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

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The BF_3-, 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] antitumor,[2] and anti-infective[3] 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 asarone (**2**) by using acidic trifluoroacetic acid (TFA) dimerization.[5] Mill *et al.*[6] had previously prepared diisoeugenol (**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 phosphoinsitide breakdown.[7] Oxidative coupling of monolignol has been studied as a model of formation of lignan-related dimers during $FeCl_3$ oxidation,[8] enzyme oxidation,[9] and free radical oxidation.[10] Anodic oxidation[11] and photolysis[12] of monolignol gave the similar arylindane-type lignans. In connection with our interest in lignans and biomimetic studies, we have examined the sensitized photooxidation of methyl (*E*)-ferulate,[13] the ferric chloride oxidation of isoeugenol,[8] and the photooxidation of isoeugenol in protic and aprotic solvents.[14] Recently, we used a higher oxidative potential system, CrO_3–$HClO_4$–CH_3CN, to oxidize dioxygenated 1-arylpropene and prepared tetralone 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 (BF_3-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 fragmentation patterns of AL-A can be rationalized according to Chart 1 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.

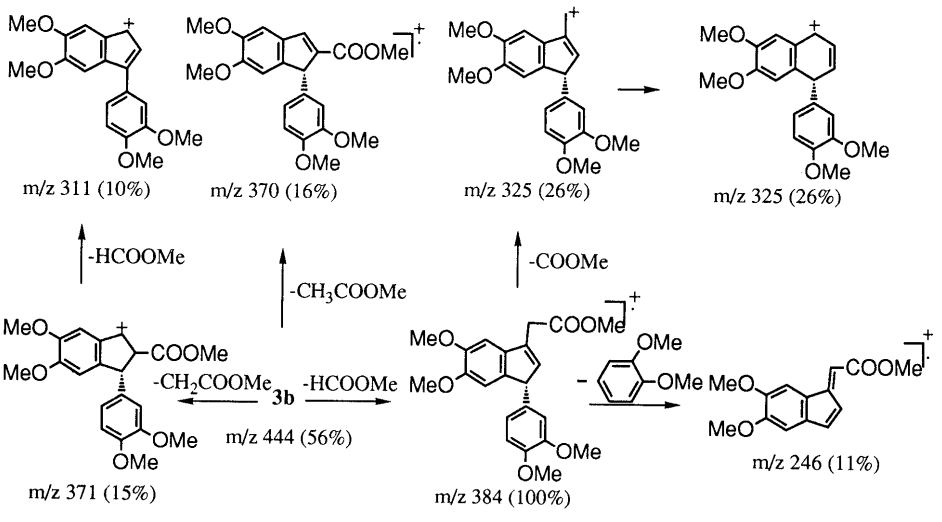

Chart 1

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Table 1. ^{1}H-NMR Data for **3c**, **3d**, **9a**, **9b**, and **9c** (in $CDCl_3$, TMS as Standard)

H	3c[a]	3d[b]	9a[b]	9b[b]	9c[b]
2	6.74 s	6.74 s	6.83 s	6.95 s	6.92 s
5	6.40 s	6.59 s	6.31 s	6.34 s	6.31 s
7	3.94 m	4.00 m	3.40 m	3.95 m	3.91 m
8	2.43 dd (16.0, 8.2)[c]	2.48 dd (16.2, 8.3)	10.8 d (7.0)	2.41 dd (15.0, 9.1)	2.42 dd (16.0, 8.1)
	2.57 dd (16.0, 6.7)	2.62 dd (16.2, 6.5)		2.64 dd (15.0, 11.0)	2.64 dd (16.0, 6.9)
2′	6.66 d (1.9)	6.6—6.8 m	6.6—6.8 m	6.75 d (2.0)	6.74 d (2.0)
5′	6.81 d (8.2)	6.81 d (8.2)	6.6—6.8 m	6.78 d (8.1)	6.81 d (8.2)
6′	6.68 dd (8.2, 1.9)	6.6—6.8 m	6.6—6.8 m	6.65 dd (8.1, 2.0)	6.58 dd (8.2, 2.0)
7′	4.60 d (10.0)	4.68 d (10.2)	4.61 d (9.0)	4.68 d (10.1)	4.58 d (10.1)
8′	3.41 dd (10.0, 8.2)	3.46 dd (8.4, 8.2)	3.40 m	3.41 m	
$COOCH_3$	3.61 s	3.63 s	3.64 s	3.61 s	3.60 s
	3.65 s	3.67 s			
$ArOCH_3$	3.79 s	3.73 s	3.77 s	3.78 s	3.75 s
	3.84 s	3.77 s	3.85 s	3.82 s	3.80 s
O ‖ $ArOCCH_2$		2.23 s 2.29 s			

