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A stereoselective total synthesis of (+)-α-herbertenol

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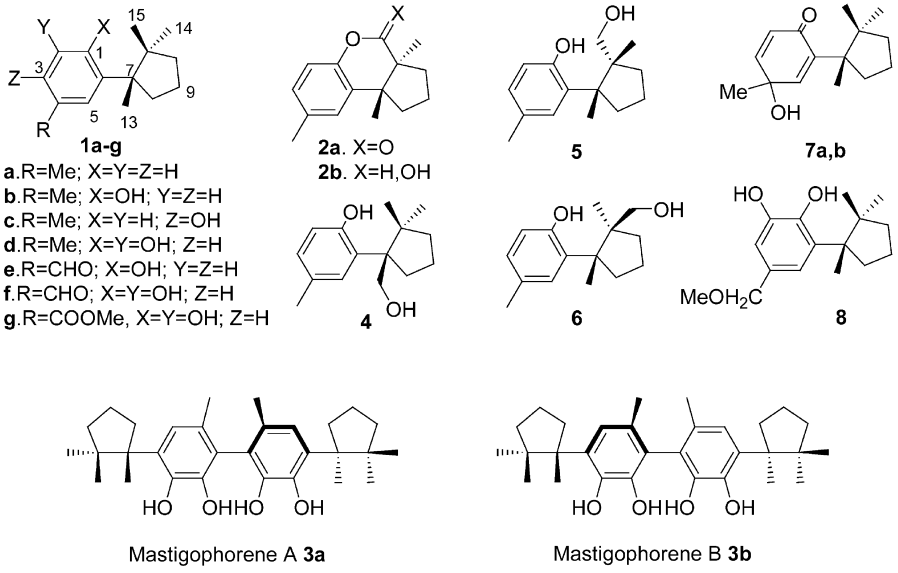
Abstract—A stereoselective total synthesis of (+)-α-herbertenol starting from the allyl alcohol **12**, readily available in three steps from the monoterpene (*R*)-limonene, is described. Claisen rearrangement of the aryl allyl ether **10** and concomitant cyclisation furnished a 5:3 mixture of the tricyclic compounds **13** and **14**. Degradation of the isopropenyl group followed by cleavage of the central ring and functional group manipulation transformed **13** into (+)-α-herbertenol (**1b**).

1. Introduction

Herbertanes are a small group of sesquiterpenes, which are considered as chemical markers for the liverworts belonging to the genus *Herbertus*.[1a] Isolation of the first members of the herbertane group 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*. The phenolic herbertanes, for example, **1b**–**d** have been shown to possess interesting biological properties such as growth inhibiting activity, antifungal, antilipid peroxidation and neurotropic activities.[1,2] The dimeric herbertanes mastigophorenes A and B **3a** and **3b**, isolated[3] along with their isomers mastigophorenes C and D and herbertenols from the liverwort *Mastigophora diclados*, were shown to stimulate nerve growth. Recently,[1a] Asakawa and co-workers reported the isolation of seven new members of the herbertane group herbertenelactol **2b**, 1,13-herbertenediol **4**, 1,14-herbertenediol **5**, 1,15-herbertenediol **6**, herbertenones A and B **7a**,**b** and 12-methoxy-herbertenediol **8** along with dimeric herbertanes mastigophorenes A–C, from the Japanese liverwort *Herberta sakuraii*.

The presence of two vicinal quaternary carbons on a cyclopentane moiety and associated biological activities



