CHEMISTRY LETTERS, pp. 1821-1824, 1994.

Synthesis of Z-1,1-Dichloro-2-[4-(2-dimethylaminoethoxy)phenyl]-2-(4-hydroxyphenyl)-3-phenyl Cyclopropane and Z-1,1-Dichloro-2-[4-(2-dimethylaminoethoxy)phenyl]-2-(4-chlorophenyl)-3-phenyl Cyclopropane

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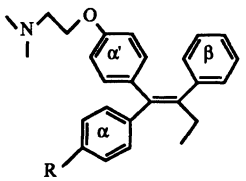
The synthesis of title compounds is described. The key steps in the synthesis are the preparation of the pure Z-ethene, the stereospecific addition of dichlorocarbene, amino-dehalogenation and deprotection of the phenol. Heptafluorotolyl protecting group is used in the synthesis of pure Z-ethene which is stable under basic heterogenous cyclopropanation reaction conditions.

Although tamoxifen (**1**) is the drug currently used for the treatment of hormone-dependent breast cancer[1] and for long term adjuvant therapy in postmenopausal women,[2] the development of tamoxifen resistance and the increased risk of endometrial carcinoma[3] has encouraged the design of more effective antihormonal agents; particularly, to prevent the increased risk in hormone-resistant breast cancer.[2]

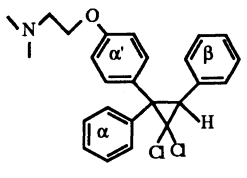
In order to develop a pure antiestrogen with greater therapeutic utility, a series of di- and triarylcyclopropyl compounds were synthesized and evaluated for their antiestrogenic activity in our laboratory.[4] Recently, we reported[5] that compound Z-1,1-dichloro-2,3-diphenyl-2-[4-(2-dimethylamino)ethoxy]phenyl cyclopropane (**3**) exhibited greater estrogen receptor binding affinity and was more potent in reducing the density of microvilli (MV) on MCF-7 cells than tamoxifen. Further, **3** was equipotent to tamoxifen (**1**) in reducing MCF-7 cell proliferation.

Tamoxifen (**1**) is metabolized in the plasma of patients,[6] and of the several known metabolites the hydroxylated derivative (**2**) has a much greater potency than the parent drug. [7-9] The higher activity of metabolite **2** resulted from its higher binding affinity to estrogen receptors because the phenolic group is thought to be functionally equivalent to the C-3 hydroxyl group in 17-β-estradiol (**4**). It is possible that the 4-hydroxylated metabolite of **3** (**21**) might analogously play a significant role in the overall activity of **3**. In addition, the 4-chloro derivative (**18**) was prepared for future in vivo evaluation to determine the importance of the oxidative step during the metabolism of **3**.

In this communication we wish to report the synthesis of Z-1,1-dichloro-2-[4-(2-dimethylaminoethoxy)phenyl]-2-(4-hydroxyphenyl)-3-phenyl cyclopropane (**21**) and Z-1,1-dichloro-2-[4-(2-



1; R=H
2; R=OH



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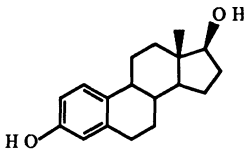

