

Syntheses of Two Cytotoxic Sinapyl Alcohol Derivatives and Isolation of Four New Related Compounds from *Ligularia nelumbifolia*

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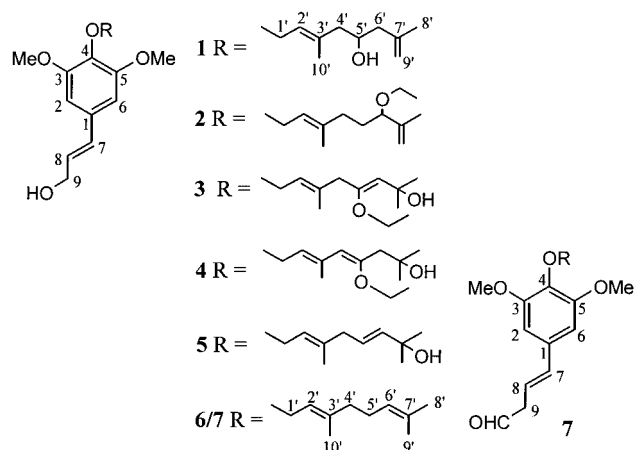
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Phytochemical reinvestigation on *Ligularia nelumbifolia* afforded four novel sinapyl alcohol analogues named nelumols B–E (**1**–**4**) and three known sinapyl alcohol derivatives (**5**–**7**). Their structures were elucidated by NMR techniques. Total syntheses of cytotoxic geranyloxy sinapyl alcohol (**6**) and geranyloxy sinapyl aldehyde (**7**) were carried out via two different paths. The 4-*O*-benzyl-substituted analogues (**20** and **27**) as well as the 4-*O*-(2-methylbutenyl) derivatives (**34** and **35**) were also synthesized. The cytotoxicities of **6** and **7** were measured using A-549, HL-60, and KB cancer cell lines.

The genus *Ligularia* has been used medicinally for a long time in China. Distributed in damp shadowy regions beside brooks and sloping fields, the whole plant of *Ligularia nelumbifolia* [(Bur. Et Franch) Hand.-Mazz] (family Compositae, Chinese folk name Lian Ye Tuo Wu) has been used as folk medicine for pulmonary tuberculosis and apoplexy.¹ Previous phytochemical examination of *Ligularia* species revealed eremophilane derivatives.^{2–6} Interestingly, no eremophilane derivatives were found in the species investigated by us; however, several sinapyl alcohol derivatives and aromatic components were isolated.³ Thorough examination of this species has now afforded five further sinapyl alcohol derivatives (**1**–**5**), four of which (**1**–**4**) are new compounds. In the course of our continuing search for pharmacologically active compounds, two major principles of this species, geranyloxy sinapyl alcohol (**6**)^{3,7} and geranyloxy sinapyl aldehyde (**7**), were found to be cytotoxic to KB cell with an IC₅₀ of 3.0 × 10⁻⁶ and 2.6 × 10⁻⁶ M, respectively. This prompted us to reinvestigate further analogues in this plant and to synthesize compounds **6** and **7** as well as several analogues for further pharmacological activity studies.

Results and Discussion

Nelumol B (**1**) was obtained as colorless gum. EIMS and elemental analysis indicated its molecular formula to be C₂₁H₃₀O₅. Showing the molecular ion peak at *m/z* 362, the EIMS of **1** also exhibited a base peak due to a sinapyl alcohol fragment at *m/z* 210. The ¹H and ¹³C NMR spectra of **1** showed close similarities with those of the geranyloxy sinapyl alcohol (**6**).^{3,7} In the ¹H NMR spectrum (Table 1), the only differences were the presence in **1** of an olefinic methylene multiplet (H-9') at δ 5.00 (1H, brs) and 4.98 (1H, brs), as well as an olefinic methyl signal (H-8') at δ 1.73 (brs, 3H) in place of the olefinic H-6' and Me-9' signals of **6**. Furthermore, a signal was detected at δ 3.88 (m, 1H),



suggesting a secondary OH group at the C-5' position. This was supported by an OH absorption band at 3399 cm⁻¹ in the IR spectrum of **1**. The ¹³C NMR spectrum of **1** was in complete accord with the proposed structure (Table 2).

Comparison of the ¹H and ¹³C NMR spectra of **2** with those of **1** indicated that **2** had an oxygenated C-6', since H-6' was shifted downfield (from δ 2.06 to 4.55) when compared to **1**, thus disclosing that H-6' was vicinal to the 7'(9') double bond in the case of **2**. Furthermore, the ¹H NMR spectrum of **2** revealed the presence of an ethoxy group at C-6'. EIMS gave the molecular ion peak at *m/z* 390, which was consistent with the molecular formula C₂₃H₃₄O₅. Since ethanol was exclusive during the extraction and isolation procedure, compound **2** might be derived biosynthetically from precursor **6**.

The ¹H NMR spectrum of nelumol D (**3**) exhibited some differences from that of geranyloxy sinapyl alcohol **6**. The methylene proton (H-5') of **6** could not be found in the ¹H NMR spectrum of **3**, while two olefinic hydrogens were observable at δ 5.58 (m, 2H). Furthermore, the methyl singlets appeared at δ 1.33 (s, 6H), somewhat higher field than those of **6** in the ¹H NMR spectrum, suggesting that an OH group was most likely connected to C-7', in agreement with the corresponding ¹³C resonance appearing at δ 82.04 (s, C-7'). The olefinic carbons attributable to a trisubstituted double bond at δ 140.16 (s) and 127.88 (d)

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Table 1. ^1H NMR Spectral Data [400 MHz, δ_{H} (J, Hz)] for Nelumols B–E (1–4) in CDCl_3

position	1	2	3	4
2	6.59 s	6.60 s	6.61 s	6.61 s
6	6.59 s	6.60 s	6.61 s	6.61 s
7	6.52 dt (15.8, 1.4)	6.52 dt (15.9, 1.4)	6.55 dt (15.9, 1.4)	6.55 dt (16.0, 1.5)
8	6.28 dt (15.8, 5.8)	6.28 dt (15.9, 5.8)	6.30 dt (15.9, 6.0)	6.30 dt (16.0, 6.0)
9	4.32 dd (5.8, 1.4)	4.32 dd (5.8, 1.4)	4.32 dd (6.0, 1.4)	4.33 dd (6.0, 1.5)
1'	4.54 br d (7.2)	4.54 br d (7.1)	4.55 br d (7.0)	4.54 br d (7.2)
2'	5.66 tq (7.2, 1.0)	5.58 tq (7.1, 1.0)	5.58 m	5.61 tq (7.1, 1.0)
4'	2.06 m	2.02 m	2.74 m	5.47 dt (2.0, 1.5)
5'	3.88 m	2.00 m		
6'	2.06 m	4.55 br dt (7.0, 1.5)	5.58 m	2.74 dd (6.6, 2.0)
8'	1.73 br s	1.63 br s	1.31 s	1.26 s
9'	5.00 br s	4.92 br dd (1.5, 1.5)	1.31 s	1.26 s
	4.98 br s	4.83 br dd (1.5, 1.5)		
10'	1.65 d (1.0)	1.65 d (1.0)	1.63 d (0.9)	1.63 d (1.0)
OMe	3.86 s	3.87 s	3.87 s	3.86 s
OEt		3.65 q (7.0)	3.49 q (7.0)	3.32 q (7.0)
		1.24 t (7.0)	1.22 t (7.0)	1.14 t (7.0)

