Studies on Acidic Dimerization of 3,4-Dioxygenated Cinnamate or 1-Phenylpropene to Arylindane Lignans

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The BF₃·OEt₂-, TsOH- or HCOOH-catalyzed dimerization of 3,4-dioxygenated cinnamate or 1-arylpropene offers a route to arylindane lignans. The structures of the products were elucidated and a mechanism is proposed for the reactions. The structures of the dimeric products assigned as aryltetralin lignans by Botta et al.

Key words  dioxygenated cinnamate; arylpropene; arylindane lignan; acidic dimerization; mechanism

Aryltetralin lignans are common natural products. They possess many pharmacological activities, including cytotoxic,1,13 antitumor,1 and anti-infective3 activities. In 1986 the arylindane lignan γ-diasarone (1)4 was isolated from nature for the first time. Al-Farhan et al. prepared it from asaron (2) by using acidic trifluorooicetic acid (TFA) dimerization.5 Mill et al.6 had previously prepared diiseugenol (3a) (an arylindane lignan of the same type as 1) from isoeugenol by refluxing in 90% HCOOH. Recently, we found that this compound inhibits platelet thromboxane formation and phosphoinsitde breakdown.7 Oxidative coupling of monolignol has been studied as a model of formation of lignan-related dimers during FeCl₃ oxidation,8 enzyme oxidation,9 and free radical oxidation.10 Anodic oxidation11 and photolysis12 of monolignol yields the similar arylindane-type lignans. In connection with our interest in lignans and biometnetic studies, we have examined the sensitized photooxidation of methyl (E)-ferulate,13 the ferric chloride oxidation of isoeugenol,14 and the photooxidation of isoeugenol in protic and aprotic solvents.15 Recently, we used a higher oxidative potential system, CrO₃·HClO₄·CH₃CN, to oxidize dioxygenated 1-arylpropene and prepared tetraicline lignan [cayayanone (4)] in a single step.15 We concluded that oxidative coupling of monolignol would give benzofuran-type lignan and acidic dimerization would afford arylindane-type lignan. But Botta et al.16 reported that acidic dimerization (BF₃-etherate) of (E)-3,4-dimethoxycinnamic acid methyl ester yielded two aryltetraline lignans, named AL-A and AL-B, which were assigned the structures 5a and 6a, respectively. Because the yield of AL-A was greater than that of AL-B, Botta et al. concluded that AL-A is more stable than AL-B. They carried out MM2 calculations, which indicated that the conformation of AL-A showed a minimal energy ca. 0.8 kcal/mol lower than that of AL-B. Surprisingly, the 8,8′-cis compound predominates.17 We considered the structures of AL-A and AL-B were likely to be 3b and 7, respectively, for the following reasons. The reported nuclear Overhauser effects (NOEs)16 are consistent with the structure 3b. The C-7 proton in AL-A exhibited a slight NOE with one of the C-7 protons (axial), which is incompatible with the structure 5a. The mass fragmentaion patterns of AL-A can be rationalized according to Chart I for the structure 3b, rather than the structure 5a. The structure 5a is inconsistent with the MS fragment peaks, especially those at m/z 370 and 371. We synthesized compound 6a, and when it was treated with NaH overnight or refluxed with 2 N HCl in MeOH, only the reactant was recovered. This shows that 6a is more stable than 5a. The result suggested that the energy calculation using the MM2 process is incorrect. The results described below prove that the structures of AL-A and AL-B are 3b and 7, respectively, i.e., the arylindane-type lignans.

![Diagram of chemical structures](chart1.png)

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(E)-Ferulic acid was reacted with p-toluenesulfonic acid under reflux in methanol solution for 6 h, and the reaction solution was mixed with silica gel then heated in vacuo on a water bath at 60 °C to remove the solvent. After half an hour, the dry silica gel coated with the products was placed on top of a silica gel column. Six products, methyl (Z)-ferulate, methyl (E)-ferulate (8a), 9a, 3c, 9b, and 9c, were isolated after repeated purification on silica gel. The structures of the latter four products were elucidated in the following ways.

