the dropwise addition of a 1:1 solution of tetrahydrofuran–ethyl acetate, followed by 10% hydrochloric acid until strongly acidic. Product isolation (ethyl acetate, sodium sulfate) gave a solid that was shown to be a three-component mixture by TLC, the most polar component being estradiol-17β. The solid was dissolved in tetrahydrofuran and adsorbed on to 0.80 g of silica gel that was layered on to a column of silica gel (35 g). Elution with 5% ethyl acetate–benzene gave 16α-chloroestradiol-17α (**13d**; 69 mg, 26%) and 16α-chloroestradiol-17β (**13c**; 178 mg, 67%). Analytical samples were obtained by crystallization from benzene.

16α-Chloroestradiol-17β (**13c**): mp 212–214 °C (lit.[30] 213–214 °C); ^{1}H NMR (MeSO-d_6) δ 0.70 (s, 3, 18-methyl), 3.60 (m, 1, 17α-H), 4.10 (m, 1, 16β-H), 5.27 (m, 1, 17β-OH), 6.77, 6.86, 7.10 (3), 8.93 (m, 1, OH); mass spectrum (70 eV), m/e (relative intensity) 308 (33), 306 (100, M$^+$), 220 (29), 185 (28), 172 (30), 160 (34), 159 (40), 133 (30), 43 (26), 28 (21).

16α-Chloroestradiol-17α (**13d**): mp 225–226 °C (lit.[30] 228–229 °C); ^{1}H NMR (MeSO-d_6) δ 0.73 (s, 3 H, 18-methyl), 3.53 (m, 1, 17β-H), 4.60 (m, 1, 16β-H), 4.93 (m, 1, 17α-OH), 6.40, 6.47, 7.00 (3), 8.90 (s, 1, OH); mass spectrum (70 eV) m/e (relative intensity) 308 (34), 306 (100, M$^+$), 220 (21), 185 (23), 172 (25), 160 (38), 159 (38), 133 (31), 41 (21).

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Estrogen Receptor Based Imaging Agents. 2. Synthesis and Receptor Binding Affinity of Side-Chain Halogenated Hexestrol Derivatives

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We have synthesized as potential imaging agents for human breast tumors a series of hexestrol analogues bearing the halogens fluorine, chlorine, bromine, and iodine at the terminus of the hexane chain. The binding affinity of these compounds for the estrogen receptor from uterine tissues forms a monotonically decreasing series, starting at 129% of that of estradiol for the fluoro analogue and decreasing to 60% for the iodo analogue. Such a modest decrease in binding affinity is thought to reflect the preference of the receptor for lipophilic groups and for substituents of moderate steric size at this site, parameters which change in opposite directions in the halogen sequence going from fluorine to iodine. Three estrogenic bis(trifluoromethyl)diphenylethylenes, prepared by DuPont, also showed substantial binding affinities for the estrogen receptor. In terms of ease of radiolabeling and high receptor binding selectivity, the compound that appears to be the most promising candidate for a breast tumor imaging agent in these series is the chain terminal fluorohexestrol.

γ-Emitting analogues of estrogens have the potential for being concentrated in tissues and tumors that contain estrogen receptors. An application of particular interest would be the use of such agents to provide diagnostic information about human breast tumors that have significant levels of estrogen receptor.[1] Such information would assist in the selection of the most appropriate therapeutic approach.[2]

We have undertaken a systematic investigation of various halogenated estrogen analogues in order to determine what structural features are important in attaining high binding selectivity, that is, high affinity for the estrogen receptor with relatively low affinity for other nonreceptor sites. In this paper, we describe synthesis of a series of hexestrol analogues that bear a halogen at the terminus of the hexane chain. We have also measured the binding affinity of these compounds together with some others that have been prepared elsewhere, for the estrogen receptor from uterine tissue. In related papers,[3] we describe the synthesis and receptor binding affinity of other potential estrogen receptor based imaging agents,[3a,b] the preparation of some of those compounds in tritium- and γ-labeled form,[3c,d] studies on their binding selectivity in vitro,[3c] and their target tissue and selective uptake in vivo.[3c,d]

Results

Chemical Synthesis. *erythro*-3,4-Bis(4-hydroxyphenyl)-1-hexanol (7). The approach to side-chain functionalized hexestrols is shown in Scheme I. Deoxyanisoin (1) was ethylated by sequential treatment with sodium hydride and ethyl iodide, giving a good yield (85%) of α-ethyldeoxyanisoin (2). The functionalized side chain was introduced by a Reformatsky reaction using methyl bromoacetate and zinc, producing a mixture of diastereomeric β-hydroxy esters (3). Although these diastereomers

(1) For reviews, see McGuire, W. L.; Horwitz, K. B.; Pearson, O. H.; Segaloff, A. *Cancer* **1977**, *39*, 2394. McGuire, W. L.; Horwitz, K. B.; Zava, D. T.; Garola, R. E.; Chamness, G. C. *Metabolism* **1978**, *27*, 487. McGuire, W. L.; Carbone, P. P.; Vollmer, G. P. "Estrogen Receptors in Human Breast Cancer"; Raven Press: New York, 1975. Allegra, J. C.; Lippman, M. E.; Thompson, E. B.; Simon, R.; Barlock, A.; Green, L.; Huff, K. K.; Do, H. M. T.; Aitken, S. C. *Cancer Res.* **1979**, *39*, 1447.

(2) LeClerq, G.; Heuson, J. C. *Curr. Probl. Cancer* **1976**, *1*, 1. Garola, R. E.; McGuire, W. L. *Cancer Res.* **1977**, *37*, 3333. Horwitz, K. B.; McGuire, W. L.; Pearson, O. H.; Segaloff, A. *Science* **1975**, *189*, 726.

(3) (a) Heiman, D. F.; Katzenellenbogen, J. A.; Neeley, R. J. *J. Med. Chem.*, preceding paper in this issue. (b) Allison, K. J.; Katzenellenbogen, J. A., in preparation. (c) Katzenellenbogen, J. A.; Carlson, K. E.; Heiman, D. F.; Goswami, R. *J. Nucl. Med.* **1980**, *21*, 550. (d) Katzenellenbogen, J. A.; Senderoff, S. G.; Welch, M. J.; McElvaney, K. D., in preparation. (e) Katzenellenbogen, J. A.; Heiman, D. F.; Carlson, K. E.; Lloyd, J. E. In "Receptor Binding Radiotracers" (Uniscience Series "Radiotracers in Biology and Medicine"; Colombetti, L. G., Ed.); Eckelman, W. C., Ed.; CRC Press, Boca Raton, FL, in press.

