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Dimerization of ferulic acid and structure determination of phenylindane derivatives

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Abstract Ferulic acid dimers with phenylindane skeletons were obtained from ferulic acid **1** in an acidic ethanol solution. The reaction conditions used to prepare the dimers or the ester were examined in detail, and the stereochemistries of the dimers were determined. The structural features of the dimers and the diastereoselective formation mechanisms involved in forming the two types of dimers (the racemic diastereomer **8α**, which was a major product, and the racemic diastereomer **8γ**, which was a minor product) were characterized.

Keywords Ferulic acid · Dimerization · Cycloaddition · Phenylindane

Introduction

Ferulic acid **1** is a propenylbenzene for which we have developed a mass production method, starting from rice bran [1, 2], while **1** is commonly found in cereals, grasses, vegetables, and so on [3]. Interest in the industrial use of **1** and its derivatives has intensified in recent years, for example, it has been used in cancer preventative agents [2–7], agents for controlling germination [8], UV absorbers [9], and insulin secretagogues [10]. In a number of the related compounds of **1**, various types of dimerized products of **1** are known, for example, 5-5-, 8-5-, and 8-8-

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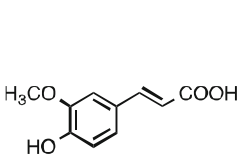
coupled diferulates are important components in plant cell walls [11–15]. The oxidative dimerization of feruloyl ester has been shown to afford dihydrobenzofuran analogue **2**, which is biologically active [16]. The photodimerization of *O*-substituted ferulic acid in the crystal state was found to stereospecifically afford its dimer **3** [17].



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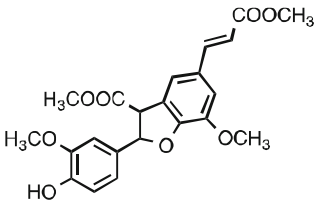

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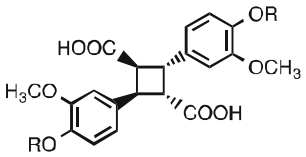

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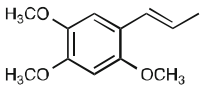
In our preliminary experiment, dimerized products were found to be produced, to some extent, when **1** was esterified under acidic conditions, and the major product was identified as being a phenylindane derivative. Various lignane-related dimers have been found to be derived from propenylbenzene through biosyntheses or organic syntheses. In particular, asarone dimer **5**, which has a phenylindane structure, has been found in the essential oil of *Acorus calamus*, and this oil is an insect growth regulator [18]. Synthetic approaches to prepare the dimers from asarone **4** or other starting materials have also been investigated under acidic conditions [19–21]. Interest in the potential for the phenylindane skeleton to be a valuable structure in pharmaceuticals has led to the stereoselective synthesis of compounds containing an indane ring to be investigated using different types of reactions and starting materials [22–28]. Phenylindanes dimerized from ferulic acid have been obtained from the reaction of **1** in methanol in the presence of *p*-toluenesulfonic acid [29], and various phenylindane derivatives **6a–d** were identified from this reaction. Phenylindane **6a** was the major product, and no other diastereomers have been found from this reaction. However, the method used for this reaction was poorly reproducible because the synthetic details were not explored in any depth.



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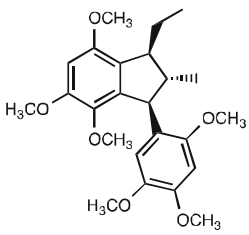

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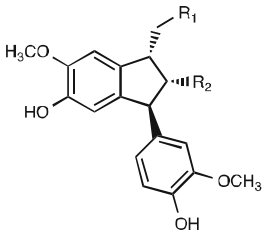


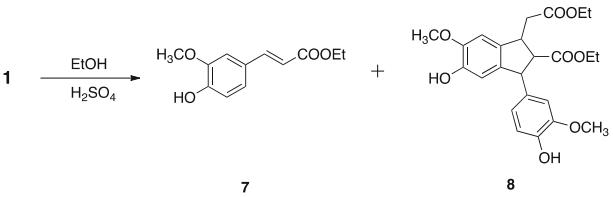
6a: R_1=COOMe, R_2=COOMe
b: R_1=COOMe, R_2=COOH
c: R_1=COOH, R_2=COOMe
d: R_1=H, R_2=COOMe

Here, we report the details of the synthesis and the stereochemistry of racemic diastereomers with phenylindane structure that were prepared from ferulic acid.

