Synthesis of herbertenediol and mastigophorenes A-D

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Dedicated to Professor S. Swaminathan

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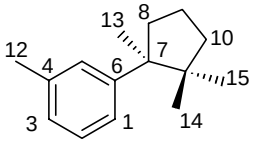
Abstract

Formal total synthesis of (±)-herbertenediol and mastigophorenes A-D, starting from vanillin, has been described. A combination of alkylation, Wacker oxidation and intramolecular aldol condensation was employed for the generation of the cyclopentenone with two vicinal quaternary carbon atoms.

Keywords: Herbertanes, sesquiterpene synthesis, intramolecular aldol condensation, vicinal quaternary carbon atoms

Introduction

Liverworts from the genus *Herbertus* contain herbertane sesquiterpenoids which are considered as chemical markers of the genus.[1] The herbertane group is a class of aromatic sesquiterpenes, containing sterically crowded 1-aryl-1,2,2-trimethylcyclopentane carbon framework incorporating two vicinal quaternary carbon atoms on a cyclopentane ring. The first member of this class of sesquiterpenes, herbertene **1**, was isolated in 1981 by Matsuo and coworkers from the ethyl acetate extract of the liverwort *Herberta adunca* (Dicks.) S. Gray belonging to the family Herbertaceae.[2]



1 (Herbertene)

In 1982, research groups of Matsuo and Asakawa have reported isolation of three phenolic herbertanes, α-herbertenol **2**, α-formylherbertenol **3** and β-herbertenol **4** along with herbertene **1**

and cuparene sesquiterpenes from the species *H. aduncus, H. sakuraii* and *H. subdetatus*.[3] Isolation of two more herbertenoids herbertenediol **5** and herbertenolide **6** was reported in 1983 by Matsuo and coworkers.[4] In 1988 and 1991 Asakawa and coworkers reported the isolation of the dimeric herbertanes, mastigophorenes A-D **7**-**10**, dimers of herbertenediol **5**, from the liverwort *Mastigophora diclados* (Mastigophoraceae).[5] The mastigophorenes A-D **7**-**10** are presumably formed by one electron oxidative phenolic coupling of herbertenediol **5**. Subsequently, isolation of several herbertenoids **11**-**21** from various liverworts was reported.[1,6] Structures of the herbertanes and mastigophorenes known so far are depicted in Chart 1.