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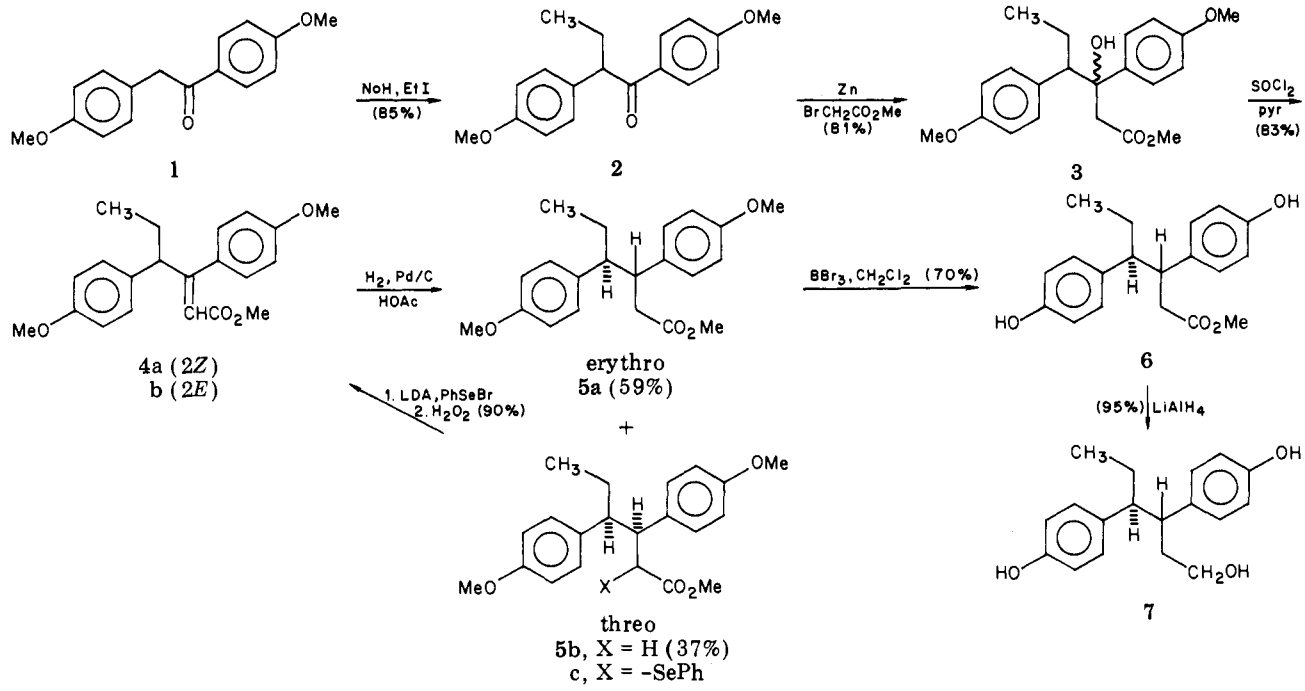
Scheme I



were separated and characterized individually, in practice they need not be separated, since both of them were converted by treatment with thionyl chloride in pyridine to predominantly one isomer (**4a**) of the unsaturated ester **4**. The major isomer of **4** was tentatively assigned the *Z* conformation; a small amount of the *E* isomer (**4b**) was also obtained.

Catalytic hydrogenation of either the pure *Z* isomer or the mixture of *E* and *Z* isomers over palladium on charcoal in acetic acid gave a mixture of the saturated esters **5a** and **5b**, predominating in the desired erythro diastereomer **5a**. These isomers could be separated only with difficulty by chromatography, but they separated quite cleanly by recrystallization from methylene chloride/hexane.

Assignment of configuration to the diastereomeric esters (**5a** and **5b**) was made on the basis of melting points and proton magnetic resonance chemical shifts of the methyl protons. *meso*-Hexestrol has a melting point of 185 °C[4] and its methyl protons resonate at δ 0.53, while the methyl groups of *d,l*-hexestrol resonate at δ 0.72, and it crystallizes only with difficulty, although it has a melting point of 130–131.5 °C (D. F. Heiman, unpublished results). The diastereomer of **4** to which we have assigned the erythro configuration is a crystalline solid melting at 116.5–117.5 °C and having a methyl resonance at δ 0.58, and that which we have designated threo is an oil with a methyl resonance at δ 0.74.

The methyl ether groups in **5a** were smoothly removed with boron tribromide in dichloromethane to give a 70% yield of the bisphenolic ester **6**. This compound was then reduced with lithium aluminum hydride in nearly quantitative yield to the triol **7**, which is the precursor for all of the side-chain halogenated hexestrols (**9–12**).

In earlier efforts we had attempted to introduce the functionalized side chain in compound **4** in one step by an Emmons-modified Wittig reaction.[5] Using deoxyanisoin as a model, our attempts to add the triethylphosphonoacetate anion produced only 7 to 15% of condensed product, with the majority of the starting material being recovered unchanged. An attempted adol-type condensation with deoxyanisoin using the anion generated from ethyl acetate by lithium diisopropylamide was completely unsuccessful, with only starting material being recovered, and the addition of ethynylmagnesium bromide to the carbonyl group of deoxyanisoin produced only a 15% yield of the desired ethynylcarbinol. All of the above failures may be the result of α deprotonation of this relatively acidic ketone by the reagents.

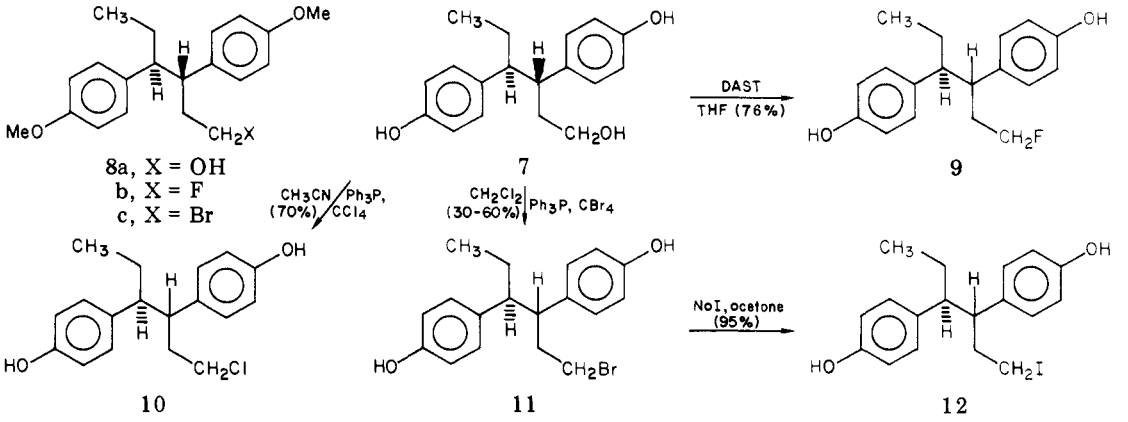
Direct reductions of benzylic alcohols to the corresponding saturated compounds have been reported.[6] While two attempts at the direct conversion of **3** to **5** with hydrogen over palladium/charcoal in ethanolic HCl were unsuccessful,[6a] this conversion could be effected with triethylsilane in trifluoroacetic acid.[6b] Unfortunately, the mixture of diastereomeric esters (**5a** and **5b**) thus produced contained considerably less of the desired erthro isomer **5a** (28%) than is obtained by catalytic hydrogenation of **4** (59%).

We have been able to increase the overall efficiency of our route to **5a** by recycling the undesired threo diastereomer (**5b**). Reaction of the lithium enolate of **5b** with phenylselenyl bromide or chloride gives the α-phenylselenyl ester **5c**, which upon oxidation with hydrogen peroxide undergoes elimination to the unsaturated ester **4** (produced as a 1:1 mixture of **4a** and **4b**), in an overall yield of 90%.[7]

1-Halogenated *erythro*-3,4-Bis(4-hydroxyphenyl)-hexanes. Originally, we expected that an aliphatic fluoride would survive the conditions of an aryl methyl ether cleavage. Thus, the methyl ester **5a** was reduced to 3,4-bis(4-methoxyphenyl)-1-hexanol (**8a**) with lithium aluminum hydride, and the alcohol was converted into the

(4) Dodds, E. C.; Golberg, L.; Lawson, W.; Robinson, R. *Proc. R. Soc. London, Ser. B.* **1939**, *127*, 130–167.
(5) Wadsworth, W. S.; Emmons, W. D. In "Organic Syntheses"; Baumgarten, H. E., Ed.; Wiley: New York, 1973; Collect. Vol. V, pp 547–549.
(6) (a) Augustine, R. L. "Catalytic Hydrogenations", Marcel Dekker: New York, 1965; p 135. (b) West, C. T.; Donelly, S. J.; Kooistra, D. A.; Doyle, M. T. *J. Org. Chem.* **1973**, *38*, 2675.
(7) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.

