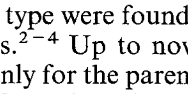
Bryophyte Constituents; 6: Synthesis of Herbertene-Derived Sesquiterpenes from *Herberta adunca*

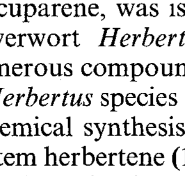
Theophil Eicher,* Frank Servet, Andreas Speicher*
Fachbereich 11 Organische Chemie, Universität des Saarlandes, D-66041 Saarbrücken, Germany
Fax +49(681)3022409 E-mail: th.eicher@rz.uni-sb.de

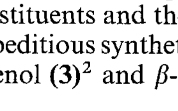
Received 29 December 1995

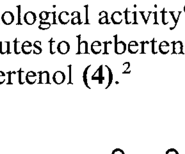
Efficient total syntheses are described for the racemic sesquiterpenes herbertenolide **(2)**, α-herbertenol **(3)** and β-herbertenol **(4)** from *Herberta adunca*. *ent*-Herbertenolide [(+)-**2**] was prepared from enantiopure (−)-ethyl (1*R*)-1-methyl-2-oxocyclopentanecarboxylate **(9)** obtained from ethyl 2-oxocyclopentanecarboxylate **(19)** via reduction with baker's yeast.

(−)-Herbertene **(1)**, the parent compound of a new type of sesquiterpenes isomeric to cuparene, was isolated by Matsuo et al.[1] from the liverwort *Herberta adunca (Dicks.) S. Gray* in 1981. Numerous compounds of this structure type were found in *Herbertus* species and other liverworts.[2–4] Up to now, chemical synthesis was performed only for the parent system herbertene **(1)**.[5] In the course of our interdisciplinary investigations on bryophyte constituents and their biological activity[6] we elaborated expeditious synthetic routes to herbertenolide **(2)**,[4] α-herbertenol **(3)**[2] and β-herbertenol **(4)**.[2]

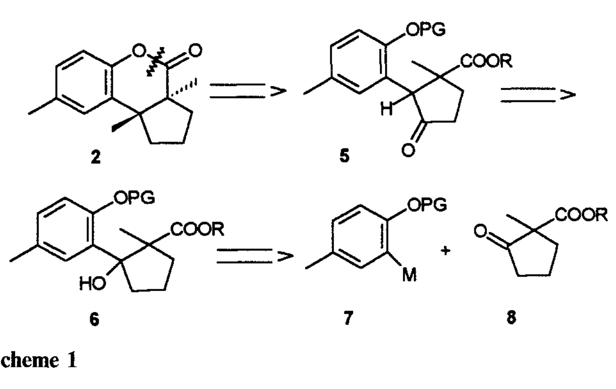

1


2


3


4

From retrosynthetic considerations, the strategy for the synthesis of **2** (Scheme 1) was directed to a key intermediate **5**, which should arise from the tertiary alcohol **6** resulting from addition of an OH-protected *p*-cresol unit **7** to the cyclopentanone moiety **8**.



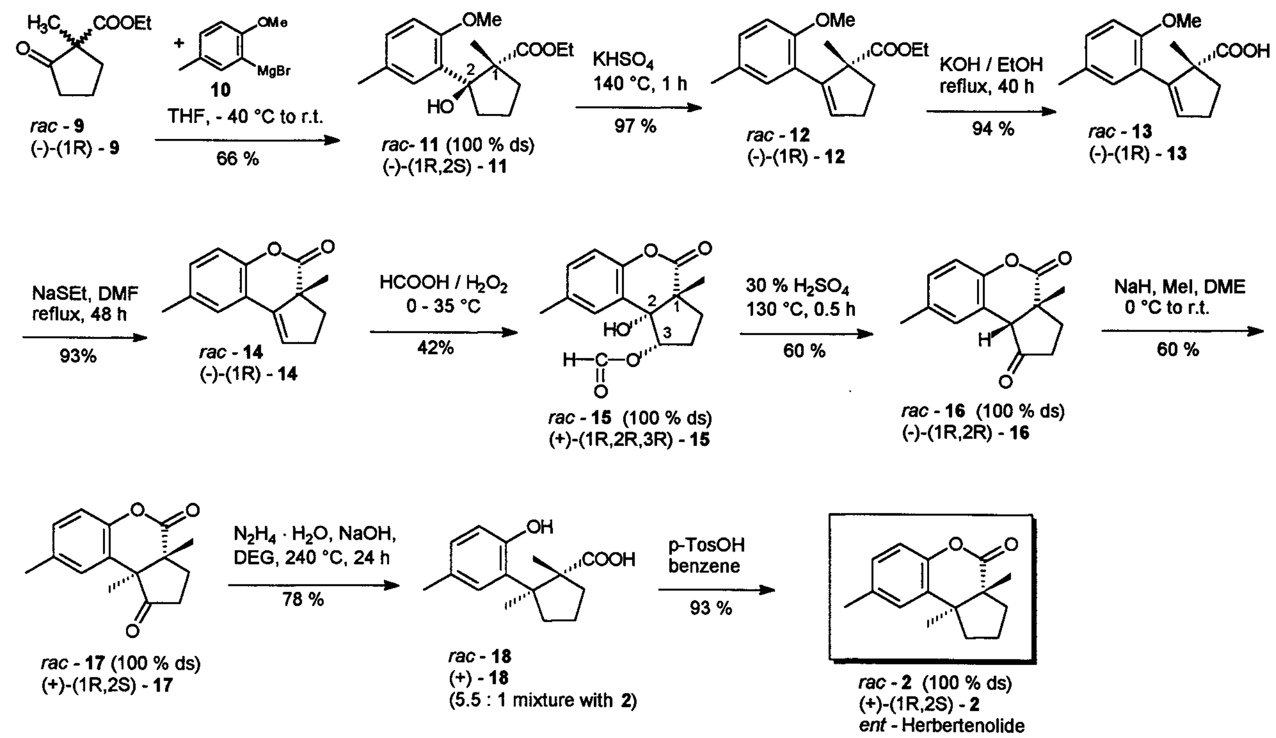
Scheme 1

The synthesis of herbertenolide **(2)** started with ethyl 1-methyl-2-oxocyclopentanecarboxylate [*rac*-**(9)**][7]. Diastereoselective coupling with the Grignard reagent **10** derived from 2-bromo-4-methylanisole[8] yielded the tertiary alcohol *rac*-**11**. Dehydration[9] to the olefin *rac*-**12** followed by saponification (to *rac*-**13**) and cleavage of the methyl ether led to spontaneous formation of the lactone *rac*-**14**. Introduction of the desired carbonyl group could be achieved by epoxidation, oxirane opening with formic acid and subsequent treatment with sulfuric acid.[10] The unexpected stereostructure[11] of the intermediate *rac*-**15** was deduced from an X-ray analysis,[12] the oxolactone *rac*-**16** was obtained as a single diastereomer. Methylation[10] of the angular benzyl position gave *rac*-**17** with the desired *trans*-arrangement of the methyl groups at the C-2/C-3 centers. The carbonyl group of the cyclopentanone **17** was reduced according to the Wolff-Kishner procedure yielding *rac*-**18** (5.5:1 mixture with the lactone **2**) and the lactone ring closure was completed by treatment with acid. Thus, the target molecule *rac*-herbertenolide **(2)** was obtained as a single diastereomer in 6% overall yield in a racemic but diastereoselective 9-step sequence (Scheme 2). The structure of **2** was confirmed by X-ray analysis,[12] all spectroscopic data were identical with the literature.[13]

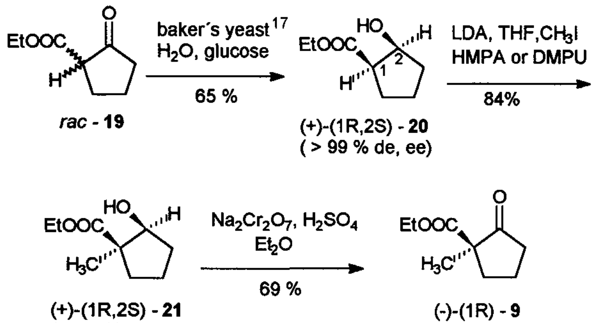
For an enantioselective approach to **2** enantiopure starting material analogous to *rac*-**9** was required in a preparative scale.[14] Enantiopure methyl (1*R*)-1-methyl-2-oxocyclopentane-1-carboxylate can be synthesized by an enzymatic route[15] or – though in lower optical yield – by an enantioselective alkylation method.[16] We prepared ethyl (1*R*)-1-methyl-2-oxocyclopentane-1-carboxylate [(−)-(1*R*)-**9**] by an improved procedure according to Scheme 3, namely by reduction of *rac*-ethyl 2-oxocyclopentane-1-carboxylate **(19)** with baker's yeast (*Saccharomyces cerevisiae*) to the hydroxy ester (+)-**20**,[17] diastereoselective (> 98% de) methylation to (+)-**21**[18] and oxidation.[17] The synthetic route outlined in Scheme 2 was then performed with (−)-(1*R*)-**9** and resulted in the formation of (+)-(1*R*,2*S*)-*ent*-herbertenolide **(2)** in enantiopure form.