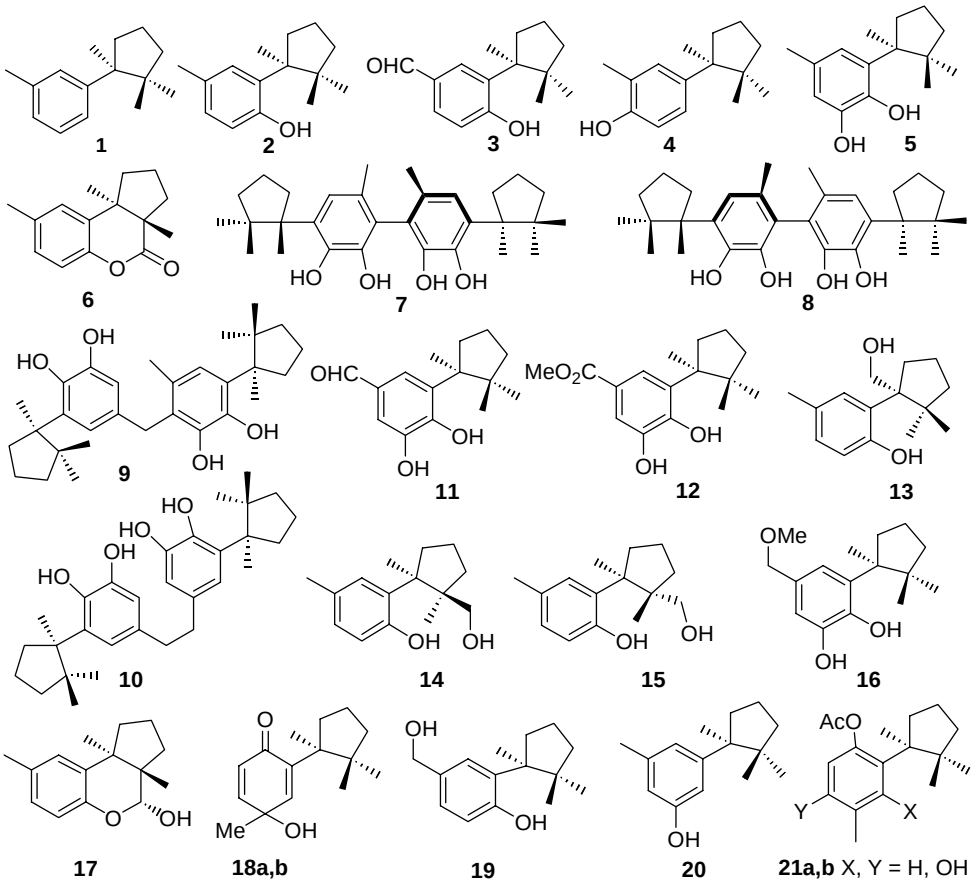


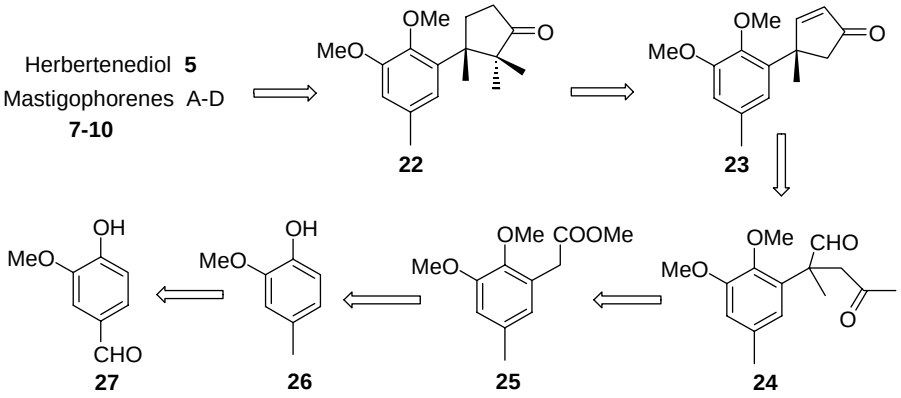
Chart 1

The herbertane sesquiterpenes, mainly the phenolic herbertanes have been shown to possess interesting biological properties such as growth inhibiting activity, antilipid peroxidation activity.[3,4,6] The growth inhibiting activity of a few herbertenoids was tested on some plant pathogenic fungi. Some of the phenolic herbertanes were found to be strong inhibitors of the plant pathogenic fungi, *Botrytis cinerea, Rhizoctonia solani* and *Pythium debaryanum.* Mastigophorenes A-D **7**-**10** were found to exhibit intriguing neurotropic properties i.e. promote neuronal out growth and enhance choline acetyl transferase activity in the primary cultures of fetal rat cerebral hemisphere.

Presence of an interesting carbon framework, sterically crowded 1-aryl-1,2,2-trimethylcyclopentane, the difficulty associated with the construction of vicinal quaternary carbon atoms on a cyclopentane ring, and the novel biological properties associated with the phenolic herbertanes made the herbertenoids and mastigophorenes challenging synthetic targets. Even though, herbertanes were known since 1981, very little synthetic effort was reported in the literature on the synthesis of phenolic herbertanes prior to 1999. However during the past five years more than 25 publications appeared in the literature on the synthesis of herbertanes.[7-9] During the same time, three approaches have been reported for the synthesis of mastigophorenes A and B **7** and **8**, and one of which has been extended to the synthesis of mastigophorenes C and D **9** and **10**.[8] Herein, we report the details of the formal total synthesis of (±)-herbertenediol and mastigophorenes A-D.[9]

Results and Discussion

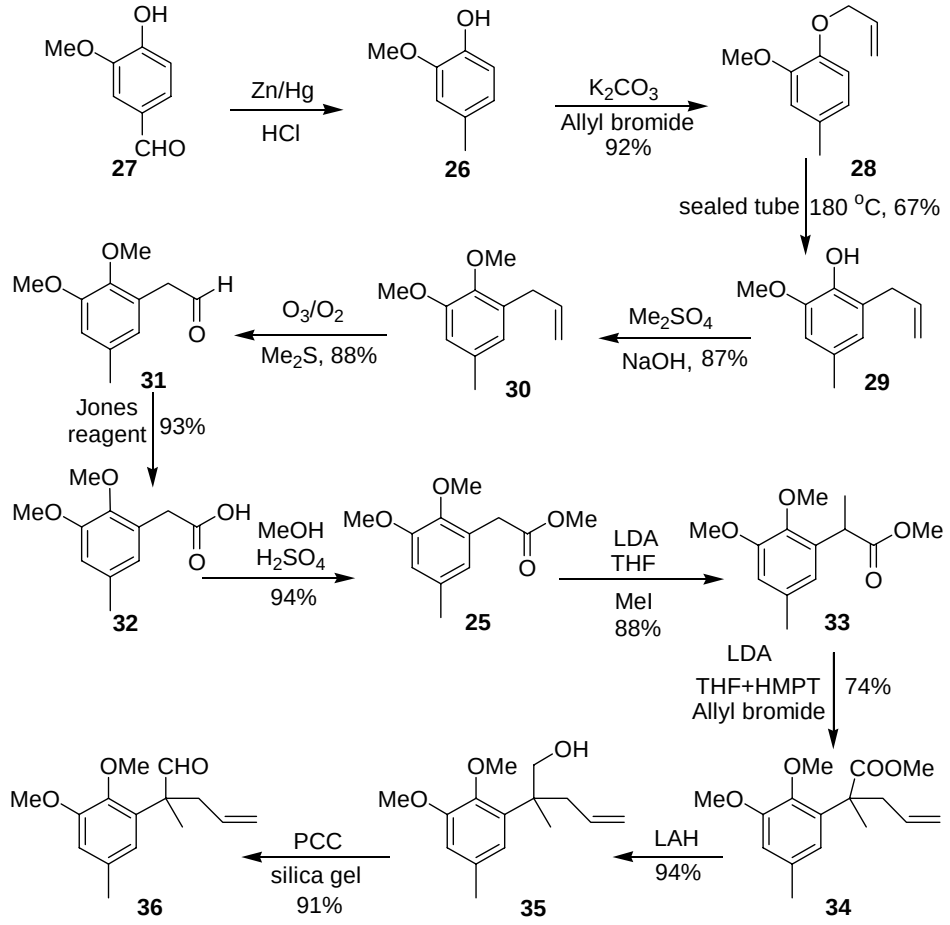
For the formal total synthesis of herbertenediol and mastigophorenes cyclopentanone **22** was chosen as the target molecule, since its conversion to herbertenediol **5** and mastigophorenes A-D **7-10** has already been reported in the literature.[7h,8a,d] An intramolecular aldol condensation based strategy was contemplated for the construction of the cyclopentanone **22** as depicted in the retrosynthetic scheme 1. Presence of two ortho oriented oxygen substituents prompted us to choose 2-methoxy-4-methylphenol **26**, which could be readily obtained from vanillin **27**, as the starting material. A Claisen rearrangement was considered as an ideal methodology for the introduction of a side chain at the C-6 position, which could be elaborated into cyclopentanone **22**.



