Nonsteroidal Estrogens: Synthesis and Estrogen Receptor Binding Affinity of Derivatives of (3*R**,4*S**)-3,4-Bis(4-hydroxyphenyl)hexane (Hexestrol) and (2*R**,3*S**)-2,3-Bis(4-hydroxyphenyl)pentane (Norhexestrol) Functionalized on the Side Chain

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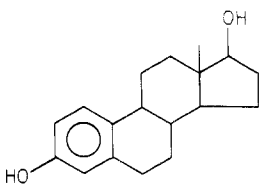
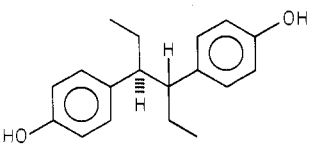
A series of nonsteroidal, side-chain functionalized estrogens based on (3*R**,4*S**)-3,4-bis(4-hydroxyphenyl)hexane (hexestrol) and (2*R**,3*S**)-2,3-bis(4-hydroxyphenyl)pentane (norhexestrol) has been prepared; these include amide, diazo ketone, ester, alcohol, ketone, fluoro, bromo, iodo, and saturated hydrocarbon derivatives. Analysis of the binding affinity of these compounds to the uterine estrogen receptor, measured by competitive binding assay, reveals trends that can be related to the steric size, the hydrophobicity, and the hydrogen bond accepting character of the side-chain substituents. Comparison of binding affinities between norhexestrol and hexestrol derivatives indicates that, in general, the norhexestrols show significantly higher receptor binding affinities, making this series of compounds ideally suited as functional probes for the estrogen receptor.

The biological activity of steroidal hormones, such as estrogens, is dependent on their interaction with certain high-affinity binding proteins called receptors. Our studies on the estrogen receptor have centered around receptor affinity labels[1] and receptor-based breast tumor imaging agents.[2] In the course of this work, two series of receptor reagents have been developed: one based on steroidal estrogens, such as 17β-estradiol (1), and the other based on nonsteroidal estrogens, such as *meso*-hexestrol [(3*R**,4*S**)-3,4-bis(4-hydroxyphenyl)hexane (2)].[3]

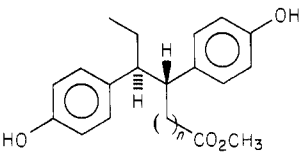


17β-estradiol (1)

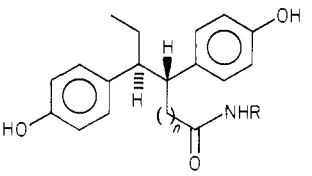


meso-hexestrol (2)

Scheme I



3, *n* = 0
4, *n* = 1



5, *n* = 0; R = H (100%)
6, *n* = 1; R = H (47%)
7, *n* = 0; R = *n*-C_5H_{11} (63%)
8, *n* = 1; R = *n*-C_5H_{11} (61%)

Hexestrol derivatives offer a number of advantages over the use of estradiol-based derivatives.[4] First, hexestrol exhibits a binding affinity for the estrogen receptor that is three times greater than estradiol, while it also has a lower affinity for certain specific estrogen binding proteins in serum, such as alphafetoprotein (in the rat) and sex steroid binding protein (in the human).[5] Second, nonsteroidal estrogens have a simpler chemistry than their steroidal counterparts, and, finally, hexestrol derivatives can often be more extensively substituted and functionalized without depressing their binding to the estrogen receptor.[6]

Our recent work on stereochemical considerations in the binding of nonsteroidal estrogens to the estrogen receptor,[7] in which a series of hexestrol and norhexestrol [(2*R**,3*S**)-2,3-bis(4-hydroxyphenyl)pentane][3] esters was prepared, indicated that the norhexestrol esters bound to the estrogen receptor significantly better than the ho-

(1) For reviews, see (a) Katzenellenbogen, J. A.; Johnson, H. J., Jr.; Myers, H. N.; Carlson, K. E.; Kempton, R. J. *Bioorg. Chem.* **1978**, *4*, 207–237. (b) Katzenellenbogen, J. A., *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1978**, *37*(2), 174. See also (c) Katzenellenbogen, J. A.; Kilbourn, M. R.; Carlson, K. E. *Ann. N.Y. Acad. Sci.* **1980**, *246*, 18. (d) Katzenellenbogen, J. A.; McGorrin, R. J.; Tatee, T.; Kempton, R. J.; Carlson, K. E.; Kinder, D. H. *J. Med. Chem.* **1981**, *24*, 435.

(2) Katzenellenbogen, J. A.; Carlson, K. E.; Heiman, D. F.; Lloyd, J. E. In "Radiopharmaceuticals: Structure–Activity Relationships"; Spencer, R. P., Ed.; Grune & Stratton: New York, 1981; Chapter 2, pp 23–86. (b) Katzenellenbogen, J. A.; Heiman, D. F.; Carlson, K. E.; Lloyd, J. E. In "Receptor-Binding Radiotracers"; Eckelman, W. C., Ed.; CRC Press, Boca Raton, FL, 1982; Chapter 6, p 93–127. See also (c) Katzenellenbogen, J. A.; Senderoff, S. G.; McElvany, K. D.; O'Brien, H. A., Jr.; Welch, M. J. *J. Nucl. Med.* **1981**, *22*, 42. (d) Katzenellenbogen, J. A.; McElvany, K. D.; Senderoff, S. G.; Carlson, K. E.; Landvatter, S. W.; Welch, M. J. *Ibid.* **1982**, *23*, 411. (e) McElvany, K. D.; Carlson, K. E.; Welch, M. J.; Senderoff, S. G.; Katzenellenbogen, J. A. *Ibid.* **1982**, *23*, 420. (f) McElvany, K. D.; Katzenellenbogen, J. A.; Shafer, K. E.; Siegel, B. A.; Senderoff, S. G.; Welch, M. J. *Ibid.* **1982**, *23*, 425.

(3) The *R**,*S** system of designating relative stereochemistry (IUPAC 1968 Tentative Rules, Section E) is used to define unambiguously the appropriate diastereomer of each hexestrol and norhexestrol derivative. In this system, the *R**,*S** diastereomers correspond in each case to those referred to traditionally as the meso or erythro diastereomers. The other diastereomers (*R**,*R**, *dl* or *threo*) have much lower binding affinity for the estrogen receptor (Kilbourn, M. R.; Arduengo, A. J.; Park, J. T.; Katzenellenbogen, J. A. *Mol. Pharmacol.* **1981**, *19*, 388).

(4) Katzenellenbogen, J. A.; Carlson, K. E.; Johnson, H. J.; Myers, H. N. *J. Toxicol. Environ. Health, Suppl. 1* **1976**, *205*.

(5) Nunez, E.; Valette, G.; Benassayag, C.; Jayle, M. F., *Biochem. Biophys. Res. Commun.* **1974**, *57*, 126. (b) Petra, P. H. *J. Steroid Biochem.* **1979**, *11*, 245.

(6) Katzenellenbogen, J. A.; Johnson, H. J. Jr.; Myers, H. N. *Biochemistry* **1973**, *12*, 4085.

(7) Landvatter, S. W.; Katzenellenbogen, J. A. *Mol. Pharmacol.* **1981**, *20*, 43.

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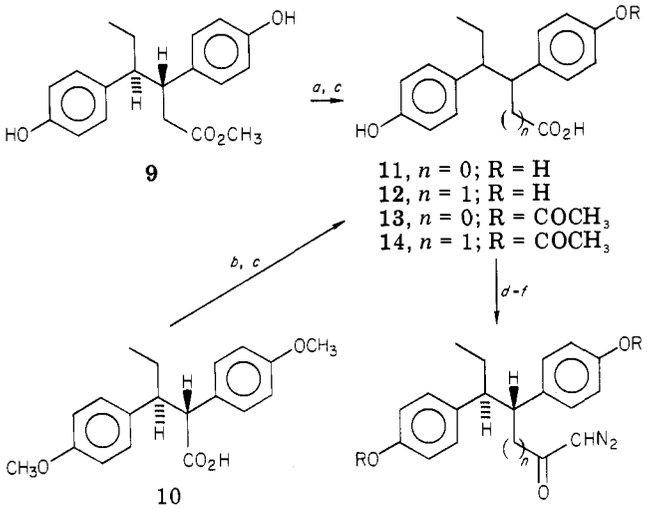
Scheme II



[a] NaOH (97%). [b] BBr_3 (97%). [c] Ac_2O (98, 94%). [d] $SOCl_2$. [e] CH_2N_2 (52, 63%). [f] K_2CO_3–MeOH (89, 64%).

