The First Total Synthesis of (±)-Herbertenones A and B

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Abstract: The first total synthesis of (±)-herbertenones A and B, employing Claisen rearrangement–metathesis reaction based approaches, is described.

Key words: total synthesis, natural products, rearrangement, ring-closure, metathesis

Liverworts from the genus *Herbertus* contain herbertane sesquiterpenoids, which are considered as chemical markers of the genus.[1] The herbertanes are a small group of aromatic sesquiterpenes, isomeric to cuparanes, containing a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane carbon framework incorporating two vicinal quaternary carbon atoms on a cyclopentane ring. Even though cuparene (**1**), isomeric to herbertene (**2**), has been known[2] since 1958, the herbertane family of sesquiterpenes was reported only in the 1980s. The first member of the family, herbertene (**2**) was isolated in 1981 by Matsuo and co-workers from the ethyl acetate extract of the liverwort *Herberta adunca* (Dicks) S. Gray belonging to the family herbertaceae.[3] Subsequently a few other phenolic herbertanes **3**–**9** were isolated from a variety of *Herbertus* sources (Figure 1).[4] In 2000, Asakawa and co-workers reported[5] the isolation of seven herbertenes, herbertene-acetal (**10**), herbertene-1,14-diol (**11**), herbertene-1,15-diol (**12**), herbertenones A and B (**13** and **14**), herbertene-1,13-diol (**15**), and 12-methoxyherbertenediol (**16**) from the diethyl ether and ethyl acetate extracts of the Japanese liverwort *Herbertus sakuraii*. The herbertane sesquiterpenes, mainly the phenolic herbertanes, have been shown to possess interesting biological properties such as growth inhibiting activity and antilipid peroxidation activity.[1,4]

The presence of a sterically crowded 1-aryl-1,2,2-trimethylcyclopentane carbon framework, the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring, and the significant biological properties associated with the phenolic herbertanes make herbertenoids interesting and challenging synthetic targets. Prior to 1999, there were only three reports appeared in the literature on the synthesis of phenolic herbertanes. However, during the last eight years, more than forty reports have appeared in the literature on the synthesis of phenolic herbertanes making it a topic of contemporary interest.[6] Herbertenones A and B (**13** and **14**) are the only members of the group where the aromaticity of the A ring is disturbed, perhaps produced by biogenetic oxidation of α-herbertenol (**3**). So far, there are no reports in the literature on the synthesis of herbertenones A and B. In continuation of our interest in the synthesis of sesquiterpenes containing contiguous quaternary carbon atoms,[7] herein, we describe the first total synthesis of (±)-herbertenones A and B (**13** and **14**), employing a combination of Claisen rearrangement and ring-closing metathesis (RCM) reaction based methodologies.[6c]

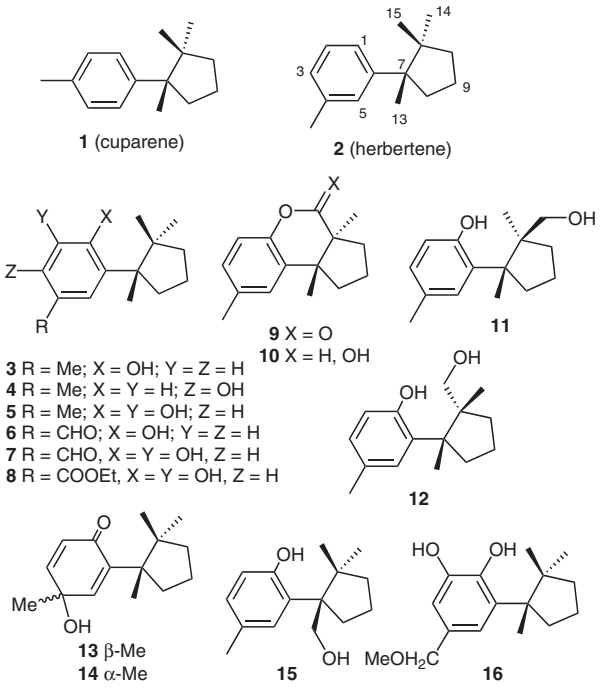

Figure 1

Retrosynthetic analysis is depicted in Scheme 1. It was contemplated that 1,4-dimethoxybenzene could be employed as a masked benzoquinone, which can be converted into the 4-hydroxy-4-methylcyclohexa-2,5-dienone moiety present in herbertenones **13** and **14** at the end of the sequence. It was anticipated[6c] that 4-aryl-4,5,5-trimethylcyclopentenone **17**, containing the requisite two vicinal quaternary carbons, could be obtained from the hydroxydiene **18** via an RCM reaction.[8] The hydroxydiene **18** could be prepared from the dimethoxyacetophenone **19** via the allyl alcohol **20** and the aldehyde **21**.

First attention was focused on the synthesis of the cyclopentenone **17** starting from the acetophenone **19** (Scheme 2). Horner–Wadsworth–Emmons reaction of acetophenone **19** with triethyl phosphonoacetate and sodium hydride in refluxing tetrahydrofuran furnished a 5:2

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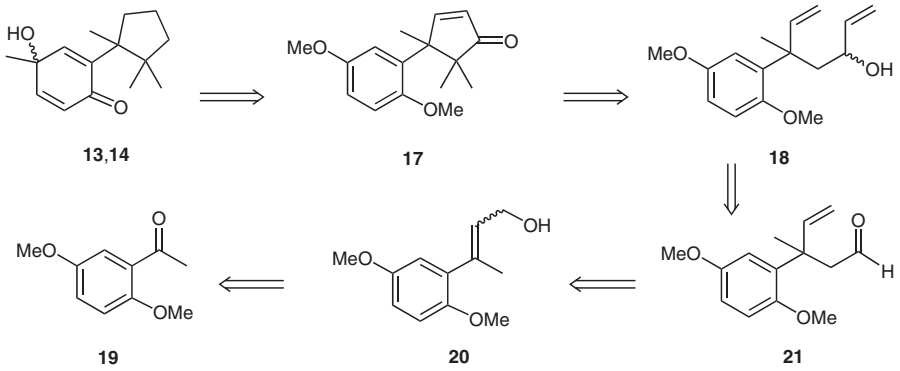
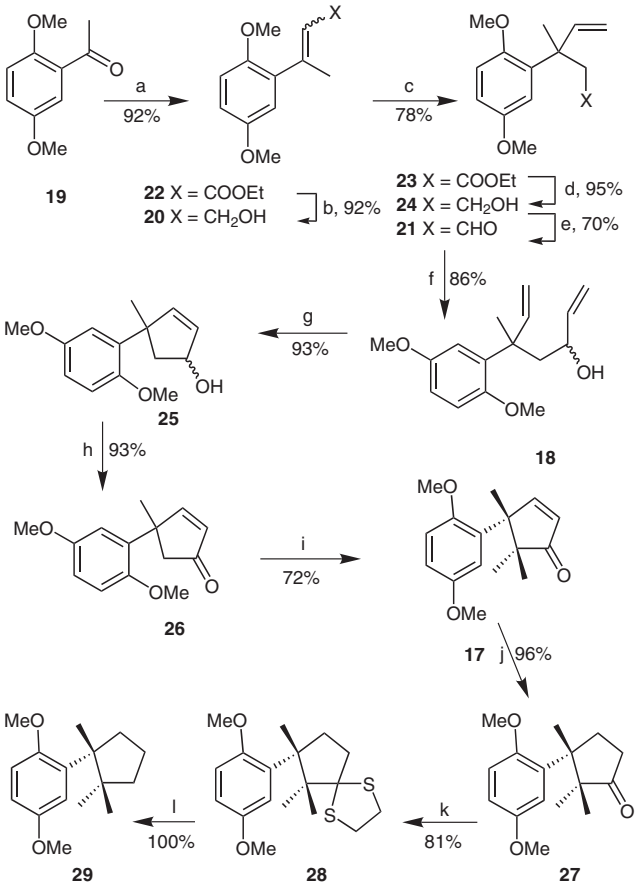


