Synthesis of (*Z*)-4-Hydroxytamoxifen and (*Z*)-2-[4-[1-(*p*-Hydroxyphenyl)-2-phenyl]-1-butenyl]phenoxyacetic Acid

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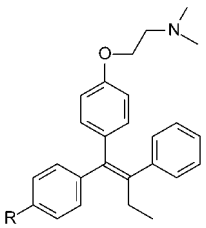
Abstract: The synthesis of (*Z*)-4-hydroxytamoxifen and (*Z*)-2-[4-[1-(*p*-hydroxyphenyl)-2-phenyl]-1-butenyl]phenoxyacetic acid was accomplished using a McMurry reaction as the key step. The perfluorotolyl derivatives of the McMurry products enabled the separation of the minor undesirable geometrical isomer. The methodology proceeds without *E*,*Z* isomerization, employs a very mild final debenzylation step compatible with a large array of functional groups, and can be applied to the generation of a variety of 4-hydroxytamoxifen analogues.

Tamoxifen, (*Z*)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethanamine (**1**), a selective estrogen receptor modulator (SERM), is the treatment of choice for all stages of hormone-responsive breast cancer and has recently been approved by the FDA for the chemoprevention of this disease.[1] (*Z*)-4-Hydroxytamoxifen (**2**) is the active metabolite of tamoxifen; it possesses a high in vitro potency for the estrogen receptor, but it is a weaker agent than the parent compound in vivo, due to rapid clearance. (*Z*)-4-Hydroxytamoxifen has an affinity for the estrogen receptor about three times that of estradiol but it readily equilibrates into a *Z*/*E* mixture, and the (*E*) isomer has an affinity of only 5%.[2]



1 R = H
2 R = OH

We were interested in synthesizing analogues of (*Z*)-4-hydroxytamoxifen that would retain the beneficial characteristics and would be devoid of the metabolic disadvantages of the parent compound. Several strategies have been devised for the synthesis of 4-hydroxytamoxifen, the majority of which results in the generation of an equimolar mixture of geometrical isomers[3−5] separable only by preparative TLC using an elution system of benzene/piperidine[6] or by HPLC.[2] To date, only two stereospecific approaches to 4-hydroxytamoxifen have been reported. One involves carbometalation of alkynylsilanes[7] and the other, by Gauthier et al.,[8] utilizes a McMurry reaction between monopivaloated 4,4′-dihydroxybenzophenone and propiophenone as the key step and furnishes a 14:1 *E*/*Z* ratio in favor of the desired triarylethylene derivative. The final step of the latter synthetic sequence requires removal of the pivaloyl ester using MeLi at −78 °C. These conditions however, are not compatible with the synthesis of a number of 4-hydroxytamoxifen analogues, for example, those bearing acidic side chains. This class of compounds has also been found to have selective estrogenic activity, i.e., to prevent against bone loss in ovariectomized (OVX) rats while displaying estrogen antagonist activity in the uterus.[9−12]

More recent attempts toward (*Z*)-4-hydroxytamoxifen analogues employed benzylmonoprotected 4,4′-dihydroxybenzophenone (**3**) in the above-mentioned McMurry reaction. However, they were not synthetically useful because they resulted in mixtures of geometrical isomers that could not be separated by trituration, recrystallization, or column chromatography.[10,13] We decided to focus our efforts on investigating further this synthetic route, since the benzyl protecting group could be removed in the final step under mild conditions without cis−trans isomerization and double-bond hydrogenation. Thus, coupling of compound **3** with propiophenone under McMurry conditions afforded the two isomeric triarylethylenes **4a** and **4b** in a 4:1 ratio, in 72% yield. We expected that the isomer in excess had the desired *E* configuration since previous work on hydroxytamoxifen analogues has identified the tendency of monoprotected 3,4′- or 4,4′-dihydroxybenzophenones used in the McMurry reaction with propiophenone to favor the formation of that product that has a trans arrangement of the ethyl side chain relative to the phenolic system.[14,15] We were very gratified to find that when compounds **4a** and **4b** were transformed to the corresponding perfluorotolyl ethers **5a** and **5b**, the desired geometrical isomer **5a** was obtained preferentially by crystallization from pentane (Scheme 1).