Table 2. ^{13}C NMR Spectral Data [100 MHz, δ (ppm)] for Nelumols B–E (1–4) in CDCl_3^a

C no.	1 (mult)	2 (mult)	3 (mult)	4 (mult)
1	136.5 s	136.3 s	136.6 s	138.0 s
2	103.5 d	103.3 d	103.3 d	103.4 d
3	153.7 s	153.6 s	153.7 s	153.7 s
4	139.8 s	141.0 s	139.8 s	140.0 s
5	153.7 s	153.6 s	153.7 s	153.7
6	103.5 d	103.3 d	103.3 d	103.4 s
7	131.2 d	131.1 d	131.2 d	131.2 d
8	129.0 d	127.8 d	127.9 d	127.9 d
9	63.6 t	63.5 t	63.7 t	63.7 t
1'	69.2 t	69.2 t	69.3 t	69.4 t
2'	121.4 d	120.6 d	121.2 d	121.2 d
3'	132.4 s	132.3 s	132.3 s	132.3 s
4'	39.5 t	35.4 t	42.2 t	126.9 d
5'	88.9 d	32.5 t	140.2 s	140.2 s
6'	28.7 t	75.2 d	127.9 d	42.6 t
7'	143.8 t	147.2 s	70.8s	74.8 s
8'	17.1 q	17.4 q	29.7 q	26.4 q
9'	114.1 t	111.0 t	29.7 q	26.4 q
10'	16.1 q	16.1 q	16.3 q	16.2 q
OMe	56.1 q	56.0 q	56.0 q	56.0 q
OEt		63.8 t	56.0 t	57.7 t

^a Assignment in the same column could be exchangeable.

were assigned to C-5' and C-6', respectively. This side chain is similar to that of the sinapyl alcohol derivative **5**, previously isolated from *Ligularia duciformis*.⁸ However, the molecular ion peak of **3** appearing at m/z 406, i.e., 44 mass units higher than that of **5**, as well as the NMR data all indicated that **3** was an C-5'-OEt derivative of **5** (Tables 1 and 2). Compound **3** might be another artifact or the enzymatic derivative of **5**, as mentioned above.

Nelumol E (**4**) had a molecular ion peak and NMR data similar to those of **3**. Elemental analysis and a DEPT spectrum revealed its molecular formula to be $\text{C}_{23}\text{H}_{34}\text{O}_6$, apparently isomeric with **3**. Scrutiny of its ^1H and ^{13}C NMR spectra with those of **3** led to the assignment of a 2'(3'),4'-(5')-diene system in compound **4** (Tables 1 and 2). A COLOC experiment on **4** exhibited correlations of olefinic H-4' with C-2' and C-10', consistent with the presence of a conjugated diene moiety in **4**. This enol ether could be either an artifact or a biosynthetic derivative, as discussed above.

As **6** and **7** were cytotoxic to KB cells (Table 3) and appeared as principle metabolites in *L. nelumbifolia*, syntheses of further sinapyl alcohol derivatives become interesting. Thus, **6** and **7** were selected to be totally synthesized.

The first path used commercially available sinapinic acid **8** as starting material. After esterification,⁹ a Mitsunobu

Table 3. IC_{50} of **6** and **7** on Some Selected Pharmacological Models

	A-549 cell	HL-60 cell	KB cell
6	3.4×10^{-5} M	6.7×10^{-6} M	3.0×10^{-6} M
7	2.2×10^{-5} M	1.2×10^{-5} M	2.6×10^{-6} M

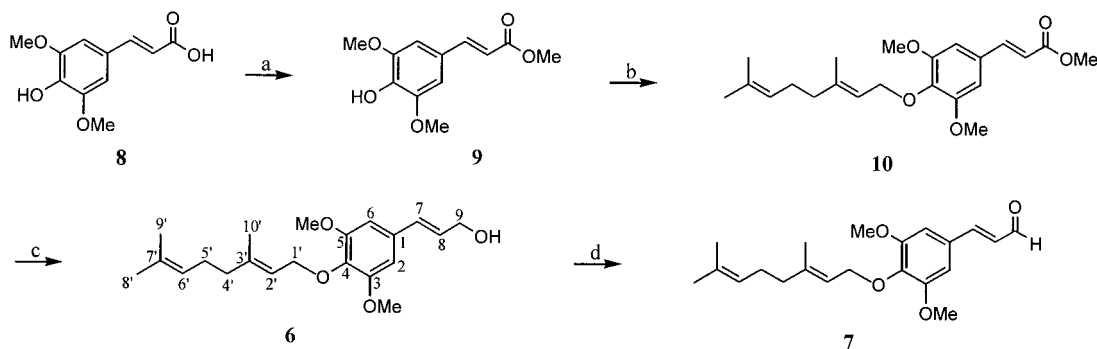
reaction of the resulting methyl ester **9** with geranyl alcohol led to the geranyl derivative **10**.¹⁰ Reduction of **10** by DIBAH afforded geranyloxy sinapyl alcohol **6** in an 86% yield, while oxidation of **6** by magnesium dioxide gave geranyloxy sinapyl aldehyde **7** in 92% yield (Scheme 1).

Another synthetic path started from methyl gallate (**11**) (Scheme 2) Acetylation led to product **12**, which was subjected to a selective substitution reaction,¹¹ during which the 4-acetoxy group was replaced by a geranyl moiety to yield compound **13b**. The unexpected mono-deacetylated product **13a** was also formed in the reaction. The reaction time and the temperature influenced the yields of **13a** and **13b**. The mixture of **13a** and **13b** was treated with aqueous K_2CO_3 to give **14**, which was then transformed to the methoxy derivative **15** (82% yield over two steps). Reduction of **15** by LAH afforded primary alcohol **16**, which was oxidized to aldehyde **17** by pyridinium chlorochromate in 86% yield. A Knoevenagel condensation of **17** with malonic acid in the presence of piperidine afforded the *E*-form of acid **18**. Reduction of **18** by LAH afforded, apart from the 80% yield of expected target molecule **6**, the 1,4-addition product **19** in 5% yield. Finally, geranyloxy sinapyl aldehyde **7** was obtained by manganese dioxide oxidation in 92% yield. The total yield of **8** was 28%. Cytotoxic screening results of synthetic **6** and **7** against A-549, HL-60, and KB cell lines are shown in Table 3.

