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New Practical Synthesis of Panomifene. The Effect of 2-Trifluoromethyl Substituent on the Stereoselectivity of Dehydration of 1,1,2-Triarylethanols.

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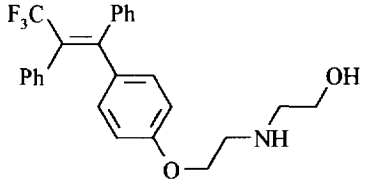
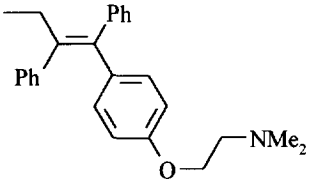
Abstract: Highly stereoselective eliminations were achieved by acid-catalysed dehydration of 1-(4-alkoxy)-3,3,3-trifluoro-1,2-diphenylpropan-1-ols (**10, 11, 15**). The influence of the trifluoromethyl group on the stereochemistry of the elimination has been discussed. The observed high stereoselectivity has been applied to give a new, practical synthesis of antiestrogenic drug panomifene (**1**).

INTRODUCTION

Panomifene (**1**, EGIS-5650, GYKI-13504)[1] is a follow-up molecule of tamoxifen (**2**), the well known triarylethylene type antiestrogenic drug for the treatment of mammary tumours. In the patented synthesis of panomifene the olefin was prepared by dehydrogenation of the corresponding alkane with dichlorodicyanobenzoquinone[2].



1 (panomifene)
(GYKI-13504, EGIS-5650)

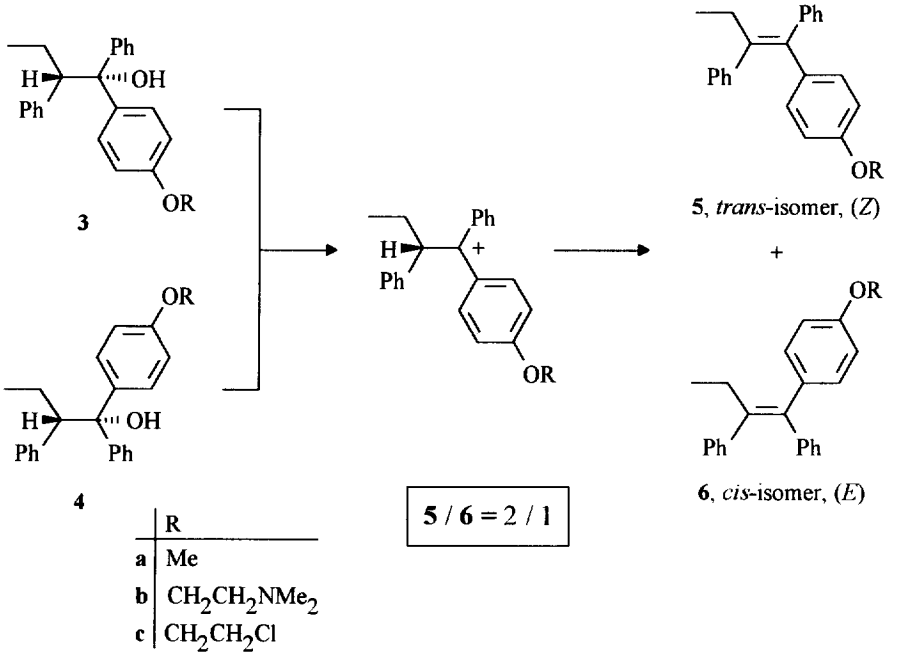


2 (tamoxifen)

We report now an improved synthesis of panomifene constructing the double bond by dehydration of the corresponding triarylethanol. A similar method is well elaborated for the synthesis of tamoxifen and related compounds[3], however, the presence of the trifluoromethyl group in panomifene has raised several new synthetic and stereochemical problems. The practical synthesis of some trifluoromethylated building blocks required for the new construction of panomifene has been published recently[4,5].

