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An efficient synthesis of (±)-β-herbertenol by a 1,3-cyclopentadione annelation strategy

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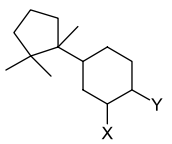
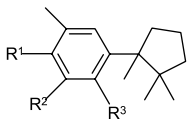
Abstract—A simple and efficient synthesis of sesquiterpene (±)-β-herebertenol is described. The formation of cyclopentadione onto the aromatic moiety is the key feature of this protocol.

1. Introduction

Numerous herbertene type sesquiterpenoids, an expanding group of natural products possessing a 3-methyl-1-(1,2,2-trimethylcyclopentyl) cyclohexane skeleton **1** have been isolated from *Herbertous* species and other *liverworts*.[1,2] Some of these compounds, particularly, those with an oxygenated aromatic six-membered ring [e.g. (−)-α-herbertenol,[3] (−)-herbertenediol[4] and (−)-β-herbertenol[5]] show a wide spectrum of biological properties which include potent antifungal,[1a,b] neurotrophic,[3] and anti-lipid peroxidation[4] activities. Some complicated dimeric phenols, belonging to this class are also biologically active.



X = CH_3, Y = H: Herbertene skeleton **(1)**
X = H, Y = CH_3: Cuparene skeleton **(2)**



$R^1 = R^2 = H$; $R^3 = OH$: (±)-α-Herbertenol **(3)**
$R^1 = H$, $R^2 = R^3 = OH$: (±)-Herbertenediol **(4)**
$R^1 = OH$, $R^2 = R^3 = H$: (±)-β-Herbertenol **(5)**
$R^1 = R^2 = R^3 = H$; (±)-Herbertene **(6)**

The total synthesis of herbertene-type **1** as well as cuparene-type **2** sesquiterpenoids have attracted attention due to the difficulty associated with the construction of the vicinal quaternary carbons in the cyclopentane ring. A literature survey indicates that, even though several synthetic strategies are reported towards (±)-herbertene **6**,[5b] (±)-α-herbertenol **3**,[5a,e,6] (±)-herbertenediol **4**[5d] and their asymmetric syntheses, only one synthetic strategy is reported towards (±)-β-herbertenol **5**.[6]

In continuation of our interest towards the total synthesis of cuparene-type sesquiterpenoid, viz. (±)-α-cuparenone,[7] we attempted the synthesis of (±)-β-herbertenol **5**.

2. Results and discussion

The central idea of our synthetic route is to construct the cyclopenta-1,3-dione system **9** where the tertiary methyl group would be introduced at an early stage in the synthesis and then to elaborate it to β-herbertenol. To investigate this idea, cyclopenta-1,3-dione **9** was prepared by annelation of 1,3-dioxalane **7** and 1,2-disilyloxycyclobutene **8**.[8] Cyclopenta-1,3-dione **9** was subjected to Wittig reaction and mono-olefination was explited. Under optimized reaction conditions, cyclopentadione **9** was added at room temperature to the in situ generated ylide (1 equiv. prepared from Wittig salt $PPh_3^+MeI^-$ and K^+*tert.* BuO^- in refluxing benzene for 1 h) stirred for 15 min, followed by addition of Wittig salt (1 equiv.) and the base (1 equiv.) and refluxing it for 15 min followed by further addition of Wittig salt (0.25 equiv) and the base (0.25 equiv.) and further refluxing the reaction mixture for 15 min to ensure the completion of the reaction. Thus the exomethylene derivative **10** was obtained in 73% yield as a major product along with minor amounts (3%) of the di-exomethylene compound. If the Wittig salt (in all 2.25 equiv.) and the base (in all 2.25 equiv.) were mixed in a single portion and all the ylide was generated at the start, cyclopentadione **9** furnished the di-exomethylene compound as the major product.

