afforded 3.88 g (64%) of **6f** as a clear liquid following medium pressure liquid chromatography (silica gel, 3:1 hexane/acetone eluent): ^{1}H NMR ($CDCl_3$) δ 6.94 (distorted dd, 2 H, H_2C=, J = 33.7 and 37.1), 4.06–3.99 (m, 8 H, $-OCH_2-$), 1.66–1.50 (m, 8 H, $-OCH_2CH_2-$), 1.26 (br s, 40 H, $-OCH_2CH_2(CH_2)_5CH_3$), 0.85 (br t, 12 H, CH_3, J = 5); ^{13}C NMR ($CDCl_3$) δ 148.9 (s, H_2C=), 132.3 (t, PCP, J = 166), 66.6 (s, $-OCH_2-$), 31.9, 30.5, 29.2, 25.6, 22.7 (all s, $OCH_2(CH_2)_6CH_3$), 14.1 (s, CH_3); ^{31}P NMR ($CDCl_3$) δ +13.2; ammonia CI mass spectrum, m/e 637 $(M + H)^+$, 654 $(M + NH_4)^+$. Anal. Calcd for $C_{34}H_{70}O_6P_2$: C, 64.12; H, 11.08; P, 9.73. Found: C, 63.95; H, 10.87; P, 9.96.

Dealkylation of 6a. Bromotrimethylsilane (61.4 g, 0.40 mol) was added via syringe to a solution of ester **6a** (15.0 g, 0.05 mol) in 300 mL of dry CCl_4. The mixture was stirred for 72 h and then concentrated under vacuum. Methanol (200 mL) was added and the solution again concentrated. The crude product was dissolved in methanol (150 mL) and precipitated by addition of methanolic KOH solution. The mixture was filtered and the precipitate washed with methanol and then dried under vacuum. The white solid product was dissolved in 75 mL of water and stirred overnight with excess Rexyn 101(H) resin (Fisher Scientific). The ion-exchange resin was removed by filtration and the solution freeze-dried to afford 8.49 g (90%) of acid **1** as a white, hygroscopic solid: ^{1}H NMR (D_2O) δ 6.44 (t, H_2C=, J = 36.1); ^{13}C NMR (D_2O) δ 146.9 (s, H_2C=), 138.2 (t, PCP, J = 162); ^{31}P NMR (D_2O) δ +11.1.

Registry No. **1**, 34162-79-3; **5a**, 1660-94-2; **5b**, 16001-93-7; **5c**, 1660-95-3; **5d**, 28254-31-1; **5e**, 6997-56-4; **5f**, 13088-08-9; **6a**, 37465-31-9; **6b**, 67293-68-9; **6c**, 48074-47-1; **6d**, 103457-07-4; **6e**, 103457-08-5; **6f**, 103457-09-6; **7**, 103457-10-9.

Asymmetric Lignan Synthesis: Isolariciresinol Dimethyl Ether

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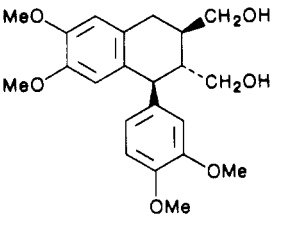
Received April 15, 1986

An asymmetric synthesis of the lignan (+)-isolariciresinol dimethyl ether **1** in nine steps and 13% yield (83% optical purity) from veratraldehyde is described. Veratraldehyde was converted to 6-(3,4-dimethoxybenzyl)-veratraldehyde **3** by bromination, acetal formation, metalation, and coupling to 3,4-dimethoxybenzyl bromide. **3** was irradiated in the presence of SO_2 to give the 3-hydroxy-1-aryl-1,3-dihydrobenzo[*c*]thiophene 2,2-dioxide **4**, which was converted to the (*R*)-1-phenylethoxy derivative **5b**. **5b** on heating with dimethyl fumarate gave a mixture of primarily two diastereomeric cycloadducts **7b** and **7b′**, both of which had the 1,2-trans, 2,3-trans, 3,4-cis stereochemistry. The major adduct **7b** was subsequently assigned the stereochemistry 1*S*,2*R*,3*S*,4*S*. Separation and hydrogenolysis of the major adduct gave the diester **8**, 1*S*,2*R*,3*R*, which was reduced with $LiAlH_4$ to give (+)-isolariciresinol dimethyl ether **1**. A racemic synthesis was also carried out via the methoxy sulfone **5a** and its trans isomer **5a′** in 33% yield.

