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An expeditious synthesis of tamoxifen, a representative SERM (selective estrogen receptor modulator), via the three-component coupling reaction among aromatic aldehyde, cinnamyltrimethylsilane, and β-chlorophenetole

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Abstract—Two new synthetic pathways to the anti-cancer agent tamoxifen and its derivatives were developed. The first route involved the aldol reaction of benzyl phenyl ketone with acetaldehyde followed by Friedel–Crafts substitution with anisole in the presence of $Cl_2Si(OTf)_2$ to produce 1,1,2-triaryl-3-acetoxybutane, a precursor of the tamoxifen derivatives. The second one utilized the novel three-component coupling reaction among aromatic aldehydes, cinnamyltrimethylsilane, and aromatic nucleophiles using $HfCl_4$ as a Lewis acid catalyst to produce 3,4,4-triarylbutene, that is also a valuable intermediate of the tamoxifen derivatives. The former strategy requires a total of 10 steps from the aldol formation to the final conversion to tamoxifen, whereas the latter needs only three or four steps to produce tamoxifen and droloxifene including the installation of the side-chain moiety and the base-induced double-bond migration to form the tetra-substituted olefin structure. This synthetic strategy seems to serve as a new and practical pathway to prepare not only the tamoxifen derivatives but also the other SERMs (selective estrogen receptor modulators) including estrogen-dependent breast cancer and osteoporosis agents.

1. Introduction

Tamoxifen (**1**) has been therapeutically used for women's breast cancer as an anti-estrogenic agent since the 1970s (Fig. 1). It was found that **1** also functioned as an estrogenic agent against bone and fat metabolism, that meant its effect was variable depending on the tissue or organ. Therefore, **1** is now recognized as one of the selective estrogen receptor modulators (SERMs).[1–5] Based on this investigation, a large number of studies to develop new agents for osteoporosis from the tamoxifen derivatives have been examined. Droloxifene (**2**), one of the hydroxy derivatives of tamoxifen, had first been developed as a breast cancer agent,[6–9] but is also expected to be a therapeutic drug candidate for postmenopausal and senile osteoporosis.[4,10–12]

There are three types of general methods for the construction of the basic skeleton of **1** and its derivatives (Scheme 1). One of them includes the formation of the double-bond functionalities of the olefin **III** by a dehydration reaction of the resulting tertiary alcohols **II** which are generated by the Grignard reaction of benzyl phenyl ketones **I** with aromatic nucleophiles (Eq. 1).[13–17] On the other hand, the desired tetra-substituted olefin **III** could be also synthesized by the reductive cross-coupling reaction of unsymmetrical aromatic carbonyl compounds **IV** and **V** using low-valent titanium species (Eq. 2).[18,19] In the other syntheses, ethylene moieties are constructed during the early synthetic stage and the successive coupling of the olefins with

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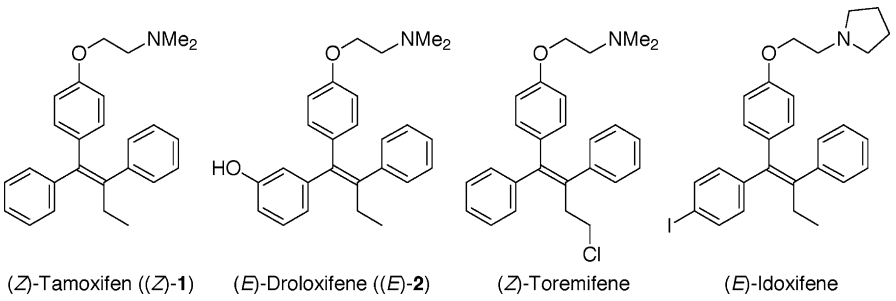
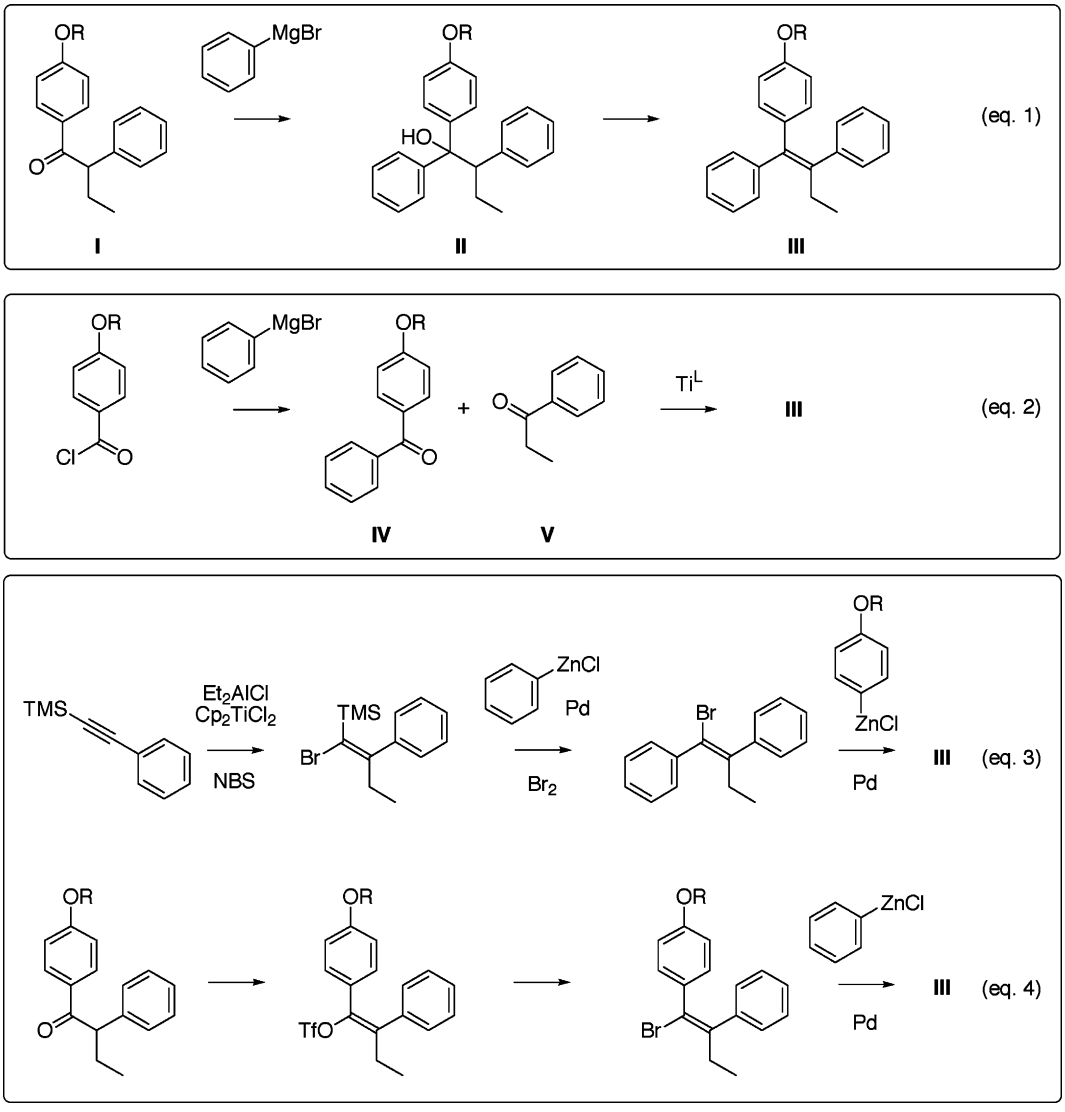


Figure 1. Representative selective estrogen receptor modulators (SERMs).



Scheme 1. General strategies to produce tamoxifen structure (Eqs. 1–4).

metallated aromatics is carried out in the presence of a transition metal catalyst such as palladium, nickel, and platinum species to produce the desired substituted olefins **III** as shown in Eqs. 3 and 4.[20–27]

Although several approaches classified into the above strategies for the synthesis of the tamoxifen derivatives have been developed, multiple synthetic steps are required to produce **1** and its derivatives.

We now report a new synthetic route to SERMs including tamoxifen via the aldol reaction of benzyl phenyl ketone with acetaldehyde or the novel three-component coupling reaction among aromatic aldehydes, cinnamyltrimethylsilane, and aromatic nucleophiles.[28] The latter method was finally optimized for the preparation of **1** and **2**, and it was proved that these compounds were produced in very short steps (three steps for **1**, and four steps for **2**).[29]

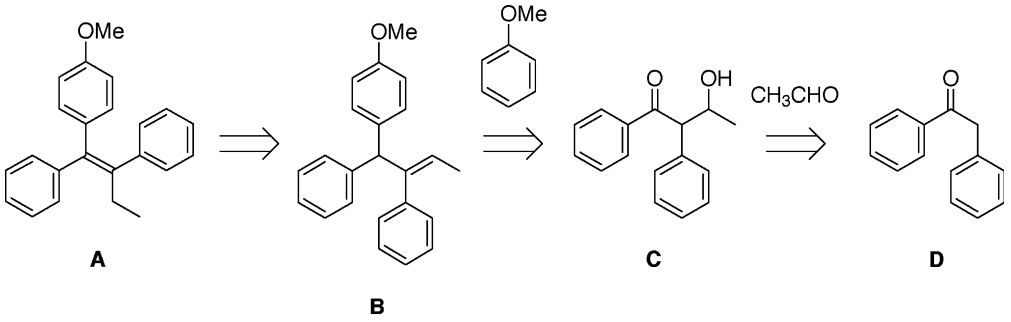
2. Result and discussion

2.1. Chemistry

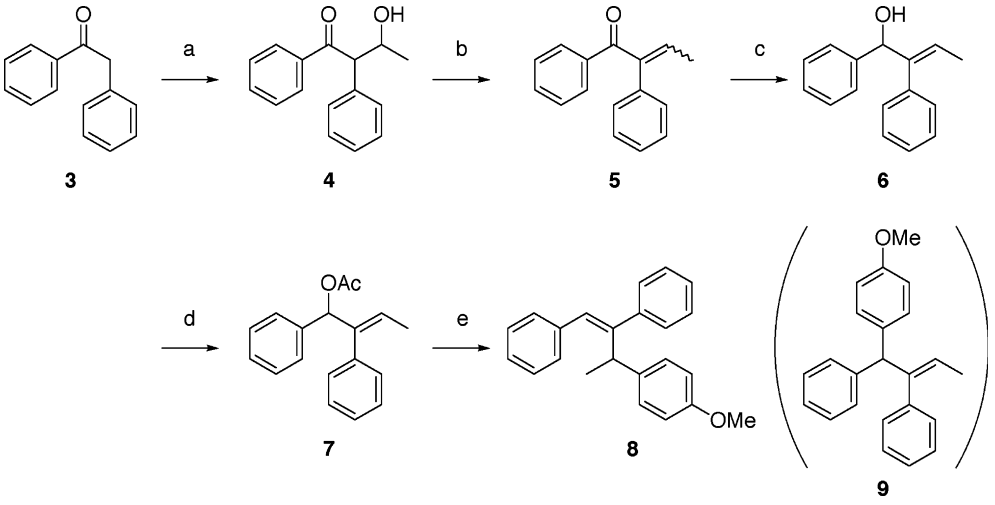
2.1.1. Synthesis of tamoxifen through aldol reaction. We first considered that a novel route to access the basic skeleton **A** could be developed using the intermediate 3,4,4-triaryl-2-butene **B** because the double-bond in **B** should be migrated to the position of that in the stable structure **A** as shown in Scheme 2 The aldol product **C** derived from aromatic ketone **D** could be a suitable compound to be converted into **B** by introducing the anisole fragment at the C-1 position of **C**.

According to this retrosynthetic analysis, the preliminary experiments depicted in Scheme 3 were carried out. Allylic acetate **7** was first obtained via three steps from alcohol **4**, which was prepared by the aldol reaction of benzyl phenyl ketone (**3**) with acetaldehyde. Next, the Friedel–Crafts aromatic substitution of **7** with anisole was examined using the molybdenum carbonyl catalyst developed by Kočovský et al. for the reaction of cinnamyl acetate with anisole;[30] however, the γ-attacked product **8** was predominantly produced without forming the desired 3,4,4-triaryl-2-butene (**9**).

Next, we tried to perform the Friedel–Crafts alkylation of 1,3-diacetoxy compound **11a** and **11b** in Scheme 4 with anisole in the presence of $Cl_2Si(OTf)_2$, which was found in our previous study to be a suitable catalyst for the reaction of benzyl silyl ether with an aromatic compound.[31,32] The mixture of stereoisomers of aldol **4** was first reduced to the corresponding 1,3-diols **10a** and **10b** by $LiBH_4$. Relative stereochemistries of these compounds were determined by the NOE experiment after converting to the acetonide derivatives **12a** and **12b**, as depicted in Scheme 4. Treatment of *syn*,*anti*-diol **10a** and *syn*,*syn*-diol **10b** with acetic anhydride in the presence of DMAP afforded the intermediary diacetates **11a** and **11b**, respectively, in satisfactory yields. Fortunately, the desired electrophilic substitution reaction of **11a** and **11b** smoothly proceeded and the targeted 1,1,2-triaryl-3-acetoxybutanes **13a** and **13b** were obtained in good yields. The successive transformations of **13a** and **13b** were carried out to produce the desired identical *syn*-3,4,4-triarylbutene **15** via three steps.



Scheme 2. Retrosynthetic route to the basic skeleton of tamoxifen via the aldol reaction.

