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New Highly Stereoselective Synthesis of (*E*)-Droloxifene via Selective Protection of 3,4′-Dihydroxybenzophenone and McMurry Reaction

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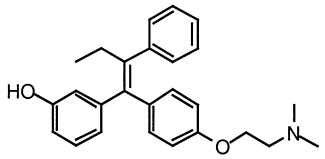
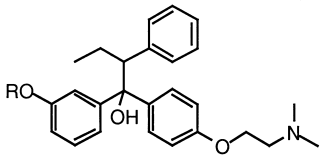
Abstract—A new, highly stereoselective synthesis of (*E*)-droloxifene is reported. Deprotection of 3,4′-dimethoxybenzophenone and selective pivaloylation of the 3′-phenolic position gave 4-hydroxy-3′-(trimethylacetoxy)benzophenone. A McMurry reaction between the preceding benzophenone and propiophenone gave the (*E*)-olefin as a major product (14:1 *E*/*Z* ratio in crude reaction), which was then alkylated with 2-dimethylaminoethyl chloride and deprotected to yield (*E*)-droloxifene with a >100:1 *E*/*Z* ratio (5 steps, 13%). Attempts to use this strategy as a suitable stereoselective method to obtain (*Z*)-droloxifene were not successful.

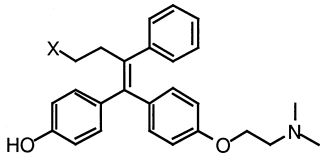
(*E*)-Droloxifene (**1**) is a new antiestrogen currently undergoing clinical trials as an advanced breast cancer treatment in postmenopausal women.[1] Moreover, the possible use of (*E*)-droloxifene (**1**) to help to reverse the effects of osteoporosis[2] was suggested when its estrogenic activity was discovered in the bone tissue of rats.[3] More examples of the potential use of (*E*)-droloxifene (**1**) in such cases as endometriosis and uterine fibroid disease,[4] cardiovascular pathologies,[5] Alzheimer's disease,[6] and others,[7] can be found in patent literature. All of the known approaches used to synthesize (*E*)-droloxifene (**1**) employ dehydration of alcohols **2**.[8] However, this procedure is not used frequently as the resulting products are not of pharmaceutical grade.[9] Thus, for all these reasons better means of synthesizing (*E*)-droloxifene (**1**) should be explored. Recently, we reported a highly stereoselective synthesis of (*Z*)-4-hydroxytamoxifen (**3**) and (*Z*)-4-hydroxytoremifene (**4**) via the McMurry reaction.[10] We obtained an excellent >100:1 *Z*/*E* ratio after purification of compounds **3** and **4**. In the present work, we describe a novel stereoselective synthesis of (*E*)-droloxifene (**1**) through the McMurry reaction.



(*E*)-1



2 R=H,THP



3 X=H
4 X=Cl

The synthesis of (*E*)-droloxifene (**1**) is outlined in Scheme 1. This strategy proceeds by the McMurry reaction between 4′-hydroxy-3-(trimethylacetoxy)benzophenone (**10**) and propiophenone. We predicted a reasonably high coupling stereoselectivity based on the success of the reaction between 4-hydroxy-4′-(trimethylacetoxy)benzophenone and propiophenone in the synthesis of (*Z*)-4-hydroxytamoxifen (**3**).[10] The synthesis of the pivotal 4′-hydroxy-3-(trimethylacetoxy)benzophenone (**10**) was investigated first. Deprotection of 3,4′-dimethoxybenzophenone (**5**)[11] was accomplished with pyridine hydrochloride to afford 3,4′-dihydroxybenzophenone (**6**) in 95% yield. Direct pivaloylation of benzophenone **6** under standard conditions (PvCl, NaH, DMF, 0°C; PvCl, pyr, 0°C) gave a product with