The exomethylene compound **10** was reduced with $NaBH_4$ in ethanol at room temperature to furnish the secondary alcohol which was subjected to hydroboration[9] with BMS complex followed by oxidative work up with alkaline H_2O_2 to furnish diol **11**. Diol **11** thus obtained was protected regioselectively as a pivaloate ester[10] followed by its conversion to xanthate derivative **12**[11] by treating it with NaH/CS_2 and methyl iodide. The xanthate derivative **12**,

Keywords: (±)-β-herebertenol; Wittig reaction; reduction; annelation; xanthates.

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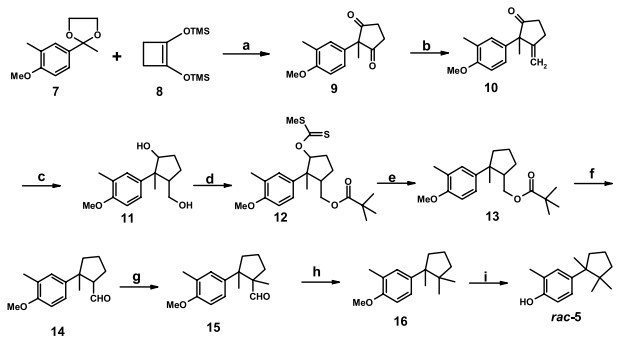

Scheme 1. *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, −78°C, 68%. (b) $PPh_3^{+-}MeI^-$ (2.25 equiv.), $K^+tertBuO^-$ (2.25 equiv.) C_6H_6, reflux–room temperature, 72%. (c) (i) $NaBH_4$ (1.5 equiv.), EtOH, room temperature, 30 min, 98%; (ii) BMS (2.5 equiv.), THF, 0°C, 2 h then at room temperature 24 h, then H_2O_2, HO^-, 0°C–room temperature, 1 h, 71%. (d) (i) $(CH_3)_3CCOCl$ (1.5 equiv.), Et_3N (2.5 equiv.), DCM, 0°C–room temperature, 84%; (ii) NaH (1.5 equiv.) THF:CS_2, 4:1, room temperature, 3 h, then MeI (3 equiv.) room temperature 16 h, 86%. (e) TBTH (5 equiv.), AIBN, toluene, reflux, 1.5 h, 83%. (f) (i) $LiAlH_4$ (2 equiv.), THF, room temperature 92%; (ii) PCC (1.5 equiv.), CH_2Cl_2, 0°C–room temperature, 1 h, 86%. (g) NaH (1.2 equiv.), DME, 0°C, 30 min, MeI (1.6 equiv.), 0°C, 3 h, then at room temperature 16 h, 65%. (h) $H_2NNH_2{\cdot}H_2O$ (7 equiv.), NaOH (9 equiv.), TEG, 195°C, 7 h, 52%. (i) BBr_3 (5 equiv.), CH_2Cl_2, −78°C–room temperature, 1 h 81%.

thus obtained was subjected to deoxygenation[11a,12] with tri-*n*-butyltinhydride in refluxing toluene with AIBN as an initiator to furnish the compound **13**. Compound **13** thus obtained was reductively cleaved with $LiAlH_4$ in anhydrous THF at room temperature to furnish primary alcohol which was then oxidized with PCC in dichloromethane to furnish compound **14**. Aldehyde **14** was alkylated[13] with CH_3I/NaH to furnish **15**. The aldehyde functionality of the aldehyde **15** was reduced to a methyl group by Wolff–Kishner reduction in 52% yield. Compound **16** was demethylated with BBr_3[14] in dichloromethane at −78°C to furnish (±)-β-herbertenol **5**. (±)-β-Herbertenol **5** had physical and spectral properties identical with the ones reported in the literature (Scheme 1).[1a,6]

3. Conclusion

A convenient and practical total synthesis of (±)-β-herbertenol has been achieved in 6.5% overall yield. The formation of cyclopentadione **9** onto the aromatic moiety, which is better than the reported synthesis, is the key feature of this protocol. This methodology by virtue of involvement of prochiral intermediate i.e. cyclopentadione **9** has a potential to synthesize chiral compounds of this family by chemical and/or enzymatic desymmetrization protocols. Studies towards an asymmetric synthesis of β-herbertenol are under progress and will be published in due course.

