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Formal total synthesis of (±)-herbertenediol and (±)-mastigophorenes A and B

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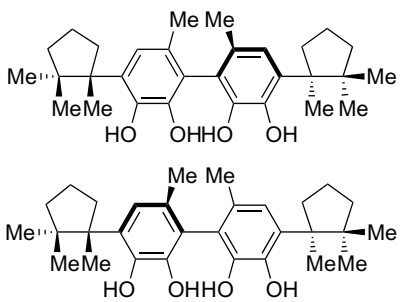
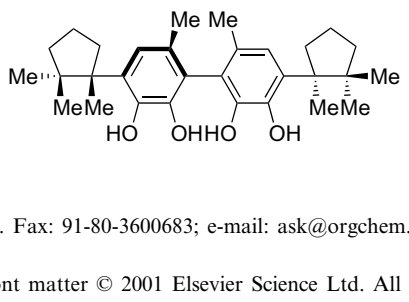
Abstract—A simple and straightforward formal total synthesis of the sesquiterpene herbertenediol and its dimers mastigophorenes A and B, starting from vanillin, is described.

The dimeric sesquiterpene phenols mastigophorenes A and B **1** and **2**, isolated[1] along with their isomers mastigophorenes B and C from the liverwort *Mastigophora diclados*, were shown to stimulate nerve growth. On the other hand, the logical monomeric precursor of mastigophorenes, herbertenediol **3**, isolated[2] along with other herbertenes from the liverwort *Herberta adunca*, was recently found to exhibit a potent anti-lipid peroxidation activity.[3] The interesting structure and associated biological activities make mastigophorenes and herbertenediol intriguing synthetic targets of current interest. The first synthesis of herbertenediol **3** was accomplished[2b,3] via hydroxylation of the sesquiterpene α-herbertenol **4**, whereas recently Mukherjee and co-workers reported[4] the synthesis of (±)-herbertenediol **3** from a tetralone derivative. The first synthesis of mastigophorenes A and B **1** and **2** was achieved[5] in 1999 via the phenolic coupling of natural herbertenediol **3**. Almost at the same time,[6] Meyers and Degnan reported an enantioselective synthesis of herbertenediol (−)-**3** and its conversion to mastigophorenes A and B (−)-**1** and (−)-**2**. In continuation of our interest in the synthesis of natural products containing multiple contiguous quaternary carbon atoms,[7] we herein describe a simple and straightforward formal total synthesis of racemic herbertenediol and mastigophorenes A and B starting from vanillin.

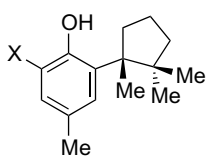
The differential nature of the two *ortho* substituted oxygen functionalities in vanillin **5** was exploited for the introduction of a side chain at the C-5 position via a Claisen rearrangement. The synthetic sequence starting from the phenol **6**, obtained by Clemmensen's reduction of vanillin **5**, is depicted in Scheme 1. Thus, allylation of the hydroxy group in **6** generated the allyl ether **7**. Thermal activation of the allyl ether **7** at 180°C furnished the *ortho* Claisen product **8**, which on etherification with dimethyl sulfate and sodium hydroxide generated the dimethoxy compound **9**. Ozonolytic cleavage of the allyl group in **9**, followed by further oxidation of the resultant aldehyde **10** and esterification furnished the ester **11** in 94% overall yield. Alkylation of the ester **11** with LDA and methyl iodide generated the ester **12**, which on further alkylation with LDA,



Mastigophorene A **1**



Mastigophorene B **2**



X = OH Herbertenediol **3**
X = H α-Herbertenol **4**

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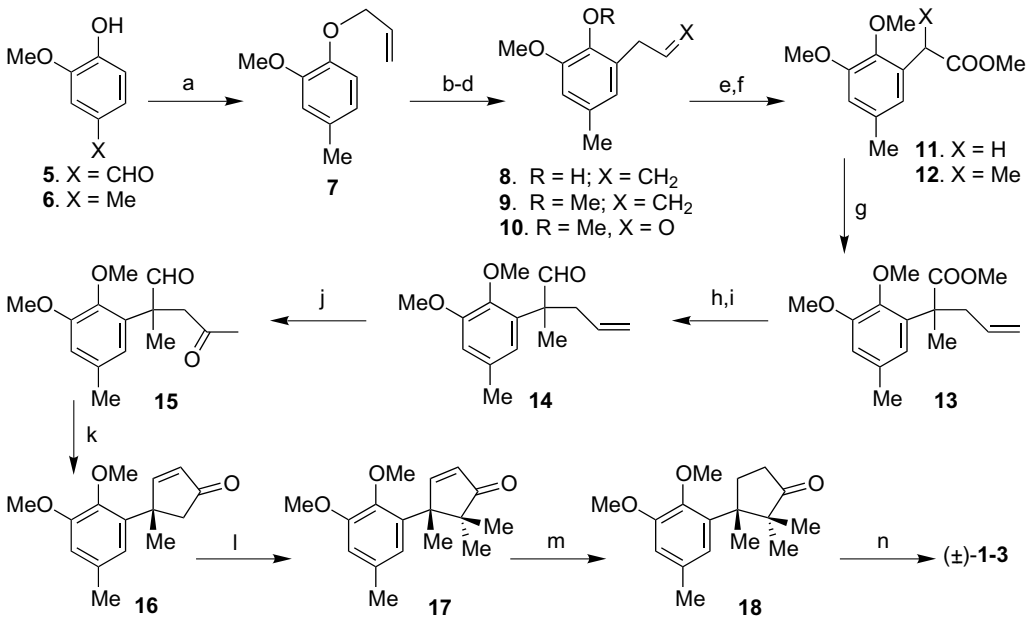

