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First enantiospecific synthesis of (+)-β-herbertenol

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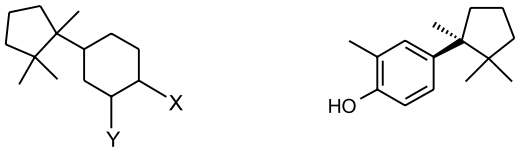
Abstract—The first enantiospecific synthesis of (+)-β-herbertenol, from naturally occurring *R*-(+)-citronellal, employing Taber's diazo decomposition protocol as the key step, is described.

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] Recently, Asakawa and co-workers reported the isolation of seven new herbertanes and two new cuperanes from Japanese liverworts.[3] Many of these compounds, particularly those with an oxygenated aromatic six membered ring, show a wide spectrum of biological properties, which include potent antifungal, neurotrophic and anti-lipid peroxidation activities (Fig. 1).[1a,b,4,5]



X= H, Y= Me; Herbertene skeleton (**1**)

X= Me, Y= H; Cuparene skeleton (**2**)

(-)-β-Herbertenol (**3**)

Figure 1. Herbertene and cuparene skeleton.

Because of the difficulties associated with the construction of the vicinal quaternary carbons in the cyclopentane ring, herbertanes and cuparanes have become popular synthetic targets in recent years.[6] Although, there are synthetic strategies reported towards (±)-β-herbertenol, not a single asymmetric synthesis is reported. Our interest in these skeletons has led to the synthesis of cuparenones[6i,j] and recently in the facile synthesis of (±)-β-herbertenol.[6k] In continuation of our efforts towards the synthesis of homochiral β-herbertenol, we describe herein the first enantiospecific synthesis of (+)-β-herbertenol.

2. Results and discussion

The idea central to our synthetic route is to make use of naturally occurring chiral citronellal for asymmetric synthesis of β-herbertenol using Taber's protocol of diazo decomposition of α-diazo-β-ketoester **8** by $Rh_2(OAc)_4$ to provide the five membered ring with retention of configuration at the chiral center.[7,8]

To investigate the idea, *R*-(+)-citronellal was converted into α-diazo-β-ketoester **8** as depicted in Scheme 1. Enone **4a** was synthesized from *R*-(+)-citronellal.[9] It was then converted into its silyl enol ether using LDA as base,[10] and the resultant silyl enol ether was treated with NBS[11] to give the corresponding haloderivative **4b** as a mixture of diastereomers, and as we were going to destroy the centers during aromatization in the next step, we did not establish the diastereomeric ratio. Thus, the halo derivative **4b** on dehydrohalogenation[12] provided the phenol **5a** in 75% overall yield. The phenol thus obtained was then protected as methyl ether **5b** and converted into acid **6**, by Weinreb's method.[13] Acid **6** was then converted into β-ketoester **7** using Meldrum's acid in 78% yield. Diazotransfer was carried out by Regitz's protocol to give α-diazo-β-ketoester **8**.[14] The crucial insertion reaction was performed on **8** using rhodium catalyzed cyclization to furnish cyclized β-ketoester **9** as a diastereomeric mixture in 40% overall yield starting from **7**. Having secured the key

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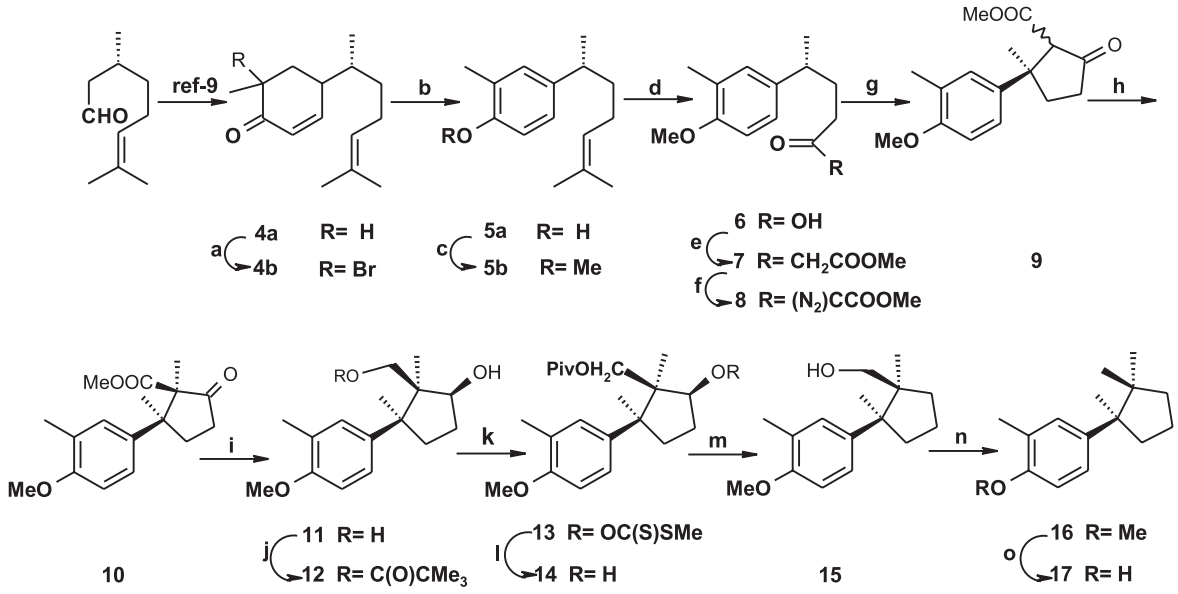

