Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 9393–9402

Structure revision of HM-3, an aromatic sesquiterpene isolated from the phytopathogenic fungus *Helicobasidium mompa*. First total syntheses of HM-3 and HM-4

A. Srikrishna* and P. C. Ravikumar

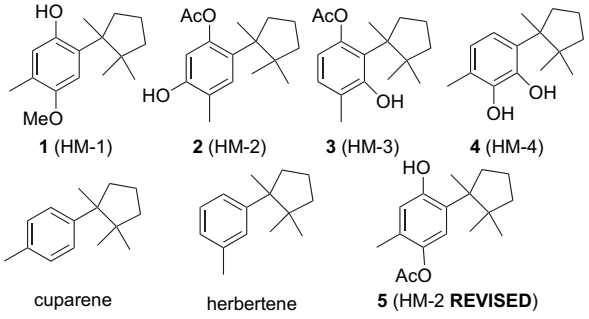
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, Karnataka, India

Received 24 April 2006; revised 2 July 2006; accepted 20 July 2006
Available online 10 August 2006

Abstract—The first total syntheses of HM-3 and HM-4, aromatic sesquiterpenes isolated from the phytopathogenic fungus *Helicobasidium mompa*, have been accomplished. The structure assigned to the sesquiterpene HM-3 was found to be incorrect by total synthesis. A Claisen rearrangement–RCM reaction based strategy was employed for the total synthesis of the aromatic sesquiterpene HM-4 (cuparene-1,2-diol), which on selective monoacetylation established the structure of HM-3, a cuparene derivative.

1. Introduction

The phytopathogenic fungus *Helicobasidium mompa* Tanaka is responsible for the violet root rot against mulberry and several other fruit trees. In the course of a study on the mechanism of violet root rot, Nohara and co-workers have investigated the fungus, and reported the isolation and structure elucidation of four aromatic sesquiterpenes from the methanolic extract of the mycelium grown with *H. mompa*, which was obtained from infected mulberry roots.[1] Based on preliminary observations, it was speculated that all the compounds possessed anti-oxidant as well as antibiotic activities similar to those of the higher oxygenated cuparene analogues, lagopodins and helicobasidins.[2] Of the four sesquiterpenes, two, HM-1 (**1**) and HM-4 (**4**), were found to belong to the cuparene class, whereas the structures of the remaining two, HM-2 (**2**) and HM-3 (**3**), were assigned as herbertanes on the basis of the 1D and 2D NMR spectroscopy. Incidentally, isolation of HM-4 (**4**) (same as cuparene-1,2-diol) has been reported earlier in 1982 from the liverwort *Raduia perrottetii* and subsequently from the liverwort *Herbertus aduncus*, and from the Japanese liverworts *Lejeunea aquatica* and *Lejeunea japonica*.[3] Since herbertanes are considered as chemical markers of the liverworts belonging to the genus *Herbertus*,[4] and *Helicobasidium* is known to contain helicobasidins,[2] which are higher oxygenated derivatives of cuparenes, we have undertaken the synthesis of HM-1 to 4 **1**–**4**. Recently, we carried out the total synthesis of putative structure **2** of HM-2, as well as cuparene-1,4-diol and its methyl and acetyl derivatives and revised the structure of HM-2 as cuparene-1,4-diol monoacetate **5**.[5] In continuation, herein, we describe our studies on the synthesis[6] of the compound having structure **3** and cuparene-1,2-diol **4**, and revision of the structure for HM-3 as a cuparenoid.

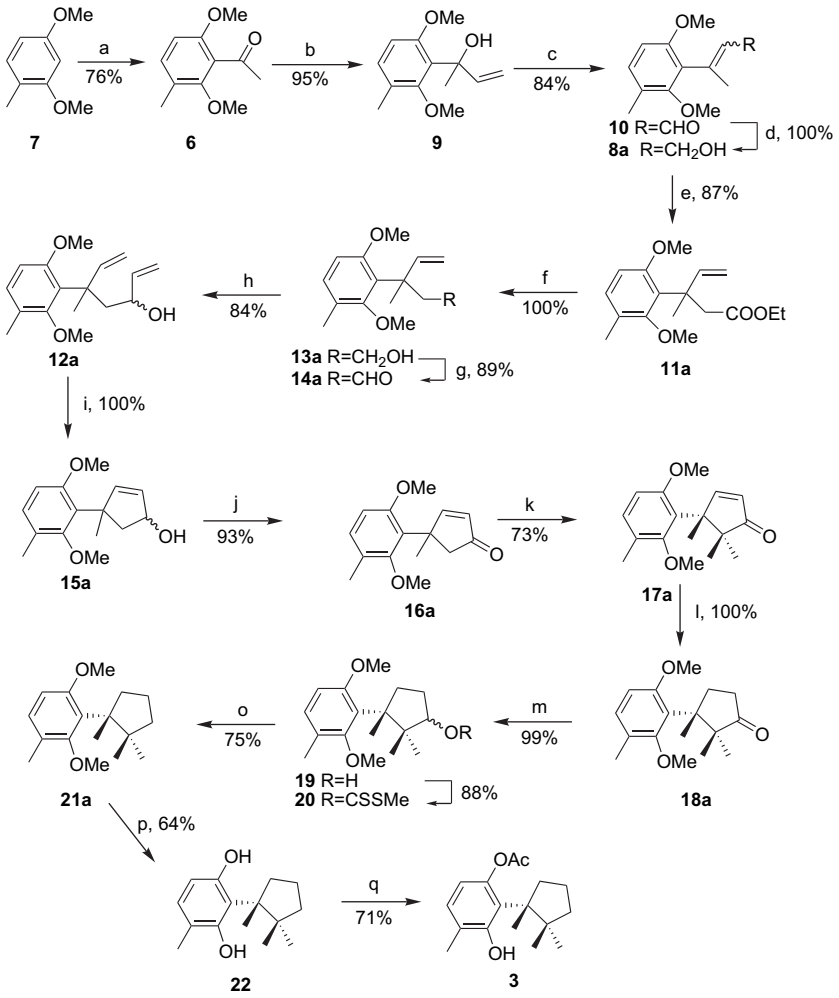


2. Results and discussion

For the synthesis of the putative structure **3** of HM-3, an orthoester Claisen rearrangement[7] and a ring-closing metathesis reaction (RCM)[8] based strategy were employed (Scheme 1) starting from 2,6-dimethoxy-3-methylacetophenone **6**. The acetophenone[9] **6** was prepared from 4-methylresorcinol dimethyl ether **7** in three steps (formylation, Grignard reaction, and oxidation). Since the Wittig or Horner–Wadsworth–Emmons reactions were unsuccessful, probably due to the steric crowding of the ketone group, a three-step protocol was used for the efficient conversion of the acetophenone **6** into the cinnamyl alcohol **8a**, the precursor for the Claisen rearrangement. Thus, Grignard reaction of the acetophenone **6** with vinylmagnesium bromide

* Corresponding author. Tel. +91 80 22932215; fax: +91 80 23600529; e-mail: ask@orgchem.iisc.ernet.in

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.07.062



Scheme 1. Reagents and conditions: (a) (i) *n*-BuLi, TMEDA, DMF, THF, 0 °C→rt, 4 h; (ii) MeMgI, Et_2O, 0 °C, 30 min; (iii) PCC, silica gel, CH_2Cl_2, 8 h; (b) CH_2=CHMgBr, THF, 0 °C→rt, 4 h; (c) PCC, silica gel, CH_2Cl_2, 8 h; (d) LAH, Et_2O, −50 °C, 45 min; (e) $CH_3C(OEt)_3$, $EtCO_2H$ (catalytic), 180 °C, 48 h; (f) LAH, Et_2O, 0 °C, 30 min; (g) PCC, silica gel CH_2Cl_2, 15 min; (h) CH_2=CHMgBr, THF, −20 °C, 10 min; (i) PhCH=$RuCl_2(PCy_3)_2$ (5 mol %), CH_2Cl_2, 3 h; (j) PCC, silica gel, CH_2Cl_2, 1 h; (k) NaH, CH_3I, THF, DMF, rt, 12 h; (l) H_2 (1 atm), 10% Pd–C, EtOH, 1 h; (m) $NaBH_4$, MeOH, 0 °C, 5 min; (n) NaH, THF, imidazole (catalytic), CS_2, CH_3I, reflux, 4.5 h; (o) *n*-Bu_3SnH, AIBN, C_6H_6, reflux, 3 h; (p) MeMgI, *p*-cymene, reflux, 8 h; (q) Ac_2O, py, DMAP, CH_2Cl_2, rt, 2 h.

