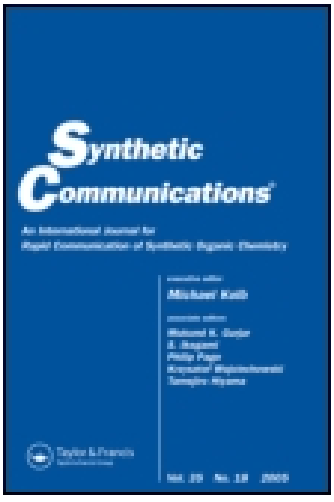

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# Synthesis of (±)-12-Methoxyherbertenediol Dimethyl Ether

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# Synthesis of (±)-12-Methoxyherbertenediol Dimethyl Ether

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**Abstract:** Efficient total synthesis of (±)-12-methoxyherbertenediol dimethyl ether and 12-homoherbertenediol was accomplished starting from vanillin employing a Claisen rearrangement–RCM reaction–based approach.

**Keywords:** metathesis, natural products, rearrangement, ring closure, total synthesis

The herbertane group[1] is a small group of aromatic sesquiterpenes, isomeric to cuparanes, containing a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane carbon framework incorporating two vicinal quaternary carbon atoms on a cyclopentane ring. Even though cuparene **1**, isomeric to herbertane, has been known[2] since 1958, the herbertane family of sesquiterpenes was reported only in the 1980s. Isolation of the first member of the family, herbertene **2**, was reported in 1981 by Matsuo and coworkers from the ethyl acetate extract of the liverwort *Herberta adunca* (Dicks) S. Gray belonging to the family herbertaceae.[3] Subsequently, a few other phenolic herbertanes **3**–**9** were isolated from a variety of *Herbertus* sources, (Fig. 1).[4] In 2000, Asawaka and coworkers reported[5] the isolation of seven herbertenes: herbertene-acetal **10**, herbertene-1,14-diol **11**, herbertene-1,15-diol **12**, herbertene-1,13-diol **13**, herbertenones A and B **14** and **15**, and 12-methoxyherbertenediol **16** from the ether and ethyl acetate extracts of the Japanese liverwort *Herbertus sakuraii*.

The herbertane sesquiterpenes, mainly the phenolic herbertanes,[1,5] have been shown to possess interesting biological properties, such as

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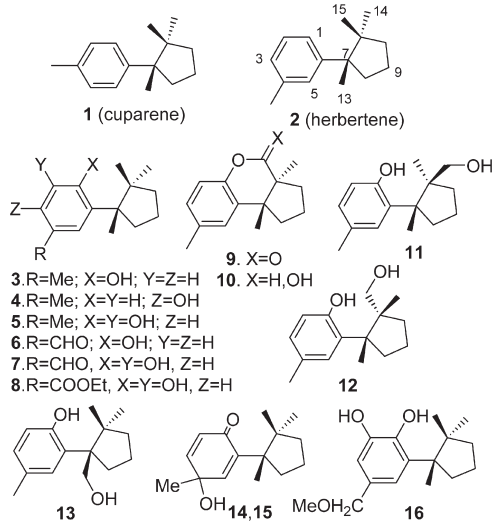
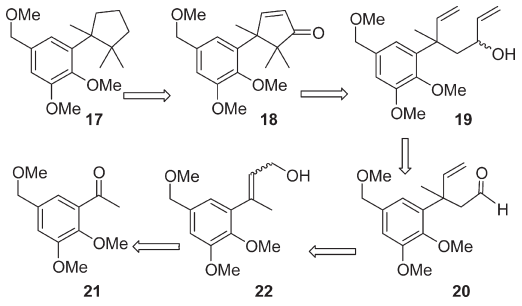



***Figure 1.*** Herbertane sesquiterpenes isolated from *Herbertus* species.

growth-inhibiting activity. Some of the phenolic herbertenes were found to be strong inhibitors of the plant pathogenic fungi *Botrytis cinerea*, *Rhizoctonia solani*, and *Pythium debaryanum*.[4] Presence of a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane carbon framework, the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring and the significant biological properties associated with the phenolic herbertanes made herbertenoids interesting and challenging synthetic targets. Prior to 1999, only 3 reports appeared in the literature on the synthesis of phenolic herbertanes. However, during the past seven years, nearly 40 reports appeared in the literature on the synthesis of phenolic herbertanes, making it a topic of contemporary interest.[6] We have developed a combination of Claisen rearrangement and ring-closing metathesis (RCM) reactions[6b] for the synthesis of phenolic herbertenes. Herein we describe the first total synthesis of 12-methoxyherbertenediol dimethyl ether and 12-homoherbertenediol.

Retrosynthetic analysis is depicted in Scheme 1. It was anticipated that 12-methoxyherbertenediol dimethyl ether **17** could be obtained from the enone **18**, containing the requisite two vicinal quaternary carbons, which in turn could be obtained from the hydroxydiene **19** via an RCM reaction.[7] The hydroxydiene **19** could be prepared from the aldehyde **20**, which in turn could be obtained from the acetophenone **21** via the Claisen rearrangement of the cinnamyl alcohol **22**.

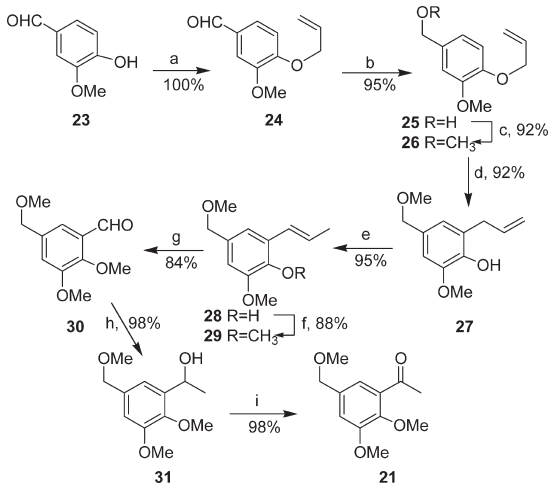
Because synthesis of 2,3-dimethoxy-5-(methoxymethyl)acetophenone **21** is not reported in the literature, attention was first focused on the synthesis of the acetophenone **21**. Presence of two-ortho oriented oxygen substituents




