# Fluorine-Substituted Cyclofenil Derivatives as Estrogen Receptor Ligands: Synthesis and Structure−Affinity Relationship Study of Potential Positron Emission Tomography Agents for Imaging Estrogen Receptors in Breast Cancer

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*Received November 29, 2005*

In a search for estrogen receptor (ER) ligands to be radiolabeled with fluorine-18 for imaging of ER-positive breast tumors with positron emission tomography (PET), we investigated cyclofenil analogues substituted at the C3 or C4 position of the cyclohexyl group. McMurry coupling of 4,4′-dihydroxybenzophenone with various ketones produced key cyclofenil intermediates, from which C3 and C4 substituents containing alkyl and various oxygen or fluorine-substituted alkyl groups were elaborated. Binding assays to both ERα and ER$\beta$ revealed that the C3 site is more tolerant of steric bulk and polar groups than the C4 site, consistent with a computational model of the ERα ligand binding pocket. Fluorine substitution is tolerated very well at some sites, giving some compounds having affinities comparable to or higher than that of estradiol. These fluoro and fluoroalkyl cyclofenils merit further consideration as fluorine-18 labeled ER ligands for PET imaging of ERs in breast tumors.

## Introduction

The estrogen receptor (ER)[a,1,2] is a ligand-dependent transcription factor, whose conformation and activity are modulated by the binding of endogenous steroid hormones, such as 17$\beta$-estradiol ($E_2$). Estrogens, acting through the ER, regulate many important physiological processes, such as the maintenance of bone mineral density,[3,4] cardiovascular health,[5,6] neuroprotection,[7,8] and the development and function of the female reproductive system.[9,10]

The discovery that there are two ER subtypes, ERα and ER$\beta$,[11,12] provided impetus to develop novel estrogen pharmaceuticals able to activate or inhibit these subtypes selectively. Most estrogen target tissues have both ERα and ER$\beta$, though in varying ratios; ERα is the principal subtype expressed in breast and uterine tissue, while ER$\beta$ is found at higher levels in ovary, prostate, bone, vascular epithelium, and certain brain regions.[13−15] While difficult to generalize, ER$\beta$ is usually less active as a transcription factor and exerts a restraining effect on the more active ERα.[16−20] It is notable that in breast cancer the level of ER$\beta$ relative to ERα declines with disease progression[21] as one might expect with the transition to a more proliferative and invasive tumor phenotype. Thus, if the independent quantification of ERα and ER$\beta$ levels in breast cancer could be achieved by imaging—using fluorine-18 labeled ER subtype-selective ligands with positron emission tomography (PET)—it might provide information predictive of disease staging and tumor response to hormone therapies. Differential imaging of the two ER subtypes, however, has proved to be a major challenge (see below).

The ligand binding domains of ERα and ER$\beta$ have only 58% sequence identity,[22] and the volume of the ER$\beta$ ligand binding pocket is smaller than that of ERα.[23,24] Otherwise, the pockets are very similar, with only 2 out of 24 residues being different, and these being conservative substitutions (Leu384 and Met421 in ERα corresponding to Met and Ile in ER$\beta$, respectively). Despite this similarity, it has proved possible to develop ER ligands that bind to and activate either ERα or ER$\beta$ with a high level of selectivity (as has been reviewed[25−27]), and a reasonable pharmacophore model has been advanced to guide the design of subtype-selective ligands (Figure 1).[28,29] ER ligands with varying core structures have been reported: pyrazoles,[30] pyrroles,[31] and furans[31] as ERα-selective ligands; tetrahydrochrysenes,[32] diarylpropionitriles,[33] cyclofenils,[34] and benzofused heterocyclic analogues[35−37] as ER$\beta$-selective ligands. In prior studies, we have investigated some fluorine-18 labeled analogues of these ligands as PET imaging agents selective for ERα[38] and ER$\beta$,[39] but thus far our success has been limited.

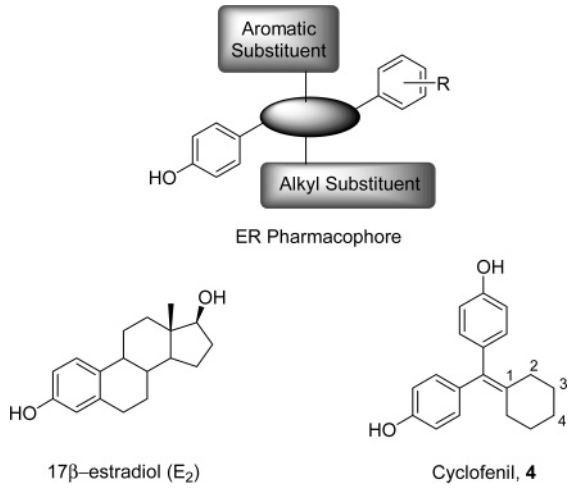


**Figure 1.** ER ligands and a pharmacophore model.

Cyclofenil (bis-(4-hydroxyphenyl)methylidenecyclohexane, **4**) and its analogues, while only slightly ER$\beta$-selective, have very high binding affinity, often comparable to or greater than that of estradiol.[34] After cyclofenil was reported,[40] its conformation

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[a] Abbreviations: $E_2$, 17$\beta$-estradiol; ER, estrogen receptor; F-18, fluorine-18; PET, positron emission tomography; SERM, selective estrogen receptor modulator.

10.1021/jm0512037 CCC: $33.50 
Published on Web 03/21/2006

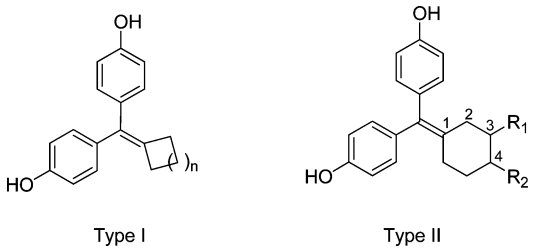



**Figure 2.** Two types of cyclofenil analogues.

was investigated by X-ray crystallography, and its binding to uterine receptors[41] was compared to that of estradiol ($E_2$).[42] Notably, cyclofenil has mixed agonist antagonist activity typical for a nonsteroidal selective estrogen receptor modulator (SERM), such as tamoxifen or raloxifene, and it has been used for ovulation induction.[43]

Recently, we prepared cyclofenil derivatives that have bicyclic core units to examine the degree to which a three-dimensional topology in the central hydrophobic core of a ligand would be tolerated by the ERs.[34] It was encouraging to find that several of the 1,1-diarylethylene motif bridged bicyclic or tricyclic core cyclofenil analogues had very high binding affinities, up to 3−5 times greater than that of estradiol in both ER subtypes. The torsion angles between the two hydroxyphenyl groups seem to correlate with the binding affinity, although other factors such as nonoptimal orientation of the phenyl ring and lack of ligand steric complementarity with the binding pocket also play important roles.[44] These factors were not investigated in the SAR and X-ray conformational studies of cyclofenil derivatives reported previously.[41,42]

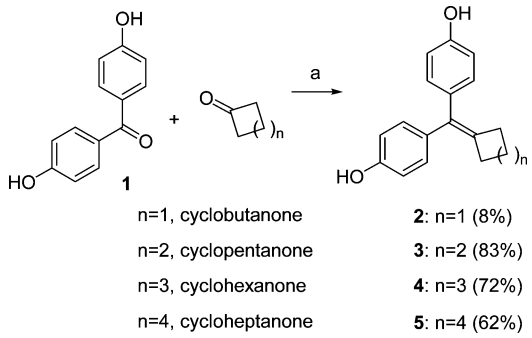
Thus, in our search for agents to image ERs in breast cancer by PET, we undertook a further investigation of substituted cyclofenil ligands to establish where it might be feasible to introduce polar substituents such as fluorine, as would be needed for labeling with the positron emitting radionuclide, fluorine-18. Because we wanted to establish a structure−activity relationship independent of effects that would result from changes in the critical torsion angle of the dihydroxyphenyl group, we investigated substituents only on the C3 and C4 positions of the cyclohexane ring (Figure 1), sites where substitution is not expected to affect this torsion angle. We thought that such C3- and C4-substituted cyclofenil derivatives would help probe for differences in the largely similar hydrophobic ligand binding pockets of the ERα and ER$\beta$. We hoped, as well, to identify ER$\beta$-selective ligands of high affinity[33,45] that are tolerant of the fluorine substitution needed for F-18 labeled PET imaging agents.

Herein, we report the syntheses of 24 cyclofenil derivatives, many of which are substituted at the C3 or C4 positions, as well as ones with different ring sizes, and an evaluation of their relative binding affinities (RBAs) to ERα and ER$\beta$. Through this study, we have established a useful structure−activity relationship relating ERα and ER$\beta$ binding affinities to the size and polarity of the C3 or C4 substituent in the cyclofenil series. In addition, we have identified a few fluoro- or fluoroalkyl cyclofenil analogues that have binding affinity for ERα and ER$\beta$ comparable to or greater than that of the endogenous ligand, estradiol, though their ER subtype selectivity is limited. These compounds are being considered for further investigation as PET imaging agents for ER in breast cancer.

## Results

**Synthesis of Cyclofenil Analogues.** The compounds we have synthesized can be divided into two types (Figure 2). One series of analogues (type I, compounds **2**−**5**) has different cycloalkyl core units, ranging from cyclobutane to cycloheptane. The other series (type II) has a fixed cyclohexyl moiety onto which we have introduced various substituents at the C3 or C4 position. All of the cyclofenil derivatives or their precursors were prepared by a McMurry coupling reaction between 4,4′-dihydroxybenzophenone and a cyclic ketone. Some of the cyclic ketones are commercially available or can be readily obtained in a few steps from commercially available material. In many cases, the substituents were elaborated from functional precursors after the cyclofenil system was prepared by McMurray coupling.

**Scheme 1**[a]



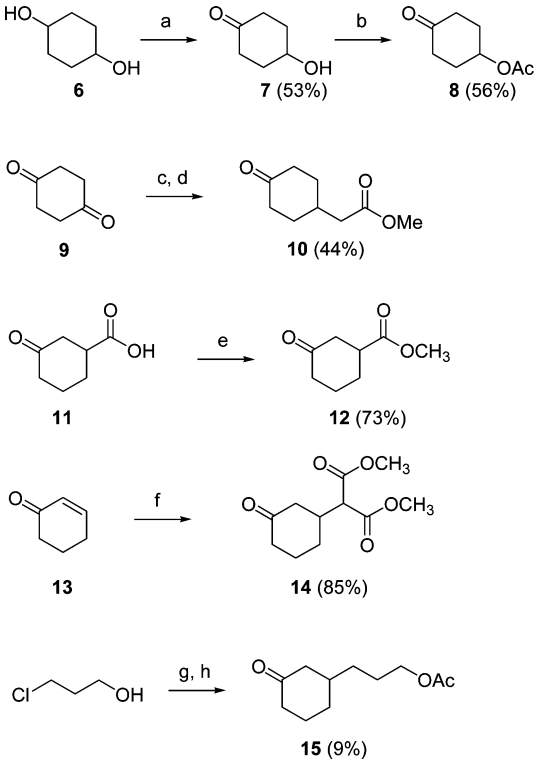

[a] Reagents: (a) $TiCl_4$, Zn, THF, reflux, 4 h.

**Synthesis of Type I Cyclofenil Analogues.** McMurry coupling reaction with low-valent titanium activated by zinc was used to prepare the various ring sized cyclofenil analogues **2**−**5** (Scheme 1) according to a previously reported procedure.[34,46,47] It is of note that this coupling is tolerant of free phenols. All of the reactions gave reasonable yields (62−83%) except the cyclobutyl compound **2** (8%).

**Synthesis of Cyclohexanone Precursors for Type II Cyclofenil Analogues.** Scheme 2 shows how various cyclohexanone precursors, functionalized at the C4 or C3 position, were prepared. 1,4-Dihydroxycyclohexane (**6**) was oxidized to 4-hydroxycyclohexanone (**7**) using freshly prepared Jones reagent and was acetylated to give 4-acetoxycyclohexanone (**8**). A Wittig reaction of cyclohexan-1,4-dione (**9**) with methyl (triphenylphosphoranylidene)acetate produced methyl (4-oxo-cyclohexylidene)acetate, which, following hydrogenation over a palladium catalyst, yielded the cyclohexyl acetate **10** that was used as a source of two-carbon substituents at the C4 position.[48] The C3-alkylated cyclohexanone precursor with one carbon atom (**12**) was prepared by esterification of the commercially available acid (**11**). The two-carbon substituent precursor (**14**) was prepared by Michael addition of dimethyl malonate to cyclohexanone (**13**).[49] The synthesis of the cyclohexanone with a linear three-carbon unit on the C3 position (**15**) involved copper-catalyzed 1,4-addition to cyclohexenone of the organomagnesium reagent generated in two steps from 3-chloropropanol (via the 3-chloropropylmagnesium alkoxide), with subsequently acetylation.[50] All compounds functionalized at C3 position are chiral and were used as racemates.

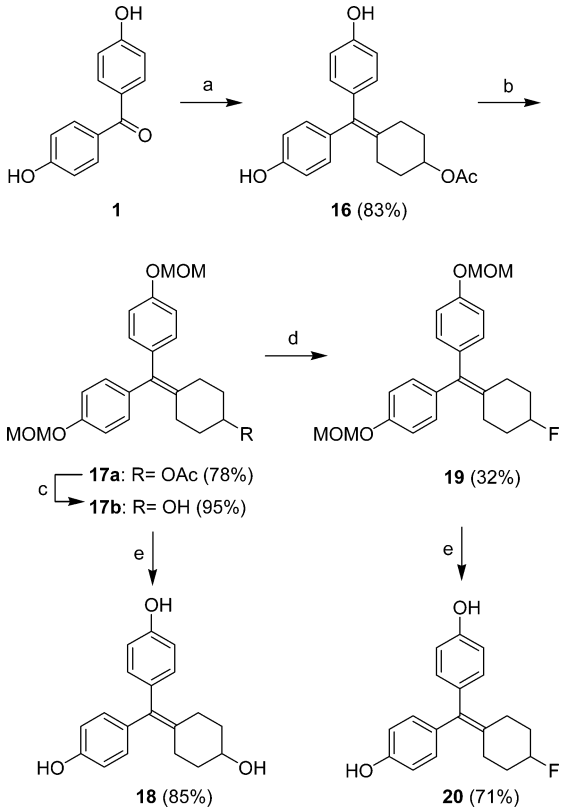
**Synthesis of C4-Substituted Cyclofenil Analogues.** Scheme 3 shows the preparation of the C4-functionalized cyclofenil derivatives. McMurry coupling of 4,4′-dihydroxybenzophenone with 4-acetoxycyclohexanone (**8**) yielded the C4 acetoxy analogue **16**; the phenolic hydroxy groups were then protected as methoxymethyl (MOM) ethers. The C4-hydroxy cyclofenil **17b**, obtained after alkaline hydrolysis of the acetate, was converted to the protected 4-fluorocyclofenil derivative **19** in 32% yield by treatment with (diethylamino)sulfur trifluoride

**Scheme 2.** Syntheses of Cyclohexanones[a]




[a] Reagents: (a) Jones reagent, acetone, 0 °C to room temp, 45 min; (b) $Ac_2O$, pyridine, room temp, 24 h; (c) methyl (triphenylphosphoranylidene)acetate, toluene, 110 °C, 8 h; (d) Pd/C, $H_2$, EtOH, room temp, 6 h; (e) $SOCl_2$, MeOH, room temp, 3 h; (f) dimethyl malonate, NaOEt (catalyst), room temp, 2 h; (g) (i) MeMgCl, THF, −78 °C to room temp, 20 min; (ii) Mg, 1,2-dibromoethane, THF, room temp to 90 °C, 2 h; (iii) **13**, CuBr, THF, −78 to 0 °C, 1 h; (h) $Ac_2O$, pyridine, $CH_2Cl_2$, room temp, 18 h.

**Scheme 3**[a]




[a] Reagents: (a) **8**, $TiCl_4$, Zn, THF, reflux, 4 h; (b) methoxymethyl chloride, NaH, DMF, 0 °C to room temp, 1 h; (c) $K_2CO_3$, MeOH:$H_2O$ (5:1), room temp, 12 h; (d) DAST, $CH_2Cl_2$, −78 °C to room temp, 1 h; (e) HCl, MeOH, room temp, 12 h.

