Dimerization of 3,4-Disubstituted Cinnamic Acids and Esters

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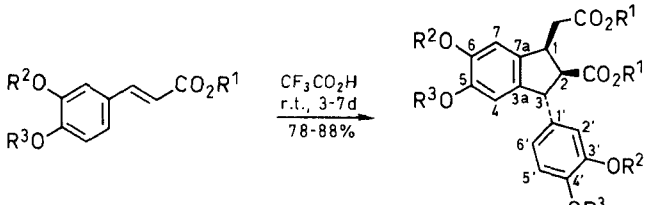
Cinnamic (3-phenylpropenoic) acids and esters bearing hydroxy and/or alkoxy groups at C-3 and C-4 on the benzene ring, **1**, undergo cyclodimerization on treatment with trifluoroacetic acid to yield the corresponding [*t*-3-aryl-*c*-2-carboxy[or alkoxycarbonyl]-*r*-1-indanyl]acetic acids or esters **2**.

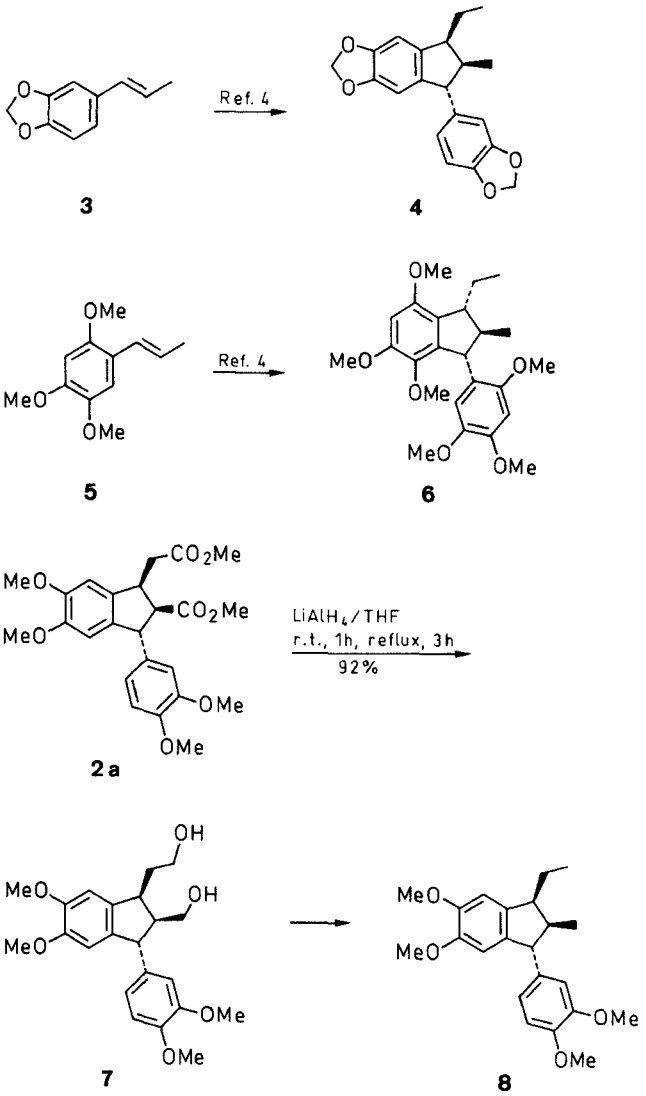
It was discovered in 1929 that ferulic acid ([3-(4-hydroxy-3-methoxyphenyl)propenoic acid **1f**] under Fischer–Speier esterification conditions (methanol/sulfuric acid) yielded a dimeric product for which cyclobutane-based structures were tentatively proposed[1]. Freudenberg later showed[2] that methyl 3-(3,4-dimethoxyphenyl)propenoate (**1a**) also underwent dimerization on treatment with aqueous perchloric acid, and presented evidence for an arylindane structure analogous to that of products formed by acid treatment of arylpropenes such as isoeugenol, and whose structures were finally established in 1969,[3] after much controversy. We have recently shown that some arylpropenes undergo cyclization to arylindanes in high yield and stereoselectivity by treatment with trifluoroacetic acid (neat or dilute solution in chloroform).[4] Thus, isosafrole **3** gave the α-dimer (*r*-1, *c*-2, *t*-3) **4** and asarone **5** gave the γ-dimer (*r*-1, *t*-2, *c*-3) **6**. We have now examined application of this simple procedure to analogous cinnamic acids and esters bearing common phenol and/or phenolic ether functionality at positions C-3 and C-4.



