81159-16-2; (±)-10, 72581-32-9; (±)-11, 81203-31-8; (±)-12, 72581-33-0; 13, 81159-17-3; (±)-cis-15, 33783-53-8; (±)-trans-15, 81159-18-4; (±)-cis-16, 81159-19-5; (±)-trans-16, 81159-20-8; (±)-17, 81159-21-9; (±)-18, 81159-22-0; 19, 1002-37-5; 20, 77493-17-5; (±)-cis-21, 81159-23-1; (±)-trans-21, 81159-24-2; (±)-trans-22, 81159-25-3; (±)-trans-22 hydrazone, 81159-26-4; (±)-23 (isomer I), 81159-27-5; (±)-24 (isomer I), 81159-28-6; (±)-25, 81159-29-7; (±)-25 hydrazone, 81159-30-0; (±)-25 Na, 81159-31-1; 25 copper chelate, 81177-95-9; 26, 69285-46-7; (±)-27, 81203-32-9; (±)-cis-28, 81159-32-2; (±)-trans-29, 81159-33-3; (±)-30, 81203-33-0; (±)-31, 81203-34-1; (±)-32 (isomer I), 81203-35-2; (±)-32 (isomer II), 81203-36-3; (±)-33 (isomer I), 81203-37-4; (±)-33 (isomer II), 81203-38-5; (±)-34 (isomer I), 81203-39-6; (±)-34 (isomer II), 81203-40-9; (±)-35, 81159-34-4; (±)-36, 81159-35-5; (±)-37 (isomer I), 81159-36-6; (±)-38, 81159-37-7; (±)-39, 81159-38-8; (±)-40, 81159-39-9; (±)-41, 81159-40-2; (±)-42, 81159-41-3; 43, 81159-42-4; methyl cyclohex-3-enecarboxylate, 49543-03-5; ethyl bromide, 74-96-4; 1-chloro-4-pentyne, 14267-92-6; 6-cyano-2-hexyn-1-ol, 69285-47-8; pent-2-ynol, 6261-22-9; pent-2-ynyl mesylate, 81159-43-5; benzyl alcohol, 100-51-6; (±)-23 (isomer II), 81159-44-6; (±)-24 (isomer II), 81159-45-7; (±)-37 (isomer II), 81159-46-8.

Synthesis of the *E* and *Z* Isomers of the Antiestrogen Tamoxifen and Its Metabolite, Hydroxytamoxifen, in Tritium-Labeled Form

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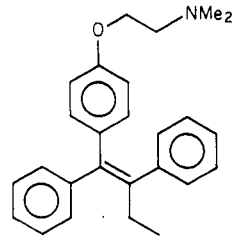
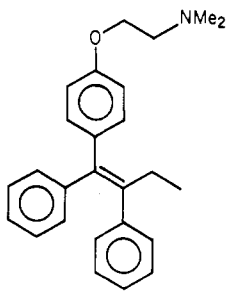
Received November 6, 1981

Both isomers of the potent antiestrogen tamoxifen (1,2-diphenyl-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-butene: *E* isomer = ICI-47699; *Z* isomer = ICI-46474, Nolvadex) and its metabolite, hydroxytamoxifen (1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-(4-hydroxyphenyl)-2-phenyl-1-butene), have been synthesized in a high specific activity, tritium-labeled form by catalytic tritium–halogen exchange performed on brominated precursors. The synthesis of another precursor to labeled tamoxifen which would enable the incorporation of three tritium atoms into the molecule by tritium–halogen exchange is reported.

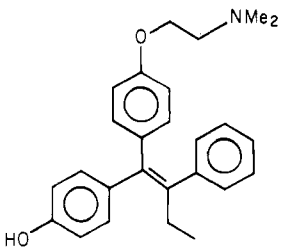
Antiestrogens are a group of compounds which block, at least in part, the action of estrogens on estrogen target tissues. Although originally prepared as potential human antifertility agents,[1] an application for which they have not proven useful, antiestrogens are used clinically for controlling mammary and endometrial carcinomas and managing a number of endocrine disorders.[2] They have also been useful as tools for probing the action of estrogens on a molecular level.[3] Recently, much interst has been focused on tamoxifen[4] (1, ICI-46,474, Nolvadex), an antiestrogen first described by Harper and Walpole.[5] Tamoxifen inhibits the development and growth of mammary tumors in rats[6] and is effective in treating estrogen-dependent, metastatic breast cancer in humans.[7] In vivo, tamoxifen is transformed to hydroxytamoxifen (3), which has a much higher binding affinity for the estrogen receptor and appears to be the compound responsible, in part, for the biological actions of tamoxifen.[8] Enigmatically, the *E* isomer of tamoxifen, usually referred to as *cis*-tamoxifen (2, ICI-47,699), has no clinical uses and is not antiestrogenic; in fact, in the rat it is a full estrogen agonist.[9]



tamoxifen
(1, *Z* isomer, ICI-46,474)



cis-tamoxifen
(2, *E* isomer, ICI-47,699)



hydroxytamoxifen (3)

To continue our studies on the mechanism of action, metabolism, and pharmacokinetics of antiestrogens,[10] we needed tamoxifen and hydroxytamoxifen in a high specific activity, tritium-labeled form.[11] We also desired to have

(1) Lerner, L. J.; Holthaus, J. F.; Thompson, C. R. *Endocrinology (Baltimore)* **1958**, *63*, 295–318.

(2) For reviews of the pharmacological uses of antiestrogens, see: Henningsen, B.; Linder, F.; Steichele, C., Eds. "Recent Results in Cancer Research"; Springer-Verlag: West Berlin, 1980; Vol 71. Lunan, C. B.; Klopper, A. *Clin. Endocrinol. (Oxford)* **1975**, *4*, 551–572. Tagnon, H. J. *Cancer* **1977**, *39*, 2959–2964.

(3) Katzenellenbogen, B. S. *Annu. Rev. Physiol.* **1980**, *42*, 17–35 and references cited therein.

(4) Produced by ICI, Ltd., under the trade name Nolvadex. For reviews of the pharmacology see: Heel, R. C.; Brogden, R. N.; Speight, T. M.; Avery, G. S. *Drugs* **1978**, *16*, 1–24. Furr, B. J.; Patterson, J. S.; Richardson, D. N.; Slater, S. R.; Wakeling, A. E. In "Pharmacological and Biochemical Properties of Drug Substances"; Goldberg, M. E., Ed.; American Pharmaceutical Association: Washington, DC, 1979; Vol. 2, pp 335–399.

(5) Harper, M. J. K.; Walpole, A. L. *Nature (London)* **1966**, *212*, 87.

(6) Jordan, V. C. *J. Steroid Biochem.* **1974**, *5*, 354. Jordan, V. C. *Eur. J. Cancer* **1976**, *12*, 419–424. Jordan, V. C., Allen, K. E. *Ibid.* **1980**, *16*, 239–251.

(7) Wasterberg, H. *Cancer Treat. Rep.* **1980**, *64*, 117–121. Lerner, H. J.; Band, P. R.; Israel, L.; Leung, B. S. *Ibid.* **1976**, *60*, 1431–1435 and subsequent papers in this issue. Kiang, D. T.; Frenning, D. H.; Vosika, G. J.; Kennedy, B. J. *Cancer* **1980**, *45*, 1322–1325.

(8) Borgna, J.-L.; Rochefort, H. *C. R. Hebd. Seances Acad. Sci.* **1979**, *289*, 1141–1144; *J. Biol. Chem.* **1981**, *256*, 859–868. Fromson, J. M.; Pearson, S.; Bramah, S. *Xenobiotica* **1973**, *3*, 693–709, 711–714. Jordan, V. C.; Collins, M. M.; Rowsby, L.; Prestwich, C. *J. Endocrinol.* **1977**, *75*, 305–316.

