A Formal Total Synthesis of (±)-1,13-Herbertenediol

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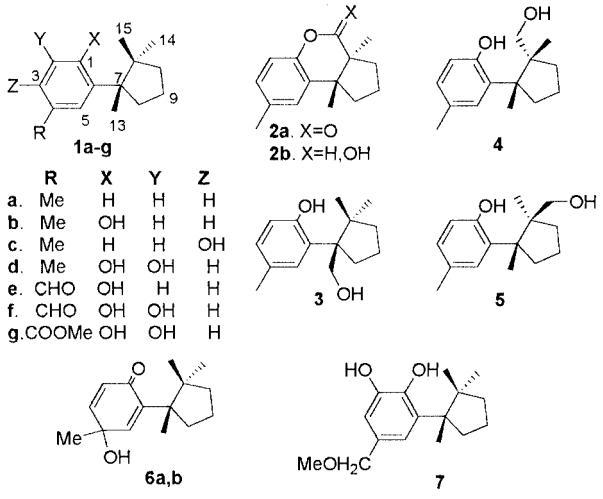
A formal total synthesis of (±)-1,13-herbertenediol, employing a ring-closing metathesis reaction of the 4-arylhepta-1,6-diene-4-carboxylate **15** as the key reaction, is described.

Introduction

Herbertanes are a small group of sesquiterpenes, which are considered as chemical markers for the liverworts belonging to the genus *Herbertus*.[1a] Isolation of the first members of the herbertane group **1a**−**e** and **2a** from *H. adunca* was reported earlier by Matsuo and co-workers.[1b] Subsequently,[1c] Rycroft et al. reported the isolation of the aldehyde **1f** and the ester **1g** from *H.s aduncus*. Recently,[1a] Asakawa and co-workers reported the isolation from the Japanese liverwort *H. sakuraii* of seven new members of this group: herbertenelactol (**2b**), 1,13-herbertenediol (**3**), 1,14-herbertenediol (**4**), 1,15-herbertenediol (**5**), herbertenones A and B (**6a,b**) and 12-methoxyherbertenediol (**7**) along with dimeric herbertanes mastigophorenes A−C. The phenolic herbertanes, e.g. **1b**−**d** and the dimeric mastigophorenes have been shown to possess interesting biological properties such as growth-inhibiting, antifungal, antilipid peroxidation and neurotropic activities.[1,2]



	R	X	Y	Z
a.	Me	H	H	H
b.	Me	OH	H	H
c.	Me	H	H	OH
d.	Me	OH	OH	H
e.	CHO	OH	H	H
f.	CHO	OH	OH	H
g.	COOMe	OH	OH	H

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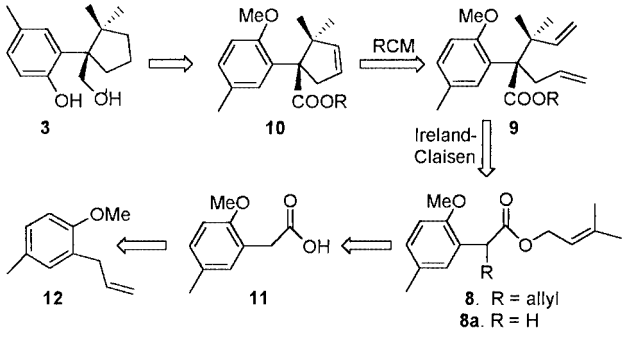
The sesquiterpenes cuparanes and herbertanes are interesting synthetic targets owing to the presence of a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane moiety, and the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring. The significant biological properties of the phenolic herbertanes make them important synthetic targets of current interest.[3] Since its isolation, there are two reports on the synthesis of 1,13-herbertenediol (**3**). In 2001, Fukuyama et al., reported the first synthesis employing an intramolecular Heck reaction.[4] Recently,[3g] we have reported the synthesis of 1,13-herbertenediol (**3**) along with α- and β-herbertenols (**1b**) and (**1d**) employing orthoester Claisen rearrangement as the key reaction for the creation of the two vicinal quaternary carbon atoms. Herein we wish to describe an alternate strategy for the synthesis of 1,13-herbertenediol ((±)-**3**).

