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Synthesis and Biological Evaluation of Cyclopropyl Analogs of the Antiestrogen MER 25

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In an effort to prepare effective nonsteroidal antiestrogens without intrinsic estrogenicity and with greater antagonism than the triarylethylenes (tamoxifen), four (*E*)- and (*Z*)-1,1-dichloro-2-phenyl-2-[4-(2-diethylaminoethoxy)phenyl]-3-(4-methoxyphenyl)cyclopropane analogs of the antiestrogen MER 25, of which two of the compounds had a 4-heptafluorotolyl group in the α-ring, were prepared. The (*E*)- and (*Z*)-gem-dichlorotriarylcyclopropanes were tested for their ability to inhibit the growth of estrogen receptor (ER)-positive MCF-7E3 and ER-negative MDA-MB-231 human breast cancer cells in culture. All compounds, except **18E,** exhibited a statistically significant ($P < 0.01$) reduction in estradiol-stimulated growth (antiestrogenic activity) at 1.0 μM concentration in the MCF-7E3 cells: **11Z** (88%), **11E** (106%), **18Z** (65%), and the test compounds **7A(Z)** (85%), **7A(E)** (53%), MRL 37 (91%), MER 25 (71%), and ICI 182,780 (102%). Inhibition of estradiol-stimulated growth at concentrations lower than 1.0 μM was demonstrated by **11E,** MER 25, and ICI 182,780. Compound **11E** produced weak inhibition at 0.1 nM (19%) and nearly complete inhibition (79–112%) over a concentration range of 1.0 to 100 nM. MER 25 produced inhibition of estradiol-stimulated growth at 1.0 (39%), 10 (102%), and 100 nM (100%) concentrations. ICI 182,780 completely inhibited estrogen-stimulated growth from 0.1 nM to 1.0 μM concentrations. Two compounds exhibited estrogenic activity: **18E** (from 1.0 nM to 1.0 μM concentrations) and MER 25, which had antiestrogenic action at the lower concentration ranges, but exhibited estrogenic properties at 100 nM to 1.0 μM concentrations. None of the test compounds or standards were active in the MDA-MB-231 cell line at the concentrations studied (0.01 nM to 1.0 μM). In addition, none of the compounds inhibited cell growth below control in the MCF-7E3 cell line. The results from both cell lines suggest that the test compounds are devoid of any antitumor properties, which is thought to be mediated through a nonreceptor mechanism. Analog **11E** has the potential to be useful in the treatment of hormone-responsive breast cancer.

Key Words: synthesis; biological evaluation; gem-dichlorocyclopropanes; MCF-7E3; MDA-MB-231; antiestrogen; breast cancer.

INTRODUCTION

Nonsteroidal antiestrogens (competitive estrogen antagonists) represent a major advance in the treatment of hormone-dependent breast cancer in postmenopausal females and in the prevention and therapy of the disease in premenopausal women.

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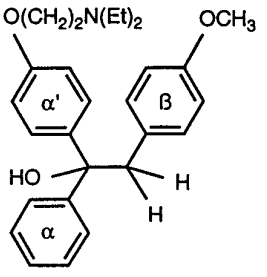
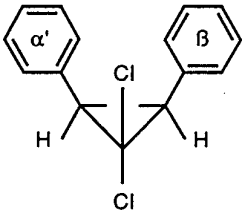
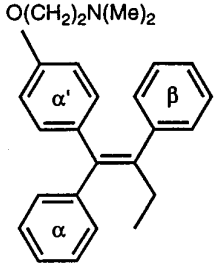


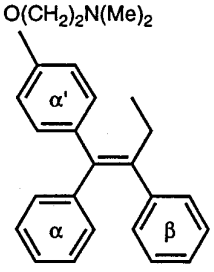
MER 25



Analog II



Z-Tamoxifen



E-Tamoxifen

SCHEME 1

The representative of this class is tamoxifen (TAM), the only clinically available adjuvant with surgery in the treatment of primary breast cancer in postmenopausal women (*1*, *2*). Because of the partial agonist activity found in TAM and other antiestrogens, workers have synthesized both nonsteroidal (*3–7*) and steroidal (*8–15*) antiestrogens in an attempt to find pure antiestrogens which would compete effectively with estradiol or act as effective agents in the treatment of estrogen receptor (ER)-negative breast tumors and in TAM-resistant disease.

