Enantioselective Synthesis of Herbertane Sesquiterpenes. Synthesis of (−)-Herbertene and (−)-α-Herbertenol

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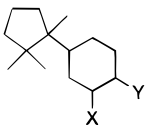
Introduction

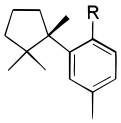
Numerous herbertane-type sesquiterpenoids, an expanding group of natural products possessing a 3-methyl-1-(1,2,2-trimethylcyclopentyl)cyclohexane skeleton (**1**), have been isolated from *Herbertus* species and other liverworts.[1] Some of these compounds, particularly those with an oxygenated aromatic six-membered ring, show a wide spectrum of biological properties, which include potent antifungal,[2] neurotrophic,[3] and *anti*-lipid peroxidation activities.[4]

We have recently described a procedure for the enantioselective construction of the 1,2,2-trimethylcyclopentane nucleus common to all the herbertane-type and structurally related cuparane-type sesquiterpenoids (e.g., **2**),[5] which has been successfully used for the synthesis of two members of the latter group of sesquiterpenes, (−)-cuparene and (−)-*δ*-cuparenol.[6] In this paper, we report the adaptation of this chemistry to the enantioselective synthesis of two representative compounds of the herbertane family: (−)-herbertene (**3**) and (−)-α-herbertenol (**4**), initially isolated from the liverwort *Herberta adunca* (Dicks.) S. Gray[7,2] and more recently from other *Herbertus* species (see ref 1).[8]



1 Herbertane skeleton: X=CH_3; Y=H

2 Cuparane skeleton: X=H; Y=CH_3



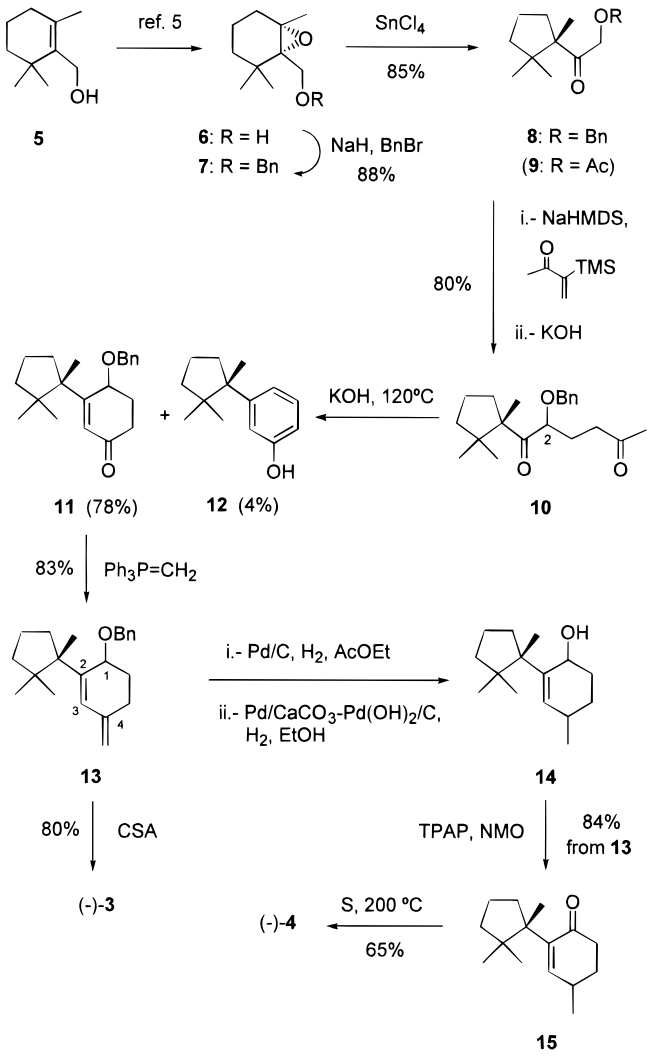
3 R=H

4 R=OH

Results and Discussion

As in the previous syntheses, the enantiopure (1*S*,2*S*)-epoxy alcohol **6**, prepared in 89% yield (98% ee) from readily available *β*-cyclogeraniol (**5**) by means of a Katsuki−Sharpless asymmetric epoxidation, was used as the starting material (Scheme 1). The hydroxyl group of **6** was protected as the benzylic ether with BnBr and NaH in DMF[9] to give **7** in 88% yield. Treatment of the epoxy benzylic ether **7** with one equivalent of tin(IV) chloride in dichloromethane at low temperature (from −50 to −15 °C) for 3 h afforded the α-benzyloxy ketone **8** in 85% yield. An enantiomeric excess of 98% was determined for this compound,[10] showing that the tin(IV) chloride promoted pinacollic rearrangement of **7** to **8** occurs without loss of