Scheme 1

The synthetic sequence is depicted in schemes 2 and 3. To begin with, vanillin **27** was converted into the phenol **26** *via* Clemmensen's reduction.[10] Treatment of the phenol **26** with anhydrous potassium carbonate and allyl bromide in refluxing acetone generated the allyl aryl

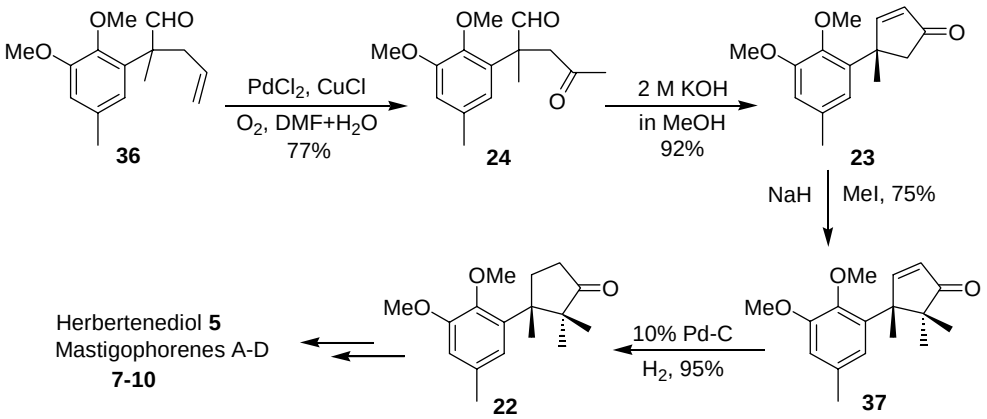
ether **28** in 92% yield, which on thermal activation at 180 °C furnished the *ortho* Claisen product **29** in 67% yield. The phenol **29** on etherification with dimethyl sulfate and 10% aqueous sodium hydroxide generated the dimethoxy compound **30** in 87% yield. Ozonolytic cleavage of the allyl group in the compound **30** in methanol and methylene chloride followed by reductive workup with dimethyl sulfide gave the aldehyde **31** in 88% yield. Oxidation of the aldehyde **31** with 2.5 M Jones reagent in acetone at 0 °C furnished the acid[8a] **32** in 93% yield, which on esterification with methanol in the presence of sulfuric acid generated the ester **25** in 94% yield.



Scheme 2

For creating the first quaternary center, sequential alkylation of the ester **25** was explored. Thus, generation of the lithium enolate of the ester **25** with lithium diisopropylamide (LDA) in THF at –70 °C followed by alkylation with methyl iodide furnished the ester **33** in 88% yield, whose structure rests secured from the spectral data. For the projected intramolecular aldol condensation for the generation of cyclopentenone **23**, an allyl group was chosen as the acetone equivalent. Generation of the lithium enolate of the ester **33** with LDA in THF and HMPA at –70 °C followed by alkylation with allyl bromide generated the ester **34** in 74% yield. To avoid

regiochemical problems at a later stage, the ester moiety in **34** was converted into an aldehyde. Consequently, reduction of the ester **34** using lithium aluminum hydride (LAH) in ether gave the primary alcohol **35** in 94% yield, which on oxidation with pyridinium chlorochromate (PCC) and silica gel in methylene chloride furnished the aldehyde **36** in 91% yield.



For the conversion of the terminal vinyl group in the pentenal **36** into an acetyl moiety, Wacker oxidation was chosen.[11] Thus, treatment of the pentenal **36** with 0.2 equivalent of palladium chloride and 3 equivalents of cupric chloride in *N*,*N*-dimethylformamide (DMF) and water in oxygen atmosphere (balloon), produced the keto-aldehyde **24** in 77% yield. Intramolecular aldol condensation of the ketoaldehyde **24** with 2 *M* methanolic potassium hydroxide in THF at room temperature generated the cyclopentenone **23** in 92% yield. Presence of the molecular ion peak at m/z 246 ($C_{15}H_{18}O_3$) in the mass spectrum and in the IR spectrum presence of an absorption band at 1715 cm^{-1} due to the cyclopentenone carbonyl group suggested the formation of the aldol product **23**. In the ^1H NMR spectrum, presence of two typical doublets at δ 7.80 and 6.15 due to the β and α protons, respectively, of a cyclopentenone, and an AB quartet at 2.66 and 2.55 ppm due to the methylene α to the ketone, established the structure of the cyclopentenone **23**. The ^{13}C NMR spectrum with characteristic resonances, a quaternary carbon at δ 208.8 due to the ketone, two methines at 170.7 and 130.7 due to the β and α olefinic carbons, respectively, of a cyclopentenone and a methylene at 51.0 ppm due to the C-5 carbon, in addition to other resonances confirmed the structure of the cyclopentenone **23**. Dialkylation of the cyclopentenone **23** using sodium hydride and methyl iodide in dry THF and DMF at room temperature, created the second quaternary centre and generated the enone **37** in 75% yield, whose structure was established from its spectral data, in particular the resonance at 0.65 ppm in the ^1H NMR spectrum due to the C-5 methyl group, which is *cis* to the aromatic ring and experiencing the shielding effect of the aromatic π-cloud. Finally, hydrogenation of the enone **37** using 10% palladium over carbon as the catalyst at one atmospheric pressure (balloon) of hydrogen in ethanol, furnished the cyclopentanone **22** in 95% yield, which exhibited ^1H and ^{13}C NMR spectra identical to those of the sample obtained by Mukherjee and coworkers.[7h] Since the cyclopentanone **22** has already been converted[7h,8a,d] into herbertenediol **5** and mastigophorenes A-D **7-10**, the present sequence constitutes a formal synthesis of these terpenoids.