*Scheme 1.*

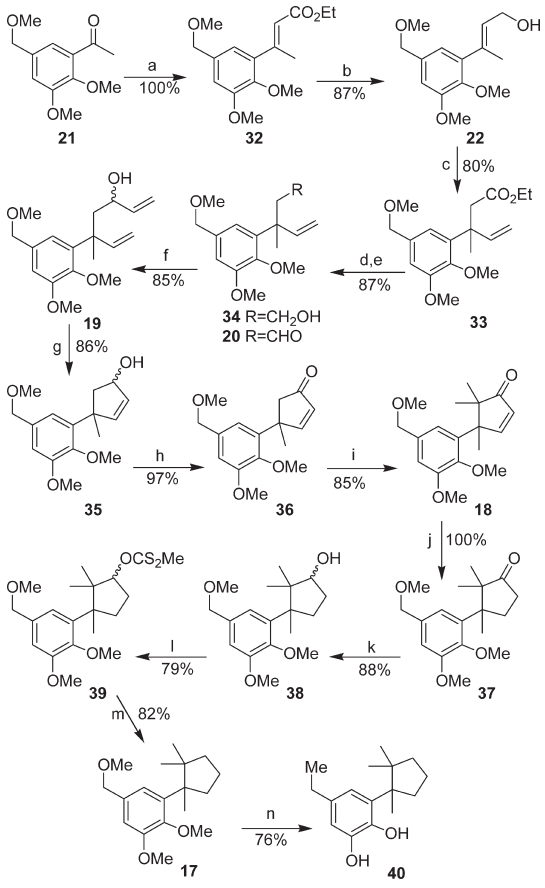
prompted us to choose vanillin **23** as the appropriate starting material. An aromatic Claisen rearrangement was contemplated for the introduction of the side chain at the C-5 position of vanillin, as the aldehyde group could easily be converted into a methoxymethyl group (Scheme 2). Thus, reaction of vanillin **23** with allyl bromide and potassium carbonate in refluxing acetone furnished the allyl ether **24** in quantitative yield. Reduction of the aldehyde group in **24** with sodium borohydride in methanol gave the benzyl alcohol **25**, which on treatment with sodium hydride and methyl iodide in a mixture of THF and DMF in the presence of tetrabutylammonium iodide (TBAI) generated the methyl ether **26** in 87% yield (for two steps). Claisen rearrangement of the allyl ether **26** by thermal activation to 180°C in a sealed tube furnished the phenol **27** in 92% yield. Methanolic potassium hydroxide–mediated isomerization of the terminal olefin in **27** furnished the phenol **28**, which on treatment with sodium hydroxide and dimethyl sulfate generated the styrene **29** in 83% yield (for two steps). Ozonolysis of the styrene **29** followed by reductive workup with dimethyl sulfide furnished the aldehyde **30** in 84% yield. A two-step protocol was adopted for the conversion of the aldehyde **30** into the acetophenone **21**. Accordingly, reaction of the aldehyde **30** with methylmagnesium iodide in ether at ice temperature followed by oxidation of the resultant benzyl alcohol **31** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride at room temperature, which generated the acetophenone **21** in 96% yield, whose structure was established from its spectral data.

Horner–Wadsworth–Emmons reaction of the acetophenone **21** with triethyl phosphonoacetate and sodium hydride in refluxing THF furnished a ~15:1 *E*:*Z* mixture of the cinnamate **32**, which on regioselective reduction at low temperature (−50°C) with lithium aluminium hydride (LAH) gave an *E,Z*-mixture of the allyl alcohol **22** (Scheme 3). Next, attention was focused on the creation of the first quaternary carbon atom, and Johnson's orthoester variant[8] of the Claisen rearrangement was employed. Thus, thermal activation of the allyl alcohol **22** with triethyl orthoacetate in the presence of a catalytic amount of propionic acid in a sealed tube at 180°C




***Scheme 2.*** (a) $K_2CO_3$, acetone, $CH_2{=}CHCH_2Br$; (b) $NaBH_4$, MeOH; (c) NaH, THF-DMF, TBAI, MeI; (d) 180°C; (e) KOH, MeOH; (f) NaOH, $Me_2SO_4$; (g) $O_3$, MeOH-$CH_2Cl_2$; $Me_2S$; (h) MeMgI, $Et_2O$; (i) PCC, silica gel, $CH_2Cl_2$.

for 48 h generated the $\gamma,\delta$-unsaturated ester **33** in 80% yield. Reduction of the ester **33** with LAH in ether at 0°C furnished the primary alcohol **34**, which on oxidation with PCC and silica gel furnished the aldehyde **20** in 87% yield (for two steps). Grignard reaction of the aldehyde **20** with vinylmagnesium bromide in dry THF at room temperature generated, as expected, a 1:1 epimeric mixture of the hydroxydiene **19** in 85% yield. Treatment of the hydroxydiene **19** with 5 mol% of Grubbs's first-generation catalyst [$PhCH{=}Ru(PCy_3)_2Cl_2$] in anhydrous methylene chloride at room temperature for 1 h furnished a 1:1 diastereomeric mixture of the cyclopentenol **35** in 86% yield, which on oxidation with PCC and anhydrous sodium acetate furnished the cyclopentenone **36** in 97% yield. Presence of the molecular ion peak at $m/z$ 276 ($C_{14}H_{16}O_2$) in the mass spectrum and in the IR spectrum presence of a strong carbonyl absorption band at 1716 $cm^{-1}$ due to cyclopentenone indicated the formation of the enone **36**. In the $^1H$ NMR spectrum, the presence of two typical doublets at $\delta$ 7.77 and 6.10 due to the $\beta$ and $\alpha$ protons, respectively, of a cyclopentenone, two singlets at 4.31 and 3.35 due to methoxymethyl group, an AB quartet at 2.65 and 2.53 due to the diastereotopic methylene adjacent to the ketone, and a singlet at 1.54 ppm due to the tertiary methyl group established the structure of the cyclopentenone **36**. The 16-line $^{13}C$ NMR spectrum with diagnostic quaternary carbon resonance at $\delta$ 208.7 due to the ketone carbon, two methines at 170.5 and 130.8 due to the $\beta$ and $\alpha$-olefinic carbons, respectively, of a cyclopentenone, and a methylene at 50.9 ppm due to the carbon adjacent to the ketone in addition to other resonances confirmed the structure of the cyclopentenone **36**. Reaction of the cyclopentenone **36** with sodium hydride and methyl




***Scheme 3.*** (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (b) LAH, $Et_2O$; (c) $MeC(OEt)_3$, $EtCO_2H$, Δ; (d) LAH, $Et_2O$; (e) PCC, silica gel, $CH_2Cl_2$; (f) $CH_2{=}CH$-MgBr, THF; (g) $PhCH{=}Ru(PCy_3)_2Cl_2$, $CH_2Cl_2$; (h) PCC, NaOAc, $CH_2Cl_2$; (i) NaH, THF, DMF, MeI; (j) $H_2$, 10% Pd-C, EtOH; (k) $NaBH_4$, MeOH; (l) NaH, imidazole, $CS_2$, MeI; (m) n-$Bu_3SnH$, AIBN, $C_6H_6$; (n) MeMgI, xylene.

iodide in dry THF and DMF at room temperature generated the enone **18**, in 85% yield. Hydrogenation of the enone **18** using 10% palladium over carbon as the catalyst at one atmospheric pressure (balloon) of hydrogen in ethanol for 2 h quantitatively furnished the cyclopentanone **37**, whose structure was established from its spectral data. As the cyclopentanone **37** was found to be sensitive to acidic condition (due to the presence of benzylic methoxy group), Barton's radical deoxygenative strategy[9] was adopted for the reductive deoxygenation of the ketone in **37**. Thus, reaction of the cyclopentanone **37** with sodium borohydride furnished a ∼2:1 diastereomeric mixture of the alcohol **38**. Treatment of the alcohol **38** with sodium hydride and imidazole in THF followed by reaction of the resultant alkoxide with

carbon disulfide and methyl iodide generated the dithiocarbonate **39**. Reaction of the dithiocarbonate **39** with tri-n-butyltin hydride and a catalytic amount of azobisisobutyronitrile (AIBN) in refluxing benzene furnished 12-methoxyherbertenediol dimethyl ether **17**, whose structure was established from its NMR spectral data. Because the benzylic methoxy group was found to be sensitive to acidic conditions, a Grignard reagent–mediated demethylation of the aromatic methoxy groups was explored. However, treatment of the trimethyl ether **17** with an excess of methylmagnesium iodide in refluxing xylene furnished 12-homoherbertenediol **40** in 76% yield, whose structure was established from its spectral data, in particular the presence of a quartet at $\delta$ 2.52 and a triplet at 1.18 ppm.