The synthesis of **2** could be improved (Scheme 4), when for the introductory step the benzyl ether protected Grignard reagent **22**[19] instead of the methyl ether **10** was used. Again, after dehydration and saponification of the resulting tertiary alcohol **23** (to **24**) the carbonyl group was introduced via epoxidation and oxirane ring opening; deprotection of **25** yielded the lactone **16** described in Scheme 2. By this modification, the overall yield of *rac*-herbertenolide **(2)** was raised to 13% (8 steps).

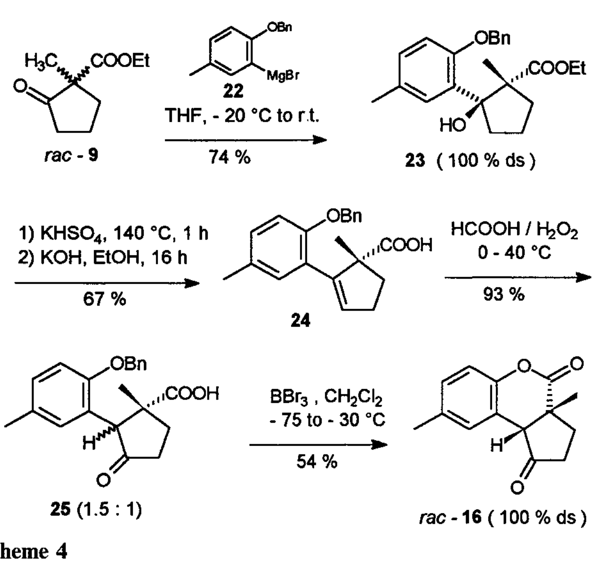
The strategy of the synthesis developed for **2** could be successfully applied also to the synthesis of *rac*-α- and β-herbertenol (**3** and **4**). According to Scheme 5, first the carboxylate function of the key intermediate **12** was reduced (via aldehyde **26**) to the saturated methyl group of the cyclopentene **27**.[20] The carbonyl auxiliary was



Scheme 2. Total Synthesis of *rac*- and *ent*-(+)-Herbertenolide (**2**) (DME: 1,2-dimethoxyethane, DEG: diethylene glycol)



Scheme 3 (DMPU: dimethylpropyleneurea)

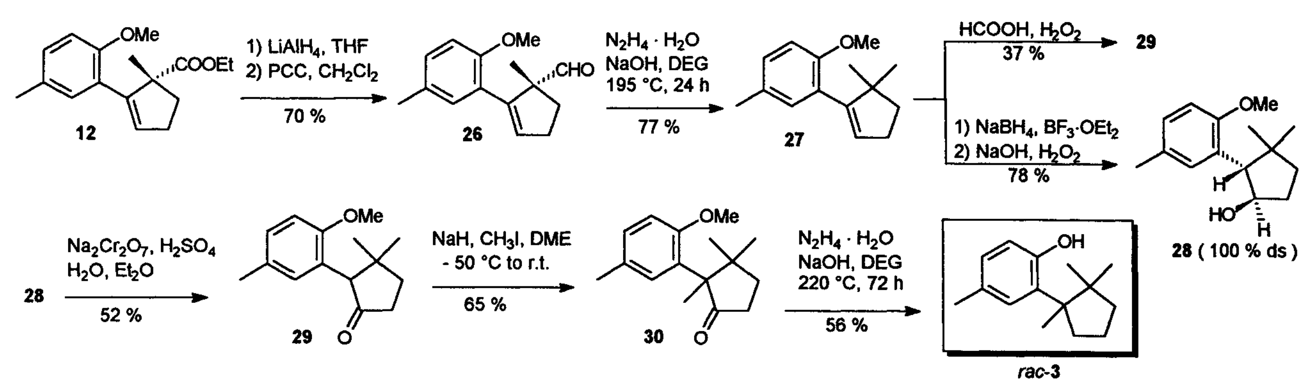


Scheme 4

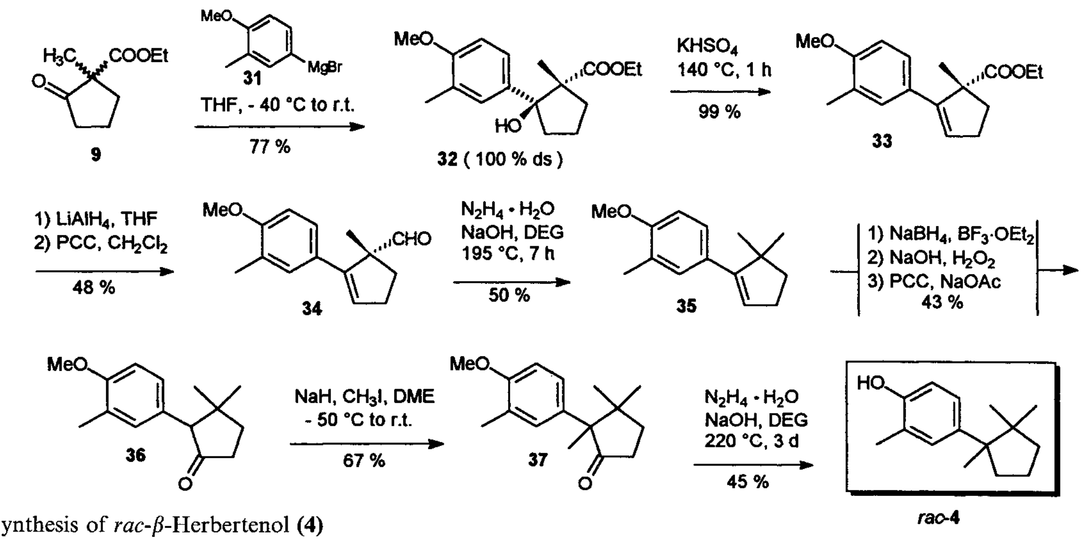
introduced via epoxidation or, with better results, by hydroboration/oxidation followed by Jones oxidation to give the cyclopentanone **29**. The intermediate alcohol **28** was obtained as a single diastereomer. Methylation of **29** proceeded regioselectively to give **30**. When **30** was subjected to Wolff-Kishner reduction with hydrazine hydrate/NaOH additional cleavage of the methyl ether protective group occurred giving rise to *rac*-α-herbertenol (**3**) (8 % overall yield in a 7-step sequence). All spectroscopic data were identical with the literature.[13]

The isomeric β-herbertenol (**4**) was synthesized (Scheme 6) starting with cyclopentanone derivative **9**, and the Grignard reagent **31** derived from 4-bromo-2-methylanisole.[21] The tertiary alcohol **32** was transformed via intermediates **33**/**34** to the dimethylcyclopentene **35** using the foregoing procedure (see Schemes 2 and 5). Hydroboration/oxidation followed by oxidation with pyridinium chlorochromate in acetate buffer gave the best results for introducing the carbonyl auxiliary function in **36**. The synthesis was completed according to Scheme 5 as already described for compound **3**. *rac*-β-Herbertenol (**4**) was obtained in 3 % overall yield in this 9-step sequence. All spectroscopic data were identical with the literature.[13]

^{1}H NMR and ^{13}C NMR (TMS as internal standard): Bruker AM 400. IR: Beckmann Acculab 8. MS: Finnigan MAT 90 or Varian MAT 311. Optical rotations: Perkin-Elmer polarimeter 241. Microanalyses: Leco CHNS-932. TLC: Merck aluminium roll silica gel 60 F_{254} pre-coated. Column chromatography (CC): Silica gel (J.T. Baker, 63–200 μm). Anhydrous solvents were dried by conventional methods. All reactions sensitive against air or moisture were carried out under N_2. Satisfactory microanalyses obtained for all new compounds: C ± 0.3, H ± 0.29.



Scheme 5. Synthesis of *rac*-α-Herbertenol (3) (PCC: pyridinium chlorochromate)



Scheme 6. Synthesis of *rac*-β-Herbertenol (4)

Ethyl (1*R,2*S**)-2-Hydroxy-2-(2-methoxy-5-methylphenyl)-1-methylcyclopentane-1-carboxylate (11):**

To Grignard reagent **10**, prepared from Mg (9.72 g, 0.40 mol, 30 mL anhyd THF) and 2-bromo-4-methylanisole[8] (80.4 g, 0.40 mol in 200 mL anhyd THF; reflux, 1 h) was added anhyd THF (100 mL) followed by *rac*-**9** (54.4 g, 0.32 mol) in anhyd THF (100 mL) at −40 °C. The mixture was allowed to warm to r.t. within 10 h. Ice-cold sat. aq NH_4Cl (400 mL) was added at 5 °C and the mixture was separated. The aqueous layer was extracted with Et_2O (3 x 200 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by distillation; yield: 61.6 g (66 %) of *rac*-**11**; colourless oil; bp 133–135 °C/0.005 mbar.

IR (film): ν = 3510 (OH), 1725 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.00 (d, J = 1.1 Hz, 1 H), 6.98 (dd, J = 8.4, 1.1 Hz, 1 H), 6.77 (d, J = 8.4 Hz, 1 H), 5.29 (d, J = 2.4 Hz, 1 H, OH), 3.83 (s, 3 H, OCH_3), 3.66–3.55 (m, 2 H), 2.72–2.69 (m, 1 H), 2.38–2.31 (m, 1 H), 2.23 (s, 3 H, $ArCH_3$), 2.02–1.88 (m, 3 H), 1.72–1.69 (m, 1 H), 1.37 (s, 3 H, CH_3), 0.86 (t, J = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 176.6, 155.8, 130.0, 129.7, 128.7, 128.3, 111.4, 87.1, 60.0, 59.5, 55.5, 38.7, 37.6, 21.7, 20.6, 19.5, 13.6.

