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First syntheses of 1,13- and 1,15-dihydroxyherbertenes, and herbertenolide by applying intramolecular Heck reaction for the construction of adjacent quaternary centers

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Abstract—1,13- and 1,15-Dihydroxyherbertenes and hebertenolide, typical herbertane-type sesquiterpenes with an oxidized methyl group, were synthesized by using intramolecular Heck reaction for the construction of adjacent quaternary centers.

1. Introduction

Cuparane and herbertane are sesquiterpenes which differ in the substitution pattern of the aromatic ring. Both series of compounds contain two contiguous quaternary carbon centers on a cyclopentane ring. A number of herbertane-type sesquiterpenes have been found in a wide variety of liverworts[1] since (−)-herbertene was first isolated from the liverwort *Herberta adunca*[2] (Fig. 1).

Recently, we reported the isolation of 1,13-, 1,14- and 1,15-dihydroxyherbertenes (**6**, **2** and **3**) and hebertenolide (**5**).[3] The herbetanes such as herbertenediol (**1**)[2] and its dimer mastigophorenes A and B[4] exhibit significant biological activity, e.g. antifungal,[5] antilipidoxidation[6] and neurotrophic activities.[7] The interesting biological properties of the herbertanes and their unique carbon framework have stimulated extensive synthetic efforts from many research groups.[8] In recent years we have developed an enantioselective general approach to the synthesis of herbertane-type sesquiterpenes. This approach, based on intramolecular Heck reaction used for the construction of quaternary carbon centers followed by elaboration of the *geminal* methyl groups, has been successfully used for the preparation of (−)-herbertenediol (**1**),[6] (−)-1,14-dihydroxyherbertene (**2**),[9] mastigophorenes A and B,[9] and (−)-laurequinone.[10] In connection with this related project, we describe the first and efficient syntheses of 1,13- and 1,15-dihydroxyherbetene (**6** and **3**) and herbertenolide (**5**), typical number of herbertenols in which one of three methyl groups on a cyclopentane ring is oxidized.

Our basic plan for the preparation of **3** and **5** and **6** involves two-steps procedure consisting of intramolcular Heck reaction used for the construction of the quaternary carbon centers and interconversion of the ester group to the corresponding methyl and/or hydroxyl groups (Scheme 1).

2. Results and discussion

2.1. Synthesis of 1,15-dihydroxyherbertene (3) and herbertenolide (5)

The C-15 methyl group among three methyls attached on the cyclopentane ring is oxidized in herbertenol **3** and

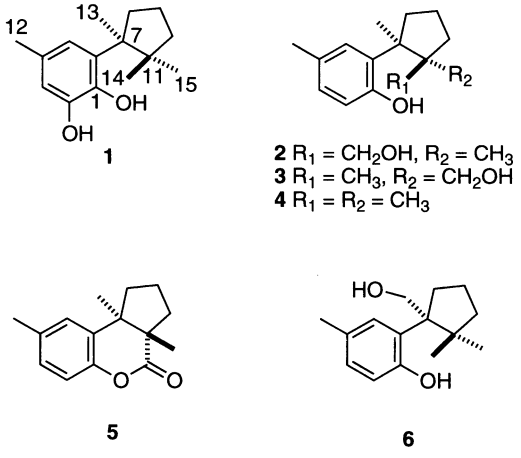

Figure 1.

Keywords: 1,13-dihydroxyherbertene; 1,15-dihydroxyherbertene; hebertenolide; herbertane-type sesquiterpene; Heck reaction; palladium.

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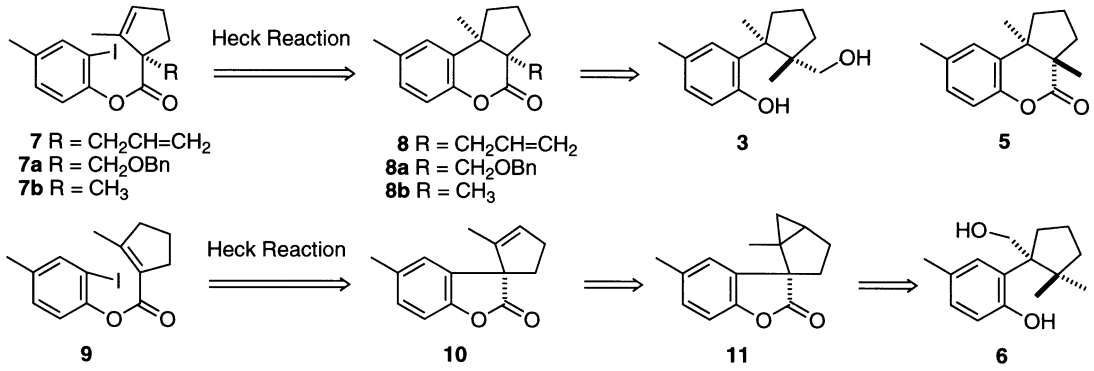
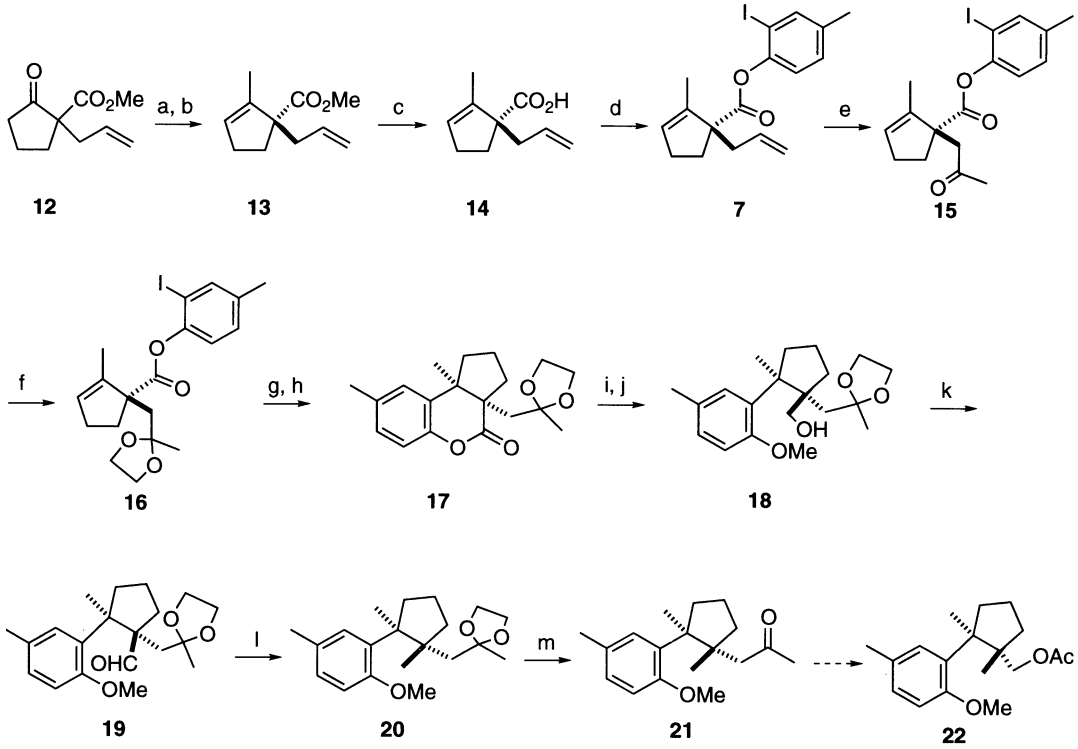


