and the precipitated solid was collected by filtration. Recrystallization from cyclohexane gave 4.3 g (100%) of **32**.

Diethyl [2-[4-(Benzothiazol-2-yl)phenoxy]ethyl]-phosphonate (14). A mixture of chloride **32** (2.0 g, 0.0069 mol) and triethyl phosphite (3 mL) was heated at 190–200 °C for 5 h. After the reaction mixture had cooled, the precipitated solid was collected by filtration. The crude phosphonate was chromatographed on a silica gel column by eluting with a benzene/EtOAc mixture to give 1.5 g (56%) of **14**. Recrystallization from cyclohexane yielded **14** as colorless needles: mp 93.0–94.0 °C.

Effect on Coronary Flow in the Isolated Guinea Pig Heart. Male guinea pigs of 400–500-g body weight were killed and exsanguinated and promptly thoracotomized. After cannulation of the ascending aorta, the heart was enucleated. The isolated heart was then perfused with Krebs–Henseleit fluid which was oxygenated with a gaseous mixture of 95% O_2 and 5% CO_2, at 34 ± 1 °C under a perfusion pressure of 60 cm of H_2O by the methods of Langendorff. The test compound, dissolved in propylene glycol to a concentration of 100 μg/mL, was then infused at a rate of 0.1 mL/min. The coronary flow was measured with a square wave electromagnetic flow meter (Nihon Kohden, MF-26) with an extracorporal probe (Nihon Kohden, FE) set at the top of the cannula and recorded with a multipurpose polygraph (Nihon Kohden, RM-85). The coronary flows before and after infusion were measured, and the percentage gain in coronary flow was obtained.

Registry No. **2**, 41716-26-1; **3**, 120332-20-9; **4**, 2682-86-2; **5**, 41806-42-2; **6**, 120332-21-0; **7**, 120332-22-1; **8**, 120332-23-2; **9**, 120332-24-3; **10**, 83524-89-4; **11**, 120332-25-4; **12**, 120332-26-5; **13**, 120332-27-6; **14**, 120332-28-7; **15**, 41806-41-1; **16**, 41716-19-2; **17**, 67273-40-9; **18**, 2227-61-4; **19**, 120332-29-8; **20**, 23222-36-8; **21**, 60-23-1; **22**, 4434-13-3; **23**, 120332-30-1; **24**, 120332-31-2; **25**, 120332-32-3; **26**, 19654-19-4; **27**, 2182-80-1; **28**, 1660-94-2; **29**, 120332-33-4; **30**, 6265-55-0; **31**, 84396-09-8; **32**, 84396-10-1; triethyl phosphite, 122-52-1; 2-(benzimidazol-2-yl)-5-(bromomethyl)-pyridine, 120332-34-5; diethyl phosphite, 762-04-9; fostedil, 75889-62-2.

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

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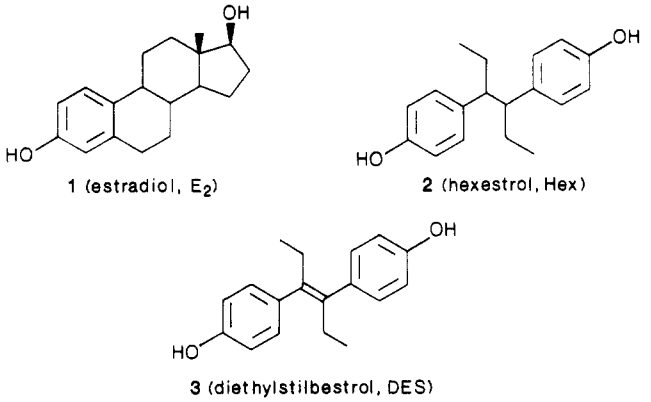
The syntheses of diethylstilbestrol derivatives with a C_4 side chain at the double bond bearing various functional and potentially alkylating groups (**9–25**, **38–40**, **43**, **44**) as well as the coupling product with daunorubicine (**41**) are described. Derivatives with *free* phenolic groups show easy isomerization to (*Z*)-stilbenes and styrenes, which could be minimized with silyl protecting groups. Estrogen receptor binding is decreased by polar groups such as carboxylic acids (**10**) as well as sterically demanding substituents.

The chemotherapy of cancer in its present form suffers from the fact that, in principle, no difference is made between normal and tumor cells, regardless of whether the drug belongs to the group of alkylants, enzyme inhibitors, or DNA intercalators.[1] A certain degree of selectivity is mainly due to the higher sensitivity of rapidly growing cells to various kinds of toxic compounds. Numerous efforts have been made to increase the selectivity toward cells and to decrease the systemic toxicity. A possibility for selectivity is offered by hormone-dependent tumors, such as certain breast tumors, which selectively concentrate natural and synthetic estrogens.[2] The idea to induce cyto*toxic* effects to hormone-dependent tumor cells by covalent linkage of N-mustard groups to the steroidal skeleton was tested in the late sixties.[3] Since that time many compounds have been synthesized and tested in which various cytotoxic groups were linked to estradiol[4–9] (**1**) (E_2), hexestrols[10–13] (**2**) (HEX), diethylstilbestrols[5,10–14] (**3**) (DES), or the antiestrogen tamoxifen[15] (Chart I).

A prerequisite for specificity of these cytotoxic agents is a sufficient binding of the drug to the estrogen receptor, which allows the selective uptake into the hormone sensitive cells (relative binding affinity compared to E_2 = 100%; RBA). Calculations on the basis of the number of receptors per cell (about 1000–10000) and the possible drug concentration show that the RBA value should be at least 1% of that of E_2.[16] However, chemical modification of estrogens usually produces a dramatic decrease in the binding affinity. Early work on the chemically easy derivatization of the hydroxy groups in E_2 (**1**), HEX (**2**), and

Chart I



DES (**3**) gave products with very low or no RBA, thus establishing the essential function of both hydroxy groups

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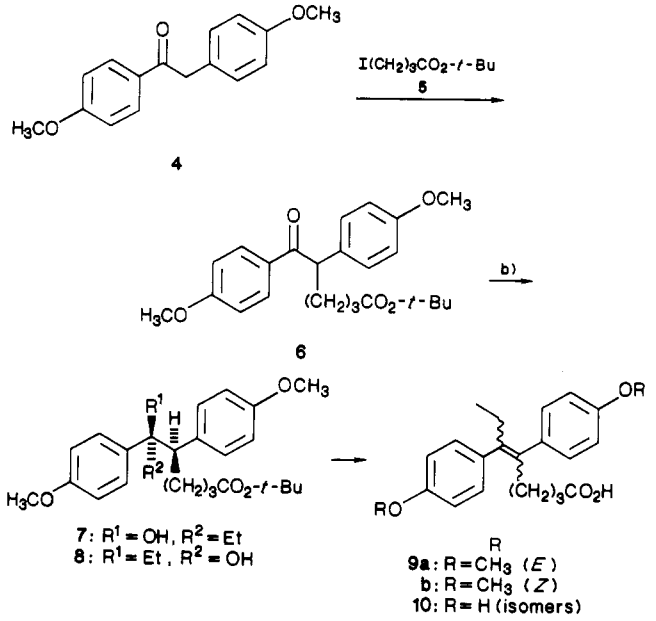
Scheme I

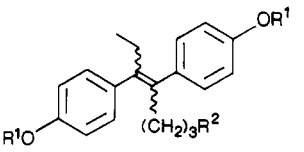


in receptor binding.[4,17] On the basis of these results and the fact that DES and HEX are known to have high RBA values[18] we worked out a program to investigate the chemistry and receptor binding affinity of DES and HEX derivatives bearing longer chains in the middle part of the molecule remote from the essential hydroxy groups. Of particular interest was the investigation of the influence of side-chain length and polarity of substituents. The present paper on DES and the folowing on HEX report our observations in this regard, including information on the chemical synthesis of such compounds about which little has yet been published.[19,20]

