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Total synthesis of (±)-1,13-herbertenediol, (±)-α-herbertenol and (±)-β-herbertenol

A. Srikrishna* and G. Satyanarayana

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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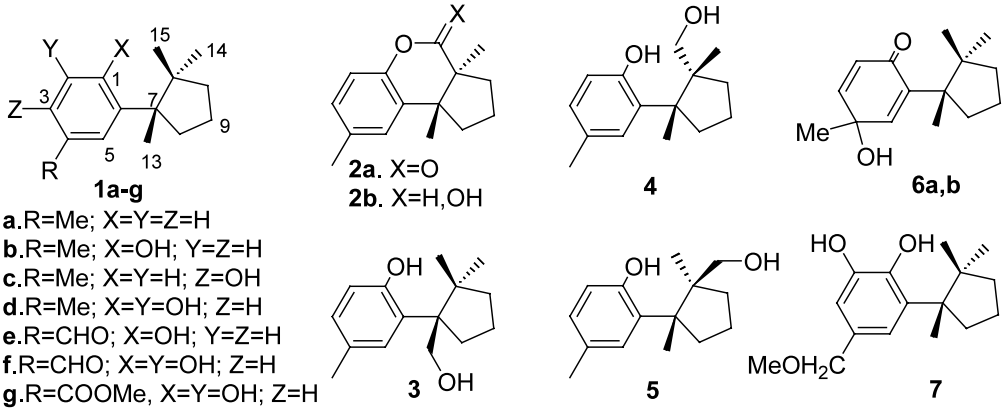
Abstract—Total synthesis of α-herbertenol, β-herbertenol and 1,13-herbertenediol, employing a Claisen rearrangement and ring-closing metathesis as key reactions for the generation of the cyclopentane containing vicinal quaternary carbons, has been described.

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 herbertene **1a**, α-herbertenol **1b**, β-herbertenol **1c**, herbertenediol **1d**, herbertenal **1e** and herbertenolide **2a** from *Herberta 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 *Herbertus aduncus*. Recently,[1a] Asakawa and co-workers reported the isolation 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, from the Japanese liverwort *Herberta sakuraii*. The phenolic herbertanes, e.g. **1b**–**d** and the dimers mastigophorenes have been shown to possess interesting biological properties such as growth inhibiting activity, antifungal, antilipid peroxidation and neurotropic activities.[1,2] 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.

Until recently, unlike the parent hydrocarbon, the phenolic herbertanes have received very little attention from synthetic chemists despite their interesting biological properties.[3,4] Since its isolation, there is only one report on the synthesis of 1,13-herbertenediol **3** by Fukuyama et al., via an intramolecular Heck reaction.[4] Recently,[3h] we have reported the synthesis of 1,14-herbertenediol **4**. Now we have developed a new strategy for the total synthesis of 1,13-herbertenediol **3**, α-herbertenol **1b** and β-herbertenol **1c** employing a Claisen



* Corresponding author. Fax: 91-80-3600683; 3600529; e-mail: ask@orgchem.iisc.ernet.in