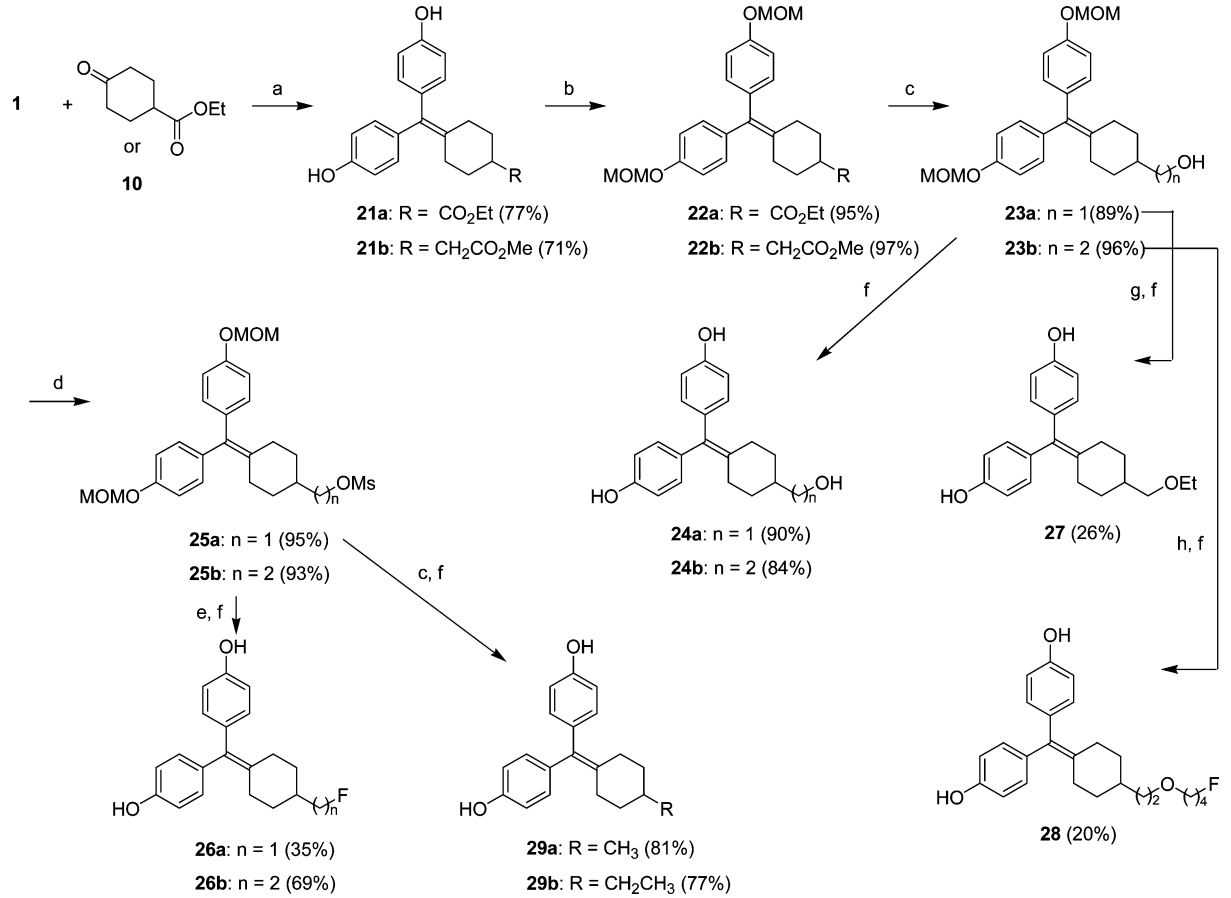
(DAST). Acid cleavage of the MOM groups in both **19** and **17b** produced the C4-hydroxy and fluoro cyclofenil analogues **18** and **20** in 71% and 85% yield, respectively.

The preparation of cyclofenil derivatives with carbon chains at the C4 position is shown in Scheme 4. Ethyl 4-oxocyclohexanecarboxylate, a commercially available ketone that has a one-carbon unit at the C4 position, or methyl (4-oxo-cyclohexyl)acetate (**10**), which has a two-carbon unit at the C4 position (prepared as in Scheme 2), were reacted with 4,4-dihydroxybenzophenone (**1**) using the same McMurry coupling procedure. In this manner, we obtained cyclofenil 4-carboxylate **21a** and acetate **21b** in approximately 70% yield. The phenols in both compounds were protected as MOM ethers, and the carboxylic esters in both **22a** and **22b** were reduced to the corresponding primary alcohols with lithium aluminum hydride. These alcohols, **23a** and **23b**, served as intermediates for further synthesis. After MOM deprotection, they gave the C4 hydroxymethyl and 2-hydroxyethyl cyclofenils (**24a**,**b**). As the MOM ethers, they served as precursors of the C4-ethoxymethyl compound **27** and the fluorobutyloxymethyl compound **28**. They were also converted to the methanesulfonates **25a**,**b**. Fluoride ion substitution to produce the fluoromethyl and fluoroethyl analogues (**26a**,**b**) from these methanesulfonates was accomplished by reaction with cesium fluoride in an ionic liquid.[51] The use of this medium for fluoride ion substitutions minimizes side reactions, such as elimination, that would produce various alkenes, which are sometimes difficult to separate from the desired fluorine-substituted products. On the basis of precedent in other systems, this ionic liquid fluorination would likely be effective for labeling of these compounds with F-18, even in the presence of small amounts water which typically remain after reagent drying by azeotrope distillation.[52] Reductive cleavage of the methanesulfonates, followed by deprotection of the MOM ethers, yielded the C4 methyl and ethyl cyclofenil analogues (**29a**,**b**).

**Synthesis of C3-Substituted Cyclofenil Analogues.** We used similar procedures to introduce substituents and functional groups at the C3 position of cyclofenil (Scheme 5). A McMurry reaction with the cyclohexanones **12**, **14**, and **15** produced coupled ester compounds **30a**, **30b**, and **30c**, respectively. Hydrolysis of **30b** and subsequent decarboxylation and esterification produced the C3 carboxymethyl compound **32**. The phenols of all three cyclofenil derivatives (**30a**, **30c**, and **32**) were protected as MOM ethers. Reduction of **33a** and **33b** with lithium aluminum hydride and hydrolysis of **33c** with potassium carbonate gave hydroxymethyl, hydroxyethyl, and hydroxypropyl cyclofenil derivatives (**34a**−**c**), respectively.

Fluoride substitution was accomplished by two different procedures: in the case of **34a** and **34c**, the free hydroxyl group was directly converted to fluoride by treatment with DAST, and in case of **34b**, the hydroxylethyl group was converted to a fluoroethyl group by fluoride ion substitution on the methanesulfonate intermediate **36b**. Removal of the MOM-protective group to obtain the free fluoro compounds was attempted in acidic media, but strangely the color of all three fluorinated products (**37a**−**c**) slowly changed to red. Even after the deprotected fluoro compounds were purified again by column chromatography, they developed color upon standing. When each compound was recrystallized, however, their stability increased quite a bit, but they still decomposed slowly. It proved to be especially difficult to obtain **37a** in pure form, and because of its instability, it was not evaluated for binding.

**Scheme 4**[a]




[a] Reagents: (a) $TiCl_4$, Zn, THF, reflux, 4 h; (b) methoxymethyl chloride, NaH, DMF, 0 °C to room temp, 1 h; (c) LAH (1 M solution in THF), THF, 0 °C to room temp, 1 h; (d) methanesulfonyl anhydride, TEA, $CH_2Cl_2$, 0 °C to room temp, 1 h; (e) CsF, $H_2O$, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][$BF_4$]), acetonitrile, 100 °C, 2 h; (f) HCl, MeOH, room temp, 12 h; (g) bromoethane, NaH, DMF, 100 °C, 24 h; (h) 1-bromo-4-fluorobutane, NaH, DMF, 0−100 °C, 24 h.

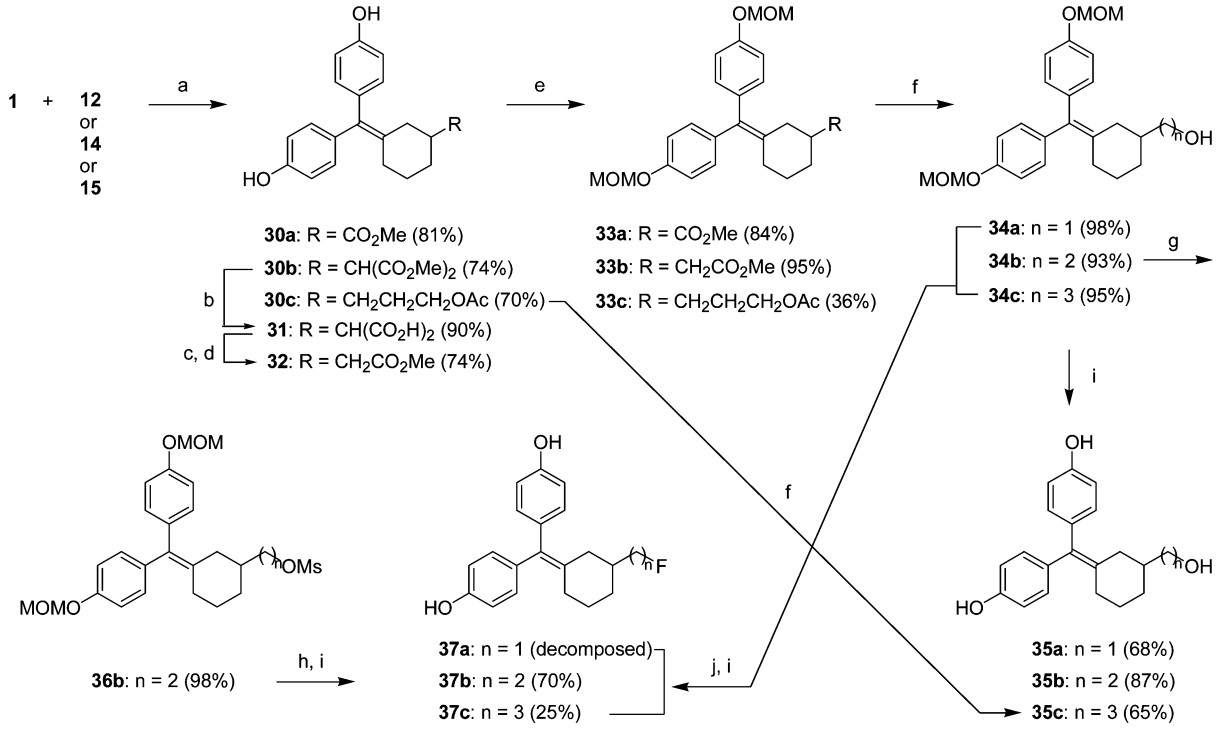
**Estrogen Receptor Binding Assay.** The relative binding affinities (RBAs) of cyclofenil analogues were determined using a competitive radiometric binding assay with purified full-length human ERα and ER$\beta$, according to published procedures.[53] The RBA value was expressed as binding affinity relative to that of estradiol (100%). RBA values of the 24 cyclofenil analogues evaluated are listed in Table 1. It is notable that the tracer and standard, estradiol, has a modest binding preference for ERα ($K_d$(ERα) = 0.2 nM and $K_d$(ER$\beta$) = 0.5 nM).

**Binding Affinity of Type I Compounds.** We have previously reported a structure−activity relationship (SAR) of 1,1-diarylethylene derivatives that have bridged bicyclic cores, but from this earlier study, it was not obvious what effect the bicyclic core size had on binding affinity.[34] Thus, we prepared the first type of cyclofenil analogues (**2**−**5**, type I) to evaluate the RBA values of cyclofenil compounds having different ring size core units (Figure 1 and Table 1). In general, the RBA values range from 5.6 to 124 for ERα and from 20 to 354 for ER$\beta$. Interestingly, when the ring size is increased from cyclobutyl **2** to cycloheptyl **5**, binding affinities for both ERα and ER$\beta$ increase, and all compounds (**2**−**5**) show selectivity for ER$\beta$ of ca. 3-fold in terms of the RBA $\beta/\alpha$ ratio (which is comparable to that of estradiol, 2.5; see Table 1, footnote b), except for the cyclopentyl compound **3**, which on this scale was 7.7-fold ER$\beta$ selective (the most ER$\beta$ selective of all compounds prepared). These data suggest that an increase in lipophilic character in the cyclic core could lead to high binding affinity for both ERα and ER$\beta$ but not a large increase in ER$\beta$ selectivity.

**Binding Affinity of Type II Compounds with C4 Substituents.** Twelve cyclofenil derivatives with different C4 substituents, such as alkyl (**29a**,**b**), hydroxyalkyl (**18**, **24a**,**b**), alkyl carboxylate (**21a**,**b**, **27**, **28**), and fluoroalkyl substituents (**20**, **26a**,**b**), were investigated to compare the effects on ER binding affinity of introducing alkyl groups of different carbon lengths and substitution of these groups with electronegative and/or polar units (fluoride and hydroxide).

In all cases (except the C4 methyl compound **29a** with ER$\beta$), any substitution at C4 reduced binding affinity to both ERα and ER$\beta$, but the degree to which binding was lowered depended on substituent size and polarity. In general, groups that were small and/or nonpolar had the highest binding affinity. Thus, the C4 methyl and ethyl compounds (**29a**,**b**) still had good binding affinity compared to the cyclofenil parent (**4**). Direct substitution at C4 with fluorine (**20**) caused some reduction in ER binding but much less than direct substitution with hydroxyl (**18**); the latter (hydroxy) substitution dropped ERα binding 380-fold and ER$\beta$ binding 930-fold. Similar trends are noted for fluorine and hydroxy substitution in the C4 methyl series (**29a**, **26a**, and **24a**) and the C4 ethyl series (**29b**, **26b**, and **24b**): both substituents lower binding, but fluorine, which is less polar, is tolerated much better than hydroxy. These trends are consistent with computational models of the C4-substituted compounds in the ligand binding pocket of ERα (see below and Figure 3), in which these C4 substituents are shown to project into a constrained, hydrophobic environment. The other four analogues (**27**, **28**, **21a**, and **21b**) are all of intermediate

**Scheme 5**[a]




[a] Reagents: (a) $TiCl_4$, Zn, THF, reflux, 4 h; (b) 2 M NaOH, MeOH, reflux, 2 h; (c) diglyme, 160 °C, 1 h; (d) $SOCl_2$, MeOH, room temp, 90 min; (e) methoxymethyl chloride, NaH, DMF, 0 °C to room temp, 1 h; (f) (i) in the case of **33a**,**b**, LAH (1 M solution in THF), THF, 0 °C to room temp, 1 h and (ii) in the case of **30c** and **33c**, $K_2CO_3$, MeOH−$H_2O$ (5:1), room temp, 12 h; (g) methanesulfonyl anhydride, TEA, $CH_2Cl_2$, 0 °C to room temp, 1 h; (h) CsF, $H_2O$, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][$BF_4$]), acetonitrile, 100 °C, 2 h; (i) HCl, MeOH, room temp, 12 h; (j) DAST, $CH_2Cl_2$, −78 °C to room temp, 1 h.

polarity, and all have relatively low affinity. It is of note that the highest binding C4-substitued cyclofenil containing fluorine is the direct 4-fluorocyclofenil (**20**), with ERα and ER$\beta$ RBA values of 27 and 62, respectively.

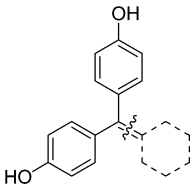
It is worthwhile to consider not just the ERα and ER$\beta$ binding affinities but also the ERα/ER$\beta$ binding selectivities of these cyclofenil analogues. One notes an overall trend that when a more polar group is attached to a C4-alkyl group, the $\beta/\alpha$ RBA ratio decreases. This is clearly evident in the C4 methyl series: methyl **29a** ($\beta/\alpha = 4.1$), fluoromethyl **26a** ($\beta/\alpha = 2.3$), and hydroxylmethyl **24a** ($\beta/\alpha = 0.99$). Also, this is reasonably evident in the C4-ethyl series: ethyl **29b** ($\beta/\alpha = 1.2$), fluoroethyl **26b** ($\beta/\alpha = 1.2$), and hydroxyethyl **24b** ($\beta/\alpha = 0.14$). Despite this shift in ER-subtype binding preference from ER$\beta$ to ERα, the overall RBA values for both ERs decrease considerably, consistent with the generally poor tolerance of polarity in the core of ER ligands. If one looks at $\beta/\alpha$ RBA ratios as a function of the length of homologous substituents (alkanes **4**, **29a**,**b**; fluoroalkanes **20**, **26a**,**b**; hydroxyalkanes **18**, **24a**,**b**), in each case, the selectivity for ER$\beta$ seems to be highest with the two-carbon species. This preference for substituents of intermediate length is also apparent, to some degree, in the other C4 analogues (**27**, **28**, and **21a**,**b**). Of greatest interest to this study, however, is the fact that among the C4-substituted cyclofenils, there is one fluorine-substituted analogue, 4-fluorocyclofenil (**20**), that has a binding affinity for ER$\beta$ that is nearly comparable to that of estradiol.

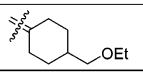
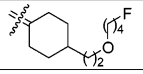
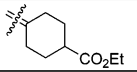
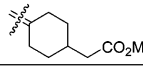
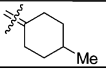
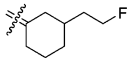
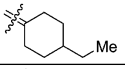
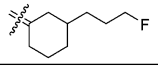
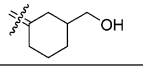
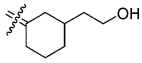
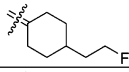
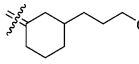
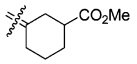
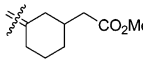
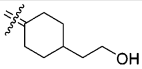
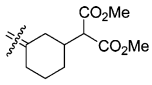
**Binding Affinity of Type II Compounds with C3 Substituents.** In those cases where the RBA values of C3-substituted cyclofenils can be directly compared to their C4-substituted analogues having the same substituents (**37b** with **26b**, **35a** with **24a**, **35b** with **24b**, and **32** with **21b**), the C3-substituted cyclofenils have significantly greater binding affinity and a greater tolerance for polar substituents. It is notable that the homologous C3 fluoroethyl and propyl compounds (**37b**,**c**) have rather similar ERα and ER$\beta$ relative binding affinities; this is true to a somewhat lesser degree with the C4 fluoroalkyl compounds (**20**, **26a**,**b**), where increasing size causes a somewhat greater decrease in affinity. In the C3-substituted cyclofenil series, both fluorine-substituted compounds (**37b**,**c**) are high-affinity ligands for both ERs.

