2,3-dihydroxynaphthalene (1.90 g, 12.0 mmol) in CH_2Cl_2 (40 mL) was added 47% $BF_3 \cdot OEt_2$ in Et_2O (0.400 mL, 1.30 mmol) and TMSCl (1.20 mL, 9.47 mmol) at 0 °C. The mixture was stirred at room temperature for 9 h, then MeOH (2 mL) was added at 0 °C. The whole was washed with 10% aqueous NaOH, H_2O, and brine, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 10:1) gave the 2,3-dihydroxynaphthalene ketal product (75%). ^{1}H NMR ($CDCl_3$) δ 1.42 (2H, br qua, J = 13.2 Hz), 1.73 (2H, br d, J = 13.7 Hz), 1.82 (2H, td, J = 13.2, 3.9 Hz), 2.09 (2H, br d, J = 12.2 Hz), 2.16 (1H, quat, J = 10.7, 3.4 Hz) 3.52 (1H, d, J = 10.7 Hz), 3.76 (6H, s), 6.82 (4H, d, J = 8.8 Hz), 7.01 (2H, d, J = 7.3 Hz), 7.21 (4H, d, J = 8.8 Hz), 7.27–7.29 (2H, m), 7.62 (2H, dt, J = 6.3, 2.9 Hz); HRMS Calcd for $C_{31}H_{30}O_4$ 466.2145. Found 466.2138. To a solution of this compound (34.0 mg, 0.0730 mmol) in CH_2Cl_2 (1 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (0.560 mL, 0.560 mmol) at −60 °C. The mixture was stirred at −40 °C for 7 days, then poured

into ice water, and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 1:1) gave **5** (81%). **5**: colorless needles (toluene); mp 93–94 °C; ^{1}H NMR ($CDCl_3$) δ 1.38–1.49 (4H, m), 2.09 (1H, quat, J = 10.6, 4.3 Hz), 2.33 (2H, td, J = 15.0, 3.9 Hz), 2.65 (2H, br d, J = 13.0 Hz), 3.42 (1H, d, J = 11.1 Hz), 4.61 (1H, s), 4.62 (1H, s), 6.73 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.10 (4H, ddd, J = 8.7, 2.9, 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ 30.2, 39.8, 49.0, 56.7, 71.5, 115.4, 128.8, 136.2, 153.8; HRMS Calcd for $C_{19}H_{20}{}^{78}Br_2O_2$ 437.9831. Found: 437.9817; Anal. Calcd for $C_{19}H_{20}Br_2O_2{\cdot}1.0C_7H_8$: C, 58.67; H, 5.30. Found: C, 58.49; H, 5.31.

4.2.11. 4-[Bis(4-hydroxyphenyl)methylene]cyclohexanone ethylene ketal (6)

McMurry coupling of 4,4′-dihydroxybenzophenone and 1,4-cyclohexanedione mono-ethylene ketal was performed by the same method as that used for preparation of **17**. Purification by silica gel column chromatography (eluent: $CHCl_3$/AcOEt, 2:1) gave the product (69%). ^{1}H NMR ($CDCl_3$) δ 1.71 (4H, br t, J = 6.3 Hz), 2.39 (4H, br t, J = 6.3 Hz), 3.97 (4H, s), 4.69 (2H, s), 6.74 (4H, ddd, J = 8.3, 2.9, 2.0 Hz), 6.97 (4H, ddd, J = 8.3, 2.9, 2.0 Hz); HRMS Calcd for $C_{21}H_{22}O_4$ 338.1519. Found 338.1517. This compound was reduced by the same method as that used for preparation of **19** to give the hydrogenated product. Purification by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 3:1) gave **6** (quant). **6**: white columns (Et_2O–*n*-hexane); mp 230–231 °C; ^{1}H NMR (acetone-d_6) δ 0.97–1.08 (2H, m), 1.32 (2H, td, J = 12.8, 3.9 Hz), 1.42 (2H, br d, J = 13.5 Hz), 1.51 (2H, br d, J = 12.6 Hz), 2.00 (1H, quat, J = 11.1, 3.4 Hz), 3.26 (1H, d, J = 10.6 Hz), 3.72 (4H, s), 6.59 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.02 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.90 (2H, s); ^{13}C NMR (DMSO-d_6) δ 28.7, 30.7, 33.8, 55.8, 63.5, 108.2, 115.0, 128.5, 135.5, 155.2; HRMS Calcd for $C_{21}H_{24}O_4$ 340.1675. Found 340.1675; Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found C, 74.41; H, 7.13.

