Nonsteroidal Estrogens: Synthesis and Estrogen Receptor Binding Affinity of Derivatives of $(3R^*, 4S^*)$ -3,4-Bis(4-hydroxyphenyl)hexane (Hexestrol) and $(2R^*, 3S^*)$ -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 $(3R^*,4S^*)$ -3,4-bis(4-hydroxyphenyl)hexane (hexestrol) and $(2R^*,3S^*)$ -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 labels¹ 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 $[(3R^*,4S^*)-3,4$ -bis(4-hydroxyphenyl)hexane (2)].³



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- (3) The R*,S* system of designating relative stereochemistry (IU-PAC 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).

Scheme I



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 $[(2R^*,3S^*)-2,3-bis(4-hydroxyphenyl)pentane]^3$ esters was prepared, indicated that the norhexestrol esters bound to the estrogen receptor significantly better than the ho-

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Scheme II



 a NaOH (97%). b BBr₃ (97%). c Ac₂O (98, 94%). SOCl₂. e CH₂N₂ (52, 63%). f K₂CO₃-MeOH (89, 64%). d SOCl₂.

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 9⁹ 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

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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 Wawzonek¹¹ 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, Posner¹⁰ and Crabbé¹³ 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

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Scheme IV



^{*a*} Ph₃P=CH₂ (95%). ^{*b*} B₂H₆. ^{*c*} H₂O₂ (65%). ^{*d*} LiAlH₄ (100%). ^{*e*} CH₃SO₂Cl (96%). ^{*f*} NaCN (75%). ^{*g*} CH₃MgBr (79%). ^{*h*} BBr₃ (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 -ethyldeoxyanisoin⁹ (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% Scheme V



^a PPh₃-CBr₄ or PBr₃ (30-38%, with **26**). ^b LiBr (86%, with **27**). ^c BBr₃ (90%). ^d NaI-acetone (98%).

Scheme VI





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}



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

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Table I.	Comparative	e Binding	of Hexestrols and
Norhexes	strols for the	Estrogen	Receptor

	ratio of assoc constants $\times 100^{a}$ (compd) ^b		
compd	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, [³H]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 $\pm 30\%$. ^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- \hat{a} -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*methylurea¹⁶ 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 (¹H 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 (¹⁹F 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 ¹H NMR spectra showed resonance characteristics for the hexestrol skeleton: $\delta \sim 0.50$ (t, 3 H, J = 7 Hz, CH₂CH₃), ~ 1.20 (m, 2 H, CH₂CH₃), ~ 2.40 (m, 1 H or 2 H, benzylic CH), $\sim 6.6-7.2$ (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).

 $(2R^*, 3S^*)$ -2,3-Bis(4-hydroxyphenyl)pentanamide (5). Methyl $(2R^*, 3S^*)$ -2,3-bis(4-methoxyphenyl)pentanoate (3; 80 mg, 0.24 mmol) was dissolved in 5 mL of CH₂Cl₂ and cooled to -78 °C. A 1 M BBr₃ solution in CH₂Cl₂ (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 NH₃. After warming to room temperature, the resulting residue was partitioned between H₂O and EtOAc. The layers were separated, and the organic layer was dried (MgSO₄). 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; ¹H NMR (Me₂SO-d₆) 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. (C₁₇H₁₉NO₃) C, H, N.

 $(3R^*,4S^*)$ -3,4-Bis(4-hydroxyphenyl)hexanamide (6). This compound was prepared in 47% yield from methyl (3 $R^*,4S^*$)-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; ¹H NMR (Me₂SO-d₆) δ 6.38 (s, 2 H, NH₂); mass spectrum (70 eV), m/z (relative intensity) 299 (2, M⁺), 135 (100). Anal. (highresolution mass spectrum) Calcd for C₁₈H₂₁NO₃: 299.1521. Found: 299.1520.