(9) Jordan, V. C.; Haldeman, B.; Allen, K. E. *Endocrinology (Baltimore)* **1981**, *108*, 1353–1361 and references cited therein.

(10) Katzenellenbogen, B. S.; Pavlik, E. J.; Robertson, D. W.; Katzenellenbogen, J. A. *J. Biol. Chem.* **1981**, *256*, 2098–2915. Tatee, T.; Carlson, K. E.; Katzenellenbogen, J. A.; Robertson, D. W.; Katzenellenbogen, B. S. *J. Med. Chem.* **1979**, *22*, 1509–1517. Katzenellenbogen, B. S.; Katzenellenbogen, J. A.; Eckert. R. L.; Hayes, J. R.; Robertson, D. W.; Tatee, T.; Tsai, T. L. *Prog. Cancer Res. Ther.* **1980**, *14*, 309–320. Hayes, J. R.; Rorke, E. A.; Robertson, D. W.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Endocrinology (Baltimore)* **1981**, *107*, 164–172.

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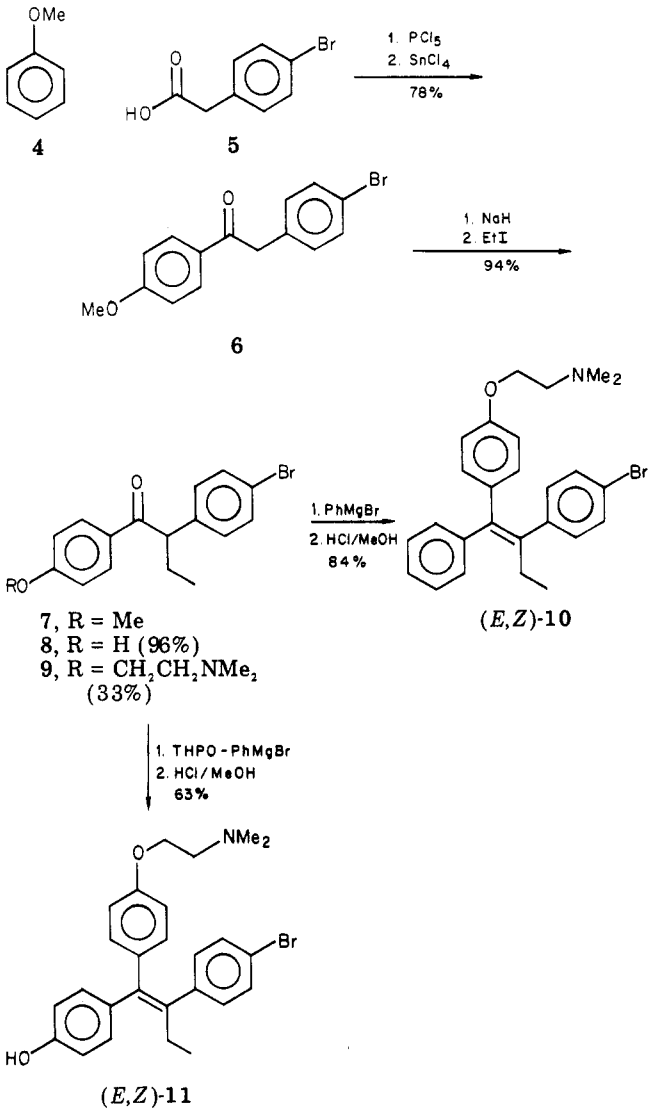
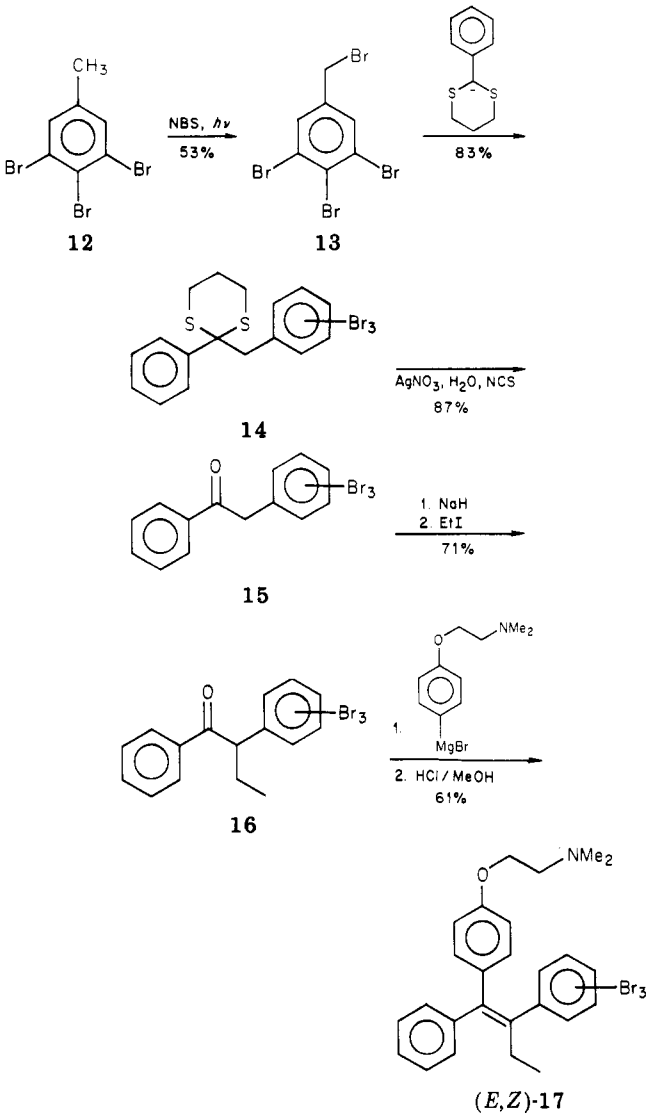
Scheme I



Scheme II



both of the geometrical isomers of these compounds in radiolabeled form, so as to able to investigate, on a molecular level, the basis for the contrasting hormonal properties of the cis and trans isomers of tamoxifen. In this account, we describe synthetic routes that can be used to prepare halogenated precursors to the tritium-labeled aniestrogens, and we describe the use of these precursors to prepare, in the high specific activity, tritium-labeled form, the *E* and *Z* isomers of both tamoxifen and hydroxytamoxifen.

Results and Discussion

Chemical Syntheses. The [^{3}H]tamoxifen precursor used for the preparation of the radiolabeled material is the bromotamoxifen **10** (Scheme I). The synthesis of this material began with a Friedel–Crafts acylation involving anisole (**4**) and (4-bromophenyl)acetic acid (**5**), giving he ketone **6** in 78% yield. Alkylation was effected by treating the sodium enolate of the ketone with ethyl iodide to give **7** (94%). Deprotection of the phenol was carried out by using lithium ethanethiolate in DMF (96%), and the resulting product was alkylated with 2-(dimethylamino)ethyl chloride (33%, >70% based on recovered starting material) to give **9**. Reaction of ketone **9** with phenylmagnesium bromide and dehydration of the resuling alcohol in methanolic hydrogen chloride gave a mixture (**10**) of bromotamoxifen and its cis analogue (trans/cis ratio of 1.3:1) in 84% yield. In model experiments for the tritiation, it was found that catalytic hydrogen–halogen exchange over 5% palladium on carbon (atmospheric pressue, 1 h) gave a mixture of tamoxifen (**1**) and its cis isomer (**2**), in 92% overall yield.

The geometrical isomers of tamoxifen are separable by silica gel TLC with benzene/triethylamine (9:1) as the developing solvent, and the identity of these isomers is easily ascertained by ^{1}H NMR. The AA′XX′ pattern for the disubstituted aromatic ring in the more mobile *Z* isomer is significantly upfield (0.4 ppm) relative to the corresponding resonance in the *E* isomer.[12]

Bromohydroxytamoxifen **11** may also be prepared from ketone **9**. Reaction of the ketone with [4-[(2-tetrahydropyranyl)oxy]phenyl]magnesium bromide (prepared by

(11) [^{3}H]- and [^{14}C]tamoxifen have been prepared by ICI, Ltd., but the syntheses have never been published. After our work was completed, a synthesis of [^{3}H]tamoxifen bearing one tritium was described: Seitz, D. E.; Milius, R. A.; El-Wakil, H. *Synth. Commun.* **1981**, *11*, 281–286.