4.2.12. 1,1′-(3,3-Dimethylcyclohexylidenemethylene)bis(4-methoxy)benzene (22)

To a suspension of zinc powder (1.50 g, 23.1 mmol) in THF (15 mL) was added dropwise titanium(IV) chloride (1.20 mL, 10.9 mmol) at −10 °C under Ar. The mixture was refluxed with stirring for 3 h, and a solution of 4,4′-dimethoxybenzophenone (726 mg, 3.00 mmol) and 3,3-dimethylcyclohexanone (0.420 mL, 3.03 mmol) in THF (13 mL) was added dropwise. The mixture was refluxed with stirring for 2 h. The reaction mixture was cooled to room temperature, and poured slowly into saturated aqueous $NaHCO_3$. Et_2O was added to the aqueous solution, and the heterogeneous mixture was filtered through Celite. The filtrate was extracted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 40:1) gave **22** (90%). ^{1}H NMR ($CDCl_3$) δ 0.86 (6H, s), 1.39 (2H, t, J = 6.1 Hz), 1.58–1.64 (2H, m), 2.00 (2H, s), 2.18 (2H, t, J = 6.3 Hz), 3.776 (3H,s), 3.781 (3H, s), 6.77–6.83 (4H, m), 7.00 (2H, d, J = 8.8 Hz), 7.04 (2H, d, J = 8.8 Hz); HRMS Calcd for $C_{23}H_{28}O_2$ 336.2090. Found 336.2083.

4.2.13. 1,1′-(3,3-Dimethylcyclohexylmethylene)bis(4-methoxy)benzene (24)

To a solution of the above compound (67.0 mg, 0.183 mmol) in CH_2Cl_2 (1.6 mL) was added 57% aqueous hydriodic acid (1.60 mL, 7.13 mmol). The mixture was refluxed with stirring for 24 h, then cooled to room temperature, washed with aqueous $Na_2S_2O_3$, and brine, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 100:1) gave **24** (11%). ^{1}H NMR ($CDCl_3$) δ 0.70 (2H, td, J = 12.4, 3.7 Hz), 0.81 (3H, s), 0.9 (s, 3H), 1.05 (1H, td, J = 13.2, 4.5 Hz), 1.25–1.41 (5H, m), 2.19 (1H, qua, J = 11.1 Hz), 3.30 (1H, d, J = 10.6 Hz), 3.75 (3H, s), 3.76 (3H, s), 6.78 (2H, d, J = 8.7 Hz), 6.80 (2H, d, J = 8.7 Hz), 7.14 (4H, d, J = 8.7 Hz); HRMS Calcd for $C_{23}H_{30}O_2$ 338.2247. Found 338.2234.

4.2.14. 4,4′-[(3,3-Dimethylcyclohexyl)methylene]bisphenol (7)

To a solution of **24** (200 mg, 0.592 mmol) in CH_2Cl_2 (5 mL) was added dropwise a 1.0 M solution of BBr_3 in CH_2Cl_2 (1.20 mL, 1.20 mmol) at 0 °C under argon gas. The mixture was stirred at room temperature for 9 h, then poured into ice water, and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 1:1) gave **7** (quant). **7**: white leaflets (Et_2O–*n*-hexane); mp 192–193 °C; ^{1}H NMR (acetone-d_6) δ 0.61–0.73 (2H, m), 0.79 (3H, s), 0.90 (3H, s), 1.06 (1H, td, J = 12.9, 5.0 Hz), 1.25–1.60 (5H, m), 2.26 (1H, quat, J = 11.4, 2.9 Hz), 3.26 (1H, d, J = 10.6 Hz), 6.69–6.71 (4H, m), 7.10–7.12 (4H, m), 8.01, (1H, s), 8.03 (1H, s); ^{13}C NMR (acetone-d_6) δ 23.1, 25.0, 31.5, 32.8, 33.9, 38.0, 40.0, 46.0, 58.9, 115.8, 115.9, 129.6, 136.9, 137.2, 156.2; HRMS Calcd for $C_{21}H_{26}O_2$ 310.1934. Found 310.1939; Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found C, 81.19; H, 8.36.

4.2.15. 1,1′-(3,3,5,5-Tetramethylcyclohexylidenemethylene)bis(4-methoxy)benzene (23)

McMurry coupling of 4,4′-dimethoxybenzophenone and 3,3,5,5-tetramethylcyclohexanone was performed by the same method as that used for preparation of **22**. Purification by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 40:1) gave **23** (83%). ^{1}H NMR ($CDCl_3$) δ 0.93 (12H, s), 1.28 (2H, s), 1.98 (4H, s), 3.78 (3H, s), 3.79 (3H, s), 6.80 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.07 (4H, ddd, J = 8.7, 2.9, 1.9 Hz); HRMS Calcd for $C_{25}H_{32}O_2$ 364.2404. Found 364.2397.