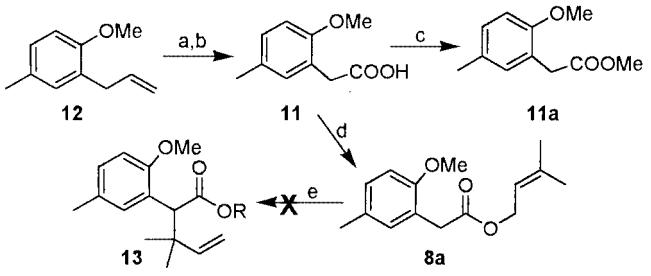


Scheme 1

Initially we envisioned (Scheme 1) that Ireland ester Claisen rearrangement[5] of ester **8** (or rearrangement of **8a** and subsequent allylation) followed by a ring-closing metathesis (RCM) reaction[6] of the resulting diene **9** would generate the cyclopentene carboxylate **10** containing the requisite two vicinal quaternary carbon atoms, which could be transformed into 1,13-herbertenediol (**3**). The arylacetic acid **11** required for the generation of ester **8a** could be obtained from allyl 4-methylphenyl ether via Claisen re-

arrangement followed by oxidative cleavage of the allyl group.

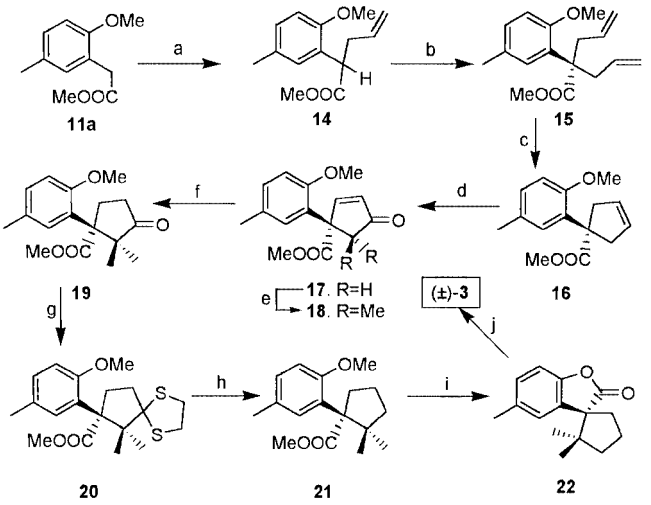
Accordingly, we started by preparing allylanisole (**12**) from allyl 4-methylphenyl ether in a straightforward manner via thermolysis followed by etherification. Ozonolytic cleavage of allylanisole (**12**) followed by oxidation of the resulting aldehyde with Jones reagent generated the arylacetic acid **11**, which on esterification furnished ester **11a** (Scheme 2).[7]



Scheme 2. Reagents, conditions and yields: (a) O_3/O_2, CH_2Cl_2/MeOH (4:1); Me_2S, 4 h; 86%; (b) Jones reagent, Me_2CO, 0 °C → room. temp., 2 h, 88%; (c) MeOH, H_2SO_4, reflux, 8 h, 90%; (d) $Me_2C{=}CHCH_2OH$, DCC, DMAP, CH_2Cl_2, 6 h, room temp., 88%; (e) LDA, TBDMSCl; Δ

Coupling of **11** with 3-methylbut-2-enol in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino-)pyridine (DMAP) furnished ester **8a**. To avoid steric crowding during the [3,3]-sigmatropic shift, it was contemplated that the allylation could be carried out after the Ireland ester Claisen rearrangement of **8a**. However, quite surprisingly and contrary to our expectations, the enolate or the corresponding silyl enol ether of **8a** failed to undergo the Claisen rearrangement to generate **13** under a variety of conditions. Hence, the strategy was altered and it was decided to create the second quaternary centre at a later stage. The synthetic sequence is depicted in Scheme 3.

Sequential allylation of ester **11a** with lithium diisopropylamide (LDA) and allyl bromide generated the diallylated ester **15** via ester **14**, in 79% yield. RCM reaction of **15** in dichloromethane with 5 mol% of first-generation Grubbs' catalyst at room temperature furnished the cyclopentenecarboxylate **16** in near quantitative yield. Allylic oxidation of **16** with pyridinium dichromate (PDC) in pyridine furnished enone **17** in a highly regioselective manner, whose structure was deduced from its spectroscopic data, in particular from the two doublets at δ = 6.34 and 7.75 ppm for the α- and β-olefinic protons of the cyclopentenone moiety (it is well established that the other regioisomer would generate two triplets of doublet signals for the cyclopentenone olefinic protons). One-step dialkylation of **17** with sodium hydride and methyl iodide in dimethoxyethane (DME) generated the second quaternary carbon atom to furnish enone **18**, which on hydrogenation using 5% palladium over carbon as the catalyst furnished cyclopentanone **19**. Thioketalisation of **19** with ethanedithiol and boron trifluoride etherate followed by Raney nickel-mediated desulfurisation of thioketal **20** furnished ester **21**. Finally, boron tribromide-mediated cleavage of the methyl ether transformed **21** into



