# SYNTHESES OF E- AND Z-PSEUDODIETHYLSTILBESTROL AND Z-1-HYDROXYPSEUDODIETHYLSTILBESTROL

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## ABSTRACT

The synthesis and characterization of E- and Z-3,4-bis(4-hydroxyphenyl)-2-hexene (E- and Z-pseudo-DES) and of Z-3,4-bis(4-hydroxyphenyl)-2-hexen-1-ol (Z-1-hydroxypseudo-DES) are described. These compounds are useful as probes in the study of hormone action.

## INTRODUCTION

The potent synthetic estrogen diethylstilbestrol (DES) has been the subject of much recent investigation due to its involvement in human cancer etiology [1]. A large body of information has been developed concerning its metabolism [2], and continued attention focuses on the biological properties of DES analogs and metabolites [3]. Recent reports describe the syntheses of several of these compounds [4].

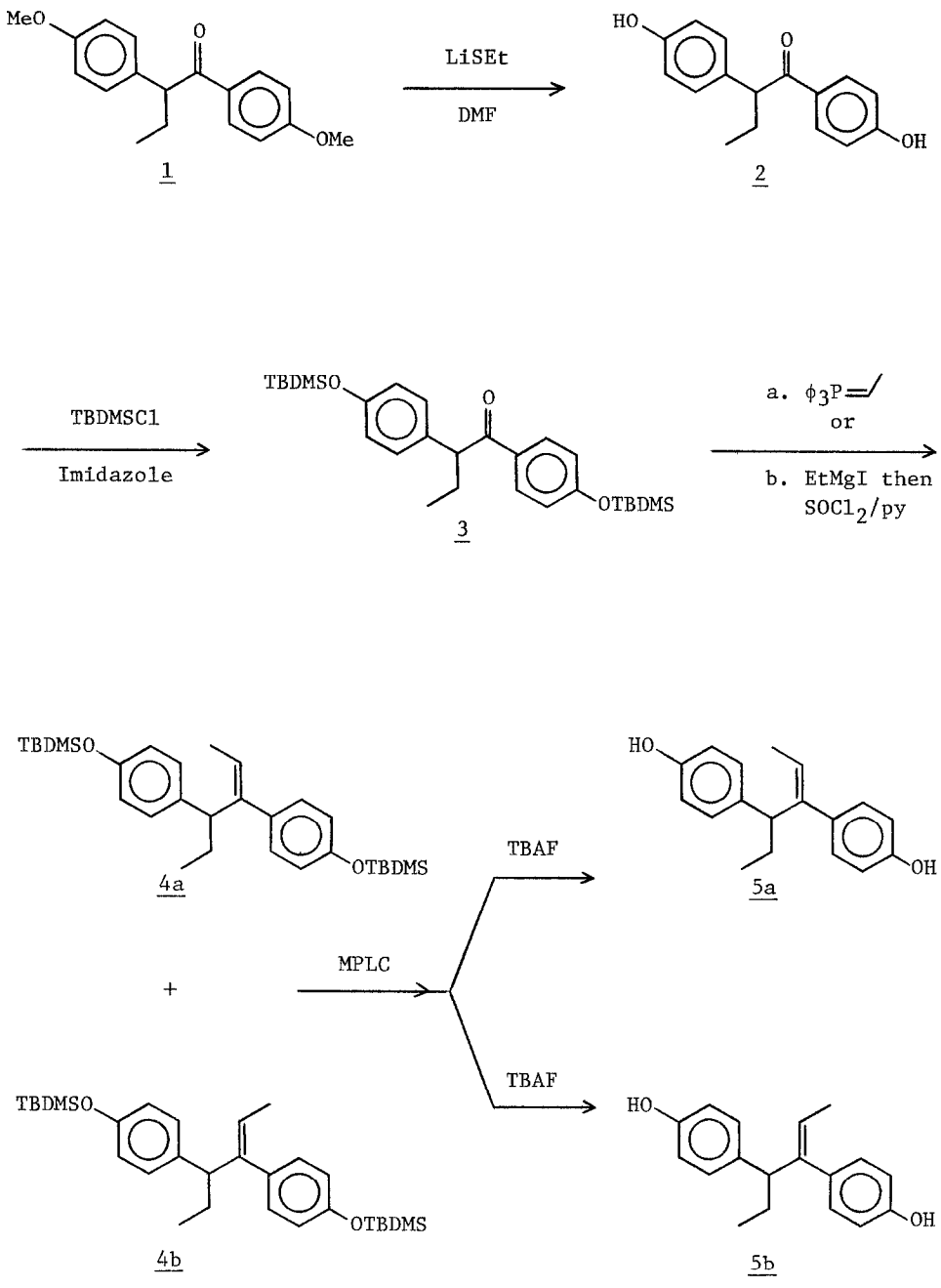
Recently, synthetic work in our laboratories has been directed toward preparation of a number of labeled and unlabeled DES metabolites and related compounds. 1-Hydroxypseudo-DES has been reported as a urinary metabolite of mice [5], but its configuration is not known. We have synthesized and characterized the Z-isomer for use in various biological studies. The two isomers of pseudo-DES were isolated by tedious procedures as early as 1940 [6], and it was recognized that there were great differences in their estrogenicity [7]. The configurations of the isomers were not known until the recent report of Airy and Sinsheimer [8], which describes the isolation of one isomer and determination of its configuration as Z. We herein report a useful preparation of both E- and Z-pseudo-DES.

