SYNTHESIS OF METABOLIC INTERMEDIATES OF DIETHYLSTILBESTROL

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ABSTRACT

This report details the synthesis of 1) 3,4,4'-trihydroxy-α,α'-diethyl-trans-stilbene; 2) 3,4-bis-(p-hydroxyphenyl)-trans-3-hexenol; 3) 3,4-bis-(p-hydroxyphenyl)-2,4-cis,cis-hexadienol; 4) 3,4-bis-(3'-methoxy-4'-hydroxyphenyl)-trans-3-hexene; 5) 3,4-bis-(3',4'-dimethoxyphenyl)-trans-3-hexene. These compounds are suspected metabolites of diethylstilbestrol.

INTRODUCTION

The metabolism of the synthetic estrogen diethylstilbestrol (DES) has recently attracted the attention of investigators due to the finding that it has been linked to the occurrence of vaginal adenocarcinoma in adolescent daughters whose mothers had received DES during pregnancy [1,2,3]. Current research trends indicate additional problems for this group [4]. Furthermore, the use of DES in agricultural feeds constitutes an additional potential hazard to human health. In order to facilitate the metabolic investigations and assess the mutagenic and carcinogenic potential of DES, it was necessary to prepare certain authentic compounds which were suspected to be metabolic intermediates. This report details the synthesis of 1) 3,4,4'-trihydroxy-α,α'-diethyl-trans-stilbene (7); 2) 3,4-bis-(p-hydroxyphenyl)-trans-3-hexenol (16);

3) 3,4-bis-(p-hydroxyphenyl)-2,4-cis,cis-hexadienol (22); 4) 3,4-bis-(3'-methoxy-4'-hydroxyphenyl)-trans-3-hexene (27); and 5) 3,4-bis-(3',4'-dimethoxyphenyl)-trans-3-hexene (30).

RESULTS AND DISCUSSION

The synthetic approach to 3,4,4'-trihydroxy-α,α'-diethyl-trans-stilbene (7) is shown in Scheme 1. The ketone (2) was prepared via a modified glycidic ester condensation [5] in high yield, and was alkylated under phase transfer conditions [6] with ethyl iodide to give the alkyl ketone (3). Condensation of the aryl anion prepared from p-bromoanisole (BuLi/THF) with the ketone (3) gave the alcohol (4). Under a variety of conditions, dehydration of the alcohol (4) gave largely the isomer (5) which could be isomerized in the presence of iodine to a 1:1 mixture of the desired isomer (6) and (5). Separation of the mixture of these isomers was readily achieved by "dry column" chromatography. The recovered isomer (5) was once again isomerized to gain an additional amount of (6). In this manner, a high yield of the desired compound (6) could be obtained. It was later determined that the alcohol (4) could be converted to the same mixture of isomers by the action of iodine in refluxing xylene [7]. Finally, demethylation with boron tribromide gave the triol (7).

The preparation of 3,4-bis-(p-hydroxyphenyl)-trans-3-hexenol (16) (Ω-hydroxydiethylstilbestrol) is shown in Scheme 2. Condensation of α-ethyldesoxyanisoin (8) with lithium t-butyl acetate [8] gave the hydroxyester (9) which was dehydrated with the methanesulfonyl chloride:sulfur dioxide reagent [9] to give the α,β-unsaturated ester (10). Isomerization of the ester (10) to a 1:1 mixture of (E)- and (Z)-β-γ, unsaturated esters, (11) and (12), was effected by potassium t-butoxide

in dimethyl sulfoxide (DMSO). The desired (E)-isomer (11) was separated by "dry column" chromatography and reduced with lithium aluminum hydride to yield the Ω-hydroxy compound (13). Attempted demethylation of the alcohol (13) with boron tribromide [10] resulted in the conversion of the primary hydroxyl functionality to the corresponding primary bromo derivative (17). Protection of the primary alcohol as an acetate (14), and subsequent demethylation under controlled conditions with boron tribromide gave Ω-acetoxy DES (15). Finally, hydrolysis of the acetate (15) gave the desired product (16) in good yield.

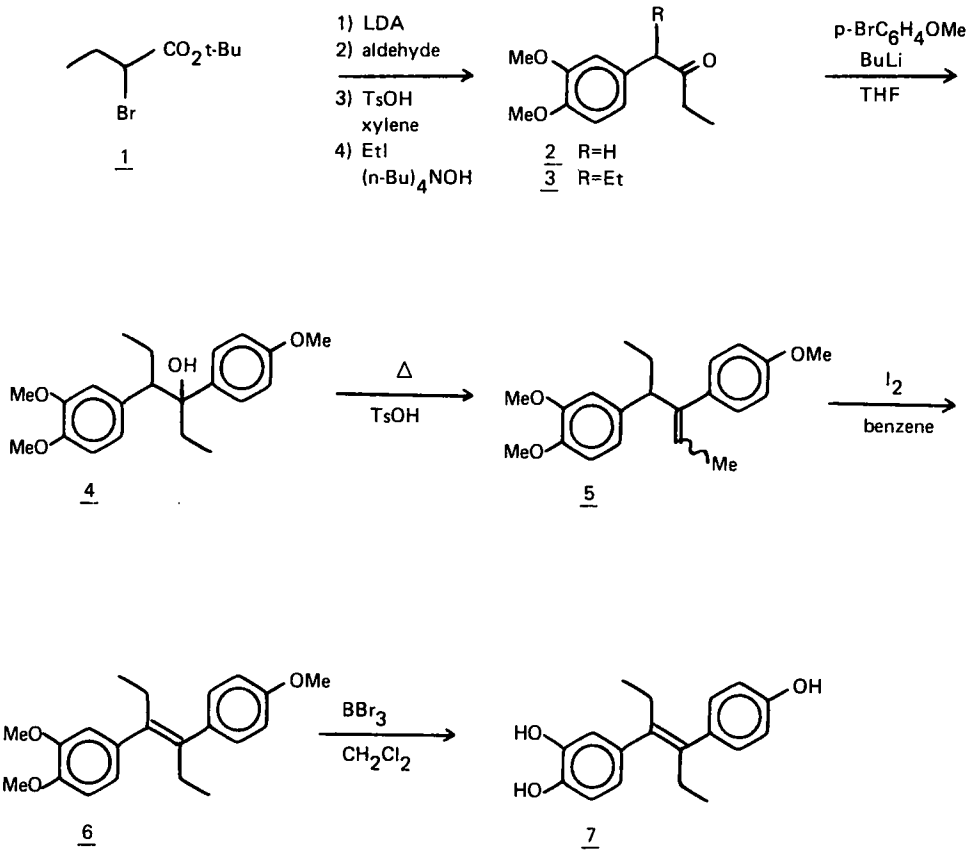
3,4-Bis-(p-hydroxyphenyl)-2,4-cis,cis-hexadienol (Ω-hydroxydienestrol) was prepared as shown in Scheme 3. The isomeric ester mixture (11) and (12), prepared as shown in Scheme 2, was reduced with lithium aluminum hydride to give a mixture of (E)-and (Z)-homoallylic alcohols (13) and (18). The hexenols (13) and (18) were converted to the corresponding acetates (14) and (19) and demethylated with boron tribromide as before (Scheme 2). The (E)-isomer (15) could be crystallized from this mixture, if desired. The mixture of dihydroxy-acetates (15) and (20) was oxidized in low yield to Ω-acetoxydienestrol (21) by the action of lead tetraacetate [11]. No attempt was made to maximize the yield. The Z,Z structure (21) was assigned on the basis of spectral data and in accordance with the expected structure based on the reaction of diethylstilbestrol with lead tetraacetate [11]. During the course of this work, Metzler [12] reported the preparation of Ω-hydroxydienestrol (22) by an alternate route. Hydrolysis of the monoacetate (21) gave Ω-hydroxydienestrol (22) whose spectral data are identical to those reported by Metzler [12]. The Ω-hydroxydienestrol (22) was unstable in our hands and was best stored as the monoacetate