Methyl (E)- and (Z)-ferulates were identical with authentic samples.12 Compound 3c was formulated as C22H24O8 (dimer of methyl ferulate) on the basis of elemental analysis and MS measurement (MS m/z: 416). The infrared (IR) spectrum shows absorptions due to aromatic and ester functions. The 1H-NMR signals (Table 1) reveal three ABX system protons (=CH2CHO2O–), four methoxy groups, two vicinal methine protons, two singlet phenyl protons, and three ABX system phenyl protons. Decoupling and NOE experiments provided the correct structure. Compound 3c gave 3d on acetylation. The dibenzyl derivative 3e [δ 4.95 and 5.11 (each 2H, s, –OCH2Ph)] was obtained from 3c. On reduction with lithium aluminum hydride in dry THF, 3e gave the glycol 3f. Compound 3f, dissolved in dry pyridine, was treated with p-toluenesulfonyl chloride, and ditosylate 3g was obtained together with 3h, 10a, and 10b. The major product, the ditosylate 3g, was identified on the basis of its spectral data. Formation of the cyclic ether 10b indicated that the two substituents on the ring must be in cis relation. Reduction of the ditosylate 3g with lithium aluminum hydride gave 3i.13 Catalytic hydrogenolysis of 3i gave diosoneguelin (3a).6,12,15 On the basis of the above evidence, the structure of 3c was confirmed unambiguously. Compounds 9b and 9c are isomers, based on their elementary analysis. Both of them reacted with excess diazomethane in methanol (10 min) to give the same product, 3c. Chromatographically, compound 9c is more polar than 9b, so we assigned the polar carboxylic acid group to the less hindered C-9 in 9c and the more hindered C-9' in 9b. Compound 9a shows signal due to three methoxyl groups, and one secondary methyl group (Table 1) in its 1H-NMR spectrum. It was considered that 9a was produced by decarboxylation of 9c. In order to confirm this, 9b or 9c was heated in 95% formic acid under reflux. Compound 9c gave the single product 9a, and 9b was recovered unchanged.

When we used formic acid as the solvent, two products, 9a and 3c, were obtained from methyl (E)-ferulate (8a). The above results indicate that 3',4'-dioxynated 1-phenylpropene or cinnamateimerized with acids (TsoH, HCOOH or TFA18) to give arylindanes but not aryltetralins. Methylation of 3c with diazomethane yielded a product 3b which was identical with AL-A on direct comparison.

We repeated the procedure of Botta et al. to prepare AL-A and AL-B. Reduction of AL-A afforded a dihydroxy product 3j. In order to confirm the structure of 3j, the decoupling method was used. Irradiation at δ 1.56 (H-8) or 2.03 (H-8, 8) simplified the signals at δ 3.43 (H-7) and 3.67–3.84 (H-9). This 1H-NMR behavior is not compatible with the structure 11. Acetylation of 3j yielded the diacetate 3k. In our previous experiment,13 we obtained 12 by the photoxoygenation of methyl (E)-ferulate. Catalytic hydrogenation of 12 afforded two products, 5b and 6b, with the ratio of 1:17. Many reports8,18–20 indicate that the major reductive product is in all-trans form. The 1H-NMR spectral data for 5b and 6b are shown in Table 2. The methylation of 6b with diazomethane in methanol produced 6a, which was identical with the product prepared by Mann et al.21) Because the 1H-NMR data for 6a and AL-B are different, Botta claimed incorrectly that the 1H-NMR assignments for 6a by Mann et al. were ambiguous. Our data for 6a are presented in Table 2. From the above results, we concluded that the acidic coupling of 3',4'-dioxynated cinnamate or 1-arylpropene using p-TsoH, HCOOH or TFA affords arylindane-type lignans but not aryltetralin-type lignans, even with BF3-etherate. Finally, the formation of the products by Lewis acid (BF3) coupling of 8b may be rationalized in terms of the mechanism in Chart 2.
Table 2. \(^1\)H-NMR Data for 3k, 3l, 5b, 6b, and 6a (in CDCl\(_3\), TMS as Standard)

