5,6-Bis(4-hydroxyphenyl)-5-octenyl methanesulfonate (43): yield 167 (97%) of an oil; ^{1}H NMR (400 MHz, acetone-d_6) δ 0.76 (t, 8-CH_3), 0.88 (t, 8-CH_3, styrene), 0.92 (t, 8-CH_3, (*Z*)-stilbene), 1.30 (quint, CH_2), 1.47 (d, CH_3), 1.54 quint, CH_2), 1.63–1.863 (m, CH_2), 1.90 (d, CH_3), 2.18 (q, 7-CH_2), 2.22 (t, 4-CH_2), 2.56 (q, 7-CH_2), (*Z*)-stilbene), 2.60 (t, 4-CH_2, (*Z*)-stilbene), 2.98 (s, SO_3CH_3), 3.01 and 3.04 (each s, SO_3CH_3) 3.33 and 3.46 (each t, benzylic H), 4.03 (t, 1-CH_2), 4.15–4.22 (several t, 1-CH_2), 5.56 (t, vinylic styrene H), 6.54–7.09 (m, Ar-H), 8.1–8.3 (br, OH); MS (160 °C) *m/z* 390, (78, M^+), 294 (46), 279 (16), 265 (87), 253 (57), 239 (75), 237 (61), 223 (54), 181 (31), 171 (48); exact mass calcd for $C_{21}H_{26}O_5S$ 390.1501, found 390.1504.

2-[[[[5,6-Bis(4-hydroxyphenyl)-5-octen-1-yl]oxy]carbonyl]amino]-2-chloroethane (44): yield 50 mg (93%) of an oil; IR ($CHCl_3$) 3450 (NH), 3330 (OH), 1710 cm^{-1} (urethane C=O); ^{1}H NMR (90 MHz, $CDCl_3$, acetone-d_6/D_2O) δ 0.73 (t, 3 H, 8-CH_3), 1.11–1.55 (m, 4 H, CH_2), 2.00–2.24 (m, 4 H, CH_2), 3.33–3.66 (m, 4 H, NCH_2CH_2Cl), 3.87 (t, 2 H, 1-CH_2), 5.25 (t, 1 H, NH), 6.77–7.07 (m, 8 H, Ar-H); MS (200 °C) *m/z* 419 (41 5, M^+), 417 (100, M^+), 332 (25), 330 (74), 265 (44), 253 (59), 239 (66), 237 (74), 224 (26), 223 (20), 161 (60); exact mass calcd for $C_{23}H_{28}NO_4Cl$, 417.1707, found 417.1699.

Registry No. **1**, 50-28-2; **3**, 56-53-1; **4**, 120-44-5; **5**, 6182-78-1; **6**, 67566-88-5; **7**, 120743-85-3; **8**, 120743-41-1; **9a**, 120743-42-2; **9b**, 120743-72-8; *E*-**10**, 120743-43-3; *Z*-**10**, 120743-73-9; *E*-**11**, 120743-44-4; *Z*-**11**, 120743-74-0; *E*-**12**, 120743-45-5; *Z*-**12**, 120743-75-1; *E*-**13**, 120788-27-4; *Z*-**13**, 120743-76-2; *E*-**14**, 120743-46-6; *Z*-**14**, 120743-77-3; *E*-**17**, 120743-47-7; *Z*-**17**, 120743-78-4; *E*-**18**, 120743-48-8; *E*-**19**, 120743-49-9; *Z*-**19**, 120743-79-5; *E*-**20**, 120743-50-2; *Z*-**20**, 120743-80-8; *E*-**21**, 120743-51-3; *Z*-**21**, 120743-81-9; *E*-**22**, 120743-52-4; *Z*-**22**, 120743-82-0; **23**, 120743-53-5; *E*-**24**, 120743-54-6; *E*-**25**, 120743-55-7; *Z*-**25**, 120743-83-1; *E*-**26**, 120771-41-7; *E*-**27**, 120743-56-8; *E*-**28**, 120743-57-9; *E*-**29**, 120743-58-0; *E*-**30**, 120771-42-8; **31**, 120743-59-1; *E*-**32**, 120743-60-4; *E*-**33**, 120743-61-5; **34**, 120743-62-6; *E*-**35**, 120743-63-7; *E*-**36**, 120743-64-8; *Z*-**36**, 120743-84-2; *E*-**37**, 120743-65-9; *E*-**38**, 120743-66-0; *Z*-**38**, 120771-43-9; *E*-**39**, 120743-67-1; *E*-**40**, 120743-68-2; **41**·HCl, 120743-69-3; **43**, 120743-70-6; **44**, 120743-71-7; *p*-ClC_6H_4OH, 106-48-9; *p*-$O_2NC_6H_4OH$, 100-02-7; *tert*-butyl 4-chlorobutyrate, 3153-32-0; ethyl bromide, 74-96-4; octyl bromide, 111-83-1; 4-nitrophenol, 100-02-7; *tert*-butylphenol, 27178-34-3; pentachlorophenol, 87-86-5; diethanolamine, 111-42-2; daunorubicin hydrochloride, 23541-50-6; β-chloroethylammonium chloride, 870-24-6.

Hexestrol-Linked Cytotoxic Agents: Synthesis and Binding Affinity for Estrogen Receptors

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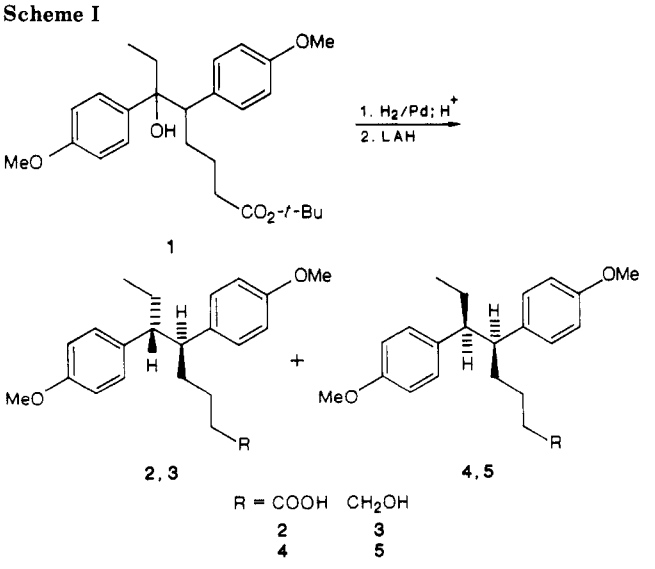
With the *erythro*-hexestrol derivative **2** as the starting material, a variety of cytotoxic linked hexestrol (HEX) compounds were prepared including the HEX-N-lost derivative **36**, the HEX–(chloroethyl)nitrosourea **38**, the HEX-cyclophosphamide **44**, and the HEX–epoxide **68**. Relative binding affinity to estradiol receptors were in the magnitude of 1%, similar to that of comparable diethylstilbestrol compounds. HEX derivatives with long polyether spacers (**64**, **65**, **70**, **71**) showed no significant decrease in binding affinity in contrast to derivatives with other bulky side chains.

In the preceding paper[1] we outlined the general concept of linking cytotoxic groups to synthetic estrogens. The basic idea is to increase the specificity in the treatment of hormone-dependent cancers by reducing the systemic toxicity of the drugs (compare ref 2–4). A series of diethylstilbestrol (DES) derivatives were prepared and the receptor binding affinity was measured.[1] However, the chemical investigation revealed that unsymmetrically substituted DES derivatives equilibrate in solution to a mixture of the corresponding (*E*)- and (*Z*)-stilbenes and also, to some extent, to the two isomeric styrenes. It is known that hexestrol (HEX) has comparable binding affinity as DES,[5,6] and we now present an extensive investigation on the chemical derivatization and binding properties of HEX derivatives. The chemically stable skeleton now allowed the synthesis of isomerically pure compounds and the attachment of highly reactive cytotoxic groups.

HEX derivatives that are substituted in the aromatic ring were obtained from the parent hexestrol.[7–11] Side-chain derivatives can be synthesized in a number of ways such as the condensation of 4-methoxybenzaldehyde with 4-methoxybenzyl cyanide,[4] the addition of silylketene acetals with allylsilanes,[12] or the Reformatzky[13] or the McMurry reaction[14–16] followed by hydrogenation. It is

Scheme I



† Institut für Organische Chemie der Technischen Universität Braunschweig.

‡ Institut J. Bordet.

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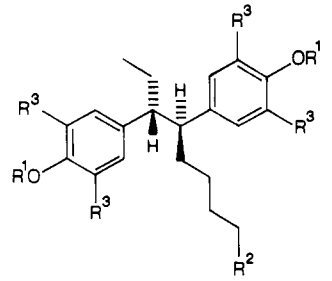
Chart I



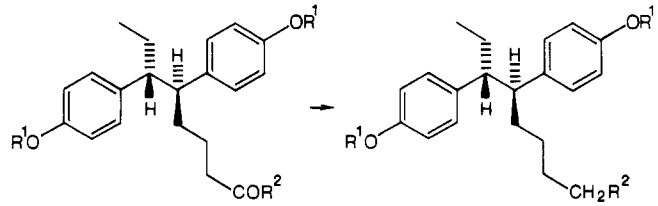
3, 6-17: R^3 = H
18: R^1 = H, R^2 = CH_2OH, R^3 = Br
3/11: R^1 = Me/H, R^2 = OH
6/12: R^1 = Me/H, R^2 = Cl
7/13: R^1 = Me/H, R^2 = Br
8/14: R^1 = Me/H, R^2 = I
9/15: R^1 = Me/H, R^2 = SEt
10/16: R^1 = Me/H, R^2 = H
17: R^1 = H, R^2 = SEtOH

known that relatively high binding affinity is only maintained if both phenolic hydroxy groups of the HEX derivatives are free.[2,3,9,17,18] In addition, larger groups neighboring the hydroxy groups decrease the binding affinity.[7,11,19]

Chemical Synthesis

Thus, as in the preceding paper,[1] we linked the cytotoxic groups to the side chain with a spacer of varying length. The synthesis started from the readily available tertiary alcohol 1,[20] which is obtained from deoxyanisoin as a 1:4

Scheme II



19: R^1 = Me, R^2 = OC_6Cl_5
20: R^1 = Me, R^2 = $OC_6H_4NO_2$
21: R^1 = Me, R^2 = NH_2
22: R^1 = Me, R^2 = NHMe
23: R^1 = Me, R^2 = $N[(CH_2)_2OH]_2$
24: R^1 = Me, R^2 = $NH[(CH_2)_2OH]$
25: R^1 = Me, R^2 = $NH(CH_2)_2CO_2Et$
26: R^1 = H, R^2 = NH_2
27: R^1 = H, R^2 = NHMe
28: R^1 = H, R^2 = $N[(CH_2)_2OH]_2$
29: R^1 = H, R^2 = $NH[(CH_2)OH]$
30: R^1 = Me, R^2 = NH_2
31: R^1 = Me, R^2 = $N[(CH_2)_2OH]_2$
32: R^1 = Me, R^2 = $NH[(CH_2)_2OH]$
33: R^1 = H, R^2 = NH_2
34: R^1 = H, R^2 = $N[(CH_2)_2OH]_2$
35: R^1 = H, R^2 = $NH[(CH_2)_2OH]$
36: R^1 = H, R^2 = $N[(CH_2)_2Cl]_2 \cdot HCl$
37: R^1 = H, R^2 = $NH[(CH_2)_2Cl] \cdot HCl$
38: R^1 = H, R^2 = $NHCON(NO)(CH_2)_2Cl$

mixture of isomers.[1] The benzylic hydroxy group of 1 could be removed by hydrogenation in the presence of acid[21] with simultaneous ester cleavage to quantitatively produce a 1:1 mixture of the erythro and threo acids 2 and 4 as shown in Scheme I. The ratio of the erythro and threo acids 2 and 4 was irrespective of the isomeric ratio of the starting material 1. Fortunately, the biologically more active erythro compound crystallized and all the subsequent derivatives were prepared in isomerically pure form. The structural assignment of acids 2 and 4 were made on the corresponding alcohols 3 and 5, which were obtained by reduction with lithium aluminum hydride (LAH). Extensive 2D NMR studies (INADEQUATE and ^{13}C, ^1H correlation techniques) enabled a correct assignment of all NMR signals and the structural determination could be made from the coupling constants of the nonequivalent benzylic protons.[22]

In the course of the syntheses a careful choice of the protecting groups had to be made depending on the chemical stability of the attached electrophilic groups. The methoxy group of the starting material 2 could be carried through a long reaction sequence if the acidic conditions of the ether cleavage with boron tribromide could be tolerated. In other cases the *tert*-butyldimethylsilyl (TBDMS) group or the benzyl group offered advantages and sometimes a direct attachment to the free bisphenol was possible.