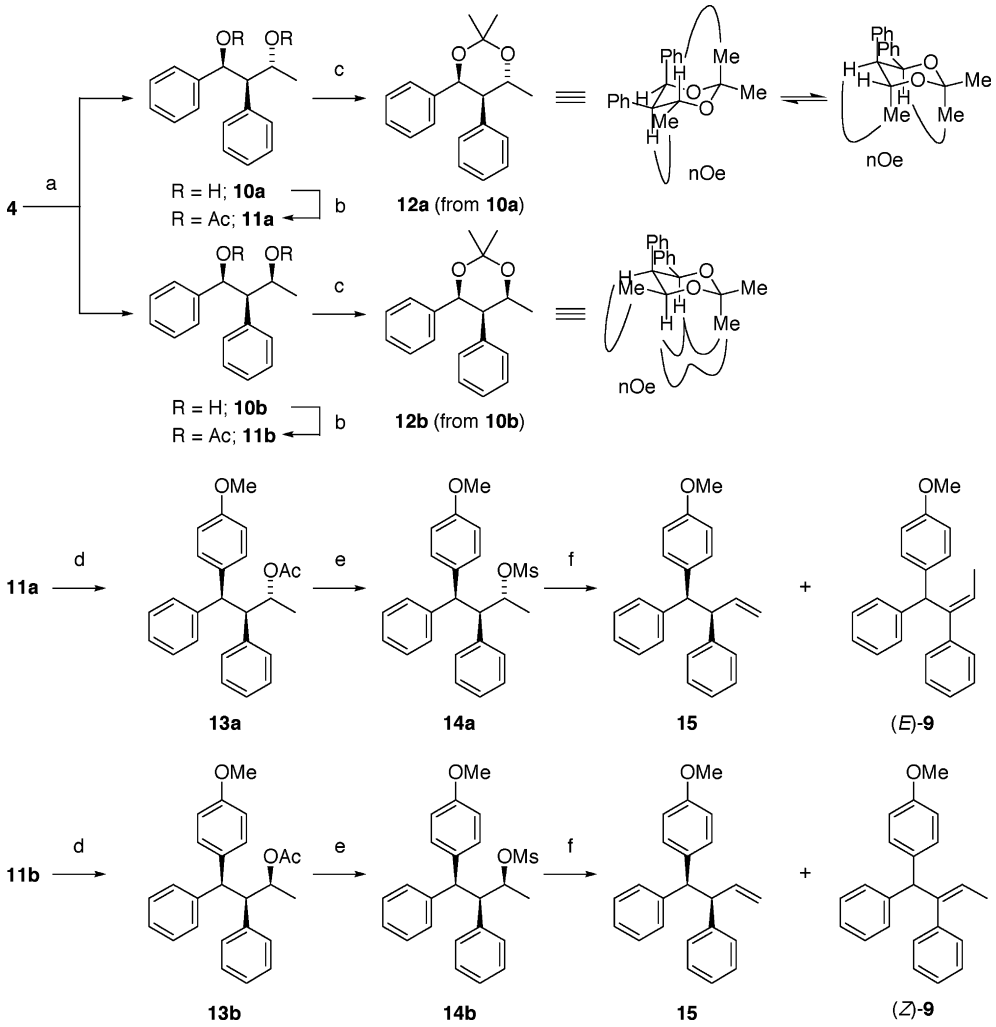


Scheme 3. Preliminary synthetic approach to triarylbutene structure via aldol condensation and Friedel–Crafts alkylation of allylic benzylic alcohol and anisole. Reagents and conditions: (a) LDA, CH_3CHO, THF, −78 °C, 1 h (94%); (b) *p*-TsOH·H_2O, Na_2SO_4, benzene, reflux, 1 h (86%, *E*/*Z* = 1:1); (c) i—$NaBH_4$, $CeCl_3$, MeOH, 0 °C, 15 min; ii—$NaBH_4$, $CeCl_3$, MeOH, rt, 12 h (90% from (*E*)-**5**); (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 15 min (78%); (e) $[Mo(CO)_4Br_2]_2$, anisole, rt, 5 min (97%).

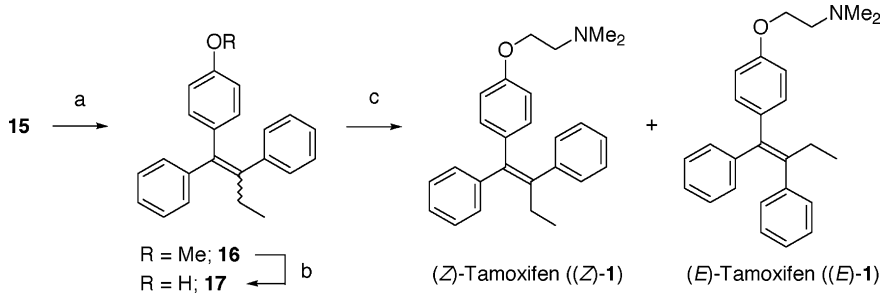
After several trials to migrate the double-bond in **15** under basic or acidic conditions, it was found that ^{t}BuOK in DMSO promoted the desired reaction to form the requisite olefin **16** from **15** in 97% yield (Scheme 5).[33] We finally obtained tamoxifen (**1**) via the successive deprotection of **16** and installation of the dimethylaminoethyl moiety into the hydroxyl group of **17** by a conventional method.

2.1.2. Synthesis of tamoxifen through three-component coupling reaction. As described in the former section, we found a new pathway to tamoxifen (**1**) using the aldol reaction as a key step to prepare the desired backbone via electrophiles **11a** and **11b**; however, this route required more than 10 steps to form the final targeted compound. At this stage, we decided to use the intermediate **B′** (in Scheme 6) identified with **15** (in Scheme 4) for reducing the number of steps to prepare **1**. It was anticipated that the preparation of the key intermediates **B′** could be realized by the acid catalyzed substitution of **C′** with anisole because several substituted diarylmethanes were synthesized by the Friedel–Crafts alkylation reaction of aromatic nucleophiles, such as anisole with benzyl silyl ethers.[31] Furthermore, **C′** might be easily prepared from benzaldehyde by the allylation with cinnamyl-type nucleophile **D′** in the presence of a Lewis acid catalyst. Therefore, it was planned to explore an improved method for the synthesis of **1** through the intermediate **B′** using the coupling reactions among aromatic aldehydes, allylic nucleophile **D′**, and aromatic nucleophiles, followed by the double-bond migration.

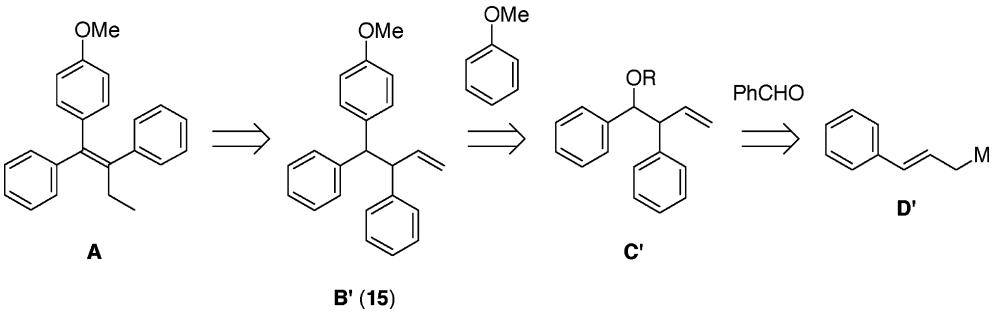
Based on the above hypothesis, we examined to develop a novel three-component coupling reaction to afford 3,4,4-triaryl butenes **VII** through the allylation reaction of aromatic aldehydes and successive Friedel–Crafts type alkylation of the resulting homoallyl silyl ethers **VI** with aromatic nucleophiles (Ar–H) in the presence of a Lewis acid catalyst (Scheme 7).[32] Since this intermediate **VII** could be transformed into the tetra-substituted olefin **VIII** already shown in Scheme 5, we considered that this methodology might be applied to the synthesis



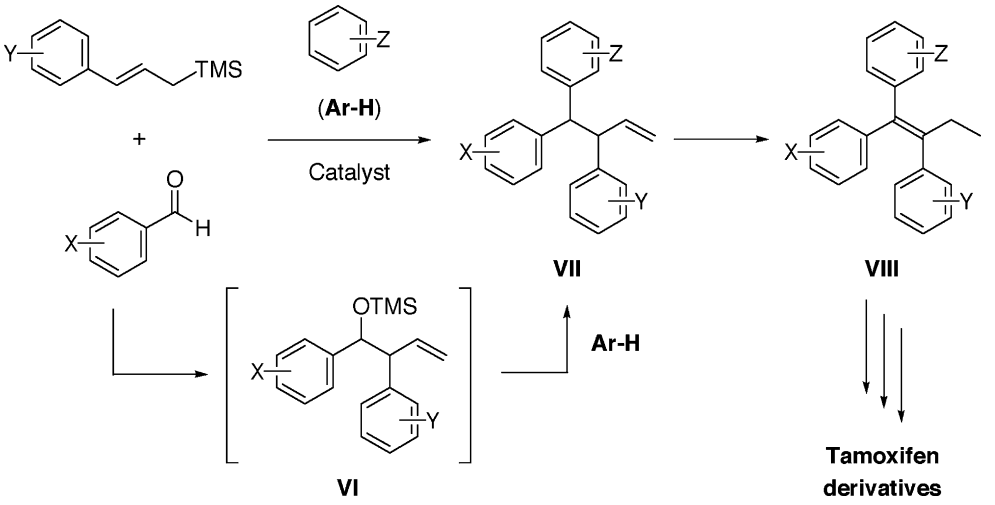
Scheme 4. A preliminary study of tamoxifen synthesis via aldol and Friedel–Crafts type alkylation of benzylic acetate and anisole. Reagents and conditions: (a) $LiBH_4$, THF, −78 °C, 30 min (66% of **10a**, 22% of **10b**); (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h (99% of **11a**, 82% of **11b**); (c) $Me_2C(OMe)_2$, *p*-TsOH·H_2O, CH_2Cl_2, rt, 5 min (91% of **12a**, quant. of **12b**); (d) anisole, $Cl_2Si(OTf)_2$, rt, 4 h (98% of **13a**, 92% of **13b**); (e) i—NaOH, MeOH, 50 °C, 5 h (81% from **13a**, 99% from **13b**); ii—MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 1 h (quant. of **14a**, quant. of **14b**); (f) NaOH, MeOH, 75 °C, 4 h (95% of **15** and 5% of (*E*)-**9** from **14a**, 60% of **15** and 40% of (*Z*)-**9** from **14b**).



Scheme 5. Double-bond migration reaction and installation of the side-chain structure of tamoxifen. Reagents and conditions: (a) ^{t}BuOK, DMSO, rt, 15 min (97%, *E*/*Z* = ca. 1:1); (b) BBr_3, CH_2Cl_2, −78 °C, 2 h (quant.); (c) NaH, $ClCH_2CH_2NMe_2$, DMF, 50 °C, 30 min (95%, *E*/*Z* = 46:54).



Scheme 6. Revised retrosynthetic route to the basic skeleton of tamoxifen via allylation.

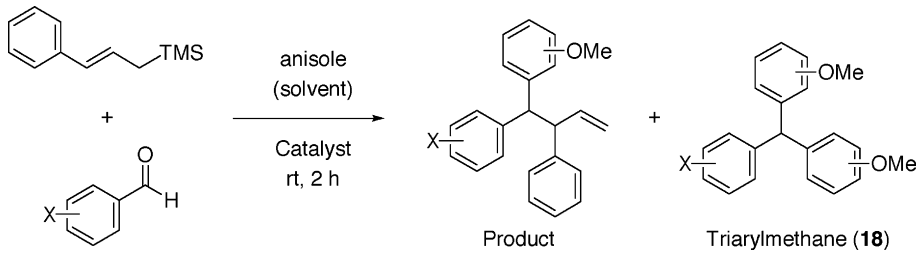


Scheme 7. An improved synthetic pathway to tamoxifen derivatives via the three-component coupling reaction.

of tamoxifen derivatives; that is, the three-component coupling among benzaldehyde, cinnamyltrimethylsilane,[34,35] and anisole to produce intermediate **VII**, followed by the successive double-bond migration and the side-chain installation to form 1,1,2-triaryl butenes **VIII** which correspond to the basic skeleton of **1**.[28,29,36]

First, benzaldehyde and cinnamyltrimethylsilane were chosen as substrates to optimize the reaction conditions for the three-component coupling reaction (Table 1). Unfortunately, $HfCl_4$ is not very effective for the reaction of benzaldehyde with cinnamyltrimethylsilane in the anisole solvent because the reactivity of cinnamyltrimethylsilane is lower compared to that of allyltrimethylsilane (Entry 1). When $Cl_2Hf(OTf)_2$ or $Hf(OTf)_4$ was used for the reaction, a regioisomeric mixture of the corresponding triarylmethanes **18** was only obtained in 51% or 23% yield (Entry 3 or 4). Second, TMSCl or TMSOTf was added to the reaction mixture as a co-catalyst in order to increase the activity of $HfCl_4$ as shown in Entries 5-8.[37] It was then proved that the use of a mixture of a stoichiometric amount of $HfCl_4$ and 50 mol% TMSOTf was the most effective combination for this reaction, and the desired trisubstituted butene **15** was produced in 57% yield via a one-pot operation (Entry 8). As shown in Entries 9–12, the three-component coupling reaction among the halogenated aromatic aldehydes,

Table 1. The three-component coupling reaction among aromatic aldehydes, cinnamyltrimethylsilane, and anisole using Lewis acid catalysts



Entry	X	Catalyst	Product	Yield/%	(*o*-)/(*p*-)	Yield of **18**/%
1	H	$HfCl_4$	**15**	36	30/70	20
2	H	$Cl_3Hf(OTf)$	**15**	49	30/70	15
3	H	$Cl_2Hf(OTf)_2$	**15**	0	—	51
4	H	$Hf(OTf)_4$	**15**	0	—	23
5	H	$HfCl_4$ + TMSCl (0.5)	**15**	39	27/73	14
6	H	$HfCl_4$ + TMSCl (1)	**15**	33	27/73	11
7	H	$HfCl_4$ + TMSOTf (0.2)	**15**	37	31/69	6
8	H	$HfCl_4$ + TMSOTf (0.5)	**15**	57	30/70	4
9	3-Br	$HfCl_4$	**19**	73	19/81	18
10[a]	3-I	$HfCl_4$	**20**	61	35/65	3
11	4-Br	$HfCl_4$	**21**	70	9/91	14
12	4-I	$HfCl_4$	**22**	73	16/84	7
13	3-PivO	$HfCl_4$ + TMSOTf (0.5)	**23**	72	19/81	11
14[a]	4-PivO	$HfCl_4$	**24**	79	2/98	1

[a] The reaction was carried out for 1 h.