The geometry of the olefinic compound **5a** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1).

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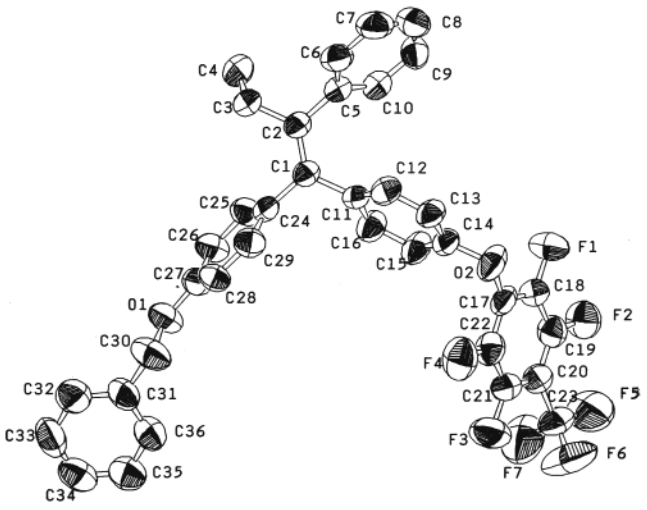
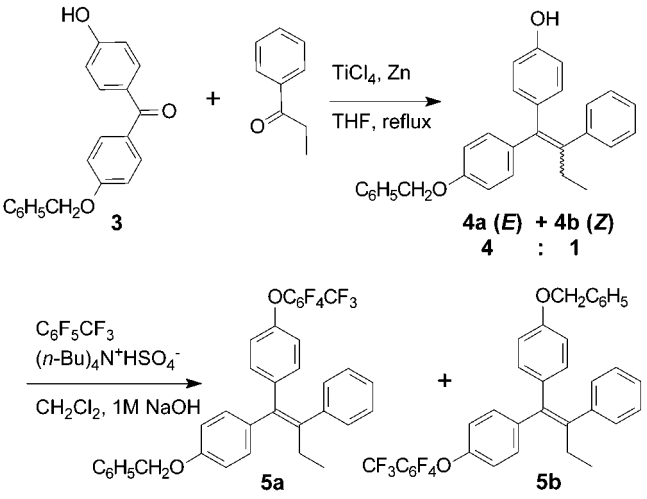


Figure 1. ORTEP diagram of perfluorotolyl derivative (*E*)-1-[4-(benzyloxy)phenyl]-1-[4-(perfluorotolyloxy)phenyl]-2-phenylbut-1-ene (**5a**).

Scheme 1



The perfluorotolyl group has been previously employed by McCague et al. for the separation of the geometrical isomers of triarylethylenes.[16,17] However, compounds **5a** and **5b** have not been prepared previously. The singlets corresponding to the benzylic protons are very characteristic for the two geometrical isomers of triarylethylenes **4a** and **4b** or **5a** and **5b**. The peak corresponding to the benzylic CH_2 of the triarylethylene isomer that eventually leads to (*Z*)-4-hydroxytamoxifen appears more downfield (5.07 ppm) than the one of the undesired geometrical isomer (4.92 ppm).

Compound **5a** was treated with NaOMe in DMF to remove the perfluorotolyl function without any cis−trans isomerization. Alkylation of the resulting alcohol **4a** with 2-chloro-*N*,*N*′-dimethylethylamine afforded 4-benzyloxytamoxifen (**6**), which upon removal of the benzyl group by catalytic hydrogenolysis gave (*Z*)-4-hydroxytamoxifen (**2**) in pure stereochemical configuration (Scheme 2). It is worth noting that the debenzylation reaction proceeds smoothly, in quantitative yield, when it is performed in ethyl acetate. Previous reports[9] of debenzylation reactions of triarylethylene analogues using catalytic hydrogenolysis resulted in fully hydrogenated products when MeOH was used as the solvent, while in THF the reaction was not always reproducible.