4. Experimental

4.1. General

Melting points were uncorrected. ^1H and ^{13}C NMR spectra were recorded on 200 and 50 MHz in $CDCl_3$ using TMS as an internal standard. IR spectra were recorded in $CHCl_3$ on FT-IR spectrometer. THF was freshly distilled from sodium benzophenone ketyl prior to use. All the reactions were monitored by TLC on 0.25 mm Merck Kieselgel TLC plate using ethanolic *p*-anisaldehyde solution with heating for visualization. Chromatography were performed on silica gel (60–120 mesh).

4.1.1. 2-(4-Methoxy-3-methylphenyl)-2-methyl cyclopentane-1,3-dione [9]. In an inert and moisture free atmosphere, $BF_3{\cdot}Et_2O$ (55.56 g, 49 mL, 0.39 mol) was added dropwise to the solution of 1,3-dioxolane **7** (8.13 g, 0.039 mol) and trimethylsilyloxy cyclobutene **8** (27 g, 0.12 mol) in dry dichloromethane (85 mL) at −78°C. The reaction mixture was stirred at −78°C for 8 h, then slowly brought to room temperature over 1 h and stirred overnight. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (100 mL) and quenched by addition of saturated $NaHCO_3$ (80 mL) in portions. The organic layer was washed with water (2×50 mL), brine (50 mL), dried over anhydrous sodium sulphate, filtered and the solvent removed under reduced pressure to furnish cyclopentadione **9**. The product was purified by crystallization from hexane–ethyl acetate 90:10.

Yield 6.16 g (68%). White solid. Mp 71–72°C. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2975, 1765, 1725, 1505, 1440, 1301, 1254, 1217, 1145, 1030, 815, 757, 668. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.39 (s, 3H), 2.18 (s, 3H), 2.61–2.98 (m, 4H), 3.81 (s, 3H), 6.82 (d, 1H, J=8.5 Hz), 6.94–6.99 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.07 (q), 19.46 (q), 35.01 (t, 2×–CH_2), 110.51 (d), 124.81 (d), 127.82 (s), 157.45 (s), 212.85 (s). Mass (*m*/*z*): 232 (M^+, 82), 189 (8), 176 (34), 162 (36), 148 (100), 133 (62), 115 (22), 103 (24), 91 (20), 77 (48), 55 (16). HRMS: M^+, found 232.1094. $C_{14}H_{16}O_3$ requires 232.1099.

4.1.2. 2-[4-Methoxy-3-methylphenyl)-2-methyl-3-methylene cyclopentenone [10]. The exomethylene compound **10** was obtained by the Wittig reaction of corresponding cyclopentadione **9**. Thus the ylide was generated from Wittig salt PPh_3CH_3I (6.97 g, 17.24 mmol) and *t*-BuOK (1.93 g, 17.24 mmol) in refluxing benzene (35 mL) for 1 h. It was cooled to room temperature and cyclopentadione **9** (4 g, 17.24 mmol) in dry benzene (15 mL) was added dropwise over 10 min. The reaction mixture was stirred at room temperature for 15 min. Again Wittig salt $PPh_3^{\oplus}CH_3I^{\ominus}$ (6.97 g, 17.24 mmol) and *tert*-BuOK (1.93 g, 17.24 mmol) were added and refluxed for 30 min. The reaction was monitored by TLC. To ensure the completion of the reaction, Wittig salt $PPh_3^{\oplus}CH_3I^{\ominus}$ (1.75 g, 4.32 mmol) and *tert*-BuOK (0.485 g, 4.32 mmol) were added and refluxing was continued for further 10 min. The reaction mixture was allowed to cool to room temperature diluted with ethyl acetate (75 mL), saturated NH_4Cl solution (50 mL) was added and stirred at room temperature for 30 min. The organic layer thus separated was washed with water (2×100 mL), saturated NH_4Cl (100 mL), dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to furnish crude exomethylene compound **10**. Column chromatography on silica gel (60–120 mesh, eluent: ethyl acetate–petroleum ether 3:97) furnished pure exomethylene compound **10** in 73% yield.