A common structural feature in the triphenylethylenes (TPE), such as TAM, is the presence of three aryl rings with a central ethylenic bridge. Structure–activity relationships and X-ray crystallographic data of tamoxifen and its analogs (*16*, *17*) have demonstrated that the *Z* arrangement of the α' and β rings is essential for antiestrogenic activity. In addition, only the *Z* diastereomers of cyclopropane derivatives prepared in our laboratory have exhibited antiestrogenic activity (Scheme 1) (*6*, *7*).

MER 25, also known as ethamoxytriphetol, the first nonsteroidal antiestrogen, was found to inhibit estrogen in all species of animals tested (*18*). Crystal structure determination (*19*) and conformational studies of MER 25 (*20*) were performed to identify the preferred conformation of the molecule in various energy states. Molec-

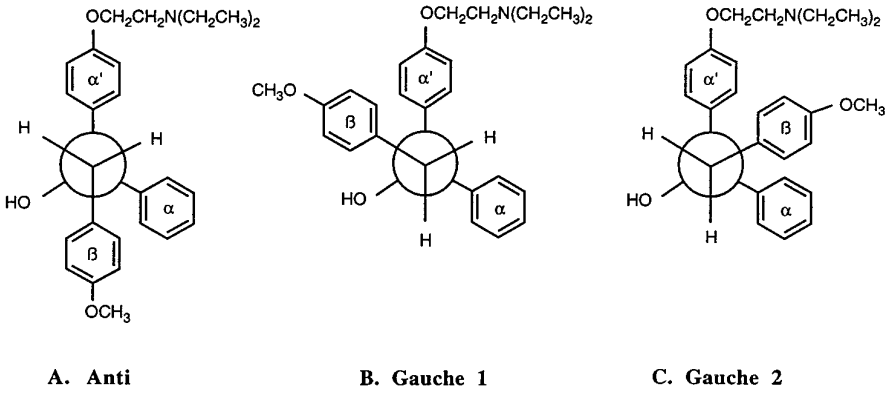
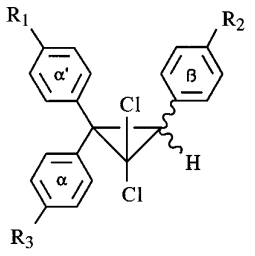


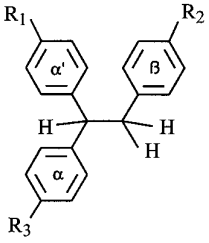
FIG. 1. Newman projection formulas of MER 25.

ular mechanics calculations and steric energy profile searches identified three low-energy conformers: anti, gauche$_1$, and gauche$_2$ (Fig. 1), with the anti conformation as the global minimum. The second-lowest energy conformer of MER 25 is the gauche$_1$ conformation, which closely resembles the antiestrogenic *Z* isomer of tamoxifen. Difference decoupling and NOE NMR studies of MER 25 in CD_3OD at temperatures ranging from -60 to 50°C at 300 MHz likewise demonstrated that the molecule existed in the anti conformation. Since the molecular mechanics calculations have shown that the gauche conformation is the second most stable conformer of MER 25, it is possible that the anti conformation could be perturbed into the gauche conformation when approaching and attaching to the receptor, thereby producing antiestrogenic action.

Previous reports from our laboratory (*3*, *6*, *21*) have demonstrated that the introduction of a dichlorocyclopropyl moiety in place of an olefinic double bond prevents the isomerization seen with the TPE antiestrogens. The incorporation of this moiety into a structure resembling MER 25 provided diastereomers which effectively fixed the anti and gauche conformations of the molecule into nonisomerizable *Z* and *E* diastereomers. The biological activity of each diastereomer was evaluated to discern which isomer was associated with the antiestrogenic activity.

