Lipase-Promoted Access to Phenolic Herbertane-Type Sesquiterpenes: (+)-1,14-Herbertenediol, (−)-α-Herbertenol, (−)-Herbertenediol and Their Enantiomers

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An enantioselective synthesis of (+)-1,14-herbertenediol, and a formal enantioselective synthesis of (–)-α-herbertenol and (–)-herbertenediol, employing a lipase-promoted and a key stereoselective alkylation of a cyclopentane unit based methodology, are described. Molecular mechanics considerations that could account for the major role played by the substitution pattern of the benzene nucleus in the herbertane framework in comparison with those of the cuparane framework are described.

Introduction

Cuparanes and herbertanes belong to an expanding family of sesquiterpenes that possess two vicinal quaternary carbon centers, some of which exhibit interesting biological activities. Herbertanes are considered as chemical markers for the liverworts belonging to the genus *Herbertus*.[1] Asakawa and co-workers have recently reported the isolation of (+)-1,14-herbertenediol (**1**), along with other new members of the herbertane group and the dimeric herbertanes mastigophorenes, from the japanese liverwort *Herberta sakuraii* (Figure 1).[1] Isolation of (−)-α-herbertenol (**2**) and (−)-herbertenediol (**3**), along with other herbertenes, from the liverwort *Herberta adunca* was reported earlier by Matsuo and co-workers.[2]

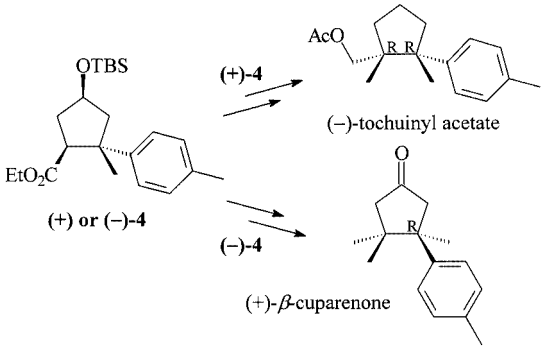
(+)-1,14-herbertenediol **1**

X = H (–)-α-herbertenol **2**
X = OH (–)-herbertenediol **3**

Figure 1

The presence of two vicinal quaternary carbon atoms on the cyclopentane ring, and their associated biological activities, make phenolic herbertanes interesting synthetic targets of current interest, and significant numbers of racemic[3] or enantioselective[4] syntheses have been reported.

We have recently described a lipase-catalyzed kinetic resolution for the enantioselective approach toward cuparane-type sesquiterpenoids.[5] The application of this strategy led to the enantioselective synthesis of representative members of this type of sesquiterpene, such as (−)-tochuinyl acetate and (+)-β-cuparenone, with a TBS-protected enantiopure cyclopentanol **4** and its enantiomer as intermediates in the key stereoselective alkylation step (Scheme 1).[6] As a continuation of this work, we now wish to report the adaptation of this chemistry to the enantioselective synthesis of three representative compounds of the herbertane family − (+)-1,14-herbertenediol (**1**), (−)-α-herbertenol (**2**), (−)-herbertenediol (**3**) − and their enantiomers.



Scheme 1

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Because the only difference between cuparane and herbertane (isocuparane)-type sesquiterpenes is the substitution pattern of the benzene nucleus, any synthetic method relying on the construction of the cyclopentane unit seems to be applicable to a synthesis of the other sesquiterpene when a route to either cuparane or herbertane framework has been found.

This paper points out the major part played by the substitution pattern of the benzene nucleus in the herbertane type versus the cuparane-type sesquiterpenes during the key stereoselective alkylation step of the cyclopentane unit. A molecular mechanics study of the different possible conformers explains this difference.

Results and Discussion

As shown in Scheme 2, our synthesis starts from ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate, which is readily available.[7]

The $Ni(acac)_2$-catalyzed 1,4-addition of the organozinc reagent prepared from two equivalents of 2-methoxy-5-methyl-phenylmagnesium bromide and one equivalent of zinc chloride afforded the keto-ester (±)-**5**, stereoselectively, in 96% yield.[8] Subsequent reduction of (±)-**5** with $NaBH_4$/$CeCl_3$ (Luche reduction)[9] gave the single stereoisomer (±)-**6** in nearly quantitative yield. The stereochemistry of the three stereocenters in (±)-**6** was determined from ^1H NMR NOESY experiments (Figure 2). A strong NOESY correlation between H−C(1) and H−C(4), which resonate at δ = 3.58 and δ = 4.46 ppm, respectively, and, in addition, strong NOESY correlations between these two protons and the aromatic proton at δ = 7.12 ppm, established the *cis* spatial orientation between these protons and the aromatic group.

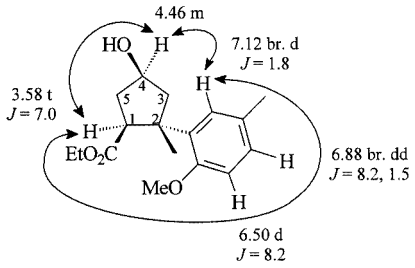
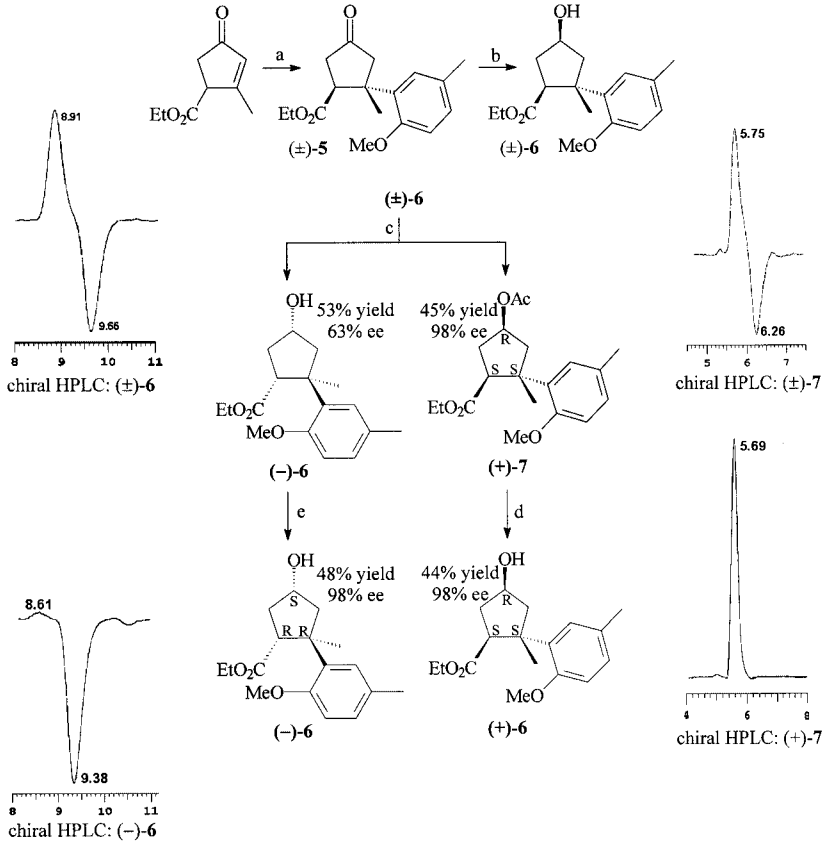