<table>
<thead>
<tr>
<th>H</th>
<th>3k(^{a})</th>
<th>3l(^{a})</th>
<th>5b(^{b})</th>
<th>6b(^{b})</th>
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<td>6.37 s</td>
<td>6.31 s</td>
<td>6.28 s</td>
<td>6.18 s</td>
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<td>7</td>
<td>3.43 m</td>
<td>3.32 m</td>
<td>3.10–3.23 m</td>
<td>3.0–3.1 m</td>
<td>3.0–3.1 m</td>
</tr>
<tr>
<td>8</td>
<td>1.56 m</td>
<td>1.66 m</td>
<td>3.10–3.23 m</td>
<td>3.0–3.1 m</td>
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<tr>
<td>9</td>
<td>2.03 m</td>
<td>1.98 m</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2'</td>
<td>3.6–3.8 m</td>
<td>4.1–4.3 m</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5'</td>
<td>6.60 d (1.8)(^c)</td>
<td>6.58 d (1.9)</td>
<td>6.19 d (8.1)</td>
<td>6.45 d (8.1)</td>
<td>6.45 d (8.1)</td>
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<tr>
<td>6'</td>
<td>6.77 d (8.1)</td>
<td>6.91 d (8.1)</td>
<td>6.77 d (8.1)</td>
<td>6.77 d (8.1)</td>
<td>6.81 d (8.1)</td>
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<td>7'</td>
<td>6.66 dd (8.1, 1.8)</td>
<td>6.67 dd (8.1, 1.9)</td>
<td>6.71 dd (8.1, 1.8)</td>
<td>6.59 dd (8.1, 1.8)</td>
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<tr>
<td>8'</td>
<td>3.84 d (10.2)</td>
<td>3.96 d (9.8)</td>
<td>4.14 d (3.0)</td>
<td>4.07 d (10.8)</td>
<td>4.12 d (10.9)</td>
</tr>
<tr>
<td>9'</td>
<td>2.67 m</td>
<td>2.78 m</td>
<td>3.10–3.23 m</td>
<td>3.00 dd (10.8, 10.6)</td>
<td>2.98 dd (10.9, 10.8)</td>
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<td>3.81 s</td>
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\(^a\) 300 MHz. \(^b\) 90 MHz. \(^c\) Figures in parentheses are coupling constants in Hz.

**Experimental**

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO A102 spectrometer. \(^1\)H-NMR spectra were run on a Varian EM-390 at 90 MHz or a Bruker AM300 at 300 MHz in CDCl\(_3\) solution with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in \(\delta\) values and coupling constants (\(J\)) are given in hertz (Hz). Electron impact-mass spectra (EI-MS) were taken on a Finnigan MAT TSQ-46C spectrometer.

**Dimerization of (E)-Ferulic Acid** A solution of (E)-ferulic acid (10 g) in 50 ml of methanol was heated with p-toluenesulfonic acid (1 g) under reflux for 6 h. Then silica gel (Merck 7734, 70–230 mesh) (30 g) was added to the reaction mixture after it had cooled to ambient temperature. The mixture was heated in vacuo at 60°C on a water bath. After 90 min, the dry silica gel coated with products was placed on a column of silica gel. Six products, methyl (Z)-ferulate (100 mg), methyl (E)-ferulate (8a) (1.5 g), 9a (280 mg), 3e (7.09 g), 9b (2.15 mg), and 9e (160 mg), were eluted in that order. Methyl (E)- and (Z)-ferulate were identical with authentic samples.\(^{19}\) The physical data of the new products were as follows.

\(^9\)a: mp 213–214°C. IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3400, 3260, 1720, 1600, 1520, 1500, 1260, 1200, 1140. \(^{1}\)H-NMR: Table 1. Anal. Calcd for C\(_{22}\)H\(_22\)O\(_4\): C, 67.02; H, 6.19. Found: C, 67.14; H, 6.24.