The *p*-methoxy group in the β ring of MER 25 distinguishes the antiestrogen from the many tamoxifen-related compounds, which possess various substitutions only on the α and α' rings. In addition to the stereochemistry of MER 25, the *p*-methoxy group was of interest to us in the development of more effective antiestrogens. Computer-aided molecular studies (*20*) revealed that the β ring of MER 25 was directed toward the D ring in estradiol such that the *p*-methoxyphenyl group was in the vicinity of the 17-β-hydroxy group when MER 25 was in the gauche$_1$ conformer, but not when in the anti conformer (Fig. 1). To evaluate the effect of the β-ring *p*-methoxy group on antiestrogenic activity, two compounds previously synthesized in our laboratory, **7A(Z)** and **7A(E)** (Fig. 2), which resemble **11Z** and **11E** (Fig. 2), but without the methoxy group, were evaluated in the *in vitro* biological





11Z and **E** $R_1 = O(CH_2)_2N(CH_2CH_3)_2$; $R_2 = OCH_3$; $R_3 = H$

18Z and **E** $R_1 = O(CH_2)_2N(CH_2CH_3)_2$; $R_2 = OCH_3$; $R_3 = OC_7F_7$

7A(Z) and **(E)** $R_1 = O(CH_2)_2N(CH_3)_2$; $R_2 = H$; $R_3 = H$

MRL 37 $R_1 = O(CH_2)_2N(CH_2CH_3)_2$; $R_2 = OCH_3$; $R_3 = H$

FIG. 2. MRL 37, **7A(Z), 7A(E),** and gem-dichlorocyclopropyl analogs of MER 25.

assays with the test compounds. Comparison of the biological activity between *Z* and *E* isomers of compounds, with and without the *p*-methoxy group in the β ring, should demonstrate the influence of this moiety on biological activity.

Inclusion of the dichlorocyclopropyl group into the structure provided diastereomers without the ethanolic hydroxyl group found in MER 25. To determine the importance of the OH group in MER 25, des-hydroxy MER 25 (Fig. 2), also known as MRL 37, was prepared and tested in conjunction with MER 25 to confirm if its previously reported *in vivo* antiestrogenic activity was comparable to an *in vitro* system.

This report describes the synthesis and biological evaluation of four cyclopropyl analogs of MER 25. Two structures have the α' and β rings in the *E* (**11E**) and *Z* (**11Z**) conformation, and two have a heptafluorotolyl ether substituent in the 4-position of the α ring in the *E* (**18E**) and *Z* (**18Z**) analogs of MER 25. A fifth compound known as MRL 37 (des-hydroxy MER 25) was included in this study. Their *in vitro* antiestrogenic effects in the ER-positive MCF-7E3 and ER-negative MDA-MB-231 human breast cancer cells are reported.

EXPERIMENTAL

Materials and Methods

The melting points were determined in open capillary tubes with a Thomas–Hoover capillary melting-point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab Ltd. (Indianapolis, IN). The structures of all

compounds were supported by their proton NMR spectra of intermediate compounds obtained with a Varian EM-360A spectrometer; spectra of final compounds were recorded on a Varian XL-300 spectrometer. The chemical shifts are reported in parts per million (δ) with reference to tetramethylsilane as the internal standard. All starting reagents were used without further purification and were obtained from Aldrich Chemical Co. (Milwaukee, WI 53233), with the exception of octafluorotoluene, which was purchased from PCR, Inc. (Gainesville, FL 32602). Solvents were either HPLC or ACS grade and were obtained from Fisher Scientific (Fair Lawn, NJ 07410).