Note Added in Proof: A description of [^{14}C]tamoxifen by ICI, Ltd. workers has just appeared: Burns, J.; Rutter, D. *J. Labelled Compd. Radiopharm.* **1982**, *19*, 229–238.

(12) For a discussion of the differences in the ^{1}H NMR spectra of the *E* and *Z* isomers of substituted triarylethylenes, see: Collins, D. J.; Hobbs, J. J.; Emmens, C. W. *J. Med. Chem.* **1971**, *14*, 952–957. Bedford, G. R.; Richardson, D. N. *Nature (London)* **1966**, *212*, 733–734.

addition of the corresponding organolithium compound to an ethereal solution of magnesium bromide) with **9**, followed by dehydration and deprotection in methanolic hydrogen chloride, gave the product **11** as a mixture of geometrical isomers (ca. 1:1 *E*/*Z*) in 63% yield. Hydrogen–halogen exchange to give a mixture of hydroxytamoxifen (**3**) and its cis isomer proceeded without difficulty.

Since some biochemical and biological experiments require radiolabeled material of greater specific activity than can be provided with one tritium atom per molecule (≤29.12 Ci/mmol),[13] the [^{3}H]tamoxifen precursor **17** (Scheme II) was synthesized to allow the introduction of three tritium atoms. 1-(Bromomethyl)-3,4,5-tribromobenzene (**13**) was synthesized by bromination of tribromotoluene **12**[14] with *N*-bromosuccinimide in carbon tetrachloride. The crude product was a mixture of the desired substance, starting material, and 1-(dibromomethyl)-3,4,5-tribromobenzene in an approximately 2:1:1 ratio as judged by ^{1}H NMR analysis, and the desired product was obtained by fractional crystallization from carbon tetrachloride/hexane (53%). Reaction of this tetrabromobenzene derivative with 2-lithio-2-phenyl-1,3-dithiane gave the tribromodeoxybenzoin protected as the trimethylene thioketal (**14**) in 83% yield. Hydrolysis was effected by using *N*-chlorosuccinimide and silver nitrate in moist acetonitrile,[15] affording the ketone **15** in 87% yield after purification. Alkylation of this ketone via standard methodology gave the tribromobutanone **16** in 71% yield. Finally, reaction of the butanone with [4-[2-(dimethylamino)ethoxy]phenyl]magnesium bromide and dehydration of the resulting alcohol in methanolic hydrogen chloride provided a mixture of the isomers of tribromotamoxifen (**17**, ca. 1:1 *E*/*Z*) in 61% yield. Subjection of these isomers to catalytic hydrogenolysis afforded a mixture of *cis*- and *trans*- tamoxifen.

Production of Labeled Compounds. A mixture of bromotamoxifen and its cis isomer was subjected to catalytic reduction with 25 Ci of carrier-free tritium gas, and the reaction mixture was purified, and the isomers were separated by silica gel TLC with benzene–triethylamine (9:1) as the developing solvent.[16] Tamoxifen is more mobile than its cis isomer under these conditions, and both isomers could be obtained routinely at greater than 98% radiochemical purity. Thin-layer chromatograms of both isomers of [^{3}H]tamoxifen are shown in Figure 1AB.

The UV spectra of the tritiated compounds were identical with those of the unlabeled compounds. The specific activity of [^{3}H]tamoxifen, determined by quantitation of its absorbance at 238 nm, was 12.2 Ci/mmol (32.7 μCi/μg), whereas the specific activity of the cis isomer, determined by using its absorbance at 279 nm, was found to be 6.5 Ci/mmol (17.4 μCi/μg).[17]

[^{3}H]Hydroxytamoxifen was prepared by reduction of (*E*,*Z*)-**11** in the presence of 25 Ci of carrier-free tritium gas. The purification and isomer separation was similar to that of [^{3}H]tamoxifen. Benzene–piperidine (9:1) was used as the developing solvent, and, in contrast to the tamoxifen

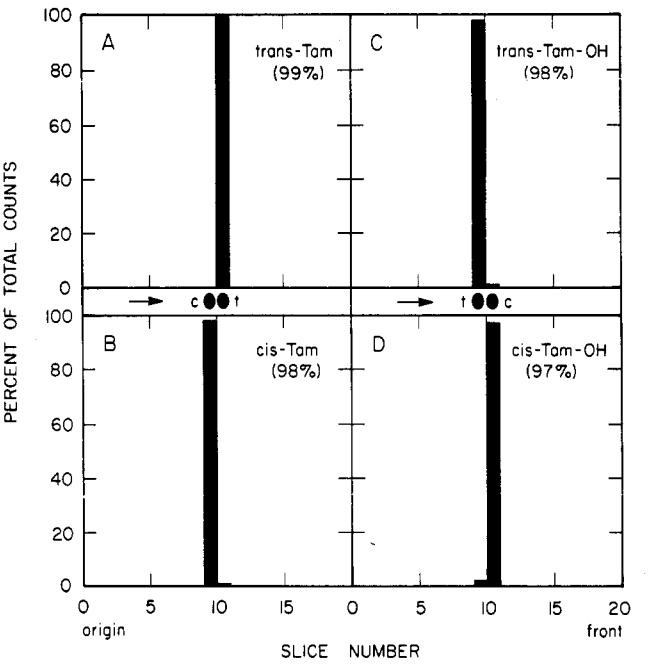


Figure 1. Thin-layer chromatographic determination of radiochemical purity of the isomeric tamoxifens (panels A and B) and hydroxytamoxifens (panels C and D). The tritium-labeled compounds were applied to the plastic-backed TLC plates on top of a spot containing authentic samples of both isomers. Plates were developed twice in benzene–triethylamine (9:1, panels A and B) and benzene–piperidine (9:1, panels C and D). Migration of the authentic isomers was determined under UV illumination; the plates were cut into 20 sections, and the radioactivity was determined by liquid scintllation counting.

case, the *Z* isomer is less mobile than the *E* isomer under these conditions. The tritiated compounds were separately eluted from the silica gel and were quickly dissolved in THF containing butylated hydroxytoluene (BHT) to prevent isomerization.[18] Radiochemical and isomeric purities in excess of 95% were obtained; thin-layer chromatograms of the purified isomers are shown in Figure 1CD.

From its absorbance at 286 nm the specific activity of *trans*-hydroxytamoxifen was calculated to be 29.5 Ci/mmol (75.7 μCi/μg). This specific activity is slightly higher than the theoretical maximum for one tritium per molecule (29.12 Ci/mmol); thus, some nonspecific exchange must have occurred in the reaction.[19] Because of isomer equilibration prior to purification and storage in THF containing BHT, the specific activity of the cis isomer was assumed to be the same.

Conclusion

In this report we have presented the preparation of both isomers of the antiestrogen tamoxifen and its metabolite, hydroxytamoxifen, in tritium-labeled form. In addition, the preparation of another precursor to labeled tamoxifen which would allow the preparation of material of greater

(13) Although 29.12 Ci/mmol is the maximum theoretical specific activity for one tritium per molecule, lower specific activities are often obtained due to isotopic exchange and impurites in the tritium source. See: Evans, E. A. "Tritium and Its Compounds"; Wiley: New York, 1974; p 321.

(14) Cohen, J. B.; Dutt, P. K. *J. Chem. Soc.* **1914**, 501–521.

(15) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553–3560.

(16) The tritiation was conducted at New England Nuclear by using conditions developed in our laboratory. The purification and isomer separation was performed in our laboratory.