Figure 2. High-field ^1H NMR analysis and NOESY correlations of (±)-**6**

Having completed the synthesis of alcohol (±)-**6**, our attention turned towards the lipase-catalyzed kinetic resolution in order to provide access to both enantiomers. Five commercially available lipases were screened in our previous work dealing with the cuparane family.[5] A similar screen-



Scheme 2. Synthesis and lipase AK enzymatic resolution of (±)-**6**; conditions and reagents: (a) i. 2-bromo-4-methylanisole, Mg, Et_2O reflux; ii. $ZnCl_2$, THF, 0 °C; iii. $Ni(acac)_2$, THF, 0 °C, 96% 3 steps; (b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, −78 °C, quant.; (c) lipase AK, vinyl acetate, room temp., 2 d; (d) Na_2CO_3, MeOH, room temp., 97%; (e) lipase AK, vinyl acetate, room temp., 13 h

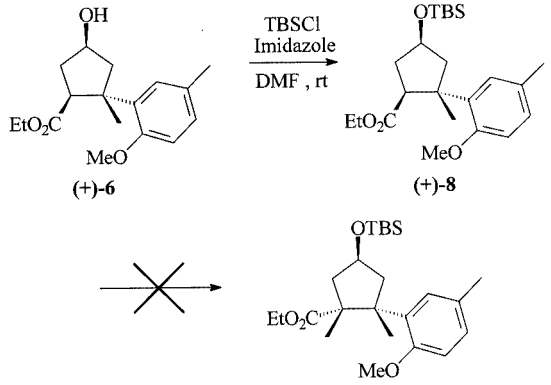
Table 1. Lipases screening performed on (±)-**6**

Entry	Lipase	Reaction time	Conversion (%)[a]	Remaining alcohol *ee* (%)[b]	Produced acetate *ee* (%)[b]
1	PPL	3 d	0	–	–
2	CRL	13 d	24	10	6
3	RML	13 d	19	16	66
4	PFL	2 d	49	90	92
5	CAL-B	2 d	51	93	87

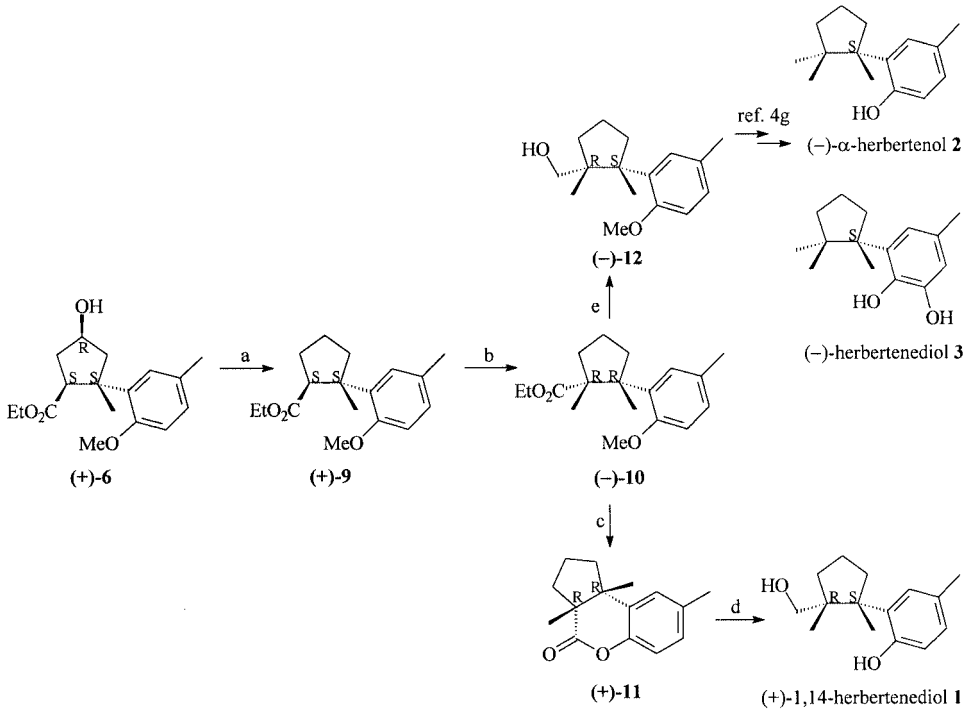
[a] Measured by GC on a capillary column (CP-Wax-52). [b] Measured by chiral HPLC (Chiracel OD-H) after isolation by column chromatography.

ing test (see Exp. Sect.) with the same five lipases and under the same conditions (Table 1) indicated that lipase AK (from *Pseudomonas fluorescens*, PFL) is the enzyme of choice for the transesterification of (±)-**6** (a little less for CAL-B). The results are outlined in Scheme 2.