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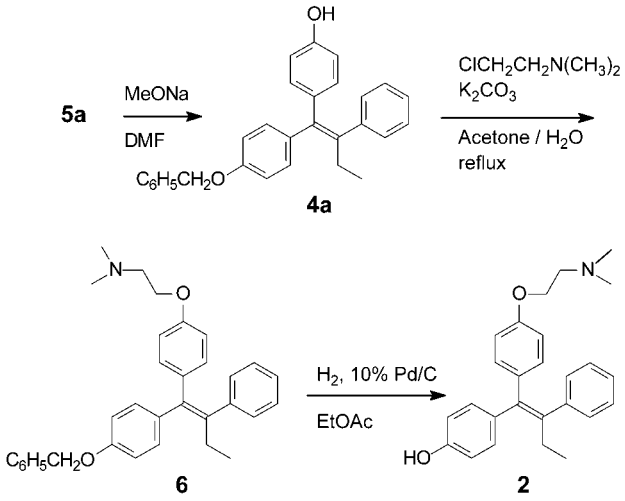
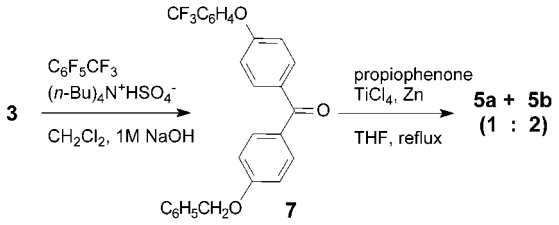
Scheme 2



Scheme 3



To investigate whether we can improve the ratio of the desired compound **5a**, we performed the McMurry reaction using 4-benzyloxy-4′-perfluorotolyloxybenzophenone (**7**) and propiophenone. Unfortunately, this reaction gave a mixture of **5a** and **5b** in a 1:2 ratio (Scheme 3).

The observed stereoselectivity of the McMurry reaction between 4-benzyloxy-4′-hydroxybenzophenone and propiophenone could be explained by the following mechanism. Reduction of the ketones by metallic titanium to give a radical anion species is followed by homolytic coupling of the mixed carbonyl compounds, and subsequent deoxygenation of the pinacolic intermediate gives the desired olefin. Due to steric hindrance, the bulkier benzyloxyphenyl substituent and the ethyl group should lie on the same side, thus leading to the preferential formation of derivative **4a** (Figure 2). In the case of the McMurry coupling between 4-benzyloxy-4′-perfluorotolyloxybenzophenone (**7**) and propiophenone, the steric bulk of the benzyl group and the perfluorotolyl group is slightly different leading to a preference for triarylethylene derivative **5b** but only in a 2-fold excess (Figure 2).

The minor geometrical *Z* isomer **5b** could potentially afford **2** by sequential debenzylation, alkylation, and removal of the perfluorotolyl group. This would give the opportunity to utilize both products of the McMurry coupling to obtain the desired (*Z*)-4-hydroxytamoxifen (**2**). However, catalytic hydrogenolysis of compound **5b** in ethyl acetate resulted both in debenzylation and partial double-bond hydrogenation.

