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Total synthesis of (±)-herbertenediol

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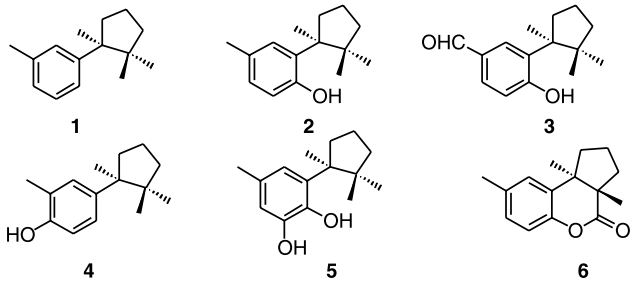
Abstract—A formal total synthesis of the sesquiterpene (±)-herbertenediol and its dimers mastigophorenes A–D has been accomplished, starting from vanillin via 2,3-dimethoxy-5-methylbenzaldehyde. A combination of Claisen rearrangement and ring-closing metathesis reactions were employed for the generation of the two vicinal quaternary carbons on a cyclopentane ring.

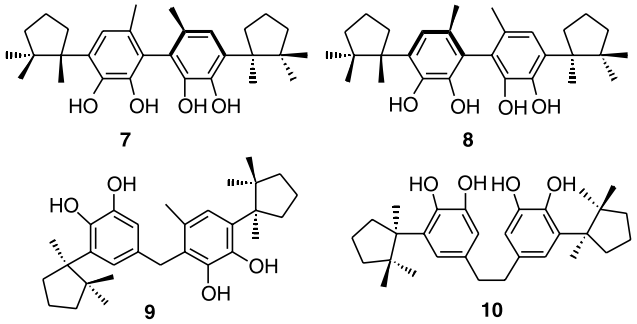
1. Introduction

Liverworts, belonging to the Hepaticae family, are endowed with a rich and wide variety of mono-, sesqui- and diterpenoids and/or lipophilic aromatic compounds. An important endogenous character of the Hepaticae family is that most of the sesquiterpenoids isolated from liverworts are enantiomeric to those isolated from the higher plants.[1] Several compounds obtained from liverworts show a wide spectrum of biological properties such as muscle relaxing activity, antimicrobial, antifungal, 5-lipoxygenase, cyclo-oxygenase, cytotoxic, insect antifeedant, neurotropic sprouting, piscicidal, cathepsin B and L, calmodulin inhibitory and anti-HIV activities. Liverworts from the genus *Herbertus* contain herbertane sesquiterpenoids, which are considered as chemical markers of the genus.[2] The herbertane group is a small group of aromatic sesquiterpenes, isomeric to cuparenes, containing a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane carbon framework incorporating two vicinal quaternary carbon atoms on a cyclopentane ring. The first member of this class of sesquiterpenes, herbertene **1**, was isolated in 1981 by Matsuo and co-workers from the ethyl acetate extract of the liverwort *Herberta adunca* (Dicks) Gray.[3] In 1982, Matsuo and co-workers reported the isolation of three phenolic herbertanes, α-herbertenol **2**, α-formylherbertenol **3** and β-herbertenol **4** along with herbertene **1** and cuparene sesquiterpenes from the same liverwort.[4] Asakawa and co-workers in 1982 reported the isolation of herbertene **1** and the phenolic herbertenes, α-herbertenol **2** and β-herbertenol **4** from *H. aduncus*, *H. sakuraii* and *H. subdetatus*. Isolation of more herbertenoids, herbertenediol **5** and herbertenolide **6** was reported in 1983 by Matsuo and co-workers.[4]



1 **2** **3** **4** **5** **6**

In 1988 and 1991 Asakawa and co-workers reported the isolation of the dimeric herbertanes, mastigophorenes A–D **7**–**10**, dimers of herbertenediol **5**, from the liverwort *Mastigophora diclados* (Mastigophoraceae).[5] The mastigophorenes A–D **7**–**10** are presumably formed by one electron oxidative phenolic coupling of herbertenediol **5**. Subsequently, isolation of a few other phenolic herbertanes have been reported.[2,6]



7 **8** **9** **10**

The phenolic herbertanes[4–7] have been shown to possess interesting biological properties such as growth inhibiting

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activity and antilipid peroxidation activity. Mastigophorenes A–D **7–10** were found to exhibit intriguing neurotropic properties, that is, promote neuronal outgrowth and enhance choline acetyl transferase activity in the primary cultures of fetal rat cerebral hemisphere.

The presence of an interesting carbon framework, a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane, the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring, and the biological properties associated with the phenolic herbertanes and mastigophorenes made them challenging synthetic targets.[8,9] Recently, a large number of reports have appeared on the synthesis of these sesquiterpenes making them a topic of contemporary interest. Herein, we describe the formal synthesis of herbertenediol and mastigophorenes.[10]

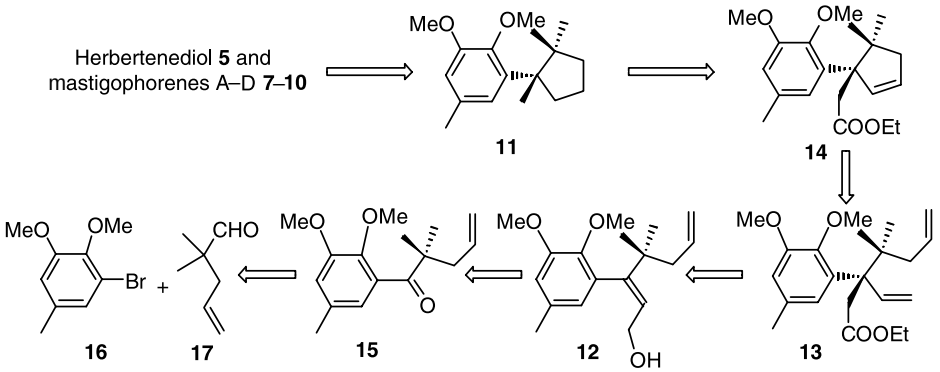
2. Results and discussion

Olefin metathesis[11] is an important reaction in which two olefins undergo bond reorganization leading to redistribution of the alkylidene moieties. With the advent of efficient catalysts, the metathesis reaction has emerged as a powerful tool, in particular the intramolecular version, that is, ring-closing metathesis (RCM), for the formation of C–C bonds in organic synthesis.[12] Recently,[10] we have developed a methodology for the total synthesis of α- and β-herbertenols starting from 2,2-dimethylpent-4-enaldehyde and appropriate aryl bromides employing a combination of orthoester Claisen rearrangement and RCM reactions. Extrapolation of this methodology has been investigated for the formal total synthesis of herbertenediol **5** and mastigophorenes A–D **7–10**. The retrosynthesis is depicted in Scheme 1. Since herbertenediol dimethyl ether **11** has already been transformed into herbertenediol **5** and mastigophorenes A–D **7–10**, it was chosen as the target molecule. It was envisioned that orthoester Claisen rearrangement[13] of the allyl alcohol **12** followed by RCM reaction of the diene **13** would generate cyclopenteneacetate **14**, containing the two vicinal quaternary carbon atoms, which is a higher homologue of herbertenediol **5** and could be transformed into **11** by one carbon degradation. It was thought that the cinnamyl alcohol **12** could be generated from the ketone **15** employing a Wittig reaction based methodology, and the ketone **15** could be obtained from the bromide **16** and the aldehyde **17**.

