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# Synthesis and Chiral Separation of Some Antitumor Agents

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Four Z-isomers of 1,1-dichloro-2,2,3-triarylcyclopropane (DTACs), designed as potent antitumor agents, were synthesized from their appropriately substituted ethenes, which were prepared from the Grignard reaction followed by the dehydration of their intermediate carbinols. The stereospecific addition of dichlorocarbene to the ethenes followed by fractional crystallization afforded (*Z*)-1,1-dichloro-2-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-3-phenylcyclopropane and (*Z*)-1,1-dichloro-2,3-diphenyl-2-(4-methoxyphenyl)cyclopropane. Displacement of the bromo group from the ethoxy side chain intermediates with dimethylamine gave the desired basic side chain compounds, (*Z*)-1,1-dichloro-2,3-diphenyl-2-[4-(2-dimethylaminoethoxy)phenyl]cyclopropane and (Z)-1,1-dichloro-2-[4-(2-dimethylaminoethoxy)phenyl]-2-(4-methoxyphenyl)-3-phenylcyclopropane. While both E- and Z-stereoisomers of the DTACs were isolated using fractional crystallization, only the Z-compounds were resolved on a chiral stationary phase consisting of amylose tris-3,5-dimethylphenyl carbamate coated on silica gel. Complete resolution of the E-compounds was not observed with this system. 

## INTRODUCTION

Breast cancer is one of the most common and serious diseases affecting women. Current estimates indicate that one in eight American women who reach age 95 will develop breast cancer (*1*). It is generally believed that estrogen can directly stimulate the growth of breast cancer, therefore, its inhibition with antiestrogens at the estrogen receptor (ER) can provide a particularly useful strategy for the treatment of hormone-dependent breast tumors in postmenopausal females and possibly in premenopausal women and can act as a chemosuppressant in women at high risk of developing breast cancer. Nonsteroidal antiestrogens which exhibit potent antitumor effects represent a major advance in the management of breast cancer. The representative of this class is tamoxifen, (*Z*)-1-[*p*-(2-dimethylaminoethoxy)phenyl]-1,2-diphenylbut-1-ene (Chart **1**), the only antiestrogen clinically available for the adjunctive treatment of primary breast cancer in postmenopausal women (*2*, *3*). Its principal action is ascribed to its competition with natural hormone estradiol (Chart **1**) for binding to the estrogen receptor protein, thereby reducing the ability of estradiol to stimulate nuclear transcription and consequent cell growth

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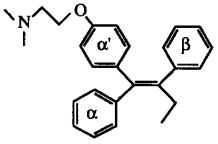
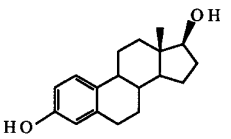
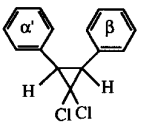



**1; Tamoxifen**



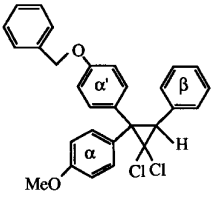

**2; Estradiol**



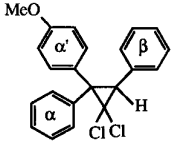

**3; Analog II**

CHART 1

(*2*). Tamoxifen, however, has partial agonist activity which can lead to thromboembolitic events and secondary endometrial tumors, and virtually all patients with metastatic disease develop tamoxifen resistance (*4–6*). Because of the partial agonist activity of tamoxifen, researchers have been synthesizing both nonsteroidal and steroidal antiestrogens in an attempt to find pure antiestrogens (those devoid of any uterotropic activity) (*7–12*). The reasoning behind the search for pure antiestrogens is based on the recognition that antiestrogens generally possess partial estrogenic activity and complete blockade of estrogen action cannot be achieved by agents like tamoxifen. Novel pure antiestrogens should be more effective than partial agonists in reducing the mitogenic action of estrogen on the growth of breast tumors and complete ablation of hormonal-dependent tumor growth is very desirable since it could provide a more rapid and longer-lasting remission. In addition, pure antiestrogens could prove more effective in patients who experience relapse during tamoxifen therapy, serving as second-line treatment, and could dem-




**4**

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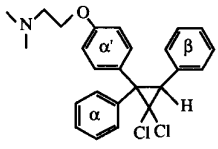
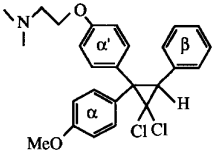
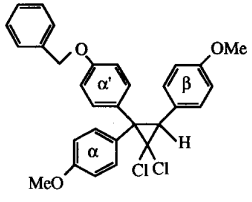



**6**




**7**




**8**

CHART 2

onstrate a greater efficacy in first-line treatment of advanced breast cancer (*11*, *13*, *14*).