In conclusion, we have accomplished the first total synthesis of ($\pm$)-12-methoxyherbertenediol dimethyl ether **17** and 12-homoherbertenediol **40**. In the present synthesis, a combination of Claisen rearrangement, RCM, and alkylation reactions were employed for the efficient generation of the requisite cyclopentane containing two vicinal quaternary carbon atoms. The requisite starting material, acetophenone **21**, was prepared efficiently from vanillin in 9 steps with an average yield of 93.5% for each step. The acetophenone **21** was then efficiently converted into the target molecule **17** in 13 steps in 21% overall yield.

## EXPERIMENTAL SECTION

IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. $^1$H (300 MHz) and $^{13}$C (75 MHz) NMR spectra were recorded on a JNM $\lambda$-300 spectrometer. The chemical shifts ($\delta$ ppm) and coupling constants (Hz) are reported in the standard fashion with reference to either internal tetramethylsilane (for $^1$H) or the central line (77.0 ppm) of $CDCl_3$ (for $^{13}$C). In the $^{13}$C NMR spectra, the nature of the carbons (C, CH, $CH_2$ or $CH_3$) was determined by recording DEPT-135 spectra and is given in parentheses. Low-resolution mass spectra were recorded using a Shimadzu QP-5050A GCMS instrument using direct inlet mode. Relative intensities are given in parentheses. High-resolution mass spectra were recorded on a Micromass Q-TOF micromass spectrometer using electron spray ionization mode. Hydrogenation reactions at one atmospheric pressure were carried out using a balloon filled with hydrogen. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product). All small-scale dry reactions were carried out using the standard syringe-septum technique.

### 4-Allyloxy-3-methoxybenzaldehyde (24)

A magnetically stirred suspension of vanillin **23** (2.5 g, 13.3 mmol), anhydrous $K_2CO_3$ (4.59 g, 33.25 mmol), and allyl bromide (2.85 ml,

33.25 mmol) in acetone (5 ml) was refluxed for 5 h. The reaction mixture was cooled to rt, and the solvent was evaporated under vacuum. Water (8 ml) was added to the residue and extracted with ether (3 × 6 ml). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:4) as eluent furnished the allyl ether **24** (3.25 g, 100%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 2731, 1683, 1650, 1586, 1508, 1268. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 9.80 (1H, s), 7.40–7.30 (2H, m), 6.91 (1H, d, *J* 8.7 Hz), 6.06 (1H, ddt, *J* 17.4, 11.7 and 5.1 Hz), 5.43 (1H, dq, *J* 17.4 and 1.5 Hz), 5.32 (1H, dq, *J* 11.7 and 1.5 Hz), 4.66 (2H, dt, *J* 5.4 and 1.5 Hz), 3.92 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 189.8 (CH, CHO), 153.4 (C), 150.0 (C), 132.4 (CH), 130.3 (C), 126.2 (CH), 118.4 ($CH_2$), 111.8 ($CH_2$), 109.3 (CH), 69.5 ($CH_2$), 55.7 ($CH_3$). Mass: $m/z$ 192 ($M^+$, 89%), 151 (91), 149 (12), 109 (13), 105 (11), 95 (100). HRMS: $m/z$ calcd. for $C_{11}H_{12}O_3Na$ (M + Na): 215.0684. Found: 215.0681.

### 4-Allyloxy-3-methoxybenzyl alcohol (25)

To a magnetically stirred solution of the aldehyde (2 g, 10.4 mmol) in anhydrous methanol (3 ml) at 0°C, $NaBH_4$ (117 mg, 3.13 mmol) was added in portions and stirred for 5 min. The solvent was then removed under vacuum at rt. Water (5 ml) was added to the residue and extracted with ether (3 × 5 ml). Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:3) as eluent furnished the alcohol **25** (2.13 g, 95%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 3253, 1591, 1514, 1139, 926, 853, 806. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.83 (1H, s), 6.75 (2H, s), 6.03 (1H, ddt, *J* 17.4, 10.5, 5.4 Hz), 5.37 (1H, dq, *J* 17.4 and 1.5 Hz), 5.24 (1H, d, *J* 10.5 and 1.5 Hz), 4.53 (2H, d, *J* 5.4 Hz), 4.50 (2H, s), 3.82 (3H, s), 2.17 (1H, brs). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 149.7 (C), 147.5 (C), 134.2 (C), 133.5 (CH), 119.2 (CH), 117.7 ($CH_2$), 113.6 (CH), 111.0 (CH), 69.9 ($CH_2$), 64.9 ($CH_2$), 55.7 ($CH_3$). Mass: $m/z$ 194 ($M^+$, 68%), 153 (100), 121 (42), 105 (10), 97 (77), 95 (18), 94 (43). HRMS: $m/z$ calcd. for $C_{11}H_{14}O_3Na$ (M + Na): 217.0837. Found: 217.0835.

### Allyl 2-Methoxy-4-(methoxymethyl)phenyl Ether (26)

A suspension of sodium hydride (210 mg, 60% dispersion in oil, 5.26 mmol) in hexanes (2 ml) under nitrogen atmosphere was magnetically stirred for 10 min, and the solvent was syringed out. The oil-free sodium hydride was then suspended in dry THF (2 ml). Anhydrous DMF (0.5 ml), methyl iodide (0.38 ml. 6.18 mmol), tetra n-butylammonium iodide (0.05 g), and the alcohol **25** (1 g, 5.15 mmol) in THF (3 ml) were added sequentially. The reaction mixture was magnetically stirred for 12 h at rt. It was

then quenched with water (5 ml) and extracted with ether (3 × 5 ml). The combined ether extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica-gel column using methylene chloride–hexane (1:9) as eluent furnished the product **26** (986 mg, 92%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 1592, 1514, 1262, 926, 854, 805. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.84 (1H, d, *J* 1.2 Hz), 6.79 (1H, d, *J* 7.8 Hz), 6.75 (1H, dd, *J* 7.8 and 1.2 Hz), 6.05 (1H, ddt, *J* 17.1, 10.2 and 5.4 Hz), 5.38 (1H, dq, *J* 17.1 and 1.5 Hz), 5.25 (1H, dq, *J* 10.2 and 1.5 Hz), 4.56 (2H, dt, *J* 5.4 and 1.5 Hz), 4.34 (2H, s), 3.87 (3H, s), 3.33 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 149.7 (C), 147.7 (C), 133.6 (CH), 131.2 (C), 120.1 (CH), 117.7 ($CH_2$), 113.4 (CH), 111.5 (CH), 74.5 ($CH_2$), 69.9 ($CH_2$), 57.7 ($CH_3$), 55.7 ($CH_3$). HRMS: $m/z$ calcd. for $C_{12}H_{16}O_3Na$ (M + Na): 231.0993. Found: 231.0993.