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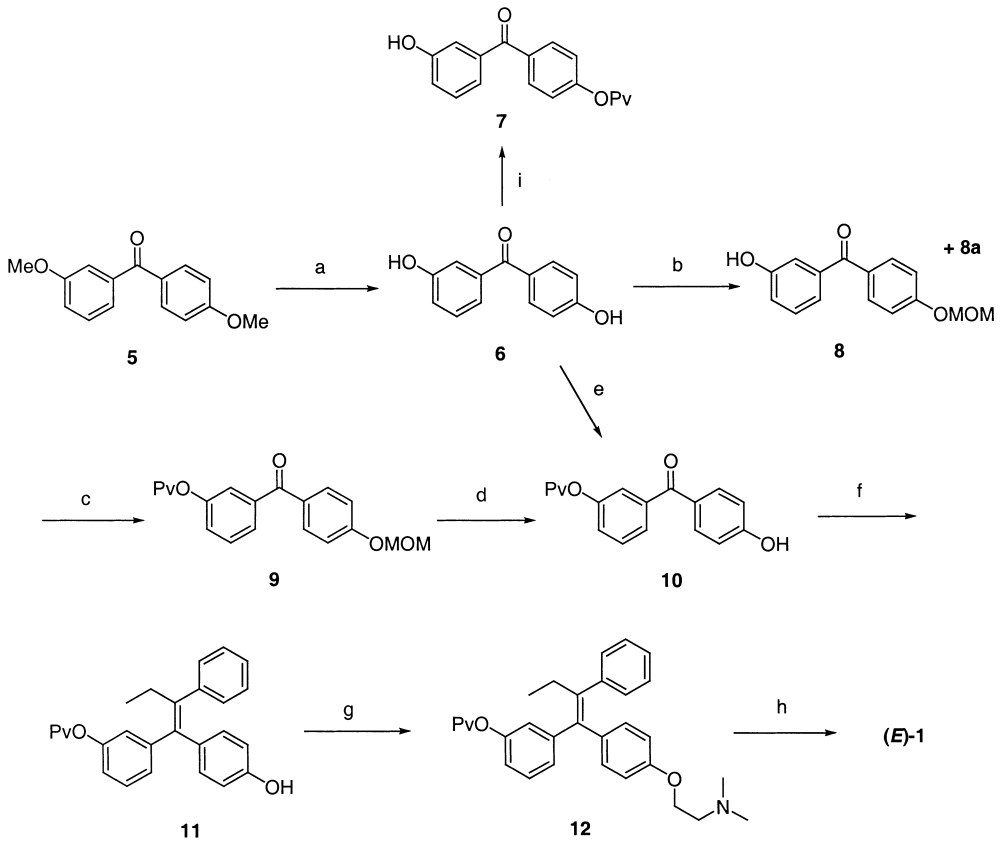
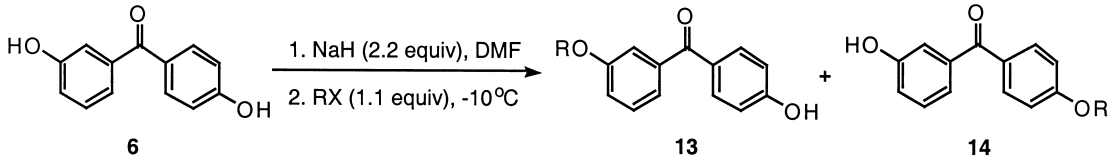


Scheme 1. Reagents and conditions: (a) Pyr·HCl, 220°C, 95%; (b) MOMCl, DIPEA, THF, 0°C to rt, 51%; (c) PvCl, Et_3N, THF, 0°C to rt, 100%; (d) 15% AcOH, 80°C, 76%; (e) NaH (2.2 equiv.), PvCl, DMF, −10°C, 85%; (f) propiophenone, $TiCl_4$, Zn, THF, reflux, 65%; (g) $Cl(CH_2)_2N(CH_3)_2$, K_2CO_3, acetone, H_2O, reflux, 42%; (h) MeLi, THF, −78°C, 61%; (i) PvCl, NaH, DMF, 0°C to rt, 47%.

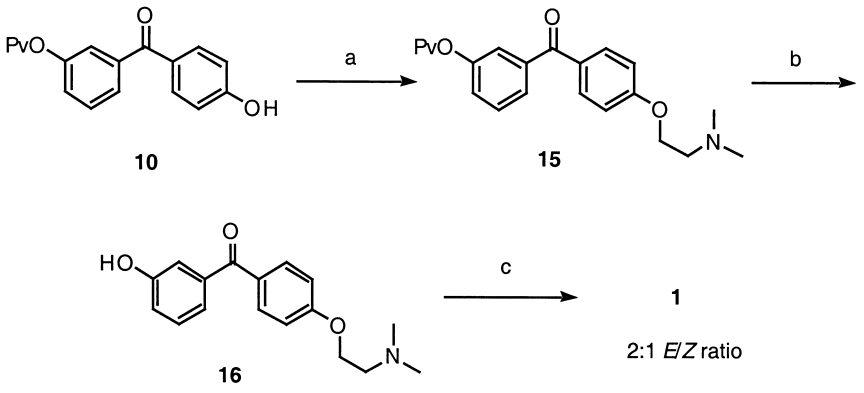
an unwanted exclusive *para*-phenolic substitution (benzophenone **7**, 47% yield). In view of this *para*-phenolic reactivity, 3,4′-dihydroxybenzophenone (**6**) was selectively protected at the 4′-position by a MOM ether group with a 15:1 4′-/3-substitution ratio. Chloromethyl methyl ether (3 equiv.), *N*,*N*-diisopropylethylamine (2 equiv.) in THF then afforded 3-hydroxy-4′-(methoxymethoxy)benzophenone (**8**) in 51% yield after flash chromatography. Varying certain conditions (MOMCl, Na_2CO_3, DMF–CH_3CN; MOMCl, NaH, THF, −10°C; addition rate of MOMCl) did not improve the regioselectivity or the yield of compound **8**, this was due mainly to the formation of the diprotected product **8a**. Pivaloylation of benzophenone **8** and subsequent cleavage of the MOM ether group under acidic conditions afforded the desired 4′-hydroxy-3-(trimethylacetoxy)benzophenone (**10**) in a 76% yield after recrystallization from CH_2Cl_2–hexanes. The conditions were varied to improve the efficiency of the preparation of pivalate **10**. For example, in a one-pot procedure, the silylation (TMSCl), pivaloylation, and desilylation of diphenol **6** gave the undesired *para*-phenolic pivalate **7**. Alternatively, treatment of sodium diphenolate of compound **6** with