furnished the tertiary allyl alcohol **9** in 95% yield. Oxidation of the alcohol **9** with pyridinium chlorochromate (PCC) and silica gel in methylene chloride led to the 1,3-transposition[10] to generate the cinnamaldehyde **10**, which on reduction with lithium aluminum hydride (LAH) in ether generated the cinnamyl alcohol **8a** in 84% yield (two steps). Johnson's orthoester variant of the Claisen rearrangement was employed for the generation of the γ,δ-unsaturated ester containing the first quaternary carbon atom. Thermal activation of the cinnamyl alcohol **8a** with triethyl orthoacetate and a catalytic amount of propionic acid in a sealed tube furnished the pentenoate **11a** in 87% yield. A three-step protocol was employed for the conversion of the ester **11a** into the heptadienol **12a**, the precursor for the RCM reaction. Thus, reduction of the ester **11a** with LAH followed by oxidation of the resultant primary alcohol **13a** with PCC and silica gel in methylene chloride furnished the aldehyde **14a**. Grignard reaction of the aldehyde **14a** with vinylmagnesium bromide generated the heptadienol **12a**. RCM reaction of the dienol **12a** in methylene chloride with 5 mol % of Grubbs' first generation catalyst [PhCH=$RuCl_2(PCy_3)_2$] generated the cyclopentenol **15a** in quantitative yield, which on oxidation with PCC and silica gel in methylene chloride furnished the cyclopentenone **16a**. One-step dimethylation of the cyclopentenone **16a** with sodium hydride and methyl iodide in THF and DMF created the second quaternary carbon atom vicinal to the first one to furnish the cyclopentenone **17a** containing the complete carbon framework of herbertanes. Hydrogenation with 10% palladium over carbon as the catalyst quantitatively transformed the enone **17a** into cyclopentanone **18a**. Barton's radical deoxygenation protocol[11,12] was employed for the reductive deoxygenation of the ketone **18a**. Reduction of the ketone **18a** with sodium borohydride generated an epimeric mixture of the alcohol **19** in quantitative yield. Treatment of the alcohol **19** with sodium hydride and imidazole in THF followed by reaction of the resultant alkoxide with carbon disulfide and methyl iodide generated the dithiocarbonate **20**. Reaction of the dithiocarbonate **20** with tri-*n*-butyltin hydride and a catalytic amount of azobisisobutyronitrile (AIBN) in refluxing benzene furnished herbertene-1,5-diol dimethyl ether **21a**. Boron tribromide or other acidic reagents mediated cleavage of the methyl ether in **21a**, however, failed to generate the herbertenediol **22**, and produced only the cleaved product,

4-methylresorcinol. Hence, demethylation was carried out using a Grignard reagent. Thus, refluxing a *p*-cymene solution of the dimethyl ether **21a** with methylmagnesium iodide furnished herbertene-1,5-diol **22**. Regioselective acetylation of the less hindered alcohol in the diol **22** with pyridine and acetic anhydride in methylene chloride for 2 h furnished the monoacetate **3** in 71% yield. The ^{1}H NMR spectrum of the monoacetate **3**, however, was found to be different[13] from that reported[1] for HM-3, which clearly established that the proposed structure needs to be revised.

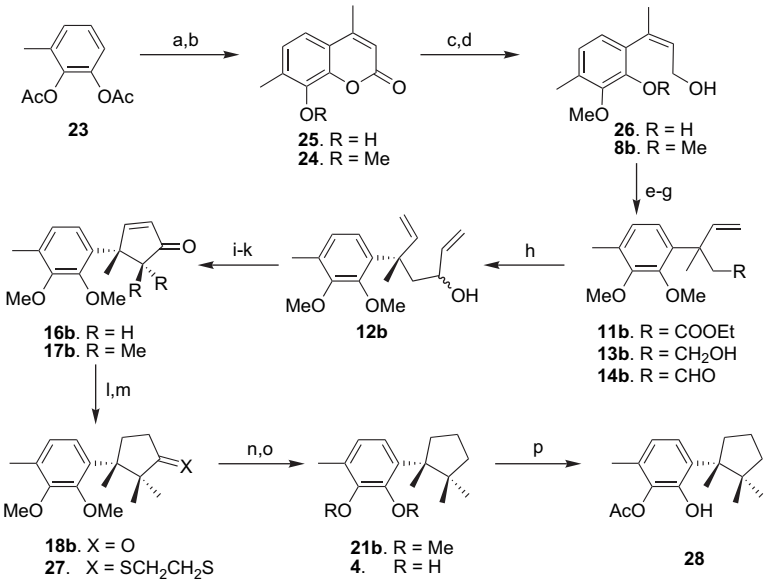
It was reasoned, like HM-1 (**1**), HM-2 (**5**),[5] and HM-4 (**4**), that HM-3 might also be a derivative of cuparene, and an acetate analog of HM-4 (cuparene-1,2-diol **4**) was considered as a possibility, since the NMR spectrum of the natural HM-3 clearly indicated that it contains two *ortho* coupled aromatic protons. To test the validity of this hypothesis and also to confirm the structure of HM-4,[6] the synthesis of cuparene-1,2-diol **4** was undertaken, Scheme 2.

The cinnamyl alcohol **8b** was identified as a suitable starting material, which was prepared starting from 3-methylcatechol diacetate **23** via the coumarin **24** as reported in the literature.[14] Thus, Pechmann reaction of the diacetate **23** with ethyl acetoacetate and 80% sulfuric acid generated the coumarin **25**, which on etherification with potassium carbonate and methyl iodide furnished the coumarin **24**. Reduction of the coumarin **24** with LAH in THF at −50 °C followed by regioselective etherification of the phenolic hydroxy group in the resultant diol **26** with potassium carbonate and methyl iodide in refluxing acetone furnished the cinnamyl alcohol **8b** in 81% yield. The orthoester Claisen rearrangement of the cinnamyl alcohol **8b** with triethyl orthoacetate and propionic acid generated the pentenoate **11b**, which was converted into the aldehyde **14b** via the alcohol **13b**. Grignard reaction of the aldehyde **14b** with vinylmagnesium bromide followed by RCM reaction of the resultant dienol **12b** with Grubbs' catalyst generated the cyclopentenol **15b**, which on PCC oxidation furnished the enone **16b**. One-pot dimethylation of the enone **16b** followed by catalytic hydrogenation of the resultant enone **17b** furnished 1,2-dimethoxy-α-cuparenone **18b**. Treatment of the ketone **18b** with 1,2-ethanedithiol in the presence of a catalytic amount of iodine[15] generated the thioketal **27**, which on desulfurization with Raney nickel furnished cuparene-1,2-diol dimethyl ether **21b** in 80% yield (two steps). Cleavage of the methyl ethers in **21b** with boron tribromide furnished cuparene-1,2-diol **4**, which exhibited ^{1}H NMR spectrum identical to that reported[1,3] for HM-4. Regioselective acetylation of the less hindered alcohol in the diol **4** with acetic anhydride and pyridine in methylene chloride furnished the monoacetate **28**. The ^{1}H NMR spectral data of the monoacetate **28** was found to be identical to that reported[1] for HM-3, which established the structure of the natural product HM-3 as a cuparene derivative **28**.[16]

In conclusion, we have accomplished an efficient total synthesis (in 16 steps from the acetophenone **6** with an average yield of 88% for each step) of the putative structure **3** of HM-3 and proved that the structure needs revision. We reasoned it to be a cuparene derivative. To substantiate further, the first total synthesis of cuparene-1,2-diol (HM-4) **4** was accomplished (in 13 steps from the coumarin **24** with an average yield of 90% for each step). Selective monoacetylation of cuparene-1,2-diol **4** established the structure of HM-3 as **28**. A combination of a Claisen rearrangement, a RCM reaction and an alkylation was strategically employed for the efficient construction of cyclopentanes containing two vicinal quaternary carbon atoms.

3. Experimental

Melting points were recorded using Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. IR



Scheme 2. Reagents and conditions: (a) CH_3COCH_2COOEt, 80% aq H_2SO_4, 80 °C, 45 min; (b) K_2CO_3, Me_2CO, MeI, reflux, 5 h; (c) LAH, THF, −50 °C, 30 min, 92%; (d) K_2CO_3, MeI, Me_2CO, reflux, 5 h, 88%; (e) $CH_3C(OEt)_3$, $EtCO_2H$, sealed tube, 180 °C, 36 h, 80%; (f) LAH, THF, 0 °C, 30 min, 95%; (g) PCC, silica gel CH_2Cl_2, rt, 15 min, 84%; (h) CH_2=CHMgBr, THF, −20 °C, 10 min, 77%; (i) PhCH=$RuCl_2(PCy_3)_2$ (5 mol %), CH_2Cl_2, 3 h, 100%; (j) PCC, silica gel, CH_2Cl_2, 1 h, 96%; (k) NaH, CH_3I, THF, DMF, rt, 12 h, 98%; (l) H_2 (1 atm), 10% Pd–C, EtOH, 1 h, 100%; (m) $(CH_2SH)_2$, I_2, 0 °C→rt, 12 h, 93%; (n) Raney Ni, EtOH, reflux, 3 h, 100%; (o) BBr_3, CH_2Cl_2, −40 °C, 4 h, 62%; (p) Ac_2O, py, CH_2Cl_2, rt, 3 h, 68%.

spectra were recorded on Jasco FTIR 410 spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on JNM λ-300 spectrometer. Unless otherwise specified a 1:1 mixture of $CDCl_3$ and CCl_4 was used as solvent for preparing the NMR samples. The chemical shifts (δ 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 the DEPT-135 spectra, and is given in parentheses. High-resolution mass spectra were recorded using Micromass Q-TOF micromass spectrometer using electrospray ionization.