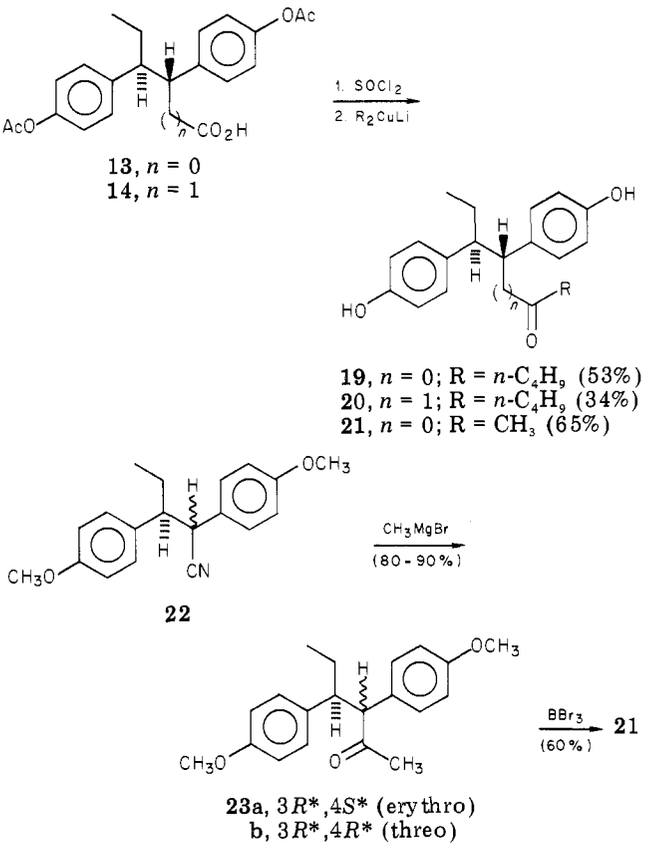
mologous hexestrol esters. In this report we present the synthesis of several hexestrol and norhexestrol derivatives bearing a wide range of functionality on the side chain, and we describe the measurement of the binding affinity of these derivatives for the uterine receptor. Analysis of these data has enabled us to formulate a model for receptor binding in which factors such as the steric size, the hydrophobicity, and the hydrogen bond accepting character of the substituent on these nonsteroidal estrogen analogues can be related to their binding affinity for the estrogen receptor. This model is useful in the development of new functional probes for the estrogen receptor.

Results

Synthesis of Side-Chain Functionalized Hexestrols and Norhexestrols. A series of hexestrol and norhexestrol amides have been synthesized by a modification of a procedure developed by Yazawa, whereby functional group interchange (ester to amide) and methyl ether deprotection are achieved in one reaction vessel (Scheme I).[8] Treatment of the methyl ether protected methyl esters **3** and **4**[9] with boron tribromide, followed by quenching at 0 °C with pentylamine, affords moderate yields of the unprotected pentyl amides **7** and **8**. We have also been able to extend this reaction to the synthesis of primary amides **5** and **6** by quenching at −78 °C with liquid ammonia.

Bisphenolic diazo ketones **17** and **18**, which may also be of use as estrogen receptor photoaffinity labels, were synthesized as outlined in Scheme II. Methyl ether cleavage of the noracid **10**[7] with boron tribromide and base-catalyzed ester hydrolysis of methyl ester **9**[9] gives the bisphenolic acids **11** and **12**, respectively. Reprotection with acetic anhydride, followed by successive treatment with thionyl chloride and diazomethane, affords the acetoxy diazo ketones **15** and **16**, which are deprotected in potassium carbonate–methanol to give the desired

Scheme III



disphenolic diazo ketones **17** and **18**.

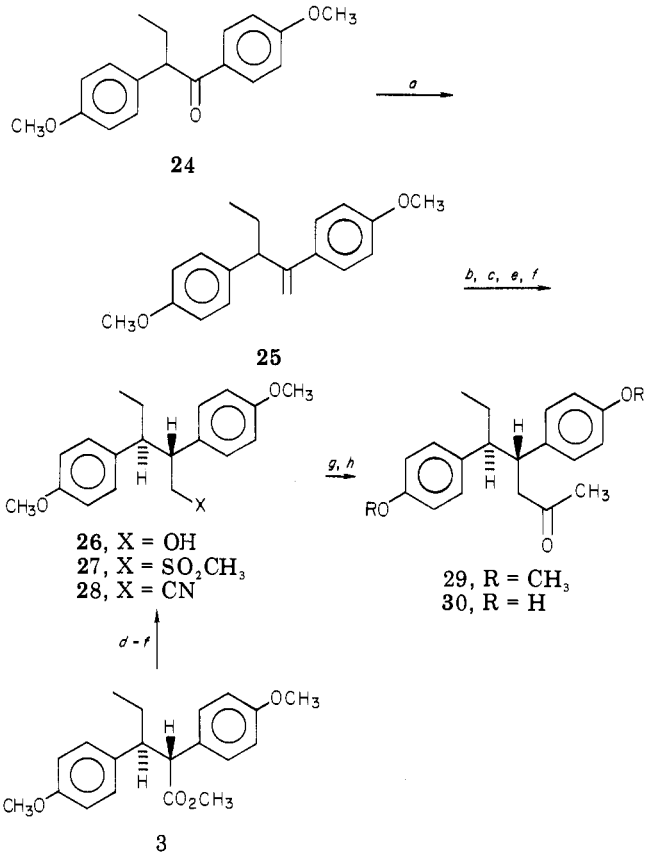
A series of hexestrol and norhexestrol ketones have also been synthesized. The butyl ketones **19** and **20** are obtained in moderate yield from the acetoxy acids **13** and **14**, respectively, via treatment with thionyl chloride, followed by lithium dibutylcuprate, according to the method of Posner (Scheme III).[10] It is of note that this procedure also results in complete cleavage of the acetoxy protecting groups. The normethyl ketone **21** is obtained in a similar fashion from acetoxy acid **13**, but a more efficient route to this ketone involves methyl Grignard addition to nitrile **22**, as previously reported by Wawzonek[11] and Burckhalter and Sam,[12] giving the methyl ketone **23** as a 1:1 mixture of erythro and threo diastereomers. Methyl ether cleavage (BBr_3) gives the desired bisphenolic methyl ketone (**21**).

The synthesis of hexestrol methyl ketone **30** proved more problematical, as reaction of the acid chloride of **14** with lithium dimethylcuprate failed to give the expected ketone. Instead, after quenching with methanol, hexestrol methyl ester **9**[9] is obtained. Similar results are obtained with dimethylcadmium. The ability of the acid chloride from **14** to undergo reaction with lithium dibutylcuprate but not with lithium dimethylcuprate is curious; however, Posner[10] and Crabbé[13] have noted similar anomalies in these cuprate reactions.

Hexestrol methyl ketone **30** was successfully obtained by the sequence shown in Scheme IV. Methanesulfonylation of alcohol **26**, followed by treatment with sodium cyanide, gives nitrile **28**, which upon addition of methylmagnesium bromide and methyl ether cleavage

(8) Yazawa, H.; Tanaka, K.; Karigene, K. *Tetrahedron Lett.* **1974**, 3991.
(9) Goswami, R.; Harsy, S. G.; Heiman, D. F.; Katzenellenbogen, J. A. *J. Med. Chem.* **1980**, *23*, 1002.
(10) Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106.
(11) Wawzonek, S. *J. Am. Chem. Soc.* **1951**, *73*, 5746.
(12) Burckhalter, J. H.; Sam, J. *J. Am. Chem. Soc.* **1952**, *74*, 187.
(13) Crabbé, P.; Valarde, E. *J. Chem. Soc. D* **1972**, 241.