Scheme II

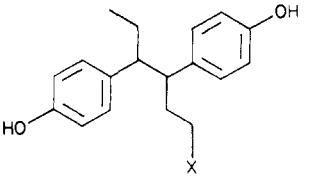


fluoro compound **8b** in 62% yield upon treatment with the mild fluorinating agent FAR (fluoroalkylamine reagent)[8] or in somewhat lower (nonoptimized) yield with the more recently developed (diethylamino)sulfur trifluoride (DAST).[9] However, attempted demethylation of **8b** with boron tribromide led to the fluorophenol **9** in a form that was badly contaminated by other products. A more satisfactory route proceeded through the bisphenolic alcohol **7**, which gave **9** in 76% yield upon treatment with DAST (Scheme II).

The 1-chloro compound (**10**) was prepared in 70% yield by refluxing the triol **7** with triphenylphosphine in carbon tetrachloride[10] using acetonitrile as the cosolvent, and the bromide **11** was prepared from **7** in a similar fashion using triphenylphosphine and carbon tetrabromide in dichloromethane.[11] The best yield in this latter conversion was 61%, but repeated experiments showed that this reaction is very sensitive to the purity of carbon tetrabromide. Bromination of the protected methoxy alcohol **8a** to give **8c**, followed by demethylation to give **11** (80% overall), proved to be less problematical. The iodo compound **12** was prepared from the bromo analogue **11** by refluxing with sodium iodide in acetone.

Binding Affinity for the Uterine Estrogen Receptor. The binding affinity of nonradiolabeled estrogen analogues for the estrogen receptor can be measured readily by a competitive binding assay. The affinities are obtained relative to the tracer compound, [^{3}H]estradiol, and are conveniently expressed on a percent scale, where the binding of estradiol is 100%.[12] The relative binding affinities of the series of side-chain terminal halogenated hexestrols are shown in Table I. It is interesting to compare the binding affinities of these compounds with that of the parent compound hexestrol, which has a relative affinity of 300, or 3 times that of estradiol. As the size of the halogen increases, the relative binding affinity decreases from 129 for the fluoro compound to 60 for the iodo compound. This relatively modest decrease in binding affinity is suggestive of two processes operating simultaneously that nearly offset each other: the somewhat greater tendency of the binding affinity to decrease as the steric size of the group increases (indicating the limits of steric tolerance at this site) vs. the somewhat smaller tendency of the binding affinity to increase as the lipophilicity of these groups increases (indicating the preference of this site on the receptor for nonpolar groups).

Table I. Estrogen Receptor Binding Affinity of Side-Chain Terminal Halohexestrols[a]



X	compd	RAC × 100[b]
I	12	60
Br	11	71
Cl	10	113
F	9	129
H [Hex]		300
[E_2]		100

[a] Various concentrations of unlabeled compound (10^{-4} to 10^{-10} M) were incubated with 10^{-8} M [^{3}H]estradiol with with lamb uterine cytosol (ca. 2.5 nM receptor site concentration) for 16 h at 0 °C. Free ligands were removed by a brief treatment with dextran-coated charcoal. For details, see ref 12. [b] The affinity relative to that of estradiol is expressed by RAC × 100, which is the ratio of association constants ($K_a^{compd}/K_a^{estradiol}$) × 100. For details, see ref 12.

The binding affinity of iodohexestrol **12** is nearly as great as the highest affinity member in another series of iodinated stilbestrols, α-iodo-α′-isopropylstilbestrol.[3b] Thus, this compound may have an affinity sufficiently great to be useful as a breast tumor imaging agent. The bromohexestrol **11**, with a somewhat higher affinity, could be prepared in bromine-77 labeled form and may well have promise as an imaging agent. However, the compound of greatest promise as an imaging agent is the fluorohexestrol **9**, which has an affinity even greater than that of estradiol (although not as great as the parent compound hexestrol). Since there are no γ-emitting isotopes of chlorine suitable for labeling in vivo radiopharmaceutical agents of this type, the chlorohexestrol **10**, though a good receptor binder, is not to be considered as an imaging agent.

We obtained three diphenylethylenes bearing fluorinated side chains which had been prepared by the DuPont Co.[13] The estrogen receptor binding affinity of these compounds is shown in Table II and, again, can be compared with those of the closest nonhalogenated parent

(8) Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 158–173.
(9) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(10) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801.
(11) Heather, J. B.; Mittal, R. S. D.; Sih, C. J. *J. Am. Chem. Soc.* **1976**, *98*, 3661.
(12) Katzenellenbogen, J. A.; Johnson, H. J., Jr.; Myers, H. N. *Biochemistry* **1973**, *12*, 4085.
(13) (a) Middleton, W. J. U.S. Patent 3683009 (1972); *Chem. Abstr.* **1970**, *73*, 14425*m*. (b) Middleton, W. J. U.S. Patent 3678117 (1972); *Chem. Abstr.* **1972**, *77*, 101125*q*. (c) Middleton, W. J. U.S. Patent 3751485 (1973); *Chem. Abstr.* **1973**, *79*, 91770*w*.

compounds. Hexafluorodimethylstilbestrol (**13b**)[13a] binds more than twice as well as the parent compound dimethylstilbestrol (DMS, **15a**). This is probably a reflection of the higher lipophilicity of trifluoromethyl vs. methyl groups. Its affinity is not so great as that of diethylstilbestrol (DES, **15b**), however. As expected, the analogue lacking one of the phenolic hydroxyl groups (**13a**)[13a] binds with somewhat lower affinity than **13b**. It is interesting that the isomer of **13a**, the 1,1-diphenylethylene compound **14**,[13b,c] binds with greater affinity than **13a**. Other members of this series, for example, compound **16** (sometimes called cyclofenyl), have high affinity for the estrogen receptor (J. A. Katzenellenbogen and B. S. Schwartz, unpublished results).

Discussion

We have described a straightforward synthetic sequence to a series of hexestrol analogues bearing a halogen substituent at the terminus of the hexane chain. All the members of this series have a relatively high affinity for the estrogen receptor, so those that can be labeled with γ-emitting radionuclides are potential candidates as imaging agents for human breast tumors.

Relatively few hexestrol analogues with functional groups in the side chain have been prepared. A number of metabolites of hexestrol and diethylstilbestrol identified by Metzler[14] have side-chain hydroxyl groups. Some of these metabolites have been synthesized.[15] Krohn and Hemme[16] have synthesized some side-chain functionalized stilbestrols as potential haptens for the development of radioimmunoassays for diethylstilbestrol. Collins and Hobbs[17] and more recently Lee et al.[18] have prepared norhexestrol derivatives bearing side-chain acid or amino functions.