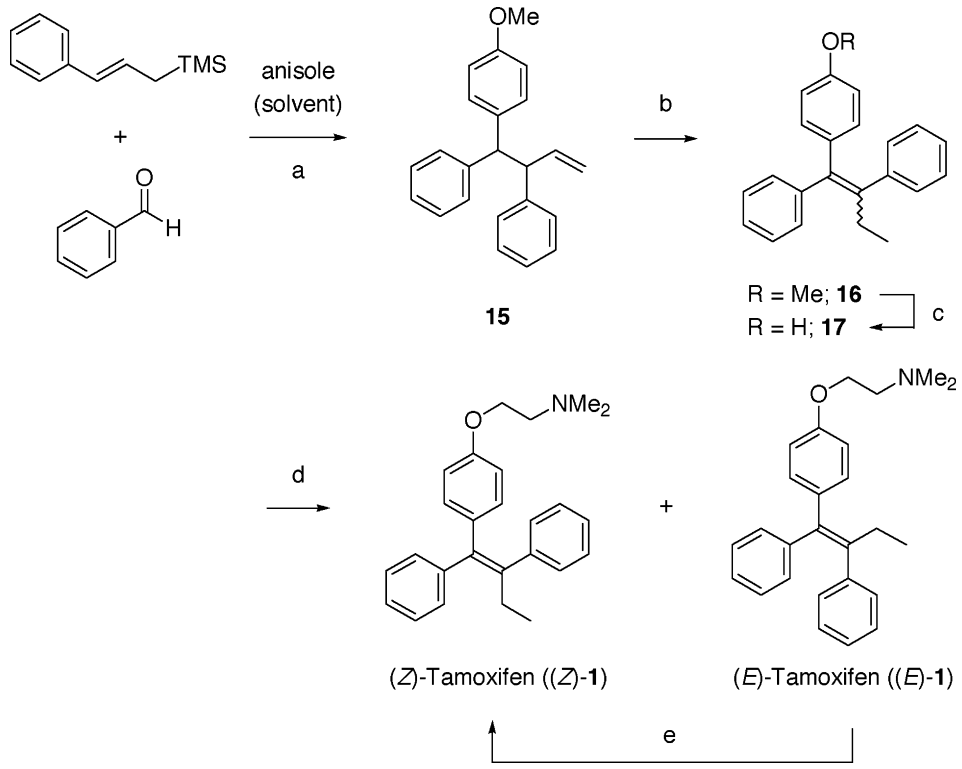
cinnamyltrimethylsilane, and anisole, smoothly proceeded to give the products **19**–**22** in the presence of $HfCl_4$ without a co-catalyst since the reactivity of these substituted aromatic aldehydes is higher than that of benzaldehyde. Furthermore, 3- or 4-pivaloyloxybenzaldehyde was also utilized for this system using the combined catalyst or $HfCl_4$ alone to form the corresponding butene **23** or **24** in good yield (Entries 13 and 14).

The migration of the double-bond in *p*-**15** was then carried out according to the procedure developed in Scheme 5 (vide supra), and a geometric mixture of the tetra-substituted alkenes **16** was produced in nearly quantitative yield (Scheme 8). The deprotection of **16** and alkylation of the phenol moieties afforded an isomeric mixture of the target compounds **1** and then these isomers were separated by preparative TLC.[15,38] According to this improved method, we accomplished the total synthesis of (*Z*)-**1** in only four steps from benzaldehyde. Furthermore, the resulting (*E*)-**1** was isomerized to enrich the desired *Z*-isomer (*Z*/*E* = ca. 1:1) by the reported procedure;[16,39] therefore, (*Z*)-**1** was obtained in a 28% total yield from the starting substrate (benzaldehyde) using this transformation and the second separation of the geometric isomers.

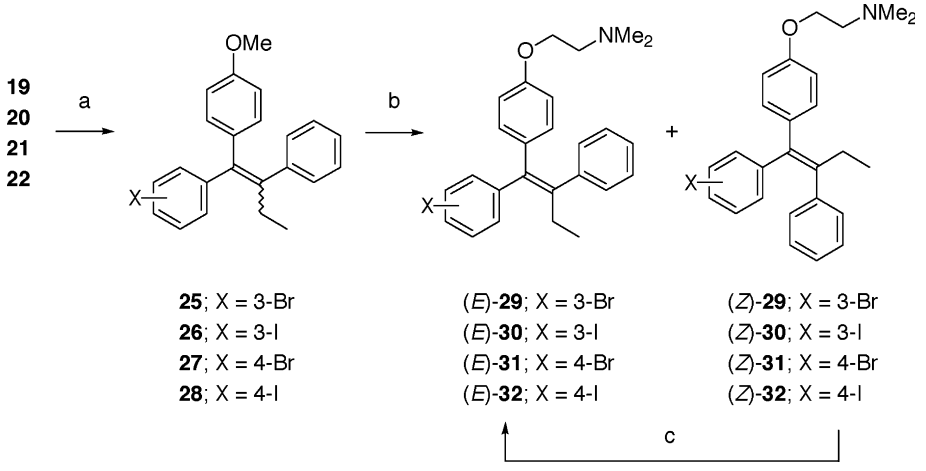
The substituted derivatives of **1** were also prepared in good yields by a similar protocol as shown in Scheme 9. Successive double-bond migrations of **19**–**22** again took place to afford the desired tetra-substituted olefins in good yields. The usual treatments of these isomers with BBr_3 and $NaH/ClCH_2CH_2NMe_2{\cdot}HCl$ produced the 3- or 4-halogenated tamoxifen relatives ((*E*)-**29**–**32**)[40] in good total yields from the corresponding aromatic aldehydes. It is noted that these halogenated derivatives might not be efficiently prepared by the transition metal coupling methodology since the aryl halide parts competitively react to form by-products under the cross-coupling reaction conditions.

2.1.3. Synthesis of droloxifene through improved three-component coupling reaction. Next, we planned to apply this strategy to the synthesis of droloxifene (**2**) as shown in Scheme 10. The three-component coupling reaction among 3-pivaloyloxybenzaldehyde, cinnamyltrimethylsilane, and anisole proceeded to give the corresponding 3,4,4-trisubstituted butene **23** in a satisfactory yield (Table 1, Entry 13) and it was then converted to the desired intermediate **33** as well as the case for the synthesis of **1**. However, the chemoselective installation of the *N*,*N*-dimethylaminoethyl sidechain to the framework of **33** required a complicated roundabout pathway (eight steps) due to the existence of a deprotection step for cleaving the *O*-methyl group of **33** that originated from the anisole moiety of the three-component coupling.[29]

Based on the preliminary study of the synthesis of **2** using anisole in the key coupling, it was again planned to use β-chlorophenetole (2-chloroethyl phenyl ether) as a second nucleophile instead of anisole to the intermediary homoallyl silyl ethers **C**′ in order to decrease the total steps for the synthesis of **2** from the starting materials (Scheme 11). It seems that the chloroethoxy group in the coupling product **B**″ will be easily converted to the corresponding dialkylaminoethoxy group in **A**″ by the treatment with a secondary dialkylamine before carrying out the olefin migration promoted by the basic catalyst. This synthetic approach would be practically applicable



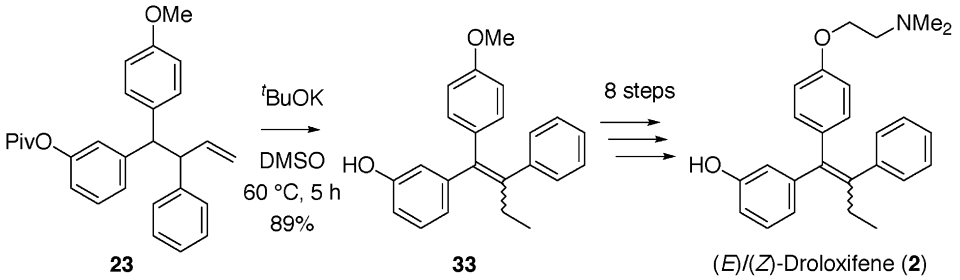
Scheme 8. New synthetic pathway to tamoxifen via three-component coupling reaction. Reagents and conditions: (a) $HfCl_4$, TMSOTf, rt, 2 h, (57%, (*o*-)/(*p*-) = 30:70); (b) ^{t}BuOK, DMSO, rt, 15 min (97% from *p*-**15**, *E*/*Z* = ca. 1:1); (c) BBr_3, CH_2Cl_2, −78 °C, 2 h (quant.); (d) NaH, $ClCH_2CH_2NMe_2$, DMF, 50 °C, 30 min (51% of (*Z*)-**1**, 44% of (*E*)-**1**); (e) TfOH, CH_2Cl_2, 0 °C, 3 h, (97% of **1** [51% of (*Z*)-**1**, 46% of (*E*)-**1**] from (*E*)-**1**).



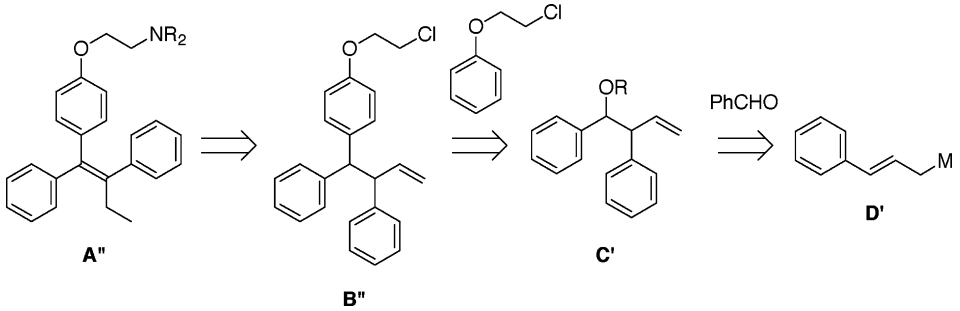
Scheme 9. New synthetic pathway to tamoxifen derivatives via three-component coupling reaction. Reagents and conditions: (a) ^{t}BuOK, DMSO, rt, 15 min (68% of **25**, 26% of **26**, 89% of **27**, 85% of **28**); (b) i—BBr_3, CH_2Cl_2, −78 °C, 2 h (94% from **25**, 89% from **26**, 92% from **27**, 95% from **28**); ii—NaH, $ClCH_2CH_2NMe_2$·HCl, DMF, 50 °C, 8–13 h (82% of **29** [46% of (*E*)-**29**, 36% of (*Z*)-**29**]), (75% of **30** [37% of (*E*)-**30**, 38% of (*Z*)-**30**]), (88% of **31** [45% of (*E*)-**31**, 43% of (*Z*)-**31**]), (95% of **32** [44% of (*E*)-**32**, 51% of (*Z*)-**32**]); (c) TfOH, CH_2Cl_2, 0 °C, 3 h (88% of **29** [44% of (*E*)-**29**, 44% of (*Z*)-**29**] from (*Z*)-**29**), (75% of **30** [38% of (*E*)-**30**, 37% of (*Z*)-**30**] from (*Z*)-**30**), (89% of **31** [46% of (*E*)-**31**, 43% of (*Z*)-**31**] from (*Z*)-**31**), (87% of **32** [42% of (*E*)-**32**, 45% of (*Z*)-**32**] from (*Z*)-**32**).

for the effective production of novel tamoxifen-type SERMs.

The results of the three-component coupling reaction among 3-pivaloyloxybenzaldehyde, cinnamyltrimethylsilane, and β-chlorophenetole are summarized in Table 2. First, amount of the co-catalyst was investigated by the reaction of 3-pivaloyloxybenzaldehyde with cinnamyltrimethylsilane in the β-chlorophenetole solvent to optimize the suitable ratio of TMSOTf to $HfCl_4$. When no co-catalyst was added to the reaction system, a large amount of the starting 3-pivaloyloxybenzaldehyde was recovered and the corresponding homoallyl alcohol derived from the intermediate alkyl silyl ether was

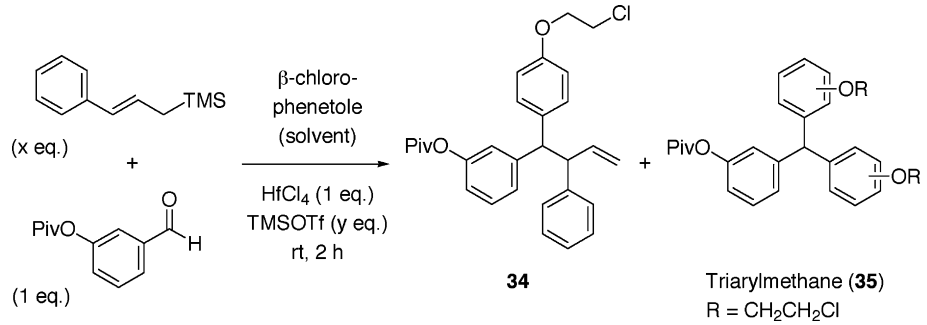


Scheme 10. Preliminary synthetic route for the preparation of droloxifene using the three-component coupling reaction.[29]



Scheme 11. Retrosynthetic route to the basic skeleton of tamoxifen via allylation.