 $(2R^*, 3S^*)$ -N-Pentyl-2,3-bis(4-hydroxyphenyl)pentanamide (7). Methyl $(2R^*, 3S^*)$ -2,3-bis(4-methoxyphenyl)pentanoate⁷ (3; 82 mg, 0.24 mmol) was dissolved in 5 mL of CH₂Cl₂ and cooled to -78 °C. A 1 M solution of BBr₃ in CH₂Cl₂ (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 (MgSO₄). 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; ¹H NMR (Me₂SO- 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 C₂₂H₂₉NO₃: 355.2147. Found: 355.2140.

(3 $\tilde{R}^*, 4\tilde{S}^*$)-N-Pentyl-3,4-bis(4-hydroxyphenyl)hexanamide (8). Hexanamide 8 was prepared in 61% yield from methyl (3 $R^*, 4S^*$)-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; ¹H NMR (Me₂SO-d₆) δ 2.06 (d, 2 H, COCH₂), 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 C₂₃H₃₁NO₃: 369.2304. Found: 369.2301.

(2R*.3S*)-2.3-Bis(4-hydroxyphenyl)pentanoic Acid (11). (2R*,3S*)-2,3-Bis(4-methoxyphenyl)pentanoic acid (10; 250 mg, $0.80 \text{ mmol})^7$ was dissolved in 10 mL of CHCl₃ and cooled to -40 °C in a CH_3CN -dry ice bath. A 1 M BBr₃ 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 NaHCO₃ and CH₂Cl₂. The aqueous layer was separated and acidified with concentrated HCl. The resulting precipitate was collected and partitioned between H₂O and EtOAc. The EtOAc layer was dried (MgSO₄). Removal of solvent gave 221 mg (97%) of white crystalline 11: mp 246-248 °C; IR 3450 (OH), 1700 (C=O) cm⁻¹; ¹H 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 C₁₇H₁₈O₄: 286.1205. Found: 286.1206.

3.4-Bis(4-hydroxyphenyl)hexanoic Acid (12). Methyl $(3R^*, 4S^*)$ -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; ¹H 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 (CDCl₃) δ 2.34 (s, 6 H, COCH₃), 3.74 (d, 1 H, CHCOOH); mass spectrum (70 eV), m/z (relative intensity) 370 (1, M⁺), 135 (100). Anal. (C₂₁H₂₂O₆) C, H.

 $(3R^*, 4S^*)$ -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 (CDCl₃) δ 2.37 (s, 6 H, COCH₃). Anal. (C₂₂H₂₄O₆) C, H.

(3R*,4S*)-3,4-Bis(4-acetoxyphenyl)-1-diazo-2-hexanone (15). (2R*,3S*)-2,3-Bis(4-acetoxyphenyl)pentanoic acid (13; 60 mg, 0.16 mmol) was dissolved in 5 mL of EtOH-free CHCl₃ (prepared by filtration through neutral alumina and drying over 4Å molecular sieves). Thionyl chloride (125 μ L) 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 CHCl₃ 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 CHCl₃ and 3 mL of dry CH₂N₂ 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 (CHCl₃/Et₂O, 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 (CDCl₃) δ 2.30 (s, 6 H, COCH₃), 3.62 (d, 1 H, CHCO), 4.90 (s, 1 H, CHN₂); mass spectrum (10 eV), m/z (relative intensity) 366 (2, M – N₂), 135 (100); mass spectrum on M – N₂ ion) Calcd for C₂₂H₂₂O₅: 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 \equiv N), 1768 (C=O), 1636 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 2.40 (s, 6 H, COCH₃), 4.90 (s, 1 H, CHN₂); mass spectrum (10 eV), *m/z* (relative intensity) 380 (5, M - N₂), 177 (100), 135 (87). Anal. (high-resolution mass spectrum on M - N₂ ion) Calcd for C₂₃H₂₄O₅: 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 CH₃OH, and 1 mL of saturated aqueous K₂CO₃ was added. The resulting mixture was stored for 18 h at room temperature in the dark. Removing the solvent, extracting (EtOAc), drying (MgSO₄), 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-d₆) δ 3.82 (d, 1 H, CHCO), 5.54 (s, 1 H, CHN₂); mass spectrum (70 eV), *m/z* (relative intensity) 282 (10, M - N₂), 135 (100); mass spectrum (FD), *m/z* 310 (M⁺). Anal. (high-resolution mass spectrum) calcd for C₁₈H₁₈O₃: 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 \equiv N), 1635 (C \equiv O) cm⁻¹; ¹H NMR (acetone-*d*₈) δ 5.39 (s, 1 H, CHN₂); mass spectrum (15 eV), *m/z* (relative intensity) 296 (39, M⁺ - N₂), 135 (100). Anal. (high-resolution mass spectrum) Calcd for C₁₉H₂₀O₃: 296.1410. Found: 296.1408.