(21) or the triacetate (23), both of which could be converted to the desired compound (22) when required.

The preparation of 3,4-bis-(3'-methoxy-4'-hydroxyphenyl)-trans-3-hexene (27) and 3,4-bis-(3',4'-dimethoxyphenyl)-trans-3-hexene (30) is illustrated in Scheme 4. Vanillin (24) was chosen as the starting material for both compounds. For the preparation of 3,3'-dimethoxy-diethylstilbestrol (27), vanillin (24) was converted to the methoxy-ethoxymethyl (MEM) ether (25) [13]. Condensation of aldehyde (25) with ethyl magnesium bromide, followed by oxidation of the crude alcohol with pyridinium chlorochromate [14] gave the ketone (26) in good yield. Purification of the ketone (26) was accomplished with preparative HPLC. The ketone (26) was converted in one step to 3,3'-dimethoxy DES (27) by the action of lithium aluminum hydride-titanium trichloride (McMurry's reagent) [15]. Purification of the crude product was effected by "dry column" chromatography and subsequent crystallization. The pure trans product was rapidly isomerized to a 75:25 (trans:cis) mixture in solution. The pure trans product (27) [16] was crystallized directly from this mixture.

In a similar manner, the tetramethoxy compound (30) was prepared. Vanillin (24) was converted to the known dimethoxybenzaldehyde (28) [17] and to the ketone (29) by the sequence utilized previously. Condensation of the ketone (29) in the presence of the titanium reagent [18] gave the tetramethoxy DES derivative (30) in good yield.

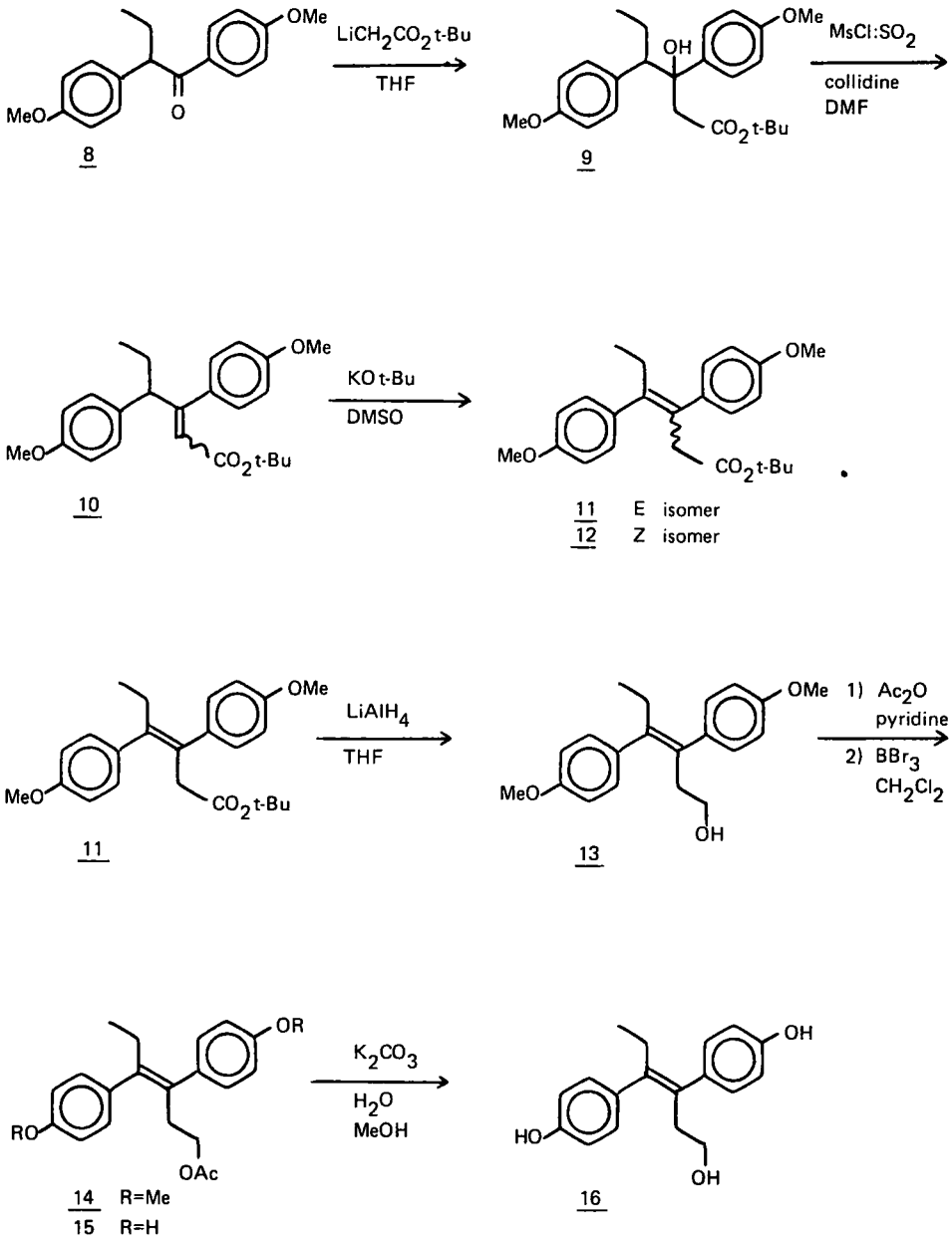
SCHEME 1



Abbreviations used throughout schemata:

LDA = lithium diisopropylamide; aldehyde = 3,4-dimethoxybenzaldehyde; THF = tetrahydrofuran; DMF = N,N-dimethylformamide.