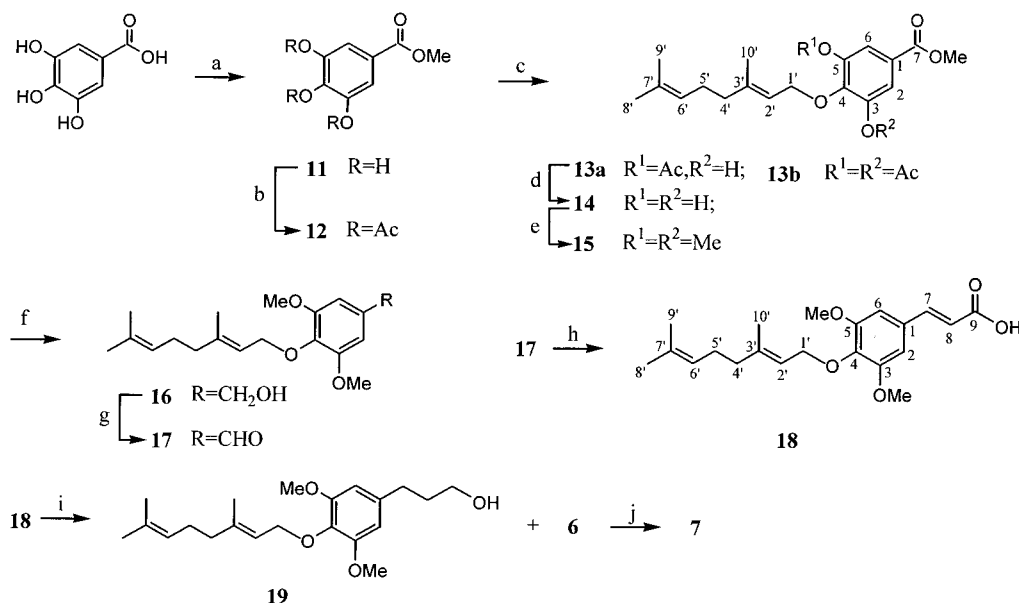
To examine the importance of the C-4 side chain on cytotoxicity, we designed another target molecule (**20**) with a benzyl group attached to O-C(4). Furthermore, a five-carbon side chain (compound **34**) was also introduced to extend the SAR concept. Two paths were examined to synthesize these analogues, which are shown in Schemes 2 and 3. Cytotoxicity screening of **20**, **27**, **34**, and **35** is shown in Table 4. It was seen that compounds **20** and **27** were less cytotoxic to KB cells than **6** and **7**, while the five-carbon side chain derivatives **34** and **35** had cytotoxicities to KB cells similar to those of **1** and **2**.

Experimental Section

General Experimental Procedures. ^1H NMR and ^{13}C NMR spectra were measured on Bruker AM-400 MHz and Bruker AC-300 MHz NMR instruments, with TMS as internal

Scheme 1^a

^a (a) H₂SO₄, MeOH, reflux, 2 h, 98%; (b) geranyl alcohol, Ph₃P, DEAD, 24 h, 50%; (c) DIBALH, THF, -78 °C, 2 h, 86%; (d) 1: PCC, CH₂Cl₂, rt, 6 h, 81%; 2: MnO₂, EtOAc, rt, 92%.

Scheme 2^a

^a (a) H₂SO₄, MeOH, reflux, 2 h, 96%; (b) Ac₂O, Py, rt, 12 h, 93%; (c) geranyl bromide, K₂CO₃, DMF, 0 °C, 24 h, 50% of **13b**, 29% of **13a**; (d) K₂CO₃, MeOH-H₂O, rt, 0.5 h, 90%; (e) MeI, K₂CO₃, reflux, 3 h, 91%; (f) LAH, ether, 0 °C, 90%; (g) PCC, CH₂Cl₂, rt, 6 h, 86%; (h) malonic acid, piperidine, Py, reflux, 4 h, 86%; (i) LAH, ether, 0 °C, 80% of **6**, 5% of **19**; (j) MnO₂, EtOAc, rt, 2 h, 92%.

Table 4. IC₅₀ of Compounds **20**, **27**, **34**, and **35** on KB Cells (mol/L)

20	27	34	35
8.6 × 10 ⁻⁴	6.4 × 10 ⁻⁴	7.8 × 10 ⁻⁶	5.3 × 10 ⁻⁶

standard. HREIMS and EIMS were performed on a VG Auto Spec-3000 MS instrument. EIMS: direct inlet, 70 eV. Solvents and reagents were purified according to standard laboratory techniques. IR spectra were recorded on a Perkin-Elmer 577 spectrometer.

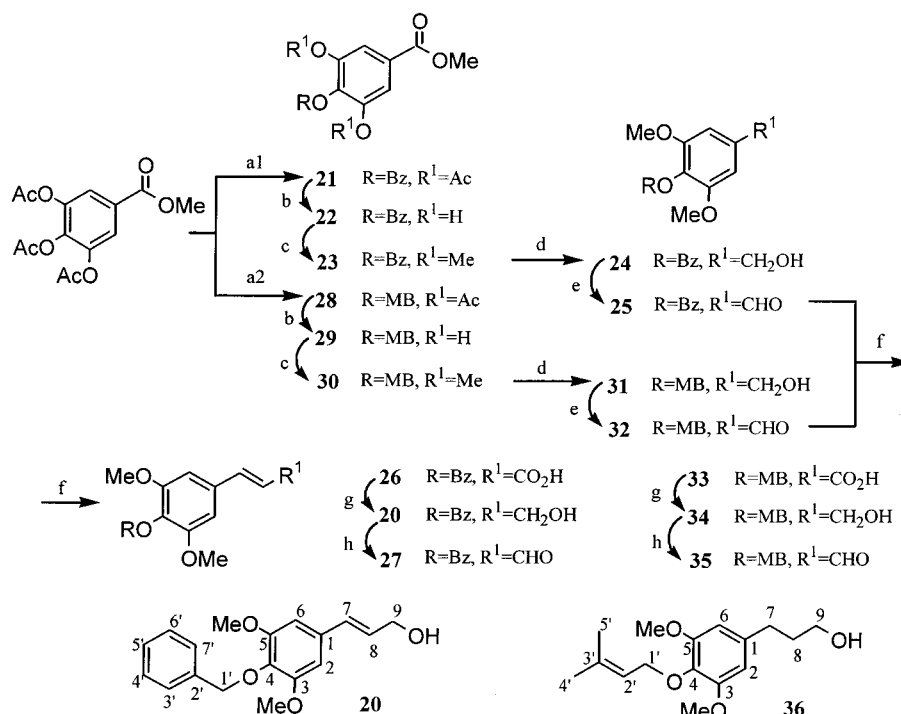
Plant Material. The material plant was collected in August 2000, Zhaotong County, Yunnan Province, China, and identified by Prof. Hua Peng. A voucher specimen (no. 20000806) is deposited in the Laboratory of Phytochemistry, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, Yunnan Province, China.

