New Highly Stereoselective Synthesis of (*Z*)-4-Hydroxytamoxifen and (*Z*)-4-Hydroxytoremifene via McMurry Reaction

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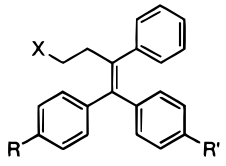
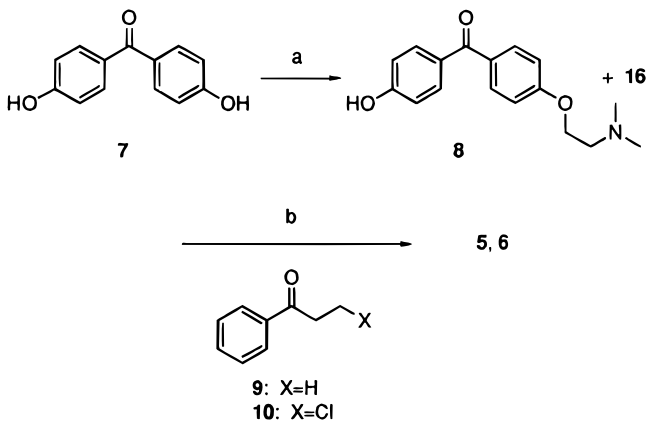
(*Z*)-Tamoxifen (**1**) is the first antiestrogen to be widely used for the treatment of breast cancer, and this drug is presently being evaluated for preventive therapy for breast cancer in normal women.[1] (*Z*)-Toremifene (**2**) has recently been introduced for the treatment of advanced breast cancer.[2] (*Z*)-4-Hydroxytamoxifen (**3**), a metabolite of (*Z*)-tamoxifen (**1**),[3] is the active antiestrogenic compound.[4] We presume that (*Z*)-4-hydroxytoremifene (**4**), a metabolite of (*Z*)-toremifene (**2**),[5] has a role similar to that of (*Z*)-4-hydroxytamoxifen (**3**).[6] Our interest in these hydroxylated triphenylethylene derivatives is to reach a better understanding of their contribution in the observed (*Z*)-tamoxifen (**1**) and (*Z*)-toremifene (**2**) biological activities, and the development of resistance to treatment.



	R	R'	X
1	H	$O(CH_2)_2N(CH_3)_2$	H
2	H	$O(CH_2)_2N(CH_3)_2$	Cl
3	OH	$O(CH_2)_2N(CH_3)_2$	H
4	OH	$O(CH_2)_2N(CH_3)_2$	Cl
5	$O(CH_2)_2N(CH_3)_2$	OH	H
6	$O(CH_2)_2N(CH_3)_2$	OH	Cl

The known routes of synthesis of (*Z*)-4-hydroxytamoxifen (**3**) are long and involve the separation of *E* and *Z* isomers[7] except the last reported synthesis,[8] which is stereoselective and uses carbometalation of alkynylsilanes.[9] The synthesis of (*Z*)-4-hydroxytoremifene (**4**) has not yet been reported in the literature. The challenge in the preparation of compounds **3** and **4** is to obtain good stereoselectivity, avoid isomerization,[10] introduce an additional chloro functionality in compound **4**,[11] and have a convergent and scalable approach. According to the preceding criteria and the success of a described stereoselective synthesis of (*Z*)-tamoxifen (**1**),[12] the McMurry reaction became a possible strategy for a new stereoselective synthesis of (*Z*)-4-hydroxytamoxifen (**3**) and (*Z*)-4-hydroxytoremifene (**4**).

Scheme 1[a]



[a]Reagents and conditions: (a) $Cl(CH_2)_2N(CH_3)_2 \cdot HCl$ Cs_2CO_3, DMF, 80 °C, 18 h; (b) **9** or **10**, $TiCl_4$, Zn, THF, reflux, 5 h.