In addition, as an example of the application of our approach in the synthesis of (*Z*)-4-hydroxytamoxifen analogues bearing acidic side chains, compound **9** was

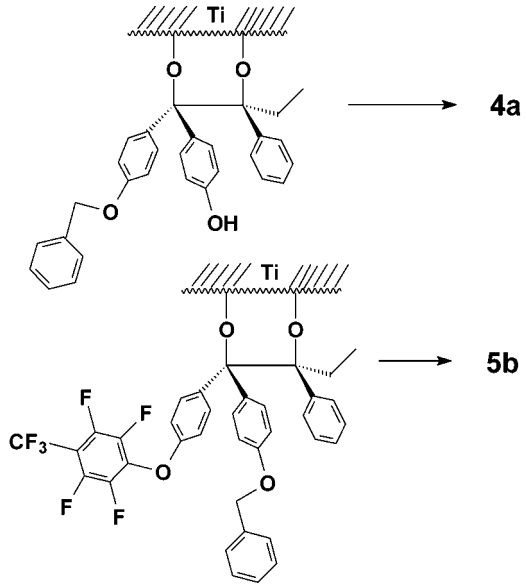
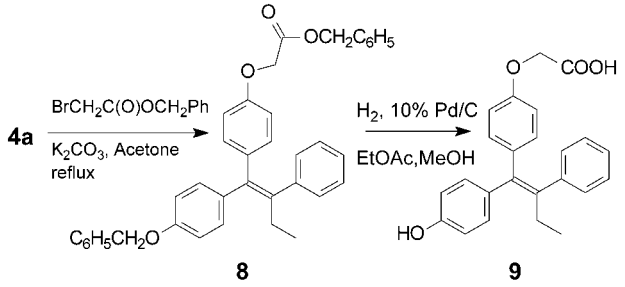


Figure 2. Proposed intermediates of the McMurry coupling of 4-benzyloxy-4′-hydroxybenzophenone and 4-benzyloxy-4′-perfluorotolyloxybenzophenone with propiophenone.

Scheme 4



synthesized in excellent yield as the pure *Z* geometrical isomer. Previous attempts to generate compound **9** or other related derivatives always resulted in an equimolar mixture of the two geometrical isomers that could not be separated.[9−11] Thus, the biological evaluation was carried out with the mixture and the effect of geometric isomerism on estrogen receptor affinity or bioactivity could not be deciphered. We opted to use benzyl 2-bromoacetate as the alkylating agent for the phenolic derivative **4a** since catalytic hydrogenolysis would remove both the benzyl ether and the benzyl ester functionalities and would generate the desired hydroxytriarylethylene oxyalkanoic acid in one step. As planned, (*E*)-1-(4-hydroxyphenyl)-1-(4-benzyloxyphenyl)-2-phenylbut-1-ene (**4a**) was treated with benzyl 2-bromoacetate and K_2CO_3 to afford the triarylethylene oxyalkanoic acid benzyl ester derivative **8** in quantitative yield without double-bond isomerization. Treatment with H_2 and 10% Pd/C at 1 atm in ethyl acetate/methanol (6/1) removed both benzyl groups and afforded hydroxy-triarylethylene oxyalkanoic acid **9** in quantitative yield as the pure (*Z*)-geometrical isomer (Scheme 4).

In summary, we presented the synthesis of (*Z*)-4-hydroxytamoxifen and (*Z*)-4-hydroxytamoxifen acetic acid analogue **9** in pure stereochemical form employing a McMurry reaction as the key step and using the perfluorotolyl group as a means to remove the minor undesirable geometrical isomer. The intermediate perfluorotolyl derivative **5a** allows the synthesis of a variety of side-chain analogues of (*Z*)-4-hydroxytamoxifen, and it can be stored until further modifications are required without *E*/*Z* interconversion. The methodology proceeds without double-bond isomerization, employs a very mild final debenzylation step which is compatible with a large array of functional groups, and can be scaled up to produce gram quantities of the desired products.

Experimental Section

Materials and Methods. NMR spectra were measured at 300 MHz (^{1}H), 75 MHz (^{13}C), and 282 MHz (^{19}F) in $CDCl_3$ unless otherwise specified. Chemical shifts for ^{19}F are reported relative to trifluoromethyl benzene as external standard ($\delta = -73.732$ ppm). Reactions requiring air-sensitive manipulations were conducted under argon. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled from Na/benzophenone and DMF was dried over molecular sieves (3 Å). Analytical thin-layer chromatography was carried out using precoated silica gel plates Merck F254. Analytical visualization was accomplished with ultraviolet light and/or 7% phosphoromolybdic acid in ethanol stain with heating. Flash column chromatography was performed with silica gel (200−400 mesh). Melting points are reported in degrees Celsius and are uncorrected.