Yield 2.89 g (73%). Colorless thick syrup which solidified upon standing. Mp 62–63°C. IR ($CHCl_3$) ν_{max} (cm^{-1}): 2960, 2930, 1741, 1660, 1605, 1503, 1465, 1440, 1300, 1280, 1120, 895, 754. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.42 (s, 3H) 2.20 (s, 3H), 2.25–2.48 (m, 2H), 2.59–2.67 (m, 2H), 3.81 (s, 3H), 5.12 (s, 1H), 5.33 (s, 1H), 6.76 (d, 1H, J= 7.9 Hz), 7.11–7.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 16.00 (q), 22.91 (q), 27.5 (t), 34.03 (t), 54.71 (q), 60.71 (s), 109.73 (d), 109.81 (t), 124.63 (d), 126.73 (s), 128.41 (d), 132.72 (s), 153.18 (s), 156.82 (s), 212.85 (s). Mass (*m/z*): 230 (M^+, 48), 187 (100), 173 (16), 159 (17), 144 (8), 128 (13), 115 (16), 105 (58), 91 (14), 77 (41). HRMS: M^+, found 230.1311. $C_{15}H_{18}O_2$ requires 230.1307.

4.1.3. 3-Hydroxymethyl-2-(4-methoxy-3-methylphenyl)-2-methylcyclopentanol [11]. To the solution of ketoolefin **8** (2.028 g, 8.82 mmol) in ethanol (25 mL), $NaBH_4$ (0.502 g, 13.22 mmol) was added portion wise over 10 min at room temperature. Then the reaction mixture was stirred at room temperature for 30 min further. The reaction was monitored by TLC. After completion of the reaction, ethanol was removed under reduced pressure. The crude residue thus obtained was extracted with ethyl acetate. The organic layer was washed with water (20 mL), brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish secondary alcohol as white solid. The alcohol was purified by crystallization from ethyl acetate–petroleum ether (5:95). Yield 2 g, (98%). White solid. Mp 128°C. IR ($CHCl_3$) ν_{max} (cm^{-1}): 3450 (broad), 2960, 1650, 1630, 1500, 1410, 1385, 1220, 1140, 1035, 768. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.49 (s, 3H), 1.52–1.68 (m, 1H), 1.89–2.09 (m, 1H), 2.24 (s, 3H), 2.41–2.88 (m, 2H), 3.84 (s, 3H), 3.81–3.85 (m, 1H), 4.88 (s, 1H), 5.16 (s, 1H), 6.80 (d, 1H, J=8.0 Hz), 7.17–7.21 (m, 2H). Mass (*m/z*): 232 (M^+, 88), 214 (16), 199 (24), 189 (52), 173 (100), 157 (23), 149 (35), 115 (92), 91 (23), 77 (17).

The diol **11** was obtained by hydroboration of cyclopentanol with boranedimethylsulphide complex followed by oxidative alkaline hydrolysis with H_2O_2. Thus to the solution of cyclopentanol (2 g, 8.62 mmol) in dry THF (30 mL) at 0°C, BMS complex (2 M solution in THF, 1.638 g, 10.6 mL, 21.55 mmol) was added dropwise. The reaction mixture was brought to room temperature and stirred overnight. The reaction mixture was then cooled to 0°C, 30% NaOH (8 mL) was added in a single lot followed by H_2O_2 (30%, 8 mL) dropwise. The reaction mixture was stirred at room temperature for 30 min and then diluted with ethyl acetate. The organic layer thus separated was washed with water (2×30 mL), brine (30 mL), dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish crude diol **11**. Column chromatography of the diol on silica gel (60–120 mesh, eluent: ethyl acetate–petroleum ether 25:75) furnished pure diol **11** as crystalline white solid.