The first attempt for the synthesis of (*Z*)-4-hydroxytamoxifen (**3**) and (*Z*)-4-hydroxytoremifene (**4**) is outlined in Scheme 1. This strategy consists of a McMurry reaction between benzophenone derivative **8** containing a 2-(dimethylamino)ethoxy chain and propiophenone derivatives **9** or **10**. 4,4′-Dihydroxybenzophenone (**7**) was monoalkylated with 2-(dimethylamino)ethyl chloride hydrochloride in the presence of cesium carbonate in DMF at 80 °C to yield benzophenone **8** in 40%.[13a] Then, several McMurry conditions[12] between equimolar quantities of benzophenone **8** and propiophenone (**9**) were tried in order to reach the best stereoselectivity ($TiCl_3$ (4 equiv)−Li (14 equiv)/DME, 13% yield, 1:3 **3**:**5** ratio; $TiCl_4$ (3 equiv)−Zn (6 equiv)/DME, 33% yield, 1:1.7 **3**:**5** ratio; $TiCl_4$ (3 equiv)−Zn (6 equiv)/THF, 41% yield, 1:2.3 **3**:**5** ratio; yield and ratio were obtained from crude material).[14] The cross-coupling products **3** and **5** were favored, and the $TiCl_4$ (4 equiv)−Zn (8 equiv)−propiophenone (**9**) (3 equiv)/THF system under darkness conditions gave the best result (87% yield, 1:5.7 **3**:**5** ratio after chromatography with 19:1 dichloromethane−methanol). Unfortunately, the McMurry reaction gave the expected (*Z*)-4-hydroxytamoxifen (**3**) as the minor product. The isomeric mixture was separated by preparative TLC.[10a] However,

(1) Jordan, V. C. *Breast Cancer Res. Treat.* **1994**, *31*, 41.
(2) Valavaara, R.; Pyrrhonen, S.; Heikkinen, M.; Rissanen, P.; Blanco, G.; Tholix, E.; Nordman, E.; Taskinen, P.; Holsti, L.; Hajba, A. *Eur. J. Cancer Clin. Oncol.* **1988**, *24*, 785.
(3) (a) Jordan, V. C. *Breast Cancer Res. Treat.* **1982**, *2*, 123. (b) Daniel, C. P.; Gaskell, S. J.; Bishop, H.; Nicholson, R. I. *J. Endocrinol.* **1979**, *83*, 401.
(4) (a) Jordan, V. C.; Collins, M. M.; Rowsby, L.; Prestwich, G. *J. Endocrinol.* **1977**, *75*, 305. (b) Binart, N.; Catelli, M. G.; Geynet, C.; Puri, V.; Hahnel, R.; Mester, J.; Baulieu, E. E. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 812.
(5) Sipilä, H.; Kangas, L.; Vuorilehto, L.; Kalapudas, A.; Eloranta, M.; Söderwall, M.; Toivala, R.; Anttila, M. *J. Steroid Biochem.* **1990**, *36*, 211.
(6) Simberg, N. H.; Murai, J. T.; Siiteri, P. K. *J. Steroid Biochem.* **1990**, *36*, 197.
(7) (a) Grafe, I.; Schickaneder, H.; Jungblut, P. W.; Ahrens, K. H. EP 287690 A1 881026, Heumann Pharma G.m.b.H. und Co. (b) McCague, R. *J. Chem. Res., Synop.* **1986**, *2*, 58. (c) McCague, R. *J. Chem. Res., Miniprint* **1986**, 771. (d) Forster, A. B.; Jarman, M.; Leung, O. T.; McCague, R.; Leclercq, G.; Devleeschouwer, N. *J. Med. Chem.* **1985**, *28*, 1491. (e) Toivola, R. J.; Karjalainen, A. J.; Kurbela, K. O. A.; Soderwall, M. L.; Kangas, L. V. M.; Blanco, G. L.; Sundquist, H. K. EP 95875 A2 831207, Farmos Group Ltd. (f) Richardson, D. N. DE 2807599 780831, Imperial Chemical Industries Ltd.
(8) Al-Hassan, M. I. *Synth. Commun.* **1989**, *19*, 1619.
(9) Miller, R. B.; Al-Hassan, M. I. *J. Org. Chem.* **1985**, *50*, 2121.
(10) (a) Robertson, D. W.; Katzenellenbogen, J. A. *J. Org. Chem.* **1982**, *47*, 2387. (b) Katzenellenbogen, B. S.; Norman, M. J.; Eckert, R. L.; Peltz, S. W.; Mangel, W. F. *Cancer Res.* **1984**, *44*, 112. (c) Katzenellenbogen, J. A.; Carlson, K. E.; Katzenellenbogen, B. S. *J. Steroid Biochem.* **1985**, *22*, 589.
(11) We believe that carbometalation of alkynylsilanes cannot be a successful method for the preparation of compound **4**.
(12) Coe, P. L.; Scriven, C. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 475.
(13) (a) We recovered 45% of starting material and 8% of corresponding dialkylated compound **16**. (b) We recovered 30% of starting material and 25% of corresponding dipivaloate compound **17**.