1 2

1, 2	R^1	R^2	R^3	1, 2	R^1	R^2	R^3
a	Me	Me	Me	**e**	Et	$-CH_2-$	
b	Me	Me	H	**f**	H	Me	H
c	Me	Me	Et	**g**	H	Me	Me
d	Me	$-CH_2-$		**h**	H	Me	Et

The action of trifluoroacetic acid on five representative cinnamates **1a–e** and three related cinnamic acids **1f–h**, was examined, and in every case the corresponding dimer **2a–h** with arylindane structure and α-configuration was obtained. The dimerization was simply effected by allowing a solution of the substrate **1** in neat trifluoroacetic acid to stand at room temperature for a few days until completion of reaction. Removal of solvent under reduced pressure and examination of the ^1H NMR spectrum of the residue confirmed the presence of one major constituent (≥ 90% of total reaction mixture), which could be isolated directly by crystallization without resort to chromatography. Comparison of the NMR spectra (Tables 1–4) indicated that all products had the same relative configurations. Assignment of the α-configuration (*r*-1, *c*-2, *t*-3) to these arylindane products was substantiated by NOE experiments on the dimer **2a** obtained from methyl 3,4-dimethoxycinnamate **1a**. Additionally, reduction of **2a** with lithium aluminum hydride yielded the diol **7** which had already been converted[2] to di-isoeugenol dimethyl ether **8** and for which the α-configuration has since been established.[3]



3 4 5 6 2a 7 8

NMR spectra were recorded with a Varian XL-300 spectrometer at 300 MHz for ^1H (with TMS as internal standard) and at 75 MHz for ^{13}C (using solvent signals, $CDCl_3$, δ = 77.00 and DMSO-d_6, δ = 39.50 ppm as standards). Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. Steady state driven Nuclear Overhauser Enhancement (NOE) difference spectra were recorded on the same instrument; dissolved oxygen was removed by freeze–thaw degassing. NOE spectra were obtained by selective saturation on-resonance for 10 seconds (π/2

Table 1. ^{1}H NMR Data of Alkyl (Arylindanyl)acetates **2**, δ, J (Hz) ($CDCl_3$)