Table 1. Selective *meta*-phenolic protection of 3,4′-dihydroxybenzophenone (**6**)



Entry	RX[a]	**13**/**14** ratio	yield
1	*t*-BuCOCl	>100:1	85
2	Ac_2O	>100:1	59
3	$(BOC)_2O$	>100:1	62
4	Allyl bromide	>100:1	52[b]
5	Ethyl iodide	19:1	50[b]

[a] Disubstitution was the only observed reaction with chloromethyl methyl ether.
[b] Presence of 25–30% of disubstitution.



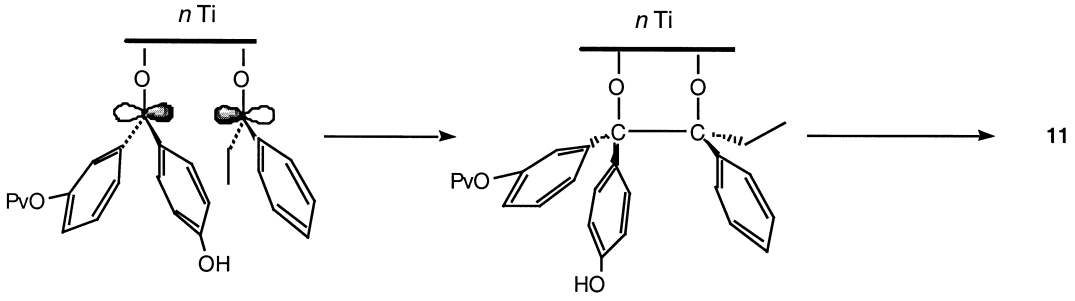
Scheme 2. Reagents and conditions: (a) $Cl(CH_2)_2N(CH_3)_2$, K_2CO_3, acetone, H_2O, reflux, 61%; (b) 2 N KOH, EtOH, 86%; (c) propiophenone, $TiCl_4$, Zn, THF, reflux, 60%.

trimethylacetyl chloride (1.1 equiv.) at −10°C directly afforded an 85% yield of the very highly regioselective *meta*-phenolic pivalate **10**. Incidentally, these conditions[12] were also used to prepare various protected *meta*-phenolic 3,4′-dihydroxybenzophenones **13** (Table 1) as esters, carbonates, and ethers.

The last three steps of our synthesis were performed as we previously reported.[10] A McMurry reaction between benzophenone **10** and propiophenone afforded crude olefin **11** with an excellent 14:1 *E*/*Z* ratio. This ratio was nearly identical to the one that we reported using 4-hydroxy-4′-(trimethylacetoxy)benzophenone,[10] thereby indicating that *para*- and *meta*-substitutions exert similar stereoselectivity in McMurry reactions. Recrystallization of olefin **11** from 4:1 methanol–water resulted in a 100:1 *E*/*Z* ratio in a 65% yield. Phenol derivative **11** was next alkylated with 2-(dimethylamino)ethyl chloride to give amine **12** (crude 14:1 *E*/*Z* ratio) in a 42% yield with a 100:1 *E*/*Z* ratio after recrystallization. Finally, **12** was deprotected with methyllithium at −78°C to yield the desired (*E*)-droloxifene (**1**)[13] with a crude 33:1 *E*/*Z* ratio. Recrystallization of this material from ethanol furnished **1** (>100:1 *E*/*Z*) in 61% yield.