(17) The reason for the almost two-fold difference in specific activities for the two isomers is unknown. The measurements have been checked and are reproducible.

(18) Hydroxytamoxifen and other 4-hydroxystilbenes such as diethylstilbestrol (DES) undergo a facile *E*–*Z* interconversion process which is favored by solvents of low dielectric constants. The isomerization process for hydroxytamoxifen occurs in all common laboratory solvents but is precluded by storage of the compound at −25 °C in the dark as a THF solution containing ca. 0.025% BHT (Robertson, D. W.; Katzenellenbogen, J. A., unpublished observations). Under these conditions the hydroxy tamoxifens have been stored for 6 months with less than 5% loss in isomeric and radiochemical purity. For a discussion of the *E*–*Z* interconversion of DES, see: Winkler, V.; Nyman, M.; Egan, R. *Steroids* **1971**, *17*, 197–207.

(19) Evans, E. A. "Tritium and Its Compounds"; Wiley: New York, 1974; Chapter 4 and p 327.

specific activity is reported. By obtaining these compounds in a state of high specific activity and radiochemical purity, we have been able to learn some intriguing things concerning the interaction of these compounds with the estrogen receptor and their metabolic fate. These results have been presented elsewhere.[20]

Experimental Section

Reagents and Solvents. *n*-Butyllithium as a solution in hexane and 50% sodium hydride in oil were purchased from Alfa (Ventron), 5% palladium on carbon from Engelhard, 4-Å molecular sieves from Union Carbide (Linde), Triton X-114 from Central Solvents and Chemical Corp., 2,5-diphenyloxazole from Research Products International Corp., and *p*-bis(5-phenyloxazol-2-yl)benzene from Sigma. 2-(4-Bromophenyl)-1-(4-methoxyphenyl)-1-ethanone (**6**),[21] 4-[(2-tetrahydropyranyl)oxy]phenyl bromide,[22] 3,4,5-tribromotoluene,[14] and 2-phenyl-1,3-dithiane[23] may be prepared according to the indicated references. Other reagents and solvents were of analytical reagent grade or better and were purchased from Aldrich, Baker, Burdick and Jackson, Fisher, Eastman, Mallinckrodt, or Sigma.

Solvents and reagents were used as purchased, except that tetrahydrofuran (THF) was dried immediately before use by distillation from sodium by using sodium benzophenone ketyl as an indicator of dryness, and dimethylformamide (DMF) was dried by distillation from calcium hydride, purged free of oxygen with argon, and then stored over 4-Å molecular sieves.

Instrumentation and General Procedures. Analytical thin-layer chromatography was performed by using 0.20-mm silica gel plastic-backed plates (precoated TLC sheets, silica gel 60 F254, Merck Catalog No. 5775), and compounds were visualized by ultraviolet light (254 nm) or iodine vapor. Preparative thin-layer chromatography was carried out by using 2.0-mm glass-backed silica gel plates (precoated TLC plates, silica gel F254, Merck), and the plates were predeveloped with ethyl acetate prior to use. Column chromatography was performed by using 0.05–0.20-mm silica gel (Brinkmann). Flash chromatography was performed according to the method of Still[24] by using 0.404–0.063 mm silica gel 60 (Merck No. 9385). Medium-pressure liquid chromatography (MPLC) was performed with a system described previously.[25] All chromatography solvent mixtures are given in parentheses and are reported on a volume per volume basis.

Melting points were determined on a Fisher-Johns melting point apparatus and are not corrected. Infrared spectra were taken as potassium bromide pellets or as carbon tetrachloride, chloroform, or carbon disulfide solutions, as indicated parenthetically in the experimental procedures. Data are presented in reciprocal centimeters, and only the important diagnostic bands are reported. Proton magnetic resonance spectra (^{1}H NMR) were obtained at 90 MHz on a Varian EM-390 spectrometer or at 220 MHz on a Varian HR-220 spectrometer. Chemical shifts are reported in the δ system of units relative to tetramethylsilane as an internal standard. Routine mass spectra were obtained on a Varian MAT Model CH-5 mass spectrometer; exact mass determinations were obtained on a Varian Model 731 instrument. Ultraviolet spectra were measured on a Varian Techtron Model 635 UV–vis spectrophotometer. Microanalytical data were provided by the Microanalytical Service Laboratory of the University of Illinois School of Chemical Sciences.

Radioactivity was measured in a Nuclear Chicago Isocap 300 liquid scintillation counter in minivials by using ca. 5 mL of a xylene-based cocktail containing 0.55% 2,5-diphenyloxazole, 0.01% *p*-bis(5-phenyloxazol-2-yl)benzene, and 25% Triton X-114. The tritium counting efficiency was 30–55%. Radiochemical purity determinations were performed by using 0.20-mm silica gel plastic-backed plates (precoated TLC sheets, silica gel 60 F254, Merck Catalog No. 5775). The labeled material was spotted on top of unlabeled carrier. After development, the carrier spot was visualized by illumination under 254-nm light, and the chromatogram was cut into strips which were then placed in minivials for radioactivity determination. Samples were allowed to stand in the dark for a minimum of 4 h prior to counting.

2-(4-Bromophenyl)-1-(4-methoxyphenyl)-1-butanone (7). Sodium hydride (400 mg of a 50% dispersion in oil, 8.33 mmol) was rinsed with THF (2 × 10 mL) to remove the oil and then suspended in 30 mL of THF at 0 °C. To this suspension was added dropwise a solution of 2-(4-bromophenyl)-1-(4-methoxyphenyl)-1-ethanone (**6**;[21] 2 g, 6.55 mmol) in 50 mL of THF. After the addition was complete, the solution was stirred for 1 h at room temperature and then cooled to 0 °C. Ethyl iodide (3 g, 19.23 mmol) was added in one portion, resulting in the formation of a white precipitate (sodium iodide). The mixture was stirred for 40 min at 0 °C, and then the reaction was quenched by the slow addition of 5% hydrochloric acid (15 mL). The mixture was poured into 100 mL of water and extracted twice with ether. The extracts were washed with brine and dried ($MgSO_4$). Removal of solvent in vacuo and chromatography (MPLC, 2.5 × 75 cm silica gel column eluted with 25% ethyl acetate in hexane, R_f 0.33) gave **7** as a colorless oil: 2.05 g (94%); IR (CCl_4) 1680 cm^{-1} (C=O); ^{1}H NMR (CCl_4) δ 0.83 (t, 2 J = 7.4 Hz, CH_2CH_3), 1.53–2.22 (m, 2, CH_2CH_3), 3.65 (s, 3, OCH_3), 4.23 (t, 1, J = 7, $CHCH_2CH_3$), 6.67 (d, 2, J = 8.8 Hz, Ar H ortho to OCH_3), 7.03 (d, 2, J = 8.7 Hz, Ar H ortho to alkyl), 7.22 (d, 2, J = 8.7 Hz, Ar H ortho to Br), 7.79 (d, 2, J = 8.8 Hz, Ar H ortho to carbonyl); mass spectrum (10 eV), m/e (relative intensity) 334 (1, M$^+$), 332 (1, M$^+$), 135 (100); mol wt calcd for $C_{17}H_{17}{}^{79}BrO_2$ 332.0412, found 332.0420.