	2a	**2b**	**2c**	**2d**	**2e**
H-8a	2.48 dd (J = 16.1, 8.3)	2.47 dd (J = 16.1, 8.3)	2.48 dd (J = 16.0, 8.2)	2.46 dd (J = 16.1, 8.1)	2.43 dd (J = 16.0, 8.6)
H-8b	2.63 dd (J = 16.1, 6.7)	2.62 dd (J = 16.1, 6.7)	2.63 dd (J = 16.0, 6.8)	2.60 dd (J = 16.1, 6.8)	2.60 dd (J = 16.0, 6.4)
H-2	3.45 dd (J = 10.0, 8.1)	3.45 dd (J = 10.0, 8.1)	3.44 dd (J = 10.0, 8.1)	3.43 dd (J = 9.9, 8.2)	3.41 dd (J = 9.9, 8.2)
H-1	3.99 ddd (J = 8.3, 8.1, 6.7)	3.97 ddd (J = 8.3, 8.1, 6.7)	3.99 (under OCH_2CH_3)	3.96 ddd (J = 8.2, 8.0, 6.8)	3.94 ddd (J = 8.6, 8.2, 6.4)
H-3	4.70 d (J = 10.0)	4.63 d (J = 10.0)	4.68 d (J = 10.0)	4.60 d (J = 9.8)	4.60 d (J = 10.0)
CO_2Me	3.65 s, 3.69 s	3.64 s, 3.68 s	3.65 s, 3.68 s	3.64 s, 3.69 s	–
ArOMe	3.73 s, 3.81 s 3.87 s, 3.88 s	3.80 s, 3.86 s	3.79 s, 3.86 s	–	–
H-4	6.41 s	6.46 d (J = 0.8)	6.41 s	6.34 s	6.34 s
H-2′	6.70 s	6.68 d (J = 1.9)	6.70 d (J = 1.8)	6.64 d (J = 1.5)	6.64 d (J = 1.5)
H-6′	6.79 dd (J = 8.2, 1.8)	6.71 dd (J = 8.0, 1.9)	6.76 dd (J = 8.2, 1.8)	6.70 dd (J = 8.0, 1.5)	6.70 dd (J = 8.0, 1.5)
H-7	6.79 s	6.76 s	6.78 s	6.69 s	6.71 s
H-5′	6.83 d (J = 8.2)	6.83 d (J = 8.0)	6.81 d (J = 8.2)	6.74 d (J = 8.0)	6.74 dd (J = 8.0, 0.5)
OH	–	5.63 br s	–	–	–
OCH_2CH_3	–	–	1.37 t (J = 7.0) 1.46 t (J = 7.0)	–	–
OCH_2CH_3	–	–	3.95 q (J = 7.0) 4.09 q (J = 7.0)	–	–
OCH_2O	–	–	–	5.90 d (J = 1.4) 5.92 d (J = 1.4) 5.93 s	5.89 d (J = 1.4) 5.92 d (J = 1.4) 5.93 s
$CO_2CH_2CH_3$	–	–	–	–	1.23 t (J = 7.1) 1.26 t (J = 7.1)
$CO_2CH_2CH_3$	–	–	–	–	4.10 q (J = 7.1) 4.15 q (J = 7.1)

Table 2. ^{1}H NMR Data of (Arylindanyl)acetic Acids **2**, δ, J (Hz) (DMSO-d_6)

	2f	**2g**	**2h**
H-8a	2.33 dd (J = 16.0, 8.4)	2.41 dd (J = 15.9, 8.1)	2.39 dd (J = 16.1, 8.3)
H-8b	2.53 dd (J = 16.0, 6.5)	2.56 dd (J = 15.9, 6.8)	2.55 dd (J = 16.1, 6.8)
H-2	3.36 dd (J = 9.5, 8.1)	3.37 dd (J = 9.3, 8.1)	3.35 dd (J = 9.0, 8.5)
H-1	3.76 ddd (J = 8.4, 8.1, 6.5)	3.83 ddd (J = 8.1, 8.1, 6.8)	3.83 ddd (J = 8.5, 8.3, 6.8)
H-3	4.40 d (J = 9.5)	4.54 d (J = 9.3)	4.51 d (J = 9.0)
ArOMe	3.70 s, 3.71 s	3.59 s, 3.69 s, 3.73 s (× 2)	3.68 s, 3.73 s
H-4	6.20 s	6.37 s	6.33 s
H-6′	6.56 dd (J = 7.6, 1.7)	6.71 dd (J = 8.2, 1.8)	6.67 dd (J = 8.2, 1.9)
H-2′	6.69 d (J = 1.7)	6.75 d (J = 1.8)	6.72 d (J = 1.9)
H-5′	6.70 d (J = 7.6)	6.89 d (J = 8.2)	6.87 d (J = 8.2)
H-7	6.81 s	6.91 s	6.89 s
–OH	8.78 s, 8.84 s	–	–
$-OCH_2CH_3$	–	–	1.22 t (J = 7.0), 1.31 t (J = 7.0)
$-OCH_2CH_3$	–	–	3.83 q (overlaps H-1), 3.97 q (J = 7.0)

pulse = 32.3 μs) followed by acquisition with the decoupler off. Reference spectra were obtained similarly with the decoupler set on a empty region of the spectrum.