MS (CI, 120 eV): m/z (%) = 292 (56, M^+), 275 (100), 218 (21), 201 (87), 179 (8), 171 (28), 157 (7), 149 (20), 142 (6), 125 (7).

(−)-(1*R*)-**9** (29.8 g, 0.175 mmol) was transformed analogously to (1*R*,2*S*)-**11**; $[\alpha]_D^{20}$ −40.8 (c = 1.32, $CHCl_3$).

Ethyl 2-(2-Methoxy-5-methylphenyl)-1-methylcyclopent-2-ene-1-carboxylate (12):

A mixture of *rac*-**11** (19.8 g, 67.7 mmol) and $KHSO_4$ (1.00 g, 7.34 mmol) was heated to 140 °C for 1 h, cooled, taken up in Et_2O (150 mL), washed (sat. aq $NaHCO_3$, brine), dried ($MgSO_4$) and concentrated. The crude product was purified by CC (short column, Et_2O/hexane, 1 : 3). yield: 18.1 g (97 %) of *rac*-**12**; colourless oil.

IR (film): ν = 1735 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.01 (d, J = 1.9 Hz, 1 H), 6.98 (m, 1 H), 6.72 (d, J = 8.2 Hz, 1 H), 6.10 (t, J = 2.5 Hz, 1 H, C=CH), 4.22–4.04 (m, 2 H), 3.68 (s, 3 H, OCH_3), 2.68–2.61 (m, 1 H), 2.46–2.33 (m, 2 H), 2.25 (s, 3 H, $ArCH_3$), 1.92–1.84 (m, 1 H), 1.25 (s, 3 H, CH_3), 1.20 (t, J = 7.1 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 176.9, 154.8, 145.1, 132.8, 130.9, 129.4, 128.7, 125.4, 110.7, 60.1, 56.5, 54.9, 40.0, 31.2, 22.7, 20.4, 14.2.

MS (CI, 120 eV): m/z (%) = 274 (62, M^+), 202 (100), 200 (48), 186 (5), 172 (3), 159 (5), 145 (15), 142 (5), 128 (3), 121 (6), 115 (5), 105 (2), 69 (2).

(−)-(1*R*,2*S*)-**11** (25.7 g, 87.3 mmol) was transformed analogously yielding (1*R*)-**12**; $[\alpha]_D$ −2.2 (c = 1.02, $CHCl_3$).

2-(2-Methoxy-5-methylphenyl)-1-methylcyclopent-2-ene-1-carboxylic Acid (13):

A mixture of *rac*-**12** (83.6 g, 0.305 mol) and KOH (52.2 g, 0.935 mol) in EtOH (800 mL) was heated to reflux for 40 h. The solvent was removed in vacuo, the residue taken up in H_2O (200 mL) and extracted with Et_2O (3 x 50 mL). The aqueous layer was acidified with conc. HCl and the carboxylic acid was extracted with Et_2O, the Et_2O layer was washed with brine and dried ($MgSO_4$). The crude product after evaporation could be crystallized from Et_2O/hexane; yield: 70.9 g (94 %) of *rac*-**13**, colourless crystals; mp 153 °C.

IR (film): ν = 3500–3000 (OH), 1695 (C=O), 1500 (C=C) cm^{-1}.

^{1}H NMR (CDCl$_3$): $\delta = 7.03$ (s, 1 H), 7.00 (d, $J = 1.8$ Hz, 1 H), 6.72 (d, $J = 8.1$ Hz, 1 H), 6.13 (t, $J = 2.4$ Hz, 1 H, C=CH), 3.67 (s, 3 H, OCH$_3$), 2.75–2.69 (m, 1 H), 2.47–2.39 (m, 2 H), 2.25 (s, 3 H, ArC*H*$_3$), 1.97–1.89 (m, 1 H), 1.35 (s, 3 H, CH$_3$).

^{13}C NMR (CDCl$_3$): $\delta = 183.4$, 154.4, 145.2, 133.3, 131.1, 129.6, 129.0, 125.2, 110.7, 56.2, 54.5, 40.5, 31.1, 22.3, 20.4.

MS (CI, 120 eV): *m*/*z* (%) = 246 (45, M$^+$), 239 (2), 215 (7), 201 (100), 200 (41), 193 (13), 187 (10), 171 (3), 159 (2), 153 (13), 145 (3), 139 (3).

(–)-(1*R*)-**12** (20.3 g, 74.0 mmol) was transformed analogously to (1*R*)-**13**; $[\alpha]_D^{20}$ – 1.1 (*c* = 1.09, CHCl$_3$).

2-(2-Hydroxy-5-methylphenyl)-1-methylcyclopent-2-ene-1-carboxylic Acid Lactone (14):

To a NaSEt solution, prepared (exothermic reaction, 0 °C to r.t., 1 h) from ethanethiol (46.5 g, 0.75 mol) and NaH (18.0 g, 0.75 mol) in anhyd DME (500 mL), was added *rac*-**13** (44.3 g, 0.18 mol) at r.t. The mixture was heated to 150 °C for 48 h, cooled and poured into 10 % aq HCl (100 mL), stirred for 3 h and extracted with Et$_2$O (4 × 300 mL). The combined organic layers were washed with H$_2$O and sat. aq NaCl, dried (MgSO$_4$) and concentrated. The crude product was purified by CC (short column, CHCl$_3$); yield: 35.9 g (93 %), colourless oil.

IR (film): *v* = 1775 (C=O), 1485 (C=C) cm^{-1}.

^{1}H NMR (CDCl$_3$): $\delta = 7.27$ (d, $J = 1.8$ Hz, 1 H), 7.07 (dd, $J = 8.3$, 1.8 Hz, 1 H), 6.96 (d, $J = 8.3$ Hz, 1 H), 6.04 (t, $J = 2.6$ Hz, 1 H, C=CH), 2.57–2.53 (m, 2 H), 2.46–2.36 (m, 1 H), 2.33 (s, 3 H, ArC*H*$_3$), 2.18–2.13 (m, 1 H), 1.29 (s, 3 H, CH$_3$).

^{13}C NMR (CDCl$_3$): $\delta = 173.2$, 149.0, 138.5, 133.9, 130.2, 125.7, 125.4, 118.4, 116.5, 51.6, 34.6, 30.2, 23.5, 20.7.

MS (CI, 120 eV): *m*/*z* (%) = 215 (100, M$^+$ + 1), 214 (26, M$^+$), 186 (10), 171 (4), 158 (2), 121 (2).

(–)-(1*R*)-**13** (15.3 g, 62.0 mmol) was transformed analogously yielding (1*R*)-**14**; $[\alpha]_D^{20}$ – 73.5 (*c* = 2.00, CHCl$_3$).

(1*R,2*R**,3*R**)-3-Formyloxy-2-hydroxy-2-(2-hydroxy-5-methylphenyl)-1-methylcyclopentane-1-carboxylic Acid Lactone (15):**

To a cooled mixture of *rac*-**14** (25.0 g, 0.117 mol) and 85 % aq formic acid (190 mL) was added dropwise 30 % aq H$_2$O$_2$ (39.7 g, 0.35 mol). After removal of the ice bath, the reaction temperature was raised to 35 °C and the mixture was stirred for additional 20 h at room temp. H$_2$O (200 mL) was added, the product collected and washed with H$_2$O; yield: 13.5 g (42 %); colourless crystals; mp 200 °C.

IR (film): *v* = 3435 (OH), 1770 (C=O), 1700 (HC=O) cm^{-1}.

^{1}H NMR (CDCl$_3$): $\delta = 8.24$ (s, 1 H), 7.15 (dd, $J = 8.2$, 1.2 Hz, 1 H), 7.01 (d, $J = 8.2$ Hz, 1 H), 6.95 (d, $J = 1.2$ Hz, 1 H), 5.63–5.60 (m, 1 H), 2.74 (s, 1 H, OH), 2.71–2.63 (m, 2 H), 2.32 (s, 3 H, ArC*H*$_3$), 1.93–1.86 (m, 1 H), 1.81–1.76 (m, 1 H), 1.03 (s, 3 H, CH$_3$).

^{13}C NMR (CDCl$_3$): $\delta = 171.2$, 160.0, 150.4, 134.2, 130.7, 125.4, 124.7, 116.7, 79.9, 74.9, 50.6, 28.8, 28.2, 20.8, 20.2.

MS (CI, 120 eV): *m*/*z* (%) = 277 (100, M$^+$ + 1), 276 (32, M$^+$), 259 (30), 243 (3), 231 (56), 213 (10), 205 (18), 203 (12), 187 (12), 149 (9), 135 (8).

(–)-(1*R*)-**14** (15.3 g, 62.0 mmol) was transformed analogously to (1*R*,2*R*,3*R*)-**15**; $[\alpha]_D^{20}$ + 77.4 (*c* = 1.04, CHCl$_3$).