Extraction and Isolation. Air-dried roots of *Ligularia nelumbifolia* [Bur. Et Franch] Hand.-Mazz] (2.0 kg) were powdered and extracted with petroleum ether (60–90 °C)–Et₂O–MeOH (1:1:1) at room temperature (3 days × 3) to give 85 g of crude extract, which was subjected to column chromatography on 1 kg of silica gel with petroleum ether containing gradually increasing amounts of EtOAc (1:0–1:1). Ten crude fractions (F₁–F₁₀) were obtained. F₁–F₇ contained, by TLC, mainly the same products reported previously.³ F₈ (2.1 g) afforded, after repeated column chromatography, 86 mg of **6**

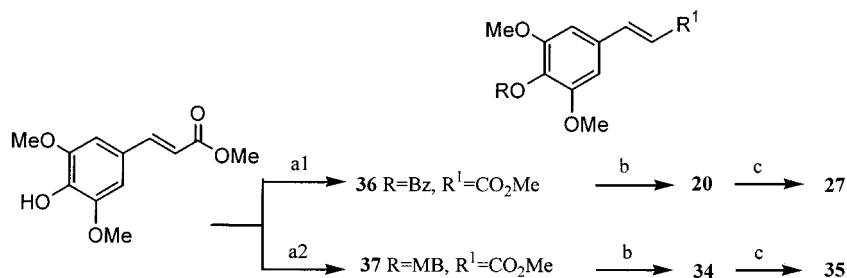
and 35 mg of **7**. F₉ (3.2 g) was chromatographed (200 g of silica gel gel, 200–300 mesh) using a CHCl₃–Me₂CO (20:1–1:1) step gradient. Eluates 25–28 (150 mL each) were combined and purified by PTLC (CHCl₃–Me₂CO, 3:1) to give 14 mg of **1** (*R*_f = 0.46). Eluate 14 (120 mL) was evaporated and purified by PTLC (C₆H₆–Me₂CO, 4:1) to give 21 mg of **2**. Eluate 17 (80 mL) contained 26 mg of **5**, which was obtained by PTLC with C₆H₆–Me₂CO, 8:1 (*R*_f = 0.65). F₁₀ (6.6 g) was rechromatographed over silica H (200 g) with a CHCl₃–EtOAc (10:1–1:2) solvent system. Eluates 16–17 (125 mL each) were combined and evaporated, and the residue (86 mg) was purified through PTLC (CHCl₃–MeOH, 8:1) to afford 17 mg of **3** (*R*_f = 0.57) and 15 mg of **4** (*R*_f = 0.49).

4-O-[(2E)-3,7-Dimethyl-2,7-octadien-5-ol]sinapyl alcohol (1): gum; IR (KBr) ν_{max} 3399 (OH), 3349 (OH), 2977, 1659, 1583, 1504, 1459, 1420, 1332, 1241, 1127, 963 cm⁻¹; EIMS *m/z* (rel int) 362 [M]⁺ (16), 347 (3), 344 (5), 329 (6), 306 (14), 277 (10), 252 (18), 238 (50), 210 (100), 182 (36), 167 (42), 154 (18); ¹H NMR (CDCl₃) data, see Table 1; ¹³C NMR (CDCl₃) data, see Table 2; anal. C 69.56%, H 8.27%, calcd for C₂₁H₃₀O, C 69.61%, H 8.29%.

4-O-[(2E)-3,7-Dimethyl-6-ethoxy-2,7-octadienyl]sinapyl alcohol (2): gum; IR (KBr) ν_{max} 3398 br (OH), 3072, 2939, 1653, 1583, 1504, 1456, 1418, 1333, 1241, 1128, 992, 904, 629 cm⁻¹; EIMS *m/z* (rel int) 390 [M]⁺, (15), 375 (22), 349 (18), 344 (16), 277 (10), 210 (100), 182 (55), 167 (43), 137 (16), 121 (14), 113 (20), 69 (72), 46 (23); ¹H NMR (CDCl₃) data, see Table

Scheme 3^a

^a (a1) Benzyl bromide, DMF, 0 °C, 24 h; (a2) 2-methylbutenyl bromide, K₂CO₃, DMF, 0 °C, 10 h; (b) K₂CO₃, MeOH–H₂O, rt, 0.5 h; (c) MeI, K₂CO₃, reflux, 3 h; (d) LAH, ether, 0 °C; (e) PCC, CH₂Cl₂, rt, 6 h; (f) malonic acid, piperidine, Py, reflux, 4 h; (g) LAH, ether, 0 °C; (h) MnO₂, EtOAc, rt, 2 h (MB = 2-methylbutenyl).

Scheme 4^a

^a (a1) Benzol, Ph₃P, DEAD, 24 h, 65%; (a2) 2-methylbutenol, Ph₃P, DEAD, 24 h, 60%; (b) DIBAH, THF, –78 °C, 2 h; 88% of **20**, 80% of **34**; (c) 1: PCC, CH₂Cl₂, rt, 6 h; 83% of **27**, 81% of **35**; 2: MnO₂, EtOAc, rt, 92% of **27**, 94% of **35** (MB = 2-methylbutenyl).

1; ¹³C NMR (CDCl₃) data, see Table 2; *anal.* C 70.73%, H 8.72%, calcd for C₂₃H₃₄O₅, C 70.77%, H 8.72%.

4-O-[(2E,5E)-3,7-Dimethyl-5-ethoxy-2,5-octadiene-7-ol]-sinapyl alcohol (3): gum; IR (KBr) ν_{\max} 3408 br (OH), 2967, 2926, 1665, 1582, 1504, 1459, 1417, 1332, 1240, 1127, 969, 914, 744 cm⁻¹; EIMS *m/z* (rel int) 406 [M]⁺, (8), 391 (2), 389 (5), 360 (6), 314 (15), 264 (3), 210 (100), 197 (3), 182 (25), 167 (42), 154 (16), 69 (18), 46 (48); ¹H NMR (CDCl₃) data, see Table 1; ¹³C NMR (CDCl₃) data, see Table 2; *anal.* C 67.90%, H 8.31%, calcd for C₂₃H₃₄O₆, C 67.98%, H 8.37%.

4-O-[(2E,4E)-3,7-Dimethyl-5-ethoxy-2,4-octadien-7-ol]-sinapyl alcohol (4): gum; IR (KBr) ν_{\max} 3402 br (OH), 3349, 2973, 2933, 1673, 1582, 1503, 1457, 1418, 1333, 1240, 1128, 969, 844 cm⁻¹; EIMS *m/z* (rel int) 406 [M]⁺, (12), 391 (4), 389 (8), 374 (4), 360 (2), 343 (5), 210 (100), 197 (6), 182 (38), 167 (44), 154 (23), 128 (6), 69 (18), 46 (36); ¹H NMR (CDCl₃) data, see Table 1; ¹³C NMR (CDCl₃) data, see Table 2; *anal.* C, 67.90%, H, 8.31%, calcd for C₂₃H₃₄O₆, C, 67.98%, H, 8.37%.

Sinapic Acid Methyl Ester (9). NMR and physical data were identical with a previous publication.⁹ EIMS: *m/z* 238 [M]⁺ (100), 223 (9), 207 (95), 175 (33), 163 (11), 119 (10), 91 (6). HREIMS: 238.0856 (calcd for C₁₂H₁₄O₅, 238.0841).

Etherification of 9. To a stirred solution of 313 mg (1.2 mmol) of Ph₃P and 240 mg of **9** (1.0 mmol) in dry THF (10 mL) was added 150 mg of geraniol (1.0 mmol) and DEAD (262 μ L, 1.2 mmol) at room temperature under nitrogen. The

solution was stirred overnight and then refluxed for 0.5 h. The cooled solution was partitioned between H₂O (30 mL) and EtOAc (30 mL \times 3) and dried (MgSO₄). After filtration, the solvent was evaporated and the residue was subjected to CC (petroleum ether–Et₂O, 5:1–2:1); 186 mg of **10** was isolated (50%).

