Stereo-Defined Synthetic Route to (E)- and (Z)-Tamoxifen Derived from (E)-1-Bromo-2-iodoalkenes.

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EXPERIMENTAL SECTION

1. General Information.

All reactions sensitive to air or moisture were carried out under an argon atmosphere and anhydrous conditions unless otherwise noted. Dry solvents were purchased and used without further purification and dehydration. All reagents were purchased and used without further purification. Analytical thin layer chromatography was carried out on Merck silica 60F254. Column chromatography was carried out with silica gel 60 N (Kanto Chemical Co.). HRMS were reported on the basis of TOF (time of flight)-MS (MALDI-TOF or LCMS-IT-TOF; Shimadzu), and DART (Direct Analysis in Real Time)-MS. ¹H and ¹³C NMR spectra were recorded with a 5 mm QNP probe at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in d (ppm) with reference to residual solvent signals [¹H NMR: CHCl₃ (7.26), C₇H₈ (2.08), C₆H₆ (7.16), CH₂Cl₂ (5.32); ¹³C NMR: CDCl₃ (77.36)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

2. Gram-scale synthesis of (E)-(1-bromobut-1-ene-1,2-diyl)dibenzene (2) (Table 2, entry 4).

Under an argon atmosphere, to a 300 mL flask charged with solution of 1 (5.39 g, 16.0 mmol) in toluene (96 mL) was added tributyl(phenyl)tin (7.83 mL, 24.0 mmol), and then Copper (I) thiophene-2-carboxylate (4.58 g, 24.0 mmol), namely CuTC, was suspended. After stirred at 105 ºC for 19 h, the reaction mixture was allowed to cool to ambient temperature, and followed by filtration through a pad of celite and frolisil (eluent; 60 mL of toluene), and washing with brine (50 mL), and evaporation. The resultant residue of green oil was purified with silica-gel column chromatography (hexane only) to yield 2.91 g of 2 as a yellow oil in 63% (~95% purity).
Further chromatography by silica-gel (eluent; hexane/EtOAc=50/1) enabled us to obtain 2 in totally pure form. $^1$H NMR (400 MHz, CDCl$_3$) 7.15-6.99 (m, 10H), 2.81 (q, $J = 7.5$ Hz, 2H), 1.06 (t, $J = 7.5$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 144.8, 141.3, 140.8, 130.5, 129.4, 128.3, 128.0, 127.7, 127.1, 120.9, 33.5, 12.0 ppm. MS (DART-TOF) $m/z$: 286 [M(79)]$^+$; IR (neat): 3052, 2965, 2928, 2869, 1483, 1440, 763, 690 cm$^{-1}$; HRMS (DART-TOF) calcd for C$_{16}$H$_{15}$Br(79): 286.0352 [M]$^+$, Found 286.0336; Anal. Calcd for C$_{16}$H$_{15}$Br: C, 66.91; H, 5.26. Found: C, 66.75; H, 5.22.

3. Synthesis of (E)-Tamoxifen from 2 through the intermediate 4, and 5: (see Scheme 2).

For synthesis of (E)-(1-(4-methoxyphenyl)but-1-ene-1,2-diyl)dibenzene (4); Under an argon atmosphere, to a 20 mL flask charged with solution of 2 (3.25 g, 11.3 mmol) in DMF (56 mL) was added 4-methoxyphenylboronic acid (2.58 g, 17 mmol), and K$_2$CO$_3$ (3.12 g, 22.6 mmol), and Pd(PPh$_3$)$_4$ (1.31 g, 1.1 mmol). After stirred at 105 ºC for 7 h, the reaction mixture was allowed to cool to ambient temperature. The mixture was filtered through a pad of celite and frolisil, and the filtrate was evaporated off. The resultant residue was dissolved into toluene (100 mL), and washed with water (80 mL). The aqueous phase was extracted with toluene (15 mL x 3), and the combined organic layers were washed with brine (80 mL), and dried over Na$_2$SO$_4$, and concentrated in vacuo to give a crude product as orange solid and oil mixture materials. Purification with silica gel column chromatography (hexane/toluene=4/1) afforded 2.73 g of 4 as white solid materials of a totally pure form in 77% yield. Further purification by recrystallization from CH$_3$OH (18.7 mL/g) yielded 4 in pure form in 69%. $^1$H NMR (400 MHz, CDCl$_3$) 7.18-7.08 (m, 7H), 7.03-6.95 (m, 3H), 6.91-6.87 (m, 4H), 3.83 (s, 3H), 2.51 (q, $J = 7.4$ Hz, 2H), 0.95 (t, $J = 7.4$ Hz, 3H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) 158.6, 143.7, 142.7, 142.2, 138.7, 136.3, 131.1, 130.9, 130.0, 128.1, 127.6, 126.4, 126.0, 113.8, 55.5, 29.3, 13.9 ppm. MS (DART-TOF) $m/z$: 315 [MH]$^+$; IR (neat):

