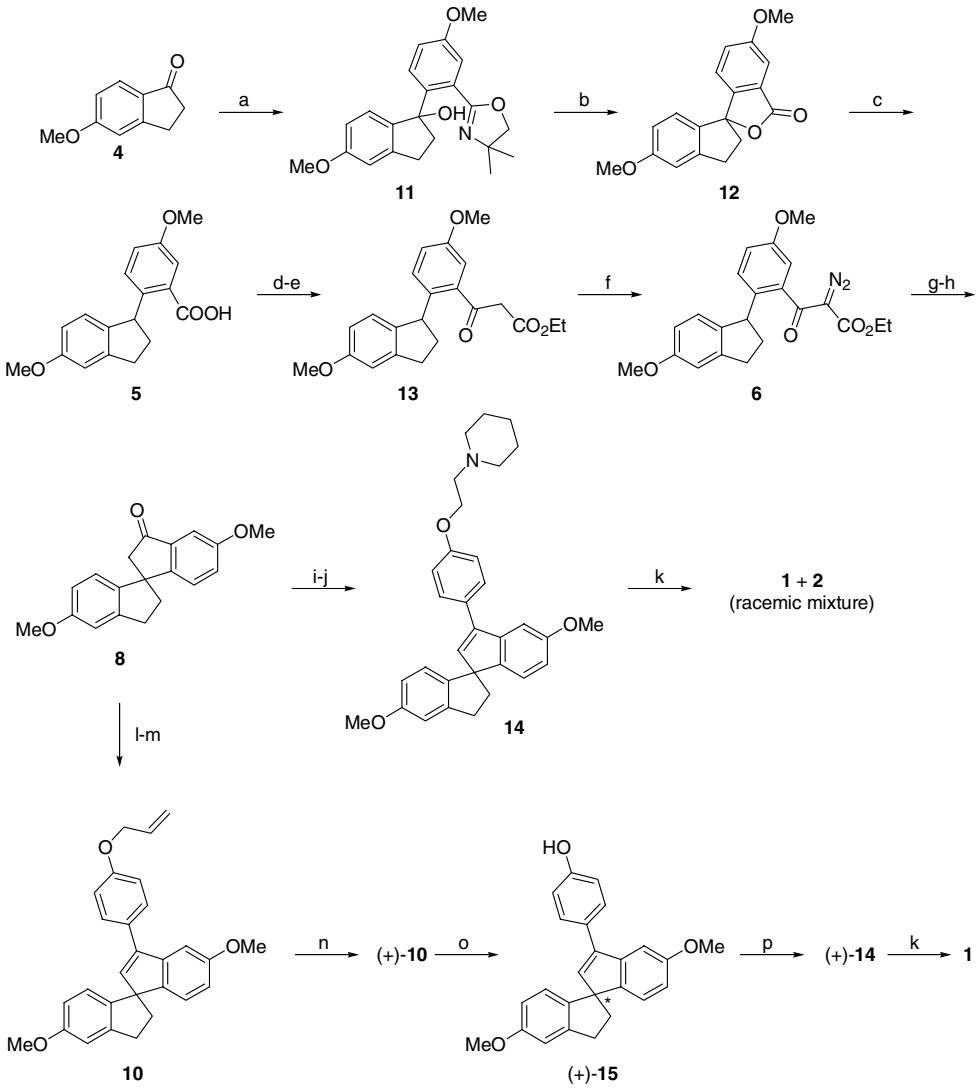
SUPPORTING INFORMATION

Discovery and Preclinical Characterization of (+)-3-[4-(1-piperidinoethoxy)phenyl]-spiro[indene-1,1'-indane]-5,5'-diol Hydrochloride: A Promising Nonsteroidal Estrogen Receptor Agonist for Hot Flush.