Scheme 3. Reagents, conditions and yields: (a) LDA, THF, −70 °C; $CH_2{=}CHCH_2Br$, → room temp., 4 h; 92%; (b) LDA, THF, HMPT, −70 °C; $CH_2{=}CHCH_2Br$, → room temp., 8 h; 86%; (c) 5 mol % [$PhCH{=}RuCl_2(PCy_3)_2$], CH_2Cl_2, room temp., 4 h, 95%; (d) PDC, py, 100 °C, 8 h, 65%; (e) NaH, DME, MeI, room temp., 12 h, 71%; (f) H_2 (1 atm), 5% Pd/C, EtOH, 2 h, 90%; (g) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, C_6H_6, 0 °C → room temp., 4 h, 83%; (h) Raney Ni, EtOH, reflux, 3 h, 85%; (i) BBr_3, CH_2Cl_2, −40 °C → room temp., 4 h, 65%; (j) ref.[4]

the lactone **22**, which exhibited the spectroscopic data (IR, ^1H and ^{13}C NMR) identical to that of an authentic sample. Since lactone **22** has already been transformed into herbertene-1,13-diol by lithium aluminium hydride reduction[4] the present sequence constitutes a formal total synthesis of herbertene-1,13-diol ((±)-**3**).

In conclusion, we have developed a RCM-based methodology for the synthesis of 1,13-herbertenediol (**3**). Failure of the Ireland ester Claisen rearrangement of ester **8a** made the sequence longer than anticipated. Currently, we are investigating the possibility of extension of this methodology for other bioactive herbertenes and mastigophorenes.

Experimental Section

IR spectra were recorded with a Jasco FTIR 410 spectrophotometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with a Jeol 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 (δ = 77.0 ppm) of $CDCl_3$ (for ^{13}C). In the ^{13}C NMR spectra, the nature of the carbon atoms (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 spectrum, and is given in parentheses. Low-resolution mass spectra were recorded using a Shimadzu GCMS-QP5050A instrument using direct inlet mode. Relative intensities are given in parentheses. High-resolution mass spectra (HRMS) were recorded with a Micromass Q-Tof micro™ instrument. Ozonolysis was carried out using a Fischer 502 ozone generator, whose parameters were adjusted to provide 1 mmol of ozone every four minutes. Hydrogenation at one atmospheric pressure was carried out using a hydrogen-filled balloon. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with Acme's silica-gel G containing 13% calcium sulfate as binder, and various combinations of ethyl acetate and

hexane were used as eluent. Visualization of spots was accomplished by exposure to iodine vapour. Acme's silica gel (100−200 mesh) was used for column chromatography. All small-scale dry reactions were carried out using the standard syringe septum technique. Dry THF was obtained by distillation over sodium/benzophenone ketyl. Dry diethyl ether was obtained by distillation over sodium and stored over sodium wire. Dry dichloromethane was prepared by distillation over P_2O_5 or calcium hydride. Dry diisopropylamine was obtained by distillation over KOH and stored over KOH.

Methyl (2-Methoxy-5-methylphenyl)acetate (11a): A pre-cooled (−78 °C) mixture of ozone in oxygen was passed through a cold (−78 °C) solution of the methyl ether **12** (1.0 g, 6.17 mmol) and a catalytic amount of $NaHCO_3$ in methanol (2 mL) and CH_2Cl_2 (8 mL) for 24 min. The reaction mixture was flushed off with oxygen, and dimethyl sulfide (1.80 mL, 24.7 mmol) was added to the reaction mixture. This was then slowly warmed to room temp. 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 (2-methoxy-5-methylphenyl)acetaldehyde (860 mg, 86%) as an oil: IR (neat): $\tilde{\nu}_{max.}$ = 1725, 1612, 1504, 1462, 1252, 1230, 1130, 1033, 809 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 2.27 (s, 3 H, $ArCH_3$), 3.56 (d, *J* = 2.1 Hz, 2 H, CH_2CHO), 3.78 (s, 3 H, OCH_3), 6.75 (d, *J* = 8.2 Hz, 1 H, H-3′), 6.91 (s, 1 H, H-6′), 7.02 (d, *J* = 8.2 Hz, 1 H, H-4′), 9.62 (t, *J* = 2.1 Hz, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 20.4 (CH_3), 45.4 (CH_2), 55.3 (CH_3), 110.3 (CH), 120.9 (C), 129.1 (CH), 129.9 (C), 132.0 (CH), 155.5 (C), 199.4 (CH, CHO) ppm. MS: *m*/*z* (%) = 164 (5) [M^+], 163 (50), 152 (13), 149 (58), 135 (100), 121 (10), 105 (45), 91 (28)].