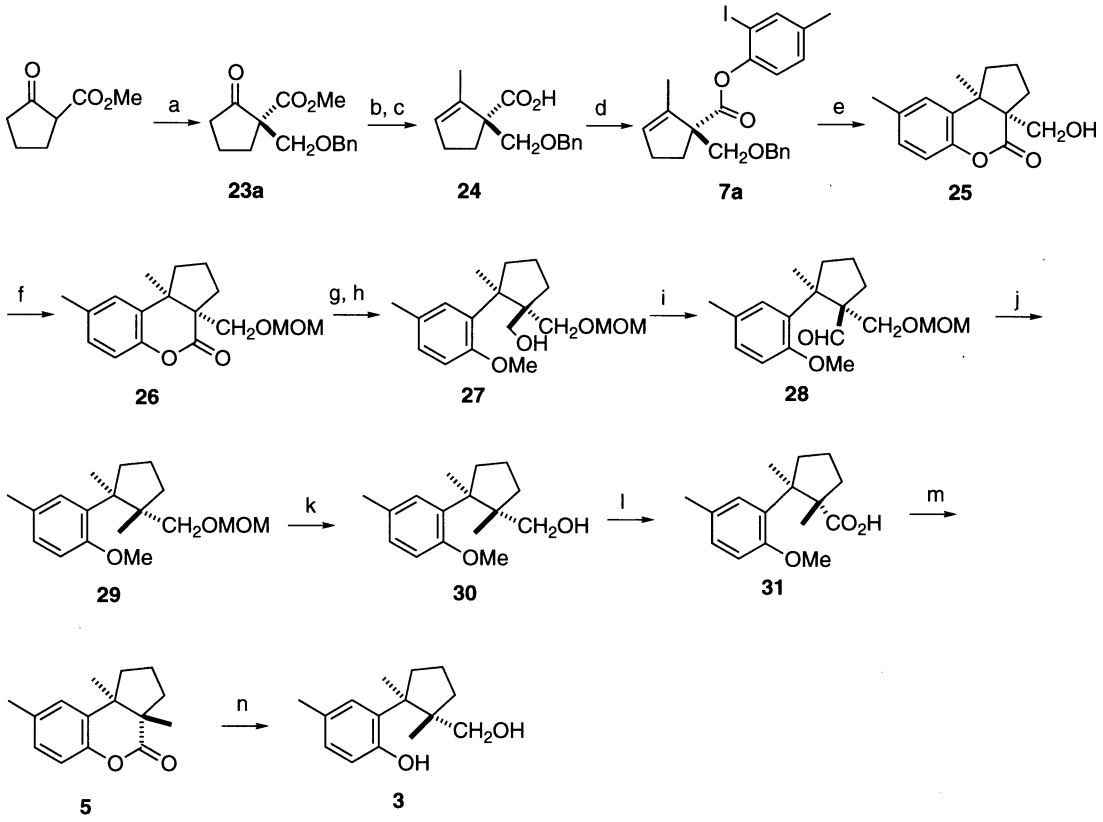
Scheme 1.

herbertenolide **5**. We have envisioned that an allyl group is suitable for later conversion to a hydroxymethyl group after two-steps process involving intramolecular Heck reaction and conversion of the ester group to the C-14 methyl group.

The readily prepared **12** was converted to **13** according to the previously reported procedure.[6,9] The methyl ester in **13** was hydrolyzed to the carboxylic acid, which was coupled with 2-iodo-*p*-cresol under DCC conditons giving rise to an ester **7** in 69% yield. The allyl group in **7** must be transformed to some unreactive functional group before Heck reaction. Thus, Wacker reaction[11] of **7** afforded a methyl ketone, which was protected as an ethylene acetal to give **16** in 56% yield. Intramolecular Heck reaction of **16** was employed under the established condititon[6,9] such as 10 mol% $Pd(OAc)_2$, 20 mol% $(o\text{-tol})_3P$ and $n\text{-Bu}_3N$ in DMF, followed by hydrogenation, giving rise to a δ-lactone **17** in 95% yield. Reduction of **17** with $LiAlH_4$ gave a diol, the phenolic hydroxyl group of which was selectively methylated under the standard basic conditions to afford **18** in 79% yield. Swern oxidation of the primary alcohol in **18** yielded the aldehyde **19**, which was subjected to Huang–Minlon reduction giving rise to **20** in 58% yield over two steps. Subsequent acid treatment of **20** afforded the methyl ketone **21**. The remaining elaboration seems to be simple conversion of the methyl ketone to a primary alcohol by Baeyer–Villiger oxidation. Baeyer–Villiger oxidation of **21**, however, under standard *m*CPBA and



Scheme 2. *Reagents, conditions and yields*: (a) MeMgI, ether, (b) P_2O_5, benzene, 69% over two steps, (c) NaOH, MeOH–H_2O (1:1), 92%, (d) 2-iodo-*p*-cresol, DCC, DMAP, 65%, (e) $PdCl_2$, CuI, O_2, DMF–H_2O (7:1), 56%, (f) ethylene glycol, *p*-TsOH, benzene, 100%, (g) 10 mol% $Pd(OAc)_2$, 20 mol% tris-(2-methylphenyl)phosphine, $n\text{-Bu}_3N$, DMF, 120°C, (h) 10% Pd/C, H_2, EtOH, 95% over two steps. (i) $LiAlH_4$, THF, 0°C, (j) MeI, K_2CO_3, acetone, 79% over two steps, (k) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C and then 0°C, 96%, (l) $NH_2NH_2{\cdot}H_2O$, NaOH, diethylene glycol, 150°C, 59%, (m) 2.5 M HCl, THF, 100%.



Scheme 3. *Reagents, conditions and yields*: (a) 60% NaH, $PhCH_2OCH_2Cl$, toluene, 49%, (b) MeMgI, ether, (c) P_2O_5, benzene, and then NaOH, MeOH–H_2O (1:1), 66% over three steps, (d) 2-iodo-*p*-cresol, DCC, DMAP, CH_2Cl_2, 87%, (e) 10 mol% $Pd(OAc)_2$, 20 mol% dppf, 2 equiv. *n*-Bu_3N, DMF, 120°C, and then 10% Pd/C, H_2, EtOH, 71%, (f) CH_3OCH_2Cl, Et_3N, CH_2Cl_2, 97%, (g) $LiAlH_4$, THF, 0°C, (h) MeI, K_2CO_3, acetone, 89% over two steps, (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78°C and then 0°C, 74%, (j) $NH_2NH_2{\cdot}H_2O$, NaOH, diethylene glycol, 150°C, 76%, (k) 40% HBr, MeOH, 87%, (l) Jones reagent, acetone, 64%, (m) BBr_3, CH_2Cl_2, rt, 46%, (n) $LiAlH_4$, THF, 0°C, 83%.

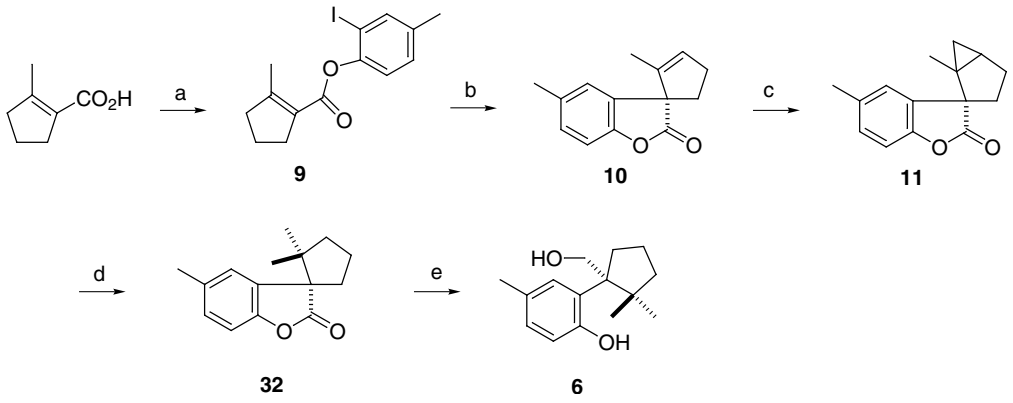
oxone[12] conditions gave no acetate **22**, but totally the recovery presumably due to the hindered neopentyl position of the corresponding methylene (Scheme 2).