Scheme S1[a]



[a]Reagents and conditions: (a) **3**, THF, rt; (b) 6 N H_2SO_4, dioxane, reflux; (c) H_2 (1 atm), 20% $Pd(OH)_2$-C, AcOH; (d) $(COCl)_2$, toluene; (e) AcOEt, KHMDS, THF; (f) p-acetoamidobenzenesulfonyl azide, Et_3N, MeCN; (g) 0.5 mol% $Rh_2(OAc)_4$, $PhCF_3$, 60 ºC; (h) 90% aq. DMSO, 150 ºC; (i) **9**, THF, -78 ºC; (j) TsOH, toluene, reflux; (k) Ph_2PH, n-BuLi, THF, reflux; (l) 4-allyloxybromobenzene, Mg, THF, reflux; (m) TsOH, toluene, reflux; (n) HPLC chiral separation with CHIRALPAK OJ column; (o) HCO_2H, $Pd(OAc)_2$, Ph_3P, benzene, reflux; (p) piperidineethanol, DIAZO, PPh_3, THF

Experimental section

Unless otherwise noted, reagents were obtained from commercial suppliers and used without further purification. Melting points were determined on a cover glass with an electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on JNMLA300 (JEOL, 300 MHz) and chemical shifts are expressed in ppm downfield from internal TMS. Mass spectra were measured with M-1000 (Hitachi). Optical rotation was measured with P-1020 (JASCO). Silica gel column chromatography was performed on Silica gel 60 (70-230 mesh, Merck). Basic silica gel column chromatography was performed on Chromatorex NH (100-200 mesh, Fuji Silysia). Reactions requiring anhydrous conditions were performed under argon atmosphere.

1-[2-(4,4-dimethyl(1,3-oxazolin-2-yl))-4-methoxyphenyl]-5-methoxyindan-1-ol (11)

To a stirred mixture of magnesium turnings (22.3 g, 0.917 gatm) in dry THF (400 mL) were added a small portion of a solution of 2-(2-bromo-5-methoxyphenyl)-4,4-dimethyl-4,5-dihydrooxazole (243 g, 0.855 mol) in dry THF (2L) and a catalytic amount of iodine. The mixture was heated to reflux to initiate the reaction. After the vigorous reaction was subsided, the remaining solution of the aryl bromide was added over a period of 1 h upon heating and then the reflux was continued for 2 h. To this brown solution was added a solution of **4** (118 g, 0.728 mol) in dry THF (1 L) over a period of 30 min at 0 °C. The mixture was stirred overnight at room temperature and the reaction was quenched with saturated aqueous NH_4Cl (400 mL). The layers were separated and the organic layer was washed sequentially with water and brine, dried over Na_2SO_4, and then concentrated to dryness under reduced pressure. The resulting oil was used for the next reaction without further purification. For characterization, a small portion of the oil was subjected to chromatography to give pure **11**; ^{1}H NMR ($CDCl_3$) δ 0.78 (6H, s), 3.25 (2H, s), 3.49 (2H, s), 3.80 (3H, s), 3.88 (3H, s), 6.39 (1H, t, J = 2.0 Hz), 6.80 (1H, dd, J = 8.4, 2.3 Hz), 7.00-7.05 (2H, m), 7.10 (1H, d, J = 2.3 Hz), 7.27 (1H, d, J = 7.9 Hz), 7.40 (1H, d, J = 2.7 Hz).

5,5'-dimethoxy-3-oxospiro[3-hydroisobenzofuran-1,1'-indane] (12)

A suspension of the above **11** in 1,4-dioxane (1 L) and 6 M aqueous sulfuric acid (500 mL) was refluxed for 6 h. The reaction mixture was concentrated under reduced pressure and ethyl acetate (1 L), n-hexane (500 mL) and water (1 L) were added to the residue. The layers were separated, and the organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The resulting oil was used for the next reaction without further purification. For characterization, a small portion of the oil was subjected to chromatography to give pure **12**; ^{1}H NMR ($CDCl_3$) δ 2.61 (2H, m), 3.04 (1H, m), 3.30 (1H, m), 3.79 (3H, s), 3.88 (3H, s), 6.67 (2H, m), 6.85 (1H, m), 7.15 (1H,

d, *J* = 8.3 Hz), 7.21 (1H, dd, *J* = 8.3, 2.3 Hz), 7.34 (1H, d, *J* = 2.3 Hz).