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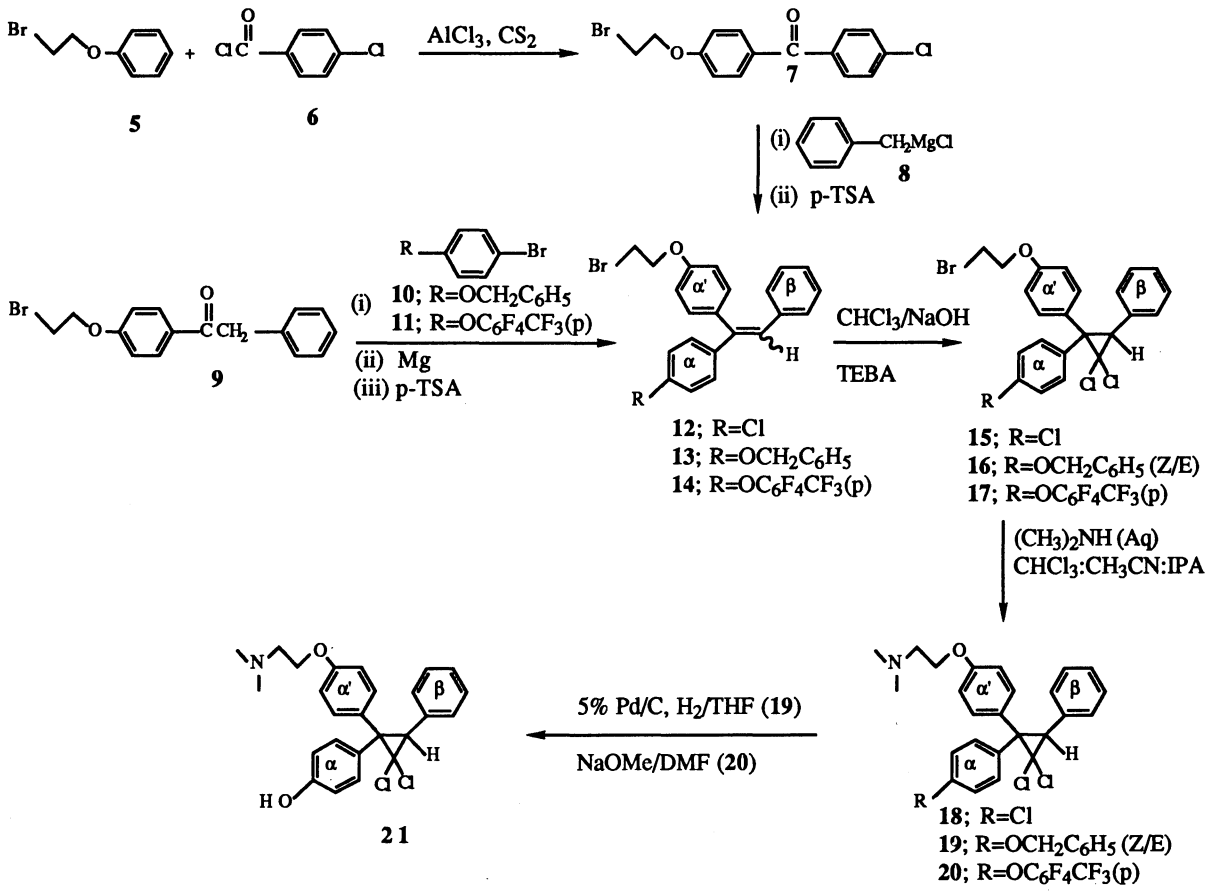
dimethylaminoethoxy)phenyl]-2-(4-chlorophenyl)-3-phenyl cyclopropane (**18**). Compound **21** was synthesized by two different synthetic methods which assist in the proof[10,11] of the stereochemistry of the Z and E isomers.[12] The single crystal X-ray analysis of the structure of **18** has been determined.[13]

The Z/E ethenes **12-14** were conveniently obtained by using the Grignard reaction involving p-bromoethoxyphenyl ketones (**7** and **9**) followed by dehydration in the presence of p-TSA as depicted in Scheme 1. Although this reaction proceeded as reported for the corresponding preparations of dimethylaminoethoxy derivatives,[14] to furnish the required Z isomer, the dehydration step yielded 1:1 mixture of ethenes. The reaction using 4-(heptafluorotolyloxy)phenyl bromide with Mg was sluggish and occurred only in the presence of 1,2-dibromoethane.[15] The ethenes then were reacted with dichlorocarbene generated by the catalytic phase-transfer method[16-18] involving 50% aqueous solution of sodium hydroxide, chloroform and benzyltriethylammonium chloride (TEBA; as the anion-transfer agent) to yield the dichlorotriarylcyclopropanes (DTACs; **15-17**; 58-65%). The dimethylamino derivatives **18-20** were prepared in the presence of aqueous dimethylamine solution added to **15-17** in the $CHCl_3$:MeCN:IPA (3:5:5) solvent system at 55 °C and were obtained in 80- 85% yield.[19] The final step involved the removal of the benzyl (**19**) and the heptafluorotolyl (**20**) group to produce the desired phenol (**21**), which was accomplished by the hydrogenolysis of **19** in THF and 5% Pd/C[20] or by the hydrolysis of **20** in the presence of sodium methoxide in DMF.[15]