Scheme 1



(7) Matsuo, A.; Yuki, S.; Nakayama, M.; Hayashi, S. *J. Chem. Soc., Chem. Commun.* **1981**, 864.

(8) For previous synthesis of herbertane-type sesquiterpenoids, see: (a) Tori, M.; Miyake, T.; Hamaguchi, T.; Sono, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2731, and references therein. (b) Eicher, T.; Servet, F.; Speicher, A. *Synthesis*, **1996**, 863, and references therein. (c) Poon, T.; Mundy, B. P.; Favarolo, F. G.; Goudrean, C. A.; Creenberg, A.; Sullivan, R. *Synthesis* **1998**, 832. (d) Mandelt, K.; Fitjer, L. *Synthesis* **1998**, 1523, and references therein.

(9) Takaku, H.; Kamaike, K.; Tsuchiya, H. *J. Org. Chem.* **1984**, *49*, 51.

(10) The optical purity of the benzyloxy ketone **8** was determined after its conversion to the corresponding acetate **9**, prepared from **8** by hydrogenolysis of the benzyl ether moiety [H_2, $Pd(OH)_2$/C−Pd/$CaCO_3$, EtOH, rt] followed by acetylation of the free alcohol (Ac_2O, pyridine, rt). An enantiomeric excess of 98% for this compound and hence for **8** was determined by ^{1}H NMR experiments with Eu(hfc)$_3$, by observing the CH_3 signals that are resolved for racemic samples.

(1) Connolly, J. D.; Hill, R. A. In *Dictionary of Terpenoids*, 1st ed.; Chapman and Hall: London, 1991; Vol. 1, pp 299−300. Also see: Fraga, B. M. *Nat. Prod. Rep.* **1992**, *9*, 217; **1993**, *10*, 397; **1994,** *11*, 533; **1995**, *12*, 303; **1996**, *13*, 307; **1997**, *14*, 145; **1998**, *15*, 73.

(2) Matsuo, A.; Yuki, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 701.

(3) Fukuyama, Y.; Asakawa, Y.; *J. Chem. Soc., Perkin Trans. 1* **1991**, 2737.

(4) Fukuyama, Y.; Kiriyama, Y.; Kodama, M. *Tetrahedron Lett.* **1996**, *37*, 1261.

(5) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Zaragozá, R. J. *Synlett* **1993**, 895. See also: errata and addenda, *Synlett*, **1994**, 154.

(6) Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; García, M. T.; Zaragozá, R. J. *J. Org. Chem.* **1996**, *61*, 5916.

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optical purity. As previously shown,[5] with other protecting groups of the hydroxyl function (e.g., a *tert*-butyldimethylsilyl ether), a slight loss of the optical purity occurs during the rearrangement.

To prepare the cyclohexane ring, the sodium enolate obtained by treatment of **8** with *N*-sodiohexamethyldisilazane (NaHMDS) was subjected to reaction with α-trimethylsilyl vinyl ketone[11] to yield, after treatment of the crude product with potassium hydroxide in methanol to complete the cleavage of the trimethylsilyl moiety and chromatographic purification, the benzyloxy diketone **10** in 80% overall yield.[12] Completion of the synthesis of the cyclohexene ring was effected by treatment of **10** with aqueous KOH in MeOH at 120 °C in a sealed tube for 6 h. Under these conditions, an epimeric mixture of cyclohexenone **11** was obtained in 78% yield,[13,14] together with a small amount of the phenol **12** (3−5%), formed from **11** by elimination of the benzyloxy moiety.