SCHEME 2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MeO
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11
LiAlH4
THF
OMe
MeO
OH
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1) Ac2O
pyridine
2) BBr3
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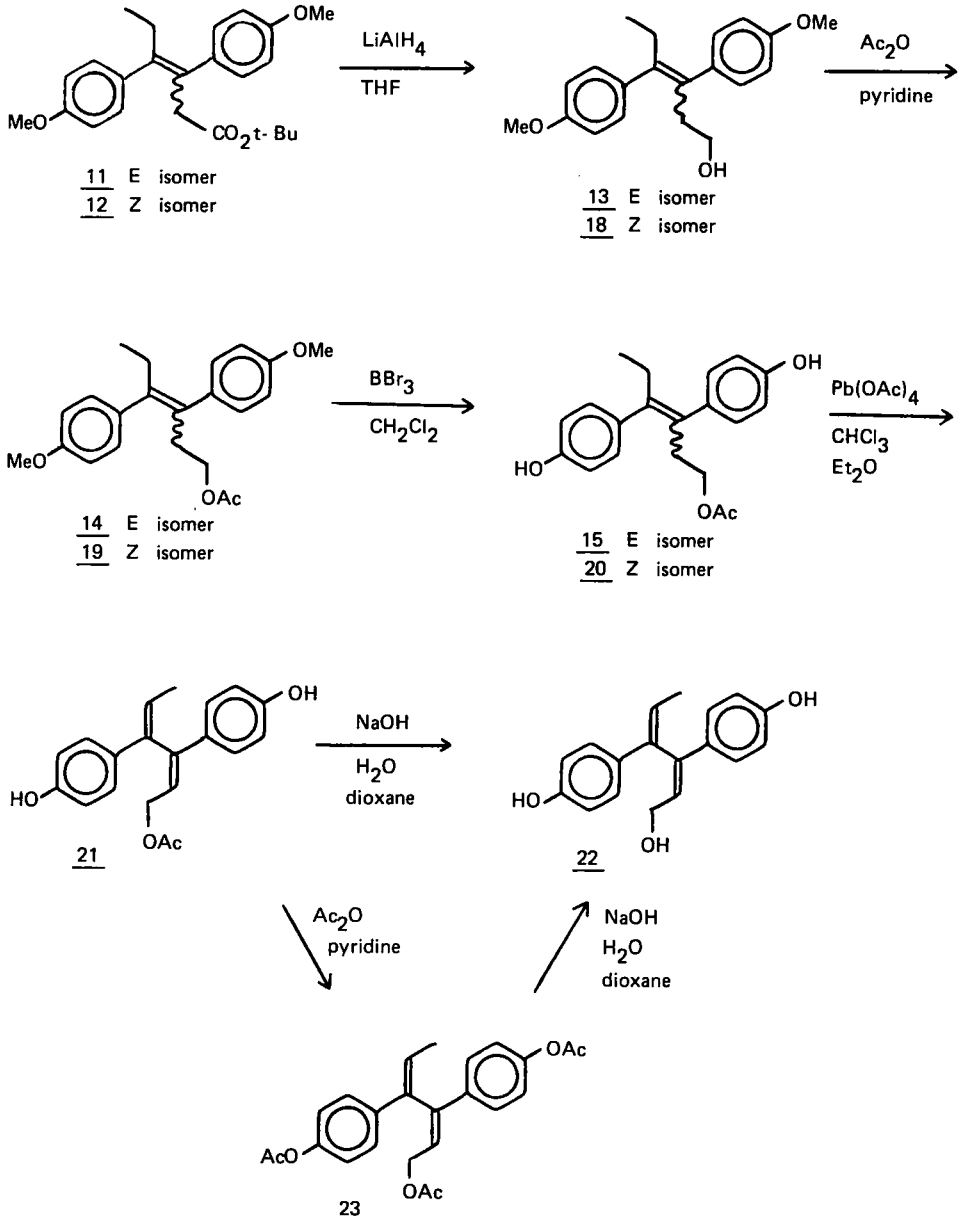
SCHEME 3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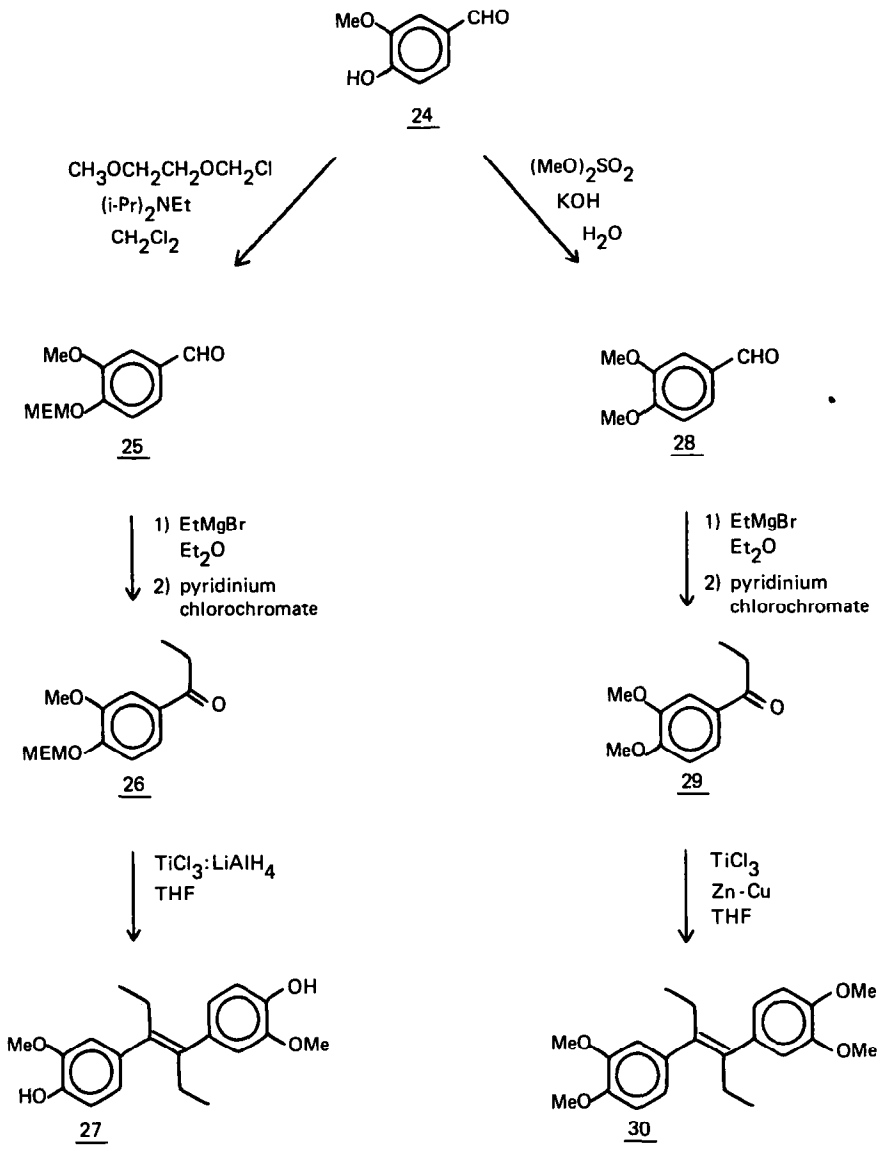
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OMe
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OMe
MeO
30