5-methoxy-2-(5-methoxy-1-indanyl)benzoic acid (5)

To a solution of crude **12** obtained above in acetic acid (2 L) was added 20% $Pd(OH)_2$ on carbon (50 g) and the mixture was stirred under H_2 atmosphere at room temperature. After a 12 h of stirring, the resulting precipitate was dissolved by addition of chloroform (600 mL) and the reaction mixture was filtrated. The filtrate was concentrated under reduced pressure and the residue was triturated with ethanol (300 mL). Filtration followed by washing with ethanol gave **5** (135 g, 0.452 mol) as a white solid; mp 180-181°C; ^{1}H NMR ($CDCl_3$) δ 1.93 (1H, m), 2.70 (1H, m), 2.8-3.0 (2H, m), 3.78 (3H, s), 3.81 (3H, s), 5.20 (1H, t, *J* = 7.7 Hz), 6.68 (1H, dd, *J* = 8.3, 2.2 Hz), 6.81-6.85 (2H, m), 6.92-7.00 (2H, m), 7.49 (1H, d, *J* = 2.4 Hz).

3-[5-methoxy-2-(5-methoxy-1-indanyl)phenyl]-3-oxopropionic acid ethyl ester (13)

To a suspension of **5** (83 g, 0.278 mol) in toluene (300 mL) were added oxalyl chloride (33.2 mL, 0.381 mol) and *N*,*N*-dimethylformamide (0.1 mL). The reaction mixture was stirred for 4 h at room temperature. The mixture was concentrated under reduced pressure to afford the crude corresponding acid chloride, which was used for the subsequent reaction. Ethyl acetate (68 mL) was added dropwise to 20% toluene solution of potassium bis(trimethylsilyl)amide (789 mL) diluted with dry THF (700 mL) over a period of 1 h at –78 °C and the mixture was stirred for an additional 1 h at the same temperature. To this solution the acid chloride in THF (300 mL) was added over a period of 1 h and the resulting mixture was stirred at –78 °C for an additional 1 h. Then saturated aqueous NH_4Cl (600 mL) was added to the solution and the layers were separated. The organic layer was washed sequentially with water and brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The resulting oil **13** was used for the next reaction without further purification; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, m), 1.92 (1H, m), 2.63 (1H, m), 2.8-3.0 (2H, m), 3.78 (3H, s), 3.79 (3H, s), 4.0-4.3 (2H, m), 4.68 (1H, m), 6.66 (1H, m), 6.7-7.0 (4H, m), 7.06 (1H, m). The NMR spectrum was complicated because of keto-enol tautomerism of **13**.

2-diazo-3-[5-methoxy-2-(5-methoxy-1-indanyl)phenyl]-3-oxopropionic acid ethyl ester (6)

To a solution of the above **13** in acetonitrile (600 mL) were added 4-acetoamidobenzenesulfonyl azide (80 g, 0.333 mol) and triethylamine (92 mL). This reaction mixture was stirred for 2 h at room temperature. After filtration of the reaction mixture, the filtrate was concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (ethyl acetate/n-hexane) afforded **6** (106 g, 0.279 mol) as pale yellow plates; mp 97-99°C; ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, t, *J* = 7.1 Hz), 1.95 (1H, m), 2.50 (1H, m), 2.7-3.0 (2H, m), 3.76 (3H, s), 3.77 (3H, s), 4.17 (2H, q, *J* = 7.1 Hz), 4.31 (1H, m), 6.65 (1H, dd, *J* = 8.4, 2.4 Hz), 6.72 (1H, d, *J* = 2.6

Hz), 6.78-6.90 (3H, m), 6.98 (1H, d, *J* = 8.6 Hz).

5,5'-dimethoxy-3-oxospirobi-1,1'-indane (8)

To a vigorously stirring suspension of rhodium(II) acetate monohydrate (1.0 g, 2.09 mmol) in α,α,α-trifluorotoluene (100 mL) was added a solution of **6** (106 g, 0.279 mol) in α,α,α-trifluorotoluene (700 mL) over a period of 2 h at room temperature and stirring was continued for further 0.5 h at 60 °C. Then the solvent was concentrated by reduced pressure and the residue was passed through a short column of silica gel (ethyl acetate/n-hexane). The resulting oil **7** was dissolved in 90% aqueous dimethylsulfoxide (750 mL) and stirred at 150 °C for 1 h. After being cooled to room temperature, the reaction mixture was taken up in water (1.5 L) and the resulting precipitate was collected by suction filtration, washed sequentially with water and n-hexane and dried to afford **8** as an off-white solid (65 g, 0.221 mol); mp 94-96°C; ^{1}H NMR ($CDCl_3$) δ 2.31 (1H, m), 2.46 (1H, m), 2.79 (1H, d, *J* = 18.8 Hz), 2.96 (1H, d, *J* = 18.8 Hz), 3.03-3.09 (2H, m), 3.77 (3H, s), 3.83 (3H, s), 6.66 (2H, m), 6.82 (1H, s), 7.10-7.17 (3H, m).