At this stage, the OH function of (+)-**6** was not first deoxygenated before alkylation so as to eliminate the need to protect and deprotect because, in our approach applied to the cuparane skeleton,[6] we found, like Taber,[10] that the ethoxycarbonylcyclopentane ring alkylation furnished a 85:15 ratio of diastereoisomers. Thus, alcohol (+)-**6** was protected as its *tert*-butyldimethylsilyl ether (+)-**8** and the remaining elaboration seemed to be a simple stereoselective alkylation of the protected ester as in our earlier methodology (Scheme 3). However, this step proved to be more problematic than initially expected. Attempted alkylation of (+)-**8** with methyl iodide with LDA as base in THF gave no methylated product. In another experiment the failure to incorporate a deuterium atom upon addition of D_2O showed that the expected enolate is not formed, presumably due to the steric hindrance of the substituents of the phenolic moiety.



Scheme 3



Scheme 4. Conditions and reagents: (a) i. NaH, CS_2, MeI, THF; ii. Bu_3SnH, AIBN, toluene, 98% 2 steps; (b) LDA, HMPA, MeI, THF, −90 °C → room temp., 65%; (c) BBr_3, CH_2Cl_2, −70 °C → room temp., 90%; (d) $LiAlH_4$, Et_2O, 0 °C, 96%; (e) $LiAlH_4$, Et_2O, 0 °C, 98%

To support this assumption, esters (+)-**4**, (+)-**8**, and (+)-**9** (obtained from Barton−McCombie deoxygenation of alcohol (+)-**6**, Scheme 4) were studied by molecular mechanics calculations to identify their stable conformers. Due to the presence of the OTBS protecting group in (+)-**4** and (+)-**8**, we used the well-validated second generation forcefield CFF91 that includes suitable parameters for O−Si and C−Si bonds.[11,12] A preliminary systematic exploration of the conformational space by rotating all possible torsion angles allowed us to identify the torsions that lead to significantly different molecular structures for each compound. We thus selected the dihedral angles around the bonds between the cyclopentane ring and its substituents (C−CO_2Et, C−Ar, C−OTBS), and the O−Si bonds [(+)-**4** and (+)-**8**] were varied step by step, rejecting conformations with energies 100 kcal·mol^{-1} above the lowest value. The sample conformations generated this way exhibited a cyclopentane ring with a variety of shapes and every possible orientation of the substituents. All these conformations were then optimized with the highest convergence criteria and redundant structures were removed to afford, for each ester, a set of unique stable conformers [17 for (+)-**4**, 16 for (+)-**8**, and 10 for (+)-**9**]. Strikingly, the most stable ones appeared to be very similar in shape and energy, with only minor differences in torsion-angle values, although these correspond to distinct minima. Any deviation from the stable geometry found resulted in a significant increase of the energy, preventing equilibration with other conformations exhibiting a different pattern. This clearly indicates that these structures correspond to the characteristic conformation of each compound; representative models are depicted in Figure 3 (conformers A).

The potentially reactive conformer of each compound could be derived from these fundamental conformations by rotating the extracyclic bond between the carbon atom C1 and the ethoxycarbonyl substituent, and optimizing the resulting structures. In these conformations, the hydrogen atom to be abstracted should be nearly perpendicular to the

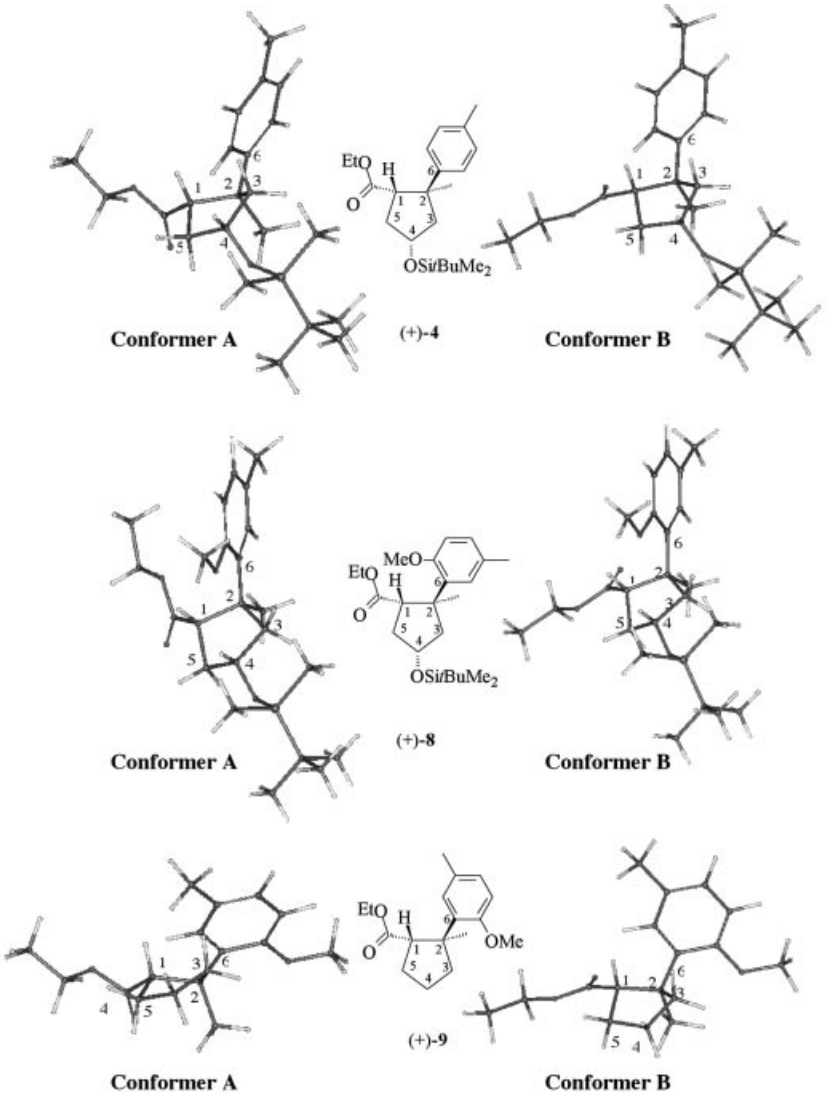


Figure 3. Representation of the characteristic conformations of (+)-**4**, (+)-**8** and (+)-**9**: (A) fundamental conformer; (B) potentially reactive conformer