4-Geranyl sinapic acid methyl ester (10): gum; ¹H NMR (CDCl₃, 400 MHz) 7.57 (1H, d, *J* = 16.0 Hz, H-7), 6.72 (2H, s, H-2, H-6), 6.32 (1H, d, *J* = 15.8 Hz, H-8), 5.53 (1H, brt, *J* = 7.0 Hz, H-2'), 5.05 (1H, m, H-6'), 4.55 (2H, d, *J* = 7.1 Hz, H-1'), 3.86 (6H, s, OMe-3, OMe-5), 3.79 (3H, s, CO₂Me), 2.03 (4H, m, H-4', H-5'), 1.65 (3H, s, H-8'), 1.63 (3H, s, H-9'), 1.57 (3H, s, H-10'); ¹³C NMR (CDCl₃, 100 MHz) δ 167.3 (s, C-9), 153.82 (s, C-3, C-5), 144.90 (d, C-7), 141.6 (s, C-4), 139.0 (s, C-2), 131.5 (s, C-3'), 129.7 (s, C-7), 123.92 (d, C-6'), 119.97 (d, C-2'), 116.77 (d, C-8), 105.17 (d, C-2, C-6), 69.50 (t, C-1'), 56.09 (q, OMe-3, OMe-5), 51.62 (q, CO₂Me), 39.57 (t, C-4'), 26.39 (t, C-5'), 25.62 (t, C-8'), 17.61 (q, C-9'), 16.31 (q, C-10'); EIMS *m/z* 374 [M]⁺ (1), 343 (1), 305 (2), 266 (1), 248 (1), 238 (100), 223 (3), 207 (8), 175 (3), 163 (2), 135 (2), 69 (13); HREIMS *m/z* 374.2082 (calcd for C₂₂H₃₀O₅, 374.2093).

Reduction of 10. To a stirred solution of 374 mg (1.0 mmol) of **10** in dry Et₂O (10 mL) was added DIBAH (1.0 mL, 1.0 M in hexane) at –78 °C under nitrogen. The solution was stirred for 0.5 h, 3 mL of H₂O was added at –78 °C to quench the reaction, and the solution was allowed to warm to room

temperature. Ten milliliters of 1 M HCl was added, and the solution was extracted with EtOAc (15 mL \times 3). The organic layers were combined and dried (MgSO₄). Purification by flash column afforded 299 mg of **6** (86%). Physical and NMR data for compound **6** have been reported in an earlier publication.³

Allylic Oxidation of 6 by MnO₂. To a stirred suspension of 105 mg (1.2 mmol) of MnO₂ in EtOAc (15 mL) was added 345 mg (1.0 mmol) of **6** in EtOAc (5 mL) at room temperature, and the solution was stirred for 4 h. After filtration, the eluate was evaporated to dryness and was partitioned between H₂O (20 mL) and Et₂O (60 mL). The organic layer was combined and dried (MgSO₄), and the solvent was evaporated to afford **7** (317 mg, 92%). Physical and NMR data for compound **7** have been reported in an earlier publication.³

Deacetylation of 12. To a stirred solution of 15.5 g of **12** (50 mmol) in dry DMF (150 mL) was added 20.7 g of K₂CO₃ (150 mmol) at 0 °C. The solution was stirred for 20 min and 10.85 g (9.9 mL) of geranyl bromide (60 mmol) in dry DMF (60 mL) was added in 10 min. The solution was stirred for 10 h. After suction filtration, 300 mL of H₂O was added. The mixture was extracted with EtOAc (600 mL), followed by Et₂O (600 mL). The organic layers were combined, washed with brine (100 mL), and dried (MgSO₄). The solution was evaporated, and the residue was subjected to CC (hexane–Et₂O, 5:1) to afford 10.11 g (25 mmol) of **13b** (50%) and 5.25 g (14.5 mmol) of **13a** (29%). Also, 925 mg (3.0 mmol) of **12** (6%) was recovered.

4-Geranoyl-3,5-diacetoxybenzoic acid methyl ester (13b): gum; ¹H NMR (CDCl₃, 300 MHz) δ 7.64 (2H, s, H-2, H-6), 5.42 (1H, brt, J = 7.0 Hz, H-2'), 5.09 (1H, m, H-6'), 4.59 (2H, d, J = 7.2 Hz, H-1'), 3.89 (3H, s, CO₂Me), 2.36 (3H, s, OCOCH₃), 2.09 (4H, m, H-4', H-5'), 1.70 (3H, s, H-8'), 1.68 (3H, s, H-9'), 1.62 (3H, s, H-10'); HREIMS m/z 404.1818 (calcd for C₂₂H₂₈O₇, 404.1835).

4-Geranoyl-3-acetoxy-5-hydroxysinapic acid methyl ester (13a): gum; ¹H NMR (CDCl₃, 300 MHz) δ 7.52 (1H, brs, H-2), 7.36 (1H, brs, H-6), 5.90 (1H, brs, OH-5), exchanged in D₂O), 5.48 (1H, t, J = 7.0 Hz, H-2'), 5.08 (1H, m, H-6'), 4.63 (1H, d, J = 7.1 Hz, H-1'), 3.90 (3H, s, CO₂Me), 2.36 (3H, s, OCOCH₃), 2.10 (4H, m, H-4', H-5'), 1.70 (3H, s, H-8'), 1.66 (3H, s, H-9'), 1.61 (3H, s, H-10'); HREIMS m/z 362.1709 (calcd for C₂₀H₂₆O₆, 362.1729).

Deacetylation of 13 (13a and 13b) (e.g., 13a). To a stirred solution of **13a** (2.91 g, 8.0 mmol) in MeOH (200 mL) at 0 °C was added 5.66 g (43.2 mmol) of K₂CO₃ in H₂O (60 mL) in 10 min. The solution was stirred for 20 min, and the solvent was evaporated. Then 1 M HCl was added to adjust the pH value to 2, and the aqueous solution was extracted by EtOAc (300 mL). The organic layers were combined and dried (MgSO₄), and the solvent was evaporated to afford 2.32 g (7.2 mmol) of **14** (90%).

4-Geranoyl-3,5-hydroxybenzoic acid methyl ester (14): gum; ¹H NMR (300 MHz, CDCl₃) δ 7.25 (2H, s, H-2, H-6), 5.91 (1H, s, exchanged in D₂O, ArOH), 5.60 (1H, brt, J = 7.0 Hz, H-2'), 5.09 (1H, m, H-6'), 4.66 (2H, d, J = 7.1 Hz, H-1'), 3.90 (3H, s, CO₂Me), 2.08 (4H, m, H-4', H-5'), 1.70 (3H, s, H-8'), 1.66 (3H, s, H-9'), 1.61 (3H, s, H-10'); ¹³C NMR (75 MHz, CDCl₃) δ 166.9 (s, C-7), 149.2 (s, C-3, C-5), 145.2 (s, C-1), 137.4 (s, C-4), 132.1 (s, C-3'), 126.1 (s, C-7'), 123.5 (s, C-6'), 118.7 (s, C-2'), 109.5 (d, C-2, C-6), 69.9 (t, C-1'), 52.2 (q, CO₂Me), 39.6 (t, C-4'), 26.2 (t, C-5'), 25.6 (q, C-8'), 17.7 (q, C-9'), 16.4 (q, C-10'); HREIMS δ 320.1622 (calcd for C₁₈H₂₄O₅, 320.1624).