The synthesis of the (*Z*)-isomer of droloxifene (**1**) via the McMurry reaction between benzophenone **16** and propiophenone was also attempted (Scheme 2). (*Z*)-Droloxifene was synthesized,[8b,c] and certain of its pharmacological properties were evaluated.[14] We anticipated a reasonably high coupling stereoselectivity based on the success of the reaction between 4-[2-(*N*,*N*-dimethylamino)ethoxy]-4′-hydroxybenzophenone and propiophenone in the synthesis of (*E*)-4-hydroxytamoxifen.[10] Direct alkylation of 3,4′-dihydroxybenzophenone (**6**) with 2-(dimethylamino)ethyl chloride was not sufficiently regioselective (4:1 *para*-substitution/*meta*-substitution ratio). Alternatively, a preparation of amine **16** (52% yield) was realized by treating the protected benzophenone **10** with 2-(dimethylamino)ethyl chloride followed by deprotecting under basic conditions. Unfortunately, the McMurry reaction between benzophenone **16** and propiophenone gave the anticipated (*Z*)-droloxifene only as a minor product (2:1 *E*/*Z* ratio). Adjusting the McMurry conditions ($TiCl_3$, Zn, DME[15]; Ti, TMSCl, DME[16]) did not improve this ratio.

In all of our results, the stereoselectivity of the McMurry reaction[10] (benzophenone and propiophenone derivatives) can be explained by steric hindrance (Scheme 3). According to the proposed mechanism of the McMurry reaction,[17] the carbonyl compounds are reduced by metallic titanium to give a radical anion species. Homolytic coupling of mixed carbonyl compounds occurs, then deoxygenation of pinacolic intermediate gives the desired olefin. We presume that 3-substituents are more encumbered than 4′-substituents. Consequently, the ethyl chain is found on the same side as the bulkier aromatic moiety of the benzophenone derivatives in the final product, hence the stereoselectivity. But this does not explain the formation of (*Z*)-tamoxifen via the McMurry reaction.[18] McMurry[17] himself proposed that a diaryl ketone could accept two electrons to yield a dianion and then undergo nucleophilic addition to propiophenone. Dihydroxybenzophenones are less likely than monohydroxybenzophenones to enter into dianion formation. This would explain the stereoselectivity of McMurry-based formation of the two



Scheme 3.

resulting stereoisomers of droloxifene, 4-hydroxytamoxifen,[10] and tamoxifen.[18] A detailed study would have to be done to verify this hypothesis.

This study reports the successful selective protection of 3,4′-dihydroxybenzophenone (**6**) and a highly efficient McMurry strategy for the synthesis of the (*E*)-droloxifene (**1**). Steric hindrance seems to be an important factor affecting the stereoselectivity of the McMurry reaction. A clearer understanding of this observed stereoselectivity could lead to an expansion of this class of compounds.

Experimental

General procedures

All reagents were purchased from Aldrich Chemical Co. All reactions were carried out in flame-dried glassware under positive atmosphere of dry Ar. THF was freshly distilled from sodium/benzophenone. Column chromatography was carried out using a silica gel (230–400 mesh) (EM Science). Melting points were uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600. Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker WH 300 at 300 MHz for ^{1}H and at 75 MHz for ^{13}C. High-resolution (IE, 70 eV) mass spectra were provided by Le Laboratoire de Spectrométrie de Masse, Université de Sherbrooke, Sherbrooke, Canada. Elemental analyses and Karl Fisher (KF) were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

3,4′-Dihydroxybenzophenone (6). A mixture of 3,4′-dimethoxybenzophenone (**5**)[11] (15.5 g, 6.35 mmol) and pyridine hydrochloride (56.6 g, 49.1 mmol) was heated at reflux for 0.5 h. After cooling at rt, the reaction mixture was poured into iced 1 N HCl (150 mL). The solid was collected, washed with water, and recrystallized from 1:4 ethanol–water (150 mL) to give after drying (with P_2O_5, under high vacuum), the dihydroxybenzophenone **6** (13.4 g, 95%) as a white solid: mp 188–189°C; IR (KBr) 3200–2250, 1650 cm^{-1}; ^{1}H NMR (CD_3OD) δ 6.87 (d, J=8.7 Hz, 2H), 7.01 (d, J=7.8 Hz, 1H), 7.10 (s, 1H), 7.12 (m, 1H), 7.30 (t, J=7.9 Hz, 1H), 7.71 (d, J=8.5 Hz, 2H); ^{13}C NMR (CD_3OD) δ 116.1, 117.0, 120.1, 121.9, 130.4, 133.6, 134.0, 141.0, 158.6, 163.7, 197.8. HRMS calcd for $C_{13}H_{10}O_3$: 214.0630. Found: 214.0635.