## RESULTS AND DISCUSSION

### E- and Z-Pseudo-Des

The readily available α-desoxyanisoin (1) [9] (Scheme I) is a convenient starting material for many DES-related compounds, and in our hands Wittig ethylidenation or Grignard addition-dehydration provided E/Z mixtures of O,O'-dimethylpseudo-DES in good yield. However, deprotection using a variety of reagents resulted in at least partial double bond isomerization to DES. Therefore, α-ethyldesoxyanisoin was demethylated using lithium thioethoxide in refluxing dimethylformamide [10]; treatment with boron tribromide or hydriodic acid failed to effectively remove the 4-O-methyl group from the benzoyl ring. The resulting diphenol 2 was converted to the bis(t-butyldimethylsilyl) (TBDMS) ether 3 [11] in 64% yield from α-ethyldesoxyanisoin. Wittig olefination using ethylidenetriphenylphosphorane provided, in 85% yield, a clear oil consisting, by HPLC analysis, of two components in the ratio of ca. 3:7. The 60 MHz NMR spectrum of the mixture included two doublets ($J \cong 7$ Hz) at δ 1.88 and 1.48, shifts reasonable for the vinyl methyls of the expected E- and Z-pseudo-DES derivatives 4a and 4b, respectively. This determination rested upon correlation with the NMR shifts of α-(E,E) and β-(Z,Z) dienestrol [4b] and with other trisubstituted $\Delta^2$ E/Z olefin pairs. The 3:7 product ratio evident from HPLC was confirmed in the NMR, which revealed that the predominant isomer possessed the E configuration.

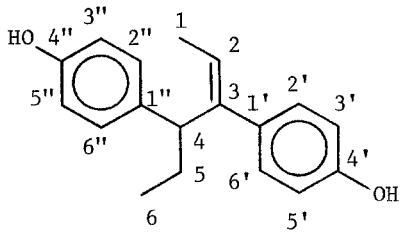
Reaction on the other hand of disilyl ketone 3 with excess ethylmagnesium bromide followed by dehydration using thionyl chloride in pyridine gave a moderate yield of E/Z-pseudo-DES disilyl ether mixture which HPLC and NMR analysis indicated was a ca. 1:4 mixture, predominating in the Z-isomer.



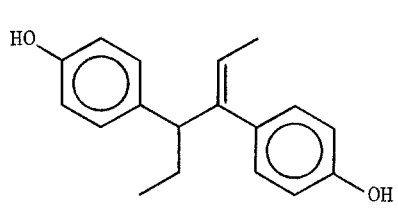

Scheme I. Synthesis of E- and Z-Pseudo-DES.

Repeated recrystallization of the 1:4 mixture provided material which contained ∿ 95% Z-isomer, but separation of isomer mixtures was more effectively carried out using reverse phase medium pressure liquid chromatography (MPLC). Chromatography of 100- to 200-mg quantities of a mixture as described in the Experimental section provided the first eluting Z-isomer in ≧ 99% isomeric purity. Reinjection of the E-enriched fraction usually provided E-isomer in ≧ 99% purity.