Alcohol 3 served as the parent compound for a number of derivatives listed in Chart I in which the hydroxy group was exchanged by a halide or a thioethanol group. Halides 6 and 8 were prepared by reaction of 3 with thionyl chloride or *N*-methyldicyclohexylcarbodiimidium iodide.[23] Treatment of alcohol 3 with 48% hydrogen bromide was accompanied by methyl ether cleavage to 13. Nucleophilic displacement of iodide in 8 with thioethanol afforded thioether 9. A derivative in which the halide is replaced by hydrogen was obtained by hydrogenation of a Grignard adduct similar to 1 (CO_2-*t*-Bu replaced by CH_3).[1] Again, a 1:1 mixture of isomers resulted and the erythro derivative 10 crystallized. All of the arylmethyl ethers were cleanly cleaved with BBr_3 in dichloromethane at −70 °C to afford the bisphenols 11–16. The 2-hydroxyethyl octyl thioether

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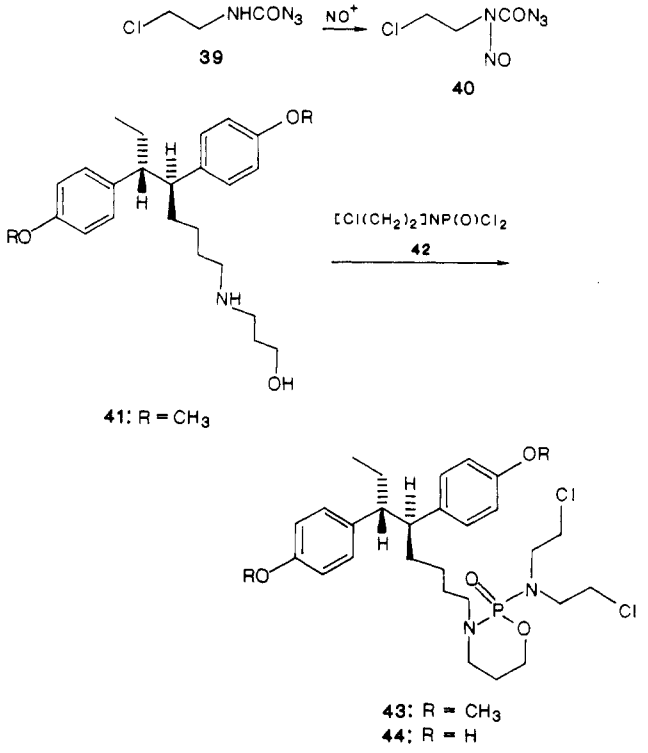
Scheme III

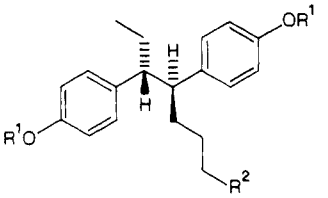


17 was available by direct iodide displacement of bisphenol 14 with mercaptoethanol. An interesting compound for binding studies, in which all the positions ortho to the phenol are blocked, was obtained on treatment of 3 with triphenylphosphine and bromine[24] to afford 18.

A common feature of all the compounds prepared next (Scheme II) is the nitrogen atom replacing the heteroatom in the side chain in 6–16. They were prepared via the activated 4-nitrophenyl or pentachlorophenyl esters 19 and 20 by reaction with the corresponding amines (NH_3, NH_2CH_3, $NH(CH_2CH_2OH)_2$, $NH_2CH_2CH_2OH$, $NH_2CH_2CH_2CO_2Et$) to afford amides 21–25. For the purpose of binding studies the methyl ethers were cleaved with BBr_3 to yield the corresponding bisphenols 26–29. Amides 21, 23, and 24 were reduced with LAH to amines 30–32. For the preparation of the cytotoxic N-lost compounds 36 and 37, the aryl methyl ethers of amines 31 and 32 were cleaved with BBr_3 and the resulting phenols 34 and 35 were treated with $SOCl_2$ to give chlorides 36 and 37. Nitrogen-lost compounds are potent alkylants and a number of derivatives are used in cancer treatment.[25] The bisalkylation derivative 36 is particularly well adapted for cross-linking DNA strands. The HEX-linked lost compound 36 has a spacer that is three carbons longer than the similar compound prepared by Hamacher and Mangold.[4]

Another group of potent anticancer drugs are derived from *N*-nitrosourea and some drugs of this kind are in clinical use (Carnustin, Lomustin).[25] The (2-chloroethyl)nitrosourea group does not survive BBr_3 treatment and alkaline or hydrogenating conditions are also insuitable. We therefore designed a synthesis in which an appropriately activated 2-chloroethyl-*N*-nitroso group is directly attached to the bisphenolic primary amine 33. As a precursor, the known[26-28] crystalline azide 39 was nitrosated to the oily nitroso azide 40 (Scheme II). Coupling of 40 with amine 33 in pyridine directly provided the HEX-linked nitrosourea compound 38. Interestingly, the predominant fragmentation in the mass spectrum was the formation of an isocyanate. Isocyanate formation is also a process of biotransformation and the alkylation of amines present in the cell is believed to be responsible for the cytostatic activity.[25]

Chart II



45/51: R^1 = TBDMS/H, R^2 = COOH
46/11: R^1 = TBDMS/H, R^2 = CH_2OH
47/52: R^1 = TBDMS/H, R^2 = CH_2OCOCH_3
48/53: R^1 = TBDMS/H, R^2 = CH_2OCOCH_2Cl
49/54: R^1 = TBDMS/H, R^2 = CH_2OMs
50/55: R^1 = TBDMS/H, R^2 = CH_2OTs

Next, the very well known cyclophosphamide group was linked to the HEX molecule as shown in Scheme III. Cyclophosphamides (e.g. endoxane) are widely used in anticancer treatment in humans.[29] The in vivo activation occurs by enzymatic hydroxylation of the C-4 position, ring opening, and elimination of acrolein.[30] A good choice to link the HEX molecule to cyclophosphamide would be the secondary nitrogen atom which is not eliminated during the bioactivation process. However, a direct coupling of the prebuilt cyclophosphamide to an electrophilic HEX derivative such as iodide 14 was not possible. Cyclophosphamide 43 was eventually constructed by condensation of *N,N*-bis(2-chloroethyl)phosphoric acid amide dichloride 42 with amino alcohol 41 in pyridine (94%). Amino alcohol 41 was obtained by LAH reduction of the β-amino ester 25 to 41. The other building block 42 was prepared according to a procedure of Friedmann and Seligmann.[31] A new chiral center was introduced with the tetracoordinated phosphorus and a mixture of diastereomers would be expected to result from the coupling. In fact, two signals could be seen in the ^{31}P NMR spectrum for the phosphorus atom.

A number of functional groups which we intended to link to HEX were not compatible with the ether cleavage conditions with BBr_3. The *tert*-butyldimethylsilyl (TBDMS) group was therefore introduced by reaction of phenolic acid 51 with *tert*-butyldimethylsilyl chloride and imidazole in DMF. An intermediate silyl ester was cleaved by addition of methanol to afford bis(silyl ether) 45. Acid 45 (Chart II) was then reduced with LAH to give alcohol 46 in 86% yield. Prolonged reaction and elevated reaction temperatures lead to partial silyl ether cleavage and the reaction had to be carefully monitored by TLC. Alcohol 46 was then converted into a number of electrophilic esters by reaction with the corresponding acid chlorides in pyr-

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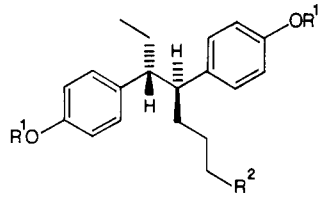
Chart III



56: R^1 = Bn, R^2 = CO_2Bn
57: R^1 = H, R^2 = CO_2Me
58: R^1 = Bn, R^2 = CH_2OH
59: R^1 = Bn, R^2 = CH_2I
60/69: R^1 = Bn/H, R^2 = $CH_2O(CH_2)_2OH$
61/70: R^1 = Bn/H, R^2 = $CH_2(OCH_2CH_2)_2OH$
62/71: R^1 = Bn/H, R^2 = $CH_2(OCH_2CH_2)_3OH$
63: R^1 = H, R^2 = CH_2OCH_2Cl
64: R^1 = H, R^2 = $CH_2(OCH_2CH_2)_2Cl$
65: R^1 = H, R^2 = $CH_2(OCH_2CH_2)_3Cl$
66: R^1 = H, R^2 = CHO
67: R^1 = H, R^2 = $CH{=}CH_2$
68: R^1 = H, R^2 = 

idine. The silyl ether cleavage could finally be effected by fluoride ion treatment under essentially neutral conditions to afford phenols **11** and **52–55**.

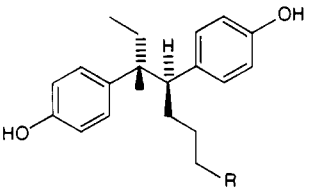
As a third protecting group the base- and acid-stable benzyl ether group was introduced by converting phenolic acid **51** to perbenzylated ester **56**. LAH reduction of **56** afforded alcohol **58**, which was converted to iodide **59** by treatment with *N*-methyldicyclohexylcarbodiimidium iodide[23] (Chart III). Displacement reactions of **59** with mono-, di-, and triethylene glycol gave the corresponding alcohols **60–62**. Hydrogenolysis liberated free phenols **69–71** and chlorination with thionyl chloride gave chlorides **63–65**.

Finally, it was intended to introduce an epoxy function as a potent electrophilic group. Acid **51** was converted to methyl ether **57** by treatment with diazomethane. Methyl ester **57** was reduced with diisobutylaluminum hydride (DIBAH) to aldehyde **66** and subsequent Wittig reaction furnished the terminal olefin **67**, which was epoxidized with *m*-chloroperbenzoic acid (MCPBA) to epoxide **68**.

Estrogen Receptor Binding

Table I gives the relative binding affinities (RBA, E_2 = 100) for selected HEX derivatives. The magnitude of the binding is comparable to that of the analogous DES derivatives published in the preceding paper.[1] Again, acidic groups like carboxylic acids (compound **51**) strongly decreased the RBA. No such decrease can be seen in the amine hydrochlorides (e.g. **34**, **36**) which also have higher RBA as the corresponding amides (**28** and **27**). A similar decrease in the RBA is observed with the tetrabromo HEX derivative **18** in which the phenolic hydroxy groups are blocked by four neighboring bromo atoms. Generally, larger side chains with hydrophobic as well as hydrophilic terminating groups decrease the RBA (compare ref 5). This is demonstrated with the homologous halides in which iodide **14** has a lower RBA (0.2) than the corresponding bromide **13** (1.0) or chloride **12** (1.5) (compare ref 13). However, no such decrease occurs in the polyether compounds **63–65** and **69–71** even with very long side chains. An explanation of this remarkable effect might be found in the random coil conformation of longer hydrophobic side chains whereas the polyether spacers could assume a more linearly stretched conformation due to hydrogen bonding with water molecules. This hypothesis is supported by the much lower RBA of the corresponding thioether compounds **15** and **17** since sulfur is less able to form hydrogen bonds in aqueous solution. This might be of general importance if biologically active molecules are attached to spacers. Data on the potential therapeutic value of such compounds are too few to be reported here. However, it should be stressed that preliminary in vitro studies on MCF-7 breast cancer cells (for experimental protocol, see ref 3) revealed no major cytotoxicity for compounds **34** and **36**. Since mustine is extremely toxic in this model,[3] it appears that the grafting of the alkylating group largely reduces its efficiency. However, the relatively high RBA of the N-lost compound **33**, the *N*-nitrosourea **38**, and the cyclophosphamide **44** merits further in vivo investigation in the treatment of estrogen-dependent tumors. It should be noted that irreversible receptor binding of some of the strongly alkylating derivatives tested is possible.[32] The present data on HEX and DES[1] show that the grafting of a cytotoxic moiety on diphenolic estrogens reduces their binding affinity for the receptor even in the presence of a spacer. However, this observation should not reject the approach since the reduction is not as strong as usually found with a direct lincage. The synthesis of spacer-containing estrogenic platinum complexes, reported at the time of submission of our studies,[33] totally supports this impression.

Table I. Estradiol Receptor Binding Affinities of HEX Derivatives



no.	R	RBA
51	COOH	0.1
29	$CONHCH_2CH_2OH$	0.1
18	CH_2OH, R^3 = Br	0.1
57	CO_2CH_3	0.2
28	$CONH(CH_2CH_2OH)_2$	0.2
14	CH_2I	0.2
15	CH_2SEt	0.2
27	$CONHCH_3$	0.2
54	$CH_2OSO_2CH_3$	0.3
63	$CH_2OCH_2CH_2Cl$	0.3
17	$CH_2SCH_2CH_2OH$	0.4
65	$CH_2(OCH_2CH_2)_3Cl$	0.5
26	$CONH_2$	0.9
34	$CH_2N(CH_2CH_2OH)_2$	0.9
16	CH_3	1.0
38	$CH_2NHCON(NO)CH_2CH_2Cl$	1.0
37	$CH_2NHCH_2CH_2Cl{\cdot}HCl$	1.0
13	CH_2Br	1.0
52	CH_2OCOCH_3	1.0
66	CHO	1.0
67	$CH{=}CH_2$	1.0
68	$CH(O)CH_2$	1.0
69	$CH_2OCH_2CH_2OH$	1.0
70	$CH_2(OCH_2CH_2)_2OH$	1.0
71	$CH_2(OCH_2CH_2)_3OH$	1.0
64	$CH_2(OCH_2CH_2)_2Cl$	1.0
44	CH_2-cyclophosphamide	1.0
12	CH_2Cl	1.5
11	CH_2OH	1.5
33	CH_2NH_2	2.0
36	$CH_2N[(CH_2)_2Cl]_2{\cdot}HCl$	2.5

Experimental Section

For general methods and measurement of binding affinities, see ref 1 and 34. The following range of bands in the IR and

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UV spectra were found for HEX ethers: UV λ_{max} (log ϵ) 210–212 (4.1), 226–228 (4.3), 272–277 (3.5), 280–285 nm (3.4); IR 3020–2830, 1610–1615, 1580–1585, 1509–1510, 1255–1255, 1175–1180, 1040–1035, 812–835 cm^{-1}. The corresponding HEX derivatives had the following values: UV λ_{max} (log ϵ) 208–216 (4.1), 227–228 (4.3), 278–279 (3.6), 283–285 nm (3.5); IR 3260–3240, 3020–2850, 1610–1612, 1600, 1510–1513, 1450–1457, 1377–1385, 1238–1264, 1113–1105, 1013, 830–835 cm^{-1}.