Intra- and intermolecular cycloadditions of dienophiles to *o*-quinodimethanes (*o*-QDMs) have been successfully used in a variety of natural product syntheses.[1-9] In some instances asymmetric syntheses have been achieved by controlling the face selectivity of the addition step.[5,8-9] In recent publications we have shown that chiral groups in the α position of an *o*-QDM can control the face selectivity of the addition.[10,11] The face selectivity with respect to the dienophile (exo vs. endo) is controlled by secondary orbital effects between the substituent groups on the dienophile and the *o*-QDM to yield, in most cases, the endo product.[10,11] While this asymmetric cycloaddition appears suitable for natural product lignan syntheses, it was not known how other substituents on the *o*-QDM would affect the stereoselectivity of the cycloaddition step. In this paper we describe both the racemic and asymmetric synthesis of (+)-isolariciresinol dimethyl ether.



1

The absolute stereochemistry of (+)-isolariciresinol dimethyl ether was first established by Schrecker and Hartwell in 1954 by synthesis from α-conidendrin whose structure was well established.[12] This was later repeated by Stevenson and Williams during their investigation of phyltetralin (the enantiomer of isolariciresinol tetramethyl ether).[13] More recently Mann has published a synthesis of both racemic isolariciresinol dimethyl ether and racemic phyltetralin.[14]

Results and Discussion

The general scheme for the synthesis is shown in Scheme I. The synthesis of the intermediate *o*-QDM **6** is accomplished via our recently developed photochemical route to the 1-hydroxydihydrobenzo[*c*]thiophene 2,2-dioxide.[15,16,11]

(1) Oppolzer, W. *Synthesis* **1978**, 793.
(2) Funk, R. L.; Volhardt, P. C. *Chem. Soc. Rev.* **1980**, *9*, 41.
(3) Oppolzer, W. *Heterocycles* **1980**, *14*, 1614.
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(9) Frank, R. W.; John, T. V.; Olejniczak, J. *J. Am. Chem. Soc.* **1982**, *104*, 1106.
(10) Charlton, J. L. *Tetrahedron Lett.* **1985**, *26*, 3413.
(11) Charlton, J. L. *Can. J. Chem.* **1986**, *64*, 720.
(12) Schrecker, A. W.; Hartwell, J. L. *J. Am. Chem. Soc.* **1955**, *77*, 432.
(13) Stevenson, R.; Williams, J. R. *Tetrahedron* **1977**, *33*, 2913.
(14) Mann, J.; Piper, S. E.; Yeung, L. P. *J. Chem. Soc., Perkin Trans. 1*, **1984**, 2081.

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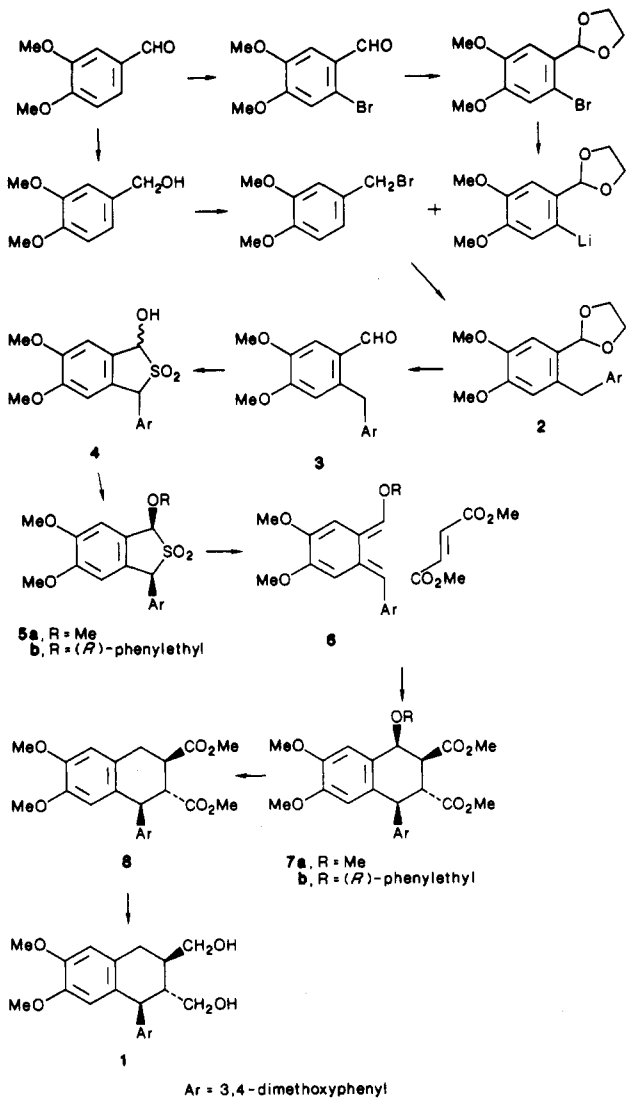
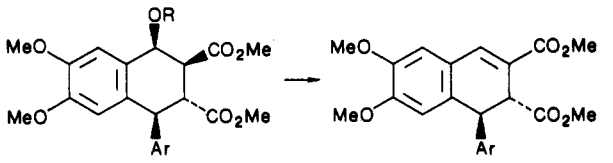
Scheme I