plane of the ester carboxy group on C1. As can be seen in Figure 3 (conformers B), the most stable resulting computed conformations exhibit strictly similar patterns to the corresponding fundamental conformers. In particular, the hydrogen atom on C1 lies in a sterically hindered region in compound (+)-**8**, whereas it is easily available in compounds (+)-**4** and (+)-**9**. The phenyl group in compound (+)-**9** adopts a pseudoequatorial orientation towards the five-membered ring, while the methyl group on the same C2 carbon atom lies in a pseudoaxial position. In this conformation, the least-hindered torsion angle around the C2−C6 bond corresponds to a nearly perpendicular position between the aromatic ring and the methyl group on C2, the methoxy substituent lying away from the ethoxycarbonyl group on C1. Consequently, the methoxy group lies away from the acidic hydrogen atom on C1. In compounds (+)-**8** and (+)-**4**, due to *syn*-1,3 repulsive interactions between the bulky silyloxy group on C4 and the C2 methyl group, the latter, together with the phenyl group, are forced to adopt bissected positions towards the five-membered ring. In the case of (+)-**8**, the *o*-methoxy-substituted phenyl group must adopt an orientation that minimizes the *syn* interactions with the hydrogen atoms on C1 and C3. Moreover, in this position, the *o*-methoxy substituent lies above the five-membered ring in an *anti* position with respect to the C2 methyl group rather than a sterically crowded *syn* position. This methoxy substituent is therefore located in the same half-space as the acidic hydrogen atom on C1, the distance between the latter and the oxygen atom of *o*-MeO being only 2.66 Å. Therefore, the *o*-methoxy group would block the approach of the bulky diisopropylamide anion to this area. In compound (+)-**4**, the phenyl group bearing only a *p*-methyl substituent, this steric hindrance does not exist.

Molecular mechanics calculations therefore allowed us to fully rationalize the difference in reactivity towards alkylation of esters (+)-**4** and (+)-**9** on one hand, and (+)-**8** on the other hand, in terms of steric hindrance. The acidic hydrogen atom on C1 in both (+)-**4** and (+)-**9** is in a nearly axial position and appears to be easily accessible to LDA for abstraction.

In view of the above results, we modified the synthetic concept and an alternative approach for the construction of the quaternary carbon atom based on a Barton−McCombie deoxygenation[13] of (+)-**6**, which we had discarded in the first analysis, was explored (Scheme 4). Towards this end, the alcohol (+)-**6** was transformed into the corresponding xanthate and the crude reaction product was smoothly reduced with tri-*n*-butyltin hydride to provide the cyclopentane derivative (+)-**9** in a 98% overall yield for the two steps. In agreement with our conformational study, alkylation of (+)-**9** with LDA and methyl iodide created the second quaternary carbon atom and afforded the ester (−)-**10** in 65% yield. We were gratified to find that the desired compound was produced in this case as a single isomer with the requisite stereochemistry (vide infra).[14] Treatment of the ester (−)-**10** with boron tribromide in dichloromethane furnished *epi*-herbertenolide (+)-**11** in 90% yield, upon hydrolysis of the methyl ether and intramolecular lactonisation. In the ^{1}H NMR spectrum of (+)-**11**, resonances at δ = 1.22 (s, 3 H) and 1.25 ppm (s, 3 H) established the *cis* relationship between the two vicinal methyl groups (ref.[4g] δ = 1.24 and 1.27 ppm; ref.[3a] for herbertenolide, which presents a *trans* relationship for the methyl groups, δ = 0.92 and 1.12 ppm). Finally, reduction of the lactone (+)-**11** with $LiAlH_4$ furnished (+)-1,14-herbertenediol (**1**), which exhibits ^{1}H and ^{13}C NMR spectroscopic data identical to those reported previously.[3i,4g] As for the magnitude of the specific rotation of (+)-**1**, the values reported by Fukuyama[4g] {$[\alpha]_D^{27}$ = +15.5 (c = 1.14, $CHCl_3$)} and Asakawa[1] {$[\alpha]_D^{21}$ = +33.5 (c = 0.19, $CHCl_3$)} are very different. We found an $[\alpha]_D^{25}$ value of +11.8 (c = 1.00, $CHCl_3$) and so corroborated the results reported by Fukuyama.

Reduction of ester (−)-**10** with $LiAlH_4$ furnished alcohol (−)-**12** in 98% yield. Since alcohol (−)-**12** has already been used as a key building block for the synthesis of (−)-α-herbertenol (−)-**2** and (−)-herbertenediol (−)-**3**,[4g] the present sequence constitutes a formal synthesis of these natural products.

Conclusion

In conclusion, starting from a readily available ethoxycarbonylcyclopentenone, we have described herein the enantioselective synthesis of representative members of the herbertane family using a lipase-catalyzed kinetic resolution and a stereocontrolled alkylation of the cyclopentane unit.

A conformational analysis performed using molecular mechanics methods has been used to explain the major role played by the substitution pattern of the benzene nucleus in the herbertane framework, in comparison with that of the cuparane framework, during the stereocontrolled alkylation step.