With **11** in hand, we focused on the elaboration of the C6-ring functionality of target herbertanes. The preparation of the simpler member of the herbertane family, (−)-herbertene (**3**), could be easily accomplished in a two-step sequence as follows. Standard Wittig methylenation of the mixture of epimeric benzyloxy enones **11** gave epimeric dienes **13** in 83% yield. Treatment of this mixture with an equimolecular amount of camphorsulfonic acid (CSA) in methylene chloride at room temperature cleanly produced (−)-herbertene (**3**) in 80% yield after chromatography on silica gel, probably via isomerization of the exocyclic double bond to the endocyclic position followed by elimination of the benzyloxy moiety. The synthetic herbertane thus prepared had physical and spectroscopic data that were in agreement with those reported in the literature.[1]

The preparation of (−)-α-herbertenol (**4**) was also efficiently effected from the same key intermediate **13** as follows. Chemoselective hydrogenation of the exocyclic double bond with Pd on carbon in AcOEt followed by hydrogenolysis of the benzyl group, using $Pd(OH)_2$/C−Pd/$CaCO_3$ in EtOH,[15] resulted in the formation of diastereomeric allylic alcohols **14**, which were not purified but rather oxidized with catalytic tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) to the corresponding ketone. In this manner, we were able to realize a 84% overall yield from **13** of the cyclohexenone **15**, as a mixture of epimers at C4, after chromatography of the oxidation mixture. Final aromatization of the cyclohexane ring was effected in 65% yield by treatment of **15** with sulfur at 200 °C in a sealed tube for 45 min.[16] All spectroscopic data of synthetic (−)-α-herbertenol (**4**) also agreed very well with those reported in the literature.[1]

In conclusion, we have demonstrated that the general procedure previously developed by us for the enantioselective preparation of the 1,2,2-trimethylcyclopentane nucleus may be adapted for the preparation of herbertane-type sesquiterpenoids. Two representative members of this family of natural products have thus been prepared from *β*-cyclogeraniol **5** in a reasonable number of steps and with acceptable overall yields [(−)-**3**, 7 steps, 28% yield and (−)-**4**, 10 steps, 19% yield].[17]

Experimental Section[18]

(1a*S*,5a*S*)-1a-Benzyloxymethyl-2,2,5a-trimethylperhydrobenzo[*b*]oxirene (7). To a stirred slurry of prewashed sodium hydride (147 mg, 3.67 mmol) in dry DMF (5 mL) cooled at −50 °C was added, dropwise via syringe, epoxy alcohol **6**[6] (415.4 mg, 2.44 mmol) in DMF (4 mL). After hydrogen evolution had ceased, the reaction mixture was stirred at −20 °C for 30 min. Benzyl bromide (0.45 mL, 3.79 mmol) was added dropwise, and the mixture was stirred for 1 h before being carefully quenched with saturated NH_4Cl solution. Following dilution with water, the mixture was extracted with CH_2Cl_2 and worked up. Product purification by chromatography on silica gel, using pentane/ether 95:5 as eluent, furnished the benzylic ether **7** (560 mg, 88%) as a colorless oil: $[\alpha]^{19}_D$ +15.5 (*c* 2.1, $CHCl_3$); IR (film) 1491, 1088, 732, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (5 H, m), 4.53 and 4.44 (1 H each, each d, J = 12.0 Hz), 3.79 and 3.39 (1 H each, each d, J = 10.2 Hz), 1.38 (3 H, s), 1.15 (3 H, s), 1.05 (3 H, s); HRMS calcd for $C_{17}H_{25}O_2$ ($M^+ + 1$) 261.1849, found 261.1849.

2-Benzyloxy-1-[(1*S*)-1,2,2-trimethylcyclopentyl]-1-ethanone (8). To a solution of the benzylic ether **7** (3.28 g, 12.62 mmol) under N_2 in dry CH_2Cl_2 (95 mL) cooled at −50 °C was added dropwise a solution of tin(IV) chloride in CH_2Cl_2 (12.2 mL of a 1 M solution, 12.2 mmol). The stirred solution was allowed to come to −15 °C over 3 h. The mixture was treated with 12 mL of 5% aqueous $NaHCO_3$ and poured into water. The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic phases were washed with water and brine and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue obtained was purified by column chromatography, using pentane/ether 9:1 as eluent, to provide the ketone **8** (2.78 g, 85%) as a colorless oil: $[\alpha]^{19}_D$ −21.4 (*c* 5.9, $CHCl_3$); IR (film) 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (5 H, m), 4.58 (2 H, s), 4.27 and 4.21 (1

(11) Boeckmam, R. K., Jr.; Blum, D. M.; Ganem, B.; Halvey, N. *Organic Syntheses;* Wiley: New York, 1988; Collect. Vol. VI, p 1033.