MATERIALS AND METHODS

Solvents and reagents: All chemicals were analytical reagent grade and were used without further purification. All solvents were reagent grade and used without purification with the following exceptions. Tetrahydrofuran was distilled from lithium aluminum hydride just prior to use. Collidine, dimethyl sulfoxide, pyridine, hexanes (a mixture of hexane isomers), and acetic anhydride were distilled.

Proof of chemical purity was established by normal spectral (IR, NMR, MS) and analytical (TLC, HPLC, and chemical analysis) techniques. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were determined in a potassium bromide disc using a Perkin-Elmer Model 467 grating spectrometer. NMR spectra were obtained with a Varian EM-390 spectrometer in deuterochloroform (unless otherwise specified) and are reported in ppm downfield from the internal standard tetramethylsilane. NMR data shown at 80 mHz were obtained on a Varian CFT-20 spectrometer operating in the proton mode. MS were determined on a Finigan quadrupole mass spectrometer. "Dry column" chromatography was performed on Woelm silica gel in a nylon column as described by Loev and Goodman [19]. The microanalyses were performed by Midwest Microlab, Indianapolis, Indiana.

EXPERIMENTAL

t-Butyl 2-ethyl-2,3-epoxy-3-(3',4'-dimethoxyphenyl)-propanoate

To diisopropylamine (5.7 ml, 41 mmol) in 90 ml tetrahydrofuran at -78°C was added the butyllithium (1.6 M in hexane, 23 ml, 37 mmol) dropwise. The mixture was stirred at -78°C for 15 min and then was treated with t-butyl 2-bromobutyrate (7.92 g, 35.5 mmol) over a 20 min period. Stirring was continued at -78°C for an additional 40 min. The dimethoxybenzaldehyde (6.1 g, 36.7 mmol) was dissolved in 40 ml tetrahydrofuran and added to the reaction mixture. After stirring for 1 h at -78°C the cooling bath was removed and stirring was continued overnight. Normal workup gave 12.6 of crude product which was not further purified, but was used directly in the next reaction. Distillation (Kugelrohr short path) gave no apparent increase in purity. IR: ν_{max} 1735, 1518, 1155 cm^{-1}; NMR: 0.98 (t, J = 7 Hz, 3 H, $-CH_3$), 1.54 (s, 9 H, t-Bu), 3.0 (s, 6 H, $-OCH_3$), 4.24 (s, 1 H, -CH)ppm.

1-(3',4'-dimethoxyphenyl)-2-butanone (2)

The glycidic ester (7.5 g, crude) was dissolved in 225 ml xylene and treated with several crystals of p-toluenesulfonic acid. The reaction mixture was heated at reflux for 5-1/2 h. Normal workup gave 4.3 g of the ketone (2). Spectral data and thin layer chromatography (ether-hexanes, 2:1) indicated that the product was pure enough to be used directly in the next reaction. IR: ν_{max} 1712 cm^{-1}.

4-(3',4'-dimethoxyphenyl)-3-hexanone (3)

To a solution of tetra-n-butyl ammonium hydrogen sulfate (7.74 g, 22.8 mmol) and sodium hydroxide (1.80 g, 45 mmol) in 20 ml water was added a mixture of the ketone (2, 3.96 g, 19.0 mmol) and ethyl iodide (3.6 ml, 45 mmol) in 35 ml dichloromethane. The reaction was allowed to stir at room temperature for 16 h. The layers were separated and the aqueous layer extracted further with dichloromethane (2x). The combined organic phases were evaporated in vacuo and the residue triturated with ether. The slurry was filtered and the filtrate washed with ether. Solvent removal gave 4.1 g of product (3) which was pure enough by thin layer chromatography (ether-hexanes, 2:1) and spectral analysis to be used directly in the next reaction. IR: ν_{max} 1712, 1515, 1262 cm^{-1}; NMR: 0.83 and 0.98 (t, J = 7 Hz, 6 H, $-CH_3$), 1.50 - 2.56 (m, 4 H, $-CH_2$), 3.51 (t, J = 7 Hz, 1 H, -CH), 3.88 (s, 6 H, $-OCH_3$), 6.73 - 6.90 (m, 3 H, aromatic)ppm.

3-(p-methoxyphenyl)-4-(3',4'-dimethoxyphenyl)-3-hexanol (4)

To a solution of p-bromoanisole (2.7 ml, 21.6 mmol) in 90 ml tetrahydrofuran at -78°C was added butyllithium (1.5 M in hexane, 13 ml, 19.5 mmol). The mixture was stirred at -78°C for 1 h and then treated with the ketone (3, 4.1 g, 17.4 mmol) in 40 ml tetrahydrofuran. After an additional 20 min of stirring at -78°C, the cooling bath was removed and stirring continued for 30 min. Normal workup with ethyl acetate gave 7 g crude product (4). Trituration with ether gave 4.2 g of (4), mp 126-127°C. The mother liquors gave an additional 1.9 g of slightly less pure material. IR: ν_{max} 3540, 1610, 1590 cm^{-1}; NMR: 0.58 (t, J = 7 Hz, 6 H, $-CH_3$), 1.20 - 2.0 (m, 4 H, $-CH_2$), 2.63 - 2.84 (m, 1 H, -CH), 3.82 (s, 6 H, $-OCH_3$), 3.90 (s, 3 H, $-OCH_3$), 6.60 - 7.40 (m, 7 H, aromatic)ppm. Anal: calc'd. for $C_{21}H_{28}O_4$: C, 73.23; H, 8.19; found: C, 73.42; H, 8.19.