Scheme IV



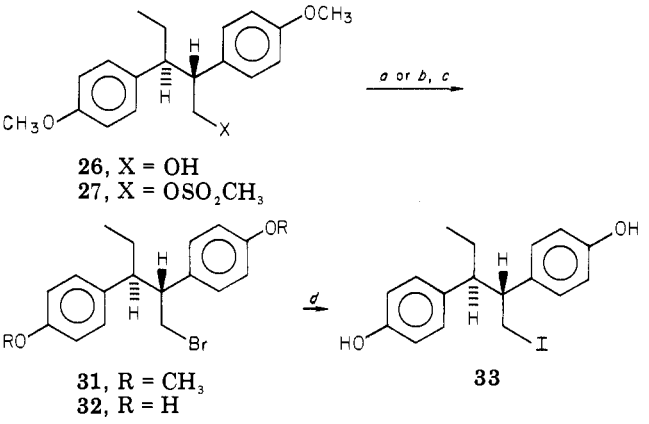
[a] $Ph_3P{=}CH_2$ (95%). [b] B_2H_6. [c] H_2O_2 (65%). [d] $LiAlH_4$ (100%). [e] CH_3SO_2Cl (96%). [f] NaCN (75%). [g] CH_3MgBr (79%). [h] BBr_3 (76%).

gives the desired bisphenolic hexestrol ketone **30**. The starting alcohol (**26**) is available via two routes: by lithium aluminum hydride reduction of normethyl ester **3** or by Wittig olefination of α-ethyldeoxyanisoin[9] (**24**), followed by hydroboration of the pentene **25**. This latter route offers a much shorter and more efficient (52 vs. 21%) synthetic path to alcohol **26** from commercially available starting materials (deoxyanisoin).

A series of norhexestrols halogenated on the side-chain terminus has also been prepared. Bromonorhexestrol **32** is quantitatively obtained via boron tribromide methyl ether cleavage of methyl ether bromide **31**, a compound that is available either by the treatment of the methanesulfonate **27** with lithium bromide in acetone in excellent yield or by the reaction of the methyl ether noralcohol **26** with phosphorus tribromide or carbon tetrabromide–triphenylphosphine. It is of note that while this latter route affords only low yields (9–30%) of bromide **31**, similar reaction conditions produce the homologous hexestrol bromide in 96% yield from the appropriate alcohol.[9] The bisphenolic iodonorhexestrol **33** is obtained in nearly quantitative yield by refluxing the bromide **32** with sodium iodide in acetone (Scheme V).

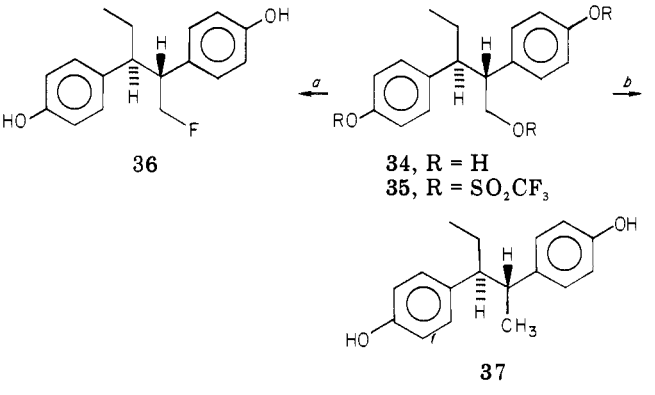
The synthesis of fluoronorhexestrol **36** proved troublesome, as treatment of the nortriol **34**[7] with the mild fluorinating reagent diethylaminosulfur trifluoride (DAST)[14] gives no reaction. Similar reaction conditions have been shown to produce the homologous fluorohexestrol in 76% yield.[9] The desired fluoride is, however, available in two steps from nortriol **34** (Scheme VI). Conversion of this alcohol to the tris(trifluoromethanesulfonate) (**35**) and addition of a tenfold excess of tetrabutylammonium fluoride give the bisphenolic fluoride **36** directly. In the second reaction, fluoride is acting both as a base (in cleaving triflate protecting groups) and as a nucleophile (in triflate displacement). Finally, the parent compound in the norhexestrol series, norhexestrol or pentestrol (**37**), is obtained by lithium aluminum hydride reduction of tris(triflate) **35** (Scheme VI). The synthesis of a number of other compounds, **38–44**, whose binding properties to the estrogen receptor are discussed in this work, has been described elsewhere.[7,9]

Scheme V

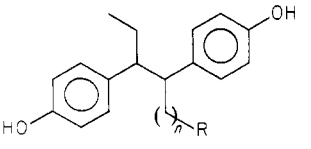


[a] PPh_3-CBr_4 *or* PBr_3 (30–38%, with **26**). [b] LiBr (86%, with **27**). [c] BBr_3 (90%). [d] NaI-acetone (98%).

Scheme VI



[a] n-Bu_4NF (52%). [b] $LiAlH_4$ (83%).



38, n = 0; R = CO_2CH_3
39, n = 0; R = CO_2-n-C_5H_{11}
40, n = 1; R = CO_2-n-C_5H_{11}
41, n = 2; R = OH
42, n = 2; R = F
43, n = 2; R = Br
44, n = 2; R = I

Binding Affinity of Hexestrols and Norhexestrols for the Uterine Estrogen Receptor. The binding affinity of nonradiolabeled estrogen analogues for the uterine estrogen receptor can be measured readily by a competitive binding assay.[15] The affinities are obtained relative to that

(14) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574. (b) Markovski, L. N.; Pashinnik, V. E.; Kipsanov, A. V. *Synthesis* **1973**, 787. (c) Markovski, L. N.; Pashinnik, V. E. *Ibid.* **1973**, 801.

Table I. Comparative Binding of Hexestrols and Norhexestrols for the Estrogen Receptor

compd	ratio of assoc constants × 100[a] (compd)[b] norhexestrols	hexestrols	norhex/hex
alkane	137 (37)	300 (2)	0.5
fluoro	129 (36)	129[d] (42)	1.0
bromo	150 (32)[c]	71[d] (43)	2.1
iodo	127 (33)[c]	60[d] (44)	2.1
triol	8.9[e] (34)	15[e] (41)	0.6
Me ketone	58 (21)	21 (30)	2.8
Bu ketone	81 (19)	9.4 (20)	8.6
Me ester	70[e] (38)	19[e] (9)	3.7
pentyl ester	61[e] (39)	3.8[e] (40)	16.1
1-diazo-2-keto	10.9 (17)	2.8 (18)	3.9
1° amide	0.20 (5)	0.09 (6)	2.2
pentyl amide	0.29 (7)	0.15 (8)	1.9

[a] The ratio of association constants were determined in a competitive binding assay with lamb uterine cytosol as a source of estrogen receptor, [^{3}H]estradiol as a tracer, and charcoal-dextran adsorption to separate free from bound tracer. Affinities are measured relative to estradiol (= 100). Values are the average of at least two determinations and are reproducible within ±30%. [b] Numbers in parentheses are compound numbers. [c] Compounds **32** and **33** are solvolytically unstable (cf. ref 15). However, studies with bromine-77 labeled **32** and iodine-125 labeled **33** have demonstrated that essentially no degradation occurs in lamb uterine cytosol after 24 h at 0 °C. [d] Data are from ref 9. [e] Data are from ref 7.

of the tracer compound [^{3}H]estradiol and are conveniently expressed as a ratio of association constants (RAC) on a percent scale, where the binding of estradiol is defined as 100%. The binding affinities of the hexestrol and norhexestrol derivatives are shown in Table I.

It is readily evident that the norhexestrols do, in general, show higher binding affinities for the estrogen receptor than their hexestrol homologues. In fact, most of the norhexestrol derivatives show two- to fourfold binding enhancements over their hexestrol counterparts, while two derivatives, the norpentyl ester **39** and butyl ketone **19**, show greater than 16- and 8-fold enhancements, respectively. The only exceptions to this general trend are the nortriol **34**, which binds only 61% as well as its homologue (**41**), norhexestrol (**37**) itself, which binds only 46% as well as hexestrol (**2**), and fluoronorhexestrol **36**, which binds with identical affinity as fluorohexestrol (**42**).