Since it was difficult to separate the Z and E isomers of the ethene (**13**) using column chromatography, the heptafluorotolyl group (**11**) was used in place of the benzyl group (**10**) as the protecting group for the p-



Scheme 1.

bromophenol.[21] It was anticipated that because of the lipophilicity and electron withdrawing nature of the heptafluorotolyl group, the geometrical isomers would be easier to separate.[15] Besides, an important aim in this work was to determine if the heptafluorotolyloxy group would survive the dichlorocyclopropanation reaction conditions (**14**→**17**). Pure Z ethene (**14**) was indeed obtained by this method after chromatographic separation and fractional crystallization from light petroleum ether (40-60) and characterized by ^{1}H NMR. The O-methylene protons of the bromoethoxy side chain (OCH_2CH_2Br) in **14** appeared relatively at a higher field in comparison to the E isomer of ethene **14**, owing to the shielding effect of the adjacent phenyl ring.[22-24] The C-2 olefinic proton (H-2) also appeared slightly upfield for the Z isomer compared to E isomer. The relevant ^{1}H NMR data are shown in Table 1.

Table 1. Characterization of Z/E Isomers

Compound No.	Isomer	Elemental analysis[a]	^{1}H NMR data[b,c]				
			OCH_2CH_2	OCH_2CH_2			NCH_3
12	Z	$C_{22}H_{18}BrClO$	4.31	3.65	6.88		
	E		4.32	3.67	6.89		
13	Z	$C_{29}H_{25}BrO_2$	4.32	3.66	6.88		
	E		4.33	3.69	6.89		
14	Z	$C_{29}H_{18}BrF_7O_2$	4.32	3.66	6.92		
	E		4.37	3.68	6.93		
15	Z	$C_{23}H_{18}BrCl_3O$	4.21	3.58		3.47	
	E		4.23	3.60		3.51	
16	Z	$C_{30}H_{25}BrCl_2O_2$	4.23	3.60		3.50	
	E		4.25	3.60		3.51	
17	Z	$C_{30}H_{18}BrCl_2F_7O_2$	4.23	3.60		3.49	
	E		4.25	3.60		3.52	
18	Z	$C_{25}H_{24}Cl_3NO$	4.00	2.71		3.47	2.38
	E		4.06	2.69		3.52	2.31
19	Z	$C_{32}H_{31}Cl_2NO_2$	4.07	2.87		3.46	2.44
	E		4.09	2.89		3.49	2.42
20	Z	$C_{32}H_{24}Cl_2F_7NO_2$	3.97	2.66		3.45	2.28
	E		3.99	2.68		3.49	2.31
21	Z	$C_{25}H_{25}Cl_2NO_2$	4.09	2.90		3.48	2.46
	E		4.10	2.87		3.51	2.45

a) Analyses for C H N Br Cl F N were obtained within ± 0.4% of the calculated values. b) ^{1}H NMR spectra were run on Varian XL-300 NMR spectrometer with TMS as internal standard in $CDCl_3$. The chemical shifts are given in ppm (δ). c) Compared to the ^{1}H NMR of the X-ray structure of the (Z)-triarylcyclopropanes.[10,11]

The pure Z-1,1-dichloro-2-[4-(2-dimethylaminoethoxy)phenyl]-2-(4-hydroxyphenyl)-3-phenyl cyclopropane (**21**) was thus obtained from the pure Z ethene (**14**) following the reaction sequences shown in Scheme 1. As anticipated the C-3 cyclopropyl protons (H-3) and methylene protons of the bromoethoxy side chain in **20** and **21** were observed at higher fields (Table 1).

We acknowledge the Presbyterian Health Foundation (PHF) Grant No. 836, Oklahoma City, OK 73104 for financial assistance

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(Received June 23, 1994)