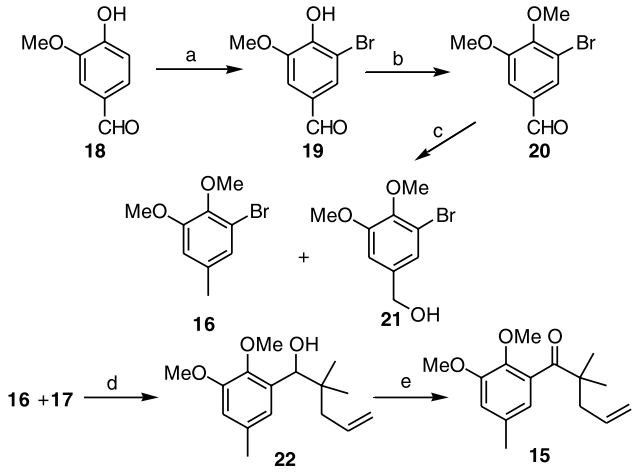
Attention was first focused on the synthesis of the aryl ketone **15** via the bromide **16**,[14] and vanillin **18** containing two oxygen atoms on vicinal carbons was chosen as the suitable starting material, as depicted in Scheme 2. Thus, bromination of vanillin **18** followed by methylation of bromovanillin **19** furnished bromoveratraldehyde **20**.[14] An ionic hydrogenation methodology[15] was explored for the reductive deoxygenation of the aldehyde group in **20**. Reaction of the aldehyde **20** with sodium cyanoborohydride in the presence of boron trifluoride etherate in refluxing THF for 10 h gave a 1:2 mixture of the bromoarene **16** and the benzyl alcohol **21** in 95% yield. Conventional Grignard and transmetallation reactions failed to couple the bromide **16** with the aldehyde **17**. Sonochemically accelerated Barbier reaction of the bromide **16** with the aldehyde **17** and lithium in THF generated the benzyl alcohol **22** in very low yield (16%), which on oxidation with PCC and silica gel in methylene chloride at rt furnished the ketone **15**.

Since the coupling of the bromide **16** with aldehyde **17** was inefficient, an alternative strategy was investigated for the synthesis of the ketone **15** via the aldehyde **23** (Scheme 3). Thus, Clemensen reduction of vanillin **18** with amalgamated zinc generated the phenol **24**, which on etherification with allyl bromide furnished the allyl aryl ether **25**. Claisen rearrangement of the allyl aryl ether **25**, followed by base catalyzed isomerisation of the double bond in the resultant *o*-allylphenol **26** generated the phenol[16] **27**. Etherification of the phenol **27** with sodium hydroxide and dimethyl sulfate, followed by ozonolysis of the double bond in the resultant styrene **28** furnished the aldehyde **23**.[17] Grignard reaction of the aldehyde **23** with isopropylmagnesium bromide in ether for 3 h furnished the benzyl alcohol **29** in 88% yield, which on oxidation with pyridinium chlorochromate (PCC) and silica gel in methylene chloride at rt for 2 h generated the ketone **30**. Reaction of the ketone **30** with sodium hydride and allyl bromide in refluxing THF for 10 h generated a mixture of the *C*-allylated ketone **15** and the allyl enol ether **31**, which on thermal rearrangement at 180 °C in a sealed tube for 30 min gave the ketone **15** in 91% yield. The structure of the ketone **15** was established from its spectral data, in particular the presence of a carbonyl absorption band at 1693 cm^{-1} in the IR spectrum, presence of a singlet at δ 1.10 in ^1H NMR and a two carbon signal at 24.3 ppm in the ^{13}C NMR for the two symmetric tertiary methyl groups in addition to other signals.

Initially for the conversion of the ketone **15** into the ciannamyl alcohol **12**, Wittig reaction followed by



Scheme 1.

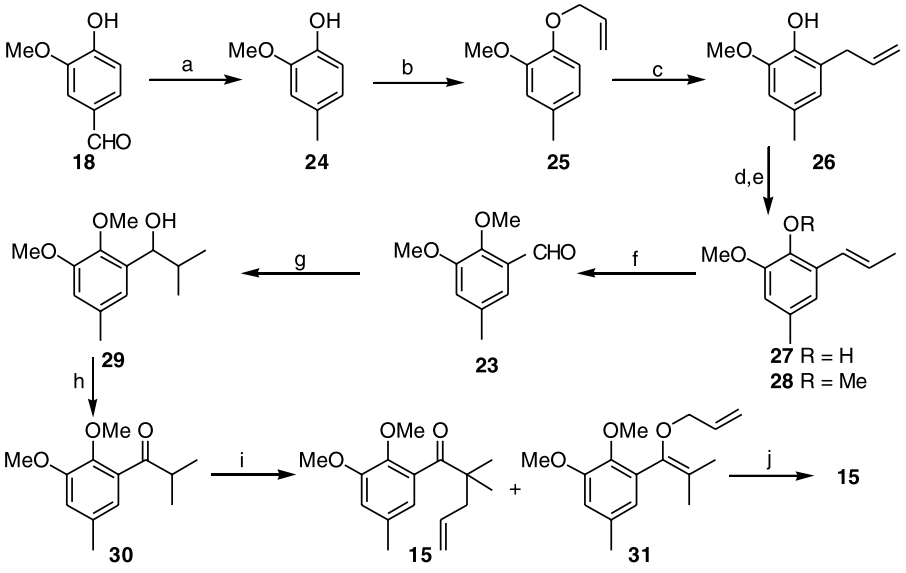


Scheme 2. (a) Br_2, CH_2Cl_2, 0 °C, 30 min, 98%; (b) K_2CO_3, MeI, acetone, reflux, 30 h, 57%; (c) $NaCNBH_3$, $BF_3 \cdot Et_2O$, THF, reflux, 10 h, 95% (**16**:**21** 1:2); (d) Li, THF, 1 h 16%; (e) PCC, silica gel, CH_2Cl_2, rt, 3 h, 90%.