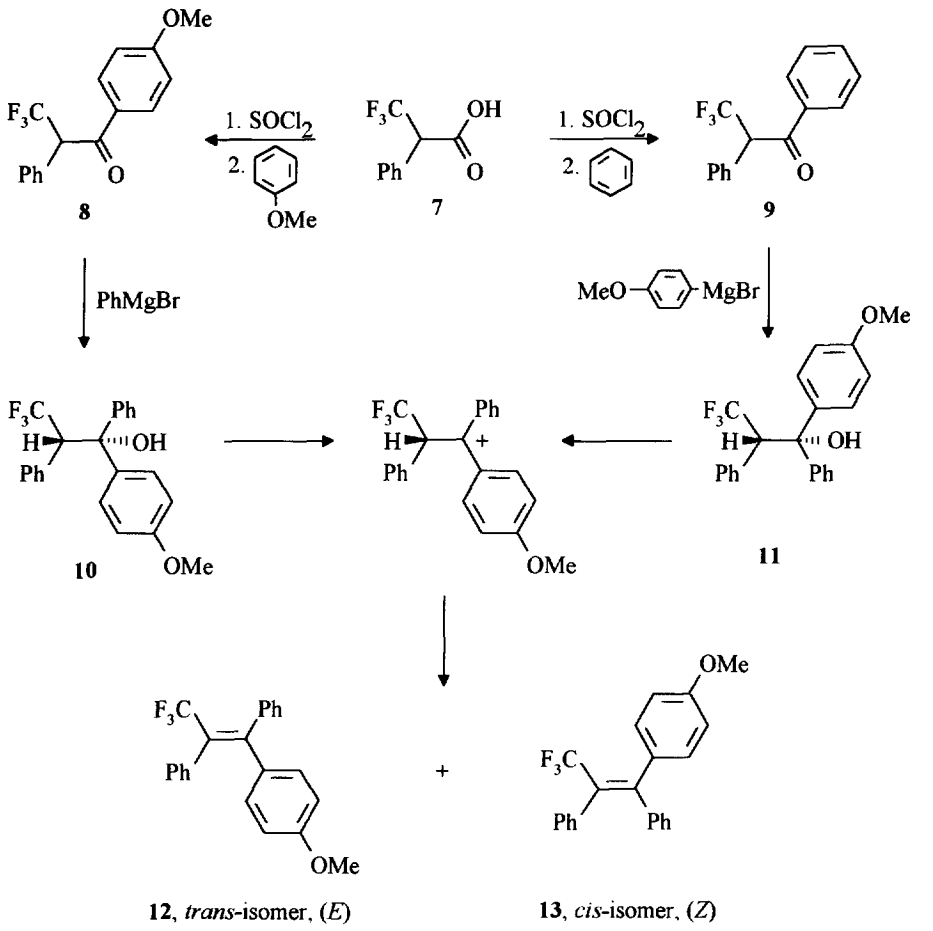
RESULTS AND DISCUSSION

In connection with the synthesis of tamoxifen (**2**) it has been reported that acid-catalysed dehydration of either diastereomer of 1-(4-methoxyphenyl)-1,2-diphenylbutan-1-ols (**3a, 4a**) affords a 2:1 mixture of the *trans* and *cis* isomers[6] of 1-(4-methoxyphenyl)-1,2-diphenylbut-1-enes (**5a** and **6a**) *via* a common carbenium ion intermediate (Scheme 1). Changes in the alkoxy side-chain of the substrate do not influence the stereochemical result of the elimination as shown in the case of ethanols **3b** and **3c**[7].



Scheme 1

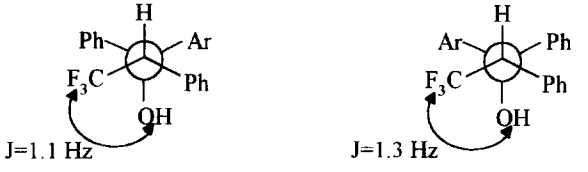
In order to study the effect of the trifluoromethyl group on the stereochemical outcome of a similar dehydration reaction, we synthesized the diastereomeric 3,3,3-trifluoro-1-(4-methoxyphenyl)-1,2-diphenyl-propan-1-ols (**10** and **11**). Friedel-Crafts acylation of the corresponding arenes with α-(trifluoromethyl)phenyl-acetyl chloride (obtained from the corresponding acid **7**[4]) afforded ketones **8** and **9**. The tertiary alcohol **10** was prepared by the reaction of ketone **8** with phenylmagnesium bromide and its diastereomer **11** from ketone **9** with (4-methoxyphenyl)magnesium bromide (Scheme 2). The Grignard reactions proceeded selectively (> 98 %) in accordance with Cram's rule[8], as reported for similar reactions[7]. Structures of the single diastereomers have been determined by ^{1}H NMR spectroscopy as described in the literature for similar compounds[9].