2-(4-Bromophenyl)-1-(4-hydroxyphenyl)-1-butanone (8). Sodium hydride (9 g of a 50% dispersion in oil, 187.5 mmol) was rinsed free of oil with THF (2 × 40 mL), suspended in 350 mL dry DMF, and cooled to 0 °C. Ethanethiol (13.42 g, 216.04 mmol) was added dropwise at such a rate as to prevent foaming and excessive heat evolution. The mixture was stirred for 10 min after the addition was complete and then 2-(4-bromophenyl)-1-(4-methoxyphenyl)-1-butanone (**7**; 18.0 g, 54.01 mmol) in 100 mL of DMF was added in one portion. The mixture was warmed to 90 °C for 9 h at which time TLC analysis indicated the reaction was complete (25% ethyl acetate in hexane; starting material R_f 0.27, product R_f 0.10). The mixture was cooled to room temperature and poured into 1100 mL of 10% aqueous hydrochloric acid. The mixture was extracted twice with ether, and the combined extracts were washed twice with 10% aqueous hydrochloric acid and brine. Drying ($MgSO_4$) and concentration under reduced pressure gave a light yellow oil which was purified by chromatography (800 g of silica gel, 35% ethyl acetate in hexane), affording **8**: 16.55 g (96%); colorless, highly viscous oil; IR ($CHCl_3$) 3590 and 3320 (OH), 1670 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3, J = 7.4 Hz, CH_2CH_3), 1.57–2.20 (m, 2, CH_2CH_3), 4.22 (t, 1, J = 7 Hz, $CHCH_2CH_3$), 6.52 (d, 2, J = 8.8 Hz, Ar H ortho to OH), 6.82 (d, 2, J = 8 Hz, Ar H ortho to alkyl), 7.04 (d, 2, J = 8 Hz, Ar H ortho to Br), 7.52 (d, 2, J = 8.8 Hz, Ar H ortho to carbonyl), 7.70 (br s, 1, OH, D_2O exchangeable); mass spectrum (70 eV), m/e (relative intensity) 320 (1, M$^+$), 318 (1, M$^+$) 121 (100), 61 (12), 45 (14), 43 (89); mol wt calcd for $C_{16}H_{15}{}^{79}BrO_2$ 318.0255, found 318.0253.

2-(4-Bromophenyl)-1-[4-[2-(dimethylamino)ethoxy]-phenyl]-1-butanone (9). A sodium ethoxide solution was prepared by the addition of freshly cut sodium (1.44 g, 62.61 mmol) to 100 mL of absolute ethanol. To this solution was added in one portion 2-(4-bromophenyl)-1-(4-hydroxyphenyl)-1-ethanone (**8**; 9.3 g, 29.13 mmol) in 100 mL of ethanol. A solution of 2-(dimethylamino)ethyl chloride hydrochloride (4.82 g, 33.46 mmol) in 100 mL warm ethanol was then added in one portion to the phenolate solution, resulting in the immediate precipitation of sodium chloride. The mixture was refluxed for 12 h, cooled, and poured into 1.5 L of water. The product was extracted three times with ether, and the combined extracts were washed three times with 5% aqueous sodium hydroxide and brine. Drying ($MgSO_4$) and removal of solvent in vacuo gave the crude product as a light brown oil which was purified by chromatography (400 g of silica

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gel, benzene/triethylamine (9/1), R_f 0.21), afforded pure **9**: light yellow oil; 3.75 g (33%); IR (CCl_4) 1681 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 0.87 (t, 3, J = 7.3 Hz, CH_2CH_3), 1.52–2.20 (m, 2, CH_2CH_3), 2.27 (s, 6, $N(CH_3)_2$), 2.67 (t, 2, J = 5.8 Hz, OCH_2CH_2N), 4.02 (t, 2, J = 5.8 Hz, OCH_2CH_2N), 4.30 (t, 1, J = 6 Hz, $CHCH_2CH_3$), 6.81 (d, 2, J = 8.8 Hz, Ar H ortho to OR), 7.13 (d, 2, J = 8.5 Hz, Ar H ortho to alkyl), 7.35 (d, 2, J = 8.5 Hz, Ar H ortho to Br), 7.85 (d, 2, J = 8.8 Hz, Ar H ortho to carbonyl); mass spectrum (70 eV), m/e (relative intensity) 391 (1, M^+), 389 (1, M^+), 205 (2), 165 (3), 135 (6), 72 (13), 58 (100); mol wt calcd for $C_{20}H_{24}{}^{79}BrNO_2$ 389.0987, found 389.0981.

(*E*,*Z*)-2-(4-Bromophenyl)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-phenyl-1-butene (10). Bromobenzene (3.93 g, 25 mmol) was dissolved in ethyl ether (20 mL), and a small portion (2 mL) of the solution was added to magnesium turnings (608 mg, 25 mmol) in ether (10 mL). After Grignard formation had begun, the remainder of the bromobenzene solution was added dropwise at such a rate as to maintain gentle reflux. After the addition was complete, the mixture was stirred for 2 h a room temperature, and then 5 mL (ca. 4.16 mmol) of the Grignard reagent was added dropwise to a solution of 2-(4-bromophenyl)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-butanone (**9**; 650 mg, 1.66 mmol) in 20 mL of ether at 0 °C. The solution was warmed to room temperature and stirred for 2 h. Saturated aqueous ammonium chloride and water were slowly added, the layers were separated, and the aqueous portion was extracted with ether. The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo yielding the alcohol as a light brown oil.

The crude tertiary carbinol was dissolved in methanol (30 mL) containing 0.5 mL of concentrated hydrochloric acid and stirred at room temperature for 3 h. The solvent was removed in vacuo, and 0.5 N sodium hydroxide (100 mL) was added. The mixture was extracted with ether, and the combined extracts were washed with brine and dried (Na_2SO_4). Gaseous hydrogen chloride was passed through the ether solution for 5 min, and the bromotamoxifen hydrochloride separated as an oil. The ether was removed in vacuo, and the residue was crystallized from ethyl acetate/hexane, giving 680 mg (84%, 2 crops) of **10** as an off-white powder, mp 175–190 °C. The product was 1.3:1 mixture of isomers with the trans isomer predominating as judged by ^1H NMR assay. The isomers could be separated by analytical TLC (benzene/triethylamine (9/1), R_f 0.28 and 0.33). The product gave the following: ^1H NMR (MeOH-d_4) δ 0.92 (dt, 3, CH_3CH_3), 244 (dq, 2, CH_2CH_3), 2.92 and 2.99 (s, 6, $N(CH_3)_2$·HCl), 3.42 (br m, 2, OCH_2CH_2N), 4.13 (br m, 2, OCH_2CH_2N), 6.68–7.34 (m, 13, Ar H); mass spectrum (10 eV), m/e (relative intensity) 451 (4, M^+), 449 (5, M^+), 72 (40), 58 (100), 36 (4); mol wt calcd for $C_{28}H_{28}{}^{79}BrNO$ 449.1354, found 449.1355.

Tamoxifen and *cis*-Tamoxifen by Hydrogenation of 10. The hydrochloride of bromotamoxifen [(*E*,*Z*)-**10**; 100 mg, 0.205 mmol] was dissolved in 15 mL of DMF, 300 mg of 5% palladium on carbon was added, and after degassing the mixture was stirred under hydrogen at atmospheric pressure for 1 h. The mixture was filtered through a small pad of Celite and washed through with 10 mL of ethanol. The solvents were removed under reduced pressure, and 0.5 N sodium hydroxide (30 mL) was added. The mixture was extracted twice with ether, and the extracts were washed with water and brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo gave 70 mg (92%) of a mixture of tamoxifen and *cis*-tamoxifen whose TLC mobility and mass, NMR, and IR spectra were identical with those of authentic sample.

These conditions, without modification, were also used for the reduction of **11** and **17**.