a) 300 MHz. *b*) 90 MHz. *c*) Figures in parentheses are coupling constants in Hz.

(*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.[13] Compound **3c** was formulated as $C_{22}H_{24}O_8$ (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 ^{1}H-NMR signals (Table 1) reveal three ABX system protons (=$CHCH_2COO$–), four methoxyl 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, –OCH_2Ph)] 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 ditoxylate **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**.[15] Catalytic hydrogenolysis of **3i** gave diisoeugenol (**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 ^{1}H-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′-dioxygenated 1-phenylpropene or cinnamate dimerized with acids (TsOH, HCOOH or TFA[5]) 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 dihydroxyl product **3j**. In order to confirm the structure of **3j**, the decoupling method was used. Irradiation at δ 1.56 (H_a-8) or 2.03 (H_b-8) simplified the signals at 3.43 (H-7) and 3.67—3.84 (H-9). This ^{1}H-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 photooxygenation of methyl (*E*)-ferulate. Catalytic hydrogenation of **12** afforded two products, **5b** and **6b**, with the ratio of 1:17. Many reports[8,18–20] indicate that the major reductive product is in all-*trans* form. The ^{1}H-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 ^{1}H-NMR data for **6a** and AL-B are different, Botta claimed incorrectly that the ^{1}H-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-dioxygenated cinnamate or 1-arylpropene using *p*-TsOH, HCOOH or TFA affords arylindane-type lignans but not aryltetralin-type lignans, even with BF_3-etherate. Finally, the formation of the products by Lewis acid (BF_3) coupling of **8b** may be rationalized in terms of the mechanism in Chart 2.

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Table 2. ^{1}H-NMR Data for **3k**, **3l**, **5b**, **6b**, and **6a** (in $CDCl_3$, TMS as Standard)

H	3k[a]	3l[a]	5b[b]	6b[a]	6a[a]
2	6.80 s	6.75 s	6.81 s	6.55 s	6.56 s
5	6.35 s	6.37 s	6.31 s	6.28 s	6.18 s
7	3.43 m	3.32 m	3.10—3.23 m	3.0—3.1 m	3.0—3.1 m
8	1.56 m	1.66 m	3.10—3.23 m	3.0—3.1 m	3.0—3.1 m
	2.03 m	1.98 m			
9	3.6—3.8 m	4.1—4.3 m			
2′	6.60 d (1.8)[c]	6.58 d (1.9)	6.70 d (1.8)	6.52 d (1.8)	6.53 s
5′	6.77 d (8.1)	6.79 d (8.1)	6.81 d (8.1)	6.79 d (8.1)	6.64 d (8.1)
6′	6.66 dd (8.1, 1.8)	6.67 dd (8.1, 1.9)	6.71 dd (8.1, 1.8)	6.59 dd (8.1, 1.8)	6.75 d (8.1)
7′	3.88 d (10.2)	3.98 d (9.8)	4.14 d (3.0)	4.07 d (10.8)	4.12 d (10.9)
8′	2.67 m	2.78 m	3.10—3.23 m	3.00 dd (10.8, 10.6)	2.98 dd (10.9, 10.8)
9′	3.6—3.8 m	4.1—4.3 m			
$COOCH_3$			3.49 s	3.43 s	3.43 s
			3.63 s	3.67 s	3.54 s
$ArOCH_3$	3.67 s, 3.75 s	3.69 s, 3.77 s	3.72 s	3.77 s	3.75 s
O	3.83 s, 3.84 s	3,84 s, 3.86 s	3.85 s	3.85 s	3.81 s
$ArO\overset{\overset{O}{\|}}{C}CH_3$		1.94 s, 2.05 s			