3.1. 2,6-Dimethoxy-3-methylbenzaldehyde

To a cold (0 °C) magnetically stirred solution of 4-methylresorcinol dimethyl ether **7** (1.11 g, 7.24 mmol) and *N*,*N*,*N*,*N*-tetramethylethylenediamine (1.14 mL, 7.6 mmol) in anhydrous THF (5 mL) was added drop wise a solution of *n*-BuLi (2.5 M in hexane, 3.48 mL, 8.69 mmol) over a period of 10 min and stirred at rt for 1 h. It was cooled to 0 °C and DMF (0.85 mL, 10.9 mmol) was added drop wise and stirred at rt for 4 h. It was slowly poured onto cold saturated aq NH_4Cl (20 mL) and extracted with ether (2×10 mL). The combined organic layer was washed with 3 N aq HCl (20 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 (1:10) as eluent furnished 2,6-dimethoxy-3-methylbenzaldehyde[9a] (1.21 g, 92%) as a solid. Mp: 87–88 °C; IR (Neat): ν_{max}/cm^{-1} 2767, 1690, 1597, 1581; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 10.41 (1H, s), 7.28 and 6.63 (2H, 2×d, *J* 9.0 Hz), 3.87 (3H, s), 3.80 (3H, s), 2.21 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 188.7 (CH), 160.4 (C), 160.3 (C), 136.8 (CH), 123.9 (C), 118.8 (C), 106.7 (CH), 61.9 (CH_3), 55.8 (CH_3), 15.0 (CH_3).

3.2. 2,6-Dimethoxy-3-methylacetophenone (6)

To a freshly prepared magnetically stirred cold (−20 °C) solution of MeMgI [prepared from Mg (297 mg, 12.22 mmol) and MeI (1.14 mL, 18.33 mmol) in dry ether (5 mL)] was added a solution of 2,6-dimethoxy-3-methylbenzaldehyde (1.1 g, 6.11 mmol) in dry ether (3 mL) over a period of 10 min and stirred at rt for 30 min. The reaction mixture was poured into ice cold aq NH_4Cl solution and extracted with ether (3×10 mL). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished 1-(2,6-dimethoxy-3-methylphenyl)ethanol (1.15 g, 97%) as oil. IR (Neat): ν_{max}/cm^{-1} 3566, 1603; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.97 and 6.57 (2H, 2×d, *J* 8.4 Hz), 5.15 (1H, dq, *J* 11.4 and 6.6 Hz), 3.84 (3H, s), 3.74 (3H, s), 3.66 (1H, d, *J* 11.4 Hz), 2.21 (3H, s), 1.52 (3H, d, *J* 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.4 (C), 156.0 (C), 129.6 (CH), 126.1 (C), 123.5 (C), 106.8 (CH), 64.8 (CH), 60.9 (CH_3), 55.4 (CH_3), 24.4 (CH_3), 15.8 (CH_3); HRMS: *m*/*z* calcd for $C_{11}H_{16}O_3Na$ (M+Na): 219.0997, found: 219.0992.

To a magnetically stirred suspension of PCC (2.52 g, 11.7 mmol) and silica gel (2.5 g) in CH_2Cl_2 (8 mL) was added a solution of the alcohol (1.15 g, 5.87 mmol) obtained above in CH_2Cl_2 (4 mL) and vigorously stirred for 8 h at rt. The reaction mixture was then filtered through a small silica gel column with excess CH_2Cl_2. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the acetophenone **6** (970 mg, 85%) as oil.[9b,c] IR (Neat): ν_{max}/cm^{-1} 1706, 1600; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.07 and 6.56 (2H, 2×d, *J* 8.4 Hz), 3.78 (3H, s), 3.70 (3H, s), 2.46 (3H, s), 2.21 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 202.0 (C), 155.2 (C), 154.7 (C), 131.7 (CH), 126.1 (C), 123.4 (C), 106.6 (CH), 62.0 (CH_3), 55.7 (CH_3), 32.3 (CH_3), 15.2 (CH_3); HRMS: *m*/*z* calcd for $C_{11}H_{14}O_3Na$ (M+Na): 217.0841, found: 217.0846.

3.3. 2-(2,6-Dimethoxy-3-methylphenyl)but-3-en-2-ol (9)

To a cold (−20 °C) magnetically stirred solution of the ketone **6** (520 mg, 2.68 mmol) in THF (3 mL) was added a solution of vinylmagnesium bromide [prepared from Mg (129 mg, 5.36 mmol) and vinyl bromide (0.57 mL, 8.04 mmol) in THF (8 mL)] and stirred at −20 °C for 30 min. The reaction was then quenched with cold saturated aq NH_4Cl solution and extracted with ether (2×10 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 (1:20) as eluent furnished the tertiary alcohol **9** (567 mg, 95%) as oil. IR (Neat): ν_{max}/cm^{-1} 3454, 1597; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.96 and 6.57 (2H, 2×d, *J* 8.4 Hz), 6.27 (1H, dd, *J* 17.1 and 10.2 Hz), 5.81 (1H, s), 5.16 (1H, dd, *J* 17.1 and 1.5 Hz), 4.91 (1H, dd, *J* 10.2 and 1.5 Hz), 3.78 (3H, s), 3.65 (3H, s), 2.19 (3H, s), 1.68 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.8 (C), 156.2 (C), 146.0 (CH), 129.8 (CH), 127.4 (C), 124.4 (C), 109.9 (CH_2), 108.2 (CH), 75.9 (C), 61.0 (CH_3), 55.8 (CH_3), 29.5 (CH_3), 16.1 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154, found: 245.1166.

3.4. *E*-3-(2,6-Dimethoxy-3-methylphenyl)but-2-enal (10)

To a magnetically stirred suspension of PCC (1.36 g, 6.3 mmol) and silica gel (1.35 g) in CH_2Cl_2 (5 mL) was added a solution of the alcohol **9** (560 mg, 2.52 mmol) in CH_2Cl_2 (4 mL) and vigorously stirred for 8 h at rt. The reaction mixture was then filtered through a small silica gel column with excess 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 aldehyde **10** (466 mg, 84%) as oil. IR (Neat): ν_{max}/cm^{-1} 2752, 1672, 1635, 1598; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 10.15 (1H, d, *J* 8.1 Hz), 7.01 and 6.54 (2H, 2×d, *J* 8.4 Hz), 5.93 (1H, d, *J* 8.1 Hz), 3.73 (3H, s), 3.63 (3H, s), 2.42 (3H, s), 2.20 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 190.2 (CH), 155.6 (C), 155.1 (C), 154.7 (C), 131.5 (CH), 130.8 (CH), 125.8 (C), 123.4 (C), 106.6 (CH), 60.9 (CH_3), 55.7 (CH_3), 18.9 (CH_3), 15.7 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{16}O_3Na$ (M+Na): 243.0997, found: 243.1008.

3.5. *E*-3-(2,6-Dimethoxy-3-methylphenyl)but-2-en-1-ol (8a)

To a cold (−30 °C) magnetically stirred solution of the aldehyde **10** (900 mg, 4.1 mmol) in ether (5 mL) was added

LAH (156 mg, 4.1 mmol) in portions. The reaction mixture was stirred at the same temperature for 30 min and ethyl acetate (2 mL) was added to consume the excess LAH. 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 ethyl acetate–hexane (2:5) as eluent furnished the alcohol **8a** (896 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 3425, 1598; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.98 and 6.55 (2H, 2×d, *J* 8.4 Hz), 5.88 (1H, t, *J* 7.5 Hz), 3.74 (3H, s), 3.69 (2H, dd, *J* 6.6 and 2.7 Hz), 3.61 (3H, s), 2.30 (1H, br s), 2.20 (3H, s), 2.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.0 (C), 155.5 (C), 134.0 (C), 129.9 (CH), 128.2 (CH), 123.5 (C), 123.3 (C), 106.9 (CH), 60.6 (CH_2), 60.2 (CH_3), 55.8 (CH_3), 24.2 (CH_3), 15.8 (CH_3); HRMS: *m/z* calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154, found: 245.1161.