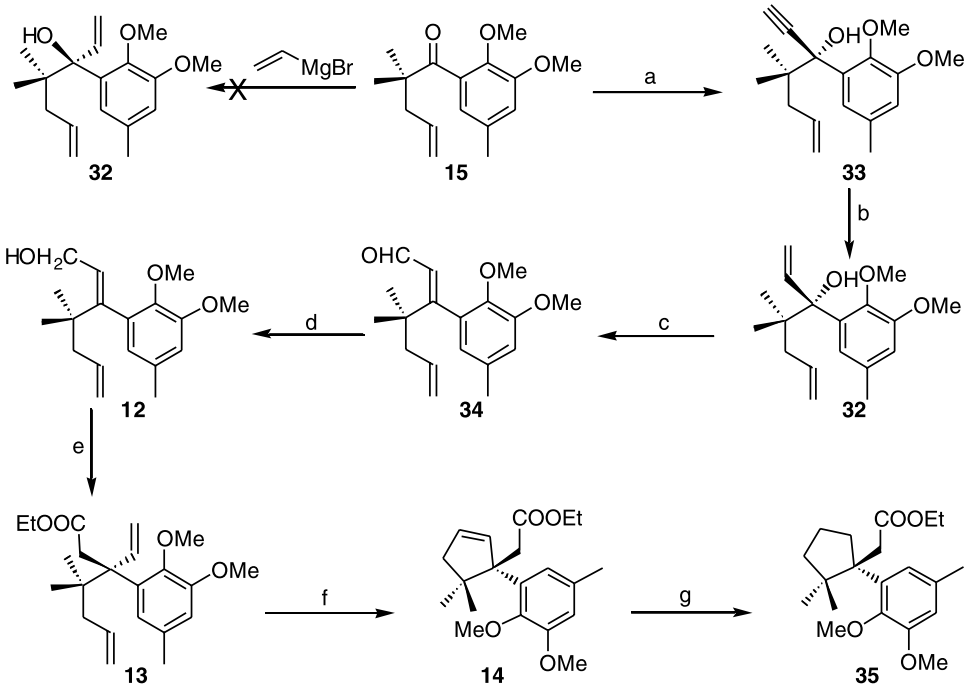
reduction was considered. As in the case of earlier examples,[10] the Wittig reaction and its Horner–Wadsworth–Emmons variant failed, presumably due to steric reasons. Subsequently, a 1,3-transposition methodology[18] was contemplated via addition of a vinyl group followed by rearrangement (Scheme 4). However, reaction of the aryl ketone **15** with vinylmagnesium bromide failed to generate the tertiary alcohol **32**, and resulted in the replacement of one of the aromatic methoxy groups with a vinyl group. Hence, an alternate methodology via the corresponding acetylene was chosen. Thus, reaction of the ketone **15** with lithiumacetylide ethylenediamine complex in dry THF for 2 h furnished the tertiary alcohol **33**, whose structure was established from the spectral data. Presence of an absorption band at 3447 cm^{-1} due to the hydroxy group in the IR spectrum; presence of a singlet at δ 2.55 in the ^1H NMR due to the acetylenic proton, and two quaternary carbons at 86.4 and 81.6, and a methine at 73.5 due to the propargylic alcohol part of the compound in addition to other signals confirmed the structure of the enynol **33**. Controlled hydrogenation of the acetylene group with Lindlar's catalyst in ethanol for 24 h at rt gave the tertiary alcohol **32** in 97% yield. Reaction of the alcohol **32** with PCC and silica gel in methylene chloride at rt for 30 h generated the aldehyde **34** in 85% yield, which on regioselective reduction with sodium borohydirde in methanol at 0 °C for 1.5 h furnished the alcohol **12** in 75% yield.

The orthoester Claisen rearrangement of the allyl alcohol **12** with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube at 180 °C for 48 h furnished the γ,δ-unsaturated ester **13** in 28% yield. The steric crowding experienced in the transition state in generating a quaternary centre in-between the already existing quaternary centre and the tetrasubstituted aryl group is presumably the reason for the low yield in the Claisen rearrangement. Next, the key step in the sequence, RCM reaction of the diene ester **13** was investigated. RCM reaction of the diene **13** with 7 mol% Grubbs' first generation catalyst in methylene chloride furnished the cyclopenteneacetate **14** in 80% yield, whose structure was established from its spectral data. The absence of signals due to the terminal olefinic protons and carbons in the NMR spectra, and the presence of two doublets at δ 6.20 and 5.70 due to the cyclopentene olefinic protons and a high field shifted methyl singlet at 0.51 (typical for the methyl group cis to the aryl group in cuparene and herbertenoids) established the structure of the ester **14**. This was further confirmed by the presence of signals due to four methine and five quaternary sp^2 carbons, and six methyl, three methylene and two quaternary aliphatic carbons in the ^{13}C NMR spectrum of the ester **14**. Hydrogenation of the olefin in **14** with 10% palladium on activated charcoal as the catalyst in ethanol furnished the cyclopentaneacetate **35** in 99% yield.

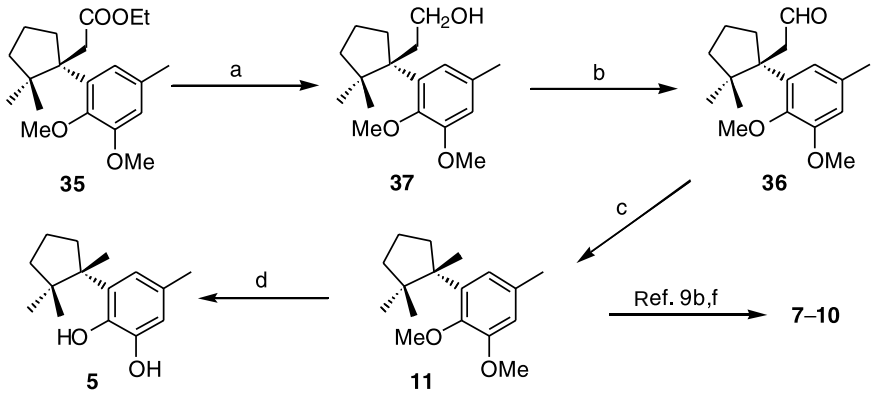
For the conversion of the ester **35** into herbertenol dimethyl ether **11**, degradation of one carbon was required. A three-step protocol via the aldehyde **36** was explored for the



Scheme 3. (a) Zn, concd HCl, EtOH, reflux, 3 h, 80%; (b) K_2CO_3, $CH_2{=}CHCH_2Br$, acetone, reflux, 6 h, 95%; (c) sealed tube, 180 °C, 24 h, 90%; (d) KOH, MeOH, reflux, 10 h, 95%; (e) Me_2SO_4, NaOH, reflux, 1 h, 96%; (f) O_3/O_2, CH_2Cl_2, MeOH, −70 °C; Me_2S, rt, 6 h, 80%; (g) *i*-PrMgBr, Et_2O, 0 °C→rt, 3 h, 88%; (h) PCC, silica gel, CH_2Cl_2, rt, 2 h, 96%; (i) NaH, THF, reflux; $CH_2{=}CHCH_2Br$, 10 h, 99%; (j) sealed tube, 180 °C, 0.5 h, 92%.