This route employs commercial lipase, high-yielding reaction steps, and is completely stereoselective at each step in controlling the configuration of the quaternary centers of chirality. Furthermore, starting from the enantiomers of the utilized building blocks, the methodology can be applied to the synthesis of the unnatural isomers of the present target molecules.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or C_6D_6 solutions with a Bruker AM-300 spectrometer (Bruker AM 500 spectrophotometer for NOESY experiments). Infrared spectra were obtained as films or KBr pellets using a Perkin−Elmer 1600 FT-IR spectrophotometer. Routine monitoring of reactions was performed using Merck Silica gel 60 F_{254} coated on aluminum-supported TLC plates. Column chromatography was performed with silica gel 60 (230−400 mesh) and gradients of pentane/diethyl ether as eluent, unless otherwise stated. GC analyses were carried out with a Chrompack 9001 using a WCOT fused-silica column (25 m × 0.32 mm i.d.; CP-Wax-52 CB stationary phase; N_2 carrier gas: 50 kPa). Enantiomeric excess determinations were carried out using a MEGADEX DETTBSβ fused-silica col-

umn (30 m × 0.25 mm i.d.; N_2 carrier gas: 75 kPa) or a commercial column from Daiser: CHIRALCEL OD-H® (250 × 4.6 mm; 10 μm) with hexane/*i*PrOH (95:5, v/v) and a flow rate of 1 mL/min. Specific rotations were recorded with a Perkin−Elmer 341 polarimeter. Microanalyses were performed with a ThermoFinnigan EA 1112 analyzer at our University. Melting points were not corrected and were determined by using a Büchi Totolli apparatus. Unless otherwise stated, the solutions were dried with magnesium sulfate and concentrated in a rotary evaporator under reduced pressure. Lipase from *Candida rugosa* type VII (CRL) was purchased from Sigma (St. Quentin Fallavier, France). Lipase from porcine pancreas (PPL) was purchased from Fluka (Buchs, Swizerland). Lipase AK (from *Pseudomonas fluorescens*, PFL) was a gift from Amano Pharmaceutical (Nagoya, Japan). Novozyme 435 (from *Candida antartica B* lipase, CAL-B) and Lipozyme RM IM (from *Rhizomucor miehei* lipase, RML) were gifts from Novo Nordisk A/S (Bagsværd, Denmark).

Ethyl 2-(2-Methoxy-5-methylphenyl)-2-methyl-4-oxocyclopentanecarboxylate [(±)-5]: The Grignard reagent freshly prepared from 2-bromo-4-methylanisole (2.20 g, 109 mmol) and magnesium (3.00 g, 123 mmol) in diethyl ether (50 mL) was added dropwise to a 1 M $ZnCl_2$ solution in diethyl ether (54.8 mL, 54.8 mmol) at 0 °C under argon. The mixture was allowed to warm to room temp. and stirred for 2 h to produce the organozinc reagent. The prepared organozinc reagent was added dropwise at 0 °C to a stirred suspension of ethyl 2-methyl-4-oxocyclopent-2-enecarboxylate (2.00 g, 11.9 mmol) and $Ni(acac)_2$ (612 mg, 2.38 mmol) in THF (50 mL), and the mixture was allowed to warm to room temp. After 15 h, the solution was poured into an NH_4Cl-saturated aqueous solution, and extracted with diethyl ether. The organic layers were combined, washed with brine, dried, and the solvents evaporated. The residue was purified by column chromatography to afford (±)-**5** as a white solid in 96% yield (3.32 g, 11.42 mmol). M.p. 72−73 °C. IR (KBr): $\tilde{\nu}$ = 3095, 3059, 1746, 1232 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.05 (s, 1 H), 7.04 and 6.81 (AB, J = 7.9 Hz, 2 H), 6.81 (d, J = 7.9 Hz, 1 H), 4.14 (dq, J = 10.8, 7.2 Hz, 1 H), 3.98 (dq, J = 10.8, 7.2 Hz, 1 H), 3.91 (t, J = 8.8 Hz, 1 H), 3.81 (s, 3 H), 3.12 (d, J = 18.3 Hz, 1 H), 2.81 (ddd, J = 18.9, 8.7, 1.5 Hz, 1 H), 2.44 (ddd, J = 18.9, 8.5, 1.2 Hz, 1 H), 2.36 (dd, J = 18.3, 1.4 Hz, 1 H), 2.27 (s, 3 H), 1.41 (s, 3 H), 1.11 (t, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.5 (C), 173.0 (C), 154.9 (C), 132.6 (C), 129.3 (C), 128.2 (CH), 127.8 (CH), 111.3 (CH), 60.2 (CH_2), 54.9 (CH), 51.5 (CH_2), 47.7 (CH_3), 44.4 (C), 39.8 (CH_2), 22.8 (CH_3), 20.6 (CH_3), 14.0 (CH_3) ppm. $C_{17}H_{22}O_4$ (290.4): calcd. C 70.32, H 7.64; found C 70.49, H 7.59.

Ethyl 4-Hydroxy-2-(2-methoxy-5-methylphenyl)-2-methylcyclopentanecarboxylate [(±)-6]: A solution of ketone **5** (2.50 g, 8.61 mmol) and $CeCl_3 \cdot 7H_2O$ (3.90 g, 10.5 mmol) in absolute EtOH (200 mL) was stirred at room temp. for 1 h. The solution was then cooled to −90 °C and treated with $NaBH_4$ (600 mg, 15.9 mmol) in five portions. The reaction mixture was stirred for an additional 6 h before being concentrated under reduced pressure to provide a residue that was partitioned between 200 mL of water and 200 mL of CH_2Cl_2. After separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined extracts were dried with $MgSO_4$ and concentrated in vacuo. The residue was column-chromatographed to afford 2.47 g (98%) of pure alcohol **6** as a foam. IR (neat): $\tilde{\nu}$ = 3411, 3049, 1739, 1209 cm^{-1}. ^1H NMR (500 MHz, C_6D_6): δ = 7.12 (br. d, J = 1.8 Hz, 1 H, H arom.), 6.88 (br. dd, J = 8.2, 1.5 Hz, 1 H, H arom.), 6.50 (d, J = 8.2 Hz, 1 H, H arom.), 4.46 (m, 1 H, 4-H), 3.97 and 3.85 (2 × dq, J = 10.8, 7.1 Hz, 2 H, CH_2O), 3.58 (t, J = 7.0 Hz, 1 H, 1-H), 3.28 (s, 3 H, CH_3O), 2.79 (dd, J = 14.1, 7.7 Hz, 1 H, 3-H_a), 2.53 (br. s, 1 H, OH), 2.23−2.15 (m, 1 H, 5-H_b), 2.17 (s, 3 H, CH_3-φ), 2.12 (dt, J = 13.8, 7.1 Hz, 1 H, 5-H_a), 1.93 (dd, J = 14.1, 5.6 Hz, 1 H, 3-H_b), 1.60 (s, 3 H, 2-CH_3), 0.90 (t, J = 7.1 Hz, 3 H, CH_3-CH_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.0 (C), 155.1 (C), 134.7 (C), 129.0 (C), 127.6 (CH), 127.5 (CH), 111.3 (CH), 72.0 (CH), 60.2 (CH_2), 54.9 (CH), 50.9 (CH_3), 49.1 (CH_2), 48.3 (C), 38.0 (CH_2), 24.3 (CH_3), 20.7 (CH_3), 14.1 (CH_3) ppm. $C_{17}H_{24}O_4$ (292.4): calcd. C 69.84, H 8.27; found C 70.15, H 8.31.