We have decided that the hydoxymethyl group should be introduced before intramolecular Heck reaction. Alkylation of methyl 2-cyclopentanonecarboxylate with allyl bromide using NaH as base in THF as solvent gave the C-alkylated product **12** quantitatively, whereas alkylation using benzyloxymethyl chloride as an electrophile under the same basic conditions gave exclusively an O-alkylated product.[13] After several attempts, toluene was found to be only solvent for effecting the C-alkylation. Thus, the requisite **23a** (49%) was obtained along with the O-alkylated product **23b** (41%) from the reaction of methyl 2-cyclopentanonecarboxylate with NaH in toluene followed by adding benzyloxymethyl chloride. With **23a** in hand, similar procedures used for **12** were applied to the synthesis of **3**. At first, **23a** was converted to the carboxylic acid **24** in 66% yield over three steps, and then **24** was coupled with 2-iodo-*p*-cresol by DCC method to give **7a** in 78% yield. Intramolecular Heck reaction of **7a**, followed by hydrogenation, smoothly proceeded to afford the lactone **25** in 71% yield. The liberated hydroxyl group was protected again as a MOM ether and then the $LiAlH_4$ reduction of **26** gave the diol, selective methylation of which afforded **27** in 89% yield. Swern oxidation of the primary alcohol in **27** yield the aldehyde **28**, and then subsequent Huang–Minlon reduction converted the aldehyde function to the corresponding methyl group giving rise to **29** in 76% yield. Deprotection of the MOM group with 45% HBr, followed by Jones oxidation, afforded the carboxylic acid **31**. Finally, treatment of **31** with BBr_3 gave herbertenolide (**5**) in 46% yield, whereas **5** was reduced with $LiAlH_4$ to give rise to 1,15-dihydroxyherbetene (**3**). The synthesized compounds are identical in the ^1H and ^{13}C NMR spectra with those of natural ones (Scheme 3).

2.2. Synthesis of 1,13-dihydroxyherbertene (6)

Our intramolecuar Heck reactions were successfully employed through an ester linkage for the construction of the adjacent quaternary carbon centers composed by a benzene ring and three methyl groups. The methyl group attached on the C-7 quaternary center with a benzene moiety, however, had to be converted from the ester linkage by three-steps elaboration. On the other hand, synthesis of 1,13-hydroxyherbetrene (**6**) only requires the introduction of one of the dimethyl groups on the C-11 position. Thus, 2-methylcyclopentenecarboxylic acid[14] was selected as a partner of intramolecular Heck reaction (Scheme 4).

The ester **9** prepared from 2-methylcyclopentenecarboxylic acid and 2-iodo-*p*-cresol by Yamaguchi method[15] was subjected to Heck reaction under the same conditions (10 mol% $Pd(OAc)_2$, 20 mol% (*o*-tol)$_3$P and *n*-Bu_3N in



Scheme 4. *Reagents, conditions and yields*: (a) 2,4,6-tri-ClBzCl, Et_3N, and then 2-iodo-*p*-cresol, 75%, (b) 10 mol% $Pd(OAc)_2$, 20 mol% tri-*o*-tolylphosphine, DMF, 120°C, 95%, (c) CH_2I_2, Zn–Cu, ether, 92%, (d) PtO_2, NaOAc, H_2, AcOH, 32%, (e) $LiAlH_4$, THF, rt, 100%.

DMF). The cyclization reaction was smoothly preceded in a 5-*exo*-trig manner[16] to give rise to a spiro-lactone **10** in 95% yield. In the next stage, a cyclpropane ring can replace a requisite methyl group. Thus, a cyclopropane **11** was obtained in 92% yield by applying Simmons–Smith reaction[17] to **10**. Subsequent hydrogenation of the cyclopropane ring was troublesome. After several attempts, the cyclopropane ring of **11** was cleaved over PtO_2 in AcOH containing NaOAc giving rise to the dimethyl lactone **32** in 32% yield. Finally, reduction of **32** with $LiAlH_4$ afforded 1,13-dihydroxyherbertene (**6**), quantitatively. Its NMR spectra were superimposed with those of natural ones.

In conclusion, we have succeeded in applying an intramolecular Heck reaction through an ester linkage to syntheses of all herbertenols, which have one oxidized methyl group among three methyl groups vicinally placed on the cyclopentane ring. Our approach to the contraction of the adjacent quaternary centers using the intramolecular Heck reaction provides a suitable way to synthesize a variety of herbertane-type and cuparane-type sesquiterpenes.

3. Experimental

3.1. General

IR spectra were recorded on JASCO 5300 FT IR, Shimadzu UV 300 and JASCO J-500 spectrometer. ^1H and ^{13}C NMR spectra were taken on a Varian unity-200 or a JEOL GX-400 spectrometer. Chemical shifts are expressed in δ units (ppm downfield from Me_4Si). Mass spectra (MS) were recorded on a JEOL AX-500. Air- and moisture-sensitive reagents were transferred via syringe or cannula, and reactions involving these materials were carried out in oven-dried flasks under a positive pressure of argon. Silica gel (Wako, C-300) was used for column chromatography. Analytical thin-layer chromatography (TLC) was performed with Merck precoated TLC plates (Kieselgel 60 F_{254}, 0.25 mm), and spots were visualized with ultraviolet light, iodide, and 40% $CeSO_4$–H_2SO_4.

3.2. Synthesis of 1,15-dihydroxyherbertene and herbertenolide

3.2.1. Methyl 1-allyl-2-cyclopentanonecarboxylate (12). To a suspension of 60% sodium hydride (8.5 g, 0.21 mol) in THF (130 mL) was added a solution of methyl 2-cyclopentanonecarboxylate (25 g, 0.18 mol) in THF at 0°C, and the mixture was stirred for 3 h. To this solution was added allyl bromide (15 mL, 0.18 mol) and then the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched by adding water, extracted with ether, washed with aqueous $NaHCO_3$ solution, water, saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture (43 g), which was chromatographed on silica gel (hexane/EtOAc=4:1) to give **12** (31 g, 97%) as an oil: IR (film) 1745, 1725 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.89–2.15 (2H, m), 2.19–2.52 (5H, m), 2.67 (1H, m), 3.71 (3H, s), 5.06–5.15 (2H, m), 5.68 (1H, m); HREIMS *m/z* 182.0918 [M^+] (calcd 182.0942 for $C_{10}H_{14}O_3$).