Discussion

The binding affinities of the side-chain substituted hexestrol and norhexestrol derivatives (Table I) can be rationalized by a receptor-binding model sensitive to three factors: (1) the steric size of the substituent, (2) the lipophilicity of the substituent, and (3) the ability of certain polar substituents, suitably positioned (on carbon-2 of the hexane chain), to engage in a productive, binding-enhancing interaction. Hexestrol is clearly the ideal case, with a binding affinity of 300. It is predicted by our model that substituents that are larger than the ethyl side chain will lower receptor-binding affinity and that substituents that are smaller or are polar, and hence less lipophilic, will also decrease binding, unless a polar substituent is diposed in a position where it can engage in a specific productive interaction. (This latter interaction, which may be a hydrogen bond, appears to be similar to that responsible for chiral recognition by the receptor of the enantiomerically pure norhexestrol esters **36** and **37** and norhexestrol alcohol **31**.[7])

The interplay between steric factors, lipophilicity, and the productive polar interaction is perhaps best illustrated in the halogenated hexestrols and norhexestrols. The effect of lipophilicity, but the dominance of steric effects (where increased size coincides with decreased binding affinity), are easily seen in the 1-halohexestrols. Fluorohexestrol (**42**) suffers from decreased lipophilicity; so, although it is approximately isosteric with hexestrol (RAC = 300), it binds somewhat less well to the receptor (RAC = 129). In contrast, the bromo- and iodohexestrols, while much better in terms of lipophilicity, are too large sterically and have yet lower affinities than fluorohexestrol (RAC = 71, 60).

The relative effect of the binding factors is different in the nor series: With the shorter side chain, steric effects are not dominant, lipophilicity becomes important, and the productive polar interaction is encountered. Thus, the bromo- and iodonorhexestrols (**32** and **33**), which are roughly isosteric with hexestrol and are quite lipophilic, have very high receptor binding. It appears that fluoronorhexestrol (**36**) should be too small and insufficiently lipophilic; yet the receptor binding of this compound is surprisingly high. In fact, it binds just as well as norhexestrol (**37**, RAC = 137) [Note: Fluorohexestrol (**42**) bound less than half as well as hexestrol (**2**)]. The reason for the enhanced binding of fluoronorhexestrol is most likely due to the productive interaction of the fluorine with a hydrogen bond donor on the receptor, which enhances binding. This interaction is probably similar to that responsible, again, for the chiral recognition of the norhexestrol carbonyl compounds.[7] As we noted before, this interaction should not operate in fluorohexestrol (**42**), since the topographical presentation of the fluorine is one methylene unit removed, compared to its position in fluoronorhexestrol.

A similar analysis can explain the increased binding of norhexestrol diazo ketone **17**, esters **38** and **39**, and ketones **19** and **21** vis-à-vis their hexestrol homologues. Although the compounds in the nor series have a shorter and thus less lipophilic side chain, the enhanced binding of these derivatives is probably the result of their ability to engage in the same binding-enhancing hydrogen-bonding interaction with their carbonyl group. Again, the hexestrols do not gain the benefit of this productive interaction, since the carbonyl group is one methylene unit removed from this interaction.[7]

Within the norhexestrol series, in general, lipophilic effects seem to predominate over steric effects. For example, pentyl ester **39** binds 86% as well as methyl ester **38**, in spite of the large increase in the size of the substituent. A more dramatic example is the butyl ketone **19**; in this case, increasing lipophilicity by lengthening the side chain results in a 1.5-fold increase in binding over the methyl ketone **21**.

The hexestrols, with the longer side chain, appear to be more susceptible to steric effects. Thus, the pentyl ester **40** binds only 20% as well as hexestrol methyl ester **9**, this being twice as great a decrease as is observed in the norhexestrol esters **38** and **39**. Also, the butyl ketone **20** has an affinity less than half that of methyl ketone **30**, in marked contrast to the norhexestrol ketones, where a 1.5-fold binding *increase* is seen in going from the methyl to the butyl ketone (**20** vs. **30**).

Even the amides **5–8**, which all have extremely poor affinities for the estrogen receptor, conform to the model we have proposed. It is not unexpected that these com-

(15) Further studies on these two compounds are presented in Landvatter, S. W.; Katzenellenbogen, J. A.; McElvany, K. D.; Welch, M. J. *J. Med. Chem.*, following paper in this issue.

pounds have such low affinity, since the amide functionality is highly polarized and, therefore, very hydrophilic. Nonetheless, the beneficial effect of increasing lipophilicity is evident in going from the primary amides (**5** and **6**) to the pentyl amides (**7** and **8**), where, in spite of their large size, binding is enhanced nearly twofold. Also, the norhexestrol amides, which can engage in the productive hydrogen bonding, have higher affinities than their hexestrol counterparts.

In conclusion, it is apparent that the binding of hexestrols and norhexestrols to the estrogen receptor involves a complex interplay of substituent size, lipophilicity, and productive hydrogen bonding, but that a satisfactory analysis of structure–binding affinity relationships can be made in terms of the proposed model. The effects of these factors on binding have been especially exploited in the 1-halonorhexestrols, where 1-bromonorhexestrol (**32**) and 1-iodonorhexestrol (**33**) are among the highest binding halogenated estrogens yet synthesized.[15] In fact, since the norhexestrols as a whole generally show higher receptor binding affinities than their hexestrol homologues, this series of compounds seems ideally suited as probes for studying the estrogen receptor.

Experimental Section

Boron tribromide (99.9%) was purchased from Apache Chemical Inc. Diazomethane was prepared from *N*-nitroso-*N*-methylurea[16] and was distilled and dried over KOH pellets prior to use. Trifluoromethanesulfonic anhydride was prepared by distillation of trifluoromethanesulfonic acid from phosphorus pentoxide,[17] and tetrabutylammonium fluoride was prepared and dried as described by Corey.[18] Other reagents and solvents were of analytical reagent grade or better.

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were measured on a Beckman IR-12 spectrophotometer (KBr pellet). Proton magnetic resonance spectra (^{1}H NMR) were obtained at 90 MHz on a Varian EM-390 spectrometer; chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard (δ scale). Fluorine magnetic resonance (^{19}F NMR) were obtained at 84.6 MHz on a Varian EM-390 spectrometer or at 338.8 MHz on a Nicolet NT-360 spectrometer; chemical shifts are reported in parts per million downfield from fluorotrichloromethane as an internal standard. Mass spectral data were obtained on a Varian Model CH-5 mass spectrometer (electron impact at 70 or 10 eV) or a Varian 311A mass spectrometer (field desorption). High-resolution mass spectra were obtained on a Varian 731 high-resolution mass spectrometer. Microanalytical data were provided by the Microanalytical Service Laboratory of the University of Illinois.

Silica gel *medium-pressure* liquid chromatography (MPLC) was performed with a system previously described.[19] Only selected spectroscopic data on the isolated products are reported. All ^{1}H NMR spectra showed resonance characteristics for the hexestrol skeleton: δ ~0.50 (t, 3 H, J = 7 Hz, CH_2CH_3), ~1.20 (m, 2 H, CH_2CH_3), ~2.40 (m, 1 H or 2 H, benzylic CH), ~6.6–7.2 (8 H, J = 9 Hz, aromatic AA'BB' pattern). All mass spectra showed prominent fragmentations from cleavage of the doubly benzylic bond. In each case, the assigned structures are consistent with the complete spectroscopic data. All new compounds were chromatographically pure (TLC and/or HPLC).

(2*R,3*S**)-2,3-Bis(4-hydroxyphenyl)pentanamide (5).** Methyl (2*R**,3*S**)-2,3-bis(4-methoxyphenyl)pentanoate (**3**; 80 mg, 0.24 mmol) was dissolved in 5 mL of CH_2Cl_2 and cooled to −78 °C. A 1 M BBr_3 solution in CH_2Cl_2 (1.46 mL, 1.46 mmol) was added dropwise. Stirring was continued for 1 h at −78 °C, followed by storage at +4 °C for 4 h. The reaction mixture was recooled to −78 °C and quenched with 5 mL of liquid NH_3. After warming to room temperature, the resulting residue was partitioned between H_2O and EtOAc. The layers were separated, and the organic layer was dried ($MgSO_4$). Removal of solvent in vacuo gave a quantitative yield (70 mg) of the norhexestrol amide **5**. An analytical sample was prepared by recrystallization from absolute EtOH and gave **5** as a flocculent white precipitate: mp 248–250 °C; IR 3440 (OH + NH), 1660 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.51 (d, 1 H, CHCO), 6.22 (s, 1 H, NH), 6.43 (s, 1 H, NH); mass spectrum (70 eV), m/z (relative intensity) 285 (2, M$^+$), 135 (100). Anal. ($C_{17}H_{19}NO_3$) C, H, N.