(5*S,6*R**)-5,6-Bis(4-methoxyphenyl)-1-octanoic Acid (2) and (5*S**,6*S**)-5,6-Bis(4-methoxyphenyl)-1-octanoic Acid (4).** A solution of 8.00 g of alcohol 1 in 100 mL of acetic acid was treated with 100 mg of Pd/C and 5 drops of perchloric acid. Hydrogenation was effected at 3 bar. The catalyst was filtered off, the filtrate was neutralized with $NaHCO_3$ solution, and the product was extracted with dichloromethane. The solvent was removed under reduced pressure and the residue (6.65 g, 100%) cyrstallized from 5 mL of dichloromethane to afford 3.00 g (45.5% of the pure erythro compound **2**. Data for **2**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.51 (t, J = 7.5 Hz, 3 H, 8-H), 1.20–1.46 (m, 6 H, 3, 4, 7-H), 2.09 (m, 2 H, 2-H), 2.45 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.58 (m, 1 H, 5-H), 3.79 and 3.81 (each s, 3 H, 2 OCH_3), 6.86 (d, 2 H, J = 8.5 Hz, 4 H, ArH ortho to OCH_3), 7.06 (d, 2 H, J = 8.5 Hz, 4 H, ArH); IR (KBr) 1708 cm^{-1} (CO); MS (160 °C) m/z 207 (62), 189 (5), 171 (19), 161 (8), 149 (100).

Data for **4**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.73 (t, J = 7.5 Hz, 3 H, 8-H), 1.14–1.87 (m, 6 H, 3, 4, 7-H), 2.17–2.31 (m, 2 H, 2-H), 2.64 (ddd, J = 4.5, 6.5, 10 Hz, 1 H, 6-H), 2.77 (ddd, J = 4.5, 6.5, 10 Hz, 1 H, 5-H), 3.74, 3.75 (s, 3 H, OCH_3), 6.69 (d, J = 8.5 Hz, 4 H, ArH), 6.74 (d, J = 8.5 Hz, 4 H, ArH); IR (CCl_4) 1710 cm^{-1} (CO).

(5*S,6*R**)-*erythro*-5,6-Bis(4-methoxyphenyl)-1-octanol (3).** A suspension of 0.08 g (2.1 mmol) of lithium aluminum hydride (LAH) in 10 mL of absolute THF at 0 °C was treated with a solution of 1.00 g (2.8 mmol) of acid **2**. After stirring for 4 h at room temperature, the mixture was hydrolyzed with 30 mL of 1 N HCl and the product was extracted with diethyl ether. The ethereal solution was washed with a $NaHCO_3$ solution and water, dried with Na_2SO_4, filtered, and evaporated, and the residue was crystallized from dichloromethane/petroleum ether to afford 0.89 g (93%) of **3**: mp 59–61 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.52 (t, J = 7.5 Hz, 3 H, 8-H), 0.85–1.75 (m, 8 H, 2-, 3-, 4-, 7-H), 2.46 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.58 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.41 (m, 2 H, 1-H), 3.81 (s, 6 H, 2 OCH_3), 6.85 (2 d, J = 8.5 Hz, 4 H, ArH), 7.07 (d, 2, J = 8.5 Hz, 4 H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.18 (q, C-8), 23.63 (t, C-3), 27.34 (t, C-7), 32.55 (t, C-2), 34.17 (t, C-4), 51.46 (d, C-5), 53.67 (d, C-6), 55.18 (q, 2 OCH_3), 62.78 (t, C-1), 113.65 (d, C-11, 13, 17, 19), 129.12 (d, C-10, 14, 16, 20), 136.46 (s, C-9, C-15), 157.87 (s, C-12, C-18).

(5*S,6*S**)-*threo*-5,6-Bis(4-methoxyphenyl)-1-octanol (5).** One gram (2.8 mmol) of threo acid **4** was reduced with 0.08 g (2.1 mmol) of LAH to afford 0.86 g (89%) of oily alcohol **5**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (t, J = 7 Hz, 3 H, 8-H), 1.08–1.21 (m, 2 H, 3-H), 1.40–1.84 (m, 6 H, 2-, 4-, 7-H), 1.86 (s, 1 H, OH), 2.63 (ddd, J = 4.5, 6.5, 10 Hz, 1 H, 6-H), 2.75 (ddd, J = 4.5, 6.5, 10.0 Hz, 1 H, 5-H), 3.51 (dt, 2 H, 1-H), 3.72 (s, 6 H, 2 OCH_3), 6.69 (2 d, J = 8.5 Hz, 4 H, ArH), 6.74 (d, J = 8.5 Hz, 4 H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.32 (q, C-8), 23.91 (t, C-3), 26.06 (t, C-7), 32.79 (t, C-2), 33.10 (t, C-4), 50.40 (d, C-5), 52.62 (d, C-6), 55.03 (q, 2 OCH_3), 62.72 (t, C-1), 112.90 (d, C-11, 13, 17, 19), 129.88 (d, C-10, 14, 16, 20), 134.85 (s, C-9, C-15), 157.62 (s, C-12, C-18).

***erythro*-5,6-Bis(4-methoxyphenyl)-1-octyl Chloride (6).** A solution of 443 mg (1.3 mmol) of alcohol **3** in 10 mL of CCl_4 was treated with 1 mL of DMF and 0.15 mL (1.9 mmol) of thionyl chloride and stirred for 2 h. The mixture was then poured into water, the organic solvent was evaporated under reduced pressure, and the residue was crystallized from ethyl acetate to yield 421 mg (91%) of **6**: mp 65 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 0.51 (t, J = 7 Hz, 3 H, 8-H), 0.78–1.71 (m, 8 H, 2, 3, 4, 7-H), 2.39–2.67 (m, 2 H, 5, 6-H), 3.25 (t, 2 H, 1-H), 3.79 (s, 6 H, OCH_3), 6.82 (d, J = 8 Hz, 4 H, ArH), 7.06 (d, J = 8 Hz, 4 H, ArH).

***erythro*-5,6-Bis(4-methoxyphenyl)-1-octyl Iodide (8).** A solution of 0.30 g (0.88 mmol) of alcohol **3** and 1.02 g (1.84 mmol) of *N*-methyl-*N*,*N*'-dicyclohexylcarbodiimidium iodide[23] in 15 mL of absolute THF was stirred overnight at room temperature. The solution was diluted with 50 mL of diethyl ether, washed with water and a solution of sodium thiosulfate, dried with Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2) and crystallized from ethyl acetate/petroleum ether to give 0.38 g (91%) of iodide **8**: mp 86 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 0.53 (t, J = 7.5 Hz, 3 H, 8-H), 0.89–1.9 (m, 8 H, 2, 3, 4, 7-H), 2.40–2.64 (m, 2 H, 5, 6-H), 2.91 (t, J = 7 Hz, 2 H, 1-H), 3.80 (s, 6 H, OCH_3), 6.82 (d, J = 8 Hz, 4 H, ArH), 7.05 (d, J = 8 Hz, 4 H, ArH).

***erythro*-5,6-Bis(4-methoxyphenyl)octyl Ethyl Thioether (9).** A solution of 0.2 mL of ethanethiol in 3.0 mL of dry THF was treated with 10 mg of NaH. After 0.5 h 100 mg (0.2 mmol) of iodide **8** was added and stirring was continued for 8 h at 20 °C. The mixture was neutralized with 2 N HCl and extracted with diethyl ether. The dried solution was evaporated and the residue crystallized from diethyl ether to afford 81 mg (98%) of thioether **9**: mp 46 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 0.40–0.71 (m, 6 H, 8, 2'-H), 0.96–1.60 (m, 8 H, 2-, 3-, 4-, 7-H), 2.16–2.71 (m, 6 H, 1-, 1'-, 5-, 6-H), 3.78 (s, 6 H, OCH_3), 6.84 (d, J = 8 Hz, 4 H, ArH), 7.07 (d, J = 8 Hz, 4 H, ArH).

***erythro*-3,4-Bis(4-methoxyphenyl)octane (10).** A solution of 1.22 g (3.76 mmol) of 3,4-bis(4-methoxyphenyl)-3-octene[1] in 30 mL of ethanol/acetic acid (2.1) was hydrogenated as described for **2** to afford 1.16 g (95%) of oily **10** as a 1:1 mixture of the erythro and threo compounds. The erythro derivative **10** crystallized from ethyl acetate (0.49 g, 40%): mp 74 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.52 (t, J = 7.5 Hz, 3 H, 1-H), 0.67 (t, J = 7.5 Hz, 3 H, 8-H), 0.84–1.44 (m, 8 H, alkyl-H), 2.45 (dt, J = 3.5, 10, 10 Hz, 1 H, 3-H), 2.56 (dt, J = 4.0, 10, 10 Hz, 1H, 4-H), 3.81 (s, 6 H, OCH_3), 6.83 (d, J = 8.5 Hz, 4 H, ArH), 7.07 (2 d, J = 8.5 Hz, 4 H, ArH); MS (70 °C m/z 326 (2, M^+), 177 (86), 149 (88), 134 (26), 121 (100), 91 (35).

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octanol (11).** A solution of 500 mg (1.5 mmol) of alcohol **3** in 20 mL of dry CH_2Cl_2 was treated at −50 °C with 0.2 mL of BBr_3 (2.24 mmol). The solution was stirred for 3.5 h at room temperature, poured onto 100 mL of ice–water, and extracted with diethyl ether. The etheral solutions were dried (Na_2SO_4), evaporated, and crystallized from petroleum ether/ethyl acetate to afford 4.16 g (91%) of oily phenol **11**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.52 (t, J = 7.5 Hz, 3 H, 8-H), 0.80–1.47 (m, 8 H, 2-, 3-, 4-, 7-H), 2.43 (m, 1 H, 6-H), 2.54 (m, 1 H, 5-H), 3.43 (m, 2 H, 1-H), 4.67 (s, 2 H, ArOH), 6.78 (d, 2, J = 8.5 Hz, 4 H, ArH), 7.00 (d, 2, J = 8.5 Hz, 4 H, ArH); MS (150 °C) m/z 314 (0.7, M^+), 212 (5), 199 (3), 179 (55), 161 (83), 135 (88). Anal. ($C_{20}H_{26}O_3$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl Chloride (12).** Methyl ether **6** (156 mg (0.4 mmol) was cleaved with 0.15 mL of boron tribromide as described for **11** to afford 100 mg (70%) of phenol **12**: mp 166 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, J = 7.5 Hz, 3 H, 8-H), 1.00–1.66 (m, 8 H, 2-, 3-, 4-, 7-H), 2.44 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.56 (dt, J = 4.5 Hz, 10, 10 Hz, 1 H, 5-H), 3.30 (m, 2 H, 1-H), 4.60 (s, 2 H, ArOH), 6.79 (d, J = 8.5 Hz, 4 H, ArH), 7.00 (2 d, J = 8.5 Hz, 4 H, ArH); MS (150 °C) m/z 332 (M^+, Cl = 35), 212, 197, 181, 161, 147, 135 (100), 120. Anal. ($C_{20}H_{25}O_2Cl$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl Bromide (13).** A solution of 30 mg (0.09 mmol) of alcohol **3** in 10 mL of 48% HBr and 5 mL of acetic acid was refluxed for 2 h. The reaction mixture was diluted with 100 mL of water and extracted with diethyl ether. The organic phase was washed with water and $NaHCO_3$ solution, dried with Na_2SO_4, and evaporated at reduced pressure. The product was purified by preparative TLC (silical gel, CH_2Cl_2/2% MeOH) and crystallized from dichloromethane to yield 19 mg (57%) of bromide **13**: mp 160–161 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.54 (t, J = 7 Hz, 3 H, 8-H), 0.98–1.75 (m, 8 H, 2-, 3-, 4-, 7-H), 2.44 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.55 (dt, J = 5.0, 10, 10 Hz, 1 H, 5-H), 3.16 (m, 2 H, 1-H), 4.65 (br s, 2 H, ArOH), 6.80 (d, J = 8.5 Hz, 4 H, ArH), 7.01 (2 d, J = 8.5 Hz, 4 H, ArH); MS (120 °C) m/z 376/378 (M^+), 243 (63), 241 (63), 161 (43), 135 (97), 120 (65), 107 (100), 91 (45); exact mass calcd for $C_{20}H_{25}O_2{}^{79}Br$ 376.1038, found 376.1013.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl Iodide (14).** Fifty milligrams (0.11 mmol) of methyl ether **8** was cleaved with 1 mL of 1 M BBr_3 solution in CH_2Cl_2 to yield 36 mg (79%): mp 153

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°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53 (t, J = 7.5, 3 H, 8-H), 1.02 (m, 2 H, 3-H), 1.18–1.42 (m, 6 H, 4-, 7-H), 2.43 (dt, 1 H, 6-H), 2.53 (dt, 1 H, 5-H), 2.95 (m, 2 H, 1-H), 4.61 (s, 2 H, ArOH), 6.78 (d, J = 8.5 Hz, 4 H, ArH), 7.01 (2 d, J = 8.5 Hz, 4 H, ArH); MS (110 °C) m/z 424 (0.2, M^+), 289 (17), 161 (4), 135 (100), 107 (80); exact mass calcd for $C_{20}H_{25}O_2J$ 424.0898, found 424.0897.