The synthesis of 6-bromoveratraldehyde ethylene glcyol acetal and 3,4-dimethoxybenzyl bromide followed standard procedures which can be found in the Experimental Section. The coupling reaction followed by hydrolysis to yield the aldehyde **3** followed a procedure similar to that outlined by Durst et al.[17] The yield for this step was variable as it appears that the metalated acetal was quite unstable even at −78 °C. Traces of acid in the very reactive benzyl bromide also reduced the yield substantially. With care we have obtained overall yields of 56% for **3** based on veratraldehyde. The conversion of the aldehyde **3** to the hydroxy sulfone follows from our previously described procedure.[11,15,16] **4** was a mixture of cis and trans isomers as evidenced by the NMR spectrum. **4** was converted to **5a** (R = Me) in 98% yield by refluxing in a 50:50 mixture of methanol in methylene chloride containing a trace of *p*-toluenesulfonic acid (ptsa). **5b** (R = (*R*)-1-phenylethyl) was obtained in the presence of (*R*)-1-phenylethanol. **5a** was obtained as a 65:35 mixture with the corresponding trans compound **5a′** from which it could be separated by chromatography. Since **5b** contains three chiral centers there were four diastereomers possible. Fortunately the reaction produced predominantly one of the cis diastereomers. **5a** and **5b** were both reacted with dimethyl fumarate in benzene at reflux in the presence of zinc oxide and/or potassium carbonate which served to neutralize traces of acid.[11] It was important to follow the thermolysis reactions by thin-layer chromatography since prolonged reaction times led to the elimination reaction producing the dihydronaphthalene **9**. The cycloadduct **7a** (R = Me)

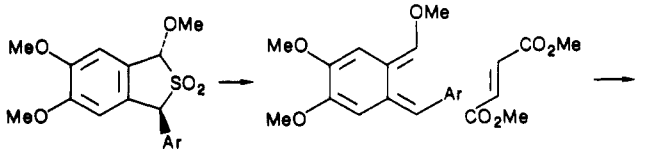


9

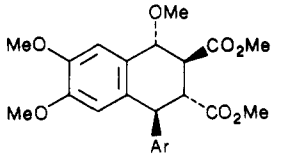
Ar = 3,4-dimethoxyphenyl

contains four chiral centers and hence there are eight diastereomers possible. However, as with our previous experience, only one major product was formed.[15] The NMR spectrum was completely assignable and compatible only with the 1,2-trans-2,3-trans-3,4-cis configuration as shown in Scheme I. This allowed assignment of the cis geometry to **5a** since only the cis sulfone would be able to produce the (*E*,*E*)-*o*-QDM **6** and hence **7a** with the aryl and alkoxy group cis. The alternative *Z*,*Z* configuration for **6**, also attainable by pericyclic extrusion of SO_2 from **5**, is considered unlikely on steric grounds. The cycloadduct **7a** was reduced with H_2/Pd/C to the crystalline diester **8** (racemic) which in turn was reduced with $LiAlH_4$ to give the crystalline (±)-isolariciresinol dimethyl ether **1**.

In an attempt to optimize the yield of racemic **1**, the entire sequence from the aldehyde **3** to **1** was carried out without purification of the intermediates at each step. For a racemic synthesis of **1**, it was not necessary to separate **5a** from its trans isomer **5a′**. On the basis of an analogy to our earlier work[18] the trans isomer of **5a** should react as shown. Hydrogenolysis of **10** should also give **8**. As



trans-**5a**



10

expected, the mixture of cis and trans alkoxy sulfones **5a** and **5a′** did give a mixture of cycloadducts (**7a** and presumably **10**) which were not separated but on hydrogenolysis did yield the diester **8** as the only product. By not isolating the intermediate compounds the overall yield of **1** from veratraldehyde was raised to 33%.

The NMR spectrum of racemic isolariciresinol has been recorded and assigned previously.[14] While our spectrum was identical with that published, our assignment of the CH_2 on C_2, which we confirmed by difference decoupling, differs slightly from the previous assignment (see Experimental Section).