5,5'-dimethoxy-3-[4-(2-piperidinoethoxy)phenyl]spiro[indene-1,1'-indane] (14)

To a solution of 1-bromo-4-(2-piperidinoethoxy)benzene (4.23 g, 14.9 mmol) in dry THF (20 mL) was added n-butyllithium (1.6 M solution in hexane, 9.3 mL, 14.9 mmol) at -78 °C and the stirring was continued at the same temperature for 0.5 h. Then, a solution of **8** (2.00 g, 6.79 mmol) in dry THF (10 ml) was added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and stirring was continued for 1 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was dissolved in toluene (50 mL) and was azeotropically refluxed for 0.5 h in the presence of *p*-toluenesulfonic acid monohydrate (3.90 g, 20.5 mmol). After being cooled to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH) to afford **14** as a colorless oil (2.00 g, 4.15 mmol); ^{1}H NMR ($CDCl_3$) δ 1.4-1.7 (6H, m), 2.49 (2H, t, *J* = 6.6 Hz), 2.9-3.1 (4H, m), 2.81 (2H, t, *J* = 6.0 Hz), 3.1-3.4 (2H, m), 3.79 (3H, s), 3.82 (3H, s), 4.16 (2H, t, *J* = 6.6 Hz), 6.48 (1H, s), 6.5-6.6 (2H, m), 6.71 (1H, dd, *J* = 8.1, 2.1 Hz), 6.89 (1H, brs), 6.97 (2H, m), 7.05-7.10 (2H, m), 7.54 (2H, m).

3-(4-allyloxyphenyl)-5-5'-dimethoxyspiro[indene-1-1'-indane] (10)

To a stirred mixture of magnesium turnings (2.91 g, 0.120 gatm) and a catalytic amount of iodine in dry THF (100 mL) was added a small portion of a solution of 4-allyloxybromobenzene (22.1 g,

0.104 mol) in dry THF (100 mL). After the vigorous reaction was subsided, the remaining solution of 4-allyloxybromobenzene was added over a period of 0.5 h upon heating and then the reflux was continued for further 0.5 h. The reaction mixture was cooled to room temperature and a solution of **8** (15 g, 50.0 mmol) in THF (50 mL) was added to this mixture. The stirring was continued overnight at room temperature, and then the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The reaction mixture was concentrated and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dissolved in toluene (150 mL) and was azeotropically refluxed for 2 h in the presence of *p*-toluenesulfonic acid monohydrate (300 mg, 1.58 mmol). After being cooled to room temperature, the reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/n-hexane) to afford **10** as a colorless oil (16.2 g); ^{1}H NMR ($CDCl_3$) δ 2.50 (2H, t, *J* = 7.1 Hz), 3.1-3.3 (2H, m), 3.79 (3H, s), 3.82 (3H, s), 4.59 (2H, d, *J* = 5.3 Hz), 5.31 (1H, dd, *J* = 10.5, 1.3 Hz), 5.44 (1H, dd, *J* = 17.2, 1.3 Hz), 6.10 (1H, m), 6.49 (1H, s), 6.55-6.63 (2H, m), 6.71 (1H, dd, *J* = 8.3, 2.2 Hz), 6.89 (1H, brs), 6.99 (2H, d, *J* = 8.6 Hz), 7.06-7.10 (2H, m), 7.54 (2H, d, *J* = 8.6 Hz).

Chiral separation of 3-(4-allyloxyphenyl)-5-5'-dimethoxyspiro[indene-1-1'-indane] (10)

Chiral separation of **10** (11 g) was conducted by HPLC on a preparative CHIRALCEL OJ column and 4.9 g of each enantiomer was obtained with up to 99% ee. Retention time: (+)-**10** 17.27 min; (-)-**10** 32.39 min.