Table 2. The three-component coupling reaction among 3-pivaloyloxybenzaldehyde, cinnamyltrimethylsilane, and β-chlorophenetole using $HfCl_4$ and TMSOTf as the catalysts



Entry	*x*	*y*	Yield of **34**/%	Yield of **35**/%
1	1.0	0	12	Trace
2	1.0	0.05	26	21
3	1.0	0.1	27	15
4	1.0	0.2	21	23
5	1.0	0.3	19	26
6	1.0	0.5	Trace	30
7	1.5	0.1	38	5
8	2.0	0.1	43	18

mainly obtained (Entry 1). In Entries 5 and 6, a large amount of triarylmethanes **35**, which were produced from a 1 M amount of 3-pivaloyloxybenzaldehyde and 2 M amounts of β-chlorophenetole, was preferentially produced by the addition of 30–50 mol% of the co-catalyst to the reaction mixture because the aldehyde was over-activated by TMSOTf. On the other hand, the desired three-component coupling product **34** was obtained in a better yield when 10 mol% of TMSOTf was additionally used with a stoichiometric amount of $HfCl_4$ as shown in Entry 3. The yield of the desired three-component coupling product was finally improved up to 43% using a twofold amount of cinnamyltrimethylsilane to 3-pivaloyloxybenzaldehyde (Entry 8). It was also revealed that all of the reactions afforded nearly equal amounts of the *syn*- and *anti*-diastereomers of the 3,4,4-trisubstituted butenes by the careful analysis using HPLC-MS. Furthermore, the formation of a trace amount of *o*-isomers that originated from the nucleophilic substitution of β-chlorophenetole with intermediary homoallyl silyl ethers was also detected by the HPLC-MS analysis ((*o*-)/(*p*-) = 2:98).

Next, the *N*,*N*-dimethylamination was successfully accomplished by heating the three-component coupling product **34** with 30% dimethylamine in ethanol at 110 °C in a sealed vessel for 8 h to produce a mixture of *syn*- and *anti*-3,4,4-trisubstituted butenes **36** having the side-chain in good yield (Scheme 12). The pivaloyl protective group was simultaneously removed under these reaction conditions. The *syn*- and *anti*-isomers are separable at this stage by silica gel column chromatography, however, no further purification was carried out since it is unnecessary to separate these compounds for preparing the identical 1,1,2-trisubstituted butene **2** by the double-bond migration in the next step.

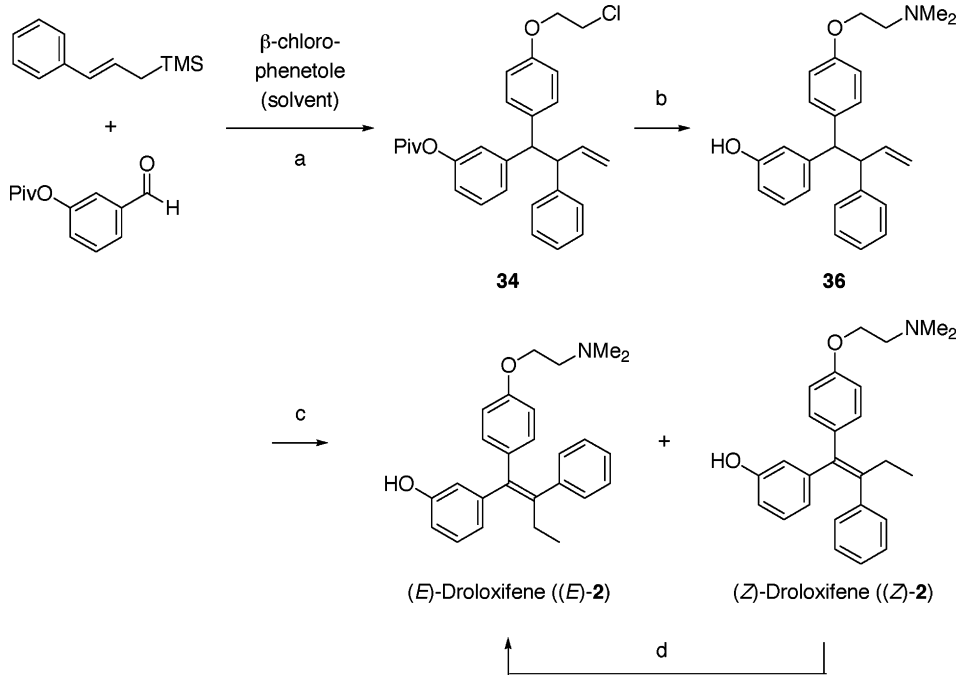
Finally, the desired (*E*)-**2** was prepared in 49% yield from the 3,4,4-trisubstituted butenes **36** by treatment with an excess amount of ^{t}BuOK in DMSO at 50 °C via the base catalyzed double-bond migration reaction established for the synthesis of **1** (Scheme 5). Although this olefin transformation produced the desired compound (*E*)-**2** together with a nearly amount of (*Z*)-**2**, the isomers are easily separable by silica gel chromatography or fractional crystallization of the corresponding acid salts. Furthermore, each isomer could be facilely transformed into a mixture of (*E*)-**2** and (*Z*)-**2** again by the treatment with trifluoromethanesulfonic acid in CH_2Cl_2, therefore, the combined yield of (*E*)-**2** could be increased to nearly 70% by involving this isomerization procedure.

2.1.4. Synthesis of tamoxifen through improved three-component coupling reaction. As a final study, the improved method for the preparation of droloxifene (**2**) was applied to the synthesis of tamoxifen (**1**) as shown in Scheme 13. The three-component coupling reaction among benzaldehyde, cinnamyltrimethylsilane, and β-chlorophenetole successfully proceeded in the presence of $HfCl_4$ without a co-catalyst to afford the key intermediate **37** in 43% yield. Successive transformations similar to the method for the preparation of **2** were successfully carried out by way of two steps via **38**, and the total synthesis of **1** was then accomplished through a very short pathway (three steps).

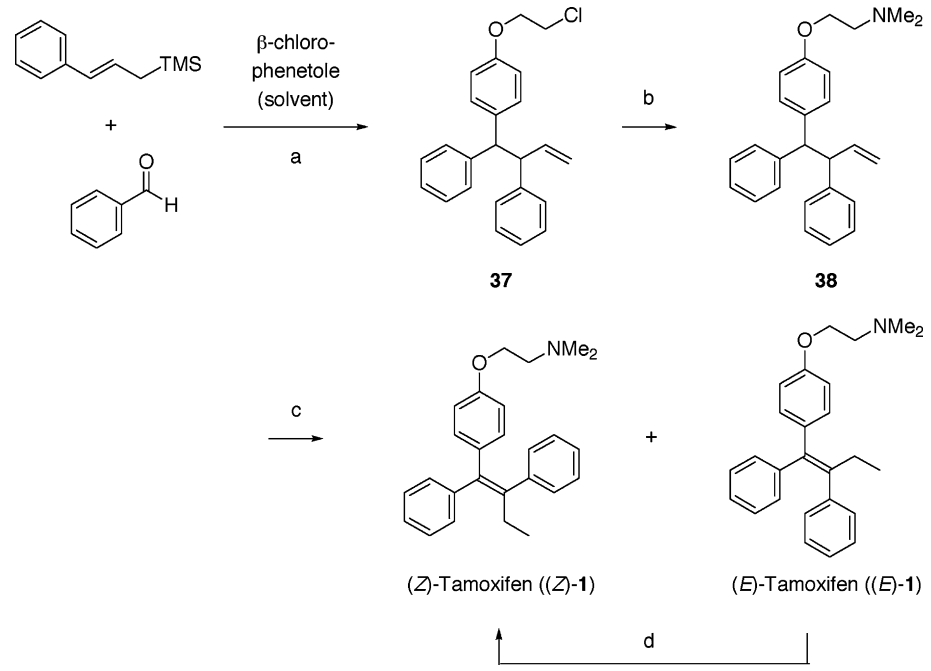
2.2. Biological evaluations of the coupling products against HL-60 promyelocytic leukemia

The potency of the anti-tumor activities of tamoxifen derivatives was assessed in this study. In order to evaluate the anti-tumor activities of our compounds against the HL-60 human acute promyelocytic leukemia, we tried to determine the efficiency of the synthesized compounds decreasing the cell viability by the MTT (3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide) assay, a method of determining cell viability by measuring the mitochondrial succinic dehydrogenase activity.

The effects of tamoxifen, 4-bromotamoxifen, 3-iodotamoxifen, and idoxifene on growth of the HL-60 human cell line were first measured by the MTT assay after a 4-h incubation (Table 3). A treatment of the HL-60 cells with 5 μg/mL of tamoxifen gave ca. 50% of the final viability of the inhibited cells compared with the cell viability at 0 h. A similar result was obtained when 5 μg/mL of 4-bromotamoxifen was used under the same conditions for the inhibition of the cell viability. On the other hand, 5 μg/mL of 3-iodotamoxifen showed no affect on the viability of the HL-60 cells after 4 h.



Scheme 12. Synthesis of droloxifene (**2**) through improved three-component coupling reaction. Reagents and conditions: (a) $HfCl_4$, TMSOTf, rt, 2 h (43%, (*o*-)/(*p*-) = 2:98); (b) 30% dimethylamine, EtOH, 110 °C, 8 h (81%); (c) ^{t}BuOK, DMSO, 50 °C, 2 h (49% of (*E*)-**2**, 38% of (*Z*)-**2**); (d) TfOH, CH_2Cl_2, 0 °C, 2 h, (73% of **2** [37% of (*E*)-**2**, 36% of (*Z*)-**2**] from (*Z*)-**2**).



Scheme 13. Synthesis of tamoxifen (**1**) through improved three-component coupling reaction. Reagents and conditions: (a) $HfCl_4$, rt, 4 h (43%); (b) 30% dimethylamine, 110 °C, 8 h (93%); (c) ^{t}BuOK, DMSO, rt, 1 h (39% of (*Z*)-**1**, 37% of (*E*)-**1**); (d) TfOH, CH_2Cl_2, 0 °C, 3 h, (97% of **1** [51% of (*Z*)-**1**, 46% of (*E*)-**1**] from (*E*)-**1**).

Table 3. Inhibition of the cell viability of the HL-60 cell lines at various concentrations

Concentration (μg/mL)	0	1	5	10	20
Tamoxifen (line a)	100	96.1704	53.5425	15.9127	5.4447
4-Bromotamoxifen (line b)	100	99.9285	59.2228	13.1845	7.01505
3-Iodotamoxifen (line c)	100	108.523	103.916	97.2073	36.055
Idoxifene (line d)	100	105.706	82.701	25.4653	8.71871

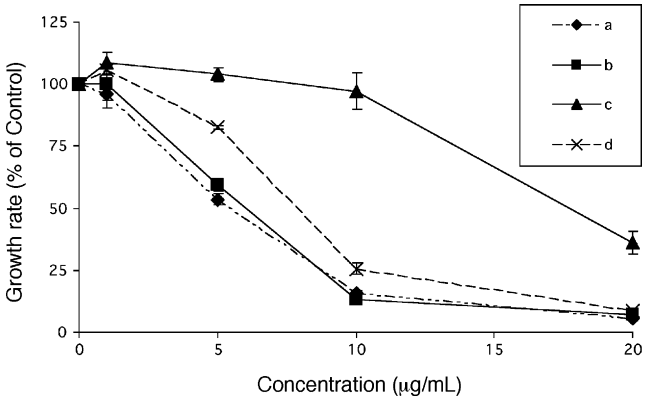


Figure 2. Effects of tamoxifen (line a), 4-bromotamoxifen (line b), 3-iodotamoxifen (line c), and idoxifene (line d) on the cell viability after a 4-h incubation. The dose-dependent effects of tamoxifen derivatives to HL-60 cells were measured by the MTT assay. The cell viability obtained from the absorbance of formazan at 0 h was 100%.

We next investigated the effects on the dose-dependent viability of the HL-60 cells treated with tamoxifen, 4-bromotamoxifen, 3-iodotamoxifen, and idoxifene at various concentrations after a 4-h treatment (Table 3 and Fig. 2). Tamoxifen and 4-bromotamoxifen in the final concentrations of 5, 10, and 20 μg/mL decreased the cell viability in a dose-dependent manner. A 4-h incubation with 10 μg/mL final concentration of tamoxifen and 4-bromotamoxifen inhibited the cell viability more than 80% as measured by the MTT assay. Idoxifene in 10 μg/mL concentration inhibited the cell viability more than 70% after a 4-h treatment, whereas 3-iodotamoxifen in 5 and 10 μg/mL concentrations did not inhibit the cell viability at all under the same conditions. Among them, tamoxifen, 4-bromotamoxifen, and idoxifene clearly induced, dose-dependently, cell death to a greater extent than 3-iodotamoxifen as shown in Figure 2. The median growth-inhibitory concentrations (IC_{50}) against the HL-60 cells after a 4-h incubation with tamoxifen, 4-bromotamoxifen, and idoxifene were calculated as 5.9, 6.0, and 7.7 μg/mL, respectively. Although tamoxifen, 4-bromotamoxifen, and idoxifene have strong cytotoxic activities inducing apoptosis of the HL-60 cells, 3-iodotamoxifen shows very low activity on the same cells (IC_{50} = 19.0 μg/mL).

3. Conclusions

We have developed new protocols to prepare tamoxifen and its derivatives. The first route involved the aldol

reaction of benzyl phenyl ketone with acetaldehyde followed by the Friedel–Crafts substitution with anisole in the presence of $Cl_2Si(OTf)_2$ to produce 1,1,2-triaryl-3-acetoxybutane, a precursor of the tamoxifen derivatives. The alternative approach utilized the novel three-component coupling reaction among aromatic aldehydes, cinnamyltrimethylsilane, and aromatic nucleophiles using $HfCl_4$ as a Lewis acid catalyst to produce 3,4,4-triarylbutene, that is also a valuable intermediate of tamoxifen derivatives. The latter synthesis needs only three or four steps to produce the basic skeleton of SERMs including the installation of the side-chain moiety and the double-bond migration to form the tetra-substituted olefin structure. Although 3-iodotamoxifen has very low biological activity during the MTT assay, tamoxifen, 4-bromotamoxifen, and idoxifene showed significant anti-tumor activities against the HL-60 human acute promyelocytic leukemia. This synthetic strategy seems to serve as a new and practical pathway to prepare not only the tamoxifen derivatives, but also other SERMs including estrogen-dependent breast cancer, leukemia, and osteoporosis agents.