A particularly dramatic difference between the C3 and C4 series is noted in the ER's binding affinity of the C3 hydroxyethyl (**35b**; RBA $\alpha = 34$, $\beta = 58$) and the C4 hydroxyethyl (**24b**; RBA $\alpha = 2.6$, $\beta = 0.37$) compounds; the affinity ratio is 154-fold in case of ER$\beta$ in favor of the C3-substituted series. A similar, though somewhat less dramatic comparison can be made with the hydroxymethyl C3 and C4 analogues (**35a** RBA $\alpha = 25$, $\beta = 40$ vs **24a** RBA $\alpha = 0.85$, $\beta = 0.84$), again with the C3-substituted systems having higher affinities. These trends are consistent with computational models of the ERα ligand binding pocket (see below and Figure 3) in which it can be seen that the C3 substituent encounters less steric hindrance and has an opportunity to extend toward and interact with a key histidine residue (H524 in ERα and H474 in ER$\beta$). Again, of principal interest to this study is the fact that we have identified two cyclofenil analogues, compounds **37b** and **37c**, that bind better to ERα and, in the case of **37b**, also to ER$\beta$ better than does estradiol.

**Molecular Modeling of C4- and C3-Substituted Cyclofenils in ER Ligand Binding Pocket of ERα.** To understand why the estrogen receptor differed so greatly in its tolerance of the bulk and polarity of substituents at the C4 and C3 positions of cyclofenil, we examined how some of these compounds fit into the ligand binding pocket of ERα by computational modeling (Figure 3). A model for the ERα ligand binding domain was generated from the ERα-estradiol structure (1ERE in the RCSB) by deleting the ligand and then placing various

**Table 1.** Relative Binding Affinity (RBA)[a] of Cyclofenil Derivatives for the Estrogen Receptors α and *β*



| # | structure | RBA ($E_2$ = 100)[a] | | β/α[b] | # | structure | RBA ($E_2$ = 100)[a] | | β/α[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | ERα | ERβ | | | | ERα | ERβ | |
| **2** |  | 5.61 | 20.5 | 3.7 | **27** |  | 4.88 | 2.82 | 0.58 |
| **3** |  | 17.8 | 137 | 7.7 | **28** |  | 3.77 | 1.45 | 0.38 |
| **4** |  | 124 | 285 | 2.3 | **21a** |  | 6.77 | 3.02 | 0.45 |
| **5** |  | 110 | 354 | 3.2 | **21b** |  | 10.7 | 1.72 | 0.16 |
| **29a** |  | 66.5 | 274 | 4.1 | **37b** |  | 122 | 129 | 1.1 |
| **29b** |  | 62.7 | 75.6 | 1.2 | **37c** |  | 160 | 91.4 | 0.57 |
| **20** |  | 27.0 | 61.8 | 2.3 | **35a** |  | 24.8 | 39.6 | 1.6 |
| **26a** |  | 18.1 | 41.5 | 2.3 | **35b** |  | 33.9 | 57.6 | 1.7 |
| **26b** |  | 15.9 | 18.9 | 1.2 | **35c** |  | 47.2 | 46.1 | 0.98 |
| **18** |  | 0.327 | 0.307 | 0.94 | **30a** |  | 23.7 | 36.5 | 1.5 |
| **24a** |  | 0.846 | 0.841 | 0.99 | **32** |  | 58.5 | 10.3 | 0.18 |
| **24b** |  | 2.61 | 0.372 | 0.14 | **30b** |  | 19.5 | 0.234 | 0.012 |

[a] Relative binding affinity (RBA) values are determined by a competitive radiometric binding assay with [$^3$H]estradiol and full length human ERα and ER*β*, using methods described in the Experimental Section. The RBA of estradiol ($E_2$) is defined as 100, and the measured RBA values represent the mean of two or more independent determinations (CV < 0.3). [b] The binding affinity of the tracer estradiol to the ERs is $K_d$(ERα) = 0.2 nM and $K_d$(ER*β*) = 0.5 nM. Thus, on an absolute scale of binding affinities, the *β*/α ratios would be reduced by a factor of 2.5.

C3- and C4-substituted cyclofenils into this pocket using the FlexiDoc routine within the Sybyl 7.1 molecular modeling software (Tripos Inc.). The initial docking orientation of substituted cyclofenil was based on initial models with unsubstituted cyclofenil (data not shown), where one phenol occupies a position equivalent to that of the A-ring of estradiol, the second projects in roughly a "steroid 11*β* direction", and the cyclohexyl ring occupies roughly the "steroid 7α subpocket" (see Figure 3, part A).

To challenge this ligand orientation, the cyclofenil analogues were initially modeled with one phenol as the steroid A-ring mimic, but intentionally "misorienting" the cyclohexyl ring in the "steroid 11*β* direction" of the binding pocket (opposite of what was found on cyclofenil), so that the other phenol occupied the "steroid 7α subpocket". Despite this deliberate initial misorientation of the ligand, the FlexiDoc routine reoriented the cyclofenil core in a characteristic manner. In all cases, one of the phenol rings of cyclofenil remained in place of the A-ring of estradiol, where the hydroxyl group could engage in the canonical hydrogen bonds with the Glu and Arg residues (353 and 394 in ERα and 305 and 346 in ER*β*, respectively). In all but a few cases, the cyclofenil core was reoriented to place the other phenol in a roughly "steroid 11*β* direction"; in this orientation, the second hydroxyl is within 3 Å of a threonine residue (T347 in ERα and T299 in ER*β*). Final optimization of the model included a three-step minimization process that has been reported elsewhere (see Experimental Section).

Modeling of the achiral C4-substituted cyclofenils was relatively straightforward; in these, the cyclohexane ring can adopt two chair conformations on each of which the substituent can be either axial or equatorial. Many of these cases were modeled to give stable structures. Docking always revealed one phenol as the steroidal A-ring mimic and typically placed the second pendent phenol in the "steroid 11*β* direction." In most cases, the C4 substituents project toward a region of the ligand binding pocket that is somewhat flexible but essentially hydrophobic (I424 and L428 in ERα or I376 and L380 in ER*β*) (see Figure 3, part B). This view is consistent with the behavior of these analogues in which alkyl groups (**29a**,**b**) were very well tolerated, the electronegative fluoro (**20**) and fluoroalkyl

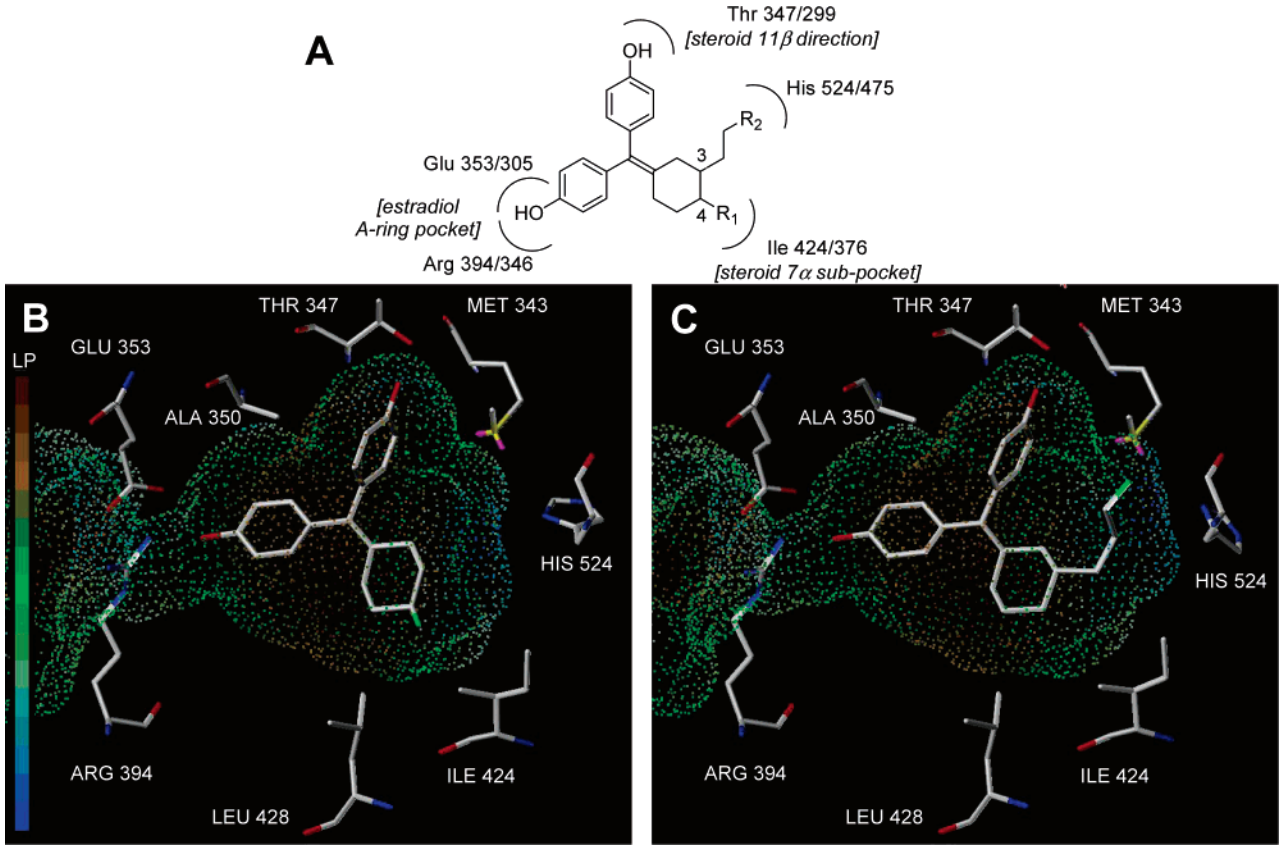



**Figure 3.** Schematic and computational model of substituted cyclofenil interaction with the ligand binding pocket of the estrogen receptor, ERα: (A) schematic picture of the interactions of the phenolic hydroxyls and the C3 and C4 cyclofenil substituents with residues in the ligand binding pocket. ERα residue numbers precede ER$\beta$ residue numbers. (B) Representative computational model of 4-fluorocyclofenil (**20**) in the ligand binding pocket of ERα. The hydrophobic residues near the C4 position are indicated. The surface shown is the ERα binding pocket displayed as dots mapped with the lipophilic potential. Residues identities are for ERα. (C) Representative computational model of 3-(2-fluoropropyl)cyclofenil (**37c**) in the ligand binding pocket of ERα. The surface is the same as in panel B. Residues identities are for ERα.

groups (**26a**,**b**) were reasonably well tolerated, but the polar hydroxy (**18**) and hydroxyalkyl groups (**24a**,**b**) bind very poorly.

The chiral C3-substituted cyclofenils present a greater challenge for modeling, because each enantiomer can adopt two chair conformations, each of which can have the substituent disposed in an axial or equatorial position. Modeling was done with some analogues in most of these orientations, from which a consistent pattern also emerged, as is illustrated in Figure 3, part C. By alternate choice of the phenols and chair conformation, each C3-substituted enantiomer can adopt an orientation in which the substituent can be extended toward His 524, the residue in ERα with which the 17$\beta$-hydroxyl group of estradiol forms a hydrogen bond. Thus, this model provides a satisfying rationale for the fact that at this site the ER can tolerate both bulky and electronegative fluoroalkyl (**37b**,**c**) as well as the more polar hydroxyalkyl (**35a**−**c**) groups. It is of note that substituents originating from the C4 carbon cannot access His 524. Attempts were not made to explain the relatively modest ERα versus ER$\beta$ binding selectivities of the compounds in this series by modeling.

## Conclusions

In summary, in our search for PET imaging agents for the estrogen receptors, we have focused on the preparation of C3- and C4-substituted cyclofenil derivatives so that we could explore the introduction of alkyl and functionalized alkyl substituents in a manner that would not affect the rotational mode of both bis(hydroxyphenyl) groups, a conformational parameter that is very important for ER binding. We hoped, thereby, to discover ER ligands in which an electronegative substituent, — fluorine in particular, —might be well tolerated, perhaps even ones in which the fluorine-substituted analogue would retain the "higher than estradiol" binding affinity of the cyclofenil parent, so that they might be useful as PET imaging agents for ER in breast tumors.

From the binding affinities of the 24 compounds we have investigated, we find that cyclofenils with six- and seven-membered rings bind best to ER. Except for one case, introduction of the various C3 and C4 substituents into the cyclohexane ring of cyclofenil decreases binding affinity, particularly when the substituents bear polar and/or electronegative groups, but less so with fluorine than with hydroxyl. In general, groups that are small or of intermediate size are better tolerated, and those substituted at C3 bind better than those substituted at C4, in some cases dramatically better. The pattern of affinity dependence on the site of substitution and the size and polarity of the substituent can be nicely rationalized by computational modeling of the ligand binding pocket. Overall, however, there appears to be relatively little binding selectivity for either ERα or ER$\beta$.

The principal motivation for this study was to identify cyclofenil analogues in which a fluorine substituent could be introduced with retention of high ERα and/or ER$\beta$ binding affinity, as would be needed to develop F-18 labeled ligands for PET imaging of the ERs in breast tumors. In terms of binding affinity, our study was successful, because we have found three fluorine-substituted compounds, 4-fluorocyclofenil (**20**), 3-fluoroethylcyclofenil (**37b**), and 3-fluoropropylcyclofenil (**37c**),

that bind to the ERs with an affinity that is comparable to or greater than that of estradiol. We did not find compounds having marked affinity preference or either ERα or ER$\beta$, however. Further work on the radiolabeling and in vivo evaluation of some of these compounds will be reported elsewhere.

## Experimental Section

All reagents and solvents were purchased from Aldrich, Acros, or Fisher. Anhydrous THF, $Et_2O$, and $CH_2Cl_2$ were collected using a solvent dispensing system built by J. C. Meyer based on a design developed by Pangborn.[54] Reaction progress was followed by TLC on 0.25 mm silica gel glass plates containing F-254 indicator (Merck). Visualization on TLC was monitored by UV light or phosphomolybdic acid indicator. The chemical shifts were reported in parts per million and were referenced to the internal solvent peaks. Coupling constants were reported in hertz. $^1$H spectra were obtained on 400 or 500 MHz spectrometers. $^{13}$C NMR spectra were acquired at 100 or 125 MHz. Melting points were checked using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Low- and high-resolution electron impact (EI, 70 eV) spectra were obtained on a Micromass 70-VSE spectrometer. Elemental analyses were performed by the Microanalytical Service Laboratory of the University of Illinois or the Center for Collaborative Instruments at Inha University. Reactions were performed under a nitrogen atmosphere unless noted otherwise.

**General Procedure for McMurry Coupling Reaction.** A two-necked, round-bottom flask containing zinc powder (1.2 g, 18 mmol) was fitted with a reflux condenser, evacuated for 10 min, and charged with nitrogen gas. After THF (15 mL) was added, the reaction mixture was cooled in an acetone−water bath (−10 °C) and then titanium(IV) chloride (1.64 g, 8.62 mmol) was added slowly. Addition of titanium(IV) chloride released a yellow fume, and the reaction mixture turned a yellow-green color. The reaction was refluxed for 2 h at 100 °C and then cooled to room temperature. A solution of dihydroxybenzophenone (**1**, 500 mg, 2.33 mmol) and each ketone (2.33 mmol) dissolved in THF (15 mL) was injected by syringe, and the reaction was refluxed for 2 h. The cooled reaction mixture was slowly poured into a $NaHCO_3$ solution (200 mL), and $Et_2O$ (200 mL) was added with vigorous stirring. The heterogeneous solution was filtered through Celite. After the organic layer was decanted and saved, the aqueous layer was extracted with additional $Et_2O$ (100 mL). The combined organic layer was dried over $MgSO_4$ and concentrated. Flash column chromatography (EtOAc/hexane; 3:7 or 4:6) gave each coupled compound. Compounds for bioassay were recrystallized from $Et_2O$ and hexane or from EtOAc and hexane.

**General Procedure for MOM Protection.** To a solution of bisdihydroxyphenyl (4.4 mmol) in anhydrous DMF (15 mL) was added sodium hydride (10 mmol) in an ice-bath with $N_2$. The cooling was removed, and methoxymethyl chloride (9.7 mmol) was slowly added dropwise by syringe with stirring. Almost at the end of the addition, the mixture turned into an off-white solution and was stirred 1 h more. After the ice-bath was replaced, the reaction was quenched by water (1.0 $\mu$L) and transferred to a separatory funnel. Saturated ammonium chloride solution (100 $\mu$L) was added to remove the DMF, and the organic layer was extracted with EtOAc (100 $\mu$L). This was washed with brine (2 × 100 $\mu$L), dried over $MgSO_4$, and concentrated under reduced pressure. Flash column chromatography (EtOAc/hexane; 2:8) gave the MOM protected compound.