(1*R,2*R**)-2-(2-Hydroxy-5-methylphenyl)-1-methyl-3-oxocyclopentane-1-carboxylic Acid Lactone (16):**

To 30 % aq H$_2$SO$_4$ (135 mL) was added *rac*-**15** (13.5 g, 48.9 mmol) in one portion at 130 °C and stirring was continued for 0.5 h. The mixture was cooled, diluted with ice-cold H$_2$O (100 mL) and extracted with CH$_2$Cl$_2$ (3 × 100 mL). The organic layers were washed with sat. aq NaHCO$_3$ (3 × 100 mL) and dried (MgSO$_4$). The product obtained after evaporation was recrystallized from EtOH; yield: 6.72 g (60 %); colourless crystals; mp 101 °C.

IR (film): *v* = 1760 (OC=O), 1755 (C=O) cm^{-1}.

^{1}H NMR (CDCl$_3$): $\delta = 7.11$–7.09 (m, 2 H), 6.92 (d, $J = 8.9$ Hz, 1 H), 3.22 (s, 1 H), 2.88–2.81 (m, 1 H), 2.54–2.46 (m, 1 H), 2.35–2.25 (m, 1 H), 2.33 (s, 3 H, ArC*H*$_3$), 1.97–1.89 (m, 1 H), 1.47 (s, 3 H, CH$_3$).

^{13}C NMR (CDCl$_3$): $\delta = 212.5$, 171.2, 148.3, 134.7, 130.0, 116.5, 115.8, 57.0, 45.5, 35.7, 32.1, 23.4, 20.7.

MS (CI, 120 eV): *m*/*z* (%) = 231 (100, M$^+$ + 1), 230 (22, M$^+$), 215 (2), 205 (2), 203 (3), 175 (7).

(+)-(1*R*,2*R*,3*R*)-**15** (5.53 g, 20.0 mmol) was transformed analogously to (1*R*,2*R*)-**16**; $[\alpha]_D^{20}$ – 48.7 (*c* = 1.12, CHCl$_3$).

(1*R,2*S**)-2-(2-Hydroxy-5-methylphenyl)-1,2-dimethyl-3-oxocyclopentane-1-carboxylic Acid Lactone (17):**

To *rac*-**16** (6.90 g, 30.0 mmol) in anhyd DME (100 mL) was added NaH (790 mg, 33.0 mmol) in one portion at – 78 °C. Hydrogen evolution was induced by removing the cooling agent and the temperature was allowed to rise up to 0 °C. MeI (6.80 g, 47.9 mmol) in anhyd DME (30 mL) was added to the suspension and stirring was continued for 20 h at r.t. H$_2$O (200 mL) was added and the mixture extracted with Et$_2$O (4 × 100 mL). The organic layers were washed twice with H$_2$O, brine and dried (MgSO$_4$). The product obtained after evaporation was crystallized from EtOH; yield: 4.39 g (60 %); colourless crystals; mp 127 °C.

IR (film): *v* = 1780 (OC=O), 1750 (C=O) cm^{-1}.

^{1}H NMR (CDCl$_3$): $\delta = 7.89$ (d, $J = 2.0$ Hz, 1 H), 7.07 (dd, $J = 8.3$, 2.0 Hz, 1 H), 6.95 (d, $J = 8.3$ Hz, 1 H), 2.71–2.66 (m, 1 H), 2.54–2.42 (m, 2 H), 2.35 (s, 3 H, ArC*H*$_3$), 2.10–2.04 (m, 1 H), 1.32 (s, 3 H, CH$_3$), 1.04 (s, 3 H), CH$_3$).

^{13}C NMR (CDCl$_3$): $\delta = 211.5$, 171.6, 148.9, 134.6, 128.9, 127.3, 125.1, 116.1, 51.3, 47.4, 34.3, 25.2, 22.6, 21.0, 20.4.

MS (CI, 120 eV): *m*/*z* (%) = 245 (100, M$^+$ + 1), 244 (33, M$^+$), 227 (29), 217 (23), 205 (14), 189 (15), 160 (15), 151 (10), 125 (15), 111 (15), 97 (17).

(–)-(1*R*,2*R*)-**16** (2.53 g, 11.0 mmol) was transformed analogously to (1*R*,2*S*)-**17**; $[\alpha]_D^{20}$ + 110 (*c* = 1.02, CHCl$_3$).

2-(2-Hydroxy-5-methylphenyl)-1,2-dimethylcyclopentane-1-carboxylic Acid (18):

A mixture of *rac*-**17** (3.00 g, 12.3 mmol), hydrazine monohydrate (1.86 g, 37.1 mmol), NaOH (2.22 g, 55.5 mmol) and diethylene glycol (40 mL) was heated to 240 °C (bath temp.) for 24 h. After cooling, H$_2$O (300 mL) was added, the mixture extracted with Et$_2$O (2 × 100 mL), acidified with conc. HCl and the carboxylic acid was extracted with Et$_2$O (4 × 100 mL). The combined organic layers were washed with brine, dried (MgSO$_4$) and concentrated; yield: 2.37 g (78 %) of a colourless oil, 5.5 : 1 mixture of **18** and **2** according to ^{1}H NMR.

IR (film): *v* = 3440 (OH), 1675 (C=O) cm^{-1}.

^{1}H NMR (CDCl$_3$): $\delta = 7.84$ (s, 1 H, OH), 7.03 (d, $J = 2.2$ Hz, 1 H), 6.88 (dd, $J_1 = 8.0$ Hz, $J_2 = 2.2$ Hz, 1 H), 6.68 (d, $J = 8.0$ Hz, 1 H), 2.61–2.50 (m, 2 H), 2.25 (s, 3 H, ArC*H*$_3$), 1.99–1.69 (m, 4 H), 1.49 (s, 3 H, CH$_3$), 0.97 (s, 3 H, CH$_3$).

^{13}C NMR (CDCl$_3$): $\delta = 185.5$, 152.0, 132.6, 129.2, 128.8, 117.1, 54.0, 53.3, 40.2, 39.5, 31.5, 24.8, 23.6, 21.0.

MS (EI, 70 eV): *m*/*z* (%) = 248 (7, M$^+$).

(+)-(1*R*,2*S*)-**17** (1.22 g, 5.00 mmol) was transformed analogously to (1*R*,2*R*,*S*)-**18**; 5.5 : 1 mixture with (+)-**2**; $[\alpha]_D^{20}$ + 56.2 (*c* = 0.72, CHCl$_3$).

(1*R,2*S**)-2-(2-Hydroxy-5-methylphenyl)-1,2-dimethylcyclopentane-1-carboxylic Acid Lactone (*rac*-herbertenolide) (2):**

A mixture of *rac*-**18** (1.99 g, 8.00 mmol), *p*-TosOH · H$_2$O (385 mg, 2.00 mmol) and toluene (200 mL) was heated to reflux for 48 h, cooled, washed with H$_2$O (2 × 50 mL), sat. aq NaHCO$_3$ (2 × 50 mL) and dried (MgSO$_4$). The crude product after concentration was recrystallized from hexane; yield: 1.71 g (93 %); colourless crystals; mp 74 °C.

IR (film): *v* = 3050, 3010, 2965, 2930, 2870, 2850, 1770, 1490, 1380, 1275, 1210, 1125, 1085, 1050, 930 cm^{-1}.

^{1}H NMR (CDCl$_3$): $\delta = 7.01$ (dd, $J = 8.2$, 1.6 Hz, 1 H), 6.92 (d, $J = 8.2$ Hz, 1 H), 6.88 (d, $J = 1.6$ Hz, 1 H), 2.32 (s, 3 H, ArC*H*$_3$), 2.21–2.16 (m, 1 H), 2.02–1.88 (m, 4 H), 1.79–1.73 (m, 1 H), 1.12 (s, 3 H, CH$_3$), 0.92 (s, 3 H, CH$_3$); the *trans*-substitution was confirmed by NOESY-technique.

^{13}C NMR ($CDCl_3$): $\delta = 173.6$, 149.7, 134.1, 133.1, 128.1, 125.3, 115.8, 50.8, 47.1, 29.7, 29.1, 25.4, 20.9, 19.9, 19.8.

MS (EI, 70 eV): m/z (%) = 230 (63, M^+), 215 (59), 202 (30), 187 (100), 173 (19), 159 (65), 145 (27), 134 (12), 121 (15), 115 (16), 105 (16), 91 (20), 79 (19), 69 (5), 55 (14), 40 (34).

The spectroscopical data were identical with the literature.[13]

(+)-(1*R*,2*R*)-**18** (1.00 g, 4.00 mmol) was transformed yielding (1*R*,2*S*)-**2**, *ent*-herbertenolide (100% de, > 98% ee); $[\alpha]_D^{20}$ +96.8 ($c = 1.08$, $CHCl_3$); Lit.[13] $[\alpha]_D$ −86.4.

(+)-Ethyl (1*R*,2*S*)-2-Hydroxycyclopentane-1-carboxylate (20):

In a 3 L Erlenmeyer flask connected to a stirring or shaking apparatus, baker's yeast (225 g; Pleser, Darmstadt) was suspended in a solution of sugar (225 g) in H_2O (1.5 L). After 0.5 h ethyl 2-oxocyclopentane-1-carboxylate (**19**; 22.5 g, 143 mmol) and Triton®X 114 (450 mg, Fluka) were added and the mixture was stirred for 48 h. Hyflow Super Cel® (80 g, Fluka) was added in portions with stirring and the mixture was filtered through a G2-frit, saturated with NaCl, extracted with Et_2O (4 × 300 mL) and dried ($MgSO_4$). Four such experiments were combined and the residue purified by distillation; yield: 62.6 g (65%); colourless oil; bp 95°C/10 mbar. All spectroscopic data were identical with the literature;[22] $[\alpha]_D^{20}$ +15.1 ($c = 2.25$, $CHCl_3$), Lit.[22] $[\alpha]_D$ +14.7 ($c = 2.08$, $CHCl_3$).