3.6. Ethyl 3-(2,6-dimethoxy-3-methylphenyl)-3-methylpent-4-enoate (11a)

A solution of the allyl alcohol **8a** (130 mg, 0.59 mmol), triethyl orthoacetate (0.5 mL, 2.93 mmol), and a catalytic amount of propionic acid (5 μL) was placed in a sealed tube and heated to 180 °C for 36 h in an oil bath. The reaction mixture was cooled, diluted with ether (5 mL), washed with 3 N aq HCl (5 mL), saturated aq $NaHCO_3$ 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 pentenoate **11a** (148 mg, 87%) as oil. IR (Neat): ν_{max}/cm^{-1} 1734, 1633, 1595; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.94 (1H, d, *J* 8.4 Hz), 6.55 (1H, dd, *J* 17.7 and 11.1 Hz), 6.52 (1H, d, *J* 8.4 Hz), 4.88 (1H, d, *J* 17.7 Hz), 4.80 (1H, d, *J* 11.1 Hz), 3.93 (2H, q, *J* 6.9 Hz), 3.73 (3H, s), 3.49 (3H, s), 3.12 and 2.85 (2H, 2×d, *J* 15.0 Hz), 2.19 (3H, s), 1.58 (3H, s), 1.07 (3H, t, *J* 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 171.7 (C), 158.1 (C), 157.4 (C), 148.5 (CH), 129.3 (CH), 127.3 (C), 124.3 (C), 107.8 (CH), 105.7 (CH_2), 60.5 (CH_3), 59.4 (CH_2), 55.5 (CH_3), 46.5 (CH_2), 43.2 (C), 25.5 (CH_3), 14.2 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{24}O_4Na$ (M+Na): 315.1572, found: 315.1551.

3.7. 3-(2,6-Dimethoxy-3-methylphenyl)-3-methylpent-4-en-1-ol (13a)

LAH (39 mg, 1.03 mmol) was added to a magnetically stirred solution of the pentenoate **11a** (300 mg, 1.03 mmol) in dry ether (2 mL) at 0 °C and stirred for 1 h. EtOAc (1 mL) was carefully added to consume excess reagent and the reaction was quenched with ice cold water (10 mL). The solution was then filtered through a sintered funnel and the residue thoroughly washed with ether (3×5 mL). The ether layer was separated, washed with brine, and dried (Na_2SO_4). Evaporation of the solvent furnished the primary alcohol **13a** (258 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 3367, 1633, 1594; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.97 and 6.56 (2H, 2×d, *J* 8.4 Hz), 6.44 (1H, dd, *J* 17.4 and 10.5 Hz), 4.88 (1H, d, *J* 17.4 Hz), 4.79 (1H, d, *J* 10.5 Hz), 3.76 (3H, s), 3.50 (3H, s), 3.53–3.47 (2H, m), 3.50 (1H, br s), 2.40–2.10 (2H, m), 2.21 (3H, s), 1.54 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 158.2 (C), 157.7 (C), 149.3 (CH), 129.3 (CH), 127.5 (C), 124.4 (C), 107.9 (CH), 104.9 (CH_2), 60.6 (CH_2), 60.5 (CH_3), 55.4 (CH_3), 43.5 (C), 43.4 (CH_2), 25.9 (CH_3), 16.4 (CH_3); HRMS: *m/z* calcd for $C_{15}H_{22}O_3Na$ (M+Na): 273.1467, found: 273.1474.

3.8. 3-(2,6-Dimethoxy-3-methylphenyl)-3-methylpent-4-enal (14a)

To a magnetically stirred suspension of PCC (555 mg, 2.58 mmol) and silica gel (550 mg) in CH_2Cl_2 (2 mL) was added a solution of the alcohol **13a** (258 mg, 1.03 mmol) in CH_2Cl_2 (2 mL) and stirred at rt for 15 min. The reaction mixture was then filtered through a small silica gel column with excess 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 aldehyde **14a** (220 mg, 89%) as oil. IR (Neat): ν_{max}/cm^{-1} 2737, 1717, 1677, 1597; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.52 (1H, t, *J* 2.7 Hz), 6.99 and 6.56 (2H, 2×d, *J* 8.4 Hz), 6.39 (1H, dd, *J* 17.7 and 10.5 Hz), 4.88 (1H, d, *J* 17.7 Hz), 4.87 (1H, d, *J* 10.5 Hz), 3.73 (3H, s), 3.51 (3H, s), 3.01 and 2.80 (2H, 2×dd, *J* 16.8 and 2.7 Hz), 2.20 (3H, s), 1.60 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 202.3 (CH), 158.0 (C), 157.0 (C), 148.2 (CH), 130.0 (CH), 126.2 (C), 124.6 (C), 108.0 (CH), 106.9 (CH_2), 60.3 (CH_3), 55.3 (CH_3), 53.9 (CH_2), 42.4 (C), 26.3 (CH_3), 16.4 (CH_3); HRMS: *m/z* calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310, found: 271.1309.

3.9. 5-(2,6-Dimethoxy-3-methylphenyl)-5-methylhepta-1,6-dien-3-ol (12a)

To a cold (−20 °C) magnetically stirred solution of the aldehyde **14a** (160 mg, 0.645 mmol) in THF was added a solution of vinylmagnesium bromide [prepared from Mg (31 mg, 1.29 mmol) and vinyl bromide (0.136 mL, 1.94 mmol) in THF (3 mL)] and stirred for 10 min. The reaction was then quenched with cold saturated aq NH_4Cl (5 mL) and extracted with ether (3×3 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 (1:10) as eluent furnished a ≈1:1 diastereomeric mixture of the dienol **12a** (151 mg, 84%) as oil. IR (Neat): ν_{max}/cm^{-1} 3457, 1631, 1594, 917; ^1H NMR (300 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 6.98 (1H, d, *J* 8.4 Hz), 6.64–6.47 (2H, m), 5.81–5.71 (1H, m), 5.10–4.78 (4H, m), 4.04 (1H, br s), 3.75 (3H, s), 3.52 (3H, s), 2.30–2.03 (2H, m), 2.21 (3H, s), 1.90–1.70 (1H, br s), 1.60 and 1.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 158.4 (C), 157.6 and 157.5 (C), 150.0 (CH), 142.2 (CH), 129.5 (CH), 127.6 (C), 127.5 and 124.6 (C), 112.9 and 112.7 (CH_2), 108.2 and 107.8 (CH), 105.3 and 104.6 (CH_2), 71.2 and 70.9 (CH), 60.7 and 60.6 (CH_3), 55.5 and 55.3 (CH_3), 48.0 and 47.8 (CH_2), 44.3 and 44.0 (C), 26.6 and 26.5 (CH_3), 16.5 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1625.

3.10. 4-(2,6-Dimethoxy-3-methylphenyl)-4-methylcyclopent-2-enol (15a)

To a magnetically stirred solution of a 1:1 diastereomeric mixture of the diene **12a** (150 mg, 0.60 mmol) in anhydrous

CH_2Cl_2 (20 mL) was added a solution of Grubbs' catalyst (25 mg, 5 mol %) in CH_2Cl_2 (10 mL) and stirred at rt for 3 h. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished a 1:1 diastereomeric mixture of the enol **15a** (133 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 3410, 1595; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.92 (1H, d, *J* 8.1 Hz), 6.68 (1H, d, *J* 5.1 Hz), 6.55 (1H, d, *J* 8.1 Hz), 5.65 (1H, m), 4.70–4.90 (1H, m), 3.80 (3H, s), 3.58 and 3.47 (3H, s), 2.74 and 2.54 (1 H, dd, *J* 14.1 and 7.2 Hz), 2.19 (3H, s), 2.02 (1H, dd, *J* 14.7 and 4.2 Hz), 1.40 and 1.53 (3H, s), 1.60 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 157.3 and 157.2 (C), 156.9 (C), 145.5 and 145.3 (CH), 130.6 and 130.5 (C), 128.9 and 128.7 (CH), 127.2 and 126.8 (CH), 124.0 and 123.9 (C), 107.6 (CH), 60.9 and 60.8 (CH_3), 55.4 (CH_3), 51.4 and 50.3 (C), 50.8 and 50.2 (CH_2), 30.8 and 29.3 (CH_3), 16.4 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1317, found: 271.1310.