3.2.2. Methyl 1-allyl-2-methyl-2-cyclopentenecarboxylate (13). To the stirred MeMgI ether solution (100 mL, 84 mmol) was added a solution of **12** (13.6 g, 75 mmol) in ether (235 mL) at room temperature and the mixture was stirred for 10 h. The mixture quenched by the addition of saturated NH_4Cl solution was extracted with ether, washed with saturated $NaHCO_3$ solution, water and saturated NaCl solution, dried over $MgSO_4$. Evaporation of ether afforded a residue (14 g). To a solution of the residue in benzene (250 mL) was added phosphorus pentaoxide (15 g). The mixture was stirred at room temperature for 12 h. Water was added and the mixture was extracted with ether. The organic layer was washed with saturated NaCl solution, and dried over $MgSO_4$. Evaporation of solvent gave the residue (9.7 g), which was chromatographed on silica gel (hexane/EtOAc=4:1) to give **13** (9.3 g, 69%) as an oil: IR (film) 2951, 1738, 1641 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.70 (3H, brs), 1.87 (1H, m), 2.30 (4H, m), 2.62 (2H, m), 3.68 (3H, s), 5.07 (2H, m), 5.63 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.1, 30.2, 32.9, 39.4, 51.4, 60.5, 117.5, 128.5, 134.3, 140.2, 175.5; EIMS *m/z* (rel. int.) 180 [M^+] (13), 139 (100), 107 (54), 79 (76), 44 (84); HREIMS *m/z* 180.1150 [M^+] (calcd 180.1162 for $C_{11}H_{16}O_2$).

3.2.3. 1-Allyl-2-methyl-2-cyclopentenecarboxylate (14). To a solution of **13** (2.56 g, 14.2 mmol) in a mixture of methanol–water (1:1, 120 mL) was added NaOH (2.56 g, 64 mmol), and the mixture was stirred for 12 h. This solution was acidified with 2 M HCl, and then extracted

with ether. The organic layer was extracted with saturated $NaHCO_3$ solution. The resulting aqueous layer was acidified with 2 M HCl, and then extracted with ether. The extract was washed with water and saturated NaCl solution, dried over $MgSO_4$, concentrated, and purified by column chromatography (hexane/EtOAc=4:1) to give **14** (2.3 g, 92%) as an oil: IR (film) 2932, 1703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.73 (3H, s), 1.89 (1H, m), 2.26 (4H, m), 2.60 (1H, m), 5.09 (2H, m), 5.65 (2H, m); HREIMS *m/z* 166.0994 [M^+] (calcd 166.0994 for $C_{10}H_{14}O_2$).

3.2.4. 2-Iodo-4-methylphenyl 1-allyl-2-methyl-2-cyclopentenecarboxylate (7). To a solution of **14** (3.3 g, 20 mmol) in benzene (230 mL) was added DCC (8.3 g, 40.2 mmol) and DMAP (2.5 g, 20.1 mmol). To this stirring mixture was added 2-iodo-*p*-cresol (7.07 g, 30.2 mmol). The mixture was stirred at room temperature for 12 h. After being filtered, the filtrate was washed with water, $Cu(NO_3)_2$ solution, $NaHCO_3$ solution and saturated NaCl solution and dried over $MgSO_4$. Evaporation of solvent gave a crude product (11.6 g), which was chromatographed on silica gel (hexane/methylene chloride=1:1) to afford **7** (4.97 g, 65%) as an oil: IR (film) 2924, 1750, 1481 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.84 (3H, s), 2.01 (1H, m), 2.30 (3H, s), 2.64 (5H, m), 5.15 (2H, m), 5.77 (2H, m), 6.89 (1H, d, *J*=8.3 Hz), 7.12 (1H, dd, *J*=8.3, 1.6 Hz), and 7.63 (1H, d, *J*=1.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 20.1, 30.5, 33.1, 39.4, 60.6, 89.7, 118.0, 122.2, 129.82, 129.88, 134.0, 137.1, 139.4, 139.6, 149.0, 173.1; EIMS *m/z* (rel. int.) 382 [M^+] (2), 121 (100), 93 (35); HREIMS *m/z* 382.0399 [M^+] (calcd for 382.0430 for $C_{17}H_{19}O_2I$).

3.2.5. Wacker oxidation of 7. A mixture of **7** (6 g, 15.7 mmol), palladium(II) chloride (0.85 g, 4.7 mmol), and CuCl (1.57 g, 15.7 mmol) in 100 mL of DMF and water (7:1) was stirred at room temperature under oxygen atmosphere for 19 h. The reaction mixture was diluted with 2 M HCl and extracted with ether. The resulting organic solution was washed with water and saturated NaCl solution, and dried over $MgSO_4$. The solvent was removed and the residue was chromatographed on silica gel (hexane/EtOAc=4:1) to afford **15** (3.5 g, 56%) as an oil: IR (film) 2922, 1748, 1715, 1483 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.80 (3H, s), 2.19 (3H, s), 2.29 (3H, s), 2.57 (1H, d, *J*=17.9 Hz), 3.45 (1H, *J*=17.9 Hz), 5.67 (1H, m), 7.02 (1H, d, *J*=8.4 Hz), 7.12 (1H, dd, *J*=8.4, 1.8 Hz), 7.60 (1H, d, *J*=1.8 Hz); EIMS *m/z* (rel. int.) 398 [M^+] (50), 234 (58), 137 (100); HREIMS *m/z* 398.0374 [M^+] (calcd for 398.0379 for $C_{17}H_{19}O_3I$).

3.2.6. Ethylene acetalization of 15. A solution of **15** (175 mg, 0.44 mmol) in benzene (7 mL) containing *p*-toluenesulfonic acid (9.6 mg) was refluxed under removal of the formed water by a Dean–Stark apparatus for 20 h. The cooled solution was diluted with ether and washed with saturated $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$. Removal of solvent gave an acetal **16** (194 mg, 100%) as an oil: IR (film) 2979, 1754, 1483 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.39 (3H, s), 1.84 (1H, d, *J*=14.4 Hz),. 1.86 (3H, d, *J*=0.7 Hz), 2.01–2.27 (2H, m), 2.28 (3H, s), 2.50–2.80 (2H, m), 2.84 (1H, d, *J*=14.4 Hz), 3.84–4.00 (4H, m), 5.62 (1H, m), 7.02 (1H, d, *J*=8.3 Hz), 7.12 (1H, dd, *J*=8.3, 1.5 Hz), 7.60 (1H, d, *J*=1.5 Hz); EIMS *m/z* (rel. int.) 442 [M^+] (11), 320 (21), 289 (18), 87 (100); HREIMS *m/z* 442.0639 [M^+] (calcd for 442.0641 for $C_{19}H_{23}O_4I$).

3.2.7. Heck reaction of 16. To a solution of **16** (100 mg, 0.23 mmol) in DMF (10 mL) was added palladium acetate (5.2 mg, 0.023 mmol), tris(2-methylphenyl)phosphine (14 mg, 0.046 mmol) and tri-*n*-butylamine (0.13 mL, 0.46 mmol). The mixture was heated at 120°C for 18 h. The cooled mixture was diluted with water and washed with water and saturated NaCl solution, dried over $MgSO_4$. Removal of solvent afforded the residue, which was chromatographed on silica gel (hexane/EtOAc=3:1) to afford a γ-lactone (68 mg), which was hydrogenated in EtOH (5 mL) containing palladium carbon (Pd/C, Pd: 10%, 5 mg) under an atmosphere of hydrogen for 10 h. The reaction mixture was filtered, concentrated to afford **17** (69 mg, 95%) as an oil: IR (film) 2955, 1755, 1494 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (3H, s), 1.34 (3H, s), 1.63–1.89 (5H, m), 2.34 (3H, s), 3.00 (1H, m), 3.58 (1H, m), 3.71–3.92 (3H, m), 6.93 (1H, d, *J*=8.1 Hz), 7.03 (1H, dd, *J*=8.1, 1.3 Hz), 7.09 (1H, d, *J*=1.3 Hz); EIMS *m/z* (rel. int.) 316 [M^+] (16), 87 (100), 83 (42); HREIMS *m/z* 316.1617 [M^+] (calcd for 316.1674 for $C_{19}H_{24}O_4$).