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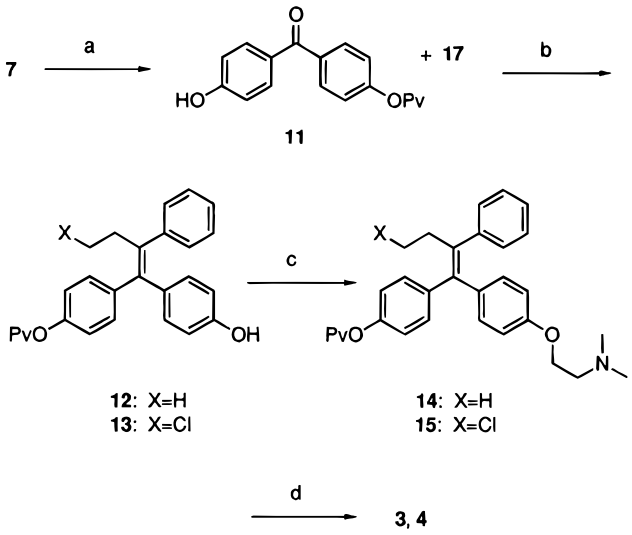
Scheme 2[a]



[a]Reagents and conditions: (a) PvCl, NaH, THF, 0 °C to rt, 2 h; (b) **9** or **10**, $TiCl_4$, Zn, THF, reflux, 5 h; (c) $Cl(CH_2)_2N(CH_3)_2$, K_2CO_3, acetone, H_2O, reflux, 5 h; (d) MeLi, THF, -78 °C, 2 h.

when separation was performed by column chromatography, (*Z*)-4-hydroxytamoxifen (**3**) could not be obtained as a pure isomeric material (3:1 **3**:**5** ratio after three chromatography with 99:1 benzene−piperidine) but chromatographed (*E*)-4-hydroxytamoxifen (**5**) became pure after recrystallization. We finally found that (*E*)-4-hydroxytamoxifen (**5**) could be directly purified by trituration and recrystallization from ethanol to achieve a 66:1 **5**:**3** ratio in 26% yield.

The above-described reaction was expanded to the first synthesis of (*E*)-4-hydroxytoremifene (**6**) (20% yield for the last step) with the same *E*:*Z* ratio of the crude and purified product as observed for compound **5**, using 3-chloropropiophenone (**10**). Thus, the McMurry reaction between monoalkylated benzophenone **8** and propiophenones **9** or **10** gave *E* isomer as the major product. This observation is contrary to the reported synthesis of (*Z*)-tamoxifen (**1**) where the *Z* isomer is the major product.[12] Current knowledge of the mechanisms of the mixed carbonyl-coupling reaction does not provide an explanation for the observed stereoselectivity.[15]