a) 300 MHz. *b*) 90 MHz. *c*) Figures in parentheses are coupling constants in Hz.

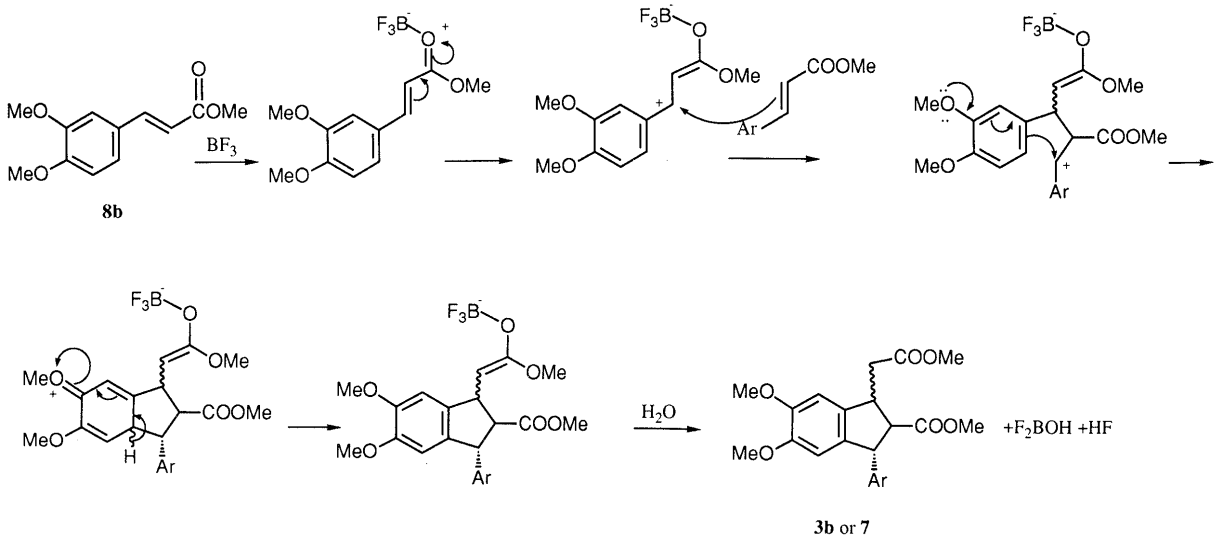

Chart 2

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 δ-values and coupling constants (δ) 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), **3c** (7.09 g), **9b** (150 mg), and **9c** (160 mg), were eluted in that order. Methyl (*E*)- and (*Z*)-ferulate were identical with authentic samples.[13] The physical data of the new products were as follows.

9a: mp 213—214 °C. IR ν_{max}^{KBr} cm^{-1}: 3400, 3260, 1720, 1600, 1520, 1500, 1260, 1200, 1140. ^{1}H-NMR: Table 1. *Anal.* Calcd for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: C, 67.14; H, 6.24.

3c: mp 122—123 °C. IR ν_{max}^{KBr} cm^{-1}: 3442, 3030, 1740, 1720, 1599, 1495, 1229, 1165. MS *m/z*: 416 (M^+, 91), 370 (17), 356 (100), 297 (16), 283 (14). ^{1}H-NMR: Table 1. *Anal.* Calcd for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.61; H, 5.87.