General Procedure for Lipase Screening for the Acylation of (±)-6: The lipase (50 mg) was added to a solution of (±)-**6** (50 mg) in vinyl acetate (3 mL) and the mixture was stirred magnetically in a hermetically stoppered one-necked flask. The course of the reaction was monitored by GC and TLC. After the period indicated in Table 1, the reaction mixture was filtered through a pad of Celite, and the cake was washed with dry Et_2O. The filtrate was concentrated in vacuo and chromatographed on a column. Acetate **7** (the first eluted compound) and alcohol **6** were separated and analyzed on the chiral HPLC column. Results of the lipase-mediated acylations are reported in Table 1.

Lipase-Catalyzed Acylation of (±)-6: A mixture of (±)-**6** (4.90 g, 16.8 mmol) and Amano AK (500 mg) in 20 mL of vinyl acetate was magnetically stirred at room temp. and the reaction progress monitored by GC. After 2 d and 46% conversion, a chiral HPLC analysis showed that the formed acetate (+)-**7** had a 98% *ee*. At this stage, the reaction was stopped by filtration. Removal of the solvent followed by separation on a column yielded 2.60 g (53%) of unchanged (−)-**6** (63% *ee*) and 2.52 g (45%) of the formed acetate (+)-**7** (98% *ee*). **(+)-7:** $[\alpha]_D^{25}$ = +37.4 (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3088, 3041, 1759, 1196, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, J = 1.9 Hz, 1 H), 7.01 (dd, J = 8.3, 1.7 Hz, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 5.30 (qd, J = 13.6, 7.8 Hz, 1 H), 4.12 (dq, J = 10.8, 7.2 Hz, 1 H), 3.96 (dq, J = 10.7, 7.1 Hz, 1 H), 3.82 (s, 3 H), 3.52 (dd, J = 10.6, 7.5 Hz, 1 H), 2.72 (dd, J = 14.0, 8.5 Hz, 1 H), 2.42 (dt, J = 13.8, 7.6 Hz, 1 H), 2.28 (s, 3 H), 2.29−2.18 (m, 1 H), 2.05 (s, 3 H), 1.81 (dd, J = 14.0, 5.8 Hz, 1 H), 1.41 (s, 3 H), 1.12 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6 (C), 171.0 (C), 155.0 (C), 134.7 (C), 129.0 (C), 127.8 (CH), 127.7 (CH), 111.2 (CH), 74.1 (CH), 59.9 (CH_2), 55.0 (CH), 49.9 (CH_3), 46.2 (C), 45.8 (CH_2), 34.4 (CH_2), 23.9 (CH_3), 21.2 (CH_3), 20.7 (CH_3), 14.1 (CH_3) ppm. $C_{19}H_{26}O_5$ (334.4): calcd. C 68.24, H 7.84; found C 67.89, H 7.88. Acetate (+)-**7** (2.52 g, 7.53 mmol) was allowed to react with Na_2CO_3 (3.20 g, 30.2 mmol) in 30 mL of MeOH at room temp. for 2 d. An excess of NH_4Cl (4.27 g, 80.0 mmol) was added, and the reaction mixture was concentrated to remove MeOH, then diluted with CH_2Cl_2, filtered, and concentrated. Purification by column chromatography gave 2.12 g (96%) of (+)-**6** as an oil. *ee* = 98%, $[\alpha]_D^{25}$ = +64.0 (c = 1.0, $CHCl_3$). The ^1H and ^{13}C NMR spectroscopic data are identical with those reported for (±)-**6**. The unreacted alcohol (−)-**6** (*ee* = 63%) was resubjected under the same conditions to lipase-catalysed acylation using the recovered active enzyme, and the progress of the reaction was monitored by chiral HPLC. After 13 h, HPLC analysis showed that one enantiomer of the alcohol had been completely consumed. The reaction was stopped by filtration. Removal of the solvent followed by column chromatography yielded 2.35 g of alcohol (−)-**6** [48% overall yield from (±)-**6**]. *ee* = 98%, $[\alpha]_D^{25}$ = −64.2 (c = 1.0, $CHCl_3$). The ^1H and ^{13}C NMR spectroscopic data were identical with those reported for (±)-**6**.

Ethyl 4-(*tert*-Butyldimethylsilanyloxy)-2-(2-methoxy-5-methylphenyl)-2-methylcyclopentanecarboxylate [(+)-8]: The alcohol (+)-**6** (300 mg, 1.03 mmol) was dissolved in DMF (5 mL), imidazole (210

mg, 3.08 mmol) and *tert*-butyldimethylsilyl chloride (232 mg, 1.54 mmol) were added, and the mixture was stirred at room temp. for 1 h. The solution was then poured into water and extracted with diethyl ether. The combined organic extracts were washed with water, brine, dried, filtered, and concentrated. Column chromatography gave 413 mg (99%) of (+)-**8** as an oil. $[\alpha]_D^{25} = +33.6$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3044, 1752, 1209, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, J = 2.1 Hz, 1 H), 7.00 (dd, J = 8.3, 2.1 Hz, 1 H), 6.78 (d, J = 8.3 Hz, 1 H), 4.50 (quint, J = 7.5 Hz, 1 H), 4.11 (dq, J = 10.8, 7.2 Hz, 2 H), 3.95 (dq, J = 14.2, 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.41 (dd, J = 10.4, 8.7 Hz, 1 H), 2.52 (dd, J = 13.2, 8.3 Hz, 1 H), 2.28 (s, 3 H), 2.23−2.16 (m, 2 H), 1.68 (dd, J = 13.4, 6.6 Hz, 1 H), 1.42 (s, 3 H), 1.12 (t, J = 7.0 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9 (C), 155.1 (C), 136.0 (C), 129.0 (C), 127.9 (CH), 127.4 (CH), 111.1 (CH), 72.0 (CH), 59.7 (CH_2), 54.9 (CH), 50.0 (CH_2), 49.9 (CH), 45.5 (C), 38.0 (CH_2), 25.9 (3 × CH_3), 24.7 (CH_3), 20.8 (CH_3), 18.2 (C), 14.2 (CH_3), −4.7 (2 × CH_3-Si) ppm. $C_{23}H_{38}O_4Si$ (406.6): calcd. C 67.94, H 9.42; found C 67.81, H 9.37.