3.2.8. 1-Hydroxylmethyl-1-(2,2-ethylenedioxypropyl)-2-methyl-2-(2-methoxy-5-methyl phenyl)cyclopentane (18). To a solution of **17** (107 mg, 0.34 mmol) in THF (3 mL) was added $LiAlH_4$ (60 mg, 1.6 mmol) at 0°C and the mixture was stirred for 3 h at room temperature. The reaction mixture was treated with water, and then was extracted with ether. The ether layer was washed with saturated NaCl solution, dried over $MgSO_4$. Removal of solvent gave a diol (88 mg, 81%) as a colorless oil, which was dissolved in acetone (10 mL). To this solution was added K_2CO_3 (60 mg) and iodomethane (0.20 mL) and the reaction mixture was refluxed for 11 h. The reaction mixture was diluted with water and extracted with ether. The resulting organic layer was washed with saturated NaCl solution, dried over $MgSO_4$. Evaporation of organic solvent gave the residue, which was chromatographed on silica gel (hexane/EtOAc=6:1) to afford **18** (117 mg, 98%) as an oil: IR (film) 3505, 2955, 1499 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (3H, s), 1.43 (3H, s), 1.53–2.04 (6H, m), 3.78 (3H, s), 3.95 (4H, s), 6.77 (1H, d, *J*=8.2 Hz), 6.98 (1H, dd, *J*=8.2, 1.7 Hz), 7.13 (1H, d, *J*=1.7 Hz); EIMS *m/z* (rel. int.) 334 [M^+] (8), 149 (100); HREIMS *m/z* 334.2130 [M^+] (Calcd for 334.2144 for $C_{20}H_{30}O_4$).

3.2.9. 1-Formyl-1-(2,2-ethylenedioxypropyl)-2-methyl-2-(2-methoxy-5-methylphenyl) cyclopentane (19). To a solution of dimethyl sulfoxide (0.08 mL, 0.99 mmol) in CH_2Cl_2 (1 mL) was added oxalyl chloride (0.06 mL, 0.66 mmol) at −78°C, and stirring was continued for 10 min. A solution of **18** (101 mg, 0.3 mmol) in CH_2Cl_2 (2 mL) was added to this solution, and the reaction mixture was stirred for 1 h at the same temperature and then treated with Et_3N (0.09 mL, 0.65 mmol). After further stirring for 30 min at 0°C, the reaction mixture was treated with saturated NH_4Cl solution and extracted with ether. The organic layer was washed with water and saturated NaCl solution, dried over $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel (hexane/

EtOAc=2:1) to afford **19** (96 mg, 96%) as an oil: IR (film) 2961, 2890, 1713, 1502 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (3H, s), 1.43 (3H, s), 2.09 (1H, d, J=15.0 Hz), 2.25 (3H, s), 2.94 (1H, d, J=15.0 Hz), 3.78 (3H, s), 6.77 (1H, d, J=8.1 Hz), 7.00 (1H, dd, J=8.1, 1.5 Hz), 7.04 (1H, dd, J=1.5 Hz), 9.00 (1H, s); EIMS m/z (rel. int.) 332 [M^+] (15), 241 (23), 87 (100); HREIMS m/z 332.1978 [M^+] (calcd 332.1988 for $C_{20}H_{28}O_4$).

3.2.10. 1,2-Dimethyl-1-(2,2-ethylenedioxypropyl)-2-(2-methoxy-5-methylphenyl) cyclopentane (20). To a solution of **19** (60 mg, 0.18 mmol) in diethylene glycol (8 mL) was added hydrazine monohydrate (2 mL, 40 mmol). After being stirred at 150°C for 5 h, NaOH (100 mg, 1.78 mmol) was added. The reaction mixture was stirred at 190°C for additional 7 h. The reaction mixture was extracted with ether, washed with water, saturated NaCl solution, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc=5:1) to afford **20** (34 mg, 59%) as an oil: IR (film) 2954, 1497 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (3H, s), 1.34 (3H, s), 1.39 (3H, s), 1.93 (1H, d, J=14.8 Hz), 2.28 (3H, s), 2.33 (1H, d, J=14.8 Hz), 3.75 (3H, s), 3.77–4.05 (4H, m), 6.76 (1H, d, J=8.4 Hz), 6.97 (1H, dd, J=8.4, 2.2 Hz), 7.18 (1H, d, J=2.2 Hz); EIMS m/z (rel. int.) 318 [M^+] (5), 149 (60), 87 (100); HREIMS m/z 318.2202 [M^+] (calcd 318.2194 for $C_{20}H_{30}O_3$).

3.2.11. 1,2-Dimethyl-1-(2-oxopropyl)-2-(2-methoxy-5-methylphenyl)cyclopentane (21). To a solution of **20** (12 mg, 0.037 mmol) in THF (1.5 mL) was added 3.5 mL of 2.5 M HCl, and the mixture was stirred at room temperature for 15 min. The reaction mixture was extracted with ether, washed with saturated $NaHCO_3$ solution and saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent afford **21** (10.1 mg, 100%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 0.75 (3H, s), 1.35 (3H, s), 2.15 (3H, s), 2.28 (3H, s), 2.67 (1H, d, J=14.8 Hz), 3.03 (1H, d, J=14.8 Hz), 3.79 (3H, s), 6.77 (1H, d, J=8.1 Hz), 7.02 (1H, dd, J=8.1, 1.5 Hz), 7.12 (1H, d, J=1.5 Hz); ^{13}C NMR (200 MHz, $CDCl_3$) δ 20.4, 20.8, 22.2, 24.2, 30.0, 38.0, 38.3, 51.3, 52.0, 54.8, 59.2, 111.8, 127.5, 129.2, 129.9, 124.4, 156.5, 208.4.

3.2.12. Methyl 1-benzyloxymethyl-2-cyclopentanonecarboxylate (23a). To a suspension of 60% sodium hydride (169 mg, 4.22 mmol) in toluene (10 mL) was added a solution of methyl 2-cyclopentanonecarboxylate (500 mg, 3.5 mmol) in toluene at 0°C, and the mixture was stirred for 30 min. To this solution was added benzylchloromethyl-ether (0.73 mL, 5.3 mmol) and then the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by adding water and extracted with ether, washed with aqueous $NaHCO_3$ solution, water and saturated NaCl solution, and dried over $MgSO_4$. Evaporation of the solvent gave a crude mixture (1.45 g), which was chromatographed on silica gel (hexane/EtOAc=4:1) to give **23a** (450 mg, 49%) and an O-alkylated product **23b** (376 mg, 41%) as an oil, respectively. **23a**: IR (film) 2955, 1755 and 1728 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.95–2.58 (6H, m), 3.69 (3H, s), 3.63 (1H, d, J=7.9 Hz), 3.86 (1H, d, J=7.9 Hz), 4.46 (1H, d, J=12.1 Hz), 4.53 (1H, d, J=12.1 Hz), 7.24–7.39 (5H, m).