4-Benzyloxy-4′-hydroxybenzophenone (3). To a solution of 4,4′-dihydroxybenzophenone (2 g, 9.4 mmol) in dry DMF (20 mL) were added benzyl bromide (1.22 mL, 10.2 mmol) and K_2CO_3 (1.4 g, 10.2 mmol), and the mixture was heated at 60 °C for 48 h. After being cooled to room temperature, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in EtOAc, and the solution was washed with 1 M HCl and brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting crude product was purified by flash column chromatography (8:2 petroleum ether 40−60°/acetone) to afford 4-benzyloxy-4′-hydroxybenzophenone (**3**) (2.1 g, 6.8 mmol, 72%) as a white solid: mp 158−160 °C; ^{1}H NMR δ 8.62 (s, 1H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.59 (d, $J = 8.5$ Hz, 2H), 7.33−7.20 (m, 5H), 6.90 (d, $J = 8.5$ Hz, 2H), 6.81 (d, $J = 8.5$ Hz, 2H), 5.02 (s, 2H).

(*E*,*Z*)-1-[4-(Benzyloxy)phenyl]-1-(4-hydroxyphenyl)-2-phenylbut-1-ene (4). $TiCl_4$ (2.86 mL, 26 mmol) was added to a stirred suspension of zinc powder (3.4 g, 53 mmol) in dry THF (60 mL), under Ar, at −10 °C. When the addition was complete, the mixture was warmed to room temperature and then refluxed for 2 h. To the cooled suspension of the titanium reagent was added a solution of 4-benzyloxy-4′-hydroxybenzophenone (2 g, 6.6 mmol) and propiophenone (2.6 mL, 19.7 mmol) in dry THF (125 mL) at 0 °C, and the mixture was refluxed in the dark for 2.5 h. After cooling, the reaction mixture was poured into 10% aqueous potassium carbonate and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash column chromatography (9:1 petroleum ether 40−60°/acetone) afforded **4** (1.91 g, 4.7 mmol, 72%) as a 4:1 mixture of (*E*)-**4a**/(*Z*)-**4b** isomers: mp 126−129 °C; ^{1}H NMR δ 7.47−7.34 (m, 5H), 7.22−7.11 (m, 7H), 6.99 (d, $J = 7.9$ Hz, 1.6H), 6.82 (d, $J = 8.5$ Hz, 0.8H), 6.66 (d, $J = 8.5$ Hz, 0.4H), 6.76 and 6.49 (d, $J = 7.9$ Hz, 1.6H each), 5.75 (bs, 1H), 5.09 and 4.93 (s, 1.6 and 0.4, 2H), 2.53 (q, $J = 7.3$ Hz, 2H), 0.97 (t, $J = 7.3$ Hz, 3H).

(*E*,*Z*)-1-[4-(Benzyloxy)phenyl]-1-[4-(perfluorotolyloxy)-phenyl]-2-phenylbut-1-ene (5). A mixture of **4** (700 mg, 1.7 mmol), octafluorotoluene (0.25 mL, 1.75 mmol), tetrabutylammonium hydrogen sulfate (290 mg, 0.85 mmol), CH_2Cl_2 (15 mL), and aqueous sodium hydroxide (1 M, 15 mL) was stirred at room temperature for 1 h. The organic phase was separated, and the aqueous phase was acidified with aqueous hydrochloric acid (10%) and extracted with CH_2Cl_2. The organic phases were combined, dried (Na_2SO_4), and concentrated in vacuo. The yellowish residue was washed with 2:1 petroleum ether 40−60°/diethyl ether (3 × 20 mL), and the ethereal washings were evaporated in vacuo. The solid product (**5a**:**5b** 4:1, 950 mg, 1.5 mmol, 90%) was dissolved in the minimum volume of CH_2Cl_2, 60 mL of pentane was added, and the solution was kept in the