(+)-Ethyl (1*R*,2*S*)-2-Hydroxy-1-methylcyclopentane-1-carboxylate (21):

To a solution of LDA, prepared (−78°C, then 0°C, 1 h) from diisopropylamine (60.7 g, 0.60 mol) in anhyd THF (225 mL) and MeLi (375 mL, 0.60 mol, 1.6 M in Et_2O) was added in one portion at −50°C the carboxylate **20** (40.1 g, 0.25 mol) in anhyd THF (60 mL). The temperature was raised up to −10°C and stirring was continued for 0.5 h at this temperature. MeI (49.7 g, 0.35 mol) in HMPA (125 mL) was added the temperature rising up to +40°C. Stirring was continued for 20 h at r.t. and the mixture was poured into sat. aq NH_4Cl (1000 mL), extracted with Et_2O (4 × 200 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by distillation; yield: 36.1 g (84%); colourless oil; bp 99°C/10 mbar; $[\alpha]_D^{20}$ +28.4 ($c = 1.61$, $CHCl_3$).

Note: MeLi can be replaced by BuLi (2.5 M in hexane) and HMPA by DMPU; yield: 84%.

IR (film): $\nu = 3455$ (OH), 1730, 1720, 1705 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 4.18$ (q, $J = 7.1$ Hz, 2H), 4.00–3.96 (m, 1H), 3.19 (m, 1H), 2.27–2.18 (m, 1H), 2.02–1.98 (m, 1H), 1.86–1.82 (m, 1H), 1.73–1.64 (m, 2H), 1.59–1.53 (m, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.18 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): $\delta = 177.2$, 80.0, 60.6, 54.1, 33.3, 32.0, 22.4, 20.5, 14.2.

MS (CI, 120 eV): m/z (%) = 173 (100, $M^+ + 1$), 172 (1, M^+), 155 (6), 127 (3), 81 (3).

(−)-Ethyl (1*R*)-1-Methyl-2-oxocyclopentane-1-carboxylate (9):

To a solution of (+)-(1*R*,2*S*)-**21** (34.4 g, 0.20 mol) in Et_2O (200 mL) was added dropwise a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (89.4 g, 0.30 mol) and conc. H_2SO_4 (75 g) in H_2O (200 mL) at 0–5°C and stirring was continued for 20 h at r.t. H_2O (220 mL) was added and the mixture was extracted with Et_2O (4 × 200 mL) and the combined organic layers were washed with sat. aq $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The crude product was purified by distillation; yield: 23.5 g (69%), colourless oil; bp 96°C/10 mbar; $[\alpha]_D^{20}$ −13.3 ($c = 1.09$, $CHCl_3$).

IR (film): $\nu = 1750$ (C=O), 1735 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 4.15$ (q, $J = 7.1$ Hz, 2H), 2.53–2.39 (m, 2H), 2.35–2.27 (m, 1H), 2.11–2.02 (m, 1H), 1.96–1.82 (m, 2H), 1.30 (s, 3H, CH_3), 1.24 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR ($CDCl_3$): $\delta = 215.7$, 172.4, 61.3, 55.9, 37.6, 36.3, 19.6, 19.4, 14.1.

MS (CI, 120 eV): m/z (%) = 171 (100, $M^+ + 1$), 170 (4, M^+), 142 (18), 125 (14), 113 (4).

Ethyl (1*R,2*S**)-2-(Benzyloxy-5-methylphenyl)-2-hydroxy-1-methylcyclopentane-1-carboxylate (23):**

To Grignard reagent **22**, prepared from Mg (8.77 g, 0.36 mol, 20 mL anhyd THF) and 4-benzyloxy-3-bromotoluene (100 g, 0.36 mol in 300 mL anhyd THF; reflux, 1 h) was added *rac*-**9** (54.4 g, 0.32 mol) in anhyd THF (100 mL) at −20°C. The mixture was allowed to warm to r.t. within 10 h. Ice-cold sat. aq NH_4Cl (400 mL) was added at −5°C and the mixture was separated (any precipitate formed was hydrolysed with sat. aq NH_4Cl). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The solid residue was sufficiently pure; yield: 90.4 g (74%); colourless crystals; mp 74°C (crude product).

IR (film): $\nu = 3485$ (OH), 1710 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 7.44$–7.33 (m, 5H), 6.99–6.97 (m, 2H), 6.87–6.84 (m, 1H), 5.44 (d, $J = 2.5$ Hz, 1H, OH), 5.11/5.05 (d, $J = 11.0$ Hz, 2H, $PhCH_2$), 3.64 (q, $J = 7.1$ Hz, 2H), 2.75–2.72 (m, 1H), 2.35–2.28 (m, 1H), 2.23 (s, 3H, $ArCH_3$), 1.99–1.87 (m, 3H), 1.69–1.63 (m, 1H), 1.28 (s, 3H, CH_3), 0.88 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR ($CDCl_3$): $\delta = 176.6$, 155.2, 136.1, 130.0, 129.9, 128.8, 128.7, 128.4, 127.9, 112.5, 87.3, 71.1, 60.0, 59.8, 38.7, 37.1, 21.7, 20.6, 19.6, 13.6.

MS (CI, 120 eV): m/z (%) = 368 (24, M^+), 351 (100), 305 (4), 278 (27), 187 (7), 142 (2), 135 (3), 109 (3), 91 (8).

2-(2-Benzyloxy-5-methylphenyl)-1-methylcyclopent-2-ene-1-carboxylic Acid (24):

A mixture of **23** (88.4 g, 0.24 mol) and $KHSO_4$ (3.00 g, 22.0 mmol) was heated to 140°C for 1 h, cooled, taken up in Et_2O (300 mL), washed (sat. aq $NaHCO_3$, brine) and dried ($MgSO_4$). The crude product after concentration (83.2 g, 0.238 mol, 99%) was taken up in EtOH (700 mL), KOH (42.0 g, 0.75 mol) was added and the mixture heated to reflux for 24 h. The solvent was removed in vacuo and the residue taken up in H_2O (150 mL) and extracted with Et_2O (3 × 50 mL). The aqueous layer was acidified with conc. HCl, the carboxylic acid was filtered and recrystallized from Et_2O/hexane (1:1); yield: 52.2 g (68%); colourless crystals; mp 117°C.

IR (film): $\nu = 3500$–3000 (OH), 1690 (C=O), 1495 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 7.34$–7.21 (m, 5H), 6.99 (d, $J = 1.9$ Hz, 1H), 6.88 (dd, $J = 8.3$, 1.9 Hz, 1H), 6.65 (d, $J = 8.3$ Hz, 1H), 6.12 (t, $J = 2.4$ Hz, 1H, C=CH), 5.00 (s, 2H, $PhCH_2$), 2.63–2.57 (m, 1H), 2.41–2.26 (m, 2H), 2.19 (s, 3H, $ArCH_3$), 1.88–1.80 (m, 1H), 1.27 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): $\delta = 183.0$, 153.8, 144.2, 137.6, 133.6, 130.9, 129.7 128.8, 128.4, 127.5, 126.9, 125.6, 112.7, 70.0, 56.5, 40.1, 31.1, 22.4, 20.4.

MS (CI, 120 eV): m/z (%) = 322 (41, M^+), 305 (29), 277 (100), 214 (14), 185 (14), 145 (2), 91 (14).

2-(2-Benzyloxy-5-methylphenyl)-1-methyl-3-oxocyclopentane-1-carboxylic Acid (25):

To 85% aq formic acid (190 mL) was added dropwise 30% aq H_2O_2 (21.5 g, 0.19 mol) at 0°C. After stirring for 0.5 h **24** (51.6 g, 0.16 mol) was added in small portions and the ice-bath removed the reaction temperature rising up to 40°C. The mixture was stirred for an additional 2 h at this temperature, cooled and poured into ice-cold H_2O (200 mL) containing $NaHSO_3$. The yellow oil formed was extracted with Et_2O, washed twice with H_2O, dried ($MgSO_4$) and concentrated; yield: 50.4 g (93%); yellow oil; mixture of diastereomers.

IR (film): $\nu = 3500$–3000 (OH), 1735 (C=O), 1700 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 9.10$ (s, 1H, OH), 7.38–7.27 (m, 5H), 6.88–6.77 (comb. m, 3H), 4.97–4.86 (m, 2H, $PhCH_2$), 4.05/3.81 (s, 1H, ArC*H*), 2.68–2.63, 2.48–2.12 (m, 3H), 2.25/2.18 (s, 3H, $ArCH_3$), 1.93–1.81 (m, 1H), 1.39/1.05 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): $\delta = 216.9$, 215.6, 182.8, 180.9, 164.7, 155.1, 154.5, 136.9, 136.6, 133.3, 131.8, 130.5, 130.3, 130.0, 129.4, 128.5, 128.1, 127.9, 127.8, 127.7, 124.6, 123.0, 112.1, 111.6, 70.7, 70.6, 65.8, 60.0, 58.2, 52.7, 50.8, 36.9, 36.8, 32.8, 32.5, 24.2, 20.5, 19.5, 15.1.