For synthesis of (\(E\))-4-(1,2-diphenylbut-1-en-1-yl)phenol (\(5\)): Under a nitrogen atmosphere, to a solution of \(4\) (314 mg, 1 mmol) in DMF (5 mL) was added NaSCH\(_2\)CH\(_3\) (841 mg, 10 mmol), and the mixture was refluxed for 1 h. The reaction was quenched at 0 °C with 3 M aqueous HCl (15 mL), and the mixture was stirred at room temperature for 30 min. The whole media diluted with 30 mL of toluene was transferred into a 100 mL separatory funnel, and the aqueous layer was extracted with toluene (10 mL x 3). The combined organic phases were washed with 3 M HCl (10 mL x 3), brine (15 mL x 3), and dried over Na\(_2\)SO\(_4\), and concentrated \textit{in vacuo} to give a crude of 300 mg as a white solid. Purification by just washing with hexane (2 mL x 3) afforded 283 mg of \(5\) in 94% with \(E/Z\) > 99/1 as white powders, which were enough pure to use in next step\(^1\) (\textbf{CAUTION}: All the glass-apparatus were thoroughly washed with aq. 1% v/v sodium hypochlorite of NaClO for the deodorization.) For data of \(5\): \(^1\)H NMR (400 MHz, CDCl\(_3\)) 7.17-7.08 (m, 7H), 7.03-6.96 (m, 3H), 6.88-6.86 (m, 2H), 6.81 (d, \(J = 8.4\) Hz, 2H), 4.68 (brs, 1H), 2.51 (q, \(J = 7.4\) Hz, 2H), 0.94 (t, \(J = 7.4\) Hz, 3H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 154.5, 143.6, 142.7, 142.3, 138.6, 136.5, 131.1 (two peaks are over lapped), 130.0, 128.1, 127.6, 126.4, 126.0, 115.3, 29.3, 13.9 ppm; MS (DART-IT-TOF) \(m/z\): 301 \([\text{MH}]^+\); IR (neat): 3362, 3035, 2963, 2963, 2922, 2866, 1505, 1219, 694 cm\(^{-1}\); HRMS (DART-T-TOF) calcd for C\(_{22}\)H\(_{21}\)O: 301.1587 [MH]\(^+\), Found 301.1566.

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\(^1\) We didn’t filter the crude product through a glass-filter because we always observed not only the terrible static electricity but also unexpected erosion of \(E/Z\) ratios (~88/12), although we don’t know yet if an electrostatic action causes the loss of stereochemistry in \(5\).
For (E)-tamoxifen\(^2\); Then, the phenolic compound was provided to the etherification step: to a solution of 5 (174 mg, 0.58 mmol) in toluene/ethanol (6 mL/6 mL) was added 2-(dimethyl amino)ethyl chloride hydrochloride (173 mg, 1.2 mmol) and K\(_2\)CO\(_3\) (318 mg, 2.3 mmol). After stirred for 3 h at 85 °C, and the mixture was allowed to cool to ambient temperature. The reaction was quenched with satd. aq. NH\(_4\)Cl (15 mL) at 0 °C, and the resultant mixture was stirred for 40 min at room temperature. To the mixture was added toluene (15 mL), and the aqueous phase was extracted with toluene (10 mL x 3). The combined organic layers were washed with water (15 mL x 2), and brine (15 mL), and dried over Na\(_2\)SO\(_4\), and concentrated in vacuo to give 208 mg of desired (E)-Tamoxifen with 97% yield and E/Z = 96/4 ratio as a yellowish white viscous materials of sufficient purity without need for purification. Further purification by recrystallization from hexane yielded 45% of (E)-Tamoxifen with E/Z = ~100/0. \(^1\)H NMR (400 MHz, CDCl\(_3\)) 7.16-7.09 (m, 7H), 7.02-6.97 (m, 3H), 6.91-6.86 (m, 4H), 4.08 (t, \(J = 5.8\) Hz, 2H), 2.74 (t, \(J = 5.8\) Hz, 2H), 2.51 (q, \(J = 7.4\) Hz, 2H), 2.35 (s, 6H), 0.94 (t, \(J = 7.4\) Hz, 3H) ppm; \(^13\)C NMR (100 MHz, CDCl\(_3\)) 157.9, 143.7, 142.7, 142.2, 138.7, 136.3, 131.1, 130.9, 130.0, 128.1, 127.6, 126.3, 125.9, 114.4, 66.2, 58.7, 46.3, 29.3, 13.9 ppm; MS (DART-TOF) \(m/z\): 372 [MH]+; IR (neat): 2945, 2861, 2810, 2769, 1606, 1503, 1240, 1029, 694 cm\(^{-1}\); HRMS (DART-IT-TOF) calcd for C\(_{26}\)H\(_{30}\)NO: 372.2322 [MH]+, Found: 372.2317.