***erythro*-5,6-Bis(4-hydroxyphenyl)octyl Ethyl Thioether (15).** Fifty milligrams (0.13 mmol) of methyl ether **9** was cleaved with 0.1 mL of a 1 M solution of BBr_3 as described for **11** to afford 36 mg (77%) of bisphenol **15**: mp 117 °C (diethyl ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.54 (t, J = 7.5 Hz, 3 H, 8-H), 1.0 (m, 2 H, 3-H), 1.17 (t, J = 7 Hz, 3 H, 2′-H), 1.23–1.43 (m, 6 H, 2-, 4-, 7-H), 2.15–2.32 (m, 2 H, 1-H), 2.41 (q, J = 7 Hz, 2 H, 1′-H), 2.41 (m, 1 H, 6-H), 2.55 (dt, 1 H, 5-H), 4.65 (s, 2 H, ArOH), 6.78 (d, J = 8.5 Hz, 4 H), 7.0 (2 d, J = 8.5 Hz, 4 H, ArH); IR (KBr) 3400 (OH), 3020–2860 (CH), 1610, 1600, 1510 (Ar), 1450, 1240, 1175, 830 cm^{-1}; UV λ_{max} (log ε) 217 sh (4.11), 228 (4.29), 279 (3.54), 285 nm (3.46); MS (100 °C) m/z 223 (100, M^+), 161 (64), 135 (57), 120 (34), 107 (79), 91 (24), 75 (44), 67 (21), 55 (23), 41 (30); exact mass calcd for $C_{13}H_{19}OS$ 223.1156, found 223.1156.

***erythro*-3,4-Bis(4-hydroxyphenyl)octane (16).** Four hundred milligrams (1.23 mmol) of methyl ether was cleaved with 0.15 mL of BBr_3 as described for **11** to afford 331 mg (89%) of bisphenol **16**: mp 180–182 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.53 (t, 3 H, 1-H), 0.68 (t, 3 H, 8-H), 0.81–1.48 (m, 8 H, 2-, 5-, 6-, 7-H), 2.44 (dt, 1 H, 3-H), 2.56 (dt, 1 H, 4-H), 4.58 (br s, 2 H, ArOH), 6.78 (d, 4 H, ArH), 7.00 (2 d, 4 H, ArH); MS (130 °C) m/z 298 (M^+), 212, 199, 181, 163, 135, 120, 107 (100). Anal. ($C_{20}H_{26}O_2$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)octyl 2-Hydroxyethyl Thioether (17).** Iodide **14** (50 mg, 0.12 mmol) was converted to the thioether as described for **9** with 16 mg (0.39 mmol) of NaH and 0.1 mL (1.43 mmol) of 2-mercaptoethanol to yield 36 mg (81%) of **17**: mp 127–128 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 0.51 (t, J = 7.5 Hz, 3 H, 8-H), 1.02 (m, 2 H, 3-H), 1.22–1.40 (m, 6 H, 2-, 4-, 7-H), 2.29 (m, 2 H, 1-H), 2.47 (dt, 1 H, 6-H), 2.51 (t, 2 H, RSCH_2CH$_2$O), 2.59 (m, 1 H, 5-H), 3.60 (m, 2 H, CH$_2$O), 6.80 (2 d, J = 8.5 Hz, ArH), 7.06 (2 d, J = 8.5 Hz, ArH), 8.08 (s, 2 H, ArOH); MS (240 °C) m/z 299, 271, 265, 255, 239, 161, 135; exact mass calcd for $C_{13}H_{19}O_2S$ 239.1106, found 239.1103.

***erythro*-5,6-Bis(3,5-dibromo-4-hydroxyphenyl)-1-octanol (18).** A solution of 50 mg (0.15 mmol) of alcohol **3** and 41 mg (0.15 mmol) of triphenylphosphine in 3 mL of absolute DMF was treated under nitrogen with a diluted DMF solution of bromine until the color of bromine persisted. Usual workup afforded the TLC separation 41 mg (44%) of oily tetrabromide **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (t, J = 7 Hz, 3 H, 8-H), 0.87–1.72 (m, 8 H, 2-, 3-, 4-, 7-H), 2.32 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.53 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.48 (m, 2 H, 1-H), 5.85 (br s, 2 H, ArOH), 7.20, 7.21 (s, 2 H, ArH); MS (250 °C) m/z 630 (M^+), 528, 515, 460, 448, 381, 368, 337, 319, 293, 265, 238, 212, 131; exact mass calcd for $C_{20}H_{22}O_3{}^{79}Br_2{}^{81}Br_2$ 629.8265, found 629.8245.

***erythro*-Pentachlorophenyl 5,6-Bis(4-methoxyphenyl)octanoate (19).** A solution of 1.00 g (2.8 mmol) of acid **2**, 752 mg (3.6 mmol) of dicyclohexyl carbodiimide (DCCI), and 0.97 g (3.6 mmol) of pentachlorophenol in 20 mL of absolute THF was stirred overnight. The solution was diluted with diethyl ether, washed with $NaHCO_3$ solution, dried with Na_2SO_4, and evaporated. The dicyclohexylurea was filtered off, the filtrate was evaporated to dryness, and the residue was crystallized from ethyl acetate to yield 1.53 g (90%) of ester **19**: mp 148 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.11–1.56 (m, 6 H, 3-, 4-, 7-H), 2.33–2.69 (m, 4 H, 2-, 5-, 6-H), 3.08 (s, 6 H, 2 OCH$_3$), 6.75–7.13 (m, 8 H, ArH); IR (KBr) 1775 cm^{-1} (CO).

***p*-Nitrophenyl *erythro*-5,6-Bis(4-methoxyphenyl)octanoate (20).** The activated 4-nitrophenyl ester **20** was prepared from 1.00 g (2.8 mmol) of acid **2**, 0.51 g (3.6 mmol) of *p*-nitrophenol, and 0.75 g (3.6 mmol) of DCCI as described for **19** to afford **20** quantitatively: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.53 (t, 3 H, 8-H), 1.18–2.10 (m, 6 H, 3-, 4-, 7-H), 2.24–2.71 (m, 4 H, 2-, 5-, 6-H), 3.76 (s, 6 H, OCH$_3$), 6.76–7.22 (m, 10 H, ArH), 8.14 (d, 2 H, ArH); IR (KBr) 1760 cm^{-1} (CO).

***erythro*-5,6-Bis(4-methoxyphenyl)octanamide (21).** A stream of dry ammonia was bubbled through a solution of 1.34 g (2.8 mmol) of *p*-nitrophenyl ester **20** in 20 mL of dichloromethane for 0.5 h and the solution was stirred for 2 h at 20 °C. The solution was washed with $NaHCO_3$ solution and water, dried with Na_2SO_4, and evaporated. The residue crystallized from diethyl ether to yield 0.82 g (82%) of amide **21**: mp 139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.52 (t, J = 7.5 Hz, 3 H, 8-H), 1.01–1.75 (m, 6 H, 3-, 4-, 7-H), 1.85–2.07 (m, 2 H, 2-H), 2.45 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.57 (ddd, 1 H, 5-H), 3.81 (s, 6 H, OCH$_3$), 5.13 (br s, 2 H, CONH$_2$), 6.86 (d, J = 8.5 Hz, 4 H, ArH), 7.04 (2 d, J = 8.5 Hz, 4 H, ArH); IR (KBr) 3420–3170 (NH), 1705 cm^{-1} (CO). Anal. ($C_{22}H_{29}O_3N$) C, H.

***erythro*-5,6-Bis(4-methoxyphenyl)-*N*-methyloctanamide (22).** A solution of 150 mg (0.31 mmol) of ester **20** in 5 mL of THF was treated with 32 mg (0.47 mmol) of methylamine hydrochloride and 2 mL of pyridine and stirred for 4 h. After usual workup 111 mg (97%) of methylamide **22** was obtained by crystallization from diethyl ether/petroleum ether: mp 122–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, J = 7.5 Hz, 3 H, 8-H), 1.17–1.43 (m, 6 H, 3-, 4-, 7-H), 1.82–2.02 (m, 2 H, 2-H), 2.44 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.58 (ddd, 1 H, 5-H), 2.64, 2.68 (s, 3 H, NHCH$_3$), 3.82 (s, 6 H, 2 OCH$_3$), 6.86 (d, J = 8.5 Hz, 4 H, ArH), 7.07 (2 d, J = 8.5 Hz, 4 H, ArH); IR (KBr) 3320 (NH), 1650 cm^{-1}.

***erythro*-5,6-Bis(4-methoxyphenyl)-*N*,*N*-bis(2-hydroxyethyl)octanamide (23).** A solution of 0.89 g (1.5 mmol) of pentachlorophenyl ester **19** in 20 mL of absolute THF was treated with 1 mL of diethanolamine and the mixture stirred overnight. After usual workup the product was purified by preparative TLC (SiO_2, CH_2Cl_2/4% MeOH) to afford 0.65 g (98%) of oily amide **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.51 (t, J = 7.5 Hz, 1 H, 8-H), 1.20–1.43 (m, 6 H, 3-, 4-, 7-H), 2.0–2.20 (m, 2 H, 2-H), 2.46 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.57 (ddd, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.27 (t, J = 5 Hz, 2 H, NCH$_2$), 3.42 (m, 2 H, NCH$_2$), 3.63 (t, J = 5 Hz, 2 H, CH$_2$O), 3.72 (t, J = 5 Hz, 2 H, CH$_2$O), 3.80, 3.82 (s, 3 H, OCH$_3$), 6.83 (d, 2, J = 8.5 Hz, 4 H, ArH), 7.05 (d, 2, J = 8.5 Hz, 4 H, ArH); IR (KBr) 3360 (OH), 1620 (CO). Anal. ($C_{26}H_{37}O_5N$) C, H.

***erythro*-5,6-Bis(4-methoxyphenyl)-*N*-(2-hydroxyethyl)octanamide (24).** A solution of 440 mg (0.73 mmol) of activated ester **19** was treated with 2 mL of ethanolamine in absolute THF as described for **23** to afford 225 mg (77%) of amide **24**: mp 128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.51 (t, J = 7.5 Hz, 3 H, 8-H), 1.17–1.42 (m, 6 H, 3-, 4-, 7-H), 2.94 (m, 2 H, 2-H), 2.45 (dt, 1 H, 6-H), 2.54 (m, 1 H, 5-H), 3.26 (m, 2 H, NHCH$_2$), 3.58 (t, J = 5 Hz, 2 H, CH$_2$O), 3.81 (s, 6 H, OCH$_3$), 5.60 (br s, 1 H, NH), 6.85 (d, 2, J = 8.5 Hz, 4 H, ArH), 7.07 (d, 2, J = 8.5 Hz, 4 H, ArH); IR (KBr) 3320–3100 (OH, NH), 1640, 1565 cm^{-1} (CO).

***erythro*-5,6-Bis(4-methoxyphenyl)-*N*-(3-ethoxy-3-oxopropyl)octanamide (25).** A solution of 2.50 g (5.2 mmol) of activated ester **20** in 20 mL of dry THF/triethylamine was treated under nitrogen with 1.29 g (8.4 mmol) of β-alanine ethyl ester hydrochloride. After stirring for 24 h at room temperature, the mixture was diluted with diethyl ether, washed with $NaHCO_3$ solution, water, and diluted hydrochloric acid, and dried with Na_2SO_4. The solvent was evaporated under reduced pressure and the residue purified by TLC to afford 1.51 g (63%) of amide **25**: mp 72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.51 (t, J = 7.5 Hz, 3 H, 8-H), 1.19–1.42 (m, 6 H, 3-, 4-, 7-H), 1.25 (t, J = 7 Hz, 3 H, CO$_2$CH$_2$CH_3), 1.90 (m, 2 H, CH_2CONHR), 2.41 (t, J = 6 Hz, 2 H, CH$_2$COOR), 2.45 (m, 1 H, 6-H), 2.56 (m, 1 H, 5-H), 3.38 (dt, 2 H, CONHCH_2R), 3.81 (s, 6 H, OCH$_3$), 4.11 (q, J = Hz, 2 H, CO$_2$CH_2CH$_3$), 5.80 (br t, 1 H, NH), 6.86 (d, J = 8.5 Hz, 4 H, ArH), 7.06 (2 d, J = 8.5 Hz, 4 H, ArH); IR (KBr) 3330 (NH), 1730 (CO$_2$Et), 1645 cm^{-1} (CONHR).

***erythro*-5,6-Bis(4-hydroxyphenyl)octanamide (26).** A solution of 75 mg (0.21 mmol) of methyl ether **21** was cleaved with 0.2 mL of a 1 M solution of BBr_3 in dichloromethane to afford 68 mg (98%) of **26**: mp 177–179 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 0.50 (t, J = 7.5 Hz, 3 H, 8-H), 1.18–1.45 (m, 6 H, 3-, 4-, 7-H), 2.00–2.26 (m, 2 H, 2-H), 2.50 (ddd, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.67 (ddd, 1 H, 5-H), 6.80 (d, 2, J = 8.5 Hz, 4 H, ArH), 7.07 (2 d, J = 8.5 Hz, 4 H, ArH); IR (KBr) 3480–3150 (OH, NH), 1670, 1650 cm^{-1} (CONH$_2$); MS (180 °C) m/z 327 (M^+), 192 (100), 175 (29), 135 (61); exact mass calcd for $C_{20}H_{25}O_3N$ 327.1834, found 327.1834.