Chemistry

Starting Materials. The starting material for the synthesis of the side-chain DES derivatives was the acid **9** that was previously prepared in connection with a radioimmunoassay for DES.[21] The synthesis is outlined in Scheme I and starts with the commercially available deoxyanisoin (**4**) that was alkylated with iodo ester **5** to yield **6**[22] (for improvements on the original procedure, see the Experimental Section). The subsequent Grignard reaction of **6** with ethylmagnesium bromide gave a 92% yield of a 4:1 mixture of the threo and erythro esters **7** and **8**. Fortunately, the major isomer **7** could be isolated in pure form by crystallization. The stereocenters are lost on dehydration and both isomers **7** and **8** can be transformed to the corresponding stilbenes. On treatment with *p*-toluenesulfonic acid at 110 °C both dehydration and ester cleavage take place to afford a mixture of at least five compounds, the major components being the (*E*)- and (*Z*)-stilbenes **9a** and **9b** (65%) together with 35% of isomeric styrenes as shown by analysis of the 400-MHz ^{1}H NMR spectrum. A chromatographic purification of the most important (*E*)-stilbene methyl ether was possible. Styrene formation does normally not occur in the formation of DES, but it is known to take place with unsymmetrically substituted derivatives.[23] A simultaneous dehydration/ester and ether cleavage is effected by treatment with boron tribromide in dichloromethane[22] or with potassium hydroxide in ethylene glycol at 200 °C[24] to afford phenolic acid **10** (90%) as a mixture of isomers as shown in Scheme I.

Chart II



11-18: $R^1 = CH_3$
19-25: $R^1 = H$

	R_2
11/19	CH_2OH
12/20	CH_2Cl
13/21	CH_2I
14/22	CH_2OEt
15/23	CH_3
16/24	$(CH_2)_4CH_3$
17/25	$CONEt_2$
18:	CO_2-*t*-BuPh

Our first goal was the synthesis of the DES alkyl halides which are potential alkylants. To this end acids **9a**/**9b** were reduced to alcohol **11** (mixture of isomers) with lithium aluminum hydride in 94% yield and converted to chloride **12** with triphenylphosphine/carbon tetrachloride[25] (Chart II). It was possible to purify pure (*E*)-stilbene **12** and also the other derivatives **13**–**18** from the reaction mixtures containing (*Z*)-stilbenes and styrenes by using a special TLC technique (see the Experimental Section). (Structural assignment was based on the chemical shift of the methyl group in the ^{1}H NMR spectrum at 0.77 ppm, which is characteristic for the *E* configuration[26]). A one-step conversion of alcohol **11** to the corresponding iodide **13** was possible by using the method of Scheffold by treatment of **11** with *N*,*N*-dicyclohexyl-*N*-methyldicyclohexylcarbodiimide.[27] For binding studies it was of interest to include long-chain ethers, which were obtained by treatment of **11** with sodium hydride and ethyl iodide to afford the ethyl ether **14**. Longer aliphatic chains could be attached by alkylation of deoxyanisoin (**4**) with *n*-butyl bromide and *n*-octyl bromide followed by Grignardation with ethylmagnesium bromide and dehydration to provide intermediates **15** and **16**, respectively. The final stage of the reaction sequence was the liberation of the phenolic groups. Crystalline pure (*E*)-stilbenes **23** and **24** were isolated after methyl ether cleavage with BBr_3 or KOH.

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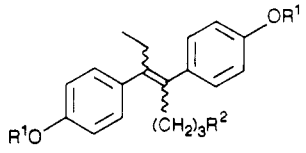
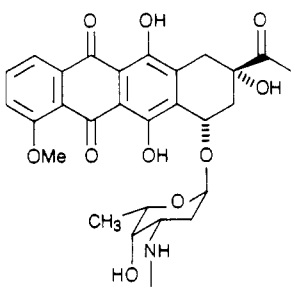
Chart III



26-37: R^1 = TBDMS
39-44: R^1 = H

R^2

26/10	COOH
27/38	CO_2CH_3
28/39	$CO_2C_6H_5$
29/40	$CO_2C_6H_4Cl$
30	$CO_2C_6H_5NO_2$
31	$CO_2C_6Cl_5$
32	$CONH(CH_2)_2OH$
33	$CON[(CH_2)_2OH]_2$
34/41	CONH-dau
35/19	CH_2OH
36/43	$CH_2SO_3CH_3$
37/44	$CH_2OCONHCH_2CH_2Cl$



42 (dau)

However, treatment of the alkali-labile halides **12** and **13** with BBr_3 and alcohol **11** and ether **14** with KOH at 200 °C resulted again in mixtures of (*E*)- and (*Z*)-stilbenes **19–22** as well as styrenes in a similar ratio previously observed for **10**.

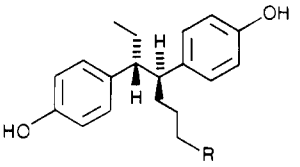
In order to study the chemical stability in comparison to similar N-mustards some amides and esters were prepared from acids **9a**/**9b**. The coupling of an activated *p*-nitrophenyl ester[28] with diethylamine afforded amide **17**. The corresponding 4-*tert*-butylphenyl ester **18** was synthesized in a similar manner. Chromatographic separation of the pure (*E*)-stilbene was possible, but BBr_3 treatment of **17** again gave a mixture of phenolic isomers. Careful analysis of the 400-MHz ^1H NMR spectrum showed the presence of about 60% of (*E*)-stilbene 17% of (*Z*)-stilbene, and 23% of styrenes. The easy *E*–*Z* isomerization of nonsteroidal estrogens is known,[29] but the isomerization to styrenes had no precedent. The extreme tendency of the unsymmetrically substituted DES derivatives toward double-bond isomerization made it necessary to liberate the phenols under much milder conditions.

The phenolic acid **10** (as a mixture of isomers) was silylated with *tert*-butyldimethylsilyl chloride and subsequent selective ester cleavage of a persilated intermediate gave acid **26** that was the starting material for a number of acyl derivatives listed in Chart III. Methyl ether **27** was obtained on treatment of **26** with diazomethane, and the substituted phenyl esters **28–31** were prepared with DCCI in the coupling reaction of acid **26** with the corresponding phenols. The pentachlorophenyl ester **31** proved to be an excellent precursor for the further preparation of acyl amides. Treatment with diethanolamine afforded the bis(hydroxyethyl)amide **33** accompanied by some mono(hydroxyethyl) amide **32** from impurities of the diethanolamine. All of these phenyl esters and amides could be chromatographically purified to the pure (*E*)-stilbenes.

In order to investigate the biological activity and RBA of DNA intercalators linked to estrogens, the antitumor antibiotic daunorubicin was reacted with the activated ester **31** to afford the N-coupled adduct **34**.

A number of DES derivatives were prepared from alcohol **35**, which is readily available by lithium aluminum hydride reduction of pure (*E*)-stilbene ester **27**. Mesylation of **35** gave mesylate **36**. A carbamidic β-chloroethylamino function was introduced by using the method of Staab[30] by reaction of protected alcohol **35** with carbonyldiimidazole followed by treatment with β-chloroethylamine to afford **37**. Fluoride deprotection of the isomerically pure (*E*)-stilbenes **26–29** and **34–37** gave the bisphenols **10**, **38–40**, and **41–44** containing less than 10% of isomeric (*Z*)-stilbenes and styrenes as shown by ^1H NMR. However, the compounds smoothly isomerized in aqueous solution to equilibrium of (*E*)- and (*Z*)-stilbenes and styrenes.