3-Hydroxy-4′-(trimethylacetoxy)benzophenone (7). To a solution of diphenol **6** (108 mg, 0.500 mmol) in dry DMF (5 mL), was added sodium hydride (60% oil dispersion, 24 mg, 0.55 mmol). The solution was stirred at rt for 0.5 h, cooled to 0°C, treated with trimethylacetyl chloride (0.074 mL, 0.60 mmol), and stirred for 2 h after removing the ice-water bath. The reaction mixture was quenched with water (100 mL) and extracted with ethyl acetate (3×20 mL). The combined organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography (CH_2Cl_2–EtOAc 19:1) and recrystallization (CH_2Cl_2–hexanes 1:9) afforded monopivalate **7** (70 mg, 47%) as a white solid: mp 104–105°C; IR($CHCl_3$) 3585, 1749, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 5.36 (br s, 1H), 7.07 (dd, J=7.3 and 2.0 Hz, 1H), 7.17 (d, J=8.3 Hz, 2H), 7.33 (s, 1H), 7.35 (m, 2H), 7.85 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.0, 39.2, 116.4, 120.0, 121.5, 122.4, 129.5, 131.8, 134.7, 138.6, 154.5, 156.2, 177.1, 196.0. HRMS calcd for $C_{18}H_{18}O_4$: 298.1205. Found: 298.1210.

3-Hydroxy-4′-(methoxymethoxy)benzophenone (8). MOMCl (5.7 mL, 75 mmol) was added dropwise, to a chilled solution of 3,4′-dihydroxybenzophenone (**6**) (5.40 g, 252 mmol) and DIPEA (8.7 mL, 50 mmol) in dry THF (50 mL). After removing the cooling bath, the solution was stirred for 4 h. The reaction mixture was quenched with water (100 mL) and extracted with EtOAc (3×100 mL). The combined organic phase was dried ($MgSO_4$) and concentrated. Flash chromatography of the residue (CH_2Cl_2–EtOAc 19:1) followed by trituration (CH_2Cl_2–hexanes 9:1), gave the compound **8** (3.31 g, 51%) as a white solid: mp 94–95°C; IR ($CHCl_3$) 3596, 3369, 1646, 1597, 1574 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 3H), 5.24 (s, 2H), 6.80 (br s, 1H), 7.07 (d, J=7.8 Hz, 2H), 7.23–7.34 (m, 3H), 7.34 (s, 1H), 7.81 (d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 56.3, 94.0, 115.6, 116.5, 119.7, 122.2, 129.4, 130.7, 132.6, 139.1, 156.2, 161.0, 196.4. HRMS calcd for $C_{15}H_{14}O_4$: 258.0892. Found: 258.0898. Anal. calcd for $C_{15}H_{14}O_4 \cdot 0.035H_2O$: C, 69.57; H, 5.43. Found: C, 69.76; H, 5.46. During the flash chromatography, the diprotected compound **8a** was isolated as a yellow oil (2.36 g, 31%): IR (neat) 1648, 1599, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 3H), 3.50 (s, 3H), 5.22 (s, 2H), 5.25 (s, 2H), 7.10 (d, J=8.8 Hz, 2H), 7.22–7.25 (m, 1H), 7.36 (s, 1H), 7.38 (m, 2H), 7.81 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 56.1, 56.2, 94.1, 94.4, 115.5, 117.3, 119.9, 123.4, 129.2, 131.0, 132.4, 139.5, 157.0, 160.8, 195.0. HRMS calcd for $C_{17}H_{18}O_5$: 302.1154. Found: 302.1161.

4′-Methoxymethoxy-3-(trimethylacetoxy)benzophenone (9). A solution of diphenol **6** (3.29 g, 12.6 mmol) in dry THF (40 mL) at 0°C was treated with triethylamine (2.63 mL, 18.9 mmol) and trimethylacetyl chloride (1.71 mL, 13.9 mmol) and stirred at rt for 3 h. The reaction mixture was poured in water (50 mL), then extracted with EtOAc (3×50 mL). The combined organic phase was washed once with 1 N HCl (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Compound **9** was obtained quantitatively as a yellow oil (4.2 g) which was used without purification in the next step: IR (neat) 1743, 1652, 1600, 1584 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9H), 3.51 (s, 3H), 5.26 (s, 2H), 7.11 (d, J=8.8 Hz, 2H), 7.28 (d, J=8.8 Hz, 1H), 7.47 (m, 2H), 7.60 (d, J=7.6 Hz, 1H), 7.82 (d, J=8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.0, 39.0, 56.2, 94.0, 115.6, 122.7, 125.2, 126.9, 129.1, 130.7, 132.3, 139.4, 150.9, 160.9, 176.8, 194.3. HRMS calcd for $C_{20}H_{22}O_5$: 342.1467. Found: 342.1475.