Results and discussion

The ferulic acid reaction was performed in the presence of sulfuric acid and ethanol, and the products were separated using a SiO_2 column [eluted with a 1:1 mixture of hexane and ethyl acetate (EtOAc)] to afford the ester **7** and a mixture of the diastereomeric dimers **8**, which each have a phenylindane structure (Scheme 1).

The indane **8** has three chiral carbons, so it has four different racemic diastereomers (α, β, γ, and δ) [30], which are shown in Fig. 1. HPLC–MS (ESI-TOFF) analysis showed four components indicating m/z of 443.1695, 443.1691, 443.1703, and 443.1689. These values agreed with the corresponding indane **8** (m/z 443.1706 $[M–H^+]^-$), suggesting four different enatiomeric racemates were included (see Supplementary data). However, we could not isolate the diastereomers using column chromatography because the two predominant dimers have almost the same R_f values. Therefore, we recrystallized the major diastereomer again and again from a mixture of hexane and EtOAc to give white crystals. The ^{1}H NMR spectrum of these crystals is shown in Fig. 2a. The crystals were identified as indane **8α** from ^{1}H and ^{13}C NMR, COSY, NOESY, and ESI-TOFMS spectral data. The ^{1}H NMR signals for the protons, 1-H, 2-H, and 3-H bound to the three chiral carbons appeared at $\delta = 3.97$, 3.41, and 4.62 ppm, respectively, and the inter-proton coupling constants $J_{1–2}$ and $J_{2–3}$ for **8α** were 8.2 and 10.3 Hz, respectively. The 3-H is on the opposite side of the **8α** to the 2-H, and the 1-H is on the same side as the 2-H. No cross peak was, therefore, observed between 1-H and 3-H in the NOESY spectrum for **8α**, but cross peaks between 1-H and 2-H and between 2-H and 3-H were observed. The structure of the crystals was also determined by X-ray diffraction, and the result of this analysis agreed with the molecular structure of **8α** (Fig. 3a). Two enantiomers were packed in the crystal lattice, as shown in Fig. 4a. Therefore, indane **8α** crystals were found to be racemates of **8α** (*cis–trans*). Another dimer **8γ** was isolated from the residual solid, which was obtained after recrystallization of **8α**, by preparative HPLC. The NMR and ESI-TOFMS spectra of **8γ** were used to determine its molecular structure. The ^{1}H NMR spectral data for **8γ** are shown in Fig. 2b. Proton signals for 1-H, 2-H, and 3-H appeared at $\delta = 3.8$ (overlapping the methoxy proton signal), 3.00, and 4.47 ppm, respectively, and the



Scheme 1 Synthesis of phenylindanes under the esterification conditions

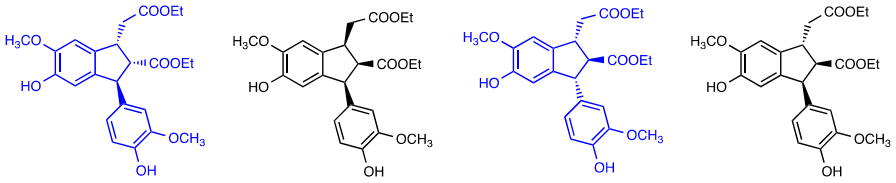
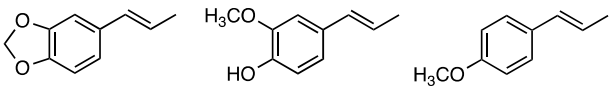