Scheme 4. (a) HC≡CLi·$(NH_2CH_2)_2$, THF, 15–20 °C, 2 h, 90%; (b) H_2, Pd–$CaCO_3$, EtOH, 24 h, 97%; (c) PCC, silica gel, CH_2Cl_2, rt, 30 h, 85%; (d) $NaBH_4$, MeOH, 0 °C→rt, 1.5 h, 75%; (e) $CH_3C(OEt)_3$, EtCOOH, 180 °C, 48 h, 28%; (f) $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, rt, 6 h, 80%; (g) H_2 (1 atm), 10% Pd–C, EtOH, 3 h, 99%.



Scheme 5. (a) LAH, Et_2O, 0 °C, 1 h, 98%; (b) PCC, silica gel, CH_2Cl_2, rt, 0.5 h, 89%; (c) $(Ph_3P)_3RhCl$ (20 mol%), C_6H_6, sealed tube, 120–130 °C, 20 h, 77%; (d) BBr_3, CH_2Cl_2, −40 °C→rt, 2 h, 98%.

degradation (Scheme 5). Reduction of the ester **35** with LAH in ether gave the alcohol **37** in 98% yield, which on oxidation with PCC and silica gel furnished the aldehyde **36**. Wilkinson catalyst mediated decarbonylation of the aldehyde **36** in benzene at 120–130 °C in a sealed tube for 20 h furnished herbertenediol dimethyl ether **11** in 77% yield, which exhibited spectral data identical to that of an authentic sample. Finally, demethylation of the ether **11** with boron tribromide in methlylene chloride furnished (±)-herbertenediol **5** in 98% yield. Since the dimethyl ether **11** has already been transformed into mastigophorenes A–D **7**–**10**, the present sequence constitutes a formal total synthesis of these terpenoids.

In conclusion, we have accomplished synthesis of the sesquiterpene (±)-herbertenediol **5** and its dimers mastigophorenes A–D **7**–**10** starting from vanillin **18** via 2,3-dimethoxy-5-methylbenzaldehyde **16**. A combination of Claisen rearrangement and ring-closing metathesis reactions have been employed for the generation of the two vicinal quaternary carbons on a cyclopentane ring. Even though the conversion of the alcohol **12** to **13** by the orthoester Claisen rearrangement is low yielding, it is reasonably compensated by the high efficiency of the other steps. An overall yield of 6% was obtained for the conversion of the aldehyde **23** into herbertenediol in 15 steps.

3. Experimental

3.1. General

IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on JNM λ-300 spectrometer. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in

the standard fashion with reference to either internal tetramethylsilane (for ^1H) or the central line (77.1 ppm) of $CDCl_3$ (for ^{13}C). NMR samples were prepared using a 1:1 mixture of $CDCl_3$ and CCl_4 as solvent. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) were determined by recording the DEPT-135 and are given in parentheses. Low-resolution mass spectra were recorded using a Shimadzu QP-5050A GCMS instrument using direct inlet (EI) mode. Relative intensities are given in parentheses. High-resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Ozonolysis experiments were carried out using Fischer 502 ozone generator. The oxygen flow was adjusted and calibrated to generate 1 mmol of ozone per 4 min. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product). Dry THF was obtained by distillation over sodium-benzophenone ketyl. Dry ether was obtained by distillation over sodium and stored over sodium wire. Dry CH_2Cl_2 was prepared by distilling over calcium hydride. All the commercial reagents were used as such without further purification.

3.1.1. 3-Bromo-1,2-dimethoxy-5-methylbenzene (16). To a magnetically stirred solution of the aldehyde **20** (301 mg, 1.23 mmol) in dry THF (5 mL) were added $Na(CN)BH_3$ (387 mg, 6.16 mmol) and $BF_3{\cdot}Et_2O$ (1.09 mL, 8.63 mmol) and refluxed for 10 h. The reaction mixture was cooled to rt; aqueous $NaHCO_3$ solution (5 mL) was added to the reaction mixture and extracted with ether (3×3 mL). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue using ethyl acetate–hexane (1/20) as eluent furnished the ether **16** (87 mg, 31%) as an oil.[14] IR (neat): ν_{max}/cm^{-1} 1598, 1568; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.88 (1H, s), 6.57 (1H, s), 3.81 (3H, s), 3.76 (3H, s), 2.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 153.4 (C), 144.5 (C), 134.6 (C), 125.1 (CH), 117.4 (C), 112.6 (CH), 60.3 (CH_3), 55.9 (CH_3), 21.1 (CH_3). Further elution of the column using ethyl acetate–hexane (1/20) furnished the benzyl alcohol **21** (195 mg, 64%) as an oil.[19] IR (neat): ν_{max}/cm^{-1} 3384, 1599, 1570; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.94 (1H, s), 6.72 (1H, s), 4.45 (2H, s), 3.78 (3H, s), 3.74 (3H, s), 2.94 (1H, br s).

3.1.2. 1-(2,3-Dimethoxy-5-methylphenyl)-2,2-dimethylpent-4-en-1-ol (22). To a sonochemically irradiated suspension of lithium (48 mg, 6.92 mmol) in dry THF (1 mL) in a round bottom flask, placed in an ultrasonic cleaning bath, was added a mixture of the aldehyde **17** (77 mg, 0.69 mmol) and the bromoarene **16** (320 mg, 1.38 mmol) in THF (1 mL) at 15–20 °C over a period of 2 min, and sonochemically irradiated for 1 h. Then the reaction mixture was decanted from the excess lithium, quenched with saturated aqueous NH_4Cl solution (3 mL) and extracted with ether (3×3 mL). The 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 (1/20) as eluent furnished the benzyl alcohol **22** (30 mg, 16%) as an oil. IR (neat): ν_{max}/cm^{-1} 3470, 1638, 1589; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.70 (1H, s), 6.58 (1H, s), 6.00–5.78 (1H, m), 5.10–5.00 (2H, m), 4.72 (1H, s), 3.83 (3H, s), 3.78 (3H, s), 2.31 (3H, s), 2.23 (1H, br s), 2.14 (1H, dd, J=13.8, 7.5 Hz), 2.05 (1H, dd, J=13.8, 7.5 Hz), 0.88 (3H, s), 0.81 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 151.8 (C), 144.9 (C), 135.8 (CH), 134.6 (C), 132.3 (C), 121.3 (CH), 117.2 (CH_2), 112.2 (CH), 75.5 (CH), 60.4 (CH_3), 55.6 (CH_3), 43.6 (CH_2), 39.4 (C), 23.2 (CH_3), 22.5 (CH_3), 21.6 (CH_3); Mass: m/z 264 (M^+, 1%), 182 (13), 181 (100), 153 (55), 151 (25), 138 (17), 123 (13); HRMS: m/z Calcd for $C_{16}H_{24}O_3Na$ (M+Na): 287.1623. Found: 287.1606.