Scheme 2

Combined conformation and configuration analyses of diastereomeric pairs of 1,1,2-triarylethanes and 1,1,2-triarylethanols led to the conclusion that the predominant conformer of these compounds contains the less gauche relation between the four bulky substituents. The predominant conformers of diastereomers **10** and **11** are depicted on Scheme 3. In our case the structure of the predominant rotamers is supported by an additional evidence: a through-space interaction between the trifluoromethyl and the hydroxyl groups resulting in a quadruplet multiplicity (J =1.1 and 1.3 Hz) of the signal of the hydoxyl proton has been observed. As the bulky benzene rings on the neighbouring carbon atoms are about parallel (propeller-like arrangement), their mutual anisotropic effect results in a diamagnetic shift of the signal of aromatic protons. Therefore, a diamagnetic shift of the signal of the p-substituted benzene ring can be expected only in the *1R,2S (1S,2R)*

diastereomer. Comparing the ^{1}H NMR spectra of compounds **10** and **11**, a diamagnetic shift of the para-substituted benzene ring has been observed in the case of compound **10** indicating *1R,2S (1S,2R)* configuration of the chiral centers.

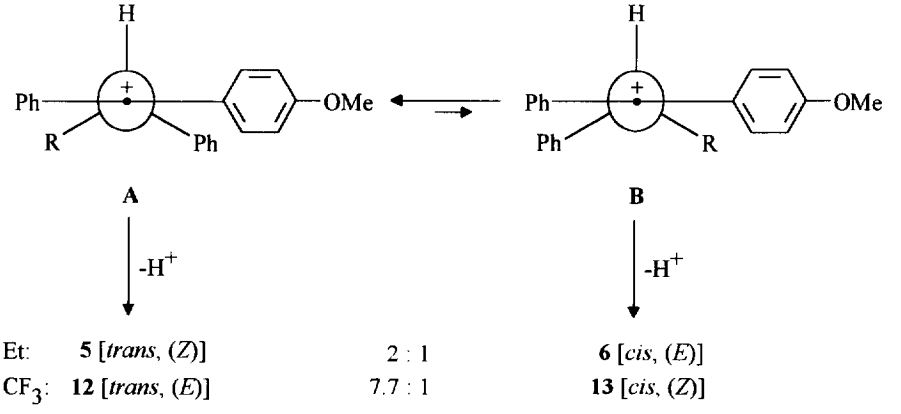


10 (*1R,2S*) **11** (*1S,2S*)

Ar = 4-MeO-C_6H_4

Scheme 3

Dehydration of tertiary alcohols **10** and **11** by hydrochloric acid in ethanol afforded practically the same 7.7:1 and 7.6:1 ratios of *trans* (**12**) and *cis* (**13**) isomers of the olefinic product indicating the presence of a common carbenium ion intermediate in the course of the eliminations. That is, much higher stereoselectivity was now observed than in the elimination reactions of triarylethanols **3** and **4** . The structure of the geometrical isomers could be easily assigned on the basis of literary data[10,11]. In the spectra of the *cis* isomer the signals of all three aromatic ring protons overlap, whereas in the spectra of their *trans* pairs the AA'XX' multiplets of the para-disubstituted ring protons partly or wholly separate at lower chemical shifts.