Table I. Estradiol Receptor Binding Affinities of DES Derivatives



no.	R	RBA
41	daunomycin	no binding
10	COOH	0.1
24	$(CH_2)_4CH_3$	0.2
39	$COOC_6Cl_5$	0.3
40	$COOC_6H_4Cl$	0.3
25	$CON(C_2H_5)_2$	1.0
44	$CH_2OCONH(CH_2)_2Cl$	1.0
22	$CH_2OC_2H_5$	1.2
19	CH_2OH	1.5
21	CH_2I	1.5
43	$CH_2OSO_2CH_3$	1.8
20	CH_2Cl	3.0
23	CH_3	10.0

Estrogen Receptor Binding

Table I gives the relative binding affinity (E_2 = 100) for several of the synthetic DES derivatives. With the exception of the daunomycin derivative **41**, which is totally devoid of binding affinity (RBA ≪ 0.01), all compounds display a weak but substantial binding affinity. Interestingly, RBA values are drastically decreased by the presence of polar groups such as the carboxylic group in **10**. Steric effects also decrease the affinity. Thus, esters of bulky alcohols such as **40** show only low RBA, and a difference was found between the smaller chloride **20** and the bulkier iodide **21**. Similarly, compound **24** with a C_8 side chain shows very small receptor binding and the very bulky daunorubicin-linked DES derivative **41** shows none. In contrast, side chains comparable in size to the n-C_8H_{17} group but with lone electron pairs that can form hydrogen bonds with water (ether **22**, mesylate **43**, and urethane **44**) do not show a similar decrease in RBA. However, the observed structural influence of RBA cannot account for the isomerization that takes place with all of these derivatives in solution. The influence of these isomers (e.g. the styrenes) on the experimental conditions of the binding assay is not known. In addition, compounds with reactive groups may interact with proteins other than receptors, thereby reducing their concentrations as well as their binding potency. Binding affinity for such DES derivatives may therefore be significantly higher than expected from RBA values.

Experimental Section

General Procedures. Relative Binding Affinity for Estrogen Receptor. For details, see ref 31. Rat uterine cytosol was incubated at 18 °C for 30 min with 5×10^{-9} [^3H]estradiol in the absence and presence of increasing amounts (10^{-9} to 10^{-5} M) of the test compound or unlabeled estradiol (control). Unbound

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compounds were then removed with dextran-coated charcoal, and the amounts of estrogen receptor bound [^{3}H]estradiol were measured. The relative concentrations of estradiol and test compound required to achieve 50% inhibition of [^{3}H]estradiol binding is the RBA; i.e. RBA = ([I_{50}] estradiol/[I_{50}] test compound) × 100.

Chemical Methods. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions with Me_4Si as internal standard if not otherwise stated (60 MHz, Varian T-60; 300 MHz, Bruker AM 300; 400 MHz, Bruker WM-400). IR spectra were recorded on Perkin-Elmer 157 G and 1420 instruments and UV spectra on a Beckman 5230 instrument. Mass spectra were obtained with AEI MS-9 (electron impact, 70 eV) and Kratos MS-50 (FAB) with Kratos MS-902 S (high resolution) instruments (numbers in brackets represent relative intensity). Melting points were determined on a Dr. Tottoli apparatus (Büchi). Silica gel 60 (Merck) and TLC plates from Schleicher & Schüll were used for chromatography. For difficult separations of (*E*)- and (*Z*)-isomers a special TLC technique with continuous flow of the eluant was used in which evaporation of the solvent from the open end of the chamber was permitted. The DES ethers showed adsorptions in the IR spectra in the range of 2960–2830, 1608–1603, 1510–1501, 1283–1243, 918–912 ($OSiMe_3$), and 840–828 cm^{-1} (OCH_3). The UV spectra showed bands at λ_{max} (log ϵ) 210–208 (4.3), 236–230 (4.3), 274–267 (sh, 3.8), and 282–280 nm (sh, 3.6). The corresponding values for the DES derivatives are as follows: IR 3250–3240, 3035–3030, 2950–2820, 1610–1606, 1592–1570, 1510–1509, 837–831 cm^{-1}; UV λ_{max} (log ϵ) 208–207 (4.2), 233–236 (4.2), 274–272 nm (sh, 3.7).

***tert*-Butyl 4-Iodobutyrate (5). Phase-Transfer Procedure.** A mixture of 80.00 g (0.45 mol) of *tert*-butyl 4-chlorobutyrate,[22] 136.00 g (0.9 mol) of sodium iodide, 14.20 g (0.17 mol) of sodium hydrogen carbonate, 4.80 g (0.01 mol) of tetrabutylammonium iodide, and 80 mL of water was stirred for 3 days at 70 °C. The mixture was poured on 200 mL of an aqueous sodium thiosulfate solution and extracted twice with 100 mL of diethyl ether. The organic phase was dried and distilled under vacuum to afford 79.74 g (66%) of **5**, $bp_{0.02}$ 41 °C.

***tert*-Butyl 5,6-Bis(4-methoxyphenyl)octanoate (6).** A solution of 50.00 g (0.195 mol) deoxyanisoin (**4**) and 72.00 g (0.270 mol) of iodo ester **5** in 600 mL of dry dimethylforamide (DMF) was added with stirring under nitrogen to a suspension of 9.00 g of sodium hydride (80%) in 50 mL of dry diethyl ether. The solution was stirred an additional 20 min and was then poured on 1 kg of ice–water and extracted with 500 mL of diethyl ether. The solution was dried ($NaSO_4$) and evaporated at reduced pressure. The product crystallized on addition of petroleum ether to afford 69.35 g (89%) of **6**, mp 89–90 °C (lit.[22] mp 89–90 °C).

(5*R,6*S**)-*tert*-Butyl 6-Hydroxy-5,6-bis(4-methoxyphenyl)octanoate (7) and (5*R**,6*R**)-*tert*-Butyl 6-Hydroxy-5,6-bis(4-methoxyphenyl)octanoate (8).** A Grignard reagent was prepared from 7.30 g (0.30 mol) of magnesium and 23 mL (0.30 mol) of ethyl bromide in 375 mL of dry diethyl ether. A solution of 60.00 g (0.15 mol) of ketone **6** in 500 mL of dry tetrahydrofuran (THF) was added, and the mixture was stirred for 3 h under nitrogen at 20 °C and was then hydrolyzed with 1 L of 10% aqueous ammonium chloride. The ethereal extract was dried and evaporated and the residue crystallized from diethyl ether/petroleum ether to afford 34.10 g of the pure threo isomer **7**, mp 92–93 °C (lit.[22] mp 83–84 °C). A mixture of isomers **7** and **8** crystallized on evaporation of the mother liquor (total yield 59.00 g, **7**:**8** = 4:1). Data for **7**: IR (KBr) 3490–3430, 1705 (C=O), 1610, 1580, 1512 (Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (t, 3 H, 8-H), 1.22–2.15 (m, 8 H, 2-, 3-, 4-, 7-H), 1.37 (s, 9 H, *t*-Bu), 1.76 (s, 1 H, OH), 2.84 (dd, 1 H, 5-H), 3.74 (s, 3 H, OCH_3), 6.84 (d, J = 8.5 Hz, 2 H, Ar-H), 7.07 (d, J = 8.5 Hz, 2 H, Ar-H).

(*E*)- and (*Z*)-5,6-Bis(4-methoxyphenyl)-5-octenoic Acid (9a and 9b). Ten grams (23 mmol) of esters **7** and **8** and 0.5 of *p*-toluenesulfonic acid were heated to 110 °C. After 45 min the mixture was dissolved in 150 mL of dichloromethane and the organic solution was washed with water, dried, and evaporated to afford 7.7 g (94%) of an oil. The 60-MHz ^{1}H NMR spectrum was identical with literature data[22] and the 400-MHz spectrum revealed the presence of 65% of (*E*)-stilbene and 20% of (*Z*)-stilbene and 15% of two styrenes.