(3R*,4S*)-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*-Bu₂CuLi⁹ 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 NH₄Cl, and the organic layer was dried (MgSO₄). Removal of solvent gave a pale yellow solid, which was purified by MPLC (10% EtOAc-CH₂Cl₂) and recrystallized from Et-OAc-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-d₆) δ 0.80–1.53 (m, 8 H, CH₂), 4.00 (d, 1 H, CHCO); mass spectrum (70 eV), m/z (relative intensity) 326 (3, M⁺), 135 (100), 107 (75). Anal. (high-resolution mass spectrum) Calcd for C₂₁H₂₆O₃: 326.1890. Found: 326.1885.

(7R*,8S*)-7,8-Bis(4-hydroxyphenyl)-5-decanone (20). Decanone 20 was prepared in 34% yield (60 mg) from (3R*,4S*)-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, CH₂); mass spectrum (70 eV), m/z (relative intensity) 340 (1, M⁺), 135 (100). Anal. (high-resolution mass spectrum) Calcd for C₂₂H₂₈O₃: 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 Me₂CuLi⁹ (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 NH₄Cl) and dried (MgSO₄). 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, COCH₃), 3.83 (d, 1 H, CHCO); 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. $(3R^*, 4S^*)^{-3}, 4^{-3}Bis(4 - methoxyphenyl)^{-2}$ -hexanone (23a; 691 mg, 2.21 mmol) was dissolved in 25 mL of CH₂Cl₂ and cooled to -78 °C. A 1 M solution of BBr₃ in CH₂Cl₂ (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 ($3R^*,4S^*$) and threo ($3R^*,4R^*$) diastereomers, which are separable by fractional crystallization from EtOH or chromatography (MPLC, CH₂Cl₂). ($3R^*,4S^*$)-Hexanone 23a: mp 143 °C; IR 1720 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 1.80 (s, 3 H, COCH₃), 3.14 (dt, 1 H, J = 4 and 11 Hz, CHCH₂), 3.78 (s, 3 H, Ar OCH₃), 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.

 $(3R^*,4R^*)$ -Hexanone **23b**: mp 103 °C; IR 1715 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 2.13 (s, 3 H, COCH₃); mass spectrum (70 eV), m/z (relative intensity) 312 (1, M⁺), 149 (100). Anal. (C₂₀H₂₄O₃) 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 (H₂O), dried (MgSO₄), and concentrated in vacuo to give a pale yellow oil, which was purified by chromatography (MPLC, pentane to 1:1 pentane-CH₂Cl₂). Pentene **25** was isolated as a clear, colorless oil (0.94 g, 95%): ¹H NMR (CCl₄) δ 1.78 (octet, 2 H, CH₂CH₃), 3.47 (t, 1 H, CHCH₂), 3.70 (s, 6 H, Ar OCH₃), 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 C₁₉H₂₂O₂: 282.1620. Found: 282.1623.