Scheme 1

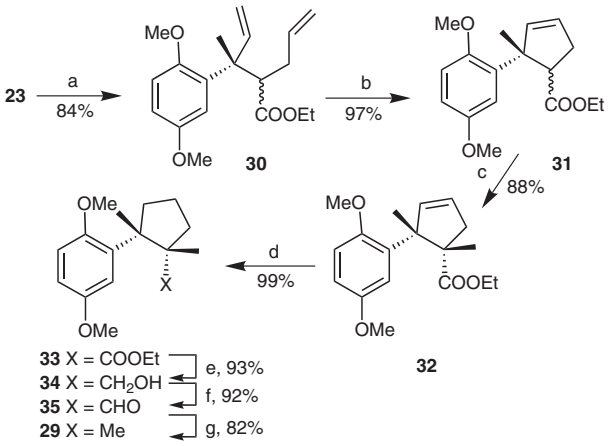
E/*Z* mixture of the cinnamate **22**, which on regioselective reduction with lithium aluminum hydride at low temperature gave an *E*/*Z* mixture of the allyl alcohol **20**. Johnson's ortho ester variant[9] of the Claisen rearrangement was chosen for the generation of the first quaternary carbon atom. Thus, thermal activation of the allyl alcohol **20** with triethyl orthoacetate in the presence of a catalytic amount of propanoic acid in a sealed tube at 180 °C for 36 hours generated the γ,δ-unsaturated ester **23** in 78% yield, whose structure was established from its spectral data. Reduction of the ester **23** with lithium aluminum hydride furnished the primary alcohol **24**, which on oxidation with pyridinium chlorochromate and silica gel furnished the aldehyde **21**. Grignard reaction of the aldehyde **21** with vinylmagnesium bromide at room temperature generated, as expected, a 1:1 epimeric mixture of the hydroxydiene **18** in 86% yield. Treatment of the hydroxydiene **18** with 5 mol% of Grubbs' first-generation catalyst [$PhCH{=}Ru(PCy_3)_2Cl_2$] in anhydrous dichloromethane at room temperature for one hour furnished a 1:1 diastereomeric mixture of the cyclopentenol **25** in 93% yield, which on oxidation with pyridinium chlorochromate and anhydrous sodium acetate furnished the cyclopentenone **26** in 93% yield, whose structure was established from its spectral data. Reaction of the cyclopentenone **26** with sodium hydride and methyl iodide in anhydrous tetrahydrofuran and *N*,*N*-dimethylformamide at room temperature generated the enone **17** in 72% yield. Hydrogenation of the enone **17** using 10% palladium over carbon as the catalyst with one bar pressure (balloon) of hydrogen in ethanol furnished the cyclopentanone **27**. Reaction of the cyclopentanone **27** with ethane-1,2-dithiol and a catalytic amount of iodine[10] in dichloromethane at room temperature produced the thioketal **28** in 81% yield. Desulfurization of the thioketal **28** with Raney nickel in refluxing ethanol furnished quantitatively the deoxygenation product, norherbertane **29**, whose structure was established from its spectral data.



Scheme 2 *Reaction conditions*: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (b) LAH, Et_2O; (c) $MeC(OEt)_3$, $EtCO_2H$, heat; (d) LAH, Et_2O; (e) PCC, silica gel, CH_2Cl_2; (f) $H_2C{=}CHMgBr$, THF; (g) $PhCH{=}Ru(PCy_3)_2Cl_2$, CH_2Cl_2; (h) PCC, NaOAc, CH_2Cl_2; (i) NaH, THF, DMF, MeI; (j) H_2, 10% Pd/C, EtOH; (k) I_2, $(CH_2SH)_2$, CH_2Cl_2; (k) Raney Ni, EtOH.

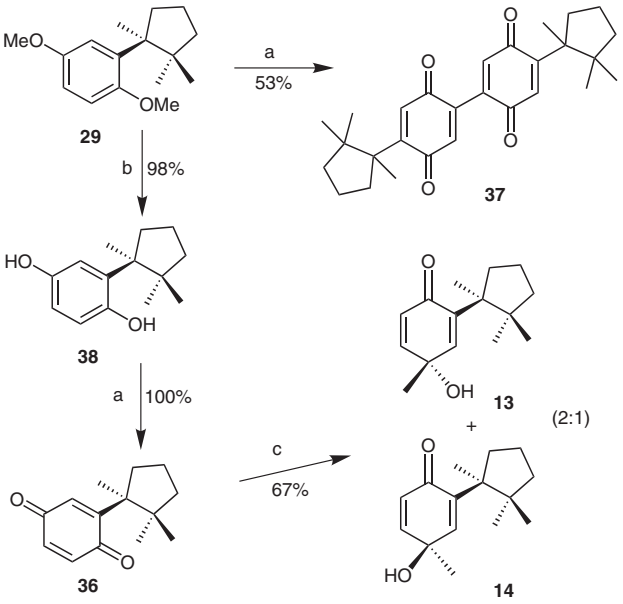
An alternative strategy[6c] was also investigated for the synthesis of **29** starting from the γ,δ-unsaturated ester **23** (Scheme 3) via the RCM reaction of the ester **30**. Generation of the lithium enolate of the ester **23** with lithium diisopropylamide in tetrahydrofuran at –70 °C followed by alkylation with allyl bromide generated a 1:1 diastereomeric mixture of the ester **30** in 84% yield. RCM reaction of the diene ester **30** with 5 mol% of Grubbs' first-generation catalyst in anhydrous dichloromethane at room temperature furnished the ester **31** in near quantitative yield. Generation of the lithium enolate of the ester **31** with lithium diisopropylamide in tetrahydrofuran and hexamethylphosphoramide at –30 °C followed by treatment with methyl iodide furnished the alkylated product **32** in 88%

yield, in a highly stereoselective manner, via the approach of the electrophile from the less hindered face of the enolate (opposite to aryl group). Catalytic hydrogenation using 10% palladium over carbon transformed the ester **32** in to the saturated ester **33** in 99% yield. The ester in **32** was converted into a methyl group in three steps. Thus, reduction of the ester **33** with lithium aluminum hydride in diethyl ether at 0 °C furnished the primary alcohol **34**, which on oxidation with pyridinium chlorochromate and silica gel generated the aldehyde **35**. Treatment of the aldehyde **35** with hydrazine hydrate in diethylene glycol in a sealed tube at 125 °C followed by treatment of the hydrazone with potassium hydroxide in diethylene glycol at 200 °C furnished the deoxygenated compound **29**, which exhibited TLC and spectral data identical to the sample obtained earlier.



Scheme 3 *Reaction conditions*: (a) LDA, THF, $H_2C{=}CHCH_2Br$; (b) $PhCH{=}Ru(PCy_3)_2Cl_2$, CH_2Cl_2; (c) LDA, THF, HMPA, MeI; (d) H_2, 10% Pd/C, EtOH; (e) LAH, Et_2O; (f) PCC, silica gel, CH_2Cl_2; (g) $NH_2NH_2.H_2O$, diethylene glycol, KOH.

Next conversion of the aromatic moiety in **29** into a quinone via direct oxidation of the norherbertane **29** into the benzoquinone **36** using ceric ammonium nitrate[11] was investigated (Scheme 4). However, treatment of the norherbertanediol dimethyl ether **29** with ceric ammonium nitrate in aqueous acetonitrile (1:1) furnished the bisquinone **37**. Hence, a two-step methodology was carried out for the conversion of dimethyl ether **29** into benzoquinone **36**. Accordingly, treatment of the dimethyl ether **29** with boron tribromide in anhydrous dichloromethane furnished the diol **38** in 98% yield. Oxidation of the diol **38** with ceric ammonium nitrate in aqueous acetonitrile furnished the benzoquinone **36** in quantitative yield, whose structure was established from its spectral data. Finally, Grignard reaction of the benzoquinone **36** with one equivalent of methylmagnesium bromide in anhydrous tetrahydrofuran at –30 °C for two minutes furnished a 2:1 mixture of herbertenones A and B (**13** and **14**), which exhibited ^1H and ^{13}C NMR and GC-MS spectral data identical[5] to those reported for the natural products.



Scheme 4 *Reaction conditions*: (a) CAN, MeCN; (b) BBr_3, CH_2Cl_2; (c) MeMgBr, Et_2O.