***erythro*-5,6-Bis(4-hydroxyphenyl)-*N*-methyloctanamide (27).** A solution of 80 mg (0.22 mmol) of amide **22** in 5 mL of CH_2Cl_2 was treated with 0.2 mL of a 1 M solution of BBr_3 to afford

61 mg (82%) of bisphenol **27**: mp 152 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 0.50 (t, J = 7.5 Hz, 3 H, 8-H), 1.22–1.40 (m, 6 H, 3-, 4-, 7-H), 1.82–1.96 (m, 2 H, 2-H), 2.46 (dt, 1 H, 6-H), 2.55, 2.56 (s, 3 H, NCH_3), 2.62 (m, 1 H, 5-H), 6.71 (br s, 1 N, NH), 6.79 (d, J = 8.5 Hz, 4 H, ArH), 7.04 (2 d, J = 8.5 Hz, 4 H, ArH), 8.11, 8.12 (each s, each 1 H, OH); IR (KBr) 3500–3100 (OH, NH), 1645 cm^{-1} (CONH); MS (210 °C) m/z 342 (100, MH$^+$), 206 (88), 185 (27), 150 (25); exact mass calcd for $C_{21}H_{28}O_3N$ 342.2060, found 342.2069.

***erythro*-5,6-Bis(4-hydroxyphenyl)-*N*,*N*-bis(2-hydroxyethyl)octanamide (28).** Methyl ether **23** (100 mg, 0.23 mmol) was cleaved with 0.1 mL of a 1 M BBr_3 solution in dichloromethane to afford after TLC on silica gel (CH_2Cl_2/10% MeOH) 71 mg (76%) of phenol **28**: ^{1}H NMR (250 MHz, acetone-d_6) δ 0.51 (t, J = 7.5 Hz, 8-H), 1.11–1.45 (m, 6 H, 2-, 3-, 7-H), 2.06–2.33 (m, 2 H, 2-H), 2.46 (dt, 1 H, 6-H), 2.63 (m, 1 H, 5-H), 3.00 (s, 4 H, OH), 3.37 (m, 4 H, NCH_2), 3.58 (m, 4 H, CH_2OH), 6.80 (d, J = 8.5 Hz, 4 H, ArH), 7.06 (d, 2, J = 8.5 Hz, 4 H, ArH); IR (CH_3CN) 3560–3360 (OH), 1640 cm^{-1} (CO); MS (200 °C) m/z 280 (92), 262 (52), 193 (43), 176 (58); exact mass calcd for $C_{15}H_{22}NO_4$ 280.1448, found 280.1470.

***erythro*-5,6-Bis(4-hydroxyphenyl)-*N*-(2-hydroxyethyl)octanamide (29).** Seventy-two milligrams (0.18 mmol) of methyl ether **24** were cleaved with 0.1 mL of a 1 M solution of BBr_3 in CH_2Cl_2 to afford after TLC (CH_2Cl_2/10% MeOH) and crystallization from ethyl acetate/petroleum ether 48 mg (72%) of **29**: mp 106 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 0.48 (t, J = 7.5 Hz, 3 H, 8-H), 1.05–1.42 (m, 6 H, 3-, 4-, 7-H), 1.84–1.94 (m, 2 H, 2-H), 2.42 (dt, 1 H, 6-H), 2.60 (ddd, 1 H, 5-H), 3.06 (br s, OH), 3.13 (m, 2 H, $NHCH_2$), 3.44 (t, J = 5.5 Hz, 2 H, CH_2OH), 6.76 (d, J = 8.5 Hz, 4 H, ArH), 7.00 (2 d, J = 8.5 Hz, 4 H, ArH); IR (KBr) 3500–3200 (OH, NH), 1630 cm^{-1} (CO); MS (220 °C) m/z 372 (0.04, MH$^+$), 353 (0.4), 236 (100), 218 (71); exact mass calcd for $C_{22}H_{30}NO_4$ 372.2175, found 372.2164.

***erythro*-5,6-Bis(4-methoxyphenyl)-1-octylamine (30).** Two grams (5.6 mmol) of amide **21** was reduced with 0.25 g (6.7 mmol) of LAH as described for **31** to yield after TLC (CH_2Cl_2/10% MeOH) purification 1.80 g (94%) of an amorphous solid that was directly transformed to bisphenol **33**: IR (KBr) 3320 cm^{-1} (NH).

***erythro*-5,6-Bis(4-methoxyphenyl)-*N*,*N*-bis(2-hydroxyethyl)-1-octylamine (31).** A suspension of 25 mg (0.66 mmol) of LAH in 30 mL of absolute THF was treated with a solution of 550 mg (1.24 mmol) of amide **23** in 10 mL of THF and the mixture stirred for 5 h at room temperature. A diluted solution of ammonia was added and the precipitate was filtered off and extracted with diethyl ether. The filtrate was extracted with diethyl ether, and the combined organic phases were dried, evaporated, and purified by TLC (CH_2Cl_2/10% MeOH) to afford 260 mg (49%) of oily amine **31**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.53 (t, 3 H, 8-H), 0.89–1.51 (m, 8 H, 2-, 3-, 4-, 7-H), 1.58–1.71 (m, 2 H, 1-H), 230 (m, 2 H, 5-, 6-H), 2.53 (t, 4 H, NCH_2), 3.49 (t, 4 H, CH_2OH), 3.82 (s, 6 H, OCH_3), 3.97 (s, 2 H, OH), 6.83 (d, 4 H, ArH), 7.07 (d, 4 H, ArH).

***erythro*-5,6-Bis(4-methoxyphenyl)-*N*-(2-hydroxyethyl)-1-octylamine (32).** A solution of 150 mg (0.38 mmol) of amide **24** was reduced with 11 mg (0.29 mmol) of LAH as described for **31** to afford 67 mg (46%) of oily amine **32**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.53 (t, 3 H, 8-H), 0.82–1.44 (m, 8 H, 2-, 3-, 4-, 7-H), 1.58–1.77 (m, 2 H, 1-H), 2.29–2.73 (m, 2 H, 5-, 6-H), 3.47–3.73 (m, 4 H, $NHCH_2CH_2O$), 3.63 (s, 1 H, OH), 4.13 (s, 1 H, NH), 3.85 (s, 6 H, OCH_3), 6.84 (d, 4 H, ArH), 7.07 (d, 4 H, ArH); IR (CCl_4) 3320 cm^{-1} (OH, NH).

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octylamine (33).** Methyl ether **30** (1.77 g, 5.2 mmol) was cleaved (10 mL of a 1 M BBr_3 solution) to yield 0.98 g (60%) of an amorphous solid: ^{1}H NMR (400 MHz, acetone-d_6) δ 0.49 (t, 3 H, 8-H), 0.83–1.06 (m, 2 H, 3-H), 1.18–1.46 (m, 6 H, 2-, 4-, 7-H), 2.45 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.60 (dt, J = 4.5, 10, 10 Hz; 1 H, 5-H), 2.96 (m, 2 H, 1-H), 6.78 (d, J = 8.5 Hz, 4 H, ArH), 7.04 (d, 2, J = 8.5 Hz, 4 H, ArH); MS (90 °C) m/z 313 (4, M$^+$), 284 (3), 206 (6), 192 (6), 178 (100), 161 (55); exact mass calcd for $C_{20}H_{27}NO_2$ 313.20417, found 313.20537.

***erythro*-5,6-Bis(4-hydroxyphenyl)-*N*,*N*-bis(2-hydroxyethyl)-1-octylamine (34).** Diethyl ether **31** (260 mg, 0.61 mmol) was cleaved with 0.2 mL of a 1 M BBr_3 solution in CH_2Cl_2 to afford 128 mg (53%) of the oily phenol after TLC separation (CH_2Cl_2/20% MeOH): ^{1}H NMR (250 MHz, acetone-d_6) δ 0.50 (t, 3 H, 8-H), 0.87–1.65 (m, 8 H, 2-, 3-, 4-, 7-H), 2.48 (dt, 1 H, 6-H), 2.65 (m, 1 H, 5-H), 2.79 (t, 2 H, 1-H), 3.04 (t, 4 H, NCH_2) 3.76 (t, 4 H, CH_2OH), 6.85 (d, 2, 4 H, ArH), 7.09 (d, 2, ArH); MS (170 °C) m/z 401 (1, M$^+$), 370 (100), 340 (2), 294 (2), 266 (37), 236 (21), 204 (38), 157 (42); exact mass calcd for $C_{24}H_{35}NO_4$ 401.2566, found 401.2541.

***erythro*-5,6-Bis(4-hydroxyphenyl)-*N*-(2-hydroxyethyl)-1-octylamine (35).** A solution of 67 mg (0.17 mmol) of methyl ether **32** was cleaved with 0.1 mL of a 1 M solution of BBr_3 to yield 34 mg (54%) of oily bisphenol **35**: ^{1}H NMR (250 MHz, acetone-d_6) δ 0.5 (t, 3 H, 8-H), 0.92–1.13 (m, 2 H, 3-H), 1.23–1.80 (m, 3 H, 2-, 4-, 7-H), 2.47 (m, 1 H, 6-H), 2.70 (m, 1 H, 5-H), 2.87 (m, 2 H, 1-H), 3.14 (m, 2 H, 1-H), 3.84 (m, 2 H, CH_2O), 6.82 (2 d, 4 H, ArH), 7.10 (d, 2, 4 H, ArH).

***erythro*-5,6-Bis(4-hydroxyphenyl)-*N*,*N*-bis(2-chloroethyl)-1-octylamine Hydrochloride (36).** A solution of 58 mg (0.14 mmol) of **34** in 5 mL of absolute dichloromethane was treated with 0.1 mL (1.42 mmol) of thionyl chloride and stirred for 3 h at room temperature. The solvent was removed under reduced pressure and the residue crystallized from ethyl acetate/diethyl ether to yield 52 mg (76%) of bischloride **36**: mp 300–202 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 0.50 (t, J = 7.5 Hz, 3 H, 8-H), 0.90–1.04 (m, 2 H, 3-H)8 1.18–1.45 (m, 6 H, 2-, 4-, 7-H), 1.68 (cm, 2 H, 1-H), 2.46 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.65 (ddd, 1 H, 5-H), 3.51 (t, J = 6.5 Hz, 4 H, 1′H), 4.09 (t, J = 6.5 Hz, 4 H, CH_2Cl), 6.80 (2 d, J = 8.5 Hz, 4 H, ArH), 7.07 (2 d, J = 8.5 Hz, 4 H, ArH), 8.28 (br s, 2 H, ArOH); MS (180 °C) m/z 439/437 (M$^+$, Cl = 37/35), 388, 348, 332, 302 (21), 254, 240, 212 (8), 204 (12), 197 (84), 161 (41); exact mass calcd for $C_{24}H_{33}NO_2{}^{35}Cl_2$ 437.1888, found 437.1870.

***erythro*-5,6-Bis(4-hydroxyphenyl)-*N*-(2-chloroethyl)-1-octylamine Hydrochloride (37).** A solution of 25 mg (0.07 mmol) of amino alcohol **35** was chlorinated with 0.1 mL of thionyl chloride as described for **36** to yield 19 mg (75%) of chloride **37**: mp 167 °C; ^{1}H NMR (250 MHz, acetone-d_6) δ 0.50 (t, 3 H, 8-H), 0.86–1.83 (m, 8 H, 2-, 3-, 4-, 7-H), 2.30 (m, 2 H, 1-H), 2.47 (m, 1 H, 6-H), 2.67 (m, 1 H, 5-H), 3.36 (t, 2 H, 1′-H), 4.04 (t, 2 H, CH_2Cl), 6.82 (2 d, 4 H, ArH), 7.09 (m, 4 H, ArH); MS (200 °C) m/z 340 (M$^+$ – Cl), 326, 302, 300, 272, 270, 240, 222 (90), 178 (60), 135 (81); exact mass calcd for $C_{22}H_{30}NO_2$ 340.2276, found 340.2265.

***N*-Nitroso-*N*-(2-chloroethyl)-*N*′-[5,6-bis(hydroxyphenyl)octyl]urea (38).** A solution of 30 mg (0.10 mmol) of amine **33** in 5 mL of dry pyridine was treated with 200 mg of *N*-nitrosoazide **40**[26–28] in absolute diethyl ether and stirred overnight. The solvent was removed under reduced pressure. Methanol was added repeatedly and evaporated. The residue was purified by TLC (CH_2Cl_2/5% MeOH) to afford 29 mg (68%) of oily **38**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53 (t, J = 7.5 Hz, 3 H, 8-H), 0.86–1.05 (m, 2 H, 3-H), 1.19–1.51 (m, 6 H, 2-, 4-, 7-H), 2.43 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.55 (dt, J = 4.5, 10, 10 Hz; 1 H, 5-H), 3.24 (m, 2 H, 1-H), 3.45 (t, J = 7 Hz, 2 H, NCH_2CH_2Cl), 4.13 (t, J = 7 Hz, 2 H, NCH_2CH_2Cl), 4.71 (br s, 2 H, OH), 6.65 (br t, 1 H, NH), 6.78 (2 d, J = 8.5 Hz, 4 H, ArH), 7.01 (d, J = 8.5 Hz, ArH); MS (280 °C) m/z 382 (M$^+$ – NO – Cl) 339 (M$^+$ – $HON_2CH_2CH_2Cl$), 311, 309, 284, 247, 204, 135, 107, 56, 36; negative FAB-MS m/z 419/417 (M$^+$ – NO), 381, 339, 338, 312, 275, 211, 183; exact mass calcd for $C_{23}H_{30}N_2O_3$ 382.22564, found 382.22563; for $C_{21}H_{25}NO_3$ 339.18343, found 339.18288; for $C_{16}H_{22}N_2O_2{}^{37}Cl$ 311.13403, found 311.13575.