Ethyl (1*S*,2*S*)-2-(2-Methoxy-5-methylphenyl)-2-methylcyclopentanecarboxylate [(+)-9]: Alcohol (+)-**6** (1.00 g, 3.42 mmol) was added to a suspension of sodium hydride (275 mg, 6.88 mmol, 60% dispersion) in 20 mL of THF at 0 °C. After stirring the mixture at 0 °C for 30 min, carbon disulfide (1.60 g, 1.27 mL, 13.8 mmol) and iodomethane (3.90 g, 1.71 mL, 27.4 mmol) were added. The resulting mixture was stirred for another 1 h, then carefully poured onto ice and extracted with diethyl ether. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an oily residue, which was immediately used for the next step. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.13 (d, J = 2.1 Hz, 1 H), 7.02 (dd, J = 8.1, 1.7 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 1 H), 6.02 (qd, J = 7.5, 6.4 Hz, 1 H), 4.06 (m, 2 H), 3.84 (s, 3 H), 3.56 (dd, J = 10.6, 7.7 Hz, 1 H), 2.88 (dd, J = 14.2, 8.2 Hz, 1 H), 2.56 (s, 3 H), 2.54−2.38 (m, 2 H), 2.28 (s, 3 H), 1.97 (dd, J = 14.2, 5.3 Hz, 1 H), 1.45 (s, 3 H), 1.14 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.1 (C), 173.3 (C), 155.0 (C), 134.4 (C), 129.1 (C), 127.8 (CH), 127.7 (CH), 111.3 (CH), 83.8 (CH), 59.9 (CH_2), 55.1 (CH), 49.8 (CH_3), 46.3 (CH_2), 45.4 (C), 34.0 (CH_2), 23.7 (CH_3), 20.7 (CH_3), 18.8 (CH_3), 14.1 (CH_3) ppm. Tri-*n*-butyltin hydride (1.58 g, 1.44 mL, 5.43 mmol) was added to a solution of crude xanthate (1.19 g, 3.40 mmol) and AIBN (30 mg) in toluene (20 mL) and the reaction mixture heated under reflux for 40 min, then cooled and concentrated in vacuo. Rapid purification of the residue on a silica gel column furnished 926 mg of (+)-**9** [98% from the alcohol (+)-**6**]. $[\alpha]_D^{25} = +55.1$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3092, 3047, 1743, 1181 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, J = 1.9 Hz, 1 H), 6.99 (dd, J = 8.1, 1.5 Hz, 1 H), 6.78 (d, J = 8.1 Hz, 1 H), 4.12 (dq, J = 10.8, 7.0 Hz, 1 H), 4.00 (dq, J = 10.8, 7.2 Hz, 1 H), 3.81 (s, 3 H), 3.44 (t, J = 8.1 Hz, 1 H), 2.28 (s, 3 H), 2.28−2.17 (m, 1 H), 2.13−2.01 (m, 1 H), 1.98−1.71 (m, 4 H), 1.32 (s, 3 H), 1.15 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.3 (C), 155.6 (C), 136.0 (C), 129.0 (C), 128.0 (CH), 127.3 (CH), 111.3 (CH), 59.6 (CH_2), 55.0 (CH), 51.9 (CH_3), 48.5 (C), 40.1 (CH_2), 28.6 (CH_2), 23.2 (CH_2), 23.1 (CH_3), 20.8 (CH_3), 14.2 (CH_3) ppm. $C_{17}H_{24}O_3$ (276.4): calcd. C 73.88, H 8.75; found C 74.17, H 8.79.

Ethyl (1*R*,2*R*)-2-(2-Methoxy-5-methylphenyl)-1,2-dimethylcyclopentanecarboxylate [(−)-10]: HMPA (0.62 mL, 3.56 mmol) and a solution of the ester (+)-**9** (200 mg, 0.724 mmol) in 3 mL of dry THF were added successively over a period of 30 min to a cold (−90 °C) magnetically stirred solution of LDA [prepared from diisopropylamine (0.50 mL, 3.57 mmol) and *n*-BuLi (2.89 mmol, 1.81 mL of a 1.6 M solution in hexane)] in 10 mL of dry diethyl ether. The reaction mixture was stirred at this temperature for 2 h. Methyl iodide (0.72 mL, 11.6 mmol) was then added to the reaction mixture, which was slowly warmed up to 0 °C and stirred overnight. The reaction mixture was partioned between diethyl ether and, sequentially, 5% aqueous HCl and 10% aqueous $NaHCO_3$. The organic layers were dried ($MgSO_4$), concentrated, and chromatographed to give the alkylated ester (−)-**10** (136 mg, 65% yield) as an oil. $[\alpha]_D^{25} = -27.5$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3089, 3051, 1746, 1197 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.04 (d, J = 1.9 Hz, 1 H), 6.92 (dd, J = 8.1, 1.5 Hz, 1 H), 6.69 (d, J = 8.1 Hz, 1 H), 3.72 (s, 3 H), 3.62 (m, 2 H), 2.63 (br. q, J = 9.6 Hz, 1 H), 2.25 (s, 3 H), 2.33−2.19 (m, 1 H), 1.95−1.73 (m, 3 H), 1.73−1.62 (m, 1 H), 1.46 (s, 3 H), 1.34 (s, 3 H), 0.83 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.7 (C), 155.9 (C), 136.2 (C), 128.7 (C), 128.3 (CH), 127.0 (CH), 111.0 (CH), 59.5 (CH_2), 55.5 (CH_3), 54.6 (C), 52.1 (C), 41.1 (CH_2), 40.5 (CH_2), 23.9 (CH_3), 21.9 (CH_2), 21.7 (CH_3), 20.7 (CH_3), 13.5 (CH_3) ppm. $C_{18}H_{26}O_3$ (290.4): calcd. C 74.45, H 9.02; found C 74.07, H 8.95.