Scheme 1. *Reagents, conditions and yields*: (a) K_2CO_3, $Me_2C{=}O$, $CH_2{=}CHCH_2Br$, reflux, 8 h, 92%; (b) sealed tube, 180°C, 15 h, 67%; (c) 10% aq. NaOH, Me_2SO_4, 87%; (d) O_3/O_2, CH_2Cl_2–MeOH, −70°C; Me_2S, rt, 3 h; (e) 2.5 M Jones reagent, $Me_2C{=}O$, 0°C→rt, 1 h; MeOH, H_2SO_4, 6 h; 94% from **9**; (f) LDA, THF, MeI, −70°C→rt, 4 h, 88%; (g) LDA, THF, HMPA, $CH_2{=}CHCH_2Br$, −70°C→rt, 4 h, 74%; (h) $LiAlH_4$, Et_2O, 1.5 h; (i) PCC, CH_2Cl_2, rt, 2 h; 87% from **13**; (j) $PdCl_2$, CuCl, DMF, H_2O, O_2, rt, 16 h, 77%; (k) 2 M KOH in MeOH, THF, rt, 5 h, 92%; (l) NaH (excess), THF, DMF, MeI, rt, 8 h, 76%; (m) 10% Pd-C, H_2, EtOH, rt, 1 atm., 1 h, 95%; (n) Refs. 4 and 6.

HMPT and allyl bromide furnished the key intermediate pentenoate **13**.† A two-step conversion of the ester group into an aldehyde transformed the ester **13** into the aldehyde **14**. Oxidation of the terminal olefin in the pentenal **14** under Wacker conditions[8] ($PdCl_2$, CuCl, DMF, H_2O, O_2) followed by intramolecular aldol condensation of the resultant keto-aldehyde **15** furnished the cyclopentenone **16**† in 71% overall yield. Dimethylation using sodium hydride and methyl iodide followed by catalytic hydrogenation of the resultant enone **17** transformed the cyclopentenone **16** into cyclopentanone **18** in 72% yield, which exhibited spectral data identical to those of an authentic sample.[4] Since the cyclopentanone **18** has already been transformed[4] into herbertenediol **3**, which is converted[6] into mastigophorenes A and B **1** and **2**, the present sequence constitutes a formal total synthesis of these natural products.

† All compounds exhibited spectral data consistent with their structures. Yields (unoptimised) refer to isolated and chromatographically pure compounds. Selected spectral data for the pentenoate **13**: IR (neat): ν_{max}/cm^{-1} 1735, 1640, 1587, 917. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.59 (1H, s), 6.54 (1H, s), 5.60–5.35 (1H, m), 4.97 (1H, d, *J* 18 Hz), 4.95 (1H, d, *J* 7.5 Hz), 3.80 (3H, s), 3.71 (3H, s), 3.61 (3H, s), 2.30–2.00 (2H, m), 2.29 (3H, s), 1.39 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 176.4, 152.0, 144.3, 136.9, 134.3, 131.9, 118.9, 117.8, 112.4, 59.8, 55.5, 51.4, 47.2, 42.3, 23.4, 21.6. For the cyclopentenone **16**: IR (neat): ν_{max}/cm^{-1} 1714. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.79 (1H, d, *J* 6 Hz), 6.59 (1H, s), 6.50 (1H, s), 6.09 (1H, d, *J* 6 Hz), 3.80 (3H, s), 3.73 (3H, s), 2.66 and 2.53 (2H, 2×d, *J* 18.3 Hz), 2.55 (3H, s), 1.53 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 209.8 (C), 170.7 (CH), 152.4 (C), 145.2 (C), 138.0 (C), 132.6 (C), 130.6 (CH), 119.1 (CH), 112.5 (CH), 60.3 (CH_3), 55.6 (CH_3), 50.9 (CH_2), 47.2 (C), 28.3 (CH_3), 21.5 (CH_3).

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