1720, 1675, 880 cm^{-1}; ^{1}H NMR δ 4.58 (2 H, s), 3.62 (3 H, s), 2.60 (2 H, m), 2.38 (2 H, m), 1.80–1.30 (3 H, m), 1.23 (3 H, s), 1.00 (1 H, d, J = 12 Hz).

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Registry No. **2**, 2207-27-4; **3**, 64145-36-4; **4N**, 96166-47-1; **5**, 64145-42-2; **6N**, 96166-48-2; **6X**, 96194-21-7; **7**, 96166-49-3; **8N**, 96166-50-6; **8X**, 96166-51-7; **9**, 96166-52-8; **10**, 96166-53-9; **11N**, 53969-64-5; **11X**, 53969-65-6; **12N**, 94294-31-2; **12X**, 96166-54-0; **14**, 94323-92-9; **19**, 96194-22-8; **20**, 96166-55-1; **22**, 96166-56-2; **24**, 96166-57-3; **25**, 96166-58-4; **26**, 96166-59-5; **27**, 96166-60-8; CH_2=$C(CH_3)CO_2Me$, 80-62-6; CH_2=$CHCO_2Me$, 96-33-3; CH_2=$C(CH_3)CN$, 126-98-7.

Stereospecific Synthesis of (*Z*)-Tamoxifen via Carbometalation of Alkynylsilanes

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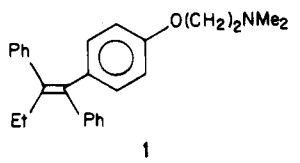
A stereospecific synthesis of (*Z*)-tamoxifen, a tetrasubstituted alkene with antiestrogenic activity, is described. The key reaction that establishes the olefin stereochemistry is a carbometalation of phenyl(trimethylsilyl)acetylene with diethylaluminum chloride–titanocene dichloride. A key intermediate that would lead to (*E*)-tamoxifen was also prepared in an analogous stereospecific manner.

(*Z*)-Tamoxifen[1,2] (1) (1 citrate = ICI-46,474, Nolvadex) is an antiestrogenic agent that inhibits the development and growth of mammary tumors in rats[3] and is effective in treating estrogen-dependent, metastatic breast cancer in humans.[4] On the other hand, (*E*)-tamoxifen, usually referred to as *cis*-tamoxifen (**2**, ICI-47,699), has no clinical



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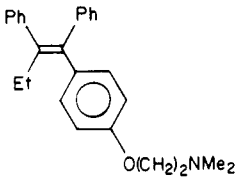

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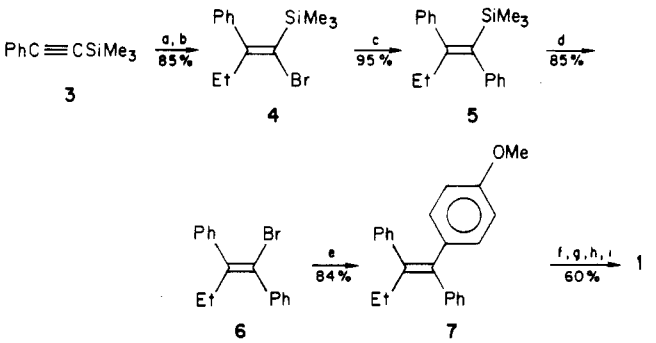
uses and is not only not antiestrogenic but in rats is an estrogen agonist.[5] To date, synthetic approaches to the tamoxifens have been nonstereospecific, producing mixtures of *Z* and *E* isomers which were separated by fractional crystallization techniques.[6] In this paper we report a stereospecific synthesis of (*Z*)-tamoxifen using the carbometalation of an alkynylsilane as the key step.

Results and Discussion

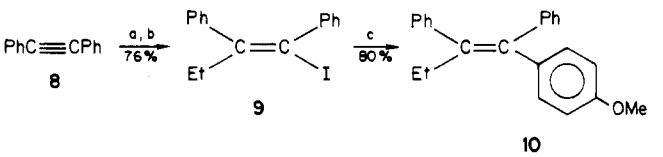
The initial step in the synthesis is based upon our recently published synthesis of 1-halo-1-(trimethylsilyl)-2,2-dialkyl olefins[7] and establishes the stereochemistry about the double bond. Thus phenyl(trimethylsilyl)-acetylene (**3**) was carbometalated with diethylaluminum chloride–titanocene dichloride to give an organometallic intermediate which was cleaved with *N*-bromosuccinimide at −78 °C. The product, **4**, by analogy to our earlier work,[7] was assinged the *E* stereochemistry. The bromine group was stereospecifically replaced by a phenyl group by palladium-catalyzed coupling[8] of **4** with phenylzinc chloride