(15) Durst, T.; Kozma, E. C.; Charlton, J. L. *J. Org. Chem.* **1985**, *50*, 4829.
(16) Charlton, J. L.; Durst, T. *Tetrahedron Lett.* **1984**, *25*, 2663.
(17) Glinski, M. B.; Durst, T. *Can. J. Chem.* **1982**, *61*, 573.
(18) Charlton, J. L.; Alauddin, M. M.; Penner, G. L. *Can. J. Chem.* **1986**, *64*, 793.

The cycloadduct from **5b** (R = (*R*)-1-phenylethyl) was a 70:30 mixture of diasteriomers (**7b** and **7b'**) which could be separated by chromatography. The absolute configuration of **7b** was presumed to be 1*S*,2*R*,3*S*,4*S* on the basis of the previous model studies.[11] Catalytic reduction of the major diastereomer **7b** gave the crystalline diester **8**. Recrystallization of **8** from isopropyl alcohol gave a mp of 143–145 °C, which is considerably above that of the racemic material (126–127 °C). The specific rotation was +19.9°.

Reduction of **8** gave (+)-isolariciresinol dimethyl ether with a rotation of +13.2°. Schrecker and Hartwell have determined the rotation of the natural product to be +15.8° (although higher values have been recorded[12]) which would give our material an optical purity of 83%. The fact that the material is not 100% optically pure is probably due to our inability to separate the major diasteriomer **7b** from **7b'** by chromatography. The sign of the rotation nevertheless confirms that the prediction of the effect of the *R*-chiral auxilliary on the diastereoselectivity of the cycloaddition was correct and that all four chiral centers could be introduced selectively in a single step. We are continuing our search for more effective chiral auxilliaries and hope to extend the method to other aryltetralin compounds of interest.

Experimental Section

^{1}H NMR spectra were recorded on a Bruker AM-300 instrument using tetramethylsilane as internal standard. IR spectra were recorded on a Unicam 1000 spectrometer. Mass spectra were recorded on a Finnigan 1015 mass spectrometer, and only the major peaks are reported. Merck Kieselgel 60 was used for all chromatography. Elemental analyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, Canada. Exact mass/mass spectra were obtained on an Analytical VG 7070-E instrument at the University of Ottawa, Ottawa, Canada. Melting points were recorded on a hot stage instrument and are uncorrected.

6-Bromoveratraldehyde. A solution of bromine (10 g) in acetic acid (20 mL) was added over 15 min at 22–25 °C to a solution of veratraldehyde (5 g, 0.3 mol) in acetic acid (50 mL). The mixture was stirred for 5 h at room temperature, an equal volume of water added, and the mixture then cooled to 4 °C. The product was filtered off and recrystallized from methanol/water (6:1) to yield 5.9 g (80%), mp 148–150 °C (lit. mp 149–151 °C[19]).

6-Bromoveratraldehyde Ethylene Glycol Acetal. 6-Bromoveratraldehyde (3.6 g, 1.48×10^{-2} mol), ethylene glycol (1.8 g, 2.9×10^{-2} mol, 2 equiv), and *p*-toluenesulfonic acid (50 mg) were mixed in benzene (40 mL). The reaction mixture was refluxed under a Dean–Stark trap for 2 h. After the mixture was cooled, sodium bicarbonate (0.3 g) was added and the mixture filtered through a short silica gel column with 50% EtOAc/hexane. The eluant was evaporated to yield 4.17 g (98%): ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 6 H), 4.00–4.28 (m, 4 H), 6.00 (s, 1 H), 7.01 (s, 1 H), 7.14 (s, 1 H); mass spectrum, *m/e* (relative intensity) 290 (40), 289 (44), 287 (42), 246 (32), 245 (47), 243 (48), 229 (40), 218 (92), 216 (100), 209 (12), 149 (96), 119 (52). Anal. Calcd for $C_{11}H_{13}BrO_4$: C, 45.70; H, 4.53; Br, 27.64. Found: C, 45.46; H, 4.65; Br, 27.53.