9b: mp 128—129 °C. IR ν_{max}^{KBr} cm^{-1}: 3150—2560, 1720, 1680, 1600, 1120, 1000. ^{1}H-NMR: Table 1. *Anal.* Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51. Found: C, 62.79; H, 5.49.

9c: mp 203—204 °C. IR ν_{max}^{KBr} cm^{-1}: 3210—2628, 1724, 1600, 1510, 1200, 1140, 1020. ^{1}H-NMR: Table 1. *Anal.* Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51. Found: C, 62.59; H, 5.54.

Acetylation and Benzylation of 3c A solution of **3c** (50 mg) in a mixture of 0.5 ml of Ac_2O and 1 ml of pyridine was allowed to stand overnight at ambient temperature. The usual work-up afforded the diacetate **3d** (46 mg) [mp 145—147 °C. IR ν_{max}^{KBr} cm^{-1}: 1760, 1740, 1720, 1600, 1500, 1240, 1140. ^{1}H-NMR: Table 1. Compound **3c** (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 × 3) to afford **3e** (2.7 g) after purification by silica gel chromatography. **3e** [mp 119—120 °C. IR ν_{max}^{KBr} cm^{-1}: 3020, 1720, 1600, 1500, 1240, 1040, 1010. ^{1}H-NMR ($CDCl_3$) δ: 2.42 (1H, dd, J=15.1, 5.9 Hz, H_a-8), 2.66 (1H, dd, J=15.1, 4.2 Hz, H_b-8), 3.40 (1H, dd, J=11.1, 6.2 Hz, H-8′), 3.59, 3.65, 3.71, 3.85 (each 3H, s, –OMe), 4.02 (1H, m, H-7), 4.65 (1H, d, J=11.1 Hz, H-7′). 4.95, 5.11 (each 2H, s, $-OCH_2Ph$), 6.45, 6.79 (each 1H, s, H-5, H-2), 6.59, 6.61 (each 1H, d, J=8.1 Hz, H-5′, H-6′), 6.67 (1H, s, H-2′), 7.15—7.50 (10H, m, $-OCH_2Ph$)].

Reduction of 3e with Lithium Aluminum Hydride $LiAlH_4$ (500 mg)