(*E*,*Z*)-2-(4-Bromophenyl)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-(4-hydroxyphenyl)-1-butene (11). *n*-Butyllithium (1.6 mL of a 2.4 M solution in hexane, 3.84 mmol) was added dropwise to a solution of 4-[(2-tetrahydropyranyl)oxy]-phenyl bromide[22] (1.04 g, 4.04 mmol) in 15 mL THF at −78 °C. The solution was stirred for 30 min at −78 °C and then transferred via a gas-tight syringe to a stirred mixture of magnesium bromide (4.8 mmol, prepared from 0.117 g of magnesium and 0.902 g of ethylene bromide) in 15 mL THF at 0 °C. Triethylamine (0.109 g, 1.08 mmol) was added to the Grignard reagent, and stirring was continued for 15 min. A solution of 2-(4-bromophenyl)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-butanone (**9**; 0.750 g, 1.92 mmol) in 10 mL THF was added dropwise to the Grignard reagent, and then the reaction mixture was warmed to room temperature. After stirring for 8 h the reaction was quenched with saturated ammonium chloride (30 mL) and the mixture poured into 100 mL of water. The mixture was extracted twice with ether, and the combined extracts were washed with brine and dried (Na_2SO_4). The solvent was removed in vacuo, and the crude carbinol was dissolved in 30 mL of methanol containing 0.5 mL concentrated hydrochloric acid. After being stirred for 4 h at room temperature, solvent was removed from the reaction mixture in vacuo, and 75 mL of water was added. The mixture was taken to pH 7 with 6 N sodium hydroxide and then extracted three times with ether. The extracts were washed with brine and dried (Na_2SO_4). Removal of solvent under reduced pressure and flash chromatography (acetone/triethylamine (20/1), R_f 0.28) gave 0.564 g (63%) of the two isomers of product **11** as an off-white solid, mp 99–104 °C. Crystallization of a small portion from THF/hexane gave an off-white solid: mp 107–115 °C; IR (KBr) 3460 cm^{-1} (OH); ^1H NMR (acetone-d_6) δ 0.85 (t, 3, J = 7.2 Hz, CH_2CH_3), 2.12 and 2.19 (s, 6, $N(CH_3)_2$), 2.25–2.60 (m, 4, OCH_2CH_2N, and CH_2CH_3), 3.78–4.04 (m, 2, OCH_2CH_2N), 6.27–7.16 (m, 12, Ar H); mass spectrum (10 eV), m/e (relative intensity) 467 (20, M^+), 465 (19, M^+), 72 (54), 58 (100); mol wt calcd for $C_{26}H_{28}{}^{79}BrNO_2$ 465.1303, found 465.1298.

1-(Bromomethyl)-3,4,5-tribromobenzene (13). A mixture of 1-methyl-3,4,5-tribromobenzene[14] (5 g, 15.20 mmol), *N*-bromosuccinimide (2.71 g, 15.22 mmol), and benzoyl peroxide (20 mg) was refluxed in carbon tetrachloride (50 mL) under sunlamp irradiation (275 W, 1 ft) for 3 h. The mixture was cooled, and the succinimide was removed by filtration. ^1H NMR analysis of the filtrate indicated a 2:1:1 mixture of product, starting material, and dibrominated material. The carbon tetrachloride solution was washed with 5% sodium bisulfite and dried ($MgSO_4$). Removal of solvent in vacuo and recrystallization of the residue from carbon tetrachloride/hexane gave 3.28 g (53%) of **13** (pure by ^1H NMR) as small white prisms, mp 120–125 °C. A small portion was recrystallized again from carbon tetrachloride/hexane to give the analytical sample: mp 129–131 °C; ^1H NMR (CCl_4) δ 4.3 (s, 2, CH_2Br), 7.56 (s, 2, Ar H); mass spectrum (10 eV), m/e (relative intensity) 412 (5, M^+) 410 (15, M^+), 408 (22, M^+), 406 (16, M^+), 404 (4, M^+), 331 (16), 329 (56), 327 (67), 325 (21), 247 (100), 233 (13), 231 (7), 229 (7), 105 (3).

Anal. Calcd for $C_7H_4Br_4$: C, 20.62; H, 0.99; Br, 78.39. Found: C, 20.55; H, 1.04; Br, 78.22.

2-Phenyl-2-(3,4,5-tribromobenzyl)-1,3-dithiane (14). *n*-Butyllithium (1.73 mL of a 2.45 M solution in hexane, 4.24 mmol) was added dropwise to a solution of 2-phenyl-1,3-dithiane (833 mg, 4.24 mmol) in 20 mL of THF at −78 °C. The yellow-orange anion solution was stirred for 1.5 h at −78 °C, and then 1-(bromomethyl)-3,4,5-tribromobenzene (**13**; 1.73 g, 4.24 mmol) in THF (8 mL) was added in one portion, resulting in the formation of a dark green solution which later faded to light yellow. The reaction mixture was warmed to room temperature, stirred for 15 h, and quenched by pouring into 150 mL of water. The mixture was extracted twice with ether, and the combined extracts were washed with brine. Drying ($MgSO_4$) and concentration under reduced pressure gave a solid which was recrystallized from carbon tetrachloride/hexane, affording 1.84 g (83%) of **14** as white crystals. The analytical sample was prepared by recrystallization of a small portion from THF/acetonitrile, giving white prisms: mp 137.5–138.5 °C; IR (KBr) 915 cm^{-1} (1,3-dithiane); ^1H NMR (CCl_4) δ 1.90–1.95 (m, 2, ring CH_2 nonadjacent to S), 2.62–2.68 (m, 4, ring CH_2 adjacent to S), 3.05 (s, 2, Ar CH_2), 6.83 (s, 2, Ar H ortho to Br), 7.25–7.40 (m, 3, Ar H meta and para to dithiane), 7.69–7.74 (m, 2, Ar H ortho to dithiane); mass spectrum (70 eV), m/e (relative intensity) 331 (2), 329 (5), 327 (6), 325 (2), 195 (100), 176 (6), 121 (71), 119 (87), 117 (90), 82 (22), 77 (21), 57 (62).

Anal. Calcd for $C_{17}H_{15}Br_3S_2$: C, 39.03; H, 2.89; Br, 45.82; S, 12.26. Found: C, 39.06; H, 2.91; Br, 45.86; S, 12.53.

1-Phenyl-2-(3,4,5-tribromophenyl)-1-ethanone (15). 2-Phenyl-2-(3,4,5-tribromobenzyl)-1,3-dithiane (**14**; 1.36 g, 2.60 mmol) in 10 mL of THF was added in one portion to a rapidly stirred solution of *N*-chlorosuccinimide (1.39 g, 10.41 mmol) and silver nitrate (1.99 g, 11.7 mmol) in 60 mL of acetonitrile/water (4:1) at room temperature. A voluminous white precipitate appeared immediately (silver chloride), and the liquid phase became

yellow. The mixture was stirred for 12 min and then treated successively at 1-min intervals with 1 mL each of saturated aqueous sodium sulfite, saturated aqueous sodium carbonate, and brine. Hexane/methylene chloride (1:1, 60 mL) was then added, and the mixture was filtered through Super-Cel. The filter cake was washed thoroughly with hexane/methylene chloride (1:1), and the organic phase of the filtrate was dried ($MgSO_4$). The solvent was removed in vacuo, and the residue was chromatographed (125 g of silica gel, 20% ethyl acetate in hexane, R_f 0.26), affording **15** (0.98 g, 87%) as a white solid. The analytical sample was prepared by recrystallizing a small portion from ethanol/methanol (1:1), giving white plates: mp 113–114 °C; IR ($CHCl_3$) 1695 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 4.12 (s, 2, Ar CH_2), 7.45 (s, 2, Ar H ortho to Br), 7.44–7.56 (m, 3, Ar H meta and para to dithiane), 7.91–7.95 (m, 2, Ar H ortho to dithiane); mass spectrum (10 eV), *m/e* (relative intensity) 434 (1, M^+), 432 (1, M^+), 105 (100); mol wt calcd 429.8202, found 429.8210.

Anal. Calcd for $C_{14}H_9Br_3O$: C, 38.84; H, 2.09; Br, 55.37. Found: C, 38.76; H, 2.19; Br, 55.42.