4-Geranoyl-3,5-methoxybenzoic acid methyl ester (15). To a stirred solution of **14** (320 mg, 1.0 mmol) in dry DMF (30 mL) was added 8 mg of K₂CO₃ (6.0 mmol) at room temperature under argon, then 0.312 mL (5.0 mmol) of MeI in DMF (5 mL) was added. The solution was heated at 100 °C for 3 h and was cooled to 25 °C. After suction filtration, the filtrate was partitioned between H₂O (120 mL) and EtOAc–ether (100 mL/100 mL). The organic layers were combined and dried (MgSO₄). The solution was evaporated under reduced pressure, and the residue was subjected to PTLC; 315 mg (0.91 mmol) of **15** was obtained (91%): gum; ¹H NMR (CDCl₃, 300 MHz) δ 7.30 (2H, s, H-2, H-6), 5.55 (1H, brt, J = 7.0 Hz, H-2'), 5.05 (1H, m, H-6'), 4.59 (1H, d, J = 7.0 Hz, H-1'), 3.93 (3H, s, H-9'), 3.89 (6H, s, OMe-3, OMe-5), 2.04 (4H, m, H-4', H-5'), 1.66 (3H, s, C-8'),

1.64 (3H, s, C-9'), 1.60 (3H, s, C-10'); ¹³C NMR (CDCl₃, 75 MHz) δ 166.8 (s, C-7), 153.4 (s, C-3, C-5), 141.9 (s, C-1), 141.2 (s, C-4), 131.6 (s, C-3'), 125.1 (s, C-7'), 123.9 (d, C-6'), 119.9 (s, C-2'), 109.6 (d, C-2, C-6), 69.4 (t, C-1'), 56.2 (q, OMe-3, OMe-5), 52.2 (q, CO₂Me), 39.6 (t, C-4'), 26.4 (t, C-5'), 25.6 (q, C-8'), 17.6 (q, C-9'), 16.3 (q, C-10'); HREIMS δ 348.1925 (calcd for C₂₀H₂₈O₅, 348.1937).

4-Geranoyl-3,5-dimethoxybenzyl Alcohol (16). To a stirred suspension of LAH (49 mg, 1.28 mmol) in Et₂O (50 mL) at 0 °C was added a solution of **15** (280 mg, 0.8 mmol) in dry Et₂O (20 mL) under argon atmosphere. The solution was stirred for 10 min and was quenched by H₂O (8 mL). Then 50 mL of 1 N HCl was added, and the mixture was extracted by Et₂O (150 mL). The ether layers were combined and dried (MgSO₄). Evaporation of the solvent followed by PTLC afforded 230 mg of **16** (0.72 mmol, 90%): gum; ¹H NMR (CDCl₃, 300 MHz) δ 6.62 (2H, brs, H-2, H-6), 5.60 (1H, brt, J = 7.0 Hz, H-2'), 5.05 (1H, m, H-6'), 4.69 (2H, brs, H-7), 4.52 (2H, d, J = 7.1 Hz, H-1'), 3.89 (6H, s, OMe-3, OMe-5), 2.10 (4H, m, H-4', H-5'), 1.70 (3H, s, H-8'), 1.68 (3H, s, H-9'), 1.63 (3H, s, H-10'); HREIMS m/z 320.1966 (calcd for C₁₉H₂₈O₄, 320.1988).

4-Geranoyl-3,5-dimethoxybenzaldehyde (17). To a stirred suspension of PCC (225 mg, 1.04 mmol) in CH₂Cl₂ (30 mL) at 0 °C was added 208 mg of **16** (0.65 mmol) in CH₂Cl₂ (10 mL). The solution was stirred at 0 °C for 5 h. The suspension was filtered and washed by Et₂O (60 mL) and partitioned between Et₂O (90 mL) and H₂O (30 mL). The ether layers were combined, dried (MgSO₄), and evaporated to afford a residue. PTLC of the residue afforded finally 178 mg of **17** (0.56 mmol, 86%): gum; ¹H NMR (CDCl₃, 300 MHz) δ 9.86 (1H, s, H-7), 7.13 (2H, s, H-2, H-6), 5.60 (1H, brt, J = 6.9 Hz, H-2'), 5.05 (1H, m, H-6), 4.77 (2H, brd, J = 7.0 Hz, H-1'), 3.94 (6H, s, OMe-3, OMe-5), 2.04 (4H, m, H-4', H-5'), 1.64 (3H, s, H-8'), 1.63 (3H, s, H-9'), 1.57 (3H, s, H-10'); ¹³C NMR (CDCl₃, 75 MHz) δ 191.2 (s, C-7), 154.2 (s, C-3, C-5), 142.5 (s, C-1), 142.3 (s, C-4), 131.7 (s, C-3'), 131.8 (s, C-7'), 123.9 (d, C-6'), 119.78 (d, C-2'), 106.6 (d, C-2, C-6), 69.6 (t, C-1'), 56.3 (q, OMe-3, OMe-5), 39.6 (t, C-4'), 26.4 (t, C-5'), 25.7 (q, C-8'), 17.7 (q, C-9'), 16.4 (q, C-10'); HREIMS m/z 318.1822 (calcd for C₁₉H₂₆O₄, 318.1831).

4-Geranoylsinapic Acid (18). To a stirred solution of malonic acid (156 mg, 1.5 mmol) in Py (15 mL) at room temperature was added 475 mg (1.5 mmol) of **17** in Py (10 mL). Piperidine (20 mg) was added to the solution. The mixture was heated at 120 °C for 4 h. The solvent was evaporated and dried (MgSO₄), evaporated, and followed by CC (CHCl₃–MeOH, 8:1) to afford 463 mg of **18** (1.3 mmol, 86%): gum; ¹H NMR (CDCl₃, 400 MHz) δ 7.69 (1H, d, J = 15.9 Hz, H-7), 6.75 (2H, s, H-2, H-6), 6.34 (d, J = 15.8 Hz, H-8), 5.53 (1H, brt, J = 7.2 Hz, H-2'), 5.05 (1H, m, H-6'), 4.57 (2H, brd, J = 7.1 Hz, H-1'), 3.87 (6H, s, OMe-3, OMe-5), 2.03 (4H, m, H-4', H-5'), 1.65 (3H, s, H-8'), 1.64 (3H, s, H-9'), 1.57 (3H, s, H-10'); ¹³C NMR (CDCl₃, 100 MHz) δ 172.1 (s, C-9), 154.0 (s, C-3, C-5), 147.1 (d, C-7), 141.8 (s, C-4), 139.4 (s, C-1), 131.6 (s, C-3'), 129.4 (s, C-7'), 134.0 (d, C-6'), 120.0 (d, C-2'), 116.2 (d, C-8), 105.5 (d, C-2, C-6), 69.6 (t, C-1'), 56.2 (q, OMe-3, OMe-5), 39.6 (t, C-4'), 26.4 (t, C-5'), 25.7 (q, C-8'), 17.7 (q, C-9'), 16.4 (q, C-10'); EIMS m/z 360 [M]⁺, (3), 345 (1), 331 (11), 316 (3), 224 (100), 209 (4), 198 (26), 181 (4), 69 (23); HREIMS m/z 360.1927 (calcd for C₂₁H₂₈O₅, 360.1937).