The second attempt for the synthesis of compounds **3** and **4** utilized monoprotected 4,4′-dihydroxybenzophenone in the McMurry reaction in order to reverse the olefin stereochemistry (Scheme 2). Thus, 4,4′-dihydroxybenzophenone (**7**) was monoprotected to give the monopivaloate **11**[13b] which was treated under the McMurry reaction conditions described above. Crude compound **12** has a very encouraging 14:1 *E*/*Z* ratio[14] and was purified by trituration from methanol to give a >100:1 *E*/*Z* ratio in 82% yield. An improved *E* stereoselectivity of compound **12** over compound **5** (14:1 vs 5.7:1 *E*/*Z* ratio) was obtained. According to the present and previous work,[12] the phenol functionality is always on the opposite side of the ethyl chain in the McMurry product, thus providing an important element of the involved mechanism. Variation in the stereoselectivity depends upon the nature of substituents on benzophenone. Thus, phenol derivative **12** was alkylated with 2-(dimethylamino)ethyl chloride (2.0 equiv) in the presence of potassium carbonate (1.27 equiv) in acetone−water to give the amine **14** in 46% yield with a 99:1 *E*/*Z* ratio. The small decrease in the crude *E*/*Z* ratio (32:1) could be explained by transesterification.[16] Finally, the amine **14** was deprotected with methyllithium at −78 °C in THF to yield the desired (*Z*)-4-hydroxytamoxifen (**3**) with a crude 99:1 *Z*/*E* ratio, which was then triturated from ethanol to a >100:1 *Z*/*E* ratio in 66% yield. The present synthesis was expanded with success in an analogous manner to obtain the first described synthesis of (*Z*)-4-hydroxytoremifene (**4**) using 3-chloropropiophenone (**10**) (crude compound **13**, 22:1 *E*/*Z* ratio; purified compound **4**, >100:1 *Z*/*E* ratio, four steps, 10% overall yield).

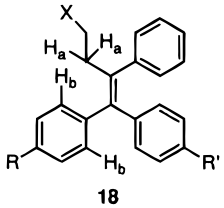
The present study demonstrates the high efficiency of the McMurry strategy for the synthesis of the *Z* and *E* isomers of both 4-hydroxytamoxifen and 4-hydroxytoremifene. Investigation of mechanisms responsible for this observed stereoselectivity could lead to an expansion of this class of compounds.

Experimental Section

General Procedures. All reagents were purchased from Aldrich Chemical Co. All reactions were carried out in flame-dried glassware under a positive atmosphere of dry Ar. THF was freshly distilled from sodium/benzophenone prior to use. All extracts were dried over $MgSO_4$, and solvents were removed by rotary evaporation under reduced pressure. Column chromatography was carried out using silica gel (230−400 mesh) (EM Science). Compounds **3**−**6** were synthetized under reduced light and kept in the dark at −20 °C. Melting points are uncorrected. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz. Mass spectra were provided by Le Centre Régional de Spectrométrie de Masse, Université de Montréal, Montréal, Canada. Elemental analyses and Karl Fisher (KF) were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

4-[2-(*N*,*N*-Dimethylamino)ethoxy]-4′-hydroxybenzophenone (8) and 4,4′-Bis[2-(*N*,*N*-dimethylamino)ethoxy]-benzophenone (16). A solution of 4,4′-dihydroxybenzophenone (**7**) (10 g, 47 mmol) in DMF (100 mL) was treated with Cs_2CO_3 (46 g, 141 mmol) and heated in an oil bath at 80 °C. The resulting suspension was treated with 2-(dimethylamino)ethyl chloride hydrochloride (7.5 g, 51 mmol) in three portions over a 2 h period and stirred for 16 h. The reaction mixture was cooled to rt, quenched with saturated ammonium chloride (300 mL), and extracted with ethyl acetate (4 × 150 mL). The combined organic phase was washed with brine (4 × 150 mL), dried, and concentrated. Flash chromatography (methanol−ethyl acetate 1:9) and trituration (hexanes−CH_2Cl_2 9:1) afforded compound

(14) The stereochemistry of the olefin **18** (compounds **3**, **4**, **5**, **6**, **12**, and **13**) was determined using NOE NMR experiments. The irradiation of allylic methylene protons (H_a) of these compounds showed a NOE with aryl protons (H_b). Moreover, *Z* isomers **3** and **4** have upfield NMR signals of the 2-dimethylaminoethoxy chain protons compared to the corresponding *E* isomers **5** and **6** (see ref. 7c, 7d and 10a).