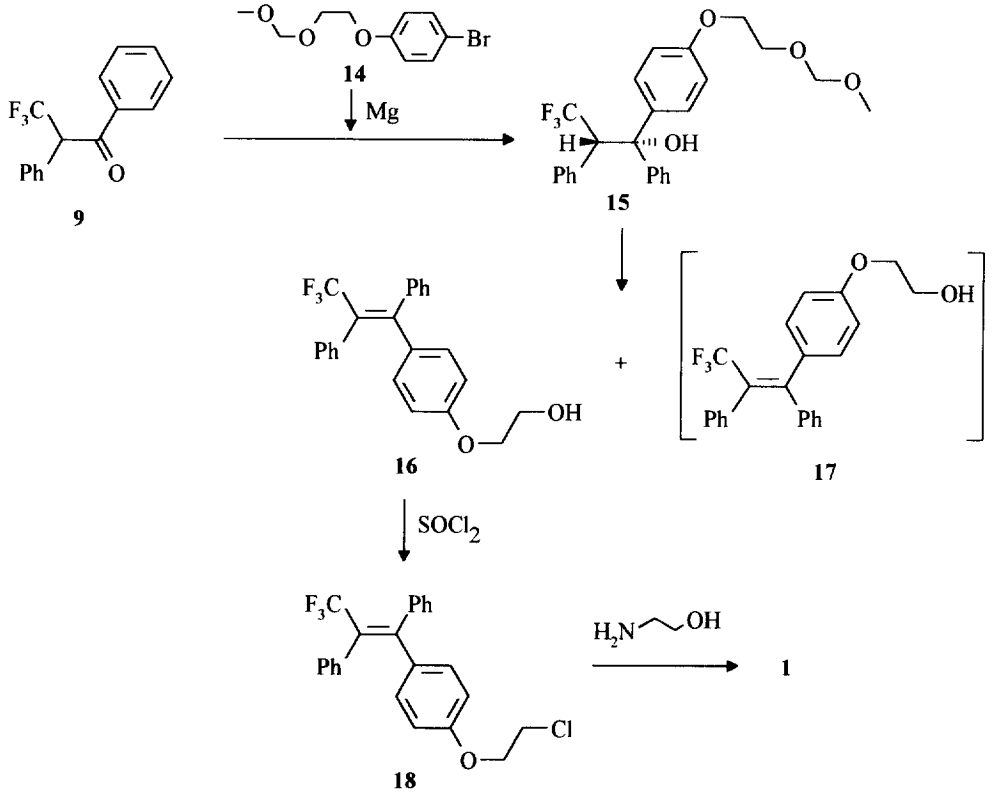


Scheme 4

The stereoselectivity of the dehydration of alcohols **3** and **4** has been explained by the enhanced stability of conformer **A** when compared with conformer **B** of the corresponding carbenium ion (Scheme 4). Among the substituents of the cationic center the p-alkoxyphenyl group is expected to be the most effective at stabilizing a carbocation. In conformer **A**, the stabilization of the carbenium ion by the oxygen bearing ring is assisted by an

electron-donating field effect of the adjacent 2-phenyl group. The increased stereoselectivity observed in the dehydration reactions of alcohols **10** and **11** can be explained by the effect of the trifluoromethyl group on the population of the rotational conformers of the intermediate carbenium ion. Replacement of the ethyl by the electron-withdrawing trifluoromethyl group decreases the stabilization of conformer **B** changing the population of rotational conformers much more in favour of conformer **A**.

In spite of the favourable result of the elimination reaction compound **12** was not a suitable intermediate of panomifene (**1**), because acidic demethylation of methoxy group afforded a 1:1 mixture of the corresponding *trans* and *cis p*-hydroxy derivatives as a result of the known facile isomerization of such phenols[12]. In order to avoid this problem ketone **9** was reacted with Grignard reagent obtained from compound **14** and the resulting alcohol (**15**) was dehydrated (Scheme 5). The Grignard reaction proceeded according to Cram's rule as expected and the dehydration afforded a 7.9 :1 mixture of olefins **16** and **17** from which the required isomer **16** could be crystallized with excellent yield. Chlorination of alcohol **16** followed by ethanolamine treatment of compound **18** gave panomifene **1**.



Scheme 5

EXPERIMENTAL SECTION

The melting points were determined on a Büchi 535 apparatus and are uncorrected. The IR spectra were recorded on an Aspect 2000 computer controlled Bruker IFS-113v vacuum optic FT spectrometer, using KBr pellets for solids or liquid films. The NMR spectra were run on a Bruker WM-250 FT, or a Varian Gemini-200, or a Varian Unity Inova 400 spectrometer.