A magnetically stirred solution of the aldehyde (800 mg, 4.88 mmol), obtained above, in acetone (3 mL) was treated with a freshly prepared solution of Jones' reagent (2.5 M solution, 2.2 mL, 5.5 mmol) at 0 °C and the reaction mixture was stirred at room temp. for 2 h. Excess reagent was decomposed by adding a few drops of propan-2-ol and the reaction mixture was extracted with diethyl ether. The extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the acid **11** (770 mg, 88%).[7] A solution of **11** (750 mg, 4.16 mmol) in MeOH (4 mL) and a catalytic amount of concd. H_2SO_4 was refluxed for 6 h. The reaction mixture was then concentrated under vacuum and extracted with diethyl ether (3 × 5 mL). The combined diethyl 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 ester **11a** (730 mg, 90%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 3051, 1741, 1614, 1505, 1460, 1436, 1338, 1256, 1233, 1164, 1128, 1032, 808 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 2.27 (s, 3 H, $ArCH_3$), 3.55 (s, 2 H, H-2), 3.67 (s, 3 H) and 3.68 (s, 3 H, 2 × OCH_3), 6.72 (d, *J* = 8.1 Hz, 1 H, H-3′), 6.95 (s, 1 H, H-6′), 7.00 (d, *J* = 8.1 Hz, 1 H, H-4′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 20.6 (CH_3), 35.6 (CH_2), 51.7 (CH_3), 55.5 (CH_3), 110.4 (CH), 122.7 (C), 128.8 (CH), 129.5 (C), 131.7 (CH), 155.4 (C), 172.0 (C, OC=O) ppm. MS: *m*/*z* (%) = 194 (50) [M^+], 135 (100), 105 (80), 91 (35). HRMS: *m*/*z* calcd. for $C_{11}H_{14}O_3Na$ [M + Na]: 217.0841, found 217.0841.

3-Methylbut-2-enyl (2-Methoxy-5-methylphenyl)acetate (8a): DCC (206 mg, 1.00 mmol), DMAP (40 mg, 0.33 mmol) and 3-methylbut-2-enol (0.07 mL, 0.67 mmol) were added to a magnetically stirred solution of **11** (120 mg, 0.67 mmol) in anhydrous CH_2Cl_2 (4 mL) and stirred at room temp. for 6 h. The reaction mixture was then concentrated under reduced pressure and filtered through a short silica-gel column using ethyl acetate. Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate/hexane (1:20) as eluent furnished the ester **8a** (145 mg, 88%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 1739, 1615, 1505, 1445, 1378, 1340, 1256, 1159, 1035, 973, 807 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 1.70 (s, 3 H) and 1.76 (s, 3 H) [2 × olefinic CH_3], 2.27 (s, 3 H, $ArCH_3$), 3.54 (s, 2 H, CH_2CO), 3.77 (s, 3 H, OCH_3), 4.56 (d, *J* = 7.2 Hz, 2 H, OCH_2), 5.32 (t of d, *J* = 7.2, 1.5 Hz, 1 H, olefinic H), 6.71 (d, *J* = 8.1 Hz, 1 H, H-3′), 6.95 (s, 1 H, H-6′), 6.98 (d, *J* = 8.1 Hz, 1 H, H-4′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 18.1 (CH_3), 20.6 (CH_3), 25.9 (CH_3), 35.8 (CH_2), 55.4 (CH_3), 61.4 (CH_2), 110.4 (CH), 119.2 (CH), 122.9 (C), 128.7 (CH), 129.4 (C), 131.7 (CH), 138.3 (C), 155.5 (C), 171.5 (C, OC=O) ppm. MS: *m*/*z* (%) = 248 (25) [M^+], 180 (2), 149 (2), 136 (12), 135 (100), 122 (3), 105 (60), 91 (13), 79 (12), 69 (65). HRMS: *m*/*z* calcd. for $C_{15}H_{20}O_3Na$ [M + Na]: 271.1310, found 271.1301.