4.2.16. 1,1′-(3,3,5,5-Tetramethylcyclohexylmethylene)bis(4-methoxy)benzene (25)

Compound **25** was prepared from 200 mg of **23** by the same method as that used for preparation of **24**. Purification by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 80:1) gave **25** (48%). ^{1}H NMR ($CDCl_3$) δ 0.63 (1H, d, J = 12.6 Hz), 0.66 (1H, d, J = 12.6 Hz), 0.80 (6H, s), 0.99 (6H, s), 1.00 (1H, d, J = 13.0 Hz), 1.23 (1H, d, J = 14.0 Hz), 1.33 (2H, d, J = 13.0 Hz), 2.40 (1H, quat, J = 10.6, 2.9 Hz), 3.33 (1H, d, J = 10.6 Hz), 3.79 (6H, s), 6.80 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.14 (4H, ddd, J = 8.7, 2.9, 1.9 Hz); HRMS Calcd for $C_{25}H_{34}O_2$ 366.2560. Found 366.2563.

4.2.17. 4,4′-[(3,3,5,5-Tetramethylcyclohexyl)methylene]bisphenol (12)

Compound **12** was prepared from 200 mg of **25** by the same method as that used for preparation of **7**. Purification by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 2:1) gave **12** (96%). **12**: white lamellar solid (Et_2O–*n*-hexane); mp 203 °C; ^{1}H NMR ($CDCl_3$) δ 0.62 (1H, d, J = 12.6 Hz), 0.65 (1H, d, J = 12.6 Hz), 0.80 (6H, s), 0.98 (6H, s), 1.00 (1H, d, J = 12.6 Hz), 1.23 (1H, d, J = 13.5 Hz), 1.31 (2H, d, J = 12.6 Hz), 2.36 (1H, quat, J = 10.6, 2.4 Hz), 3.30 (1H, d, J = 10.6 Hz), 4.53 (2H, s), 6.72 (4H, ddd, J = 8.2, 2.9, 1.9 Hz), 7.09 (4H, ddd, J = 8.2, 2.9, 1.9 Hz); ^{13}C NMR ($CDCl_3$) δ 27.4, 31.7, 34.3, 35.4, 45.2, 52.4, 57.5, 115.3, 128.9, 137.4, 153.5; HRMS Calcd for $C_{24}H_{30}O_2$ 338.2247. Found 338.2234; Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.62; H, 8.93. Found C, 81.60; H, 9.05.

4.2.18. 3-[Bis(4-hydroxyphenyl)methylene]cyclohexanone (26)

McMurry coupling of 4,4′-dihydroxybenzophenone and 1,3-cyclohexanedione mono-ethylene ketal was performed by the same method as that used for preparation of **22**. Purification by

silica gel column chromatography (eluent: *n*-hexane/AcOEt, from 3:1 to 2:1) gave the methylene product (45%). ^{1}H NMR ($CDCl_3$) δ 1.62–1.68 (2H, m), 1.77 (2H, t, J = 5.8 Hz), 2.25 (2H, t, J = 5.8 Hz), 2.41 (2H, s), 3.82–3.94 (4H, m), 4.79 (2H, s), 6.73 (4H, d, J = 8.7 Hz), 6.98 (2H, d, J = 8.7 Hz), 7.05 (2H, d, J = 8.7 Hz); HRMS Calcd for $C_{21}H_{22}O_4$ 338.1519. Found 338.1522. To a solution of this compound (1.92 g, 5.68 mmol) in acetone (30 mL) was added 1.0 M aqueous HCl (0.290 mL, 0.290 mmol) at 0 °C. The mixture was stirred at room temperature for 48 h, then saturated aqueous $NaHCO_3$ and H_2O were added, and acetone was removed. The residue was extracted with AcOEt, and the organic solution was washed with brine, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography (eluent: *n*-hexane/AcOEt, from 2:1 to 1:1) gave the unsaturated ketone product (74%). ^{1}H NMR (DMSO-d_6) δ 1.84 (2H, qua, J = 6.3 Hz), 2.21 (2H, t, J = 5.8 Hz), 2.26 (2H, t, J = 6.5 Hz), 4.79 (1H, s), 5.35 (1H, s), 6.69 (4H, d, J = 8.2 Hz), 6.91 (4H, d, J = 8.2 Hz), 9.31 (2H, s); HRMS Calcd for $C_{19}H_{18}O_3$ 294.1256. Found 294.1245. A suspension of this compound (30 mg, 0.102 mmol) and 10% palladium on carbon (5.02 mg, 4.74 μmol) in EtOH (1 mL) was stirred at room temperature under hydrogen gas for 48 h, then filtered through Celite, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 2:1) gave **26** (88%). ^{1}H NMR (acetone-d_6) δ 1.25–1.37 (1H, m), 1.57 (1H, quat, J = 12.2, 4.1 Hz), 1.72–1.82 (1H, m), 1.91–1.99 (2H, m), 2.11–2.23 (2H, m), 2.28 (1H, td, J = 13.2, 5.6 Hz), 2.57 (1H, quat, J = 10.8, 3.6 Hz), 3.54 (1H, d, J = 10.6 Hz), 6.72 (2H, d, J = 8.2 Hz), 6.74 (2H, d, J = 8.2 Hz), 7.13 (2H, ddd, J = 8.2, 2.9, 1.9 Hz), 7.18 (2H, ddd, J = 8.2, 2.9, 1.9 Hz), 8.11 (1H, s), 8.12 (1H, s). HRMS Calcd for $C_{29}H_{20}O_3$ 296.1413. Found 296.1410.