Deprotection of the separated isomers with tetrabutylammonium fluoride in THF [11] provided high yields of E- and Z-pseudo-DES (5a and 5b) as crystalline solids. The IR, mass spectral, and NMR (250 MHz) data for the Z-isomer are consonant with those reported by Airy and Sinsheimer [8]. The mass spectra (70 eV) of the two isomers are nearly superimposable, and the IR and UV spectra are very similar. However, the NMR spectra are distinctly different (see Experimental). It is interesting to note that the vinyl protons at C2 (see Figure 1) possess nearly the same chemical shift in the two isomeric compounds (E, δ 5.55; Z, δ 5.57), a finding contrary to that predicted upon consideration of empirical additive increment correlations alone [8,12]. These relative shifts are




E-Pseudo-DES




Z-Pseudo-DES

Figure 1

analogous to those for the equivalent protons in methyl E- and Z-3,4-bis(4-methoxyphenyl)-2-hexenoate (δ 5.76 and 5.78, respectively), reported by Goswami et al. [13], and of ring hydroxylated E- and Z-pseudo-DES [14]. On the other hand, the shifts of the methine protons at C4 have the expected relationship to one another (E: δ 3.98; Z: δ 3.31) with the one having the vinyl methyl group on the same side of the double bond (E-pseudo-DES) shifted well downfield relative to the other. In fact, it is this proton which seems to show a diagnostic chemical shift, appearing for the Z-isomers of a number of similar compounds at δ 3.2-3.5 and for the E-isomers at δ 3.8-5.2.

Expansion of the aromatic regions of the 250 MHz spectra (Figure 2) allows some relatively straightforward assignments. For the E-isomer of pseudo-DES, the downfield (δ 7.02) multiplet, representing two hydrogens, and its companion at δ 6.74 comprise one AA'BB' system, while the sets at δ 6.695 and 6.59 make another. The additional 0.7 Hz splitting of the 7.02 signal indicates benzylic coupling [15] to an exocyclic hydrogen, which must be the C4 methine. Therefore, the δ 7.02 signal arises from the C2",C6" hydrogens and that at δ 6.70 those at C3",C5". The AA'BB' systems at δ 6.695 and 6.59 represent the hydrogens at C3',C5' and C2',C6'. In the spectrum of the Z-isomer, long range coupling of the downfield two-hydrogen signal at δ 6.93 is smaller than ca. 0.4 Hz and not readily observable in this spectrum, but Airy and Sinsheimer [8] have assigned this to C2",C6" on the basis of an NOE measurement. The four hydrogens of the C3-phenyl ring fall coincidentally into a singlet at δ 6.71.