Methyl 2-(2-Methoxy-5-methylphenyl)pent-4-enoate (14): A solution of *n*BuLi (2.5 M in hexane, 2.24 mL, 5.60 mmol) was slowly added to a cold (−78 °C), magnetically stirred solution of diisopropylamine (0.9 mL, 6.20 mmol) in anhydrous THF (3 mL) and stirred for 10 min. A solution of **11a** (600 mg, 3.10 mmol) in anhydrous THF (2 mL) was added dropwise to the LDA thus formed and stirred for 40 min at the same temperature. The enolate was treated with allyl bromide (0.52 mL, 6.20 mmol) and stirred for 3 h. The reaction mixture was then diluted with water and extracted with diethyl ether (3 × 4 mL). The combined diethyl ether extract was washed sequentially with 3 N aqueous HCl, saturated aqueous $NaHCO_3$ solution and 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 pentenoate **14** (665 mg, 92%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 3076, 1736, 1641, 1611, 1503, 1462, 1438, 1348, 1247, 1168, 1121, 1033, 916, 808 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 2.27 (s, 3 H, $ArCH_3$), 2.41 (t of d, *J* = 14.0, 7.0 Hz, 1 H) and 2.73 (t of d, *J* = 14.0, 7.0 Hz, 1 H, H-3), 3.64 (s, 3 H) and 3.80 (s, 3 H, 2 × OCH_3), 4.01 (t, *J* = 7.5 Hz, 1 H, H-2), 4.94 (d, *J* = 10 Hz, 1 H) and 5.02 (d, *J* = 17 Hz, 1 H, H-5), 5.72 (t of dd, *J* = 17.0, 10.0, 7.0 Hz, 1 H, H-4), 6.72 (d, *J* = 8.1 Hz, 1 H, H-3′), 6.98 (d, *J* = 8.1 Hz, 1 H, H-4′), 7.00 (s, 1 H, H-6′), ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 20.7 (CH_3), 36.8 (CH_2), 43.9 (CH_3), 51.7 (CH_3), 55.6 (CH), 110.7 (CH), 116.5 (CH_2), 127.2 (C), 128.5 (CH), 129.0 (CH), 129.8 (C), 136.0 (CH), 154.7 (C), 174.1 (C, OC=O) ppm. MS: *m*/*z* (%) = 234 (29) [M^+], 193 (76), 175 (100), 165 (30), 163 (32), 149 (19), 135 (64), 105 (46), 91 (24). HRMS: *m*/*z* calcd. for $C_{14}H_{18}O_3Na$ [M + Na]: 257.1154, found 257.1172.

Methyl 2-Allyl-2-(2-methoxy-5-methylphenyl)pent-4-enoate (15): A solution of *n*BuLi (2.5 M in hexane, 2 mL, 5.0 mmol) was slowly added to a cold (−78 °C), magnetically stirred solution of diisopropylamine (0.8 mL, 5.56 mmol) in anhydrous THF (3 mL) and stirred for 10 min. A solution of **14** (650 mg, 2.78 mmol) in anhydrous THF (2 mL) and HMPA (1 mL) were added dropwise to the LDA thus formed and stirred for 40 min at the same temperature. The enolate was treated with allyl bromide (0.47 mL, 5.56 mmol) and stirred for 7 h. The reaction mixture was then diluted with water and extracted with diethyl ether (3 × 4 mL). The combined diethyl ether extract was washed sequentially with 3 N aqueous HCl, saturated aqueous $NaHCO_3$ solution and 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 ester **15** (655 mg, 86%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 3074, 1740, 1640, 1609, 1498, 1443, 1230, 1207, 1134, 1035, 916, 809 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 2.31 (s,

3 H, $ArCH_3$), 2.60 (dd, J = 13.8, 8.1 Hz, 2 H) and 2.76 (dd, J = 13.8, 6.3 Hz, 2 H, 2 × allylic CH_2), 3.58 (s, 3 H) and 3.73 (s, 3 H, 2 × OCH_3), 5.00 (d, 2 H, J = 12 Hz), 5.01 (d, J = 15.3 Hz, 2 H), 5.55−5.40 (m, 2 H), 6.72 (d, J = 8.4 Hz, 1 H, H-3′), 6.92 (s, 1 H, H-6′), 7.00 (d, J = 8.4 Hz, 1 H, H-4′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 21.1 (CH_3), 38.0 (2 C, CH_2), 50.6 (C, C-2), 51.4 (CH_3), 55.3 (CH_3), 111.0 (CH), 118.1 (2 C, CH_2), 127.9 (CH), 128.3 (CH), 129.2 (C), 130.7 (C), 133.9 (2 C, CH), 154.6 (C), 175.6 (C, OC=O) ppm. MS: m/z (%) = 274 (20) [M^+], 233 (31), 201 (80), 173 (100), 158 (44), 145 (26), 128 (22), 115 (24), 105 (17). HRMS: m/z calcd. for $C_{17}H_{22}O_3Na$ [M + Na]: 297.1467, found 297.1477. For $C_{17}H_{23}O_3$ [M + 1]: 275.1647, found 275.1656.