4′-Hydroxy-3-(trimethylacetoxy)benzophenone (10). Crude compound **9** (4.2 g) was dissolved in 15% acetic acid (12 mL) and heated at 80°C for 20 h. After cooling at rt, the reaction mixture was concentrated under high vacuum. Flash chromatography (CH_2Cl_2–EtOAc 19:1) and recrystallization (CH_2Cl_2–hexanes 1:3) afforded compound **10** (2.84 g, 76%) as a white solid: mp 117–119°C; IR ($CHCl_3$) 3585, 1747, 1652, 1604, 1584 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9H), 5.77 (br s, 1H), 6.86 (d, J=8.7 Hz, 2H), 7.27 (d, J=7.3 Hz, 1H), 7.46 (m, 2H), 7.58

(d, J=7.9 Hz, 1H), 7.73 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.0, 39.2, 115.4, 122.8, 125.2, 127.2, 128.1, 129.3, 133.0, 139.5, 150.8, 161.1, 177.6, 195.4. HRMS calcd for $C_{18}H_{18}O_4$: 298.1205. Found: 298.1199. Anal. calcd for $C_{18}H_{18}O_4 \cdot 0.037H_2O$: C, 72.29; H, 6.05. Found: C, 72.17; H, 6.18.

General procedure for selective *meta*-phenolic protection of 3,4′-dihydroxybenzophenone (6). A solution of benzophenone **6** (214 mg, 0.990 mmol) in DMF (5 mL) was added via a cannula to a cold suspension (0°C) of NaH (60% oil dispersion, 88 mg, 2.2 mmol) in DMF (5 mL). The resulting yellow solution was stirred for 1 h, cooled to −10°C over iced acetone, treated dropwise with the electrophile (1.1 mmol), and stirred for an additional hour. The reaction mixture was quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine (2×20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the crude residue (CH_2Cl_2–EtOAc 19:1) gave the protected *meta*-phenolic benzophenone **13**.

4′-Hydroxy-3-(trimethylacetoxy)benzophenone (10) (Table 1, entry 1). 85% yield; white solid identical as described above.

3-Acetoxy-4′-hydroxybenzophenone (Table 1, entry 2). 59% yield; white solid: mp 118–120°C; IR ($CHCl_3$) 3578, 3330, 1760, 1652, 1605, 1582 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H), 6.90 (d, J=8.7 Hz, 2H), 7.28 (dd, J=1.8 and 7.3 Hz, 1H), 7.47 (m, 2H), 7.60 (d, J=7.5 Hz, 1H), 7.73 (d, J=8.6 Hz, 2H), 8.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.1, 115.5, 123.0, 125.3, 127.3, 128.7, 129.4, 133.1, 139.5, 150.3, 161.5, 169.8, 195.4. HRMS calcd for $C_{15}H_{12}O_4$: 256.0736. Found: 256.0734.

3-*tert*-Butoxycarbonyloxy-4′-hydroxybenzophenone (Table 1, entry 3). 62% yield; white solid: mp 142–144°C; IR ($CHCl_3$) 3550, 3346, 1745, 1648, 1615, 1594 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 9H), 6.01 (br s, 1H), 6.88 (d, J=8.7 Hz, 2H), 7.40 (d, J=7.3 Hz, 1H), 7.45 (m, 1H), 7.57 (s, 1H), 7.60 (m, 1H), 7.77 (d, J=8.6 Hz, 2H); ^{13}C NMR (acetone-d_6) δ 27.8, 84.0, 116.1, 123.1, 125.5, 127.5, 129.7, 130.3, 133.5, 140.8, 152.1, 152.4, 162.8, 194.0. HRMS (CI, NH_3) calcd for $C_{18}H_{19}O_5$ (MH^+): 315.1232. Found: 315.1243.

4′-Hydroxy-3-(2-propenoxy)benzophenone (Table 1, entry 4). 52% yield; white solid: mp 63–65°C; IR ($CHCl_3$) 3578, 3323, 1646, 1601, 1579 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.56 (d, J=5.2 Hz, 2H), 5.28 (dd, J=1.1 and 10.9 Hz, 1H), 5.40 (dd, J=10.5 and 17.6 Hz, 1H), 6.02 (m, 1H), 6.94 (d, J=8.7 Hz, 2H), 7.13 (d, J=7.3 Hz, 1H), 7.29–7.30 (m, 3H), 7.77 (d, J=8.6 Hz, 2H), 8.00 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 69.0, 115.4, 115.5, 118.1, 119.3, 122.7, 129.3, 132.8, 133.3, 139.2, 158.4, 161.5, 197.1. HRMS calcd for $C_{16}H_{14}O_3$: 254.0943. Found: 254.0937.

3-Ethoxy-4′-hydroxybenzophenone (Table 1, entry 5). 50% yield; white solid: mp 98–100°C; IR ($CHCl_3$) 3580, 3284, 1636, 1598, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J=7.2 Hz, 3H), 4.06 (q, J=7.2 Hz, 2H), 6.93 (d, J=8.7 Hz, 2H), 7.10 (d, J=7.3 Hz, 1H), 7.27–7.36 (m, 3H), 7.77 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.7, 63.7, 115.0, 115.4, 119.0, 122.4, 129.2, 129.4, 133.1, 139.3, 158.8, 160.9, 196.7. HRMS calcd for $C_{15}H_{14}O_3$: 242.0943. Found: 242.0937.