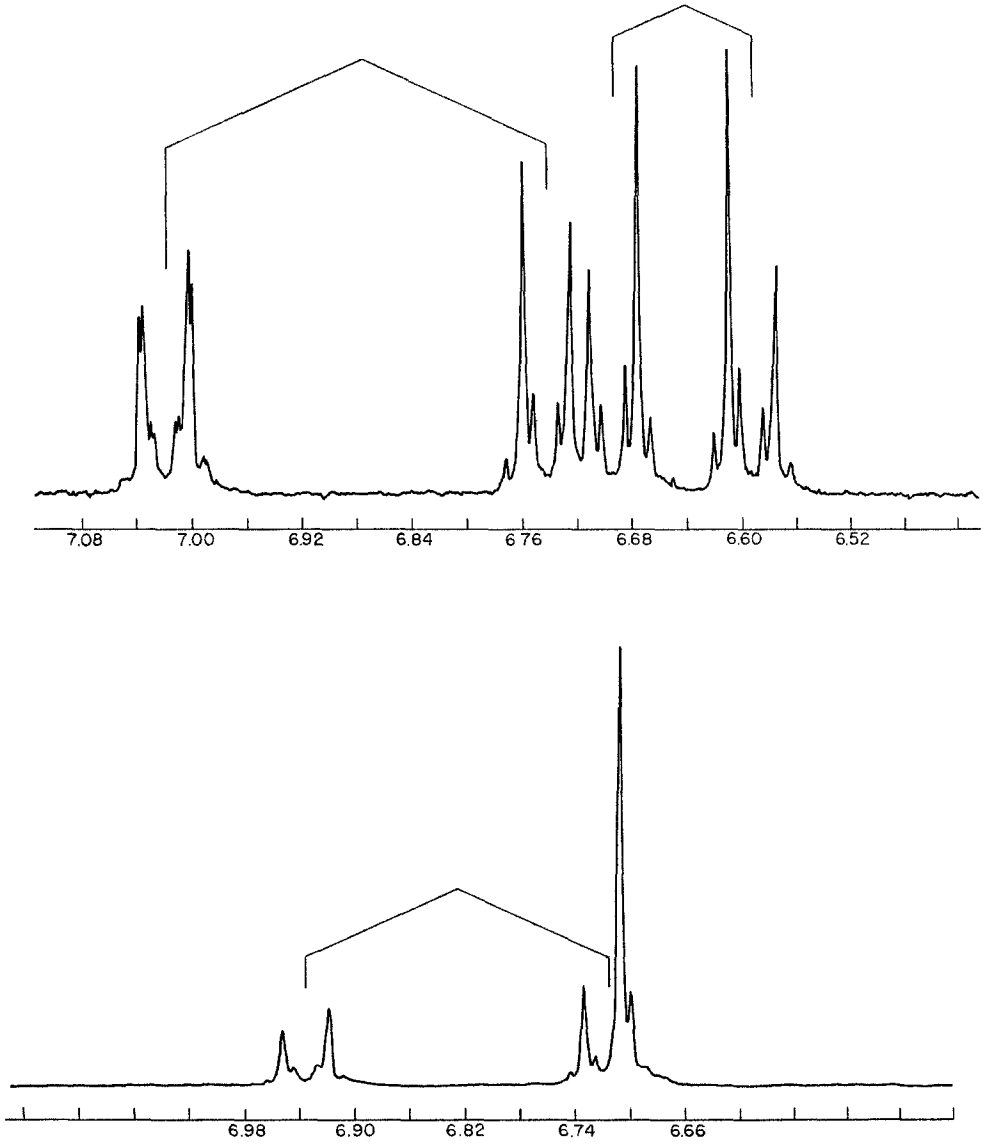
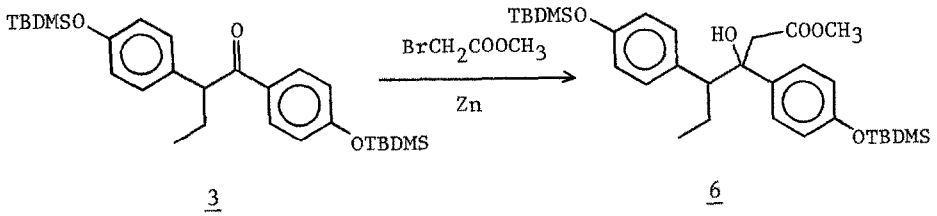



Figure 2. Aromatic Regions of NMR Spectra (250 MHz) of E-Pseudo-DES (top) and Z-Pseudo-DES (bottom)

Z-1-Hydroxypseudo-DES

The synthetic method, outlined in Scheme II, commenced with the disilyl ketone 3. Paralleling the work of Goswami et al. [13] on the

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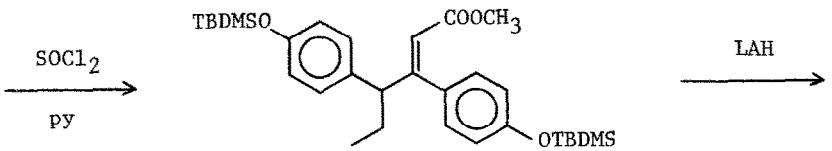


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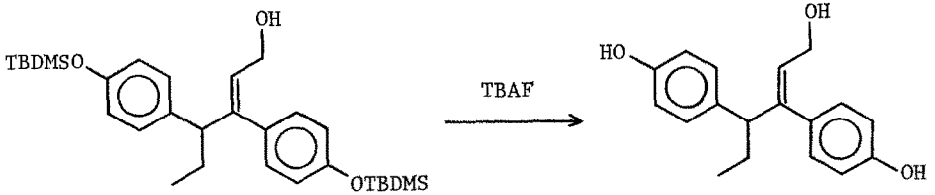


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Scheme II. Synthesis of Z-1-Hydroxypseudo-DES.

corresponding dimethyl ether, the two-carbon side chain was added in a Reformatsky reaction using methyl bromoacetate, in 70% yield. The diastereomeric alcohol mixture 6 was dehydrated using thionyl chloride in pyridine, providing 7 as mainly the Z-isomer, as determined by comparison of the NMR chemical shifts of the C4 methine (δ 3.38) and the ester methyl group (3.47) with those of the corresponding dimethyl ether of Goswami et al. (δ 3.34 and 3.40, respectively, as opposed to δ 5.31 and 3.60, respectively, for the E-isomer) [13]. Lithium aluminum hydride reduction gave the allylic alcohol in 82% yield, and deprotection gave Z-1-hydroxypseudo-DES, m.p. 167-168°, in 20% overall yield. As with the pseudo-DES isomers themselves, the mild desilylation conditions provided final product without double bond isomerization.