One important characteristic of a synthetic sequence for the preparation of an imaging agent that will ultimately be prepared with a short-lived γ-emitting radionuclide is the facility with which the radionuclide can be introduced. The situation with the side-chain terminal halogenated hexestrols is particularly favorable, as the halogen can be introduced in the last step (or the next to last step, if protective groups are employed) by a simple halide ion displacement reaction. The hexafluorodiphenylethylene compounds, prepared by DuPont, would be distinctly more difficult to prepare in a form labeled with fluorine-18.

The synthesis and estrogen receptor binding affinities of other series of halogenated estrogen analogues that we have prepared as potential imaging agents for human breast tumors are described in other papers.[3a,b] Futhermore, in separate publications, we have described studies on the binding selectivity of these compounds (i.e., their affinity for receptor vs. nonreceptor binding proteins[3e]), the preparation of some of them in high specific activity tritiated and γ-emitting form,[3c,d] and studies on their target tissue- and tumor-selective uptake in vivo.[3c,d]

Experimental Section

Deoxyanisoin was purchased from Aldrich, 4 Å molecular sieves from Union Carbide (Linde), trifluoromethanesulfonic anhydride from Aldrich, carbon tetrabromide from Eastman Kodak Co., and boron tribromide (99.9%) from Apache Chemicals, Inc. Diethylaminosulfur trifluoride (DAST) was synthesized according to a literature procedure[9] or purchased from PCR, Inc. **Caution: This reagent and its hydrolysis product (HF) are corrosive and extremely toxic. Use only in a well-ventilated hood with adequate protection from contact.** Other reagents and solvents employed were of analytical reagent grade or better and were purchased from Aldrich, Baker, Fisher, or Mallinckrodt.

Medium-pressure liquid chromatography (MPLC) was performed with a system described previously.[3a] Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Infrared spectra were measured on a Beckman IR-12 spectrophotometer except as noted. Proton magnetic resonance spectra (^{1}H NMR) were obtained at 60 MHz on a Varian EM-390 spectrometer; proton chemical shifts are reported in δ relative to tetramethylsilane (Me_4Si) as an internal standard. Fluorine magnetic resonance spectra (^{19}F NMR) were obtained at 84.6 MHz on a Varian EM-390 spectrometer, and chemical shifts are reported in parts per million downfield from internal fluorotrichloromethane (−50.0 ppm). Mass spectral data were obtained on a Varian Model CH-5 mass spectrometer.

Microanalytical data were provided by the Microanalytical Service Laboratory of the University of Illinois.

Except where mentioned otherwise, a standard procedure was used for product isolations; this involved quenching by addition to water, exhaustive extraction with a solvent (washing of extract with aqueous solutions, on occasion), drying over an anhydrous salt, and evaporation of solvent under reduced pressure. The particular solvents, aqueous washes (if used), and drying agents are mentioned in parentheses after the phrase "product isolation".

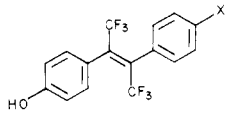
***d,l*-1,2-Bis(4-methoxyphenyl)-1-butanone (2).** Sodium hydride (2.3 g of a 57% dispersion in oil, 60 mmol) was rinsed twice with ca. 10-mL portions of dry THF to remove the oil. Deoxyanisoin (**1**; 10 g, 39 mmol) was dissolved by warming in 40 mL of dry THF and added slowly to the sodium hydride under a dry nitrogen atmosphere. After being stirred for ca. 1 h to allow completion of the reaction (no further evolution of gas), the enolate solution was added to 18.3 g (117 mmol) of ethyl iodide, also under nitrogen. After the reaction was stirred overnight, product isolation (CH_2Cl_2, $MgSO_4$) and chromatography (MPLC, SiO_2, CH_2Cl_2) gave 9.49 g (85%) of α-ethyldeoxyanisoin (**2**) as a colorless oil. Crystallization could not be induced, although the compound is reported to melt at 47–51 °C:[19] mass spectrum (70 eV), *m/e* (relative intensity) 284 (6.1, M^+), 149 (29), 135 (100), 121 (17). Anal. ($C_{18}H_{20}O_3$) C, H.

Methyl 3-Hydroxy-3,4-bis(4-methoxyphenyl)hexanoate (3). Granular zinc (20 mesh) was washed on a sintered glass funnel with dilute hydrochloric acid, twice with water, and once each with ethanol and diethyl ether and dried in a vacuum desiccator. To 32.8 g of this washed zinc (500 mmol) under nitrogen was added ca. 15 mL of a solution of 34.2 g (120 mmol) ethyldeoxyanisoin (**2**) and 76.5 g (500 mmol) methyl bromoacetate in 100 mL of dry benzene. The flask containing the zinc was heated briefly to reflux, initiating the reaction. The remainder of the reagent solution was then added dropwise, and the mixture was heated to reflux for 30 min after the addition was complete. The organozinc intermediate was hydrolyzed by the gradual addition of 5% aqueous sulfuric acid, and, after separation of the phases, the organic layer was washed successively with 5% sulfuric acid, water, 5% sodium hydrogen carbonate, and again with water, dried ($MgSO_4$), and filtered through 15 g of neutral alumina before removal of solvent. The semisolid residue was chromatographed (MPLC, Florisil eluted with 5% ether in hexane) to give a total of 35 g (81%) of a mixture of diastereomers of 3-hydroxyl-3,4-bis(4′-methoxyphenyl)hexanoic acid methyl ester (**3**).

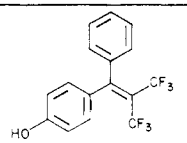
The chromatography produced a partial separation of the diastereomers, allowing independent characterization of the two compounds with samples from the front and tail of the broad peak. More mobile diastereomer: mp 125.5–127.5 °C after recrystallization from ethyl acetate/methanol; IR (KBr) 3508 (OH), 1708 cm^{-1} (ester C=O); ^{1}H NMR ($CDCl_3$) δ 0.51 (t, 3, J = 7.5 Hz, C_6

(14) Metzler, M. *J. Toxicol. Environ. Health Suppl.* **1976**, *1*, 21. Metzler, M.; McLachlan, J. A. *Biochem. Pharmacol.* **1978**, *27*, 1087.
(15) Metzler, M. *Tetrahedron* **1978**, *34*, 3113.
(16) Krohn, K.; Hemme, C. *Liebigs Ann. Chem.* **1978**, 726.
(17) Collins, D. J.; Hobbs, J. J. *Aust. J. Chem.* **1970**, *23*, 119. Collins, D. J.; Hobbs, J. J. *Ibid.* **1970**, *23*, 1605.
(18) Lee, Y. J.; Notides, A. C.; Tsay, Y.-G.; Kende, A. S. *Biochemistry* **1977**, *16*, 2896.
(19) (a) Shoppee, C. W.; Cymerman-Craig, J.; Lack, R. E. *J. Chem. Soc.* **1961**, 2291; (b) Wilds, A. L.; Biggerstaff, W. R. *J. Am. Chem. Soc.* **1945**, *67*, 789.

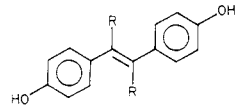
Table II. Estrogen Binding Affinity of Other Side-Chain Fluorinated Diphenylethylenes[a]



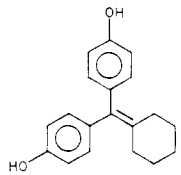
13a (X = H), RAC × 100[b] = 10
b (X = OH), RAC × 100 = 48



14, RAC × 100 = 21



15a (R = CH_3), RAC × 100 = 20; dimethylstilbestrol
b (R = CH_3CH_2) RAC × 100 = 300; diethylstilbestrol



16, RAC × 100 = 32;[c] cyclofenyl

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] J. A. Katzenellengoben and B. S. Schwartz, unpublished results.