(12) Obtained as a 1:1 mixture of diastereomers (epimers at C2) that could be partially separated by careful MPLC. Although their spectroscopic data could be determined independently (see Experimental Section), the configuration of C2 of each diastereoisomer could not be assigned. This is of no consequence, as the C2 stereogenic center is lost during subsequent transformations.

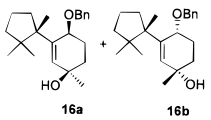
(13) As expected, treatment of each of the epimers of **10** at C2 under these conditions led to the same mixture of diastereomers of **11**. Obviously, epimerization of the C2−OBn position occurs under the basic conditions used in the aldol condensation.

(14) Although the two diastereomers formed in this reaction could not be separated by any conventional purification procedure, the ^1H and ^{13}C NMR spectra of the mixture showed distinctive sets of signals for the hydrogen and carbon atoms, respectively, of each diastereomer. Partial assignment of the ^1H and ^{13}C NMR resonance signals of each diastereomer could be effected by a combination of HMQC and NOE experiments performed on the mixture (see Experimental Section and Supporting Information).

(15) Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995**, *117*, 8106.

(16) Conversion of **15** into **4** was also achieved via selenation and oxidation. However, a lower yield of **4** was obtained by this method (ca. 35%).

(17) Compound **3** was also obtained from epimeric benzylic ethers **11** as follows. Reaction of **11** at low temperature with methyllithium afforded a chromatographically inseparable 1:1 mixture of diastereomeric alcohols **16** in 67% yield. Treatment of this mixture with an equimolecular amount of CSA in methylene chloride at room temperature afforded (−)-herbertene (**3**) in 80% yield (see Supporting Information).



16a **16b**

(18) For general experimental information, please see: Abad, A.; Agulló, C.; Arnó, M.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *J. Org. Chem.* **1998**, *63*, 5100.

H each, each d, $J = 17.4$ Hz), 1.08 (3 H, s), 1.03 (3 H, s), 0.85 (3 H, s); HRMS calcd for $C_{17}H_{25}O_2$ ($M^+ + 1$) 261.1855, found 261.1849.

2-Benzyloxy-1-[(1*S*)-1,2,2-trimethylcyclopentyl]-hexane-1,5-dione (10). To a stirred solution of NaHMDS in THF (1.04 mL of a 1 M solution, 1.04 mmol) was added dropwise a solution of the α-benzyloxyketone **8** (266 mg, 1.02 mmol) in THF (2 mL) at −78 °C. The mixture was stirred for 30 min, 3-trimethylsilyl-3-buten-2-one (174 μL, 1.05 mmol) was then added dropwise, and the resulting solution was allowed to warm slowly to room temperature over 3 h. The stirring was continued at the same temperature for 1 h, and saturated aqueous NH_4Cl solution was added. The mixture was poured into water and extracted with ethyl acetate. Work-up as usual gave a residue, which was dissolved in a mixture of methanol (3.5 mL) and 4% aqueous potassium hydroxide (0.5 mL). After being stirred at room temperature for 6 h, the reaction mixture was poured into water and extracted with ether. The combined organic layers were washed with brine and dried. Chromatography of the residue left after evaporation of the solvent, using hexane/ethyl acetate 4:1 as eluent, afforded diketone **10** (269 mg, 80%) as a 1:1 mixture of epimers at C2 as shown by ^{1}H NMR analysis. Both diastereomers could be partially separated by MPLC using hexane/ethyl acetate 5:1 as eluent, and their spectroscopic data were determined independently. Less polar diastereoisomer: $[\alpha]^{19}_D$ −51 (*c* 2.9, $CHCl_3$); IR (film) 1709 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (5 H, m), 4.49 and 4.29 (1 H each, each d, $J = 11.2$ Hz), 4.26 (1 H, dd, $J = 7.2$ and 4.1 Hz), 2.09 (3 H, s), 1.14 (3 H, s), 1.13 (3 H, s), 0.87 (3 H, s); HRMS calcd for $C_{21}H_{31}O_3$ ($M^+ + 1$) 331.2281, found 331.2277. More polar diastereoisomer: IR (film) 1708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (5 H, m), 4.49 and 4.29 (1 H each, each d, $J = 11.2$ Hz), 4.37 (1 H, dd, $J = 6.8$ and 4.4 Hz), 2.08 (3 H, s), 1.12 (3 H, s), 1.11 (3 H, s), 0.91 (3 H, s); HRMS calcd for $C_{21}H_{31}O_3$ ($M^+ + 1$) 331.2281, found 331.2279.