**General Procedure for Reduction.** A mixture of $LiAlH_4$ solution in THF (1 M, 5.7 mL) and THF (15 mL) was slowly added to each ester compound (5.7 mmol) under ice-bath cooling. After addition, the cooling was removed, and the reaction was stirred for about 1 h. The ice-bath was replaced, and the reaction was quenched carefully by water (100 $\mu$L), 2 M sodium hydroxide solution (100 $\mu$L), and water (100 $\mu$L) in turn. Additional stirring for about 20 min gave a white precipitate that was filtered through Celite. The filtrate was concentrated, and flash column chromatography (EtOAc/hexane; 3:7) of the residue gave each alcohol product.

**General Procedure for Methanesulfonylation.** A two-necked round-bottom flask, which contained the alcohol compound (0.23 mmol), was charged with nitrogen. Freshly distilled $CH_2Cl_2$ (5 mL) was added to the round-bottom flask, and the reaction was stirred in an ice-bath. Methanesulfonic anhydride (94 mg, 0.54 mmol) was added in several portions, followed by the slow addition of small portions of triethylamine (68 mg, 0.68 mmol). The reaction mixture was stirred at room temperature for about 1 h. The reaction was quenched by water (10 mL) and vigorous stirring, and the mixture was extracted with additional $CH_2Cl_2$ (50 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Flash column chromatography (EtOAc/hexane; 4:6) gave each alcohol product.

**General Procedure for Fluorination with Cesium Fluoride.**[51] To methanesulfonate (0.35 mmol) and cesium fluoride (1.75 mmol) in a 10 mL vial was added *N*-butyl-*N*′-methylimidazolium tetrafluoroborate (1.5 mL), acetonitrile (1.5 mL), and $H_2O$ (50 $\mu$L). After the vial was tightly capped, the reaction mixture was stirred for 2 h at 100 °C. After the mixture was cooled, $Et_2O$ was added to the reaction mixture, which was shaken and decanted five times. The combined organic layer was dried over $MgSO_4$ and concentrated. Flash column chromatography (EtOAc/hexane; 1:9) gave each fluorinated compound.

**General Procedure for MOM Deprotection.** Concentrated HCl (200 $\mu$L) was added to a solution of the MOM protected compound (0.31 mmol) in methanol (10 mL). In the case of some compounds, $Et_2O$ (5 mL) was added to dissolve the compounds. The reaction mixture was stirred for 12 h, then quenched by water (10 mL), and extracted by EtOAc (50 mL). After removal of the solvent, short flash column chromatography (EtOAc/hexane; 1:1) gave bis-(dihydroxyphenyl)methylene compounds. Compounds for bioassay were recrystallized from $Et_2O$ and hexane or from EtOAc and hexane.

**Bis(4-hydroxyphenyl)methylenecyclobutane (2).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 500 mg, 2.33 mmol), cyclobutanone (163 mg, 2.33 mmol), Zn (1.2 g, 18 mmol), and titanium(IV) chloride (1.64 g, 8.62 mmol), **2** (45 mg, 8%) was obtained as a white solid: mp 177−179 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 6.97 (d, $J$ = 8.8 Hz, 4H), 6.76 (d, $J$ = 8.8 Hz, 4H), 2.86 (t, $J$ = 8.0 Hz, 4H), 1.99 (quintet, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 156.6, 137.7, 133.4, 133.1, 130.7, 115.6, 32.5, 17.7; MS (EI) $m/z$ 252 ($M^+$, 100), 223, 107. HRMS (EI) $m/z$ calcd for $C_{17}H_{16}O_2$, 252.1150; found, 252.1152. Anal. ($C_{17}H_{16}O_2 \cdot 0.1H_2O$) C, H.

**Bis(4-hydroxyphenyl)methylenecyclopentane (3).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 500 mg, 2.33 mmol), cyclopentanone (196 mg, 2.33 mmol), Zn (1.2 g, 18 mmol), and titanium-(IV) chloride (1.64 g, 8.62 mmol), **3** (518 mg, 83%) was obtained as a white solid: mp 194−195 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.90 (d, $J$ = 8.4 Hz, 4H), 6.66 (d, $J$ = 8.4 Hz, 4H), 2.26 (bt, $J$ = 6.4 Hz, 4H), 1.60 (bt, $J$ = 6.4 Hz, 4H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 155.4, 139.9, 134.2, 132.2, 129.9, 114.7, 32.7, 26.5; MS (EI) $m/z$ 266 ($M^+$, 100), 223, 168, 141, 115. Anal. ($C_{18}H_{18}O_2$) C, H.

**Bis(4-hydroxyphenyl)methylenecyclohexane (4).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 500 mg, 2.33 mmol), cyclohexanone (229 mg, 2.33 mmol), Zn (1.2 g, 18 mmol), and titanium(IV) chloride (1.64 g, 8.62 mmol), **4** was obtained as a white solid (518 mg, 83%): mp 235−237 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.83 (d, $J$ = 8.4 Hz, 4H), 6.66 (d, $J$ = 8.8 Hz, 4H), 2.10−2.21 (m, 4H), 1.42−1.60 (m, 6H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 155.6, 136.3, 133.9, 133.7, 130.4, 114.7, 31.9, 28.2, 26.3; MS (EI) $m/z$ 280 ($M^+$), 199 (100), 107. Anal. ($C_{19}H_{20}O_2$) C, H.

**Bis(4-hydroxyphenyl)methylenecycloheptane (5).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 500 mg, 2.33 mmol), cyclohexanone (261 mg, 2.33 mmol), Zn (1.2 g, 18 mmol), and titanium-(IV) chloride (1.64 g, 8.62 mmol), **5** (518 mg, 83%) was obtained

as a white solid: mp 198−199 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 6.96 (d, $J$ = 8.8 Hz, 4H), 6.74 (d, $J$ = 8.8 Hz, 4H), 2.26−2.34 (m, 4H), 1.50−1.61 (m, 8H); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 156.3, 139.0, 138.2, 136.1, 131.0, 115.5, 33.9, 29.9, 28.8; MS (EI) $m/z$ 294 ($M^+$, 100), 237, 199, 107. HRMS (EI) $m/z$ calcd for $C_{20}H_{22}O_2$, 294.1620; found, 294.1618. Anal. ($C_{20}H_{22}O_2$) C, H.

**4-Hydroxyhexanone (7).** In a three-necked round-bottom flask (500 mL) fitted with a mechanical stirrer, cyclohexane-1,4-diol (5.8 g, 50 mmol) was dissolved in 200 mL of acetone. The solution was cooled in an ice bath, and freshly prepared Jones reagent (1.6 M in acetone) was added over 25 min. The green-blue solution was allowed to warm to room temperature over 15 min. The reaction mixture was filtered through Celite and then evaporated. Flash column chromatography (EtOAc/hexane; 7:3) gave **7** (3.0 g, 53%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.17−4.23 (m, 1H), 2.55−2.66 (m, 2H), 2.25−2.36 (m, 2H), 1.91−2.11 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 211.0, 66.3, 37.1, 33.7. Registry No. 13482-22-9.

**4-Acetoxycyclohexanone (8).** To a solution of **7** (2.0 g, 18 mmol) in $CH_2Cl_2$ (20 mL) was added acetic anhydride (2.1 g, 21 mmol). Pyridine was added dropwise to the reaction mixture, which was stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure, and the residual oil was dissolved in EtOAc (100 mL). The EtOAc layer was washed with 2 M HCl solution (100 mL), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Flash column chromatography (EtOAc/hexane; 4:6) gave **8** (1.5 g, 56%) as an oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.15 (m, 1H), 2.49−2.57 (m, 2H), 2.32−2.37 (m, 2H), 2.09 (s, 3H), 2.03−2.08 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.2, 30.7, 37.2, 170.4, 209.8. Registry No. 41043-88-3.

**Methyl (4-Oxocyclohexylidene)acetate.** A mixture of 1,4-cyclohexanedione (4.7 g, 42 mmol) and methyl (triphenylphosphoranylidene)acetate (7.0 g, 21 mmol) in toluene (100 mL) was heated to 110 °C for 8 h. After the reaction was cooled to room temperature, the solvent was evaporated. $Et_2O$ (200 mL) was added, and the precipitate was filtered. The filtered organic layer was concentrated, and the residual oil was absorbed on silica gel. Flash column chromatography (EtOAc/hexane; 4:6) gave methyl (4-oxocyclohexylidene)acetate (3.1 g, 88%) as a white solid: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.85 (bt, $J$ = 1.5 Hz, 1H), 3.72 (s, 3H), 3.21 (td, $J$ = 7.5, 2.0 Hz, 2H), 2.66 (td, $J$ = 6.0, 1.5 Hz, 2H), 2.46−2.53 (m, 2H). Registry No. 91158-10-0.

**Methyl (4-Oxocyclohexyl)acetate (10).** To a solution of methyl (4-oxocyclohexylidene)acetate (2.97 g, 1.77 mmol) in ethanol (10 mL) was added 10% palladium charcoal (300 mg), and it was placed in a hydrogenation system. The reaction mixture was stirred at room temperature for 6 h. The solution was filtered through Celite and concentrated under reduced pressure. Flash column chromatography (EtOAc/hexane; 2:8) gave **10** (1.5 g, 50%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.69 (s, 3H), 2.42−2.35 (m, 4H), 2.22−2.35 (m, 2H), 2.04−2.13 (m, 2H), 1.04−1.54 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 211.2, 172.8, 51.6, 40.5, 40.0, 33.1, 32.4. Registry No. 66405-41-2.

**Methyl 3-Oxocyclohexanecarboxylate (12).** To a solution of 3-oxo-1-cyclohexanecarboxylic acid (1.0 g, 7.03 mmol) in methanol (12 mL) was added thionyl chloride (1.0 g, 8.4 mmol), slowly, at room temperature. The reaction mixture was stirred for 3 h and then quenched slowly by three drops of $H_2O$ in an ice bath. The reaction was neutralized by saturated $NaHCO_3$ solution, and the organic layer was extracted with EtOAc (30 mL). The organic layer was washed by $H_2O$ (10 mL) and dried over $Na_2SO_4$. After removal of the solvent, flash column chromatography (EtOAc/hexane; 2:8) gave **12** (0.803 g, 73%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.69 (s, 3H), 2.75−2.84 (m, 1H), 2.53 (d, $J$ = 8.0 Hz, 2H), 2.25−2.40 (m, 2H), 2.00−2.14 (m, 2H), 1.76−1.88 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 209.1, 174.1, 52.0, 43.1, 43.0, 40.9, 27.7, 24.4. Registry No. 13148-83-9.

**Dimethyl [2-(3-Oxocyclohexyl)]malonate (14).** To a solution of 2-cyclohexen-1-one (2.9 g, 30 mmol) and dimethyl malonate (4.4 g, 33 mmol) in THF (20 mL) was added potassium *tert*-butoxide (330 mg, 3.0 mmol). The reaction mixture was stirred at room temperature for 2 h. Water (5 mL) was added to the reaction mixture, and then more water (200 mL) was added. The organic layer was extracted with EtOAc (100 mL) and dried over $MgSO_4$. EtOAc was evaporated under reduced pressure, and flash column chromatography (EtOAc/hexane; 3:7) gave **14** (5.8 g, 85%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.75 (s, 3H), 3.74 (s, 3H), 3.34 (d, $J$ = 8.0 Hz, 1H), 2.48−2.59 (m, 1H), 2.36−2.46 (m, 2H), 2.20−2.30 (m, 2H), 2.02−2.12 (m, 1H), 1.89−1.97 (m, 1H), 1.60−1.75 (m, 1H), 1.44−1.56 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 209.5, 168.25, 168.16, 56.6, 53.0, 45.1, 41.0, 38.1, 28.8, 24.5. Registry No. 33646-18-3.

**3-(3-Acetoxy-*n*-propyl)cyclohexanone (15).** 3-Chloropropanol (1.9 g, 20 mmol) was added to a two-necked, round-bottom flask containing freshly distilled THF (40 mL), and the reaction was cooled to −78 °C under nitrogen. Methylmagnesium chloride (6.8 mL, 20 mmol, 22 w/w % in THF) solution was added slowly by syringe. The mixture was allowed to warm, and it was stirred at room temperature for 20 min. After addition of Mg (583 mg, 24 mmol), the reaction mixture was heated at 90 °C, and 1,2-dibromoethane (37 $\mu$L, 0.48 mmol) was added. The solution was refluxed for 1 h. After cooling, the reaction mixture was slowly added dropwise over 30 min by cannulus to a one-necked flask containing 2-cyclohexen-1-one (1.94 mL, 20 mmol) and copper(I) bromide (286 mg, 2 mmol) in THF at −78 °C. As soon as the addition was finished, the reaction temperature was increased to 0 °C and decreased again to −78 °C. The reaction was quenched by HCl, and it was dissolved in ether (1.0 M, 40 mL) and saturated ammonium chloride (15 mL). The reaction temperature was increased to room temperature. The mixture was filtered, and the solvent was evaporated under reduced pressure. The residual oil was dissolved with EtOAc (100 mL) and washed with ammonium chloride solution (100 mL) and brine (100 mL). The organic layer was dried by sodium sulfate, and flash column chromatography (EtOAc/hexane; 6:4) gave 3-(3-hydroxy-*n*-propyl)cyclohexanone (590 mg, 19%) as an oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.57 (d, $J$ = 6.0 Hz, 2H), 2.15−2.52 (m, 4H), 1.92−2.10 (m, 2H), 1.82−1,92 (m, 1H), 1.69−1.82 (m, 1H), 1.46−1.68 (m, 3H), 1.24−1.67 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 212.2, 62.5, 48.0, 41.3, 38.8, 32.5, 31.1, 29.6, 25.1. Registry No. 69441-81-2. Purified 3-(3-hydroxy-*n*-propyl)cyclohexanone (580 mg, 3.71 mmol) was stirred with acetic anhydride (450 $\mu$L, 4.83 mmol) and pyridine (780 mL, 9.65 mmol) in $CH_2Cl_2$ (15 mL) at room temperature. After the solution was stirred for 18 h, $CH_2Cl_2$ (50 mL) was added, and the reaction was placed in a separatory funnel. The organic layer was washed with a saturated $NaHCO_3$ solution and saturated ammonium chloride solution, dried over $Na_2SO_4$, filtered, and concentrated. Flash column chromatography (EtOAc/hexane; 3:7) gave **15** (329 mg, 45%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.03 (t, $J$ = 6.4 Hz, 2H), 2.38−2.46 (m, 1H), 2.31−2.38 (m, 1H), 2.18−2.29 (m, 1H), 2.18−2.09 (m, 2H), 2.03 (s, 3H), 1.85−1.94 (m, 1H), 1.71−1.83 (m, 1H), 1.57−1.70 (m, 3H), 1.27−1.45 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 211.5, 171.1, 64.3, 48.0, 41.2, 38.7, 32.7, 31.1, 25.8, 25.1, 20.9; MS (EI) $m/z$ 198 ($M^+$), 155, 138, 110, 97 (100), 84, 67. HRMS (EI) $m/z$ calcd for $C_{11}H_{18}O_3$, 198.1256; found, 198.1253.

**4-Acetoxy-1-[bis(4-hydroxyphenyl)methylene]cyclohexane (16).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 1.17 g, 5.4 mmol), **8** (850 mg, 5.4 mmol), Zn (2.7 g, 41 mmol), and titanium(IV) chloride (3.8 g, 20.1 mmol), **16** (1.5 g, 83%) was obtained as a white solid: mp 208−210 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 6.93 (d, $J$ = 8.4 Hz, 4H), 6.75 (d, $J$ = 8.4 Hz, 4H), 4.90 (septet, $J$ = 4.0 Hz, 1H), 2.55−2.45 (m, 2H), 2.11−2.21 (m,, 2H), 1.93 (s, 3H), 1.92−1.83 (m, 2H), 1.62−1.51 (m, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 169.9, 155.8, 135.2, 133.8, 133.4, 130.3, 114.7, 72.2, 32.2, 28.1, 21.1; MS $m/z$ (EI) 338 ($M^+$), 278 (100). HRMS (EI) $m/z$ calcd for $C_{21}H_{22}O_4$, 338.1518; found, 338.1517.