Synthesis

4-Methoxydesoxy benzoin (***6***). Aluminum chloride (85.66 g, 0.642 mol) and dry benzene (60.0 ml) were anhydrously combined at 0°C, followed by the dropwise addition of *p*-methoxyphenylacetyl chloride (**5**) (53.94 g, 0.292 mol) [^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.74 (s, 3H, OCH_3), 4.02 (s, 2H, $ArCH_2$), 6.88 (d, J = 8 Hz, 2H, ArH (m to OCH_3)), 7.18 (d, J = 8 Hz, 2H, ArH (o to OCH_3))] dissolved in 30.0 ml benzene. The reaction was then allowed to sit at room temperature overnight (14 h). The reaction vessel was subsequently cooled on ice and 100 ml H_2O was added. Complete dissociation of the $AlCl_3$ (detectable by the change in color of the reaction mixture from dark red to yellow) was accomplished by the dropwise addition of concentrated HCl. The mixture was transferred to a separation funnel and the organic phase was extracted with three 50-ml portions of benzene. The combined organic layers were washed with 10% sodium hydroxide (to remove any unreacted acid chloride) and dried over magnesium sulfate. Following filtration of the drying agent and removal of the solvent, 20.0 g of yellow-brown solid was obtained. The crude ketone was purified via column chromatography (silica gel; CH_2Cl_2) and recrystallized with petroleum ether: CH_2Cl_2 to yield 53.91 g (82%) of off-white solid, mp = 92.5–93.5°C. ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.80 (s, 3H, OCH_3), 4.23 (s, 2H, $ArCH_2$), 6.96 (d, J = 8 Hz, 2H, ArH (m to OCH_3)), 7.30 (d, J = 8 Hz, 2H, ArH (o to OCH_3)), d 7.51 (m, 3H, ArH (m to C=O)), d 8.05 (m, 2H, ArH (o to C=O)).

(*Z and E*)*-1-*{*4-*[*2,3,5,6-tetrafluoro-4-*(*trifluoromethyl*)*phenoxy*]*phenyl*}*-1-phenyl-2-*(*4-methoxyphenyl*)*ethene* (***7***). A modified version of the procedure used by McCague (*22*) was employed. Magnesium (3.76 g, 154.61 mmol), 4-(perfluorotolyloxy)phenyl bromide (**2**) (40.1 g, 103.07 mmol) [^{1}H NMR ($CDCl_3$, 60 MHz) δ 6.91 (d, J = 8 Hz, 2H, ArH (o to Br)), 7.53 (d, J = 8 Hz, 2H, ArH (m to Br))], and 100 ml of THF (freshly distilled from Ca_2H) were combined. Dibromoethane (9.68 g, 51.54 mmol) dissolved in 50 ml THF was then added dropwise over a 4-h period. Following the complete addition of the dibromoethane and the disappearance of the magnesium, **6,** dissolved in 50 ml THF, was injected into the reaction. The reaction was stirred at room temperature for 60 h. The reaction mixture was subsequently transferred to a separatory funnel and 100 ml of 0.5 M HCl was added. The organic phase was removed and the aqueous phase was extracted with three 25-ml portions of Et_2O. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed, yielding 28.43 g of brown oil. The oil was

dissolved in 125 ml benzene, and *p*-toluenesulfonic acid (1.14 g, 5.99 mmol) was added. The mixture was refluxed for 18 h. Upon cooling to room temperature, 100 ml of H_2O was added to the reaction vessel and the solution was transferred to a separatory funnel. The aqueous phase was removed and the organic phase was extracted with three 50-ml portions of benzene. The combined benzene layers were dried over $MgSO_4$ and filtered, and the solvent was removed, yielding 27.3 g of brown oil. The oil was purified via column chromatography (silica gel, 1 : 1 petroleum ether : CH_2Cl_2) to give 11.20 g (78%) of yellow oil.