Methyl 1-(2-Methoxy-5-methylphenyl)cyclopent-3-ene-1-carboxylate (16): A solution of Grubbs' catalyst (22 mg, 5 mol%) in anhydrous CH_2Cl_2 was added to a magnetically stirred solution of diene **15** (150 mg, 0.55 mmol) in anhydrous CH_2Cl_2 (5 mL) and stirred at room temp. for 4 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 cyclised compound **16** (128 mg, 95%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 3054, 1737, 1498, 1459, 1294, 1240, 1201, 1124, 1081, 1035, 809 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 2.30 (s, 3 H, $ArCH_3$), 2.68 and 3.15 (2 × d, J = 15.6 Hz, 4 H, H-2 and H-5), 3.61 (s, 3 H) and 3.75 (s, 3 H, 2 × OCH_3), 5.66 (s, 2 H, H-3 and H-4), 6.72 (d, J = 8.1 Hz, 1 H, H-3′), 6.93 (s, 1 H, H-6′), 6.98 (d, J = 8.1 Hz, 1 H, H-4′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 21.0 (CH_3), 43.1 (2 C, CH_2, C-2 and C-5), 52.0 (CH_3, $COOCH_3$), 54.0 (C, C-1), 55.4 (CH_3, $ArOCH_3$), 110.9 (CH, C-3′), 126.9 (CH, C-4′), 128.0 (CH, C-6′), 128.3 (2 C, CH, C-3 and C-4), 129.2 (C, C-1′), 133.0 (C, C-5′), 154.5 (C, C-2′), 177.1 (C, OC=O) ppm. MS: m/z (%) = 246 (25) [M^+], 187 (82), 172 (28), 159 (12), 145 (43), 128 (25), 122 (100). HRMS: m/z calcd. for $C_{15}H_{18}O_3Na$ [M + Na]: 269.1154, found 269.1153.

Methyl 1-(2-Methoxy-5-methylphenyl)-3-oxocyclopent-4-ene-1-carboxylate (17): PDC (100 mg) was added to a solution of **16** (100 mg, 0.40 mmol) in pyridine (4 mL). The reaction mixture was heated at 100 °C for 8 h, then cooled, filtered through a short silica-gel column, and the column eluted with more CH_2Cl_2. Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate/hexane (1:5) as eluent first furnished the unchanged starting material (20 mg). Further elution of the column with the same solvent furnished the enone **17** (55 mg, 65% based on starting material consumed) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 3030, 1739, 1720, 1614, 1500, 1463, 1430, 1246, 1194, 1150, 1135, 1034, 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 2.28 (s, 3 H, $ArCH_3$), 2.26 and 3.56 (2 × d, J = 18.3 Hz, 2 H, H-2), 3.67 (s, 3 H) and 3.78 (s, 3 H, 2 × OCH_3), 6.34 (d, J = 6.0 Hz, 1 H, H-4), 6.75 (d, J = 8.1 Hz, 1 H, H-3′), 6.78 (s, 1 H, H-6′), 7.04 (d, J = 8.1 Hz, 1 H, H-4′), 7.75 (d, J = 6.0 Hz, 1 H, H-5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 20.8 (CH_3, $ArCH_3$), 46.0 (CH_2, C-2), 52.8 (CH_3) and 55.5 (CH_3, 2 × OMe), 57.6 (C, C-1), 111.0 (CH, C-3′), 127.3 (CH, C-6′), 129.2 (CH, C-4′), 130.0 (C), 130.7 (C), 135.3 (CH, C-4), 154.4 (C, C-2′), 161.9 (CH, C-5), 172.6 (C, OC=O), 206.8 (C=O) ppm. MS: m/z (%) = 260 (29) [M^+], 201 (100), 186 (46), 158 (11), 128 (19), 115 (17). HRMS: m/z calcd. for $C_{15}H_{16}O_4Na$ [M + Na]: 283.0946, found 283.0943. For $C_{15}H_{17}O_4$ [M + 1]: 261.1126, found 261.1129.