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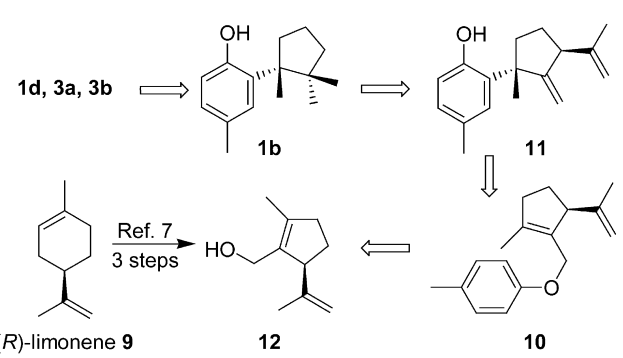
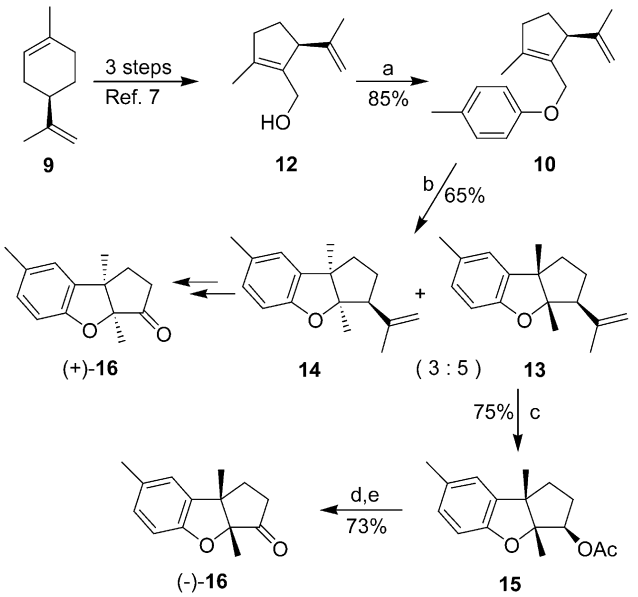
made mastigophorenes and herbertenols interesting synthetic targets of current interest. Until recently, unlike the parent hydrocarbon, the phenolic herbertanes have received very little attention from synthetic chemists despite their interesting biological properties. However, the scenario has been changed and significant synthetic activity is reported since 1999.[2,4–6] The first enantioselective synthesis of (−)-α-herbertenol **1b** was reported[5a] by Abad and co-workers in 1999. The first synthesis of mastigophorenes A and B **3a** and **3b** was achieved[5b] in 1999 via the phenolic coupling of natural herbertenediol **1d**. Almost at the same time,[5c] Meyers and Degnan reported an enantioselective synthesis of herbertenediol (−)-**1d** and its conversion to mastigophorenes A and B (−)-**3a** and (−)-**3b**. In 2001, Fukuyama and co-workers reported[5f] the enantioselective synthesis of (−)-α-herbertenol **1b** and its conversion to (−)-herbertenediol **1d** and mastigophorenes **3a** and **3b**. Recently, Kita and co-workers have developed[6a] an enantioselective synthesis of herbertenediol **1d** via rearrangement of an epoxytosylate, and later extended[6b] the methodology for the synthesis of α-herbertenol **1b**. Herein we wish to report a stereoselective total synthesis of (+)-α-herbertenol starting from the readily and abundantly available monoterpene (*R*)-limonene **9** employing Claisen rearrangement as the key reaction for the generation of the chiral quaternary carbon atom.

It was contemplated that Claisen rearrangement of the aryl ether **10** generates methylenecyclopentane **11** containing the requisite chiral quaternary carbon atom, which can be further elaborated into α-herbertenol **1b** (Scheme 1). Visualising the isopropenyl group as a masked hydroxy group, the allyl alcohol **12** was chosen as the appropriate chiral starting material, which could be readily obtained[7] from the abundantly available monoterpene (*R*)-limonene **9**.

The synthetic sequence is depicted in Schemes 2 and 3. To begin with, the allyl alcohol **12** was prepared from *R*-limonene in three steps,[7] viz. chemoselective ozonolysis of the ring olefin followed by intramolecular aldol condensation and regioselective reduction. The allyl alcohol **12** was then coupled with *p*-cresol under Mitsunobu conditions.[8] Thus, reaction of the allyl alcohol **12** with *p*-cresol in the presence of triphenylphosphine and diisopropyl azodicarboxylate (DIAD) furnished the ether **10** in 85% yield. Thermal activation of the ether **10** in *N*,*N*-dimethylaniline in a sealed tube at 180 °C generated, instead of the phenol **11**, a ≈5:3 mixture of the cyclised products **13** and **14**, in 65% yield, which were separated by silica gel and

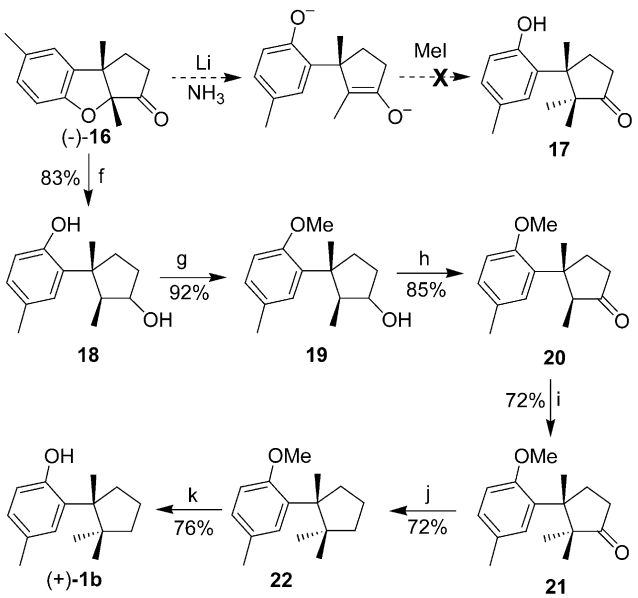


Scheme 1.