The purpose of this earlier research was to search for antiestrogens that were devoid of estrogen agonist activity. Efforts in this area have led to several interesting experimental compounds (*15–23*). Reports from our laboratory (*15*, *16*) and others (*20*, *23*) have demonstrated that the introduction of a dichlorocyclopropyl or dihydroclopropyl moiety in place of the olefinic bridge in estrogenic stilbenes greatly reduces or abolishes their estrogenic action. One compound, analog II (Chart **1**), has antiestrogenic properties without estrogen agonist activity in the mouse and is comparable in activity to tamoxifen against the hormone-dependent 7,12-dimethyl benz[a]anthracene-induced rat mammary tumor model (*24*, *25*). Structure–activity relationship studies of some of the analog II derivatives (*15–17*, *26*) led us to design more effective cyclopropyl antiestrogens. Starting with analog II as the lead compound, we synthesized a series *Z*-1,1-dichloro-2,2,3-triarylcyclopropanes (Z-DTACs, **4–8**) by introducing a third phenyl ring and a polar substituent in analog II so that the compounds possess the structural features of both analog II and the clinically useful Z-triarylethylenes (Chart **2**). These Z-diastereomers were found to be antiestrogenic without any estrogenic activity in the mouse and inhibited the growth of ER positive MCF-7 human breast cancer cells in culture (*19*). As stereoisomers often exhibit distinct bioactivities, separating the enantiomers was necessary to fully evaluate the antitumor activity of the Z-DTACs. Unfortunately the synthetic methods used to prepare these compounds did not yield substantial amounts of the pure diastereomers required for further testing. In addition, unlike tamoxifen, the DTAC stereoisomers consist of enantiomeric pairs. In this study, we report a modified and improved synthetic method for the Z-DTACs, and the chiral separation of Z-isomers (**4–7**) into their (+) and (−) enantiomers for biological evaluation. The E-diastereomers of compounds **6** and **7** were also obtained for testing.

## EXPERIMENTAL

### *Materials and Methods*

Unless otherwise stated, all the starting materials were obtained from Aldrich Chemical Co. (Milwaukee, WI) and were used without further purification. Aqueous dimethylamine was obtained from Fluka Chemical Corp. (Ronkonkoma, NY). HPLC grade solvents, which were purchased from Fisher Scientific (Houston, TX) were filtered through a 0.45-$\mu$m nylon-66 membrane filter (Ranin Instrument Co., Inc., Woburn, MA) and manually mixed by volume prior to use. Anhydrous THF was freshly distilled from $CaH_2$.

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analysis was performed by Midwest Microlab Ltd. (Indianapolis, IN). $^1$H NMR spectra were recorded on a Varian EM-360A or XL-300 spectrometer. Ultraviolet-visible spectra were recorded on a Shimadzu UV 160U spectrophotometer. Optical rotations were determined with a Rudolph Autopol III autonomic polarimeter.

*HPLC Conditions*

A Beckman Gold HPLC system equipped with dual Model 110 (A and B) pumps (only one pump was used) and 320SX controller, a 210A loop injector (20- and 500-$\mu$l loops were used), a 163 variable wavelength uv detector, and an Analog Interface Module 406 was used. Chiralpak AD columns, either analytical (250 $\times$ 4.6 mm, i.d.) or semipreparative (250 $\times$ 10 mm, i.d.) (Diacel Chemical Industries, CA) were used for chiral separation. These columns consisted of amylose tris-3,5-dimethylphenyl carbamate as chiral stationary phase coated on a 10-$\mu$m silica gel. A short nitrile guard column (5 $\mu$m, 10 $\times$ 3 mm, i.d.) (Regis Chemical Company, IL) was used with both columns. The columns were maintained at ambient temperature throughout the separation. Dead time was estimated with 1,3,5-tri-*t*-butylbenzene (*27*).

Three solvent systems were used at a flow rate of 1 ml/min for analytical analysis. Solvent system A consisted of hexane : ethanol (9 : 1; v/v), B consisted of hexane : 2-propanol (9 : 1; v/v), and C consisted of hexane : 2-propanol : dimethylamine (9 : 1 : 0.1; v/v). A volume of 5 $\mu$l containing 1 mg/ml of compound in the same solvent mixture was injected into the HPLC system. For semipreparative separation the same solvent system (A, B, and C) were used at 2.4 ml/min flow rate. A volume of 100–500 $\mu$l containing 6–7 mg/ml of compound dissolved in either hexane : 2-propanol (2 : 1 or 3 : 2) or hexane : chloroform (4 : 1) was injected.

*Synthesis*

*Benzyl-4-benzyloxyphenyl ketone* **(*10*).** The method of Iyer and Gopalachari (*28*) was used to prepare ketone **10.** A white solid crystallized from ethanol/benzene yielded white needles (7.1 g, 81%), mp 134–136°C (lit. (*28*) 132°C). $^1$H NMR ($CDCl_3$; 60 MHz): $\delta$ 4.24 (s, 2H, $ArCH_2O$), 5.18 (s, 2H, $CH_2CO$), 7.04 (d, 2H, Ar), 7.28–7.42 (overlapping s, 10H, ArH), 8.07 (d, 2H, ArH).

(*Z/E*)-*1*-(*4-Benzyloxyphenyl*)-*1*-(*4-methoxyphenyl*)-*2-phenyl ethene* **(*12*).** A solution of Grignard reagent was generated from 4-bromoanisole (**11;** 7.5 ml, 59.6 mmol) and magnesium turnings (1.1 g, 43.7 mmol) in 280 ml of anhydrous THF which was refluxed for 2 h. A solution of **10** (12.0 g, 39.7 mmol) in THF (60 ml) was added and a gentle reflux was maintained for 16 h. The mixture was allowed to cool to room temperature and a saturated solution of $NH_4Cl$ (12 ml) was added. The mixture was transferred to a separatory funnel and ether (15 ml) and water (5 ml) were added. The aqueous layer was removed and the ether layer was extracted with water (3 $\times$ 10 ml). The aqueous layers were combined and extracted with ether (3 $\times$ 15 ml). The combined ether layers were dried over anhydrous $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. Without further purification, the intermediate carbinol was dehydrated with 2N $H_2SO_4$ (30 ml) in 95% ethanol (150 ml) at room temperature for 1 h. The mixture was then transferred to a separatory funnel, extracted with ether (3 $\times$ 15 ml), and the combined ether layers were washed first with a saturated aqueous solution of sodium bicarbonate followed by water until neutral. The organic layer was dried (anhydrous $MgSO_4$), filtered, concentrated, and purified over silica gel (pet ether/$CH_2Cl_2$, 6 : 1 to 1 : 1) to yield 9.2 g (63%) of an oil. Fractional crystallization from pet ether/acetone gave