1-Phenyl-2-(3,4,5-tribromophenyl)-1-butanone (16). Sodium hydride (200 mg of a 50% dispersion in oil, 4.16 mmol) was rinsed free of oil with THF (2 × 10 mL) and suspended in 4 mL of THF. A solution of 1-phenyl-2-(3,4,5-tribromophenyl)-1-ethanone (**15**; 630 mg, 1.45 mmol) in 8 mL of THF was added dropwise, and the mixture was stirred for 1 h at room temperature. The vigorously stirred yellow enolate solution was cooled to 0 °C, and then ethyl iodide (1.15 g, 7.37 mmol) was added in one portion. The reaction mixture was warmed to room temperature, and after 2 h the mixture was quenched by the slow addition of 5% hydrochloric acid (2 mL). Water (50 mL) was added, and the mixture was extracted twice with ether. The extracts were washed with brine and dried ($MgSO_4$). Removal of solvent in vacuo gave a yellow oil which was chromatographed [two 20 × 20 cm preparative TLC plates, 5% ethyl acetate in hexane, R_f 0.35 (two developments)], affording **16** as a very light yellow oil: 476 mg (71%); IR (CCl_4) 1691 cm^{-1} (C=O); ^1H NMR (CCl_4) δ 0.91 (t, 3, J = 7.3 Hz, CH_2CH_3), 1.73–2.23 (m, 2, CH_2CH_3), 4.33 (t, 1, J = 7.2 Hz, $CHCH_2CH_3$), 7.37–7.54 (m, 3, Ar H meta and para to carbonyl), 7.51 (s, 2, Ar H ortho to Br), 7.88–7.92 (m, 2, Ar H ortho to carbonyl); mass spectrum (70 eV), *m/e* (relative intensity) 135 (9), 105 (100), 77 (19), 51 (3); mol wt calcd for $C_{16}H_{13}{}^{79}Br_3O$ 457.8515, found 457.8510.

4-[2-(Dimethylamino)ethoxy]phenyl Bromide. This compound was prepared by the general procedure used for the preparation of **9**, except that the product was purified by distillation rather than by chromatography. The following reagent quantities were used: 24.70 g (142.77 mmol) of 4-bromophenol, 22.62 g (157.03 mmol) of 2-(dimethylamino)ethyl chloride hydrochloride, and 6.95 g (302 mmol) of sodium. Distillation gave the product as a colorless liquid: 23.2 g (65%); bp 109.5–111 °C (0.03 torr); IR (CCl_4) 1250 and 1040 cm^{-1} (ArOR); ^1H NMR (CCl_4) δ 2.27 (s, 6, $N(CH_3)_2$), 2.59 (t, 2, J = 6 Hz, OCH_2CH_2N), 3.84 (t, 2, J = 6 Hz, OCH_2CH_2N), 6.52 (d, 2, J = 8.9 Hz, Ar H ortho to OR), 7.10 (d, 2, J = 8.9 Hz, Ar H ortho to Br); mass spectrum (10 eV), *m/e* (relative intensity) 245 (6, M^+), 243 (6, M^+), 58 (100).

Anal. Calcd for $C_{10}H_{14}BrNO$: C, 49.20; H, 5.78; Br, 32.73; N, 5.74. Found: C, 49.31; H, 5.80; Br, 32.67; N, 5.78.

(*E,Z*)-1-[4-[2-(Dimethylamino)ethoxy]phenyl]-1-phenyl-2-(3,4,5-tribromophenyl)-1-butene (17). A mixture of 4-[2-(dimethylamino)ethoxy]phenyl bromide (500 mg, 2.05 mmol) and magnesium (6.17 mmol, 150 mg) was refluxed in 30 mL of THF. Ethylene bromide (0.772 g, 4.11 mmol) was added in small portions over a 3-h period to facilitate formation of the Grignard reagent. After the 3-h reflux period, the mixture was cooled and added in portions via a gas-tight syringe to a solution of 1-phenyl-2-(3,4,5-tribromophenyl)ethanone (0.228 g, 0.484 mmol) in 10 mL of THF at room temperature. After the Grignard reagent had been transferred, the reaction mixture was stirred for 2 h and then quenched by the addition of saturated aqueous ammonium chloride (5 mL) and water (75 mL). The mixture was extracted twice with ether, and the extracts were washed with brine and dried (Na_2SO_4). Removal of solvent in vacuo yielded a light brown oil. ^1H NMR analysis indicated that no starting ketone was present.

The crude tertiary carbinol was dissolved in 50 mL of methanol containing 0.5 mL of concentrated hydrochloric acid and refluxed for 4 h. The solvent was removed in vacuo, and 0.5 N aqueous sodium hydroxide (100 mL) was added. The mixture was extracted twice with ether, and the extracts were washed with brine. Drying (Na_2SO_4) and removal of solvent in vacuo gave a brown oil which was purified by preparative TLC (two 20 × 20 cm plates developed with benzene/triethylamine (9/1), two developments, R_f 0.64). The product **17** (183 mg, 61%) was a light yellow, viscous oil and was a 1:1 mixture of isomers by ^1H NMR analysis: ^1H NMR (CCl_4) δ 0.93 (dt, 3, J = 7.4 Hz, CH_2CH_3), 2.22 and 2.27 (s, 6, $N(CH_3)_2$), 2.07–2.68 (m, 4, CH_2CH_3, and OCH_2CH_2N), 3.90 (dt, 2, J = 6 Hz), OCH_2CH_2N), 6.42–7.30 (m, 11, Ar H); mass spectrum (10 eV), *m/e* (relative intensity) 611 (1, M^+) 609 (2, M^+), 607 (2, M^+), 605 (1, M^+).

Preparation of [^{3}H]Tamoxifen and *cis*-[^{3}H]Tamoxifen.[16] A mixture of brominated tamoxifen and *cis*-tamoxifen **10** (50 mg, 0.1 mmol) was dissolved in 5 mL of DMF. To this solution was added 150 mg of 5% palladium on carbon, and the reaction mixture was stirred at room temperature under 25 Ci of carrier-free tritium gas for 1 h. Labile tritium was removed in vacuo by using ethanol as the solvent. After filtration from the catalyst, the product was taken to dryness in vacuo once more, and redissolved in 10 mL of ethanol. A total of 645 mCi of product was produced.

The preferred method for purification and isomer separation was by thin-layer chromatography with 0.25-mm silica gel glass-backed plates containing F-254 indicator (precoated TLC plates, silica gel 60 F-254, Merck). Up to 30 mCi of the crude product was dissolved in 100 μL of ethanol and applied as a streak to a 20 × 20 cm plate which had been previously activated by heating at 110 °C for 1 h. The plate was developed twice in the dark with benzene/triethylamine (9/1), which gave two cleanly separated bands as indicated by brief UV (254 nm) visualization. The higher band was [^{3}H]tamoxifen (R_f 0.53) whereas the lower band was *cis*-[^{3}H]tamoxifen (R_f 0.46). The bands were separately removed from the plate, and the tritiated compounds were eluted from the silica gel by using freshly prepared acetone/triethylamine (5:1). The solvent was removed immediately under a gentle stream of nitrogen, and the samples were dissolved in ethanol (approximately 1 mCi/mL) for analysis and long-term storage at −25 °C. In a typical purification using 30 mCi of crude material, 16.2 mCi of [^{3}H]tamoxifen (99.6% radiochemical purity, 99.8% isomeric purity) and 7.23 mCi of *cis*-[^{3}H]tamoxifen (99.7% radiochemical purity, 99.6% isomeric purity) were obtained, representing a 78% recovery. By this procedure a total of 216 mCi of [^{3}H]tamoxifen and 39.1 mCi of *cis*-[^{3}H]tamoxifen were obtained. After storage at −25 °C for 1 year, both compounds showed radiochemical and isomeric purities of >95% and >98%, respectively.