## EXPERIMENTAL

### Apparatus

Melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Ultraviolet-visible spectra were recorded on a Varian Super Scan 3 spectrometer. IR spectra were obtained on a Beckman AccuLab 1 infrared spectrometer in solution or as nujol mulls. Mass spectra were determined by direct inlet with a Varian-MAT-A double focusing mass spectrometer or a Varian-MAT CH4 single focusing mass spectrometer and Finnigan/Incos 2400 data system at 70 eV. Proton NMR data were recorded at 60 MHz on a Varian EM 360A spectrometer reporting chemical shifts downfield from tetramethylsilane or at 250 MHz on a Bruker WMT 250 spectrometer. HPLC was performed on a Varian Model 5020 with a Schoeffel Model SF7700 detector at 254 nm. MPLC was carried out using a Michel-Miller type glass column, 37 x 350 mm, packed with Chro-Media reverse phase LRP-1 with a guard column, Michel-Miller type glass, filled with the same material. An FMI Lab Pump Model PP-SY-ICSC with Lo-Flow kit was used to pump the solvent.

### 1,2-Bis(4-t-butyldimethylsilyloxyphenyl)-1-oxobutane (3)

Lithium thioethoxide (6.2 g, 91 mmoles, prepared by reaction of ethanethiol with n-butyllithium) was added to a solution of α-ethyldesoxyanisoin (1) [9] (5.0 g, 18 mmoles) in 100 ml of dry dimethylformamide and the mixture brought to reflux. Monodemethylation was complete within 3 hr, but heating was continued for a total of 18 hr to complete the demethylation. Water was added to the cooled solution, and the mixture was extracted with ether. The aqueous layer was acidified with dilute HCl and reextracted with 3 x 100 ml of ether. The combined organics

were washed with water, dried ($MgSO_4$), and evaporated in vacuo to give a yellow oil. This was dissolved in 100 ml of dimethylformamide and treated with t-butyldimethylchlorosilane (7.2 g, 48 mmoles) and imidazole (6.5 g, 95 mmoles) at room temperature. After 3.5 hr, water was added and normal workup with ether yielded a colorless oil which was purified on a silica gel column eluted with 1:1 $CH_2Cl_2$:hexanes to provide 4.3 g (64% yield) product 3 as a colorless oil. $TLC_1$($SiO_2$, $CH_2Cl_2$) $R_f$ = 0.56; IR = $\lambda_{max}$ 1678, 1600, 1510, 1270, 925, 950 $cm^{-1}$; NMR (60 MHz, $CCl_4$), δ: 0.15 (s, 6H, $SiCH_3$), 0.18 (s, 6H, $SiCH_3$), 0.82 (t, J = 7, 3H, C4-$H_3$), 0.91 (s, 18H, t-Bu), 1.55-2.22 (m, 2H, C3-$H_2$-), 4.18 (t, J = 7, 1H, C2-H), 6.66 and 7.78 (AA'BB', $J_{AB}$ = 8, 1-phenyl ArH), 6.60 and 7.02 (AA'BB', $J_{AB}$ = 8.2, 2-phenyl ArH).

Wittig Reaction of Ketone 3

To (ethyl)triphenylphosphonium bromide (2.3 g, 6.2 mmoles) in 160 ml of dry ether was added 1.55 M n-butyllithium in hexane (6.5 mmoles) under an argon atmosphere. After stirring 15 min the homogeneous red solution was treated by slow addition of a solution of ketone 3 (2.3 g, 4.75 mmoles) in 50 ml of ether. The reaction was refluxed 1 hr, quenched with water, and worked up in a normal fashion. The crude product was purified by chromatography on silica gel eluted with $CH_2Cl_2$:hexanes 1:9 to give 2.0 g (85% yield) of O,O'-bis(t-butyldimethylsilyl)-pseudo-DES isomer mixture. The 60 MHz NMR indicated an E/Z ratio of 68:32 by integration of the vinyl methyl doublets at δ 1.87 and 1.47, respectively. TLC: $SiO_2$, $CH_2Cl_2$:hexanes 1:1, $R_f$ = 0.75.