4. Experimental

All melting points were measured on a Yanaco MP-S3 micro-melting point apparatus. IR spectra were recorded on a Horiba FT-300 infrared spectrometer or a Perkin Elmer spectrum One FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270L, a JEOL JNM-AL300, or a JEOL JNM-LA500 spectrometer with tetramethylsilane (TMS) or chloroform (in chloroform-d) as internal standards. High-resolution mass spectra were recorded on a JEOL JMS-SX102A instrument using 4-nitrobenzyl alcohol as a matrix or an Applied Biosystems Mariner system 5055 or Bruker Daltonics micro TOF focus instrument. HPLC was carried out using a Hitachi L-4000 UV detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator with a Senshu Pak Pegasil ODS-II (4.6 mm ID × 250 mm L).

Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. Thin layer chromatography was performed on Wakogel B5F. All reactions were carried out under an argon atmosphere in dried glassware, unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4A, toluene and DMF were distilled from diphosphorus pentoxide, and dried over MS 4A, and THF was distilled from sodium/benzophenone immediately prior to use. Other reagents and solvents were purchased from Tokyo Kasei Kogyo Co., Ltd; Kanto Chemical Co., Inc.; or Aldrich Chemical Co., Inc., and used without further purification unless otherwise noted.

4.1. (2*RS*,3*RS*)/(2*RS*,3*SR*)-3-Hydroxy-1,2-diphenylbutanone (4)

To a solution of diisopropylamine (6.00 mL, 42.7 mmol) in THF (250 mL) at 0 °C was added a solution of *n*-butyllithium in hexane (1.56 M, 25.1 mL, 39.2 mmol). After the reaction mixture had been stirred for 30 min at 0 °C, a solution of 1,2-diphenylbutanone (**3**) (7.00 g, 35.6 mmol) in THF (50 mL) was added at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and then a solution of acetaldehyde (2.40 mL, 42.7 mmol) in THF (50 mL) was added. After the reaction mixture had been stirred for 1 h at −78 °C, saturated aqueous ammonium chloride was added. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford a mixture of diastereomers of **4** (8.00 g, 94%, *anti*/*syn* = 73:27) as a colorless oil; IR (neat): 3487, 3433, 1674 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.93–7.87 (m, 2H, Ph), 7.48–7.14 (m, 8H, Ph), 4.56–4.42 (m, 2H, 2-H, 3-H), 2.70 (br s, 1H, OH), 1.19, 1.14 (d, J = 6.1, 5.8 Hz, 3H, 4-H).

4.2. (*E*)- and (*Z*)-1,2-Diphenylbut-2-eneone (5)

To a solution of **4** (7.36 g, 30.6 mmol) in benzene (60 mL) at room temperature were added *p*-toluenesulfonic acid monohydrate (263 mg, 1.53 mmol) and sodium sulfate (2.18 g, 15.3 mmol). The reaction mixture was refluxed for 1 h and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford a mixture of geometric isomers of **5** (5.85 g, 86%, *E*/*Z* = 1:1) as a colorless oil; ^1H NMR ($CDCl_3$): δ 7.90–7.63 (m, 2H, Ph), 7.46–7.12 (m, 8H, Ph), 6.34, 6.24 (q, J = 7.3 Hz, 1H, 3-H), 1.78, 1.67 (d, J = 7.3 Hz, 3H, 4-H).

4.3. (*E*)-1,2-Diphenylbut-2-enol (6)

To a solution of **5** (6.44 g, 31.4 mmol) in methanol (80 mL) at 0 °C were added cerium trichloride (11.7 g, 31.4 mmol) and sodium borohydride (1.18 g, 31.4 mmol). The reaction mixture was stirred for 15 min at 0 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the titled compound **6** (880 mg, 15%), its geometric isomer (2.92 g, 50%), and the unreacted (*E*)-**5** (2.25 g, 35% recovery).

To a solution of (*E*)-**5** (2.00 g, 9.00 mmol) in methanol (36 mL) at 0 °C were added cerium trichloride (3.35 g, 9.00 mmol) and sodium borohydride (341 mg, 9.00 mmol). The reaction mixture was stirred for 12 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent,

the crude product was purified by column chromatography to afford the titled compound **6** (646 mg, 30%) as a colorless oil; IR (neat): 3410 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.30–6.98 (m, 10H, Ph), 5.87 (s, 1H, 1-H), 5.79 (q, J = 7.1 Hz, 1H, 3-H), 2.18 (br s, 1H, OH), 1.79 (d, J = 7.1 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 142.5, 142.3, 140.0, 128.2, 128.2, 127.9, 127.9, 126.8, 126.7, 125.6, 70.9, 14.1.

4.4. (*E*)-4-Acetoxy-3,4-diphenylbut-2-ene (7)

To a solution of **6** (300 mg, 1.34 mmol) in dichloromethane (3 mL) at 0 °C were added triethylamine (0.28 mL, 2.0 mmol), acetic anhydride (0.18 mL, 1.6 mmol), and DMAP (32.7 mg, 0.268 mmol). The reaction mixture was stirred for 15 min at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the titled compound **7** (279 mg, 78%) as a colorless oil; IR (neat): 1743 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.23–7.10 (m, 10H, Ph), 6.95 (s, 1H, 4-H), 5.90 (q, J = 7.1 Hz, 1H, 2-H), 2.00 (s, 3H, Ac), 1.90 (d, J = 7.1 Hz, 3H, 1-H); ^{13}C NMR ($CDCl_3$): δ 170.1, 140.5, 139.1, 138.7, 128.3, 128.1, 127.9, 127.9, 127.4, 126.8, 126.2, 73.3, 21.1, 14.1.

4.5. (*Z*)-3-(4-Methoxyphenyl)-1,2-diphenylbut-1-ene (8)

To a solution of **7** (79.9 mg, 0.300 mmol) in anisole (1.2 mL) at room temperature was added a solution of $[Mo(CO)_4Br_2]_2$ (9.4 mg, 0.013 mmol) in anisole (0.3 mL). The reaction mixture was stirred for 5 min at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the titled compound **8** (91.5 mg, 97%) as a colorless oil; IR (neat): 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.21–6.70 (m, 14H, Ph), 6.40 (s, 1H, 1-H), 3.78 (q, J = 7.1 Hz, 1H, 3-H), 3.70 (s, 3H, OMe), 1.38 (d, J = 7.1 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 158.0, 147.5, 140.8, 137.3, 136.2, 129.0, 129.0, 128.9, 128.1, 127.8, 126.7, 126.1, 126.1, 113.5, 55.1, 47.9, 22.0; HR MS (FAB) calcd for $C_{23}H_{22}O$ [M^+] 314.1670, found 314.1672.

4.6. (1*RS*,2*SR*,3*SR*)-1,2-Diphenylbutane-1,3-diol (10a) and (1*RS*,2*SR*,3*RS*)-1,2-diphenylbutane-1,3-diol (10b)

To a solution of **4** (2.00 g, 8.32 mmol) in THF (33 mL) at −78 °C was added a solution of lithium borohydride in THF (2.0 M, 4.37 mL, 8.74 mmol). The reaction mixture was stirred for 30 min at −78 °C and then saturated aqueous ammonium chloride was added. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the titled compound **10a** (1.32 g, 66%) as a colorless solid and **10b** (451 mg, 22%) as a colorless oil. **10a**; mp 134–136 °C; IR (KBr): 3433 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.24–6.95 (m, 10H, Ph), 5.29 (d, J = 4.3 Hz, 1H, 1-H), 4.30 (dq, J = 8.6, 6.3 Hz, 1H, 3-H), 2.91 (dd, J = 4.3, 8.6 Hz, 1H, 2-H), 1.09 (d, J = 6.3 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 141.4, 138.1, 129.7, 128.0, 127.9, 127.3, 126.8, 126.6, 75.1, 68.7, 60.1, 22.3. **10b**; IR (neat): 3356 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.19–7.13 (m, 10H, Ph), 5.10 (d, J = 6.9 Hz, 1H, 1-H), 3.88 (dq, J = 3.6, 6.4 Hz, 1H, 3-H), 2.61 (dd, J = 3.6, 6.9 Hz, 1H, 2-H), 2.27 (br s, 2H, OH), 0.85 (d, J = 6.4 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 142.6, 136.6, 130.4, 128.0, 127.7, 127.4, 127.0, 126.5, 76.1, 68.6, 59.9, 22.0.

4.7. (1*RS*,2*SR*,3*SR*)-1,3-Diacetoxy-1,2-diphenylbutane (11a)

To a solution of **10a** (2.05 g, 8.47 mmol) in dichloromethane (33 mL) at 0 °C were added triethylamine (4.1 mL, 30 mmol), acetic anhydride (2.60 mL, 27.6 mmol), and DMAP (207 mg, 1.69 mmol). The reaction mixture was stirred for 1 h at room temperature and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the titled compound **11a** (2.72 g, 99%) as a colorless solid; mp 103–106 °C; IR (KBr): 1705 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.20–6.28 (m, 10H, Ph), 6.27 (d, J = 4.5 Hz, 1H, l-H), 5.38 (dq, J = 6.3, 10.2 Hz, 1H, 3-H), 3.08 (dd, J = 4.5, 10.2 Hz, 1H, 2-H), 2.05 (s, 3H, Ac), 2.04 (s, 3H, Ac), 1.01 (d, J = 6.3 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 171.5, 171.5, 142.2, 136.7, 129.8, 127.9, 127.9, 127.7, 126.9, 125.9, 72.7, 71.1, 58.8, 21.1, 21.1, 19.1; Anal. calcd for $C_{20}H_{22}O_4$, C 73.60; H, 6.79, found: C, 73.61; H, 6.84.

4.8. (1*RS*,2*SR*,3*RS*)-1,3-Diacetoxy-1,2-diphenylbutane (11b)

To a solution of **10b** (1.00 g, 4.13 mmol) in dichloromethane (16.5 mL) at 0 °C were added triethylamine (1.74 mL, 12.5 mmol), acetic anhydride (1.10 mL, 11.7 mmol), and DMAP (102 mg, 0.835 mmol). The reaction mixture was stirred for 1 h at room temperature and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the titled compound **11b** (1.11 g, 82%) as a colorless solid; mp 103–104 °C; IR (KBr): 1736 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.23–7.17 (m, 10H, Ph), 6.12 (d, J = 9.4 Hz, 1H, 1-H), 4.73 (dq, J = 6.3, 4.3 Hz, 1H, 3-H), 3.06 (dd, J = 4.3, 9.4 Hz, 1H, 2-H), 2.00 (s, 3H, Ac), 1.71 (s, 3H, Ac), 0.97 (d, J = 6.3 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 170.1, 170.0, 138.7, 137.2, 129.8, 128.6, 128.5, 127.9, 127.0, 127.0, 76.0, 70.1, 56.4, 21.2, 20.8, 18.5; Anal. calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79, found: C, 73.56; H, 6.76.

4.9. (1*RS*,2*SR*,3*SR*)-3-Acetoxy-1-(4-methoxyphenyl)-1,2-diphenylbutane (13a)

To a solution of silver trifluoromethanesulfonate (257 mg, 1.00 mmol) in anisole (2.5 mL) at 0 °C was added tetrachlorosilane (0.059 mL, 0.51 mmol). After the reaction mixture had been stirred for 15 min at 0 °C, a solution of **11a** (160 mg, 0.49 mmol) in anisole (2 mL) was added. The reaction mixture was stirred for 4 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford the titled compound **13a** (179 mg, 98%) as a colorless solid; mp 126–128 °C; IR (KBr): 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.37–6.94 (m, 12H, Ar), 6.50 (d, J = 8.7 Hz, 2H, Ar), 5.00 (dq, J = 6.4, 5.6 Hz, 1H, 3-H), 4.21 (d, J = 12.0 Hz, 1H, 1-H), 3.92 (dd, J = 5.6, 12.0 Hz, 1H, 2-H), 3.53 (s, 3H, OMe), 1.70 (s, 3H, Ac), 0.96 (d, J = 6.4 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 170.5, 157.3, 143.6, 138.6, 135.5, 129.9, 128.9, 128.7, 127.7, 127.7, 126.4, 126.4, 113.5, 72.1, 54.9, 53.1, 52.1, 21.0, 15.8; Anal. calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00, found: C, 80.28; H, 7.03.

4.10. (1*RS*,2*SR*,3*RS*)-3-Acetoxy-1-(4-methoxyphenyl)-1,2-diphenylbutane (13b)

To a solution of silver trifluoromethanesulfonate (257 mg, 1.00 mmol) in anisole (2.5 mL) at 0 °C was added tetrachlorosilane (0.059 mL, 0.51 mmol). After the reaction mixture had been stirred for 15 min at 0 °C, a solution of **11b** (150 mg, 0.458 mmol) in anisole (2 mL) was added. The reaction mixture was stirred for 4 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford the titled compound **13b** (158 mg, 92%) as a colorless solid; mp 131–132 °C; IR (KBr): 1728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.24–6.96 (m, 12H, Ar), 6.51 (d, J = 8.7 Hz, 2H, Ar), 4.79 (dq, J = 6.4, 2.8 Hz, 1H, 3-H), 4.32 (d, J = 12.3 Hz, 1H, l-H), 3.54 (s, 3H, OMe), 3.40 (dd, J = 2.8, 12.3 Hz, 1H, 2-H), 2.00 (s, 3H, Ac), 0.87 (d, J = 6.4 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 170.0, 157.4, 143.5, 139.0, 135.2, 130.1, 129.0, 128.8, 127.7, 127.7, 126.6, 126.4, 113.5, 70.7, 54.9, 54.5, 53.2, 21.2, 18.7; Anal. calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00, found: C, 80.09; H, 6.99.