(+)-3-(4-hydroxyphenyl)-5,5'-dimethoxyspiro[indene-1,1'-indane] ((+)-15)

A mixture of (+)-**10** (0.5 g, 1.22 mmol), palladium(II) acetate (27 mg, 0.120 mmol), triphenylphosphine (0.12 g, 0.458 mmol) and formic acid (1 mL) in benzene (10 mL) was refluxed for 1 h. Then, saturated aqueous $NaHCO_3$ was added to the reaction mixture and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (ethyl acetate/n-hexane) afforded **(+)-15** as a colorless oil (0.43 g, 1.16 mmol); ^{1}H NMR ($CDCl_3$) δ 2.50 (2H, t, *J* = 7.1 Hz), 3.21 (2H, m), 3.79 (3H, s), 3.82 (3H, s), 4.90 (1H, brs), 6.49 (1H, s), 6.55-6.63 (2H, m), 6.71 (1H, dd, *J* = 8.1, 2.5 Hz), 6.89-6.93 (3H, m), 7.06-7.10 (2H, m), 7.51 (2H, d, *J* = 8.6 Hz); (+)-**15** $[\alpha]_D^{24}$ +82.6° (*c* 1.34, $CHCl_3$).

(-)-**15** was obtained from (-)-**10** by the same method; (-)-**15** $[\alpha]_D^{24}$ -82.4° (*c* 1.42, $CHCl_3$).

(+)-5,5'-dimethoxy-3-[4-(2-piperidinoethoxy)phenyl]spiro[indene-1,1'-indane] ((+)-14)

To a solution of (+)-**15** (0.41 g, 1.11 mmol), 1-piperidineethanol (0.3 g, 2.32 mmol) and

triphenylphosphine (0.61 g, 2.33 mmol) in dry THF (5 mL) was added dropwise diisopropyl azodicarboxylate (0.46 mL, 2.34 mmol) at 0 °C. The reaction mixture was stirred overnight at room temperature, and then concentrated under reduced pressure. Purification of the residue by basic silica gel column chromatography (ethyl acetate/n-hexane) afforded (+)-**14** as a colorless oil (0.41 g, 0.851 mmol); (+)-**14** $[\alpha]_D^{24}$ +58.6° (*c* 0.56, $CHCl_3$).

(-)-**14** was obtained from (-)-**15** by the same method; (-)-**14** $[\alpha]_D^{24}$ -58.8° (*c* 0.72, $CHCl_3$).

3-[4-(2-piperidinoethoxy)phenyl]spiro[indene-1,1'-indane]-5,5'-diol hydrochloride

To a solution of diphenylphosphine (1.68 mL, 9.65 mmol) in dry THF (20 mL) was added n-butyllithium (1.6 M solution in hexane, 6.0 mL, 9.60 mmol) at 0 °C and the resulting red solution was stirred at the same temperature for 0.5 h. Then, a solution of **14** (0.58 g, 1.20 mmol) in dry THF (10 mL) was added to the reaction mixture. After a 20 h of reflux, the reaction was quenched with saturated aqueous NH_4Cl (20 mL), and the layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by basic silica gel column chromatography ($CHCl_3$/MeOH) to afford the title compound as a colorless oil (0.37 g, 0.816 mmol), which was freeze-dried from aqueous methanol/10% aqueous HCl to afford its hydrochloride salt (0.75 hydrate) as a slightly red solid; ^{1}H NMR (DMSO-d_6) δ 1.03-1.6 (6H, m), 2.49 (2H, t, *J* = 6.6 Hz), 2.2-2.5 (6H, m), 2.6-2.7 (2H, m), 2.9-3.3 (2H, m), 4.11 (2H, brt, *J* = 6.0 Hz), 6.29 (1H, d, *J* = 8.1 Hz), 6.40 (1H, brd, *J* = 8.1 Hz), 6.49 (1H, s), 6.53 (1H, dd, *J* = 8.1, 2.1 Hz), 6.71 (1H, brs), 6.85-6.90 (2H, m), 7.03 (2H, d, *J* = 8.7 Hz), 7.50 (2H, d, *J* = 8.7 Hz), 8.30 (1H, s), 9.15 (1H, s), 9.21 (1H, s); MS (APCI) *m/z* 453 $(M+H)^+$; Anal. Calcd for $C_{14}H_{18}O_4$ C 71.56%, H 6.71%, N 2.78%, Cl 7.04%, Found C 71.64%, H 6.65%, N 2.83%, Cl 7.05%.

1 and **2** were obtained from (+)-**14** and (-)-**14** respectively by the same method; **1** $[\alpha]_D^{24}$ +51.2° (*c* 0.41, MeOH); **2** $[\alpha]_D^{24}$ –51.4° (*c* 0.52, MeOH).