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(15) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.

(16) When the benzoate as a protecting group was used in the synthesis, we obtained low yield (20−30%) and decreased *E*/*Z* ratio (19:1 in the best cases) of desired amine. This phenomena could be explained via the transesterification. In order to decrease the amount of diester olefin and other byproducts, the less reactive pivaloate as a protecting group was used.

(17) 2-(Dimethylamino)ethyl chloride was obtained by treating 2-(dimethylamino)ethyl chloride hydrochloride with saturated sodium carbonate for 30 min. Then, the amine was extracted with ether, and the solution was dried and distilled under atmospheric pressure (bp 95−100 °C, 80% yield).

8 (5.35 g, 40%) as a white solid: mp 150−153 °C; IR (KBr) 3200−2200, 1642 cm^{-1}; ^1H NMR (CD_3OD) δ 2.36 (s, 6H), 2.81 (t, J = 5.5 Hz, 2H), 4.18 (t, J = 5.5 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.72 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 45.82, 58.95, 66.89, 115.21, 116.20, 130.30, 132.17, 133.25, 133.70, 163.59, 196.80. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.28; H, 6.70; N, 4.76. Compound **16** was isolated by flash chromatography (methanol−ethyl acetate 2:3) to give 1.31 g (8%) of a white solid. A sample was recrystallized from methanol: mp 89−91 °C; IR (KBr) 3100−2300, 1639, 1602 cm^{-1}; ^1H NMR (CD_3OD) δ 2.36 (s, 12H), 2.81 (t, J = 5.4 Hz, 4H), 4.21 (t, J = 5.4 Hz, 4H), 7.07 (d, J = 8.8 Hz, 4H), 7.76 (d, J = 8.8 Hz, 4H); ^{13}C NMR δ 45.86, 58.96, 66.98, 115.26, 131.87, 133.36, 163.80, 196.60. Anal. Calcd for $C_{21}H_{28}N_2O_3 \cdot 0.05H_2O$: C, 70.58; H, 7.93; N, 7.84. Found: C, 70.62; H, 7.89; N, 7.79 (KF = 0.25%).

***(E)*-4-Hydroxytamoxifen (5).** To a suspension of zinc (1.8 g, 28 mmol) in 30 mL of dry THF, under Ar, was added dropwise $TiCl_4$ (1.6 mL, 14 mmol). The mixture was refluxed for 2 h. A solution of ketone **8** (1.0 g, 3.5 mmol) and propriophenone (**9**) (1.4 mL, 10.5 mmol) in 50 mL of dry THF was added at once, and the reflux was continued for 5 h. The reaction mixture was cooled to rt, quenched with 10% K_2CO_3 (100 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic phase was washed with 10% K_2CO_3 (2 × 50 mL) and brine (50 mL), dried, and concentrated. Trituration of the crude solid from ethanol (20 mL) yielded 0.78 g (57%) of 1:32 **3**/**5** isomeric mixture ratio. Recrystallization of the mixture from ethanol decreased to 1.5% the *Z* isomer **3** and gave compound **5** (0.35 g, 26%): mp 155−157 °C; IR (KBr) 3500−2200, 1606 cm^{-1}; ^1H NMR (CD_3OD) δ 0.90 (t, J = 7.5 Hz, 3H), 2.26 (s, 6H), 2.45 (q, J = 7.5 Hz, 2H), 2.79 (t, J = 5.4 Hz, 2H), 4.12 (t, J = 5.4 Hz, 2H), 6.39 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 7.08−7.15 (m, 7H); ^{13}C NMR δ 13.91, 29.85, 45.84, 59.18, 66.64, 115.14, 126.95, 128.85, 130.90, 131.62, 133.03, 136.00, 137.95, 139.74, 141.86, 144.12, 156.40, 158.94; FAB-MS (thio), *m/e* 388 (100, $[M + H]^+$), 217 (17). Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.40; H, 7.40; N, 3.62.