3,4-Dimethoxybenzyl Alcohol. $NaBH_4$ (1.14 g, 0.03 mol) was added slowly to a solution of veratraldehyde (10 g, 0.06 mol) in isopropyl alcohol (50 mL). The reaction mixutre was stirred at room temperature for 15 min and then refluxed for 10 min. Dilute HCl (10%) was cautiously added until the solution was acidic. After most of the isopropyl alcohol was removed in vacuo the solution was extracted with CH_2Cl_2 and the extract washed with 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated, giving a viscous liquid (10 g, 99%): ^{1}H NMR ($CDCl_3$) δ 3.06 (br s, 1 H), 3.86 (s, 6 H), 4.53 (s, 2 H), 6.80–6.93 (m, 3 H). The NMR was identical with that given in the literature.[20]

3,4-Dimethoxybenzyl Bromide. 3,4-Dimethoxybenzyl alcohol (3.0 g, 0.018 mol) and PBr_3 (3.24 g, 2 equiv) were stirred in CH_2Cl_2 (30 mL) overnight at room temperature. CH_2Cl_2 and PBr_3 were removed in vacuo, and the residue was dissolved in CH_2Cl_2 and stirred with a moist paste of $NaHCO_3$. The solution was filtered through $MgSO_4$, evaporated to dryness, and pumped at high vacuum for 5 h, during which time the sample solidified to yield 3.35 g (82%): ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 6 H), 4.55 (s, 2 H), 6.80–7.20 (m, 3 H). The bromide was quite unstable and had to be stored at low temperature under nitrogen.

6-(3,4-Dimethoxybenzyl)veratraldehyde Ethylene Glycol Acetal (2). The 6-bromoveratraldehyde ethylene glycol acetal (1.0 g) was dissolved in THF (5 mL) and cooled to −78 °C and tetramethylethylene diamine (TMEDA) (0.5 mL) added. *n*-Butyllithium in hexane (2.8 mL, 1.1 M) was added, followed immediately by $(n\text{-}Bu)_3P$-CuI (1.0 g in 3 mL of THF) and 3,4-dimethoxybenzyl bromide (1.05 g in 4 mL THF). The mixture was stirred at −78 °C for 15 min and at room temperature for 0.5 h and then quenched with saturated NH_4Cl (10 mL). Water (20 mL) was added, the mixture extracted (CH_2Cl_2); and the organic phase dried ($MgSO_4$) and evaporated in vacuo. Chromatography (30% EtOAc/hexane) yielded 0.94 g of the coupled acetal (75%), which could be recrystallized from hexane/CH_2Cl_2: mp 122–124 °C; ^{1}H NMR ($CDCl_3$) δ 3.783 (s, 3 H), 3.811 (s, 3 H), 3.849 (s, 3 H), 3.902 (s, 3 H), 3.995–4.020 (m, 2 H), 4.037 (s, 2 H), 4.135–4.158 (m, 2 H), 5.888 (s, 1 H), 6.602 (s, 1 H), 6.712–6.795 (m, 3 H), 7.151 (s, 1 H); mass spectrum, *m/e* (relative intensity) 360 (24), 299 (27), 298 (65), 284 (10), 283 (9), 269 (6), 268 (7), 221 (13), 222 (100) 194 (8), 151 (6), 150 (6). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.80; H, 6.91.

6-(3,4-Dimethoxybenzyl)veratraldehyde (3). Acetal **2** (165 mg) was dissolved in ether (10 mL) and HCl (10%) added with stirring at room temperature. After 2 h the ether was separated, the aqueous layer was extracted (CH_2Cl_2), and the organic extracts were combined, dried ($MgSO_4$), and evaporated to give 138 mg of the aldehyde (95%), which was recrystallized from hexane/CH_2Cl_2: mp 91–92.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.813 (s, 3 H), 3.845 (s, 3 H), 3.897 (s, 3 H), 3.939 (s, 3 H), 4.330 (s, 2 H), 6.60–6.80 (m, 4 H), 7.418 (s, 1 H), 10.200 (s, 1 H); IR (CH_2Cl_2) 1682 cm^{-1}; mass spectrum, *m/e* (relative intensity) 316 (90), 301 (19), 299 (28), 298 (20), 285 (47), 254 (20), 253 (14), 178 (28), 151 (43), 150 (100), 115 (80). Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.33; H, 6.38. Found: C, 67.99; H, 6.68.