(*E*)-1-(4′-Hydroxyphenyl)-1-[3-(trimethylacetoxy)phenyl]-2-phenylbut-1-ene (11). To a suspension of zinc (2.6 g, 40 mmol) in dry THF (25 mL) was added dropwise $TiCl_4$ (2.2 mL, 20 mmol). The mixture was refluxed for 2 h. To the resulting black suspension, a solution of benzophenone **10** (1.49 g, 4.99 mmol) and propiophenone (1.99 g, 14.8 mmol) in dry THF (10 mL) was added at once, and reflux was continued for 5 h in the dark. After cooling at rt, the reaction mixture was quenched with 10% K_2CO_3 (50 mL), diluted with EtOAc (50 mL), and filtered through celite. The organic phase was washed with 10% K_2CO_3 (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Trituration of the resulting oil from hexanes and flash chromatography (EtOAc–hexanes 9:1) of the mother liquors yielded 1.59 g of compound **11** as a 14:1 *E*/*Z* isomeric mixture. Recrystallization from 4:1 methanol–water gave compound **11** (1.30 g, 65%) with a 100:1 *E*/*Z* ratio as a white solid: mp 120–122°C; IR (KBr) 3335, 1728, 1609, 1577 cm^{-1}; ^{1}H NMR (CD_3OD) δ 0.89 (t, J=7.5 Hz, 3H), 1.34 (s, 9H), 2.45 (q, J=7.5 Hz, 2H), 6.41 (d, J=6.6 Hz, 2H), 6.67 (d, J=6.7 Hz, 2H), 6.88 (s, 1H), 6.97 (d, J=7.3 Hz, 1H), 7.08–7.19 (m, 6H), 7.37 (t, J=7.9 Hz, 1H); ^{13}C NMR (CD_3OD) δ 13.8, 27.5, 29.8, 115.3, 120.7, 123.5, 127.2, 127.9, 128.9, 130.1, 130.8, 132.8, 133.0, 135.1, 139.1, 142.8, 143.6, 146.7, 152.4, 156.6, 178.7. HRMS calcd for $C_{27}H_{28}O_3$: 400.2038. Found: 400.2033. Anal. calcd for $C_{27}H_{28}O_3 \cdot 0.60H_2O$: C, 78.87; H, 7.10. Found: C, 78.37; H, 7.11.

(*E*)-1-{4′-[2-(*N*,*N*-Dimethylamino)ethoxy]phenyl}-1-[3-(trimethylacetoxy)phenyl]-2-phenylbut-1-ene (12). A solution of phenol **11** (1.30 g, 3.25 mmol) in 19:1 acetone–water (60 mL) was treated with freshly distilled 2-(dimethylamino)ethyl chloride[10] (0.71 g, 6.5 mmol) and K_2CO_3 (0.54 g, 3.9 mmol) and refluxed for 5 h in the dark. The reaction mixture was cooled to rt, dried (Na_2SO_4), and evaporated. The crude product was purified by flash chromatography (CH_2Cl_2–methanol 19:1) then recrystallized from isopropyl alcohol to give amine **12** (0.70 g, 42%) as a white solid: mp 76–78°C; IR($CHCl_3$) 1740, 1610, 1585 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J=7.4 Hz, 3H), 1.35 (s, 9H), 2.29 (s, 6H), 2.45 (q, J=7.4 Hz, 2H), 2.65 (t, J=5.7 Hz, 2H), 3.93 (t, J=5.7 Hz, 2H), 6.57 (d, J=8.7 Hz, 2H), 6.77 (d, J=8.4 Hz, 2H), 6. 99 (s, 1H), 7.09 (s, 1H), 7.11–7.17 (m, 6H), 7.35 (d, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 27.1, 29.0, 39.0, 45.8, 58.2, 65.6, 113.4, 119.6, 122.4, 126.1, 126.7, 127.8, 128.9, 129.6, 131.8, 134.8, 137.3, 141.9, 142.1, 145.1, 150.9, 156.8, 176.9. HRMS calcd for $C_{31}H_{37}NO_3$: 471.2773. Found: 471.2765. Anal. calcd for $C_{31}H_{37}NO_3$: C, 78.93; H, 7.91; N, 2.97. Found: C, 78.62; H, 7.92; N, 2.96.