(3*R,4*S**)-3,4-Bis(4-hydroxyphenyl)hexanamide (6).** This compound was prepared in 47% yield from methyl (3*R**,4*S**)-3,4-bis(4-methoxyphenyl)hexenoate (**4**)[7] in the same manner as noramide **5**: mp 244 °C; IR 3430 (OH + NH), 1655 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 6.38 (s, 2 H, NH_2); mass spectrum (70 eV), m/z (relative intensity) 299 (2, M$^+$), 135 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{18}H_{21}NO_3$: 299.1521. Found: 299.1520.

(2*R,3*S**)-*N*-Pentyl-2,3-bis(4-hydroxyphenyl)pentanamide (7).** Methyl (2*R**,3*S**)-2,3-bis(4-methoxyphenyl)pentanoate[7] (**3**; 82 mg, 0.24 mmol) was dissolved in 5 mL of CH_2Cl_2 and cooled to −78 °C. A 1 M solution of BBr_3 in CH_2Cl_2 (1.46 mL, 1.46 mmol) was added dropwise. Stirring was continued for 1 h at −78 °C, followed by storage at +4 °C for 4 h. The reaction was cooled to 0 °C and quenched with 5 mL of pentylamine. The reaction mixture was taken to dryness in vacuo, and the residue was partitioned between H_2O and EtOAc. The organic layer was separated and dried ($MgSO_4$). Removal of solvent gave an oil, which crystallized upon tituration with Et_2O to give 57 mg (63%) of white crystalline **7**: mp 241–242 °C; IR 3380 (OH + NH), 1650 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.29 (d, 1 H, CHCO), 7.49 (t, 1 H, NH); mass spectrum (70 eV), m/z (relative intensity) 355 (2, M$^+$), 221 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{22}H_{29}NO_3$: 355.2147. Found: 355.2140.

(3*R,4*S**)-*N*-Pentyl-3,4-bis(4-hydroxyphenyl)hexanamide (8).** Hexanamide **8** was prepared in 61% yield from methyl (3*R**,4*S**)-3,4-bis(4-methoxyphenyl)hexanoate (**4**)[9] in similar fashion as pentanamide **7**: mp 236 °C; IR 2210 (OH + NH), 1640 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.06 (d, 2 H, $COCH_2$), 7.22 (t, 1 H, NH); mass spectrum (70 eV), m/z (relative intensity) 369 (2, M$^+$), 235 (72), 135 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{23}H_{31}NO_3$: 369.2304. Found: 369.2301.

(2*R,3*S**)-2,3-Bis(4-hydroxyphenyl)pentanoic Acid (11).** (2*R**,3*S**)-2,3-Bis(4-methoxyphenyl)pentanoic acid (**10**; 250 mg, 0.80 mmol)[7] was dissolved in 10 mL of $CHCl_3$ and cooled to −40 °C in a CH_3CN–dry ice bath. A 1 M BBr_3 solution in CH_2Cl_2 (4 mL, 4 mmol) was added dropwise over 1 h. After stirring for an additional 30 min at −40 °C, the reaction was stored at +4 °C for 4 h. The reaction was cooled to 0 °C and quenched with H_2O. The mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous layer was separated and acidified with concentrated HCl. The resulting precipitate was collected and partitioned between H_2O and EtOAc. The EtOAc layer was dried ($MgSO_4$). Removal of solvent gave 221 mg (97%) of white crystalline **11**: mp 246–248 °C; IR 3450 (OH), 1700 (C=O) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.70 (d, 1 H, CHCO); mass spectrum (70 eV), m/z (relative intensity) 286 (1, M$^+$), 135 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{17}H_{18}O_4$: 286.1205. Found: 286.1206.

3,4-Bis(4-hydroxyphenyl)hexanoic Acid (12). Methyl (3*R**,4*S**)-3,4-bis(4-hydroxyphenyl)hexanoate (**9**; 750 mg, 2.39 mmol)[9] was dissolved in 15 mL of THF, and 1.5 mL of a 5 N NaOH solution was added. The resulting mixture was heated to reflux for 2 h. To the cold reaction mixture was added 7.5 mL of a 1 N NaOH solution, and the aqueous layer was washed with ether. The aqueous layer was acidified with 6 N HCl, and the precipitate was collected and dried, giving 694 mg (97%) of hexanoic acid **12**, which was used directly in the next step without further purification: mp 249 °C; IR 3460 (OH), 1690 (C=O) cm^{-1}; ^{1}H NMR (acetone-d_6) δ 2.38 (d, 2 H, $CHCOOH$), 8.74 (s, 2 H, Ar OH); mass spectrum (70 eV), m/z (relative intensity) 300 (1, M$^+$), 135 (100).

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(2*R,3*S**)-2,3-Bis(4-acetoxyphenyl)pentanoic Acid (13).** (2*R**,3*S**)-2,3-Bis(4-hydroxyphenyl)pentanoic acid (**11**; 100 mg, 0.35 mmol) was added to 1 mL of acetic anhydride. Concentrated H_2SO_4 (2 drops) was added, at which point the reaction mixture became homogeneous. After stirring for 20 min at room temperature, the reaction was quenched by pouring into 4 mL of H_2O. After stirring for 5 min to destroy excess Ac_2O, the reaction was cooled to 0 °C. The precipitate that formed was collected and dried, giving 127 mg (98%) of white crystalline **13**. An analytical sample was prepared by recrystallization from EtOAc: mp 218 °C; IR 3500 (OH), 1765 (C=O), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.34 (s, 6 H, $COCH_3$), 3.74 (d, 1 H, C*H*COOH); mass spectrum (70 eV), *m/z* (relative intensity) 370 (1, M^+), 135 (100). Anal. ($C_{21}H_{22}O_6$) C, H.

(3*R,4*S**)-3,4-Bis(acetoxyphenyl)hexanoic Acid (14).** This compound was prepared from bisphenolic acid **12** in 94% yield in similar fashion as acetoxy-protected acid **13**: ^1H NMR ($CDCl_3$) δ 2.37 (s, 6 H, $COCH_3$). Anal. ($C_{22}H_{24}O_6$) C, H.

(3*R,4*S**)-3,4-Bis(4-acetoxyphenyl)-1-diazo-2-hexanone (15).** (2*R**,3*S**)-2,3-Bis(4-acetoxyphenyl)pentanoic acid (**13**; 60 mg, 0.16 mmol) was dissolved in 5 mL of EtOH-free $CHCl_3$ (prepared by filtration through neutral alumina and drying over 4Å molecular sieves). Thionyl chloride (125 μL) was added, the mixture was heated to 50 °C, and 2 drops of pyridine was added. After the mixture was stirred for 18 h, the solvent was removed in vacuo, 1 mL of EtOH-free $CHCl_3$ was added, and the solvent was again taken to dryness. This procedure was repeated twice.

The crude acid chloride thus obtained was dissolved in 1 mL of EtOH-free $CHCl_3$ and 3 mL of dry CH_2N_2 in ether added at 0 °C in the dark. This was slowly allowed to warm to room temperature. After standing at room temperature for 24 h, purification by preparative TLC ($CHCl_3/Et_2O$, 5:2) gave 34 mg (52%) of **15** as pale yellow crystals: mp 124 °C dec; IR 2120 (N≡N), 1770 (C=O), 1645 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, 6 H, $COCH_3$), 3.62 (d, 1 H, CHCO), 4.90 (s, 1 H, CHN_2); mass spectrum (10 eV), *m/z* (relative intensity) 366 (2, M − N_2), 135 (100); mass spectrum (FD), *m/z* 394 (M^+). Anal. (high-resolution mass spectrum on M − N_2 ion) Calcd for $C_{22}H_{22}O_5$: 366.1467. Found: 366.1461.