TABLE 1
Characterization of Z/E Isomers

| Comp. No. | Isomer | M.p. (°C) | $^1$H NMR data[a,b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Cyclopropyl H | $OCH_3$ | $OCH_2C_6H_5$ | $OCH_2CH_2$ | $OCH_2CH_2$ | $NCH_3$ |
| **4** | Z | 153–156 | 3.53 | 3.79 | 5.02 | | | |
| | E | 134–136 | 3.53 | 3.78 | 5.03 | | | |
| **5** | Z | 128–130 | 3.53 | 3.75 | | | | |
| | E | 116–120 | 3.53 | 3.76 | | | | |
| **24** | Z | 92–96 | 3.54 | | | 4.23 | 3.63 | |
| | E | 113–115 | 3.52 | | | 4.24 | 3.59 | |
| **25** | Z | 128–129 | 3.50 | 3.76 | | 4.22 | 3.60 | |
| | E | 114–120 | 3.52 | 3.79 | | 4.25 | 3.62 | |
| **6** | Z | 111–112 | 3.52 | | | 4.02 | 2.69 | 2.31 |
| | E | 112–114 | 3.53 | | | 4.05 | 2.75 | 2.34 |
| **7** | Z | 120 | 3.49 | 3.76 | | 4.01 | 2.69 | 2.31 |
| | E | 108–111 | 3.52 | 3.77 | | 4.04 | 2.72 | 2.33 |

[a] $^1$H NMR spectra were run on a Varian XL-300 spectrometer with TMS as internal standard in $CDCl_3$. The chemical shifts are given in ppm ($\delta$).
[b] Compared to the $^1$H NMR of the X-ray structure of the (Z)-triarylcyclopropanes (*37, 38*).

E-isomer (2.21 g, 14%) mp 114–115.5°C. $^1$H NMR ($CDCl_3$; 300 MHz): $\delta$ 3.85 (s, 3H, $OCH_3$), 5.10 (s, 2H $ArCH_2O$), 6.85 (s, 1H, vinyl H), 6.85–7.00 (m, 4H, ArH), 7.02–7.20 (m, 7H, ArH), 7.23–7.32 (m, 2H, ArH), 7.32–7.52 (m, 5H, ArH).

The Z-isomer was obtained from mother liquor by fractional crystallization from pet ether/acetone (**12;** 3.41 g, 22%) mp 60–61°C. $^1$H NMR ($CDCl_3$; 300 MHz): $\delta$ 3.86 (s, 3H, $OCH_3$), 5.10 (s, 2H, $ArCH_2O$), 6.86 (s, 1H, vinyl H), 6.87–7.00 (m, 4H, ArH), 7.05–7.20 (m, 7H, ArH), 7.27–7.31 (m, 2H, ArH), 7.35–7.52 (m, 5H, ArH).

*(Z)-1,1-Dichloro-2-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-3-phenylcyclopropane* **(*4*).** The Z-ethane of **12** (3.2 g, 8.2 mmol) was stirred with 50% aq NaOH solution (13 ml), benzyltriethylammonium chloride (TEBA, 0.3 g, 1.3 mmol) and chloroform (40 ml) for 72 h at room temperature. The organic and aqueous layers were separated and the aqeous layer was extracted three times with 25 ml of dichloromethane. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was partially purified over silica gel (pet ether/benzene, 1:1) and recrystallized from pet ether/ethyl acetate to afford 1.9 g (49%) of the Z isomer as a white solid. The E-isomer of **4** was obtained in a similar manner from *E*-1-(4-benzyloxyphenyl)-1-(4-methoxyphenyl)-2-phenyl ethene in 41% yield after being recrystallized from pet ether/ethanol. $^1$H NMR data are shown in Table 1.

*(Z/E)-1-(4-Methoxyphenyl)-1,2-diphenyl ethene* **(*16*).** Method A: A solution of 4-bromoanisole (**11:** 15.3 ml, 122 mmol) in THF (60 ml) was slowly added to a flame-dried flask containing magnesium turnings (2.69 g, 112 mmol) and THF (65 ml). The Grignard reaction was facilitated by iodine crystals and heat. The mixture was heated and refluxed for 2 h. Deoxybenzoin (**13;** 20.0 g, 102 mmol) in THF (65

ml) was then added and a gentle reflux was maintained for 5.5 h, cooled to room temperature, and treated with a saturated aqueous $NH_4Cl$ solution (20 ml) for 30 min, then filtered and the filtrate extracted with ether (3 × 25 ml). Removal of solvent afforded an oil (8.0 g), which was dissolved in benzene (150 ml) and heated to reflux for 2.5 h in the presence of p-TSA (1.5 g). The mixture was transferred to a separatory funnel and extracted two times with 10 ml of saturated sodium bicarbonate solution. The aqueous extracts were combined and washed with benzene (3 × 20 ml). The benzene layers were combined, dried (anhydrous $MgSO_4$), filtered, concentrated under vacuum, and the resulting oil was purified over silica gel (pet ether/$CH_2Cl_2$, 1 : 0 to 7 : 1) to afford 23.0 g (79%) of the Z/E ethene mixture. $^1$H NMR ($CDCl_3$; 60 MHz): $\delta$ 3.83 (s, 3H, $OCH_3$), 6.70–7.40 (m, 15H, ArH and vinyl H).