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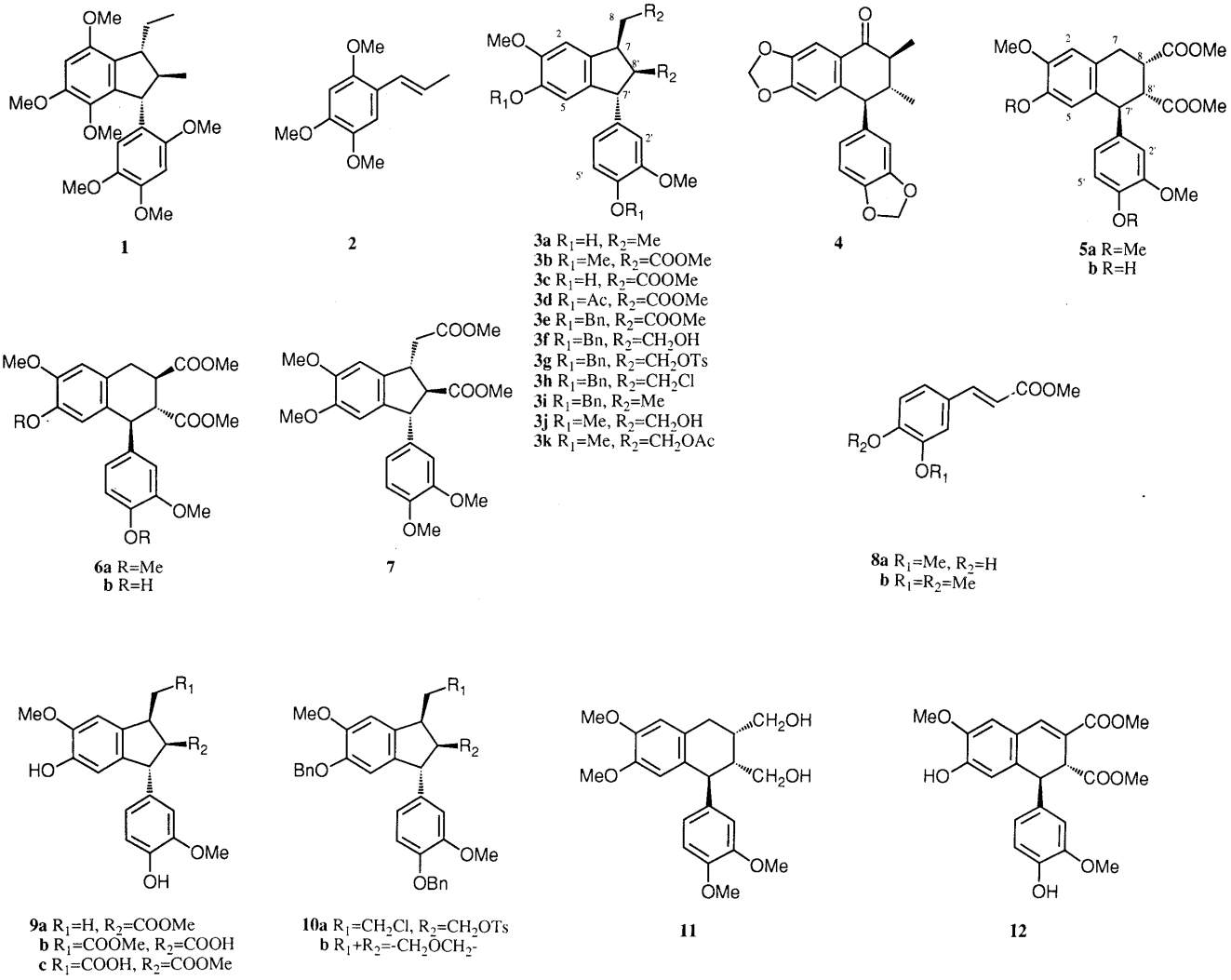

Chart 3

was added to a solution of **3e** (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 obtained. 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 ν_{max}^{KBr} cm^{-1}: 3500, 3040, 1600, 1500, 1260, 1100, 1020. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (2H, m, H-8), 2.11 and 2.62 (each 1H, m, H-8′, H-7), 3.31—3.71 (5H, m, H-7′, 2×-C$\underline{H}_2$OH), 3.66, 3.81 (each 3H, s), 4.89, 5.11 (each 2H, s, -OC$\underline{H}_2$Ph), 6.41—6.82 (5H, m), 7.10—7.42 (10H, m, -OCH$_2$$\underline{Ph}$)].