Yield 1.53 g (71%). White solid. Mp 149–151°C. IR ($CHCl_3$) ν_{max} (cm^{-1}): 3450 (broad), 3020, 1250, 1210, 761, 669. ^1H NMR ($CDCl_3$, 200 MHz): δ1.24 (s, 3H), 1.77–1.89 (m, 1H), 1.91–2.24 (m, 3H), 2.22 (s, 3H), 2.26–2.37 (m, 1H), 3.52 (dd, 1H, J=3.9, 10.7 Hz,), 3.80 (dd, 1H, J= 3.9, 10.7 Hz), 3.82 (s, 3H), 4.18–4.20 (m, 1H), 6.78 (d, 1H, J=9.0 Hz), 7.09–7.15 (m, 2H) ^{13}C NMR ($CDCl_3$, 50 MHz): δ 16.07 (q), 24.37 (t), 31.39 (q), 32.50 (t), 49.11 (d), 53.52 (s), 54.9 (q), 63.04 (t), 79.03 (d), 109.76 (d), 126.01 (s), 126.21 (d), 130.57 (d), 135.05 (s), 155.53 (s). Mass (*m/z*): 250 (M^+, 11), 232 (5), 217 (5), 189 (10), 175 (12), 149 (100), 135 (8), 115 (9), 91 (15), 77 (6). HRMS: M^+, found 250.1573. $C_{14}H_{16}O_3$ requires 250.1569.

4.1.4. Xanthate derivative [12]. To an ice-cold solution of the diol **11** (1.53 g, 6.12 mmol.), Et_3N (1.55 g, 2.12 mL, 15.3 mmol) and DMAP (catalytic) in dry DCM (45 mL) was added pivaloyl chloride (0.886 g, 0.9 mL, 7.35 mmol) dropwise. The reaction mixture was stirred at 0°C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (2×20 mL), brine (20 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to yield crude pivoloate ester. Column chromatography on silica gel (60–120 mesh, eluent: ethyl acetate–petroleum ether 12:88) yielded pure pivaloate ester as colorless oil. Yield 1.67 g. (84%). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3020, 2970, 1717, 1506, 1480, 1290, 1254, 1160, 765, 668. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.18 (s, 9H), 1.33 (s, 3H), 1.77–2.11 (m, 3H), 2.15–2.42 (m, 2H), 2.22 (s, 3H), 3.81 (s, 3H), 3.84 (dd, 1H, J=9.3, 11.3 Hz), 4.15 (m, 2H), 6.80 (d, 1H, J= 8.8 Hz), 7.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 16.19 (q), 25.49 (t), 27.00 (q, 3×–CH3), 28.83 (q), 31.44 (t), 38.47 (s), 46.92 (d), 52.69 (s), 55.04 (q), 66.36 (t), 80.59 (d), 110.03 (d), 126.46 (d), 130.43 (d), 132.86 (s), 156.05 (s), 178.15 (s). Mass (*m/z*): 334 (M^+, 8), 232 (10), 217 (7), 199 (4), 189 (14), 175 (21), 162 (9), 149 (100), 135 (9), 115 (7), 91 (10), 77 (6).