Methyl 1-(2-Methoxy-5-methylphenyl)-2,2-dimethyl-3-oxocyclopent-4-ene-1-carboxylate (18): A solution of keto ester **17** (50 mg, 0.19 mmol) in DME (2 mL) was added to a magnetically stirred suspension of NaH (46 mg, 60% dispersion in oil, 1.15 mmol, washed with dry hexanes) in DME (2 mL) and stirred for 40 min at room temp. Methyl iodide (0.07 mL, 1.15 mmol) was added to the reaction mixture, which was stirred at room temp. for 12 h. It was then quenched with water (5 mL) and extracted with diethyl ether (3 × 3 mL). The combined diethyl 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 keto ester **18** (39 mg, 71%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 1736, 1716, 1504, 1457, 1238, 1213, 1038 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 0.63 (s, 3 H) and 1.39 (s, 3 H, 2 × *tert*-CH_3), 2.28 (s, 3 H, $ArCH_3$), 3.61 (s, 3 H) and 3.72 (s, 3 H) [2 × OCH_3], 6.25 (d, J = 6.0 Hz, 1 H, H-4), 6.70 (d, J = 7.5 Hz, 1 H, H-3′), 6.74 (s, 1 H, H-6′), 7.00 (d, J = 7.5 Hz, 1 H, H-4′), 7.50 (d, J = 6.0 Hz, 1 H, H-5) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 21.0 (CH_3), 21.3 (CH_3), 26.4 (CH_3), 52.1 (CH_3), 52.7 (C, C-2), 55.0 (CH_3), 66.4 (C, C-1), 111.2 (CH, C-3′), 127.1 (C, C-1′), 129.1 (CH), 129.5 (C, C-5′), 130.2 (CH), 132.1 (CH, C-4), 155.2 (C, C-2′), 158.1 (CH, C-5), 171.5 (C, OC=O), 210.6 (C, C=O) ppm. MS: m/z = 288 (19) [M^+], 229 (100), 214 (3), 145 (8), 115 (10). HRMS: m/z calcd. for $C_{17}H_{20}O_4Na$ [M + Na]: 311.1259, found 311.1248.

Methyl 1-(2-Methoxy-5-methylphenyl)-2,2-dimethyl-3-oxocyclopentane-1-carboxylate (19): A solution of enone **18** (30 mg, 0.10 mmol) in ethanol (2 mL) was added to 5% Pd−C (5 mg). The reaction mixture was stirred for 2 h at room temp. 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 cyclopentanone **19** (27 mg, 90%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 3030, 1743, 1726, 1499, 1465, 1250, 1120, 1028, 810 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 0.80 (s, 3 H) and 1.16 (s, 3 H, 2 × *tert*-CH_3) 2.31 (s, 3 H, $ArCH_3$), 2.65−2.30 (m, 4 H), 3.63 (s, 3 H) and 3.71 (s, 3 H, 2 × OCH_3), 6.76 (d, J = 8.5 Hz, 1 H, H-3′), 6.93 (s, 1 H, H-6′), 7.03 (d, J = 8.5 Hz, 1 H, H-4′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 21.0 (CH_3), 21.1 (CH_3) 21.5 (CH_3), 27.6 (CH_2), 32.8 (CH_2), 51.7 (CH_3), 52.6 (C, C-2), 55.0 (CH_3, OMe), 58.8 (C, C-1), 111.3 (CH, C-3′), 127.5 (C), 128.7 (CH), 128.8 (CH), 129.2 (C), 155.2 (C, C-2′), 174.8 (C, OC=O), 217.7 (C, C=O). MS: m/z (%) = 290 (38) [M^+], 258 (25), 231 (100), 215 (23), 189 (42), 188 (75), 159 (30), 149 (39), 145 (42), 115 (30), 105 (32). HRMS: m/z calcd. for $C_{17}H_{22}O_4Na$ [M + Na]: 313.1416, found 313.1410.

Methyl 1-(2-Methoxy-5-methylphenyl)-2,2-dimethylcyclopentanecarboxylate (21): A solution of **19** (5 mg, 0.017 mmol), ethanedithiol (0.004 mL, 0.051 mmol) and $BF_3{\cdot}Et_2O$ (1 drop) in dry benzene (1 mL) was magnetically stirred at 0 °C to room temp. for 4 h. The reaction was then quenched with aqueous $NaHCO_3$ solution and extracted with diethyl ether. The diethyl ether extract was washed with 5% aqueous NaOH solution and 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 thioketal **20** (5 mg, 83%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 1739, 1498, 1464, 1248, 1193, 1131, 1034, 808 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 0.65 (s, 3 H) and 1.57 (s, 3 H, 2 × *tert*-CH_3), 2.30 (s, 3 H, $ArCH_3$), 2.80−2.05 (m, 4 H), 3.35−3.00 (m, 4 H), 3.53 (s, 3 H) and 3.71 (s, 3 H, 2 × OCH_3), 6.66 (d, J = 8.4 Hz, 1 H, H-3′), 6.95 (d, J = 8.4 Hz, 1 H, H-4′), 7.00 (s, 1 H, H-6′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$ + CCl_4): δ = 21.0, 23.0, 30.4, 35.6, 38.0, 38.7, 45.1, 51.3, 52.1, 54.9, 59.1, 82.8 (S−C−S), 110.4, 128.0, 128.5, 128.8, 131.5, 155.3, 175.4 (OC=O) ppm. MS: m/z (%) = 366 (5) [M^+], 335 (5), 206 (18), 189 (5), 173 (5), 159 (5), 145 (8), 131 (100), 115 (5), 105 (6).