Dimerization of Methyl 3-(3,4-Dimethoxyphenyl)propenoate (1a):
A solution of the ester **1a** (2.0 g) in CF_3CO_2H (ca. 5 mL) was stored at r.t. for 3 d, then evaporated under reduced pressure. Crystallization of the residue from MeOH gave methyl [5,6-dimethoxy-*c*-2-(methoxycarbonyl)-*t*-3-(3,4-dimethoxyphenyl)-*r*-1-indanyl]acetate **(2a)** as fine needles (1.71 g, 85.5%); mp 141.5–142.5 °C (Lit.[2] mp 142–142.5 °C).

NOE experiments: δ = 3.99 (H-1) (irr.) → 3.45 (H-2) (+16% NOE); 4.70 (H-3) (−1% NOE); 3.45 (H-2) (irr.) → 3.99 (H-1) (+18% NOE); 4.70 (H-3) (+3% NOE); 4.70 (H-3) (irr.) → 3.99 (H-1) (<0.5% NOE); 3.45 (H-2) (+1% NOE).

Dimerization of Methyl 3-(4-Hydroxy-3-methoxyphenyl)propenoate (1b):
A solution of **1b** (1.15 g) in CF_3CO_2H (ca. 20 mL) was allowed to stand at r.t. for 5 d, then evaporated under reduced pressure. Crystallization of the residue from MeOH gave methyl [5-hydroxy-*t*-3-(4-hydroxy-3-methoxyphenyl)-6-methoxy-*c*-2-(methoxycarbonyl)-*r*-1-indanyl]acetate **(2b)** as prisms (0.92 g, 80%), mp 150–151 °C (Lit.[1] mp 165–165.5 °C for monohydrated form).

Dimerization of Methyl 3-(4-Ethoxy-3-methoxyphenyl)propenoate (1c):
A solution of **1c** (100 mg) in CF_3CO_2H (ca. 5 mL) was allowed to stand at r.t. for 3 d (^{1}H NMR spectrum showed reaction to be complete). Evaporation under reduced pressure and crystallization of the oily residue from MeOH or EtOH gave methyl [5-ethoxy-*t*-3-(4-ethoxy-3-methoxyphenyl)-6-methoxy-*c*-2-(methoxycarbonyl)-*r*-1-indanyl]acetate **(2c)** as prisms (81 mg, 81%); mp 124–125 °C.

$C_{26}H_{32}O_8$	calc.	C 66.08	H 6.83
(472.5)	found	66.47	6.86

Dimerization of Methyl 3-(3,4-Methylenedioxyphenyl)propenoate (1d):
A solution of **1d** (300 mg) in CF_3CO_2H (7 mL) was allowed to stand 7 d at r.t. Crystallization of the oily residue, obtained after solvent evaporation, from EtOH gave methyl [*c*-2-(methoxycarbonyl)-5,6-methylenedioxy-*t*-3-(3,4-methylenedioxyphenyl)-*r*-1-indanyl]acetate **(2d)** as prisms (235 mg, 78%); mp 145–148 °C.