3.2.13. 1-Benzyloxymethyl-2-methyl-2-cyclopentenecarboxylate (24). To a solution of **23a** (397 mg, 1.51 mmol) in ether (15 mL) was added the MeMgI ether solution (2.15 mL, 1.81 mmol) at room temperature and the mixture was stirred for 19 h. The reaction mixture was quenched by the addition of saturated NH_4Cl solution, extracted with ether, washed with saturated $NaHCO_3$ solution, water and saturated NaCl solution, dried over $MgSO_4$. Evaporation of ether afforded a residue (369 mg). To a solution of this residue in benzene (5 mL) was added phosphorus pentaoxide (0.43 g). The mixture was stirred at room temperature for 14 h. Water was added and the mixture was extracted with ether. The organic layer was washed with saturated NaCl solution, and dried over $MgSO_4$. Evaporation of solvent gave the residue, which was chromatographed on silica gel (hexane/EtOAc=4:1) to give a methyl ester (360 mg), which was dissolved in methanol and water (1:1, 2 mL) and then NaOH (390 mg) was added. After being stirred at room temperature for 10 h, this reaction mixture was acidified with 2 M HCl, and then extracted with ether. The organic layer was extracted with saturated $NaHCO_3$ solution. The resulting aqueous layer was acidified with 2 M HCl, and then extracted with ether. The combined extracts were washed with water and saturated NaCl solution, dried over $MgSO_4$, concentrated, and purified by column chromatography (hexane/EtOAc=4:1) to give **24** (245 mg, 66%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 1.73 (3H, s), 3.52 (1H, d, J=8.9 Hz), 3.75 (1H, d, J=8.9 Hz), 4.54 (1H, d, J=12.5 Hz), 4.62 (1H, d, J=12.5 Hz), 5.60 (1H, m), 7.30–7.40 (5H, m); EIMS m/z (rel. int.) 246 [M^+] (2), 123 (39), 91 (100); HREIMS m/z 246.1246 [M^+] (calcd 246.1256 for $C_{15}H_{18}O_3$).

3.2.14. 2-Iodo-4-methylphenyl 1-benzyloxymethyl-2-methyl-2-cyclopentenecarboxylate (7a). To a solution of **24** (500 mg, 2.03 mmol) in benzene (20 mL) was added DCC (639 mg, 3.1 mmol) and DMAP (250 mg, 2.03 mmol). To this stirring mixture was added 2-iodo-*p*-cresol (475 mg, 2.03 mmol). The mixture was stirred at room temperature for 17 h. After being filtered, the filtrate was washed with water, $Cu(NO_3)_2$ solution, $NaHCO_3$ solution and saturated NaCl solution and dried over $MgSO_4$. Evaporation of the solvent gave a crude product (11.6 g), which was chromatographed on silica gel (hexane/EtOAc=9:1) to afford **7a** (821 mg, 87%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 1.85 (3H, d, J=1.8 Hz), 2.29 (3H, s), 3.72 (1H, d, J=8.8 Hz), 3.98 (1H, d, J=8.8 Hz), 4.57 (1H, d, J=12.5 Hz), 4.65 (1H, d, J=12.5 Hz), 5.68 (1H, m), 6.89 (1H, d, J=8.1 Hz), 7.11 (1H, dd, J=8.1, 1.8 Hz), 7.25–7.40 (5H, m) and 7.62 (1H, d, J=1.8 Hz); EIMS m/z (rel. int.) 462 [M^+] (5), 234 (48), 93 (91); HREIMS m/z 462.0665 [M^+] (calcd 462.0692 for $C_{22}H_{23}O_3I$).

3.2.15. Heck reaction of 7a. To a solution of **7a** (2 g, 4.33 mmol) in DMF (400 mL) was added palladium acetate (100 mg, 0.433 mmol), 1,1′-bis(diphenylphosphino)ferrocene (480 mg, 0.866 mmol) and tri-*n*-butylamine (2.1 mL, 8.66 mmol). The mixture was heated at 120°C for 14 h. The cooled mixture was diluted with water and washed with water and saturated NaCl solution, dried over $MgSO_4$. Removal of solvent afforded the residue, which was chromatographed on silica gel (hexane/EtOAc=9:1) to afford δ-lactone (860 mg, 4.33 mmol), which was

hydrogenated in EtOH (9 mL) containing palladium carbon (Pd/C, Pd: 10%, 90 mg) under an atmosphere of hydrogen for 10 h. The reaction mixture was filtered, concentrated to afford **25** (756 mg, 71%) as an oil: IR (film) 3450, 2966, 1741, 1494 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (3H, s), 2.34 (3H, s), 3.60 (1H, m), 4.03 (1H, m), 6.91 (1H, d, J=8.1 Hz), 7.05 (1H, dd, J=8.1, 1.5 Hz), 7.11 (1H, d, J=1.5 Hz); EIMS m/z (rel. int.) 246 [M^+] (100), 201 (60), 91 (11); HREIMS m/z 246.1265 [M^+] (calcd for 246.1256 for $C_{15}H_{18}O_3$).

3.2.16. Methoxymethylation of 25. A solution of **25** (346 mg, 1.4 mmol), choromethylmethylether (0.13 mL) and triethylamine in methylene chloride (10 mL) was stirred at room temperature for 10 h. The reaction mixture was diluted with water and extracted with ether. The organic layer was washed with 2 M HCl and saturated NaCl solution, dried over $MgSO_4$. Removal of solvent afforded the residue, which was chromatographed on silica gel (hexane/EtOAc=4:1) to give **26** (396 mg, 97%) as an oil: IR (film) 2949, 1747, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38 (3H, s), 2.33 (3H, s), 3.20 (3H, s), 3.69 (2H, s), 4.42 (1H, d, J=6.8 Hz), 4.45 (1H, d, J=6.8 Hz), 6.89 (1H, d, J=8.2 Hz), 7.02 (1H, dd, J=8.2, 1.5 Hz), 7.09 (1H, d, J=1.5 Hz); EIMS m/z (rel. int.) 290 [M^+] (96), 185 (66), 45 (100); HREIMS m/z 290.1525 (calcd for 290.1518 for $C_{17}H_{22}O_4$).

3.2.17. 1-Hydroxymethyl-1-methoxymethyloxymethyl-2-methyl-2-(2-methoxy-5-methylphenyl)cyclopentane (27). To a solution of **26** (479 mg, 1.65 mmol) in THF (16 mL) was added $LiAlH_4$ (479 mg, 12.8 mmol) at 0°C, and stirring was continued at room temperature for 3 h. After being cooled down to 0°C, EtOAc (8 mL) and water were successively added to the reaction mixture. After being filtered, the filterate was condensed in vacuo to give diol (396 mg), which was dissolved in acetone (20 mL). To this solution was added iodomethane (0.15 mL, 2.48 mmol) and K_2CO_3 (342 mg, 2.48 mmol), and the mixture was refluxed for 12 h. After being cooled, the reaction mixture was extracted with ether, washed with water and saturated NaCl solution, dried over $MgSO_4$. Evaporation of solvent afforded the residue, which was chromatographed on silica gel (hexane/EtOAc=3:1) to give **27** (452 mg, 89%) as an oil: IR (film) 3441, 1498 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.35 (3H, s), 2.28 (3H, s), 2.70 (1H, dd, J=9.9, 2.9 Hz), 3.31 (1H, dd, J=9.9, 2.9 Hz), 3.40 (3H, s), 3.66 (1H, d, J=8.9 Hz), 3.88 (3H, s), 4.32 (1H, d, J=8.9 Hz), 4.64 (1H, d, J=6.4 Hz), 4.69 (1H, d, J=6.4 Hz), 6.78 (1H, d, J=8.1 Hz), 7.01 (1H, dd, J=8.1, 1.5 Hz), 7.08 (1H, d, J=1.5 Hz); EIMS m/z (rel. int.) 308 [M^+] (5), 276 (73), 149 (100); HREIMS 308.1989 (cacld 308.1988 for $C_{18}H_{28}O_4$).