Scheme I[a]



[a] (a) Et_2AlCl, Cp_2TiCl_2, CH_2Cl_2; (b) NBS, −78 °C; (c) PhZnCl, $Pd(PPh_3)_4$ (catalyst), THF, reflux; (d) Br_2, CH_2Cl_2, NaOMe/MeOH, −78 °C → room temperature; (e) *p*-$MeOC_6H_4ZnCl$, $Pd(PPh_3)_4$ (catalyst), THF, reflux; (f) NaSEt, DMF, reflux; (g) $ClCH_2CH_2NMe_2$·HCl, NaOEt, EtOH, reflux; (h) HCl(g), Et_2O; (i) 0.5 N NaOH.

Scheme II[a]



[a] (a) Et_2AlCl, Cp_2TiCl_2, CH_2Cl_2; (b) I_2, −78 °C; (c) *p*-$MeOC_6H_4ZnCl$, $Pd(PPh_3)_4$ (catalyst), THF, reflux.

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to give the vinylsilane **5**. Initial attempts to replace the trimethylsilyl group by bromine or iodine using cyanogen bromide–aluminum chloride[9] or iodine in methylene chloride,[10] respectively, failed. However, a facile substitution was accomplished by treatment of **5** with bromine–sodium methoxide[11] at −78 °C to give the vinyl bromide **6** in good yield (see Scheme I).

Attempts to couple the vinyl bromide **6** directly with zinc reagents derived from organometallic derivatives (magnesium and lithium) of 4-[2-(dimethylamino)ethoxy]phenyl bromide[6] proved unsuccessful under a variety of conditions. However, vinyl bromide **6** coupled very nicely with the (*p*-methoxyphenyl)zinc reagent to give ethyl triaryl olefin, **7**.

To ensure that **7** was produced without contamination by the *E* isomer, this latter compound was prepared as shown in Scheme II. Diphenylacetylene (**8**) was carbometalated with diethylaluminum chloride–titanocene dichloride, and the organometallic intermediate was cleaved with iodine to give the vinyl iodide **9**. Coupling of **9** with the (*p*-methoxyphenyl)zinc reagent gave the *E* isomer **10**. Both the aromatic region and methoxyl absorption in the ^{1}H NMR spectra of **7** and **10** are sufficiently different to demonstrate that each was produced in a stereospecific manner at the level of NMR analysis.

The methoxyaryl compound **7** was transformed into tamoxifen by first demethylation with sodium ethylthiolate in refluxing dimethylformamide followed by reaction of the phenoxide ion with 2-(dimethylamino)ethyl chloride. The crude tamoxifen was purified as its hydrochloride salt and regenerated by treatment with dilute base to give crystalline tamoxifen in 60% overall yield from **7** (see Scheme I).

Conclusion

We have demonstrated that (*Z*)-tamoxifen can be stereospecifically synthesized from alkynylsilanes using a carbometalation–halogenation sequence to establish the initial stereochemistry about the double bond. A key intermediate that could lead to the *E* isomer is also available by this methodology.

Experimental Section

Melting points are reported uncorrected. Infrared (IR) spectra were recorded on a Beckman IR-8 spectrophotometer, with only selected absorptions being reported. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian EM-390 instrument; chemical shifts are reported as δ values in parts per million (ppm) downfield from internal tetramethylsilane or δ^* values in ppm downfield from the trimethylsilyl absorption of the silicon-containing compound. High-resolution mass spectra were obtained on a Du Pont 492 mass spectrometer by Kei Miyano through the Facility for Advanced Instrumentation, University of California, Davis. Combustion analyses were performed by the Microanalysis Laboratory, University of California, Berkeley.

Diethylaluminum chloride (Texas Alkyls) was used as a neat liquid and assumed to be 7.6 M. All reactions were stirred magnetically and carried out under an atmosphere of nitrogen in oven-dried (150 °C) glassware.

