

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

Satendra SINGH and Robert A. MAGARIAN*

Medicinal Chemistry/Pharmacodynamics Section, College of Pharmacy, University of Oklahoma, Health Sciences Center, Oklahoma City, OK 73190, U.S.A.

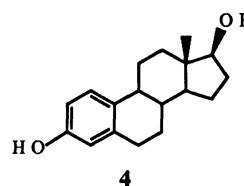
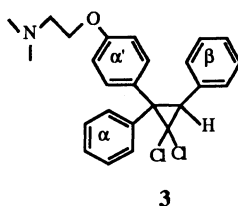
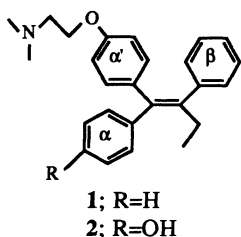
The synthesis of title compounds is described. The key steps in the synthesis are the preparation of the pure Z-ethene, the stereospecific addition of dichlorocarbene, amino-dehalogenation and deprotection of the phenol. Heptafluorotolyl protecting group is used in the synthesis of pure Z-ethene which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

Although tamoxifen (**1**) is the drug currently used for the treatment of hormone-dependent breast cancer¹⁾ and for long term adjuvant therapy in postmenopausal women,²⁾ the development of tamoxifen resistance and the increased risk of endometrial carcinoma³⁾ 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 reported⁵⁾ 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**.

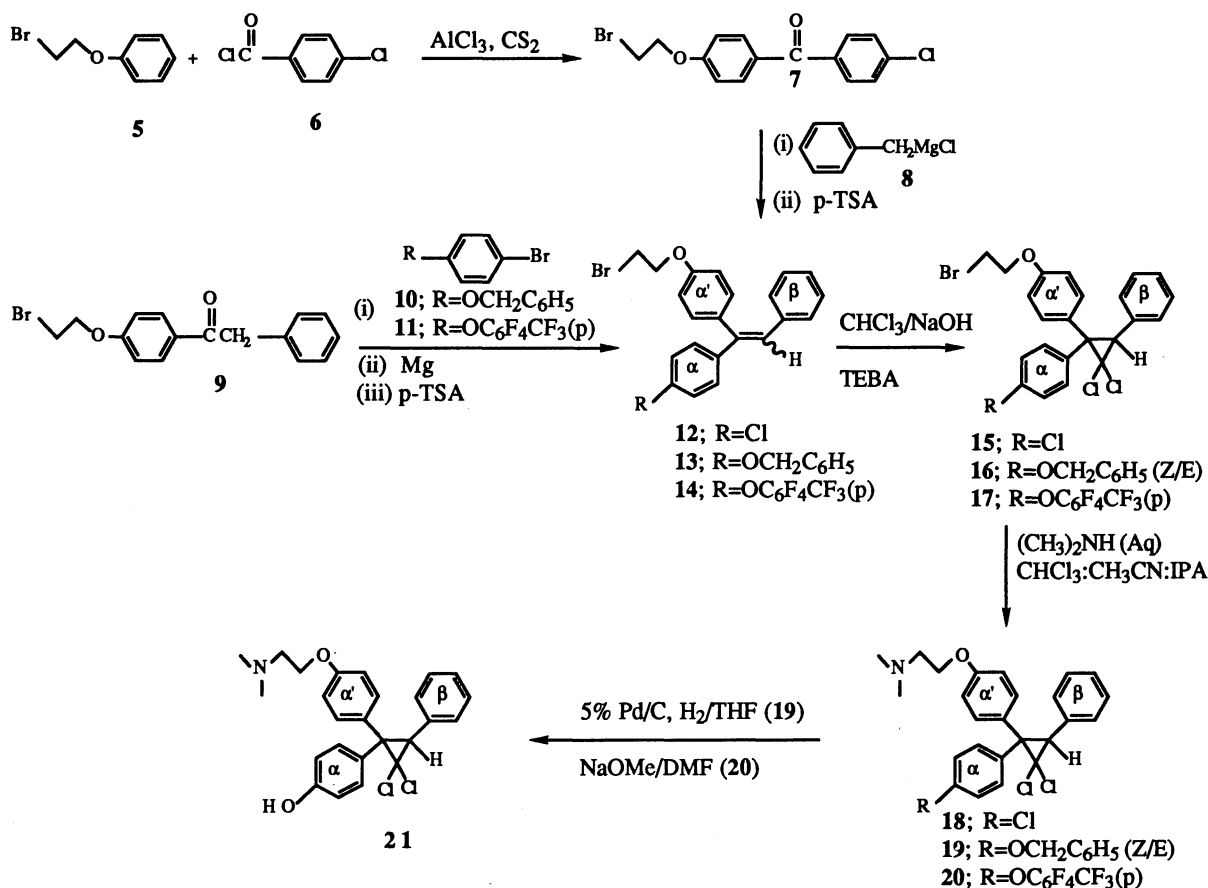
In this communication we wish to report the synthesis of Z-1,1-dichloro-2-[4-(2-dimethylaminoethoxy)phenyl]-2-(4-hydroxyphenyl)-3-phenyl cyclopropane (**21**) and Z-1,1-dichloro-2-[4-(2-