### 2-Allyl-6-methoxy-4-methoxymethylphenol (27)

Allyl ether **26** (750 mg, 3.61 mmol) was heated at 180°C in a sealed tube for 24 h. It was then cooled to rt. Purification of the residue on a silica-gel column using ethyl acetate–hexane (3:17) as eluent furnished the phenol **27** (690 mg, 92%). IR (neat): $\nu_{max}/cm^{-1}$ 3414, 1638, 1605, 1498, 1077, 911. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.71 (1H, s), 6.64 (1H, s) 5.95 (1H, ddt, *J* 17.1, 9.9 and 6.3 Hz), 5.64 (1H, s), 5.05 (1H, dd, *J* 17.1 and 1.2 Hz), 5.01 (1H, dd, *J* 9.9 and 1.2 Hz), 4.31 (2H, s), 3.88 (3H, s), 3.37 (1H, d, *J* 6.6 Hz), 3.32 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 146.3 (C), 143.0 (C), 136.6 (CH), 129.2 (C), 125.4 (C), 122.0 (CH), 115.6 ($CH_2$), 108.2 (CH), 74.8 ($CH_2$), 57.6 ($CH_3$), 55.9 ($CH_3$), 33.9 ($CH_2$). HRMS: $m/z$ calcd. for $C_{11}H_{13}O_2$ (M-OMe): 177.0917. Found: 177.0912.

### 2-(Propen-1-yl)-6-methoxy-4-methoxymethylphenol (28)

A solution of the phenol **27** (300 mg, 1.44 mmol) in saturated methanolic KOH (5 ml) was refluxed for 8 h. The reaction mixture was then cooled to rt, acidified with 3 *N* HCl, and extracted with ether (3 × 4 ml). Evaporation of the solvent and purification of the residue furnished the isomerized product **28** (286 mg, 95%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 3413, 1597, 1079, 970. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.88 (1H, s), 6.67 (1H, s), 6.62 (1H, d, *J* 15.9 Hz), 6.24 (1H, dq, *J* 15.9 and 6.3 Hz), 5.83 (1H, s), 4.32 (2H, s), 3.86 (3H, s), 3.32 (3H, s), 1.89 (2H, d, *J* 6.3 Hz). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 146.6 (C), 142.1 (C), 128.9 (C), 126.3 (CH), 125.3 (CH), 123.7 (C), 118.4 (CH), 108.1 (CH), 74.8 ($CH_2$), 57.5 ($CH_3$), 55.8 ($CH_3$), 18.9 ($CH_3$). HRMS: $m/z$ calcd. for $C_{11}H_{13}O_2$ (M-OMe): 177.0912. Found: 177.0917.

### 1,2-Dimethoxy-5-methoxymethyl-3-(1-propenyl)benzene (29)

To a cold (0°C), magnetically stirred solution of the phenol **28** (256 mg, 1.23 mmol) in 3 M aqueous NaOH (3 ml), dimethyl sulfate (0.17 ml, 2.46 mmol) [washed with cold water and cold saturated aq. $NaHCO_3$] was added, and the reaction mixture was gently refluxed for 3 h. It was cooled to rt and extracted with hexane (2 × 3 ml). The hexane layer was washed with 40% aqueous NaOH solution (6 ml) and brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica-gel column using hexane as eluent furnished the product **29** (240 mg, 88%). IR (neat): $\nu_{max}/cm^{-1}$ 1580, 1147, 1101. $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.94 (1H, s), 6.73 (1H, s), 6.67 (1H, dd, *J* 15.6 and 1.5 Hz), 6.22 (1H, dq, *J* 15.6 and 6.6 Hz), 4.35 (2H, s), 3.86 (3H, s), 3.77 (3H, s), 3.36 (3H, s), 1.91 (3H, dd, *J* 6.6 and 1.5 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 153.0 (C), 145.6 (C), 133.7 (C), 131.6 (C), 126.8 (CH), 125.4 (CH), 117.2 (CH), 109.9 (CH), 74.7 ($CH_2$), 60.6 ($CH_3$), 57.9 ($CH_3$), 55.7 ($CH_3$), 19.0 ($CH_3$). HRMS: $m/z$ calcd. for $C_{12}H_{15}O_2$ (M-OMe): 191.1068. Found: 191.1070.

### 2,3-Dimethoxy-5-methoxymethylbenzaldehyde (30)

Precooled dry ozone gas was passed through a cold (−70°C) suspension of the olefin **29** (2.2 g, 9.91 mmol) and $NaHCO_3$ (50 mg) in 1:4 MeOH-$CH_2Cl_2$ (30 ml) for 25 min. Excess ozone was flushed off with oxygen. Evaporation of the solvent under vacuum and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:4) as eluent furnished the aldehyde **30** (1.75 g, 84%). IR (neat): $\nu_{max}/cm^{-1}$ 2753, 1687, 1606, 1586, 1147, 998. $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 10.38 (1H, s), 7.29 (1H, s), 7.15 (1H, s), 4.40 (2H, s), 3.97 (3H, s), 3.93 (3H, s), 3.37 (3H, s). $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 189.3 (CH), 153.2 (C), 152.2 (C), 134.4 (C), 129.3 (C), 118.0 (CH), 116.9 (CH), 73.9 ($CH_2$), 62.1 ($CH_3$), 58.1 ($CH_3$), 56.0 ($CH_3$). HRMS: $m/z$ calcd. for $C_{11}H_{15}O_4$ (M + H): 211.0966. Found: 211.0961.

### 1-(2,3-Dimethoxy-5-methoxymethylphenyl)ethanol (31)

To a cold (0°C), magnetically stirred solution of MeMgI [freshly prepared from Mg (316 mg, 13 mmol) and MeI (1.01 ml, 16.2 mmol) in dry ether (4 ml)], a solution of the aldehyde **30** (1.35 g, 6.5 mmol) in dry ether (4 ml) was added over a period of 10 min and stirred at rt for 30 min. The reaction mixture was poured into ice-cold aqueous $NH_4Cl$ solution (10 ml) and extracted with ether (3 × 5 ml). The ether extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent furnished the alcohol **31**

(1.46 g, 98%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 3429, 1591, 1061. $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.89 (1H, s), 6.81 (1H, s), 5.08 (1H, q, $J$ 6.6 Hz), 4.36 (2H, s), 3.87 (3H, s), 3.85 (3H, s), 3.37 (3H, s), 2.45 (1H, brs), 1.46 (3H, d, $J$ 6.6 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 152.5 (C), 145.5 (C), 138.9 (C), 134.2 (C), 117.3 (C), 110.7 (CH), 74.6 ($CH_2$), 65.9 (CH), 60.7 ($CH_3$), 58.1 ($CH_3$), 55.7 ($CH_3$), 24.2 ($CH_3$). HRMS: $m/z$ calcd. for $C_{12}H_{18}O_4Na$ (M + Na): 249.1098. Found: 249.1115.