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×3). The combined ethyl acetate extracts were washed with 1 N H_2SO_4, aqueous $NaHCO_3$, and water. The residue, after removal of the solvent, was purified on silica gel to give four products, **3h** (87 mg), **10a** (100 mg), **3g** (785 mg), and **10b** (120 mg). The physical data of the products were as follows: **3h**: mp 102—103 °C. IR ν_{max}^{KBr} cm^{-1}: 3060, 1600, 1510, 1160, 1080, 800, 740. MS *m/z*: 576 (M^+, $C_{34}H_{34}O_4Cl_2$, 50), 578 (M^++2, 31), 580 (M^++4, 5). ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.41 (3H, m, H-8′, 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, -OC$\underline{H}_2$Ph), 6.51—6.93 (5H, m), 7.22—7.54 (10H, m, -OCH$_2$$\underline{Ph}$). **10a**: Amorphous solid. IR ν_{max}^{KBr} cm^{-1}: 3040, 1600, 1510, 1420, 1220, 1020, 1140, 810, 700. MS *m/z*: 712 (M^+, $C_{41}H_{41}SCl$). ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.22 (3H, m, H-8′, H-8), 2.41 (3H, s, Ar-C$\underline{H}_3$), 3.11 (1H, m, H-7), 3.52 (2H, m, H-9), 3.74, 3.85 (each 3H, s), 3.91—4.22 (3H, m, H-7′, H-9′), 4.95, 5.10 (each 2H, s, -OC$\underline{H}_2$Ph), 6.45, 6.71 (each 1H, s, H-5, H-2), 6.38 (1H, dd, J=8.1, 2.0 Hz, H-6′), 6.58 (1H, d, J=2.0 Hz, H-2′), 6.72 (1H, d, J=8.1 Hz, H-5′), 7.15—7.53 (12H, m, -OCH$_2$$\underline{Ph}$, -SO$_2$-C$_6H_4$-Me), 7.75 (2H, d, J=8.3 Hz, -SO$_2$-C$_6$H$_4$-Me). **3g**: Amorphous solid. IR ν_{max}^{KBr} cm^{-1}: 3040, 1600, 1500, 1350, 1240, 1140, 1020. ^{1}H-NMR ($CDCl_3$) δ: 2.01 (2H, m, H-8), 2.22 (1H, m, H-8′), 2.42 (6H, s, Ar-C$\underline{H}_3$), 3.12 (1H, m, H-7), 3.78, 3.88 (each 3H, s), 4.01—4.33 (5H, m, H-7′, H-9, H-9′), 4.92, 5.11 (each 2H, s, -OC$\underline{H}_2$Ph), 6.42—6.65 (5H, m), 7.22—7.51 (14H, m, -OCH$_2$$\underline{Ph}$, -SO$_2$-C$_6H_4$-Me), 7.72 (4H, d, J=8.1 Hz, -SO$_2$-C$_6$H$_4$-Me). **10b**: mp 129—131 °C. IR ν_{max}^{KBr} cm^{-1}: 3020, 1600, 1500, 1220, 1020, 1000. MS *m/z*: 522 (M^+, $C_{34}H_{34}O_5$). ^{1}H-NMR ($CDCl_3$) δ: 1.62 (2H, m, H-8), 2.12 (1H, m, H-8′), 3.42—3.61 (4H, m, H-9, H-9′), 3.74, 3.87 (each 3H, s), 4.12 (1H, d, J=9.1 Hz, H-7′), 4.96, 5.11 (each 2H, s, -OC$\underline{H}_2$Ph), 6.51—6.83 (5H, m), 7.22—7.54 (10H, m, -OCH$_2$$\underline{Ph}$).

Reduction of 3g with Lithium Aluminum Hydride Reduction of **3g** (785 mg) with $LiAlH_4$ was conducted under the same conditions as mentioned above, to afford **3i** (mp 78—79 °C, lit.[15] 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 H_2. 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).[6,12,15]

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 CH_2N_2. The reaction mixture was washed with aqueous $NaHCO_3$, and the organic layer afforded **3c** (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).[16]

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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 × 3), and the combined ether extract was washed with aqueous $NaHCO_3$, and then dried over $MgSO_4$. 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 $LiAlH_4$ was achieved in the same manner as mentioned above to afford **3j** (79 mg) [mp 138—139 °C. IR ν_{max}^{KBr} cm^{-1}: 3508, 3030, 1602, 1500, 1497, 1212. 1151. 1137. 1098, 1023. MS *m/z*: 388 (M^+, 100), 370 (24), 325 (80), 232 (20); ^{1}H-NMR ($CDCl_3$) δ: Table 2].