4. Synthetic procedure of (E)-1-(1-bromo-2-iodobut-1-en-1-yl)-4-methoxybenzene (6) (Scheme 3).

To a 200 mL two-neck flask charged with a solution of 4-iodoanisole (3.5 g, 15 mmol) in toluene (30 mL) and Et3N (30 mL) at 0 ºC was added PdCl2(PPh3)2 (526 mg, 0.75 mmol) and CuI (286 mg, 1.5 mmol) and trimethylsilylacetylene (2.49 mL, 18 mmol). After stirred at room temperature for 0.5 h, the mixture was filtered through a pad of celite and florisil (eluent, 240 mL toluene), and the filtrate was evaporated off. The resultant residue was diluted with 80 mL of toluene was transferred into a 200 mL separatory funnel, and washed with water (60 mL x 2), brine (60 mL x 2), and dried over Na2SO4, and concentrated in vacuo to give a crude of dark brown oil (8.48 g). The crude product was purified with short-plugged column chromatography (hexane/toluene = 9/1), which afforded 2.89 g of coupling adducts in 94% yield. 1H NMR (400 MHz, CDCl3) 7.41 (d, J = 8.8 Hz, 2 H), 6.82 (d, J = 8.8 Hz, 2 H), 3.81 (s, 3 H), 0.24 (s, 9 H) ppm. The product was provided to the next step without further purification.

Under an argon atmosphere, to a solution of ((4-methoxyphenyl)ethynyl)trimethylsilane (1.63 g, 8 mmol) in DMSO (24 mL) was added EtI (3 mL, 37 mmol) at room temperature, and to the mixture was added CsF (1.46 g, 9.6 mmol). After stirred for 5.5 h, the reaction mixture was allowed to cool to 0 ºC and quenched with saturated aqueous NH4Cl (40 mL), and warmed to room temperature. The mixture was transferred into a 200 mL separatory funnel with 70 mL of toluene, and the aqueous layer was extracted with toluene (20 mL x 3). The combined organic phases were washed with brine (40 mL), and dried over
Na$_2$SO$_4$, and filtered off, and concentrated in vacuo to give a crude as an orange oil of 1.25 g, in which the molar ratio of desired ethylated molecule to 4-methoxyphenyl acetylene was 76:24. Purification by silica-gel column chromatography (eluent, hexane/toluene = 9/1) afforded 894 mg of 1-(but-1-yn-1-yl)-4-methoxybenzene as a colorless oil in 70% yield as a 97% purity. $^1$H NMR (400 MHz, CDCl$_3$) 7.33 (d, $J$ = 8.8 Hz, 2 H), 6.81 (d, $J$ = 8.8 Hz, 2 H), 3.80 (s, 3 H), 2.40 (q, $J$ = 7.5 Hz, 2 H), 1.23 (t, $J$ = 7.5 Hz, 3 H) ppm.