H), 1.20–2.03 (m, 2, C_5 H), 2.40 (d, 1, J = 16 Hz, CH_2CO), 2.56 (m, 1, C_4 H), 2.74 (d, 1, J = 16 Hz, CH_2CO), 3.35 (s, 3, $COOCH_3$), 3.45 (s, 6, $ArOCH_3$), 4.30 (s, 1, OH), 6.71–6.93 (m, 4, ArH ortho to methoxyl), 7.11–7.42 (m, 4, ArH ortho to alkyl); mass spectrum (10 eV), m/e (relative intensity) 209 (100), 149 (3), 135 (30). Anal. ($C_{21}H_{26}O_5$) C, H.

Less mobile diastereomer: mp 120.5–122 °C after recrystallization from ethyl acetate/ethanol; IR ($CHCl_3$) 3510 (OH), 1721 cm^{-1} (ester C=O); ^1H NMR (CCl_4) δ 0.70 (t, 3, J = 7 Hz, C_6 H), 1.00–1.54 (m, 2, C_5 H), 1.75–2.20 (m, 1, C_4 H), 3.15 (d, 1, J = 16 Hz, CH_2CO), 3.29 (d, 1, J = 16 Hz, CH_2CO), 3.42 (s, 3, $COOCH_3$), 3.71 (s, 6, $ArOCH_3$), 4.25 (s, 1, OH), 6.56 (d, 2, J = 9 Hz, ArH ortho to methoxyl), 6.57 (m, 4, ArH), 6.88 (d, 2, J = 9 Hz, ArH ortho to carbinol); mass spectrum (10 eV), m/e (relative intensity) 209 (48), 149 (8), 135 (100), 121 (11.5), 107 (4). Anal. ($C_{21}H_{26}O_5$) C, H.

(*E*)- (4b) and (*Z*)-Methyl 3,4-Bis(4-methoxyphenyl)-2-hexenoate (4a). Method I. From 3. A mixture of both diastereomers of the benzylic alcohol (**3**; 33.05 g, 92 mmol) was dissolved in 150 mL of pyridine (dried by distillation from barium oxide), and 12.9 mL of thionyl chloride (21.4 g, 180 mmol) was added gradually (ca. 5 min). The mixture was stirred for 45 min; 150 mL of benzene was added to precipitate the pyridinium hydrochloride byproduct, and the solid was removed by filtration, rinsing with 100 mL of benzene. The solution was washed twice with water, dried ($MgSO_4$), and filtered through ca. 10 g of neutral alumina, and the solvent was removed. The product was chromatographed (MPLC, silica gel, 7 to 20% ether in hexane gradient) giving first 1.66 g of a clear oil identified as the *E* isomer of the product (**4b**; 5%), then 3.12 g (12%) of ethyldeoxyanisoin (**2**), and finally 26.2 g of another clear oil identified as the *Z* isomer of the product (**4a**; 83%).

Spectral data for the more mobile isomer (**4b**) are as follows: IR ($CHCl_3$) 1717 cm^{-1} (conjugated ester C=O); ^1H NMR (CCl_4) δ 0.89 (t, 3, J = 7 Hz, C_6 H), 1.40–2.01 (m, 2, C_5 H), 3.60 (s, 3, $COOCH_3$), 3.66 (s, 6, $ArOCH_3$), 5.31 (t, 1, J = 6 Hz, C_4 H), 5.76 (s, 1, vinyl H), 6.41–6.76 (m, 6, ArH), 6.99 (d, 2, J = 9 Hz, ArH ortho to vinyl); mass spectrum (10 eV), m/e (relative intensity) 340 (100, M^+), 309 (13), 308 (44), 293 (18), 232 (10), 149 (60), 121 (10). Anal. ($C_{21}H_{24}O_4$) C, H.

The less mobile isomer (**4a**) gave IR ($CHCl_3$) 1732 cm^{-1} (conjugated ester C=O); ^1H NMR (CCl_4) δ 0.86 (t, 3, J = 7 Hz, C_6 H), 1.49–2.03 (m, 2, C_5 H), 3.34 (t, 1, J = 7 Hz, C_4 H), 3.40 (s, 3, $COOCH_3$), 3.70 (s, 6, $ArOCH_3$), 5.78 (s, 1, vinyl H), 6.64 (m, 4, ArH), 6.68 (d, 2, J = 9 Hz, ArH ortho to methoxyl), 6.89 (d, 2, J = 9 Hz, ArH ortho to vinyl); mass spectrum (10 eV), m/e (relative intensity) 340 (100, M^+), 309 (14), 308 (40), 293 (19), 232 (12), 149 (84), 121 (13). Anal. ($C_{21}H_{24}O_4$) C, H.

Method II. From the Threo Diastereomer 5b. To a solution of 0.42 mL (3.0 mmol) of diisopropylamine in 5 mL of dry THF was slowly added 1.5 mL of 2.0 M *n*-butyllithium in hexane. The resulting mixture was cooled to −78 °C under nitrogen atmosphere, and, after 10 min, a solution of 800 mg (2.34 mmol) of the *threo*-methyl ester **5b** in 4 mL of dry THF was slowly added. Stirring was continued for 15 min at −78 °C. A THF solution of phenylselenyl bromide [prepared by adding 81 μL (3.0 mmol) of bromine to 470 mg (3.0 mmol) of diphenyl diselenide in 4 mL of THF, followed by stirring for 10 min] was added to the cold ester enolate solution via a syringe (commercially available phenylselenyl chloride can also be used). The resulting mixture was slowly warmed to room temperature, and TLC analysis (9.5:9.5:0.5 hexane/ether/ethyl acetate, two developments) showed that the reaction was complete after 20 min at 25 °C. Water (2 mL) was added, followed by 0.4 mL of acetic acid. The mixture was then cooled in an ice bath and 1.5 mL of 30% hydrogen peroxide was added. While no vigorous reaction was evident at this point, 5 min after the mixture was allowed to warm to room temperature it warmed and evolved a gas. After an additional 20 min, product isolation [Et_2O, $NaHCO_3$ (aq), 0.1 M HCl, Na_2SO_4] gave a residue that was purified by preparative TLC (silica gel, 2% EtOAc in 1:1 hexane/ether, three developments) to give 720 mg (90%) of a 1:1 mixture of **4a** and **4b**.

***erythro*- (5a) and *threo*-Methyl 3,4-Bis(4-methoxyphenyl)hexanoate (5b).** (*Z*)-3,4-Bis(4-methoxyphenyl)-2-hexenoic acid methyl ester (**4a**; 9.15 g, 26.9 mmol) was dissolved in 75 mL of absolute ethanol, and 10 mL of glacial acetic acid and 1 g of 5% palladium on charcoal was added. The mixture was stirred under hydrogen at ambient temperature and pressure for 12 h, by which time 625 mL (ca. 27 mmol) of hydrogen had been consumed and uptake by hydrogen had ceased. Filtration from catalyst and removal of solvent, followed by recrystallization from methylene chloride/hexane, gave 5.48 g (59.5%) of the white crystalline erythro isomer (**5a**). A second recrystallization from ethanol/water gave the analytical sample: mp 116.5–117.5 °C; IR (KBr) 1741 cm^{-1} (ester C=O); ^1H NMR (CCl_4) δ 0.58 (t, 3, J = 7 Hz, C_6 H), 1.03–1.53 (m, 2, C_5 H), 2.13–2.63 (m, 3, C_4 H + CH_2CO), 2.90–3.10 (m, 1, C_3 H), 3.28 (s, 3, $COOCH_3$), 3.71 (s, 6, $ArOCH_3$), 6.70 (d, 2, J = 9 Hz, ArH ortho to methoxyl), 6.73 (d, 2, J = 9 Hz, ArH ortho to methoxyl), 6.99 (d, 4, J = 9 Hz, ArH ortho to alkyl); mass spectrum (70 eV), m/e (relative intensity) 342 (3, M^+), 193 (12), 150 (14), 149 (100), 121 (26), 91 (8). Anal. ($C_{21}H_{26}O_4$) C, H.