Scheme 1. Reagents and conditions: (a) (i) LDA, THF, −78 °C, TMSCl; (ii) NBS, THF, 0 °C, 0.5 h; (b) Li_2CO_3, LiBr, DMF, 135 °C, 4 h, 75% from **4a**; (c) K_2CO_3, Me_2SO_4, acetone, reflux, 12 h, 90%; (d) OsO_4 (cat), Jones' reagent, acetone, rt, 5 h, 80%; e) (i) $SOCl_2$, CH_2Cl_2, reflux, 2 h; (ii) Meldrum's acid, pyridine, CH_2Cl_2, 0 °C–rt, 2 h; (iii) MeOH, reflux, 4 h, 78%; (f) Et_3N, MsN_3, CH_2Cl_2, −10 °C–rt, overnight; (g) $Rh_2(OAc)_4$ (cat.), CH_2Cl_2, rt, 40% for 2 steps; (h) K_2CO_3, MeI, acetone, rt, 85%; (i) LAH, THF, 0 °C–rt, 5 h, 80%; (j) Pivaloyl chloride, Et_3N, CH_2Cl_2, −10 °C–rt, 4 h, 65%; (k) NaH, CS_2, THF, 0 °C, 1.5 h, then MeI, rt, 5 h, 95%; (l) TBTH, AIBN (cat), toluene, reflux, 2 h, 80%; (m) LAH, THF, rt, 2 h, 95%; (n) (i) PDC, CH_2Cl_2, 0 °C, 3 h; (ii) NH_2NH_2–H_2O, diethyleneglycol, 150 °C, 4 h, 190 °C, 3 h, 73% for 2 steps; (o) BBr_3, CH_2Cl_2, −78 °C–rt, overnight, 93%.

cyclopentanone in place, the remaining problem was to convert **9** into the geminal dialkylated cyclopentane skeleton. Accordingly, ester **9** was methylated using K_2CO_3, MeI in dry acetone, which gave single diasteteomer **10** in which methyl group and the aryl group on the adjacent quaternary carbon are anti to each other. The ^{1}H NMR spectrum of the compound **10** support this, in which the ester methyl signal appeared at 3.33 ppm because of the shielding of methoxy carbonyl group by the vicinal *cis* aryl group. The β-ketoester **10** was then reduced using LAH to the corresponding diol **11** as a single diastereomer. The stereochemistry of compound **11** was deduced by X-ray analysis of the racemic alcohol diol **11** (Fig. 2). The X-ray structure not only confirms the relative configuration of newly generated hydroxy group in **11**, but also the relative stereochemistry of methyl group in **10**. The primary alcohol of diol **11** was protected as a pivaloyl ester to give **12**. The secondary alcohol group was then deoxygenated by employing Barton's protocol[15] to give pivaloyl ester **14**, which on reduction using LAH gave the corresponding alcohol **15**. This alcohol was then oxidized to the corresponding aldehyde using PDC, followed by deoxygenation under Huang–Minlon conditions to give the methyl ether of β-herbertenol **16**, which on deprotection using BBr_3 gave the final product, that is, (+)-β-herbertenol **17**.

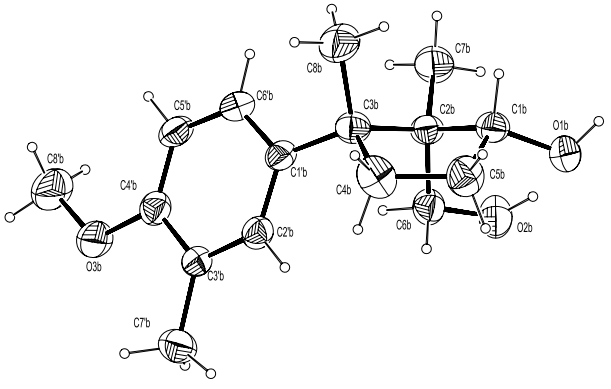

Figure 2. ORTEP view of *rac*-**11**.

3. Conclusion

Thus, (+)-β-herbertenol has been synthesized from naturally occurring *R*-(+)-citronellal employing carbene insertion as the key step. The same idea can be applicable to the synthesis of naturally occurring (−)-β-herbertenol and other herbertanes.