MS (CI, 120 eV): *m*/*z* (%) = 338 (17, M$^+$), 321 (18), 293 (56), 247 (11) 231 (25), 203 (21), 135 (9), 91 (100), 75 (50).

(1*R,2*R**)-2-(2-Hydroxy-5-methylphenyl)-1-methyl-3-oxocyclopentane-1-carboxylic Acid Lactone (16)** (*from* **25**):

To **25** (2.00 g, 5.91 mmol) in anhyd CH_2Cl_2 (100 mL) was added BBr_3 (20 mL, 1 M in CH_2Cl_2, 20.0 mmol) at − 70 °C. The mixture was allowed to warm to − 30 °C within 4 h and poured into ice-cold H_2O (150 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with sat. aq $NaHCO_3$ (2 × 100 mL), brine (2 × 50 mL), dried ($MgSO_4$) and concentrated. Benzyl bromide was removed by filtering through a silica gel pad eluting with petroleum ether and the product was eluted with Et_2O and crystallized from Et_2O/hexane (1:1); yield: 730 mg (54 %); colourless crystals; mp 101 °C. The spectroscopic data were identical with the product *rac*-**16** obtained from *rac*-**15** (see above).

2-(2-Methoxy-5-methylphenyl)-1-methylcyclopent-2-ene-1-carbaldehyde (26):

To *rac*-**12** (50.0 g, 182 mmol) in anhyd THF (180 mL) was added dropwise $LiAlH_4$ (9.00 g, 237 mmol) in anhyd THF (250 mL). The mixture was heated to reflux for 3 h, cooled and hydrolysed with ice-cold H_2O and 1 N NaOH. The aqueous layer was filtered and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The product crystallized after evaporation of the solvent; yield: 40.7 g (96 %); an analytical sample could be obtained from hexane.

The crude primary alcohol (40.0 g, 172 mmol) was dissolved in anhyd CH_2Cl_2 (600 mL) and treated with pyridinium chlorochromate (55.8 g, 258 mmol) in one portion. The mixture was stirred at room temperature for 24 h, the solvent removed in vacuo and the residue dissolved in Et_2O (5 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by filtration through a silica gel pad eluting with CH_2Cl_2; yield: 28.8 g (73 %); yellow oil.

IR (film): ν = 2795 (CH=O), 2700 (CH=O), 1725 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.64 (s, 1 H), 7.02 (dd, *J* = 8.4, 2.1 Hz, 1 H), 6.98 (d, *J* = 2.1 Hz, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 6.10 (t, *J* = 2.4 Hz, 1 H, C=H), 3.61 (s, 3 H, OCH_3), 2.56–2.52 (m, 1 H), 2.48–2.41 (m, 1 H), 2.29–2.23 (m, 1 H), 2.27 (s, 3 H, ArC*H*$_3$), 1.91–1.83 (m, 1 H), 1.07 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 203.0, 154.3, 145.0, 133.3, 131.3, 129.7, 129.3, 125.2, 110.4, 61.1, 54.3, 36.8, 30.9, 20.4, 18.5.

MS (CI, 120 eV): *m*/*z* (%) = 230 (33, M$^+$), 202 (74), 173 (39), 171 (51), 159 (59), 145 (100), 141 (31), 128 (68), 121 (47), 115 (59), 105 (48), 91 (50), 77 (52), 61 (35), 51 (33), 46 (86), 45 (94).

2-(2-Methoxy-5-methylphenyl)-3,3-dimethylcyclopentane (27):

A mixture of **26** (20.1 g, 87.2 mmol), $N_2H_4 \cdot H_2O$ (14.1 g, 0.28 mol), NaOH (16.9 g, 0.42 mol) and diethylene glycol (250 mL) was heated to 195 °C (bath temp.) for 24 h. After cooling H_2O (600 mL) was added and the mixture extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The product was purified by distillation; yield: 14.5 g (77 %); colourless oil; bp 85 °C/0.01 mbar.

IR (film): ν = 3035, 1610, 1505 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.01 (dd, *J* = 8.3, 2.1 Hz, 1 H), 6.82 (d, *J* = 2.1 Hz, 1 H), 6.76 (d, *J* = 8.3 Hz, 1 H), 5.52 (t, *J* = 2.3 Hz, 1 H, C=CH), 3.72 (s, 3 H, OCH_3), 2.39 (td, J_1 = 7.0 Hz, J_2 = 2.3 Hz, 2 H), 2.26 (s, 3 H, ArC*H*$_3$), 1.85 (t, *J* = 7.0 Hz, 2 H), 1.04 (s, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): δ = 155.6, 149.6, 131.9, 128.9, 128.3, 127.8, 127.4, 110.8, 55.6, 48.0, 41.0, 30.0, 27.3, 20.5.

MS (CI, 120 eV): *m*/*z* (%) = 216 (100, M$^+$), 201 (74), 186 (7), 173 (15), 159 (10), 145 (20), 137 (7), 121 (7).

2-(2-Methoxy-5-methylphenyl)-3,3-dimethylcyclopentan-1-ol (28):

The olefin **27** (17.5 g, 80.9 mmol) was dissolved in anhyd THF (480 mL), $NaBH_4$ (1.05 g, 27.7 mmol) and $Et_2O \cdot BF_3$ (6.68 g, 5.80 mL, 47.1 mmol) were added and the mixture was stirred for 20 h at r.t. 3 N aq NaOH (32 mL) was added dropwise followed by 30 % aq H_2O_2 (30 mL) with additional stirring for 20 h. The mixture was saturated with NaCl and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed twice with brine, dried ($MgSO_4$) and concentrated. The product was purified by CC (CH_2Cl_2); yield: 14.8 g (78 %); colourless oil.

IR (film): ν = 3400 (OH), 3020 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 6.98–6.96 (m, 2 H), 6.75 (d, *J* = 8.9 Hz, 1 H), 4.62–4.56 (m, 1 H, CHO), 3.72 (s, 3 H, OCH_3), 3.21 (s, 1 H, OH), 2.27 (s, 3 H, Ar-C*H*$_3$), 2.20–2.13 (m, 1 H), 1.82–1.75 (m, 2 H), 1.71–1.64 (m, 1 H), 1.59–1.52 (m, 1 H), 1.00 (s, 3 H, CH_3), 0.67 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 156.7, 129.6, 129.1, 127.6, 127.5, 110.7, 76.8, 56.6, 55.4, 41.8, 39.2, 31.8, 29.9, 25.1, 20.7.

MS (CI, 120 eV): *m*/*z* (%) = 234 (100, M$^+$), 219 (13), 165 (10), 136 (25), 105 (13), 99 (20), 84 (12), 81 (11), 4 (25).

2-(2-Methoxy-5-methylphenyl)-3,3-dimethylcyclopentanone (29) (*from* **28**):

To a solution of **28** (14.8 g, 63.1 mmol) in Et_2O (110 mL) was added dropwise a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (33.8 g, 0.11 mol) and conc. H_2SO_4 (15 g) in H_2O (80 mL) at 0–5 °C and stirring was continued for 20 h at r.t. Ice-cold H_2O (220 mL) was added and the mixture extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The crude oil was purified by CC (CH_2Cl_2); yield: 7.60 g (52 %); colourless crystals; mp 62 °C.

IR (film): ν = 3060, 3025, 1735 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.01 (dd, *J* = 8.3, 2.1 Hz, 1 H), 6.76 (d, *J* = 8.3 Hz, 1 H), 6.73 (d, *J* = 2.1 Hz, 1 H), 3.71 (s, 3 H, OCH_3), 3.65 (s, 1 H, ArC*H*), 2.39 (dt, *J* = 2.6, 7.6 Hz, 2 H), 2.26 (s, 3 H, ArC*H*$_3$), 1.92–1.82 (m, 2 H), 1.13 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 218.8, 155.8, 132.3, 129.4, 128.6, 124.5, 110.8, 61.1, 55.4, 41.6, 36.8, 35.9, 29.4, 23.2, 10.6.

MS (CI, 120 eV): *m*/*z* (%) = 232 (100, M$^+$), 177 (47), 162 (46), 149 (28), 135 (97), 121 (33), 112 (18), 105 (43), 97 (19), 91 (26), 77 (18).

2-(2-Methoxy-5-methylphenyl)-3,3-dimethylcyclopentanone (29) (*from* **27**):

To **27** (2.00 g, 9.25 mmol) in formic acid (20 mL) was added dropwise 30 % aq H_2O_2 (1.67 g, 14.7 mmol) at 0 °C. The mixture was stirred (0 °C, 1 h, 20 °C, 20 h) and poured into ice-cold H_2O (150 mL) containing a trace of $NaHSO_3$. The yellow oil formed was extracted with Et_2O (3 × 50 mL), washed with 2 % aq NaOH (25 mL) and brine, dried ($MgSO_4$) and concentrated. The crude oil was purified by CC (CH_2Cl_2) and recrystallized from hexane; yield: 800 mg (37 %); colourless crystals; mp 62 °C.

All spectroscopic data were identical with the product obtained from **28** (see above).