The xanthate derivative **12** was prepared by using general literature method. NaH (60% dispersion in oil, 0.3 g., 7.5 mmol) was successively washed with dry hexane under an inert atmosphere. To this, pivaloate ester (1.67 g, 5 mmol) in dry THF (16 mL) was added dropwise. The reaction mixture was stirred at room temperature for 3 h, then carbon disulphide (4 mL) was added dropwise. The reaction mixture was stirred further for 3 h, methyl iodide (2.13 g, 15 mmol) in dry THF (4 mL) was added. The reaction mixture was stirred for an additional 16 h at room temperature. The reaction was monitored by TLC. After the completion of the reaction, THF was removed under reduced pressure. The residue was extracted with ethyl acetate (2×30 mL). The organic layer was washed with water (2×15 mL), brine (15 mL), dried over anhydrous sodium sulphate, filtered, concentrated in vacuum to furnish crude xanthate derivative **12**. Column chromatography on silica gel (60–120 mesh, eluent: ethyl acetate–petroleum ether 3:97) furnished xanthate **12** as colorless oil.

Yield 1.817 g (86%) IR ($CHCl_3$) ν_{max} (cm^{-1}): 3020, 1716, 1505, 1215, 1160, 770, 670. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.21 (s, 9H), 1.34 (s, 3H), 1.84–2.18 (m, 3H), 2.21 (s, 3H), 2.31 (s, 3H), 2.48–2.66 (m, 2H), 3.81 (s, 3H), 3.82–3.96 (m, 1H), 4.24–4.28 (m, 1H), 5.98–6.02 (m, 1H), 6.76 (d, 1H, J=8 Hz), 6.98–7.02 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 17.09 (q), 19.13 (q), 20.21 (t), 27.98 (q, 3×CH_3), 30.49 (t), 31.16 (q), 39.46 (s), 47.82 (d), 53.86 (s), 55.94 (q), 66.99 (t), 91.83 (d), 110.51 (d), 120.62 (d), 126.72 (s), 130.90 (d), 134.31 (s), 156.72 (s), 179.06 (s), 215.13 (s).

Mass (*m*/*z*): 424 (6), 316 (4), 231 (4), 215 (100), 199 (18), 187 (15), 173 (17), 135 (28), 91 (26), 77 (7).

4.1.5. Pivaloate ester [13]. This pivaloate ester was obtained by deoxygenation of xanthate derivative **12**. Thus a mixture of xanthate derivative **12** (1.812 g, 4.27 mmol), tri-*n*-butyltinhydride (6.22 g, 5.66 mL, 21.37 mmol) and AIBN (catalytic) in dry toluene was refluxed for 3 h. The reaction mixture was cooled to room temperature and the reaction mixture was diluted with ethyl acetate (50 mL). The excess of tri-*n*-butyltinhydride was destroyed by aqueous KF (10% solution, 20 mL). The organic layer was successively washed with aqueous KF (10%, 3×20 mL), water (2×20 mL), brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated in vacuum to furnish crude pivaloate ester. Column chromatography on silica gel (60–120 mesh, eluent: ethyl actetate–petroleum ether 1:99) furnished the pure pivaloate ester **13**. Yield 1.11 g (83%). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3020, 1713, 1605, 1508, 1215, 1160, 770, 670. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.17 (s, 9H), 1.37 (s, 3H), 1.44–2.08 (m, 4H), 2.12–2.20 (m, 3H), 2.21 (s, 3H), 3.48 (dd, 1H, *J*=8.6, 2.5 Hz), 3.72 (dd, 1H, *J*=*J*=5.5 Hz), 3.81 (s, 3H), 6.74 (d, 1H, *J*=8 Hz), 7.05–7.09 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 16.14 (q), 21.65 (t), 26.91 (q, 3×CH_3), 27.1 (t), 29.70 (q), 37.64 (d), 37.76 (s), 47.75 (s), 48.63 (d), 54.96 (q), 66.20 (t), 109.32 (d), 124.80 (d), 125.57 (s), 129.10 (d), 137.73 (s), 155.60 (s), 178.17 (s). HRMS: M^+, found 318.2193. $C_{20}H_{30}O_3$ requires 318.2195.