Grignard Addition-Dehydration of Ketone 3

Ethyl Grignard reagent, prepared from 3.2 g (20 mmoles) of ethyl iodide and magnesium in anhydrous ether was treated dropwise at 0° with a solution of 3.4 g (7.0 mmoles) of ketone 3 in 50 ml of ether. After the addition was complete, the mixture was heated to reflux for 30 min, cooled, and the reaction quenched by addition of water and saturated $NH_4Cl$. Normal workup and passage through a short silica gel column provided the mixture of diestereomeric alcohols as a nearly colorless oil (3.4 g). TLC showed a single component, and IR showed the absence of carbonyl stretch at 1678 $cm^{-1}$.

To 1 g of the product dissolved in pyridine (2 ml) under an argon atmosphere was added thionyl chloride (0.4 ml). After stirring 2 hr at room temperature, water was added and the mixture was extracted with 1:1 benzene:ether. The organic layer was washed, dried ($MgSO_4$), and the solvent evaporated in vacuo. The residue was purified by chromatography on silica gel eluted with $CH_2Cl_2$:hexanes to provide 0.58 g of clear oil (56% yield). NMR analysis (60 MHz) showed an E:Z ratio of 22:78.

Separation of E- and Z-O,O'-Bis(t-butyldimethylsilyl)-pseudo-DES

The medium pressure (50-120 psi) chromatographic separation was carried out using a system consisting of a glass Michel-Miller type column (37 x 350 mm) preceded by a 25-ml capacity precolumn, both packed with Whatman ChroMedia LRP-1 (13-24 μm) equilibrated with 97% methanol.

One-to two-hundred-milligram quantities of the disilyl ether mixture dissolved in a minimum of 1:1 THF:methanol were injected at a flow rate of 1.8 to 2 ml/min 97% methanol. Examination (HPLC or NMR) of fractions collected during product elution between 18 and 22 hr usually revealed that the bulk of the first-eluting Z-isomer could be collected with little or no contamination by E-isomer. The later eluting isomer usually contained 10 to 20% Z-isomer, but reinjection of such E-enriched material usually resulted in purification of the E-isomer to the ≥ 99% level. Isolated from several injections were 314 mg of Z-isomer (4b) and 278 mg of E-isomer (4a), both of > 99% purity by HPLC (LDC Spherisorb $C_{18}$ 5 μm, 15 cm x 3.6 mm ID, 90% ethanol at 1.0 ml/min, E: $R_f$ = 20.3 min; Z: $R_f$ = 18.7 min).

E-O,O'-Bis(t-butyldimethylsilyl)-pseudo-DES (4a): NMR (60 MHz, $CCl_4$): δ 0.15 (s, 6H, $SiCH_3$), 0.18 (s, 6H, $SiCH_3$), 0.90 (t, J = 6, 3H, C6-$H_3$), 0.96 (s, 9H, t-butyl), 0.99 (s, 9H, t-butyl), 1.55-204 (m, 2H, C5-$H_2$), 1.87 (d, J = 7, 3H, C1-$H_3$), 3.91 (dd, J = 6, 8, 1H, C4-H), 5.49 (q, J = 7, 1H, C2-H), 6.47-7.07 (m, 8H, ArH); MS, m/e (%): 497 (22.9), 496 (52.0), 469 (15.2), 468 (40.8), 467 (100.0), 249 (39.3), 248 (19.0), 247 (82.0), 191 (41.7), 73 (96.9); IR (neat) 2955, 2925, 2860, 1600, 1509, 1260 (br), 920, 845 $cm^{-1}$.

Z-O,O'-Bis(t-butyldimethylsilyl)-pseudo-DES (4b): NMR (60 MHz, $CCl_4$): δ 0.17 (s, 12H, $SiCH_3$), 0.87 (t, J = 6, 3H, C6-$H_3$), 0.97 (s, 18H, t-butyl), 1.48 (d, J = 7, 2H, C1-$H_3$), 1.52-2.02 (m, 2H, C5-$H_2$), 3.23 (t, J = 7, C4-H), 5.50 (q, J = 7, C2-H), 6.40-6.96 (m, 8H, ArH); MS, m/e (%): 497 (23.0), 496 (51.1), 469 (15.2), 468 (41.3), 467 (100.0), 249 (37.1), 248 (19.4), 247 (80.2), 191 (41.6), 73 (94.6); IR (neat): 2960, 2930, 2860, 1605, 1505, 1260 (br), 925, 845 $cm^{-1}$.