1-(3,4-Dimethoxyphenyl)-3-hydroxy-5,6-dimethoxy-1,3-dihydrobenzo[*c*]thiophene 2,2-Dioxide (4). The aldehyde **3** was dissolved in thiophene-free benzene (300 mL) containing SO_2 (20 g) and the solution irradiated with a water-jacketed 450-W Hanovia medium-pressure mercury lamp immersed in the solution, for 8 h under a blanket of nitrogen. The solvent was evaporated in vacuo, the residue dissolved in CH_2Cl_2, and this extracted three times with 5% aqueous bicarbonate. The basic extract was acidified with HCl (10%) and extracted (CH_2Cl_2) and the organic extract dried ($MgSO_4$) and evaporated to leave a glassy solid (790 mg, 67%). Unreacted aldehyde **3** (120 mg) was isolated from the neutral organic material. Yield, based on aldehyde consumed, was 77%. A mixture of two isomers could be discerned in the NMR spectrum: ^{1}H NMR ($CDCl_3$) δ [isomer 1] 3.782 (s, 3 H), 3.810 (s, 3 H), 3.891 (s, 3 H), 3.945 (s, 3 H), 5.315 (s, 1 H, H_1), 5.687 (s, 1 H, H_3), 6.557 (s, 1 H), 6.77–6.95 (m, 3 H), 7.066 (s, 1 H), [isomer 2] 3.774 (s, 3 H), 3.828 (s, 3 H), 3.906 (s, 3 H), 3.945 (s, 3 H), 5.473 (s, 1 H, H_1), 5.646 (s, 1 H, H_3), 6.522 (s, 1 H), 6.77–6.95 (m, 3 H), 7.066 (s, 1 H) [the OH protons were not observed and were probably obscured beneath the methoxy signals]; IR (CH_2Cl_2) 3600, 1522, 1472, 1232, 1120, 1030 cm^{-1}; mass spectrum, *m/e* (relative intensity) 316 (51, M − SO_2), 285 (51), 178 (51), 165 (56), 151 (61), 150 (100), 139 (61), 115 (66).

1-(3,4-Dimethoxyphenyl)-3,5,6-trimethoxy-1,3-dihydrobenzo[*c*]thiophene 2,2-Dioxide (5a). Hydroxy sulfone **4** (104 mg) and toluenesulfonic acid (30 mg) were refluxed in a 50:50 mixture of methanol and CH_2Cl_2 (7 mL) for 1 h. The solvent was evaporated in vacuo at 20 °C and the residue passed through a short silica gel column with 90% EtOAc/hexane. Evaporation of the eluant yielded an oil (105 mg, 98%). ^{1}H NMR indicated

(19) *Dictionary of Organic Compounds*, 5th ed.; Chapman and Hall: New York, 1982; Vol. 1.

(20) *The Sadtler Standard NMR Spectra*; Sadtler Research Laboratories: Philadelphia, PA, 1969; Spectrum 6930M. Sadtler Research Laboratories, Philadelphia, PA, USA 19104.

the presence of two isomers in the approximate ratio of 65:35 (cis/trans). These could be separated by chromatography (35% EtOAc/hexane): ^{1}H NMR ($CDCl_3$) δ [cis isomer] 3.782 (s, 3 H), 3.808 (s, 3 H), 3.860 (s, 3 H), 3.892 (s, 3 H), 3.949 (s, 3 H), 5.232 (s, 1 H, H_1), 5.337 (s, 1 H, H_3), 6.541 (s, 1 H), 6.718–6.915 (m, 3 H), 6.984 (s, 1 H), [trans isomer] 3.763 (s, 3 H), 3.835 (s, 3 H), 3.878 (s, 3 H), 3.913 (s, 3 H), 3.950 (s, 3 H), 5.306 (s, 1 H, H_3), 5.479 (s, 1 H, H_1), 6.502 (s, 1 H), 6.665–6.932 (m, 3 H), 6.995 (s, 1 H); IR (CH_2Cl_2) 1612, 1532, 1472, 1232, 1120–1170 cm^{-1}; mass spectrum (of mixture), *m/e* (relative intensity) 330 (11, M – SO_2), 316 (49), 299 (26), 298 (18), 285 (32), 240 (23), 224 (37), 209 (67), 194 (67), 193 (50), 166 (52), 165 (98), 154 (100), 151 (67), 139 (67). Elemental analysis was not possible due to instability.

(*R*)-Phenylethoxy Sulfone 5b. The hydroxy sulfone **4** (234 mg) and (*R*)-1-phenylethanol (Aldrich) (1.1 g) were added to CH_2Cl_2 (12 mL) followed by *p*-toluenesulfonic acid (20 mg) and $MgSO_4$ (100 mg). After 6 h at room temperature the solution was evaporated in vacuo and chromatographed with 25% EtOAc/hexane as eluant to yield 230 mg (77%): ^{1}H NMR ($CDCl_3$) δ 1.583 (d, 3 H, J = 6.45 Hz), 3.760 (s, 3 H), 3.826 (s, 3 H), 3.895 (s, 3 H), 3.905 (s, 3 H), 5.152 (s, 1 H, H_1), 5.166 (q, 1 H, J = 6.45 Hz), 5.267 (s, 1 H, H_3), 6.520 (s, 1 H), 6.727 (s, 1 H), 6.747–6.887 (m, 3 H), 7.389–7.545 (m, 5 H); mass spectrum, *m/e* (relative intensity) 420 (<1, M – SO_2), 329 (9), 316 (50), 315 (54), 299 (27), 298 (18), 285 (31), 166 (22), 165 (45), 154 (68), 151 (27), 150 (54), 139 (100). Elemental analysis was not possible due to instability.