4.2.19. 4,4′-[(3,3-Difluorocyclohexyl)methylene]bisphenol (8)

To a solution of **26** (296 mg, 1.00 mmol) in CH_2Cl_2 was added DAST (0.780 mL, 5.81 mmol) at 0 °C. The mixture was stirred at room temperature for 22 h, then MeOH/H_2O (1:1) was added at 0 °C, and the whole was extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 3:1) and recrystallization (Et_2O–*n*-hexane) gave **8** (46%). **8**: white lamellar solid (Et_2O–*n*-hexane); mp 194–195 °C; ^{1}H NMR (actone-d_6) δ 0.93 (1H, qua, J = 12.9 Hz), 1.26–1.50 (2H, m), 1.55–1.79 (3H, m), 1.83–1.98 (2H, m), 2.38 (1H, qua, J = 11.1 Hz), 3.46 (1H, d, J = 11.1 Hz), 6.73 (2H, d, J = 8.2 Hz), 6.74 (2H, d, J = 8.2 Hz), 7.14 (2H, d, J = 8.2 Hz), 7.16 (2H, d, J = 8.2 Hz), 8.07 (1H, s), 8.09 (1H, s); ^{13}C NMR (acetone-d_6) δ 22.7, 30.5, 34.3, 39.8, 40.0, 57.5, 116.0, 116.1, 125.2, 129.6, 135.8, 136.2, 156.5, 156.5; HRMS Calcd for $C_{19}H_{20}F_2O_2$ 318.1432. Found 318.1429; Anal. Calcd for $C_{19}H_{20}F_2O_2$: C, 71.68; H, 6.33. Found C, 71.71; H, 6.22.

4.2.20. 4,4′-[(3,3-Dichlorocyclohexyl)methylene]bisphenol (9)

Compound **26** was converted to the benzyl ether by the same method as used for preparation of **4**. Purification by trituration with Et_2O gave the benzyl-protected product (70%). ^{1}H NMR ($CDCl_3$) δ 1.29 (1H, br qua, J = 12.1 Hz), 1.61 (1H, quat, J = 12.1, 3.9 Hz), 1.82 (1H, br d, J = 13.0 Hz), 1.91–2.03 (2H, m), 2.21–2.37 (3H, m), 2.53 (1H, quat, J = 11.1, 3.1 Hz), 3.53 (1H, d, J = 10.6 Hz), 4.99 (2H, s), 5.00 (2H, s), 6.86 (2H, d, J = 8.7 Hz), 6.89 (2H, d, J = 8.7 Hz), 7.12 (2H, d, J = 8.7 Hz), 7.16 (2H, d, J = 8.7 Hz), 7.29–7.41 (10H, m); HRMS Calcd for $C_{33}H_{32}O_3$ 476.2353. Found 476.2350. The benzyl ether was converted to the dichloro product by the same method as that used for preparation of **4**. Purification by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 20:1) gave the dichloro product (11%, 2 steps). ^{1}H NMR ($CDCl_3$) 0.81–0.91 (1H, m), 1.59–1.75 (4H, m), 2.00–2.08 (1H, m), 2.52–2.58 (3H, m), 3.42 (1H, d, J = 10.6 Hz), 5.00 (2H, s), 5.02 (2H, s), 6.88 (2H, d, J = 8.7 Hz), 6.91 (2H, d, J = 8.7 Hz), 7.12 (2H, d, J = 8.7 Hz), 7.16 (2H, d, J = 8.2 Hz), 7.29–7.43 (10H, m); HRMS Calcd for $C_{33}H_{32}{}^{35}Cl_2O_2$ 530.1782 Found 530.1794. To a solution of the dichloro product (49.8 mg, 0.0938 mmol) in CH_2Cl_2 (1 mL) was added dropwise a 1.0 M solution of BCl_3 in CH_2Cl_2 (0.200 mL, 0.200 mmol) at 0 °C. The mixture was stirred at room temperature for 110 h, then poured into ice water, and the whole was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography (eluent: CH_2Cl_2/AcOEt, 3:1) gave **9** (59%). **9**: white leaflets (toluene); mp 77–78; ^{1}H NMR ($CDCl_3$) δ 0.80–0.90 (1H, m), 1.60–1.74 (4H, m), 2.00–2.08 (1H, m), 2.50–2.57 (3H, m), 3.39 (1H, d, J = 10.6 Hz), 4.61 (1H, s), 4.64 (1H, s), 6.73 (2H, ddd, J = 8.7, 2.9, 1.9 Hz), 6.76 (2H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.09 (2H, d, J = 8.2 Hz), 7.11 (2H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 23.5, 30.1, 39.2, 46.2, 51.3, 56.5, 91.9, 115.4, 115.6, 125.3, 128.2, 128.87, 128.90, 129.0, 135.4, 136.1, 153.85, 153.92; HRMS Calcd for $C_{19}H_{20}{}^{35}Cl_2O_2$ 350.0842. Found: 350.0833; Anal. Calcd for $C_{19}H_{20}Cl_2O_2{\cdot}C_7H_8$: C, 70.43; H, 6.36. Found: C,70.63; H, 6.50.