4. Experimental

4.1. General methods

All solvents were freshly distilled before use and dry solvents were distilled under argon from Na/benzophenone. Melting points are uncorrected. Chemical shifts in ^{1}H and ^{13}C NMR are reported relative to residual solvents. Abbreviations for ^{1}H NMR: s=singlet, d=doublet, m=multiplet. Progress of the reactions were monitored by TLC using Merck silica gel 60 F_{254} precoated plates and visualized by flourescence quenching or by charring after treatment with the mixture of *p*-anisaldehyde-H_2SO_4 in ethanol. The products were purified by column chromatography (SiO_2). Analytical data of all known compounds were compared with the literature, and new compounds were fully characterized.

4.1.1. 6-Bromo-4-(1,5-dimethyl-hex-4-enyl)-6-methyl-cyclohex-2-enone (4b). A 1 L round bottomed flask equipped with a magnetic stir bar and a condenser was charged with diisopropylamine (18.01 g, 178 mmol) and dry THF (250 mL) under N_2, and cooled to −78 °C. To this mixture, *n*-BuLi (102.5 mL of a 1.6 M solution in hexane, 164 mmol) was added dropwise and stirred for 10 min, followed by dropwise addition of the conjugated ketone (30 g, 136 mmol) in dry THF (50 mL). Reaction mixture was stirred for 1.5 h at −78 °C and then quenched with chlorotrimethylsilane (16.296 g, 150 mmol). The reaction mixture was allowed to come to 0 °C within 4 h and quenched with saturated $NaHCO_3$ solution (200 mL). The mixture was extracted with pet ether (250 mL×3) and combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated to give 38 g of crude silyl enol ether, which was confirmed by ^{1}H NMR and used directly for the next step. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.15 (s, 9H), 0.84–0.89 (m, 3H), 1.17–1.36 (m, 3H), 1.58 (s, 3H), 1.62 (s, 3H), 1.66 (s, 3H), 1.90–2.08 (m, 4H), 2.21–2.26 (m, 1H), 5.06 (t, J=6.4 Hz, 1H), 5.45–5.53 (m, 1H), 5.60–5.66 (m, 1H).

To an ice-cold solution of crude silyl enol ether (38 g) in dry THF (300 mL) was added *N*-bromosuccinimide (26.7 g, 150 mmol) portionwise and reaction mixture was stirred for 30 min at 0 °C and quenched with saturated $NaHCO_3$ solution (300 mL). The reaction mixture was then extracted with pet. ether (300 mL×2) and combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated to give 37 g of crude α-bromo enone **4b**, which was directly used for the dehydrohalogenation. IR (neat) ν_{max} (cm^{-1}): 2964, 1688, 1504, 1446, 1377, 1259.^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.84 (d, J=7.33 Hz, 1.5H), 0.87 (d, J=7.33 Hz, 1.5H), 1.16–1.40 (m, 2H), 1.56 (s, 3H), 1.63 (s, 3H), 1.71–1.78 (m, 2H), 1.81 (s, 3H), 1.89–2.05 (m, 2H), 2.14–2.27 (m, 1H), 2.60–2.74 (m, 1H), 5.02 (t, J=6.8 Hz, 1H), 5.92–5.99 (m, 1H), 6.69–6.78 (m, 1H). MS-ESI *m/z* 301 $(M+2)^+$. Anal. Calcd for $C_{15}H_{23}BrO$: C, 60.21%; H, 7.75%. Found: C, 60.47%; H, 7.49%.

4.1.2. 4-(1,5-Dimethyl-hex-4-enyl)-2-methyl-phenol (5a). To a solution of crude α-bromo enone in dry DMF (300 mL) under N_2 was added lithium carbonate (30.23 g, 409 mmol) and lithium bromide (23.69 g, 273 mmol) and the mixture was stirred at 130–135 °C for 3 h. The mixture was allowed to come to room temperature and DMF was removed under reduced pressure. The residue was diluted with water (300 mL) and extracted with CH_2Cl_2 (300 mL×3). The combined organic layer was washed with water (600 mL×2) and brine solution (600 mL×1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was chromatographed using flash silica gel (pet. ether: EtOAc 96:4 as eluent) to provide phenol **5a** (22.2 g, 75% overall) as colorless oil. $[\alpha]_D^{25}$=−39.1 (c=0.92, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3416, 2961, 1611, 1509, 1453, 1260. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19 (d, J=6.8 Hz, 3H), 1.52 (s, 3H), 1.49–1.60 (m, 2H), 1.67 (s, 3H), 1.80–1.88 (m, 2H), 2.23 (s, 3H), 2.58 (m, 1H), 5.07 (t, J=5.9 Hz, 1H), 6.66 (d, J=7.8 Hz, 1H), 6.87–6.92 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.1 (CH_3), 17.9 (CH_3), 22.9 (CH_3), 25.9 (CH_3), 26.5 (CH_2), 38.9 (CH), 38.9 (CH_2), 115.1 (CH), 123.8 (CH), 125.0 (CH), 125.6 (C), 129.9 (CH), 131.4 (C), 140.1 (C), 151.9 (C). MS-ESI *m/z* 218 (M^+). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52%; H, 10.16%. Found: C, 82.31%; H, 10.19%.