9a: ^{1}H NMR (400 Hz, $CDCl_3$) δ 0.77 (t, 8-CH_3), 1.66 (quint, 3-CH_2), 2.12–2.20 (m, 2-, 4-, and 7-CH_2), 3.81 and 3.85 (2 s, OCH_3), 6.88–7.14 (2 AA'BB' systems). **9b**: ^{1}H NMR (400 Hz, $CDCl_3$) δ 0.92 (t, 8-CH_3), 2.31–2.36 (2 t of 2-CH_2), 2.52 (q, 7-CH_2), 2.58 (t, 4-CH_2), 3.71 (2 s, OCH_3), 6.60–6.86 (2 AA'BB' systems).

5,6-Bis(4-hydroxyphenyl)-5-octenoic Acid (10) (Ether Cleavage with KOH). A mixture of 1.0 g of acids **9a** and **9b**, 10 mL of ethylene glycol, and 2.00 g of KOH was heated in a cyclindric Teflon block with an air condenser at 200 °C for 2 days. The solution was diluted with cold hydrochloric acid and extracted twice with 100 mL of diethyl ether. The ^{1}H NMR spectrum of **10** was in agreement with the data obtained from BBr_3 cleavage of **9a** and **9b**:[22] MS (150 °C) m/z 326 (M$^+$, 100), 297 (24), 253 (36), 239 (71), 237 (54), 224 (33), 203 (34), 193 (43), 191 (43), 159 (35).

5,6-Bis(4-methoxyphenyl)-5-octenol (11). A solution of 1.00 g (2.8 mmol) of acid **9a**/**9b** in 15 mL of dry THF was treated with 200 mg of lithium aluminum hydride. The mixture was hydrolyzed by careful addition of diluted sulfuric acid, and the products were isolated by extraction with diethyl ether to afford 0.90 g (94%) of alcohol **11** as an oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.76 and 0.93 (2 t, 3 H, 8-CH_3), 1.13–2.80 (m, 2-, 3-, 4-, 7-CH_2), 3.70, 3.768 3.83 (3 s, 6 H, OCH_3), 5.59 (q, vinylic-H), 6.53–7.23 (m, 8 H, Ar-H).

1-Chloro-5,6-bis(4-methoxyphenyl)-5-octene (12). A mixture of 148 mg (0.43 mmol) of alcohol **11**, 200 mg of triphenyl phosphine, 5.5 mL of tetrachloromethane, 3 mL of THF, and 2 mL of acetonitrile was refluxed for 12 h. Triphenylphosphine oxide was filtered off and the product was purified by filtration through a short column of silica gel (eluant petroleum ether/acetone = 8:2) to afford 114 mg (73%) of an oil. Pure (*E*)-stilbene **12** was obtained from the zone of lowest polarity by TLC with continuous flow of the eluent: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, J = 7.5 Hz, 3 H, 8-CH_3), 1.29 (tt, 2 H, 2-CH_2), 1.58 (quint, 2 H, 3-CH_2), 2.15 (q and t, 4 H, 4- and 7-CH_2), 3.32 (t, J = 7.0 Hz, 2 H, 1-CH_2), 3.83 (2 s, 6 H, OCH_3), 6.90–6.94 ($A_1A_1' + A_2A_2'$ part, 4 H), 7.09–7.15 ($X_1X_1' + X_2X_2'$ part, 4 H); MS (70 °C) m/z (M$^+$, 48), 358 (M$^+$, 100), 329 (15), 281 (73), 267 (43), 252 (44), 237 (27), 173 (52).

1-Iodo-5,6-bis(4-methoxyphenyl)-5-octene (13). A solution of 489 mg (1.4 mmol) of alcohol **11** and 1.56 g of *N*-methyl-*N*,*N*'-dicyclohexylcarbodiimidium iodide[27] in 15 mL of dry THF was stirred for 24 h. Fifty milliliters of ethyl acetate and a solution of sodium sulfite was added and the organic phase was dried and evaporated. Excess of the reagent was converted to *N*-acylurea by addition of trifluoroacetic acid and the iodide was purified by TLC to afford 333 mg (53%) of an oily mixture of isomers. Pure (*E*)-stilbene **13** was obtained by TLC (petroleum ether/CH_2Cl_2 = 4:1) as described for **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, J = 7.5 Hz, 3 H, 8-CH_3), 1.25 (quint, 2 H, 2-CH_2), 1.63 (quint, 2 H, 3-CH_3), 2.15 (q and t, 4 H, 4- and 7-CH_2), 2.96 (t, J = 7.0 Hz, 1-CH_2), 3.84 (2 s, 6 H, OCH_3), 6.89–6.93 ($A_1A_1' + A_2A_2'$ part, 4 H), 7.09–7.14 ($X_1X_1' + X_2X_2'$ part, 4 H).

1-Ethoxy-5,6-bis(4-methoxyphenyl)-5-octene (14). A solution of 154 mg (0.45 mmol) of **11** and 1 mL of ethyl iodide in 2 mL of dry DMF was treated with 30 mg of NaH. After 30 min, the mixture was poured on ice and extracted with diethyl ether. Filtration over a short silica gel column and evaporation gave 238 mg (82%) of **14** as a mixture of isomers: MS (90 °C) m/z 368 (M$^+$, 79), 293 (29), 281 (44), 267 (76), 252 (39), 219 (40), 191 (40), 175 (46), 173 (52).

3,4-Bis(4-hydroxyphenyl)-3-octene (23). Deoxyanisoin (**4**; 1.30 g, 5 mmol) was alkylated with butyl bromide and reacted with ethylmagnesium bromide as described for **6** and **7** (compare ref 22 and 32). The threo/erythro mixture was dehydrated as described for **9** to afford methyl ether **15** that was deprotected with KOH as described for **10** to afford 470 mg (32%) of the crystalline (diethyl ether) bisphenol **23**: mp 162–163 °C; ^{1}H NMR (400 MHz, $CDCl_3/CD_3OD$) δ 0.70 (t, J = 7.0 Hz, 3 H, 8-CH_3), 0.76 (t, J = 7.5 Hz, 3 H, 1-CH_3), 1.05–1.20 (m, 4 H, 6- and 7-CH_2), 2.10 (t, J = 7.0 Hz, 2 H, 5-CH_2), 2.13 (q, J = 7.5 Hz, 2 H, 2-CH_2), 6.80 and 6.83 ($A_1A_1' + A_2A_2'$ part, 4 H, Ar-H), 7.01–7.04 (m, $X_1X_1' + X_2X_2'$ part, 4 H, Ar-H); MS (130 °C) m/z 296 (M$^+$, 100), 281 (10), 267 (52), 253 (70), 239 (67), 224 (52), 210 (26), 195 (12).

(*E*)-3,4-Bis(4-hydroxyphenyl)-3-dodecene (24). Deoxy-

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anisoin (**4**; 1.30 g, 5 mmol) was converted to **24** as described for **23** with octyl bromide in the alkylation step to afford 510 mg (29%) of the (*E*)-stilbene **24**; mp 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, J = 7.5 Hz, 3 H, 1-CH_3), 0.86 (t, J = 7.3 Hz, 3 H, 12-CH_3), 1.06–1.31 (m, 12 H, 6-, 11-CH_2), 2.09 (t, J = 7.5 Hz, 2 H, 2-CH_2), 2.13 (q, J = 7.5 Hz, 2 H, 5-CH_2), 6.80 and 6.84 (A_1A_1' + A_2A_2' part, 4 H, Ar-H), 7.04–7.07 (m, X_1X_1' + X_2X_2' part, 4 H, Ar-H); MS (110 °C) m/z 352 (M^+, 100), 337 (3), 323 (15), 253 (79), 239 (45), 224 (25), 210 (8), 181 (7), 159 (45). Anal. ($C_{24}H_{32}O_2$) C, H.