4.2.21. 3-[Bis(4-hydroxyphenyl)methylene]cyclohexanone trimethylenethioketal (10)

To a solution of **26** (116 mg, 0.392 mmol) and 1,3-propanedithiol (82.0 μL, 0.820 mmol) in CH_2Cl_2 (4 mL) was added dropwise 47% $BF_3{\cdot}OEt_2$ in Et_2O (351 μL, 1.17 mmol) at 0 °C under argon gas. The mixture was stirred at room temperature for 2.5 h, then poured into saturated aqueous $NaHCO_3$, and extracted with Et_2O. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 2:1) gave **10** (78%). **10**: white fibrous solid (toluene); mp 86–87 °C; ^{1}H NMR ($CDCl_3$) δ 0.82 (1H, quad, J = 12.1, 3.9 Hz), 1.17–1.24 (1H, m), 1.52–1.62 (3H, m), 1.72 (1H, quat, J = 13.0, 2.9 Hz), 1.89–1.94 (2H, m), 2.26 (1H, d, J = 12.1 Hz), 2.34 (1H, dd, J = 13.5, 1.9 Hz), 2.49–2.62 (2H, m), 2.67–2.75 (3H, m), 3.35 (1H, d, J = 11.1 Hz), 4.60 (1H, s), 4.62 (1H, s), 6.72 (2H, d, J = 8.7 Hz), 6.75 (2H, d, J = 8.7 Hz), 7.10 (2H, d, J = 8.7 Hz), 7.14 (2H, d, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 21.9, 25.8, 26.0, 26.1, 31.6, 37.2, 38.0, 42.8, 50.6, 57.0, 115.3, 115.5, 128.6, 128.9, 136.4, 136.6, 153.68, 153.71; HRMS Calcd for $C_{22}H_{26}O_2S_2$ 386.1376. Found 386.1377; Anal. Calcd for $C_{22}H_{26}O_2S_2{\cdot}1/2H_2O$: C, 66.80; H, 6.75. Found: C, 66.88; H, 6.91.

4.2.22. Spiro[5,5]undecane-2-carboxaldehyde (28)

To a solution of DMF (0.800 mL, 10.4 mmol) in CH_2Cl_2 (9 mL) was added $POCl_3$ (0.860 mL, 8.99 mmol) at 0 °C under argon gas. The mixture was stirred at room temperature for 1 h, then a solution of **27** (1.10 g, 6.63 mmol) in CH_2Cl_2 (9 mL) was added at 0 °C. Stirring was continued at room temperature for 20 h, then saturated aqueous $NaHCO_3$ was added, and the whole was extracted with AcOEt. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 60:1) gave the formylate product (67%). ^{1}H NMR ($CDCl_3$) δ 1.23–1.45 (10H, m), 1.60 (2H, t, J = 6.6 Hz), 2.14 (2H, t, J = 2.2 Hz), 2.57 (2H, tt, J = 6.6, 2.2 Hz), 10.2 (1H, s); HRMS Calcd for $C_{12}H_{17}{}^{35}ClO$ 212.0969 (100%), $C_{12}H_{17}{}^{37}ClO$ 214.0939 (33%). Found 212.0968 (33%), 214.0927 (11%). To a suspension of this compound (986 mg, 4.65 mmol) and 10% palladium on carbon (247 mg, 0.233 mmol) in EtOH (18 mL) was added Et_3N (1.4 mL, 10.1 mmol) at room temperature. The mixture was stirred at room temperature under hydrogen gas for 24 h, then filtered through Celite, and concentrated. The residue was dissolved in H_2O and extracted with AcOEt. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 80:1) gave **28** (84%). ^{1}H NMR ($CDCl_3$) δ 0.98 (1H, td, J = 13.0, 3.9 Hz), 1.01 (1H, t,

J = 13.0 Hz), 1.15–1.27 (2H, m), 1.34–1.51 (10H, m), 1.57–1.70 (2H, m), 1.84 (1H, dt, *J* = 13.0, 1.4 Hz), 1.90 (1H, dqui, *J* = 13.0, 1.4 Hz), 2.38 (1H, ttd, *J* = 12.3, 3.9, 1.4 Hz), 9.59 (1H, d, *J* = 1.4 Hz); HRMS Calcd for $C_{12}H_{20}O$ 180.1515. Found 180.1508.