refrigerator overnight to afford **5a** as a white solid (622 mg, 1 mmol, 59%). Evaporation of the mother liquor afforded a 4:1 mixture of **5b**/**5a** (328 mg, 0.5 mmol, 31%), which was subjected to column chromatography (8:2 petroleum ether 40−60°/ CH_2Cl_2) to afford pure **5b** (262 mg, 0.4 mmol, 25%).

(*E*)-1-[4-(Benzyloxy)phenyl]-1-[4-(perfluorotolyloxy)phenyl]-2-phenylbut-1-ene (5a): TLC (7:3 petroleum ether 40−60°/ CH_2Cl_2) R_f = 0.57; mp 165−167 °C; ^{1}H NMR δ 7.47−7.33 (m, 5H), 7.17−7.06 (m, 7H), 6.97 (d, J = 8.5 Hz, 2H), 6.84 and 6.63 (d, J = 8.5 Hz, 2H each), 5.08 (s, 2H), 2.50 (q, J = 7.9 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 157.74, 154.38, 142.54, 142.05, 139.89, 137.04, 135.81, 132.25, 130.60, 129.63, 128.60, 127.98, 127.92, 127.53, 126.24, 114.98, 114.46, 70.04, 28.99, 13.53; ^{19}F NMR δ −162.9 (m, 2F), −151.6 (m, 2F), −66.8 (t, J = 23.5 Hz, 3F).[18] Anal. Calcd for $C_{36}H_{25}F_7O_2$: C, 69.45; H, 4.05. Found: C, 69.19; H, 4.17.

(*Z*)-1-[4-(Benzyloxy)phenyl]-1-[4-(perfluorotolyloxy)phenyl]-2-phenylbut-1-ene (5b): TLC (7:3 petroleum ether 40−60°/ CH_2Cl_2) R_f = 0.54; mp 120−122 °C; ^{1}H NMR δ 7.36−7.10 (m, 12H), 6.98 (d, J = 8.5 Hz, 2H), 6.77 and 6.64 (d, J = 8.5 Hz, 2H each), 4.92 (s, 2H), 2.47 (q, J = 7.3 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 156.90, 155.19, 142.15, 141.99, 140.21, 136.94, 135.39, 131.93, 131.02, 129.60, 128.50, 127.92, 127.53, 126.17, 115.66, 113.72, 69.79, 29.02, 13.59; ^{19}F NMR δ −162.7 (m, 2F), −151.3 (m, 2F), −66.8 (t, J = 22.3 Hz, 3F).[18] Anal. Calcd for $C_{36}H_{25}F_7O_2$: C, 69.45; H, 4.05. Found: C, 69.08; H, 4.28.

(*E*)-1-[4-(Benzyloxy)phenyl]-1-(4-hydroxyphenyl)-2-phenylbut-1-ene (4a). Compound **5a** (600 mg, 0.96 mmol,) and freshly prepared MeONa (5.18 g, 96 mmol) were dissolved in dry DMF (90 mL), and the mixture was stirred in the dark for 1.5 h. The mixture was diluted with water (30 mL), acidified with aqueous hydrochloric acid (10%), and extracted with diethyl ether (5 × 30 mL). The combined extracts were dried (Na_2SO_4), and the solvent was evaporated in vacuo to afford **4a** (388 mg, 0.96 mmol, 100%): ^{1}H NMR δ 7.44−7.35 (m, 5H), 7.16−7.10 (m, 7H), 6.95 (d, J = 8.5 Hz, 2H), 6.72 and 6.46 (d, J = 7.9 Hz, 2H each), 5.07 (s, 2H), 2.48 (q, J = 6.7 Hz, 2H), 0.92 (t, J = 6.7 Hz, 3H);^{13}C NMR δ 157.55, 156.74, 142.64, 141.15, 137.75, 137.04, 136.56, 135.94, 132.23, 130.69, 129.79, 128.68, 128.06, 127.90, 127.66, 125.99, 114.37, 114.28, 70.01, 28.91, 13.49. Anal. Calcd for $C_{29}H_{26}O_2$: C, 85.68; H, 6.45. Found: C, 85.71; H, 6.69.