In conclusion, we have accomplished the first total synthesis of (±)-herbertenones A and B (**13** and **14**), confirming the structures of the natural products. In the present synthesis, a combination of Claisen rearrangement, RCM, and alkylation reactions were employed for the efficient generation of the requisite cyclopentane containing two vicinal quaternary carbon atoms.

IR spectra were recorded on a Jasco FTIR 410 spectrophotometer. ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a JNM λ-300 spectrometer, and samples were prepared using a 1:1 mixture of $CDCl_3$ and CCl_4 as solvent and either internal TMS (for ^1H) or the central line (δ = 77.0) of $CDCl_3$ (for ^{13}C) as reference. In ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined by recording DEPT-135 spectra and is given in parentheses. LRMS spectra were recorded using a Shimadzu QP-5050A GCMS instrument using direct inlet mode. HRMS were recorded on a Micromass Q-TOF micro mass spectrometer using ESI mode. Hydrogenation reactions at 1 bar pressure were carried out using a balloon filled with H_2. Acme's silica gel (100–200 mesh) was used for column chromatography (approximately 15–20 g per 1 g of the crude product). All small-scale dry reactions were carried out using standard syringe-septum techniques.

Ethyl 3-(2,5-Dimethoxyphenyl)but-2-enoate (22)

A suspension of NaH (278 mg, 60% dispersion in oil, 6.94 mmol) in hexanes under a N_2 atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil-free NaH was then suspended in anhyd THF (4 mL) and cooled in an ice bath. Triethyl phosphonoacetate (1.65 mL, 8.34 mmol) was added dropwise and the mixture was stirred at r.t. for 30 min. A soln of **19** (500 mg, 2.78 mmol) in anhyd THF (2 mL) was added dropwise to the mixture and it was stirred at r.t. for 4 h. The reaction was then quenched by careful addition of sat. aq NH_4Cl soln and extracted with Et_2O (3 × 4 mL). The combined Et_2O extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent followed by column chromatography (silica gel, EtOAc–hexane, 1:20) furnished a 5:2 *E*/*Z*-mixture of **22** (638 mg, 92%). Small samples of *E* and *Z*-isomers

were separated by careful column chromatography (silica gel) and characterized.

***E*-Isomer**

IR (neat): 1713, 1633, 1584, 1497, 1465, 1420, 1367, 1337, 1310, 1288, 1264, 1215, 1181, 1160, 1095, 1069, 1044, 945, 871, 806, 751, 705, 608 cm^{-1}.

^1H NMR: δ = 6.75 (br s, 2 H), 6.66 (br s, 1 H), 5.84 (s, 1 H), 4.16 (q, *J* = 6.9 Hz, 2 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 2.44 (s, 3 H), 1.29 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR: δ = 166.4 (C), 156.3 (C), 153.5 (C), 150.5 (C), 134.0 (C), 119.4 (CH), 114.8 (CH), 113.8 (CH), 112.2 (CH), 59.6 (CH_2), 56.0 (CH_3), 55.6 (CH_3), 19.8 (CH_3), 14.5 (CH_3).

MS: *m*/*z* (%) = 250 (M^+, 26), 219 (55), 205 (16), 191 (100), 161 (20), 162 (18), 147 (20).

***Z*-Isomer**

IR (neat): 1725, 1649, 1583, 1498, 1465, 1370, 1277, 1223, 1180, 1155, 1139, 1046, 805 cm^{-1}.

^1H NMR: δ = 6.80–6.65 (m, 2 H), 6.54 (d, *J* = 3 Hz, 1 H), 5.88 (br s, 1 H), 3.95 (q, *J* = 7.2 Hz, 2 H), 3.72 (s, 6 H), 2.12 (s, 3 H), 1.06 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 165.2 (C), 153.4 (C), 152.5 (C), 149.6 (C), 131.4 (C), 119.1 (CH), 114.2 (CH), 112.8 (CH), 111.8 (CH), 59.4 (CH_2), 56.1 (CH_3), 55.5 (CH_3), 26.2 (CH_3), 14.1 (CH_3).

MS: *m*/*z* (%) = 250 (M^+, 30), 236 (10), 219 (54), 205 (19), 191 (100), 177 (9), 165 (19), 161 (23), 147 (23), 135 (10), 119 (8), 103 (11), 91 (20).

HRMS: *m*/*z* [M + Na] calcd for $C_{14}H_{18}NaO_4$: 273.1103; found: 273.1105.

3-(2,5-Dimethoxyphenyl)but-2-en-1-ol (20)

To a cold (–50 °C) magnetically stirred soln of a 5:2 mixture of **22** (960 mg, 3.84 mmol) in anhyd Et_2O (5 mL) was added LAH (146 mg, 3.84 mmol) and stirred for 1 h. EtOAc (0.5 mL) was added to the mixture to consume the excess LAH. The reaction was then quenched with H_2O (10 mL) and extracted with Et_2O (3 × 5 mL). The combined Et_2O extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent and column chromatography of the residue (silica gel, EtOAc–hexane, 1:3) furnished an *E*/*Z* mixture of **20** (735 mg, 92%).

***E*-Isomer**

IR (neat): 3397, 1582, 1496, 1419, 1283, 1261, 1220, 1178, 1147, 1099, 1047, 1023, 873, 804, 747, 709 cm^{-1}.

^1H NMR: δ = 6.74–6.60 (m, 3 H), 5.63 (t, *J* = 6.6 Hz, 1 H), 4.26 (d, *J* = 6.6 Hz, 2 H), 3.73 (s, 3 H), 3.72 (s, 3 H), 2.19 (br s, 1 H), 1.97 (s, 3 H).

^{13}C NMR: δ = 153.5 (C), 150.7 (C), 137.8 (C), 134.8 (C), 128.6 (CH), 115.4 (CH), 112.5 (CH), 111.8 (CH), 59.3 (CH_2), 55.9 (CH_3), 55.5 (CH_3), 17.2 (CH_3).

MS: *m*/*z* (%) = 208 (M^+, 100), 193 (27), 177 (23), 175 (25), 165 (91), 150 (33), 137 (26), 135 (26), 121 (20), 115 (20), 105 (31), 91 (39).

HRMS: *m*/*z* [M – OH] calcd for $C_{12}H_{15}O_2$: 191.1072; found: 191.1076.

Ethyl 3-(2,5-Dimethoxyphenyl)-3-methylpent-4-enoate (23)

A soln of **20** (397 mg, 1.91 mmol), triethyl orthoacetate (1.4 mL, 7.65 mmol), and $EtCO_2H$ (10 μL) was placed in a sealed tube and heated to 180 °C for 36 h in an oil bath. The mixture was cooled, diluted with Et_2O (5 mL), washed with 3 M HCl (5 mL), sat. aq $NaHCO_3$ (5 mL), and brine, and dried (Na_2SO_4). Evaporation of the solvent and column chromatography (silica gel, EtOAc–hexane, 1:40) furnished **23** (415 mg, 78%) as an oil.

IR (neat): 1732, 1635, 1608, 1585, 1497, 1465, 1418, 1367, 1302, 1282, 1224, 1180, 1118, 1031, 916, 873, 803, 734, 703 cm^{-1}.

^1H NMR: δ = 6.78 (d, *J* = 3.0 Hz, 1 H), 6.71 (d, *J* = 8.7 Hz, 1 H), 6.63 (dd, *J* = 8.7, 3.0 Hz, 1 H), 6.28 (dd, *J* = 17.1, 10.5 Hz, 1 H), 5.00 (d, *J* = 10.5 Hz, 1 H), 4.95 (d, *J* = 17.1 Hz, 1 H), 3.91 (q, *J* = 7.2 Hz, 2 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.04 and 2.83 (2 d, *J* = 14.4 Hz, 2 H), 1.53 (s, 3 H), 1.04 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 171.3 (C), 153.4 (C), 152.2 (C), 145.6 (CH), 135.2 (C), 115.3 (CH), 112.3 (CH), 111.5 (CH_2), 111.0 (CH), 59.5 (CH_2), 55.5 (CH_3), 55.3 (CH_3), 43.5 (CH_2), 42.9 (C), 24.6 (CH_3), 14.2 (CH_3).