***erythro*-5,6-Bis(4-methoxyphenyl)-*N*-(3-hydroxypropyl)-1-octylamine (41).** A THF solution of 1.30 g (2.9 mmol) of amide **25** was reduced with 0.16 g (4.3 mmol) of LAH as described for **31** to afford 0.75 g (65%) of **41**: mp 154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.51 (t, J = 7.5 Hz, 3 H, 8-H), 0.91 (m, 2 H, 3-H), 1.30 (m, 4 H, 4-, 7-H), 1.55 (m, 2 H, 2-H), 1.88 (m, 2 H, 2′-H), 2.42 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.54 (m, 1 H, 5-H), 2.62 (t, 2 H, 1-H), 2.95 (t, 2 H, 1′-H), 3.67 (t, 2 H, 3′-H), 3.80 (s, 6 H, OCH_3), 6.83 (2 d, J = 8.5 Hz, 4 H, ArH), 7.05 (2 d, J = 8.5 Hz, 4 H, ArH); positive FAB-MS m/z 400 (MH$^+$).

***N*,*N*-Bis(2-chloroethyl)-*N*′-(*erythro*-5,6-bis(4-methoxyphenyl)-1-octyl)-*N*′,*O*-propylenephosphoric Acid Ester Diamide (43).** A solution of 194 mg (0.49 mmol) of *N*-(3-hydroxypropyl)octylamine **41** and 164 mg (0.63 mmol) of *N*,*N*-bis(2-chloroethyl)phosphoric acid dichloride[31] (**42**) in 15 mL of dry pyridine was stirred for 12 h under nitrogen. The solvent was removed under reduced pressure and the residue treated with

methanol and again evaporated. The residue was taken up in 30 mL of dichloromethane, washed with water, dried (Na_2SO_4), evaporated, and purified by TLC (dichloromethane/5% methanol) to afford 268 mg (94%) of oily **43**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52 (t, 3 H, 8-H), 0.87 (m, 2 H, 3-H), 1.23–1.37 (m, 6 H, 2-, 4-, 7-H), 1.70–1.94 (m, 2 H, $PNCH_2CH_2CH_2O$), 2.44 (dt, 1 H, 6-H), 2.55 (m, 1 H, 5-H), 2.55–2.69 (m, 2 H, NCH_2), 2.91–3.09 (m, 2 H, NCH_2), 3.15–3.25 (m, 2 H, NCH_2), 3.31–3.42 (m, 2 H, NCH_2), 3.52 (m, 4 H, $N(CH_2CH_2Cl)_2$), 3.82 (s, 6 H, OCH_3), 4.09–4.36 (m, 2 H, $POCH_2R$), 6.86 (d, 4 H, ArH), 7.06 (2 d, 4 H, ArH); ^{31}P NMR (24.3 MHz, $CDCl_3$) δ 13.50 (s), 13.87 (s); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.19 (q, C-8), 25.05, 25.10 (t, C-3), 26.20, 26.26 (t, C-2), 27.17, 27.23 (t, C-7), 27.36, 27.43 (t, C-4), 34.17, 34.26 (t, $PNCH_2CH_2O$), 42.31 (t, 2 CH_2Cl), 46.44 (t, NCH_2CH_2Cl), 47.98 (t, NCH_2CH_2Cl), 49.40 (t, C-1, $PNCH_2(CH_2)_2O$), 51.46, 51.60 (d, C-5), 53.67, 53.76 (d, C-6), 55.20 (q, oCH_3), 66.88, 66.97 (t, $POCH_2$), 113.63, 113.68 (d, C-11, 13, 17, 19), 129.05, 129.13 (d, C-10, 14, 16, 20), 136.36, 136.47 (s, C-9, 15), 157.85 (s, C-12, 18), 1250 cm^{-1} (PO); MS (180 °C) m/z 584 (M^+, Cl = 35), 549, 481, 435, 273, 259, 211, 149; exact mass calcd for $C_{29}H_{43}N_2O_4Cl_2P$ 582.21808, found 582.21697.

***N,N*-Bis(2-chloroethyl)-*N'*-(*erythro*-5,6-bis(4-hydroxyphenyl)-1-octyl)-*N',O*-propylenephosphoric Acid Ester Diamide (44).** A solution of 130 mg (0.22 mmol) of cyclophosphamide **43** in 10 mL of dry dichloromethane was treated with 1 mL of a 1 M BBr_3 solution as described for **34**. After usual workup 121 mg (98%) of oily HEX-linked cyclophosphamide **44** was isolated: ^{1}H NMR (400 MHz, acetone-d_6) δ 0.51 (t, J = 7.5 Hz, 3 H, 8-H), 0.92 (m, 2 H, 3-H), 1.21–1.51 (m, 6 H, 2-, 4-, 7-H), 1.76–1.98 (m, 2 H, $PNCH_2CH_2CH_2O$), 2.48 (dt, 1 H, 6-H), 2.58 (m, 1 H, 5-H), 2.58–2.79 (m, 2 H, NCH_2), 2.97–3.13 (m, 2 H, NCH_2), 3.25–3.48 (m, 4 H, 2 NCH_2), 3.64 (t, 4 H, $N(CH_2CH_2Cl)_2$), 4.15 –4.30 (m, 2 H, $PNCH_2CH_2CH_2O$), 6.80 (2 d, 4 H, ArH), 7.06 (2 d, 4 H, ArH), 8.47 (2 s, 2 H, ArOH); ^{31}P NMR (162 MHz, acetone-d_6) δ 14.55 (s), 14.71 (s); ^{13}C NMR (100.6 MHz, acetone-d_6) δ 12.54 (t, C-8), 25.82 (t, C-3), 26.91 (t, C-2), 28.00 (t, C-7, C-4), 35.09 (t, $PNCH_2CH_2CH_2O$), 42.91 (t, CH_2Cl), 47.27 (t, NCH_2CH_2Cl), 48.73 (t, NCH_2CH_2Cl), 50.00 (t, C-1, $PNCH_2CH_2CH_2O$), 52.18 (d, C-5), 54.36 (d, C-6), 68.14 (t, $POCH_2$), 115.82 (d, C-11, 13, 17, 19), 129.45 (C-10, 14, 16, 20), 136.04 (s, C-9, 15), 156.54 (s, C-12, 18); MS (250 °C) m/z 421, 385, 359, 273, 254, 239, 149, 135, 120, 107, 92, 70, 57, 41. Anal. ($C_{27}H_{39}Cl_2N_2O_4P$) C, H, N.

***erythro*-5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]octanoic Acid (45).** A solution of 1.00 g (3.1 mmol) of acid **51**, 2.06 g (13.7 mmol) dimethyl-*tert*-butylsilyl chloride, and 1.56 (22.9 mmol) of imidazole in 5 mL of dry DMF was stirred under nitrogen at room temperature. After 12 h 1 mL of methanol was added and stirring was continued for 1 h. The mixture was diluted with 100 mL of diethyl ether and extracted three times with 10 mL of water. The organic phase was dried and evaporated under reduced pressure and crystallized from diethyl ether/petroleum ether to afford 1.58 mg (93%) of acid **45**: mp 105–106 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 6 H, CH_3Si), 0.51 (t, J = 7 Hz, 3 H, 8-H), 0.97 (s, 18 H, *tert*-butyl-H), 1.16–1.46 (m, 6 H, 3-, 4-, 7-H), 1.96–2.16 (m, 2 H, 2-H), 2.41 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.54 (m, 1 H, 5-H), 6.75 (d, J = 8.5 Hz, 4 H, ArH), 6.96 (2 d, J = 8.5 Hz, 4 H, ArH); IR (KBr) 1710 cm^{-1} (CO).

***erythro*-5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-1-octanol (46).** A mixture of 1.51 g (2.7 mmol) of acid **45** and 0.08 g (2.1 mmol) of LAH in 25 mL of absolute THF was stirred for 4 h. Workup was carried out as described for **31** to afford 1.27 g (86%) of alcohol **46**: mp 84–86 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.20 (s, 12 H, CH_3Si), 0.50 (t, J = 7 Hz, 3 H, 8-H), 1.00 (s, 18 H, *tert*-butyl-H), 1.10–1.62 (m, 8 H, 2-, 3-, 4-, 7-H), 2.56–2.69 (m, 2 H, 5, 6-H), 3.40 (t, J = 6 Hz, 2 H, 1-H), 6.77 (d, J = 8 Hz, 4 H, ArH), 6.94 (d, J = 8 Hz, 4, ArH).

***erythro*-5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-1-octyl Acetate (47).** A solution of 100 mg (0.18 mmol) of alcohol **46** in 3 mL of dry pyridine was acetylated with 0.3 mL (3.00 mmol) of acetic anhydride. Usual workup afforded 158 mg of crude acetate **47**, which was directly desilylated to **52**.

***erythro*-5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-1-octyl Chloroacetate (48).** To a solution of 158 mg (0.29 mmol) of alcohol **46** in 10 mL of absolute pyridine and 10 mL of absolute diethyl ether was added dropwise a solution of 0.04 mL (0.44 mmol) of chloroacetic acid chloride in 10 mL of absolute diethyl ether. After stirring for 1 h the solvent was removed under reduced pressure and the residue was dissolved in diethyl ether. The organic phase was washed with an aqueous solution of ammonium chloride and water, dried, and evaporated. The oily product **48** was separated from the mixture by TLC, the polar fraction yielding 75 mg: ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.2 (s, 12 H, CH_3Si), 0.52 (t, J = 7 Hz, 3 H, 8-H), 1.03 (s, 18 H, *tert*-butyl-H), 0.82–1.70 (m, 8 H, 2-, 3-, 4-, 7-H), 0.82–1.70 (m, 8 H, 2-, 3-, 4-, 7-H), 2.27–2.67 (m, 2 H, 5-, 6-H), 3.9 (s, 2 H, $COCH_2Cl$), 4.0 (m, 2 H, 1-H), 6.80 (d, J = 8 Hz, 4 H, ArH), 7.03 (d, J = 8 Hz, 4 H, ArH).

***erythro*-5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-1-octyl Mesylate (49).** A solution of 134 mg (0.25 mmol) of alcohol **46** in 4 mL of pyridine was mesylated with 0.1 mL (1.24 mmol) of mesyl chloride by standard procedures to afford 120 mg (78%) of **49**, which was directly desilylated.

***erythro*-5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-1-octyl Tosylate (50).** A solution of 138 mg (0.25 mmol) of alcohol **46** in 4 mL of dry pyridine was tosylated with 255 mg (1.34 mmol) of tosyl chloride to yield 107 mg (60%) of crude product which was directly desilylated.