3-(p-methoxyphenyl)-4-(3'-4'-dimethoxyphenyl)-3-hexene (6)

The alcohol (4, 2.005 g, 5.82 mmol) was mixed with 100 mg p-toluenesulfonic acid and heated at 190°C, under nitrogen, for 1 h. Normal workup gave 2.8 g of the Δ^2 isomer (5) with very little of the desired isomer (6). The crude product was dissolved in 100 ml benzene and treated with 100 mg iodine. The mixture reached an equilibrium (as judged by t.l.c., hexanes-ether, 8:2) after 2 days at room temperature. "Dry column" chromatography (hexanes-ether, 8:2) gave approximately 50% of the desired isomer (6). The remaining material (largely Δ^2 isomer) could be recycled to give additional material. Solvent removal gave crystalline product (6), mp 87-88°C. IR: ν_{max} 1512, 1248 cm^{-1}; NMR: 0.81 (t, J = 7 Hz, 6 H, $-CH_3$), 2.19 (q, J = 7 Hz, 4 H, $-CH_2$), 3.86 (s, 3 H, $-OCH_3$), 3.93 (s, 6 H, $-OCH_3$), 6.72 - 7.32 (m, 7 H, aromatic)ppm; MS: m/e = 326 (M^+). Anal: calc'd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03; found: C, 77.16; H, 7.88.

3-(p-hydroxyphenyl)-4-(3',4'dihydroxyphenyl)-3-hexene (7)

The trimethoxy olefin (6, 845 mg, 2.59 mmol) was dissolved in 60 ml dichloromethane and cooled to -78°C. The cooled solution was treated dropwise with boron tribromide (0.78 ml, 8.09 mmol). The reaction mixture was stirred at -78°C for several h and then allowed to warm to room temperature during the course of a night. The reaction was then cooled to 0°C and treated wtih ice/$CaCO_3$. Normal workup with ether gave 850 mg crude product. Crystallization from ether-petroleum ether gave 360 mg of (7), mp 165.5-166°C. A second crop gave an additional 120 mg of (7), mp 165.5-166°C. The pure product tends to decompose slowly with storage. IR: ν_{max} 3320, 1610, 1510 cm^{-1}; NMR: 0.76 (t, J = 7 Hz, 6 H, CH_3), 1.96 - 2.30 (m, 4 H, $-CH_2$), 6.43 - 7.12 (m, 7 H, aromatic)ppm; MS: m/e = 284 (M^+). Anal: calc'd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09; found: C, 76.05; H, 6.93.

t-Butyl 3-hydroxy-3,4-bis-(p-methoxyphenyl)-hexanoate (9)

t-Butyl acetate (3.75 ml, 27.8 mmol) was added dropwise at -78°C under a nitrogen atmosphere to lithium diisopropylamide prepared from diisopropylamine (4.32 ml, 31.1 mmol) and n-butyllithium (14.4 ml, 28.0 mmol), in 40 ml tetrahydrofuran. The mixture was stirred for 10 min and warmed to 0°C. A solution of α-ethyldesoxyanisoin (8, 4.8 g, 16.9 mmol) in 90 ml tetrahydrofuran was gradually added during 30 min and the reaction mixture stirred at 0°C for 1-1/2 h. The reaction mixture was decomposed with ice, most of the tetrahydrofuran distilled in vacuo at low temperature, and the residue poured into ice-cold 5% acetic acid. The crude product was isolated with ether to give a white crystalline solid (9, 6.8 g, 100%), mp 112-115°C. NMR: 0.60 (t, 3 H, J = 7.5 Hz, $-CH_2CH_3$), 1.18 (s, 9 H, t-BuO), 1.28 - 2.15 (m, 2 H, $-CH_2CH_3$), 2.58 - 2.83 (m, 3 H, $-CH_2COO$t-Bu and benzylic methine at C-4), 3.78 (s, 6 H, $-OCH_3$), and 6.66 - 7.16 aromatic protons) ppm. Anal: calc'd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05; found: C, 71.85; H, 8.11.

t-Butyl 3,4-bis-(p-methoxyphenyl)-2-hexenoate (10)

A solution of the hydroxy ester (9, 6.76 g) in 65 ml N,N-dimethylformamide and 13.9 ml collidine was cooled to 10°C under an atmosphere of nitrogen. The cooling bath was removed and 5.2 ml methanesulfonyl chloride containing 7% sulfur dioxide was added dropwise. The reaction mixture was stirred at room temperature for 45 h, poured into ice-cold 2% sulfuric acid, and the organic material was isolated with ether. The oily crude product (10, 7.27 g, 97%) was crystallized from petroleum ether, mp 75-77°C. NMR: 0.88 (t, 3 H, J = 7.5 Hz, $-CH_2CH_3$), 1.17 (s, 9 H, t-BuO), 1.60 - 1.88 (m, 2 H, $-CH_2CH_3$), 3.18 - 3.53 (m, 1 H, C-4H), 3.78 (s, 6 H, aromatic $-OCH_3$), 5.81 (s, 1 H, C-2H, and 6.72 - 7.11 (m, 8 H, aromatic protons)ppm. Anal: calc'd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91; found: C, 75.22; H, 8.00.

(E)-t-Butyl 3,4-bis-(p-methoxyphenyl)-3-hexenoate (11) and (Z)-t-Butyl 3,4-bis-(p-methoxyphenyl)-3-hexenoate (12)

A solution of potassium t-butoxide (5.51 g, 49 mmol) in 60 ml DMSO was added under nitrogen atmosphere to the α,β-unsaturated ester (10, 6.27 g, 16.4 mmol) and stirred at room temperature for 1 h. The dark orange-red reaction mixture was poured into ice and 100 ml of 10% acetic acid, and the product isolated with ether. The crude product was chromatographed on a "dry" silica gel column using ethyl acetate-hexane (1:9) as the developing solvent to give three fractions:

Fraction 1: (1.63 g, 26%) was crystallized from ether-hexane to afford (E)-t-butyl 3,4-bis-(p-methoxyphenyl)-3-hexenoate (11), mp 105-107°C. NMR: 0.79 (t, 3 H, J = 7.5 Hz, $-CH_3$), 1.20 (s, 9 H), 3.82 (s, 6 H, aromatic $-OCH_3$), 6.85 - 7.34 (m, 8 H, aromatic protons)ppm.