Experimental Section

General Procedures. IR 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. 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 DEPT-135 spectra, and are given in parentheses. Low-resolution mass spectra were recorded using Jeol JMS-DX 303 and Shimadzu QP-5050A GCMS instruments using direct inlet mode. Relative intensities are given in parentheses. High resolution mass spectra were recorded on a Micromass Q-TOF micro mass spectrometer using electron spray ionization mode. Ozonolysis experiments were carried out using Fischer 502 ozone generator. The oxygen flow was adjusted and calibrated to generate one mmole of ozone per four minutes. Hydrogenation reactions at one atmospheric pressure were carried out using a balloon filled with hydrogen. Acme's silica gel (100-200 mesh) was used for column chromatography. All small-scale dry reactions were carried out using standard syringe-septum technique. Low temperature reactions were conducted in a bath made of alcohol and liquid nitrogen.

2-Methoxy-4-methylphenyl allyl ether (28). To a magnetically stirred solution of the phenol **26** (3.0 g, 21.7 mmol) in dry acetone (10 ml) was added allyl bromide (1.82 ml, 21.7 mmol) and anhydrous K_2CO_3 (3.0 g, 21.7 mmol) and the reaction mixture was refluxed for 8 h. It was then cooled, quenched with water (10 ml) and extracted with ether (3 x 5 ml). The combined ether extract was washed with 2 *N* 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 (1:10) as eluent furnished the allyl ether **28** (3.56 g, 92%) as oil.[12] IR (neat): ν_{max}/cm^{-1} 2932, 2862, 1646, 1590, 1512, 1462, 1416, 1264, 1230, 1150, 1141, 1033, 996, 926 ($CH=CH_2$), 845, 801. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.73 (1 H, d, J=8.1 Hz, H-5), 6.66 (1 H, s, H-3), 6.62 (1 H, d, J=8.1 Hz, H-6), 6.05 (1 H, t of dd, J=17.1, 10.2 and 5.4 Hz, H-2'), 5.37 (1 H, dd, J=17.1 and 1.8 Hz) and 5.24 (1 H, dd, J=10.2 and 1.8 Hz) [H-3'], 4.55 (2 H, d, J=5.4 Hz, H-1'), 3.84 (3 H, s, OCH_3), 2.29 (3 H, s, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 149.5 (C) and 146.0 (C) [C-1 and 2], 133.8 (CH, C-2'), 130.8 (C, C-4), 120.9 (CH, C-5), 117.6 (CH_2, C-3'), 114.1 (CH) and 113.0 (CH) [C-3 and 6], 70.1 (CH_2, C-1'), 55.8 (CH_3, OCH_3), 21.1 (CH_3, $ArCH_3$).

2,3-Dimethoxy-5-methyl-1-allylbenzene (30). A solution of the allyl ether **28** (1.0 g, 5.62 mmol) was placed in a Carius tube and heated to 180 °C for 15 h under nitrogen atmosphere. The reaction mixture was then cooled and purified on a silica gel column using ethyl acetate-hexane (1:10) as eluent to furnish the phenol **29** (670 mg, 67%) as oil.[12] IR (neat): ν_{max}/cm^{-1} 3536 (OH), 3075, 3005, 2914, 1638, 1608, 1361, 1294, 1234, 1212, 1150, 1076, 996, 943, 910 ($CH=CH_2$), 834, 790. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.50 (2 H, s, Ar-H), 5.95 (1 H, t of dd, J=17.1, 10.5 and 6.6 Hz, H-2'), 5.43 (1 H, s, OH), 5.06 (1 H, dd, J=17.1 and 1.8 Hz) and 5.02 (1 H, dd, J=10.5 and 1.8 Hz) [H-3'], 3.85 (3 H, s, OCH_3), 3.34 (2 H, d, J=6.6 Hz, H-1'),