***N*,*N*-Diethyl-5,6-bis(4-methoxyphenyl)-5-octenamide (17).** A solution of 4.00 g (11.3 mmol) of acids **9a**/**96b** and 1.60 g (11.5 mmol) of 4-nitrophenol in 30 mL of CH_2Cl_2 and 6 mL of dry THF was treated with 2.30 g of DCCI. The solution was stirred for 1.5 h at 20 °C and 3 mL of diethylamine was added. The solution was filtered, the solvent evaporated at reduced pressure, and the residue purified by filtration over a short silica gel column (petroleum ether/diethyl ether = 4:1) to giver 2.3 g (50%) of oil **17** as a mixture of isomers. Separation of 40 mg into three fractions, (*E*)- and (*Z*)-stilbenes and styrenes, was effected by using the TLC technique with continuous flow of the eluants; ^{1}H NMR (400 MHz, $CDCl_3$) ((*E*)-stilbene) δ 0.78 (t, 8-CH_3), 1.00–1.15 (m, CH_3, *N*-ethyl), 2.05 (t, 2-CH_2), 2.15 (q, 7-CH_2), 2.16 (t, 4-CH_2), 2.25 (m), 3.09–3.36 (m, CH_2, *N*-ethyl), 3.81 (2 s, OCH_3), 6.58–7.14 (m, AA′XX′ systems, Ar-H), ((*Z*)-stilbene) 0.93 (t, 8-CH_3), 2.55 (q, 7-CH_2), 2.60 (t, 4-CH_2), 3.69 (2 s, OCH_3), 6.58–7.14 (m, AA′XX′ systems, Ar-H); MS (110 °C) m/z 409 (M^+, 26), 381 (4), 340 (29), 294 (23), 279 (26), 265 (55), 260 (57), 250 (18), 239 (34), 237 (33), 223 (14), 207 (19). Anal. ($C_{26}H_{35}NO_3$) C, H, N.

4-*tert*-Butylphenyl 5,6-Bis(4-methoxyphenyl)-5-octenoate (18). A solution of 2.00 g (5.64 mmol) of acid **9a**, 0.86 g (5.73 mmol) of *tert*-butylphenol in 30 mL of CH_2Cl_2 was treated with 1.15 g (5.58 mmol) of DCCI and stirred for 3 h at 20 °C. The solution was filtered and evaporated to give 2.55 g (90%) of a crude mixture of isomers. (*E*)-Stilbene **18** was obtained by column chromatography on silicl gel (petroleum ether/acetone = 93:7) from the fraction of medium polarity (0.97 g, 35%): mp 80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.73 (t, J = 7.5 Hz, 3 H, 8-CH_3), 1.31 (s, 9 H, $C(CH_3)_3$), 1.62 (quint, J = 8.0 Hz, 2 H, 3-CH_3), 2.17 (q, J = 7.5 Hz, 2 H, 7-CH_2), 2.26 (t, J = 8.0 Hz, 2 H, 2-CH_2), 2.32 (t, J = 7.5 Hz, 2 H, 4-CH_2), 3.81 and 3.84 (2 s, 6 H, OCH_3), 6.79–6.83 (A_3A_3' part, 2 H, Ar-H), 6.89–6.94 (A_1A_1' + A_2A_2' part, 4 H, stilbene, Ar-H), 7.11–7.18 (X_1X_1' + X_2X_2' part, 4 H, stilbene, Ar-H), 7.31–7.35 (X_3X_3' part, 2 H, Ar-H); MS (170 °C) m/z 486 (M^+, 83), 410 (12), 354 (11), 353 (11), 337 (14), 281 (16), 279 (17), 269 (23), 265 (19), 229 (65), 201 (24), 189 (20). Anal. ($C_{32}H_{38}O_4$) C, H, O.

1-Chloro-5,6-bis(4-hydroxyphenyl)-5-octene (20). A solution of 40 mg (0.11 mmol) of dimethyl ether **11** in 2 mL of CH_2Cl_2 was treated with 0.5 mL of BBr_3 at −10 °C as described in the literature[22] to afford 21 mg (57%) of the bisphenol **20** as a mixture of isomers: ^{1}H NMR (90 MHz, $CDCl_3/CD_3OD$) δ 0.74 (t, 8-CH_3, (*E*)-stilbene), 0.91 (t, 8-CH_3, (*Z*)-stilbene), 1.11–2.66 (m, aliph CH_2), 1.46 (d, 8-CH_3, styrene), 3.30 (t, 1-CH_2, (*E*)-stilbene), 3.47 (t, 1-CH_2), 5.44 (t, vin H, styrene), 5.55 (q, vin H, styrene), 6.46–7.07 (m, Ar-H); MS (150 °C) m/z 330 (M^+, 94), 315 (10), 303 (32), 301 (65), 253 (78), 239 (88), 224 (63), 210 (34), 159 (62), 145 (68). Anal. ($C_{20}H_{23}O_2Cl$) C, H, O, Cl.

1-Iodo-5,6-bis(4-hydroxyphenyl)-5-octene (21). Sixty-five milligrams (0.14 mmol) of **13** was deprotected with BBr_3[22] to afford 57 mg of **21** (oil): ^{1}H NMR (400 MHz, acetone-d_6) δ 0.76 (t, 8-CH_3), 1.21–1.98 (m, aliph CH_2), 2.14 (t + q, 4- and 7-CH_2), 2.97 (t, 1-CH_2), 6.53–7.08 (m, Ar-H), MS (100 °C) m/z 422 (M^+, 100), 407 (3), 393 (33), 253 (53), 239 (75), 224 (30), 210 (16), 159 (44), 145 (53). Anal. ($C_{20}H_{23}O_2I$) C, H, O, I.

1-Ethoxy-5,6-bis(4-hydroxyphenyl)-5-octene (22). Eighty-eight milligrams of **14** were deprotected as described for **10** to afford 58 mg (71%) of the ethyl ether **22**: ^{1}H NMR (400 MHz, acetone-d_6) δ 0.76 (t, J = 7.5 Hz, 8-CH_3), 1.05 (t, J = 7.0 Hz, OCH_2CH_3), 2.16 (q and t, J = 7.5 Hz, 4- and 7-CH_2), 3.18 (t, J = 6.5 Hz, 1-CH_2), 3.30 (q, J = 7.0 Hz, OCH_2CH_3), 6.84–7.07 (m, AA′XX′ systems, Ar-H), 7.95–8.39 (phenol); MS (150 °C) m/z 340 (M^+, 60), 265 (32), 253 (30), 239 (69), 224 (38), 223 (35), 205 (37), 161 (49), 159 (53), 145 (65). Anal. ($C_{22}H_{28}O_3$) C, H, O.

***N*,*N*-Diethyl-5,6-bis(4-hydroxyphenyl)-5-octenamide (25).** A solution of 100 mg (0.24 mmol) of **17** was deprotected with BBr_3 to afford 73 mg (78%) of the bisphenol **25** as a mixture of isomers: ^{1}H NMR (400 MHz, CD_3OD) δ 0.82 (t, 8-CH_3), 1.05–1.20 (m, CH_3, $N(Et)_2$), 1.31–1.88 (m, aliph CH_2), 2.14 (t, 2-CH_2), 2.23 (q, 7-CH_2), 2.25 (t, 4-CH_2), 3.20–3.38 (m, CH_2, $N(Et)_2$), 6.51–7.08 (m, Ar-H); MS (180 °C) m/z 381 (M^+, 82), 353 (12), 352 (9), 266 (45), 248 (52), 247 (66), 246 (63), 237 (78). Anal. ($C_{24}H_{31}O_3N$) C, H, O, N.