Fig. 1 Stereoisomers of ferulic acid dimer **8**

coupling constants J_{1-2} and J_{2-3} were similar ($J = 9.3$ Hz). This indicates that, in indane **8γ**, 1-H and 3-H are both either on the same side of the molecule as 2-H or on the opposite side of the molecule to 2-H. Cross-peaks between 1-H, 2-H, and 3-H were all observed in the NOESY spectrum of **8γ**. Fortunately, a crystal of indane **8γ** was obtained, despite the small amount of the product that was isolated, and its molecular structure, shown in Fig. 3b, was determined. The crystal contained two enantiomers packed in the crystal lattice, as shown in Fig. 4b, therefore, the most likely configuration is **8γ** because 1-H and 3-H are on the opposite side of this molecule to 2-H allowing the bulky substituents to be arranged in a sterically unhindered configuration.

The acid catalyzed [3 + 2] cycloadditions of various propenylbenzenes such as isosafrole **9**, isohomogenol **10**, and anethol **11** were investigated by Morris et al. [31], and the configurations of the 1-H, 2-H, and 3-H in the α-, β-, and γ-racemates were established. The α-racemate is a major product of reactions of **9** and **10**, and the γ-racemate is a major product of **11**. The asarone dimer **5** also has a γ-racemate as a major product. Therefore, the configuration of the major dimer product seems to depend on the substituent connected to the propenylbenzene aromatic ring.



9 **10** **11**

The reaction conditions for the dimerization of ferulic acid were investigated in detail. The effects of the sulfuric acid concentration on the yields of the ester **7** and dimers **8α** and **8γ** are shown in Table 1. At sulfuric acid to **1** molar ratios of below ca. 5, the ester **7** was the main product (Table 1, Entry 1 and 2) and at molar ratios of 10–30, dimers **8α** and **8γ** were produced in 30–35 and 11–15 % yields, respectively (Table 1, Entry 3–6). Next, the effects of the ethanol to **1** molar ratio on the yields of **7**, **8α**, and **8γ** were determined, and these are also shown in Table 1. The maximum yields of indane **8α** were obtained at molar ratios of 50 and 60 (Table 1, Entry 12 and 13), and the yield decreased as the ratio was increased further. Ester **7** was produced as a major product when the molar ratio was higher than 70 (Table 1, Entry 14 and 15). Indane **8γ** was formed in approximately 14–16 % yield when the molar ratio was between 30 and 60 (Table 1, Entry 10–13). Shorter reaction time gave better yields. The reaction profiles for products **7**, **8α,** and