MS: *m*/*z* (%) = 278 (M^+, 38), 191 (100).

HRMS: *m*/*z* [M + Na] calcd for $C_{16}H_{22}NaO_4$: 301.1416; found: 301.1405.

3-(2,5-Dimethoxyphenyl)-3-methylpent-4-en-1-ol (24)

Reduction of **23** (410 mg, 1.5 mmol) with LAH (56 mg, 1.5 mmol) in anhyd Et_2O (2 mL) at 0 °C for 30 min, followed by column chromatography (silica gel, EtOAc–hexane, 1:3) furnished **34** (334 mg, 95%) as an oil.

IR (neat): 3380, 1633, 1608, 1584, 1495, 1417, 1282, 1223, 1180, 1051, 912, 875, 803, 733 cm^{-1}.

^1H NMR: δ = 6.75 (d, *J* = 3.0 Hz, 1 H), 6.72 (d, *J* = 8.7 Hz, 1 H), 6.62 (dd, *J* = 8.7, 3.0 Hz, 1 H), 6.18 (dd, *J* = 17.7, 10.8 Hz, 1 H), 4.98 (dd, *J* = 10.8, 1.2 Hz, 1 H), 4.94 (dd, *J* = 17.7, 1.2 Hz, 1 H), 3.73 (s, 3 H), 3.71 (s, 3 H), 3.52–3.30 (m, 2 H), 2.32 and 2.03 (2 ddd, *J* = 13.5, 8.1, 6.0 Hz, 2 H), 1.42 (s, 3 H), 1.50–1.40 (br s, 1 H).

^{13}C NMR: δ = 153.4 (C), 152.3 (C), 146.7 (CH), 135.9 (C), 115.4 (CH), 112.5 (CH), 111.0 (CH_2), 110.6 (CH), 60.1 (CH_2), 55.7 (CH_3), 55.3 (CH_3), 43.0 (C), 41.4 (CH_2), 24.9 (CH_3).

MS: *m*/*z* (%) = 236 (M^+, 44), 191 (100), 176 (11), 161 (19), 160 (17), 149 (9), 137 (8), 121 (15).

HRMS: *m*/*z* [M + Na] calcd for $C_{14}H_{20}NaO_3$: 259.1310; found: 259.1316.

3-(2,5-Dimethoxyphenyl)-3-methylpent-4-enal (21)

To a magnetically stirred suspension of PCC (752 mg, 3.5 mmol) and NaOAc (697 mg, 8.40 mmol) in anhyd CH_2Cl_2 (2 mL) was added a soln of **24** (330 mg, 1.4 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred at r.t. for 2 h. It was then filtered through a small column (silica gel, excess CH_2Cl_2). Evaporation of the solvent furnished **21** (225 mg, 70%) as an oil.

IR (neat): 2735, 1719, 1607, 1584, 1495, 1416, 1282, 1225, 1180, 1053, 1025, 918, 878, 805, 732 cm^{-1}.

^1H NMR: δ = 9.46 (s, 1 H), 6.82 (d, *J* = 3.0 Hz, 1 H), 6.78 (d, *J* = 9.3 Hz, 1 H), 6.69 (dd, *J* = 9.3, 3.0 Hz, 1 H), 6.22 (dd, *J* = 17.4, 10.8 Hz, 1 H), 5.10 (d, *J* = 10.8 Hz, 1 H), 5.01 (d, *J* = 17.4 Hz, 1 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 3.04 and 2.85 (2 d, *J* = 15.6 Hz, 2 H), 1.53 (s, 3 H).

^{13}C NMR: δ = 202.4 (CH), 153.5 (C), 151.8 (C), 145.1 (CH), 134.2 (C), 115.4 (CH), 112.5 (CH), 112.2 (CH_2), 111.3 (CH), 55.5 (CH_3), 55.4 (CH_3), 51.5 (CH_2), 42.2 (C), 25.4 (CH_3).

MS: *m*/*z* (%) = 234 (49, M^+), 191 (100), 176 (7), 161 (16), 160 (17), 121 (14).

HRMS: *m*/*z* [M + Na] calcd for $C_{14}H_{18}NaO_3$: 257.1154; found: 257.1152.

5-(2,5-Dimethoxyphenyl)-5-methylhepta-1,6-dien-3-ol (18)
To a cold (–20 °C) magnetically stirred soln of **21** (225 mg, 0.96 mmol) in THF (4 mL) was added dropwise a soln of vinylmagnesium bromide [prepared from Mg (234 mg, 9.60 mmol) and vinyl bromide (0.8 mL, 11.52 mmol) in THF (8 mL)] and stirred at –20 °C for 5 min. The reaction was quenched with cold sat. aq NH_4Cl (10 mL) and extracted with Et_2O (2 × 4 mL). The organic layer was washed with H_2O and brine and dried (Na_2SO_4). Evaporation of the solvent and column chromatography of the residue (silica gel, EtOAc–hexane, 1:9) furnished a ~1:1 diastereomeric mixture of **18** (217 mg, 86%) as an oil.

IR (neat): 3452, 1634, 1607, 1585, 1492, 1464, 1281, 1223, 1180, 1051, 1027, 991, 918, 876, 802, 734 cm^{-1}.

^1H NMR: δ (mixture of diastereomers) = 6.83 and 6.82 (d, *J* = 3.0 Hz, 1 H), 6.75 and 6.74 (d, *J* = 8.7 Hz, 1 H), 6.67 (dd, *J* = 8.7, 3 Hz) and 6.65 (dd, *J* = 8.7, 2.7 Hz) [1 H], 6.31 and 6.29 (dd, *J* = 17.4, 10.8 Hz, 1 H), 5.85–5.65 (m, 1 H), 5.10–4.86 (m, 4 H), 4.10–3.90 (m, 1 H), 3.75 and 3.74 (s, 3 H), 3.73 (s, 3 H), 2.35–2.20 (m, 1 H), 2.05–1.95 (m, 1 H), 1.53 and 1.46 (s, 3 H), 1.50 (br s, 1 H).

^{13}C NMR: δ (mixture of diastereomers) = 153.5 (C), 152.3 (C), 147.2 and 147.1 (CH), 142.3 and 142.2 (CH), 135.9 (C), 115.6 (CH), 113.1 and 113.0 (CH_2), 112.5 and 112.4 (CH), 111.0 (CH_2), 110.9 and 110.7 (CH), 70.9 and 70.8 (CH), 55.6 (CH_3), 55.3 (CH_3), 46.2 and 45.8 (CH_2), 43.6 (C), 25.4 and 25.3 (CH_3).

MS: *m*/*z* (%) = 262 (M^+, 84), 192 (100), 176 (33), 175 (30), 161 (75), 160 (65), 149 (29), 139 (70), 121 (53), 115 (33).

HRMS: *m*/*z* [M + Na] calcd for $C_{16}H_{22}NaO_3$: 285.1467; found: 285.1478.

4-(2,5-Dimethoxyphenyl)-4-methylcyclopent-2-en-1-ol (25)
To a magnetically stirred soln of a 1:1 diastereomeric mixture of **18** (205 mg, 0.78 mmol) in anhyd CH_2Cl_2 (58 mL) was added a soln of Grubbs' catalyst $PhCH{=}Ru(PCy_3)_2Cl_2$ (32 mg, 5 mol%) in anhyd CH_2Cl_2 (20 mL) and the mixture was stirred at r.t. for 1 h. Evaporation of the solvent under reduced pressure and column chromatography (silica gel, EtOAc–hexane, 1:10–1:5) furnished a 1:1 diastereomeric mixture of **25** (170 mg, 93%) as an oil.

IR (neat): 3392, 1607, 1585, 1496, 1417, 1282, 1222, 1179, 1114, 1067, 1049, 1028, 873, 801, 728 cm^{-1}.