Scheme 2. Reagents, conditions and yields: (a) *p*-cresol, PPh_3, DIAD, THF, room temperature, 10 h, 85%; (b) $PhNMe_2$, sealed tube, 180 °C, 72 h, 65%; (c) O_3/O_2, CH_2Cl_2–MeOH (5:1), −70 °C; Ac_2O, NEt_3, DMAP, C_6H_6, reflux, 75%; (d) K_2CO_3, MeOH, room temperature. 4 h, 83%; (e) PCC, NaOAc, CH_2Cl_2, room temperature, 2 h, 88%.

silver nitrate impregnated silica gel column chromatography (see Section 2). After creating the requisite new chiral quaternary carbon atom, the original chiral centre was disposed off via degradation of the isopropenyl group employing a Criegee rearrangement.[9] Thus, ozonolysis of the compound **13** in methylene chloride-methanol followed by treatment of the resulting methoxy-hydroperoxide with acetic anyhydride, triethylamine and 4-dimethylaminopyridine (DMAP) in refluxing benzene generated the acetate **15** in 75% yield. Hydrolysis of the acetate group followed by oxidation of the resultant alcohol with pyridinium



Scheme 3. Reagents, conditions and yields: (f) Li, liq. NH_3, THF, 0.5 h 83%; (g) K_2CO_3, MeI, $Me_2C{=}O$, room temperature, 4 h, 92%; (h) PCC, silica gel, CH_2Cl_2, 85%; (i) NaI, MeI, DME, room temperature, 12 h, 72%; (j) $NH_2NH_2.H_2O$, digol, 125 °C, 3 h; KOH, 190 °C, 12 h, 72%; (k) BBr_3, CH_2Cl_2, 0 °C–room temperature, 2 h, 76%.

chlorochromate (PCC) in the presence of sodium acetate transformed the acetate **15** into the ketone (−)-**16** $[\alpha]_D^{25}=-290$ (*c* 1.28, $CHCl_3$). Quite expectedly, the same sequence transformed the minor isomer **14** into the enantiomeric ketone (+)-**16**, $[\alpha]_D^{24}=+320$ (*c* 1.25, $CHCl_3$).

Next attention was turned to the conversion of the ketone (−)-**16** into α-herbertenol **1b**. It was contemplated that reductive methylation of the keto ether **16**, employing alkali metal in liquid ammonia and methyl iodide, followed by Wolff–Kishner reduction of the resulting phenolic ketone **17** would directly furnish **1b**. However, all our attempts (which include different experimental procedures of lithium or sodium in liquid ammonia with and without proton source; samarium iodide; zinc and acetic acid; etc.) to convert the tricyclic compound **16** directly into the ketone **17** were unsuccessful, and reductive cleavage of the central ring using lithium in liquid ammonia conditions furnished only the diol **18**, in 83% yield.[10] Treatment of the diol **18** with potassium carbonate and methyl iodide followed by oxidation of the resultant monomethyl ether **19** furnished the cyclopentanone **20**. The stereochemistry of the secondary methyl group in **20** was assigned as *trans* to aryl group on the basis of the chemical shift of the secondary methyl group (δ 1.02 ppm) in the ^{1}H NMR spectrum. Alkylation of the ketone **20** with sodium hydride and methyl iodide in dimethoxyethane (DME) generated the ketone **21**, which on Wolff–Kishner reduction furnished the methyl ether **22** of α-herbertenol. Finally, boron tribromide mediated cleavage of the methyl ether **22** furnished (+)-α-herbertenol **1b**, $[\alpha]_D^{26}=+52.9$ (*c* 0.7, $CHCl_3$) {lit.[1b] for (−)-**1b**, $[\alpha]_D=-55$}. The methyl ether **22** and α-herbertenol exhibited spectroscopic data (IR, ^{1}H and ^{13}C NMR) identical to those reported in the literature.