4-Geranoyl-7,8-dihydroxysinapic Acid (19). To a stirred solution of LAH (41 mg, 1.09 mmol) in dry Et₂O (15 mL) at 0 °C was added 195 mg (0.54 mmol) of **18** in dry Et₂O (10 mL) under argon. The mixture was stirred for 1 h at 0 °C and was quenched by H₂O (6 mL). Then 1 N HCl (10 mL) was added and extracted by Et₂O (30 mL). The ether layer was dried (MgSO₄), evaporated, and subjected to CC (petroleum ether–Et₂O, 1:2) to afford 150 mg of **7** (0.43 mmol, 80%) and 10 mg of **19** (0.03 mmol, 5%): gum; ¹H NMR (CDCl₃, 300 MHz) δ 6.46 (2H, brs, H-2, H-6), 5.58 (1H, brt, J = 7.0 Hz, H-2'), 5.07 (1H, m, H-6'), 4.55 (2H, brd, J = 7.0 Hz, H-1'), 3.86 (2H, brt, J = 7.6 Hz, H-9), 3.90 (6H, s, OMe-3, OMe-5), 2.79 (2H, brt, J = 7.6 Hz, H-7), 2.01–1.94 (2H, m, H-8); HREIMS m/z 348.2298 (calcd for C₂₁H₃₂O₄, 348.2300).

4-O-Benzyl-3,5-diacetoxybenzoic Acid Methyl Ester (21). The method of preparation of **21** was similar to that used

for the preparation of **13**. The yield **21** from **12** was 67%. This compound was identical to that reported by Pearson et al.¹¹ It was noticeable that no mono-deacetylated compound was obtained in this reaction.

4-O-Benzyl-3,5-dihydroxybenzoic Acid Methyl Ester (22). The method of preparation of **22** was similar to that used for the preparation of **14**. The yield of **22** from **21** was 92%: gum; ¹H NMR (CDCl₃, 300 MHz) δ 7.43–7.36 (5H, m, H-3'–H-7'), 7.25 (2H, s, H-2, H-6), 5.80 (brs, exchanged in D₂O, ArOH), 5.16 (2H, s, H-1'), 3.90 (3H, s, CO₂Me); HREIMS *m/z* 274.0870 (calcd for C₁₅H₁₄O₄, 274.0841). This compound was first reported by Pearson et al.¹⁶

4-O-Benzyl-3,5-dimethoxybenzoic Acid Methyl Ester (23). The method of preparation of **23** was similar to that used for the preparation of **15**. The yield of **23** from **22** was 90%: gum; ¹H NMR (CDCl₃, 300 MHz) δ 7.25–7.5 (5H, m, H-2'–H-7'), 5.10 (2H, s, H-1'), 3.93 (3H, s, Me-8), 3.90 (3H, s, OMe-3, OMe-5); ¹³C NMR (CDCl₃, 75 MHz) δ 166.8 (s, C-7), 153.3 (s, C-3, C-5), 141.0 (s, C-1), 137.5 (s, C-4), 128.5 (d, C-3', C-7'), 128.27 (d, C-4', C-6'), 128.1 (d, C-5'), 125.4 (s, C-2'), 106.9 (d, C-2, C-6), 75.0 (t, C-1'), 56.3 (q, OMe-3, OMe-5), 52.3 (q, CO₂Me); HREIMS *m/z* 302.1133 (calcd for C₁₇H₁₈O₅, 302.1154). This compound was first reported by Jurd et al.¹⁴

4-O-Benzyl-3,5-dimethoxybenzyl Alcohol (24). The method of preparation of **24** was similar to that used for the preparation of **16**. The yield of **24** from **23** is 94%. This compound was identical to that reported by Battersby et al.¹⁵

4-O-Benzyl-3,5-dimethoxybenzaldehyde (25). The method of preparation of **25** was similar to that used for the preparation of **17**. The yield of **25** from **24** was 88%. This compound was identical to that reported by Battersby et al.¹⁶

4-O-Benzylsinapic Acid (26). The method of preparation of **26** was similar to that used for the preparation of **18**. The yield of **26** from **25** was 90%. This compound was identical to that reported by Kametani et al.¹⁷

4-O-Benzylsinapyl Alcohol (20). The method of preparation of **20** was similar to that used for the preparation of **7**. The yield of **20** from **26** was 87%: gum; ¹H NMR (CDCl₃, 300 MHz) δ 7.51–7.20 (5H, m, H-3'–H-7'), 6.56 (2H, brs, H-2, H-6), 6.50 (1H, d, *J* = 15.8 Hz, H-7), 6.28 (1H, dt, *J* = 15.8, 5.7 Hz, H-8), 5.06 (2H, brs, H-1), 3.88 (6H, s, OMe-3, OMe-5); HREIMS *m/z* 300.1341 (calcd for C₁₈H₂₀O₄, 300.1362).

4-O-Benzylsinapaldehyde (27). The method of preparation of **27** was similar to that used for the preparation of **7**. The yield of **27** from **20** was 94%: gum; ¹H NMR (CDCl₃, 300 MHz) δ 9.68 (1H, d, *J* = 7.5 Hz, H-9), 7.52–7.22 (6H, m, H-3'–H-7', H-7), 6.74 (2H, brs, H-2, H-6), 6.61 (1H, dd, *J* = 15.8, 7.5 Hz, H-8), 5.09 (2H, brs, H-1'), 3.90 (6H, s, OMe-3, OMe-5); HREIMS *m/z* 298.1229 (calcd for C₁₈H₁₈O₄, 298.1205).

4-O-(2-Methyl-2-butenyl)-3,5-diacetoxybenzoic Acid Methyl Ester (28). The method of preparation of **28** was similar to that used for the preparation of **13**. The yield of **28** from **12** was 60%: gum; ¹H NMR (CDCl₃, 400 MHz) δ 7.65 (2H, s, H-2, H-6), 5.37 (1H, t, *J* = 7.0 Hz, H-2'), 4.48 (2H, d, *J* = 7.25 Hz, H-1'), 3.86 (3H, s, CO₂Me), 2.31 (6H, s, OCOCH₃-3, OCOCH₃-5), 1.74 (3H, s, H-4'), 1.64 (3H, s, H-5'); EIMS *m/z* 336 [M]⁺ (1), 321 (1), 295 (1), 281 (2), 286 (6), 253 (2), 237 (4), 226 (41), 195 (3), 184 (60), 153 (5), 121 (4), 85 (14), 69 (100); HREIMS *m/z* 336.1208 (calcd for C₁₇H₂₀O₇, 336.1209).

4-O-(2-Methyl-2-butenyl)-3,5-dihydroxybenzoic Acid Methyl Ester (29). The method of preparation of **29** was similar to that used for the preparation of **14**. The yield of **29** from **28** was 91%: gum; ¹H NMR (CDCl₃, 400 MHz) δ 7.20 (2H, s, H-2, H-6), 5.96 (1H, brs, exchanged in D₂O, ArOH), 5.50 (1H, t, *J* = 7.0 Hz, H-2'), 4.60 (2H, d, *J* = 7.0 Hz, H-1'), 3.86 (3H, s, CO₂Me), 1.75 (3H, s, H-4'), 1.63 (3H, s, H-5'); EIMS *m/z* 252 [M]⁺ (21), 235 (8), 226 (75), 211 (33), 205 (18), 184 (44), 167 (5), 153 (46), 149 (8), 69 (100); HREIMS *m/z* 252.0978 (calcd for C₁₃H₁₆O₅, 252.0998).