^1H NMR: δ (mixture of diastereomers) = 6.80–6.55 (m, 3 H), 6.19 (d, *J* = 5.4 Hz, 1 H), 5.84 (m, 1 H), 4.82 and 4.70 (m, 1 H), 3.78 (s, 3 H), 3.73 and 3.71 (s, 3 H), 2.60 (dd, *J* = 14.4, 7.2 Hz) and 2.52 (dd, *J* = 10.1, 7.5 Hz) [1 H], 2.03 (dd, *J* = 14.4, 3.9 Hz) and 1.92 (dd, *J* = 14.1, 4.2 Hz) [1 H], 1.65 (br s, 1 H), 1.50 and 1.38 (s, 3 H).

^{13}C NMR: δ (mixture of diastereomers) = 153.4 and 153.2 (C), 151.9 and 151.5 (C), 142.4 (CH), 138.6 and 138.1 (C), 132.1 and 131.9 (CH), 113.8 and 113.7 (CH), 112.4 and 112.0 (CH), 110.5 and 110.3 (CH), 77.3 and 77.2 (CH), 55.7 and 55.5 (CH_3), 55.4 (CH_3), 51.7 and 50.4 (C), 49.2 and 48.5 (CH_2), 29.2 and 27.9 (CH_3).

MS: *m*/*z* (%) = 234 (M^+, 61), 219 (100), 204 (7), 191 (14), 177 (12), 175 (12), 161 (16) 115 (10).

HRMS: *m*/*z* [M + Na] calcd for $C_{14}H_{18}NaO_3$: 257.1154; found: 257.1161.

4-(2,5-Dimethoxyphenyl)-4-methylcyclopent-2-enone (26)
To a magnetically stirred soln of PCC (382 mg, 1.78 mmol) and NaOAc (236 mg, 2.84 mmol) in CH_2Cl_2 (3 mL) was added a soln of **25** (165 mg, 0.71 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at r.t. for 1 h and filtered through a column (silica gel, excess CH_2Cl_2). Evaporation of the solvent furnished **26** (152 mg, 93%).

IR (neat): 1715, 1588, 1498, 1370, 1341, 1285, 1230, 1178, 1086, 1044, 1025, 932, 897, 869, 804, 729 cm^{-1}.

^1H NMR: δ = 7.75 (d, *J* = 5.7 Hz, 1 H), 6.80–6.60 (m, 3 H), 6.13 (d, *J* = 5.7 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 2.72 and 2.53 (2 d, *J* = 18.6 Hz, 2 H), 1.56 (s, 3 H).

^{13}C NMR: δ = 209.0 (C), 169.8 (CH), 153.4 (C), 151.7 (C), 134.5 (C), 131.4 (CH), 114.4 (CH), 112.1 (CH), 111.0 (CH), 55.5 (CH_3), 55.4 (CH_3), 50.0 (CH_2), 47.1 (C), 27.4 (CH_3).

MS: *m*/*z* (%) = 233 (M + H, 17), 232 (M^+, 100), 217 (59), 202 (7), 189 (21), 174 (16), 163 (15), 115 (15).

HRMS: *m*/*z* [M + H] calcd for $C_{14}H_{17}O_3$: 233.1177; found: 233.1177.

4-(2,5-Dimethoxyphenyl)-4,5,5-trimethylcyclopent-2-enone (17)
A suspension of NaH (150 mg, 60% dispersion in oil, 3.75 mmol) in hexanes (1 mL) under a N_2 atmosphere was magnetically stirred for 10 min and the solvent was syringed out. The oil free NaH was then suspended in anhyd THF (3 mL), added sequentially, anhyd DMF (0.4 mL), MeI (0.31 mL, 5.04 mmol), and **26** (145 mg, 0.63 mmol). The mixture was magnetically stirred at r.t. for 12 h. It was then quenched with H_2O (3 mL) and extracted with Et_2O (3 × 4 mL). The combined Et_2O extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent and column chromatography (silica gel, EtOAc–hexane, 1:9) furnished **17** (117 mg, 72%) as an oil.

IR (neat): 1708, 1585, 1500, 1381, 1339, 1285, 1228, 1180, 1120, 1081, 1041, 1025, 839, 804, 765, 729 cm^{-1}.

^1H NMR: δ = 7.83 (d, *J* = 5.7 Hz, 1 H), 6.78 (d, *J* = 9.3 Hz, 1 H), 6.69 (dd, *J* = 9.3, 3.0 Hz, 1 H), 6.60 (br s, 1 H), 6.09 (d, *J* = 5.7 Hz, 1 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 1.48 (s, 3 H), 1.25 (s, 3 H), 0.65 (s, 3 H).

^{13}C NMR: δ = 214.1 (C), 169.9 (CH), 153.5 (C), 152.1 (C), 133.4 (CH), 128.0 (C), 115.8 (CH), 111.8 (CH), 110.8 (CH), 55.4 (CH_3), 55.2 (CH_3), 54.8 (C), 50.7 (C), 25.6 (2 C, CH_3), 20.1 (CH_3).

MS: *m*/*z* (%) = 260 (M^+, 38), 246 (15), 245 (100), 230 (11), 215 (6), 202 (4), 123 (7).

HRMS: *m*/*z* [M + Na] calcd for $C_{16}H_{20}NaO_3$: 283.1310; found: 283.1325.

3-(2,5-Dimethoxyphenyl)-2,2,3-trimethylcyclopentanone (27)
To activated 10% Pd/C (30 mg) was added a soln of **17** (110 mg, 0.42 mmol) in EtOH (2 mL) and the mixture was stirred at r.t. for 1 h under an atmosphere of H_2 created by evacuative replacement of air (balloon). The catalyst was then filtered off using a small column (silica gel). Evaporation of the solvent furnished **27** (105 mg, 96%) as an oil.

IR (neat): 1736, 1608, 1587, 1497, 1465, 1372, 1285, 1226, 1181, 1090, 1050, 1027, 867, 801, 753, 721 cm^{-1}.

^1H NMR: δ = 6.89 (d, *J* = 3.0 Hz, 1 H), 6.80 (d, *J* = 8.7 Hz, 1 H), 6.66 (dd, *J* = 8.7, 3.0 Hz, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 2.55–2.35 (m, 3 H), 2.05–1.95 (m, 1 H), 1.38 (s, 3 H), 1.21 (s, 3 H), 0.66 (s, 3 H).

^{13}C NMR: δ = 221.8 (C), 153.4 (C), 152.4 (C), 136.3 (C), 115.9 (CH), 111.4 (CH), 110.1 (CH), 55.4 (CH_3), 54.7 (CH_3), 52.6 (C), 48.9 (C), 34.4 (CH_2), 32.7 (CH_2), 23.5 (CH_3), 21.9 (CH_3), 21.8 (CH_3).

MS: *m*/*z* (%) = 262 (M^+, 83), 247 (14), 213 (10), 192 (28), 191 (100), 178 (28), 177 (22), 163 (28), 161 (22), 149 (10), 135 (10), 121 (14), 105 (8).

HRMS: *m*/*z* [M + Na] calcd for $C_{16}H_{22}NaO_3$: 285.1467; found: 285.1472.

7-(2,5-Dimethoxyphenyl)-6,6,7-trimethyl-1,4-dithiaspiro[4.4]nonane (28)

To a magnetically stirred soln of **27** (100 mg, 0.38 mmol) in anhyd CH_2Cl_2 (0.22 mL) was added ethane-1,2-dithiol (0.32 mL, 3.8 mmol) and I_2 (20 mg, 25 mol%) and the mixture was stirred at r.t. for 1 h. Then 1 M aq $Na_2S_2O_3$ (1 mL) was added followed by 10% aq NaOH (5 mL) and the mixture was stirred for 5 min. It was extracted with CH_2Cl_2 (2 × 3 mL) and the extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–hexane, 1:9) furnished **28** (105 mg, 81%) as an oil.

IR (neat): 1581, 1493, 1465, 1410, 1378, 1281, 1220, 1179, 1048, 1036, 1025, 867, 799, 727 cm^{-1}.

^1H NMR: δ = 6.85 (d, *J* = 3.0 Hz, 1 H), 6.72 (d, *J* = 9.0 Hz, 1 H), 6.62 (dd, *J* = 9.0, 3.0 Hz, 1 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.30–3.10 (m, 4 H), 2.85–2.40 (m, 2 H), 2.30 (m, 1 H), 1.73–1.63 (m, 1 H), 1.53 (s, 3 H), 1.25 (s, 3 H), 0.74 (s, 3 H).