Fraction 2: (2.0 g, 32%) was an oil (Z)-t-butyl 3,4-bis-(p-methoxyphenyl)-3-hexenoate (12), NMR: 0.91 (t, 3 H, J = 7.5 Hz, $-CH_2CH_3$), 1.35 (s, 9 H, t-BuO), 2.57 (q, 2 H, J = 7.5 Hz, $-CH_2CH_3$), 3.45 (s, 2 H, $-CH_2COOtBu$), 3.70 (s, 6 H, aromatic $-OCH_3$), 6.57 - 7.07 (m, 8 H, aromatic protons)ppm.

Fraction 3: (1.47 g, 23%) is a mixture of (E)- and (Z)-3,4-bis-(p-methoxyphenyl)-3-hexenoic acids.

Isomerization of (Z)-t-butyl 3,4-bis-(p-methoxyphenyl)-3-hexenoate (12)

A solution of potassium t-butoxide (2.76 g) in 25 ml DMSO was added under nitrogen to the (Z)-β,γ-unsaturated ester (12, 2.0 g) and stirred at room temperature for 1 h. The deep red reaction mixture was poured into ice and 100 ml of 10% acetic acid and the product isolated with ether. Thin layer chromatography of the crude product indicated that the substance is an approximately 1:1 mixture of the (E)- and (Z)-esters and some acidic material.

(E)-3,4-bis-(p-methoxyphenyl)-3-hexenol (13)

The (E)-β,γ-unsaturated ester (11, 0.764 g, 2 mmol) was added to a slurry of lithium aluminum hydride (0.114 g, 3 mmol) in 15 ml tetrahydrofuran at 0°C in an atmosphere of nitrogen. The mixture was stirred at room temperature for 10 min and then heated at reflux for 2 h. The reaction mixture was cooled in ice, decomposed with water-sodium hydroxide solution and filtered. The filtrate was dried over potassium hydroxide pellets and the solvent distilled off in vacuo to give a white crystalline solid (13, 0.62 g, 99%), mp 116-118°C; NMR: 0.78 (t, 3 H, J = 7.5 Hz, $-CH_2CH_3$), 2.17 (q, 2 H, J = 7.5 Hz, $-CH_2CH_3$), 2.43 (t, 2 H, J = 7.5 Hz, $-CH_2CH_2OH$), 3.25 - 3.58 (m, 2 H, $-CH_2CH_2OH$), 3.78 (s, 6 H, aromatic $-OCH_3$), and 6.84 - 7.32 (m, 8 H, aromatic protons)ppm. Anal: calc'd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74; found: C, 76.86; H, 7.57.

(E)-3,4-bis-(p-methoxyphenyl)-3-hexenol acetate (14)

(E)-3,4-bis-(p-methoxyphenyl)-3-hexenol (13, 0.77 g) was dissolved in 7 ml of a 1:1 mixture of acetic anhydride-pyridine and the solution let stand for 24 h at room temperature. Acetic anhydride and pyridine were removed in vacuo in a stream of nitrogen. The residue was purified on a short column of silica gel to give the acetate (14) as an oil. NMR: 0.78 (t, 3 H, J = 7.5 Hz, $-CH_2\underline{CH_3}$), 1.89 (s, 3 H, $-OCO\underline{CH_3}$), 2.19 (q, 2 H, J = 7.5 Hz, $-\underline{CH_2}CH_3$), 2.46 (t, 2 H, J = 7.5 Hz, $-\underline{CH_2}CH_2OCOCH_3$), 3.80 (t, 2 H, J = 7.5 Hz, $-CH_2\underline{CH_2}OCOCH_3$) 3.80 (s, 6 H, aromatic $-O\underline{CH_3}$), and 6.80 - 7.30 (m, 8 H, aromatic protons)ppm.

(E)-3,4-bis-(p-hydroxyphenyl)-3-hexenol acetate (15)

A solution of dimethoxy-acetate (14, 0.240 g, 0.68 mmol) in 20 ml dichloromethane was cooled to -78°C and treated with boron tribromide (2 mmol) under nitrogen. The reaction mixture was then stirred at 0°C for 1 h, decomposed by addition of calcium carbonate and ice, and the product isolated with dichloromethane as a crystalline solid (15, 0.220 g, 99%); IR: ν_{max} 3490, 1735, 1705, 1610, 1595, 1310 cm^{-1}; NMR: ($CDCl_3$ + acetone-d_6), 0.75 (t, 3 H, J = 7.5 Hz, $-CH_2\underline{CH_3}$), 1.89 H, (s, 3 H, $-OCO\underline{CH_3}$), 2.19 (q, 2 H, J = 7.5 Hz, $-\underline{CH_2}CH_3$), 2.45 (t, 2 H, J = 7.5 Hz, $-\underline{CH_2}CH_2OCOCH_3$), 3.82 (t, 2 H, J = 7.5 Hz, $\underline{CH_2}OCOCH_3$), and 6.70 - 7.20 (m, 8 H, aromatic protons)ppm. Anal: calc'd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79; found: C, 73.33; H, 6.84.

Ω-Hydroxydiethylstilbestrol (16)

Nitrogen was bubbled through a stirred solution of Ω-acetoxydiethylstilbestrol (15, 0.22 g, .675 mmol) in 12 ml of 85% methanol for 30 min at room temperature. Anhydrous potassium carbonate (0.47 g, 3.4 mmol) was added and the stirring continued under nitrogen for 4 h. Methanol was removed in vacuo under a stream of nitrogen. The residue was taken up in water, cooled in ice and acidified with 10% acetic acid. The product was isolated with ethyl acetate and purified by preparative layer chromatography on silica gel to give Ω-hydroxydiethylstilbestrol (16, 0.145 g, 75%) as a crystalline solid; mp 213-215°C; IR: ν_{max} 3350, 1610, 1590 cm^{-1}; NMR: ($CDCl_3$ + acetone-d_6 + D_2O) 0.78 (t, 3 H, J = 7.5 Hz, $-CH_2\underline{CH_3}$), 2.41 (t, 2 H, J = 7.5 Hz, $-\underline{CH_2}CH_2OH$), 3.40 (t, 2 H, J = 7.5 Hz, $-CH_2\underline{CH_2}OH$), and 6.75 - 7.25 (m, 8 H, aromatic protons)ppm; MS: m/e = 284 (M^+). Anal: calc'd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09; found: C, 75.91; H, 6.94.

(E)-3,4-bis-(p-methoxyphenyl)-3-hexenol (13) and (Z)-3,4-bis-(p-methoxyphenyl-3-hexenol (18)

Lithium aluminum hydride (3.00 g) was gradually added to an ice-cooled solution of esters (11 and 12, 20.00 g) in 300 ml tetrahydrofuran. The cooling bath was removed, the mixture was stirred at room temperature for 10 min and then refluxed for 2 h. The reaction mixture was cooled in ice, decomposed with water and sodium hydroxide, and filtered. The filtrate was dried over anhydrous sodium sulfate and the solvent distilled in vacuo to give a viscous oil (17.00 g) identified as homoallylic alcohols (13 and 18) by comparison with authentic samples.