\(^3\)e: mp 222–223°C. IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3442, 3020, 1740, 1599, 1495, 1229, 1165. MS m/z: 416 M\(^+\) (91), 370 (17), 356 (100), 297 (16), 263 (14). \(^{1}\)H-NMR: Table 1. Anal. Calcd for C\(_{22}\)H\(_22\)O\(_4\): C, 63.45; H, 5.81.

\(^9\)b: mp 203–204°C. IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3210–2628, 1724, 1600, 1510, 1200, 1140, 1020. \(^{1}\)H-NMR: Table 1. Anal. Calcd for C\(_{22}\)H\(_22\)O\(_4\): C, 62.68; H, 5.51. Found: C, 62.79; H, 5.49.

**Acetylation and Benzoylation of 3c** A solution of 3c (50 mg) in a mixture of 0.5 ml of Ac\(_2\)O and 1 ml of pyridine was allowed to stand overnight at ambient temperature. The usual work-up afforded the diaacetate 3d (46 mg) \([\text{mp} 145–147°C. IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3170, 1740, 1730, 1600, 1500, 1240, 1140. \(^{1}\)H-NMR: Table 1. Compound 3e (2.0 g), benzyl bromide (2.0 ml), and potassium carbonate (1.2 g) were added to dry acetone (50 ml). The reaction mixture was heated under reflux for 20 h. After evaporation of the solvent, 100 ml of water was added to the residue, and the mixture was extracted with ethyl acetate (30 ml x 3) to afford 3e (2.7 g) after purification by silica gel chromatography. 3e \([\text{mp} 119–120°C. IR \(\nu_{\text{max}}\) cm\(^{-1}\): 3020, 1720, 1600, 1500, 1240, 1040, 1010. \(^{1}\)H-NMR: \(\nu_{\text{max}}\) \(\text{CDCl}_3\): 2.42 (1H, dd, J=15.1, 5.9 Hz, H-8), 2.66 (1H, dd, J=15.1, 4.2 Hz, H-8), 3.40 (1H, dd, J=11.1, 6.2 Hz, H-8'), 3.59, 3.65, 3.71, 3.85 (each 3H, s, =0Me), 4.02 (1H, m, H-7), 4.65 (1H, d, J=11.1 Hz, H-7), 4.95, 5.11 (each 2H, s, =OCH\(_3\)Ph), 6.45, 6.79 (each 1H, s, H-5, H-2), 6.59, 6.61 (each 1H, d, J=8.1 Hz, H-3, H-6), 6.67 (1H, s, H-7), 7.15–7.50 (10H, m, =OCH\(_3\)Ph).]

**Reduction of 3c with Lithium Aluminate Hydride** LiAlH\(_4\) (500 mg)
was added to a solution of 3c (1.001 g) in dry tetrahydrofuran (THF) (20 ml) and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with 0.1 ml of water, 10% NaOH aqueous solution (0.1 ml) was added to the mixture and the whole was stirred for 5 min. Water (1 ml) was added, and mixing was continued until a white precipitate was formed. After filtration, the filtrate was purified by silica gel chromatography (50% ethyl acetate in hexane) to yield the diol 3f (0.82 g) [mp 109—110°C. IR νmax cm⁻¹: 3500, 3040, 1600, 1500, 1260, 1100, 1020. 1H-NMRS (CDCl3) δ: 1.50 (2H, m, -H-8), 2.11 and 2.62 (each 1H, m, -H-7), 3.31—3.71 (5H, m, -H-7, 2 × -CH2OH), 3.66, 3.81 (each 3H, s), 4.89, 5.11 (each 2H, s, -OCH2Ph), 6.41—6.82 (5H, m), 7.10—7.42 (10H, m, -OCH2Ph)].