The product was provided to the next step without further purification. Under an argon atmosphere, to a solution of 1-(but-1-yn-1-yl)-4-methoxybenzene (240 mg, 1.5 mmol) in dry toluene (6 mL) at -78 ºC was added TMSBr (2.3 mL, 1 M CH$_2$Cl$_2$ solution) dropwise over 3 min, and the mixture was stirred for 5 min. Then, NIS (517 mg, 2.3 mmol) in 4.6 mL of CH$_3$CN (0.5 M solution) was slowly added over 5 min, and the cooling-bath was removed to warm to room temperature. After additional stirring for 1 h, the reaction was quenched at 0 ºC with saturated aqueous sodium thiosulfate (Na$_2$S$_2$O$_3$), and stirred for 10 min, and warmed to ambient temperature. The aqueous phase was extracted with toluene (10 mL x 3), and the combined organic phases were washed with brine (15 mL), and then dried over Na$_2$SO$_4$, and concentrated in vacuo to give 528 mg of crude product as a yellow oil. Purification by short-plugged silica-gel column chromatography (eluent, hexane/EtOAc 50/1) afforded 487 mg of 6 in 88% yield as brownish white solid materials. Data of 6: $^1$H NMR (400 MHz, CDCl$_3$) 7.25 (d, $J$ = 8.8 Hz, 2 H), 6.88 (d, $J$ = 8.8 Hz, 2 H), 3.83 (s, 3 H), 2.85 (q, $J$ = 7.4 Hz, 2 H), 1.18 (t, $J$ = 7.4 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$) 159.9, 136.6, 131.0, 117.3, 114.0, 103.8, 55.6, 39.9 ppm. IR (neat): 2968, 2829, 1591, 1496, 1243, 1025, 606 cm$^{-1}$. MS (DART-IT-TOF) m/z: 366 [M(79)]$^+$. HRMS (DART-IT-TOF) calcd for C$_{11}$H$_{12}$Br(79)IO: 365.9116 [M(79)]$^+$, Found 365.9096.
5. Synthesis of (E)-4-(1-bromo-2-phenyloct-1-en-1-yl)phenyl benzoate (8a): (see Table 3).

Under an argon atmosphere, to a solution of (E)-4-(1-bromo-2-iodoct-1-enyl)phenyl benzoate (257 mg, 0.5 mmol) in toluene (5 mL) was added tributyl(phenyl)tin (844 mg, 0.75 mL, 2.25 mmol), and then CuTC (439 mg, 2.25 mmol) was suspended. After stirred at 105 ºC for 2 h, the reaction mixture was allowed to cool to ambient temperature, and followed by filtration through a pad of celite (eluent; 10 mL of toluene). The organic phase was washed with brine (13 mL), and evaporated off. The resultant residue of yellow oil was purified by silica-gel column chromatography (eluent; hexane/CH2Cl2=4/1) to yield 105 mg (45%) of 8a as colorless viscous materials. Data of 8a: ¹H NMR (400 MHz, CDCl₃) 8.14 (d, J = 7.8 Hz, 2H), 7.62 (dd, J = 7.8 Hz, 7.8 Hz, 1H), 7.49 (dd, J = 7.8 Hz, 7.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.12-7.16 (m, 3H), 7.01 (d, J = 8.1 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 1.27-1.46 (m, 8H), 0.87 (t, J = 6.8 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) 165.1, 150.1, 144.2, 140.9, 139.0, 133.9, 131.7, 130.4, 129.8, 129.4, 128.8, 128.4, 127.2, 121.1, 120.3, 40.2, 31.9, 29.4, 27.4, 22.9, 14.4 ppm; MS (DART-IT-TOF) m/z: 480 [M(79)+NH₄]+; IR (neat): 2921, 2849, 1734 (C=O), 1595, 1499, 1447, 1257, 1208, 1061, 703 cm⁻¹; HRMS (DART-IT-TOF) calcd for C₂₇H₃₁Br(79)NO₂: 480.1533 [M+NH₄]+, Found 480.1514; Anal. Calcd for C₂₇H₂₇BrO₂: C, 69.98; H, 5.87. Found: C, 69.98; H, 5.87.