MS: *m*/*z* (%) = 338 (M^+, 7), 324 (4), 278 (4), 263 (4), 220 (11), 207 (33), 178 (100), 163 (26), 151 (16), 131 (10).

HRMS: *m*/*z* [M + H] calcd for $C_{18}H_{27}O_2S_2$: 339.1452; found: 339.1464.

1,4-Dimethoxy-2-(1,2,2-trimethylcyclopentyl)benzene (29)

To a magnetically stirred soln of **28** (36 mg, 0.107 mmol) in anhyd EtOH (3 mL) was added Raney nickel (100 mg, excess) and the mixture was refluxed for 5 h. It was then cooled and filtered through a short column (silica gel, excess CH_2Cl_2). Evaporation of the solvent furnished **29** (26 mg, 100%) as an oil.

IR (neat): 1585, 1493, 1465, 1415, 1371, 1282, 1224, 1179, 1055, 1030, 797, 726 cm^{-1}.

^1H NMR: δ = 6.85 (d, *J* = 3.0 Hz, 1 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 6.60 (dd, *J* = 8.4, 3.0 Hz, 1 H), 3.73 (s, 6 H), 2.60–2.40 (m, 1 H), 1.80–1.40 (m, 5 H), 1.34 (s, 3 H), 1.13 (s, 3 H), 0.69 (s, 3 H).

^{13}C NMR: δ = 153.2 (2 C, C), 137.5 (C), 116.4 (CH), 112.0 (CH), 109.8 (CH), 55.4 (CH_3), 55.3 (CH_3), 51.5 (C), 44.4 (C), 42.1 (CH_2), 40.0 (CH_2), 27.7 (CH_3), 26.1 (CH_3), 23.2 (CH_3), 20.7 (CH_2).

HRMS: *m*/*z* [M + Na] calcd for $C_{16}H_{24}NaO_2$: 271.1674; found: 271.1678.

Ethyl 2-Allyl-3-(2,5-dimethoxyphenyl)-3-methylpent-4-enoate (30)

To a cold (–70 °C) magnetically stirred soln of *i*-Pr_2NH (0.39 mL, 2.79 mmol) in anhyd THF (4 mL) was added a 2.35 M *n*-BuLi in hexane (1.1 mL, 2.52 mmol) and the mixture was stirred for 10 min. To LDA thus formed was added dropwise a soln of **23** (350 mg, 1.26 mmol) in anhyd THF (3 mL) and the mixture was stirred for 40 min. Allyl bromide (0.16 mL, 1.9 mmol) was added to the mixture and it was stirred at r.t. for 4 h. The mixture was then diluted with H_2O and extracted with Et_2O (3 × 4 mL). The combined Et_2O extracts were washed with 3 M aq HCl, sat. aq $NaHCO_3$, and brine and dried (Na_2SO_4). Evaporation of the solvent and column chromatography (silica gel, EtOAc–hexane, 1:20) furnished a 1:1 diastereomeric mixture of **30** (335 mg, 84%).

IR (neat): 1727, 1640, 1608, 1584, 1495, 1465, 1373, 1350, 1280, 1227, 1181, 1049, 1027, 916, 804, 731 cm^{-1}.

^1H NMR: δ (1:1 mixture of diastereomers) = 6.76–6.45 (m, 4 H), 5.75–5.55 (m, 1 H), 5.15–4.85 (m, 4 H), 4.00–3.60 (m, 3 H), 3.82 (s, 3 H), 3.71 (s, 3 H), 2.50–2.20 (m, 1 H), 2.10–1.80 (m, 1 H), 1.52 and 1.51 (s, 3 H), 1.02 and 0.91 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ (1:1 mixture of diastereomers) = 173.8 and 173.4 (C), 153.4 and 153.2 (C), 152.4 and 152.2 (C), 143.6 and 143.4 (CH), 136.6 and 136.5 (CH), 135.1 and 135.0 (C), 116.0 (CH_2), 115.7 and 115.1 (CH), 113.3 and 113.1 (CH_2), 112.3 (CH), 111.1 and 111.0 (CH), 59.5 and 59.4 (CH_2), 55.7 and 55.6 (CH_3), 55.4 and 55.3 (CH_3), 50.7 and 50.5 (CH), 46.4 (C), 32.7 and 32.4 (CH_2), 19.9 and 19.8 (CH_3), 14.2 and 14.1 (CH_3).

MS: *m*/*z* (%) = 318 (M^+, 8), 191 (100), 176 (7), 161 (10), 160 (10), 149 (8), 121 (10).

HRMS: *m*/*z* [M + Na] calcd for $C_{19}H_{26}NaO_4$: 341.1729; found: 341.1730.

Ethyl 2-(2,5-Dimethoxyphenyl)-2-methylcyclopent-3-enecarboxylate (31)

To a magnetically stirred soln of a 1:1 diastereomeric mixture of **30** (300 mg, 0.95 mmol) in anhyd CH_2Cl_2 (60 mL) was added a soln of Grubbs' catalyst $PhCH{=}Ru(PCy_3)_2Cl_2$ (40 mg, 5 mol%) in anhyd CH_2Cl_2 (10 mL) and the mixture was stirred at r.t. for 5 h. Evaporation of the solvent under reduced pressure and column chromatography (silica gel, EtOAc–hexane, 1:30) furnished a 1:1 diastereomeric mixture of **31** (265 mg, 97%) as an oil. Small samples of pure *cis*- and *trans*-isomers were separated by careful column chromatography (silica gel).

***trans*-Isomer**

IR (neat): 1730, 1585, 1497, 1464, 1419, 1370, 1341, 1280, 1228, 1179, 1049, 801, 724 cm^{-1}.

^1H NMR: δ = 6.88 (d, *J* = 3.0 Hz, 1 H), 6.76 (d, *J* = 8.7 Hz, 1 H), 6.67 (dd, *J* = 8.7, 3.0 Hz, 1 H), 5.80 (dt, *J* = 5.7, 1.8 Hz, 1 H), 5.72 (dt, *J* = 5.7, 2.1 Hz, 1 H), 4.17 and 4.11 (2 dq, *J* = 10.8, 7.2 Hz, 2 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.44 (dd, *J* = 8.7, 6.9 Hz, 1 H), 2.77 (ddt, *J* = 16.5, 7.2, 2.1 Hz, 1 H), 2.56 (ddt, *J* = 16.5, 5.7, 2.1 Hz, 1 H), 1.39 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 174.3 (C), 153.3 (C), 152.0 (C), 138.5 (CH), 137.1 (C), 126.8 (CH), 114.7 (CH), 112.1 (CH), 110.9 (CH), 59.8 (CH_2), 55.4 (2 C, CH_3), 54.5 (C), 51.9 (CH), 35.4 (CH_2), 22.1 (CH_3), 14.5 (CH_3).

MS: *m*/*z* (%) = 290 (M^+, 60), 229 (100), 217 (24), 216 (21), 201 (65), 191 (38), 188 (31), 185 (35), 175 (25), 165 (36), 161 (25), 138 (24), 115 (36).

HRMS: *m*/*z* [M + Na] calcd for $C_{17}H_{22}NaO_4$: 313.1416; found: 313.1414.

***cis*-Isomer**

IR (neat): 1730, 1606, 1587, 1498, 1419, 1369, 1342, 1282, 1228, 1180, 1097, 1065, 1048, 871, 801, 730 cm^{-1}.

^1H NMR: δ = 6.82 (d, *J* = 2.7 Hz, 1 H), 6.67 (d, *J* = 9.0 Hz, 1 H), 6.62 (dd, *J* = 9.0, 2.7 Hz, 1 H), 5.93–5.85 (m, 1 H), 5.73 (dt, *J* = 5.4, 2.1 Hz, 1 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.80–3.55 (m, 2 H), 3.30 (dd, *J* = 7.8, 4.5 Hz, 1 H), 2.80–2.59 (m, 2 H), 1.52 (s, 3 H), 0.83 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 174.1 (C), 153.1 (C), 151.9 (C), 137.7 (CH), 134.5 (C), 127.1 (CH), 115.0 (CH), 111.2 (CH), 111.0 (CH), 59.4 (CH_2), 55.8 (C), 55.4 (CH_3), 55.1 (CH_3), 53.7 (CH), 36.5 (CH_2), 28.2 (CH_3), 13.8 (CH_3).