2-(2-Methoxy-5-methylphenyl)-2,3,3-trimethylcyclopentanone (30):

To **29** (5.40 g, 23.2 mmol) in anhyd DME (100 mL) was added NaH (612 mg, 25.5 mmol) in one portion at − 50 °C. Hydrogen evolution was induced by removing the cooling agent and the temperature was allowed to rise up to 0 °C. Iodomethane (5.24 g, 36.9 mmol) in anhyd DME (20 mL) was added dropwise and stirring was continued (3 h at 0 °C, 20 h at r.t.). The mixture was poured into H_2O (150 mL) and extracted with Et_2O (3 × 100 mL). The organic layers were washed with brine and dried ($MgSO_4$). The product obtained after evaporation was purified by CC (Et_2O/hexane, 1:2); yield: 3.73 g (65 %); colourless crystals; mp 66 °C.

IR (film): ν = 3025, 1735 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.00–6.98 (m, 2 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 3.63 (s, 3 H, OCH_3), 2.71–2.61 (m, 1 H), 2.39–2.31 (m, 1 H), 2.27 (s, 3 H, ArC*H*$_3$), 1.85–1.73 (m, 2 H), 1.29 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 221.1, 154.7, 131.5, 130.1, 129.6, 128.3, 112.9, 56.6, 55.5, 43.7, 35.5, 35.4, 26.1, 25.5, 20.8, 20.5.

MS (CI, 120 eV): *m*/*z* (%) = 246 (63, M$^+$), 191 (11), 176 (20), 161 (17), 149 (100), 135 (41), 119 (13), 112 (19), 105 (22), 91 (19), 77 (11).

1-(2-Hydroxy-5-methylphenyl)-1,2,2-trimethylcyclopentane (*rac*-**3**, *rac*-α-Herbertenol):

A mixture of **30** (1.00 g, 4.06 mmol), $N_2H_4 \cdot H_2O$ (1.22 g, 24.4 mmol), NaOH (1.46 g, 36.5 mmol) and diethylene glycol (40 mL) was heated to 220 °C (bath temp.) for 72 h. After cooling, H_2O (200 mL) was added and the mixture extracted with Et_2O (3 × 50 mL). The organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude oil was purified by CC (Et_2O/hexane, 1:4); yield: 500 mg (56 %); colourless oil.

IR (film): $\nu = 3605, 3535$ (OH), 1610, 1510, 1410, 1390, 1375, 1250, 1170, 1150, 810 cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 7.09$ (d, $J = 2.0$ Hz, 1 H), 6.84 (dd, $J = 7.9$, 2.0 Hz, 1 H), 6.54 (d, $J = 7.9$ Hz, 1 H), 4.65 (s, 1 H, OH), 2.60–2.57 (m, 1 H), 2.25 (s, 3 H, ArCH_3), 1.77–1.61 (m, 4 H), 1.57–1.52 (m, 1 H), 1.40 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 0.75 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): $\delta = 152.3$, 133.1, 130.1, 129.0, 127.3, 116.8, 51.0, 44.7, 41.4, 39.5, 27.0, 25.6, 23.0, 20.9, 20.4.

MS (CI, 120 eV): m/z (%) = 218 (100, M^+), 203 (5), 175 (7), 161 (21), 148 (61), 135 (53), 121 (13), 105 (7), 91 (5), 79 (2), 69 (3), 41 (4).

All spectroscopic data were identical with the literature.[13]

Ethyl 2-Hydroxy-2-(4-methoxy-3-methylphenyl)-1-methylcyclopentane-1-carboxylate (32):

To the Grignard reagent **31**, prepared from Mg (8.46 g, 0.35 mol, 30 mL anhyd THF) and 4-bromo-2-methylanisole (70.0 g, 0.35 mol in 250 mL anhyd THF; reflux, 1 h) was added *rac*-**9** (53.8 g, 0.315 mol) in anhyd THF (80 mL) at −40 °C. The mixture was allowed to warm to r. t. within 10 h, re-cooled to −20 °C and the precipitate was filtered and hydrolysed with sat. aq NH_4Cl. The aqueous layer was extracted with Et_2O (3 × 150 mL) and the organic layers were dried ($MgSO_4$) and concentrated; yield: 71.1 g (77 %); colourless oil.

IR (film): $\nu = 3505$ (OH), 1725 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 7.20$–7.17 (m, 2 H), 6.72 (d, $J = 8.3$ Hz, 1 H), 3.78 (s, 3 H, OCH_3), 3.82–3.69 (m, 2 H), 2.67–2.64 (m, 1 H), 2.36–2.31 (m, 1 H), 2.18 (s, 3 H, ArCH_3), 2.12 (s, 1 H, OH), 1.96–1.86 (m, 3 H), 1.82–1.75 (m, 1 H), 1.32 (s, 3 H, CH_3), 0.92 (t, $J = 7.1$ Hz, 3 H).

^{13}C NMR ($CDCl_3$): $\delta = 176.4$, 156.9, 135.5, 128.2, 125.6, 124.2, 109.1, 84.8, 60.2, 58.3, 55.3, 38.9, 35.8, 20.6, 18.7, 16.4, 13.7.

MS (CI, 120 eV): m/z (%) = 292 (22, M^+), 218 (34), 170 (21), 149 (21), 142 (24), 122 (100), 115 (29), 107 (27), 91 (18), 87 (20), 77 (15).

Ethyl 2-(4-Methoxy-3-methylphenyl)-1-methylcyclopent-2-ene-1-carboxylate (33):

A mixture of the alcohol **32** (61.4 g, 0.21 mol) and $KHSO_4$ (3.00 g, 22.0 mmol) was heated to 140 °C for 1 h, cooled, taken up in Et_2O (150 mL) washed (sat. aq $NaHCO_3$, brine) dried ($MgSO_4$) and concentrated; yield: 57.0 g (99 %); colourless oil.

IR (film): $\nu = 1725$ (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 7.11$ (d, $J = 2.0$ Hz, 1 H), 6.96 (dd, $J = 8.4$, 2.0 Hz, 1 H), 6.71 (d, $J = 8.4$ Hz, 1 H), 6.03 (t, $J = 2.5$ Hz, 1 H, C=CH), 4.17–4.10 (m, 2 H), 3.78 (s, 3 H, OCH_3), 2.57–2.39 (m, 3 H), 2.18 (s, 3 H, ArCH_3), 1.96–1.89 (m, 1 H), 1.42 (s, 3 H, CH_3), 1.16 (t, $J = 7.1$ Hz, 3 H).

^{13}C NMR ($CDCl_3$): $\delta = 177.6$, 157.0, 146.2, 129.0, 127.9, 127.8, 126.3, 124.4, 109.6, 60.6, 56.0, 55.3, 39.8, 30.8, 22.6, 16.3, 14.1.

MS (CI, 120 eV): m/z (%) = 274 (72, M^+), 201 (100), 149 (15), 142 (15), 115 (28), 91 (15), 87 (21), 69 (26), 58 (26), 56 (15), 43 (63), 41 (30).

2-(4-Methoxy-3-methylphenyl)-1-methylcyclopent-2-ene-1-carbaldehyde (34):

To the carboxylate **33** (54.8 g, 0.20 mol) in anhyd THF (200 mL) was added dropwise $LiAlH_4$ (10.2 g, 0.27 mol) in anhyd THF (280 mL). The mixture was heated to reflux for 4 h, cooled and hydrolysed with ice-cold H_2O and 1 N NaOH (200 mL). The aqueous layer was filtered and extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated; yield: 46.0 g (99 %); yellow oil.

The crude material (44.1 g, 0.19 mol) in anhyd CH_2Cl_2 (800 mL) was treated with pyridinium chlorochromate (61.5 g, 0.285 mol) in one portion. The mixture was stirred at 20 °C for 24 h, the solvent removed in vacuo and the residue extracted with Et_2O (5 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by CC (CH_2Cl_2); yield: 21.0 g (48 %); yellow oil.

IR (film): $\nu = 2800$ (CH=O), 2700 (CH=O), 1725 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 9.64$ (s, 1 H, CHO), 7.08 (d, $J = 1.9$ Hz, 1 H), 7.01 (dd, $J = 8.4$, 1.9 Hz, 1 H), 6.70 (d, $J = 8.4$ Hz, 1 H), 6.17 (t, $J = 2.6$ Hz, 1 H, C=CH), 3.78 (s, 3 H, OCH_3), 2.54 (td, $J = 7.0$, 2.6 Hz, 2 H), 2.36–2.29 (m, 1 H), 2.17 (s, 3 H, ArCH_3), 1.85–1.78 (m, 1 H), 1.32 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): $\delta = 203.7$, 157.3, 144.0, 129.9, 128.9, 127.5, 126.6, 124.8, 109.7, 61.5, 55.3, 35.4, 30.6, 18.4, 16.2.

MS (CI, 120 eV): m/z (%) = 230 (42, M^+), 214 (28), 201 (100), 185 (20), 149 (15), 141 (12), 128 (13), 115 (14), 91 (10), 43 (14).

2-(4-Methoxy-3-methylphenyl)-3,3-dimethylcyclopentene (35):

A mixture of **34** (20.7 g, 90.0 mmol), $N_2H_4 \cdot H_2O$ (15.0 g, 0.30 mol), NaOH (17.6 g, 0.44 mol) and diethylene glycol (250 mL) was heated to 195 °C (bath temp) for 7 h. After cooling H_2O (600 mL) was added and the mixture extracted with Et_2O (3 × 200 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The product was purified by CC (hexane); yield: 9.75 g (50 %); yellow oil.