In conclusion, we have developed a convenient methodology for the stereoselective synthesis of α-herbertenol **1b** starting from the readily available monoterpene (*R*)-limonene. Since the natural α-herbertenol has already been transformed[5f] into natural herbertenediol **1d** and mastigophorenes **3a** and **3b**, the present sequence provides a convenient route for the synthesis of the optical antipodes of these natural products. Currently, we are investigating the extension of the methodology for the enantiospecific synthesis of other herbertane and cuparene sesquiterpenoids.

2. Experimental

2.1. Data for compounds

2.1.1. (+)-((5*S*)-5-Isopropenyl-2-methylcyclopent-1-enyl)methyl 4-methylphenyl ether (10). To a magnetically stirred solution of triphenylphosphine (4.12 g, 15.8 mmol) in dry THF (4 ml) was added DIAD (2.84 ml, 14.46 mmol) and stirred for 15 min at room temperature. A solution of the allyl alcohol[7] **12** (2.0 g, 13.15 mmol) and *p*-cresol (1.42 g, 13.15 mmol) in dry THF (2 ml) was added to the reaction mixture and stirred for 10 h at room temperature. It was then diluted with CH_2Cl_2 (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 (1:20) as eluent furnished the allyl aryl ether **10** (2.7 g, 85%) as colourless oil. $[\alpha]_D^{25}=100$ (*c* 1.03, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3070, 1644, 1510, 1235, 1009. ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 7.00 (2H, d, *J*=7.2 Hz), 6.76 (2H, d, *J*=7.2 Hz), 4.67 (2H, s), 4.48 and 4.23 (2H, 2×d, *J*=10.5 Hz), 3.51 (1H, m), 2.50–2.15 (2H, m), 2.26 (3H, s), 2.15–1.95 (1H, m), 1.78 (3H, s), 1.75–1.55 (1H, m), 1.62 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 157.2 (C), 147.5 (C), 139.9 (C), 132.5 (C), 129.7 (2 C, CH), 129.5 (C), 114.6 (2 C, CH), 110.9 (CH_2), 63.1 (CH_2), 54.8 (CH), 38.0 (CH_2), 28.0 (CH_2), 20.5 (CH_3), 19.3 (CH_3), 14.3 (CH_3). Mass: *m*/*z* 242 (M^+, 2%), 241 (3), 199 (10), 149 (11), 135 (15), 134 (15), 121 (26), 119 (23), 108 (100), 107 (47), 93 (35), 91 (41). HRMS: *m*/*z* Calcd for $C_{17}H_{23}O$ (M+1): 243.1749. Found: 243.1752.

2.1.2. (3*S*,3a*S*,8b*S*)-*cis*-3-Isopropenyl-3a,7,8b-trimethyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta-(*b*)benzofuran (13). A solution of the allyl aryl ether **10** (2.2 g, 9.09 mmol) and *N*,*N*-dimethylaniline (1.2 ml) was placed in a sealed tube under N_2 atmosphere and heated to 180 °C for 3 days in an oil bath. The reaction mixture was then cooled and diluted with hexane. It was stirred with 6 N HCl for 1 h and then extracted with hexane (3×5 ml). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using benzene–hexane (1:20) as eluent furnished a 5:3 mixture of cyclised products **13** and **14** (1.4 g, 65%) as oil. Further separation on a silver nitrate impregnated silica gel column furnished **13** (885 mg, 41%) as oil, and **14** (520 mg, 24%) as a colourless solid, which was recrystallised from hexanes.

Major isomer **13**: $[\alpha]_D^{26}=-83.9$ (*c* 1.18, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1644, 1609, 1245, 887, 808. ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.85 (2H, brs), 6.58 (1H, d, *J*=8.4 Hz), 4.88 (1H, s), 4.70 (1H, s), 2.64 (1H, dd, *J*=9.0 and 9.0 Hz), 2.28 (3H, s), 2.15–1.85 (2H, m), 1.86 (3H, s), 1.70–1.55 (2H, m), 1.21 (3H, s), 1.16 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 154.7 (C), 144.9 (C), 138.3 (C), 129.5 (C), 128.4 (CH), 123.8 (CH), 111.3 (CH_2), 109.6 (CH), 98.4 (C), 56.2 (CH), 53.7 (C), 39.1 (CH_2), 26.5 (CH_2), 24.6 (CH_3), 23.5 (CH_3), 21.0 (CH_3), 16.7 (CH_3). Mass: *m*/*z* 242 (M^+, 42%), 227 (19), 174 (15), 173 (10), 161 (39), 160 (100), 159 (65), 145 (23). HRMS: *m*/*z* Calcd for $C_{17}H_{22}ONa$ (M+Na): 265.1568. Found: 265.1577.