E-Pseudo-DES (5a)

A 238-mg (0.48 mmole) portion of the disilyl ether was dissolved in 2.5 ml of dry THF and treated with 1.2 mmoles of tetra-n-butylammonium fluoride in THF. After 1.5 hr the solution was diluted with water and worked up with ethyl acetate to give 157 mg of oil. Trituration with hexane and recrystallization from ethyl acetate-hexane provided 88 mg (68%) of E-pseudo-DES, m.p. 139-141°, as white microcrystals (lit. [6] 143.5°). HPLC analysis (μPorasil, 3.6 mm x 25 cm, 3% isopropanol in isooctane, 2.0 ml/min, λ = 254 nm, $R_T$ = 9.6 min) indicated a purity of ≥ 98%. NMR (250 MHz, acetone-$d_6$): δ 0.89 (t, J = 7.4, 3H, C6-$H_3$), 1.63 (m, 1, C5-H), 1.87 (m, 1H, C5-H), 1.88 (d, J = 7.2, 3H, C1-$H_3$), 3.98 (dd, J = 5.7, 8.3, 1H, C4-H), 5.55 (q, J = 7.2, 1H, C2-H), 6.59 (m, 2H, ArH), 6.72 (m, 4H, ArH), 7.02 (m, 2H, ArH), 8.12 (s, OH); MS, m/e (%): 268 (49.6), 240 (17.4), 239 (100.0), 145 (42.4), 135 (27.5), 133 (54.5), 107 (42.4), 105 (12.2); UV (EtOH), nm (ε): 284 (sh), 279 (3620), 230 (15,200); IR (nujol): 3300, 2960, 1625, 1605, 1530, 1235, 845 $cm^{-1}$.

Z-Pseudo-DES (5b)

In the same manner as the other isomer, a 296-mg portion of Z-O,O'-bis(t-butyldimethylsilyl)-pseudo-DES was deprotected and the crude product triturated with hexane to yield 108 mg (67% yield) of Z-pseudo-DES, m.p. 150-151.5° (lit. [6] 153°). HPLC analysis as on the E-isomer (no

difference in retention time) indicated a ≧ 98% purity. NMR (250 MHz, acetone-$d_6$): δ 0.85 (t, J = 7.3, 3, C6-$H_3$), 1.48 (dd, J = 7.0, 0.9, 3H, C1-$H_3$), 1.65 (m, 1H, C5-H), 1.76 (m, 1H, C5-H), 3.31 (t, J = 7.3, 1H, C4-H), 5.57 (dq, J = 7.0, 0.9, 1H, C2-H), 6.70 (m, 6H, ArH), 6.93 (m, 2H, ArH), 8.03 (s, OH), 8.13 (s, OH); MS, m/e (%): 268 (52.7), 240 (17.9), 239 (100.0), 145 (40.8), 135 (29.3), 133 (59.9), 107 (42.5), 105 (12.2); UV (EtOH), nm (ε): 283 (sh), 278 (2980), 229 (16500); IR (nujol): 3310, 2940, 1615, 1600, 1510, 1450, 1250, 1230, 830 $cm^{-1}$.

Methyl 3-Hydroxy-3,4-bis(4-t-butyldimethylsilyloxyphenyl)hexanoate (6)

To zinc metal (22 g, 33 mmoles) under a nitrogen atmosphere was slowly added a solution of ketone 3 (4.3 g, 11 mmoles) and freshly distilled methyl bromoacetate (5.0 g, 33 mmoles) in 10 ml of benzene. External heating was used to initiate the reaction, and after the addition was complete, the mixture was refluxed for 1 hr. The reaction was quenched with saturated ammonium chloride solution and worked up by ether extraction, etc., to provide 4.3 g (70% yield) of the diastereomers of 6 as a clear oil. The 60 MHz NMR spectrum is similar to that reported for the aromatic dimethoxy analogues [13]. The material was used without further purification in the next step.