3.11. 4-(2,6-Dimethoxy-3-methylphenyl)-4-methylcyclopent-2-enone (16a)

To a magnetically stirred suspension of PCC (288 mg, 1.34 mmol) and silica gel (288 mg) in CH_2Cl_2 (1 mL) was added a solution of the alcohol **15a** (133 mg, 0.54 mmol) in CH_2Cl_2 (1 mL) and stirred at rt for 1 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 **16a** (123 mg, 93%) as oil. IR (Neat): ν_{max}/cm^{-1} 1711, 1588; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 8.23 (1H, d, *J* 5.7 Hz), 6.90 and 6.51 (2H, 2×d, *J* 8.4 Hz), 5.93 (1H, d, *J* 5.7 Hz), 3.76 (3H, s), 3.37 (3H, s), 2.65 and 2.53 (2H, 2×d, *J* 18.9 Hz), 2.14 (3H, s), 1.51 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 208.7 (C), 173.7 (CH), 156.9 (C), 156.1 (C), 129.7 (CH), 127.9 (C), 126.8 (CH), 123.8 (C), 107.5 (CH), 61.0 (CH_3), 55.5 (CH_3), 51.5 (CH_2), 46.8 (C), 27.8 (CH_3), 16.1 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{18}O_3Na$ (M+Na): 247.1334, found: 247.1334.

3.12. 4-(2,6-Dimethoxy-3-methylphenyl)-4,5,5-trimethylcyclopent-2-enone (17a)

A solution of the ketone **16a** (220 mg, 0.894 mmol) in THF (1 mL) was added to a suspension of NaH (180 mg, 60% dispersion in oil, 4.47 mmol, washed with dry hexanes) in THF (2 mL) and DMF (0.2 mL) and stirred at rt for 15 min. Methyl iodide (0.42 mL, 6.7 mmol) was added to the reaction mixture and stirred for 12 h at rt. Water (5 mL) was added to the reaction mixture and extracted with ether (3×5 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 (1:10) as eluent furnished the enone **17a** (180 mg, 73%) as oil. IR (Neat): ν_{max}/cm^{-1} 1700, 1593; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 8.17 (1H, d, *J* 5.7 Hz), 6.99 and 6.58 (2H, 2×d, *J* 7.8 Hz), 5.89 (1H, d, *J* 5.7 Hz), 3.83 (3H, s), 3.37 (3H, s), 2.21 (3H, s), 1.53 (3H, s), 1.25 (3H, s), 0.78 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 214.1 (C), 173.6 (CH), 157.1 (C), 156.8 (C), 129.6 (CH), 126.5 (C), 123.8 (C), 120.6 (CH), 107.0 (CH), 59.9 (CH_3), 54.8 (CH_3), 54.5 (C), 49.5 (C), 25.2 (CH_3), 24.3 (CH_3), 21.6 (CH_3), 16.2 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{22}O_3Na$ (M+Na): 275.1647, found: 275.1651.

3.13. 3-(2,6-Dimethoxy-3-methylphenyl)-2,2,3-trimethylcyclopentanone (18a)

To activated 10% Pd–C (20 mg) was added a solution of the enone **17a** (180 mg, 0.656 mmol) in ethanol (2 mL) and stirred for 1 h at rt in an atmosphere of hydrogen created by evacuative replacement of air (balloon). The catalyst was then filtered off. Evaporation of the solvent under reduced pressure furnished the saturated ketone **18a** (181 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 1734, 1579; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.97 and 6.51 (2H, 2×d, *J* 8.1 Hz), 3.67 (3H, s), 3.62 (3H, s), 2.45–2.20 (4H, m), 2.22 (3H, s), 1.56 (3H, s), 1.19 (3H, s), 0.69 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 159.0 (C), 157.4 (C), 129.4 (CH), 124.5 (C), 106.5 (CH), 60.8 (CH_3), 54.0 (CH_3), 34.9 (CH_2), 16.5 (CH_3) (other signals are very broad probably due to fluxional behavior of the molecule); HRMS: *m*/*z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1610.

3.14. 3-(2,6-Dimethoxy-3-methylphenyl)-2,2,3-trimethylcyclopentanol (19)

To an ice cold magnetically stirred solution of the ketone **18a** (181 mg, 0.66 mmol) in dry methanol (1 mL) was added $NaBH_4$ (47 mg, 1.31 mmol) and stirred for 5 min. The solvent was removed under reduced pressure. Water (3 mL) followed by 3 N aq HCl (4 mL) were added to the reaction mixture 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 (1:20–1:10) as eluent furnished an epimeric mixture of the alcohol **19** (180 mg, 99%) as oil. IR (Neat): ν_{max}/cm^{-1} 3411, 1591; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.94 and 6.93 (1H, d, *J* 8.1 Hz), 6.52 (1H, d, *J* 8.1 Hz), 3.89–3.76 (1H, m), 3.73 and 3.71 (3H, s), 3.60 (3H, s), 3.05–2.50 (1H, m), 2.16 (3H, s) 2.20–1.26 (4H, m), 1.50 and 1.48 (3H, s), 1.09 and 1.07 (3H, s), 0.66 (3H, s); HRMS: *m*/*z* calcd for $C_{17}H_{26}O_3Na$ (M+Na): 301.1780, found: 301.1775.

3.15. 4-Methyl-2-(1,2,2-trimethylcyclopentyl)benzene-1,3-diol dimethyl ether (21a)

To a magnetically stirred suspension of NaH (29 mg, 60% dispersion in oil, 0.72 mmol) in dry THF (1 mL) was added a solution of the alcohol **19** (40 mg, 0.144 mmol) in dry THF (0.5 mL) followed by a catalytic amount of imidazole. The reaction mixture was heated to 60 °C for 15 min. It was cooled to rt, added CS_2 (0.09 mL, 1.44 mmol), and refluxed for 15 min. It was cooled to rt, added MeI (0.09 mL, 1.44 mmol), 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 purification of the residue on a silica gel column using CH_2Cl_2–hexane (1:10) as eluent furnished the dithiocarbonate **20** (47 mg, 88%) as yellow oil. IR (Neat): ν_{max}/cm^{-1} 1591, 1390, 1375, 1240; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.96 and 6.54 (2H, 2×d, *J* 8.4 Hz), 5.70–5.50 (1H, m), 3.72 (3H, s), 3.63

and 3.61 (3H, s), 3.26 (1H, br s), 2.56 and 2.51 (3H, s), 2.40–2.32 (1H, m), 2.23 (3H, s), 1.92–1.42 (5H, m), 1.19 and 1.16 (3H, s), 0.75 (3H, s). A solution of the dithiocarbonate **20** (47 mg, 0.128 mmol), *n*-Bu_3SnH (0.14 mL, 0.512 mmol), and a catalytic amount of AIBN in dry benzene (2 mL) was refluxed for 3 h. The reaction mixture was cooled, diluted with ether (4 mL), washed successively with 1% aq NH_4OH, water, and brine, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using hexane as eluent furnished the deoxygenated product **21a** (25 mg, 75%) as colorless oil. IR (Neat): ν_{max}/cm^{-1} 1591; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.91 and 6.50 (2H, 2×d, *J* 8.1 Hz), 3.70 (3H, s), 3.58 (3H, s), 3.13 (1H, br s), 2.21 (3H, s), 2.00–1.90 (1H, m), 1.65–1.40 (4H, m), 1.34 (3H, s), 1.12 (3H, s), 0.66 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 158.5 (2C, C), 129.0 (C), 128.7 (CH), 124.4 (C), 106.9 (CH), 61.0 (CH_3), 54.5 (CH_3), 52.6 (C), 45.4 (C), 43.6 (CH_2), 40.3 (CH_2), 29.1 (CH_3), 27.3 (CH_3), 24.1 (CH_3), 21.6 (CH_2), 16.8 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{26}O_2K$ (M+K): 301.1570, found: 301.1577.

3.16. 4-Methyl-2-(1,2,2-trimethylcyclopentyl)benzene-1,3-diol (herbertene-1,5-diol 22)

Methylmagnesium iodide solution in ether (5 mL) was prepared using Mg (50 mg, 2.1 mmol) and CH_3I (0.16 mL) and the solvent was evaporated under vacuum. A solution of the methyl ether **21a** (14 mg, 0.053 mmol) in dry *p*-cymene (2 mL) was added to MeMgI and refluxed for 8 h. It was then cooled to rt, carefully added to cold saturated aq NH_4Cl solution (5 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 the diol **22** (8 mg, 64%). IR (Neat): ν_{max}/cm^{-1} 3606, 3531, 1605; ^1H NMR (300 MHz, $CDCl_3$): δ 6.73 and 6.11 (2H, 2×d, *J* 7.8 Hz), 4.82 (1H, s), 4.57 (1H, br s), 3.31 (1H, br s), 2.13 (3H, s), 1.80–1.50 (5H, m), 1.49 (3H, s), 1.18 (3H, s), 0.85 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.4 (C), 154.8 (C), 128.0 (2C, CH), 115.8 (C), 109.5 (C), 52.3 (C), 46.3 (C), 42.1 (CH_2), 40.8 (CH_2), 27.7 (CH_3), 26.3 (CH_3), 24.8 (CH_2), 21.8 (CH_3), 16.3 (CH_3) (some of the signals are very broad due to fluxional behavior); HRMS: *m*/*z* calcd for $C_{15}H_{22}O_2Na$ (M+Na): 273.1467, found: 273.1479.