2.25 (3 H, s, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 146.1 (C), 141.1 (C), 136.8 (CH, C-2'), 128.5 (C), 125.5 (C), 122.6 (CH, C-5), 115.4 (CH_2, C-3'), 109.5 (CH, C-3), 55.9 (CH_3, OCH_3), 33.9 (CH_2, C-1'), 21.1 (CH_3, $ArCH_3$). Mass: ($C_{11}H_{14}O_2$) m/z 178 (M^+, 57%), 177 (100), 163 (10), 145 (12), 135 (13), 115 (18), 105 (11), 91 (30). To a cold (10 °C) magnetically stirred solution of the phenol **29** (650 mg, 3.65 mmol) in 10% aqueous NaOH solution (5 ml) was added Me_2SO_4 (0.35 ml, 3.65 mmol) drop wise and the reaction mixture was refluxed for 1 h at 70 °C. It was then cooled and extracted with ether (3 x 3 ml). The ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the methyl ether **30** (610 mg, 87%) as oil. IR (neat): ν_{max}/cm^{-1} 3076, 2936, 2830, 1638, 1589, 1491, 1463, 1326, 1289, 1231, 1184, 1147, 1100, 1078, 1012, 911 ($CH=CH_2$), 834. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.54 (1 H, s) and 6.53 (1 H, s) [Ar-H], 5.90 (1 H, t of dd, J=16.9, 10.3 and 6.6 Hz, H-2'), 5.06 (1 H, dd, J=16.9 and 1.5 Hz) and 5.02 (1 H, dd, J=10.3 and 1.5 Hz) [H-3'], 3.82 (3 H, s) and 3.75 (3 H, s) [2 x OCH_3], 3.34 (2 H, d, J=6.6 Hz, H-1'), 2.27 (3 H, s, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.5 (C), 145.0 (C), 137.5 (CH, C-2'), 133.4 (C), 133.2 (C), 122.5 (CH, C-6), 115.5 (CH_2, C-3'), 111.5 (CH, C-4), 60.6 (CH_3) and 55.7 (CH_3) [2 x OCH_3], 34.1 (CH_2, C-1'), 21.4 (CH_3, $ArCH_3$). Mass: ($C_{12}H_{16}O_2$) m/z 192 (M^+, 18%), 191 (55), 175 (100), 135 (37), 115 (24), 105 (41), 91 (71).

Methyl 2-(2,3-dimethoxy-5-methylphenyl)acetate (25). A pre-cooled (–70 °C) mixture of ozone in oxygen was passed through a cold (–70 °C) solution of the ether **30** (500 mg, 2.60 mmol) and a catalytic amount of $NaHCO_3$ in methanol (1 ml) and CH_2Cl_2 (5 ml) for 12 min. The reaction mixture was flushed off with oxygen, and Me_2S (1.3 ml) was added to the reaction mixture. It was then slowly warmed up to RT and magnetically stirred for 8 h. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the aldehyde **31** (444 mg, 88%) as oil. IR (neat): ν_{max}/cm^{-1} 2939, 2832, 2724 (H-C=O), 1723 (C=O), 1590, 1494, 1463, 1330, 1287, 1233, 1148, 1093, 1007, 838. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.66 (1 H, t, J=2.1 Hz, CH_2CHO), 6.64 (1 H, s) and 6.52 (1 H, s) [Ar-H], 3.85 (3 H, s) and 3.76 (3 H, s) [2 x OCH_3], 3.59 (2 H, d, J=2.1 Hz, H-2), 2.29 (3 H, s, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 198.8 (CH, CHO), 152.5 (C), 145.4 (C), 133.7 (C), 125.9 (C), 123.2 (CH, C-6'), 113.0 (CH, C-4'), 60.4 (CH_3) and 55.6 (CH_3) [2 x OCH_3], 45.2 (CH_2, C-2), 21.2 (CH_3, $ArCH_3$). To a magnetically stirred solution of the aldehyde **31** (400 mg, 2.06 mmol) in acetone (4 ml) was added a freshly prepared solution of Jones reagent (2.5 *M* solution, 5.0 ml) at 0 °C. The reaction mixture was then stirred at RT for 2 h. Excess of the reagent was decomposed by adding a few drops of propan-2-ol and the reaction mixture was extracted with ether (3 x 4 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent furnished the acid[8a] **32** (403 mg, 93%). A solution of the acid **32** (400 mg, 1.90 mmol) in MeOH (5 ml) and a catalytic amount of conc. H_2SO_4 was refluxed for 6 h. The reaction mixture was then concentrated under *vacuo*. The residue was taken in ether (15 ml), 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 methyl ester **25** (400 mg, 94%) as oil. IR (neat): ν_{max}/cm^{-1} 2948, 2835, 1740 (OC=O), 1592, 1496, 1468, 1434, 1316, 1236, 1162, 1090, 1011, 837, 782, 657. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.61 (1 H, s) and 6.58 (1 H, s) [Ar-H], 3.83 (3 H, s) and 3.77 (3 H, s) [2 x $ArOCH_3$], 3.68 (3 H, s, $COOCH_3$), 3.58 (2 H, s, H-2), 2.28 (3 H, s, $ArCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 171.9 (C, OC=O), 152.4 (C), 145.3 (C), 133.3 (C), 127.8 (C), 123.0 (CH, C-6'), 112.7 (CH, C-4'), 60.4 (CH_3), 55.6 (CH_3), 51.8 (CH_3), 35.5 (CH_2, C-2), 21.3 (CH_3, $ArCH_3$). Mass: m/z 224 (M^+, 91%), 209 (33), 177 (16), 165 (39), 150 (100), 149 (45), 105 (57), 91 (50). HRMS: m/z Calcd. for $C_{12}H_{16}O_4Na$ (M+Na): 247.0946. Found: 247.0952.