**4-Acetoxy-1-[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane (17a).** According to the general procedure for MOM

protection with **16** (1.5 g, 4.4 mmol), methoxymethyl chloride (779 mg, 9.7 mmol), sodium hydride (380 mg, 10 mmol), and DMF (15 mL), **17a** (1.5 g, 78%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 9.0 Hz, 4H), 6.95 (d, $J$ = 9.0 Hz, 4H), 5.15−5.18 (m, 4H), 5.03−4.93 (m, 1H), 3.46−3.50 (m, 6H), 2.51−2.56 (m, 2H), 2.13−2.18 (m, 2H), 2.04−2.07 (m, 3H), 1.89−1.92 (m, 2H), 1.61−1.64 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 170.6, 155.7, 136.5, 135.5, 135.0, 130.7, 115.6, 94.4, 71.9, 56.0, 32.6, 28.5, 21.4; MS (EI) *m*/*z* 426 ($M^+$), 366 (100). HRMS (EI) *m*/*z* calcd for $C_{25}H_{30}O_6$, 426.2042; found, 426.2036.

**4-[Bis(4-methoxymethoxyphenyl)methylene]cyclohexanol (17b).** Compound **16** (1.4 g, 3.3 mmol) was dissolved in methanol (15 mL) and $H_2O$ (3 mL). After the addition of potassium carbonate (2.3 g, 16 mmol), the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was slowly added to a two-phase solution of EtOAc (100 mL) and $H_2O$ (100 mL) with stirring, and the mixture was neutralized by 2 M HCl solution. The organic layer was collected and dried over sodium sulfate. After the solvent was removed, flash column chromatography (EtOAc/hexane; 4:6) gave **17b** (1.2 g, 95%) as a white solid: mp 74−76 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.02 (d, $J$ = 9.0 Hz, 4H), 6.94 (d, $J$ = 9.0 Hz, 4H), 5.15 (s, 4H), 3.89 (septet, $J$ = 4.5 Hz, 1H), 3.48 (s, 6H), 2.57 (dt, $J$ = 11.2, 4.3 Hz, 2H), 2.01−2.11 (m, 2H), 1.98−1.88 (m, 2H), 1.54−1.42 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.7, 136.7, 136.1, 134.7, 130.7, 115.6, 94.4, 69.7, 56.0, 36.3, 28.7; MS *m*/*z* (EI) 384 ($M^+$, 100), 366. HRMS (EI) *m*/*z* calcd for $C_{23}H_{28}O_5$, 384.1937; found, 384.1928.

**4-[Bis(4-hydroxyphenyl)methylene]cyclohexanol (18).** According to the general procedure for MOM deprotection with **17b** (120 mg, 0.31 mmol), HCl (200 $\mu$L), and methanol (10 mL), **18** (78 mg, 85%) was obtained as an off-white solid: mp 209 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.82 (d, $J$ = 8.4 Hz, 4H), 6.66 (d, $J$ = 8.8 Hz, 4H), 3.60−3.70 (m, 1H), 2.34−2.44 (m, 2H), 1.90−2.00 (m, 2H), 1.70−1.82 (m, 2H), 1.24−1.36 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 155.6, 135.3, 134.2, 133.7, 130.4, 114.7, 67.6, 36.3, 28.5; MS (EI) *m*/*z* 296 ($M^+$, 100), 278, 237, 199, 107. HRMS (EI) *m*/*z* calcd for $C_{19}H_{20}O_3$, 296.1412; found, 296.1419. Anal. ($C_{19}H_{20}O_3 \cdot 0.2H_2O$) C, H.

**4-Fluoro[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (19).** In a one-necked round-bottom flask, which contained **17b** (200 mg, 0.52 mmol), $CH_2Cl_2$ (5 mL) was added under nitrogen, and the reaction mixture was cooled to −78 °C. Diethylaminosulfur trifluoride (120 mg, 0.62 mmol) was dropped very slowly by syringe at −78 °C. The cooling was removed, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was cooled again to −78 °C, and methanol (200 $\mu$L) was added. The solution was additionally stirred for 30 min after removal of the dry ice bath, and the reaction was quenched by saturated $NaHCO_3$ solution and extracted with excess EtOAc. The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography (EtOAc/hexane; 1:9) gave **19** (65 mg, 32%) as a slightly yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 8.5 Hz, 4H), 6.94 (d, $J$ = 8.5 Hz, 4H), 5.16 (s, 4H), 4.81 (dm, $^2J_{HF}$ = 48.5 Hz, 1H), 3.48 (s, 6H), 2.45−2.52 (m, 2H), 2.16−2.25 (m, 2H), 1.78−1.93 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.7, 136.5, 135.4, 135.1, 130.7, 115.7, 94.4, 90.5 (d, $^1J_{CF}$ = 168.6 Hz), 56.0, 33.3 (d, $^2J_{CF}$ = 19.3 Hz), 27.3 (d, $^3J_{CF}$ = 6.4 Hz); MS (EI) *m*/*z* 386 ($M^+$, 100). HRMS (EI) *m*/*z* calcd for $C_{23}H_{27}O_4F$, 386.1893; found, 386.1889.

**4-Fluoro[bis(4-hydroxyphenyl)methylene]cyclohexane (20).** According to the general procedure for MOM deprotection with **19** (45 mg, 0.12 mmol), HCl (100 $\mu$L), and methanol (4 mL), **20** (25 mg, 71%) was obtained as an off-white solid: mp 202−203 °C; $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 6.93 (d, $J$ = 9.0 Hz, 4H), 6.75 (d, $J$ = 8.5 Hz, 4H), 4.78 (dm, $^2J_{HF}$ = 49.0 Hz, 1H), 2.41−2.48 (m, 2H), 2.16−2.24 (m, 2H), 1.82−1.95 (m, 2H), 1.69−1.79 (m, 2H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 156.79, 136.72, 135.23, 135.05, 131.48, 115.55, 90.53 (d, $^1J_{CF}$ = 168.6 Hz), 34.05 (d, $^2J_{CF}$ = 19.3 Hz), 28.11 (d, $^3J_{CF}$ = 6.38 Hz); MS (EI) *m*/*z* 298 ($M^+$), 184, 141, 128, 115, 77 (100). HRMS (EI) *m*/*z* calcd for $C_{19}H_{19}O_2F$, 298.1369; found 298.1362. Anal. ($C_{19}H_{19}O_2F \cdot 0.1H_2O$) C, H.

**Ethyl 4-[Bis(4-hydroxyphenyl)methylene]cyclohexanecarboxylate (21a).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 2.1 g, 10 mmol), ethyl 4-oxocyclohexanecarboxylate (1.7 g, 10 mmol), Zn (4.9 g, 75 mmol), and titanium(IV) chloride (7.0 g, 37 mmol), **21a** (2.7 g, 77%) was obtained as a white solid: mp 198−200 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 7.01 (d, $J$ = 8.5 Hz, 4H), 6.94 (d, $J$ = 8.5 Hz, 4H), 4.08 (q, $J$ = 7.2 Hz, 2H), 2.49−2.64 (m, 3H), 1.90−2.10 (m, 4H), 1.50−1.64 (m, 2H), 1.21 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 206.2, 175.4, 156.7, 136.2, 135.9, 135.2, 131.5, 115.5, 60.5, 43.6, 31.3, 29.6, 14.5; MS (EI) *m*/*z* 352 ($M^+$, 100), 278, 237, 199, 107. HRMS (EI) *m*/*z* calcd for $C_{22}H_{24}O_4$, 352.1675; found, 352.1677. Anal. ($C_{22}H_{24}O_4 \cdot 0.2H_2O$) C, H.

**Ethyl 4-[Bis(4-methoxymethylphenyl)methylene]cyclohexanecarboxylate (22a).** According to the general procedure for MOM protection with **21a** (2.1 g, 6.0 mmol), methoxymethyl chloride (1.6 g, 20 mmol), sodium hydride (440 mg, 13 mmol), and DMF (15 mL), **22a** (2.5 g, 95% yield) was obtained as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 8.8 Hz, 4H), 6.93 (d, $J$ = 8.4 Hz, 4H), 5.15 (s, 4H), 4.13 (q, $J$ = 7.2 Hz, 2H), 3.48 (s, 6H), 2.60 (bd, $J$ = 12.8 Hz, 2H), 2.48−2.68 (m, 1H), 1.92−2.06 (m, 4H), 1.54−1.69 (m, 2H), 1.25 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.6, 155.6, 136.5, 136.1, 134.7, 130.7, 115.6, 94.4, 60.2, 56.0, 43.1, 30.7, 30.5, 14.2; MS (EI) *m*/*z* 440 ($M^+$, 100). HRMS (EI) *m*/*z* calcd for $C_{26}H_{32}O_6$, 440.2199; found, 440.2204.

**4-Hydroxymethyl[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane (23a).** According to the general procedure for reduction with **22a** (2.5 g, 5.7 mmol), $LiAlH_4$ in THF solution (1 M, 5.7 mL), and THF (15 mL), **23a** (2.0 g, 89%) was obtained as a white foam: mp 72 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.02 (d, $J$ = 8.8 Hz, 4H), 6.94 (d, $J$ = 8.8 Hz, 4H), 5.15 (s, 4H), 3.49 (d, $J$ = 6.4 Hz, 2H), 3.48 (s, 6H), 2.65 (bd, $J$ = 13.6 Hz, 2H), 1.90−2.01 (m, 2H), 1.81−1.90 (m, 2H), 1.63−1.80 (m, 1H), 1.03−1.18 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.5, 137.7, 136.8, 133.9, 130.8, 115.5, 94.4, 68.0, 56.0, 40.4, 31.1, 31.0; MS (EI) *m*/*z* 398 ($M^+$), 303 (100), 247, 111. HRMS (EI) *m*/*z* calcd for $C_{24}H_{30}O_5$, 398.2093; found, 398.2101.

**4-Hydroxymethyl[bis(4-hydroxyphenyl)methylene]cyclohexane (24a).** According to the general procedure for MOM deprotection with **23a** (100 mg, 0.25 mmol), HCl (300 $\mu$L), and methanol (4 mL), **24a** (69 mg, 90%) was obtained as a white solid: mp 211−212 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 6.91 (d, $J$ = 8.8 Hz, 4H), 6.74 (d, $J$ = 8.8 Hz, 4H), 3.38 (d, $J$ = 6.0 Hz, 2H), 2.62 (bd, $J$ = 13.6 Hz, 2H), 1.80−1.98 (m, 4H), 1.61−1.73 (m, 1H), 1.02−1.15 (m, 2H); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 156.6, 137.7, 135.6, 135.4, 131.5, 115.4, 67.7, 41.6, 32.1, 32.0; MS (EI) *m*/*z* 310 ($M^+$), 256 (100), 225, 199, 107, 64. HRMS (EI) *m*/*z* calcd for $C_{20}H_{22}O_3$, 310.1569; found, 310.1562. Anal. ($C_{20}H_{22}O_3$) C, H.

**4-Methanesulfonyloxymethyl[bis(4-methoxymethoxyphenyl)-methylene]cyclohexane (25a).** According to the general procedure for methanesulfonylation with **24a** (90 mg, 0.23 mmol), methanesulfonic anhydride (94 mg, 0.54 mmol), triethylamine (68 mg, 0.68 mmol), and $CH_2Cl_2$ (5 mL), **25a** (102 mg, 95%) was obtained as an off-white solid: mp 79−80 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 9.0 Hz, 4H), 6.94 (d, $J$ = 9.5 Hz, 4H), 5.15 (s, 4H), 4.08 (d, $J$ = 6.5 Hz, 2H), 3.48 (s, 6H), 3.00 (s, 3H), 2.66 (bd, $J$ = 13.5 Hz, 2H), 1.97−2.04 (m, 3H), 1.84−1.96 (m, 2H), 1.14−1.24 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.6, 136.5, 136.4, 134.7, 130.7, 115.6, 94.4, 74.1, 55.9, 37.4, 37.1, 30.7, 30.5; MS (EI) *m*/*z* 476 ($M^+$, 100), 446, 41, 380, 335. HRMS (EI) *m*/*z* calcd for $C_{25}H_{32}O_7S$, 476.1869; found, 476.1873.

**4-Fluoromethyl[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane.** According to the general procedure for fluorination with **25a** (167 mg, 0.35 mmol), cesium fluoride (266 mg, 1.8 mmol), $H_2O$ (50 $\mu$L) in 1-butyl-3-methyl-imidazolium tetrafluoroboronate (1.5 mL), and acetonitrile (1.5 mL), 4-fluoromethyl-[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (89 mg, 63%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$

7.02 (d, $J$ = 9.0 Hz, 4H), 6.94 (d, $J$ = 9.0 Hz, 4H), 5.16 (s, 4H), 4.26 (dd, $^2J_{HF}$ = 47.5 Hz, $J$ = 6.0 Hz, 2H), 3.48 (s, 6H), 2.66 (bd, $J$ = 13.5 Hz, 2H), 1.89−2.02 (m, 3H), 1.81−1.89 (m, 2H), 1.12−1.24 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.6, 137.1, 136.7, 134.4, 130.8, 115.6, 94.5, 88.0 (d, $^1J_{CF}$ = 166.6 Hz), 56.0, 38.5 (d, $^2J_{CF}$ = 18.3 Hz), 30.9, 30.0 (d, $^3J_{CF}$ = 5.5 Hz); MS (EI) *m*/*z* 400 ($M^+$, 100), 355, 149. HRMS (EI) *m*/*z* calcd for $C_{24}H_{29}O_4F$, 400.2050; found, 400.2045.

**4-Fluoromethyl[bis(4-hydroxyphenyl)methylene]cyclohexane (26a).** According to the general procedure for MOM deprotection with 4-fluoromethyl[bis(4-methoxymethoxyphenyl)-methylene]-cyclohexane (89 mg, 0.22 mmol), HCl (100 $\mu$L), and methanol (8 mL), **26a** (38 mg, 55%) was obtained as a white solid: mp 201−202 °C; $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 6.92 (d, $J$ = 8.5 Hz, 4H), 6.75 (d, $J$ = 8.5 Hz, 4H), 4.28 (dd, $^2J_{HF}$ = 47.5 Hz, $J$ = 6.0 Hz, 2H), 2.64 (bd, $J$ = 13.5 Hz, 2H), 1.86−2.01 (m, 3H), 1.78−1.85 (m, 2H), 1.12−1.22 (m, 2H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 156.7, 136.8, 135.9, 135.4, 131.5, 115.5, 88.5 (d, $^1J_{CF}$ = 165.8 Hz), 39.4 (d, $^2J_{CF}$ = 18.3 Hz), 31.6, 30.7 (d, $^3J_{CF}$ = 5.5 Hz); MS (EI) *m*/*z* 312 ($M^+$, 100), 199, 149, 107. HRMS (EI) *m*/*z* calcd for $C_{20}H_{21}O_2F$, 312.1526, found, 312.1524. Anal. ($C_{20}H_{21}O_2F$) C, H.

**4-Ethoxymethyl[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane.** To a solution of **23a** (200 mg, 0.49 mmol) in DMF (7 mL), which was contained in a pressure tube, was added sodium hydride (35 mg, 0.97 mmol) under $N_2$. After the solution was stirred for 10 min, bromoethane (158 mg, 0.15 mmol) was added. The pressure tube was tightly capped, and the temperature of the reaction mixture was increased to 100 °C. The mixture was stirred for 24 h and cooled. The mixture was poured into $H_2O$ (50 mL) and EtOAc (100 mL) solution. The extracted organic layer was washed with saturated ammonium chloride (100 mL × 2) solution and saturated brine (100 mL) and dried ($MgSO_4$). The organic layer was concentrated, and flash column chromatography (EtOAc/hexane; 15:85) gave 4-ethoxymethyl[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (74 mg, 36%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.02 (d, $J$ = 8.8 Hz, 4H), 6.93 (d, $J$ = 8.8 Hz, 4H), 5.15 (s, 4H), 3.44−3.52 (m, 7H), 3.27 (d, $J$ = 6.0 Hz, 2H), 2.62 (bd, $J$ = 13.6 Hz, 2H), 1.76−2.01 (m, 5H), 1.20 (t, $J$ = 6.8 Hz, 3H), 1.14−1.24 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.5, 138.0, 136.9, 133.8, 130.8, 115.5, 94.4, 75.9, 66.4, 56.0, 38.1, 31.7, 31.2, 15.2; MS (EI) *m*/*z* 426 ($M^+$, 100), 302, 287, 149; HRMS (EI) *m*/*z* calcd for $C_{26}H_{34}O_5$, 426.2406; found, 426.2400.

**4-Ethoxymethyl[bis(4-hydroxyphenyl)methylene]cyclohexane (27).** According to the general procedure for MOM deprotection with 4-ethoxymethyl[bis(4-methoxymethoxyphenyl)-methylene]cyclohexane (74 mg, 0.17 mmol), HCl (200 $\mu$L), and methanol (5 mL), **27** (43 mg, 73%) was obtained as a white crystal: mp 209−210 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 6.91 (d, $J$ = 8.8 Hz, 4H), 6.74 (d, $J$ = 8.8 Hz, 4H), 3.41 (q, $J$ = 6.8 Hz, 2H), 3.23 (d, $J$ = 6.0 Hz, 2H), 2.61 (bd, $J$ = 13.6 Hz, 2H), 1.87−1.98 (m, 2H), 1.71−1.86 (m, 3H), 1.03−1.16 (m, 5H); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 156.5, 137.5, 135.5, 135.4, 131.5, 115.4, 76.3, 66.7, 39.1, 32.4, 31.9, 15.5; MS (EI) *m*/*z* 338 ($M^+$, 100), 199, 149. HRMS (EI) *m*/*z* calcd for $C_{22}H_{26}O_3$, 338.1882; found, 338.1887. Anal. ($C_{22}H_{26}O_3$) C, H.