***(E)*-4-Hydroxytoremifene (6).** The same procedure for compound **5** was used, starting from benzophenone **8** (1.16 g, 4.1 mmol) and 3-chloropropiophenone (**10**). Trituration of the crude solid (CCl_4−ethanol 9:1) yielded 1.08 g (63%) of 1:16 **4**/**6** isomeric mixture ratio. Recrystallization of the mixture from ethanol decreased to 1.5% the *Z* isomer **4** and gave compound **6** (0.342 g, 20% yield): mp 167−169 °C; IR ($CHCl_3$) 3500−2200, 1608 cm^{-1}; ^1H NMR (CD_3OD) δ 2.37 (s, 6H), 2.81 (t, J = 5.5 Hz, 2H), 2.91 (t, J = 7.6 Hz, 2H), 3.40 (t, J = 7.6 Hz, 2H), 4.14 (t, J = 5.5 Hz, 2H), 6.41 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 7.00−7.21 (m, 7H); ^{13}C NMR (DMSO-d_6) δ 38.01, 42.95, 45.53, 57.74, 65.72, 114.13, 114.33, 126.31, 128.00, 129.30, 130.21, 131.18, 133.13, 134.08, 134.93, 140.94, 141.06, 155.45, 157.34; FAB-MS (thio), *m/e* 422 (100, $[M + H]^+$), 388 (26, $[M + 2H - Cl]^+$). Anal. Calcd for $C_{26}H_{28}ClNO_2$: C, 74.01; H, 6.69; Cl, 8.40, N, 3.32. Found: C, 73.80; H, 6.70; Cl, 8.54; N, 3.29.

4-Hydroxy-4′-(trimethylacetoxy)benzophenone (11) and 4,4′-Bis(trimethylacetoxy)benzophenone (17). Sodium hydride in 60% dispersion in mineral oil (5.1 g, 77 mmol) was added to a solution of 4,4′-dihydroxybenzophenone (**7**) (15.0 g, 70 mmol) in dry THF (160 mL). The solution was stirred at rt for 30 min, cooled to 0 °C, treated with trimethylacetyl chloride (9.5 mL, 77 mmol) and stirred for 2 h after removing the ice−water bath. The reaction mixture was quenched with distilled water (100 mL) and extracted with ethyl acetate (4 × 200 mL). The combined organic phase was dried and concentrated. Flash chromatography (CH_2Cl_2−ethyl acetate 19:1) and trituration (hexanes−CH_2Cl_2 9:1) afforded compound **11** (8.7 g, 42%) as a white solid: mp 171−173 °C; IR ($CHCl_3$) 3585, 3360, 1748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9H), 6.90 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.52 (br s, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H); ^{13}C NMR δ 27.08, 39.23, 115.38, 121.45, 129.45, 131.44, 132.98, 135.51, 154.11, 160.86, 177.21, 195.46. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.44; H, 6.24. Compound **17** was isolated by flash chromatography (CH_2Cl_2) and trituration (hexanes−CH_2Cl_2 9:1) to give 6.7 g (25%) of a white solid: mp 163−164 °C; IR ($CHCl_3$) 1749, 1203 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (s, 18H), 7.18 (d, J = 8.7 Hz, 4H), 7.84 (d, J = 8.7 Hz, 4H); ^{13}C NMR δ 27.08, 39.23, 121.52, 131.52, 134.82, 154.47, 176.58, 194.40. Anal. Calcd for $C_{23}H_{26}O_5$: C, 72.23; H, 6.85. Found: C, 72.22; H, 6.74.

***(E)*-1-(4-Hydroxyphenyl)-1-[4-(trimethylacetoxy)phenyl]-2-phenylbut-1-ene (12).** The same procedure for compound **5** was used, starting from benzophenone **11** (2.0 g, 7.0 mmol) and propiophenone (**9**). Trituration of the crude solid from methanol (13 mL) gave compound **12** (2.29 g, 82%) with a >100:1 *E*/*Z* ratio as a white solid: mp 165−167 °C; IR (KBr) 3600−3100, 1754 cm^{-1}; ^1H NMR (CD_3OD) δ 0.91 (t, J = 7.4 Hz, 3H), 1.36 (s, 9H), 2.46 (q, J = 7.4 Hz, 2H), 6.40 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 8.7 Hz, 2H), 7.02−7.25 (m, 9H); ^{13}C NMR δ 13.85, 27.49, 29.82, 40.12, 115.24, 122.21, 127.13, 128.90, 130.85, 131.50, 133.00, 135.49, 142.68, 142.85, 143.79, 151.20, 156.58, 178.80. Anal. Calcd for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26. Found: C, 80.35; H, 7.15.