4.11. (2*RS*,3*RS*,4*SR*)-4-(4-Methoxyphenyl)-3,4-diphenylbutan-2-ol (13a′)

To a solution of **13a** (65.8 mg, 0.176 mmol) in methanol (1.8 mL) at room temperature was added sodium hydroxide (8.1 mg, 0.20 mmol). The reaction mixture was stirred for 5 h at 50 °C and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford the titled compound **13a′** (47.0 mg, 81%) as a colorless solid; mp 97–101 °C; IR (KBr): 3433 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.36–7.01 (m, 12H, Ar), 6.55 (d, J = 8.7 Hz, 2H, Ar), 4.27 (br d, J = 11.9 Hz, 1H, 4-H), 3.80–3.75 (m, 2H, 2-H, 3-H), 3.57 (s, 3H, OMe), 1.29 (br s, 1H, OH), 0.94 (d, J = 6.3 Hz, 3H, 1-H); ^{13}C NMR ($CDCl_3$): δ 157.4, 143.9, 138.0, 135.4, 130.1, 129.0, 128.9, 127.9, 127.7, 126.4, 126.4, 113.5, 68.4, 55.7, 54.9, 52.5, 18.4; HR MS (FAB) calcd for $C_{23}H_{24}O_2Na$ $[M+Na]^+$ 355.1674, found 355.1673.

4.12. (2*RS*,3*SR*,4*RS*)-4-(4-Methoxyphenyl)-3,4-diphenylbutan-2-ol (13b′)

To a solution of **13b** (2.20 g, 5.86 mmol) in methanol (60 mL) at room temperature was added sodium hydroxide (269 mg, 6.73 mmol). The reaction mixture was stirred for 5 h at 50 °C and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the titled compound **13b′** (1.92 g, 99%) as a colorless solid; mp 101–103 °C; IR (KBr): 3541, 3471 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45–7.10 (m, 12H, Ar), 6.51 (d, J = 8.7 Hz, 2H, Ar), 4.64 (d, J = 12.3 Hz, 1H, 4-H), 3.79 (dq, J = 2.3, 6.4 Hz, 1H, 2-H), 3.61 (s, 3H, OMe), 3.37 (dd, J = 2.3, 12.3 Hz, 1H, 3-H), 1.26 (br s, 1H, OH), 0.90 (d, J = 6.4 Hz, 3H, 1-H); ^{13}C NMR ($CDCl_3$): δ 157.2, 144.6, 138.5, 135.7, 130.0, 129.3, 128.7, 128.1, 127.9, 126.3, 126.2, 113.4, 66.6, 56.0, 54.9, 52.2, 22.7; HR MS (FAB) calcd for $C_{28}H_{24}O_2Na$ $[M+Na]^+$ 355.1674, found 355.1667.

4.13. (1*RS*,2*SR*,3*SR*)-3-Methanesulfonyl-1-(4-methoxyphenyl)-1,2-diphenylbutane (14a)

To a solution of **13a′** (5.71 g, 15.2 mmol) in dichloromethane (15 mL) at 0 °C were added triethylamine (3.45 mL, 36.6 mmol), methanesulfonyl chloride (2.36 mL, 30.5 mmol), and DMAP (372 mg, 3.05 mmol). The reaction mixture was stirred for 1 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the titled compound **14a** (6.25 g, quant.) as a colorless solid; mp 52–54 °C; IR (KBr): 1350 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.38–7.00 (m, 12H, Ar), 6.52 (d, J = 8.7 Hz, 2H, Ar), 4.82 (dd, J = 4.0, 6.4 Hz, 1H, 3-H), 4.22–4.10 (m, 2H, l-H, 2-H), 3.54 (s, 3H, OMe), 2.70 (s, 3H, Ms), 1.15 (d, J = 6.4 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 157.5, 142.6, 136.4, 134.6, 130.3, 129.1, 128.8, 127.9, 127.6, 126.9, 126.8, 113.6, 79.5, 54.9, 53.2, 52.0, 38.0, 15.9; Anal. calcd for $C_{24}H_{26}O_4S$: C, 70.22; H, 6.38, found: C, 70.33; H, 6.55.

4.14. (1*RS*,2*SR*,3*RS*)-3-Methanesulfonyl-1-(4-methoxyphenyl)-1,2- diphenylbutane (14b)

To a solution of **13b′** (1.00 g, 3.01 mmol) in dichloromethane (3 mL) at 0 °C were added triethylamine (0.681 mL, 7.22 mmol), methanesulfonyl chloride (0.521 mL, 6.62 mmol), and DMAP (80.7 mg, 0.662 mmol). The reaction mixture was stirred for 1 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford the titled compound **14b** (1.24 g, quant.) as a colorless solid; mp 60–62 °C; IR (KBr): 1342 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40–6.91 (m, 12H, Ar), 6.60 (d, J = 8.6 Hz, 2H, Ar), 4.90 (dq, J = 6.3, 2.8 Hz, 1H, 3-H), 4.45 (d, J = 12.1 Hz, 1H, 1-H), 3.54 (s, 3H, OMe), 3.45 (dd, J = 2.8, 12.1 Hz, 1H, 2-H), 2.71 (s, 3H, Ms), 1.14 (d, J = 6.3 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 157.4, 142.8, 136.4, 134.6, 130.3, 129.1, 128.8, 127.8, 127.6, 126.9, 126.8, 113.6, 79.5, 55.1, 54.9, 52.5, 39.1, 20.2; Anal. calcd for $C_{24}H_{16}O_4S$: C, 70.22; H, 6.38, found: C, 70.14; H, 6.49.

4.15. (3*RS*,4*RS*)-4-(4-Methoxyphenyl)-3,4-diphenylbut-1-ene (*syn*-15)

To a solution of **14a** (300 mg, 731 mmol) in methanol (2.9 mL) at room temperature was added sodium hydroxide (2.9 mg, 0.073 mmol). The reaction mixture was stirred for 4 h at 75 °C and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford *syn*-**15** (218 mg, 95%) as a colorless solid; mp 84–86 °C; IR (KBr): 1728, 1504, 1257 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.29–6.93 (m, 12H, Ar), 6.54 (d, J = 8.7 Hz, 2H, Ar), 5.83 (ddd, J = 7.7, 10.0, 14.8 Hz, 1H, 2-H), 4.87 (d, J = 10.0 Hz, 1H, 1-H), 4.83 (d, J = 14.8 Hz, 1H, 1-H), 4.19 (d, J = 11.5 Hz, 1H, 4-H), 4.05 (dd, J = 7.7, 11.5 Hz, 1H, 3-H), 3.56 (s, 3H, OMe); ^{13}C NMR ($CDCl_3$): δ 157.3, 143.8, 142.8, 141.0, 135.4, 129.1, 128.5, 128.3, 128.2, 128.2, 126.1, 126.0, 115.8, 113.5, 56.1, 55.0, 54.6; Anal. calcd for $C_{23}H_{22}O$: C, 87.86; H, 7.05, found: C, 87.76; H, 7.02.

4.16. (*E*)- and (*Z*)-1-(4-Methoxyphenyl)-1,2-diphenylbut-1-ene (16)

To a solution of **15** (197 mg, 0.627 mmol) in DMSO (1.6 mL) at room temperature was added potassium *tert*-butoxide (123 mg, 1.10 mmol). The reaction mixture was stirred for 15 min at room temperature and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford a mixture of geometric isomers of **16** (191 mg, 97%, E/Z = ca. 1:1) as a colorless oil; IR (neat): 1605, 1504, 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.28–6.69 (m, 12H, Ar), 6.47 (d, J = 8.6 Hz, 2H, Ar), 3.76 and 3.74 (s, 3H, OMe), 2.43 and 2.38 (q, J = 7.4 Hz, 2H, 3-H), 0.87 and 0.85 (t, J = 7.4 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 158.3, 157.4, 143.8, 143.3, 142.4, 142.3, 141.8, 141.3, 138.4, 138.2, 136.0, 135.4, 131.8, 130.8, 130.6, 129.7, 129.4, 128.1, 127.8, 127.7, 127.3, 126.5, 126.0, 125.6, 113.4, 112.7, 55.1, 54.9, 29.0, 13.6.

4.17. (*E*)- and (*Z*)-1-(4-Hydroxyphenyl)-1,2-diphenylbut-1-ene (17)

To a solution of **16** (2.54 g, 8.08 mmol) in dichloromethane (80 mL) at −78 °C was added boron tribromide (13.0 mL, 4.06 mmol). The reaction mixture was stirred for 2 h at −78 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford a mixture of geometric isomers of **17** (2.42 g, quant.) as a colorless oil; IR (neat): 3518, 3386 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.30–6.65 (m, 12H, Ar), 6.39 (d, J = 8.5 Hz, 2H, Ar), 2.44 and 2.35 (q, J = 7.6 Hz, 2H, 3-H), 0.88 and 0.83 (t, J = 7.6 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 154.3, 153.4, 143.7, 143.3, 142.3, 141.9, 141.3, 138.3, 138.1, 136.0, 135.5, 132.0, 130.8, 130.7, 129.6, 129.4, 128.1, 127.8, 127.7, 127.2, 126.5, 126.0, 125.6, 115.0, 114.3, 28.9, 13.6.

4.18. 1-(4-[2-Dimethylaminoethoxy]phenyl)-1,2-diphenylbut-1-ene (1, tamoxifen)

To a suspension of sodium hydride (60%, 333 mg, 8.33 mmol) in DMF (7.3 mL) at 0 °C was added a solution of **17** (1.00 g, 3.33 mmol) in DMF (3 mL). After the reaction mixture had been stirred for 30 min at 0 °C, a solution of *N*,*N*-dimethylaminoethylchloride (1.07 g, 9.95 mmol) in DMF (3 mL) was added. The reaction mixture was stirred for 30 min at 50 °C and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford a mixture of geometric isomers of tamoxifen (**1**) as a colorless solid (1.22 g, 95%, E/Z = 46:54). Each compound was isolated by preparative reversed-phase HPLC (methanol–0.01 M HCl = 7:3) or thin layer chromatography (benzene–triethylamine = 19:1) using preparative TLC plates (Merck, Silica gel 60 F_{254}). [The plate was developed twice in the dark.] (*Z*)-**1**; ^1H NMR ($CDCl_3$): δ 7.29–6.82 (m, 10H, Ar), 6.69 (d, J = 8.7 Hz, 2H, Ar), 6.48 (d, J = 8.7 Hz, 2H, Ar), 3.87 (t, J = 5.7 Hz, 2H, OCH_2), 2.60 (t, J = 5.7 Hz, 2H, NCH_2), 2.38 (q, J = 7.5 Hz, 2H, 3-H), 2.23 (s, 6H, NMe_2), 0.85 (t, J = 7.5 Hz, 3H, 4-H). (*E*)-**1**; ^1H NMR ($CDCl_3$): δ 7.19–6.77 (m, 14H, Ar), 4.01 (t, J = 6.0 Hz, 2H, OCH_2), 2.68 (t, J = 6.0 Hz, 2H, NCH_2), 2.43 (q, J = 7.5 Hz, 2H, 3-H), 2.28 (s, 6H, NMe_2), 0.87 (t, J = 7.5 Hz, 3H, 4-H).

4.19. Isomerization of (*E*)-tamoxifen to (*Z*)-tamoxifen

To a solution of (*E*)-tamoxifen ((*E*)-**1**, 3.3 mg, 8.8 μmol) in dichloromethane (0.3 mL) at 0 °C was added trifluoromethanesulfonic acid (12 μL, 0.135 mmol). The reaction mixture was stirred for 3 h at 0 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (dichloromethane–methanol = 9:1) to afford a mixture of geometric isomers of **1** (3.2 mg, 97%, *E*/*Z* = 47:53) as a colorless oil.

4.20. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-(4-Methoxyphenyl)-3,4-diphenylbut-1-ene (15)

To a suspension of hafnium tetrachloride (75.6 mg, 0.236 mmol) and trimethylsilyl trifluoromethanesulfonate (26.2 mg, 0.118 mmol) in anisole (1.2 mL) at 0 °C was added a solution of cinnamyltrimethylsilane (57.9 mg, 0.283 mmol) and benzaldehyde (25.0 mg, 0.236 mmol) in anisole (1.2 mL). The reaction mixture was stirred for 2 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (hexane–ethyl acetate = 17:1) [developed twice] to afford a mixture of diastereomers of *p*-**15** (29.7 mg, 40%, (3*RS*,4*SR*)/(3*RS*,4*RS*) = ca. 6:4) and a mixture of diastereomers of *o*-**15** (12.7 mg, 17%, (3*RS*,4*SR*)/(3*RS*,4*RS*) = ca. 1:1) as colorless oils. A mixture of *syn*- and *anti*-isomers of *p*-**15**; ^{1}H NMR ($CDCl_3$): δ 7.28–6.74 (m, 12H, Ar), 6.55–6.53 (m, 2H, Ar), 5.90–5.79 (m, 1H, 2-H), 4.86–4.74 (m, 2H, 1-H), 4.18 (d, J = 11.6 Hz, 1H, 4-H), 4.05 (dd, J = 8.0, 11.2 Hz, 1H, 3-H), 3.68 and 3.56 (s, 3H, OMe).

4.21. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-(3-Bromophenyl)-4-(4-methoxyphenyl)-3-phenylbut-1-ene (19)

The title compound was prepared according to the similar procedure for Section 4.23. ^{1}H NMR ($CDCl_3$): δ 7.33–6.81 (m, 11H, Ar), 6.63 (d, J = 8.7 Hz, 2H, Ar), 5.95–5.82 (m, 1H, 2-H), 4.97–4.81 (m, 2H, 1-H), 4.20 (d, J = 11.0 Hz, 1H, 4-H), 4.08 (dd, J = 7.6, 11.6 Hz, 1H, 3-H), 3.75 and 3.67 (s, 3H, OMe).