Minor isomer **14**: mp 122–123 °C (crystallised from hexane). $[\alpha]_D^{25}=116.4$ (*c* 1.40, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3071, 1640, 1611, 1262, 1137, 1062, 912, 889, 807. ^{1}H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.81 (1H, d, *J*=7.5 Hz), 6.79 (1H, s), 6.51 (1H, d, *J*=7.5 Hz), 4.93 (1H, s), 4.80 (1H, s), 2.50–2.25 (2H, m), 2.26 (3H, s), 2.00–1.90 (1H, m), 1.81 (3H, s), 1.65–1.50 (2H, m), 1.33 (3H, s), 1.32 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 156.7 (C), 144.4 (C), 135.6 (C), 129.1 (C), 128.5 (CH), 123.4 (CH), 113.7 (CH_2), 108.3 (CH), 98.9 (C), 58.7 (CH), 54.3 (C), 42.4 (CH_2), 27.7 (CH_2), 23.7 (CH_3), 22.1 (CH_3), 21.0 (CH_3), 20.6 (CH_3). Mass: *m*/*z* 242 (M^+, 37%), 227 (18), 174 (18), 161 (47), 160 (100), 159 (72), 145 (25), 135 (16). HRMS: *m*/*z* Calcd for $C_{17}H_{23}O$ (M+1): 243.1749. Found: 243.1758.

2.1.3. (−)-(3*R*,3a*R*,8b*S*)-*cis*-3a,7,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta(*b*)benzofuran-3-yl acetate (15). Pre-cooled dry ozone in oxygen gas was passed through a cold (−70 °C) suspension of the ether **13** (400 mg, 1.65 mmol) and $NaHCO_3$ (5 mg) in 4:1 CH_2Cl_2–MeOH (5 ml) until reaction mixture turns blue and then the excess ozone was flushed off with oxygen. The solvent was evaporated in vacuo and the residue was taken in dry benzene (3 ml). Acetic anhydride (2.33 ml, 24.75 mmol), triethylamine (2.3 ml, 16.5 mmol) and a catalytic amount of DMAP (5 mg) were added to the reaction mixture and refluxed for 4 h. It was then cooled, diluted with water and extracted with ether (3×4 ml). The ether extract was washed with 3 N aqueous HCl and brine, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue over a silica gel column using ethyl acetate–hexane (1:10) as eluent furnished the acetate **15** (320 mg, 75%) as oil. $[\alpha]_D^{23}=-58.6$ (*c* 2.54, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1742, 1610, 1237, 1072, 810. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.83 (1H, d, *J*=7.8 Hz), 6.80 (1H, s), 6.53 (1H, d, *J*=8.1 Hz), 5.26–5.18 (1H, m), 2.26 (3H, s), 2.07 (3H, s), 2.00–1.55 (4H, m), 1.36 (3H, s), 1.30 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 169.3 (C), 155.5 (C), 135.4 (C), 129.7 (C), 128.8 (CH), 123.5 (CH), 109.0 (CH), 98.7 (C), 81.8 (CH), 53.5 (C), 41.3 (CH_2), 29.0 (CH_2), 22.9 (CH_3), 21.1 (CH_3), 21.0 (CH_3), 17.0 (CH_3). Mass: *m*/*z* 260 (M^+, 30%), 218 (25), 203 (100), 173 (14), 161 (18), 160 (29), 159 (48), 145 (29). HRMS: *m*/*z* Calcd for $C_{16}H_{20}O_3Na$ (M+Na): 283.1310. Found: 283.1314.