(*E*)-Droloxifene (1). A solution of amine **12** (430 mg, 0.912 mmol) in dry THF (20 mL) was cooled to −78°C, treated with MeLi (2.0 mL of 1.4 M in ether, 2.8 mmol), and stirred for 2 h. The reaction mixture was quenched with saturated NH_4Cl (5 mL), diluted with water (10 mL), and extracted with EtOAc (3×20 mL). The combined

organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residual solid was recrystallized from ethanol to give (*E*)-droloxifene (**1**) (216 mg, 61%) with a >100:1 *E*/*Z* ratio as a white solid: mp 162–163°C; IR (KBr) 2928, 1582, 1505, 1451, 1288 cm^{-1}; ^1H NMR (CD_3OD) δ 0.89 (t, *J*=7.5 Hz, 3H), 2.28 (s, 6H), 2.46 (q, *J*=7.2 Hz, 2H), 2.48 (t, *J*=5.5 Hz, 2H), 3.95 (t, *J*=5.6 Hz, 2H), 6.57 (d, *J*=8.8 Hz, 2H), 6.67–6.78 (m, 4H), 7.10–7.15 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 13.5, 28.9, 45.4, 58.0, 65.0, 113.2, 113.8, 116.6, 120.8, 125.8, 127.7, 128.9, 129.6, 131.7, 135.4, 138.1, 140.9, 142.4, 145.1, 156.5, 156.6. HRMS calcd for $C_{26}H_{29}NO_2$: 387.2202. Found: 387.2198. Anal. calcd for $C_{26}H_{29}NO_2 \cdot 0.11H_2O$: C, 80.14; H, 7.51; N, 3.59. Found: C, 80.29; H, 7.43, N, 3.42.

4′-[2-(*N*,*N*-Dimethylamino)ethoxy]-3-(trimethylacetoxy)-benzophenone (15). The same procedure for compound **12** was used, starting from benzophenone **10** (2.53 g, 0.848 mmol). Flash chromatography (EtOAc–methanol 19:1) gave amine **15** as a light yellow solid (1.49 g, 61%): mp 60–62°C; IR ($CHCl_3$) 1747, 1652, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (s, 9H), 2.35 (s, 6H); 2.77 (t, *J*=5.6 Hz, 2H), 4.14 (t, *J*=5.6 Hz, 2H), 6.97 (d, *J*=8.5 Hz, 2H), 7.24 (d, *J*=7.3 Hz, 1H), 7.57 (m, 2H), 7.45 (m, 1H), 7.80 (d, *J*=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.1, 39.1, 45.9, 58.0, 66.2, 114.2, 122.7, 125.7, 126.9, 129.1, 129.8, 132.5, 139.5, 150.9, 162.6, 176.8, 194.3. HRMS calcd for $C_{22}H_{27}NO_4$: 369.1940. Found: 369.1934.

4′-[2-(*N*,*N*-Dimethylamino)ethoxy]-3-hydroxybenzophenone (16). A solution of amine **15** (743 mg, 2.01 mmol) in EtOH (5 mL) was treated with 2 N KOH (1.5 mL, 3.0 mmol) and stirred for 5 h. The reaction mixture was brought to pH 8–9 with 10% HCl, concentrated, and extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with saturated $NaHCO_3$ (2×10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated to afford without further purification the amine **16** (494 mg, 86%) as a white solid: mp 96–98°C; IR ($CHCl_3$) 2912, 1650, 1597 cm^{-1}; ^1H NMR (CD_3OD) δ 2.37 (s, 6H), 2.81 (t, *J*=5.7 Hz, 2H), 4.12 (t, *J*=5.7 Hz, 2H), 6.84 (d, *J*=8.7 Hz, 2H), 7.20 (d, *J*=7.5 Hz, 2H), 7.22 (s, 1H), 7.35 (m, 1H), 7.67 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (CD_3OD) δ 45.8, 58.8, 66.9, 115.2, 117.2, 120.4, 121.9, 130.4, 131.3, 133.6, 140.7, 158.7, 164.0, 197.4. HRMS calcd for $C_{17}H_{19}NO_3$: 285.1365. Found: 285.1370. Anal. calcd for $C_{17}H_{19}NO_3 \cdot 0.044H_2O$: C, 71.34; H, 6.67; N, 4.89. Found: C, 71.29; H, 6.79; N, 4.88.

McMurry reaction between amine (16) and propiophenone. The same procedure for compound **11** was used, starting from benzophenone **16** (287 mg, 1.01 mmol) and propiophenone (402 mg, 2.99 mmol). Flash chromatography (CH_2Cl_2–methanol 9:1) afforded compound **1** (230 mg, 60%) as an inseparable 2:1 mixture of *E*/*Z* isomers. (*Z*)-Droloxifene: ^1H NMR (CD_3OD) δ 2.33 (s, 6H), 2.75 (t, *J*=5.5 Hz, 2H), 4.08 (t, *J*=5.5 Hz, 2H), 6.34 (m, 2H), 6.90 (m, 2H).

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