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 method¹⁶⁻¹⁸ involving 50% aqueous solution of sodium hydroxide, chloroform and benzyltriethylammonium chloride (TEBA; as the anion-transfer agent) to yield the dichlorotriaryl cyclopropanes (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 CHCl₃: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/C²⁰ 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 ¹H NMR. The O-methylene protons of the bromoethoxy side chain (OCH₂CH₂Br) 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 ¹H 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 ₂ CH ₂	OCH ₂ CH ₂	$\begin{array}{c} \diagup \\ \text{H} \\ \diagdown \end{array}$	$\begin{array}{c} \diagup \\ \text{H} \\ \diagdown \\ \text{Cl Cl} \end{array}$	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 ₇ O ₂	4.32	3.66	6.92		
	E		4.37	3.68	6.93		
15	Z	C ₂₃ H ₁₈ BrCl ₃ O	4.21	3.58		3.47	
	E		4.23	3.60		3.51	
16	Z	C ₃₀ H ₂₅ BrCl ₂ O ₂	4.23	3.60		3.50	
	E		4.25	3.60		3.51	
17	Z	C ₃₀ H ₁₈ BrCl ₂ F ₇ O ₂	4.23	3.60		3.49	
	E		4.25	3.60		3.52	
18	Z	C ₂₅ H ₂₄ Cl ₃ NO	4.00	2.71		3.47	2.38
	E		4.06	2.69		3.52	2.31
19	Z	C ₃₂ H ₃₁ Cl ₂ NO 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 ₂ F ₇ NO 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 ₂ NO 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 $\pm 0.4\%$ of the calculated values. b) ¹H NMR spectra were run on Varian XL-300 NMR spectrometer with TMS as internal standard in CDCl₃. The chemical shifts are given in ppm (δ). c) Compared to the ¹H 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

References

- 1) B. J. A. Furr and V. C. Jordan, *Pharmacol. Ther.*, **25**, 127 (1984).
- 2) C. S. Murphy, C. J. Parker, R. McCague, and V. C. Jordan, *Mol. Pharmacol.*, **39**, 421 (1991).
- 3) M. A. Killackey, T. B. Hakes, and V. K. Pierce, *Cancer Treat. Rep.*, **69**, 237 (1985).
- 4) B. W. Day, R. A. Magarian, P. T. Jain, J. T. Pento, G. K. Mousissian, and K. L. Meyer, *J. Med. Chem.*, **34**, 842 (1991); M. T. Griffin, R. A. Magarian, P. Jain, J. T. Pento, G. K. Mousissian, and D. C. Graves, *Anti-Cancer Drug Des.*, **7**, 49 (1992).
- 5) P. T. Jain, J. T. Pento, and R. A. Magarian, *Breast cancer Res. Treat.*, **25**, 225 (1993).
- 6) C. P. Daniel, S. J. Gaskell, H. Bishop, and R. I. Nicholson, *J. Endocrinol.*, **83**, 401 (1979).
- 7) V. C. Jordan, M. Collins, L. Rowsby, and G. Prestwich, *J. Endocrinol.*, **75**, 305 (1977).
- 8) N. Binart, M. G. Catelli, C. Geynet, V. Puri, R. Hahnel, J. Mester, and E. E. Baulieu, *Biochem. Biophys. Res. Commun.*, **91**, 812 (1979).
- 9) A. E. Wakeling and S. R. Slater, *Cancer Treat. Rep.*, **64**, 741 (1980).
- 10) L. Du, M. B. Hossain, X. Ji, D. van der Helm, R. A. Magarian, and B. W. Day, *Acta Cryst.*, **C48**, 887 (1992).
- 11) M. B. Hossain, D. van der Helm, F. J. Schmitz, E. O. Pordesimo, R. A. Magarian, K. L. Meyer, L. B. Overacre, and B. W. Day, *J. Med. Chem.*, **37**, 1670 (1994).
- 12) The terms Z and E are not unambiguous. Here Z refers to the cis arrangement of α' and β phenyl rings while E refers to the trans arrangement of α' and β phenyl rings.
- 13) M. B. Hossain, D. van der Helm, R. A. Magarian, and S. Singh, unpublished data.
- 14) P. Sohar, G. Schneider, G. Abraham, T. Horvath, and Z. Mehesalvi, *Acta Chim. Acad. Sci. Hung.*, **105**, 201 (1980).
- 15) R. McCague, *J. Chem. Res. (Miniprint)*, **1985**, 771.
- 16) M. Makosza and W. Wawrzyniewicz, *Tetrahedron Lett.*, **1969**, 4659.
- 17) E. W. von Dehmlow and J. Schonefeld, *Liebigs Ann. Chem.*, **744**, 42 (1971).
- 18) E. W. Dehmlow and S. S. Dehmlow, "Phase Transfer Catalysis," Verlag Chemie, Deerfield Beach.(1980), p. 177.
- 19) A. Wissner, P. E. Sum, R. Schaub, C. A. Kohler, and B. M. Goldstein, *J. Med. Chem.*, **27**, 1174 (1984).
- 20) E. J. Corey and J. G. Smith, *J. Am. Chem. Soc.*, **101**, 1038 (1979).
- 21) R. McCague, G. Leclercq, N. Legros, J. Goodman, G. M. Blackburn, M. Jarman, and A. B. foster, *J. Med. Chem.*, **32**, 2527 (1989).
- 22) D. J. Collins, J. J. Hobbs, and C. W. Emmens, *J. Med. Chem.*, **14**, 952 (1971).
- 23) G. R. Bedford and D. N. Richardson, *Nature (London)*, **212**, 733 (1967).
- 24) P. Sohar, G. Abraham, G. Schneider, T. Horvath, and E. Fuggerth, *Acta Chim. Acad. Sci. Hung.*, **100**, 69 (1979).

(Received June 23, 1994)