MS: *m*/*z* (%) = 290 (M^+, 52), 275 (8), 229 (100), 201 (62), 187 (23), 165 (22), 138 (19), 115 (29).

HRMS: *m*/*z* [M + Na] calcd for $C_{17}H_{22}NaO_4$: 313.1416; found: 313.1411.

Ethyl *cis*-2-(2,5-Dimethoxyphenyl)-1,2-dimethylcyclopent-3-enecarboxylate (32)

To a cold (–30 °C) magnetically stirred soln of LDA [prepared from *i*-Pr_2NH (0.22 mL, 1.55 mmol) and a soln of 2.3 M *n*-BuLi in hexane (0.57 mL, 1.30 mmol) in anhyd THF (3 mL)] was added dropwise a soln of **31** (150 mg, 0.517 mmol) in a mixture of anhyd THF (1 mL) and anhyd HMPA (2.5 mL) and stirred at this temperature

for 40 min. MeI (0.1 mL, 1.55 mmol) was added to the mixture and it was stirred at r.t. for 7 h. The mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3 × 4 mL). The combined Et_2O layers were washed with 3 M aq HCl (5 mL), sat. aq $NaHCO_3$ soln (5 mL), and brine, and dried (Na_2SO_4). Evaporation of the solvent and column chromatography (silica gel, EtOAc–hexane, 1:20) furnished **32** (138 mg, 88%) as an oil.

IR (neat): 1723, 1586, 1498, 1416, 1378, 1282, 1228, 1198, 1180, 1113, 1060, 1042, 1028, 799, 736 cm^{-1}.

^1H NMR: δ = 6.76 (d, *J* = 3.0 Hz, 1 H), 6.68 (d, *J* = 8.7 Hz, 1 H), 6.61 (dd, *J* = 8.7, 3.0 Hz, 1 H), 5.80–5.70 (m, 2 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.43, 3.34 (2 dq, *J* = 10.8, 7.5 Hz, 2 H), 3.01 and 2.26 (2 d, *J* = 16.5 Hz, 2 H), 1.50 (s, 3 H), 1.49 (s, 3 H), 0.81 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR: δ = 176.2 (C), 153.1 (C), 153.0 (C), 139.1 (CH), 135.1 (C), 127.2 (CH), 115.9 (CH), 111.7 (CH), 111.3 (CH), 59.6 (CH_2), 59.0 (2 C, C), 55.5 (CH_3), 55.3 (CH_3), 46.4 (CH_2), 23.3 (CH_3), 21.5 (CH_3), 13.7 (CH_3).

MS: *m*/*z* (%) = 304 (M^+, 58), 231 (23), 227 (27), 215 (22), 203 (34), 202 (100), 199 (43), 191 (55), 190 (82), 187 (55), 175 (44), 161 (32), 139 (72), 115 (52).

HRMS: *m*/*z* [M + Na] calcd for $C_{18}H_{24}NaO_4$: 327.1572; found: 327.1559.

Ethyl *cis*-2-(2,5-Dimethoxyphenyl)-1,2-dimethylcyclopentanecarboxylate (33)

Catalytic hydrogenation of **32** (115 mg, 0.38 mmol) with activated 10% Pd/C (25 mg) in EtOH (3 mL) at 1 bar of H_2 at r.t. for 2 h furnished **33** (115 mg, 99%) as an oil.

IR (neat): 1723, 1609, 1586, 1498, 1380, 1366, 1285, 1226, 1180, 1141, 1103, 1054, 1029, 870, 802, 725 cm^{-1}.

^1H NMR: δ = 6.81 (d, *J* = 3.0 Hz, 1 H), 6.67 (d, *J* = 8.7 Hz, 1 H), 6.59 (dd, *J* = 8.7, 3.0 Hz, 1 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 3.75–3.50 (m, 2 H), 2.70–2.50 (m, 1 H), 2.24 (dt, *J* = 12.0, 9.3 Hz, 1 H), 1.95–1.60 (m, 4 H), 1.44 (s, 3 H), 1.32 (s, 3 H), 0.82 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 177.3 (C), 153.2 (C), 152.3 (C), 138.0 (C), 114.9 (CH), 111.5 (CH), 110.3 (CH), 59.6 (CH_2), 55.6 (CH_3), 55.1 (CH_3), 52.4 (2 C, C), 41.2 (CH_2), 40.7 (CH_2), 24.0 (CH_3), 21.9 (CH_3), 22.0 (CH_2), 13.8 (CH_3).

MS: *m*/*z* (%) = 306 (M^+, 95), 232 (16), 204 (13), 193 (34), 192 (100), 179 (34), 173 (43), 165 (35), 163 (29), 161 (30), 151 (40), 115 (71).

HRMS: *m*/*z* [M + Na] calcd for $C_{18}H_{26}NaO_4$: 329.1729; found: 329.1731.

cis-2-(2,5-Dimethoxyphenyl)-1,2-dimethylcyclopentanemethanol (34)

Reduction of **33** (110 mg, 0.36 mmol) with LAH (27 mg, 0.72 mmol) in Et_2O (3 mL) at –20 °C for 30 min, with purification by column chromatography (silica gel, EtOAc–hexane, 1:19) furnished **34** (88 mg, 93%) as an oil.

IR (neat): 3446, 1608, 1585, 1491, 1465, 1414, 1376, 1283, 1223, 1179, 1040, 1026, 872, 801, 726 cm^{-1}.

^1H NMR: δ = 6.81 (d, *J* = 3.0 Hz, 1 H), 6.76 (d, *J* = 9.0 Hz, 1 H), 6.63 (dd, *J* = 9.0, 3.0 Hz, 1 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.04 (s, 2 H), 2.45–2.30 (m, 1 H), 2.00 (br s, 1 H), 1.85–1.50 (m, 4 H), 1.36–1.23 (m, 1 H), 1.38 (s, 3 H), 1.15 (s, 3 H).

^{13}C NMR: δ = 153.7 (C), 152.6 (C), 137.0 (C), 116.2 (CH), 112.7 (CH), 110.4 (CH), 70.3 (CH_2), 55.8 (CH_3), 55.3 (CH_3), 50.7 (C), 49.1 (C), 42.1 (CH_2), 37.0 (CH_2), 24.2 (CH_3), 21.3 (CH_2), 21.0 (CH_3).

MS: *m*/*z* (%) = 264 (M^+, 59), 191 (19), 178 (30), 166 (30), 165 (100), 151 (28), 135 (24), 121 (17).

HRMS: *m*/*z* [M + Na] calcd for $C_{16}H_{24}NaO_3$: 287.1623; found: 287.1609.

cis-2-(2,5-Dimethoxyphenyl)-1,2-dimethylcyclopentanecarbaldehyde (35)

Oxidation of **34** (85 mg, 0.322 mmol) with PCC (208 mg, 0.97 mmol) and silica gel (208 mg) in CH_2Cl_2 (1 mL) at r.t. for 30 min, followed by column chromatography (silica gel, EtOAc–hexane, 1:20) furnished **35** (78 mg, 92%) as an oil.

IR (neat): 2721, 1717, 1608, 1586, 1497, 1463, 1377, 1284, 1226, 1180, 1052, 1027, 917, 878, 803, 729 cm^{-1}.

^1H NMR: δ = 9.00 (s, 1 H), 6.81 (d, *J* = 2.7 Hz, 1 H), 6.69 (d, *J* = 8.7 Hz, 1 H), 6.64 (dd, *J* = 8.7, 2.7 Hz, 1 H), 3.73 (s, 3 H), 3.68 (s, 3 H), 2.38 (dt, *J* = 12.6, 8.1 Hz, 1 H), 2.05–1.75 (m, 4 H), 1.55–1.43 (m, 1 H), 1.32 (s, 3 H), 1.27 (s, 3 H).