***epi*-Herbertenolide [(+)-11]:** A solution of BBr_3 (1 M in CH_2Cl_2, 459 μL, 0.459 mmol) was slowly added at −70 °C to a solution of (−)-**10** (100 mg, 0.344 mmol) in CH_2Cl_2 (10 mL), and the mixture was allowed to warm to room temp. and stirred for 5 h. The reaction mixture was extracted with CH_2Cl_2, washed with water and saturated NaCl solution, and dried with $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on silica gel to afford (+)-**11** (71 mg, 90%) as an oil. $[\alpha]_D^{25} = +33.9$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1761, 1615, 1235, 1108 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.11 (d, J = 1.6 Hz, 1 H), 7.01 (dd, J = 8.1, 2.1 Hz, 1 H), 6.89 (d, J = 8.1 Hz, 1 H), 2.33 (s, 3 H), 2.42−2.31 (m, 1 H), 2.13−2.04 (m, 1 H), 1.90−1.57 (m, 4 H), 1.25 (s, 3 H), 1.22 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7 (C), 147.5 (C), 134.0 (C), 128.6 (CH), 128.5 (C), 126.8 (CH), 116.4 (CH), 50.9 (C), 47.6 (C), 38.8 (CH_2), 35.7 (CH_2), 21.7 (CH_3), 21.0 (CH_3), 20.0 (CH_2), 18.0 (CH_3) ppm. $C_{15}H_{18}O_2$ (230.3): calcd. C 78.23, H 7.88; found C 78.53, H 7.81.

(*R*,*S*)-1,14-Herbertenediol (+)-1: A solution of (+)-**11** (50 mg, 0.217 mmol) in dry diethyl ether (5 mL) was slowly added to a stirred slurry of $LiAlH_4$ (28 mg, 0.738 mmol) in dry diethyl ether (2 mL) at 0 °C. The solution was allowed to rise to room temp. After 2 h, Celite (1 g) and $Na_2SO_4 \cdot 10H_2O$ (1 g) were added and the solution was stirred for a further 30 min. The mixture was filtered through a pad of $MgSO_4$ and concentrated. Purification of the residue on a silica gel column furnished 1,14-herbertenediol (+)-**1** (49 mg, 96%) as a solid compound which exhibited ^1H and ^{13}C NMR spectra identical to those of the natural product. M.p. 116−117 °C. $[\alpha]_D^{25} = +11.8$ (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3161, 1613, 1227, 1029 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.96 (d, J = 1.7 Hz, 1 H), 6.90 (dd, J = 7.9, 1.7 Hz, 1 H), 6.72 (d, J = 7.9 Hz, 1 H), 3.33 and 3.26 (AB, J = 11.3 Hz, 2 H), 2.50−2.35 (m, 1 H), 2.26 (s, 3 H), 2.00−1.73 (m, 4 H), 1.55 (s, 3 H), 1.45−1.34 (m, 1 H), 1.31−1.24 (m, 1 H), 1.22 (s, 3 H) ppm. ^{13}C NMR (75MHz, $CDCl_3$): δ = 153.1 (C), 132.9 (C), 129.8 (C), 129.2 (CH), 128.0 (CH), 117.8 (CH), 70.7 (CH_2), 50.9 (C), 48.9 (C), 42.3 (CH_2), 36.0 (CH_2), 24.0 (CH_3), 21.2 (CH_2), 21.0 (CH_3), 20.5 (CH_3) ppm. $C_{15}H_{22}O_2$ (234.3): calcd. C 76.88, H 9.46; found C 76.65, H 9.57.

(1*R*,2*S*)-1-(Hydroxymethyl)-2-(2-methoxy-5-methylphenyl)-1,2-dimethylcyclopentane [(−)-12]: A solution of (−)-**10** (100 mg, 0.344 mmol) in dry diethyl ether (5 mL) was slowly added to a stirred slurry of $LiAlH_4$ (30 mg, 0.790 mmol) in dry diethyl ether (4 mL) at 0 °C. The solution was allowed to rise to room temp. After 1 h, Celite (1 g) and $Na_2SO_4 \cdot 10H_2O$ (1 g) were added and the solution

was stirred for a further 30 min. The mixture was filtered through a pad of $MgSO_4$ and concentrated. Column chromatography of the oil afforded 84 mg (98%) of pure (−)-**12**. $[\alpha]_D^{25} = -17.9$ ($c = 1.0$, $CHCl_3$). IR (neat): $\tilde{\nu} = 3432, 1599, 1496, 1246, 1030\ cm^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.08$ (d, $J = 1.7$ Hz, 1 H), 7.00 (dd, $J = 8.3, 1.7$ Hz, 1 H), 6.80 (d, $J = 8.3$ Hz, 1 H), 3.79 (s, 3 H), 3.11 (s, 2 H), 2.45 (m, 1 H), 2.27 (s, 3 H), 1.86−1.63 (m, 4 H), 1.40 (s, 3 H), 1.39−1.22 (m, 2 H), 1.19 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.3$ (C), 135.2 (C), 129.9 (C), 129.4 (CH), 127.7 (CH), 112.0 (CH), 70.6 (CH_2), 55.3 (CH_3), 50.4 (C), 48.9 (C), 42.0 (CH_2), 37.1 (CH_2), 24.1 (CH_3), 21.3 (CH_2), 20.9 (CH_3), 20.9 (CH_3) ppm. $C_{16}H_{24}O_2$ (248.4): calcd. C 77.38, H 9.74; found C 77.17, H 6.69.

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