Method B: A solution of benzyl magnesium chloride (**15;** 2 M solution, 32 ml, 64 mmol) in THF was added dropwise to the reaction flask contianing 4-methoxybenzophenone (**14;** 12.0 g, 5 mol) and THF (45 ml). The reaction was warmed slowly and heated to reflux, which was maintained overnight. The reaction mixture was cooled and a saturated $NH_4Cl$ solution (25 ml) was added. The mixture was transferred to a separatory funnel and other (50 ml) and water (25 ml) were added. The aqueous layer was separated and the ether layer was extracted with water (3 × 25 ml). The combined aqueous layers were extracted with ether (3 × 50 ml). The combined ether layers were dried (anhydrous $MgSO_4$), filtered, and concentrated under vacuum. The intermediate carbinol (18.5 g) was obtained and dehydrated with 1.4 g p-TSA in 90 ml benzene for 3.5 h at reflux. The mixture was cooled and the benzene layer was extracted with water until free of acid, dried (anhydrious $MgSO_4$), and concentraetd under vacuum. The residual oil was purified over silica gel (pet ether/$CH_2Cl_2$; 4 : 1), which afforded 8.91 g (56%) of a clear oil.

(*Z*)-*1,1-Dichloro-2,3-diphenyl-2-*(*4-methoxyphenyl*) *cyclopropane* **(*5*).** Ethene (**16;** 4.49 g, 15.7 mmol), 50% aq NaOH (25 ml), chloroform (40 ml), and TEBA (0.30 g, 1.3 mmol) were mixed together and stirred at room temperature for 72 h. The two layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 50 ml). The combined organic layers were dried (anhydrous $MgSO_4$), filtered, and concentrated under vacuum to afford 5.9 g crude product, which was purified over silica gel (pet ether/$CH_2Cl_2$, 100 : 1 to 4 : 1). Recrystallization of the white solid from pet ether followed by pet ether/acetone gave the Z-isomer as white crystals (0.69 g, 12%). The E-isomer (2.2 g) was obtained from the mother liquor. Recrystallization of the *E*-1,1-dichloro-2,3-diphenyl-2-(4-methoxyphenyl) cyclopropane from pet ether and then from pet ether/acetone gave 0.49 g (8.5%) of white crystals (see Table 1 for $^1$H NMR data of Z- and E-isomers).

*4-*(*2-Bromoethoxy*)*benzophenone* **(*20*).** A mixture of 4-hydroxybenzophenone (**17;** 40.0 g, 202 mmol) and 1,2-dibromoethane (140 ml) was added to a flask containing 10% aqueous NaOH solution (140 ml) and TEBA (4.8 g, 20 mmol). The mixture was refluxed for 48 h and allowed to cool to room temperature at which time two layers separated. The aqueous layer was extracted four times with 100 ml of $CH_2Cl_2$ and the combined organic layers were washed free of base. Removal of the solvent and the recrystallization of the brown solid from 95% EtOH yielded 35.5 g (57%) of a light tan solid, mp 68–70.5°C (lit. (*29*) 62°C and lit. (*30*) 77°C).

$^1$H NMR ($CDCl_3$; 60 MHz): $\delta$ 3.68 (t, J = 6.3Hz, 2H, $CH_2Br$), 4.39 (t, J = 6.3Hz, 2H, $CH_2O$), 6.98 (d, 2H, ArH), 7.39–7.89 (m, 7H, ArH).

*4-(2-Bromoethoxy)-4'-methoxybenzophenone* **(*21*).** 4-Methoxybenzoic acid (**18;** 13.0 g, 85.5 mmol) and $\beta$-bromophenetole (**19;** 13 g, 65 mmol) were added to a flask equipped with a mechanical stirrer containing pyrophosphoric acid (PPA; 140 g). The reaction mixture was warmed to 100°C and stirred vigorously for 4 h. It was then cooled, ice/water was added, and the mixture was filtered. The filtrate was extracted with ether. The solvent was removed under vacuum, and residue was dissolved in $CHCl_3$ and extracted with 10% aqueous NaOH solution. Removal of solvent and recrystallization from MeOH afforded 15.7 g (72%) solid, mp 110–111°C (lit. (*31*) 111.5–113°C). $^1$H NMR ($CDCl_3$; 60 MHz): $\delta$ 3.67 (t, 2H, J = 6.3Hz, $CH_2Br$), 3.91 (s, 3H, $OCH_3$), 4.39 (t, 2H, J = 6.3Hz, $CH_2O$), 6.96 (b, 4H, ArH), 7.85 (b, 4H, ArH).

(*Z/E*)*-1-*[*4-*(*2-Bromoethoxy*)*phenyl*]*-1,2-diphenyl ethene* **(*22*).** To a solution of ketone (**20;** 17.5 g, 57 mmol) in dry THF (50 ml) was added benzyl magnesium chloride in THF (2 M solution, 30 ml, 60 mmol), which was diluted with additional THF (20 ml). The resulting reaction mixture was refluxed overnight. The reaction mixture was cooled and a saturated solution of $NH_4Cl$ (25 ml) was added. The product was extracted four times with 100 ml of ether which was washed with water until neutral (4 × 50 ml). Removal of the solvent afforded the intermediate carbinol, which was dehydrated using p-TSA (1.15 g) by heating to reflux for 4 h in benzene (90 ml). The reaction mixture was cooled and the organic layer was extracted with water until neutral (3 × 50 ml). Removal of solvent yielded an oil which was purified over silica gel (pet ether/$CH_2Cl_2$, 4:1) to afford a white solid 16.6 g (77%) of a mixture of Z/E-ethene, mp 92–94°C. $^1$H NMR ($CDCl_3$; 300 MHz): $\delta$ 3.67 (t, 2H, J = 6.3 Hz, $CH_2Br$), 4.32 (t, 2H, J = 6.3Hz, $CH_2O$), 6.87 (s, 1H, vinyl H), 6.90–7.36 (m, 14 H, ArH).