(±)-Cycloadduct 7a. ZnO (30 mg, anhydrous) was added to a solution of the sulfone **5a** (99.5 mg) and dimethyl fumarate (143 mg, 4 equiv) in benzene (8 mL). The reaction mixture was flushed with nitrogen, refluxed 15 h, evaporated, and chromatographed through a short silica gel column (30% EtOAc/hexane) to yield an oil (98 mg, 82%): ^{1}H NMR ($CDCl_3$) δ 3.263 (dd, 1 H, H_3, J = 2.91, 12.15), 3.415 (s, 3 H), 3.512 (s, 3 H), 3.519 (dd, 1 H, H_2, J = 10.86, 12.15 Hz), 3.622 (s, 3 H), 3.761 (s, 3 H), 3.791 (s, 3 H), 3.882 (s, 3 H), 3.922 (s, 3 H), 3.966 (d, 1 H, H_1, J = 10.86 Hz), 4.653 (d, 1 H, H_4, J = 2.91 Hz), 6.324 (s, 1 H), 6.617–6.929 (m, 4 H); IR (CH_2Cl_2) 1742, 1732, 1522, 1242 cm^{-1}; mass spectrum, *m/e* (relative intensity) 474 (28), 382 (100), 381 (42), 351 (57), 252 (43), 222 (28), 59 (42); exact mass calcd for $C_{25}H_{30}O_9$ 474.1889, found 474.1861.

(±)-Diester 8. The cycloadduct **7a** (98 mg) and Pd/C (5%, 150 mg, Aldrich) were stirred in methanol (20 mL) under hydrogen for 15 h. The mixture was filtered and evaporated to give a solid (88 mg, 96%) which could be recrystallized from 2-propanol: mp 126–127 °C (lit. mp 127 °C[14]); the NMR and IR spectra were identical with that reported previously;[14] mass spectrum, *m/e* (relative intensity) 444 (60), 384 (45), 325 (100), 259 (60), 222 (45), 151 (45).

(±)-Isolariciresinol Dimethyl Ether 1. (±)-Diester 8 (13 mg) was dissolved in dry THF (3 mL) and cooled to 0 °C and $LiAlH_4$ (4 mg) added. The solution was stirred for 1 h at 20 °C and then refluxed for 15 min. Water (1 drop) and 10% aqueous HCl (ca. 0.5 mL) were added, and then the solution was dried ($MgSO_4$) and evaporated to give a solid (12 mg, ca. 100%). Recrystallization from EtOAc/hexane gave crystals: mp 150–153 °C (lit. mp 150–152 °C[14]); ^{1}H NMR ($CDCl_3$) δ 1.788–1.895 (m, 1 H, H_2), 1.945–2.185 (m, 1 H, H_3), 2.295–2.615 (br s, 1 H, OH), 2.723 (dd, 1 H, H_4 cis to H_3, J = 5.1, 15.0 Hz), 2.821 (dd, 1 H, H_4 trans to H_3, J = 11.3, 15.0 Hz), 3.505 (dd, 1 H, one of the CH_2 protons at C_2, J = 5.2, 11.2 Hz), 3.571 (s, 3 H), 3.772–3.880 (m, 4 H, H_1, one of the CH_2 protons at C_2 and the CH_2 protons at C_3), 3.802 (s, 3 H), 3.847 (s, 3 H), 3.878 (s, 3 H), 6.201 (s, 1 H), 6.596–6.603 (m, 2 H), 6.65–6.68 (m, 2 H); IR identical with that in the literature; mass spectrum, *m/e* (relative intensity) 388 (100), 340 (92), 269 (7 3), 189 (42), 151 (73).