3.1.3. 1,2-Dimethoxy-5-methyl-3-(prop-1-enyl)benzene (28). To a cold (10 °C) magnetically stirred solution of the phenol **27** (700 mg, 3.93 mmol) in 10% aqueous NaOH solution (8 mL) was added dimethyl sulfate (0.37 mL, 3.93 mmol) drop-wise. The reaction mixture was refluxed for 1 h. It was then cooled and extracted with ether (3×3 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent followed by purification over a silica gel column using ethyl acetate–hexane (1/10) as eluent furnished the methyl ether **28** (724 mg, 96%) as an oil.[16] IR (neat): ν_{max}/cm^{-1} 1579; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.76 (1H, s), 6.62 (1H, dq, J=16.2, 1.8 Hz), 6.50 (1H, s), 6.14 (1H, dq, J=16.8, 6.6 Hz), 3.81 (3H, s), 3.72 (3H, s), 2.27 (3H, s), 1.90 (3H, dd, J=6.6, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.7 (C), 144.3 (C), 132.9 (C), 131.5 (C), 126.2 (CH), 125.7 (CH), 118.4 (CH), 111.8 (CH), 60.6 (CH_3), 55.7 (CH_3), 21.6 (CH_3), 19.0 (CH_3); Mass: ($C_{12}H_{16}O_2$) m/z 192 (M^+, 16%), 177 (7), 161 (4), 149 (8), 135 (2), 119 (4), 117 (5), 115 (3), 105 (4), 91 (9), 49 (100).

3.1.4. 2,3-Dimethoxy-5-methylbenzaldehyde (23). A mixture of dry ozone in oxygen was passed through a cold (−70 °C) solution of the ether **28** (640 mg, 3.34 mmol) and a catalytic amount of $NaHCO_3$ in 1:4 methanol/CH_2Cl_2 (10 mL) for 13 min. The reaction mixture was flushed off with oxygen to remove excess ozone, and dimethyl sulfide (1.6 mL) was added to the reaction mixture. It was then slowly warmed up to rt and magnetically stirred for 8 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexane (1/10) as eluent furnished the aldehyde **23** (477 mg, 80%) as an oil.[17] IR (neat): ν_{max}/cm^{-1} 2750, 1693, 1682, 1607, 1586; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 10.32 (1H, s), 7.14 (1H, s), 6.89 (1H, s), 3.89 (3H, s), 3.85 (3H, s), 2.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 189.6 (CH), 152.6 (C), 150.6 (C), 133.7 (C), 129.3 (C), 119.0 (CH), 118.9 (CH), 62.1 (CH_3), 55.8 (CH_3), 21.1 (CH_3).

3.1.5. 1-(2,3-Dimethoxy-5-methylphenyl)-2-methylpropan-1-ol (29). A solution of isopropylmagnesium bromide (5.5 mmol), prepared from Mg (152 mg, 6.33 mmol), isopropyl bromide (0.71 mL, 7.6 mmol) and a catalytic amount of iodine in 3 mL of dry ether, was added to a cold (0 °C), magnetically stirred solution of the aldehyde **23** (228 mg, 1.26 mmol) in dry ether (1 mL). The reaction mixture was slowly warmed up to rt and stirred for 3 h. It was then poured into saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (3×3 mL). The 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 (1/20) as eluent furnished the secondary alcohol **29** (250 mg, 88%)

as an oil. IR (neat): ν_{max}/cm^{-1} 3449, 1590; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.64 (1H, s), 6.57 (1H, s), 4.43 (1H, br s), 3.83 (3H, s), 3.80 (3H, s), 2.29 (3H, s), 2.15 (1H, s), 2.00–1.80 (1H, m), 1.02 (3H, d, $J=6.6$ Hz), 0.79 (3H, d, $J=6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.1 (C), 144.4 (C), 136.8 (C), 133.1 (C), 120.1 (CH), 112.2 (CH), 75.9 (CH), 60.7 (CH_3), 55.6 (CH_3), 35.0 (CH), 21.6 (CH_3), 19.9 (CH_3), 18.7 (CH_3); Mass: *m/z* 224 (M^+, 11%), 181 (100), 166 (17), 153 (77), 151 (24), 138 (34), 123 (15), 91 (17); HRMS: *m/z* Calcd for $C_{13}H_{20}O_3Na$ (M+Na): 247.1310. Found: 247.1300.

3.1.6. 1-(2,3-Dimethoxy-5-methylphenyl)-2-methylpropan-1-one (30). To a magnetically stirred suspension of PCC (721 mg, 3.34 mmol) and silica gel (721 mg) in dry CH_2Cl_2 (1 mL) was added a solution of the *sec*-alcohol **29** (250 mg, 1.11 mmol) in CH_2Cl_2 (1 mL) and stirred vigorously for 2 h at rt. The reaction mixture was then filtered through a small silica gel column, and the column eluted with more CH_2Cl_2. Evaporation of the solvent furnished the ketone **30** (238 mg, 96%) as an oil. IR (neat): ν_{max}/cm^{-1} 1693, 1603, 1586; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.70 (1H, s), 6.67 (1H, s), 3.80 (3H, s), 3.74 (3H, s), 3.26 (1H, septet, $J=6.9$ Hz), 2.26 (3H, s), 1.08 (6H, d, $J=6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 207.4 (C), 152.4 (C), 145.0 (C), 134.4 (C), 133.5 (C), 120.6 (CH), 115.5 (CH), 61.4 (CH_3), 55.7 (CH_3), 40.1 (CH), 21.2 (CH_3), 18.6 (2C, CH_3); Mass: *m/z* 222 (M^+, 10%), 207 (4), 180 (12), 179 (100), 136 (17), 91 (15); HRMS: *m/z* Calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154. Found: 245.1146.

3.1.7. 1-(2,3-Dimethoxy-5-methylphenyl)-2,2-dimethylpent-4-en-1-one (15). To a magnetically stirred suspension of NaH (234 mg, 60% dispersion in oil, 5.85 mmol, washed with dry hexanes) in dry THF (1 mL) was added a solution of the ketone **30** (260 mg, 1.17 mmol) in dry THF (2 mL) and stirred for 40 min at rt. Allyl bromide (0.5 mL, 5.85 mmol) was added to the reaction mixture and stirred for 10 h at rt. It was then quenched with water (5 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 over a silica gel column using ethyl acetate–hexane (1/20) as eluent furnished a mixture of *O*-allylated and *C*-allylated compounds (**31** and **15**), which was taken into a sealed tube (neat) and heated at 180 °C for 30 min. Purification of the reaction mixture over a silica gel column using ethyl acetate–hexane (1/20) as eluent furnished the ketone **15** (279 mg, 91%) as an oil. IR (neat): ν_{max}/cm^{-1} 1693, 1639, 1588; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.62 (1H, s), 6.31 (1H, s), 5.85–5.60 (1H, m), 5.10–4.90 (2H, m), 3.79 (3H, s), 3.66 (3H, s), 2.26 (3H, s), 2.35–2.25 (2H, m), 1.10 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 211.4 (C), 152.1 (C), 142.4 (C), 136.5 (C), 134.4 (CH), 133.4 (C), 117.8 (CH_2), 117.6 (CH), 113.3 (CH), 61.2 (CH_3), 55.4 (CH_3), 47.7 (C), 43.8 (CH_2), 24.3 (2C, CH_3), 21.3 (CH_3); Mass: *m/z* 262 (M^+, 3%), 180 (11), 179 (100), 136 (8), 91 (8); HRMS: *m/z* Calcd for $C_{16}H_{22}O_3Na$ (M+Na): 285.1467. Found: 285.1452.