(*Z/E*)*-1-*[*4-*(*2-Bromoethoxy*)*phenyl*]*-1-*(*4-methoxyphenyl*)*-2-phenyl ethene* **(*23*).** Ethene **23** was prepared as described above using the ketone (**21;** 5.50 g, 16.4 mmol) and benzyl chloride (2 M solution, 10.7 ml, 21.4 mmol) in THF. The reaction mixture was heated to reflux which continued overnight. The reaction mixture was cooled and ether (35 ml) and water (15 ml) were added. The two layers were separated and the aqueous layer was extracted with ether (3 × 35 ml). The combined ether layers were dried (anhydrous $MgSO_4$), filtered, and concentrated to obtain 7.78 g crude carbinol, which was dehydrated with p-TSA (0.6 g) in benzene (70 ml) while refluxing overnight. The benzene layer was washed with water (3 × 30 ml) until free of acid and stripped off under vacuum. Purification of the product by column chromatography over silica gel (pet ether/$CH_2Cl_2$, 4:1) yielded 5.20 g (78%) oil. $^1$H NMR ($CDCl_3$; 300 MHz): $\delta$ 3.67, 3.69 (t, J = 6.6 Hz, 2H, $CH_3Br$), 3.86, 3.87 (s, 3H, $OCH_3$), 4.33, 4.34 (t, J = 6.6Hz, 2H, $CH_2O$), 6.89, 6.90 (s, 1H, vinyl H), 6.85–7.52 (m, 13H, ArH).

(*Z/E*)*-1,1-Dichloro-2,3-diphenyl-2-*[*4-*(*2-bromoethoxy*)*phenyl*]*cycloproane* **(*24*).** Ethene (**22;** 5.0 g, 13.2 mmol), TEBA (0.5 g,2.2 mmol), 50% aqueous NaOH solution (30 ml), and chloroform (55 ml) were stirred at room temperature for 95 h. The two layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (4 × 25 ml). The combined organic layers were dried and concentrated. After purification

of the crude product over silica gel (pet ether/$CHCl_3$, 10:1 to 1:1) an oil was obtained. Fractional crystallization from MeCN afforded the E-isomer of **24** (1.5 g, 25%). The filtrate was concentrated and the oil was crystallized from pet ether/benzene to afford the Z isomer (**24;** 1.34 g, 20%) as a white solid (Table 1 for $^1$H NMR).

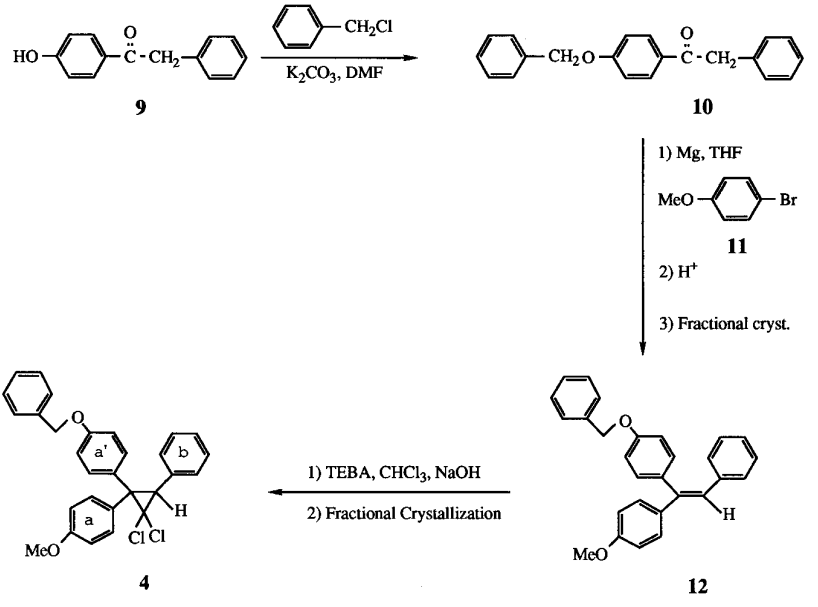
(*Z/E*)*-1,1-Dichloro-2-*[*4-*(*2-bromoethoxy*)*phenyl*]*-2-*(*4-methoxyphenyl*)*-3-phenyl cyclopropane* **(*25*).** Ethene (**23;** 5.21 g, 12.7 mmol), TEBA (0.5 g, 2.2 mmol), chloroform (60 ml), and 50% aqueous NaOH solution (30 ml) were combined and stirred at room temperature for 72 h. The two layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (4 × 25 ml). The solvent was removed under vacuum, which yielded 5.5 g of a brown solid, which was purified over silica gel (pet ether/$CH_2Cl_2$, 1:1) to afford 4.0 g of a light yellow solid. The complete separation of the Z/E isomers could not be achieved; however, fractions enriched in either Z- or E-isomer were obtained. The Z-enriched isomer (**25**) was obtained after two recrystallizations from MeCN (0.43 g) (Table 1). The mother liquor was reduced and the solid was crystallized from abs. EtOH giving the E-enriched-isomer (1.84 g) (Table 1).