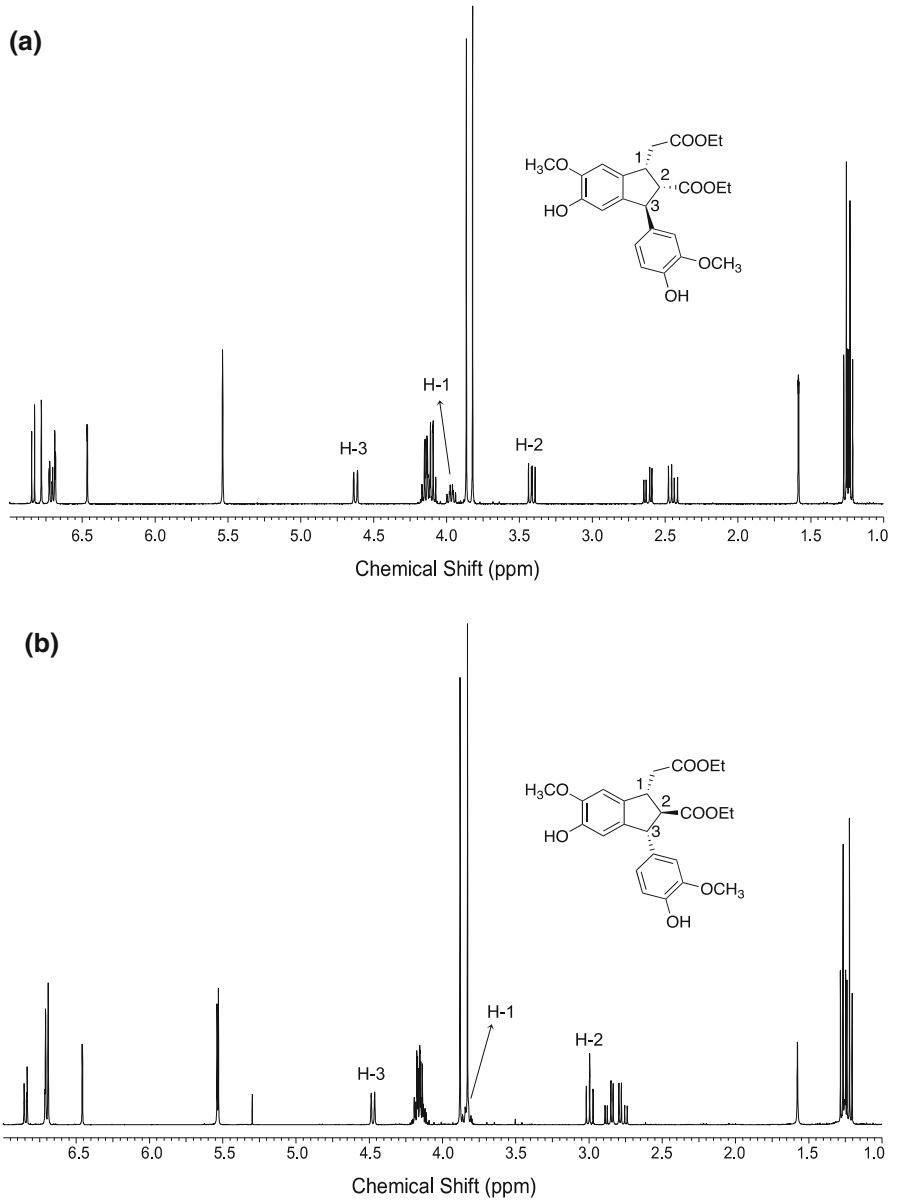


Fig. 2 ^{1}H NMR (400 MHz, $CDCl_3$) spectra of **a** **8α** and **b** **8γ**

8γ over time were investigated, and the results are shown in Fig. 5. The concentration of ester **7** increased in the initial stage of the reaction, and then it decreased as the concentration of indanes **8α** and **8γ** increased. The concentration of each of the indanes stopped increasing after 30 min, despite the continuing decreases in the concentration of ester **7**. Other products of the transformation of the

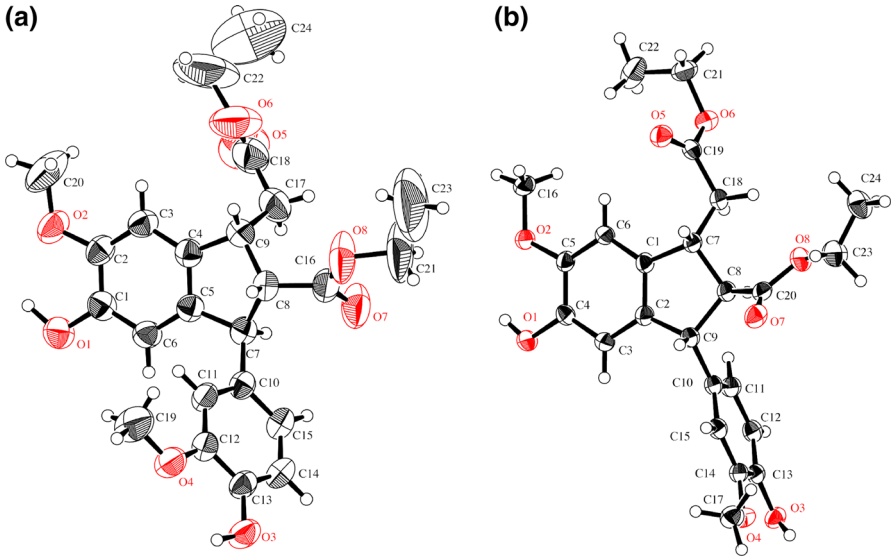


Fig. 3 ORTEP drawing of indane **a 8α** and **b 8γ**. The displacement ellipsoids are drawn at the 50 % probability level, except for the H atoms