4.22. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-(3-Iodophenyl)-4-(4-methoxyphenyl)-3-phenylbut-1-ene (20)

The title compound was prepared according to the similar procedure for Section 4.23. ^{1}H NMR ($CDCl_3$): δ 7.38–6.47 (m, 13H, Ar), 5.82–5.66 (m, 1H, 2-H), 4.83–4.69 (m, 2H, 1-H), 4.08–3.89 (m, 2H, 3-H, 4-H), 3.61 and 3.52 (s, 3H, OMe).

4.23. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-(4-Bromophenyl)-4-(4-methoxyphenyl)-3-phenylbut-1-ene (21)

To a suspension of hafnium tetrachloride (1.73 g, 5.40 mmol) in anisole (26 mL) at 0 °C was added a solution of cinnamyltrimethylsilane (1.23 g, 6.46 mmol) in anisole (28 mL) and 4-bromobenzaldehyde (1.00 g, 5.40 mmol). The reaction mixture was stirred for 2 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford a mixture of diastereomers of *p*-**21** (1.37 g, 64%, (3*RS*,4*RS*)/(3*RS*,4*SR*) = 85/15) and a mixture of diastereomers of *o*-**21** (131 mg, 6%, (3*RS*,4*SR*)/(3*RS*,4*RS*) = 61/39) as colorless oils. A mixture of *syn*- and *anti*-isomers of *p*-**21**; ^{1}H NMR ($CDCl_3$): δ 7.33–6.52 (m, 13H, Ar), 5.88–5.71 (m, 1H, 2-H), 4.86–4.71 (m, 2H, 1-H), 4.16–4.10 (m, 1H, 4-H), 4.05–3.95 (m, 1H, 3-H), 3.67 and 3.56 (s, 3H, OMe).

4.24. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-(4-Iodophenyl)-4-(4-methoxyphenyl)-3-phenylbut-1-ene (22)

The title compound was prepared according to the similar procedure for Section 4.23. ^{1}H NMR ($CDCl_3$): δ 7.32–6.51 (m, 13H, Ar), 5.84–5.75 (m, 1H, 2-H), 4.85–4.73 (m, 2H, 1-H), 4.12 (d, J = 11.7 Hz, 1H, 4-H), 3.99–3.95 (m, 1H, 3-H), 3.67 and 3.55 (s, 3H, OMe).

4.25. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-(4-Methoxyphenyl)-3-phenyl-4-(3-pivaloyloxyphenyl)but-1-ene (23)

The title compound was prepared according to the similar procedure for Section 4.20. ^{1}H NMR ($CDCl_3$): δ 7.32–6.60 (m, 13H, Ar), 5.94–5.83 (m, 1H, 2-H), 4.95–4.82 (m, 2H, 1-H), 4.27–4.04 (m, 2H, 3-H, 4-H), 3.72 and 3.62 (s, 3H, OMe), 1.33 and 1.32 (s, 9H, *t*-Bu).

4.26. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-(4-Methoxyphenyl)-3-phenyl-4-(4-pivaloyloxyphenyl)but-1-ene (24)

The title compound was prepared according to the similar procedure for Section 4.23. ^{1}H NMR ($CDCl_3$): δ 7.32–6.75 (m, 11H, Ar), 6.57 (d, J = 8.6 Hz, 2H, Ar), 5.94–5.84 (m, 1H, 2-H), 4.90–4.80 (m, 2H, 1-H), 4.25 (d, J = 11.6 Hz, 1H, 4-H), 4.06 (dd, J = 7.1, 9.6 Hz, 1H, 3-H), 3.66 (s, 3H, OMe), 1.31 (s, 9H, *t*-Bu).

4.27. (*E*)- and (*Z*)-1-(3-Bromophenyl)-1-(4-methoxyphenyl)-2-phenylbut-1-ene (25)

The title compound was prepared according to the similar procedure for Section 4.29. ^{1}H NMR ($CDCl_3$): δ 7.33–6.76 (m, 11H, Ar), 6.53 (d, J = 7.9 Hz, 2H, Ar), 3.80 and 3.65 (s, 3H, OMe), 2.48 and 2.45 (q, J = 7.0 Hz, 2H, 3-H), 0.95 and 0.92 (t, J = 7.0 Hz, 3H, 4-H).

4.28. (*E*)- and (*Z*)-1-(3-Iodophenyl)-1-(4-methoxyphenyl)-2-phenylbut-1-ene (26)

The title compound was prepared according to the similar procedure for Section 4.29. ^{1}H NMR ($CDCl_3$): δ 7.36–6.53 (m, 13H, Ar), 3.81 and 3.69 (s, 3H, OMe), 2.48 and 2.45 (q, J = 7.8 Hz, 2H, 3-H), 0.95 and 0.92 (t, J = 7.8 Hz, 3H, 4-H).

4.29. (*E*)- and (*Z*)-1-(4-Bromophenyl)-1-(4-methoxyphenyl)-2-phenylbut-1-ene (27)

To a solution of **21** (121 mg, 0.307 mmol) in DMSO (0.75 mL) at 0 °C was added potassium *tert*-butoxide (103 mg, 0.921 mmol). The reaction mixture was stirred for 15 min at room temperature and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford a mixture of geometric isomers of **27** (108 mg, 89%) as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.42–6.76 (m, 11H, Ar), 6.52 (d, J = 6.7 Hz, 2H, Ar), 3.78 and 3.62 (s, 3H, OMe), 2.51 and 2.45 (q, J = 7.6 Hz, 2H, 3-H), 0.94 and 0.92 (t, J = 7.6 Hz, 3H, 4-H).

4.30. (*E*)- and (*Z*)-1-(4-Iodophenyl)-1-(4-methoxyphenyl)-2-phenylbut-1-ene (28)

The title compound was prepared according to the similar procedure for Section 4.29. ^{1}H NMR ($CDCl_3$): δ 7.28–6.45 (m, 13H, Ar), 3.75 and 3.74 (s, 3H, OMe), 2.42 and 2.39 (q, J = 7.4 Hz, 2H, 3-H), 0.87 and 0.85 (t, J = 7.4 Hz, 3H, 4-H).

4.31. (*E*)- and (*Z*)-1-(3-Bromophenyl)-1-(4-hydroxyphenyl)-2-phenylbut-1-ene (25′)

The title compound was prepared according to the similar procedure for Section 4.33. ^{1}H NMR ($CDCl_3$): δ 7.33–6.70 (m, 11H, Ar), 6.47 (d, J = 7.4 Hz, 2H, Ar), 2.48 and 2.46 (q, J = 7.0 Hz, 2H, 3-H), 0.93 and 0.91 (t, J = 7.0 Hz, 3H, 4-H).

4.32. (*E*)- and (*Z*)-1-(4-Hydroxyphenyl)-1-(3-iodophenyl)-2-phenylbut-1-ene (26′)

The title compound was prepared according to the similar procedure for Section 4.33. ^{1}H NMR ($CDCl_3$): δ 7.34–6.45 (m, 13H, Ar), 2.47 and 2.45 (q, J = 7.3 Hz, 2H, 3-H), 0.96–0.89 (m, 3H, 4-H).

4.33. (*E*)- and (*Z*)-1-(4-Bromophenyl)-1-(4-hydroxyphenyl)-2-phenylbut-1-ene (27′)

To a solution of **27** (373 mg, 0.949 mmol) in dichloromethane (5 mL) at −78 °C was added boron tribromide in heptane (1.0 M, 9.50 mL, 9.50 mmol). The reaction mixture was stirred for 2 h at −78 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography to afford a mixture of geometric isomers of the title compound **27′** (331 mg, 92%) as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.45–6.68 (m, 11H, Ar), 6.45 (d, J = 6.8 Hz, 2H, Ar), 2.47 and 2.43 (q, J = 7.2 Hz, 2H, 3-H), 0.92 and 0.91 (t, J = 7.2 Hz, 3H, 4-H).

4.34. (*E*)- and (*Z*)-1-(4-Hydroxyphenyl)-1-(4-iodophenyl)-2-phenylbut-1-ene (28′)

The title compound was prepared according to the similar procedure for Section 4.33. ^{1}H NMR ($CDCl_3$): δ 7.29–6.38 (m, 13H, Ar), 2.42 and 2.39 (q, J = 7.4 Hz, 2H, 3-H), 0.87 and 0.85 (t, J = 7.4 Hz, 3H, 4-H).

4.35. 1-(3-Bromophenyl)-1-(4-[2-dimethylaminoethoxy]phenyl)-2-phenylbut-1-ene (29)

The title compound was prepared according to the similar procedure for Section 4.37. (*E*)-**29**; ^{1}H NMR ($CDCl_3$): δ 7.37–6.54 (m, 13H, Ar), 3.93 (t, J = 5.9 Hz, 2H, OCH_2), 2.67 (t, J = 5.9 Hz, 2H, NCH_2), 2.45 (q, J = 7.3 Hz, 2H, 3-H), 2.30 (s, 6H, NMe_2), 0.92 (t, J = 7.3 Hz, 3H, 4-H). (*Z*)-**29**; ^{1}H NMR ($CDCl_3$): δ 7.37–6.54 (m, 13H, Ar), 4.09 (t, J = 5.9 Hz, 2H, OCH_2), 2.76 (t, J = 5.9 Hz, 2H, NCH_2), 2.48 (q, J = 7.3 Hz, 2H, 3-H), 2.36 (s, 6H, NMe_2), 0.94 (t, J = 7.3 Hz, 3H, 4-H).

4.36. 1-(3-Iodophenyl)-1-(4-[2-dimethylaminoethoxy]phenyl)-2-phenylbut-1-ene (30)

The title compound was prepared according to the similar procedure for Section 4.37. (*E*)-**30**; ^{1}H NMR ($CDCl_3$): δ 7.61–7.59 (m, 2H, Ar), 7.34–6.54 (m, 11H, Ar), 3.94 (t, J = 5.9 Hz, 2H, OCH_2), 2.66 (t, J = 5.9 Hz, 2H, NCH_2), 2.45 (q, J = 6.2 Hz, 2H, 3-H), 2.30 (s, 6H, NMe_2), 0.91 (t, J = 6.2 Hz, 3H, 4-H). (*Z*)-**30**; ^{1}H NMR ($CDCl_3$): δ 7.61–7.59 (m, 2H, Ar), 7.34–6.54 (m, 11H, Ar), 4.10 (t, J = 5.9 Hz, 2H, OCH_2), 2.77 (t, J = 5.9 Hz, 2H, NCH_2), 2.50 (q, J = 6.2 Hz, 2H, 3-H), 2.36 (s, 6H, NMe_2), 0.95 (t, J = 6.2 Hz, 3H, 4-H).

4.37. 1-(4-Bromophenyl)-1-(4-[2-dimethylaminoethoxy]phenyl)-2-phenylbut-1-ene (31)

To a suspension of sodium hydride (60%, 204 mg, 5.10 mmol) in DMF (3.5 mL) at 0 °C was added a solution of **27′** (194 mg, 0.510 mmol) in DMF (1.5 mL). After the reaction mixture had been stirred for 15 min at room temperature, *N*,*N*-dimethylaminoethylchloride hydrochloride (294 mg, 2.04 mmol) was added in portions at room temperature. The reaction mixture was stirred for 12 h at 50 °C and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by silica gel column

chromatography (dichloromethane–methanol = 19:1) to afford a mixture of geometric isomers of **31** (201 mg, 88%, *E*/*Z* = 51/49) as a colorless solid. Each compound was isolated by thin layer chromatography (benzene–triethylamine = 19:1) using preparative TLC plates (Merck, Silica gel 60 F_{254}). [The plate was developed twice in the dark.] (*E*)-**31**; ^{1}H NMR ($CDCl_3$): δ 7.34–6.54 (m, 13H, Ar), 3.92 (t, J = 5.8 Hz, 2H, OCH_2), 2.63 (t, J = 5.8 Hz, 2H, NCH_2), 2.45 (q, J = 7.0 Hz, 2H, 3-H), 2.34 (s, 6H, NMe_2), 0.93 (t, J = 7.0 Hz, 3H, 4-H). (*Z*)-**31**; ^{1}H NMR ($CDCl_3$): δ 7.34–6.54 (m, 13H, Ar), 4.08 (t, J = 5.8 Hz, 2H, OCH_2), 2.74 (t, J = 5.8 Hz, 2H, NCH_2), 2.48 (q, J = 7.0 Hz, 2H, 3-H), 2.39 (s, 6H, NMe_2), 0.93 (t, J = 7.0 Hz, 3H, 4-H).

4.38. 1-(4-Iodophenyl)-1-(4-[2-dimethylaminoethoxy]phenyl)-2-phenylbut-1-ene (32)

The title compound was prepared according to the similar procedure for Section 4.37. (*E*)-**32**; ^{1}H NMR ($CDCl_3$): δ 7.27–6.47 (m, 13H, Ar), 3.86 (t, J = 5.7 Hz, 2H, OCH_2), 2.58 (t, J = 5.7 Hz, 2H, NCH_2), 2.37 (q, J = 7.0 Hz, 2H, 3-H), 2.22 (s, 6H, NMe_2), 0.85 (t, J = 7.0 Hz, 3H, 4-H). (*Z*)-**32**; ^{1}H NMR ($CDCl_3$): δ 7.27–6.47 (m, 13H, Ar), 4.02 (t, J = 5.7 Hz, 2H, OCH_2), 2.68 (t, J = 5.7 Hz, 2H, NCH_2), 2.40 (q, J = 7.0 Hz, 2H, 3-H), 2.28 (s, 6H, NMe_2), 0.85 (t, J = 7.0 Hz, 3H, 4-H).