(5*S,6*R**)-5,6-Bis(4-hydroxyphenyl)octanoic Acid (51).** Two grams (5.6 mmol) of dimethyl ether **2** was treated at –50 °C with 0.5 mL of BBr_3 (5.6 mmol) as described for **11** to afford 1.71 g (93%) of **51**: mp 101 °C; ^{1}H NMR (400 MHz, $CDCl_3$/dioxane) δ 0.52 (t, J = 7 Hz, 3 H, 8-H), 1.18–1.45 (m, 6 H, 3-, 4-, 7-H), 2.07 (m, 2 H, 2-H), 2.42 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.57 (dt, J = 4, 10, 10 Hz, 1 H, 5-H), 6.74 (d, J = 8.5 Hz, 4 H, ArH), 7.00 (2 d, J = 8.5 Hz, 4 H, ArH); IR (KBr) 1700 cm^{-1} (COOH); MS (140 °C) m/z 328 (6, M^+), 193 (81), 175 (18), 165 (6), 147 (18), 135 (100); exact mass calcd for $C_{20}H_{24}O_4$ 328.16744, found 328.1674.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl Acetate (52).** Desilylation of acetate **47** (see **54**) afforded 36 mg (60%) of bisphenol **52**: mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, J = 7 Hz, 3 H, 8-H), 0.96 (m, 2 H, 3-H), 1.18–1.53 (m, 6 H, 2-, 4-, 7-H), 1.96 (s, 3 H, $COCH_3$), 2.45 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.56 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.85 (m, 2 H, 1-H), 9.97 (br s, 2 H, OH), 6.80 (d, J = 8.5 Hz, 4 H, ArH), 7.01 (d, 2, J = 8.5 Hz, 4 H, ArH); IR (CH_2Cl_2) 3580 (OH), 1730 cm^{-1} (CO); MS (130 °C) m/z 356 (2, M^+), 221 (83), 179 (20), 161 (96), 149 (20), 135 (100). Anal. ($C_{22}H_{28}O_4$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl Chloroacetate (53).** A solution of 75 mg (0.12 mmol) of chloroacetate **48** in 5 mL of THF (Teflon block) was treated with 100 mg of KF and ca. 30 mg of 18-crown-6 and stirred for 0.5 h. The product was purified by TLC and crystallized from diethyl ether/petroleum ether: yield 29 mg (61%) of phenol **53**; mp 119–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, J = 7 Hz, 3 H, 8-H), 0.96 (m, 2 H, 3-H), 1.19–1.75 (m, 6-H, 2-, 4-, 7-H), 2.44 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.55 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 4.86 (s, 2 H, $COCH_2Cl$), 4.95 (m, 2 H, 1-H), 4.78 (br s, 2 H, OH), 6.86 (d, J = 8 Hz, 4 H, ArH), 7.01 (d, J = 8 Hz, 4 H, ArH); MS (160 °C) m/z 392/390 (M^+), 284, 257, 255, 228, 213, 185, 149, 135 (100), 129, 111, 97, 73, 69, 57, 55, 43, 41. Anal. ($C_{22}H_{27}O_4Cl$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl Mesylate (54).** Crude mesylate **49** (107 mg, 0.15 mmol) was desilylated as described for **52** to yield 64 mg (89%) of oily bisphenol **54**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, J = 7 Hz, 3 H, 8-H), 1.01 (m, 2 H, 3-H), 1.19–1.74 (m, 6 H, 2-, 4-, 7-H), 2.44 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.53 (dt, J = 4.0, 10, 10 Hz, 1 H, 5-H), 2.87 (s, 3 H, OSO_2CH_3), 3.99 (m, 2 H, 1-H), 4.88 (br s, 2 H, OH), 6.79 (2 d, J = 8.5 Hz, 4 H, ArH), 7.02 (2 d, J = 8.5 Hz, 4 H, ArH); IR (acetone) 1265, 1180 cm^{-1} (SO_3); MS (200 °C) m/z 294, 293, 257, 197, 161, 149, 135. Anal. ($C_{21}H_{28}O_5S$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl Tosylate (55).** The desilylation of **50** afforded 64 mg (89%) of oily bisphenol **55**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52 (t, J = 7.5 Hz, 3 H, 8-H), 0.91 (m, 2 H, 3-H), 1.14–1.52 (m, 6 H, 2-, 4-, 7-H), 2.40 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.45 (s, 3 H, CH_3), 2.49 (dt, J = 4.5, 10, 10 Hz, 1 H, 5 H), 3.79 (m, 2 H, 1-H), 4.92 (s, 2 H, OH), 6.79 (2 d, J = 8.5, 4 H, ArH), 6.98 (2 d, J = 8.5 Hz, 4 H, ArH); IR (acetone) 1265, 1180 cm^{-1} (SO_3); MS (275 °C) m/z 468 (M^+), 457, 431, 363, 333, 297, 267, 203, 172. Anal. ($C_{27}H_{32}O_5S$) C, H.

***erythro*-Benzyl 5,6-Bis[4-(benzyloxy)phenyl]octanoate (56).** A solution of 3.80 g (12 mmol) of acid **51** in 50 mL of dry THF was treated with 5.5 g (49 mmol) of potassium *tert*-butoxide and 4.50 mL (38 mmol) of benzyl bromide. After 4 h at reflux the solution was diluted with 200 mL of diethyl ether, washed with water and diluted HCl, dried, and evaporated. Crystallization from diethyl ether/petroleum ether afforded 6.7 g (97%) of benzyl ester **56**: mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, 3 H, 8-H), 1.18–1.46 (m, 6 H, 3-, 4-, 7-H), 2.11 (m, 2 H, 2-H), 2.45 (dt, 1 H, 6-H), 2.58 (m, 1 H, 5-H), 5.98 (s, 2 H, $COOCH_2Ph$), 5.03 (s, 4 H, $ArOCH_2Ph$), 6.92 (d, 4 H, ArH), 7.04 (2 d, 4 H, ArH), 7.22–7.45 (m, 15 H, phenyl-H), 1710 cm^{-1} (CO).

Methyl *erythro*-5,6-Bis(4-hydroxyphenyl)octanoate (57). A solution of 1.00 g (3.1 mmol) acid **51** in 50 mL of diethyl ether was treated with a 0.5 M ethereal solution of diazomethane so that the yellow color of the solution persisted for 2 min. The solvent and excess diazomethane were removed under reduced pressure and the residue crystallized from dichloromethane to yield 0.99 g (95%) of ester **57**: mp 109–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (t, J = 7.5 Hz, 3 H, 8-H), 1.18–1.46 (m, 6 H, 3-, 4-, 7-H), 2.00–2.18 (m, 2 H, 2-H), 2.44 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.57 (m, 1 H, 5-H), 3.55 (s, 3 H, OCH_3), 4.89, 4.93 (s, 1 H, ArOH), 6.78 (d, J = 8.5 Hz, 4 H, ArH), 7.00 (2 d, J = 8.5 Hz, 4 H, ArH); IR 1710 cm^{-1} (CO); MS (120 °C) m/z 342 (2 M$^+$), 311 (10), 293 (6), 279 (2), 207 (84), 175 (46), 147 (16), 135 (86), 133 (100). Anal. ($C_{21}H_{26}O_4$) C, H.

***erythro*-5,6-Bis[4-(benzyloxy)phenyl]-1-octanol (58).** A solution of 1.82 g (3.04 mmol) of benzyl ester **57** in 20 mL of THF was reduced with 0.06 g (1.52 mmol) of LAH as described for **3** to give 1.49 g (99%) of alcohol **58**: mp 123–124 °C (diethyl ether/petroleum ether); ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.49 (t, 3 H, 8-H), 0.78–1.56 (m, 8 H, 2-, 3-, 4-, 7-H), 2.30–2.67 (m, 2 H, 5-, 6-H), 3.38 (t, J = 3 Hz, 2 H, 1-H), 5.0 (s, 4 H, $ArOCH_2Ph$), 6.89 (d, J = 8 Hz, 4 H, ArH), 7.04 (d, J = 8 Hz, 4 H, ArH), 7.27–7.51 (m, 10 H, phenyl-H); MS (250 °C) m/z 494 (M$^+$), 493, 492, 269, 225.

***erythro*-5,6-Bis[4-(benzyloxy)phenyl]-1-octyl Iodide (59).** Alcohol **58** (1.75 g, 3.54 mmol) was reacted with 3.68 g (10.6 mmol) of dicyclohexylcarbodiimidium iodide[23] as described for **8** to yield 1.95 g (88%) of iodide **59**: mp 119 °C (diethyl ether/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.54 (t, 3 H, 8-H), 0.99 (m, 2 H, 3-H), 1.18–1.72 (m, 6 H, 2-, 4-, 7-H), 2.45 (dt, 1 H, 6-H), 2.56 (m, 1 H, 5-H), 2.94 (m, 2 H, 1-H), 5.05, 5.06 (each s, each 2 H, $ArOCH_2$), 6.94 (d, 4 H, ArH), 7.07 (2 d, 4 H, ArH), 7.32–7.47 (m, 10 H, phenyl-H).

***erythro*-5,6-Bis[4-(benzyloxy)phenyl]-1-octyl 2-Hydroxyethyl Ether (60).** A solution of 0.2 mL (3.59 mmol) of ethylene glycol in 10 mL of dry THF was treated with 72 mg (1.79 mmol) of sodium hydride (60% in oil) and stirred for 0.5 h at 20 °C and then 370 mg (0.61 mmol) of iodide **59** was added. The product was crystallized from diethyl ether after usual workup to afford 262 mg (79%) of **60**: mp 129–130 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (t, 3 H, 8-H), 0.96 (m, 2 H, 3-H), 1.19–1.47 (m, 6 H, 2-, 4-, 7-H), 2.46 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.58 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.24 (m, 2 H, 1-H), 3.40 (m, 2 H, $ROCH_2CH_2OH$), 3.63 (m, 2 H, CH_2OH), 5.04 (s, 2 H, $ArOCH_2Ph$), 6.93 (2 d, J = 8.5 Hz, 4 H, ArH), 7.06 (2 d, J = 8.5 Hz, 4 H, ArH), 7.31–7.48 (m, 10 H, phenyl-H). Anal. ($C_{36}H_{42}O_4$) C, H.

***erythro*-5,6-Bis[4-(benzyloxy)phenyl]-1-octyl Diethylene Glycol Monoether (61).** From 370 mg (0.61 mmol) of iodide **59**, 0.3 mL (3.16 mmol) of diethylene glycol, and 38 mg (1.58 mmol) of sodium hydride, 277 mg (78%) of **61** was prepared as described for **60**: mp 102–103 °C (diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52 (t, 3 H, 8-H), 0.95 (m, 2 H, 3-H), 1.18–1.49 (m, 6 H, 2-, 4-, 7-H), 2.45 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.58 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.22 (m, 2 H, 1-H), 3.45 (m, 2 H, OCH_2CH_2OR), 3.57 (m, 4 H, $ROCH_2CH_2OCH_2CH_2OH$), 3.67 (m, 2 H, CH_2OH), 5.06 (2 s, 4 H, $ArOCH_2Ph$), 6.92 (d, 4 H, ArH), 7.05 (2 d, 4 H, ArH), 7.31–7.46 (m, 10 H, phenyl-H). Anal. ($C_{38}H_{46}O_5$) C, H.

***erythro*-5,6-Bis[4-(benzyloxy)phenyl]-1-octyl Triethylene Glycol Monoether (62).** From 370 mg (0.61 mmol) of iodide **59**, 0.3 mL (2.25 mmol) of triethylene glycol, and 45 mg (1.12 mmol) of sodium hydride, 285 mg (74%) of **62** was prepared as described for **60**: mp 79 °C (diethyl ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, J = 7.5 Hz, 3 H, 8-H), 0.95 (m, 2 H, 3-H), 1.20–1.47 (m, 6 H, 2-, 4-, 7-H), 2.45 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.57 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.22 (m, 2 H, 1-H), 3.39–3.77 (m, 12 H, $R(OCH_2CH_2)_3OH$), 5.06 (2 s, 4 H, OCH_2Ph), 6.92 (2 d, J = 8.5 Hz, 4 H, ArH), 7.05 (2 d, J = 8.5 Hz, 4 H, ArH), 7.30–7.50 (m, 10 H, phenyl-H). Anal. ($C_{40}H_{50}O_6$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl 2-Chloroethyl Ether (63).** A solution of 55 mg (0.15 mmol) of alcohol **69** was chlorinated with 0.2 mL of thionyl chloride as described for **6** to yield after TLC purification (dichloromethane/2% methanol) 46 mg (80%) of chloride **63**: mp 108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.52 (t, 3 H, 8-H), 0.97 (m, 2 H, 3-H), 1.22–1.44 (m, 6 H, 2-, 4-, 7-H), 2.43 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.55 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.25 (m, 2 H, CH_2Cl), 3.53 (m, 4 H, CH_2OCH_2), 4.67 (s, 2 H, ArOH), 6.79 (2 d, 4 H, ArH), 7.00 (2 d, 4 H, ArH); MS (140 °C) m/z 376 (17, M$^+$), 327 (9), 241 (39), 161 (97), 135 (88), 120 (8), 107 (100); exact mass calcd for $C_{22}H_{29}O_3{}^{35}Cl$ 376.1805, found 376.1815. Anal. ($C_{22}H_{29}O_3Cl$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl 2-(2-Chloroethoxy)ethyl Ether (64).** Alcohol **70** (46 mg, 0.11 mmol) was chlorinated with 0.2 mL of thionyl chloride as described for **6** to yield 38 mg (79%) of oily chloride **64**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.52 (t, 3 H, 8-H), 0.95 (m, 2 H, 3-H), 1.20–1.44 (m, 6 H, 2-, 4-, 7-H), 2.42 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.54 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.23 (t, 2 H, CH_2Cl), 3.47 (m, 2 H, 1-H), 3.58 (m, 4 H, OCH_2CH_2OR), 3.69 (m, 2 H, OCH_2CH_2Cl), 4.81, 4.85 (s, 1 H, ArOH), 6.77 (2 d, 4 H, ArH), 7.00 (2 d, 4 H, ArH); MS (160 °C) m/z 422/420 (13/40, M$^+$, Cl = 37/35), 327 (13), 285 (51), 161 (99), 135 (87). Anal. ($C_{24}H_{33}O_4Cl$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl 2-[(2-Chloroethoxy)ethoxy]ethyl Ether (65).** Alcohol **71** (63 mg, 0.14 mmol) was chlorinated with 0.2 mL of thionyl chloride as described for **6** to yield 51 mg (77%) of oily chloride **65**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.52 (t, 3 H, 8-H), 0.85–0.98 (m, 2 H, 3-H), 1.20–1.42 (m, 6 H, 2-, 4-, 7-H), 2.42 (dt, J = 3.5, 10, 10 Hz, 1 H, 6-H), 2.53 (dt, J = 4.5, 10, 10 Hz, 1 H, 5-H), 3.19 (t, 2 H, CH_2Cl), 3.40–3.77 (m, 12 H, $RCH_2(OCH_2CH_2)_2OCH_2CH_2Cl$), 5.01, 5.20 (each s, each 1 H, ArOH), 6.77 (2 d, 4 H, ArH), 7.00 (d, 4 H, ArH); MS (165 °C) m/z 464 (M$^+$), 329, 161, 135, 107 (100); exact mass calcd for $C_{17}H_{26}O_4Cl$ 329.1520, found 329.1515.