4.1.3. 4-(1,5-Dimethyl-hex-4-enyl)-1-methoxy-2-methyl-benzene (5b). To a stirred solution of phenol (**5a**) (21 g, 96 mmol) in dry acetone (200 mL) was added anhydrous K_2CO_3 (33.28 g, 241 mmol) and dimethyl sulphate (30.38 g, 241 mmol) under N_2. The mixture was refluxed for 12 h and then acetone was removed under reduced pressure followed by dilution with water. The mixture was stirred overnight and then extracted with CH_2Cl_2 (200 mL×3). The combined organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet. ether/EtOAc 99:1 as eluent to provide the methyl ether **5b** (20.2 g, 90%) as colorless oil. $[\alpha]_D^{25}$=−44.2 (c=1.3, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 2957, 1609, 1505, 1463, 1376, 1251, 1135. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, J=6.8 Hz, 3H), 1.50–1.60 (m, 2H), 1.55 (s, 3H), 1.70 (s, 3H), 1.83–1.94 (m, 2H), 2.23 (s, 3H), 2.60 (m, 1H), 3.80 (s, 3H), 5.10 (t, J=5.9 Hz, 1H), 6.74 (d, J=8.8 Hz, 1H), 6.94–6.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.6 (CH_3), 17.9 (CH_3), 22.9 (CH_3), 26.0 (CH_3), 26.5 (CH_2), 38.9 (CH), 38.9 (CH_2), 55.4 (CH_3), 110.0 (CH), 125.1 (CH) 125.2 (CH), 126.5 (C), 129.7 (CH), 131.3 (C), 139.5 (C), 156.2 (C). MS-ESI *m/z* 231 $(M-1)^+$. Anal. Calcd for $C_{16}H_{24}O$: C, 82.71%; H, 10.41%. Found: C, 82.58%; H, 10.80%.

4.1.4. 4-(4-Methoxy-3-methyl-phenyl)-pentanoicacid (6). A 500 mL round bottomed flask equipped with magnetic stir bar and 100 mL addition funnel was charged with olefin **5b** (16.34 g, 70.4 mmol) and acetone (200 mL). The mixture was cooled to 0 °C and catalytic amount of OsO_4 (2 mL of 1% solution in toluene) was added to it, which was stirred for 15 min followed by dropwise addition of Jones' reagent (94 mL). The reaction mixture was stirred at room temperature for 5 h before excess of Jones' reagent was quenched by isopropanol (15 mL). Acetone was removed under reduced pressure followed by dilution with water and extraction with CH_2Cl_2 (150 mL×3). The combined organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by flash column chromatography using pet. ether/EtOAc 9:1 as eluent to give acid **6** (12.5 g, 80%) as colorless oil. $[\alpha]_D^{25}$=−19.5 (c=0.8, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 2957, 1709, 1610, 1507, 1456, 1377, 1252, 1182. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.27 (d, J=6.9 Hz, 3H), 1.84–1.97 (m, 2H), 2.23 (s, 3H), 2.24–2.26 (m, 2H), 2.67 (m, 1H), 3.82 (s, 3H), 6.75 (d, J=8.2 Hz, 1H), 6.95–6.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.5 (CH_3), 22.8 (CH_3), 32.6 (CH_2), 33.4 (CH_2), 38.8 (CH), 55.5 (CH_3), 110.1 (CH), 125.3 (CH), 126.8 (C), 129.5 (CH), 137.9 (C), 156.5 (C), 180.6 (C). MS-ESI *m/z* 221 $(M-1)^+$. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24%; H, 8.16%. Found: C, 70.44%; H, 8.33%.

4.1.5. 6-(4-Methoxy-3-methyl-phenyl)-3-oxo-heptanoic-acidmethylester (7). To a solution of acid (**6**) (14 g, 63 mmol) in dry CH_2Cl_2 (150 mL) was added thionyl chloride (9 g, 75.6 mmol) and catalytic amount of DMF

(0.5 mL), under N_2. The reaction mixture was refluxed for 2 h and then CH_2Cl_2 was removed at atmospheric pressure. To remove the excess of thionyl chloride, dry benzene (25 mL) was added to the residue and distilled off under reduced pressure. The residue was as such used for the next step.