2.1.4. (−)-(3*R*,8b*S*)-*cis*-3a,7,8b-Trimethyl-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-3-one (16). To a magnetically stirred solution of the acetate **15** (300 mg, 1.15 mmol) in methanol (4 ml) was added K_2CO_3 (317 mg, 2.30 mmol) and stirred at room temperature for 2 h. Water (10 ml) was then added to the reaction mixture and extracted with CH_2Cl_2 (3×4 ml). The combined CH_2Cl_2 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 (1:5) as eluent furnished the alcohol (208 mg, 83%) as oil, {$[\alpha]_D^{25}=-34.3$ (*c* 4.4, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3351, 1607, 1264, 1241, 1024, 809. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.82 (1H, d, *J*=7.5 Hz), 6.81 (1H, s), 6.51 (1H, d, *J*=7.5 Hz), 4.16 (1H, brs), 2.26 (3H, s), 2.06 (1H, ddd, *J*=12.0, 12.0, 6.9 Hz), 1.86 (1H, ddd, *J*=12.0, 6.9, 2.3 Hz), 1.80–1.50 (3H, m), 1.37 (3H, s), 1.35 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 155.5 (C), 136.1 (C), 129.6 (C), 128.5 (CH), 123.6 (CH), 108.7 (CH), 99.6 (C), 80.2 (CH), 53.0 (C), 41.0 (CH_2), 31.1 (CH_2), 23.3 (CH_3), 21.0 (CH_3), 16.8 (CH_3)}, which was taken in 2 ml of CH_2Cl_2 and added to a magnetically stirred suspension of PCC (490 mg, 2.30 mmol) and sodium acetate (490 mg) in CH_2Cl_2 (2 ml). The reaction mixture was stirred at room temperature for 2 h, filtered through a silica gel column, and the column was eluted with more CH_2Cl_2. The solvent was evaporated to furnish the ketone **16** (217 mg, 88%) which was recrystallised from ether. Mp 96–98 °C. $[\alpha]_D^{25}=290.6$ (*c* 1.28, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1744, 1608, 1233, 1056, 819. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.90 (2H, brs), 6.23 (1H, d, *J*=8.4 Hz), 2.40–2.20 (2H, m), 2.28 (3H, s), 2.03 (1H, ddd, *J*=18.0, 12.3, 9.0 Hz), 1.85 (1H, ddd, *J*=12.3, 12.3, 7.2 Hz), 1.35 (3H, s), 1.34 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 215.6 (C), 155.9 (C), 133.2 (C), 130.8 (C), 129.4 (CH), 123.3 (CH), 109.6 (CH), 91.4 (C), 51.3 (C), 35.6 (CH_2), 32.4 (CH_2), 23.5 (CH_3), 21.0 (CH_3), 14.6 (CH_3). Mass: *m*/*z* 216 (M^+, 20%), 202 (13), 187 (19), 173 (17), 160 (100), 159 (59), 145 (34), 115 (13). HRMS: *m*/*z* Calcd for $C_{14}H_{16}O_2Na$ (M+Na): 239.1048. Found: 239.1045.

2.1.5. (−)-2-[(1*R*,2*S*,3*R*)-3-Hydroxy-1,2-dimethylcyclopentyl]-4-methylphenol (18). To a magnetically stirred, freshly distilled (over sodium and ferric chloride) ammonia (100 ml) in a two necked flask, equipped with Dewar condenser, was added freshly cut lithium (25 mg, 3.68 mmol) followed by a solution of the ketone **16** (200 mg, 0.92 mmol) in anhydrous THF (3 ml). The resulting blue coloured solution was stirred for 15 min. at −33 °C and then the reaction was quenched with solid NH_4Cl. After evaporation of ammonia, the residue was taken in water (5 ml) and extracted with ether (3×5 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 (1:5) as eluent, furnished the diol **18** (168 mg, 83%) which was recrystallised from ether. Mp 72–74 °C. $[\alpha]_D^{25}=-23.6$ (*c* 0.93, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3349, 1608, 1251, 1213, 1124, 1047, 1000, 813. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.95 (1H, s), 6.83 (1H, d, *J*=8.1 Hz), 6.58 (1H, d, *J*=8.1 Hz), 3.97 (1H, q, *J*=6.5 Hz), 2.55–2.40 (2H, m), 2.26 (3H, s), 2.15–1.90 (1H, m), 1.80–1.55 (3H, m), 1.23 (3H, s), 0.99 (3H, d, *J*=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 152.0 (C), 134.8 (C), 128.9 (C), 127.8 (CH), 127.5 (CH), 117.0 (CH), 81.0 (CH), 49.2 (CH), 45.5 (C), 36.9 (CH_2), 33.1 (CH_2), 22.5 (CH_3), 21.0 (CH_3), 13.5 (CH_3). Mass: *m*/*z* 220 (M^+, 20%), 202 (60), 187 (100), 173 (40), 159 (80), 147 (40), 133 (20), 118 (40), 105 (20). HRMS: *m*/*z* Calcd for (M-OH) $C_{14}H_{19}O$: 203.1436. Found: 203.1436.