Crystallization of the oil from petroleum ether resulted in 1.10 g **7E** (mp = 108.0–109.5°C from petroleum ether 40–60°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.77 (s, 3H, OCH_3), d 6.70 (d, J = 4.4 Hz, 2H, ArH (o to OCH_3)), d 6.92–6.97 (m, 4H, ArH), d 7.00 (s, 1H, olefinic H), d 7.19–7.29 (m, 7H, ArH). Crystallization of the mother liquor with isopropanol/ether provided 932 mg **7Z** (mp = 91.5–93.0°C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 3H, OCH_3), 6.67 (d, J = 8.7 Hz, 2H, ArH (o to OCH_3)), 6.87 (s, 1H, olefinic H), 6.93–6.96 (m, 4H, ArH), 7.19–7.36 (m, 7H, ArH).

(*Z and E*)-*1*-[*4-bromoethoxyphenyl*]-*1-phenyl-2*-(*4-methoxyphenyl*)*ethene* (***9***). Compound **7E** (932 mg, 1.80 mmol) in 20 ml dry DMF was anhydrously combined with sodium methoxide (1.07 g, 19.78 mmol). The reaction was stirred at room temperature for 16 h. The reaction mixture was transferred to a separatory funnel and 50 ml of ether and 50 ml of saturated $NaHCO_3$ were added. The organic phase was extracted with two additional 50-ml portions of saturated $NaHCO_3$. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed, yielding a yellow oil. The oil was subjected to the identical reaction conditions (the reaction was stirred for only 2 h) and workup procedure a second time (the reaction produces an intermediate product which requires the duplication of the process to obtain the desired product). Purification of the oil was accomplished with column chromatography (silica gel, 1 : 1 petroleum ether : CH_2Cl_2 to 100% CH_2Cl_2). A total of 322 mg (49%) of **8E** was obtained as a clear oil. Due to the instability of phenolic moiety, the oil was immediately subjected to alkylation. To a 50-ml round-bottom flask equipped with a reflux condenser and stir bar was added **8E** (322 mg, 1.06 mmol), dibromoethane (15.26 g, 81.23 mmol), triethylbenzylammonium chloride (TEBA) (34 mg, 0.15 mmol), and 7 ml of 10% NaOH. The reaction was heated at 45°C for 16 h and was subsequently cooled to room temperature. The reaction mixture was transferred to a separatory funnel and 20 ml CH_2Cl_2 and 20 ml water were added. The organic phase was removed and the aqueous phase was extracted with three 20-ml portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered, and the low boiling solvents were removed. The excess dibromoethane was removed under vacuum (6 mm Hg). Purification of the resulting yellow oil was accomplished with column chromatography (silica gel, 1 : 1 petroleum ether : CH_2Cl_2). A total of 332 mg (76%) of **9E** was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70 (t, J = 6.3 Hz, 2H, CH_2Br), 3.79 (s, 3H, OCH_3), 4.35 (t, J = 6.3 Hz, 2H, OCH_2), 6.71–7.34 (m, 13 H, ArH), 6.89 (s, 1H, olefinic H).

Compounds **8Z** and **9Z** were generated in a manner analogous to those used for the *E* isomers. Compound **7E** (1.10 g, 2.12 mmol) was reacted two times with NaOMe (1.26 g, 23.34 mmol) in 20 ml dry THF. Following standard workup and

purification, 316 mg (49%) of **8Z** was obtained as a clear oil. **8Z** (316 mg, 1.05 mmol) was reacted with dibromoethane (13.1 g, 69.62 mmol) and TEBA (30 mg, 0.132 mmol) in 6 ml of 10% NaOH. Following workup and purification, a total of 324 mg (76%) of **9Z** was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64 (t, J = 6.3 Hz, 2H, CH_2Br), 3.74 (s, 3H, OCH_3), 4.29 (t, J = 6.3 Hz, 2H, OCH_2), 6.65–7.85 (m, 13 H, ArH), 6.83 (s, 1H, olefinic H).