5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-5-octenoic Acid (26). A mixture of 0.90 g (2.76 mmol) of acid **10** and 1.90 g (12.6 mmol) of *tert*-butyldimethylsilyl chloride and 1.4 g of imidazole in 10 mL of DMF was stirred for 1 h. One milliliter of methanol was then added to cleave the silyl ester. The mixture was poured on ice, extracted with 200 mL of diethyl ether, washed twice with water, dried, and evaporated to afford 1.42 g (93%) of the bis(silyl ether) **26**. The product was characterized as its methyl ester **27**.

Methyl 5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-5-octenoate (27). A solution of 50 mg of **26** in 2 mL of CH_2Cl_2 was treated with 1 mL of an ethereal diazomethane solution to afford the ester **27** quantitatively: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (2 s, 12 H, $SiCH_3$), 0.75 (t, J = 7.5 Hz, 3 H, 8-CH_3), 1.00 (s, 18 H, $SiC(CH_3)_3$), 1.47 (quint, J = 7.5 Hz, 2 H, 3-CH_2), 2.07 (t, J = 8 Hz, 2 H, 2-CH_2), 2.12 and 2.13 (q + t, J = 7.5 and 7.0 Hz, 4 H, 4- and 7-CH_2), 3.54 (s, 3 H, CO_2CH_3), 6.79–6.83 (A_1A_1' + A_2A_2' part, 4 H, Ar-H), 6.98–7.02 (X_1X_1' part, 2 H, Ar-H), 7.02–7.05 (X_2X_2' part, 2 H, Ar-H); MS (150 °C) m/z 569 (M^+, 14), 568 (M^+, 31), 467 (6), 322 (39), 291 (15), 265 (100), 247 (25), 233 (26), 221 (86), 205 (32), 195 (24).

Phenyl 5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-5-octenoate (28). A solution of 277 mg (0.5 mmol) of acid **26** and 0.55 mmol of phenol in 10 mL of dry THF was treated with 0.55 mmol of DCCI. The solution was filtered after 1 h, evaporated to dryness, and purified by column chromatography on silica gel (petroleum ether/diethyl ether = 96:4) to yield 142 mg (45%) of ester **28**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.22 (2 s, $SiCH_3$), 0.77 (t, J = 7.3 Hz, 8-CH_3), 1.00 (2 s, $SiC(CH_3)_3$), 1.52–1.88 (m, aliph CH_2), 2.15 (q, J = 7.3 Hz, 7-CH_2), 2.24 (m, 4-CH_2), 2.32 (t, J = 7.5 Hz, 2-CH_2), 6.51–7.39 (m, Ar-H); MS (170 °C) k/z 630 (M^+, 88), 602 (15), 467 (57), 383 (35), 339 (43), 329 (54), 301 (32), 287 (42), 271 (37), 259 (39), 249 (68), 247 (100), 235 (57), 221 (44), 205 (39), 189 (46), 177 (33).

4-Chlorophenyl 5,6-Bis[4-(*tert*-butyldimethylsiloxy)-phenyl]-5-octenoate (29). 27 (277 mg, 0.5 mmol) was converted to 232 mg (70%) of **29** as described for **28**. The pure (*E*)-stilbene was obtained on TLC separation: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (d, 12 H, $SiCH_3$), 0.77 (t, J = 7.5 Hz, 3 H, 8-CH_3), 1.01 (d, 1, H, $SiC(CH_3)_3$), 1.60 (quint, J = 7.6 Hz, 2 H, 3-CH_2), 2.16 (q, J = 7.5 Hz, 2 H, 7-CH_2), 2.25 (t, J = 7.7 Hz, 2 H, 4-CH_2), 2.31 (t, J = 7.5 Hz, 2 H, 2-CH_2), 6.80–6.85 (m, 6 H, Ar-H), 7.02–7.09 (m, 4 H, Ar-H), 7.27–7.31 (m, Ar-H); MS (150 °C) m/z 664 (M^+, 100), 481 (20), 467 (16), 329 (63), 317 (17), 301 (24), 289 (28), 271 (21), 263 (26), 247 (68) 235 (52), 221 (28), 205 (29).

4-Nitrophenyl 5,6-Bis[4-(*tert*-butyldimethylsiloxy)-phenyl]-5-octenoate (30). 26 (277 mg, 0.5 mmol) was converted to 270 mg (80%) of **30** as described for **29**. The pure (*E*)-stilbene was obtained on TLC separation: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22 (d, 12 H, $SiCH_3$), 0.77 (t, J = 7.5 Hz, 3 H, 8-CH_3), 1.00 (d, 18 H, $SiC(CH_3)_3$), 1.62 (quint, J = 7.7 Hz, 2 H, 3-CH_2), 2.17 (q, J = 7.5 Hz, 2 H, 7-CH_2), 2.27 (t, J = 7.7 Hz, 2 H, 4-CH_2), 2.37 (t, J = 7.5 Hz, 2 H, 2-CH_2), 6.82 (t, 4 H, Ar-H), 7.02–7.09 (m, 6 H, Ar-H), 8.20–8.24 (m, 2 H, Ar-H); MS (170 °C) m/z 675 (M^+, 81), 618 (13), 568 (10), 537 (10), 495 (3), 481 (34), 480 (29), 479 (47), 329 (55), 313 (22), 301 (59), 287 (42), 271 (30).

Pentachlorophenyl 5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-5-octenoate (31). 26 (277 mg, 0.5 mmol) was converted to 363 mg (90%) of **31** as described for **28**. The pure (*E*)-stilbene was obtained on TLC separation: IR (CCl_4) 1787 cm^{-1} (C=O, ester); ^{1}H NMR (400 MHZ, $CDCl_3$) δ 0.21 (d, 12 H, $SiCH_3$), 0.76 (t, J = 7.5 Hz, 3 H, 8-CH_3), 1.00 (d, 18 H, $SiC(CH_3)_3$), 1.65 (quint, J = 7.7 Hz, 2 H, 3-CH_2), 2.15 (q, J = 7.5 Hz, 2 H, 7-CH_2), 2.27 (t, J = 7.7 Hz, 2 H, 4-CH_2), 2.43 (t, Jj = 7.5 Hz, 2 H, 2-CH_2), 6.81–6.85 (m, 4 H, Ar-H), 7.01–7.08 (m, 4 H, Ar-H); MS (170 °C) m/z 806 (M^+, 33), 804 (M^+, 79), 802 (M^+, 100), 800 (M^+, 57), 537 (37), 481 (63), 479 (49), 330 (96), 302 (49), 248 (94).