(E)- and (Z)-3,4-bis-(p-methoxyphenyl)-3-hexenol acetates (14 and 19)

A solution of hexenols (13 and 18, 17.00 g) in 140 ml of a 1:1 mixture of acetic anhydride-pyridine was let stand for 24 h at room temperature. Acetic anhydride and pyridine were removed in vacuo in a stream of nitrogen. The residue was purified on a short column of silica gel to give hexenol acetates (14 and 19, 19.00 g) identified with authentic samples by t.l.c.

(E)- and (Z)-3,4-bis-(p-hydroxyphenyl)-3-hexenol acetates (15 and 20)

A solution of dimethoxy-acetates (14 and 19, 3.60 g) in 150 ml dichloromethane was cooled to -78°C and treated with 2.79 ml boron tribromide under nitrogen. The reaction mixture was then stirred at 0°C for 1 h, decomposed by addition of solid sodium bicarbonate followed by ice-cold saturated sodium bicarbonate solution, and the product isolated with dichloromethane. "Dry column" chromatography of the crude product on silica gel, using 2:1 hexane-ethyl acetate as eluant, afforded the dihydroxy-hexenol acetates (15 and 20, 2.30 g) identified with authentic samples by t.l.c. Part of the product was crystallized from ether-petroleum ether to give (E)-3,4-bis-(p-hydroxyphenyl)-3-hexenol acetate (15, 0.8 g).

Ω-Acetoxydienestrol (21)

Lead tetraacetate (4.9 g) was dried in vacuo in the dark at room temperature for 2 h and gradually added to a solution of dihydroxy-acetates (15 and 20, 3.7 g) in a mixture of 126 ml chloroform and 63 ml ether under nitrogen atmosphere at room temperature over a 30 min period. The reaction mixture was stirred for 1 h and the lead salts were filtered. The filtrate was passed through a short column of silica gel. Evaporation of solvent gave a gummy material, which on "dry column" chromatography followed by crystallization from ether-ethyl acetate-hexane afforded Ω-acetoxydienestrol (21, 0.6 g) as a pale yellow solid; mp 150-152°C; NMR: ($CDCl_3$ + CD_3OD) 1.65 (d, 3 H, J = 7.5 Hz, $\underline{CH_3}$-CH=C), 2.01 (s, 3 H, -OCO-$\underline{CH_3}$), 4.60 (d, 2 H, J = 7.5 Hz, AcO-$\underline{CH_2}$-CH=C), 6.15 (m, 2 H, CH_3-$\underline{CH}$=C- and $AcOCH_2\underline{CH}$=C-) and 6.50 - 7.35 (m, 8 H, aromatic protons)ppm; MS: m/e = 324 (M^+) Anal: calc'd. for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21; found: C, 73.76; H, 6.24.

Ω-Hydroxydienestrol triacetate (23)

A solution of Ω-acetoxydienestrol (21, 0.125 g) in a 1:1 acetic anhydride-pyridine mixture (2 ml) was let stand at room temperature for 24 h. Acetic anhydride and pyridine were removed in vacuo in a stream of nitrogen. Purification of the residue by preparative layer chromatography followed by crystallization from hexane containing ethanol furnished white crystals (60 mg); mp 100-102°C; IR: ν_{max} 1750 cm^{-1}; NMR: (Acetone-d_6) 1.75 (d, 3 H, =CH-$\underline{CH_3}$), 1.97 (s, 3 H, $\underline{CH_3}$-COO), 2.20 (s, 6 H, $\underline{CH_3}$-COO-), 4.60 (d, 2 H, =CH-$\underline{CH_2}$-OAc), 6.41 (2t, 2 H, =$\underline{CH}$-CH_2-), and 6.85-7.50 (8 h, aromatic hydrogens)ppm; MS: m/e = 408 (M^+). Anal. calc'd. for $C_{24}H_{24}O_6$: C, 70.58; H, 5.92; found: C, 70.28; H, 5.79.

Ω-Hydroxydienestrol (22)

Nitrogen was bubbled through sodium hydroxide solution (0.5 N, 45 ml in 1:1 dioxane-water) for 30 min. Ω-Acetoxydienestrol (21, 190 mg) was added and the light brown solution stirred at room temperature under nitrogen for 20 min. The reaction mixture was cooled in ice and acidified to pH 6 with 1 N hydrochloric acid. Half of the solvent was distilled off in vacuo in a stream of nitrogen and the organic material was isolated with ether. Purification of the crude product by preparative layer chromatography afforded Ω-hydroxydienestrol (22) as a bright yellow foam (130 mg). NMR: (Acetone-d_6) 1.67 (d, 3 H, =CH-CH_3), 2.90 - 4.00 (br.s, 1.5 H, -OH), 4.15 (d, 2 H, =CH-CH_2-OH), 6.17 - 6.27 (2t, 2 H, =CH-CH_2-), 6.65 - 7.40 (m, 8 H, aromatic H) and 8.30 (br.s, 1.5 H, -OH)ppm; MS: m/e = 282 (M^+). Anal: calc'd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43; found: C, 73.10; H, 6.53.

3-Methoxy-4-[2'-(methoxyethoxy)methoxy]-benzaldehyde (25)

Vanillin (24, 30.4 g) was dissolved in 400 ml methylene chloride and 50 ml diisopropylethylamine was added. MEM chloride (34 ml) was added dropwise over a period of 20 min and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ether and washed with 2% sulfuric acid followed by 5% sodium hydroxide. Evaporation of solvents gave the MEM ether (25, 52.5 g) bp 138-140°C at 2 mm Hg. IR: ν_{max} 1690, 1595, 1270 cm^{-1}; NMR: 3.38 (s, 3 H, -$OCH_2OCH_2CH_2OCH_3$), 3.58 and 3.88 (m, 4 H, -$OCH_2OCH_2CH_2OCH_3$), 3.96 (s, 3 H, -OCH_3), 5.44 (s, 2 H, -$OCH_2OCH_2CH_2OCH_3$), 7.40 (m, 3 H, aromatic), 9.92 (s, 1 H, aldehyde H)ppm. Anal: calc'd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71; found: C, 59.95; H, 6.97.