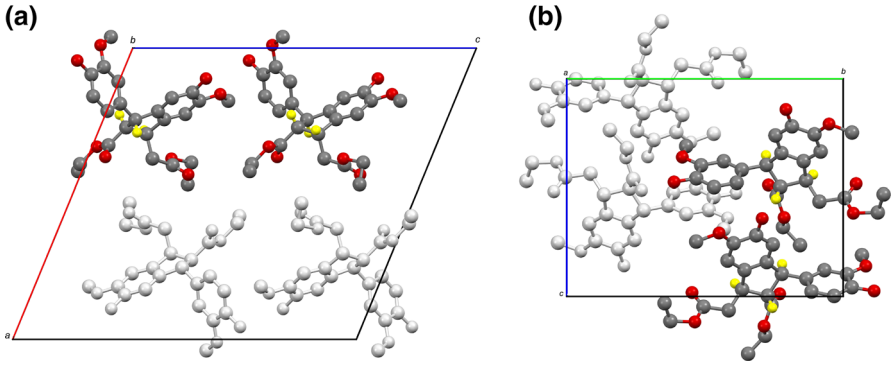


Fig. 4 Crystal structure of indane **a 8α** and **b 8γ**. Hydrogen atoms 1-H, 2-H, and 3-H are shown in *yellow*, and the other hydrogen atoms are omitted to improve the clarity of the diagrams. The projection is along the *b* axis of the unit cell for **8α** and along the *a* axis of the unit cell for **8γ**. (Colour figure online)

ester were not identified because only small amounts of these complex mixtures were detected by TLC and only a trace of the mixtures were separated by column chromatography.

This dimerization reaction is known to proceed by a formal [2 + 3] cycloaddition, and, assuming that the reaction follows a stepwise pathway, some points related to the diastereoselectivity of the reaction were deduced, and these are shown in Scheme 2. Ester **7** is first produced during the reaction, then the protonation of **7** affords benzylic cation **12**. The methoxy group connected to the phenyl ring of **1** stabilizes the stacking configuration through CH–π interactions [32]. We assumed

Table 1 Synthesis of ester and indanes in the different amounts of acid and ethanol

Entry	H_2SO_4/1 (mol/mol)	EtOH/1 (mol/mol)	Time (h)	Yield (%)		
				7	**8α**	**8γ**
1	0.61	63.4	2	68.2	0.0	0.0
2	5.14	63.4	2	92.7	0.6	0.0
3	10.0	63.4	2	59.6	33.3	11.2
4	15.1	63.4	2	27.4	32.9	11.4
5	21.2	63.4	2	1.3	34.8	14.7
6	29.4	63.4	2	0.7	30.1	15.1
7	25	63.4	1	16.4	41.5	17.2
8	25	10	1	0.0	0.1	0.1
9	25	20	1	0.2	1.5	1.7
10	25	30	1	0.5	21.3	13.6
11	25	40	1	0.7	30.8	14.7
12	25	50	1	5.5	40.9	16.0
13	25	60	1	18.6	43.0	16.1
14	25	70	1	39.4	30.2	6.2
15	25	100	1	78.0	1.5	0.0

Reaction conditions: 1.35 mmol of **1**, reflux temperature. The yields were estimated by HPLC