### 2,3-Dimethoxy-5-methoxymethylacetophenone (21)

To a magnetically stirred suspension of PCC (3.55 g, 16.5 mmol) and silica gel (3.5 g) in dry $CH_2Cl_2$ (3.5 ml), a solution of the alcohol **31** (1.48 g, 6.61 mmol) in dry $CH_2Cl_2$ (1 ml) was added and stirred vigorously for 2 h at rt. The reaction mixture was then filtered through a small silica-gel column, and the column was eluted with excess $CH_2Cl_2$. Evaporation of the solvent furnished the acetophenone **21** (1.46 g, 98%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 1680, 1605, 1583, 1060. $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 7.07 (1H, s), 7.01 (1H, s), 4.32 (2H, s), 3.85 (3H, s), 3.84 (3H, s), 3.31 (3H, s), 2.55 (3H, s). $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 199.0 (C), 153.0 (C), 148.0 (C), 134.0 (C), 132.9 (C), 119.7 (CH), 114.7 (CH), 73.8 ($CH_2$), 60.9 ($CH_3$), 57.8 ($CH_3$), 55.8 ($CH_3$), 31.0 ($CH_3$). Mass: $m/z$ 224 ($M^+$, 99%), 209 (100), 193 (72), 179 (18), 161 (37). HRMS: $m/z$ calcd. for $C_{12}H_{16}O_4Na$ (M + Na): 247.0942. Found: 247.0936.

### Ethyl 3-(2,3-Dimethoxy-5-methoxymethylphenyl)but-2-enoate (32)

A suspension of sodium hydride (313 mg, 60% dispersion in oil, 7.81 mmol) in hexanes under a nitrogen atmosphere was magnetically stirred for 10 min, and the solvent was syringed out. The oil-free NaH was then suspended in dry THF (3 ml) and cooled in an ice bath. Triethyl phosphonoacetate (1.77 ml, 8.92 mmol) was added dropwise, and the reaction mixture was stirred for 30 min at rt. A solution of the acetophenone **21** (500 mg, 2.23 mmol) in dry THF (2 ml) was added dropwise to the reaction mixture and stirred for 8 h at rt. The reaction was then quenched by careful addition of saturated aqueous $NH_4Cl$ solution and extracted with ether (3 × 3 ml). The combined ether extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate–hexane (1:9) as eluent furnished predominantly *E*-isomer of the cinnamate **32** (656 mg, 100%). IR (neat): $\nu_{max}/cm^{-1}$ 1718, 1637, 1584, 848. $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.86 (1H, s), 6.66 (1H, s), 5.86 (1H, q, $J$ 1.2 Hz), 4.35 (2H, s), 4.18 (2H, q, $J$ 7.2 Hz), 3.88 (3H, s), 3.76 (3H, s), 3.37 (3H, s), 2.49 (3H, d, $J$ 1.2 Hz), 1.31 (3H, t, $J$ 7.2 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 166.2 (C), 155.9 (C), 152.9 (C), 145.6 (C),

138.0 (C), 134.0 (C), 119.8 (CH), 119.4 (CH), 111.6 (CH), 74.3 ($CH_2$), 60.9 ($CH_3$), 59.5 ($CH_2$), 58.1 ($CH_3$), 55.8 ($CH_3$), 20.1 ($CH_3$), 14.5 ($CH_3$). Mass: $m/z$ 294 ($M^+$, 20%), 264 (16), 263 (100), 235 (81), 217 (16), 203 (27), 189 (11), 175 (31). HRMS: $m/z$ calcd. for $C_{16}H_{22}O_5Na$ (M + Na): 317.1365. Found: 317.1366.

### *E* 3-(2,3-Dimethoxy-5-methoxymethylphenyl)but-2-enol (22)

To a cold (−50°C), magnetically stirred solution of the cinnamate **32** (800 mg, 2.72 mmol) in dry ether (6 ml), LAH (100 mg, 2.72 mmol) was added and stirred for 1 h. Ethyl acetate (0.5 ml) was added to the reaction mixture to consume the excess LAH. The reaction mixture was then quenched with water (10 ml) and extracted with ether (3 × 5 ml). The combined ether extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:3) as eluent furnished the alcohol **22** (600 mg, 87%). IR (neat): $\nu_{max}/cm^{-1}$ 3426, 1653, 1584, 1008. $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.81 and 6.66 (2H, 2 × d, $J$ 2.1 Hz), 5.67 (1H, t, $J$ 6.9 Hz), 4.35 (2H, s), 4.29 (2H, d, $J$ 6.9 Hz), 3.87 (3H, s), 3.75 (3H, s), 3.37 (3H, s), 2.03 (3H, s). $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 152.7 (C), 145.8 (C), 138.7 (C), 137.5 (C), 133.8 (C), 128.7 (CH), 120.8 (CH), 110.7 (CH), 74.5 ($CH_2$), 60.6 ($CH_3$), 59.5 ($CH_2$), 58.1 ($CH_3$), 55.8 ($CH_3$), 17.6 ($CH_3$). Mass: $m/z$ 252 ($M^+$, 63%), 221 (33), 205 (71), 191 (66), 189 (100), 177 (71), 185 (66), 161 (33), 151 (31). HRMS: $m/z$ calcd. for $C_{14}H_{20}O_4Na$ (M + Na): 275.1259. Found: 275.1255.

### Ethyl 3-(2,3-Dimethoxy-5-methoxymethylphenyl)-3-methylpent-4-enoate (33)

A solution of the allyl alcohol **22** (670 mg, 2.38 mmol), triethyl orthoacetate (2.5 ml, 11.9 mmol), and propionic acid (10 μl) was placed in a sealed tube and heated to 180°C for 48 h in an oil bath. The reaction mixture was cooled to rt; diluted with ether (5 ml); washed with 3*N* HCl (5 ml), saturated aqueous $NaHCO_3$ (5 ml), and brine; and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:20) as eluent furnished the pentenoate **33** (676 mg, 80%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 1733, 1584, 1099, 914, 848. $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.81 (1H, d, $J$ 1.8 Hz), 6.76 (1H, d, $J$ 1.8 Hz), 6.28 (1H, dd, $J$ 17.4 and 10.8 Hz), 5.04 (1H, d, $J$ 10.8 Hz), 4.97 (1H, d, $J$ 17.4 Hz), 4.34 (2H, s), 3.93 (2H, q, $J$ 6.9 Hz), 3.85 (3H, s). 3.80 (3H, s), 3.35 (3H, s), 3.07 (1H, d, $J$ 14.1 Hz), 2.83 (1H, d, $J$ 14.1 Hz), 1.55 (3H, s), 1.06 (3H, t, $J$ 6.9 Hz). $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 171.3 (C), 153.0 (C), 147.3 (C), 146.5, (CH), 138.6 (C), 132.5 (C), 119.2 (CH),

111.3 ($CH_2$), 110.7 (CH), 74.8 ($CH_2$), 60.0 ($CH_3$), 59.5 ($CH_2$), 57.9 ($CH_3$), 55.6 ($CH_3$), 44.1 ($CH_2$), 42.8 (C), 25.6 ($CH_3$), 14.1 ($CH_3$). Mass: $m/z$ 322 ($M^+$, 38%), 280 (20), 235 (29), 219 (24), 204 (45), 203 (100), 202 (75), 189 (72), 177 (52). HRMS: $m/z$ calcd. for $C_{18}H_{26}O_5Na$ (M + Na): 345.1678. Found: 345.1689.