(*Z*) *- 1,1 - Dichloro - 2,3 - diphenyl - 2 -* [*4 - (2 - dimethylaminoethoxy*)*phenyl*]*cyclopropane* **(*6*).** *Z*-bromide **24** (0.6 g, 1.3 mmol) and dimethyl amine (7.8 M aqueous solution, 6 ml, 46.8 mmol) were dissolved in $CHCl_3$:MeCN:2-PrOH (3:5:5, 13 ml) and heated at 48 ± 2°C for 20 h. The solution was cooled, and the solvent mixture was removed under vacuum, leaving a residue that was dissolved in ether. The ether solution was extracted with water (10 ml), 10% aq NaOH, dried over anhydrous $MgSO_4$, filtered, and the solvent stipped off. The residue was crystallized from pet ether to afford 0.28 g (51%) of a white solid (Table 1). The E-isomer of **6** was similarly obtained from *E*-1,1-dichloro-2,3-diphenyl-2-[4-(2-bromoethoxy)-phenyl]cyclopropane and crystallized from EtOH in 39% yield (Table 1).

*(Z)-1,1-Dichloro-2-[4-(2-dimethylaminoethoxy)phenyl]-2-(4-methoxyphenyl)-3-phenyl cyclopropane* **(*7*).** *Z*-bromide **25** (0.52 g, 1.06 mmol) and dimethyl amine (7.8 M aq solution 7 ml, 54.6 mmol) in $CHCl_3$:MeCN:2-PrOH (3:5:5, 15 ml) were heated at 48 ± 2°C for 20 h. The solution was cooled to room temperature and the solvent mixture was removed under vacuum leaving a solid residue, which was dissolved in ether. The ether solution was extracted with water (10 ml), 10% aqueous NaOH, dried over anhydrous $MgSO_4$, filtered, and the solvent stripped off. The resulting solid was crystallized from pet ether to afford 0.14 g (29%) white solid. The E-isomer of **7** was similarly prepared from *E*-1,1-dichloro-2-[4-(2-bromoethoxy) phenyl]-2-(4-methoxyphenyl)-3-phenyl cyclopropane and crystallized from pet ether in 35% yield (see Table 1 for $^1$H NMR data of Z- and E-isomers).

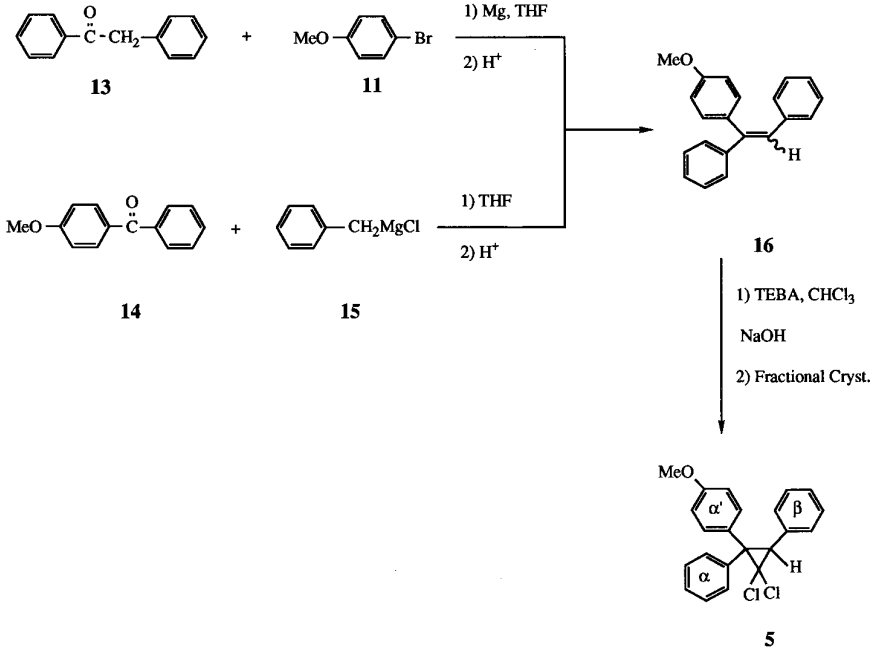
## RESULTS AND DISCUSSION

The Z-isomers of four 1,1-dichloro-2,2,3-triarylcyclopropanes (DTACs) (Chart 2) were synthesized as shown in Schemes I–III. In addition, their E-diastereomers were also obtained. The stereoselective synthesis of **8** has been previously reported by Meyer and Magarian (*32*). In the di- and triaryl structures, the phenyl rings