4.39. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-[4-(2-Chloroethoxy)phenyl]-4-[3-(pivaloyloxy)phenyl]-3-phenylbut-1-ene (34)

To a suspension of hafnium tetrachloride (490 mg, 1.53 mmol) and trimethylsilyl trifluoromethanesulfonate (34.0 mg, 0.153 mmol) in β-chlorophenetole (1 mL) at room temperature with cooling by a water bath to maintain the settled temperature was added a mixture of cinnamyltrimethylsilane (583 mg, 3.06 mmol) and 3-pivaloyloxybenzaldehyde (316 mg, 1.53 mmol) in β-chlorophenetole (1 mL). The reaction mixture was stirred for 2 h at room temperature and then poured into saturated aqueous sodium hydrogencarbonate at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane–ethyl acetate = 9:1) followed by thin layer chromatography (toluene–hexane = 17:3) to afford a mixture of isomers of **34** (308 mg, 43%, (*o*-)/(*p*-) = 2:98, (3*RS*,4*RS*)/(3*RS*,4*SR*) = ca. 55:45) as a colorless oil; IR (neat): 2974, 1750, 1609, 1587, 1511, 1480, 1453, 1244, 1146, 1116, 1032, 914, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.31–6.63 (m, 13H, Ar), 5.93–5.86 (m, 1H, 2-H), 4.94–4.90 (m, 2H, 1-H), 4.24–4.05 (m, 2H, 3-H, 4-H), 4.18 and 4.07 (t, J = 6.0 Hz, 2H, OCH_2), 3.77 and 3.69 (t, J = 6.0 Hz, 2H, $ClCH_2$), 1.34 and 1.33 (s, 9H, *t*-Bu); ^{13}C NMR ($CDCl_3$): δ 176.9, 176.8, 156.6, 156.2, 151.0, 144.4, 140.3, 140.2, 136.1, 136.0, 129.8, 129.7, 129.4, 129.3, 129.0, 128.6, 128.4, 128.2, 125.7, 125.6, 121.4, 119.1, 119.0, 116.5, 114.6, 114.4, 68.0, 67.9, 56.1, 54.3, 41.9, 39.0, 27.2, 27.1; HR MS (ESI) calcd for $C_{29}H_{32}ClO_3$ $[M+H]^+$, 463.2035, found 463.2038.

4.40. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-(4-[2-Dimethylaminoethoxy]phenyl)-4-(3-hydroxyphenyl)-3-phenylbut-1-ene (36)

The coupling product **34** (421 mg, 0.909 mmol) was dissolved in a solution of dimethylamine in ethanol (30%, 3 mL). After the reaction mixture had been stirred for 8 h at 110 °C in a sealed vessel, it was cooled down to room temperature. The residue was diluted with ethyl acetate and then the solvent was removed by evaporation. The crude product was purified by thin layer chromatography (chloroform–methanol = 9:1) to afford a mixture of diastereomers of **36** (285 mg, 81%) as a colorless oil; IR (neat): 3402, 3028, 2953, 1599, 1511, 1454, 1244, 1180, 1031, 915, 775, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.31–6.47 (m, 13H, Ar), 5.91–5.78 (m, 1H, 2-H), 4.89–4.80 (m, 2H, 1-H), 4.20 (d, J = 11.5 Hz, 1H, 4-H), 4.06 and 3.87 (t, J = 5.5 and 5.3 Hz, 2H, OCH_2), 4.02 (dd, J = 7.9, 11.5 Hz, 1H, 3-H), 2.83 and 2.77 (t, J = 5.5 and 5.3 Hz, 2H, NCH_2), 2.40 and 2.37 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 156.7, 156.5, 156.3, 156.0, 144.6, 143.8, 143.5, 140.9, 136.1, 129.6, 129.3, 128.6, 128.4, 128.3, 128.1, 126.2, 125.8, 120.3, 120.0, 115.9, 115.6, 114.4, 114.2, 113.4, 64.9, 64.2, 57.8, 57.4, 56.0, 54.5, 45.2, 44.8; HR MS (ESI) calcd for $C_{26}H_{30}NO_2$ $[M+H]^+$, 388.2271, found 388.2267.

4.41. 1-(4-[2-Dimethylaminoethoxy]phenyl)-1-(3-hydroxyphenyl)-2-phenylbut-1-ene (2, droloxifene)

To a solution of potassium *tert*-butoxide (373 mg, 3.32 mmol) in DMSO (1 mL) at room temperature was added a solution of **36** (199 mg, 0.512 mmol) in DMSO (1 mL). The reaction mixture was stirred for 2 h at 50 °C and then poured into saturated aqueous ammonium chloride at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (ammoniacal chloroform–methanol = 19:1) to afford (*E*)-droloxifene ((*E*)-**2**) (97.4 mg, 49%) and (*Z*)-droloxifene ((*Z*)-**2**) (74.5 mg, 38%) as colorless solids, respectively. (*E*)-**2**; mp 161–162 °C; IR (KBr): 3422, 2979, 1608, 1592, 1509, 1470, 1444, 1287, 1243, 1173, 1116, 785 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.36–6.54 (m, 13H, Ar), 3.98 (t, J = 5.5 Hz, 2H, OCH_2), 2.74 (t, J = 5.5 Hz, 2H, NCH_2), 2.41 (q, J = 7.3 Hz, 2H, 3-H), 2.34 (s, 6H, NMe_2), 0.92 (t, J = 7.3 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 157.3, 157.2, 144.7, 144.5, 142.1, 138.8, 136.6, 132.4, 130.0, 129.4, 128.7, 127.1, 122.1, 117.1, 114.0, 113.7, 65.7, 58.5, 45.6, 29.6, 13.7; HR MS (ESI) calcd for $C_{26}H_{30}NO_2$ $[M+H]^+$, 388.2271, found 388.2269. (*Z*)-**2**; mp 146–149 °C; IR (KBr): 3422, 2953, 1664, 1606, 1591, 1508, 1445, 1286, 1236, 1174, 1022, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.22–6.55 (m, 13H, Ar), 5.70 (br, 1H, OH), 4.08 (t, J = 5.7 Hz, 2H, OCH_2), 2.76 (t, J = 5.7 Hz, 2H, NCH_2), 2.43 (q, J = 7.3 Hz, 2H, 3-H), 2.33 (s, 6H, NMe_2), 0.92 (t, J = 7.3 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 157.3, 156.2, 143.9, 143.3, 141.8, 138.0, 136.1, 130.6, 130.5, 128.8, 127.2, 125.6, 121.5, 116.7, 114.0, 113.4, 65.5, 58.0, 45.5, 29.0, 13.5; HR MS (ESI) calcd for $C_{26}H_{30}NO_2$ $[M+H]^+$, 388.2271, found 388.2280.

4.42. Isomerization of (*Z*)-droloxifene to (*E*)-droloxifene

To a solution of (*Z*)-droloxifene (73.0 mg, 0.158 mmol) in dichloromethane (2 mL) at 0 °C was added trifluoromethanesulfonic acid (140 μL, 1.58 mmol). The reaction mixture was stirred for 2 h at 0 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (ammoniacal chloroform–methanol = 19:1) to afford (*E*)-droloxifene ((*E*)-**2**) (26.7 mg, 37%) and (*Z*)-droloxifene ((*Z*)-**2**) (26.4 mg, 36%) as colorless solids, respectively.

4.43. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-[4-(2-Chloroethoxy)phenyl]-3,4-diphenylbut-1-ene (37)

To a suspension of hafnium tetrachloride (401 mg, 1.25 mmol) in β-chlorophenetole (4.25 mL) at room temperature with cooling by a water bath to maintain the settled temperature was added a mixture of benzaldehyde (133 mg, 1.25 mmol) and cinnamyltrimethylsilane (286 mg, 1.50 mmol) in β-chlorophenetole (2 mL). The reaction mixture was stirred for 4 h at room temperature and then poured into saturated aqueous sodium hydrogencarbonate at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (hexane–ethyl acetate = 10:1) to afford a mixture of diastereomers of *p*-**37** (193 mg, 43%, (3*RS*,4*SR*)/(3*RS*,4*RS*) = ca. 55:45) as a colorless oil; IR (neat): 3027, 2915, 1610, 1509, 1494, 1453, 1302, 1244, 1178, 1041, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.32–6.94 (m, 10H, Ar), 7.24 and 7.00 (d, J = 8.4 and 9.0 Hz, 2H, Ar), 6.81 and 6.59 (d, J = 8.4 and 9.0 Hz, 2H, Ar), 5.92–5.83 (m, 1H, 2-H), 4.91–4.79 (m, 2H, 1-H), 4.24 (d, J = 11.7 Hz, 1H, 4-H), 4.15 and 4.02 (t, J = 6.0 Hz, 2H, OCH_2), 4.09 (dd, J = 7.8, 11.7 Hz, 1H, 3-H), 3.74 and 3.66 (t, J = 6.0 Hz, 2H, $ClCH_2$); ^{13}C NMR ($CDCl_3$): δ 156.5, 156.1, 143.7, 143.4, 142.7, 140.9, 136.4, 136.2, 129.6, 129.3, 128.5, 128.3, 128.2, 128.1, 126.2, 126.0, 125.7, 116.0, 115.9, 114.5, 114.3, 67.9, 67.7, 56.1, 54.5, 41.9; HR MS (ESI) calcd for $C_{24}H_{27}ClNO$ $[M+NH_4]^+$ 380.1776, found 380.1768.

4.44. (3*RS*,4*RS*)/(3*RS*,4*SR*)-4-(4-[2-Dimethylaminoethoxy]phenyl)-3,4-diphenylbut-1-ene (38)

The coupling product **37** (113 mg, 0.310 mmol) was dissolved in a solution of dimethylamine in ethanol (30%, 2 mL). After the reaction mixture had been stirred for 8 h at 110 °C in a sealed vessel, it was cooled down to room temperature. The residue was diluted with ethyl acetate and then the solvent was removed by evaporation. The crude product was purified by thin layer chromatography (chloroform–methanol = 9:1) to afford a mixture of diastereomers of **38** (107 mg, 93%) as a colorless oil; IR (neat): 3027, 2942, 2821, 2772, 1610, 1509, 1494, 1453, 1249, 1177, 1032, 914, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.29–6.90 (m, 10H, Ar), 7.19 and 6.95 (d, J = 9.3 and 9.6 Hz, 2H, Ar), 6.78 and 6.57 (d, J = 9.3 and 9.6 Hz, 2H, Ar), 5.93–5.80 (m, 1H, 2-H), 4.87–4.75 (m, 2H, 1-H), 4.19 (d, J = 12.6 Hz, 1H, 4-H), 4.05 (dd, J = 8.4, 12.6 Hz, 1H, 3-H), 3.97 and 3.84 (t, J = 6.3 Hz, 2H, OCH_2), 2.65 and 2.57 (t, J = 6.3 Hz, 2H, NCH_2), 2.26 and 2.21 (s, 6H, NMe_2); ^{13}C NMR ($CDCl_3$): δ 157.5, 157.1, 144.2, 143.9, 143.2, 141.4, 136.1, 135.9, 129.9, 129.5, 128.9, 128.7, 128.6, 128.5, 128.4, 126.5, 126.4, 126.1, 116.2, 114.7, 114.5, 66.1, 66.0, 58.6, 56.5, 46.2; HR MS (ESI) calcd for $C_{26}H_{30}NO$ $[M+H]^+$ 372.2322, found 372.2319.

4.45. 1-(4-[2-Dimethylaminoethoxy]phenyl)-1,2-diphenylbut-1-ene (1, tamoxifen)

To a solution of potassium *tert*-butoxide (257 mg, 2.29 mmol) in DMSO (1 mL) at room temperature was added a solution of **38** (83.7 mg, 0.225 mmol) in DMSO (1 mL). The reaction mixture was stirred for 1 h at room temperature and then saturated aqueous ammonium chloride was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (dichloromethane–methanol = 9:1) to afford a mixture of geometric isomers of **1** (63.3 mg, 76%, *E*/*Z* = 49:51) as a colorless oil. Each compound was isolated by preparative reversed-phase HPLC (methanol–0.01 M HCl = 7:3) or thin layer chromatography (benzene–triethylamine = 19:1) using preparative TLC plates (Merck, Silica gel $60F_{254}$). [The plate was developed twice in the dark.] (*Z*)-**1**; mp 94–95 °C; IR (KBr): 1458, 1250, 1034 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.29–6.82 (m, 10H, Ar), 6.69 (d, J = 8.7 Hz, 2H, Ar), 6.48 (d, J = 8.7 Hz, 2H, Ar), 3.87 (t, J = 5.7 Hz, 2H, OCH_2), 2.60 (t, J = 5.7 Hz, 2H, NCH_2), 2.38 (q, J = 7.5 Hz, 2H, 3-H), 2.23 (s, 6H, NMe_2), 0.85 (t, J = 7.5 Hz, 3H, 4-H); ^{13}C NMR ($CDCl_3$): δ 156.6, 143.8, 142.4, 141.3, 138.2, 135.6, 131.2, 129.7, 129.4, 128.1, 127.8, 126.5, 126.0, 113.3, 65.5, 58.2, 45.8, 28.9, 13.5.

4.46. HL-60 human acute promyelocytic leukemia

The HL-60 cells were supplied by the Cell Resource Center for Biomedical Research, Tohoku University (Sendai, Japan). The cells were maintained at 37 °C with 5% CO_2 in RPMI 1640 medium supplemented with kanamycin sulfate (64 mg/L), 2-mercaptoethanol (3.5 μL/L), sodium bicarbonate (2 g/L), and heat-inactivated 10% (v/v) fetal bovine serum. The cells were diluted with the medium to the constant concentrations of 4.0×10^5 cells/mL.

4.47. MTT assay

HL-60 cells were incubated in 96-well plates at 37 °C, and then, 11 μL of 20 mg/mL 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT; Sigma) in phosphate-buffered saline (PBS) was added to each well. The plates were incubated at 37 °C for 1 h. The plates were centrifuged at 350*g* for 5 min, the supernatants were

discarded, and 100 μL of DMSO was added to dissolve the MTT formazan. The absorbance of each well was measured using a microplate reader at 570 nm. The percentage of cell viability was taken as the percent absorbance at 570 nm for the SERMs-treated cells and control.

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