### 3-(2,3-Dimethoxy-5-methoxymethylphenyl)-3-methylpent-4-en-1-ol (34)

To a cold (0°C), magnetically stirred solution of the pentenoate **33** (560 mg, 1.88 mmol) in dry ether (3 ml), LAH (70 mg, 1.88 mmol) was added. The reaction mixture was stirred at the same temperature for 30 min. Ethyl acetate (0.2 ml) was added to the reaction mixture to consume the excess LAH. The reaction mixture was then quenched with water (10 ml) and extracted with ether (3 × 4 ml). The combined ether extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:3) as eluent furnished the alcohol **34** (480 mg, 99%). IR (neat): $\nu_{max}/cm^{-1}$ 3421, 1583, 1007. $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.79 (1H, s), 6.73 (1H, s), 6.17 (1H, dd, $J$ 17.4 and 10.8 Hz), 5.02 (1H, d, $J$ 10.8 Hz), 4.97 (1H, d, $J$ 17.4 Hz), 4.33 (2H, s), 3.84 (3H, s), 3.77 (3H, s), 3.60–3.30 (2H, m), 3.36 (3H, s), 2.45–2.30 (1H, m), 2.20–1.95 (2H, m), 1.44 (3H, s). $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 153.2 (C), 147.7 (CH), 147.5 (C), 139.4 (C), 132.7 (C), 119.1 (CH), 110.8 ($CH_2$), 110.6 (CH), 74.9 ($CH_2$), 60.0 ($CH_2$), 58.0 ($CH_3$), 55.6 ($CH_3$), 43.0 (C), 42.1 ($CH_2$), 25.9 ($CH_3$). Mass: $m/z$ 280 ($M^+$, 46%), 254 (15), 235 (18), 217 (21), 205 (27), 204 (45), 203 (100), 191 (41), 189 (45), 175 (26). HRMS: $m/z$ calcd. for $C_{16}H_{24}O_4Na$ (M + Na): 303.1572. Found: 303.1574.

### 3-(2,3-Dimethoxy-5-methoxymethylphenyl)-3-methylpent-4-enal (20)

To a magnetically stirred suspension of PCC (753 mg, 3.42 mmol) and anhydrous NaOAc (284 mg, 3.42 mmol) in anhydrous $CH_2Cl_2$ (3 ml), a solution of the alcohol **34** (480 mg, 1.71 mmol) in $CH_2Cl_2$ (1 ml) was added and stirred at rt for 4 h. The reaction mixture was then filtered through a small silica-gel column, and the column was eluted with excess $CH_2Cl_2$. Evaporation of the solvent furnished the aldehyde **20** (425 mg, 89%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 2735, 1063, 1006, 916, 850. $^1H$ NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 9.46 (1H, brs), 6.84 (1H, s), 6.77 (1H, s), 6.20 (1H, dd, $J$ 17.4 and 10.5 Hz), 5.12 (1H, d, $J$ 10.5 Hz), 5.02 (1H, d, $J$ 17.4 Hz), 4.35 (2H, s), 3.87 (3H, s), 3.81 (3H, s), 3.38 (3H, s), 3.12 (1H, d, $J$ 15.3 Hz), 2.81 (1H, d, $J$ 15.3 Hz), 1.54 (3H, s). $^{13}C$ NMR (75 MHz, $CDCl_3 + CCl_4$):

$\delta$ 202.4 (CH), 153.3 (C), 147.2 (C), 146.1 (CH), 137.8 (C), 133.0 (C), 118.8 (CH), 112.0 ($CH_2$), 111.0 (CH), 74.7 ($CH_2$), 60.1 ($CH_3$), 58.1 ($CH_3$), 55.7 ($CH_3$), 52.1 ($CH_2$), 42.2 (C), 26.3 ($CH_3$). HRMS: $m/z$ calcd. for $C_{16}H_{22}O_4Na$ (M + Na): 301.1416. Found: 301.1429.

### 5-(2,3-Dimethoxy-5-methoxymethylphenyl)-5-methylhepta-1,6-dien-3-ol (19)

To a cold (0°C), magnetically stirred solution of the aldehyde **20** (340 mg, 1.22 mmol) in THF (4 ml), a solution of vinylmagnesium bromide [prepared from Mg (73 mg, 3.05 mmol) and vinyl bromide (0.26 ml, 3.66 mmol) in THF (6 ml)] was added dropwise and stirred at 0°C for 5 min. The reaction mixture was then quenched with cold saturated aqueous $NH_4Cl$ (10 ml) and extracted with ether (2 × 4 ml). The organic layer was washed with water and brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:4) as eluent furnished a ≈ 1:1 diastereomeric mixture of the alcohol **19** (318 mg, 85%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 3431, 1636, 1584, 916, 848. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.80 (2H, brs), 6.27 (1H, dd, $J$ 17.4 and 10.5 Hz), 5.90–5.70 (1H, m, H-2), 5.70–4.85 (4H, m), 4.34 (2H, s), 4.04 and 3.95 (1H, 2 × brs), 3.84 (3H, s), 3.80 and 3.77 (3H, s), 3.36 (3H, s), 2.40–2.20 (1H, m), 2.05–1.90 (1H, m), 1.75 (1H, br s), 1.54 and 1.49 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 153.1 (C), 148.4 and 147.9 (CH), 147.5 (C), 142.2 and 142.1 (CH), 139.4 (C), 132.8 and 132.5 (C), 119.4 and 119.1 (CH), 113.2 and 112.9 ($CH_2$), 110.8 ($CH_2$), 110.7 (CH), 74.81 and 74.75 ($CH_2$), 70.5 (CH), 60.0 ($CH_3$), 57.9 ($CH_3$), 55.6 ($CH_3$), 46.7 and 46.2 ($CH_2$), 43.6 and 43.4 (C), 26.3 ($CH_3$). Mass: $m/z$ 306 ($M^+$, 7%), 236 (61), 203 (57), 191 (84), 189 (42), 173 (43), 151 (100). HRMS: $m/z$ calcd. for $C_{18}H_{26}O_4Na$ (M + Na): 329.1729. Found: 329.1717.

### 4-(2,3-Dimethoxy-5-methoxymethylphenyl)-4-methylcyclopent-2-en-1-ol (35)

To a magnetically stirred solution of a 1:1 diastereomeric mixture of the hydroxydiene **19** (230 mg, 0.75 mmol) in anhydrous $CH_2Cl_2$ (50 ml), a solution of Grubbs' first generation catalyst (31 mg, 5 mol%) in anhydrous $CH_2Cl_2$ (20 ml) was added. The reaction mixture was stirred at rt for 1 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:10–1:5) as eluent furnished a 1:1 diastereomeric mixture of the cyclopentenol **35** (180 mg, 86%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 3407, 1584, 1143, 1060, 847. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.79 and 6.77 (1H, s), 6.75 and 6.66 (1H, s), 6.22 (d, $J$ 6 Hz) and 6.12 (d, $J$ 5.1 Hz) [1H], 5.90–5.80 (1H, m),

4.90–4.75 (1H, m), 4.34 and 4.32 (2H, s), 3.86 (3H, s) and 3.84 and 3.82 (3H, s), 3.38 and 3.37 (3H, s), 2.65–2.50 (1H, m), 2.05–1.90 (2H, m), 1.53 and 1.41 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 153.2 (C), 147.0 and 146.8 (C), 142.8 and 142.5 (CH), 141.8 and 141.7 (C), 132.9 and 132.6 (C), 131.6 and 131.5 (CH), 118.0 and 117.9 (CH), 110.34 and 110.29 (CH), 77.3 and 77.1 (CH), 74.8 ($CH_2$), 60.4 and 60.2 ($CH_3$), 58.0 and 58.0 ($CH_3$), 55.6 ($CH_3$), 51.8 and 50.5 (C), 50.3 and 49.3 ($CH_2$), 30.4 and 29.0 ($CH_3$). Mass: $m/z$ 308 ($M^+$, 16%), 306 (9), 222 (7), 205 (27), 191 (22), 175 (16). HRMS: $m/z$ calcd. for $C_{16}H_{22}O_4Na$ (M + Na): 301.1416. Found: 301.1414.