4-Benzyloxy-3[(1*S*)-1,2,2-trimethylcyclopentyl]-2-cyclohexen-1-one (11). A solution of epimeric diketones **10** (735 mg, 2.23 mmol) in a mixture of methanol (63 mL) and 20% aqueous potassium hydroxide (12 mL) was heated at 120 °C in a sealed tube under argon for 6 h. The mixture was poured into water and extracted with CH_2Cl_2. Work-up as usual afforded an oily residue, which was purified by chromatography using pentane/ether 8:2 as eluent to afford the cyclohexenone **11** (542 mg, 78%) as an equimolecular mixture of epimers at C4: IR (film) 1673, 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.2 (5 H, m), 6.02 and 5.94 (total 1 H, two s), 4.62 and 4.61 (total 1 H, overlapping d, $J = 11$ Hz), 4.482 and 4.478 (total 1 H, overlapping d, $J = 11$ Hz), 4.25 and 4.20 (total 1 H, two br s), 2.72 (1 H, m), 2.41 (1 H, m), 2.3 (1 H, m), 1.17 and 1.11 (total 3 H, two s), 1.02 and 0.96 (total 3 H, two s), 0.802 and 0.799 (total 3 H, two s); HRMS calcd for $C_{21}H_{29}O_2$ 313.2168, found 313.2165.

Benzyl 4-Methylene-2-[(1*S*)-1,2,2-trimethylcyclopentyl]-2-cyclohexeny1-ether (13). A solution of methyl triphenylphosphonium bromide (942 mg, 2.64 mmol) in DMSO (3 mL) was added to a solution of $NaCH_2SOCH_3$, prepared from sodium hydride (102 mg of 60% dispersion in oil, 2.54 mmol) and DMSO (2 mL), at room temperature. After 15 min of stirring, a solution of the unsaturated ketone **11** (274 mg, 0.44 mmol) in DMSO (1.5 mL) was added, and the resulting mixture was stirred at room temperature for 30 min. The reaction mixture was cooled in an ice bath and quenched by the addition of saturated aqueous NH_4Cl solution, and the product was isolated by extraction with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried, and evaporated. The residue was purified by chromatography on silica gel using pentane/ether 8:2 as eluent to give compound **13** (225 mg, 83%) as a 1:1 mixture of epimers at C1 (^{1}H NMR analysis): IR (film) 1628, 1593, 926, 883 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.2 (5H, m), 6.21 and 6.11 (total 1 H, two s), 4.83 (2 H, m), 4.58 (1 H, d, $J = 10.9$ Hz), 4.42 and 4.41 (total 1 H, two d, $J = 10.9$ Hz), 4.08 and 4.04 (total 1 H, two m), 1.15 and 1.09 (total 3 H, two s), 0.99 and 0.96 (total 3 H, two s), 0.77 and 0.76 (total 3 H, two s); HRMS calcd for $C_{22}H_{30}O$ 310.2297, found 310.2305.