3.17. 3-Hydroxy-4-methyl-2-(1,2,2-trimethylcyclopentyl)phenyl acetate (3)

To a magnetically stirred solution of the diol **22** (6 mg, 0.026 mmol) in CH_2Cl_2 (0.3 mL) was added sequentially Ac_2O (5 μL, 0.052 mmol), pyridine (50 μL, 0.615 mmol), and DMAP (1 mg), and stirred at rt for 2 h. Water (1 mL) was added to the reaction mixture and extracted with 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 acetate **3** (5 mg, 71%) as oil. IR (Neat): ν_{max}/cm^{-1} 3516, 1749, 1664, 1587; ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 and 6.33 (2H, 2×d, *J* 7.8 Hz), 4.88 (1H, br s), 2.90–2.80 (1H, m), 2.24 (3H, s), 2.20 (3H, s), 1.74–1.51 (5H, m), 1.42 (3H, s), 1.26 (3H, s), 0.79 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4 (C), 154.3 (C), 148.7 (C), 128.2 (CH), 126.0 (C), 121.1 (C), 116.3 (CH), 52.2 (C), 45.3 (C), 42.7 (CH_2), 40.3 (CH_2), 28.5 (CH_3), 26.8 (CH_3), 22.9 (CH_3), 21.7 (CH_3), 21.4 (CH_2), 16.3 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1619.

3.18. *Z*-(2-Hydroxy-3-methoxy-4-methylphenyl)but-2-en-1-ol (26)

To a cold (−50 °C) magnetically stirred solution of the coumarin[14] **25** (520 mg, 2.55 mmol) in dry THF (3 mL) was added LAH (93 mg, 2.5 mmol) in portions and stirred for 30 min. Ethyl acetate (2 mL) was added to the reaction mixture to consume the excess LAH. The reaction 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 ethyl acetate–hexane (2:5) as eluent furnished the alcohol **26** (488 mg, 92%). IR (Neat): ν_{max}/cm^{-1} 3398, 1655, 1616, 1575; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.65 (2H, s), 6.23 (1H, br s), 5.81 (1H, td, *J* 7.8 and 1.5 Hz), 3.86 (2H, d, *J* 7.8 Hz), 3.79 (3H, s), 2.28 (3H, s), 2.20 (1H, br s), 2.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 145.6 (C), 145.2 (C), 136.2 (C), 129.6 (C), 127.4 (CH), 126.0 (C), 124.5 (CH), 122.1 (CH), 60.6 (CH_2), 60.5 (CH_3), 25.2 (CH_3), 15.9 (CH_3); HRMS: *m*/*z* calcd for $C_{12}H_{16}O_3Na$ (M+Na): 231.0997, found: 231.1004.

3.19. *Z*-(2,3-Dimethoxy-4-methylphenyl)but-2-en-1-ol (8b)

A solution of the diol **26** (320 mg, 1.54 mmol), anhydrous K_2CO_3 (425 mg, 3.08 mmol), and CH_3I (0.19 mL, 3.08 mmol) in acetone (6 mL) was refluxed for 5 h. Solvent was evaporated under reduced pressure. The residue was taken in water and extracted with ether (3×15 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 (1:5) as eluent furnished the cinnamyl alcohol **8b** (520 mg, 97%). IR (Neat): ν_{max}/cm^{-1} 3400; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.85 and 6.67 (2H, 2×d, *J* 8.0 Hz), 5.79 (1H, td, *J* 7.5 and 1.5 Hz), 3.83 (3H, s), 3.79 (2H, d, *J* 7.5 Hz), 3.75 (3H, s), 2.25 (3H, s), 2.05 (3 H, s), 2.00 (1 H, br s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 151.5 (C), 149.8 (C), 136.5 (C), 133.3 (C), 131.4 (C), 127.4 (CH), 125.9 (CH), 124.0 (CH), 60.8 (CH_3), 60.6 (CH_2), 60.2 (CH_3), 25.5 (CH_3), 15.9 (CH_3); HRMS: *m*/*z* calcd for $C_{13}H_{18}O_3Na$ (M+Na): 245.1154, found: 245.1162.

3.20. Ethyl 3-(2,3-dimethoxy-4-methylphenyl)-3-methylpent-4-enoate (11b)

A solution of the allyl alcohol **8b** (300 mg, 1.35 mmol), triethyl orthoacetate (1.24 mL, 6.76 mmol), and a catalytic amount of propionic acid (10 μL) was placed in a sealed tube and heated to 180 °C for 36 h in an oil bath. Work-up as described for the ester **11a**, followed by purification on a silica gel column using ethyl acetate–hexane (1:40) as eluent furnished the ester **11b** (316 mg, 80%) as oil. IR (Neat): ν_{max}/cm^{-1} 1734, 1635; ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.83 and 6.74 (2H, 2×d, *J* 8.1 Hz), 6.25 (1H, dd, *J* 17.4 and 10.8 Hz), 5.02 (1H, dd, *J* 10.8 and 1.2 Hz), 4.94 (1H, dd,

J 17.4 and 0.9 Hz), 3.92 (2H, q, *J* 7.5 Hz), 3.83 (3H, s), 3.74 (3H, s), 3.06 and 2.77 (2H, 2×d, *J* 14.1 Hz), 2.21 (3H, s), 1.53 (3H, s), 1.05 (3H, t, *J* 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 171.2 (C), 151.9 (C), 151.7 (C), 146.7 (CH), 136.8 (C), 130.8 (C), 124.3 (CH), 122.2 (CH), 111.0 (CH_2), 59.6 (CH_3), 59.4 (CH_2), 59.2 (CH_3), 44.1 (CH_2), 42.7 (C), 25.7 (CH_3), 15.6 (CH_3), 14.1 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{24}O_4Na$ (M+Na): 315.1572, found: 315.1586.

3.21. 3-(2,3-Dimethoxy-4-methylphenyl)-3-methylpent-4-en-1-ol (13b)

Reduction of the pentenoate **11b** (316 mg, 1.08 mmol) with LAH (40 mg, 1.08 mmol) in dry ether (3 mL) at 0 °C for 30 min and work-up as described for the alcohol **13a**, followed by purification over silica gel column using ethyl acetate–hexane (3:7) furnished the alcohol **13b** (257 mg, 95%) as oil. IR (Neat): ν_{max}/cm^{-1} 3368; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.82 and 6.75 (2H, 2×d, *J* 8.1 Hz), 6.16 (1H, dd, *J* 17.1 and 10.5 Hz), 5.01 (1H, dd, *J* 10.5 and 0.9 Hz), 4.95 (1H, dd, *J* 17.1 and 0.9 Hz), 3.81 (3H, s), 3.74 (3H, s), 3.60–3.40 (2H, m), 2.42–2.29 (1H, m), 2.21 (3H, s), 2.05–1.96 (1H, m), 1.42 (3H, s), 1.45 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.2 (C), 152.0 (C), 147.9 (CH), 137.7 (C), 130.9 (C), 124.7 (CH), 122.3 (CH), 110.7 (CH_2), 60.2 (CH_2), 59.7 (CH_3), 59.3 (CH_3), 42.8 (C), 42.2 (CH_2), 25.9 (CH_3), 15.7 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{22}O_3Na$ (M+Na): 273.1467, found: 273.1470.

3.22. 3-(2,3-Dimethoxy-4-methylphenyl)-3-methylpent-4-enal (14b)

Oxidation of the alcohol **13b** (250 mg, 1.0 mmol) with PCC (538 mg, 2.5 mmol) and silica gel (540 mg) in CH_2Cl_2 (3 mL) at rt for 15 min and work-up as described for the aldehyde **14a**, followed by purification on a silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the aldehyde **14b** (210 mg, 84%) as oil. IR (Neat): ν_{max}/cm^{-1} 2733, 1720, 1681, 1635, 1603; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.46 (1H, t, *J* 2.7 Hz), 6.84 and 6.76 (2H, 2×d, *J* 7.8 Hz), 6.16 (1H, dd, *J* 17.4 and 10.5 Hz), 5.08 (1H, d, *J* 10.5 Hz), 4.98 (1H, d, *J* 17.4 Hz), 3.82 (3H, s), 3.72 (3H, s), 3.07 (1H, dd, *J* 15.3 and 2.7 Hz), 2.76 (1H, dd, *J* 15.3 and 2.7 Hz), 2.20 (3H, s), 1.51 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 202.2 (CH), 152.2 (C), 151.9 (C), 146.3 (CH), 136.1 (C), 131.6 (C), 124.9 (CH), 122.2 (CH), 111.8 (CH_2), 59.8 (CH_3), 59.4 (CH_3), 52.2 (CH_2), 42.1 (C), 26.4 (CH_3), 15.7 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310, found: 271.1324.