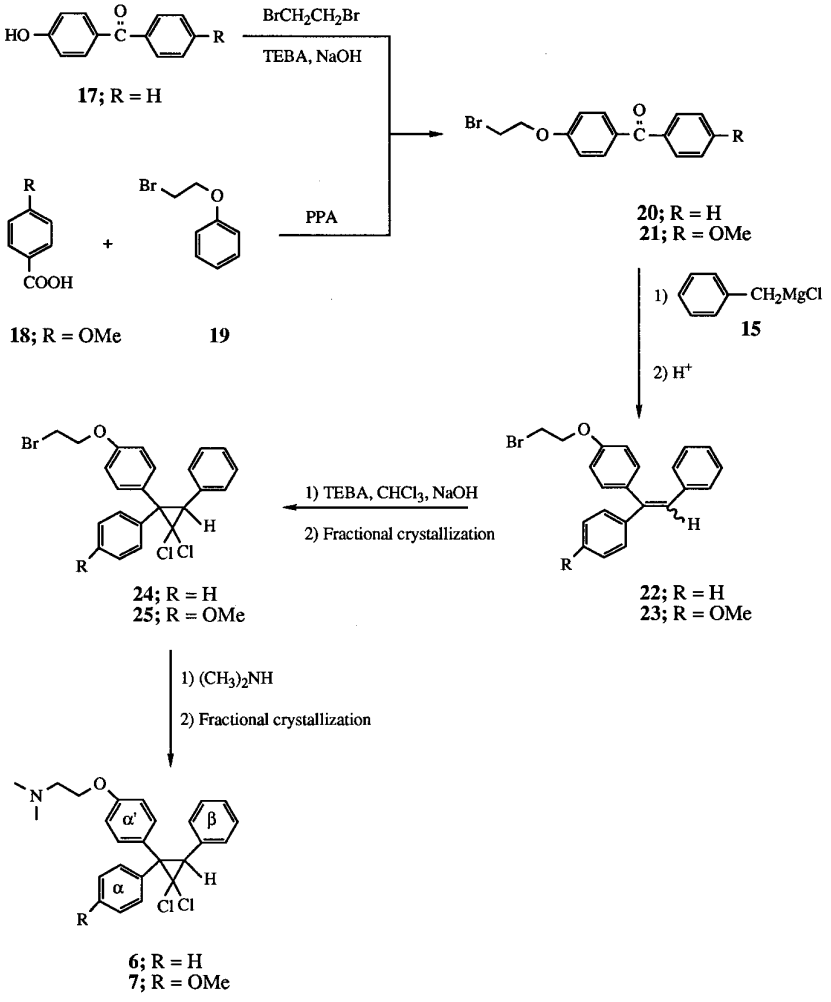

**9** **10** **11** **4** **12**

SCHEME I




**13** **11** **14** **15** **16** **5**

SCHEME II




SCHEME III

are denoted $\alpha$, $\alpha'$, and $\beta$ to conform with current notations used in nonsteroidal antiestrogens.

In general, the preparation of these compounds required the synthesis of the appropriately substituted ethenes via a Grignand reaction followed by the dehydration of the intermediate carbinols. Dichlorocyclopropanation of the ethene followed, which was accomplished by the stereospecific addition of the dichlorocarbene generated from chloroform and 50% aq NaOH in the presence of TEBA as the anion transfer agent (*33*). Fractional crystallization was employed to separate the diastereomers. Displacement of the side chain bromide with dimethyl amine followed by fractional crystallization furnished the basic side chain compounds (*34*).

TABLE 2
Retention Time and Characterization of Enantiomers

| Compound No. | Solvent system[a] | Retention time (min) | Optical rotation[b] | Enantiomeric purity (%)[c] |
|---|---|---|---|---|
| **4** | A | 5.3 | −30.76 | 100 |
| | | 6.5 | +26.02 | 99.1 |
| **5** | B | 4.2 | −31.94 | 99.5 |
| | | 4.6 | +34.41 | 100 |
| **6** | C | 4.9 | −38.69 | 100 |
| | | 6.3 | +38.97 | 100 |
| **7** | C | 6.7 | −26.89 | 100 |
| | | 9.5 | +26.75 | 99.8 |

[a] A, hexane : ethanol (9 : 1); B, hexane : 2-propanol (9 : 1); C, hexane : 2-propanol : diethylamine (9 : 1 : 0.01).
[b] Optical rotations were determined in $CH_2Cl_2$ at ambient temperature, $\lambda = 589$ nm.
[c] The overall purity of enantiomers was >98% as determined from HPLC chromatograms.

Synthesis of **4** involved the protection of the 4-hydroxyl group of ketone **9** before subjecting it to a Grignand reaction to obtain the ethene **12** as shown in Scheme I. Fractional crystallization at the ethene stage afforded enriched Z- and E-isomers. The individual isomers were converted into their dichlorocyclopropanes to obtain both the Z- and E-isomers of **4.**

The synthesis of **5** required two steps. Two different Grignard reagents were used for the synthesis of ethene **16** as shown in Scheme II. The yields with these reagents (**11** and **15**) were 79 and 56%, respectively. Although, the yield with reagent **11** was higher, the availability of **15** commercially made the synthesis simple and less tedious. After the cyclopropanation reaction fractional crystallization was performed in pet ether/acetone to afford the Z- and E-isomers of **5.**

The synthesis of **6** and **7** was performed as depicted in Scheme III. The first step involved the synthesis of the bromoethoxy ketones (**20, 21**). The bromoethyl group was used for two purposes: first it served as the protective group in **17** for the Grignard reaction, and second, the bromo group was easily displaced by the dimethyl amino group. Ketone **20** was prepared by the O-alkylation of **17** using 1,2-dibromoethane in a phase transfer reaction (*29*). However, **21** was obtained by the electrophilic aromatic substitution involving **18** and **19** in the presence of PPA, which served as the dehydrating agent. The ethenes (**22, 23**) were then obtained from the Grignard reaction. The fractional crystallization of the cyclopropanes (**24, 25**) and the subsequent dimethylamination of the individual diastereoisomers, followed by fractional crystallization, afforded the pure diastereoisomers **6** and **7.**

The $^1$H NMR resonances for the *O*-methylene protons in: (1) the benzyloxy side chain ($O\underline{CH_2}C_6H_5$) in Z-**4,** (2) the *O*-methyl protons in Z-**5,** (3) the *O*-methylene protons of the bromoethoxy side chain ($O\underline{CH_2}CH_2Br$) in **24** and **25,** and (4) the *N*,*N*-dimethylethoxy side chain ($O\underline{CH_2}CH_2N(\underline{CH_3})_2$) in **6** and **7** appear at a relatively higher field in comparison to their E-isomers, owing to the shielding effect of the adjacent phenyl ring (*35, 36*). The relevant $^1$H NMR data are shown in Table 1.