(*E*)-1-Bromo-2-phenyl-1-(trimethylsilyl)-1-butene (4). To a three-necked, roundbottomed flask fitted with two addition funnels and a low-temperature thermometer and containing titanocene dichloride (10.01 g, 40.2 mmol, 1.4 equiv) in dichloromethane (200 mL) was added diethylaluminum chloride (5.32 mL, 40.2 mmol, 1.4 equiv) at room temperature. To this dark green solution was added dropwise phenyl(trimethylsilyl)acetylene[11] (5.0 g, 28.7 mmol), and the resultant dark red solution was stirred for 6 h at room temperature. After cooling to −78 °C (dry ice/acetone bath) the solution was diluted with dichloromethane (70 mL). Solid *N*-bromosuccinimide (11.75 g, 66.01 mmol, 2.3 equiv) was added at a rate such that the temperature remained below −70 °C, and the mixture was stirred an additional 0.5 h at −78 °C. The resultant suspension was poured into hexane and washed with an ice-cold sodium sulfite–3 N sodium hydroxide mixture. The solids were removed by filtration, and the filtrate was washed with sodium sulfite solution, 3 N hydrochloric acid, and saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. After removal of the solvent, the colorless residue was chromatographed on silica gel (100 g, eluted with hexane) to give 6.9 g (85% yield) of colorless product: IR (neat) 3100–3040 (m), 2980 (s), 1590 (m), 1250 (s), 870 (s), 830 (s), 760 (s), 700 (s), cm^{-1}; ^{1}H NMR (CCl_4) δ^* 0.00 (s, 9 H, $(CH_3)_3Si$), 1.05 (t, 3 H, J = 7.5 Hz, CH_3CH_2), 2.80 (q, 2 H, J = 7.5 Hz, CH_3CH_2C=), 7.25 (m, 5 H, aromatic H); high-resolution mass spectrum, calcd m/e for $C_{13}H_{19}{}^{79}BrSi$ 282.0440, found 282.0448.

(*Z*)-1,2-Diphenyl-1-(trimethylsilyl)-1-butene (5). A solution of phenylzinc chloride was prepared by adding phenyllithium (25.5 mL of a 2.2 M solution, 56.2 mmol, 3 equiv) to a solution of anhydrous zinc chloride (7.65 g, 56.2 mmol, 3 equiv) in dry tetrahydrofuran (187 mL) at such a rate that a slow reflux was maintained. The resultant solution was refluxed for an additional 30 min and then cooled to room temperature.

To a separate flask containing $Pd(PPh_3)_4$ (1.082 g, 0.936 mmol, 0.05 equiv) was added (*E*)-1-bromo-2-phenyl-1-(trimethylsilyl)-1-butene (5.3 g, 18.7 mmol) in dry tetrahydrofuran (47 mL), followed by addition of the phenylzinc chloride solution prepared above. The reaction mixture was refluxed for 10 h, cooled to room temperature, quenched with 3 N hydrochloric acid, and extracted with hexane. The combined organic layers were washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on silica gel (100 g, eluted with hexane) to give 4.98 g (95% yield) of colorless product: IR (neat) 3100–3040 (m), 2980 (s), 1595 (s), 1250 (s), 885 (s), 835 (s), 760 (s), 700 (s), cm^{-1}; ^{1}H NMR (CCl_4) δ^* 0.00 (s, 9 H, $(CH_3)_3Si$), 1.05 (t, 3 H, J = 7 Hz, CH_3CH_2), 2.45 (q, 2 H, J = 7 Hz, CH_3CH_2C=), 7.45 (m, 10 H, aromatic H); high-resolution mass spectrum, calcd m/e for $C_{19}H_{24}Si$ 280.1648, found 280.1623.

(*Z*)-1-Bromo-1,2-diphenyl-1-butene (6). To a solution of (*Z*)-1,2-diphenyl-1-(trimethylsilyl)-1-butene (3.36 g, 12 mmol) in dichloromethane (7 mL) cooled to −78 °C (dry ice/acetone bath) was added dropwise a solution of brimine (2.304 g, 14.4 mmol, 1.2 equiv) in dichloromethane (5 mL), followed by addition of a 1 M solution of sodium methoxide in methanol (24 mL, 24 mmol, 2 equiv). The resultant mixture was stirred for 5 min at −78 °C, allowed to warm to room temperature, and then stirred an additional 2 h. At the end of this time, the mixture was poured into water and extracted with hexane. The organic layer was dried over anhydrous sodium sulfate, and the solvent was removed to give a solid residue. After recrystallization from aqueous methanol, the material was dried in a vacuum desiccator to give 2.93 g (85% yield) of white crystalline product: mp (MeOH–H_2O) 101–102 °C; IR (CCl_4) 3100–3040 (m), 2980 (s), cm^{-1}; NMR (CCl_4) δ 0.85 (t, 3 H, J = 7.5 Hz, CH_3CH_2), 2.30 (q, 2 H, J = 7.5 Hz, CH_3CH_2C=), 7.25 (s, 5 H, aromtic H), 7.35 (s, 5 H, aromtic H). Anal. Calcd for $C_{16}H_{15}Br$: C, 66.91; H, 5.26; Br, 27.82. Found: C, 66.90; H, 5.36; Br, 27.63.