Tosylation of 3f p-Toluenesulfonyl chloride (1.5 g) was added to compound 3f (0.82 g) in dry pyridine (3 ml) at 0°C over 1 h with stirring and the mixture was left overnight at 10°C. It was then poured into excess ice-water and extracted with ethyl acetate (30 ml x 3). The combined ethyl acetate extracts were washed with 1 N H2SO4 aqueous NaHCO3, and water. The residue, after removal of the solvent, was purified on silica gel to give four products, 3b (87 mg), 10a (100 mg), 3g (785 mg), and 10b (120 mg). The physical data of the products were as follows: 3b: mp 102—103°C. IR νmax cm⁻¹: 3060, 1600, 1510, 1160, 1080, 800, 740. MS m/z: 576 (M⁺, C34H32O6Cl2), 50, 578 (M⁺ - 2, 31), 580 (M⁺ - 4, 5). 1H-NMR (CDCl3) δ: 2.00—2.41 (3H, m, -H-8), 3.31 (1H, m, -H-7), 3.52—3.73 (4H, m, -H-9, H-9), 3.77, 3.91 (each 3H, s). 4.25 (1H, d, J = 7.5 Hz, -H-7), 5.02, 5.15 (each 2H, s, -OCH2Ph), 6.51—6.93 (5H, m), 7.22—7.54 (10H, m, -OCH2Ph). 10a: Amorphous solid. IR νmax cm⁻¹: 3040, 1600, 1450, 1220, 1020, 1140, 810, 700. MS m/z: 712 (M⁺, C34H34S2Cl). 1H-NMRS (CDCl3) δ: 1.90—2.22 (3H, m, -H-8, H-8), 2.41 (3H, s, Ar-CH3), 3.11 (1H, m, -H-7), 3.52 (2H, m, -H-9), 3.74, 3.85 (each 3H, s), 3.91—4.22 (3H, m, -H-7, H-9), 4.95, 5.10 (each 2H, s, -OCH2Ph), 6.45, 6.71 (each 1H, s, H-5, H-2), 6.38 (1H, dd, J = 8.1, 2.0 Hz, H-6), 6.59 (1H, d, J = 2.0 Hz, H-2), 6.72 (1H, d, J = 8.1 Hz, H-5), 7.15—7.53 (12H, m, -OCH3Ph, -SO2OCH3Me). 7.75 (2H, d, J = 8.3 Hz, -SO2OCH3Me). 3g: Amorphous solid. IR νmax cm⁻¹: 3040, 1600, 1500, 1350, 1240, 1140, 1020. 1H-NMR (CDCl3) δ: 2.01 (2H, m, -H-8), 2.22 (1H, m, -H-8), 2.42 (6H, s, Ar-Cl2), 3.12 (2H, m, -H-7), 3.78, 3.88 (each 3H, s), 4.01—4.33 (5H, m, H-7, H-9, H-9), 4.92, 5.11 (each 2H, s, -OCH2Ph), 6.42—6.65 (5H, m), 7.22—7.51 (14H, m, -OCH2Ph, -SO2OCH3Me). 7.72 (4H, d, J = 8.1 Hz, -SO2OCH3Me). 10b: mp 129—131°C. IR νmax cm⁻¹: 3020, 1600, 1500, 1220, 1020, 1000. MS m/z: 522 (M⁺, C34H34O2). 1H-NMR (CDCl3) δ: 1.62 (2H, m, -H-8), 2.12 (1H, m, -H-8), 3.42—3.61 (4H, m, H-9, H-9), 3.74, 3.87 (each 3H, s), 4.12 (1H, d, J = 9.1 Hz, H-7), 4.96, 5.11 (each 2H, s, -OCH2Ph), 6.51—6.83 (5H, m), 7.22—7.54 (10H, m, -OCH2Ph).

Reduction of 3g with Lithium Aluminum Hydride Reduction of 3g (785 mg) with LiAlH4 was conducted under the same conditions as mentioned above, to afford 3i (mp 78—79°C, lit.139 amorphous solid).