4.1.6. 2-(4-Methoxy-3-methylphenyl)-2-methylcyclopentane-1-carbaldehyde [14]. $LiAlH_4$ (0.266 g, 7 mmol) was added to THF solution (25 mL) of pivaloate ester **13** (1.11 g, 3.5 mmol) and stirred at room temperature. The reaction was slightly exothermic and was monitored by TLC. After the completion of reaction, THF was removed under reduced pressure and the residue was extracted with diethyl ether (3×25 mL). The organic layer was washed with dilute HCl (5%, 20 mL), water (3×25 mL), brine (30 mL) dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to yield crude alcohol. The column chromatography on silica gel (60–120 mesh, eluent ethyl acetate–petroleum ether 12:88) furnished the pure product as colorless oil.

Yield 0.726 g. (92%). IR ($CHCl_3$) ν_{max} (cm^{-1}): 3450 (broad), 3020, 2910, 1205, 1160, 770, 668. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.34 (s, 3H), 1.61–1.72 (m, 2H), 1.74–1.99 (m, 3H), 2.02–2.18 (m, 2H), 2.22 (s, 3H), 3.02–3.15 (m, 1H), 3.26–3.39 (m, 1H), 3.82 (s, 3H), 6.76 (d, 1H, *J*=8 Hz), 7.06–7.12 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): 16.21 (q), 21.73 (t), 27.18 (t), 29.85 (q), 37.39 (t), 47.71 (s), 51.92 (d), 54.99 (q), 64.37 (t), 109.32 (d), 124.70 (d), 125.68 (s), 129.11 (d), 139.43 (s), 155.56 (s).

To an ice-cold solution of primary alcohol (0.421 g, 1.78 mmol) in dry dichloromethane (20 mL), pyridinium chlorochromate (0.578 g, 2.67 mmol) was added in a single portion. As the reaction proceeds, the orange colored reaction mixture turned black. The reaction was monitored by TLC. After completion of the reaction, diethyl ether (30 mL) was added in order to precipitate out chromous salts, filtered through a short bed of celite. The filtrate was successively washed with water (3×20 mL), brine (2×20 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under vacuum to yield aldehyde **14**.

Yield 0.359 g (86%). IR ($CHCl_3$) ν_{max} (cm^{-1}): 2960, 1703, 1611, 1505, 1250, 771, 670. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.36 (s, 3H), 1.90–2.15 (m, 6H), 2.21 (s, 3H), 2.80–2.85 (m, 1H), 3.81 (s, 3H) 6.76 (d, 1H, *J*=8 Hz), 7.05–7.08 (m, 2H),9.17 (d, 1H, *J*=4 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 15.64 (q), 21.78 (t), 24.57 (t), 29.79 (q), 36.85 (t), 48.69 (s), 54.53 (q), 60.71 (d), 109.12 (d), 124.33 (d), 125.73 (s), 128.56 (d), 136.72 (s), 155.39 (s), 203.73 (d). Mass (*m*/*z*): 232 (M^+, 12), 189 (14), 175 (100), 162 (78), 147 (32), 137 (17), 115 (21), 105 (15), 91 (48), 77 (34).

4.1.7. 1-Methyl-2-(4-methoxy-3-methylphenyl)-2-methylcyclopentane-1-carbaldehyde [15]. NaH (60% dispersion in oil, 0.070 g, 1.65 mmol) was successively washed with dry *n*-haxane (2×5 mL). To this, aldehyde **14** (0.320 g, 1.38 mmol) in dry DME (10 mL) was added dropwise at −10°C. Hydrogen evolution was induced by warming up the reaction mixture to 0°C, stirred at 0°C for 30 min. Methyl iodide (0.313 g, 2.2 mmol) in dry DME (4 mL) was added dropwise. The reaction mixture was stirred at 0°C for 3 h and then at room temperature for 16 h. Then the reaction mixture was poured into water (5 mL) and extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine and then dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish aldehyde **15**. The column chromatography on silica gel (60–120 mesh, eluent ethyl acetate–petroleum ether 1:99) furnished the pure aldehyde.