Acetylation of 3j with Ac_2O and Pyridine Compound **3j** (20 mg) was dissolved in a mixture of Ac_2O (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 ν_{max}^{KBr} cm^{-1}: 3030, 1736, 1601, 1498, 1273, 1154, 1030, 859. MS *m/z*: 472 (M^+, 73), 412 (48), 352 (56), 325 (100), 214 (28). ^{1}H-NMR ($CDCl_3$) 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 $NaHCO_3$, 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 porducts, **5b** (5 mg) and **6b** (85 mg) were eluted in that order. Physical data for **5b** and **6b** were as follows. **5b**: Amorphous. IR ν_{max}^{KBr} cm^{-1}: 3400, 1720, 1600, 1500 , 1290, 1100. ^{1}H-NMR ($CDCl_3$) δ: Table 2. **6b**: mp 150—151 °C. IR ν_{max}^{KBr} cm^{-1}: 3434, 3030, 1740, 1599, 1509, 1259, 1120, 734. MS *m/z*: 416 (M^+, 100), 356 (50), 297 (47), 208 (15), 149 (11). ^{1}H-NMR ($CDCl_3$) 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).[20]

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References

1) Gottlieb O. R., "New Natural Product and Plant Drugs with Pharmacological, Biological or Therapeutical Activity," Springer-Verlag, Berlin, Heidelberg, 1977, pp. 227—248.
2) Jardine I., "Anti-cancer Agents Based on Natural Product Models," ed. by Cassady J. M., Douros, J. D., Academic Press, New York, 1980, Chapter 9.
3) Ganeshpure P. A., Schneiders G. E., Stevenson R., *Tetrahedron Lett.*, **22**, 293 (1981).
4) Saxena D. B., *Phytochemistry*, **25**, 553 (1986).
5) Al-Farhan E., Keehn P. M., Stevenson R., *J. Chem. Res. (S)*, **1992**, 36.
6) Miller A., Mezare M., Kormendy K., Kucman A., *J. Org. Chem.*, **17**, 787 (1952).
7) Lin C. H., Kuo Y. H., Lin Y. L., Teng C. M., *J. Pharm. Pharmacol.* **46**, 54 (1994).
8) *a*) Kuo Y. H., Lin S. T., *Experientia*, **39**, 991 (1983); *b*) Wallis A. F. A., *Aust. J. Chem.*, **28**, 1571 (1973).
9) Sarkanen K. V., Wallis A. F. A., *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1869.
10) Miller I. J., *Tetrahedron Lett.*, **1972**, 4955.
11) Iguchi M., Nishiyama A., Hara M., Terada Y., Yamamura S., *Chem. Lett.*, **1979**, 1015.
12) *a*) Leary G., *Aust. J. Chem.*, **30**, 1133 (1977); *b*) Chiang H. C., Li S. F., *J. Chin. Chem. Soc.*, **25**, 141 (1978).
13) Kuo Y. H., Kuo P. C., Lin S. T., *Proc. Natl. Sci. Counc.* B, *R.O.C.*, **7**, 28 (1983).
14) Kuo Y. H., Chen L. H., Wang L. M., *Chem. Pharm. Bull.*, **39**, 2196 (1991).
15) Kuo Y. H., Lin S. T., *Chem. Pharm. Bull.*, **41**, 1507 (1993).
16) Botta B., Iacomacci P., Vinciguerra V., Monache G. D., Gacs-Baitz E., Botta M., Misiti D., *Chem. Pharm. Bull.*, **38**, 3238 (1990).
17) Ward R. S., *Nat. Prod. Rep.*, **10**, 12 (1993).
18) Stevenson R., Williams J. R., *Tetrahedon*, **33**, 2913 (1977).
19) Ahmed R., Schreiber F. G., Stevenson R., Williams J. R., Yeo H. M., *Tetrahedron*, **32**, 1339 (1976).
20) Kuo Y. H., Kao S. T., Lin Y. T., *Experientia*, **32**, 828 (1976).
21) Mann J., Piper S. E., Yeung L. K. P., *J. Chem. Soc., Perkin Trans. 1*, **1984**, 2081.

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