Data of (E)-1-(1-bromo-2-phenyloct-1-en-1-yl)-4-(trifluoromethoxy)benzene (8b): ¹H NMR (400 MHz, CDCl₃) 7.14-7.16 (m, 5H), 6.98 (d, J = 7.2 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 2.79 (t, J = 7.2 Hz, 2H), 1.44 (tt, J = 7.2Hz, 7.2 Hz, 2H), 1.28-1.39 (m, 6H), 0.88 (t, J = 7.2 Hz, 3H) ppm.; ¹³C NMR (100 MHz, CDCl₃) 148.3, 144.8, 140.6, 140.0, 132.0, 129.3, 128.5, 127.3, 120.7 (J_c-f = 256.0 Hz), 120.2, 119.4, 40.2, 31.9, 29.4, 27.4, 22.9, 14.4 ppm; ¹⁹F NMR (376 MHz, CDCl₃) 181.89

(E)-4-(1-bromo-2-phenyloct-1-en-1-yl)phenyl 2,3,4,5,6-pentafluorobenzoate (8c): ¹H NMR (400 MHz, CDCl₃) 7.19 (d, J = 8.6 Hz, 2H), 7.14 (m, 3H), 7.00 (m, 4H), 2.78 (t, J = 6.9 Hz, 2H), 1.28 (m, 8H), 0.96 (t, J = 6.9 Hz, 3H) ppm.; ¹³C NMR (100 MHz, CDCl₃) 149.1, 146.1 (¹J_C-F = 267 Hz, ²J_C-F = 14.3 Hz), 144.7, 144.0 (¹J_C-F = 259.1 Hz), 140.7, 140.0, 138.1 (¹J_C-F = 256.0 Hz, ²J_C-F = 13.1 Hz, ³J_C-F = 5.7 Hz), 131.9, 129.4, 129.0 (J_C-F = 40.0 Hz), 128.5, 127.3, 120.7, 119.7, 108.0 (J_C-F = 15.0 Hz), 40.2, 32.0, 29.4, 27.4, 22.9, 14.4 ppm; MS (DART-IT-TOF) m/z: 552 [M(79)]⁺; IR (neat): 2928, 2853, 1753, 1650 (C=O), 1499, 1326, 1203, 1001 cm⁻¹; HRMS (DART-TOF) calcd for C₂₇H₂₆BrF₅NO₂: 570.1067 [M(79)+NH₄]⁺, Found: 570.1038.

6. Synthesis of 10 and 11 (Table 4):

To a solution of 1-(but-1-yn-1-yl)-4-methoxybenzene (1.14 g, 7.1 mmol) in DMF (35 mL) was suspended NaSEt (5.97 g, 71 mmol). After refluxed (oilbath temp. 175 ºC) for 15 min, the resultant orange solution was allowed to cool to room temperature. The reaction was quenched with 3 M aqueous HCl (75 mL) at 0 ºC. The mixture was transferred into a separatory funnel, and the aqueous phase was extracted with toluene (30 mL x 3). The combined organic layers were washed with 3 M aqueous HCl (30 mL x 3), brine (30 mL x
3), dried over Na$_2$SO$_4$, and concentrated in vacuo to give a crude product of 1.04 g as orange oil. The sample was provided to the next step without further purification.

To the solution of 4-(but-1-yn-1-yl)phenol was dissolved in CH$_3$CN (39 mL) at 0 ºC was added N-methyl imidazole (2.38 g, 29 mmol), and N, N, N, N-tetramethyl ethylenediamine (3.37 g, 29 mmol), and benzoyl chloride (4.08 g, 29 mmol). After stirred at room temperature for 15 h, the mixture was filtered through a pad of celite and silica-gel and followed by quenching with saturated aqueous NaHCO$_3$ (200 mL). The resultant solution was transferred into a separatory funnel, and washed with brine (100 mL x 2), and dried over Na$_2$SO$_4$, and concentrated in vacuo to give a crude product of orange oil in 6.51 g. Purification with silica-gel column chromatography afforded 3.30 g of 4-(but-1-yn-1-yl)phenyl benzoate in 68% yield as white solid materials.