(4*R,5*S**)-4,5-Bis(acetoxyphenyl)-1-diazo-2-heptanone (16).** This compound was prepared in 63% yield from acid **14** in similar fashion as diazo ketone **15**: mp 123–124 °C; IR 2117 (N≡N), 1768 (C=O), 1636 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 6 H, $COCH_3$), 4.90 (s, 1 H, CHN_2); mass spectrum (10 eV), *m/z* (relative intensity) 380 (5, M − N_2), 177 (100), 135 (87). Anal. (high-resolution mass spectrum on M − N_2 ion) Calcd for $C_{23}H_{24}O_5$: 380.1620. Found: 380.1617.

(3*R,4*S**)-3,4-Bis(4-hydroxyphenyl)-1-diazo-2-hexanone (17).** Diazo ketone **15** (16 mg, 0.04 mmol) was dissolved in 2 mL of CH_3OH, and 1 mL of saturated aqueous K_2CO_3 was added. The resulting mixture was stored for 18 h at room temperature in the dark. Removing the solvent, extracting (EtOAc), drying ($MgSO_4$), and removing the solvent in vacuo gave 11 mg (89%) of **17** as a yellow oil, which crystallized on standing. The product may be recrystallized from EtOAc–hexane: mp 143 °C dec; IR 3430 (OH), 2110 (N≡N) cm^{-1}; ^1H NMR (acetone-d_6) δ 3.82 (d, 1 H, CHCO), 5.54 (s, 1 H, CHN_2); mass spectrum (70 eV), *m/z* (relative intensity) 282 (10, M − N_2), 135 (100); mass spectrum (FD), *m/z* 310 (M^+). Anal. (high-resolution mass spectrum) calcd for $C_{18}H_{18}O_3$: 282.1256. Found: 282.1259.

(4*R,5*S**)-4,5-Bis(4-hydroxyphenyl)-1-diazo-2-heptanone (18).** This compound was obtained in 64% yield via deprotection of acetoxy acid **16** in a similar fashion as diazo ketone **17**: mp 143–144 °C; IR 3465 (OH), 2130 (N≡N), 1635 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ 5.39 (s, 1 H, C*H*N_2); mass spectrum (15 eV), *m/z* (relative intensity) 296 (39, M^+ − N_2), 135 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{19}H_{20}O_3$: 296.1410. Found: 296.1408.

(3*R,4*S**)-3,4-Bis(4-hydroxyphenyl)-5-nonanone (19).** Acetoxy acid **13** (154 mg, 0.42 mmol) was converted to its acid chloride as described in the preparation of diazo ketone **12**. A THF solution of this acid chloride was added via a precooled syringe to 232 mg (1.26 mmol) of *n*-Bu_2CuLi[9] at −78 °C and stirred for 20 min. Methanol (5 mL) was added, and the mixture was allowed to slowly warm to room temperature. The solvent was removed in vacuo, the residue was taken up in EtOAc and washed with saturated NH_4Cl, and the organic layer was dried ($MgSO_4$). Removal of solvent gave a pale yellow solid, which was purified by MPLC (10% EtOAc–CH_2Cl_2) and recrystallized from EtOAc–cyclohexane to give 72 mg (53%) of ketone **19** as white needles: mp 158–160 °C; IR 3270 (OH), 1695 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ 0.80–1.53 (m, 8 H, CH_2), 4.00 (d, 1 H, C*H*CO); mass spectrum (70 eV), *m/z* (relative intensity) 326 (3, M^+), 135 (100), 107 (75). Anal. (high-resolution mass spectrum) Calcd for $C_{21}H_{26}O_3$: 326.1890. Found: 326.1885.

(7*R,8*S**)-7,8-Bis(4-hydroxyphenyl)-5-decanone (20).** Decanone **20** was prepared in 34% yield (60 mg) from (3*R**,4*S**)-bis(4-acetoxyphenyl)hexanoic acid (**14**) in a similar fashion as nonanone **19**: mp 152–153 °C; IR 3400 (OH), 1700 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ 0.94–1.59 (m, 8 H, CH_2); mass spectrum (70 eV), *m/z* (relative intensity) 340 (1, M^+), 135 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{22}H_{28}O_3$: 340.2024. Found: 340.2031.

(3*R,4*S**)-3,4-Bis(4-hydroxyphenyl)-2-hexanone (21). Method A.** Acetoxypentanoic acid **13** was converted to its acid chloride as previously described in the preparation of diazo ketone **12**. The acid chloride thus obtained (100 mg, 0.26 mmol) in THF was added via precooled syringe to 78 mg of Me_2CuLi[9] (0.78 mmol) at −78 °C. After the mixture was stirred 20 min, 0.5 mL of anhydrous MeOH was added, and the solution was allowed to come to room temperature slowly. The solvent was removed, and the was residue taken up in EtOAc. The organic layer was washed (saturated NH_4Cl) and dried ($MgSO_4$). Solvent removal gave 48 mg (65%) of white crystalline ketone **21**, which may be recrystallized from THF–hexane: mp 216 °C; IR 3350 (OH), 1785 (C=O) cm^{-1}; ^1H NMR (acetone-d_6) δ 1.68 (s, 3 H, $COCH_3$), 3.83 (d, 1 H, C*H*CO); mass spectrum (70 eV), *m/z* (relative intensity) 284 (1, M^+), 135 (99), 107 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{18}H_{20}O_3$: 284.1412. Found: 284.1411.

Method B. (3*R**,4*S**)-3,4-Bis(4-methoxyphenyl)-2-hexanone (**23a**; 691 mg, 2.21 mmol) was dissolved in 25 mL of CH_2Cl_2 and cooled to −78 °C. A 1 M solution of BBr_3 in CH_2Cl_2 (13.3 mL, 13.3 mmol) was added dropwise. After stirring for 1 h at −78 °C and storage at +4 °C for 4 h, the reaction was quenched at −78 °C with anhydrous MeOH. Solvent removal and filtration though neutral alumina gave crude ketone **21**. Recrystallization from THF–hexane afforded 377 mg of pure ketone **21** (60%).

3,4-Bis(4-methoxyphenyl)-2-hexanone (23). Hexanone **23**, prepared according to the method of Burckhalter,[11] gave a 1:1 mixture of erythro (3*R**,4*S**) and threo (3*R**,4*R**) diastereomers, which are separable by fractional crystallization from EtOH or chromatography (MPLC, CH_2Cl_2). (3*R**,4*S**)-Hexanone **23a**: mp 143 °C; IR 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (s, 3 H, $COCH_3$), 3.14 (dt, 1 H, J = 4 and 11 Hz, C*H*CH_2), 3.78 (s, 3 H, Ar OCH_3), 3.90 (s, 1 H, CHCO); mass spectrum (70 eV), *m/z* (relative intensity) 312 (1, M^+), 149 (100). Anal. ($C_{20}H_{24}O_3$) C, H.

(3*R**,4*R**)-Hexanone **23b**: mp 103 °C; IR 1715 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3 H, $COCH_3$); mass spectrum (70 eV), *m/z* (relative intensity) 312 (1, M^+), 149 (100). Anal. ($C_{20}H_{24}O_3$) C, H.

2,3-Bis(4-methoxyphenyl)-1-pentene (25). In a flame-dried, three-neck, round-bottom flask equipped with an addition funnel and water cooled condensor were placed 10 mL of ether and 2.96 mL of *n*-BuLi (2.4 M in hexane, 7.04 mmol). Methyltriphenylphosphonium bromide (2.52 g, 7.04 mmol) was added slowly, and the resultant yellow solution was stirred for 4 h at room temperature. A solution of α-ethyldeoxyanisoin (**24**; 1 g, 3.52 mmol) in 10 mL of ether was added dropwise, and the solution was refluxed for 24 h. The solid was filtered and washed with ether. The combined organic phases were washed (H_2O), dried ($MgSO_4$), and concentrated in vacuo to give a pale yellow oil, which was purified by chromatography (MPLC, pentane to 1:1 pentane–CH_2Cl_2). Pentene **25** was isolated as a clear, colorless oil (0.94 g, 95%): ^1H NMR (CCl_4) δ 1.78 (octet, 2 H, CH_2CH_3), 3.47 (t, 1 H, C*H*CH_2), 3.70 (s, 6 H, Ar OCH_3), 5.00 (s, 1 H, C=CH), 5.17 (s, 1 H, C=CH); mass spectrum (10 eV), *m/z* (relative intensity) 282 (100, M^+). Anal. (high-resolution mass spectrum) Calcd for $C_{19}H_{22}O_2$: 282.1620. Found: 282.1623.