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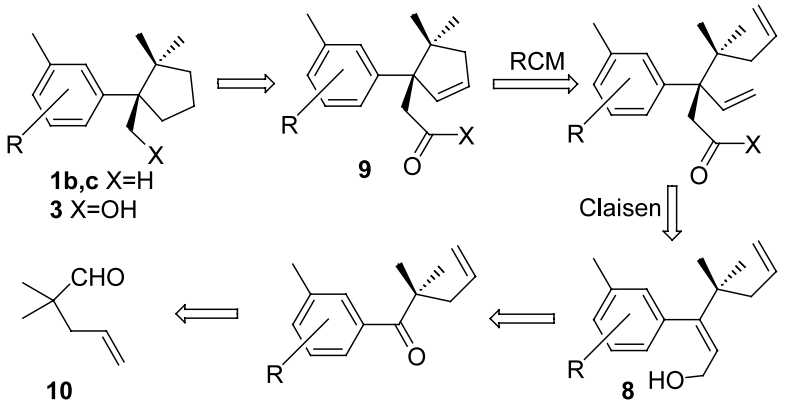
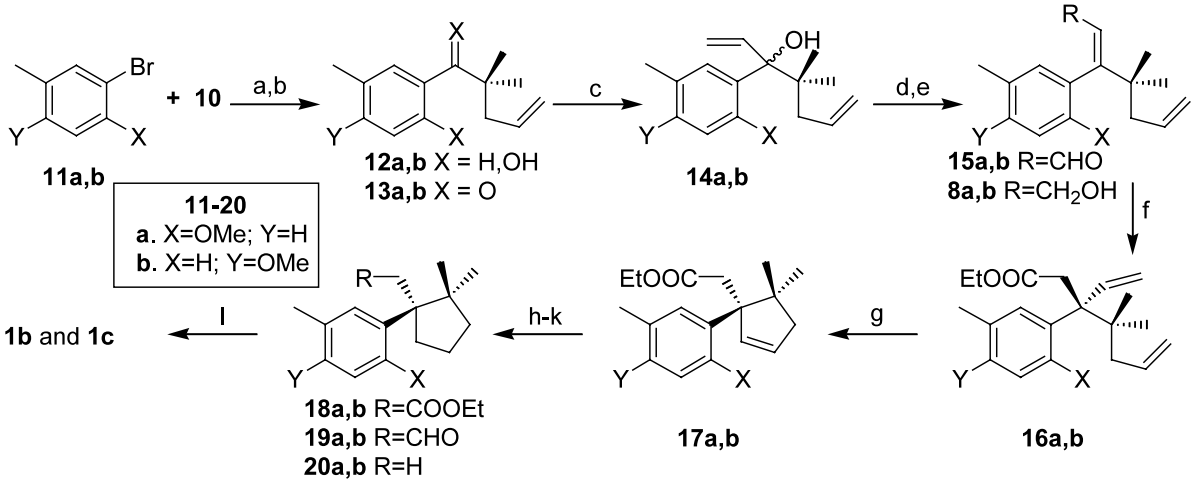
rearrangement and ring closing metathesis (RCM) as key reactions.

It was envisioned (Scheme 1) that Claisen rearrangement of the allyl alcohol **8** followed by a ring-closing metathesis (RCM) reaction would generate the cyclopentene **9** containing two quaternary carbon atoms, which could be transformed into herbertanes.[5] Coupling of a suitably substituted aromatic bromide with 2,2-dimethylpent-4-enal **10** could be adopted for the generation of the allyl alcohol **8**.

The synthetic sequence starting from 2-bromo-4-methylanisole **11a** and 4-bromo-2-methylanisole **11b** is depicted in Scheme 2. Thus, a sonically accelerated Barbier reaction of the bromides **11a**,**b** and 2,2-dimethylpent-4-enal[6] **10** in the presence of lithium furnished the benzyl alcohols **12a**,**b**, which on oxidation with pyridinium chlorochromate (PCC) and silica gel in methylene chloride furnished the ketones **13a**,**b**. Since the conventional Wittig as well as Horner–Wadsworth–Emmons reactions failed due to steric crowding, a vinylation and transposition was adopted for the conversion of the ketones **13a**,**b** into the allyl alcohols **8a**,**b**. Consequently, reaction of the ketones **13a**,**b** with vinylmagnesium bromide furnished the allylic alcohols **14a**,**b**. Oxidative transposition (PCC-silica gel) of the allyl alcohols **14a**,**b** followed by regioselective reduction of the resultant aldehydes **15a**,**b** with sodium borohydride in methanol generated the alcohols **8a**,**b**. An *ortho* ester variant of the Claisen rearrangement[7] with triethyl orthoacetate and a catalytic amount of propionic acid



Scheme 1.