Yield 0.220 g (65%). ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.25 (s, 1.5H), 1.31 (s, 1.5H), 1.34 (s, 1.5H), 1.40 (s, 1.5H), 1.56–1.63 (m, 2H), 1.77–1.94 (m, 2H), 2.11–2.41 (m, 2H), 2.21 (s, 3H), 3.81 (s, 3H), 6.76 (d, 1H, *J*=7.86 Hz), 7.09–7.12 (m, 2H), 9.04 (s, 1H).

4.1.8. 1,1-Dimethyl-2-methyl-2-(4-methoxy-3-methylphenyl)-2-methylcyclopentane [16]. A mixture of **15** (0.2 g,0.81 mmol), hydrazine hydrate (0.285 g, 0.35 mL, 5.69 mmol), NaOH (0.287 g, 7.15 mmol) and triethylene glycol (5 mL) was heated at 195°C (oil bath temperature) for 7 h. After cooling to room temperature, water (5 mL) was added and the mixture extracted with diethyl ether (4×20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous sodium sulphate, filtered and concentrated to furnish compound **16**. Column chromatography on silica gel (60–120 mesh, eluent: ethyl acetate–petroleum ether 1:99) furnished the pure product **16**.

Yield 98 mg (52%). ^1H NMR ($CDCl_3$, 200 MHz) δ:0.59 (s, 3H), 1.08 (s, 3H), 1.27 (s, 3H), 1.53–1.86 (m, 5H), 2.25 (s, 3H), 2.43–2.60 (m, 1H), 3.84 (s, 3H) 6.76 (d, 1H, *J*=7.9 Hz), 7.14–7.18 (m, 2H) ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 16.74 (q), 19.90 (t), 24.46 (q), 24.68 (q), 26.70 (q), 37.14 (t), 39.94 (t), 44.39 (s), 50.08 (s), 55.34 (q), 109.12 (d), 125.29 (d), 129.75 (d), 139.40 (s), 155.73 (s).

4.1.9. (±)-β-Herbertenol [5]. BBr_3 (1 M solution in

CH_2Cl_2, 0.251 g, ~1 mL, 1 mmol) was added dropwise to methyl ether **16** (45 mg, 0.19 mmol) in dry CH_2Cl_2 (5 mL) at −78°C. The reaction mixture was brought to room temperature and stirred for 30 min. The reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and excess of BBr_3 was quenched with saturated $NaHCO_3$ (1 mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure to furnish crude (±)-β-herbertenol **5**. It was purified by column chromatography (SiO_2) (eluent: ethyl acetate–pet. ether 5:95).

Yield 34 mg (81%). Mp 85–86°C (84°C)[6] IR ($CHCl_3$) ν_{max} (cm^{-1}): 3450 (broad), 3020, 2960, 1610, 1215, 1106, 766, 670. ^1H NMR ($CDCl_3$, 200 MHz) δ: 0.58 (s, 3H), 1.06 (s, 3H), 1.25 (s, 3H), 1.48–1.52 (m, 1H), 1.56–1.73 (m, 2H), 1.73–1.84 (m, 2H), 2.27 (s, 3H), 2.39–2.53 (m, 1H), 4.75 (bs, 1H), 6.72 (d, 1H, J=7.9 Hz), 7.05–7.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 16.29 (q), 20.02 (t), 24.57 (q), 24.84 (q), 26.79 (q), 37.32 (t), 40.13 (t), 44.49 (s), 50.26 (s), 114.29 (d), 122.59 (s), 125.92 (d), 129.98 (d), 140.20 (s), 151.77 (s). Mass (*m/z*): 218 (M^+, 24), 161 (52), 148 (100), 135 (48), 121 (23), 91 (21), 77 (22), 55 (27). HRMS: M^+, found 218.1669. $C_{20}H_{30}O_3$ requires 218.1671.

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