Under an argon atmosphere, to a solution of 4-(but-1-yn-1-yl)phenyl benzoate (1.74 g, 7.0 mmol) in dry toluene (28 mL) at -78 ºC was added TMSBr (10.5 mL, 1 M CH$_2$Cl$_2$ solution) dropwise over 5 min, and the mixture was stirred for 5 min. Then, NIS (2.57 g, 10.5 mmol) in 21 mL of CH$_3$CN (0.5 M solution) was slowly added over 5 min, and the cooling-bath was removed to warm to room temperature. After additional stirring for 1 h, the reaction was quenched at 0 ºC with saturated aqueous sodium thiosulfate (Na$_2$S$_2$O$_3$), and stirred for 10 min, and warmed to ambient temperature. The aqueous phase was extracted with toluene (10 mL x 3), and the combined organic phases were washed with brine (30 mL), and then dried over Na$_2$SO$_4$, and concentrated in vacuo to give 3.12 g of crude product as a yellow solid. Purification by silica-gel column chromatography (eluent, hexane/CH$_2$Cl$_2$ 4/1) afforded 2.45 g of 10 in 77% yield as white solid materials (90% purity owing to inseparable 10% minor isomer). Data of 10: $^1$H NMR (400 MHz, CDCl$_3$) 8.21 (d, $J$ = 8.4 Hz, $J$ = 8.4 Hz, 2H), 7.65 (dd, $J$ = 8.4 Hz, $J$ = 8.4 Hz, 1H), 7.53 (dd, $J$ = 8.4 Hz, $J$ = 8.4 Hz, 2H), 7.38 (d, $J$ = 8.8 Hz, 2H), 7.24 (d, $J$ = 8.8 Hz, 2H), 2.88 (q, $J$ = 7.4 Hz, 2H), 1.20 (t, $J$ = 7.4 Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 161.1, 151.2, 141.7, 134.1,

For synthesis of (E)-4-(1-bromo-2-phenylbut-1-en-1-yl)phenyl benzoate 11: Under an argon atmosphere, to a solution of 10 (7.31 g, 16 mmol) in toluene (160 mL) was added tributyl(phenyl)tin (13.2 g, 11.7 mL, 72 mmol), and then CuTC (13.7 g, 72 mmol) was suspended. After stirred at 105 ºC for 4 h, the reaction mixture was allowed to cool to ambient temperature, and followed by filtration through a pad of celite (eluent; 250 mL of toluene). The organic phase was washed with brine (200 mL), and evaporated off. The resultant residue of yellow oil was purified by silica-gel column chromatography (eluent; hexane/CH₂Cl₂=4/1) to yield 2.95 g (45%) of 11 as white solid materials. Data of 11: ¹H NMR (400 MHz, CDCl₃) 8.14 (d, J = 7.4 Hz, 2H), 7.62 (dd, J = 7.4 Hz, J = 7.4 Hz, 1H), 7.49 (dd, J = 7.4 Hz, J = 7.4 Hz, 2H), 7.20-7.11 (m, 5H), 7.03 (d, J = 7.5 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 2.82 (q, J = 7.4 Hz, 2H), 1.06 (t, J = 7.4 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) 165.1, 150.1, 145.3, 140.6, 138.9, 133.9, 131.7, 130.4, 129.7, 129.4, 128.9, 128.4, 127.2, 121.1, 119.9, 33.6, 11.9 ppm; MS (MALDI-IT-TOF) m/z: 429 [M+Na]+; IR (neat): 1717 (C=O), 1595, 1499, 1444, 1247, 1200, 705 cm⁻¹; HRMS (MALDI-IT-TOF) calcd for C₂₃H₁₉Br(79)O₂: 409.0466 [M+Na]+, Found 429.0454. Anal. Calcd for C₂₃H₁₉Br(79)O₂: C, 67.82 ; H, 4.70. Found: C, 67.76; H, 4.70.