Scheme 2. *Reagents*, *conditions and yields*: (a) Li, THF,))), 45 min, 72 and 79%; (b) PCC, silica gel, CH_2Cl_2, 2 h, 91 and 89%; (c) CH_2=CHMgBr, THF, 4 h, 78 and 80%; (d) PCC, silica gel, CH_2Cl_2, 24 h, 84 and 76%; (e) $NaBH_4$, MeOH, 0–5°C, 89 and 81%; (f) $MeC(OEt)_3$, EtCOOH, sealed tube, 180°C, 36 and 48 h, 30 and 45%; (g) $PhCH{=}RuCl_2(PCy_3)_2$ (5 mol%), CH_2Cl_2, rt, 6 and 10 h, 88 and 94%; (h) H_2, 10%Pd/C, EtOH, 6 h, 99 and 99%; (i) LAH, Et_2O, 0–5°C, 1 h, 94 and 96%; (j) PCC, silica gel, CH_2Cl_2, 0.5 h, 86 and 84%; (k) $(Ph_3P)_3RhCl$, C_6H_6, sealed tube, 120°C, 24 h, 80 and 66%; (l) BBr_3, CH_2Cl_2, −40°C to rt, 1.5 h, 95 and 89%.

in a sealed tube transformed the allyl alcohols **8a**,**b** into the esters **16a**,**b**, thus creating the vicinal quaternary carbon atoms. RCM reactions[8] of the dienes **16a**,**b** with 5 mol% of Grubbs' catalyst [$PhCH{=}RuCl_2(PCy_3)_2$] in methylene chloride generated the cyclopentenes† **17a**,**b** in a very efficient manner, which on hydrogenation with 10% palladium over carbon as the catalyst furnished the homoherbertane esters **18a**,**b**. A reduction–oxidation protocol transformed the esters **18a**,**b** into the aldehydes† **19a**,**b**. Wilkinson's catalyst mediated decarbonylation of the aldehydes **19a**,**b** followed by demethylation of the resultant ethers **20a**,**b** with boron tribromide furnished α-herbertenol **1b** and β-herbertenol **1c**, mp 81°C (lit.[1b] 80–81°C), respectively, which exhibited ^1H and ^{13}C NMR spectral data identical to those reported in the literature.[1b,3]

For the synthesis of 1,13-herbertenediol **3**, degradation of the homoherbertene ester **18a** was explored (Scheme 3). Thus, reaction of the ester **18a** with an excess of phenyllithium followed by dehydration of the resultant tertiary alcohol with phosphorus oxychloride furnished the olefin **21**. However, attempted ozonolysis of **21** failed to generate the requisite aldehyde **22**, as the electron rich aromatic ring in **21** is preferentially cleaved prior to the olefin under the conditions employed. On the other hand, reaction of the ester **18a** with an excess of methylmagnesium iodide followed by dehydration of the resultant tertiary alcohol **23** with phosphorus oxychloride furnished a regioisomeric mixture of the olefin **24**. Ozonolysis of the olefinic mixture **24** and reductive work-up furnished a 5:4 mixture of the aldehyde† **22** and the ketone **25**, which were separated by silica gel column chromatography. Grignard reaction transformed the ketone **25** back into the alcohol **23**. Oxidation[9] of the aldehyde **22** with sodium chlorite[10] followed by esterification with diazomethane furnished the ester **26**. Boron tribromide mediated demethylation transformed the ester **26** into the lactone[4†] **27**. Finally, reduction of the lactone **27** with lithium aluminium hydride furnished 1,13-herbertenediol **3**, which exhibited ^1H and ^{13}C NMR spectral data identical to that of the natural compound.[1a]

In conclusion, we have developed a methodology for the synthesis of α- and β-herbertenols **1b**,**c** and 1,13-herbertenediol **3**. Conversion of α-herbertenol **1b** into herbertenediol **1d** and the dimeric herbertanes mastigophorenes has already been established.[2,3] Currently, we are investigating the extension of this methodology for other oxidised herbertenes such as **1e**–**g** and **7**.