$C_{22}H_{20}O_8$	calc.	C 64.07	H 4.89
(412.4)	found	64.11	4.91

Table 3. ^{13}C NMR Data of Alkyl (Arylindanyl)acetates **2**, δ, J (Hz) ($CDCl_3$)

	2a	2b	2c	2d	2e
C-8	36.61	36.73	36.71	36.63	36.76
C-2	42.25	42.21	42.34	42.09	42.02
C-1	51.38	51.23	51.44	51.25	51.26
$CO_2\underline{Me}$	51.50, 51.62	51.57, 51.69	51.55, 51.66	51.61, 51.70	–
OMe (4′, 5)	55.74, 55.77	–	–	–	–
OMe (6, 3′)	55.92, 55.92	55.86, 56.05	55.88, 56.05	–	–
C-3	58.59	58.44	58.65	58.47	58.65
ArCH	106.86, 107.79, 111.08, 111.24	106.41, 110.80, 110.97, 114.32	107.20, 109.34, 111.56, 112.51	104.40, 105.56, 108.19, 108.44	104.56, 105.55, 108.14, 108.48
C-6′	120.65	121.26	120.71	121.84	121.88
C-1′, 3a, 7a	134.89, 135.46, 135.84	134.10, 134.85, 136.92	134.94, 135.51, 135.93	136.09, 136.57, 137.29	136.26, 136.75, 137.38
Ar$\underline{C}$OR	147.90, 148.59, 148.88, 149.08	144.53, 145.61, 146.09, 146.48	147.26, 148.39, 148.94, 149.21	146.55, 147.18, 147.59, 147.80	146.51, 147.10, 147.53, 147.77
C=O	172.49, 172.76	172.66, 172.86	172.60, 172.88	172.34, 172.59	171.96, 172.13
$ArOCH_2\underline{C}H_3$	–	–	14.64, 14.83	–	–
$ArO\underline{C}H_2CH_3$	–	–	64.20, 64.33	–	–
OCH_2O	–	–	–	100.91, 101.13	100.90, 101.10
$-CO_2CH_2\underline{C}H_3$	–	–	–	–	14.13, 14.15
$-CO_2\underline{C}H_2CH_3$	–	–	–	–	60.49, 60.63

Table 4. ^{13}C NMR Data of (Arylindanyl)acetic Acids **2**, δ, J (Hz) (DMSO-d_6)

	2f	2g	2h
C-8	36.58	36.41	36.47
C-2	41.47	41.60	41.66
C-1	50.75	51.19	51.18
C-3	57.47	57.88	57.93
OMe	55.61, 55.68	55.46 (×2), 55.58, 55.61	55.44, 55.58
ArCH	108.23, 111.32, 112.15, 115.34	107.91, 108.00, 111.71, 111.82	108.08, 109.29, 111.80, 112.86
C-6′	120.44	120.30	120.37
C-1′, 3a, 7a	133.67, 134.10, 136.86	135.23, 135.90, 136.08	135.26, 136.00, 136.14
Ar$\underline{C}$OR	145.28, 146.26, 146.89, 147.49	147.68, 148.31, 148.72, 148.75	146.93, 147.88, 148.55, 148.93
C=O	173.09, 173.59	173.11, 173.57	173.14, 173.60
$OCH_2\underline{C}H_3$	–	14.73, 14.88	–
$O\underline{C}H_2CH_3$	–	63.68, 63.90	–

Dimerization of Ethyl 3-(3,4-Methylenedioxyphenyl)propenoate (1e): A solution of **1e** (1.1 g) in CF_3CO_2H (ca. 3 mL) was allowed to stand at r.t. for 3 d. Examination of the ^1H NMR spectrum of the oily residue after solvent evaporation under reduced pressure indicated absence of starting material and presence of two stereoisomeric dimers in ca. 10:1 ratio. Crystallization from MeOH gave ethyl [*c*-2-(ethoxycarbonyl)-5,6-methylenedioxy-*t*-3-(3,4-methylenedioxyphenyl)-*r*-1-indanyl]acetate **(2e)** (910 mg, 83%, mp 98–99 °C) as a solid which on recrystallization from Et_2O/light petroleum ether or CH_2Cl_2/light petroleum ether yielded large prisms, mp 101–102.5 °C.