7. Synthesis of (Z)-Tamoxifen from 11 through the intermediate 12 and 13: (Scheme 4).

For synthesis 12, (Z)-(1-(4-methoxyphenyl)but-1-ene-1,2-diyl)dibenzene: Under an argon atmosphere, to a 300 mL flask charged with solution of 11 (4.07 g, 10 mmol) in 1,4-dioxane (80 mL) was added phenylboronic acid (3.66 g, 30 mmol), and Cs₂CO₃ (6.52 g, 20 mmol), and Pd(PPh₃)₄ (924 mg, 0.8
mmol). After stirred at 95 ºC for 4 h, the reaction mixture was allowed to cool to ambient temperature. The mixture was filtered through a pad of celite, and the filtrate was evaporated off. The resultant residue was dissolved into toluene (50 mL), and washed with brine (80 mL), and dried over Na₂SO₄, and concentrated in vacuo to give a crude product as dark brown solid materials. Purification with silica gel column chromatography (hexane/toluene=2/1) afforded 3.74 g of 12 in isomeric pure form as white solid materials in 92% yield. ¹H NMR (400 MHz, CDCl₃) 8.12 (d, J = 7.8 Hz, 2H), 7.60 (dd, J = 7.8 Hz, 7.8 Hz, 1H), 7.47 (dd, J = 7.8 Hz, 7.8 Hz, 2H), 7.37 (dd, J = 7.1 Hz, 7.1 Hz, 2H), 7.28 (dd, J = 7.8 Hz, 7.8 Hz, 3H), 7.20 (dd, J = 7.8 Hz, 7.8 Hz, 2H), 7.14 (dd, J = 7.1 Hz, 7.1 Hz, 3H), 6.93 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 2.49 (q, J = 7.5 Hz, 2H), 0.95 (t, J = 7.5 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) 165.3, 149.1, 143.6, 143.0, 142.3, 140.9, 138.3, 133.8, 132.1, 130.4, 130.0, 129.9, 129.9, 128.8, 128.5, 128.3, 127.1, 126.7, 29.4, 13.9 ppm; MS (MALDI-IT-TOF) m/z: 404 [M]+; IR (neat): 1725, 1499, 1264, 1197, 1061, 699 cm⁻¹; HRMS (MALDI-IT-TOF) calcd for C₂₉H₂₄O₂: 404.1776 [M]+, Found: 404.1798; Anal. Calcd for C₂₉H₂₄O₂: C, 86.11 ; H, 5.98. Found: C, 85.96; H, 5.92.

For synthesis of (Z)-4-(1,2-diphenylbut-1-en-1-yl)phenol 13; Under an argon atmosphere, to a solution of 12 (607 mg, 1.5 mmol) in DMF (7.5 mL) was added NaSCH₂CH₃ (1.26 g, 15 mmol), and the mixture was refluxed for 15 min. The reaction was quenched at 0 ºC with 3 M aqueous HCl (23 mL), and the mixture was stirred at room temperature for 1 h. The whole media diluted with 20 mL of toluene was transferred into a 100 mL separatory funnel, and the aqueous layer was extracted with toluene (15 mL x 3). The combined organic phase were washed with 3 M HCl (15 mL x 3), brine (15 mL x 3), and dried over Na₂SO₄, and concentrated in vacuo to give a crude of 626 mg as pale yellow solid materials. The mixture was filtered through a short-plugged chromatographic column (silica-gel, toluene
eluent). Purification by washing with hexane (2 mL x 3) afforded 397 mg of 13 in pure form as white powders (88%, $E/Z = >1/99$). $^1$H NMR (400 MHz, CDCl$_3$) 7.35 (dd, $J = 7.6$ Hz, 7.6 Hz, 2H), 7.23-7.39 (m, 3H), 7.18 (dd, $J = 6.5$ Hz, 6.5 Hz, 2H), 7.10-7.13 (m, 2H), 6.74 (d, $J = 8.7$ Hz, 2H), 6.48 (d, $J = 8.7$ Hz, 2H), 4.48 (s, 1H), 2.46 (q, $J = 7.4$ Hz, 2H), 0.93 (t, $J = 7.4$ Hz, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 153.6, 144.1, 142.7, 141.8, 138.4, 136.1, 132.4, 130.0, 129.8, 128.4, 126.9, 126.4, 114.6, 29.3, 13.9 ppm; MS (ESI) m/z: 299 [M]+; IR (neat): 3402, 3044, 2965, 2865, 1595, 1503, 1436, 1232, 822, 587 cm$^{-1}$; HRMS (ESI) calcd for C$_{22}$H$_{19}$O: 299.1436 [M-H]$^-$, Found 299.1430.