3.23. 5-(2,3-Dimethoxy-4-methylphenyl)-5-methylhepta-1,6-dien-3-ol (12b)

Grignard reaction of the aldehyde **14b** (210 mg, 0.847 mmol) in THF with vinylmagnesium bromide [prepared from Mg (41 mg, 1.69 mmol) and vinyl bromide (0.12 mL, 1.69 mmol) in THF (2 mL)] for 10 min at −20 °C and work-up as described for the dienol **12a**, followed by purification on a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished a ≈1:1 diastereomeric mixture of the dienol **12b** (180 mg, 77%) as oil. IR (Neat): ν_{max}/cm^{-1} 3437, 1634, 917; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 6.88 and 6.87 (1H, d, *J* 8.1 Hz), 6.78 and 6.76 (1H, d, *J* 8.1 Hz), 6.25 and 6.24 (1H, dd, *J* 17.7 and 10.8 Hz), 5.84–5.69 (1H, m), 5.12–4.89 (4H, m), 4.04 and 3.96 (1H, m), 3.84 and 3.81 (3H, s), 3.74 and 3.73 (3H, s), 2.38–2.25 (1H, m), 2.22 (3H, s), 1.99–1.89 (1H, m), 1.52 and 1.47 (3H, s), 1.50–1.30 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 152.2 (C), 152.11 and 52.08 (C), 148.6 and 148.2 (CH), 142.3 and 142.2 (CH), 137.7 and 137.6 (C), 131.2 and 131.0 (C), 124.9 and 124.7 (CH), 122.6 and 122.4 (CH), 113.3 and 113.1 (CH_2), 110.8 (CH_2), 70.9 and 70.7 (CH), 59.8 (CH_3), 59.4 and 59.3 (CH_3), 47.0 and 46.5 (CH_2), 43.6 and 43.4 (C), 26.5 and 26.4 (CH_3), 15.8 (CH_3); HRMS: *m*/*z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1622.

3.24. 4-(2,3-Dimethoxy-4-methylphenyl)-4-methylcyclopent-2-en-1-ol (15b)

RCM reaction of a 1:1 diastereomeric mixture of the diene **12b** (200 mg, 0.72 mmol) with Grubbs' catalyst (30 mg, 5 mol %) in CH_2Cl_2 (30 mL) at rt for 3 h and work-up as described for the cyclopentenol **15a**, followed by purification on a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished a 1:1 diastereomeric mixture of the enol **15b** (180 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 3392, 908; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4, mixture of diastereomers): δ 6.85–6.65 (2H, m), 6.18 and 6.09 (1H, d, *J* 5.4 Hz), 5.82 (1H, t, *J* 5.4 Hz), 4.90–4.75 (1H, m), 3.86 (3H, s), 3.76 (3H, s), 2.58–2.50 (1H, m), 2.21 and 2.20 (3H, s), 1.97 and 1.96 (1H, d, *J* 14.1 Hz), 1.52 and 1.39 (3H, s); HRMS: *m*/*z* calcd for $C_{15}H_{20}O_3Na$ (M+Na): 271.1310, found: 271.1313.

3.25. 4-(2,3-Dimethoxy-4-methylphenyl)-4-methylcyclopent-2-enone (16b)

Oxidation of the alcohol **15b** (183 mg, 0.74 mmol) with PCC (397 mg, 1.84 mmol) and silica gel (400 mg) in CH_2Cl_2 (3 mL) at rt for 1 h and work-up as described for the enone **16a**, furnished the enone **16b** (179 mg, 96%) as oil. IR (Neat): ν_{max}/cm^{-1} 1715, 1589; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.73 (1H, d, *J* 5.4 Hz), 6.78 (2H, s), 6.12 (1H, d, *J* 5.4 Hz), 3.82 (3H, s), 3.75 (3H, s), 2.68 and 2.52 (2H, 2×d, *J* 18.3 Hz), 2.22 (3H, s), 1.56 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 208.6 (C), 170.4 (CH), 152.0 (C), 151.7 (C), 136.4 (C), 131.7 (C), 130.8 (CH), 124.9 (CH), 121.3 (CH), 59.9 (CH_3), 59.4 (CH_3), 51.0 (CH_2), 47.1 (C), 28.4 (CH_3), 15.7 (CH_3); HRMS: *m*/*z* calcd for $C_{15}H_{19}O_3$ (M+H): 247.1334, found: 247.1335.

3.26. 4-(2,3-Dimethoxy-4-methylphenyl)-4,5,5-trimethylcyclopent-2-enone (17b)

One-pot dialkylation of the ketone **16b** (100 mg, 0.406 mmol) with NaH (243 mg, 60% dispersion in oil, 6.09 mmol, washed with dry hexanes) and methyl iodide (0.51 mL, 8.12 mmol) in THF (5 mL) and DMF (0.25 mL) for 12 h at rt and work-up as described for the enone **17a**, followed by purification over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the alkylated product **17b** (110 mg, 98%) as oil. IR (Neat): ν_{max}/cm^{-1} 1708, 1600; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.87 (1H, d, *J* 5.7 Hz), 6.80 and 6.70 (2H,

2×d, *J* 7.8 Hz), 6.06 (1H d, *J* 5.7 Hz), 3.87 (3H, s), 3.75 (3H, s), 2.24 (3H, s), 1.47 (3H, s), 1.22 (3H, s), 0.63 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 214.0 (C), 170.7 (CH), 151.9 (2C, C), 134.6 (C), 131.4 (C), 125.0 (CH), 123.0 (2C, CH), 60.0 (CH_3), 59.3 (CH_3), 54.6 (C), 50.9 (C), 26.0 (2C, CH_3), 19.9 (CH_3), 15.7 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{23}O_3$ (M+H): 275.1647, found: 275.1646.

3.27. 3-(2,3-Dimethoxy-4-methylphenyl)-3,4,4-trimethylcyclopentanone (18b)

Hydrogenation of the enone **17b** (110 mg, 0.4 mmol) with 10% Pd–C (20 mg) as the catalyst in ethanol (2 mL) for 1 h and work-up as described for the compound **18a**, furnished the saturated ketone **18b** (111 mg, 100%) as oil. IR (Neat): ν_{max}/cm^{-1} 1738; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.94 and 6.78 (2H, 2×d, *J* 8.4 Hz), 3.84 (3H, s), 3.75 (3H, s), 2.70–2.53 (1 H, m), 2.45–2.35 (2H, m), 2.23 (3H, s), 2.07 (1H, ddd, *J* 12.6, 6.6, and 4.2 Hz), 1.33 (3H, s), 1.23 (3H, s), 0.71 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 222.1 (C), 152.7 (C), 152.1 (C), 136.8 (C), 130.8 (C), 124.7 (CH), 122.8 (CH), 59.8 (CH_3), 59.4 (CH_3), 53.4 (C), 49.4 (C), 34.1 (CH_2), 32.0 (CH_2), 24.5 (CH_3), 22.3 (CH_3), 20.5 (CH_3), 15.6 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1630.

3.28. 7-(2,3-Dimethoxy-4-methylphenyl)-6,6,7-trimethyl-1,4-dithiaspiro[4.4]nonane (27)

To a magnetically stirred solution of the ketone **18b** (92 mg, 0.34 mmol) in dry CH_2Cl_2 (0.3 mL) was added 1,2-ethanedithiol (0.28 mL, 1.12 mmol) and iodine (16 mg, 20 mol %) and stirred at rt for 30 min. To the reaction mixture 1 M aq $Na_2S_2O_3$ (2 mL) and 10% aq NaOH (10 mL) were added and stirred for 5 min, and extracted with CH_2Cl_2 (2×4 mL). The CH_2Cl_2 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 CH_2Cl_2–hexane (1:10) as eluent furnished the thioketal **27** (94 mg, 80%) as oil. IR (Neat): ν_{max}/cm^{-1} 1397, 1277, 1093, 1057, 1021; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.89 and 6.73 (2H, 2×d, *J* 8.1 Hz), 3.86 (3H, s), 3.72 (3H, s), 3.30–3.10 (4H, m), 2.72–2.65 (1H, m), 2.52 (1H, br s), 2.32–2.34 (1H, m), 2.21 (3H, s), 1.76–1.65 (1H, m), 1.54 (3H, s), 1.22 (3H, s), 0.72 (3H, s); HRMS: *m/z* calcd for $C_{19}H_{28}O_2S_2Na$ (M+Na): 375.1428, found: 375.1429.