Elimination Product 9. The cycloadduct **7a** (12 mg) and *p*-toluenesulfonic acid (5 mg) were refluxed in toluene (3 mL) for 16 h. The mixture was filtered through a silica gel column to give an oil (11 mg, 99%): ^{1}H NMR ($CDCl_3$) δ 3.642 (s, 3 H), 3.755 (s, 3 H), 3.789 (s, 3 H), 3.809 (s, 3 H), 3.828 (s, 3 H), 3.911 (s, 3 H), 4.002 (d, 1 H, H_2, J = 2.6 Hz), 4.642 (d, 1 H, H_1, J = 2.6 Hz), 6.450 (dd, 1 H), 6.620–6.700 (m, 3 H), 6.873 (s, 1 H), 7.672 (s, 1 H, H_4); IR (CH_2Cl_2) 1740, 1710, 1517 cm^{-1}; mass spectrum, *m/e* (relative intensity) 442 (28), 383 (43), 382 (100), 352 (16), 351 (68), 324 (8), 128 (17), 91 (16); exact mass calcd for $C_{24}H_{26}O_8$ 442.1628, found 442.1643.

Cycloadduct 7b. The alkoxy sulfone **5b** (230 mg) was dissolved in benzene (10 mL) with dimethyl fumarate (280 mg). ZnO (100 mg) and K_2CO_3 (90 mg) were added, and the mixture was refluxed for 1 h. The mixture was chromatographed with 40% EtOAc/hexane to give an oil (208 mg, 78%). TLC and NMR indicated the presence of two isomeric adducts. Rechromatography using 25% EtOAc/hexane gave the major isomer as an oil (116 mg, 43%): ^{1}H NMR ($CDCl_3$) δ 1.422 (d, 3 H, J = 6.5 Hz), 3.241 (dd, 1 H, H_3, J = 2.9, 12.0 Hz), 3.530 (s, 3 H), 3.553 (s, 3 H), 3.565 (s, 3 H), 3.645 (dd, 1 H, H_2, J = 11.0, 12.0 Hz), 3.694 (s, 3 H), 3.823 (s, 3 H), 3.878 (s, 3 H), 3.925 (d, 1 H, J = 11.0 Hz), 4.578 (q, 1 H, J = 6.5 Hz), 4.922 (d, 1 H, H_4, J = 2.85 Hz), 6.068 (s, 1 H), 6.209 (s, 1 H), 6.55–6.85 (m, 3 H), 7.20–7.50 (m, 5 H); IR 1740, 1520, 1250 cm^{-1}; mass spectrum, *m/e* (relative intensity) 564 (3.5), 442 (27), 383 (43), 382 (100), 352 (16), 351 (65), 316 (10), 315 (11), 122 (18); exact mass calcd for $C_{32}H_{36}O_9$ 564.2359, found 564.2342.

Diester 8 (1*S*,2*R*,3*R*). The cycloadduct **7b** (113 mg) was dissolved in methanol containing 25% acetic acid (13 mL) with Pd/C (5%, 50 mg) and the mixture stirred under hydrogen for 15 h at 20 °C. The mixture was filtered, evaporated, and chromatographed (25% EtOAc/hexane) to give a solid (84 mg, 92%) which was recrystallized from isopropyl alcohol, mp 143–145 °C. The spectra (NMR and IR) were identical with those of racemic **8**, $[\alpha]^{20}_D$ +19.9° (*c* 0.44, chloroform).

(+)-Isolariciresinol Dimethyl Ether 1. The optically active diester **8** (35.5 mg) was reduced in a manner identical with that used for racemic **8** to yield 29.5 mg (100%). Spectra (NMR and IR) were identical with the racemic material: mp 167–169 °C (lit. mp 167–169 °C[12]); $[\alpha]^{20}_D$ +13.2° (*c* 0.58, chloroform).

Acknowledgment. We gratefully acknowledge the assistance of M. Hrytsak, University of Ottawa, who measured the optical rotations. We also acknowledge the assistance of the Natural Sciences and Engineering Research Council of Canada, who provided research funding.

Registry No. 1, 21966-92-7; (±)-**1**, 61248-24-6; **2**, 103477-67-4; **3**, 103477-59-4; (±)-**4**, 103477-60-7; (±)-**4'**, 103477-61-8; (±)-**5a**, 103477-62-9; (±)-**5a'**, 103477-63-0; **5b**, 103477-64-1; (±)-**7a**, 103477-65-2; **7b**, 103477-66-3; **7b'**, 103531-50-6; (±)-**8**, 82837-97-6; **8**, 78178-29-7; (±)-**9**, 103531-49-3; (±)-**10**, 103531-51-7; 6-bromoveratraldehyde, 5392-10-9; veratraldehyde, 120-14-9; 6-bromoveratraldehyde ethylene glycolacetal, 103477-58-3; 3,4-dimethoxybenzyl alcohol, 93-03-8; 3,4-dimethoxybenzyl bromide, 21852-32-4; (*R*)-1-phenylethanol, 1517-69-7; dimethyl fumarate, 624-49-7.