3-Methoxy-4-[2'-(methoxyethoxy)methoxy]-propiophenone (26)

A solution of the aldehyde (25, 25 g, 0.104 mol) in anhydrous ethyl ether was cooled to 0°C and ethyl magnesium bromide (0.147 mol, 2.94 M in ether) was added slowly. The reaction mixture was warmed to room temperature and stirred for 18.5 h then cooled and quenched with 2% sulfuric acid (approx. 200 ml). The reaction product was isolated with ether. Evaporation of solvents gave the alcohol (27.7 g). IR: ν_{max} 3450, 1595, 1515, 1270 cm^{-1}; NMR: 0.78 (t, J = 7.5 Hz, 3 H, -CH_3), 1.77 (q, J = 7.5 Hz, 2 H, -CH_2), 3.33 (s, 3 H, -$OCH_2OCH_2CH_2OCH_3$), 3.57 and 3.87 (m, 4 H, -$OCH_2OCH_2CH_2OCH_3$), 3.83 (s, 3 H, -OCH_3), 4.51 (m, 1 H, CHOH), 5.27 (s, 2 H, -$OCH_2OCH_2CH_2OCH_3$), 7.11 (m, 3 H, aromatic)ppm.

The crude alcohol (27.7 g) in 100 ml methylene chloride was added dropwise to a suspension of pyridinium chlorochromate (37.6 g) in 525 ml methylene chloride. The mixture was stirred at room temperature for 2 h and the methylene chloride solution was decanted from the dark brown residue formed. The methylene chloride was evaporated and the residue was triturated with ether and passed through a column of Florisil (60-100 mesh). The solvents were evaporated and purification by high pressure liquid chromatography using a PrepPak-500/silica column with 40% ethyl acetate and 60% hexane as the solvent (200 ml/min) gave the

ketone (26, 9.0 g). IR: ν_{max} 1675, 1590, 1265 cm^{-1}; NMR: 1.20 (t, J = 7.5 Hz, 3 H, $-CH_2\underline{CH_3}$), 3.57 and 3.92 (m, 4 H, $-OCH_2\underline{OCH_2CH_2}OCH_3$), 3.93 (s, 3 H, $-OCH_3$), 5.40 (s, 2 H, $-\underline{OCH_2}OCH_2CH_2OCH_3$), 7.41 (m, 3 H, aromatic)ppm; MS: m/e = 268 (M^+). Anal: calc'd. for $C_{14}H_{20}O_5$: C, 62.67; H 7.51; found: C, 62.79; H, 7.26.

3,4-Bis-(3'-methoxy-4'-hydroxyphenyl)-3-hexene (27)

McMurry's reagent (titanium trichloride-lithium aluminum hydride, 4:1, Alfa Inorganics, 10.2 g) was weighed cautiously and added portionwise with stirring to 150 ml anhydrous tetrahydrofuran under a slow stream of nitrogen. The ketone (26, 3.0 g) in 150 ml tetrahydrofuran was added to the suspension of McMurry's reagent over a period of 0.5 h at room temperature. The reaction mixture was heated at reflux for 21 h then cooled and poured into 1 liter of ice water. The crude reaction product was isolated with ethyl acetate purified on several "dry" silica gel columns using ether-hexane (1:1) as the developing solvent. Crystallization from ether-petroleum ether gave the trans compound (27); mp 136-138°C. IR: ν_{max} 3440, 1600, 1510 cm^{-1}; NMR: 0.79 (t, J = 7.5 Hz, 6 H, $-CH_2\underline{CH_3}$), 2.14 (q, J = 7.5 Hz, 4 H, $-\underline{CH_2}CH_3$), 3.92 (s, 6 H, $-OCH_3$), 5.58 (s, 2 H, -OH), 6.82 (m, 6 H, aromatic)ppm; MS: m/e = 328 (M^+). Anal: calc'd. for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37; found: C, 73.33; H, 7.57.

3,4-Dimethoxypropiophenone (29)

To a cooled solution of 3,4-dimethoxybenzaldehyde (28, 33.2 g, 0.2 M) in 1200 ml ether was added dropwise ethyl magnesium bromide in ether (~100 ml of a 2.94 M solution). The reaction was stirred at room temperature overnight and treated with 200 ml dilute sulfuric acid to solubilize the precipitate. Normal workup afforded 38.5 g of crude alcohol.

Pyridinium chlorochromate (71.5 g, 0.33 M) was suspended in 800 ml dry dichloromethane. The crude alcohol from above was dissolved in 200 ml dichloromethane and added rapidly to the oxidant. The reaction mixture was stirred at room temperature for 4 h. The solvent was decanted and the residue washed twice with additional dichloromethane. The organic solvent was removed and the residue taken up in ether. Filtration through Florisil (60-100 mesh) with ether gave approx. 30 g crude product. Upon standing, a solid separated. Trituration with petroleum ether gave 18.0 g (46% yield) 3,4-dimethoxypropiophenone (29), mp 59-60°C. NMR: 1.22 (t, J = 7.5 Hz, 3 H, $-CH_2\underline{CH_3}$), 2.97 (q, J = 7.5 Hz 2 H, $-\underline{CH_2}CH_3$), 3.94 (s, 6 H, $-OCH_3$), 6.91 (br.d, J = 8 Hz, 1H, C-6H), 7.58 (br.s., 1H, C-2H), 7.61 (br.d., J = 8 Hz, 1H, C-5H)ppm.

3,4-Bis-(3',4'-dimethoxyphenyl)-hex-3-ene (30)

The titanium trichloride (Alfa Inorganics, 10.3 g) and the Zn-Cu couple [18] (10.0 g) were suspended in 200 ml tetrahydrofuran and heated at reflux, under nitrogen, for 0.5 h. Dimethoxypropiophenone (29, 2.33 g, 12.0 mmol) was dissolved in 70 ml tetrahydrofuran and added to the reaction mixture. After heating at reflux for 16 h, the reaction was allowed to cool and was filtered through Florisil. Normal

workup with ethyl acetate gave 2.5 g crude product which was crystallized from ether-hexanes to give 1.9 g of the olefin (30); mp 100-101°C. IR: ν_{max} 1605, 1580, 1512, 1268, 1224 cm^{-1}; NMR: 0.97 (t, J = 7 Hz, 6 H, $-CH_2\underline{CH_3}$), 2.53 (q, J = 7 Hz, 4 $-\underline{CH_2}CH_3$), 3.58 (s, 6 H, $-OCH_3$), 3.78 (s, 6 H, $-OCH_3$), 6.45 6.59, and 6.62 (br.s, 6 H, aromatic)ppm. Anal: calc'd. for $C_{23}H_{28}O_4$: C, 74.13, H, 7.92; found: C, 74.24; H, 8.14.

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