(2*R,3*S**)-2,3-Bis(4-methoxyphenyl)-1-pentanol (26). Method A.** Methyl (2*R**,3*S**)-2,3-bis(4-methoxyphenyl)pentanoate (**3**; 305 mg, 0.93 mmol) was dissolved in 10 mL of THF. A

0.63 M solution of lithium aluminum hydride in THF (2 mL, 1.26 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 10 min and quenched by successive addition of H_2O (48 μL), 15% NaOH (48 μL), and H_2O (144 μL). The solution was filtered, and solvent was removed in vacuo to give a quantitative yield of pentanol **26** (279 mg), which can be recrystallized from THF–hexane: mp 121–123 °C; IR 3430 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.46 (d, 2 H, CH_2OH), 3.83 (s, 6 H, Ar OCH_3); mass spectrum (70 eV), *m/z* (relative intensity) 300 (4, M^+), 149 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{19}H_{24}O_3$: 300.1725. Found: 300.1722.

Method B. Pentene **25** (150 mg, 0.53 mmol) was dissolved in 5 mL of dry THF. A 1 M solution of B_2H_6 in THF (0.53 mL, 0.53 mmol) was added, and the solution was stirred for 2.5 h at room temperature. The reaction was warmed to 50 °C, and 2 mL of H_2O, 0.15 mL of 3 N NaOH, and 0.15 mL of 30% H_2O_2 were added. The organic layer was separated, washed (saturated NaCl), and dried ($MgSO_4$). Chromatography (MPLC, 5% EtOAc to 10% EtOAc–CH_2Cl_2) afforded 103 mg (65%) of pentanol **26**.

(2*R,3*S**)-2,3-Bis(4-methoxyphenyl)-1-pentyl Methanesulfonate (27).** Pentanol **26** (106 mg, 0.35 mmol) and triethylamine (0.297 mL, 212 mg, 2.12 mmol) were dissolved in 5 mL of CH_2Cl_2. To this was added 55 μL of methanesulfonyl chloride (81 mg, 0.71 mmol), and the mixture was stirred for 5 min at 0 °C. The solution was concentated under reduced pressure, the oily residue was taken up in CH_2Cl_2 and filtered through neutral alumina, and the solvent was removed to give a clear oil, which crystallized on standing. Trituration with ether gave 128 mg (96%) of white crystalline methanesulfonate **27**: mp 109 °C; IR 1355 (sulfonate) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (s, 3 H, SO_2CH_3), 3.82 (s, 6 H, Ar OCH_3), 4.06 (d, 2 H, CH_2OS); mass spectrum (70 eV), *m/z* (relative intensity) 278 (3, M^+), 149 (100). Anal. ($C_{20}H_{26}O_5$) C, H.

(3*R,4*S**)-3,4-Bis(4-methoxyphenyl)hexanenitrile (28).** Methanesulfonate **27** (100 mg, 0.26 mmol) and NaCN (25 mg, 5.2 mmol) were dissolved in 4 mL of anhydrous dimethyl sulfoxide and heated to 90 °C for 18 h. The mixture was cooled to room temperature and partitioned between CH_2Cl_2 and H_2O. The organic layer was separated, dried ($MgSO_4$), and taken to dryness in vacuo. The crude product thus obtained was recrystallized from EtOH to give 60 mg (75%) of nitrile **28** as white needles: mp 131–132 °C; IR 2250 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.19–2.30 (m, 2 H, CH_2CN), 3.87 (s, 6 H, Ar OCH_3); mass spectrum (70 eV), *m/z* (relative intensity) 309 (3, M^+), 149 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{20}H_{23}NO_2$: 309.1723. Found: 309.1726.

(4*R,5*S**)-4,5-Bis(4-methoxyphenyl)-2-heptanone (29).** Heptanone **29** was obtained in a similar fashion as hexanone **23** from nitrile **28**. Recrystallization from EtOH gave a 79% yield of (4*R**,5*S**)-heptanone **29**: mp 129.5 °C; IR 1714 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.73 (s, 3 H, $COCH_3$), 3.82 (s, 6 H, Ar OCH_3); mass spectrum (70 eV), *m/z* (relative intensity) 326 (3, M^+), 149 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{21}H_{26}O_3$: 326.1868. Found: 326.1875.

(4*R,5*S**)-4,5-Bis(4-hydroxyphenyl)-2-heptanone (30).** Heptanone **30** was obtained in 76% yield from (4*R**,5*S**)-4,5-bis(4-methoxyphenyl)-2-heptanone (**29**) via BBr_3 methyl ether cleavage in a similar fashion as hexanone **21** (method B). An analytical sample was obtained via recrystallization from EtOH: mp 201 °C; IR 3500 (OH) cm^{-1}; ^1H NMR (acetone-d_6) δ 1.76 (s, 3 H, $COCH_3$); mass spectrum (70 eV), *m/z* (relative intensity) 298 (2, M^+), 135 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{19}H_{22}O_3$: 298.1569. Found: 298.1570.

(2*R,3*R**)-2,3-Bis(4-methoxyphenyl)-1-bromopentane (31). Method A.** (2*R**,3*S**)-2,3-Bis(4-methoxyphenyl)-1-pentanol (**26**; 106 mg, 0.35 mmol) and 145 mg of CBr_4 (0.44 mmol) were dissolved in 2 mL of CH_2Cl_2 and cooled to 0 °C. Triphenylphosphine (119 mg, 0.44 mmol) in 1 mL of CH_2Cl_2 was added dropwise. After the solution was stirred for 24 h, purification by preparative TLC (2:1 Et_2O/hexane) gave 38 mg (30%) of white crystalline bromide **31**. An analytical sample was prepared by recrystallization from THF–cyclohexane: mp 152–154 °C, ^1H NMR ($CDCl_3$) δ 2.90–3.41 (m, 3 H, $CHCH_2Br$), 3.82 (s, 6 H, Ar OCH_3); mass spectrum (70 eV), *m/z* (relative intensity) 282 (1, M^+ – HBr) 149 (100). Anal. ($C_{19}H_{23}BrO_2$) C, H.

Method B. Pentanol **26** (62 mg, 0.21 mmol) was dissolved in 5 mL of ether and cooled to 0 °C. Phosphorous tribromide (25 mg, 15 μL, 0.09 mmol) was added dropwise. After stirring for 10 min at 0 °C, the reaction was warmed to room temperature and quenched by the addition of crushed ice. The layers were separated, and the organic layer was dried ($MgSO_4$). The crude product was purified by treatment with Norit and filtration through neutral alumina. Solvent removal gave 28 mg (38%) of bromide **31**.

Method C. (2*R**,3*S**)-2,3-Bis(4-methoxyphenyl)-1-pentanyl methanesulfonate (**27**; 67 mg, 0.18 mmol) and LiBr (156 mg, 1.80 mmol) were dissolved in 10 mL of acetone and heated at reflux 3 h. The solvent was removed in vacuo, the residue was partitioned between EtOAc and H_2O, the layers were separated, and the organic layer was dried ($MgSO_4$). Removal of solvent gave a quantitative yield of crude bromide **31**. Recrystallization from THF–cyclohexane gave 55 mg (86%) of white crystalline **31**.

(2*R,3*S**)-2,3-Bis(4-hydroxyphenyl)-1-bromopentane (32).** Bisphenolic bromopentane **31** was obtained in 90% yield from methyl ether bromide **31** via BBr_3 methyl ether cleavage according to the usual procedure. The product was recrystallized from EtOAc–hexane: mp 168 °C; IR 3430 (OH) cm^{-1}; ^1H NMR (acetone-d_6) δ 3.28–3.47 (m, 3 H, $CHCH_2Br$); mass spectrum (10 eV), *m/z* (relative intensity) 336, 334 (2, both M^+), 135 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{17}H_{19}BrO_2$: 334.0569. Found: 344.0568.