(*E*)-1-[4-(Benzyloxy)phenyl]-1-[4-(2-dimethylaminoethoxy)phenyl)]-2-phenylbut-1-ene (6). Preparation of 2-chloro-*N*,*N*-dimethylethylamine: 2-(dimethylamino)ethyl chloride hydrochloride (552 mg, 3.84 mmol) was treated with K_2CO_3 (1.06 g, 7.68 mmol) in a solution of 19:1 acetone−water (40 mL). The mixture was stirred at 0 °C for 0.5 h.

Compound **4a** (380 mg, 0.94 mmol) was dissolved in 20 mL of the above solution, K_2CO_3 (312 mg, 2.26 mmol) was added, and the mixture was refluxed in the dark for 4 h. The solids were filtered off, and the filtrate was concentrated in vacuo. The yellowish oily product was purified by flash column chromatography (98:2 CH_2Cl_2/MeOH) to afford **6** (352 mg, 0.74 mmol, 73%): ^{1}H NMR δ 7.48−7.34 (m, 5H), 7.18−7.10 (m, 7H), 6.96 (d, J = 8.5 Hz, 2H), 6.77 and 6.56 (d, J = 8.5 Hz, 2H each), 5.07 (s, 2H), 3.94 (t, J = 6.1 Hz, 2H), 2.66 (t, J = 6.1 Hz, 2H), 2.50 (q, J = 7.3 Hz, 2H), 2.30 (s, 6H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 157.52, 156.68, 142.60, 141.05, 137.78, 137.07, 136.56, 135.84, 131.93, 130.60, 129.66, 128.56, 127.79, 127.53, 125.85, 114.30, 113.33, 70.01, 65.61, 58.3, 45.85, 28.99, 13.59. Anal. Calcd for $C_{33}H_{25}NO_2$: C, 82.98; H, 7.39; N, 2.93. Found: C, 83.30; H, 7.64; N, 2.89.

(*Z*)-1-[4-(2-Dimethylaminoethoxy)phenyl)]-1-(4-hydroxyphenyl)-2-phenylbut-1-ene ((*Z*)-4-Hydroxytamoxifen) (2). To a solution of **6** (350 mg, 0.73 mmol) in EtOAc (25 mL) was added of 10% palladium on carbon (175 mg). The suspension was stirred under 1 atm of hydrogen gas in the dark until completion of the reaction (ca 2.5 h). The reaction mixture was filtered through Celite, and the filtrate was concentrated in vacuo to afford (*Z*)-hydroxytamoxifen (**2**) (280 mg, 0.73 mmol, 100%): ^{1}H NMR δ 7.16−7.02 (m, 7H), 6.76 (d, J = 7.9 Hz, 2H), 6.67 and 6.23 (d, J = 8.5 Hz, 2H each), 3.90 (t, J = 5.5 Hz, 2H), 2.75 (t, J = 5.5 Hz, 2H), 2.49 (q, J = 7.3 Hz, 2H), 2.36 (s, 6H), 0.90 (t, J = 7.3 Hz, 3H).