3.1.8. 3-(2,3-Dimethoxy-5-methylphenyl)-4,4-dimethylhept-6-en-1-yn-3-ol (33). To a sonochemically irradiated suspension of lithiumacetylide ethylenediamine complex (1.23 g, 13.3 mmol) in dry THF (1 mL) in a round bottom flask, placed in an ultrasonic cleaning bath, was added a solution of the ketone **15** (700 mg, 2.67 mmol) in dry THF (2 mL) at 15–20 °C over a period of 3 min, and the reaction mixture was sonochemically irradiated for 2 h. It was then quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with ether (3×7 mL). The 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 (1/10) as eluent furnished the tertiary alcohol **33** (693 g, 90%) as an oil. IR (neat): ν_{max}/cm^{-1} 3447, 3301, 1637, 1585, 912; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.93 (1H, s), 6.61 (1H, s), 5.80–5.50 (1H, m), 4.97 (1H, d, $J=9.9$ Hz), 4.96 (1H, d, $J=17.1$ Hz), 3.86 (3H, s), 3.82 (3H, s), 2.55 (1H, s), 2.29 (3H, s), 2.29–2.10 (2H, m), 1.23 (1H, br s), 0.91 (3H, s), 0.90 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.0 (C), 145.2 (C), 135.8 (2C, C and CH), 131.7 (C), 123.6 (CH), 117.4 (CH_2), 112.9 (CH), 86.4 (C), 81.6 (C), 73.5 (CH), 61.3 (CH_3), 55.7 (CH_3), 44.1 (C), 41.2 (CH_2), 22.0 (CH_3), 21.6 (CH_3), 21.5 (CH_3); Mass: *m/z* 273 (M^+-Me, 2%), 205 (100), 191 (14), 190 (33), 179 (29), 121 (10); HRMS: *m/z* Calcd for $C_{18}H_{24}O_3Na$ (M+Na): 311.1623. Found: 311.1618.

3.1.9. 3-(2,3-Dimethoxy-5-methylphenyl)-4,4-dimethylhept-6-en-3-ol (32). To activated Lindlar's catalyst (200 mg) was added a solution of the enynol **33** (500 mg, 1.73 mmol) in ethanol (2 mL). The reaction mixture was stirred for 24 h at rt in an atmosphere of hydrogen, created by evacuative replacement of air (balloon), and then the catalyst was filtered off. Evaporation of the solvent furnished the dienol **32** (488 mg, 97%) as an oil. IR (neat): ν_{max}/cm^{-1} 3475, 1637, 1583, 914; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): 6.70 (1H, dd, $J=16.8$, 10.5 Hz), 6.67 (1H, s), 6.57 (1H, s), 5.76 (1H, ddt, $J=18.0$, 9.0, 7.5 Hz), 5.46 (1H, d, $J=16.8$ Hz), 5.17 (1H, d, $J=10.5$ Hz), 4.95 (1H, d, $J=9.0$ Hz), 4.94 (1H, d, $J=18.0$ Hz), 4.60 (1H, br s), 3.82 (6H, s), 2.32 (3H, s), 2.15–1.95 (2H, m), 0.84 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.4 (C), 145.2 (C), 141.6 (CH), 136.4 (CH), 135.9 (C), 131.6 (C), 122.9 (CH), 117.1 (CH_2), 113.9 (CH_2), 112.1 (CH), 82.2 (C), 61.1 (CH_3), 55.7 (CH_3), 42.8 (C), 41.4 (CH_2), 22.4 (CH_3), 22.0 (CH_3), 21.8 (CH_3); Mass: *m/z* 207 ($M^+-C_6H_{11}$, 73%), 175 (12); HRMS: *m/z* Calcd for $C_{18}H_{26}O_3Na$ (M+Na): 313.1780. Found: 313.1770.

3.1.10. 3-(2,3-Dimethoxy-5-methylphenyl)-4,4-dimethylhepta-2,6-dienal (34). To a magnetically stirred suspension of PCC (3.62 g, 16.8 mmol) and silica gel (3.62 g) in dry CH_2Cl_2 (10 mL) was added a solution of the tertiary alcohol **32** (488 mg, 1.68 mmol) in CH_2Cl_2 (2 mL) and stirred vigorously for 30 h at rt. The reaction mixture was then filtered through a small silica gel column, and the column eluted with more CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1/20) as eluent furnished the enal **34** (412 mg, 85%) as an oil. IR (neat): ν_{max}/cm^{-1} 2748, 1676, 1638, 1583, 916; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 9.25 (1H, d, $J=8.1$ Hz), 6.68 (1H, s), 6.37 (1H, s), 6.15 (1H, d, $J=8.1$ Hz), 5.85–5.65 (1H, m), 5.07 (1H, d, $J=9.0$ Hz), 5.04 (1H, d, $J=16.2$ Hz), 3.87 (3H, s), 3.68 (3H, s), 2.32 (3H, s), 2.24 (2H, d, $J=6.9$ Hz), 1.13 (3H, s), 1.07 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 193.5 (CH), 171.0

(C), 152.3 (C), 144.0 (C), 134.5 (CH), 132.8 (C), 130.9 (C), 128.5 (CH), 121.9 (CH), 117.9 (CH_2), 112.9 (CH), 60.1 (CH_3), 55.4 (CH_3), 45.8 (CH_2), 40.7 (C), 26.9 (CH_3), 26.7 (CH_3), 21.3 (CH_3); Mass: *m/z* 288 (M^+, 10%), 259 (64), 257 (100), 216 (63), 189 (39), 173 (20); HRMS: *m/z* Calcd for $C_{18}H_{24}O_3Na$ (M+Na): 311.1623. Found: 311.1619.

3.1.11. 3-(2,3-Dimethoxy-5-methylphenyl)-4,4-dimethylhepta-2,6-dien-1-ol (12). To an ice cold, magnetically stirred solution of the aldehyde **34** (360 mg, 1.25 mmol) in dry methanol (3 mL) was added $NaBH_4$ (47.5 mg, 1.25 mmol) and stirred for 90 min at the same temperature. The solvent was removed under reduced pressure, diluted with water (5 mL) followed by quenched with 3 N aqueous HCl (5 mL) and extracted with CH_2Cl_2 (5×6 mL). The combined CH_2Cl_2 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 (1/20–1/10) as eluent furnished the primary alcohol **12** (271 mg, 75%) as an oil. IR (neat): ν_{max}/cm^{-1} 3423, 1638, 1583, 911; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.56 (1H, s), 6.26 (1H, s), 5.95–5.60 (2H, m), 5.00–4.90 (2H, m), 3.79 (3H, s), 3.68 (3H, s), 3.80–3.40 (2H, m), 2.24 (3H, s), 2.24–2.00 (2H, m), 1.98 (1H, br s), 1.02 (3H, s), 0.96 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.2 (C), 147.8 (C), 143.9 (C), 135.9 (CH), 132.8 (C), 132.4 (C), 125.7 (CH), 122.8 (CH), 116.8 (CH_2), 112.1 (CH), 60.8 (CH_2), 60.2 (CH_3), 55.4 (CH_3), 46.1 (CH_2), 38.8 (C), 27.7 (CH_3), 27.3 (CH_3), 21.3 (CH_3); Mass: *m/z* 290 (M^+, 42%), 260 (44), 249 (39), 231 (69), 207 (85), 205 (75), 179 (87), 175 (98), 165 (80), 151 (65), 115 (50), 97 (80), 91 (80); HRMS: *m/z* Calcd for $C_{18}H_{26}O_3Na$ (M+Na): 313.1780. Found: 313.1787.