2.1.6. (−)-(1*R*,2*S*,3*R*)-2,3-Dimethyl-3-(2-methoxy-5-methylphenyl)cyclopentanol (19). To a magnetically stirred solution of the diol **18** (150 mg, 0.68 mmol) in acetone (4 ml) was added K_2CO_3 (188 mg, 1.36 mmol) and MeI (0.43 ml, 1.36 mmol) and stirred at room temperature for 4 h. Water (5 ml) was then added to the reaction mixture and extracted with CH_2Cl_2 (3×4 ml). The combined CH_2Cl_2 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 **19** (145 mg, 92%) as oil. $[\alpha]_D^{24}=-36.1$ (*c* 0.36, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3368, 1288, 1239, 1052, 1032, 807. ^1H NMR (300 MHz, $CDCl_3+CCl_4$): δ 6.95 (1H, s), 6.92 (1H, d, *J*=8.1 Hz), 6.72 (1H, d, *J*=8.1 Hz), 3.88 (1H, q, *J*=7.2 Hz), 3.80 (3H, s), 2.40–2.00 (3H, m), 2.28 (3H, s), 1.82 (1H, ddd, *J*=12.5, 8.0, 8.0 Hz), 1.75–1.50 (2H, m), 1.18 (3H, s), 1.03 (3H, d, *J*=7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3+CCl_4$): δ 156.0 (C), 137.5 (C), 129.1 (C), 127.5 (CH), 127.2 (CH), 111.6 (CH), 80.0 (CH), 55.1 (CH_3), 49.2 (CH), 45.7 (C), 37.0 (CH_2), 33.0 (CH_2), 22.7 (CH_3), 21.0 (CH_3), 13.2 (CH_3). Mass: *m*/*z* 234 (M^+, 17%), 165 (100), 149 (15), 147 (23), 145 (15), 135 (15), 119 (18), 105 (11). HRMS: *m*/*z* Calcd for $C_{15}H_{22}O_2Na$ (M+Na): 257.1517. Found: 257.1512.

2.1.7. (+)-(2*S*,3*R*)-2,3-Dimethyl-3-(2-methoxy-5-methylphenyl)cyclopentanone (20). To a magnetically stirred suspension of PCC (258 mg, 1.20 mmol) and silica gel (258 mg) in 2 ml dry CH_2Cl_2 was added a solution of the alcohol **19** (140 mg, 0.60 mmol) in 2 ml dry CH_2Cl_2 and stirred vigorously for 2 h at room temperature. 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 ketone **20** (118 mg, 85%) as oil. $[\alpha]_D^{22}$=31.2 (*c* 1.25, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3030, 1738, 1610, 1234, 1071, 808. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 6.98 (1H, d, *J*=8.1 Hz), 6.96 (1H, s), 6.77 (1H, d, *J*=8.1 Hz), 3.82 (3H, s), 3.02 (1H, q, *J*=6.9 Hz), 2.50–2.10 (4H, m), 2.30 (3H, s), 1.22 (3H, s), 1.02 (3H, d, *J*=6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 219.9 (C), 156.2 (C), 134.6 (C), 129.4 (C), 127.9 (2 C, CH), 111.7 (CH), 55.1 (CH_3), 51.8 (CH), 45.9 (C), 35.0 (CH_2), 32.8 (CH_2), 21.0 (CH_3), 20.0 (CH_3), 9.5 (CH_3). Mass: *m*/*z* 232 (M^+, 79%), 217 (51), 199 (22), 175 (100), 161 (40), 149 (43), 147 (50), 145 (35), 115 (31), 105 (39), 91 (40). HRMS: *m*/*z* Calcd for $C_{15}H_{21}O_2$ (M+1): 233.1541. Found: 233.1547.

2.1.8. (+)-(3*S*)-2,2,3-Trimethyl-3-(2-methoxy-5-methylphenyl)cyclopentanone (21). To a magnetically stirred suspension of NaH (2.8 mg, 60% dispersion in oil, 0.07 mmol, washed with dry hexane) in DME (1 ml) was added a solution of the ketone **20** (20 mg, 0.086 mmol) in DME (1 ml), and stirred for 0.5 h at room temperature. Methyl iodide (0.05 ml) was then added to the reaction mixture and stirred for 12 h. It was then quenched with water (2 ml) and extracted with ether (3×3 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 (1:20) as eluent furnished the ketone **21** (10 mg, 72%, based on the starting material consumed) as oil.[5i] $[\alpha]_D^{26}$=58.9 (*c* 0.9, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1738, 1501, 1244, 1029, 807. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.08 (1H, d, *J*=1.8 Hz), 6.98 (1H, d, *J*=8.1 Hz), 6.72 (1H, d, *J*=8.1 Hz), 3.73 (3H, s), 2.60–2.35 (3H, m), 2.30 (3H, s), 2.15–1.85 (1H, m), 1.38 (3H, s), 1.21 (3H, s), 0.64 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 222.1 (C), 156.0 (C), 134.5 (C), 129.1 (C), 128.6 (CH), 127.7 (CH), 111.0 (CH), 54.2 (CH_3), 52.3 (C), 48.7 (C), 34.5 (CH_2), 32.8 (CH_2), 23.5 (CH_3), 22.0 (CH_3), 21.9 (CH_3), 21.0 (CH_3). Mass: *m*/*z* 246 (M^+, 74%), 231 (16), 213 (14), 197 (14), 175 (100), 161 (32), 147 (45), 115 (33), 105 (36), 91 (46). HRMS: *m*/*z* Calcd for $C_{16}H_{22}O_2Na$ (M+Na): 269.1517; Found: 269.1536.