4.2.23. 4,4′-[(Spiro[5,5]undecan-2-yl)methylene]bisphenol (11)

To a solution of **28** (700 mg, 3.89 mmol) in phenol (2.90 g, 30.9 mmol) was added H_2SO_4 (0.100 mL, 1.88 mmol) at 70 °C. The mixture was heated with stirring at the same temperature for 19 h, and then saturated aqueous $NaHCO_3$ was added. The whole was extracted with AcOEt. The organic solution was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by crystallization ($CHCl_3$, −25 °C), trituration ($CHCl_3$), and silica gel column chromatography (eluent: *n*-hexane/AcOEt, from 10:1 to 4:1) gave **11** (32%). **11**: white leaflets (Et_2O); mp 228 °C; ^{1}H NMR ($CDCl_3$) δ 0.54 (1H, t, *J* = 12.6 Hz), 0.71 (1H, quad, *J* = 12.6, 4.3 Hz), 0.88 (1H, td, *J* = 13.0, 4.3 Hz), 1.04–1.16 (2H, m), 1.21–1.47 (10H, m), 1.52 (1H, br d, *J* = 11.6 Hz), 1.56 (1H, br d, *J* = 13.0 Hz), 1.63 (1H, br d, *J* = 12.6 Hz), 2.16 (1H, quat, *J* = 11.1, 3.1 Hz), 3.26 (1H, d, *J* = 10.6 Hz), 4.70 (2H, s), 6.70 (2H, ddd, *J* = 8.7, 2.9, 1.9 Hz), 6.73 (2H, ddd, *J* = 8.7, 2.9, 1.9 Hz), 7.06–7.10 (4H, m); ^{13}C NMR (acetone-d_6) δ 22.2, 22.3, 33.2, 33.4, 33.9, 37.0, 37.8, 43.0, 43.6, 59.0, 115.8, 115.9, 129.5, 129.6, 137.1, 137.3, 156.2; HRMS Calcd for $C_{24}H_{30}O_2$ 350.2247. Found 350.2255; Anal. Calcd for $C_{24}H_{30}O_2$: C, 82.24; H, 8.63. Found C, 82.17; H, 8.73.

4.2.24. 4,4′-(Cyclopentylmethylene)bis(4-methoxy)phenol (29)

To a solution of cyclohexene oxide (2.0 g, 20.4 mmol) and anisole (5 mL) was added boron trifluoride ether complex (7.24 g, 50.9 mmol) at −78 °C. The mixture was stirred for 12 h at 50 °C, then cooled, poured into water, and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography with 1:25 to 1:15 AcOEt/*n*-hexane to give **29** (22%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.05–1.20 (m, 2H), 1.45–1.70 (m, 6H), 2.59 (m, 1H), 3.47 (d, *J* = 11.2 Hz, 1H), 3.73 (s, 6H), 6.78 (d, *J* = 8.7 Hz, 4H), 7.17 (d, *J* = 8.6 Hz, 4H); HRMS Calcd for $C_{20}H_{24}O_2$ 296.1776. Found: 296.1757.

4.2.25. 4,4′-(Cyclopentylmethylene)bisphenol (13)

To a solution of **25** (0.35 g, 1.18 mmol) in CH_2Cl_2 (3 mL) was added a 1 M solution of BBr_3 in CH_2Cl_2 (2.9 mL, 2.90 mmol) at −78 °C. The mixture was stirred at room temperature for 1 h, then poured onto ice, and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography with 1:3 to 1:1 AcOEt/*n*-hexane to give **13** (92%). Colorless needles (AcOEt–hexane) mp 190.0–191.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.05–1.20 (m, 2H), 1.45–1.70 (m, 6H), 2.56 (m, 1H), 3.44 (d, *J* = 11.2 Hz, 1H), 4.61 (s, 2H), 6.71 (d, *J* = 8.6 Hz, 4H), 7.11 (d, *J* = 8.6 Hz, 4H); ^{1}HRMS Calcd for $C_{18}H_{20}O_2$: 268.1463. Found: 268.1450: Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found C, 80.28; H, 7.48.

4.2.26. [Bis(4-(*tert*-butyldimethyl)siloxyphenyl)](1,12-dicarba-*closo*-dodecarboran-1-yl)methanol (30)

To a solution of 1,12-dicarbora-*closo*-dodecaborane (72.0 mg, 0.500 mmol) in Et_2O (1 mL) was added a 2.56 M solution of *n*-BuLi in *n*-hexane (0.210 mL, 0.538 mmol) at 0 °C under argon gas. The mixture was stirred at room temperature for 30 min. To the reaction mixture was added dropwise a solution of 4,4′-di(*tert*-butyl)(dimethyl)siloxybenzophenone (243 mg, 0.548 mmol) in Et_2O (1.5 mL) at −30 °C for 30 min. Stirring was continued at the same temperature for 30 min, and then saturated aqueous NH_4Cl was added dropwise at the same temperature. The resulting suspension was stirred at 0 °C, and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 40:1) gave **30** (58%). ^{1}H NMR ($CDCl_3$) δ 0.18 (12H, s), 0.97 (18H, s), 2.65 (1H, s), 2.79 (1H, s), 1.36–3.02 (10H, br m), 6.74 (4H, d, *J* = 8.7 Hz), 7.46 (4H, d, *J* = 8.7 Hz); HRMS Calcd for $C_{27}H_{50}{}^{10}B_2{}^{11}B_8O_3Si_2$ 586.4304. Found 586.4297.