(*Z*)-1,2-Diphenyl-1-(*p*-methoxyphenyl)-1-butene (7). A solution of (*p*-methoxyphenyl)zinc chloride was prepared by adding (*p*-methoxyphenyl)lithium [prepared by reacting *p*-bromoanisole (1.68 g, 9 mmol, 3 equiv) with lithium metal (0.249 g, 36 mmol, 12 equiv) in 6 mL of anhydrous ether at room temperature for 2 h] to a solution of anhydrous zinc chloride (1.23 g, 9 mmol, 3 equiv) in dry tetrahydrofuran (12 mL). The resultant solution was refluxed for 30 min and then cooled to room temperature.

To a separate flask containing $Pd(PPh_3)_4$ (0.173 g, 0.05 equiv) was added (*Z*)-1-bromo-1,2-diphenyl-1-butene (0.861 g, 3 mmol) in dry tetrahydrofuran (7 mL), followed by addition of the (*p*-methoxyphenyl)zinc chloride solution prepared above. The reaction mixture was refluxed for 12 h, cooled to room temperature, quenched with 3 N hydrochloric acid, and extracted with hexane.

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(11) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424.

The combined organic layers were washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate. After removal of the solvent, the solid residue was recrystallized from aqueous methanol. This material was dried in a vacuum desiccator to give 0.79 g (84% yield) of white crystalline product: mp (MeOH–H_2O) 116–119 °C (lit.[12] mp 117–118 °C); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, CH_3CH_2), 2.45 (q, 2 H, J = 7 Hz, CH_3CH_2C=), 3.65 (s, 3 H, OCH_3), 6.50 (d, 2 H, J = 10 Hz, BB′ portion of AA′BB′ pattern), 6.70 (d, 2 H, J = 10 Hz, AA′ portion of AA′BB′ pattern), 7.10 (s, 5 H, aromatic H), 7.20 (s, 5 H, aromtic H).

(E)-1,2-Diphenyl-1-iodo-1-butene (9). In the manner previously described, titanocene dichloride (3.13 g, 12.35 mmol, 1.3 equiv) in dichloromethane (66 mL) was treated with diethylaluminum chloride (1.63 mL, 12.35 mmol, 1.3 equiv). To this solution was added dropwise diphenylacetylene (1.69 g, 9.5 mmol, Aldrich) in dichloromethane. The resultant solution was cooled to −78 °C, diluted with dichloromethane (23 mL), and treated with solid iodine (14.48 g, 57.0 mmol, 6 equiv). The mixture was stirred 1 h at −78 °C, warmed to room temperature, and stirred an additional 30 min. After workup as previously described, the solvent was removed to give a residue which was chromatographed on silica gel (40 g, eluted with hexane), yielding 2.41 g (76% yield) of a colorless product: IR (neat) 3100–3040 (m), 3000 (s), 1600 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, 3 H, J = 7.5 Hz, CH_3CH_2), 2.85 (q, 2 H, J = 7.5 Hz, CH_3CH_2C=), 7.05 (m, 10 H, aromatic H); high-resolution mass spectrum, calcd m/e for $C_{16}H_{15}I$ 334.0220, found 334.0448.

(E)-1,2-Diphenyl-1-(p-methoxyphenyl)-1-butene (10). As described previously, a tetrahydrofuran solution (12 mL) of (p-methoxyphenyl)zinc chloride was prepared from anhydrous zinc chloride (1.23 g, 9 mmol, 3 equiv) and (p-methoxyphenyl)lithium. This solution was reacted, in a separate flask, with a mixture of $Pd(PPh_3)_4$ (0.173 g, 0.05 equiv) and (E)-1,2-diphenyl-1-iodo-1-butene (1.00 g, 3 mmol) in dry tetrahydrofuran (7 mL). The resultant mixture was refluxed for 1 h and worked up as before. The crude product was chromatographed on silica gel (30 g, eluted with 80:20 hexane–dichloromethane) to give 0.754 g (80% yield) of white crystalline product: mp 99–101 °C (lit.[13] mp 101–103 °C); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, CH_3CH_2), 2.43 (q, 2 H, J = 7 Hz, CH_3CH_2), 3.81 (s, 3 H, OCH_3), 6.87 (d, 2 H, J = 10 Hz, BB′ portion of AA′BB′ pattern), 6.94 (m, 5 H, aromatic H), 7.12 (s, 5 H, aromatic H), 7.20 (d, 2 H, J = 10 Hz, AA′ portion of AA′BB′ pattern).