Evaporation of the mother liquor and washings from the first recrystallization left 3.45 g of the threo isomer (**5b**) as a colorless oil (37.5%): ^1H NMR (CCl_4) δ 0.74 (t, 3, J = 7 Hz, C_6 H), 1.38–1.92 (m, 2, C_5 H), 2.20–2.78 (m, 3, CH_2CO + C_4 H), 3.17–3.42 (m, 1, C_3 H), 3.49 (s, 3, $COOCH_3$), 3.69 (s, 6, $ArOCH_3$), 6.62 (m, 8, ArH); mass spectrum (70 eV), m/e (relative intensity) 342 (1, M^+), 193 (9), 150 (12), 149 (100), 121 (22). Anal. ($C_{21}H_{26}O_4$) C, H.

Methyl *erythro*-3,4-Bis(4-hydroxyphenyl)hexanoate (6). *erythro*-3,4-Bis(4-methoxyphenyl)hexanoic acid methyl ester (**5a**; 5.13 g, 15 mmol) was dissolved in 25 mL of methylene chloride (dried over 4 Å molecular sieves). The solution was cooled in a dry ice/2-propanol bath, and 5.7 mL of boron tribromide (15.1 g, 60 mmol) was added dropwise. After being stirred for 1 h at −78 °C, the mixture was stored in a refrigerator at +4 °C for 4 h, cooled again in a dry ice/2-propanol bath, and quenched by the dropwise addition of absolute methanol. The solvents were removed under a stream of dry nitrogen, and the residue was taken up in ethyl acetate, filtered through ca. 5 g of neutral alumina, and again taken to dryness in vacuo. The crude product was recrystallized from ethyl acetate/cyclohexane and then ethanol/water to give 3.30 g (70%) of the phenolic methyl ester (**6a**) as a white crystalline solid. A final recrystallization from ethyl acetate/cyclohexane gave the analytical sample: mp 175.5–176.5 °C; IR (KBr) 3400 (ArOH), 1712 cm^{-1} (ester C=O); ^1H NMR (acetone-d_6) δ 0.51 (t, 3, J = 7 Hz, C_6 H), 1.06–1.56 (m, 2, J = 7 Hz, C_5 H), 2.34 (d, 2, J = 7 Hz, CH_2CO), 2.37–2.80 (m, 1, C_4 H), 3.00–3.24 (m, 1, C_3 H), 3.34 (s, 3, $COOCH_3$), 6.78 (d, 2, J = 8.5 Hz, ArH ortho to hydroxyl), 6.82 (d, 2, J = 8.5 Hz, ArH ortho to hydroxyl), 7.07 (d, 2, J = 8.5 Hz, ArH ortho to alkyl), 7.09 (d, 2, ArH ortho to alkyl), 8.08 (s, 2, ArOH); mass spectrum (10 eV), m/e (relative intensity) 314 (5, M^+), 179 (8), 135 (100), 134 (43). Anal. ($C_{19}H_{22}O_4$) C, H.

***erythro*-3,4-Bis(4-hydroxyphenyl)-1-hexanol (7).** Lithium aluminum hydride (950 mg, 6.4 mmol) was dissolved in 40 mL of dry THF and added dropwise to a solution of 2.01 g (6.4 mmol) of *erythro*-3,4-bis(4-hydroxyphenyl)hexanoic acid methyl ester

(**6a**) in 40 mL of 1:1 THF/ether. After being stirred for 15 min, the reaction was quenched by the cautious addition of methanol followed by removal of solvent. Product isolation (EtOAc, 5% aqueous HCl, H_2O, $MgSO_4$) gave 1.73 g (95%) of *erythro*-3,4-bis(4-hydroxyphenyl)-1-hexanol (**7**) as a white crystalline solid: mp 232–234.5 °C after recrystallization from THF/hexane; IR (KBr) 3420 and 1247 (ArOH), 3290 (sh) and 1028 cm^{-1} (alcohol COH); ^1H NMR (acetone-d_6) δ 0.53 (t, 3, J = 7 Hz, C_6 H), 1.10–1.83 (m, 4 C_2 H and C_5 H), 2.41–2.92 (m, 2, C_3 H and C_4 H), 2.86 (s, 1, alkyl OH), 3.18 (t, 2, J = 7 Hz, C_1 H), 6.75 (d, 4, J = 9 Hz, ArH ortho to hydroxyl), 6.98 (d, 2, J = 9 Hz, ArH ortho to alkyl), 7.01 (d, 2, J = 9 Hz, ArH ortho to alkyl), 7.98 (s, 2, ArOH); mass spectrum (70 eV), m/e (relative intensity) 286 (0.56, M^+), 151 (37), 135 (97), 134 (12), 121 (38), 107 (100). Anal. ($C_{18}H_{22}O_3$) C, H.

***erythro*-3,4-Bis(4-methoxyphenyl)-1-hexanol (8a).** Lithium aluminum hydride (76 mg, 2 mmol) dissolved in 8 mL of dry THF was added slowly to 346 mg (1 mmol) of methyl *erythro*-3,4-bis(4-methoxyphenyl)hexanoate (**5a**), dissolved in 10 mL of dry THF. After being stirred for 10 min, the reaction was quenched by the cautious addition of MeOH and the solvent was removed. Product isolation (EtOAc, 5% aqueous HCl, H_2O, $MgSO_4$) gave 308 mg of white crystalline **8a** (97%): mp 147–148 °C after recrystallization from EtOH; IR ($CHCl_3$) 3640 (OH), 1257 cm^{-1} (ArOMe); ^1H NMR ($CDCl_3$) δ 0.55 (t, 3, J = 7.5 Hz, C_6 H), 1.17–1.79 (m, 4, C_2 H and C_5 H), 2.41–3.03 (m, 2, C_3 H and C_4 H), 3.37 (m, 2, C_1 H), 3.94 (s, 6, $ArOCH_3$), 7.10 (d, 4, J = 9 Hz, ArH ortho to OCH_3), 7.31 (d, 2, J = 9 Hz, ArH ortho to alkyl), 7.33 (d, 2, J = 9 Hz, ArH ortho to alkyl); mass spectrum (70 eV), m/e (relative intensity) 314 (2, M^+), 165 (53), 149 (100), 148 (10), 135 (26), 121 (53). Anal. ($C_{20}H_{26}O_3$) C, H.