Catalytic Hydrogenolysis of 3i Compound 3i (423 mg) was dissolved in 10 ml of MeOH, then 25 mg of 10% Pd-C previously suspended in 5 ml of MeOH was added and the mixture was saturated with H2. After 48 h, the catalyst was removed by filtration and washed several times with MeOH. The combined filtrate and washing yielded 3a (260 mg) (mp 179—180°C).138,139

Methylation of 9b and 9c with Diazomethane Excess diazomethane in ether was added dropwise to a solution of 9b (20 mg) or 9c (20 mg) in methanol (3 ml). After 10 min, acetic acid was added to destroy excess CH3N2. The reaction mixture was washed with aqueous NaHCO3 and the organic layer afforded 3e (21 mg) in both cases. When the reaction time was extended to 48 h, both compounds afforded the same product, 3b (mp 141—142°C).140
Decarboxylation of 9c in Formic Acid  Compound 9c (70 mg) was dissolved in 3 ml of 95% formic acid and the solution was heated under reflux for 1 h. After the solution had cooled to ambient temperature, excess water (50 ml) was added. The aqueous solution was extracted with ether (30 ml x 3), and the combined ether extract was washed with aqueous NaHCO₃, and then dried over MgSO₄. Evaporation of the ether gave 9a (30 mg).

Dimerization of Methyl (E)-Ferulate with Formic Acid  Methyl (E)-ferulate (280 mg) was heated with 2 ml of 95% formic acid under reflux for 1 h. The usual work-up afforded two products, 9a (20 mg) and 3c (80 mg).

Reduction of 3b (AL-A) with Lithium Aluminum Hydride  Reduction of 3b (100 mg) with LiAlH₄ was achieved in the same manner above to afford 3j (79 mg) [mp 138–139°C. IR ν₄ν₄cm⁻¹: 3508, 3030, 1602, 1500, 1497, 1212, 1151, 1137, 1098, 1023. MS m/z: 388 (M⁺, 100), 370 (24), 325 (80), 232 (20)]. 1H-NMR (CDCl₃) δ: Table 2.

Acetylation of 3j with Ac₂O and Pyridine  Compound 3j (20 mg) was dissolved in a mixture of Ac₂O (0.5 ml) and pyridine (0.5 ml) and the solution was allowed to stand overnight at ambient temperature. The usual work-up afforded 3k (24 mg) [amorphous. IR ν₄ν₄cm⁻¹: 3030, 1736, 1601, 1498, 1273, 1154, 1030, 859. MS m/z: 472 (M⁺, 73), 412 (48), 352 (56), 325 (100), 214 (29)]. 1H-NMR (CDCl₃) δ: Table 2.

Catalytic Hydrogenation of 12 with Pd-C as the Catalyst  Hydrogen gas was bubbled into a solution of compound 12 (100 mg), p-TsOH (10 mg), and 10% Pd-C (10 mg) in MeOH (6 ml) for 6 h. The mixture was neutralized with aqueous NaHCO₃, and the solvent was evaporated in vacuo to give a residue, which was extracted with ethyl acetate and subjected to chromatography on silica gel. Two products, 5b (5 mg) and 6b (85 mg) were eluted in that order. Physical data for 5b and 6b were as follows. 5b: Amorphous. IR ν₄ν₄cm⁻¹: 3400, 1720, 1600, 1500, 1290, 1100. 1H-NMR (CDCl₃) δ: Table 2. 6b: mp 150–151°C. IR ν₄ν₄cm⁻¹: 3434, 3030, 1740, 1599, 1509, 1259, 1120, 734. MS m/z: 416 (M⁺, 100), 356 (50), 297 (47), 208 (15), 149 (11). 1H-NMR (CDCl₃) δ: Table 2.

Methylation of 6b with Diazomethane  A solution of 6b (30 mg) in 3 ml of MeOH was treated with excess diazomethane in ether for 3 d at ambient temperature. Usual work-up afforded 6a (31 mg).

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References