1-Methoxy-4-(3,3,3-trifluoro-2-phenylpropionyl)-benzene (8): 3,3,3-Trifluoro-2-phenylpropionic acid (9.5 g, 0.046 mol) was refluxed with thionyl chloride (50 ml) for 1 h and evaporated. The residue was dissolved in anisole (22.8 g, 23 ml, 0.21 mol) and aluminium chloride (12.2 g, 0.09 mol) was added. The mixture was stirred at 75°C for 1.5 h. After cooling it was poured on ice (80 g), extracted with dichloromethane (3 x 50 ml) and evaporated. The residual oil was chromatographed on silica gel column (eluent : toluene) to give compound **8** (2.4 g, 22 %): mp 62-64 °C (petroleum ether, bp 80-100 °C); IR (KBr) 1681 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* 9.1 Hz), 7.50-7.30 (5H, m), 6.86 (2H, d, *J* 8.9 Hz), 5.24 (1H, q, $^3J_{HF}$ 8.3 Hz), 3.80 (3H, s); ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 189.7, 164.1, 131.2, 130.1, 129.8, 129.2, 129.1, 128.3, 124.4 (q, $^1J_{CF}$ 280.2 Hz), 114.0, 56.0 (q, $^2J_{CF}$ 26.4 Hz), 53.3. Anal. Calcd for $C_{16}H_{13}F_3O_2$ (294.28): C, 65.30; H, 4.45. Found: C, 65.13; H, 4.58.

3,3,3-Trifluoro-2-phenylpropiophenone (9): 3,3,3-Trifluoro-2-phenylpropionic acid (10.2 g, 0.05 mol) was refluxed with thionyl chloride (50 ml) for 1 h and evaporated. The solution of the residual oil in benzene (10 ml) was added drop by drop into a mixture of aluminium chloride (8.7 g, 0.065 mol) and benzene (12 ml) at 10-15°C. After stirring for 1 h at ambient temperature the mixture was poured on ice (60 g) and extracted with chloroform (3 x 50 ml), washed with saturated aqueous sodium hydrogen carbonate (15 ml), dried ($MgSO_4$) and evaporated. Rescrystallization from petroleum ether (bp 80-100 °C) gave compound **9** (9.3 g, 70 %) as colourless crystals: mp 81-82 °C; IR (KBr) 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.92-7.88 (2H, m); 7.54-7.35 (8H, m); 5.30 (1H, q, $^3J_{HF}$ 8.2 Hz). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 191.2, 135.3, 133.8, 129.8, 129.6, 129.3, 129.2, 128.8, 128.7, 124.3 (q, $^1J_{CF}$ 280.2 Hz), 56.4 (q, $^2J_{CF}$ 26.6 Hz); Anal. Calcd for $C_{15}H_{11}F_3O$ (264.25): C, 68.18; H, 4.20; F 21.57. Found: C, 68.07; H, 4.17; F, 21.42.

***(1RS,2SR)*-3,3,3-Trifluoro-1-(4-methoxyphenyl)-1,2-diphenylpropan-1-ol (10):** A solution of 4-(3,3,3-trifluoro-2-phenylpropionyl)methoxybenzene (**8**, 1.00 g, 3.4 mmol) in tetrahydrofuran (4 ml) was added to a solution of phenylmagnesium bromide [prepared from brombenzene (1.60 g, 10.2 mmol) and magnesium (0.25 g, 10.3 mmol) in tetrahydrofuran (12 ml)] at 20-25°C. After 1 h at 25 °C the resulting mixture was poured into cooled (10 °C) dilute hydrochloric acid (0.5 M, 50 mL), extracted with dichloromethane

(2 x 25 ml). The combined organic phases were washed with water (25 mL) evaporated and the residue chromatographed on silica gel (type: Kieselgel 60, 0.063-0.200 mm, 120 g). Elution with toluene gave compound **10** (0.42 g, 33 %): mp 128-129 °C (2-propanol); IR (KBr) 3569 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.65 (2H, d, *J* 7.6 Hz), 7.5-7.1 (10H, m), 6.59 (2H, d, *J* 8.9 Hz), 4.59 (1H, q, $^3J_{HF}$ 9.2 Hz), 3.62 (3H, s), 2.82 (1H, q, $^5J_{HF}$ 1.1 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.9, 145.5, 136.8, 132.8, 131.1, 128.2, 128.0, 127.9, 127.1, 126.7, 126.3 (q, $^1J_{CF}$ 282.7 Hz), 125.3, 113.1, 78.9, 57.3 (q, $^2J_{CF}$ 22.9 Hz), 55.0. Anal. Calcd for $C_{22}H_{19}F_3O_2$ (372.40): C, 70.96; H, 5.14. Found: C, 71.11; H, 5.19 .