A 500 mL round-bottomed flask equipped with stir bar was charged with Meldrum's acid (9.54 g, 66.3 mmol) and dry CH_2Cl_2 (150 mL) under N_2. The mixture was cooled to −5 °C and pyridine (12.46 g, 158 mmol) was added to it. After stirring for 30 min at 0 °C, acid chloride in dry CH_2Cl_2 (20 mL) was added dropwise to it. The mixture was stirred at 0 °C for 1 h and at room temperature for an additional hour followed by dilution with CH_2Cl_2. The reaction mixture was poured to 2 N HCl solution (175 mL) containing crushed ice and aqueous layer was extracted with CH_2Cl_2 (150 mL×2). The combined organic layer was washed with 2 N HCl solution, water and finally with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude acyl meldrum derivative, which was taken in dry methanol (300 mL) and refluxed for 4–5 h. Methanol was concentrated under reduced pressure and residue was chromatographed using flash silica gel (pet. ether/EtOAc 92:8 as eluent) to give β-keto ester (13.67 g, 78%) as yellow oil. $[\alpha]_D^{25} = -19.9$ ($c=1.95$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 2955, 1747, 1718, 1505, 1453, 1306, 1252. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23 (d, $J=6.2$ Hz, 3H), 1.69–2.12 (m, 2H), 2.30–2.54 (m, 2H), 2.18 (s, 3H), 2.56–2.66 (m, 1H), 3.33 (s, 2H), 3.69 (s, 3H), 3.79 (s, 3H), 6.74 (d, $J=8.8$ Hz, 1H), 6.89–6.92 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3 (CH_3), 22.7 (CH_3), 31.7 (CH_2), 38.3 (CH), 41.1 (CH_2), 48.8 (CH_2), 51.9 (CH_3), 55.0 (CH_3), 109.7 (CH), 124.9 (CH), 126.3 (C), 129.1 (CH), 137.7 (C), 158.1 (C), 167.4 (C), 202.3 (C). MS-ESI *m/z* 279 $(M+1)^+$. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04%; H, 7.97%. Found: C, 69.04%; H, 8.16%.

4.1.6. 2-(4-Methoxy-3-methyl-phenyl)-2-methyl-5-oxo-cyclopentanecarboxylic acid methylester (9). A 500 mL round-bottomed flask equipped with a magnetic stir bar was charged with ketoester (**7**) (9 g, 32.37 mmol) in dry CH_2Cl_2 (175 mL) and triethylamine (8.19 g, 80.9 mmol). The reaction mixture was cooled to −5 °C and mesyl azide (4.7 g, 38.8 mmol) in CH_2Cl_2 (25 mL) was added, dropwise. The reaction mixture was stirred overnight at room temperature, cooled to 0 °C and quenched with 5 M NaOH solution (100 mL); and extracted using CH_2Cl_2 (100 mL×2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product, α-diazo-β-keto ester, was purified by filtering it through a short pad of silica gel using pet. ether/EtOAc 9:1 as eluent and confirmed by IR. IR (neat) ν_{max} (cm^{-1}): 2956, 2136, 1724, 1656, 1616, 1506, 1375, 1252, 1136.

The oil was transferred to a flame dried 1 L round-bottomed flask equipped with a magnetic stir bar and maintained under N_2. CH_2Cl_2 (500 mL), dried by filtering through anhydrous K_2CO_3 was added, followed by rhodium (II) acetate dimer (0.150 g, 2% by weight). The reaction mixture was stirred at room temperature until evolution of nitrogen ceased (30 min). The reaction mixture was concentrated in vacuo and product was purified by flash column chromatography using pet. ether/EtOAc 93:7 as eluent to give cyclized β-keto ester (**9**) (3.13 g, 40% yield) as colorless oil. IR (neat) ν_{max} (cm^{-1}): 2954, 1758, 1728, 1652, 1612, 1508, 1444, 1347, 1252, 1147. HRMS: M+, $C_{16}H_{20}O_4$ requires 276.1361, found 276.1363. As this product was unstable, it was used immediately for the next step.

4.1.7. 2-(4-Methoxy-3methyl-phenyl)-1,2-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester (10). To a solution of β-keto ester **9** (1.5 g, 5.44 mmol) in dry acetone (20 mL) was added anhydrous K_2CO_3 (0.751 g, 5.44 mmol), followed by iodomethane (0.41 mL, 6.52 mmol) under N_2 at 20 °C and reaction mixture was stirred at room temperature for 24 h. Reaction mixture was, then, filtered through celite, solvent was evaporated under reduced pressure and residue was then chromatographed using flash silica gel (eluent; pet. ether/EtOAc 94:6) to give the desired product **10** (1.34 g, 85% yield) as colorless oil. $[\alpha]_D^{25} = +126.3$ ($c=0.6$, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 2952, 1745, 1713, 1511, 1454, 1383, 1300, 1253, 1141. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (s, 3H), 1.40 (s, 3H), 1.88–2.80 (m, 4H), 2.22 (s, 3H), 3.33 (s, 3H), 3.82 (s, 3H), 7.01–7.17 (m, 2H), 7.76 (d, $J=7.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.9 (CH_3), 16.6 (CH_3), 25.7 (CH_3), 31.5 (CH_2), 35.7 (CH_2), 49.4 (C), 51.7 (CH_3), 55.1 (CH_3), 64.7 (C), 109.5 (CH), 124.1 (CH), 126.1 (CH), 128.3 (C), 135.9 (C), 156.5 (C), 171.1 (C), 215.5 (C). MS-ESI *m/z* 291 $(M+1)^+$. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.30%; H, 7.64%. Found: C, 70.10%; H, 7.34%.