(*Z and E*)-*1,1,-dichloro-2-*[*4-*(*2-bromoethoxy*)*phenyl*]-*2-phenyl-3-*(*4-methoxyphenyl*)*cyclopropane* (***10***). Compound **9E** (332 mg, 0.811 mmol), TEBA (32 mg, 0.140 mmol), 7 ml $CHCl_3$, and 5 ml 50% NaOH were combined. The reaction was stirred at room temperature for 72 h. The reaction mixture was transferred to a separatory funnel and 20 ml water and 20 ml CH_2Cl_2 were added. The organic phase was removed and the aqueous layer was extracted with three 20-ml portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed, yielding a brown oil. The oil was purified via column chromatography (silica gel, 1 : 1 petroleum ether : CH_2Cl_2). A total of 271 mg (68%) of **10E** was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.52 (s, 1H, cyclopropyl H), 3.63 (t, J = 6.3 Hz, 2H, CH_2Br), 3.82 (s, 3H, OCH_3), 4.25 (t, J = 6.3 Hz, 2H, OCH_2), 6.79–7.53 (m, 13H, ArH). The same procedure was employed for **10Z.** Compound **9Z** (324 mg, 0.792 mmol) was reacted with TEBA (32 mg, 0.140 mmol), 7 ml $CHCl_3$, and 5 ml 50% NaOH. Following workup and purification, a total of 191 mg (49%) was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.51 (s, 1H, cyclopropyl H), 3.62 (t, J = 6.3 Hz, 2H, CH_2Br), 3.8 (s, 3H, OCH_3), 4.24 (t, J = 6.3 Hz, 2H, OCH_2), 6.78–7.50 (m, 13H, ArH).

(*Z and E*)-*1,1-dichloro-2-*[*4-*(*2-diethylaminoethoxy*)*phenyl*]-*2-phenyl-3-*(*4-methoxyphenyl*)*cyclopropane* (***11***). Compound **10E** (260 mg, 0.528 mmol) was reacted with diethylamine (0.35 g, 4.83 mmol) in 5 ml acetonitrile. The reaction was stirred at room temperature for 16 h. The solvent was subsequently removed and the resulting orange semisolid was dissolved in 5 ml ether and 5 ml saturated sodium bicarbonate. The mixture was transferred to a separatory funnel, the aqueous phase was removed, and the ether layer was extracted with three 25-ml portions of saturated $NaHCO_3$. The organic layer was dried over $NaSO_4$ and filtered, and the solvent was removed, yielding an orange-brown oil. The oil was purified via column chromatography (silica gel, 9 : 1 petroleum ether : ether). A total of 121 mg (47%) of **11E** was collected as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, J = 7.2 Hz, 6H, NCH_2CH_3), 2.73 (q, J = 7.2 Hz, 4H, NCH_2CH_3), 2.95 (t, 2H, J = 6.3 Hz, 2H, CH_2N), 3.51 (s, 1H, cyclopropyl H), 3.81 (s, 3H, OCH_3), 4.08 (t, J = 6.3 Hz, 2H, OCH_2), 6.78–7.52 (m, 13H, ArH).

The same procedure was employed to obtain **11Z.** Compound **10Z** (185 mg, 0.376 mmol) was combined with diethylamine (0.35 g, 4.83 mmol) in 5 ml of acetonitrile and was stirred for 16 h at room temperature. Following an identical workup procedure and purification process, a total of 75 mg (41%) **11E** was obtained as a light yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (t, J = 7.2 Hz, 6H, NCH_2CH_3), 2.66 (q, J = 7.2 Hz, 4H, NCH_2CH_3), 2.88 (t, 2H, J = 6.3 Hz, 2H, CH_2N), 3.51 (s, 1H, cyclopropyl H), 3.81 (s, 3H, OCH_3), 4.04 (t, J = 6.3 Hz, 2H, OCH_2), 6.77–7.45 (m, 13H, ArH).