(2*R,3*S**)-2,3-Bis(4-hydroxyphenyl)-1-iodopentane (33).** Bisphenolic bromide **32** (47 mg, 0.14 mmol) was dissolved in 5 mL of saturated NaI solution in acetone and refluxed for 6 h in the dark. The solution was taken to dryness, and the residue was partitioned between EtOAc and H_2O. The organic layer was separated, washed (saturated $NaHSO_3$, saturated NaCl, H_2O), and dried ($MgSO_4$). Solvent removal gene 53 mg (98%) of white crystalline iodide **33**. An analytical sample was obtained by filtration through SiO_2 and recrystallization from EtOAc–hexane: mp 159 °C dec; IR 3400 (OH) cm^{-1}; ^1H NMR (acetone-d_6) δ 2.93–3.30 (m, 3 H, $CHCH_2I$); mass spectrum (70 eV), *m/z* (relative intensity) 382 (0.4, M^+), 135 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{17}H_{19}IO_2$: 382.0428. Found: 382.0403.

(2*R,3*S**)-2,3-Bis[4-[(trifluoromethanesulfonyl)oxy]phenyl]-1-pentyl Trifluoromethanesulfonate (35).** (2*R**,3*S**)-2,3-Bis(4-hydroxyphenyl)-1-pentanol (**34**; 136 mg, 0.5 mmol) was dissolved in 0.7 mL of 2,6-lutidine (2,6-dimethylpyridine), diluted with 3 mL of CH_2Cl_2, and cooled in an ice–salt bath. Trifluoromethanesulfonic anhydride (0.3 mL, 1.75 mmol) was added, and the reaction mixture was stirred for 30 min. The reaction was quenched with 2 mL of 1 M trifluoromethanesulfonic acid, and the organic layer was separated, washed (1 M trifluoromethanesulfonic acid, H_2O), and dried ($MgSO_4$). Chromatography (MPLC, 1:1 CH_2Cl_2/pentane) gave 136 mg (41%) of tris(trifluoromethanesulfonate) **35** as a clear, colorless oil, which crystallized on standing: mp 72–73 °C; ^1H NMR (CD_2Cl_2) δ 4.46 (d, 2 H, CH_2OS), 7.53–7.57 (m, 8 H, Ar H); ^{19}F NMR (CD_2Cl_2) –72.33 (s, 6 F, Ar OSO_2CF_3), –74.32 (s, 3 F, $CH_2OSO_2CF_3$); mass spectrum (10 eV), *m/z* (relative intensity) 518 (39, M^+ – TfOH), 366 (100). Anal. ($C_{20}H_{17}FO_9S_3$) H; C: calcd, 35.93; found, 36.37.

(2*R,3*S**)-2,3-Bis(4-hydroxyphenyl)-1-fluoropentane (36).** Tris(trifluoromethanesulfonate) **35** (150 mg, 0.22 mmol) was dissolved in 5 mL of acetone and heated to reflux. To this was added 2.2 mL of a 1 M solution of n-$Bu_4N^+F^-$ (2.2 mmol). After the solution was refluxed for 2 h, the solvent was removed, the residue was partitioned between EtOAc and H_2O, the layers were separated, and the organic layer was dried ($MgSO_4$). Chromatography (MPLC, 10% EtOAc–CH_2Cl_2) gave 32 mg (52%) of white crystalline fluoride **36**. An analytical sample was prepared by recrystallization from $CHCl_3$–CCl_4: mp 177 °C; IR 3430 (OH) cm^{-1}; ^1H NMR (acetone-d_6) δ 4.28 (dd, 2 H, J = 5 and 48 Hz, CH_2F); ^{19}F NMR (acetone-d_6) –233.26 (dt, 1 F, J = 23.7 and 47.8 Hz, $CHCH_2F$); mass spectrum (10 eV), *m/z* (relative intensity) 274 (2, M^+), 135 (100). Anal. (high-resolution mass spectrum) Calcd for $C_{17}H_{19}FO_2$: 274.1364. Found: 274.1367.

(2*R,3*S**)-2,3-Bis(4-hydroxyphenyl)pentane (37).** Tris(trifluoromethanesulfonate) **35** (138 mg, 0.21 mmol) was dissolved in 3 mL of dry THF and cooled to 0 °C. A 0.9 M lithium aluminum hydride solution in THF (2.3 mL, 2.1 mmol) was added dropwise. The mixture was allowed to warm to room temperature

over a 2-h period. The reaction was quenched by cautious addition of EtOAc. Pentane and 5% HCl were added, the layers were separated, and the organic layer was dried ($MgSO_4$). Solvent removal and recrystallization from benzene gave 44 mg (83%) of norhexestrol (37) as white needles: mp 183.5 °C; IR 3460 (OH) cm^{-1}; ^1H NMR (acetone-d_6) δ 0.98 (d, 3 H, $CHCH_3$); mass spectrum (70 eV), m/z (relative intensity) 257 (2, M^+), 135 (100). Anal. ($C_{17}H_{20}O_2$) C, H.

Binding Affinity to the Uterine Estrogen Receptor. The determination of the binding affinity of these derivatives to the estrogen receptor in cytosol preparations from lamb uterus was measured in a competitive binding assay with [^{3}H]estradiol as a tracer and charcoal–dextran as an adsorbant of free ligand. In earlier competitive binding studies, receptor preparations from both rat[6] and lamb[7] uterus have been used with essentially equivalent results. The full details of this method have been described.[6]

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(2*R**,3*S**)-1-[^{125}I]Iodo-2,3-bis(4-hydroxyphenyl)pentane ([^{125}I]Iodonorhexestrol) and (2*R**,3*S**)-1-[^{77}Br]Bromo-2,3-bis(4-hydroxyphenyl)pentane ([^{77}Br]Bromonorhexestrol), Two γ-Emitting Estrogens That Show Receptor-Mediated Uptake by Target Tissues in Vivo

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Two γ-emitting estrogen analogues, (2*R**,3*S**)-1-[^{125}I]iodo-2,3-bis(4-hydroxyphenyl)pentane ([^{125}I]iodonorhexestrol) and (2*R**,3*S**)-1-[^{77}Br]bromo-2,3-bis(4-hydroxyphenyl)pentane ([^{77}Br]bromonorhexestrol), have been prepared by halide ion displacement on a labile trifluoromethanesulfonate derivative of a suitably protected precursor, followed by mild acid deprotection. Although halide displacement on a more stable tristrifluoromethanesulfonate derivative was successful, the basic conditions required for deprotection of this precursor resulted in destruction of the products by a base-induced spiroelimination reaction. In immature female rats, both of these halonorhexestrols demonstrated preferential uptake by the uterus that could be blocked selectively by coadministration of a large dose of unlabeled estradiol. In a double label comparison with 16α-[^{125}I]iodo-17β-estradiol the uterine uptake of [^{77}Br]bromonorhexestrol was notably less selective. Stability studies in vitro and in vivo have indicated that both iodo- and bromonorhexestrol are quite labile, and this lability compromises the selectivity of their uptake by estrogen target tissues in vivo. *p*-Hydroxyphenethyl halides are known to be unusually prone to a base-catalyzed solvolysis, via cyclization of the phenolate to a spirocyclohexadienone intermediate. This unusual solvolytic mechanism may contribute to the lability of these halonorhexestrols in vivo.

The estrogen receptor, a specific, high-affinity binding protein present in estrogen-sensitive tissues, is thought to be the principal mediator of estrogen action. A large portion of human breast tumors are also found to have significant levels of estrogen receptor.[1] The measurement of estrogen receptor levels in these tumors is of vital importance, since tumor receptor content has provided a resonable basis for selecting the most appropriate therapeutic approach for managing the progress of breast cancer.[2,3]

Through selective uptake mediated by the estrogen receptor, estrogens at physiological concentrations are known to be concentrated in target tissues several-fold over nontarget tissues.[4–7] Thus, selective localization of a γ-emitting estrogen in a receptor-positive breast tumor should allow its receptor content to be assayed noninvasively. Similarly, this selective uptake would provide a means of detecting primary and metastatic tumors.

The achievement of a high uptake selectivity with such a radiopharmaceutical reagent is predicated upon an estrogen that has high affinity for estrogen receptor, low binding to other estrogen-specific binding proteins, reasonable metabolic stability, and high specific activity.[8] We have recently synthesized two γ-emitting steroidal estrogens, 16α-[^{77}Br]bromo-17β-estradiol[9] and 16α-[^{77}Br]-bromo-11β-methoxy-17β-estradiol,[10] which satisfy these requirements. We are also exploring the use of non-

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