$C_{24}H_{24}O_8$	calc.	C 65.44	H 5.49
(440.4)	found	64.98	5.65

Dimerization of 3-(4-Hydroxy-3-methoxyphenyl)propenoic Acid (1f): A solution of **1f** (1.1 g) in CF_3CO_2H (ca. 10 mL) was allowed to stand at r.t. for 5 d (^1H NMR examination showed reaction to have 10–15% starting material present after 3 d). Evaporation of solvent and crystallization of the residue from EtOH gave [*c*-2-carboxy-5-hydroxy-*t*-3-(4-hydroxy-3-methoxyphenyl)-6-methoxy-*r*-1-indanyl]-acetic acid **(2f)** as prisms (890 mg, 81%); mp 251–252 °C (lit.[1] mp 251–251.5 °C).

Dimerization of 3-(3,4-Dimethoxyphenyl)propenoic Acid (1g): A solution of **1g** (200 mg) in minimum volume of CF_3CO_2H was stored at r.t. for 6 d, then evaporated under reduced pressure. Crystallization of the residue from acetone gave [*c*-2-carboxy-5,6-dimethoxy-*t*-3-(3,4-dimethoxyphenyl)-*r*-1-indanyl]acetic acid **(2g)** as prisms (160 mg, 80%); mp 224–226 °C. Crystallization from MeOH gave prisms, mp 216–218 °C (lit.[1] mp 216–217 °C).

Dimerization of 3-(4-Ethoxy-3-methoxyphenyl)propenoic Acid (1h): A solution of **1h** (0.80 g) in CF_3CO_2H (20 mL) was allowed to stand at r.t. for 5 d, then evaporated under reduced pressure. Crystallization of the oily residue from Et_2O gave [*c*-2-carboxy-5-ethoxy-*t*-3-(4-ethoxy-3-methoxyphenyl)-6-methoxy-*r*-1-indanyl]acetic acid **(2h)** as prisms (0.64 g, 80%), mp 192–194 °C.

$C_{24}H_{28}O_8$	calc.	C 64.85	H 6.35
(444.4)	found	64.72	6.42

Reduction of Dimer 2a with Lithium Aluminum Hydride: To a suspension of $LiAlH_4$ (375 mg) in dry THF (25 mL) was added a solution of arylindane **2a** (1.25 g) in the same solvent (30 mL) dropwise over 1 h. The mixture was then heated under reflux for 3 h, and after addition of EtOAc (to decompose excess reagent), H_2O was added, and the mixture extracted with benzene (3 × 20 mL). The washed and dried extract was then evaporated under reduced pressure to give an oil (1.1 g) which crystallized from benzene to give 2-[*c*-2-hydroxymethyl-5,6-dimethoxy-*t*-3-(3,4-dimethoxyphenyl)-*r*-indanyl]ethanol **(7)** as rosettes of needles (1.01 g, 92%) mp 148–150 °C (Lit.[2] mp 150–151 °C).

^1H NMR ($CDCl_3$): δ = 1.60 (m, H-8a), 2.08 (m, H-8b), 2.71 (m, H-2), 3.44 (m, H-1), 2.76 (br s, OH), 3.74 (m, $C\underline{H}_2OH$), 3.83 (m, $C\underline{H}_2OH$), 3.71, 3.79, 3.87, 3.88 (s, 4 × OMe), 3.92 (d, J = 10.0 Hz, H-3), 6.39 (s, H-4), 6.64 (d, J = 2.0 Hz, H-2), 6.70 (dd, J = 8.2, 2.0 Hz, H-6), 6.81 (d, J = 8.2 Hz, H-5), 6.84 (s, H-7).

^{13}C NMR (DMSO-d_6): δ = 31.92 (C-8), 41.30 (c-1), 51.70 (C-3), 56.60 (C-2), 55.82 (×2), 55.96, 56.06 (4 × OMe), 61.05 (CH_2OH), 61.22 (CH_2OH), 107.76, 108.03, 111.02, 111.17, 120.75 (5 × ArCH), 135.86, 137.19, 138.50, 147.77, 148.09, 148.40, 149.00 (7 × ArC).

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