 $(2\overline{R}^*, 3S^*)$ -2,3-Bis(4-methoxyphenyl)-1-pentanol (26). Method A. Methyl $(2R^*, 3S^*)$ -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 H₂O (48 μ L), 15% NaOH (48 μ L), and H₂O (144 μ L). 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 (CDCl₃) δ 3.46 (d, 2 H, CH₂OH), 3.83 (s, 6 H, Ar OCH₃); mass spectrum (70 eV), m/z (relative intensity) 300 (4, M⁺), 149 (100). Anal. (high-resolution mass spectrum) Calcd for C₁₉H₂₄O₃: 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 (MgSO₄). Chromatography (MPLC, 5% EtOAc to 10% EtOAc-CH₂Cl₂) 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 CH₂Cl₂. To this was added 55 μ L 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 CH₂Cl₂ 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 (CDCl₃) δ 2.49 (s, 3 H, SO₂CH₃), 3.82 (s, 6 H, Ar OCH₃), 4.06 (d, 2 H, CH₂OS); mass spectrum (70 eV), m/z (relative intensity) 278 (3, M⁺), 149 (100). Anal. (C₂₀H₂₆O₅) C, H.

 $(3R^*, 4S^*)$ -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 CH₂Cl₂ and H₂O. The organic layer was separated, dried (MgSO₄), 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 (CDCl₃) δ 2.19-2.30 (m, 2 H, CH₂CN), 3.87 (s, 6 H, Ar OCH₃); mass spectrum (70 eV), m/z (relative intensity) 309 (3, M⁺), 149 (100). Anal. (high-resolution mass spectrum) Calcd for C₂₀H₂₃NO₂: 309.1723. Found: 309.1726.

 $(4R^*,5S^*)$ -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 $(4R^*,5S^*)$ -heptanone 29: mp 129.5 °C; IR 1714 (C=O) cm⁻¹; ¹H NMR (CDCl₃) δ 1.73 (s, 3 H, COCH₃), 3.82 (s, 6 H, Ar OCH₃); mass spectrum (70 eV), m/z (relative intensity) 326 (3, M⁺), 149 (100). Anal. (high-resolution mass spectrum) Calcd for C₂₁H₂₆O₃: 326.1868. Found: 326.1875.

(4R*,5S*)-4,5-Bis(4-hydroxyphenyl)-2-heptanone (30). Heptanone 30 was obtained in 76% yield from (4R*,5S*)-4,5bis(4-methoxyphenyl)-2-heptanone (29) via BBr₃ 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, COCH₃); mass spectrum (70 eV), m/z (relative intensity) 298 (2, M⁺), 135 (100). Anal. (high-resolution mass spectrum) Calcd for C₁₉H₂₂O₃: 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 CBr₄ (0.44 mmol) were dissolved in 2 mL of CH₂Cl₂ and cooled to 0 °C. Triphenylphosphine (119 mg, 0.44 mmol) in 1 mL of CH₂Cl₂ was added dropwise. After the solution was stirred for 24 h, purification by preparative TLC (2:1 Et₂O/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 (CDCl₃) δ 2.90-3.41 (m, 3 H, CHCH₂Br), 3.82 (s, 6 H, Ar OCH₃); mass spectrum (70 eV), *m/z* (relative intensity) 282 (1, M⁺ – HBr) 149 (100). Anal. (C₁₉H₂₃BrO₂) 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 μ L, 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 (MgSO₄). 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. $(2R^*, 3S^*)$ -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 H₂O, the layers were separated, and the organic layer was dried (MgSO₄). Removal of solvent gave a quantitative yield of crude bromide 31. Recrystallization from THF-cyclohexane gave 55 mg (86%) of white crystalline 31.