***erythro*-1-Fluoro-3,4-Bis(4-methoxyphenyl)hexane (8b).** Diethylaminosulfur trifluoride (DAST; 0.31 mL, 2.5 mmol) was added dropwise to a solution of 628 mg (2 mmol) of *erythro*-3,4-bis(4-methoxyphenyl)-1-hexanol in 4 mL of dichloromethane (dried over 4 Å molecular sieves) cooled in a dry ice/2-propanol bath. After being warmed to room temperature and stirred for a total of 3 h, the reaction was quenched by the addition of aqueous $NaHCO_3$, washed (H_2O), dried ($MgSO_4$), concentrated, and chromatographed (MPLC, SiO_2, 10% EtOAc/hexane) to give 282 mg of white crystalline **8b** (45%): mp 157.5–159.5 °C; ^1H NMR ($CDCl_3$) δ 0.54 (t, 3, J = 7 Hz, C_6 H), 1.15–1.99 (m, 4, C_2 H and C_5 H), 2.35–2.96 (m, 2, C_3 H and C_4 H), 3.60–4.37 (m, 2, C_2 H), 3.77 (s, 6, $ArOCH_3$), 6.70 (d, 4, J = 9 Hz, ArH ortho to OMe), 7.02 (d, 4, J = 9 Hz, ArH ortho to alkyl); ^{19}F NMR (CCl_4) δ 219.2 (10 peaks, J = 49 and 17 Hz); mass spectrum (70 eV), m/e (relative intensity) 316 (3, M^+), 167 (19), 149 (100), 121 (32). Anal. ($C_{20}H_{25}FO_2$) C, H.

***erythro*-1-Fluoro-3,4-bis(4-hydroxyphenyl)hexane (9).** *erythro*-3,4-Bis(4-hydroxyphenyl)-1-hexanol (**7**; 270 mg, 0.39 mmol) was dissolved in 20 mL of THF (dried by distillation from sodium and benzophenone) and cooled in an ice/salt bath under a nitrogen atmosphere. Diethylaminosulfur trifluoride[9] (0.40 mL, 3.2 mmol) was added, and the mixture was allowed to warm to ambient temperature. After a total time of 7 h, the reaction was quenched by the addition of aqueous sodium hydrogen carbonate, and the solvent was removed. Product isolation (ethyl acetate extraction, chromatography: MPLC, SiO_2, 45:45:10 hexane/dichloromethane/ethyl acetate) gave 208 mg (76%) of white crystalline 1-fluoro-3,4-bis(4-hydroxyphenyl)hexane (**9**): mp 183–183.5 °C after recrystallization from THF/hexane; ^1H NMR (acetone-d_6) δ 0.53 (t, 3, J = 7 Hz, C_6 H), 1.08–1.57 (m, 2, C_5 H), 1.57–1.95 (m, 2, C_2 H), 2.32–2.92 (m, 2, C_3 H and C_4 H), 3.97 (m, 2, J_{HF} = 46 Hz, C_1 H), 6.75 (d, 4, J = 9 Hz, ArH ortho to hydroxyl), 6.98 (d, 4, J = 9 Hz, ArH ortho to alkyl), 7.97 (s, 2, ArOH); ^{19}F NMR (acetone-d_6) δ 217.9 (10 peaks, J = 46 and 17 Hz); mass spectrum (70 eV), m/e (relative intensity) 288 (2, M^+), 153 (14), 135 (100), 107 (45). Anal. ($C_{18}H_{21}FO_2$) C, H.

***erythro*-1-Chloro-3,4-bis(4-hydroxyphenyl)hexane (10).** Carbon tetrachloride (7 mL) was added to a mixture of 200 mg (0.76 mmol) of the phenolic alcohol **7** and 250 mg (0.95 mmol) of triphenylphosphine, followed by 1 mL of dry THF and 2 mL of acetonitrile. The homogeneous reaction mixture was then refluxed for 90 min. Solvents were removed from the reaction mixture under reduced pressure to give an oily residue. Triphenylphosphine oxide separated upon addition of THF, and the soluble material was purified by preparative TLC (silica gel, 2:1 EtOAc/CH_2Cl_2), affording 150 mg (70.5% yield) of the desired chloro compound **10**. The analytical sample was obtained by recrystallization from THF–cyclohexane: mp 159–159.5 °C; ^1H NMR (acetone-d_6) δ 0.50 (t, 3, J = 7 Hz, C_6 H), 1.00–1.20 (m, 2, C_5 H), 1.55–1.85 (m, 2, C_2 H), 2.30–3.20 (overlapping m, 4, C_1 H, C_3 H, and C_4 H), 6.75 (d, 4, J = 9 Hz, ArH ortho to hydroxyl), 7.00 (d of d, 4, J = 3 and 9 Hz; ArH ortho to alkyl), 7.95 (br s, 2, ArOH); mass spectrum (70 eV), m/e (relative intensity) 306 (1), 304 (2, both M^+), 169 (9), 135 (100), 107 (37). Anal. ($C_{18}H_{21}O_2Cl$) C, H, Cl.

***erythro*-1-Bromo-3,4-bis(4-hydroxyphenyl)hexane (11).** Acetonitrile (10 mL) was added to a mixture of 100 mg (0.35 mmol) of the phenolic alcohol **7**, 130 mg (0.50 mmol) of triphenylphosphine, and 130 mg (0.39 mmol) of carbon tetrabromide, followed by 1 mL each of methylene chloride and dry THF. The resulting suspension was heated to 90 °C (bath temperature) for 2 min to effect dissolution, and the solution was stirred at room temperature under nitrogen for 90 min. After evaporation of the solvents under reduced pressure, the residue was purified by preparative TLC on silica gel (1:1 CH_2Cl_2/EtOAc) to give 75 mg (61.4%) of the desired bromo compound **11**. The analytical sample was prepared by recrystallization from THF/cyclohexane. This compound is not stable at room temperature over a period of 7 days: mp 152 °C; ^1H NMR (acetone-d_6) δ 0.50 (t, 3, J = 7.5 Hz, C_6 H), 1.10–1.50 (m, 2, C_5 H), 1.65–2.00 (m, 2, J = 7.5 Hz, C_2 H), 2.40–3.15 (overlapping m, 4, C_1 H, C_3 H, and C_4 H), 6.75 (d, 4, J = 9 Hz, ArH ortho to hydroxyl), 7.05 (m, 4, ArH ortho to alkyl), 8.05 (br, 2, ArOH); mass spectrum (10 eV), m/e (relative intensity) 350 (2), 348 (2, both M^+), 268 (11), 215 (3), 213 (3), 135 (100). Anal. ($C_{18}H_{21}O_2Br$) C, H, Br.

This phenolic bromide (**11**) can be prepared in better overall yield by the following procedure: *erythro*-3,4-bis(4-methoxyphenyl)-1-hexanol (**8a**; 535 mg, 1.7 mmol) and carbon tetrabromide (700 mg, 2.11 mmol) were dissolved in 10 mL of CH_2Cl_2 and the resulting solution was cooled by an ice bath under nitrogen atmosphere. A methylene chloride (5 mL) solution of triphenylphosphine (570 mg, 2.17 mmol) was slowly added to this solution, and the resulting mixture was stirred for 30 min. Solvents were evaporated and the residue was purified by preparative TLC (1:1 hexane/ether) to give 613 mg (95.6%) of the methoxy bromide (**8c**): ^1H NMR ($CDCl_3$) δ 0.50 (t, 3, J = 7.5 Hz, C_6 H), 1.20–1.70 (m, 4, C_2 H and C_5 H), 2.30–2.95 (m, 2, C_3 H and C_4 H), 3.10–3.40 (m, 2, C_1 H), 3.75 (s, 6, $ArOCH_3$), 6.70–7.15 (m, AA'BB' pattern, 8, ArH); mass spectrum (10 eV), m/e (relative intensity) 378 (2), 376 (2, both M^+), 229 (4), 227 (4), 149 (100).