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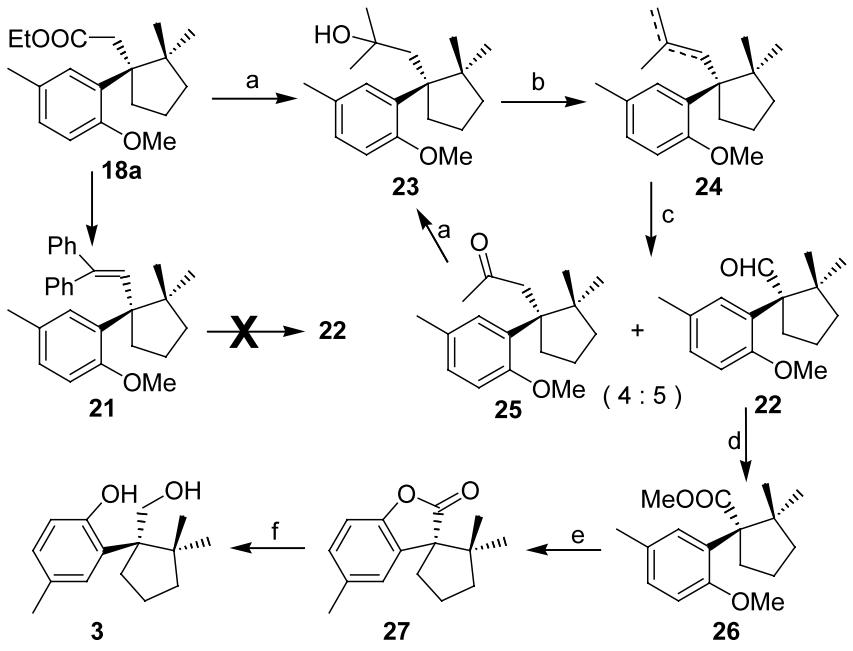
We thank Professor Y. Asakawa for providing a copy of the ^1H NMR spectrum of the diol **3**, and the C.S.I.R., New Delhi for the award of a research fellowship to G.S.