Methyl 2-(2,3-dimethoxy-5-methylphenyl)propionate (33). To a cold (–70 °C), magnetically stirred solution of diisopropylamine (0.96 ml, 6.67 mmol) in anhydrous THF (3 ml) was slowly added a solution of ^{n}BuLi (1.6 *M* in hexane, 3.67 ml, 5.87 mmol) and stirred for 10 min. To LDA thus formed was added drop wise a solution of the ester **25** (600 mg, 2.67 mmol) in anhydrous THF (3 ml) and stirred for 40 min at the same temperature. The enolate was then treated with MeI (0.4 ml, 6.67 mmol) and stirred for 3 h at RT. The reaction mixture was then diluted with water and extracted with ether (3 x 4 ml). The combined 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 (1:10) as eluent furnished the ester **33** (560 mg, 88%) as oil. IR (neat): ν_{max}/cm^{-1} 2940, 2833, 1739 (OC=O), 1589, 1492, 1462, 1332, 1297, 1231, 1201, 1058, 1008, 951, 906, 838, 781, 629. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.57 (2 H, s, Ar-H), 4.00 (1 H, q, J=6.6 Hz, H-2), 3.80 (3 H, s) and 3.76 (3 H, s) [2 x $ArOCH_3$], 3.62 (3 H, s, $COOCH_3$), 2.26 (3 H, s, $ArCH_3$), 1.38 (3 H, d, J=6.6 Hz, H-3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 174.9 (C, OC=O), 152.2 (C), 144.2 (C), 134.3 (C), 133.5 (C), 120.0 (CH, C-6'), 112.1 (CH, C-4'), 60.5 (CH_3), 55.5 (CH_3) and 51.7 (CH_3) [3 x OCH_3], 38.6 (CH, C-2), 21.4 (CH_3, $ArCH_3$), 18.1 (CH_3, C-3). Mass: m/z 238 (M^+, 60%), 179 (77), 164 (100), 150 (47), 149 (28), 135 (13), 121 (31), 105 (12), 91 (26). HRMS: m/z Calcd. for $C_{13}H_{18}O_4Na$ (M+Na): 261.1103. Found: 261.1088.

Methyl 2-methyl-2-(2,3-dimethoxy-5-methylphenyl)pent-4-enoate (34). Allylation of the ester **33** (500 mg, 2.10 mmol), employing the same procedure as above, using LDA [prepared from diisopropylamine (0.9 ml, 6.3 mmol) and ^{n}BuLi (1.6 *M* in hexane, 3.6 ml, 5.88 mmol)] and allyl bromide (0.6 ml, 7.35 mmol) in THF (3 ml) and HMPA (2 ml), furnished the ester **34** (432 mg, 74%) as oil. IR (neat): ν_{max}/cm^{-1} 3073, 2978, 2943, 2834, 1735 (OC=O), 1640, 1587, 1480, 1463, 1450, 1323, 1279, 1234, 1144, 1066, 1008, 916 ($CH=CH_2$), 835, 781. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.62 (1 H, s) and 6.57 (1 H, s) [Ar-H], 5.48 (1 H, t of dd, J=17.4, 9.6 and 7.5 Hz, H-4), 5.00 (1 H, d, J=17.4 Hz) and 4.96 (1 H, d, J=9.6 Hz) [H-5], 3.82 (3 H, s) and 3.74 (3 H, s) [2 x $ArOCH_3$], 3.65 (3 H, s, $COOCH_3$), 2.75-2.55 (2 H, m, H-3), 2.31 (3 H, s, $ArCH_3$), 1.42 (3 H, s, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 176.4 (C, OC=O), 151.9 (C), 144.3 (C), 136.8 (C), 134.2 (CH, C-4), 131.9 (C), 118.9 (CH, C-6'), 117.8 (CH_2, C-5), 112.4 (CH, C-4'), 59.7 (CH_3), 55.5 (CH_3), 51.4 (CH_3), 47.4 (C, C-2), 42.3 (CH_2, C-3), 23.4 (CH_3, *tert*-CH_3), 21.6 (CH_3, $ArCH_3$). Mass: m/z 278 (M^+, 31%), 219 (64), 205 (66), 193 (26), 179 (35), 178 (35), 177 (100), 149 (36), 117 (29), 91 (60). HRMS: m/z Calcd. for $C_{16}H_{22}O_4Na$ (M+Na): 301.1416.

Found: 301.1404.