A methylene chloride (10 mL) solution of this methoxy bromide (**8c**; 613 mg) was cooled to −78 °C under a nitrogen atmosphere. Boron tribromide (2 mL of a 5 M solution in CH_2Cl_2) was slowly added and the reaction mixture was stirred for 8 h. The excess BBr_3 was destroyed by careful addition of anhydrous methanol (at −78 °C). Solvents were removed under reduced pressure and the residue after product isolation was purified by preparative TLC (1:1 CH_2Cl_2/EtOAc) to give 476 mg (80% overall) of the phenolic bromide (**11**).

***erythro*-1-Iodo-3,4-bis(4-hydroxyphenyl)hexane (12).** A saturated solution of sodium iodide in acetone (10 mL) was added to 170 mg (0.49 mmol) of *erythro*-1-bromo-3,4-bis(4-hydroxyphenyl)hexane (**11**), and the resulting solution was refluxed in the dark for 8 h. The reaction mixture was cooled, and acetone was evaporated under reduced pressure. Product isolation [EtOAc, $NaHSO_3$ (aq), H_2O, NaCl (aq), $MgSO_4$] gave a residue that was purified by preparative TLC (silica gel, 5% EtOAc in CH_2Cl_2) to give 193 mg (95%) of the desired iodo compound (**12**), which was recrystallized from ethyl acetate/hexane. This compound must be stored in the dark: mp 155–156 °C; ^1H NMR (acetone-d_6) δ 0.50 (t, 3, J = 7.5 Hz, C_6 H), 1.10–1.50 (m, 2, C_5 H), 1.60–1.90 (m, 2, C_2 H), 2.40–3.05 (overlapping m, 4, C_1 H, C_3 H, and C_4 H), 6.75 (d, 4, J = 9 Hz, ArH ortho to hydroxyl), 7.05 (m, 4, ArH ortho to alkyl), 8.05 (br, 2, ArOH); mass spectrum (10 eV), m/e (relative intensity) 396 (3, M^+), 261 (7), 135 (100), 107 (7). Anal. (high-resolution mass spectrum) Calcd for $C_{19}H_{21}O_2I$: 396.0585. Found: 396.0593.

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25836). J.A.K. is a Camille and Henry Dreyfus Teacher-Scholar, and D.F.H. is a Procter and Gamble Fellow. Kurt W. Raack assisted in the preparation of diethylaminosulfur trifluoride (DAST). The binding affinity measurements to the uterine estrogen receptor were performed by Kathryn E. Carlson. The high-resolution mass spectrometry equipment used in this study was provided by a grant from the National Cancer Institute (CA 11388).

Aporphines. 31. Synthesis and Antitumor Activity of Aporphine Nitrogen Mustards[1a]

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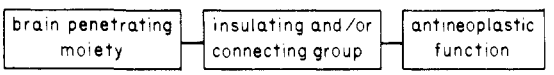
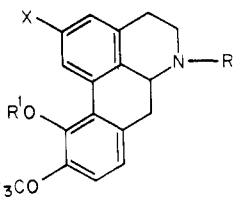
A series of aporphine nitrogen mustards and their congeners (**1b–g**) has been prepared. *N*-[[Bis(2-chloroethyl)-amino]acetyl]-2,11-dihyroxy-10-methoxynoraporphine (**1b**) and its mono- and diacetyl ester derivatives (**1c–d**) were prepared from *N*-(chloroacetyl)-2,11-diacetoxy-10-methoxynoraporphine (**2**). Reaction of **2** with diethanolamine under various conditions and different solvents resulted in the corresponding *N*-[[bis(2-hydroxyethyl)amino]acetyl] precursors, which were subsequently treated with $SOCl_2$ to yield the target compounds. *N*-(2-Choroethyl)norapocodeine (**1e**) was obtained from the chlorination of *N*-(2-hydroxyethyl)norapocodeine (**9**) with $SOCl_2$. Prolonging such treatment was found to result in the formation of *N*-[2-(chloroethoxy)ethyl]norapocodeine (**1f**) at the expense of **1e**. *N*-[[[*N'*-(2-Chloroethyl)carbamyl]oxy]ethyl]norapocodeine (**1g**) and its 11-(2-chloroethyl)carbamyl derivative (**1h**) were also prepared. All the double-armed aporphine amide nitrogen mustards (**1b–d**) were found to have antitumor activity. The single-armed aporphine nitrogen mustard (**1e**) was also active in P388 but the activity was less than that observed with **1b–d**. The lead compound **1a** was inactive in the LE1210 and P388 systems at the doses tested. Similarly, the two aporphine mustard congeners (**1f,g**) were also inactive in the P388 system. All the activity was observed in the intraperitoneally innoculated tumor systems.

In a continuing effort to design central nervous system (CNS) penetrating antitumor agents, our approach was the development of multiple-component drugs containing both CNS-penetrating moieties and antineoplastic functions. Thus, the overall drug structure may be viewed as a three-component compound incorporating the following structural features:



This approach has been used successfully by Driscoll[2] et al. who utilized the concept of attaching alkylating functions to such CNS-penetrating agents as the hydantoins,[2a] phenothiazines,[2b] and benzoquinones.[2c,d] When we utilized the CNS-penetrating 3-amino-4-(*p*-aryl and alkyl)isoquinolines as the brain-penetrating moiety, incorporating a nitrogen mustard as the antineoplastic function,[3] or when a bis(2-chloroethyl)aminoethyl moiety was attached directly to the nitrogen atom in 2,10,11-trimethoxynoraporphine[4] (**1a**), inactive antitumor compounds resulted. We attributed such inactivity to the apparent high lipophilic character of these compounds. Consequently, derivatives **1b–g** were synthesized in an effort to increase the hydrophilicity of the molecule without sacrificing its potential CNS-penetrating properties. The structural modifications featuring (a) replacements of the 2- and 11-methoxy groups with H and OH or metabolically labile acetoxy groups, (b) attachment of the nitrogen mustard moiety to the aporphine nitrogen atom via an amide bond as opposed to the hydrocarbon chain existing in **1a**, or (c) direct attachment of the chloroethyl group to the aporphine nitrogen atom led to antitumor activity of these compounds in one or several tumor systems.



1a (NSC 278462), X = OCH_3; R^1 = CH_3; R = $CH_2CH_2N(CH_2CH_2Cl)_2$
b (NSC 311484), X = OH; R^1 = H; R = $COCH_2N(CH_2CH_2Cl)_2$
c (NSC 294134), X = $OCOCH_3$; R^1 = $COCH_3$; R = $COCH_2N(CH_2CH_2Cl)_2$
d (NSC 279847), X = OH; R^1 = $COCH_3$; R = $COCH_2N(CH_2CH_2Cl)_2$
e (NSC 304688), X = H; R^1 = H; R = CH_2CH_2Cl
f (NSC 311483), X = H; R^1 = H; R = $CH_2CH_2OCH_2CH_2Cl$
g (NSC 316161), X = H; R^1 = H; R = $CH_2CH_2OCONHCH_2CH_2Cl$
h (NSC 322369), X = H; R^1 = $CONHCH_2CH_2Cl$; R = $CH_2CH_2OCONHCH_2CH_2Cl$

We wish to report the synthesis of the active antitumor agents **1b–d** as well as the antitumor activity of the single-armed mustard, **1e**. The synthesis of **1e** has been

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