(Z)-Tamoxifen (1). To a slurry of sodium hydride [0.398 g (8.29 mmol) of a 50% mineral oil dispersion washed twice with dry tetrahydrofuran (10 mL)] in dry dimethylformamide (18 mL) cooled to 9 °C was added ethanethiol (0.593 g, 9.55 mmol) dropwise at such a rate as to prevent foaming. The mixture was stirred for 10 min after the addition was completed, and then (Z)-1,2-diphenyl-1-(p-methoxyphenyl)-1-butene (0.75 g, 2.39 mmol) in dry dimethylformamide (5 mL) was added in one portion. The resultant mixture was refluxed for 10 h, cooled to room temperature, poured into 3 N hydrochloric acid, and extracted with ether. The combined organic layers were washed with 3 N hydrochloric acid and saturated sodium chloride solution and dried over anhydrous sodium sulftate. Evaporation for the solvent gave a solid product (0.666 g, 93% crude yield) which was used without further purification:[14] ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, CH_3CH_2), 2.40 (q, 2 H, J = 7 Hz, CH_3CH_2C=), 6.40 (d, 2 H, J = 9 Hz, BB′ portion of AA′BB′ pattern), 6.70 (d, 2 H, J = 9 Hz, AA′ portion of AA′BB′ pattern), 7.10 (s, 5 H, aromtic H), 7.25 (s, 5 H, aromatic H).

To a solution of sodium ethoxide in ethanol [prepared by adding sodium metal (0.15 g, 6.53 mmol) to absolute ethanol (15 mL)] was added the crude (Z)-1,2-diphenyl-1-(p-hydroxyphenyl)-1-butene (0.632 g), obtained above, in absolute ethanol (15 mL). To this mixture was then added in one portion a solution of 2-(dimethylamino)ethyl chloride hydrochloride (0.607 g, 4.21 mmol) in warm absolute ethanol (15 mL). The resultant mixture was refluxed for 24 h, cooled to room temperature, poured into water, and extracted with ether. The combined organic layers were washed with 5% sodium hydroxide solution (3 times) and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.70 g of crude (Z)-tamoxifen as a highly viscous oil which resisted attempts at crystallization. This crude material was dissolved in anhydrous ether (10 mL), and hydrogen chloride gas was passed through the solution for 5 min. Evaporation of the solvent gave a residue which was recrystallized from ethyl acetate–hexane to give 0.560 g of (Z)-tamoxifen hydrochloride as a white crystalline solid, mp 189–191 °C. This material was treated with an aqueous solution of 0.5 N sodium hydroxide (80 mL), and the product was extracted with ether. The combined organic layers were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 0.50 g (60% overall yield from (Z)-1,2-diphenyl-1-(p-methoxyphenyl)-1-butene) of (Z)-tamoxifen as a white crystalline material: mp 95–97 °C (lit.[1] mp 96–98 °C); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz, CH_3CH_2), 2.25 (s, 6 H, $(CH_3)_2N$), 2.3–2.8 (m 4 H, CH_3CH_2C= and NCH_2), 3.90 (t, 2 H, J = 6 Hz, OCH_2), 6.50 (d, 2 H, J = 10 Hz, BB′ portion of AA′BB′ pattern), 6.75 (d, 2 H, J = 10 Hz, AA′ portion of AA′BB′ pattern), 7.15 (s, 5 H, aromatic H), 7.30 (s, 5 H, aromatic H).

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Registry No. 1, 10540-29-1; 4, 96212-84-9; 5, 96212-85-0; 6, 96212-86-1; 7, 6462-18-6; 9, 96212-87-2; 10, 6462-19-7; PhC≡CSiMe$_3$, 2170-06-1; Et_2AlCl, 96-10-6; PhZnCl, 28557-00-8; p-$MeOC_6H_4ZnCl$, 93296-09-4; PhC≡CPh, 501-65-5; $Me_2N(CH_2)_2Cl$·HCl, 4584-46-7; p-$MeOC_6H_4Li$, 14774-77-7; (Z)-1,2-diphenyl-1-(p-hydroxyphenyl)-1-butene, 69967-80-2.

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(14) Compounds similar to this, such as diethylstilbestrols, undergo facile Z–E isomerization; see: Winkler, V. W.; Nyman, M. A.; Egan, R. S. *Steroids* **1971**, *17*, 197.