***N*-(2-Hydroxyethyl)-5,6-bis[4-(*tert*-butyldimethylsiloxy)phenyl]-5-octenamide (32) and *N*,*N*-Bis(2-hydroxy-**

ethyl)-5,6-bis[4-(*tert*-butyldimethylsiloxy)phenyl]-5-octenamide (33). A solution of 230 mg (0.29 mmol) of **31** in 5 mL of THF was treated with 1 mL of commercial diethanolamine for 12 h. After usual workup the crude mixture was separated by TLC to afford 43 mg of **32** (mp 117–119 °C) from the less polar zone and 82 mg of **33** (mp 132–133 °C) from the polar zone. Data for **32**: IR (CCl_4) 3440 and 3350 (N–H, amide), 1656 cm^{-1} (C=O, amide); ^1H NMR (400 MHz, $CDCl_3/D_2O$) δ 0.23 (s, 12 H, $SiCH_3$), 0.74 (t, J = 7.5 Hz, 3 H, 8-CH_3), 1.00 (s, 18 H, $SiC(CH_3)_3$), 1.47 (quint, J = 7.6 Hz, 2 H, 3-CH_2), 1.96 (t, J = 7.7 Hz, 2 H, 2-CH_2), 2.13 (q and t, J = 7.5 Hz, 4 H, 4- and 7-CH_2), 3.24 (q, J = 7.5 Hz, 2 H, $CONHCH_2CH_2OH$), 3.57 (t, J = 5.2 Hz, 2 H, $CONHCH_2CH_2OH$), 5.59 (t, J = 5 Hz, 1 H, $CONHR$), 6.80–6.84 (m, $A_1A_1' + A_2A_2'$ part, 4 H, Ar-H), 7.00–7.05 (m, $X_1X_4' + X_2X_2'$ part, 4 H, Ar-H); MS (155 °C) m/z 597 (M^+, 25), 579 (10), 494 (71), 465 (100), 348 (33), 330 (22), 249 (80), 232.5 (24). Anal. ($C_{34}H_{65}NO_4Si_2$) C, H, N, O, Si. Data for **33**: IR (CCl_4) 3380 (OH), 1623 cm^{-1} (C=O, amide); ^1H NMR (400 MHz, $CDCl_3$) δ 0.22 (2 s, 12 H, $SiCH_3$), 0.74 (t, J = 7.5 Hz, 3 H, 8-CH_3), 1.00 (2 s, 18 H, $SiC(CH_3)_3$), 1.48 (quint, J = 7.6 Hz, 2 H, 3-CH_2), 2.09–2.18 (m, 6 H, 2-, 4-, and 7-CH_2), 3.28 (t, J = 5.2 Hz, 2 H, $CONCH_2CH_2OH$), 3.42 (t, J = 4.9 Hz, 2 H, $CONCH_2CH_2OH$), 3.62 (t, J = 5.2 Hz, 2 H, $CONCH_2CH_2OH$), 3.72 (t, J = 4.9 Hz, 2 H, $CONCH_2CH_2OH$), 6.79–6.82 (m, $A_1A_1' + A_2A_2'$ part, 4 H, Ar-H), 7.00–7.06 (m, $X_1X_1' + X_2X_2'$ part, 4 H, Ar-H); MS (170 °C) m/z 641 (M^+, 12), 623 (22), 494 (100), 465 (100), 294 (45), 254.5 (37), 249 (65). Anal. ($C_{36}H_{59}NO_5Si_2$) C, H, N, O, Si.

Coupling of Daunorubicin to the Activated Octanoic Ester 31. A solution of 10 mg of daunorubicin hydrochloride, 0.2 mL of triethylamine, and 40 mg of ester **31** in 3 mL of dry THF was stirred for 17 h at room temperature. The reaction mixture was partitioned between water and diethyl ether. The ethereal solution was washed twice with ammonium hydrochloride solution, dried with Na_2SO_4, and evaporated. The residue was purified by preparative TLC (silica gel, CCl_4/CH_3OH) to afford 18 mg (94%) of adduct **34**: IR (CCl_4) 1715 (C=O), 1669 cm^{-1} (C=O); ^1H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 12 H, $SiCH_3$), 0.72 (t, 3 H, CH_3), 1.00 (2 s, 18 H, $SiC(Me)_3$), 1.27 (d, 3 H, CH_3), 1.42 (quint, 2 H, CH_2), 1.62 (d t, 1 H), 1.78 (dd, 1 H), 1.87 (t, 2 H, CH_2), 2.10–2.30 (m, 5 H), 2.43 (s, 3 H, $COCH_3$), 2.95 (d, 1 H), 3.25 (d, 1 H), 3.50–4.02 (1 H), 4.10 (s, 3 H, OCH_3), 4.20 (q, 1 H), 4.45 (s, 1 H, OH), 5.28 (s, 1 H), 5.47 and 5.50 (each s, each 1 H), 6.76 (t, 4 H), 7.00–7.02 (m, 4 H), 7.39 (d, 1 H), 7.39 (d, 1 H), 7.80 (t, 1 H), 8.07 (d, 1 H), 13.30 and 14.00 (each s, each 1 H, OH).

5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-5-octen-1-ol (35). A solution of 1.4 g (2.5 mmol) of acid **21** in 10 mL of dry THF was added to a −10 °C suspension of 0.3 g (7.9 mmol) of lithium aluminum hydride in 10 mL of dry THF. The mixture was stirred for an additional 10 min at room temperature and was then poured on ice and extracted with diethyl ether. The organic phase was washed with water, dried, filtered, and evaporated to dryness to afford 838 mg (62%) of a colorless oil. Column chromatography on silica gel (petroleum ether/ethyl acetate = 9:1) gave the pure (*E*)-stilbene **35**: ^1H NMR (400 MHz, CCl_4/D_2O) δ 0.23 (s, 12 H, SiMe), 0.76 (t, 3 H, CH_3), 1.01 (s, 18 H, $SiCMe_3$), 1.17–1.42 (m, 2 H, CH_2), 2.12–2.17 (m, 4 H, CH_2), 3.41 (t, 2 H, CH_2), 6.80–6.84 (m, 4 H, Ar-H), 7.01–7.06 (m, 4 H, Ar-H); MS (120 °C) m/z 540 (100 M^+), 481 (15), 249 (18), 221 (15), 204 (19); exact mass calcd for $C_{32}H_{52}O_3Si_2$ 540.3455, found 540.3433.

5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-5-octenyl Methanesulfonate (36). A solution of 270 mg (0.5 mmol) of alcohol **35** in 5 mL of dry pyridine was treated for 10 min with a 5-fold excess of mesyl chloride. The solution was diluted with 50 mL of diethyl ether and extracted repeatedly with an aqueous solution of citric acid. The solution was dried with Na_2SO_4 and evaporated to dryness to afford 272 mg (88%) of an oil as an inseparable mixture of isomers: IR (CCl_4) 1173 (SO_2O), 912 cm^{-1} (Si–O); ^1H NMR (60 MHz, CCl_4) δ 0.10, 0.16, 0.20 (each s, SiMe), 0.75 (t, 3 H, CH_3) 0.96 (br s, $SiCMe_3$), 1.16–2.26 (m, CH_2), 1.45 (d, styrene CH_3), 2.73–2.81 (several s, SO_3Me), 3.13–3.55 (m, benzylic CH_2), 3.80–4.20 (m, CH_2), 5.31–5.73 (m, vinylic styrene-H), 6.38–7.10 (Ar-H); MS (150 °C) m/z 618 (51, M^+), 561 (24), 467 (78), 371 (62), 353 (63), 315 (37), 287 (47), 275 (56), 259 (48).

1-[[[[5,6-Bis[4-(*tert*-butyldimethylsiloxy)phenyl]-5-octen-1-yl]oxy]carbonyl]amino]-2-chloroethane (37). A solution of 75 mg (0.14 mmol) of alcohol **35** in 3 mL of dry THF was treated with 25 mL (0.15 mmol) of carbonyldiimidazole. After 1 h of stirring at room temperature, 150 mg (1.45 mmol) of β-chloroethylammonium chloride followed by 1.5 mL of triethylamine was added. The mixture was stirred for 12 h and partitioned between diethyl ether and water. The ethereal solution was washed with water, dried with Na_2SO_4, and evaporated to afford 90 mg (100%) of an oil: IR (CCl_4) 3460 (NH), 1727 cm^{-1} (urethane C=O), ^1H NMR (250 MHz, $CDCl_3$) δ 0.23 (s, 12 H, SiMe), 0.76 (t, 3 H, CH_3), 1.00 (s, 18 H, $SiCMe_3$), 1.14–1.22 (m, 2 H, CH_2), 1.32–1.45 (m, 2 H, CH_2), 2.08–2.17 (m, 4 H, CH_2), 3.44–3.66 (m, 4 H, CH_2), 3.87 (t, 2 H, CH_2), 4.95 (br 1 H, NH), 6.80–6.84 (m, 4 H, Ar-H), 7.00–7.05 (m, 4 H, Ar-H); MS (130 °C) m/z 645 (100, M^+), 609 (15), 540 (68), 524 (65), 481 (21), 408 (17), 293 (27), 275 (68), 249 (76); exact mass calcd for $C_{35}H_{56}NO_4Si_2Cl$ 645.3436, found 345.3429.