4.1.8. 2-Hydroxymethyl-3-(4-methoxy-3-methyl-phenyl)2,3-dimethyl-cyclopentandiol (11). A 50 mL two neck round-bottomed flask equipped with magnetic stir bar was charged with LAH (0.328 g, 8.6 mmol) and dry THF (10 mL) under N_2. Reaction mixture was cooled to 0 °C and ketoester **10** was added to it using dry THF (10 mL). It was stirred for additional 5 h at room temperature, cooled to 0 °C and excess of LAH was quenched by dilute HCl solution. THF was evaporated under reduced pressure and aqueous layer was extracted with CH_2Cl_2 (25 mL×3). The combined organic layer was washed with water (50 mL×2), brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet ether/EtOAc 8:2 as eluent to give diol **11** (0.725 g, 80% yield) as white solid. MP 133–134 °C. $[\alpha]_D^{25} = +58.7$ ($c=1.1$, $CHCl_3$); IR ($CHCl_3$) ν_{max} (cm^{-1}): 3625, 3350, 3017, 2966, 1506, 1251. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19 (s, 3H), 1.21 (s, 3H), 1.51–1.80 (m, 2H), 2.20 (s, 3H), 2.63–2.89 (m, 2H), 3.59 (d, $J=11.2$ Hz, 1H), 3.76 (d, $J=11.2$ Hz, 1H), 3.80 (s, 3H), 4.22 (dd, $J=6.4$, 8.8 Hz, 1H), 6.71 (d, $J=9.3$ Hz, 1H), 7.08 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.9 (CH_3), 17.4 (CH_3), 27.0 (CH_3), 30.9 (CH_2), 34.2 (CH_2), 48.9 (C), 50.2 (C), 55.4 (CH_3), 67.6 (CH_2), 82.7 (CH), 109.6 (CH), 125.0 (CH), 126.1 (C), 129.3 (CH), 137.4 (C), 156.2 (C). MS-ESI *m/z* 265 $(M+1)^+$. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69%; H, 9.15%. Found: C, 72.36%; H, 9.01%.

Diffraction analysis of racemic (**11**) *($C_{16}H_{24}O_3$, $M=264.35$).* Single crystal of compound **X** obtained from

ethyl acetate–petroleum ether mixture. X-ray intensity data were collected on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo Kα= 0.71073 Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Crystal data: crystal size, $0.40\times0.19\times0.12$ mm^3; temperature, 293(2) K; crystal system, triclinic; spce group $P1$; $a=7.606(5)$ Å; $b=9.793(6)$ Å; $c=10.946(7)$ Å; $\alpha=103.240(12)°$; $\beta=107.106(11)°$; $\gamma=96.723(15)°$; $V=743.5(8)$ Å^3; $Z=2$; $F(000)=288$; d calc [g cm^{-3}]$=1.181$; μ [mm^{-1}]$=0.080°$; absorption correction, multi-scan; $T_{min}=0.9688$; $T_{max}=0.9905$; reflection collected, 7089; unique reflections, 5082; observed reflections, 3305; index range, $-9\le h\le9$, $-11\le k\le11$, $-12\le l\le12$; R_1 [$I>2\sigma(I)$]$=0.0577$; WR2$=0.1323$; goodness of fit, 1.004; $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})$=-0.155$, 0.160. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-254163. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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4.1.9. 2,2-Dimethyl-propionicacid 5-hydroxy-2-(4-methoxy-3-methyl-phenyl)-1,2-dimethyl-cyclopentylmethyl ester (12). To a solution of diol **11** (0.59 g, 2.24 mmol) in dry CH_2Cl_2 (20 mL) was added triethylamine (0.27 g, 2.68 mmol), followed by cooling to -10 °C and addition of pivaloyl chloride (0.28 g, 2.35 mmol) in dry CH_2Cl_2 (5 mL). Reaction mixture was stirred at 0 °C for 2.5 h and diluted with water (50 mL). The aqueous layer was extracted using CH_2Cl_2 (25 mL×3), the combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet. ether/EtOAc 9:1 as eluent to provide corresponding pivaloyl ester **12** (0.51 g, 65%) as colorless oil. $[\alpha]_D^{25}=+23.54$ ($c=0.9$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 3407, 3018, 2972, 1718, 1608, 1504, 1465, 1288, 1157. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 3H), 1.17 (s, 9H), 1.31 (s, 3H), 1.64–1.78 (m, 2H), 2.18 (s, 3H), 2.33–2.41 (m, 1H), 2.66–2.72 (m, 1H), 3.73 (d, $J=11.5$ Hz, 1H), 3.76 (d, $J=11.5$ Hz, 1H), 3.80 (s, 3H), 4.08 (dd, $J=4.8$, 8.7 Hz, 1H), 6.72 (d, $J=8.4$ Hz, 1H), 7.12–7.15 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.9 (CH_3), 18.5 (CH_3), 27.0 (CH_3), 27.5 (CH_3), 31.7 (CH_2), 35.0 (CH_2), 39.1 (C), 49.3 (C), 51.2 (C), 55.4 (CH_3), 68.0 (CH_2), 81.6 (CH), 109.6 (CH), 125.3 (CH), 126.1 (C), 129.7 (CH), 137.6 (C), 156.3 (C), 178.6 (C). MS-ESI m/z 349 $(M+1)^+$. Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38%; H, 9.26%. Found: C, 72.74%; H, 8.96%.