***(1RS,2RS)*-3,3,3-Trifluoro-1-(4-methoxyphenyl)-1,2-diphenylpropan-1-ol (11):** A solution of 3,3,3-trifluoro-2-phenylpropiophenone (**9**, 2.01 g, 7,6 mmol) in tetrahydrofuran (8 ml) was added to a solution of p-methoxyphenylmagnesium bromide [prepared from (p-methoxy)bromobenzene (4.26 g, 22.8 mmol) and magnesium (0.55 g, 22.6 mmol) in tetrahydrofuran (23 ml)] at 20-25°C. After 1 h at 25 °C the resulting mixture was poured into cooled (10 °C) dilute hydrochloric acid (0.5 M, 100 ml) and extracted with dichloromethane (2 x 50 ml). The combined organic phases were washed with water (50 ml), evaporated and the residue chromatographed on silica gel (type: Kieselgel 60, 0.063-0.200 mm, 260 g). Elution with toluene gave compound **11** (1.12 g, 40 %): mp 92-93 °C (2-propanol); IR (KBr) 3434 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* 8.7 Hz), 7.5-6.9 (10H, m), 6.88 (2H, d, *J* 8.7 Hz), 4.58 (1H, q, $^3J_{HF}$ 9.2 Hz), 3.77 (3H, s), 2.81 (1H, q, $^5J_{HF}$ 1.3 Hz). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 158.6, 144.8, 137.4, 132.7, 131.1, 127.9, 127.8, 127.7, 126.7, 126.4, 126.4 (q, $^1J_{CF}$ 283.3 Hz), 125.3, 113.5, 78.9, 57.1 (q, $^2J_{CF}$ 23.1 Hz), 55.2. Anal. Calcd for $C_{22}H_{19}F_3O_2$ (372.40): C, 70.96; H, 5.14 . Found: C, 70.74; H, 5.20.

(*E*)- and (*Z*)-3,3,3-Trifluoro-1-(4-methoxyphenyl)-1,2-diphenylpropene (12 and 13): Triarylethanol **11** (1.00 g, 2.7 mmol) was refluxed in the mixture of ethanol (10 ml) and concentrated hydrochloric acid (2 ml) for 30 min. The solution was poured into water (20 ml) and extracted with dichloromethane (2 x 10 ml). The combined organic phases were dried ($MgSO_4$) and evaporated to give 0.92 g (97 %) colourless oil, which is a 7.7:1 mixture of **12** [*trans*, (*E*)] and **13** [*cis*, (*Z*)] olefines as determined by ^1H NMR measurements on the basis of the intensity ratio of the signals corresponding to the aromatic and methoxy protons of **12** [^1H NMR δ 6.81 (2H), 6.55 (2H), 3.67 (3H)] and **13** [^1H NMR δ 7.10-7.00 (3H), 6.95-6.85 (4H), 3.83 (3H)], respectively. The residual oil was recrystallized from methanol (11 ml) to give olefine **12** (0.4 g, 42 %) as colourless crystals: mp 77.5-78 °C; IR (KBr) 1607 cm^{-1}; ^1H NMR(200 MHz, $CDCl_3$) δ 7.4-7.2 (10 H, m), 6.81 (2H, d, *J* 8.8 Hz), 6.55 (2H, d, *J* 8.8 Hz), 3.67 (3H, s) . ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 158.8, 149.9 (q, $^3J_{CF}$ 3.4 Hz), 141.0, 135.5, 133.3, 131.6, 131.4, 128.7 (q, $^3J_{CF}$ 2.2 Hz), 128.1, 128.0, 127.8, 127.8, 123.8 (q, $^1J_{CF}$ 275.6 Hz), 113.1, 55.0. Anal. Calcd for $C_{22}H_{17}F_3O$ (354.38): C, 74.57; H, 4.84 . Found: C, 74.08; H, 4.85.

A small sample of olefine **13** was obtained by repeated column chromatography and preparative TLC: IR (KBr): 1609 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.3-7.15 (7 H, m), 7.10-7.0 (3H, m) 6.95-6.85 (4H, m), 3.83 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.4, 150.3 (q, $^3J_{CF}$ 3.0 Hz), 141.4, 135.3, 132.9, 131.5, 130.1 (q, $^3J_{CF}$ 2.3 Hz), 129.8, 127.8, 127.7, 127.6, 127.3, 123.7 (q, $^1J_{CF}$ 275.4 Hz), 113.4, 55.2.