Methyl 5,6-Bis(4-hydroxyphenyl)-5-octenoate (38). A solution of 400 mg (1.23 mmol) of acid **10** in 10 mL of diethyl ether was treated for 5 min with an ethereal solution of diazomethane. The solvent was evaporated to afford 395 mg (95%) of ester **38** as a mixture of isomers. ^1H NMR (400 MHz, CD_3OD) δ 0.79 (t, 8-CH_3), 1.23–1.89 (m, aliph CH_2), 2.13 (t, 2-CH_2), 2.19 and 2.20 (q and t, 4- and 7-CH_2), 3.55 (s, CO_2CH_3), 6.52–7.06 (m, Ar-H); MS (100 °C) m/z 340 (M^+, 97), 312 (25), 279 (51), 265 (22), 253 (44), 239 (95), 237 (83), 224 (46), 207 (53), 181 (35).

General Desilylation Procedure (Procedure A for Esters 28 and 29). A solution of 0.1 mmol of esters **28** and **29** in 2 mL of THF was treated with 1 mL of concentrated aqueous HF for 5 min. The mixtures were poured onto water and extracted with diethyl ether. The organic phases were washed with water, dried, and evaporated to dryness. The residues were purified by TLC to afford phenols **39** and **40** in 80–90% yield.

Phenyl 5,6-bis(4-hydroxyphenyl)-5-octenoate (39): IR (Et_2O) 3330 (OH), 1765 (C=O, ester), 1610 and 1590 cm^{-1} (Ar); ^1H NMR (400 MHz, acetone-d_6) δ 0.77 (t, J = 7.5 Hz, 8-CH_3), 1.56–1.92 (m, aliph CH_2), 2.20 (q, J = 7.5 Hz, 7-CH_2), 2.31 (t, J = 7.0 Hz, 4-CH_2), 2.37 (t, J = 7.5 Hz, 2-CH_2), 6.56–7.41 (m, Ar-H), 8.02–8.27 (m, phenol H); MS (150 °C) m/z 402 (M^+, 54), 340 (22), 279 (27), 253 (20), 251 (23), 239 (64), 237 (63), 225 (37), 215 (53), 173 (46), 159 (46), 145 (63), 135 (51), 133 (100), 121 (73), 107 (99), 94 (81). Anal. ($C_{26}H_{26}O_4$) C, H, O.

4-Chlorophenyl 5,6-bis(4-hydroxyphenyl)-5-octenoate (40): ^1H NMR (400 MHz, acetone-d_6) δ 0.77 (t, J = 7.5 Hz, 8-CH_3), 1.54–1.91 (m, aliph CH_2), 2.19 (q, J = 7.5 Hz, 7-CH_2), 2.30 (t, J = 7.5 Hz, 4-CH_2), 2.37 (t, J = 7.5 Hz, 2-CH_2), 6.55–7.14 (m, Ar-H), 7.36–7.45 (m, Ar-H), 8.00–8.42 (phenol H); MS (180 °C) m/z 438 (M^+, 3), 436 (M^+, 8), 239 (15), 237 (17), 215 (21), 189 (15), 173 (22).

General Desilylation Procedure for the Silyl Ethers 41–44 (Procedure B). A solution of the silyl ethers in THF was treated with ca. 100 mg of KF and 10 mg of 18-crown-6. A few drops of methanol were added, and the solution was stirred for 15–60 min (TLC monitoring). Workup was performed as described in procedure A.

Coupling product of the octanoic acid 10 to daunorubicin (41): yield 4.6 mg (98%); IR (KBr) 3420 (OH), 1715 (C=O amide), 1615 cm^{-1} (C=O, quinone); ^1H NMR (400 MHz, $CDCl_3$/acetone-d_6) δ 0.65 (t, 3 H, CH_3), 1.20 (d, 3 H, CH_3), 1.38 (quint, 2 H, CH_2), 1.63–1.75 (m, 2 H, CH_2), 1.88 (q, 2 H), 2.35 (s, 3 H, $COCH_3$), 2.91 (d, 1 H), 3.18 (d, 1 H), 3.40 (m, 1 H), 4.03 (s, 3 H, OCH_3), 4.15 (q, 1 H), 5.20 (s, 1 H, 1-H), 5.41 (d, 1 H), 6.03 (d, 1 H, NH), 6.75 (m, 4 H, Ar-H), 6.93 (t, 4 H, Ar-H), 7.40 (d, 1 H, Ar-H), 7.75 (t, 1 H, Ar-H), 7.98 (d, 1 H, Ar-H), 13.28 and 13.96 (each s, each 1 H, OH); MS (FAB$^-$) m/z 836 (M + H), 835 (M), 382, 381 (aglycon), 380; MS (FAB$^+$) 838 (M + 3 H), 837 (M + 2 H), 836 (M + H).

5,6-Bis(4-hydroxyphenyl)-5-octen-1-ol (19): yield 3.65 g of an oil (mixture of isomers, quantitative); ^1H NMR (400 MHz, acetone-d_6/D_2O) δ 0.73 (t, 8-CH_3), 0.85 (t, 8-CH_3, styrene), 0.89 (t, 8-CH_3, (*Z*)-stilbene), 1.17–1.80 (m, CH_2), 1.45 and 1.87 (each d, CH_3, styrene), 2.13 (q and t, CH_2), 2.51 (q and t, CH_2, (*Z*)-stilbene), 3.38 (t, CH_2), 3.49 (m, CH_2), 5.51 (m, vinylic-H of styrenes), 5.56 (q, vinylic-H), 6.51–7.01 (m, Ar-H); MS (190 °C) m/z 312 (100, M^+), 283 (20), 265 (26), 253 (60), 239 (83), 224 (48), 223 (47), 210 (26), 189 (21); exact mass calcd for $C_{20}H_{24}O_3$ 312.1725, found 312.1730.

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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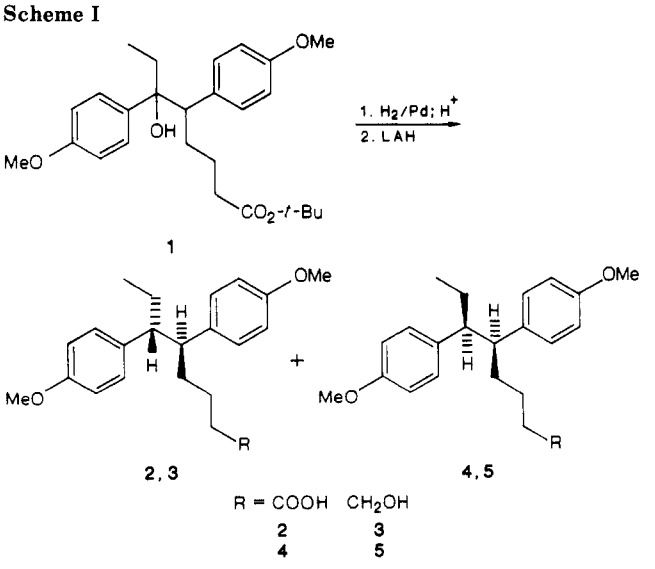
With the *erythro*-hexestrol derivative **2** as the starting material, a variety of cytotoxic linked hexestrol (HEX) compounds were prepared including the HEX-N-lost derivative **36**, the HEX–(chloroethyl)nitrosourea **38**, the HEX-cyclophosphamide **44**, and the HEX–epoxide **68**. Relative binding 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



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