3.2.18. 1-Formyl-1-methoxymethyloxymethyl-2-methyl-2-(2-methoxy-5-methylphenyl) cyclopentane (28). To solution of dimethyl sulfoxide (0.14 mL, 1.96 mmol) in CH_2Cl_2 (3.2 mL) was added oxalyl chloride (0.12 mL, 1.31 mmol) at −78°C, and stirring was continued for 10 min. A solution of **27** (200 mg, 0.65 mmol) in CH_2Cl_2 (6 mL) was added to this solution, and the reaction mixture was stirred for 1 h at the same temperature and then treated with triethylamine (0.64 mL, 4.58 mmol). After further stirring for 30 min at 0°C, the reaction mixture was treated with saturated NH_4Cl solution and then extracted with ether. The organic layer was washed with water and saturated NaCl solution, dried over $MgSO_4$. The solvent was removed in vacuo and the residue was chromatographed on silica gel (hexane/EtOAc=4:1) to afford **28** (147 mg, 74%) as an oil: IR (film) 2946, 1720, 1499 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.38 (3H, s), 2.26 (3H, s), 3.36 (3H, s), 3.71 (1H, d, J=9.5 Hz), 3.75 (3H, s), 4.46 (1H, d, J=9.5 Hz), 4.64 (2H, s), 6.73 (1H, d, J=8.1 Hz), 7.02 (1H, dd, J=8.1, 1.5 Hz), 7.04 (1H, d, J=1.5 Hz), 9.17 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 21.9, 22.8, 30.7, 40.6, 50.9, 54.4, 55.2, 61.4, 69.6, 96.8, 111.1, 128.3, 128.6, 129.7, 132.4, 155.3, 204.3; EIMS m/z (rel. int.) 306 [M^+] (15), 175 (100), 149 (31); HREIMS m/z 306.1832 [M^+] (calcd 306.1831for $C_{18}H_{26}O_4$).

3.2.19. 1-Methyl-1-methoxymethyloxymethyl-2-methyl-2-(2-methoxy-5-methylphenyl) cyclopentane (29). To a solution of **28** (140 mg, 0.46 mmol) in diethylene glycol (27 mL) was added hydrazine monohydrate (6.8 mL). After being stirred at 150°C for 5 h, NaOH (340 mg, 6 mmol) was added. The reaction mixture was stirred at 190°C for additional 7 h. The reaction mixture was extracted with ether, washed with water and saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/EtOAc=5:1) to afford **30** (102 mg, 76%) as an oil: IR (film) 2947, 1498 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.70 (3H, s), 1.34 (3H, s), 2.28 (3H, s), 3.38 (3H, s), 3.67 (1H, d, J= 9.0 Hz), 3.76 (3H, s), 3.78 (1H, d, J=9.0 Hz), 4.64 (1H, d, J=6.4 Hz), 4.67 (1H, d, J=6.4 Hz), 6.75 (1H, d, J=8.2 Hz), 6.98 (1H, dd, J=8.2, 2.0 Hz), 7.12 (1H, d, J=2.0 Hz); EIMS m/z (rel. int.) 292 [M^+] (7), 83 (100), 78 (32); HREIMS m/z 292.2035 [M^+] (calcd 292.2039 for $C_{18}H_{28}O_3$).

3.2.20. 1-Methyl-1-hydroxymethyl-2-methyl-2-(2-methoxy-5-methylphenyl) cyclopentane (30). To a solution of **29** (45 mg, 0.16 mmol) in MeOH (6 mL) was added one drop of 48% HBr. The mixture was refluxed for 1 h and then condensed in vacuo to give the residue, which was chromatographed on silica gel (hexane/EtOAc=4:1) to afford **30** (34 mg, 87%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 0.71 (3H, s), 1.39 (3H, s), 2.28 (3H, s), 3.48 (1H, d, J=11.5 Hz), 3.83 (3H, s), 3.93 (1H, d, J= 11.5 Hz), 6.80 (1H, d, J=8.2 Hz), 7.00 (1H, dd, J=8.2, 1.5 Hz), 7.16 (1H, d, J=1.5 Hz).

3.2.21. 1-Carboxy-1,2-dimethyl-(2-methoxy-5-methylphenyl)-cyclopentane (31). To a cooled solution of **30** (12 mg, 0.048 mmol) in acetone (0.8 mL) was added Jones reagent (1.3 mL), and the mixture was stirred for 19 h. The reaction mixture was treated with Na_2SO_3 and water was added. The solution was extracted with ether, washed with water and saturated NaCl solution, and dried over $MgSO_4$. Removal of solvent afforded the residue (12 mg), which was chromatographed on silica gel (hexane/EtOAc=2:1) to give carboxylic acid **31** (8.0 mg, 64%) as an oil; IR (film) 2960, 1683, 1501, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, s), 1.47 (3H, s), 2.28 (3H, s), 3.68 (3H, s), 6.72 (1H, d, J=8.2 Hz), 7.02 (1H, dd, J=8.2, 2.0 Hz), 7.04 (1H. d, J=2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 20.8, 22.8, 25.2, 39.7, 39.8, 53.1, 53.6, 53.7, 110.2, 127.5, 128.8, 129.2, 135.2, 155.0,

183.0; EIMS *m/z* (rel. int.) 262 [M^+] (100), 161 (67), 230 (66); HREIMS *m/z* 262.1560 [M^+] (Calcd 262.1569 for $C_{16}H_{22}O_3$).

3.2.22. Herbertenolide (5). To a solution of **31** (11 mg, 0.042 mmol) in methylene chloride (1.5 mL) was added boron tribromide (0.17 mL, 1.0 M solution in methylene chloride) at room temperature. After stirring was continued for 22 h, water was added. The solution was extracted with ether, washed with water and saturated NaCl solution, dried over $MgSO_4$. Removal of solvent afforded the residue (12 mg), which was chromatographed on silica gel (hexane/EtOAc=5:1) to give herbertenolide (**5**) (4.4 mg, 46%) as a colorless oil; IR (film) 1775, 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, s), 1.12 (3H, s), 2.33 (3H, s), 6.89 (1H, d, *J*=2.2 Hz), 6.93 (1H, d, *J*=8.0 Hz), 7.02 (1H, dd, *J*=8.0, 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 19.9, 20.9, 25.4, 29.0, 29.7, 47.1, 50.8, 115.8, 125.3, 128.0, 133.0, 134.1, 149.6, 173.6; EIMS *m/z* (rel. int.) 230 [M^+] (100), 187 (78), 215 (66); HREIMS *m/z* 230.1313 [M^+] (calcd 230.1307 for $C_{15}H_{18}O_2$). These spectral data were identical with those of natural one.