4-[2-(Methoxymethoxy)-ethoxy]bromobenzene (14): Phosphorus pentoxide (101 g, 0.71 mol) was added to a mixture of 2-(4-bromophenoxy)-ethanol (7.5 g, 0.035 mol)[13] and formaldehyde dimethyl acetal (250 ml, 177 g, 2.33 mol) in chloroform (150 ml) maintaining the temperature at 20-25°C. After stirring for 45 min the mixture was poured into an aqueous sodium carbonate solution (10 %) at 10-15°C. It was extracted with chloroform (6 x 200 ml), the combined organic layers were extracted with brine, dried ($MgSO_4$) and evaporated. Fractional distillation of the residue *in vacuo* gave compound **14** (4.0 g, 44 %): bp 154-160°C (4 Hgmm); n_D^{25} 1.5286; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* 8.9 Hz), 6.81 (2H, d, *J* 9.1 Hz), 4.71 (2H, s), 4.11 (2H, t, *J* 4.4 Hz), 3.9 (2H, t, *J* 4.5 Hz), 3.39 (3H, s). Anal. Calcd for $C_{10}H_{13}BrO_3$ (261.12): C, 45.39; H, 5.02; Br 30.60. Found: C, 45.22; H, 4.94; Br 30.37.

***(1RS,2RS)*-3,3,3-Trifluoro-1-{4-[2-methoxymethoxy)ethoxy]phenyl}-1,2-diphenylpropan-1-ol (15):** A solution of 3,3,3-trifluoro-2-phenylpropiophenone (**9**, 13.5 g, 0.051 mol) in tetrahydrofuran (25 ml) was added to the Grignard reagent, prepared from 4-[2-(methoxymethyloxy)ethoxy]bromobenzene (**14**, 40.0 g, 0.153 mol) and magnesium (3.72 g, 0.153 mol) in tetrahydrofuran (75 ml), at 0-5 °C. After stirring for 2 h at 0-5 °C the reaction mixture was quenched with cold 1 M aqueous hydrochloric acid solution (400 ml) and extracted with dichloromethane (2 x 60 ml). The combined organic phases were washed with water (3 x 60 ml) dried ($MgSO_4$) and evaporated. The residual oil was extracted with hot hexane (3 x 300 ml). The product precipitated from the hexane solution overnight at ambient temperature was recrystallized two times from 2-propanol to afford compound **15** (13.4 g, 59 %): mp 100-102°C ; IR (KBr) 3412 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* 8.9 Hz), 7.40-6.95 (10 H, m), 6.91 (2H, d, *J* 8.9 Hz), 4.69 (2H, s), 4.57 (1H, q, $^5J_{HF}$ 9.2 Hz), 4.15-4.10 (2H, m), 3.90-3.85 (2H, m), 3.38 (3H, s), 2.85 (1H, q, $^5J_{HF}$ 1.3 Hz). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 157.9, 144.9, 137.8, 132.8, 131.2, 128.0, 127.9, 127.8, 126.8, 126.4, 126.4 (q, $^1J_{CF}$ 282.9 Hz), 125.5, 114.2, 96.6, 78.9, 67.2, 65.9, 57.1 (q, $^2J_{CF}$ 22.9 Hz), 55.2. Anal. Calcd for $C_{25}H_{25}F_3O_4$ (446.48): C, 67.26; H, 5.64. Found: C, 67.44; H, 5.64.

***(E)*-3,3,3-Trifluoro-1-[4-(2-hydroxyethoxy)phenyl]-1,2-diphenylpropene (16):** A solution of *(1RS,2RS)*-3,3,3-trifluoro-1-{4-[2-methoxymethyloxy)ethoxy]phenyl}-1,2-diphenylpropan-1-ol (**15**, 7.0 g, 15.7 mmol) in the mixture of methanol (70 ml) and concentrated hydrochloric acid (14 ml) was refluxed for 1 h. The reaction mixture was diluted with water (21 ml) and left to crystallize for 1 h at 0 °C. The crystals were filtered and