**4-Methyl[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane.** According to the general procedure for reduction with **25a** (300 mg, 0.63 mmol), $LiAlH_4$ in THF solution (1 M, 900 $\mu$L), and THF (8 mL), 4-methyl[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (240 mg, 99%) was obtained as an oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.03 (d, $J$ = 8.8 Hz, 4H), 6.94 (d, $J$ = 8.8 Hz, 4H), 5.16 (s, 4H), 3.49 (s, 6H), 2.59 (bd, $J$ = 13.6 Hz, 2H), 1.94 (td, $J$ = 12.8, 4.0 Hz, 2H), 1.72−1.80 (m, 2H), 1.55−1.68 (m, 1H), 1.01−1.14 (m, 2H), 0.93 (d, $J$ = 6.4 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.4, 138.2, 137.0, 133.4, 130.8, 115.5, 94.4, 56.0, 36.8, 32.7, 31.7, 22.0; MS (EI) *m*/*z* 382 ($M^+$, 100). HRMS (EI) *m*/*z* calcd for $C_{24}H_{30}O_4$, 382.2144; found, 382.2135.

**4-Methyl[bis(4-hydroxyphenyl)methylene]cyclohexane (29a).** According to the general procedure for MOM deprotection with 4-methyl[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (240 mg, 0.63 mmol), HCl (200 $\mu$L), methanol (5 mL), and $Et_2O$ (2.5 mL), **29a** (152 mg, 82%) was obtained as an off-white solid: mp 183−184 °C; $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ 6.86 (d, $J$ = 8.8 Hz, 4H), 6.66 (d, $J$ = 8.8 Hz, 4H), 2.57 (bd, $J$ = 14.0 Hz, 2H), 1.94 (td, $J$ = 13.4, 3.6 Hz, 2H), 1.69−1.79 (m, 2H), 1.53−1.67 (m, 1H), 0.97−1.10 (m, 2H), 0.92 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, methanol-$d_4$) $\delta$ 156.7, 137.9, 136.2, 135.9, 131.9, 115.5, 38.0, 34.1, 32.8, 22.5; MS (EI) *m*/*z* 294 ($M^+$, 100), 199, 107. Anal. ($C_{20}H_{22}O_2 \cdot 0.1H_2O$) C, H.

**Methyl {4-[Bis(4-hydroxyphenyl)methylene]cyclohexyl}acetate (21b).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 957 mg, 4.5 mmol), **10** (760 mg, 4.5 mmol), Zn (2.2 g, 34 mmol), and titanium(IV) chloride (3.1 g, 17 mmol), **21b** (1.1 g, 71%) was obtained as a white solid: mp 201−203 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 6.91 (d, $J$ = 8.8 Hz, 4H), 6.74 (d, $J$ = 8.8 Hz, 4H), 3.60 (s, 3H), 2.59 (bd, $J$ = 13.6 Hz, 2H), 2.23 (d, $J$ = 6.8 Hz, 2H), 1.89−2.02 (m, 3H), 1.76−1.85 (m, 2H), 1.06−1.18 (m, 2H); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 173.3, 156.6, 136.8, 135.7, 135.4, 131.5, 115.4, 51.4, 41.5, 35.7, 35.0, 32.0; MS (EI) *m*/*z* 352 ($M^+$), 166, 107 (100), 77. HRMS (EI) *m*/*z* calcd for $C_{22}H_{24}O_4$, 352.1675; found, 352.1670. Anal. ($C_{22}H_{24}O_4$) C, H.

**Methyl {4-[Bis(4-methoxymethoxyphenyl)methylene]cyclohexyl}acetate (22b).** According to the general procedure for MOM protection with **21b** (980 mg, 2.8 mmol), methoxymethyl chloride (736 mg, 9.1 mmol), sodium hydride (309 mg, 9.1 mmol), and DMF (15 mL), **22b** (1.2 g, 97%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.00 (d, $J$ = 9.0 Hz, 4H), 6.92 (d, $J$ = 8.5 Hz, 4H), 5.15 (s, 4H), 3.66 (s, 3H), 3.48 (s, 6H), 2.60 (bd, $J$ = 14.0 Hz, 2H), 2.24 (d, $J$ = 7.5 Hz, 2H), 1.92−2.08 (m, 3H), 1.78−1.86 (m, 2H), 1.08−1.19 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.5, 155.6, 137.2, 136.8, 134.1, 130.8, 115.6, 94.4, 56.0, 51.4, 41.2, 34.8, 34.4, 31.3; MS (EI) *m*/*z* 440 ($M^+$), 320, 210, 180, 151, 121 (100), 84. HRMS (EI) *m*/*z* calcd for $C_{26}H_{32}O_6$, 440.2199; found, 440.2196.

**4-(2-Hydroxyethyl)[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane (23b).** According to the general procedure for reduction with **22b** (1.15 g, 2.6 mmol), $LiAlH_4$ in THF solution (1 M, 2.6 mL), and THF (10 mL), **23b** (1.0 g, 96%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 8.5 Hz, 4H), 6.93 (d, $J$ = 9.0 Hz, 4H), 5.15 (s, 4H), 3.70 (t, $J$ = 6.5 Hz, 2H), 3.48 (s, 6H), 2.60 (bd, $J$ = 14.0 Hz, 2H), 1.89−1.99 (m, 2H), 1.79−1.85 (m, 2H), 1.62−1.71 (m, 1H), 1.52 (q, $J$ = 6.5 Hz, 2H), 1.05−1.15 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.5, 138.0, 136.9, 136.7, 130.8, 115.6, 94.5, 60.9, 56.00, 55.99, 39.6, 34.8, 34.2, 31.6; MS (EI) *m*/*z* 412 ($M^+$, 100). HRMS (EI) *m*/*z* calcd for $C_{25}H_{32}O_5$, 412.2250; found, 412.2246.

**4-(2-Hydroxyethyl)[bis(4-hydroxyphenyl)methylene]cyclohexane (24b).** According to the general procedure for MOM deprotection with **23b** (45 mg, 0.11 mmol), HCl (200 $\mu$L), and methanol (5 mL), **24b** (30 mg, 84%) was obtained as a white solid: mp 183 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 6.91 (d, $J$ = 8.8 Hz, 4H), 6.74 (d, $J$ = 6.8 Hz, 4H), 3.58 (bt, $J$ = 6.4 Hz, 2H), 2.59 (bd, $J$ = 13.2 Hz, 2H), 1.94 (td, $J$ = 13.2, 4.4 Hz, 2H), 1.77−1.86 (m, 2H), 1.61−1.75 (m, 1H), 1.44 (q, $J$ = 6.8 Hz, 2H), 1.00−1.13 (m, 2H); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 156.5, 137.7, 135.6, 135.2, 131.6, 115.4, 60.3, 40.6, 35.6, 35.1, 32.3; MS (EI) *m*/*z* 324 ($M^+$, 100), 137, 199, 107. HRMS (EI) *m*/*z* calcd for $C_{21}H_{24}O_3$, 324.1725; found, 324.1726. Anal. ($C_{21}H_{24}O_3$) C, H.

**4-(2-Methanesulfonyloxyethyl)[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (25b).** According to the general procedure for methanesulfonylation with **24b** (448 mg, 1.1 mmol), methanesulfonic anhydride (284 mg, 1.6 mmol), triethylamine (331 mg, 3.3 mmol), and $CH_2Cl_2$ (6 mL), **25b** (500 mg, 93%) was obtained as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.00 (d, $J$ = 8.8 Hz, 4H), 6.93 (d, $J$ = 8.8 Hz, 4H), 5.15 (s, 4H), 4.28 (t, $J$ = 6.4 Hz, 2H), 3.48 (s, 6H), 3.30 (s, 3H), 2.61 (bd, $J$ = 13.6 Hz, 2H), 1.95 (td, $J$ = 13.2, 3.6 Hz, 2H), 1.78−1.87 (m, 2H), 1.65−1.75 (m, 3H), 1.05−1.17 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.6, 137.2, 137.0, 134.1, 130.8, 115.6, 94.4, 68.2, 56.0, 37.4,

35.7, 34.3, 34.0, 31.3; MS (EI) *m/z* 490 ($M^+$), 446, 427 (100). HRMS (EI) *m/z* calcd for $C_{26}H_{34}O_7S$, 490.2025; found 490.2024.

**4-(2-Fluoroethyl)[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane.** According to the general procedure for fluorination with **25b** (150 mg, 0.31 mmol), cesium fluoride (235 mg, 1.6 mmol), $H_2O$ (20 $\mu$L), 1-butyl-3-methyl-imidazolium tetrafluoroboronate (1.0 mL), and acetonitrile (1.0 mL), 4-(2-fluoroethyl)[bis-(4-methoxymethoxyphenyl)methylene]cyclohexane (106 mg, 82%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.03 (d, $J$ = 8.5 Hz, 4H), 6.95 (d, $J$ = 8.5 Hz, 4H), 5.16 (s, 4H), 4.51 (dt, $^2J_{HF}$ = 47 Hz, $J$ = 6.0 Hz, 2H), 3.49 (s, 6H), 2.63 (bd, $J$ = 13.5 Hz, 2H), 1.96 (td, $J$ = 13.0, 3.5 Hz, 2H), 1.81−1.90 (m, 2H), 1.60−1.78 (m, 3H), 1.07−1.18 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.5, 137.7, 136.8, 133.8, 130.8, 115.5, 94.4, 82.4 (d, $^1J_{CF}$ = 163.0 Hz), 55.94, 55.91, 37.0 (d, $^2J_{CF}$ = 19.3 Hz), 34.5, 34.0 (d, $^3J_{CF}$ = 4.6 Hz), 31.4; MS (EI) *m/z* 414 ($M^+$, 100), 149. HRMS (EI) *m/z* calcd for $C_{25}H_{31}O_4F$, 414.2206; found, 414.2202.

**4-(2-Fluoroethyl)[bis(4-hydroxyphenyl)methylene]cyclohexane (26b).** According to the general procedure for MOM deprotection with 4-(2-fluoroethyl)[bis(4-methoxymethoxyphenyl)-methylene]cyclohexane (100 mg, 0.24 mmol), HCl (200 $\mu$L), and methanol (5 mL), **26b** (66 mg, 84%) was obtained as a white solid: mp 192−193 °C; $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 6.91 (d, $J$ = 8.5 Hz, 4H), 6.74 (d, $J$ = 8.5 Hz, 4H), 4.49 (dt, $^2J_{HF}$ = 48.0 Hz, $J$ = 6.0 Hz, 2H), 2.60 (bd, $J$ = 14.0 Hz, 2H), 1.94 (td, $J$ = 13.5, 3.5 Hz, 2H), 1.80−1.87 (m, 2H), 1.64−1.74 (m, 1H), 1.62 (dq, $^3J_{HF}$ = 25.5 Hz, $J$ = 6.5 Hz, 2H), 1.05−1.17 (m, 2H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 156.6, 137.3, 135.54, 135.46, 131.6, 115.5, 82.9 (d, $^1J_{CF}$ = 162.0 Hz), 37.8 (d, $^2J_{CF}$ = 19.3 Hz), 35.3, 34.96 (d, $^3J_{CF}$ = 4.6 Hz), 32.2; MS (EI) *m/z* 326 ($M^+$), 168, 141, 115, 77, 57 (100). HRMS (EI) *m/z* calcd for $C_{21}H_{23}O_2F$, 326.1682; found, 326.1680. Anal. ($C_{21}H_{23}O_2F\cdot 0.1H_2O$) C, H.

**4-[2-(4-Fluorobutoxy)ethyl][bis(4-methoxymethoxyphenyl)-methylene]cyclohexane.** To a solution of **23b** (120 mg, 0.29 mmol) in DMF (4 mL) was added sodium hydride (15 mg, 0.44 mmol) at 0 °C under nitrogen. After addition of 1-bromo-4-fluorobutane (54 mg, 0.35 mmol), the reaction mixture was stirred at 100 °C for 24 h and cooled to room temperature. The mixture was poured into $H_2O$ (50 mL) and EtOAc (100 mL) solution, and the organic layer was extracted. This was washed with saturated ammonium chloride (100 mL × 2) solution and saturated brine (100 mL) and dried over $MgSO_4$. After removal of the solvent, flash column chromatography (EtOAc/hexane; 3:7) gave 4-[2-(4-fluorobutoxy)ethyl][bis-(4-methoxymethoxyphenyl)methylene]cyclohexane (37 mg, 26%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.01(d, $J$ = 9.0 Hz, 4H), 6.93 (d, $J$ = 9.0 Hz, 4H), 5.15 (s, 4H), 4.45 (dt, $^2J_{HF}$ = 47.0 Hz, $J$ = 6.0 Hz, 2H), 3.48 (s, 6H), 3.46 (t, $J$ = 6.0 Hz, 2H), 3.44 (t, $J$ = 6.0 Hz, 2H), 2.59 (bd, $J$ = 13.5 Hz, 2H), 1.94 (td, $J$ = 13.0, 3.5 Hz, 2H), 1.58−1.86 (m, 7H), 1.52 (q, $J$ = 7.0 Hz, 2H), 1.04−1.14 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.5, 138.2, 136.9, 133.5, 130.8, 115.5, 94.4, 84.0 (d, $^1J_{CF}$ = 163.9 Hz), 70.2, 68.8, 55.97, 55.96, 36.4, 34.8, 34.6, 31.6, 27.3 (d, $^2J_{CF}$ = 20.1 Hz), 25.5 (d, $^3J_{CF}$ = 5.5 Hz); MS (EI) *m/z* 486 ($M^+$, 100), 426, 287, 149, 121. HRMS (EI) *m/z* calcd for $C_{29}H_{39}O_5F$, 486.2781; found, 486.2778.

**4-[2-(4-Fluorobutoxy)ethyl][bis(4-hydroxyphenyl)methylene]-cyclohexane (28).** According to the general procedure for MOM deprotection with 4-[2-(4-fluorobutoxy)ethyl][bis(4-methoxymethoxyphenyl)methylene]cyclohexane (32 mg, 0.066 mmol), HCl (200 $\mu$L), and methanol (3 mL), **28** (20 mg, 76%) was obtained as a white solid: mp 129 °C; $^1$H NMR (500 MHz, acetone-$d_6$) $\delta$ 6.91 (d, $J$ = 8.5 Hz, 4H), 6.74 (d, $J$ = 9.0 Hz, 4H), 4.44 (dt, $^2J_{HF}$ = 47.5 Hz, $J$ = 6.0 Hz, 2H), 3.44 (t, $J$ = 6.5 Hz, 2H), 3.41 (t, $J$ = 6.0 Hz, 2H), 2.59 (bd, $J$ = 13.5 Hz, 2H), 1.92 (td, $J$ = 13.0, 4.0 Hz, 2H), 1.77−1.85 (m, 2H), 1.59−1,77 (m, 5H), 1.48 (q, $J$ = 7.0 Hz, 2H), 1.03−1.13 (m, 2H); $^{13}$C NMR (125 MHz, acetone-$d_6$) $\delta$ 156.6, 137.6, 135.6, 135.3, 131.6, 115.4, 84.5 (d, $^1J_{CF}$ = 162.1 Hz), 70.7, 69.3, 37.3, 35.60, 35.57, 32.3, 28.2 (d, $^2J_{CF}$ = 20.1 Hz), 26.3 (d, $^3J_{CF}$ = 5.5 Hz); MS (EI) *m/z* 446 ($M^+$, 100), 398, 199, 107. HRMS (EI) *m/z* calcd for $C_{25}H_{31}O_3F$, 398.2257; found, 398.2265. Anal. ($C_{21}H_{24}O_3\cdot 0.1H_2O$) C, H.

**4-Ethyl[bis(4-methoxymethoxyphenyl)methylene]cyclohexane.** According to the general procedure for reduction with **25b** (175 g, 0.35 mmol), $LiAlH_4$ in THF solution (1 M, 700 $\mu$L), and THF (10 mL), 4-ethyl[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane (130 mg, 92%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 8.5 Hz, 4H), 6.93 (d, $J$ = 9.0 Hz, 4H), 5.15 (s, 4H), 3.48 (s, 6H), 2.59 (bd, $J$ = 13.5 Hz, 2H), 1.91 (td, $J$ = 13.0, 4.0 Hz, 2H), 1.77−1.84 (m, 2H), 1.32−1.43 (m, 1H), 1.19−1.30 (m, 3H), 0.98−1.08 (m, 2H), 0.89 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 155.5, 138.7, 137.1, 133.3, 130.9, 115.5, 94.5, 56.0, 39.4, 34.5, 31.7, 29.3, 11.6; MS (EI) *m/z* 396 ($M^+$, 100), 251, 287. HRMS (EI) *m/z* calcd for $C_{25}H_{32}O_4$, 396.2301; found, 396.2307.