4.2.27. 4,4′-[(1,12-Dicarba-*closo*-dodecaboran-1-yl)methylene] bisphenol (14)

To a solution of **30** (169 mg, 0.288 mmol) and Et_3SiH (0.160 mL, 1.01 mmol) in CH_2Cl_2 (3 mL) was added dropwise 47% $BF_3{\cdot}OEt_2$ in Et_2O (0.300 mL, 0.993 mmol) at 0 °C under argon gas. The reaction mixture was stirred at room temperature for 23 h, and then 47% $BF_3{\cdot}OEt_2$ in Et_2O (0.300 mL, 0.993 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 24 h, then poured into saturated aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/AcOEt, 3:1) gave **14** (88%). **14**: white plates (Et_2O); mp 259–260 °C; ^{1}H NMR ($CDCl_3$) δ 1.42–3.67 (10H, br m), 2.67 (1H, s), 3.98 (1H, s), 4.86 (2H, s), 6.72 (4H, d, *J* = 8.7 Hz), 7.13 (4H, d, *J* = 8.7 Hz). ^{13}C NMR (CD_3OD) δ 60.0, 61.5, 92.0, 115.8, 131.2, 134.0, 157.4; HRMS Calcd for $C_{15}H_{22}{}^{10}B_2{}^{11}B_8O_2$:342.2624. Found: 342.2616; Anal. Calcd for $C_{15}H_{22}B_{10}O_2$: C, 52.61; H, 6.48. Found C, 52.52; H, 6.44.

4.2.28. [Bis(4-(*tert*-butyldimethyl)siloxyphenyl)](1,7-dicarba-*closo*-dodecarboran-1-yl)methanol (31)

Compound **31** was prepared from 1,7-dicarba-*closo*-dodecaborane by the same method as that used for preparation of **30**. Purification by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 60:1) gave a mixture of **31** and bis(4-(*tert*-butyldimethyl)siloxyphenyl)ketone (98:2, 1.96 g). ^{1}H NMR ($CDCl_3$) δ 0.19 (12H, s), 0.97 (18H, s), 2.76 (1H, br s), 2.85 (1H, s), 1.62–2.85 (10H, br m), 6.78 (4H, ddd, *J* = 8.8, 3.4, 2.0 Hz), 7.57 (4H, ddd, *J* = 8.8, 3.4, 2.0 Hz); HRMS Calcd for $C_{27}H_{50}{}^{10}B_2{}^{11}B_8O_3Si_2$ 586.4304. Found 586.4297.

4.2.29. 4,4′-[(1,7-Dicarba-*closo*-dodecaboran-1-yl)methylene] bisphenol (15)

Compound **15** was prepared from **31** by the same method as that used for preparation of **14**. Purification by trituration with $CHCl_3$ gave **15** (57%, 2 steps). **15**: white lamellar solid (Et_2O); mp 221–222 °C; ^{1}H NMR (CD_3OD) δ 1.06–2.97 (10H, br m), 3.33 (1H, br s), 4.35 (1H, s), 6.70 (4H, d, *J* = 8.7 Hz), 7.24 (4H, d, *J* = 8.7 Hz).

^{13}C NMR (CD_3OD) δ 56.4, 58.4, 84.5, 116.0, 131.4, 134.2, 157.7; HRMS Calcd for $C_{15}H_{22}{}^{10}B_2{}^{11}B_8O_2$ 342.2624. Found Anal. Calcd for $C_{15}H_{22}B_{10}O_2{\cdot}1/2H_2O$: C, 51.26; H, 6.45. Found: C, 51.52; H, 6.51.

4.2.30. 1,1′-[(1,2-Dicarba-*closo*-dodecaboran-1-yl)methylene] bis(4-methoxy)benzene (32)

To a solution of 1′,2′-dicarba-*closo*-dodecarborane (72.0 mg, 0.500 mmol) in Et_2O (1 mL) was added dropwise a 2.14 M solution of *n*-BuLi in *n*-hexane (0.300 mL, 0.642 mmol) at 0 °C under Ar. The mixture was stirred at room temperature for 30 min. To the reaction mixture was added dropwise a solution of bis(4-methoxyphenyl)bromomethane (200 mg, 0.649 mmol) in Et_2O (1 mL) at 0 °C. Stirring was continued at room temperature for 2 h, and then saturated aqueous NH_4Cl was added dropwise at 0 °C. The whole was warmed to room temperature and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/CH_2Cl_2, 5:1) gave **32** (28%). ^{1}H NMR ($CDCl_3$) δ 1.38–2.92 (10H, br m), 3.25 (1H, br s), 3.79 (6H, s), 4.73 (1H, s), 6.87 (4H, ddd, *J* = 8.8, 2.9, 2.4 Hz), 7.36 (4H, ddd, *J* = 8.8, 2.9, 2.4 Hz); HRMS Calcd for $C_{17}H_{26}{}^{10}B_2{}^{11}B_8O_2$ 370.2937. Found 370.2941.