 $(2R^*, 3S^*)$ -2,3-Bis(4-hydroxyphenyl)-1-bromopentane (32). Bisphenolic bromopentane 31 was obtained in 90% yield from methyl ether bromide 31 via BBr₃ 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-d₆) δ 3.28-3.47 (m, 3 H, CHCH₂Br); mass spectrum (10 eV), m/z (relative intensity) 336, 334 (2, both M⁺), 135 (100). Anal. (high-resolution mass spectrum) Calcd for C₁₇H₁₉BrO₂: 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 H₂O. The organic layer was separated, washed (saturated NaHSO₃, saturated NaCl, H₂O), and dried (MgSO₄). Solvent removal gene 53 mg (98%) of white crystalline iodide 33. An analytical sample was obtained by filtration through SiO₂ and recrystallization from EtOAc-hexane: mp 159 °C dec; IR 3400 (OH) cm⁻¹; ¹H NMR (acetone-d₆) δ 2.93-3.30 (m, 3 H, CHCH₂I); mass spectrum (70 eV), *m/z* (relative intensity) 382 (0.4, M⁺), 135 (100). Anal. (high-resolution mass spectrum) Calcd for C₁₇H₁₉IO₂: 382.0428. Found: 382.0403.

(2R*,3S*)-2,3-Bis[4-[(trifluoromethanesulfonyl)oxy]phenyl]-1-pentyl Trifluoromethanesulfonate (35). (2R*,3S*)-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 CH₂Cl₂, 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, H₂O), and dried (MgSO₄). Chromatography (MPLC, 1:1 CH₂Cl₂/pentane) gave 136 mg (41%) of tris(trifluoromethanesulfonate) 35 as a clear, colorless oil, which crystallized on standing: mp 72–73 °C; ¹H NMR (CD₂Cl₂) δ 4.46 (d, 2 H, CH₂OS), 7.53–7.57 (m, 8 H, Ar H); ¹⁹F NMR (CD_2Cl_2) -72.33 (s, 6 F, Ar OSO₂CF₃), -74.32 (s, 3 F, CH₂OSO₂CF₃); 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*-Bu₄N⁺F⁻ (2.2 mmol). After the solution was refluxed for 2 h, the solvent was removed, the residue was partitioned between EtOAc and H₂O, the layers were separated, and the organic layer was dried (MgSO₄). Chromatography (MPLC, 10% EtOAc-CH₂Cl₂) gave 32 mg (52%) of white crystalline fluoride 36. An analytical sample was prepared by recrystallization from CHCl₃-CCl₄: mp 177 °C; IR 3430 (OH) cm⁻¹; ¹H NMR (acetone-d₆) δ 4.28 (dd, 2 H, J = 5 and 48 Hz, CH₂F); ¹⁹F NMR (acetone-d₆) -233.26 (dt, 1 F, J = 23.7 and 47.8 Hz, CHCH₂F); mass spectrum (10 eV), m/z (relative intensity) 274 (2, M⁺), 135 (100). Anal. (high-resolution mass spectrum) Calcd for C₁₇H₁₉FO₂: 274.1364. Found: 274.1367.

(2R*,3S*)-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 (MgSO₄). 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, CHCH₃); mass spectrum (70 eV), m/z (relative intensity) 257 (2, M⁺), 135 (100). Anal. (C₁₇H₂₀O₂) 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 [³H]estradiol as a tracer and charcoal-dextran as an adsorbant of free ligand. In

earlier competitive binding studies, receptor preparations from both rat⁶ and lamb⁷ uterus have been used with essentially equivalent results. The full details of this method have been described.⁶

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$(2R^*, 3S^*)-1-[^{125}I]$ Iodo-2,3-bis(4-hydroxyphenyl)pentane ([^{125}I]Iodonorhexestrol) and (2R^*, 3S^*)-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, $(2R^*, 3S^*)$ -1- $[^{125}I]$ iodo-2,3-bis(4-hydroxyphenyl)pentane ($[^{125}I]$ iodonorhexestrol) and $(2R^*, 3S^*)$ -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 -[⁷⁷Br]bromo-17 β -estradiol⁹ and 16α -[⁷⁷Br]-

bromo-11 β -methoxy-17 β -estradiol,¹⁰ which satisfy these requirements. We are also exploring the use of non-

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