3.29. 6-Methyl-3-(1,2,2-trimethylcyclopentyl)benzene-1,2-diol dimethyl ether (21b)

To a magnetically stirred solution of the thioketal **27** (94 mg, 0.267 mmol) in dry ethanol (6 mL) was added Raney nickel (200 mg, excess) and refluxed for 3 h. The reaction mixture was cooled and filtered through a short silica gel column using excess CH_2Cl_2. Evaporation of the solvent furnished the deoxygenated product **21b** (70 mg, 100%). IR (Neat): ν_{max}/cm^{-1} 1277, 1094, 1054, 1023; ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.91 and 6.73 (2H, 2×d, *J* 8.1 Hz), 3.81 (3H, s), 3.75 (3H, s), 2.57–2.52 (1H, m), 2.21 (3H, s), 1.85–1.40 (5H, m), 1.35 (3H, s), 1.11 (3H, s), 0.68 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 153.1 (C), 152.1 (C), 138.5 (C), 129.8 (C), 124.2 (CH), 123.6 (CH), 59.9 (CH_3), 59.3 (CH_3), 51.5 (C), 45.0 (C), 41.1 (CH_2), 39.3 (CH_2), 26.9 (CH_3), 25.5 (CH_3), 24.1 (CH_3), 20.5 (CH_2), 15.6 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{26}O_2Na$ (M+Na): 285.1830, found: 285.1838.

3.30. 3-(1,2,2-Trimethylcyclopentyl)-6-methylbenzene-1,2-diol (HM-4 or cuparene-1,2-diol 4)

To a cold (−40 °C) magnetically stirred solution of the dimethyl ether **21b** (40 mg, 0.15 mmol) in dry CH_2Cl_2 (2 mL) was added drop wise a solution of BBr_3 (1 M in CH_2Cl_2, 0.86 mL, 0.86 mmol) and stirred at the same temperature for 4 h. The reaction was then quenched with saturated aq $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×3 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 over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished cuparene-1,2-diol **4** (22 mg, 62%). IR (Neat): ν_{max}/cm^{-1} 3613, 3516, 1506; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 and 6.53 (2H, 2×d, *J* 8.4 Hz), 5.52 (1H, br s), 4.87 (1H, br s), 2.65–2.56 (1H, m), 2.20 (3H, s), 1.85–1.40 (5H, m), 1.40 (3H, s), 1.17 (3H, s), 0.75 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.2 (C), 141.9 (C), 131.2 (C), 121.2 (C), 120.7 (CH), 120.5 (CH), 50.9 (C), 44.8 (C), 40.8 (CH_2), 39.2 (CH_2), 26.7 (CH_3), 25.3 (CH_3), 22.9 (CH_3), 20.2 (CH_2), 15.3 (CH_3); HRMS: *m/z* calcd for $C_{15}H_{22}O_3Na$ (M+Na): 257.1517, found: 257.1512.

3.31. 2-Hydroxy-3-(1,2,2-trimethylcyclopentyl)-6-methylphenyl acetate (HM-3, 28)

Acetylation of the diol **4** (15 mg, 0.064 mmol) with Ac_2O (6 μL, 0.064 mmol) and pyridine (5 μL, 0.064 mmol) in dry CH_2Cl_2 for 3 h at rt and work-up as described for the acetate **3**, followed by purification over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the monoacetate **28** (12 mg, 68%) as oil. IR (Neat): ν_{max}/cm^{-1} 3406, 1770, 1738, 1618; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 and 6.69 (2H, 2×d, *J* 8.4 Hz), 5.18 (1H, s), 2.65–2.44 (1H, m), 2.37 (3H, s), 2.11 (3H, s), 1.82–1.48 (5H, m), 1.40 (3H, s), 1.15 (3H, s), 0.74 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6 (C), 146.4 (C), 137.9 (C), 132.9 (C), 128.2 (C), 126.2 (CH), 121.0 (CH), 51.2 (C), 44.8 (C), 41.1 (CH_2), 39.4 (CH_2), 26.8 (CH_3), 25.5 (CH_3), 22.8 (CH_3), 20.6 (CH_3), 20.4 (CH_2), 16.0 (CH_3); HRMS: *m/z* calcd for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623, found: 299.1636.

Acknowledgements

We thank the Council of Scientific and Industrial Research, New Delhi for the award of a research fellowship to P.C.R.

Supplementary data

Copies of the ^{1}H and ^{13}C NMR spectra of cuparene-1,2-diol (**4**), HM-3 (revised) (**28**), and the putative structure of HM-3 (**3**). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.07.062.

References and notes

1. Kajimoto, T.; Yamashita, M.; Imamura, Y.; Nohara, T.; Shibata, M. *Chem. Lett.* **1989**, 527.
2. Thomson, R. H. *Naturally Occurring Quinones*; Academic: 1971; Nishikawa, H. *Agric. Biol. Chem.* **1962**, *26*, 696; Takai, S. *Phytopathol. Zeit.* **1962**, *43*, 175; Natori, S.; Ogawa, H.; Yamaguchi, K.; Nishikawa, H. *Chem. Pharm. Bull.* **1963**, *11*, 1343; Natori, S.; Nishikawa, H.; Ogawa, H. *Chem. Pharm. Bull.* **1964**, *12*, 236; Bollinger, P. Thesis, Eidgenossischen Technischen Hochschule, 1965; Natori, S.; Inouye, Y.; Nishikawa, H. *Chem. Pharm. Bull.* **1967**, *15*, 380; Carey, B. B.; Donald, J. S. *Phytochemistry* **1975**, *14*, 1433; Bu'Lock, J. D.; Darbyshire, J. *Phytochemistry* **1976**, *15*, 2004; Bottom, C. B.; Siehr, D. J. *Phytochemistry* **1975**, *14*, 1433.
3. Asakawa, Y.; Matsuda, R.; Schofield, W. B.; Gradstein, S. R. *Phytochemistry* **1982**, *10*, 2471; Asakawa, Y.; Takikawa, K.; Toyota, M.; Takemoto, T. *Phytochemistry* **1982**, *10*, 2481; Toyota, M.; Koyama, H.; Asakawa, Y. *Phytochemistry* **1997**, *46*, 145.
4. Irita, H.; Hashimoto, T.; Fukuyama, Y.; Asakawa, Y. *Phytochemistry* **2000**, *55*, 247.
5. Srikrishna, A.; Ravikumar, P. C. *Tetrahedron Lett.* **2005**, *46*, 6105.
6. To the best of our knowledge there is no report in the literature on the synthesis of HM-3 and HM-4 (cuparene-1,2-diol).
7. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
8. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013; (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.
9. (a) Yamaguchi, S.; Nedachi, M.; Yokoyama, H.; Hirai, Y. *Tetrahedron Lett.* **1999**, *40*, 7363; (b) Cram, D. J.; Cranz, F. W. *J. Am. Chem. Soc.* **1950**, *72*, 595; (c) Sprenger, R. D.; Ruoff, P. M. *J. Org. Chem.* **1946**, *11*, 189.
10. Buchi, G.; Egger, B. *J. Org. Chem.* **1971**, *36*, 2021; Srikrishna, A.; Sharma, G. V. R.; Danieldoss, S.; Hemamalini, P. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1305.
11. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, 939; Barton, D. H. R.; Bridon, D.; Fernandez-Picot, I.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 2733.
12. It is worth mentioning that thioketalization reaction of the ketone in **18a** using standard procedure was unsuccessful due to the acid catalyzed cleavage of the cyclopentane moiety from the aromatic part (probably due to the presence of two methoxy groups on the aromatic ring *ortho* to cyclopentane moiety) resulting in the formation of 4-methylresorcinol dimethyl ether. Hence, reductive deoxygenation of the ketone in **18a** was carried out employing Barton's radical protocol.
13. The signals due to three tertiary methyl groups for the synthetic monoacetate **3** appeared at δ 1.42, 1.26, and 0.79, whereas 1.40, 1.15, and 0.74 ppm were reported for HM-3. Similarly, considerable difference is there for the signals due to aromatic protons, e.g., for the two aromatic protons $\Delta\delta$ reported for HM-3 is 0.39, whereas $\Delta\delta$ observed for synthetic **3** is 0.59.
14. Mills, F. D. *J. Heterocycl. Chem.* **1980**, *17*, 1597.
15. Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527.
16. With the structure revision of HM-2[5] and HM-3 as cuparene derivatives, only one herbertenoid, γ-herbertenol isolated from *Tylimanthus renifolius*,[17] is reported to be isolated from a liverwort, which does not belong to *Herbertus*. Currently, we are investigating the total synthesis of γ-herbertenol to confirm its structure.
17. Feld, H.; Zapp, J.; Becker, H. *Phytochemistry* **2003**, *64*, 1335.