3.1.12. Ethyl 3-vinyl-3-(2,3-dimethoxy-5-methylphenyl)-4,4-dimethylhept-6-enoate (13). A solution of the allyl alcohol **12** (244 mg, 0.84 mmol), triethyl orthoacetate (1.53 mL, 8.41 mmol) and a catalytic amount of propionic acid was placed in a sealed tube and heated to 180 °C for 2 days in an oil bath. The reaction mixture was then cooled, diluted with ether (5 mL), washed with 3 N aqueous HCl (5 mL) followed by saturated $NaHCO_3$ solution (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 (1/40) as eluent furnished the diene ester **13** (85 mg, 28%) as an oil. IR (neat): ν_{max}/cm^{-1} 1746, 1637, 1582, 911; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.84 (1H, dd, *J*=18.0, 10.4 Hz), 6.61 (1H, s), 6.57 (1H, s), 5.85–5.55 (1H, m), 5.12 (1H, d, *J*=11.1 Hz), 5.04 (1H, d, *J*=17.4 Hz), 5.00–4.85 (2H, m), 3.97 (2H, q, *J*=6.9 Hz), 3.81 (3H, s), 3.68 (3H, s), 2.79 (1H, d, *J*=17.4 Hz), 2.26 (3H, s), 2.30–1.90 (3H, m), 1.14 (3H, t, *J*=6.9 Hz), 0.83 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 171.8 (C), 152.6 (C), 147.1 (C), 142.1 (2C, C and CH), 136.0 (CH), 130.3 (C), 123.8 (CH), 117.3 (CH_2), 114.0 (CH_2), 111.7 (CH), 60.2 (CH_3), 55.6 (CH_3), 59.5 (CH_2), 53.0 (C), 41.9 (CH_2), 41.4 (C), 37.4 (CH_2), 22.7 (2C, CH_3), 21.8 (CH_3), 14.3 (CH_3); Mass: *m/z* 360 (M^+, 1%), 278 (42), 231 (20), 203 (100), 189 (28), 173 (18); HRMS: *m/z* Calcd for $C_{22}H_{32}O_4Na$ (M+Na): 383.2198. Found: 383.2211.

3.1.13. Ethyl 2-[1-(2,3-dimethoxy-5-methylphenyl)-5,5-dimethylcyclopent-2-enyl]acetate (14). To a magnetically stirred solution of the diene ester **13** (130 mg, 0.36 mmol) in anhydrous CH_2Cl_2 (13 mL) was added a solution of Grubbs' catalyst (21 mg, 7 mol%) in anhydrous CH_2Cl_2 (10 mL) and the reaction mixture was stirred at rt for 6 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexane (1/30) as eluent furnished the cyclopentene ester **14** (67 mg, 80%) as an oil. IR (neat): ν_{max}/cm^{-1} 1738, 1584; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.59 (1H, s), 6.54 (1H, s), 6.20 (1H, d, *J*=6.0 Hz), 5.70 (1H, d, *J*=6.0 Hz), 3.92 (2H, q, *J*=7.2 Hz), 3.81 (3H, s), 3.80 (3H, s), 3.51 (1H, d, *J*=15.3 Hz), 2.39 (1H, d, *J*=15.3 Hz), 2.34 (1H, d, *J*=16.5 Hz), 2.26 (3H, s), 2.13 (1H, dd, *J*=16.5, 1.5 Hz), 1.25 (3H, s), 0.51 (3H, s), 1.06 (3H, t, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 172.2 (C), 152.4 (C), 146.1 (C), 139.6 (CH), 134.9 (C), 131.4 (C), 127.2 (CH), 122.1 (CH), 111.9 (CH), 60.0 (CH_3), 59.5 (CH_2), 58.8 (C), 55.6 (CH_3), 48.4 (CH_2), 45.7 (C), 41.1 (CH_2), 28.5 (CH_3), 24.4 (CH_3), 21.7 (CH_3), 14.2 (CH_3); Mass: *m/z* 332 (M^+, 62%), 258 (52), 245 (86), 243 (58), 215 (100), 189 (45), 185 (41), 175 (43), 149 (69), 115 (50), 91 (66); HRMS: *m/z* Calcd for $C_{20}H_{28}O_4Na$ (M+Na): 355.1885. Found: 355.1883.

3.1.14. Ethyl 2-[1-(2,3-dimethoxy-5-methylphenyl)-2,2-dimethylcyclopent-1-yl]acetate (35). To an activated 5% Pd–C (15 mg) was added a solution of the ester **14** (35 mg, 0.10 mmol) in ethanol (1 mL). The reaction mixture was stirred for 3 h at rt in an atmosphere of hydrogen, created by evacuative replacement of air (balloon), and then the catalyst was filtered off. Evaporation of the solvent furnished the cyclopentane ester **35** (35 mg, 99%) as an oil. IR (neat): ν_{max}/cm^{-1} 1737, 1582; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.59 (1H, s), 6.54 (1H, s), 3.87 (2H, q, *J*=6.9 Hz), 3.80 (3H, s), 3.77 (3H, s), 3.42 and 2.37 (2H, 2×d, *J*=15.3 Hz), 2.85–2.50 (1H, m), 2.26 (3H, s), 2.15–2.00 (1H, m), 1.85–1.65 (2H, m), 1.54 (1H, d, *J*=9.0 Hz), 1.51 (1H, d, *J*=6.9 Hz), 1.10 (3H, s), 1.01 (3H, t, *J*=6.9 Hz), 0.64 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 172.2 (C), 152.4 (C), 146.8 (C), 136.0 (C), 130.9 (C), 122.2 (CH), 112.0 (CH), 59.9 (CH_3), 59.2 (CH_2), 55.6 (CH_3), 53.8 (C), 46.1 (C), 41.1 (CH_2), 39.4 (CH_2), 36.3 (CH_2), 27.3 (CH_3), 25.7 (CH_3), 21.9 (CH_3), 20.8 (CH_2), 14.3 (CH_3); Mass: *m/z* 334 (M^+, 68%), 252 (100), 219 (41), 189 (61), 172 (53), 165 (35), 149 (70); HRMS: *m/z* Calcd for $C_{20}H_{30}O_4Na$ (M+Na): 357.2042. Found: 357.2056.