***(E)*-1-[4-[2-(*N*,*N*-Dimethylamino)ethoxy]phenyl]-1-[4-(trimethylacetoxy)phenyl]-2-phenylbut-1-ene (14).** A solution of phenol **12** (0.60g, 1.5 mmol), freshly distilled 2-(dimethylamino)ethyl chloride[17] (0.32 g, 3.0 mmol) and K_2CO_3 (0.27g, 1.9 mmol) in 19:1 acetone−water (20 mL) was refluxed for 5 h in the dark. The reaction mixture was cooled to rt, dried, and evaporated. Flash chromatography (CH_2Cl_2−methanol 19:1) and recrystallization from isopropyl alcohol gave compound **14** (0.32 g, 46%) with a 99:1 *E*/*Z* ratio as a white solid: mp 114−116 °C; IR ($CHCl_3$) 1744, 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.4 Hz, 3H), 1.37 (s, 9H), 2.29 (s, 6H), 2.46 (q, J = 7.4 Hz, 2H), 2.64 (t, J = 5.8 Hz, 2H), 3.93 (t, J = 5.8 Hz, 2H), 6.56 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 7.04−7.26 (m, 9H); ^{13}C NMR δ 13.54, 27.16, 29.00, 39.09, 45.92, 58.32, 65.77, 113.43, 121.07, 126.05, 127.87, 129.66, 130.41, 131.88, 135.31, 137.43, 141.17, 141.68, 142.32, 149.71, 156.87, 177.08. Anal. Calcd for $C_{31}H_{37}NO_3 \cdot 0.06H_2O$: C, 78.76; H, 7.91; N, 2.96. Found: C, 78.76; H, 8.14; N, 2.89 (KF = 0.24%).

***(Z)*-4-Hydroxytamoxifen (3).** MeLi (4.2 mL of a solution 1.4 M in ether, 5.8 mmol) was added to a solution of amine **14** (0.92g, 1.9 mmol) in dry THF (40 mL) at −78 °C. The reaction mixture was stirred for 2 h, quenched with saturated ammonium chloride (2 mL), allowed to warm to rt, and extracted with ethyl acetate (4 × 50 mL). The combined organic phase was dried and concentrated. Trituration from ethanol (25 mL) gave compound **3** (0.49 g, 66%) with a >100:1 *Z*/*E* ratio as a white solid: mp 140−143 °C; IR (KBr) 3602, 3491, 3250−2100, 1606 cm^{-1}; ^1H NMR (CD_3OD) δ 0.90 (t, J = 7.4 Hz, 3H), 2.28 (s, 6H), 2.47 (q, J = 7.4 Hz, 2H), 2.68 (t, J = 5.5 Hz, 2H), 3.94 (t, J = 5.5 Hz, 2H), 6.55 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.6 Hz, 2H), 7.00−7.15 (m, 7H); ^{13}C NMR δ 12.41, 28.40, 44.29, 57.60, 64.91, 112.87, 114.37, 125.46, 127.36, 129.41, 130.10, 131.54, 134.84, 136.09, 138.28, 140.56, 142.65, 155.80, 156.60; FAB-MS (thio), *m/e* 388 (100, $[M + H]^+$), 217 (28). Anal. Calcd for $C_{26}H_{29}NO_2 \cdot 0.34H_2O$: C, 79.33; H, 7.60; N, 3.56. Found: C, 79.73; H, 7.60; N, 3.44 (KF = 0.69%).