4.2.31. 4,4′-[(1,2-Dicarba-*closo*-dodecaboran-1-yl)methylene] bisphenol (16)

To a solution of **33** (171 mg, 0.445 mmol) in CH_2Cl_2 (5 mL) was added a 1.0 M solution of BBr_3 in CH_2Cl_2 (0.920 mL, 0.920 mmol) at 0 °C under Ar. The mixture was stirring at room temperature for 43 h, then poured into ice water, and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel column chromatography (eluent: *n*-hexane/Et_2O, 1:1) gave **16** (78%). **16**: white fibrous solid (Et_2O); mp 237–238 °C; ^1H NMR (CD_3OD) δ 1.35–2.89 (10H, br m), 3.84 (1H, br s), 4.66 (1H, s), 6.72 (4H, ddd, J = 8.7, 2.9, 1.9 Hz), 7.27 (4H, ddd, J = 8.7, 2.9, 1.9 Hz); ^{13}C NMR (CD_3OD) δ 58.7, 63.4, 82.4, 116.4, 131.5, 132.1, 158.3; HRMS Calcd for $C_{15}H_{22}{}^{10}B_2{}^{11}B_8O_2$ 342.2624. Found 342.2621; Anal. Calcd for $C_{15}H_{22}B_{10}O_2$ C, 52.61; H, 6.48. Found C, 52.52; H, 6.42.

4.3. Biological evaluation

4.3.1. ER ligand binding assay

The binding activity of ligands to human ERα (hERα) or ERβ (hERβ) was determined by means of the nitrocellulose filter binding assay method. Either hERα or hERβ (0.5 μg/tube) was diluted with binding assay buffer (20 mM Tris–HCl pH 8.0, 0.3 M NaCl, 1 mM EDTA pH 8.0, 10 mM 2-mercaptoethanol, 0.2 mM phenylmethylsulfonyl fluoride), and incubated with 4 nM [6,7-^{3}H]-17β-estradiol in the presence or absence of an unlabeled competitor at 4 °C for 18 h (in duplicate). The incubation mixture was absorbed by suction onto a nitrocellulose membrane that had been soaked in binding assay buffer. The membrane was washed twice with buffer (20 mM Tris–HCl pH 8.0, 0.15 M NaCl), and washed with 25% EtOH in distilled water. Radioactivity that remained on the membrane was measured in Atomlight by using a liquid scintillation counter.

4.3.2. MCF-7 proliferation assay

The human breast adenocarcinoma cell line MCF-7 was routinely cultivated in D-MEM supplemented with 10% FBS, 100 IU/mL penicillin and 100 μg/mL streptomycin at 37 °C in a 5% CO_2 humidified incubator. Before assay, MCF-7 cells were switched to D-MEM (low glucose phenol red-free supplemented with 5% sFBS, 100 IU/mL penicillin and 100 μg/mL streptomycin). Cells were trypsinized from the maintenance dish with phenol red-free trypsin–EDTA and seeded in a 96-well plate at the density of 2000 cells per final volume of 100 μL D-MEM supplemented with 5% sFBS, 100 IU/mL penicillin and 100 μg/mL streptomycin. After 24 h, the medium was changed to 90 μL of the drug solution, supplemented with serial dilutions of compounds or DMSO (control) in the presence or absence of 0.1 nM estradiol. Cells were incubated in triplicate microcultures for 4 days, and the medium with compounds or DMSO (control) in the presence or absence of 0.1 nM estradiol was replaced once after 2 days. At the end of the incubation period, WST-8 (10 nM) was added to the microcultures, and cell proliferation was evaluated 2–4 h later by measuring the absorbance at 450 nm as a parameter of the number of living cells in the culture.

4.4. Docking simulation

The docking procedures were similar to those described in our previous paper.[25] The computational docking trials were performed with GOLD 5.2 software[26] using the default settings. The 3D structures of human ERα were retrieved from the Protein DataBank (PDB) (PDB IDs: 1ERE, 3UU7, and 3UUC). Missing hydrogen atoms in the PDB structures were computationally added by Hermes.[27] The center of the active site was defined as the center of the ligand in 1ERE, 3UU7 or 3UUC, as appropriate, and the active site radius was set to 10.0 Å. Structural optimizations of ligands were carried out at the B3LYP/6-31G(d,p) level using Gaussian 09, Revision C.01.[28]

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