**4-Ethyl[bis(4-hydroxyphenyl)methylene]cyclohexane (29b).** According to the general procedure for MOM deprotection with 4-ethyl[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (130 mg, 0.33 mmol), HCl (200 $\mu$L), methanol (2.5 mL), and THF (2.5 mL), **29b** (85 mg, 84%) was obtained as a white solid: mp 188 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.97 (d, $J$ = 8.5 Hz, 4H), 6.73 (d, $J$ = 7.5 Hz, 4H), 2.58 (bd, $J$ = 13.0 Hz, 2H), 1.91 (td, $J$ = 13.5, 3.5 Hz, 2H), 1.33−1.42 (m, 1H), 1.25 (quintet, $J$ = 7.5 Hz, 2H), 0.98−1.08 (m, 2H), 0.89 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 153.7, 138.5, 136.1, 133.2, 114.7, 39.4, 34.5, 31.7, 29.4, 11.6; MS (EI) *m/z* 308 ($M^+$, 100), 199. Anal. ($C_{21}H_{24}O_2$) C, H.

**Methyl 3-[Bis(4-hydroxyphenyl)methylene]cyclohexane-carboxylate (30a).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 1.1 g, 5.1 mmol), **12** (0.8 g, 5.1 mmol), Zn (2.5 g, 38 mmol), and titanium(IV) chloride (3.6 g, 19 mmol), **30a** (1.4 g, 81%) was obtained as a white solid: mp 144−146 °C; $^1$H NMR (400 MHz, acetone-$d_6$) $\delta$ 6.83 (d, $J$ = 8.8 Hz, 2H), 6.82 (d, $J$ = 8.0 Hz, 2H), 6.67 (d, $J$ = 8.8 Hz, 2H), 6.65 (d, $J$ = 8.0 Hz, 2H), 3.53 (s, 3H), 2.63 (bd, $J$ = 10.4 Hz, 1H), 2.34−2.46 (m, 2H), 2.02 (t, $J$ = 12.4 Hz, 1H), 1.72−1.96 (m, 3H), 1.45−1.61 (m, 1H), 1.28−1.42 (m, 3H); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 174.7, 155.7, 135.7, 133.4, 133.3, 130.29, 130.26, 114.7, 114.6, 51.3, 43.6, 33.9, 30.9, 28.7, 26.2; MS (EI) *m/z* 338 ($M^+$, 100), 278, 199. HRMS (EI) *m/z* calcd for $C_{21}H_{22}O_4$, 338.1518; found, 338.1518. Anal. ($C_{21}H_{22}O_4$) C, H.

**Methyl 3-[Bis(4-methoxymethoxyphenyl)methylene]cyclo-hexanecarboxylate (33a).** According to the general procedure for MOM protection with **30a** (1.2 g, 3.6 mmol), methoxymethyl chloride (0.66 g, 8.2 mmol), sodium hydride (0.4 g, 8.9 mmol), and DMF (15 mL), **33a** (1.3 g, 84%) was obtained as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 8.8 Hz, 2H), 7.00 (d, $J$ = 9.2 Hz, 2H), 6.93 (d, $J$ = 8.8 Hz, 4H), 5.153 (s, 2H), 5.15 (s, 2H), 3.62 (s, 3H), 3.481 (s, 3H), 3.476 (s, 3H), 2.73−2.81 (m, 1H), 2.51−2.61 (m, 1H), 2.40−2.49 (m, 1H), 2.15 (t, $J$ = 12.4 Hz, 1H), 1.97−2.07 (m, 1H), 1.82−1.96 (m, 2H), 1.58−1.70 (m, 1H), 1.34−1.48 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 175.8, 155.73, 155.69, 136.6, 136.3, 135.6, 135.2, 130.73, 130.72, 115.7, 115.6, 94.5, 77.2, 56.0, 51.6, 44.6, 34.1, 31.5, 29.4, 26.9; MS (EI) *m/z* 426 ($M^+$), 302, 286 (100), 241, 165. HRMS (EI) *m/z* calcd for $C_{25}H_{30}O_6$, 426.2042; found, 426.2041.

**3-Hydroxymethyl[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane (34a).** According to the general procedure for reduction with **33a** (0.65 g, 1.5 mmol), $LiAlH_4$ in THF solution (1 M, 1.5 mL), and THF (10 mL), **34a** (0.59 g, 98%) was obtained as an colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 8.8 Hz, 2H), 7.01 (d, $J$ = 8.4 Hz, 2H), 6.93 (d, $J$ = 8.4 Hz, 4H), 5.149 (s, 2H), 5.148 (s, 2H), 3.48 (s, 6H), 3.64−3.67 (m, 2H), 2.61 (d, $J$ = 10 Hz, 1H), 2.55 (d, $J$ = 13.6 Hz, 1H), 1.78−1.98 (m, 3H), 1.62−1.75 (m, 2H), 1.35−1.48 (m, 2H), 1.17−1.29 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.60, 155.57, 136.9, 136.73, 136.70, 134.4, 130.7, 115.7, 115.6, 94.5, 68.0, 56.0, 42.1, 34.9, 32.1, 29.4, 27.0; MS (EI) *m/z* 398 ($M^+$), 302 (100). HRMS (EI) *m/z* calcd for $C_{24}H_{30}O_5$, 398.2093; found, 398.2956.

**3-Hydroxymethyl[bis(4-hydroxyphenyl)methylene]cyclo-hexane (35a).** According to the general procedure for MOM deprotection with **34a** (0.34 g, 0.84 mmol), HCl (200 $\mu$L), and methanol (7.0 mL), **35a** (178 mg, 68%) was obtained as a white

solid: mp 219−221 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.82 (d, $J$ = 8.4 Hz, 4H), 6.66 (d, $J$ = 8.4 Hz, 2H), 6.65 (d, $J$ = 8.4 Hz, 2H), 3.11−3.26 (m, 2H), 2.54 (bd, $J$ = 11.6 Hz, 1H), 2.44 (bd, $J$ = 12.8 Hz, 1H), 1.68−1.87 (m, 3H), 1.42−1.60 (m, 2H), 1.21−1.35 (m, 1H), 1.10−1.20 (m, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 155.50, 155.49, 135.5, 134.2, 133.9, 133.7, 130.43, 130.36, 114.6, 66.2, 42.0, 35.0, 31.9, 29.3, 26.8; MS (EI) *m*/*z* 310 ($M^+$, 100). HRMS (EI) *m*/*z* calcd for $C_{20}H_{22}O_3$, 310.1569; found, 310.1573. Anal. ($C_{20}H_{22}O_3$) C, H.

**Dimethyl 2-{3-[Bis(4-hydroxyphenyl)methylene]cyclohexyl}-malonate (30b).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 4.3 g, 20 mmol), **14** (4.6 g, 20 mmol), Zn (9.9 g, 150 mmol), and titanium(IV) chloride (14 g, 74 mmol), **30b** (6.1 g, 74%) was obtained as a white solid: mp 148−149 °C; $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ 6.87(d, $J$ = 8.8 Hz, 2H), 6.85 (d, $J$ = 8.4 Hz, 2H), 6.68 (d, $J$ = 8.4 Hz, 2H), 6.67 (d, $J$ = 8.8 Hz, 2H), 3.67 (s, 3H), 3.49 (s, 3H), 3.26 (d, $J$ = 9.6 Hz), 2.45−2.56 (m, 2H), 2.13−2.25 (m, 1H), 1.86−1.98 (m, 1H), 1.72−1.85 (m, 3H), 1.32−1.46 (m, 1H), 1.21−1.32 (m, 1H); $^{13}$C NMR (100 MHz, methanol-$d_4$) $\delta$ 170.5, 170.3, 156.9, 156.8, 137.5, 135.8, 135.7, 135.6, 131.87, 131.81, 115.60, 115.58, 58.4, 52.8, 52.7, 40.9, 37.0, 32.7, 31.8, 30.0; MS (ESI) *m*/*z* 411 ($M^+$ + 1), 279 (100). HRMS (ESI) *m*/*z* calcd for $C_{24}H_{26}O_6$, 441.1808; found, 441.1812. Anal. ($C_{24}H_{26}O_6$) C, H.

**2-{3-[Bis(4-hydroxyphenyl)methylene]cyclohexyl}malonic Acid (31).** To a solution of **30b** (4.5 g, 11 mmol) in methanol (20 mL) was added NaOH (2 M, 25 mL), and then the reaction mixture was refluxed at 100 °C for 2 h. After the reaction was cooled to room temperature, it was acidified with HCl (2 M, 40 mL) in an ice bath. Water (10 mL) was added, and a precipitate appeared which was collected by filtration. The white powder obtained was dried under vacuum, providing **31** (3.8 g, 90%) as white solid: mp 207−208 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.81 (d, $J$ = 8.4 Hz, 2H), 6.80 (d, $J$ = 8.8 Hz, 2H), 6.65 (d, $J$ = 8.4 Hz, 2H), 6.62 (d, $J$ = 8.8 Hz, 2H), 3.99 (d, $J$ = 9.2 Hz, 1H), 2.57 (bd, $J$ = 12.0 Hz, 1H), 2.40 (bd, $J$ = 12.8 Hz, 1H), 1.96−2.11 (m, 1H), 1.62−1.88 (m, 4H), 1.24−1.32 (m, 2H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 169.9, 169.7, 155.6, 155.5, 135.1, 134.4, 133.8, 133.2, 130.5, 114.7, 114.6, 57.8, 38.5, 35.4, 31.6, 30.2, 26.7; MS (ESI) *m*/*z* 383 ($M^+$ + H), 279 (100). HRMS (ESI) *m*/*z* calcd for $C_{22}H_{22}O_6$, 383.1495; found, 383.1499.

**Methyl 2-{3-[Bis(4-hydroxyphenyl)methylene]cyclohexyl}-acetate (32).** Compound **31** (3.8 g, 9.9 mmol) was dissolved with diglyme (15 mL), and the reaction mixture was heated to 160 °C for 1 h. When no bubbles were detected, the reaction mixture was cooled, and diglyme was removed under vacuum. The organic mixture was filtered through short silica gel and eluted with solvents (50% EtOAc, 47% hexane, 2% methanol, and 1% acetic acid), and the solvents were evaporated. Without further purification, the residual oil was dissolved in methanol (10 mL) under nitrogen. Thionyl chloride (1.3 g, 11 mmol) was added slowly at room temperature, and the mixture was stirred for 1.5 h. The reaction was quenched by saturated $NaHCO_3$ solution (50 mL) under ice bath cooling, and $H_2O$ (100 mL) was added. The product was extracted by ethyl acetate, and the organic layer was washed by brine. After drying with $MgSO_4$, the extract was concentrated and purified by flash column chromatography (EtOAc/hexane; 4:6). Recrystallization ($Et_2O$ and hexane) gave **32** (2.6 g, 74%) as a off-white solid: mp 157−158 °C; $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ 6.87 (d, $J$ = 8.8 Hz, 2H), 6.85 (d, $J$ = 8.4 Hz, 2H), 6.674 (d, $J$ = 8.8 Hz, 2H), 6.670 (d, $J$ = 8.4 Hz, 2H), 3.55 (s, 3H), 2.47−2.60 (m, 2H), 2.10−2.28 (m, 2H), 1.72−1.99 (m, 4H), 1.60−1.69 (m, 1H), 1.32−1.46 (m, 1H), 1.23−1.27 (m, 1H); $^{13}$C NMR (100 MHz, methanol-$d_4$) $\delta$ 175.0, 156.77, 156.75, 136.9, 136.5, 135.9, 135.8, 131.86, 131.84, 115.5, 51.9, 42.1, 39.2, 38.0, 34.0, 32.8, 28.2; MS (EI) *m*/*z* 352 ($M^+$), 278, 167 (100). HRMS (EI) *m*/*z* calcd for $C_{22}H_{24}O_4$, 352.1675; found, 352.1670. Anal. ($C_{22}H_{24}O_4$) C, H.

**Methyl 2-{3-[Bis(4-methoxymethoxyphenyl)methylene]-cyclohexyl}acetate (33b).** According to the general procedure for MOM protection with **32** (2.1 g, 5.9 mmol), methoxymethyl chloride (1.2 g, 14 mmol), sodium hydride (1.0 g, 30 mmol), and DMF (15 mL), **23b** (2.5 g, 95%) was obtained as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 8.8 Hz, 2H), 6.99 (d, $J$ = 8.8 Hz, 2H), 6.93 (d, $J$ = 8.8 Hz, 4H), 5.15 (s, 4H), 3.59 (s, 3H), 3.48 (s, 3H), 3.47 (s, 3H), 2.48−2.61 (m, 2H), 2.15−2.27 (m, 2H), 1.94−2.04 (m, 1H), 1.73−1.94 (m, 3H), 1.62−1.73 (m, 1H), 1.35−1.48 (m, 1H), 1.12−1.28 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 173.2, 155.5, 136.7, 136.55, 136.53, 134.5, 130.8, 115.5, 94.40, 94.38, 55.99, 55.95, 51.4, 41.3, 38.2, 36.5, 32.7, 31.7, 27.0; MS (EI) *m*/*z* 440 ($M^+$, 100), 366, 167. HRMS (EI) *m*/*z* calcd for $C_{26}H_{32}O_6$, 440.2199; found, 440.2198.

**3-(2-Hydroxyethyl)[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane (34b).** According to the general procedure for reduction with **33b** (2.4 g, 5.5 mmol), $LiAlH_4$ in THF solution (1 M, 5.5 mL), and THF (25 mL), **34b** (2.1 g, 93%) was obtained as a white solid: mp 72−74 °C; $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ 6.98 (d, $J$ = 8.8 Hz, 2H), 6.95 (d, $J$ = 8.8 Hz, 2H), 6.92 (d, $J$ = 8.8 Hz, 2H), 6.91 (d, $J$ = 8.8 Hz, 2H), 5.141 (s, 2H), 5.137 (s, 2H), 3.49 (td, $J$ = 6.8, 2.0 Hz, 2H), 3.434 (s, 3H), 3.429 (s, 3H), 2.58 (bd, $J$ = 9.2 Hz, 1H), 2.49 (bd, $J$ = 9.2 Hz, 1H), 1.74−1.97 (m, 3H), 1.56−1.70 (m, 2H), 1.33−1.49 (m, 3H), 1.13−1.26 (m, 1H); $^{13}$C NMR (100 MHz, methanol-$d_4$) $\delta$ 157.12, 157.09, 138.5, 138.2, 138.1, 116.72, 116.70, 95.51, 95.49, 60.7, 56.14, 56.11, 40.5, 39.8, 37.3, 34.2, 33.2, 28.4; MS (EI) *m*/*z* 412 ($M^+$, 100), 278. HRMS (EI) *m*/*z* calcd for $C_{25}H_{32}O_5$, 412.2250; found, 440.2251.

**3-(2-Hydroxyethyl)[bis(4-hydroxyphenyl)methylene]cyclohexane (35b).** According to the general procedure for MOM deprotection with **34b** (250 mg, 0.61 mmol), HCl (200 $\mu$L), methanol (7.0 mL), **35b** (172 mg, 87%) was obtained as a white solid: mp 203−205 °C; $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ 6.87 (d, $J$ = 8.8 Hz, 2H), 6.85 (d, $J$ = 8.4 Hz, 2H), 6.68 (d, $J$ = 8.8 Hz, 2H), 6.67 (d, $J$ = 8.4 Hz, 2H), 3.43−3.54 (m, 2H), 2.58 (bd, $J$ = 9.6 Hz, 1H), 2.52 (bd, $J$ = 13.6 Hz, 1H), 1.73−1.95 (m, 3H), 1.53−1.68 (m, 2H), 1.31−1.48 (m, 3H), 1.12−1.23 (m, 1H); $^{13}$C NMR (100 MHz, methanol-$d_4$) $\delta$ 156.7, 137.4, 136.20, 136.16, 136.0, 131.91, 131.86, 115.5, 60.7, 40.6, 39.8, 37.3, 34.3, 33.3, 28.5; MS (EI) *m*/*z* 324 ($M^+$, 100), 278, 199, 149. Anal. ($C_{21}H_{24}O_3$) C, H.

**3-(2-Methanesulfonyloxyethyl)[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (36b).** According to the general procedure for methanesulfonylation with **35b** (349 mg, 0.82 mmol), methanesulfonic anhydride (215 mg, 1.2 mmol), triethylamine (331 mg, 2.5 mmol), and $CH_2Cl_2$ (10 mL), **36b** (393 mg, 98%) was obtained as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.002 (d, $J$ = 8.8 Hz, 2H), 6.999 (d, $J$ = 8.8 Hz, 2H), 6.94 (d, $J$ = 8.8 Hz, 2H), 6.93 (d, $J$ = 8.8 Hz, 2H), 5.154 (s, 2H), 5.153 (s, 2H), 4.21−4.23 (m, 2H), 3.479 (s, 3H), 3.477 (s, 3H), 2.88 (s, 3H), 2.60 (bd, $J$ = 10.0 Hz, 1H), 2.53 (bd, $J$ = 13.6 Hz, 1H), 1.75−1.97 (m, 3H), 1.60−1.74 (m, 4H), 1.34−1.47 (m, 1H), 1.12−1.26 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.62, 155.58, 136.7, 136.56, 136.51, 134.5, 130.77, 130.75, 115.7, 115.6, 94.4, 68.1, 56.03, 56.02, 38.0, 37.0, 35.6, 35.5, 32.7, 32.0, 27.0; MS (EI) *m*/*z* 490 ($M^+$, 100), 211, 141. HRMS (EI) *m*/*z* calcd for $C_{26}H_{34}O_7S$, 490.2025; found, 490.2015.