***erythro*-5,6-Bis(4-hydroxyphenyl)octanol (66).** A solution of 135 mg (0.40 mmol) of ester **57** in 50 mL of toluene and 5 mL of dry diethyl ether was treated at −70 °C with 0.4 mL of diisobutylaluminum hydride (DIBAH) (1.2 M in toluene) for 2.5 h. An aqueous solution of citric acid was added and the mixture was repeatedly extracted with diethyl ether. The solution was dried and evaporated and the residue separated by TLC (dichloromethane/5% methanol) to afford 54 mg (0.24 mmol) of starting ester **57** and 63 mg (0.20 mmol) of aldehyde **66** (85% based on converted ester): mp 141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (t, J = 7 Hz, 3 H, 8-H), 1.20–1.37 (m, 6 H, 3-, 4-, 7-H), 2.17 (m, 2 H, 2-H), 2.44 (dt, 1 H, 6-H), 2.55 (m, 1 H, 5-H), 4.70 (s, 2 H, ArOH), 6.78 (2 d, J = 8.5 Hz, 4 H), 7.00 (2 d, J = 8.5 Hz, 4 H, ArH), 9.53 (t, J = 2 Hz, 1 H, 1-H); IR (KBr) 1715 cm^{-1} (CO); MS (160 °C) m/z 312 (1, M$^+$), 212 (3), 177 (41), 135 (98); exact mass calcd for $C_{20}H_{24}O_3$ 312.1725, found 312.1739.

***erythro*-6,7-Bis(4-hydroxyphenyl)-1-nonene (67).** A solution of 457 mg (1.28 mmol) of triphenylmethylphosphonium bromide in 10 mL of dry THF was treated with 234 mg (1.92 mmol) of potassium *tert*-butoxide. A solution of 100 mg (0.32 mmol) of aldehyde **66** in 5 mL of THF was then added and the mixture was stirred for 2 h at 20 °C. The mixture was acidified with an aqueous solution of citric acid and extracted with diethyl ether. The ethereal solution was dried and evaporated and the residue purified by TLC to afford 51 mg (51%) of olefin which crystallized from diethyl ether: mp 162 °C; ^{1}H NMR (300 MHz, $CDCl_3$/acetone-d_6) δ 0.52 (t, J = 7.3 Hz, 3 H, 9-H), 0.96–1.05 (m, 2 H, 4-H), 1.18–1.43 (m, 4 H, 5-, 8-H), 1.70–1.89 (m, 2 H, 3-H), 2.42 (dt, 1 H, 7-H), 2.55 (dt, 1 H, 6-H), 4.75–4.84 (m, 2 H, 1-H), 5.58 (ddt, J = 6.5, 10, 17 Hz, 1 H, 2-H), 6.90 (d, J = 8.5 Hz, 4 H, ArH), 7.00 (2 d, J = 8.5 Hz, 4 H, ArH), 7.43, 7.44 (each s, each 1 H, OH); MS (80 °C) m/z 310 (0.7, M$^+$), 212 (1), 175 (37), 135 (77), 119 (14), 107 (100); exact mass calcd for $C_{21}H_{26}O_2$ 310.19327, found 310.19304.

***erythro*-6,7-Bis(4-hydroxyphenyl)-1,2-epoxynonane (68).** A solution of 32 mg (0.10 mmol) of olefin **67** and 21 mg (0.12 mmol) of *m*-chloroperbenzoic acid in dry diethyl ether was stirred for

5 h at 20 °C. The solution was reduced to one-third of the volume, filtered to remove *m*-chlorobenzoic acid, and evaporated and the residue was purified by TLC (dichloromethane/5% methanol) to yield 21 mg (62%) of epoxide **68**: mp 50–51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.52 (t, *J* = 7.5 Hz, 3 H, 9-H), 1.07–1.39 (m, 8 H, 3-, 4-, 5-, 7-H), 2.30 (m, 1 H, 1-H), 2.44 (dt, *J* = 3.5, 10, 10 Hz, 1 H, 7-H), 2.55 (dt, *J* = 4.5, 10, 10 Hz, 1 H, 6-H), 2.60 (m, 1 H, 1-H), 2.67 (m, 1 H, 2-H), 4.66 (br s, 2 H, ArOH), 6.78 (2 d, *J* = 8.5 Hz, 4 H, ArH), 7.01 (2 d, *J* = 8.5 Hz, 4 H, ArH); MS (250 °C) *m/z* 326 (M^+), 297, 241, 227, 212, 191; exact mass calcd for $C_{21}H_{26}O_3$ 326.1882, found 326.1875.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-octyl 2-Hydroxyethyl Ether (69).** A solution of 244 mg (0.45 mmol) of benzyl ether **60** in 100 mL of cyclohexane was hydrogenated for 4 h in the presence of ca. 50 mg of Pd/C. The catalyst was filtered off, the filtrate was evaporated, and the residue was crystallized from diethyl ether to yield 162 mg (100%) of bisphenol **69**: mp 114–115 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 0.51 (t, *J* = 7.5 Hz, 3 H, 8-H), 0.97 (m, 2 H, 3-H), 1.21–1.40 (m, 6 H, 2-, 4-, 7-H), 2.46 (dt, *J* = 3.5, 10, 10 Hz, 1 H, 6-H), 2.61 (m, 1 H, 5-H), 3.61 (dt, 2 H, 1-H), 3.32 (m, 2 H, $ROCH_2CH_2OH$), 3.51 (m, 2 H, CH_2OH), 6.81 (2 d, *J* = 8.5 Hz, 4 H, ArH), 7.05 (2 d, *J* = 8.5 Hz, 4 H, ArH), 8.08 (s, 2 H, ArOH); MS (150 °C) *m/z* 358 (35, M^+), 241 (16), 223 (61), 161 (100), 147 (8), 135 (87). Anal. $C_{22}H_{30}O_4$) C, H.

***erythro*-5,6-Bis(4-hydroxyphenyl)octyl Diethylene Glycol Monoether (70).** Benzyl ether **61** (254 mg, 0.44 mmol) was hydrogenated as described for **69** to afford 158 mg (90%) of oily bisphenol **70**: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.51 (t, 3 H, 8-H), 0.97 (m, 2 H, 3-H), 1.21–1.42 (m, 6 H, 2-, 4-, 7-H), 2.47 (dt, *J* = 3.5, 10, 10 Hz, 1 H, 6-H), 2.60 (dt, *J* = 5.0, 10, 10 Hz, 1 H, 5-H), 3.18 (dt, 2 H, 1-H), 3.38 (m, 2 H, OCH_2R), 3.47 (m, 4 H, $OCH_2CH_2OCH_2CH_2OH$), 3.58 (m, 2 H, CH_2OH), 6.79 (2 d, *J* = 8.5 Hz, 4 H, ArH), 7.06 (2 d, *J* = 8.5 Hz, 4 H, ArH, 8.07 (s, 2 H, ArOH); MS (190 °C) *m/z* 402 (5, M^+), 345 (8), 267 (17), 207 (8), 161 (100); exact mass calcd for $C_{24}H_{34}O_5$ 402.2406, found 402.2385.

***erythro*-5,6-Bis(4-hydroxyphenyl)-1-triethylene Glycol Monooctyl Ether (71).** Benzyl ether **62** (268 mg, 0.43 mmol) was hydrogenated as described for **69** to yield 173 mg (91%) of oily bisphenol **71**: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.51 (t, *J* = 7.5 Hz, 3 H, 8-H), 0.98 (m, 2 H, 3-H), 1.20–1.42 (m, 6 H, 2-, 4-, 7-H), 2.47 (dt, *J* = 3.5, 10, 10 Hz, 1 H, 6-H), 2.60 (dt, *J* = 5, 10, 10 Hz, 1 H, 5-H), 3.18 (dt, 2 H, 1-H), 3.36–3.63 (m, 12 H, $R(OCH_2CH_2)_3OH$), 6.81 (2 d, *J* = 8.5 Hz, 4 H, ArH), 7.07 (2 d, *J* = 8.5 Hz, 4 H, ArH), 8.08 (s, 2 H, ArOH); MS (270 °C) *m/z* 447 (MH^+), 329, 311, 161, 151, 135; exact mass calcd for $C_{26}H_{39}O_6$ 447.27464, found 447.27411.

Registry No. (±)-*erythro*-**1**, 120578-46-3; (±)-*threo*-**1**, 120579-13-7; (±)-**2**, 120578-47-4; (±)-**3**, 120608-65-3; (±)-**4**, 120578-48-5; (±)-**5**, 120578-49-6; (±)-**6**, 120608-66-4; (±)-**8**, 120578-50-9; (±)-**9**, 120578-51-0; (±)-**10**, 120578-52-1; (±)-*threo*-**10**, 120579-15-9; (±)-**11**, 120578-53-2; (±)-**12**, 120578-54-3; (±)-**13**, 120578-55-4; (±)-**14**, 120578-56-5; (±)-**15**, 120578-57-6; (±)-**16**, 120578-58-7; (±)-**17**, 120578-59-8; (±)-**18**, 120578-60-1; (±)-**19**, 120578-61-2; (±)-**20**, 120578-62-3; (±)-**21**, 120578-63-4; (±)-**22**, 120578-64-5; (±)-**23**, 120578-65-6; (±)-**24**, 120578-66-7; (±)-**25**, 120578-67-8; (±)-**26**, 120578-68-9; (±)-**27**, 120578-69-0; (±)-**28**, 120578-70-3; (±)-**29**, 120578-71-4; (±)-**30**, 120578-72-5; (±)-**31**, 120578-73-6; (±)-**32**, 120578-74-7; (±)-**33**, 120578-75-8; (±)-**34**, 120578-76-9; (±)-**35**, 120578-77-0; (±)-**36**, 120579-12-6; (±)-**36**·HCl, 120578-78-1; (±)-**37**, 120579-11-5; (±)-**37**·HCl, 120578-79-2; (±)-**38**, 120578-80-5; **40**, 60784-40-9; (±)-**41**, 120578-81-6; **42**, 127-88-8; (±)-**43**, 120578-82-7; (±)-**44**, 120578-83-8; (±)-**45**, 120578-84-9; (±)-**46**, 120578-85-0; (±)-**47**, 120578-86-1; (±)-**48**, 120578-87-2; (±)-**49**, 120578-88-3; (±)-**50**, 120578-89-4; (±)-**51**, 120578-90-7; (±)-**52**, 120578-91-8; (±)-**53**, 120578-92-9; (±)-**54**, 120578-93-0; (±)-**55**, 120578-94-1; (±)-**56**, 120578-95-2; (±)-**57**, 120578-96-3; (±)-**58**, 120578-97-4; (±)-**59**, 120578-98-5; (±)-**60**, 120578-99-6; (±)-**61**, 120579-00-2; (±)-**62**, 120579-01-3; (±)-**63**, 120579-02-4; (±)-**64**, 120579-03-5; (±)-**65**, 120579-04-6; (±)-**66**, 120579-05-7; (±)-**67**, 120579-06-8; **68**, 120579-07-9; (±)-**69**, 120579-08-0; (±)-**70**, 120579-09-1; (±)-**71**, 120579-10-4; 4-$MeOC_6H_4C(Et)$=$C(n$-$C_4H_9)C_6H_4OMe_4$, 120579-14-8; $H_2N(CH_2)_2CO_2Et$·HCl, 4244-84-2; $(C_6H_5)_3P^+Me\ Br^-$, 1779-49-3; diethanolamine, 111-42-2.

Synthesis and Biological Evaluation of Certain 3-β-D-Ribofuranosyl-1,2,4-triazolo[4,3-*b*]pyridazines Related to Formycin Prepared via Ring Closure of Pyridazine Precursors

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All three amino-substituted 3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*b*]pyridazines (**5**, **19**, and **20**) structurally related to formycin A were prepared and tested for their antitumor and antiviral activity in cell culture. Dehydrative coupling of 4-amino-5-chloro-3-hydrazinopyridazine (**7**) with 3,4,6-tri-*O*-benzoyl-2,5-anhydro-D-allonic acid (**6**) in the presence of DCC and subsequent thermal ring closure of the reaction product (**8**) provided 8-amino-7-chloro-3-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-1,2,4-triazolo[4,3-*b*]pyridazine (**9**). Dehalogenation of **9**, followed by debenzoylation, gave the formycin congener 8-amino-3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*b*]pyridazine (**5**). Similar condensation of 5-amino-4-chloro-3-hydrazinopyridazine (**13**) with **6** and dehalogenation of the cyclized product (**16**), followed by debenzoylation, gave the isomeric 7-amino-3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*b*]pyridazine (**19**). DCC-mediated coupling of **6** with 6-chloro-3-hydrazinopyridazine (**12**), followed by ammonolysis of the cyclized product (**21**) with liquid NH_3, provided a convenient route to 6-amino-3-β-D-ribofuranosyl-1,2,4-triazolo[4,3-*b*]pyridazine (**20**). The structural assignment of **5** was made by single-crystal X-ray diffraction analysis. Compounds **5**, **19**, **20**, and certain deprotected nucleoside intermediates were evaluated against L1210, WI-L2, and CCRF-CEM tumor cell lines, as well as against DNA and RNA viruses in culture. These compounds did not exhibit any significant antitumor or antiviral activity in vitro.

Since the isolation[1,2] and structural elucidation[3,4] of the naturally occurring C-nucleoside antibiotic formycin A (7-amino-3-β-D-ribofuranosyl-1*H*-pyrazolo[4,3-*d*]pyrimidine, **1**), several reports have appeared in the literature describing its diverse biological properties.[5-7] Formycin

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