4.1.10. 2,2-Dimethyl-propionic acid 2-(4-methoxy-3-methyl-phenyl)-1,2-dimethyl-5-methylsulfanylthiocaboxyoxy-cyclopentylmethyl ester (13). A 50 mL two-necked round-bottomed flask equipped with a magnetic stir bar was charged with NaH (60%) (0.12 g, 3 mmol) and dry THF (7 mL). Alcohol (**11**) (0.7 g, 2 mmol) in dry THF (7 mL) was added to it at 0° under N_2 and reaction mixture was stirred for 30 min. Then, carbon disulphide (0.23 g, 3 mmol) was added to it at 0 °C and stirred for 2 h at room temperature followed by addition of iodomethane (0.85 g, 6 mmol) at 0 °C. The reaction mixture was stirred for additional 5 h at room temperature. After completion of reaction, mixture was diluted with ice water and extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet. ether/EtOAc 98:2 as eluent to give xanthate derivative (0.83 g, 94%) as colorless oil. $[\alpha]_D^{25}=+11.4$ ($c=1.6$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 2971, 1725, 1608, 1508, 1479, 1397, 1252, 1151. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.16 (s, 3H), 1.16 (s, 9H), 1.39 (s, 3H), 1.76–1.82 (m, 1H), 1.90–1.96 (m, 1H), 2.19 (s, 3H), 2.30 (s, 3H), 2.55–2.63 (m, 1H), 2.76–2.82 (m, 1H), 3.59 (d, $J=11.1$ Hz, 1H), 3.80 (s, 3H), 3.86 (d, $J=11.1$ Hz, 1H), 5.75 (dd, $J=4.8$, 8.8 Hz, 1H), 6.72 (d, $J=8.3$ Hz, 1H), 7.08–7.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.9 (CH_3), 18.7 (CH_3), 19.0 (CH_3), 26.7 (CH_3), 27.6 (CH_3), 29.6 (CH_2), 36.4 (CH_2), 49.9 (C), 51.3 (C), 55.5 (CH_3), 66.8 (CH_2), 92.2 (CH), 109.6 (CH), 116.4 (C), 125.7 (CH), 126.0 (C), 129.9 (CH), 136.7 (C), 156.5 (C), 178.2 (C), 215.1 (C). MS-ESI m/z 440 $(M+2)^+$. Anal. Calcd for $C_{23}H_{34}O_4S_2$. C, 62.97%; H, 7.81%. Found: C, 63.32%; H, 7.53.

4.1.11. 2,2-Dimethyl-propionic acid 2-(4-methoxy-3-methyl-phenyl)-1,2-dimethyl-cyclopentylmethyl ester (14). To a stirred solution of xanthate (**13**) (0.53 g, 1.21 mmol) in dry toluene (20 mL) was added tributyltinhydride (0.39 g, 1.33 mmol) and AIBN (0.020 g, catalytic) under N_2. The mixture was stirred at reflux temperature for 2 h, the solvent was removed under reduced pressure and residue was chromatographed using flash silica gel (pet. ether/EtOAc 98:2 as eluent) to give required product (0.32 g, 80% yield) as colorless oil. $[\alpha]_D^{25}=+16.7$ ($c=1.05$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 2966, 1728, 1608, 1508, 1464, 1382, 1252, 1156. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.11 (s, 3H), 1.17 (s, 9H), 1.34 (s, 3H), 1.48–1.84 (m, 6H), 2.19 (s, 3H), 3.29 (d, $J=11.1$ Hz, 1H), 3.63 (d, $J=11.1$ Hz, 1H), 3.79 (s, 3H), 6.72 (d, $J=9.5$ Hz, 1H), 7.10–7.14 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.9 (CH_3), 19.9 (CH_3), 20.7 (CH_2), 25.5 (CH_3), 27.6 (CH_3), 35.2 (CH_2), 38.3 (CH_2), 39.1 (C), 48.1 (C), 49.9 (C), 55.5 (CH_3), 70.9 (CH_2), 109.6 (CH), 125.3 (CH), 125.9 (C), 129.7 (CH), 137.9 (C), 156.3 (C), 178.5 (C). MS-ESI m/z 231 $(M-OPiv.)^+$. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86%; H, 9.7%. Found; C, 75.46%; H, 9.76%.