Methyl 3,4-Bis(4-t-butyldimethylsilyloxyphenyl)-2(Z)-hexenoate (7)

Compound 6 (3.0 g, 5.4 mmoles) was dissolved in 12 ml of pyridine and treated with 0.78 ml (10.7 mmoles) of thionyl chloride at room temperature for 15 min. Water was added and the reaction was worked up via hexane extraction. TLC analysis ($SiO_2$, $CH_2Cl_2$) indicated partial deprotection, and the product was resilylated by the usual procedure. The resulting crude product was purified by column chromatography ($SiO_2$, 1:1 $CH_2Cl_2$:hexane) to provide 0.45 g of ketone 3 and 1.35 g (46% yield, or 62% based on recovered starting material) of α,β-unsaturated ester 7. Assignments of Z-configuration was based on NMR comparison to E- and Z-methyl 3,4-bis(4-methoxyphenyl)-2-hexenoate [17]. NMR (60 MHz, $CDCl_3$): δ 0.17 (s, 12H, $SiCH_3$), 0.88 (t, J = 7, 3H, C6-$H_3$), 0.97 (s, 18H, t-butyl), 1.52-2.06 (m, 2H, C5-$H_2$), 3.38 (t, J = 7, 1H, C4-H), 3.47 (s, 3H, $COOCH_3$), 5.90 (s, 1H, C2-H), 6.53-6.96 (m, 8H, ArH); IR (nujol): 2960, 2940, 1730, 1605, 1505, 1260, 925, 845 $cm^{-1}$.

3,4-Bis(4-t-butyldimethylsilyloxyphenyl)-2(Z)-hexenol (8)

Ester 7 (1.35 g, 2.5 mmoles) was dissolved in anhydrous ether and treated portionwise at room temperature with lithium aluminum hydride (190 mg, 5.0 mmoles). After 10 min the reaction was quenched by addition of saturated ammonium chloride solution and water. The mixture was filtered and the solids rinsed with more ether. The filtrate was dried ($Na_2SO_4$) and stripped of solvent to provide alcohol 8 as a colorless oil (1.05 g, 82% yield). HPLC (5 μm $C_{18}$ reverse phase, 90% methanol in water, λ = 254 nm) indicated a purity of 98%. NMR (60 MHz, $CDCl_3$): δ 0.16 (s, 12H, $SiCH_3$), 0.87 (t, J = 7, 3H, C6-$H_3$), 0.98 (s, 18H, t-butyl), 1.50-2.08 (m, 2H, C5-$H_2$), 3.30 (t, J = 7, C4-H), 3.90 (d, J = 7, 2H, C1-$H_2$), 5.70 (t, J = 7, 1H, C2-H), 6.46-7.02 (m, 8H, ArH); IR (neat): 3340, 2970, 2940, 1605, 1505, 1260, 925, 845 $cm^{-1}$.

Z-1-Hydroxypseudo-DES (9)

A 1.00 g portion of 8 was deprotected by use of excess tetra-n-butylammonium fluoride in THF [11], yielding a clear oil. Trituration with hexane solidified the material, which was recrystallized from ethyl acetate-hexane to provide Z-1-hydroxypseudo-DES (381 mg, 69% yield) as colorless needles, m.p. 167-168°, purity ≥ 98% by HPLC (5 μm Spherisorb $C_{18}$, 35% methanol in water for 15 min, then 70% methanol in water for 15 min, λ = 254 nm, $R_T$ = 20.0 min). NMR (60 MHz, acetone-$d_6$): δ 0.85 (t, J = 7, 3H, C6-$H_3$), 1.75 (m, 2H, C5-$H_2$), 3.33 (t, J = 7, 1H, C4-H), 3.85 (s, 1H, aliphatic OH), 3.91 (d, J = 7, 2H, C1-$H_2$), 5.68 (t, J = 7, 1H, C2-H), 6.52-7.16 (m, 8H, ArH), 8.17 (s, ArOH); MS, m/e (%): 284 (4.7), 266 (48.5), 237 (60.0), 151 (14.6), 149 (14.2), 135 (100.0), 121 (16.2), 119 (15.4), 107 (72.1); UV (EtOH), nm(ε): 284 (sh), 278 (3110), 230 (16600); IR (nujol): 3380, 3240, 2940, 1600, 1515, 1460, 1380, 1250 $cm^{-1}$.

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