2.1.9. (+)-(*R*)-1-(2-Methoxy-5-methylphenyl)-1,2,2-trimethylcyclopentane (22). A solution of the ketone **21** (5 mg, 0.02 mmol), potassium hydroxide (11 mg, 0.2 mmol) and hydrazine hydrate (0.2 ml, 0.4 mmol) in diethylene glycol (2 ml) was taken in a sealed tube and heated to 125 °C for 3 h and then to 190 °C for 12 h. The reaction mixture was then cooled, acidified with 3 N aqueous HCl (5 ml) and extracted with CH_2Cl_2 (3×3 ml). The combined CH_2Cl_2 extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over silica gel column using ethyl acetate–hexane (1:20) as eluent furnished the deoxygenated product **22** (3.5 mg, 72%) as oil.[6b] $[\alpha]_D^{26}$=41.0 (*c* 1.0, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 1607, 1241, 1179, 1034, 806. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.04 (1H, s), 6.88 (1H, dd, *J*=8.1, 1.8 Hz), 6.68 (1H, d, *J*=7.8 Hz), 3.74 (3H, s), 2.60–2.45 (1H, m), 2.26 (3H, s), 1.80–1.40 (5H, m), 1.33 (3H, s), 1.13 (3H, s), 0.66 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 156.7 (C), 135.8 (C), 129.6 (CH), 128.7 (C), 127.1 (CH), 111.5 (CH), 54.8 (CH_3), 51.3 (C), 44.3 (C), 42.3 (CH_2), 40.0 (CH_2), 27.9 (CH_3), 26.2 (CH_3), 23.2 (CH_3), 21.1 (CH_3), 20.7 (CH_2). Mass: *m*/*z* 233 (M+1, 12%), 232 (74), 175 (30), 162 (63), 161 (29), 150 (30), 149 (100), 147 (70), 145 (31), 135 (34), 119 (29), 105 (22), 91 (28).

2.1.10. (+)-4-Methyl-2-(*R*-1,2,2-trimethylcyclopentyl)-phenol (α-herbertenol 1b). A solution of BBr_3 (1 M in CH_2Cl_2, 0.04 ml, 0.04 mmol) was added drop wise to a solution of the ether **22** (5 mg, 0.02 mmol) in CH_2Cl_2 (1.5 ml) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, then quenched with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3×3 ml). The combined organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate–hexane (1:5) as eluent furnished *ent*-α-herbertenol **1b** (3.5 mg, 76%) as oil. $[\alpha]_D^{26}$=52.8 (*c* 0.7, $CHCl_3$). IR (neat): ν_{max}/cm^{-1} 3531, 1506, 1251, 1165, 808. ^1H NMR (300 MHz, $CDCl_3$+CCl_4): δ 7.03 (1H, s), 6.80 (1H, d, *J*=8.1 Hz), 6.50 (1H, d, *J*=8.1 Hz), 4.51 (1H, s), 2.65–2.45 (1H, m), 2.25 (3H, s), 1.90–1.30 (5H, m), 1.40 (3H, s), 1.17 (3H, s), 0.75 (3H, s). ^{13}C NMR (75 MHz, $CDCl_3$+CCl_4): δ 152.3 (C), 132.9 (C), 130.1 (CH), 128.8 (C), 127.3 (CH), 116.7 (CH), 51.1 (C), 44.8 (C), 41.5 (CH_2), 39.6 (CH_2), 27.3 (CH_3), 25.8 (CH_3), 23.1 (CH_3), 21.1 (CH_3), 20.5 (CH_2). Mass: *m*/*z* 218 (M^+, 32%), 161 (23), 148 (81), 147 (38), 135 (83), 121 (36), 105 (22).

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