***(E)*-1-(4-Hydroxyphenyl)-1-[4-(trimethylacetoxy)phenyl]-2-phenyl-4-chlorobut-1-ene (13).** The same procedure for compound **12** was used, starting from benzophenone **11** (2.5 g, 8.3 mmol) and 3-chloropropiophenone (**10**) to afford compound **13** (1.7 g, 47%). Flash chromatography (hexanes−ethyl acetate 9:1) on the mother liquors gave 1.1 g of supplementary material for an overall yield of 77% with a >100:1 *Z*/*E* ratio: mp 161−163 °C; IR ($CHCl_3$) 2977, 1743, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 9H), 2.93 (t, J = 7.2 Hz, 2H), 3.40 (t, J = 7.2 Hz, 2H), 5.19 (s, 1H), 6.45 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 7.05−7.31 (m, 9H); ^{13}C NMR δ 27.14, 38.36, 39.12, 42.75, 114.43, 121.32, 126.64, 128.22, 129.52, 130.48, 131.91, 134.73, 135.62, 140.18, 140.84, 150.00, 153.93, 177.20. Anal. Calcd for $C_{26}H_{27}ClO_3$: C, 73.84; H, 6.43; Cl, 8.38. Found: C, 73.98; H, 6.27; Cl, 8.09.

***(E)*-1-[4-[2-(*N*,*N*-Dimethylamino)ethoxy]phenyl]-1-[4-(trimethylacetoxy)phenyl]-2-phenyl-4-chlorobut-1-ene (15).** The same procedure for compound **14** was used, starting from phenol **13** (1.5 g, 3.7 mmol). Flash chromatography (ethyl acetate−methanol 19:1) and recrystallization from ethanol gave compound **15** (0.81 g, 43%) with a 99:1 *E*/*Z* ratio as a white solid: mp 125−127 °C; IR ($CHCl_3$) 3690, 3597, 1743, 1607 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 9H), 2.28 (s, 6H), 2.64 (t, J = 5.8 Hz, 2H), 2.94 (t, J = 7.3 Hz, 2H), 3.41 (t, J = 7.3 Hz, 2H), 3.92 (t, J = 5.8 Hz, 2H), 6.56 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.6 Hz, 2H), 7.06−7.32 (m, 9H); ^{13}C NMR δ 27.14, 38.40, 39.12, 42.76, 45.92, 58.29, 65.81, 113.54, 121.31, 126.61, 128.21, 129.52, 130.47, 131.70, 134.67, 135.52, 140.21, 140.84, 140.95, 150.01, 157.16,

177.01. Anal. Calcd for $C_{31}H_{36}ClNO_3$: C, 73.57; H, 7.17; Cl, 7.01; N, 2.77. Found: C, 73.29; H, 7.24; Cl, 6.72; N, 2.52.

(*Z*)-4-Hydroxytoremifene (4). The same procedure for compound **3** was used, starting from amine **15** (0.20 g, 0.39 mmol). Trituration from isopropyl alcohol (5 mL) gave compound **4** (0.13 g, 75%) with a >100:1 *Z*/*E* ratio as a white solid: mp 160−164 °C; IR (KBr) 3630, 3200−2200, 1609 cm^{-1}; ^1H NMR (CD_3OD) δ 2.30 (s, 6H), 2.70 (t, J = 5.4 Hz, 2H), 2.94 (t, J = 7.4 Hz, 2H), 3.40 (t, J = 7.4 Hz, 2H), 3.96 (t, J = 5.4 Hz, 2H), 6.58 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 7.10−7.19 (m, 7H); ^{13}C NMR δ 39.76, 43.59, 45.78, 59.08, 66.42, 114.46, 116.05, 127.46, 129.14, 130.81, 131.66, 132.86, 135.50, 136.28, 137.05, 142.90, 143.14, 157.62, 158.36; FAB-MS (thio), *m*/*e* 422 (100, $[M + H]^+$), 388 (18, $[M + 2H - Cl]^+$). Anal. Calcd for $C_{26}H_{28}ClNO_2$: C, 74.01; H, 6.69; Cl, 8.40; N, 3.32. Found: C, 73.99; H, 6.45; Cl, 8.37; N, 3.17.

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