3.1.15. 2-[1-(2,3-Dimethoxy-5-methylphenyl)-2,2-dimethylcyclopent-1-yl]ethanol (37). To a cold (0 °C), magnetically stirred solution of the ester **35** (20 mg, 0.06 mmol) in 1 mL of dry ether was added $LiAlH_4$ (11.37 mg, 0.29 mmol) and stirred for 1 h. The reaction mixture was then diluted with ether (3 mL) and carefully quenched with two drops of water. The organic layer was separated and the aqueous phase was extracted with ether (3×2 mL). The combined organic phase 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 (1/10–1/5) as eluent furnished the primary alcohol **37** (17 mg, 98%). IR (neat): ν_{max}/cm^{-1} 3363, 1579; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.57 (1H, s), 6.54 (1H, s), 3.81 (3H, s), 3.78 (3H, s), 3.45 (1H, td, *J*=9.6, 5.7 Hz), 3.30 (1H, td, *J*=9.6, 5.4 Hz), 2.70–2.30 (2H, m), 2.26 (3H, s), 2.00–1.80 (1H, m), 1.80–1.40 (6H, m), 1.34 (3H, s), 0.66 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+$

CCl_4): δ 152.6 (C), 146.9 (C), 136.7 (C), 131.5 (C), 122.1 (CH), 111.7 (CH), 61.6 (CH_2), 60.1 (CH_3), 55.6 (CH_3), 53.9 (C), 45.9 (C), 40.8 (CH_2), 37.3 (CH_2), 29.8 (CH_2), 27.1 (CH_3), 25.5 (CH_3), 21.7 (CH_3), 20.9 (CH_2); Mass: *m/z* 292 (M^+, 74%), 210 (100), 207 (30), 191 (45), 179 (66), 166 (61), 165 (50), 149 (62), 115 (33), 105 (31), 91 (57); HRMS: *m/z* Calcd for $C_{18}H_{28}O_3Na$ (M+Na): 315.1936. Found: 315.1925.

3.1.16. 2-[1-(2,3-Dimethoxy-5-methylphenyl)-2,2-dimethylcyclopent-1-yl]acetaldehyde (36). To a magnetically stirred suspension of PCC (62.7 mg, 0.29 mmol) and silica gel (62.7 mg) in dry CH_2Cl_2 (0.5 mL) was added a solution of the primary alcohol **37** (17 mg, 0.06 mmol) in CH_2Cl_2 (0.5 mL) and stirred vigorously for 30 min at rt. The reaction mixture was then filtered through a small silica gel column, and the column eluted with more CH_2Cl_2. Evaporation of the solvent furnished the aldehyde **36** (15 mg, 89%) as an oil, which was found to decompose slowly. IR (neat): ν_{max}/cm^{-1} 2729, 1719, 1579; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 9.43 (1H, t, $J=3.0$ Hz), 6.69 (1H, s), 6.66 (1H, s), 3.83 (3H, s), 3.79 (3H, s), 3.50 (1H, d, $J=16.2$ Hz), 2.83–2.62 (1H, m), 2.39 (1H, dd, $J=16.2$, 3.0 Hz), 2.29 (3H, s), 1.95–1.68 (5H, m), 1.11 (3H, s), 0.69 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 205.3 (CH), 152.7 (C), 146.4 (C), 135.1 (C), 132.0 (C), 121.9 (CH), 112.1 (CH), 60.1 (CH_3), 55.6 (CH_3), 52.7 (C), 48.4 (CH_2), 45.8 (C), 40.5 (CH_2), 36.6 (CH_2), 26.5 (CH_3), 25.3 (CH_3), 21.6 (CH_3), 20.5 (CH_2).

3.1.17. 1-(2,3-Dimethoxy-5-methylphenyl)-1,2,2-trimethylcyclopentane (11). Wilkinson catalyst (23 mg, 0.025 mmol) was added to a solution of the aldehyde **36** (15 mg, 0.05 mmol) in dry benzene (0.5 mL) and heated at 120–130 °C for 20 h in a sealed tube. Evaporation of the solvent under reduced pressure followed by purification on a silica gel column using ethyl acetate–hexane (1/30) as eluent furnished herbertenediol dimethyl ether **11** (9 mg, 77% based on consumed aldehyde **36**). IR (neat): ν_{max}/cm^{-1} 1580; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.75 (1H, s), 6.62 (1H, s), 3.85 (3H, s), 3.77 (3H, s), 2.70–2.50 (1H, m), 2.30 (3H, s), 1.85–1.30 (5H, m), 1.36 (3H, s), 1.12 (3H, s), 0.70 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 153.0 (C), 146.6 (C), 140.1 (C), 131.6 (C), 121.6 (CH), 111.0 (CH), 60.4 (CH_3), 55.6 (CH_3), 51.5 (C), 45.0 (C), 40.8 (CH_2), 38.9 (CH_2), 26.8 (CH_3), 25.2 (CH_3), 24.1 (CH_3), 21.7 (CH_3), 20.3 (CH_2); Mass: *m/z* 262 (M^+, 29%), 257 (25), 180 (52), 179 (20), 165 (13), 149 (9); HRMS: *m/z* Calcd for $C_{17}H_{26}O_2Na$ (M+Na): 285.1830. Found: 285.1831. Further elution of the column with ethyl acetate–hexane (1/30) as eluent furnished the unreacted aldehyde **36** (2 mg).

3.1.18. 1-(2,3-Dihydroxy-5-methylphenyl)-1,2,2-trimethylcyclopentane [(±)-herberenediol 5]. A solution of BBr_3 (1 M in CH_2Cl_2, 0.30 mL, 0.30 mmol) was added drop-wise to a magnetically stirred solution of the ether **11** (8 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) at −40 °C. The reaction mixture slowly warmed up to rt and stirred for 2 h at rt. It was then quenched with saturated aqueous $NaHCO_3$ solution (1 mL) and extracted with CH_2Cl_2 (3×2 mL). The combined organic layer 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 (1/10) as eluent furnished herbertenediol **5** (7 mg, 98%). IR (neat): ν_{max}/cm^{-1} 3526, 1599; ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.68 (1H, s), 6.56 (1H, s), 5.39 (1H, s), 5.23 (1H, br s), 2.70–2.59 (1H, m), 2.22 (3H, s), 1.82–1.43 (5H, m), 1.41 (3H, s), 1.18 (3H, s), 0.76 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 143.5 (C), 141.2 (C), 133.6 (C), 128.4 (C), 122.0 (CH), 113.6 (CH), 51.3 (C), 45.0 (C), 41.1 (CH_2), 39.4 (CH_2), 27.0 (CH_3), 25.6 (CH_3), 23.0 (CH_3), 21.3 (CH_3), 20.4 (CH_2); Mass: *m/z* 234 (M^+, 43%), 164 (40), 152 (85), 151 (100).

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References and notes

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