^{13}C NMR: δ = 203.6 (CH), 153.5 (C), 151.7 (C), 135.2 (C), 115.3 (CH), 111.4 (CH), 110.7 (CH), 57.6 (C), 55.3 (CH_3), 54.7 (CH_3), 50.9 (C), 41.2 (CH_2), 36.9 (CH_2), 24.3 (CH_3), 22.2 (CH_2), 17.9 (CH_3).

MS: *m*/*z* (%) = 262 (M^+, 30), 192 (33), 191 (100), 161 (10), 149 (10), 135 (6), 121 (15).

HRMS: *m*/*z* [M + Na] calcd for $C_{16}H_{22}NaO_3$: 285.1467; found: 285.1459.

1,4-Dimethoxy-2-(1,2,2-trimethylcyclopentyl)benzene (29)

A soln of **35** (78 mg, 0.30 mmol) and hydrazine hydrate (0.15 mL, 3.0 mmol) in diethylene glycol (2 mL) was heated to 125 °C for 3 h in a sealed tube and then cooled to r.t. KOH (168 mg, 3.0 mmol) was added to the mixture and it was heated to 200 °C for 12 h. The mixture was then cooled to r.t., acidified with 3 M aq HCl (5 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined CH_2Cl_2 extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–hexane, 1:20) furnished **29** (61 mg, 82%), which exhibited TLC and spectral data (IR, ^1H and ^{13}C NMR) identical to the sample obtained earlier.

4,4′-Bis(1,2,2-trimethylcyclopentyl)bi(cyclohexa-1,4-dienyl)-3,3′,6,6′-tetrone (37)

To a magnetically stirred soln of **29** (17 mg, 0.07 mmol) in MeCN (1 mL) and H_2O (1 mL) was added CAN (77 mg, 0.14 mmol). The mixture was stirred at r.t. for 1 h and extracted with CH_2Cl_2 (3 × 3 mL). The combined CH_2Cl_2 layers were washed with brine and dried (Na_2SO_4). Evaporation of the solvent and column chromatography (silica gel, EtOAc–hexane, 1:10) furnished **37** (8 mg, 53%) as yellow oil.

IR (neat): 1655, 1589, 1462, 1386, 1371, 1347, 1305, 1291, 1091, 1019, 927, 831, 790 cm^{-1}.

^1H NMR: δ = 6.79 (s, 2 H), 6.70 (s, 2 H), 2.20–2.35 (m, 2 H), 1.50–1.80 (m, 10 H), 1.32 (s, 6 H), 1.14 (s, 6 H), 0.79 (s, 6 H).

HRMS: *m*/*z* [M + K] calcd for $C_{28}H_{34}KO_4$: 473.2130; found: 473.2094.

2-(1,2,2-Trimethylcyclopentyl)benzene-1,4-diol (38)

To a cold (–40 °C) magnetically stirred soln of **29** (74 mg, 0.3 mmol) in anhyd CH_2Cl_2 (1 mL) was added dropwise 1 M BBr_3 in CH_2Cl_2 (0.8 mL, 0.8 mmol) and the mixture was stirred at this temperature for 30 min and then stirred at r.t. for 5 h. The mixture was then quenched with sat. aq $NaHCO_3$ soln (4 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined CH_2Cl_2 extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent and column chromatography (silica gel, EtOAc–hexane, 1: 20) furnished **38** (66 mg, 98%).

IR (neat): 3318, 1651, 1592, 1508, 1445, 1386, 1372, 1294, 1200, 1140, 1056, 939, 872, 806, 769 cm^{-1}.

^1H NMR: δ = 6.77 (s, 1 H), 6.51 (s, 2 H), 4.44 (br s, 1 H), 4.38 (br s, 1 H), 2.60–2.40 (m, 1 H), 1.81–1.50 (m, 5 H), 1.39 (s, 3 H), 1.16 (s, 3 H), 0.76 (s, 3 H).

^{13}C NMR: δ = 148.63 (C), 148.57 (C), 134.9 (C), 117.5 (CH), 116.6 (CH), 113.2 (CH), 51.1 (C), 44.7 (C), 41.2 (CH_2), 39.4 (CH_2), 27.0 (CH_3), 25.6 (CH_3), 22.8 (CH_3), 20.3 (CH_2).

MS: *m*/*z* (%) = 220 (M^+, 48), 163 (14), 150 (61), 149 (32), 138 (38), 137 (100), 135 (32), 123 (30), 107 (21).

HRMS: *m*/*z* [M + Na] calcd for $C_{14}H_{20}NaO_2$: 243.1361; found: 243.1375.

2-(1,2,2-Trimethylcyclopentyl)-1,4-benzoquinone (36)

To a magnetically stirred soln of **38** (30 mg, 0.14 mmol) in MeCN (3 mL) and H_2O (3 mL) was added CAN (230 mg, 0.42 mmol). The mixture was stirred at r.t. for 1 h. Workup as described for **37**, followed by column chromatography (silica gel, EtOAc–hexane, 1:10) furnished **36** (30 mg, 100%) as yellow oil.

IR (neat): 1654, 1589, 1462, 1372, 1347, 1306, 1292, 1091, 1019, 927, 832, 788 cm^{-1}.

^1H NMR: δ = 6.65 (s, 2 H), 6.62 (s, 1 H), 2.35–2.15 (m, 1 H), 1.80–1.45 (m, 5 H), 1.29 (s, 3 H), 1.12 (s, 3 H), 0.74 (s, 3 H).

^{13}C NMR: δ = 187.7 (C), 187.6 (C), 154.9 (C), 138.7 (CH), 134.6 (CH), 133.9 (CH), 51.6 (C), 44.2 (C), 41.6 (CH_2), 38.6 (CH_2), 28.0 (CH_3), 25.4 (CH_3), 23.0 (CH_3), 20.0 (CH_2).

MS: *m*/*z* (%) = 218 (M^+, 5), 203 (20), 189 (2), 175 (44), 161 (24), 150 (100), 147 (25), 137 (28), 135 (25), 108 (14), 91 (40).

HRMS: *m*/*z* [M + Na] calcd for $C_{14}H_{18}NaO_2$: 241.1204; found: 241.1214.

UV: λ = 307, 269.5 nm.

4-Hydroxy-4-methyl-2-(1,2,2-trimethylcyclopentyl)cyclohexa-2,5-dienone (Herbertenones A and B, 13 and 14)

To a cold magnetically stirred soln of **36** (25 mg, 0.115 mmol) at –30 °C in anhyd THF (4 mL) was added 0.5 M MeMgBr in THF (0.5 mL, 0.25 mmol) dropwise over a period of 2 min. It was stirred for 1 min, the reaction was quenched with cold sat. aq NH_4Cl (4 mL) and extracted with Et_2O (3 × 3 mL). Evaporation of the solvent and column chromatography (silica gel, EtOAc–hexane, 1:12) furnished a 2:1 mixture of herbertenone A (**13**) and herbertenone B (**14**) (18 mg, 67%) as an oil.

IR (neat): 3396, 1665, 1629, 1463, 1387, 1370, 1257, 1127, 1055, 1020, 899, 835, 736 cm^{-1}.

^1H NMR: δ (2:1 mixture of **13** and **14**) = 6.76 (dd, *J* = 9.6, 3 Hz, 1 H), 6.71 (d, *J* = 3 Hz, 1 H), 6.03 (d, *J* = 9.6 Hz, 1 H), 2.40–2.17 (m, 1 H), 1.96 and 2.03 (br s, 1 H), 1.75–1.50 (m, 5 H), 1.46 (s, 3 H), 1.25 and 1.27 (s, 3 H), 1.13 and 1.11 (s, 3 H) and 0.72 (s, 3 H).

^{13}C NMR: δ (2:1 mixture of **13** and **14**) = 185.8 (C), 148.8 and 148.7 (CH), 148.1 and 147.8 (CH), 142.59 and 142.57 (C), 129.2 and 129.0 (CH), 68.1 and 67.8 (C), 50.41 and 50.39 (C), 43.7 and 43.5 (C), 41.62 and 41.56 (CH_2), 38.7 and 38.6 (CH_2), 27.6 and 27.7 (CH_3), 27.5 and 27.4 (CH_3), 25.53 and 25.46 (CH_3), 22.4 and 22.7 (CH_3).

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