(*Z and E*)-*1,1-dichloro-2-*[*4-*(*2-diethylaminoethoxy*)*phenyl*]-*2-phenyl-3-*(*4-me-*

thoxyphenyl)cyclopropane citrate salt (***11***). To the free base of **11E** (96 mg, 0.200 mmol) was added 0.5 ml isopropanol. Anhydrous citric acid (38 mg, 0.200 mmol) was likewise dissolved in 0.5 ml isopropanol. The two solutions were combined and stirred at 42°C for 30 min. The isopropanol was subsequently removed and the resulting oil was treated with 3 ml ether. The citrate salt of **11E** fell out of solution as a white solid and was recrystallized from isopropanol : ether to yield 100 mg (74%), mp = 86.5–87.5°C. $C_{34}H_{39}Cl_2NO_9$ (Found: C 59.87, H 5.94, N 2.07. Calcd: C 60.36, H 5.81, N 2.07). The citrate salt of **11Z** (50 mg, 0.103 mmol) was obtained in a similar manner using citric acid (20 mg, 0.103 mmol) in isopropanol. Following recrystallization with isopropanol : ether, 48 mg (69%) of **11Z** citrate salt, mp = 91.0–92.0°C. $C_{34}H_{39}Cl_2NO_9$ (Found: C 60.16, H 5.94, N 2.12. Calcd: C 60.36, H 5.81, N 2.07).

4-Bromoethoxy-4′-methoxybenzyl ketone (***13***). A modified version of the procedure used by McCague (*22*) was followed. 4-Methoxyphenylacetic acid (11.2 g, 67.5 mmol) and trifluoroacetic anhydride (15.1 g, 72.0 mmol) were combined. The reaction was stirred at room temperature until the acid completely dissolved. β-Bromophenetole (15.0 g, 75 mmol) was subsequently added in one portion. The reaction was stirred overnight (16 h) at 20°C. The reaction underwent several color changes from yellow to magenta and eventually to brown (at which point a precipitate had formed). Water (20 ml) and CH_2Cl_2 (20 ml) were added to the reaction vessel and the mixture was transferred to a separatory funnel. The organic phase was extracted with three 50-ml portions of 10% $NaHCO_3$. The combined organic phases were dried over $MgSO_4$ and filtered, and the solvent was removed, yielding a red-brown solid. The addition of 50 ml ether to the solid resulted in the production of 16.97 g (72%) of the desired compound as a white solid, mp = 129.0–130.5°C (from EtOAC : petroleum ether). ^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.51 (t, J = 6 Hz, 2H, CH_2Br), 4.11 (s, 3H, OCH_3), 4.29 (t, J = 6 Hz, 2H, OCH_2), 6.72–7.18 (m, 6H, ArH), 7.96 (d, J = 6, Hz, 2H, o to C=O).

(*Z and E*)*-1-*{*4-*[*2,3,5,6-tetrafluoro-4-*(*trifluoromethyl*)*phenoxy*]*phenyl*}*-1-*[*4-*(*2-bromoethoxy*)*phenyl-2-*(*4-methoxyphenyl*)*ethene* (***16***). A modified version of the procedure used by McCague (*22*) was followed. Magnesium (3.84 g, 157.94 mmol), **2** (40.72 g, 104.66 mmol), and 100 ml of THF (freshly distilled from Ca_2H) were combined, and dibromoethane (9.8 g, 52.23 mmol) dissolved in 50 ml THF was then added dropwise over a 4-h period. Following the complete addition of the dibromoethane and the disappearance of the magnesium, **13,** dissolved in 50 ml THF, was injected into the reaction. The reaction was stirred at room temperature for 60 h. The reaction mixture was subsequently transferred to a separatory funnel and 100 ml of 0.5 M HCl was added. The organic phase was removed and the aqueous phase was extracted with three 25-ml portions of Et_2O. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed, yielding 15.26 g of brown oil. The oil was dissolved in 125 ml benzene, and *p*-toluenesulfonic acid (0.763 g, 4.00 mmol) was added. The mixture was refluxed for 18 h. Upon cooling to room temperature, 100 ml of H_2O was added to the reaction vessel and the solution was transferred to a separatory funnel. The organic phase was removed and the aqueous phase was extracted with three 50-ml portions of benzene. The combined benzene layers were dried over $MgSO_4$ and filtered, and