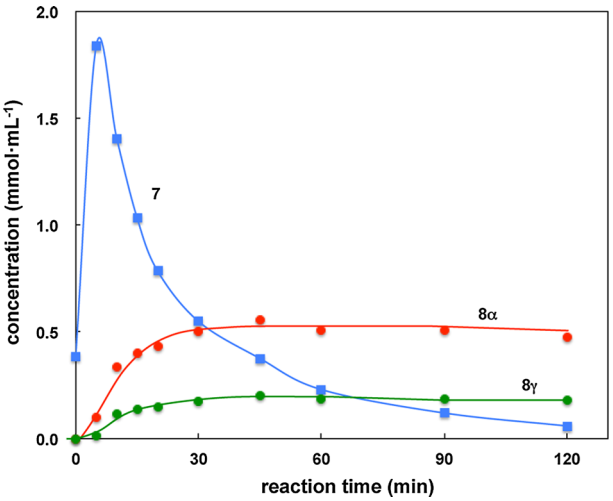
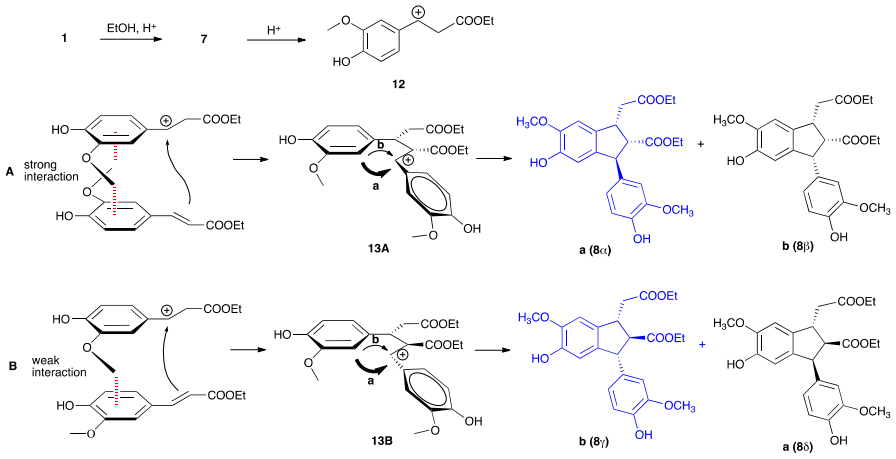


Fig. 5 Time courses of the concentrations of **7**, **8α**, and **8γ** during the reaction. Conditions: 2.70 mmol of **1**, 10 mL of EtOH, 67.5 mmol of H_2SO_4, reflux

that cation **12** could react with an ester in two different ways (A) with strong interactions between the phenyl rings of the esters or (B) with relatively weak interactions between the phenyl rings of the esters. The A and B reaction modes of cation **12** will afford benzylic cations **13A** and **13B**, respectively, retaining the *trans*



Scheme 2 Proposed reaction mechanism for the formation of the indanes

configuration of the ferulic acid moiety [28]. When the reaction occurs, **13A** is the major product, and it immediately cyclizes to afford **8α** as the main product, because it retains the former *trans* configuration of the cation (path **a**). The other cation **13B**, which can be produced, gives indane **8γ** as the main product (path **b**) for the reason mentioned above. The 2-H and 3-H are most likely on opposite sides of the indane **8α** and **8γ** molecules, which indicate that the bulky phenyl ring will be arranged in a sterically unhindered position. To support these results, experimental work on the effect of the methoxy group connected to the phenyl ring of **1** to produce phenylindanes enatioselectively are in progress.

Conclusion

Ferulic acid **1** is a renewable natural product that can be obtained from rice bran, and now commercially available. It is important to develop a wide range of useful derivatives of this molecule because of their potential uses. Here, we have presented the synthesis of two types of dimers, having phenyl indane structure from **1**, and we have discussed the diastereoselectivity of the dimers. It was speculated that the methoxy group at the meta position of the phenyl ring has an important role for phenylindane derivative deastereoselectively. The optimum reaction conditions (50–60 equiv ethanol, >10 equiv H_2SO_4, >0.5 h reaction time, reflux temperature) gave dimers **8α** and **8γ** in 30–43 % and ca. 15 % yields, respectively.

Experimental

All solvents and reagents were obtained commercially and used without further purification. ^{1}H NMR, ^{13}C NMR, and two-dimensional NMR spectra were recorded on a Bruker Avance-400 instrument using TMS as an internal standard.