**3-(2-Fluoroethyl)[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane.** According to the general procedure for fluorination with **36b** (350 mg, 0.71 mmol), cesium fluoride (541 mg, 3.6 mmol), $H_2O$ (20 $\mu$L), 1-butyl-3-methyl-imidazolium tetrafluoroboronate (2.0 mL), and acetonitrile (2.0 mL), 3-(2-fluoroethyl)[bis-(4-methoxymethoxyphenyl)methylene]cyclohexane (235 mg, 80%) was obtained as a slightly yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.01 (d, $J$ = 8.8 Hz, 2H), 7.00 (d, $J$ = 8.8 Hz, 2H), 6.938 (d, $J$ = 8.8 Hz, 2H), 6.935 (d, $J$ = 8.8 Hz, 2H), 5.161 (s, 2H), 5.156 (s, 2H), 4.42 (dm, $^2J_{HF}$ = 47.6 Hz, 2H), 3.49 (s, 3H), 3.48 (s, 3H), 2.60 (bd, $J$ = 9.2 Hz, 1H), 2.54 (bd, $J$ = 14 Hz, 1H), 1.74−1.97 (m, 3H), 1.54−1.73 (m, 4H), 1.33−1.46 (m, 1H), 1.14−1.27 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.57, 155.52, 137.0, 136.8, 136.7, 134.2, 130.80, 130.76, 115.56, 115.54, 94.46, 94.43, 136.7, 136.56, 136.51, 134.5, 130.77, 130.75, 115.7, 115.6, 94.46, 94.43, 81.4 (d, $^1J_{CF}$ = 162.4 Hz), 56.02, 55.99, 38.4, 37.0 (d, $^2J_{CF}$ = 18.9

Hz), 35.7 (d, $^3J_{CF}$ = 4.6 Hz), 32.8, 32.1, 27.2; MS (EI) *m*/*z* 414 ($M^+$, 100). HRMS (EI) *m*/*z* calcd for $C_{25}H_{31}O_4F$, 414.2206; found, 414.2205.

**3-(2-Fluoroethyl)[bis(4-hydroxyphenyl)methylene]cyclohexane (37b).** According to the general procedure for MOM deprotection with 3-(2-fluoroethyl)[bis(4-methoxymethoxyphenyl)-methylene]cyclohexane (215 mg, 0.52 mmol), HCl (200 $\mu$L), methanol (3.0 mL), and $Et_2O$ (1 mL), **37b** (172 mg, 87%) was obtained as a white solid: mp 100−105 °C; $^1$H NMR (400 MHz, methanol-$d_4$) $\delta$ 6.87 (d, $J$ = 8.8 Hz, 4H), 6.68 (d, $J$ = 8.4 Hz, 2H), 6.67 (d, $J$ = 8.8 Hz, 2H), 6.935 (d, $J$ = 8.8 Hz, 2H), 4.36 (dm, $^2J_{HF}$ = 47.6 Hz, 2H), 2.61 (bd, $J$ = 9.2 Hz, 1H), 2.52 (bd, $J$ = 13.2 Hz, 1H), 1.73−1.97 (m, 3H), 1.44−1.69 (m, 4H), 1.32−1.44 (m, 1H), 1.14−1.31 (m, 1H); $^{13}$C NMR (100 MHz, methanol-$d_4$) $\delta$ 156.76, 156.73, 137.1, 136.4, 136.1, 136.0, 131.9, 115.54, 115.53, 82.9 (d, $^1J_{CF}$ = 162.3 Hz), 39.4, 38.3 (d, $^2J_{CF}$ = 19.7 Hz), 37.1 (d, $^3J_{CF}$ = 3.8 Hz), 34.2, 33.2, 28.4; MS (EI) *m*/*z* 326 ($M^+$, 100), 199. HRMS (EI) *m*/*z* calcd for $C_{21}H_{23}O_2F$, 326.1682; found, 326.1672.

**3-(3-Acetoxy-*n*-propyl)-1-[bis(4-hydroxyphenyl)methylene]-cyclohexane (30c).** According to the general procedure for the McMurry coupling reaction with 4,4′-dihydroxybenzophenone (**1**, 0.35 g, 1.6 mmol), **15** (0.32 g, 1.6 mmol), Zn (0.79 g, 12 mmol), and titanium(IV) chloride (1.1 g, 6.0 mmol), **30c** (0.43 g, 70%) was obtained as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.91−6.96 (m, 4H), 6.738 (d, $J$ = 8.8 Hz, 2H), 6.733 (d, $J$ = 8.4 Hz, 2H), 4.00 (t, $J$ = 6.8 Hz, 2H), 2.54 (bt, $J$ = 13.6 Hz, 2H), 2.05 (s, 3H), 1.72−1.93 (m, 3H), 1.47−1.65 (m, 3H), 1.30−1.47 (m, 3H), 1.38−1.47 (m, 1H), 1.30−1.38 (m, 1H), 1.19−1.30 (m, 2H), 1.06−1.18 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.2, 153.89, 153.85, 137.1, 135.8, 135.6, 133.9, 131.0, 130.9, 114.73, 114.68, 65.2, 39.1, 38.5, 33.0, 32.8, 32.2, 27.3, 25.8, 21.1; MS (EI) *m*/*z* 380 ($M^+$), 214 (100). HRMS (EI) *m*/*z* calcd for $C_{24}H_{28}O_4$, 380.1987; found, 380.1993.

**3-(3-Acetoxy-*n*-propyl)-1-[bis(4-methoxymethoxyphenyl)-methylene]cyclohexane (33c).** According to the general procedure for MOM protection with **30a** (0.43 g, 1.1 mmol), methoxymethyl chloride (0.20 g, 2.5 mmol), sodium hydride (69 mg, 2.8 mmol), and DMF (10 mL), **33c** (191 mg, 36%) was obtained as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.013 (d, $J$ = 8.8 Hz, 2H), 7.008 (d, $J$ = 9.2 Hz, 2H), 6.38 (d, $J$ = 8.8 Hz, 2H), 6.932 (d, $J$ = 8.8 Hz, 2H), 5.16 (s, 2H), 5.15 (s, 2H), 4.01 (t, $J$ = 6.8 Hz, 2H), 3.48 (s, 3H), 3.47 (s, 3H), 2.50−2.63 (m, 2H), 2.04 (s, 3H), 1.72−1.95 (m, 3H), 1.30−1.68 (m, 5H), 1.20−1.30 (m, 2H), 1.09−1.20 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 171.1, 155.44, 155.41, 137.4, 136.8, 136.7, 133.8, 130.73, 130.71, 115.46, 115.43, 94.4, 94.3, 64.7, 55.90, 55.87, 39.1, 38.5, 32.86, 32.83, 32.1, 27.3, 25.8, 20.9; MS (EI) *m*/*z* 468 ($M^+$, 100), 446, 302, 286. HRMS (EI) *m*/*z* calcd for $C_{28}H_{36}O_6$, 468.2512; found, 468.2498.

**3-(3-Hydroxypropyl)[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (34c).** To a solution of **33c** (185 mg, 0.39 mmol) in methanol (4 mL), $Et_2O$ (1 mL), and $H_2O$ (1 mL) was added $K_2CO_3$ (450 mg, 3.3 mmol). The mixture was stirred at room temperature for 4 h. It was then quenched by $H_2O$ and extracted with EtOAc (50 mL). The organic layer was washed with saturated ammonium chloride solution (50 mL) and concentrated. Flash column chromatography (EtOAc/hexane; 3:7) gave **34c** (159 mg, 95%) as a colorless oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.02 (d, $J$ = 8.8 Hz, 2H), 7.08 (d, $J$ = 8.8 Hz, 2H), 6.93 (d, $J$ = 8.4 Hz, 4H), 5.150 (s, 2H), 5.147 (s, 2H), 3.56 (t, $J$ = 6.4 Hz, 2H), 3.478 (s, 3H), 3.473 (s, 3H), 2.59 (d, $J$ = 14.4 Hz, 1H), 2.53 (d, $J$ = 13.2 Hz, 1H), 1.74−2.15 (m, 3H), 1.31−1.67 (m, 5H), 1.21−1.31 (m, 2H), 1.08−1.21 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.4, 137.7, 136.9, 136.8, 133.6, 130.77, 130.75, 115.49, 115.46, 94.39, 94.34, 63.1, 55.95, 55.92, 39.4, 38.6, 33.0, 32.8, 32.2, 30.0, 27.4; MS (EI) *m*/*z* 426 ($M^+$, 100). HRMS (EI) *m*/*z* calcd for $C_{26}H_{34}O_5$, 426.2406; found, 426.2415.

**3-(3-Hydroxy-*n*-propyl)-1-[bis(4-hydroxyphenyl)methylene]-cyclohexane (35c).** To a solution of **30c** (130 mg, 0.34 mmol) in methanol (7.5 mL) and $H_2O$ (2.5 mL) was added $K_2CO_3$ (500 mg, 3.6 mmol). The mixture was stirred at room temperature for 4 h, quenched by $H_2O$, and extracted with EtOAc (50 mL). The organic layer was washed with saturated ammonium chloride solution (50 mL) and concentrated. Flash column chromatography (EtOAc/hexane; 4:6) gave **35c** (75 mg, 65%) as an off-white solid: mp 175−176 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.810 (d, $J$ = 8.8 Hz, 2H), 6.807 (d, $J$ = 8.4 Hz, 2H), 6.64 (d, $J$ = 8.4 Hz, 4H), 3.30 (dd, $J$ = 7.6, 6.4 Hz, 2H), 2.41 (bd, $J$ = 13.2 Hz, 1H), 1.65−1.87 (m, 3H), 1.47−1.57 (m, 1H), 1.20−1.41 (m, 4H), 1.00−1.20 (m, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 155.55, 155.52, 135.7, 134.1, 133.8, 133.7, 130.4, 114.6, 61.0, 38.2, 32.9, 31.8, 31.0, 29.9, 27.1, 22.1; MS (EI) *m*/*z* 338 ($M^+$, 100), 215, 199. HRMS (EI) *m*/*z* calcd for $C_{22}H_{26}O_3$, 338.1882; found, 338.1878. Anal. ($C_{22}H_{26}O_3$) C, H.

**3-(3-Fluoropropyl)[bis(4-methoxymethoxyphenyl)methylene]-cyclohexane.** To a solution of **34c** (190 mg, 0.45 mmol) in $CH_2Cl_2$ (5 mL) was added slowly diethylaminosulfur trifluoride (865 mg, 0.5 mmol) at −78 °C under nitrogen. The cooling was removed, and the reaction mixture was stirred for 1 h at room temperature. It was then placed in an ice-bath, and methanol (200 $\mu$L) and $H_2O$ (200 $\mu$L) were added. The ice-bath was removed, and the mixture was allowed to stir for 30 min. EtOAc (50 mL) was added, and the organic layer was washed with $NaHCO_3$ solution (50 mL) and ammonium chloride solution (50 mL). The organic layer was dried over sodium sulfate and concentrated. Flash column chromatography (EtOAc/hexane; 1:9 to 3:7) gave 3-(3-fluoro-*n*-propyl)-1-[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (71 mg, 37%) as an oil: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.99−7.04 (m, 4H), 6.92−6.97 (m, 4H), 5.164 (s, 2H), 5.158 (s, 2H), 4.39 (dt, $^2J_{HF}$ = 47.6, 6.4 Hz, 2H), 3.489 (s, 3H), 3.482 (s, 3H), 2.30−2.64 (m, 2H), 1.75−1.95 (m, 3H), 1.63−1.75 (m, 3H), 1.40−1.63 (m, 1H), 1.24−1.40 (m, 3H), 1.08−1.20 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 155.50, 155.45, 137.48, 136.9, 136.8, 133.8, 130.80, 130.75, 115.50, 115.49, 94.43, 94.38, 84.4 (d, $^1J_{CF}$ = 163 Hz), 55.98, 55.96, 39.2, 38.5, 32.9, 32.15, 32.12, 27.7 (d, $^2J_{CF}$ = 18.9 Hz), 27.3; MS (EI) *m*/*z* 428 ($M^+$), 302 (100), 286, 165. HRMS (EI) *m*/*z* calcd for $C_{26}H_{33}O_4F$, 428.2363; found, 428.2353.

**3-(3-Fluoro-*n*-propyl)-1-[bis(4-hydroxyphenyl)methylene]-cyclohexane (37c).** According to the general procedure for MOM deprotection with 3-(3-fluoropropyl)[bis(4-methoxymethoxyphenyl)methylene]cyclohexane (70 mg, 0.16 mmol), concentrated HCl (200 $\mu$L) in methanol (4.0 mL), and $Et_2O$ (1 mL), **37c** (36 mg, 69%) was obtained as an off-white solid: mp 85 °C (decomposed to dark brown color): $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.82 (d, $J$ = 8.4 Hz, 4H), 6.65 (d, $J$ = 8.4 Hz, 4H), 4.38 (dt, $^2J_{HF}$ = 47.6 Hz, $J$ = 6.4 Hz, 2H), 2.36−2.52 (bm, 2H), 1.67−1.90 (m, 3H), 1.44−1.64 (m, 3H), 1.34−1.44 (m, 1H), 1.16−1.34 (m, 3H), 1.02−1,16 (m, 1H); $^{13}$C NMR (100 MHz, acetone-$d_6$) $\delta$ 156.6, 156.5, 137.0, 135.6, 135.5, 131.6, 115.5, 115.4, 84.7 (d, $^1J_{CF}$ = 164 Hz), 40.1, 39.2, 33.9, 32.5 (d, $^3J_{CF}$ = 5.3 Hz), 32.9, 28.5 (d, $^2J_{CF}$ = 19.7 Hz), 28.1; MS (EI) *m*/*z* 340 ($M^+$, 100), 199. HRMS (EI) *m*/*z* calcd for $C_{22}H_{25}O_2F$, 340.1839; found, 340.1841.

**Molecular Modeling.** The experimental details of the computational method used have been reported elsewhere.[55] Briefly, 4 of 8 possible docking orientations of C4-substituted molecules were individually examined using the FlexiDoc routine in Sybyl 7.1 (Tripos Inc.) to account for both the axial/equatorial orientation of the ring substituent and the ring flips of the cyclohexane ring. Docking of the C3-substituted cyclofenils was further complicated because they were prepared as a mixture of enantiomers, so 8 of 16 orientations were examined. We eliminated half of the docking orientations by starting from an unfavorable orientation where one pendent phenol was overlaid with the A-ring of estradiol while the other phenol was placed away from a hydrogen-bonding partner (Thr347/299). The docking routine typically reoriented the cyclofenil core, placing the second phenol within hydrogen-bonding distance with the Thr residue. The top ranked docking orientation in the ER binding pocket was minimized by a three-step process that has been reported elsewhere.[55]

**Estrogen Receptor Binding Affinity.** Relative binding affinities were determined by a competitive radiometric binding assay as previously described,[52] using 10 nM [$^3$H]estradiol as tracer ([6,7-$^3$H]estra-1,3,5,(10)-triene-3,17-$\beta$-diol, 51−53 Ci/mmol, Amersham

BioSciences, Piscataway, NJ), and purified full-length human ERα and ER$\beta$ were purchased from PanVera/Invitrogen (Carlsbad, CA). Incubations were for 18−24 h at 0 °C. Hydroxyapatite (BioRad, Hercules, CA) was used to absorb the receptor−ligand complexes, and free ligand was washed away. The binding affinities are expressed as relative binding affinity (RBA) values with the RBA of estradiol set to 100%. The values given are the average ± range or SD of two to three independent determinations. Estradiol binds to ERα and uterine cytosol ER with a $K_d$ of 0.2 nM and to ER$\beta$ with a $K_d$ of 0.5 nM.

**Acknowledgment.** This work was supported by grants from the National Institutes of Health (Grant No. PHS 5R37CA25836), the National Research and Development Program of MOST, Korea (Grant No. 2005-03184), and the Postdoctoral Fellowship Program of Korea Science and Engineering Foundation (KOSEF).

**Supporting Information Available:** Elemental analysis data of **2**−**5**, **18**, **20**, **21a**,**b**, **24a**,**b**, **26a**,**b**, **27**, **28**, **29a**,**b**, **30a**,**b**, **32**, and **35a**−**c**, HPLC purity data and traces of **37b**,**c**, $^1$H and $^{13}$C NMR spectra of **2**−**5**, **7**, **10**, **12**, **14**−**16**, **17a**,**b**, **18**−**20**, **21a**,**b**, **22a**,**b**, **23a**,**b**, **24a**,**b**, **25a**,**b**, **26a**,**b**, **28**, **29b**, **30a**−**c**, **31**, **32**, **33a**−**c**, **34a**−**c**, **35a**−**c**, **36b**, and **37b**,**c**, and some key intermediates. This material is available free of charge via a Internet at http://pubs.acs.org.

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JM0512037