### 4-(2,3-Dimethoxy-5-methoxymethylphenyl)-4-methylcyclopent-2-enone (36)

To a magnetically stirred suspension of PCC (350 mg, 1.62 mmol) and anhydrous NaOAc (161 mg, 1.94 mmol) in anhydrous $CH_2Cl_2$ (3 ml), the allyl alcohol **35** (180 mg, 0.647 mmol) in $CH_2Cl_2$ (1 ml) was added and stirred at rt for 6 h. The reaction mixture was then filtered through a small silica-gel column, and the column was eluted with excess $CH_2Cl_2$. Evaporation of the solvent furnished the enone **36** (175 mg, 97%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 1716, 1585, 1056, 1006. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 7.77 (1H, d, $J$ 5.4 Hz), 6.78 (1H, s), 6.66 (1H, s), 6.10 (1H, d, $J$ 5.4 Hz), 4.31 (2H, s), 3.83 (3H, s), 3.76 (3H, s), 3.35 (3H, s), 2.65 and 2.53 (2H, 2 × d, $J$ 18.6 Hz), 1.54 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 208.7 (C), 170.4 (CH), 153.2 (C), 146.9 (C), 138.2 (C), 133.2 (C), 130.8 (CH), 117.9 (CH), 111.0 (CH), 74.6 ($CH_2$), 60.3 ($CH_3$), 58.2 ($CH_3$), 55.7 ($CH_3$), 50.9 ($CH_2$), 47.3 (C), 28.3 ($CH_3$). Mass: $m/z$ 276 ($M^+$, 100%), 245 (40), 229 (39). HRMS: $m/z$ calcd. for $C_{16}H_{20}O_4Na$ (M + Na): 299.1259. Found: 299.1247.

### 4-(2,3-Dimethoxy-5-methoxymethylphenyl)-4,5,5-trimethylcyclopent-2-enone (18)

A suspension of sodium hydride (149 mg, 60% dispersion in oil, 3.72 mmol) in hexanes (1 ml) under nitrogen atmosphere was magnetically stirred for 10 min, and the solvent was syringed out. The oil-free sodium hydride was then suspended in dry THF (1.0 ml). Anhydrous DMF (0.1 ml), methyl iodide (0.39 ml, 6.2 mmol), and the enone **36** (170 mg, 0.62 mmol) were added sequentially and magnetically stirred for 12 h at rt. It was then quenched with water (4 ml) and extracted with ether (3 × 4 ml). The combined ether extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:5) as eluent furnished the enone **18** (160 mg, 85%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 1709, 1006, 840. $^1$H NMR (300 MHz,

$CDCl_3 + CCl_4$): $\delta$ 7.89 (1H, d, $J$ 5.4 Hz), 6.79 (1H, s), 6.59 (1H, s), 6.06 (1H, d, $J$ 5.4 Hz), 4.34 (2H, s), 3.87 (3H, s), 3.83 (3H, s), 3.36 (3H, s), 1.48 (3H, s), 1.23 (3H, s), 0.64 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 213.5 (C), 170.4 (CH), 153.1 (C), 147.1 (C), 136.3 (C), 133.2 (C), 119.5 (CH), 110.6 (CH), 74.6 ($CH_2$), 60.2 ($CH_3$), 58.0 ($CH_3$), 55.6 ($CH_3$), 54.7 (C), 50.8 (C), 26.2 ($CH_3$), 19.9 ($CH_3$). Mass: $m/z$ 304 ($M^+$, 52%), 289 (100), 259 (100), 273 (5), 229 (8). HRMS: $m/z$ calcd. for $C_{18}H_{24}O_4Na$ (M + Na): 327.1572. Found: 327.1583.



### 4-(2,3-Dimethoxy-5-methoxymethylphenyl)-2,3,3-trimethylcyclopentanone (37)

Activated 10% Pd-C (100 mg) was added to a suspension of the enone **18** (140 mg, 0.46 mmol) and $Na_2CO_3$ (100 mg) in ethanol (1 ml). The reaction mixture was stirred for 2 h at rt in an atmosphere of hydrogen created by evacuative replacement of air (balloon). The catalyst was then filtered using a small silica-gel column. Evaporation of the solvent furnished the saturated ketone **37** (141 mg, 100%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 1737, 1097, 847. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.88 (1H, s), 6.80 (1H, s), 4.36 (2H, s), 3.87 (3H, s), 3.81 (3H, s), 3.38 (3H, s), 2.71–2.63 (1H, m), 2.50–2.35 (2H, m), 2.25–2.00 (1H, m), 1.35 (3H, s), 1.25 (3H, s), 0.72 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 221.6 (C), 153.1 (C), 147.9 (C), 138.2 (C), 132.6 (C), 119.4 (CH), 110.2 (CH), 74.8 ($CH_2$), 60.0 ($CH_3$), 57.9 ($CH_3$), 55.5 ($CH_3$), 53.3 (C), 49.5 (C), 33.9 ($CH_2$), 31.8 ($CH_2$), 24.3 ($CH_3$), 22.1 ($CH_3$), 20.3 ($CH_3$). Mass: $m/z$ 306 ($M^+$, 46%), 274 (20), 259 (25), 243 (10), 231 (10), 215 (20), 205 (100), 189 (25), 173 (48). HRMS: $m/z$ calcd. for $C_{17}H_{23}O_3$ (M-OMe): 275.1648. Found: 275.1652.

### 3-(2,3-Dimethoxy-5-methoxymethylphenyl)-2,2,3-trimethylcyclopentanol (38)

To an ice-cold magnetically stirred solution of the ketone **37** (110 mg, 0.131 mmol) in dry methanol (1 ml), $NaBH_4$ (10 mg, 2.61 mmol) was added and stirred for 5 min. The solvent was evaporated under reduced pressure. Water (3 ml) followed by 3 N aqueous HCl were added to the reaction mixture (4 ml) and extracted with ether (3 × 3 ml). The combined ether extract was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:19–1:10) as eluent furnished a ≈ 2:1 epimeric mixture of the alcohol **38** (35 mg, 88%) as oil. IR (neat): $\nu_{max}/cm^{-1}$ 3434, 1580, 1060, 1009, 846. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.88 and 6.75 (2H, brs), 4.35 (2H, brs), 3.98 (dd, $J$ 8.4 and 6.9 Hz) and 3.71 (t, $J$ 7.5 Hz) [1H], 3.85 (3H, s), 3.78 (3H, s), 3.36 (3H, s), 2.77–2.67 and 2.45–2.35 (1H, m), 2.26–2.14 (1H, m),

1.85–1.50 (3H, m), 1.48 and 1.33 (3H, s), 1.13 and 1.02 (3H, s), 0.64 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 153.5 and 153.3 (C), 148.0 and 148.2 (C), 140.0 and 139.9 (C), 120.5 and 120.4 (CH), 110.0 and 109.9 (CH), 81.0 and 80.8 (CH), 75.0 ($CH_2$), 60.3 ($CH_3$), 57.9 ($CH_3$), 55.6 ($CH_3$), 51.0 and 50.9 (C), 47.9 and 47.8 (C), 36.8 and 35.0 ($CH_2$), 31.3 and 30.0 ($CH_2$), 25.4 and 25.2 ($CH_3$), 24.3 and 23.0 ($CH_3$), 18.8 and 18.4 ($CH_3$). Mass: $m/z$ 278 ($M^+$, 75%), 263 (55), 231 (100), 215 (17), 201 (35), 191 (24), 172 (68). HRMS: $m/z$ calcd. for $C_{18}H_{28}O_4Na$ (M + Na): 331.1885. Found: 331.1878.