1-Methyl-3-[(1*S*)-1,2,2-trimethylcyclopentyl]benzene [(−)-Herbertene (3)]. A solution of diastereomeric benzylic ethers **13** (71.6 mg, 0.23 mmol) and camphorsulfonic acid monohydrate (60 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 2 h. Chromatography of the residue left after evaporation of solvent under reduced pressure, using pentane as eluent, afforded (−)-herbertene (**3**) (37.3 mg, 80%) as a colorless and relatively volatile oil: $[\alpha]^{19}_D$ −56 (*c* 1.4, $CHCl_3$) (lit.[2] $[\alpha]_D$ −48.3); IR (film) 1604, 1462, 784, 707 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (3 H, m), 7.0 (1 H, m), 2.6−2.4 (1 H, m), 2.35 (3 H, s), 1.8−1.6 (4 H), 1.6−1.5 (1 H), 1.26 (3 H, s), 1.07 (3 H, s), 0.56 (3 H, s); HRMS calcd for $C_{15}H_{22}$ 202.1722, found 202.1716.

4-Methyl-2-[(1*S*)-1,2,2-trimethylcyclopentyl]-2-cyclohexen-1-one (15). A mixture of **13** (518 mg, 1.67 mmol) and 10% palladium on carbon (77 mg) in ethyl acetate (60 mL) was shaken at room temperature under an H_2 atmosphere for 1 h. After removal of the catalyst by filtration through a pad of silica gel, the filtrate was concentrated in vacuo. A mixture of the residual oil obtained, $Pd(OH)_2$ on carbon (20%, 779 mg), and palladium on calcium carbonate (5%, 779 mg) in absolute EtOH (46 mL) was stirred at room temperature under 1 atm of H_2 for 30 min. Removal of the palladium catalysts by filtration through Celite, followed by evaporation of the filtrate under reduced pressure, afforded a diastereomeric mixture of allylic alcohols **14** (337 mg).

To a stirred mixture of the crude product obtained above (337 mg, 1.52 mmol), NMO (267 mg, 2.28 mmol), and powdered 4 Å molecular sieves (783 mg) in CH_2Cl_2 (3 mL) was added solid TPAP (31 mg, 0.09 mmol) in one portion at room temperature. After 25 min of stirring at the same temperature, the mixture was filtered through a short pad of Celite, eluting with acetone. Chromatography of the residue left after evaporation of the solvent, using pentane/ether 8:2 as eluent, afforded methyl enone **15** (305 mg, 84% overall yield from **13**) as a 1:1 mixture of epimers at C4: IR (film) 1680 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (1 H, br s), 1.20 and 1.19 (total 3 H, two s), 1.12 (total 3 H, overlapping d, $J = 7$ Hz), 1.07 and 1.05 (total 3 H, two s), 0.69 (3 H, s); HRMS calcd for $C_{15}H_{24}O$ 220.1827, found 220.1827.

4-Methyl-2-[(1*S*)-1,2,2-trimethylcyclopentyl]phenol [(−)-α-Herbertenol (4)]. An intimate mixture of epimeric methyl ketones **15** (43.8 mg, 0.21 mmol) and sulfur (8.1 mg, 0.24 mmol) was heated in a sealed tube at 200 °C under argon for 1.5 h. The reaction mixture was dissolved into CH_2Cl_2 and filtered through a short pad of silica gel. Chromatography of the residue left after

evaporation of the solvent, using hexane/ethyl acetate 95:5 as eluent, afforded (−)-α-herbertenol (**4**) (28.2 mg, 65%) as a colorless oil: $[\alpha]^{19}_{D}$ −46 (*c* 5.9, $CHCl_3$) (lit.[2] $[\alpha]_D$ −55); IR (film) 3525, 1665, 1507 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.1 (1 H, s), 6.86 (1 H, d, J = 7.9 Hz), 6.57 (1 H, d, J = 7.9 Hz), 4.63 (1 H, s), 2.26 (3 H, s), 1.41 (3 H, s), 1.18 (3 H, s), 0.76 (3 H, s); HRMS calcd for $C_{15}H_{22}O$ 218.1671, found 218.1667.

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Supporting Information Available: List of infrared and mass spectral data, ^1H and ^{13}C NMR peak assignments, copies of ^1H NMR spectra for all compounds described in the Experimental Section, and spectroscopic data and experimental procedure for the preparation of compounds mentioned in ref 17. This material is available free of charge via the Internet at http://pubs.acs.org.

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