IR (film): $\nu = 3035$, 1610, 1505 (C=C) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 7.13$–7.11 (m, 2 H), 6.73 (d, $J = 9.1$ Hz, 1 H), 5.64 (t, $J = 2.5$ Hz, 1 H, C=CH), 3.79 (s, 3 H, OCH_3), 2.33 (td, $J = 7.0$, 2.5 Hz, 2 H), 2.20 (s, 3 H, ArCH_3), 1.83 (t, $J = 7.0$ Hz, 2 H), 1.19 (s, 6 H, 2 CH_3).

^{13}C NMR ($CDCl_3$): $\delta = 156.7$, 151.8, 130.1, 126.0, 125.9, 125.7, 109.4, 55.2, 46.5, 42.5, 29.3, 27.5, 16.3.

MS (CI, 120 eV): m/z (%) = 216 (100, M^+).

2-(4-Methoxy-3-methylphenyl)-3,3-dimethylcyclopentanone (36):

To **35** (8.40 g, 38.8 mmol) in anhyd THF (220 mL) were added $NaBH_4$ (500 mg, 13.2 mmol) and $Et_2O \cdot BF_3$ (2.31 g, 2.00 mL, 16.3 mmol) and the mixture was stirred for 20 h at r. t. 3 N aq NaOH (16 mL) was added dropwise followed by 30 % aq H_2O_2 (14 mL) with additional stirring for 2 h. The organic layer was separated, the aqueous layer saturated with NaCl and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$) and concentrated. The crude product in anhyd CH_2Cl_2 (60 mL) was added in one portion to a slurry of PCC (12.5 g, 58.2 mmol) and anhyd NaOAc (10.0 g, 122 mmol) in anhyd CH_2Cl_2 (250 mL). The mixture was stirred for 20 h at r. t. and filtered through a silica gel pad eluting with CH_2Cl_2. The crude material was purified by CC (CH_2Cl_2); yield: 3.90 g (43 %); colourless oil.

IR (film): $\nu = 1745$ (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 6.84$–6.77 (m, 3 H), 3.80 (s, 3 H, OCH_3), 3.10 (s, 1 H, ArCH), 2.46–2.34 (m, 2 H), 2.19 (s, 3 H, ArCH_3), 1.94–1.78 (m, 2 H), 1.15 (s, 3 H, CH_3), 0.74 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): $\delta = 218.4$, 156.9, 132.5, 128.6, 126.8, 126.3, 109.8, 67.1, 55.3, 41.2, 36.1, 35.4, 28.7, 22.5, 16.3

MS (CI, 120 eV): m/z (%) = 232 (100, M^+).

2-(4-Methoxy-3-methylphenyl)-2,3,3-trimethylcyclopentanone (37):

To **36** (2.10 g, 9.00 mmol) in anhyd DME (50 mL) was added NaH (230 mg, 9.50 mmol) in one portion at −50 °C. Hydrogen evolution was induced by removing the cooling agent and the temperature was allowed to rise up to 0 °C for 0.5 h. MeI (3.00 g, 21.1 mmol) in anhyd DME (5 mL) was added dropwise and stirring was continued (3 h at 0 °C, 20 h at r. t.). The mixture was poured into H_2O (75 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated; yield: 1.50 g (67 %); colourless oil.

IR (film): $\nu = 1740$ (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 6.93$–6.89 (m, 2 H), 6.72 (d, $J = 8.4$ Hz, 1 H), 3.78 (s, 3 H, OCH_3), 2.49–2.45 (m, 2 H), 2.19 (s, 3 H, $ArCH_3$), 1.86–1.69 (m, 2 H), 1.29 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 0.66 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): $\delta = 222.1$, 156.3, 132.7, 130.3, 126.2, 125.6, 109.3, 59.6, 55.3, 42.8, 36.0, 33.5, 26.6, 23.9, 19.4, 16.4.

MS (CI, 120 eV): m/z (%) = 246 (63, M^+), 149 (100).

1-(4-Hydroxy-3-methylphenyl)-1,2,2-trimethylcyclopentane (*rac*-4, *rac*-β-Herbertenol):

A mixture of **37** (1.48 g, 6.00 mmol), $N_2H_4 \cdot H_2O$ (1.80 g, 36.0 mmol), NaOH (2.20 g, 55.0 mmol) and diethylene glycol (60 mL) was heated to 220 °C (bath temp) for 72 h. After cooling, H_2O (300 mL) was added and the mixture extracted with Et_2O (3 x 100 mL). The combined organic layers were washed (brine), dried ($MgSO_4$) and concentrated. The crude material was purified by CC (CH_2Cl_2) and recrystallized from hexane; yield: 600 mg (45 %); colourless crystals; mp 84 °C.

IR (film): $\nu = 3330$, 1510, 1385, 1375, 1365, 1320, 1275, 1125, 995, 815 cm^{-1}.

^1H NMR ($CDCl_3$): $\delta = 7.08$ (d, $J = 2.2$ Hz, 1 H), 7.03 (dd, $J = 8.4$, 2.2 Hz, 1 H), 6.66 (d, $J = 8.4$ Hz, 1 H), 4.90 (s, 1 H, OH), 2.48–2.40 (m, 1 H), 2.23 (s, 3 H, $ArCH_3$), 1.78–1.72 (m, 2 H), 1.69–1.61 (m, 2 H), 1.56–1.49 (m, 1 H), 1.22 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 0.55 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): $\delta = 151.5$, 140.0, 129.7, 125.6, 122.4, 114.1, 50.0, 44.2, 39.9, 37.0, 26.5, 24.6, 24.3, 19.8, 16.1.

MS (EI, 70 eV): m/z (%) = 218 (25, M^+), 203 (5), 175 (6), 161 (51), 148 (100), 135 (59), 121 (28), 105 (14), 91 (30), 77 (26), 69 (15), 55 (34), 41 (10).

All spectroscopic data were identical with the literature.[13]

(1) Matsuo, A.; Yuki, S.; Nakayama, M.; Hayashi, S. *J. Chem. Soc., Chem. Commun.* **1981**, 864.
(2) Matsuo, A.; Yuki, S.; Nakayama, M.; Hayashi, S. *Chem. Lett.* **1982**, 463.
(3) Fukuyama, Y.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2737.
(4) Matsuo, A.; Yuki, S.; Nakayama, M. *Chem. Lett.* **1983**, 1041.
(5) (a) Leriverend, M.-L.; Vazeux, M. *J. Chem. Soc., Chem. Commun.* **1982**, 866.
(b) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 329.
(c) Saha, A.K.; Das, S.; Mukherjee, D.; Fronczek, F.R. *Tetrahedron Lett.* **1994**, *35*, 3353.
(6) (a) Zinsmeister, H.D.; Becker, H.; Eicher, T. *Angew. Chem.* **1991**, *103*, 134; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 130.
(b) Speicher, A.; Eicher, T. *Synthesis* **1995**, 998.
(7) Sato, K.; Suzuki, S.; Kojima, Y. *J. Org. Chem.* **1967**, *32*, 339.
(8) Koenig, K.E.; Lein, G.M.; Stuckler, P.; Kaneda, T.; Cram, D.J. *J. Am. Chem. Soc.* **1979**, *101*, 3553.
(9) Bird, C.W.; Yeong, Y.C. *Synthesis* **1974**, 27.
(10) Yamada, K.; Yazawa, H.; Uemura, D.; Toda, M.; Hirata, Y. *Tetrahedron* **1969**, *25*, 3509.
(11) (a) Roesen, W.E.; Dorfman, L.; Linfield, M.P. *J. Org. Chem.* **1964**, *29*, 1723.
(b) Balsamo, A.; Berti, G.; Crotti, P.; Ferretti, M.; Macchia, B.; Macchia, F. *J. Org. Chem.* **1974**, *39*, 2596.
(12) We thank Dr. V. Huch and Prof. Dr. M. Veith, Fachbereich Anorganische Chemie, Universität des Saarlandes for performing X-ray analyses of compounds **15** and **2**.
(13) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 701.
(14) (a) Saigo, K.; Koda, H.; Nohira, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3119.
(b) Valli, V.L.K.; Sarma, G.V.M.; Choudary, B.M. *Ind. J. Chem.* **1990**, *29B*, 481.
(c) The synthesis of methyl (1*S*)- and (1*R*)-1-methyl-2-oxocyclopentanecarboxylate (99/92 % ee) was reported:
Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron* **1994**, *50*, 3315. In our hands the method applied did not prove to be suitable for the preparation of (*S*)-**9** in a preparative scale.
(15) Sato, T.; Maeno, H.; Noro, T.; Fujisawa, J. *Chem. Lett.* **1988**, 1739.
(16) Enders, D.; Zamponi, A.; Schäfer, T.; Nübling, C.; Eichenauer, H.; Sitki Demir, A.; Raabe, G. *Chem. Ber.* **1994**, *127*, 1707.
(17) Frater, G. *Helv. Chim. Acta* **1980**, *63*, 1383.
(18) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825, 2829.
(19) Orth, U.; Pfeiffer, H.-P.; Breitmaier, E. *Chem. Ber.* **1986**, *119*, 3507.
(20) Wolff-Kishner procedure at more than 215 °C induced cleavage of the methyl ether.
(21) Nasipuri, D.; Roy, D.N. *J. Ind. Chem. Soc.* **1963**, *40*, 334.
(22) Seebach, D.; Roggo, D.; Maetzke, T. *Helv. Chim. Acta* **1987**, *70*, 1605.