### 1-(2,3-Dimethoxy-5-methoxymethylphenyl)-1,2,2-trimethylcyclopentyl Methyl Dithiocarbonate (39)

To a magnetically stirred suspension of NaH (43 mg, 60% dispersion in oil, 1.07 mmol) in dry THF (1 ml), a solution of the alcohol **38** (33 mg, 0.107 mmol) in dry THF (0.5 ml) was added followed by a catalytic amount of imidazole. The reaction mixture was heated to 60°C for 15 min. It was cooled to rt; $CS_2$ (0.19 ml, 3.21 mmol) was added and refluxed for 15 min. It was recooled to rt; MeI (0.2 ml, 3.21 mmol) was added and refluxed for 4 h. It was then cooled to rt, diluted with water (2 ml), and extracted with ether (3 × 2 ml). The combined organic layer was washed with brine and dried ($Na_2SO_4$). Evaporation of the solvent and rapid purification of the residue on a silica-gel column using $CH_2Cl_2$–hexane (1:10) as eluent furnished the dithiocarbonate **39** (33 mg, 79%) as a yellow oil, which was found to be unstable on standing. IR (neat): $\nu_{max}/cm^{-1}$ 1581, 1236, 1057, 847. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.83 and 6.78 (1H, s), 6.75 (1H, s), 5.51 (dd, $J$ 7.5 and 5.4 Hz) and 5.69 (dd, $J$ 7.8 and 5.4 Hz) [1H], 4.33 (2H, s) 3.84 and 3.85 (3H, s), 3.78 and 3.77 (3H, s), 3.33 and 3.34 (3H, s), 2.67–2.43 (2H, m), 2.53 and 2.50 (3H, s), 2.00–1.80 (2H, m), 1.51 and 1.40 (3H, s), 1.16 and 1.19 (3H, s), 0.73 and 0.78 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 215.3 and 214.9 (C), 153.5 and 148.5 (C), 138.9 and 138.6 (C), 132.4 and 132.3 (C), 120.3 and 120.2 (CH), 110.3 and 110.2 (CH), 93.0 and 92.7 (CH), 75.0 ($CH_2$), 60.3 and 60.2 ($CH_3$), 57.9 ($CH_3$), 55.7 ($CH_3$), 51.2 and 51.0 (C), 49.0 and 48.4 (C), 36.8 and 35.4 ($CH_2$), 28.5 and 26.8 ($CH_2$), 25.1 and 24.9 ($CH_3$), 24.7 and 23.2 ($CH_3$), 20.7 and 19.9 ($CH_3$), 18.9 ($CH_3$).

### 5-Methoxymethyl-3-(1,2,2-trimethylcyclopentyl)catechol Dimethyl Ether (12-Methoxyherbertenediol Dimethyl Ether 17)

A solution of the dithiocarbonate **39** (33 mg, 0.08 mmol), $^n$Bu$_3$SnH (0.05 ml, 0.19 mmol), and a catalytic amount of AIBN (5 mg) in dry benzene (1 ml) was refluxed for 3 h. The reaction mixture was cooled; diluted with ether (2 ml); washed successively with 1% aq $NH_4OH$, water, and brine; and dried

($Na_2SO_4$). Evaporation of the solvent and purification of the residue on a silica-gel column using hexane as eluent furnished 12-methoxyherbertenediol dimethyl ether **17** (20 mg, 82%) as a colorless oil. IR (neat): $\nu_{max}/cm^{-1}$ 1581, 1143, 1009. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.89 (1H, d, $J$ 1.8 Hz), 6.80 (1H, d, $J$ 1.8 Hz), 4.38 (2H, s), 3.86 (3H, s), 3.79 (3H, s), 3.38 (3H, s), 2.70–2.55 (1H, m), 1.90–1.20 (5H, m), 1.37 (3H, s), 1.13 (3H, s), 0.69 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 153.4 (C), 148.6 (C), 140.2 (C), 131.9 (C), 120.7 (CH), 109.8 (CH), 75.2 ($CH_2$), 60.3 ($CH_3$), 57.9 ($CH_3$), 55.7 ($CH_3$), 51.7 (C), 45.2 (C), 41.1 ($CH_2$), 39.2 ($CH_2$), 27.1 ($CH_3$), 25.5 ($CH_3$), 24.3 ($CH_3$), 20.4 ($CH_2$). HRMS: $m/z$ calcd. for $C_{17}H_{25}O_2$ (M-OMe): 261.1848. Found: 261.1852.

### 5-Ethyl-3-(1,2,2-trimethylcyclopentyl)catechol (12-homoherbertenediol 40)

Methylmagnesium iodide in ether (5 ml) was prepared using Mg (50 mg, 2.06 mmol) and $CH_3I$ (0.16 ml, 2.5 mmol). Solvent was evaporated under vacuum. To the solid MeMgI, a solution of the dimethyl ether **17** (7 mg, 0.03 mmol) in dry xylene (2 ml) was added and refluxed for 8 h. It was then cooled to rt, added to a cold saturated aq. $NH_4Cl$ solution (3 ml), and extracted with ether (2 × 2 ml). Evaporation of the solvent and purification of the residue on a silica-gel column using ethyl acetate–hexane (1:20) as eluent furnished 12-homoherbertenediol **40** (5 mg, 76%). IR (neat): $\nu_{max}/cm^{-1}$ 3517, 1597, 951, 854. $^1$H NMR (300 MHz, $CDCl_3 + CCl_4$): $\delta$ 6.70 (1H, d, $J$ 1.8 Hz), 6.58 (1H, d, $J$ 1.8 Hz), 5.36 (1H, brs), 5.04 (1H, brs), 2.70–2.55 (1H, m), 2.52 (2H, q, $J$ 7.5 Hz), 1.85–1.50 (5H, m), 1.42 (3H, s), 1.18 (3H, s), 1.18 (3H, t, $J$ 7.5 Hz), 0.76 (3H, s). $^{13}$C NMR (75 MHz, $CDCl_3 + CCl_4$): $\delta$ 143.4 (C), 141.1 (C), 134.9 (C), 133.4 (C), 120.8 (CH), 112.1 (CH), 51.2 (C), 44.9 (C), 40.9 ($CH_2$), 39.2 ($CH_2$), 28.5 ($CH_2$), 26.8 ($CH_3$), 25.4 ($CH_3$), 22.9 ($CH_3$), 20.3 ($CH_2$), 15.8 ($CH_3$). HRMS: $m/z$ calcd. for $C_{16}H_{24}O_2Na$ (M + Na): 271.1674. Found: 271.1686.



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