FT-IR spectra were recorded using a single reflection horizontal ATR. HRMS (ESI-TOF) spectra and HPLC–MS (ESI-TOF) equipped with an octadecylsiliyl column (150 mm long, 2 mm diameter) were measured in negative ionization mode, and the data are reported in the form of m/z values. Melting points were determined by using a differential scanning calorimeter and the peak top temperatures are reported.

Preparation of indane 8α and 8γ

To a solution of 900 mg of ferulic acid (4.64 mmol) in ethanol (15 mL), which was cooled in an ice bath and kept under an Ar atmosphere, was added 5.4 mL of sulfuric acid (101 mmol). The mixture was stirred for 1 h at reflux temperature, then ice water was added to stop the reaction. The products were extracted with dichloromethane, and the extract was washed with water, water saturated with sodium bicarbonate, and water again. The organic portion was dried over $MgSO_4$. After evaporating the solvent, the product was dissolved and purified through a SiO_2 column (eluted with a 1:1 mixture, by volume, of hexane and EtOAc), which afforded 86 mg of ester **7** and 500 mg of the indane mixture (containing two diastereomers **8α** and **8γ**). The mixture was recrystallized from a mixture of hexane and EtOAc several times to give white crystals (indane **8α**). Indane **8γ** was isolated form the residual mixture by a preparative HPLC to give 9 mg of solid.

8α: 35 % yield (estimated from ^{1}H NMR). mp 162 °C (from hexane/EtOAc). (ATR) ν_{max} (ATR) 3387 (OH), 1732 (CO). δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.23 (3H, t, $J = 7.3$ Hz, CH_2CH_3), 1.26 (3H, t, $J = 7.3$ Hz, CH_2CH_3,), 2.45 (1H, dd, $J = 15.9$, 8.9 Hz, CH_2), 2.62 (1H, dd, $J = 16.1$, 6.0 Hz, CH_2), 3.41 (1H, dd, $J = 10.0$, 8.3 Hz, CH), 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.97 (1H, td, $J = 8.5$, 8.5, 6.1 Hz, CH), 4.07–4.17 (4H, m, CH_2CH_3), 4.62 (1H, d, $J = 10.3$ Hz, CH), 5.54 (2H, s, OH), 6.47 (1H, d, $J = 1.0$ Hz, ArH), 6.69 (2H, d, $J = 2.0$ Hz, ArH), 6.71 (2H, dd, $J = 8.0$, 2.0 Hz, ArH), 6.78 (1H, s, ArH), 6.84 (1H, d, $J = 8.0$ Hz, ArH). δ_C (100 MHz, $CDCl_3$, Me_4Si) 14.2, 14.3, 36.9, 42.2, 51.3, 56.0, 56.1, 58.7, 60.5, 60.7, 106.6, 110.9, 111.0, 114.3, 121.4, 134.4, 135.1, 137.1, 144.5, 145.6, 146.1, 146.5, 172.3, 172.5. HRMS (ESI-TOFF) m/z found: 443.1682 $[M–H^+]^-$ calcd. for $[C_{24}H_{27}O_8]^-$: 443.1706.