For synthesis of (Z)-Tamoxifen$^4$: To a solution of 13 (174 mg, 0.58 mmol) in toluene/ethanol (6 mL/6 mL) was added 2-dimethylaminoethyl chloride hydrochloride (173 mg, 1.2 mmol) and K$_2$CO$_3$ (318 mg, 2.3 mmol). After stirred for 4.5 h at 85 ºC the mixture was allowed to cool to ambient temperature. The reaction was quenched with saturated aqueous NH$_4$Cl (15 mL) at 0 ºC, and the resultant mixture was stirred for 40 min at room temperature. To the mixture was added toluene (15 mL), and the aqueous phase was extracted with toluene (10 mL x 3). The combined organic layers were washed with water (15 mL x 2), and brine (15 mL), and dried over Na$_2$SO$_4$, and concentrated in vacuo to give a crude as a pale yellow viscous material. The crude was purified by short-plugged column chromatography (CH$_2$Cl$_2$/MeOH = 9/1) to afford 179 mg of desired (Z)-Tamoxifen in 83% yield with $E/Z = 4/96$ ratio as white solid materials. Further purification by recrystallization from hexane yielded 30% of (Z)-Tamoxifen with $E/Z = 0/100$. $^1$H NMR (400 MHz, CDCl$_3$) 7.34 (dd, $J = 7.4$ Hz, 7.4 Hz, 2H), 7.23-7.28 (m, 3H), 7.17 (dd, $J = 7.5$ Hz, 7.5 Hz, 2H), 7.09-7.12 (m, 3H), 6.76 (d, $J = 8.5$ Hz, 2H), 6.56 (d, $J = 8.5$ Hz, 2H), 3.92 (t, $J = 5.8$ Hz, 2H), 2.64 (t, $J = 5.8$ Hz, 2H), 2.45 (q, $J = 7.4$ Hz, 2H), 2.28 (s, 6H), 0.92 (t, $J = 7.4$ Hz, 3H)

ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 157.1, 144.1, 142.7, 141.6, 138.6, 135.8, 132.1, 130.0, 129.8, 128.4, 128.2, 126.8, 126.3, 113.7, 66.0, 58.6, 46.2, 29.3, 13.9 ppm; MS (ESI) m/z: 372 [M]$^+$; IR (neat): 2933, 2814, 2762, 1606, 1507, 1244, 818, 767, 595 cm$^{-1}$; HRMS (ESI) calcd for C$_{26}$H$_{30}$NO: 372.2327 [M+H]$^+$, Found 372.2319.

8. $^1$H NMR and $^{13}$C NMR spectra for all new compounds of 2, 4, 5, 6, 8a, 8b, 8c, 10, 11, 12, 13 and ($E$)- and ($Z$)-tamoxifen.
Compound 2; $^1$H NMR spectrum in CDCl$_3$
Compound 2; $^{13}$C NMR spectrum in CDCl$_3$
Compound 4; $^1$H NMR spectrum in CDCl$_3$
Compound 4; $^{13}$C NMR spectrum in CDCl$_3$
Compound 5; $^1\text{H}$ NMR spectrum in CDCl$_3$
Compound 5; $^{13}$C NMR spectrum in CDCl$_3$
Compound 6; $^1$H NMR spectrum in CDCl$_3$
Compound 6: $^{13}$C NMR spectrum in CDCl$_3$
Compound 8a; $^1$H NMR spectrum in CDCl$_3$
Compound 8a; $^{13}$C NMR spectrum in CDCl$_3$
Compound 8b; $^1$H NMR spectrum in CDCl$_3$
Compound 8b; $^{13}$C NMR spectrum in CDCl$_3$
Compound 8b; $^{19}$F NMR spectrum in CDCl$_3$ (1,4-difluorobenzene was used as an internal standard at 120.05 ppm).
Compound 8c; $^1$H NMR spectrum in CDCl$_3$
Compound 8c; $^{13}$C NMR spectrum in CDCl$_3$
Compound 8c; $^{19}$F NMR spectrum in CDCl$_3$ (1,4-difluorobenzene was used as an internal standard at 120.05 ppm).
Compound 10; $^1$H NMR spectrum in CDCl$_3$
Compound 10; $^{13}$C NMR spectrum in CDCl$_3$
Compound 11; $^1$H NMR spectrum in CDCl$_3$
Compound 11; $^{13}$C NMR spectrum in CDCl$_3$
Compound 12; $^1$H NMR spectrum in CDCl$_3$
Compound 12; $^{13}$C NMR spectrum in CDCl$_3$
Compound 13; $^1$H NMR spectrum in CDCl$_3$
Compound 13; $^{13}$C NMR spectrum in CDCl$_3$
Compound (E)-Tamoxifen; $^1$H NMR spectrum in CDCl$_3$
Compound (E)-Tamoxifen; $^{13}$C NMR spectrum in CDCl$_3$
Compound (Z)-Tamoxifen; $^1$H NMR spectrum in CDCl$_3$
Compound (Z)-Tamoxifen; $^{13}$C NMR spectrum in CDCl$_3$