4.1.12. [2-(4-Methoxy-3methyl-phenyl)-1,2-dimethyl-cyclopentyl]-methanol (15). To a stirred solution of ester **14** (0.3 g, 0.9 mmol) in dry THF (10 mL) was added LAH (0.69 g, 1.8 mmol) portionwise at room temperature and reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, excess of LAH was quenched with dilute HCl solution, THF was evaporated

under reduced pressure and aqueous layer was extracted using CH_2Cl_2 (30 mL×3). The combined organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet. ether/EtOAc 9:1 as eluent to give alcohol **15** (0.22 g, quantitative yield) as colorless oil. $[\alpha]_D^{25}=42.1$ ($c=0.75$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 3378, 2954, 1608, 1506, 1464, 1376, 1296, 1172. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.14 (s, 3H), 1.30 (s, 3H), 1.48–1.87 (m, 6H), 2.22 (s, 3H), 3.06 (d, $J=11.1$ Hz, 1H), 3.15 (d, $J=11.1$ Hz, 1H), 3.82 (s, 3H), 6.76 (d, $J=8.4$ Hz, 1H), 7.07–7.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.9 (CH_3), 19.7 (CH_3), 20.5 (CH_2), 25.5 (CH_3), 35.2 (CH_2), 37.7 (CH_2), 49.3 (C), 49.4 (C), 55.4 (CH_3), 69.6 (CH_2), 109.6 (CH), 125.1 (CH), 126.1 (C), 129.4 (CH), 138.1 (C), 156.2 (C). MS-ESI *m/z* 230 $(M-H_2O)^+$. Anal. Calcd for $C_{16}H_{24}O_2$. C, 77.38%; H, 9.74%. Found: C, 77.19%; H, 9.58%.

4.1.13. 1-Methoxy-2-methyl-4-(1,2,2-trimethyl-cyclopentyl)-benzene (16). To a stirred solution of alcohol (**15**) (0.1 g, 0.4 mmol) in dry CH_2Cl_2 (10 mL) was added pyridinium dichromate (0.228 g, 0.6 mmol) portionwise at 0 C within 5 min and allowed to stir at room temperature for 3 h. Reaction mixture was then diluted with diethyl ether (25 mL) and filtered through a short pad of celite, which was washed with diethyl ether (25 mL×2). Organic layer was then washed with water and brine solution, dried over sodium sulphate and concentrated. The residue (0.11 g) was directly used for the next step, as aldehyde is unstable. ^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).

To a stirred solution of crude aldehyde in diethylene glycol (4 mL) was added hydrazine monohydrate (0.024 g, 0.48 mmol) and sodium hydroxide (0.355 g, 8.875 mmol) at room temperature and mixture was stirred at 150 °C for 4 h and at 190 °C for additional 3 h. The reaction mixture was diluted with water (25 mL) and extracted using diethyl ether (15 mL×2). The combined organic layer was then washed with water and brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (pet. ether/EtOAc, 99:1 as eluent) to give (**12**) (0.068 g, 73% for 2 steps) as colorless liquid. $[\alpha]_D^{25}=+56$ ($c=1.25$, $CHCl_3$). ^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, $J=7.9$ Hz, 1H), 7.14–7.18 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.8 (CH_3), 19.9 (CH_2), 24.5 (CH_3), 24.9 (CH_3), 26.7, (CH_3), 37.1 (CH_2), 39.9 (CH_2), 44.4 (C), 50.1 (C), 55.3 (CH_3), 109.1 (CH), 125.3 (CH), 129.8 (CH), 139.4 (C), 155.7 (C).

4.1.14. (+)-β-Herbertenol (17). BBr_3 (1 M solution in CH_2Cl_2, 0.251 g, ~1 mL, 1 mmol) was added dropwise to methyl ether **12** (0.045 g, 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 BBr_3 was quenched with saturated $NaHCO_3$ (1 mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated at reduced pressure to furnish crude (+)-β-herbertenol. It was purified by flash column chromatography (pet. ether/EtOAc 95:5 as eluent) to give pure (+)-β-herbertenol. (0.039 g, 93%). MP 79–80 °C. $[\alpha]_D^{25}=+61.2$ ($c=0.7$, $CHCl_3$). IR ($CHCl_3$) ν_{max} (cm^{-1}) 3450 (broad), 3020, 2960, 1610, 1215, 1106. ^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, $J=7.9$ Hz 1H), 7.05–7.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3 (CH_3), 20.0 (CH_2), 24.6 (CH_3), 24.8 (CH_3), 26.8 (CH_3), 37.3 (CH_2), 40.1 (CH_2) 44.5 (C), 50.3 (C), 114.3 (CH), 122.6 (C), 125.9 (CH), 129.9 (CH), 140.2 (C), 151.8 (C). Mass *m/z* 218 (M^+). HRMS: M^+, found 218.1669. $C_{15}H_{22}O$ requires 218.1671. [For (−)-β-herbertenol; MP 80–81 °C and $[\alpha]_D^{25}=-47$ (*c* 0.7, $CHCl_3$)].

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