An excess of Raney nickel was added to a magnetically stirred solution of **20** (4 mg, 0.01 mmol) in dry ethanol (1 mL) and refluxed

for 3 h. The reaction mixture was cooled and filtered through a short silica-gel column to remove the catalyst. Evaporation of the solvent and purification of the residue over a silica-gel column using ethyl acetate/hexane (1:50) as eluent furnished the ester **21** (2.5 mg, 85%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 1738, 1248, 1195, 807 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 0.69 (s, 3 H) and 1.25 (s, 3 H, 2 × *tert*-CH_3), 1.65−1.50 (m, 1 H), 1.85−1.70 (m, 2 H), 2.25−1.95 (m, 2 H), 2.31 (s, 3 H, $ArCH_3$), 2.60−2.48 (1 H, t of d, *J* = 13.5, 6.0 Hz), 3.54 (s, 3 H) and 3.70 (s, 3 H, 2 × OCH_3), 6.69 (d, *J* = 8.1 Hz, 1 H, H-3′), 6.97 (d, *J* = 8.1 Hz, 1 H, H-4′), 7.05 (s, 1 H, H-6′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 20.1 (CH_2, C-4), 21.2 (CH_3), 25.1 (CH_3), 27.7 (CH_3), 34.8 (CH_2), 39.9 (CH_2), 45.5 (C, C-2), 51.0 (CH_3), 54.9 (CH_3), 60.3 (C, C-1), 110.7 (CH, C-3′), 127.9 (CH, C-6′), 128.6 (C, C-1′), 128.9 (CH, C-4′), 129.9 (C, C-5′), 155.4 (C, C-2′), 175.5 (C, OC=O) ppm. MS: *m*/*z* (%) = 276 (18) [M^+], 217 (11), 207 (21), 194 (36), 175 (100), 162 (23), 149 (84), 147 (74), 135 (40), 119 (22), 105 (27), 91 (35). HRMS: *m*/*z* calcd. for $C_{17}H_{24}O_3Na$ [M + Na]: 299.1623, found 299.1630.

2′,2′,5-Trimethylspiro[1-benzofuran-3,1′-cyclopentan]-2-one (22): A solution of BBr_3 (1 M in CH_2Cl_2, 0.3 mL, 0.3 mmol) was added dropwise to a solution of **21** (13 mg, 0.047 mmol) in CH_2Cl_2 (1 mL) at −40 °C and the reaction mixture was stirred for 3 h at room temp. It was then quenched with saturated aqueous $NaHCO_3$ solution 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 the lactone **22** (7 mg, 65%) as an oil. IR (neat): $\tilde{\nu}_{max.}$ = 1798, 1643, 1617, 1038 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$ + CCl_4): δ = 0.92 (s, 3 H) and 1.03 (s, 3 H, 2 × *tert*-CH_3), 2.40−1.64 (m, 6 H), 2.36 (s, 3 H, $ArCH_3$), 6.94 (d, *J* = 8.4 Hz, 1 H, H-7), 6.96 (s, 1 H, H-4), 7.04 (d, *J* = 8.4 Hz, 1 H, H-6) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ + CCl_4): δ = 21.0 (CH_2, C-4′), 21.5 (CH_3), 23.6 (CH_3), 25.4 (CH_3), 34.7 (CH_2), 38.7 (CH_2), 47.6 (C, C-2′), 60.1 (C, C-3), 110.1 (CH, C-7), 125.6 (CH, C-4), 128.9 (CH, C-6), 129.3 (C, C-3a), 132.5 (C, C-5), 151.7 (C, C-7a), 179.4 (C, C-2) ppm. MS: *m*/*z* (%) = 230 (11) [M^+], 161 (100), 160 (81), 148 (16), 135 (37), 115 (11), 91 (15). HRMS: *m*/*z* calcd. for $C_{15}H_{18}O_2Na$ [M + Na]: 253.1204, found 253.1218.

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