2-(2,3-Dimethoxy-5-methylphenyl)-2-methylpent-4-enal (36). To a cold (–20 ^{o}C) magnetically stirred solution of the ester **34** (250 mg, 0.90 mmol) in dry ether (4 ml) was added LAH (17 mg, 0.45 mmol) in one portion. The reaction mixture was stirred at the same temperature for 2 h and allowed to warm to 0 ^{o}C over a period of 30 min. Ethyl acetate (2 ml) was carefully introduced to consume the excess reagent and the reaction was quenched with ice-cold water (5 ml). The solution was filtered through a sintered funnel and the residue thoroughly washed with ether (3 x 5 ml). The ether layer was separated, 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 primary alcohol **35** (210 mg, 94%) as oil. IR (neat): ν_{max}/cm^{-1} 3431 (OH), 3072, 2950, 2936, 2832, 1638, 1581, 1464, 1417, 1321, 1279, 1232, 1187, 1145, 1062, 1036, 1007, 912 (CH=CH_2), 835, 779. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.59 (2 H, s, Ar-H), 5.52 (1 H, t of dd, J=16.5, 10.8 and 6.6 Hz, H-4), 4.97 (1 H, d, J=16.5 Hz) and 4.91 (1 H, d, J=10.8 Hz) [H-5], 3.92 and 3.58 (2 H, 2 x d, J=10.8 Hz, H-1), 3.82 (6 H, s, 2 x OCH_3), 2.70 (1 H, dd, J=13.5 and 6.6 Hz), 2.33 (1 H, dd, J=13.5 and 7.8 Hz), 2.27 (3 H, s, $ArCH_3$), 1.87 (1 H, br s, OH), 1.31 (3 H, s, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.7 (C), 145.8 (C), 136.4 (C), 135.3 (CH, C-4), 132.5 (C), 121.7 (CH, C-6'), 116.9 (CH_2, C-5), 112.1 (CH, C-4'), 70.3 (CH_2, CH_2OH), 60.3 (CH_3) and 55.5 (CH_3) [2 x OCH_3], 44.0 (C, C-2), 42.0 (CH_2, C-3), 23.7 (CH_3, *tert*-CH_3), 21.6 (CH_3, $ArCH_3$). To a magnetically stirred suspension of PCC (344 mg, 1.6 mmol) and silica gel (344 mg) in dry CH_2Cl_2 (4 ml) was added a solution of the alcohol **35** (200 mg, 0.80 mmol) in CH_2Cl_2 (2 ml) and stirred vigorously for 1 h at RT. The reaction mixture was then filtered through a small silica gel column, and the column eluted with more CH_2Cl_2. Evaporation of the solvent furnished the aldehyde **36** (180 mg, 91%) as oil. IR (neat): ν_{max}/cm^{-1} 3074, 2938, 2707 (H-C=O), 1725 (C=O), 1586, 1482, 1464, 1322, 1236, 1145, 1055, 1004, 915 (CH=CH_2), 836. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.55 (1 H, s, CHO), 6.64 (1 H, s) and 6.57 (1 H, s) [Ar-H], 5.52 (1 H, t of dd, J=16.5, 11.1 and 7.5 Hz, H-4), 4.99 (1 H, d, J=16.5 Hz) and 4.97 (1 H, d, J=11.1 Hz) [H-5], 3.84 (3 H, s) and 3.72 (3 H, s) [2 x OCH_3], 2.58 (2 H, d, J=7.5 Hz, H-3), 2.32 (3 H, s, $ArCH_3$), 1.28 (3 H, s, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 201.9 (CH, CHO), 152.3 (C), 144.3 (C), 135.2 (C), 133.8 (CH, C-4), 133.0 (C), 120.0 (CH, C-6'), 118.2 (CH_2, C-5), 112.8 (CH, C-4'), 60.3 (CH_3) and 55.6 (CH_3) [2 x OCH_3], 51.4 (C, C-2), 40.4 (CH_2, C-3), 21.7 (CH_3), 20.5 (CH_3).

2-(2,3-Dimethoxy-5-methylphenyl)-2-methyl-4-oxovaleraldehyde (24). A suspension of palladium chloride (23 mg, 0.13 mmol) and cuprous chloride (257 mg, 1.92 mmol) in DMF (2 ml) and water (1 ml) was magnetically stirred in an oxygen atmosphere, created via evacuative displacement of air using an oxygen balloon, for 1 h at RT. A solution of the enal **36** (160 mg, 0.64 mmol) in DMF (2 ml) was added to the reaction mixture and stirred for 16 h at RT in the oxygen atmosphere. Then 3 *N* aq. HCl (5 ml) was added to the reaction mixture and extracted with ether (3 x 4 ml). The combined ether extract was washed with saturated aq. $NaHCO_3$ 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 (1:10) as eluent furnished the

ketoaldehyde **24** (131 mg, 77%) as oil. IR (neat): ν_{max}/cm^{-1} 2960, 2939, 2835, 2721 (H-C=O), 1716 (C=O), 1587, 1483, 1464, 1425, 1360, 1320, 1280, 1236, 1186, 1151, 1061, 1002, 960, 836, 775. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.60 (1 H, s, CHO), 6.65 (1 H, s) and 6.60 (1 H, s) [Ar-H], 3.83 (3 H, s) and 3.75 (3 H, s) [2 x OCH_3], 3.03 and 3.00 (2 H, AB q, J=16.5 Hz, H-3), 2.32 (3 H, s, $ArCH_3$), 1.98 (3 H, s, $COCH_3$), 1.48 (3 H, s, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 206.2 (C, C=O), 201.9 (CH, CHO), 152.1 (C), 143.8 (C), 135.1 (C), 133.1 (C), 119.7 (CH, C-6'), 112.9 (CH, C-4'), 60.2 (CH_3) and 55.6 (CH_3) [2 x OCH_3], 50.1 (C, C-2), 49.6 (CH_2, C-3), 31.0 (CH_3, C-5), 21.5 (CH_3), 20.7 (CH_3, *tert*-CH_3).