4-Benzyloxy-4′-perfluorotolyloxybenzophenone (7). Compound **7** was prepared following the procedure described for the synthesis of compound **5**, using 4-benzyloxy-4′-hydroxybenzophenone (**3**) (500 mg, 1.64 mmol), octafluorotoluene (0.25 mL, 1.75 mmol), tetrabutylammonium hydrogen sulfate (290 mg, 0.85 mmol), CH_2Cl_2 (15 mL), and aqueous sodium hydroxide (1 M, 15 mL): yield 740 mg, 0.14 mmol, 87%; mp 160−162 °C; ^{1}H NMR δ 7.80 (m, 4H), 7.45−7.37 (m, 5H), 7.08−7.03 (m, 4H), 5.15 (s, 2H); ^{13}C NMR δ 194.05, 162.60, 159.05, 136.21, 134.56, 132.50, 132.27, 130.21, 128.79, 128.35, 127.55, 115.41, 114.57, 70.17; ^{19}F NMR δ −162.30 (s, 2F), −150.54 (d, J = 24.4 Hz, 2F), −66.90 (d, J = 24.4 Hz, 3F).

Preparation of 5a and 5b from Compound 7. McMurry reaction of compound **7** (500 mg, 0.96 mmol) and propiophenone (0.4 mL, 2.8 mmol) following the procedure described for the synthesis of compound **4** afforded a mixture of **5a** and **5b** in 1:2 ratio (358 mg, 0.58 mmol, 60%).

(*Z*)-2-[4-[1-(*p*-Hydroxyphenyl)-2-phenyl]-1-butenyl]phenoxyacetic Acid Benzyl Ester (8). Benzyl 2-bromoacetate (0.25 mL, 1.6 mmol) and K_2CO_3 (100 mg, 0.75 mmol) were added to a solution of **6** (130 mg, 0.3 mmol) in acetone (4 mL), and the mixture was refluxed in the dark for 1 h. Excess solids were filtered off, and the solvent was evaporated in vacuo. Addition of 1:1 diethyl ether/petroleum ether 40−60 °C to the oily residue afforded **8** as a white solid (143 mg, 0.26 mmol, 86%): mp 138−140 °C; ^{1}H NMR δ 7.47−7.32 (m, 10H), 7.16−7.09 (m, 7H), 6.95 (d, J = 8.5 Hz, 2H), 6.76 and 6.53 (d, J = 8.5 Hz, 2H each), 5.18 (s, 2H), 5.07 (s, 2H), 4.52 (s, 2H), 2.48 (q, J = 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ 168.81, 157.55, 155.61, 142.41, 141.41, 137.53, 137.04, 136.88, 136.33, 135.13, 131.99, 130.60, 129.66, 128.66, 128.60, 128.50, 128.40, 127.98, 127.82, 127.56, 125.98, 114.30, 113.46, 70.01, 66.91, 65.26, 29.02, 13.63. Anal. Calcd for $C_{38}H_{34}O_4$: C, 82.28; H, 6.18. Found: C, 82.49; H, 6.35.

(*Z*)-2-[4-[1-(*p*-Hydroxyphenyl)-2-phenyl]-1-butenyl]phenoxyacetic Acid (9). To a solution of **8** (140 mg, 0.25 mmol) in EtOAc (25 mL) and MeOH (2.5 mL) was added 10% palladium on carbon (70 mg). The suspension was stirred under 1 atm of hydrogen gas for ca. 40 min in the dark (the reaction was monitored by TLC). The reaction mixture was filtered through Celite, which was washed with EtOAc and MeOH, and the solvents were evaporated in vacuo to afford pure (*Z*)-2-[4-[1-(*p*-hydroxyphenyl)-2-phenyl]-1-butenyl]phenoxyacetic acid (**9**) (116 mg, 0.25 mmol, 100%): ^{1}H NMR (acetone-d_6) δ 7.18−7.06 (m, 7H), 6.86 (d, J = 8.5, 2H), 6.81 (d, J = 8.5, 2H), 6.60 (d, J = 8.5 Hz, 2H), 4.58 (s, 2H), 2.49 (q, J = 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H). Anal. Calcd for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92. Found: C, 76.65; H, 6.18.

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Supporting Information Available: Tables, in CIF format, of positional parameters, bond lengths, and bond angles of compound **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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