8γ: 14 % yield (estimated from ^{1}H NMR). mp 141 °C (from hexane/EtOAc). ν_{max} (ATR) 3390 and 3348 (OH), 1724 and 1709 (CO). δ_H (400 MHz, $CDCl_3$, Me_4Si) 1.22 (3H, t, $J = 7.2$ Hz, CH_2CH_3), 1.27 (3H, t, $J = 7.2$ Hz, CH_2CH_3), 2.77 (1H, dd, $J = 15.8$, 6.8 Hz, CH_2), 2.86 (1H, dd, $J = 15.6$, 6.3 Hz, CH_2), 3.00 (1H, t, $J = 9.3$ Hz, CH) 3.83 (3H, s, OCH_3), 3.81–3.86 (1H, m, CH), 3.88 (3H, s, OCH_3), 4.11–4.19 (4H, m, CH_2CH_3), 4.47 (1H, d, $J = 9.3$ Hz, CH), 5.53 (1H, s, OH), 5.54 (1H, s, OH), 6.46 (1H, d, $J = 1.0$ Hz, ArH), 6.69–7.71 (3H, m, ArH), 6.85 (1H, dd, $J = 7.5$, 1.0 Hz, ArH). δ_C (100 MHz, $CDCl_3$, Me_4Si) 14.26, 14.28, 39.3, 43.8, 53.6, 56.0, 56.1, 60.6, 60.7, 61.2, 105.6, 110.75, 110.77, 114.3, 121.3, 134.5, 135.0, 137.1, 144.6, 145.5, 146.3, 146.6, 172.1, 173.9. HRMS (ESI-TOFF) m/z found: 443.1692 $[M–H^+]^-$ calcd. for $[C_{24}H_{27}O_8]^-$: 443.1706.

Crystal structure analysis of 8α and 8γ

Single crystals of **8α** and **8γ** were recrystallized from hexane/EtOAc. X-ray diffraction data were measured on a diffractometer (Rigaku R-AXIS RAPID II) using graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å) at 298 K for **8α** and using CuKα radiation ($\lambda = 1.54187$ Å) at 123 K (cold gas stream) for **8γ**. The crystal data have been deposited at the Cambridge Crystallographic Data Centre and have deposition number CCDC 995488 for **8α** and CCDC 995489 for **8γ**. Copies of these data can be obtained free of change on application to CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk) or from http://www.ccdc.cam.ac.uk/data_request/cif.

Crystal data

8α, $M = 444.48$, monoclinic, $a = 18.879(6)$, $b = 6.5980(16)$, $c = 20.643(5)$ Å, $U = 2376.4(11)$ Å^3, $T = 298$ K, space group $P2/c$ (no. 13), $Z = 4$, 22,244 reflections measured, 5361 were unique ($R_{int} = 0.054$) and were used in all of the calculations. The final $wR(F_2)$ was 0.2024 (all data). **8γ**, $M = 444.48$, monoclinic, $a = 10.6707(2)$, $b = 16.1524(3)$, $c = 12.7293(3)$ Å, $U = 2185.57(7)$ Å^3, $T = 123$ K, space group $P2_1/c$ (no. 14), $Z = 4$, 21,639 reflections measured, 3992 were unique ($R_{int} = 0.0361$) and were used in all calculations. The final $wR(F_2)$ was 0.1166 (all data).

Determination of yields of the products at the various conditions

To a solution of 300 mg of ferulic acid (1.35 mmol) in ethanol (13.5–135 mmol), which was cooled in an ice bath and kept under Ar atmosphere, was added sulfuric acid (0.61–29.4 mmol). The mixture was stirred at reflux temperature for 1–2 h and then ice water was added to stop the reaction. The products were extracted with dichloromethane, and the extract was washed with water, water saturated with sodium bicarbonate, and water again. The organic portion was dried over $MgSO_4$. After evaporating the solvent, the product was analyzed by HPLC, in which **7**, **8α**, and **8γ** were separated using an octadecylsilyl column (75 mm long, 4 mm diameter) at 30 °C and detected at a wavelength of 290 nm. The mobile phase was a 60:40 mixture of methanol and 0.2 % aq. formic acid, and it was used at a flow rate of 1 mL/min.

Time-course measurement for the conversion of ferulic acid to ester and indanes

To a solution of 600 mg of ferulic acid (2.70 mmol) in ethanol (10 mL), which was cooled in an ice bath and kept under Ar atmosphere, was added 3.6 mL of sulfuric acid (67.5 mmol). The mixture was stirred at reflux temperature. An aliquot was withdrawn from the reaction mixture at each of the defined time points, and the same volume of a 1:1 mixture, by volume, of methanol and water was then added to

the original reaction mixture to keep its volume at 10 mL. The samples were analyzed by HPLC.

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