washed with water to give compound **16** (5.1 g, 84 %): mp 119-120°C (hexane); IR (KBr) 3353, 1607, 1095 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45-7.10 (10H, m), 6.81(2H, d, *J* 8.8 Hz), 6.55 (2H, d, *J* 8.8 Hz), 3.95-3.75 (4H, m), 2.06 (1H, bs); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 157.8, 149.8 (q, $^3J_{CF}$ 3.4 Hz), 140.8, 135.3, 133.7, 131.5, 131.4, 128.6 (q, $^3J_{CF}$ 2.2 Hz), 128.4 (q, $^2J_{CF}$ 28.6 Hz), 128.0, 127.9, 127.8, 127.7, 123.7 (q, $^1J_{CF}$ 275.6 Hz), 113.6, 68.9, 61.0. Anal. Calcd for $C_{23}H_{19}F_3O_2$ (384.41): C, 71.87; H, 4.98; F, 14.83. Found: C, 71.91; H, 4.94; F, 15.12.

***(E)*-3,3,3-Trifluoro-1-[4-(2-chloroethoxy)phenyl]-1,2-diphenylpropene (18):** A solution of *(E)*-3,3,3-trifluoro-1-[4-(2-hydroxyethoxy)phenyl]-1,2-diphenylpropene (**16**, 4.00 g, 10.4 mmol) in thionyl chloride (12 ml) and pyridine (0.2 ml) was refluxed for 1 h. After evaporation of thionyl chloride, the residue was recrystallized from methanol (58 ml) to afford compound **18** (3.73 g, 89 %): mp 108-109°C; IR (KBr) 1608 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.45-7.10 (10H, m), 6.82 (2H, d, *J* 8.8 Hz), 6.56 (2H, d, *J* 8.8 Hz), 4.06 (2H, t, *J* 5.9 Hz), 3.69 (2H, t, *J* 5.9 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 157.4, 149.8 (q, $^3J_{CF}$ 3.4 Hz), 140.8, 135.3, 134.0, 131.5, 131.5, 128.7 (q, $^3J_{CF}$ 2.2 Hz), 128.6 (q, $^2J_{CF}$ 28.8 Hz), 128.1, 128.0, 127.9, 127.8, 123.8 (q, $^1J_{CF}$ 275.7 Hz), 113.8, 67.7, 41.6. Anal. Calcd for $C_{23}H_{18}ClF_3O$ (402.85): C, 68.58; H, 4.50; Cl, 8.80. Found: C, 69.00; H, 4.53; Cl, 8.49.

***(E)*-3,3,3-Trifluoro-1-{4-[2-(2-hydroxyethylamino)ethoxy]phenyl}-1,2-diphenylpropene (panomifene, 1):** A mixture of *(E)*-3,3,3-Trifluoro-1-[4-(2-chloroethoxy)phenyl]-1,2-diphenylpropene (**18**, 4.03 g, 10 mmol), 2-aminoethanol (6.1 g, 100 mmol) and 2-methoxyethanol (10 ml) was refluxed for 1 h. It was diluted with dichloromethane (80 ml) and washed with 4 % aqueous NaOH solution (15 ml) and water (6 x 25 ml), dried ($MgSO_4$) and evaporated. Crystallization of the residual oil from ethyl acetate afforded 3.53 g (83 %) panomifene (**1**): mp 96-98°C, (lit.[2] mp 96-98 °C); IR (KBr) 1607, 1097 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.40-7.15 (10H, m), 6.80 (2H, d, *J* 8.8 Hz), 6.53 (2H, d, *J* 8.8 Hz), 3.89 (2H, t, *J* 5.0 Hz), 3.59 (2H, t, *J* 5.0 Hz), 2.89 (2H, t, *J* 5.0 Hz), 2.74 (2H, t, *J* 5.0 Hz), 2.38 (2H, bs). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 157.9, 149.8 (q, $^3J_{CF}$ 3.3 Hz), 140.7, 135.3, 133.4, 131.4, 131.3, 128.5 (q, $^3J_{CF}$ 2.1 Hz), 128.3 (q, $^2J_{CF}$ 28.6 Hz), 127.9, 127.8, 127.7, 127.7, 123.7 (q, $^1J_{CF}$ 275.7 Hz), 113.5, 66.9, 60.5, 51.0, 48.1. Anal. Calcd for $C_{25}H_{24}F_3NO_2$ (427.48): C, 70.44; H, 5.66; N, 3.28. Found: C, 70.70; H, 5.50; N, 3.22.

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