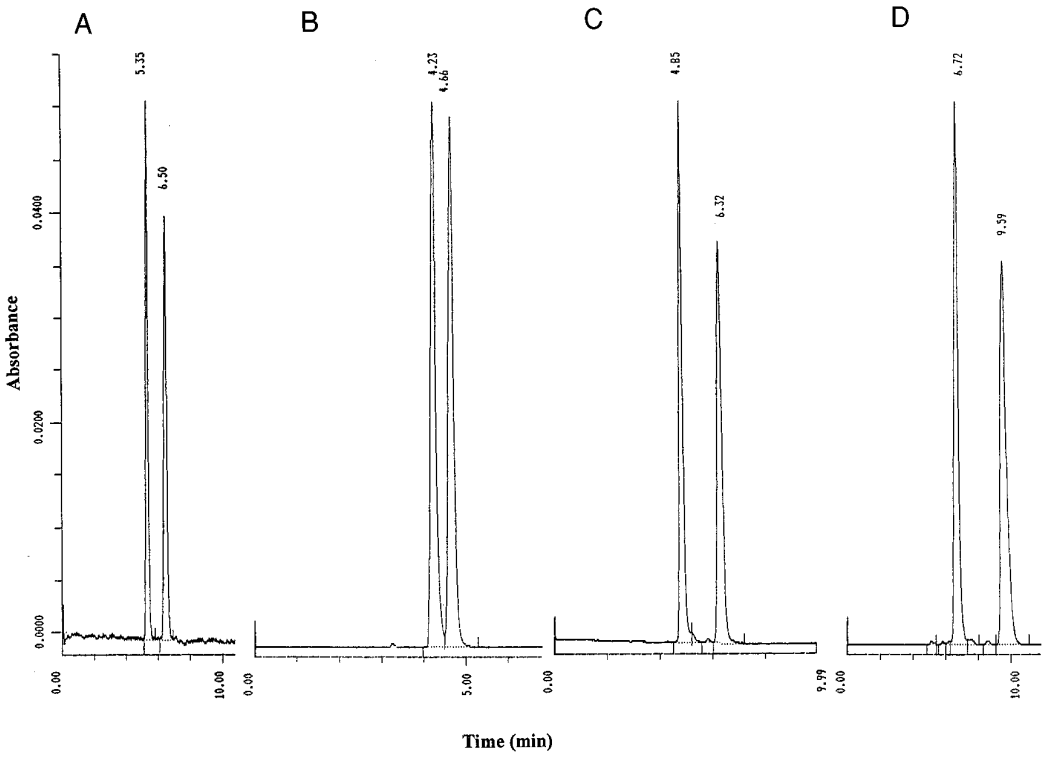



FIG. 1. HPLC chromatograms of (A) (±)-Z-**4,** (B) (±)-Z-**5,** (C) (±)-Z-**6,** and (D) (±)-Z-**7.** (For separation conditions see Experimental.)

Single crystal X-ray analysis was used to determine the configuration of both the Z- and E-isomers (*37, 38*).

Enantiomeric resolution is one of the most important subjects in the field of fine chemistry. A variety of racemates have been resolved (*39*) using two different techniques: the direct and indirect method (*40*). The direct technique involves the chromatographic separation of enantiomers using chiral stationary phase or chiral mobile phase, and the indirect technique is the method of derivatization of diastereoisomers prior to chromatographic separation. The direct method was chosen to separate the enantiomers in this work.

The semipreparative resolution of the enantiomers from the (Z) diastereoisomers (**4–8**) into their respective enantiomers was accomplished using chiral chromatography. Table 2 shows the results of the chiral separation. Solvent systems containing hexane and an alcohol are recommended for separation on a chiral stationary phase, amylose tris-3,5-dimethylphenyl carbamate, to prevent deterioration of the column material. Three solvent systems consisting of hexane/EtOH (A; 9:1), hexane/2-PrOH (B; 9:1), and hexane/2-PrOH/diethylamine (C; 9:1:0.01) were evaluated in this study. In order to find the best conditions for the chiral separation of each

compound, their capacity factor (K), column plate number (N), separation factor ($\alpha$), and resolution factor (Rs) were determined using solvent systems A, B, and C. These parameters were calculated using the chiral analytical column. When selecting the appropriate solvent system for each compound, emphasis was placed upon the resolution factor since this value incorporates all other parameters. The addition of diethylamine to solvent system B resulted in significant improvement in the resolution factor of **6** (6.18 vs 4.15) and **7** (8.14 vs 6.51); therefore, solvent C was chosen for the separation of compounds **6** and **7** using a semipreparative column. The addition of diethylamine led to shorter retention times. The values of resolution factors for **4** and **5** using solvent systems A and B were 5.00 vs 5.21 and 1.36 vs 2.23, respectively. The chromatograms of compounds **4–7** are shown in Fig. 1 (A–D). Since these compounds were only partially soluble in the HPLC eluent, they were dissolved in hexane/$CHCl_3$ (4 : 1; **4**), hexane/2-PrOH (2 : 1; **5**), or hexane/2-PrOH (3 : 2; **6, 7**). Following the separation of the individual enantiomers, samples were reinjected on the analytical column to establish enantiomeric purity. It is important to note that the enantiomers of the E-diastereoisomers could not be separated successfully on this column under similar separation conditions. Other chiral columns were also evaluated for the separation of the Z-isomers, but were unsuccessful in separating the optical isomers.

In summary, the Z-isomers of 1,1-dichloro-2,2,3-triarylcyclopropanes as potent antitumor agents were synthesized and characterized by high-resolution NMR. Enantiomers of each isomer were separated using semipreparative chiral HPLC. Appropriate solvent systems were evaluated and optical rotations were determined.

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