† All the compounds exhibited spectral data consistent with their structures. Yields (unoptimised) refer to isolated and chromatographically pure compounds. Spectral data for the cyclopentene ester **17a**: IR (neat): ν_{max}/cm^{-1} 1732. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.97 (1H, s), 6.89 (1H, d, J 8.4 Hz), 6.66 (1H, d, J 8.4 Hz), 6.17 (1H, d, J 6 Hz), 5.76 (1H, d, J 6 Hz), 3.83 (2H, q, J 6.9 Hz), 3.77 (3H, s), 3.70 and 2.31 (2H, 2×d, J 14.4 Hz), 2.35 and 2.15 (2H, 2×d, J 15.6 Hz), 2.24 (3H, s), 1.26 (3H, s), 0.96 (3H, t, J 6.9 Hz), 0.54 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 172.2 (C), 156.3 (C), 139.3 (CH), 130.6 (C), 130.4 (CH), 128.7 (C), 127.7 (2 C, CH), 110.8 (CH), 59.2 (CH_2), 59.0 (C), 54.8 (CH_3), 49.0 (CH_2), 45.3 (C), 40.5 (CH_2), 28.8 (CH_3), 25.3 (CH_3), 20.9 (CH_3), 14.2 (CH_3). For the cyclopentene ester **17b**: IR (neat): ν_{max}/cm^{-1} 1738. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.97 (1H, d, J 7.8 Hz), 6.95 (1H, s), 6.64 (1H, d, J 8.4 Hz), 6.26 (1H, d, J 5.4 Hz), 5.83 (1H, d, J 5.4 Hz), 3.87 (2H, q, J 6.9 Hz), 3.78 (3H, s), 3.00 and 2.44 (2H, 2×d, J 14.7 Hz), 2.29 and 2.13 (2H, 2×d, J 16.8 Hz), 2.17 (3H, s), 1.13 (3H, s), 1.02 (3H, t, J 6.9 Hz), 0.44 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 171.2 (C), 156.1 (C), 138.8 (CH), 133.9 (C), 129.1 (2 C, C), 125.4 (C), 124.8 (CH), 109.0 (CH), 59.5 (CH_2), 57.6 (C), 54.9 (CH_3), 47.3 (CH_2), 45.8 (C), 41.3 (CH_2), 28.0 (CH_3), 23.7 (CH_3), 16.8 (CH_3), 14.3 (CH_3). For the aldehyde **19a**: IR (neat): ν_{max}/cm^{-1} 2732, 1717. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.26 (1H, brs), 7.02 (1H, s), 6.96 (1H, d, J 8.4 Hz), 6.70 (1H, d, J 8.4 Hz), 3.72 (3H, s), 3.68 (1H, dd, J 15.0 and 2.7 Hz), 2.65–2.50 (1H, m), 2.28 (3H, s), 2.21 (1H, dd, J 15.0 and 2.1 Hz), 1.95–1.70 (3H, m), 1.60–1.49 (2H, m), 1.09 (3H, s), 0.67 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 204.0 (CH), 156.0 (C), 130.8 (C), 130.3 (CH), 129.2 (C), 128.3 (CH), 111.2 (CH), 54.7 (CH_3), 52.5 (C), 48.0 (CH_2), 45.7 (C), 40.7 (CH_2), 37.6 (CH_2), 26.3 (CH_3), 25.8 (CH_3), 21.1 (CH_3), 20.9 (CH_2). For the aldehyde **19b**: IR (neat): ν_{max}/cm^{-1} 2733, 1716. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.21 (1H, brs), 7.03 (1H, s), 7.03 (1H, d, J 9.3 Hz), 6.68 (1H, d, J 9.3 Hz), 3.80 (3H, s), 2.96 (1H, d, J 15.6 Hz), 2.53–2.40 (1H, m), 2.33 (1H, dd, J 15.6 and 3.0 Hz), 2.19 (3H, s), 1.95–1.75 (3H, m), 1.65–1.50 (2H, m), 1.07 (3H, s), 0.57 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 202.8 (CH), 156.2 (C), 134.7 (C), 129.9 (2 C, C and CH), 125.9 (CH), 109.2 (CH), 55.0 (CH_3), 51.5 (C), 48.9 (CH_2), 45.4 (C), 39.3 (CH_2), 33.9 (CH_2), 26.1 (CH_3), 24.4 (CH_3), 20.0 (CH_2), 16.9 (CH_3). For the aldehyde **22**: IR (neat): ν_{max}/cm^{-1} 2710, 1725. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 9.54 (1H, s), 7.04 (1H, s), 7.02 (1H, d, J 7.8 Hz), 6.75 (1H, d, J 7.8 Hz), 3.72 (3H, s), 2.60–2.40 (1H, m), 2.32 (3H, s), 2.17–2.00 (1H, m), 1.91–1.50 (4H, m), 1.16 (3H, s), 0.67 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 200.2 (CH), 155.2 (C), 130.0 (CH), 129.5 (C), 128.8 (CH), 127.9 (C), 111.5 (CH), 64.5 (C), 55.2 (CH_3), 44.7 (C), 40.5 (CH_2), 30.9 (CH_2), 28.5 (CH_3), 24.0 (CH_3), 21.1 (CH_3), 19.7 (CH_2). For the lactone **27**: IR (neat): ν_{max}/cm^{-1} 1798, 1796. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.04 (1H, d, J 8.4 Hz), 6.96 (1H, s), 6.94 (1H, d, J 8.4 Hz), 2.36 (3H, s), 2.40–1.64 (6H, m), 1.03 (3H, s), 0.92 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 179.4 (C), 151.7 (C), 132.5 (C), 129.3 (C), 128.9 (CH), 125.6 (CH), 110.1 (CH), 60.1 (C), 47.6 (C), 38.7 (CH_2), 34.7 (CH_2), 25.4 (CH_3), 23.6 (CH_3), 21.5 (CH_3), 21.0 (CH_2).



Scheme 3. *Reagents, conditions and yields*: (a) MeMgI, Et_2O, 4 h, 83%; (b) $POCl_3$, py, 0.5 h, 68%; (c) i. O_3/O_2, MeOH–CH_2Cl_2 (1:4), −70°C; ii. Me_2S, rt, 3 h, 70%; (d) i. $NaClO_2$, NaH_2PO_4, *t*-BuOH, cyclohexene, H_2O, 3 h; ii. CH_2N_2, Et_2O, 0°C, 20 min; 66%; (e) BBr_3, CH_2Cl_2, −40°C to rt, 40 min, 65%; (f) LAH, THF, 0–5°C, 1 h, 95%.

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5. An alternate strategy was also explored for the synthesis of α-herbertenol via Claisen rearrangement of the aryl ether **i**. However, as depicted below, on heating, the aryl ether **i** underwent a facile Cope rearrangement to furnish the diene **ii**, and did not generate any detectable amount of the Claisen product **iii**.
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