4-O-(2-Methyl-2-butenyl)-3,5-dimethoxybenzoic Acid Methyl Ester (30). The method of preparation of **30** was similar to that used for the preparation of **15**. The yield of **30** from **29** was 92%: gum; ¹H NMR (CDCl₃, 400 MHz) δ 7.26 (2H, s, H-2, H-6), 5.52 (1H, brt, *J* = 7.2 Hz, H-2'), 4.55 (2H, d, *J* = 7.3 Hz, H-1'), 3.89 (3H, s, CO₂Me), 3.88 (3H, s, OMe-3,

OMe-5), 1.72 (3H, s, H-4'), 1.64 (3H, s, H-5'); HREIMS *m/z* 280.1300 (calcd for C₁₅H₂₀O₅, 280.1311).

4-O-(2-Methyl-2-butenyl)-3,5-dimethoxybenzyl Alcohol (31). The method of preparation of **31** was similar to that used for the preparation of **16**. The yield of **31** from **30** was 89%: gum; ¹H NMR (CDCl₃, 400 MHz) δ 6.53 (2H, s, H-2, H-6), 5.51 (1H, brt, *J* = 7.1 Hz, H-2'), 4.56 (2H, s, H-7), 4.42 (1H, d, *J* = 7.2 Hz, H-1'), 3.79 (6H, s, OMe-3, OMe-5), 1.69 (3H, s, H-5'), 1.62 (3H, s, H-4'); EIMS *m/z* 252 [M]⁺ (6), 239 (6), 235 (5), 226 (28), 211 (10), 205 (33), 184 (100), 182 (2), 167 (14), 155 (12), 153 (8), 127 (8), 123 (12), 109 (9), 69 (18); HREIMS δ 252.1374 (calcd for C₁₄H₂₀O₄, 252.1362).

4-O-(2-Methyl-2-butenyl)-3,5-dimethoxybenzaldehyde (32). The method of preparation of **32** was similar to that used for the preparation of **17**. The yield of **32** from **31** was 85%: gum; ¹H NMR (CDCl₃, 400 MHz) δ 9.81 (1H, s, H-7), 7.07 (2H, s, H-2, H-6), 5.49 (1H, t, *J* = 7.1 Hz, H-2'), 4.56 (2H, d, *J* = 7.3 Hz, H-1'), 3.87 (6H, s, OMe-3, OMe-5), 1.69 (3H, s, H-5'), 1.62 (3H, s, H-4'); EIMS *m/z* 250 [M]⁺ (1), 235 (1), 226 (16), 196 (2), 182 (100), 167 (8), 153 (2), 139 (4), 125 (5), 110 (6), 95 (7); HREIMS *m/z* 250.1199 (calcd for C₁₄H₁₈O₄, 250.1205).

4-O-(2-Methyl-2-butenyl)sinapic Acid (33). The method of preparation of **33** was similar to that used for the preparation of **18**. The yield of **33** from **32** was 88%: gum; ¹H NMR (CDCl₃, 400 MHz) δ 7.68 (1H, d, *J* = 15.7 Hz, H-7), 6.75 (1H, s, H-2, H-6), 6.34 (1H, d, *J* = 15.8 Hz, H-8), 5.53 (1H, dt, *J* = 7.2, 1.3 Hz, H-2'), 4.57 (2H, d, *J* = 7.2 Hz, H-1'), 3.86 (6H, s, OMe-3, OMe-5), 1.72 (3H, s, H-4'), 1.65 (3H, s, H-5'); EIMS *m/z* 292 [M]⁺ (6) 277 (2), 265 (5), 250 (3), 224 (100), 209 (40), 197 (3), 195 (3), 181 (10), 163 (12), 149 (8), 135 (9), 121 (15), 69 (69); HREIMS *m/z* 292.1303 (calcd for C₁₆H₂₀O₅, 292.1311).

4-O-(2-Methyl-2-butenyl)sinapyl Alcohol (34). The method of preparation of **34** was similar to that used for the preparation of **6** from **18**. The yield of **34** from **33** was 81%, while the yield of byproduct **36** was 8%: gum; ¹H NMR (CDCl₃, 400 MHz) δ 6.59 (2H, s, H-2, H-6), 6.52 (1H, d, *J* = 16.0, H-7), 6.27 (1H, dt, *J* = 15.6, 5.7 Hz, H-8), 5.54 (1H, m, H-2'), 4.47 (2H, brd, *J* = 7.1 Hz, H-1'), 4.30 (2H, brd, *J* = 5.7 Hz, H-9), 3.84 (6H, s, OMe-3, OMe-5), 1.72 (3H, H-4'), 1.65 (3H, s, H-5'); HREIMS *m/z* 278.1532 (calcd for C₁₆H₂₂O₄, 278.1518).

4-O-(2-Methyl-2-butenyl)sinapaldehyde (35). The method of preparation of **35** was similar to that used for the preparation of **7** from **6**. The yield of **35** from **34** was 91%: gum; ¹H NMR (CDCl₃, 400 MHz) δ 9.66 (1H, d, *J* = 7.6 Hz, H-9), 7.40 (1H, d, *J* = 15.9 Hz, H-7), 6.77 (2H, br. s, H-2, H-6), 6.60 (1H, dd, *J* = 15.9, 7.6 Hz, H-8), 5.54 (1H, brt, *J* = 7.2 Hz, H-2'), 4.56 (2H, brd, *J* = 7.2 Hz, H-1'), 3.89 (6H, s, OMe-3, OMe-5), 1.72 (3H, s, H-4'), 1.65 (3H, s, Me-5'); HREIMS *m/z* 276.1351 (calcd for C₁₆H₂₀O₄, 276.1362).

4-O-(2-Methyl-2-butenyl)-7,8-dihydrosinapyl alcohol (36): gum; ¹H NMR (CDCl₃, 400 MHz) δ 6.48 (2H, brs, H-2, H-6), 5.53 (1H, brt, *J* = 7.2 Hz, H-2'), 4.51 (2H, brd, *J* = 7.1 Hz, H-1'), 3.90 (2H, brt, *J* = 7.5 Hz, H-9), 3.88 (6H, s, OMe-3, OMe-5), 2.81 (2H, brt, *J* = 7.5 Hz, H-7), 2.03–1.96 (2H, m, H-8), 1.71 (3H, s, H-4'), 1.65 (3H, s, H-5'); HREIMS *m/z* 278.1509 (calcd for C₁₆H₂₂O₄, 278.1518).

Cytotoxicity Assay. KB cells were obtained from the American type culture collection.¹² Effects of compounds on the growth of the cells were monitored at the Laboratoire de Cultures Cellulaires, ICSN, Gif-sur-Yvette, France. The IC₅₀ values refer to the concentration of drug corresponding to 50% growth inhibition after 72 h incubation.¹³ The assays of A-549 and HL-60 were carried out at the Institute of Shanghai Material Medica and were performed according to published techniques.^{18–20}

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