4-Methyl-4-(2,3-dimethoxy-5-methylphenyl)cyclopent-2-enone (23). To a magnetically stirred solution of the ketoaldehyde **24** (100 mg, 0.38 mmol) in THF (4 ml) was added 2 *M* KOH in MeOH (0.2 ml, 0.38 mmol) and the reaction mixture was stirred for 5 h. Solvent was evaporated under reduced pressure. It was then taken in ether (10 ml) and 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 cyclopentenone **23** (86 mg, 92%) as oil. IR (neat): ν_{max}/cm^{-1} 2934, 1715 (C=O), 1584, 1483, 1464, 1419, 1320, 1237, 1151, 1055, 1007, 835, 803, 777. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.80 (1 H, d, J=6.0 Hz, H-3), 6.62 (1 H, s) and 6.53 (1 H, s) [Ar-H], 6.15 (1 H, d, J=6.0 Hz, H-2), 3.83 (3 H, s) and 3.76 (3 H, s) [2 x OCH_3], 2.66 and 2.55 (2 H, AB q, J=18.3 Hz, H-5), 2.28 (3 H, s, $ArCH_3$), 1.56 (3 H, s, *tert*-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 208.8 (C, C=O), 170.7 (CH, C-3), 153.0 (C), 145.3 (C), 138.1 (C), 132.6 (C), 130.7 (CH, C-2), 119.2 (CH, C-6'), 112.6 (CH, C-4'), 60.3 (CH_3) and 55.7 (CH_3) [2 x OCH_3], 51.0 (CH_2, C-5), 47.3 (C, C-4), 28.4 (CH_3, *tert*-CH_3), 21.5 (CH_3, $ArCH_3$). Mass: m/z 246 (M^+, 100%), 231 (38), 216 (29), 203 (26), 200 (20), 187 (32), 172 (20), 128 (19), 115 (32), 91 (29). HRMS: m/z Calcd. for $C_{15}H_{18}O_3Na$ (M+Na): 269.1154. Found: 269.1155.

4-(2,3-Dimethoxy-5-methylphenyl)-4,5,5-trimethylcyclopent-2-enone (37). To a magnetically stirred suspension of NaH (22 mg, 60% dispersion in oil, 0.54 mmol, washed with dry hexanes) in THF (1 ml) was added a solution of the ketone **23** (22 mg, 0.09 mmol) in THF (2 ml) and DMF (2 ml), and stirred for 40 min at RT. To the reaction mixture was added methyl iodide (0.03 ml, 0.54 mmol) and stirred for 12 h at RT. It was then quenched with water (3 ml) and extracted with ether (3 x 3 ml). The combined ether extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the enone **37** (18 mg, 75%) as oil. IR (neat): ν_{max}/cm^{-1} 2969, 2936, 2871, 1707 (C=O), 1586, 1475, 1463, 1419, 1319, 1236, 1148, 1056, 1006, 835. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.89 (1 H, d, J=5.4 Hz, H-3), 6.61 (1 H, s) and 6.45 (1 H, s) [Ar-H], 6.04 (1 H, d, J=5.4 Hz, H-2), 3.84 (3 H, s) and 3.80 (3 H, s) [2 x OCH_3], 2.29 (3 H, s, $ArCH_3$), 1.47 (3 H, s), 1.23 (3 H, s) and 0.65 (3 H, s) [3 x *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 213.6 (C=O), 170.4 (C-3), 152.9 (2 C), 145.7, 136.3, 132.4, 120.9, 112.4, 60.3, 55.7, 54.7, 50.9, 26.2, 21.6, 20.0 (2 C). Mass: m/z 274 (M^+, 42%), 259 (100), 229 (12), 216 (7), 200 (8), 115 (13), 91 (14). HRMS: m/z Calcd. for $C_{17}H_{22}O_3Na$ (M+Na): 297.1467. Found: 297.1471.

3-(2,3-Dimethoxy-5-methylphenyl)-2,2,3-trimethylcyclopentanone (22). To activated 10%

Pd-C (5 mg) was added a solution of the enone **37** (18 mg, 0.06 mmol) in ethanol (2 ml). The reaction mixture was stirred for 1 h at RT in an atmosphere of hydrogen, created by evacuative replacement of air (balloon) and then the catalyst was filtered off. Evaporation of the solvent furnished the saturated ketone **22** (17 mg, 95%) as oil. IR (neat): ν_{max}/cm^{-1} 2965, 2832, 1736 (C=O), 1583, 1463, 1415, 1376, 1322, 1270, 1233, 1187, 1147, 1085, 1057, 1006, 961, 835, 781, 749. ^{1}H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.69 (1 H, s) and 6.59 (1 H, s) [Ar-H], 3.81 (3 H, s) and 3.76 (3 H, s) [2 x OCH_3], 2.65 (1 H, q, J=11.1 Hz), 2.50-2.30 (2 H, m), 2.28 (3 H, s, Ar-CH_3), 2.06 (1 H, ddd, J=12.6, 7.5 and 3.3 Hz), 1.30 (3 H, s), 1.22 (3 H, s) and 0.70 (3 H, s) [3 x *tert*-CH_3]. ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 221.9 (C, C=O), 153.0 (C), 146.5 (C), 138.2 (C), 132.0 (C), 120.7 (CH), 111.9 (CH), 60.1 (CH_3), 55.6 (CH_3), 53.5 (C), 49.6 (C), 34.0 (CH_2), 31.9 (CH_2), 24.5 (CH_3), 22.3 (CH_3), 21.7 (CH_3), 20.3 (CH_3). Mass: m/z 276 (M^+, 100%), 261 (14), 243 (14), 227 (28), 206 (28), 205 (96), 191 (23), 177 (44), 175 (40), 174 (46), 173 (43), 159 (19), 131 (22), 115 (27), 105 (22), 91 (59). HRMS: m/z Calcd. for $C_{17}H_{24}O_3Na$ (M+Na): 299.1623. Found: 299.1623.

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