The remainder of the crude material was purified by preparative TLC on one 20 × 20 cm plate (2-mm layer). Approximately 430 mCi of material was applied, and the plate was developed four times with benzene/triethylamine (9/1). Visualization by UV irradiation revealed two poorly separated bands. Three zones of silica gel were removed from the plate, and the tritiated compounds were eluted as previously described. By this procedure 216 mCi of [^{3}H]tamoxifen (99.8% radiochemical purity, 99.1% isomeric purity), 49.1 mCi of *cis*-[^{3}H]tamoxifen (97% radiochemical purity, 98.9% isomeric purity), and 77.5 mCi of a mixture of two isomers (99% radiochemical purity, 53% of counts resulting from [^{3}H]tamoxifen) were obtained, representing 79% of the crude material applied to the plate.

Thus, a total of 302 mCi of [^{3}H]tamoxifen and 88.2 mCi of *cis*-[^{3}H]tamoxifen was obtained in addition to 77.5 mCi of a mixture of the two. The total yield of the tritiated products was 467.7 mCi, representing 73% of the material in the crude tritiation product.

Determination of the Specific Activity of [^{3}H]Tamoxifen and *cis*-[^{3}H]Tamoxifen. Tamoxifen has an ultraviolet absorbance pattern with maxima at 238 nm (ϵ 20 500) and 277 (13 000); the corresponding maxima for *cis*-tamoxifen are 242 nm (ϵ 18 100) and 279 (14 300). The UV spectra of the tritiated compounds were essentially identical with the spectra of the unlabeled compounds. The concentration of a sample of each isomer in ethanol was measured by using the absorbance at 238 nm for [^{3}H]tamoxifen and at 279 nm for *cis*-[^{3}H]tamoxifen, and the radioactivity present in each solution was then determined. These measurements were repeated on samples containing various concentrations of the

labeled compounds. The specific activities were calculated to be 12.2 Ci/mmol (32.7 μCi/μg) for [^{3}H]tamoxifen and 6.5 Ci/mmol (17.5 μCi/μg) for *cis*-[^{3}H]tamoxifen.

Preparation of [^{3}H]Hydroxytamoxifen and *cis*-[^{3}H]-Hydroxytamoxifen.[16] The procedural details for the preparation of this compound are very similar to those for the preparation of the tritiated tamoxifen isomers. A mixture (11) of bromohydroxytamoxifen and *cis*-bromohydroxytamoxifen was exposed to 25 Ci of carrier-free tritium gas over a palladium on carbon catalyst in DMF for 1 h. Approximately 1803 mCi of tritiated product was produced, and the purification and isomer separation were again effected by silica gel TLC on 20 × 20 cm plates with a layer thickness of 0.25 mm. Up to 46 mCi of the crude product could be applied, and after two developments in benzene/piperidine (9:1), clean separation of the tritiated isomers was observed. In contrast to the tamoxifen case, the *Z* isomer is less mobile than the *E* isomer. The tritiated compounds were separately eluted from the silica gel and were *quickly dissolved in THF containing butylated hydroxytoluene (BHT) to prevent isomerization.*[18]

By this procedure 167 mCi of *cis*-[^{3}H]hydroxytamoxifen and 231 mCi of [^{3}H]hydroxytamoxifen were isolated (63% of the crude material applied), with the radiochemical purities being approximately 99%. The compounds were stored at approximately 1 mCi/mL in THF containing BHT at −25 °C. After storage for 6 months, both isomers showed radiochemical and isomeric purities of >95% and >90%, respectively.

Determination of the Specific Activity of [^{3}H]-Hydroxytamoxifen. Hydroxytamoxifen has an ultraviolet absorbance pattern with maxima at 247 nm (ε 21 300) and 286 (13 200). The UV spectrum of [^{3}H]hydroxytamoxifen was essentially identical with that of the unlabeled compound, and from the absorbance at 286 nm the specific activity was calculated to be 29.5 Ci/mmol (75.7 μCi/μg).

Acknowledgment. Support for this research was provided by a grant from the National Institutes of Health (USPH AM 15556). D.W.R. was supported by fellowships from the University of Illinois and the Lubrizol Corp. The high-resolution mass spectrometry equipment was provided by a grant from the National Cancer Institute (CA 11388). We are grateful to Dr. A. H. Todd (ICI Ltd., Macclesfield, England) and Dr. L. Trench (ICI, U.S.A.) for supplying samples of *cis*-tamoxifen, *trans*-tamoxifen, and *trans*-hydroxytamoxifen for comparison purposes.

Registry No. 1, 10540-29-1; [^{3}H]-1, 81278-36-6; 2, 13002-65-8; [^{3}H]-2, 81278-37-7; [^{3}H]-3, 81278-38-8; *cis*-[^{3}H]-3, 81278-39-9; 4, 100-66-3; 5, 1878-68-8; 6, 67205-73-6; 7, 81278-40-2; 8, 81278-41-3; 9, 81278-42-4; (*E*)-10, 81278-43-5; (*E*)-10·HCl, 81278-44-6; (*Z*)-10, 81278-45-7; (*Z*)-10·HCl, 81278-46-8; (*E*)-11, 81278-47-9; (*Z*)-11, 76579-87-8; 12, 73557-59-2; 13, 81278-48-0; 14, 81278-49-1; 15, 81278-50-4; 16, 81278-51-5; (*E*)-17, 81278-52-6; (*Z*)-17, 81278-53-7; 2-(dimethylamino)ethyl chloride hydrochloride, 4584-46-7; 2-(4-bromophenyl)-1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-hydroxy-1-phenylbutane, 81278-54-8; 4-[(2-tetrahydropyranyl)oxy]phenyl bromide, 36603-49-3; 2-(4-bromophenyl)-1-[4-[2-(dimethylamino)-ethoxy]phenyl]-1-hydroxy-1-(4-hydroxyphenyl)butane, 76579-93-6; 2-phenyl-1,3-dithiane, 5425-44-5; 4-[2-(dimethylamino)ethoxy]phenyl bromide, 2474-07-9; 4-bromophenol, 106-41-2; 1-[4-[2-(dimethylamino)ethoxy]phenyl]-1-hydroxy-1-phenyl-2-(3,4,5-tribromophenyl) butane, 81278-55-9.

An Efficient and Remarkably Regioselective Synthesis of Benzocyclobutenones from Benzynes and 1,1-Dimethoxyethylene

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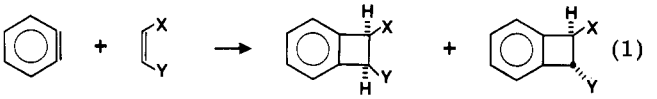
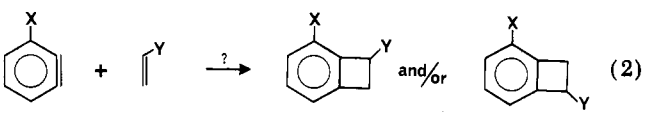
Received August 3, 1981

New efficient methodology for the synthesis of substituted benzocyclobutenones is presented that involves the [2 + 2] cycloaddition of various substituted benzynes to 1,1-dimethoxyethylene followed by hydrolysis to the corresponding ketone. In most cases studied a high degree of regioselectivity was observed. These observations are consistent with a nonsynchronous mechanism wherein steric and inductive considerations can be used to account for the products observed.

In recent years benzocyclobutenes have been established as valuable intermediates in organic synthesis.[1] A number of methods have been developed for the synthesis of such systems. Of these, the thermal [2 + 2] cycloaddition of benzynes to olefins is certainly the most direct route.[2] Such cycloadditions involving benzyne and 1,2-disubstituted olefins (eq 1) have been shown to yield mixtures of stereoisomers (stereoretention predominating), thereby establishing mechanistically a stepwise course of reaction.[3] From a purely preparative point of view, the synthesis of





benzocyclobutenes via such [2 + 2] cycloadditions has not been utilized extensively. This can be attributed in part to the modest yields (<50%) usually obtained and to the fact that the regiochemistry of such cycloadditions involving unsymmetric olefin and benzyne partners (eq 2) has received very little attention.[4] In connection with studies aimed at the total synthesis of certain complex

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