3.2.23. 1,15-Hydroxyherbertene (3). To a solution of **5** (7.2 mg, 0.031 mmol) in THF (1 mL) was added $LiAlH_4$ (4.8 mg) at 0°C. The reaction mixture was stirred at room temperature for 28 h. The reaction was terminated by adding water and EtOAc, and the solution was acidified with 2 M HCl and was extracted with EtOAc. The organic layer was washed with water and dried over $MgSO_4$. Removal of solvent afforded the residue (8 mg), which was chromatographed on silica gel (hexane/EtOAc=2:1) to give 1,15-dihydroxyherbertene (**3**) (6 mg, 83%) as a colorless oil; ^1H NMR data (200 MHz, $CDCl_3$) δ 0.81 (3H, s), 1.49 (3H, s), 2.27 (3H, s), 3.47 (1H, d, *J*=11.0 Hz), 4.91 (1H, d, *J*=11.0 Hz), 6.75 (1H, d, *J*=8.1 Hz), 6.93 (1H, dd, *J*=8.1, 1.5 Hz), 7.12 (1H, d, *J*=1.5 Hz); ^{13}C NMR data (75 MHz, $CDCl_3$) δ 20.8, 21.0, 21.9, 24.2, 39.5, 42.2, 48.1, 49.3, 69.2, 118.8, 127.9, 128.9 (×2), 132.9, 152.5.

3.3. Synthesis of 1,13-dihydroxyherbertene (6)

3.3.1. 2-Iodo-4-methylphenyl 2-methyl-cyclopentenecarboxylate (9). To a solution of 2-methylcyclopentenecarboxylic acid (215 mg, 1.71 mmol) was added triethylamine (0.24 mL, 1.71 mmol) and 2,4,6-trichlorobenzoyl chloride (0.27 mmol) and the solution was stirred at room temperature for 4 h. After filtering off the precipitate, the filterate was condensed in vacuo to leave the residue, which was dissolved in benzene (15 mL). To this solution was added 2-iodo-*p*-cresol (600 mg, 2.65 mmol) and 4-dimethylaminopyridine (418 mg, 3.24 mmol). The mixture was stirred at room temperature for 13 h. Water was added and the solution was extracted with ether, washed with saturated $Cu(NO_3)_2$ solution, saturated $NaHCO_3$ solution and saturated NaCl solution and dried over $MgSO_4$. Evaporation of solvent gave a crude product (1.3 g), which was chromatographed on silica gel (hexane/methylene chloride=2:1) to afford **9** (441 mg, 75%) as an oil: IR (film) 1732, 1644 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.31 (3H, s),7.00 (1H, d, *J*=8.1 Hz), 7.15 (1H, dd, *J*=8.1, 2.2 Hz), 7.65 (1H, d, *J*=2.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.5, 20.2, 21.2, 33.4, 40.9, 90.4, 122.6, 129.9, 137.1, 139.4, 149.0. 159.8, 163.4; EIMS *m/z* (rel. int.) 342 [M^+] (4), 234 (23), 109 (100); HREIMS *m/z* 342. 0102 (calcd 342.0117 for $C_{14}H_{15}O_2I$).

3.3.2. Heck reaction of 9. To a solution of **9** (440 mg, 1.29 mmol) in DMF (130 mL) was added palladium acetate (28.9 mg, 0.13 mmol) and tri-*o*-tolylphosphine (78.4 mg, 0.26 mmol) and tributylamine (0.62 mL, 2.58 mmol), and the mixture was stirred at 120°C for 22 h. Water was added and the solution was extracted with ether. The organic layer was washed with 2 M HCl, water and saturated NaCl solution, dried over $MgSO_4$. Evaporation of solvent afforded the residue (404 mg), which was chromatographed on silica gel (methylene chloride/hexane=1:1) to give a γ-lactone **10** (262 mg, 95%) as an oil: IR (film) 1800 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (3H, s), 2.63 (5.81 (1H, m), 6.93 (1H, d, *J*=1.3 Hz), 6.99 (1H, d, *J*=8.1 Hz), 7.08 (1H, dd, *J*=8.1, 1.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.0, 21.1, 31.4, 37.6, 62.2, 110.2, 123.9, 129.2, 130.8, 131.3, 134.2, 139.4, 151.0, 180.1; EIMS *m/z* (rel. int.) 214 [M^+] (100), 186 (82), 171 (65); HREIMS *m/z* 214.1003 [M^+] (calcd 214.0994 for $C_{14}H_{12}O_2$).

3.3.3. Simmons–Smith reaction of 10. To a solution of **10** (260 mg, 1.22 mmol) in ether (10 mL) was added Zn–Cu couple (623 mg, 4.86 mmol). The mixture was heated under gentle refluxing. To this mixture was added dropwise diiodomethane (0.25 mL, 3.0 mmol) and then the reaction mixture was refluxed for 48 h. Water was added and the mixture was extracted with ether. The organic layer was washed with 2 M HCl, water and saturated $NaHCO_3$ solution, and dried over $MgSO_4$. Evaporation of solvent afforded the residue (296 mg), which was chromatographed on silica gel (hexane/methylene chloride=1:1) to give **11** (253 mg, 92%) as an oil: IR (KBr) 2924, 1804 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.49 (1H, dd, *J*=7.0, 5.3 Hz), 0.86 (3H, s), 1.03 (1H, dd, *J*=7.0, 7.0 Hz), 2.37 (3H, s), 7.01 (1H, dd, *J*=8.4, 2.3 Hz), 7.04 (1H, d, *J*=8.3 Hz), 7.10 (1H, d, *J*=2.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.2, 17.4, 21.2, 24.5, 27.9, 33.2, 34.9, 55.6, 110.3, 123.9, 128.8, 131.8, 133.8, 150.3, 180.5; EIMS *m/z* (rel. int.) 228 [M^+] (52), 213 (27), 185 (45), 160 (100), 149 (72); HREIMS *m/z* 228.1164 [M^+] (calcd 228.1150 for $C_{15}H_{16}O_2$).

3.3.4. Hydrogenation of 32. To a solution of **11** (10 mg, 0.044 mmol) in acetic acid (1 mL) was added PtO_2 (10 mg) and NaOAc (5 mg). This mixture was stirred under hydrogen atmosphere at room temperature for 45 min. After being filtered, the filtrate was extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution, water and saturated NaCl solution, dried over $MgSO_4$. Removal of solvent afforded the residue, which was purified by prep. TLC (hexane/methylene dichloride=1:1) to give **32** (3 mg, 32%) as an oil: ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (3H, s), 1.02 (3H, s), 2.36 (3H, s), 6.96 (1H, d, *J*=8.1 Hz), 7.00 (1H, d, *J*=1.0 Hz), 7.08 (1H, dd, *J*=8.1, 1.8 Hz); EIMS *m/z* (rel. int.) 230 [M^+] (42), 161 (100), 148 (17); HREIMS *m/z* 230.1281 (calcd 230.1306 for $C_{15}H_{18}O_2$).

3.3.5. 1,13-Dihydroxyherbertene (6). To a solution of **32** (2.6 mg, 0.011 mmol) in THF (1 mL) was added $LiAlH_4$

(4.3 mg). The reaction mixture was stirred at room temperature for 1 h. The reaction was terminated by adding EtOAc and the solution was acidified with 2 M HCl, and then extracted with ether. The organic layer was washed with water and saturated NaCl solution, dried over $MgSO_4$. Removal of solvent afforded the residue, which was chromatographed on silica gel (hexane/EtOAc=2:1) to give **6** (2.6 mg, 100%) as an colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (3H, s), 1.24 (3H, s), 2.27 (3H, s), 3.78 (1H, d, J=10.6 Hz), 4.40 (1H, d, J=10.6 Hz), 6.69 (1H, d, J=8.1 Hz), 6.92 (1H, dd, J=8.1, 2.0 Hz), 7.02 (1H, d, J=2.0 Hz); EIMS m/z (rel. int.) 234 [M^+] (34), 216 (58), 202 (82), 187 (100), 173 (64), 159 (69), 121 (75), 95 (56); HREIMS m/z 234.1588 (calcd 234.1620 for $C_{15}H_{22}O_2$).

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